Synthesis and Structure−Activity Relationships of 7-Substituted 3-(2,6-Dichlorophenyl)-1,6-naphthyridin-2(1*H*)-ones as Selective Inhibitors of pp60^{c-src}

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7-Substituted 3-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-ones are potent inhibitors of protein tyrosine kinases, with some selectivity for c-Src. The compounds were prepared by condensing 4,6-diaminonicotinaldehyde with 2,6-dichlorophenylacetonitrile and selectively converting the 2- and 7-amino groups of the product to hydroxy and fluoro groups, respectively, by prolonged diazotization in 50% aqueous fluoboric acid. *N*-Methylation, followed by treatment with aliphatic diamines, aromatic amines, or their derived lithium anions, gave the desired compounds. Selected isomeric 1,8-naphthyridin-2(1*H*)-ones were also prepared in order to evaluate the relative contributions of both ring A aza atoms of the related pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones to the inhibitory activity. The compounds were evaluated for their ability to prevent phosphorylation of a model substrate by c-Src, FGF-1 receptor, and PDGF-β receptor enzymes. Overall, there was a high degree of correlation of the activities against the different kinases, with c-Src being generally the most sensitive to structural changes. 1,6-Naphthyridin-2(1*H*)-one analogues bearing basic aliphatic side chains [7-NH$(CH_2)_n$NRR, 7-NHPhO$(CH_2)_n$NRR, or 7-NHPhN$(CH_2)_4$NMe] were the most potent against c-Src (IC_{50}s of 10−80 nM), showing good selectivity with respect to PDGFR (10−300-fold) but less with respect to FGFR. The 1,6-naphthyridin-2(1*H*)-ones showed broadly similar activity to the analogous pyrido[2,3-*d*]-pyrimidin-7(8*H*)-ones, whereas the 1,8-naphthyridin-2(1*H*)-ones were at least 10^3-fold less potent. These results, indicating that the 3-aza atom in the pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones is mandatory, whereas the 1-aza atom is not, support the published binding model for these compounds to c-Src (*J. Med. Chem.* **1998**, *41*, 1752), where the 3-aza and 2-NH atoms form a bidentate H-bond donor−acceptor motif that interacts with Met341 and the 1-aza atom is not involved in specific binding interactions.

Introduction

The cytoplasmic protein pp60^{c-src} (c-Src) is a ubiquitous nonreceptor tyrosine kinase which is overexpressed and/or activated in many types of tumors,[1] including colon[2,3] and small- and non-small-cell lung cancer,[4] neuroblastoma,[5] and breast carcinoma.[6] In the latter case, 70% of the elevation in tyrosine kinase activity has been attributed to activated c-Src. The protein is also involved in oncogenic signal transduction by the receptor tyrosine kinases EGFR/HER1, HER2, and PDGFR.[7] For these and other reasons, c-Src has been suggested as an important anticancer target.[7] A recent crystal structure determination of a fragment of human c-Src containing the regulatory and kinase domains has been published.[8]

A number of small molecule inhibitors of Src family kinases have been reported.[9] The natural product protein kinase inhibitors, including the quinonoid/fused lactone compounds herbimycin A[10] and ellagic acid (**1**),[11] show some selectivity for c-Src. A series of simpler derived carbazoles (e.g., **2**) showed similar potency to the parent (IC_{50}s 0.4−3 μM) but increased specificity, being pure ATP site competitive inhibitors.[11] Dihydropyrimido[4,5-*b*]quinolinones (e.g., **3**) are also c-Src inhibitors of moderate (low micromolar) potency and selectivity.[12] The pyrazolopyrimidine PP1 (**4**) is a selective inhibitor of various Src family kinases, including c-Src (IC_{50} 170 nM).[13] Recently, a large series of pyrrolo-[2,3-*d*]pyrimidines have been described,[14] some with inhibitory potencies as low as 50 nM against c-Src and with good selectivities over other tyrosine kinases.[9] Finally, a series of pyrido[2,3-*d*]pyrimidines have recently been shown to be potent, broad-spectrum ATP site inhibitors of tyrosine kinases, with 2,6-dichlorophenyl derivatives (e.g., **5**) being particularly effective against c-Src and FGF.[15−17] Related 6-(2,6-dichlorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **6** (e.g., **6n**: R = NHPh; **6q**: R = NHPhO$(CH_2)_2NEt_2$) were recently reported as potent ATP site c-Src inhibitors, some with considerable selectivity for c-Src over both PDGFR and FGFR.[18,19] We now report the synthesis and structure−activity relationships of the related 3-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-ones **7** and **8** and 3-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-ones **9**. These

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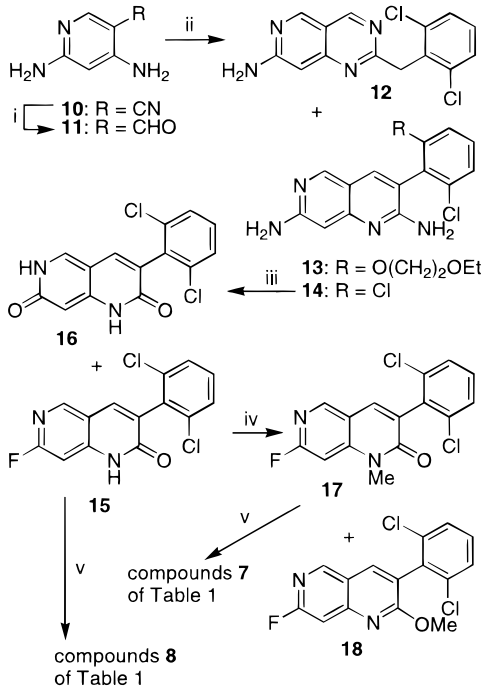
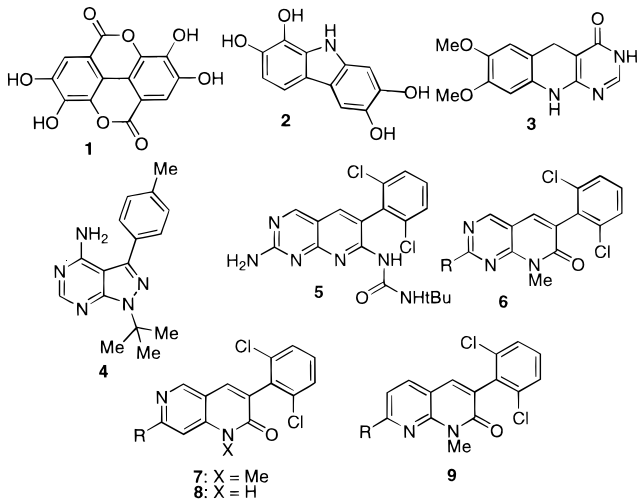
Scheme 1[a]



[a] (i) H_2/W-7 Raney nickel/H_2O/HCO_2H/9 days; (ii) Na/EtO$(CH_2)_2$-OH/2,6-diClPhCH_2CN/reflux/30 min; (iii) HBF_4/$NaNO_2$/−20 °C/5 days; (iv) MeI/NaH/DMF/0 °C/2 h; (v) HNRR/2-PrOH or 2-pentanol/90−170 °C/30 min−3 days, or $ArNH_2$/170−175 °C/1−4 h, or $ArNH_2$/LDA/THF/−78 to 20 °C/40−60 h.

studies were carried out, in part, to evaluate the relative importance of the aza atoms in ring A of the pyrido-[2,3-*d*]pyrimidinone moiety (**6**) for the c-Src inhibitory activity shown by these compounds.



Chemistry

The 3-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-ones of Table 1 were prepared by the methods described in Scheme 1. The known[20] 4,6-diaminonicotinonitrile (**10**) was converted into the corresponding known[21] 4,6-diaminonicotinaldehyde (**11**) by hydrogenation over Raney nickel catalyst in aqueous formic acid at 20 °C (a modification of the method described by Staskun[22] for nicotinonitrile). Optimal conditions for this reaction were found to vary greatly with the grade and amount of catalyst used. Thus, for freshly prepared W-7 catalyst,[23] yields of 0−70% were obtained, depending on the quantity of catalyst added, and best results were obtained by employing multiple additions of small amounts of catalyst over several days.

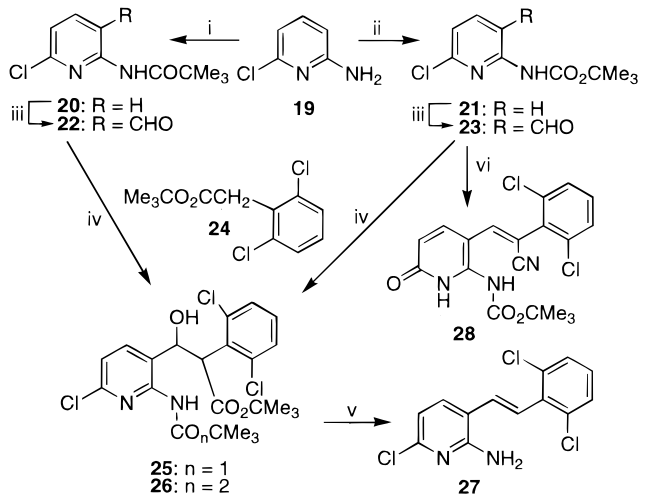
Condensation of **11** with 2,6-dichlorophenylacetonitrile in boiling 2-ethoxyethanol in the presence of the corresponding sodium alkoxide (from addition of sodium or sodium hydride), after the manner described by Hawes,[24] gave the desired 3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7-diamine (**14**),[21] together with a small amount (up to 10%) of the pyrido[4,3-*d*]pyrimidine **12** (resulting from a condensation reaction across the nitrile triple bond) and traces (<1%) of the solvolysis product **13** (Scheme 1). Although good yields (68%) of **14** could be obtained with 1.1 equiv of the nitrile and 0.4 equiv of base, better yields (82%) were obtained with a 2-fold excess of both nitrile and base, as reported.[24]

Selective functionalization of the amino groups of **14** was achieved by diazotization in 50% aqueous fluoboric acid, as reported in our more extensive study,[25] giving **15** in 58% yield, together with the hydrolysis product **16**. Alkylation of **15** with MeI/NaH in DMF gave the *N*-methyl analogue **17**, together with traces of the *O*-alkylation product **18** (Scheme 1). Treatment of **17** with excess aliphatic diamines in boiling 2-pentanol (or with Me_2NH, $MeNH_2$, or NH_3 in 2-propanol at 90−170 °C in a pressure vessel) then gave generally excellent yields (82−99%) of the desired 7-substituted amino-1-methyl-1,6-naphthyridin-2(1*H*)-ones **7**. Similar treatment of **15** gave the corresponding nonmethylated derivatives **8**. Displacement with aromatic amines required more forcing conditions, with the amine as solvent and temperatures of 170−175 °C. Although this method gave a good yield for aniline itself (83%), much poorer yields (12−38%) were obtained for alkoxy-substituted anilines due to acid-catalyzed decomposition. Furthermore, with 4-aminopyridine the only isolable product was the 7-amino compound **7a** (56%). For these weakly basic amines, an alternative and superior method was to treat **17** with their derived lithium anions in THF at −78 to 20 °C for 2 or 3 days, although this was unsuccessful for **8r** due to concomitant formation of the naphthyridin-2(1*H*)-one anion of **15**, which rendered the 7-fluorine unreactive toward displacement.

The required known[26−28] 4-(dialkylaminoalkoxy)anilines were prepared by the general method of Kaye[26] as modified by Buchi,[29] involving alkylation of sodium 4-nitrophenoxide by known substituted alkyl chlorides,[30−32] followed by catalytic reduction. Similarly, 1-methyl-4-(*p*-aminophenyl)piperazine[33] was obtained by alkylation of 1-methylpiperazine with 4-nitrofluorobenzene, followed by catalytic reduction (Pd/C). 5-Diethylaminopentylamine[34] was prepared from 5-bromovaleronitrile by displacement with diethylamine, after the manner described by Utermohlen,[35] followed by reduction of the nitrile with borane−dimethyl sulfide complex.

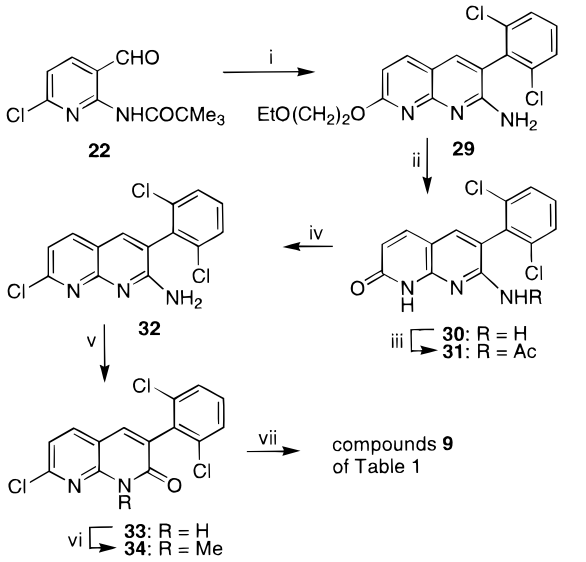
The initial approach to the 1,8-naphthyridine system (Scheme 2) followed the literature procedure of Turner,[36] seeking a direct synthesis of the 7-chloro derivative **33** (Scheme 3), but ring closure to the desired product could not be achieved. The known[36] protected aminoaldehyde **22** was prepared by conversion of 2-amino-6-chloropyridine (**19**) to the amide **20** and subsequent formylation.

Scheme 2[a]



[a] (i) Pivaloyl chloride/Et_3N/CH_2Cl_2/0−20 °C/2 h; (ii) NaHMDS/$(BOC)_2O$/THF/0−20 °C/15 min; (iii) BuLi/TMEDA/THF/−78 to −10 °C/2 h, then DMF/−78 to 20 °C; (iv) **24**/LDA/Et_2O/−78 °C/30 min, then add **22** or **23**/−78 °C/30 min; (v) dioxane/3 M HCl/reflux/2 h; (vi) 2,6-di$ClPhCH_2CN$/LDA/THF/−78 °C/30 min, then add **23**/−78 to 20 °C/16 h.

Scheme 3[a]



[a] (i) 2,6-di$ClPhCH_2CN/EtO(CH_2)_2OH$/Na/reflux/3 h; (ii) concd HCl/dioxane/reflux/15 h; (iii) AcOH/Ac_2O/reflux/1 h; (iv) $POCl_3$/reflux/1 h, then dioxane/2 M KOH/reflux/30 min; (v) TFA/$NaNO_2$/−10 °C/30 min; (vi) MeI/NaH/DMF/0 °C/15 min; (vii) see step v of Scheme 1.

Condensation of **22** with *tert*-butyl 2-(2,6-dichlorophenyl)acetate (**24**) in the presence of LDA at −78 °C proceeded as expected to give the diester **25** (Scheme 2), but heating of this with aqueous acid under reflux failed to induce ring closure to the desired naphthyridin-2(1*H*)-one, giving only the stilbene derivative **27**. In an attempt to facilitate hydrolysis of the protected amine and allow ring closure to occur at a lower temperature, the carbamate **23** corresponding to **22** was prepared from **19** via **21**. However, condensation of **23** with **24**, followed by treatment of the resulting intermediate **26** under hydrolysis conditions, also did not result in ring closure.

Replacement of the ester **24** by the analogous nitrile (2,6-dichlorophenylacetonitrile) was also investigated, but in this case no reaction with **23** occurred at −78 °C. Condensation did occur on allowing the reaction mixture to warm to room temperature, although water was eliminated to give the unsaturated nitrile **28** in which the chloropyridine moiety was also hydrolyzed to the (undesired) pyridone (Scheme 2). This compound was initially obtained as an isomeric mixture, but recrystallization from methanol gave a single isomer, which was stable only in nonpolar solvents, reverting to an isomeric mixture on dissolution in polar solvents.

