# Structure−Activity Relationships for 1-Phenylbenzimidazoles as Selective ATP Site Inhibitors of the Platelet-Derived Growth Factor Receptor

Brian D. Palmer,[†] Jeff B. Smaill,[†] Maruta Boyd,[†] Diane H. Boschelli,[‡] Annette M. Doherty,[‡] James M. Hamby,[‡] Sonya S. Khatana,[‡] James B. Kramer,[‡] Alan J. Kraker,[‡] Robert L. Panek,[‡] Gina H. Lu,[‡] Tawny K. Dahring,[‡] R. Thomas Winters,[‡] H. D. Hollis Showalter,[‡] and William A. Denny*[,†]

*Auckland Cancer Society Research Centre, Faculty of Medicine and Health Sciences, The University of Auckland School of Medicine, Private Bag 92019, Auckland, New Zealand, Parke-Davis Pharmaceutical Research, Division of the Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48106-1047*

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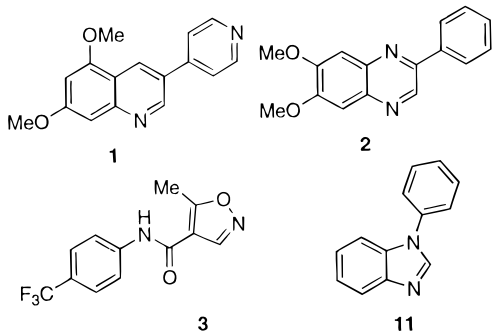
1-Phenylbenzimidazoles are shown to be a new class of ATP-site inhibitors of the platelet-derived growth factor receptor (PDGFR). Structure−activity relationships (SARs) are narrow, with closely related heterocycles being inactive. A systematic study of substituted 1-phenylbenzimidazoles showed clear SARs. Substituents at the 4′- and 3′-positions of the phenyl ring are tolerated but do not significantly improve activity, while substituents at the 2′-position abolish it. Substituents in the 2-, 4-, and 7-positions of the benzimidazole ring (with the exception of 4-OH) also abolish activity. Most substituents at the 5- and 6-positions maintain or increase activity, with the 5-OH, 5-OMe, 5-COMe, and 5-$CO_2$Me analogues being >10-fold more potent than the parent 1-phenylbenzimidazole. The 5-OMe analogue was both the most potent inhibitor, and showed the highest selectivity (50-fold) between PDGFR and FGFR isolated enzymes, and also a moderately effective inhibitor ($IC_{50}$ = 1.9 $\mu$M) of PDGF-stimulated PDGFR autophosphorylation in rat aorta smooth muscle cells.

The platelet-derived growth factor (PDGF) plays a vital role as a regulator of cell growth.[1,2] Binding of PDGF to its transmembrane receptor (PDGFR) results in tyrosine phosphorylation of natural substrates that act by a number of pathways, including through phosphatidylinositol 3-kinase.[3] While there is major interest in PDGFR inhibitors as drugs to prevent restenosis following vascular interventions,[4,5] such compounds are also potentially valuable as anticancer agents. Expression of genes encoding PDGF is involved in the development of tumor angiogenesis.[6] Many tumors, particularly gliomas and sarcomas, undergo autocrine PDGFR activation[7,8] that can be inhibited by PDGF antisera.[9] A number of different classes of compounds have recently been reported as reasonably selective inhibitors of the activity of the PDGFR.[10] One class is the 3-arylquinolines,[11,12] of which one member (**1**) had an $IC_{50}$ of 80




nM for inhibition of autophosphorylation of PDGFR derived from vascular smooth muscle cells, acting by inhibition of ATP binding. The quinoxaline (**2**) showed an $IC_{50}$ of 300 nM for inhibition of autophosphorylation of PDGFR in a 3T3 cell line.[13] The isoxazole carboxamide (**3**; leflunomide; SU101) has also been reported[14] to inhibit PDGF-mediated signaling and to be in clinical trial for the treatment of glioma.[15]

We now report a new class of selective PDGFR inhibitors, the 1-phenylbenzimidazoles (parent compound **11**), and discuss structure−activity relationships and some mechanism of action studies with this class of compounds.

## Chemistry

The compounds (**4**−**11**) listed in Table 1 have all been reported previously and were prepared by known methods.[16−22] 1-Phenylbenzimidazoles are also a well-known class of compounds, and a number of 5-, 6-, 7-, and phenyl-substituted analogues have been reported.[23−26] The most widely used synthetic route to 1-phenylbenzimidazoles is the base-catalyzed condensation of 2-nitrohalobenzenes with anilines to give substituted 2-nitrodiphenylamines, followed by reduction to 2-aminodiphenylamines and cyclization of these using formic acid, formamidine acetate, or trialkyl orthoformates (Scheme 1). Many of the compounds of Table 2 were prepared by this method, including the known derivatives (**16**, **21**, **51**−**53**, **64**, **70**, **71**, and **77**), and transformation of these using standard methods gave many of the other required compounds. Analogues substituted in the 4-position, which have not been reported previously, were prepared by a variation of the above route (Scheme 2). Copper-catalyzed (Ullmann) condensation of bromobenzene with 3-methyl- and 3-methoxy-2-nitroanilines gave the corresponding 3-substituted 2-nitrodiphenylamines, and these were reduced

[†] The University of Auckland School of Medicine.
[‡] Parke-Davis Pharmaceutical Research.

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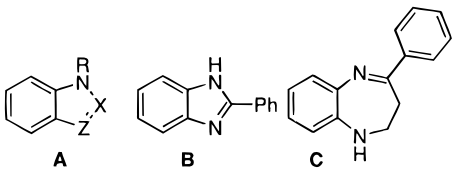
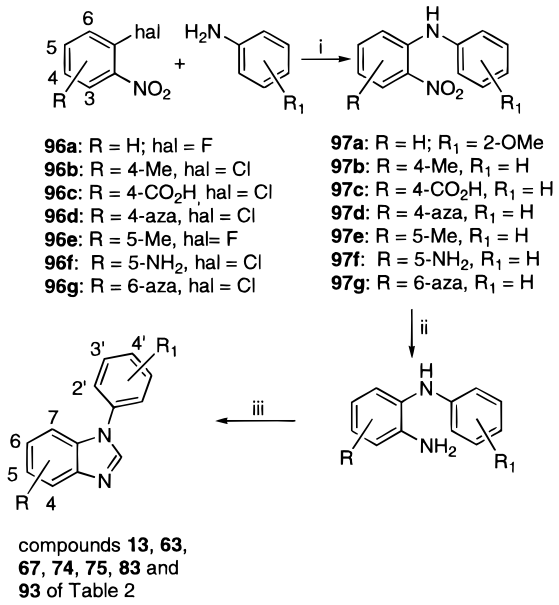
**Table 1.** Inhibition of PDGFR and FGFR by 1-Phenylbenzimidazole and Analogues




| no. | type | R | X | Z | ref | PDGFR[a] $IC_{50}$ | FGFR[b] $IC_{50}$ |
|---|---|---|---|---|---|---|---|
| **4** | A | $CH_2Ph$ | CH | N | 16 | >50 | >50 |
| **5** | A | COPh | CH | N | 17 | >50 | >50 |
| **6** | B | | | | *c* | >50 | >50 |
| **7** | C | | | | 18 | >50 | >50 |
| **8** | A | Ph | CH | CH | 19 | >50 | >50 |
| **9** | A | Ph | N | CH | 20 | >50 | >50 |
| **10** | A | Ph | N | N | 21 | >50 | >50 |
| **11** | A | Ph | CH | N | 22 | 9.3 | >50 |

[a,b] $IC_{50}$: concentration of drug ($\mu$M) to inhibit the phosphorylation of a random glutamate/tyrosine (4:1) copolymer by lysates of transfected SF9 insect cells overexpressing PDGFR or FGFR proteins. See Experimental Section for details. [c] Obtained from Aldrich Chemical Co.

**Scheme 1**[a]



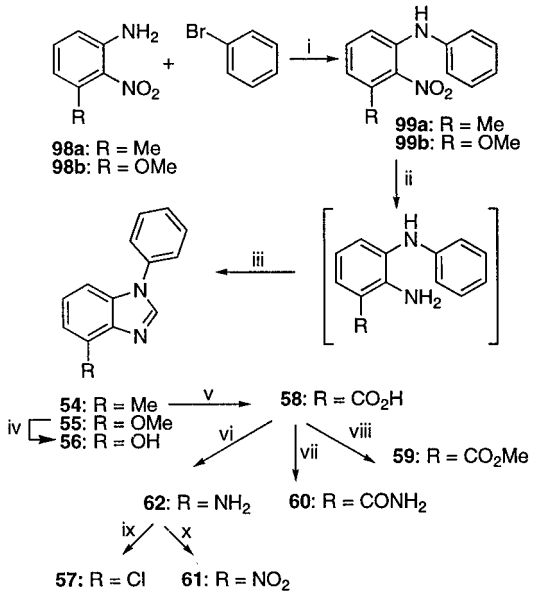

[a] (i) Base/various conditions (see text); (ii) $H_2$/Pd−C/MeOH; (iii) formamidine acetate/2-methoxyethanol/reflux/3 h.

and cyclized as in Scheme 1 to give the 4-methyl- and 4-methoxy-1-phenylbenzimidazoles (**54** and **55**), respectively. Transformation of these using standard methods then gave the other 4-substituted analogues (**56**−**62**). 1-Phenylbenzimidazoles have also been prepared by the direct base-catalyzed arylation of benzimidazole with halobenzenes,[24] and a number of known and new analogues were prepared by this method (Scheme 3). Finally, the 1-thienylbenzimidazoles (**94** and **95**) were synthesized by copper-catalyzed condensation of 2-nitro-4-methoxyaniline and bromothiophenes, followed by reduction and cyclization of the resulting 4-methoxy-2-nitro-*N*-(thienyl)anilines (Scheme 4).

