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

M. Jonathan Fray,*,† Kelvin Cooper,†,§ M. John Parry,‡ Kenneth Richardson,† and John Steele†

Departments of Discovery Biology and Discovery Chemistry, Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K.

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Following the discovery of moderately potent antagonist activity against platelet-activating factor (PAF) in 2-methyl-1-phenylimidazo[4,5-*c*]pyridine (**2**) (IC_{50} = 840 nM), 19 derivatives (**3**–**21**) were prepared which incorporated various lipophilic groups attached to the phenyl 4-position. 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. [1,5]Benzodiazepines, e.g., **14** (2,3-dihydro-1-methyl-4-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-1*H*-[1,5]benzodiazepin-2-one) (IC_{50} = 4.9 nM, ED_{50} = 0.03 mg/kg po), were found to possess equivalent or superior potency to the 1,4-dihydropyridine PAF antagonist UK-74,505 (**1**, 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) *in vitro* and *in vivo*. Furthermore, a potent benzazepine, **21** (7,8-dichloro-1-methyl-4-[4-(methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one) (IC_{50} = 0.5 nM, ED_{50} = 0.03 mg/kg po), was discovered. These investigations prompted the synthesis and evaluation of additional diazepine derivatives, which are described in the following paper. The relationship between the key PAF antagonist pharmacophores of 2-methyl-1-phenylimidazo[4,5-*c*]pyridine, a triazolothienodiazepine (WEB2170), and a pyrrolothiazolidine (RP-52,770) is discussed.

Platelet-activating factor (PAF, 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphocholine) is an ether phospholipid which, in addition to potent platelet-aggregating activity, possesses a wide spectrum of biological activities elicited directly or via the release of other mediators. There has been considerable recent interest in elucidating the role of PAF in several diseases such as asthma, allergic rhinitis, and endotoxic shock, among others.[1] It has therefore been of primary importance to develop potent and specific PAF antagonists to help evaluate and validate the part PAF plays in *in vitro* and *in vivo* settings, as well as in clinical end points.[2–4]

We have described how investigation of the structure–activity relationships for a series of 1,4-dihydropyridines culminated in the discovery of UK-74,505 (**1**, 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).[5] Compound **1** (for structure, see Figure 1) is a potent PAF antagonist both *in vitro* (PAF-induced rabbit platelet aggregation IC_{50} = 4.3 nM) and *in vivo* (PAF-induced murine lethality ED_{50} = 0.26 mg/kg po), with a long duration of action.[6] However, the pharmacological profile of **1** was difficult to improve. During the course of this work, we measured pharmacokinetic parameters in the dog for a series of 17 1,4-dihydropyridine derivatives, which all showed promising oral efficacy *in vivo*, with the aim of identifying a backup development candidate with potential for once-daily dosing in man. No compound had a plasma half-life of greater than 3 h, and we therefore concluded that we were unlikely to find another 1,4-dihydropyridine derivative which was superior to **1**.

Several other factors aided our decision to seek a new structural class of PAF antagonist. Firstly, analysis of the structure–activity relationships (SARs) of the dihydropyridine series suggested that the dihydropyridine ring was merely a semirigid template upon which a variety of groups could be attached to achieve potent antagonists.[5,7] Secondly, the fact that many other structural classes of PAF antagonists had been discovered was evidence that a 1,4-dihydropyridine was not, of itself, a PAF antagonist pharmacophore. Furthermore, since many of our most potent compounds *in vitro* possessed the same 2-position substituent, namely 2-methyl-1-phenylimidazo[4,5-*c*]pyridine (**2**), and minor alterations caused potency to be diminished, we were prompted to initiate a synthetic program based on simpler elaborations of **2**. This paper describes our initial efforts. Although **2** and two synthetic intermediates, **3** and **4**, possessed promising *in vitro* potency, a series of planar, rigid derivatives, **5**–**8**, constituted no improvement. However, we discovered that the benzodiazepines and benzazepines **9**–**21** were, in most cases, significantly more potent, and the best examples, **14** and **21**, were superior to **1**, both *in vitro* and *in vivo*. The following paper[8] describes the optimization of the oral *in vivo* potency and duration of action of these series.

Chemistry

The syntheses of **2**–**8** are shown in Schemes 1 and 2. Compound **3** was prepared starting with 4-iodoaniline and 4-chloro-3-nitropyridine[9] followed by reduction to the diaminopyridine and ring closure. Removal of the iodine atom by metal–halogen exchange and protona-

† Department of Discovery Chemistry.
‡ Department of Discovery Biology.
§ Present address: Central Research, Pfizer Inc., Groton, CT 06340.
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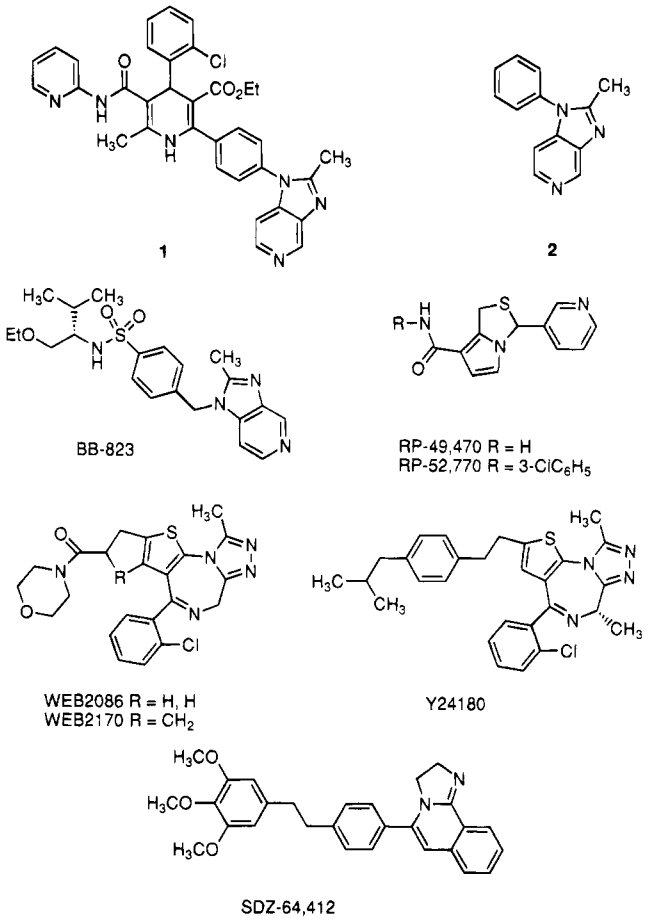
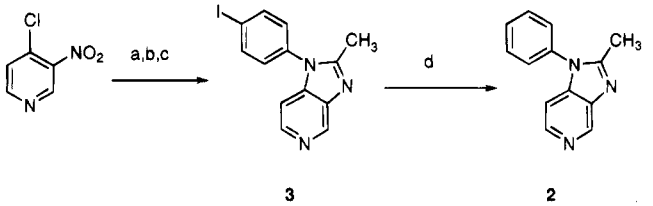


Figure 1.

Scheme 1[a]

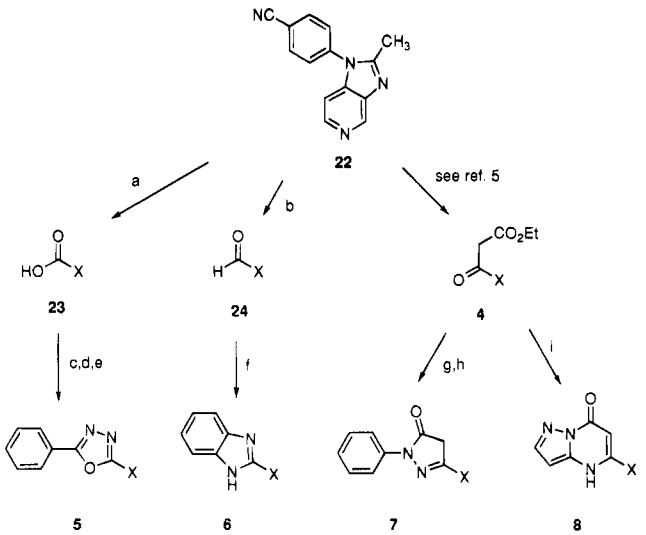


[a] (a) *p*-Iodoaniline, EtOH, 20 °C; (b) $SnCl_2$, EtOH, reflux; (c) Ac_2O, $(EtO)_3CH$, reflux; (d) *n*-BuLi, THF, −78 °C, then NH_4Cl (aq).