The required compounds were successfully prepared by the less direct method outlined in Scheme 3. Treatment of the protected aldehyde **22** with 2,6-dichlorophenylacetonitrile in 2-ethoxyethanol/sodium resulted in sequential deprotection, condensation, and chloride solvolysis to give the 7-(2-ethoxyethoxy)-1,8-naphthyridin-2-amine derivative **29** in moderate yield (40%). Acid hydrolysis gave the 2-aminonaphthyridin-7(8*H*)-one **30**. *N*-Acetylation of this to **31**, followed by rechlorination with $POCl_3$ and subsequent acetamide hydrolysis of the crude product with 2 M KOH, gave the 7-chloronaphthyridin-2-amine **32** directly. This was converted by sodium nitrite/TFA[37] to the naphthyridin-2(1*H*)-one **33**, which was then *N*-methylated as above to yield the desired precursor **34**. Treatment of **34** with amines by the methods described above gave the compounds **9** of Table 1.

Results and Discussion

The 1,6-naphthyridines were evaluated for their ability to prevent phosphorylation of a model glutamate-tyrosine copolymer substrate by isolated avian c-Src, human FGF-1 receptor, and mouse PDGF-β receptor tyrosine kinase enzymes. The FGFR and PDGFR proteins were fragments encoding the intracellular tyrosine kinase domains, while c-Src was a recombinant protein. The IC_{50} values are the concentration of inhibitor required to reduce by 50% the level of ^{32}P (from added [^{32}P]ATP) incorporated into the copolymer substrate. A curve-fitting analysis[18] of inhibition of FGF receptor by the representative 7-$NHPhO(CH_2)_2NEt_2$ derivative **7q** with respect to ATP concentration indicated that it behaves as an ATP competitive inhibitor, with a K_i of 94 nM, compared with a K_i of 34 nM for the analogous pyrido[2,3-*d*]pyrimidin-7(8*H*)-one **6q** in the same assay (averages of duplicate calculated means; SEMs < 10%). The latter compound **6q** has also been reported previously[18] to be an ATP competitive c-Src inhibitor (K_i 4.9 nM).

The series of 7-substituted 1,6-naphthyridin-2(1*H*)-ones in Table 1 allow an evaluation of stucture−activity relationships for the 7-side chain. For the 23 1-methyl compounds (**7a**−**7w**) where data for all three kinases was obtained (excluding only the tertiary amine analogue **7c**), eqs 1 and 2 can be derived:

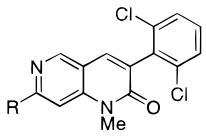
$$\log[IC_{50}(\text{c-Src})] = 0.96(\pm 0.18)\log[IC_{50}(\text{PDGFR})] - 1.07(\pm 0.30) \quad (1)$$

$$n = 23,\ r = 0.77,\ F = 27$$

$$\log[IC_{50}(\text{c-Src})] = 0.85(\pm 0.12)\log[IC_{50}(\text{FGFR})] - 0.40(\pm 0.22) \quad (2)$$

$$n = 23,\ r = 0.84,\ F = 50$$

Table 1. Kinase Inhibitory Activities of 7-Substituted 1,6- and 1,8-Naphthyridin-2(1*H*)-ones



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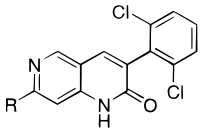

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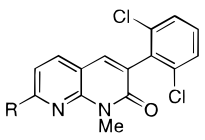

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		IC_{50} (μM)[a]		
no.	R	c-Src	PDGF	FGF
7a	NH_2	0.35	3.6	0.38
7b	NHMe	0.42	8.0	0.21
7c	NMe_2	>50	>50	>50
7d	$NH(CH_2)_2NEt_2$	13	>50	33
7e	$NH(CH_2)_3NEt_2$	0.30	4.6	0.15
7f	$NH(CH_2)_4NEt_2$	0.044	2.4	0.080
7g	$NH(CH_2)_5NEt_2$	0.024	0.74	0.080
7h	$NH(CH_2)_3$(4-Me-pip)[b]	0.059	2.8	0.17
7i	$NH(CH_2)_4$(4-Me-pip)[b]	0.041	1.1	0.17
7j	$NH(CH_2)_5$(4-Me-pip)[b]	0.035	9.9	0.11
7k	$NH(CH_2)_3$(morph)[c]	0.20	5.8	0.57
7l	$NH(CH_2)_4$(morph)[c]	0.045	3.1	0.23
7m	$NH(CH_2)_3$(1-imid)[d]	0.54	3.2	0.21
7n	NHPh	0.79	1.4	2.2
7o	NH(4-pyridinyl)	0.55	6.9	3.5
7p	NHPhOMe[e]	1.8	6.8	2.2
7q	$NHPhO(CH_2)_2NEt_2$[e]	0.078	0.10	0.13
7r	$NHPhO(CH_2)_3NEt_2$[e]	0.032	0.36	0.25
7s	$NHPhO(CH_2)_2$(4-Me-pip)[b,e]	0.016	0.26	0.21
7t	$NHPhO(CH_2)_3$(4-Me-pip)[b,e]	0.028	0.90	0.12
7u	NHPh(4-Me-pip)[b,e]	0.023	0.26	0.042
7v	NHPh(morph)[c,e]	0.25	2.8	8.7
7w	$NHPh(4\text{-}CONEt_2)$	1.0	16	1.9
8f	$NH(CH_2)_4NEt_2$	0.042	1.1	0.17
8h[f]	$NH(CH_2)_3$(4-Me-pip)[b]	0.11	1.4	0.072
8r	$NHPhO(CH_2)_3NEt_2$[e]	0.011	0.79	0.44
9a	NH_2	>50	>50	>50
9e	$NH(CH_2)_3NEt_2$	>50	>50	>50
9h	$NH(CH_2)_3$(4-Me-pip)[b]	>50	>50	>50
9n	NHPh	>50	>50	>50
9p	NHPhOMe[e]	>50	>50	>50
9q	$NHPhO(CH_2)_2NEt_2$[e]	29	>50	>50

[a] Concentration of drug (μM) to inhibit the phosphorylation of a random glutamate-tyrosine (4:1) copolymer by c-Src, PDGFR, or FGFR proteins. For active compounds, values are an average of two or more separate determinations; variation was generally ±30%. [b] 4-Methylpiperazin-1-yl. [c] *N*-Morpholinyl. [d] Imidazolyl. [e] Para-substituted benzene ring. [f] Ref 25.

These indicate a high degree of correlation between the activities against the different kinases, with c-Src being generally the most sensitive to structural changes (on average, compounds were about 20-fold more potent against c-Src than against PDGFR). The parent 7-NH_2 and 7-NHMe compounds **7a** and **7b** showed moderate inhibitory potency (IC_{50} 300−400 nM) against c-Src and FGFR. In contrast, the 7-NMe_2 analogue **7c** was inactive against all kinases (IC_{50}s >50 μM). Since the 7-NMe_2 group should be essentially planar due to resonance effects with the adjacent pyridine nitrogen, this is probably not primarily a steric effect. Modeling studies[38] on the binding of the closely related 6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **6** to the c-Src enzyme show that the 2-NH (together with the adjacent 3-aza atom) is part of a bidentate H-bond donor−acceptor motif that interacts specifically with a Met341 residue on the extended coil stretch region of the enzyme. The corresponding 7-NH and 6-aza atoms of the 1,6-naphthyridin-2(1*H*)-ones are expected to form similar H-bond interactions.

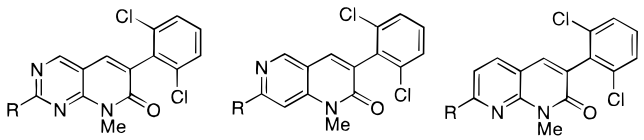
Compounds **7d**−**7m** explored the use of various amino functions which we have previously shown to be useful in solubilizing pyrido[*d*]pyrimidine-based EGFR inhibitors.[39] Derivatives **7d**−**7g** show the striking effect of the positioning of a positive charge (from amine protonation) with respect to the chromophore. While the shortest chain $NH(CH_2)_2NEt_2$ analogue **7d** is a less effective inhibitor against all three enzymes than the NHMe derivative **7b**, activity improves steadily as the chain is lengthened, with the $NH(CH_2)_5NEt_2$ analogue **7g** being one of the most potent inhibitors of c-Src (IC_{50} 0.024 μM). The same effect was also shown by the two morpholides **7k** and **7l** and, although to a much lesser extent, by the three 4-methylpiperazines **7h**−**7j**. Overall, the longer chain cationic derivatives were the most potent c-Src and FGFR inhibitors, with good selectivity (6−300-fold) over PDGFR.

Compounds **7n**−**7w** explored the utility of 7-NH-aryl derivatives. The simple phenyl and pyridyl analogues **7n** and **7o** retained reasonable potency, but the *p*-anisyl compound **7p** was less effective. Nevertheless, the effect of adding solubilizing cationic functions off this substituent was explored in **7q**−**7t**. As in the above aliphatic series, these substitutions dramatically increased activity (by 20−120-fold for c-Src) over the simple anisyl derivative **7p**. The length of the chain (positioning of the cationic charge) had a lesser effect in these compounds, with the $O(CH_2)_2$-piperazine analogue **7s** being the most potent c-Src inhibitor (IC_{50} 0.016 μM) of the whole 1-methyl series **7a**−**7w**. Similarly, the cationic 4-(4-methylpiperazine) derivative **7u** displayed enhanced activity over the almost neutral 4-morpholino and 4-$CONEt_2$ analogues **7v** and **7w**.

Finally, compounds **8f**, **8h**, and **8r** compared the effect of a nonmethylated versus a methylated naphthyridinone ring. No consistently significant differences in inhibitory activities were seen, but the $NHPhO(CH_2)_3NEt_2$ analogue **8r** was the most potent of all the 1,6-naphthyridinones as a c-Src inhibitor (IC_{50} 0.011 μM). It was one of the most selective for c-Src over PDGFR (70-fold compared with an average of about 20-fold) and was also 40-fold selective for c-Src over FGFR, whereas most of the analogues showed little selectivity between these kinases.

In contrast to the above potent kinase inhibitory activity of many of the 1,6-naphthyridin-2(1*H*)-ones, the smaller set of isomeric 1,8-naphthyridin-2(1*H*)-ones **9** prepared were virtually all inactive. Table 2 directly compares selected 1,6-naphthyridin-2(1*H*)-ones with the analogous previously reported[19] pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones and with the corresponding 1,8-naphthyridin-2(1*H*)-ones (where made). For the compounds with cationic aliphatic side chains (**6d**/**7d**, **6e**/**7e**, **6h**/**7h**, **6i**/**7i**, **6j**/**7j**, **6k**/**7k**) the 1,6-naphthyridin-2(1*H*)-ones show slightly superior inhibitory activity (2−3-fold) against both c-Src and FGFR compared with the pyrido[2,3-*d*]-pyrimidin-7(8*H*)-ones. For analogues with nearly neutral aromatic side chains (**6n**/**7n**, **6o**/**7o**, **6p**/**7p**, **6v**/**7v**, **6w**/**7w**) the opposite is true (by 30−90-fold against c-Src), although the differences are smaller for those (**6q**/**7q**, **6u**/**7u**) with cationic aromatic side chains (2−9-fold). The only 1,8-naphthyridin-2(1*H*)-one derivative with measurable activity (**9q**) was 3×10^3-fold less potent

Table 2. Comparison of the Kinase Inhibitory and Growth Delay Activities of 2-Substituted Pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **6**, 7-Substituted 1,6-Naphthyridin-2(1*H*)-ones **7**, and 7-Substituted 1,8-Naphthyridin-2(1*H*)-ones **9**



6 **7** **9**

		IC_{50} (μM)[a]			IC_{50} (μM)[b]		
no.	R	c-Src	PDGF	FGF	HCT-8	SW-620	HT-29
6a[c]	NH_2	0.26	4.9	1.3	4.9	2.6	
7a	NH_2	0.35	3.6	0.38	2.2		1.9
9a	NH_2	>50	>50	>50			
6b[c]	NHMe	0.75	6.2	2.5	7.8	5.0	4.1
7b	NHMe	0.42	8.0	0.21	1.7		2.8
6d[d]	$NH(CH_2)_2NEt_2$	>50	>50	>50			
7d	$NH(CH_2)_2NEt_2$	13	>50	33			
6e[c]	$NH(CH_2)_3NEt_2$	0.96	8.9	14			
7e	$NH(CH_2)_3NEt_2$	0.30	4.6	0.15			
9e	$NH(CH_2)_3NEt_2$	>50	>50	>50			
6h[c]	$NH(CH_2)_3$(4-Me-pip)[e]	0.15	2.8	0.38	2.5	7.5	15
7h	$NH(CH_2)_3$(4-Me-pip)[e]	0.059	2.8	0.17	2.8	7.6	2.2
9h	$NH(CH_2)_3$(4-Me-pip)[e]	>50	>50	>50			
6i[c]	$NH(CH_2)_4$(4-Me-pip)[e]	0.07	0.89	0.32	>25	>25	
7i	$NH(CH_2)_4$(4-Me-pip)[e]	0.041	1.1	0.17	2.4	2.6	1.6
6j[c]	$NH(CH_2)_5$(4-Me-pip)[e]	0.06	0.71	0.24			
7j	$NH(CH_2)_5$(4-Me-pip)[e]	0.035	9.9	0.11			
6k[c]	$NH(CH_2)_3$(morph)[f]	0.53	6.8	1.4			
7k	$NH(CH_2)_3$(morph)[f]	0.20	5.8	0.57			
6n[c]	NHPh	0.02	0.40	0.46			
7n	NHPh	0.79	1.4	2.2			
9n	NHPh	>50	>50	>50			
6o[c]	NH(4-pyridinyl)	0.010	0.10	0.19	16		0.14
7o	NH(4-pyridinyl)	0.55	6.9	3.5	7.3	8.7	3.7
6p[c]	NHPhOMe[g]	0.02	0.68	0.41			
7p	NHPhOMe	1.8	6.8	2.2			
9p	NHPhOMe	>50	>50	>50			
6q[c]	$NHPhO(CH_2)_2NEt_2$[g]	0.009	0.079	0.043	0.42	0.27	0.28
7q	$NHPhO(CH_2)_2NEt_2$	0.078	0.10	0.13	2.8	6.7	0.75
9q	$NHPhO(CH_2)_2NEt_2$	29	>50	>50			
6u[c]	NHPh(4-Me-pip)[e,g]	0.010	0.11	0.028	0.24	0.12	0.24
7u	NHPh(4-Me-pip)[e]	0.023	0.26	0.042	2.1	4.3	0.83
6v[d]	NHPh(morph)[f,g]	0.008	0.64	0.10	1.5	0.17	0.20
7v	NHPh(morph)[f]	0.25	2.8	8.7			
6w[d]	$NHPh(4\text{-}CONEt_2)$	0.014	0.29	0.18			
7w	$NHPh(4\text{-}CONEt_2)$	1.0	16	1.9			

[a] Concentration of drug (μM) to inhibit the phosphorylation of a random glutamate-tyrosine (4:1) copolymer by c-Src, PDGFR, or FGFR proteins (see Table 1 footnotes). [b] Drug concentration to inhibit the growth of HCT-8, SW-620, and HT-29 human colon adenocarcinoma cells to 50% of control cultures, using a 72-h drug exposure. [c] Data from ref 19. [d] Prepared by reacting the 2-(methyl sulfone) of ref 19 with 4 equiv of amine at 90 °C for 4−6 h in 0.25 M DMSO; 97% pure by HPLC/MS (M. Barvian, unpublished work). [e] 4-Methylpiperazin-1-yl. [f] *N*-Morpholinyl. [g] Para-substituted benzene ring.

against c-Src than the corresponding pyrido[2,3-*d*]-pyrimidin-7(8*H*)-one (**6q**). These results show that the 6-aza atom is mandatory, whereas the 8-aza atom is not. This supports the hypothesis that these naphthyridin-2(1*H*)-one derivatives bind to c-Src with the 6-aza and 7-NH atoms forming a bidentate H-bond donor−acceptor motif that interacts with Met341 and with the 8-aza atom not involved in specific binding interactions, in a fashion similar to the pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones.[38]

Compounds **7f**, **7h**, and **7q** were assessed for their ability to inhibit the kinase activities of EGFR, IRK, and PKC. All were inactive against IRK and PKC (IC_{50}s >50 μM) and only moderately effective (IC_{50}s 3.80, 3.23, and 0.59 μM, respectively) against EGFR. Compounds **7f**, **7q**, and **7s** were moderately potent inhibitors of autophosphorylation of PDGFR in rat aorta vascular smooth muscle cells (IC_{50}s 0.49, 0.23, and 0.81 μM, respectively).

