Structure−Activity Relationships for 5-Substituted 1-Phenylbenzimidazoles as Selective Inhibitors of the Platelet-Derived Growth Factor Receptor

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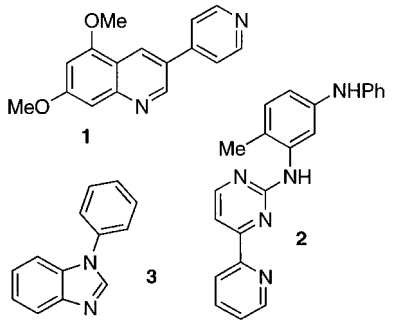
Following an earlier discovery of 1-phenylbenzimidazoles as ATP-site inhibitors of the platelet-derived growth factor receptor (PDGFR), further structure−activity relationships for analogues (particularly 5-substituted derivatives) are reported. The data are consistent with a binding model (constructed from the homology-modeled structure of the catalytic subunit of the PDGFR using protein kinase A as the template) in which the ligand binds in the relatively narrow ATP site, with the phenyl ring pointing toward the interior of the pocket and the 5-position of the benzimidazole ring toward the mouth of the pocket. The narrow binding pocket allows a maximum torsion angle between the phenyl and benzimidazole rings of about 40°, consistent with that calculated (43.6°) for the minimum-energy conformation of the unsubstituted free ligand. The inactivity of 7- or 2′-substituted analogues is consistent with the greater torsion angle (and thus larger ligand cross-section) of such substituted analogues. There is substantial bulk tolerance for 5-substituents, which protrude out of the mouth of the hydrophobic pocket, with the most effective analogues being those bearing weak bases. On the basis of this model, 5-OR derivatives bearing cationic side chains were prepared as soluble analogues, and these showed sub-micromolar potencies against the isolated PDGFR enzyme. They were also moderately effective inhibitors of autophosphorylation of PDGFR in rat aortic vascular smooth muscle cells, with IC_{50}s in the range 0.1−1 μM.

Inhibitors of the platelet-derived growth factor receptor (PDGFR) have been of interest as drugs to prevent restenosis following vascular interventions.[1,2] Such inhibitors are also of interest as potential anticancer drugs, because the expression of genes encoding PDGFR are also involved in the development of tumor angiogenesis[3] and other growth regulatory pathways.[4] Several classes of inhibitors aimed at this therapeutic use have been reported recently.[5] In particular, the 3-arylquinolines,[6,7] (e.g., **1**) and phenylaminopyrimidines[8,9] (e.g., **2**) are potent inhibitors both of the isolated enzyme



and of PDGF-stimulated autophosphorylation of PDGFR in vascular smooth muscle cells, acting at the ATP binding site. We recently reported[10] that 1-phenylbenzimidazoles (e.g., **3**) are a new class of selective PDGFR inhibitors also acting at the ATP binding site. We showed these had quite narrow structure−activity relationships (SAR), with only substituents in the 5- and 6-positions (particularly the 5-positions) enhancing activity. We now report an expansion of these SAR for inhibition of the isolated enzyme and inhibition of PDGFR autophosphorylation in cells.

Chemistry

Ether-linked benzimidazoles **7**−**21** were prepared by treatment of the sodium or cesium salts of 5-hydroxy-1-phenybenzimidazole (**5**) with the appropriate alkyl halide. For those compounds bearing basic side chains, an excess of sodium hydride was used to generate the benzimidazole salt, which was then reacted with the hydrochloride salt of the aminoalkyl chloride. The butylamino ethers **18** and **21** were obtained by displacement of the mesylate (derived from the alcohol **12**) with dimethylamine or morpholine, while the dihydroxypropyl ether (**14**) was prepared by neutral permanganate oxidation of the allyl ether (**11**). The thioethers **24** and **25** were synthesized by similar alkylation of the thiophenol (**23**), which was obtained by thermal rearrangement of the *O*-benzimidazolyl dimethylthiocarbamate (**26**) to the *S*-benzimidazolyl compound (**45**), followed by base hydrolysis (Scheme 1). Claisen rearrangement of the allyl ether (**11**) occurred regioselectively to give the 4-allyl compound (**33**) as the sole product, from which the cyclic ether (**34**) was obtained by acid-catalyzed dehydration. In an attempt to block the 4-position of **11**, thereby directing the rearrangement to the alternative 6-position, the phenol (**5**) was treated with *N*-

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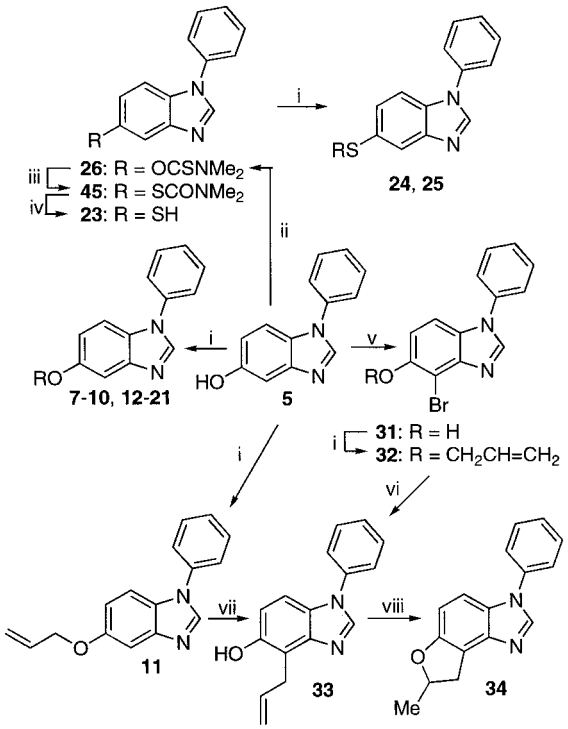
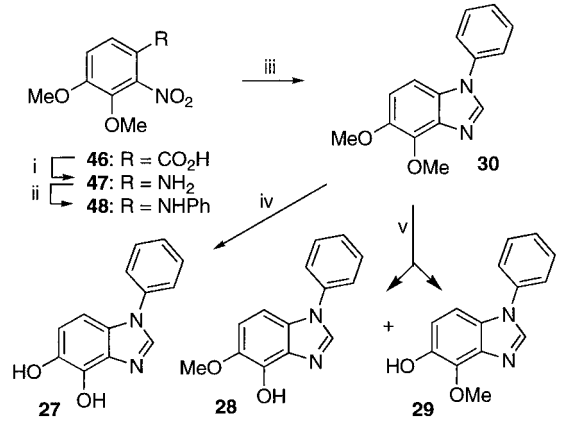
Scheme 1[a]



[a] Reagents and conditions: (i) NaH/THF/DMF, then R-halogen; (ii) NaH/THF/DMF, then Me_2NCSCl; (iii) sulfolane/reflux; (iv) MeOH/6 N KOH reflux; (v) NBS/DMF; (vi) *i*PrOH/heat/200 °C (pressure); (vii) *i*PrOH/heat/190 °C (pressure); (viii) AcOH/HBr/reflux.

Scheme 2[a]

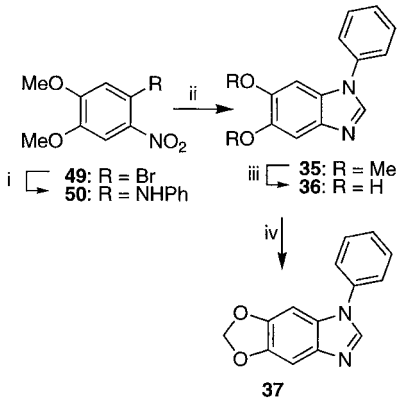


[a] Reagents and conditions: (i) $SOCl_2$/reflux, then NaN_3/Me_2CO, then AcOH/water/reflux; (ii) PhBr/CuI/K_2CO_3/reflux; (iii) H_2/Pd, then formamidine acetate/$MeOCH_2CH_2OH$/reflux; (iv) MeSLi/DMF, 120 °C; (v) BBr_3/CH_2Cl_2.

bromosuccinimide to give 4-bromo-5-hydroxy-1-phenylbenzimidazole (**31**) in near quantitative yield. However the derived allyl ether (**32**) again rearranged stereoselectively to give the 4-allyl phenol (**33**), with concomitant debromination (Scheme 1). An analogous strong regiochemical preference for thermal rearrangement of a 6-allyloxy indole has been reported.[11]

The 4,5-dimethoxybenzimidazole (**30**) was prepared from 3,4-dimethoxy-2-nitrobenzoic acid (**46**), which was converted via Curtius rearrangement to the aniline (**47**) (Scheme 2). Treatment with excess bromobenzene under copper (I) catalysis gave the diphenylamine (**48**), from which the benzimidazole (**30**) was obtained by nitro-group reduction followed by treatment of the resulting

Scheme 3[a]



[a] Reagents and conditions: (i) $PhNH_2/CuI/K_2CO_3$/reflux; (ii) H_2/Pd, then formamidine acetate/$MeOCH_2CH_2OH$/reflux; (iii) Py·HCl/220 °C; (iv) CH_2Br_2/TBAB/aqueous NaOH/reflux.

o-phenylenediamine with formamidine acetate. Demethylation of **30** with excess lithium methanethiolate at 130 °C gave the corresponding dihydroxy compound (**27**) as the sole product, while reaction with 1 equiv of boron tribromide gave a 4.3:1 mixture of the mono-demethylated ethers **28** and **29**, respectively. Assignment of regiochemistry to the isomers was based on detailed NOE studies of their ^1H NMR spectra, with only the 5-hydroxy-4-methoxy compound (**29**) displaying a strong NOE effect between its hydroxyl proton and the upfield doublet at ca. δ 6.99 resulting from the H-6 proton.

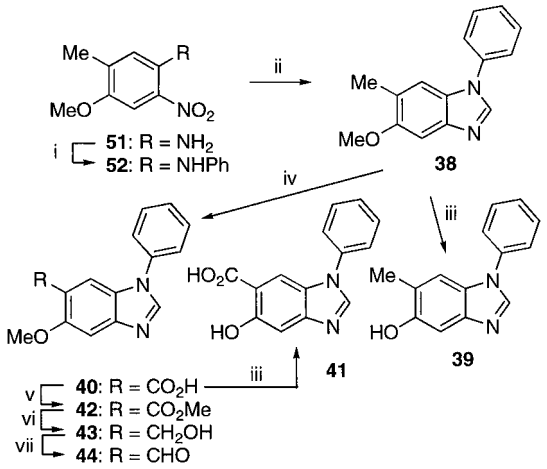
The known[12] 5,6-dimethoxybenzimidazole (**35**) was more conveniently prepared by reaction of 2-bromo-4,5-dimethoxynitrobenzene (**49**) with excess aniline under copper catalysis to give the diphenylamine (**50**), followed by nitro group reduction and benzimidazole formation using formamidine acetate (Scheme 3). Demethylation of **35** with pyridinium hydrochloride at 220 °C gave the catechol (**36**), from which the methylenedioxy ether (**37**) was obtained by phase-transfer catalyzed reaction with dibromomethane. Finally, 4-methoxy-5-methyl-2-nitroaniline (**51**) was similarly converted, through the phenylamine **52**, to 6-methoxy-5-methylbenzimidazole (**38**), from which other 5,6-disubstituted benzimidazoles (**39**–**44**) were synthesized by standard transformations (Scheme 4).

