Novel Antagonists of Platelet-Activating Factor. 2. Synthesis and Structure–Activity Relationships of Potent and Long-Acting Heterofused [1,5]Benzodiazepine and [1,4]Diazepine Derivatives of 2-Methyl-1-phenylimidazo[4,5-*c*]pyridine

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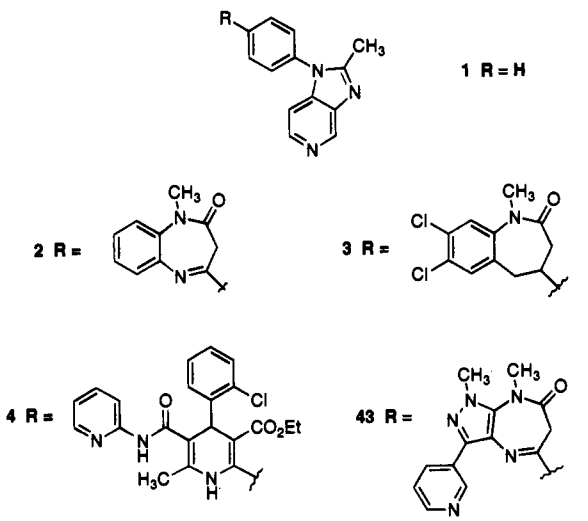
Received December 30, 1994®

The optimization of *in vitro* activity and oral potency and duration of action *in vivo* is described for three novel structural types of platelet-activating factor (PAF) antagonist: [1,5]benzodiazepines **5**–**12** onto which a variety of other heterocyclic rings were fused, pyrido[2,3-*b*][1,4]-diazepinones **13**–**26**, and pyrazolo[3,4-*b*][1,4]diazepinones **27**–**46**. Compounds **5**–**12** were prepared by elaboration of the [1,5]benzodiazepine-2-thiones **47** and **48**, and **13**–**46** were prepared by cyclocondensation reactions of a variety of 2,3-diaminopyridine and 4,5-diaminopyrazole derivatives with ethyl 4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoylacetate (**53**). The presence of imine–enamine tautomerism was observed in certain diazepine derivatives and is discussed. Structure–activity relationships were evaluated where PAF antagonist activity was measured *in vitro* by determining the concentration of compound (IC_{50}) required to inhibit 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. In addition, the duration of action in conscious dogs was measured by determining the oral dose of selected compounds required to inhibit completely PAF-induced whole blood aggregation *ex vivo*. The most potent compound was 1,6,7,8-tetrahydro-1,8-dimethyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-7-oxo-3-(3-pyridyl)pyrazolo[3,4-*b*][1,4]diazepine (**43**, UK-91,473) (IC_{50} = 2.4 nM, ED_{50} = 0.01 mg/kg po), which was found to be significantly more potent *in vivo* (murine lethality) than the dihydropyridine PAF antagonist 4-(2-chlorophenyl)-1,4-dihydro-3-(ethoxycarbonyl)-6-methyl-4-[(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-5-[*N*-(2-pyridyl)carbamoyl]pyridine (**4**, UK-74,505) (ED_{50} = 0.26 mg/kg po). Compound **43** also possessed a longer duration of action than compound **4** in the conscious dog at one-fourth of the dose. The crystal structure of compound **43**, established by X-ray diffraction, is reported.

In the preceding paper,[1] we described the synthesis and structure–activity relationships (SARs) of certain derivatives of 2-methyl-1-phenylimidazo[4,5-*c*]pyridine (**1**), an antagonist of platelet-activating factor (PAF), which inhibits PAF-induced aggregation of rabbit washed platelets at submicromolar concentrations *in vitro*. This program led to the discovery of a series of benzodiazepine and benzazepine analogues, e.g., **2** and **3**, which possess superior potency (up to 10-fold *in vitro* and 5-fold *in vivo*) compared to UK-74,505 (**4**) (PAF-induced rabbit platelet aggregation IC_{50} = 4.3 nM, PAF-induced murine lethality ED_{50} = 0.26 mg/kg po),[2,3] one of the most potent PAF antagonists discovered.

This paper describes our attempts to optimize the potency and duration of action of the benzodiazepine series. Potency was measured using PAF-induced aggregation of rabbit washed platelets *in vitro* and PAF-induced murine lethality *in vivo*, as previously reported.[2,3] In addition, the duration of action of selected compounds was measured by determining the oral dose in dogs required to inhibit completely PAF-induced whole blood aggregation *ex vivo*. Three structural types of analogues were explored; benzodiazepines **5**–**12**, in which a further heterocyclic ring was fused onto the diazepine ring, pyrido-fused diazepinones **13**–**26**, and pyrazolo-fused diazepinones **27**–**46**, in which a pyridine or pyrazole ring replaced the benzene ring of **2**. The most potent compound, 1,6,7,8-tetrahydro-1,8-dimethyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-7-oxo-3-(3-pyridyl)pyrazolo[3,4-*b*][1,4]diazepine (**43**, UK-91,473), was equipotent with **4** *in vitro* but possessed significantly superior efficacy *in vivo* (murine lethality ED_{50} = 0.01 mg/kg po). Compound **43** also possessed superior potency and duration of action to both compound **4** and the thienotriazolodiazepine derivative bepafant



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® Abstract published in *Advance ACS Abstracts*, August 1, 1995.

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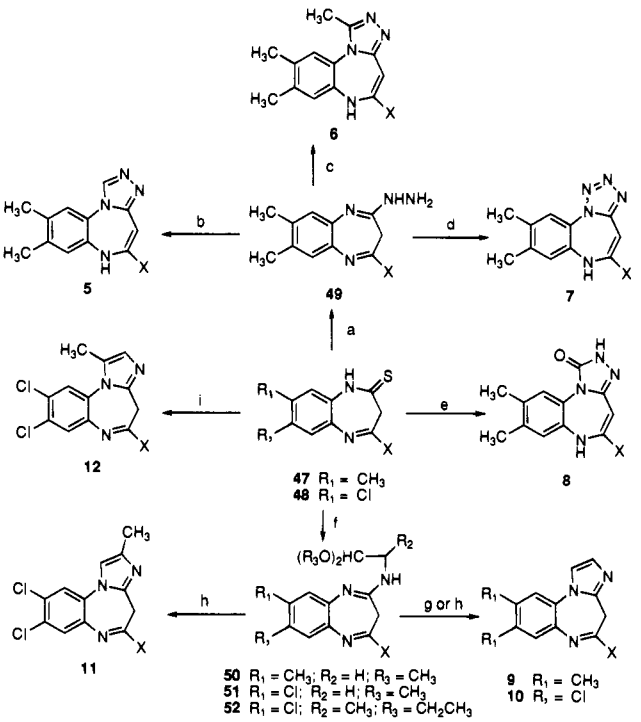
Scheme 1[a]



[a] X = 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl. (a) NH_2NH_2, TsOH, *n*-butanol, 100 °C; (b) $(EtO)_3CH$, HCO_2H, reflux; (c) $(EtO)_3CCH_3$, CH_3CO_2H, reflux; (d) HCl(aq), $NaNO_2$, −5 °C; (e) NH_2NHCO_2Et, TsOH, *n*-butanol, reflux, then NaH, THF, 20 °C; (f) $H_2NCH_2CH(OCH_3)_2$ or $H_2NCH(CH_3)CH(OCH_2CH_3)_2$, TsOH or HgO, *n*-butanol, reflux; (g) concentrated H_2SO_4, 100 °C; (h) HCO_2H, reflux; (i) $HC{\equiv}CCH_2NH_2$, HgO, *n*-butanol, reflux.

(WEB2170)[4] in the conscious dog (inhibition of PAF-induced whole blood aggregation *ex vivo*).

Chemistry

The syntheses of compounds **5**−**12** are shown in Scheme **1**. Compounds **5**−**9** were prepared from the dimethylbenzodiazepinethione **47**[1] and **10**−**12** from its corresponding dichloro analogue **48**.[1] Thus, **47** was treated with hydrazine hydrate in refluxing *n*-butanol in the presence of *p*-toluenesulfonic acid to give the hydrazino derivative **49**, which was then cyclized to give **5**−**7** by reaction with triethyl orthoformate, triethyl orthoacetate, and nitrous acid, respectively.[5−7] In a similar manner, condensation of **47** with ethyl carbazate followed by ring closure[5] afforded the triazolone **8**. The imidazo-fused derivatives **9** and **10** were prepared by first condensing the required benzodiazepinethiones **47** and **48** with 1-amino-2,2-diethoxyethane using either *p*-toluenesulfonic acid as catalyst or, preferably, red mercuric oxide to give **50** and **51** and then ring closing using hot concentrated sulfuric acid[7,8] or, preferably formic acid at reflux. The imidazole **11** was prepared via **52** in a manner analogous to that of **10**, using 2-amino-1,1-diethoxypropane[9] as the three-carbon synthon, whereas its isomer **12** was obtained directly on treatment of **48** with 1-amino-2-propyne in the presence of red mercuric oxide.[8]

For compounds **5**−**12**, the possibility exists for imine−enamine tautomerism within the diazepine ring. It is interesting to note that, whereas the triazolodiazepines **5**, **6**, and **8** and the tetrazolodiazepine **7** were isolated in the enamine form, the related imidazo-fused analogues **9** and **10** exhibited predominantly the imine

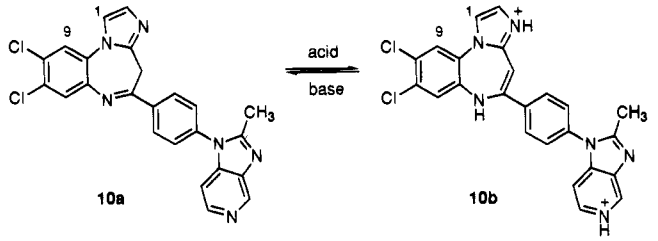
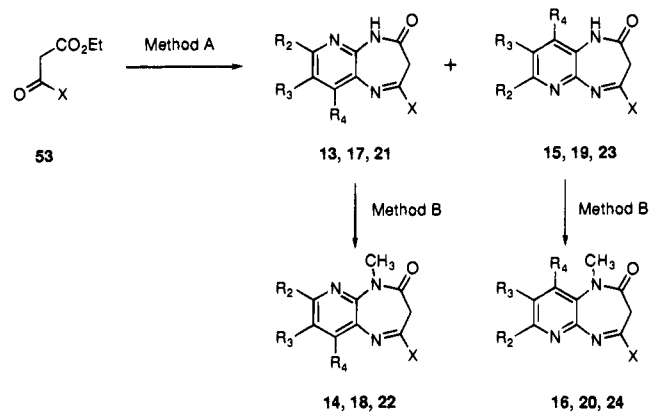


Figure 1. Tautomeric forms of compound 10 under basic and acidic conditions.

