Structural Modification of 5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinoline Platelet Activating Factor Receptor Antagonists

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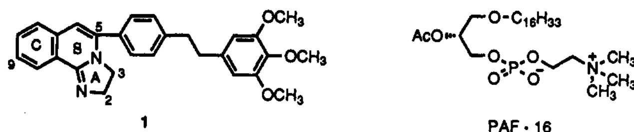
Received April 5, 1993[●]

In an effort to determine the effect of modification of the imidazo[2,1-*a*]isoquinoline portion of the PAF-receptor antagonist SDZ 64-412 (1), several new analogs were prepared and evaluated *in vitro* and *in vivo*. One of these, 5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]-2,3-dihydroimidazo[1,2-*a*]thieno[2,3-*c*]pyridine (6) was 4–5 times more potent than 1 in inhibiting PAF-induced bronchoconstriction and hemoconcentration when administered po to the guinea pig.

Introduction

The search for substances that antagonize platelet activating factor (PAF) by a receptor-mediated mechanism has resulted in a number of compounds structurally related to PAF (charged PAF antagonists) and a variety of open-chain and cyclic systems that do not contain a formal charge (noncharged PAF antagonists).[1-4] Our laboratory has been involved in the design of noncharged PAF receptor antagonists using the PAF molecule as a template. We recently reported on one such class of compounds, the 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines, as having good *in vitro* and *in vivo* PAF antagonist activity.[5,6] From this series the 5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]-phenyl] analog 1 (SDZ 64-412) has been selected for further



studies as an orally active PAF receptor antagonist.[7] In this paper we report on our findings where the imidazo-[2,1-*a*]isoquinoline framework (rings A, B, and C) in 1 is modified. One or two methyl groups (**4a**, **4b**) or a double bond (**8a**, **8b**) was added to ring A, and the imidazo ring was enlarged (**5a**, **5b**) or replaced by a triazolo ring system (**12**). In ring B the carbon–carbon double bond was replaced by a carbon–nitrogen double bond (**16**), and in ring C the benzo ring was replaced by a thiopheno (**6**) or furano (**7**) system.[8]

Chemistry

The synthesis of the 2-methyl (**4a**) and 2,2-dimethyl (**4b**) analogs of 1 was carried out by the procedures given in Scheme I. Lithiation[9] of the 2-(2′-methylphenyl)-imidazolines **2a** and **2b** followed by treatment with methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate gave the labile alcohols **3a** and **3b**. These were readily dehydrated (**4a** and **4b**) by refluxing in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid. The pyrimido-[2,1-*a*]isoquinolines **5a** and **5b** were prepared by lithiation of the corresponding 2-(2′-methylphenyl)tetrahydropyrimidines (**17a**, **17b**) followed by the procedures b–d given in Scheme I. The imidazo[1,2-*a*]thieno[2,3-*c*]pyridine **6** and the furo[2,3-*c*]imidazo[1,2-*a*]pyridine **7** were also prepared in a similar manner starting with the appropriate 2-(2-thienyl) or 2-(2-furyl)imidazoline (**18** and **19**).

The dehydro compounds **8a** and the 2-methyl analog **8b** were conveniently prepared by treatment of the corresponding 2,3-dihydro analogs **1** and **2a** with activated manganese dioxide in methylene chloride.

Treatment of lithiated *N*-*tert*-butyl-*o*-toluamide (**9**) with methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate gave keto amide **10** which was cyclized and de-*tert*-butylated to the 1-isoquinolinone **11** by heating to 90 °C in polyphosphoric acid. Conversion of **11** to the 1-chloroisoquinoline with phosphorus oxychloride, followed by treatment with hydrazine hydrate and then refluxing with acetyl chloride in pyridine–toluene, gave **12** (Scheme II).

The imidazo[1,2-*c*]quinazoline **16** (Scheme III) was prepared by reaction of anthranilic acid with methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate in the presence of DCC to give the 3,1-benzoxazin-4-one **14** followed by treatment with ethylenediamine to give **15**, which was in turn cyclized by treatment with phosphorous pentasulfide in refluxing pyridine.

Biological Results

Compounds were evaluated for PAF-antagonist activity *in vitro* by determining their competition with [^{3}H]PAF for binding to the PAF-receptor of human platelets. *In vivo* activity was assayed by oral administration of the compounds to anesthetized guinea pigs 2 h before intravenous PAF injection and then measuring the inhibition of PAF-induced bronchoconstriction and hemoconcentration. Table I shows the *in vitro* and *in vivo* PAF-antagonist activity for all compounds tested.

