Synthesis and Structure−Activity Relationships of Soluble 7-Substituted 3-(3,5-Dimethoxyphenyl)-1,6-naphthyridin-2-amines and Related Ureas as Dual Inhibitors of the Fibroblast Growth Factor Receptor-1 and Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinases

Andrew M. Thompson,*,† Amy M. Delaney,‡ James M. Hamby,‡ Mel C. Schroeder,‡ Teresa A. Spoon,‡ Sheila M. Crean,‡ H. D. Hollis Showalter,‡ and William A. Denny†

Auckland Cancer Society Research Centre, School of Medical Sciences, The University of Auckland, Private Bag 92019, Auckland 1000, New Zealand, and Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, Michigan 48106-1047

Received January 31, 2005

7-Substituted 3-aryl-1,6-naphthyridine-2,7-diamines and related 2-ureas are inhibitors of fibroblast growth factor receptor-1 (FGFR-1) and vascular endothelial growth factor receptor-2 (VEGFR-2). 3-(3,5-Dimethoxyphenyl) and 3-phenyl analogues were prepared from 7-acetamido-2-*tert*-butylureas by alkylation with benzyl ω-iodoalkyl ethers, debenzylation, and amination, followed by selective cleavage of the 7-*N*-acetamide. 3-(2,6-Dichlorophenyl) analogues were prepared from the 7-fluoro-2-amine by displacement with substituted alkylamines, followed by selective acylation of the resulting substituted naphthyridine-2,7-diamines with alkyl isocyanates. The 3-(3,5-dimethoxyphenyl) derivatives were low nanomolar inhibitors of both FGFR and VEGFR and were highly selective (>100-fold) over PDGFR and c-Src. Variations in the base strength or spatial position of the 7-side chain base had only small effects on the potency (<5-fold) or selectivity (<20-fold). The 3-(2,6-dichlorophenyl)-2-urea derivatives were slightly less active against VEGFR and less selective, being more effective against PDGFR (ca. 10-fold) and c-Src (ca. 500-fold). The 3-(3,5-dimethoxyphenyl)-1,6-naphthyridines were generally more potent than the corresponding pyrido[2,3-*d*]pyrimidines against both VEGFR and FGFR (2- to 20-fold), with only slightly increased PDGFR and c-Src activity. The 3-(3,5-dimethoxyphenyl)-1,6-naphthyridine 2-ureas were also low nanomolar inhibitors of the growth of human umbilical vein endothelial cells (HUVECs) stimulated by serum, FGF, or VEGF, at concentrations that did not affect the growth of representative tumor cell lines, and were more (3- to 65-fold) potent than the corresponding pyrido[2,3-*d*]pyrimidines.

Introduction

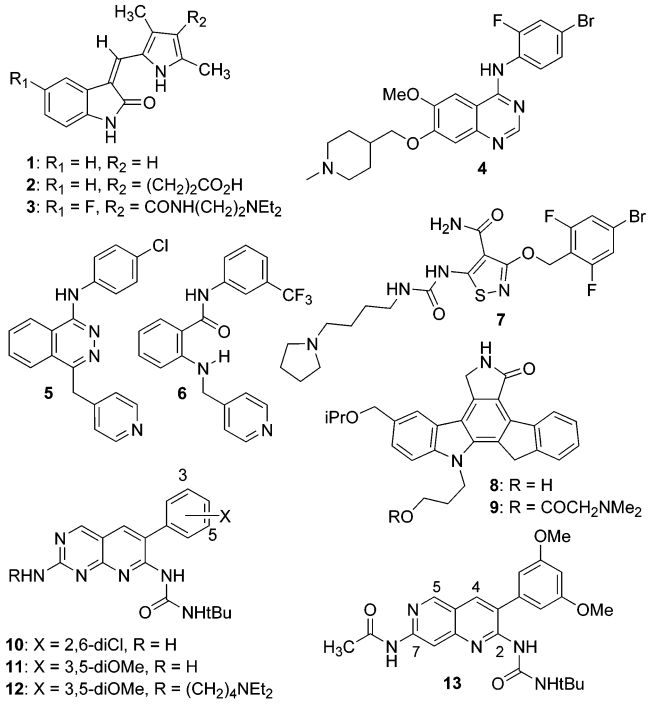
Angiogenesis, the formation of new blood vessels from existing vasculature, plays a major role in the progression of many human diseases, including cancer, where it is essential for the growth and survival of solid tumors.[1,2] A number of polypeptide growth factors are involved in mediating this process.[3−5] Among the most potent and important of these are members of the fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) families.[6] These exert their effect through cell surface receptors (FGFRs and VEGFRs) that have protein tyrosine kinase activity.[7−9] Overexpression of FGFRs, their ligands, or other aberrant kinase function has been implicated in various diseases, including not only human tumors (e.g., breast,[10] prostate,[11] and pancreatic[12] cancers) but also rheumatoid arthritis[13] and atherosclerosis.[14] Similarly, both VEGFs and their receptors have been implicated in the angiogenesis of many solid tumors (e.g., glioma,[15] breast,[16] bladder,[17] and colon[18]) as well as hematopoietic tumors,[19] and inhibition of tumor growth has been demonstrated using blocking antibodies and dominant-negative strategies.[20,21] Thus, the inhibition of FGF and VEGF receptor tyrosine kinases is a potentially effective strategy to develop new antiangiogenic agents as anticancer drugs.[22]

Several small-molecule inhibitors of VEGFR kinases have been reported to be in advanced development.[23,24] The indolin-2-ones SU5416 (**1**) and SU6668 (**2**) represent potent inhibitors of VEGFR-1, -2, and -3, as well as platelet-derived growth factor receptor kinase-β (PDGFR-β), also implicated in angiogenesis, and colony stimulating factor receptor-1 kinase (CSF-1R) (IC_{50} = 10−250 nM).[23] Both compounds showed broad-spectrum antitumor efficacy,[25,26] and clinical responses to SU5416 have been seen in patients with acute myeloid leukemia,[27] renal carcinoma, and soft tissue sarcoma.[28] A new analogue with improved solubility properties, SU11248 (**3**), provided similar potency, selectivity, and antitumor effects[29,30] and is reportedly showing promise in early clinical evaluation as an oral agent (phase I/II). The 4-anilinoquinazoline ZD6474 (**4**), a dual inhibitor of EGFR and VEGFR-2 (IC_{50} values of 16 and 17 nM, respectively[23]), also has broad-spectrum antitumor activity[31] and is progressing into phase III clinical trial. The anilinophthalazine PTK787/ZK222584 (**5**) is a much more selective VEGFR inhibitor (KDR IC_{50} = 37 nM)

* To whom correspondence should be addressed. Phone: +64-9-373-7599, extension 86145. Fax: +64-9-373-7502. E-mail: am.thompson@auckland.ac.nz.
† The University of Auckland.
‡ Ann Arbor Laboratories.

10.1021/jm0500931 CCC: $30.25
Published on Web 06/17/2005

with antitumor properties,[32] having oral activity, and has shown encouraging clinical responses in colorectal cancer (phase III clinical evaluation has commenced).[33] A cocrystal structure of the VEGFR-2 enzyme containing the structurally related anthranilimide inhibitor AAL993 (**6**) (VEGFR-2 and -3 IC_{50} values of 23 and 18 nM, respectively) shows that the drug binds to an inactive conformation of the protein, possibly accounting for the high selectivity of these inhibitors.[23] The isothiazole CP-547632 (**7**) was recently identified as a potent dual inhibitor of the VEGFR-2 and FGFR-2 kinases (IC_{50} values of 11 and 9 nM, respectively). It has oral activity in a range of human xenografts in nude mice and is reported to be in phase I/II clinical trial.[34] Finally, the pyrrolocarbazole CEP-5214 (**8**) also has very potent pan-VEGFR kinase inhibitory activity (IC_{50} values of 16, 8, and 4 nM against human VEGFR-1, -2, and -3 kinases, respectively) and antitumor effects,[35] and the water-soluble dimethylglycine ester prodrug derivative, CEP-7055 (**9**), of this is in phase I clinical trial.[36]



Small-molecule inhibitors of the FGFR include the general class of 6-arylpyrido[2,3-*d*]pyrimidines (e.g., **10**). These are broad-spectrum ATP-competitive inhibitors of a number of tyrosine kinase enzymes, including PDGFR, FGFR, EGFR, and c-Src.[37] Structure−activity relationship (SAR) studies showed that analogues of **10** bearing a 3,5-dimethoxyphenyl substituent at C-6 (e.g., **11**) were potent and very selective inhibitors of the FGFR-1 tyrosine kinase.[38] A soluble analogue of **11**, PD173074 (**12**), displayed potent antiangiogenic and antitumor effects[39,40] (both in vitro and in vivo, being efficacious orally in combination with photodynamic therapy[39]), and a crystal structure of **12** bound in the ATP site of FGFR-1 has also been reported.[40] We have recently described[41] the synthesis and biological evaluation of 1-deaza analogues of **11** (3-aryl-1,6-naphthyridine-2,7-diamines and the corresponding 2-ureas) that are equally potent and selective. The 7-acetamido derivative **13** displayed substantial antiangiogenic activity in vitro, being a potent inhibitor of growth, microcapillary formation, and invasion of human umbilical vein endothelial cells (HUVECs) and suppressed tumor growth in vivo.[41] The 7-(morpholinopropylamino) derivative **14** (Table 1), which possessed improved aqueous solubility, retained good potency (FGFR IC_{50} = 31 nM) and displayed better selectivity than **13** for FGFR. These compounds (and the related pyrido[2,3-*d*]pyrimidines) have now also been found to be very potent inhibitors of VEGFR-2 (Flk-1/KDR) (e.g., **13** and **14** IC_{50} values of 3 and 9 nM, respectively) so that they can be considered as dual FGFR/VEGFR inhibitors. Given the known redundancy in angiogenic signaling pathways that allows larger tumors to switch angiogenic factors,[16] such dual inhibitors may prove to be advantageous in the clinical development of an effective antiangiogenic agent.

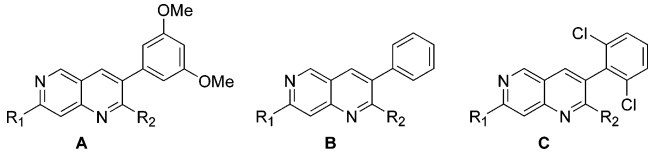
The promising results above prompted us to carry out a more extensive SAR study in the naphthyridine series, particularly focusing on a range of soluble alkylamino derivatives related to **14**. Selected analogues in the 3-phenyl and 3-(2,6-dichlorophenyl) series were also prepared and evaluated for comparative purposes. We describe here the synthesis, SAR, and further biological evaluation of these compounds alongside related pyrido-[2,3-*d*]pyrimidine analogues.

Chemistry

6-(3,5-Dimethoxyphenyl) Analogues. The most attractive route to 7-substituted naphthyridines was via an intermediate with a displaceable 7-halo group for direct reaction with the appropriate amines. We had developed a diazotization route[42] to 7-chloro or 7-fluoro derivatives in the 3-(2,6-dichlorophenyl) and 3-phenyl series, starting from 1,6-naphthyridine-2,7-diamines. However, initial problems with diazotization of the electron-rich 3-(3,5-dimethoxyphenyl)-1,6-naphthyridine-2,7-diamine[42] led us to employ a less direct approach to these compounds.[41] Thus, we previously described the preparation of the 7-morpholinopropylamino derivative **14**, by alkylation of acetamide **13** (obtained in two steps from the diamine) with substituted alkyl chlorides. However, this method was not suitable for the current SAR study, which involved chain lengths of three to five carbons and a wider range of solubilizing moieties, because many of the required dialkylaminoalkyl chloride alkylating agents are difficult to obtain and unstable (because offacile intramolecular reaction). These reagents are also hygroscopic, resulting in undesired side reactions (e.g., hydrolysis, bis-alkylation).[41] It was also desirable to have a more reactive reagent so that the alkylation could be performed at lower temperature, thereby further minimizing side reactions. Therefore, benzyl ω-iodoalkyl ethers were selected for the alkylation reaction, enabling the preparation of all the target compounds through a series of functional group manipulations (Schemes 1−3).

The required known benzyl ω-iodoalkyl ethers[43−45] were prepared in good yield by monobenzylation[44] of the diols (0.35 equiv of BnCl/1.0 equiv of NaH/DMF) to give known ω-(benzyloxy)-1-alkanols[46−48] followed by iodination[49] (I_2/PPh_3/imidazole/benzene). Treatment of the preformed (assumed) dianion of acetamide urea **13** (generated from excess NaH/DMF at 20 °C) with these iodoalkyl ethers (0−20 °C over 1−2 days) gave good

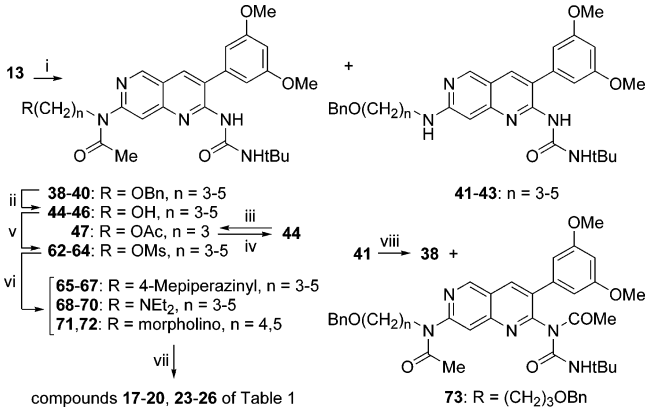
Table 1. Structure and Kinase Inhibitory Activities of Solubilized 1,6-Naphthyridines



				IC_{50} (μM)[a]				
compd	form	R_1	R_2	FGFR	FGFR#[b]	VEGFR[b]	PDGFR	c-Src
14[c]	A	$NH(CH_2)_3$morph[d]	NHCONH*t*Bu	0.031	0.012	0.009	45	>50
15[e]	A	$NH(CH_2)_3$4-Mepip[f]	NH_2	0.044	0.083	0.18	50	>50
16	A	$NH(CH_2)_3$4-Mepip	NHCONHEt	0.021	0.021	0.051	30	14
17	A	$NH(CH_2)_3$4-Mepip	NHCONH*t*Bu	0.024	0.005	0.005	16	9.1
18	A	$NH(CH_2)_3NEt_2$	NHCONH*t*Bu	0.060	0.008	0.015	18	16
19	A	$NH(CH_2)_4$morph[d]	NHCONH*t*Bu	0.030	0.007	0.006	15	21
20	A	$NH(CH_2)_4$4-Mepip[f]	NHCONH*t*Bu	0.024	0.006	0.003	3.6	4.1
21	A	$NH(CH_2)_4NEt_2$	NH_2	0.087	0.046	0.22	>50	26
22	A	$NH(CH_2)_4NEt_2$	NHCONHEt	0.024	0.013	0.046	6.5	7.0
23	A	$NH(CH_2)_4NEt_2$	NHCONH*t*Bu	0.025	0.006	0.006	2.6	4.6
24	A	$NH(CH_2)_5$morph[d]	NHCONH*t*Bu	0.033	0.009	0.007	>50	16
25	A	$NH(CH_2)_5$4-Mepip[f]	NHCONH*t*Bu	0.070	0.010	0.008	27	6.1
26	A	$NH(CH_2)_5NEt_2$	NHCONH*t*Bu	0.028	0.006	0.004	5.0	3.6
27[e]	B	$NH(CH_2)_3$4-Mepip[f]	NH_2	2.2	4.6	2.9	8.8	1.6
28	B	$NH(CH_2)_3$4-Mepip	NHCONH*t*Bu	0.19	0.14	0.054	1.2	0.23
29[e]	B	$NH(CH_2)_3$4-Mepip	$NH(CH_2)_3$4-Mep[f]	12	23	8.7	>50	6.8
30	B	$NH(CH_2)_4NEt_2$	NH_2	7.3	3.1	3.6	12	1.4
31	B	$NH(CH_2)_4NEt_2$	NHCONH*t*Bu	0.30	0.20	0.18	0.45	0.11
32[e]	C	$NH(CH_2)_3$4-Mepip[f]	NH_2	0.12	0.22	1.8	4.7	0.069
33	C	$NH(CH_2)_3$4-Mepip	NHCONHEt	0.032	0.016	0.11	0.54	0.019
34	C	$NH(CH_2)_3$4-Mepip	NHCONH*t*Bu	0.026	0.007	0.014	0.62	0.019
35	C	$NH(CH_2)_4NEt_2$	NH_2	0.35	0.63	1.2	4.0	0.042
36	C	$NH(CH_2)_4NEt_2$	NHCONHEt	0.029	0.016	0.13	0.16	0.014
37	C	$NH(CH_2)_4NEt_2$	NHCONH*t*Bu	0.025	0.007	0.025	0.48	0.014

[a] IC_{50}: concentration of drug (μM) that inhibits the phosphorylation of a random glutamate/tyrosine (4:1) copolymer by FGFR, VEGFR, PDGFR, or c-Src proteins. For active compounds, values are an average of two or more separate determinations; variation was generally ±30%. [b] DELFIA assay; see Experimental Section. [c] Reference 41. [d] *N*-Morpholinyl. [e] Reference 42. [f] 4-Methylpiperazin-1-yl.

Scheme 1[a]



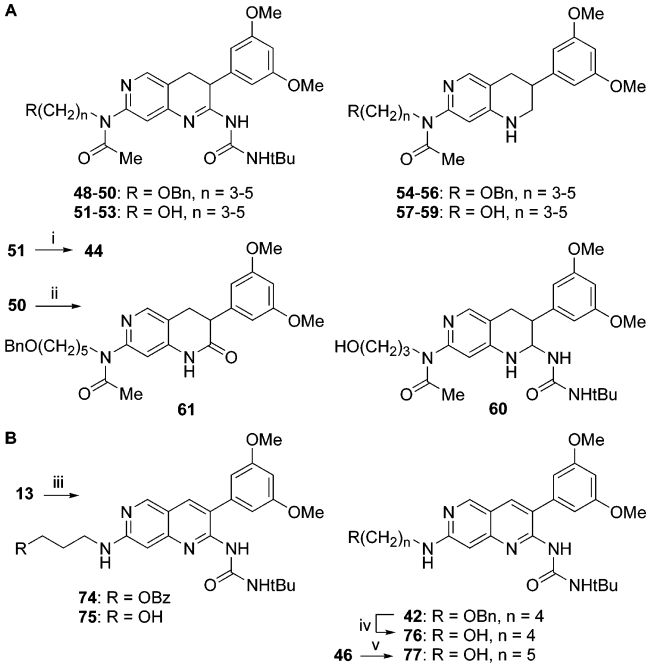
[a] (i) NaH/DMF/20 °C/20−40 min, then benzyl ω-iodoalkyl ether/DMF/0−20 °C/1−2 days; (ii) H_2/Pd−C/EtOH/20 °C/36−48 h or DDQ/CH_2Cl_2/20 °C/4 days; (iii) Ac_2O/py/20 °C/14 h; (iv) K_2CO_3/MeOH/water/20 °C/1 h; (v) MsCl/NMM/THF/20 °C/12−17 h; (vi) amine/THF/20−52 °C/1−4 days; (vii) NaOH/MeOH/water/20 °C/2−5 days; (viii) AcCl/NMM/THF/20 °C/21 h.

yields of the alkylated products **38**−**40** (73−80% on a 1.5−2 g scale), together with small amounts of the deacetylated products **41**−**43** (5−9%) and recovered **13** (4−8%) (Scheme 1). Importantly, this demonstrated both the desired selectivity for alkylation and, unlike previous results,[41] almost complete retention of the acetamide, which was required later in the synthesis. Attempted reacetylation of the propyl benzyl ether **41** (excess AcCl/NMM/THF) gave some of the desired product **38** (>36%), but a major side reaction was acetylation on the urea, giving the poorly separable bis-acetamide **73** (by HRFABMS and ^{1}H NMR), making this route unsuitable (Ac_2O/py/20 °C gave no reaction at all).

Hydrogenolysis (H_2/Pd−C) of the benzyl ethers **38**−**40** in various solvents (MeOH, EtOH, THF) proved to be difficult because of competing ring hydrogenation (as reported by Armarego[50] for the unsubstituted 1,6-naphthyridine), which could not be prevented and was more problematic with shorter side chain lengths. Considerable experimentation showed that the optimal conditions were H_2/5% Pd−C (1.2 mass equiv)/EtOH/20 °C/36−48 h, stopping the reaction after ca. 60% of the starting material was consumed, to give ca. 30−40% of the desired products after chromatography, together with recovered starting material. After several cycles through this process, moderate overall yields (45−51%) of the required alcohols **44**−**46** were obtained, albeit in varying purity (ca. 70, 90, and 100% for the propyl, butyl, and pentyl derivatives, respectively). Since the propyl alcohol **44** could not be further purified from byproducts directly, a portion was purified by acetylation (Ac_2O/py) and chromatography of the acetate **47**, followed by mild alkaline hydrolysis (K_2CO_3/MeOH/water). Subsequently, an alternative debenzylation method (excess DDQ in CH_2Cl_2 alone, with no added water[51]), developed for the 3-phenyl analogues (see below), was found to provide pure **44** more directly and in higher yield (69% after reaction at 20 °C/4 days).

The major byproducts from the hydrogenolysis reactions above were the 3,4-dihydro derivatives **48**−**53** (Scheme 2A), identified by HRFABMS and ^{1}H and ^{13}C NMR (assigned by 2D heteronuclear multiple-quantum

Scheme 2[a]

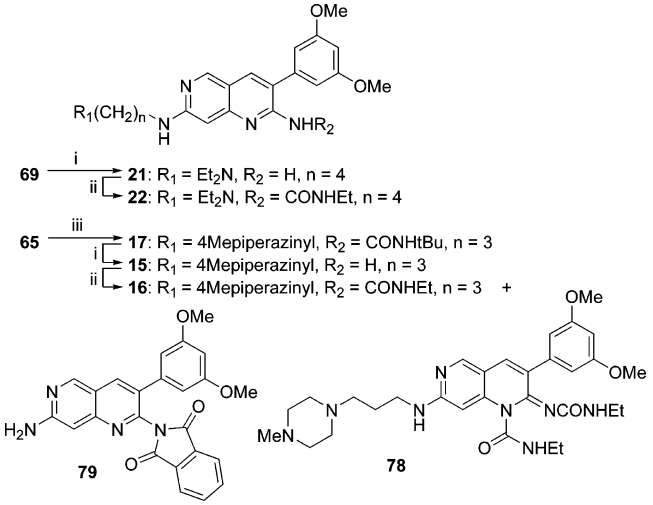


[a] (i) DDQ/CH_2Cl_2/20 °C/3 h; (ii) NaOH/MeOH/water/20 °C/40 h; (iii) NaH/DMF/20 °C/15 min, then 3-iodopropyl benzoate/DMF/0−20 °C/1 day; (iv) H_2/Pd−C/EtOH/20 °C/48 h; (v) NaOH/MeOH/water/20 °C/7 days.

coherence (HMQC) and heteronuclear multiple-bond correlation (HMBC) experiments on **50**). These dihydro derivatives were readily dehydrogenated by treatment with DDQ in CH_2Cl_2 at 20 °C so that **44** was obtained in quantitative yield from **51**. Base hydrolysis of **50** unexpectedly gave predominantly the 3,4-dihydro-1,6-naphthyridin-2(1*H*)-one **61**. Further minor reduction byproducts from the hydrogenolysis reactions were the 1,2,3,4-tetrahydro derivatives **54**−**59** in which the 2-urea was removed (*tert*-butylurea itself was also isolated). Even smaller amounts of the less stable acylaminals having the 2-urea still attached were also observed (TLC, HRFABMS) and in one case (**60**) purified. These results are consistent with those reported for 2-aminopyridines, 2-pyridones, and carbostyrils.[52]

Mesylation of alcohols **44**−**46** (excess MsCl/1-Me morpholine or 1-Me imidazole/THF) gave the unstable mesylate products **62**−**64** essentially quantitatively, which were used directly (Scheme 1). The use of these mild amine bases avoided deprotonation and reaction of the urea, while the acetamide protection of the 7-NH was also critical, since similar mesylation of the 7-NH analogue **77** gave a large number of products. Reaction of the crude mesylate solutions with a large excess (75−300 equiv) of 1-methylpiperazine, diethylamine, or morpholine (50−52 °C/1−4 days) gave the amine displacement products **65**−**72** in variable yield (77−85% for the butyl and pentyl compounds but only 21−30% for the propyl compounds because of the low stability and higher reactivity of propyl mesylate **62**). Subsequent experimentation (described for the phenyl derivatives below) led to a higher yield (64%) of the (4-methylpiperazinyl)propylamino analogue **65**, by treatment of the mesylate **62** with 1-methylpiperazine at lower temperature (20 °C/1 day, then 32 °C/1 day). Mild alkaline hydrolysis of the displacement products **65**−**72** (0.8−1.0 M NaOH/MeOH/water/20 °C/2−5 days) then enabled

Scheme 3[a]



[a] (i) NaOH/dioxane/water/98 °C/5−6 days; (ii) NaH/DMSO/40−50 °C/15 min, then EtNCO/DMSO/20 °C/1 day; (iii) NaOH/MeOH/water/49 °C/17 h.

selective cleavage of the N,N-disubstituted acetamide in the presence of the urea[41] to give the final products (**17**−**20**, **23**−**26**) in very good yield (74−85%) (although a small amount of urea hydrolysis was often also observed, which increased with stronger base and/or higher temperatures).

The (diethylamino)propylamino compound **18** was alternatively prepared by direct alkylation of acetamide **13** using freshly prepared and dried (by azeotroping with dry benzene) diethylaminopropyl chloride[53] (ca. 2 equiv/NaH/DMF/39 °C/40 h). This gave a mixture of **18** and its acetamide derivative **68**, which, upon mild alkaline hydrolysis, gave **18** in 48% overall yield.

The 1,6-naphthyridin-2-amine derivatives **15** and **21** were prepared by hydrolysis of the acetamide derivatives **65** and **69** using either single or two-step procedures (Scheme 3). Hydrolysis of the (diethylamino)-butylamino derivative **69** under forcing conditions (NaOH/dioxane/water/reflux/6 days) gave **21** directly in very good yield (81%), but some difficulties were encountered in monitoring the reaction and purifying the product because of the formation of a partly hydrolyzed intermediate of similar polarity to the final product (possibly the 2-amino-7-acetamide derivative). A two-step procedure was therefore employed for the hydrolysis of the (4-methylpiperazinyl)propylamino analogue **65**. The acetamide was first hydrolyzed (NaOH/MeOH/water/49 °C/17 h), and then the crude product (mostly **17**) was treated as above (NaOH/dioxane/water/reflux/5 days) to give **15** cleanly in excellent yield (91%).

Synthesis of the ethylureas **16** and **22** was accomplished in contrasting yields, using the optimized conditions previously reported[41] for 3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7-diamine (NaH/DMSO, then EtNCO/DMSO). The (diethylamino)butylamino derivative **22** was obtained in good yield (77% following chromatography and two recrystallizations to remove a bis-urea contaminant). However, only a 37% yield of the purified (4-methylpiperazinyl)propylamino analogue **16** could be obtained because of a much greater amount of the bis-urea contaminant being formed. The latter was purified by preparative reversed phase (C-18)

HPLC and proposed to have the acylimine structure **78** (Scheme 3) on the basis of its ^{1}H and ^{13}C NMR chemical shifts (assigned by 2-D HSQC and HMBC NMR experiments). These were very different from those for **16** (especially for C-3, C-8, C-8a) and a previously reported[41] (unstable) 2-phthalimide derivative **79** (especially for C-8).

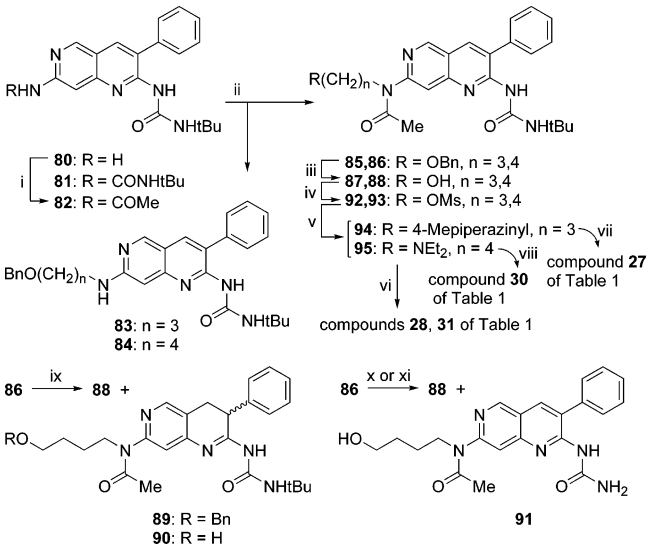
The homologous alcohols **75**−**77** were synthesized by various methods (Scheme 2B). 3-Iodopropyl benzoate[54] was prepared by iodination[49] (I_2/PPh_3/imidazole) of 3-hydroxypropyl benzoate, which was made by monobenzoylation of the diol (0.17 equiv of Bz_2O/Et_3N/DMAP/CH_2Cl_2/THF/20 °C/16 h).[55] Alkylation of **13** by 3-iodopropyl benzoate (NaH/DMF/0−20 °C/1 day) gave the propyl alcohol **75** directly, albeit in moderate yield (40%). In this case, hydrolysis of both the benzoate ester and acetamide functionalities occurred during alkylation, and only a small amount (7%) of the benzoate ester product **74** was obtained, along with recovered **13** (32%). The butyl alcohol **76** was obtained by hydrogenolysis of the benzyl ether derivative **42**, although the reaction was slower than for the acetamide analogue **39** and gave a poorer yield (21% after three cycles and purification). The pentyl alcohol **77** was obtained by hydrolysis of the acetamide derivative **46** (84% yield).

3-Phenyl Analogues. We have previously prepared the 7-substituted 3-phenyl-1,6-naphthyridin-2-amine **27** by reaction of 7-chloro-3-phenyl-1,6-naphthyridin-2-amine with 3-(4-methyl-1-piperazinyl)propylamine under forcing conditions (neat amine, 160 °C/5 d).[42] However, this route gave a very poor yield (7.5%) of **27,** instead giving predominantly the 2,7-bis-substitution product **29** (60%). This result was quite different from that observed for the 3-(2,6-dichlorophenyl) series,[42] where more selective reaction at C-7 was achieved probably because of a greater steric crowding of the C-2 position. The target amines and ureas in the 3-phenyl series were therefore prepared by a route similar to that described above.

The reported[41] 2-*tert*-butylurea **80** was prepared in improved yield (88%), together with bis-urea **81** (2%), by an alternative procedure[37,41] [addition of the neat isocyanate (at 0 °C) to the preformed anion of the diamine (NaH/DMF/20 °C/20 min) followed by reaction (20 °C/1 day)]. Acetylation of **80** (Ac_2O/py) then gave acetamide **82** (92%), which was alkylated with benzyl 3-iodopropyl ether or benzyl 4-iodobutyl ether (NaH/DMF/0−20 °C/2.5 days) to give the benzyl ethers **85** and **86** in good yield (63% and 75%, respectively), together with small amounts of the NH derivatives **83** and **84** (11% and 4%, respectively) (Scheme 4). Additional minor products were also observed, suggesting that the alkylation reaction was not completely selective, but these were not isolated. Unfortunately, small-scale hydrogenolysis of benzyl ether **86** under the optimized conditions used above for the 3-(3,5-dimethoxyphenyl) analogues gave a poor result, with ring hydrogenation products predominating. Only 11% of the desired alcohol **88** was obtained, together with the dihydro derivatives **89** (39%) and **90** (23%), recovered **86** (9%), and several more minor products. Therefore, alternative debenzylation conditions were sought.

