PERKIN 1

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

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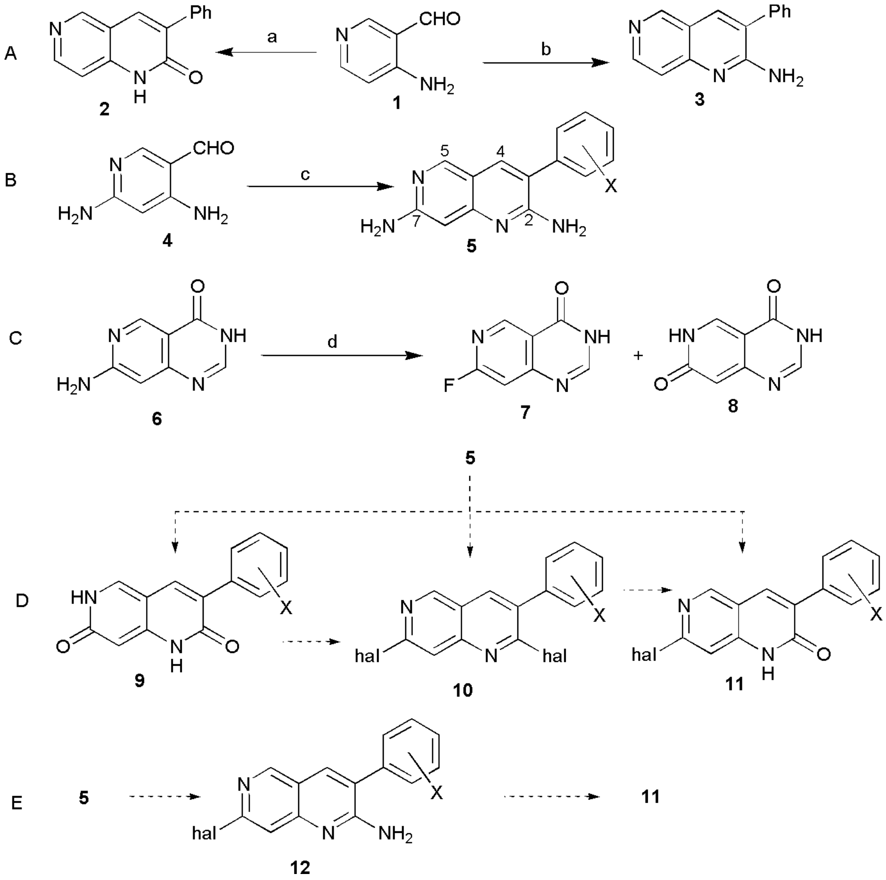
Received (in Cambridge, UK) 3rd April 2000, Accepted 14th April 2000
Published on the Web 1st June 2000

The preparation of 3-aryl-7-halo-1,6-naphthyridin-2-amines and 3-aryl-7-halo-1,6-naphthyridin-2(1*H*)-ones from the diazotization of 3-aryl-1,6-naphthyridine-2,7-diamines is reported. The reactions were investigated in various solvents (concentrated HCl, 50% HBF_4, 70% HF–pyridine, 20% and 90% H_2SO_4, dilute HCl, and neat TFA). By appropriate choice of solvent and other conditions, good yields of the target compounds could be obtained, although in some cases a variety of different side products was also produced. Subsequent displacement of the 7-halogen substituents with alkylamines provides a route to more complex 7-substituted 1,6-naphthyridine derivatives that are potential tyrosine kinase inhibitors.

Introduction

In current work we required 3-aryl-7-halo-1,6-naphthyridin-2(1*H*)-ones **11** and 3-aryl-7-halo-1,6-naphthyridin-2-amines **12** as intermediates for the synthesis of various 7-substituted alkylamino analogues as potential inhibitors of tyrosine kinase enzymes.[1,2] The synthesis of (3-substituted) 1,6-naphthyridin-2(1*H*)-ones commonly involves the condensation of 4-aminonicotinaldehyde **1** with substituted ethyl acetates, malonates or malonamides.[3,4] However, 3-phenyl-1,6-naphthyridin-2(1*H*)-



Scheme 1 Literature background and proposed routes to 1,6-naphthyridine derivatives. *Reagents and conditions*: a, $PhCH_2CO_2Et$–piperidine–EtOH (ref. 4); b, $PhCH_2CN$–NaOH–EtOH–water (ref. 5); c, $XPhCH_2CN$–Na–2-ethoxyethanol (ref. 6); d, $NaNO_2$–50% HBF_4 (ref. 15).

DOI: 10.1039/b002599m

Table 1 Results for the diazotization–fluorodediazoniation of **5b** using either the modified Schiemann method, 'A' ($NaNO_2$ in 50% HBF_4) or Fukuhara's method, 'B' ($NaNO_2$ in 70% HF–pyridine)

Method	Scale (Mass **5b**/g)	Equiv. $NaNO_2$	Reaction conditions	Products and yields (%)
A	0.25	8	4 h/0 °C, 2 d/−20 °C	**18** (42), **14b** (34), **19** (10), **20** (3)
A	1.0	8	5 h/0 °C, 4 d/−20 °C	**18** (25), **14b** (37), **19** (30), **20** (5)
A	1.55	8	5 h/−5 °C, 5 d/−20 °C	**19** (58), **20** (29)
A	4.0	8	8 h/−5 °C, 6 d/−20 °C	**19** (54), **20** (26)
A	2.0	1.6	4 h/−5 °C, 5 d/−20 °C	**18** (55), **14b** (33)
B	0.25	8 then 16	0.5 h/0 °C, 1 h/20 °C, 6 d/−20 °C, then 1 h/0 °C, 6 h/20 °C, 3 d/−20 °C	**18** (42), **19** (36), **23** (0.4), **24** (0.4), **25** (0.2)
B	0.10	1.7 then 0.5	0.5 h/0 °C, 1 h/20 °C, then 1 h/20 °C	**18** (75)

one **2** was reported to be formed in very poor yield (21%) despite reaction for several days[4] (Scheme 1A), suggesting that this was not a viable general route to the more complex compounds **11**. Related (3-substituted) 1,6-naphthyridin-2-amines have been similarly prepared by the condensation of **1** with variously substituted acetonitriles; in this case 3-phenyl-1,6-naphthyridin-2-amine **3** was reported to be formed readily and in high yield (68%) by the condensation of **1** with phenylacetonitrile[5] (Scheme 1A). In a similar fashion, a small series of 3-(substituted phenyl)-1,6-naphthyridine-2,7-diamines **5** was prepared[6] in good yield from 4,6-diaminonicotinaldehyde **4** (Scheme 1B). However, compounds **12** were not directly available by this methodology because of the difficulty in preparing the appropriate 4-amino-6-halonicotinaldehydes, and because of the expected reactivity of the displaceable halogen substituent during the base catalysed condensation reaction.

There have been several reports[7–11] of the facile and high yielding preparation of 1,8-naphthyridin-2(1*H*)-ones (including 3-phenyl analogues) by diazotization of the corresponding 2-amino derivatives in 2 M HCl, concentrated H_2SO_4, 40% H_2SO_4 and TFA. The preparation of 2-halopyridines by the diazotization–halodediazoniation of 2-aminopyridines is also well established.[12–14] For example, we have recently employed a modified Schiemann method[14] ($NaNO_2$–50% HBF_4) to diazotize 7-aminopyrido[4,3-*d*]pyrimidin-4(3*H*)-one **6** to a 3 : 2 mixture of 7-fluoro- and 7(6*H*)-one derivatives (**7** and **8**)[15] (Scheme 1C). We therefore envisaged that *double* diazotization of 3-(substituted phenyl)-1,6-naphthyridine-2,7-diamines **5** would enable the preparation of key 2,7-dihalo derivatives **10**, either directly, or indirectly *via* the halogenation of 1,6-naphthyridine-2,7(1*H*,6*H*)-diones **9**, as reported[8] in the 1,8-naphthyridine series (Scheme 1D). We expected that the two halogen substituents in **10** would display quite different reactivities toward nucleophiles (or hydrolysis to give **11**) on the basis of our experiences with amine displacements in isomeric fluoropyrido[*d*]pyrimidines[15] and the results of Chapman and Russell-Hill,[16] who reported that the chloro substituents of 2-chloroquinoline and 3-chloroisoquinoline differed markedly in reaction rate toward displacement by ethoxide (a factor of 5×10^4), with 3-chloroisoquinoline being virtually unactivated. Alternatively, a selective diazotization–halodediazoniation of the 7-amino group would enable direct preparation of the desired 3-aryl-7-halo-1,6-naphthyridin-2-amines **12**, and thus a potential two step synthesis of the 3-aryl-7-halo-1,6-naphthyridin-2(1*H*)-ones **11** (Scheme 1E).

We report here studies on the diazotization of various 3-(substituted phenyl)-1,6-naphthyridine-2,7-diamines **5** using a range of solvents and conditions, and discuss the varying reactivities of the halogen substituted products towards amine displacement.

Results and discussion

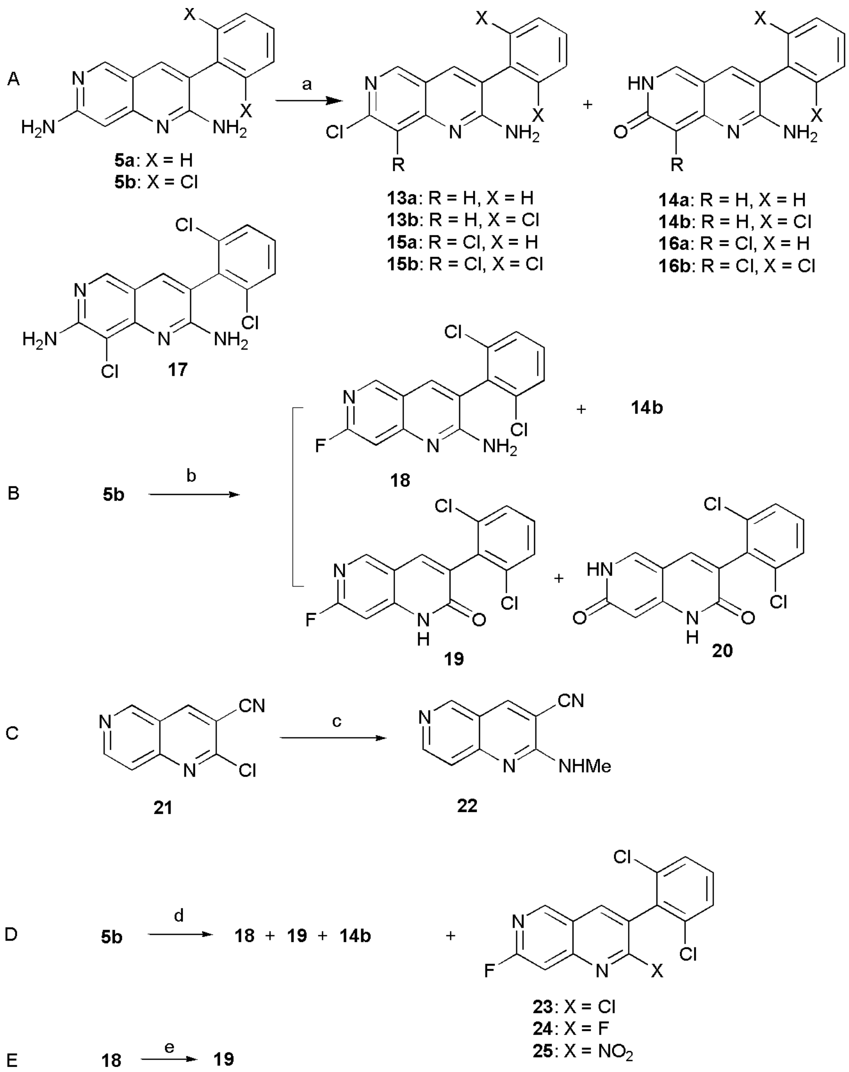
The required 3-(substituted phenyl)-1,6-naphthyridine-2,7-diamines **5** were prepared in excellent yield by the condensation of the known[1,6] 4,6-diaminonicotinaldehyde **4** (from Raney nickel reduction of 4,6-diaminonicotinonitrile[17]) with substituted phenylacetonitriles in boiling 2-ethoxyethanol in the presence of the sodium alkoxide (Scheme 1B), as described previously.[6,18]