In the PAF-receptor binding assay, one methyl group at C-2 (**4a**) in ring A of 1 resulted in *ca.* 4-fold loss of activity, while the dimethyl analog **4b** retained the same level of activity. Introduction of a double bond in ring A of either 1 or **4a** gave compounds (**8a**, **8b**) that were 1500 and 600 times less active, respectively. When ring A in 1 was replaced by a pyrimidine ring the unsubstituted **5a** was *ca.* equal to 1 while the 3,3-dimethyl analog **5b** was 1/9 as active in the PAF binding assay. Replacement of ring A by a triazolo ring (**12**) or ring B by a pyrimidino ring (**16**) resulted in marked loss of activity. Replacement of the benzo ring C by a thiopheno or furano system gave compounds **6** and **7** which, respectively, were found to be 6 times more potent and equipotent relative to 1.

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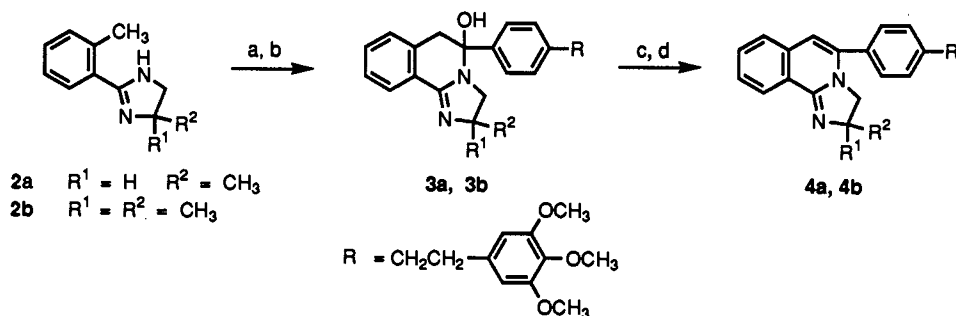
● Abstract published in *Advance ACS Abstracts*, September 15, 1993.

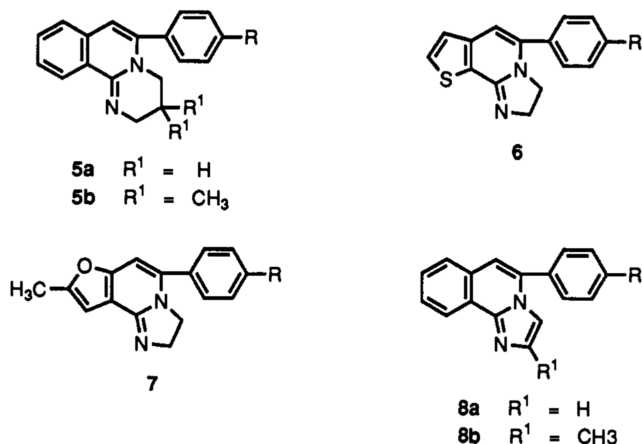
0022-2623/93/1836-3098$04.00/0 © 1993 American Chemical Society

Scheme I[a]



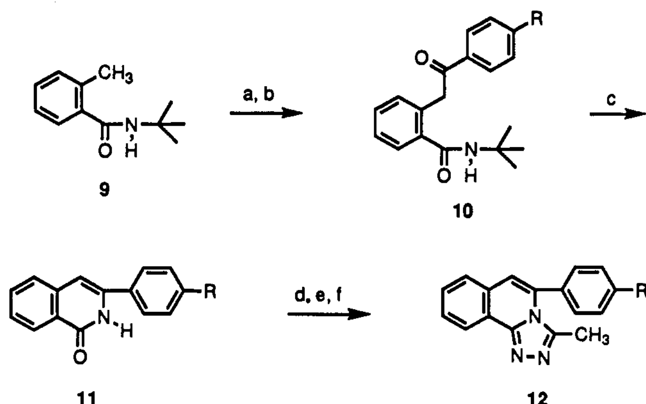
[a] Reagents/conditions: (a) *n*-BuLi, TMEDA, THF, 0 °C, 3 h; (b) methyl 4-R-benzoate, THF, −50 ± 5 °C; (c) *p*-toluenesulfonic acid, toluene, reflux; (d) HCl, EtOH.

Chart I[a]



[a] See Scheme I for definition of R.

