(Pyridylcyanomethyl)piperazines as Orally Active PAF Antagonists

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Received February 7, 1992

A series of (pyridylcyanomethyl)piperazines was prepared and evaluated for PAF-antagonist activity. Compounds were tested in vitro in a PAF-induced platelet aggregation assay and in vivo in a PAF-induced hypotension test in normotensive rats. Oral activity was ascertained through a PAF-induced mortality test in mice. The main structure–activity trends of the series were established. Activity was mainly found in four skeletons: 1-acyl-4-(3-pyridylcyanomethyl)-piperazine, 1-acyl-4-(4-pyridylcyanomethyl)piperazine, 1-acyl-4-(3-pyridylcyanomethyl)piperidine, and 1-acyl-4-cyano-4-(3-pyridylamino)piperidine. The acyl substituents, diphenylacetyl and 3,3-diphenylpropionyl, provided the most active compounds, and the introduction of an amine or hydroxy group in the 3,3-diphenylpropionyl substituent led to further improvement in oral activity. As a result, three of the most active compounds (**100**, **114**, and **115**) have been selected for further pharmacological development.

Introduction

There has been an ongoing effort to discover PAF antagonists in the last decade. Although PAF has been recognized as having a key role in numerous pathological processes, no clear clinical application of this class of compounds has yet been firmly demonstrated. Medicinal chemists nevertheless continue to shed light on the structure–activity relationships that govern this field by describing new products and optimizing structural variables. The search for novel chemical entities has focused on the preparation of charged structural analogues of PAF, the screening of natural products, and the evaluation of a variety of synthetic compounds, some having known pharmacological activity.[1] Among synthetic compounds, triazolodiazepine is the nucleus that has received the most attention and in which there are orally potent PAF antagonists, such as compound **1** (WEB 2086).[2] Other chemically unrelated structures in this group are pyrrolodihydrothiazole **2** (RP 59227),[3] dihydroimidazoisoquinoline **3** (SDZ 64-412),[4] pyridylthiazolidine **4** (YM 461),[5] and pyridocarboxamide **5** (RO 24-0238).[6]

We recently described a series of ionic tetrahydrofuran, dioxolane, and glycol derivatives with potent PAF antagonist activity.[7] In the present paper we report the results of a parallel search for novel noncharged structures with good oral bioavailability.

From a preliminary screening, bis(3,4,5-trimethoxybenzoyl)piperazine[8] (**30**), a compound described in 1968 as analgesic, was identified as a relatively potent PAF antagonist in vitro and in vivo. In an effort to prepare more potent compounds, we explored the chemical modification of this structure to identify structural features necessary for optimal activity. We first ascertained the effect of replacing one of the 3,4,5-trimethoxybenzoyl substituents at the symmetric known compound **30** by a pyridine-containing substituent, leading us to identify cyanomethylpyridine **36** as a lead compound. In fact, the pyridine ring and the amide group separated by a given distance found in this molecule is a common feature in several known PAF antagonists (see structures **2**, **4**, and **5**). Subsequent synthetic and structure–activity studies based on **36** resulted in the preparation of a new class of potent orally active PAF antagonists. The present work discusses the synthesis and evaluation of the PAF-antagonist activity of these compounds.

Chemistry

The carboxamides **31–36** (Table I) and compounds **66–69**, **71**, **75**, **79**, and **80** (Table IV) were prepared as outlined in Scheme I. Acylation of piperazine with 3,4,5-trimethoxybenzoyl chloride under controlled pH gave a 1.7:1 mixture of amine **7a** and compound **30**. The *N*-formyl derivatives **6b,c** were obtained by acylation of *N*-formylpiperazine with appropriate carboxylic acids using HOBT and DCC in DMF (method A). Acid hydrolysis of **6b,c** yielded piperazines **7b,c**, which together with **7a** were the starting material for a series of reactions. Compounds **31**, **32**, **68**, and **69** were prepared from **7a–c** by a second acylation with the appropriate carboxylic acid by method

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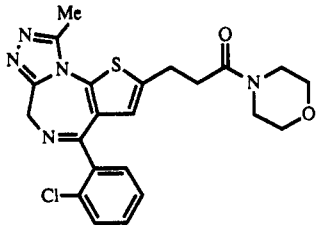
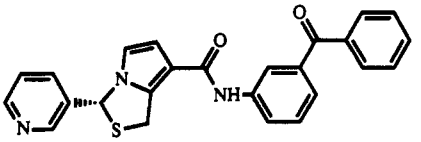
Chart I



1 (WEB 2086)



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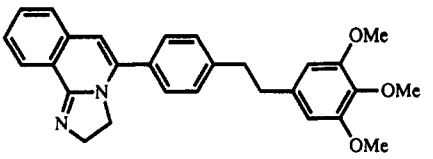
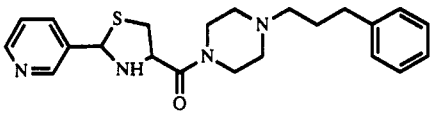
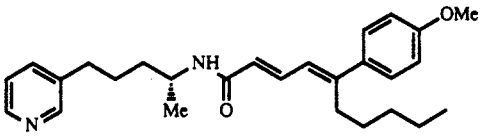


3 (SDZ 64-412)

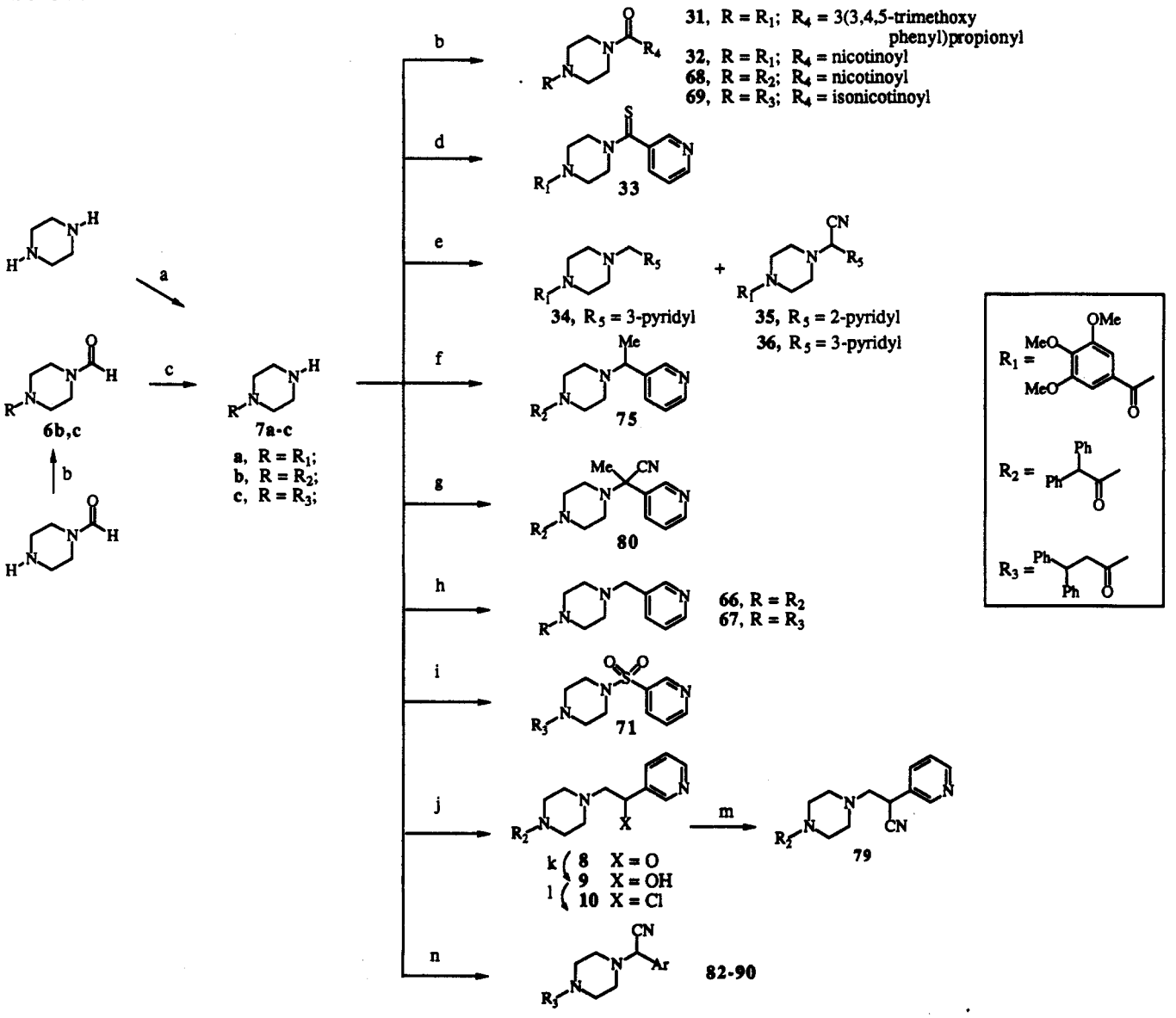


4 (YM 461)



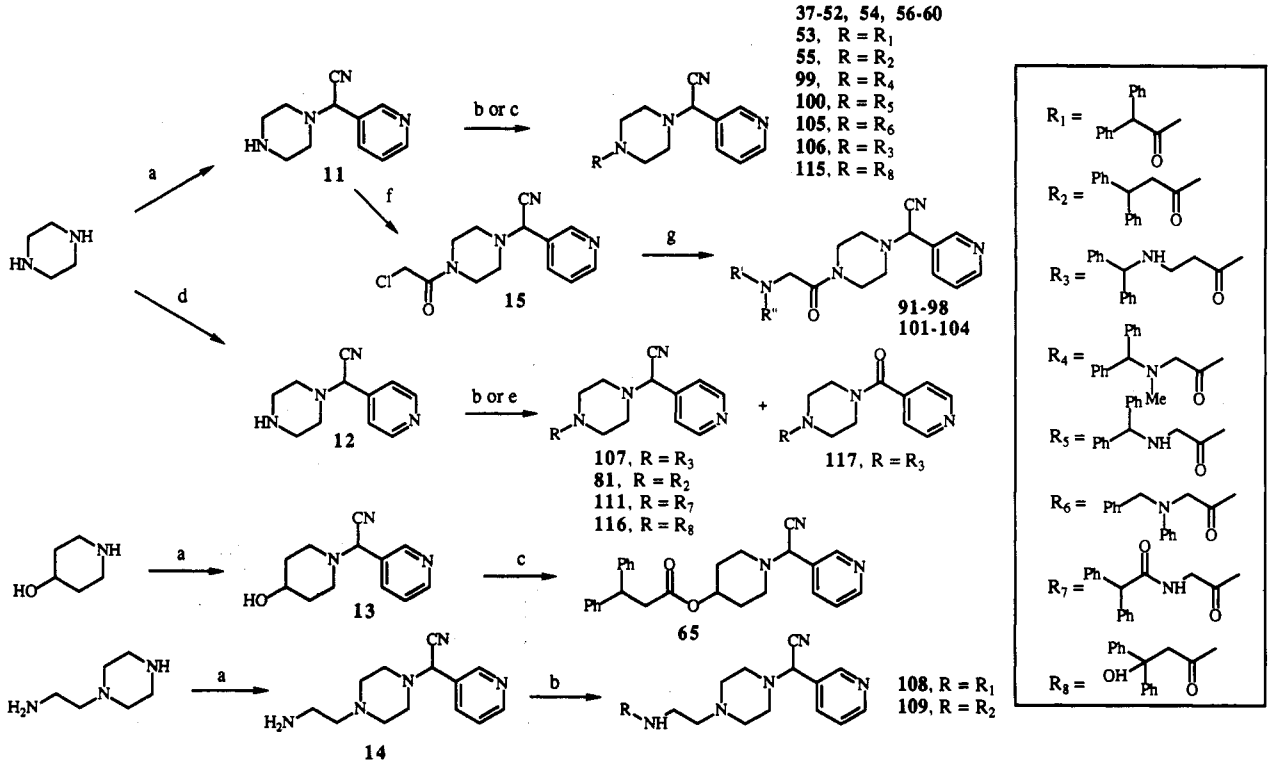
5 (RO 24-0238)

Scheme I [a]



[a] (a) 3,4,5-Trimethoxybenzoyl chloride, THF/H_2O, pH = 2–3.5, room temperature, 2 h; (b) RCOOH, DCC, HOBT, DMF, room temperature, 18 h (method A); (c) aqueous HCl, MeOH, 100 °C, 1 h; (d) pyridine-3-carboxaldehyde, sulfur, DMF, 100 °C, 3 h; (e) pyridine-2-carboxaldehyde or pyridine-3-carboxaldehyde, $NaBH_3CN$, MeOH, pH = 6–8, room temperature, 24 h; (f) 3-acetylpyridine, $NaBH_3CN$, MeOH, pH = 6–8, room temperature, 24 h; (g) (1) 3-acetylpyridine, TsOH, toluene, reflux; (2) KCN, AcOH, room temperature, 18 h; (h) 3-(chloromethyl)pyridine hydrochloride, TEA, $CHCl_3$, room temperature, 48 h; (i) pyridine-3-sulfonyl chloride hydrochloride, TEA, $CHCl_3$, room temperature, 18 h; (j) 3-(2-bromoacetyl)pyridine hydrobromide, TEA, $CHCl_3$, room temperature, 18 h; (k) $NaBH_4$, MeOH, 0 °C, 0.5 h; (l) $SOCl_2$, $CHCl_3$, room temperature, 1 h, then reflux, 1 h; (m) KCN, DMSO, 90 °C, 6 h; (n) ArCHO, KCN, MeOH/H_2O, pH = 7, room temperature, 18 h.

Scheme II [a]



[a] (a) Pyridine-3-carboxaldehyde, KCN, MeOH/H_2O, pH = 7, room temperature, 18 h; (b) RCOOH, DCC, HOBT, DMF, room temperature, 18 h (method A); (c) RCOOCl, TEA, $CHCl_3$, room temperature, 18 h (method B); (d) pyridine-4-carboxaldehyde, KCN, MeOH/H_2O, pH = 7, room temperature, 18 h; (e) reagent prepared from 3-[*N*-(diphenylmethyl)amino]propanoic acid, *N*-hydroxysuccinimide, DCC, DME, room temperature, 2 h; DME, room temperature, 2 h, and then 60 °C, 30 min; (f) chloroacetyl chloride, TEA, $CHCl_3$, 0 °C, 1 h; (g) R'R''NH, TEA, $CHCl_3$, room temperature, 48 h (method C).