## Results and Discussion

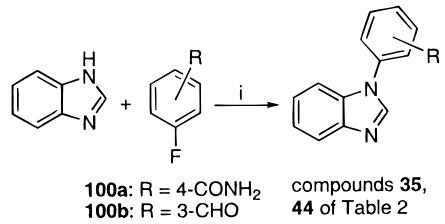
The activity of the parent 1-phenylbenzimidazole (**11**) (Table 1) was discovered on screening of a compound library for their ability to inhibit the phosphorylation

**Scheme 2**[a]



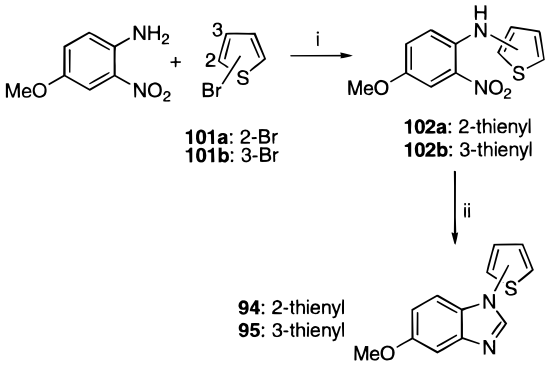

[a] (i) CuI/$K_2CO_3$/DMF/125 °C/18 h; (ii) Pd−C/$H_2$/MeOH; (iii) formamidine acetate/MeO$(CH_2)_2$OH/reflux/3 h; (iv) HBr/AcOH/reflux/4 h; (v) $KMnO_4$/*t*-BuOH−$H_2O$/reflux/48 h; (vi) $SOCl_2$, then $NaN_3$, then AcOH−$H_2O$/reflux/5 h; (vii) $SOCl_2$, then $NH_4OH$; (viii) $SOCl_2$, then MeOH; (ix) $NaNO_2$, then CuCl; (x) $NaNO_2$/HCl/$CuSO_4$/20 °C/48 h.

**Scheme 3**[a]




[a] (i) KH or $K_2CO_3$/DMF or DMSO.

**Scheme 4**[a]

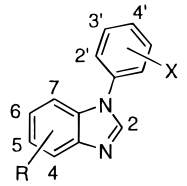



[a] (i) CuI/$K_2CO_3$/excess bromothiophene/reflux/18 h; (ii) Pd−C/$H_2$, then formamidine acetate.

of a model glutamate−tyrosine copolymer substrate by isolated human FGF-1 receptor and mouse PDGF-$\beta$ receptor tyrosine kinase enzymes. The FGFR and PDGFR proteins were fragments encoding the intracellular tyrosine kinase domains.[27,28] $IC_{50}$ 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.

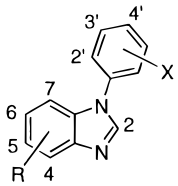
A small series of analogues (**4**−**11**) were then prepared to determine the scope of structure−activity

**Table 2.** Physicochemical and Biological Properties of Substituted 1-Phenylbenzimidazoles Evaluated as Inhibitors of Autophosphorylation of PDGF and $\beta$-FGF Receptors




| no. | R | X | mp | formula | analyses | PDGFR[a] $IC_{50}$ ($\mu$M) | FGFR[b] $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| **12** | H | 2′-Me | 190−193[d] | $C_{14}H_{12}N_2 \cdot HCl$ | C, H, N | >50 | >50 |
| **13** | H | 2′-OMe | 203−204 | $C_{14}H_{12}N_2O \cdot HCl$ | C, H, N | >50 | >50 |
| **14** | H | 2′-OH | 174−175.5 | $C_{13}H_{10}N_2O \cdot HCl \cdot 0.25H_2O$ | C, H, N | >50 | >50 |
| **15** | H | 2′-Cl | 190−192 | $C_{13}H_9ClN_2 \cdot HCl$ | C, H, N | >50 | >50 |
| **16** | H | 2′-COOH | ref 23 | | | >50 | >50 |
| **17** | H | 2′-COOEt | oil | $C_{16}H_{14}N_2O_2 \cdot 0.25H_2O$ | C, H, N | >50 | >50 |
| **18** | H | 2′-$CONH_2$ | 198−200.5 | $C_{14}H_{11}N_3$ | C, H, N | >50 | >50 |
| **19** | H | 2′-$NO_2$ | oil | $C_{13}H_9N_3O_2 \cdot 0.5H_2O$ | C, H, N | >50 | >50 |
| **20** | H | 2′-$NH_2$ | 112.5−113 | $C_{13}H_{11}N_3$ | C, H, N | >50 | >50 |
| **21** | H | 2′-COMe | 197−199[c] | $C_{15}H_{12}N_2O \cdot HCl$ | C, H, N | >50 | >50 |
| **22** | H | 2′-CHO | 63−71 | $C_{14}H_{10}N_2O$ | C, H, N | >50 | >50 |
| **23** | H | 2′-CN | 106−107.5 | $C_{14}H_9N_3$ | C, H, N | >50 | >50 |
| **24** | H | 2′-aza | broad | $C_{12}H_9N_3 \cdot HCl$ | C, H, N | >50 | >50 |
| **25** | H | 3′-Me | oil | $C_{14}H_{12}N_2 \cdot 0.25H_2O$ | C, H, N | 28 | >50 |
| **26** | H | 3′-OMe | 199.5 | $C_{14}H_{12}N_2O \cdot HCl$ | C, H, N | 25 | 50 |
| **27** | H | 3′-OH | 119 (dec) | $C_{13}H_{10}N_2O \cdot HCl \cdot 0.25H_2O$ | C, H, N | 3.8 | 50 |
| **28** | H | 3′-Cl | 201−204 | $C_{13}H_{11}ClN_2 \cdot HCl$ | C, H, N | 47 | 50 |
| **29** | H | 3′-COOH | 238−243 | $C_{14}H_{10}N_2O_2 \cdot HCl \cdot 0.25H_2O$ | C, H, N | >50 | >50 |
| **30** | H | 3′-COOEt | oil | $C_{16}H_{14}N_2O_2 \cdot 0.4H_2O$ | C, H, N | >50 | >50 |
| **31** | H | 3′-$CONH_2$ | 184−186 | $C_{14}H_{11}N_3O \cdot 0.125H_2O$ | C, H, N | >50 | >50 |
| **32** | H | 3′-$NO_2$ | 146−147 | $C_{13}H_9N_3O_2$ | C, H, N | 16 | 35 |
| **33** | H | 3′-$NH_2$ | 93−95 | $C_{13}H_{11}N_3$ | C, H, N | 3.6 | >50 |
| **34** | H | 3′-COMe | 198−200 | $C_{15}H_{12}N_2O \cdot HCl \cdot 0.25H_2O$ | C, H, N | 19 | >50 |
| **35** | H | 3′-CHO | 196−201 | $C_{14}H_{10}N_2O \cdot HCl \cdot 0.5H_2O$ | C, H, N | 6.8 | 50 |
| **36** | H | 3′-CN | 98−105 | $C_{14}H_9N_3$ | C, H, N | >50 | >50 |
| **37** | H | 3′-aza | 215 | $C_{12}H_9N_3 \cdot 2HCl \cdot 0.25H_2O$ | C, H, N | >50 | >50 |
| **38** | H | 4′-Me | 50−54 | $C_{14}H_{12}N_2$ | C, H, N | >50 | >50 |
| **39** | H | 4′-OMe | 214−215 | $C_{14}H_{12}N_2O \cdot HCl$ | C, H, N | 13 | >50 |
| **40** | H | 4′-OH | 255 | $C_{13}H_{10}N_2O \cdot HCl$ | C, H, N | 1.8 | 5.8 |
| **41** | H | 4′-Cl | 220−225 | $C_{13}H_9ClN_2 \cdot HCl$ | C, H, N | 50 | >50 |
| **42** | H | 4′-COOH | 234−236 | $C_{14}H_{10}N_2O_2$ | C, H, N | >50 | >50 |
| **43** | H | 4′-COOMe | 105−107 | $C_{15}H_{12}N_2O_2$ | C, H, N | 7.2 | 50 |
| **44** | H | 4′-$CONH_2$ | 208−210.5 | $C_{14}H_{11}N_3O$ | C, H, N | 23 | >50 |
| **45** | H | 4′-$NO_2$ | 181−182 | $C_{13}H_1N_3O_2$ | C, H, N | 30 | >50 |
| **46** | H | 4′-$NH_2$ | gum | $C_{13}H_{11}N_3 \cdot 2HCl \cdot 0.25H_2O$ | C, H, N | 5.6 | >50 |
| **47** | H | 4′-COMe | 133−135 | $C_{15}H_{12}N_2O$ | C, H, N | 24 | >50 |
| **48** | H | 4′-CHO | 98−99 | $C_{14}H_{10}N_2O$ | C, H, N | 13 | >50 |
| **49** | H | 4′-CN | 130−131 | $C_{14}H_9N_3 \cdot 0.5H_2O$ | C, H, N | 16 | >50 |
| **50** | H | 4′-aza | 238 | $C_{12}H_9N_3 \cdot 2HCl$ | C, H, N | 12 | >50 |
| **51** | 2-Me | H | ref 29 | | | >50 | >50 |
| **52** | 2-OH | H | ref 30 | | | >50 | >50 |
| **53** | 2-$NH_2$ | H | ref 31 | | | >50 | >50 |
| **54** | 4-Me | H | 206−208 | $C_{14}H_{12}N_2 \cdot HCl$ | C, H, N | >50 | >50 |
| **55** | 4-OMe | H | 191−193 | $C_{14}H_{12}N_2O \cdot HCl$ | C, H, N | 50 | >50 |
| **56** | 4-OH | H | 238−240 | $C_{13}H_{10}N_2O \cdot 0.25H_2O$ | C, H, N | 11 | >50 |
| **57** | 4-Cl | H | 117−118 | $C_{13}H_9ClN_2$ | C, H, N | >50 | >50 |
| **58** | 4-COOH | H | 245−248 | $C_{14}H_{10}N_2O_2 \cdot HCl$ | C, H, N | >50 | >50 |
| **59** | 4-COOMe | H | 187−189 | $C_{15}H_{12}N_2O_2 \cdot HCl \cdot 1.5H_2O$ | C, H, N | >50 | >50 |
| **60** | 4-$CONH_2$ | H | 242−244 | $C_{14}H_{11}N_3O \cdot HCl$ | C, H, N | >50 | >50 |
| **61** | 4-$NO_2$ | H | 204−206 | $C_{13}H_9N_3O_2$ | C, H, N | >50 | >50 |
| **62** | 4-$NH_2$ | H | 246−250 | $C_{13}H_{11}N_3 \cdot HCl \cdot 0.25H_2O$ | C, H, N | >50 | >50 |
| **63** | 5-Me | H | 196−200 | $C_{14}H_{12}N_2 \cdot HCl$ | C, H, N | 4.4 | 50 |
| **64** | 5-OMe | H | ref 33 | | | 0.43 | 22 |
| **65** | 5-OH | H | 247−249 | $C_{13}H_{10}N_2O$ | C, H, N | 0.44 | 6.4 |
| **66** | 5-Cl | H | 115−116 | $C_{13}H_9ClN_2$ | C, H, N | 4.0 | 51 |
| **67** | 5-COOH | H | 240 | $C_{14}H_{10}N_2O_2 \cdot HCl \cdot 1.5H_2O$ | C, H, N | 9.3 | 28 |
| **68** | 5-COOMe | H | 100−102 | $C_{15}H_{12}N_2O_2$ | C, H, N | 0.83 | 6.6 |
| **69** | 5-$CONH_2$ | H | 225 | $C_{14}H_{11}N_3O \cdot HCl \cdot 0.25H_2O$ | C, H, N | 16 | 10 |
| **70** | 5-$NO_2$ | H | ref 34 | | | 16 | >50 |
| **71** | 5-$NH_2$ | H | ref 34 | | | 2.7 | 36 |
| **72** | 5-COMe | H | 106−108 | $C_{15}H_{12}N_2O$ | C, H, N | 0.86 | 14 |
| **73** | 5-CHO | H | 114−116 | $C_{14}H_{10}N_2O$ | C, H, N | 8.4 | >50 |
| **74** | 5-aza | H | 231−232 | $C_{12}H_9N_3 \cdot HCl \cdot 0.25H_2O$ | C, H, N | 10 | 49 |
| **75** | 6-Me | H | 192−195 | $C_{14}H_{12}N_2 \cdot HCl \cdot 0.5H_2O$ | C, H, N | 40 | >50 |
| **76** | 6-OMe | H | 71−73 | $C_{14}H_{12}N_2O$ | C, H, N | 6.4 | >50 |
| **77** | 6-OH | H | ref 33 | | | 2.1 | >50 |