Selected pairs of compounds were also evaluated for growth inhibition in three human colon adenocarcinoma cell lines (HCT-8, SW-620, and HT-29) that overexpress c-Src[19] (Table 2). Overall, the nature of the side chain appeared to have a less dramatic effect on cellular potency, with several compounds of widely differing side chain structure (**7a**, **7b**, **7h**, **7i**, **7o**, **7q**, **7u**) showing IC_{50}s from 0.8 to 7 μM in both HCT-8 and HT-29 cells. For the analogues with aliphatic side chains (**6a**/**7a**, **6b**/**7b**, **6h**/**7h**, **6i**/**7i**), the 1,6-naphthyridin-2(1*H*)-ones were equivalent to or better than the pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones. However, in the aromatic series (**6o**/**7o**, **6q**/**7q**, **6u**/**7u**), the 1,6-naphthyridin-2(1*H*)-ones again show significantly (3−40-fold) lower potencies. A more extensive study of the growth inhibitory effects of a total of 13 1,6-naphthyridin-2(1*H*)-ones on the HT-29 cell line (with IC_{50}s for the additional 6 compounds **7f**, **7g**, **7r**−**7t**, and **8r** being 1.5, 1.4, 0.96, 0.90, 0.87, and 0.53 μM,

respectively) gave a reasonable correlation of this cellular activity with c-Src inhibitory potency (eq 3):

$$\log[IC_{50}(\text{HT-29})] = 0.37(\pm 0.15)\log[IC_{50}(\text{c-Src})] + 0.58(\pm 0.21) \quad (3)$$

$$n = 13,\ r = 0.82,\ F = 22$$

This suggests that the HT-29 cell line is dependent on c-Src for its growth; however, no such correlation was observed for the other two cell lines. The most potent analogue, **8r**, also strongly inhibited the phosphorylation of p130cas, a substrate for c-Src, in HT-29 cells (91% inhibition at 1 μM).

Conclusions

The broadly similar structure−activity relationships found for the 1,6-naphthyridin-2(1*H*)-ones **7** prepared here and the analogous, previously reported pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **6** are in dramatic contrast to the isomeric 1,8-naphthyridin-2(1*H*)-ones **9**, which proved to be at least 10^3-fold less potent. These results suggest that the naphthyridin-2(1*H*)-ones bind to c-Src in a manner similar to that proposed[38] for the pyrido[2,3-*d*]-pyrimidin-7(8*H*)-ones, with the 6-aza and 7-NH atoms forming a bidentate H-bond to Met341 and the 8-aza atom not being involved in specific binding interactions. The inactivity of the 7-NMe_2 analogue **7c**, compared with the highly active 7-NH_2 and 7-NHMe compounds **7a** and **7b**, also supports this binding model, which requires a free 7-NH (together with the adjacent 6-aza atom) to form the bidentate H-bond.

The high potency of the 1,6-naphthyridin-2(1*H*)-ones **7** against c-Src, FGFR, and, to a lesser extent, PDGFR, combined with their selectivity for these kinases compared with EGFR, IRK, and PKC, marks this class of compounds as worthy of further study.

Experimental Section

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined using an Electrothermal model 9200 digital melting point apparatus and are as read. NMR spectra were measured on Bruker AC-200 or DRX-400 spectrometers and referenced to Me_4Si. Mass spectra were recorded on a Varian VG-70SE spectrometer at nominal 5000 resolution. HPLC was carried out using a Bondclone 10 C18 reverse-phase silica gel column, with a Phillips PU4100M gradient elution pump and a Phillips PU 4120 diode array detector, and eluting with the appropriate ratios of 80% MeCN/20% water (solvent A) and ammonium formate buffer (solvent B; 28 g ammonium formate + 2.55 mL formic acid, made up to 1 L in deionized water, pH 4.5).

4,6-Diaminonicotinaldehyde (11). A solution of 4,6-diaminonicotinonitrile (**10**)[20] (5.00 g, 37.3 mmol) and freshly prepared W-7 Raney nickel (120 mg wet catalyst, in absolute EtOH) in 99% formic acid (150 mL) and water (40 mL) was hydrogenated (60 psi/20 °C) for 2 days. Fresh catalyst was added (130 mg) and the reaction continued for 5 days, then further catalyst was added (207 mg) and the reaction continued for a final 2 days. The resulting solution was filtered over Celite, washing with formic acid, and the combined filtrates were evaporated under reduced pressure. The residue was diluted with water (150 mL), then excess Na_2CO_3 was added and the solution extracted with EtOAc (15 × 100 mL). Removal of the solvent gave a solid (3.65 g, 71%) which was used directly. Chromatography of a sample on neutral alumina, eluting with 1−3% MeOH in $CHCl_3$, gave 4,6-diaminonicotinaldehyde[21] (**11**): mp (MeOH/$CHCl_3$/light petroleum) 343 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 9.48 (s, 1 H, CHO), 8.04 (s, 1 H, H-2), 7.12, 6.46 (2 br s, 2 × 2 H, $2NH_2$), 5.55 (s, 1 H, H-5); ^{13}C NMR δ 190.27 (d, CHO), 162.34 (s, C-4 or 6), 159.77 (d, C-2), 155.14 (s, C-4 or 6), 110.45 (s, C-3), 86.98 (d, C-5); HREIMS calcd for $C_6H_7N_3O$ *m/z* (M^+) 137.0589, found 137.0591. Anal. ($C_6H_7N_3O$·HCl) C, H, N.

3-(2,6-Dichlorophenyl)-1,6-naphthyridine-2,7-diamine (14). 2,6-Dichlorophenylacetonitrile (1.40 g, 7.53 mmol) and **11** (502 mg, 3.66 mmol) were added to a solution of sodium (169 mg, 7.35 mmol) dissolved in 2-ethoxyethanol (7.0 mL), and the mixture was then stirred at reflux for 30 min. The resulting solution was diluted with aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL), and the solvents were removed under reduced pressure. Chromatography of the residue on silica gel, eluting with 2−3% MeOH/CH_2Cl_2, gave first a mixed fraction, which on crystallization from $CHCl_3$/light petroleum gave 2,6-dichlorophenylacetamide (165 mg): mp (MeOH/CH_2Cl_2) 211.5−213 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.53 (br s, 1 H, NH), 7.44 (d, J = 8.1 Hz, 2 H, H-3,5), 7.30 (dd, J = 8.5, 7.6 Hz, 1 H, H-4), 7.02 (br s, 1 H, NH), 3.77 (s, 2 H, CH_2); ^{13}C NMR δ 169.60 (s, $CONH_2$), 135.56 (s, 2 C, C-2,6), 132.67 (s, C-1), 129.22 (d, C-4), 128.09 (d, 2 C, C-3,5), 37.31 (t, CH_2). Anal. ($C_8H_7Cl_2NO$) C, H, N.

Further crystallization of the liquors gave 7-amino-2-[(2,6-dichlorophenyl)methyl]pyrido[4,3-*d*]pyrimidine (**12**) (42 mg, 4%): mp (MeOH/$CHCl_3$/light petroleum) 205−206 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.12, 8.93 (2 s, 2 H, H-4,5), 7.50 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.35 (dd, J = 8.5, 7.7 Hz, 1 H, H-4′), 6.91 (br s, 2 H, NH_2), 6.36 (s, 1 H, H-8), 4.55 (s, 2 H, CH_2); ^{13}C NMR δ 166.88 (s, C-2), 162.45 (s, C-7), 160.45 (d, C-4), 154.27 (d, C-5), 153.96 (s, C-8a), 135.64 (s, 2 C, C-2′,6′), 134.12 (s, C-1′), 129.23 (d, C-4′), 128.22 (d, 2 C, C-3′,5′), 112.88 (s, C-4a), 95.01 (d, C-8), 40.86 (t, CH_2); HRCIMS (NH_3) calcd for $C_{14}H_{11}Cl_2N_4$ *m/z* (MH^+) 309.0302, 307.0331, 305.0361, found 309.0324, 307.0348, 305.0374. Anal. ($C_{14}H_{10}Cl_2N_4$) C, H, N.

Further elution of the column with 4−4.5% MeOH/CH_2Cl_2 gave 3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7-diamine (**14**) (920 mg, 82%): mp (CH_2Cl_2/light petroleum) 218−219 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.40 (s, 1 H, H-5), 7.59 (d, J = 7.8 Hz, 2 H, H-3′,5′), 7.59 (s, 1 H, H-4), 7.46 (dd, J = 8.7, 7.4 Hz, 1 H, H-4′), 6.29 (s, 1 H, H-8), 6.26, 5.94 (2 br s, 2 × 2 H, $2NH_2$); ^{13}C NMR δ 159.84, 157.68 (2 s, C-2,7), 153.27 (s, C-8a), 150.40 (d, C-5), 136.91 (d, C-4), 135.26 (s, 2 C, C-2′,6′), 134.52 (s, C-1′), 130.61 (d, C-4′), 128.48 (d, 2 C, C-3′,5′), 116.30, 112.72 (2 s, C-3,4a), 95.43 (d, C-8); HREIMS calcd for $C_{14}H_{10}Cl_2N_4$ *m/z* (M^+) 308.0224, 306.0253, 304.0283, found 308.0215, 306.0249, 304.0277. Anal. ($C_{14}H_{10}Cl_2N_4$) C, H, N.

On some runs, further elution of the column with 5% MeOH/CH_2Cl_2 gave a crude material, which was further purified by successive chromatography on silica gel (eluting with 4−10% MeOH/EtOAc) then on alumina (eluting with 1% MeOH/CH_2Cl_2) to give traces (<1%) of 3-[2-chloro-6-(2-ethoxyethoxy)-phenyl]-1,6-naphthyridine-2,7-diamine (**13**): mp (MeOH/$CHCl_3$/light petroleum) 193−195 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.36 (s, 1 H, H-5), 7.50 (s, 1 H, H-4), 7.39 (t, J = 8.2 Hz, 1 H, H-4′), 7.17 (d, J = 7.5 Hz, 1 H, H-3′ or 5′), 7.12 (d, J = 8.5 Hz, 1 H, H-3′ or 5′), 6.29 (s, 1 H, H-8), 5.99, 5.86 (2 br s, 2 × 2 H, $2NH_2$), 4.08 (t, J = 4.7 Hz, 2 H, OCH_2), 3.53, 3.50 (2 dt, J = 11.6, 4.7 Hz, 2 H, OCH_2), 3.27, 3.25 (2 dq, J = 11.4, 7.0 Hz, 2 H, OCH_2), 0.89 (t, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR δ 159.55, 158.55, 157.99 (3 s, C-2,7,6′), 153.03 (s, C-8a), 150.03 (d, C-5), 137.09 (d, C-4), 134.22 (s, C-2′), 130.15 (d, C-4′), 124.95 (s, C-1′), 121.61 (d, C-3′), 115.13, 113.10 (2 s, C-3,4a), 111.87 (d, C-5′), 95.60 (d, C-8), 68.63, 67.84, 65.67 (3 t, $3OCH_2$), 14.89 (q, CH_3); HREIMS calcd for $C_{18}H_{19}ClN_4O_2$ *m/z* (M^+) 360.1167, 358.1197, found 360.1166, 358.1186. Anal. ($C_{18}H_{19}ClN_4O_2$·0.5H_2O) H, N; C: calcd, 58.8; found, 58.3.

3-(2,6-Dichlorophenyl)-7-fluoro-1-methyl-1,6-naphthyridin-2(1*H*)-one (17). A stirred solution of 3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2(1*H*)-one (**15**)[25] (2.00 g, 6.47 mmol) in dry DMF (50 mL) at 0 °C was treated with NaH (0.31 g of 60%, 7.75 mmol), followed by MeI (0.48 mL, 8.03 mmol), and the mixture stirred at 0 °C for 2 h. The solvent was removed under reduced pressure, and the residue was diluted

with aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 150 mL). The solvent was removed, then chromatography of the residue on silica gel, eluting with 33% light petroleum/CH_2Cl_2, gave first 3-(2,6-dichlorophenyl)-7-fluoro-2-methoxy-1,6-naphthyridine (**18**) (39 mg, 2%): mp (CH_2Cl_2/light petroleum) 165−165.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.05 (s, 1 H, H-5), 8.51 (s, 1 H, H-4), 7.66 (d, J = 8.2 Hz, 2 H, H-3′,5′), 7.53 (dd, J = 8.6, 7.6 Hz, 1 H, H-4′), 7.49 (s, 1 H, H-8), 4.02 (s, 3 H, OCH_3); ^{13}C NMR δ 163.68 (d, J_{C-F} = 234 Hz, C-7), 162.59 (s, C-2), 152.93 (d, J_{C-F} = 13 Hz, C-8a), 150.80 (dd, J_{C-F} = 18 Hz, C-5), 139.53 (d, C-4), 134.33 (s, 2 C, C-2′,6′), 133.02 (s, C-1′), 131.11 (d, C-4′), 128.27 (d, 2 C, C-3′,5′), 122.19 (d, J_{C-F} = 2.4 Hz, C-3), 119.46 (d, J_{C-F} = 3.0 Hz, C-4a), 102.52 (dd, J_{C-F} = 37 Hz, C-8), 54.58 (q, OCH_3). Anal. ($C_{15}H_9Cl_2FN_2O$) C, H, N.

Further elution with CH_2Cl_2 gave **17** (1.88 g, 90%): mp (CH_2Cl_2/light petroleum) 201−203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.70 (s, 1 H, H-5), 8.16 (s, 1 H, H-4), 7.61 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.50 (dd, J = 8.7, 7.3 Hz, 1 H, H-4′), 7.38 (s, 1 H, H-8), 3.66 (s, 3 H, NCH_3); ^{13}C NMR δ 164.21 (d, J_{C-F} = 234 Hz, C-7), 159.23 (s, C-2), 149.16 (dd, J_{C-F} = 19 Hz, C-5), 148.57 (d, J_{C-F} = 12 Hz, C-8a), 137.48 (d, C-4), 134.47 (s, 2 C, C-2′,6′), 133.85 (s, C-1′), 130.88 (d, C-4′), 128.51 (d, J_{C-F} = 2.7 Hz, C-3), 128.11 (d, 2 C, C-3′,5′), 114.64 (d, J_{C-F} = 3.0 Hz, C-4a), 93.91 (dd, J_{C-F} = 43 Hz, C-8), 29.90 (q, NCH_3). Anal. ($C_{15}H_9Cl_2FN_2O$) C, H, N, F.