Reaction of 3-phenyl-1,6-naphthyridine-2,7-diamine **5a** in concentrated HCl (HCl saturated) with a large excess of solid $NaNO_2$ (8 equivalents) at −10 to +20 °C, gave a readily separable mixture of mostly 7-chloro-3-phenyl-1,6-naphthyridin-2-amine **13a** (61%) and 2-amino-3-phenyl-1,6-naphthyridin-7(6*H*)-one **14a** (19%). However, minor amounts of **15a** and **16a**, resulting from ring chlorination at C-8, were also obtained (1 and 5%, respectively) (Scheme 2A). The 2-amino group appeared essentially inert under these conditions, despite the large excess of reagent, enabling selective diazotization of the 7-amine. This large differential in reactivity was ascribed to the steric hindrance of the 2-amine by the neighbouring 3-phenyl group. Reaction of 3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7-diamine **5b** under the same conditions gave analogous results (compounds **13b**–**16b**), but with slightly lower yields, along with small amounts of recovered starting material and its 8-chloro derivative **17**. Thus the direct preparation of a 2,7-dichloro derivative **10** (X = H or 2,6-diCl, hal = Cl) was not feasible under these conditions.

Diamine **5a** was then treated with a large excess of solid $NaNO_2$ in 90% H_2SO_4, in an attempt to prepare the dione **9** (X = H) for potential conversion to the corresponding 2,7-dihalo derivative **10** (X = H). However, a complex mixture resulted, in which **14a** could be detected but not separated. Similar results were obtained with analogous reactions in dilute HCl, 20% H_2SO_4, and neat TFA, indicating the unsuitability of this approach.

The observed byproducts in the diazotization of **5a** and **5b** in concentrated HCl, together with the desire for a more easily displaced halogen substituent than chlorine, led us to examine the modified Schiemann method.[14] The results of various reactions of **5b** with $NaNO_2$ in 50% HBF_4 are summarized in Table 1 and Scheme 2B. An initial small scale reaction (0.25 g) with excess $NaNO_2$ (Table 1, entry 1) gave mainly 3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2-amine **18** (42% yield) and 2-amino-3-(2,6-dichlorophenyl)-1,6-naphthyridin-7(6*H*)-one **14b** (34% yield), similar to the results above using HCl. However, when the scale of the reaction was increased (keeping concentrations the same) and the reaction mixture was left for longer times at −20 °C prior to workup, increasing amounts of 3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2(1*H*)-one **19** and 3-(2,6-dichlorophenyl)-1,6-naphthyridin-2,7(1*H*,6*H*)-dione **20** were formed, and were the eventual sole reaction products (54–58% and 26–29% yields respectively; Table 1, entries 3 and 4).

The formation of **19** but not the 2,7-difluoro derivative **24** under these conditions suggests that the initially formed 2-fluorine substituent is very reactive, hydrolysing *in situ* during the reaction and/or subsequent workup (although some **19** could also arise from **18** by direct hydrolysis of the 2-diazonium salt). This is consistent with the results of Hawes and Gorecki,[3] who found that the chlorine of 2-chloro-3-cyano-1,6-naph-



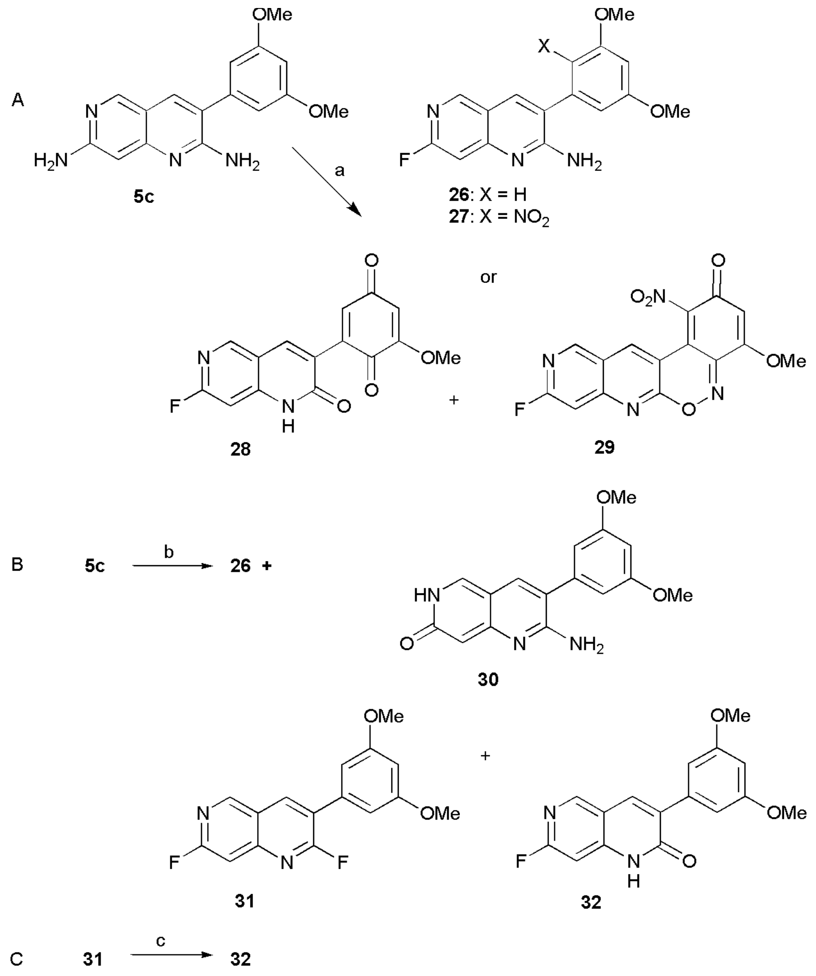
Scheme 2 *Reagents and conditions*: a, $NaNO_2$–conc. HCl; b, $NaNO_2$–50% HBF_4; c, $MeNH_2$-2-PrOH (ref. 3); d, $NaNO_2$–70% HF–pyridine; e, $NaNO_2$–TFA.

thyridine **21** was easily displaced by nucleophiles (*e.g.*, $MeNH_2$, 1 h at 20 °C to give **22**, Scheme 2C), and a fluorine substituent should be even more reactive. Preliminary attempts to activate **20** to the 2,7-dichloro derivative **10** (X = 2,6-diCl, hal = Cl) using $POCl_3$ or $SOCl_2$ were unsuccessful, although the method used by Hawes and Gorecki[3] in the preparation of **21** (PCl_5–$POCl_3$) from the corresponding 1,6-naphthyridin-2(1*H*)-one was not examined. The best conditions found for the preparation of **18** (55% yield) using the modified Schiemann method (Table 1, entry 5) involved the diazotization of **5b** with a small excess (1.6 equivalents) of $NaNO_2$ in 50% HBF_4 (with 1.1 equivalents of $NaNO_2$, unreacted **5b** could still be detected by TLC after 3 days at −20 °C). However, it should be noted that the reaction times employed here were not optimized, and with more careful monitoring it may be possible to reduce these considerably.

The above methodology was not suitable for elaboration of the corresponding 3-(3,5-dimethoxyphenyl)-1,6-naphthyridine-2,7-diamine **5c**, which contained a more electron-rich phenyl ring. Reaction of **5c** in 50% HBF_4 with varying stoichiometries of $NaNO_2$ gave only complex mixtures of products, many of which were unstable. From a reaction employing 1.5 equivalents of $NaNO_2$, two products were isolated in very low yield (each *ca.* 3%) following extensive chromatography (Scheme 3A). The less polar compound was the desired 3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2-amine **26** by HREIMS and ^1H NMR. The more polar compound **27** was the 2′-nitro derivative of **26**, resulting from nitrosation of the electron-rich 3,5-dimethoxyphenyl ring, followed by aerial oxidation. A larger scale reaction using 8 equivalents of $NaNO_2$ gave small amounts of only two isolable products (each 4% yield), the quinone derivative **28** and a compound which is probably (based on NMR, HREIMS and analytical data) the quinone imine derivative **29** (Scheme 3A). Compound **28** could arise from **26** by diazotization–hydrolysis at C-2, nitrosation at C-2′, demethylation of the 5′-methoxy group, and oxidation/hydrolysis. Similarly, compound **29** could arise from nitrosation (twice), demethylation of one methoxy group, (partial) oxidation and O-coupling of one NO group at C-2, either by displacement of a 2-fluorine substituent or a 2-diazonium salt. Reaction of **5c** with excess $NaNO_2$ in concentrated HCl also gave a complex mixture of products.

Recently it has been demonstrated that fluoropyridines can be prepared in considerably higher yields by diazotization–fluorodediazoniation of the amino derivative in HF–pyridine.[19] This is likely to be due at least in part to the more anhydrous nature of this solvent system (which reduces the proportion of hydrolysis), since recycling the HF–pyridine reportedly lowered its activity, due to increased water content from the diazotization and consumption of HF.[20] We expected that these conditions offered the best possibility for the isolation of the 2,7-difluoro derivative **24** from **5b**, as well as for the formation of **18** and/or **19** in higher yield.

Reaction of **5b** with a large excess of $NaNO_2$ in 65–70% HF–pyridine (monitored by TLC) gave rapid formation of **18** (complete after 1 h at 20 °C), then very slow further conversion to **19**

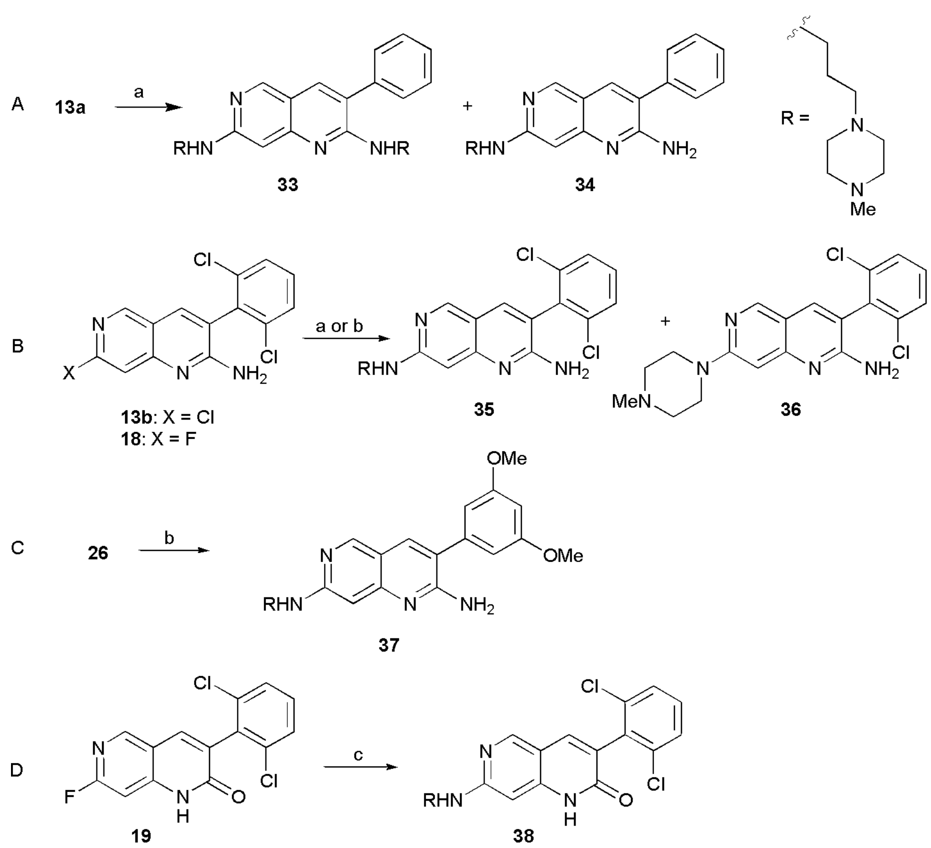


Scheme 3 *Reagents and conditions*: a, $NaNO_2$–50% HBF_4; b, $NaNO_2$–70% HF–pyridine, pyridine; c, NaOH–water–THF, 53 °C, 3 days.