tion then afforded **2**. Compound **4** has been reported previously.[5] Compounds **5** and **6** were constructed in a conventional manner via the carboxylic acid **23** and the carboxaldehyde **24**, respectively. Compounds **7** and **8** were formed by treating the keto ester **4** with phenylhydrazine and 3-aminopyrazole, respectively.[10]

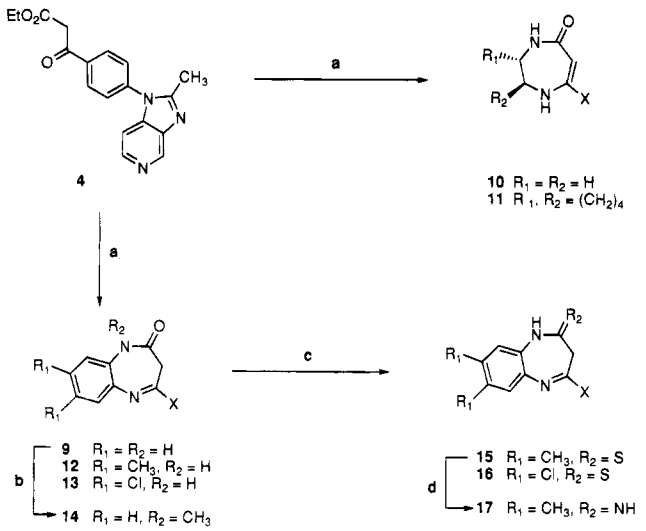
The syntheses of **9**–**17** are shown in Scheme 3. Condensation of keto ester **4** with a variety of 1,2-diamines in hot toluene afforded diazepines **9**–**13**.[11] Whereas **10** and **11** were isolated as enamine tautomers, the corresponding benzodiazepines **9**, **12**, and **13** existed entirely in the imine tautomer.[12] The type of link between the two nitrogen atoms of the diamine would appear to be responsible for determining the prevalent tautomeric form. In the case of **10** and **11**, a torsional angle of 60° between the two nitrogens is possible, which relieves angle strain in the 7-membered ring, and thus permits the 5-nitrogen atom to enter into conjugation with the $\alpha\beta$-unsaturated carbonyl moiety. In contrast, the benzodiazepines, e.g., **9**, have the nitrogen–nitrogen torsional angle fixed at 0°, which imparts considerable

Scheme 2[a]



[a] X = 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl. (a) NaOH (aq), EtOH, reflux; (b) Ni/Al alloy, HCO_2H/H_2O, 120 °C; (c) $(COCl)_2$, CH_2Cl_2, 20 °C; (d) $PhCONHNH_2$, 20 °C; (e) $POCl_3$, PCl_5, reflux; (f) 1,2-diaminobenzene, $Na_2S_2O_5$, $MeCONMe_2$, 100 °C; (g) $PhNHNH_2$, $CaCl_2$, 20 °C; (h) HOAc, concentrated H_2SO_4, 20 °C; (i) 3-aminopyrazole, HOAc, reflux.

Scheme 3[a]



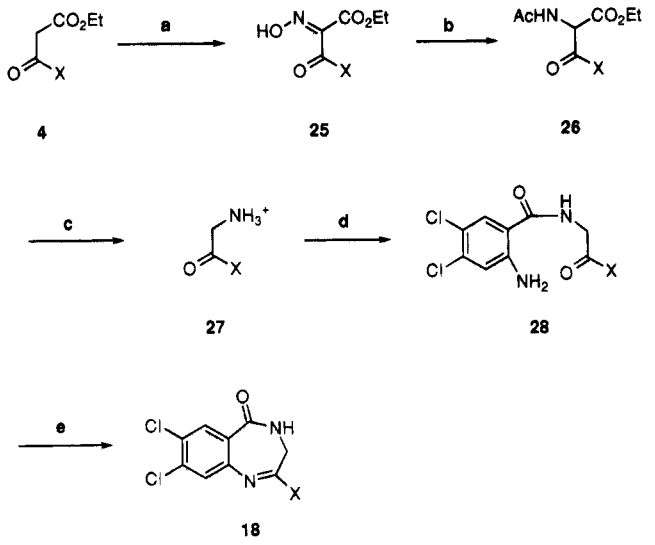
[a] X = 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl. (a) 1,2-Diamine, toluene, reflux; (b) NaH, THF, CH_3I, 20 °C; (c) P_2S_5, pyridine, reflux; (d) NH_3 (g), HgO (red), *n*-butanol, reflux.

angle strain into the enamine tautomer. The imine tautomer is therefore favored, since the methylene carbon (C3) can lie out of the plane described by the other atoms in the ring. Conjugation of the imine group with the fused benzene ring in **9** may be another reason for that tautomer being preferred. Such conjugation is, of course, not possible for **10** and **11**.

Calculations go some way to support these arguments. Thus, the calculated heat of formation[13] (simulated aqueous phase) for the imine tautomer of **9** was 4 kcal/mol lower than that for the enamine tautomer. In contrast, no clear tautomer preference was evident from the calculated heat of formation for **11**, since the energy difference was <1 kcal/mol.

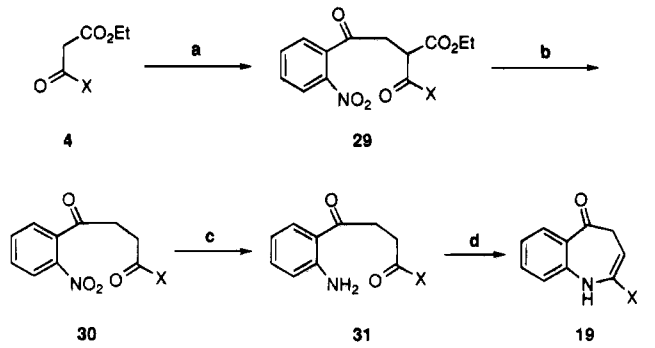
The role of the amide group of the benzodiazepines was investigated by preparing the *N*-methyl derivative **14**, using sodium hydride and methyl iodide in tetrahydrofuran, and the thioamides **15** and **16**, using phos-

Scheme 4[a]



[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. (a) $NaNO_2$, $HOAc/H_2O$, 5 °C; (b) H_2 (50 psi), Pd/C, $HOAc/Ac_2O$, 30 °C; (c) HCl (aq), reflux; (d) 4,5-dichloroisatoic anhydride, Na_2CO_3 (aq), CH_2Cl_2, 20 °C; (e) *p*-TsOH, CH_2Cl_2, reflux.

Scheme 5[a]



[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. (a) 2′-Nitrobromoacetophenone, NaH, THF, 20 °C; (b) HCl (aq), reflux; (c) H_2 (30 psi), Pd/C, EtOH, 22 °C; (d) HOAc, toluene, reflux.

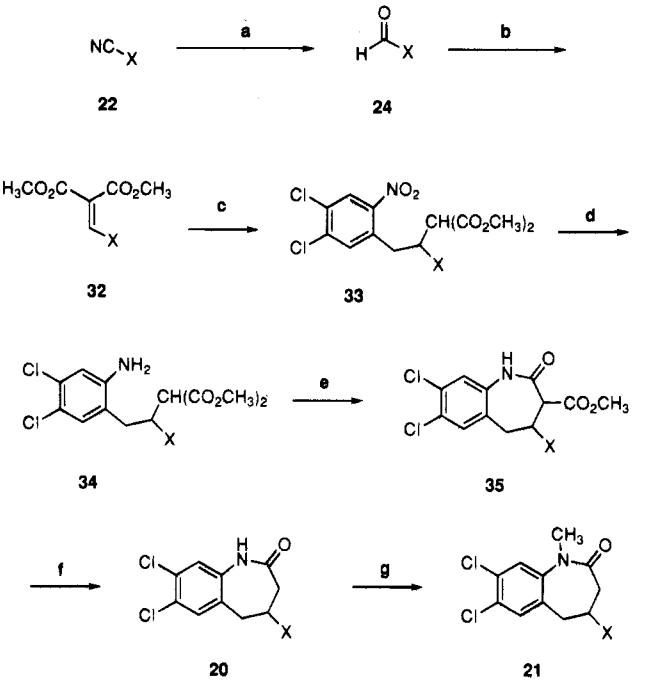
phorus pentasulfide,[14] starting from compounds **12** and **13**, as indicated. Compound **15** was relatively unreactive toward nucleophiles, and the preparation of **17** required heating **15** in *n*-butanol saturated with ammonia in the presence of red mercuric oxide as a sulfur scavenger.

We also wished to examine the effect of reversing the amide functionality in **13** and replacing one or other of the nitrogen atoms of the diazepine ring with a methylene to give **18**–**21**. These syntheses are shown in Schemes 4–6.

