(6.0 g, 20.9 mmol) and azidotri-*n*-butylstannane (13.9 g, 41.8 mmol) was heated at 80 °C for 3 days and then heated overnight at 100 °C with 125 mL of 6 N aqueous hydrochloric acid. The mixture was cooled and extracted four times with 200 mL each of ether, and then the aqueous layer was concentrated in vacuo. Ion exchange chromatography (Dowex 50-X8 [100–200 mesh], 4- X 18-cm column, loaded in water, eluted with 10% pyridine/water) afforded a solid (after concentration of the product containing fractions[8]) which was washed with water, acetone, and ether and dried in vacuo at 80 °C to afford 3.5 g (74%) of (−)-1 monohydrate: $[\alpha]_D$ = −20.4° (*c* = 1, 1 N HCl), mp 199–201 °C. Anal. ($C_8H_{13}N_5O_2 \cdot H_2O$) C, H, N. Similarly, 2.6 g (9.5 mmol) of (−)-4 and 6.3 g (19.0 mmol) of azidotri-*n*-butylstannane gave 1.2 g (55%) of (+)-1 monohydrate: $[\alpha]_D$ = +19.9° (*c* = 1, 1 N HCl), mp 200–202 °C. Anal. ($C_8H_{13}N_5O_2 \cdot H_2O$) C, H, N.

**X-ray Experimental Data for (+)-8.** (+)-8 ($C_{33}H_{38}N_2O_{10}$) crystallized in the orthorhombic space group $P2_12_12$, with a unit cell having the dimensions *a* = 13.932 (4) Å, *b* = 29.450 (9) Å, *c* = 9.862 (5) Å and a calculated density of 1.022 g cm$^{-3}$. The unit cell contained four molecules of water. A total of 3150 unique reflections with $2\theta$ less than 116.0° were measured on an automated four-circle diffractometer (Siemens R3m/V) using monochromatic copper radiation (Cu K$\alpha$, $\lambda$ = 1.54178 Å). The structure was solved using direct methods using the Siemens SHELXTL PLUS (VMS) system[21] and was refined by the full-matrix least-squares method with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms were included with isotropic temperature factors at calculated positions. The final *R* factor was 0.0997 for 2677 observed reflections. Maximum peak height in final difference Fourier map is 0.71 eÅ$^{-3}$. Figure 1 in the supplementary material gives the structure of (+)-8 showing the numbering of the non-hydrogen atoms. Tables 1–5 in the supplementary material give the atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and H-atom coordinates.

**[$^3$H]CGS 19755 Binding.** The method for this assay has been published. See ref 16.

**Cortical Wedge Assay.** The method for this assay has been published. See ref 17.

**NMDA-Induced Convulsions in Neonatal Rats.** The method for this assay has been published. See ref 18.

**NMDA-Induced Lethality in Mice.** The method for this assay has been published. See ref 19.

**NMDA-Induced Striatal Neurotoxicity.** The method for this assay has been published. See ref 20.

**Acknowledgment.** The authors thank Ron Lawson and Charles C. Hillman, Jr., for their technical assistance and the Physical Chemistry Department of Lilly Research Laboratories for spectral data and elemental analyses.

**Supplementary Material Available:** X-ray crystallographic data (structure, atomic coordinates, bond lengths, bond angles, anisotropic displacment coefficients and H-atom coordinates) for (+)-8 (6 pages). Ordering information is given on any current masthead page.

(21) Sheldrick, G. M. Shelxtl, Rev 4, Instrument Corporation, 1983.

# 1,4-Dihydropyridines as Antagonists of Platelet Activating Factor. 1. Synthesis and Structure-Activity Relationships of 2-(4-Heterocyclyl)phenyl Derivatives

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A novel class of 2-(4-heterocyclylphenyl)-1,4-dihydropyridines (**2–38**) possessing antagonist activity against platelet activating factor (PAF) was prepared by the Hantzsch synthesis from a variety of ethyl 4′-heterocyclic-substituted benzoylacetates, aryl or heteroaryl aldehydes, and substituted 3-aminocrotonamides or 3-aminocrotonate esters. Structure–activity relationships were evaluated where PAF antagonist activity was measured in vitro by determining the concentration of compound ($IC_{50}$) required to inhibit the PAF-induced aggregation of rabbit washed platelets, and in vivo by determining the oral dose ($ED_{50}$) which protected mice from a lethal injection of PAF. The nature of the substituent at the dihydropyridine 2-position was found to be important for both in vitro and in vivo activity, whereas there was greater flexibility for structural variation at the 4- and 5-positions. The most potent compound was 4-(2-chlorophenyl)-1,4-dihydro-3-(ethoxycarbonyl)-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-5-[*N*-(2-pyridyl)carbamoyl]pyridine (**17**, UK-74,505), $IC_{50}$ = 4.3 nM, $ED_{50}$ = 0.26 mg/kg po, which was found to be approximately 33 times more potent in vitro (rabbit platelet aggregation) and about 8 times more potent in vivo (murine lethality) than WEB2086. Compound **17** also exhibited a long duration of action in the dog (inhibition of PAF-induced whole blood aggregation ex vivo was maintained for >24 h following a single oral dose of 75 $\mu$g/kg) and was highly selective as a PAF antagonist, showing only weak affinity ($IC_{50}$ = 6600 nM) for the [$^3$H]nitrendipine binding site. As a result of its high oral potency, selectivity, and duration of action, UK-74,505 has been selected for clinical evaluation.

Platelet activating factor (PAF, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is an ether phospholipid which exhibits, in addition to potent platelet aggregating activity, a wide spectrum of biological activities elicited directly or via the release of other mediators.[1] Research studies have implicated PAF as a potential mediator in a number of pathophysiological conditions.[2] Particular interest has focussed on the role of PAF in bronchial hyperreactivity and the delayed bronchospasm following allergen challenge, and it is thought that PAF antagonists will be especially useful for controlling asthma,[3] although results from definitive clinical trials have yet to be reported. Other disease states in which PAF may play a role include inflammatory conditions usch as rhinitis, psoriasis and

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(1) (a) Cooper, K.; Parry, M. J. PAF Antagonists. *Annu. Rep. Med. Chem.* **1989**, *24*, 81–90, and references therein. (b) Hosford, D.; Braquet, P.; Antagonists of Platelet-Activating Factor: Chemistry, Pharmacology and Clinical Applications. *Prog. Med. Chem.* **1990**, *27*, 325–380.
(2) Snyder, F., Ed. *Platelet-Activating Factor and Related Lipid Mediators*; Plenum Press: New York, 1987.
(3) Chung, K. F.; Barnes, P. J. PAF Antagonists: Their Potential Therapeutic Role in Asthma. *Drugs* **1988**, *35*, 93–103.

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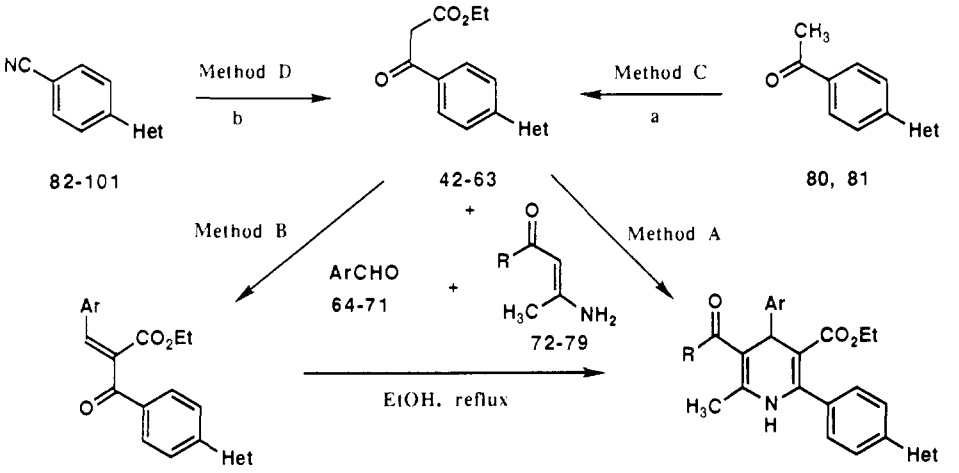
**Scheme I**[a]




39 Ar = 2-chlorophenyl
Het = 3,5-dimethyl-1,2,4-triazol-1-yl

40 Ar = benzo[d]dioxolan-4-yl
Het = imidazo[4,5-c]pyrid-1-yl

2-38 except 26, 31

[a] (a) NaH, $(EtO)_2CO$, THF, reflux; (b) $BrCH_2CO_2Et$, Zn, THF, reflux, then TFA, $H_2O$.

endotoxic shock, and ischaemic events such as stroke. The development of potent, specific PAF antagonists as pharmacological tools, and as drugs to treat these conditions is therefore of great interest.

In this paper we describe the synthesis, biological activity, and structure–activity relationships (SAR's) of a novel class of dihydropyridine PAF antagonists.[4] Our studies were initiated by reports of weak PAF antagonist activity in diltiazem and verapimil,[5] and therefore a limited number of our own calcium antagonists were evaluated.[6] It was discovered that dihydropyridine **1**[7] possessed potent PAF antagonist activity, displacing [$^3$H]PAF from rabbit washed platelets ($K_i$ = 12 nM) and inhibiting PAF-induced aggregation of rabbit washed platelets ($IC_{50}$ = 25 nM). A program of synthesis was therefore undertaken with the aim of identifying novel compounds in which the calcium antagonist activity was eliminated, and which were potent PAF antagonists in vitro and in vivo. We found that modifications of the 5-carboxylic ester and the imidazole-containing 2-position substituent of **1** were the most fruitful. Thus, 5-carboxamide analogues of **1** possessed greatly reduced calcium antagonist activity[8] while retaining potent PAF antagonist activity, and a phenyl link in the 2-position substituent could be introduced to reduce the flexibility of the side chain. We wish to report here the SAR's for a series of dihydropyridine 2-position analogues (**2–23**), which bear various heterocyclic groups linked through a phenyl spacer and, additionally, two shorter series of 4- and 5-position analogues (**24–38**). From this work we identified compound **17**,[9] which has been selected for progression into clinical studies.

## Chemistry

The general method shown in Scheme I was used to prepare the target dihdyropyridines (**2–38**), which have been divided into three groups for the purposes of discussion. Tables I–III detail the heterocyclic variants of the 2-position side chain, the 5-carboxyl derivatives, and the 4-aryl analogues, respectively. The synthesis proceeded in two steps, via the key intermediate keto esters (**42–63**) (Table IV), which were then reacted according to the Hantzsch synthesis[10] (method A) with a selection of aryl

(4) Recently, PAF antagonist activity in a different series of 1,4-dihydropyridines has been reported: (a) Sunkel, M.; de Casa-Juana, M. F.; Santos, M.; Gomez, M. M.; Villarroya, M.; Gonzalez-Morales, M. A.; Priego, J. G.; Ortega, M. P.; 4-Alkyl-1,4-dihydropyridines Derivatives as Specific PAF-acether Antagonists. *J. Med. Chem.* **1990**, *33*, 3205–3210. (b) Ortega, M. P.; Garcia, M. D. C.; Gijon, M. A.; de Casa-Juana, M. F.; Priego, J. G.; Sanchez, M.; Sunkel, M.; 1,4-Dihydropyridines, a New Class of Platelet-Activating Receptor Antagonists: In Vitro Pharmacologic Studies. *J. Pharm. Exp. Ther.* **1990**, *255*, 28–33. (c) Fernandez-Gallardo, S.; Ortega, M. P.; Priego, J. G.; de Casa-Juana, M. F.; Sunkel, M.; Sanchez, M. Pharmacological Actions of PCA 4248, a New Platelet-Activating Factor Receptor Antagonist: In Vivo Studies. *J. Pharm. Exp. Ther.* **1990**, *255*, 34.

(5) Valone, F. H. In *New Horizons in Platelet Activating Factor Research*; Lee, M. L., Winslow, C. M.; Eds.; Wiley: New York, 1985, 34.

(6) Cross, P. E.; Parry, M. J. Unpublished results.