A. Treatment of **7a** with pyridine-3-carboxaldehyde and sulfur in DMF[9] furnished compound **33**. Reaction of **7a** with pyridine-3-carboxaldehyde and $NaBH_3CN$[10] led to a 1.2:1 mixture of amine **34** and cyanomethylamine **36**. Under the same conditions, the reaction of **7b** with 3-acetylpyridine gave mainly compound **75**. Condensation of **7b** with 3-acetylpyridine under acid catalysis, followed by treatment with KCN in HOAc, afforded compound **80**.[11] Amines **66** and **67** were prepared by alkylation of **7b,c** with 3-(chloromethyl)pyridine hydrochloride. Sulfonamide **71** was prepared by coupling **7c** with pyridine-3-sulfonyl chloride hydrochloride.[12]

The homologous cyanomethylpyridine **79** was synthesized through the alkylation of **7b** with 3-(2-bromoacetyl)-pyridine[13] followed by reduction with sodium borohydride, conversion of the resulting alcohol **9** into chloride **10** by treatment with $SOCl_2$, and finally reaction with KCN in DMSO.

Compounds **81–90** listed in Table V were prepared by reacting **7c** with the appropriate aromatic or heterocyclic aldehydes in the presence of KCN.[11] The substituted benzaldehydes and 1-methylpyrrole-3-carboxaldehyde are commercial products, and the remaining heterocyclic aldehydes were prepared as described in the literature.[14]

Looking for a more efficient way to prepare 1-acyl-4-(3-pyridylcyanomethyl)piperazines, we tried direct condensation of pyridine-3-carboxaldehyde with an excess of piperazine in the presence of KCN. This reaction gave an 85% yield of cyanomethylpiperazine **11** accompanied by only traces of dimer product; we were thus able to avoid use of a protecting group for piperazine (see Scheme II). All compounds listed in Table II were prepared by coupling amine **11** with the appropriate carboxylic acid by means of the aforementioned standard method A or through the mediation of an acid chloride (method B).

Under conditions similar to those used for preparation of **11**, intermediates **12**, **13**, and **14** were obtained in 82%, 95% and 24% yields, respectively, starting from the appropriate aldehyde and amine. In coupling **12** with carboxylic acids to give compounds **81**, **111**, **116**, and **107** by method A, concomitant formation of the corresponding isonicotinoyl piperazine derivative (for example **117** in the case of R = R_3) was observed. A related process, the base-catalyzed autoxidation of α-amino nitriles as an efficient method for converting aldehydes to amides, has been recently reported.[15] Undesired amide formation

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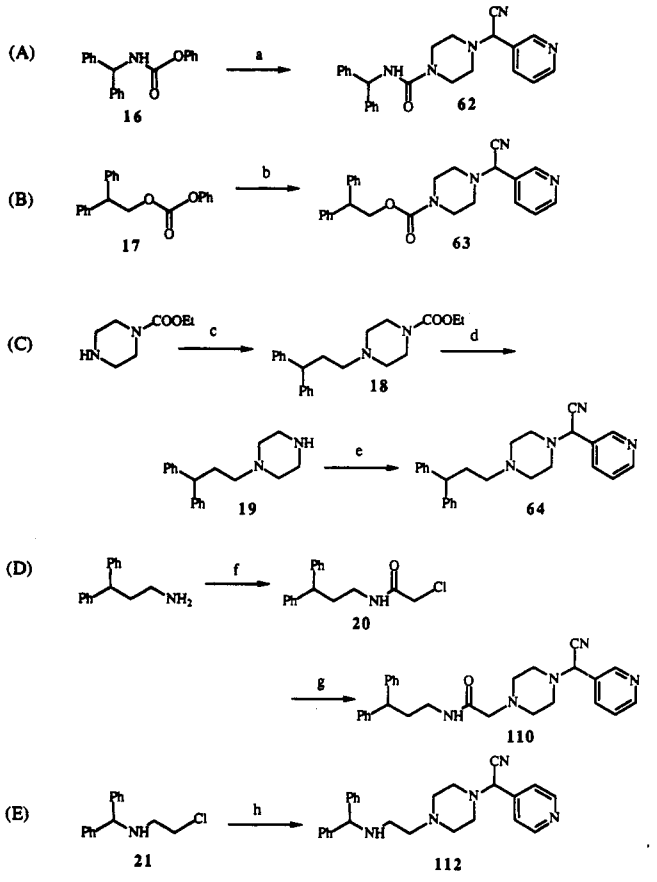
Scheme III [a]



[a] (a) 11, pyr, reflux, 48 h; (b) 11, K_2CO_3, DMF, 80 °C, 12 h; (c) (1) 3,3-diphenylpropanoyl chloride, TEA, $CHCl_3$, room temperature, 18 h; (2) $POCl_3$, toluene, 50 °C, 0.5 h, and then DME, $NaBH_4$, room temperature, 18 h; (d) 10% NaOH, EtOH, 100 °C, 18 h; (e) pyridine-3-carboxaldehyde, KCN, MeOH/H_2O, pH = 7, room temperature, 24 h; (f) chloroacetyl chloride, TEA, $CHCl_3$, room temperature, 18 h; (g) 11, TEA, $CHCl_3$, room temperature, 48 h; (h) 12, TEA, $CHCl_3$, reflux, 48 h.

reaction was reduced in the synthesis of **107** by the isolation of the *N*-hydroxysuccinimide ester of 3-[*N*-(diphenylmethyl)amino]propionic acid prior to reaction with **12** in DME.

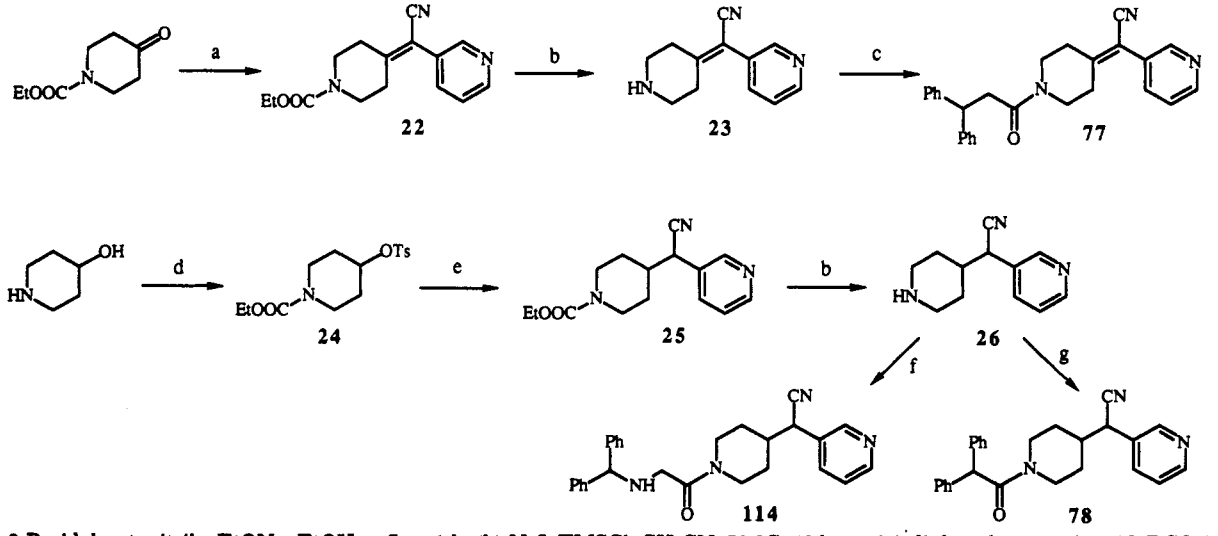
Compounds **91–106** (Table VI), which are glycine or β-alanine derivatives, were obtained through two methods (see Scheme II). In the first, amine **11** was coupled with the previously prepared amino acids[16] by method A to give compounds **99, 100, 105, 106,** and **115** (Table VI). In the second, intermediate **15**, prepared by the reaction of amine **11** and chloroacetyl chloride, was quickly treated with the appropriate aralkylamine (method C). In this way, compounds **91–98** and **101–104** were obtained.

Compounds **62–64** (Table III) and **110, 112** (Table VI) were prepared as shown in Scheme III. Thus, compounds **62** and **63** having urea and carbamate functions, respectively, were formed by the reaction of **11** with intermediates **16** and **17** (eq A and B). For the preparation of **64**, *N*-(ethoxycarbonyl)piperazine was acylated with 3,3-diphenylpropionic acid, and the amide formed was reduced with $POCl_3$ and $NaBH_4$.[17] The resulting alkylpiperazine **18** was subjected to basic hydrolysis to give **19**, which was condensed with pyridine-3-carboxaldehyde in the presence of KCN (eq C). Compound **110** with the carbonyl group in a shifted position was prepared via coupling of chloroacetyl chloride with (3,3-diphenylpropyl)amine and treatment of the resulting chloride **20** with amine **11** (eq D). Compound **112** was obtained by alkylation of amine **12** with *N*-(2-chloroethyl)-*N*-diphenylmethylamine **21** (eq E).

The carba analogues of 1-acyl-4-(3-pyridylcyanomethyl)-piperazines, compounds **77, 78,** and **114**, were prepared by the sequence shown in Scheme IV. Aldol condensation of *N*-(ethoxycarbonyl)-4-piperidone with 3-pyridylacetonitrile in refluxing NaOEt/EtOH gave **22**, which was deprotected by TMSI generated in situ[18] to yield amine **23**, and this was acylated by standard method A to give compound **77**. The strategy used to prepare amine **26** was to alkylate 3-pyridylacetonitrile with tosylate **24** followed by deprotection of the amine group, again using TMSI generated in situ. The conversion of **26** to **78** and **114** was accomplished by standard method A.

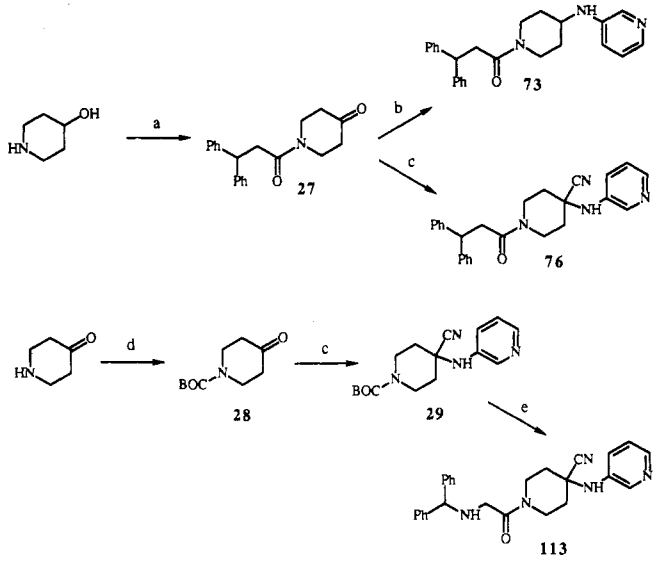
(Pyridylamino)piperidines **73, 76,** and **113** were prepared as shown in Scheme V. Thus, ketone **27**, which was derived by acylation of 4-hydroxypiperidine using method A followed by oxidation with CrO_3/pyridine, was treated with

Scheme IV [a]



[a] (a) 3-Pyridylacetonitrile, EtONa, EtOH, reflux, 1 h; (b) NaI, TMSCl, CH_3CN, 50 °C, 48 h; (c) 3,3-diphenylpropanoic acid, DCC, HOBT, DMF, room temperature, 18 h (method A); (d) (1) EtOCOCl, $CHCl_3$, TEA, room temperature, 18 h; (2) TsCl, TEA, CH_2Cl_2, room temperature, 18 h; (e) 3-pyridylacetonitrile, NaH, DMF, 50 °C, 18 h; (f) [*N*-(diphenylmethyl)amino]acetic acid, method A; (g) [*N*-(diphenylmethyl)amino]acetic acid, method A.

Scheme V [a]



[a] (a) (1) 3,3-diphenylpropanoic acid, DCC, HOBT, DMF, room temperature, 18 h (method A); (2) CrO_3, pyr, CH_2Cl_2, room temperature, 18 h; (b) 3-aminopyridine, $NaBH_3CN$, MeOH, pH = 6–8, room temperature, 24 h; (c) 3-aminopyridine, KCN, AcOH, 60 °C, 18 h; (d) di-*tert*-butyl dicarbonate, 1 N NaOH, THF, room temperature, 2 h; (e) (1) $HCl_{(g)}$/dioxane, $CHCl_3$, 0 °C, 0.5 h; (2) [*N*-(diphenylmethyl)amino]acetic acid, method A.

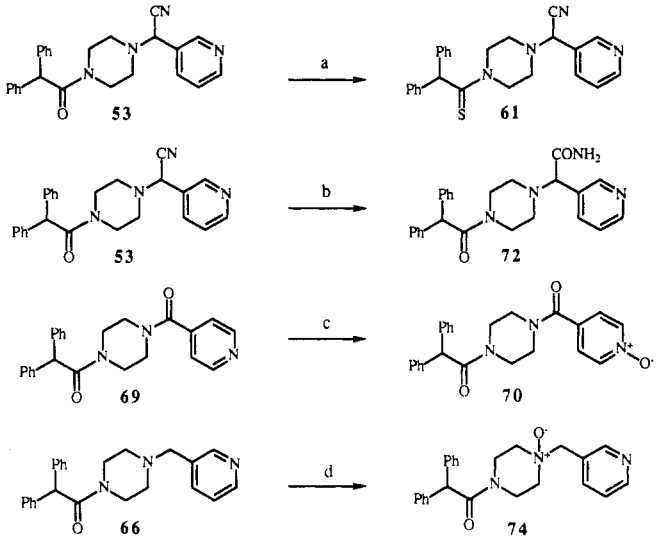
3-aminopyridine and $NaBH_3CN$ to furnish **73**. Reaction of ketone **27** with pyridine-3-carboxaldehyde in the presence of KCN in HOAc[11] gave compound **76**. Under similar conditions, *N*-BOC-4-piperidone (**28**) was converted to **29**, which was deprotected by treatment with $HCl_{(g)}$ in dioxane and coupled with [*N*-(diphenylmethyl)-amino]acetic acid using method A to give compound **113**.

One analogue bearing a thioamide group (**61**) was prepared by treating **53** with Lawesson reagent (Scheme VI). Compound **53** was also converted to amide **72** by the action of $HCl_{(g)}$ in MeOH. Finally, the oxidation of **66** and **69** with MCPBA yielded **70** and **74**, respectively.

Results and Discussion

Compounds were evaluated for PAF-antagonist activity using the in vitro PAF-induced platelet aggregation assay[19] and the in vivo PAF-induced hypotension test in normotensive rats.[20] In the latter, initial intravenous doses of 5 mg/kg of the test compounds were administered before PAF injection. Only when more than 50% inhibition of the hypotension response was achieved were more doses tested in order to obtain the ID_{50} values. Many compounds

Scheme VI [a]



[a] (a) Lawesson's reagent, toluene, reflux, 18 h; (b) $HCl_{(g)}$/MeOH, room temperature, 18 h; (c) MCPBA, $CHCl_3$, room temperature, 1 h; (d) MCPBA, CH_2Cl_2, 0 °C, 1 h.