The preparation of **18** proceeded in five steps starting from keto ester **4**. Firstly, nitrosation gave the oxime **25**, which was reduced by hydrogen over palladium on charcoal in the presence of acetic anhydride to give the acetamido derivative **26**. Next, acidic hydrolysis of **26** with simultaneous decarboxylation afforded the amino ketone salt **27**, which was then treated with 6,7-dichloroisatoic anhydride[15] to give the keto amide **28**. Finally, ring closure occurred on heating **28** in dichloromethane in the presence of *p*-toluenesulfonic acid to give **18**.

Benzazepinone **19** was prepared in two steps from the 1,4-diketone intermediate **30**, by reduction of the nitro group and intramolecular condensation of the resulting

Scheme 6[a]



[a] X = 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl. (a) Raney alloy, HCO_2H, reflux; (b) dimethyl malonate, $TiCl_4$, pyridine, THF, 20 °C; (c) 4,5-dichloro-2-nitrotoluene, NaH, DMF, 20 °C; (d) $TiCl_3$, H_2O/MeOH, 20 °C; (e) NaOMe, MeOH, reflux; (f) LiI, pyridine reflux; (g) NaH, DMF, CH_3I, 20 °C.

amino diketone **31**. Compound **30** was prepared by a standard protocol, involving first the alkylation of **4** with 2′-nitrobromoacetophenone followed by hydrolysis and decarboxylation of **29**.

The synthesis of the benzazepinone **20** was based on elegant methodology described for making calcium channel blockers related to diltiazem.[16] Firstly, nitrile **22** was converted to the aldehyde **24** using Raney alloy in refluxing formic acid.[17] Some care is required when performing this reaction, since it is vigorous and exothermic, once initiated. A detailed procedure is therefore given in the Experimental Section. Although traditional Knoevenagel conditions (dimethyl malonate, piperidine, acetic acid, toluene at reflux) failed to transform **24** into the benzylidene malonate derivative **32**, the alternative procedure using titanium tetrachloride and pyridine in THF[18] worked well. Conjugate addition[16] of the anion from 4,5-dichloro-2-nitrotoluene, generated *in situ* using sodium hydride, to **32** gave, after workup, the malonate derivative **33**. Reduction of the nitro group in **33** was best achieved using titanium trichloride in aqueous methanol at room temperature.[19] Treatment with sodium methoxide at reflux effected ring closure of **34** to give **35**, which was decarboxylated using lithium iodide in pyridine.[20] Benzazepine **20** was methylated, using sodium hydride and methyl iodide in dimethylformamide, to give **21**.

Results and Discussion

Compounds **2**–**21** were first evaluated as PAF antagonists *in vitro* using an assay involving rabbit washed platelets, and then the activity of selected compounds was determined *in vivo* by the ability to protect mice from the lethal effects of an injection of PAF.

The *in vitro* SARs for compounds **2**–**21** will be discussed first (see Table 1). The simple 2-methyl-1-

Table 1. Platelet-Activating Factor Antagonist Activity of Benzodiazepine and Benzazepine Derivatives of 2-Methyl-1-phenylimidazo[4,5-*c*]pyridine

compd	formula	anal.	IC_{50}[a] (nM)	ED_{50}[b] (mg/kg po)
2	$C_{13}H_{11}N_3 \cdot 0.25H_2O$	C,H,N	840	NT[c]
3	$C_{13}H_{10}IN_3$	*d*	67	NT
4	$C_{18}H_{17}N_3O_3$	C,H,N	600	NT
5	$C_{21}H_{15}N_5O$	C,H,N	44	NT
6	$C_{20}H_{15}N_5 \cdot 1.25H_2O$	C,H,N	350	NT
7	$C_{22}H_{17}N_5O$	*d*	190	NT
8	$C_{19}H_{14}N_6O \cdot H_2O$	C,H[e]	2800	NT
9	$C_{22}H_{17}N_5O \cdot 0.5H_2O$	C,H,N	5	0.5
10	$C_{18}H_{17}N_5O \cdot 0.5H_2O$	C,H,N	2600	NT
11	$C_{22}H_{23}N_5O \cdot 2H_2O$	C,H,N	200	NT
12	$C_{24}H_{21}N_5O \cdot 0.5H_2O \cdot 0.4EtOH$	C,H,N	0.7	0.12
13	$C_{22}H_{15}Cl_2N_5O \cdot 0.5H_2O \cdot 0.33EtOH$	C,H,N	0.9	0.07
14	$C_{23}H_{19}N_5O \cdot 0.25H_2O$	C,H,N	4.9	0.03
15	$C_{24}H_{21}N_5O$	*d*	0.6	NT
16	$C_{22}H_{15}Cl_2N_5S$	*d*	0.5	NT
17	$C_{24}H_{22}N_6 \cdot 0.33H_2O$	C,H,N	1.9	NT
18	$C_{22}H_{15}Cl_2N_5O \cdot H_2O$	C,H[f]	4	0.2
19	$C_{23}H_{18}N_4O$	*d*	15	0.75
20	$C_{23}H_{18}Cl_2N_4O \cdot 0.5H_2O$	C,H,N	0.5	0.05
21	$C_{24}H_{20}Cl_2N_4O \cdot 0.25EtOAc$	C,H,N	0.5	0.03
1			4.3 ± 0.73[g]	0.26 ± 0.03[g]
bepafant (WEB2170)			73	0.1

[a] Single determination, unless stated otherwise. A difference of less than 2-fold should not be regarded as significant. [b] Average of two determinations. [c] NT = not tested. [d] Characterized by spectroscopy. [e] N: found, 22.71; calcd, 23.32. [f] N: found, 14.94; calcd, 15.40. [g] From ref 5.

phenylimidazo[4,5-*c*]pyridine (**2**) possesses a submicromolar IC_{50}, which is remarkable for such a small molecule. This result emphasizes the importance of the contribution that this moiety imparts to the potency of UK-74,505 (**1**). Recently Whittaker and co-workers have also reported potent PAF antagonist activity in relatively simple imidazo[4,5-*c*]pyridine derivatives.[21] The iodophenyl intermediate **3** was approximately 10-fold more potent than **2**, which can be rationalized by increased lipophilic binding to the receptor. The keto ester **4**, on the other hand, was approximately equipotent with **2**.

Compounds **5**–**8** were designed to probe the extent and spatial requirements of the lipophilic pocket. They all possess an aromatic ring (phenyl, or in the case of **8**, pyrazole) which is attached to the phenylimidazopyridine moiety via a two- or three-atom spacer. The spacer groups were chosen to be flat, aromatic rings for ease of synthesis, and as a contrast to the 1,4-dihydropyridines previously explored. As can be seen from Table 1, compounds **5**–**8** were not particularly potent. We therefore sought to evaluate further derivatives of **2** in which the attached ring system was constrained nonplanar. Consequently we were delighted to discover that benzodiazepine **9** was 70 times more potent than the corresponding benzimidazole **6**. Compounds **10**–**13** were prepared to probe the role of the benzodiazepine ring in determining the potency. The weak potency of **10** and **11** demonstrated the requirement for an aromatic, lipophilic group fused to the diazepine ring, although the slightly different shape of the diazepine ring caused by the different tautomeric form may also be partially responsible. Addition of methyl or chloro groups resulted in an increase in potency for **12** and **13** over **9**, which suggested an increase in lipophilic binding to the receptor rather than an electronic component of binding by the benzene ring.

Modifications of the amide moiety in **9** were then investigated. The *N*-methyl compound **14** was equipotent *in vitro* with **9**, and the thioamides **15** and **16** were equipotent with **12** and **13**. The amidine **17** was approximately 3-fold less potent than **15**. Moving the carbonyl group to a position adjacent to the benzene ring, as in compounds **18** and **19**, was detrimental and resulted in a 3–6-fold loss in potency in comparison to their nearest analogues **13** and **9**. In contrast, replacement of the imine moiety of **13** by two sp^3 carbon atoms as in **20** resulted in full retention of potency. N-Methylation of **20**, as with **9**, caused no change in *in vitro* potency.

In the light of these findings, we would wish to comment on the model of the human PAF receptor recently proposed by Hodgkin, Miller, and Whittaker.[22] According to this model, our compounds lie in the group of PAF antagonists which feature heterocyclic rings bearing an sp^2 nitrogen atom, such as BB-823, RP-48,740, RP-52,770, WEB2086, WEB2170, SDZ-64,412, Y-24180, UK-74,505 (**1**), *inter alia* (for structures, see Figure 1).

