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Synthesis and cytotoxic activity of carboxamide derivatives of benzo[*b*][1,6]naphthyridin-(5*H*)ones

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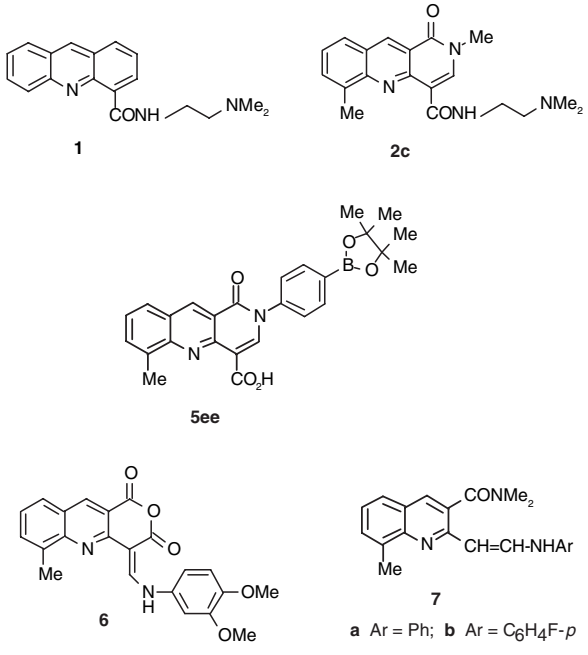
Abstract—A previous reaction leading to 2-substituted 6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acids has been extended to encompass a broad range of 2-substituents. Derived carboxamides, particularly 4-*N*-[2-(dimethylamino)ethyl], were tested for growth inhibitory properties. Potent cytotoxicity against murine P388 leukemia and Lewis lung carcinoma (LLTC) was retained for compounds bearing a remarkably diverse range of 2-substituents with a number having IC_{50} values <10 nM. Five of the new compounds were tested in vivo against subcutaneous colon 38 tumors in mice; a single dose (1.8 mg/kg) proved curative for the 2-(4-fluorophenyl) derivative, a further increase in potency over the very effective 2-methyl analogue reported previously.

1. Introduction

The investigation of topoisomerase poisons as potential anticancer agents continues to be of interest. Tricyclic chromophores bearing a flexible cationic side chain make up one subclass, typified by the acridine-4-carboxamides (e.g., DACA, **1**[1,2]). With respect to DACA, it has been found that the *peri* arrangement between the amide function and the central ring nitrogen is essential for anticancer activity.[1] We recently reported that carboxamide derivatives of the benzo[*b*][1,6]naphthyridine system were topoI/II inhibitors and potent cytotoxins, and initial in vivo testing against subcutaneous colon 38 tumors in mice showed that, for example, a single dose (3.9 mg/kg) of compound **2c** was curative.[3] This encouraging result prompted us to further investigate this series; in particular, the synthesis allows a wide variation in the nature of the 2-substituent. We report here the preparation of an extended series of such derivatives, along with some variations in benzo-ring substituents and carboxamide side chain, their growth inhibitory properties against tumor cell lines and in vivo activity of selected examples.



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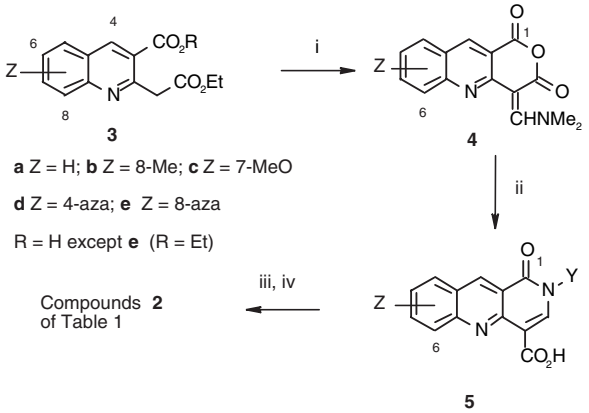
2. Results and discussion

2.1. Chemistry

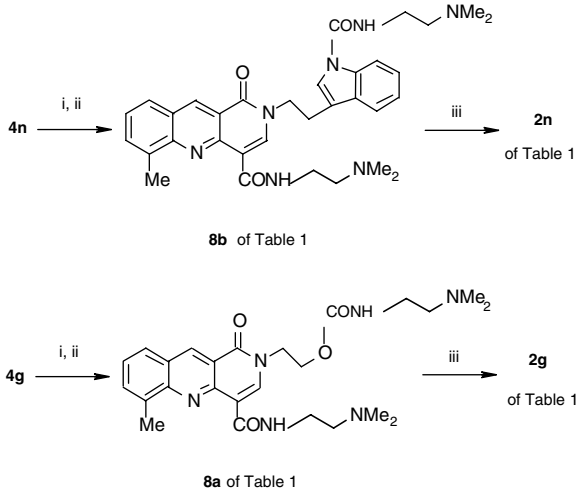
The general synthetic scheme is that reported previously.[3] The homophthalic acid analogues **3a**–**d** were prepared by adapting a method for the pyridine example.[4] Analogue **3e** was prepared from 2-aminonicotinaldehyde and diethyl 1,3-acetonedicarboxylate by the method reported for the dimethyl analogue.[5] Reaction of **3** with Vilsmeier reagent gave the key intermediates **4** (Scheme 1).[6] In our previous paper,[3] compounds **4a** and **4b** were reacted with a limited selection of amines under generally very mild conditions, to give the acids **5a**–**c**,**e**,**o**,**r**,**u** mostly in good yields. This has now been extended to the additional **4c**–**e**, and a much wider selection of amines to introduce considerable variation in the 2-substituent.

Reaction of **4** in dimethylformamide with nucleophilic alkyl amines was straightforward; an excess of amine could be used, as previously,[3] or with more expensive amines and those available as hydrochloride salts, a 10% excess in combination with a larger excess of triethylamine was also satisfactory. The acid products **5** were generally insoluble and could be filtered directly, though minor workup variations were required in some cases.[7]

The reaction with less nucleophilic arylamines was more complicated. In the sole example reported previously,[3] using 3,4-dimethoxyaniline and triethylamine, the initial solid was the very insoluble **6** and reaction of this with more amine in refluxing pyridine gave the target **5u**. However, in the arylamine examples now reported, the presumed analogues of **6** did not precipitate and the reaction proceeded to the target **5**. But an unwanted side reaction occurred since the dimethylamine liberated in the first step competed efficiently with the arylamine in the second step to form **7**. A 10-fold excess of the arylamine was therefore used in order to minimize this reaction and compounds **5** were able to be readily isolated. In the case of the expensive boron containing compound, the excess was kept to 2-fold and the target was isolated in only 20% yield; in this example, water was carefully omitted from the workup because the compound was more readily handled at this stage with the boron in the readily hydrolyzed tetramethyl-1,3,2-dioxaborolane protected form (**5ee**). The boronic acid functionality was liberated at the final amide-forming stage (**2v**).

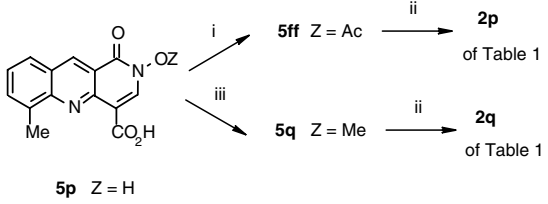


Scheme 1. Reagents and conditions: (i) $POCl_3$/DMF/0 °C; (ii) excess YNH_2/DMF/20 °C OR 1.1 molequiv YNH_2/excess NEt_3/DMF/20 °C OR (for Y = Ar) 10 molequiv YNH_2/excess NEt_3/DMF/20 °C; (iii) $SOCl_2$/reflux OR CDI/dioxan/reflux; (iv) RNH_2/CH_2Cl_2.



Scheme 2. Reagents and conditions: (i) CDI/dioxan/reflux; (ii) excess $Me_2N(CH_2)_2NH_2/CH_2Cl_2$; (iii) 10% NaOH/EtOH/reflux.

The desired amides were formed by reaction of the appropriate amine with an intermediate acid chloride (from reaction with thionyl chloride, and not isolated) or imidazolide (from reaction with 1,1′-carbonyldiimidazole (CDI), and not isolated). The desmethyl amide **2dd** was prepared by reacting the acid chloride with chloroethylamine and then displacing the chlorine with methylamine. When the 7-methoxy acid **5w** was reacted with thionyl chloride, clean chlorination *ortho* to the methoxy group also occurred so that the amide isolated was **2x**. Two acids with reactive functionality in the 2-substituent caused complications in the CDI reaction; a reaction of CDI with the terminal OH in **5g** and indole NH in **5n** occurred so that the amides isolated also contained carbamate (**8a**) and urea (**8b**) groups, respectively (Scheme 2). Careful alkaline hydrolysis removed each of these while leaving the 4-carboxamide intact (**2g** and **2n**).



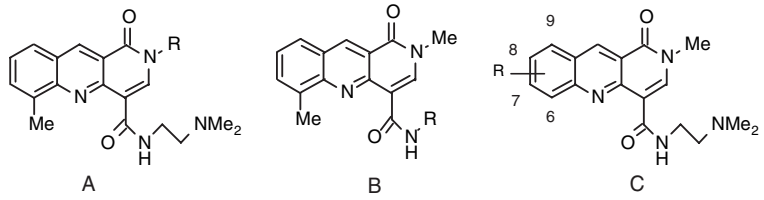
Scheme 3. Reagents and conditions: (i) Ac_2O/AcOH/60 °C/2 h; (ii) $SOCl_2$/reflux 15 min then evap. and add excess $Me_2N(CH_2)_2NH_2/CH_2Cl_2$/20 °C/16 h; (iii) 1.1 molequiv NaOEt/EtOH and evaporate, then excess MeI/DMF/110 °C/1 h.

