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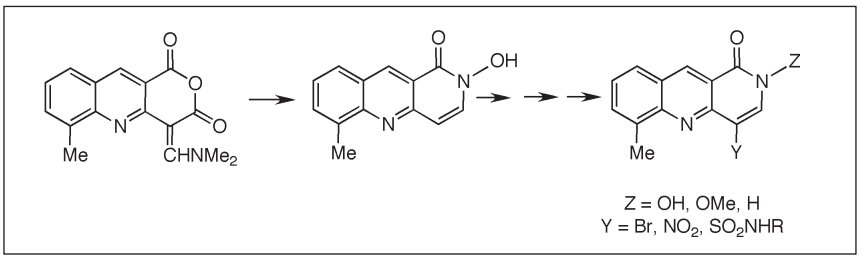

An efficient synthesis of 2-hydroxy-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one was devised. The hydroxy group was alkylated, acylated and replaced by hydrogen. Electrophilic nitration, bromination and chlorosulfonation occurred readily in the 4-position. From the last, various sulfonamide derivatives were prepared. A selection of the products was screened by the National Cancer Institute. Cytotoxicities were generally low.

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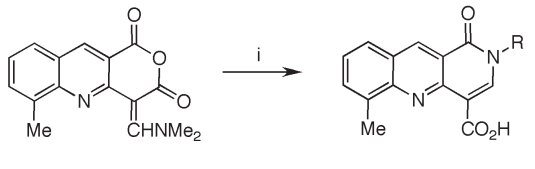
Compound **1** was reported as a product from reaction of Vilsmeier reagent with the appropriate quinoline analogue of homophthalic acid [1]. We subsequently found that **1** reacted readily with a variety of amines to give **2**, precursors to a new series of potential antitumor carboxamides (Scheme 1) [2]. Analogues of **1** react in the same way [3].

The change from **1** to **2** clearly involves ring opening and ring closing, but details of timing of the various steps has not been established. The only intermediate isolated is **3** (Figure 1), where this very insoluble first product precipitated from the reaction mixture, but this says nothing about how the later ring interconversion occurs.

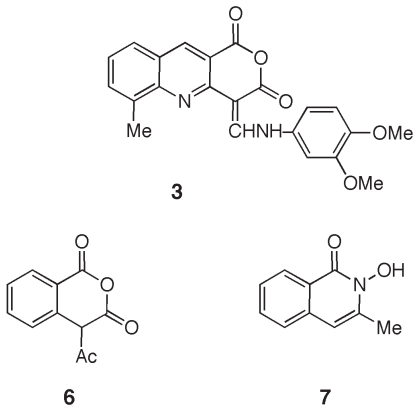
Scheme 1



1 **2**

(i) Excess RNH_2/DMF/20° **OR** 1.1 mol RNH_2/excess NEt_3/DMF/20°.

The standard conditions generally give high yields of **2** but, during further studies on the scope of the change from **1** to **2**, we have found that hydroxylamine provides an interesting case where a simple change in reaction conditions can provide a high proportion of **2a** (**2** with R=OH) or the decarboxylated compound **4a** (Scheme 2). This access to **4a** prompted us to investigate the chemistry of this novel system, and this paper reports on the preparation of various derivatives, some of which have been screened for anticancer activity. Compounds containing a 2-hydroxy substituent, such as **4a**, are metal chelators forming, for example, a deep red colour with Fe^{3+}, but this aspect has not yet been investigated.



3 **6** **7**

Figure 1

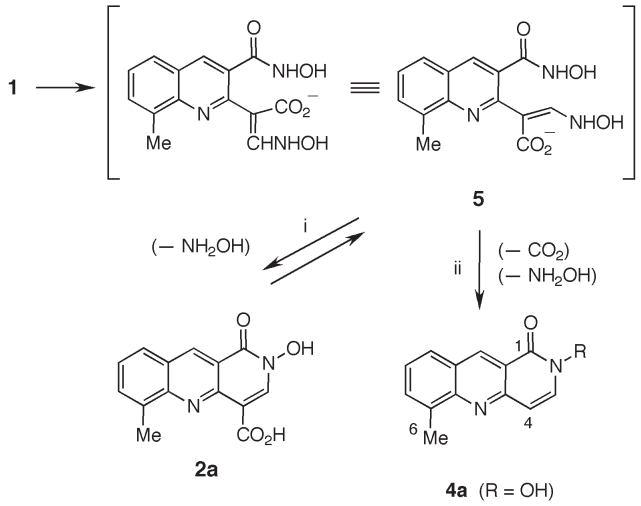
Formation of **4a**.

Compound **1** was reacted with 2.2 equivalents of hydroxylamine hydrochloride and excess triethylamine in *N*,*N*-dimethylformamide (DMF) at room temperature for 16 hours. In the reaction of **1** with most amines, the insoluble product **2** precipitates from the reaction mixture within a short time. But, with hydroxylamine, the precipitated solid was a water soluble triethylamine salt of **2a** along with triethylamine hydrochloride. If aqueous sodium hydroxide was added and the solution then acidified, **2a** was precipitated (64%). However, if the reaction mixture was heated at 100° for 1 hour before evaporation of the volatiles and addition of water to the residue, **4a** was obtained as a filterable solid (79%). The ^1H nmr spectrum was characteristic in that the singlet for H-3 in **2a** (8.6 ppm) was replaced by a set of doublets at 7.9 (H-3) and 6.7 (H-4) ppm in **4a**; the

upfield doublet was a useful diagnostic feature as it could be seen in the spectra of complex mixtures.

Both hydroxylamine and the *N*-OH function appear to be important in favoring the formation of the decarboxylated product, though it is not evident why this should be so. The pathway summarized in Scheme 2 reflects the overall result though it does not explain the complexities. Thus, **2a** is stable when heated as a solid, or as a solution in DMF (with or without triethylamine), but the addition of 1.2 equivalents of hydroxylamine gives efficient conversion to **4a**. Also, **2b** (**2** with R=butyl) was significantly less reactive under the same conditions (DMF/triethylamine/hydroxylamine/heat) and the result was more complicated. Five equivalents of hydroxylamine were required to produce appreciable reaction. After 16 hours at 100°, about 40% of **4b** (R=butyl) was formed, the rest being **2b** and unidentified minor byproducts. One can postulate that a

Scheme 2



(i) 1.2 mol NH_2OH•HCl/NEt_3/DMF/20°/16 h. (ii) 2.2 mol NH_2OH•HCl/NEt_3/DMF/20°/16 h, then 100°/1 h.

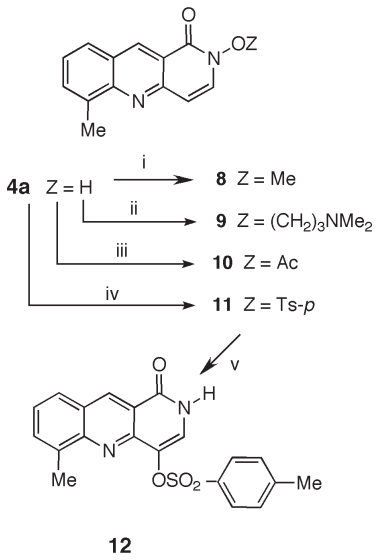
ring opened species like **5** is formed, both in the initial reaction from **1** and also from the product **2a**, and decarboxylation, where it occurs, does so from this α,β-unsaturated acid prior to ring closure to **4a**.

4-Acetylisochromandione (**6**) (Figure 1) was reported to undergo this type of rearrangement, with decarboxylation, when heated with hydroxylamine hydrochloride in pyridine, to give **7** [4].

Reactions of the 2-Hydroxy Function.

Alkylation, acylation and sulfonylation were easily achieved (Scheme 3). Thus, reaction at 100° with iodomethane in DMF containing solid potassium carbonate gave the methoxy compound **8**, and reaction under these conditions with 3-(dimethylamino)propyl chloride, but for a longer time, gave the analogous **9**. Conventional acetylation with acetic anhydride/acetic acid at 60° gave the acetoxy compound **10**. Tosylation to **11** was achieved with tosyl chloride, at room temperature in DMF containing triethylamine. In accord with literature reports of the behaviour of *N*-tosyloxyisocarbostyryl [5], **11** when refluxed in nitromethane for 5 hours underwent a clean rearrangement to the 4-tosyloxy isomer **12**. Interestingly, **14**, the 4-bromo analogue of **11** (prepared from **13**—below and Scheme 4), underwent the same reaction, with loss of the bromo group, to give the same **12**.

Scheme 3



(i) excess MeI/excess K_2CO_3/DMF/100°/3 h. (ii) 2 mol $Cl(CH_2)_3NMe_2$.HCl/excess K_2CO_3/DMF/100°/16 h. (iii) Ac_2O/AcOH/60°/1 h. (iv) 2.5 mol *p*-TsCl/excess NEt_3/DMF/20°/6 h. (v) $MeNO_2$/reflux/5 h.

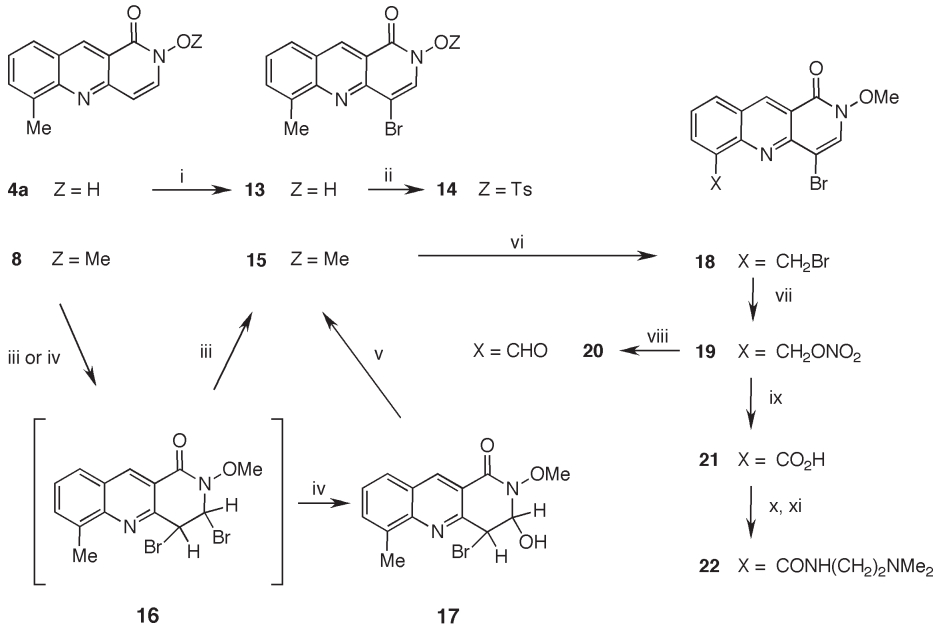
Other Reactions at the 4-Position.

The 2-hydroxy (**4a**), 2-methoxy (**8**) and 2-acetoxy (**10**) compounds were potential substrates but most reactions were done on **8**. It has been noted that *N*-methylisoquinolin-1-one readily undergoes electrophilic substitution reactions at the 4-position [6,7], and similar reactivity was seen with the present compounds.