Scheme II[a]



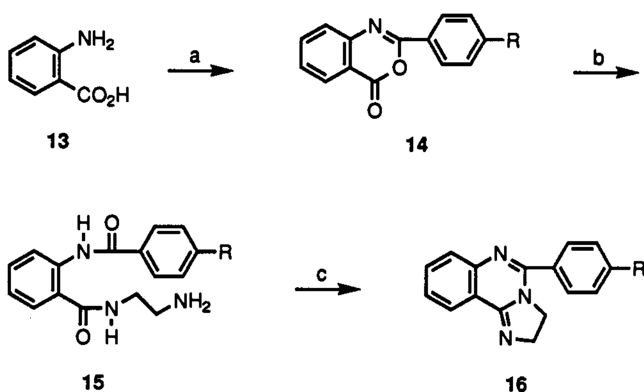
[a] Reagents/conditions: see Scheme I for definition of R; (a) *n*-BuLi, TMEDA, THF, 0 °C to rt; (b) methyl 4-R-benzoate, THF, −78 °C; (c) PPA, 90 °C, 2 h; (d) $POCl_3$, reflux, 4 h; (e) NH_2NH_2, EtOH, reflux, 5 h; (f) CH_3COCl, pyridine, toluene, reflux, 16 h.

Inhibition of the PAF-induced bronchoconstriction and hemoconcentration in guinea pig by oral administration gave results in parallel with those obtained on the PAF receptor with several notable exceptions. The dimethyl analog **4b** has a receptor IC_{50} value equal to **1** but is considerably weaker *in vivo* and furano **7** is *ca* 2.5 times less potent *in vivo* than expected from the binding data.

Discussion and Conclusions

We previously compared the structural components of PAF-16 and **1** and postulated that the phosphate (PO_4^-), trimethylammonium ($N(CH_3)_3^+$), ether oxygen (*O*-alkyl), and the C-16 alkyl groups in PAF-16 are mimicked in **1** by the benzo ring (ring C), protonated form of the C=N in ring A (C=NH$^+$), CH=C in ring B and the [(3,4,5-trimethoxyphenyl)ethyl]phenyl groups, respectively.[5]

Scheme III[a]



[a] Reagents/conditions: see Scheme I for definition of R; (a) methyl 4-R-benzoate, DCC, CH_2Cl_2, rt, 40 h; (b) 1,2-diaminoethane, P_2S_5, reflux, 6 h; (c) P_2S_5, pyridine, 136 °C, 16 h.

Table I. *In Vitro* and *in Vivo* PAF-Antagonist Activity in the Guinea Pig

compd[a]	human platelets receptor: IC_{50}, μM	PAF-induced bronchoconstriction: ED_{50}[d] or % inhibition[e] mg/kg po	PAF-induced hemoconcentration ED_{50}[d] or % inhibition[e] mg/kg po
1	0.06	4.2	5.0
4a	0.22	16.0	10.0
4b	0.06	24.0*[,b]	17.9*[,b]
5a	0.04	4.7	3.0
5b	0.50	17.0*[,b]	23.0*[,b]
6	0.01	0.8	1.1
7	0.05	>10	10.0
8a	89.0	c	c
8b	35.0	–	–
12	9.5	–	–
16	1.14	31.4	31.9

[a] Compound **12** is a free base. All other compounds are HCl salts. [b] Determined at a dose of 20 mg/kg where three to five animals are evaluated. [c] Not determined. [d] ED_{50} values are derived from dose–response curves, where four to seven animals are tested per dose and at least five different doses are evaluated. [e] Asterisk denotes % inhibition.

The present findings indicate that the C=NH$^+$ in ring A ($N(CH_3)_3^+$ mimic) plays an important role in the binding of **1** at the PAF receptor site. Conversion of the C=N from a strong base (imidazoline) to a weak base (imidazoles **8a** and **8b**) result in a marked loss (600–1500 times) of binding. A similar loss is seen when the C=N is placed in the weakly basic triazolo ring (**12**). The binding site for the C=N appears to tolerate an increase in ring size to a tetrahydropyrimidine ring (**5a**) and one (**4a**) or two (**4b**,

5b) methyl groups. The reason that the dimethyl analog (**4b**) is 3 times more effective in binding than the monomethyl (**4a**) is not readily apparent.

In the pyrimidino analog **16** where the HC=C group in **1** is replaced by N=C there is a 19-fold loss of activity. If the HC=C is mimicking the ether oxygen in PAF-16, replacement by the more electron-rich N=C should increase binding. A possible explanation for the decreased binding in **16** may be due to the N being attached to a benzene ring (anilino N) and partial protonation.

The increase in PAF receptor binding seen with the more electron-rich thiopheno analog **6** is expected if the benzo ring **1** is mimicking the electron-rich phosphate group in PAF-16. The 8-methylfurano **7** has the same binding ability as **1**, but would be expected to be a more effective binder because of the increased electron density in the furano ring. Apparently the 8-methyl group has an adverse effect on the binding to the PAF receptor. Additional studies are needed to clarify the present findings.

In conclusion, it has been found that modification of the imidazo (ring A) or benzo (ring C) in the PAF receptor antagonist **1** by ring expansion (**5**), or introduction of a hetero ring system (**6**, **7**), results in compounds of similar or greater PAF antagonist activity. Introduction of a double bond (**8a**, **8b**), two methyl groups (**5b**), or an additional nitrogen atom (**12**) in ring A, or a nitrogen atom (**16**) in ring B, resulted in loss of activity.