The potentially complicating 2-OH group in acid **5p** was acetylated prior to amide formation, and deacetylation readily occurred during this latter reaction of excess *N*,*N*-dimethylethylenediamine with the intermediate acid chloride to give **2p** (Scheme 3). Also from **5p**, the hydroxy group was successfully methylated with methyl iodide and the product, **5q**, was converted to the 2-methoxy amide **2q** (Scheme 3).

2.2. Structure–activity relationships

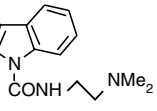
The compounds were evaluated for growth inhibitory properties, measured as IC_{50} values, against murine P388 leukemia cells and Lewis lung carcinoma cells (LLTC). These lines are commonly used for cytotoxicity evaluations and the results, along with those of reference compounds, are summarized in Table 1. The overriding

Table 1. Growth inhibitory activity of 1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamides and reference compounds



No	Fm	R	IC_{50}[a] (nM)	
			P388[b]	LLTC[c]
		DACA[d]	100	189
		DACA, 5-Me[d]	6.4	5.6
		Doxorubicin	31	22
		Etoposide	147	160
2b[e]	A	H	11	10
2c[e]	A	Me	2.1	1.7
2d	A	Et	3.7	7.3
2e[e]	A	$(CH_2)_3Me$	14	15
2f	A	CH_2CF_3	61	7
2g	A	$(CH_2)_2OH$	4.8	3.4
2h	A	CH_2CO_2Et	24	16
2i	A	$(CH_2)_3CO_2Et$	11	26
2j	A	CH_2(3,4-diOMePh)	160	36
2k	A	$(CH_2)_2$(3,4-diOMePh)	810	250
2l	A	CH_2(2-pyridyl)	13	20
2m	A	$(CH_2)_3$(*N*-pyrrolid-2-one)	10	26
2n	A	$(CH_2)_2$(3-indolyl)	210	220
2o[e]	A	$(CH_2)_2NMe_2$	6.8	3.7
2p	A	OH	110	105
2q	A	OMe	5.6	5
2r[e]	A	CH(*S*-Me)Ph	590	161
2s	A	Ph	12	2.6
2t	A	4-FPh	10	22
2u[e]	A	3,4-diOMePh	12	4.4
2v	A	$4\text{-}B(OH)_2Ph$	7.1	3.4
8a	A	$(CH_2)_2OCO(CH_2)_2NMe_2$	30	24
8b	A	$(CH_2)_2Z$[f]	140	110
2aa	B	$CH(S\text{-}Me)CONMe_2$	17,600	20,000
2bb	B	$CH(S\text{-}Me)CH_2NMe_2$	13	27
2cc	B	$CH(R\text{-}Me)CH_2NMe_2$	7.4	11
2dd	B	CH_2CH_2NHMe	3.1	3.5
2a	C	H	14[e]	24
2w	C	7-OMe	36	23
2x	C	6-Cl, 7-OMe	60	25
2y	C	6-Aza	19	38
2z	C	10-Aza	3600	870

[a] Concentration of drug to reduce cell number to 50% of control cultures (see text).
[b] Murine P388 leukemia.
[c] Murine Lewis lung carcinoma.
[d] Data from Ref. 10.
[e] Data from Ref. 3.
[f] Z =



feature is that high cytotoxicity is retained over a wide range of 2-substituent types, but some general trends are evident. Within alkyl groups, there is a tendency for activity to diminish with an increase in length of the carbon chain (Me **2c** to Bu **2e**) and the introduction of a polar terminal group has, surprisingly, little effect (e.g., pairs **2d/2g** and **2e/2i**). We noted previously[3] that branching at the α-carbon (**2r**), was not tolerated and so in the present set all alkyl groups have an α-CH_2 group. The various terminal groups in **2f–o**, **8a**, **8b** convey no particular advantage over the original methyl in **2c**.

It was noted previously that the only 2-aryl substituent included in the original set (**2u**) was highly active. Now, when successive methylene groups are introduced between ring N and the same aryl group (**2j** and **2k**), activity rapidly drops away.

It was of considerable interest that direct attachment of a benzene ring, in **2u**, produced activity comparable with the simple alkyl analogues.[3] It is now evident that this was not a specific function of the methoxy substituents, since the 'parent' **2s** is equally active and groups as diverse as 4-borono (**2v**) and 4-fluoro (**2t**) are also tolerated. The latter result is of interest as the fluoro substituent blocks a potentially metabolically reactive site.[8]

Limited variations in the carboxamide function have been studied. The fundamental importance of the terminal nitrogen function is evident; when this is part of a nonbasic amide (**2aa**), cytotoxicity is very low in comparison with a basic amine (**2bb**). There is little difference in activity between compounds with terminal NHMe (**2dd**) and NMe_2 (**2c**) groups. In related benzophenazine carboxamides, the introduction of an α-methyl group into the 2-(dimethylamino)ethyl side chain provided an increase in activity, especially for the (*R*)-enantiomer.[9] There is also a slight preference for the (*R*)-enantiomer in the present set (**2cc**), though activity is not as great as for the nonbranched chain in **2c**.

In this series, we have concentrated on compounds with the 6-methyl group since results with DACA analogues established that small 5-substituents gave greater cytotoxicity,[10] and **2a** was less active than **2c**. Nonetheless, a few other variations in benzo and center ring substituents have been included (**2w–z**), but none is as good as the 6-methyl and the additional ring nitrogen in **2z** has a profound deleterious effect.

2.3. In vivo studies

The curative in vivo activity against subcutaneously implanted colon 38 tumors in mice previously found with **2u** [2-(3,4-diOMePh)] and especially **2c** (2-Me),[3] prompted further in vivo work with both 2-alkyl and 2-aryl substituted compounds. This advanced colon 38 tumor model was chosen since it is fairly refractory to standard clinical topo II agents, as well as to antimetabolites and alkylating agents.[11] In vivo colon 38 tumor models have been shown to be the best predictors for clinical utility to date.[12] A selection of the new compounds was therefore studied under a single-dose schedule and the results, along with those of **2c**, **2u**, and reference compounds, are summarized in Table 2. None of the 'alkyl' subset, **2d** (2-Et), **2i** [2-$(CH_2)_3CO_2Et$], **2l** [2-CH_2(2-pyridyl)] improved on the activity produced by the original **2c**. However, within the aryl examples, **2t** (4-FPh) provided a noteworthy result where a single dose as low as 1.8 mg/kg had a curative effect. In contrast, multiple dosing of the established compounds listed in Table 2 gave varying growth delays but no cures.

Table 2. In vivo activity of 1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamides and reference compounds against subcutaneous colon 38 tumors in mice

Drug	Dose[a]	Sched.[b]	Growth delay days[c]	Cures[d]
2c[e]	8.9	sd	>20	3/5
	5.9	sd	>20	10/10
	3.9	sd	>20	4/4
	2.6	sd	6.0	0/5
2d	8.9	sd	>20	3/5
	5.9	sd	15	1/5
2i	8.9	sd	2.5	0/5
2l	13.3	sd	4.5	2/3
	8.9	sd	6.0	0/4
	5.9	sd	5.0	0/4
2u[e]	3.9	sd	>20	4/5
	2.6	sd	16	0/5
2s	5.9	sd	>20	0/5
	3.9	sd	7	1/5
	2.6	sd	4.5	0/5
2t	5.9	sd	>20	4/4
	3.9	sd	>20	5/5
	2.6	sd	>20	5/5
	1.8	sd	>20	4/5
Doxorubicin[e]	2.6	q4d × 3	8	0/5
Etoposide[e]	45	q4d × 3	1.5	0/5
Irinotecan[e]	65	q4d × 3	7	0/5

[a] $mg\,kg^{-1}\,day^{-1}$. Drugs were administered as an intraperitoneal dose in aqueous solution at a volume of 10 μL/g body weight. Doses indicated did not induce deaths from toxicity.

[b] sd = single dose; q4d × 3 = every 4 days × 3.

[c] Growth delays were calculated from the times of control and drug treated groups took to reach four times the mean pre-treatment tumor volume. The pre-treatment tumor volume was typically 14 mm^3.

[d] Cured mice were defined as having no evidence of a measurable tumor after 20 days. Other experiments with drugs in this series indicated that when such mice were kept for longer times, tumors did not reappear.

[e] Data from Ref. 3.

3. Conclusions

The 4-*N*-[2-(dimethylamino)ethyl]-2-substituted-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamides are confirmed as a class of potent antitumor agents, with some showing curative in vivo activity in the sc colon 38 model in a single dosing protocol. In particular, the 2-(4-fluorophenyl) and 2-methyl derivatives provide promising candidates to further investigate efficacy and mechanism of action.

4. Experimental

NMR spectra were recorded on a Bruker Avance 300 spectrometer, operating at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C), and a Bruker DRX-400 spectrometer operating at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C). Chemical shifts are reported as δ values (ppm) relative to Me_4Si. Standard PENDANT, HSQC, and HMBC spectra were used in making the NMR assignments. EI and LSI (3-nitrobenzyl alcohol as liquid matrix) mode high-resolution mass spectra were obtained by Dr. N. Davies, University of Tasmania, Australia. Melting points are uncorrected. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

Precursor compounds **3a**–**d** were prepared by adapting a method for the pyridine analogue.[4,6]

4.1. Ethyl (3-carboxyquinolin-2-yl)acetate (3a)

Ethyl (3-carboxyquinolin-2-yl)acetate (**3a**), obtained as a beige solid, mp 170–171 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.1 Hz, 3H), 4.20 (q, J = 7.1 Hz, 2H), 4.57 (s, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 9.00 (s, 1H), 12.28 (br s, 1H).