Scheme 2[a]



[a] X = 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl. For definitions of R_2−R_4, see Table 7. Method A: diaminopyridine, toluene, reflux. Method B: NaH, CH_3I, DMF, 20 °C.

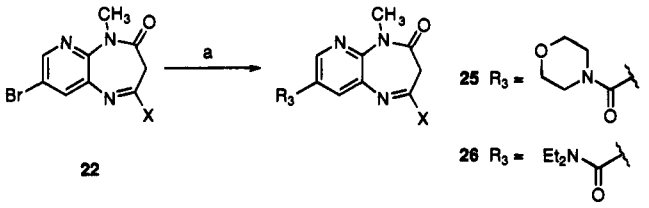
tautomer. A more detailed study of compound **10** revealed that in acidic solution it exists entirely as the enamine tautomer, presumably as the dication **10b** (see Figure 1), as evidenced by the proton NMR spectrum. A dimesylate salt of **10** can be formed, which is a stable, water-soluble, deep orange-red powder. However, on neutralization, a mixture of **10a** and its enamine tautomer was isolated. The two tautomers have different R_fs on silica gel TLC, although equilibration of the tautomers during the elution of the TLC plate, was observed by running the TLC a second time in a direction perpendicular to the first. Equilibration between the tautomers also occurred in chloroform solution, the mixture reverting (>24 h at 20 °C, within 2 h at reflux) to a ca. 20:1 mixture of **10** and its enamine tautomer. A similar phenomenon has been observed for a dihydropyrido[2,3-*b*][1,4]diazepinone.[10]

The predominance of **10b** in acid solution may be explained by the extended conjugation possible in this tautomer. Favorable conjugation may also underlie the preference for **5**−**8** to exist as the enamine tautomers even in neutral solution, since the additional heterocycle fused to the diazepine (triazole or tetrazole) is more electron-withdrawing than the imidazole.

A further feature of note in the proton NMR spectra of **9**, **10**, and **12** is the signal corresponding to the methylene protons. In the case of **9** and **10**, the signal is a slightly broadened singlet, whereas in **12** there are two one-proton doublets (J = 13 Hz) at δ 3.26 and 4.77. The diazepine ring undergoes a tub−tub conformational interconversion which is fast on the NMR time scale for **9** and **10** but which is slowed markedly by the introduction of a 1-position methyl group.

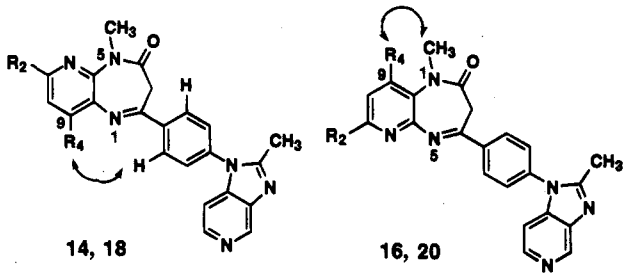
The syntheses of the pyrido-fused diazepinones **13**−**26** are shown in Schemes 2 and 3. When the keto ester **53**[2] was heated in toluene with 2,3-diaminopyridine

Scheme 3[a]



[a] X = 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl. (a) Morpholine or diethylamine, tetrakis(triphenylphosphine)palladium(0), *N,N*-dimethylacetamide, CO (1 atm), 120 °C.

Table 1. Confirmation of Structure for Isomeric Pyridodiazepinones by Measurement of Nuclear Overhauser Enhancements



proton irradiated	compd	enhancement of phenylene H (%)	compd	enhancement of 1-CH_3 (%)
9-H	**14**	1	**16**	3
9-CH_3	18	2.1	**20**	3.8

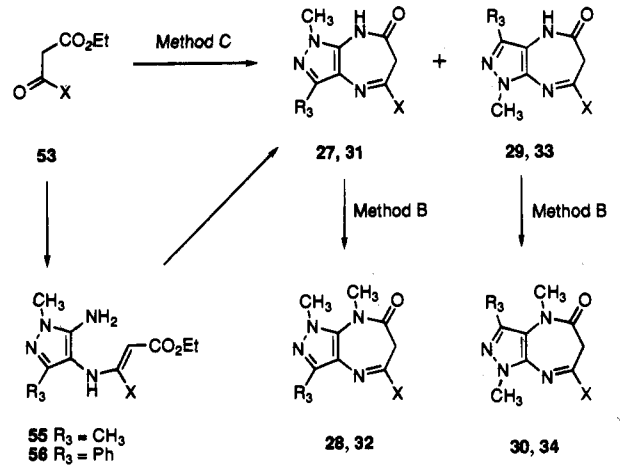
(method A), in the presence of silica gel with azeotropic removal of water, a mixture of isomeric products, **13** and **15**, was formed. Compounds **13** and **15** were separated by column chromatography and then methylated using methyl iodide in DMF with sodium hydride as base (method B). In a similar manner, cyclocondensation of **53** with 2,3-diamino-4,6-dimethylpyridine[11] and 5-bromo-2,3-diaminopyridine (**54**)[12] followed by methylation gave compounds **17**–**20** and **21**–**24**, respectively. Compound **54** was most conveniently prepared from the corresponding 3-nitropyridine[12] by reduction using hydrazine in ethanol over a catalytic quantity of 10% ruthenium on carbon, since the sensitive product may be isolated rapidly and in very high yield. Compounds **25** and **26** were prepared from compound **22** by palladium-catalyzed carbonylation[13] in the presence of the appropriate amine (morpholine or diethylamine), as shown in Scheme 3.

The assignment of structure for regioisomeric pairs **14** and **16**, and **18** and **20** was based on nuclear Overhauser enhancements in the proton NMR spectra (see Table 1). Thus, the pyrido[2,3-*b*]diazepines (**14** and **18**) were characterized by an NOE between the substituent R_4 and the phenylene protons adjacent to the diazepine ring.[14] In complementary fashion, the observation of NOEs between R_4 and the methyl group attached to N-1 of the diazepine confirmed the identity of the isomeric pyrido[3,2-*b*]diazepines **16** and **20**.

Another feature of interest in the proton NMR spectra of the pyridodiazepinone isomers was that compounds **13**, **17**, and **21** existed entirely as the imine tautomer in deuteriochloroform, whereas the regio-isomers **15**, **19**, and **23** existed as approximately 1:1 mixtures of enamine and imine tautomers.

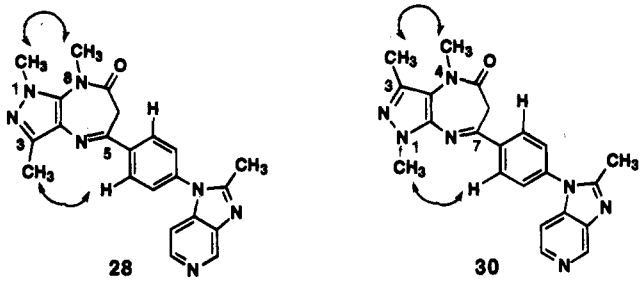
The syntheses of the pyrazolo-fused diazepinones **27**–**33** are shown in Scheme 4. Reaction of keto ester **53**

Scheme 4[a]



[a] X = 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl. For definitions of R_3, see Table 7. Method C: diaminopyrazole derivative, toluene, reflux, then NaH, EtOH, 20 °C. Method B: NaH, CH_3I, DMF, 20 °C.

Table 2. Confirmation of Structure for Isomeric Pyrazolodiazepinones by Measurement of Nuclear Overhauser Enhancements



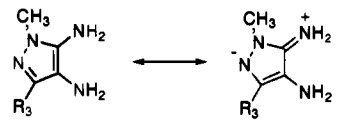
proton irradiated	enhancement (%)	proton irradiated	enhancement (%)
1-CH_3	8-CH_3, 4	3-CH_3	4-CH_3, 4
8-CH_3	1-CH_3, 4	4-CH_3	3-CH_3, 4
3-CH_3	phenylene H, 0	1-CH_3	phenylene H, 5.5
phenylene H	3-CH_3, 0	phenylene H	1-CH_3, 0

with 4,5-diamino-1,3-dimethylpyrazole[15] and 4,5-diamino-1-methyl-3-phenylpyrazole[16] in refluxing toluene afforded mixtures of regioisomeric pyrazolodiazepinones **27** and **29**, and **31** and **33**, respectively, together with uncyclized enamines **55** and **56**. Treatment of the crude product mixtures with sodium ethoxide at room temperature effected ring closure of **55** and **56** to give **27** and **31**, respectively (method C).[17] The regioisomers were separated by column chromatography and subsequently methylated (method B) to afford compounds **28**, **30**, and **32**. Compound **34** was not successfully obtained, presumably due to the severe steric hindrance of the adjacent phenyl group. The structures of regioisomers **28** and **30** were established by NOE measurements (see Table 2) in an analogous way to the pyridodiazepinones.[14] In contrast to the pyridodiazepinones, all the pyrazolodiazepinones existed as the imine tautomers in deuteriochloroform.