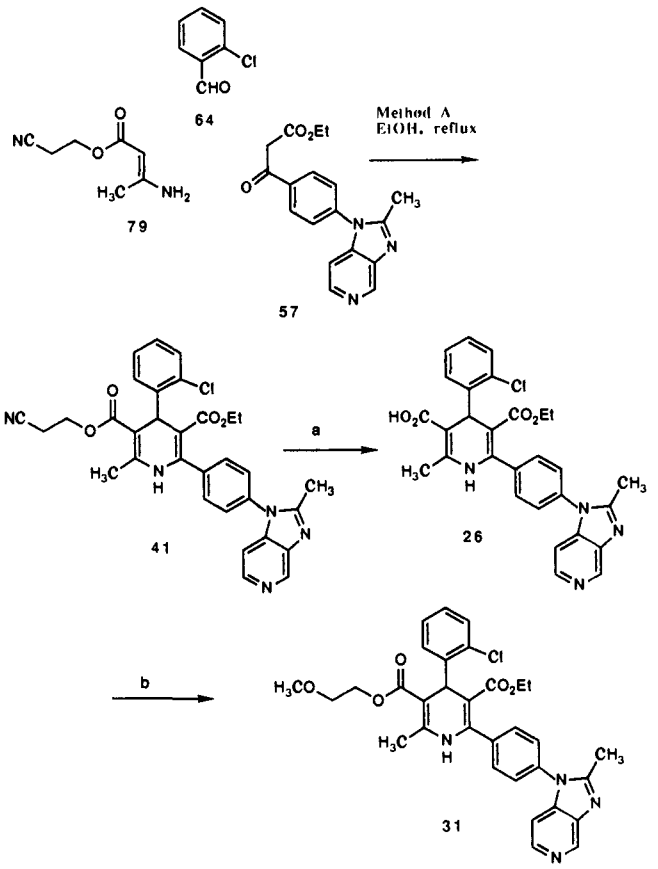
(7) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. Long-Acting Dihydropyridine Calcium Antagonists. 5. Synthesis and Structure-Activity Relationships for a Series of 2-[[(N-Substituted-heterocyclyl)ethoxy]-methyl]-1,4-dihydropyridine Calcium Antagonists. *J. Med. Chem.* **1990**, *35*, 1805–1811.

(8) (a) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. "Hantzsch-Type" Dihydropyridine Hypotensive Agents. 3. *J. Med. Chem.* **1974**, *17*, 956–965. (b) Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a New Class of Highly Active Calcium antagonists. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762–769.

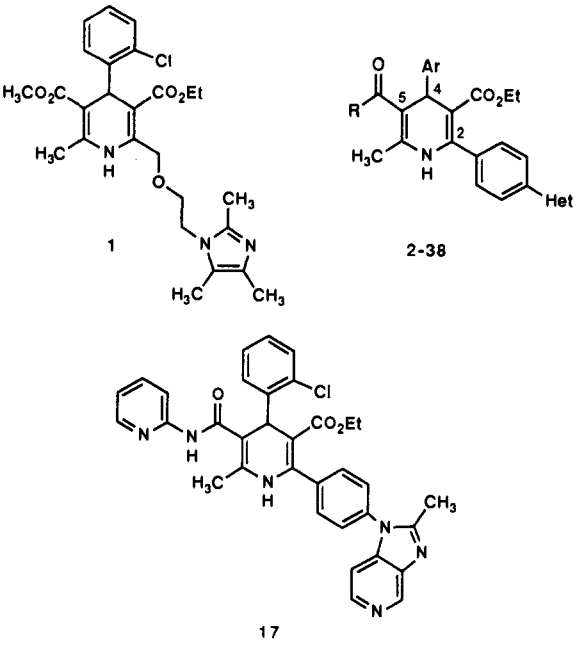
(9) (a) Parry, M. J.; Alabaster, V. A.; Cheeseman, H. E.; de Souza, R. N.; Keir, R. F. In Vitro and In Vivo Profile of UK-74,505; a Novel, Highly Potent and Selective Dihydropyridine PAF Antagonist. "Advances in Platelet-Activating Factor Research", IUPHAR Satellite Meeting, Paris, June 28, 29th, 1990: published in *J. Lipid Mediators* **1990**, *2*, 181. (b) Cooper, K.; Fray, M. J.; Richardson, K.; Steele, J. UK-74,505, a Novel and Highly Potent Dihydropyridine PAF Antagonist: Synthesis and Structure-activity Relationships. "Advances in Platelet-Activating Factor Research", IUPHAR Satellite Meeting, Paris, June 28, 29th, 1990: published in *J. Lipid Mediators* **1990**, *2*, 212. (c) Alabaster, V. A.; Keir, R. F.; Parry, M. J.; de Souza, R. N. In *New Drugs for Asthma Therapy*; Anderson, G. P., Chapman, I. D., Morley, J., Eds.; (*Agents Actions Suppl. 34*, 221) Birkhauser Verlag: Basel, 1991.

(10) Kuthan, J.; Kurfurst, A. Development in Dihydropyridine Chemistry. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191–261.

**Scheme II**[a]



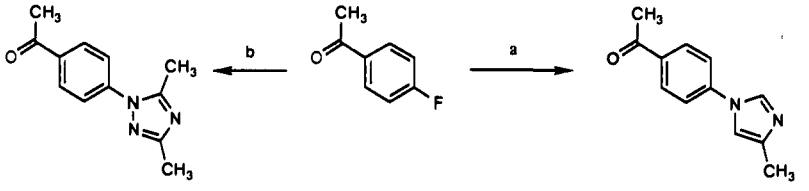

[a] (a) NaOH, dioxane, $H_2O$, then HCl; (b) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, $CH_2Cl_2$, then 2-methoxyethanol.




aldehydes (**64–71**) (Table V) and aminocrotonamides or aminocrotonates (**72–79**) (Table VI).

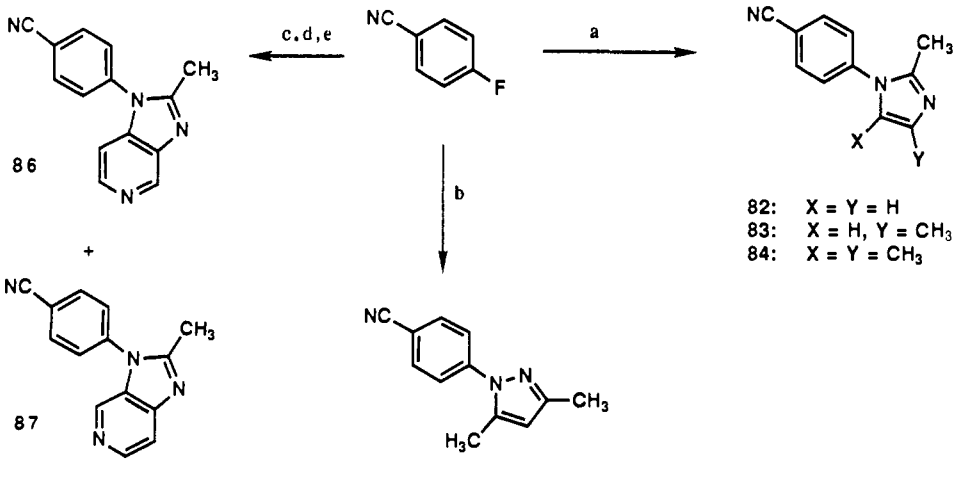
There were four exceptions to the general reaction scheme. For the synthesis of compounds **12** and **34** (Scheme I), the Hantzsch reaction was performed in two steps (method B) via the intermediate Knoevenagel products **39** and **40**, which were then reacted with enamine component **72**. The syntheses of carboxylic acid **26** and ester **31** are shown in Scheme II. Thus, the standard Hantzsch reaction was used to prepare the cyanoethyl ester **41**, which was cleaved by sodium hydroxide in aqueous

**Scheme III**[a]



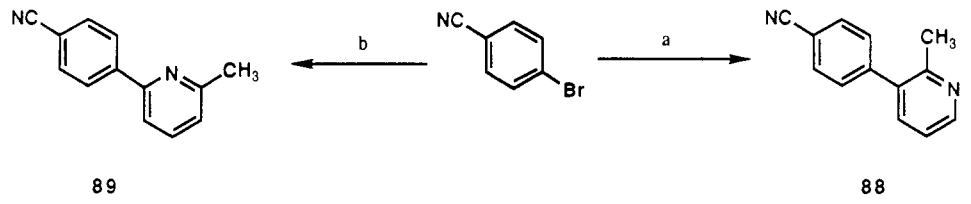

[a] (a) 4-methylimidazole, $K_2CO_3$, DMF, reflux; (b) 3,5-dimethyltriazole, $K_2CO_3$, DMF, reflux.

**Scheme IV**[a]




[a] (a) 2-methylimidazole or 2,4-dimethylimidazole or 2,4,5-trimethylimidazole, $K_2CO_3$, DMF, reflux; (b) 2,4-dimethylpyrazole, $K_2CO_3$, DMF, reflux; (c) imidazo[4,5-c]pyridine 5-oxide, $K_2CO_3$, DMF; (d) Fe (powder), HOAc, 100 °C; (e) column chromatography.

**Scheme V**[a]




89 88

[a] (a) *t*-BuLi, THF, $ZnCl_2$, $Pd(PPh_3)_4$, 3-bromo-2-methylpyridine; (b) *t*-BuLi, THF, $ZnCl_2$, $Pd(PPh_3)_4$, 2-bromo-6-methylpyridine.

dioxane to give the acid **26**. Activation of **26** was achieved by forming the mixed anhydride in situ with 2,4,6-triisopropylbenzenesulfonyl chloride[11] in the presence of *N,N*-dimethyl-4-aminopyridine, followed by reaction with 2-methoxyethanol to give compound **31**. As may be seen from Tables I–III, yields in the Hantzsch reaction were often low, and also varied considerably from one example to another. This variation was usually a reflection of the difficulty in obtaining analytically pure samples, since the dihydropyridines for the most part could not be crystallized, and had to be precipitated from solution or triturated with a solvent, which usually resulted in a considerable loss of material.

The heterocyclic-substituted β-keto esters (**42–63**) (Scheme I) were either prepared from the acetophenones, **80** and **81** by a Claisen condensation with diethyl carbonate using sodium hydride as base (method C) or from the benzonitriles **82–101** using a modified Blaise reaction (method D).[12] Due to difficulties in their purification and crystallization, the β-keto esters were only characterized by proton NMR spectroscopy and then used directly for the Hantzsch reactions.

The intermediate acetophenones **80** and **81** and benzonitriles **82–101** were prepared from a variety of precursors, as shown in Schemes III–VII.

One very useful strategy for the synthesis of the intermediates **80–86** was by nucleophilic displacement of fluoride from *p*-fluoroacetophenone (Scheme III) or *p*-fluorobenzonitrile using the appropriate heterocycle (Scheme IV) in the presence of potassium carbonate in dimethylformamide.[13] This type of reaction was found to be sensitive to steric effects, so that compounds **80**, **81**, and **83** were obtained selectively via reaction of the less hindered nitrogen atom of the nucleophile. For the synthesis of nitriles **86** and **87**, 2-methylimidazo[4,5-*c*]pyridine was protected as the pyridine 5-oxide, so that subsequent arylation was thereby directed equally onto N-1 and N-3. Finally, the mixture of regioisomers was deoxygenated using iron powder in acetic acid, and the isomers were separated by chromatography. The identity of **86** was confirmed by unambiguous synthesis using a different route (Scheme VI).

For the carbon-linked pyridine derivatives **86** and **89**, *p*-bromobenzonitrile was lithiated, converted to the arylzinc reagent, and then coupled with 3-bromo-2-methylpyridine or 2-bromo-6-methylpyridine under palladium (0) catalysis in tetrahydrofuran at reflux (Scheme V).[14]

Another approach, used for the benzonitriles **86** and **90–97**, was to build up the required heterocyclic rings from *p*-cyanoaniline (Scheme VI). For the 3,5-dimethyltriazole **90**, *p*-cyanoaniline was first acetylated and then converted to the thioacetanilide[15] derivative, followed by condensation with hydrazine and finally ring closure with triethyl orthoacetate.[16] Similar three-step routes were employed for the synthesis of imidazopyridine derivatives **86** and **91–96**. Thus *p*-cyanoaniline reacted with 2-chloro-3-nitropyridine to afford the aminonitropyridine derivative, which was then reduced to the diaminopyridine and cyclized using acetic anhydride to give imidazo[4,5-*b*]pyridine **91**.[17] Alternatively, starting with 4-chloro-3-nitropyridine[18] or 4-chloro-2,6-dimethyl-3-nitropyridine,[19] a similar sequence gave imidazo[4,5-*c*]pyridines **86** and **96**. The intermediates **92–95** were also obtained by cyclization of the diaminopyridine used for the preparation of **86**. For these compounds, propionic anhydride, trifluoroacetaldehyde/sodium metabisulfite,[20] valeric anhydride, and carbonyl diimidazole replaced acetic anhydride. The purine **97** was prepared in four steps starting with the condensation of *p*-cyanoaniline and 5-amino-4,6-dichloropyrimidine. Treatment of the resulting adduct with acetic anhydride at reflux led to the formation of the triacetyl derivative **102**, which was cyclized by heating in vacuo at 240 °C.