4.2. Ethyl (3-carboxy-8-methylquinolin-2-yl)acetate (3b)

Ethyl (3-carboxy-8-methylquinolin-2-yl)acetate (**3b**), as reported.[6]

4.3. Ethyl (3-carboxy-7-methoxyquinolin-2-yl)acetate (3c)

Ethyl (3-carboxy-7-methoxyquinolin-2-yl)acetate (**3c**), obtained as an orange solid, mp 193–195 °C (dec) (from ethanol). Occasionally, the compound was obtained as a red oil, which solidified on trituration with cold acetonitrile. Recrystallization was not necessary prior to use in the next step. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.02 (s, 3H, $ArOCH_3$), 4.16 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.65 (s, 2H, CH_2CO_2Et), 7.33 (dd, J = 9.1, 1.8 Hz, 1H), 7.88 (m, 2H), 9.05 (s, 1H).

4.4. Ethyl (3-carboxyquinoxalin-2-yl)acetate (3d)

Ethyl (3-carboxyquinoxalin-2-yl)acetate (**3d**), obtained as a brown semi-solid, which was used in this state in the next step.

4.5. Ethyl (3-ethoxycarbonyl[1,8]naphthyridin-2-yl)acetate (3e)

Ethyl (3-ethoxycarbonyl[1,8]naphthyridin-2-yl)acetate (**3e**) was prepared from 2-aminonicotinaldehyde and diethyl 1,3-acetonedicarboxylate by the method reported for the dimethyl analogue,[5] as an orange solid, mp 79–80 °C (from ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$-2), 1.39 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$-3), 4.13 (q, J = 7.1 Hz, 2H, 2-$CO_2CH_2CH_3$), 4.38 (q, J = 7.1 Hz, 2H, 3-$CO_2CH_2CH_3$), 4.49 (s, 2H, CH_2CO_2Et), 7.52 (dd, J = 8.0, 4.2 Hz, 1H, H-6), 8.27 (d, J = 7.9 Hz, 1H, H-5), 8.84 (s, 1H, H-4), 9.15 (d, J = 2.4 Hz, 1H, H-7).

4.6. 4-Dimethylaminomethylene-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (4a) and 4-dimethylaminomethylene-6-methyl-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (4b)

4-Dimethylaminomethylene-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (**4a**) and 4-dimethylaminomethylene-6-methyl-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (**4b**) were prepared as reported previously.[6] The following diones were prepared in the same manner.

4.7. 4-Dimethylaminomethylene-7-methoxy-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (4c)

From **3c**, and obtained as a bright yellow solid (95%), mp 273–277 °C (after forming needles >230 °C). ^{1}H NMR (DMSO-d_6): δ 3.33 (s, 3H, NCH_3), 3.62 (s, 3H, NCH_3), 3.94 (s, 3H, $ArOCH_3$), 7.18 (dd, J = 8.9, 1.7 Hz, 1H), 7.57 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.97 (s, 2H).

4.8. 4-Dimethylaminomethylene-4*H*-pyrano[3,4-b]quinoxaline-1,3-dione (4d)

From crude **3d**, with a ratio of 1 g **3d**: 0.8 mL $POCl_3$: 1.6 mL DMF. The reaction mixture was heated, with moisture exclusion, at 75 °C for 16 h, then cooled, diluted with cold dichloromethane, and kept at −18 °C for 1 h. The brick red solid was filtered and washed exhaustively, with thorough stirring, with cold dichloromethane to give the dione (22% from 3-chloroquinoxaline-2-carboxylic acid), mp 133–139 °C. ^{1}H NMR (DMSO-d_6): δ 3.27 (s, 3H, NCH_3), 3.57 (s, 3H, NCH_3), 7.66 (ddd, J = 8.3, 6.6, 1.6 Hz, 1H), 7.81–7.92 (m, 2H), 8.04 (d, J = 7.8 Hz, 1H), 8.66 (s, 1H, $=HCNMe_2$). ^{13}C NMR (DMSO-d_6): δ 45.0 (CH_3), 48.3 (CH_3), 87.0 (C), 127.2 (CH), 128.3 (CH), 130.3 (CH), 133.3 (C), 133.7 (CH), 139.4 (C), 143.2 (C), 150.3 (C), 157.6 (C), 159.7 (C), 161.1 (CH).

4.9. 9-Dimethylaminomethylene-9*H*-pyrano[4,3-*b*][1,8]-naphthyridine-6,8-dione (4e)

From diester **3e**, with a ratio of 1 g **3e**: 0.8 mL $POCl_3$: 1.6 mL DMF. The reaction mixture was heated, with moisture exclusion, at 75 °C for 16 h, then cooled, diluted with cold dichloromethane, and kept on ice for 1 h. The orange solid was filtered and washed exhaustively, with thorough stirring, with cold dichloromethane. The mass of orange dione obtained represented >100% yield. It was used in further reaction in this state within 24 h, since it decomposed on long standing. ^{1}H NMR (DMSO-d_6): δ 3.33 (s, 3H, NCH_3), 3.62 (s, 3H, NCH_3), 7.67 (dd, J = 7.8, 4.9 Hz, 1H), 8.77 (s, 1H), 8.82 (d, J = 8.1 Hz, 1H), 9.07 (d, J = 4.9 Hz, 1H), 9.15 (s, 1H).

4.10. 2,6-Dimethyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5c)

4.10.1. Method (a) for acid formation.[3] A solution of methylamine in tetrahydrofuran (7.0 mL, 2 M) was

added to a suspension of **4b** (0.8 g) in dimethylformamide (20 mL) and the whole was stirred for 16 h at room temperature. The solid was collected by filtration and washed with cold acetone to give the product as a bright yellow solid (0.60 g, 79%), mp >300 °C (formed cubic crystals above 290 °C). ^{1}H NMR (DMSO-d_6): δ 2.75 (s, 3H, CH_3), 3.67 (s, 3H, NCH_3), 7.67 (t, J = 7.7 Hz, 1H, H-8), 7.95 (d, J = 6.6 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 8.83 (s, 1H), 9.52 (s, 1H), 16.03 (s, 1H, COOH). Anal. Calcd for $C_{15}H_{12}N_2O_3 \cdot 0.2H_2O$: C, 66.3; H, 4.6; N, 10.3. Found: C, 66.6; H, 4.4; N, 10.4%.

The following compounds were made using a similar procedure.

4.11. 7-Methoxy-2-methyl-1-oxo-1,2-dihydrobenzo-[*b*][1,6]naphthyridine-4-carboxylic acid (5w)

From **4c** and methylamine, as for **5c**, and obtained as a yellow solid (86%), mp >300 °C (from dimethyl sulfoxide/1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.61 (s, 3H, NCH_3), 3.99 (s, 3H, $ArOCH_3$), 7.34 (d, J = 8.0 Hz, 1H, H-8), 7.54 (s, 1H, H-6), 8.21 (d, J = 9.1 Hz, 1H, H-9), 8.73 (s, 1H, H-3), 9.31 (s, 1H, H-10), 15.82 (s, 1H, COOH).

4.12. 7-Methyl-6-oxo-6,7-dihydropyrido[2,3-*b*][1,6]naphthyridine-9-carboxylic acid (5y)

From **4e** and methylamine, as for **5c** except that, after reaction, the volatiles were removed at reduced pressure and water was added. The resultant suspension was stirred and basified with 10% sodium hydroxide, then acidified with concentrated hydrochloric acid (dropwise) and the brown solid was filtered to give 5y, mp >300 °C (from dimethyl sulfoxide/1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.64 (s, 3H, NCH_3), 7.76 (dd, J = 8.2, 4.2 Hz, 1H, H-3), 8.81 (d, J = 8.2 Hz, 1H, H-4), 8.85 (s, 1H, H-8), 9.28 (dd, J = 3.9, 1.7 Hz, 1H, H-2), 9.58 (s, 1H, H-5), 15.68 (s, 1-H, COOH).

4.13. 2-Methyl-1-oxo-1,2-dihydropyrido[3,4-*b*]quinoxaline-4-carboxylic acid (5z)

From **4d** and methylamine, as for **5c** except that, after reaction, the volatiles were removed at reduced pressure to leave the methylamine salt of **5z** as a yellow-brown solid. This was suspended in a small amount of water and 10% sodium hydroxide was added dropwise, with stirring, until a solution was obtained. This was acidified with a minimum amount of concentrated hydrochloric acid and the solid, which separated was filtered and washed with water to give the free acid as a yellow solid (52%), mp >300 °C (from dimethyl sulfoxide/1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.66 (s, 3H, NCH_3), 7.97 (t, J = 7.5 Hz, 1H), 8.08 (t, J = 7.6 Hz, 1H), 8.25–8.32 (m, 2H), 8.79 (s, 1H), 14.03 (br s, 1H, COOH).

4.14. 6-Methyl-1-oxo-2-(2,2,2-trifluoroethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5f)

4.14.1. Method (b) for acid formation. To a stirring suspension of dione **4b** (1.00 g, 3.54 mmol) in *N*,*N*-dimethylformamide (15 mL) was added triethylamine (2.5 mL) with constant stirring. 2,2,2-Trifluoroethylamine (0.40 g, 4.04 mmol) was added and the whole was stirred at room temperature for 16 h. The solid was filtered and washed with water to give the yellow acid (64%), mp 297–300 °C (formed needles at 234–235 °C). ^{1}H NMR (DMSO-d_6): δ 2.67 (s, 3H, $ArCH_3$), 5.12 (q, J = 9.0 Hz, 2H, CH_2CF_3), 7.63 (t, J = 7.6 Hz, 1H, H-8), 7.90 (d, J = 6.9 Hz, 1H, H-7), 8.17 (d, J = 8.2 Hz, 1H, H-9), 8.81 (s, 1H, H-3), 9.46 (s, 1H, H-10), 15.91 (br s, 1H, COOH).