7-Amino-3-(2,6-dichlorophenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (7a). A solution of **17** (80 mg, 0.25 mmol) and 25% aqueous ammonia (5.0 mL, 66 mmol) in 2-propanol (30 mL) was saturated with ammonia (gas) and stirred at 170 °C in a pressure vessel for 3 days. The solvent was removed, then the residue was diluted with aqueous Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The solvent was removed, then chromatography of the residue on silica gel, eluting with 1−2% MeOH/CH_2Cl_2, gave **7a** (70 mg, 88%): mp 239−240 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.37 (s, 1 H, H-5), 7.76 (s, 1 H, H-4), 7.56 (d, J = 8.2 Hz, 2 H, H-3′,5′), 7.43 (dd, J = 8.7, 7.4 Hz, 1 H, H-4′), 6.65 (br s, 2 H, NH_2), 6.30 (s, 1 H, H-8), 3.49 (s, 3 H, NCH_3); ^{13}C NMR δ 161.24, 159.76 (2 s, C-2,7), 150.91 (d, C-5), 146.26 (s, C-8a), 138.32 (d, C-4), 135.07 (s, 2 C, C-2′,6′), 135.03 (s, C-1′), 130.23 (d, C-4′), 127.96 (d, 2 C, C-3′,5′), 122.19 (s, C-3), 108.18 (s, C-4a), 88.28 (d, C-8), 28.76 (q, NCH_3); HREIMS calcd for $C_{15}H_{11}Cl_2N_3O$ m/z (M^+) 323.0220, 321.0250, 319.0279, found 323.0227, 321.0255, 319.0280. Anal. $C_{15}H_{11}Cl_2N_3O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-(methylamino)-1,6-naphthyridin-2(1*H*)-one (7b). Similar treatment of **17** with excess 40% aqueous methylamine (180 equiv) in 2-propanol at 100 °C (pressure vessel) for 5 h gave **7b** (97%): mp (CH_2Cl_2/light petroleum) 252−253.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.42 (s, 1 H, H-5), 7.76 (s, 1 H, H-4), 7.56 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.43 (dd, J = 8.7, 7.3 Hz, 1 H, H-4′), 7.15 (br q, J = 4.8 Hz, 1 H, N*H*CH_3), 6.20 (s, 1 H, H-8), 3.53 (s, 3 H, NCH_3), 2.88 (d, J = 4.9 Hz, 3 H, NHC*H*$_3$); ^{13}C NMR δ 160.76, 159.77 (2 s, C-2,7), 150.71 (d, C-5), 146.15 (s, C-8a), 138.32 (d, C-4), 135.05 (s, 2 C, C-2′,6′), 135.04 (s, C-1′), 130.19 (d, C-4′), 127.93 (d, 2 C, C-3′,5′), 122.03 (s, C-3), 108.03 (s, C-4a), 86.98 (br d, C-8), 28.82, 28.23 (2 q, 2NCH_3). Anal. ($C_{16}H_{13}Cl_2N_3O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-(dimethylamino)-1-methyl-1,6-naphthyridin-2(1*H*)-one (7c). Similar treatment of **17** with excess 40% aqueous dimethylamine (125 equiv) in 2-propanol at 90 °C (pressure vessel) for 30 min gave **7c** (97%): mp (CH_2Cl_2/light petroleum) 265−266 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1 H, H-5), 7.54 (s, 1 H, H-4), 7.39 (d, J = 8.2 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.09 (s, 1 H, H-8), 3.67 (s, 3 H, NCH_3), 3.22 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR δ 160.90, 160.02 (2 s, C-2,7), 150.15 (d, C-5), 146.95 (s, C-8a), 138.29 (d, C-4), 135.88 (s, 2 C, C-2′,6′), 135.01 (s, C-1′), 129.48 (d, C-4′), 127.91 (d, 2 C, C-3′,5′), 123.80 (s, C-3), 108.33 (s, C-4a), 86.64 (d, C-8), 38.40 (q, 2 C, $N(CH_3)_2$), 29.27 (q, NCH_3). Anal. ($C_{17}H_{15}Cl_2N_3O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[2-(diethylamino)ethyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7d). Similar treatment of **17** with *N*,*N*-diethylethylenediamine (10 equiv) in 2-pentanol at 115 °C for 15 h, followed by chromatography on silica gel, eluting with 2% MeOH/CH_2Cl_2 containing 0.3% Et_3N, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), followed by chromatography on alumina, eluting with 0.25−0.3% MeOH/CH_2Cl_2, gave **7d** (62%): mp (hexane/Et_2O) 100−102 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.39 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.5, 7.7 Hz, 1 H, H-4′), 6.07 (s, 1 H, H-8), 5.67 (br s, 1 H, NH), 3.65 (s, 3 H, NCH_3), 3.38 (q, J = 5.6 Hz, 2 H, NHC*H*$_2$), 2.75 (t, J = 6.0 Hz, 2 H, NCH_2), 2.60 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 1.06 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 160.80, 159.93 (2 s, C-2,7), 150.77 (d, C-5), 147.16 (s, C-8a), 138.31 (d, C-4), 135.86 (s, 2 C, C-2′,6′), 134.91 (s, C-1′), 129.51 (d, C-4′), 127.92 (d, 2 C, C-3′,5′), 123.98 (s, C-3), 109.27 (s, C-4a), 87.23 (d, C-8), 51.16 (t, NCH_2), 46.53 (t, 2 C, $N(CH_2)_2$), 39.76 (t, NCH_2), 29.37 (q, NCH_3), 11.69 (q, 2 C, 2CH_3). Anal. ($C_{21}H_{24}Cl_2N_4O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[3-(diethylamino)propyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7e). Similar treatment of **17** with 3-(diethylamino)propylamine (10 equiv) in 2-pentanol at reflux for 17 h, followed by chromatography on silica gel, eluting with 2−4% MeOH/CH_2Cl_2 containing 0.3% Et_3N, treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (3 × 50 mL), gave **7e** (94%): mp (CH_2Cl_2/light petroleum) 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 1 H, H-5), 7.51 (s, 1 H, H-4), 7.39 (d, J = 8.3 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.36 (br s, 1 H, NH), 6.01 (s, 1 H, H-8), 3.64 (s, 3 H, NCH_3), 3.43 (td, J = 6.1, 5.3 Hz, 2 H, NHC*H*$_2$), 2.60 (t, J = 6.3 Hz, 2 H, NCH_2), 2.57 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 1.83 (pentet, J = 6.3 Hz, 2 H, CH_2), 1.07 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 160.82, 160.05 (2 s, C-2,7), 150.87 (d, C-5), 147.14 (s, C-8a), 138.36 (d, C-4), 135.88 (s, 2 C, C-2′,6′), 134.96 (s, C-1′), 129.48 (d, C-4′), 127.91 (d, 2 C, C-3′,5′), 123.72 (s, C-3), 109.11 (s, C-4a), 86.65 (d, C-8), 51.87 (t, NCH_2), 47.01 (t, 2 C, $N(CH_2)_2$), 42.34 (t, NCH_2), 29.32 (q, NCH_3), 25.95 (t, CH_2), 11.81 (q, 2 C, 2CH_3). Anal. ($C_{22}H_{26}Cl_2N_4O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[4-(diethylamino)butyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7f). Similar treatment of **17** with excess 4-(diethylamino)butylamine[40] (11 equiv) in 2-pentanol at reflux for 1 day, followed by chromatography on silica gel, eluting with 2−5% MeOH/CH_2Cl_2 containing 0.3% Et_3N, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), followed by chromatography on alumina, eluting with 0.5−1% MeOH/CH_2Cl_2, gave **7f** (87%): mp (pentane) 123−124.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.39 (d, J = 8.4 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.5, 7.6 Hz, 1 H, H-4′), 6.03 (s, 1 H, H-8), 5.59 (br s, 1 H, NH), 3.64 (s, 3 H, NCH_3), 3.35 (td, J = 6.5, 4.6 Hz, 2 H, NHC*H*$_2$), 2.56 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 2.49 (t, J = 7.1 Hz, 2 H, NCH_2), 1.74 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.62 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.05 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 160.81, 159.92 (2 s, C-2,7), 150.80 (d, C-5), 147.17 (s, C-8a), 138.32 (d, C-4), 135.86 (s, 2 C, C-2′,6′), 134.92 (s, C-1′), 129.51 (d, C-4′), 127.91 (d, 2 C, C-3′,5′), 123.89 (s, C-3), 109.21 (s, C-4a), 86.72 (d, C-8), 52.57 (t, NCH_2), 46.69 (t, 2 C, $N(CH_2)_2$), 42.47 (t, NCH_2), 29.34 (q, NCH_3), 27.37, 24.91 (2 t, 2CH_2), 11.47 (q, 2 C, 2CH_3). Anal. ($C_{23}H_{28}Cl_2N_4O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[5-(diethylamino)pentyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7g). Similar treatment of **17** with crude (ca. 90%) 5-(diethylamino)pentylamine[34] (10 equiv) in 2-pentanol at reflux for 18 h, followed by chromatography on silica gel, eluting with 1−2% MeOH/CH_2Cl_2 containing 0.3% Et_3N, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), followed by chromatography on alumina, eluting with 1% EtOH/$CHCl_3$, gave **7g** (93%): foam; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.40 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.04 (s, 1 H, H-8), 5.06 (br t, J = 5.4 Hz, 1 H, N*H*CH_2), 3.65 (s, 3 H, NCH_3), 3.34 (td, J = 6.9, 5.7 Hz, 2 H, NHC*H*$_2$), 2.53 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 2.44 (t, J = 7.4 Hz, 2 H, NCH_2), 1.73 (pentet, J = 7.2 Hz, 2 H, CH_2), 1.54, 1.46 (2 pentet, J = 7.5 Hz, 2 × 2 H,