(11) (a) Lohrmann, R.; Khorana, H. G.; Studies on Polynucelotides. LII. The Use of 2,4,6-Triisopropylbenzenesulfonyl Chloride for the Synthesis of Internucleotide Bonds. *J. Am. Chem. Soc.* **1966**, *88*, 829–833. (b) Itakura, K.; Katagari, N.; Bahl, C. P.; Wightman, R. H.; Narang, S. A. Improved Tri-ester Approach for the Synthesis of Pentadecathymidylic Acid. *J. Am. Chem. Soc.* **1975**, *97*, 7327–7332.

(12) Hannick, S. M.; Kishi, Y. Improved Procedure for the Blaise Reaction: A Short, Practical Route to the Key Intermediates of the Saxitoxin Synthesis. *J. Org. Chem.* **1983**, *48*, 3833–3835.

(13) Uno, T.; Takamatsu, M.; Iuchi, K.; Tsukamoto, G. *European Patent*, 115,049, 1984.

(14) (a) Yamamoto, Y.; Azuma, Y.; Mitoh, H. General Method for Synthesis of Bipyridines: Palladium Catalysed Cross-coupling Reaction of Trimethylstannyl-pyridines with Bromopyridines. *Synthesis*, **1986**, 564–565. (b) Ishikura, M.; Kamada, M.; Terashima, M. An Efficient Synthesis of 3-Heteroarylpyridines Via Diethyl-(3-pyridyl)borane. *Synthesis* **1984**, 936–938. (c) Negishi, E.; Luo, F-T.; Frisbee, R.; Matsushita, H. A Regiospecific Synthesis of Carbosubstituted Heteroaromatic Derivatives Via Palladium-Catalysed Cross Coupling. *Heterocycles* **1982**, *18*, 117–122.

(15) Mizuno, Y.; Adachi, K.; Benzothiazoles. III. Synthesis of 2-Methylbenzothiazoles with Electron-attracting Groups. *J. Pharm. Soc. Jpn* **1952**, *72*, 739–742. *Chem. Abstr.* **48**, 2688g.

(16) (a) Hester, J. B.; Rudzik, A. D.; Kamdar, B. V.; 6-Phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines Which Have Central Nervous Depressant Activity. *J. Med. Chem.* **1971**, *14*, 1078–1081. (b) Meguro, K.; Tawada, H.; Miyano, H.; Sato, Y.; Kuwada, Y.; Heterocycles. VI. Synthesis of 4*H*-*s*-Triazolo-[4,3-*a*][1,4]benzodiazepines, Novel Tricyclic Psychosedatives. *Chem. Pharm. Bull.* **1973**, *21*, 2382–2390.

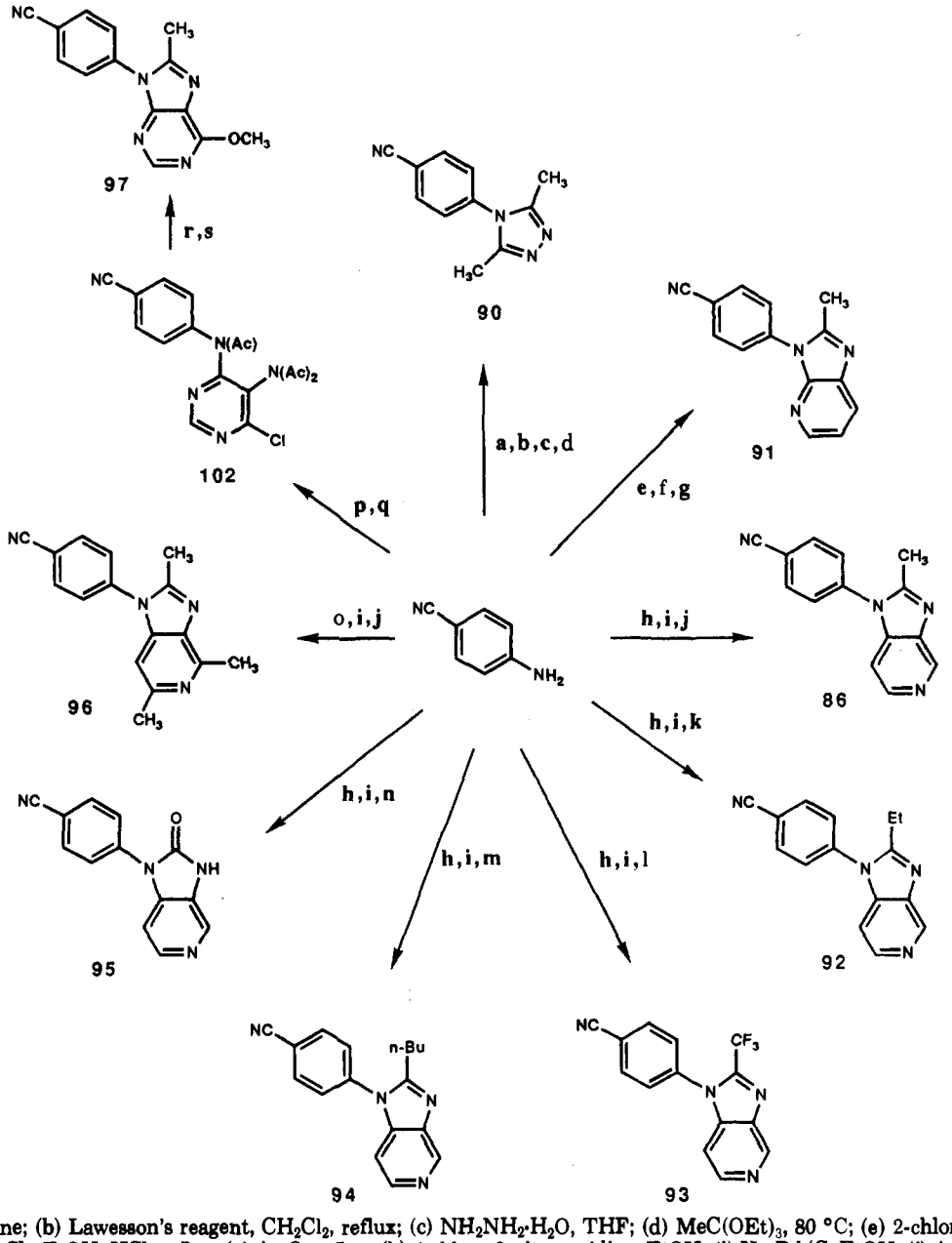
(17) Rousseau, R. J.; Robins, R. K. The Synthesis of Various Chloroimidazo[4,5-c]pyridines and Related Derivatives. *J. Heterocyl. Chem.* **1965**, *2*, 196–201.

(18) (a) Ducrocq, C.; Bisagni, E.; Rivalle, C.; Mispelter, J.; N-1 Substitution of 4-Arylamino-3-nitropyridines by a Heterocyclic Ring-opening Reaction. *J. Chem. Soc. Perkin Trans. 1* **1979**, 135–137. (b) Delarge, J.; Lapiere, C. L. Syntheses Starting From 4-Hydroxy-3-nitropyridine. *Pharm. Acta. Helv.* **1975**, *50*, 188–191.

(19) Kato, T.; Hayashi, H.; Anzai, T. Synthesis of Methylpyridine Derivatives. XXIII. Chlorination of 2,6-Lutidine Derivatives. *Yakugaku Zasshi* **1967**, *87*, 387–389. *Chem. Abstr.* **67**, 64211k.

(20) Ridley, H. F.; Spickett, R. G. W.; Timmis, G. M.; A New Synthesis of Benzimidazoles and Aza-analogues. *J. Heterocyl. Chem.* **1965**, *2*, 453–456.

**Scheme VI**[a]




[a] (a) $Ac_2O$, pyridine; (b) Lawesson's reagent, $CH_2Cl_2$, reflux; (c) $NH_2NH_2 \cdot H_2O$, THF; (d) $MeC(OEt)_3$, 80 °C; (e) 2-chloro-3-nitropyridine, EtOH, reflux; (f) $SnCl_2$, EtOH, HCl, reflux; (g) $Ac_2O$, reflux; (h) 4-chloro-3-nitropyridine, EtOH; (i) $H_2$, Pd/C, EtOH; (j) $Ac_2O$, HOAc, reflux; (k) $(EtCO)_2O$, $EtCO_2H$; (l) $CF_3CHO \cdot H_2O$, $Na_2S_2O_5$, dimethylacetamide, reflux; (m) $(n\text{-}BuCO)_2O$, $n\text{-}BuCO_2H$; (n) carbonyldiimidazole, $CH_2Cl_2$; (o) 4-chloro-2,6-dimethyl-3-nitropyridine, EtOH; (p) 5-amino-4,6-dichloropyrimidine, *n*-BuOH, reflux; (q) $Ac_2O$, reflux; (r) 240 °C, 50 mmHg; (s) NaOMe, MeOH, reflux.

Finally, displacement of the chloro substituent by methoxide gave **97**.[21,22]

The syntheses of the four remaining benzonitriles **98–101** were achieved via the common intermediate bromo ketone **103** (Scheme VII). Thus *p*-cyanobenzaldehyde was first condensed with nitroethane, followed by reduction and in situ Nef reaction to afford *p*-cyanophenylacetone,[23] which was then brominated regioselectively. Treatment of **103** with formamide, thioacetamide, 2-aminopyridine, or 2-aminothiazole completed the synthesis of heterocycles **98–101**.

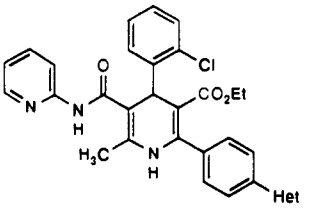
## Results and Discussion

The dihydropyridines **2–38** were first evaluated as PAF antagonists in vitro using an assay involving rabbit washed platelets, and activity in vivo was demonstrated by the ability to protect mice from the lethal effects of an injection of PAF (see Experimental Section).

The SAR's of the 2-position analogues (Table I) will be discussed first. Consideration of the in vitro results for compounds **2–12** suggest that potent PAF antagonist activity can be achieved with a wide range of monocyclic heterocycles. Thus pyridine **6** possessed increased potency compared with the imidazoles **2–4**, which were similar in potency. Interestingly, transposing the methyl group and nitrogen atom in the pyridyl analogue **6** (to give **7**) abol-

(21) Albert, A.; Brown, D. J. Purine Studies. Part 1. Stability to Acid and Alkali. Solubility. Ionization. Comparison with Pteridines. *J. Chem. Soc.* **1954**, 2060–2071.
(22) Huber, G.; Zur Darstellung Von 6-Alkoxy-purinen. *Chem. Ber.* **1957**, *90*, 698–700.
(23) Ferreira, A. B. B.; Salisbury, K.; Substituent Effects in the Di-π-methane Rearrangement of 1,1-Dicyano-2-methyl-3-phenylpropene. *J. Chem. Soc. Perkin Trans. 2*, 1978, 995–1001.

**Table I.** Physicochemical Data and Yields of Dihydropyridines (2 position analogues)



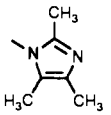
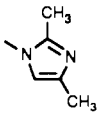
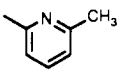
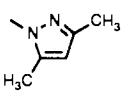
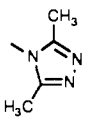
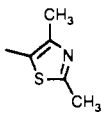
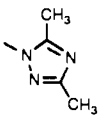
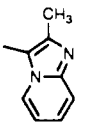
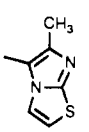
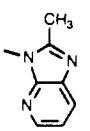
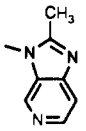
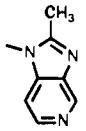
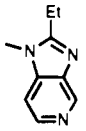
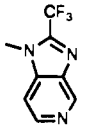
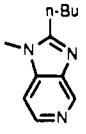
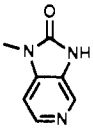
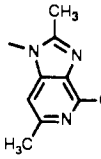
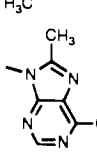
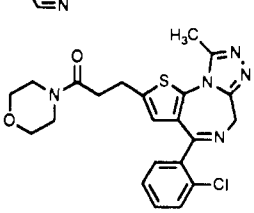

| compd | het | mp (°C) | yield[a] (%) | formula | anal. | $IC_{50}$[b] (nM) | $ED_{50}$[c] (mg/kg) |
|---|---|---|---|---|---|---|---|
| 2 |  | 188–193 | 2 | $C_{33}H_{32}ClN_5O_3$ | C,H,N | 15 | 10.5 |
| 3 |  | 232–236 | 7 | $C_{31}H_{28}ClN_5O_3 \cdot 0.5H_2O$ | C,H,N | 25 | 22 |
| 4 |  | 221–225 | 14 | $C_{32}H_{30}ClN_5O_3$ | C,H,N | 13 | 3 |
| 5 |  | 229–234 | 15 | $C_{31}H_{28}ClN_5O_3 \cdot 0.25EtOAc$ | C,H,N | 580 | NT[d] |
| 6 |  | 188–192 | 9 | $C_{33}H_{29}ClN_4O_3$ | C,H,N | 1.8 | 3.7 |
| 7 |  | 201–203 | 15 | $C_{33}H_{29}ClN_4O_3$ | C,H,N | >10000 | NT |
| 8 |  | 161–163 | 4 | $C_{32}H_{30}ClN_5O_3$ | C,H,N | >10000 | NT |
| 9 |  | 188–189 | 43 | $C_{30}H_{34}ClN_5O_3 \cdot 0.5H_2O$ | C,H,N | 12 | 34 |
| 10 |  | 215 | 8 | $C_{32}H_{29}ClN_4O_3S \cdot 0.5H_2O$ | C,H,N | 10 | 7.4 |
| 11 |  | 176–179 | 5 | $C_{31}H_{27}ClN_4O_4 \cdot 0.5Et_2O$ | C,H,N | 200 | NT |
| 12 |  | 130 | 6[e] | $C_{30}H_{34}ClN_5O_3$ | C,H,N | 3000 | NT |
| 13 |  | 190–191 | 15 | $C_{35}H_{30}ClN_5O_3 \cdot 0.75H_2O$ | C,H,N | 2.1 | 92 |
| 14 |  | 164–166 | 6 | $C_{33}H_{28}ClN_5O_3S$ | C,H,N | 5 | 5.4 |
| 15 |  | 197–199 | 10 | $C_{34}H_{29}ClN_6O_3 \cdot 0.5H_2O$ | C,H,N | 28 | 23 |