The following compounds were made using a similar procedure.

4.15. 2-Ethyl-6-methyl-1-oxo-1,2-dihydrobenzo-[*b*][1,6]naphthyridine-4-carboxylic acid (5d)

From **4b** and ethylamine, as for **5f** except that the initial addition of ethylamine was carried out at 0 °C and a positive pressure of nitrogen was maintained throughout, and obtained as a yellow solid (72%), mp 251–253 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.65 (s, 3H, $ArCH_3$), 4.12 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.59 (t, J = 7.6 Hz, 1H, H-8), 7.86 (d, J = 6.8 Hz, 1H, H-7), 8.12 (d, J = 8.3 Hz, 1H, H-9), 8.74 (s, 1H, H-3), 9.36 (s, 1H, H-10), 15.89 (s, 1H, COOH).

4.16. 2-(2-Hydroxyethyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5g)

From **4b** and ethanolamine, as for **5f**, and obtained as a yellow solid (64%), mp 258–261 °C. ^{1}H NMR (DMSO-d_6): δ 2.64 (s, 3H, $ArCH_3$), 3.70 (t, J = 6.2 Hz, 2H, CH_2CH_2OH), 4.15 (t, J = 5.0 Hz, 2H, CH_2CH_2OH), 7.57 (t, J = 7.6 Hz, 1H, H-8), 7.85 (d, J = 6.8 Hz, 1H, H-7), 8.11 (d, J = 8.3 Hz, 1H, H-9), 8.62 (s, 1H, H-3), 9.35 (s, 1H, H-10), 15.85 (s, 1H, COOH).

4.17. 2-(Ethoxycarbonylmethyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5h)

From **4b** and glycine ethyl ester hydrochloride, as for **5f** except that water was added to the reaction mixture before the acid was filtered. The product was obtained as a yellow solid (65%), mp 277–280 °C. ^{1}H NMR (DMSO-d_6): δ 1.20 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.70 (s, 3H, $ArCH_3$), 4.17 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.97 (s, 2H, CH_2CO_2Et), 7.64 (t, J = 7.7 Hz, 1H, H-8), 7.91 (d, J = 6.9 Hz, 1H, H-7), 8.18 (d, J = 8.2 Hz, 1H, H-9), 8.85 (s, 1H, H-3), 9.44 (s, 1H, H-10), 15.89 (br s, 1H, COOH).

4.18. 2-(3-Ethoxycarbonylpropyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5i)

From **4b** and ethyl 4-aminobutyrate hydrochloride, as for **5f** except that 1,4-dioxane was used as solvent. After 16 h, water was added to the reaction mixture and the yellow solid was filtered and washed with a little 3% hydrochloric acid, then with water to give the acid **5i** (59%), mp 186–188 °C. This was used in the next step without further purification but can be recrystallized from toluene as a yellow solid. ^{1}H NMR ($CDCl_3$): δ

1.23 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$), 2.15 (quintet, $J = 7.1$ Hz, 2H, $CH_2CH_2CH_2$), 2.41 (t, $J = 7.1$ Hz, 2H, $NCH_2CH_2CH_2$), 2.76 (s, 3H, $ArCH_3$), 4.07–4.18 (m, 4H, $CO_2CH_2CH_3$, $NCH_2CH_2CH_2$), 7.54 (t, $J = 7.6$ Hz, 1H, H-8), 7.77 (d, $J = 6.9$ Hz, 1H, H-7), 7.87 (d, $J = 8.3$ Hz, 1H, H-9), 8.57 (s, 1H, H-3), 9.25 (s, 1H, H-10), 15.93 (s, 1H, COOH). ^{13}C NMR ($CDCl_3$): δ 14.1 ($CO_2CH_2CH_3$), 18.1 ($ArCH_3$), 24.3 ($CH_2CH_2CH_2$), 31.1 ($NCH_2CH_2CH_2$), 49.3 ($NCH_2CH_2CH_2$), 60.7 ($CO_2CH_2CH_3$), 105.3 (C-4), 118.9 (C-10a), 126.4 (C-9a), 127.4 (CH, C-8), 127.6 (CH, C-9), 134.3 (CH, C-7), 134.8 (C-6), 141.3 (CH, C-10), 145.2 (CH, C-3), 146.5 (C-5a), 148.5 (C-4a), 161.7 (C-1), 166.0 (COOH), 172.1 (CO_2Et).

4.19. 2-(3,4-Dimethoxybenzyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5j)

From **4b** and veratrylamine, as for **5f**, and obtained as a yellow solid (77%), mp 256–257 °C. ^{1}H NMR (DMSO-d_6): δ 2.70 (s, 3H, $ArCH_3$), 3.69 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2Ph), 6.88–6.97 (m, 2H, H-5′, H-6′), 7.07 (s, 1H, H-2′), 7.63 (t, $J = 7.6$ Hz, 1H, H-8), 7.90 (d, $J = 7.0$ Hz, 1H, H-7), 8.19 (d, $J = 8.2$ Hz, 1H, H-9), 8.81 (s, 1H, H-3), 9.49 (s, 1H, H-10), 15.97 (br s, 1H, COOH).

4.20. 2-[2-(3,4-Dimethoxyphenyl)ethyl]-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5k)

From **4b** and 3,4-dimethoxyphenethylamine, as for **5f**, and obtained as a yellow solid (79%), mp 280–282 °C. ^{1}H NMR (DMSO-d_6): δ 2.70 (s, 3H, $ArCH_3$), 2.94 (t, $J = 7.3$ Hz, 2H, CH_2CH_2Ph), 3.66 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.31 (t, $J = 7.2$ Hz, 2H, CH_2CH_2Ph), 6.71 (d, $J = 8.1$ Hz, 1H, H-5′), 6.80 (d, $J = 8.1$ Hz, 1H, H-6′), 6.91 (s, 1H, H-2′), 7.64 (t, $J = 7.8$ Hz, 1H, H-8), 7.92 (d, $J = 6.8$ Hz, 1H, H-7), 8.21 (d, $J = 8.4$ Hz, 1H, H-9), 8.67 (s, 1H, H-3), 9.48 (s, 1H, H-10), 15.89 (br s, 1H, COOH).

4.21. 6-Methyl-1-oxo-2-(pyridin-2-yl)methyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5l)

From **4b** and 2-aminomethylpyridine, as for **5f**, and obtained as a yellow solid (57%), mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 2.72 (s, 3H, $ArCH_3$), 5.47 (s, 2H, CH_2Pyr), 7.27 (dd, $J = 7.0$, 5.2 Hz, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.78 (t, $J = 7.7$ Hz, 1H), 7.92 (d, $J = 6.7$ Hz, 1H), 8.18 (d, $J = 8.3$ Hz, 1H), 8.44 (d, $J = 4.6$ Hz, 1H), 8.90 (s, 1H, H-3), 9.43 (s, 1H, H-10), 15.98 (br s, 1H, COOH).

4.22. 6-Methyl-1-oxo-2-[3-(2-oxopyrrolidin-1-yl)propyl]-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5m)

From **4b** and *N*-(3-aminopropyl)-2-pyrrolidinone, as for **5f**, and obtained as a yellow solid (0.43 g, 64%), mp 226–228 °C. ^{1}H NMR (DMSO-d_6+trace CF_3CO_2H): δ 1.84–1.96 (m, 4H), 2.20 (t, $J = 8.0$ Hz, 2H), 2.56 (s, 3H, $ArCH_3$), 3.25 (t, $J = 6.8$ Hz, 2H), 3.34 (t, $J = 7.0$ Hz, 2H), 4.02 (t, $J = 7.3$ Hz, 2H), 7.54 (t, $J = 7.7$ Hz, 1H, H-8), 7.81 (d, $J = 7.0$ Hz, 1H, H-7), 8.04 (d, $J = 8.2$ Hz, 1H, H-9), 8.82 (s, 1H, H-3), 9.35 (s, 1H, H-10).

4.23. 2-[2-(1*H*-Indol-3-yl)ethyl]-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5n)

From **4b** and tryptamine, as for **5f**, and obtained as a yellow solid (91%), mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 2.69 (s, 3H, $ArCH_3$), 3.14 (t, $J = 7.2$ Hz, 2H, CH_2CH_2Indole), 4.36 (t, $J = 7.1$ Hz, 2H, CH_2CH_2-Indole), 6.91 (t, $J = 7.4$ Hz, 1H), 7.02 (t, $J = 7.5$ Hz, 1H), 7.14 (s, 1H, H-2′), 7.30 (d, $J = 8.0$ Hz, 1H), 7.58–7.65 (m, 2H), 7.90 (d, $J = 6.8$ Hz, 1H), 8.19 (d, $J = 7.9$ Hz, 1H), 8.54 (s, 1H, H-3), 9.49 (s, 1H, H-10), 10.83 (s, 1H, NH), 15.91 (s, 1H, COOH).