Treatment of **86** with the Lewis acids $FeCl_3$[56] and BF_3·Et_2O/EtSH[57] gave complete debenzylation in both

Scheme 4[a]

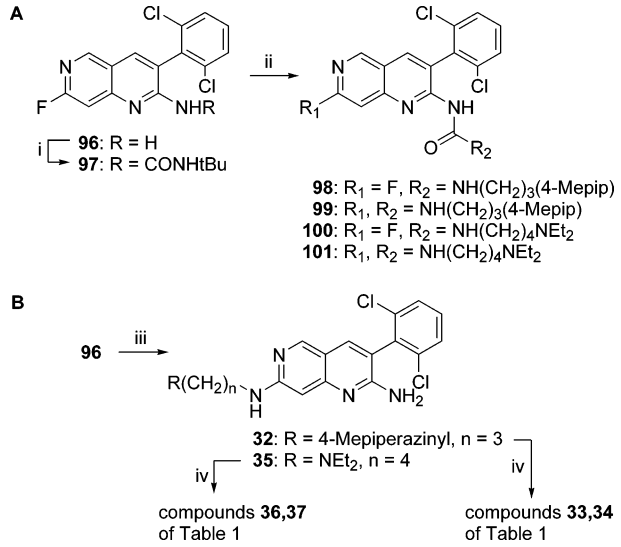


[a] (i) Ac_2O/py/20 °C/10 h; (ii) NaH/DMF/20 °C/30 min, then benzyl ω-iodoalkyl ether/DMF/0−20 °C/2.5 days; (iii) DDQ/CH_2Cl_2/20 °C/2−4 days; (iv) MsCl/NMM/THF/20 °C/12−16 h; (v) amine/THF/20−50 °C/2−4 days; (vi) NaOH/MeOH/water/20 °C/3.5−4 days; (vii) NaOH/MeOH/water/52 °C/18 h, then NaOH/dioxane/water/96 °C/4 days; (viii) NaOH/dioxane/water/97 °C/7 days; (ix) H_2/Pd−C/EtOH/20 °C/48 h; (x) BF_3·Et_2O/EtSH/CH_2Cl_2/20 °C/2 days; (xi) $FeCl_3$/CH_2Cl_2/20 °C/1 h.

cases, but also significant (39−100%) loss of the *tert*-butyl group, to give the urea **91**. The oxidants PCC[58] and PDC gave little reaction, while RuO_2/$NaIO_4$[59] gave an inseparable mixture of starting material and the expected benzoate ester (^{1}H NMR and HRFABMS) in moderate yield (63%), together with more polar byproducts. Treatment with excess DDQ[51] (5 equiv/CH_2Cl_2/water/20 °C/1 day) gave a relatively clean reaction on a small scale to the desired alcohol **88** (63% yield with 28% recovered **86**). However, on a slightly larger scale and with a more concentrated solution, the yields dropped markedly probably because of acid-catalyzed decomposition resulting from the hydrolysis of DDQ.[51,60] Addition of amine bases or aqueous buffers did not give useful results, but performing the reaction in the absence of water[51] (CH_2Cl_2 alone) gave a major improvement in yield (due to the dramatically reduced decomposition rate of the DDQ[60]), allowing relatively clean reaction over several days at 20 °C. Further improvements were obtained by excluding light, adding a reducing agent to the basic workup, and repeating extractions of the basic aqueous portion after 1 and 2 days to recover the initially quinone-bound product, which was slowly released by reaction with base. Thus, both alcohols **87** and **88** were obtained in very good overall yields (60% and 85%, respectively) by this method, although the reaction of **85** to give propyl alcohol **87** was much slower.

One-pot mesylation of the butyl alcohol **88** and displacement of the crude mesylate (**93**) with diethylamine (as above) gave **95** in excellent yield (83%). Similar small-scale mesylation of the propyl alcohol **87** and displacement of the crude mesylate (**92**) with 1-methylpiperazine at a lower temperature than normal (20 °C/1 day and then 32 °C/1 day rather than 50 °C) gave **94** in 66% yield. Mild alkaline hydrolysis of the acetamide derivatives **94** and **95** gave the ureas **28** and

Scheme 5[a]



[a] (i) NaH/DMF/20 °C/2 min, then *t*BuNCO/20 °C/1.5 h; (ii) amine/2-pentanol/120 °C/2 h; (iii) amine/2-EtO$(CH_2)_2$OH/135 °C/5 days; (iv) NaH/DMSO/40−50 °C/10−15 min, then EtNCO or *t*BuNCO/DMSO/20 °C/16−24 h.

31, respectively, and complete hydrolysis using the methods described above gave the 2-amino derivatives **27** and **30**, respectively, in excellent yield.

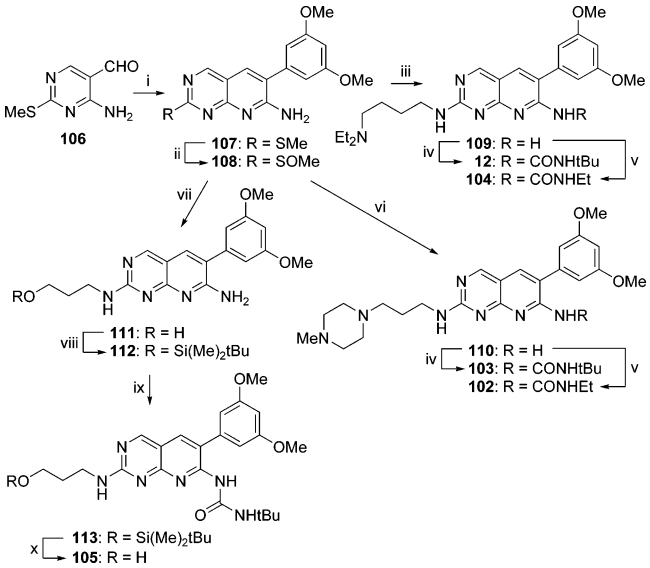
3-(2,6-Dichlorophenyl) Analogues. The initial approach to 7-solubilized 2-*tert*-butylureas in this series (**34**, **37**) was via amine displacements on the 7-fluoro-2-*tert*-butylurea derivative **97**, prepared from the previously reported[42] amine **96** (Scheme 5A), to avoid the formation of poorly separable bis-urea contaminants such as **78**. However, amine displacement reactions on **97** (amine/2-pentanol/120 °C/2 h) instead gave predominantly the derivatized ureas **98** and **100** (75%), together with small amounts (9−10%) of 7-substituted analogues **99** and **101**. Therefore, amine **96** was first converted into the 7-alkylamino derivatives **32**[42] and **35** (amine/2-ethoxyethanol/135 °C/5 days) in moderate yield (36−46%) (Scheme 5B), and then the target ureas (**33**, **34**, **36**, **37**) were obtained as above (NaH/DMSO, then EtNCO or *tert*-BuNCO/DMSO) in good yield (49−72%).

Pyrido[2,3-*d*]pyrimidines. These analogues (**12**, **102**−**105**) were accessed via amine displacements on the key methylsulfinyl derivative **108**, prepared from known[61,62] aldehyde **106** by condensation with 3,5-(dimethoxyphenyl)acetonitrile under basic conditions, followed by oxidation of the methylsulfanyl substituent (Scheme 6). Urea formation on the diamine derivatives, as above, gave the desired products in good yield, although in the case of **105**, prior protection of the hydroxyl group (as a TBDMS ether) was required.

Results and Discussion

The 7-substituted 1,6-naphthyridines **16**−**26**, **28**, **30**, **31** and **33**−**37** (together with the previously reported[41,42] analogues **14**, **15**, **27**, **29**, **32**) listed in Table 1 were evaluated for their ability to prevent phosphorylation of a model glutamate−tyrosine copolymer substrate by isolated human bFGF receptor (FGFR-1),[38] mouse PDGF-β receptor (PDGFR), and avian c-Src tyrosine kinase (all full length enzymes), using published methods.[38,63,64] The compounds were additionally evaluated

Scheme 6[a]



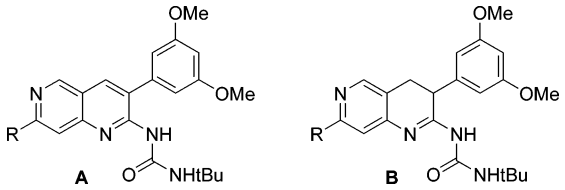
[a] (i) 3,5-DiOMePhCH_2CN/NaH/THF/20 °C/1.5 h, then **106**/20 °C/16 h; (ii) (2-PhSO_2-3-Ph)-oxaziridine/$CHCl_3$/20 °C/1 day; (iii) $Et_2N(CH_2)_4NH_2$/dioxane/50 °C/16 h; (iv) NaH/DMF/20 °C/1.5 h, then *t*BuNCO/20 °C/16 h; (v) NaH/DMF/20 °C/1.5 h, then EtNCO/20 °C/16 h; (vi) 4-Me-pip$(CH_2)_3NH_2$/dioxane/50 °C/16 h; (vii) $HO(CH_2)_3NH_2$/dioxane/reflux/18 h; (viii) TBDMSCl/imidazole/DMF/16 h; (ix) NaH/DMF/20 °C/30 min, then *t*BuNCO/20 °C/18 h; (x) H_2SiF_6/MeCN/THF/20 °C/2 h.

against highly purified and phosphorylated kinase constructs of the cytoplasmic domains of human FGFR-1 kinase (designated FGF# in Table 1) and of human VEGFR-2 (lacking 50 residues in the kinase insert domain[65]) using assays in DELFIA (dissociation-enhanced lanthanide fluoroimmunoassay) format. IC_{50} is defined as the concentration of inhibitor that reduces by 50% the level of ^{32}P (from added [^{32}P]-ATP) incorporated into the copolymer substrate.

The 3-(3,5-dimethoxyphenyl) analogues **14**−**26** were all highly selective (>100-fold, often much greater) for FGFR and VEGFR over both PDGFR and c-Src (Table 1). Compounds with 2-amino substituents (**15**, **21**) were less effective against all kinases than the corresponding 2-urea analogues, as expected.[41] The two ethylurea derivatives (**16**, **22**) showed significantly lower potency than the corresponding *tert*-butylurea derivatives (**17**, **23**) against VEGFR (by 8- to 10-fold) but against the other kinases were equivalent to or only slightly less potent than **17** and **23**.

The main interest among the *tert*-butylurea derivatives was the comparison with the previously reported[41] compound **14** as the positioning and nature of the cationic center (from amine protonation) on the 7-substituent was varied. We had elected to investigate chain lengths from three to five carbons and strongly (NEt_2), moderately (Me-piperazine), and weakly (morpholide) basic solubilizing functions, which we have found to be effective in previous studies.[66] In the event, there was no significant effect on FGFR or VEGFR inhibition; all of the compounds were potent (low nanomolar) inhibitors, with IC_{50} values varying less than 3-fold or 5-fold, respectively (Table 1). A chain length of four carbons maximized PDGFR activity, while c-Src activity was greatest for chain lengths of four or five carbons, as found previously.[66] The more weakly basic morpholides were less effective than the corresponding NEt_2 and Me-

Table 2. Structure and Kinase Inhibitory Activities of Nonsolubilized 1,6-Naphthyridines and Their 3,4-Dihydro Derivatives



			IC_{50} (μM)[a]				
compd	form	R	FGFR	FGFR#[b]	VEGFR[b]	PDGFR	c-Src
38	A	N(Ac)$(CH_2)_3$OBn	1.5	0.33	0.084	>50	>50
39	A	N(Ac)$(CH_2)_4$OBn	5.1	2.4	0.67	>50	>50
40	A	N(Ac)$(CH_2)_5$OBn	12	3.3	0.65	>50	>50
44	A	N(Ac)$(CH_2)_3$OH	28	1.4	1.9	>50	>50
45	A	N(Ac)$(CH_2)_4$OH	>50	8.4	13	>50	>50
46	A	N(Ac)$(CH_2)_5$OH	>50	7.5	7.6	>50	>50
41	A	NH$(CH_2)_3$OBn	0.91	0.19	0.18	>50	>50
42	A	NH$(CH_2)_4$OBn	1.1	0.26	0.18	>50	>50
43	A	NH$(CH_2)_5$OBn	3.3	0.33	0.096	>50	>50
75	A	NH$(CH_2)_3$OH	0.049	0.004	0.005	32	>50
76	A	NH$(CH_2)_4$OH	0.052	0.008	0.008	23	>50
77	A	NH$(CH_2)_5$OH	0.093	0.010	0.006	11	>50
48	B	N(Ac)$(CH_2)_3$OBn	>50	9.0	15	>50	>50
49	B	N(Ac)$(CH_2)_4$OBn	14	1.1	1.4	>50	>50
50	B	N(Ac)$(CH_2)_5$OBn	>50	20	55	>50	>50
51	B	N(Ac)$(CH_2)_3$OH	>50	7.9	6.6	>50	>50
52	B	N(Ac)$(CH_2)_4$OH	>50	8.7	10	>50	>50
53	B	N(Ac)$(CH_2)_5$OH	>50	7.7	20	>50	>50

[a] IC_{50}: concentration of drug (μM) that inhibits the phosphorylation of a random glutamate/tyrosine (4:1) copolymer by FGFR, VEGFR, PDGFR, or c-Src proteins. For active compounds, values are an average of two or more separate determinations; variation was generally ±30%. [b] DELFIA assay; see Experimental Section.

piperazine derivatives against both PDGFR (by 2- to >10-fold) and c-Src (by 3- to >5-fold). Thus, lead compound **14** was overall the most selective inhibitor in this series, although compounds **17**, **20**, **23**, and **26** were slightly more potent dual FGFR/VEGFR inhibitors. Finally, as expected, all compounds tested (**14**, **16**, **18**−**20**, **22**, **23**, **25**, **26**) showed excellent aqueous solubility (at least 40 mM as their hydrochloride salts; see Supporting Information).

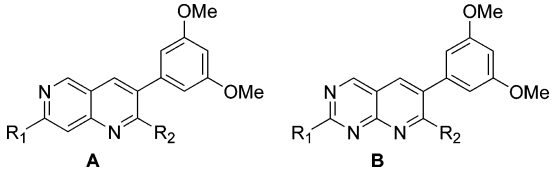
As demonstrated previously for both pyridopyrimidines[37] and 1,6-naphthyridines,[41] the nature of the substituents on the 3-phenyl ring are critically important in determining the pattern of kinase activity. In the proposed binding model[67] and the crystal structure of **12**,[40] this ring is buried deep in the binding cleft of the enzymes in a pocket not used by ATP. Two residues (Val559 and Val561 in FGFR-1, also conserved in VEGFR-1 and VEGFR-2) whose side chains form part of this hydrophobic pocket have been described as key to the selectivity conferred by the 3,5-dimethoxyphenyl substituents.[40] Most protein kinases have residues with larger side chains at one or both positions, which modeling studies indicate would sterically interfere with these substituents.[40,67] Thus, pyridopyrimidines **12**, **102**, **103**, and **104** also showed >100-fold selectivity for FGFR and VEGFR over both PDGFR and c-Src (Table 3). Additionally, these compounds showed an excellent selectivity profile over a wider range of kinases (IC_{50} > 50 μM against EGFR, IR, MEK, and PKC).[40]

The 3-phenyl analogues **27**−**31** had similar, albeit moderate, levels of activity against all kinases tested (Table 1). Compared with their 3-(3,5-dimethoxyphenyl) counterparts, they had significantly greater activity against PDGFR (by ca. 10-fold) and c-Src (by ca. 20- to 40-fold) but lower potency against FGFR and VEGFR, with the 2-urea derivatives (**28**, **31**) about 10- to 30-fold less potent (for both enzymes) and the 2-amino compounds (**27**, **30**) about 50- to 80-fold less potent against FGFR and 16-fold less potent against VEGFR. Compound **29**, having a soluble side chain at both C-2 and C-7, was about 3- to 5-fold less potent than the corresponding 2-amino analogue **27** against all kinases.

The 3-(2,6-dichlorophenyl) derivatives **32**−**37** generally retained the high FGFR potencies of the 3-(3,5-dimethoxyphenyl) compounds (except amino derivatives **32**, **35**) but had slightly lower VEGFR potencies (by 2- to 10-fold), much higher c-Src activity (of similar magnitude to their FGFR activity), and higher PDGFR potency (by 5- to 55-fold). They thus resemble the corresponding 3-(2,6-dichlorophenyl)pyrido[2,3-*d*]pyrimidines as "pan-kinase inhibitors".[37] Again, the 2-amino compounds (**32**, **35**) were less potent, while ethylurea derivatives (**33**, **36**) were essentially equivalent to *tert*-butylurea derivatives (**34**, **37**) against all kinases except VEGFR (where they were 5- to 8-fold less potent). Overall, the urea derivatives in this series were actually more potent (by 3- to 6-fold against c-Src, FGFR, and PDGFR) than analogous 7-substituted 3-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-ones, which we recently reported as c-Src inhibitors.[66]

Table 2 includes kinase inhibition data for some intermediates and byproducts from syntheses of the compounds above, briefly exploring SAR for other 7-side chain and chromophore modifications in the 3-(3,5-dimethoxyphenyl) series. These show that compounds with simple alcohol side chains (**75**−**77**) are almost as active as the base-containing analogues, suggesting little binding role for the cationic center. These compounds also have selectivity profiles similar to the profiles of the bases for FGFR and VEGFR over both

Table 3. Comparison of the Kinase Inhibitory Activities of 1,6-Naphthyridines (A) and Pyrido[2,3-*d*]pyrimidines (B)



				IC$_{50}$ (μM)[a]				
compd	form	R_1	R_2	FGFR	FGFR#[b]	VEGFR[b]	PDGFR	c-Src
16	A	NH(CH$_2$)$_3$4-Mepip[c]	NHCONHEt	0.021	0.021	0.051	30	14
102	B	NH(CH$_2$)$_3$4-Mepip	NHCONHEt	0.033	0.018	0.062	45	35
17	A	NH(CH$_2$)$_3$4-Mepip[c]	NHCONH*t*Bu	0.024	0.005	0.005	16	9.1
103	B	NH(CH$_2$)$_3$4-Mepip	NHCONH*t*Bu	0.019	0.011	0.021	31	26
22	A	NH(CH$_2$)$_4$NEt$_2$	NHCONHEt	0.024	0.013	0.046	6.5	7.0
104	B	NH(CH$_2$)$_4$NEt$_2$	NHCONHEt	0.035	0.086	0.19	27	22
23	A	NH(CH$_2$)$_4$NEt$_2$	NHCONH*t*Bu	0.025	0.006	0.006	2.6	4.6
12	B	NH(CH$_2$)$_4$NEt$_2$	NHCONH*t*Bu	0.028	0.019	0.12	14	20[d]
75	A	NH(CH$_2$)$_3$OH	NHCONH*t*Bu	0.049	0.004	0.005	32	>50
105	B	NH(CH$_2$)$_3$OH	NHCONH*t*Bu	0.038	0.049	0.071	>50	>50

[a] IC$_{50}$: concentration of drug (μM) that inhibits the phosphorylation of a random glutamate/tyrosine (4:1) copolymer by FGFR, VEGFR, PDGFR, or c-Src proteins. For active compounds, values are an average of two or more separate determinations; variation was generally ±30%. [b] DELFIA assay; see Experimental Section. [c] 4-Methylpiperazin-1-yl. [d] Data from ref 40.

PDGFR and c-Src. The corresponding benzyl derivatives (**41**−**43**) were significantly less active (by ca. 15- to 50-fold against both FGFR and VEGFR). The *N*-acetyl alcohols (**44**−**46**) demonstrated even less potency (by 350- to 1600-fold against both kinases), as expected, because of the essential role of the exocyclic NH in binding to the enzyme as described previously.[40,66,67] Surprisingly, however, the *N*-acetylbenzyl derivatives (**38**−**40**) retained modest activity, which was only slightly weaker than the 7-NH benzyl derivatives (**41**−**43**). 3,4-Dihydro-1,6-naphthyridine analogues (**48**−**53**) were generally less potent than the corresponding unsaturated compounds (**38**−**40**, **44**−**46**) against both FGFR and VEGFR, suggesting that a planar bicyclic ring system is slightly more favorable for binding in the ATP site of these enzymes.

The kinase inhibition data for some 1,6-naphthyridines and analogous pyrido[2,3-*d*]pyrimidines are compared in Table 3. While the potency of both series against FGFR is similar in the original assay, as found previously,[41] the naphthyridines generally show greater potency than the pyrido[2,3-*d*]pyrimidines in the new FGFR assay and against VEGFR (by 2- to 20-fold in 4/5 cases), with only slightly (up to 5-fold) higher PDGFR and c-Src activity.

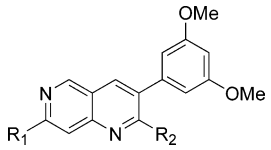
The FGFR/VEGFR-selective 3-(3,5-dimethoxyphenyl) compounds (**14**−**26**, **75**−**77**) were also evaluated for their ability to inhibit the growth of two tumor cell lines (C6 glioma, A90 ovarian carcinoma)[41] and of human umbilical vein endothelial cells (HUVECs), stimulated by serum, FGF, or VEGF[39] (Table 4). Overall, the compounds displayed moderate inhibition of the FGFR-overexpressing A90 cell line (10/16 compounds had IC$_{50}$ < 0.65 μM), weaker inhibition of the PDGF-dependent C6 cell line (expressing moderate FGFR levels), but much higher potency toward HUVECs, whose growth has been shown to be FGF-dependent.[68] (A similar pattern of cell selectivity was previously reported for **12**, allowing an assessment of its specific antiangiogenic effects.[39]) For both serum-stimulated HUVECs and the A90 and C6 cell lines, the same activity trends of 2-amine < 2-ethylurea < 2-*tert*-butylurea were observed. Many compounds, including the alcohols, displayed much higher potency than the lead compound **14**, with analogues **20** and **24** being particularly effective. Additionally, all of the compounds tested were active in inhibiting FGF-stimulated HUVEC growth, at similar or slightly (up to 5-fold) higher potency levels compared to those observed for serum-stimulated growth. However, the compounds were significantly less potent at inhibiting VEGF-stimulated HUVEC growth (by 7- to 180-fold), despite their high potency in the VEGFR enzyme assay (the reason for this is unclear, but the activity trends correlate well; e.g., ethylureas and diethylaminopropyl derivative **18** were less effective). A comparison of some 1,6-naphthyridines and analogous pyrido[2,3-*d*]pyrimidines (Table 5) again shows the naphthyridines to be superior in all growth delay assays, especially for HUVECs (by about 3- to 65-fold). These results, together with their increased potency against VEGFR and good selectivity profile, distinguish the 1,6-naphthyridines from the related pyrido[2,3-*d*]pyrimidines and suggest that they should be evaluated further as antiangiogenesis agents.

Conclusions

We have shown that 7-solubilized 3-(3,5-dimethoxyphenyl)-1,6-naphthyridine 2-ureas are potent inhibitors of both FGFR-1 and VEGFR-2, with very high selectivity for these kinases compared with PDGFR and c-Src. The inhibitory potencies do not vary markedly with the nature (base strength) or disposition of the terminal amine on the 7-substituent. This may be advantageous in providing scope for the optimization of pharmacokinetic properties for these compounds as potential drugs. The flexible synthesis reported here will further assist such development. Following the initial alkylation, the critical second step is removal of the *O*-benzyl protecting group with DDQ in the absence of water rather than by hydrogenolysis (to avoid concomitant reduction of the 1,6-naphthyridine); one-pot mesylation/amine displacement and selective cleavage of the acetamide completes the synthesis.

The SAR for inhibition of VEGFR is also similar to that of FGFR with respect to substituents on the phenyl

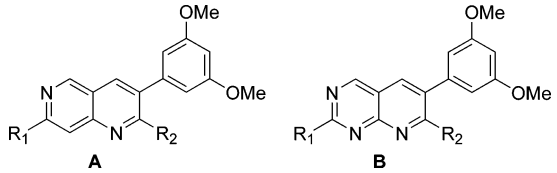
Table 4. In Vitro Growth Delay Activities of 7-Substituted 1,6-Naphthyridines



			IC$_{50}$ (μM)[a]				
			HUVEC[b]				
compd	R$_1$	R$_2$	serum	FGF	VEGF	A90[c]	C6[d]
14	NH(CH$_2$)$_3$morph[e]	NHCONH*t*Bu	0.085	0.001	0.037	1.9	3.4
15	NH(CH$_2$)$_3$4-Mepip[f]	NH$_2$	0.15			6.4	9.1
16	NH(CH$_2$)$_3$4-Mepip	NHCONHEt	0.015	0.0036	0.88	4.8	7.5
17	NH(CH$_2$)$_3$4-Mepip	NHCONH*t*Bu	0.0019	0.001	0.073	0.33	1.8
18	NH(CH$_2$)$_3$NEt$_2$	NHCONH*t*Bu	0.012	0.002	0.28	1.7	4.0
19	NH(CH$_2$)$_4$morph[e]	NHCONH*t*Bu	0.0044	0.003	0.082	0.35	2.7
20	NH(CH$_2$)$_4$4-Mepip[f]	NHCONH*t*Bu	0.0004	0.0027	0.066	0.20	1.3
21	NH(CH$_2$)$_4$NEt$_2$	NH$_2$	0.13			12	5.9
22	NH(CH$_2$)$_4$NEt$_2$	NHCONHEt	0.014	0.0026	0.53	4.5	3.5
23	NH(CH$_2$)$_4$NEt$_2$	NHCONH*t*Bu	0.0027	0.0005	0.043	0.56	2.1
24	NH(CH$_2$)$_5$morph[e]	NHCONH*t*Bu	0.0005	0.002	0.091	0.34	2.9
25	NH(CH$_2$)$_5$4-Mepip[f]	NHCONH*t*Bu	0.003			0.17	0.98
26	NH(CH$_2$)$_5$NEt$_2$	NHCONH*t*Bu	0.002	0.002	0.19	0.20	1.5
75	NH(CH$_2$)$_3$OH	NHCONH*t*Bu	0.006	0.0027	0.047	0.056	1.8
76	NH(CH$_2$)$_4$OH	NHCONH*t*Bu	0.006	0.0047	0.041	0.042	1.2
77	NH(CH$_2$)$_5$OH	NHCONH*t*Bu	0.004	0.003	0.047	0.63	3.4

[a] IC$_{50}$: concentration of drug (μM) that inhibits in vitro cell growth. For active compounds, values are an average of two or more separate determinations. [b] FGF-dependent human umbilical vein endothelial cells stimulated by serum, FGF, or VEGF (see ref 39). [c] FGFR overexpressing human ovarian carcinoma. [d] PDGF-dependent rat glioma (expressing moderate FGFR levels). [e] *N*-Morpholinyl. [f] 4-Methylpiperazin-1-yl.

Table 5. Comparison of the in Vitro Growth Delay Activities of 1,6-Naphthyridines (A) and Pyrido[2,3-*d*]pyrimidines (B)



				IC$_{50}$ (μM)[a]				
				HUVEC[b]				
compd	form	R$_1$	R$_2$	serum	FGF	VEGF	A90[c]	C6[d]
16	A	NH(CH$_2$)$_3$4-Mepip[e]	NHCONHEt	0.015	0.0036	0.88	4.8	7.5
102	B	NH(CH$_2$)$_3$4-Mepip	NHCONHEt	0.088	0.015	0.93	6.8	12
17	A	NH(CH$_2$)$_3$4-Mepip[e]	NHCONH*t*Bu	0.0019	0.001	0.073	0.33	1.8
103	B	NH(CH$_2$)$_3$4-Mepip	NHCONH*t*Bu	0.028	0.006	0.22	4.6	7.9
22	A	NH(CH$_2$)$_4$NEt$_2$	NHCONHEt	0.014	0.0026	0.53	4.5	3.5
104	B	NH(CH$_2$)$_4$NEt$_2$	NHCONHEt	0.43	0.033	1.8	25	>25
23	A	NH(CH$_2$)$_4$NEt$_2$	NHCONH*t*Bu	0.0027	0.0005	0.043	0.56	2.1
12	B	NH(CH$_2$)$_4$NEt$_2$	NHCONH*t*Bu	0.015	0.007	0.19	13	17
75	A	NH(CH$_2$)$_3$OH	NHCONH*t*Bu	0.006	0.0027	0.047	0.056	1.8
105	B	NH(CH$_2$)$_3$OH	NHCONH*t*Bu	0.037	0.020	3.0	6.8	11

[a] IC$_{50}$: concentration of drug (μM) that inhibits in vitro cell growth. For active compounds, values are an average of two or more separate determinations. [b] FGF-dependent human umbilical vein endothelial cells stimulated by serum, FGF, or VEGF (see ref 39). [c] FGFR overexpressing human ovarian carcinoma. [d] PDGF-dependent rat glioma (expressing moderate FGFR levels). [e] 4-Methylpiperazin-1-yl.

ring (3,5-diOMe > 2,6-diCl ≫ H in potency), with both 3-(2,6-dichlorophenyl) derivatives and 3-phenyl derivatives being less selective. However, inhibition of VEGFR appears to be more sensitive to the nature of the 2-substituent (*t*Bu urea > Et urea > NH$_2$). Pairwise comparisons of solubilized 3-(3,5-dimethoxyphenyl)-1,6-naphthyridines and the corresponding pyrido[2,3-*d*]-pyrimidines show the former to have superior potencies both against the isolated VEGFR enzyme and in HUVEC cultures. This confirms[41,66] that the 1-aza atom of the pyrido[2,3-*d*]pyrimidines is not advantageous for inhibition of any of the kinases examined and suggests that the 1,6-naphthyridines (e.g., **17**, **23**) are worthy of further evaluation as antiangiogenesis agents.

Experimental Section

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined using an Electrothermal model 9200 digital melting point apparatus and are as read. NMR spectra were measured on a Bruker DRX-400 spectrometer and referenced to Me$_4$Si. 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 95% MeCN/5% water (solvent A) and 0.45 M ammonium formate buffer (solvent B, pH 3.45).

***N*-[3-(Benzyloxy)propyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]acetamide (38).** A solution of *N*-[2-[[(*tert*-butylamino)-carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]acetamide[41] (**13**) (2.00 g, 4.58 mmol) in dry DMF (50 mL) was treated with 60% NaH (0.75 g, 18.8 mmol). Then the reaction flask was immediately sealed with a rubber septum, degassed (water pump vacuum), and filled with dry N_2 (balloon), and the mixture was stirred at 20 °C for 40 min, then at 0 °C for 1 h. A solution of benzyl 3-iodopropyl ether[43] (1.65 g, 5.98 mmol) in dry DMF (5 mL, then 2 × 5 mL to rinse) was added (syringe), and then the mixture was foil-covered and stirred at 0−20 °C for 1 day. The resulting solution was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (250 mL) and extracted with EtOAc (10 × 200 mL). The extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−0.5% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 0.5% MeOH/CH_2Cl_2 yielded crude material which, upon crystallization twice from CH_2Cl_2/hexane, gave *N*-[7-[[3-(benzyloxy)propyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]-*N*′-*tert*-butylurea (**41**) (145 mg, 6%): mp (CH_2Cl_2/hexane) 135−137 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1 H, NH), 8.70 (s, 1 H, H-5), 7.99 (s, 1 H, H-4), 7.31 (m, 5 H, H-2″,3″,4″,5″,6″), 7.04 (br s, 1 H, NH), 6.91 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.63 (s, 3 H, H-2′,4′,6′), 6.40 (s, 1 H, H-8), 4.48 (s, 2 H, O*C*H_2Ph), 3.81 (s, 6 H, 2OCH_3), 3.56 (t, J = 6.2 Hz, 2 H, OCH_2), 3.38 (m, 2 H, NHCH_2), 1.87 (pentet, J = 6.5 Hz, 2 H, CH_2), 1.39 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 161.14 (s, 2 C, C-3′,5′), 159.54 (s, C-7), 152.41, 152.06 (2 s, CONH, C-2), 151.39 (d, C-5), 149.38 (s, C-8a), 138.59 (s, C-1″), 137.47 (d, C-4), 137.41 (s, C-1′), 128.17, 127.35 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.29 (d, C-4″), 121.13 (s, C-3), 113.18 (s, C-4a), 107.10 (d, 2 C, C-2′,6′), 100.21 (d, C-4′), 94.62 (br d, C-8), 71.87 (t, O*C*H_2Ph), 67.53 (t, OCH_2), 55.41 (q, 2 C, 2OCH_3), 49.95 (s, *C*(CH_3)$_3$), 38.53 (t, NCH_2), 29.08 (t, CH_2), 28.66 (q, 3 C, C(*C*H_3)$_3$). Anal. ($C_{31}H_{37}N_5O_4$) C, H, N.

Further elution with 0.5−0.75% MeOH/CH_2Cl_2 yielded crude material which, upon crystallization twice from CH_2Cl_2/light petroleum, gave recovered **13** (143 mg, 7%).

Further elution with 0.75−1% MeOH/CH_2Cl_2 gave **38** (2.00 g, 75%): foam; ^{1}H NMR [$(CD_3)_2SO$] δ 9.87 (br s, 1 H, NH), 9.12 (s, 1 H, H-5), 8.34 (s, 1 H, H-4), 7.69 (s, 1 H, H-8), 7.25 (m, 6 H, NH, H-2″,3″,4″,5″,6″), 6.70 (s, 3 H, H-2′,4′,6′), 4.35 (s, 2 H, O*C*H_2Ph), 3.97 (t, J = 7.1 Hz, 2 H, NCH_2), 3.82 (s, 6 H, 2OCH_3), 3.46 (t, J = 6.2 Hz, 2 H, OCH_2), 1.99 (s, 3 H, $COCH_3$), 1.80 (pentet, J = 6.6 Hz, 2 H, CH_2), 1.41 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 169.41 (s, C=O), 161.20 (s, 2 C, C-3′,5′), 154.35, 153.00, 151.55 (3 s, CONH, C-2,7), 151.25 (d, C-5), 148.82 (s, C-8a), 138.36 (s, C-1″), 136.98 (d, C-4), 136.54 (s, C-1′), 128.04, 127.19 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.17 (d, C-4″), 127.00 (s, C-3), 118.59 (s, C-4a), 115.50 (d, C-8), 107.05 (d, 2 C, C-2′,6′), 100.63 (d, C-4′), 71.69 (t, O*C*H_2Ph), 67.08 (t, OCH_2), 55.45 (q, 2 C, 2OCH_3), 50.16 (s, *C*(CH_3)$_3$), 44.76 (t, NCH_2), 28.65 (q, 3 C, C(*C*H_3)$_3$), 28.13 (t, CH_2), 22.93 (q, CH_3). Anal. ($C_{33}H_{39}N_5O_5$) C, H, N.

