Articles

A New Series of PDGF Receptor Tyrosine Kinase Inhibitors: 3-Substituted Quinoline Derivatives

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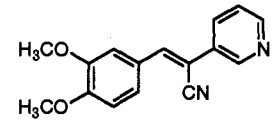
A series of 63 3-substituted quinoline derivatives has been prepared and tested for inhibition of cell-free platelet derived growth factor receptor tyrosine kinase (PDGF-RTK) activity. The compounds were generally prepared either by a Friedlander condensation between an arylacetaldehyde and an *o*-aminobenzaldehyde or by a palladium-catalyzed coupling between an aryl bromide or triflate and an organostannane or organozinc chloride. The presence of 6,7-dimethoxy groups on the quinoline ring was found to be advantageous although not essential for potent inhibition of PDGF-RTK. A lipophilic group attached to the quinoline 3-position contributed substantially to activity. The lipophilic groups generally consisted of monocyclic aromatics or small alkynyl, alkenyl, and alkyl groups. Optimum activity of ca. ≤20 nM (IC_{50}) was observed when 6,7-dimethoxyquinoline was substituted in the 3-position with 4-methoxyphenyl (**15d**), 3-fluoro-4-methoxyphenyl (**17m**), 3-fluorophenyl (**17b**), 4-hydroxyphenyl (**24**), 6-methoxypyridin-3-yl (**15o**), 5-pyridin-2(1*H*)-one (**23**), *trans*-β-styryl (**15e**), thiophene-3-yl (**2e**), 5-chlorothiophene-2-yl (**15f**), or cyclopentenyl (**17n**) groups. Most of the compounds in the series were tested for inhibition of cell-free epidermal growth factor receptor tyrosine kinase activity and found to be inactive.

Platelet-derived growth factor (PDGF) receptors are integral, transmembrane glycoproteins whose expression is generally limited to cells of mesodermal origin.[1] Abnormal expression of PDGF and/or PDGF receptors has been linked to a number of pathophysiological processes which include various forms of neoplasia, atherosclerosis, rheumatoid arthritis, pulmonary fibrosis, myelofibrosis, and abnormal wound healing.[2] Upon ligand binding, the intrinsic tyrosine kinase activity of the PDGF receptor is activated. This leads to tyrosine phosphorylation of numerous proteins, including the receptor itself. Receptor autophosphorylation is essential for all subsequent steps of signal transduction. Importantly, the signaling cascade that follows from the action of PDGF on smooth muscle cell (SMC) PDGF receptors is believed to result in a significant contribution to the process of SMC proliferation and chemotaxis.[3] This process is a crucial component of the sequence of events leading to restenosis after percutaneous transluminal coronary angioplasty procedures.[4] An inhibitor of the PDGF receptor tyrosine kinase activity would block its action. Such an inhibitor could potentially be utilized in the treatment of proliferative disorders linked to PDGF receptors, including postangioplasty restenosis.

A series of 2,3-diarylacrylonitrile compounds has been prepared in our laboratories as epidermal growth factor receptor tyrosine kinase (EGF-RTK) inhibitors.[5] With several exceptions, these compounds were generally poor PDGF-RTK inhibitors. Compound 1 (RG13022),[6] however, displayed modest inhibitory activity in both the EGF-RTK[7] and PDGF-RTK cell-free assays (IC_{50} = 0.5–3 and 0.7–4 μM, respectively). As part of an effort to identify lead structures as PDGF-RTK inhibitors, we decided to synthesize compounds derived from conformationally restricted analogues of 1. Two such compounds were quinolines **2a** and **2b**, which can be envisioned simply by attachment of the nitrile nitrogen of 1 to either of the two open positions of the adjacent dimethoxybenzene ring.[8] The quinolines differ from the parent in several important respects. The polarized double bond of the acrylonitrile has been deleted. We have observed that 1 and similar compounds have a propensity to undergo light-induced cis/trans isomerization and 2 + 2 cycloadditions. The acrylonitrile system also has the potential to act as a Michael acceptor. In addition, the quinoline nitrogen of **2a** and **2b** introduces a new basic center which can serve as a potential hydrogen-bond acceptor.



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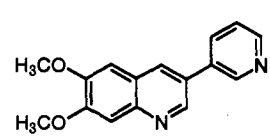
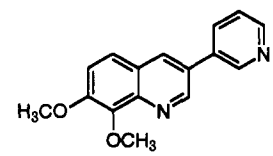


2a



2b

In vitro screening of **2a** and **2b** revealed a fortuitous result. Quinoline **2a** showed good inhibition of PDGF-RTK (IC_{50} = 0.1–0.8 μM) and excellent selectivity against EGF-RTK (IC_{50} > 25 μM) while **2b** showed poor inhibition of both EGF-RTK (IC_{50} > 25 μM) and PDGF-RTK (IC_{50} > 50 μM). Thus, **2a** served as the starting point for an extensive chemical analogue program. In this paper, we

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will present the chemistry and in vitro PDGF-RTK structure–activity relationships for a series of 3-substituted quinolines.

Chemistry

Our initial approach to 3-substituted quinoline synthesis was via a simple Friedlander condensation of *o*-aminobenzaldehydes and arylacetaldehydes as shown in Scheme 1, method A (structures defined in Table 1). By condensation of **3a**,[9], **3b**,[10] **3g**, or **3h**[11] with aldehydes **4a**,[12] **4c**,[13] **4e**,[14] or **4f**, 3-arylquinolines **2a–h** were obtained. While this method provided a rapid entry into the series, its usefulness with regard to analogue synthesis is limited by the availability and stability of the prerequisite *o*-aminobenzaldehydes or arylacetaldehydes. For example, indole-3-acetaldehyde is unstable and must be used quickly after preparation. Other arylacetaldehydes are unstable in basic solution. Likewise, the availability of substituted *o*-aminobenzaldehydes is variable, and their stability and/or reactivity is highly dependent upon the nature of the substituents. We therefore required a more direct approach that could be used to quickly construct a larger variety of analogues.

The use of palladium-catalyzed coupling reactions for the construction of substituted heterocycles has been well-documented[15] and has simplified the synthesis of many important pharmaceutical intermediates. Our need to prepare a series of 3-substituted quinoline derivatives was well-suited to take advantage of this chemistry. Appropriately substituted quinoline-3-triflates could be used to couple with organostannane[16] or organozinc[17] compounds to provide rapid access to the desired analogues.

The sequence of reactions for the preparation of 3-hydroxyquinolines **9a–i** from anilines **5a–h** makes use a previously described[18] protocol and is shown in Scheme 2. The overall yields in the sequence are quite variable and depend mainly on the success (or lack thereof) of the polyphosphoric acid-induced cyclization of nitromalonaldehyde adducts **6a–h** to give 3-nitroquinolines **7a–i**. The (methylenedioxy)quinoline compound **7j** was prepared by an alternative literature[19] route which we found to be operationally inferior to the one depicted. Triflates **10a–j** were obtained by reaction of **9a–j** with triflic anhydride in methylene chloride/pyridine.

The organostannanes used to couple with **10a–j** were prepared by the methods shown in Schemes 3 and 4. All of the bromides indicated were purchased from commercial sources except for **11f**.[20] Arylstannanes **12a–f** (Scheme 3, method B) were synthesized by palladium-catalyzed coupling of triflate **11a** or bromides **11b–f** with hexamethylditin.[16] The remaining organostannanes **14a–k** were prepared by reacting the corresponding organolithium compounds (from **13a–k**, Scheme 4, method C) with trimethyltin chloride. Method C is procedurally more convenient than method B but is obviously unsuitable for use with compounds unstable to organolithium reagents.

Organostannanes **12a–f** and **14a–k** were coupled to the indicated quinoline-3-triflates (Scheme 5, method D) using prescribed conditions[16b] to give **15a–w** and **15y**. Similar coupling of 3-bromoquinoline (**13e**) with **14j**, and of **14e** with *trans*-β-bromostyrene (**13i**), gave **15x** and **15z**, respectively. Isolated reaction yields were generally very good, ranging from 51 to 99% in most cases. The low yield in the coupling of **10j** with **14j** (→**15t**) was due in part to difficulties in purifying **10j** and its preceding intermediates.[19]

The remaining coupling products **17a–p** were synthesized by palladium-catalyzed reaction of the organozinc chlorides obtained from **16a–p** with **10a** (Scheme 6, method E). The bromides are commercially available except for **16h**[21] and **16n**.[22] Method E was more convenient in comparison to method D and afforded the desired coupling products in shorter time, using lower temperatures and without isolation of the intermediate organometallics. Alkynes **16o,p** were subjected to the same procedure to give **17o,p** in excellent yields. Compounds **18–27** were prepared from the appropriate precursors as indicated in Table 1.

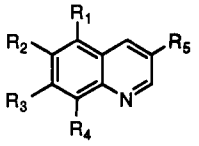
Results and Discussion

It became obvious early in our studies that the placement of certain substituents in the quinoline 8-position was deleterious to PDGF-RTK inhibitory activity as can be seen from the comparison of **2a** and **2b**. A very similar result was observed with the 3-(indol-3-yl)quinolines **2c** and **2d** (see Table 1), which were also conceptually derived from a nonselective (EGF/PDGF-RTK) 2,3-diarylacrylonitrile-based inhibitor (RG13291)[23] analogous to **1**. This point was further supported by comparing the effect of varying methyl substitution on the quinoline ring. The 5,7-dimethylquinoline **15y** is a very potent inhibitor; however, movement of one of the methyl groups from the 7- to the 8-position (**15p**) results in a dramatic loss of activity. In addition, the presence of the quinoline nitrogen was found to be essential for activity in the series as was illustrated by the lack of activity ($IC_{50} > 50\ \mu M$) associated with the naphthalene analogue[24] of **2e**.