The ratio of regioisomers obtained by the reaction of 2,3-diaminopyridines and 4,5-diaminopyrazoles with keto ester **53** (see Table 3) deserves some comment. In the case of the pyrazolo-fused compounds **27**, **29**, **31**, and **33**, the major isomers were **27** and **31**. This result can be rationalized by preferential attack of the more reactive 4-amino group of the pyrazole on the keto group

Table 3. Isomeric Ratios of Pyrido- and Pyrazolodiazepinones

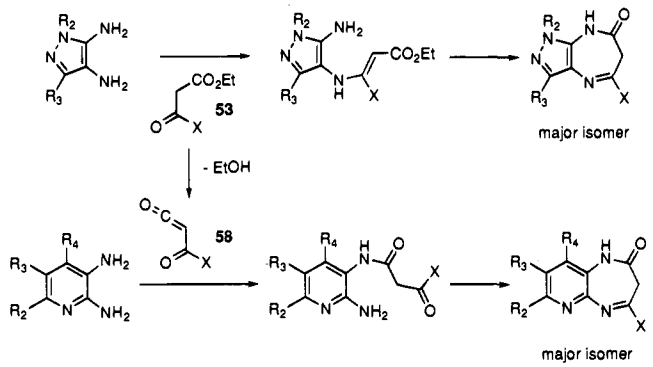
pyridodiazepines	ratio	pyrazolodiazepines	ratio
13:15	38:62	**27:29**	95:5
17:19	28:72	**31:33**	85:15
21:23	47:53		



57 57a

Figure 2. Canonical form **57a** rationalizes the low reactivity of the pyrazole 5-amino group.

Scheme 5[a]

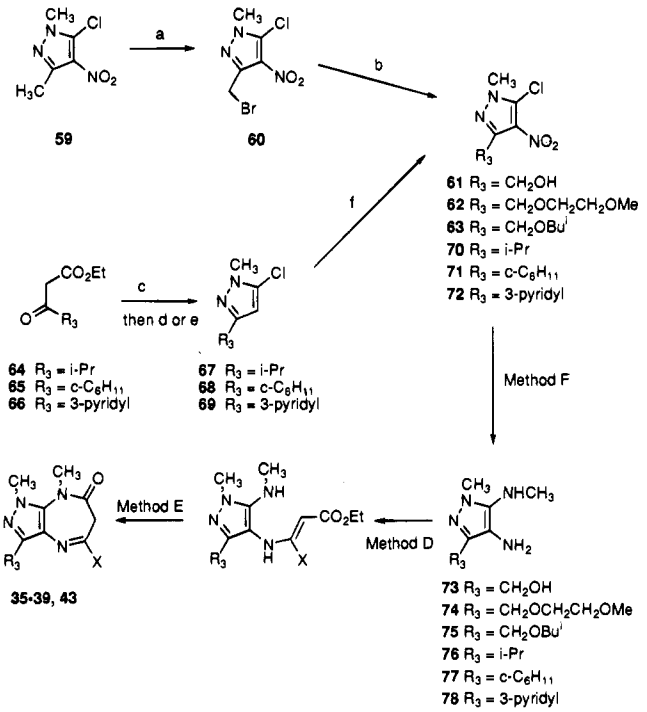


[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl.

of **53** (see Scheme 4). The formation of the intermediate enamines **55** and **56** is evidence of the poor nucleophilicity of the 5-amino group. The influence of canonical form **57a** is proposed to be responsible for the lower nucleophilicity of the 5-amino group (see Figure 2). We were therefore surprised to find that the compounds **15**, **19**, and **23** predominated in the mixtures of pyrido-fused diazepinones, since the 3-amino group in 2,3-diaminopyridines was anticipated to be the more nucleophilic and no enamine intermediates analogous to **55** and **56** were ever isolated. We suspect that the reaction of 2,3-diaminopyridine does not proceed by the same mechanism as that of the 4,5-diaminopyrazoles, even though similar reaction conditions were used to obtain the cyclized products. We suggest that the former reaction proceeds via the acyl ketene **58** (see Scheme 5). The more reactive 3-amino group of the pyridine is thereby acylated first, leading to the observed major isomer. It is recognized that the differences in isomer ratios are quite small, and it is perfectly possible that both mechanisms shown in Scheme 5 may be followed. It is interesting to note that Israel and Jones[18] reported that the reaction between 2,3-diaminopyridine and ethyl benzoylacetate in refluxing xylene gave only one regioisomer (65% yield), whose structure corresponded with **13**, not **15**.

Further *N*-methylpyrazolodiazepinones **35–44** were prepared to investigate how varying the R_3 substituent would influence potency and duration of action while retaining methyl groups on the 1- and 7-position nitrogen atoms. The syntheses of these compounds are shown in Schemes 6 and 7. Thus, a series of 4,5-diaminopyrazoles (**73–78**) with varying 3-position substituents was prepared and reacted with keto ester **53** regioselectively (methods D and E)[19] to obtain **35–39** and **43**. In the first step, selective reaction of the

Scheme 6[a]



[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. (a) Br_2, CCl_4, 500 W lamp, reflux; (b) H_2O or 2-methoxyethanol or isobutyl alcohol, $AgBF_4$, heat; (c) CH_3NHNH_2, ethanol, reflux; (d) $POCl_3$, reflux; (e) $PhPOCl_2$, 170–180 °C; (f) fuming HNO_3, concentrated H_2SO_4, −10–5 °C; (method F) CH_3NH_2, ethanol, 100 °C, then NH_2NH_2, Raney Ni, ethanol, 50 °C; (method D) **53**, $ZnCl_2$ (cat.), ethanol, reflux; (method E) NaH, ethanol, 20 °C.

4-amino group of the pyrazole occurred in refluxing ethanol containing a catalytic quantity of anhydrous zinc chloride. The resulting enamino esters were then treated with sodium ethoxide at room temperature to effect ring closure. Diaminopyrazoles **73–78** were obtained by nucleophilic displacement of chloride from the corresponding 5-chloro-4-nitropyrazoles **61–63** and **70–72** using methylamine followed by reduction of the nitro group (method F; see Table 4).

Intermediates **61–63** were prepared starting with 5-chloro-1,3-dimethyl-4-nitropyrazole[20] (**59**), which was first brominated to give **60**, and then reacted with water, 2-methoxyethanol or isobutyl alcohol in the presence of silver tetrafluoroborate (see Scheme 6). Intermediates **70–72** were prepared in three steps from the keto esters **64–66**. Firstly, condensation with methylhydrazine in refluxing ethanol afforded the corresponding 5-pyrazolones, which were then chlorinated using phosphorus oxychloride or phenylphosphonic dichloride to give the chloropyrazoles **67–69**.[21] Finally, nitration[20,22] of **67–69** proceeded smoothly to give **70–72**.

Compounds **40–42** and **44** were prepared by methods analogous to those for **28** and **35**, as shown in Scheme 7. Thus, the 4,5-diaminopyrazoles **79–82**[23] were condensed with keto ester **53** to give the pyrazolodiazepines **83–86** (method C, or D and then E) followed by N-methylation (method B).

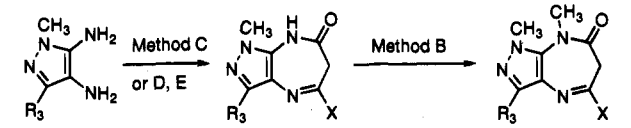
The syntheses of the tricyclic analogues **45** and **46** are shown in Schemes 8 and 9, respectively. Diaminopyrazole **87**[23] was converted to the pyrazolodiazepinone **88** by method C followed by ring closure under Mitsunobu conditions to give **45**. A slightly different strategy had to be employed for **46**. Thus, pyrazole **89**[24]

Table 4. Substituted 4-Nitro-5-amino- and 4,5-Diaminopyrazoles Prepared by Method F

compd	yield (a) substitution (%)	4-nitro 5-amino derivative ^{1}H NMR (300 MHz, $CDCl_3$)	yield (b) reduction (%)	4,5-diamino derivative ^{1}H NMR (300 MHz, $CDCl_3$)
73	73	δ 3.17 (1H, t, J = 5 Hz), 3.27 (3H, d, J = 5 Hz), 3.92 (3H, s), 4.75 (2H, d, J = 5 Hz), 7.10 (1H, br s)	96	δ 2.66 (4H, br s), 2.82 (3H, s), 3.66 (3H, s), 4.62 (2H, s)
74	95	δ 3.24 (3H, d, J = 5 Hz), 3.40 (3H, s), 3.63 (2H, t, J = 4 Hz), 3.80 (2H, t, J = 4 Hz), 3.91 (3H, s), 4.81 (2H, s), 7.01 (1H, br s)	100	δ 2.83 (6H, m), 3.39 (3H, s), 3.58 (2H, m), 3.65 (2H, m), 3.68 (3H, s), 4.58 (2H, m)
75	94	δ 0.92 (6H, d, J = 5 Hz), 1.97 (1H, m), 3.24 (3H, d, J = 4 Hz), 3.39 (2H, d, J = 5 Hz), 3.92 (3H, s), 4.71 (2H, s), 7.01 (1H, br s)	100	δ 0.93 (6H, d, J = 5 Hz), 1.92 (1H, m), 2.60 (3H, br s), 2.83 (3H, s), 3.26 (2H, d, J = 5 Hz), 3.68 (3H, s), 4.48 (2H, s)
76	82	δ 1.28 (6H, d, J = 6 Hz), 3.23 (3H, d, J = 5 Hz), 3.50 (1H, septet, J = 6 Hz), 3.87 (3H, s), 7.16 (1H, br s)	98	δ 1.30 (6H, d, J = 5 Hz), 2.40 (2H, br s), 2.80 (1H, br s), 2.82 (3H, br s), 2.98 (1H, m), 3.67 (3H, s)
77	97	δ 1.28–1.99 (10H, complex), 3.20 (1H, m), 3.24 (3H, d, J = 4 Hz), 3.87 (3H, s), 7.15 (1H, s)	97	δ 1.2–2.0 (10H, m), 2.30 (3H, br s), 2.60 (1H, t, J = 5 Hz), 2.80 (3H, s), 3.63 (3H, s)
92	51[a]	δ[b] 1.2–2.1 (14H, complex), 3.30 (1H, m), 3.50 (2H, m), 3.85 (2H, t, J = 6 Hz), 6.84 (1H, br s)	c	

[a] 4-Amino-1-butanol replaced methylamine. [b] Spectrum measured at 500 MHz. [c] Crude product used directly for preparation of **46** without formal characterization.