Results and Discussion

The compounds were evaluated for their ability to inhibit the phosphorylation of a model glutamate-tyrosine copolymer substrate by isolated human FGF-1 receptor, mouse PDGF-β receptor, and avian c-Src tyrosine kinase enzymes, and the results are given in Table 1. The FGFR and PDGFR proteins were fragments encoding the intracellular tyrosine kinase domains, while c-Src was a recombinant protein.[13,14] IC_{50} values were defined as the concentration of inhibitor to reduce the level of ^{32}P (from added [^{32}P]-ATP) incorporated into the copolymer substrate.

The parent 1-phenylbenzimidazole (**3**) is a moderately potent ATP site inhibitor of the tyrosine kinase activity of PDGFR (IC_{50} 9.3 μM), with some selectivity over FGFR and c-Src (IC_{50}s > 50 μM).[10] A systematic initial study showed tight SAR for the class, with 5-substituents being the most beneficial. Several 5-substituted compounds proved more active than **3**, with the 5-OMe

Scheme 4[a]



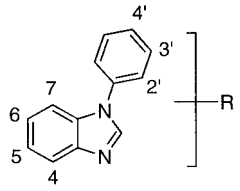
[a] Reagents and conditions: (i) PhBr/CuI/K_2CO_3/reflux; (ii) H_2/Pd, then formamidine acetate/$MeOCH_2CH_2OH$/reflux; (iii) AcOH/HBr/reflux; (iv) $KMnO_4$/*t*BuOH/water/reflux; (v) $SOCl_2$, then MeOH; (vi) BH_3·Me_2S/THF; (vii) MnO_2/EtOAc/reflux.

analogue (**6**) being both the most potent and the most PDGFR-selective compound of those evaluated.[10] In the present study, compounds **7**−**25** of Table 1 were prepared to further explore the SAR for 5-substituents. The simple lipophilic series **6**−**11** suggests there is considerable bulk tolerance at this position. While the O^{i}Pr analogue **9** was the least potent, it is likely this is due to lipophilicity rather than steric bulk, since analogues with even larger substituents (e.g., **18**, **21**) retained potency.

Compounds **12**−**21** explored the use of neutral (oxygen derivatives **12**−**14**), strongly basic (compounds **15**−**18**), and weakly basic (morpholines **19**−**21**) solubilizing side chains. Such functions have been shown previously[15] to be compatible with good inhibitory activity against EGFR. In the present case, all of the compounds were about 10-fold more potent than **3**, with IC_{50}s for PDGFR inhibition all below 1 μM. The most active compounds were the aminoalkoxy derivatives **17**−**21**, with IC_{50}s of 0.15−0.27 μM. Because a 4′-NH_2 substituent was shown previously[10] to be mildly beneficial (about twice as potent as **3** itself), the 5-OMe, 4′-NH_2 analogue **22** was also evaluated. While it was slightly more potent than **6**, the difference was, at best, only additive. Three S-linked analogues (**23**−**25**) were also evaluated. Direct comparisons of OR and SR analogues showed broadly similar profiles for the OMe/SMe pair (**6**/**24**), but in the OH/SH (**5**/**23**) and O/S(CH_2)$_3$morpholide pairs (**20**/**25**) the S-containing compounds were considerably less potent. The compounds were generally less effective against c-Src than PDGFR, with only the 5-O-alkylaminoalkyl derivatives **16**, **17**, and **21** showing significant activity against the former, except for **27**, which was surprisingly potent against c-Src. Compounds **5** and **6** were ca. 10-fold more potent in the cellular than the enzyme assay, but the reasons for this were not investigated.

No self-consistent SAR for the potencies of the 5-monosubstituted analogues could be discerned. As noted previously for the general class,[10] all of these showed some selectivity for PDGFR over FGFR. Equation 1 shows that the two IC_{50} values were closely correlated, with a slope of unity but with the compounds being on

Table 1. PDGFR, β-FGFR, and c-Src Inhibitory Activity of 5-Substituted 1-Phenylbenzimidazoles



		IC_{50} (μM)		
no.	R	PDGFR[a]	FGFR[b]	c-Src[c]
3	H[d]	9.3	>50	>50
4	4-OH[d]	14	>50	>50
5	5-OH[d]	0.44	6.4	>50
6	5-OMe[d]	0.43	22	>50
7	5-OEt	0.24	26	>50
8	5-O-nPr	0.25	35	>50
9	5-O-^{i}Pr	3.1	ca. 50	>50
10	5-O-^{n}Bu	1.3	50	>50
11	5-$OCH_2CH{=}CH_2$	0.61	35	>50
12	5-O(CH_2)$_4$OH	0.45	25	25
13	5-OCH_2(oxiranyl)	0.32	18	ca. 50
14	5-$OCH_2CH(OH)CH_2OH$	0.31	15	>50
15	5-O(CH_2)$_2NH_2$	0.65	27	>50
16	5-O(CH_2)$_2NMe_2$	1.5	45	28
17	5-O(CH_2)$_3NMe_2$	0.15	4.1	14
18	5-O(CH_2)$_4NMe_2$	0.16	6.8	ca. 50
19	5-O(CH_2)$_2$Nmorph	0.73	28	ca. 50
20	5-O(CH_2)$_3$Nmorph	0.17	9.8	ca. 50
21	5-O(CH_2)$_4$Nmorph	0.27	12	25
22	5-OMe, 4′-NH_2	0.28	18	>50
23	5-SH	3.3	>50	>50
24	5-SMe	0.74	27	>50
25	5-S(CH_2)$_3$Nmorph	>50	24	>50
26	5-$OCSNMe_2$	4.6	>50	>50
27	4,5-diOH	25	1.9	0.46
28	4-OH, 5-OMe	7.1	>50	40
29	4-OMe, 5-OH	>50	>50	>50
30	4,5-diOMe	>50	>50	>50
31	4-Br, 5-OH	>50	>50	>50
32	4-Br, 5-$OCH_2CH{=}CH_2$	>50	>50	>50
33	4-$CH_2CH{=}CH_2$, 5-OH	>50	>50	>50
34	4-CH_2CH(Me)O-5	29	>50	>50
35	5,6-diOMe	1.2	25	40
36	5,6-diOH	2.3	11	ca. 50
37	5,6-OCH_2O	2.2	27	>50
38	5-OMe, 6-Me	1.0	>50	>50
39	5-OH, 6-Me	2.5	>50	>50
40	5-OMe, 6-COOH	21	>50	>50
41	5-OH, 6-COOH	4.3	22	33.5
42	5-OMe, 6-COOMe	0.87	ca. 50	33.3
43	5-OMe, 6-CH_2OH	0.37	11	50
44	5-OMe, 6-CHO	1.0	25	>50

[a−c] IC_{50}; concentration of drug (μM) to inhibit the phosphorylation of a random glutamate/tyrosine (4:1) copolymer by PDGFR, FGFR, or c-Src proteins. For active compounds, values are an average of two or more separate determinations; variation was generally ±15%. See Experimental Section for details. [d] Data from ref 10.

average about 40-fold more potent against PDGFR than FGFR (ranging from 140-fold for **8** to 16-fold for **9**).

$$\log(IC_{50})[\text{PDGFR}] = 0.98(\pm0.19)\log(IC_{50})[\text{FGFR}] - 1.63(\pm0.26) \quad (1)$$

$$n = 15 \qquad r = 0.82 \qquad F = 25.7$$

As previously noted,[10] while 4-substituted analogues of **3** were generally inactive, the 4-OH analogue (**4**) showed modest effectiveness (an IC_{50} of 14 μM), and a small series of 4,5-disubstituted compounds (**27**−**30**) were prepared to see whether a combination of these

substituents was favorable. However, the 4,5-diOH derivative **27** was considerably less effective than either the 4-OH or 5-OH analogues (IC_{50}s 25, 14, and 0.44 μM, respectively). Potency was retained in the 4-OH, 5-OMe compound **28**, but the reverse 4-OMe, 5-OH analogue was inactive, consistent with the lack of activity of the 4-OMe derivative.[10] Compounds **31**−**33** were prepared as intermediates in the synthesis of the tricyclic analogue **34**. The latter compound can be considered as a combination of 4-Me and 5-OMe substituted analogues, and in view of the complete inactivity of the 4-Me compound,[10] its measurable (albeit low) activity (IC_{50} 29 μM) was surprising.

In the initial studies,[10] 6-substitution was found to be generally tolerated, with some substituents (6-OMe, 6-OH) slightly enhancing activity. A small series of 5,6-disubstituted analogues (**35**−**44**), primarily 5-OMe, 6-substituted, were therefore also prepared. Generally these showed inhibitory activities intermediate between the two corresponding monosubstituted compounds (where both of these were known), all being less active than the 5-OMe derivative **6**. An exception was the 5-OMe, 6-CH_2OH compound **43**, with an IC_{50} of 0.37 μM.

To assist in understanding these SAR in respect of enzyme binding, a 3D model of the PDGFR was constructed. We have described in detail the use of a 3D model of the EGFR tyrosine kinase constructed by homology modeling from the structure of cAMP-dependent protein kinase to assist in developing SAR for the EGFR-inhibitory activities of a series of bi- and tricyclic compounds.[16,17] In the present case, a 3D model of the PDGFR was constructed using the homology-modeling module implemented in LOOK[18] with PKA as the template.[16] A complex of this model and the 4′-NH_2, 5-OMe analogue (**22**) was constructed in SYBYL6.2 as discussed previously,[16,17] by docking the ligand manually into the ATP binding site and optimizing geometry with the Tripos Force Field implemented in SYBYL6.2 to relieve unfavorable steric contacts. A picture of the optimized complex between **22** and the modeled PDGFR protein is shown in Figure 1 and is consistent with the broad features of the SAR defined above and in the previous study.[10] In this model, the ligand binds in the relatively narrow ATP site, with the phenyl lying in a hydrophobic pocket in the interior of the binding site and the 5-position of the benzimidazole ring lying at the mouth of the pocket. A hydrogen bond is formed between N-3 of the benzimidazole and cysteine-652, which lies on the extended coil stretch of the ATP binding site of murine β-PDGFR.