It also became clear that changes in the quinoline 3-aromatic group had a marked effect on potency. Replacement of the pyridine of **2a** with phenyl (**2f**) improved activity somewhat while replacement with a thiophene-3-yl group (**2e**) had a dramatic effect by decreasing the IC_{50} to 1–20 nM. The importance of the lipophilic or aromatic group attached to the quinoline 3-position can be seen by noting the absence of activity observed in compounds where such groups are lacking. For example, the 3-nitro-, 3-amino-, and 3-hydroxyquinolines **7a**, **8a**, and **9a** were inactive. We also tested the parent 6,7-dimethoxyquinoline[25] (**21**) and found it to lack inhibitory activity. When **8a** or **9a** were benzylated (i.e., compounds **19** and **20**), activity was restored such that <100 nM IC_{50} values were obtained. The addition of a methoxy group to the pyridine of **2a** (**15o**) increased potency by ca. 10-fold, and similar activity was observed with the related pyridone **23**. Minor changes to the thiophene of **2e** also influenced potency. Comparison of the 3-(thiophene-2-yl)quinoline compound **15l** with **2e** reveals a weakening effect on the IC_{50} value. The 5-chlorothiophene-2-yl compound **15f** was ca. 10-fold more active than the analogous 5-methoxy compound **17e**. Movement of the thiophene 5-chloro substituent of **15f** to the 3-position (**15g**) reduced activity by 100-fold.

Substituent changes to the phenyl ring of **2f** significantly varied inhibitory potency. The 4-methoxyphenyl compound **15d** was at least 10-fold more active than **2f**, and addition of an *o*-fluoro substituent (**17m**) produced a compound of comparable potency. Methoxy substitution in either the 2- or 3-phenyl positions (**17c** and **15h**) resulted in much less active compounds relative to **15d**. Both the 3-fluorophenyl and the 4-fluorophenyl compounds **17b** and **17a** were potent inhibitors. Relative to the parent **2f**, it

Table 1

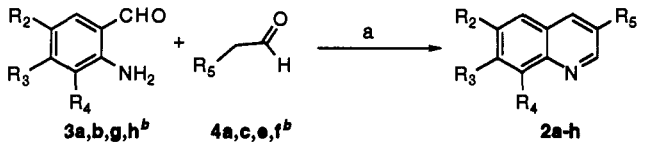


no.	R_1	R_2	R_3	R_4	R_5	method	% yield[a]	IC_{50} (μM)[b]
2a	H	OCH_3	OCH_3	H	3-pyridyl	A	79	0.1–0.8
2b	H	H	OCH_3	OCH_3	3-pyridyl	A	62	>50
2c	H	OCH_3	OCH_3	H	3-indolyl	A	23	0.1–0.6
2d	H	H	OCH_3	OCH_3	3-indolyl	A	14	>50
2e	H	OCH_3	OCH_3	H	3-thienyl	A	75	0.001–0.02
2f	H	OCH_3	OCH_3	H	C_6H_5	A	61	0.07–0.15
2g	H	H	H	H	3-indolyl	A	32	2–8
2h	H	OCH_3	H	H	3-thienyl	A	63	0.05–0.07
7a	H	OCH_3	OCH_3	H	NO_2	*c*	–	>50
8a	H	OCH_3	OCH_3	H	NH_2	*c*	–	>50
9a	H	OCH_3	OCH_3	H	OH	*c*	–	≥20
15a	H	OCH_3	OCH_3	H	2-naphthyl	D	62	≥20
15b	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}C_6H_5)$	D	66	>50
15c	H	OCH_3	OCH_3	H	$C_6H_3(3,4\text{-}Cl_2)$	D	83	1–7
15d	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}OCH_3)$	D	74	0.001–0.015
15e	H	OCH_3	OCH_3	H	*trans*-β-styryl	D	91	0.001–0.005
15f	H	OCH_3	OCH_3	H	2-thienyl(5-Cl)	D	56	0.007–0.03
15g	H	OCH_3	OCH_3	H	2-thienyl(3-Cl)	D	68	1
15h	H	OCH_3	OCH_3	H	$C_6H_4(3\text{-}OCH_3)$	D	91	1–2
15i	H	OCH_3	OCH_3	H	$C_6H_2[3,4,5\text{-}(OCH_3)_3]$	D	51	>50
15j	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}NO_2)$	D	97	0.07–0.15
15k	H	OCH_3	OCH_3	H	$C_6H_3(3\text{-}NO_2,4\text{-}OCH_3)$	D	99	0.15–0.5
15l	H	OCH_3	OCH_3	H	2-thienyl	D	82	0.04–0.08
15m	H	OCH_3	OCH_3	H	$C_6H_3(3,4\text{-}F_2)$	D	90	0.09–0.2
15n	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}CO_2Et)$	D	93	0.1–0.2
15o	H	OCH_3	OCH_3	H	3-pyridyl(6-OCH_3)	D	86	0.008–0.07
15p	CH_3	H	H	CH_3	3-thienyl	D	86	>50
15q	H	F	F	H	3-thienyl	D	86	2–4
15r	H	Cl	Cl	H	3-thienyl	D	75	1–2
15s	H	H	OCH_3	H	3-thienyl	D	99	0.002–0.06
15t	H	$-OCH_2O-$		H	3-thienyl	D	34	0.2–0.6
15u	OCH_3	H	OCH_3	H	3-thienyl	D	86	0.025–0.03
15v	F	H	H	H	3-thienyl	D	92	0.02
15w	H	H	F	H	3-thienyl	D	92	0.004–0.025
15x	H	H	H	H	3-thienyl	D	74	0.2–0.25
15y	CH_3	H	CH_3	H	3-thienyl	D	80	0.001–0.005
15z	H	H	H	H	*trans*-β-styryl	D	33	0.1–0.2
17a	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}F)$	E	99	0.035–0.06
17b	H	OCH_3	OCH_3	H	$C_6H_4(3\text{-}F)$	E	65	0.015–0.025
17c	H	OCH_3	OCH_3	H	$C_6H_4(2\text{-}OCH_3)$	E	90	2
17d	H	OCH_3	OCH_3	H	$C_6H_4[4\text{-}N(CH_3)_2]$	E	91	10
17e	H	OCH_3	OCH_3	H	2-thienyl(5-OCH_3)	E	81	0.1–0.25
17f	H	OCH_3	OCH_3	H	$C_6H_3[2,4\text{-}(OCH_3)_2]$	E	99	>50
17g	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}OCH_2C_6H_5)$	E	75	>30
17h	H	OCH_3	OCH_3	H	*trans*-β-styryl(4-OCH_3)	E	65	0.03–0.1
17i	H	OCH_3	OCH_3	H	$C_6H_3(3\text{-}CH_3,4\text{-}OCH_3)$	E	36	0.1–0.4
17j	H	OCH_3	OCH_3	H	$C_6H_3[3,4\text{-}(OCH_3)_2]$	E	93	2–10
17k	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}CH_3)$	E	92	0.5–2
17l	H	OCH_3	OCH_3	H	$C_6H_2(3,5\text{-}F_2,4\text{-}OCH_3)$	E	99	0.2–0.4
17m	H	OCH_3	OCH_3	H	$C_6H_3(3\text{-}F,4\text{-}OCH_3)$	E	34	0.003–0.005
17n	H	OCH_3	OCH_3	H	1-cyclopentenyl	E	62	0.02–0.04
17o	H	OCH_3	OCH_3	H	ethynyl(2-C_6H_5)	E	99	0.05–0.02
17p	H	OCH_3	OCH_3	H	ethynyl(2-cyclohexyl)	E	99	0.3–1
18	H	OH	OH	H	3-pyridyl	*d*	98	6–10
19	H	OCH_3	OCH_3	H	$NHCH_2C_6H_5$	*e*	91	0.02–0.08
20	H	OCH_3	OCH_3	H	$OCH_2C_6H_5$	*f*	76	0.04–0.07
21	H	OCH_3	OCH_3	H	H	*g*	76	20–30
22	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}CO_2H)$	*h*	75	0.7–5
23	H	OCH_3	OCH_3	H	5-pyridin-2(1*H*)-one	*i*	55	0.015–0.03
24	H	OCH_3	OCH_3	H	$C_6H_4(4\text{-}OH)$	*j1*	80	0.02–0.03
25	H	OCH_3	OCH_3	H	ethyl[2-$C_6H_4(4\text{-}OCH_3)$]	*j2*	99	0.2–0.8
26	H	OCH_3	OCH_3	H	ethyl(2-cyclohexyl)	*j3*	68	0.3–0.5
27	H	OCH_3	OCH_3	H	cyclopentyl	*j4*	92	0.1–0.5