4.24. 2-Hydroxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5p)

From **4b** and hydroxylamine hydrochloride, as for **5f** except that, after reaction, 10% sodium hydroxide was added dropwise until a solution was obtained. The phase was then made acidic with concentrated hydrochloric acid (dropwise) and the resultant brown solid was filtered to give the acid **5p** (64%), mp 262–264 °C (twice from ethanol). ^{1}H NMR (DMSO-d_6, 100 °C): δ 2.66 (s, 3H, $ArCH_3$), 7.61 (t, $J = 7.6$ Hz, 1H, H-8), 7.88 (d, $J = 6.8$ Hz, 1H, H-7), 8.16 (d, $J = 8.2$ Hz, 1H, H-9), 8.63 (s, 1H, H-3), 9.45 (s, 1H, H-10), 12.29 (br s, 1H, NOH), 15.89 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 100 °C): δ 17.2 ($ArCH_3$), 103.2 (C-4), 119.5 (C-10a), 126.0 (C-9a), 127.3 (CH, C-8), 127.9 (CH, C-9), 133.9 (C-6), 134.3 (CH, C-7), 140.9 (CH, C-10), 143.1 (CH, C-3), 146.1 (C-5a), 147.6 (C-4a), 158.1 (C-1), 164.4 (COOH). Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.2; H, 3.7; N, 10.4. Found: C, 62.0; H, 3.4; N, 10.3%.

4.25. 6-Methyl-1-oxo-2-phenyl-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5s)

From **4b** and aniline (10 mol equiv), as for **5f** except that the product when filtered was washed thoroughly with acetone. The acid was a lemon colored solid (41%), mp >310 °C, which was used in the next step without further purification but can be recrystallized from 1,4-dioxane. ^{1}H NMR (DMSO-d_6): δ 2.73 (s, 3H, $ArCH_3$), 7.51–7.59 (m, 5H, Ph), 7.66 (t, $J = 7.6$ Hz, 1H, H-8), 7.95 (d, $J = 6.9$ Hz, 1H, H-7), 8.23 (d, $J = 8.3$ Hz, 1H, H-9), 8.46 (s, 1H, H-3), 9.51 (s, 1H, H-10), 15.99 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{14}N_2O_3 \cdot 0.4H_2O$: C, 71.2; H, 4.4; N, 8.3. Found: C, 71.3; H, 4.0; N, 8.3%.

The filtrate was taken to dryness at reduced pressure, water was added, and the resultant yellow solid was filtered and washed with water to give *N*,*N*-dimethyl-2-[2-(phenylamino)vinyl]-8-methylquinoline-3-carboxamide (**7a**) (32%), mp 143–146 °C [from light petroleum (bp 90–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.79 (s, 6H, $ArCH_3$, NCH_3), 3.06 (s, 3H, NCH_3), 5.31 (d, $J = 8.5$ Hz, 1H, HC=), 6.93 (t, $J = 7.3$ Hz, 1H, H-4′), 7.17 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 7.30–7.38 (m, 3H, H-6, H-3′, H-5′), 7.52–7.62 (m, 2H, =CH, H-7), 7.69

(d, $J = 7.9$ Hz, 1H, H-5), 8.05 (s, 1H, H-4), 11.95 (d, $J = 11.7$ Hz, 1H, NH—exchanges with added D_2O). ^{13}C NMR (DMSO-d_6): δ 18.8 ($ArCH_3$), 34.3 (NCH_3), 38.2 (NCH_3), 94.5 (HC═), 115.0 (2 × CH, C-2′, C-6′), 121.6 (CH, C-4′), 124.0 (C-4a), 125.0 (CH, C-6), 126.1 (CH, C-5), 129.5 (C-3), 129.9 (2 × CH, C-3′, C-5′), 130.5 (CH, C-7), 133.5 (CH, C-4), 133.7 (C-8), 136.4 (═CH), 141.5 (C-1′), 145.3 (C-8a), 153.8 (C-2), 168.4 ($CONMe_2$). HRMS (EI) calcd for $C_{21}H_{21}N_3O$: 331.1686. Found: 331.1686.

4.26. 6-Methyl-1-oxo-2-(4-fluorophenyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5t)

From **4b** and 4-fluoroaniline (10 mol equiv), as for **5s**. The first filtered product was a triethylamine salt of the target acid. This was dissolved in hot 5% sodium hydroxide, filtered, and the filtrate was cooled and acidified with concentrated hydrochloric acid to give the acid as a yellow solid (26%). ^1H NMR (DMSO-d_6): δ 2.75 (s, 3H, CH_3), 7.38–7.43 (m, 2H), 7.60–7.70 (m, 3H), 7.95 (d, $J = 6.0$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.48 (s, 1H), 9.53 (s, 1H).

Addition of water to the first filtrate gave a yellow-green solid, which was recrystallized twice from methanol to give *N*,*N*-dimethyl-2-[2-((4-fluorophenyl)amino)vinyl]-8-methylquinoline-3-carboxamide (**7b**), mp 172–173 °C after changing form ca. 100 °C. ^1H NMR (DMSO-d_6): δ 2.78 (s, 3H, CH_3) 2.79 and 3.06 [2 × s, 6H, $N(CH_3)_2$], 5.28 (d, $J = 8.5$ Hz, 1H), 7.13–7.20 (m, 4H), 7.36 (t, $J = 7.4$ Hz, 1H), 7.50 (dd, $J = 11.7$, 8.5 Hz, 1H), 7.61 (d, $J = 6.8$ Hz, 1H), 7.70 (d, $J = 7.9$ Hz, 1H), 8.06 (s, 1H), 11.96 (d, $J = 11.7$ Hz, 1H).

4.27. 6-Methyl-1-oxo-2-[4-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)phenyl]-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5ee)

From **4b** and 2 mol equiv of 4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)aniline, as for **5f**. A solution formed slowly and, after 16 h, the volume was reduced to ca 1/3 at reduced pressure, and the whole was cooled on ice. The solid which separated was filtered off, washed with cold toluene and the recrystallized from toluene to give the acid as a yellow solid (20%), mp >300 °C. ^1H NMR ($CDCl_3$): δ 1.36 (s, 12H, 4 × CH_3), 2.87 (s, 3H, $ArCH_3$), 7.46 (d, $J = 8.0$ Hz, 2H, ArH), 7.61 (t, $J = 7.6$ Hz, 1H, H-8), 7.85 (d, $J = 6.8$ Hz, 1H, H-7), 7.95–8.00 (m, 3H, H-9, ArH), 8.72 (s, 1H, H-3), 9.42 (s, 1H, H-10), 16.16 (s, 1H, COOH).

The filtrate from the reaction mixture (containing DMF, triethylamine, and toluene) was taken to dryness at reduced pressure, and the residue was recrystallized from toluene to give the starting aniline as a yellow solid (45% recovery).

4.28. 2-Methoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5q)

To a suspension of the hydroxylacid **5p** (0.26 g, 0.96 mmol) in hot ethanol (50 mL) was added sodium ethoxide [prepared from sodium (25 mg, 1.09 mmol) in ethanol (10 mL)]. The volatiles were removed at reduced pressure, *N*,*N*-dimethylformamide (20 mL) was added to the residue, and the whole was heated at 110 °C, with stirring, for 5 min. Iodomethane (1 mL) was added and stirring was continued at the same temperature for 1 h (dissolution occurred during this time). The solution was evaporated to dryness at reduced pressure and ice-water was added to the brown residue. The phase was made acidic with concd hydrochloric acid and the resultant yellow solid was filtered and washed with water to give the methoxy acid **5q** (0.23 g, 84%), mp 277–278 °C (from *N*,*N*-dimethylformamide as yellow needles). ^1H NMR (DMSO-d_6): δ 2.70 (s, 3H, $ArCH_3$), 4.09 (s, 3H, OCH_3), 7.66 (t, $J = 7.7$ Hz, 1H, H-8), 7.93 (d, $J = 6.9$ Hz, 1H, H-7), 8.20 (d, $J = 8.2$ Hz, 1H, H-9), 8.90 (s, 1H, H-3), 9.51 (s, 1H, H-10), 15.96 (s, 1H, COOH).

4.29. 2-Acetoxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (5ff)

A suspension of the pulverized hydroxylacid **5p** (0.23 g, 0.85 mmol), acetic acid (1.5 mL), and acetic anhydride (12 mL) was heated, with stirring, at 60 °C for 2 h. The reaction mixture was cooled, filtered and washed with acetone to give the acetoxylacid **5ff** as a yellow solid (0.22 g, 83%), which contained <10% starting hydroxylacid **5p**. Recrystallization from acetonitrile gave **5ff** as yellow needles, mp 264–265 °C. ^1H NMR (DMSO-d_6): δ 2.40 (s, 3H, $COCH_3$), 2.73 (s, 3H, $ArCH_3$), 7.69 (t, $J = 7.6$ Hz, 1H, H-8), 7.97 (d, $J = 6.9$ Hz, 1H, H-7), 8.25 (d, $J = 8.2$ Hz, 1H, H-9), 9.08 (s, 1H, H-3), 9.56 (s, 1H, H-10), 15.99 (s, 1H, COOH).