The previously postulated PAF binding site model[5] has proven to be useful in explaining structural modification of **1**.

Compound **6** has been selected for further investigation in a number of pharmacological models in which PAF is believed to be implicated.

Experimental Section

General. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken on JEOL-FX-90 (90 MHz) or Bruker (200 MHz) spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS). ^{13}C-NMR were determined at 22.5 or 50.1 MHz on a Bruker, with $CDCl_3$ (δ 77.0) and TMS (δ 0.0) as internal reference. Infrared (IR) spectra were determined on an Analect FX-6260 using either KBr pellets or $CHCl_3$ solutions. Mass spectra (MS) were obtained on a Finnigan MAT 4600 GC/MS instrument applying a desorption chemical ionization method using ammonia (or isobutane) as the reagent gas. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Carlo Erba Instruments Model EA1108-Elemental Analyzer and are within ±0.4% of theory unless noted otherwise. If not otherwise specified, chemicals and reagents were obtained from the Aldrich Chemical Co. Solvents were of reagent grade and dried prior to use. Reaction progress and purity of final products were determined on E. Merck Silica Gel 60 chromatography plates. Column chromatography was carried out using E. Merck Silica Gel CH83 (0.06–0.20 mesh) with the indicated eluents.

2-Aryl-2(1*H*)-imidazolines and 2-Aryl-1,4,5,6-tetrahydropyrimidines (2a,b,17a,b,18,19). DL-3-Methyl-2-(2′-methylphenyl)imidazoline (2a). Method A. A solution of DL-2-methyl-1,2-diaminoethane (9.11 g, 0.12 mmol), *o*-toluonitrile (12.0 g, 0.10 mol), *p*-toluenesulfonic acid monohydrate (11.7 g, 0.06 mol), and ethylene glycol (100 mL) was refluxed for 64 h. The solution was allowed to cool to room temperature and poured into H_2O (100 mL), and the aqueous phase was saturated with solid NaOH, extracted with CH_3CN, dried ($MgSO_4$), and filtered. Distillation in a bulb-to-bulb apparatus gave 12.6 g (71%) of **2a**: bp 130 °C (0.2 mm); ^{1}H-NMR ($CDCl_3$) δ 1.29 (d, 3H), 2.49 (s, 3H), 3.2–4.3 (m, 4H), 7.05–7.50 (m, 4H); MS *m/z* 175 (MH^+). Anal. ($C_{11}H_{14}N_2$) C, H, N.

3,3-Dimethyl-2-(2′-methylphenyl)imidazoline (2b): obtained as a white solid (68%), mp 109–110 °C (CH_2Cl_2/hexane); ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 6H), 2.47 (s, 3H), 3.49 (s, 2H), 4.61 (bs, 1H), 7.09–7.45 (m, 4H); MS *m/z* 189 (MH^+). Anal. ($C_{12}H_{16}N_2$) C, H, N.

2-(2′-Methylphenyl)-1,4,5,6-tetrahydropyrimidine (17a): obtained as a white solid (57%), mp 145–146 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 1.90 (q, 2H), 2.39 (s, 3H), 3.56 (t, 4H), 7.05–7.34 (m, 4H). Anal. ($C_{11}H_{14}N_2$) C, H, N.

5,5-Dimethyl-2-(2′-methylphenyl)-1,4,5,6-tetrahydropyrimidine (17b): obtained as a white solid (56%), mp 202–204 °C (CH_3OH/acetone); ^{1}H-NMR ($CDCl_3$) δ 1.07 (s, 6H), 2.43 (s, 3H), 3.10 (s, 4H), 7.05–7.34 (m, 4H); MS *m/z* 203 (MH^+). Anal. ($C_{13}H_{18}N_2$) C, H, N.

4,5-Dihydro-2-(3-methyl-2-thienyl)-1*H*-imidazole (18). To a stirred solution of 2 M trimethylaluminum (47 mL, 0.094 mol) in a toluene (20 mL) at 0 °C under N_2 was added dropwise a solution of ethylenediamine (5.4 g, 0.089 mol) in toluene (50 mL). After stirring for 1 h the mixture was treated dropwise at 0 °C with a solution of methyl 3-methylthiophenecarboxylate (7.0 g, 0.045 mol) in toluene, refluxed for 3 h, cooled to room temperature, treated dropwise with H_2O (32 mL), MeOH (100 mL) and $CHCl_3$ (100 mL), and then refluxed for 1 h. The mixture was dried ($MgSO_4$), filtered, and then evaporated to give 5.86 g (79%) of **18**: mp 88–90 °C; ^{1}H-NMR ($CDCl_3$) δ 2.51 (s, 3H), 3.78 (s, 4H), 6.87 (d, 1H), 7.23 (d, 2H); MS *m/z* 167 (MH^+). Anal. ($C_8H_{10}N_2S$) C, H, N, S.