(Table 1, entry 6) which, on a small scale (0.25 g), could not be forced to completion. Separation of the major products gave **18** (42%) and **19** (36%), along with a mixture of three less polar components (2.5 mg) which were further separated by preparative TLC. The least polar of these (Scheme 2D) was 2-chloro-3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridine **23** (0.4%), as shown by HREIMS and ^1H NMR, and may have arisen from displacement of the 2-fluorine of **24** by adventitious chloride ion, due to possible salt contamination of the salt–ice cooled reaction solution just prior to or during workup. The second component was the desired 3-(2,6-dichlorophenyl)-2,7-difluoro-1,6-naphthyridine **24** (0.4%), identified by the characteristically large *meta* HF coupling to H-4 in the ^1H NMR (9.8 Hz) and by HREIMS. The most polar component was 3-(2,6-dichlorophenyl)-7-fluoro-2-nitro-1,6-naphthyridine **25** (0.2%), identified by HREIMS (showing characteristic loss of NO_2 and NO from the parent ion) and the strongly downfield ^1H NMR resonances for H-4, 5 and 8 (0.2–0.3 ppm further downfield than observed for **24**). This compound is probably formed by direct displacement of the diazonium salt (or possibly the 2-fluorine) by nitrite ion (present in a very large excess). Overall, the yield of fluorinated products was much higher with HF–pyridine than aqueous HBF_4, and neutralization of the final product solution was also easier in this system.

The 2,7-difluoro compound **24** was stable in neutral aqueous MeOH (20 °C, 1 h) and (aqueous) DMSO (20 °C, several hours). Therefore the low yield of **24** from the above reaction, relative to the amount of the hydrolysis product **19** observed, is probably due simply to the general acid catalysis of nucleophilic displacements from basic heterocyclic systems as previously reported.[16,21] Protonation of N-1 could cause behaviour more similar to that of α-halo quaternary quinolinium salts, which are known to be many orders of magnitude more reactive towards nucleophilic displacement than the corresponding α-halo quinolines.[22] An improved yield of **18** (75%) was obtained on a small scale by the diazotization of **5b** with a small excess (2.2 equivalents) of $NaNO_2$ in 65–70% HF–pyridine (Table 1, entry 7) (with 1.7 equivalents of $NaNO_2$, unreacted **5b** could still be detected by TLC after 1 h at 20 °C). We then examined the further diazotization of **18** to **19** under alternative reaction conditions (for comparison with the modified Schiemann method). Surprisingly, diazotization of **18** with $NaNO_2$ in neat TFA[10] (2.5 h at 20 °C) gave an almost quantitative conversion to **19** (96%) on a small scale (little reaction was observed at 0 °C). Therefore this two step procedure (Schemes 2D, 2E) for the preparation of **19** (employing a small excess of $NaNO_2$ in the first step) is preferred over the modified Schiemann method.

Small scale treatment of **5c** under similar conditions (Scheme 3B), employing a small excess (2.1 equivalents) of $NaNO_2$ in 65–70% HF–pyridine at −5 °C, unexpectedly gave an excellent yield of 3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2-amine **26** (81%), together with the hydrolysis product, 2-amino-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7(6*H*)-one **30** (15%) and a small amount of 2,7-difluoro-3-(3,5-dimethoxyphenyl)-1,6-naphthyridine **31** (4%). However, the reaction was found to be very sensitive to the exact condition of the HF–pyridine employed, since a larger scale reaction using a fresh batch of reagent (fuming with HF, unlike the older batch used in the reactions above) gave almost complete decomposition (<6% yield of crude **26**). In contrast, when this fresh HF–pyridine was diluted with dry pyridine, diazotization was much slower (requiring several hours at 20 °C), but even more effective (being more anhydrous). Thus, with a slightly larger excess of



Scheme 4 *Reagents and conditions*: 1-(3-aminopropyl)-4-methylpiperazine: a, neat, 160 °C, 3–5 days; b, 2-ethoxyethanol, 135 °C, 5 days; c, pentan-2-ol, 118 °C, 15 h.

$NaNO_2$ (3 equivalents), a higher yield of the difluoro derivative **31** was obtained (18%), together with a comparable yield of **26** (78%), and a very small amount of 3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2(1*H*)-one **32** (2%).

Diazotization of **26** with $NaNO_2$ in neat TFA was ineffective as a route to **32**, as expected (due to the strong acidity of this solvent), giving a low yield (28%) of the 2′-nitro derivative **27** as the only isolable product. However, partial hydrolysis of difluoro compound **31** (NaOH–water–THF, 20 or 53 °C) gave **32** essentially quantitatively (Scheme 3C). This provides a potentially efficient two step synthesis of **32**, since the yield of difluoro derivative **31** could clearly be optimized by further diazotization of **26** (and **5c**) under the improved conditions described (fresh 70% HF–pyridine diluted with pyridine, using larger excesses of $NaNO_2$ and/or longer reaction times). Partial hydrolysis of **31** was also demonstrated under these (still acidic) diazotization reaction conditions (without $NaNO_2$) in the presence of added water, although purified **31** had extremely poor solubility in this solvent mixture, accounting for an incomplete reaction (54% conversion to **32** after 2 days at 20 °C, with 45% recovered **31**).

The reactivity of the various halogenated naphthyridines with the amine nucleophile 1-(3-aminopropyl)-4-methylpiperazine was also examined (Scheme 4). Reaction of the 7-chloro-3-phenyl analogue **13a** required forcing conditions (neat amine at 160 °C for 5 days) and gave predominantly the 2,7-bis-substitution product **33** (60%), together with a small amount of the expected 2-amino-7-substituted derivative **34** (7.5%). Similar reaction of the 7-chloro-3-(2,6-dichlorophenyl) derivative **13b** (160 °C for 3 days) gave a higher yield of the 2-amino-7-substituted derivative **35** (44%). As expected, the 7-fluoro derivative **18** was significantly more reactive than **13b**, undergoing displacement in boiling 2-ethoxyethanol (135 °C for 5 days) to give **35** (46%), together with a small amount of the 7-(4-methylpiperazine) derivative **36** (6%) [the latter was prepared independently in high yield (78%) by treatment of **18** with 1-methylpiperazine in boiling pentan-2-ol (118 °C for 7 days)]. Reaction of 3-(3,5-dimethoxyphenyl)-7-fluoro derivative **26** in boiling 2-ethoxyethanol was slower than that of **18**, requiring a larger excess of amine (40 equivalents for 5 days), but gave the 7-substituted derivative **37** in comparable purified yield (43%). Finally, reaction of the more electron-deficient 7-fluoro-1,6-naphthyridin-2(1*H*)-one **19** in boiling pentan-2-ol (118 °C for 15 h) was even more facile and gave an excellent yield (82%) of the 7-substituted derivative **38**.

In conclusion, we have investigated the diazotization chemistry of 3-aryl-1,6-naphthyridine-2,7-diamines and shown that, by variation of the reaction conditions, good yields of either 3-aryl-7-halo-1,6-naphthyridin-2(1*H*)-ones **11** or 3-aryl-7-halo-1,6-naphthyridin-2-amines **12** can be obtained. This opens the way to the synthesis of more complex 7-substituted 1,6-naphthyridine derivatives.

Experimental

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined using an Electrothermal Model 9200 digital melting point apparatus, and are as read. Routine NMR spectra were measured on a Bruker DRX-400 spectrometer at 400 MHz (^1H) or 100 MHz (^{13}C), with Me_4Si as an internal standard, and *J* values are given in Hz. Mass spectra were determined on a VG-70SE mass spectrometer at nominal 5000 resolution. Light petroleum refers to the fraction boiling at 40–60 °C. Reactions using HF–pyridine were optimally conducted in capped plastic vials.

3-Phenyl-1,6-naphthyridine-2,7-diamine 5a

4,6-Diaminonicotinaldehyde hydrochloride was prepared from the free base **4**[1] by taking the filtered solution from the reported[6] hydrogenation of the precursor nitrile[17] (26 g in 160 cm^3 of water and 80 cm^3 of formic acid) and diluting it with conc. HCl (40 cm^3). The mixture was evaporated to a brown powder that was triturated in Et$_2$O. The solid was collected and recrystallized from water to give the hydrochloride of **4** (13 g), mp >200 °C (decomp.). A mixture of this hydrochloride (13 g, 74.9 mmol) and phenylacetonitrile (11.5 g, 98.2 mmol) in 2-ethoxyethanol (100 cm^3) was treated with a solution of NaOMe (5.60 g, 104 mmol) in 2-ethoxyethanol (100 cm^3). The resultant mixture was stirred under reflux for 3 h, cooled, and concentrated. The residue was triturated in cold water containing a few drops of dilute aq. NaOH, and the resultant solids were collected by filtration, washed with cold water and air dried to leave 18.4 g of crude product. Further purification by double crystallization afforded pure *diamine* **5a** (10.5 g, 59%), mp 200–201 °C (from EtOH) (Found: C, 71.4; H, 4.9; N, 24.0. $C_{14}H_{12}N_4$ requires C, 71.2; H, 5.1; N, 23.7%); δ_H([$^2H_6$]DMSO) 8.43 (1 H, s, 5-H), 7.65 (1 H, s, 4-H), 7.48 (4 H, m, 2′,3′,5′,6′-H), 7.40 (1 H, m, 4′-H), 6.31 (1 H, s, 8-H), 6.26 (2 H, br s, 2-NH$_2$), 5.91 (2 H, br s, 7-NH$_2$); δ_C([$^2H_6$]DMSO) 159.59, 158.30 (2 s, 2,7-C), 152.64 (s, 8a-C), 150.37 (d, 5-C), 137.59 (s, 1′-C), 136.01 (d, 4-C), 128.88, 128.60 (2 × 2 C, 2 d, 2′,3′,5′,6′-C), 127.51 (d, 4′-C), 120.96 (s, 3-C), 113.52 (s, 4a-C), 95.54 (d, 8-C).