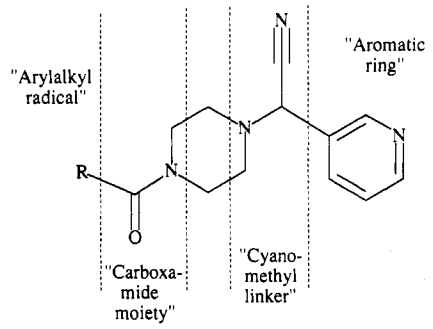


Figure 1.

were also tested for oral activity in the PAF-induced mortality test in mice.[21]

Table I shows data for compounds in which one of the 3,4,5-trimethoxybenzoyl groups of known compound **30** was changed by a pyridine-containing substituent. The cyanomethylpyridine **36** and especially its analogues **37** and **38** with enlarged aralkyl chains showed a modest but significant increase in activity that encouraged us to search for even more potent compounds based on their structure.

Tables II–VI list a series of compounds generated by the systematic variation of four main features found for the aforementioned lead compound **36**: the aralkyl chain, the carboxamide moiety, the cyanomethyl linker, and the aromatic ring (Figure 1).

We first focused our attention on the aralkyl chain (Table II). Within a homogeneous phenylalkanoyl series (**39–42**), 3-phenylpropanamide **41** was the most potent compound and nearly equipotent to its trimethoxy-substituted analogue **38**. Linear alkanoyl derivatives **44–47** and aralkanoyl derivatives with condensed aromatic rings **48–51** were generally less active than 3-phenylpropanamide **41**. However, the presence of a diphenylmethyl moiety in the acyl substituent (**53–55** and **59**) increased activity in the aggregation test to about 50 times that of **41**. The hypotension test was more selective; 3,3-diphenylpropanamide **55** and 3,3-diphenylpropenamide **59** were

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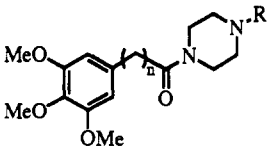
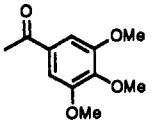
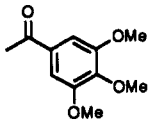
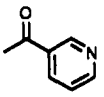
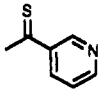
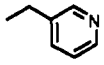
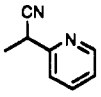
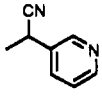
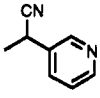
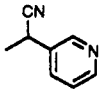
Table I. Characterization and PAF-Antagonist Activity of 3,4,5-Trimethoxybenzoylpiperazine Derivatives



compd	R	n	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 po	mp, °C	solvents[d]	formula[e]	anal.[f]
30		0	9.4 (4.7–19)	4.7 (2.7–8.3)	>100	224–225	Cl	$C_{24}H_{30}N_2O_8 \cdot {}^1/_2H_2O$	C, H, N
31		2	73 (15–350)	>5	–	86–87	D/Et_2O	$C_{26}H_{34}N_2O_8 \cdot {}^1/_2H_2O$	C, H, N
32		0	5.2 (1.0–27)	>5	>100	89–105	EA/Et_2O	$C_{20}H_{23}N_3O_5 \cdot HCl \cdot H_2O$	C, H, N
33		0	1.3 (0.89–1.9)	>5	30–100	231–232	EA/Et_2O	$C_{20}H_{23}N_3SO_4 \cdot HCl \cdot {}^1/_2H_2O$	C, H, N
34		0	17 (6.9–43)	>5	>100	153–158	EA/Et_2O	$C_{20}H_{25}N_3O_4 \cdot 2HCl \cdot 2H_2O$	C, H, N
35		0	44 (33–58)	>5	–	89–95	EA/Et_2O	$C_{21}H_{24}N_4O_4 \cdot HCl \cdot {}^1/_4H_2O$	C, H, N
36		0	1.9 (1.2–3.1)	4.4 (3.5–5.5)	>100	86–87	EA/Et_2O	$C_{21}H_{24}N_4O_4 \cdot 2HCl \cdot H_2O$	C, H, N
37		1	0.46 (0.21–1.0)	2.5 (0.98–6.3)	>50	161–162	EA	$C_{22}H_{26}N_4O_4 \cdot {}^1/_2H_2O$	C, H, N
38		2	0.40 (0.30–0.53)	2.0 (0.18–0.22)	30–100	<30	EA/Et_2O	$C_{23}H_{26}N_4O_4 \cdot 2HCl \cdot H_2O$	C, H, N

[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%. Parentheses contain 95% confidence limits. [d] Solvents: A = acetonitrile, Cl = chloroform, D = dichloromethane, H = hexane, EA = ethyl acetate. [e] Empirical formula with amount of water of hydration. [f] Analytical results for the indicated elements are within ±0.4% of the calculated values unless indicated otherwise.

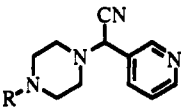
the best compounds (ID_{50} less than 0.1 mg/kg iv). The activities of the last two compounds surpassed those of reference compound **1** and met our threshold activity criteria in the aggregation and hypotension tests although not in the mortality test.

Attempts to improve activity by modifying the carboxamide unit (Table III) were not successful. Only carbamate **63** maintained activity in the two first screening tests; nevertheless, this compound failed in the oral test. As a result, carboxamide moiety was left untouched in the remaining compounds.

A study of the nature of the linker between piperazine and pyridine rings (Table IV) revealed a significant role for the cyano group in determining activity. Neither the replacement of this group (**66**, **67**, **72**, **74**, **75**) nor the substitution of the cyanomethyl moiety by a carboxamide or sulfonamide (**68–71**) was compatible with activity, as can be seen by comparison of these compounds with 3-(cyanomethyl)pyridines **53** and **55**. That the cyano group is a key feature of this class of compounds was further corroborated by the fact that other compounds carrying this group retained the high potency observed in **53** and **55**. Examples are compound **76**, in which the amine and cyano group shifted their positions; **77** with a carbon–carbon double bond; and compound **78**, the carba analogue of **53**. Finally, the insertion of a methylene group between the piperazine ring and the cyanomethyl linker (**79**) or additional substitution in the carbon atom bearing the cyano group (**80**) led to significant loss of activity.

Investigation into the nature of the aromatic ring (Table V) revealed that the antagonist effect almost disappeared when the pyridine ring was replaced by substituted phenyl rings or five-membered nitrogen-containing heterocycles. With regard to the position of nitrogen in the pyridine, 4-pyridine **81** retained the overall activity of its 3-pyridine analogue **55**. It was half as active in the platelet aggregation

Table II. The "Arylalkyl Chain": Characterization and PAF-Antagonist Activity of 1-Acyl-4-(3-pyridylcyanomethyl)piperazine Derivatives



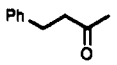
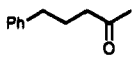
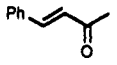
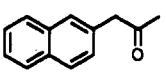
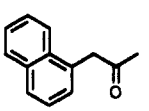
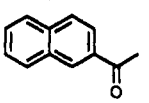
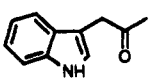
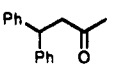
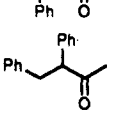
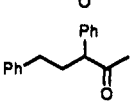
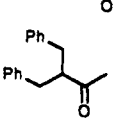
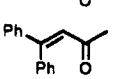
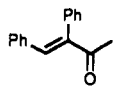
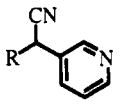
compd	R	PAF-induced platelet aggregation IC_{50},[a] μM	PAF-induced hypotension ID_{50},[b] mg/kg iv	PAF-induced mortality ID_{50},[c] mg/kg po	mp, °C	solvents[d]	formula[e]	anal[f]
39		4.8 (2.8–2.3)	>5	–	39–45	EA/Et_2O	$C_{18}H_{18}N_4O$·2HCl	C, H, N
40		2.7 (1.6–4.8)	1.5 (0.9–2.6)	20–50	150–151	Et_2O	$C_{19}H_{20}N_4O$·$^1/_2H_2O$	C, H, N
41		0.52 (0.52–0.53)	1.2 (1.0–1.4)	44 (34–56)	29–35	EA/Et_2O	$C_{20}H_{22}N_4O$·2HCl·$^1/_4H_2O$	C, H, N
42		0.26 (0.09–0.74)	57% inhib at 5 mg/kg	30–50	154–159	EA	$C_{21}H_{24}N_4O$·$^1/_4H_2O$	C, H, N
43		2.5 (1.1–5.7)	0.24 (0.11–0.52)	50–100	180–181	A	$C_{20}H_{20}N_4O$	C, H, N
44	*n*-C_4H_9CO	2.6 (1.7–4.0)	4.3 (0.18–100)	>50	101–102	EA	$C_{16}H_{22}N_4O$	C, H, N
45	*n*-$C_7H_{15}CO$	0.92 (0.47–1.8)	1.2 (0.46–4.2)	50–100	126–130	D/Et_2O	$C_{19}H_{28}N_4O$·HCl·$^3/_4H_2O$	C, H, N
46	*n*-$C_{15}H_{31}CO$	>200	>5	–	67–70	EA/H	$C_{27}H_{44}N_4O$	C, H, N
47	$(CH_3)_3CCO$	5.2 (4.3–6.3)	>5	–	134–136	EA/H	$C_{16}H_{22}N_4O$	C, H, N
48		0.72 (0.63–0.81)	56% inh at 5 mg/kg	–	182–186	Et_2O	$C_{23}H_{22}N_4O$·$^1/_4H_2O$	C, H, N
49		0.076 (0.064–0.091)	1.3 (0.35–4.6)	>50	152–153	A	$C_{23}H_{22}N_4O$	C, H, N
50		25 (19–33)	55% inh at 5 mg/kg	–	119–125	EA/Et_2O	$C_{22}H_{20}N_4O$·2HCl	C, H, N
51		0.45 (0.23–0.89)	3.3 (1.3–8.3)	>50	116–120	EA/Et_2O	$C_{21}H_{21}N_5O$·3HCl·$^1/_2H_2O$	C, H, N
52		0.021 (0.010–0.043)	0.26 (0.19–0.38)	>50	85–92	EA/Et_2O	$C_{20}H_{22}N_4O$·2HCl	C, H, N
53		0.010 (0.0076–0.012)	0.11 (0.085–0.15)	12 (11–14)	191–195	EA/H	$C_{25}H_{24}N_4O$	C, H, N
54		0.0019 (0.0014–0.0027)	0.14 (0.06–0.34)	>30	128–129	EA/Et_2O	$C_{26}H_{26}N_4O$·2HCl	C, H, N
55		0.020 (0.016–0.024)	0.013 (0.0062–0.026)	12 (8–19)	160–161	Et_2O	$C_{26}H_{26}N_4O$	C, H, N
56		0.23 (0.18–0.29)	0.12 (0.0048–0.31)	>50	155–157	Et_2O	$C_{26}H_{26}N_4O$·$^3/_4H_2O$	C, H, N
57		2.6 (0.97–6.8)	0.73 (0.35–1.5)	–	111–115	Et_2O	$C_{27}H_{28}N_4O$	C, H, N
58		0.011 (0.008–0.015)	0.68 (0.42–1.1)	50–100	83–89	EA/Et_2O	$C_{27}H_{28}N_4O$·2HCl·$^1/_2H_2O$	C, H, N
59		0.010 (0.0068–0.015)	0.049 (0.032–0.076)	30–50	69–71	EA	$C_{26}H_{24}N_4O$	C, H, N

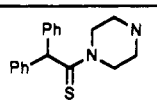
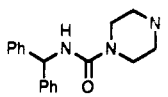
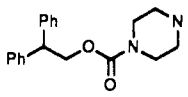
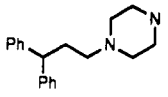
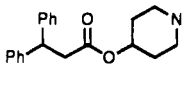
Table II. (Continued)

compd	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 po	mp, °C	solvents[d]	formula[e]	anal.[f]
60		0.0075 (0.0053–0.011)	0.17 (0.09–0.34)	>20	132–133	D/Et_2O	$C_{26}H_{24}N_4O\cdot{}^3/_4H_2O$	C, H, N

[a-f] See footnotes in Table I.

Table III. The "Carboxamide Moiety": Characterization and PAF-Antagonist Activity of Compounds 61–65



compd	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 po	mp, °C	solvents[d]	formula[e]	anal.[f]
61		0.023 (0.016–0.032)	0.45 (0.28–0.71)	>50	212–215	EA/H	$C_{25}H_{24}N_4S\cdot{}^1/_2H_2O$	C, H, N
62		0.36 (0.18–0.73)	0.29 (0.13–0.66)	50% inhib at 30 mg/kg	204–205	A	$C_{25}H_{25}N_5O\cdot{}^1/_2H_2O$	C, H, N
63		0.026 (0.021–0.032)	0.078 (0.057–0.089)	>30	97–98	EA/Et_2O	$C_{26}H_{26}N_4O_2\cdot 2HCl\cdot{}^3/_4H_2O$	C, H, N
64		0.63 (0.47–0.84)	3.1 (1.7–5.9)	15 (9–24)	115–122	EA/Et_2O	$C_{26}H_{28}N_4\cdot 3HCl\cdot{}^1/_2H_2O$	C, N, H[g]
65		2.6 (1.3–4.9)	>5	–	124–130	EA/Et_2O	$C_{27}H_{27}N_3O_2\cdot 2HCl\cdot{}^1/_2H_2O$	C, H, N

[a-f] See footnotes in Table I. [g] H calcd, 5.52; found, 6.06.

and hypotension tests but performed slightly better in the mortality test. The 2-pyridine derivatives were discarded in an earlier stage of this study due to the lack of activity of compound **35** (Table I).

Once the main structure–activity trends of this series had been established, we chose the aralkyl chain to make a final attempt to further improve oral activity, since this variable had shown greater flexibility. The protection shown by amine **64** (Table III) in the mortality test, exceptional considering the compound's level of activity, suggested the idea of inserting an amino group into the aralkanoyl substituent (Table VI). Before examining the oral activity of the new compounds, we checked the activities in the aggregation and hypotension tests. Comparison of these amino acid derivatives with their carba analogues in Table II revealed absolute coincidence in the substitution pattern required for high level of activity. Pairs of compounds which only differ from one another in the insertion of an amino group (see **92**, vs **40**, **93** vs **41**, **98** vs **48**, and **100** vs **55**) showed similar potency at different ranges in the aggregation and hypotension tests. The diphenylmethyl moiety is again present in the most active compounds (**100**, **106**, and **107**). Comparison of **101** with **106** suggested that the optimal position for the amino group was next to the diphenylmethyl moiety. The additional substitution of the amino group by a methyl group was detrimental to activity in the four pairs of compounds tested (**91** vs **92**, **94** vs **95**, **96** vs **97**, and **99** vs **100**). Other isomeric patterns different from [(diphenylmethyl)amino]-acetyl or [(diphenylmethyl)amino]propionyl (**103**–**105**), although with similar levels of activity in the aggregation test, were inferior in the hypotension test. Disminished activity was also observed for compounds **108**–**110** with shifted carbonyl group positions, for compound **111** with two amide functions and **112** with two amine functions.