4,5-Dihydro-2-(2,5-dimethyl-3-furanyl)-1*H*-imidazole (19). To a stirred solution of 2 M trimethylaluminum (27 mL, 0.054 mol) in toluene (30 mL) at 0 °C under N_2 there was added dropwise a solution of ethylenediamine (2.4 mL, 0.036 mol) in toluene (13 mL). After stirring for 1 h the mixture was treated dropwise at 0 °C with a solution of methyl 2,5-dimethyl-3-furancarboxylate (2.7 mL, 0.018 mol) in toluene (21 mL), refluxed for 3 h, cooled to room temperature, treated dropwise with H_2O (8 mL), MeOH (25 mL) and CH_2Cl_2 (30 mL), and then refluxed for 1 h. The mixture was dried ($MgSO_4$), filtered, and then evaporated to give an oil (4.9 g) which was mixed with phosphorus pentasulfide (0.64 g, 0.0014 mol) and pyridine (30 mL) and then refluxed for 2 h. Solvent was evaporated and the residue was filtered through a short column of basic alumina (activity I, 60 g) using CH_2Cl_2–MeOH (9:1) as an eluent. The filtrate was evaporated and the residue was distilled in a bulb-to-bulb apparatus to give 1.8 g (61%) of **19**: mp 101–103 °C; ^{1}H-NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.52 (s, 3H), 3.70 (s, 4H), 4.38 (bs, 1H), 6.09 (s, 1H); MS *m/z* 165 (MH^+). Anal. ($C_9H_{12}N_2O$) C, H, N.

Preparation of Compounds 4a, 4b, 5a, and 5b. 2-Methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (4a). Method B. A stirred solution of **2a** (2.0 g, 0.011 mol), *N,N,N′,N′*-tetramethylethylenediamine (2.9 g, 0.025 mol) in THF (100 mL) under a N_2 atmosphere was treated dropwise with 1.6 M *n*-BuLi in hexane (15 mL, 0.024 mol) while maintaining the temperature at 0 °C. After an additional 3 h at 0 °C, the mixture was cooled to −50 °C, treated with a solution of methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate (3.8 g, 0.011 mol) in THF (10 mL), allowed to come to room temperature for 4 h, treated with saturated NH_4Cl solution (10 mL), and then extracted with EtOAc. The combined organic extracts were washed with H_2O, saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated in vacuo to give 6.0 g of crude **3a** as a foam. A solution of crude **3a** (5.4 g), *p*-toluenesulfonic acid (0.2 g), and C_6H_6 (200 mL) was refluxed for 16 h with continuous removal of H_2O (Dean–Stark trap). The solution was then washed with saturated $NaHCO_3$ solution, H_2O, saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was dissolved in anhydrous EtOH (100 mL), treated with HCl gas, evaporated *in vacuo*, and triturated with acetone–hexane to give 1.6 g (32%) of **4a**·HCl: mp 215–217 °C; MS *m/z* 455 (MH^+ − HCl); ^{1}H-NMR ($CDCl_3$) δ 1.62 (d, 3H), 2.90–3.10 (m, 4H), 3.87 (bs, 10H), 4.50–4.83 (m, 2H), 6.41 (s, 2H), 6.80 (s, 1H), 7.30–7.90 (m, 7H), 9.15 (d, 1H), 12.89 (bs, 1H). Anal. ($C_{29}H_{30}N_2O_3$·HCl) C, H, Cl, N.

2,2-Dimethyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline (4b): obtained (38%) as HCl salt from **2b**, mp 182–5 °C (acetone/hexane); MS *m/z* 469 (MH^+ − HCl); ^{1}H-NMR ($CDCl_3$) δ 1.73 (s, 6H), 2.82–

3.07 (m, 4H), 3.85 (s, 9H), 4.09 (s, 2H), 6.39 (s, 2H), 6.80 (s, 1H), 7.33 (bs, 3H), 7.70 (q, 4H), 9.18 (d, 1H), 13.00 (bs, 1H). Anal. ($C_{30}H_{32}N_2O_3$·HCl) C, H, Cl, N.