***N*-[4-(Benzyloxy)butyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]acetamide (39).** Similar reaction of a stirred solution of **13** (2.00 g, 4.58 mmol) in dry DMF (50 mL) with 60% NaH (0.79 g, 19.8 mmol) under N_2 at 20 °C for 25 min, then at 0 °C for 35 min, followed by reaction with benzyl 4-iodobutyl ether[44] (1.66 g, 5.72 mmol) in dry DMF (5 mL, then 2 × 5 mL) at 0−20 °C for 2 days and chromatography of the resulting product on silica gel (eluting with 0.5% MeOH/CH_2Cl_2) gave (after crystallization twice from CH_2Cl_2/hexane) *N*-[7-[[4-(benzyloxy)butyl]-amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]-*N*′-*tert*-butylurea (**42**) (237 mg, 9%): mp (CH_2Cl_2/hexane) 106−109 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.30 (m, 5 H, H-2″,3″,4″,5″,6″), 7.02 (br s, 1 H, NH), 6.92 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.0 Hz, 1 H, H-4′), 6.62 (d, J = 1.8 Hz, 2 H, H-2′,6′), 6.39 (s, 1 H, H-8), 4.46 (s, 2 H, O*C*H_2Ph), 3.80 (s, 6 H, 2OCH_3), 3.48 (t, J = 5.8 Hz, 2 H, OCH_2), 3.31 (m, 2 H, NHCH_2), 1.65 (m, 4 H, 2CH_2), 1.39 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 161.16 (s, 2 C, C-3′,5′), 159.58 (s, C-7), 152.42, 152.10 (2 s, CONH, C-2), 151.40 (d, C-5), 149.37 (s, C-8a), 138.65 (s, C-1″), 137.49 (d, C-4), 137.43 (s, C-1′), 128.18, 127.34 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.27 (d, C-4″), 121.08 (s, C-3), 113.16 (s, C-4a), 107.11 (d, 2 C, C-2′,6′), 100.21 (d, C-4′), 94.68 (br d, C-8), 71.75 (t, O*C*H_2-Ph), 69.43 (t, OCH_2), 55.43 (q, 2 C, 2OCH_3), 49.98 (s, *C*(CH_3)$_3$), 41.06 (t, NCH_2), 28.68 (q, 3 C, C(*C*H_3)$_3$), 26.81, 25.68 (2 t, 2CH_2). Anal. ($C_{32}H_{39}N_5O_4$) C, H, N.

Further elution with 0.5−1% MeOH/CH_2Cl_2 gave (after crystallization twice) recovered **13** (160 mg, 8%).

Further elution with 1% MeOH/CH_2Cl_2 gave **39** (1.99 g, 73%): foam; ^{1}H NMR [$(CD_3)_2SO$] δ 9.86 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.68 (s, 1 H, H-8), 7.26 (m, 6 H, NH, H-2″,3″,4″,5″,6″), 6.70 (s, 3 H, H-2′,4′,6′), 4.39 (s, 2 H, O*C*H_2Ph), 3.90 (m, 2 H, NCH_2), 3.82 (s, 6 H, 2OCH_3), 3.38 (t, J = 5.5 Hz, 2 H, OCH_2), 1.98 (s, 3 H, $COCH_3$), 1.54 (m, 4 H, 2CH_2), 1.40 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 169.29 (s, C=O), 161.20 (s, 2 C, C-3′,5′), 154.21, 153.03, 151.53 (3 s, CONH, C-2,7), 151.29 (d, C-5), 148.80 (s, C-8a), 138.52 (s, C-1″), 136.99 (d, C-4), 136.54 (s, C-1′), 128.06, 127.20 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.15 (d, C-4″), 127.03 (s, C-3), 118.58 (s, C-4a), 115.54 (d, C-8), 107.05 (d, 2 C, C-2′,6′), 100.63 (d, C-4′), 71.63 (t, O*C*H_2Ph), 69.14 (t, OCH_2), 55.45 (q, 2 C, 2OCH_3), 50.15 (s, *C*(CH_3)$_3$), 46.76 (t, NCH_2), 28.63 (q, 3 C, C(*C*H_3)$_3$), 26.40, 24.61 (2 t, 2CH_2), 22.94 (q, CH_3). Anal. ($C_{34}H_{41}N_5O_5$·0.5H_2O) C, H, N.

***N*-[5-(Benzyloxy)pentyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]acetamide (40).** Similar reaction of a stirred solution of **13** (1.51 g, 3.45 mmol) in dry DMF (50 mL) with 60% NaH (0.571 g, 14.3 mmol) under N_2 at 20 °C for 20 min, then at 0 °C for 40 min, followed by reaction with benzyl 5-iodopentyl ether[45] (1.31 g, 4.31 mmol) in dry DMF (5 mL, then 2 × 5 mL) at 0−20 °C for 2 days and chromatography of the resulting product on silica gel (eluting with 0.5−0.75% MeOH/CH_2Cl_2) gave (after crystallization twice from CH_2Cl_2/hexane) *N*-[7-[[5-(benzyloxy)pentyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]-*N*′-*tert*-butylurea (**43**) (97 mg, 5%): mp (CH_2Cl_2/hexane) 116−117 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.30 (m, 5 H, H-2″,3″,4″,5″,6″), 7.02 (br s, 1 H, NH), 6.91 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.2 Hz, 1 H, H-4′), 6.62 (d, J = 2.1 Hz, 2 H, H-2′,6′), 6.39 (s, 1 H, H-8), 4.44 (s, 2 H, O*C*H_2Ph), 3.80 (s, 6 H, 2OCH_3), 3.44 (t, J = 6.4 Hz, 2 H, OCH_2), 3.29 (q, J = 6.2 Hz, 2 H, NHCH_2), 1.59 (pentet, J = 7.0 Hz, 4 H, 2CH_2), 1.43 (m, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 161.11 (s, 2 C, C-3′,5′), 159.56 (s, C-7), 152.36, 152.02 (2 s, CONH, C-2), 151.34 (d, C-5), 149.33 (s, C-8a), 138.63 (s, C-1″), 137.43 (d, C-4), 137.40 (s, C-1′), 128.11, 127.29 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.20 (d, C-4″), 120.99 (s, C-3), 113.07 (s, C-4a), 107.07 (d, 2 C, C-2′,6′), 100.16 (d, C-4′), 94.56 (br d, C-8), 71.71 (t, O*C*H_2Ph), 69.52 (t, OCH_2), 55.38 (q, 2 C, 2OCH_3), 49.91 (s, *C*(CH_3)$_3$), 41.08 (t, NCH_2), 28.96 (t, CH_2), 28.64 (t, CH_2), 28.63 (q, 3 C, C(*C*H_3)$_3$), 23.31 (t, CH_2). Anal. ($C_{33}H_{41}N_5O_4$) C, H, N.

Further elution with 0.75% MeOH/CH_2Cl_2 gave (after crystallization twice) recovered **13** (66 mg, 4%).

Further elution with 1−1.5% MeOH/CH_2Cl_2 gave **40** (1.70 g, 80%): foam; ^{1}H NMR [$(CD_3)_2SO$] δ 9.87 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.66 (s, 1 H, H-8), 7.28 (m, 6 H, NH, H-2″,3″,4″,5″,6″), 6.70 (s, 3 H, H-2′,4′,6′), 4.40 (s, 2 H, O*C*H_2Ph), 3.87 (t, J = 7.2 Hz, 2 H, NCH_2), 3.82 (s, 6 H, 2OCH_3), 3.36 (t, J = 6.4 Hz, 2 H, OCH_2), 1.98 (s, 3 H, $COCH_3$), 1.50 (pentet, J = 7.0 Hz, 4 H, 2CH_2), 1.41 (s, 9 H, C(CH_3)$_3$), 1.32 (m, 2 H, CH_2); ^{13}C NMR δ 169.27 (s, C=O), 161.19 (s, 2 C, C-3′,5′), 154.24, 153.02, 151.54 (3 s, CONH, C-2,7), 151.26 (d, C-5), 148.79 (s, C-8a), 138.58 (s, C-1″), 136.99 (d, C-4), 136.53 (s, C-1′), 128.08, 127.20 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.16 (d, C-4″), 127.01 (s, C-3), 118.56 (s, C-4a), 115.40 (d, C-8), 107.05 (d, 2 C, C-2′,6′), 100.62 (d, C-4′), 71.64 (t, O*C*H_2Ph), 69.35 (t, OCH_2), 55.45 (q, 2 C, 2OCH_3), 50.16 (s, *C*(CH_3)$_3$), 46.93 (t, NCH_2), 28.75 (t, CH_2), 28.63 (q, 3 C, C(*C*H_3)$_3$), 27.53 (t, CH_2), 22.96 (q, CH_3), 22.94 (t, CH_2). Anal. ($C_{35}H_{43}N_5O_5$) C, H, N.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-(3-hydroxypropyl)acetamide (44).** A solution of **38** (353 mg, 0.603 mmol) in absolute EtOH (280 mL) was hydrogenated over 5% Pd/C (425 mg) at 60 psi and 20 °C for 48 h. The resulting solution was Celite filtered, washing with 25% MeOH/CH_2Cl_2. Then the Celite and catalyst were further extracted by stirring in refluxing 25% MeOH/CH_2Cl_2 for 10 min and then refiltering and washing as before. The filtrates were then combined, the solvents were removed, and the residue was chromatographed on silica gel. Elution with 0−1% MeOH/CH_2Cl_2 gave foreruns, and then further elution with 1−1.2% MeOH/CH_2Cl_2 gave recovered **38** (115 mg, 33%). Elution with 1.5−1.6% MeOH/CH_2Cl_2 gave *N*-[3-(benzyloxy)propyl]-*N*-[2-[[(*tert*-butylamino)-carbonyl]amino]-3-(3,5-dimethoxyphenyl)-3,4-dihydro-1,6-naphthyridin-7-yl]acetamide (**48**) (57 mg, 16%): mp (EtOAc/hexane) 108−110 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.90 (br s, 1 H, NH), 9.78 (br s, 1 H, NH), 8.12 (s, 1 H, H-5), 7.27 (m, 5 H, H-2″,3″,4″,5″,6″), 7.06 (s, 1 H, H-8), 6.33 (t, J = 2.1 Hz, 1 H, H-4′), 6.22 (d, J = 2.1 Hz, 2 H, H-2′,6′), 4.35 (d, J = 12.1 Hz, 1 H, OC*H*Ph), 4.31 (d, J = 12.0 Hz, 1 H, OC*H*Ph), 3.96 (br d, J = 6.6 Hz, 1 H, H-3), 3.80 (t, J = 7.3 Hz, 2 H, NCH_2), 3.59 (s, 6 H, $2OCH_3$), 3.40 (t, J = 6.2 Hz, 2 H, OCH_2), 3.27 (br dd, J = 16.7, 7.2 Hz, 1 H, H-4), 3.01 (br d, J = 16.3 Hz, 1 H, H-4), 1.88 (s, 3 H, $COCH_3$), 1.70 (pentet, J = 6.6 Hz, 2 H, CH_2), 1.36 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.10 (s, C=O), 163.03 (s, C-2), 160.34 (s, 2 C, C-3′,5′), 155.15 (s, C-7), 152.34 (s, CONH), 151.75 (s, C-8a), 147.19 (d, C-5), 140.40 (s, C-1′), 138.39 (s, C-1″), 128.08, 127.32 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.22 (d, C-4″), 118.97 (s, C-4a), 115.08 (d, C-8), 105.30 (d, 2 C, C-2′,6′), 98.44 (d, C-4′), 71.72 (t, O*C*H_2Ph), 67.06 (t, OCH_2), 54.91 (q, 2 C, $2OCH_3$), 49.94 (s, *C*$(CH_3)_3$), 44.33 (t, NCH_2), 39.70 (d, C-3), 28.53 (q, 3 C, C(*C*$H_3)_3$), 28.09 (t, CH_2), 27.85 (t, C-4), 22.64 (q, CH_3). Anal. ($C_{33}H_{41}N_5O_5\cdot H_2O$) C, H, N.

Further elution with 1.6−2.2% MeOH/CH_2Cl_2 gave a mixture of **44** and **54** (86 mg) (see below).

Further elution with 2.2−3% MeOH/CH_2Cl_2 gave *N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-3,4-dihydro-1,6-naphthyridin-7-yl]-*N*-(3-hydroxypropyl)acetamide (**51**) (22 mg, 7%): mp (CH_2Cl_2/hexane) 162−164 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.78 (br s, 1 H, NH), 8.13 (s, 1 H, H-5), 7.05 (s, 1 H, H-8), 6.35 (t, J = 2.1 Hz, 1 H, H-4′), 6.22 (d, J = 2.1 Hz, 2 H, H-2′,6′), 4.43 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.96 (br d, J = 6.3 Hz, 1 H, H-3), 3.76 (t, J = 7.2 Hz, 2 H, NCH_2), 3.61 (s, 6 H, $2OCH_3$), 3.38 (m, 2 H, C*H*$_2$-OH), 3.28 (br dd, J = 16.1, 6.5 Hz, 1 H, H-4), 3.01 (br d, J = 16.5 Hz, 1 H, H-4), 1.88 (s, 3 H, $COCH_3$), 1.57 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.36 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.14 (s, C=O), 163.02 (s, C-2), 160.34 (s, 2 C, C-3′,5′), 155.13 (s, C-7), 152.34 (s, CONH), 151.71 (s, C-8a), 147.16 (d, C-5), 140.45 (s, C-1′), 118.91 (s, C-4a), 115.06 (d, C-8), 105.28 (d, 2 C, C-2′,6′), 98.52 (d, C-4′), 58.23 (t, OCH_2), 54.94 (q, 2 C, $2OCH_3$), 49.95 (s, *C*$(CH_3)_3$), 44.51 (t, NCH_2), 39.68 (d, C-3), 31.04 (t, CH_2), 28.54 (q, 3 C, C(*C*$H_3)_3$), 27.81 (t, C-4), 22.66 (q, CH_3). Anal. ($C_{26}H_{35}N_5O_5$) C, H, N.

Further elution with 5% MeOH/CH_2Cl_2 gave *N*-[3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]-*N*-(3-hydroxypropyl)acetamide (**57**) (17 mg, 7%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.82 (s, 1 H, H-5), 7.05 (m, 1 H, NH), 6.49 (d, J = 2.1 Hz, 2 H, H-2′,6′), 6.38 (t, J = 2.1 Hz, 1 H, H-4′), 6.35 (s, 1 H, H-8), 4.52 (br s, 1 H, CH_2O*H*), 3.73 (s, 6 H, $2OCH_3$), 3.65 (t, J = 7.2 Hz, 2 H, NCH_2), 3.42 (m, 2 H, C*H*$_2$-OH), 3.39 (m, 1 H, H-2), 3.26 (br dd, J = 12.0, 9.7 Hz, 1 H, H-2), 2.87 (m, 3 H, H-3, 2H-4), 1.83 (s, 3 H, $COCH_3$), 1.58 (pentet, J = 6.9 Hz, 2 H, CH_2); ^{13}C NMR δ 169.05 (s, C=O), 160.51 (s, 2 C, C-3′,5′), 153.83, 151.68 (2 s, C-7,8a), 147.57 (d, C-5), 145.52 (s, C-1′), 114.89 (s, C-4a), 105.48 (d, 2 C, C-2′,6′), 104.11 (d, C-8), 98.19 (d, C-4′), 58.40 (t, OCH_2), 55.07 (q, 2 C, $2OCH_3$), 46.06 (t, C-2), 44.37 (t, NCH_2), 36.55 (d, C-3), 31.00 (t, CH_2), 30.52 (t, C-4), 22.44 (q, CH_3); HRFABMS calcd for $C_{21}H_{28}N_3O_4$ *m/z* (MH^+) 386.2080, found 386.2088.

Further elution with 10% MeOH/CH_2Cl_2 gave *N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]-*N*-(3-hydroxypropyl)acetamide (**60**) (4.5 mg, 1.5%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.92 (s, 1 H, H-5), 7.61 (br d, J = 3.5 Hz, 1 H, NH), 6.54 (d, J = 2.1 Hz, 2 H, H-2′,6′), 6.45 (s, 1 H, H-8), 6.37 (t, J = 2.1 Hz, 1 H, H-4′), 6.29 (br d, J = 9.4 Hz, 1 H, NH), 5.66 (br s, 1 H, NH), 5.21 (dt, J = 9.3, 3.4 Hz, 1 H, H-2), 4.48 (br s, 1 H, CH_2O*H*), 3.73 (s, 6 H, $2OCH_3$), 3.64 (t, J = 6.7 Hz, 2 H, NCH_2), 3.42 (m, 2 H, C*H*$_2$OH), 3.73 (s, 6 H, $2OCH_3$), 3.64 (t, J = 6.7 Hz, 2 H, NCH_2), 3.40 (m, 2 H, C*H*$_2$OH), 3.13 (m, 1 H, H-3), 2.93 (m, 2 H, 2H-4), 1.83 (br s, 3 H, $COCH_3$), 1.57 (pentet, J = 6.7 Hz, 2 H, CH_2), 1.14 (s, 9 H, (s, $C(CH_3)_3$); HRFABMS calcd for $C_{26}H_{38}N_5O_5$ *m/z* (MH^+) 500.2873, found 500.2858.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-(4-hydroxybutyl)acetamide (45).** Similar hydrogenation of **39** (398 mg, 0.664 mmol) in absolute EtOH (320 mL) over 5% Pd/C (480 mg) at 60 psi and 20 °C for 36 h and chromatography of the resulting product on silica gel (eluting with 1−1.4% MeOH/CH_2Cl_2) gave firstly recovered **39** (136 mg, 34%). Elution with 1.7−2% MeOH/CH_2Cl_2 gave *N*-[4-(benzyloxy)butyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-3,4-dihydro-1,6-naphthyridin-7-yl]acetamide (**49**) (50 mg, 13%): mp (EtOAc/hexane) 107−109.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.90 (br s, 1 H, NH), 9.78 (br s, 1 H, NH), 8.12 (s, 1 H, H-5), 7.28 (m, 5 H, H-2″,3″,4″,5″,6″), 7.04 (s, 1 H, H-8), 6.34 (t, J = 2.2 Hz, 1 H, H-4′), 6.21 (d, J = 2.1 Hz, 2 H, H-2′,6′), 4.39 (s, 2 H, O*C*H_2-Ph), 3.96 (br d, J = 6.7 Hz, 1 H, H-3), 3.73 (m, 2 H, NCH_2), 3.60 (s, 6 H, $2OCH_3$), 3.35 (t, J = 5.9 Hz, 2 H, OCH_2), 3.28 (br dd, J = 16.8, 7.4 Hz, 1 H, H-4), 3.01 (br d, J = 16.3 Hz, 1 H, H-4), 1.87 (s, 3 H, $COCH_3$), 1.48 (m, 4 H, $2CH_2$), 1.35 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 168.99 (s, C=O), 163.02 (s, C-2), 160.34 (s, 2 C, C-3′,5′), 155.05 (s, C-7), 152.36 (s, CONH), 151.73 (s, C-8a), 147.25 (d, C-5), 140.43 (s, C-1′), 138.54 (s, C-1″), 128.09, 127.26 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.19 (d, C-4″), 118.93 (s, C-4a), 115.08 (d, C-8), 105.30 (d, 2 C, C-2′,6′), 98.48 (d, C-4′), 71.66 (t, O*C*H_2Ph), 69.13 (t, OCH_2), 54.91 (q, 2 C, $2OCH_3$), 49.94 (s, *C*$(CH_3)_3$), 46.50 (t, NCH_2), 39.69 (d, C-3), 28.51 (q, 3 C, C(*C*$H_3)_3$), 27.84 (t, C-4), 26.40, 24.62 (2 t, $2CH_2$), 22.63 (q, CH_3). Anal. ($C_{34}H_{43}N_5O_5\cdot H_2O$) C, H, N.

Further elution with 2% MeOH/CH_2Cl_2 gave a minor mixture (13 mg), which was combined with similar mixtures from subsequent repeat runs and crystallized from DMSO/water and then EtOAc/hexane to give *N*-[4-(benzyloxy)butyl]-*N*-[3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]acetamide (**55**) (19 mg, 1% overall): mp (EtOAc/hexane) 80−84 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.81 (s, 1 H, H-5), 7.30 (m, 5 H, H-2″,3″,4″,5″,6″), 7.03 (br d, J = 3.1 Hz, 1 H, NH), 6.48 (d, J = 2.3 Hz, 2 H, H-2′,6′), 6.38 (t, J = 2.2 Hz, 1 H, H-4′), 6.34 (s, 1 H, H-8), 4.41 (s, 2 H, O*C*H_2Ph), 3.72 (s, 6 H, $2OCH_3$), 3.62 (t, J = 6.6 Hz, 2 H, NCH_2), 3.39 (t, J = 5.9 Hz, 2 H, OCH_2), 3.35 (m, 1 H, H-2), 3.25 (br dd, J = 12.0, 9.7 Hz, 1 H, H-2), 2.87 (m, 3 H, H-3, 2H-4), 1.82 (s, 3 H, $COCH_3$), 1.49 (m, 4 H, $2CH_2$); ^{13}C NMR δ 168.75 (s, C=O), 160.45 (s, 2 C, C-3′,5′), 153.69, 151.58 (2 s, C-7,8a), 147.55 (d, C-5), 145.46 (s, C-1′), 138.59 (s, C-1″), 128.12, 127.28 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.20 (d, C-4″), 114.77 (s, C-4a), 105.41 (d, 2 C, C-2′,6′), 104.03 (d, C-8), 98.15 (d, C-4′), 71.66 (t, O*C*H_2Ph), 69.23 (t, OCH_2), 55.01 (q, 2 C, $2OCH_3$), 46.29, 45.99 (2 t, C-2, NCH_2), 36.51 (d, C-3), 30.48 (t, C-4), 26.46, 24.49 (2 t, $2CH_2$), 22.38 (q, CH_3); HRFABMS calcd for $C_{29}H_{36}N_3O_4$ *m/z* (MH^+) 490.2706, found 490.2712. Anal. ($C_{29}H_{35}N_3O_4\cdot H_2O$) C, H, N.

Further elution with 2−3% MeOH/CH_2Cl_2 gave the desired **45** (122 mg, 36%): mp (EtOAc/Et_2O/hexane) 133−135 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.87 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.66 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.71 (d, J = 1.7 Hz, 2 H, H-2′,6′), 6.70 (t, J = 2.0 Hz, 1 H, H-4′), 4.36 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.88 (t, J = 7.2 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 3.33 (m, 2 H, C*H*$_2$OH), 1.98 (s, 3 H, $COCH_3$), 1.50 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.39 (m, 2 H, CH_2); ^{13}C NMR δ 169.29 (s, C=O), 161.21 (s, 2 C, C-3′,5′), 154.25, 153.06, 151.57 (3 s, CONH, C-2,7), 151.31 (d, C-5), 148.82 (s, C-8a), 137.02 (d, C-4), 136.56 (s, C-1′), 127.06 (s, C-3), 118.60 (s, C-4a), 115.50 (d, C-8), 107.09 (d, 2 C, C-2′,6′), 100.64 (d, C-4′), 60.31 (t, OCH_2), 55.47 (q, 2 C, $2OCH_3$), 50.20 (s, *C*$(CH_3)_3$), 46.96 (t, NCH_2), 29.69 (t, CH_2),

28.66 (q, 3 C, C(*C*H_3)$_3$), 24.52 (t, CH_2), 22.97 (q, CH_3). Anal. ($C_{27}H_{35}N_5O_5$) C, H, N.

Further elution with 3.5−4.5% MeOH/CH_2Cl_2 gave *N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-3,4-dihydro-1,6-naphthyridin-7-yl]-*N*-(4-hydroxybutyl)acetamide (**52**) (23 mg, 7%): mp (CH_2Cl_2/hexane) 165−167.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.78 (br s, 1 H, NH), 8.13 (s, 1 H, H-5), 7.03 (s, 1 H, H-8), 6.35 (t, J = 2.2 Hz, 1 H, H-4′), 6.21 (d, J = 2.1 Hz, 2 H, H-2′,6′), 4.34 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.96 (br d, J = 7.0 Hz, 1 H, H-3), 3.74 (dt, J = 14.1, 7.1 Hz, 1 H, NCH), 3.69 (dt, J = 13.8, 7.0 Hz, 1 H, NCH), 3.61 (s, 6 H, 2OCH_3), 3.33 (m, 2 H, C*H*$_2$OH), 3.28 (br dd, J = 16.7, 7.2 Hz, 1 H, H-4), 3.00 (br d, J = 16.6 Hz, 1 H, H-4), 1.87 (s, 3 H, $COCH_3$), 1.40 (m, 4 H, 2CH_2), 1.36 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 168.94 (s, C=O), 163.05 (s, C-2), 160.35 (s, 2 C, C-3′,5′), 155.05 (s, C-7), 152.34 (s, CONH), 151.73 (s, C-8a), 147.23 (d, C-5), 140.45 (s, C-1′), 118.92 (s, C-4a), 115.05 (d, C-8), 105.30 (d, 2 C, C-2′,6′), 98.50 (d, C-4′), 60.30 (t, OCH_2), 54.93 (q, 2 C, 2OCH_3), 49.96 (s, *C*(CH_3)$_3$), 46.64 (t, NCH_2), 39.71 (d, C-3), 29.66 (t, CH_2), 28.54 (q, 3 C, C(*C*H_3)$_3$), 27.83 (t, C-4), 24.47 (t, CH_2), 22.65 (q, CH_3). Anal. ($C_{27}H_{37}N_5O_5$) C, H, N.

Further elution with 10% MeOH/CH_2Cl_2 gave *N*-[3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]-*N*-(4-hydroxybutyl)acetamide (**58**) (13 mg, 5%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.82 (s, 1 H, H-5), 7.07 (br s, 1 H, NH), 6.49 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.38 (t, J = 2.2 Hz, 1 H, H-4′), 6.34 (s, 1 H, H-8), 4.37 (m, 1 H, CH_2O*H*), 3.73 (s, 6 H, 2OCH_3), 3.60 (t, J = 7.3 Hz, 2 H, NCH_2), 3.36 (m, 1 H, H-2), 3.34 (m, 2 H, C*H*$_2$OH), 3.26 (br dd, J = 12.0, 9.8 Hz, 1 H, H-2), 2.88 (m, 3 H, H-3, 2H-4), 1.82 (s, 3 H, $COCH_3$), 1.39 (m, 4 H, 2CH_2); ^{13}C NMR δ 168.71 (s, C=O), 160.46 (s, 2 C, C-3′,5′), 153.66, 151.61 (2 s, C-7,8a), 147.49 (d, C-5), 145.48 (s, C-1′), 114.80 (s, C-4a), 105.43 (d, 2 C, C-2′,6′), 104.08 (d, C-8), 98.14 (d, C-4′), 60.36 (t, OCH_2), 55.02 (q, 2 C, 2OCH_3), 46.45, 46.00 (2 t, C-2, NCH_2), 36.50 (d, C-3), 30.48 (t, C-4), 29.74, 24.37 (2 t, 2CH_2), 22.41 (q, CH_3); HRFABMS calcd for $C_{22}H_{30}N_3O_4$ *m/z* (MH^+) 400.2236, found 400.2247.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-(5-hydroxypentyl)acetamide (46).** Similar hydrogenation of **40** (401 mg, 0.654 mmol) in absolute EtOH (320 mL) over 5% Pd/C (480 mg) at 60 psi and 20 °C for 48 h and chromatography of the resulting product on silica gel (eluting with 1−1.25% MeOH/CH_2Cl_2) gave firstly recovered **40** (156 mg, 39%). Elution with 1.5−1.8% MeOH/CH_2Cl_2 gave *N*-[5-(benzyloxy)pentyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-3,4-dihydro-1,6-naphthyridin-7-yl]acetamide (**50**) (40 mg, 10%): mp (EtOAc/hexane) 120−121 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.90 (br s, 1 H, NH), 9.79 (br s, 1 H, NH), 8.12 (s, 1 H, H-5), 7.29 (m, 5 H, H-2″,3″,4″,5″,6″), 7.03 (s, 1 H, H-8), 6.35 (t, J = 2.1 Hz, 1 H, H-4′), 6.22 (d, J = 2.1 Hz, 2 H, H-2′,6′), 4.40 (s, 2 H, OC*H*$_2$Ph), 3.96 (br d, J = 6.6 Hz, 1 H, H-3), 3.76 (dt, J = 14.1, 7.1 Hz, 1 H, NCH), 3.70 (dt, J = 13.4, 6.8 Hz, 1 H, NCH), 3.61 (s, 6 H, 2OCH_3), 3.35 (t, J = 6.3 Hz, 2 H, OCH_2), 3.27 (br dd, J = 16.8, 7.4 Hz, 1 H, H-4), 3.00 (br d, J = 16.3 Hz, 1 H, H-4), 1.88 (s, 3 H, $COCH_3$), 1.47 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.38 (pentet, J = 7.4 Hz, 2 H, CH_2), 1.36 (s, 9 H, C(CH_3)$_3$), 1.27 (pentet, J = 7.7 Hz, 2 H, CH_2); ^{13}C NMR δ 168.94 (s, C=O), 163.04 (s, C-2), 160.34 (s, 2 C, C-3′,5′), 155.04 (s, C-7), 152.33 (s, CONH), 151.72 (s, C-8a), 147.21 (d, C-5), 140.41 (s, C-1′), 138.59 (s, C-1″), 128.09, 127.33 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.18 (d, C-4″), 118.90 (s, C-4a), 114.99 (d, C-8), 105.32 (d, 2 C, C-2′,6′), 98.43 (d, C-4′), 71.66 (t, O*C*H_2Ph), 69.33 (t, OCH_2), 54.91 (q, 2 C, 2OCH_3), 49.93 (s, *C*(CH_3)$_3$), 46.56 (t, NCH_2), 39.69 (d, C-3), 28.76 (t, CH_2), 28.51 (q, 3 C, C(*C*H_3)$_3$), 27.83 (t, C-4), 27.47, 22.85 (2 t, 2CH_2), 22.66 (q, CH_3); HRFABMS calcd for $C_{35}H_{46}N_5O_5$ *m/z* (MH^+) 616.3499, found 616.3500. Anal. ($C_{35}H_{45}N_5O_5$·0.5H_2O) C, H, N.

Further elution with 1.8% MeOH/CH_2Cl_2 gave a minor mixture (8 mg), which was combined with similar mixtures from subsequent repeat runs and fractionally crystallized from CH_2Cl_2/hexane to give *tert*-butylurea (6 mg): mp (CH_2Cl_2/hexane) 179−181.5 °C (lit.[69] 182−184 °C); ^{1}H NMR [$(CD_3)_2$-SO] δ 5.71 (br s, 1 H, NH), 5.13 (br s, 2 H, NH_2), 1.20 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 158.00 (s, CONH), 48.67 (s, *C*(CH_3)$_3$), 29.14 (q, 3 C, C(*C*H_3)$_3$); HREIMS calcd for $C_5H_{12}N_2O$ *m/z* (M^+) 116.094 96, found 116.094 73.

The remaining liquors were crystallized from DMSO/water and then EtOAc/hexane to give *N*-[5-(benzyloxy)pentyl]-*N*-[3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]acetamide (**56**) (25 mg, 2% overall): mp (EtOAc/hexane) 88−90 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.81 (s, 1 H, H-5), 7.30 (m, 5 H, H-2″,3″,4″,5″,6″), 7.00 (br d, J = 3.4 Hz, 1 H, NH), 6.48 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.38 (t, J = 2.2 Hz, 1 H, H-4′), 6.34 (s, 1 H, H-8), 4.42 (s, 2 H, OC*H*$_2$Ph), 3.72 (s, 6 H, 2OCH_3), 3.60 (t, J = 7.2 Hz, 2 H, NCH_2), 3.38 (t, J = 6.5 Hz, 2 H, OCH_2), 3.37 (m, 1 H, H-2), 3.25 (br dd, J = 12.0, 9.8 Hz, 1 H, H-2), 2.87 (m, 3 H, H-3, 2H-4), 1.82 (s, 3 H, $COCH_3$), 1.51 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.42 (pentet, J = 7.4 Hz, 2 H, CH_2), 1.28 (pentet, J = 7.7 Hz, 2 H, CH_2); ^{13}C NMR δ 168.69 (s, C=O), 160.44 (s, 2 C, C-3′,5′), 153.74, 151.54 (2 s, C-7,8a), 147.55 (d, C-5), 145.44 (s, C-1′), 138.62 (s, C-1″), 128.09, 127.25 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.17 (d, C-4″), 114.71 (s, C-4a), 105.39 (d, 2 C, C-2′,6′), 103.96 (d, C-8), 98.14 (d, C-4′), 71.65 (t, O*C*H_2-Ph), 69.42 (t, OCH_2), 54.99 (q, 2 C, 2OCH_3), 46.37, 45.98 (2 t, C-2, NCH_2), 36.50 (d, C-3), 30.46 (t, C-4), 28.78, 27.39, 22.92 (3 t, 3CH_2), 22.38 (q, CH_3); HRFABMS calcd for $C_{30}H_{38}N_3O_4$ *m/z* (MH^+) 504.2862, found 504.2860. Anal. ($C_{30}H_{37}N_3O_4$) C, H, N.