[a] Indicates unoptimized isolated yields. [b] Concentration of compound required to inhibit phosphorylation of isolated human PDGF receptor by 50% (minimum of two dose–response assays). For a detailed description of the assay see the Experimental Section. [c] Refer to Scheme 2 and ref 18. [d] By reaction of refluxing 48% aqueous HBr with **2a**. [e] By reaction of benzaldehyde with **8a** and $NaCNBH_3$. [f] By reaction of benzyl bromide with **9a** and sodium hydride. [g] By Skraup reaction with **5a**, ref 25. [h] By reaction of NaOH/EtOH with **15n**. [i] By reaction of pyridine–HCl at 160 °C, 5 min with **15o**. [j] By reaction of H_2, Pd/C with: [1]**17g**; [2]**17h**; [3]**17p**; [4]**17n**.

appears that optimum activity can be obtained by introducing methoxy (**15d**), hydroxy (**24**), or fluoro (**17a**) substituents at the 4-position of the phenyl ring. Substitution of the phenyl ring at the 4-position with either

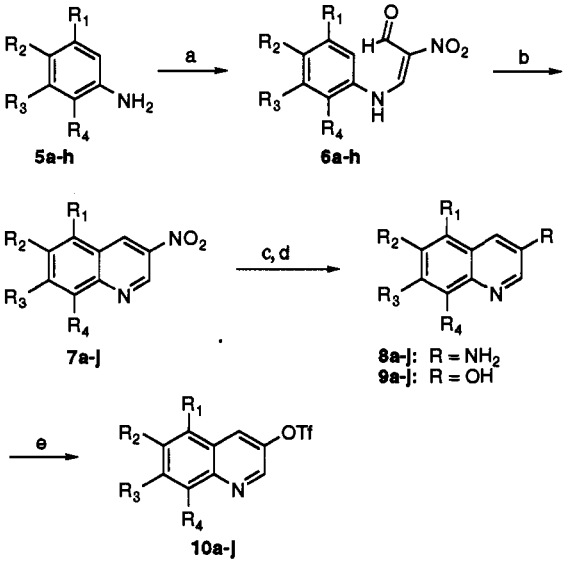
Scheme 1. Method A[a]



3a,b,g,h[b] **4a,c,e,f**[b] **2a-h**

[a] Key: (a) EtOH, dilute aqueous NaOH. [b] R_2–R_5 substituents analogous to derivatives of **2**, Table 1.

Scheme 2 [a]

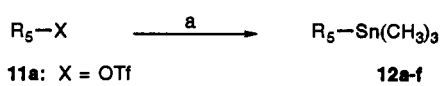


5a-h **6a-h** **7a-j** **8a-j**: R = NH_2 **9a-j**: R = OH **10a-j**

analog	R_1	R_2	R_3	R_4	%yield[b]
a	H	OCH_3	OCH_3	H	19
b	CH_3	H	H	CH_3	18
c	H	F	F	H	4
d	H	Cl	Cl	H	1
e	H	H	OCH_3	H	31
f	CH3	H	CH3	H	18
g	OCH_3	H	OCH_3	H	30
h	F	H	H	H	1
i	H	H	F	H	11
j	H	O-CH_2-O		H	c

[a] Key: (a) Sodium nitromalonaldehyde, EtOH, H_2O; (b) PPA, 160 °C; (c) H_2, Pd/C; (d) $NaNO_2$, HCl; (e) Tf_2O, pyridine, CH_2Cl_2. [b] Unoptimized overall yield of **9a-i** from **5a-h**. [c] See ref 19.

Scheme 3. Method B[a]



11a: X = OTf **11b-f**: X = Br **12a-f**

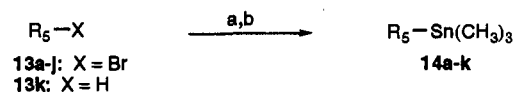
analog	R_5	%yield
a	C_6H_2[3,4,5-$(OCH_3)_3$]	67
b	C_6H_4(4-NO_2)	26
c	C_6H_3(3-NO_2,4-OCH_3)	50
d	C_6H_3(3,4-F_2)	99
e	C_6H_4(4-CO_2Et)	89
f	3-pyridyl(6-OCH_3)	66

[a] Key: (a) $[(CH_3)_3Sn]_2$, $Pd(PPh_3)_4$, dioxane, LiCl for **11a**; $[(CH_3)_3Sn]_2$, $Pd(PPh_3)_4$, toluene for **11b-f**.

a nitro (**15j**) or ethoxycarbonyl (**15n**) group gave compounds ca. equipotent to **2f** while the 4-methyl (**17k**), 4-carboxy (**22**), and 4-dimethylamino (**17d**) compounds were less active.

The size and shape of the 3-substituent can also substantially influence the degree of inhibition. The naphthylquinoline **15a**, the biphenylylquinoline **15b**, and the [(benzyloxy)phenyl]quinoline **17g** had no appreciable

Scheme 4. Method C[a]

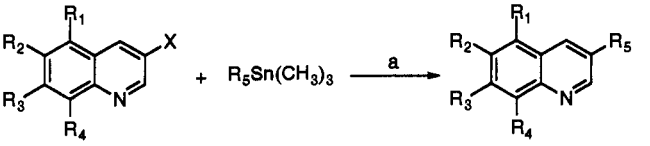


13a-j: X = Br **13k**: X = H **14a-k**

analog	R_5	%yield	analog	R_5	%yield
a	2-naphthyl	99	g	2-thienyl(3-Cl)	93
b	C_6H_4(4-C_6H_5)	99	h	C_6H_4(3-OCH_3)	90
c	C_6H_3(3,4-Cl_2)	90	i	(*trans*)-β-styryl	51
d	C_6H_4(4-OCH_3)	82	j	3-thienyl	97
e	3-quinolyl	50	k	2-thienyl	56
f	2-thienyl(5-Cl)	73			

[a] Key: (a) *t*-BuLi 220 M% −78 °C, Et_2O for **13a-h**; *t*-BuLi 200 M%, −115 °C for **13i** (ref 29); *n*-BuLi 100 M%, −78 °C, Et_2O for **13j**; *n*-BuLi 120 M%, 22 °C, Et_2O for **13k**; (b) $(CH_3)_3SnCl$.

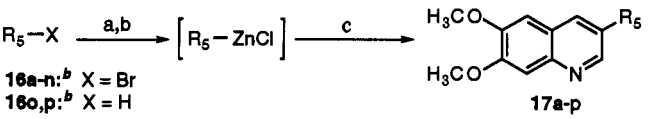
Scheme 5. Method D[a]



10a-j: X = OTf **13e**: X = Br **12a-f** **14a-k** **15a-y** **15z**[b]

[a] Key: (a) $Pd(PPh_3)_4$, dioxane, LiCl for **10a-j**; $Pd(PPh_3)_4$, DMF for **13e** and **14e**. [b] Reaction of **14e** with *trans*-β-bromostyrene (**13i**).

Scheme 6. Method E[a]



16a-n:[b] X = Br **16o,p**:[b] X = H **17a-p**

[a] Key: (a) *t*-BuLi 210 M%, −78 °C for **16a-n**; *n*-BuLi 100 M%, −78 °C for **16o,p**; (b) $ZnCl_2$, Et_2O; (c) $Pd(PPh_3)_4$, dioxane, **10a**. [b] R_5 substituent analogous to derivatives of **17**, Table 1.

inhibitory effect. Placement of a styryl group in the quinoline 3-position (**15e**), however, resulted in one of the most potent inhibitors synthesized. This observation is interesting in light of the comparison of **15a** with **15e**. The naphthalene group of **15a** can be viewed as a ring-constrained version of the styryl group of **15e**. The electronic and/or steric variation imposed by this conformational restriction produces a dramatic decrease in potency.

The contribution to activity of the 6,7-dimethoxy groups can be seen clearly by comparison of **2c**, **2e**, and **15e** with their 6,7-unsubstituted quinoline counterparts **2g**, **15x**, and **15z**. Most of the activity was retained when only one of the two methoxy groups of **2e** is removed (i.e., **2h** and **15s**). Constraining the 6,7-dimethoxy groups in the form of a methylenedioxy unit (i.e., **15t**) substantially reduced inhibitory potency. Conversion of **2a** to its 6,7-dihydroxy analogue **18** also resulted in a significant reduction in PDGF-RTK inhibition. Unlike **2a**, compound **18** displayed inhibition of EGF-RTK (IC_{50} = 0.5–2 μM). This was not unexpected as it is known that compounds containing ortho or para hydroquinone/quinone functionality frequently inhibit EGF-RTK.[26] With the exception of **15n**, **15q**, **15v**, and **22**, which were not tested, all the remaining compounds in Table 1 had EGF-RTK $IC_{50's}$ of >20 μM. Compounds **2e**, **15d**, and **15u** were also tested for inhibition of protein kinase A[27] and found to be inactive ($IC_{50's}$ > 200 μM).

Several quinoline derivatives were prepared in which the 3-substituent was held constant in the form of 3-thienyl and the 5-, 6-, and 7-substituents were varied (**15p-y**).

The 6,7-dimethoxy groups of **2e** can also be replaced with 5,7-dimethoxy groups (**15u**) without loss of activity. Replacement of methoxy with methyl (**15y**) is also acceptable. The 5- and 7-monofluoro compounds **15v** and **15w** had activities comparable to their 6,7-dimethoxy counterpart **2e**, but the 6,7-difluoro analogue **15q** was significantly less active.