In this configuration, the narrow hydrophobic pocket in the PDGFR limits the cross-sectional area of the ligand, allowing a maximum angle between the phenyl and benzimidazole rings of about 40°. Previous calculations[10] show that this is close to the angle of 43.6° calculated for the minimum-energy conformation of the unsubstituted free ligand, using the MM2 force field in MacroModel. However, the increased van der Waals interactions resulting from substitution by even small groups in the 7- or 2′-positions increases this angle, and thus the cross-sectional area of such ligands, limiting their access to the hydrophobic binding pocket.[10] In this binding model there is also very little bulk tolerance for 2- and 4-substituents and limited tolerance for 3′-, 4′-, and 6-substituents, but there is substantial bulk tolerance for 5-substituents, which protrude out of the mouth of the hydrophobic pocket (Figure 1). Analogues with cationic chains (e.g., **17**; $O(CH_2)_3NMe_2$, IC_{50} 0.15 μM) were slightly more effective than those with either neutral hydrophilic (e.g., **14**; 5-$OCH_2CH(OH)CH_2OH$, IC_{50} 0.31 μM) or neutral lipophilic (e.g., **10**; 5-O-^{n}Bu, IC_{50} 1.3 μM) chains of comparable size. It is possible that cationic groups at the 5-position may interact favorably with acidic residues sited near the entrance to the binding pocket.

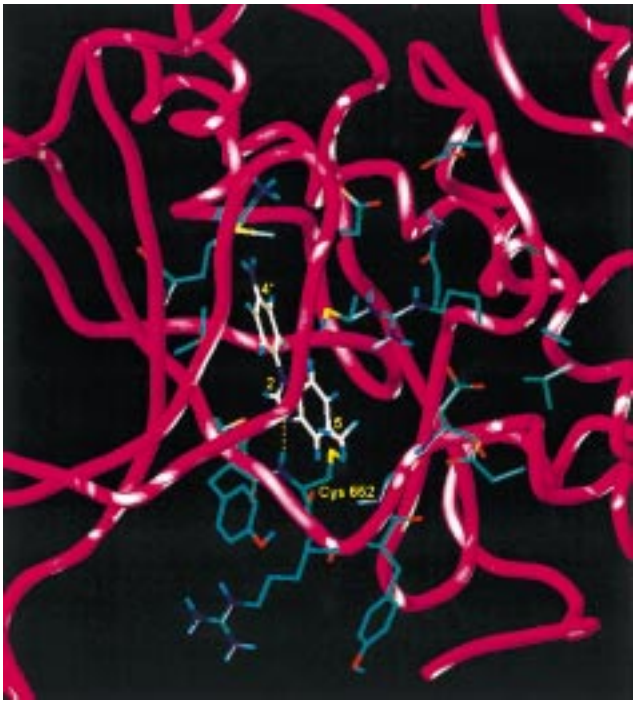


Figure 1. Compound **22** docked into the ATP binding pocket of the PDGFR. The 5-OMe group is located at the entrance to the pocket.

Table 2. Inhibition of PDGFR Autophosphorylation in Rat Aorta Vascular Smooth Muscle Cells (RAVSMC) by 1-Phenylbenzimidazole Analogues; Comparison with PDGFR Inhibition

	IC_{50} (μM)	
no.	PDGFR[a]	RAVSMC[b]
5	6.4	0.13
6	22	1.9
19	0.73	0.79
22	0.28	1.36

[a] Data from Table 1. [b] See ref 13 for details of the assay.

Several of the more potent inhibitors of the isolated PDGFR enzyme were evaluated for their ability to inhibit autophosphorylation of PDGFR in rat aortic vascular smooth muscle cells (Table 2).[13] The most potent in this regard was the 5-OH derivative **5**, with an IC_{50} of 0.13 μM. Both the 5-OMe and the 5-$O(CH_2)_2$-Nmorpholide analogues (**6** and **19**) were less effective (IC_{50}s 1.9 and 0.79 μM respectively).

Conclusions

Previous studies[10] on the 1-phenylbenzimidazoles defined a well-defined SAR for the selective inhibition of PDGFR enzyme compared with FGFR, with the 5-OMe derivative **6** being both the most potent and the

most PDGFR-selective. The SAR found were consistent with a binding model where the ligands bind in a relatively narrow hydrophobic pocket, with the phenyl ring sited toward the interior and the 5-position of the benzimidazole ring toward the mouth of the pocket. On this basis, the present study explored the considerable bulk tolerance at the 5-position. Analogues bearing solubilizing cationic groups at this position retained and even increased potency for PDGFR (the 5-O$(CH_2)_3NMe_2$ analogue **17**, with an IC_{50} of 0.15 μM, was about 3-fold more potent than **6**), while retaining good selectivity over FGFR and c-Src.

Experimental Section

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined using an Electrothermal Model 9200 digital melting point apparatus and are as read. NMR spectra were measured on a Bruker AM-400 spectrometer and referenced to Me_4Si for organic solutions and 3-(trimethylsilyl)propionic-*2,2,3,3-d*$_4$ acid, sodium salt, for D_2O solutions. Mass spectra were recorded on a Varian VG 7070 spectrometer at nominal 5000 resolution.

5-Ethoxy-1-phenylbenzimidazole Hydrochloride (7). A solution of 5-hydroxy-1-phenylbenzimidazole[10] **(5)** (0.12 g, 0.57 mmol) in 1:1 THF/DMF (5 mL) was added under nitrogen to a stirred suspension of NaH (16 mg, 0.68 mmol) in THF (5 mL). After 5 min, ethyl iodide (55 mL, 0.68 mmol) was added, and the solution was stirred at 20 °C for 2 h, then poured into brine, and extracted with diethyl ether. The ether extract was washed with 2 N NaOH and then water. Evaporation of the organic layer gave a residue that was dissolved in EtOAc and percolated through a plug of silica gel to give **7** (94 mg, 69%). HCl salt: mp (MeOH/Et_2O) 210−213 °C; ^{1}H NMR (D_2O) δ 9.37 (s, 1 H, H-2), 7.75−7.71 (m, 3 H, Ph), 7.68−7.65 (m, 2 H, Ph), 7.61 (d, J = 9.2 Hz, 1 H, H-7), 7.38 (d, J = 2.3 Hz, 1 H, H-4), 7.22 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.21 (q, J = 7.0 Hz, 2 H, OCH_2), 1.46 (t, J = 7.0 Hz, 3 H, CH_2CH_3); ^{13}C NMR δ 160.63 (s), 141.72 (d), 135.87 (s), 134.57 (s), 133.34 (d), 133.14 (d), 128.55 (s), 127.28 (d), 120.11 (d), 116.73 (d), 100.66 (d), 67.98 (t), 16.55 (q). Anal. ($C_{15}H_{14}N_2O$·HCl) C, H, N.

The following ethers were obtained from **5** in a similar manner:

1-Phenyl-5-propoxybenzimidazole Hydrochloride (8) (76%): mp (MeOH/Et_2O) 204−206 °C; ^{1}H NMR δ (D_2O) 9.38 (s, 1 H, H-2), 7.75−7.71 (m, 3 H, Ph), 7.69−7.65 (m, 2 H, Ph), 7.62 (d, J = 9.2 Hz, 1 H, H-7), 7.39 (d, J = 2.3 Hz, 1 H, H-4), 7.24 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.11 (t, J = 6.6 Hz, 2 H, OCH_2), 1.86 (txq, J = 7.5, 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 1.06 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$); ^{13}C NMR δ 160.87 (s), 141.69 (d), 135.86 (s), 134.48 (s), 133.36 (d), 133.15 (d), 128.53 (s), 127.30 (d), 120.18 (d), 116.75 (d), 100.72 (d), 73.86 (t), 24.54 (t), 12.40 (q). Anal. ($C_{16}H_{16}N_2O$·HCl) C, H, N.

5-Isopropoxy-1-phenylbenzimidazole Hydrochloride (9) (66%): mp (MeOH/Et_2O) 210−211 °C; ^{1}H NMR (D_2O) δ 9.38 (s, 1 H, H-2), 7.76−7.71 (m, 3 H, Ph), 7.70−7.66 (m, 2 H, Ph), 7.63 (d, J = 9.2 Hz, 1 H, H-7), 7.44 (d, J = 2.3 Hz, 1 H, H-4), 7.24 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.79 (sp, J = 6.1 Hz, 1 H, $OCH(CH_3)_2$) 1.41 (d, J = 6.1 Hz, 6 H, $OCH(CH_3)_2$); ^{13}C NMR δ 159.32 (s), 141.93 (d), 135.87 (s), 134.62 (s), 133.32 (d), 133.13 (d), 128.74 (s), 127.29 (d), 121.23 (d), 116.80 (d), 102.87 (d), 75.51 (d), 23.66 (q). ($C_{16}H_{16}N_2O$·HCl) C, H, N.

5-Butoxy-1-phenylbenzimidazole Hydrochloride (10) (72%): mp (MeOH/EtOAc) 196−197 °C; ^{1}H NMR (D_2O) δ 9.38 (s, 1 H, H-2), 7.75−7.68 (m, 5 H, Ph), 7.65 (d, J = 9.2 Hz, 1 H, H-7), 7.41 (d, J = 2.2 Hz, 1 H, H-4), 7.26 (dd, J = 9.2, 2.2 Hz, 1 H, H-6), 4.16 (t, J = 6.6 Hz, 2 H, OCH_2^-), 1.82 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 0.97 (t, J = 7.5 Hz, 3 H, CH_3); ^{13}C NMR δ 160.90 (s), 141.71 (d), 135.89 (s), 134.40 (s), 133.38 (d), 133.13 (d), 128.64 (s), 127.42 (d), 120.23 (d), 116.80 (d), 100.74 (d), 72.09 (t), 33.11 (t), 21.33 (t), 15.78 (q). Anal. ($C_{17}H_{18}N_2O$·HCl·0.25H_2O) C, H, N.

5-Allyloxy-1-phenylbenzimidazole Hydrochloride (11) (88%): mp (MeOH/Et_2O) 200−202 °C; ^{1}H NMR (D_2O) δ 9.40 (s, 1 H, H-2), 7.76−7.72 (m, 3 H, Ph), 7.67−7.64 (m, 2 H, Ph), 7.59 (d, J = 9.2 Hz, 1 H, H-7), 7.38 (d, J = 2.3 Hz, 1 H, H-4), 7.22 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 6.18−6.11 (m, 1 H, CH=CH_2), 5.51 (dd, J 17.3, 1.4 Hz, 1 H, CH=CHH), 5.42 (dd, J = 10.8, 1.4 Hz, 1 H, CH=CHH), 4.69 (d, J = 5.4 Hz, 2 H, OCH_2); ^{13}C NMR δ 160.22 (s), 141.79 (d), 135.77 (s), 135.04 (d), 134.45 (s), 133.34 (d), 133.15 (d), 128.53 (s), 127.16 (d), 121.48 (t), 120.19 (d), 116.73 (d), 101.08 (d), 72.57 (t). Anal. ($C_{16}H_{14}N_2O$·HCl) C, H, N.