Bromination.

Molecular bromine reacted readily without the need for a catalyst. Thus, **4a** with bromine in hot 1,4-dioxane gave the 4-bromo compound **13** within 1 minute, while **8** was reacted similarly in benzene to give **15** (Scheme 4); the initial precipitate in each case was the corresponding hydrobromide salt. Substitution in the 4- rather than 3-position was confirmed by an HMBC nmr experiment on **13** where $^3J_{CH}$ coupling was seen between H-3 and the two quaternary carbons C-1 and C-4a.

Scheme 4

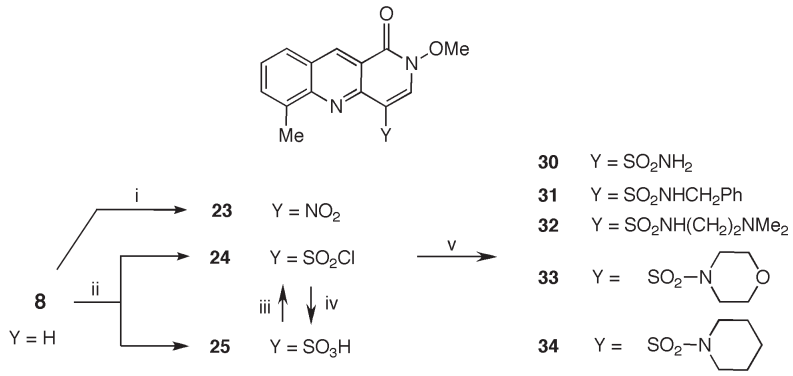


(i) Br_2/1,4-dioxane/reflux/1 min. (ii) 2.5 mol *p*-TsCl/excess NEt_3/DMF/20°/1 h. (iii) excess Br_2/C_6H_6/reflux/10 min. (iv) excess Br_2/CH_2Cl_2/–10°/10 min. (v) heat >170°. (vi) 1.2 mol NBS/cat. Bz_2O_2/C_6H_6/reflux/50 min. (vii) 1 mol $Hg_2(NO_3)_2$•$2H_2O$/$(MeOCH_2)_2$/reflux/1 h. (viii) 10 mol $NEt_3/(MeOCH_2)_2$/reflux/4 h. (ix) Ceased reflux of viii and added 50 mol AcOH /5 mol solid $NaClO_2$/vigorous stir 20°/16 h. (x) 2.5 mol CDI/1,4-dioxane/reflux/16 h. Recharge with 2.5 mol CDI/reflux/8 h. (xi) $NH_2(CH_2)_2NMe_2/CH_2Cl_2$/20°/16 h.

We have evidence that the bromination reaction follows an addition-elimination pathway. Thus, when bromine was added to a solution of **8** in deuteriochloroform in an nmr tube, the development of two doublets at 6.3 and 5.7 ppm (J = 2.5 Hz) could be seen, consistent with intermediacy of **16**, though the spectrum was not clean. When this solution was heated, these signals diminished and the low field singlet for H-10 of **15** appeared.

On a preparative scale, the reaction was done at –10° in dichloromethane and it was necessary to carry out a wash with dilute carbonate and water before isolating a clean product. All data for this were consistent with the bromo-hydroxy compound **17** and it was stable to recrystallization from acetonitrile. When the solid was heated above its melting point, a clean change to **15** occurred. The formation of a bromo-hydroxy addition compound has previously been reported from a somewhat related reaction of an *N*-methylisoquinolinone [6].

Scheme 5



(i) $AcONO_2/Ac_2O$/50°/30 min. (ii) $ClSO_3H$/70°/16 h. (iii) $SOCl_2$/DMF/reflux/45 min. (iv) 10% K_2CO_3/20°/8 h, then H^+. (v) amine/$NEt_3/CH_2Cl_2/N_2$/<4°/30 min, then 20°/16 h.

Compound **8** was also reacted with *N*-bromosuccinimide (NBS)/benzoyl peroxide in refluxing benzene. It was evident that in these conditions also, the 4-position was the most reactive but the overall product was not as clean as when **15**, preformed as above, was subjected to NBS bromination and the bromomethyl compound **18** was produced. This compound was then converted in a sequence we have developed [8], through nitrate ester **19** to acid **21** (Scheme 4). Finally, this was converted to the carboxamide **22**, an analogue of a series whose antitumor activity we have previously reported [2].

Nitration.

Neither **4a** nor **10** was successfully nitrated but **8** reacted readily with acetyl nitrate under mild conditions to give a 59% yield of **23** (Scheme 5) (reaction with potassium nitrate/concentrated sulfuric acid was not as clean and also gave probable nitration in the benzo ring).

Chlorosulfonation.

Reaction of the 2-methoxy compound (**8**) with chlorosulfonic acid at 70° for 16 hours gave, on addition to ice, a mixture of 4-sulfonyl chloride (**24**) and 4-sulfonic acid (**25**) as their hydrochloride salts (Scheme 5). Similar behaviour has been reported for chlorosulfonation of some quinolines and isoquinolines [9]. Reaction under more forcing conditions failed to eliminate the acid, but this was achieved by treating the above mixture with hot thionyl chloride and DMF, and the free base **24** was obtained by careful treatment with dilute potassium carbonate. A sample of the sulfonic acid **25** was obtained by mild alkaline hydrolysis of the hydrochloride of **24**.

The reaction of **4a** with chlorosulfonic acid under the above conditions was similar but in this case the sulfonic acid **26** was the sole isolated product (Scheme 6). When this was treated with thionyl chloride/DMF, not only was the sulfonyl chloride formed but the functionalities at the 1- and 2-positions were also affected and the fully aromatic **27** was formed. The crude product was sufficiently pure for direct use in further reactions.

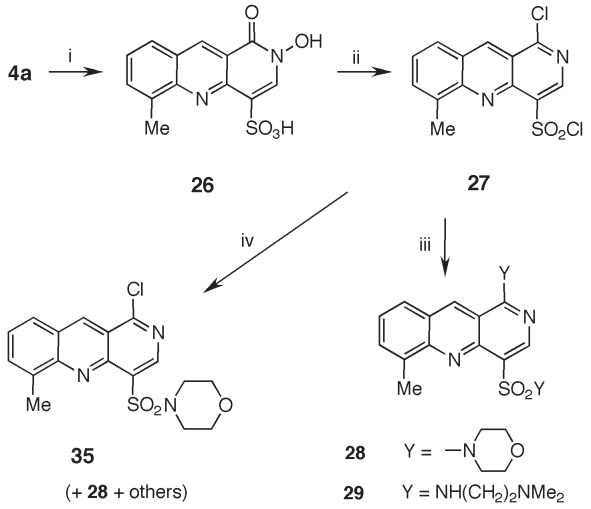
Further Reactions of the Sulfonyl Chlorides.

The sulfonamide class of drugs has diverse pharmacological activities [10] and the ready synthesis of **24** and **27** prompted us to synthesize some sulfonamide and related derivatives for anticancer testing.

When **27** was reacted with an excess of an amine in dichloromethane at room temperature [11], both chlorines were displaced and the sulfonamides **28** and **29** were formed (Scheme 6).

The potential of **27** as an intermediate would be enhanced if the chlorines could be replaced by two different amines. To this end, we looked at reaction with one equivalent of morpholine but the result was disappointing.

Scheme 6



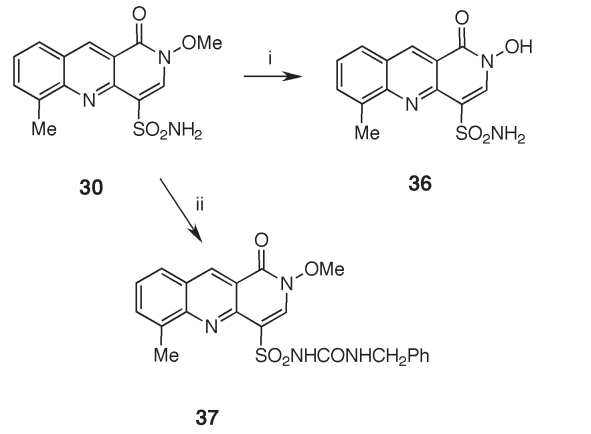
(i) $ClSO_3H$/70°/5 h. (ii) $SOCl_2$/DMF/reflux/45 min. (iii) amine/NEt_3/CH_2Cl_2/N_2/<4°/30 min, then 20°/16 h. (iv) 1 mol morpholine/1 mol NEt_3/CH_2Cl_2/N_2/–18°/16 h.

The product was a mixture but chromatography provided samples of one monosubstituted compound, assigned as **35**, along with, surprisingly, an appreciable but variable amount of the disubstituted compound **28**. This was not a viable source of **35** and an alternative synthesis, which also confirmed the above assignment, is described below.

With only the sulfonyl chloride present in **24**, reaction with a selection of amines, as above, gave the sulfonamides **30**–**34**.

Further transformations were carried out on **30** (Scheme 7). Since, as described above, the 2-hydroxy group of **26** did not survive thionyl chloride treatment, the 2-hydroxy sulfonamide **36** was prepared by demethylation of **30** in refluxing acetic acid/aqueous hydrobromic acid. It has

Scheme 7



(i) 40% HBr/HOAc/130°/16 h. (ii) $PhCH_2NCO/K_2CO_3$/acetone/reflux/16 h.

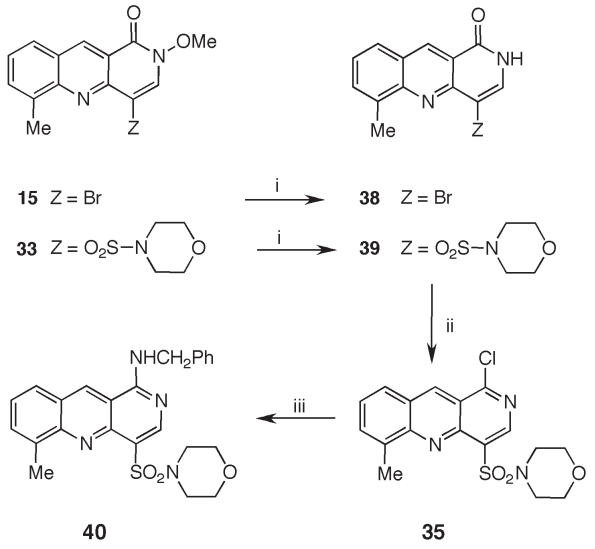
been stated that conversion of *N*-methoxyamides to *N*-hydroxyamides is more difficult to achieve than demethylation of phenol methyl ethers [12]. But, in the present case, the reaction occurred quite readily; the reflux time was important since overreaction resulted in the replacement of the *N*-OH by *N*H. It was therefore necessary to stop the reaction with some **30** still present and to separate this from **36** by chromatography.

In a different type of reaction, an example of a sulfonylurea **37** was prepared by reacting **30** with benzylisocyanate in refluxing acetone containing solid potassium carbonate. These literature conditions [13] were more successful than the use of triethylamine/acetone or aqueous base.