**Table 2** (Continued)




| no. | R | X | mp | formula | analyses | PDGFR[a] $IC_{50}$ ($\mu$M) | FGFR[b] $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| **78** | 6-Cl | H | 95−97 | $C_{13}H_9ClN_2$ | C, H, N | 5.4 | >50 |
| **79** | 6-COOH | H | 278−280 | $C_{14}H_{10}N_2O_2$ | C, H, N | 50 | 50 |
| **80** | 6-COOMe | H | 200−203 | $C_{15}H_{12}N_2O_2$ | C, H, N | 13 | >50 |
| **81** | 6-$CONH_2$ | H | 244−246 | $C_{14}H_{11}N_3O\cdot HCl$ | C, H, N | 25 | >50 |
| **82** | 6-$NO_2$ | H | 156−158 | $C_{13}H_9N_3O_2$ | C, H, N | 50 | 39 |
| **83** | 6-$NH_2$ | H | 204 (dec) | $C_{13}H_{11}N_3\cdot 2HCl$ | C, H, N | 23 | >50 |
| **84** | 7-Me | H | 221−223 | $C_{14}H_{12}N_2\cdot HCl$ | C, H, N | >50 | >50 |
| **85** | 7-OMe | H | 239−241 | $C_{14}H_{12}N_2O\cdot HCl$ | C, H, N | 37 | 50 |
| **86** | 7-OH | H | 228−232 | $C_{13}H_{10}N_2O\cdot HCl\cdot H_2O$ | C, H, N | >50 | 50 |
| **87** | 7-Cl | H | 115−117 | $C_{13}H_9ClN_2\cdot HCl$ | C, H, N | >50 | >50 |
| **88** | 7-COOH | H | 218−222 | $C_{14}H_{10}N_2O_2\cdot HCl$ | C, H, N | >50 | >50 |
| **89** | 7-COOMe | H | 121−122 | $C_{15}H_{12}N_2O_2$ | C, H, N | >50 | >50 |
| **90** | 7-$CONH_2$ | H | 268−270 | $C_{14}H_{11}N_3O\cdot HCl\cdot 0.25MeOH$ | C, H, N | >50 | >50 |
| **91** | 7-$NO_2$ | H | 102−103 | $C_{13}H_9N_3O_2$ | C, H, N | >50 | 40 |
| **92** | 7-$NH_2$ | H | 207−209 | $C_{13}H_{11}N_3\cdot 2HCl$ | C, H, N | >50 | >50 |
| **93** | 7-aza | H | 205−209 | $C_{12}H_9N_3\cdot HCl$ | C, H, N | 28 | >50 |
| **94** | 5-OMe | 2-thienyl | 169−172 | $C_{12}H_{10}N_2SO\cdot HCl\cdot 0.5H_2O$ | C, H, N | 2.5 | 5.3 |
| **95** | 5-OMe | 3-thienyl | 219−221 | $C_{12}H_{10}N_2SO\cdot HCl$ | C, H, N | 0.70 | 6.5 |

[a,b] $IC_{50}$: concentration of drug ($\mu$M) to inhibit the phosphorylation of a random glutamate/tyrosine (4:1) copolymer by lysates of transfected SF9 insect cells overexpressing PDGFR or FGFR proteins. For active compounds, values are an average of two or more separate determinations; variation was generally ±15%. See Experimental Section for details. [c] Reference 36 reports the free base as an oil. [d] Reference 26 reports the free base as an oil.

relationships (SARs) around this parent nucleus, and the results (Table 1) show that these SARs are quite narrow. Replacement of the phenyl ring of (**11**) with either benzyl (**4**) or benzoyl (**5**), or its shift to the 2-position (**6**), abolishes inhibitory activity, as does destroying the coplanarity of the bicyclic system in **7**. The 3-nitrogen of the benzimidazole ring is essential, for its loss in compounds **8** and **9** also abolishes activity. Finally, and somewhat surprisingly, the benzotriazole **10** is also inactive.

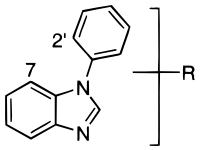
While the 1-phenylbenzimidazole (**11**) has only modest inhibitory activity against PDGFR ($IC_{50}$ = 9.3 $\mu$M), it did show clear selectivity for PDGFR over $\beta$-FGFR ($IC_{50}$ > 50 $\mu$M) and other tyrosine kinase enzymes, including EGFR ($IC_{50} \gg 50$ $\mu$M). A curve-fitting analysis of inhibition of PDGFR by a 5-OMe substituted analogue (**64**) with respect to ATP concentration indicated it behaves as an ATP competitive compound with a $K_i$ of 21 $\mu$M (data not shown). This selectivity, the narrow SAR around the parent structure, the ATP inhibitory mechanism, and the novelty of the lead made the 1-phenylbenzimidazole lead worthy of further development. The next step was a study of monosubstitution at all available positions, using a set of relatively small substituents. Table 2 shows results for a series of monosubstituted 1-phenylbenzimidazoles (**12**−**95**) bearing twelve different substituents varying widely in electronic ($\sigma_p$ values from 0.78 [$NO_2$] to −0.66 [$NH_2$]), hydrophobic ($\pi$ values from 0.56 [Me] to −1.5 [aza]), and H-bond donor/acceptor characteristics. Most of these substituents were evaluated at all the available substituent positions.