Further elution of the column with 2−3% MeOH/CH_2Cl_2 gave the desired **46** (137 mg, 40%): mp (EtOAc/hexane) 113−115 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.66 (s, 1 H, H-8), 7.29 (br s, 1 H, NH), 6.71 (d, J = 2.0 Hz, 2 H, H-2′,6′), 6.70 (t, J = 2.0 Hz, 1 H, H-4′), 4.32 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.86 (t, J = 7.4 Hz, 2 H, NCH_2), 3.82 (s, 6 H, 2OCH_3), 3.33 (td, J = 6.3, 5.2 Hz, 2 H, C*H*$_2$OH), 1.98 (s, 3 H, $COCH_3$), 1.47 (pentet, J = 7.5 Hz, 2 H, CH_2), 1.42 (s, 9 H, C(CH_3)$_3$), 1.37 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.28 (pentet, J = 7.5 Hz, 2 H, CH_2); ^{13}C NMR δ 169.24 (s, C=O), 161.19 (s, 2 C, C-3′,5′), 154.24, 153.04, 151.54 (3 s, CONH, C-2,7), 151.28 (d, C-5), 148.79 (s, C-8a), 136.99 (d, C-4), 136.54 (s, C-1′), 127.03 (s, C-3), 118.56 (s, C-4a), 115.43 (d, C-8), 107.07 (d, 2 C, C-2′,6′), 100.63 (d, C-4′), 60.41 (t, OCH_2), 55.45 (q, 2 C, 2OCH_3), 50.17 (s, *C*(CH_3)$_3$), 47.04 (t, NCH_2), 32.09 (t, CH_2), 28.64 (q, 3 C, C(*C*H_3)$_3$), 27.59 (t, CH_2), 22.96 (q, CH_3), 22.69 (t, CH_2). Anal. ($C_{28}H_{37}N_5O_5$·0.5H_2O) C, H, N.

Further elution with 3−10% MeOH/CH_2Cl_2 gave a mixture of the above compound and more polar products (29 mg). Chromatography of similar mixtures, combined from subsequent repeat runs, on silica gel, eluting with 2.5−4% MeOH/CH_2Cl_2, gave *N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-3,4-dihydro-1,6-naphthyridin-7-yl]-*N*-(5-hydroxypentyl)acetamide (**53**) (65 mg, 5% overall): mp (EtOAc/hexane) 138−140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.90 (br s, 1 H, NH), 9.78 (br s, 1 H, NH), 8.13 (s, 1 H, H-5), 7.03 (s, 1 H, H-8), 6.35 (t, J = 2.1 Hz, 1 H, H-4′), 6.21 (d, J = 2.1 Hz, 2 H, H-2′,6′), 4.32 (br t, J = 5.2 Hz, 1 H, CH_2O*H*), 3.96 (br d, J = 7.0 Hz, 1 H, H-3), 3.73 (dt, J = 13.6, 6.8 Hz, 1 H, NCH), 3.67 (m, 1 H, NCH), 3.61 (s, 6 H, 2OCH_3), 3.32 (m, 2 H, C*H*$_2$-OH), 3.27 (br dd, J = 16.7, 7.2 Hz, 1 H, H-4), 3.00 (br d, J = 16.3 Hz, 1 H, H-4), 1.87 (s, 3 H, $COCH_3$), 1.37 (m, 4 H, 2CH_2), 1.36 (s, 9 H, C(CH_3)$_3$), 1.24 (m, 2 H, CH_2); ^{13}C NMR δ 168.95 (s, C=O), 163.05 (s, C-2), 160.36 (s, 2 C, C-3′,5′), 155.07 (s, C-7), 152.36 (s, CONH), 151.77 (s, C-8a), 147.26 (d, C-5), 140.45 (s, C-1′), 118.93 (s, C-4a), 115.05 (d, C-8), 105.33 (d, 2 C, C-2′,6′), 98.47 (d, C-4′), 60.44 (t, OCH_2), 54.94 (q, 2 C, 2OCH_3), 49.97 (s, *C*(CH_3)$_3$), 46.73 (t, NCH_2), 39.69 (d, C-3), 32.13 (t, CH_2), 28.54 (q, 3 C, C(*C*H_3)$_3$), 27.85 (t, C-4), 27.57 (t, CH_2), 22.67 (t + q, CH_2, CH_3). Anal. ($C_{28}H_{39}N_5O_5$) C, H, N.

Further elution of the latter column with 10% MeOH/CH_2-Cl_2 gave *N*-[3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]-*N*-(5-hydroxypentyl)acetamide (**59**) (65 mg, 6% overall) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.81 (s, 1 H, H-5), 7.03 (m, 1 H, NH), 6.49 (d, J = 2.1 Hz, 2 H, H-2′,6′), 6.38 (t, J = 2.0 Hz, 1 H, H-4′), 6.33 (s, 1 H, H-8), 4.33 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.72 (s, 6 H, 2OCH_3), 3.58 (t, J = 7.3 Hz, 2 H, NCH_2), 3.39 (m, 1 H, H-2), 3.36 (m, 2 H, C*H*$_2$OH), 3.26 (br dd,

J = 12.0, 9.7 Hz, 1 H, H-2), 2.88 (m, 3 H, H-3, 2H-4), 1.81 (s, 3 H, $COCH_3$), 1.37 (pentet, J = 7.1 Hz, 4 H, $2CH_2$), 1.23 (pentet, J = 7.2 Hz, 2 H, CH_2); ^{13}C NMR δ 168.68 (s, C=O), 160.45 (s, 2 C, C-3′,5′), 153.71, 151.59 (2 s, C-7,8a), 147.52 (d, C-5), 145.48 (s, C-1′), 114.76 (s, C-4a), 105.42 (d, 2 C, C-2′,6′), 104.01 (d, C-8), 98.13 (d, C-4′), 60.45 (t, OCH_2), 55.01 (q, 2 C, $2OCH_3$), 46.53, 45.99 (2 t, C-2, NCH_2), 36.50 (d, C-3), 32.13 (t, CH_2), 30.47 (t, C-4), 27.46, 22.69 (2 t, $2CH_2$), 22.41 (q, CH_3); HRFABMS calcd for $C_{23}H_{32}N_3O_4$ *m/z* (MH^+) 414.2393, found 414.2392.

Purification of 44 and Alternative Preparations. A. Via Acetylation/Hydrolysis. A solution of crude **44** above (68 mg of ca. 80%, 0.11 mmol) in pyridine (7 mL) was treated with acetic anhydride (0.70 mL, 7.43 mmol), then the mixture was stirred at 20 °C for 14 h. The resulting solution was diluted with CH_2Cl_2, then treated with a mixture of ice and aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were washed with water and then evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 0−1% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 1−1.25% MeOH/CH_2Cl_2 gave 3-[acetyl[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]amino]propyl acetate (**47**) (59 mg, 100%) as an oil: ^1H NMR [$(CD_3)_2SO$] δ 9.86 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.36 (s, 1 H, H-4), 7.71 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (m, 3 H, H-2′,4′,6′), 4.02 (t, J = 6.5 Hz, 2 H, OCH_2), 3.95 (t, J = 6.9 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 1.97 (s, 3 H, $NCOCH_3$), 1.94 (s, 3 H, $OCOCH_3$), 1.81 (pentet, J = 6.7 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$); HRFABMS calcd for $C_{28}H_{36}N_5O_6$ *m/z* (MH^+) 538.2665, found 538.2663.

Further elution with 2−4% MeOH/CH_2Cl_2 gave *N*-[3-(benzyloxy)propyl]-*N*-[3-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]acetamide (**54**) (9 mg) as an oil: ^1H NMR [$(CD_3)_2SO$] δ 7.81 (s, 1 H, H-5), 7.30 (m, 5 H, H-2″,3″,4″,5″,6″), 7.02 (br d, J = 3.2 Hz, 1 H, NH), 6.48 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.38 (t, J = 2.2 Hz, 1 H, H-4′), 6.35 (s, 1 H, H-8), 4.38 (s, 2 H, OC*H*$_2$Ph), 3.72 (s, 6 H, $2OCH_3$), 3.69 (t, J = 7.3 Hz, 2 H, NCH_2), 3.42 (t, J = 6.3 Hz, 2 H, OCH_2), 3.37 (m, 1 H, H-2), 3.24 (m, 1 H, H-2), 2.85 (m, 3 H, H-3, 2H-4), 1.83 (s, 3 H, $COCH_3$), 1.70 (pentet, J = 6.9 Hz, 2 H, CH_2); HRFABMS calcd for $C_{28}H_{34}N_3O_4$ *m/z* (MH^+) 476.2549, found 476.2546.

A solution of **47** (58 mg, 0.108 mmol) in MeOH (27 mL) was treated with K_2CO_3 (61 mg, 0.44 mmol) and water (3 mL), stirring at 20 °C for 1 h. The resulting solution was diluted with water (120 mL) and extracted with CH_2Cl_2 (5 × 100 mL). The combined extracts were washed with water (120 mL), and then the aqueous portion was further extracted with CH_2Cl_2 (3 × 100 mL). The resulting extracts were evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 0−1.2% MeOH/CH_2Cl_2 gave foreruns, then further elution with 1.2−3% MeOH/CH_2Cl_2 gave **44** (50 mg, 94%): mp (EtOAc/hexane) 154−157 °C; ^1H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.69 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 4.51 (br t, J = 5.2 Hz, 1 H, CH_2OH), 3.93 (t, J = 7.2 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 3.42 (td, J = 6.2, 5.2 Hz, 2 H, C*H*$_2$OH), 2.00 (s, 3 H, $COCH_3$), 1.65 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.98 (s, C=O), 161.44 (s, 2 C, C-3′,5′), 154.42, 153.25, 151.90 (3 s, CONH, C-2,7), 151.56 (d, C-5), 149.04 (s, C-8a), 137.24 (d, C-4), 136.72 (s, C-1′), 127.29 (s, C-3), 118.86 (s, C-4a), 115.79 (d, C-8), 107.25 (d, 2 C, C-2′,6′), 100.83 (d, C-4′), 58.48 (t, OCH_2), 55.67 (q, 2 C, $2OCH_3$), 50.47 (s, *C*$(CH_3)_3$), 45.09 (t, NCH_2), 31.24 (t, CH_2), 28.85 (q, 3 C, C(*C*$H_3)_3$), 23.12 (q, CH_3). Anal. ($C_{26}H_{33}N_5O_5$) C, H, N.

B. DDQ Debenzylation of 38. A solution of **38** (305 mg, 0.521 mmol) and DDQ (615 mg, 2.71 mmol) in CH_2Cl_2 (58 mL) was stirred in a sealed flask (foil-covered) at 20 °C for 4 days. The resulting solution was treated with a mixture of aqueous Na_2CO_3/Na_2SO_3 (350 mL) and extracted with CH_2Cl_2 (5 × 150 mL), sequentially washing each extract with (the same) additional solutions of aqueous Na_2CO_3/Na_2SO_3 (300 mL), aqueous Na_2CO_3 (300 mL), and water (2 × 300 mL). The aqueous portions were further extracted after 18 and 42 h (3 × 150 mL). Then the combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−1% MeOH/CH_2Cl_2 gave foreruns, and then further elution with 1−1.5% MeOH/CH_2Cl_2 gave crude recovered **38** (36 mg, 12%). Elution with 1.75−2.5% MeOH/CH_2Cl_2 gave **44** (178 mg, 69%).

C. DDQ Dehydrogenation of 51. Similar reaction of **51** (42 mg, 84.5 μmol) with DDQ (29 mg, 0.128 mmol) in CH_2Cl_2 (8 mL) at 20 °C for 3 h and then workup (as above) and chromatography of the resulting product on silica gel (eluting with 1−2% MeOH/CH_2Cl_2) gave **44** (41 mg, 98%).

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]acetamide (65).** A stirred solution of (pure) **44** (217 mg, 0.438 mmol) in dry THF (30 mL) under N_2 at 0 °C was treated with dry *N*-methylmorpholine (1.00 mL, 9.11 mmol), followed by mesyl chloride (0.17 mL, 2.20 mmol, added dropwise by syringe). Then the mixture was stirred at 0−20 °C for 12 h. 1-Methylpiperazine (10.0 mL, 90.3 mmol) was then added, and the mixture was stirred at 20 °C for 1 day and then at 32 °C for 1 day. Triethylamine (1.0 mL, 7.19 mmol) was added, and the mixture was concentrated under reduced pressure (to ca. 10 mL). The resulting solution was cooled in ice, then treated with ice/aqueous Na_2CO_3 (150 mL) and extracted with CH_2Cl_2 (6 × 100 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−6% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 7−8% MeOH/CH_2Cl_2 gave [after treatment with aqueous Na_2CO_3 (50 mL) and extraction with CH_2Cl_2 (8 × 50 mL)] an oil (182 mg), which was further chromatographed on silica gel. Elution with 0−3% MeOH/EtOAc containing 1% Et_3N gave foreruns, and then further elution with 3−6% MeOH/EtOAc containing 1% Et_3N gave (after base washing) **65** (162 mg, 64%): oil; ^1H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.68 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 3.89 (t, J = 7.2 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 2.6−2.0 (br s, 8 H, $N(CH_2)_4N$), 2.25 (t, J = 7.0 Hz, 2 H, NCH_2), 2.09 (s, 3 H, NCH_3), 1.99 (s, 3 H, $COCH_3$), 1.63 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.42 (s, C=O), 161.21 (s, 2 C, C-3′,5′), 154.28, 153.03, 151.59 (3 s, CONH, C-2,7), 151.21 (d, C-5), 148.78 (s, C-8a), 137.01 (d, C-4), 136.56 (s, C-1′), 127.01 (s, C-3), 118.55 (s, C-4a), 115.43 (d, C-8), 107.08 (d, 2 C, C-2′,6′), 100.65 (d, C-4′), 55.47 (q, 2 C, $2OCH_3$), 54.82 (t, NCH_2), 54.64, 52.45 (2 t, 2 × 2 C, $2N(CH_2)_2$), 50.19 (s, *C*$(CH_3)_3$), 45.66 (q, NCH_3), 45.49 (t, NCH_2), 28.67 (q, 3 C, C(*C*$H_3)_3$), 25.10 (t, CH_2), 23.02 (q, CH_3); HRFABMS calcd for $C_{31}H_{44}N_7O_4$ *m/z* (MH^+) 578.3455, found 578.3452.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[4-(4-methyl-1-piperazinyl)butyl]acetamide (66).** Similar reaction of a stirred solution of **45** (148 mg, 0.291 mmol) and dry *N*-methylmorpholine (0.50 mL, 4.55 mmol) in dry THF (20 mL) under N_2 with mesyl chloride (0.116 mL, 1.50 mmol) at 20 °C for 16 h followed by reaction with 1-methylpiperazine (3.25 mL, 29.3 mmol) at 52 °C for 1 day and chromatography of the resulting product on silica gel (eluting with 4−8% MeOH/EtOAc containing 1% Et_3N) gave (after base washing) crude **66** (164 mg, <95%) as an oil: ^1H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.36 (s, 1 H, H-4), 7.67 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 3.88 (t, J = 6.6 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 2.5−2.0 (br s, 8 H, $N(CH_2)_4N$), 2.18 (t, J = 6.7 Hz, 2 H, NCH_2), 2.09 (s, 3 H, NCH_3), 1.98 (s, 3 H, $COCH_3$), 1.46 (m, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.40 (m, 2 H, CH_2); ^{13}C NMR δ 169.31 (s, C=O), 161.21 (s, 2 C, C-3′,5′), 154.20, 153.03, 151.56 (3 s, CONH, C-2,7), 151.29 (d, C-5), 148.80 (s, C-8a), 137.01 (d, C-4), 136.54 (s, C-1′), 127.04 (s, C-3), 118.59 (s, C-4a), 115.55 (d, C-8), 107.06 (d, 2 C, C-2′,6′), 100.63 (d, C-4′), 57.24 (t, NCH_2), 55.46 (q, 2 C, $2OCH_3$), 54.66, 52.52 (2 t, 2 × 2 C, $2N(CH_2)_2$), 50.18 (s, *C*$(CH_3)_3$), 46.78 (t, NCH_2), 45.65 (q, NCH_3), 28.66 (q, 3 C, C(*C*$H_3)_3$), 25.60, 23.41

(2 t, $2CH_2$), 22.97 (q, CH_3); HRFABMS calcd for $C_{32}H_{46}N_7O_4$ *m/z* (MH^+) 592.3611, found 592.3611.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[5-(4-methyl-1-piperazinyl)pentyl]acetamide (67).** Similar reaction of a stirred solution of **46** (151 mg, 0.289 mmol) and dry *N*-methylmorpholine (0.475 mL, 4.33 mmol) in dry THF (20 mL) under N_2 with mesyl chloride (0.112 mL, 1.45 mmol) at 20 °C for 15 h followed by reaction with 1-methylpiperazine (3.2 mL, 28.9 mmol) at 52 °C for 1 day and chromatography of the resulting product on silica gel (eluting with 4−8% MeOH/EtOAc containing 1% Et_3N) gave (after base washing) crude **67** (171 mg, <98%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.36 (s, 1 H, H-4), 7.66 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 3.86 (t, J = 7.4 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 2.5−2.0 (br s, 8 H, $N(CH_2)_4N$), 2.15 (t, J = 7.0 Hz, 2 H, NCH_2), 2.10 (s, 3 H, NCH_3), 1.98 (s, 3 H, $COCH_3$), 1.48 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.33 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.24 (pentet, J = 7.0 Hz, 2 H, CH_2); ^{13}C NMR δ 169.29 (s, C=O), 161.22 (s, 2 C, C-3′,5′), 154.26, 153.04, 151.57 (3 s, CONH, C-2,7), 151.30 (d, C-5), 148.81 (s, C-8a), 137.02 (d, C-4), 136.54 (s, C-1′), 127.04 (s, C-3), 118.59 (s, C-4a), 115.48 (d, C-8), 107.07 (d, 2 C, C-2′,6′), 100.63 (d, C-4′), 57.68 (t, NCH_2), 55.46 (q, 2 C, $2OCH_3$), 54.67, 52.61 (2 t, 2 × 2 C, $2N(CH_2)_2$), 50.19 (s, $C(CH_3)_3$), 46.87 (t, NCH_2), 45.66 (q, NCH_3), 28.67 (q, 3 C, $C(CH_3)_3$), 27.64, 25.84, 24.10 (3 t, $3CH_2$), 22.97 (q, CH_3); HRFABMS calcd for $C_{33}H_{48}N_7O_4$ *m/z* (MH^+) 606.3768, found 606.3757.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[3-(diethylamino)propyl]acetamide (68).** Similar reaction of a stirred solution of crude **44** (163 mg of ca. 70%, 0.231 mmol) and dry *N*-methylmorpholine (0.57 mL, 5.19 mmol) in dry THF (20 mL) under N_2 with mesyl chloride (0.135 mL, 1.74 mmol) at 20 °C for 16 h followed by reaction with diethylamine (7.1 mL, 68.8 mmol) at 50 °C for 42 h and chromatography of the resulting product on silica gel (eluting with 5% MeOH/CH_2Cl_2 containing 0.5% Et_3N) gave (after base washing) an oil (41 mg). Further chromatography of this material on silica gel (eluting with 0.25−0.5% MeOH/EtOAc containing 1% Et_3N) gave (after base washing) **68** (26 mg, 21%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.67 (s, 1 H, H-8), 7.29 (br s, 1 H, NH), 6.71 (d, J = 1.9 Hz, 2 H, H-2′,6′), 6.69 (t, J = 2.0 Hz, 1 H, H-4′), 3.89 (t, J = 7.4 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 2.37 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.36 (t, J = 7.0 Hz, 2 H, NCH_2), 1.98 (s, 3 H, $COCH_3$), 1.59 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.41 (s, 9 H, $C(CH_3)_3$), 0.88 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 169.40 (s, C=O), 161.23 (s, 2 C, C-3′,5′), 154.27, 153.07, 151.60 (3 s, CONH, C-2,7), 151.32 (d, C-5), 148.80 (s, C-8a), 137.03 (d, C-4), 136.57 (s, C-1′), 127.07 (s, C-3), 118.61 (s, C-4a), 115.54 (d, C-8), 107.09 (d, 2 C, C-2′,6′), 100.69 (d, C-4′), 55.49 (q, 2 C, $2OCH_3$), 50.21 (s, $C(CH_3)_3$), 49.49 (t, NCH_2), 46.12 (t, 2 C, $N(CH_2)_2$), 45.62 (t, NCH_2), 28.67 (q, 3 C, $C(CH_3)_3$), 25.45 (t, CH_2), 23.01 (q, CH_3), 11.61 (q, 2 C, $2CH_3$); HRFABMS calcd for $C_{30}H_{43}N_6O_4$ *m/z* (MH^+) 551.3346, found 551.3361.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[4-(diethylamino)butyl]acetamide (69).** Similar reaction of a stirred solution of **45** (456 mg, 0.896 mmol) and dry *N*-methylmorpholine (1.50 mL, 13.7 mmol) in dry THF (60 mL) under N_2 with mesyl chloride (0.35 mL, 4.52 mmol) at 20 °C for 17 h followed by reaction with diethylamine (18 mL, 0.174 mol) at 50 °C for 4 days and chromatography of the resulting product on silica gel (eluting with 1−2% MeOH/EtOAc containing 1% Et_3N) gave (after base washing) **69** (0.39 g, 77%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.65 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 3.88 (t, J = 6.9 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 2.36 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.28 (t, J = 7.0 Hz, 2 H, NCH_2), 1.98 (s, 3 H, $COCH_3$), 1.46 (pentet, J = 7.4 Hz, 2 H, CH_2), 1.41 (s, 9 H, $C(CH_3)_3$), 1.36 (pentet, J = 7.4 Hz, 2 H, CH_2), 0.87 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 169.32 (s, C=O), 161.22 (s, 2 C, C-3′,5′), 154.27, 153.05, 151.58 (3 s, CONH, C-2,7), 151.32 (d, C-5), 148.81 (s, C-8a), 137.02 (d, C-4), 136.55 (s, C-1′), 127.06 (s, C-3), 118.61 (s, C-4a), 115.51 (d, C-8), 107.08 (d, 2 C, C-2′,6′), 100.66 (d, C-4′), 55.47 (q, 2 C, $2OCH_3$), 51.76 (t, NCH_2), 50.19 (s, $C(CH_3)_3$), 46.89 (t, NCH_2), 46.15 (t, 2 C, $N(CH_2)_2$), 28.66 (q, 3 C, $C(CH_3)_3$), 25.75, 23.88 (2 t, $2CH_2$), 22.98 (q, CH_3), 11.67 (q, 2 C, $2CH_3$); HRFABMS calcd for $C_{31}H_{45}N_6O_4$ *m/z* (MH^+) 565.3502, found 565.3504.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[5-(diethylamino)pentyl]acetamide (70).** Similar reaction of a stirred solution of **46** (151 mg, 0.289 mmol) and dry *N*-methylmorpholine (0.475 mL, 4.33 mmol) in dry THF (20 mL) under N_2 with mesyl chloride (0.112 mL, 1.45 mmol) at 20 °C for 15 h followed by reaction with diethylamine (3.0 mL, 29.0 mmol) at 50 °C for 2 days and then with additional diethylamine (3.0 mL, 29.0 mmol) at 50 °C for 2 days and chromatography of the resulting product on silica gel (eluting with 1−2% MeOH/EtOAc containing 1% Et_3N) gave (after base washing) **70** (141 mg, 84%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.66 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 3.86 (t, J = 7.3 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 2.36 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.25 (t, J = 7.0 Hz, 2 H, NCH_2), 1.98 (s, 3 H, $COCH_3$), 1.48 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.30 (pentet, J = 6.7 Hz, 2 H, CH_2), 1.24 (pentet, J = 7.2 Hz, 2 H, CH_2), 0.87 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 169.24 (s, C=O), 161.20 (s, 2 C, C-3′,5′), 154.28, 153.02, 151.54 (3 s, CONH, C-2,7), 151.28 (d, C-5), 148.78 (s, C-8a), 136.99 (d, C-4), 136.52 (s, C-1′), 127.01 (s, C-3), 118.56 (s, C-4a), 115.45 (d, C-8), 107.05 (d, 2 C, C-2′,6′), 100.62 (d, C-4′), 55.44 (q, 2 C, $2OCH_3$), 51.96 (t, NCH_2), 50.15 (s, $C(CH_3)_3$), 46.93 (t, NCH_2), 46.15 (t, 2 C, $N(CH_2)_2$), 28.63 (q, 3 C, $C(CH_3)_3$), 27.59, 26.17, 24.07 (3 t, $3CH_2$), 22.95 (q, CH_3), 11.63 (q, 2 C, $2CH_3$); HRFABMS calcd for $C_{32}H_{47}N_6O_4$ *m/z* (MH^+) 579.3659, found 579.3646.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[4-(4-morpholino)butyl]acetamide (71).** Similar reaction of a stirred solution of **45** (152 mg, 0.299 mmol) and dry *N*-methylmorpholine (0.50 mL, 4.55 mmol) in dry THF (20 mL) under N_2 with mesyl chloride (0.116 mL, 1.50 mmol) at 20 °C for 16 h followed by reaction with morpholine (2.6 mL, 29.9 mmol) at 52 °C for 43 h and chromatography of the resulting product on silica gel (eluting with 6−10% MeOH/EtOAc) gave (after base washing) crude **71** (162 mg, <94%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.87 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.67 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.70 (s, 3 H, H-2′,4′,6′), 3.89 (t, J = 6.8 Hz, 2 H, NCH_2), 3.82 (s, 6 H, $2OCH_3$), 3.50 (t, J = 4.5 Hz, 4 H, $O(CH_2)_2$), 2.26 (m, 4 H, $N(CH_2)_2$), 2.20 (t, J = 6.8 Hz, 2 H, NCH_2), 1.98 (s, 3 H, $COCH_3$), 1.46 (m, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.42 (m, 2 H, CH_2); ^{13}C NMR δ 169.30 (s, C=O), 161.19 (s, 2 C, C-3′,5′), 154.21, 153.03, 151.54 (3 s, CONH, C-2,7), 151.28 (d, C-5), 148.80 (s, C-8a), 136.99 (d, C-4), 136.53 (s, C-1′), 127.03 (s, C-3), 118.57 (s, C-4a), 115.50 (d, C-8), 107.06 (d, 2 C, C-2′,6′), 100.62 (d, C-4′), 66.08 (t, 2 C, $O(CH_2)_2$), 57.76 (t, NCH_2), 55.45 (q, 2 C, $2OCH_3$), 53.20 (t, 2 C, $N(CH_2)_2$), 50.17 (s, $C(CH_3)_3$), 46.79 (t, NCH_2), 28.64 (q, 3 C, $C(CH_3)_3$), 25.62, 23.06 (2 t, $2CH_2$), 22.96 (q, CH_3); HRFABMS calcd for $C_{31}H_{43}N_6O_5$ *m/z* (MH^+) 579.3295, found 579.3289.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]-*N*-[5-(4-morpholino)pentyl]acetamide (72).** Similar reaction of a stirred solution of **46** (121 mg, 0.231 mmol) and dry *N*-methylmorpholine (0.38 mL, 3.46 mmol) in dry THF (10 mL) under N_2 with mesyl chloride (0.090 mL, 1.16 mmol) at 20 °C for 16 h followed by reaction with morpholine (2.0 mL, 23.0 mmol) at 52 °C for 36 h and chromatography of the resulting product on silica gel (eluting with 8−10% MeOH/EtOAc) gave (after base washing) **72** (117 mg, 85%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.87 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.65 (s, 1 H, H-8), 7.30 (br s, 1 H, NH), 6.69 (s, 3 H, H-2′,4′,6′), 3.87 (t, J = 7.3 Hz, 2 H, NCH_2), 3.82 (s, 6 H,

$2OCH_3$), 3.51 (t, J = 4.6 Hz, 4 H, $O(CH_2)_2$), 2.25 (m, 4 H, $N(CH_2)_2$), 2.17 (t, J = 7.2 Hz, 2 H, NCH_2), 1.98 (s, 3 H, $COCH_3$), 1.49 (pentet, J = 7.4 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.36 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.26 (pentet, J = 7.2 Hz, 2 H, CH_2); ^{13}C NMR δ 169.25 (s, C=O), 161.19 (s, 2 C, C-3′,5′), 154.26, 153.03, 151.53 (3 s, CONH, C-2,7), 151.28 (d, C-5), 148.79 (s, C-8a), 137.00 (d, C-4), 136.52 (s, C-1′), 127.03 (s, C-3), 118.56 (s, C-4a), 115.44 (d, C-8), 107.05 (d, 2 C, C-2′,6′), 100.62 (d, C-4′), 66.09 (t, 2 C, $O(CH_2)_2$), 58.08 (t, NCH_2), 55.44 (q, 2 C, $2OCH_3$), 53.26 (t, 2 C, $N(CH_2)_2$), 50.16 (s, $C(CH_3)_3$), 46.86 (t, NCH_2), 28.64 (q, 3 C, $C(CH_3)_3$), 27.60, 25.47, 24.00 (3 t, $3CH_2$), 22.95 (q, CH_3); HRFABMS calcd for $C_{32}H_{45}N_6O_5$ m/z (MH^+) 593.3452, found 593.3490.

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[[3-(4-methyl-1-piperazinyl)propyl]amino]-1,6-naphthyridin-2-yl]urea (17).** A stirred solution of **65** (78 mg, 0.135 mmol) in MeOH (22.5 mL) at 0 °C was treated with NaOH (0.815 g, 20.4 mmol) and water (2.5 mL, added dropwise). Then the mixture was stirred at 0 °C for 2 h and then at 20 °C for 3 days. A solution of excess $NaHCO_3$ (2.02 g, 24.0 mmol) in ice/water (150 mL) was then added, and the mixture was extracted with CH_2Cl_2 (6 × 70 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on neutral alumina. Elution with CH_2Cl_2 gave foreruns. Then further elution with 1% EtOH/$CHCl_3$ gave material that was treated with aqueous Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (5 × 50 mL). Crystallization of the resulting solid from CH_2Cl_2/hexane gave **17** (53 mg, 73%): mp (CH_2Cl_2/hexane) 137−139 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.03 (br s, 1 H, NH), 6.95 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.63 (m, 3 H, H-2′,4′,6′), 6.38 (s, 1 H, H-8), 3.80 (s, 6 H, $2OCH_3$), 3.31 (m, 2 H, NHC*H*$_2$), 2.6−2.1 (br s, 8 H, $N(CH_2)_4N$), 2.38 (t, J = 7.0 Hz, 2 H, NCH_2), 2.16 (s, 3 H, NCH_3), 1.72 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 161.13 (s, 2 C, C-3′,5′), 159.55 (s, C-7), 152.39, 152.04 (2 s, CONH, C-2), 151.39 (d, C-5), 149.36 (s, C-8a), 137.46 (d, C-4), 137.39 (s, C-1′), 121.01 (s, C-3), 113.13 (s, C-4a), 107.08 (d, 2 C, C-2′,6′), 100.18 (d, C-4′), 94.57 (br d, C-8), 55.67 (t, NCH_2), 55.40 (q, 2 C, $2OCH_3$), 54.76, 52.70 (2 t, 2 × 2 C, $2N(CH_2)_2$), 49.95 (s, $C(CH_3)_3$), 45.70 (q, NCH_3), 39.80 (t, NCH_2), 28.68 (q, 3 C, $C(CH_3)_3$), 25.96 (t, CH_2). Anal. ($C_{29}H_{41}N_7O_3$) C, H, N.

Further base hydrolysis of the mother liquors, followed by chromatography of the resulting product on neutral alumina, as above, gave additional **17** (9 mg, 12%).

***N*-(*tert*-Butyl)-*N*′-[7-[[3-(diethylamino)propyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]urea (18). Method A.** Similar hydrolysis of **68** (26 mg, 47.3 μmol) in MeOH (7.2 mL) with NaOH (317 mg, 7.93 mmol) and water (0.8 mL) at 0 °C for 1 h and then at 20 °C for 2 days and chromatography of the resulting product on silica gel (eluting with 0.3% MeOH/CH_2Cl_2 containing 1% Et_3N) gave (after base washing) **18** (20 mg, 83%): mp (CH_2Cl_2/hexane) 138−140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.22 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.03 (br s, 1 H, NH), 6.96 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.62 (m, 3 H, H-2′,4′,6′), 6.37 (s, 1 H, H-8), 3.80 (s, 6 H, $2OCH_3$), 3.29 (m, 2 H, NHC*H*$_2$), 2.47 (t, J = 7.2 Hz, 2 H, NCH_2), 2.46 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 1.69 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$), 0.95 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 161.12 (s, 2 C, C-3′,5′), 159.56 (s, C-7), 152.34, 152.01 (2 s, CONH, C-2), 151.39 (d, C-5), 149.41 (s, C-8a), 137.45 (d, C-4), 137.40 (s, C-1′), 120.99 (s, C-3), 113.12 (s, C-4a), 107.07 (d, 2 C, C-2′,6′), 100.18 (d, C-4′), 94.24 (br d, C-8), 55.39 (q, 2 C, $2OCH_3$), 50.17 (t, NCH_2), 49.93 (s, $C(CH_3)_3$), 46.34 (t, 2 C, $N(CH_2)_2$), 39.89 (t, NCH_2), 28.65 (q, 3 C, $C(CH_3)_3$), 26.32 (t, CH_2), 11.67 (q, 2 C, $2CH_3$). Anal. ($C_{28}H_{40}N_6O_3$) C, H, N.

Method B. A solution of **13** (151 mg, 0.346 mmol) in dry DMF (10 mL) was treated with 60% NaH (90 mg, 2.25 mmol). Then the mixture was sealed under N_2 (as above) and stirred at 20 °C for 10 min and then at 0 °C for 30 min. A solution of 3-diethylaminopropyl chloride[53] (104 mg, 0.696 mmol) in dry DMF (1 mL) was added (syringe), and the mixture was then stirred at 39 °C for 40 h. The resulting solution was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (7 × 50 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−0.25% MeOH/EtOAc containing 1% Et_3N gave foreruns. Then further elution with 0.25% MeOH/EtOAc containing 1% Et_3N gave (after base washing) an oil (100 mg) (a mixture of **18** and **68**). Similar hydrolysis of this oil in MeOH (27 mL) with NaOH (1.06 g, 26.5 mmol) and water (3 mL) at 0 °C for 1.5 h and then at 20 °C for 44 h and chromatography of the resulting product on silica gel (eluting with 0.3−0.5% MeOH/CH_2Cl_2 containing 1% Et_3N) gave (after base washing and crystallization) **18** (76 mg, 43%). The mother liquors were further purified by chromatography on silica gel (eluting with 0.25−1% MeOH/EtOAc containing 1% Et_3N) to give a mixture of **18** and **68**, which was subjected to base hydrolysis and workup as above. Then the product was filtered on neutral alumina (eluting with 1% EtOH/$CHCl_3$) to give additional **18** (8 mg, 5%).