With the problems encountered in trying to control the direction of monosubstitution in the dichloro compound **27** (above), an alternative approach was investigated. We found that reactions of *N*-OMe compounds with solid potassium hydroxide in hot DMF brought about a clean conversion to the *N*H analogues without otherwise affecting the tricycle or substituents. Thus, neither the 4-bromo (**15** →**38—**Scheme 8) nor sulfonamide (**33**→**39**) was affected. It has been reported that the strong, sterically hindered base, lithium diisopropylamide achieved the demethoxylation of *N*-methoxyamides by an E_2 elimination of formaldehyde [14]. Presumably a similar mechanism is involved in the present case; the *N*-OH compound **4a** was unaffected by these conditions.

The ability to use this route to control the identity of the amine moiety in 1,4-disubstituted compounds was now demonstrated by further reactions of **39**. Reaction with phosphoryl chloride gave **35** (and thereby confirmed this as the product from mono-morpholine substitution in **27**, Scheme 6) and we used benzylamine to illustrate the ready displacement of the chlorine to form **40**.

Scheme 8



(i) KOH/DMF/100°/30 min. (ii) $POCl_3$/reflux/8 h. (iii) $PhCH_2NH_2/NEt_3/CH_2Cl_2/N_2$/20°/16 h.

Biological Activity.

Our prime interest is in anticancer agents; testing for biological activity in this potentially interesting set has been limited to this area and compounds **4a**, **9**, **12**, **22**, **25**, **28**, **30**, **32**, **33**, **36**, **37** were submitted to the National Cancer Institute, USA. Of these, only **9** and **22** satisfied the prescreen toxicity criteria. A particular point of interest is that the sulfonamide **32** is a direct analogue of a carboxamide that shows potent *in vitro* cytotoxicity [3]. In the full assay for cytotoxicity against 60 human cancer cell lines, both **9** [most active GI_{50} [15], 3.4 μM (SN12C renal cancer); MGM [16], 28.2 μM] and **22** [most active GI_{50}, 0.68 μM (HCC-2998 colon cancer); MGM, 4.0 μM] showed unexceptional activity. The result for **22** indicates that the positioning of the carboxamide on the chromophore is crucial, since we have reported other benzonaphthyridinone carboxamides as potent antitumor agents [2,3].

EXPERIMENTAL

^{1}H Nuclear Magnetic Resonance (nmr) spectra and ^{13}C nmr spectra were recorded at 300.13 MHz and 75.47 MHz, respectively, on a Bruker Avance 300 spectrometer. Chemical shifts are reported as delta values (δ) in parts per million relative to tetramethylsilane. Standard PENDANT, HSQC, HMBC and COSY spectra were used to make proton and carbon assignments. Melting points were recorded on a Reichert "Thermopan" microscope hot stage apparatus and are uncorrected. Electrospray mass spectra (esms) were recorded by Mr C. Verdon, La Trobe University, on a VG BioQ triple quadrupole mass spectrometer using positive ion mode with acetonitrile–water (1:1) containing 1% formic acid as mobile phase; unless otherwise stated, the cone voltage was 50 V. High resolution mass spectra (hrms) were recorded at the University of Tasmania, Australia, using liquid secondary ionisation mode with 3-nitrobenzyl alcohol as liquid matrix. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Commercial reagents were used without further purification. Silica gel (silica gel 60, 230–400 mesh ASTM) and preparative layer chromatography (plc) plates (20 × 20 cm, silica gel 60 F_{254}, 2 mm) were supplied by Merck Chemicals. Unless otherwise stated, the eluent used for flash chromatography was ethyl acetate–hexane (1:1).

4-[(Dimethylamino)methylene]-6-methyl-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (**1**).

The previously reported method [1] was slightly modified: To *N*,*N*-dimethylformamide (16 mL) at 0° (salt-ice bath) was added phosphoryl chloride (3.2 mL), dropwise, with constant stirring. Ethyl (3-carboxy-8-methylquinolin-2-yl)acetate (3.17 g, 12.05 mmol) was added, the salt-ice bath was removed, and stirring was continued for a further 2 hours. The reaction mixture was filtered and washed with a little cold dichloromethane to afford **1** as

an orange solid (2.93 g, 86%), with mp and nmr data as previously reported.

2-Hydroxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (**2a**) [3] and 2-butyl-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (**2b**) [2] were prepared as previously reported.

2-Hydroxy-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**4a**).

To a stirred suspension of the dione **1** (3.45 g, 12.23 mmol) in *N*,*N*-dimethylformamide (60 mL) was added triethylamine (15 mL), followed by hydroxylamine hydrochloride (1.89 g, 27.22 mmol). The whole was stirred for 16 hours at room temperature, and then the mixture was heated at 100° for 1 hour, during which time dissolution occurred. The volatiles were removed under reduced pressure, water was added, and the red solid was filtered and washed with water to give **4a** (2.18 g, 79%), which was used directly in further reactions. Recrystallization from ethanol gave **4a** as mustard coloured needles, mp 252–254°. A solution in ethanol gave a deep red coloration upon the addition of Fe^{3+}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.73 (s, 3H, $ArCH_3$), 6.73 (d, J = 7.9 Hz, 1H, H-4), 7.51 (t, J = 7.5 Hz, 1H, H-8), 7.74 (d, J = 6.8 Hz, 1H, H-7), 7.88 (d, J = 8.0 Hz, 1H, H-3), 8.06 (d, J = 8.3 Hz, 1H, H-9), 9.28 (s, 1H, H-10), 11.61 (br s, 1H, OH—exchanged with added deuterium oxide); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.9 ($ArCH_3$), 105.8 (C-4), 120.4 (C-10a), 125.7 (C-9a), 126.2 (C-8), 127.6 (C-9), 132.1 (C-7), 136.0 (C-6), 136.1 (C-3), 137.8 (C-10), 149.3 (C-5a), 150.2 (C-4a), 158.2 (C-1).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.70; H, 4.41; N, 12.42.

2-Methoxy-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**8**).

The *N*-hydroxy compound **4a** (2.72 g, 12.04 mmol), potassium carbonate (2.72 g, 19.68 mmol), iodomethane (3 mL, 48.19 mmol), and *N*,*N*-dimethylformamide (60 mL) were combined, and the whole was heated at 100° for 3 hours. The reaction mixture was stripped of solvent under reduced pressure, ice-water was added, and the solid was collected by filtration and washed with water to furnish **8** (2.49 g, 86%) as bronze flakes, mp 212–214° (methanol); ^{1}H nmr (deuteriochloroform): δ 2.83 (s, 3H, $ArCH_3$), 4.13 (s, 3H, OCH_3), 6.85 [17] (d, J = 8.1 Hz, 1H, H-4), 7.46 (dd, J = 8.0, 7.3 Hz, 1H, H-8), 7.53 (d, J = 8.0 Hz, 1H, H-3), 7.68 (d, J = 6.8 Hz, 1H, H-7), 7.84 (d, J = 8.2 Hz, 1H, H-9), 9.25 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.9 ($ArCH_3$), 64.2 (OCH_3), 107.4 (C-4), 120.8 (C-10a), 125.7 (C-9a), 126.2 (C-8), 126.8 (C-9), 132.1 (C-7), 132.9 (C-3), 136.4 (C-6), 138.3 (C-10), 149.2 (C-5a), 149.9 (C-4a), 158.1 (C-1).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.03; H, 4.89; N, 11.61.

2-[3-(Dimethylamino)propoxy]-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**9**).

The *N*-hydroxy compound **4a** (0.40 g, 1.77 mmol), 3-(dimethylamino)propyl chloride hydrochloride (0.56 g, 3.54 mmol) and potassium carbonate (1.12 g) in *N*,*N*-dimethylformamide (35 mL) were heated at 100° for 16 hours. The volatiles were removed under reduced pressure, water was added, and the product was extracted with dichloromethane (× 3). The organic fraction was washed with brine (× 3), dried over magnesium sulfate, filtered and the filtrate was evaporated under reduced pressure to leave the crude product as a brown oil that solidified (0.40 g). This was purified by flash column chromatography; the column was washed with acetone and the product was eluted with acetone–methanol–triethylamine (100:5:1) (R_f, 0.2). The *O*-alkylated derivative **9** was thus obtained as a lemon coloured solid (0.26 g, 47%), mp 75–78° [petroleum spirit (bp 80–110°)]; ^{1}H nmr (deuteriochloroform): δ 1.95 (quintet, J = 6.8 Hz, 2H, $CH_2C\mathbf{H_2}CH_2$), 2.24 [s, 6H, $N(CH_3)_2$], 2.51 [18] (t, J = 7.2 Hz, 2H, $CH_2CH_2C\mathbf{H_2}$), 2.76 (s, 3H, $ArCH_3$), 4.32 (t, J = 6.4 Hz, 2H, $C\mathbf{H_2}CH_2CH_2$), 6.75 (d, J = 8.1 Hz, 1H, H-4), 7.37 (t, J = 7.6 Hz, 1H, H-8), 7.48 (d, J = 8.1 Hz, 1H, H-3), 7.59 (d, J = 6.8 Hz, 1H, H-7), 7.75 (d, J = 8.3 Hz, 1H, H-9), 9.14 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.7 ($ArCH_3$), 25.8 ($CH_2\mathbf{C}H_2CH_2$), 45.0 [$N(CH_3)_2$], 55.5 ($CH_2CH_2\mathbf{C}H_2$), 75.0 ($\mathbf{C}H_2CH_2CH_2$), 107.5 (C-4), 120.7 (C-10a), 125.7 (C-9a), 126.0 (C-8), 126.7 (C-9), 131.7 (C-7), 133.3 (C-3), 136.6 (C-6), 137.8 (C-10), 149.6 (C-5a), 150.0 (C-4a), 158.4 (C-1).

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.27; H, 6.54; N, 13.48.

2-Acetoxy-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**10**).

The *N*-hydroxy compound **4a** (0.50 g, 2.21 mmol), acetic anhydride (15 mL) and acetic acid (3 mL) were heated at 60° for 1 hour. Dissolution occurred slowly during this time, and the resultant solution was poured onto ice (150 mL). The initially-formed oil solidified after stirring for 1 hour, and the solid was filtered and washed with water to give **10** as a pale yellow solid (0.48 g, 81%). A sample for analysis was heated to above its melting point and, after being cooled, was purified by flash column chromatography (R_f, 0.5) to give a pale yellow solid, mp 178–186°; ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 3H, $COCH_3$), 2.83 (s, 3H, $ArCH_3$), 6.88 [17] (d, J = 8.1 Hz, 1H, H-4), 7.34 (d, J = 8.1 Hz, 1H, H-3), 7.46 (t, J = 7.6 Hz, 1H, H-8), 7.68 (d, J = 6.9 Hz, 1H, H-7), 7.83 (d, J = 8.3 Hz, 1H, H-9), 9.21 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.6 ($CO\mathbf{C}H_3$), 17.8 ($ArCH_3$), 107.6 (C-4), 120.4 (C-10a), 125.8 (C-9a), 126.4 (C-8), 126.8 (C-9), 132.2 (C-7), 132.5 (C-3), 136.7 (C-6), 138.5 (C-10), 149.6 (C-5a), 150.0 (C-4a), 157.2 (C-1), 166.6 ($\mathbf{C}OCH_3$).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.29; H, 4.65; N, 10.52.