Scheme 7[a]



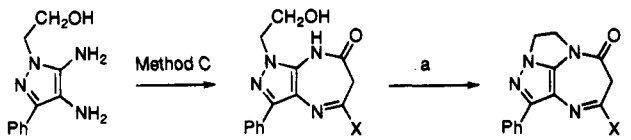
79 R_3 = 2-thienyl
80 R_3 = 4-ClC_6H_4
81 R_3 = 2-pyridyl
82 R_3 = 4-pyridyl

83 R_3 = 2-thienyl
84 R_3 = 4-ClC_6H_4
85 R_3 = 2-pyridyl
86 R_3 = 4-pyridyl

40 R_3 = 2-thienyl
41 R_3 = 4-ClC_6H_4
42 R_3 = 2-pyridyl
44 R_3 = 4-pyridyl

[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. For definitions of methods B–E, see Schemes 4 and 6.

Scheme 8[a]



87 **88** **45**

[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. (a) PPh_3, $EtO_2CN{=}NCO_2Et$, THF, 20 °C. For definition of method C, see Scheme 4.

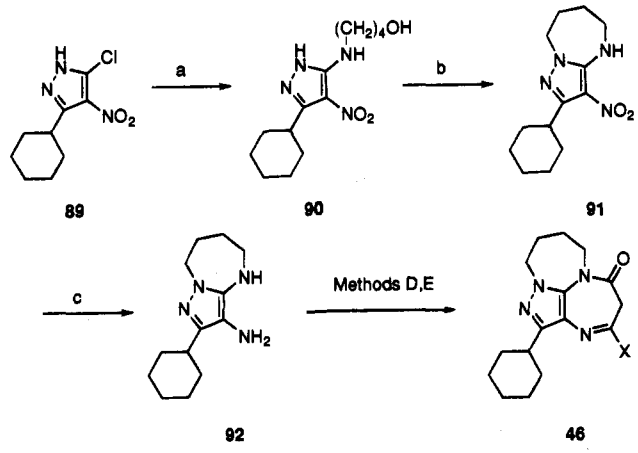
was reacted with 4-aminobutanol to give **90**, which was then cyclized to the pyrazolodiazepine **91**. After reduction to the diaminopyrazole **92**, cyclization via methods D and E afforded **46**. The synthetic methods employed, yields, and physical data for the various heterofused diazepinones are summarized in Table 5.

The proton NMR spectrum of **46** deserves comment. The ring inversions of both diazepine rings A and B were found to be slow on the NMR time scale, as evidenced by a very broad signal at ca. δ 4.2, corresponding to all the protons attached to C-5, C-7, and C-10 (see Figure 3). On heating a sample to 75 °C in 1,2-dichloroethane, a series of less broad signals appeared (δ 3.65 and 4.25, both two hydrogens, 7-CH_2 and 10-CH_2, and δ 2.70 and 3.82, both one hydrogen, 5-CH_2). Thus, it appears that the rate of ring inversion of one diazepine ring is slowed by the conformational restriction of the other, thereby leading to the interesting non-first-order NMR spectrum.

Results and Discussion

The PAF antagonist activity of test compounds was assessed using an *in vitro* assay involving rabbit washed

Scheme 9[a]



89 **90** **91** **92** **46**

[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. (a) 4-Aminobutanol, EtOH, 100 °C; (b) PPh_3, $EtO_2CN{=}NCO_2Et$, THF, 20 °C; (c) NH_2NH_2, Raney Ni, EtOH, 50 °C. For details of methods D and E, see Scheme 6.

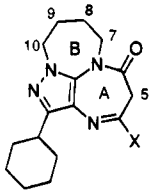
platelets and *in vivo* by measuring the ability of compounds to protect mice from the lethal effects of an injection of PAF.[2] Certain compounds which proved to be particularly active in the mouse were profiled further in an assay to measure their duration of action in conscious dogs. In this experiment, test compound was administered orally, and after 2 h, a blood sample was withdrawn and treated with a multiple of the minimum amount of PAF required to cause irreversible aggregation. This multiple was usually 10 to provide a more severe test of a compound's efficacy. The minimum amount of PAF (30–50 nM) required was established for each dog by aggregating control samples prior to dosing. If no inhibition of aggregation was observed, a second, larger dose of compound was administered and a blood sample taken after a further 2 h. If, in the first sample, the response to PAF was inhibited, further blood samples were withdrawn at various intervals until the predose PAF response returned. The duration of action at this dose was thereby recorded. Data for compound **4** and bepafant (WEB2170)[4] are shown for comparison in the results tables.

The SARs of the heterofused benzodiazepines (Table 6) will be discussed first. Two methyl or chloro sub-

Table 5. Yields and Analytical Data for Heterofused Diazepinones

compd	method	yield (%)	mp (°C)	formula	anal.
13	A	14	252–253	$C_{21}H_{16}N_6O{\cdot}0.5H_2O$	C,H,N
14	B	50	252–255	$C_{22}H_{18}N_6O$	C,H,N
15	A	23	228–230	$C_{21}H_{16}N_6O{\cdot}0.25H_2O$	C,H,N
16	B	20	155–156	$C_{22}H_{18}N_6O$	C,H,N
20	B	25	230–233	$C_{24}H_{22}N_6O{\cdot}0.25H_2O$	C,H,N
21	A	24	258–260	$C_{21}H_{15}BrN_6O{\cdot}0.5H_2O$	C,H,N
22	B	77	252–254	$C_{22}H_{17}BrN_6O$	C,H,N
23	A	27	250–252	$C_{21}H_{15}BrN_6O{\cdot}0.25H_2O$	C,H,N
24	B	38	249–251	$C_{22}H_{17}BrN_6O$	C,H,N
28	B	48	250–253	$C_{22}H_{21}N_7O$	C,H,N
30	B	37	258–260	$C_{22}H_{21}N_7O{\cdot}$methanol	C,H,N
31	C	22	245–248	$C_{26}H_{21}N_7O{\cdot}0.5H_2O$	C,H,N
32	B	47	232	$C_{27}H_{23}N_7O$	C,H,N
33	C	4	>300	$C_{26}H_{21}N_7O$	C,H,N
35	D then E	29	299–300	$C_{22}H_{21}N_7O_2{\cdot}0.5H_2O$	C,H[a]
36	D then E	28	142–144	$C_{25}H_{27}N_7O_3$	C,H,N
37	D then E	17	140	$C_{26}H_{29}N_7O_2{\cdot}0.25H_2O$	C,H,N
38	D then E	36	206–208	$C_{24}H_{25}N_7O$	C,H,N
39	D then E	33	189–191	$C_{27}H_{29}N_7O_2{\cdot}0.5H_2O$	C,H,N
40	B	42	278–280	$C_{25}H_{21}N_7OS$	C,H,N
41	B	47	218–220	$C_{27}H_{22}ClN_7O$	C,H,N
42	B	22	272	$C_{26}H_{22}N_8O$	C,H,N
44	B	11	200	$C_{26}H_{22}N_8O{\cdot}0.5H_2O$	C,H,N
46	D then E	65	206–207	$C_{29}H_{31}N_7O{\cdot}0.75H_2O$	C,H,N
83	D then E	60	305–307 dec	$C_{24}H_{19}N_7OS{\cdot}0.5H_2O$	C,H,N
84	C	39	>325	$C_{26}H_{20}ClN_7O$	C,H,N
85	D then E	36	305–310	$C_{25}H_{20}N_8O$	C,H,N
86	D then E	71	326–328	$C_{25}H_{20}N_8O$	*b*
88	C	39	185–190	$C_{27}H_{23}N_7O_2{\cdot}H_2O$	C,H,N

[a] N: found, 23.57; calcd 23.10. [b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (3H, s), 3.86 (2H, s), 4.03 (3H, s), 7.15 (1H, d, J = 4 Hz), 7.54 (2H, d, J = 6 Hz), 8.10 (2H, d, J = 5 Hz), 8.38 (2H, d, J = 6 Hz), 8.43 (1H, d, J = 4 Hz), 8.73 (2H, d, J = 5 Hz), 9.09 (1H, s).



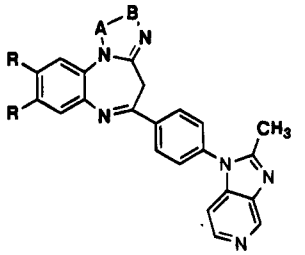
46

Figure 3. Numbering system used in compound **46**.

stituents in the 7- and 8-positions were chosen since their introduction into the parent benzodiazepine had been found to increase *in vitro* potency by approximately 5–7-fold.[1] The introduction of the heterocycle was generally well-tolerated, with the *in vitro* potency being close to that of the parent benzodiazepinone[1] (IC_{50} = 0.7–0.9 nM), except for the tetrazole and triazolone derivatives **7** and **8**. The most potent compounds *in vitro* were the imidazoles **9–12**, which were also most potent *in vivo*, whereas the triazoles **5** and **6** lacked potency *in vivo*. From this group, compound **10** was selected for evaluation in the conscious dog (see below).

The SARs of the pyrido- and pyrazolodiazepinones **13–46** (Table 7) will be discussed next. Considering the first four pyrido-fused derivatives **13–16**, the regioisomers **13** and **15** were not particularly potent. However, N-methylation caused a significant increase in potency for one regioisomer (**14**) but not for the other (**16**). The discovery of potent *in vivo* activity in **14** prompted us to examine other substituted pyridine derivatives. Compounds **17–20** and **21–24** possessed two additional methyl groups and one bromine atom, respectively, which caused an increase in potency. The potency trend between isomeric series was maintained in the dimethyl analogues but was much less apparent in the bromo

Table 6. Structure–Activity Relationships for Heterofused Benzodiazepines[a]



compd	R	A–B	IC_{50}[b] (nM)	ED_{50}[c] (mg/kg po)
5	CH_3	CH=N	2.3	>10
6	CH_3	$C(CH_3)$=N	2.4	>12.5
7	CH_3	N=N	11	6.6
8	CH_3	CO–NH	55	44
9	CH_3	CH=CH	1.3	0.1
10	Cl	CH=CH	1.7 ± 0.07[d]	0.2 ± 0.02[e]
11	Cl	CH=$C(CH_3)$	0.3	0.2
12	Cl	$C(CH_3)$=CH	1.2	0.1
4 (UK-74,505)			4.3 ± 0.73	0.26 ± 0.03
bepafant (WEB2170)			73	0.1

[a] Although the generic structure depicts the imine tautomer, some of the compounds in Table 1 were isolated as the corresponding enamine tautomers. For details, see Scheme 1 and the Experimental Section. [b] Single detection. A difference of less than 2-fold should not be regarded as significant. [c] Average of two determinations. [d] n = 3. [e] n = 6.