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[[4-(4-morpholino)butyl]amino]-1,6-naphthyridin-2-yl]urea (19).** Similar hydrolysis of crude **71** (160 mg) in MeOH (45 mL) with NaOH (1.90 g, 47.5 mmol) and water (5 mL) at 0 °C for 2 h and then at 20 °C for 4.5 days and chromatography of the resulting product on silica gel (eluting with 3−3.5% MeOH/CH_2Cl_2) gave (after base washing and crystallization) **19** (46 mg, 29% overall from **45**): mp (Et_2O/hexane) 74−77 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.02 (br s, 1 H, NH), 6.94 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.63 (m, 3 H, H-2′,4′,6′), 6.38 (s, 1 H, H-8), 3.80 (s, 6 H, $2OCH_3$), 3.56 (t, J = 4.6 Hz, 4 H, $O(CH_2)_2$), 3.29 (m, 2 H, NHC*H*$_2$), 2.33 (m, 4 H, $N(CH_2)_2$), 2.29 (t, J = 7.1 Hz, 2 H, NCH_2), 1.59 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.52 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 161.11 (s, 2 C, C-3′,5′), 159.55 (s, C-7), 152.37, 152.01 (2 s, CONH, C-2), 151.34 (d, C-5), 149.33 (s, C-8a), 137.43 (d, C-4), 137.39 (s, C-1′), 121.01 (s, C-3), 113.08 (s, C-4a), 107.07 (d, 2 C, C-2′,6′), 100.16 (d, C-4′), 94.54 (br d, C-8), 66.12 (t, 2 C, $O(CH_2)_2$), 57.96 (t, NCH_2), 55.38 (q, 2 C, $2OCH_3$), 53.27 (t, 2 C, $N(CH_2)_2$), 49.92 (s, $C(CH_3)_3$), 41.13 (t, NCH_2), 28.65 (q, 3 C, $C(CH_3)_3$), 26.65, 23.48 (2 t, $2CH_2$). Anal. ($C_{29}H_{40}N_6O_4 \cdot 0.5H_2O$) C, H, N.

Further purification of the mother liquors by chromatography on neutral alumina (eluting with 0.25% MeOH/CH_2Cl_2) gave additional **19** (62 mg, 39% from **45**) as a foam.

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[[4-(4-methylpiperazin-1-yl)butyl]amino]-1,6-naphthyridin-2-yl]urea (20).** Similar hydrolysis of crude **66** (164 mg) in MeOH (45 mL) with NaOH (1.95 g, 48.8 mmol) and water (5 mL) at 0 °C for 2 h and then at 20 °C for 3 days and chromatography of the resulting product on silica gel (eluting with 0.75−2% MeOH/CH_2Cl_2 containing 1% Et_3N) gave (after base washing and crystallization) **20** (110 mg, 69% overall from **45**): mp (CH_2Cl_2/hexane) 148−150 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.03 (br s, 1 H, NH), 6.93 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.1 Hz, 1 H, H-4′), 6.62 (d, J = 2.0 Hz, 2 H, H-2′,6′), 6.38 (s, 1 H, H-8), 3.80 (s, 6 H, $2OCH_3$), 3.29 (br q, J = 6.1 Hz, 2 H, NHC*H*$_2$), 2.6−2.0 (br s, 8 H, $N(CH_2)_4N$), 2.28 (t, J = 7.0 Hz, 2 H, NCH_2), 2.13 (s, 3 H, NCH_3), 1.58 (pentet, J = 6.7 Hz, 2 H, CH_2), 1.51 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 161.16 (s, 2 C, C-3′,5′), 159.58 (s, C-7), 152.41, 152.10 (2 s, CONH, C-2), 151.41 (d, C-5), 149.39 (s, C-8a), 137.50 (d, C-4), 137.44 (s, C-1′), 121.05 (s, C-3), 113.14 (s, C-4a), 107.11 (d, 2 C, C-2′,6′), 100.20 (d, C-4′), 94.69 (br d, C-8), 57.58 (t, NCH_2), 55.43 (q, 2 C, $2OCH_3$), 54.73, 52.64 (2 t, 2 × 2 C, $2N(CH_2)_2$), 49.99 (s, $C(CH_3)_3$), 45.72 (q, NCH_3), 41.20 (t, NCH_2), 28.70 (q, 3 C, $C(CH_3)_3$), 26.74, 23.93 (2 t, $2CH_2$). Anal. ($C_{30}H_{43}N_7O_3$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[7-[[4-(diethylamino)butyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]urea (23).** Similar hydrolysis of **69** (130 mg, 0.23 mmol) in MeOH (36 mL) with NaOH (1.46 g, 36.5 mmol) and water (4 mL) at 0 °C for 2 h and then at 20 °C for 3 days and chromatography of the resulting product on silica gel (eluting with 0.25−0.5% MeOH/CH_2Cl_2 containing 0.5−1% Et_3N) gave (after base washing and crystallization) **23** (62 mg, 52%): mp (CH_2Cl_2/hexane) 113−114 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1 H,

NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.02 (br s, 1 H, NH), 6.94 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.1 Hz, 1 H, H-4′), 6.62 (d, J = 1.7 Hz, 2 H, H-2′,6′), 6.37 (s, 1 H, H-8), 3.80 (s, 6 H, 2OCH_3), 3.28 (m, 2 H, NHCH_2), 2.44 (q, J = 7.1 Hz, 4 H, N(CH_2)$_2$), 2.39 (t, J = 7.1 Hz, 2 H, NCH_2), 1.58 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.48 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$), 0.94 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 161.12 (s, 2 C, C-3′,5′), 159.54 (s, C-7), 152.32, 152.00 (2 s, CONH, C-2), 151.36 (d, C-5), 149.35 (s, C-8a), 137.43 (d, C-4), 137.40 (s, C-1′), 120.96 (s, C-3), 113.08 (s, C-4a), 107.06 (d, 2 C, C-2′,6′), 100.16 (d, C-4′), 94.45 (br d, C-8), 55.38 (q, 2 C, 2OCH_3), 51.99 (t, NCH_2), 49.92 (s, *C*(CH_3)$_3$), 46.17 (t, 2 C, N(CH_2)$_2$), 41.15 (t, NCH_2), 28.64 (q, 3 C, C(*C*H_3)$_3$), 26.79, 24.26 (2 t, 2CH_2), 11.65 (q, 2 C, 2CH_3). Anal. ($C_{29}H_{42}N_6O_3$) C, H, N.

Further base hydrolysis of the mother liquors followed by chromatography of the resulting product on neutral alumina (eluting with 1% EtOH/$CHCl_3$) and crystallization gave additional **23** (27 mg, 22%).

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[[5-(4-morpholino)pentyl]amino]-1,6-naphthyridin-2-yl]urea (24).** Similar hydrolysis of **72** (133 mg, 0.225 mmol) in MeOH (36 mL) with NaOH (1.48 g, 37.0 mmol) and water (4 mL) at 0 °C for 2 h and then at 20 °C for 5 days and chromatography of the resulting product on neutral alumina (eluting with 1% EtOH/$CHCl_3$) gave (after crystallization) **24** (92 mg, 74%): mp (CH_2Cl_2/hexane) 116−119.5 °C; ^{1}H NMR [(CD_3)$_2$SO] δ 10.24 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.03 (br s, 1 H, NH), 6.90 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.62 (m, 3 H, H-2′,4′,6′), 6.38 (s, 1 H, H-8), 3.81 (s, 6 H, 2OCH_3), 3.55 (t, J = 4.6 Hz, 4 H, O(CH_2)$_2$), 3.28 (m, 2 H, NHCH_2), 2.31 (m, 4 H, N(CH_2)$_2$), 2.25 (t, J = 7.2 Hz, 2 H, NCH_2), 1.59 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.46 (pentet, J = 7.2 Hz, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$), 1.37 (m, 2 H, CH_2); ^{13}C NMR δ 161.12 (s, 2 C, C-3′,5′), 159.56 (s, C-7), 152.37, 152.03 (2 s, CONH, C-2), 151.34 (d, C-5), 149.33 (s, C-8a), 137.44 (d, C-4), 137.40 (s, C-1′), 121.00 (s, C-3), 113.08 (s, C-4a), 107.08 (d, 2 C, C-2′,6′), 100.16 (d, C-4′), 94.54 (br d, C-8), 66.13 (t, 2 C, O(CH_2)$_2$), 58.25 (t, NCH_2), 55.39 (q, 2 C, 2OCH_3), 53.33 (t, 2 C, N(CH_2)$_2$), 49.93 (s, *C*(CH_3)$_3$), 41.12 (t, NCH_2), 28.68 (t, CH_2), 28.65 (q, 3 C, C(*C*H_3)$_3$), 25.70, 24.41 (2 t, 2CH_2). Anal. ($C_{30}H_{42}N_6O_4$) C, H, N.

Further purification of the mother liquors by chromatography on silica gel (eluting with 2−2.5% MeOH/CH_2Cl_2) gave (after base washing) additional **24** (11 mg, 9%).

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[[5-(4-methylpiperazin-1-yl)pentyl]amino]-1,6-naphthyridin-2-yl]urea (25).** Similar hydrolysis of crude **67** (170 mg) in MeOH (45 mL) with NaOH (1.95 g, 48.8 mmol) and water (5 mL) at 0 °C for 2 h and then at 20 °C for 4 days and chromatography of the resulting product on neutral alumina (eluting with 1% EtOH/$CHCl_3$) gave (after base washing and crystallization) **25** (97 mg, 60% from alcohol **46**): mp (CH_2Cl_2/hexane) 128−130 °C; ^{1}H NMR [(CD_3)$_2$SO] δ 10.25 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.03 (br s, 1 H, NH), 6.90 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.0 Hz, 1 H, H-4′), 6.62 (d, J = 2.0 Hz, 2 H, H-2′,6′), 6.38 (s, 1 H, H-8), 3.80 (s, 6 H, 2OCH_3), 3.28 (br td, J = 6.6, 5.8 Hz, 2 H, NHCH_2), 2.6−2.0 (br s, 8 H, N(CH_2)$_4$N), 2.24 (t, J = 7.2 Hz, 2 H, NCH_2), 2.12 (s, 3 H, NCH_3), 1.58 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.45 (pentet, J = 7.4 Hz, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$), 1.35 (m, 2 H, CH_2); ^{13}C NMR δ 161.11 (s, 2 C, C-3′,5′), 159.56 (s, C-7), 152.36, 152.02 (2 s, CONH, C-2), 151.34 (d, C-5), 149.32 (s, C-8a), 137.44 (d, C-4), 137.40 (s, C-1′), 120.98 (s, C-3), 113.07 (s, C-4a), 107.07 (d, 2 C, C-2′,6′), 100.16 (d, C-4′), 94.54 (br d, C-8), 57.81 (t, NCH_2), 55.39 (q, 2 C, 2OCH_3), 54.69, 52.66 (2 t, 2 × 2 C, 2N(CH_2)$_2$), 49.92 (s, *C*(CH_3)$_3$), 45.68 (q, NCH_3), 41.12 (t, NCH_2), 28.68 (t, CH_2), 28.65 (q, 3 C, C(*C*H_3)$_3$), 26.09, 24.46 (2 t, 2CH_2). Anal. ($C_{31}H_{45}N_7O_3$) C, H, N.

Further base hydrolysis of the mother liquors followed by chromatography of the resulting product on neutral alumina (as above) and crystallization gave additional **25** (18 mg, 11% from **46**).

***N*-(*tert*-Butyl)-*N*′-[7-[[5-(diethylamino)pentyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]urea (26).** Similar hydrolysis of **70** (137 mg, 0.237 mmol) in MeOH (45 mL) with NaOH (1.83 g, 45.8 mmol) and water (5 mL) at 0 °C for 3 h and then at 20 °C for 4 days and chromatography of the resulting product on silica gel (eluting with 0.25% MeOH/CH_2Cl_2 containing 0.5% Et_3N) gave (after base washing and crystallization) **26** (76 mg, 60%): mp (diisopropyl ether/hexane) 91−93.5 °C; ^{1}H NMR [(CD_3)$_2$SO] δ 10.25 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.03 (br s, 1 H, NH), 6.89 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.1 Hz, 1 H, H-4′), 6.62 (d, J = 1.9 Hz, 2 H, H-2′,6′), 6.38 (s, 1 H, H-8), 3.81 (s, 6 H, 2OCH_3), 3.28 (br td, J = 6.7, 6.2 Hz, 2 H, NHCH_2), 2.42 (q, J = 7.1 Hz, 4 H, N(CH_2)$_2$), 2.34 (t, J = 7.0 Hz, 2 H, NCH_2), 1.59 (pentet, J = 7.1 Hz, 4 H, 2CH_2), 1.40 (s, 9 H, C(CH_3)$_3$), 1.35 (m, 2 H, CH_2), 0.92 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 161.12 (s, 2 C, C-3′,5′), 159.56 (s, C-7), 152.36, 152.03 (2 s, CONH, C-2), 151.34 (d, C-5), 149.33 (s, C-8a), 137.43 (d, C-4), 137.40 (s, C-1′), 120.98 (s, C-3), 113.07 (s, C-4a), 107.07 (d, 2 C, C-2′,6′), 100.17 (d, C-4′), 94.47 (br d, C-8), 55.39 (q, 2 C, 2OCH_3), 52.14 (t, NCH_2), 49.92 (s, *C*(CH_3)$_3$), 46.21 (t, 2 C, N(CH_2)$_2$), 41.21 (t, NCH_2), 28.71 (t, CH_2), 28.64 (q, 3 C, C(*C*H_3)$_3$), 26.44, 24.51 (2 t, 2CH_2), 11.67 (q, 2 C, 2CH_3). Anal. ($C_{30}H_{44}N_6O_3$) C, H, N.

Further purification of the mother liquors by chromatography on neutral alumina (eluting with 1% EtOH/$CHCl_3$) gave additional **26** (24 mg, 19%).

3-(3,5-Dimethoxyphenyl)-*N*^{7}-[3-(4-methyl-1-piperazinyl)-propyl]-1,6-naphthyridine-2,7-diamine (15). A stirred solution of **65** (217 mg, 0.376 mmol) in MeOH (54 mL) was treated with NaOH (2.40 g, 60.0 mmol) and water (6 mL), and the mixture was then sealed under N_2 and stirred at 49 °C for 17 h. The resulting mixture was concentrated under reduced pressure (to ca. 5 mL), then treated with a solution of excess $NaHCO_3$ (6.0 g, 71.4 mmol) in water (150 mL) and extracted with CH_2Cl_2 (7 × 70 mL). The combined extracts were evaporated to dryness, and the residue (mostly **17**) was then dissolved in dioxane (27 mL), treated with NaOH (2.39 g, 59.8 mmol), and water (3 mL) and then sealed under N_2 and stirred at 98 °C for 5 days. The resulting mixture was concentrated under reduced pressure (to ca. 3 mL), then treated with excess aqueous $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (7 × 70 mL) and EtOAc (2 × 70 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−3% MeOH/CH_2Cl_2 containing 1% Et_3N gave foreruns. Then further elution with 3−5% MeOH/CH_2Cl_2 containing 1% Et_3N gave (after base washing and crystallization from CH_2Cl_2/hexane) **15**[42] (144 mg, 88%). Further purification of the mother liquors by chromatography on silica gel (as above) gave (after base washing) additional **15** (5 mg, 3%).

***N*^{7}-[4-(Diethylamino)butyl]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridine-2,7-diamine (21).** Similar hydrolysis of **69** (287 mg, 0.509 mmol) in dioxane (45 mL) with NaOH (4.01 g, 100 mmol) and water (5 mL) under N_2 at 98 °C for 6 days and chromatography of the resulting product on silica gel (eluting with 4−7% MeOH/EtOAc containing 1% Et_3N) gave (after base washing and crystallization) **21** (148 mg, 69%): mp (CH_2Cl_2/hexane) 120−122.5 °C; ^{1}H NMR [(CD_3)$_2$SO] δ 8.45 (s, 1 H, H-5), 7.67 (s, 1 H, H-4), 6.59 (d, J = 2.3 Hz, 2 H, H-2′,6′), 6.52 (t, J = 2.2 Hz, 1 H, H-4′), 6.45 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.28 (br s, 2 H, NH_2), 6.18 (s, 1 H, H-8), 3.79 (s, 6 H, 2OCH_3), 3.21 (br td, J = 6.5, 6.1 Hz, 2 H, NHCH_2), 2.43 (q, J = 7.1 Hz, 4 H, N(CH_2)$_2$), 2.37 (t, J = 7.1 Hz, 2 H, NCH_2), 1.56 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.46 (pentet, J = 7.1 Hz, 2 H, CH_2), 0.94 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 160.64 (s, 2 C, C-3′,5′), 159.08, 158.15 (2 s, C-2,7), 152.65 (s, C-8a), 150.33 (d, C-5), 139.55 (s, C-1′), 135.78 (d, C-4), 120.61 (s, C-3), 113.18 (s, C-4a), 106.49 (d, 2 C, C-2′,6′), 99.68 (d, C-4′), 93.71 (d, C-8), 55.17 (q, 2 C, 2OCH_3), 52.06 (t, NCH_2), 46.16 (t, 2 C, N(CH_2)$_2$), 41.49 (t, NCH_2), 26.84, 24.35 (2 t, 2CH_2), 11.68 (q, 2 C, 2CH_3). Anal. ($C_{24}H_{33}N_5O_2$) C, H, N.

Further purification of the mother liquors by chromatography on alumina (eluting with 1−1.5% MeOH/CH_2Cl_2) gave additional **21** (26 mg, 12%).

***N*-[3-(3,5-Dimethoxyphenyl)-7-[[3-(4-methyl-1-piperazinyl)propyl]amino]-1,6-naphthyridin-2-yl]-*N*′-ethy-**

lurea (16). A solution of **15** (106 mg, 0.243 mmol) in dry DMSO (5 mL) was treated with 60% NaH (14 mg, 0.35 mmol). Then the mixture was sealed under N_2 (as above) and stirred at 40−50 °C for 15 min and then at 20 °C for 20 min. A solution of ethyl isocyanate (23 μL, 0.291 mmol) in dry DMSO (1 mL, then 2 × 0.5 mL to rinse) was added (dropwise via syringe). Then the mixture was stirred at 20 °C for 1 day. The resulting mixture was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (50 mL), adjusted to pH 10 with aqueous Na_2CO_3, and extracted with CH_2Cl_2 (8 × 50 mL). The extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−4% MeOH/EtOAc containing 1% Et_3N gave foreruns. Then further elution with 6−9% MeOH/EtOAc containing 1% Et_3N gave (after base washing) a crude oil (95 mg), which was further chromatographed on silica gel. Elution with 0−1.5% MeOH/CH_2Cl_2 containing 1% Et_3N gave foreruns. Then further elution with 2% MeOH/CH_2Cl_2 containing 1% Et_3N gave (after base washing and two recrystallizations from CH_2Cl_2/hexane) **16** (45 mg, 37%): mp (CH_2Cl_2/hexane) 170−171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.91 (br t, J = 5.5 Hz, 1 H, CON*H*CH_2), 8.69 (s, 1 H, H-5), 7.99 (s, 1 H, H-4), 7.20 (br s, 1 H, NH), 6.87 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.63 (s, 3 H, H-2′,4′,6′), 6.53 (s, 1 H, H-8), 3.80 (s, 6 H, 2OCH_3), 3.31 (m, 4 H, 2NHC*H*$_2$), 2.6−2.1 (br s, 8 H, $N(CH_2)_4N$), 2.38 (t, J = 7.0 Hz, 2 H, NCH_2), 2.15 (s, 3 H, NCH_3), 1.74 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.19 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 161.10 (s, 2 C, C-3′,5′), 159.57 (s, C-7), 153.38, 152.19 (2 s, CONH, C-2), 151.35 (d, C-5), 149.72 (s, C-8a), 137.51 (s + d, 2 C, C-4,1′), 120.98 (s, C-3), 113.26 (s, C-4a), 107.05 (d, 2 C, C-2′,6′), 100.15 (d, C-4′), 94.46 (br d, C-8), 55.62 (t, NCH_2), 55.38 (q, 2 C, 2OCH_3), 54.73, 52.71 (2 t, 2 × 2 C, 2N$(CH_2)_2$), 45.68 (q, NCH_3), 39.93 (t, $NHCH_2$), 34.10 (t, CONH*C*H_2), 25.91 (t, CH_2), 15.14 (q, CH_3). Anal. ($C_{27}H_{37}N_7O_3$)-C, H, N.

Further purification of the mother liquors by preparative reversed-phase C-18 HPLC (47.5% CH_3CN/aqueous HCO_2NH_4 buffer, pH 3.45) gave two fractions, which were each basified (to pH 10) with aqueous Na_2CO_3 (50 mL), concentrated under reduced pressure (to remove CH_3CN), and extracted with CH_2Cl_2 (4 × 50 mL) to give firstly additional **16** (12 mg, 10%) and secondly (2*Z*)-3-(3,5-dimethoxyphenyl)-*N*-ethyl-2-[[(*Z*)-(ethylamino)(oxo)methyl]imino]-7-[[3-(4-methyl-1-piperazinyl)propyl]amino]-1,6-naphthyridine-1(2*H*)-carboxamide (**78**) (10 mg, 7%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 14.12, 9.78 (2 br s, 2 × 1 H, 2CON*H*CH_2), 8.58 (br s, 1 H, H-5), 8.04 (s, 1 H, H-4), 7.28 (br s, 1 H, N*H*CH_2), 6.65 (d, J = 2.3 Hz, 2 H, H-2′,6′), 6.57 (br s, 1 H, H-8), 6.55 (t, J = 2.1 Hz, 1 H, H-4′), 3.78 (m, 2 H, CONHC*H*$_2$), 3.77 (s, 6 H, 2OCH_3), 3.30 (m, 2 H, NHC*H*$_2$), 2.80 (br s, 2 H, CONHC*H*$_2$), 2.6−2.0 (br s, 8 H, $N(CH_2)_4N$), 2.35 (t, J = 6.9 Hz, 2 H, NCH_2), 2.15 (s, 3 H, NCH_3), 1.72 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.03 (t, J = 6.8 Hz, 3 H, CH_3), 0.72 (br s, 3 H, CH_3); ^{13}C NMR δ 162.53 (br s, CONH), 160.22 (s, 2 C, C-3′,5′), 159.88 (br s, C-7), 156.82 (br s, C-2), 154.20 (br s, CONH), 150.99 (d, C-5), 141.74 (br s, C-8a), 139.03 (d + s, C-4,1′), 126.82 (s, C-3), 110.44 (br s, C-4a), 107.38 (d, 2 C, C-2′,6′), 99.32 (d, C-4′), 87.69 (br d, C-8), 55.40 (t, NCH_2), 55.17 (q, 2 C, 2OCH_3), 54.70, 52.66 (2 t, 2 × 2 C, 2N$(CH_2)_2$), 45.63 (q, NCH_3), 39.65 (t, $NHCH_2$), 38.80 (t, CONH*C*H_2), 34.06 (br t, CONH*C*H_2), 25.82 (t, CH_2), 14.93, 14.15 (2 q, 2CH_3); HRFABMS calcd for $C_{30}H_{43}N_8O_4$ *m/z* (MH^+) 579.3407, found 579.3399.

***N*-[7-[[4-(Diethylamino)butyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-2-yl]-*N*′-ethylurea (22).** Similar reaction of **21** (103 mg, 0.243 mmol) in dry DMSO (5 mL) with 60% NaH (14 mg, 0.35 mmol) under N_2 at 40−50 °C for 15 min, and then at 20 °C for 15 min, followed by reaction with a solution of ethyl isocyanate (23 μL, 0.291 mmol) in dry DMSO (1 mL, then 2 × 0.5 mL) at 20 °C for 1 day and chromatography of the resulting product on silica gel (eluting with 0.5−0.75% MeOH/CH_2Cl_2 containing 0.5% Et_3N) gave (after base washing and two recrystallizations from CH_2Cl_2/hexane) **22** (93 mg, 77%): mp (CH_2Cl_2/hexane) 145−146.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.94 (br t, J = 5.5 Hz, 1 H, CON*H*CH_2), 8.69 (s, 1 H, H-5), 7.99 (s, 1 H, H-4), 7.22 (br s, 1 H, NH), 6.86 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.62 (s, 3 H, H-2′,4′,6′), 6.54 (s, 1 H, H-8), 3.80 (s, 6 H, 2OCH_3), 3.30 (m, 4 H, 2NHC*H*$_2$), 2.44 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.39 (t, J = 7.1 Hz, 2 H, NCH_2), 1.60 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.49 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.19 (t, J = 7.2 Hz, 3 H, CH_3), 0.94 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 161.16 (s, 2 C, C-3′,5′), 159.63 (s, C-7), 153.50, 152.24 (2 s, CONH, C-2), 151.41 (d, C-5), 149.77 (s, C-8a), 137.57 (s + d, 2 C, C-4,1′), 120.98 (s, C-3), 113.29 (s, C-4a), 107.10 (d, 2 C, C-2′,6′), 100.19 (d, C-4′), 94.50 (br d, C-8), 55.43 (q, 2 C, 2OCH_3), 52.04 (t, NCH_2), 46.20 (t, 2 C, $N(CH_2)_2$), 41.47 (t, $NHCH_2$), 34.17 (t, CONH*C*H_2), 26.77, 24.28 (2 t, 2CH_2), 15.16 (q, CH_3), 11.67 (q, 2 C, 2CH_3). Anal. ($C_{27}H_{38}N_6O_3$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[(3-hydroxypropyl)amino]-1,6-naphthyridin-2-yl]urea (75).** A solution of **13** (273 mg, 0.625 mmol) in dry DMF (10 mL) was treated with 60% NaH (117 mg, 2.93 mmol). Then the mixture was sealed under N_2 (as above) and stirred at 20 °C for 15 min and then at 0 °C for 1.5 h. A solution of 3-iodopropyl benzoate[54] (246 mg, 0.848 mmol) in dry DMF (1 mL, then 1 mL to rinse) was added (syringe), and the mixture was foil-covered and stirred at 0−20 °C for 1 day. The resulting solution was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (100 mL), and extracted with EtOAc (5 × 150 mL). The extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−0.6% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 0.6% MeOH/CH_2Cl_2 gave 3-[[2-[[(*tert*-butylamino)carbonyl]amino]-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7-yl]amino]propyl benzoate (**74**) (23 mg, 7%): mp (CH_2Cl_2/hexane) 165−167 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.20 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.98 (dt, J = 7.0, 1.4 Hz, 2 H, H-2″,6″), 7.66 (tt, J = 7.5, 1.2 Hz, 1 H, H-4″), 7.53 (t, J = 7.7 Hz, 2 H, H-3″,5″), 7.03 (br t, J = 5.7 Hz, 1 H, N*H*CH_2), 7.02 (br s, 1 H, NH), 6.63 (t, J = 1.7 Hz, 1 H, H-4′), 6.62 (d, J = 1.8 Hz, 2 H, H-2′,6′), 6.43 (s, 1 H, H-8), 4.39 (t, J = 6.3 Hz, 2 H, OCH_2), 3.80 (s, 6 H, 2OCH_3), 3.49 (br td, J = 6.4, 5.8 Hz, 2 H, NHC*H*$_2$), 2.05 (pentet, J = 6.5 Hz, 2 H, CH_2), 1.38 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 165.70 (s, C=O), 161.11 (s, 2 C, C-3′,5′), 159.43 (s, C-7), 152.39, 151.98 (2 s, CONH, C-2), 151.32 (d, C-5), 149.29 (s, C-8a), 137.42 (d, C-4), 137.36 (s, C-1′), 133.16 (d, C-4″), 129.76 (s, C-1″), 129.03, 128.63 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 121.20 (s, C-3), 113.20 (s, C-4a), 107.07 (d, 2 C, C-2′,6′), 100.20 (d, C-4′), 95.06 (br d, C-8), 62.71 (t, OCH_2), 55.39 (q, 2 C, 2OCH_3), 49.90 (s, *C*$(CH_3)_3$), 37.99 (t, NCH_2), 28.62 (q, 3 C, C(*C*$H_3)_3$), 28.07 (t, CH_2). Anal. ($C_{31}H_{35}N_5O_5$) C, H, N.

Further elution with 0.6−1% MeOH/CH_2Cl_2 gave (after crystallization twice) recovered **13** (87 mg, 32%).

Further elution with 1.4−1.6% MeOH/CH_2Cl_2 gave (after crystallization) the desired **75** (92 mg, 33%): mp (Et_2O/hexane) 133−138 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.22 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.02 (br s, 1 H, NH), 6.85 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.62 (s, 3 H, H-2′,4′,6′), 6.41 (s, 1 H, H-8), 4.50 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.80 (s, 6 H, 2OCH_3), 3.52 (td, J = 6.0, 5.6 Hz, 2 H, C*H*$_2$OH), 3.33 (m, 2 H, NHC*H*$_2$), 1.74 (pentet, J = 6.5 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 161.11 (s, 2 C, C-3′,5′), 159.60 (s, C-7), 152.37, 152.02 (2 s, CONH, C-2), 151.32 (d, C-5), 149.38 (s, C-8a), 137.42 (d, C-4), 137.39 (s, C-1′), 121.03 (s, C-3), 113.11 (s, C-4a), 107.08 (d, 2 C, C-2′,6′), 100.18 (d, C-4′), 94.45 (br d, C-8), 58.53 (t, OCH_2), 55.39 (q, 2 C, 2OCH_3), 49.93 (s, *C*$(CH_3)_3$), 38.35 (t, NCH_2), 32.05 (t, CH_2), 28.65 (q, 3 C, C(*C*$H_3)_3$). Anal. ($C_{24}H_{31}N_5O_4$) C, H, N.

Further purification of the mother liquors by chromatography on silica gel (eluting with 1.25−1.5% MeOH/CH_2Cl_2) gave (after crystallization) additional **75** (21 mg, 7%).

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[(4-hydroxybutyl)amino]-1,6-naphthyridin-2-yl]urea (76).** A solution of **42** (236 mg, 0.424 mmol) in absolute EtOH (190 mL) was hydrogenated over 5% Pd/C (566 mg) at 60 psi and 20 °C for 48 h. The resulting solution was Celite filtered, washing with 25% MeOH/CH_2Cl_2. Then the Celite and catalyst were further extracted by stirring in refluxing 25% MeOH/CH_2Cl_2 for 10 min and then refiltering and washing as before. The

filtrates were then combined, the solvents were removed, and the residue was chromatographed on silica gel. Elution with 0−0.5% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 0.5−0.75% MeOH/CH_2Cl_2 gave recovered **42** (176 mg, 75%). Elution with 1−1.5% MeOH/CH_2Cl_2 gave minor impurities. Then elution with 1.5−2% MeOH/CH_2Cl_2 gave a crude oil (32 mg, <16%), which was combined with similar material from subsequent repeat runs and crystallized to give **76** (42 mg, 21% overall): mp (CH_2Cl_2/hexane) 156−157.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.02 (br s, 1 H, NH), 6.90 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.62 (m, 3 H, H-2′,4′,6′), 6.39 (s, 1 H, H-8), 4.43 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.80 (s, 6 H, $2OCH_3$), 3.44 (td, J = 6.2, 5.5 Hz, 2 H, C*H*$_2$OH), 3.29 (br q, J = 6.4 Hz, 2 H, NHC*H*$_2$), 1.61 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.52 (pentet, J = 6.7 Hz, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 161.14 (s, 2 C, C-3′,5′), 159.59 (s, C-7), 152.39, 152.06 (2 s, CONH, C-2), 151.37 (d, C-5), 149.36 (s, C-8a), 137.46 (d, C-4), 137.42 (s, C-1′), 121.03 (s, C-3), 113.10 (s, C-4a), 107.10 (d, 2 C, C-2′,6′), 100.20 (d, C-4′), 94.65 (br d, C-8), 60.50 (t, OCH_2), 55.42 (q, 2 C, $2OCH_3$), 49.96 (s, *C*(CH_3)$_3$), 41.15 (t, NCH_2), 30.04 (t, CH_2), 28.67 (q, 3 C, C(*C*H_3)$_3$), 25.46 (t, CH_2). Anal. ($C_{25}H_{33}N_5O_4\cdot 0.5H_2O$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[3-(3,5-dimethoxyphenyl)-7-[(5-hydroxypentyl)amino]-1,6-naphthyridin-2-yl]urea (77).** A stirred solution of **46** (92 mg, 0.176 mmol) in MeOH (27 mL) at 0 °C was treated with NaOH (1.04 g, 26.0 mmol) and water (3 mL, added dropwise). Then the mixture was stirred at 0 °C for 1 h and then at 20 °C for 7 days. A solution of excess $NaHCO_3$ in ice/water (100 mL) was then added, and the mixture was extracted with CH_2Cl_2 (4 × 100 mL). The combined extracts were evaporated to dryness and the residue was then chromatographed on silica gel. Elution with 0−1.4% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 1.5% MeOH/CH_2Cl_2 gave **77** (77 mg, 84%): mp (CH_2Cl_2/hexane) 151−153 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.02 (br s, 1 H, NH), 6.91 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.63 (t, J = 2.1 Hz, 1 H, H-4′), 6.62 (d, J = 1.9 Hz, 2 H, H-2′,6′), 6.38 (s, 1 H, H-8), 4.36 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.80 (s, 6 H, $2OCH_3$), 3.40 (td, J = 6.3, 5.3 Hz, 2 H, C*H*$_2$OH), 3.28 (br td, J = 7.1, 5.6 Hz, 2 H, NHC*H*$_2$), 1.58 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.47 (pentet, J = 6.6 Hz, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$), 1.38 (m, 2 H, CH_2); ^{13}C NMR δ 161.11 (s, 2 C, C-3′,5′), 159.56 (s, C-7), 152.37, 152.02 (2 s, CONH, C-2), 151.34 (d, C-5), 149.32 (s, C-8a), 137.43 (d, C-4), 137.40 (s, C-1′), 120.99 (s, C-3), 113.06 (s, C-4a), 107.08 (d, 2 C, C-2′,6′), 100.17 (d, C-4′), 94.53 (br d, C-8), 60.59 (t, OCH_2), 55.39 (q, 2 C, $2OCH_3$), 49.92 (s, *C*(CH_3)$_3$), 41.22 (t, NCH_2), 32.26 (t, CH_2), 28.65 (t, CH_2), 28.64 (q, 3 C, C(*C*H_3)$_3$), 23.08 (t, CH_2). Anal. ($C_{26}H_{35}N_5O_4$) C, H, N.