Regarding the results of amino acid derivatives in the PAF-induced mortality test after oral administration, we observed that the incorporation of the amino group decreased the ID_{50} values 2- or 3-fold (**55** vs **99**, **100**, **106**, and **107**). Similar improvement was also observed for 3-hydroxy-3,3-diphenylpropanamides **115** and **116**. Furthermore, compounds **113** and **114**, bearing a [*N*-(diphenylmethyl)amino]acetate substituent incorporated in the other two cyano-containing skeletons prepared, showed better oral activity than their analogues with no amino group in the side chain (**76** and **78**). We can therefore conclude that the introduction of a polar group with the ability to establish hydrogen bonding in the aralkyl chain increases bioavailability in this series. Interestingly, 4-pyridines incorporating an aminoacyl or hydroxyacyl substituent (**107** and **116**) were again nearly as potent as their 3-pyridine analogues (**106** and **115**).

In conclusion, we report a novel series of potent and orally active PAF antagonists: 1-acyl-4-(3-pyridylcyanomethyl)piperazine, 1-acyl-4-(4-pyridylcyanomethyl)-piperazine, 1-acyl-4-(3-pyridylcyanomethyl)piperidine, and 1-acyl-4-cyano-4-(3-pyridylamino)piperidine. The PAF antagonist character of these compounds is highly dependent on the presence of a cyano group and on the nature of the aromatic ring, 3- or 4-pyridine being optimal. The

Table IV. The "Cyanomethyl Linker": Characterization and PAF-Antagonist Activity of Compounds **66–80**

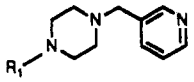
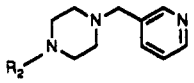
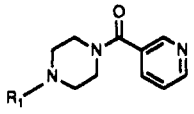
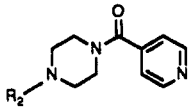
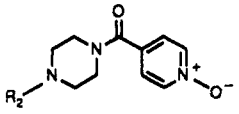
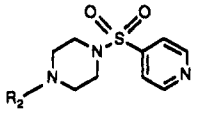
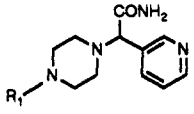
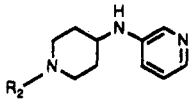
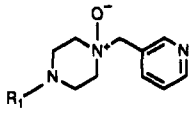
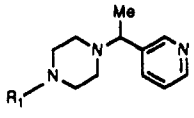
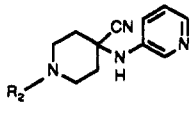
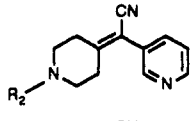
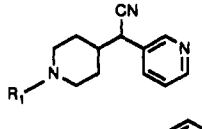
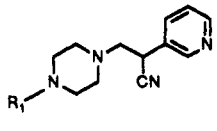
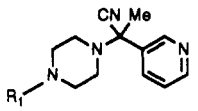
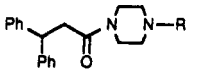
compd	R	PAF-induced platelet aggregation IC_{50},[a] μM	PAF-induced hypotension ID_{50},[b] mg/kg iv	PAF-induced mortality ID_{50},[c] mg/kg po	mp, °C	solvents[d]	formula[e]	anal.[f]
66		2.6 (1.9–3.4)	2.7 (0.82–8.7)	–	149–150	Cl	$C_{24}H_{25}N_3O$	C, H, N
67		0.52 (0.37–0.73)	0.48 (0.26–0.88)	35 (18–70)	119–120	Et_2O	$C_{25}H_{27}N_3O \cdot {}^3/_2H_2O$	C, H, N
68		23 (5.4–96)	>5	–	90–96	EA/Et_2O	$C_{24}H_{23}N_3O_2 \cdot HCl \cdot {}^3/_2H_2O$	C, H, N
69		1.9 (1.3–2.7)	–	–	110–113	EA/Et_2O	$C_{25}H_{25}N_3O_2 \cdot HCl \cdot H_2O$	C, H, N
70		1.9 (1.2–3.2)	–	>3	182–183	Et_2O	$C_{25}H_{25}N_3O_3 \cdot {}^1/_4H_2O$	C, H, N
71		11 (11–12)	>5	–	198–199	Cl	$C_{24}H_{25}N_3O_3S \cdot {}^5/_4H_2O$	C, H, N
72		200	>5	–	216–217	D/Et_2O	$C_{25}H_{26}N_4O_2$	C, H, N
73		0.87 (0.62–1.2)	2.4 (0.28–21)	–	105–109	EA/Et_2O	$C_{25}H_{27}N_3O \cdot 2HCl \cdot {}^1/_4H_2O$	C, H, N
74		44 (20–90)	>5	–	50–55	Cl/M	$C_{24}H_{25}N_3O_2 \cdot {}^7/_2H_2O$	C, N; H[g]
75		1.2 (0.23–6.0)	3.6 (0.40–33)	50–100	136–139	Et_2O	$C_{25}H_{27}N_3O \cdot {}^1/_4H_2O$	C, H, N
76		0.015 (0.011–0.020)	0.040 (0.002–0.74)	12 (9.3–16)	143–146	Et_2O	$C_{26}H_{26}N_4O \cdot {}^1/_2H_2O$	C, H, N
77		0.026 (0.018–0.037)	0.42 (0.22–0.74)	10–30	52–56	Et_2O	$C_{27}H_{25}N_3O \cdot {}^1/_4H_2O$	C, H, N
78		0.021 (0.017–0.026)	0.023 (0.017–0.037)	14 (5–39)	159–160	EA	$C_{26}H_{25}N_3O$	C, H, N
79		2.3 (2.0–2.7)	>5	–	60–64	Et_2O	$C_{26}H_{26}N_4O \cdot {}^1/_2H_2O$	C, H, N

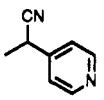
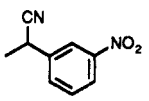
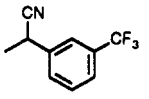
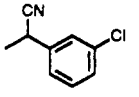
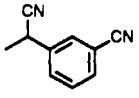
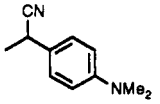
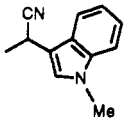
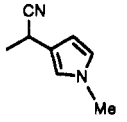
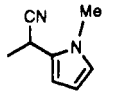
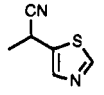
Table IV. (Continued)

compd	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 po	mp, °C	solvents[d]	formula[e]	anal.[f]
80		0.24 (0.059–0.99)	>5	>30	71–76	Et_2O	$C_{26}H_{28}N_4O \cdot {}^1/_2H_2O$	C, H, N

[a–f] See footnotes in Table I. [g] H calcd, 7.16; found, 6.48.

Table V. The "Aromatic Ring": Characterization and PAF-Antagonist Activity of Compounds **81–90**



compd	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 po	mp, °C	solvents[d]	formula[e]	anal.[f]
81		0.051 (0.039–0.066)	0.041 (0.028–0.061)	7.3 (4.5–12)	125–128	EA/Et_2O	$C_{26}H_{26}N_4O \cdot 2HCl$	C, H, N
82		11 (1.3–84)	>5	>30	185–186	A	$C_{27}H_{26}N_4O_3$	C, H; N[g]
83		9.0 (4.4–18)	>5	>30	179–180	A	$C_{28}H_{26}F_3N_3O$	C, H, N
84		21 (6.8–62)	>5	>30	162–163	A	$C_{27}H_{26}ClN_3O$	C, H, N
85		7.4 (6.8–8.1)	>5	>30	179–181	Et_2O	$C_{28}H_{26}N_4O$	C, H, N
86		210 (170–250)	–	–	178–180	A	$C_{29}H_{32}N_4O$	C, H, N
87		5.7 (5.6–5.7)	>5	–	141–143	EA/H	$C_{30}H_{30}N_4O \cdot {}^1/_2H_2O$	C, H, N
88		2.6 (1.2–4.6)	4.2 (2.9–6.0)	–	49–54	Et_2O	$C_{26}H_{28}N_4O$	C, H, N
89		25 (4.5–140)	–	–	175–176	EA/H	$C_{26}H_{28}N_4O$	C, H, N
90		0.021 (0.017–0.025)	0.75 (0.63–0.90)	25 (12–54)	144–147	EA/Et_2O	$C_{24}H_{24}N_4OS \cdot {}^1/_4H_2O$	C, H, N

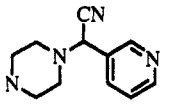
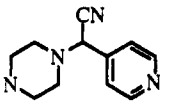
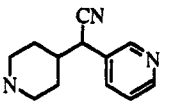
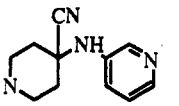
[a–f] See footnotes in Table I. [g] N calcd, 12.33; found, 12.94.

highest levels of activity are found in compounds bearing a 3,3-diphenylpropionyl and especially [*N*-(diphenylmethyl)amino]acetyl or 3-hydroxy-3,3-diphenylpropionyl as acyl substituents. The most interesting compounds to emerge from the work are **100, 106, 107, 114, and 115.** These compounds, that compare quite favorably with the reference compound **1** in the aggregation an hypotension tests, have been selected for further pharmacological development.

Experimental Section

A. Chemistry. Melting points were determined with a Mettler FP 80 central processor melting-point apparatus and are uncorrected. Melting points of organic salts varied, depending on the amount of water in the sample and should be regarded as approximate. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^1H NMR (80 MHz) and ^{13}C NMR (20.1 MHz) spectra were recorded on a Brücker AC80 spectrometer and are reported in ppm on the δ scale from the indicated reference. Combustion analyses were performed with a Carlo

Table VI. The Incorporation of an Amino or Hydroxy Group in the "Arylalkyl Chain": Characterization and PAF-Antagonist Activity of Compounds 91–116

A =  B =  C =  D = 

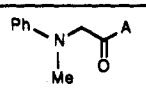
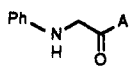
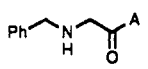
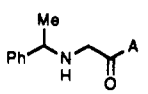
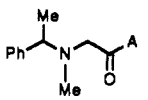
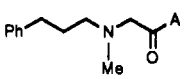
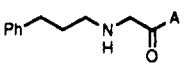
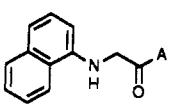
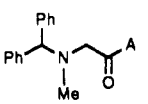
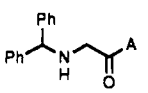
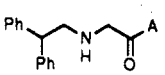
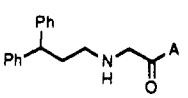
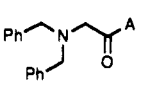
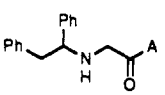
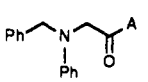
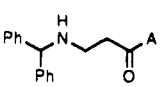
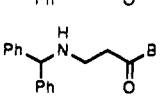
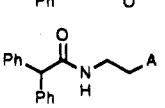
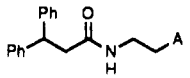
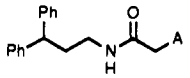
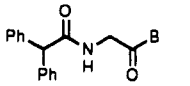
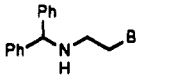
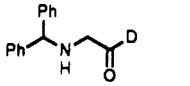
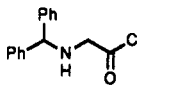
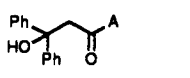
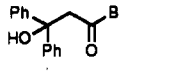
compd	R	PAF-induced platelet aggregation IC_{50},[a] μM	PAF-induced hypotension ID_{50},[b] mg/kg iv	PAF-induced mortality ID_{50},[c] mg/kg po	mp, °C	solvents[d]	formula[e]	anal./
91		2.8 (2.2–3.4)	2.2 (0.91–5.3)	–	136–138	D/Et_2O	$C_{20}H_{23}N_5O{\cdot}3HCl{\cdot}2H_2O$	C, H, N
92		0.13 (0.056–0.28)	0.49 (0.35–0.65)	28 (19–41)	138–141	EA	$C_{19}H_{21}N_5O$	C, H, N
93		0.24 (0.12–0.47)	0.80 (0.54–1.6)	50% inh at 50 mg/kg	139–142	D/Et_2O	$C_{20}H_{23}N_5O{\cdot}2HCl{\cdot}2H_2O$	C, H, N
94		0.036 (0.022–0.059)	0.39 (0.18–0.86)	18 (10–34)	108–112	D/Et_2O	$C_{21}H_{25}N_5O{\cdot}3HCl{\cdot}^3/_2H_2O$	C, H, N
95		0.24 (0.14–0.40)	0.77 (0.59–1.0)	>50	135–137	D/Et_2O	$C_{22}H_{27}N_5O{\cdot}3HCl{\cdot}2H_2O$	C, H, N
96		2.2 (1.2–4.0)	>5	–	125–130	D/Et_2O	$C_{23}H_{29}N_5O{\cdot}2HCl{\cdot}2H_2O$	C, H, N
97		0.53 (0.44–0.64)	1.3 (0.53–3.1)	30–50	67–68	EA/H	$C_{22}H_{27}N_5O$	C, H, N
98		2.6 (2.5–2.8)	2.5 (1.0–6.4)	–	138–143	D/Et_2O	$C_{23}H_{23}N_5O{\cdot}3HCl$	C, H, N
99		0.060 (0.055–0.065)	0.33 (0.21–0.52)	4.6 (2.5–8.3)	135–137	D/Et_2O	$C_{27}H_{29}N_5O{\cdot}3HCl{\cdot}H_2O$	C, H, N
100		0.0091 (0.0091–0.0092)	0.023 (0.019–0.026)	5.9 (4.4–7.9)	165–168	D/Et_2O	$C_{26}H_{27}N_5O{\cdot}3HCl{\cdot}2H_2O$	C, H, N
101		0.22 (0.16–0.30)	0.36 (0.08–2.1)	>10	188–192	D/Et_2O	$C_{27}H_{29}N_5O{\cdot}3HCl{\cdot}H_2O$	C, H, N
102		0.086 (0.056–0.13)	0.21 (0.18–0.25)	14 (9–22)	172–176	D/Et_2O	$C_{28}H_{31}N_5O{\cdot}3HCl{\cdot}^1/_2H_2O$	C, H, N
103		0.032 (0.023–0.045)	1.7 (1.1–2.6)	>10	128–132	D/Et_2O	$C_{27}H_{29}N_5O{\cdot}3HCl{\cdot}^3/_2H_2O$	C, H, N
104		0.050 (0.034–0.073)	0.38 (0.35–0.41)	>10	166–171	D/Et_2O	$C_{27}H_{29}N_5O{\cdot}3HCl{\cdot}2H_2O$	C, H, N
105		0.024 (0.019–0.030)	0.42 (0.32–0.56)	>30	195–196	D/Et_2O	$C_{26}H_{27}N_5O$	C, H, N
106		0.053 (0.038–0.074)	0.025 (0.011–0.053)	5.4 (2.4–12)	162–163	Cl	$C_{27}H_{29}N_5O{\cdot}H_2O$	C, H, N
107		0.055 (0.041–0.077)	0.037 (0.032–0.048)	3.2 (2.0–5.1)	146–148	D/Et_2O	$C_{27}H_{29}N_5O{\cdot}^1/_4H_2O{\cdot}^1/_3Et_2O$	C, H, N
108		0.036 (0.035–0.036)	0.29 (0.16–0.54)	30–50	59–63	Et_2O	$C_{27}H_{29}N_5O{\cdot}^1/_2H_2O$	C, H, N

Table VI. (Continued)

compd	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 po	mp, °C	solvents[d]	formula[e]	anal.[f]
109		5.5 (3.6–8.3)	2.2 (0.42–6.9)	–	129–132	D/Et_2O	$C_{28}H_{31}N_5O·3HCl$	C, H, N
110		0.24 (0.22–0.26)	3.0 (0.17–52)	>30	120–121	D/Et_2O	$C_{28}H_{31}N_5O·{}^3/_4H_2O$	C, H, N
111		0.68 (0.53–0.87)	0.47 (0.12–1.9)	>20	89–92	Et_2O	$C_{27}H_{27}N_5O_2$	C; H,[g] N[h]
112		0.036 (0.022–0.060)	59% inh at 5 mg/kg	29 (20–41)	180–184	D/Et_2O	$C_{26}H_{29}N_5·{}^5/_2HCl·H_2O$	C, H, N
113		0.20 (0.18–0.22)	0.096 (0.067–0.14)	10–15	73–75	Et_2O	$C_{26}H_{27}N_5O·{}^5/_4H_2O$	C, H, N
114		0.024 (0.015–0.039)	0.030 (0.019–0.047)	2.6 (0.72–9.3)	108–114	EA	$C_{27}H_{28}N_4O·{}^3/_4H_2O$	C, H, N
115		0.021 (0.015–0.029)	0.061 (0.045–0.082)	4.7 (2.7–8.0)	68–74	EA	$C_{26}H_{26}N_4O_2·{}^1/_2H_2O$	C, H, N
116		0.0027 (0.0019–0.0039)	0.061 (0.034–0.11)	7.7 (4.7–13)	78–83	EA	$C_{26}H_{26}N_4O_2·{}^3/_4H_2O$	C, H, N
1		0.091 (0.071–0.12)	0.17 (0.12–0.27)	0.97 (0.38–2.5)				

[a–f] See footnotes in Table I. [g] H calcd, 6.20; found, 5.64. [h] N calcd, 14.85; found, 13.69.