Table I (Continued)

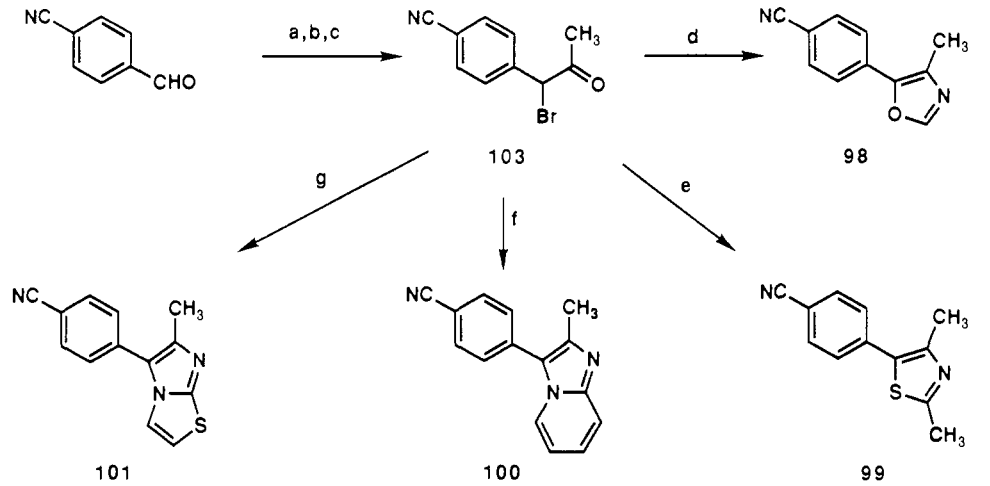
| compd | het | mp (°C) | yield[a] (%) | formula | anal. | $IC_{50}$[b] (nM) | $ED_{50}$[c] (mg/kg) |
|---|---|---|---|---|---|---|---|
| 16 |  | 238–240 | 13 | $C_{34}H_{29}ClN_6O_3$ | C,H,N | 22 | 16 |
| 17 |  | 226–228 | 31 | $C_{34}H_{29}ClN_6O_3$ | C,H,N | 4.3 ± 0.73[f] | 0.26 ± 0.03[g] |
| 18 |  | 255–257 | 13 | $C_{35}H_{31}ClN_6O_3 \cdot 0.5H_2O$ | C,H,N | 3.4 | 10.5 |
| 19 |  | 135–138 | 7 | $C_{34}H_{26}ClF_3N_6O_3$ | *h* | 30 | 25 |
| 20 |  | 202–204 | 18 | $C_{37}H_{35}ClN_6O_3 \cdot 0.25IPA^i \cdot 0.5H_2O$ | C,H,N | 190 | NT |
| 21 |  | 196–198 | 18 | $C_{33}H_{27}ClN_6O_4 \cdot H_2O$ | C,H[j] | 1400 | NT |
| 22 |  | 196–198 | 21 | $C_{36}H_{33}ClN_6O_3 \cdot H_2O$ | C,H,N | 5.9 | 0.3 |
| 23 |  | 220–222 | 27 | $C_{34}H_{30}ClN_7O_4 \cdot 0.5H_2O$ | C,H,N | 270 | NT |
| WEB2086[k] |  | | | | | 146 ± 24.7[l] | 2.03 ± 0.2[m] |

[a] Yields refer to those obtained in the Hantzsch synthesis (method A) unless stated otherwise. [b] Single determination, unless stated otherwise, with $IC_{50}$s normalized to compound 1 = 25 nM. A difference of less than 2-fold in potency should not be regarded as significant. [c] Average of two determinations, unless stated otherwise. [d] NT = not tested. [e] Method B. [f] n = 11. [g] n = 6. [h] HRMS m/z $M^+$ = 658.17042, requires 658.170701. [i] IPA = 2-propanol. [j] Found N = 12.99, requires N = 13.44%, HRMS m/z $M^+$ 606.178231, requires 606.178231. [k] Prepared by the method of Weber, K-H.; Walter, G.; Harreus, A.; Casals-Stenzel, J.; Muacevic, G.; Troger, W.; D.E. 3,502,392, 1986. [l] n = 12. [m] n = 5.

ished activity, and moving the 2-methyl substituent in **3** to the 4-position of the imidazole ring (to give **5**) also markedly lowered potency. The pyrazole **8**, like the pyridine **7**, was inactive, whereas the dimethyltriazole **9** possessed very similar in vitro potency to the imidazole **4**. In the series **10–12**, heteroatom substitution at the 5-position of the ring led to varying potency with the more lipophilic thiazole **10** being the best. The in vivo activity, however, of monocyclic analogues **2–12** was in general no better and often worse than the thienotriazolodiazepine WEB2086 (see Table I), despite better in vitro performance.

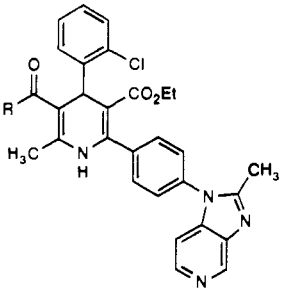
The SAR's of further heterocyclic analogues were probed by the derivatives **13–23** which have a second ring fused onto the imidazole. Compounds **13** and **14** were seven times and three times more potent, respectively, than the imidazole **2**, whereas, of the three imidazopyridines (**15–17**), the 1-substituted imidazo[4,5–c]pyridine **17** stood out as the most potent in vitro. Additionally, from the in vivo results with compounds **2–17**, it was clear that compound **17** also possessed outstanding oral potency in the mouse ($ED_{50}$ = 0.26 ± 0.03 mg/kg), and therefore the effect of substituents on the imidazopyridine was investigated. Although ethyl (compound **18**) may replace methyl with no loss of in vitro activity, oral activity was dramatically inferior, and furthermore, neither larger lipophilic groups, as in compounds **19** and **20**, nor a 2-carbonyl group, as in **21**, were well tolerated. The addition of two methyl groups to the pyridine ring gave compound **22**, which was virtually

**Scheme VII**[a]




[a] (a) $EtNO_2$, $Et_3N$, $n$-$Bu_3N$, EtOH, reflux; (b) Fe (powder), $FeCl_3$, HCl, $H_2O$, EtOH, reflux; (c) $Br_2$, $CH_2Cl_2$; (d) formamide, 120 °C; (e) thioacetamide, pyridine, toluene, 100 °C; (f) 2-aminopyridine, EtOH, reflux; (g) 2-aminothiazole, $Et_3N$, 1-butanol, reflux.

Table II. Physicochemical Data and Yields of Dihydropyridines (5 position analogues)




| compd | Het | mp (°C) | yield[a] (%) | formula | anal. | $IC_{50}$[b] (nM) | $ED_{50}$[c] (mg/kg) |
|---|---|---|---|---|---|---|---|
| **24** | $NH_2$ | 200–202 | 14 | $C_{29}H_{26}ClN_5O_3 \cdot H_2O$ | C,H[d] | 5.6 | 1.0 |
| **25** | $t$-BuNH | 156–159 | 15 | $C_{33}H_{34}ClN_5O_3$ | C,H,N | 3.2 | 2.1 |
| **26** | OH | 206–208 | 96 | $C_{29}H_{25}ClN_4O_4 \cdot 0.66H_2O$ | C,H,N | 14 | 4.7 |
| **27** | MeO | 226–228 | 46 | $C_{30}H_{27}ClN_4O_4$ | C,H,N | 1.6 | 1.5 |
| **28** | c-hexO | 164–166 | 20 | $C_{35}H_{35}ClN_4O_4$ | C,H,N | 2 | 4.7 |
| **29** | $t$-BuO | 194–197 | 36 | $C_{33}H_{33}ClN_4O_4 \cdot 0.25H_2O$ | C,H,N | 1.3 | 2.0 |
| **30** | $PhCH_2O$ | 114–120 | 27 | $C_{36}H_{31}ClN_4O_4 \cdot 0.5H_2O$ | C,H,N | 2.5 | 2.0 |
| **31** | $MeOCH_2CH_2O$ | 195–196 | 34 | $C_{32}H_{31}ClN_4O_5$ | C,H,N | 0.5 | 0.16 |

[a] Yields refer to those obtained in the Hantzsch synthesis (method A) except compounds **26** and **31**. [b,c] See Table I. [d] HRMS $m/z$ $M^+$ = 527.171343, requires 527.172417.

equipotent with **17**, whereas the introduction of a further heteroatom as in the purine **23** led to a much weaker antagonist.

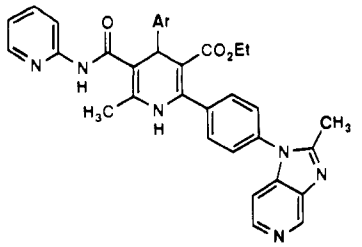
The excellent in vitro and in vivo activity of **17** was then followed up by turning our attention to a short series of analogues in which the 5-carboxyl substituent was varied (Table II). Generally high in vitro potency was achieved by a wide variety of polar, bulky and lipophilic groups in this position, as illustrated by the primary amide **24** and the acid **26**, the cyclohexyl and *tert*-butyl esters **28** and **29**, and the benzyl ester **30**, respectively. Although most of the compounds also possessed potent in vivo activity, only the methoxyethyl ester **31** approached the activity of the pyridyl amide **17**.

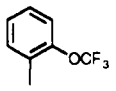
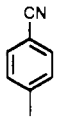
A further series of modifications (compounds **32–38**, Table III) was used to explore the SAR of the 4-position substituent. Again a wide variety of groups, both substituted phenyls and heterocycles, was tolerated in vitro, but only the close analogue of **17**, compound **32**, possessed equivalent in vitro and in vivo potency.

Compound **17** was further profiled by measuring its duration of action in conscious dogs. In this experiment, test compound was administered orally and blood samples were withdrawn at various time intervals and then treated with the minimum concentration of PAF required to cause irreversible aggregation. The concentration of PAF (30–50 nM) required was established for each dog by aggregating control samples prior to dosing. Using this protocol, compound **17**, at a dose of 75 μg/kg po, produced complete inhibition of PAF-induced aggregation for greater than 14 h, and even at the 24-h time point, a 32 ± 5% inhibition of aggregation was still observed. In a similar experiment, WEB2086 (1 mg/kg, po) exhibited a much shorter duration of action, completely inhibiting whole blood aggregation ex vivo at the 2-h time point, but gave only 10% inhibition after 6 h. Thus, compound **17** was approximately 33 times more potent than WEB2086 in vitro and about 8 times more potent in the mouse lethality test, and more importantly, exhibited a much longer duration of action in the dog after oral dosing at less than a tenth of the dose.