3-(3,5-Dimethoxyphenyl)-1,6-naphthyridine-2,7-diamine 5c

3,5-Dimethoxyphenylacetonitrile (5.80 g, 32.8 mmol) and **4**[1] (3.90 g, 28.5 mmol) were added to a solution of sodium (0.69 g, 30.0 mmol) dissolved in 2-ethoxyethanol (30 cm^3), then the mixture was stirred under reflux for 30 min. The cooled solution was treated with ice–aqueous NaHCO$_3$ and extracted with EtOAc (12 × 200 cm^3). The extracts were evaporated to dryness and the residue was then chromatographed on silica gel. Elution with 0–2% MeOH–CH$_2$Cl$_2$ gave minor impurities, then elution with 3–7% MeOH–CH$_2$Cl$_2$ gave the *diamine* **5c** (8.06 g, 96%), mp 229–232 °C (from MeOH–CHCl$_3$–light petroleum) (Found: C, 63.7; H, 5.3; N, 18.3. $C_{16}H_{16}N_4O_2\cdot 0.25H_2O$ requires C, 63.9; H, 5.5; N, 18.6%); δ_H([$^2H_6$]DMSO) 8.41 (1 H, s, 5-H), 7.67 (1 H, s, 4-H), 6.59 (2 H, d, *J* 2.2, 2′,6′-H), 6.52 (1 H, t, *J* 2.2, 4′-H), 6.31 (2 H, br s, 2-NH$_2$), 6.29 (1 H, s, 8-H), 5.90 (2 H, br s, 7-NH$_2$), 3.79 (6 H, s, 2 × OCH$_3$); δ_C([$^2H_6$]DMSO) 160.63 (2 C, s, 3′,5′-C), 159.58, 158.14 (2 s, 2,7-C), 152.62 (s, 8a-C), 150.36 (d, 5-C), 139.50 (s, 1′-C), 135.75 (d, 4-C), 120.86 (s, 3-C), 113.31 (s, 4a-C), 106.52 (2 C, d, 2′,6′-C), 99.70 (d, 4′-C), 95.49 (d, 8-C), 55.16 (2 C, q, 2 × OCH$_3$).

Diazotization of 3-phenyl-1,6-naphthyridine-2,7-diamine 5a

A solution of **5a** (1.00 g, 4.24 mmol) in 37% HCl (10 cm^3) at −15 °C was saturated with gaseous HCl, then treated with solid NaNO$_2$ (2.30 g, 33.3 mmol) and stirred at −10 °C for 5 h, then at 20 °C for 3 h, and kept at 4 °C for 2 days. The resulting mixture was cooled to −15 °C and neutralized with solid Na$_2$CO$_3$–ice, keeping the temperature below −10 °C. The resulting solid (0.98 g) was collected by filtration and washed with water. Extraction of the filtrate with EtOAc (3 × 100 cm^3) and removal of the solvent gave further material, which was combined with the above solid. Chromatography on silica gel, eluting with CH$_2$Cl$_2$, gave firstly *7,8-dichloro-3-phenyl-1,6-naphthyridin-2-amine* **15a** (10 mg, 1%), mp 271–274 °C (from MeOH–CH$_2$Cl$_2$–hexane); δ_H([$^2H_6$]DMSO) 8.72 (1 H, s, 5-H), 8.04 (1 H, s, 4-H), 7.51 (5 H, m, 2′,3′,4′,5′,6′-H), 7.30 (2 H, br s, NH$_2$); δ_C([$^2H_6$]DMSO) 159.81 (s, 2-C), 148.86 (s, 8a-C), 148.47 (d, 5-C), 146.03 (s, 7-C), 136.08 (d, 4-C), 135.94 (s, 1′-C), 129.20 (2 C, d, 3′,5′-C), 128.62 (3 C, d, 2′,4′,6′-C), 127.05 (s, 3-C), 121.90 (s, 8-C), 119.73 (s, 4a-C); *m*/*z* (HREIMS) 291.0130, 289.0163 (M$^+$, $C_{14}H_9Cl_2N_3$ requires 291.0144, 289.0174).

Further elution with 1–2% MeOH–CH$_2$Cl$_2$ gave *7-chloro-3-phenyl-1,6-naphthyridin-2-amine* **13a** (660 mg, 61%), mp 206–208 °C (from MeOH–CH$_2$Cl$_2$–hexane) (Found: C, 65.9; H, 3.8; N, 16.7. $C_{14}H_{10}ClN_3$ requires C, 65.8; H, 3.9; N, 16.4%); δ_H([$^2H_6$]DMSO) 8.77 (1 H, s, 5-H), 7.98 (1 H, s, 4-H), 7.51 (5 H, m, 2′,3′,4′,5′,6′-H), 7.39 (1 H, s, 8-H), 6.94 (2 H, br s, NH$_2$); δ_C([$^2H_6$]DMSO) 159.39 (s, 2-C), 152.43 (s, 8a-C), 151.00 (d, 5-C), 148.29 (s, 7-C), 136.36 (s, 1′-C), 135.59 (d, 4-C), 129.02, 128.54 (2 × 2 C, 2 d, 2′,3′,5′,6′-C), 128.32 (d, 4′-C), 126.49 (s, 3-C), 118.90 (s, 4a-C), 116.58 (d, 8-C); *m*/*z* (HREIMS) 257.0529, 255.0555 (M$^+$, $C_{14}H_{10}ClN_3$ requires 257.0534, 255.0563).

Further elution with 5–10% MeOH–CH$_2$Cl$_2$ gave *2-amino-8-chloro-3-phenyl-1,6-naphthyridin-7(6H)-one* **16a** (58 mg, 5%), mp 318–321 °C (from MeOH–CH$_2$Cl$_2$–hexane) (Found: C, 61.8; H, 3.4; N, 15.6. $C_{14}H_{10}ClN_3O$ requires C, 61.9; H, 3.7; N, 15.5%); δ_H([$^2H_6$]DMSO) 12.29 (1 H, br s, NH), 8.14 (1 H, s, 5-H), 7.66 (1 H, s, 4-H), 7.49 (2 H, t, *J* 7.3, 3′,5′-H), 7.43 (3 H, m, 2′,4′,6′-H), 7.00 (2 H, br s, NH$_2$); *m*/*z* (HREIMS) 273.0481, 271.0504 (M$^+$, $C_{14}H_{10}ClN_3O$ requires 273.0483, 271.0512).

Further elution with 10–12% MeOH–CH$_2$Cl$_2$ gave *2-amino-3-phenyl-1,6-naphthyridin-7(6H)-one* **14a** (187 mg, 19%), mp 270–276 °C (decomp.) (from MeOH–CH$_2$Cl$_2$–hexane) (Found: C, 68.7; H, 4.9; N, 17.1. $C_{14}H_{11}N_3O\cdot 0.5H_2O$ requires C, 68.3; H, 4.9; N, 17.1%); δ_H([$^2H_6$]DMSO) 11.37 (1 H, br s, NH), 8.23 (1 H, s, 5-H), 7.64 (1 H, s, 4-H), 7.49 (2 H, t, *J* 7.2, 3′,5′-H), 7.42 (3 H, m, 2′,4′,6′-H), 6.59 (2 H, br s, NH$_2$), 6.13 (1 H, s, 8-H); δ_C([$^2H_6$]DMSO) 163.03 (s, 7-C), 159.05 (s, 2-C), 154.75 (s, 8a-C), 142.57 (br d, 5-C), 136.87 (s, 1′-C), 136.09 (d, 4-C), 128.89, 128.57 (2 × 2 C, 2 d, 2′,3′,5′,6′-C), 127.83 (d, 4′-C), 122.91 (s, 3-C), 111.69 (s, 4a-C), 100.63 (d, 8-C); *m*/*z* (HREIMS) 237.0903 (M$^+$, $C_{14}H_{11}N_3O$ requires 237.0902).

Diazotization of 3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7-diamine 5b

(a) In HCl. A solution of **5b**[1,6] (249 mg, 0.816 mmol) in 37% HCl (10 cm^3) at 0 °C was saturated with gaseous HCl, then treated with solid NaNO$_2$ (0.45 g, 6.52 mmol) and stirred at 0 °C for 4 h, then kept at −20 °C for 2 days. The resulting mixture was neutralized with solid Na$_2$CO$_3$–ice, keeping the temperature below 0 °C, and extracted with EtOAc (3 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 20% light petroleum–CH$_2$Cl$_2$ and CH$_2$Cl$_2$, gave firstly *7,8-dichloro-3-(2,6-dichlorophenyl)-1,6-naphthyridin-2-amine* **15b** (9 mg, 3%), mp 251–253.5 °C (from MeOH–water); δ_H([$^2H_6$]DMSO) 8.72 (1 H, s, 5-H), 8.08 (1 H, s, 4-H), 7.64 (2 H, d, *J* 8.2, 3′,5′-H), 7.53 (1 H, dd, *J* 8.9 and 7.4, 4′-H), 7.40 (2 H, br s, NH$_2$); δ_C([$^2H_6$]DMSO) 159.10 (s, 2-C), 149.47 (s, 8a-C), 148.43 (d, 5-C), 146.55 (s, 7-C), 137.48 (d, 4-C), 134.67 (2 C, s, 2′,6′-C), 132.98 (s, 1′-C), 131.41 (d, 4′-C), 128.71 (2 C, d, 3′,5′-C), 122.48 (s, 3-C), 121.94 (s, 8-C), 118.87 (s, 4a-C); *m*/*z* (HREIMS) 360.9339, 358.9368, 356.9396 (M$^+$, $C_{14}H_7Cl_4N_3$ requires 360.9335, 358.9365, 356.9394).

Further elution with 0.5% MeOH–CH$_2$Cl$_2$ gave *7-chloro-3-(2,6-dichlorophenyl)-1,6-naphthyridin-2-amine* **13b** (129 mg, 49%), mp 216–218 °C (from CH$_2$Cl$_2$–light petroleum) (Found: C, 51.7; H, 2.2; N, 13.0; Cl, 33.1. $C_{14}H_8Cl_3N_3$ requires C, 51.8; H, 2.5; N, 13.0; Cl, 32.8%); δ_H([$^2H_6$]DMSO) 8.77 (1 H, s, 5-H), 8.00 (1 H, s, 4-H), 7.64 (2 H, d, *J* 8.0, 3′,5′-H), 7.52 (1 H, dd, *J* 8.9 and 7.4, 4′-H), 7.39 (1 H, s, 8-H), 7.00 (2 H, br s, NH$_2$); δ_C([$^2H_6$]DMSO) 158.73 (s, 2-C), 153.10 (s, 8a-C), 151.06 (d, 5-C), 148.80 (s, 7-C), 136.90 (d, 4-C), 134.71 (2 C, s, 2′,6′-C), 133.36 (s, 1′-C), 131.22 (d, 4′-C), 128.64 (2 C, d, 3′,5′-C), 121.94 (s, 3-C), 118.14 (s, 4a-C), 116.70 (d, 8-C).

Further elution with 1% MeOH–CH$_2$Cl$_2$ gave crude *8-chloro-3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7-diamine* **17** (8.5 mg, 3%) as an oil; δ_H([$^2H_6$]DMSO) 8.40 (1 H, s, 5-H), 7.73 (1 H, s, 4-H), 7.60 (2 H, d, *J* 8.0, 3′,5′-H), 7.47 (1 H, dd, *J* 8.7 and 7.5, 4′-H), 6.75 (2 H, br s, NH$_2$), 6.34 (2 H, br s, NH$_2$); *m*/*z* (HREIMS) 341.9847, 339.9871, 337.9894 (M$^+$, $C_{14}H_9Cl_3N_4$ requires 341.9834, 339.9863, 337.9893).

Further elution with 4% MeOH–CH$_2$Cl$_2$ gave recovered **5b** (2.4 mg, 1%).

Further elution with 4–5% MeOH–CH$_2$Cl$_2$ gave *2-amino-8-chloro-3-(2,6-dichlorophenyl)-1,6-naphthyridin-7(6H)-one* **16b**

(13 mg, 5%), mp 325–330 °C (decomp.) (from MeOH–$CHCl_3$–light petroleum); δ_H([$^2H_6$]DMSO) 12.35 (1 H, br s, NH), 8.15 (1 H, s, 5-H), 7.65 (1 H, s, 4-H), 7.60 (2 H, d, *J* 8.1, 3′,5′-H), 7.48 (1 H, dd, *J* 8.7 and 7.5, 4′-H), 7.15 (2 H, br s, NH_2); *m*/*z* (HRFABMS) 343.9763, 341.9789, 339.9824 (MH^+, $C_{14}H_9Cl_3N_3O$ requires 343.9752, 341.9782, 339.9811).