In this paper, we have demonstrated the importance of the 2-methylimidazo[4,5-*c*]pyridine moiety in the PAF antagonist pharmacophore. Both the Whittaker group[21] and ourselves[8] have shown that the pyridine nitrogen of the imidazopyridine ring increases the PAF antagonist potency compared to the corresponding benzimidazole derivatives. It is interesting, therefore, to speculate how the imidazopyridine pharmacophore fits the receptor compared to thienotriazolodiazepines, e.g., WEB2170 and Y-24180. We would agree that a methyl is optimal as the imidazopyridine 2-position substituent, and taken together with the imidazole nitrogen atom, these features form a key part of the receptor recognition. One possible overlap of compound **3** and WEB2170 is shown in Figure 2, in which the iodine atom of **3** can reside in a similar position to the middle carbon atom of the cyclopentane ring in WEB2170.[23] Compound **3** and WEB2170 were built and minimized using the computer program Sybyl.[24] The molecules were overlaid using three pairs of atoms for fitting (shown in magenta), namely the carbon atoms of the methyl groups,

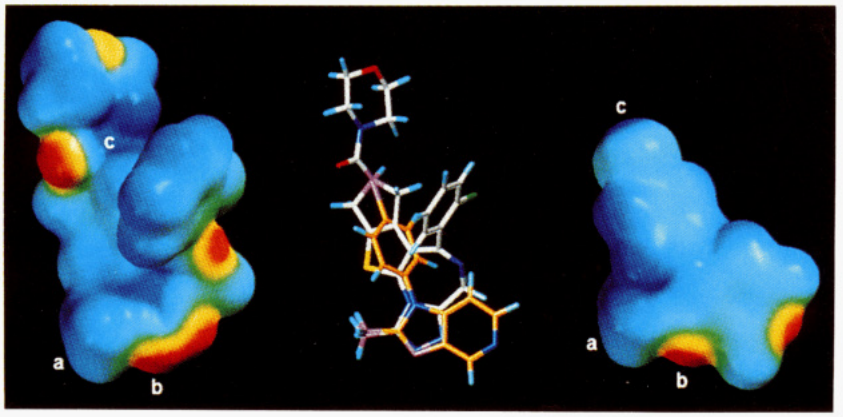


Figure 2. Superimposition of compound **3** with WEB2170. The three atom pairs, highlighted in magenta, were least squares fitted in Sybyl to an overall rms value of 0.149 Å. Their molecular electrostatic potential energy surfaces (WEB2170, left, and compound **3**, right, generated in Spartan, are shown color coded from −50 kcal/mol (red) to 20 kcal/mol (blue), with the fitted atoms indicated by the letters a−c.

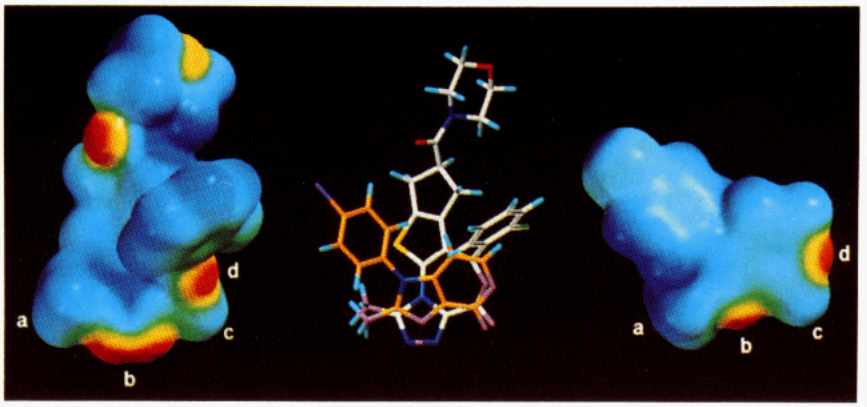


Figure 3. Alternative superimposition of compound **3** with WEB2170. The four atom pairs, highlighted in magenta, were least squares fitted in Sybyl to an overall rms value of 0.623 Å. Their molecular electrostatic potential energy surfaces (WEB2170, left, and compound **3**, right, generated in Spartan, are shown color coded from −50 kcal/mol (red) to 20 kcal/mol (blue), with the fitted atoms indicated by the letters a−d.

the sp^2 nitrogen atoms adjacent to the methyl groups, and the iodine atom of **3** with the middle carbon atom of the cyclopentane ring in WEB2170. The molecular electrostatic energy potential surfaces were also calculated using the computer program Spartan[25] and are also shown in Figure 2, with the three sets of atoms used for the overlap indicated by the letters a−c.

However, there has been debate concerning which of the triazole sp^2 nitrogen atoms in the triazolothienodiazepines forms a key interaction with the receptor.[22] We suggest that it may be pertinant to consider two additional points of similarity, namely the pyridine sp^2 nitrogen and the imine sp^2 nitrogen of the thienotriazolodiazepine, and the imidazopyridine 4-position substituent with the methylene of the thienotriazolodiazepine (where there is little known about the SARs, but that methyl substitution is tolerated). The similarity is more obvious if the Spartan[25] molecular electrostatic potential energy maps (Figure 3) of compound **3** and WEB2170 are compared. The four points for comparison are indicated by the letters a−d. Figure 3 also shows this molecular overlap using Sybyl, in which the center of the triazole N−N bond on WEB2170 is overlapped with the imidazole nitrogen of compound **3**. It can clearly be seen that the substituents on the phenyl and thienophene rings point in very different directions, in sharp contrast to the overlap shown in Figure 2. We have attempted to overlap WEB2170 and Y24180 with the compounds of this paper and 1,4-dihydropyridines,[5] seeking to place the location of common binding, but have not been able to find any interactions they share.

Compound **3** has similar or greater potency than many of the compounds which fit the receptor model proposed by Hodgkin,[22] assuming that the potency of compounds is similar for inhibition of PAF-induced aggregation of both human and rabbit platelets, but it lacks a carbonyl or sulfonyl group which was proposed to interact with a hydrogen bond donor group on the receptor. Although the more potent benzodiazepines, e.g., **9**, possess such a group, it lies in a different area of space. We suggest that the carbonyl group of our benzodiazepines is unimportant for binding to the receptor, since it may be replaced by a thiocarbonyl or amino groups (compounds **15**−**17**) with a small loss of potency, moved to an adjacent carbon (compounds **18** and **19**), or replaced altogether by a fused heterocyclic ring (see following paper).[8] Our results suggest that lipophilic binding is more important and that a lipophilic pocket exists which prefers an aromatic ring (compare results for compounds **9**−**11**) outside the plane of the phenylimidazopyridine moiety (compare results for **5**−**9**).

Our results help rationalize one important, unexplained feature of the Hodgkin model,[22] which does not explain the very significant increase in potency which

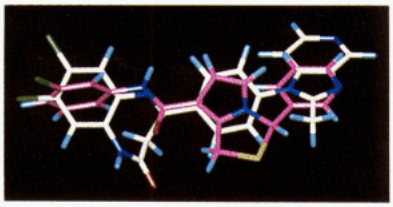


Figure 4. Superimposition of compound **13** (white) with RP-52,770 (magenta). The atom pairs used for the fit were the imidazole/pyridine sp^2 nitrogens, the two aromatic carbons on either side of the imidazole/pyridine sp^2 nitrogens, and the 3-chlorophenyl/dichlorophenyl centroids to an overall rms value of 0.375 Å.

results from attaching a 3-chlorophenyl ring onto the pyrrolothiazolidine RP-48,740 (platelet aggregation IC_{50} = 3300 nM)[26] to give RP-52,770 (pA_2 = 7.71 nM),[27] despite the fact that both compounds possess the carbonyl group necessary to satisfy the model. An overlay of RP-52,770 with compound **13** (modeled using Sybyl; see Figure 4) suggests how the pyridine and imidazopyridine rings can overlap sp^2 nitrogens, and although the nature of the linker groups is very different, nevertheless the 3-chlorophenyl and dichlorophenyl rings occupy a similar region of space. The rms deviation for the fit comprising three pairs of atoms and the 3-chlorophenyl/dichlorophenyl centroids was 0.375 Å. The incorporation of PAF antagonists with a single sp^2 nitrogen atom (e.g., RP-52,770, SDZ-64,412) into this model of the receptor is necessarily complicated, since examination of various alternative alignments of the molecule with respect to the sp^2 nitrogens are required.