Since compound **17** is a dihydropyridine, it was also important to establish its selectivity for the PAF receptor over the calcium channel and other receptors. Compound **17** was found to be highly selective, since it only displaced [$^3$H]-labeled nitrendipine, diltiazem, and desmethoxyverapamil from bovine frontal cortex membranes at high concentrations ($IC_{50}$ = 6.6 ± 1.4 μM, 6.8 ± 3.3 μM, and >10 μM, respectively), some 1000 times higher than that re-

Table III. Physicochemical Data and Yields of Dihydropyridines (4 position analogues)



| compd | Het | mp | yield[a] (%) | formula | anal. | $IC_{50}$[b] (nM) | $ED_{50}$[c] (mg/kg) |
|---|---|---|---|---|---|---|---|
| 32 |  | 235–238 | 4 | $C_{35}H_{29}F_3N_6O_4 \cdot H_2O$ | C,H,N | 2.3 | 0.2 |
| 33 |  | 246–250 | 5 | $C_{35}H_{29}N_7O_3$ | d | 25 | 1.2 |
| 34 |  | 195–199 | 4[e] | $C_{35}H_{30}N_6O_5 \cdot 1.5H_2O$ | C,H,N | 3.2 | 0.5 |
| 35 |  | 230–238 | 20 | $C_{36}H_{30}N_6O_3S \cdot 0.5H_2O$ | C,H,N | 3.1 | 0.6 |
| 36 |  | 240–250 | 21 | $C_{33}H_{29}N_7O_3 \cdot 0.5H_2O$ | C,H,N | 14 | 4.1 |
| 37 |  | 210–215 | 25 | $C_{33}H_{29}N_7O_3 \cdot 1.25H_2O$ | C,H,N | 33 | 16 |
| 38 |  | 235–245 | 26 | $C_{33}H_{28}ClN_7O_3 \cdot 0.5H_2O$ | C,H,N | 13 | 13 |

[a] Yields refer to those obtained in the Hantzsch synthesis (method A) unless stated otherwise. [b,c] See Table I. [d] HRMS $m/z$ $M^+$ = 595.23288, requires 595.233188. [e] Method B.

quired for PAF antagonism. Furthermore, the dihydropyridine receptor binding of **17** was not expressed functionally, since, in the conscious dog, a dose of 5 mg/kg po (over 60 times that required to inhibit completely whole blood aggregation ex vivo for >14 h) produced no changes in either heart rate or blood pressure. In addition, compound **17** (100 $\mu$M) did not inhibit platelet aggregation induced by thrombin, arachidonic acid, collagen, U-46619, or ADP, nor radioligand binding to adenosine ($A_1$), dopamine ($D_2$), $5HT_2$, muscarinic, or $\alpha_1$, $\alpha_2$, and $\beta$ adrenergic receptors (bovine frontal cortex membranes) at 10 $\mu$M, thus demonstrating high selectivity for the PAF receptor.

In summary, this paper describes the discovery of a new class of very potent dihydropyridine PAF antagonists. From this work, compound **17** (UK-74,505) was selected for progression into clinical studies because of its high oral potency, selectivity, and long duration of action.

## Experimental Section

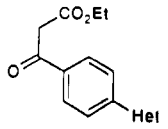
**Chemistry.** Melting points were determined using a Buchi apparatus in glass capilliary tubes or a Kofler hot stage apparatus, and are uncorrected. Spectroscopic data were recorded on Perkin-Elmer 983 (IR), VG7070F (EI) and VG7070E (FAB)(MS), and Bruker WM250 and Nicolet QE300 (NMR) instruments and were consistent with the assigned structures. Column chromatography was accomplished on Kieselgel 60, (230–400 mesh) from E. Merck, Darmstadt. Kieselgel 60 $F_{254}$ plates from E. Merck were used for TLC, and compounds were visualized with UV light or chloroplatinic acid/potassium iodide solution. Where analyses are indicated only by the symbols of the elements, results obtained were within ±0.4% of the theoretical values. In cases where compounds were analyzed as hydrates, the presence of water was evident in the enhanced peak due to water in the proton NMR spectra. The purity of compounds was carefully assessed using analytical TLC and proton NMR (300 MHz), and the latter technique was used to calculate the amount of solvent in solvated samples. In multistep sequences, the purity and structure of intermediates were verified spectroscopically by proton NMR.

**Method A. Example of the Hantzsch Synthesis. 4-(2-Chlorophenyl)-1,4-dihydro-3-(ethoxycarbonyl)-6-methyl-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-5-[*N*-(2-pyridyl)carbamoyl]pyridine (17).**

A mixture of ethyl 4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)-benzoylacetate (**57**) (475 mg, 1.47 mmol), *N*-(2-pyridyl)-3-aminocrotonamide (**72**)[24] (260 mg, 1.47 mmol), and 2-chlorobenzaldehyde (207 mg, 1.47 mmol) in absolute ethanol (8 mL)

(24) Wrotek, J.; Rutkiewicz, A. *Polish Patent*, 79,056, 1975. *Chem. Abstr.* 1976, *85*, 94228k.
(25) Kato, T.; Noda, M.; Studies on Ketene and its Derivatives. LXXVI. Reactions of Aceto-acetamide and β-Aminocrotonamide with β-Diketone, β-Keto-aldehyde and Related Compounds. *Chem. Pharm. Bull.* 1976, *24*, 303–309.
(26) Bossert, F.; Wehinger, E.; Heise, A.; Meyer, H.; Kazda, S.; Stoepel, K.; Towart, R.; Vater, W.; Schlossmann, K. *Ger. Offen.* 2,658,183, 1978. *Chem. Abstr.* 1978, *89*, 146772.
(27) Grohe, K.; Heitzer, H. Cyclo-acylation of Enamines. II. Synthesis and Reactions of 2,4-Dichloropyrimidine-5-carboxylic Acid Esters. *J. Liebigs. Ann. Chem.*, 1973, 1025–1035.
(28) Buckler, R. T.; Hartzler, H. E.; Phillips, B. M. Anti-inflammatory β-Arylamidoacrylic Acids. *J. Med. Chem.*, 1975, *18*, 509–513.

Table IV. $^1$H NMR Data and Yields for Ethyl [4′-(Heterocyclic substituted)benzoyl]acetates



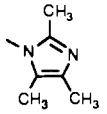
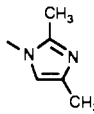
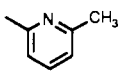
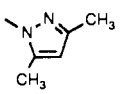
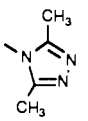
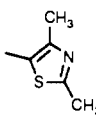
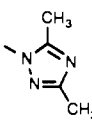
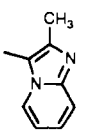
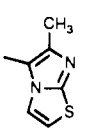
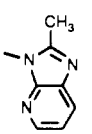
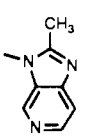
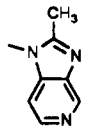
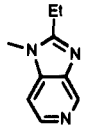
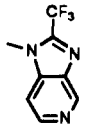
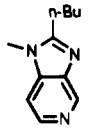
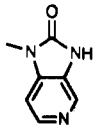
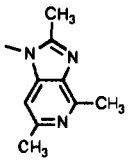
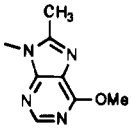
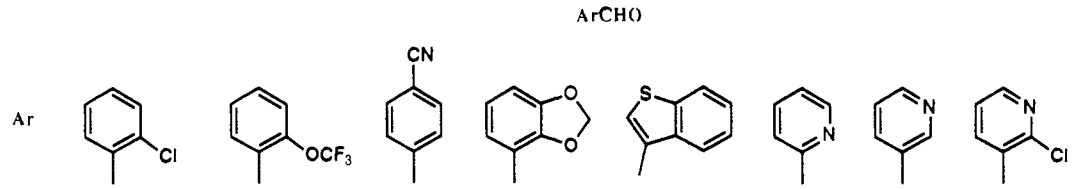

| compd | Het | yield[a] (%) | $^1$H NMR[b] (300 MHz, $CDCl_3$) |
|---|---|---|---|
| 42 |  | 31 | 1.30 (3 H, t, $J$ = 6 Hz), 1.97 (3 H, s), 2.20 (3 H, s), 2.25 (3 H, s), 4.05 (2 H, s), 4.25 (2 H, q, $J$ = 6 Hz), 7.34 (2 H, d, $J$ = 9 Hz), 8.13 (2 H, d, $J$ = 9 Hz) |
| 43 |  | 69 | 1.30 (3 H, t, $J$ = 6 Hz), 2.43 (3 H, s), 4.06 (2 H, s), 4.25 (2 H, q, $J$ = 6 Hz), 7.07 (1 H, s), 7.09 (1 H, s), 7.47 (2 H, d, $J$ = 9 Hz), 8.11 (2 H, d, $J$ = 9 Hz) |
| 44 |  | 53[c] | 1.30 (3 H, t, $J$ = 6 Hz), 2.27 (3 H, s), 2.41 (3 H, s), 4.05 (2 H, s), 4.25 (2 H, q, $J$ = 6 Hz), 6.80 (1 H, s), 7.44 (2 H, d, $J$ = 9 Hz), 8.10 (2 H, d, $J$ = 9 Hz) |
| 45 |  | 15 | 1.30 (3 H, t, $J$ = 6 Hz), 2.33 (3 H, s), 4.05 (2 H, s), 4.25 (2 H, q, $J$ = 6 Hz), 7.11 (1 H, s), 7.52 (2 H, d, $J$ = 9 Hz), 7.90 (1 H, s), 8.11 (2 H, d, $J$ = 9 Hz) |
| 46 |  | 49 | 1.30 (3 H, t, $J$ = 6 Hz), 2.54 (3 H, s), 4.06 (2 H, s), 4.25 (2 H, q, $J$ = 6 Hz), 7.25 (1 H, m), 7.45 (3 H, m), 8.08 (2 H, d, $J$ = 9 Hz), 8.67 (1 H, m) |
| 47 |  | 60 | 1.29 (3 H, t, $J$ = 6 Hz), 2.68 (3 H, s), 4.05 (2 H, s), 4.26 (2 H, q, $J$ = 6 Hz), 7.19 (1 H, d, $J$ = 8 Hz), 7.62 (1 H, d, $J$ = 8 Hz), 7.71 (1 H, t, $J$ = 8 Hz), 8.06 (2 H, d, $J$ = 8 Hz), 8.14 (2 H, d, $J$ = 8 Hz) |
| 48 |  | 84 | 1.29 (3 H, t, $J$ = 7 Hz), 2.32 (3 H, s), 2.43 (3 H, s), 4.04 (2 H, s), 4.25 (2 H, q, $J$ = 7 Hz), 6.07 (1 H, s), 7.13 (2 H, d, $J$ = 9 Hz), 8.06 (2 H, d, $J$ = 9 Hz) |
| 49 |  | 55 | 1.31 (3 H, t, $J$ = 6 Hz), 2.31 (6 H, s), 4.08 (2 H, s), 4.29 (2 H, q, $J$ = 6 Hz), 7.39 (2 H, d, $J$ = 8 Hz), 8.17 (2 H, d, $J$ = 8 Hz) |
| 50 |  | 70 | 1.32 (3 H, t, $J$ = 6 Hz), 2.52 (3 H, s), 2.74 (3 H, s), 4.02 (2 H, s), 4.27 (2 H, q, $J$ = 6 Hz), 7.53 (2 H, d, $J$ = 8 Hz), 8.01 (2 H, d, $J$ = 8 Hz) |
| 51 |  | 52 | 1.31 (3 H, t, $J$ = 7 Hz), 2.53 (3 H, s), 4.05 (2 H, s), 4.26 (2 H, q, $J$ = 7 Hz), 7.77 (2 H, d, $J$ = 8 Hz), 7.92 (1 H, s), 8.08 (2 H, d, $J$ = 8 Hz) |
| 52 |  | 63[c] | 1.30 (3 H, t, $J$ = 6 Hz), 2.47 (3 H, s), 2.60 (3 H, s), 4.04 (2 H, s), 4.25 (2 H, q, $J$ = 6 Hz), 7.66 (2 H, d, $J$ = 9 Hz), 8.11 (2 H, d, $J$ = 9 Hz) |
| 53 |  | 71 | 1.34 (3 H, t, $J$ = 7 Hz), 2.56 (3 H, s), 4.08 (2 H, s), 4.30 (2 H, q, $J$ = 7 Hz), 6.82 (1 H, t, $J$ = 6 Hz), 7.25 (1 H, t, $J$ = 6 Hz), 7.65 (1 H, d, $J$ = 6 Hz), 7.66 (2 H, d, $J$ = 8 Hz), 8.14 (2 H, d, $J$ = 8 Hz), 8.22 (1 H, d, $J$ = 6 Hz) |
| 54 |  | 70 | 1.32 (3 H, t, $J$ = 7 Hz), 2.52 (3 H, s), 4.03 (2 H, s), 4.28 (2 H, q, $J$ = 7 Hz), 6.91 (1 H, d, $J$ = 4 Hz), 7.33 (1 H, d, $J$ = 4 Hz), 7.58 (2 H, d, $J$ = 9 Hz), 8.09 (2 H, d, $J$ = 9 Hz) |
| 55 |  | 75 | 1.34 (3 H, t, $J$ = 6 Hz), 2.64 (3 H, s), 4.08 (2 H, s), 4.29 (2 H, q, $J$ = 6 Hz), 7.31 (1 H, m), 7.65 (2 H, d, $J$ = 9 Hz), 8.06 (1 H, d, $J$ = 7 Hz), 8.22 (2 H, d, $J$ = 9 Hz), 8.35 (1 H, d, $J$ = 4 Hz) |
| 56 |  | 30 | 1.30 (3 H, t, $J$ = 7 Hz), 2.62 (3 H, s), 4.11 (2 H, s), 4.29 (2 H, q, $J$ = 6 Hz), 7.71 (1 H, d, $J$ = 6 Hz), 7.99 (2 H, d, $J$ = 8 Hz), 8.25 (2 H, d, $J$ = 8 Hz), 8.52 (1 H, d, $J$ = 6 Hz), 8.60 (1 H, s) |