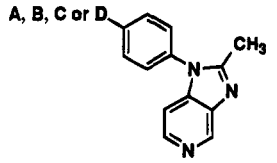
analogues. However, the N-methylated derivatives were consistently more potent *in vivo* (compare **18** with **17**, and **24** and **23**, for example). In the more potent regioisomer series, the bromine atom could be substituted by a carboxamido group (see **25** and **26**) while retaining excellent potency both *in vitro* and *in vivo*. From the pyrido-fused derivatives **13–26**, compounds **18**, **22**, **25**, and **26** were selected for evaluation in the conscious dog.

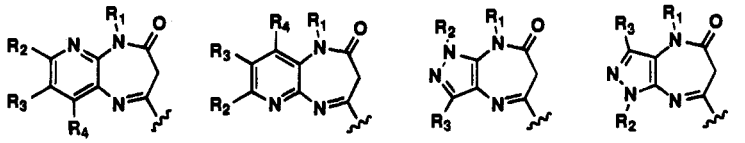
The dimethyl pyrazoles **27–30** were prepared to examine the effect of rearranging the two methyl groups and the sp^2 nitrogen atom of **17** and **19**. As with the pyrido-fused isomers, there was an approximately 20-fold difference in potency between the regioisomers **27** and **29** but only a 3-fold difference between their corresponding N-methylated analogues **28** and **30**. In this particular group of compounds, however, there was relatively little difference between them in their *in vivo* efficacy.

The pyrazoles constituted a suitable framework for the introduction of additional groups of varying types. Substitution of the pyrazole 3-methyl group in **27–30** by a phenyl gave compounds **31–33**. The methylation reaction required to give **34** failed, presumably due to steric hindrance from the adjacent phenyl ring. This change led to a small increase in potency *in vitro*, with one of the isomers, **32**, also possessing excellent potency *in vivo*.

Compounds **35–44** were prepared to explore the SARs of the pyrazole 3-position further. Introduction of a hydroxyl, as in **35**, gave potency equivalent with that of **28**, and longer branched or straight chains increased potency *in vitro* up to 20-fold (see **36–39**). In particular, **37** and the cyclohexyl analogue **39** inhibited platelet aggregation at <1 nM, and the latter was also very potent *in vivo* (ED_{50} = 0.03 mg/kg). Aromatic analogues of **32** were then explored (compounds **40–44**). The

Table 7. Structure–Activity Relationships for Pyrido- and Pyrazolo-Fused Diazepinones





compd	Het	R_1	R_2	R_3	R_4	IC_{50}[a] (nM)	ED_{50}[b] (mg/kg po)
13	A	H	H	H	H	130	NT[c]
14	A	Me	H	H	H	3.5	0.06
15	B	H	H	H	H	66	NT
16	B	Me	H	H	H	45	NT
17	A	H	Me	H	Me	6.8	0.1
18	A	Me	Me	H	Me	1.3	0.01
19	B	H	Me	H	Me	21	NT
20	B	Me	Me	H	Me	38	NT
21	A	H	H	Br	H	4	0.6
22	A	Me	H	Br	H	1.4	0.03
23	B	H	H	Br	H	5.6	7.3
24	B	Me	H	Br	H	4	0.15
25	A	Me	H	CO-4-morpholinyl	H	2.5	0.02
26	A	Me	H	$CONEt_2$	H	3.2	0.01
27	C	H	Me	Me		26	0.09
28	C	Me	Me	Me		17	0.1
29	D	H	Me	Me		1	0.03
30	D	Me	Me	Me		5	0.1
31	C	H	Me	Ph		0.6	0.33
32	C	Me	Me	Ph		0.5	0.02
33	D	H	Me	Ph		2.7	0.27
34	D	Me	Me	Ph			
35	C	Me	Me	CH_2OH		14	NT
36	C	Me	Me	$CH_2OCH_2CH_2OMe$		6.2	NT
37	C	Me	Me	CH_2O*i*-Bu		0.8	0.5
38	C	Me	Me	*i*-Pr		3.5	NT
39	C	Me	Me	c-C_6H_{11}		0.7	0.03
40	C	Me	Me	2-thienyl		1.5	NT
41	C	Me	Me	4-ClC_6H_4		0.6	0.5
42	C	Me	Me	2-pyridyl		14	NT
43	C	Me	Me	3-pyridyl		2.4 ± 0.6[d]	0.01
44	C	Me	Me	4-pyridyl		5.2	NT
45	C	$-CH_2CH_2-$		Ph		4	NT
46	C	$-CH_2CH_2CH_2CH_2-$		c-C_6H_{11}		0.4	NT
4 (UK-74,505)						4.3 ± 0.73	0.26 ± 0.03
bepafant (WEB2170)						73	0.1

[a] Single determination. A difference of less than 2-fold should not be regarded as significant. [b] Average of two determinations. [c] NT = not tested. [d] $n = 3$.

chlorophenyl analogue **41** was equipotent with **32** *in vitro*, whereas the other derivatives were slightly less potent. However, the pyridyl analogue **43** also possessed exceptional potency (ED_{50} = 0.01 mg/kg) *in vivo*. Six of the pyrazolo-fused analogues (**27**–**29**, **32**, **39**, and **43**) were selected for further profiling in the conscious dog.

Examination of molecular models suggested that introduction of a 5-membered ring bridging the pyrazole and diazepine rings would exert a flattening effect on the diazepine ring. Our previous experience[1] suggested that this would result in a loss of potency *in vitro*, and indeed this was found to be the case (**45** is 8-fold less potent than **32** *in vitro*). Models also indicated that by extending the bridge to four methylenes, as in compound **46**, the necessary conformational puckering of the diazepinone ring would again be possible. As can be seen, **46** possessed excellent *in vitro* potency (IC_{50} = 0.4 nM), essentially equipotent with its nearest analogue (compound **39**).

The duration of action of selected compounds in the conscious dog is shown in Table 8. Results obtained using the same protocol for compound **4** and bepafant (WEB2170)[4] are also shown for comparison. Compound **4** and bepafant were of similar potency and duration of action and gave complete inhibition of whole blood aggregation induced by 10 times the minimum amount of PAF for about 9 and 7 h, respectively, following doses of 0.075 and 0.1 mg/kg po, respectively. Only four of the compounds (**18**, **32**, **39**, and **43**) selected for profiling in the dog possessed equivalent or greater potency and duration of action than **4**. Of these, compound **43** was clearly the most potent. The ranking of compounds according to efficacy against PAF-induced mouse lethal-

Table 8. Duration of Action of PAF Antagonists in the Conscious Dog

compd	dose (mg/kg po)[a]	duration of action (h)
10	0.2	7
17	0.15	0
	0.5	<8
18	0.1	9
22	0.2	4–6
25	0.1	2–3
26	0.1	4
27	0.3	0
	1.0	>6
28	0.2	4–6
29	0.15	0
	0.5	>8
32	0.1	>8
39	0.025	0
	0.075	8
43	0.025	9[b]
	0.05	>10[b]
4 (UK-74,505)	0.075	8–10
bepafant (WEB2170)	0.1	7

[a] Dose is the minimum required to give 100% inhibition of dog whole blood aggregation induced by 10 times the minimum concentration of PAF (*ex vivo*). [b] Inhibition maintained with 30 times the minimum concentration of PAF.

ity and PAF-induced whole blood aggregation in the dog is thus quite different. The reasons for these differences have not been elucidated, but differences in absorption and pharmacokinetics between species may be responsible. However, the excellent duration of action of compound **4** is not due to a long plasma half-life. Studies with **4** have shown it has unusual kinetics of interaction with the PAF receptor, as evidenced by a significant increase in potency against PAF-induced platelet aggregation with incubation time.[3a] We have examined the time-dependent inhibition of platelet aggregation of compound **43**, and it also shows similar behavior.[25] Tight, but not irreversible, binding to the PAF receptor by these compounds may therefore account for the observed long duration of action *in vivo*.

The crystal structure of compound **43** has been determined by X-ray diffraction of the dinitrate salt (see Figure 4 and Experimental Section). Atomic coordinates and bond lengths and angles are available as supporting information.

Compound **43** is a highly selective PAF antagonist, since it did not prevent platelet aggregation induced by ADP or arachidonic acid at concentrations up to 50 μM and did not inhibit radioligand binding at 10 μM to the following receptors: adenosine A_1, adrenoreceptors α_1 and α_2, Ca^{2+} (non-dihydropyridine), $5HT_1$, $5HT_2$, dopamine DA_2, muscarinic, benzodiazepine, H_2, and H_3. While some displacement of H_1 and Ca^{2+} (dihydropyridine) ligands was observed, compound **43** failed to show functional activity *in vitro* at concentrations up to 20 μM, almost 10 000-fold higher than its PAF antagonist IC_{50}.

In summary, this paper describes the optimization of a new class of benzodiazepine PAF antagonists related to **2**. While it was found that the PAF receptor was tolerant of a wide variety of structural alterations, including substitution of the amide functionality by heterocycles and replacement of the benzo fusion by pyrido or pyrazolo fusion, excellent *in vivo* efficacy was a little more difficult to achieve. From a group of compounds which were very potent at protecting mice from the lethal effects of PAF, we identified UK-91,473 (compound **43**) as the most potent on the basis of its long duration of action in the conscious dog. Compound **43** possesses oral potency and duration of action which are significantly superior to those of the clinical candidate UK-74,505 (compound **4**)[26] and bepafant (WEB2170).

Experimental Section

Chemistry. Melting points were determined using a Buchi apparatus in glass capillary 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 are 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 are 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. 2,3-Diaminopyridine and 1-amino-2,2-diethoxyethane were purchased from Aldrich Chemical Co.