To summarize, we propose that the 2-methyl-1-phenylimidazo[4,5-*c*]pyridine moiety is an important PAF antagonist pharmacophore, which fits a model of the PAF receptor (Figure 3), consisting of (i) a small, size-limited lipophilic pocket which best accommodates a methyl group (marked a), (ii) an electrostatic interaction with one (or preferably two) sp^2 nitrogen atoms (marked b and d), and (iii) a second lipophilic pocket which is ill-defined but accommodates a hydrogen or a methyl group (marked c). Fulfillment of these interactions would appear to be sufficient to achieve micromolar affinity for the receptor. Further, significant increases in potency may be obtained by the incorporation of lipophilic groups (as in compounds **13** and **1**), but the exact location of the binding pockets is uncertain. Coordinates of all the fitted molecules (cssr format) can be found in the supporting information. Le Solleu and co-workers have recently compared the electrostatic and lipophilic potentials of two series of PAF antagonists, triazolothienodiazepines and diaryltetrahydrofurans,[28] and for the former series have also proposed an important role for the electronegative potential provided by the triazole and imine sp^2 nitrogens.

Much still needs to be explained. What complicates fitting molecules into this model is that it is apparently not essential to fill both sp^2 nitrogen interactions, nor even the lipophilic methyl pocket (a) (e.g., RP-52,770). Thus, a completely different alignment of an analogue of RP-52,770 has been suggested in which the pyrrole carboxamide provides the key negative electrostatic interaction with the receptor.[28] Our results shed little light on the role of the thiophene substituents in the triazolothienodiazepines or, indeed, the thiophene itself. For example, WEB2170 is particularly difficult to accommodate in either the Hodgkin model or our own. We have not been able to elucidate the role of either the 2-chlorophenyl group (which might be expected to bind in a lipophilic pocket) nor the carbonyl, which is difficult to neglect, since there is a major difference in the potency of the two enantiomers of WEB2170. It is also obvious that our model does not adequately rationalize the picomolar potency of BB-823. The molecular linker, which holds the sp^2 nitrogen-containing pharmacophore in the correct relationship to the other groups present in the molecule, undoubtedly plays an important role. It must, ideally, be highly rigid for the antagonist to have nanomolar potency, but it is unclear from our results whether it makes any specific binding interaction itself. The Hodgkin model, however, suggests a favorable role for a sulfur atom in the linking group. Further analysis is required in order to rationalize all the available data and generate a unified PAF receptor model.

The *in vivo* SARs will now be discussed. The benzodiazepinone **9** possessed potent *in vivo* activity (see Table 1). The dimethyl and dichloro derivatives **12** and **13** were 4−7 times more potent *in vivo*, as befitted their greater *in vitro* potency. Similarly, the *in vitro* potency of benzodiazepine **18** and benzazepinones **19** and **20** translated well into *in vivo* potency. Whereas N-methylation of **9** and **20** resulted in no increase in potency *in vitro*, the *in vivo* potency of **14** increased by a further 1 order of magnitude compared to **9**. However, the same effect was not observed for compound **21**. The reasons for these differences have not been elucidated but are probably related to differences in absorption of pharmacokinetics for the individual compounds in the mouse.

In summary, we report the discovery of a very simple imidazo[4,5-*c*]pyridine derivative **2** with submicromolar potency *in vitro*. A comparison of this pharmacophore with the thienotriazolodiazepines according to their molecular electrostatic potential energies is offered. Elaboration of this lead led to a novel series of benzodiazepine and benzazepine derivatives, several of which showed increased potency compared to UK-74,505 (**1**), both *in vitro* and *in vivo*. In the following paper,[8] we describe how the benzene ring may be replaced by suitably substituted pyridine or pyrazole rings, leading to significant improvements in the *in vivo* potency and duration of action.

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'-Nitrobromoacetophenone was purchased from Aldrich Chemical Co. 4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)benzonitrile (**22**) and ethyl 4'-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoylacetate (**4**) have been reported previously.[5] 6,7-Dichloroisatoic anhydride[15] and 4,5-dichloro-2-nitrotoluene[29] were prepared according to the literature methods.

2-Methyl-1-(4-iodophenyl)imidazo[4,5-*c*]pyridine (3). A mixture of 4-chloro-3-nitropyridine—CAUTION, skin irritant—(1.02 g, 6.44 mmol) and 4-iodoaniline (1.409 g, 6.44 mmol) in ethanol (20 mL) was stirred at room temperature for 21 h. The solvent was removed under reduced pressure, and the residue was partitioned between saturated aqueous sodium bicarbonate (50 mL) and ethyl acetate (3 × 50 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure to give an orange solid (950 mg, 43%), mp 137–139 °C, after recrystallization from ethyl acetate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (1H, d, J = 6 Hz), 7.09 (2H, d, J = 9 Hz), 7.84 (2H, d, J = 9 Hz), 8.32 (1H, d, J = 6 Hz), 9.34 (1H, s), 9.61 (1H, br s).

This material (1.92 g, 5.63 mmol) was heated with stannous chloride (5.34 g, 28.2 mmol) in ethanol (50 mL) under reflux for 15 min and cooled in ice/water, and excess aqueous potassium hydroxide (40%) was added slowly. The product was extracted into ethyl acetate (4 × 100 mL), and the combined extracts were washed with saturated aqueous sodium chloride (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a brown solid, which was purified by flash chromatography (eluting with ethyl acetate/methanol = 7:1 and then 5:1) to give 3-amino-4-(4-iodophenyl)-aminopyridine as a fawn solid (1.174 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (2H, br s), 5.80 (1H, br s), 6.88 (2H, d, J = 8 Hz), 7.02 (1H, d, J = 5 Hz), 7.65 (2H, d, J = 8 Hz), 8.01 (1H, d, J = 5 Hz), 8.11 (1H, s).

A mixture of 3-amino-4-(4-iodophenyl)aminopyridine (311 mg, 1.0 mmol), acetic anhydride (95 μL, 1.0 mmol), and triethyl orthoacetate (920 μL, 5.0 mmol) was heated at reflux under nitrogen for 2 h. The excess reactants were removed under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 4:1) to give 2-methyl-1-(4-iodophenyl)imidazo[4,5-*c*]pyridine (**3**) (244 mg, 73%) as a pale brown solid: mp 180–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (3H, s), 7.10 (1H, d, J = 5 Hz), 7.14 (2H, d, J = 9 Hz), 7.98 (2H, d, J = 9 Hz), 8.41 (1H, d, J = 5 Hz), 9.07 (1H, s).

2-Methyl-1-phenylimidazo[4,5-*c*]pyridine (2).[30] Compound **3** (292 mg, 0.87 mmol) was dissolved in dry THF (15 mL) and cooled to −78 °C under nitrogen. *n*-Butyllithium (3 mL, 1.6 M in hexanes, 4.8 mmol) was added dropwise with stirring, and after 15 min the mixture was treated with aqueous ammonium chloride. After being warmed to room temperature, the mixture was partitioned between water and ethyl acetate (2 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with dichloromethane/MeOH) to give the title compound (46 mg, 25%): mp 176–178 °C (from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (3H, s), 7.11 (1H, d, J = 5 Hz), 7.39 (2H, d, J = 9 Hz), 7.63 (3H, m), 8.39 (1H, d, J = 5 Hz), 9.08 (1H, s); MS (EI) m/z 209 (M^+), 77 (Ph^+). Anal. ($C_{13}H_{11}N_3$·0.25H_2O) C,H,N.

2-Methyl-1-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl]-imidazo[4,5-*c*]pyridine (5). A mixture of compound **23** (1.01 g, 4.0 mmol), oxalyl chloride (1.4 mL, 16 mmol), and DMF (40 μL) in dry dichloromethane (30 mL) was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure, diluted with dichloromethane (10 mL), and concentrated again. The residue was suspended in dry dichloromethane (30 mL), and benzhydrazide (1.09 g, 8.0 mmol) was added. The mixture was stirred at 20 °C for 54 h, diluted with dichloromethane/methanol (10:1), and washed with dilute aqueous sodium carbonate. The organic solution was evaporated onto silica gel (6 g, 230–400 μm) and applied to the top of a chromatography column (eluting with ethyl acetate/methanol = 4:1). The product, *N*-benzoyl-*N'*-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)-benzoyl]hydrazine, was obtained as an off-white solid (1.1 g, 75%): mp 153–155 °C (from methanol/ether). Anal. ($C_{21}H_{17}N_5O_2$·0.5H_2O) C,H,N.

A portion of this material (960 mg, 2.6 mmol) was suspended in phosphorus oxychloride (8 mL) and heated under reflux for 2 h. Phosphorus pentachloride (600 mg, 2.9 mmol) was added, and the mixture was refluxed for a further 2 h. After being cooled, the mixture was poured onto ice and rendered basic by the addition of solid sodium carbonate, and the product was extracted into ethyl acetate. The combined extracts were concentrated under reduced pressure; the residue was dissolved in methanol, evaporated onto silica gel (5 g, 230–400 μm), and applied to the top of a chromatography column (eluting with ethyl acetate/methanol = 4:1). The title compound was obtained as a white solid (600 mg, 65%): mp 216–218 °C (from 2-propanol). Anal. ($C_{21}H_{15}N_5O$) C,H,N.