3,4-Dihydro-6-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]-2*H*-pyrimido[2,1-*a*]isoquinoline (5a): obtained (32%) as HCl salt from **17a**, mp 250 °C dec (CH_3OH–CH_2Cl_2); MS *m/z* 455 (MH^+ – HCl); ^{1}H-NMR (DMSO-d_6) δ 2.08 (m, 2H), 2.92 (m, 4H), 3.22 (s, 9H), 3.75 (m, 4H), 6.52 (s, 2H), 7.08 (s, 1H), 7.32–7.95 (m, 7H), 8.82 (d, 1H), 10.65 (bs, 1H). Anal. ($C_{29}H_{30}N_2O_3$·HCl) C, H, Cl, N.

3,4-Dihydro-3,3-dimethyl-6-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]-2*H*-pyrimido[2,1-*a*]isoquinoline (5b): obtained (29%) as HCl salt from **17b**, mp 195 °C (CH_3OH–CH_2Cl_2); MS *m/z* 483 (MH^+ – HCl); ^{1}H-NMR (DMSO-d_6) δ 0.98 (s, 6H), 2.95 (s, 4H), 3.68 (s, 4H), 3.78 (s, 9H), 6.55 (s, 2H), 7.13 (s, 1H), 7.43 (s, 4H), 7.63–7.98 (m, 3H), 8.82 (d, 1H), 10.73 (s, 1H). Anal. ($C_{31}H_{34}N_2O_3$·HCl) C, H, Cl, N.

5-[4-[2-(3,4,5-Trimethoxyphenyl)ethyl]phenyl]-2,3-dihydroimidazo[1,2-*a*]thieno[2,3-*c*]pyridine (6). A stirred solution of 18 (2.5 g, 0.015 mol) and *N,N,N′,N′*-tetramethylethylenediamine (4.19 g, 0.036 mol) in THF (200 mL) under a N_2 atmosphere was cooled to –78 °C and treated dropwise with 1.6 M *n*-BuLi (20.7 mL, 0.033 mol). After an additional 0.5 h of stirring, the mixture was treated dropwise with a solution of methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate (4.97 g, 0.015 mol) in THF (50 mL), allowed to warm to room temperature for 4 h, treated with saturated NH_4Cl solution (10 mL), and then extracted with CH_2Cl_2 (50 mL). The organic layer was washed with H_2O, saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated to give a yellow gum (MS *m/z* 465). The gum (6.9 g), *p*-toluenesulfonic acid (0.7 g), and C_6H_6 (300 mL) were refluxed for 16 h with continuous removal of H_2O (Dean–Stark trap). The C_6H_6 was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (50 mL), washed with H_2O, saturated $NaHCO_3$ solution, H_2O, saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with CH_3OH–CH_2Cl_2 (1:3) to give 0.6 g (23%) of **6** as a foam: MS *m/z* 447 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 2.80–3.00 (m, 4H), 3.80 (s, 3H), 3.88 (s, 6H), 3.90–4.20 (m, 4H), 6.12 (s, 1H), 6.41 (s, 2H), 7.09 (d, 1H), 7.32 (q, 4H), 7.55 (d, 1H).

The base **6** in EtOH (50 mL) was treated with HCl gas and evaporated *in vacuo*, and the residue crystallized from CH_2Cl_2–EtOAc–hexane to give **6**·HCl: mp 240–242 °C; MS *m/z* 447 (MH^+ – HCl); ^{1}H-NMR ($CDCl_3$) δ 2.80–3.10 (m, 4H), 3.86 (s, 6H), 3.88 (s, 3H), 4.26 (t, 2H), 4.56 (t, 2H), 6.42 (s, 2H), 7.00 (s, 1H), 7.33 (d, 1H), 7.44 (q, 4H), 8.02 (d, 1H), 12.32 (s, 1H). Anal. ($C_{26}H_{26}N_2O_3S$·HCl) C, H, Cl, N, S.

2,3-Dihydro-8-methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]furo[3,2-*c*]imidazo[1,2-*a*]pyridine (7). Following the procedure used to prepare **6** there was obtained **7** (21%) as a yellow foam (MS *m/z* 444) that gave **7**·HCl: mp 220–222 °C (CH_2Cl_2–Et_2O); MS *m/z* 444 (M – HCl); ^{1}H-NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.88–3.08 (m, 4H), 3.88 (s, 3H), 3.89 (s, 6H), 4.21 (bs, 2H), 4.51 (bs, 2H), 6.42 (s, 2H), 6.76 (s, 2H), 7.35–7.49 (m, 5H). Anal. ($C_{27}H_{28}N_2O_4$·HCl·H_2O) C, H, Cl, N.