2-(4-Tosyloxy)-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**11**).

To a suspension of the *N*-hydroxy compound **4a** (0.30 g, 1.33 mmol) in *N*,*N*-dimethylformamide (15 mL) and triethylamine (1 mL) was added, in one portion, 4-toluenesulfonyl chloride (0.63 g, 3.30 mmol) and the whole was stirred for 6 hours. The reaction was filtered to remove a small amount of insoluble material, ice-water was added (*ca* 100 mL), and the resultant solid was collected by filtration and washed with water to give the *N*-tosyloxy compound **11** as a yellow solid (0.30 g, 59%). Recrystallization resulted in some rearrangement to the 4-tosyloxy derivative **12** (below). Therefore, the solid was dissolved in a small amount of dichloromethane, the solution was filtered, and the product was reprecipitated by the addition of petroleum spirit (bp 80–110°) and had mp 131–135°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.42 (s, 3H, $ArCH_3$-4′), 2.72 (s, 3H, $ArCH_3$-6), 6.75 (d, J = 8.3 Hz, 1H, H-4), 7.48 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 7.55 (t, J = 7.6 Hz, 1H, H-8), 7.73 (d, J = 8.3 Hz, 1H, H-3), 7.79 (d, J = 6.7 Hz, 1H, H-7), 7.88 (d, J = 8.0 Hz, 2H, H-2′, H-6′), 8.06 (d, J = 8.2 Hz, 1H, H-9), 9.17 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.8 ($ArCH_3$-6), 21.4 ($ArCH_3$-4′), 107.7 (C-4), 120.3 (C-10a), 125.8 (C-9a), 126.9 (C-8), 127.7 (C-9), 129.5 (C-2′, C-6′), 129.8 (C-1′),

130.6 (C-3′, C-5′), 132.9 (C-7), 135.2 (C-3), 136.2 (C-6), 138.9 (C-10), 147.5 (C-4′), 149.4 (C-5a), 149.9 (C-4a), 157.1 (C-1).

Anal. Calcd. for $C_{20}H_{16}N_2O_4S$: C, 63.15; H, 4.24; N, 7.36. Found: C, 62.90; H, 4.13; N, 7.49.

6-Methyl-4-(4-tosyloxy)benzo[*b*][1,6]naphthyridin-1(2*H*)-one (**12**).

The *N*-tosyloxy compound **11** (0.15 g, 0.39 mmol) and nitromethane (20 mL) were heated under reflux for *ca* 5 hours [as monitored by tlc—ethyl acetate–hexane (3:7); R_f **11**, 0.7; R_f **12**, 0.2]. The solvent was evaporated under reduced pressure to leave the 4-tosyloxy compound **12** (0.15 g, 100%) as a brown solid with mp 253–256° (ethanol × 2); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.22 (s, 3H, $ArCH_3$-4′), 2.57 (s, 3H, $ArCH_3$-6), 7.30 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 7.45–7.53 (d + t, 2H, H-3, H-8—collapsed to s + d with added deuterium oxide), 7.73 (d, J = 6.7 Hz, 1H, H-7), 7.81 (d, J = 8.0 Hz, 2H, H-2′, H-6′), 8.01 (d, J = 8.2 Hz, 1H, H-9), 9.14 (s, 1H, H-10), 11.41 (d, J = 6.0 Hz, 1H, NH—exchanged with added deuterium oxide); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.4 ($ArCH_3$-6), 21.1 ($ArCH_3$-4′), 120.0 (C-10a), 126.1 (C-9a), 126.7 (C-8), 127.5 (C-9), 127.8 (C-3), 128.5 (C-2′, C-6′), 128.7 (C-4), 129.9 (C-3′, C-5′), 132.3 (C-1′), 132.5 (C-7), 136.3 (C-6), 138.5 (C-10), 145.5 (C-4′), 145.9 (C-4a), 148.7 (C-5a), 161.4 (C-1).

Anal. Calcd. for $C_{20}H_{16}N_2O_4S$: C, 63.15; H, 4.24; N, 7.36. Found: C, 63.12; H, 4.15; N, 7.59.

4-Bromo-2-hydroxy-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**13**).

To the *N*-hydroxy compound **4a** (0.40 g, 1.77 mmol) dissolved in boiling 1,4-dioxane (60 mL) was added bromine (1 mL, 19.41 mmol), and the whole was heated under reflux for 1 minute. The reaction mixture was cooled, filtered, and the orange solid was washed with diethyl ether. This material was suspended in ethanol (100 mL) and triethylamine (5 mL) (with initial sonication to obtain homogeneity), and the mixture was evaporated to dryness under reduced pressure. Water was added, and the solid was collected by filtration and washed with water, to give **13** as a pale yellow solid (0.47 g, 87%), mp >300°. A sample was recrystallized from *n*-propanol for analysis but retained *ca* 10% solvent even after drying at 150° and *ca* 0.01 mmHg for 24 hours. A solution in ethanol gave a deep red coloration upon the addition of Fe^{3+}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.79 (s, 3H, $ArCH_3$), 7.58 (t, J = 6.8 Hz, 1H, H-8), 7.82 (d, J = 5.9 Hz, 1H, H-7), 8.13 (d, J = 7.6 Hz, 1H, H-9), 8.43 (s, 1H, H-3), 9.33 (s, 1H, H-10), 11.83 (s, 1H, OH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.5 ($ArCH_3$), 98.7 (C), 119.9 (C), 125.9 (C-9a), 127.0 (C-8), 127.3 (C-9), 132.5 (C-7), 136.3 (C-6), 136.4 (C-3), 138.5 (C-10), 146.3 (C-4a), 148.7 (C-5a), 157.9 (C-1); esms: m/z 307.2, 305.2; both $(M+H)^+$.

Anal. Calcd. for $C_{13}H_9BrN_2O_2$•0.1 C_3H_8O: C, 51.34; H, 3.17; N, 9.00. Found: C, 51.72; H, 2.98; N, 9.22.

4-Bromo-2-(4-tosyloxy)-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**14**).

From the bromo compound **13** (0.47 g, 1.54 mmol), as for the tosyloxy compound **11**, except with a greater volume of *N*,*N*-dimethylformamide (50 mL) and the reaction was carried out for 1 hour. The bromo-*N*-tosyloxy compound **14** (0.50 g, 71%) was obtained as an off white solid with mp 103–107°; the solid turned orange and began degrading upon standing for 1 week [19]; ^{1}H nmr (deuteriochloroform): δ 2.47 (s, 3H, $ArCH_3$-4′), 2.90 (s, 3H, $ArCH_3$-6), 7.37 (d, J = 8.3 Hz, 2H, H-3′, H-5′), 7.53 (t, J = 7.6 Hz, 1H, H-8), 7.76 (d, J = 7.0 Hz, 1H, H-7), 7.82 (d, J = 8.2 Hz, 1H, H-9), 7.89 (s, 1H, H-3), 7.92 (d, J = 8.3 Hz, 2H, H-2′, H-6′), 9.06 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.4 ($ArCH_3$-6), 21.6 ($ArCH_3$-4′), 102.2 (C), 119.4 (C), 126.0 (C-9a), 126.4 (C-9), 127.3 (C-8), 129.4 (C-2′, C-6′), 129.8 (C-3′, C-5′), 129.9 (C-1′), 132.6 (C-7), 133.6 (C-3), 137.7 (C-6), 139.1 (C-10), 146.0 (C-4a), 147.0 (C-4′), 149.5 (C-5a), 156.9 (C-1); esms (36 V): m/z 461.5, 459.5; both $(M+H)^+$.

4-Bromo-2-methoxy-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**15**).

To a stirred solution of the *N*-methoxy compound **8** (1.00 g, 4.16 mmol) in hot benzene (50 mL) was added bromine (1 mL, 19.41 mmol), and the resultant suspension was stirred for 10 minutes. The reaction mixture was filtered and the orange solid was washed with diethyl ether. This material (1.84 g) was partitioned between 10% potassium carbonate and dichloromethane, and the organic layer was washed twice more with base, then with water (× 3), dried over magnesium sulfate, filtered, and the filtrate was evaporated under reduced pressure to give the monobromo compound **15** (0.94 g, 71%) as an orange solid, mp 180–189° (gradually formed needles) (acetonitrile); ^{1}H nmr (deuteriochloroform): δ 2.91 (s, 3H, $ArCH_3$), 4.14 (s, 3H, OCH_3), 7.53 (t, J = 7.6 Hz, 1H, H-8), 7.75 (d, J = 6.9 Hz, 1H, H-7), 7.87–7.90 (m, 2H, H-9, H-3), 9.27 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.4 ($ArCH_3$), 64.6 (OCH_3), 101.2 (C), 120.0 (C), 125.9 (C-9a), 126.4 (C-9), 126.9 (C-8), 132.1 (C-7), 132.9 (C-3), 137.5 (C-6), 138.4 (C-10), 146.1 (C-4a), 149.3 (C-5a), 157.6 (C-1).

Anal. Calcd. for $C_{14}H_{11}BrN_2O_2$: C, 52.69; H, 3.47; N, 8.78. Found: C, 52.93; H, 3.53; N, 8.78.

4-Bromo-3-hydroxy-2-methoxy-6-methyl-3,4-dihydrobenzo[*b*]-[1,6]naphthyridin-1(2*H*)-one (**17**).

To the *N*-methoxy compound **8** (0.40 g, 1.66 mmol) dissolved in dichloromethane (40 mL) at *ca* –10° (acetone-ice bath) was added an excess of bromine (0.5 mL, 9.70 mmol) in one portion, and the whole was stirred at the same temperature for 10 minutes. The resultant suspension was diluted with more dichloromethane and was washed with ice-10% sodium carbonate (× 4, or until the organic phase was yellow) and then with ice-water. The organic fraction was dried over magnesium sulfate, filtered and the filtrate was concentrated to *ca* 5 mL under reduced pressure without heating. The resultant white solid was collected by filtration and washed with a small amount of cold dichloromethane to render the alcohol **17** as a white powder (0.36 g, 64%), mp 159–162° (acetonitrile). The white powder turned light pink over a few days and red on long standing; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.70 (s, 3H, $ArCH_3$), 3.86 (s, 3H, OCH_3), 5.51 (d, J = 2.4 Hz, 1H, H-4), 5.60 (dd, J = 5.3, 2.5 Hz, 1H, H-3—collapsed to d, J = 2.5 Hz, with added deuterium oxide), 7.49 (d, J = 5.3 Hz, 1H, OH—exchanged with added deuterium oxide), 7.59 (t, J = 7.6 Hz, 1H, H-8), 7.77 (d, J = 7.0 Hz, 1H, H-7), 8.04 (d, J = 8.1 Hz, 1H, H-9), 8.99 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.6 ($ArCH_3$), 49.4 (C-4), 62.1 (OCH_3), 85.0 (C-3), 120.6 (C-10a), 127.1 (C-9a), 127.5 (C-9), 127.9 (C-8), 132.5 (C-7), 136.4 (C-6), 138.3 (C-10), 147.4 (C-5a), 152.8 (C-4a), 159.1 (C-1).