The following intermediates were prepared according to literature procedures: **47**,[1] **48**,[1] 2-amino-1,1-diethoxypropane,[8] ethyl 4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoylacetate (**53**),[2] 2,3-diamino-4,6-dimethylpyridine,[11] 2-amino-5-bromo-3-nitropyridine,[12] 4,5-diamino-1,3-dimethylpyrazole,[15] 4,5-diamino-1-methyl-3-phenylpyrazole,[16] **59**,[20] **64**,[27] **65**,[28] **66**,[29] **68**,[21b] **79**–**82**,[23] **87**,[23] and **89**.[24] Bepafant (WEB2170)[4] was prepared in these laboratories by the published method.

7,8-Dimethyl-2-hydrazino-4-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-3*H*-[1,5]benzodiazepine (49). A mixture of compound **47** (411 mg, 1.0 mmol), hydrazine hydrate (60 mg, 1.2 mmol), and *p*-toluenesulfonic acid (10 mg) in *n*-butanol was heated at 100 °C for 1.5 h. The solvent was removed under reduced pressure and the crude product used directly. Compounds **5**–**7** were each prepared starting with 1.0 mmol of compound **47**.

8,9-Dimethyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine (5). A mixture of compound **49**, triethyl orthoformate (9 mL), and formic acid (2 mL) was heated at reflux for 10 min. The mixture was cooled, concentrated under reduced pressure, and dissolved in 2 M hydrochloric acid (10 mL). The solution was washed with ethyl acetate (20 mL), neutralized with dilute aqueous ammonia, and extracted with ethyl acetate/tetrahydrofuran = 1:1 (3 × 50 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 9:1) to give a white solid (95 mg, 23%): mp 302–304 °C (from acetone); ^{1}H NMR (300 MHz, DMSO-d_6, partial) δ 7.36 (1H, s, enamine CH), 13.65 (1H, br s, NH). Anal. ($C_{25}H_{21}N_7$) C, H, N.

5-[4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)phenyl)]-1,8,9-trimethyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine (6): prepared in a similar manner to that of **5**, using triethyl orthoacetate and acetic acid instead of triethyl orthoformate and formic acid, to give a brown solid (48 mg, 11%): mp 294–296 °C (after sonication with ethyl acetate/ether). Anal. ($C_{26}H_{23}N_7 \cdot 0.5H_2O$) C, H, N.

8,9-Dimethyl-5[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-6*H*-[1,2,3,4]tetrazolo[1,5-*a*][1,5]benzodiazepine (7). Compound **49** was dissolved in 2 M hydrochloric acid (10 mL) and cooled to −5 °C. A solution of sodium nitrite (72 mg, 1.04 mmol) in water (11 mL) was added over 2 min with stirring. The mixture was kept at −5 °C for a further 5 min

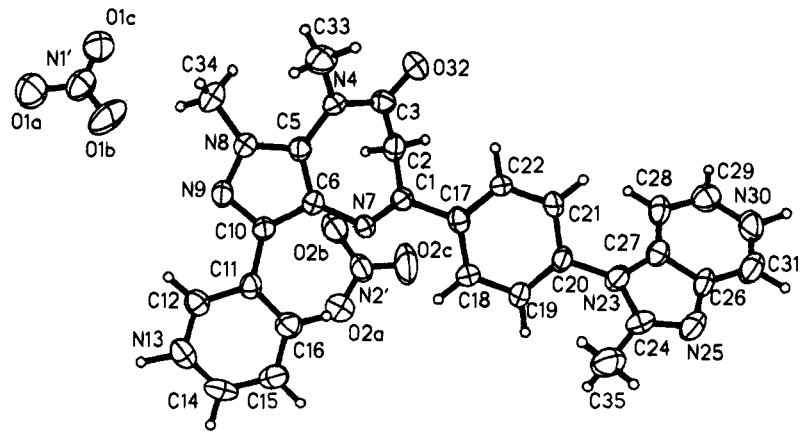


Figure 4. X-ray crystal structure of **43** dinitrate salt (SHELXTL plotting package). Disordered water molecules are not shown.

and then neutralized with 2 M aqueous sodium hydroxide. The solution was extracted with ethyl acetate/butanol = 2:1 (2 × 50 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with dichloromethane/methanol = 9:1) to give a brown solid (68 mg, 16%): mp 315 °C (from 2-propanol). Anal. ($C_{24}H_{20}N_6 \cdot 0.25H_2O$) C, H, N.

1,2-Dihydro-8,9-dimethyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-1-one (8). A solution of compound **47** (411 mg, 1.0 mmol), ethyl carbazate (210 mg, 2.0 mmol), and *p*-toluenesulfonic acid (10 mg) in *n*-butanol (5 mL) was heated at reflux for 16 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with dichloromethane/methanol = 9:1). The intermediate carbazate was then dissolved in dry tetrahydrofuran (5 mL) and treated with sodium hydride (60% dispersion in oil, 40 mg, 1.0 mmol) at room temperature for 3 h. The mixture was partitioned between 2 M hydrochloric acid (5 mL) and ethyl acetate (20 mL). The aqueous phase was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate/tetrahydrofuran = 1:1 (2 × 30 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with dichloromethane/methanol = 10:1) to give a white solid (85 mg, 20%): mp >325 °C (from methanol/dichloromethane); ^{1}H NMR (300 MHz, DMSO-d_6, partial) δ 7.64 (1H, br s, enamine CH), 11.04 (1H, br s, NH). Anal. ($C_{25}H_{21}N_7 \cdot 0.25H_2O$) C, H, N.

8,9-Dimethyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-6*H*-imidazo[1,2-*a*][1,5]benzodiazepine (9). A solution of compound **47** (575 mg, 1.4 mmol), aminoacetaldehyde dimethyl acetal (294 mg, 2.8 mmol), and *p*-toluenesulfonic acid (14 mg) in *n*-butanol (7 mL) was heated at reflux for 8 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 6:1). The intermediate **50** was dissolved in concentrated sulfuric acid (5 mL) and heated at 100 °C for 20 min. The mixture was cooled, poured onto ice, and neutralized with saturated aqueous sodium bicarbonate. The product was extracted into dichloromethane (2 × 150 mL), and the extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 6:1) to give a white solid (180 mg, 31%): mp 193–195 °C (after dissolution in methanol and precipitation with acetone). Anal. ($C_{26}H_{22}N_6 \cdot H_2O$) C, H, N.

8,9-Dichloro-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-4*H*-imidazo[1,2-*a*][1,5]benzodiazepine (10). A solution of compound **48** (1.36 g, 3.0 mmol), aminoacetaldehyde dimethyl acetal (630 mg, 6.0 mmol), and red mercuric oxide (650 mg, 3.0 mmol) in *n*-butanol (15 mL) was heated at reflux for 2.5 h. The mixture was cooled, diluted with methanol (50 mL), and filtered through Hyflo filter aid. The solvent was removed under reduced pressure, and the residue was suspended in pentane and sonicated for 5 min. The pentane was removed under reduced pressure to give compound **51** (1.10 g, 70%). This material (3.2 g, 6.12 mmol) was dissolved in 98% formic acid (50 mL) and heated at reflux for 1 h. The solvent was removed under reduced pressure, the residue was dissolved in water (50 mL), and the solution was added dropwise to excess ice-cold aqueous ammonia with stirring. The solid which precipitated was filtered off, washed with water (20 mL), and dried. The solid was dissolved in chloroform (150 mL) and stirred at reflux for 2 h to equilibrate the tautomers. The chloroform was removed under reduced pressure, and the residue was recrystallized from hot aqueous ethanol to give a fawn-colored solid (1.40 g, 50%): mp 241–243 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (3H, s), 4.08 (2H, br s), 7.12 (1H, d, J = 5 Hz), 7.21 (1H, s), 7.40 (1H, s), 7.51 (2H, d, J = 8 Hz), 7.69 (1H, s), 7.75 (1H, s), 8.37 (2H, d, J = 8 Hz), 8.42 (1H, d, J = 5 Hz), 9.08 (1H, s). Anal. ($C_{24}H_{16}Cl_2N_6 \cdot 0.5H_2O$) C, H, N.

8,9-Dichloro-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-6*H*-imidazo[1,2-*a*][1,5]benzodiazepine Dimesylate (10b). Compound **10** (1.62 g, 3.53 mmol) was dissolved in hot methanol (40 mL), and methanesulfonic acid (678 mg, 7.06 mmol) was added dropwise. The solution was kept at 5 °C overnight and the resulting orange-red solid filtered off. Recrystallization from hot aqueous ethanol gave an orange solid (1.30 g, 57%): ^{1}H NMR (300 MHz, DMSO-d_6, NH signals not observed) δ 2.72 (3H, s), 2.73 (6H, s), 5.81 (1H, s), 7.42 (1H, s), 7.58 (1H, d, J = 1 Hz), 7.71 (1H, s), 7.83 (4H, m), 8.03 (2H, d, J = 8 Hz), 8.62 (1H, d, J = 5 Hz), 9.35 (1H, s). Anal. ($C_{24}H_{16}Cl_2N_6 \cdot 2MeSO_3H$) C, H, N.

8,9-Dichloro-2-methyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-4*H*-imidazo[1,2-*a*][1,5]benzodiazepine (11). A solution of compound **48** (452 mg, 1.0 mmol), 2-amino-1,1-diethoxypropane (294 mg, 2.0 mmol), and red mercuric oxide (216 mg, 1.0 mmol) in *n*-butanol (5 mL) was heated at reflux for 4 h. The mixture was cooled and filtered through Hyflo filter aid, washing the filter cake with methanol (50 mL). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with dichloromethane/methanol = 9:1) to give compound **52** (387 mg, 68%) as a gum. This material was dissolved in 98% formic acid (5 mL) and heated at reflux for 1 h. The solvent was removed under reduced pressure; the residue was dissolved in *n*-butanol (30 mL) and washed with saturated aqueous sodium bicarbonate (30 mL). The organic layer was separated and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 6:1) to give a yellow foam which was dissolved in boiling ethyl acetate (2 mL) and precipitated with pentane. The yellow solid was filtered off and dried to afford the title compound as a 85:15 mixture of tautomers (76 mg, 16%): ^{1}H NMR (300 MHz, $CDCl_3$, imine tautomer only) δ 2.32 (3H, s), 2.62 (3H, s), 4.03 (2H, br s), 7.13 (2H, br s), 7.53 (2H, d, J = 8 Hz), 7.67 (1H, s), 7.75 (1H, s), 8.37 (2H, d, J = 8 Hz), 8.57 (1H, d, J = 5 Hz), 9.10 (1H, s). Anal. ($C_{25}H_{18}Cl_2N_6 \cdot H_2O$) C, H; N: found, 16.59; calcd, 17.10.