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). Analytical thin-layer chromatography (TLC) was performed using Macherey-Nagel 0.25-mm silica gel SIL G-25 plates. When necessary, solvents and reagents were dried prior to use. THF, Et_2O, and toluene were distilled from sodium metal/benzophenone ketyl. $CHCl_3$ was passed through an alumina column. CH_2Cl_2 and Et_3N were distilled from CaH_2. DMSO and DMF were distilled under reduced pressure from CaH_2 and stored over activated 4-Å molecular sieves. Unless otherwise specified, all nonaqueous reactions were conducted in a rigourously dried argon atmosphere, using oven-dried glassware.

C-18-PAF-acether was synthesized from (*S*)-batyl alcohol[22] following a published procedure.[23] Compound 1 was kindly provided by Boehringer Ingelheim.

1-(3,4,5-Trimethoxybenzoyl)piperazine (7a). 2 N HCl was added to a solution of piperazine (9.9 g, 0.114 mol) in water (90 mL) and THF (45 mL) until pH = 2 was attained. Then, 40% aqueous NaOAc and a solution of 3,4,5-trimethoxybenzoyl chloride (0.114 mol) in THF (45 mL) were added alternately so that the pH was kept within a range of 2–3.5. The resultant mixture was stirred at room temperature for 2 h. Then, it was saturated with K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 37.05 g of crude product. Purification by chromatography on silica gel, eluting with $CHCl_3$/MeOH/NH_3 (60:2:0.2), yielded 20 g of compound **30**[8] and 21.4 g (67%) of **7a** as an oil: IR (film) ν 3221, 2925, 2827, 1623, 1573, 1404, 1326, 1231 cm^{-1}, ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 6.62 (s, 2 H, Ar), 3.87 (s, 9 H, MeO), 3.59 (m, 4 H, pip), 2.88 (m, 4 H, pip), 1.79 (s, 1 H, NH).

1-(Diphenylacetyl)piperazine (7b). Method A. To a cooled (0 °C) mixture of *N*-formylpiperazine (9 mL, 90 mmol), diphenylacetic acid (18.6 g, 90 mmol), and HOBT (13.5 g, 0.1 mol) in DMF (200 mL), was added DCC (21 g, 0.1 mol). The mixture was stirred at room temperature overnight and diluted with EtOAc (700 mL). The insoluble solid was filtered off and the filtrate washed with saturated $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oil (**6b**, 25.05 g). To a solution of that crude in MeOH (170 mL) was added 10% HCl (300 mL), and the mixture was heated at 100 °C for 1 h. The organic solvent was removed, and the aqueous solution was extracted with $CHCl_3$, basified with 5 N NaOH solution and extracted again with $CHCl_3$. This second organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to an oil. Purification by chromatography on silica gel, eluting with $CHCl_3$/MeOH/NH_3 (60:2:0.2), gave 16.25 g (71%) of a white solid: IR (film) ν 3340, 3021, 2998, 2913, 1632, 1428, 1223, 1031 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 7.24 (m, 10 H, Ph), 5.18 (s, 1 H, $CHPh_2$), 3.50 (m, 4 H, pip), 2.63 (m, 5 H, pip, NH).

1-(3,3-Diphenylpropionyl)piperazine (7c) was prepared as described above (49%): IR (KBr) ν 3333, 3017, 2952, 1612, 1447, 1434, 1359, 1316 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 7.23 (m, 10 H, Ph), 4.66 (t, J = 7.5 Hz, 1 H, $CHPh_2$), 3.49 (m, 2 H, pip), 3.28 (m, 2 H, pip), 3.03 (d, J = 7.5 Hz, 2 H, CH_2CHPh_2), 2.60 (m, 4 H, pip), 1.59 (s, 1 H, NH).

In a similar manner, compounds **31** and **32** (Table I) and **68** and **69** (Table IV) were prepared by reaction of 3-(3,4,5-trimethoxyphenyl)propionic acid, nicotinic, and isonicotinic acid with the appropriate piperazine **7a–c**.

1-(3,4,5-Trimethoxybenzoyl)-4-thionicotinoylpiperazine (33). A mixture of **7a** (1.5 g, 5.4 mmol), pyridine-3-carboxaldehyde (0.5 mL, 5.4 mmol), and sulfur (0.204 g, 5.4 mmol) in DMF (3 mL) was heated at 100 °C for 3 h. The resulting mixture was poured into water and extracted with EtOAc. The

(22) Golding, B.; Ioannou, P. Rapid Synthesis of 3-*O*-Benzyl-*sn*-glycerol and 2-*O*-Benzylglycerol. *Synthesis* **1977**, 423–424.

(23) Wissner, A.; Kohler, C. A.; Golstein, B. M. Analogues of Platelet Activating Factor 5. Multiple Oxygen Substitution of the Alkoxy Chain. *J. Med. Chem.* **1986**, *29*, 1315–1319.

(24) Ohta, S.; Nozaki, A.; Ohashi, N.; Nishimura, Y.; Yoneda, Y.; Okamoto, Masao. An Efficient Biogenetic-Type Transformation of 3-Tertiaryhydroxyalkanoic Acids to Olefinic Compounds. *Chem. Pharm. Bull.* **1986**, *34*, 5144–5148.

organic phase was washed with water, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to an oil residue (2.2 g), which was purified by chromatography ($CHCl_3$/MeOH/NH_3 60:2:0.2) to afford 1.18 g (55%) of a yellow solid: mp 138–139 °C; IR (KBr) ν 2931, 2857, 1666, 1632, 1580, 1485, 1462, 1421, cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 8.55 (m, 2 H, pyr), 7.61 (d t, J = 7.6 Hz, J = 1.8 Hz, 1 H, pyr), 7.31 (dd, 1 H, J = 7.9 Hz, J = 4.8 Hz, pyr), 6.66 (s, 2 H, Ar), 3.85 (s, 9 H, MeO), 3.70 (m, 8 H, pip). The product (0.3 g) was dissolved in EtOAc and converted to its hydrochloride by treatment with $HCl_{(g)}$/Et_2O solution to give a yellow solid (0.2 g, 63%): mp 231–232 °C. Anal. ($C_{20}H_{23}N_3SO_4 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

1-(3,4,5-Trimethoxybenzoyl)-4-(3-pyridylmethyl)piperazine (34) and 1-(3,4,5-Trimethoxybenzoyl)-4-(3-pyridylcyanomethyl)piperazine (36). To a solution of **7a** (1.5 g, 5.3 mmol) in MeOH (10 mL) and a few drops of 2 N $HCl_{(g)}$/MeOH solution to adjust pH at 6–8 was added pyridine-3-carboxaldehyde (0.5 mL, 5.33 mmol) and $NaBH_3CN$ (0.33 g, 5.3 mmol). The resulting solution was stirred at 25 °C for 24 h. Then, additional $NaBH_3CN$ (0.1 g, 1.6 mmol) was added and stirring continued for 48 h. The reaction mixture was then treated with 0.1 N NaOH solution and the resulting suspension extracted with EtOAc. The organic phase was dried over Na_2SO_4 and fully evaporated. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to yield 0.75 g (38%) of **34** and 0.66 g (31%) of **36** as colorless oils. **34**: IR (film) ν 2933, 2825, 1625, 1579, 1455, 1421, 1325 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 8.51 (m, 2 H, pyr), 7.63 (broad d, J = 8.0 Hz, 1 H, pyr), 7.27 (dd, J = 8.0 Hz, J = 4.8 Hz, 1 H, pyr), 6.62 (s, 2 H, Ar), 3.85 (s, 9 H, CH_3O), 3.62 (m, 4 H, pip), 3.55 (s, 2 H), 2.48 (m, 4 H, pip); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ppm (TMS) 169.77 (C, CO), 153.09 (C, pyr), 150.15 (CH, pyr), 148.59 (CH, pyr), 139.5 (C), 136.32 (CH, pyr), 132.87 (C), 130.85 (C), 123.11 (CH, pyr), 104.41 (CH, Ar), 60.58 (CH_3, OCH_3), 59.76 (CH_2), 56.07 (2 CH_3, OCH_3), 52.77 (CH_2, pip), 45.00 (CH_2, pip). The product was dissolved in EtOAc and converted to its hydrochloride by treatment with $HCl_{(g)}$/Et_2O solution to give a white solid: mp 153–158 °C. Anal. ($C_{20}H_{25}N_3O_4 \cdot 2HCl \cdot 2H_2O$) C, H, N.

36: IR (film) ν 2935, 2827, 1624, 1580, 1458, 1421, 1327 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 8.79 (broad s, 1 H, pyr), 8.65 (broad d, J = 3.6 Hz, 1 H, pyr), 7.88 (broad d, J = 8.0 Hz, 1 H, pyr), 7.37 (dd, J = 8.2 Hz, J = 4.8 Hz, 1 H, pyr), 6.61 (s, 2 H, Ar), 4.97 (s, 1 H, CHCN), 3.85 (s, 9 H, CH_3O), 3.67 (m, 4 H, pip), 2.62 (m, 4 H, pip); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 169.86 (C, CO), 153.17 (C, pyr), 150.29 (CH, pyr), 149.11 (CH, pyr), 139.5 (C), 135.20 (CH, pyr), 130.40 (C), 128.22 (C), 123.33 (CH, pyr), 113.72 (CH, CN), 104.38 (CH, Ar), 60.57 (CH_3, OCH_3), 59.68 (CH, CHCN), 56.10 (CH_3, OCH_3), 49.43 (CH_2, pip), 48.00 (CH_2, pip). The hydrochloride was prepared as above to give a white solid: mp 86–87 °C. Anal. ($C_{21}H_{24}N_4O_4 \cdot 2HCl \cdot H_2O$) C, H, N.

The procedure was repeated with pyridine-2-carboxaldehyde to give **35** (Table I).

1-(Diphenylthioacetyl)-4-(3-pyridylcyanomethyl)piperazine (61). To a solution of **53** (0.238 g, 0.6 mmol) in toluene (10 mL) was added Lawesson reagent (0.24 g, 0.6 mmol). The resulting mixture was heated at reflux for 18 h. Then, the solvents were removed and the residue was purified by chromatography on silica gel (hexane/EtOAc 1:1) to yield 0.18 g (73%) of **61** as a white solid: mp 212–215 °C; IR (KBr) ν 2916, 2818, 1594, 1575, 1474, 1455, 1429, 1412, 1280, 1231 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.66 (m, 2 H, pyr), 7.80 (broad d, J = 7.9 Hz, 1 H, pyr), 7.23 (m, 11 H, pyr, Ar), 5.56 (s, 1 H, CHCN), 4.84 (s, 1 H, $CHPh_2$), 4.49 (m, 2 H, pip), 3.75 (t, J = 4.7 Hz, 2 H, pip), 2.69 (t, J = 4.7 Hz, 2 H, pip). Anal. ($C_{25}H_{24}N_4S \cdot {}^1/_2H_2O$) C, H, N.

1-(Diphenylacetyl)-4-(3-pyridylmethyl)piperazine (66). To a solution of **7b** (1.6 g, 10 mmol) and 3-(chloromethyl)pyridine hydrochloride (3 g, 10 mmol) in anhydrous $CHCl_3$ (50 mL) was added Et_3N (4 mL). The mixture was stirred for 48 h at room temperature. Then, it was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue (4.2 g) was purified by chromatography on silica gel ($CHCl_3$/MeOH 3%) to give 2 g (54%) of **66** as a white solid: mp 149–150 °C; IR (KBr) ν 3019, 2798, 2761, 1631, 1419, 1295, 1230 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 8.49 (m, 2 H, pyr), 7.60 (broad d, J = 7.8 Hz, 1 H, pyr), 7.24 (m, 11 H, pyr, Ph), 5.18 (s, 1 H, $CHPh_2$), 3.70 (t, J = 4.8 Hz, 2 H, pip), 3.44 (m, 4 H, pip, CH_2·pyr), 2.41 (t, J = 4.9 Hz, 2 H, pip), 2.14 (t, J = 4.6 Hz, 2 H, pip). Anal. ($C_{24}H_{25}N_3O$) C, H, N.

The procedure was repeated with **7c** to give **67** (Table IV).

1-(Diphenylacetyl)-4-isonicotinoylpiperazine, *N*-Oxide (70). To a solution of **69** (0.4 g, 1 mmol) in $CHCl_3$ (2 mL) was added a solution of 50% MCPBA (0.320 g) in $CHCl_3$ (1 mL) dropwise. The resulting solution was stirred for 1 h at room temperature and then quenched with 0.5 N NaOH solution. The organic phase was separated and dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH 5%) to afford 0.27 g (77%) of **70** as a colorless oil that crystallized upon addition of Et_2O: mp 182–183 °C; IR (KBr) ν 3075, 1623, 1489, 1448, 1429, 1249 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.22 (d, J = 6.8 Hz, 2 H, pyr), 7.25 (m, 12 H, pyr, Ph), 4.67 (t, 1 H, J = 7.5 Hz, $CHPh_2$), 3.35 (m, 8 H, pip), 3.08 (d, J = 7.6 Hz, 2 H, CH_2CHPh_2). Anal. ($C_{25}H_{25}N_3O_3 \cdot {}^1/_4H_2O$) C, H, N.