Anal. Calcd. for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; N, 8.31. Found: C, 50.13; H, 3.97; N, 8.45.

The dichloromethane filtrate contained primarily a mixture of more **17** (R_f, 0.5) and the monobromo compound **15** (R_f, 0.7).

Compound **17** (0.36 g, 1.07 mmol) was heated to above its melting point, then cooled, and the resultant brown solid was dis-

solved in dichloromethane and washed with 10% sodium bicarbonate and then with brine (× 3). The organic phase was dried over magnesium sulfate, filtered and evaporated under reduced pressure to give the monobromo compound **15** as an orange solid (0.24 g, 70%) with mp and nmr data as above.

4-Bromo-2-methoxy-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-6-carboxaldehyde (**20**) or 4-Bromo-2-methoxy-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-6-carboxylic Acid (**21**).

To the bromo-*N*-methoxy compound **15** (0.82 g, 2.57 mmol) dissolved in hot benzene (82 mL) was added *N*-bromosuccinimide (0.55 g, 3.09 mmol) and benzoyl peroxide (0.06 g, 0.25 mmol), and the whole was heated under reflux for 50 minutes. The resultant solution was cooled, washed with cold 10% potassium carbonate (× 2) and then with brine (× 3). The organic fraction was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to give 4-bromo-6-(bromomethyl)-2-methoxybenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**18**) as an orange solid (1.13 g), sufficiently pure for further reaction. A sample recrystallized from diisopropyl ether–dichloromethane had mp 223–225°; ^{1}H nmr (deuteriochloroform): δ 4.14 (s, 3H, OCH_3), 5.34 (s, 2H, CH_2Br), 7.61 (dd, J = 8.3, 7.1 Hz, 1H, H-8), 7.94 (s, 1H, H-3), 8.01–8.05 (m, 2H, H-9, H-7), 9.31 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 28.5 (CH_2Br), 64.6 (OCH_3), 101.1 (C), 120.8 (C), 126.1 (C-9a), 127.0 (C-8), 129.3 (C-9), 133.4 (C-7), 133.6 (C-3), 136.3 (C-6), 138.8 (C-10), 146.9 (C-4a), 147.7 (C-5a), 157.5 (C-1).

To a solution of crude **18** (0.78 g, 1.97 mmol) in hot 1,2-dimethoxyethane (35 mL) was added mercury (I) nitrate dihydrate (MW 561.2, 1.11 g, 1.97 mmol), and the whole was heated under reflux for 1 hour. While still warm, the suspension was filtered twice under suction and the filtrate was poured onto ice. The resultant solid was collected by filtration and washed with water to give 4-bromo-2-methoxy-1-oxo-1,2-dihydrobenzo[*b*][1,6]-naphthyridine-6-methanol nitrate (**19**) as a yellow solid (0.65 g, 95% from **15**) with mp 193–195°, which was used in this state in further reactions; ^{1}H nmr (deuteriochloroform): δ 4.15 (s, 3H, OCH_3), 6.30 (s, 2H, CH_2ONO_2), 7.66 (dd, J = 8.2, 7.2 Hz, 1H, H-8), 7.94–7.98 (m, 2H, H-3, H-7), 8.10 (d, J = 8.4 Hz, 1H, H-9), 9.34 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 64.7 (OCH_3), 70.4 (CH_2ONO_2), 100.7 (C), 120.8 (C), 125.9 (C-9a), 126.7 (C-8), 130.0 (C-9), 130.7 (C-6), 132.6 (C-7), 133.9 (C-3), 138.9 (C-10), 147.2 (C-4a), 147.9 (C-5a), 157.4 (C-1).

To the nitrate ester **19** (0.63 g, 1.66 mmol) in 1,2-dimethoxyethane (60 mL) was added triethylamine (1.70 g, 16.80 mmol), and the whole was heated under reflux for 4 hours. Then, either:

(a) the volatiles were removed under reduced pressure, ice-water was added, and the resultant solid was collected by filtration and washed with water to furnish the aldehyde **20** as a light brown solid (0.49 g, 89%), mp 248–250° (dec.) (*N*,*N*-dimethylformamide as yellow needles); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.04 (s, 3H, $ArCH_3$), 7.87 (t, J = 7.7 Hz, 1H, H-8), 8.39 (dd, J = 7.1, 1.4 Hz, 1H, H-7), 8.66 (dd, J = 8.3, 1.2 Hz, 1H, H-9), 8.71 (s, 1H, H-3), 9.51 (s, 1H, H-10), 11.39 (s, 1H, CHO); ^{13}C nmr (dimethyl sulfoxide-d_6, 100°): δ 64.9 (OCH_3), 98.9 (C), 121.4 (C), 126.2 (C-9a), 127.0 (C-8), 131.2 (C-6), 132.4 (C-7), 135.9 (C-9), 136.6 (C-3), 139.5 (C-10), 148.4 (C-4a), 148.9 (C-5a), 157.0 (C-1), 191.3 (CHO).

Anal. Calcd. for $C_{14}H_9BrN_2O_3$: C, 50.48; H, 2.72; N, 8.41. Found: C, 50.36; H, 3.01; N, 8.14.

or (b), the resultant dark solution was taken off reflux and, while still hot, acetic acid (5 mL) was added, followed by the immediate addition of sodium chlorite (tech. grade, 80%) (0.95 g, 8.40 mmol). The yellow suspension was stirred vigorously overnight, and then the solid collected by filtration and washed with a little acetone to give a mixture of the title compound as its triethylamine salt and triethylamine hydrochloride. This mixture was suspended in water (10 mL) containing 3% hydrochloric acid (3 mL), and the yellow free acid **21** was collected by filtration and washed with water (0.26 g, 45%). It was used in this state in the next step. A recrystallized sample from 1,4-dioxane had mp 292–295° (dec.) (after darkening >285°); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.05 (s, 3H, OCH_3), 7.92 (t, J = 7.8 Hz, 1H, H-8), 8.68 (d, J = 8.2 Hz, 1H, H-7), 8.78 (d, J = 7.3 Hz, 1H, H-9), 8.87 (s, 1H, H-3), 9.68 (s, 1H, H-10), 16.04 (s, 1H, COOH); ^{13}C nmr (dimethyl sulfoxide-d_6, 100°): δ 65.1 (OCH_3), 96.2 (C), 121.6 (C), 124.2 (C-6), 126.4 (C-9a), 127.5 (C-8), 135.1 (C-7), 138.2 (C-9), 138.5 (C-3), 141.7 (C-10), 146.8 (C-5a), 147.4 (C-4a), 156.5 (C-1), 165.5 (COOH).

4-Bromo-*N*-[2-(dimethylamino)ethyl]-2-methoxy-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-6-carboxamide (**22**).

A suspension of the acid **21** (0.25 g, 0.72 mmol) and 1,1′-carbonyldiimidazole (CDI) (0.29 g, 1.79 mmol) in 1,4-dioxane (20 mL) was heated under reflux for 16 hours. The reaction was recharged with the same amount of CDI, and reflux was continued for a further 8 hours. The volatiles were removed under reduced pressure and a solution of *N*,*N*-dimethylethylenediamine (0.5 mL, 4.55 mmol) in dichloromethane (25 mL) was added, and the solution was left stirring overnight. The solution was diluted with more dichloromethane, and washed once with 10% sodium hydroxide and then with brine (× 3). The organic layer was dried over magnesium sulfate, filtered and the filtrate was evaporated under reduced pressure to leave the crude target (0.34 g). This solid was recrystallized from acetonitrile to render the carboxamide **22** as a light brown solid (0.16 g, 53%), mp 179–181°; ^{1}H nmr (deuteriochloroform): δ 2.38 [s, 6H, $N(CH_3)_2$], 2.78 (t, J = 6.8 Hz, 2H, $CH_2C\mathbf{H_2}NMe_2$), 3.83 (q, J = 6.5 Hz, 2H, $C\mathbf{H_2}CH_2NMe_2$), 4.15 (s, 3H, OCH_3), 7.74 (t, J = 7.7 Hz, 1H, H-8), 7.97 (s, 1H, H-3), 8.13 (dd, J = 8.3, 1.3 Hz, 1H, H-9), 9.00 (dd, J = 7.4, 1.1 Hz, 1H, H-7), 9.30 (s, 1H, H-10), 11.34 (br s, 1H, CONH); ^{13}C nmr (deuteriochloroform): δ 37.6 ($\mathbf{C}H_2CH_2NMe_2$), 45.0 [$N(CH_3)_2$], 58.3 ($CH_2\mathbf{C}H_2NMe_2$), 64.8 (OCH_3), 99.4 (C), 120.1 (C), 126.2 (C-9a), 127.1 (C-8), 128.2 (C-6), 132.6 (C-9), 134.8 (C-3), 137.5 (C-7), 140.0 (C-10), 146.7 (C-4a), 147.2 (C-5a), 156.9 (C-1), 164.7 (CONH).

Anal. Calcd. for $C_{18}H_{19}BrN_4O_3 \cdot 0.5H_2O$: C, 50.48; H, 4.71; N, 13.08. Found: C, 50.42; H, 4.48; N, 13.03.

2-Methoxy-6-methyl-4-nitrobenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**23**).

To acetic anhydride (1 mL) at *ca* –10° (acetone-ice bath) was added nitric acid (0.5 mL) dropwise over 15 minutes. The resultant acetyl nitrate was added, dropwise, to a suspension of the *N*-methoxy compound **8** (0.10 g, 0.42 mmol) in acetic anhydride (3 mL) over 10 minutes. The whole was allowed to warm to room temperature and was then heated at 50° for 30 minutes. The solution was cooled, ice was added, and the phase was adjusted to pH 5 with 10% sodium hydroxide. The solid was collected by filtration and washed with water to render **23** as a yellow solid (0.07 g, 59%), mp 229–232° (ethanol); ^{1}H nmr (dimethyl sulfoxide-d_6): δ

2.71 (s, 3H, $ArCH_3$), 4.09 (s, 3H, OCH_3), 7.61 (t, J = 7.6 Hz, 1H, H-8), 7.83 (d, J = 6.9 Hz, 1H, H-7), 8.11 (d, J = 8.2 Hz, 1H, H-9), 9.33 (s, 1H, H-10), 9.40 (s, 1H, H-3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.3 ($ArCH_3$), 65.5 (CH_2Br), 119.3 (C), 125.9 (C-9*a*), 127.6 (C-9), 127.7 (C-8), 129.4 (C), 133.2 (C-7), 136.6 (C-6), 138.1 (C-3), 139.1 (C-10), 142.2 (C-4*a*), 148.6 (C-5*a*), 157.7 (C-1).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.87; H, 3.79; N, 14.83.

2-Methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonyl Chloride (**24**) or 2-Methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonic Acid (**25**).