5-[4-[2-(3,4,5-Trimethoxyphenyl)ethyl]phenyl]imidazo[2,1-*a*]isoquinoline (8a). A mixture of **1** (1.85 g), activated MnO_2 (10.0 g), and anhydrous DMF (30 mL) was stirred at room temperature for 48 h and filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in EtOH (15 mL) and treated with HCl gas and the solid filtered off to give 1.05 g (52.8%) of **8a**·HCl: mp 232 °C dec, MS *m/z* 439 (MH^+ – HCl); ^{1}H-NMR ($CDCl_3$) δ 2.99 (m, 4H), 3.82 (s, 9H), 6.40 (s, 2H), 6.97 (s, 1H), 7.46 (d, 2H), 7.50–7.73 (m, 7H), 8.65 (d, 1H). Anal. ($C_{28}H_{26}N_2O_3$·HCl) C, H, Cl, N.

2-Methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]imidazo[2,1-*a*]isoquinoline (8b). In a similar manner there was obtained **8b**·HCl (40.2%): mp 238–240 °C (EtOH); MS *m/z* 453 (MH^+ – HCl); ^{1}H-NMR ($CDCl_3$) δ 2.71 (s, 3H), 3.01 (m, 4H), 3.85 (s, 9H), 6.40 (s, 2H), 7.30–7.91 (m, 8H), 9.57 (m, 1H), 17.38 (bs, 1H). Anal. ($C_{29}H_{28}N_2O_3$·HCl) C, H, Cl, N.

3-Methyl-5-[4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenyl]-1,2,4-triazolo[3,4-*a*]isoquinoline (12). A solution of 2-methylbenzoyl chloride (10.0 g, 0.065 mol), *tert*-butylamine (4.73 g, 0.065 mol), triethylamine (7.85 g, 0.078 mol), and CH_2Cl_2 (150 mL) was stirred at room temperature for 6 h, washed with H_2O and saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and passed through a short column of silica gel and the eluent evaporated to give 8.0 g (64.5%) of **9**: mp 77–79 °C; MS *m/z* 192 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.42 (s, 3H), 5.50 (bs, 1H), 7.11–7.32 (m, 4H). Anal. ($C_{12}H_{17}NO$) C, H, N.

A stirred solution of **9** (3.0 g, 0.016 mol) and *N,N,N′,N′*-tetramethylethylenediamine (4.4 g, 0.038 mol) in THF (100 mL) under a N_2 atmosphere, cooled to 0 °C, was treated dropwise with 1.6 M *n*-BuLi in hexane (20.6 mL, 0.033 mol). The resulting red solution was stirred at room temperature for 1 h, cooled to –78 °C, treated dropwise with a solution of methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate (5.18 g, 0.016 mol), brought to room temperature for 16 h, treated with saturated NH_4Cl solution (10 mL), and extracted with EtOAc. The organic extract was washed with H_2O, saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated to give an oil that was chromatographed on silica gel, eluting with EtOAc–hexane (1:1) to give 1.49 g (19.5%) of **10**: mp 98–99 °C (EtOAc–hexane); MS *m/z* 490 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 1.32 (s, 9H), 2.91 (bs, 4H), 3.80 (s, 6H), 3.81 (s, 3H), 4.52 (s, 2H), 6.05 (bs, 1H), 6.34 (s, 2H), 7.00–7.45 (m, 6H), 7.93 (d, 2H); ^{13}C-NMR ($CDCl_3$) 197.95 (CON), 169.52 (C=O); IR (KBr) 3425 (NH), 1655 and 1686 (CO and HNCO). Anal. ($C_{30}H_{35}NO_5$·0.3H_2O) C, H, N.

A mixture of **10** (1.0 g, 0.002 mol) and polyphosphoric acid (10 g) was stirred at 90 °C for 2 h, cooled to room temperature, poured onto ice, and extracted separately with $CHCl_3$, CH_2Cl_2, and EtOAc. The combining organic extracts were dried ($MgSO_4$) and evaporated to give a yellow oil (0.80 g) that was chromatographed on silica gel, eluting with EtOAc–hexane (1:1) to give 0.28 g (33.0%) of **11**, as a white solid: MS *m/z* 416 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 2.94 (bs, 4H), 3.82 (s, 9H), 6.36 (s, 2H), 6.73 (s, 1H), 7.17–7.71 (m, 7H), 8.37 (d, 1H), 9.47 (bs, 1H).