The tyrosine kinase inhibition realized by placing substituents in the quinoline 3-position is not limited to aryl groups. As can be seen in Table 1, certain alkynyl, alkenyl, and alkyl groups are also well-tolerated. Of particular note in this regard is the strong inhibition observed with the 3-cyclopentenyl compound **17n**.

Summary

A new inhibitor (**2a**) of cell-free PDGF-RTK with selectivity versus EGF-RTK was identified by imposing a conformational restriction on the diarylacrylonitrile **1**. Although **2a** is a valence bond isomer of **1**, it differs considerably in terms of electronics, polarity, and shape. From **2a**, a series of potent inhibitors of PDGF-RTK was developed.[28] Construction of the series relied heavily on the use of palladium-catalyzed organostannane or organozinc chloride coupling reactions. These compounds are characterized by a lipophilic appendage attached to the quinoline 3-position. The appendage consisted of a variety of substituted aryl, alkynyl, alkenyl, or alkyl groups. Maximum activity was observed when the 3-substituent was 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 4-hydroxyphenyl, 6-methoxypyridin-3-yl, 5-pyridin-2(1*H*)-one, *trans*-β-styryl, thiophene-3-yl, 5-chlorothiophene-2-yl, or cyclopentenyl. Activity was particularly enhanced by the presence of 6,7-dimethoxy or 5,7-dimethyl functionality on the quinoline ring. Substitution at the quinoline 8-position abolished inhibitory activity. Structure–activity relationships were also determined for other substituted quinolines and quinoline related heterocycles and will be reported in future disclosures. The compounds are presently being evaluated in intact-cell mitogenesis assays as well as in animal models of fibroproliferative disorders associated with abnormal activation of PDGF receptors.

Experimental Section

Melting points were determined in open-ended capillaries on a Thomas-Hoover apparatus and are uncorrected. Recrystallization solvents are reported in parentheses following melting points. Combustion analyses were obtained on a Perkin-Elmer 2400 CHN elemental analyzer and are within ±0.40% of theoretical values unless otherwise indicated. Analyses obtained for all of the compounds reported are for CHN. All reported NMR data is for ^{1}H NMR at 300 MHz and was obtained on either a Bruker ACF-300 or a Bruker ARX-300 instrument. ^{1}H NMR chemical shifts are reported in δ (ppm) downfield of the TMS internal standard calibrated at 0.00 ppm. Column chromatography was conducted on EM 60 silica gel, particle size 0.040–0.063 mm, 230–400 mesh. Anhydrous solvents were used in the palladium coupling reactions and were purchased from Aldrich and used directly. All coupling reactions were conducted under nitrogen or argon. IUPAC nomenclature was generated by AUTONOM Version 1.0.

Method A. 6,7-Dimethoxy-3-thiophene-3-ylquinoline, 2e. A solution of 12.0 g (66.3 mmol) of **3a** in 80 mL of ethanol and 5 mL of aqueous 1 M NaOH was heated to 65 °C under nitrogen. To this was added, dropwise, 14.8 g (117 mmol) of freshly prepared neat **4e** (prepared by DIBAL/toluene reduction of the methyl ester at −78 °C and chromatography eluting with 9:1 pentane/ether) over a 40-min period via syringe. The solution was heated for an additional 20 min, concentrated to 1/3 volume on the rotovap, and partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The aqueous layer was back extracted with CH_2Cl_2 (3 × 30 mL), the combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$), and evaporated, and the residue was chromatographed on silica gel (eluting with 7:3 hexane/EtOAc) to give 11.83 g of pure (by NMR) **2e**. Additionally, 1.40 g of unreacted **3a** was obtained along with ca. 2.0 g of impure **2e**. The impure **2e** was suspended in 100 mL of 15% aqueous H_3PO_4 and the suspension washed with ether (100 mL). The aqueous suspension was then made basic with concentrated NH_4OH and extracted with CH_2Cl_2 (100 mL). The organic extract was dried ($MgSO_4$) and evaporated and the residue chromatographed as before to give an additional 1.59 g of pure **2e** (75% total yield of **2e**; 85% based on recovered **3a**): mp 116–118 °C (hexane/EtOAc); NMR ($CDCl_3$) 4.03 (s, 3 H), 4.05 (s, 3 H), 7.07 (s, 1 H), 7.42 (s, 1 H), 7.49 (m, 2 H), 7.59 (dd, 1 H, J = 1.6, 2.8 Hz), 8.14 (d, 1 H, J = 2.2 Hz), 9.00 (d, 1 H, J = 2.2 Hz). Anal. ($C_{15}H_{13}NO_2S$).

Compounds **2a–h** were similarly prepared by method A. Arylacetaldehydes **4c**, **4e**, and **4f** were added neat or in ethanol solution. Pyridine-3-acetaldehyde (**4a**) was used directly by basification (with 50% aqueous NaOH) of the acidic solution from which it was prepared[12] after addition of ethanol and either **3a** or **3b**.

Method B. 1,2-Difluoro-4-(trimethylstannanyl)benzene 12d. To a solution of 1.00 g (5.18 mmol) of 1-bromo-3,4-difluorobenzene (**11d**) and 1.70 g (5.18 mmol) of hexamethylditin in 20 mL of toluene was added 300 mg (0.259 mmol) of $Pd(PPh_3)_4$. The reaction was heated to 90 °C under argon for 9 h at which time the solution turned black. The mixture was partitioned between 10% NH_4OH (90 mL) and ether (100 mL) and stirred for 15 min. The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (eluting with hexane) to give 1.42 g (99%) of **12d** as a colorless liquid which was used directly in the next step without further characterization. TLC R_f = 0.69 (hexane).

Method C. 1-Methoxy-3-(trimethylstannyl)benzene, 14h. A solution of 1.50 g (8.02 mmol) of 3-bromoanisole (**13h**) in 30 mL of ether was cooled under argon to −78 °C, and 10.4 mL (17.6 mmol) of *t*-BuLi, 1.7 M in pentane, was added dropwise via syringe. The solution was stirred at −78 °C for 15 min, and 3.80 mL (10.3 mmol) of trimethyltin chloride, 2.71 M in dioxane, was injected. The mixture was then warmed to 22 °C, stirred for 45 min, quenched with 5 mL of methanol, partitioned between 10% NH_4OH (90 mL) and ether (100 mL), and stirred for 15 min. The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (eluting with hexane) to give 1.96 g (90%) of **14h** as a colorless liquid which was used directly in the next step without further characterization. TLC R_f = 0.48 (hexane).

Method D. 6,7-Dimethoxy-3-(3-methoxyphenyl)quinoline, 15h. A solution of 300 mg (0.888 mmol) of **10a**, 313 mg (115 mmol) of **14h**, 113 mg (2.66 mmol) of anhydrous LiCl, and 50 mg (0.043 mmol) of $Pd(PPh_3)_4$ in 15 mL of dioxane was refluxed under argon for 16 h. The mixture was partitioned between 10% NH_4OH (60 mL) and CH_2Cl_2 (100 mL) and stirred for 30 min. The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (eluting with 7:3 hexane/EtOAc) to give 237 mg (91%) of **15h**: mp 122.5–124 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.91 (s, 3H), 4.05 (s, 3 H), 4.06 (s, 3 H), 6.97 (dd, 1 H, J = 1.8, 6.0 Hz), 7.11 (s, 1 H), 7.22 (apparent t, 1 H, J = 1.8 Hz), 7.29 (s, 1 H), 7.43 (m, 2 H), 8.16 (d, 1 H, J = 2.1 Hz), 8.98 (d, 1 H, J = 2.1 Hz). Anal. ($C_{13}H_{17}NO_3$).

Method E. 3-(3-Fluorophenyl)-6,7-dimethoxyquinoline, 17b. A solution of 400 mg (2.29 mmol) of 1-bromo-3-fluorobenzene (**16b**) in 6 mL of THF under nitrogen was cooled to −78 °C, and 2.83 mL (4.81 mmol) of *t*-BuLi, 1.7 M in pentane, was added dropwise. The solution was stirred for 10 min, and 2.52 mL (2.52 mmol) of $ZnCl_2$, 1.0 M in ether, was injected. The solution was then allowed to warm to 22 °C and stirred for 1 h at which time a second solution of 300 mg (0.890 mmol) of **10a** and 51 mg (0.044 mmol) of $Pd(PPh_3)_4$ in 4 mL of THF was injected via canula. The reaction mixture was heated to a gentle reflux for 2 h and then partitioned between 60 mL of NH_4OH and 100 mL of CH_2Cl_2.

After stirring for 15 min the organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (eluting with $CHCl_3$) to give 218 mg (65%) of **17b**: mp 156–158 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.05 (s, 3 H), 4.07 (s, 3 H), 7.11 (m, 2 H), 7.37–7.50 (m, 4 H), 8.15 (d, 1 H, J = 2.1 Hz), 8.95 (d, 1 H, J = 2.1 Hz). Anal. ($C_{17}H_{14}NO_2F$).

6,7-Dimethoxy-3-pyridin-3-ylquinoline, 2a, was obtained from **3a** and **4a** by method A: mp 131–132 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.05 (s, 3 H), 4.07 (s, 3 H), 7.13 (s, 1 H), 7.44 (m, 1 H), 7.46 (s, 1 H), 7.99 (m, 1 H), 8.18 (d, 1 H, J = 2.2 Hz), 8.66 (br d, 1 H, J = 4.5 Hz), 8.95 (m, 2 H). Anal. ($C_{16}H_{14}N_2O_2$).