The *N*-methoxy compound **8** (2.49 g, 10.38 mmol) and chlorosulfonic acid (5 mL) were heated at 70° for 16 hours. Ice (*ca* 100 mL) was cautiously added to the cooled solution and the resultant suspension was stirred for 1 hour. The solid was collected by filtration and washed with a little cold water to give a mixture of the sulfonic acid **25** and the sulfonyl chloride **24**, as their hydrochlorides (3.06 g). Then:

(a) To this dried mixture was added thionyl chloride (35 mL) and *N*,*N*-dimethylformamide (1 mL), and the suspension was heated under reflux for 45 minutes, during which time dissolution occurred. The volatiles were removed under reduced pressure and residual thionyl chloride was azeotropically distilled with benzene. The solid was partitioned between cold dichloromethane and ice-cold 10% potassium carbonate, and the organic phase was washed once more with cold base and then with cold brine (× 2). The organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated under reduced pressure to give the sulfonyl chloride **24** (2.84 g, 81%) as a yellow solid which was used directly in further reactions. A sample for data was purified by flash column chromatography [ethyl acetate–hexane (3:7); R_f, 0.6] and recrystallized from petroleum spirit (bp 80–110°). On slow heating the solid changed form at *ca* 205° and, while some melted >225°, the mp was >300°. On rapid heating, the solid melted slowly 225–240°; ^1H nmr (deuteriochloroform): δ 2.91 (s, 3H, $ArCH_3$), 4.21 (s, 3H, OCH_3), 7.58 (d, J = 7.6 Hz, 1H, H-8), 7.79 (d, J = 6.9 Hz, 1H, H-7), 7.87 (d, J = 8.3 Hz, 1H, H-9), 8.62 (s, 1H, H-3), 9.24 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.5 ($ArCH_3$), 65.5 (OCH_3), 119.1 (C), 120.4 (C), 125.9 (C-9a), 126.5 (C-9), 127.9 (C-8), 133.0 (C-7), 138.2 (C-6), 138.9 (C-10), 139.8 (C-3), 142.9 (C-4a), 149.3 (C-5a), 158.0 (C-1).

or (b) A portion of this solid (0.32 g) was suspended and stirred in 10% potassium carbonate (30 mL) for 8 h, then acidified to pH 4 with concentrated hydrochloric acid and evaporated to dryness under reduced pressure. The solids were stirred in hot ethanol, and the liquid was filtered. After repeating this extraction twice more, the ethanol was evaporated under reduced pressure to leave the yellow sulfonic acid **25** (0.26 g, 69% from **8**), mp 300–302° (after darkening at 295°) (acetonitrile); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.75 (s, 3H, $ArCH_3$), 4.06 (s, 3H, OCH_3), 7.77 (t, J = 7.7 Hz, 1H, H-8), 8.06 (d, J = 7.0 Hz, 1H, H-7), 8.33 (d, J = 8.2 Hz, 1H, H-9), 8.71 (s, 1H, H-3), 9.79 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 16.2 ($ArCH_3$), 65.5 (OCH_3), 116.5 (C), 121.1 (C), 125.6 (C), 128.7 (C-8), 128.9 (C-9), 129.6 (C), 137.8 (C-7), 139.6 (C-5a), 141.2 (C-3), 143.1 (C-4a), 147.1 (C-10), 155.9 (C-1).

Anal. Calcd. for $C_{14}H_{12}N_2O_5S$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.60; H, 3.78; N, 9.06.

2-Hydroxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonic Acid (**26**).

From the *N*-hydroxy compound **4a** (1.84 g, 8.14 mmol) and chlorosulfonic acid (5 mL), as for the sulfonic acid **25**, except that the reaction was only heated for 5 hours, and the orange sulfonic acid **26** was obtained as its hydrochloride (1.94 g, 70%), mp >300°. This solid was used in this state in further reactions.

The free acid was liberated for nmr data and microanalysis. The hydrochloride (0.20 g, 0.58 mmol) was stirred in 10% sodium hydroxide (2 mL) for 10 minutes and the solution was filtered. The filtrate was taken to pH 4 with concentrated hydrochloric acid, cooled on ice, and the resultant sulfonic acid **26** was collected by filtration and was obtained as an orange solid (0.14 g, 78% from the hydrochloride) mp >300°. A solution in ethanol gave a deep red coloration upon the addition of Fe^{3+}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.74 (s, 3H, $ArCH_3$), 7.81 (t, J = 7.6 Hz, 1H, H-8), 8.13 (d, J = 6.9 Hz, 1H, H-7), 8.40 (d, J = 8.2 Hz, 1H, H-9), 8.57 (s, 1H, H-3), 9.94 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 16.1 ($ArCH_3$), 114.7 (C), 120.4 (C), 125.6 (C-6), 128.6 (C-8), 128.8 (C-9a), 129.0 (C-9), 138.1 (C-7), 139.1 (C-5a), 142.1 (C-4a), 142.2 (C-3), 148.0 (C-10), 156.7 (C-1); esms: m/z 307.2 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{10}N_2O_5S•0.25H_2O$: C, 50.24; H, 3.41; N, 9.01. Found: C, 50.35; H, 3.60; N, 8.93.

1-Chloro-6-methylbenzo[*b*][1,6]naphthyridine-4-sulfonyl Chloride (**27**).

From the hydrochloride of the sulfonic acid **26** (1.94 g, 5.66 mmol), as for the sulfonyl chloride **24**, and the chlorosulfonyl chloride **27** was obtained as an orange solid (1.66 g, 90%), mp 228–232° (dec.), sufficiently pure for further reactions; ^1H nmr (deuteriochloroform): δ 3.00 (s, 3H, $ArCH_3$), 7.68 (dd, J = 8.3, 7.0 Hz, 1H, H-8), 7.91 (d, J = 6.9 Hz, 1H, H-7), 8.02 (d, J = 8.4 Hz, 1H, H-9), 9.15 (s, 1H, H-3), 9.34 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.7 ($ArCH_3$), 120.7 (C), 126.6 (C-9), 127.5 (C-9a), 128.6 (C-8), 133.9 (C-7), 134.3 (C), 137.3 (C-10), 138.5 (C-6), 142.7 (C-4a), 145.0 (C-3), 151.1 (C-5a), 159.8 (C-1).

4-(6-Methyl-1-(4-morpholino)benzo[*b*][1,6]naphthyridine-4-sulfonyl)morpholine (**28**).

To the sulfonyl chloride **27** (0.24 g, 0.73 mmol) dissolved in dichloromethane (25 mL) on a salt-ice bath was added triethylamine (0.37 g, 3.66 mmol) in dichloromethane (2 mL) in one portion, followed by morpholine (0.14 g, 1.61 mmol) in dichloromethane (5 mL) dropwise. After stirring for 0.5 hour, the reaction was allowed to warm to room temperature and stirring was continued for 16 hours under a positive pressure of nitrogen. The solution was diluted with more dichloromethane and washed with 10% potassium carbonate, followed by 3% hydrochloric acid and then with water (× 3). The organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated under reduced pressure to give the sulfonamide **28** (0.26 g, 83%). Two recrystallizations from petroleum spirit (bp 80–110°) –dichloromethane, with decantation from an initially-formed oil, gave a yellow solid, mp 197–205°; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.76 (s, 3H, $ArCH_3$), 3.23–3.26 [m, 4H, $N(CH_2)_2$-4], 3.52–3.55 [m, 4H, $O(CH_2)_2$-4], 3.83 [br s, 8H, $N(CH_2)_2$-1, $O(CH_2)_2$-1], 7.56 (t, J = 7.6 Hz, 1H, H-8), 7.81 (d, J = 6.8 Hz, 1H, H-7), 8.12 (d, J = 8.2 Hz, 1H, H-9), 8.63 (s, 1H, H-3), 9.22 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.1 ($ArCH_3$), 46.3 [$N(CH_2)_2$-4], 50.9 [$N(CH_2)_2$-1], 65.9 [$O(CH_2)_2$-4], 66.2

[$O(CH_2)_2$-1], 113.0 (C), 119.4 (C), 125.4 (C-9a), 126.4 (C-8), 127.8 (C-9), 132.9 (C-7), 136.0 (C-6), 137.4 (C-10), 147.1 (C-4a), 148.8 (C-5a), 149.1 (C-3), 163.8 (C-1); esms: m/z 429.6 $(M+H)^+$.

Anal. Calcd. for $C_{21}H_{24}N_4O_4S$: C, 58.86; H, 5.65; N, 13.07. Found: C, 58.64; H, 5.43; N, 13.04.

N-[2-(Dimethylamino)ethyl]-1-[2-(dimethylamino)ethylamino]-6-methylbenzo[*b*][1,6]naphthyridine-4-sulfonamide (**29**).

From the sulfonyl chloride **27** (0.26 g, 0.79 mmol) and *N*,*N*-dimethylethylenediamine (0.15 g, 1.70 mmol), as for **28**, except that, after reaction, the solution was not washed with acid. The crude orange-brown sulfonamide **29** (0.20 g) was dissolved in tetrahydrofuran (40 mL) and hydrogen chloride gas was bubbled through the solution for 10 minutes. Diethyl ether was added, and the liquids were decanted from a sticky brown solid. This solid was washed twice more (with decantation) with diethyl ether and then recrystallized from aqueous ethanol–ether to give **29** as its yellow trihydrochloride salt (hygroscopic) (0.14 g, 33%), mp 195–200°.

Anal. Calcd. for $C_{21}H_{30}N_6O_2S\bullet 3HCl$: C, 46.71; H, 6.16; N, 15.56. Found: C, 46.62; H, 6.40; N, 15.30.

The free base was liberated as an orange-brown solid, mp 66–70°; ^{1}H nmr (deuteriochloroform): δ 1.58 [s, 6H, $N(CH_3)_2$-4], 2.22 (t, J = 5.6 Hz, 2H, $CH_2C\mathbf{H_2}NMe_2$-4), 2.43 [s, 6H, $N(CH_3)_2$-1], 2.78–2.86 (m, 7H, $ArCH_3$, $C\mathbf{H_2}CH_2NMe_2$-4, $CH_2C\mathbf{H_2}NMe_2$-1), 3.74 (t, J = 5.6 Hz, 2H, $C\mathbf{H_2}CH_2NMe_2$-1), 6.79 (br s, 1H, NH-4), 7.35 (t, J = 7.6 Hz, 1H, H-8), 7.57 (d, J = 6.7 Hz, 1H, H-7), 7.76 (d, J = 8.3 Hz, 1H, H-9), 8.66 (s, 1H, H-3), 8.78 (s, 1H, H-10) (NH-1 was not observed); ^{13}C nmr (deuteriochloroform): δ 17.6 ($ArCH_3$), 38.4 ($\mathbf{C}H_2CH_2NMe_2$-1), 40.5 ($\mathbf{C}H_2CH_2NMe_2$-4), 43.8 [$N(CH_3)_2$-4], 44.6 [$N(CH_3)_2$-1], 56.5 ($CH_2\mathbf{C}H_2NMe_2$-4), 57.1 ($CH_2\mathbf{C}H_2NMe_2$-1), 111.7 (C), 116.6 (C), 125.3 (C-9a), 126.0 (C-8), 126.6 (C-9), 131.8 (C-7), 132.7 (C-10), 136.4 (C-6), 144.9 (C-4a), 148.6 (C-5a), 149.2 (C-3), 158.4 (C-1).