Further elution with 10–15% MeOH–CH_2Cl_2 gave *2-amino-3-(2,6-dichlorophenyl)-1,6-naphthyridin-7(6H)-one* **14b** (68 mg, 27%), mp >260 °C (decomp.) (from MeOH) (Found: C, 54.6; H, 2.6; N, 13.7. $C_{14}H_9Cl_2N_3O$ requires C, 54.9; H, 3.0; N, 13.7%); δ_H([$^2H_6$]DMSO) 11.45 (1 H, br s, NH), 8.24 (1 H, s, 5-H), 7.61 (1 H, s, 4-H), 7.60 (2 H, d, *J* 8.4, 3′,5′-H), 7.47 (1 H, dd, *J* 8.7 and 7.3, 4′-H), 6.68 (2 H, br s, NH_2), 6.12 (1 H, s, 8-H); δ_C([$^2H_6$]DMSO) 163.24 (s, 7-C), 158.47 (s, 2-C), 155.41 (s, 8a-C), 142.36 (br d, 5-C), 137.52 (d, 4-C), 135.22 (2 C, s, 2′,6′-C), 133.87 (s, 1′-C), 131.08 (d, 4′-C), 128.66 (2 C, d, 3′,5′-C), 118.55 (s, 3-C), 110.78 (s, 4a-C), 100.96 (d, 8-C).

(b) In HBF_4–excess $NaNO_2$. A stirred suspension of **5b** (1.55 g, 5.08 mmol) in 50% HBF_4 (75 cm^3) at −5 °C was treated with solid $NaNO_2$ (3.0 g, 43.5 mmol, added in small portions over 5 h), then kept at −20 °C for 5 days. The resulting mixture was neutralized with solid Na_2CO_3–ice, keeping the temperature below −10 °C, and extracted with EtOAc (4 × 150 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 1–2% MeOH–CH_2Cl_2, gave firstly *3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2(1H)-one* **19** (0.91 g, 58%), mp 254.5–255.5 °C (from CH_2Cl_2–light petroleum) (Found: C, 54.0; H, 2.0; N, 9.2; F, 6.1. $C_{14}H_7Cl_2FN_2O$ requires C, 54.4; H, 2.3; N, 9.1; F, 6.2%); δ_H([$^2H_6$]DMSO) 12.54 (1 H, br s, NH), 8.66 (1 H, s, 5-H), 8.13 (1 H, s, 4-H), 7.61 (2 H, d, *J* 8.2, 3′,5′-H), 7.49 (1 H, dd, *J* 8.8 and 7.4, 4′-H), 6.89 (1 H, s, 8-H); δ_C([$^2H_6$]DMSO) 163.55 (d, $J_{C\text{-}F}$ 234, 7-C), 159.77 (s, 2-C), 148.95 (dd, $J_{C\text{-}F}$ 19, 5-C), 147.69 (d, $J_{C\text{-}F}$ 12, 8a-C), 138.13 (d, 4-C), 134.51 (2 C, s, 2′,6′-C), 133.51 (s, 1′-C), 130.85 (d, 4′-C), 129.61 (d, $J_{C\text{-}F}$ 2.5, 3-C), 128.08 (2 C, d, 3′,5′-C), 114.34 (d, $J_{C\text{-}F}$ 2.5, 4a-C), 92.95 (dd, $J_{C\text{-}F}$ 42, 8-C).

Further elution of the column with 10–12% MeOH–CH_2Cl_2 gave *3-(2,6-dichlorophenyl)-1,6-naphthyridine-2,7(1H,6H)-dione* **20** (0.45 g, 29%), mp 363–369 °C (decomp.) (from MeOH–$CHCl_3$) (Found: C, 54.6; H, 2.5; N, 9.0. $C_{14}H_8Cl_2N_2O_2$ requires C, 54.8; H, 2.6; N, 9.1%); δ_H([$^2H_6$]DMSO) 12.07, 11.55 (2 H, 2 br s, 2 × NH), 8.10 (1 H, s, 5-H), 7.67 (1 H, s, 4-H), 7.56 (2 H, d, *J* 8.1, 3′,5′-H), 7.44 (1 H, dd, *J* 8.8 and 7.5, 4′-H), 5.90 (1 H, s, 8-H); δ_C([$^2H_6$]DMSO) 161.84, 160.38 (2 s, 2,7-C), 147.87 (s, 8a-C), 139.65 (br d, 5-C), 138.60 (d, 4-C), 134.90 (2 C, s, 2′,6′-C), 133.90 (s, 1′-C), 130.50 (d, 4′-C), 127.97 (d, 2 C, 3′,5′-C), 124.18 (s, 3-C), 105.09 (s, 4a-C), 95.50 (d, 8-C); *m*/*z* (HRFABMS) 311.0015, 309.0042, 307.0067 (MH^+, $C_{14}H_9Cl_2N_2O_2$ requires 310.9982, 309.0012, 307.0041).

(c) In HBF_4–limited $NaNO_2$. A stirred suspension of **5b** (2.02 g, 6.62 mmol) in 50% HBF_4 (80 cm^3) at −5 °C was treated with solid $NaNO_2$ (0.50 g, 7.27 mmol, added in small portions over 4 h), then kept at −20 °C for 3 days. Further solid $NaNO_2$ (0.25 g, 3.62 mmol, added in small portions over 4 h) was added, then the mixture was kept at −20 °C for 2 days. The resulting mixture was neutralized with solid Na_2CO_3–ice, keeping the temperature below −10 °C, and extracted with EtOAc (8 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 1–1.5% MeOH–CH_2Cl_2, gave firstly *3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2-amine* **18** (1.12 g, 55%), mp 189–191 °C (from CH_2Cl_2–light petroleum) (Found: C, 54.8; H, 2.3; N, 13.7; F, 6.0. $C_{14}H_8Cl_2FN_3$ requires C, 54.6; H, 2.6; N, 13.6; F, 6.2%); δ_H([$^2H_6$]DMSO) 8.67 (1 H, s, 5-H), 7.99 (1 H, s, 4-H), 7.64 (2 H, d, *J* 8.1, 3′,5′-H), 7.51 (1 H, dd, *J* 8.8 and 7.4, 4′-H), 6.98 (1 H, s, 8-H), 6.95 (2 H, br s, NH_2); δ_C([$^2H_6$]DMSO) 163.81 (d, $J_{C\text{-}F}$ 231, 7-C), 158.67 (s, 2-C), 155.00 (d, $J_{C\text{-}F}$ 13, 8a-C), 149.53 (dd, $J_{C\text{-}F}$ 19, 5-C), 136.98 (d, 4-C), 134.82 (2 C, s, 2′,6′-C), 133.46 (s, 1′-C), 131.18 (d, 4′-C), 128.63 (2 C, d, 3′,5′-C), 121.05 (s, 3-C), 117.77 (d, $J_{C\text{-}F}$ 2.4, 4a-C), 99.68 (dd, $J_{C\text{-}F}$ 36, 8-C).

Further elution with 9–15% MeOH–CH_2Cl_2 gave **14b** (0.67 g, 33%).

(d) In HF–pyridine–excess $NaNO_2$. A stirred suspension of **5b** (250 mg, 0.82 mmol) in 65–70% HF–pyridine (10 cm^3) at 0 °C was treated with solid $NaNO_2$ (0.45 g, 6.52 mmol, added in portions over 30 min), then stirred at 0 °C for 1 h, then at 20 °C for 1 h and kept at −20 °C for 6 days. The mixture was further treated with solid $NaNO_2$ (0.90 g, 13.0 mmol, added in portions over 1 h) at 0 °C, then stirred at 20 °C for 6 h and kept at −20 °C for 3 days. The resulting mixture was neutralized with solid Na_2CO_3–ice, keeping the temperature below −10 °C, diluted with water (to 350 cm^3) and extracted with EtOAc (7 × 100 cm^3). The solvent was removed, then chromatography of the residue on neutral alumina, eluting with CH_2Cl_2, gave firstly an oil (2.5 mg), which was further purified by preparative silica gel TLC (developed three times in 2% EtOAc–light petroleum). Three bands were recovered and each was eluted with CH_2Cl_2. The least polar component was *2-chloro-3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridine* **23** (1.0 mg, 0.4%), isolated as an oil; δ_H([$^2H_6$]DMSO) 9.32 (1 H, s, 5-H), 8.87 (1 H, s, 4-H), 7.81 (1 H, s, 8-H), 7.73 (2 H, d, *J* 8.3, 3′,5′-H), 7.62 (1 H, dd, *J* 8.9 and 7.4 Hz, 4′-H); *m*/*z* (HREIMS) 329.9531, 327.9560, 325.9583 (M^+, $C_{14}H_6Cl_3FN_2$ requires 329.9522, 327.9551, 325.9581).

The central component was *3-(2,6-dichlorophenyl)-2,7-difluoro-1,6-naphthyridine* **24** (1.0 mg, 0.4%), isolated as an oil; δ_H([$^2H_6$]DMSO) 9.31 (1 H, s, 5-H), 9.00 (1 H, d, $J_{H\text{-}F}$ 9.8, 4-H), 7.74 (1 H, s, 8-H), 7.74 (2 H, d, *J* 8.1, 3′,5′-H), 7.62 (1 H, dd, *J* 8.9 and 7.4, 4′-H); *m*/*z* (HREIMS) 313.9824, 311.9846, 309.9876 (M^+, $C_{14}H_6Cl_2F_2N_2$ requires 313.9817, 311.9847, 309.9876).

The most polar component was *3-(2,6-dichlorophenyl)-7-fluoro-2-nitro-1,6-naphthyridine* **25** (0.5 mg, 0.2%) as an oil; δ_H([$^2H_6$]DMSO) 9.51 (1 H, s, 5-H), 9.28 (1 H, s, 4-H), 8.07 (1 H, s, 8-H), 7.73 (2 H, d, *J* 7.9, 3′,5′-H), 7.61 (1 H, dd, *J* 8.9 and 7.4, 4′-H); *m*/*z* (HREIMS) 338.9797, 336.9819 (M^+, $C_{14}H_6Cl_2FN_3O_2$ requires 338.9792, 336.9821).

Further elution of the column with 0.25% MeOH–CH_2Cl_2 gave **18** (106 mg, 42%), and with 2–5% MeOH–CH_2Cl_2 gave **19** (92 mg, 36%).

(e) In HF–pyridine–limited $NaNO_2$. A stirred suspension of **5b** (99 mg, 0.325 mmol) in 65–70% HF–pyridine (2 cm^3) at 0 °C was treated with solid $NaNO_2$ (39 mg, 0.57 mmol), then stirred at 0 °C for 30 min and then at 20 °C for 1 h. The mixture was further treated with solid $NaNO_2$ (11 mg, 0.16 mmol) at 0 °C, then stirred at 20 °C for 1 h. The resulting mixture was cooled to 0 °C, neutralized with solid Na_2CO_3–ice–water (keeping the temperature at or below 0 °C), then diluted with water (to 150 cm^3) and extracted with EtOAc (3 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 0.5% MeOH–CH_2Cl_2, gave **18** (75 mg, 75%).

Diazotization of 3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2-amine 18

A stirred solution of **18** (106 mg, 0.344 mmol) in TFA (5 cm^3) at 0 °C was treated with solid $NaNO_2$ (64 mg, 0.93 mmol, added in portions over 5 min), then stirred at 0 °C for 15 min, then at 20 °C for 2.5 h. The resulting mixture was added slowly to a mixture of aqueous $NaHCO_3$–Na_2CO_3 and ice (150 cm^3) and extracted with EtOAc (4 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 1% MeOH–CH_2Cl_2, gave **19** (102 mg, 96%).