7,8-Dimethoxy-3-pyridin-3-ylquinoline, 2b, was obtained from **3b** and **4a** by method A: mp 158–159 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.06 (s, 3 H), 4.13 (s, 3 H), 7.43 (d, 1 H, J = 9.0 Hz), 7.44 (m, 1 H), 7.66 (d, 1 H, J = 9.0 Hz), 7.99 (m, 1 H), 8.27 (d, 1 H, J = 2.2 Hz), 8.67 (br d, 1 H, J = 4.3 Hz), 8.96 (br s, 1 H), 9.16 (d, 1 H, J = 2.2 Hz). Anal. ($C_{16}H_{14}N_2O_2$).

3-(1*H*-Indol-3-yl)-6,7-dimethoxyquinoline, 2c, was obtained from **3a** and **4c** by method A: mp 204–205 °C (EtOAc); NMR ($CDCl_3$) δ 4.05 (s, 6 H), 7.11 (s, 1 H), 7.28 (m, 2 H), 7.48 (m, 3 H), 8.01 (br d, 1 H, J = 7.4 Hz), 8.27 (d, 1 H, J = 2.0 Hz), 8.77 (br s, 1 H), 9.06 (d, 1 H, J = 2.0 Hz). Anal. ($C_{19}H_{16}N_2O_2$).

3-(1*H*-Indol-3-yl)-7,8-dimethoxyquinoline, 2d, was obtained from **3b** and **4c** by method A: mp 254–255 °C (ethanol); NMR ($CDCl_3$) δ 4.06 (s, 3 H), 4.18 (s, 3 H), 7.27 (m, 2 H), 7.39 (d, 1 H, J = 9.0 Hz), 7.49–7.56 (m, 2 H), 7.63 (d, 1 H, J = 9.0 Hz), 7.99 (br d, 1 H, J = 7.4 Hz), 8.35 (d, 1 H, J = 2.2 Hz), 8.64 (br s, 1 H), 9.28 (d, 1 H, J = 2.2 Hz). Anal. ($C_{19}H_{16}N_2O_2$).

6,7-Dimethoxy-3-phenylquinoline, 2f, was obtained from **3a** and **4f** by method A: mp 126.5–128 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.04 (s, 3 H), 4.06 (s, 3 H), 7.11 (s, 1 H), 7.48 (m, 4 H), 7.70 (m, 2 H), 8.16 (d, 1 H, J = 2.2 Hz), 8.98 (d, 1 H, J = 2.2 Hz). Anal. ($C_{17}H_{15}NO_2$).

3-(1*H*-Indol-3-yl)quinoline, 2g, was obtained from **3g** and **4c** by method A: mp 173–175 °C (hexane/EtOAc then hexane/ethanol); NMR ($CDCl_3$) δ 7.22–7.36 (m, 2 H), 7.47–7.61 (m, 3 H), 7.69 (m, 1 H), 7.88 (m, 1 H), 8.02 (m, 1 H), 8.14 (br d, 1 H, J = 8.3 Hz), 8.42 (d, 1 H, J = 2.2 Hz), 8.62 (br s, 1 H), 9.26 (d, 1 H, J = 2.2 Hz). Anal. ($C_{17}H_{12}N_2 \cdot 0.15H_2O$).

6-Methoxy-3-thiophene-3-ylquinoline, 2h, was obtained from **3h** and **4e** by method A: mp 126–128 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.95 (s, 3 H), 7.10 (d, 1 H, J = 2.7 Hz), 7.35 (dd, 1 H, J = 2.8, 9.1 Hz), 7.50 (m, 2 H), 7.64 (dd, 1 H, J = 1.4, 2.8 Hz), 8.00 (d, 1 H, J = 9.2 Hz), 8.18 (d, 1 H, J = 2.1 Hz), 9.04 (d, 1 H, J = 2.1 Hz). Anal. ($C_{14}H_{11}NOS$).

6,7-Dimethoxy-3-naphth-2-ylquinoline, 15a, was obtained from **10a** and **14a** by method D: mp 162.5–165 °C (hexane/CH_2Cl_2); NMR ($CDCl_3$) δ 4.06 (s, 3 H), 4.07 (s, 3 H), 7.15 (s, 1 H), 7.51 (m, 3 H), 7.82–8.00 (m, 4 H), 8.15 (s, 1 H), 8.29 (s, 1 H), 9.11 (s, 1 H). Anal. ($C_{21}H_{17}NO_2$).

3-Biphenyl-4-yl-6,7-dimethoxyquinoline, 15b, was obtained from **10a** and **14b** by method D: mp 143–145 °C (Et_2O); NMR ($CDCl_3$) δ 4.06 (s, 3 H), 4.07 (s, 3 H), 7.13 (s, 1 H), 7.39 (d, 1 H, J = 7.2 Hz), 7.48 (m, 2 H), 7.51 (s, 1 H), 7.67 (d, 2 H, J = 7.2 Hz), 7.77 (m, 4 H), 8.22 (d, 1 H, J = 2.0 Hz), 9.04 (d, 1 H, J = 2.0 Hz). Anal. ($C_{23}H_{19}NO_2 \cdot 0.9H_2O$).

3-(3,4-Dichlorophenyl)-6,7-dimethoxyquinoline, 15c, was obtained from **10a** and **14c** by method D: mp 184–186 °C (EtOAc); NMR ($CDCl_3$) δ 4.05 (s, 3 H), 4.07 (s, 3 H), 7.11 (s, 1 H), 7.46 (s, 1 H), 7.52 (dd, 1 H, J = 2.0, 8.6 Hz), 7.58 (d, 1 H, J = 8.6 Hz), 7.77 (d, 1 H, J = 2.0 Hz), 8.14 (d, 1 H, J = 2.2 Hz), 8.91 (d, 1 H, J = 2.2 Hz). Anal. ($C_{17}H_{13}NO_2Cl_2$).

6,7-Dimethoxy-3-(4-methoxyphenyl)quinoline, 15d, was obtained from **10a** and **14d** by method D: mp 162.5–164.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.87 (s, 3 H), 4.03 (s, 3 H), 4.05 (s, 3 H), 7.04 (d, 2 H, J = 8.6 Hz), 7.08 (s, 1 H), 7.43 (s, 1 H), 7.62 (d, 2 H, J = 8.6 Hz), 8.09 (d, 1 H, J = 2.2 Hz), 8.95 (d, 1 H, J = 2.2 Hz). Anal. ($C_{18}H_{17}NO_3$).

6,7-Dimethoxy-3-*trans*-β-styrylquinoline, 15e, was obtained from **10a** and **14i** by method D: mp 104–105.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.03 (s, 3 H), 4.05 (s, 3 H), 7.06 (s, 1 H), 7.24 (d, 2 H, J = 7.3 Hz), 7.30 (m, 1 H), 7.37 (m, 3 H), 7.57 (d, 2 H, J = 7.3 Hz), 8.06 (d, 1 H, J = 2.0 Hz), 8.91 (d, 1 H, J = 2.0 Hz). Anal. ($C_{19}H_{17}NO_2$).

3-(5-Chlorothiophene-2-yl)-6,7-dimethoxyquinoline, 15f, was obtained from **10a** and **14f** by method D: mp 131.5–132.5 °C (hexane/EtOAc then methanol); NMR ($CDCl_3$) δ 4.04 (s, 3 H), 4.05 (s, 3 H), 6.96 (d, 1 H, J = 4.0 Hz), 7.06 (s, 1 H), 7.20 (d, 1 H, J = 4.0 Hz), 7.41 (s, 1 H), 8.03 (d, 1 H, J = 2.2 Hz), 8.90 (d, 1 H, J = 2.2 Hz). Anal. ($C_{15}H_{12}NO_2SCl$).

3-(3-Chlorothiophene-2-yl)-6,7-dimethoxyquinoline, 15g, was obtained from **10a** and **14g** by method D: mp 168–170 °C (hexane/EtOAc then methanol); NMR ($CDCl_3$) δ 4.03 (s, 3 H), 4.06 (s, 3 H), 7.06 (d, 1 H, J = 5.3 Hz), 7.09 (s, 1 H), 7.34 (d, 1 H, J = 5.3 Hz), 7.44 (s, 1 H), 8.28 (d, 1 H, J = 2.2 Hz), 8.98 (d, 1 H, J = 2.2 Hz). Anal. ($C_{15}H_{12}NO_2SCl$).

6,7-Dimethoxy-3-(3,4,5-trimethoxyphenyl)quinoline, 15i, was obtained from **10a** and **12a** by method D: mp 153–155 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.93 (s, 3 H), 3.97 (s, 6 H), 4.05 (s, 3 H), 4.07 (s, 3 H), 6.89 (s, 2 H), 7.12 (s, 1 H), 7.46 (s, 1 H), 8.13 (s, 1 H), 8.95 (s, 1 H). Anal. ($C_{20}H_{21}NO_5$).