$2CH_2$), 1.03 (t, J = 7.2 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 160.78, 159.86 (2 s, C-2,7), 150.76 (d, C-5), 147.25 (s, C-8a), 138.28 (d, C-4), 135.85 (s, 2 C, C-2′,6′), 134.87 (s, C-1′), 129.53 (d, C-4′), 127.92 (d, 2 C, C-3′,5′), 124.05 (s, C-3), 109.30 (s, C-4a), 86.61 (d, C-8), 52.73 (t, NCH_2), 46.86 (t, 2 C, $N(CH_2)_2$), 42.47 (t, NCH_2), 29.38 (q, NCH_3), 29.15, 26.85, 25.07 (3 t, $3CH_2$), 11.59 (q, 2 C, $2CH_3$). Anal. ($C_{24}H_{30}Cl_2N_4O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[3-(4-methylpiperazin-1-yl)propyl]amino]-1,6-naphthyridin-2(1*H*)-one (7h). Similar treatment of **17** with 1-(3-aminopropyl)-4-methylpiperazine (11 equiv) in 2-pentanol at reflux for 16 h, followed by chromatography on silica gel, eluting with 3−6% MeOH/CH_2Cl_2 containing 0.3% Et_3N, treatment with aqueous Na_2CO_3 and extraction with EtOAc (3 × 50 mL) gave **7h** (87%): mp (CH_2Cl_2/hexane) 164−166 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.40 (s, 1 H, H-5), 7.74 (s, 1 H, H-4), 7.56 (d, J = 7.9 Hz, 2 H, H-3′,5′), 7.43 (dd, J = 8.7, 7.5 Hz, 1 H, H-4′), 7.21 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.24 (s, 1 H, H-8), 3.50 (s, 3 H, NCH_3), 3.34 (q, J = 6.4 Hz, 2 H, NHC*H*$_2$), 2.6−2.1 (br s, 8 H, $N(CH_2)_4N$), 2.36 (t, J = 7.1 Hz, 2 H, NCH_2), 2.14 (s, 3 H, NCH_3), 1.71 (pentet, J = 6.9 Hz, 2 H, CH_2); ^{13}C NMR δ 160.15, 159.80 (2 s, C-2,7), 150.73 (d, C-5), 146.07 (s, C-8a), 138.32 (d, C-4), 135.07 (s, 3 C, C-1′,2′,6′), 130.23 (d, C-4′), 127.97 (d, 2 C, C-3′,5′), 122.04 (s, C-3), 108.10 (s, C-4a), 87.73 (br d, C-8), 55.53 (t, NCH_2), 54.70, 52.66 (2 t, 2 × 2 C, $N(CH_2)_4N$), 45.67 (q, NCH_3), 39.43 (t, NCH_2), 28.81 (q, NCH_3), 26.07 (t, CH_2). Anal. ($C_{23}H_{27}Cl_2N_5O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[4-(4-methylpiperazin-1-yl)butyl]amino]-1,6-naphthyridin-2(1*H*)-one (7i). Similar treatment of **17** with 1-(4-aminobutyl)-4-methylpiperazine[41] (10 equiv) in 2-pentanol at reflux for 16 h, followed by chromatography on silica gel, eluting with 2−4% MeOH/CH_2Cl_2 containing 0.3% Et_3N, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), followed by chromatography on alumina, eluting with 1% EtOH/$CHCl_3$, gave **7i** (94%): foam; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.39 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.23 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.03 (s, 1 H, H-8), 5.54 (br s, 1 H, N*H*CH_2), 3.64 (s, 3 H, NCH_3), 3.36 (td, J = 6.2, 4.4 Hz, 2 H, NHC*H*$_2$), 2.8−2.2 (br s, 8 H, $N(CH_2)_4N$), 2.42 (t, J = 7.1 Hz, 2 H, NCH_2), 2.30 (s, 3 H, NCH_3), 1.75 (pentet, J = 6.7 Hz, 2 H, CH_2), 1.66 (pentet, J = 6.9 Hz, 2 H, CH_2); ^{13}C NMR δ 160.75, 159.85 (2 s, C-2,7), 150.74 (d, C-5), 147.13 (s, C-8a), 138.27 (d, C-4), 135.81 (s, 2 C, C-2′,6′), 134.85 (s, C-1′), 129.49 (d, C-4′), 127.88 (d, 2 C, C-3′,5′), 123.88 (s, C-3), 109.19 (s, C-4a), 86.67 (d, C-8), 57.90 (t, NCH_2), 55.02, 53.11 (2 t, 2 × 2 C, $N(CH_2)_4N$), 46.00 (q, NCH_3), 42.35 (t, NCH_2), 29.34 (q, NCH_3), 27.08, 24.47 (2 t, $2CH_2$). Anal. ($C_{24}H_{29}Cl_2N_5O{\cdot}0.5H_2O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[5-(4-methylpiperazin-1-yl)pentyl]amino]-1,6-naphthyridin-2(1*H*)-one (7j). Similar treatment of **17** with 1-(5-aminopentyl)-4-methylpiperazine[41] (9 equiv) in 2-pentanol at reflux for 24 h, followed by chromatography on silica gel, eluting with 2−4% MeOH/CH_2Cl_2 containing 0.3% Et_3N, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), followed by chromatography on alumina, eluting with 0.25−0.5% MeOH/CH_2Cl_2, gave **7j** (95%): foam; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.40 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.6, 7.8 Hz, 1 H, H-4′), 6.03 (s, 1 H, H-8), 5.01 (br t, J = 5.4 Hz, 1 H, N*H*CH_2), 3.65 (s, 3 H, NCH_3), 3.34 (td, J = 6.9, 5.8 Hz, 2 H, NHC*H*$_2$), 2.8−2.1 (br s, 8 H, $N(CH_2)_4N$), 2.37 (t, J = 7.6 Hz, 2 H, NCH_2), 2.29 (s, 3 H, NCH_3), 1.73 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.58 (pentet, J = 7.5 Hz, 2 H, CH_2), 1.47 (pentet, J = 7.4 Hz, 2 H, CH_2); ^{13}C NMR δ 160.78, 159.84 (2 s, C-2,7), 150.77 (d, C-5), 147.26 (s, C-8a), 138.27 (d, C-4), 135.85 (s, 2 C, C-2′,6′), 134.86 (s, C-1′), 129.55 (d, C-4′), 127.93 (d, 2 C, C-3′,5′), 124.10 (s, C-3), 109.33 (s, C-4a), 86.62 (d, C-8), 58.45 (t, NCH_2), 55.11, 53.26 (2 t, 2 × 2 C, $N(CH_2)_4N$), 46.04 (q, NCH_3), 42.43 (t, NCH_2), 29.40 (q, NCH_3), 29.11, 26.60, 24.98 (3 t, $3CH_2$). Anal. ($C_{25}H_{31}Cl_2N_5O{\cdot}0.75H_2O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[3-(4-morpholino)propyl]amino]-1,6-naphthyridin-2(1*H*)-one (7k). Similar treatment of **17** with 4-(3-aminopropyl)morpholine (10 equiv) in 2-pentanol at reflux for 16 h, followed by chromatography on silica gel, eluting with 3−5% MeOH/CH_2Cl_2, treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (3 × 50 mL), gave **7k** (93%): mp (CH_2Cl_2/light petroleum) 157−159 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.40 (d, J = 7.9 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.6, 7.6 Hz, 1 H, H-4′), 6.03 (s, 1 H, H-8), 5.87 (br t, J = 5.2 Hz, 1 H, N*H*CH_2), 3.77 (t, J = 4.7 Hz, 4 H, $O(CH_2)_2$), 3.65 (s, 3 H, NCH_3), 3.45 (q, J = 6.1 Hz, 2 H, NHC*H*$_2$), 2.54 (t, J = 6.6 Hz, 2 H, NCH_2), 2.50 (br m, 4 H, $N(CH_2)_2$), 1.87 (pentet, J = 6.5 Hz, 2 H, CH_2); ^{13}C NMR δ 160.77, 159.95 (2 s, C-2,7), 150.82 (d, C-5), 147.18 (s, C-8a), 138.29 (d, C-4), 135.83 (s, 2 C, C-2′,6′), 134.86 (s, C-1′), 129.53 (d, C-4′), 127.92 (d, 2 C, C-3′,5′), 123.99 (s, C-3), 109.27 (s, C-4a), 86.73 (d, C-8), 67.02 (t, 2 C, $O(CH_2)_2$), 57.20 (t, NCH_2), 53.77 (t, 2 C, $N(CH_2)_2$), 41.61 (t, NCH_2), 29.36 (q, NCH_3), 25.29 (t, CH_2). Anal. ($C_{22}H_{24}Cl_2N_4O_2$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[4-(4-morpholino)butyl]amino]-1,6-naphthyridin-2(1*H*)-one (7l). Similar treatment of **17** with 4-(4-aminobutyl)morpholine[39] (10 equiv) in 2-pentanol at reflux for 15 h, followed by chromatography (three times) on silica gel, eluting with 2.5−4% MeOH/CH_2Cl_2, treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), gave **7l** (95%): foam; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-5), 7.52 (s, 1 H, H-4), 7.39 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.02 (s, 1 H, H-8), 5.48 (br s, 1 H, N*H*CH_2), 3.75 (t, J = 4.6 Hz, 4 H, $O(CH_2)_2$), 3.65 (s, 3 H, NCH_3), 3.36 (br t, J = 6.6 Hz, 2 H, NHC*H*$_2$), 2.47 (br m, 4 H, $N(CH_2)_2$), 2.41 (t, J = 7.1 Hz, 2 H, NCH_2), 1.76, 1.66 (2 pentet, J = 7.0 Hz, 2 × 2 H, $2CH_2$); ^{13}C NMR δ 160.76, 159.85 (2 s, C-2,7), 150.76 (d, C-5), 147.18 (s, C-8a), 138.27 (d, C-4), 135.81 (s, 2 C, C-2′,6′), 134.84 (s, C-1′), 129.52 (d, C-4′), 127.89 (d, 2 C, C-3′,5′), 123.97 (s, C-3), 109.23 (s, C-4a), 86.61 (d, C-8), 66.88 (t, 2 C, $O(CH_2)_2$), 58.37 (t, NCH_2), 53.66 (t, 2 C, $N(CH_2)_2$), 42.36 (t, NCH_2), 29.34 (q, NCH_3), 27.02, 24.11 (2 t, $2CH_2$). Anal. ($C_{23}H_{26}Cl_2N_4O_2{\cdot}H_2O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[3-(imidazol-1-yl)propyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7m). Similar treatment of **17** with 1-(3-aminopropyl)imidazole (10 equiv) in 2-pentanol at reflux for 16 h, followed by chromatography twice on silica gel, eluting with 3−6% MeOH/CH_2Cl_2, treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (3 × 50 mL), gave **7m** (82%): mp (CH_2Cl_2/hexane/Et_2O) 175−178 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1 H, H-5), 7.54, 7.53 (2 s, 2 H, H-4,2″), 7.39 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.24 (dd, J = 8.5, 7.6 Hz, 1 H, H-4′), 7.11, 6.97 (2 s, 2 H, H-4″,5″), 6.03 (s, 1 H, H-8), 5.09 (br t, J = 5.8 Hz, 1 H, N*H*CH_2), 4.11 (t, J = 6.8 Hz, 2 H, NCH_2), 3.61 (s, 3 H, NCH_3), 3.41 (q, J = 6.4 Hz, 2 H, NHC*H*$_2$), 2.17 (pentet, J = 6.7 Hz, 2 H, CH_2); ^{13}C NMR δ 160.69, 159.52 (2 s, C-2,7), 150.61 (d, C-5), 147.10 (s, C-8a), 138.17 (d, C-4), 137.18 (d, C-2″), 135.77 (s, 2 C, C-2′,6′), 134.72 (s, C-1′), 129.83, 129.61 (2 d, C-4′,4″), 127.93 (d, 2 C, C-3′,5′), 124.65 (s, C-3), 118.76 (d, C-5″), 109.72 (s, C-4a), 87.76 (d, C-8), 44.32, 39.02 (2 t, $2NCH_2$), 30.82 (t, CH_2), 29.39 (q, NCH_3). Anal. ($C_{21}H_{19}Cl_2N_5O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-(phenylamino)-1,6-naphthyridin-2(1*H*)-one (7n). A mixture of **17** (86 mg, 0.27 mmol) and aniline (1.0 mL, 11.0 mmol) was stirred at 175 °C for 100 min. The resulting mixture was diluted with aqueous Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). Chromatography of the residue on silica gel, eluting with 1% MeOH/CH_2Cl_2, gave **7n** (88 mg, 83%): mp (CH_2Cl_2/light petroleum) 237−239 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.52 (br s, 1 H, NH), 8.59 (s, 1 H, H-5), 7.89 (s, 1 H, H-4), 7.68 (d, J = 7.7 Hz, 2 H, H-2″,6″), 7.58 (d, J = 8.2 Hz, 2 H, H-3′,5′), 7.45 (dd, J = 8.8, 7.5 Hz, 1 H, H-4′), 7.32 (t, J = 7.9 Hz, 2 H, H-3″,5″), 6.98 (t, J = 7.3 Hz, 1 H, H-4″), 6.73 (s, 1 H, H-8), 3.56 (s, 3 H, NCH_3); ^{13}C NMR δ 159.60, 156.99 (2 s, C-2,7), 150.07 (d, C-5), 145.91 (s, C-8a), 140.77 (s, C-1″), 138.01 (d, C-4), 134.88 (s, 2 C, C-2′,6′), 134.71 (s, C-1′), 130.38 (d, C-4′), 128.70 (d, 2 C, C-3″,5″), 127.97 (d, 2 C, C-3′,5′), 124.08 (s, C-3), 121.44 (d, C-4″), 118.94 (d, 2 C, C-2″,6″), 109.84 (s, C-4a), 91.30 (d, C-8), 28.83 (q, NCH_3). Anal. ($C_{21}H_{15}Cl_2N_3O{\cdot}0.75H_2O$) C, N; H: calcd, 4.1; found, 3.6.

3-(2,6-Dichlorophenyl)-1-methyl-7-(4-pyridinylamino)-1,6-naphthyridin-2(1*H*)-one (7o). A stirred solution of **17** (100 mg, 0.31 mmol) and 4-aminopyridine (87 mg, 0.93 mmol) in THF (5.0 mL) under nitrogen at −78 °C was treated with a solution of LDA in cyclohexane (1.2 mL of 1.5 M, 1.8 mmol), then the temperature was allowed to rise slowly to 20 °C, and the mixture stirred at 20 °C for 2 days. The resulting solution was treated with aqueous Na_2CO_3 and extracted with EtOAc (4 × 50 mL), then insoluble material was collected by filtration and combined with the above extracts. The solvent was removed, then chromatography of the residue on silica gel, eluting with 0.5−5% MeOH/EtOAc gave **7o** (58 mg, 47%): mp (MeOH/$CHCl_3$/light petroleum) 275−277 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 9.99 (br s, 1 H, NH), 8.70 (s, 1 H, H-5), 8.36 (d, J = 5.8 Hz, 2 H, H-3″,5″), 7.98 (s, 1 H, H-4), 7.71 (d, J = 5.6 Hz, 2 H, H-2″,6″), 7.59 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.47 (dd, J = 8.8, 7.4 Hz, 1 H, H-4′), 6.86 (s, 1 H, H-8), 3.60 (s, 3 H, NCH_3); ^{13}C NMR δ 159.55, 156.01 (2 s, C-2,7), 149.93 (d, 2 C, C-3″,5″), 149.78 (d, C-5), 147.44 (s, C-1″), 145.96 (s, C-8a), 137.97 (d, C-4), 134.80 (s, 2 C, C-2′,6′), 134.51 (s, C-1′), 130.58 (d, C-4′), 128.05 (d, 2 C, C-3′,5′), 125.58 (s, C-3), 112.25 (d, 2 C, C-2″,6″), 110.87 (s, C-4a), 93.79 (d, C-8), 29.03 (q, NCH_3). Anal. ($C_{20}H_{14}Cl_2N_4O$·0.5CH_3OH) C, H, N (MeOH detected in NMR).

3-(2,6-Dichlorophenyl)-7-[(4-methoxyphenyl)amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7p). A mixture of **17** (200 mg, 0.62 mmol) and *p*-anisidine (1.46 g, 11.9 mmol) was stirred at 175 °C for 4 h. The resulting mixture was diluted with aqueous Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The solvent was removed, then successive chromatography of the residue (three times) on silica gel, eluting with 0−1% MeOH/CH_2Cl_2, gave **7p** (99 mg, 38%): mp (CH_2Cl_2/light petroleum) 173−175 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.30 (d, J = 8.9 Hz, 2 H, H-2″,6″), 7.24 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.97 (d, J = 8.8 Hz, 2 H, H-3″,5″), 6.95 (br s, 1 H, NH), 6.40 (s, 1 H, H-8), 3.85 (s, 3 H, OCH_3), 3.54 (s, 3 H, NCH_3); ^{13}C NMR δ 160.67, 158.79 (2 s, C-2,7), 157.24 (s, C-4″), 150.74 (d, C-5), 147.23 (s, C-8a), 138.00 (d, C-4), 135.77 (s, 2 C, C-2′,6′), 134.71 (s, C-1′), 131.88 (s, C-1″), 129.63 (d, C-4′), 127.94 (d, 2 C, C-3′,5′), 125.24 (d, 2 C, C-2″,6″), 125.03 (s, C-3), 114.95 (d, 2 C, C-3″,5″), 110.25 (s, C-4a), 87.97 (d, C-8), 55.53 (q, OCH_3), 29.41 (q, NCH_3). Anal. ($C_{22}H_{17}Cl_2N_3O_2$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7q). A mixture of **17** (100 mg, 0.31 mmol) and 4-[2-(diethylamino)-ethoxy]aniline[29] (1.18 g, 5.67 mmol) was stirred at 170 °C for 2.5 h. The resulting mixture was diluted with aqueous Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The solvent was removed, then chromatography of the residue twice on alumina, eluting with 0.25% MeOH/CH_2Cl_2, gave a crude oil. This was further purified by preparative reversed-phase (C-18) HPLC (56% CH_3CN/aqueous HCO_2NH_4 buffer, pH 4.5), then by chromatography on alumina (due to partial oxidation during previous purification), eluting with 1% MeOH/CH_2Cl_2, to give **7q** (31 mg, 20%): mp (hexane/Et_2O) 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.28 (d, J = 8.9 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.5, 7.6 Hz, 1 H, H-4′), 6.97 (d, J = 8.9 Hz, 2 H, H-3″,5″), 6.67 (br s, 1 H, NH), 6.39 (s, 1 H, H-8), 4.09 (t, J = 6.2 Hz, 2 H, OCH_2), 3.54 (s, 3 H, NCH_3), 2.91 (t, J = 6.2 Hz, 2 H, NCH_2), 2.67 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 1.09 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 160.67, 158.79 (2 s, C-2,7), 156.55 (s, C-4″), 150.72 (d, C-5), 147.24 (s, C-8a), 138.00 (d, C-4), 135.77 (s, 2 C, C-2′,6′), 134.72 (s, C-1′), 131.84 (s, C-1″), 129.63 (d, C-4′), 127.95 (d, 2 C, C-3′,5′), 125.25 (d, 2 C, C-2″,6″), 125.05 (s, C-3), 115.58 (d, 2 C, C-3″,5″), 110.26 (s, C-4a), 87.99 (d, C-8), 66.84 (t, OCH_2), 51.72 (t, NCH_2), 47.83 (t, 2 C, $N(CH_2)_2$), 29.41 (q, NCH_3), 11.74 (q, 2 C, $2CH_3$). Anal. ($C_{27}H_{28}Cl_2N_4O_2$) C, H, N.

Further elution with 5% MeOH/CH_2Cl_2 gave 3-(2,6-dichlorophenyl)-7-[[4-[2-(diethylamino)ethoxy]phenyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one *N*-oxide (4 mg, 2%): oil; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 7.8 Hz, 2 H, H-3′,5′), 7.32 (d, J = 8.9 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.7, 7.7 Hz, 1 H, H-4′), 7.09 (br s, 1 H, NH), 6.95 (d, J = 8.8 Hz, 2 H, H-3″,5″), 6.44 (s, 1 H, H-8), 4.61 (t, J = 4.4 Hz, 2 H, OCH_2), 3.58 (t, J = 4.4 Hz, 2 H, $N(O)CH_2$), 3.56 (s, 3 H, NCH_3), 3.38 (dq, J = 12.8, 7.0 Hz, 2 H, $N(O)(CH)_2$), 3.33 (dq, J = 12.7, 7.0 Hz, 2 H, $N(O)(CH)_2$), 1.38 (t, J = 7.2 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 160.67, 158.51 (2 s, C-2,7), 155.21 (s, C-4″), 150.70 (d, C-5), 147.19 (s, C-8a), 138.00 (d, C-4), 135.77 (s, 2 C, C-2′,6′), 134.70 (s, C-1′), 132.79 (s, C-1″), 129.65 (d, C-4′), 127.95 (d, 2 C, C-3′,5′), 125.13 (s, C-3), 124.94 (d, 2 C, C-2″,6″), 115.47 (d, 2 C, C-3″,5″), 110.35 (s, C-4a), 88.37 (d, C-8), 64.21, 62.09 (2 t, OCH_2, $N(O)CH_2$), 60.96 (t, 2 C, $N(O)(CH_2)_2$), 29.46 (q, NCH_3), 8.88 (q, 2 C, $2CH_3$); HRFABMS calcd for $C_{27}H_{29}Cl_2N_4O_3$ m/z (MH^+) 529.1587, 527.1617, found 529.1577, 527.1593.