***N*-(7-Amino-3-phenyl-1,6-naphthyridin-2-yl)-*N*′-*tert*-butylurea (80).** A solution of 3-phenyl-1,6-naphthyridine-2,7-diamine[42] (1.50 g, 6.36 mmol) in dry DMF (25 mL) was treated with 60% NaH (0.32 g, 8.03 mmol). Then the mixture was sealed under N_2 (as above) and stirred at 20 °C for 20 min and then at 0 °C for 1 h. *tert*-Butyl isocyanate (0.907 mL, 7.95 mmol) was added (dropwise via syringe), and then the mixture was stirred at 20 °C for 1 day. The resulting mixture was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (170 mL) and extracted with EtOAc (10 × 150 mL). The extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 25% EtOAc/light petroleum gave firstly *N*-(*tert*-butyl)-*N*′-[7-(3-*tert*-butylureido)-3-phenyl-1,6-naphthyridin-2-yl]urea (**81**) (56 mg, 2%): mp (CH_2Cl_2/hexane) 216 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 10.11, 9.05 (2 br s, 2 × 1 H, 2NH), 8.88 (s, 1 H, H-5), 8.16 (s, 1 H, H-4), 7.83 (s, 1 H, H-8), 7.60 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.55 (m, 3 H, H-2′,4′,6′), 7.29, 7.07 (2 br s, 2 × 1 H, 2 NH), 1.41, 1.34 (2 s, 2 × 9 H, 2C(CH_3)$_3$); ^{13}C NMR δ 153.46, 153.08, 152.94, 151.77 (4 s, 2CONH,C-2,7), 150.41 (d, C-5), 149.09 (s, C-8a), 137.50 (d, C-4), 135.05 (s, C-1′), 129.47, 129.09 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 128.86 (d, C-4′), 124.27 (s, C-3), 115.89 (s, C-4a), 102.06 (d, C-8), 50.05, 49.52 (2 s, 2*C*(CH_3)$_3$), 28.88, 28.64 (2 q, 2 × 3 C, 2C(*C*H_3)$_3$); HRFABMS calcd for $C_{24}H_{31}N_6O_2$ *m/z* (MH^+) 435.2509, found 435.2496.

Further elution with 33−50% EtOAc/light petroleum gave **80**[41] (1.89 g, 88%).

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]acetamide (82).** A solution of **80** (1.88 g, 5.61 mmol) in pyridine (45 mL) was treated (dropwise) with Ac_2O (5.3 mL, 56.2 mmol), and the mixture was then stirred at 20 °C for 10 h. The resulting solution was cooled in ice and then added slowly to a stirred mixture of ice and aqueous $NaHCO_3$, keeping the pH at 8 with excess $NaHCO_3$. The resulting suspension was extracted with CH_2Cl_2 (5 × 200 mL). Then the combined extracts were evaporated to dryness and the residue was crystallized directly (from warm CH_2Cl_2/light petroleum) to give **82** (1.94 g, 92%): mp 194.5−196 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 10.75, 10.14 (2 br s, 2 × 1 H, 2NH), 8.98 (s, 1 H, H-5), 8.34, 8.22 (2 s, 2 × 1 H, H-4,8), 7.61 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.56 (m, 3 H, H-2′,4′,6′), 7.12 (br s, 1 H, NH), 2.16 (s, 3 H, $COCH_3$), 1.41 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 169.41 (s, CONH), 152.95, 151.73, 151.45 (3 s, CONH, C-2,7), 150.66 (d, C-5), 148.95 (s, C-8a), 137.31 (d, C-4), 134.93 (s, C-1′), 129.48, 129.06 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 128.95 (d, C-4′), 125.19 (s, C-3), 117.09 (s, C-4a), 105.09 (d, C-8), 50.05 (s, *C*(CH_3)$_3$), 28.55 (q, 3 C, C(*C*H_3)$_3$), 23.92 (q, CH_3). Anal. ($C_{21}H_{23}N_5O_2$) C, H, N.

***N*-[3-(Benzyloxy)propyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]acetamide (85).** A solution of **82** (1.05 g, 2.79 mmol) in dry DMF (50 mL) was treated with 60% NaH (489 mg, 12.2 mmol). Then the mixture was sealed under N_2 and stirred at 20 °C for 30 min and then at 0 °C for 1 h. A solution of benzyl 3-iodopropyl ether[43] (1.00 g, 3.62 mmol) in dry DMF (5 mL, then 2 × 5 mL to rinse) was then added (syringe), and the mixture was foil-covered and stirred at 0−20 °C for 2.5 days. The resulting solution was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (300 mL) and extracted with EtOAc (5 × 200 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−0.4% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 0.5−0.75% MeOH/CH_2Cl_2 yielded crude material which, upon crystallization twice from CH_2Cl_2/hexane, gave *N*-[7-[[3-(benzyloxy)propyl]amino]-3-phenyl-1,6-naphthyridin-2-yl]-*N*′-*tert*-butylurea (**83**) (151 mg, 11%): mp (CH_2Cl_2/hexane) 149−150.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (br s, 1 H, NH), 8.71 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.58 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.51 (m, 3 H, H-2′,4′,6′), 7.31 (m, 5 H, H-2″,3″,4″,5″,6″), 6.92 (br t, J = 5.7 Hz, 1 H, N*H*CH_2), 6.92 (br s, 1 H, NH), 6.41 (s, 1 H, H-8), 4.48 (s, 2 H, OC*H*$_2$Ph), 3.56 (t, J = 6.2 Hz, 2 H, OCH_2), 3.38 (m, 2 H, NHC*H*$_2$), 1.87 (pentet, J = 6.5 Hz, 2 H, CH_2), 1.39 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 159.53 (s, C-7), 152.52, 152.03 (2 s, CONH, C-2), 151.40 (d, C-5), 149.38 (s, C-8a), 138.58 (s, C-1″), 137.77 (d, C-4), 135.50 (s, C-1′), 129.44, 129.11 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 128.54 (d, C-4′), 128.16, 127.34 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.28 (d, C-4″), 121.23 (s, C-3), 113.34 (s, C-4a), 94.65 (br d, C-8), 71.87 (t, OCH_2Ph), 67.52 (t, OCH_2), 49.95 (s, *C*(CH_3)$_3$), 38.52 (t, NCH_2), 29.07 (t, CH_2), 28.64 (q, 3 C, C(*C*H_3)$_3$). Anal. ($C_{29}H_{33}N_5O_2$) C, H, N.

Further elution with 0.75−0.8% MeOH/CH_2Cl_2 gave crude recovered **82** (0.23 g). Then further elution with 0.8−1% MeOH/CH_2Cl_2 gave **85** (918 mg, 63%): mp (EtOAc/hexane) 62−66 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.33 (s, 1 H, H-4), 7.69 (s, 1 H, H-8), 7.63 (tt, J = 7.0, 1.5 Hz, 2 H, H-3′,5′), 7.58 (m, 3 H, H-2′,4′,6′), 7.26 (m, 6 H, NH, H-2″,3″,4″,5″,6″), 4.35 (s, 2 H, OCH_2Ph), 3.96 (t, J = 7.1 Hz, 2 H, NCH_2), 3.46 (t, J = 6.1 Hz, 2 H, OCH_2), 1.99 (s, 3 H, $COCH_3$), 1.80 (pentet, J = 6.6 Hz, 2 H, CH_2), 1.41 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 169.50 (s, C=O), 154.37, 153.15, 151.60 (3 s, CONH, C-2,7), 151.33 (d, C-5), 148.85 (s, C-8a), 138.39 (s, C-1″), 137.34 (d, C-4), 134.76 (s, C-1′), 129.58 (d, 2 C, C-3′,5′), 129.20 (d, C-4′), 129.02 (d, 2 C, C-2′,6′), 128.08, 127.23 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.21 (d + s, C-3,4″), 118.79 (s, C-4a), 115.59 (d, C-8), 71.73 (t, OCH_2Ph), 67.10 (t, OCH_2), 50.21 (s, *C*(CH_3)$_3$), 44.83 (t, NCH_2), 28.67 (q, 3 C, C(*C*H_3)$_3$), 28.16 (t, CH_2), 22.97 (q, CH_3). Anal. ($C_{31}H_{35}N_5O_3$) C, H, N.

***N*-[4-(Benzyloxy)butyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]acetamide (86).** Similar reaction of a stirred solution of **82** (0.99 g, 2.63 mmol) in dry DMF (50 mL) with 60% NaH (468 mg, 11.7 mmol) under N_2 at 20 °C for 30 min and then at 0 °C for 1 h followed by reaction with benzyl 4-iodobutyl ether[44] (1.00 g, 3.45 mmol) in dry DMF (5 mL, then 2 × 5 mL) at 0−20 °C for 2.5 days and chromatography of the resulting product on silica gel (eluting with 0.4−0.6% MeOH/CH_2Cl_2) gave (after crystallization from Et_2O/hexane, then twice from CH_2Cl_2/hexane) *N*-[7-[[4-(benzyloxy)butyl]amino]-3-phenyl-1,6-naphthyridin-2-yl]-*N*′-*tert*-butylurea (**84**) (53 mg, 4%): mp (CH_2Cl_2/hexane) 107−108.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (br s, 1 H, NH), 8.70 (s, 1 H, H-5), 7.97 (s, 1 H, H-4), 7.58 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.51 (m, 3 H, H-2′,4′,6′), 7.29 (m, 5 H, H-2″,3″,4″,5″,6″), 6.93 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.91 (br s, 1 H, NH), 6.40 (s, 1 H, H-8), 4.46 (s, 2 H, O*C*H_2Ph), 3.48 (t, J = 5.8 Hz, 2 H, OCH_2), 3.31 (m, 2 H, NHCH_2), 1.65 (m, 4 H, $2CH_2$), 1.39 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 159.58 (s, C-7), 152.53, 152.09 (2 s, CONH, C-2), 151.42 (d, C-5), 149.39 (s, C-8a), 138.66 (s, C-1″), 137.80 (d, C-4), 135.53 (s, C-1′), 129.48, 129.13 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 128.56 (d, C-4′), 128.18, 127.34 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.28 (d, C-4″), 121.20 (s, C-3), 113.32 (s, C-4a), 94.72 (br d, C-8), 71.76 (t, O*C*H_2Ph), 69.44 (t, OCH_2), 49.99 (s, *C*$(CH_3)_3$), 41.06 (t, NCH_2), 28.66 (q, 3 C, C(*C*$H_3)_3$), 26.82, 25.67 (2 t, $2CH_2$). Anal. ($C_{30}H_{35}N_5O_2$) C, H, N.

Further elution with 0.6−0.75% MeOH/CH_2Cl_2 gave crude recovered **82** (0.15 g), and then further elution with 0.75−2% MeOH/CH_2Cl_2 gave **86** (1.06 g, 75%): foam; ^{1}H NMR [$(CD_3)_2$-SO] δ 9.88 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.69 (s, 1 H, H-8), 7.63 (tt, J = 7.0, 1.5 Hz, 2 H, H-3′,5′), 7.58 (m, 3 H, H-2′,4′,6′), 7.25 (m, 6 H, NH, H-2″,3″,4″,5″,6″), 4.39 (s, 2 H, O*C*H_2Ph), 3.90 (m, 2 H, NCH_2), 3.39 (m, 2 H, OCH_2), 1.98 (s, 3 H, $COCH_3$), 1.55 (m, 4 H, $2CH_2$), 1.40 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.29 (s, C=O), 154.19, 153.14, 151.53 (3 s, CONH, C-2,7), 151.33 (d, C-5), 148.80 (s, C-8a), 138.52 (s, C-1″), 137.32 (d, C-4), 134.73 (s, C-1′), 129.52 (d, 2 C, C-3′,5′), 129.14 (d, C-4′), 128.98 (d, 2 C, C-2′,6′), 128.05, 127.19 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.16 (d + s, C-3,4″), 118.74 (s, C-4a), 115.58 (d, C-8), 71.62 (t, O*C*H_2Ph), 69.14 (t, OCH_2), 50.15 (s, *C*$(CH_3)_3$), 46.77 (t, NCH_2), 28.61 (q, 3 C, C(*C*$H_3)_3$), 26.39, 24.60 (2 t, $2CH_2$), 22.94 (q, CH_3). Anal. ($C_{32}H_{37}N_5O_3$) C, H, N.

Debenzylation of 86. A. By Hydrogenation. A solution of **86** (25.6 mg, 47.5 μmol) in absolute EtOH (20 mL) was hydrogenated over 5% Pd/C (30 mg) at 60 psi and 20 °C for 48 h. The resulting solution was Celite filtered, washing with 25% MeOH/CH_2Cl_2. Then the Celite and catalyst were further extracted by stirring in refluxing 25% MeOH/CH_2Cl_2 for 10 min and then refiltering and washing as before. The filtrates were then combined, the solvents were removed, and the residue was chromatographed on silica gel. Elution with 0−1% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 1.25% MeOH/CH_2Cl_2 gave recovered **86** (2.2 mg, 9%). Elution with 1.5% MeOH/CH_2Cl_2 gave *N*-[4-(benzyloxy)butyl]-*N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-phenyl-3,4-dihydro-1,6-naphthyridin-7-yl]acetamide (**89**) (10 mg, 39%): mp (EtOAc/hexane) 106−108 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.93 (br s, 1 H, NH), 9.82 (br s, 1 H, NH), 8.08 (s, 1 H, H-5), 7.24 (m, 8 H, H-3′,4′,5′,2″,3″,4″,5″,6″), 7.04 (m, 3 H, H-2′,6′,8), 4.39 (s, 2 H, O*C*H_2Ph), 4.07 (br d, J = 6.6 Hz, 1 H, H-3), 3.72 (m, 2 H, NCH_2), 3.35 (m, 2 H, OCH_2), 3.28 (m, 1 H, H-4), 3.00 (br d, J = 16.0 Hz, 1 H, H-4), 1.87 (s, 3 H, $COCH_3$), 1.48 (m, 4 H, $2CH_2$), 1.36 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.02 (s, C=O), 163.21 (s, C-2), 155.03 (s, C-7), 152.36 (s, CONH), 151.68 (s, C-8a), 147.28 (d, C-5), 138.55 (s, C-1″), 138.10 (s, C-1′), 128.53 (d, 2 C, C-3′,5′), 128.10, 127.26 (2 d, 2 × 2 C, C-2″,3″,5″,6″), 127.19 (d, C-4″), 127.14 (d, C-4′), 126.82 (d, 2 C, C-2′,6′), 118.62 (s, C-4a), 115.07 (d, C-8), 71.65 (t, O*C*H_2Ph), 69.13 (t, OCH_2), 49.95 (s, *C*$(CH_3)_3$), 46.47 (t, NCH_2), 39.68 (d, C-3), 28.53 (q, 3 C, C(*C*$H_3)_3$), 28.22 (t, C-4), 26.39, 24.65 (2 t, $2CH_2$), 22.71 (q, CH_3). Anal. ($C_{32}H_{39}N_5O_3$) C, H, N.

Further elution of the column with 1.75% MeOH/CH_2Cl_2 gave a mixture, and then elution with 2−2.3% MeOH/CH_2Cl_2 gave crude *N*-[2-[[(*tert*-butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]-*N*-(4-hydroxybutyl)acetamide (**88**) (2.4 mg, 11%) as an oil (see below).

Further elution of the column with 2.5−3% MeOH/CH_2Cl_2 gave a minor component, and then further elution with 3% MeOH/CH_2Cl_2 gave crude *N*-[2-[[(*tert*-butylamino)carbonyl]-amino]-3-phenyl-3,4-dihydro-1,6-naphthyridin-7-yl]-*N*-(4-hydroxybutyl)acetamide (**90**) (5 mg, 23%) as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 9.92 (br s, 1 H, NH), 9.81 (br s, 1 H, NH), 8.09 (s, 1 H, H-5), 7.25 (t, J = 7.1 Hz, 2 H, H-3′,5′), 7.20 (t, J = 7.1 Hz, 1 H, H-4′), 7.05 (d, J = 7.2 Hz, 2 H, H-2′,6′), 7.03 (s, 1 H, H-8), 4.34 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 4.07 (br d, J = 6.1 Hz, 1 H, H-3), 3.71 (m, 2 H, NCH_2), 3.33 (m, 2 H, OCH_2), 3.25 (br dd, J = 16.4, 6.7 Hz, 1 H, H-4), 2.99 (br d, J = 16.0 Hz, 1 H, H-4), 1.87 (s, 3 H, $COCH_3$), 1.41 (m, 2 H, CH_2), 1.37 (s, 9 H, $C(CH_3)_3$), 1.35 (m, 2 H, CH_2); HRFABMS calcd for $C_{25}H_{34}N_5O_3$ *m/z* (MH^+) 452.2662, found 452.2664.

B. By Reaction with BF_3·Et_2O/EtSH. A solution of **86** (10.5 mg, 19.5 μmol) in CH_2Cl_2 (1 mL) was treated with EtSH (85 μL, 1.15 mmol), followed by BF_3·Et_2O (20 μL, 0.158 mmol). Then the mixture was stirred at 20 °C for 2 days. A solution of aqueous $NaHCO_3$/Na_2CO_3 (50 mL) was then added, and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−1.75% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 2−2.5% MeOH/CH_2Cl_2 gave crude **88** (5.3 mg, 61%) as an oil (see below).

Further elution with 3−5% MeOH/CH_2Cl_2 gave *N*-[2-[(aminocarbonyl)amino]-3-phenyl-1,6-naphthyridin-7-yl]-*N*-(4-hydroxybutyl)acetamide (**91**) (3.0 mg, 39%): mp (MeOH/CH_2Cl_2/hexane) 165−167 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.14 (s, 1 H, H-5), 9.12 (br s, 1 H, NH), 8.35 (s, 1 H, H-4), 7.91 (s, 1 H, H-8), 7.63 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.58 (m, 3 H, H-2′,4′,6′), 7.55, 7.28 (2 br s, 2 × 1 H, 2NH), 4.35 (br t, J = 5.1 Hz, 1 H, CH_2O*H*), 3.87 (t, J = 7.2 Hz, 2 H, NCH_2), 3.36 (m, 2 H, OCH_2), 1.98 (s, 3 H, $COCH_3$), 1.48 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.39 (pentet, J = 7.1 Hz, 2 H, CH_2); ^{13}C NMR δ 169.17 (s, C=O), 154.02, 153.76, 152.87 (3 s, CONH, C-2,7), 151.31 (d, C-5), 149.23 (s, C-8a), 137.35 (d, C-4), 134.93 (s, C-1′), 129.52 (d, 2 C, C-3′,5′), 129.10 (d, C-4′), 129.01 (d, 2 C, C-2′,6′), 127.14 (s, C-3), 118.85 (s, C-4a), 116.14 (d, C-8), 60.30 (t, OCH_2), 46.71 (t, NCH_2), 29.68 (t, CH_2), 24.42 (t, CH_2), 22.89 (q, CH_3). Anal. ($C_{21}H_{23}N_5O_3$·$0.25H_2O$) C, H, N.

C. By Reaction with $FeCl_3$. A solution of **86** (6.1 mg, 11.3 μmol) in CH_2Cl_2 (1 mL) was treated with a large excess (ca. 10-fold) of anhydrous $FeCl_3$. Then the mixture was stirred at 20 °C for 1 h. A solution of aqueous $NaHCO_3$/Na_2CO_3 (50 mL) was then added, and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−1.5% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 2% MeOH/CH_2Cl_2 gave **88** (1.6 mg, 31%). Further elution with 3−5% MeOH/CH_2Cl_2 gave **91** (3 mg, 67%). Repeated reaction with a larger excess of $FeCl_3$ gave **91** as the sole product (55%).

D. By Reaction with DDQ. A solution of **86** (617 mg, 1.14 mmol) and DDQ (1.34 g, 5.89 mmol) in CH_2Cl_2 (120 mL) was stirred in a sealed flask (foil-covered) at 20 °C for 2 days. The resulting solution was treated with a mixture of aqueous Na_2CO_3/sodium sulfite (750 mL) and extracted with CH_2Cl_2 (5 × 300 mL), sequentially washing each extract with (the same) additional solutions of aqueous Na_2CO_3/Na_2SO_3 (750 mL), aqueous Na_2CO_3 (750 mL), and water (2 × 750 mL). The aqueous portions were further extracted after 18 h (3 × 300 mL). Then the combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−1.2% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 1.2−1.4% MeOH/CH_2Cl_2 gave recovered **86** (32 mg, 5%). Elution with 1.6−1.8% MeOH/CH_2Cl_2 gave minor impurities. Then elution with 2−5% MeOH/CH_2Cl_2 gave **88** (435 mg, 85%): mp (CH_2Cl_2/hexane) 157−159 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.67 (s, 1 H, H-8), 7.63 (t, J = 7.1 Hz, 2 H, H-3′,5′),

7.58 (m, 3 H, H-2′,4′,6′), 7.21 (br s, 1 H, NH), 4.35 (br t, J = 5.1 Hz, 1 H, CH_2OH), 3.88 (t, J = 7.2 Hz, 2 H, NCH_2), 3.36 (m, 2 H, CH_2OH), 1.98 (s, 3 H, $COCH_3$), 1.50 (m, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.40 (m, 2 H, CH_2); ^{13}C NMR δ 169.31 (s, C=O), 154.23, 153.18, 151.57 (3 s, CONH, C-2,7), 151.34 (d, C-5), 148.82 (s, C-8a), 137.34 (d, C-4), 134.75 (s, C-1′), 129.54 (d, 2 C, C-3′,5′), 129.17 (d, C-4′), 129.02 (d, 2 C, C-2′,6′), 127.25 (s, C-3), 118.76 (s, C-4a), 115.55 (d, C-8), 60.32 (t, OCH_2), 50.21 (s, $C(CH_3)_3$), 46.99 (t, NCH_2), 29.70 (t, CH_2), 28.65 (q, 3 C, $C(CH_3)_3$), 24.52 (t, CH_2), 22.97 (q, CH_3). Anal. ($C_{25}H_{31}N_5O_3\cdot H_2O$) C, H, N.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]-*N*-(3-hydroxypropyl)acetamide (87).** Similar reaction of **85** (869 mg, 1.66 mmol) with DDQ (1.91 g, 8.41 mmol) in CH_2Cl_2 (175 mL) at 20 °C for 4 days, then workup (as above) and chromatography of the resulting product on silica gel (eluting with 1.2−1.4% MeOH/CH_2Cl_2) gave firstly recovered **85** (49 mg, 6%). Elution with 1.5−2% MeOH/CH_2Cl_2 gave **87** (429 mg, 60%): mp (Et_2O/hexane) 124−127 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.88 (br s, 1 H, NH), 9.14 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.70 (s, 1 H, H-8), 7.63 (t, J = 7.1 Hz, 2 H, H-3′,5′), 7.58 (m, 3 H, H-2′,4′,6′), 7.22 (br s, 1 H, NH), 4.43 (br t, J = 5.2 Hz, 1 H, CH_2OH), 3.92 (t, J = 7.3 Hz, 2 H, NCH_2), 3.41 (q, J = 5.9 Hz, 2 H, OCH_2), 1.99 (s, 3 H, $COCH_3$), 1.65 (pentet, J = 6.8 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.78 (s, C=O), 154.37, 153.29, 151.76 (3 s, CONH, C-2,7), 151.46 (d, C-5), 148.95 (s, C-8a), 137.45 (d, C-4), 134.80 (s, C-1′), 129.69 (d, 2 C, C-3′,5′), 129.33 (d, C-4′), 129.13 (d, 2 C, C-2′,6′), 127.39 (s, C-3), 118.89 (s, C-4a), 115.71 (d, C-8), 58.39 (t, OCH_2), 50.36 (s, $C(CH_3)_3$), 44.99 (t, NCH_2), 31.19 (t, CH_2), 28.77 (q, 3 C, $C(CH_3)_3$), 23.08 (q, CH_3). Anal. ($C_{24}H_{29}N_5O_3$) C, H, N.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-acetamide (94).** A stirred solution of **87** (355 mg, 0.816 mmol) in dry THF (50 mL) under N_2 at 0 °C was treated with dry *N*-methylmorpholine (1.50 mL, 14.7 mmol), followed by mesyl chloride (0.32 mL, 4.13 mmol, added dropwise by syringe). Then the mixture was stirred at 0−20 °C for 12 h. 1-Methylpiperazine (9.05 mL, 81.7 mmol) was then added, and the mixture was stirred at 20 °C for 1 day and then at 30 °C for 1 day. The resulting solution was cooled in ice, then treated with ice/aqueous Na_2CO_3 (150 mL) and extracted with CH_2Cl_2 (6 × 80 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−3% MeOH/EtOAc containing 1% Et_3N gave foreruns. Then further elution with 3−5% MeOH/EtOAc containing 1% Et_3N gave (after base washing) an oil (410 mg), which was further chromatographed on silica gel. Elution with 0−7% MeOH/CH_2Cl_2 gave foreruns. Then further elution with 7% MeOH/CH_2Cl_2 containing 1% Et_3N gave (after base washing) **94** (280 mg, 66%): oil; ^{1}H NMR [$(CD_3)_2SO$] δ 9.90 (br s, 1 H, NH), 9.13 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.69 (s, 1 H, H-8), 7.63 (t, J = 7.0 Hz, 2 H, H-3′,5′), 7.57 (m, 3 H, H-2′,4′,6′), 7.22 (br s, 1 H, NH), 3.89 (t, J = 7.2 Hz, 2 H, NCH_2), 2.5−2.0 (br s, 8 H, $N(CH_2)_4N$), 2.26 (t, J = 7.1 Hz, 2 H, NCH_2), 2.09 (s, 3 H, NCH_3), 2.00 (s, 3 H, $COCH_3$), 1.64 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 169.39 (s, C=O), 154.28, 153.13, 151.56 (3 s, CONH, C-2,7), 151.21 (d, C-5), 148.76 (s, C-8a), 137.32 (d, C-4), 134.75 (s, C-1′), 129.53 (d, 2 C, C-3′,5′), 129.15 (d, C-4′), 129.01 (d, 2 C, C-2′,6′), 127.17 (s, C-3), 118.69 (s, C-4a), 115.46 (d, C-8), 54.80 (t, NCH_2), 54.63, 52.44 (2 t, 2 × 2 C, $2N(CH_2)_2$), 50.17 (s, $C(CH_3)_3$), 45.65 (q, NCH_3), 45.49 (t, NCH_2), 28.64 (q, 3 C, $C(CH_3)_3$), 25.10 (t, CH_2), 23.01 (q, CH_3); HRFABMS calcd for $C_{29}H_{40}N_7O_2$ *m/z* (MH^+) 518.3244, found 518.3236.

***N*-[2-[[(*tert*-Butylamino)carbonyl]amino]-3-phenyl-1,6-naphthyridin-7-yl]-*N*-[4-(diethylamino)butyl]acetamide (95).** Similar reaction of a stirred solution of **88** (547 mg, 1.22 mmol) and dry *N*-methylmorpholine (2.05 mL, 18.7 mmol) in dry THF (70 mL) under N_2 with mesyl chloride (0.48 mL, 6.20 mmol) at 20 °C for 16 h, followed by reaction with diethylamine (25 mL, 0.242 mol) at 50 °C for 4 days and chromatography of the resulting product on silica gel (eluting with 1−2% MeOH/EtOAc containing 0.5% Et_3N) gave (after base washing) **95** (512 mg, 83%): oil; ^{1}H NMR [$(CD_3)_2SO$] δ 9.89 (br s, 1 H, NH), 9.15 (s, 1 H, H-5), 8.35 (s, 1 H, H-4), 7.66 (s, 1 H, H-8), 7.63 (t, J = 7.1 Hz, 2 H, H-3′,5′), 7.58 (m, 3 H, H-2′,4′,6′), 7.22 (br s, 1 H, NH), 3.89 (t, J = 7.1 Hz, 2 H, NCH_2), 2.36 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.28 (t, J = 7.0 Hz, 2 H, NCH_2), 1.98 (s, 3 H, $COCH_3$), 1.47 (pentet, J = 7.2 Hz, 2 H, CH_2), 1.42 (s, 9 H, $C(CH_3)_3$), 1.36 (pentet, J = 7.6 Hz, 2 H, CH_2), 0.87 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 169.26 (s, C=O), 154.24, 153.14, 151.54 (3 s, CONH, C-2,7), 151.32 (d, C-5), 148.78 (s, C-8a), 137.32 (d, C-4), 134.72 (s, C-1′), 129.52 (d, 2 C, C-3′,5′), 129.14 (d, C-4′), 128.99 (d, 2 C, C-2′,6′), 127.20 (s, C-3), 118.73 (s, C-4a), 115.52 (d, C-8), 51.74 (t, NCH_2), 50.16 (s, $C(CH_3)_3$), 46.87 (t, NCH_2), 46.13 (t, 2 C, $N(CH_2)_2$), 28.62 (q, 3 C, $C(CH_3)_3$), 25.72, 23.88 (2 t, $2CH_2$), 22.96 (q, CH_3), 11.66 (q, 2 C, $2CH_3$); HRFABMS calcd for $C_{29}H_{41}N_6O_2$ *m/z* (MH^+) 505.3291, found 505.3277.

***N*-(*tert*-Butyl)-*N*′-[7-[[3-(4-methyl-1-piperazinyl)propyl]-amino]-3-phenyl-1,6-naphthyridin-2-yl]urea (28).** A stirred solution of **94** (87 mg, 0.168 mmol) in MeOH (27 mL) at 0 °C was treated with NaOH (0.95 g, 23.8 mmol) and water (3 mL, added dropwise). Then the mixture was stirred at 0 °C for 2 h and then at 20 °C for 3.5 days. A solution of excess $NaHCO_3$ (2.15 g, 25.6 mmol) in ice/water (150 mL) was then added, and the mixture was extracted with CH_2Cl_2 (6 × 70 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−0.5% MeOH/CH_2Cl_2 containing 1% Et_3N gave foreruns. Then further elution with 0.75−2% MeOH/CH_2Cl_2 containing 1% Et_3N gave (after base washing and crystallization) **28** (54 mg, 68%): mp (CH_2Cl_2/hexane) 137−138 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (br s, 1 H, NH), 8.70 (s, 1 H, H-5), 7.98 (s, 1 H, H-4), 7.58 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.51 (m, 3 H, H-2′,4′,6′), 6.96 (br t, J = 5.4 Hz, 1 H, $NHCH_2$), 6.92 (br s, 1 H, NH), 6.39 (s, 1 H, H-8), 3.31 (m, 2 H, $NHCH_2$), 2.6−2.1 (br s, 8 H, $N(CH_2)_4N$), 2.38 (t, J = 6.8 Hz, 2 H, NCH_2), 2.17 (s, 3 H, NCH_3), 1.72 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 159.56 (s, C-7), 152.51, 152.04 (2 s, CONH, C-2), 151.42 (d, C-5), 149.38 (s, C-8a), 137.78 (d, C-4), 135.51 (s, C-1′), 129.45, 129.11 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 128.54 (d, C-4′), 121.19 (s, C-3), 113.31 (s, C-4a), 94.55 (br d, C-8), 55.69 (t, NCH_2), 54.77, 52.70 (2 t, 2 × 2 C, $2N(CH_2)_2$), 49.97 (s, $C(CH_3)_3$), 45.70 (q, NCH_3), 39.82 (t, NCH_2), 28.67 (q, 3 C, $C(CH_3)_3$), 25.96 (t, CH_2). Anal. ($C_{27}H_{37}N_7O\cdot0.5H_2O$) C, H, N.

Further base hydrolysis of the mother liquors followed by chromatography of the resulting product on neutral alumina (eluting with 1% EtOH/$CHCl_3$) gave additional **28** (11 mg, 14%).