6,7-Dimethoxy-3-(4-nitrophenyl)quinoline, 15j, was obtained from **10a** and **12b** by method D: mp 222–223.5 °C (EtOAc); NMR ($CDCl_3$) δ 4.06 (s, 3 H), 4.08 (s, 3 H), 7.15 (s, 1 H), 7.48 (s, 1 H), 7.86 (d, 2 H, J = 8.7 Hz), 8.24 (d, 1 H, J = 2.1 Hz), 8.38 (d, 2 H, J = 8.7 Hz), 9.00 (br s, 1 H). Anal. ($C_{17}H_{14}N_2O_4 \cdot 0.25H_2O$).

6,7-Dimethoxy-3-(4-methoxy-3-nitrophenyl)quinoline, 15k, was obtained from **10a** and **12c** by method D: mp 185–187 °C (EtOAc); NMR ($CDCl_3$) δ 4.04 (s, 3 H), 4.05 (s, 3 H), 4.07 (s, 3 H), 7.12 (s, 1 H), 7.26 (d, 1 H, J = 8.8 Hz), 7.46 (s, 1 H), 7.88 (dd, 1 H, J = 2.4, 8.8 Hz), 8.15 (d, 1 H, J = 2.2 Hz), 8.19 (d, 1 H, J = 2.4 Hz), 8.93 (br s, 1 H). Anal. Calcd for $C_{18}H_{16}N_2O_5 \cdot 0.25H_2O$: C, 62.69; H, 4.82; N, 8.12. Found: C, 62.74; H, 4.85; N, 7.32.

6,7-Dimethoxy-3-thiophene-2-ylquinoline, 15l, was obtained from **10a** and **14k** by method D: mp 122.5–124 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.02 (s, 3 H), 4.04 (s, 3 H), 7.06 (s, 1 H), 7.14 (dd, 1 H, J = 3.7, 5.1 Hz), 7.36 (br d, 1 H, J = 5.1 Hz), 7.41 (s, 1 H), 7.43 (br d, 1 H, J = 3.7 Hz), 8.13 (d, 1 H, J = 2.2 Hz), 9.00 (d, 1 H, J = 2.2 Hz). Anal. ($C_{15}H_{13}NO_2S$).

3-(3,4-Difluorophenyl)-6,7-dimethoxyquinoline, 15m, was obtained from **10a** and **12d** by method D: mp 147–149 °C (EtOAc); NMR ($CDCl_3$) δ 4.05 (s, 3 H), 4.07 (s, 3 H), 7.11 (s, 1 H), 7.40 (m, 4 H), 8.11 (s, 1 H), 8.90 (d, 1 H, J = 1.9 Hz). Anal. ($C_{17}H_{13}NO_2F_2$).

4-(6,7-Dimethoxyquinolin-3-yl)benzoic acid ethyl ester, 15n, was obtained from **10a** and **12e** by method D: mp 165–166 °C (EtOAc); NMR ($CDCl_3$) δ 1.44 (t, 3 H, J = 7.1 Hz), 4.05 (s, 3 H), 4.07 (s, 3 H), 4.42 (q, 2 H, J = 7.1 Hz), 7.13 (s, 1 H), 7.47 (s, 1 H), 7.77 (d, 2 H, J = 8.3 Hz), 8.19 (d, 2 H, J = 8.3 Hz), 8.22 (d, 1 H, J = 2.2 Hz), 9.00 (d, 1 H, J = 2.2 Hz). Anal. ($C_{20}H_{19}NO_4$).

6,7-Dimethoxy-3-(6-methoxypyridin-3-yl)quinoline, 15o, was obtained from **10a** and **12f** by method D: mp 170.5–171.5 °C (EtOAc); NMR ($CDCl_3$) δ 4.01 (s, 3 H), 4.05 (s, 3 H), 4.06 (s, 3 H), 6.89 (d, 1 H, J = 8.6 Hz), 7.10 (s, 1 H), 7.44 (s, 1 H), 7.88 (dd, 1 H, J = 2.6, 8.6 Hz), 8.09 (d, 1 H, J = 2.2 Hz), 8.49 (d, 1 H, J = 2.6 Hz), 8.91 (d, 1 H, J = 2.2 Hz). Anal. ($C_{17}H_{16}N_2O_3$).

5,8-Dimethyl-3-thiophene-3-ylquinoline, 15p, was obtained from **10b** and **14j** by method D: mp 109.5–111 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 2.69 (s, 3 H), 2.79 (s, 3 H), 7.28 (br d, 1 H, J = 7.0 Hz), 7.43 (br d, 1 H, J = 7.0 Hz), 7.50 (m, 1 H), 7.56 (m, 1 H), 7.66 (m, 1 H), 8.42 (d, 1 H, J = 2.1 Hz), 9.23 (d, 1 H, J = 2.1 Hz). Anal. ($C_{15}H_{13}NS$).

6,7-Difluoro-3-thiophene-3-ylquinoline, 15q, was obtained from **10c** and **14j** by method D: mp 141.5–143.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 7.26 (s, 1 H), 7.58 (m, 3 H), 7.86 (dd, 1 H, J = 7.9, 11.0 Hz), 8.22 (br s, 1 H), 9.16 (br s, 1 H). Anal. ($C_{13}H_7NSF_2$).

6,7-Dichloro-3-thiophene-3-ylquinoline, 15r, was obtained from **10d** and **14j** by method D: mp 167–167.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 7.50 (m, 2 H), 7.67 (apparent t, 1 H, J = 2.0 Hz), 7.95 (s, 1 H), 8.16 (d, 1 H, J = 2.0 Hz), 8.22 (s, 1 H), 9.19 (d, 1 H, J = 2.0 Hz). Anal. ($C_{13}H_7NSCl_2$).

7-Methoxy-3-thiophene-3-ylquinoline, 15s, was obtained from **10e** and **14j** by method D: mp 122–124 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.97 (s, 3 H), 7.22 (dd, 1 H, J = 2.4, 9.0 Hz), 7.43 (d, 1 H, J = 2.4 Hz), 7.49 (m, 2 H), 7.61 (m, 1 H), 7.73 (d, 1 H, J = 9.0 Hz), 8.21 (d, 1 H, J = 2.2 Hz), 9.12 (d, 1 H, J = 2.2 Hz). Anal. ($C_{14}H_{11}NOS$).

7-Thiophene-3-yl[1,3]dioxolo[4,5-*g*]quinoline, 15t, was obtained from **10j** and **14j** by method D: mp 159–160 °C (EtOAc); NMR ($CDCl_3$) δ 6.12 (s, 2 H), 7.08 (s, 1 H), 7.39 (s, 1 H), 7.48 (m,

2 H), 7.59 (m, 1 H), 8.10 (d, 1 H, J = 2.0 Hz), 8.98 (d, 1 H, J = 2.0 Hz). Anal. ($C_{14}H_9NO_2S$).

5,7-Dimethoxy-3-thiophene-3-ylquinoline, 15u, was obtained from **10g** and **14j** by method D: mp 113.5–115 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.96 (s, 3 H), 4.00 (s, 3 H), 6.54 (d, 1 H, J = 2.0 Hz), 7.03 (d, 1 H, J = 2.0 Hz), 7.46 (dd, 1 H, J = 2.9, 5.0 Hz), 7.52 (dd, 1 H, J = 1.3, 5.0 Hz), 7.61 (dd, 1 H, J = 1.3, 2.9 Hz), 8.59 (d, 1 H, J = 2.2 Hz), 9.09 (d, 1 H, J = 2.2 Hz). Anal. ($C_{15}H_{13}NO_2S$).

5-Fluoro-3-thiophene-3-ylquinoline, 15v, was obtained from **10h** and **14j** by method D: mp 87.5–89 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 7.22 (m, 1 H), 7.51 (m, 2 H), 7.59 (m, 1 H), 7.68 (m, 1 H), 7.90 (d, 1 H, J = 8.5 Hz), 8.50 (d, 1 H, J = 1.9 Hz), 9.22 (s, 1 H). Anal. ($C_{13}H_8NFS$).

7-Fluoro-3-thiophene-3-ylquinoline, 15w, was obtained from **10i** and **14j** by method D: mp 106.5–108.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 7.37 (m, 1 H), 7.51 (m, 2 H), 7.65 (m, 1 H), 7.75 (dd, 1 H, J = 2.4, 10.0 Hz), 7.86 (dd, 1 H, J = 6.0, 9.1 Hz), 8.28 (d, 1 H, J = 2.2 Hz), 9.21 (d, 1 H, J = 2.2 Hz). Anal. ($C_{13}H_8NSF$).

3-Thiophene-3-ylquinoline, 15x, was obtained from **13e** and **14j** by method D: mp 87–88.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 7.54 (m, 3 H), 7.70 (m, 2 H), 7.85 (d, 1 H, J = 8.2 Hz), 8.11 (d, 1 H, J = 8.2 Hz), 8.29 (d, 1 H, J = 2.1 Hz), 9.21 (d, 1 H, J = 2.1 Hz). Anal. ($C_{13}H_9NS$).

5,7-Dimethyl-3-thiophene-3-ylquinoline, 15y, was obtained from **10f** and **14j** by method D: mp 85–86 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 2.52 (s, 3 H), 2.69 (s, 3 H), 7.23 (s, 1 H), 7.47–7.54 (m, 2 H), 7.63 (m, 1 H), 7.74 (s, 1 H), 8.37 (m, 1 H), 9.14 (d, 1 H, J = 2.2 Hz). Anal. ($C_{15}H_{13}NS$).