5-(4-Hydroxybutoxy)-1-phenylbenzimidazole Hydrochloride (12). A mixture of **5** (0.31 g, 1.47 mmol), $CsCO_3$ (0.58 g, 1.77 mmol), and 4-chlorobutanol (0.16 mL, 1.62 mmol) in DMF (10 mL) was warmed at 115 °C for 18 h and then concentrated to dryness under reduced pressure. The residue was partitioned between EtOAc and water and then filtered, and the organic portion was worked up and chromatographed on silica gel. EtOAc eluted a trace of starting material, while MeOH/EtOAc (1:9) gave **12** (0.34 g, 82%): mp (hydrochloride salt from MeOH/EtOAc) 205−207 °C; ^{1}H NMR (D_2O) δ 9.37 (s, 1 H, H-2), 7.76−7.67 (m, 5 H, Ph), 7.66 (d, J = 9.2 Hz, 1 H, H-7), 7.41 (d, J = 1.6 Hz, 1 H, H-4), 7.28 (dd, J = 9.2, 1.6 Hz, 1 H, H-6), 4.19 (t, J = 6.4 Hz, 2 H, CH_2O), 3.69 (t, J = 6.5 Hz, 2 H, CH_2O), 1.93−1.86 (m, 2 H, CH_2), 1.79−1.71 (m, 2 H, CH_2); ^{13}C NMR δ 160.78 (s), 141.83 (d), 135.95 (s), 134.60 (s), 133.34 (d), 133.13 (d), 128.82 (s), 127.44 (d), 120.19 (d), 116.79 (d), 100.85 (d), 71.89 (t), 64.11 (t), 30.67 (t), 27.62 (t). Anal. ($C_{17}H_{18}N_2O_2$·HCl·0.5H_2O) H, N; C: found 61.8, calculated 63.3%.

5-(2,3-Epoxypropoxy)-1-phenylbenzimidazole (13) A solution of **5** (0.24 g, 1.14 mmol) 1:1 THF/DMF (5 mL) was added under nitrogen to a stirred suspension of sodium hydride (41 mg of a 60% dispersion in oil, 1.71 mmol). After 5 min, epichlorohydrin (98 mL, 1.26 mmol) was added, and the solution was refluxed for 4 h. The cooled solution was partitioned between diethyl ether and water, and the extract was washed with 2 N NaOH and worked up to give an oil which was chromatographed on silica gel. EtOAc/petroleum ether (1:1) eluted foreruns, while EtOAc eluted **13** (0.14 g, 46%): mp (EtOAc/petroleum ether) 96−97.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1 H, H-2), 7.59−7.43 (m, 5 H, Ph), 7.43 (d, J = 8.7 Hz, 1 H, H-7), 7.34 (d, J = 2.4 Hz, 1 H, H-4), 7.02 (dd, J = 8.7, 2.4 Hz, 1 H, H-6), 4.32 (dd, J = 10.9, 3.1 Hz, 1 H, ArOCHH), 4.04 (dd, J = 10.9, 5.7 Hz, 1 H, ArOCHH), 3.44−3.40 (m, 1 H, CHO), 2.94 (dd, J = 4.9, 4.3 Hz, 1 H, CHHO), 2.81 (dd, J = 4.9, 2.6 Hz, 1 H, CHHO); ^{13}C NMR δ 155.29 (s), 144.84 (s), 142.51 (d), 136.38 (s), 130.04 (d), 128.64 (s), 127.94 (d), 123.79 (d), 114.28 (d), 110.99 (d), 103.67 (d), 69.44 (t), 50.17 (d), 44.77 (t). Anal. ($C_{16}H_{14}N_2O_2$) C, N; H: found 4.7, calculated 5.3%.

5-(2,3-Dihydroxypropoxy)-1-phenylbenzimidazole Hydrochloride (14). Saturated aqueous $KMnO_4$ solution was added in portions over 3 h at 20 °C to a stirred solution of **11** (0.25 g, 1.00 mmol) in acetone (50 mL) until no starting material remained. The mixture was filtered through Celite, washing with more acetone, and the filtrate was concentrated to dryness under reduced pressure. The residue was partitioned between EtOAc and water, and the organic portion was worked up and chromatographed on silica gel. EtOAc eluted foreruns while MeOH/EtOAc (1:19) gave **14** (0.18 g, 63%). HCl salt: mp (MeOH/Et_2O) 182−183 °C; ^{1}H NMR (D_2O) δ 9.35 (s, 1 H, H-2), 7.75−7.68 (m, 5 H, Ph), 7.66 (d, J = 9.3 Hz, 1 H, H-7), 7.42 (d, J = 2.2 Hz, 1 H, H-4), 7.30 (dd, J = 9.3, 2.2 Hz, 1 H, H-6), 4.27−4.22 (m, 1 H, CHOH), 4.20−4.14 (m, 2 H, $ArOCH_2$), 3.84−3.74 (m, 2 H, CH_2OH); ^{13}C NMR δ 160.68 (s), 141.95 (d), 135.96 (s), 134.70 (s), 133.31 (d), 133.12 (d), 128.92 (s), 127.40 (d), 120.10 (d), 116.80 (d), 100.87 (d), 72.70 (d), 72.48 (t), 65.03 (t). Anal. ($C_{16}H_{16}N_2O_3$·HCl·0.5H_2O) C, H, N.

5-(2-Aminoethoxy)-1-phenylbenzimidazole Dihydrochloride (15). A solution of **5** (0.10 g, 0.47 mmol) in 1:1 THF/DMF (2 mL) was added under nitrogen to a stirred suspension of sodium hydride (28.5 mg of a 60% dispersion in oil, 1.19 mmol) in THF (4 mL). After 10 min solid 2-bromoethylamine

hydrobromide (97 mg, 0.47 mmol) was added, and the mixture was warmed at 45 °C for 30 min. A further portion of sodium hydride (28.5 mg) followed by the bromoethylamine hydrobromide (97 mg) was added, and stirring was continued at this temperature for 1 h. Water was added, followed by brine, and the mixture was extracted into EtOAc. The organic solution was extracted into 2 N HCl, the extract was basified with 2 N NaOH and extracted into ether, and the ether solution worked up to give an oil which was chromatographed on alumina. EtOAc eluted foreruns while MeOH/EtOAc (1:9) gave **15** (68.5 mg, 58%). DiHCl salt: mp (MeOH/Et_2O) 252−254 °C; ^{1}H NMR (D_2O) δ 9.43 (s, 1 H, H-2), 7.78−7.72 (m, 6 H, Ph and H-7), 7.51 (d, J = 2.3 Hz, 1 H, H-4), 7.38 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.46 (t, J = 4.9 Hz, 2 H, CH_2NH_3), 3.56 (t, J = 4.9 Hz, 2 H, OCH_2); ^{13}C NMR δ 160.02 (s), 142.22 (d), 135.96 (s), 134.61 (s), 133.40 (d), 133.16 (d), 129.29 (s), 127.54 (d), 120.04 (d), 117.02 (d), 100.97 (d), 67.55 (t), 41.64 (t). Anal. ($C_{15}H_{15}N_3O$·2HCl·0.5H_2O) C, H, N.

The following ethers were obtained from **5** and the appropriate haloamines in a similar manner:

5-[2-(*N*,*N*-Dimethylamino)ethoxy]-1-phenylbenzimidazole Dihydrochloride (16) (47%) (diHCl salt): mp (MeOH/Et_2O) 205−207 °C (hygroscopic foam); ^{1}H NMR (D_2O) δ 9.45 (s, 1 H, H-2), 7.77−7.72 (m, 6 H, Ph and H-7), 7.53 (d, J = 2.3 Hz, 1 H, H-4), 7.39 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.55 (t, J = 5.0 Hz, 2 H, $CH_2N^+Me_2$), 3.73 (t, J = 5.0 Hz, 2 H, OCH_2), 3.06 (s, 6 H, N^+Me_2); ^{13}C NMR δ 159.71 (s), 142.27 (d), 135.91 (s), 134.42 (s), 133.43 (d), 133.15 (d), 129.39 (s), 127.57 (d), 119.97 (d), 117.08 (d), 100.98 (d), 65.16 (t), 58.91 (t), 45.63 (q). Anal. ($C_{17}H_{19}N_3O$·2HCl) C, H, N.

5-[3-(*N*,*N*-Dimethylamino)propoxy]-1-phenylbenzimidazole Dihydrochloride (17) (52%) (diHCl salt): mp (MeOH/Et_2O) dec above 76 °C (hygroscopic); ^{1}H NMR (D_2O) δ 9.41 (s, 1 H, H-2), 7.75−7.71 (m, 6 H, Ph and H-7), 7.46 (d, J = 2.3 Hz, 1 H, H-4), 7.33 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.30 (t, J = 5.7 Hz, 2 H, CH_2 N^+Me_2), 3.44 (t, J = 7.7 Hz, 2 H, CH_2O), 2.98 (s, 6 H, N^+Me_2), 2.36−2.29 (m, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR δ 160.49 (s), 142.01 (d), 135.94 (s), 134.43 (s), 133.42 (d), 133.14 (d), 129.08 (s), 127.58 (d), 120.15 (d), 116.97 (d), 100.76 (d), 68.73 (t), 58.21 (t), 45.63 (q), 26.69 (t). Anal. ($C_{18}H_{21}N_3O$·2HCl·3.5H_2O) C, H, N.

5-[4-(*N*,*N*-Dimethylamino)butoxy]-1-phenylbenzimidazole Dihydrochloride (18). Methanesulfonyl chloride (0.27 mL, 3.31 mmol) was added dropwise at 20 °C to a stirred solution of the butanol **12** (0.85 g, 3.01 mmol) and Et_3N (0.50 mL, 3.61 mmol) in CH_2Cl_2 (50 mL). After 5 min the resulting solution was evaporated to dryness under reduced pressure to give the crude mesylate. Half of this was dissolved in MeOH (20 mL) containing dimethylamine (5 mL of a 40% aqueous solution), and the mixture was warmed in a pressure vessel at 80 °C for 15 h. After concentration to dryness the residue was partitioned between EtOAc and water, and the organic portion was chromatographed on alumina. EtOAc eluted foreruns while MeOH/EtOAc (1:9) gave **18** (0.32 g, 65%): mp (dihydrochloride salt from MeOH/Et_2O) 88 °C (hygroscopic foam). ^{1}H NMR (D_2O) δ 9.31 (s, 1 H, H-2), 7.75−7.70 (m, 5 H, Ph), 7.70 (d, J = 9.2 Hz, 1 H, H-7), 7.43 (d, J = 2.3 Hz, 1 H, H-4), 7.30 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.23 (t, J = 5.7 Hz, 2 H, CH_2O), 3.25 (t, J = 7.0 Hz, 2 H, CH_2N^+), 2.91 (s, 6 H, $^+NMe_2$), 2.00−1.91 (m, 4 H, CH_2). EIMS [M^+] $C_{19}H_{23}N_3O$ requires 309.1841. Found 309.1810.