Diazotization of 3-(3,5-dimethoxyphenyl)-1,6-naphthyridine-2,7-diamine 5c

(a) In HBF$_4$–limited NaNO$_2$. A stirred suspension of **5c** (52 mg, 0.176 mmol) in 50% HBF$_4$ (5 cm^3) at −10 °C was treated with solid NaNO$_2$ (18 mg, 0.26 mmol, added in small portions over 5 min), stirred at −10 °C for 3 h, and then kept at −20 °C for 3 days. The resulting mixture was neutralized with solid Na$_2$CO$_3$–ice, keeping the temperature below −5 °C, and extracted with EtOAc (6 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 1% MeOH–CH$_2$Cl$_2$, gave an oil (5 mg), which was further purified by preparative neutral alumina TLC (developed in 1% EtOH/CHCl$_3$). Two bands were recovered and each was eluted with 5% MeOH–CH$_2$Cl$_2$. The less polar component was *3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2-amine* **26** (1.5 mg, 3%), isolated as an oil (see below).

The more polar component (2.5 mg) was further purified by preparative silica gel TLC (developed in 2% MeOH–CH$_2$Cl$_2$). Recovery of the major band and elution with 6% MeOH–CH$_2$Cl$_2$ gave *3-(3,5-dimethoxy-2-nitrophenyl)-7-fluoro-1,6-naphthyridin-2-amine* **27** (2.0 mg, 3%), mp 250–260 °C (decomp.) (from MeOH–water); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 8.64 (1 H, s, 5-H), 7.91 (1 H, s, 4-H), 7.00 (2 H, br s, NH$_2$), 6.94 (1 H, s, 8-H), 6.92 (1 H, d, *J* 2.4, 6′-H), 6.64 (1 H, d, *J* 2.4, 4′-H), 3.94, 3.88 (2 × 3 H, 2 s, 2 × OCH$_3$); $\delta_{\rm C}$([^{2}H$_6$]DMSO) 163.82 (d, $J_{\text{C-F}}$ 232, 7-C), 161.89 (s, 5′-C), 159.08 (s, 2-C), 154.91 (d, $J_{\text{C-F}}$ 13, 8a-C), 153.03 (s, 3′-C), 149.64 (dd, $J_{\text{C-F}}$ 19, 5-C), 135.34 (d, 4-C), 134.38 (s, 1′-C), 131.70 (s, 2′-C), 120.66 (s, 3-C), 117.57 (s, 4a-C), 107.42 (d, 6′-C), 100.21 (d, 4′-C), 99.72 (dd, $J_{\text{C-F}}$ 36, 8-C), 56.85, 56.12 (2 q, 2 × OCH$_3$); *m*/*z* (HRFABMS) 345.1011 (MH$^+$, C$_{16}$H$_{14}$FN$_4$O$_4$ requires 345.0999).

(b) In HBF$_4$–excess NaNO$_2$. A stirred suspension of **5c** (1.00 g, 3.38 mmol) in 50% HBF$_4$ (50 cm^3) at −5 °C was treated with solid NaNO$_2$ (1.86 g, 27.0 mmol, added in small portions over 2 h), then kept at −20 °C for 4 days. The resulting mixture was neutralized with solid Na$_2$CO$_3$–ice, keeping the temperature below −5 °C, and extracted with EtOAc (6 × 150 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 1% MeOH–CH$_2$Cl$_2$, gave firstly *quinone imine* **29** (48 mg, 4%), mp 290–296 °C (decomp.) (from MeOH–CH$_2$Cl$_2$) (Found: C, 53.0; H, 2.2; N, 16.3; F, 5.3. C$_{15}$H$_7$FN$_4$O$_5$ requires C, 52.6; H, 2.1; N, 16.4; F, 5.6%); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 9.57 (1 H, s, 5-H), 8.81 (1 H, s, 4-H), 7.70 (1 H, s, 8-H), 6.52 (1 H, s, 4′-H), 4.02 (s, 3 H, OCH$_3$); $\delta_{\rm C}$([^{2}H$_6$]DMSO) 175.38 (s, C=O), 165.06 (d, $J_{\text{C-F}}$ 239, 7-C), 160.49, 158.91 (2 s, 2,2′-C), 155.36 (dd, $J_{\text{C-F}}$ 18, 5-C), 152.93 (d, $J_{\text{C-F}}$ 13, 8a-C), 143.36 (s, 3′-C), 138.49 (s, 6′-C), 138.43 (d, 4-C), 121.46, 114.74, 107.15 (3 s, 1′,3,4a-C), 106.01 (d, 4′-C), 102.70 (dd, $J_{\text{C-F}}$ 37, 8-C), 57.72 (q, OCH$_3$); *m*/*z* (HRFABMS) 343.0481 (MH$^+$, C$_{15}$H$_8$FN$_4$O$_5$ requires 343.0479).

Further elution with 1% MeOH–CH$_2$Cl$_2$ gave a mixture, then elution with 2% MeOH–CH$_2$Cl$_2$ gave *quinone* **28** (38 mg, 4%), mp 265–275 °C (decomp.) (from MeOH–CH$_2$Cl$_2$); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 12.48 (1 H, br s, NH), 8.66 (1 H, s, 5-H), 8.16 (1 H, s, 4-H), 6.98 (1 H, d, *J* 2.4, 6′-H), 6.84 (1 H, s, 8-H), 6.21 (1 H, d, *J* 2.4, 4′-H), 3.84 (3 H, s, OCH$_3$); $\delta_{\rm C}$([^{2}H$_6$]DMSO) 187.04 (s, 5′-C), 179.45 (s, 2′-C), 163.67 (d, $J_{\text{C-F}}$ 234, 7-C), 160.21, 158.89 (2 s, 2,3′-C), 149.40 (dd, $J_{\text{C-F}}$ 19, 5-C), 147.65 (d, $J_{\text{C-F}}$ 13, 8a-C), 140.46 (s, 1′-C), 138.38 (d, 4-C), 134.73 (d, 6′-C), 125.96 (d, $J_{\text{C-F}}$ 2.8, 3-C), 114.29 (d, $J_{\text{C-F}}$ 2.8, 4a-C), 107.41 (d, 4′-C), 92.87 (dd, $J_{\text{C-F}}$ 42, 8-C), 56.62 (q, OCH$_3$); *m*/*z* (HREIMS) 300.0567 (M$^+$, C$_{15}$H$_9$FN$_2$O$_4$ requires 300.0546).

(c) HF–pyridine–limited NaNO$_2$. A stirred suspension of **5c** (25.7 mg, 86.8 μmol) in 65–70% HF–pyridine (1 cm^3) at −5 °C was treated with solid NaNO$_2$ (9.3 mg, 135 μmol), then stirred at −5 °C for 2 h. The mixture was further treated with solid NaNO$_2$ (3.2 mg, 46 μmol) and stirred at −5 °C for 2 h. The resulting mixture was neutralized with solid Na$_2$CO$_3$–ice, keeping the temperature below −10 °C, diluted with water (to 150 cm^3) and extracted with EtOAc (4 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 0–0.5% MeOH–CH$_2$Cl$_2$, gave firstly *2,7-difluoro-3-(3,5-dimethoxyphenyl)-1,6-naphthyridine* **31** (1.1 mg, 4%) as an oil (see below).

Further elution with 0.5–1% MeOH–CH$_2$Cl$_2$ gave *3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2-amine* **26** (21 mg, 81%), mp 225–227 °C (from CH$_2$Cl$_2$–hexane) (Found: C, 64.0; H, 4.6; N, 14.1. C$_{16}$H$_{14}$FN$_3$O$_2$ requires C, 64.2; H, 4.7; N, 14.0%); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 8.65 (1 H, s, 5-H), 8.00 (1 H, s, 4-H), 6.96 (1 H, s, 8-H), 6.90 (2 H, v br s, NH$_2$), 6.64 (2 H, d, *J* 2.2, 2′,6′-H), 6.58 (1 H, t, *J* 2.2, 4′-H), 3.80 (6 H, s, 2 × OCH$_3$); $\delta_{\rm C}$([^{2}H$_6$]DMSO) 163.53 (d, $J_{\text{C-F}}$ 231, 7-C), 160.74 (2 C, s, 3′,5′-C), 159.20 (s, 2-C), 154.32 (d, $J_{\text{C-F}}$ 13, 8a-C), 149.36 (dd, $J_{\text{C-F}}$ 19, 5-C), 138.30 (s, 1′-C), 135.39 (d, 4-C), 125.47 (d, $J_{\text{C-F}}$ 2, 3-C), 118.34 (d, $J_{\text{C-F}}$ 2, 4a-C), 106.53 (2 C, d, 2′,6′-C), 100.36 (d, 4′-C), 99.52 (dd, $J_{\text{C-F}}$ 36, 8-C), 55.21 (2 C, q, 2 × OCH$_3$); *m*/*z* (HREIMS) 299.1069 (M$^+$, C$_{16}$H$_{14}$FN$_3$O$_2$ requires 299.1070).

Further elution with 1–6% MeOH–CH$_2$Cl$_2$ gave minor impurities, then elution with 6–12% MeOH–CH$_2$Cl$_2$ gave *2-amino-3-(3,5-dimethoxyphenyl)-1,6-naphthyridin-7(6H)-one* **30** (3.9 mg, 15%), mp 210–220 °C (decomp.) (from MeOH–CH$_2$Cl$_2$–hexane); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 11.50 (1 H, br s, NH), 8.23 (1 H, s, 5-H), 7.69 (1 H, s, 4-H), 6.77 (2 H, br s, NH$_2$), 6.57 (2 H, d, *J* 2.2, 2′,6′-H), 6.54 (1 H, t, *J* 2.1, 4′-H), 6.13 (1 H, s, 8-H), 3.78 (6 H, s, 2 × OCH$_3$); $\delta_{\rm C}$([^{2}H$_6$]DMSO) 162.92 (s, 7-C), 160.66 (2 C, s, 3′,5′-C), 158.67 (s, 2-C), 154.10 (br s, 8a-C), 142.52 (br d, 5-C), 138.51 (s, 1′-C), 136.15 (d, 4-C), 122.72 (s, 3-C), 111.22 (br s, 4a-C), 106.57 (2 C, d, 2′,6′-C), 100.46 (d, 8-C), 100.05 (d, 4′-C), 55.20 (2 C, q, 2 × OCH$_3$); *m*/*z* (HREIMS) 297.1118 (M$^+$, C$_{16}$H$_{15}$N$_3$O$_3$ requires 297.1113).