3-*trans*-β-styrylquinoline, 15z, was obtained from **14e** and **13i** by method D: mp 96–98 °C (hexane); NMR ($CDCl_3$) δ 7.27 (s, 1 H), 7.33 (m, 2 H), 7.41 (m, 2 H), 7.58 (m, 3 H), 7.69 (m, 1 H), 7.83 (d, 1 H, J = 8.3 Hz), 8.09 (d, 1 H, J = 8.3 Hz), 8.19 (d, 1 H, J = 1.8 Hz), 9.13 (d, 1 H, J = 1.8 Hz). Anal. ($C_{17}H_{13}N$).

3-(4-Fluorophenyl)-6,7-dimethoxyquinoline, 17a, was obtained from **10a** and **16a** by method E: mp 117.5–119.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.04 (s, 3 H), 4.06 (s, 3 H), 7.10 (s, 1 H), 7.20 (m, 2 H), 7.45 (s, 1 H), 7.64 (m, 2 H), 8.11 (d, 1 H, J = 2.0 Hz), 8.93 (d, 1 H, J = 2.0 Hz). Anal. Calcd for $C_{17}H_{14}NO_2F$: C, 72.07; H, 4.98; N, 4.94. Found: C, 71.51; H, 4.75; N, 4.60.

6,7-Dimethoxy-3-(2-methoxyphenyl)quinoline, 17c, was obtained from **10a** and **16c** by method E: mp 110.5–112 °C (hexane/EtOAc twice); NMR ($CDCl_3$) δ 3.86 (s, 3 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 7.08 (m, 3 H), 7.41 (m, 3 H), 8.14 (d, 1 H, J = 2.0 Hz), 8.90 (d, 1 H, J = 2.0 Hz). Anal. ($C_{18}H_{17}NO_3$).

[4-(6,7-Dimethoxyquinolin-3-yl)phenyl]dimethylamine, 17d, was obtained from **10a** and **16d** by method E: mp 157–159.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.03 (s, 6 H), 4.04 (s, 3 H), 4.05 (s, 3 H), 6.86 (d, 2 H, J = 8.7 Hz), 7.08 (s, 1 H), 7.43 (s, 1 H), 7.60 (d, 2 H, J = 8.7 Hz), 8.09 (d, 1 H, J = 1.9 Hz), 8.98 (d, 1 H, J = 1.9 Hz). Anal. ($C_{19}H_{20}N_2O_2$).

6,7-Dimethoxy-3-(5-methoxythiophene-2-yl)quinoline, 17e, was obtained from **10a** and **16e** by method E: mp 111–113 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.95 (s, 3 H), 4.02 (s, 3 H), 4.04 (s, 3 H), 6.24 (d, 1 H, J = 4.0 Hz), 7.03 (s, 1 H), 7.08 (d, 1 H, J = 4.0 Hz), 7.39 (s, 1 H), 7.96 (d, 1 H, J = 2.2 Hz), 8.90 (d, 1 H, J = 2.2 Hz). Anal. ($C_{16}H_{15}NO_3S$).

3-(2,4-Dimethoxyphenyl)-6,7-dimethoxyquinoline, 17f, was obtained from **10a** and **16f** by method E: mp 122–123.5 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.84 (s, 3 H), 3.88 (s, 3 H), 4.03 (s, 3 H), 4.05 (s, 3 H), 6.84 (m, 2 H), 7.07 (s, 1 H), 7.33 (d, 1 H, J = 8.0 Hz), 7.43 (s, 1 H), 8.09 (d, 1 H, J = 2.0 Hz), 8.87 (d, 1 H, J = 2.0 Hz). Anal. ($C_{19}H_{19}NO_4$).

3-[4-(Benzyloxy)phenyl]-6,7-dimethoxyquinoline, 17g, was obtained from **10a** and **16g** by method E: mp 163.5–165 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.03 (s, 3 H), 4.05 (s, 3 H), 5.14 (s, 2 H), 7.10 (m, 3 H), 7.41 (m, 6 H), 7.62 (d, 2 H, J = 8.7 Hz), 8.10 (d, 1 H, J = 2.2 Hz), 8.95 (d, 1 H, J = 2.2 Hz). Anal. ($C_{24}H_{21}NO_3$).

6,7-Dimethoxy-3-[2-(4-methoxyphenyl)vinyl]quinoline, 17h, was obtained from **10a** and **16h** by method E: mp 145.5–147 °C (EtOAc); NMR ($CDCl_3$) δ 3.84 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 6.93 (d, 2 H, J = 8.7 Hz), 7.03 (s, 1 H), 7.05 (d, 1 H, J = 16.4 Hz), 7.20 (d, 1 H, J = 16.4 Hz), 7.40 (s, 1 H), 7.50 (d, 2 H, J = 8.7 Hz), 8.01 (br s, 1 H), 8.88 (d, 1 H, J = 2.0 Hz). Anal. ($C_{20}H_{19}NO_3$).

6,7-Dimethoxy-3-(4-methoxy-3-methylphenyl)quinoline, 17i, was obtained from **10a** and **16i** by method E: mp 124.5–127 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.89 (s, 3 H), 4.02 (s, 3 H), 4.04 (s, 3 H), 6.94 (d, 1 H, J = 8.5 Hz), 7.08 (s, 1 H), 7.47 (m, 3 H), 8.09 (d, 1 H, J = 2.2 Hz), 8.95 (d, 1 H, J = 2.2 Hz). Anal. ($C_{18}H_{19}NO_3$).

3-(3,4-Dimethoxyphenyl)-6,7-dimethoxyquinoline, 17j, was obtained from **10a** and **16j** by method E: mp 120.5–122 °C (hexane/EtOAc twice); NMR ($CDCl_3$) δ 3.96 (s, 3 H), 4.00 (s, 3 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 7.01 (d, 1 H, J = 8.4 Hz), 7.11 (s, 1 H), 7.19 (d, 1 H, J = 2.0 Hz), 7.25 (dd, 1 H, J = 2.0, 8.4 Hz), 7.45 (s, 1 H), 8.11 (d, 1 H, J = 2.1 Hz), 8.95 (d, 1 H, J = 2.1 Hz). Anal. ($C_{19}H_{19}NO_4$).

6,7-Dimethoxy-3-*p*-tolylquinoline, 17k, was obtained from **10a** and **16k** by method E: mp 157–159 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 2.43 (s, 3 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 7.10 (s, 1 H), 7.32 (d, 2 H, J = 8.0 Hz), 7.45 (s, 1 H), 7.60 (d, 2 H, J = 8.0 Hz), 8.14 (d, 1 H, J = 2.1 Hz), 8.97 (d, 1 H, J = 2.1 Hz). Anal. ($C_{18}H_{17}NO_2$).

3-(3,5-Difluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline, 17l, was obtained from **10a** and **16l** by method E: mp 165–167.5 °C (EtOAc); NMR ($CDCl_3$) δ 4.04 (s, 3 H), 4.06 (s, 6 H), 7.10 (s, 1 H), 7.22 (s, 1 H), 7.25 (s, 1 H), 7.44 (s, 1 H), 8.08 (d, 1 H, J = 1.9 Hz), 8.88 (d, 1 H, J = 1.9 Hz). Anal. ($C_{18}H_{15}NO_3F_2 \cdot 0.2H_2O$).

3-(3-Fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline, 17m, was obtained from **10a** and **16m** by method E: mp 165.5–167 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 3.96 (s, 3 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 7.10 (m, 2 H), 7.48 (m, 2 H), 7.68 (m, 1 H), 8.09 (d, 1 H, J = 2.1 Hz), 8.92 (d, 1 H, J = 2.1 Hz). Anal. ($C_{18}H_{16}NO_3F$).

3-Cyclopent-1-enyl-6,7-dimethoxyquinoline, 17n, was obtained from **10a** and **16n** by method E: mp (HCl salt) 213–215 °C (methanol/Et_2O); NMR ($CDCl_3$, free base) δ 2.08 (m, 2 H), 2.61 (m, 2 H), 2.81 (m, 2 H), 4.02 (s, 3 H), 4.04 (s, 3 H), 6.38 (t, 1 H, J = 2.0 Hz), 7.04 (s, 1 H), 7.40 (s, 1 H), 7.86 (d, 1 H, J = 2.0 Hz), 8.93 (d, 1 H, J = 2.0 Hz). Anal. ($C_{16}H_{17}NO_2 \cdot HCl \cdot 0.6H_2O$).

6,7-Dimethoxy-3-(phenylethynyl)quinoline, 17o, was obtained from **10a** and **16o** by method E: mp 147.5–149 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.03 (s, 3 H), 4.05 (s, 3 H), 7.02 (s, 1 H), 7.39 (m, 4 H), 7.58 (m, 2 H), 8.15 (d, 1 H, J = 2.0 Hz), 8.83 (d, 1 H, J = 2.0 Hz). Anal. ($C_{19}H_{15}NO_2$).

3-(Cyclohexylethynyl)-6,7-dimethoxyquinoline, 17p, was obtained from **10a** and **16p** by method E: mp 66–67.5 °C (hexane); NMR ($CDCl_3$) δ 1.37–1.94 (m, 10 H), 2.64 (m, 1 H), 4.01 (s, 3 H), 4.03 (s, 3 H), 6.96 (s, 1 H), 7.39 (s, 1 H), 8.01 (d, 1 H, J = 1.8 Hz), 8.70 (d, 1 H, J = 1.8 Hz). Anal. ($C_{19}H_{21}NO_2$).