In terms of potency, the results of Table 2 show that any substitution at the 2′-position of the phenyl ring is unacceptable (compounds **12**−**24**). In contrast, 8/13 of the 3′-substituted compounds (**25**−**37**) showed PDGFR activity ($IC_{50}$ < 50 $\mu$M). The OH and $NH_2$ derivatives (**27** and **33**) proved slightly more active than **11** ($IC_{50}$s = 3.8 and 3.6 $\mu$M, respectively) and also showed higher selectivity over FGFR (essentially no activity shown). In the 4′-substituted series (**38**−**50**), 10/13 compounds had $IC_{50}$ values <50 $\mu$M against PDGFR, with the 4′-OH analogue (**40**) more than 5-fold more active than **11** (this was the only compound that also showed FGF activity). Among the active 3′- and 4′-substituted compounds, H-bond donor capability appeared to be an important requirement, with the OH and $NH_2$ substituents providing analogues of the highest activity.

Substitution at the 2-position in the benzimidazole ring (compounds **51**−**53**) appeared to completely abolish activity, and only a few known[29−31] representative compounds were made. Substitution at the 7-position was equally unacceptable, with none of the compounds (**84**−**93**) showing significant activity.

However, 6/9 of the 6-substituted analogues (**75**−**83**) were active against PDGFR (but not FGFR), with the most effective again being the OH compound **77** ($IC_{50}$ = 2.1 $\mu$M). In this position the next most active derivative was the OMe analogue **76** ($IC_{50}$ = 6.4 $\mu$M), with the $NH_2$ compound **83** much less effective ($IC_{50}$ = 23 $\mu$M). The most effective substitutions were at the 5-position (compounds **63**−**74**), with 10/12 derivatives having $IC_{50}$s against PDGFR below 16 $\mu$M and four being submicromolar. The most active analogues were again the OH (**65**; $IC_{50}$ = 0.44 $\mu$M) and OMe (**64**; $IC_{50}$ = 0.43 $\mu$M), which were the most active of all the monosubstituted compounds (ca. 20-fold more potent than the parent **11**). Finally, the 4-substituted derivatives (**54**−**62**) showed significant differences; 7/9 compounds were completely inactive ($IC_{50}$s > 50 $\mu$M), but

**Table 3.** Energies and Phenyl/Benzimidazole Torsion Angles for Substituted 1-Phenylbenzimidazoles




| compd | R | minimized energy[a] (kJ/mol) | torsion angle[b] (deg) | mimimized energy[c] (kJ/mol) |
|---|---|---|---|---|
| **11** | H | 88.28 | 43.6 | |
| **12** | 2′-Me | 93.42 | 54.4 | 94.35 |
| **84** | 7-Me | 98.41 | 54.6 | 99.11 |
| **19** | 2′-$NO_2$ | 50.24 | 55.8 | 51.38 |
| **91** | 7-$NO_2$ | 42.61 | 46.2 | 42.63 |
| **20** | 2′-$NH_2$ | 181.96 | 52.1 | 84.92 |
| **92** | 7-$NH_2$ | 170.07 | 48.0 | 170.28 |

[a] Minimum energy conformation, calculated using the MM2 force field in the MacroModel program. [b] Phenyl/benzimidazole bond angle for the minimum energy conformation. [c] Calculated energy when phenyl/benzimidazole bond angle is constrained to 43.6°.

the 4-OH analogue **56** was almost as potent ($IC_{50}$ = 11 $\mu$M) as the parent **11**.

With the exception of the 6- and 7-nitro compounds (**82**) and (**91**), all of the compounds that were on scale showed some selectivity for PDGFR over FGFR. For those which had measurable activity ($IC_{50}$ < 50 $\mu$M) against both, there was a modest but significant correlation (eq 1).

$$\log(IC_{50})[\text{PDGFR}] = 1.11(\pm 0.28)\log(IC_{50})[\text{FGFR}] - 1.02(\pm 0.40) \quad (1)$$

$$n = 15 \qquad r = 0.73 \qquad F = 15.2$$

This shows that compounds were, on average, about 10-fold more potent against PDGFR than FGFR but that the two $IC_{50}$ values were closely correlated (slope of unity). However, within this broad relationship there were significant individual variations, with the most selective compound being the 5-OMe derivative **64** (22/0.43 = 50-fold).

The complete inactivity of the 2′- and 7-substituted derivatives suggested that the conformation of the ligands plays an important role in their activity, presumably through modulating binding to the enzyme. The 1-phenylbenzimidazole system is fairly rigid, with only one rotatable bond—that between the phenyl and benzimidazole rings. The influence of 2′- and 7-substituents on this torsion angle was studied using the MM2 force field in the MacroModel program[32] (Table 3). In the minimum energy conformation of the unsubstituted parent compound **11**, this bond has a torsion angle of 43.6°, indicating considerable nonbonded interactions (presumably between the 2′- and 7-H atoms). The functional groups $NH_2$, Me, or $NO_2$ were then added at positions 2′- or 7-, the resulting structures were minimized, and conformational searches were carried out by use of the Monte Carlo simulation. In each case the searches revealed a single, low-energy conformation, in which the torsion angle varied from 46.2° (7-$NO_2$) to 55.8° (2′-$NO_2$) (Table 3). The complete loss of activity by the addition of a 7-$NO_2$ substituent, where the minimum energy conformation torsion angle increased by only 2.8°, suggested that the dystherapeutic effects of these substituents were exercised primarily by local steric inhibition. This view is supported by the fact that when the phenyl/benzimidazole angle was constrained to the value of 43.6° seen in the minimum energy conformation of the unsubstituted parent **11**, the resulting energies of the substituted compounds were little changed (Table 3), suggesting a very shallow minimum.

**Table 4.** Inhibitory Potencies of Selected 1-Phenylbenzimidazoles against PDGF-Stimulated PDGFR Autophosphorylation in Rat Aorta Vascular Smooth Muscle Cells

| no. | R | $IC_{50}$[a] ($\mu$M) |
|---|---|---|
| **11** | H | 2.3 |
| **46** | 4′-$NH_2$ | 2.0 |
| **56** | 4-OH | >10 |
| **64** | 5-OMe | 1.9 |
| **65** | 5-OH | 0.13 |
| **68** | 5-$CO_2$Me | 0.15 |
| **76** | 6-OMe | >10 |

[a] $IC_{50}$: concentration of drug ($\mu$M) to inhibit the autophosphorylation of PDGFR in PDGF-stimulated RAVSMC. See Experimental Section for details.

To further evaluate the importance of the 1-phenyl ring, two thienyl derivatives were also made (**94** and **95**). These contained a 5-OMe group in order to increase potency. The 3-thienyl analogue **95** proved almost as potent as the corresponding 5-OMe 1-phenyl compound **64** ($IC_{50}$ = 0.7 $\mu$M against PDGFR), with the 2-thienyl analogue **94** being less effective ($IC_{50}$ = 3.3 $\mu$M). However, both compounds were much less selective than **64**. The 1-pyridyl analogue **50** also showed moderate PDGFR activity ($IC_{50}$ = 12 $\mu$M).

A number of analogues were evaluated for their ability to inhibit PDGF-stimulated PDGFR autophosphorylation in rat aorta smooth muscle cells (Table 4). The 5-OH analogue **65** proved the most potent ($IC_{50}$ = 0.13 $\mu$M), with the 5-OMe analogue **64** being much less effective ($IC_{50}$ = 1.9 $\mu$M).

## Conclusions

The above data show a quite well-defined SAR for activity of 1-phenylbenzimidazoles in inhibiting the isolated PDGFR enzyme. Substituents at the 4′- and 3′-positions of the phenyl ring are tolerated, but do not significantly improve activity, while those at the 2′-position (and the 2-, 4-, and 7-positions of the benzimidazole ring) abolish it (with the notable exception of the 4-OH derivative). However, some substituents at the 5- and 6-positions provided significant increases in potency, with the 5-OH, 5-OMe, 5-COMe, and 5-$CO_2$Me analogues being >10-fold more potent than the parent **11**. The 5-OMe analogue **64** was both the most potent and the most PDGFR-selective compound against isolated enzymes and was also a moderately effective inhibitor of PDGF-stimulated PDGFR autophosphorylation in rat aorta smooth muscle cells ($IC_{50}$ = 1.9 $\mu$M). Studies on further 5- and 6-substituted 1-phenylbenzimidazoles as PDGFR inhibitors are in progress.

## Experimental Section

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ, or by Parke-Davis Pharmaceutical Research Analytical Department. Melting points were determined using an Electrothermal Model 9200 or

Gallenkamp digital melting point apparatus and are as read. NMR spectra were measured on Bruker AC-200 or AM-400 or Varian Unity 400 MHz spectrometers, 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 either on a Varian VG 7070 spectrometer at nominal 5000 resolution or a on Finnegan MAT 900Q spectrometer.