2-Methyl-1-[4-(1*H*-benzimidazol-2-yl)phenyl]imidazo-[4,5-*c*]pyridine (6). A mixture of compound **24** (240 mg, 1.0 mmol), 1,2-diaminobenzene (114 mg, 1.03 mmol), and sodium metabisulfite (250 mg, 1.3 mmol) in dry dimethylacetamide (2 mL) was heated at 100 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 6:1) to give, after trituration with ether, a white solid (296 mg, 91%): mp 158–161 °C (from methanol/ethyl acetate). Anal. ($C_{20}H_{15}N_5$·1.25H_2O) C,H,N.

2-Methyl-1-[4-(3,4-dihydro-3-oxo-2-phenyl-3*H*-pyrazol-5-yl)phenyl]imidazo[4,5-*c*]pyridine (7). A mixture of compound **4** (350 mg, 1.08 mmol), phenylhydrazine (107 μL, 1.08 mmol), and powdered anhydrous calcium chloride (100 mg) in dry dichloromethane (2 mL) was stirred at room temperature for 15 h. The mixture was filtered and concentrated under reduced pressure to give a yellow gum (460 mg), which was dissolved in glacial acetic acid (1 mL) and added slowly to concentrated sulfuric acid (2 mL) at room temperature with stirring. After 15 min, the mixture was poured into water and rendered basic by the addition of saturated aqueous sodium bicarbonate, and the product was extracted into dichloromethane. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography (eluting with ethyl acetate/methanol = 9:1) gave the title compound (200 mg, 50%): ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 2.36 (3H, s), 5.76 (br s, partial exchange with HOD present), 6.95 (1H, d, J = 5 Hz), 7.02 (1H, t, J = 7 Hz), 7.18–7.29 (4H, m), 7.72 (2H, d, J = 9 Hz), 7.84 (2H, d, J = 9 Hz), 8.15 (1H, d, J = 5 Hz), 8.79 (1H, s), NH exchanged with HOD present; MS (FAB) m/z 367 (M^+).

1,4-Dihydro-2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)-phenyl]-1*H*-pyrazolo[2,3-*a*]pyrimidin-4-one (8). A mixture of compound **4** (646 mg, 2.0 mmol) and 3-aminopyrazole (105 mg, 2.23 mmol) in glacial acetic acid (3 mL) was heated at 120 °C under nitrogen for 2 h, cooled, and poured onto ice. The mixture was brought to pH 4 by the addition of saturated aqueous sodium bicarbonate, and the buff precipitate was filtered off and recrystallized from hot ethanol to give the title compound (204 mg, 30%): mp 198–202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.55 (3H, s), 6.20 (1H, s), 6.26 (1H, s), 7.26 (1H, t, J = 5 Hz), 7.84 (2H, d, J = 8 Hz), 7.93 (1H, s), 8.14 (2H, d, J = 8 Hz), 8.34 (1H, d, J = 5 Hz), 8.95 (1H, s). Anal. ($C_{19}H_{14}N_6O$·H_2O) C,H; N: found, 22.71; calcd, 23.32.

2,3-Dihydro-4-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)-phenyl]-1*H*-[1,5]benzodiazepin-2-one (9). A mixture of 1,2-diaminobenzene (1.839 g, 17.03 mmol) and compound **4** (5.00 g, 15.48 mmol) in dry toluene (50 mL) was heated at reflux under nitrogen for 5 h. The mixture was cooled and the product filtered off and washed with toluene to give a buff solid (4.097 g, 72%): mp 292 °C (from ethyl acetate/methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (3H, s), 3.70 (2H, s), 7.15 (2H, m), 7.35 (2H, m), 7.52 (2H, d, J = 8 Hz), 7.58 (1H, m), 8.23 (1H, s), 8.41 (2H, d, J = 8 Hz), 8.44 (1H, d, J = 5 Hz), 9.10 (1H, s). Anal. ($C_{22}H_{17}N_5O$·0.5H_2O) C,H,N.

4-[4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-2,5,6,7-tetrahydro-1*H*-[1,5]diazepin-2-one (10): prepared as described for compound **9** using 1,2-diaminoethane instead of 1,2-diaminobenzene. The product was purified by flash chromatography (eluting with dichloromethane/methanol = 4:1): yield 38%, mp 280–283 °C (after precipitation from

2-propanol with ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (3H, s), 3.60 (2H, m), 3.76 (2H, m), 4.96 (1H, br s), 5.11 (1H, s), 6.10 (1H, br s), 7.12 (1H, d, J = 5 Hz), 7.44 (2H, d, J = 8 Hz), 7.80 (2H, d, J = 8 Hz), 8.43 (1H, d, J = 5 Hz), 9.09 (1H, s). Anal. ($C_{18}H_{17}N_5O\cdot0.5H_2O$) C,H,N.

(5a*RS*,9a*RS*)-4-[4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)-phenyl]-2,5,5a,6,7,8,9,9a-octahydro-1*H*-[1,5]benzodiazepin-2-one (11): prepared as described for compound **9** using *trans*-1,2-diaminocyclohexane instead of 1,2-diaminobenzene: yield 30%; mp 284–287 °C. Anal. ($C_{22}H_{23}N_5O\cdot2H_2O$) C,H,N.

2,3-Dihydro-7,8-dimethyl-4-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-1*H*-[1,5]benzodiazepin-2-one (12): prepared as described for compound **9** using 1,2-diamino-4,5-dimethylbenzene instead of 1,2-diaminobenzene: yield 75%; mp 238–239 °C (from trituration with ethanol). Anal. ($C_{24}H_{21}N_5O\cdot0.5H_2O\cdot0.4$ethanol) C,H,N.

7,8-Dichloro-2,3-dihydro-4-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-1*H*-[1,5]benzodiazepin-2-one (13): prepared as described for compound **9** using 1,2-diamino-4,5-dichlorobenzene instead of 1,2-diaminobenzene: yield 64%, brown solid; mp 222–224 °C (from trituration with ethanol). Anal. ($C_{22}H_{15}Cl_2N_5O\cdot0.5H_2O\cdot0.33$ethanol) C,H,N.

2,3-Dihydro-1-methyl-4-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-1*H*-[1,5]benzodiazepin-2-one (14). Compound **9** (367 mg, 1.0 mmol) was added to a suspension of sodium hydride (48 mg, 60% oil dispersion, 1.2 mmol) in dry THF, and the mixture was stirred at room temperature for 1 h under nitrogen. Methyl iodide (142 mg, 1.0 mmol) was added, and the mixture was stirred for a further 3 h. The mixture was then treated with 2 N hydrochloric acid (15 mL) and washed with toluene (15 mL). The organic layer was neutralized with saturated aqueous sodium bicarbonate, and the product was extracted into dichloromethane (2 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 3:1) to give an off-white solid (107 mg, 28%): mp 147 °C. Anal. ($C_{23}H_{19}N_5O\cdot0.25H_2O$) C,H,N.

2,3-Dihydro-7,8-dimethyl-4-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-1*H*-[1,5]benzodiazepine-2-thione (15). Phosphorus pentasulfide (2.56 g, 5.76 mmol) was added to a suspension of compound **12** (4.56 g, 11.5 mmol) in dry pyridine (23 mL) under nitrogen. The mixture was heated under reflux for 45 min and then cooled and poured onto iced water. The solid material was filtered off and dried by azeotropic distillation with toluene. The residue was dissolved in dichloromethane and adsorbed onto silica gel (230–400 μm) and the solvent evaporated. The silica gel mixture was then applied to the top of a chromatography column (silica gel 60–230 μm), and the product was eluted with dichloromethane/methanol (9:1) to give an orange solid (3.4 g, 72%): mp 233–235 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (6H, s), 2.64 (3H, s), 4.05 (2H, s), 7.00 (1H, s), 7.18 (1H, d, J = 4 Hz), 7.38 (1H, s), 7.58 (2H, d, J = 6 Hz), 8.50 (1H, d, J = 4 Hz), 8.56 (2H, d, J = 6 Hz), 9.14 (1H, s), 9.62 (1H, s).

7,8-Dichloro-2,3-dihydro-4-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-1*H*-[1,5]benzodiazepine-2-thione (16): prepared as described for compound **15** using compound **13** instead of **12**: yield 60%; mp 195–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (3H, s), 4.12 (2H, s), 7.15 (1H, br s), 7.17 (1H, d, J = 4 Hz), 7.40 (1H, s), 7.57 (2H, d, J = 6 Hz), 7.72 (1H, s), 8.43 (1H, d, J = 4 Hz), 8.55 (2H, d, J = 6 Hz), 9.10 (1H, s).