1-(3,3-Diphenylpropionyl)-4-(3-pyridylsulfonyl)piperazine (71). A solution of pyridine-3-sulfonyl chloride hydrochloride[12] (0.3 g, 1.7 mmol) in $CHCl_3$ (15 mL) and Et_3N (0.7 mL) was stirred 5 min, and to that solution was added **7c** (0.5 g, 1.7 mmol) and the stirring continued for 18 h. Then the reaction mixture was quenched with water (20 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated to a brown solid (0.7 g). Purification by chromatography ($CHCl_3$/MeOH, 3%) afforded 0.38 g (49%) of **71** as a white solid: mp 198–199 °C; IR (KBr) ν: 3020, 2832, 1612, 1487, 1464, 1419, 1352, 1324, 1175 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 8.89 (m, 2 H, pyr), 7.97 (d, of t, J = 8.0 Hz, J = 1.8 Hz, 1 H, pyr), 7.51 (dd, J = 4.7 Hz, J = 7.8 Hz, 1 H, pyr), 7.13 (m, 10 H, Ph), 4.54 (t, J = 7.7 Hz, 1 H, $CHPh_2$), 3.58 (m, 2 H, pip), 3.40 (m, 2 H, pip), 2.97 (d, J = 7.6 Hz, 2 H, CH_2CHPh_2), 2.90 (m, 2 H, pip), 2.51 (m, 2 H, pip). Anal. ($C_{24}H_{25}N_3O_3S \cdot {}^5/_4H_2O$) C, H, N.

1-(Diphenylacetyl)-4-[1-(aminocarbonyl)-1-(3-pyridyl)-methyl]piperazine (72). Through a cooled (0 °C) suspension of **53** (0.5 g, 1.2 mmol) in MeOH (10 mL) was bubbled $HCl_{(g)}$ until the solution was saturated. The resulting solution was stirred at room temperature for 18 h. Solvents were removed, and the residue was treated with 5% aqueous solution of $NaHCO_3$ (15 mL). The white solid formed was separated and purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to give 0.5 g (96%) of **72**. Crystallization from CH_2Cl_2/Et_2O provided an analytical sample: mp 216–217 °C; IR (KBr) ν 3307, 3055, 2999, 1680, 1632, 1423, 1225 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.49 (m, 2 H, pyr), 7.60 (d of t, J = 7.6 Hz, J = 1.8 Hz, 1 H, pyr), 7.25 (m, 11 H, pyr, Ph), 6.90 (m, 1 H, NH), 6.24 (m, 1 H, NH), 5.12 (s, 1 H, $CHPh_2$), 3.83 (s, 1 H, CHCO), 3.65 (m, 2 H, pip), 3.41 (m, 2 H, pip), 2.37 (m, 2 H, pip), 2.16 (m, 2 H, pip); ^{13}C NMR (20.15 MHz, $CHCl_3$) δ (TMS) 172.51 (C), 179.23 (C), 150.02 (CH), 149.44 (CH), 139.03 (C), 136.34 (CH), 128.81 (CH), 128.41 (CH), 126.94 (CH), 72.37 (CH), 54.62 (CH), 50.69 (CH_2), 45.75 (CH_2), 42.07 (CH_2). Anal. ($C_{25}H_{26}N_4O_2$) C, N, H.

1-(Diphenylacetyl)-4-(3-pyridylmethyl)piperazine 4-Oxide (74). To a cooled (0 °C) solution of **66** (0.5 g, 1.3 mmol) in CH_2Cl_2 (10 mL) was added a solution of 50% MCPBA (0.460 g, 1.3 mmol) in CH_2Cl_2 (8 mL) dropwise. The resulting solution was stirred for 1 h at 0 °C and then quenched with 0.5 N NaOH solution. The organic phase was separated and dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH 30%) to afford 0.170 g (36%) of **74** as a white solid: mp 50–55 °C; IR (KBr) ν 3600–2950, 1636, 1593, 1425 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.59 (m, 2 H, pyr), 7.88 (broad d, J = 7.5 Hz, 1 H, pyr), 7.25 (m, 11 H, pyr, Ph), 5.19 (s, 1 H, $CHPh_2$), 4.7–3.6 (complex signal, 6 H), 3.05 (m, 2 H, pip), 2.67 (m, 2 H, pip); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 170.08 (C), 152.22 (CH), 150.54 (CH), 140.27 (CH), 138.52 (C), 128.59 (CH), 127.17 (CH), 126.96 (CH), 124.79 (C), 123.25 (CH), 72.17 (CH_2), 63.18 (CH_2), 62.73 (CH_2), 54.45 (CH), 40.23 (CH_2), 36.37 (CH_2). Anal. ($C_{24}H_{25}N_3O_2 \cdot {}^7/_2H_2O$) C, H, N.

1-(Diphenylacetyl)-4-[1-(3-pyridyl)ethyl]piperazine (75) was prepared as described above for **34**. Thus, reaction of **7b** (1 g, 3.57 mmol) with 3-acetylpyridine (0.4 mL, 3.57 mmol) and $NaBH_3CN$ (0.44 g, 7.14 mmol) yielded 0.22 g (16%) of **75** as a

white solid: mp 136–139 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ ppm (TMS) 8.49 (m, 2 H, pyr), 7.60 (d of t, J = 7.8 Hz, J = 1.8 Hz, 1 H, pyr), 7.23 (m, 11 H, pyr, Ph), 5.15 (s, 1 H, $CHPh_2$), 3.68 (t, J = 4.5 Hz, 2 H, pip), 3.42 (t, J = 4.5 Hz, 2 H, pip), 3.38 (q, J = 6.7 Hz, 1 H, $CHCH_3$), 2.42 (m, 2 H, pip), 2.18 (m, 2 H, pip), 1.31 (d, J = 6.7 Hz, 3 H, $CHCH_3$). Anal. ($C_{25}H_{27}N_3O\cdot{}^1/_4H_2O$) C, H, N.

1-(Diphenylacetyl)-4-[2-(3-pyridyl)-2-oxoethyl]piperidine (8). To a solution of **7b** (4.44 g, 15 mmol) in $CHCl_3$ (50 mL) was added dropwise a solution previously prepared by addition of Et_3N (2.36 mL) to a suspension of 3-(2-bromoacetyl)pyridine hydrobromide[13] (4.23 g, 1.5 mmol) in $CHCl_3$ (80 mL). The mixture was stirred at room temperature for 18 h. It was then washed with 1 N NaOH solution, dried, and evaporated to dryness. The residue (8.6 g) was purified by chromatography on silica gel ($CHCl_3$/MeOH, 3%) to yield 4.56 g (73%) of **8** as a colorless oil: IR (film) ν 2914, 1692, 1637, 1580, 1427, 1220 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.75 (s, 1 H, pyr), 9.30 (d, J = 4.5 Hz, 1 H, pyr), 8.78 (d, J = 7.5 Hz, 1 H, pyr), 7.79 (m, 11 H, pyr, Ar), 5.74 (s, 1 H, $CHPh_2$), 4.24 (m, 4 H, CH_2CO, pip), 4.04 (m, 2 H, pip), 3.10 (m, 2 H, pip), 2.83 (m, 2 H, pip).

1-(Diphenylacetyl)-4-[2-(3-pyridyl)-2-hydroxyethyl]piperazine (9). To a solution of ketone **8** (4.56 g, 11 mmol) in MeOH (20 mL), cooled to 0 °C, was added $NaBH_4$ (0.64 g, 16.5 mmol), and the resulting mixture was stirred at 0 °C for 30 min. Then 0.1 N HCl solution (10 mL) was added. The mixture was concentrated in vacuo and partitioned between water and $CHCl_3$. The organic phase was separated and dried. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH, 5%) to yield 2.7 g (62%) of a white solid: mp 134–135 °C; IR (KBr) ν 3389, 2811, 1638, 1448, 1220 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.20 (m, 2 H, pyr), 8.52 (broad d, J = 7.6 Hz, 1 H, pyr), 7.99 (m, 11 H, pyr, Ar), 5.93 (s, 1 H, $CHPh_2$), 5.47 (t, J = 6.4 Hz, 1 H, CHOH), 4.47 (m, 2 H, pip), 4.23 (m, 2 H, pip), 3.19 (d, J = 6.5 Hz, 2 H, CH_2CHOH), 3.15 (m, 4 H, pip). Anal. ($C_{25}H_{27}N_3O_2$) C, H, N.

1-(Diphenylacetyl)-4-[2-(3-pyridyl)-2-cyanoethyl]piperazine (79). To a cooled (0 °C) solution of alcohol **9** (1.6 g, 4 mmol) in $CHCl_3$ (8 mL) was added $SOCl_2$ (0.32 mL) in $CHCl_3$ (4 mL). The mixture was stirred 1 h at room temperature and 1 h at reflux. The solvents were evaporated, and the residue was diluted with 20 mL of $CHCl_3$. Then Et_3N (1.7 mL) was added, and the solution was washed with water. The organic phase was separated and dried over anhydrous Na_2SO_4, and the solvent was removed to afford crude chloride **10**, which was dissolved in DMSO (10 mL). To this solution was added KCN (0.58 g, 9 mmol). The mixture was heated at 90 °C for 6 h, the solvents were evaporated in vacuo, and the residue was partitioned between $CHCl_3$ and 0.1 N NaOH solution. The organic phase was dried and evaporated to dryness. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH, 5%) to yield 0.15 g (10%) of **79** as an oil that crystallized upon addition of Et_2O: mp 60–64 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ (TMS) 9.18 (m, 1 H, pyr), 8.81 (m, 2 H, pyr), 7.94 (dd, J = 8.0 Hz, J = 5.5 Hz, 1 H, pyr), 7.22 (m, 10 H, Ph), 5.20 (m, 1 H, $CHPh_2$), 4.71 (t, J = 6.9 Hz, 1 H, CHCN), 3.85 (m, 2 H, pip), 3.67 (m, 2 H, pip), 3.45 (d, J = 7.0 Hz, 2 H, CH_2CHCN), 2.82 (m, 2 H, pip), 2.56 (m, 2 H, pip); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 170.03 (C), 161.00 (CH), 149.87 (CH), 149.37 (CH), 139.05 (C), 139.02 (C), 135.20 (CH), 133.05 (C), 129.02 (CH), 128.70 (CH), 128.56 (CH), 127.23 (CH), 127.06 (CH), 123.65 (CH), 117.05 (C), 62.79 (CH), 54.69 (CH), 49.76 (CH_2), 45.91 (CH_2), 42.09 (CH_2), 21.68 (CH_2). Anal. ($C_{26}H_{26}N_4O\cdot{}^1/_2H_2O$) C, H, N.

1-(Diphenylacetyl)-4-[1-(3-pyridyl)-1-cyanoethyl]piperazine (80). A mixture of amine **7b** (1.4 g, 5 mmol), 3-acetylpyridine (0.5 mL, 5 mmol), and p-TsOH (0.15 g) in toluene (75 mL) was heated in a Dean–Stark for 48 h. The solvent was removed, and the residue was partitioned between $CHCl_3$ and 0.1 N NaOH solution. The organic phase was separated and dried over Na_2SO_4, and the solvent was removed to yield 2.5 g of crude product. To a solution of this crude product in glacial HOAc (7 mL) was added KCN (0.5 g, 7.6 mmol). The mixture was stirred at room temperature for 12 h. The solvent was removed in vacuo and the residue worked up with $CHCl_3$ and 1 N NaOH solution. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated to dryness. Purification by chromatography of the residue (1.5 g) on silica gel (hexane/EtOAc, 80%) yielded 0.33 g (16%) of a colorless oil that solidified upon addition of Et_2O: mp 71–76 °C; IR (KBr) ν 3055, 3022, 2242, 1642, 1595, 1428, 1414 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.83 (m, 1 H, pyr), 8.60 (m, 1 H, pyr), 7.88 (broad d, J = 8.2 Hz, 1 H, pyr), 7.26 (m, 11 H, pyr, Ar), 5.19 (s, 1 H, $CHPh_2$), 3.70 (m, 2 H, pip), 3.47 (m, 2 H, pip), 2.48 (m, 4 H, pip), 1.72 (s, 3 H, $CHCH_3$). Anal. ($C_{26}H_{26}N_4O\cdot{}^1/_2H_2O$) C, H, N.

1-Piperazinyl-3-pyridylacetonitrile (11). To a solution of piperazine (13.95 g, 0.162 mol) and KCN (5.4 g, 0.083 mol) in water (60 mL) and 1 M, pH = 7.1 phosphate buffer solution (60 mL) was added a solution of pyridine-3-carboxaldehyde (5.1 mL, 0.054 mol) in MeOH (60 mL) dropwise. The solution was stirred 18 h at room temperature, water (80 mL) was added, and the solution was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue (17.4 g) was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to yield 8.5 g (81%) of a colorless oil: IR (film) ν 3301, 2943, 2911, 2225, 1588, 1573, 1474, 1449, 1440, 1419, 1123 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.77 (d, J = 2.3 Hz, 1 H, pyr), 8.59 (dd, J = 4.8 Hz, J = 1.4 Hz, 1 H, pyr) 7.87 (broad d, J = 6.3 Hz, 1 H, pyr), 7.36 (dd, J = 6.3 Hz, J = 4.1 Hz, 1 H, pyr), 4.91 (s, 1 H, CHCN), 2.90 (m, 4 H, pip), 2.55 (m, 4 H, pip), 1.82 (s, 1 H, NH); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 149.41 (CH), 148.82 (CH), 134.83 (CH), 128.38 (C), 122.76 (CH), 113.83 (C), 59.81 (CH), 50.29 (CH_2), 45.01 (CH_2).

1-Piperazinyl-4-pyridylacetonitrile (12) was prepared as described above for **11**, starting from pyridine-4-carboxaldehyde. After purification by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) a yellow oil was obtained (82% yield): IR (film) ν 3296, 2943, 2822, 1594, 1410, 1322 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.68 (d, J = 6.2 Hz, 2 H, pyr), 7.50 (d, J = 6.2 Hz, 2 H, pyr), 4.81 (s, 1 H, CHCN), 2.96 (t, J = 4.8 Hz, 4 H, pip), 2.55 (t, J = 4.8 Hz, 4 H, pip), 1.78 (s, 1 H, NH).

1-(2-Aminoethyl)-4-(3-pyridylcyanomethyl)piperazine (14) was prepared as described above for **11**, starting from 1-(2-aminoethyl)piperazine (24% yield): IR (film) ν 3361, 2941, 2880, 1527, 1573, 1451, 1420 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.76 (d, J = 2.4 Hz, 1 H, pyr), 8.62 (dd, J = 1.6 Hz, J = 4.8 Hz, 1 H, pyr), 7.87 (d of t, J = 1.6 Hz, J = 8.0 Hz, 1 H, pyr), 7.38 (dd, J = 5.0 Hz, J = 7.6 Hz, 1 H, pyr), 4.96 (s, 1 H, CHCN), 2.57 (m, 12 H, $NH_2CH_2CH_2$, pip), 1.75 (m, 2 H, NH_2).