8,9-Dichloro-1-methyl-5-[4-(2-methylimidazo[4,5-*c*]py-

rid-1-yl)phenyl]-4*H*-imidazo[1,2-*a*][1,5]benzodiazepine (12). A solution of compound **48** (452 mg, 1.0 mmol), propargylamine (110 mg, 2.0 mmol), and red mercuric oxide (216 mg, 1.0 mmol) in *n*-butanol (5 mL) was heated at reflux for 10 h. The mixture was cooled, diluted with methanol (50 mL), and filtered through Arbocel filter aid. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 3:1) to give a buff solid (170 mg, 38%): mp 243–246 °C (after trituration with ether); ^{1}H NMR (300 MHz, $CDCl_3$, partial) δ 3.26 and 4.77 (each 1H, d, J = 13 Hz). Anal. ($C_{25}H_{18}Cl_2N_6 \cdot H_2O$) C, H, N.

Method A: 3,5-Dihydro-7,9-dimethyl-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-4*H*-pyrido[2,3-*b*][1,4]-diazepin-4-one (17) **and 1,3-Dihydro-7,9-dimethyl-4-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-2*H*-pyrido[2,3-*b*][1,4]diazepin-2-one** (19). A mixture of 2,3-diamino-4,6-dimethylpyridine (6.85 g, 50.0 mmol), compound **53**, and silica gel (Merck Kieselgel 60, 40–63 μm, 25 g) in toluene (500 mL) was heated at reflux under nitrogen for 6 h with azeotropic removal of water using a Dean–Stark apparatus. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with dichloromethane/methanol = 19:1) to give first compound **17** (3.20 g, 16%; mp 256–259 °C (from ethyl acetate); anal. ($C_{23}H_{20}N_6O$) C, H, N) and then compound **19** (8.40 g, 42%; mp 244–248 °C; anal. ($C_{23}H_{20}N_6O \cdot 0.5H_2O$) C, H, N).

Compounds **13**, **15**, **21**, **23**, and **88** were also made by method A; for details, see Table 5.

Method B: 3,5-Dihydro-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-5,7,9-trimethyl-4*H*-pyrido[2,3-*b*][1,4]-diazepin-4-one (18). Sodium hydride (60% oil dispersion, 0.40 g, 10 mmol) was added to a stirred suspension of compound **17** (3.19 g, 8.0 mmol) in dry dimethylformamide (50 mL) under nitrogen at 20 °C. After 1 h, iodomethane (1.28 g, 10 mmol) was added, and after a further 2 h at 20 °C, the mixture was poured into water (100 mL). The product was extracted into dichloromethane (100 mL and 2 × 50 mL), and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with dichloromethane/methanol = 96:4) to give a white solid (2.99 g, 91%): mp 273–276 °C (from ethyl acetate/methanol). Anal. ($C_{24}H_{22}N_6O$) C, H, N.

Compounds **14**, **16**, **20**, **22**, **24**, **28**, **30**, **32**, **40–42**, and **44** were also made by method B; see Table 5.

3,5-Dihydro-5-methyl-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-8-(4-morpholinylcarbonyl)-4*H*-pyrido-[2,3-*b*][1,4]diazepin-4-one (25). A mixture of compound **22** (461 mg, 1.0 mmol), morpholine (435 mg, 5.0 mmol), and tetrakis(triphenylphosphine)palladium (50 mg) in *N,N*-dimethylacetamide (10 mL) was heated at 120 °C under 1 atm of carbon monoxide for 20 h. The mixture was cooled, poured into ethyl acetate (200 mL), washed with water (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (eluting with dichloromethane, dichloromethane/methanol = 97:3, and then ethyl acetate/diethylamine = 19:1) gave a solid (118 mg, 24%): mp 167–173 °C dec (after trituration with ether). Anal. ($C_{27}H_{25}N_7O_3 \cdot 0.5H_2O \cdot 0.25$ether) C, H, N.

8-(*N,N*-Diethylcarbamoyl)-3,5-dihydro-5-methyl-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-4*H*-pyrido[2,3-*b*][1,4]diazepin-4-one (26): prepared as for **25** using diethylamine in place of morpholine: yield 16%; mp 195–198 °C. Anal. ($C_{27}H_{27}N_7O_2 \cdot 0.25$ether) C, H, N.

Method C: 1,3-Dimethyl-5-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-1,6,7,8-tetrahydropyrazolo[3,4-*b*][1,4]-diazepin-7-one (27) **and 1,3-Dimethyl-7-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-*b*][1,4]diazepin-5-one** (29). A mixture of 4,5-diamino-1,3-dimethylpyrazole (8.98 g, 71.2 mmol), compound **53** (23.0 g, 71.2 mmol), silica gel (Merck Kieselgel 60, 40–63 μm, 14 g), and toluene (330 mL) was heated under nitrogen at reflux for 21 h. After being cooled, the silica gel was filtered off and washed with methanol and a mixture of methanol and dichloromethane (1:1). The filtrate was concentrated under reduced pressure, and the residue was dissolved in dry ethanol (300 mL) under nitrogen. Sodium hydride (60% oil dispersion, 2.6 g, 66 mmol) was added in portions at room temperature, and the mixture was stirred for a further 1 h. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (gradient elution with ethyl acetate/diethylamine/methanol). First eluted was compound **29**, which was further purified by recrystallization from methanol to give a bright yellow powder (600 mg, 2%): mp 237–238 °C. Anal. ($C_{21}H_{19}N_7O \cdot 0.75\ H_2O$) C, H, N. The second eluted isomer (**27**) was obtained as a pale yellow powder (10.0 g, 38%): mp 313–315 °C (from methanol). Anal. ($C_{21}H_{19}N_7O \cdot 0.75\ H_2O$) C, H, N.

Compounds **31**, **33**, and **84** were also made by method C; see Table 5.

Method D: A mixture of compound **78** (15.35 g, 59.2 mmol), compound **53** (20.08 g, 62.2 mmol), and anhydrous zinc chloride (808 mg, 5.92 mmol) in dry ethanol (350 mL) was heated under nitrogen at reflux for 20 h and cooled to 0 °C. The solution of the resulting intermediate enamino ester was used directly in method E, below.

Method E: 1,6,7,8-Tetrahydro-1,8-dimethyl-5-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-7-oxo-3-(3-pyridyl)-pyrazolo[3,4-*b*][1,4]diazepine (43). The solution of enamino ester (from method D, above) was treated with sodium hydride (60% dispersion in oil, 4.97 g, 114 mmol) in portions over 20 min. The resulting slurry was stirred at room temperature for 1 h and concentrated under reduced pressure, and the residue was dissolved in dilute sulfuric acid. The solution was washed with ether (2 × 250 mL) and basified (to pH 10) with sodium hydroxide and the solid filtered off. Recrystallization from ethanol (300 mL) followed by azeotropic drying of the crystals using boiling ethyl acetate gave a creamy-colored solid (14.95 g, 52%): mp 240–242 °C. Anal. ($C_{26}H_{22}N_8O$) C, H, N.

Compounds **35–39**, **46**, **83**, **85**, and **86** were also made by methods D and E; see Table 5. In some cases the intermediate enamino esters from method D were purified by flash chromatography prior to ring closure by method E, as for compound **43**, above.

4-[4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2,3-*ij*]pyrazolo[3,4-*b*][1,4]-diazepin-6-one (45). A mixture of compound **88** (334 mg, 0.7 mmol), diethyl azodicarboxylate (177 mg, 0.98 mmol), and triphenylphosphine (258 mg, 0.98 mmol) in dry tetrahydrofuran (15 mL) was stirred under nitrogen at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol/diethylamine = 94:3:3) to give a white solid (110 mg, 34%): mp 277 °C (from methanol). Anal. ($C_{27}H_{21}N_7O \cdot 0.25H_2O$) C, H, N.

5-Bromo-2,3-diaminopyridine (54). Ruthenium on charcoal (10%, 1.0 g) was added to a stirred suspension of 2-amino-5-bromo-3-nitropyridine (21.8 g, 0.1 mol) and hydrazine hydrate (15 mL) in ethanol (500 mL) at reflux. There was rapid gas evolution, and the nitropyridine dissolved. After 3 h, the mixture was cooled and filtered through Arbocel filter aid, and the filtrate was concentrated under reduced pressure to give a fawn solid (18.5 g, 98%), which darkened rapidly on standing: mp 163–165 °C (lit.[12] mp 164–165 °C).

3-(Bromomethyl)-5-chloro-1-methyl-4-nitropyrazole (60). 5-Chloro-1,3-dimethyl-4-nitropyrazole (43 g, 0.29 mol) was dissolved in carbon tetrachloride (430 mL), bromine (12 mL) was added, and the reaction mixture was stirred at reflux for 48 h while being illuminated by a 500 W light source. A second portion of bromine (12 mL) was added, and the reaction mixture was refluxed for a further 48 h. After being cooled, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (gradient elution with hexane/dichloromethane) to give a white solid (35 g, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (3H, s), 4.64 (2H, s).

5-Chloro-3-[(2-methoxyethoxy)methyl]-1-methyl-4-nitropyrazole (62). A mixture of compound **60** (2.42 g, 9.5 mmol) and silver tetrafluoroborate (2.22 g, 11.4 mmol) in 2-methoxyethanol (25 mL) was stirred at reflux for 6 h. The black solid was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with water (100 mL), dried ($MgSO_4$),

and concentrated under reduced pressure. Purification by flash chromatography (elution with ethyl acetate/dichloromethane = 1.9) gave a white solid (1.54 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (3H, s), 3.63 (2H, m), 3.92 (3H, s), 4.90 (2H, s).

The following compounds were prepared in a similar manner to that of **62**, using isobutyl alcohol or aqueous dimethylformamide at 100 °C instead of methoxyethanol.

5-Chloro-3-(hydroxymethyl)-1-methyl-4-nitropyrazole (61): yellow solid (84% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (1H, br s), 3.93 (3H, s), 4.91 (2H, s).