**1-(2-Methoxyphenyl)benzimidazole Hydrochloride (13) by the Method of Scheme 1: General Example.** A mixture of 2-fluoronitrobenzene (**96a**) (7.47 mL, 70 mmol), 2-methoxyaniline (7.99 mL, 70 mmol), and $K_2CO_3$ (14.69 g, 110 mmol) in DMF (60 mL) was warmed at 125 °C with stirring for 18 h. After removal of the solvent under reduced pressure, the residue was partitioned between EtOAc and 0.5 N HCl, and the EtOAc solution was worked up to give an oil. Excess 2-fluoronitrobenzene was removed by distillation under reduced pressure and the residue was recrystallized from EtOH to give 2′-methoxy-2-nitrodiphenylamine **(97a)** (7.10 g, 41%): mp 84 °C; $^1$H NMR $\delta$ ($CDCl_3$) 9.44 (br, 1 H, NH), 8.19 (dd, $J$ = 8.6, 1.6 Hz, 1 H, H-3), 7.39−7.34 (m, 2 H), 7.25 (dd, $J$ = 8.7, 1.2 Hz, 1 H), 7.2−7.16 (m, 2 H), 7.00−6.96 (m, 1 H), 6.79−6.74 (m, 1 H), 3.87 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 152.50 (s), 142.46 (s), 135.41 (d), 133.73 (s), 127.81 (s), 126.63 (d), 125.73 (d), 123.25 (d), 120.63 (d), 117.39 (d), 116.16 (d), 111.57 (d), 55.67 (q). Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

A solution of **97a** (3.00 g, 12 mmol) in MeOH/$Et_2O$ (1:1, 40 mL) was hydrogenated over 5% Pd−C for 3 h. After removal of the catalyst and concentration to dryness under reduced pressure, the residue was dissolved in 2-methoxyethanol (50 mL) containing formamidine acetate (1.28 g, 24 mmol), and the solution was heated under reflux for 3 h. After removal of the solvent under reduced pressure, the residue was partitioned between EtOAc and water. The organic portion was worked up to give an oil which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) gave **13** (2.31 g, 72%). HCl salt: mp (MeOH/$Et_2O$) 203−204 °C; $^1$H NMR ($D_2O$) $\delta$ 9.42 (s, 1 H, H-2), 7.95 (d, $J$ = 8.3 Hz, 1 H, H-4), 7.77−7.70 (m, 2 H), 7.65−7.58 (m, 2 H), 7.51 (d, $J$ = 8.4 Hz, 1 H), 7.41 (d, $J$ = 8.4 Hz, 1 H), 7.30 (dd, $J$ = 7.7, 7.7 Hz, 1 H), 3.86 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 155.98 (s), 143.75 (d), 135.23 (d), 134.26 (s), 132.72 (s), 129.94 (d), 129.82 (d), 129.70 (d), 124.07 (d), 123.78 (s), 117.45 (d), 115.99 (d), 115.97 (d), 58.60 (q). Anal. ($C_{14}H_{12}N_2O$·HCl) C, H, N.

**5-Methyl-1-phenylbenzimidazole hydrochloride (63).** A mixture of 4-chloro-3-nitrotoluene (**96b**) (1.00 mL, 7.56 mmol), aniline (6.89 mL, 0.075 mmol) and sodium acetate (1.24 g, 0.015 mol), was refluxed under nitrogen for 18 h. The cooled product was partitioned between EtOAc and water and the organic portion was washed with 2 N HCl and then brine, and worked up to give an oil which was chromatographed on silica gel. Elution with petroleum ether gave crude 4-methyl-3-nitrodiphenylamine **(97b)** as an orange oil (1.01 g, 58%) which was used directly. Hydrogenation of this over 5% Pd−C for 3 h, followed by reaction with formamidine acetate as described above, gave a crude product that was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:5) gave foreruns, while EtOAc/petroleum ether (1:1) gave **63** (0.91 g, 98%). HCl salt: mp (MeOH/$Et_2O$) 196−200 °C; $^1$H NMR ($D_2O$) $\delta$ 9.40 (s, 1 H, H-2), 7.76−7.72 (m, 3 H, Ph), 7.68 (br s, 1 H, H-4), 7.63−7.59 (m, 2 H, Ph), 7.50 (d, $J$ = 8.6 Hz, 1 H, H-7), 7.43 (br d, $J$ = 8.6 Hz, 1 H, H-6), 2.55 (s, 3 H, $CH_3$); $^{13}$C NMR $\delta$ 114.66 (d), 141.08 (s), 135.74 (s), 133.54 (s), 133.28 (d), 133.15 (d), 131.68 (s), 131.37 (d), 127.04 (d), 116.93 (d), 115.07 (d), 23.38 (q). Anal. ($C_{14}H_{12}N_2$·HCl) C, H, N.

**Methyl 1-Phenylbenzimidazole-5-carboxylate (68).** A mixture of 4-chloro-3-nitrobenzoic acid (**96c**) (5.70 g, 0.023 mol), aniline (3.17 mL, 0.035 mol), *N*-methylmorpholine (3.24 mL, 0.025 mol), and copper powder (0.10 g) in isoamyl alcohol (200 mL) was refluxed for 18 h. The cooled solution was filtered through Celite and the filtrate concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc, washed well with 3 N HCl, then water, and finally extracted with saturated aqueous $Na_2CO_3$. Acidification of the extract afforded crude 2-nitrodiphenylamine-4-carboxylic acid (**97c**) (1.64 g, 28%) which was dissolved in MeOH (50 mL). The solution was saturated with gaseous HCl and then refluxed for 18 h. After concentration to dryness the residue was partitioned between EtOAc and water, and the organic portion was worked up to give crude methyl 2-nitrodiphenylamine-4-carboxylate, which was dissolved in MeOH/EtOAc (1:1) (50 mL), hydrogenated over 5% Pd−C, and then treated with formamidine acetate as described above. Chromatography of the product on silica gel, eluting with EtOAc/petroleum ether (1:1), gave **68** (1.27 g, 23% overall): mp 100−102 °C; $^1$H NMR [$(CD_3)_2SO$] $\delta$ 3.90 (s, 3 H), 7.5−7.6 (m, 1 H), 7.6−7.8 (m, 5 H), 7.96 (dd, $J$ = 1.5, 8.5 Hz, 1 H), 8.36 (d, $J$ = 1.2, 1 H), 8.74 (s, 1 H); MS (CI) ($m$ + 1)/$z$ 253. Anal. ($C_{15}H_{12}N_2O_2$) C, H, N.

**1-Phenylimidazo-1*H*-imidazo[4,5-*c*]pyridine Hydrochloride (74).** A solution of 4-chloro-3-nitropyridine (**96d**) (3.22 g, 0.020 mol), aniline (1.85 mL, 0.020 mol), and concentrated HCl (0.17 mL, 0.02 mol) in 1:1 water/2-methoxyethanol (40 mL) was refluxed for 18 h and then concentrated to dryness. The residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the organic portion was worked up to give an oil which was chromatographed on silica gel. Petroleum ether eluted foreruns, while EtOAc/petroleum ether (1:1) gave 4-(*N*-phenylamino)-3-nitropyridine (**97d**) (2.02 g, 41%): mp (EtOAc/petroleum ether) 119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.67 (br s, 1 H, NH), 9.28 (s, 1 H, H-2), 8.25 (dd, $J$ = 6.1, 0.8 Hz, 1 H, H-6), 7.51−7.46 (m, 2 H, Ph), 7.38−7.34 (m, 1 H, Ph), 7.31−7.28 (m, 2 H, Ph), 6.94 (d, $J$ = 6.1 Hz, 1 H, H-5); $^{13}$C NMR $\delta$ 153.18 (d), 149.08 (d), 147.53 (s), 136.48 (s), 130.03 (s), 130.03 (s), 130.03 (d), 125.36 (d), 109.13 (d). Anal. ($C_{11}H_9N_3O_2$) C, H, N. Reduction of **97d** followed by reaction with formamidine acetate, as above, gave **74** (84%). HCl salt: mp (MeOH/$Et_2O$) 231−232 °C; $^1$H NMR ($D_2O$) $\delta$ 9.43 (s, 1 H, H-2), 9.00 (s, 1 H, H-4), 8.68 (d, $J$ = 6.7 Hz, 1 H, H-7), 8.20 (d, $J$ = 6.7 Hz, 1 H, H-6), 7.76−7.66 (m, 5 H, Ph); $^{13}$C NMR $\delta$ 153.34 (d), 146.29 (s), 142.53 (s), 137.82 (d), 137.04 (d), 136.14 (s), 133.15 (d), 132.76 (d), 127.05 (d), 112.48 (d). Anal. ($C_{12}H_9N_3$·HCl) C, H, N.

**6-Methyl-1-phenylbenzimidazole Hydrochloride (75).** A solution of 3-fluoro-4-nitrotoluene (**96e**) (1.00 g, 6.45 mmol), aniline (0.70 mL, 7.73 mmol), and *N*-methylmorpholine (0.90 mL, 7.09 mmol) in 2-methoxyethanol (60 mL) was refluxed for 18 h and then concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc and washed sequentially with water, 3 N HCl, and water. Work up gave crude 5-methyl-2-nitrodiphenylamine (**97e**). This was directly hydrogenated over 5% Pd−C in EtOAc/MeOH (1:1) for 2 h and then reacted with formamidine acetate as above. The product was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:5) gave foreruns, while EtOAc/petroleum ether (1:1) eluted **75** (0.61 g, 45%). HCl salt: mp (MeOH/$Et_2O$) 192−195 °C; $^1$H NMR ($D_2O$) $\delta$ 9.39 (s, 1 H, H-2), 7.78 (d, $J$ = 8.5 Hz, 1 H, H-4), 7.76−7.73 (m, 3 H, Ph), 7.66−7.62 (m, 2 H, Ph), 7.53 (dd, $J$ = 8.5, 0.9 Hz, 1 H, H-5), 7.49 (d, $J$ = 0.9 Hz, 1 H, H-7), 2.48 (s, 3 H, $CH_3$); $^{13}$C NMR $\delta$ 141.73 (d), 141.01 (s), 135.75 (s), 134.00 (s), 133.30 (d), 133.12 (d), 131.57 (d), 131.32 (s), 127.31 (d), 117.01 (d), 115.04 (d), 23.54 (q). Anal. ($C_{14}H_{12}N_2$·HCl) C, H, N.