N-Benzyl-2-methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]-naphthyridine-4-sulfonamide (**31**).

To the sulfonyl chloride **24** (0.13 g, 0.38 mmol) dissolved in dichloromethane (20 mL) on a salt-ice bath was added triethylamine (0.12 g, 1.19 mmol) in dichloromethane (2 mL), followed by benzylamine (0.05 g, 0.47 mmol) in dichloromethane (5 mL) dropwise. After being stirred for 0.5 hour, the reaction was allowed to warm to room temperature and stirring was continued for 16 hours under a positive pressure of nitrogen. The solution was diluted with more dichloromethane and washed with 10% potassium carbonate, followed by 3% hydrochloric acid and then with water (× 3). The organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated under reduced pressure to give the sulfonamide **31** as a pale yellow solid (0.12 g, 76%), with mp 173–176° after two recrystallizations from petroleum spirit (bp 80–110°)–dichloromethane; ^{1}H nmr (deuteriochloroform): δ 2.69 (s, 3H, $ArCH_3$), 4.16 (s, 5H, OCH_3, $NHC\mathbf{H_2}$), 6.49 (br s, 1H, NH), 6.99–7.05 (m, 5H, Ph), 7.55 (t, J = 7.6 Hz, 1H, H-8), 7.74 (d, J = 6.8 Hz, 1H, H-7), 7.88 (d, J = 8.2 Hz, 1H, H-9), 8.37 (s, 1H, H-3), 9.23 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 18.0 ($ArCH_3$), 47.8 ($NHCH_2$), 65.0 (OCH_3), 115.7 (C), 119.8 (C), 125.9 (C-9a), 127.0 (C-9), 127.4 (CH), 127.5 (CH), 127.8 (2 × CH, Ph), 127.9 (2 × CH, Ph), 133.2 (C-7), 135.2 (C-1′), 136.1 (C-6), 137.7 (C-3), 139.3 (C-10), 144.4 (C-4a), 148.6 (C-5a), 157.9 (C-1).

Anal. Calcd. for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26. Found: C, 61.64; H, 4.70; N, 10.13.

2-Methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonamide (**30**).

From the sulfonyl chloride **24** (1.55 g, 4.58 mmol) and a stream of ammonia gas for 20 minutes, as for the sulfonamide **31**, except that, after reaction, the volatiles were evaporated under reduced pressure, ice-water was added and the solid was collected by filtration and washed with water to give **30** as a mustard coloured solid (1.24 g, 85%), mp 231–237° (toluene). After being dried at 150° at *ca* 0.01 mmHg for 24 hours, *ca* 10% toluene remained; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.75 (s, 3H, $ArCH_3$), 4.07 (s, 3H, OCH_3), 7.05 (s, 2H, SO_2NH_2), 7.56 (t, J = 7.6 Hz, 1H, H-8), 7.79 (d, J = 6.8 Hz, 1H, H-7), 8.05 (d, J = 8.2 Hz, 1H, H-9), 8.58 (s, 1H, H-3), 9.27 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.8 ($ArCH_3$), 65.2 (OCH_3), 119.3 (C), 120.0 (C), 125.7 (C-9a), 127.4 (C-8), 127.5 (C-9), 133.1 (C-7), 136.3 (C-6), 136.8 (C-3), 139.1 (C-10), 145.0 (C-4a), 148.2 (C-5a), 157.7 (C-1); esms: m/z 319.9 $(M+H)^+$.

Anal. Calcd. for $C_{14}H_{13}N_3O_4S\bullet 0.1C_7H_8$: C, 53.74; H, 4.23; N, 12.79. Found: C, 53.66; H, 4.17; N, 13.09.

N-[2-(Dimethylamino)ethyl]-2-methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonamide (**32**).

From the sulfonyl chloride **24** (0.21 g, 0.62 mmol) and *N*,*N*-dimethylethylenediamine (0.07 g, 0.79 mmol), as for the sulfonamide **31**, except that, after reaction, the dichloromethane solution was not washed with acid, and the crude sulfonamide **32** was obtained as an orange-brown solid (0.15 g, 62%). Two recrystallizations from toluene gave a fawn solid, mp 168–175°; ^{1}H nmr (deuteriochloroform): δ 1.80 [s, 6H, $N(CH_3)_2$], 2.40 (t, J = 5.5 Hz, 2H, $CH_2C\mathbf{H_2}NMe_2$), 2.89 (s, 3H, $ArCH_3$), 3.01 (q, J = 4.3 Hz, 2H, $C\mathbf{H_2}CH_2NMe_2$), 4.18 (s, 3H, OCH_3), 6.76 (br s, 1H, NH), 7.54 (t, J = 7.6 Hz, 1H, H-8), 7.76 (d, J = 6.9 Hz, 1H, H-7), 7.87 (d, J = 8.2 Hz, 1H, H-9), 8.44 (s, 1H, H-3), 9.27 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 17.7 ($ArCH_3$), 40.3 ($\mathbf{C}H_2CH_2NMe_2$), 43.9 [$N(CH_3)_2$], 56.4 ($CH_2\mathbf{C}H_2NMe_2$), 65.0 (OCH_3), 115.0 (C), 119.7 (C), 125.9 (C-9a), 126.8 (C-9), 127.4 (C-8), 132.9 (C-7), 137.1 (C-6), 137.9 (C-3), 139.1 (C-10), 144.4 (C-4a), 148.9 (C-5a), 158.1 (C-1).

Anal. Calcd. for $C_{18}H_{22}N_4O_4S$: C, 55.37; H, 5.68; N, 14.35. Found: C, 55.61; H, 5.51; N, 14.47.

4-(2-Methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonyl)morpholine (**33**).

From the sulfonyl chloride **24** (2.45 g, 7.23 mmol) and morpholine (0.76 g, 8.72 mmol), as for the sulfonamide **31**, and **33** was obtained as an orange foam (2.41 g, 86%). A sample was recrystallized from toluene to give a pale yellow solid with mp 232–242°, which retained *ca* 10% toluene after drying at 150° and *ca* 0.01 mmHg for 24 hours; ^{1}H nmr (deuteriochloroform): δ 2.82 (s, 3H, $ArCH_3$), 3.43–3.46 [m, 4H, $N(CH_2)_2$], 3.67–3.70 [m, 4H, $O(CH_2)_2$], 4.16 (s, 3H, OCH_3), 7.52 (t, J = 7.6 Hz, 1H, H-8), 7.73 (d, J = 6.8 Hz, 1H, H-7), 7.84 (d, J = 8.2 Hz, 1H, H-9), 8.50 (s, 1H, H-3), 9.24 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 18.4 ($ArCH_3$), 46.1 [$N(CH_2)_2$], 65.0 (OCH_3), 66.3 [$O(CH_2)_2$], 115.5 (C), 119.8 (C), 125.8 (C-9a), 126.8 (C-9), 127.3 (C-8), 133.0 (C-7), 137.1 (C-6), 139.0 (C-10), 139.8 (C-3), 145.0 (C-4a), 149.2 (C-5a), 158.1 (C-1).

Anal. Calcd. for $C_{18}H_{19}N_3O_5S\bullet 0.1C_7H_8$: C, 56.34; H, 5.01; N, 10.54. Found: C, 56.27; H, 4.97; N, 10.49.

N-(2-Methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonyl)piperidine (**34**).

From the sulfonyl chloride **24** (0.44 g, 1.30 mmol) and piperidine (0.13 g, 1.53 mmol), as for the sulfonamide **31**, and **34** was obtained as an orange foam (0.43 g, 85%). A cream solid with mp 220–223° was obtained after two recrystallizations from petroleum spirit (bp 80–110°)–toluene; ^{1}H nmr (deuteriochloroform): δ 1.41–1.48 (m, 2H, piperidinyl-4-CH_2), 1.56–1.64 (m, 4H, piperidinyl-3,5-CH_2), 2.88 (s, 3H, ArCH_3), 3.41–3.45 (m, 4H, piperidinyl-2,6-CH_2), 4.16 (s, 3H, OCH_3), 7.54 (dd, J = 7.9, 7.3 Hz, 1H, H-8), 7.75 (d, J = 6.9 Hz, 1H, H-7), 7.88 (d, J = 8.2 Hz, 1H, H-9), 8.50 (s, 1H, H-3), 9.28 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 18.3 (ArCH_3), 23.3 (piperidinyl-4-CH_2), 25.4 (piperidinyl-3,5-CH_2), 46.9 (piperidinyl-2,6-CH_2), 64.9 (OCH_3), 116.5 (C), 119.8 (C), 125.8 (C-9a), 126.7 (C-9), 127.2 (C-8), 132.8 (C-7), 137.4 (C-6), 138.9 (C-10), 139.2 (C-3), 145.2 (C-4a), 149.3 (C-5a), 158.2 (C-1).

Anal. Calcd. for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.84. Found: C, 59.19; H, 5.62; N, 10.92.

2-Hydroxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonamide (**36**).

The sulfonamide **30** (0.20 g, 0.63 mmol), 40% hydrobromic acid (6 mL) and acetic acid (2 mL) were heated under reflux at 130° for 16 hours. The resultant solution was cooled, ice (100 g) was added, and the phase was adjusted to pH 5 with 10% sodium hydroxide. The solid was collected by filtration to give a mixture of the target sulfonamide and the starting material (1.6:1). The brown solid (0.13 g) was allowed to dry overnight, boiled in ethanol (80 mL) (sonication was initially required to break up the solid), filtered while hot and the hot filtrate was added to silica gel (12 g) with swirling. The ethanol was removed under reduced pressure with constant rotary evaporation and dried at 40° overnight; this rendered the compounds homogeneously adsorbed to the silica gel. The silica was washed with ethyl acetate–hexane (1:1) until no starting material eluted (R_f, 0.5). The silica gel was stirred in *N*,*N*-dimethylformamide (25 mL) for 1 hour, and decanted and filtered. After repeating this extraction process twice more, the *N*,*N*-dimethylformamide was evaporated at reduced pressure, 3% hydrochloric acid was added and the title compound **36** was collected by filtration and obtained as brown needles after recrystallization from ethanol (0.06 g, 31%), mp 266–268°. Evaporation of the ethyl acetate–hexane eluate recovered the starting material **30** (0.04 g, 20%). A solution of **36** in ethanol gave a deep red coloration upon the addition of Fe^{3+}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.78 (s, 3H, ArCH_3), 7.03 (s, 2H, SO_2NH_2), 7.59 (t, J = 7.3 Hz, 1H, H-8), 7.82 (d, J = 5.9 Hz, 1H, H-7), 8.11 (d, J = 8.1 Hz, 1H, H-9), 8.36 (s, 1H, H-3), 9.36 (s, 1H, H-10), 12.11 (s, 1H, OH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.9 (ArCH_3), 118.2 (C), 119.6 (C), 125.8 (C-9a), 127.3 (C-8), 127.6 (C-9), 133.0 (C-7), 136.4 (C-6), 137.5 (C-3), 139.0 (C-10), 144.9 (C-4a), 148.4 (C-5a), 158.6 (C-1); esms: m/z 306.4 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.63; N, 13.76. Found: C, 50.79; H, 3.81; N, 13.50.