***N*-(*tert*-Butyl)-*N*′-[7-[[4-(diethylamino)butyl]amino]-3-phenyl-1,6-naphthyridin-2-yl]urea (31).** Similar hydrolysis of **95** (148 mg, 0.294 mmol) in MeOH (45 mL) with NaOH (1.85 g, 46.3 mmol) and water (5 mL) at 0 °C for 2 h and then at 20 °C for 4 days and chromatography of the resulting product on silica gel (eluting with 0.5% MeOH/CH_2Cl_2 containing 1% Et_3N) gave (after base washing and crystallization) **31** (101 mg, 74%): mp (CH_2Cl_2/hexane) 124−125 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.25 (br s, 1 H, NH), 8.70 (s, 1 H, H-5), 7.97 (s, 1 H, H-4), 7.58 (t, J = 7.2 Hz, 2 H, H-3′,5′), 7.51 (m, 3 H, H-2′,4′,6′), 6.95 (br t, J = 5.6 Hz, 1 H, $NHCH_2$), 6.92 (br s, 1 H, NH), 6.38 (s, 1 H, H-8), 3.29 (m, 2 H, $NHCH_2$), 2.44 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.38 (t, J = 7.1 Hz, 2 H, NCH_2), 1.58 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.48 (pentet, J = 7.2 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$), 0.94 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 159.61 (s, C-7), 152.53, 152.10 (2 s, CONH, C-2), 151.45 (d, C-5), 149.42 (s, C-8a), 137.82 (d, C-4), 135.54 (s, C-1′), 129.49, 129.14 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 128.57 (d, C-4′), 121.15 (s, C-3), 113.30 (s, C-4a), 94.50 (br d, C-8), 52.03 (t, NCH_2), 50.00 (s, $C(CH_3)_3$), 46.21 (t, 2 C, $N(CH_2)_2$), 41.28 (t, NCH_2), 28.68 (q, 3 C, $C(CH_3)_3$), 26.84, 24.29 (2 t, $2CH_2$), 11.69 (q, 2 C, $2CH_3$). Anal. ($C_{27}H_{38}N_6O$) C, H, N.

***N*⁷-[3-(4-Methyl-1-piperazinyl)propyl]-3-phenyl-1,6-naphthyridine-2,7-diamine (27).** A stirred solution of **94** (220 mg, 0.426 mmol) in MeOH (54 mL) was treated with NaOH (2.37 g, 59.3 mmol) and water (6 mL), and the mixture

was then sealed under N_2 and stirred at 52 °C for 18 h. The resulting mixture was concentrated under reduced pressure (to ca. 5 mL), then treated with a solution of excess $NaHCO_3$ (6.0 g, 71.4 mmol) in water (150 mL) and extracted with CH_2Cl_2 (6 × 70 mL). The combined extracts were evaporated to dryness, and the residue (mostly **28**) was then dissolved in dioxane (27 mL), treated with NaOH (2.39 g, 59.8 mmol) and water (3 mL), and then sealed under N_2 and stirred at 96 °C for 4 days. The resulting mixture was concentrated under reduced pressure (to ca. 3 mL), then treated with excess $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (7 × 70 mL) and EtOAc (2 × 50 mL). The combined extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−4% MeOH/CH_2Cl_2 containing 1% Et_3N gave foreruns. Then further elution with 4−5% MeOH/CH_2Cl_2 containing 1% Et_3N gave (after base washing and crystallization) **27**[42] (120 mg, 75%). Further purification of the mother liquors by chromatography on silica gel (eluting with 2.5−3% MeOH/CH_2Cl_2 containing 1% Et_3N) gave (after base washing) additional **27** (12 mg, 8%).

***N*⁷-[4-(Diethylamino)butyl]-3-phenyl-1,6-naphthyridine-2,7-diamine (30).** Similar hydrolysis of **95** (382 mg, 0.758 mmol) in dioxane (63 mL) with NaOH (5.60 g, 140 mmol) and water (7 mL) under N_2 at 97 °C for 7 days and chromatography of the resulting product on silica gel (eluting with 5−7% MeOH/EtOAc containing 1% Et_3N) gave (after base washing and crystallization) **30** (180 mg, 65%): mp (CH_2Cl_2/hexane) 119−120 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.46 (s, 1 H, H-5), 7.65 (s, 1 H, H-4), 7.48 (m, 4 H, H-2′,3′,5′,6′), 7.40 (m, 1 H, H-4′), 6.45 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.21 (br s, 2 H, NH_2), 6.20 (s, 1 H, H-8), 3.21 (br td, J = 6.6, 6.1 Hz, 2 H, NHC*H*$_2$), 2.44 (q, J = 7.1 Hz, 4 H, N(CH_2)$_2$), 2.37 (t, J = 7.1 Hz, 2 H, NCH_2), 1.56 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.47 (pentet, J = 7.1 Hz, 2 H, CH_2), 0.94 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 159.11, 158.31 (2 s, C-2,7), 152.66 (s, C-8a), 150.38 (d, C-5), 137.65 (s, C-1′), 136.09 (d, C-4), 128.93, 128.63 (2 d, 2 × 2 C, C-2′,3′,5′,6′), 127.54 (d, C-4′), 120.74 (s, C-3), 113.42 (s, C-4a), 93.78 (d, C-8), 52.08 (t, NCH_2), 46.19 (t, 2 C, N(CH_2)$_2$), 41.52 (t, NCH_2), 26.87, 24.35 (2 t, 2CH_2), 11.68 (q, 2 C, 2CH_3). Anal. ($C_{22}H_{29}N_5$) C, H, N.

Further purification of the mother liquors by chromatography on alumina (eluting with 0.75−1% MeOH/CH_2Cl_2) gave additional **30** (41 mg, 15%).

***N*-[3-(2,6-Dichlorophenyl)-7-[[3-(4-methyl-1-piperazinyl)propyl]amino]-1,6-naphthyridin-2-yl]-*N*′-ethylurea (33).** A solution of 3-(2,6-dichlorophenyl)-*N*⁷-[3-(4-methyl-1-piperazinyl)propyl]-1,6-naphthyridine-2,7-diamine[42] (**32**) (112 mg, 0.252 mmol) in dry DMSO (5 mL) was treated with 60% NaH (13 mg, 0.325 mmol). Then the mixture was sealed under N_2 and stirred at 40−50 °C for 10 min and then at 20 °C for 30 min. A solution of ethyl isocyanate (24 μL, 0.304 mmol) in dry DMSO (1 mL, then 1 mL to rinse) was added (dropwise via syringe). Then the mixture was stirred at 20 °C for 1 day. The resulting mixture was cooled in ice, then treated with ice/aqueous $NaHCO_3$ (50 mL), adjusted to pH 10 with aqueous Na_2CO_3, and extracted with EtOAc (5 × 50 mL). The extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0−3% MeOH/EtOAc containing 1% Et_3N gave foreruns. Then further elution with 3−6% MeOH/EtOAc containing 1% Et_3N gave (after base washing and crystallization) **33** (94 mg, 72%): mp (CH_2Cl_2/hexane) 102−106 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 10.04 (br t, J = 5.4 Hz, 1 H, CON*H*CH_2), 8.68 (s, 1 H, H-5), 7.94 (s, 1 H, H-4), 7.77 (br s, 1 H, NH), 7.64 (d, J = 8.1 Hz, 2 H, H-3′,5′), 7.52 (dd, J = 8.7, 7.4 Hz, 1 H, H-4′), 6.95 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.53 (s, 1 H, H-8), 3.31 (m, 4 H, 2NHC*H*$_2$), 2.6−2.1 (br s, 8 H, N(CH_2)$_4$N), 2.38 (t, J = 7.0 Hz, 2 H, NCH_2), 2.15 (s, 3 H, NCH_3), 1.74 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.19 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 159.87 (s, C-7), 153.90, 152.48 (2 s, CONH, C-2), 151.51 (d, C-5), 150.17 (s, C-8a), 139.57 (d, C-4), 135.55 (s, 2 C, C-2′,6′), 132.76 (s, C-1′), 131.47 (d, C-4′), 128.80 (d, 2 C, C-3′,5′), 116.36 (s, C-3), 113.02 (s, C-4a), 94.48 (br d, C-8), 55.64 (t, NCH_2), 54.73, 52.71 (2 t, 2 × 2 C, 2N(CH_2)$_2$), 45.68 (q, NCH_3), 39.95 (t, $NHCH_2$), 34.15 (t, CONH*C*H_2), 25.90 (t, CH_2), 15.15 (q, CH_3). Anal. ($C_{25}H_{31}Cl_2N_7O$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[3-(2,6-dichlorophenyl)-7-[[3-(4-methyl-1-piperazinyl)propyl]amino]-1,6-naphthyridin-2-yl]-urea (34).** Similar reaction of **32** (115 mg, 0.258 mmol) in dry DMSO (5 mL) with 60% NaH (15 mg, 0.375 mmol) under N_2 at 40−50 °C for 15 min and then at 20 °C for 30 min followed by reaction with a solution of *tert*-butyl isocyanate (37 μL, 0.324 mmol) in dry DMSO (1 mL, then 2 × 1 mL) at 20 °C for 1 day and chromatography of the resulting product on silica gel (eluting with 3−6% MeOH/EtOAc containing 1% Et_3N) gave (after base washing and crystallization) **34** (69 mg, 49%): mp (CH_2Cl_2/hexane) 158−159.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.33 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.95 (s, 1 H, H-4), 7.65 (d, J = 8.0 Hz, 2 H, H-3′,5′), 7.53 (dd, J = 8.6, 7.6 Hz, 1 H, H-4′), 7.44 (br s, 1 H, NH), 7.03 (br t, J = 5.5 Hz, 1 H, N*H*CH_2), 6.38 (s, 1 H, H-8), 3.32 (m, 2 H, NHC*H*$_2$), 2.6−2.0 (br s, 8 H, N(CH_2)$_4$N), 2.37 (t, J = 7.0 Hz, 2 H, NCH_2), 2.14 (s, 3 H, NCH_3), 1.72 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.40 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 159.81 (s, C-7), 152.52, 152.37 (2 s, CONH, C-2), 151.49 (d, C-5), 149.73 (s, C-8a), 139.49 (d, C-4), 135.48 (s, 2 C, C-2′,6′), 132.58 (s, C-1′), 131.49 (d, C-4′), 128.77 (d, 2 C, C-3′,5′), 116.27 (s, C-3), 112.81 (s, C-4a), 94.39 (br d, C-8), 55.61 (t, NCH_2), 54.71, 52.64 (2 t, 2 × 2 C, 2N(CH_2)$_2$), 49.91 (s, *C*(CH_3)$_3$), 45.64 (q, NCH_3), 39.75 (t, $NHCH_2$), 28.64 (q, 3 C, C(*C*H_3)$_3$), 25.90 (t, CH_2). Anal. ($C_{27}H_{35}Cl_2N_7O$) C, H, N.

3-(2,6-Dichlorophenyl)-*N*⁷-[4-(diethylamino)butyl]-1,6-naphthyridine-2,7-diamine (35). A solution of **96** (251 mg, 0.815 mmol) and *N*¹,*N*¹-diethyl-1,4-butanediamine (1.19 g, 8.26 mmol) in 2-ethoxyethanol (10 mL) under N_2 was stirred at reflux for 5 days. The solvent was removed under reduced pressure, then the residue was treated with aqueous Na_2CO_3 (50 mL) and extracted with EtOAc (5 × 50 mL). The extracts were evaporated to dryness, and the residue was then chromatographed on silica gel. Elution with 0.25% MeOH/CH_2Cl_2 gave firstly recovered **96** (36 mg, 14%). Further elution with 15% MeOH/CH_2Cl_2 containing 0−0.25% Et_3N gave (after base washing and crystallization) **35** (125 mg, 36%): mp (CH_2Cl_2/hexane) 171−172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (s, 1 H, H-5), 7.59 (d, J = 8.2 Hz, 2 H, H-3′,5′), 7.57 (s, 1 H, H-4), 7.46 (dd, J = 8.7, 7.4 Hz, 1 H, H-4′), 6.49 (br t, J = 5.7 Hz, 1 H, N*H*CH_2), 6.22 (br s, 2 H, NH_2), 6.19 (s, 1 H, H-8), 3.22 (td, J = 6.5, 6.0 Hz, 2 H, NHC*H*$_2$), 2.44 (q, J = 7.1 Hz, 4 H, N(CH_2)$_2$), 2.38 (t, J = 7.1 Hz, 2 H, NCH_2), 1.57 (pentet, J = 7.0 Hz, 2 H, CH_2), 1.47 (pentet, J = 7.1 Hz, 2 H, CH_2), 0.94 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 159.28, 157.68 (2 s, C-2,7), 153.28 (s, C-8a), 150.35 (d, C-5), 136.91 (d, C-4), 135.28 (s, 2 C, C-2′,6′), 134.56 (s, C-1′), 130.60 (d, C-4′), 128.48 (d, 2 C, C-3′,5′), 116.06, 112.58 (2 s, C-3,4a), 93.67 (d, C-8), 52.03 (t, NCH_2), 46.16 (t, 2 C, N(CH_2)$_2$), 41.44 (t, $NHCH_2$), 26.78, 24.31 (2 t, 2CH_2), 11.67 (q, 2 C, 2CH_3). Anal. ($C_{22}H_{27}Cl_2N_5$) H, N. C: calcd, 61.1; found, 61.7.

***N*-[3-(2,6-Dichlorophenyl)-7-[[4-(diethylamino)butyl]-amino]-1,6-naphthyridin-2-yl]-*N*′-ethylurea (36).** Similar reaction of **35** (101 mg, 0.234 mmol) in dry DMSO (5 mL) with 60% NaH (13 mg, 0.325 mmol) under N_2 at 40−50 °C for 15 min and then at 20 °C for 30 min followed by reaction with a solution of ethyl isocyanate (23 μL, 0.291 mmol) in dry DMSO (1 mL, then 1 mL) at 20 °C for 16 h and chromatography of the resulting product on silica gel (eluting with 1−1.5% MeOH/EtOAc containing 1% Et_3N) gave (after base washing and crystallization) **36** (74 mg, 63%): mp (CH_2Cl_2/hexane) 102−109 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.04 (br t, J = 5.4 Hz, 1 H, CON*H*CH_2), 8.68 (s, 1 H, H-5), 7.94 (s, 1 H, H-4), 7.76 (br s, 1 H, NH), 7.64 (d, J = 8.3 Hz, 2 H, H-3′,5′), 7.52 (dd, J = 8.8, 7.4 Hz, 1 H, H-4′), 6.96 (br t, J = 5.6 Hz, 1 H, N*H*CH_2), 6.53 (s, 1 H, H-8), 3.30 (m, 4 H, 2NHC*H*$_2$), 2.45 (q, J = 7.2 Hz, 4 H, N(CH_2)$_2$), 2.39 (t, J = 7.2 Hz, 2 H, NCH_2), 1.60 (pentet, J = 6.9 Hz, 2 H, CH_2), 1.49 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.19 (t, J = 7.2 Hz, 3 H, CH_3), 0.94 (t, J = 7.1 Hz, 6 H, 2CH_3); ^{13}C NMR δ 159.81 (s, C-7), 153.78, 152.33 (2 s, CONH, C-2), 151.45 (d, C-5), 150.10 (s, C-8a), 139.53 (d, C-4), 135.51 (s, 2 C, C-2′,6′), 132.74 (s, C-1′), 131.41 (d, C-4′), 128.74 (d, 2 C, C-3′,5′), 116.21

(s, C-3), 112.92 (s, C-4a), 94.32 (br d, C-8), 51.95 (t, NCH_2), 46.16 (t, 2 C, $N(CH_2)_2$), 41.29 (t, $NHCH_2$), 34.02 (t, $CONHCH_2$), 26.63, 24.16 (2 t, $2CH_2$), 15.07 (q, CH_3), 11.57 (q, 2 C, $2CH_3$). Anal. ($C_{25}H_{32}Cl_2N_6O$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[3-(2,6-dichlorophenyl)-7-[[4-(diethylamino)butyl]amino]-1,6-naphthyridin-2-yl]urea (37).** Similar reaction of **35** (101 mg, 0.234 mmol) in dry DMSO (5 mL) with 60% NaH (14 mg, 0.35 mmol) under N_2 at 40−50 °C for 15 min and then at 20 °C for 30 min followed by reaction with a solution of *tert*-butyl isocyanate (32 μL, 0.281 mmol) in dry DMSO (1 mL, then 1 mL) at 20 °C for 17 h and chromatography of the resulting product on silica gel (eluting with 3−4% MeOH/EtOAc containing 0.5% Et_3N) gave (after base washing and crystallization) **37** (73 mg, 59%): mp (CH_2Cl_2/hexane) 114−116 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.34 (br s, 1 H, NH), 8.69 (s, 1 H, H-5), 7.94 (s, 1 H, H-4), 7.65 (d, J = 8.3 Hz, 2 H, H-3′,5′), 7.53 (dd, J = 8.6, 7.6 Hz, 1 H, H-4′), 7.43 (br s, 1 H, NH), 7.03 (br t, J = 5.4 Hz, 1 H, $NHCH_2$), 6.38 (s, 1 H, H-8), 3.30 (m, 2 H, $NHCH_2$), 2.44 (q, J = 7.1 Hz, 4 H, $N(CH_2)_2$), 2.38 (t, J = 7.1 Hz, 2 H, NCH_2), 1.58 (pentet, J = 7.1 Hz, 2 H, CH_2), 1.47 (pentet, J = 7.3 Hz, 2 H, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$), 0.94 (t, J = 7.1 Hz, 6 H, $2CH_3$); ^{13}C NMR δ 159.84 (s, C-7), 152.50, 152.37 (2 s, CONH, C-2), 151.48 (d, C-5), 149.74 (s, C-8a), 139.49 (d, C-4), 135.49 (s, 2 C, C-2′,6′), 132.59 (s, C-1′), 131.49 (d, C-4′), 128.77 (d, 2 C, C-3′,5′), 116.20 (s, C-3), 112.77 (s, C-4a), 94.32 (br d, C-8), 51.97 (t, NCH_2), 49.90 (s, $C(CH_3)_3$), 46.17 (t, 2 C, $N(CH_2)_2$), 41.18 (t, $NHCH_2$), 28.62 (q, 3 C, $C(CH_3)_3$), 26.72, 24.23 (2 t, $2CH_2$), 11.65 (q, 2 C, $2CH_3$). Anal. ($C_{27}H_{36}Cl_2N_6O$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[2-[[4-(diethylamino)butyl]amino]-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl]urea (12).** A 60% NaH (7.17 g, 179 mmol) sample was washed with hexane and then suspended in dry THF (250 mL). To this suspension was added (3,5-dimethoxyphenyl)acetonitrile (28.9 g, 163 mmol), and the reaction was stirred at room temperature for 1.5 h. 4-Amino-2-(methylsulfanyl)-5-pyrimidinecarbaldehyde[61,62] (**106**) (25 g, 148 mmol) was then added as fast as foaming of the reaction would allow. After being stirred overnight at room temperature, the reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The CH_2Cl_2 layer was washed twice with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated to give crude 6-(3,5-dimethoxyphenyl)-2-(methylsulfanyl)pyrido[2,3-*d*]pyrimidin-7-amine (**107**) (50.0 g, 98%): mp 175−178 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.88 (s, 1 H, H-4), 7.90 (s, 1 H, H-5), 7.67 (br s, 2 H, NH_2), 6.63 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.57 (t, J = 2.2 Hz, 1 H, H-4′), 3.80 (s, 6 H, $2OCH_3$), 2.55 (s, 3 H, CH_3), traces of starting nitrile also observed in ^{1}H NMR; APCIMS *m/z* (relative intensity) 329 (M^+ + 1, 100). Anal. ($C_{16}H_{16}N_4O_2S\cdot0.1C_{10}H_{11}NO_2$) C, H, N.

A solution of **107** (20.0 g, 60.9 mmol) in $CHCl_3$ (480 mL) was treated with 2-(phenylsulfonyl)-3-phenyloxaziridine (15.9 g, 60.9 mmol), and the reaction was stirred at room temperature for 24 h. Silica gel was then added, the suspension was evaporated to dryness, and the residue was chromatographed on silica gel, eluting with EtOAc/EtOH/Et_3N (9:1:0.5). Product was crystallized from several fractions and was filtered off and washed with eluting solvent followed by Et_2O to give 6-(3,5-dimethoxyphenyl)-2-(methylsulfinyl)pyrido[2,3-*d*]pyrimidin-7-amine (**108**) (9.38 g, 45%): mp 204.5−205.5 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1 H, H-4), 7.90 (s, 1 H, H-5), 6.53−6.64 (m, 3 H, H-2′,4′,6′), 6.14 (br s, 1 H, NH), 5.79 (br s, 1 H, NH), 3.86 (s, 6 H, $2OCH_3$), 3.05 (s, 3 H, CH_3); APCIMS *m/z* (relative intensity) 345.1 (M^+ + 1, 100). Anal. ($C_{16}H_{16}N_4O_3S$) C, H, N, S.

The remaining fractions from the chromatography were concentrated and rechromatographed on silica gel as above to give additional **108** (8.92 g, 43%).

N^1,N^1-Diethyl-1,4-butanediamine (1.15 g, 7.99 mmol) was added to a suspension of **108** (2.50 g, 7.26 mmol) in dry dioxane (20.0 mL). The suspension was warmed at 50 °C overnight, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (3×) and saturated aqueous NaCl (2×), dried ($MgSO_4$), and evaporated. The crude residue was chromatographed on silica gel, eluting with EtOAc/EtOH/Et_3N (9:2:1) to give N^2-[4-(diethylamino)-butyl]-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine (**109**) (2.26 g, 72%): mp 59.5−62.0 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1 H, H-4), 7.56 (s, 1 H, H-5), 6.58 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.50 (t, J = 2.2 Hz, 1 H, H-4′), 5.64 (br s, 1 H, NH), 5.35 (br s, 2 H, NH_2), 3.83 (s, 6 H, $2OCH_3$), 3.64−3.55 (m, 2 H, $NHCH_2$), 2.63−2.46 (m, 6 H, $3NCH_2$), 1.75−1.56 (m, 4 H, $2CH_2$), 1.04 (t, J = 7.2 Hz, 6 H, $2CH_3$); APCIMS *m/z* (relative intensity) 425.6 (M^+ + 1, 100). Anal. ($C_{23}H_{32}N_6O_2\cdot0.4H_2O$) C, H, N.

A solution of **109** (0.500 g, 1.18 mmol) in dry DMF (4 mL) was treated with 60% NaH (0.054 g, 1.34 mmol). After the mixture was stirred at room temperature for 1.5 h, *tert*-butyl isocyanate (0.150 mL, 1.34 mmol) was added and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated, and the residue was dissolved in CH_2Cl_2, extracted with saturated aqueous NH_4Cl (3x) and saturated aqueous NaCl (1x), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/EtOH/Et_3N (9:2:1), to give **12** (0.513 g, 80%): mp 82−86 °C; ^{1}H NMR ($CDCl_3$) δ 10.34 (br s, 1 H, NH), 8.70 (br s, 1 H, H-4), 7.66 (s, 1 H, H-5), 7.12 (s, 1 H, NH), 6.51 (t, J = 2.4 Hz, 1 H, H-4′), 6.47 (d, J = 2.4 Hz, 2 H, H-2′,6′), 6.00 (br s, 1 H, NH), 3.82 (s, 6 H, $2OCH_3$), 3.62−3.52 (m, 2 H, $NHCH_2$), 2.57 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 2.50 (t, J = 7.2 Hz, 2 H, NCH_2), 1.88−1.56 (m, 4 H, $2CH_2$), 1.49 (s, 9 H, $C(CH_3)_3$), 1.06 (t, J = 7.2 Hz, 6 H, $2CH_3$); APCIMS *m/z* (relative intensity) 524.5 (M^+ + 1, 32), 425.6 (M^+ + 1 − $CONC(CH_3)_3$, 100). Anal. ($C_{28}H_{41}N_7O_3\cdot0.25H_2O$) C, H, N.

***N*-[2-[[4-(Diethylamino)butyl]amino]-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl]-*N*′-ethylurea (104).** Similar reaction of **109** (0.500 g, 1.18 mmol), 60% NaH (0.054 g, 1.34 mmol), and ethyl isocyanate (0.110 mL, 1.34 mmol) gave **104** (0.378 g, 63%): mp 48−53 °C; ^{1}H NMR ($CDCl_3$/D_2O) δ 8.73 (br s, 1 H, H-4), 7.68 (s, 1 H, H-5), 6.53 (t, J = 2.2 Hz, 1 H, H-4′), 6.48 (d, J = 2.2 Hz, 2 H, H-2′,6′), 3.83 (s, 6 H, $2OCH_3$), 3.59 (t, J = 6.8 Hz, 2 H, $NHCH_2$), 3.46 (q, J = 7.2 Hz, 2 H, $NHCH_2CH_3$), 2.58 (q, J = 7.2 Hz, 4 H, $N(CH_2)_2$), 2.51 (t, J = 7.2 Hz, 2 H, NCH_2), 1.82−1.57 (m, 4 H, $2CH_2$), 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 1.06 (t, J = 7.2 Hz, 6 H, $2CH_3$); APCIMS *m/z* (relative intensity) 496.5 (M^+ + 1, 40), 451.5 (M^+ + 1 − $NH_2CH_2CH_3$, 10), 425.6 (M^+ + 1 − $CONCH_2CH_3$, 100). Anal. ($C_{26}H_{37}N_7O_3\cdot0.6H_2O$) C, H, N.

***N*-[6-(3,5-Dimethoxyphenyl)-2-[[3-(4-methyl-1-piperazinyl)propyl]amino]pyrido[2,3-*d*]pyrimidin-7-yl]-*N*′-ethylurea (102).** Reaction of **108** (0.500 g, 1.45 mmol) and 3-(4-methyl-1-piperazinyl)propylamine (0.250 g, 1.60 mmol) in dry dioxane (4.00 mL) as above followed by chromatography on silica gel, eluting with EtOAc/EtOH/Et_3N (9:2:1 then 9:2:2), gave 6-(3,5-dimethoxyphenyl)-N^2-[3-(4-methyl-1-piperazinyl)-propyl]pyrido[2,3-*d*]pyrimidine-2,7-diamine (**110**) (0.517 g, 80%): mp 77−80.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1 H, H-4), 7.56 (s, 1 H, H-5), 6.58 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.50 (t, J = 2.2 Hz, 1 H, H-4′), 6.07 (br s, 1 H, NH), 5.33 (br s, 2 H, NH_2), 3.83 (s, 6 H, $2OCH_3$), 3.71−3.60 (m, 2 H, $NHCH_2$), 2.79−2.22 (m, 13 H, $5NCH_2$, CH_3), 1.85 (pentet, J = 6.7 Hz, 2 H, CH_2); APCIMS *m/z* (relative intensity) 438.1 (M^+ + 1, 100). Anal. ($C_{23}H_{31}N_7O_2\cdot0.25H_2O$) C, H, N.

Reaction of **110** (0.200 g, 0.457 mmol), 60% NaH (0.020 g, 0.503 mmol), and ethyl isocyanate (0.040 mL, 0.503 mmol) as above gave **102** (0.134 g, 56%): mp 68−73 °C; ^{1}H NMR ($CDCl_3$/D_2O) δ 8.72 (s, 1 H, H-4), 7.67 (s, 1 H, H-5), 6.58−6.41 (m, 3 H, H-2′,4′,6′), 3.82 (s, 6 H, $2OCH_3$), 3.73−3.59 (m, 2 H, $NHCH_2$), 3.53−3.38 (m, 2 H, $NHCH_2CH_3$), 2.96−2.22 (m, 13 H, $5NCH_2$, CH_3), 1.95−1.77 (m, 2 H, CH_2), 1.30 (t, J = 7.2 Hz, 3 H, CH_3); APCIMS *m/z* (relative intensity) 509.0 (M^+ + 1, 23), 463.9 (M^+ + 1 − $NH_2CH_2CH_3$, 13), 437.9 (M^+ + 1 − $CONCH_2CH_3$, 100). Anal. ($C_{26}H_{36}N_8O_3\cdot0.6H_2O$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[6-(3,5-dimethoxyphenyl)-2-[[3-(4-methyl-1-piperazinyl)propyl]amino]pyrido[2,3-*d*]pyrimidin-7-yl]urea (103).** Similar reaction of **110** (0.223 g, 0.509 mmol), 60% NaH (0.022 g, 0.560 mmol), and *tert*-butyl isocyanate (0.064 mL, 0.560 mmol) gave **103** (0.173 g, 63%): mp 127−

132 °C; ^{1}H NMR ($CDCl_3$) δ 10.31 (br s, 1 H, NH), 8.70 (br s, 1 H, H-4), 7.65 (s, 1 H, H-5), 7.12 (s, 1 H, NH), 6.51 (t, J = 2.2 Hz, 1 H, H-4′), 6.47 (d, J = 2.2 Hz, 2 H, H-2′,6′), 6.41 (br s, 1 H, NH), 3.82 (s, 6 H, $2OCH_3$), 3.42−3.31 (m, 2 H, $NHCH_2$), 2.93−2.13 (m, 13 H, $5NCH_2$, CH_3), 1.93−1.78 (m, 2 H, CH_2), 1.49 (s, 9 H, $C(CH_3)_3$); APCIMS *m/z* (relative intensity) 537.0 ($M^+ + 1$, 15), 463.9 ($M^+ + 1 - NH_2C(CH_3)_3$, 9), 437.9 ($M^+ + 1 - CONC(CH_3)_3$, 100). Anal. ($C_{28}H_{40}N_8O_3 \cdot 0.25H_2O$) C, H, N.

***N*-(*tert*-Butyl)-*N*′-[6-(3,5-dimethoxyphenyl)-2-[(3-hydroxypropyl)amino]pyrido[2,3-*d*]pyrimidin-7-yl]urea (105).** A mixture of **108** (2.00 g, 5.81 mmol) and 3-amino-1-propanol (1.30 g, 17.42 mmol) in dioxane (25 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the residue was partitioned between hexane and saturated aqueous $NaHCO_3$. The insoluble crude product was collected by filtration and dried under high vacuum at 50 °C overnight to give crude 3-[[7-amino-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-2-yl]amino]-1-propanol (**111**) (2.0 g, 92%), which was used directly: ^{1}H NMR [$(CD_3)_2SO$] δ 8.58 (br s, 1 H, H-4), 7.61 (s, 1 H, H-5), 7.24 (br s, 1 H, NH), 6.52 (m, 2 H, H-2′,6′), 6.50 (m, 1 H, H-4′), 4.60 (br s, 1 H, OH), 3.73 (s, 6 H, $2OCH_3$), 3.68−3.44 (m, 2 H, CH_2OH), 3.43−3.40 (m, 2 H, $NHCH_2$), 1.68−1.62 (m, 2 H, CH_2); APCIMS *m/z* (relative intensity) 356 ($M^+ + 1$, 100).

To a solution of crude **111** (1.79 g, 5.04 mmol) in DMF (4 mL) was added imidazole (0.86 g, 12.6 mmol) followed by *tert*-butyl(chloro)dimethylsilane (0.91 g, 6.04 mmol). The mixture was stirred at ambient temperature overnight, and the solvent was removed under high vacuum. The residue was dissolved in EtOAc and washed with brine, followed by water, and then dried over $MgSO_4$. The suspension was filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by radial chromatography, eluting with CH_2Cl_2/MeOH (97:3), to give N^2-[3-[[*tert*-butyl(dimethyl)silyl]oxy]-propyl]-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine (**112**) (1.72 g, 73%): mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (br s, 1 H, H-4), 7.49 (s, 1 H, H-5), 6.51−6.50 (m, 2 H, H-2′,6′), 6.43−6.42 (m, 1 H, H-4′), 5.63 (br s, 1 H, NH), 5.30 (br s, 2 H, NH_2), 3.76 (s, 6 H, $2OCH_3$), 3.71 (t, J = 6.0 Hz, 2 H, OCH_2), 3.66−3.58 (m, 2 H, $NHCH_2$), 1.85−1.80 (m, 2 H, CH_2), 0.84 (s, 9 H, $(CH_3)_3CSi(CH_3)_2$), 0.00 (s, 6 H, $(CH_3)_3CSi(CH_3)_2$); APCIMS *m/z* (relative intensity) 470 ($M^+ + 1$, 100). Anal. ($C_{24}H_{35}N_5O_3Si$) C, H, N.

To a solution of **112** (1.72 g, 3.66 mmol) in DMF (20 mL) was added 60% NaH (0.16 g, 4.03 mmol) in portions. The mixture was stirred at ambient temperature for 30 min, and then *tert*-butyl isocyanate (0.40 g, 4.03 mmol) was added. The reaction mixture was stirred for 18 h at room temperature, then the solvent was removed under high vacuum and the residue was diluted with water. The insoluble crude product was collected by filtration, dried on the filter, and purified by radial chromatography, eluting with a gradient of 20−50% EtOAc/hexane, to give *N*-(*tert*-butyl)-*N*′-[2-[[3-[[*tert*-butyl(dimethyl)silyl]oxy]propyl]amino]-6-(3,5-dimethoxyphenyl)pyrido-[2,3-*d*]pyrimidin-7-yl]urea (**113**) (1.44 g, 69%): mp (broad) 120−157 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1 H, H-4), 7.57 (s, 1 H, H-5), 7.07 (br s, 1 H, NH), 6.43−6.40 (m, 1 H, H-4′), 6.40−6.38 (m, 2 H, H-2′,6′), 5.90 (br s, 1 H, NH), 3.73 (s, 6 H, $2OCH_3$), 3.72 (t, J = 5.9 Hz, 2 H, OCH_2), 3.61−3.56 (m, 2 H, $NHCH_2$), 1.83 (br m, 2 H, CH_2), 1.41 (s, 9 H, $CONHC(CH_3)_3$), 0.84 (s, 9 H, $(CH_3)_3CSi(CH_3)_2$), 0.00 (s, 6 H, $(CH_3)_3CSi(CH_3)_2$). Anal. ($C_{29}H_{44}N_6O_4Si$) C, H, N.