**6-Amino-1-phenylbenzimidazole Dihydrochloride (83).** A mixture of 3-chloro-4-nitroaniline (**96f**) (1.00 g, 5.79 mmol), aniline (5.3 mL, 0.058 mol), and anhydrous sodium acetate (0.95 g, 0.016 mol) was refluxed for 18 h under an atmosphere of nitrogen. The cooled product was partitioned between EtOAc and water, and the organic portion was washed with water and 2 N HCl and then worked up to give an oily solid which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (2:3) gave crude 5-amino-2-nitrodiphenylamine (**97f**) which was used directly. This was dissolved in 1:1 EtOAc/MeOH (60 mL) and hydrogenated over 5% Pd−C for 3 h. After removal of catalyst and solvent the residue was dissolved in 4 N HCl (50 mL) containing formic acid (3 mL), and the solution was refluxed for 1 h. After concentration to dryness under reduced pressure the residue was partitioned between aqueous $NH_3$ and EtOAc. Workup of the organic

portion afforded an oil which was chromatographed on silica gel. Elution with EtOAc gave **83** (0.48 g, 33%). DiHCl salt: mp (MeOH/$Et_2O$) 204 °C (dec); $^1$H NMR ($D_2O$) $\delta$ 9.67 (s, 1 H, H-2), 8.15 (d, $J$ = 8.9 Hz, 1 H, H-4), 7.87 (d, $J$ = 1.9 Hz, 1 H, H-7), 7.81−7.78 (m, 5 H, Ph), 7.76 (dd, $J$ = 8.9, 1.9 Hz, 1 H, H-5); $^{13}$C NMR $\delta$ 144.78 (d), 135.49 (s), 134.76 (s), 133.72 (d), 133.40 (s), 133.30 (d), 132.74 (s), 127.74 (d), 124.87 (d), 119.77 (d), 110.91 (d). Anal. ($C_{13}H_{11}N_3$·2HCl) C, H, N.

**1-Phenyl-1*H*-imidazo[5,4-*b*]pyridine Dihydrochloride (93).** A solution of 2-chloro-3-nitropyridine (**96g**) (0.50 g, 3.15 mmol), aniline (0.29 mL, 3.15 mmol), and concentrated HCl (26 $\mu$L, 0.31 mmol) in 1:1 water/2-methoxyethanol (25 mL) was refluxed for 18 h. On cooling, orange needles of 2-(*N*-phenylamino)-3-nitropyridine (**97g**) separated (0.42 g, 57%): mp 66−67 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.11 (br, 1 H, NH), 8.53 (dd, $J$ = 8.2, 1.9 Hz, 1 H, H-6), 8.48 (dd, $J$ = 4.5, 1.9 Hz, 1 H, H-4), 7.66−7.62 (m, 2 H, Ph), 7.42−7.38 (m, 2 H, Ph), 7.21−7.16 (m, 1 H, Ph), 6.83 (dd, $J$ = 8.2, 4.5 Hz, 1 H, H-5); $^{13}$C NMR $\delta$ 155.27 (d), 150.27 (s), 137.82 (s), 135.53 (d), 129.01 (d), 128.60 (s), 124.84 (d), 122.56 (d), 113.88 (d). Anal. ($C_{11}H_9N_3O_2$·0.25$H_2O$) C, H, N. Reduction of **97g** followed by reaction with formamidine acetate, as above, gave **93** (77%). DiHCl salt: mp (MeOH/$Et_2O$) 205−209 °C; $^1$H NMR ($D_2O$) $\delta$ 9.65 (s, 1 H, H-2), 8.67 (dd, $J$ = 7.0, 2.0 Hz, 1 H, H-6), 8.45 (dd, $J$ = 8.5, 2.0 Hz, 1 H, H-4), 7.81−7.70 (m, 6 H, H-5 and Ph); $^{13}$C NMR $\delta$ 150.60 (d), 145.81 (s), 144.67 (d), 134.72 (s), 133.37 (d), 132.86 (d), 128.68 (d), 128.08 (s), 127.92 (d), 125.47 (d). Anal. ($C_{12}H_9N_3$·2HCl) C, H, N.

**4-Methyl-1-phenylbenzimidazole Hydrochloride (54) by the Method of Scheme 2.** A mixture of 3-methyl-2-nitroaniline (**98a**) (12.00 g, 79 mmol), $K_2CO_3$ (6.00 g, 43 mmol), and cuprous iodide (0.20 g, 1.05 mmol) in bromobenzene (40 mL) was refluxed with vigorous stirring for 16 h and the excess of bromobenzene was removed under reduced pressure. The residue was partitioned between EtOAc and water and filtered through Celite, and the organic layer was worked up and chromatographed on silica gel. Petroleum ether eluted 3-methyl-2-nitrodiphenylamine **(99a)** (8.21 g, 45%): mp (aqueous EtOH) 59−61 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.75 (br, 1 H, NH), 7.34 (dd, $J$ = 9.4, 7.4 Hz, 1 H, H-5), 7.24−6.98 (m, 6 H, Ph and H-4), 6.72 (dd, $J$ = 7.4, 2.0 Hz, 1 H, H-6), 2.47 (s, 3 H, $CH_3$); $^{13}$C NMR $\delta$ 140.30 (s), 139.68 (s), 134.52 (s), 132.27 (d), 129.55 (d), 123.82 (d), 123.08 (s), 122.23 (d), 121.65 (d), 115.28 (d), 20.36 (q). Anal. ($C_{13}H_{12}N_2O_2$) C, H, N.

Reduction of **99a** with $H_2$/Pd−C, followed by reaction of the crude phenylenediamine with formamidine acetate, as detailed above, gave the benzimidazole **(54)** (98%). HCl salt: mp (MeOH/$Et_2O$) 206−208 °C; $^1$H NMR ($D_2O$) $\delta$ 9.49 (s, 1 H, H-2), 7.77−7.73 (m, 3 H), 7.62−7.60 (m, 2 H), 7.49−7.42 (m, 3 H), 2.66 (s, 3 H, $CH_3$); $^{13}$C NMR $\delta$ 141.89 (d), 135.73 (s), 133.27 (d), 133.15 (d), 133.00 (s), 130.24 (d), 129.83 (d), 128.52 (s), 127.02 (d), 112.79 (d), 18.49 (q). Anal. ($C_{14}H_{12}N_2$·HCl) C, H, N.

**4-Methoxy-1-phenylbenzimidazole Hydrochloride (55) by the Method of Scheme 2.** A suspension of 3-methoxy-2-nitroaniline (**98b**) (5.00 g, 0.030 mmol), $K_2CO_3$ (2.21 g, 0.016 mmol), and cuprous iodide (50 mg, 0.26 mmol) in bromobenzene (10 mL) was refluxed with vigorous stirring for 18 h and the excess of bromobenzene was removed under reduced pressure. The residue was partitioned between EtOAc and water and filtered through Celite, and the organic layer was worked up and chromatographed on silica gel. EtOAc/petroleum ether (1:19) eluted 3-methoxy-2-nitrodiphenylamine **(99b)** (4.00 g, 54%): mp (aqueous MeOH) 95 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.52 (br, 1 H, NH), 7.33 (dd, $J$ = 8.6, 8.3 Hz, 1 H, H-5), 7.23−7.08 (m, 5 H, Ph), 6.84 (dd, $J$ = 8.6, 0.8 Hz, 1 H, H-6), 6.44 (dd, $J$ = 8.3, 0.8 Hz, 1 H, H-4), 3.91 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 154.33 (s), 140.32 (s), 140.06 (s), 132.70 (d), 129.51 (d), 123.96 (d), 121.82 (d), 108.86 (d), 102.57 (d), 56.53 (q). Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

Reduction of **99b** with $H_2$/Pd−C followed by reaction of the crude phenylenediamine with formamidine acetate, as detailed above, gave the benzimidazole **(55)** (74%). HCl salt: mp 191−193 °C; $^1$H NMR ($D_2O$) $\delta$ 9.35 (s, 1 H, H-2), 7.71−7.70 (m, 3 H, Ph), 7.64−7.62 (m, 2 H, Ph), 7.53 (dd, $J$ = 8.4, 8.1 Hz, 1 H, H-6), 7.24 (d, $J$ = 8.4 Hz, 1 H, H-7), 7.15 (d, $J$ = 8.1 Hz, 1 H, H-5), 4.08 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 150.50 (s), 141.65 (d), 135.98 (s), 135.31 (s), 133.24 (d), 133.11 (d), 130.96 (d), 127.28 (d), 124.57 (s), 110.09 (d), 107.48 (d), 59.02 (q). Anal. ($C_{14}H_{12}N_2O$·HCl) C, H, N.