**Table IV** (Continued)

| compd | Het | yield[a] (%) | $^1$H NMR[b] (300 MHz, $CDCl_3$) |
|---|---|---|---|
| **57** |  | 54 | 1.32 (3 H, t, $J$ = 6 Hz), 2.61 (3 H, s), 4.09 (2 H, s), 4.28 (2 H, q, $J$ = 6 Hz), 7.16 (1 H, d, $J$ = 6 Hz), 7.55 (2 H, d, $J$ = 9 Hz), 8.23 (2 H, d, $J$ = 9 Hz), 8.46 (1 H, d, $J$ = 6 Hz), 9.09 (1 H, s) |
| **58** |  | 52 | 1.16 (3 H, t, $J$ = 7 Hz), 1.28 (3 H, t, $J$ = 7 Hz), 2.74 (2 H, q, $J$ = 7 Hz), 3.98 (2 H, s), 4.13 (2 H, q, $J$ = 7 Hz), 6.99 (1 H, d, $J$ = 7 Hz), 7.45 (2 H, d, $J$ = 8 Hz), 8.11 (2 H, d, $J$ = 8 Hz), 8.23 (1 H, d, $J$ = 7 Hz), 8.94 (1 H, s) |
| **59** |  | 22 | 1.29 (3 H, t, $J$ = 7 Hz), 4.11 (2 H, s), 4.26 (2 H, q, $J$ = 7 Hz), 7.21 (1 H, d, $J$ = 5 Hz), 7.60 (2 H, d, $J$ = 8 Hz), 8.22 (2 H, d, $J$ = 8 Hz), 8.59 (1 H, d, $J$ = 5 Hz), 9.34 (1 H, s) |
| **60** |  | 75 | 0.90 (3 H, t, $J$ = 6 Hz), 1.32 (3 H, t, $J$ = 6 Hz), 1.29–1.40 (2 H, m), 1.81 (2 H, m), 2.84 (2 H, t, $J$ = 6 Hz), 4.09 (2 H, s), 4.28 (2 H, q, $J$ = 6 Hz), 7.09 (1 H, d, $J$ = 4 Hz), 7.53 (2 H, d, $J$ = 7 Hz), 8.22 (2 H, d, $J$ = 7 Hz), 8.41 (1 H, d, $J$ = 4 Hz), 9.11 (1 H, s) |
| **61** |  | 31 | 1.32 (3 H, t, $J$ = 6 Hz), 4.07 (2 H, s), 4.30 (2 H, q, $J$ = 6 Hz), 7.14 (1 H, d, $J$ = 5 Hz), 7.75 (2 H, d, $J$ = 9 Hz), 8.20 (2 H, d, $J$ = 9 Hz), 8.40 (1 H, d, $J$ = 5 Hz), 8.50 (1 H, s), 9.03 (1 H, **br s**) |
| **62** |  | 83 | 1.36 (3 H, t, $J$ = 6 Hz), 2.59 (3 H, s), 2.62 (3 H, s), 2.90 (3 H, s), 4.09 (2 H, s), 4.19 (2 H, q, $J$ = 6 Hz), 7.55 (2 H, d, $J$ = 9 Hz), 7.97 (2 H, d, $J$ = 9 Hz), 8.21 (1 H, s) |
| **63** |  | 53 | 1.33 (3 H, t, $J$ = 7 Hz), 2.62 (3 H, s), 4.08 (2 H, s), 4.25 (3 H, s), 4.28 (2 H, q, $J$ = 7 Hz), 7.61 (2 H, d, $J$ = 8 Hz), 8.22 (2 H, d, $J$ = 8 Hz), 8.53 (1 H, s) |

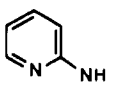
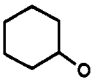
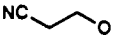
[a] By method D, unless stated otherwise. [b] Compounds were a mixture of keto and enol forms (ratio 3–20:1); data is for the keto tautomers only. [c] By method C.

**Table V.** Aryl and Heterocyclic Aldehydes Used in the Hantzsch Synthesis




| Compound | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 |
|---|---|---|---|---|---|---|---|---|

**Table VI.** Aminocrotonamides and Aminocrotonates Used in the Hantzsch Synthesis


| R |  | $NH_2$ | t-BuNH | $CH_3O$ |  | t-BuO | $PhCH_2O$ | NC  |
|---|---|---|---|---|---|---|---|---|
| Compound[ref] | 72[24] | 73[25] | 74 | 75[26] | 76[27] | 77[28] | 78[27] | 79[27] |

was heated under nitrogen at reflux for 8 h. The solution was allowed to cool, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (gradient elution with 5% diethylamine/ethyl acetate and methanol) to give a solid, which was further purified by trituration with diethyl ether/ethyl acetate, followed by filtration and drying of the pale yellow solid (280 mg, 31%) in vacuo, m.p. 226–228 °C. Anal. ($C_{34}H_{29}ClN_6O_3 \cdot 0.5H_2O$) C, H, N.

For the synthesis of compounds **10**, **11**, and **14**, a catalytic amount of glacial acetic (20 mg/mmol) was added to the reaction mixture.

Also prepared by method A was **4-(2-chlorophenyl)-5-[(2-cyanoethoxy)carbonyl]-1,4-dihydro-3-(ethoxycarbonyl)-6-methyl-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-pyridine** (**41**): 44% yield, mp 177–179 °C. Anal. ($C_{32}H_{28}ClN_5O_4$) C, H, N.

**Method B. 4-(2-Chlorophenyl)-1,4-dihydro-2-[4-(3,5-dimethyl-1,2,4-triazol-1-yl)phenyl]-3-(ethoxycarbonyl)-6-methyl-5-[*N*-(2-pyridyl)carbamoyl]pyridine** (**12**). A mixture of ethyl 4′-[(3,5-dimethyl-1,2,4-triazol-1-yl)benzoyl]acetate (**52**) (618 mg, 2.15 mmol), 2-chlorobenzaldehyde (302 mg, 2.15 mmol), and piperidine (0.04 mL) in 2-propanol (10 mL) was stirred at room temperature for 72 h. The volatile constituents of the mixture were removed under reduced pressure, and the residue was purified by flash chromatography, eluting with ethyl acetate, to give the propenoate **39** as an oil (600 mg, 68%): $^1$H NMR (300 MHz, $CDCl_3$) 1.27 (3 H, t, $J$ = 7 Hz), 2.42 (3 H, s), 2.53 (3 H, s), 4.31 (2 H, q, $J$ = 7 Hz), 7.06 (1 H, t, $J$ = 6 Hz), 7.23 (2 H, m), 7.36 (1 H, d, $J$ = 8 Hz), 7.51 (2 H, d, $J$ = 8 Hz), 8.01 (2 H, d, $J$ = 8 Hz), 8.31 (1 H, s) ppm.

A portion of the intermediate **39** (566 mg, 1.38 mmol) was added to *N*-(2-pyridyl)-3-aminocrotonamide **72**[24] (245 mg, 1.38 mmol) in ethanol (10 mL). The resulting solution was heated at reflux under nitrogen for 8 h, cooled, and was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with ethyl acetate diethylamine = 98:2, to afford a white solid (50 mg, 6%), mp 130 °C. Anal. ($C_{30}H_{34}ClN_5O_3$) C, H, N.

In a similar manner, keto ester (**57**) (1.00 g, 3.1 mmol) was condensed with benzo[*d*]dioxolane-4-carboxaldehyde (**67**) (560 mg, 3.72 mmol) in the presence of piperidine (200 mg) and dry acetonitrile (10 mL) at 20 °C for 60 h to give propenoate **40** (505 mg, 36%) as a colorless foam: $^1$H NMR (300 MHz, $CDCl_3$) 1.28 (3 H, t, $J$ = 6 Hz), 2.60 (3 H, s), 4.31 (2 H, q, $J$ = 6 Hz), 6.02 (2 H, s), 6.76 (3 H, m), 7.13 (1 H, d, $J$ = 5 Hz), 7.48 (2 H, d, $J$ = 8 Hz), 8.12 (1 H, s), 8.20 (2 H, d, $J$ = 8 Hz), 8.43 (1 H, d, $J$ = 5 Hz), 9.09 (1 H, s) ppm.

Propenoate **40** (280 mg, 0.62 mmol) and **72** (120 mg, 0.62 mmol) were reacted together as described above to give compound **34** (40 mg, 11%), mp 195–199 °C. Anal. ($C_{35}H_{30}N_6O_5 \cdot 1.5H_2O$) C, H, N.

**4-(2-Chlorophenyl)-1,4-dihydro-3-(ethoxycarbonyl)-6-methyl-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-pyridine-5-carboxylic Acid** (**26**). Compound **41** (2.91 g, 5.0 mmol) was added to a stirred solution of sodium hydroxide (600 mg, 15.0 mmol) in water/dioxane (1:3, 90 mL) at 20 °C. After 1 h, the mixture was treated with hydrochloric acid (15 mL, 1.0 M) and concentrated under reduced pressure. The yellow solid residue was suspended in water, filtered off, washed with water, and dried in vacuo at 70 °C to give the title compound (2.548 g, 96%), mp 206–208 °C. Anal. ($C_{29}H_{25}ClN_4O_4 \cdot 0.66H_2O$) C, H, N.

**4-(2-Chlorophenyl)-1,4-dihydro-3-(ethoxycarbonyl)-5-[(2-methoxyethoxy)carbonyl]-6-methyl-2-[4-(2-methylimidazo-[4,5-*c*]pyrid-1-yl)phenyl]pyridine** (**31**). A mixture of compound **26** (270 mg, 0.5 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (377 mg, 1.25 mmol) and *N*,*N*-dimethyl-4-aminopyridine (152 mg, 1.25 mmol) in dry dichloromethane (10 mL) was stirred under a nitrogen atmosphere at 20 °C for 3 h to give a yellow solution. 2-Methoxyethanol (1.0 mL) was added, and the solution was stirred at 20 °C for 20 h. The mixture was concentrated under reduced pressure and the residue was dissolved in excess hydrochloric acid (1M) and washed with ether (2 × 30 mL). The aqueous solution was rendered basic by the addition of excess saturated aqueous sodium bicarbonate and extracted with dichloromethane (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by flash chromatography to give the title compound (93 mg, 34%) as a white solid, mp 195–196 °C. Anal. ($C_{32}H_{31}ClN_4O_5$) C, H, N.

**Method C. Ethyl [4′-(4-Methylimidazol-1-yl)benzoyl]-acetate** (**45**). Acetophenone **80** (2.0 g, 10 mmol) was added slowly to a suspension of sodium hydride (0.44 g, 60% dispersion in oil, washed with hexane, 11 mmol) in diethyl carbonate (12 mL) under nitrogen at reflux. After 1 h, more sodium hydride (11 mmol) was added, and heating was continued for a further 2 h. The mixture was cooled and the excess of sodium hydride was destroyed by the addition of ethanol. The mixture was concentrated under reduced pressure and dissolved in the minimum quantity of hydrochloric acid (2 M). The solution was washed with ethyl acetate (50 mL), rendered basic by the addition of excess saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give a gum, which was purified by flash chromatography (eluting with ethyl acetate) to afford the title compound as a white solid (400 mg, 15%).

**Method D.**[12] **Ethyl [4′-(2-Methylimidazo[4,5-*c*]pyridyl)-benzoyl]acetate** (**57**). Zinc dust (894 mg, 13.7 mmol) was suspended in dry tetrahydrofuran (3 mL) under nitrogen and sonicated (Sonicor SC120 ultrasonic bath) for 10 min at room temperature. Ethyl bromoacetate (2 drops) was added, and the mixture was heated under reflux for 5 min. A solution of benzonitrile **86** (640 mg, 2.74 mmol) in dry tetrahydrofuran (6 mL) was added and the mixture refluxed for 5 min. A solution of ethyl bromoacetate (1.822 g, 10.94 mmol) in dry tetrahydrofuran (2 mL) was added dropwise over 1 h at reflux and, after a further 10 min., the mixture was allowed to cool to room temperature. Aqueous potassium carbonate (1 mL, 50% solution) was added and the mixture was stirred for 45 min, then filtered through Arbocel filter aid which was washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure to give a yellow gum. This material was treated with a mixture of 20% aqueous trifluoroacetic acid (20 mL) and dichloromethane (50 mL) and stirred at room temperature for 15 min. The mixture was neutralized by the addition of saturated aqueous sodium bicarbonate and then extracted with dichloromethane (2 × 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography (gradient elution with ethyl acetate/methanol) to give the title compound **57** (480 mg, 54%). Further purification by chromatography (ethyl acetate/methanol = 7:1) gave a white solid, mp 111–112 °C (from ethyl acetate). Anal. ($C_{18}H_{17}N_3O_3$) C, H, N.