1-(3,3-Diphenylpropionyl)-4-(3-pyridylcyanomethyl)piperazine (55). Method B. To a cooled (0 °C) solution of **11** (1 g, 4.9 mmol) and Et_3N (1.2 mL) in $CHCl_3$ (20 mL) was added a solution of 3,3-diphenylpropionyl chloride (1.37 g, 5.6 mmol) in $CHCl_3$ (5 mL) dropwise. The mixture was stirred 18 h at room temperature. The organic solution was washed with water, dried (Na_2SO_4), and evaporated. The residue (2.4 g) was purified by chromatography on silica gel (EtOAc) to yield 1.28 g (53%) of an oil that crystallized upon addition of Et_2O: mp 160–161 °C; IR (KBr) ν 3049, 3025, 2933, 1612, 1476, 1454, 1421, 1323, 1258 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.67 (m, 2 H, pyr), 7.82 (broad d, J = 7.9 Hz, 1 H, pyr), 7.23 (m, 11 H, pyr, Ar), 4.82 (s, 1 H, CHCN), 4.64 (t, J = 7.6 Hz, 1 H, $CHPh_2$), 3.55 (m, 2 H, pip), 3.35 (m, 2 H, pip), 3.04 (d J = 7.5 Hz, 2 H, CH_2CO), 2.32 (m, 4 H, pip). Anal. ($C_{26}H_{26}N_4O$) C, H, N.

The procedure was repeated with appropriate acid chlorides to yield compounds **39–41** and **43–48** (Table II). Compound **65** (Table IV) was also obtained by the same methodology from alcohol **13**.

1-(3,3-Diphenyl-3-hydroxypropionyl)-4-(3-pyridylcyanomethyl)piperazine (115). Method A. To a cooled (0 °C) mixture of 3,3-diphenyl-3-hydroxypropionic acid[24] (1.7 g, 7 mmol), compound **11** (1.2 g, 6 mmol), and HOBT (0.8 g, 6 mmol) in DMF (15 mL) was added DCC (1.22 g, 6 mmol). The mixture was stirred 18 h at room temperature. The solvents were then removed in vacuo, and the residue was stirred with EtOAc. The white solid formed was removed, and the organic solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and evaporated to dryness. The residue (2.8 g) was purified by chromatography (EtOAc) to yield 1.62 g (61%) of a white solid: mp 68–74 °C; IR (KBr) ν 3345, 3051, 2914, 1612, 1445, 1417, 1230 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.69 (m, 2 H, pyr), 7.85 (broad d, J = 8.5 Hz, 1 H, pyr), 7.31 (m, 11 H, pyr, Ar), 4.87 (s, 1 H, CHCN), 3.53 (m, 4 H, pyr), 3.20 (s, 2

H, CH_2CO), 2.45 (t, J = 5.0 Hz, 4 H, pyr). Anal. ($C_{26}H_{26}N_4O_2 \cdot {}^1/_2H_2O$) C, H, N.

1-[[*N*-(Diphenylmethyl)amino]acetyl]-4-(3-pyridylcyanomethyl)piperazine (100) was prepared as above starting from [*N*-(diphenylmethyl)amino]acetic acid.[15] After purification by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2), a colorless oil was obtained (73% yield): IR (film) ν 3315, 3052, 3019, 2911, 1643, 1419, 1235, 748, 706 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.75 (m, 1 H, pyr), 8.64 (broad d, J = 5 Hz, 1 H, pyr), 7.83 (d, J = 7.6 Hz, 1 H, pyr), 7.30 (m, 11 H), 4.88 (s, 1 H), 4.84 (s, 1 H), 3.65 (m, 2 H, pip), 3.36 (s, 2 H, CH_2CO), 3.30 (m, 2 H, pip), 2.48 (m, 5 H, pip, NH). The product was dissolved in CH_2Cl_2 and converted to its hydrochloride by treatment with $HCl_{(g)}$/Et_2O solution to give a white solid: mp 165–168 °C; IR (KBr) ν 3600–2400, 1649, 1543, 1449, 1427, 1245, 1000 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.87 (m, 3 H, pyr), 8.14 (dd, J = 7.6 Hz, J = 5 Hz, 1 H, pyr), 7.52 (s, 10 H), 5.64 (s, 1 H), 5.58 (s, 1 H), 4.10 (s, 2 H, CH_2CO), 3.59 (m, 2 H, pip), 3.38 (m, 2 H, pip), 2.60 (m, 4 H, pip). Anal. ($C_{26}H_{27}N_5O \cdot 3HCl \cdot 2H_2O$) C, H, N.

The procedure was repeated with appropriate carboxylic acids to yield compounds **37**, **38**, **42**, **49–54** and **56–60** (Table II), and **99**, **105**, and **106** (Table VI). In a similar manner, compounds **81** (Table V), **111**, and **116** (Table VI) were obtained from amine **12** and compounds **108** and **109** (Table VI) from amine **14**.

1-(2-Chloroacetyl)-4-(3-pyridylcyanomethyl)piperazine (15). To a cooled (0 °C) solution of **11** (2.5 g, 12.3 mmol) and Et_3N (1.25 mL, 12.3 mmol) in $CHCl_3$ (38 mL) was added chloroacetyl chloride (1.0 mL, 12.3 mmol) dropwise. The mixture was stirred 1 h at 0 °C. After dilution with $CHCl_3$, the organic phase was washed twice with water, dried (Na_2SO_4), and evaporated. The residue, 3.32 g (97%) of a colorless oil, was immediately used in the following reaction: ^1H NMR ($CDCl_3$) δ (TMS) 8.79 (d, J = 2.3 Hz, 1 H, pyr), 8.67 (broad d, J = 4.1 Hz, 1 H, pyr), 7.87 (broad d, J = 6.3 Hz, 1 H, pyr), 7.39 (dd, J = 6.3 Hz, J = 4.1 Hz, 1 H, pyr), 4.97 (s, 1 H, CHCN), 4.08 (s, 2 H, CH_2Cl), 3.61 (m, 4 H, pip), 2.64 (m, 4 H, pip).

1-[[*N*-(2,2-Diphenylethyl)amino]acetyl]-4-(3-pyridylcyanomethyl)piperazine (101). Method C. To a cooled (0 °C) solution of chloride **15** (1 g, 3.6 mmol) and Et_3N (0.5 mL, 3.6 mmol) in $CHCl_3$ (50 mL) was added 2,2-diphenylethylamine (1.42 g, 7.2 mmol). The mixture was stirred 18 h at room temperature. It was then washed with water and the organic layer dried (Na_2SO_4) and evaporated to dryness. The residue (2.8 g) was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to yield 1.02 g (66%) of **101** as an oil: ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.77 (d, J = 2.5 Hz, 1 H, pyr), 8.64 (dd, J = 2.5 Hz, J = 5 Hz, 1 H, pyr), 7.83 (broad d, J = 7.6 Hz, 1 H, pyr), 7.30 (m, 11 H, pyr, Ph), 4.88 (s, 1 H, CHCN), 4.17 (t, J = 7 Hz, 2 H, CH_2NH), 3.41 (m, 7 H), 2.52 (m, 4 H, pip), 1.72 (s, 1 H, NH). The product was dissolved in CH_2Cl_2 and converted to its hydrochloride by treatment with $HCl_{(g)}$/Et_2O solution to give a white solid: mp 188–192 °C; IR (KBr) ν 3600–2400, 1649, 1487, 1448, 1248, 1000 cm^{-1}; ^1H NMR (80 MHz, D_2O) δ (TMS) 8.88 (m, 3 H, pyr), 8.17 (dd, J = 7.6 Hz, J = 5 Hz, 1 H pyr), 7.42 (m, 10 H, Ph), 5.60 (s, 1 H, CHCN), 4.50 (m, 2 H), 4.13 (s, 2 H, CH_2CO), 3.9–3.3 (m, 5 H), 2.67 (m, 4 H). Anal. ($C_{27}H_{29}N_5O \cdot 3HCl \cdot H_2O$) C, H, N.

The procedure was repeated with appropriate aralkylamines to yield compounds **91–98** and **102–104** (Table VI).

1-[3-[*N*-(Diphenylmethyl)amino]propionyl]-4-(4-pyridylcyanomethyl)piperazine (107). A. 3-[*N*-(diphenylmethyl)amino]propionic acid[15] (5.1 g, 20 mmol) was coupled with **12** (4.3 g, 21 mmol) using method A. There were obtained 0.18 g (15%) of **107** (see below) and 0.28 g (25%) of **117**. **117**: mp 121–122 °C; IR (KBr) ν 3478, 3311, 2999, 2855, 1632, 1593, 1487, 1427, 1283 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.70 (broad d, J = 6.4 Hz, 2 H, pyr), 7.35 (m, 12 H, pyr, Ar), 4.84 (s, 1 H, CHNH), 3.52 (m, 8 H, pip) 2.83 (t, J = 5.6 Hz, 2 H, CH_2CO), 2.56 (t, J = 5.6 Hz, 2 H, CH_2N), 2.29 (s, 1 H, NH). Anal. ($C_{26}H_{28}N_4O_2 \cdot {}^1/_2H_2O$) C, H, N.

B. To a cooled (0 °C) solution of 3-[*N*-(diphenylmethyl)amino]propionic acid[15] (5.1 g, 20 mmol) and *N*-hydroxysuccinimide (2.3 g, 20 mmol) in 120 mL anhydrous DME was added DCC (4.1 g, 20 mmol). The mixture was stirred at 4 °C for 18 h. The precipitate was removed, and **12** (4.3 g, 21 mmol) in DME (60 mL) was added to the resulting solution. It was then stirred 2 h at room temperature and 0.5 h at 60 °C. The solvents were removed, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic solution was separated and dried (Na_2SO_4), and the solvents were removed. The residue (10 g) was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to give 3.67 g (46%) of **107** as a colorless oil. A portion was recrystallized from CH_2Cl_2/Et_2O to furnish a white solid: mp 146–148 °C; IR (KBr) ν 3313, 3020, 2908, 1636, 1592, 1447 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.69 (broad d, J = 6.4 Hz, 2 H, pyr), 7.35 (m, 12 H, pyr, Ar), 4.86 (s, 2 H, CHCN, CHNH), 3.51 (m, 4 H, pip) 2.88 (t, J = 5.6 Hz, 2 H, CH_2CO), 2.54 (m, 7 H, pip, NH, CH_2N). Anal. ($C_{27}H_{29}N_5O \cdot {}^1/_3Et_2O \cdot {}^1/_4H_2O$) C, H, N.

1-[[*N*-(Diphenylmethyl)amino]carbonyl]-4-(3-pyridylcyanomethyl)piperazine (62). To a solution of amine **11** (0.67 g, 3.3 mmol) in pyridine (30 mL) was added **16** (1 g, 3.3 mmol). The mixture was heated at reflux for 2 days. After cooling, it was poured into water (200 mL), extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to give 0.28 g (21% yield) of a solid. Recrystallization from acetonitrile afforded 0.15 g of white crystals: mp 204–205 °C; IR (KBr) ν 3311, 2996, 2948, 2928, 2227, 1612, 1524, 1492, 1411, 1293, 1236, 1135 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.70 (m, 2 H, pyr), 7.87 (broad d, J = 7.6 Hz, 1 H, pyr), 7.27 (m, 11 H), 6.56 (d, J = 7.6 Hz, 1 H, NH), 6.13 (d, J = 7.6 Hz, 1 H, $CHPh_2$), 5.07 (s, 1 H, CHCN), 3.51 (m, 4 H, pip), 2.58 (m, 4 H, pip). Anal. ($C_{25}H_{25}N_5O \cdot {}^1/_2H_2O$) C, H, N.

1-[(2,2-Diphenylethoxy)carbonyl]-4-(3-pyridylcyanomethyl)piperazine (63). A mixture of amine **11** (1.27, 6.2 mmol), **17** (2 g, 6.2 mmol), and K_2CO_3 (0.7 g) in DMF (15 mL) was heated at 80 °C for 12 h. The solvent was removed, and the resulting mixture was partitioned between $CHCl_3$ and 1 N NaOH solution. The organic phase was separated and dried (Na_2SO_4) and the solvent was removed. The residue (1.85 g) was purified by chromatography on silica gel (hexane/EtOAc, 1:1) to give 0.24 g (10%) of a colorless oil: IR (film) ν 3022, 2948, 1692, 1488, 1422, 1242 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.75 (m, 2 H, pyr), 7.82 (d, J = 7.5 Hz, 1 H, pyr), 7.25 (m, 11 H, pyr, Ar), 4.84 (s, 1 H, CHCN), 4.55 (complex signal, 3 H, $CHCH_2O$), 3.35 (m, 4 H, pip), 2.41 (m, 4 H, pip). The product was dissolved in EtOAc and converted to its hydrochloride by treatment with $HCl_{(g)}$/Et_2O solution to give a white solid (75% yield): mp 97–98 °C. Anal. ($C_{26}H_{26}N_4O_2 \cdot 2HCl \cdot {}^3/_4H_2O$) C, H, N.

1-(3,3-Diphenylpropyl)-4-(3-pyridylcyanomethyl)piperazine (64). Under the conditions used for the preparation of **11**, **19** was condensed with pyridine-3-carboxaldehyde to give **64** as a colorless oil (51%): IR (film) ν 3021, 2939, 1586, 1488, 1447, 1419 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.74 (d, J = 2.1 Hz, 1 H, pyr), 8.59 (dd, J = 4.8 Hz, J = 1.4 Hz, 1 H, pyr), 7.84 (broad d, J = 7.9 Hz, 1 H, pyr), 7.23 (m, 11 H, pyr, Ar), 4.84 (s, 1 H, CHCN), 4.00 (m, 1 H, Ph_2CH), 2.40 (complex signal, 12 H). The product was dissolved in EtOAc and converted to its hydrochloride by treatment with $HCl_{(g)}$/Et_2O solution to give a white solid (78%): mp 115–122 °C. Anal. ($C_{26}H_{28}N_4 \cdot 3HCl \cdot {}^1/_2H_2O$) C, H, N.

1-[[[*N*-(3,3-Diphenylpropyl)amino]carbonyl]methyl]-4-(3-pyridylcyanomethyl)piperazine (110). Under the conditions used for the preparation of **66**, compound **11** was treated with [*N*-(3,3-diphenylpropyl)carbonyl]methyl chloride **20** to give **110** (80%). Recrystallization from CH_2Cl_2/Et_2O gave a white solid: mp 120–121 °C; IR (KBr) ν 3357, 3020, 2937, 2821, 1659, 1518, 1488, 1448, 1429, 1294 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.78 (d, J = 2 Hz, 1 H, pyr), 8.63 (dd, J = 4.7 Hz, J = 1.3 Hz, 1 H, pyr), 7.82 (d, of t, J = 1.9 Hz, J = 7.8 Hz, 1 H, pyr), 7.27 (m, 11 H, Ar, pyr), 4.91 (s, 1 H, CHCN), 3.96 (t, J = 7.7 Hz, 1 H, Ph_2CH), 3.27 (q, J = 6.6 Hz, 2 H, CH_2NHCO), 2.93 (s, 2 H, $COCH_2N$), 2.57 (m, 8 H, pip), 2.33 (q, J = 7.7 Hz, 2 H, Ph_2CHCH_2). Anal. ($C_{28}H_{31}N_5O \cdot {}^3/_4H_2O$) C, H, N.