5-[2-(4-Morpholino)ethoxy]-1-phenylbenzimidazole Dihydrochloride (19) (57%) (diHCl salt): mp (MeOH/Et_2O) 232−234 °C (hygroscopic foam); ^{1}H NMR (D_2O) δ 9.44 (s, 1 H, H-2), 7.78−7.72 (m, 6 H, Ph and H-7), 7.53 (d, J = 2.3 Hz, 1 H, H-4), 7.39 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.60 (t, J = 4.8 Hz, 2 H, CH_2N^+), 4.19−3.95 (2 × br, 4 H, morpholino CH_2N^+), 3.79 (t, J = 4.8 Hz, 2 H, CH_2O); ^{13}C NMR δ 159.61 (s), 142.34 (d), 135.95 (s), 134.60 (s), 133.40 (d), 133.16 (d), 129.42 (s), 127.55 (d), 119.93 (d), 117.07 (d), 101.05 (d), 66.38 (t), 64.70 (t), 58.57 (t), 54.73 (t). Anal. ($C_{19}H_{21}N_3O_2$·2HCl·0.5H_2O) C, H, N.

5-[3-(4-Morpholino)propoxy]-1]phenylbenzimidazole Dihydrochloride (20) (52%) (diHCl salt): mp (MeOH/Et_2O) dec above 84 °C (hygroscopic solid); ^{1}H NMR (D_2O) δ 9.42 (s, 1 H, H-2), 7.81−7.74 (m, 5 H, Ph), 7.72 (d, J = 9.2 Hz, 1 H, H-7), 7.47 (d, J = 2.2 Hz, 1 H, H-4), 7.34 (dd, J = 9.2, 2.2 Hz, 1 H, H-6), 4.33 (t, J = 5.6 Hz, 2 H, CH_2N^+), 4.23 (br d, J = 12.9 Hz, 2 H, morpholino CH_2N^+), 3.92 (br t, J = 12.9 Hz, 2 H, morpholino CH_2N^+), 3.70 (br d, J = 12.6 Hz, 2 H, morpholino CH_2O), 3.52 (t, J = 5.6 Hz, 2 H, CH_2O), 3.36−3.28 (m, 2 H, morpholino CH_2O), 2.42−2.36 (m, 2 H, CH_2CH_2-CH_2); ^{13}C NMR δ 160.39 (s), 142.00 (d), 135.93 (s), 134.61 (s), 133.35 (d), 133.14 (d), 128.94 (s), 127.43 (d), 120.08 (d), 116.89 (d), 100.79 (d), 68.65 (t), 66.58 (t), 57.58 (t), 54.62 (t), 25.86 (t). Anal. ($C_{20}H_{23}N_3O_2$·2HCl·3.5H_2O) C, H, N.

5-[4-(4-Morpholino)butoxy]-1]phenylbenzimidazole Dihydrochloride (21). The remaining half of the crude mesylate solution obtained from **12** during preparation of **18** (see earlier) was concentrated to dryness and the residue dissolved in morpholine (10 mL) and refluxed for 30 min. After removal of excess morpholine under reduced pressure, the residue was partitioned between brine and EtOAc and the organic portion was worked up and chromatographed on alumina. EtOAc eluted **21** (0.27 g, 49%): mp (dihydrochloride salt from MeOH/Et_2O) 100−103 °C (hygroscopic powder); ^{1}H NMR (D_2O) δ 9.40 (s, 1 H, H-2), 7.75−7.72 (m, 5 H, Ph), 7.70 (d, J = 9.2 Hz, 1 H, H-7), 7.45 (d, J = 2.3 Hz, 1 H, H-4), 7.32 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 4.24 (t, J = 5.9 Hz, 2 H, CH_2O), 4.17 (dd, J = 13.2, 3.4 Hz, 2 H, CH_2O), 3.90−3.82 (m, 2 H, CH_2O), 3.61−3.59 (m, 2 H, CH_2N^+), 3.32 (t, J = 6.9 Hz, 2 H, CH_2N^+), 3.28−3.21 (m, 2 H, CH_2N^+); ^{13}C NMR δ 160.69 (s), 141.91 (d), 135.95 (s), 134.54 (s), 133.37 (d), 133.14 (d), 128.88 (s), 127.50 (d), 120.17 (d), 116.89 (d), 100.80 (d), 71.02 (t), 66.54 (t), 59.64 (t), 54.39 (t), 28.13 (t), 22.89 (t). CIMS [M + H]$^+$ $C_{21}H_{26}N_3O_2$ requires 352.2025. Found 352.2013.

1-(4-Aminophenyl)-5-methoxybenzimidazole Dihydrochloride (22). A mixture of 4-methoxy-2-nitroaniline (1.00 g, 5.95 mmol), K_2CO_3 (0.34 g, 2.46 mmol), CuI (50 mg), and 4-nitrobromobenzene (3.00 g, 0.015 mmol) was heated with stirring to 150 °C for 48 h. The cooled mixture was partitioned between EtOAc and brine, and the organic portion was worked up and chromatographed on silica gel. EtOAc/petroleum ether (1:1) eluted 4-methoxy-2-nitro-*N*-(4-methoxyphenyl)aniline (1.12 g), contaminated with some starting material, which was used directly. The mixture was dissolved in EtOAc/MeOH (1:1) (50 mL) and hydrogenated over 5% Pd−C (0.20 g) for 3 h. The solution was filtered through Celite to remove catalyst and evaporated under reduced pressure. The residue was dissolved in 4 N HCl (30 mL) containing formic acid (1 mL) the solution was heated under reflux for 90 min and then concentrated to dryness, the residue was partitioned between EtOAc and ammonia, and the organic layer was worked up and chromatographed on silica gel. EtOAc/petroleum ether (1:1) eluted foreruns while EtOAc gave **22** (0.26 g, 17%). DiHCl salt: mp (MeOH/Et_2O) 237−239 °C; ^{1}H NMR (D_2O) δ 9.44 (s, 1 H, H-2), 7.86 (d, J = 8.7 Hz, 2 H, H-3′,5′), 7.70 (d, J = 9.2 Hz, 1 H, 7), 7.69 (d, J = 8.7 Hz, 2 H, H-2′,6′), 7.46 (d, J = 2.3 Hz, 1 H, H-4), 7.33 (dd, J = 9.2, 2.3 Hz, 1 H, H-6), 3.98 (s, 3 H, OCH_3); ^{13}C NMR δ 161.69 (s), 142.02 (d), 137.08 (s), 135.28 (s), 134.53 (s), 129.41 (d), 128.71 (s), 126.89 (d), 120.08 (d), 116.64 (d), 99.97 (d), 58.90 (q). Anal. ($C_{14}H_{13}N_3O$·2HCl·0.5H_2O) C, H, N.

5-Mercapto-1-phenylbenzimidazole Hydrochloride (23). A solution of **5** (0.88 g, 4.10 mmol) in 1:1 THF/DMF (15 mL) was added dropwise under nitrogen to a stirred suspension of NaH (0.24 g of a 50% dispersion in oil, 5.00 mmol) in THF (10 mL). After 10 min a solution of dimethylthiocarbamoyl chloride (0.57 g, 4.6 mmol) in THF (5 mL) was added, and the solution was warmed at 60 °C for 1 h. The cooled solution was partitioned between ether and 2 N KOH, and the organic portion was worked up and chromatographed on silica. Elution with EtOAc/petroleum ether (7:3) gave the *O*-benzimidazolyl dimethylthiocarbamate (**26**) (0.76 g, 65%): mp (EtOAc/petroleum ether) 173−174.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.61 (s, 1 H, H-2), 7.72−7.62 (m, 4 H, Ph), 7.60 (d, J = 8.7 Hz, 1 H, H-7), 7.54−7.49 (m, 1 H, Ph), 7.45 (d, J = 2.2 Hz, 1 H, H-4), 7.04 (dd, J = 8.7, 2.2 Hz, 1 H, H-6), 3.39, 3.36 (2s, each 3 H, NMe_2); ^{13}C NMR δ 187.03 (s), 149.51 (s), 144.27 (d), 143.78

(s), 135.74 (s), 130.78 (s), 130.03 (d), 127.79 (d), 123.60 (d), 119.02 (d), 113.55 (d), 110.32 (d), 42.80 (q), 38.41 (q). Anal. ($C_{16}H_{15}N_3SO$) C, H, N.

A solution of **26** (0.40 g, 1.40 mmol) in dry sulfolane (20 mL) was refluxed under nitrogen for 5 h. The cooled solution was poured into brine, extracted with EtOAc and worked up to give an oil which was chromatographed on silica. EtOAc/petroleum ether (1:1) eluted residual sulfolane while EtOAc gave *S*-(1-phenylbenzimidazolyl)dimethylthiocarbamate (**45**) (0.36 g, 90%) as an oil. The total crude product was dissolved in MeOH (50 mL) and 6 N KOH (5 mL) and heated under reflux for 6 h. The MeOH was removed under reduced pressure, and the residue was partitioned between ether and water. The aqueous portion was carefully neutralized with concentrated HCl and extracted with EtOAc, and the extract worked up to give an oil which was chromatographed on silica gel. EtOAc eluted 5-mercapto-1-phenylbenzimidazole (**23**) as an unstable oil (0.16 g, 56%). HCl salt: mp (MeOH/Et_2O) 180−184 °C; ^{1}H NMR (D_2O) δ 9.44 (s, 1 H, H-2), 7.84 (d, J = 2.0 Hz, 1 H, H-4), 7.75−7.65 (m, 5 H, Ph), 7.63 (d, J = 8.7 Hz, 1 H, H-7), 7.54 (dd, J = 8.7, 2.0 Hz, 1 H, H-6); ^{13}C NMR δ 142.48 (d), 135.70 (s), 134.18 (s), 133.94 (s), 133.48 (d), 133.16 (d), 133.12 (s), 130.86 (d), 127.52 (d), 116.70 (d), 116.42 (d). EIMS $[M]^+$ $C_{13}H_{11}N_2S$ requires 226.0565. Found 226.0567.

5-(Methylthio)-1-phenylbenzimidazole Hydrochloride (24). A solution of **23** (0.14 g, 0.61 mmol) in 1:1 THF/DMF (5 mL) was added dropwise under nitrogen to a stirred suspension of NaH (35 mg of a 50% dispersion in oil, 0.73 mmol). After 5 min methyl iodide (42 μL, 0.67 mmol) was added, and the solution was stirred at 20 °C for 3 h, then poured into 1 N NaOH, and extracted with ether. The extract was chromatographed on silica, eluting with EtOAc/petroleum ether (1:1) to give **24** as an oil (0.09 g, 61%). HCl salt: mp (MeOH/Et_2O) 192−195 °C; ^{1}H NMR (D_2O) δ 9.45 (s, 1 H, H-2), 7.76−7.72 (m, 3 H, Ph), 7.67−7.63 (m, 3 H, Ph and H-4), 7.57 (d, J = 8.9 Hz, 1 H, H-7), 7.43 (dd, J = 8.9, 1.6 Hz, 1 H, H-6), 2.59 (s, 3 H, SCH_3); ^{13}C NMR δ 142.09 (d), 141.36 (s), 135.63 (s), 134.18 (s), 133.41 (d), 133.17 (d), 131.55 (s), 128.46 (d), 127.16 (d), 115.91 (d), 113.36 (d), 17.57 (q). Anal. ($C_{14}H_{12}N_2S$·HCl) C, H, N.