(d) Fresh HF–pyridine–pyridine–limited NaNO$_2$. Freshly opened (fuming) 65–70% HF–pyridine (8.66 cm^3) was added dropwise to dry pyridine (4.33 cm^3) at 20 °C (water bath), with rapid stirring, then **5c** (328 mg, 1.11 mmol) was added, and the mixture stirred at 20 °C for 15 min, then cooled to −10 °C. Solid NaNO$_2$ (116 mg, 1.68 mmol) was added in portions over 10 min, then the mixture was stirred at −10 °C for 30 min, and then at 20 °C for 1.5 h. The mixture was further treated with solid NaNO$_2$ (116 mg, 1.68 mmol) at 0 °C, then stirred at 20 °C for 2.5 h. The resulting mixture was cooled to −10 °C, neutralized with solid Na$_2$CO$_3$–ice, keeping the temperature below −5 °C, diluted with water (to 350 cm^3) and extracted with EtOAc (7 × 100 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with CH$_2$Cl$_2$, gave firstly *2,7-difluoro-3-(3,5-dimethoxyphenyl)-1,6-naphthyridine* **31** (59 mg, 18%), mp 154–157 °C (from CH$_2$Cl$_2$–hexane) (Found: C, 63.9; H, 4.1; N, 9.3. C$_{16}$H$_{12}$F$_2$N$_2$O$_2$ requires C, 63.6; H, 4.0; N, 9.3%); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 9.25 (1 H, s, 5-H), 8.97 (1 H, d, $J_{\text{H-F}}$ 9.8, 4-H), 7.65 (1 H, s, 8-H), 6.87 (2 H, t, *J* 1.8, 2′,6′-H), 6.65 (1 H, t, *J* 2.2, 4′-H), 3.83 (6 H, s, 2 × OCH$_3$); $\delta_{\rm C}$([^{2}H$_6$]DMSO) 163.52 (d, $J_{\text{C-F}}$ 213, 2- or 7-C), 161.11 (d, $J_{\text{C-F}}$ 227, 2- or 7-C), 160.53 (2 C, s, 3′,5′-C), 151.88 (dd, $J_{\text{C-F}}$ 18, 5-C), 150.89 (dd, $J_{\text{C-F}}$ 21 and 13, 8a-C), 141.67 (dd, $J_{\text{C-F}}$ 8, 4-C), 134.51 (d, $J_{\text{C-F}}$ 4, 1′-C), 124.30 (dd, $J_{\text{C-F}}$ 33 and 3, 3-C), 121.89 (d, $J_{\text{C-F}}$ 2, 4a-C), 107.17 (2 C, dd, $J_{\text{C-F}}$ 2, 2′,6′-C), 103.12 (dd, $J_{\text{C-F}}$ 37, 8-C), 100.63 (d, 4′-C), 55.36 (2 C, q, 2 × OCH$_3$); *m*/*z* (HREIMS) 302.0868 (M$^+$, C$_{16}$H$_{12}$F$_2$N$_2$O$_2$ requires 302.0867).

Further elution with 1% MeOH–CH$_2$Cl$_2$ gave **26** (257 mg, 78%).

Further elution with 1–1.5% MeOH–CH$_2$Cl$_2$ gave *3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2(1H)-one* **32** (6 mg, 2%), mp 266–270 °C (from MeOH–CH$_2$Cl$_2$–hexane) (Found: C, 64.0; H, 4.4; N, 9.3. C$_{16}$H$_{13}$FN$_2$O$_3$ requires C, 64.0; H, 4.4; N, 9.3%); $\delta_{\rm H}$([^{2}H$_6$]DMSO) 12.31 (1 H, br s, NH), 8.62 (1 H, s, 5-H), 8.24 (1 H, s, 4-H), 6.90 (2 H, d, *J* 2.3, 2′,6′-H), 6.83 (1 H, s, 8-H), 6.55 (1 H, t, *J* 2.2, 4′-H), 3.79 (6 H, s, 2 × OCH_3); δ_C([$^2H_6$]DMSO) 163.16 (d, $J_{C\text{-}F}$ 233, 7-C), 161.00 (s, 2-C), 159.98 (2 C, s, 3′,5′-C), 148.61 (dd, $J_{C\text{-}F}$ 19, 5-C), 146.94 (d, $J_{C\text{-}F}$ 12, 8a-C), 137.08 (s, 1′-C), 135.17 (d, 4-C), 131.58 (d, $J_{C\text{-}F}$ 3, 3-C), 115.00 (d, $J_{C\text{-}F}$ 3, 4a-C), 106.80 (2 C, d, 2′,6′-C), 100.04 (d, 4′-C), 92.29 (dd, $J_{C\text{-}F}$ 42, 8-C), 55.19 (2 C, q, 2 × OCH_3); *m*/*z* (HREIMS) 300.0907 (M^+, $C_{16}H_{13}FN_2O_3$ requires 300.0910).

Diazotization of 3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2-amine 26

A stirred solution of **26** (2.8 mg, 9.36 µmol) in TFA (1.0 cm^3) at 0 °C was treated with solid $NaNO_2$ (1.5 mg, 21.7 µmol), then stirred at 0 °C for 2.5 h. The resulting mixture was added dropwise to a mixture of aqueous $NaHCO_3$–Na_2CO_3 and ice (60 cm^3) and extracted with EtOAc (3 × 50 cm^3). The solvent was removed, then the residue was purified by preparative silica gel TLC (developed twice in 2% MeOH–CH_2Cl_2). Recovery of the major band and elution with 8% MeOH–CH_2Cl_2 gave **27** (0.9 mg, 28%).

Hydrolysis of 2,7-difluoro-3-(3,5-dimethoxyphenyl)-1,6-naphthyridine 31

(a) In NaOH–THF–water. A solution of **31** (20.4 mg, 67.6 µmol) in THF (1.8 cm^3) was treated with NaOH (0.16 g, 4.0 mmol) and water (0.2 cm^3), then the mixture was stirred at 53 °C for 3 days. The resulting suspension was diluted with aqueous $NaHCO_3$ (50 cm^3) and extracted with CH_2Cl_2 (4 × 50 cm^3) and EtOAc (3 × 50 cm^3). The solvents were removed, then chromatography of the residue on silica gel, eluting with 1% MeOH–CH_2Cl_2, gave **32** (20 mg, 99%).

(b) In HF–pyridine–pyridine–water. A suspension of **31** (10.4 mg, 34.4 µmol) in a premixed solution of fresh (fuming) 65–70% HF–pyridine (1.66 cm^3) and dry pyridine (0.83 cm^3) (prepared as described in (d) above) was treated with water (0.10 cm^3), then the mixture was stirred at 20 °C for 2 days. The resulting mixture was cooled to −10 °C, neutralized with solid Na_2CO_3–ice, keeping the temperature below −5 °C, diluted with water (to 50 cm^3) and extracted with CH_2Cl_2 (5 × 50 cm^3) and EtOAc (3 × 50 cm^3). The solvents were removed, then chromatography of the residue on silica gel, eluting with CH_2Cl_2, gave firstly recovered **31** (4.7 mg, 45%). Further elution with 1% MeOH–CH_2Cl_2 gave **32** (5.6 mg, 54%).

Reaction of 7-chloro-3-phenyl-1,6-naphthyridin-2-amine 13a with 1-(3-aminopropyl)-4-methylpiperazine

A mixture of **13a** (100 mg, 0.39 mmol) and 1-(3-aminopropyl)-4-methylpiperazine (1.0 g, 6.37 mmol) was stirred at 160 °C for 5 days. The resulting mixture was diluted with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (7 × 50 cm^3). The solvent was removed, then chromatography of the residue on alumina, eluting with 0.7% MeOH–CH_2Cl_2, gave a crude oil (161 mg), which was further purified by chromatography on silica gel. Elution with 4–5% MeOH–CH_2Cl_2 containing 0.5–0.75% conc. NH_4OH gave material which was treated with aqueous Na_2CO_3 (50 cm^3) and extracted with CH_2Cl_2 (5 × 50 cm^3) to give *7-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-phenyl-1,6-naphthyridin-2-amine* **34** (11 mg, 7.5%), mp 152–155 °C (from CH_2Cl_2–hexane) (Found: C, 69.8; H, 7.5; N, 22.1. $C_{22}H_{28}N_6$ requires C, 70.2; H, 7.5; N, 22.3%); δ_H([$^2H_6$]DMSO) 8.46 (1 H, s, 5-H), 7.65 (1 H, s, 4-H), 7.48 (4 H, m, 2′,3′,5′,6′-H), 7.40 (1 H, m, 4′-H), 6.47 (1 H, br t, *J* 5.7, N*H*CH_2), 6.21 (2 H, br s, NH_2), 6.19 (1 H, s, 8-H), 3.23 (2 H, td, *J* 6.6 and 6.0, NHC*H*$_2$), 2.6–2.0 (8 H, br s, N(CH_2)$_4$N), 2.36 (2 H, t, *J* 7.1, NCH_2), 2.15 (3 H, s, NCH_3), 1.71 (2 H, quintet, *J* 6.9, CH_2); δ_C([$^2H_6$]DMSO) 159.08, 158.33 (2 s, 2,7-C), 152.66 (s, 8a-C), 150.40 (d, 5-C), 137.63 (s, 1′-C), 136.09 (d, 4-C), 128.93, 128.63 (2 × 2 C, 2 d, 2′,3′,5′,6′-C), 127.55 (d, 4′-C), 120.81 (s, 3-C), 113.46 (s, 4a-C), 93.85 (d, 8-C), 55.82 (t, NCH_2), 54.77, 52.73 (2 × 2 C, 2 t, 2 × N(CH_2)$_2$), 45.74 (q, NCH_3), 40.11 (t, NCH_2), 26.00 (t, CH_2).

Further elution of this column with 5–10% MeOH–CH_2Cl_2 containing 0.75–1% conc. NH_4OH gave material which was treated with aqueous Na_2CO_3 (50 cm^3) and extracted with CH_2Cl_2 (5 × 50 cm^3) to give *2,7-bis{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-phenyl-1,6-naphthyridine* **33** (121 mg, 60%) as a foam (Found: C, 66.3; H, 8.5; N, 20.3. $C_{30}H_{44}N_8\cdot1.5H_2O$ requires C, 66.3; H, 8.7; N, 20.6%); δ_H([$^2H_6$]DMSO) 8.41 (1 H, s, 5-H), 7.54 (1 H, s, 4-H), 7.49 (2 H, t, *J* 7.3, 3′,5′-H), 7.44 (2 H, d, *J* 6.9, 2′,6′-H), 7.41 (1 H, t, *J* 7.1, 4′-H), 6.39 (1 H, br t, *J* 5.7, N*H*CH_2), 6.25 (1 H, s, 8-H), 6.17 (1 H, br t, *J* 5.5, N*H*CH_2), 3.47 (2 H, td, *J* 6.5 and 5.7, NHC*H*$_2$), 3.23 (2 H, td, *J* 6.6 and 6.1, NHC*H*$_2$), 2.6–2.0 (16 H, br s, 2 × N(CH_2)$_4$N), 2.36 (2 H, t, *J* 6.9, NCH_2), 2.29 (2 H, t, *J* 6.6, NCH_2), 2.15, 2.09 (2 × 3 H, 2 s, 2 × NCH_3), 1.71 (2 H, quintet, *J* 7.0, CH_2), 1.69 (2 H, quintet, *J* 6.8, CH_2); δ_C([$^2H_6$]DMSO) 159.16, 156.46 (2 s, 2,7-C), 152.55 (s, 8a-C), 150.01 (d, 5-C), 137.34 (s, 1′-C), 135.20 (d, 4-C), 128.98, 128.71 (2 × 2 C, 2 d, 2′,3′,5′,6′-C), 127.66 (d, 4′-C), 121.52 (s, 3-C), 112.84 (s, 4a-C), 94.43 (d, 8-C), 56.07, 55.60 (2 t, 2 × NCH_2), 54.73, 54.35, 52.68, 52.65 (4 × 2 C, 4 t, 4 × N(CH_2)$_2$), 45.66, 45.51 (2 q, 2 × NCH_3), 39.98, 39.68 (2 t, 2 × NCH_2), 26.03, 25.27 (2 t, 2 × CH_2); *m*/*z* (HRFABMS) 517.3752 (MH^+, $C_{30}H_{45}N_8$ requires 517.3767).