**4′-(4-Methylimidazol-1-yl)acetophenone** (**80**). A mixture of 4′-fluoroacetophenone (13.8 g, 100 mmol), 4-methylimidazole (8.2 g, 100 mmol), and potassium carbonate (20.7 g, 150 mmol) in dry dimethylformamide (190 mL) was heated at 150 °C for 23 h. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate (500 mL) and brine. The organic layer was washed with brine (3 × 200 mL), dried ($MgSO_4$), and evaporated to leave a sticky solid which was purified by flash chromatography (eluting with ethyl acetate/diethylamine = 95:5). Recrystallization from ethyl acetate/hexane afforded the title compound (4.0 g, 20%), mp 100 °C. Anal. ($C_{12}H_{12}N_2O \cdot H_2O$) C, H, N.

**4′-(3,5-Dimethyl-1,2,4-triazol-1-yl)acetophenone** (**81**). The method for compound **80** was used, substituting 3,5-dimethyl-1,2,4-triazole for 4-methylimidazole. The title compound was obtained as a yellow oil (2.5 g, 42%), which was characterized by $^1$H NMR only. $^1$H NMR (300 MHz, $CDCl_3$) 1.45 (3 H, s), 1.58 (3 H, s), 1.68 (3 H, s), 7.60 (2 H, d, $J$ = 9 Hz), 8.11 (2 H, d, $J$ = 9 Hz) ppm.

**4-(2-Methylimidazol-1-yl)benzonitrile** (**82**). A mixture of 4-fluorobenzonitrile (3.0 g, 25 mmol), 2-methylimidazolium chloride (2.96 g, 25 mmol), and potassium carbonate (7.75 g, 52 mmol) in dimethylformamide (50 mL) was heated at 145 °C for 16 h. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from hexane/ether to give a white solid (1.01 g, 22%). Anal. ($C_{11}H_9N_3$) C, H, N.

**4-(2,4-Dimethylimidazol-1-yl)benzonitrile** (**83**). The method for compound **82** was used, substituting 2,4-dimethylimidazolium chloride for 2-methylimidazolium chloride, to give the title compound as a pale yellow solid (2.6 g, 57%): mp 108–110 °C (from

hexane/ether); HRMS $m/z$ $M^+$ = 197.095580, $C_{12}H_{11}N_3$ requires $m/z$ = 197.095297; $^1H$ NMR (300 MHz, $CDCl_3$) 2.25 (3 H, s), 2.41 (3 H, s), 6.78 (1 H, s), 7.43 (2 H, d, $J$ = 9 Hz), 7.80 (2 H, d, $J$ = 9 Hz) ppm.

**4-(2,4,5-Trimethylimidazol-1-yl)benzonitrile (84).** The method for compound 82 was used, substituting 2,4,5-trimethylimidazolium chloride for 2-methylimidazolium chloride, to give the title compound (280 mg, 8%) as a pale yellow solid, mp 180–182 °C (from ether). Anal. ($C_{13}H_{13}N_3$) C, H, N.

**1-(4-Cyanophenyl)-3,5-dimethylpyrazole (85).** The method for compound 82 was used, substituting 3,5-dimethylpyrazole for 2-methylimidazolium chloride, to give the title compound as a white solid (3.2 g, 66%): mp 59–63 °C. Anal. ($C_{12}H_{11}N_3$) C, H, N.

**1-(4-Cyanophenyl)-2-methylimidazo[4,5-*c*]pyridine (86) and 3-(4-Cyanophenyl)-2-methylimidazo[4,5-*c*]pyridine (87).** A mixture of 3,4-diaminopyridine (20.0 g, 183 mmol) and acetic anhydride (360 mL) was heated at 100 °C for 16 h. The excess reagent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with ethyl acetate/methanol = 3:1, to give 2-methylimidazo[4,5-*c*]pyridine (15.5 g, 64%) as a brown solid.

This material (5.65 g, 42.5 mmol) was dissolved in a mixture of glacial acetic acid (150 mL) and 30% aqueous hydrogen peroxide[29] (15 mL), and the solution was heated at 60 °C for 6 days. The solution was concentrated under reduced pressure, and the residue was dissolved in ethanol and treated with excess solid potassium carbonate. The solid was filtered off and washed with ethanol, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 10–30% water in acetone. Fractions containing product were combined and concentrated under reduced pressure, redissolved in 2-propanol/toluene = 1:1 (200 mL), and reevaporated to give 2-methylimidazo[4,5-*c*]pyridine 5-oxide (2.94 g, 46%) as a hygroscopic solid.

A mixture of 2-methylimidazo[4,5-*c*]pyridine 5-oxide (2.06 g, 13.8 mmol), 4-fluorobenzonitrile (1.67 g, 13.8 mmol), and potassium carbonate (1.90 g, 13.8 mmol) in dry dimethylformamide (35 mL) was heated under nitrogen at 140 °C for 16 h. The mixture was filtered and concentrated under reduced pressure to give a solid, which was dissolved in glacial acetic acid (40 mL), and iron powder (1.16 g, 20.7 mmol) was added. The mixture was heated at 100 °C for 30 min, cooled, and filtered through Arbocel filter aid. The filtrate was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (150 mL) and washed with saturated aqueous sodium bicarbonate. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography, eluting with ethyl acetate/methanol = 9:1, to give three fractions. First eluted was compound 87 (415 mg, 13%): mp 176–179 °C; HRMS $m/z$ = 234.09063, $C_{14}H_{10}N_4$ requires $m/z$ = 234.090546; $^1H$ NMR (300 MHz, $CDCl_3$) 2.64 (3 H, s), 7.62 (2 H, d, $J$ = 8 Hz), 7.70 (1 H, d, $J$ = 5 Hz), 7.98 (2 H, d, $J$ = 8 Hz), 8.52 (1 H, d, $J$ = 5 Hz), 8.59 (1 H, s) ppm. Second eluted was a mixture of compounds 86 and 87 (410 mg, 13%), and third eluted was compound 86 (350 mg, 11%)(for further details see below).

An alternative route to compound 86 is as follows: A mixture of 4-cyanoaniline (6.894 g, 58.4 mmol) and 4-chloro-3-nitropyridine (9.26 g, 58.4 mmol: CAUTION—skin irritant) in ethanol (200 mL) was stirred at 20 °C for 18 h. The resulting yellow suspension was poured into excess ice-cold dilute aqueous ammonia (500 mL), and the solid was filtered off. The solid was heated with ethanol (150 mL) for 10 min, cooled, and filtered off to give the aminonitropyridine (12.15 g, 87%) as a bright yellow solid.

This compound (6.0 g, 25 mmol) was suspended in methanol/dichloromethane = 1:1 (300 mL) and hydrogenated over 10% palladium on carbon (600 mg) at 30 psi and 20 °C for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the diaminopyridine (5.15 g, 98%) as a buff solid.

The diaminopyridine (13.0 g, 61.9 mmol) was dissolved in a mixture of acetic acid (39 mL) and acetic anhydride (39 mL), and the resulting solution was heated under nitrogen at 90 °C for 2 h. The brown solution was concentrated under reduced pressure, and the residue was dissolved in water and partitioned between dichloromethane (3 × 150 mL) and excess dilute aqueous ammonia. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 10:1) to give 86 as a brown solid (11.4 g, 81%), mp 182–184 °C (from ethyl acetate). Anal. ($C_{14}H_{10}N_4$) C, H, N.

**3-(4-Cyanophenyl)-2-methylpyridine (88).** *tert*-Butyllithium (18.1 mL, 1.8 M in pentane, 32.6 mmol) was added dropwise to a stirred solution of 4-bromobenzonitrile (2.81 g, 15.4 mmol) in dry THF (100 mL) under nitrogen at −60 °C. After being stirred for 20 min, a solution of freshly fused zinc chloride (4.62 g, 33.8 mmol) in dry THF (55 mL) was added via cannula and the solution was allowed to warm to 10 °C over 10 min. Tetrakis(triphenylphosphine)palladium (0.5 g, 0.43 mmol) and 3-bromo-2-methylpyridine (3.19 g, 18.5 mmol) were added, and the red solution was then heated at reflux for 5.5 h. After being cooled, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (300 mL) and a solution of ethylenediaminetetraacetic acid disodium salt (8 g) and sodium carbonate (10 g) in water (500 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give a dark oil, which was purified by flash chromatography (gradient elution with hexane/ether) to give compound 88 (0.60 g, 20%) as a solid, which was converted to the keto ester (46) without further purification: $^1H$ NMR (300 MHz, $CDCl_3$) 2.52 (3 H, s), 7.26 (1 H, m), 7.48 (2 H, d, $J$ = 9 Hz), 7.53 (1 H, m), 7.78 (2 H, d, $J$ = 9 Hz), 8.58 (1 H, m) ppm.

**2-(4-Cyanophenyl)-6-methylpyridine (89).** *tert*-Butyllithium (24.6 mL, 1.7 M in pentane, 42 mmol) was added dropwise to a stirred solution of 4-bromobenzonitrile (3.64 g, 20 mmol) in dry THF (60 mL) under nitrogen at −60 °C. After being stirred for 20 min, a solution of freshly fused zinc chloride (2.73 g, 20 mmol) in dry THF (40 mL) was added via cannula and the solution was allowed to warm to 10 °C over 10 min. Tetrakis(triphenylphosphine)palladium (0.46 g, 0.4 mmol) and 2-bromo-6-methylpyridine (4.1 g, 24 mmol) were added, and the red solution was then heated at reflux for 5.5 h. After being cooled, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (300 mL) and a solution of ethylenediaminetetraacetic acid disodium salt (8 g) and sodium carbonate (10 g) in water (500 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give a dark oil, which was purified by flash chromatography (gradient elution with hexane/ether) to give compound 89 (1.1 g, 28%) as a solid, which was characterized only by $^1H$ NMR: $^1H$ NMR (300 MHz, $CDCl_3$) 2.67 (3 H, s), 7.20 (1 H, d, $J$ = 7 Hz), 7.58 (1 H, d, $J$ = 7 Hz), 7.71 (1 H, t, $J$ = 7 Hz), 7.77 (2 H, d, $J$ = 9 Hz), 8.14 (2 H, d, $J$ = 9 Hz) ppm.

**4-(4-Cyanophenyl)-3,5-dimethyl-1,2,4-triazole (90).** Hydrazine hydrate (1.64 mL, 34 mmol) was added dropwise to a stirred solution of 4-cyanothioacetanilide[15] (5.43 g, 30.9 mmol) in THF (50 mL) at 20 °C. After 30 min, the solution was concentrated under reduced pressure and the residue was treated with triethyl orthoacetate (40 mL). The mixture was heated at 80 °C for 30 min, cooled, and concentrated under reduced pressure. The residue was treated with ice-cold dilute aqueous ammonia (100 mL), and the product was filtered off, washed with water, and dried in vacuo to give 90 (4.85 g, 79%) as an off-white solid, mp 280–284 °C. Anal. ($C_{11}H_{10}N_4$) C, H, N.

**3-(4-Cyanophenyl)-2-methylimidazo[4,5-*b*]pyridine (91).** A mixture of 4-cyanoaniline (2.36 g, 20 mmol) and 2-chloro-3-nitropyridine (3.17 g, 20 mmol) in ethanol (60 mL) was heated under reflux for 72 h. The solid which formed was filtered off and partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the aminonitropyridine as a yellow solid (2.70 g, 56%), mp 176–177 °C (from ethanol).

This compound (1.10 g, 4.58 mmol) was dissolved in ethanol/dichloromethane = 1:1 (50 mL) and hydrogenated over 10% palladium on carbon (100 mg) at 30 psi and 20 °C for 2.5 h. The

(29) Mizuno, Y.; Itoh, T.; Saito, K.; Condensed Systems of Aromatic Nitrogenous Series. XXIV. Synthesis of 4-Substituted 1-H-Imidazo[4,5-c]pyridines. *Chem. Pharm. Bull.* **1964**, *12*, 866–872.

catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the diaminopyridine (920 mg, 95%) as a brown solid.