3-(2,6-Dichlorophenyl)-7-[[4-[3-(diethylamino)propoxy]phenyl]amino]-1-methyl-1,6-naphthyridin-2(1*H*)-one (7r). A stirred solution of **17** (82 mg, 0.25 mmol) and 4-[3-(diethylamino)propoxy]aniline[26] (0.17 g, 0.77 mmol) in THF (5.0 mL) under nitrogen at −78 °C was treated with a solution of LDA in cyclohexane (1.0 mL of 1.5 M, 1.5 mmol), then the temperature was allowed to rise slowly to 20 °C, and the mixture stirred at 20 °C for 43 h. The resulting solution was treated with aqueous Na_2CO_3 and extracted with EtOAc (4 × 50 mL). The solvent was removed, then chromatography of the residue on alumina, eluting with 0.25−0.5% MeOH/CH_2Cl_2, gave **7r** (67 mg, 50%): mp (CH_2Cl_2/hexane) 151−152 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 8.3 Hz, 2 H, H-3′,5′), 7.27 (d, J = 9.0 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.7, 7.7 Hz, 1 H, H-4′), 6.97 (d, J = 9.0 Hz, 2 H, H-3″,5″), 6.86 (br s, 1 H, NH), 6.39 (s, 1 H, H-8), 4.05 (t, J = 6.4 Hz, 2 H, OCH_2), 3.54 (s, 3 H, NCH_3), 2.63 (t, J = 7.3 Hz, 2 H, NCH_2), 2.56 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 1.95 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.05 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 160.68, 158.84 (2 s, C-2,7), 156.81 (s, C-4″), 150.76 (d, C-5), 147.24 (s, C-8a), 138.01 (d, C-4), 135.78 (s, 2 C, C-2′,6′), 134.73 (s, C-1′), 131.67 (s, C-1″), 129.63 (d, C-4′), 127.95 (d, 2 C, C-3′,5′), 125.29 (d, 2 C, C-2″,6″), 125.01 (s, C-3), 115.56 (d, 2 C, C-3″,5″), 110.24 (s, C-4a), 87.92 (d, C-8), 66.71 (t, OCH_2), 49.38 (t, NCH_2), 47.00 (t, 2 C, $N(CH_2)_2$), 29.41 (q, NCH_3), 27.05 (t, CH_2), 11.77 (q, 2 C, $2CH_3$). Anal. ($C_{26}H_{25}Cl_2N_5O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]amino]-1,6-naphthyridin-2(1*H*)-one (7s). Similar treatment of **17** and 4-[2-(4-methylpiperazin-1-yl)ethoxy]aniline[27] (3.6 equiv) with LDA (3.9 equiv) in THF under nitrogen at −78 to 20 °C for 2.5 days, followed by chromatography on alumina, eluting with CH_2Cl_2, gave first recovered **24** (49 mg, 49%). Further elution with 0.25−0.5% MeOH/CH_2Cl_2 gave a crude product, then chromatography again on alumina, eluting with 0.25−0.3% MeOH/CH_2Cl, gave **7s** (27 mg, 16%): mp (CH_2Cl_2/hexane) 170−171.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 8.4 Hz, 2 H, H-3′,5′), 7.28 (d, J = 8.9 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.7, 7.7 Hz, 1 H, H-4′), 6.97 (d, J = 8.9 Hz, 2 H, H-3″,5″), 6.83 (br s, 1 H, NH), 6.40 (s, 1 H, H-8), 4.14 (t, J = 5.8 Hz, 2 H, OCH_2), 3.54 (s, 3 H, NCH_3), 2.86 (t, J = 5.8 Hz, 2 H, NCH_2), 2.66, 2.50 (2 br s, 2 × 4 H, $N(CH_2)_4N$), 2.31 (s, 3 H, NCH_3); ^{13}C NMR δ 160.66, 158.71 (2 s, C-2,7), 156.43 (s, C-4″), 150.74 (d, C-5), 147.23 (s, C-8a), 137.99 (d, C-4), 135.77 (s, 2 C, C-2′,6′), 134.71 (s, C-1′), 131.97 (s, C-1″), 129.64 (d, C-4′), 127.95 (d, 2 C, C-3′,5′), 125.17 (d, 2 C, C-2″,6″), 125.08 (s, C-3), 115.66 (d, 2 C, C-3″,5″), 110.29 (s, C-4a), 88.02 (d, C-8), 66.25 (t, OCH_2), 57.15 (t, NCH_2), 55.02, 53.56 (2 t, 2 × 2 C, $N(CH_2)_4N$), 46.01 (q, NCH_3), 29.43 (q, NCH_3). Anal. ($C_{28}H_{29}Cl_2N_5O_2$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[4-[3-(4-methylpiperazin-1-yl)propoxy]phenyl]amino]-1,6-naphthyridin-2(1*H*)-one (7t). Similar treatment of **17** and 4-[3-(4-methylpiperazin-1-yl)propoxy]aniline[28] (3.9 equiv) with LDA (4.2 equiv) in THF under nitrogen at −78 to 20 °C for 2.5 days, followed by chromatography on alumina, eluting with 0.3−0.5% MeOH/CH_2Cl_2, gave **7t** (111 mg, 63%): mp (CH_2Cl_2/hexane) 159−160 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 7.8 Hz, 2 H, H-3′,5′), 7.28 (d, J = 8.8 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.7, 7.7 Hz, 1 H, H-4′),

6.96 (d, J = 8.8 Hz, 2 H, H-3″,5″), 6.90 (br s, 1 H, NH), 6.40 (s, 1 H, H-8), 4.05 (t, J = 6.4 Hz, 2 H, OCH_2), 3.54 (s, 3 H, NCH_3), 2.8−2.2 (br s, 8 H, $N(CH_2)_4N$), 2.56 (t, J = 7.4 Hz, 2 H, NCH_2), 2.30 (s, 3 H, NCH_3), 2.00 (pentet, J = 6.9 Hz, 2 H, CH_2); ^{13}C NMR δ 160.66, 158.79 (2 s, C-2,7), 156.69 (s, C-4″), 150.74 (d, C-5), 147.23 (s, C-8a), 138.00 (d, C-4), 135.76 (s, 2 C, C-2′,6′), 134.71 (s, C-1′), 131.76 (s, C-1″), 129.63 (d, C-4′), 127.94 (d, 2 C, C-3′,5′), 125.23 (d, 2 C, C-2″,6″), 125.01 (s, C-3), 115.55 (d, 2 C, C-3″,5″), 110.24 (s, C-4a), 87.94 (d, C-8), 66.59 (t, OCH_2), 55.13 (t, 3 C, NCH_2,$N(CH_2)_2$), 53.23 (t, 2 C, $N(CH_2)_2$), 46.04 (q, NCH_3), 29.41 (q, NCH_3), 26.79 (t, CH_2). Anal. ($C_{28}H_{29}Cl_2N_5O_2$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[4-(4-methylpiperazin-1-yl)phenyl]amino]-1,6-naphthyridin-2(1*H*)-one (7u). Similar treatment of **17** and 4-(4-methylpiperazin-1-yl)aniline[33] (3.0 equiv) with LDA (5.8 equiv) in THF under nitrogen at −78 to 20 °C for 40 h, followed by chromatography on alumina, eluting with 0.25−0.5% MeOH/CH_2Cl_2, then on silica gel, eluting with 2−3% MeOH/CH_2Cl_2, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with EtOAc (2 × 50 mL) gave **7u** (56 mg, 37%): mp (CH_2Cl_2/hexane) 153−161 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 7.8 Hz, 2 H, H-3′,5′), 7.26 (d, J = 9.0 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.6, 7.6 Hz, 1 H, H-4′), 6.99 (d, J = 9.0 Hz, 2 H, H-3″,5″), 6.68 (br s, 1 H, NH), 6.43 (s, 1 H, H-8), 3.54 (s, 3 H, NCH_3), 3.25 (t, J = 5.0 Hz, 4 H, $N(CH_2)_2$), 2.62 (t, J = 4.9 Hz, 4 H, $N(CH_2)_2$), 2.38 (s, 3 H, NCH_3); ^{13}C NMR δ 160.68, 158.69 (2 s, C-2,7), 150.75 (d, C-5), 148.86 (s, C-4″), 147.22 (s, C-8a), 138.01 (d, C-4), 135.78 (s, 2 C, C-2′,6′), 134.74 (s, C-1′), 130.93 (s, C-1″), 129.61 (d, C-4′), 127.94 (d, 2 C, C-3′,5′), 124.93 (s, C-3), 124.66 (d, 2 C, C-2″,6″), 117.06 (d, 2 C, C-3″,5″), 110.21 (s, C-4a), 87.95 (d, C-8), 55.03 (t, 2 C, $N(CH_2)_2$), 49.14 (t, 2 C, $N(CH_2)_2$), 46.05 (q, NCH_3), 29.44 (q, NCH_3). Anal. ($C_{26}H_{25}Cl_2N_5O\cdot0.5H_2O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[4-(4-morpholino)phenyl]amino]-1,6-naphthyridin-2(1*H*)-one (7v). Similar treatment of **17** and 4-(4-morpholinyl)aniline[42] (5.1 equiv) with LDA (4.8 equiv) in THF under nitrogen at −78 to 20 °C for 2.5 days, followed by chromatography on silica gel, eluting with 1−3% MeOH/CH_2Cl_2, then further chromatography (twice) on silica gel, eluting with 25% EtOAc/CH_2Cl_2, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL) gave **7v** (127 mg, 81%): mp (CH_2Cl_2/hexane) 157−161 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1 H, H-5), 7.55 (s, 1 H, H-4), 7.40 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.29 (d, J = 8.8 Hz, 2 H, H-2″,6″), 7.25 (dd, J = 8.4, 7.6 Hz, 1 H, H-4′), 6.98 (d, J = 8.9 Hz, 2 H, H-3″,5″), 6.94 (br s, 1 H, NH), 6.44 (s, 1 H, H-8), 3.89 (t, J = 4.8 Hz, 4 H, $O(CH_2)_2$), 3.54 (s, 3 H, NCH_3), 3.19 (t, J = 4.8 Hz, 4 H, $N(CH_2)_2$); ^{13}C NMR δ 160.68, 158.65 (2 s, C-2,7), 150.72 (d, C-5), 148.88 (s, C-4″), 147.24 (s, C-8a), 138.00 (d, C-4), 135.78 (s, 2 C, C-2′,6′), 134.73 (s, C-1′), 131.29 (s, C-1″), 129.63 (d, C-4′), 127.95 (d, 2 C, C-3′,5′), 125.01 (s, C-3), 124.64 (d, 2 C, C-2″,6″), 116.73 (d, 2 C, C-3″,5″), 110.25 (s, C-4a), 88.01 (d, C-8), 66.87 (t, 2 C, $O(CH_2)_2$), 49.48 (t, 2 C, $N(CH_2)_2$), 29.43 (q, NCH_3). Anal. ($C_{25}H_{22}Cl_2N_4O_2$) C, H, N.

4-[[3-(2,6-Dichlorophenyl)-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl]amino]-*N*,*N*-diethylbenzamide (7w). Similar treatment of **17** and 4-amino-*N*,*N*-diethylbenzamide[43] (5.1 equiv) with LDA (4.8 equiv) in THF under nitrogen at −78 to 20 °C for 2.5 days, followed by chromatography (twice) on silica gel, eluting with 1% EtOH/$CHCl_3$, gave a crude product. Crystallization twice from MeOH/CH_2Cl_2/hexane gave **7w** (95 mg, 59%): mp (MeOH/CH_2Cl_2/hexane) 297−299 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.73 (br s, 1 H, NH), 8.62 (s, 1 H, H-5), 7.92 (s, 1 H, H-4), 7.76 (d, J = 8.6 Hz, 2 H, H-3″,5″), 7.59 (d, J = 8.3 Hz, 2 H, H-2′,6′), 7.46 (dd, J = 8.7, 7.6 Hz, 1 H, H-4′), 7.33 (d, J = 8.6 Hz, 2 H, H-2″,6″), 6.77 (s, 1 H, H-8), 3.58 (s, 3 H, NCH_3), 3.36 (br s, 4 H, $N(CH_2)_2$), 1.12 (t, J = 7.0 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 169.95 (s, *C*ONEt$_2$), 159.62, 156.63 (2 s, C-2,7), 149.97 (d, C-5), 145.92 (s, C-8a), 141.74 (s, C-1″), 138.02 (d, C-4), 134.87 (s, 2 C, C-2′,6′), 134.66 (s, C-1′), 130.45 (d, C-4′), 129.63 (s, C-4″), 128.01, 127.23 (2 d, 2 × 2 C, C-3′,5′,3″,5″), 124.54 (s, C-3), 117.86 (d, 2 C, C-2″,6″), 110.19 (s, C-4a), 92.16 (d, C-8), 28.92 (q, NCH_3), 13.30 (br q, 2 C, $2CH_3$) [$N(CH_2)_2$ not observed]. Anal. ($C_{26}H_{24}Cl_2N_4O_2\cdot0.25H_2O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[4-(diethylamino)butyl]amino]-1,6-naphthyridin-2(1*H*)-one (8f). A solution of **15** (101 mg, 0.33 mmol) and 4-(diethylamino)butylamine[40] (0.50 g, 3.47 mmol) in 2-pentanol (10 mL) was stirred at reflux for 16 h. The solvent was removed under reduced pressure, then the residue was diluted with aqueous Na_2CO_3 (50 mL) and extracted with EtOAc (4 × 50 mL). The solvent was removed, then chromatography of the residue (twice) on silica gel, eluting with 5−7% MeOH/CH_2Cl_2 containing 0.3% Et_3N, gave a crude product, then treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (4 × 50 mL), gave **8f** (121 mg, 86%): mp (CH_2Cl_2/light petroleum) 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 11.30 (br s, 1 H, NH), 8.34 (s, 1 H, H-5), 7.59 (s, 1 H, H-4), 7.41 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.26 (dd, J = 8.5, 7.6 Hz, 1 H, H-4′), 6.06 (s, 1 H, H-8), 5.57 (br s, 1 H, NH), 3.26 (br m, 2 H, NHC*H*$_2$), 2.54 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 2.47 (t, J = 7.1 Hz, 2 H, NCH_2), 1.66 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.58 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.03 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 162.59, 159.66 (2 s, C-2,7), 150.19 (d, C-5), 145.62 (s, C-8a), 140.17 (d, C-4), 136.07 (s, 2 C, C-2′,6′), 134.34 (s, C-1′), 129.60 (d, C-4′), 127.94 (d, 2 C, C-3′,5′), 123.96 (s, C-3), 109.26 (s, C-4a), 87.48 (d, C-8), 52.56 (t, NCH_2), 46.70 (t, 2 C, $N(CH_2)_2$), 42.32 (t, NCH_2), 27.36, 24.73 (2 t, $2CH_2$), 11.45 (q, 2 C, $2CH_3$). Anal. ($C_{22}H_{26}Cl_2N_4O$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[4-[3-(diethylamino)propoxy]phenyl]amino]-1,6-naphthyridin-2(1*H*)-one (8r). Similar treatment of **15** with neat 4-[3-(diethylamino)propoxy]aniline[26] (10 equiv) at 170 °C for 2 h, then 175 °C for 1.5 h, followed by chromatography (twice) on alumina, eluting with 1.25% MeOH/CH_2Cl_2, then on silica gel, eluting with 10−12% MeOH/CH_2Cl_2, gave a crude product. Treatment with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (2 × 50 mL) gave **8r** (12%): mp (CH_2Cl_2/light petroleum) 230−232 °C; ^{1}H NMR ($CDCl_3$) δ 10.99 (br s, 1 H, NH), 8.39 (s, 1 H, H-5), 7.59 (s, 1 H, H-4), 7.38 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.25 (dd, J = 8.6, 7.6 Hz, 1 H, H-4′), 7.19 (d, J = 8.8 Hz, 2 H, H-2″,6″), 6.99 (br s, 1 H, NH), 6.88 (d, J = 8.8 Hz, 2 H, H-3″,5″), 6.39 (s, 1 H, H-8), 4.01 (t, J = 6.3 Hz, 2 H, OCH_2), 2.66 (t, J = 7.3 Hz, 2 H, NCH_2), 2.60 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 1.97 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.07 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 162.19 (s, C-2), 158.24 (s, C-7), 156.29 (s, C-4″), 150.14 (d, C-5), 145.59 (s, C-8a), 139.76 (d, C-4), 135.88 (s, 2 C, C-2′,6′), 133.99 (s, C-1′), 131.85 (s, C-1″), 129.66 (d, C-4′), 128.00 (d, 2 C, C-3′,5′), 125.16 (s, C-3), 124.67 (d, 2 C, C-2″,6″), 115.40 (d, 2 C, C-3″,5″), 110.21 (s, C-4a), 88.84 (d, C-8), 66.62 (t, OCH_2), 49.40 (t, NCH_2), 46.91 (t, 2 C, $N(CH_2)_2$), 26.93 (t, CH_2), 11.55 (q, 2 C, $2CH_3$). Anal. ($C_{27}H_{28}Cl_2N_4O_2$) C, H, N.