N-[(Benzylamino)carbonyl]-2-methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonamide (**37**).

To a suspension of the sulfonamide **30** (0.20 g, 0.63 mmol) and potassium carbonate (0.86 g, 6.22 mmol) in acetone (20 mL) was added, in one portion, benzyl isocyanate (0.25 g, 1.88 mmol) dissolved in acetone (20 mL), and the whole was heated under gentle reflux for 16 hours. The reaction mixture was cooled, filtered and the solid was washed with acetone. This solid was suspended in 3% hydrochloric acid, refiltered and washed with water (0.19 g). Recrystallization from toluene gave an analytically pure sample; the toluene filtrate contained more of the target but in a less pure state. The pure sulfonyl urea **37** was thus obtained as a pale yellow solid (0.08 g, 28%), mp 197–202°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.82 (s, 3H, ArCH_3), 4.06 (s, 5H, OCH_3, CH_2), 6.79–6.89 (m, 4H, H-2′, H-6′, H-3′, H-5′), 6.98–7.03 (m, 1H, H-4′), 7.09 (t, J = 5.9 Hz, 1H, N**H**CH_2—exchanged with added deuterium oxide), 7.61 (t, J = 7.6 Hz, 1H, H-8), 7.82 (d, J = 6.8 Hz, 1H, H-7), 8.13 (d, J = 8.2 Hz, 1H, H-9), 8.71 (s, 1H, H-3), 9.35 (s, 1H, H-10), 10.04 (s, 1H, SO_2NH—exchanged with added deuterium oxide); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.2 (ArCH_3), 42.4 (CH_2), 65.4 (OCH_3), 115.3 (C), 119.6 (C), 125.8 (C-9a), 126.4 (C-2′, C-6′), 126.7 (C-4′), 127.5 (C-9, C-8), 128.0 (C-3′, C-5′), 133.1 (C-7), 137.0 (C-6), 139.0 (C-1′), 139.2 (C-10), 141.7 (C-3), 144.6 (C-4a), 148.6 (C-5a), 151.4 (urea CO), 157.9 (C-1).

Anal. Calcd. for $C_{22}H_{20}N_4O_5S$: C, 58.40; H, 4.46; N, 12.38. Found: C, 58.35; H, 4.46; N, 12.29.

4-Bromo-6-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (**38**).

The bromo-*N*-methoxy compound **15** (0.20 g, 0.63 mmol) and an equal weight of potassium hydroxide in *N*,*N*-dimethylformamide (10 mL) were heated at 100° for 0.5 hour with constant stirring. The reaction mixture was filtered, the volatiles were removed from the filtrate under reduced pressure, and ice-water was added. The whole was acidified with 3% hydrochloric acid, and the yellow solid was collected by filtration to give **38** (0.13 g, 72%), mp >300° (after gradually darkening >270°) (*n*-propanol × 2); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.76 (s, 3H, ArCH_3), 7.53 (t, J = 7.6 Hz, 1H, H-8), 7.77 (d, J = 6.9 Hz, 1H, H-7), 7.83 (d, J = 4.5 Hz, 1H, H-3), 8.05 (d, J = 8.2 Hz, 1H, H-9), 9.17 (s, 1H, H-10), 11.57 (br s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.5 (ArCH_3), 100.4 (C), 120.7 (C), 126.3 (C-9a), 126.7 (C-8), 127.4 (C-9), 132.5 (C-7), 134.0 (C-3), 136.3 (C-6), 138.5 (C-10), 148.2 (C-4a), 149.0 (C-5a), 162.1 (C-1); esms: m/z 291.3, 289.3; both $(M+H)^+$.

Anal. Calcd. for $C_{13}H_9BrN_2O$: C, 54.00; H, 3.14; N, 9.69. Found: C, 54.22; H, 3.39; N, 9.79.

4-(6-Methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-sulfonyl)morpholine (**39**).

From the sulfonamide **33** (0.46 g, 1.18 mmol), as for **38**, and **39** was obtained as an orange-brown solid (0.29 g, 68%), mp 271–275° (after gradually forming needles *ca* 200°) (ethanol); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.74 (s, 3H, ArCH_3), 3.26–3.29 [m, 4H, N$(CH_2)_2$], 3.53–3.56 [m, 4H, O$(CH_2)_2$], 7.56 (t, J = 7.6 Hz, 1H, H-8), 7.79 (d, J = 6.9 Hz, 1H, H-7), 8.05–8.09 (m, 2H, H-3, H-9), 9.24 (s, 1H, H-10), 11.97 (d, J = 6.4 Hz, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.1 (ArCH_3), 46.1 [N$(CH_2)_2$], 65.9 [O$(CH_2)_2$], 114.2 (C), 119.8 (C), 126.1 (C-9a), 127.0 (C-8), 127.7 (C-9), 132.9 (C-7), 136.4 (C-6), 138.6 (C-10), 141.0 (C-3), 147.2 (C-4a), 148.6 (C-5a), 162.6 (C-1); esms: m/z 360.2 $(M+H)^+$.

Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.93; H, 4.87; N, 11.63.

4-(1-Chloro-6-methylbenzo[*b*][1,6]naphthyridine-4-sulfonyl)morpholine (**35**).

(a) Preferred method: The 1-oxo sulfonamide **39** (0.29 g, 0.81 mmol) and phosphoryl chloride (5 mL) were heated under gentle

reflux for 8 hours. The excess phosphoryl chloride was removed under vacuum, ice-water was added and the product was extracted with dichloromethane. The organic phase was washed with 10% sodium carbonate, followed by brine (× 3), and was evaporated to dryness under reduced pressure to give **35** as a brown foam (0.28 g, 92%), which was used in this state in further reaction. A chromatographed sample [method (b), below] was obtained as yellow needles and had mp 225–228°; ^{1}H nmr (deuteriochloroform): δ 2.92 (s, 3H, $ArCH_3$), 3.46–3.49 [m, 4H, $N(CH_2)_2$], 3.68–3.71 [m, 4H, $O(CH_2)_2$], 7.63 (dd, J = 8.3, 7.0 Hz, 1H, H-8), 7.85 (d, J = 6.8 Hz, 1H, H-7), 8.00 (d, J = 8.4 Hz, 1H, H-9), 9.08 (s, 1H, H-3), 9.32 (s, 1H, H-10); ^{13}C nmr (deuteriochloroform): δ 18.5 ($ArCH_3$), 46.1 [$N(CH_2)_2$], 66.3 [$O(CH_2)_2$], 120.5 (C), 126.9 (C-9), 127.2 (C-9a), 128.0 (C-8), 129.1 (C), 133.7 (C-7), 137.3 (C-10), 137.4 (C-6), 144.7 (C-4a), 147.0 (C-3), 150.9 (C-5a), 157.7 (C-1). Hrms Calcd. for $C_{17}H_{17}ClN_3O_3S$ [$(M+H)^+$]: 378.0680. Found: 378.0672.

(b) This compound was also obtained, in lower yield and by a more complex procedure, from reaction of the chlorosulfonyl chloride **27** with an equimolar amount of morpholine, as follows:

To a solution of the sulfonyl chloride **27** (181.4 mg, 0.55 mmol) in dichloromethane (35 mL) at –18° (acetone-ice bath) under a positive pressure of nitrogen was added a solution of triethylamine (56.1 mg, 0.55 mmol) in dichloromethane (1 mL) in one portion, followed by a 36.7 m*M* solution of morpholine in dichloromethane (15 mL, 0.55 mmol morpholine) dropwise over 10 minutes. The solution was stirred for 16 hours in the acetone-ice bath and was then washed with cold 10% potassium carbonate, followed by cold 3% hydrochloric acid, and cold water (× 3). The organic layer was dried over magnesium sulfate, filtered, and the filtrate was evaporated under reduced pressure to give a mixture of products (210 mg). Plc separation [ethyl acetate–hexane (1:1)] allowed isolation of the target chlorosulfonamide **35** (R_f, 0.4–0.6) and the *bis* morpholino sulfonamide **28** (R_f, 0.1–0.2).

4-(1-Benzylamino-6-methylbenzo[*b*][1,6]naphthyridine-4-sulfonyl)morpholine (**40**).

To the chloro compound **35** (0.28 g, 0.74 mmol) dissolved in dichloromethane (30 mL) under a positive pressure of nitrogen was added triethylamine (0.23 g, 2.27 mmol) in dichloromethane (5 mL), followed by benzylamine (1.19 g, 11.10 mmol) in dichloromethane (10 mL) in portions, and the solution was stirred at room temperature for 16 hours (or until the reaction was complete by tlc—R_f **35**, 0.6; R_f **40**, 0.5). The volatiles were evaporated under reduced pressure and some of the excess amine was removed by azeotropic distillation with toluene (× 4) and then with diethyl ether (× 4). The residue was triturated with diethyl ether and the sulfonamide **40** was collected by filtration and washed with diethyl ether, followed by 10% sodium carbonate and then exhaustively with water, and was obtained as a bright yellow solid (0.19 g, 57%), mp 257–261° (after changing form >250°) (acetonitrile); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.77 (s, 3H, $ArCH_3$), 3.19–3.22 [m, 4H, $N(CH_2)_2$], 3.52–3.55 [m, 4H, $O(CH_2)_2$], 4.88 (d, J = 5.6 Hz, 2H, $NHCH_2$), 7.21–7.26 (m, 1H, H-4′), 7.29–7.34 (m, 2H, H-3′, H-5′), 7.40–7.43 (m, 2H, H-2′, H-6′), 7.56 (t, J = 7.6 Hz, 1H, H-8), 7.80 (d, J = 6.8 Hz, 1H, H-7), 7.90 (d, J = 8.2 Hz, 1H, H-9), 8.56 (s, 1H, H-3), 9.42 (t, J = 5.7 Hz, 1H, NH), 9.56 (s, 1H, H-10); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.1 ($ArCH_3$), 44.6 ($NHCH_2$), 46.3 [$N(CH_2)_2$], 65.9 [$O(CH_2)_2$], 112.6 (C), 116.0 (C), 125.7 (C-9a), 126.6 (C-8), 127.09 (C-4′), 127.13 (C-9), 127.7 (C-2′, C-6′), 128.5 (C-3′, C-5′), 132.5 (C-7), 134.5 (C-10), 136.4 (C-6), 138.9 (C-1′), 146.4 (C-4a), 148.8 (C-5a), 152.2 (C-3), 159.7 (C-1).

Anal. Calcd. for $C_{24}H_{24}N_4O_3S$: C, 64.27; H, 5.39; N, 12.49. Found: C, 64.40; H, 5.47; N, 12.46.

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[15] The cytotoxicity GI_{50} values are the concentrations corresponding to 50% overall growth inhibition.

[16] Mean graph midpoint for growth inhibition of all human cancer cell lines successfully tested.

[17] This signal was concentration dependent and frequently occurred as a broad singlet.

[18] This signal was concentration dependent and appeared between δ 2.5 and 3.0 ppm.

[19] The compound readily rearranged to **12** during attempted recrystallization.