3-Pyridin-3-ylquinoline-6,7-diol, 18, was obtained by reaction of **2a** with refluxing 48% aqueous HBr: mp >300 °C dec (methanol); NMR (DMSO-d_6) δ 7.21 (s, 1 H), 7.27 (s, 1 H), 7.53 (dd, 1 H, J = 4.8, 7.8 Hz), 8.21 (m, 1 H), 8.40 (br s, 1 H), 8.60 (m, 1 H), 8.91 (d, 1 H, J = 2.0 Hz), 9.02 (br s, 1 H), 10.08 (br s, 2 H). Anal. ($C_{14}H_{10}N_2O_2 \cdot 0.2H_2O$).

Benzyl(6,7-dimethoxyquinolin-3-yl)amine, 19, was obtained by reaction of **8a** with benzaldehyde and $NaCNBH_3$ in methanol: mp (HCl salt) 207–209.5 °C (methanol/Et_2O); NMR ($CDCl_3$, HCl salt) δ 3.97 (s, 3 H), 4.04 (s, 3 H), 4.56 (s, 2 H), 6.86 (s, 1 H), 7.35 (br m, 6 H), 7.72 (s, 1 H), 9.19 (br s, 1 H). Anal. ($C_{13}H_{19}N_2O_2 \cdot HCl \cdot 0.5H_2O$).

3-(Benzyloxy)-6,7-dimethoxyquinoline, 20, was obtained by reaction of **9a** with benzyl bromide and sodium hydride in THF: mp 163.5–165 °C (hexane/EtOAc); NMR ($CDCl_3$) δ 4.03 (s, 3 H), 4.05 (s, 3 H), 5.14 (s, 2 H), 7.10 (m, 3 H), 7.41 (m, 6 H), 7.62 (d, 2 H, J = 8.7 Hz), 8.10 (d, 1 H, J = 2.2 Hz), 8.95 (d, 1 H, J = 2.2 Hz). Anal. ($C_{24}H_{21}NO_3$).

4-(6,7-Dimethoxyquinolin-3-yl)benzoic acid, 22, was obtained by reaction of **15n** with NaOH in ethanol: mp (HCl salt) 273–275 °C dec (methanol/CH_2Cl_2); NMR (DMSO-d_6, HCl salt) δ 4.00 (3 H, s), 4.03 (3 H, s), 7.68 (s, 1 H), 7.73 (s, 1 H), 8.03 (d, 2 H, J = 8.3 Hz), 8.10 (d, 2 H, J = 8.3 Hz), 9.15 (br s, 1 H), 9.34 (br s, 1 H). Anal. ($C_{13}H_{15}NO_4 \cdot HCl \cdot 0.9H_2O$).

5-(6,7-Dimethoxyquinolin-3-yl)-1*H*-pyridin-2-one, 23, was obtained by reaction of **15o** with pyridine hydrochloride at 160 °C for 5 min: mp 259–261 °C (methanol/EtOAc); NMR (DMSO-

d_6) δ 3.91 (s, 3 H), 3.93 (s, 3 H), 6.50 (br d, 1 H, J = 9.5 Hz), 7.31 (br s, 1 H), 7.36 (br s, 1 H), 7.90 (br s, 1 H), 7.97 (br d, 1 H, J = 9.5 Hz), 8.32 (br s, 1 H), 8.92 (br s, 1 H), 11.97 (br s, 1 H). Anal. ($C_{16}H_{14}N_2O_3$).

4-(6,7-Dimethoxyquinolin-3-yl)phenol, 24, was obtained by reaction of **17g** with H_2 and Pd/C in methanol and DMF: mp 250–251 °C (methanol); NMR ($CDCl_3$ + CD_3OD) δ 4.05 (s, 3 H), 4.07 (s, 3 H), 6.98 (d, 2 H, J = 8.7 Hz), 7.17 (s, 1 H), 7.38 (s, 1 H), 7.56 (d, 2 H, J = 8.7 Hz), 8.19 (d, 1 H, J = 2.1 Hz), 8.86 (d, 1 H, J = 2.1 Hz). Anal. ($C_{17}H_{15}NO_3$).

6,7-Dimethoxy-3-[2-(4-methoxyphenyl)ethyl]quinoline, 25, was obtained by reaction of **17h** with H_2 and Pd/C in methanol and acetic acid: mp 140–141 °C (ethanol); NMR ($CDCl_3$) δ 2.98 (m, 4 H), 3.78 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 6.82 (d, 2 H, J = 8.6 Hz), 6.97 (s, 1 H), 7.08 (d, 2 H, J = 8.6 Hz), 7.39 (s, 1 H), 7.71 (d, 1 H, J = 1.8 Hz), 8.53 (d, 1 H, J = 1.8 Hz). Anal. ($C_{20}H_{21}NO_3$).

3-(2-Cyclohexylethyl)-6,7-dimethoxyquinoline, 26, was obtained by reaction of **17p** with H_2 and Pd/C in methanol and acetic acid: oil (silica chromatography eluting with 4:1 hexane/EtOAc); NMR ($CDCl_3$) δ 0.96 (m, 2 H), 1.24 (m, 4 H), 1.55–1.81 (m, 7 H), 2.75 (t, 2 H, J = 8.0 Hz), 4.01 (s, 3 H), 4.03 (s, 3 H), 7.00 (s, 1 H), 7.40 (s, 1 H), 7.77 (s, 1 H), 8.57 (d, 1 H, d, J = 1.9 Hz). Anal. ($C_{19}H_{25}NO_2 \cdot 0.25H_2O$).

3-Cyclopentyl-6,7-dimethoxyquinoline, 27, was obtained by reaction of **17n** with H_2 and Pd/C in acetic acid: mp (HCl salt) 213.5–215 °C (methanol/Et_2O); NMR ($CDCl_3$, free base) δ 1.80 (m, 6 H), 2.16 (m, 2 H), 3.14 (m, 1 H), 4.01 (s, 3 H), 4.03 (s, 3 H), 7.01 (s, 1 H), 7.39 (s, 1 H), 7.80 (d, 1 H, J = 2.0 Hz), 8.64 (d, 1 H, J = 2.0 Hz). Anal. ($C_{16}H_{19}NO_2 \cdot HCl \cdot 0.1H_2O$).

Biology. Materials. Recombinant human PDGF-BB was obtained from R & D Systems (Minneapolis, MN), γ-^{32}P-ATP (6000 Ci/mmol) from NEN (Wilmington, DE), and cell culture reagents from GIBCO. Rabbit polyclonal anti-PDGF receptor antibodies were raised against a synthetic peptide from the COOH-terminal region (amino acids 1094–1106) of the human PDGF-β receptor.

Cell Culture and Lysis. NIH 3T3 cells (ATCC) were grown in fibronectin-coated 15-cm plates in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% calf serum, 100 units/mL penicillin–streptomycin and 2 mM glutamine. At ~90% confluency, the cells were rendered quiescent by switching to DMEM containing 0.5% calf serum for 24 h. The cells were lysed in a detergent buffer (50 mM HEPES, 1.5 mM $MgCl_2$, 150 mM NaCl, 1 mM EGTA, 10% glycerol, 1% Triton X-100, pH 7.5) containing 1 mM PMSF, 20 μg/mL aprotinin, and 2 μg/mL leupeptin (all reagents from Sigma), clarified by centrifugation at 16000g for 5 min at 4 °C and the lysates stored at −70 °C.

Cell-Free PDGF Receptor Autophosphorylation Assay. Lysates were diluted 1:2 with lysis buffer devoid of Triton X-100, stimulated with 10 ng/mL PDGF for 30 min at 4 °C and immunoprecipitated with anti-PDGF receptor antibodies adsorbed to Protein A Sepharose beads (Sigma). The immunoprecipitates were washed first with HNTG (20 mM HEPES, 150 mM NaCl, 0.1% Triton X-100, 10% glycerol, pH 7.5) followed by 10 mM Tris, pH 7.5, and suspended in ice-cold reaction buffer (50 mM Tris, 10 mM $MnCl_2$, pH 7.5). Test compounds were freshly prepared for each experiment in 100% DMSO as a 40 mM stock solution. The compounds were diluted in reaction buffer and added to the immunoprecipitates for 10 min at 4 °C. Autophosphorylation reactions were initiated by adding an ATP mixture (10 μCi γ-^{32}-P-ATP plus 2 mM unlabeled ATP) to the samples, followed by a 5-min incubation at 4 °C. The reactions were terminated by addition of 2X SDS sample buffer (0.14 M Tris, pH 6.8, 22.4% glycerol, 6% SDS, 0.02% bromophenol blue, 10% 2-mercaptoethanol), and the samples were separated by SDS–PAGE on 10% gels. The amount of incorporated ATP was quantitated by densitometry of the resulting autoradiographs. Each compound was tested in a minimum of two dose–response assays. The autophosphorylation reaction occurs essentially on a solid matrix support, and each compound is evaluated repeatedly in several experiments. Since interexperiment variability is significantly higher than the variability within a given experiment (e.g. duplicates), our overall experience with an inhibitory compound is best described by the range of IC_{50} values observed.

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