Reaction of 7-chloro-3-(2,6-dichlorophenyl)-1,6-naphthyridin-2-amine 13b with 1-(3-aminopropyl)-4-methylpiperazine

A mixture of **13b** (40 mg, 0.12 mmol) and 1-(3-aminopropyl)-4-methylpiperazine (1.0 g, 6.37 mmol) under nitrogen was stirred at 160 °C for 3 days. The resulting mixture was diluted with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (5 × 50 cm^3). The solvent was removed, then chromatography of the residue on alumina, eluting with 0.75–1% MeOH–CH_2Cl_2, gave a crude solid (39 mg), which was further purified by chromatography on silica gel. Elution with 7–10% MeOH–CH_2Cl_2 containing 0.2% Et_3N gave material which was treated with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (3 × 50 cm^3) to give *3-(2,6-dichlorophenyl)-7-{[3-(4-methylpiperazin-1-yl)propyl]amino}-1,6-naphthyridin-2-amine* **35** (24 mg, 44%), mp 152–154 °C (from CH_2Cl_2–light petroleum) (Found: C, 59.3; H, 6.2; N, 18.5. $C_{22}H_{26}Cl_2N_6$ requires C, 59.3; H, 5.8; N, 18.9%); δ_H([$^2H_6$]DMSO) 8.44 (1 H, s, 5-H), 7.59 (2 H, d, *J* 8.0, 3′,5′-H), 7.58 (1 H, s, 4-H), 7.46 (1 H, dd, *J* 8.7 and 7.5, 4′-H), 6.50 (1 H, br t, *J* 5.6, N*H*CH_2), 6.23 (2 H, br s, NH_2), 6.19 (1 H, s, 8-H), 3.23 (2 H, q, *J* 6.4, NHC*H*$_2$), 2.6–2.0 (8 H, br s, N(CH_2)$_4$N), 2.37 (2 H, t, *J* 7.1, NCH_2), 2.15 (3 H, s, NCH_3), 1.71 (2 H, quintet, *J* 7.0, CH_2); δ_C([$^2H_6$]DMSO) 159.26, 157.70 (2 s, 2,7-C), 153.28 (s, 8a-C), 150.37 (d, 5-C), 136.92 (d, 4-C), 135.28 (2 C, s, 2′,6′-C), 134.55 (s, 1′-C), 130.61 (d, 4′-C), 128.49 (2 C, d, 3′,5′-C), 116.12, 112.62 (2 s, 3,4a-C), 93.76 (d, 8-C), 55.74 (t, NCH_2), 54.72, 52.69 (2 × 2 C, 2 t, 2 × N(CH_2)$_2$), 45.68 (q, NCH_3), 40.01 (t, NCH_2), 25.95 (t, CH_2).

Reaction of 3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2-amine 18 with 1-(3-aminopropyl)-4-methylpiperazine

A solution of **18** (266 mg, 0.86 mmol) and 1-(3-aminopropyl)-4-methylpiperazine (1.37 g, 8.73 mmol) in 2-ethoxyethanol (20 cm^3) under nitrogen was stirred at reflux for 5 d. The solvent was removed under reduced pressure, then the residue was diluted with aqueous Na_2CO_3 (100 cm^3) and extracted with EtOAc (3 × 120 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 0.5–1% MeOH–CH_2Cl_2, gave firstly recovered **18** (25 mg, 9%). Further elution with 10% MeOH–CH_2Cl_2 gave a crude solid (44 mg), which was further purified by chromatography on alumina, eluting with 0.5% MeOH–CH_2Cl_2, to give *3-(2,6-dichlorophenyl)-7-(4-methylpiperazin-1-yl)-1,6-naphthyridin-2-amine* **36** (21 mg, 6%), mp 223–227 °C (from CH_2Cl_2–light petroleum) (Found: C, 58.5; H, 5.1; N, 17.8. $C_{19}H_{19}Cl_2N_5$ requires C, 58.8;

H, 4.9; N, 18.0%); δ_H([$^2H_6$]DMSO) 8.56 (1 H, s, 5-H), 7.67 (1 H, s, 4-H), 7.60 (2 H, d, *J* 8.0, 3′,5′-H), 7.47 (1 H, dd, *J* 8.7 and 7.6, 4′-H), 6.51 (1 H, s, 8-H), 6.34 (2 H, br s, NH_2), 3.53 (4 H, t, *J* 4.8, $N(CH_2)_2$), 2.44 (4 H, t, *J* 4.8, $N(CH_2)_2$), 2.24 (3 H, s, NCH_3); δ_C([$^2H_6$]DMSO) 159.32, 157.86 (2 s, 2,7-C), 153.50 (s, 8a-C), 149.73 (d, 5-C), 136.72 (d, 4-C), 135.16 (2 C, s, 2′,6′-C), 134.34 (s, 1′-C), 130.73 (d, 4′-C), 128.52 (2 C, d, 3′,5′-C), 117.41, 113.11 (2 s, 3,4a-C), 96.28 (d, 8-C), 54.26 (2 C, t, $N(CH_2)_2$), 45.74 (q, NCH_3), 45.00 (2 C, t, $N(CH_2)_2$); *m*/*z* (HREIMS) 389.0983, 387.1001 (M^+, $C_{19}H_{19}Cl_2N_5$ requires 389.0988, 387.1018).

Further elution of the first column with 11–14% MeOH–CH_2Cl_2 gave a mixture, then elution with 15% MeOH–CH_2Cl_2 containing 1% Et_3N gave material which was treated with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (3 × 50 cm^3) to give **35** (177 mg, 46%).

Reaction of 3-(3,5-dimethoxyphenyl)-7-fluoro-1,6-naphthyridin-2-amine 26 with 1-(3-aminopropyl)-4-methylpiperazine

A solution of **26** (108 mg, 0.36 mmol) and 1-(3-aminopropyl)-4-methylpiperazine (0.573 g, 3.65 mmol) in 2-ethoxyethanol (10 cm^3) under nitrogen was stirred at reflux for 5 days. Further 1-(3-aminopropyl)-4-methylpiperazine (1.72 g, 11.0 mmol) was added, and the mixture stirred under nitrogen at reflux for 5 days. The solvent was removed under reduced pressure, then the residue was diluted with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (5 × 50 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 0.5% MeOH–CH_2Cl_2, gave firstly recovered **26** (5.5 mg, 5%). Further elution with 1–4% MeOH–CH_2Cl_2 containing 0.5% conc. NH_4OH gave a mixture, then further elution with 4–8% MeOH–CH_2Cl_2 containing 0.5–0.75% conc. NH_4OH gave material which was treated with aqueous Na_2CO_3 (50 cm^3) and extracted with CH_2Cl_2 (4 × 50 cm^3) to give *3-(3,5-dimethoxyphenyl)-7-{[3-(4-methylpiperazin-1-yl)propyl]amino}-1,6-naphthyridin-2-amine* **37** (68 mg, 43%), mp 120–124.5 °C (from CH_2Cl_2–hexane) (Found: C, 61.9; H, 7.1; N, 17.8. $C_{24}H_{32}N_6O_2\cdot 1.5H_2O$ requires C, 62.2; H, 7.6; N, 18.1%); δ_H([$^2H_6$]DMSO) 8.45 (1 H, s, 5-H), 7.67 (1 H, s, 4-H), 6.59 (2 H, d, *J* 2.2, 2′,6′-H), 6.52 (1 H, t, *J* 2.1, 4′-H), 6.46 (1 H, br t, *J* 5.5, N*H*CH_2), 6.27 (2 H, br s, NH_2), 6.18 (1 H, s, 8-H), 3.79 (6 H, s, 2 × OCH_3), 3.23 (2 H, m, NHC*H*$_2$), 2.6–2.1 (8 H, br s, $N(CH_2)_4N$), 2.36 (2 H, t, *J* 7.0, NCH_2), 2.15 (3 H, s, NCH_3), 1.70 (2 H, quintet, *J* 6.9, CH_2); δ_C([$^2H_6$]DMSO) 160.65 (2 C, s, 3′,5′-C), 159.01, 158.11 (2 s, 2,7-C), 152.64 (s, 8a-C), 150.35 (d, 5-C), 139.53 (s, 1′-C), 135.78 (d, 4-C), 120.64 (s, 3-C), 113.23 (s, 4a-C), 106.49 (2 C, d, 2′,6′-C), 99.70 (d, 4′-C), 93.82 (d, 8-C), 55.79 (t, NCH_2), 55.17 (2 C, q, 2 × OCH_3), 54.76, 52.72 (2 × 2 C, 2 t, 2 × $N(CH_2)_2$), 45.71 (q, NCH_3), 39.94 (t, NCH_2), 25.98 (t, CH_2).

Reaction of 3-(2,6-dichlorophenyl)-7-fluoro-1,6-naphthyridin-2(1*H*)-one 19 with 1-(3-aminopropyl)-4-methylpiperazine

A solution of **19** (95 mg, 0.31 mmol) and 1-(3-aminopropyl)-4-methylpiperazine (0.49 g, 3.12 mmol) in pentan-2-ol (10 cm^3) was stirred at reflux for 15 h. The solvent was removed under reduced pressure, then the residue was diluted with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (5 × 50 cm^3). The solvent was removed, then chromatography of the residue on silica gel, eluting with 5–10% MeOH–CH_2Cl_2 containing 0.3% Et_3N, gave material which was treated with aqueous Na_2CO_3 (50 cm^3) and extracted with CH_2Cl_2 (3 × 50 cm^3) to give *3-(2,6-dichlorophenyl)-7-{[3-(4-methylpiperazin-1-yl)propyl]amino}-1,6-naphthyridin-2(1H)-one* **38** (112 mg, 82%), mp 189–192 °C (from CH_2Cl_2–light petroleum) (Found: C, 58.9; H, 5.8; N, 15.4. $C_{22}H_{25}Cl_2N_5O$ requires C, 59.2; H, 5.7; N, 15.7%); δ_H([$^2H_6$]DMSO) 11.65 (1 H, br s, NH), 8.37 (1 H, s, 5-H), 7.71 (1 H, s, 4-H), 7.55 (2 H, d, *J* 7.9, 3′,5′-H), 7.42 (1 H, dd, *J* 8.7 and 7.6, 4′-H), 7.11 (1 H, br t, *J* 5.5, N*H*CH_2), 6.15 (1 H, s, 8-H), 3.26 (2 H, q, *J* 6.2, NHC*H*$_2$), 2.6–2.0 (8 H, br s, $N(CH_2)_4N$), 2.34 (2 H, t, *J* 7.1, NCH_2), 2.15 (3 H, s, NCH_3), 1.69 (2 H, quintet, *J* 7.0, CH_2); δ_C([$^2H_6$]DMSO) 160.52, 159.61 (2 s, 2,7-C), 150.00 (d, 5-C), 145.37 (s, 8a-C), 139.02 (d, 4-C), 135.11 (2 C, s, 2′,6′-C), 134.72 (s, 1′-C), 130.19 (d, 4′-C), 127.94 (2 C, d, 3′,5′-C), 123.26 (s, 3-C), 108.08 (s, 4a-C), 87.33 (br d, 8-C), 55.57 (t, NCH_2), 54.72, 52.68 (2 × 2 C, 2 t, $N(CH_2)_4N$), 45.70 (q, NCH_3), 39.51 (t, NCH_2), 26.01 (t, CH_2).

3-(2,6-Dichlorophenyl)-7-(4-methylpiperazin-1-yl)-1,6-naphthyridin-2-amine 36

A solution of **18** (83 mg, 0.27 mmol) and 1-methylpiperazine (1.50 cm^3, 13.5 mmol) in pentan-2-ol (10 cm^3) was stirred at reflux for 4 days. Further 1-methylpiperazine (1.20 cm^3, 10.8 mmol) was added and the mixture stirred at reflux for 3 days. The solvent was removed under reduced pressure, then the residue was diluted with aqueous Na_2CO_3 (50 cm^3) and extracted with EtOAc (4 × 50 cm^3). The solvent was removed, then chromatography of the residue on alumina, eluting with 0.4% MeOH–CH_2Cl_2, gave **36** (82 mg, 78%).

Acknowledgements

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

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