This compound (915 mg, 4.26 mmol) was dissolved in a mixture of acetic acid (3 mL) and acetic anhydride (3 mL), and the solution was heated at reflux under nitrogen for 5 h. The solution was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (3 × 50 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate) to give **91** as a fawn solid (768 mg, 77%), mp 202–204 °C (from ethyl acetate). Anal. ($C_{14}H_{10}N_4$) C, H, N.

**1-(4-Cyanophenyl)-2-ethylimidazo[4,5-*c*]pyridine (92).** A mixture of 3-amino-4-[(4′-cyanophenyl)amino]pyridine (see preparation of compound **86**)(1.50 g, 7.1 mmol), propanoic anhydride (10 mL), and propanoic acid (10 mL) was heated under nitrogen at 120 °C for 4 h. After being cooled, the solution was poured onto ice and stirred for 30 min. The solution was rendered basic by the addition of excess dilute aqueous sodium hydroxide, and the product was extracted into dichloromethane (4 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown solid which was recrystallized from hot ethyl acetate to give buff plates (800 mg, 45%), mp 185–187 °C. Anal. ($C_{15}H_{12}N_4$) C, H, N.

**1-(4-Cyanophenyl)-2-(trifluoromethyl)imidazo[4,5-*c*]pyridine (93).** A mixture of 3-amino-4-[(4′-cyanophenyl)amino]pyridine (see preparation of compound **86**)(420 mg, 2.0 mmol), trifluoroacetaldehyde hydrate (232 mg, 2.0 mmol), and sodium metabisulfite (475 mg, 2.5 mmol) in *N*,*N*-dimethylacetamide (10 mL) was heated under reflux for 16 h. After being cooled, the mixture was diluted with ethyl acetate (200 mL), washed with saturated aqueous sodium bicarbonate (50 mL) and water (5 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with ethyl acetate/ether = 1:1) to give a cream-colored solid, (337 mg, 59%), mp 184–186 °C (from ethyl acetate). Anal. ($C_{14}H_7F_3N_4$) C, H, N.

**2-Butyl-1-(4-cyanophenyl)imidazo[4,5-*c*]pyridine (94).** A mixture of 3-amino-4-[(4′-cyanophenyl)amino]pyridine (see preparation of compound **86**)(1.50 g, 7.1 mmol), valeric anhydride (10 mL), and valeric acid (10 mL) was heated under nitrogen at 120 °C for 4 h. After being cooled, the brown solution was poured onto ice and stirred for 30 min. The mixture was rendered basic by the addition of excess dilute aqueous sodium hydroxide and extracted with dichloromethane (4 × 50 mL). The combined extracts were dried ($K_2CO_3$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/diethylamine = 95:5), followed by recrystallization from ethyl acetate/ether to give **94** as a white solid (641 mg, 33%), mp 98–100 °C. Anal. ($C_{17}H_{16}N_4$) C, H, N.

**1-(4-Cyanophenyl)-2,3-dihydroimidazo[4,5-*c*]pyridin-2-one (95).** A mixture of 3-amino-4-[(4′-cyanophenyl)amino]pyridine (see preparation of compound **86**) (3.788 g, 18.0 mmol) and *N*,*N*-carbonyliimidazole (3.507 g, 21.6 mmol) in dry dichloromethane (150 mL) was stirred under nitrogen at 20 °C for 72 h. The buff solid which precipitated was filtered off and washed with dichloromethane to give compound **95** (2.624 g, 62%): mp >340 °C; HRMS *m*/*z* $M^+$ = 236.069577, $C_{13}H_8N_4O$ requires $M^+$ = 236.069811; $^1H$ NMR (300 MHz, DMSO-$d_6$, hydroxyimidazopyridine tautomer) 7.10 (1 H, d, *J* = 5 Hz), 7.74 (2 H, d, *J* = 8 Hz), 7.97 (2 H, d, *J* = 8 Hz), 8.22 (1 H, s), 11.50 (1 H, br s) ppm.

**1-(4-Cyanophenyl)-2,4,6-trimethylimidazo[4,5-*c*]pyridine (96).** A solution of 4-chloro-2,6-dimethyl-3-nitropyridine[19] (9.8 g, 52.5 mmol: CAUTION—skin irritant) and 4-cyanoaniline (6.20 g, 52.5 mmol) in ethanol (160 mL) was stirred at 20 °C for 16 h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (200 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a gum which crystallized upon addition of ether. The yellow solid (9.80 g, 79%) was filtered off and dried in vacuo.

This compound (5.00 g, 18.6 mmol) was dissolved in a mixture of ethanol (100 mL) and dichloromethane (20 mL) and hydrogenated over 10% palladium on charcoal (500 mg) at 20 psi and 20 °C for 3 h. The catalyst was filtered off and the filtrate concentrated under reduced pressure to give the diaminopyridine (4.20 g, 94%) as a brown solid.

This compound (4.20 g, 17.6 mmol) was dissolved in a mixture of acetic acid (12.6 mL) and acetic anhydride (12.6 mL), and the solution was heated at 100 °C for 16 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in water. The solution was rendered basic by the addition of excess concentrated aqueous ammonia. The white solid which precipitated was filtered off and dried in vacuo to give compound **96** (4.06 g, 88%), mp 260–262 °C. Anal. ($C_{16}H_{14}N_4$) C, H, N.

**9-(4-Cyanophenyl)-6-methoxy-8-methylpurine (97).** A solution of 5-amino-4,6-dichloropyrimidine (7.00 g, 42.7 mmol) and 4-cyanoaniline (5.04 g, 42.7 mmol) in 1-butanol (130 mL) was heated under reflux for 16 h. After cooling the mixture, the solid which precipitated was filtered off and partitioned between dichloromethane (500 mL) and saturated aqueous sodium bicarbonate (100 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a solid (6.31 g, 60%).

This compound (6.31 g, 25.7 mmol) was heated in acetic anhydride (105 mL) at 120 °C for 6 h and then concentrated under reduced pressure. The residue was recrystallized from methanol to give **4-[*N*-acetyl-*N*-(4-cyanophenyl)amino]-6-chloro-5-(*N*,*N*-diacetylamino)pyrimidine (102)** as a white solid (4.62 g, 51%): $^1H$ NMR (300 MHz, DMSO-$d_6$) 2.15 (3 H, s), 2.38 (6 H, s), 7.40 (2 H, d, *J* = 8 Hz), 7.80 (2 H, d, *J* = 8 Hz), 8.87 (1 H, s) ppm.

Compound **102** (2.50 g, 6.73 mmol) was heated at 240 °C at 50 mmHg for 2 h. The reaction melt was cooled and purified by flash chromatography (eluting with ethyl acetate/dichloromethane = 3:1) to give the chloropurine (1.10 g, 61%), mp 170–173 °C.

This compound (1.03 g, 3.83 mmol) was added to a solution of sodium methoxide (from sodium metal (160 mg, 6.96 mmol) and dry methanol (5 mL)), and the resulting slurry was heated under reflux for 90 min. The solvent was removed under reduced pressure, and the residual gum was dissolved in dichloromethane (50 mL). The solution was washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give compound **97** (840 mg, 83%) as a fawn solid: mp 208–211 °C; *m*/*z* $M^+$ = 265.09655, $C_{14}H_{11}N_5O$ requires $M^+$ = 265.09636.

**1-Bromo-1-(4-cyanophenyl)-2-oxopropane (103).** 1-(4-Cyanophenyl)-2-oxopropane[23] (5.3 g, 33.0 mmol) was dissolved in dichloromethane (85 mL) at 25 °C, and a solution of bromine (5.28 g, 33 mmol) in dichloromethane (80 mL) was added dropwise over 1 h with stirring. After a further 30 min, the mixture was washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give **103** as a pale red oil (7.55 g, 96%): $^1H$ NMR (300 MHz, $CDCl_3$) 2.41 (3 H, s), 5.24 (1 H, s), 7.61 (2 H, d, *J* = 8 Hz), 7.73 (2 H, d, *J* = 8 Hz) ppm.

**5-(4-Cyanophenyl)-4-methyloxazole (98).** A stirred two-phase mixture of formamide (0.6 mL, 15 mmol) and compound **103** (0.8 g, 3.4 mmol) was heated at 120 °C for 2 h. After being cooled, the mixture was diluted with dichloromethane (15 mL) and saturated aqueous sodium bicarbonate (10 mL) and the organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow solid. The product was purified by flash chromatography (eluting with dichloromethane) to give compound **98** (0.29 g, 47%) as a pale yellow solid, mp 120–121 °C. Anal. ($C_{11}H_8N_2O$) C, H, N.

**5-(4-Cyanophenyl)-2,4-dimethylthiazole (99).** A mixture of compound **103** (0.9 g, 3.83 mmol), thioacetamide (0.6 g, 8.0 mmol), pyridine (0.45 mL), and toluene (2 mL) was heated at 100 °C for 1 h, cooled, and partitioned between ethyl acetate and brine. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with dichloromethane/ether = 95:5) to give compound **99** (525 mg, 64%) as a pale yellow solid, mp 109–110 °C. Anal. ($C_{12}H_{10}N_2S$) C, H, N.

**5-(4-Cyanophenyl)-4-methylimidazo[1,2-*a*]pyridine (100).** A mixture of compound **103** (576 mg, 2.42 mmol) and 2-aminopyridine (226 mg, 2.4 mmol) in ethanol (2 mL) was stirred at reflux for 5 h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and saturated aqueous sodium bicarboante (50 mL), and the organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chroma-

tography (eluting with ethyl acetate) to give compound **100** (290 mg, 52%) as a white solid, mp 153–156 °C (from methanol/water). Anal. ($C_{15}H_{11}N_3$) C, H, N.

**5-(4-Cyanophenyl)-6-methylimidazo[2,1-*b*]thiazole (101).** A mixture of comopund **103** (1.0 g, 4.2 mmol) and 2-aminothiazole (400 mg, 4.0 mmol) in 1-butanol (6 mL) was stirred at 100 °C for 2 h. Triethylamine (0.5 mL, 4 mmol) was added, and the mixture was heated for a further 2 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with hexane/ethyl acetate/diethylamine = 14:5:1) to give compound **101** as an off-white solid (340 mg, 35%), mp 91–93 °C. Anal. ($C_{13}H_9N_3S$) C, H.

**Biology. Platelet Aggregation.** Blood samples were taken from New Zealand white rabbits into 0.1 vol disodium ethylenediaminetetraacetic acid (77 mM, pH 7.0) and the samples centrifuged for 15 min (250*g*) to obtain platelet rich plasma. The plasma was further centrifuged (10 min, 2000*g*) to give a platelet pellet which was washed twice with a buffer solution (4 mM $KH_2PO_4$, 6 mM $Na_2HPO_4$, 100 mM NaCl, 56 mM glucose, and 0.1% w/v bovine serum albumin, pH 7.25) and finally resuspended in buffer solution to a concentration of $2 \times 10^8$ platelets/mL. Samples (0.5 mL) were preincubated for 2 min at 37 °C with stirring (1100 rpm) in a Biodata Platelet Aggregation Profiler (PAP-4), either with vehicle (dimethylsulfoxide) alone, or with vehicle containing the particular compound under test. $C_{16}$-PAF (Bachem (U.K.) Ltd.) was dissolved and diluted with 0.25% w/v bovine serum albumin in 0.9% w/v NaCl and added at a sufficient concentration ($10^{-8}$ to $10^{-9}$ M) to give a maximum aggregation response in the absence of test compound, and platelet aggregation was measured by following the increase in light transmission. The experiment was repeated in the presence of the test compound at a range of concentrations, and the concentration of compound required to reduce the response to 50% of its maximum value ($IC_{50}$) was calculated.

**PAF-Induced Murine Lethality.** The compounds under test were suspended in Cremaphor EL (BASF) (10% solution in 0.2 M phosphate buffer, pH 7) and then administered by gavage at several doses to groups of five mice (Tuck). After two hours, a mixture of PAF (0.05 mg/kg) and DL-propranolol (5 mg/kg) in 0.9% w/v NaCl was injected via a tail vein, which produced 100% mortality in animals treated only with the vehicle. The dose which reduced mortality by 50% was recorded as the $ED_{50}$ value. The $ED_{50}$ values reported are the average of at least two determinations.

**PAF-Induced Whole Blood Aggregation in Dogs.** Blood samples were taken from beagle dogs ($n = 4$) via an indwelling saphenous catheter into 0.1 vol 3.8% w/v trisodium citrate anticoagulant. Aggregation responses to PAF were measured by following the increase in impedance in stirred (1000 rpm) samples at 37 °C using a Chronolog Model 540 whole blood aggregometer. For each dog, the minimum concentration of PAF required to produce irreversible aggregation (30–50 nM) was established prior to dosing. Aggregation responses to this minimum concentration of PAF were measured in blood samples taken at various times after administration, by gavage, of solutions of compound **17** (0.075 mg/kg) dissolved in the minimum quantity of 0.01 M hydrochloric acid.

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