**4-Hydroxy-1-phenylbenzimidazole Hydrochloride (56).** A solution of **55** (0.25 g, 1.11 mmol) in 48% HBr in glacial AcOH (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 was worked up to give a solid. Chromatography of this on silica gel, eluting with EtOAc/petroleum ether (1:1), gave **56** (77%). HCl salt: mp 238−240 °C; $^1$H NMR ($D_2O$) $\delta$ 9.41 (s, 1 H, H-2), 7.74−7.67 (m, 5 H, Ph), 7.47 (dd, $J$ = 8.3, 8.2 Hz, 1 H, H-6), 7.22 (d, $J$ = 8.3 Hz, 1 H, H-7), 7.08 (dd, $J$ = 8.2 Hz, 1 H, H-5); $^{13}$C NMR $\delta$ 147.45 (s), 141.70 (d), 136.00 (s), 135.85 (s), 133.32 (d), 133.10 (d), 131.01 (d), 127.47 (d), 123.81 (s), 114.17 (d), 106.90 (d). Anal. ($C_{13}H_{10}N_2O$·HCl·0.25$H_2O$) C, H, N.

**1-Phenylbenzimidazole-4-carboxylic Acid Hydrochloride (58).** To a refluxing solution of the free base of **54** (3.23 g, 0.015 mmol) in *tert*-butyl alcohol (200 mL) and water (50 mL) was added powdered $KMnO_4$ in portions over 48 h (a total of 9.00 g, 0.057 mmol). The hot solution was filtered through Celite, and the filtrate was concentrated under reduced pressure to a volume of ca. 80 mL. Water was added, and the solution was washed with EtOAc. Workup of the extract afforded starting material (0.86 g, 27%). The aqueous portion was carefully neutralized with 3 N HCl to precipitate **58** (1.87 g, 52%). HCl salt: mp (MeOH/$Et_2O$) 245−248 °C; $^1$H NMR ($D_2O$) $\delta$ 9.70 (s, 1 H, H-2), 8.21 (d, $J$ = 7.5 Hz, 1 H, H-5), 8.00 (d, $J$ = 8.3 Hz, 1 H, H-7), 7.79−7.71 (m, 6 H, Ph and H-6); $^{13}$C NMR $\delta$ 169.73 (s), 143.83 (d), 135.30 (s), 134.83 (s), 133.64 (d), 133.16 (d), 132.21 (s), 132.06 (d), 129.63 (d), 127.57 (d), 121.05 (d), 120.66 (s). Anal. ($C_{14}H_{10}N_2O_2$·HCl) C, H, N.

**Methyl 1-Phenylbenzimidazole-4-carboxylate Hydrochloride (59).** A mixture of the acid **58** (0.50 g, 2.10 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 **59** (0.48 g, 91%). HCl salt: mp (MeOH/$Et_2O$) 187−189 °C; $^1$H NMR [$(CD_3)_2SO$] $\delta$ 9.72 (s, 1 H, H-2), 8.28 (d, $J$ = 8.1 Hz, 1 H, H-5), 8.04 (d, $J$ = 8.4 Hz, 1 H, H-7), 7.79−7.71 (m, 6 H, Ph and H-6), 4.11 (s, 3 H, $COOCH_3$); $^{13}$C NMR $\delta$ 168.47 (s), 144.07 (d), 135.26 (s), 134.96 (s), 133.69 (d), 133.18 (d), 132.01 (d), 131.93 (s), 129.66 (d), 127.62 (d), 121.36 (d), 119.80 (s), 55.83 (q). Anal. ($C_{15}H_{12}N_2O_2$·HCl·1.5$H_2O$) H, N. C: found, 56.5; calcd, 57.0%.

**1-Phenylbenzimidazole-4-carboxamide Hydrochloride (60).** A solution of the acid chloride [obtained from the acid **58** as described above] (0.50 g, 2.10 mmol) in $Et_2O$ (40 mL) was treated with concentrated aqueous ammonia (10 mL). After the mixture was vigorously stirred at room temperature for 10 min, saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the ether layer was removed and worked up to give **60** (0.47 g, 94%). HCl salt: mp (MeOH/$Et_2O$) 242−244 °C; $^1$H NMR ($D_2O$) $\delta$ 9.67 (s, 1 H, H-2), 8.08 (d, $J$ = 7.8 Hz, 1 H, H-5), 7.98 (d, $J$ = 8.5 Hz, 1 H, H-7), 7.78−7.72 (m, 6 H, Ph and H-5); $^{13}$C NMR $\delta$ 171.60 (s), 143.83 (d), 135.40 (s), 135.14 (s), 133.60 (d), 133.13 (d), 131.78 (s), 129.65 (d), 128.91 (d), 127.65 (d), 122.78 (s), 120.03 (d). Anal. ($C_{14}H_{13}N_3O$·HCl) C, H, N.

**4-Amino-1-phenylbenzimidazole Hydrochloride (62).** A solution of sodium azide (1.00 g, 0.015 mmol) in water (3 mL) was added to a solution of the acid chloride (obtained from the acid **58)** (0.50 g, 2.10 mmol) in $Me_2CO$ (20 mL) at 5 °C. After the mixture was stirred at this temperature for 10 min, water was added and the mixture was extracted with $CH_2Cl_2$. The extract was worked up to give crude acyl azide, which was used directly. A solution of the acyl azide in glacial acetic acid

(30 mL) and water (5 mL) was refluxed for 5 h and then concentrated to dryness under reduced pressure. The residue was partitioned between EtOAc and water, and the organic portion was worked up to give the crude amine that proved difficult to purify. The crude product was dissolved in $CH_2Cl_2$ (50 mL) and treated sequentially at room temperature with $Et_3N$ (0.58 mL, 4.20 mmol) and trifluoroacetic anhydride (0.59 mL, 4.20 mmol). After 30 min the solution was washed with water and worked up to give an oil which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:3) gave the trifluoroacetamide derivative as a colorless oil. This was immediately dissolved in MeOH (30 mL), 3 N KOH (5 mL) was added, and the solution was warmed at 50 °C for 1 h. The MeOH was removed under reduced pressure, and the residue was extracted with $CH_2Cl_2$ and worked up to give **62** (0.33 g, 75%). HCl salt: mp (MeOH/$Et_2O$) 246−250 °C; $^1$H NMR ($D_2O$) $\delta$ 9.23 (s, 1 H, H-2), 7.74−7.69 (m, 3 H, Ph), 7.66−7.63 (m, 2 H, Ph), 7.45 (dd, $J$ = 8.6, 7.5 Hz, 1 H, H-6), 7.24 (d, $J$ = 8.6 Hz, 1 H, H-7), 7.16 (d, $J$ = 7.5 Hz, 1 H, H-5); $^{13}$C NMR $\delta$ 142.62 (d), 136.28 (s), 135.71 (s), 133.61 (s), 133.04 (d), 132.98 (d), 130.18 (d), 127.34 (d), 126.70 (s), 116.65 (d), 108.06 (d). Anal. ($C_{13}H_{11}N_3$·HCl·0.25$H_2O$) C, H, N.

**4-Nitro-1-phenylbenzimidazole (61).** A solution of sodium nitrite (2.21 g, 0.017 mmol) in water (20 mL) was added to a solution of **62** (0.61 g, 2.93 mmol), copper sulfate pentahydrate (14.62 g, 0.058 mmol) and concentrated HCl (0.48 mL, 5.80 mmol) in water (1 L). After being stirred at room temperature for 48 h the mixture was extracted with EtOAc, and the extract was worked up to give an oily solid which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) gave **61** (0.21 g, 30%): mp (EtOAc/petroleum ether) 204−206 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.87 (s, 1 H, H-2), 8.15 (d, $J$ = 8.0 Hz, 1 H, H-5), 8.01 (d, $J$ = 8.1 Hz, 1 H, H-7), 7.76−7.72 (m, 2 H, Ph), 7.71−7.66 (m, 2 H, Ph), 7.59 (m, 1 H, Ph), 7.54 (dd, $J$ = 8.1, 8.0 Hz, 1 H, H-6); $^{13}$C NMR $\delta$ 146.83 (d), 138.87 (s), 136.67 (s), 135.91 (s), 134.89 (s), 130.08 (d), 128.63 (d), 124.49 (d), 122.99 (d), 119.05 (d), 117.61 (d). Anal. ($C_{13}H_9N_3O_2$) C, H, N.

**4-Chloro-1-phenylbenzimidazole (57).** A solution of sodium nitrite (0.30 g, 2.42 mmol) in water (1 mL) was slowly added to a solution of the amine **62** (0.46 g, 2.20 mmol) in concentrated HCl (6 mL) and water (6 mL) at 5 °C. After 5 min at this temperature, a solution of freshly prepared cuprous chloride (2.18 g, 0.022 mmol) in concentrated HCl (6 mL) was added in one portion and the mixture was allowed to warm to room temperature over 30 min and then was warmed at 60 °C for 30 min. The cooled mixture was basified with concentrated aqueous ammonia, extracted with EtOAc, and the extract worked up to give an oil which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:3) gave **57** (0.18 g, 42%): mp (EtOAc/petroleum ether) 117−118 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.14 (s, 1 H, H-2), 7.62−7.57 (m, 2 H, Ph), 7.53−7.48 (m, 3 H, Ph), 7.43 (dd, $J$ = 8.4, 1.0 Hz, 1 H, H-5), 7.37 (dd, $J$ − 7.7, 1.0 Hz, 1 H, H-7), 7.26 (dd, $J$ = 8.4, 7.7 Hz, 1 H, H-6); $^{13}$C NMR $\delta$ 142.70 (d), 141.25 (s), 135.92 (s), 134.78 (s), 130.15 (d), 128.49 (d), 125.36 (s), 124.26 (d), 124.22 (d), 122.79 (d), 109.25 (d). Anal. ($C_{13}H_8N_2$·HCl) C, H, N.