To a mixture of **113** (1.40 g, 2.46 mmol) in 50% CH_3CN/THF (50 mL) was added fluorosilicic acid (20−25% solution in water, 4 mL), and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, and the residue was triturated with a half-saturated aqueous solution of $NaHCO_3$. The insoluble product was collected by filtration, washed with water, and dried in air to give **105** (0.9 g, 80%): mp 157−159 °C; ^{1}H NMR ($CDCl_3$) δ 9.92 (br s, 1 H, NH), 8.67 (br s, 1 H, H-4), 7.63 (s, 1 H, H-5), 7.12 (br s, 1 H, NH), 6.48−6.46 (m, 1 H, H-4′), 6.43−6.41 (m, 2 H, H-2′,6′), 5.70 (br s, 1 H, NH), 5.05 (br s, 1 H, OH), 3.78 (s, 6 H, $2OCH_3$), 3.73−3.69 (m, 2 H, CH_2OH), 3.60−3.56 (m, 2 H, $NHCH_2$), 1.79−1.76 (m, 2 H, CH_2), 1.46 (s, 9 H, $C(CH_3)_3$); APCIMS *m/z* (relative intensity) 455 ($M^+ + 1$, 100), 356 ($M^+ + 1 - CONC(CH_3)_3$, 100). Anal. ($C_{23}H_{30}N_6O_4 \cdot 0.36EtOAc$) C, H, N.

DELFIA Assay. Clear, solid polystyrene 96-well DELFIA plates (DELFIA is a time-resolved dissociation-enhanced lanthanide fluoroimmunoassay) (EG&G Wallac, Gaithersburg MD) were coated with 100 μL/well of 0.1 mg/mL of poly(Glu-Tyr) (4:1) (Sigma, St. Louis, MO) in BupH carbonate/bicarbonate buffer (0.2 M sodium carbonate/bicarbonate buffer, pH 9.4, Pierce, Rockford, IL) overnight at room temperature. Excess substrate was removed by washing the plate 3× with 100 μL of 1× DELFIA wash reagent (EG&G Wallac, Gaithersburg MD) and stored wrapped at −20 °C. Plates are spotted with 1 μL of inhibitor (typically 10−30 μM final) or DMSO carrier control and restored as above.

Preparation of VEGFR-2 TK. The VEGFR-2 TK construct was prepared and purified at Agouron, La Jolla, CA. VEGFR-2 [also known in the literature as KDR (human) and Flk-1 (mouse)] is a member of the PDGF receptor family, a group of membrane-bound receptors that characteristically contain a kinase insert domain (KID) in the intracellular catalytic domain. The KID is a structural feature not necessary for intrinsic kinase activity but, after ligand-stimulated autophosphorylation, one that binds signaling proteins. The VEGFR-2 TK protein was designed using homology to the PDGF RTK and comprises the intracellular domain of the receptor.[65] It was further truncated by the deletion of 50 amino acids of the 68-residue KID to yield a protein of approximately 36 kDa. Removal of this internal fragment does not significantly affect kinase activity of the final construct. Protein is expressed from a baculovirus vector. Cell pellets were lysed, and the soluble portion was purified to homogeneity by successive chromatography on (a) Q-30 anion-exchange column (Pharmacia, Piscataway, NJ), (b) hydroxyapatite column (Bio-Rad, Hercules, CA), (c) Q-15 anion-exchange column (Pharmacia), (d) HP-phenyl sepharose column (Pharmacia), and (e) G-25 column (Pharmacia).[70] Final material was aliquoted and flash-frozen in liquid N_2 and stored at −70 °C. Just before use, the protein was thawed on ice and autophosphorylated as described in the assay protocol.

Human FGFR1 Kinase Domain. A baculovirus was prepared that expressed the human FGFR1 cytoplasmic, kinase domain, amino acids 456−822, with an N-terminal Flag-tag.[71] This virus was used to infect either SF9 or Hi5 insect cells, and the infected cells were harvested 48−60 h after infection. After being harvested, the cells were washed with phosphate buffered saline and frozen at −70 °C until purification. The cells from a 1 L infected culture were thawed and resuspended in 20−30 mL of buffer A (25 mM Tris-Cl, pH 7.5, 5 mM EDTA, 0.1% (v/v) NP-40) and a protease inhibitor cocktail [Boehringer-Mannheim 1836170] at 4 °C. The resuspended cells were lysed on ice with 2 × 1 min pulses from a Branson model 250 sonicator at 70% duty, output 7. Debris was pelleted from the lysed cells by centrifugation at 4 °C in a Beckman SS-34 rotor at 11 000 rpm for 10 min. NaCl was added to the soluble protein to a final concentration of 0.15 M, 3−5 mL of M2 anti-Flag antibody resin (Sigma A1205) was added, and the suspension was mixed by inversion at 4 °C for 2−4 h. The mixture was centrifuged for 1−3 min at 4 °C at 1000*g*, and the supernatant was removed. The resin was washed once with 10 mL of buffer A + 0.15 M NaCl and five times with 10−20 mL of ice cold buffer B (50 mM Tris-Cl, pH 7.5, 150 mM NaCl). Each time, the resin was resuspended in the buffer by inversion of the tube and then centrifuged for 1−3 min at 4 °C at 1000*g* and the supernatant was removed. After the final wash, the resin was resuspended in ice cold buffer B and put into a (1 cm × 10 cm) Econo column (BioRad). The resin was further washed with buffer B until no protein could be detected in the eluate using the BioRad protein detection agent (20 μL of detection reagent + ∼100 μL of eluate). The Flag-tagged FGFR1 fusion protein was eluted from the column with 4 × 5 mL of ice cold buffer B containing 100 μg/mL of Flag peptide (Sigma F3290). The eluate was buffer-exchanged into 25 mM Hepes (or Tris-Cl), pH 7.5, 50

mM NaCl, 10% (v/v) glycerol using a PD-10 column (Amersham-Pharmacia) and concentrated using a Centriprep 30 concentration unit (Amicon). Final protein concentration was determined using the Pierce BCA protein assay (usually 0.3−1.0 mg/mL), and the protein was stored at −70 °C until needed.

Kinase Autophosphorylation. Kept to a final 20× concentration, kinase was incubated in 4 mM ATP and 25 mM $MgCl_2$ agitated at 4 °C for 45 min.

Reaction with Inhibitors. Kinase solution (40 nM) was prepared by diluting stock protein preparation (typically 1−0.3 mg/mL) in a final concentration of 20 mM $MgCl_2$, 20 mM Tris, 50 mM NaCl, 5 mM DTT, 10% (v/v) glycerol, 2 Complete Mini EDTA-free protease inhibitor cocktail tablets (Boehringer Mannheim, Indianapolis IN). ATP was likewise diluted to 66.6 μM. An amount of 50 μL of each was added per well, and the plate was allowed to incubate, with agitation, for 30 min at room temperature. Plates were washed four times with 300 μL 1× DELFIA wash reagent. To block nonspecific signaling, an amount of 150 μL of blocking buffer (0.5% (w/v) BSA in DELFIA assay buffer, Sigma and EG&G, respectively) was added per well and allowed to incubate, with agitation for 30 min. Washing was repeated. An amount of 100 μL of europium-conjugated antiphosphotyrosine antibody was added to each well at a dilution of 1:14386 (7 ng per well, equivalent to 0.07 μg/mL) and allowed to gently rock for 1 h. Because residual water interferes with signaling, plates were dried inverted for 30 min on paper toweling. An amount of 100 μL of Enhancement Solution (EG&G Wallac, Gaithersburg MD) was added and allowed to stand for 5 min. Plates were read in a VICTOR 1420 time-resolved fluorometer (EG&G Wallac, Inc).

IC_{50} Calculation Method. The value for percent of control (*% C*) for each inhibitor concentration was determined using the following relationship: *% C* = [(fluorescence of sample)/(value for fluorescence of uninhibited reaction)] × 100, where the value for the uninhibited reaction is equal to the average of eight reactions in column 12, which contains vehicle in place of inhibitor concentration. Compounds are tested using half-log dilutions from 10 through 0.0001 μM. IC_{50} values are calculated by least squares regression using the Hill equation where the limits are set from 0% *C* to 100% *C* and the slope and inflection point are varied for the best fit of all the points in the dose response curve to the kinetic model.

Acknowledgment. This work was partially supported by the Auckland Division of the Cancer Society of New Zealand.

Supporting Information Available: Tables of elemental analysis results, solubility data for selected compounds (**14**, **16**, **18**−**20**, **22**, **23**, **25**, **26**) as their HCl salts, and full experimental details (including ^1H and ^{13}C NMR data) for the synthesis of 3-(benzyloxy)-1-propanol, 4-(benzyloxy)-1-butanol, 5-(benzyloxy)-1-pentanol, benzyl 3-iodopropyl ether, benzyl 4-iodobutyl ether, benzyl 5-iodopentyl ether, 3-iodopropyl benzoate, and compounds **61**, **64**, **73**, and **97**−**101**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Gasparini G. The rationale and future potential of angiogenesis inhibitors in neoplasia. *Drugs* **1999**, *58*, 17−38.
(2) Brown, J. M.; Giaccia, A. J. The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. *Cancer Res.* **1998**, *58*, 1408−1416.
(3) Relf, M.; LeJeune, S.; Scott, P. A. E.; Fox, S.; Smith, K.; Leek, R.; Moghaddam, A.; Whitehouse, R.; Bicknell, R.; Harris, A. L. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor β-1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. *Cancer Res.* **1997**, *57*, 963−969.
(4) Campbell, S. C.; Volpert, O. V.; Ivanovich, M.; Bouck, N. P. Molecular mediators of angiogenesis in bladder cancer. *Cancer Res.* **1998**, *58*, 1298−1304.
(5) Kumar, R.; Kuniyasu, H.; Bucana, C. D.; Wilson, M. R.; Fidler, I. J. Spatial and temporal expression of angiogenic molecules during tumor growth and progression. *Oncol. Res.* **1998**, *10*, 301−311.
(6) Compagni, A.; Wilgenbus, P.; Impagnatiello, M.-A.; Cotten, M.; Christofori, G. Fibroblast growth factors are required for efficient tumor angiogenesis. *Cancer Res.* **2000**, *60*, 7163−7169.
(7) Friesel, R.; Maciag, T. Fibroblast growth factor prototype release and fibroblast growth factor receptor signaling. *Thromb. Haemostasis* **1999**, *82*, 748−754.
(8) Veikkola, T.; Karkkainen, M.; Claesson-Welsh, L.; Alitalo, K. Regulation of angiogenesis via vascular endothelial growth factor receptors. *Cancer Res.* **2000**, *60*, 203−212.
(9) Cross, M. J.; Dixelius, J.; Matsumoto, T.; Claesson-Welsh, L. VEGF-receptor signal transduction. *Trends Biochem. Sci.* **2003**, *28*, 488−494.
(10) Yoshimura, N.; Sano, H.; Hashiramoto, A.; Yamada, R.; Nakajima, H.; Kondo, M.; Oka, T. The expression and localization of fibroblast growth factor-1 (FGF-1) and FGF receptor-1 (FGFR-1) in human breast cancer. *Clin. Immunol. Immunopathol.* **1998**, *89*, 28−34.
(11) Giri, D.; Ropiquet, F.; Ittmann, M. Alterations in expression of basic fibroblast growth factor (FGF) 2 and its receptor FGFR-1 in human prostate cancer. *Clin. Cancer Res.* **1999**, *5*, 1063−1071.
(12) Wagner, M.; Lopez, M. E.; Cahn, M.; Korc, M. Suppression of fibroblast growth factor receptor signaling inhibits pancreatic cancer growth in vitro and in vivo. *Gastroenterology* **1998**, *114*, 798−807.
(13) Manabe, N.; Oda, H.; Nakamura, K.; Kuga, Y.; Uchida, S.; Kawaguchi, H. Involvement of fibroblast growth factor-2 in joint destruction of rheumatoid arthritis patients. *Rheumatology* **1999**, *38*, 714−720.
(14) Katinioti, A. A.; Tousoulis, D.; Economou, E.; Stefanadis, C.; Trikas, A.; Tentolouris, C.; Pitsavos, C.; Androulakis, A.; Toutouzas, P. Basic fibroblast growth factor changes in response to coronary angioplasty in patients with stable angina. *Int. J. Cardiol.* **2002**, *84*, 195−199.
(15) Guo, P.; Xu, L.; Pan, S.; Brekken, R. A.; Yang, S.-T.; Whitaker, G. B.; Nagane, M.; Thorpe, P. E.; Rosenbaum, J. S.; Huang, H.-J. S.; Cavenee, W. K.; Cheng, S.-Y. Vascular endothelial growth factor isoforms display distinct activities in promoting tumor angiogenesis at different anatomic sites. *Cancer Res.* **2001**, *61*, 8569−8577.
(16) Yoshiji, H.; Harris, S. R.; Thorgeirsson, U. P. Vascular endothelial growth factor is essential for initial but not continued in vivo growth of human breast carcinoma cells. *Cancer Res.* **1997**, *57*, 3924−3928.
(17) O'Brien, T.; Cranston, D.; Fuggle, S.; Bicknell, R.; Harris, A. L. Different angiogenic pathways characterize superficial and invasive bladder cancer. *Cancer Res.* **1995**, *55*, 510−513.
(18) Takahashi, Y.; Kitadai, Y.; Bucana, C. D.; Cleary, K. R.; Ellis, L. M. Expression of vascular endothelial growth factor and its receptor, KDR, correlates with vascularity, metastasis, and proliferation of human colon cancer. *Cancer Res.* **1995**, *55*, 3964−3968.
(19) Bellamy, W. T.; Richter, L.; Frutiger, Y.; Grogan, T. M. Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. *Cancer Res.* **1999**, *59*, 728−733.
(20) Prewett, M.; Huber, J.; Li, Y.; Santiago, A.; O'Conner, W.; King, K.; Overholser, J.; Hooper, A.; Pytowski, B.; Witte, L.; Bohlen, P.; Hicklin, D. J. Antivascular endothelial growth factor receptor (fetal liver kinase 1) monoclonal antibody inhibits tumor angiogenesis and growth of several mouse and human tumors. *Cancer Res.* **1999**, *59*, 5209−5218.
(21) Millauer, B.; Longhi, M. P.; Plate, K. H.; Shawver, L. K.; Risau, W.; Ullrich, A.; Strawn, L. M. Dominant-negative inhibition of Flk-1 suppresses the growth of many tumor types in vivo. *Cancer Res.* **1996**, *56*, 1615−1620.
(22) Shawver, L. K.; Lipson, K. E.; Fong, T. A. T.; McMahon, G.; Plowman, G. D.; Strawn, L. M. Receptor tyrosine kinases as targets for inhibition of angiogenesis. *Drug Discovery Today* **1997**, *2*, 50−63.
(23) Manley, P. W.; Bold, G.; Bruggen, J.; Fendrich, G.; Furet, P.; Mestan, J.; Schnell, C.; Stolz, B.; Meyer, T.; Meyhack, B.; Stark, W.; Strauss, A.; Wood, J. Advances in the structural biology, design and clinical development of VEGF-R kinase inhibitors for the treatment of angiogenesis. *Biochim. Biophys. Acta* **2004**, *1697*, 17−27.
(24) Zhu, Z.; Bohlen, P.; Witte, L. Clinical development of angiogenesis inhibitors to vascular endothelial growth factor and its receptors as cancer therapeutics. *Curr. Cancer Drug Targets* **2002**, *2*, 135−156.
(25) Fong, T. A. T.; Shawver, L. K.; Sun, L.; Tang, C.; App, H.; Powell, T. J.; Kim, Y. H.; Schreck, R.; Wang, X.; Risau, W.; Ullrich, A.; Hirth, K. P.; McMahon, G. SU5416 is a potent and selective inhibitor of the vascular endothelial growth factor receptor (Flk-1/KDR) that inhibits tyrosine kinase catalysis, tumor vascularization, and growth of multiple tumor types. *Cancer Res.* **1999**, *59*, 99−106.
(26) Laird, A. D.; Vajkoczy, P.; Shawver, L. K.; Thurnher, A.; Liang, C.; Mohammadi, M.; Schlessinger, J.; Ullrich, A.; Hubbard, S. R.; Blake, R. A.; Fong, T. A. T.; Strawn, L. M.; Sun, L.; Tang,

C.; Hawtin, R.; Tang, F.; Shenoy, N.; Hirth, K. P.; McMahon, G.; Cherrington, J. M. SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors. *Cancer Res.* **2000**, *60*, 4152−4160.

(27) Fiedler, W.; Mesters, R.; Tinnefeld, H.; Loges, S.; Staib, P.; Duehrsen, U.; Flasshove, M.; Ottmann, O. G.; Jung, W.; Cavalli, F.; Kuse, R.; Thomalla, J.; Serve, H.; O'Farrell, A. M.; Jacobs, M.; Brega, N. M.; Scigalla, P.; Hossfeld, D. K.; Berdel, W. E. A phase 2 clinical study of SU5416 in patients with refractory acute myeloid leukemia. *Blood* **2003**, *102*, 2763−2767.

(28) Kuenen, B. C.; Tabernero, J.; Baselga, J.; Cavalli, F.; Pfanner, E.; Conte, P. F.; Seeber, S.; Madhusudan, S.; Deplanque, G.; Huisman, H.; Scigalla, P.; Hoekman, K.; Harris, A. L. Efficacy and toxicity of the angiogenesis inhibitor SU5416 as a single agent in patients with advanced renal cell carcinoma, melanoma, and soft tissue sarcoma. *Clin. Cancer Res*. **2003**, *9*, 1648−1655.

(29) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J.-Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. *J. Med. Chem.* **2003**, *46*, 1116−1119.

(30) Mendel, D. B.; Laird, A. D.; Xin, X.; Louie, S. G.; Christensen, J. G.; Li, G.; Schreck, R. E.; Abrams, T. J.; Ngai, T. J.; Lee, L. B.; Murray, L. J.; Carver, J.; Chan, E.; Moss, K. G.; Haznedar, J. O.; Sukbuntherng, J.; Blake, R. A.; Sun, L.; Tang, C.; Miller, T.; Shirazian, S.; McMahon, G.; Cherrington, J. M. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin. Cancer Res*. **2003**, *9*, 327−337.

(31) Wedge, S. R.; Ogilvie, D. J.; Dukes, M.; Kendrew, J.; Chester, R.; Jackson, J. A.; Boffey, S. J.; Valentine, P. J.; Curwen, J. O.; Musgrove, H. L.; Graham, G. A.; Hughes, G. D.; Thomas, A. P.; Stokes, E. S. E.; Curry, B.; Richmond, G. H. P.; Wadsworth, P. F.; Bigley, A. L.; Hennequin, L. F. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res.* **2002**, *62*, 4645−4655.

(32) Bold, G.; Altmann, K.-H.; Frei, J.; Lang, M.; Manley, P. W.; Traxler, P.; Wietfeld, B.; Bruggen, J.; Buchdunger, E.; Cozens, R.; Ferrari, S.; Furet, P.; Hofmann, F.; Martiny-Baron, G.; Mestan, J.; Rosel, J.; Sills, M.; Stover, D.; Acemoglu, F.; Boss, E.; Emmenegger, R.; Laesser, L.; Masso, E.; Roth, R.; Schlachter, C.; Vetterli, W.; Wyss, D.; Wood, J. M. New anilinophthalazines as potent and orally well absorbed inhibitors of the VEGF receptor tyrosine kinases useful as antagonists of tumor-driven angiogenesis. *J. Med. Chem.* **2000**, *43*, 2310−2323.

(33) Thomas, A. L.; Morgan, B.; Drevs, J.; Unger, C.; Wiedenmann, B.; Vanhoefer, U.; Laurent, D.; Dugan, M.; Steward, W. P. Vascular endothelial growth factor receptor tyrosine kinase inhibitors: PTK787/ZK 222584. *Semin. Oncol*. **2003**, *30* (3, Suppl. 6), 32−38.

(34) Beebe, J. S.; Jani, J. P.; Knauth, E.; Goodwin, P.; Higdon, C.; Rossi, A. M.; Emerson, E.; Finkelstein, M.; Floyd, E.; Harriman, S.; Atherton, J.; Hillerman, S.; Soderstrom, C.; Kou, K.; Gant, T.; Noe, M. C.; Foster, B.; Rastinejad, F.; Marx, M. A.; Schaeffer, T.; Whalen, P. M.; Roberts, W. G. Pharmacological characterization of CP-547,632, a novel vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for cancer therapy. *Cancer Res*. **2003**, *63*, 7301−7309.

(35) Gingrich, D. E.; Reddy, D. R.; Iqbal, M. A.; Singh, J.; Aimone, L. D.; Angeles, T. S.; Albom, M.; Yang, S.; Ator, M. A.; Meyer, S. L.; Robinson, C.; Ruggeri, B. A.; Dionne, C. A.; Vaught, J. L.; Mallamo, J. P.; Hudkins, R. L. A new class of potent vascular endothelial growth factor receptor tyrosine kinase inhibitors: structure−activity relationships for a series of 9-alkoxymethyl-12-(3-hydroxypropyl)indeno[2,1-*a*]pyrrolo[3,4-*c*]carbazole-5-ones and the identification of CEP-5214 and its dimethylglycine ester prodrug clinical candidate CEP-7055. *J. Med. Chem*. **2003**, *46*, 5375−5388.

(36) Ruggeri, B.; Singh, J.; Gingrich, D.; Angeles, T.; Albom, M.; Chang, H.; Robinson, C.; Hunter, K.; Dobrzanski, P.; Jones-Bolin, S.; Aimone, L.; Klein-Szanto, A.; Herbert, J.-M.; Bono, F.; Schaeffer, P.; Casellas, P.; Bourie, B.; Pili, R.; Isaacs, J.; Ator, M.; Hudkins, R.; Vaught, J.; Mallamo, J.; Dionne, C. CEP-7055: a novel, orally active pan inhibitor of vascular endothelial growth factor receptor tyrosine kinases with potent antiangiogenic activity and antitumor efficacy in preclinical models. *Cancer Res*. **2003**, *63*, 5978−5991.

(37) Hamby, J. M.; Connolly, C. J. C.; Schroeder, M. C.; Winters, R. T.; Showalter, H. D. H.; Panek, R. L.; Major, T. C.; Olsewski, B.; Ryan, M. J.; Dahring, T.; Lu, G. H.; Keiser, J.; Amar, A.; Shen, C.; Kraker, A. J.; Slintak, V.; Nelson, J. M.; Fry, D. W.; Bradford, L.; Hallak, H.; Doherty, A. M. Structure−activity relationships for a novel series of pyrido[2,3-*d*]pyrimidine tyrosine kinase inhibitors. *J. Med. Chem*. **1997**, *40*, 2296−2303.

(38) Panek, R. L.; Lu, G. H.; Dahring, T. K.; Batley, B. L.; Connolly, C.; Hamby, J. M.; Brown, K. J. In vitro biological characterization and antiangiogenic effects of PD 166866, a selective inhibitor of the FGF-1 receptor tyrosine kinase. *J. Pharmacol. Exp. Ther*. **1998**, *286*, 569−577.

(39) Dimitroff, C. J.; Klohs, W.; Sharma, A.; Pera, P.; Driscoll, D.; Veith, J.; Steinkampf, R.; Schroeder, M.; Klutchko, S.; Sumlin, A.; Henderson, B.; Dougherty, T. J.; Bernacki, R. J. Anti-angiogenic activity of selected tyrosine kinase inhibitors, PD166285 and PD173074: implications for combination treatment with photodynamic therapy. *Invest. New Drugs* **1999**, *17*, 121−135.

(40) Mohammadi, M.; Froum, S.; Hamby, J. M.; Schroeder, M. C.; Panek, R. L.; Lu, G. H.; Eliseenkova, A. V.; Green, D.; Schlessinger, J.; Hubbard, S. R. Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain. *EMBO J*. **1998**, *17*, 5896−5904.

(41) Thompson, A. M.; Connolly, C. J. C.; Hamby, J. M.; Boushelle, S.; Hartl, B. G.; Amar, A. M.; Kraker, A. J.; Driscoll, D. L.; Steinkampf, R. W.; Patmore, S. J.; Vincent, P. W.; Roberts, B. J.; Elliott, W. L.; Klohs, W.; Leopold, W. R.; Showalter, H. D. H.; Denny, W. A. 3-(3,5-Dimethoxyphenyl)-1,6-naphthyridine-2,7-diamines and related 2-urea derivatives are potent and selective inhibitors of the FGF receptor-1 tyrosine kinase. *J. Med. Chem*. **2000**, *43*, 4200−4211.

(42) Thompson, A. M.; Showalter, H. D. H.; Denny, W. A. Synthesis of 7-substituted 3-aryl-1,6-naphthyridin-2-amines and 7-substituted 3-aryl-1,6-naphthyridin-2(1*H*)-ones via diazotization of 3-aryl-1,6-naphthyridine-2,7-diamines. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1843−1852.

(43) Singerman, G. M.; Kimura, R.; Riebsomer, J. L.; Castle, R. N. Synthesis of alkylaminoethanethiolsulfuric acids substituted with heterocyclic moieties. *J. Heterocycl. Chem.* **1966**, *3*, 74−78.

(44) Watanabe, M.; Soai, K. Enantioselective addition of diethylzinc to aldehydes using chiral polymer catalysts possessing a methylene spacer. *J. Chem. Soc., Perkin Trans. 1* **1994**, 837−842.

(45) Sargent, M. V.; Wangchareontrakul, S. Synthesis of the cyclophane tetramethoxyturriane: a derivative of the phenolic cyclophanes of *Grevillea striata* R. Br. *J. Chem. Soc., Perkin Trans. 1* **1990**, 129−132.

(46) Genzer, J. D.; Huttrer, C. P.; v. Wessem, G. C. Phenoxy- and benzyloxyalkyl thiocyanates. *J. Am. Chem. Soc.* **1951**, *73*, 3159−3162.

(47) Sheehan, M.; Spangler, R. J.; Djerassi, C. Mass spectrometry in structural and stereochemical problems. CCIX. Functional group interaction after electron impact. Anomalous ether cleavage in bifunctional benzyloxy ethers. *J. Org. Chem.* **1971**, *36*, 3526−3532.

(48) Borjesson, L.; Csoregh, I.; Welch, C. J. Synthesis and conformational analysis of 2,9-disubstituted 1-oxaquinolizidines. *J. Org. Chem*. **1995**, *60*, 2989−2999.

(49) Garegg, P. J.; Samuelsson, B. Novel reagent system for converting a hydroxy-group into an iodo-group in carbohydrates with inversion of configuration. Part 2. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866−2869.

(50) Armarego, W. L. F. Naphthyridines. Part III. Tetrahydro- and decahydro-1,5-, -1,6-, -1,7-, and -1,8-naphthyridines. *J. Chem Soc*. **1967**, 377−383.

(51) Ikemoto, N.; Schreiber, S. L. Total synthesis of (−)-hikizimycin employing the strategy of two-directional chain synthesis. *J. Am. Chem. Soc.* **1992**, *114*, 2524−2536.

(52) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; J. Wiley & Sons: New York, 1978; pp 156−164.

(53) Slotta, K. H.; Behnisch, R. Hydrocupreine aminoalkyl ethers. *Chem. Ber.* **1935**, *68B*, 754−761.

(54) v. Braun, J. Knowledge about aliphatic dihalogenated compounds. *Chem. Ber.* **1913**, *46*, 1782−1792.

(55) Yamaguchi, M.; Takata, T.; Endo, T. Oxidation of *ω*-(benzoyloxy)-alkanols with an oxoaminium salt. *J. Org. Chem.* **1990**, *55*, 1490−1492.

(56) Park, M. H.; Takeda, R.; Nakanishi, K. Microscale cleavage reaction of (phenyl)benzyl ethers by ferric chloride. *Tetrahedron Lett.* **1987**, *28*, 3823−3824.

(57) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. Hard acid and soft nucleophile system. New efficient method for removal of benzyl protecting group. *J. Org. Chem.* **1979**, *44*, 1661−1664.

(58) Cossy, J.; Bouzbouz, S.; Lachgar, M.; Hakiki, A.; Tabyaoui, B. Specific oxidative cleavage of allylic and benzylic benzyl ethers by using pyridinium chlorochromate. *Tetrahedron Lett.* **1998**, *39*, 2561−2564.

(59) Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. A facile method for the oxidative removal of benzyl ethers: the oxidation of benzyl ethers to benzoates by ruthenium tetraoxide. *Tetrahedron Lett.* **1983**, *24*, 3829−3830.
(60) Walker, D.; Hiebert, J. D. 2,3-Dichloro-5,6-dicyanobenzoquinone and its reactions. *Chem. Rev.* **1967**, *67*, 153−195.
(61) Blankley, C. J.; Doherty, A. M.; Hamby, J. M.; Panek, R. L.; Schroeder, M. C.; Showalter, H. D. H.; Connolly, C. 6-Aryl pyrido[2,3-*d*]pyrimidines and naphthyridines for inhibiting protein tyrosine kinase mediated cellular proliferation. U.S. Patent 5,733,913, March 31, 1998.
(62) Barvian, M.; Boschelli, D. H.; Cossrow, J.; Dobrusin, E.; Fattaey, A.; Fritsch, A.; Fry, D.; Harvey, P.; Keller, P.; Garrett, M.; La, F.; Leopold, W.; McNamara, D.; Quin, M.; Trumpp-Kallmeyer, S.; Toogood, P.; Wu, Z.; Zhang, E. Pyrido[2,3-*d*]pyrimidin-7-one inhibitors of cyclin-dependent kinases. *J. Med. Chem.* **2000**, *43*, 4606−4616.
(63) Palmer, B. D.; Rewcastle, G. W.; Thompson, A. M.; Boyd, M.; Showalter, H. D. H.; Sercel, A. D.; Fry, D. W.; Kraker, A. J.; Denny, W. A. Tyrosine kinase inhibitors. 4. Structure−activity relationships among *N*- and 3-substituted 2,2′-dithiobis(1*H*-indoles) for in vitro inhibition of receptor and nonreceptor protein tyrosine kinases. *J. Med. Chem.* **1995**, *38*, 58−67.
(64) Dahring, T. K.; Lu, G. H.; Hamby, J. M.; Batley, B. L.; Kraker, A. J.; Panek, R. L. Inhibition of growth factor-mediated tyrosine phosphorylation in vascular smooth muscle by PD 089828, a new synthetic protein tyrosine kinase inhibitor. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1446−1456.
(65) McTigue, M. A.; Wickersham, J. A.; Pinko, C.; Showalter, R. E.; Parast, C. V.; Tempczyk-Russell, A.; Gehring, M. R.; Mroczkowski, B.; Kan, C.-C.; Villafranca, J. E.; Appelt, K. Crystal structure of the kinase domain of human vascular endothelial growth factor receptor 2: a key enzyme in angiogenesis. *Structure* **1999**, *7*, 319−330.
(66) Thompson, A. M.; Rewcastle, G. W.; Boushelle, S. L.; Hartl, B. G.; Kraker, A. J.; Lu, G. H.; Batley, B. L.; Panek, R. L.; Showalter, H. D. H.; Denny, W. A. 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}. *J. Med. Chem.* **2000**, *43*, 3134−3147.
(67) Trumpp-Kallmeyer, S.; Rubin, J. R.; Humblet, C.; Hamby, J. M.; Showalter, H. D. H. Development of a binding model to protein tyrosine kinases for substituted pyrido[2,3-*d*]pyrimidine inhibitors. *J. Med. Chem.* **1998**, *41*, 1752−1763.
(68) Garfinkel, S.; Hu, X.; Prudovsky, I. A.; McMahon, G. A.; Kapnik, E. M.; McDowell, S. D.; Maciag, T. FGF-1-dependent proliferative and migratory responses are impaired in senescent human umbilical vein endothelial cells and correlate with the inability to signal tyrosine phosphorylation of fibroblast growth factor receptor-1 substrates. *J. Cell Biol.* **1996**, *134*, 783−791.
(69) Baumgarten, H. E.; Chen, P. Y.-N.; Taylor, H. W.; Hwang, D.-R. Reactions of amines. 20. Syntheses of racemic and optically active alkylhydrazines and *N*-acyl-*N*-alkyl and *N*-acyl-*N*-arylhydrazines. *J. Org. Chem.* **1976**, *41*, 3805−3811.
(70) Parast, C. V.; Mroczkowski, B.; Pinko, C.; Misialek, S.; Khambatta, G.; Appelt, K. Characterization and kinetic mechanism of catalytic domain of human vascular endothelial growth factor receptor-2 tyrosine kinase (VEGFR2 TK), a key enzyme in angiogenesis. *Biochemistry* **1998**, *37*, 16788−16801.
(71) Dionne, C. A.; Crumley, G.; Bellot, F.; Kaplow, J. M.; Searfoss, G.; Ruta, M.; Burgess, W. H.; Jaye, M.; Schlessinger, J. Cloning and expression of two distinct high-affinity receptors cross-reacting with acidic and basic fibroblast growth factors. *EMBO J.* **1990**, *9*, 2685−2692.

JM0500931