A solution of **11** (0.2 g) in phosphorus oxychloride (10 mL) was refluxed for 4 h, cooled to room temperature, poured onto ice, and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 0.19 g (95%) of a light purple oil: MS *m/z* 434 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 2.97 (br, 4H), 3.82 (s, 6H), 3.83 (s, 3H), 6.40 (s, 2H), 7.30–8.42 (m, 9H). A solution of the oil (0.19 g), anhydrous hydrazine (15 mL) in EtOH (15 mL) was refluxed for 5 h and evaporated *in vacuo*, and the residue was dissolved in CH_2Cl_2, washed with H_2O and saturated NaCl, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 0.12 g (66.7%) of a yellow solid: MS *m/z* 430 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 2.95 (bs, 4H), 3.82 (s, 9H), 6.39 (s, 2H), 7.28–8.12 (m, 9H). A suspension of this yellow solid (0.12 g, 0.00028 mol), acetyl chloride (0.03 g, 0.00042 mol), pyridine (0.044 g, 0.00056 mol) and anhydrous toluene (10 mL) was refluxed for 16 h. The clear solution was washed with H_2O and saturated NaCl solution, dried ($MgSO_4$), filtered, evaporated *in vacuo*, and chromatographed on silica gel, eluting with CH_2Cl_2–MeOH (9:1) to give 0.06 g of **12**: mp 186–187 °C (EtOAc–hexane); MS *m/z* 454 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.95 (m, 2H), 3.04 (m, 2H), 3.83 (s, 3H), 3.84 (s, 6H), 6.42 (s, 2H), 6.85 (s, 1H), 7.37 (q, 4H), 7.66 (m, 3H), 8.75 (d, 1H). Anal. ($C_{28}H_{27}N_3O_3$) C, H, N.

5-[4-[2-(3,4,5-Trimethoxyphenyl)ethyl]phenyl]-2,3-dihydroimidazo[1,2-*c*]quinazoline (16). A solution of anthranilic acid (0.43 g, 0.0032 mol), methyl 4-[2-(3,4,5-trimethoxyphenyl)ethyl]benzoate (1.0 g, 0.0032 mol), and *N,N′*-dicyclohexylcarbodiimide (1.18 g, 0.0055 mol) in CH_2Cl_2 (30 mL) was stirred for 40 h at room temperature. The insoluble material was filtered off and the filtrate evaporated *in vacuo*. The resultant oil was crystallized from EtOAc–hexane to give 0.78 g (60%) of **14**: mp 152–154 °C; MS *m/z* 418 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 2.96 (bs, 4H), 3.81 (s, 6H), 3.82 (s, 3H), 6.36 (s, 2H), 7.23–7.91 (m, 4H), 8.21 (d, 4H).

A solution of **14** (0.56 g, 0.0013 mol), ethylenediamine (18 mL) and phosphorus pentasulfide (0.15 g, 0.00034 mol) was refluxed for 6 h, cooled to room temperature, poured into H_2O, and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo* to give 0.65 g of **15** as a white foam. A solution of **15** (0.64 g), phosphorus pentasulfide (0.71 g, 0.0016 mol), and pyridine (30 mL) was stirred and heated at 130 °C for 16 h and then evaporated *in vacuo*. The residue was dissolved in EtOH–CH_2Cl_2 (50 mL/20 mL), treated with HCl gas, evaporated *in vacuo*, and

crystallized from CH_2Cl_2–Et_2O to give 470 mg of 16·HCl: mp 239–240 °C; MS *m/z* 442 (MH^+ – HCl); ^{1}H-NMR ($CDCl_3$) δ 2.98 (bs, 4H), 3.81 (s, 3H), 3.82 (s, 3H), 4.35 (m, 2H), 4.75 (m, 2H), 6.40 (s, 2H), 7.30–7.90 (m, 7H), 8.91 (d, 1H). Anal. ($C_{27}H_{27}N_3O_3$·HCl) C, H, Cl, N.

PAF Receptor Assay. Methodology for evaluation in PAF receptor binding studies has previously been described.[7] Human platelets prepared for the receptor binding were incubated with [9,10-$^3H_2$]PAF (49 Ci mM^{-1}) at a final concentration of 1.5 nM for 1 h at 24 °C. Free ligand was separated by centrifugation, and the platelets were counted for 1 min in a liquid scintillation counter. Specific binding was calculated as the difference in counts per minute between bound and nonspecifically (calculated using 0.37 mM cold PAF) bound [^{3}H]PAF.

Guinea Pig Bronchoconstriction and Hemoconcentration. The methodology of hemoconcentration and bronchoconstriction (Konzett-Rossler method) induced by PAF has been described.[10] Guinea pigs were challenged with 0.05 mg/kg PAF iv and the animals were given compound po in H_2O from 0.5 to 18 h before the PAF challenge. Once the optimal predose time and duration were established the compound was evaluated in a dose–response manner using a 2-h predose time.

Acknowledgment. The authors wish to thank Dr. Michael Shapiro and Ms. Ann Archinal for NMR spectra, Mr. Harshad Anjaria for IR spectra, Mr. Eric Roos for elemental analysis, Ms. Bertha Owens and Mr. Robert Suzuki for mass spectra, and Mr. Lance Janaskie for HPLC. We also like to thank Miss Danielle Padula for typing this manuscript.

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