5-[(3-(4-Morpholino)propyl)thio]-1-phenylbenzimidazole Dihydrochloride (25). A mixture of **23** (0.16 g, 0.71 mmol), $CsCO_3$ (0.28 g, 0.85 mmol), and 3-bromopropanol (70 μL, 0.78 mmol) in acetone (30 mL) was refluxed for 3 h before concentration to dryness. The residue was partitioned between 2 N NaOH and ether, and the organic portion was worked up to give an oil which was chromatographed on silica. Elution with EtOAc gave 5-[(3-hydroxypropyl)thio]-1-phenylbenzimidazole (0.16 g, 80%) as an oil, which was used directly. A solution of this alcohol (0.13 g, 0.46 mmol) and Et_3N (76 μL, 0.55 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and treated with methanesulfonyl chloride (40 μL, 0.50 mmol). After 10 min the solution was washed with aqueous $NaHCO_3$ and worked up to give the corresponding mesylate as an oil. This material was dissolved in morpholine (5 mL) and warmed at 70 °C for 30 min. The excess of morpholine was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic portion was extracted into 2 N HCl, and this extract was then neutralized with 2 N NH_3, before re-extraction with EtOAc. Workup gave an oil which was chromatographed on silica. EtOAc eluted foreruns while MeOH/EtOAc (1:9) eluted **25** as a viscous oil (0.10 g, 62%). Dihydrochloride salt: mp 213−216 °C (hygroscopic solid from MeOH/ether); ^{1}H NMR δ (D_2O) 9.47 (s, 1H, H-2), 7.98 (br s, 1H, H-4), 7.77−7.72 (m, 6H, Ph and H-7), 7.69 (dd, J = 8.9, 1.3 Hz, 1H, H-6), 4.14 (br d, J = 13.1 Hz, 2H, CH_2O), 3.83 (t, J = 11.6 Hz, 2H, CH_2N), 3.54 (br d, J = 13.1 Hz, 2H, CH_2O), 3.39 (t, J = 9.6 Hz, 2H, CH_2S), 3.25−3.18 (m, 4H, CH_2N), 2.17−2.09 (m, 2H, CH_2); ^{13}C NMR δ 143.13 (d), 137.11 (s), 135.79 (s), 134.50 (s), 133.44 (d), 133.17 (d), 131.49 (d), 127.52 (d), 118.25 (d), 116.52 (d), 66.48 (t), 58.48 (t), 54.46 (t), 30.01 (t), 25.18 (t). Anal. ($C_{20}H_{23}N_3SO$·2HCl·1.5H_2O) C, H, N.

4,5-Dihydroxy-1-phenylbenzimidazole Hydrochloride (27). A mixture of the free base of **30** (60 mg, 0.23 mmol; for preparation see below) and lithium methanethiolate (0.20 g, 3.77 mmol) in dry DMF (10 mL) was warmed at 120 °C under an atmosphere of nitrogen for 4 h. The cooled solution was carefully neutralized with concentrated HCl, then poured into brine, and extracted into EtOAc. The extract was worked up and chromatographed on silica gel. EtOAc gave foreruns while MeOH/EtOAc (1:19) eluted **27** (46 mg, 88%): mp (hydrochloride salt from MeOH/Et_2O) 241−244 °C; ^{1}H NMR (D_2O) δ 9.27 (s, 1 H, H-2), 7.72−7.59 (m, 5 H, Ph), 7.18 (d, J = 9.0 Hz, 1 H, H-7), 7.11 (d, J = 9.0 Hz, 1 H, H-6). ^{13}C NMR δ 144.99 (s), 141.76 (d), 136.08 (s), 134.41 (s), 133.16 (d), 133.07 (d), 129.60 (s), 127.28 (d), 125.89 (s), 120.01 (d), 106.96 (d). Anal. ($C_{13}H_{10}N_2O_2$·HCl) C, H, N.

4-Hydroxy-5-methoxy-1-phenylbenzimidazole (28) and 5-Hydroxy-4-methoxy-1-phenylbenzimidazole (29). Boron tribromide (1.12 mL of a 1 N solution in CH_2Cl_2, 1.12 mmol) was added under nitrogen at 5 °C to a solution of **30** (0.24 g, 1.12 mmol) in CH_2Cl_2 (20 mL). After 1 h at this temperature, followed by 2 h at room temperature, 2 N NaOH (10 mL) was added and the mixture was stirred for 1 h. The aqueous layer was carefully neutralized with 2 N HCl and extracted with EtOAc, and the extract was worked up and chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) gave **29** (26 mg, 12%): mp (hydrochloride salt from MeOH/Et_2O) 220−222 °C; ^{1}H NMR (free base in $CDCl_3$) δ 8.00 (s, 1 H, H-2), 7.58−7.43 (m, 5 H, Ph), 7.08 (d, J = 8.7 Hz, 1 H, H-7), 6.99 (d, J = 8.7 Hz, 1 H, H-6), 5.66 (br, 1 H, OH), 4.44 (s, 3 H, OCH_3); ^{13}C NMR δ 142.54 (s), 141.45 (d), 136.77 (s), 136.57 (s), 136.29 (s), 135.51 (s), 130.02 (d), 128.03 (d), 124.03 (d), 112.43 (d), 103.99 (d), 61.10 (OCH_3). Anal. ($C_{14}H_{12}N_2O_2$·HCl) C, H; N: found 9.5, calculated 10.1%. Elution with EtOAc gave **28** (0.11 g, 50%): mp (EtOAc/petroleum ether) 196−197 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1 H, H-2), 7.60−7.45 (m, 5 H, Ph), 7.06 (d, J = 8.7 Hz, 1 H, H-7), 6.99 (d, J = 8.7 Hz, 1 H, H-6), 3.98 (s, 3 H, OCH_3), 1.27 (br, 1 H, OH). Anal. ($C_{14}H_{12}N_2O_2$) C, H, N.

4,5-Dimethoxy-1-phenylbenzimidazole Hydrochloride (30). A solution of 3,4-dimethoxy-2-nitrobenzoic acid[19] (**46**) (6.26 g, 0.027 mol), $SOCl_2$ (10.0 mL), and DMF (1 drop) in 1,2-dichloroethane (100 mL) was heated under reflux for 2 h and then concentrated to dryness under reduced pressure. The resulting crude acid chloride was dissolved in acetone (50 mL), cooled to 5 °C, and treated in one portion with a solution of excess sodium azide (10.0 g) in water (20 mL). After vigorous stirring for 10 min, the mixture was poured into water (300 mL) and the resultant precipitate of acyl azide was filtered off and washed well with water. The crude solid was slurried in acetic acid (300 mL) and water (30 mL) and heated slowly to reflux. After refluxing for 2 h the solvents were removed under reduced pressure and the residue was slurried in hot EtOH and filtered. The filtrate was concentrated to dryness and the residue was triturated with EtOAc and worked up to give 3,4-dimethoxy-2-nitroaniline (**47**) (12.96 g, 55%): mp (aqueous EtOH) 65−67 °C; ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 9.1 Hz, 1 H, H-5), 6.49 (d, J = 9.1 Hz, 1 H, H-6), 4.44 (br, 2 H, NH_2) 3.96, 3.82 (2 s, 6 H, OCH_3); ^{13}C NMR δ 145.03 (s), 144.00 (s), 139.45 (s), 135.73 (s), 119.15 (d), 111.75 (d), 61.94 (OCH_3), 57.33 (OCH_3). Anal. ($C_8H_{10}N_2O_4$) C, H, N.

A mixture of **47** (1.40 g, 7.06 mmol), K_2CO_3 (1.50 g, 0.011 mol), CuI (0.10 g), and bromobenzene (15 mL) was heated under reflux with vigorous stirring for 8 h. After removal of excess bromobenzene under reduced pressure the residue was partitioned between EtOAc and water, and the organic portion was worked up to give an oil which was chromatographed on silica gel. Petroleum ether eluted a little bromobenzene while EtOAc/petroleum ether (1:9) gave 3,4-dimethoxy-2-nitrodiphenylamine (**48**) (0.46 g, 24%): mp (EtOAc/petroleum ether) 68−69 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2 H, Ar), 7.06−6.95 (m, 5 H, Ar), 6.68 (br s, 1 H, NH), 4.00, 3.87 (2 s, 6 H, OCH_3); ^{13}C NMR δ 146.99 (s), 143.30 (s), 141.61 (s), 137.40 (s), 131.47 (s), 129.48 (d), 122.36 (d), 119.19 (d), 117.12 (d), 113.70 (d), 62.09 (OCH_3), 56.92 (OCH_3). Anal. ($C_{14}H_{14}N_2O_4$) C, H, N. Elution with EtOAc/petroleum ether (1:1) gave starting material (0.59 g).

A solution of the dimethoxydiphenylamine **(48)** (3.3 g, 0.012 mol) in 1:1 EtOAc/MeOH (60 mL) was hydrogenated at 60 psi over 5% Pd−C (300 mg) for 4 h. After removal of the catalyst the solution was concentrated to dryness to give the corresponding crude diamine, which was used directly. A solution of this material and formamidine acetate (3.43 g, 0.032 mol) in 2-methoxyethanol (60 mL) was refluxed for 4 h and then concentrated to dryness. The residue was partitioned between EtOAc and water, and the organic portion was worked up to give an oil which was chromatographed on silica. Elution with EtOAc/petroleum ether (1:1) gave **30** (2.20 g,76%): mp (hydrochloride salt from MeOH/Et_2O) 180−183 °C (dec); ^{1}H NMR (D_2O) δ 9.37 (s, 1 H, H-2), 7.72 (m, 3 H, Ph), 7.64 (m, 2 H, Ph), 7.41 (d, J = 9.1 Hz, 1 H, H-7), 7.37 (d, J = 9.1 Hz, 1 H, H-6), 4.08, 4.00 (2s, 6 H, OCH_3); ^{13}C NMR δ 152.62 (s), 142.77 (d), 137.88 (s), 135.85 (s), 133.26 (d), 133.13 (d), 129.82 (s), 128.86 (s), 127.09 (d), 117.20 (d), 111.09 (d), 64.50 (OCH_3), 59.94 (OCH_3). Anal. ($C_{15}H_{14}N_2O_2$·HCl·0.5H_2O) C, H, N.