4.30. *N*-[2-(Dimethylamino)ethyl]-2-(3-ethoxycarbonyl)-propyl-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2i)

4.30.1. Method (a) for formation of carboxamides. Acid **5i** (0.40 g, 1.09 mmol) was heated under reflux in thionyl chloride (20 mL) for 5 h. The excess of thionyl chloride was removed at reduced pressure and a solution of *N*,*N*-dimethylethylenediamine (0.5 mL, 4.56 mmol) in dichloromethane (20 mL) was added to the residue. The resulting solution was stirred at room temperature for 16 h and the solution was washed with 10% sodium hydroxide and water (×2). The solvent was removed at reduced pressure to give the product as a yellow solid (0.35 g, 74%), mp 130–132 °C [from toluene/light petroleum (bp 90–120 °C)]. ^1H NMR ($CDCl_3$): δ 1.23 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$), 2.15 (quintet, $J = 7.2$ Hz, 2H, $CH_2CH_2CH_2$), 2.40 (t, $J = 7.2$ Hz, 2H, $NCH_2CH_2CH_2$), 2.49 [s, 6H, $N(CH_3)_2$], 2.84–2.89 (m, 5H, $ArCH_3$, $CH_2CH_2NMe_2$), 3.84 (q, $J = 6.2$ Hz, 2H, $CH_2CH_2NMe_2$), 4.07–4.17 (m, 4H, $CO_2CH_2CH_3$, $NCH_2CH_2CH_2$), 7.49 (t, $J = 7.6$ Hz, 1H, H-8), 7.73 (d, $J = 6.9$ Hz, 1H, H-7), 7.86 (d, $J = 8.2$ Hz, 1H, H-9), 8.57 (s, 1H, H-3), 9.27 (s, 1H, H-10), 11.17 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 14.2 (CO_2CH_2 CH_3), 18.6 ($ArCH_3$), 24.5 ($CH_2CH_2CH_2$), 31.2 ($NCH_2CH_2CH_2$), 36.8 ($CH_2CH_2NMe_2$), 44.7 [$N(CH_3)_2$], 48.9 ($NCH_2CH_2CH_2$), 58.0 ($CH_2CH_2NMe_2$), 60.6 (CO_2-

CH_2CH_3), 109.5 (C-4), 119.4 (C-10a), 126.0 (C-9a), 126.8 (CH, C-8), 127.4 (CH, C-9), 133.1 (CH, C-7), 135.9 (C-6), 140.1 (CH, C-10), 142.9 (CH, C-3), 148.2 (C-5a), 148.6 (C-4a), 162.4 (C-1), 164.9 (CONH), 172.3 (CO_2Et). Anal. Calcd for $C_{24}H_{30}N_4O_4 \cdot 0.75H_2O$: C, 63.8; H, 7.0; N, 12.4. Found: C, 63.6; H, 7.0; N, 12.4%.

The following compounds were made using a similar procedure.

4.31. *N*-[2-(Dimethylamino)ethyl]-2-hydroxy-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2p)

From **5p**, with a reflux time of 15 min. After reaction with *N*,*N*-dimethylethylenediamine (4.2 mol equiv) for 16 h, the volatiles were removed at reduced pressure and the resultant red solid was recrystallized from moist ethanol to give the amide **2p** as orange needles (66%), mp 210–211 °C. ^{1}H NMR (DMSO-d_6, 70 °C): δ 2.24 [s, 6H, N(CH_3)$_2$], 2.56 (t, J = 6.2 Hz, 2H, CH_2CH_2NMe$_2$), 2.79 (s, 3H, ArCH_3), 3.58 (q, J = 6.0 Hz, 2H, CH_2CH_2NMe$_2$), 7.53 (t, J = 7.6 Hz, 1H, H-8), 7.80 (d, J = 6.8 Hz, 1H, H-7), 8.03 (d, J = 8.1 Hz, 1H, H-9), 8.56 (s, 1H, H-3), 9.29 (s, 1H, H-10), 10.54 (br s, 1H, CONH). ^{13}C NMR (DMSO-d_6, 70 °C): δ 17.8 (ArCH_3), 37.1 (CH_2CH_2NMe$_2$), 45.0 [N(CH_3)$_2$], 58.5 (CH_2CH_2NMe$_2$), 107.7 (C-4), 119.8 (C-10a), 125.4 (C-9a), 126.8 (CH, C-8), 127.5 (CH, C-9), 133.1 (CH, C-7), 135.4 (C-6), 139.5 (CH, C-10), 141.2 (CH, C-3), 147.4 (C-4a), 147.6 (C-5a), 158.4 (C-1), 163.0 (CONH). Anal. Calcd for $C_{18}H_{20}N_4O_3 \cdot 0.5H_2O$: C, 61.9; H, 6.1; N, 16.0. Found: C, 61.5; H, 6.1; N, 15.7%.

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

From acid **5q**, with a reflux time of 15 min, and obtained as an orange solid (77%), mp 163–164 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.33 [s, 6H, N(CH_3)$_2$], 2.67 (t, J = 6.4 Hz, 2H, CH_2CH_2NMe$_2$), 2.82 (s, 3H, ArCH_3), 3.74 (q, J = 6.1 Hz, 2H, CH_2CH_2NMe$_2$), 4.14 (s, 3H, OCH_3), 7.48 (dd, J = 8.2, 7.1 Hz, 1H, H-8), 7.71 (d, J = 6.9 Hz, 1H, H-7), 7.82 (d, J = 8.3 Hz, 1H, H-9), 8.76 (s, 1H, H-3), 9.25 (s, 1H, H-10), 10.88 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.2 (ArCH_3), 37.1 (CH_2CH_2NMe$_2$), 44.9 [N(CH_3)$_2$], 58.2 (CH_2CH_2NMe$_2$), 64.7 (OCH_3), 109.3 (C-4), 120.1 (C-10a), 125.3 (C-9a), 126.8 (CH, C-8), 126.9 (CH, C-9), 132.8 (CH, C-7), 135.7 (C-6), 139.5 (CH, C-10), 139.7 (CH, C-3), 147.3 (C-4a), 147.9 (C-5a), 158.0 (C-1), 163.4 (CONH). Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.4; H, 6.3; N, 15.8. Found: C, 64.0; H, 6.2; N, 15.7%.

4.33. *N*-[2-(Dimethylamino)ethyl]-6-methyl-2-phenyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2s)

From acid **5s**, with a reflux time of 30 min, and obtained as pale yellow needles (55%), mp 199–201 °C (from methanol). ^{1}H NMR ($CDCl_3$): δ 2.35 [s, 6H, N(CH_3)$_2$], 2.70 (t, J = 6.4 Hz, 2H, CH_2CH_2NMe$_2$), 2.88 (s, 3H, ArCH_3), 3.77 (q, J = 6.1 Hz, 2H, CH_2CH_2NMe$_2$), 7.43–7.55 (m, 6H, H-8, Ph), 7.75 (d, J = 6.9 Hz, 1H, H-7), 7.88 (d, J = 8.1 Hz, 1H, H-9), 8.71 (s, 1H, H-3), 9.32 (s, 1H, H-10), 11.06 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.6 (ArCH_3), 37.5 (CH_2CH_2NMe$_2$), 45.3 [N(CH_3)$_2$], 58.6 (CH_2CH_2NMe$_2$), 110.0 (C-4), 119.9 (C-10a), 126.2 (C-9a), 126.7 (2 × CH, Ph), 126.8 (CH, C-8), 127.4 (CH, C-9), 128.8 (CH, C-4′), 129.5 (2 × CH, Ph), 133.1 (CH, C-7), 136.1 (C-6), 140.1 (C-1′), 140.5 (CH, C-10), 143.4 (CH, C-3), 148.4 (C-5a), 148.9 (C-4*a*), 162.2 (C-1), 164.6 (CONH). Anal. Calcd for $C_{24}H_{24}N_4O_2$: C, 72.0; H, 6.0; N, 14.0. Found: C, 71.8; H, 6.0; N, 13.8%.

4.34. *N*-[2-(Dimethylamino)ethyl]-2-(4-fluorophenyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2t)

From acid **5t**, with a reflux time of 30 min, and obtained as pale yellow needles (88%), mp 219–220 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.45 [s, 6H, N(CH_3)$_2$], 2.82 [t, J = 6.3 Hz, 2H, CH_2N(CH_3)$_2$], 2.87 (s, 3H, CH_3), 3.83 (q, J = 6.4 Hz, 2H, CONHCH_2), 7.18–7.25 (m, 2H), 7.42–7.55 (m, 3H), 7.76 (d, J = 7.0 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 8.65 (s, 1H, H-3), 9.30 (s, 1H, H-10), 11.14 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.4 (C6–CH_3), 35.7 (CH_2), 43.7 [N(CH_3)$_2$], 56.9 (CH_2), 109.1 (C), 116.15 (d, J = 23.1 Hz, CH, C-3′,5′), 119.2 (C), 125.8 (C), 126.8 (CH), 127.0 (CH), 128.16 (d, J = 8.5 Hz, CH, C-2′,6′), 133.2 (CH), 135.5 (C), 140.3 (CH), 142.8 (CH), 147.8 (C), 148.0 (C), 161.8 (C), 162.0 (d, J = 244.5 Hz, C-4′), 164.8 (C). Anal. Calcd for $C_{24}H_{23}FN_4O_2$: C, 68.9; H, 5.5; N, 13.4. Found: C, 68.9; H, 5.6; N, 13.4%.

4.35. *N*-[2-(Dimethylamino)ethyl]-6-chloro-7-methoxy-2-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2x)

From acid **5w**, with a reflux time of 5 h, and obtained as a brown solid (73%), mp 209–212 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.32 [s, 6H, N(CH_3)$_2$], 2.69 (t, J = 6.8 Hz, 2H, CH_2CH_2NMe$_2$), 3.69–3.77 (m, 5H, CH_2CH_2NMe$_2$, NCH_3), 4.14 (s, 3H, ArOCH_3), 7.45 (d, J = 9.2 Hz, 1H, H-8), 7.97 (d, J = 9.2 Hz, 1H, H-9), 8.63 (s, 1H, H-3), 9.24 (s, 1H, H-10), 11.17 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 37.2 (NCH_3), 37.9 (CH_2CH_2NMe$_2$), 45.6 [N(CH_3)$_2$], 57.0 (ArOCH_3), 58.9 (CH_2CH_2NMe$_2$), 109.4 (C-4), 114.4 (CH, C-8), 116.6 (C-6), 118.2 (C-10a), 121.9 (C-9a), 129.1 (CH, C-9), 139.9 (CH, C-10), 144.5 (CH, C-3), 146.1 (C-5a), 150.5 (C-4a), 158.3 (C-7), 162.6 (C-1), 164.3 (CONH). Anal. Calcd for $C_{19}H_{21}ClN_4O_3$: C, 58.7; H, 5.4; N, 14.4. Found: C, 58.3; H, 5.4; N, 14.3%.