1-[2-[*N*-(Diphenylmethyl)amino]ethyl]-4-(4-pyridylcyanomethyl)piperazine (112). To a solution of **21** (2.0 g, 8.1 mmol) and Et_3N (2.25 mL) in $CHCl_3$ (15 mL) was added amine **12** (1.3 g, 6.4 mmol). The mixture was heated at reflux for 2 days. The resulting solution was then washed with water, the organic phase was separated and dried (Na_2SO_4), and the solvent was removed. The residue (2.58 g) was purified by chromatography on silica

gel (EtOAc/MeOH, 3%) to afford 0.380 g (15%) of a colorless oil: ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.65 (m, 2 H, pyr), 7.34 (m, 12 H, pyr, Ar), 4.84 (m, 1 H, CHCN), 4.81 (m, 1 H, $CHPh_2$), 2.54 (m, 13 H, $NHCH_2CH_2$, pip, NH). The product was dissolved in CH_2Cl_2 and converted to its hydrochloride by treatment with $HCl_{(g)}/Et_2O$ solution to give a white solid: mp 180–184 °C. Anal. ($C_{26}H_{29}N_5 \cdot {}^5/_2HCl \cdot H_2O$) C, H, N.

[1-(Ethoxycarbonyl)-4-piperidinylidene]-3-pyridylacetonitrile (22). To a solution of NaOEt (0.49 g) in EtOH (30 mL) was added 3-pyridylacetonitrile (0.75 mL, 7 mmol) and 1-(ethoxycarbonyl)-4-piperidone (1.21 g, 7 mmol), and the resulting mixture was heated at reflux for 1 h. It was allowed to cool and worked up with $CHCl_3$ and water. The organic phase was separated and dried (Na_2SO_4), and the solvent was removed. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH 5%) to afford 1.03 g (55%) of a colorless oil: ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.55 (m, 2 H, pyr), 7.68 (broad d, J = 7.0 Hz, 1 H, pyr), 7.45 (m, 1 H, pyr), 4.16 (q, J = 7.1 Hz, 2 H), 3.69 (t, J = 5.7 Hz, 2 H, pip), 3.51 (t, J = 5.6 Hz, 2 H, pip), 2.81 (t, J = 6.0 Hz, 2 H, pip), 2.44 (t, J = 6.0 Hz, 2 H, pip), 1.27 (t, J = 7.0 Hz, 3 H).

(4-Piperidinylidene)-3-pyridylacetonitrile (23). To a solution of **22** (1.36 g, 5 mmol) and sodium iodide (2.28 g) in acetonitrile (10 mL) was added trimethylsilyl chloride (0.97 mL). The resulting mixture was heated at 50 °C for 2 days. It was allowed to cool, diluted with $CHCl_3$, and washed with 0.1 N NaOH solution and 10% sodium thiosulfate solution. The organic phase was dried (Na_2SO_4), and the solvents were removed. The residue (0.95 g) was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_3 60:2:0.2) to give 0.28 g (28%) of a colorless oil: IR (film) ν 3309, 2949, 2208, 1612, 1582, 1410 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.57 (m, 2 H, pyr), 7.68 (d of t, J = 8.0 Hz, J = 1.8 Hz, 1 H, pyr), 7.42 (dd, J = 7.3 Hz, J = 2.5 Hz, 1 H, pyr), 2.95 (m, 6 H, pip), 2.38 (t, J = 5.8 Hz, 2 H, pip), 2.17 (broad s, 1 H, NH).

[1-(3,3-Diphenylpropionyl)-4-piperidinylidene]-3-pyridylacetonitrile (77). Amine **23** was coupled with 3,3-diphenylpropionic acid using method A to give **77** (75%) as a white solid: mp 52–56 °C; IR (KBr) ν 3021, 2209, 1632, 1580, 1488, 1446, 1268 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.55 (m, 2 H, pyr), 7.58 (d of t, J = 8.0 Hz, J = 1.7 hz, 1 H, pyr), 7.24 (m, 11 H, pyr, Ar), 4.67 (t, J = 7.7 Hz, 1 H, $CHPh_2$), 3.58 (m, 4 H, pip), 3.10 (m, 2 H, CH_2CON), 2.40 (m, 4 H, pip). Anal. ($C_{27}H_{25}N_3O \cdot {}^1/_4H_2O$) C, H, N.

1-(Ethoxycarbonyl)-4-(3-pyridylcyanomethyl)piperidine (25). To a cooled (0 °C) suspension of NaH (1 g, 21 mmol) in DMF (10 mL) was added 3-pyridylacetonitrile (1.9 mL, 18 mmol) in DMF (3 mL). The suspension was stirred at room temperature for 10 min, and **24** (5.9 g, 18 mmol) dissolved in DMF (5 mL) was added. The mixture was heated at 50 °C for 18 h. The solvents were removed, and the residue was partitioned between $CHCl_3$ and 0.05 N NaOH solution. The organic phase was separated and dried (Na_2SO_4), and the solvents were removed. The residue was purified by chromatography on silica gel (hexane/EtOAc/MeOH 10:10:1) to yield 2.5 g (51%) of a colorless oil: IR (film) ν 2977, 2238, 1686, 1470, 1424, 1377, 1277 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.60 (m, 2 H, pyr), 7.72 (broad d, J = 7.4 Hz, 1 H, pyr), 7.36 (m, 1 H, pyr), 4.20 (m, 2 H, pip), 4.01 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 3.84 (d, J = 6.6 Hz, 1 H, CHCN), 2.70 (m, 2 H), 2.1–1.2 (complex signal 5 H), 1.24 (t, J = 7.0 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 154.75 (C), 149.21 (CH), 148.73 (CH), 134.94 (CH), 116.13 (C), 60.85 (CH_2), 42.89 (CH_2), 40.46 (CH), 29.33 (CH_2), 28.33 (CH_2), 14.17 (CH_3).

4-(3-Pyridylcyanomethyl)piperidine (26) was obtained from **25**, under the conditions used for converting **22** into **23**, as a colorless oil in a 95% yield: IR (film) ν 3309, 2932, 2237, 1572, 1423 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.45 (m, 2 H, pyr), 7.60 (broad d, J = 7.4 Hz, 1 H, pyr), 7.28 (m, 1 H, pyr), 3.62 (d, J = 6.5 Hz, 1 H, CHCN), 3.05 (m, 2 H, pip), 2.55 (m, 2 H, pip), 2.28 (m, 1 H, NH), 1.9–1.1 (complex signal, 5 H, pip).

1-(Diphenylacetyl-4-(3-pyridylcyanomethyl)piperidine (78). Amine **26** was coupled with diphenylacetic acid using method A to give **78** (45%) as a white solid: mp 159–160 °C; IR (KBr) ν 3050, 2920, 2241, 1625, 1491, 1447, 1429 cm^{-1}; ^{1}H NMR (80 MHz, CD_3Cl) δ (TMS) 8.55 (m, 2 H, pyr), 7.60 (broad d, J = 8.2 Hz, 1 H, pyr), 7.25 (m, 11 H, pyr, Ar), 5.16 (s, 1 H, $CHPh_2$), 4.78 (m, 1 H, pip), 4.00 (m, 1 H, pip), 3.60 (d, J = 6.7 Hz, 1 H, CHCN), 2.68 (m, 2 H, pip), 2.0–1.0 (complex signal, 5 H). Anal. ($C_{26}H_{25}N_3O$) C, H, N.

The procedure was repeated with [*N*-(diphenylmethyl)amino]-acetic acid to give **114** (Table VI).

1-(3,3-Diphenylpropionyl)-4-piperidone (27). To a solution of pyridine (25.4 mL) in CH_2Cl_2 (300 mL), cooled to 0 °C, was added CrO_3 (24.37 g) in portions. The reaction was allowed to warm to room temperature, and then 1-(3,3-diphenylpropionyl)-4-hydroxypiperidine (prepared by acylation of 4-hydroxypiperidine using method A) (12 g, 39 mmol) in CH_2Cl_2 (100 mL) was added dropwise. The resulting solution was stirred at room temperature for 18 h and passed through a short column of $MgSO_4$ which was then washed with $CHCl_3$. After evaporation of the solvents, the crude was purified by chromatography on silica gel ($CHCl_3$/MeOH 5%) to yield 8.7 g (73%) of **27** as a colorless oil: IR (KBr) ν 3019, 2899, 1710, 1632, 1445, 1422, 1267 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.26 (s, 10 H, Ph), 4.72 (t, J = 7.2 Hz, 1 H, $CHPh_2$), 3.66 (m, 4 H, pip), 3.14, (d, J = 7.5 Hz, 2 H, CH_2CON), 2.29 (m, 2 H, pip), 2.04 (m, 2 H, pip).

1-(3,3-Diphenylpropionyl)-4-(3-pyridinamine)piperidine (73). Under the conditions used for the preparation of **34**, reaction of piperidone **27** with 3-aminopyridine gave **73** (13%) as a colorless oil: ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.0 (m, 2 H, pyr), 7.24 (m, 11 H, pyr, Ar), 6.82 (broad d, J = 7.3 Hz, 1 H, pyr), 4.67 (t, J = 7.7 Hz, 1 H, $CHPh_2$), 3.58 (m, 4 H, pip), 3.10 (m, 2 H, CH_2CON), 2.40 (m, 4 H, pip). The product was dissolved in EtOAc and converted to its hydrochloride by treatment with $HCl_{(g)}/Et_2O$ solution to give a white solid: mp 105–109 °C. Anal. ($C_{25}H_{27}N_3O \cdot 2HCl \cdot {}^1/_4H_2O$) C, H, N.

1-(*tert*-Butoxycarbonyl)-4-cyano-4-(3-pyridylamino)piperidine (29). To a mixture of **28** (2 g, 10 mmol) and 3-aminopyridine (0.94 g, 10 mmol) in glacial HOAc (14 mL) was added KCN (0.96 g, 18 mmol). The mixture was stirred at 60 °C for 12 h. The solvent was removed, and the residue was partitioned between $CHCl_3$ and 1 N NaOH solution. The organic phase was dried over anhydrous Na_2SO_4, and the solvent evaporated to dryness. Purification by chromatography on silica gel (EtOAc) yielded 0.5 g (17%) of a white soild: mp 123–125 °C; IR (KBr) ν 3256, 3033, 2968, 1680, 1579, 1476, 1428 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.23 (m, 2 H, pyr), 7.30 (m, 2 H, pyr), 4.06 (m, 3 H, pip), 3.31 (m, 2 H, pip), 2.6–1.6 (complex signal, 4 H, pip, NH), 1.47 (s, 9 H, BOC). Anal. ($C_{16}H_{22}N_4O_2$) C, H, N.

In a similar manner, compound **76** was prepared from ketone **27**.

1-[[(Diphenylmethyl)amino]acetyl]-4-cyano-4-(3-pyridylamino)piperidine (113). A mixture of **29** (0.48 g) in dioxane (3 mL) and $HCl_{(g)}$/dioxane solution (3 mL) was stirred at 0 °C for 30 min. Then the solvents were removed, cooled 1 N NaOH solution (10 mL) was added, and the mixture was extracted with $CHCl_3$. The organic phase was separated and dried over anhydrous Na_2SO_4, and the solvent was evaporated to dryness. The residue (0.41 g) was coupled with [*N*-(diphenylmethyl)amino]acetic acid[15] (0.48 g, 2 mmol), 1-hydroxybenzotriazole (0.30 g, 2.1 mmol), and DCC (0.42 g, 2.06 mmol) using method A. Purification by chromatography yielded 0.18 g (20%) of an oil that crystallized upon addition of Et_2O: mp 73–75 °C; IR (KBr) ν 3303, 3022, 1641, 1581, 1477, 1240 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.21 (m, 2 H, pyr), 7.30 (m, 12 H, pyr, Ar), 4.83 (s, 1 H, $CHPh_2$), 4.22 (m, 2 H, pip), 3.29 (m, 4 H, pip, CH_2-CO), 2.6–1.6 (complex signal, 5 H, pip, NH). Anal. ($C_{26}H_{27}N_5O \cdot {}^5/_4H_2O$) C, H, N.

B. Biological Methods: Inhibition of Platelet Aggregation in Vitro. Platelet-aggregation studies were done by the method of Born.[19] Blood was collected in 3.16% sodium citrate (1 volume for 9 volumes 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 C18-PAF (1.5×10^{-8} M) and measured by using a dual-channel aggregometer Chrono-log 500. Activity of the inhibitors was expressed as the IC_{50} value, i.e. the concentration required to inhibit platelet aggregatory response by 50%. The values shown in Tables I–VI 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. Hypotension studies were performed as described by Baranes.[20] 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 Beckman pressure transducer coupled to a Beckman R611 polygraph. Right and left femoral veins were catheterized to inject PAF (0.5 μg/kg) or the test compound. Test compounds were administered by intravenous injection (1 mL/kg, dissolved in saline) 3 min before PAF injection. Control animals received only the vehicle. Blood pressure was monitored and percentage inhibition of PAF-induced hypotension with respect to controls was calculated. The results were expressed as ID_{50} values, i.e. the dose of test compound required to inhibit the PAF-induced hypotension by 50%. The results were calculated by linear regression from a single experimental curve with no fewer 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.[21] Groups of 10 male Swiss mice weighing 22–26 g were used. 100 μg/kg C18-PAF plus 1 mg/kg propanolol was administered through a lateral tail vein 60 min after po administration of the test compounds (20 mL/kg) or saline (control group). Animals were observed 2 h after the PAF injection. Following this protocol we obtained a consistent mortality of 70–100% in the control group. Percent inhibition of mortality due to the treatments in comparison with the control group was calculated. Results were 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 no fewer than four data points.

Statistics. Statistical analyses of pharmacological data were made using a standard pharmacology program implemented on an IBM PC.[25]

Acknowledgment. This work was done with the support of the Plan de Fomento de la Investigación en la Industria Farmacéutica, from the Ministerio de Industria y Energía (Exp. 47/87). We thank Pere Josep Jiménez, Núria Recasens, Consol Ferreri, Guadalupe Martínez, Rosa Oliva, Teresa Gamero, and Alejandro Moliner for their excellent technical assistance.

Supplementary Material Available: Spectral data for compounds **31, 32, 35, 37–43, 48, 49, 54, 56–60, 65, 67–69, 76, 81, 91–99, 102–106, 108, 109, 111, 114,** and **116** (7 pages). Ordering information is given on any current masthead page.

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