4-Bromo-5-hydroxy-1-phenylbenzimidazole Hydrochloride (31). A solution of *N*-bromosuccinimide (0.72 g, 4.04 mmol) in DMF (5 mL) was added dropwise at room temperature to a solution of **5** (0.85 g, 4.04 mmol) in DMF (30 mL). After 1 h the solution was diluted with aqueous NaCl and extracted into EtOAc, and the extract was worked up to give a solid which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) gave foreruns, while EtOAc eluted **31** (0.88 g, 75%): mp (hydrochloride salt from MeOH/Et_2O) 244−246 °C; ^{1}H NMR δ (free base in $CDCl_3$) 8.12 (s, 1 H, H-2), 7.60−7.56 (m, 2 H, Ph), 7.50−7.46 (m, 3 H, Ph), 7.36 (d, J = Hz, 1 H, H-7), 7.08 (d, J = 8.8 Hz, 1 H, H-6), 5.85 (br, 1 H, OH); ^{13}C NMR δ 149.30 (s), 142.88 (d), 135.91 (s), 130.14 (d), 128.44 (s), 128.41 (d), 124.11 (s), 124.03 (d), 113.18 (d), 110.33 (d), 99.66 (s). Anal. ($C_{13}H_{19}BrN_2O$·HCl) C, H, N.

4-Bromo-5-allyloxy-1-phenylbenzimidazole (32). A solution of **31** (0.92 g, 3.18 mmol) in DMF (4 mL) was added under nitrogen to a stirred suspension of NaH (0.15 g of a 60% dispersion in oil, 3.81 mmol). After 5 min, allyl bromide (0.30 mL, 3.50 mmol) was added, and the solution was stirred at room temperature for 1 h and at 50 °C for 30 min. After dilution with brine the mixture was extracted with diethyl ether. The ether portion was washed with 2 N NaOH and worked up to give **32** (1.03 g, 99%): mp (EtOAc/petroleum ether) 95−96 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1 H, H-2), 7.60−7.56 (m, 2 H, Ph), 7.50−7.46 (m, 3 H, Ph), 7.38 (d, J = 8.8 Hz, 1 H, H-7), 7.02 (d, J = 8.8 Hz, 1 H, H-6), 6.16−6.09 (m, 1 H, =CH), 5.16−5.47 (m, 1 H, =C*H*H), 5.32−5.29 (m, 1 H, =CH*H*), 4.69−4.67 (m, 2 H, OCH_2); ^{13}C NMR δ 151.86 (s), 143.94 (s), 143.23 (d), 135.99 (s), 133.16 (d), 130.13 (d), 129.35 (s), 128.34 (d), 124.00 (d), 117.81 (t), 112.91 (d), 109.39 (d), 103.77 (s), 71.82 (t). Anal. ($C_{16}H_{13}BrN_2O$) C, H, N.

4-Allyl-5-hydroxy-1-phenylbenzimidazole (33). A solution of **11** (0.10 g, 0.40 mmol) in 2-propanol (50 mL) was heated in a pressure vessel at 190 °C for 24 h. The solvent was removed under reduced pressure to give **33** as the sole product (0.10 g, 100%): mp (EtOAc/petroleum ether) 210 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.06 (s, 1 H, OH), 8.38 (s, 1 H, H-2), 7.66−7.59 (m, 4 H, Ph), 7.48−7.44 (m, 1 H, Ph), 7.29 (d, J = 8.7 Hz, 1 H, H-7), 6.89 (d, J = 8.7 Hz, 1 H, H-6), 6.10−6.03 (m, 1 H, C*H*=CH_2), 5.04 (dd, J = 17.3, 2.3 Hz, 1 H, CH=C*H*H), 4.93 (dd, J = 9.9, 2.0 Hz, 1 H, CH=CH*H*), 3.70 (d, J = 6.4 Hz, 2 H, CH_2-CH=CH_2); ^{13}C NMR δ 150.28 (s), 144.01 (s), 142.44 (d), 136.73 (d), 136.28 (s), 129.95 (d), 127.22 (d), 126.49 (s), 123.06 (d), 115.62 (s), 114.50 (t), 112.82 (d), 108.05 (d), 28.86 (t). Anal. ($C_{16}H_{14}N_2O$) C, H, N.

4,5-Dihydro-5-methyl-1-phenylfuro[3,2-*e*]benzimidazole Hydrochloride (34). A solution of the phenol **33** (0.20 g, 0.80 mmol) in glacial acetic acid (50 mL) and concentrated HBr (10 mL) was refluxed for 3 h and then concentrated to dryness under reduced pressure. The residue was partitioned between diethyl ether and 2 N NaOH, and the organic solution was worked up to give an oil which was chromatographed on silica gel. EtOAc/petroleum ether (1:1) eluted the cyclic ether **34** (0.15 g, 75%). HCl salt: mp (MeOH/Et_2O) 218−220 °C; ^{1}H NMR (D_2O) δ 9.38 (s, 1 H, H-2), 7.74−7.71 (m, 3 H, Ph), 7.65−7.62 (m, 2 H, Ph), 7.74 (d, J = 8.9 Hz, 1 H, H-7), 7.04 (d, J = 8.9 Hz, 1 H, H-6), 5.29−5.21 (m, 1 H, CHO), 3.67 (dd, J = 16.0, 9.1 Hz, 1 H, C*H*H), 3.17 (dd, J = 16.0, 7.5 Hz, 1 H, CH*H*), 1.56 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR δ 161.18 (s), 142.08 (d), 135.93 (s), 133.34 (d), 133.12 (d), 131.14 (s), 129.23 (s), 127.28 (d), 127.13 (s), 115.24 (d), 112.72 (d), 85.07 (d), 36.79 (t), 23.44 (q). Anal. ($C_{16}H_{14}N_2O$·HCl) C, H, N.

5,6-Dimethoxy-1-phenylbenzimidazole Hydrochloride (35). A mixture of 1-bromo-4,5-dimethoxy-2-nitrobenzene[20] (**49**) (1.00 g, 4.34 mmol), K_2CO_3 (1.20 g, 8.70 mmol), CuI (100 mg), and aniline (5 mL) was heated under reflux under nitrogen for 5 h. After diluting with excess 3 N HCl, the mixture was extracted with EtOAc and worked up to give an oil. Chromatography of this on silica gel, eluting with EtOAc/petroleum ether (1:5), gave 4,5-dimethoxy-2-nitrodiphenylamine (**50**) (0.63 g, 60%): mp (MeOH) 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 9.87 (br, 1 H, NH), 7.64 (s, 1 H, H-6), 7.45−7.42 (m. 2 H, Ph), 7.32−7.22 (m, 3 H, Ph), 6.63 (s, 1 H, H-3), 3.90, 3.78 (2s, 6 H, OCH_3). Anal. ($C_{14}H_{14}N_2O_4$·0.5H_2O) C, H, N. Hydrogenation of **50** over Pd/C, followed by treatment of the crude diamino compound with formamidine acetate as above, gave **35** (79%). HCl salt: mp (MeOH/Et_2O) 217−218.5 °C; ^{1}H NMR δ (D_2O) 9.26 (s, 1 H, H-2), 7.77−7.72 (m, 3 H, Ph), 7.69−7.64 (m, 2 H, Ph), 7.37 (s, 1 H, H-4), 7.07 (s, 1 H, H-7), 3.95−3.83 (2s, 6 H, OCH_3); ^{13}C NMR δ 152.13 (2s), 140.18 (d), 135.95 (s), 133.39 (d), 133.23 (d), 128.31 (s), 127.66 (s), 127.42 (d), 99.13 (d), 97.27 (d), 59.00 (q), 58.91 (q). Anal. ($C_{15}H_{14}N_2O_2$·HCl) H, N; C: calculated 62.0, found 61.4%.

5,6-Dihydroxy-1-phenylbenzimidazole Hydrochloride (36). A mixture of the free base of **35** (0.80 g, 3.15 mmol) and freshly prepared pyridine hydrochloride (20 g) was warmed to 220 °C under a stream of nitrogen. After 1 h at this temperature the cooled mixture was diluted with water, basified with 2 N NaOH, and washed well with Et_2O. The aqueous portion was neutralized with 3 N HCl, extracted with EtOAc, and worked up. Chromatography of the residue on silica gel and elution with EtOAc gave foreruns, while elution with MeOH/EtOAc (1:15) gave **36** (0.54 g, 76%). HCl salt: mp (MeOH/Et_2O) 239−242 °C; ^{1}H NMR (D_2O) δ 9.16 (s, 1 H, H-2), 7.73−7.68 (m, 3 H, Ph), 7.66−7.62 (m, 2 H, Ph), 7.27 (s, 1 H, H-4), 7.08 (s, 1 H, H-7); ^{13}C NMR δ 148.46 (s), 148.43 (s), 140.09 (d), 136.12 (s), 133.17 (d), 133.10 (d), 128.35 (s), 127.54 (s), 127.34 (d), 102.43 (d), 100.83 (d). Anal. ($C_{13}H_{10}N_2O_2$·HCl·1.5H_2O) C, H, N.

5,6-Methylenedioxy-1-phenylbenzimidazole Hydrochloride (37). A mixture of **36** (0.20 g, 0.88 mmol), 50% aqueous NaOH solution (8 mL), tetrabutylammonium bromide (40 mg, 0.12 mmol), and dibromomethane (8 mL) was heated under reflux for 3 h. After dilution with CH_2Cl_2 the organic portion was worked up to give an oil that was chromatographed on silica gel. EtOAc/petroleum ether (1:1) eluted **37** (0.16 g, 75%). HCl salt: mp (MeOH/Et_2O) 239−241 °C; ^{1}H NMR (D_2O) δ 9.21 (s, 1 H, H-2), 7.73−7.69 (m, 3 H, Ph), 7.67−7.63 (m, 2 H, Ph), 7.30 (s, 1 H, H-4), 7.14 (s, 1 H, H-7), 6.15 (s, 2 H, OCH_2O); ^{13}C NMR δ 151.12 (s), 151.03 (s), 140.30 (d), 135.97 (s), 133.35 (d), 133.12 (d), 129.61 (s), 128.69 (s), 127.55 (d), 105.63 (t), 96.94 (d), 95.53 (d). Anal. ($C_{14}H_{10}N_2O_2$·HCl·0.25H_2O) C, H, N.