2-Amino-7,8-dimethyl-4-[4-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-3*H*-[1,5]benzodiazepine (17). A mixture of compound **15** (2.98 g, 7.24 mmol) and red mercuric oxide (1.57 g, 7.24 mmol) in *n*-butanol (40 mL) was saturated with ammonia gas at room temperature and then stirred at 120 °C for 3 h. After being cooled, the mixture was diluted with methanol (150 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/diethylamine = 100:10:5). Fractions containing the product were evaporated to give a bright yellow solid (1.085 g, 38%): mp 299–302 °C. Anal. ($C_{24}H_{22}N_6\cdot0.33H_2O$) C,H,N.

7,8-Dichloro-3,4-dihydro-2-[4′-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-5*H*-1,4-benzodiazepin-5-one (18). A solution of sodium nitrite (3.3 g, 47 mmol) in water (40 mL) was added dropwise to a solution of ethyl 4′-(2-methylimidazo-[4,5-*c*]pyrid-1-yl)benzoylacetate (**4**)[5] (12.6 g, 39 mmol) in glacial acetic acid (45 mL) at 5 °C with stirring. After 1.5 h, the mixture was poured into saturated aqueous sodium chloride and extracted with dichloromethane. The organic extracts were washed with saturated aqueous sodium chloride and saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure to give an oil, which rapidly crystallized upon the addition of ether. Thus was obtained ethyl 4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoyloximidoacetate (**25**) (9.61 g, 70%) (2:1 mixture of *E*/*Z* isomers): mp 168–170 °C.

A solution of **25** (6.0 g, 17 mmol) in a mixture of glacial acetic acid (33 mL) and acetic anhydride (9 mL) was hydrogenated over 5% palladium on carbon (1 g) at 50 psi at 30 °C for 5 h. The mixture was filtered through Arbocel filter aid, washing the filter cake with methanol. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (gradient elution with ethyl acetate/methanol) to afford ethyl 2-acetamido-4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoylacetate (**26**) as a colorless foam (6.1 g, 94%): mp 71–73 °C.

A solution of **26** (1.2 g, 3.2 mmol) in hydrochloric acid (2 M, 30 mL) was heated at reflux for 3 h, cooled, and concentrated under reduced pressure to give 2-amino[4-(2-methylimidazo-[4,5-*c*]pyrid-1-yl)phenyl]ethanone hydrochloride (**27**) as a colorless foam (1.35 g, >100%).

4,5-Dichloroisatoic anhydride (0.44 g, 1.9 mmol) was added to a solution of (**27**) (0.74 g, 1.9 mmol) in water (6 mL) at room temperature. After being stirred to a uniform consistency, the mixture was treated with an aqueous solution of sodium carbonate (265 mg, 2.5 mmol) followed by dichloromethane (8 mL). The two-phase mixture was stirred for a further 3 h. The mixture was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with dichloromethane/methanol) to afford 2-amino-4,5-dichloro-*N*-[2-[4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-2-oxoethyl]benzamide (**28**) (320 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (3H, s), 5.00 (2H, d, J = 8.4 Hz), 5.69 (2H, br s), 6.83 (1H, s), 7.18 (2H, m), 7.62 (3H, m), 8.33 (2H, d, J = 8.4 Hz), 8.42 (1H, d, J = 5.5 Hz), 9.11 (1H, s).

A solution of **28** (0.32 g, 0.7 mmol) and *p*-toluenesulfonic acid (90 mg) in dichloromethane (12 mL) was heated at reflux for 16 h. The mixture was washed with saturated aqueous sodium carbonate, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with ethyl acetate/methanol) to afford 7,8-dichloro-3,4-dihydro-2-[4′-(2-methylimidazo[4,5-*c*]-pyrid-1-yl)phenyl]-5*H*-1,4-benzodiazepin-5-one (**18**) (178 mg, 58%): mp 174–177 °C (from ethyl acetate/ether). Anal. ($C_{22}H_{15}Cl_2N_5O\cdot H_2O$) C,H; N: found, 14.94; calcd, 15.40.

7-[4′-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-1*H*-4,5-dihydro[2,3]benzazepin-4-one (19). Hexane-washed sodium hydride (53 mg, 2.2 mmol) was added to a stirred solution of ethyl 4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoylacetate (**4**) (0.65 g, 2.0 mmol) in dry tetrahydrofuran (8 mL) at room temperature. After 30 min, 2′-nitrobromoacetophenone (510 mg, 2.1 mmol) was added in portions, and the resulting brown solution was stirred for 1 h. The mixture was neutralized and partitioned between ethyl acetate and water, and the organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 20:1) to give ethyl 2-[4′-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoyl][2-(2′-nitrophenyl)acetyl]acetate (**29**) as a pink solid (0.61 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz), 2.67 (3H, s), 3.68 (1H, dd, J = 16, 5 Hz), 3.79 (1H, dd, J = 16, 5 Hz), 4.28 (2H, q, J = 7.5 Hz), 5.23 (1H, dd, J = 8, 5 Hz), 7.19 (1H, d, J = 5 Hz), 7.60 (2H, d, J = 8 Hz), 7.69 (2H, m), 7.83 (1H, t, J = 5 Hz), 8.18 (1H, d, J = 9 Hz), 8.40 (2H, d, J = 8 Hz), 8.50 (1H, d, J = 5 Hz), 9.12 (1H, s).

A solution of **29** (0.6 g, 1.23 mmol) in 2 M hydrochloric acid (12 mL) was heated at 100 °C for 5 h. After being cooled, the solution was basified using solid sodium bicarbonate, and the product was extracted into ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 97:3) to give 1-[4'-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]4-(2'-nitrophenyl)-butane-1,4-dione (**30**) as a yellow solid (186 mg, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (3H, s), 3.37 and 3.62 (each 2H, t, J = 6 Hz), 7.15 (1H, d, J = 6 Hz), 7.55 (2H, d, J = 8 Hz), 7.70 (2H, m), 7.80 (1H, m), 8.18 (1H, d, J = 8 Hz), 8.31 (2H, d, J = 8 Hz), 8.44 (1H, d, J = 6 Hz), 9.10 (1H, s).

A solution of **30** (180 mg, 0.43 mmol) in ethanol (8 mL) was hydrogenated over 5% palladium on carbon (300 mg) at 30 psi and 22 °C for 2 h. The catalyst was filtered off, and the filtrate was evaporated to give 1-(2'-aminophenyl)-4-[4'-(2-methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]butane-1,4-dione (**31**) as a pale yellow foam (166 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (3H, s), 3.45 and 3.54 (each 2H, t, J = 7 Hz), 6.25 (2H, br s), 6.70 (2H, m), 7.27 (2H, m), 7.52 (2H, d, J = 8.5 Hz), 7.90 (1H, d, J = 9.5 Hz), 8.32 (2H, d, J = 8.5 Hz), 8.46 (1H, d, J = 4.5 Hz), 9.08 (1H, s).

A solution of **31** (166 mg, 0.43 mmol) in toluene (16 mL) and acetic acid (2 mL) was heated at reflux for 5 h. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with ethyl acetate/methanol = 95:5) to give 7-[4'-(2-methylimidazo-[4,5-*c*]pyrid-1-yl)phenyl]-1*H*-4,5-dihydro[2,3]benzazepin-4-one (**19**) as a foam (36 mg, 23%): mp 223–227 °C (from ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (3H, s), 3.35 (2H, t, J = 7.5 Hz), 5.36 (1H, t, J = 7.5 Hz), 6.59 (1H, br s), 7.10 (3H, m), 7.43 (2H, d, J = 9 Hz), 7.53 (2H, d, J = 9 Hz), 7.72 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 8 Hz), 8.42 (1H, d, J = 5 Hz), 9.10 (1H, s).

7,8-Dichloro-4-[4-(methylimidazo[4,5-*c*]pyrid-1-yl)-phenyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (20). Titanium tetrachloride (13.2 mL, 120 mmol) was dissolved in dry THF (240 mL) at 0 °C under nitrogen. A solution of compound **24** (14.22 g, 60 mmol) and dimethyl malonate (6.84 mL, 60 mmol) in dry THF (240 mL) was added followed by dry pyridine (14.5 mL, 180 mmol), with mechanical stirring. Stirring became difficult as gummy lumps formed, but these were broken up using a spatula, and eventually a granular solid resulted. The mixture was stirred at room temperature for 27 h, then methanol (50 mL) was added, and the mixture was poured onto ice and dichloromethane (500 mL). Excess aqueous sodium bicarbonate was added, and the mixture was filtered through Arbocel filter aid, washing with dichloromethane (500 mL). The aqueous layer was separated and extracted with more dichloromethane. The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was triturated with ether and filtered off to give dimethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylidenemalonate (**32**) as a buff solid (17.16 g, 81%): mp 155–156 °C (from ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 7.14 (1H, d, J = 6 Hz), 7.43 (2H, d, J = 9 Hz), 7.70 (2H, d, J 9 Hz), 7.85 (1H, s), 8.42 (1H, d, J = 6 Hz), 9.09 (1H, s). Anal. ($C_{19}H_{17}N_3O_4$) C,H,N.