Other compounds of Table 2 were prepared by similar functional group transformations; see Supporting Information for experimental details and NMR data.

**1-(4-Carboxamidophenyl)benzimidazole (44) by the method of Scheme 3.** Benzimidazole (1.0 g, 8.5 mmol) was added in small portions to a suspension of potassium hydride (35% dispersion in mineral oil, previously washed with 2 portions of hexane) (974 mg, 8.5 mmol) in DMF (12 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. 4-Fluorobenzamide (**100a**) (1.2 g, 8.5 mmol) was then added, and the reaction was stirred at room temperature for 1 h, at 50 °C for 1 day, and then at 100 °C for 2 days. The mixture was then cooled, diluted with EtOAc, and washed 4 times with water and brine, and the organic phase was dried ($MgSO_4$), filtered, and concentrated. Trituration of the residue in hot EtOAc (50 mL) gave **44 (**1.24 g, 59%): mp (EtOAc) 208−210.5 °C; $^1$H NMR [$(CD_3)_2SO$] $\delta$ 7.35 (m, 2 H), 7.52 (br s, 1 H), 7.65−7.75 (m, 1 H), 7.81 (d, $J$ = 8.7 Hz, 2 H), 7.75−7.85 (m, 1 H), 8.13 (d, $J$ = 8.9 Hz, 2 H), 8.14 (br s, 1 H), 8.64 (s, 1 H); MS (CI) ($m$ + 1)/$z$ 238. Anal. ($C_{14}H_{11}N_3O$) C, H, N.

**1-(3-Formylphenyl)benzimidazole (35).** A solution of benzimidazole (1.00 g, 8.47 mmol) and 3-fluorobenzaldehyde (**100b**) (1.08 mL, 10.2 mmol) in DMSO (30 mL) was heated with anhydrous $K_2CO_3$ (2.34 g, 16.9 mmol) for 24 h at 100 °C. Chromatography of the product on silica gel, eluting with EtOAc/hexane (1:1) to EtOAc/hexane (3:1), gave **35**: mp (HCl salt from EtOAc/MeOH) 196−201 °C; $^1$H NMR [$(CD_3)_2SO$] $\delta$ 10.16 (s, 1 H, CHO), 9.40 (s, 1 H, H-2), 8.30 (t, $J$ = 1.6 Hz, 1 H, H-2′), 8.13 (m, 2 H, aromatic), 7.93 (m, 2 H, aromatic), 7.78 (m, 1 H, aromatic), 7.55 (m, 2 H, H-5,6). Anal. ($C_{14}H_{10}N_2O$·HCl·0.5$H_2O$) C, H, N.

Other compounds of Table 2 were prepared by this method; see Supporting Information for experimental details and NMR data.

**5-Methoxy-1-(2-thienyl)benzimidazole Hydrochloride (94) by the Method of Scheme 4.** A mixture of 4-methoxy-2-nitroaniline (1.00 g, 5.95 mmol), $K_2CO_3$ (1.00 g, 7.23 mmol), CuI (50 mg), and 2-bromothiophene (**101a**) (5 mL, 0.052 mol) was refluxed under nitrogen with stirring for 18 h. Excess bromothiophene was removed under reduced pressure, and the residue was partitioned between EtOAc and water and filtered through Celite. The organic portion was worked up to give an oil which was chromatographed on silica gel. EtOAc/petroleum ether (1:9) eluted 4-methoxy-2-nitro-*N*-(2-thienyl)aniline (**102a**) (0.37 g, 25%): mp (aqueous EtOH) 108−110 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.17 (br, 1 H, NH), 7.37 (dd, $J$ = 1.8, 1.6 Hz, 1 H), 7.15 (dd, $J$ = 5.7, 1.4 Hz, 1 H), 7.09 (d, $J$ = 1.4 Hz, 1 H), 7.08 (s, 1 H), 6.98 (dd, $J$ = 5.7, 3.6 Hz, 1 H), 6.88 (m, 1 H), 3.82 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 151.39 (s), 141.70 (s), 139.57 (s), 126.41 (d), 126.20 (d), 123.47 (d), 122.80 (d), 118.21 (s), 117.65 (d), 106.78 (d), 55.59 (q). Anal. ($C_{11}H_{10}N_2O_3S$) C, H, N.

Hydrogenation of **102a** over 5% Pd−C, followed by reaction with formamidine acetate, gave **94** (82%). HCl salt: mp (MeOH/$Et_2O$) 169−172 °C; $^1$H NMR ($D_2O$) $\delta$ 9.36 (s, 1 H, H-2), 7.68 (dd, $J$ = 1.4, 6.8 Hz, 1 H, H-5′), 7.65 (d, $J$ = 9.2 Hz, 1 H, H-7), 7.49 (dd, $J$ = 3.9, 1.4 Hz, 1 H, H-4′), 7.37 (d, $J$ = 2.3 Hz, 1 H, H-4), 7.27 (dd, $J$ = 6.8, 3.9 Hz, 1 H, H-3′), 7.25 (dd, $J$ = 9.2, 2.3 Hz, 1 H, H-6), 3.94 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 161.58 (s), 143.20 (d), 135.10 (s), 134.57 (s), 129.68 (s), 129.58 (d), 129.47 (d), 128.24 (d), 119.94 (d), 116.50 (d), 100.07 (d), 58.87 (q). Anal. ($C_{12}H_{10}N_2OS$·HCl·0.5$H_2O$) C, H, N.

**5-Methoxy-1-(3-thienyl)benzimidazole Hydrochloride (95).** Similar reactions of 4-methoxy-2-nitroaniline and 3-bromothiophene (**101b**), but for only 6 h, gave 4-methoxy-2-nitro-*N*-(3-thienyl)aniline (**102b**) (71%): mp (EtOAc/petroleum ether) 121−123 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.31 (br, 1 H, NH), 7.63 (d, $J$ = 3.0 Hz, 1 H, H-3), 7.36 (dd, $J$ = 5.1, 3.2 Hz, 1 H, H-4′), 7.18 (d, $J$ = 9.4 Hz, 1 H, H-6), 7.09 (dd, $J$ = 9.4, 3.0 Hz, 1 H, H-5), 7.05 (dd, $J$ = 3.2, 1.4 Hz, 1 H, H-2′), 7.01 (dd, $J$ = 5.1, 1.4 Hz, 1 H, H-5′), 3.82 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 151.01 (s), 138.79 (s), 138.71 (s), 132.12 (s), 126.55 (d), 126.06 (d), 124.74 (d), 117.63 (d), 115.05 (d), 106.82 (d), 55.86 (q). Anal. ($C_{11}H_{10}N_2O_3S$) C, H, N.

Hydrogenation of **102b** as above, followed by reaction with formamidine acetate, gave **95** (77%). HCl salt: mp (MeOH/$Et_2O$) 219−221 °C (dec); $^1$H NMR ($D_2O$) $\delta$ 9.36 (s, 1 H, H-2), 7.88 (dd, $J$ = 3.1, 1.5 Hz, 1 H, H-2′), 7.81 (dd, $J$ = 5.1, 3.1 Hz, 1 H, H-4′), 7.62 (d, $J$ = 9.2 Hz, 1 H, H-7), 7.44 (dd, $J$ = 5.1, 1.5 Hz, 1 H, H-5′), 7.32 (d, $J$ = 2.3 Hz, 1 H, H-4), 7.20 (dd, $J$ = 9.2, 2.3 Hz, 1 H, H-6), 3.93 (s, 3 H, $OCH_3$); $^{13}$C NMR $\delta$ 161.43 (s), 141.67 (d), 134.40 (s), 133.32 (s), 131.49 (d), 128.34 (s), 125.40 (d), 123.46 (d), 119.77 (d), 116.65 (d), 99.76 (d), 58.84 (q). Anal. ($C_{12}H_{10}N_2SO$·HCl) C, H, N.

**Recombinant Tyrosine Kinases and Assays.** The methods for production of the tyrosine kinases used in this study ($\beta$-PDGFR, FGFR, EGFR) and assay conditions for each have been previously described.[35]

**PDGF Receptor Autophosphorylation.** This assay, using rat aortic vascular smooth muscle cells, was carried out as previously described.[35] Serum-starved cells were incubated

for 2 h with the indicated concentration of compound prior to stimulation with 25 ng/mL of PDGF−BB (UBI, Lake Placid, NY). Cell lysates or immunoprecipitates were analyzed by Western blotting using anti-phosphotyrosine antibody (UBI, Lake Placid, NY). Bound antibodies were detected using the ECL Western blotting system from Amersham.

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**Supporting Information Available:** Synthetic details, melting points, and NMR data for all the compounds of Table 2 (16 pages). See any current masthead page for ordering and Internet access instructions.

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