***N*-(6-Chloro-3-formyl-2-pyridyl)-2,2-dimethylpropanamide (22).** Treatment of 2-amino-6-chloropyridine (**19**)[44] with pivaloyl chloride as reported[45] gave *N*-(6-chloro-2-pyridyl)-2,2-dimethylpropanamide (**20**) (90% yield), which was lithiated with BuLi and quenched with DMF, as reported,[36] to give **22** (75% yield): mp (EtOAc/hexane) 133−135 °C (lit.[36] mp 137−139 °C).

***tert*-Butyl *N*-(6-Chloro-3-formyl-2-pyridyl)carbamate (23).** A solution of **19** (38.6 g, 0.3 mol) in dry THF (250 mL) at 0 °C was treated successively with a 2 M solution of sodium bis(trimethylsilyl)amide in THF (330 mL, 0.66 mol) and di-*tert*-butyl dicarbonate (72 g, 0.33 mol) in THF (250 mL).[46] The resulting mixture was stirred at room temperature for 15 min, and the solvent was removed under reduced pressure. The residue was treated with a mixture of EtOAc and dilute HCl, and the organic layer was separated and dried. After removal of the EtOAc, the remaining *t*-BuOH was removed azeotropically with toluene to give an oil which was purified by chromatography on silica gel. Elution first with hexane, and then with hexane/EtOAc (9:1), followed by recrystallization from hexane, gave *tert*-butyl *N*-(6-chloro-2-pyridyl)carbamate (**21**) (58.1 g, 85%): mp 88−89.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 1 H, H-3), 7.60 (t, J = 8.0 Hz, 1 H, H-4), 7.51 (br s, 1 H, exchangeable with D_2O, NH), 6.97 (d, J = 7.6 Hz, 1 H, H-5), 1.51 (s, 9 H, CH_3); ^{13}C NMR δ 151.9 (2 s, C-2, NCO_2),

148.9 (s, C-6), 140.6 (d, C-4), 118.2 (d, C-5), 110.2 (d, C-3), 81.4 (s, CO), 28.1 (q, CH_3). Anal. ($C_{10}H_{13}ClN_2O_2$) C, H, N.

A mixture of **21** (11.44 g, 50 mmol) and TMEDA (14.5 g, 125 mmol) in dry THF (200 mL) was cooled to −78 °C and treated dropwise with a 2.5 M solution of BuLi in hexanes (50 mL, 125 mmol). The mixture was allowed to warm to −10 °C; after 2 h at that temperature the deep orange-red colored solution was recooled to −78 °C and DMF (7.3 g, 100 mmol) was added. After warming to room temperature the solution was poured into a mixture of EtOAc and dilute HCl and stirred for 15 min. The organic layer was washed successively with water and $NaHCO_3$ solution, and after drying (Na_2SO_4) the solvent was removed under vacuum. Chromatography of the residue on basic alumina, eluting with CH_2Cl_2/hexane (3:2), gave **23** (8.35 g, 65%): mp (CH_2Cl_2/hexane) 145−145.5 °C; ^{1}H NMR ($CDCl_3$) δ 10.14 (br s, 1 H, exchangeable with D_2O, NH), 9.88 (s, 1 H, CHO), 7.95 (d, J = 8.0 Hz, 1 H, H-4), 7.11 (d, J = 8.0 Hz, 1 H, H-5), 1.52 (s, 9 H, CH_3); ^{13}C NMR δ 191.6 (d, CHO), 155.9 (s, C-2), 152.0 (s, C-6), 149.8 (s, NCO_2), 145.4 (d, C-4), 117.8 (d, C-5), 115.1 (s, C-3), 82.0 (s, CO), 28.0 (q, CH_3). Anal. ($C_{11}H_{13}ClN_2O_3$) C, H, N.

***tert*-Butyl 2-(2,6-Dichlorophenyl)acetate (24).** A solution of 2,6-dichlorophenylacetyl chloride (from treatment of 12.5 g of 2,6-dichlorophenylacetic acid with excess $SOCl_2$) in CH_2Cl_2 was added to a stirred mixture of *t*-BuOH (56 g, 0.75 mol) and Et_3N (12 g, 0.12 mol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was allowed to warm to room temperature and after 2 h was diluted with water. The organic layer was washed successively with water, dilute HCl, water, and aqueous $NaHCO_3$ solution before being dried ($CaCl_2$). Removal of the solvent and chromatography of the residue on silica gel, eluting with hexane/CH_2Cl_2 (3:2), gave **24** (13.5 g, 84%): mp (hexane) 42−43.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.13 (dd, J = 8.4, 7.7 Hz, 1 H, H-4′), 3.93 (s, 2 H, CH_2), 1.45 (s, 9 H, CH_3); ^{13}C NMR δ 168.6 (s, CO_2), 136.1 (C-2′,6′), 131.9 (s, C-1′), 128.6 (d, C-4′), 127.9 (d, C-3′,5′), 81.4 (s, CO), 37.9 (t, CH_2), 27.9 (q, CH_3). Anal. ($C_{12}H_{14}Cl_2O_2$) C, H, Cl.

***tert*-Butyl 3-[6-Chloro-2-[(2,2-dimethylpropanoyl)amino]-3-pyridyl]-2-(2,6-dichlorophenyl)-3-hydroxypropanoate (25).** A solution of **24** (3.9 g, 15 mmol) in dry Et_2O (50 mL) was cooled to −78 °C and treated with 1.5 M LDA (16.7 mL, 25 mmol). After 30 min, a solution of **22** (2.41 g, 10 mmol) in the minimum volume of THF was added, and the resulting bright yellow solution was maintained at −78 °C for a further 30 min. After neutralization with dilute HCl, the reaction mixture was worked up in EtOAc and the product was chromatographed on alumina, eluting with CH_2Cl_2, to give **25** (2.0 g, 40%): mp (*i*-Pr_2O) 182−184 °C; ^{1}H NMR ($CDCl_3$) δ 9.59 (br s, 1 H, exchangeable with D_2O, NH), 7.21 and 7.10 (2 m, 1 H, H-4″), 7.05 (t, J = 8.0 Hz, 2 H, H-3′,5′), 6.96 (d, J = 8.0 Hz, 1 H, H-4′), 6.68 (d, J = 7.9 Hz, 1 H, H-5″), 5.76 (d, J = 1.6 Hz, exchangeable with D_2O, OH), 5.70 (dd, J = 9.9, 1.6 Hz, 1 H, H-3), 4.82 (d, J = 9.9 Hz, 1 H, H-2), 1.42 (s, 9 H, CH_3), 1.34 (s, 9 H, CH_3). Anal. ($C_{23}H_{27}Cl_3N_2O_4$) C, H, N.

***tert*-Butyl 3-[6-Chloro-2-(*tert*-butoxycarbonylamino)-3-pyridyl]-2-(2,6-dichlorophenyl)-3-hydroxypropanoate (26).** A solution of **24** (2.57 g, 10 mmol) was treated with **23**, as above, to give **26** (2.68 g, 52% yield): mp (*i*-Pr_2O) 139−140.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1 H, exchangeable with D_2O, NH), 7.20 and 7.10 (2 m, 1 H, H-4″), 7.06−7.00 (m, 3 H, H-3′,4′,5′), 6.63 (d, J = 7.8 Hz, 1 H, H-5″), 5.75 (dd, J = 9.7, 1.4 Hz, 1 H, H-3), 5.40 (d, J = 1.5 Hz, exchangeable with D_2O, OH), 4.82 (d, J = 9.7 Hz, 1 H, H-2), 1.54 (s, 9 H, CH_3), 1.44 (s, 9 H, CH_3). Anal. ($C_{23}H_{27}Cl_3N_2O_5$) C, H, N.

2-Amino-6-chloro-3-[(*E*)-2-(2,6-dichlorophenyl)ethenyl]-pyridine (27). A solution of **25** (1.25 g, 2.5 mmol) in dioxane (20 mL) and 3 M HCl (10 mL) was heated under reflux for 2 h before the solvent was removed under vacuum. The solid residue was treated with dilute NH_3, extracted into EtOAc, and dried. Chromatography on alumina, eluting with CH_2Cl_2, gave **27** (0.37 g, 49% yield): mp (*i*-Pr_2O) 143−144 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.83 (d, J = 7.9 Hz, 1 H, H-4), 7.53 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.32 (t, J = 8.1 Hz, 1 H, H-4′), 7.15 (d, J = 16.2 Hz, 1 H, vinyl H), 6.96 (d, J = 16.2 Hz, 1 H, vinyl H), 6.62 (d, J = 7.9 Hz, 1 H, H-5), 6.55 (br s, 2 H, exchangeable with D_2O, NH). Anal. ($C_{13}H_9Cl_3N_2$) C, H, N.

Similar treatment of **26** also gave **27** as the only isolated product (54% yield).

5-[2-Cyano-2-(2,6-dichlorophenyl)ethenyl]-6-[(2,2-dimethylpropanoyl)amino]-2(1*H*)-pyridone (28). A solution of 2,6-dichlorophenylacetonitrile (4.19 g, 22 mmol) in dry THF (100 mL) was cooled to −78 °C and treated with 1.5 M LDA (14.7 mL, 22 mmol). After 30 min, a solution of **23** (2.57 g, 10 mmol) in THF (20 mL) was added, and the resulting mixture was allowed to warm to room temperature overnight. Removal of the solvent and workup in EtOAc gave a crude product which was chromatographed on alumina, eluting with CH_2Cl_2, to give **28** (2.05 g, 50%): mp (MeOH) 146 °C dec; ^{1}H NMR ($CDCl_3$) δ 11.54 (br s, 1 H, exchangeable with D_2O, NH), 11.34 (br s, 1 H, exchangeable with D_2O, NH), 9.31 (s, 1 H, vinyl H), 7.46 (d, J = 8.3 Hz, 2 H, H-3′,5′), 7.31 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 7.14 (d, J = 9.7 Hz, 1 H, H-4), 6.71 (dd, J = 9.7, 2.0 Hz, 1 H, H-5), 1.42 (s, 9 H, CH_3); HREIMS calcd for $C_{19}H_{17}Cl_2N_3O_3$ m/z (M^+) 405.0647, 407.0617, 409.0588, found 405.0623, 407.0605, 409.0577. Anal. ($C_{19}H_{17}Cl_2N_3O_3$) C, H, N, Cl.

3-(2,6-Dichlorophenyl)-7-(2-ethoxyethoxy)-1,8-naphthyridin-2-amine (29). A mixture of **22** (8.42 g, 35 mmol) and 2,6-dichlorophenylacetonitrile (13 g, 70 mmol) in 2-ethoxyethanol (75 mL) containing dissolved sodium (2.4 g, 105 mmol), was heated under reflux for 3 h. The mixture was poured into water and the pH was adjusted to neutral. Extraction with EtOAc gave an oil which was chromatographed on alumina, eluting with CH_2Cl_2/MeOH (99.6:0.4), to give **29** (5.27 g, 40%): mp (CH_2Cl_2/*i*-Pr_2O) 191−192 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.99 (d, J = 8.5 Hz, 1 H, H-5), 7.75 (s, 1 H, H-4), 7.62 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.49 (dd, J = 8.7, 7.5 Hz, 1 H, H-4′), 6.70 (d, J = 8.5 Hz, H-6), 6.30 (br s, 2 H, exchangeable with D_2O, NH_2), 4.49 (t, J = 4.7 Hz, 2 H, CH_2O), 3.75 (t, J = 4.7 Hz, CH_2O), 3.51 (q, J = 7.0 Hz, 2 H, CH_2O), 1.14 (t, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR δ 164.0 (s), 157.7 (s), 155.4 (s), 139.2 (d), 137.9 (d), 135.1 (s, C-2′,6′), 134.3 (s, C-1′), 130.8 (d, C-4′), 128.5 (d, C-3′,5′), 117.2 (s), 112.1 (s), 107.4 (d, C-6), 68.1 (t, CH_2), 65.6 (t, CH_2), 64.8 (t, CH_2), 15.0 (q, CH_3). Anal. ($C_{18}H_{17}Cl_2N_3O_2$) C, H, N, Cl.

7-Amino-6-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (30). A solution of **29** (5.27 g, 13.9 mmol) in concentrated HCl/dioxane (1:4) (100 mL) was heated under reflux overnight, cooled, and poured onto ice/concentrated ammonia to give **30** (3.67 g, 81%): mp (MeOH) 371−372 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.65 (br s, 1 H, exchangeable with D_2O, NH), 7.67 (d, J = 9.4 Hz, 1 H, H-4), 7.59 (d, J = 7.8 Hz, 2 H, H-3′,5′), 7.54 (s, 1 H, H-5), 7.46 (dd, J = 8.7, 7.4 Hz, 1 H, H-4′), 6.38 (br s, 2 H, exchangeable with D_2O, NH_2), 6.15 (dd, J = 9.3, 1.9 Hz, 1 H, H-3); ^{13}C NMR δ 163.7 (s), 157.2 (s), 150.1 (s), 139.5 (d), 138.1 (d), 135.4 (s, C-2′,6′), 133.9 (s), 130.8 (d, C-4′), 128.5 (d, C-3′,5′), 115.5 (d, C-3), 112.9 (s), 105.1 (s). Anal. ($C_{14}H_9Cl_2N_3O$) C, H, N.

7-Acetamido-6-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (31). A mixture of **30** (0.5 g, 1.6 mmol), AcOH (15 mL) and Ac_2O (5 mL) was heated under reflux for 1 h, cooled, and diluted with water. The mixture was then poured onto ice/concentrated ammonia solution and extracted with EtOAc to give **31** (0.53 g, 93%): mp (EtOAc/MeOH) 253−255 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.25 (br s, 1 H, exchangeable with D_2O, NH), 10.10 (br s, 1 H, exchangeable with D_2O, NH), 8.06 (s, 1 H, H-5), 7.94 (d, J = 9.5 Hz, 1 H, H-4), 7.55 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.42 (dd, J = 8.6, 7.7 Hz, 1 H, H-4′), 6.55 (d, J = 9.5 Hz, 1 H, H-3), 1.94 (s, 3 H, CH_3); ^{13}C NMR δ 168.8 (s), 163.0 (s), 149.9 (s), 148.8 (s), 140.2 (d), 138.4 (d), 134.7 (s, C-2′,6′), 134.4 (s, C-1′), 130.2 (d), 128.3 (d, C-3′,5′), 122.0 (d), 120.5 (s), 111.4 (s), 23.1 (q, CH_3). Anal. ($C_{16}H_{11}Cl_2N_3O_2$) C, H, N.

7-Chloro-3-(2,6-dichlorophenyl)-1,8-naphthyridin-2-amine (32). A suspension of **31** (2.54 g, 7.3 mmol) in $POCl_3$ (50 mL) was heated under reflux for 1 h to give a clear solution. Excess $POCl_3$ was removed under vacuum, a mixture of

dioxane (80 mL) and 2 M KOH (20 mL) was added, and the resulting solution was heated under reflux for 30 min. After removal of the dioxane, the product was extracted into EtOAc and chromatographed on alumina, eluting with CH_2Cl_2/MeOH (99.6:0.4), to give **32** (1.47 g, 62%): mp (CH_2Cl_2) 282−283 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.16 (d, J = 8.2 Hz, 1 H, H-5), 7.93 (s, 1 H, H-4), 7.63 (d, J = 8.3 Hz, 2 H, H-3′,5′), 7.51 (dd, J = 8.7, 7.3 Hz, 1 H, H-4′), 7.25 (d, J = 8.2 Hz, 1 H, H-6), 6.75 (br s, 2 H, exchangeable with D_2O, NH_2); ^{13}C NMR δ 158.5 (s), 156.1 (s), 151.7 (s), 139.7 (d), 138.2 (d), 134.8 (s, C-2′,6′), 133.5 (s, C-1′), 131.1 (d, C-4′), 128.6 (d, C-3′,5′), 121.1 (s), 117.5 (d, C-6), 115.5 (s). Anal. ($C_{14}H_8Cl_3N_3$) C, H, N.