5-Methoxy-6-methyl-1-phenylbenzimidazole Hydrochloride (38). A mixture of 4-methoxy-5-methyl-2-nitroaniline[21] (**51**) (1.00 g, 5.49 mmol), K_2CO_3 (0.50 g, 3.62 mmol), CuI (100 mg), and bromobenzene (5 mL) was heated under reflux under nitrogen with stirring for 4 d. The mixture was concentrated to dryness under reduced pressure, and the residue was partitioned between EtOAc and water and filtered through Celite. The organic layer was worked up to give an oil which was chromatographed on silica gel. Petroleum ether eluted foreruns, while EtOAc/petroleum ether (1:9) gave 4-methoxy-5-methyl-2-nitrodiphenylamine (**52**) (1.26 g, 88%): mp (MeOH at −20 °C) 94−96 °C; ^{1}H NMR ($CDCl_3$) δ 9.46 (br s, 1 H, NH), 7.55 (s, 1 H, H-3), 7.42−7.38 (m, 2 H, Ph), 7.26−7.24 (m, 2 H, Ph), 7.22−7.18 (m, 1 H, Ph), 6.98 (d, J = 0.7 Hz, 1 H, H-6), 3.84 (s, 3 H, OCH_3), 2.17 (s, 3 H, CH_3); ^{13}C NMR δ 149.95 (s), 139.34 (s), 138.78 (s), 138.04 (s), 129.65 (d), 124.99

(d), 123.71 (d), 117.70 (d), 104.92 (d), 55.77 (q), 17.05 (q). Anal. ($C_{14}H_{14}N_2O_3$) C, H, N. Hydrogenation of **52** followed by reaction with formamidine acetate as described above gave **38** (71%). HCl salt: mp (MeOH/Et_2O) 214−217 °C; ^{1}H NMR (D_2O) δ 9.26 (s, 1 H, H-2), 7.73−7.70 (m, 3 H, Ph), 7.63−7.60 (m, 2 H, Ph), 7.45 (s, 1 H, H-7), 7.31 (s, 1 H, H-4), 3.96 (s, 3 H, OCH_3), 2.27 (s, 3 H,CH_3); ^{13}C NMR δ 160.20 (s), 140.38 (d), 135.91 (s), 133.21 (d), 133.08 (d), 132.73 (s), 131.48 (s), 127.86 (s), 127.14 (d), 116.15 (d), 97.82 (d), 58.79 (q), 19.08 (q). Anal. ($C_{15}H_{14}N_2O$·HCl·0.25H_2O) C, H, N.

5-Hydroxy-6-methyl-1-phenylbenzimidazole Hydrochloride (39). A solution of **38** (0.25 g, 0.53 mmol) in 48% HBr in glacial acetic acid (15 mL) was refluxed for 48 h and concentrated to dryness. The residue was partitioned between 2 N NaOH and Et_2O, the aqueous portion was carefully neutralized with 2 N HCl and extracted with EtOAc, and the extract worked up to give a solid which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) gave **39** (0.19 g, 82%). HCl salt: mp (MeOH/Et_2O) 239−243 °C; ^{1}H NMR (D_2O) δ 9.24 (s, 1 H, H-2), 7.74−7.70 (m, 3 H, Ph), 7.66−7.63 (m, 2 H, Ph), 7.49 (s, 1 H, H-7), 7.23 (s, 1 H, H-4), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 156.80 (s), 140.69 (d), 136.01 (s), 133.25 (d), 133.08 (d), 132.55 (s), 130.31 (s), 128.23 (s), 127.38 (d), 116.65 (d), 101.36 (d), 18.99 (q). Anal. ($C_{14}H_{12}N_2O$·HCl) C, H, N.

5-Methoxy-1-phenylbenzimidazole-6-carboxylic Acid Hydrochloride (40). Powdered $KMnO_4$ (4.08 g, 0.026 mmol) was added in portions over 12 h to a refluxing solution of **38** (1.50 g, 6.29 mmol) in 1:1 *tert*-butyl alcohol/water (600 mL), by which time no starting material was present. The hot mixture was filtered through Celite, washing through with water. The filtrate was concentrated under reduced pressure to a volume of ca. 100 mL and washed with EtOAc. The aqueous portion was carefully neutralized with 3 N HCl and chilled to 5 °C for 4 h, and the precipitated acid **40** (1.08 g, 64%) was removed by filtration. HCl salt: mp (MeOH/Et_2O) 279−281 °C; ^{1}H NMR (D_2O) δ 9.45 (s, 1 H, H-2), 7.99 (s, 1 H, H-7), 7.71−7.69 (m, 3 H, Ph), 7.64−7.61 (m, 2 H, Ph), 7.51 (s, 1 H, H-4), 4.00 (s, 3 H, OCH_3); ^{13}C NMR δ 171.51 (s), 160.37 (s), 144.33 (d), 137.72 (s), 135.53 (s). 133.48 (d), 133.21 (d), 127.79 (s), 127.18 (d), 122.83 (s), 119.03 (d), 100.57 (d), 59.38 (q). Anal. ($C_{15}H_{12}N_2O_3$·HCl·0.25H_2O) C, H, N.

5-Hydroxy-1-phenylbenzimidazole-6-carboxylic Acid Hydrobromide (41). A solution of **40** (0.60 g, 2.24 mmol) in a 33% solution of HBr in glacial acetic acid (50 mL) was refluxed for 30 h. After cooling to room temperature, the precipitate of the hydrobromide salt of **41** was filtered off (0.51 g, 68%): mp 288−290 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 9.67 (s, 1 H, H-2), 8.03 (s, 1 H, H-7), 7.82−7.80 (m, 2 H, Ph), 7.76−7.71 (m, 2 H, Ph), 7.68−7.64 (m, 1 H, Ph), 7.39 (s, 1 H, H-4), 6.00 (br, 2 H, OH); ^{13}C NMR δ 171.15 (s), 158.44 (s), 145.11 (d), 139.64 (s), 133.79 (s), 130.29 (d), 129.74 (d), 125.16 (s), 124.70 (d), 114.14 (d), 112.27 (s), 102.43 (d). Anal. ($C_{14}H_{10}N_2O_3$·HBr) H, N; C: calculated 50.2, found 49.6%.

Methyl 5-Methoxy-1-phenylbenzimidazole-6-carboxylate Hydrochloride (42). A suspension of **40** (0.50 g, 1.86 mmol) and $SOCl_2$ (10 mL) in 1,2-dichloroethane (50 mL) containing DMF (1 drop) was refluxed for 2 h. The solution was concentrated to dryness under reduced pressure. The resulting crude acid chloride was dissolved in methanol (20 mL) and the solution refluxed for 15 min. The methanol was removed under reduced pressure and the residue partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic solution was worked up to give **42** (0.48 g, 91%). HCl salt: mp (MeOH/Et_2O) 203−205 °C; ^{1}H NMR (D_2O) δ 9.44 (s, 1 H, H-2), 7.95 (s, 1 H, H-7), 7.73−7.69 (m, 3 H, Ph), 7.62−7.59 (m, 2 H, Ph), 7.46 (s, 1 H, H-4), 3.96−3.86 (2s, 6 H, OCH_3); ^{13}C NMR δ 169.72 (s), 160.51 (s), 144.52 (d), 138.12 (s), 135.50 (s), 133.44 (d), 133.22 (d), 127.53 (s), 127.02 (d), 121.74 (s), 119.16 (d), 100.68 (d), 59.30 (q). Anal. ($C_{16}H_{14}N_2O_3$·HCl·0.5H_2O) C, H, N.

6-Hydroxymethyl-5-methoxy-1-phenylbenzimidazole Hydrochloride (43). Borane−methyl sulfide complex (1.11 mL of 10.0 N, 0.011 mmol) was added dropwise at room temperature under nitrogen to a stirred solution of **42** (1.00 g, 3.73 mmol) in THF (60 mL). After the solution was stirred at this temperature for 3 h, the excess reagent was destroyed by careful addition of MeOH, followed by water, and the solution was acidified with 3 N HCl and stirred at room temperature for a further 30 min. The aqueous solution was washed with EtOAc, then basified with concentrated NH_3 solution, and extracted with EtOAc, and the organic portion worked up to give an oily solid which was chromatographed on silica gel. EtOAc eluted foreruns, while MeOH/EtOAc (1:15) eluted **43** (0.77 g, 81%). HCl salt: mp (MeOH/Et_2O) 260 °C (dec); ^{1}H NMR (D_2O) δ 9.33 (s, 1 H, H-2), 7.75−7.67 (m, 5 H, Ph), 7.67 (s, 1 H, H-7), 7.42 (s, 1 H, H-4), 4.73 (s, 2 H, CH_2O), 3.99 (s, 3 H, OCH_3); ^{13}C NMR δ 159.85 (s), 141.41 (d), 135.94 (s), 134.25 (s), 133.31 (d), 133.14(d), 132.85 (s), 128.05 (s), 127.34 (d), 115.28 (d), 98.60 (d), 62.38 (t), 58.86 (q). Anal. ($C_{15}H_{14}N_2O_2$·HCl) C, H, N.

5-Methoxy-1-phenylbenzimidazole-6-carboxaldehyde Hydrochloride (44). Manganese dioxide (0.20 g, 2.30 mmol) was added in four portions over 8 h to a refluxing solution of the free base of the alcohol **43** (0.10 g, 0.39 mmol) in EtOAc (10 mL), and refluxing was continued for a further 10 h. The mixture was filtered through Celite and the filtrate percolated through a short column of silica to give **44** (0.98 g, 99%). HCl salt: mp (MeOH/Et_2O) 218−220 °C; ^{1}H NMR (D_2O) δ 10.34 (s, 1 H, CHO), 9.57 (s, 1 H, H-2), 8.16 (s, 1 H, H-7), 7.73 (br s, 5 H, Ph), 7.59 (s, 1 H, H-4), 4.08 (s, 3 H, OCH_3); ^{13}C NMR δ 194.97 (d), 163.61 (s), 144.83 (d), 138.88 (s), 135.52 (s), 133.67 (d), 133.23 (d), 128.63 (s), 127.55 (d), 127.12 (s), 117.98 (d), 100.42 (d), 59.40 (q). Anal. ($C_{15}H_{14}N_2O_2$·HCl·0.25H_2O) C, H, N.

Tyrosine Kinase and Autophosphorylation Assays. The methods for the production of the enzymes used in this study (PDGFR-β, FGFR-1, s-Src), the enzyme assay conditions, and the determination of inhibition of autophosphorylation in rat aortic vascular smooth muscle cells have been published previously.[13] The kinase assays were performed in a total volume of 100 mL containing 25 mM HEPES buffer (pH 7.4), 150 mM NaCl, 10 mM $MnCl_2$, 0.2 mM sodium orthovanadate, 750 mg/mL concentrations of a random copolymer of glutamic acid and tyrosine (4:1), 60−75 ng of enzyme, and various concentrations of inhibitor. The reaction was initiated by addition of [γ^{32}P]ATP (50 mM ATP containing 0.4 μCi of [γ^{32}P]-ATP per incubation). Samples were incubated for 10 min at 25 °C, then the reaction was terminated by the addition of 15% trichloroacetic acid, and the samples were analyzed as described previously.[13]

Molecular Modeling. The details of these methods have been described previously,[16,17] using the published[22] sequence for murine β-PDGFR.

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