4.36. *N*-[2-(Dimethylamino)ethyl]-7-methyl-6-oxo-6,7-dihydropyrido[2,3-*b*][1,6]naphthyridine-9-carboxamide (2y)

From acid **5y**, with a reflux time of 1.5 h (complete dissolution did not occur). The crude amide was added to a short silica column. This was first eluted with

dichloromethane/methanol (19:1) and then with dichloromethane/methanol (1:1), which furnished the amide as a yellow solid (17%), mp 218–221 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.41 [s, 6H, $N(CH_3)_2$], 2.74 (t, J = 6.6 Hz, 2H, $CH_2CH_2NMe_2$), 3.70 (s, 3H, $ArCH_3$), 3.76 (q, J = 6.3 Hz, 2H, $CH_2CH_2NMe_2$), 7.57 (dd, J = 8.2, 4.2 Hz, 1H, H-3), 8.40 (dd, J = 8.3, 2.0 Hz, 1H, H-4), 8.68 (s, 1H, H-8), 9.27 (dd, J = 4.2, 2.0 Hz, 1H, H-2), 9.36 (s, 1H, H-5), 10.95 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 37.0 (NCH_3), 37.3 ($CH_2CH_2NMe_2$), 45.1 [$N(CH_3)_2$], 58.2 ($CH_2CH_2NMe_2$), 109.1 (C-9), 120.1 (C), 120.4 (C), 122.1 (CH, C-3), 138.3 (CH, C-4), 141.4 (CH, C-5), 145.0 (CH, C-8), 152.1 (C-9*a*), 155.2 (C-10a), 157.2 (CH, C-2), 161.9 (C-6), 163.7 (CONH). Anal. Calcd for $C_{17}H_{19}N_5O_2 \cdot H_2O$: C, 59.5; H, 6.2; N, 20.4. Found: C, 59.6; H, 5.7; N, 20.3%.

4.37. *N*-[2-(Dimethylamino)ethyl]-2-methyl-1-oxo-1,2-dihydropyrido[3,4-*b*]quinoxaline-4-carboxamide (2z)

From acid **5z**, with a reflux time of 45 min, and obtained as golden flakes (47%), mp 215–218 °C (after forming needles >109 °C) (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.41 [s, 6H, $N(CH_3)_2$], 2.65 (t, J = 6.1 Hz, 2H, $CH_2CH_2NMe_2$), 3.67 (q, J = 5.7 Hz, 2H, $CH_2CH_2NMe_2$), 3.75 (s, 3H, NCH_3), 7.80–7.86 (m, 1H), 7.88–7.95 (m, 1H), 8.08 (d, J = 8.3 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.63 (s, 1H), 10.61 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 37.1 (CH_2), 37.5 (CH_3), 44.9 [$N(CH_3)_2$], 57.5 (CH_2), 108.0 (C), 127.9 (CH), 130.4 (CH), 130.5 (CH), 133.3 (CH), 136.7 (C), 141.4 (C), 142.2 (C), 143.5 (CH), 144.9 (C), 160.9 (C), 163.2 (C).

The yellow hydrochloride had mp 218–221 °C (from ethanol). Anal. Calcd for $C_{17}H_{19}N_5O_2 \cdot HCl \cdot 0.25H_2O$: C, 55.7; H, 5.6; N, 19.1. Found: C, 55.9; H, 5.4; N, 19.1%.

4.38. (*S*)-*N*-[1-((Dimethylamino)carbonyl)ethyl]-2,6-dimethyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2aa)

From acid **5c**, with a reflux time of 45 min. To the residue from removal of the thionyl chloride was added triethylamine (2.2 mol equiv) in dichloromethane followed by (*S*)-2-amino-*N*,*N*-dimethylpropionamide (1.1 mol equiv) in dichloromethane. The standard reaction and workup gave the amide (88%) as yellow needles, mp 277–280 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.42 (d, J = 6.8 Hz, 3H, $CHCH_3$), 2.81 (s, 3H, $ArCH_3$), 2.99 [br s, 6H, $N(CH_3)_2$], 3.62 (s, 3H, NCH_3), 5.21 (quintet, J = 7.1 Hz, 1H, $CHCH_3$), 7.53 (t, J = 7.6 Hz, 1H, H-8), 7.79 (d, J = 6.8 Hz, 1H, H-7), 8.03 (d, J = 8.2 Hz, 1H, H-9), 8.55 (s, 1H, H-3), 9.26 (s, 1H, H-10), 10.84 (br d, J = 7.7 Hz, 1H, CONH). ^{13}C NMR (DMSO-d_6, 100 °C): δ 18.2 ($ArCH_3$), 18.4 ($CHCH_3$), 36.1 [br s, $N(CH_3)_2$], 36.5 (NCH_3), 44.6 ($CHCH_3$), 108.6 (C-4), 119.1 (C-10a), 125.8 (C-9a), 126.6 (CH, C-8), 127.5 (CH, C-9), 133.0 (CH, C-7), 135.7 (C-6), 139.6 (CH, C-10), 144.7 (CH, C-3), 147.8 (C-5a), 148.7 (C-4a), 162.0 (C-1), 162.8 (CONH), 172.1 ($CONMe_2$). Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.6; H, 6.1; N, 15.3. Found: C, 65.8; H, 6.0; N, 15.3%.

4.39. (*S*)-*N*-[2-(1-Dimethylamino)propyl]-2,6-dimethyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2bb)

From acid **5c**, with a reflux time of 45 min. To a suspension in dichloromethane of the residue from removal of the thionyl chloride was added a solution of (*S*)-N^1,N^1-dimethylpropane-1,2-diamine dihydrochloride (2.2 mol equiv) and triethylamine (2.2 mol equiv) in dichloromethane. The standard reaction and workup gave the amide (38%) as a light brown solid, mp 205–209 °C (from acetonitrile). ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.46 (d, J = 6.6 Hz, 3H, $CHCH_3$), 2.81 (s, 3H, $ArCH_3$), 2.84 [s, 6H, $N(CH_3)_2$], 3.31 (d, J = 6.8 Hz, 2H, CH_2NMe_2), 3.64 (s, 3H, NCH_3), 4.64 (quintet, J = 6.9 Hz, 1H, $CHCH_3$), 7.57 (t, J = 7.6 Hz, 1H, H-8), 7.84 (d, J = 6.0 Hz, 1H, H-7), 8.08 (d, J = 8.1 Hz, 1H, H-9), 8.60 (s, 1H, H-3), 9.31 (s, 1H, H-10), 10.75 (br s, 1H, CONH). ^{13}C NMR (DMSO-d_6, 100 °C): δ 18.5 ($ArCH_3$), 19.6 ($CHCH_3$), 36.6 (NCH_3), 43.4 [$N(CH_3)_2$], 62.4 (CH_2NMe_2), 108.4 (C-4), 119.2 (C-10a), 125.9 (C-9a), 126.8 (CH, C-8), 127.7 (CH, C-9), 133.3 (CH, C-7), 135.2 (C-6), 139.8 (CH, C-10), 144.9 (CH, C-3), 147.7 (C-5a), 148.7 (C-4a), 162.0 (C-1), 164.2 (CONH). Carbon $CHCH_3$ was not observed.

The hydrochloride had mp 241–245 °C after forming needles >200 °C (yellow powder from acetonitrile). Anal. Calcd for $C_{20}H_{24}N_4O_2 \cdot HCl$: C, 61.8; H, 6.5; N, 14.4. Found: C, 61.5; H, 6.2; N, 14.6%.

4.40. (*R*)-*N*-[2-(1-Dimethylamino)propyl]-2,6-dimethyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2cc)

From acid **5c**, thionyl chloride, (*R*)-N^1,N^1-dimethylpropane-1,2-diamine dihydrochloride and triethylamine as for **2bb**. The amide was obtained as a yellow solid (57%), mp 195–199 °C (from acetonitrile). ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.28 (d, J = 6.5 Hz, 3H, $CHCH_3$), 2.20 [s, 6H, $N(CH_3)_2$], 2.34 (dd, J = 12.2, 6.4 Hz, 1H, $CHNMe_2$), 2.54 (dd, J = 12.2, 7.4 Hz, 1H, $CHNMe_2$), 2.79 (s, 3H, $ArCH_3$), 3.62 (s, 3H, NCH_3), 4.31 (quintet, J = 6.9 Hz, 1H, $CHCH_3$), 7.54 (t, J = 7.6 Hz, 1H, H-8), 7.81 (d, J = 6.8 Hz, 1H, H-7), 8.05 (d, J = 8.3 Hz, 1H, H-9), 8.56 (s, 1H, H-3), 9.27 (s, 1H, H-10), 10.46 (br d, J = 6.9 Hz, 1H, CONH). ^{13}C NMR (DMSO-d_6, 100 °C): δ 18.1 ($ArCH_3$), 19.7 ($CHCH_3$), 36.5 (NCH_3), 43.2 ($CHCH_3$), 45.5 [$N(CH_3)_2$], 65.1 (CH_2NMe_2), 108.9 (C-4), 119.3 (C-10a), 125.8 (C-9a), 126.6 (CH, C-8), 127.7 (CH, C-9), 133.1 (CH, C-7), 135.2 (C-6), 139.6 (CH, C-10), 144.6 (CH, C-3), 147.7 (C-5a), 148.9 (C-4a), 162.0 (C-1), 162.9 (CONH).