7-Chloro-3-(2,6-dichlorophenyl)-1,8-naphthyridin-2(1*H*)-one (33). A solution of **32** (0.82 g, 2.5 mmol) in TFA (10 mL) was cooled to −10 °C and finely powdered $NaNO_2$ (0.4 g, 5.8 mmol) was added in portions over 5 min.[37] After a further 30 min, the mixture was poured into ice−water to give **33** (0.75 g, 91%): mp (EtOAc) 268−270 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.77 (br s, 1 H, exchangeable with D_2O, NH), 8.24 (d, J = 8.2 Hz, 1 H, H-5), 8.08 (s, 1 H, H-4), 7.88 (d, J = 7.9 Hz, 2 H, H-3′,5′), 7.49 (dd, J = 8.7, 7.4 Hz, 1 H, H-4′), 7.41 (d, J = 8.1 Hz, 1 H, H-6); ^{13}C NMR δ 160.3 (s), 151.0 (s), 149.4 (s), 139.9 (d), 138.7 (d), 134.5 (s, C-2′,6′), 133.7 (s, C-1′), 130.8 (d), 130.6 (s), 128.1 (d, C-3′,5′), 118.7 (d, C-6), 112.9 (s). Anal. ($C_{14}H_7Cl_3N_2O$) C, H, N.

7-Chloro-3-(2,6-dichlorophenyl)-1-methyl-1,8-naphthyridin-2(1*H*)-one (34). A solution of **33** (0.75 g, 2.3 mmol) in DMF (10 mL) was cooled to 0 °C, and NaH (0.12 g of a 60% dispersion in oil, 3 mmol) was added. After gas evolution had ceased, excess iodomethane was added and the mixture was stirred at 0 °C for 15 min. Dilution with water and extraction with EtOAc gave a crude solid, which was purified by chromatography on silica gel. Elution with CH_2Cl_2/hexane (1:1), gave **34** (0.62 g, 79%): mp (*i*-Pr_2O) 203−205 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.31 (d, J = 8.1 Hz, 1 H, H-5), 8.14 (s, 1 H, H-4), 7.62 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.50 (m, 2 H, H-4′,6), 3.72 (s, 3 H, CH_3); ^{13}C NMR δ 159.7 (s), 150.5 (s), 149.1 (s), 140.6 (d), 137.6 (d), 134.4 (s, C-2′,6′), 133.9 (s, C-1′), 130.8 (d), 129.5 (s), 128.1 (d, C-3′,5′), 118.7 (d, C-6), 113.7 (s), 28.6 (q, CH_3). Anal. ($C_{15}H_9Cl_3N_2O$) C, H, N.

7-Amino-3-(2,6-dichlorophenyl)-1-methyl-1,8-naphthyridin-2(1*H*)-one (9a). A mixture of **34** (0.21 g, 6 mmol) and concentrated ammonia solution (2 mL) in DMSO (20 mL) was heated in a sealed pressure vessel at 140 °C overnight. The mixture was diluted with EtOAc, washed several times with water, dried, and the solvent removed under reduced pressure. The resulting product was purified by chromatography on alumina, eluting with CH_2Cl_2, to give **9a** (0.14 g, 71%): mp (*i*-Pr_2O) 243−245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.73 (d, J = 8.6 Hz, 1 H, H-5), 7.67 (s, 1 H, H-4), 7.55 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.42 (dd, J = 8.7, 7.6 Hz, 1 H, H-4′), 6.98 (br s, 2 H, exchangeable with D_2O, NH_2), 6.42 (d, J = 8.4 Hz, 1 H, H-6), 3.62 (s, 3 H, CH_3). Anal. ($C_{15}H_{11}Cl_2N_3O$) C, H, N.

Similarly prepared were:

3-(2,6-Dichlorophenyl)-7-[[3-(diethylamino)propyl]amino]-1-methyl-1,8-naphthyridin-2(1*H*)-one (9e): 78% yield; mp (*i*-Pr_2O) 207−209 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.70 (d, J = 8.6 Hz, 1 H, H-5), 7.66 (s, 1 H, H-4), 7.63 (m, 1 H, exchangeable with D_2O, NH), 7.55 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.42 (dd, J = 8.6, 7.4 Hz, 1 H, H-4′), 6.44 (d, J = 8.6 Hz, 1 H, H-6), 3.65 (s, 3 H, CH_3), 3.38 (m, 2 H, CH_2N), 2.47 (m, 6 H, 3 × CH_2N), 1.72 (pentet, J = 7.0 Hz, 2 H, CH_2), 0.96 (t, J = 7.1 Hz, 6 H, 2 × CH_3); HREIMS calcd for $C_{22}H_{26}Cl_2N_4O$ m/z (M^+) 436.1425, 434.1454, 432.1484, found 436.1435, 434.1455, 432.1481.

3-(2,6-Dichlorophenyl)-1-methyl-7-[[3-(4-methylpiperazinyl)propyl]amino]-1,8-naphthyridin-2(1*H*)-one (9h): 70% yield; mp (*i*-Pr_2O) 202−205 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.69 (d, J = 8.6 Hz, 1 H, H-5), 7.66 (s, 1 H, H-4), 7.62 (m, 1 H, exchangeable with D_2O, NH), 7.55 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.42 (dd, J = 8.5, 7.6 Hz, 1 H, H-4′), 6.44 (d, J = 8.6 Hz, 1 H, H-6), 3.64 (s, 3 H, CH_3), 3.43 (br d, J = 5.5 Hz, 2 H, CH_2N), 2.37 (t, J = 7.0 Hz, 2 H, CH_2N), 2.34 (m, 8H, CH_2N), 2.15 (s, 3 H, CH_3), 1.75 (pentet, J = 6.9 Hz, 2 H, CH_2). Anal. ($C_{23}H_{27}Cl_2N_5O$) C, H, N.

3-(2,6-Dichlorophenyl)-1-methyl-7-(phenylamino)-1,8-naphthyridin-2(1*H*)-one (9n). A mixture of **34** (0.21 g, 0.6 mmol) and aniline (0.3 g, 3.2 mmol) in dry THF (15 mL) was cooled to −78 °C, and LDA (1.6 mL of a 1.5 M solution of in cyclohexane, 2.4 mmol) was added with stirring. The mixture was allowed to warm to room temperature overnight, then brought to neutral pH with AcOH. The solvent was removed under reduced pressure, the residue was extracted into EtOAc, and the crude product was purified by chromatography on silica gel. Elution first with CH_2Cl_2 and then CH_2Cl_2/EtOAc (9:1) gave **9n** (0.10 g, 41%): mp (EtOAc) 281−283 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.79 (br s, 1 H, exchangeable with D_2O, NH), 7.96 (d, J = 8.5 Hz, 1 H, H-5), 7.82 (d, J = 8.1 Hz, 2 H, H-2″,6″), 7.78 (s, 1 H, H-4), 7.58 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.46 (t, J = 8.3 Hz, 1 H, H-4′), 7.41 (t, J = 7.7 Hz, 2 H, H-3″,5″), 7.03 (t, J = 7.4 Hz, 1 H, H-4″), 6.78 (d, J = 8.4 Hz, 1 H, H-6), 3.73 (s, 3 H, CH_3). Anal. ($C_{21}H_{15}Cl_2N_3O$) C, H, N.

Similarly prepared were:

3-(2,6-Dichlorophenyl)-7-[(4-methoxyphenyl)amino]-1-methyl-1,8-naphthyridin-2(1*H*)-one (9p): 53% yield; mp (EtOAc) 285−287 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.63 (br s, 1 H, exchangeable with D_2O, NH), 7.87 (d, J = 8.5 Hz, 1 H, H-5), 7.76 (s, 1 H, H-4), 7.71 (br d, J = 9.1 Hz, 2 H, H-2″,6″), 7.57 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.43 (dd, J = 8.7, 7.6 Hz, 1 H, H-4′), 6.96 (br d, J = 9.1 Hz, 2 H, H-3″,5″), 6.70 (d, J = 8.6 Hz, 1 H, H-6), 3.76 (s, 3 H, CH_3O), 3.70 (s, 3 H, CH_3N). Anal. ($C_{22}H_{17}Cl_2N_3O_2$) C, H, N.

3-(2,6-Dichlorophenyl)-7-[[4-[2-(diethylamino)ethoxy]-phenyl]amino]-1-methyl-1,8-naphthyridin-2(1*H*)-one (9q): 79% yield; mp (*i*-Pr_2O) 211−211.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.63 (br s, 1 H, exchangeable with D_2O, NH), 7.87 (d, J = 8.6 Hz, 1 H, H-5), 7.76 (s, 1 H, H-4), 7.69 (br d, J = 9.0 Hz, 2 H, H-2″,6″), 7.57 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.44 (dd, J = 8.6, 7.5 Hz, 1 H, H-4′), 6.96 (br d, J = 9.0 Hz, 2 H, H-3″,5″), 6.70 (d, J = 8.5 Hz, 1 H, H-6), 4.02 (t, J = 6.1 Hz, 2 H, CH_2O), 3.69 (s, 3 H, CH_3), 2.79 (t, J = 6.0 Hz, 2 H, CH_2N), 2.57 (q, J = 7.0 Hz, 4 H, 2 × CH_2N), 0.99 (t, J = 7.1 Hz, 6 H, CH_3). Anal. ($C_{27}H_{28}Cl_2N_4O_2 \cdot H_2O$) H, N; C: calcd, 61.3; found, 61.8.

PDGF and FGF Receptor Tyrosine Kinase Assays. Full length cDNAs for the mouse PDGF-β and human FGF-1 (flg) receptor tyrosine kinases were prepared as described,[47] and PCR primers were designed to amplify a fragment of DNA that codes for the intracellular tyrosine kinase domain. The fragment was subcloned into a baculovirus vector and cotransfected with AcMNPV DNA, and the recombinant virus isolated. SF9 insect cells were infected with the virus to overexpress the protein, and the cell lysate was used for the assay. The assay was performed in 96-well plates (100 μL/incubation/well), and conditions were optimized to measure the incorporation of [^{32}P]ATP into a glutamate-tyrosine copolymer substrate. Briefly, to each well were added 82.5 μL of incubation buffer, containing 25 mM Hepes (pH 7.0), 150 mM NaCl, 0.1% Triton X-100, 0.2 mM PMSF, 0.2 mM Na_3VO_4, 10 mM $MnCl_2$, and 750 μg/mL of poly (4:1) glutamate-tyrosine, followed by 2.5 μL of inhibitor and 5 μL of enzyme lysate (7.5 μg/mL FGF-TK or 6.0 μg/mL PDGF-TK) to initiate the reaction. Following a 10-min incubation at 25 °C, 10 μL of [^{32}P]ATP (0.4 μCi plus 50 μM ATP) was added to each well and samples were incubated for an additional 10 min at 25 °C. The reaction was terminated by the addition of 100 μL of 30% trichloroacetic acid (TCA) containing 20 mM sodium pyrophosphate and precipitation of material onto glass fiber filter mats (Wallac). Filters were washed three times with 15% TCA containing 100 mM sodium pyrophosphate and the radioactivity retained on the filters was counted in a Wallac 1250 Betaplate reader. Nonspecific activity was defined as radioactivity retained on the filters following incubation of samples with buffer alone (no enzyme). Specific enzymatic activity was defined as total activity (enzyme plus buffer) minus nonspecific activity. The concentration of a compound that inhibited specific activity by 50% (IC_{50}) was determined based on the inhibition curve.

c-Src Nonreceptor Kinase Assay. c-Src kinase was purified from baculovirus-infected insect cell lysates using an antipeptide monoclonal antibody directed against the N-

terminal 2−17 amino acids. The antibody, covalently linked to 0.65-μm latex beads, was added to a suspension of insect cell lysis buffer comprising 150 mM NaCl, 50 mM Tris (pH 7.5), 1 mM DTT, 1% NP-40, 2 mM EGTA, 1 mM sodium vanadate, 1 mM PMSF, 1 μg/mL each of leupeptin, pepstatin, and aprotinin. Insect cell lysate containing the c-*src* protein was incubated with these beads for 3−4 h at 4 °C with rotation. At the end of the lysate incubation, the beads were rinsed three times in lysis buffer, resuspended in lysis buffer containing 10% glycerol, and frozen for use. These latex beads were thawed when needed, rinsed three times in assay buffer (40 mM tris pH 7.5, 5 mM $MgCl_2$), and suspended in the same buffer. The assay has been described previously.[48] Briefly, the reaction components [10 μL c-Src beads, 10 μL of 2.5 mg/mL poly GluTyr substrate, 5 μM ATP containing 0.2 μCi labeled [^{32}P]ATP, 5 μL DMSO containing inhibitors or as a solvent control, and buffer to make the final volume 125 μL] were mixed in Millipore 96-well plates with a 0.65-μm polyvinylidine membrane bottom. The reaction was started at room temperature by addition of the ATP and quenched 10 min later by the addition of 125 μL of 30% TCA, 0.1 M sodium pyrophosphate for 5 min on ice. The plate was then filtered and the wells washed with two 250-μL aliquots of 15% TCA, 0.1 M pyrophosphate. The filters were punched and counted in a liquid scintillation counter, and the data was used to determine inhibitory activity in comparison to a known inhibitor such as erbstatin.

PDGF Receptor Autophosphorylation. Rat aorta smooth muscle cells (RASMC) were isolated from the thoracic aorta of rats and explanted according to the method of Ross.[49] Cells were grown in Dulbecco's modified Eagle's medium (DMEM; Gibco) containing 10% fetal calf serum (FBS; Hyclone, Logan, UT), 1% glutamine (Gibco) and 1% penicillin/streptomycin (Gibco). RASMC were grown to confluency in 100-mm dishes. Growth medium was removed and replaced with serum-free medium and cells were incubated at 37 °C for an additional 24 h. Test compounds were then added directly to the medium and cells incubated for an additional 2 h. After 2 h, PDGF-BB was added at a final concentration of 30 ng/mL for 5 min at 37 °C to stimulate autophosphorylation of the PDGF receptor. Following growth factor treatment, the medium was removed, and cells were washed with cold phosphate-buffered saline and immediately lysed with 1 mL of lysis buffer (50 mM HEPES (pH 7.5), 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM EDTA, 1 mM EGTA, 50 mM NaF, 1 mM sodium orthovanadate, 30 mM *p*-nitrophenyl phosphate, 10 mM sodium pyrophosphate, 1 mM phenylmethanesulfonyl fluoride, 10 μg/mL aprotinin, and 10 μg/mL leupeptin). Lysates were centrifuged at 10000*g* for 10 min. Supernatants were incubated with 10 μL of rabbit anti-human PDGF type AB receptor antibody (1:1000) for 2 h. Following the incubation, protein-A-Sepharose beads were added for 2 h with continuous mixing, and immune complexes bound to the beads washed four times with 1 mL lysis wash buffer. Immune complexes were solubilized in 30 μL of Laemmli sample buffer and electrophoresed in 4−20% SDS polyacrylamide gels. Following electrophoresis, separated proteins were transferred to nitrocellulose and immunoblotted with anti-phosphotyrosine antiserum. Following incubation with [^{125}I]protein-A, the levels of tyrosine phosphorylated proteins were detected by phosphorimage analysis and protein bands quantitated via densitometry. IC_{50} values were generated from the densitometric data.

Growth Inhibition Assay. Cells were seeded into 96-well tissue culture plates 24 h prior to addition of a concentration range of the experimental compounds dissolved in DMSO and diluted into culture medium (final DMSO concentration < 0.5% vol/vol). Plates were incubated for 3 days in humidified atmosphere containing 5% CO_2 in air. Cell growth was determined by staining the cells in sulfrhodamine B and determining growth relative to solvent control treated cells.

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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