5-Chloro-3-[[(2-methyl-1-propyl)oxy]methyl]-1-methyl-4-nitropyrazole (63): pale yellow oil (74% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (6H, d, J = 5 Hz), 1.96 (1H, m), 3.39 (2H, d, J = 5 Hz), 3.93 (3H, s), 4.80 (2H, s).

5-Chloro-1-methyl-3-(3-pyridyl)pyrazole (69). A mixture of compound **66** (9.65 g, 50 mmol) and methylhydrazine (2.92 mL, 50 mmol) in ethanol (100 mL) was heated at reflux for 4 h, cooled, and concentrated under reduced pressure. The residue was triturated with ethanol to give 1-methyl-4,5-dihydro-3-(3-pyridyl)-5*H*-pyrazol-5-one (6.136 g, 70%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6, enol tautomer) δ 3.56 (3H, s), 5.88 (1H, s), 7.36 (1H, dd, J = 5, 9 Hz), 8.02 (1H, d, J = 9 Hz), 8.43 (1H, dd, J = 1, 5 Hz), 8.89 (1H, d, J = 1 Hz), 11.20 (1H, br s).

A mixture of the pyrazolone (2.37 g, 13.5 mmol) and phenylphosphonic dichloride (5.7 mL, 40.5 mmol) was heated at 180 °C for 18 h under nitrogen. The mixture was cooled, poured onto ice, and rendered basic by the addition of excess 2 M aqueous sodium hydroxide. The product was extracted into dichloromethane (3 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid (2.14 g, 82%): mp 71–73 °C (from hexane/ethyl acetate). Anal. ($C_9H_8ClN_3$) C, H, N.

The following compounds were prepared in a similar manner to that of **69**, using compounds **64** and **65** in place of **66**.

5-Chloro-1-methyl-3-(2-propyl)pyrazole (67).[21a] A mixture of compound **64** (1.9 g, 50 mmol) and methylhydrazine (2.53 g, 55 mmol) in ethanol (30 mL) was heated at reflux for 18 h. After being cooled, the solvent was removed under reduced pressure to give 4,5-dihydro-1-methyl-3-isopropyl-5*H*-pyrazol-5-one (7.0 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (6H, d, J = 5 Hz), 2.71 (1H, septet, J = 5 Hz), 3.19 (2H, s), 3.31 (3H, s).

This compound was added to phosphorus oxychloride (40 mL), and the resulting mixture was heated at reflux for 16 h. The mixture was concentrated under reduced pressure, and the residue was poured cautiously into iced water (500 mL). The solution was neutralized by the addition of potassium carbonate, and the product was extracted into dichloromethane (2 × 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil (6.1 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (6H, d, J = 5 Hz), 2.90 (1H, septet, J = 5 Hz), 3.79 (3H, s), 6.03 (1H, s).

5-Chloro-1-methyl-4-nitro-3-(3-pyridyl)pyrazole (72). Compound **69** (1.935 g, 10.0 mmol) was added in portions to a stirred mixture of fuming nitric acid (3.2 mL) and concentrated sulfuric acid (7 mL), maintaining the temperature between 0 and 10 °C by means of an ice bath. After the addition was complete, the mixture was allowed to warm to room temperature. After 4 h, the mixture was poured onto ice, and this solution was poured slowly into excess ice-cold aqueous sodium hydroxide. The product was filtered off and dried to afford white needles (2.235 g, 99%): mp 94–95 °C (from ethanol/water); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (3H, s), 7.42 (1H, dd, J = 5, 8 Hz), 7.98 (1H, dt, J = 8, 2 Hz), 8.71 (1H, dd, J = 2, 4 Hz), 8.88 (1H, d, J = 2 Hz).

The following compounds were prepared in a similar manner to that of **72**, using compounds **67** and **68** in place of **69**.

5-Chloro-4-nitro-1-methyl-3-(2-propyl)pyrazole (70): white solid (95% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (6H, d, J = 5 Hz), 3.62 (1H, septet, J = 5 Hz), 3.88 (3H, s).

5-Chloro-3-cyclohexyl-4-nitro-1-methylpyrazole (71): white solid (84% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.54 (5H, m), 1.75–1.99 (5H, m), 3.29 (1H, m), 3.88 (3H, s).

Method F: 4-Amino-5-(methylamino)-1-methyl-3-(3-pyridyl)pyrazole (78). (a) A mixture of compound **72** (1.715 g, 7.19 mmol) and ethanol (30 mL) which had been saturated with methylamine gas at 0 °C was heated in an autoclave for 5 h at 100 °C. The mixture was cooled and dissolved in dichloromethane (200 mL). The solution was washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by recrystallization from ethyl acetate/methanol to give 5-(methylamino)-1-methyl-4-nitro-3-(3-pyridyl)pyrazole (1.20 g, 72%) as yellow needles: mp 178–179 °C (from ethyl acetate/methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (3H, d, J = 5 Hz), 4.02 (3H, s), 7.23 (1H, br s), 7.38 (1H, dd, J = 5, 7 Hz), 7.97 (1H, d, J = 7 Hz), 8.68 (1H, dd, J = 5, 2 Hz), 8.87 (1H, d, J = 2 Hz). Anal. ($C_{10}H_{11}N_5O_2$) C, H, N.

(b) Hydrazine hydrate (5.0 mL, 152 mmol) was added dropwise to a mixture of the nitropyrazole (4.00 g, 17.2 mmol) and Raney nickel (ca. 1 g) in ethanol (100 mL) at 50 °C under nitrogen. After 3 h at 50 °C, the mixture was cooled and filtered through Arbocel filter aid, and the filtrate was concentrated under reduced pressure to give a brownish-purple solid (3.51 g, 100%): mp 101.5–102.5 °C (from ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (3H, s), 2.90 (3H, br s), 3.79 (3H, s), 7.33 (1H, dd, J = 5, 7 Hz), 8.10 (1H, d, J = 7 Hz), 8.54 (1H, d, J = 5 Hz), 9.05 (1H, s).

Compounds **73–77** and **92** were also prepared by method F. Yields and physical data are shown in Table 4. For compound **92**, an additional ring closure step was performed between the chloride displacement step and the reduction of the nitro group (see preparation of **91**, below, and Scheme 9).

2-Cyclohexyl-3-nitro-5,6,7,8-tetrahydro-4*H*-pyrazolo[2,3-*a*][1,3]diazepine (91). A mixture of compound **90** (2.17 g, 7.7 mmol), diethyl azodicarboxylate (1.70 mL), and triphenylphosphine (2.85 g, 10.8 mmol) in dry tetrahydrofuran (50 mL) was stirred under nitrogen at room temperature for 2 h. The solvent was removed under reduce pressure, and the residue was purified by flash chromatography (gradient elution with hexane/ethyl acetate) to give a yellow solid (0.85 g, 42%): mp 147–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–2.00 (14H, m), 3.10 (1H, m), 3.20 (2H, m), 4.05 (2H, m), 7.15 (1H, br s).

Single-Crystal X-ray Analysis of the Dinitrate Salt of 43. Crystals of the dinitrate salt of **43** were grown by slow evaporation from aqueous methanol at room temperature. A representative crystal was surveyed, and a 1 Å data set (maximum sin ϑ/λ = 0.5) was collected at room temperature on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[30] All crystallographic calculations were facilitated by the SHELXTL system.[31] Pertinent crystal, data collection, and refinement parameters: cell dimensions, a = 9.517(3) Å, b = 20.597(8) Å, c = 14.719(4) Å, α = 90.00°, β = 90.39(2)°, γ = 90.00°; formula, $C_{26}H_{22}N_8O{\cdot}2HNO_3{\cdot}2H_2O$; formula weight = 624.6; molecules/unit cell = 4; calculated density = 1.44 g cm^{-3}; space group = $P2_{1/a}$; number of reflections = 2950 of which 2134 were considered significant ($I > 3\sigma$). A trial structure was obtained by direct methods and refined routinely. A difference map revealed two disordered waters of crystallization. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogens on nitrogen were located by difference Fourier techniques. The hydrogens on the waters were not located. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.078. A final difference Fourier map revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. Coordinates, anisotropic temperature factors, distances, and angles are available as supporting information.

Biology. Platelet Aggregation and PAF-Induced Murine Lethality. The procedures used were exactly as those previously reported.[2]

PAF-Induced Whole Blood Aggregation in Dogs. Blood samples were taken from beagle dogs (n = 2) via an indwelling

cannula from the saphenous vein into 0.1 vol of 3.8% trisodium citrate anticoagulant. Aggregation responses to PAF were measured by following the increase in impedance in stirred (1000 rpm) blood samples at 37 °C using a Chronolog Model 540 whole blood aggregometer. For each dog, the minimum amount of PAF required to produce irreversible aggregation (30–50 nM) was established prior to dosing. Aggregation responses to either 10 or 30 times the minimum concentration of PAF were measured in blood samples taken at various times after administration, by gavage, of solutions of test compounds dissolved in the minimum quantity of 0.01 M hydrochloric acid. Test compounds were administered, and the first blood sample was withdrawn after 2 h. If no inhibition of whole blood aggregation was observed, a second, larger dose of compound was administered and a second blood sample withdrawn after a further 2 h. If the response to PAF was inhibited, then further blood samples were withdrawn at various time intervals until the predose aggregation response to PAF returned. The duration of action at this dose was thereby determined.

Acknowledgment. The authors wish to thank Drs. V. A. Alabaster and K. Richardson for advice and acknowledge the able technical assistance of Mr. H. E. Cheeseman, Miss V. Powell, Mr. S. A. Rogers, and Miss S. F. C. Baber. We also thank Dr. J. Bordner (Pfizer Central Research, Groton, CT) and Ms. Debra Decosta for determining the crystal structure of compound **43** by X-ray diffraction. We are indebted to Dr. D. V. Bowen and his staff for measuring spectroscopic data (particularly Dr. M. E. Gerrard for NOE measurements) and to Mr. P. F. Wadsworth and his staff for analytical data.

Supporting Information Available: Atomic coordinates, isotropic and anisotropic thermal parameters, and bond lengths and angles for the X-ray crystal structure of compound **43** (4 pages). Ordering information is given on any current masthead page.

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JM940876E