A solution of 4,5-dichloro-2-nitrotoluene (2.472 g, 12.0 mmol) in dry dimethylformamide (5 mL) was added over 2 min by syringe to a suspension of sodium hydride (600 mg, 60% dispersion in oil, 15.0 mmol) and **32** in dry dimethylformamide (40 mL) while maintaining the temperature below 15 °C. The resulting brown solution was stirred at 20 °C for 3 h, and then glacial acetic acid (2 mL) was added. The mixture was poured into ethyl acetate (400 mL), and the solution was rendered basic by the addition of saturated aqueous sodium bicarbonate. The organic layer was washed with water (3 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient elution with ethyl acetate/methanol) to give dimethyl 2-(4,5-dichloro-2-nitrophenyl)-1-[4-(methylimidazo[4,5-c]pyrid-1-yl)phenyl]ethylmalonate (**33**) as a white solid (3.119 g, 56%): mp 94–96 °C (from methanol). Anal. ($C_{26}H_{22}Cl_2N_4O_6 \cdot 1.5H_2O$) C,H,N.

A solution of 25% aqueous titanium trichloride (4 mL, 6.5 mmol) was added dropwise to a solution of **33** (557 mg, 1.0 mmol) in degassed methanol (15 mL) under nitrogen at room temperature. The solution was stirred for 1 h, poured into dichloromethane (50 mL), and rendered basic by the addition of saturated aqueous sodium bicarbonate. The precipitated salts were filtered off and washed with dichloromethane (150 mL). The filtrate layers were separated, dried ($MgSO_4$), and concentrated under reduced pressure to give dimethyl 2-(2-amino-4,5-dichlorophenyl)-1-[4-methylimidazo[4,5-c]pyrid-1-yl)phenyl]ethylmalonate (**34**) as a colorless solid (452 mg, 86%): mp 186–188 °C (from methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (3H, s), 2.59 (1H, d, J = 12 Hz), 3.15 (1H, dd J = 12, 2 Hz), 3.55 (3H, s), 3.70 (1H, dt J = 12, 2 Hz), 3.91 (3H, s), 3.96 (1H, d, J = 12 Hz), 4.44 (2H, br s), 6.25 (1H, s), 6.78 (1H, s), 7.03 (1H, d, J = 6 Hz), 7.29 (4H, s), 8.39 (1H, d, J = 6 Hz), 9.07 (1H, s).

Sodium metal (846 mg, 36.8 mmol) was dissolved in dry methanol (250 mL) under nitrogen. Compound **34** (16.15 g, 30.16 mmol) was added, and the mixture was heated under reflux for 4.5 h. The mixture was cooled and poured into hydrochloric acid (4 M, 15 mL) and ice. The mixture was neutralized using saturated aqueous sodium bicarbonate, and the product was extracted into dichloromethane (4 × 150 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give (3*RS*,4*SR*)-7,8-dichloro-3-(methoxycarbonyl)-4-[4-(methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**35**) as a colorless solid (14.62 g, 96%): mp 221–223 °C (from methanol/dichloromethane). Anal. ($C_{25}H_{20}Cl_2N_4O_3$) C,H,N.

A mixture of **35** (14.42 g, 29.1 mmol) and lithium iodide (19.36 g, 145.5 mmol) in dry pyridine (200 mL) was heated at reflux under nitrogen for 2 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (gradient elution with ethyl acetate/methanol) to give 7,8-dichloro-4-[4-(methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**20**) (9.52 g, 75%): mp 314–316 °C (from methanol/dichloromethane). Anal. ($C_{23}H_{18}Cl_2N_4O \cdot 0.5H_2O$) C,H,N.

7,8-Dichloro-1-methyl-4-[4-(methylimidazo[4,5-*c*]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (21). A mixture of **20** (1.093 g, 2.5 mmol) and sodium hydride (150 mg, 60% dispersion in oil, 3.75 mmol) in dry dimethylformamide (10 mL) under nitrogen at room temperature was sonicated for 5 min and then stirred for a further 1 h. Methyl iodide (171 μL, 2.75 mmol) was added, and the mixture was stirred for 1.25 h and then poured into excess ice-cold dilute hydrochloric acid. The solution was rendered basic by the addition of saturated aqueous sodium bicarbonate, and the produce was extracted into dichloromethane (4 × 125 mL). The combined extracts were 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 colorless solid (848 mg, 75%): mp 259–261 °C (from ethyl acetate). Anal. ($C_{24}H_{20}Cl_2N_4O \cdot 0.25EtOAc$) C,H,N.

4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)benzoic Acid (23). 4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)benzonitrile[5] (36 g, 154 mmol) was added to a solution of sodium hydroxide (66 g, 1.65 mol) in aqueous ethanol (1:1, 330 mL), and the mixture was heated at reflux under nitrogen for 1.5 h. After being cooled, the mixture was concentrated under reduced pressure and the residual slurry dissolved in water (100 mL). The solution was treated with glacial acetic acid (to pH 6) with cooling, and the resulting precipitate was filtered off, washed with water (100 mL), and dried *in vacuo* to give the title compound (32.8 g, 84%) as an off-white solid: sublimes >240 °C; ν_{max} (KBr) 1703, 1603 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (3H, s), 7.25 (1H, d, J = 6 Hz), 7.72 (2H, d, J = 8 Hz), 8.17 (2H, d, J = 8 Hz), 8.30 (1H, d, J = 6 Hz), 8.92 (1H, s).

4-(2-Methylimidazo[4,5-*c*]pyrid-1-yl)benzaldehyde (24). Nickel–aluminum alloy (Ni:Al = 42:58, 16 g) was added to a stirred solution of 4-(2-methylimidazo[4,5-*c*]pyrid-1-yl)benzonitrile (**22**) (15 g, 64 mmol) in 90% formic acid (200 mL) and water (25 mL) in a 1 L round-bottomed flask equipped with a

stir bar and a long, wide-bore condensor. The mixture was heated to 120 °C at which point a strongly exothermic reaction initiated. The heating bath was removed until the reaction had subsided. The reaction flask was returned to the heating bath, and heating at reflux was continued for 1 h. The solution was cooled and filtered through Arbocel filter aid, and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed with saturated sodium bicarbonate. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless solid (11.2 g, 74%): mp 158–160 °C (from 2-propanol); ν_{max} (KBr) 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (3H, s), 7.16 (1H, d, J = 6 Hz), 7.61 (2H, d, J = 8 Hz), 8.19 (2H, d, J = 8 Hz), 8.61 (1H, d, J = 6 Hz), 9.10 (1H, s), 10.17 (1H, s). Anal. ($C_{14}H_{11}N_3O$) H,N.

Biology. Platelet Aggregation and PAF-Induced Murine Lethality. The procedures used were exactly as those reported previously.[5]

Molecular Modeling Studies. The work was carried out on a Silicon Graphics Indigo 2 Extreme workstation using the computer programs Sybyl 6.1a[24] and Spartan[25] SGI version 3.1.2 GL.

The molecules were built and energy minimized (MAXIMIN2) in Sybyl using Gasteiger/Huckel partial charges. In each case full systematic conformational searches were carried out to locate the lowest energy conformation. This conformation was then energy minimized using MAXIMIN2. The fitted conformations are within 1 kcal/mol of the minimum energy conformations. In the case of compound **13**, both low-energy conformations of the benzodiazepine (related by tub–tub ring inversion) were overlapped with RP-52,770 and the best fit was chosen.

Compound **3** and WEB-2170 were PM3 geometry optimized in Spartan and molecular electrostatic potential energy surfaces generated. These surfaces are displayed in Figures 2 and 3, using an energy range of −50 kcal/mol (red) to 20 kcal/mol (blue). These surfaces indicate that the most electronegative regions are located on the N3 of the imidazopyridine of compound **13** and the two adjacent nitrogens of the triazole of WEB-2170.

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Supporting Information Available: Atomic coordinates of the molecules in Figures 2–4 (cssr format) (5 pages). Ordering information is given on any current masthead page.

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