The hydrochloride had mp 232–240 °C after changing form at 200 °C and forming needles >205 °C [yellow solid from acetonitrile (hygroscopic)]. Anal. Calcd for $C_{20}H_{24}N_4O_2 \cdot HCl$: C, 61.8; H, 6.5; N, 14.4. Found: C, 62.1; H, 6.4; N, 14.4%.

4.41. *N*-[2-(Methylamino)ethyl]-2,6-dimethyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2dd)

Acid **5c** (0.5 g) was taken to crude acid chloride with thionyl chloride. A suspension of this and 2-chloroethylamine hydrochloride (0.54 g) in dichloromethane (10 mL) was stirred and cooled on ice. Triethylamine (3 mL) was added and the mixture was stirred at 20 °C overnight (solid was present at all times). The solvent was evaporated, water was added to the residue and the yellow solid was filtered and washed with water to give the intermediate chloroethyl amide (0.54 g, 82%), mp 240–243 °C. ^{1}H NMR ($CDCl_3$): δ 2.85 (s, CH_3), 3.70 (s, CH_3), 3.80 (t, J = 5.7 Hz, 2H, CH_2), 3.96 (q, J = 5.7 Hz, 2H, CH_2), 7.51 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 8.60 (s, 1H), 9.29 (s, 1H), 11.46 (s, 1H, NH).

A mixture of this amide (0.25 g) and 2 M methylamine in tetrahydrofuran (3.5 mL) was heated in a sealed tube at 90–100 °C for 2.5 days. Some solid was present at all times. Water was added (the solid dissolved) and the solution was extracted (×3) with dichloromethane. The combined extracts were washed (×2) with water, dried, and the solvent evaporated to leave an orange glass (0.25 g). Crystallization from acetonitrile gave the amide **2dd** (0.09 g), though still slightly impure. Further purification was achieved by preparing an oxalate salt in ethanol. Recrystallization from methanol/water/ether gave a yellow solid, mp 230–232 °C (dec). ^{1}H NMR (DMSO-d_6+trace CF_3CO_2H): δ 2.59 (t, J = 4.6 Hz, 3H, $^+NH_2CH_3$), 2.76 (s, 3H, 6-CH_3), 3.18 (br s, 2H, CH_2), 3.70 (s, 2H, CH_3-2), 3.75 (q, J = 5.7 Hz, 2H, CH_2), 7.58 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 6.7 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 8.53 (br s, 2H, $^+NH_2CH_3$), 8.63 (s, 1H, H-3), 9.36 (s, 1H, H-10), 11.10 (s, 1H, CONH). Anal. Calcd for $C_{18}H_{20}N_4O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$: C, 57.3; H, 5.4; N, 13.4. Found: C, 57.3; H, 5.2; N, 13.3%.

4.42. *N*-[2-(Dimethylamino)ethyl]-2-ethyl-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2d)

4.42.1. Method (b) for carboxamide formation. A mixture of acid **5d** (0.23 g, 0.81 mmol) and 1,1′-carbonyldiimidazole (CDI) (0.66 g, 4.07 mmol) in 1,4-dioxane (15 mL) was heated under reflux for 24 h, during which time dissolution occurred. The solvent was removed at reduced pressure and to the residue was added, *N*,*N*-dimethylethylenediamine (1 mL, 9.1 mmol) in dichloromethane (25 mL). The solution was then stirred for 16 h at room temperature. More dichloromethane was added and the solution was washed with 10% sodium hydroxide (×1) and water (×3). The organic fraction was dried over magnesium sulfate and the solvent was removed at reduced pressure to give the amide **2d** as a bright yellow solid (0.26 g, 91%), mp 157–158 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.23 [s, 6H, $N(CH_3)_2$], 2.54 (t, J = 6.5 Hz, 2H, $CH_2CH_2NMe_2$), 2.66 (s, 3H, $ArCH_3$), 3.63 (q, J = 6.2 Hz, 2H, $CH_2CH_2NMe_2$), 4.05 (q, J = 7.2 Hz, 2H, CH_2CH_3), 7.32 (dd, J = 8.0, 7.2 Hz, 1H, H-8), 7.55 (d, J = 6.9 Hz, 1H, H-7), 7.65 (d, J = 8.2 Hz, 1H, H-9), 8.48 (s, 1H, H-3), 8.99 (s, 1H, H-10), 10.73 (br t, J = 5.1 Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_2CH_3), 18.3 ($ArCH_3$), 37.5 ($CH_2CH_2NMe_2$), 44.6 (CH_2CH_3), 45.3 [$N(CH_3)_2$], 58.7 ($CH_2CH_2NMe_2$), 109.5 (C-4), 119.2 (C-10a), 125.5 (C-9a), 126.2 (CH, C-8), 127.1 (CH, C-9), 132.4 (CH, C-7), 135.6 (C-6), 139.4 (CH, C-10), 142.4 (CH, C-3), 147.7 (C-5a), 148.4 (C-4a), 161.9 (C-1), 164.3 (CONH). Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.2; H, 6.9; N, 15.9. Found: C, 68.5; H, 6.8; N, 16.1%.

The following compounds were prepared in a similar manner.

4.43. *N*-[2-(Dimethylamino)ethyl]-6-methyl-1-oxo-2-(2,2,2-trifluoroethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2f)

From acid **5f**, and obtained as a yellow solid (83%), mp 227–230 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.30 [s, 6H, $N(CH_3)_2$], 2.63 (t, J = 6.4 Hz, 2H, $CH_2CH_2NMe_2$), 2.85 (s, 3H, $ArCH_3$), 3.72 (q, J = 6.1 Hz, 2H, $CH_2CH_2NMe_2$), 4.73 (q, J = 8.4 Hz, 2H, CH_2CF_3), 7.51 (t, J = 7.6 Hz, 1H, H-8), 7.74 (d, J = 6.9 Hz, 1H, H-7), 7.85 (d, J = 8.2 Hz, H-1, H-9), 8.58 (s, 1H, H-3), 9.27 (s, 1H, H-10), 10.84 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.4 ($ArCH_3$), 37.8 ($CH_2CH_2NMe_2$), 45.4 [$N(CH_3)_2$], 48.3 (q, J = 35.3 Hz, CH_2CF_3), 58.8 ($CH_2CH_2NMe_2$), 111.3 (C-4), 119.1 (C-10a), 123.4 (q, J = 280 Hz, CH_2CF_3), 126.3 (C-9a), 127.2 (CH, C-8), 127.4 (CH, C-9), 133.4 (CH, C-7), 136.3 (C-6), 140.6 (CH, C-10), 142.1 (CH, C-3), 148.6 (C-5a), 148.7 (C-4a), 162.3 (C-1), 164.0 (CONH). Anal. Calcd for $C_{20}H_{21}F_3N_4O_2$: C, 59.1; H, 5.2; N, 13.8. Found: C, 59.4; H, 5.4; N, 13.9%.

4.44. *N*-[2-(Dimethylamino)ethyl]-2-(ethoxycarbonylmethyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2h)

From acid **5h**, with a reflux time of 48 h and a recharge with an equal amount of CDI after 24 h, and obtained as a yellow solid (79%), mp 214–215 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.29 [s, 6H, $N(CH_3)_2$], 2.62 (t, J = 6.4 Hz, 2H, $CH_2CH_2NMe_2$), 2.87 (s, 3H, $ArCH_3$), 3.72 (q, J = 5.9 Hz, $CH_2CH_2NMe_2$), 4.25 (q, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.78 (s, 2H, CH_2CO_2Et), 7.51 (t, J = 7.6 Hz, 1H, H-8), 7.74 (d, J = 6.9 Hz, 1H, H-7), 7.87 (d, J = 8.2 Hz, 1H, H-9), 8.53 (s, 1H, H-3), 9.28 (s, 1H, H-10), 10.96 (br t, J = 4.8 Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 13.7 ($CO_2CH_2CH_3$), 18.1 ($ArCH_3$), 37.3 ($CH_2CH_2NMe_2$), 45.1 [$N(CH_3)_2$], 50.1 (CH_2CO_2Et), 58.4 ($CH_2CH_2NMe_2$), 61.6 ($CO_2CH_2CH_3$), 109.8 (C-4), 118.7 (C-10a), 125.5 (C-9a), 126.4 (CH, C-8), 126.9 (CH, C-9), 132.6 (CH, C-7), 135.6 (C-6), 139.6 (CH, C-10), 142.7 (CH, C-3), 147.8 (C-5a), 148.4 (C-4a), 162.0 (C-1), 163.9 (CONH), 166.9 (CO_2Et). Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.4; H, 6.4; N, 13.7. Found: C, 64.5; H, 6.4; N, 13.9%.

4.45. *N*-[2-(Dimethylamino)ethyl]-2-(3,4-dimethoxybenzyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2j)

From acid **5j**, with a reflux time of 48 h and a recharge with an equal amount of CDI after 24 h, and obtained as a yellow solid (85%), mp 213–214 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.22 [s, 6H, $N(CH_3)_2$], 2.52 (t, J = 6.4 Hz, 2H, $CH_2CH_2NMe_2$), 2.63 (s, 3H, $ArCH_3$), 3.62 (q, J = 6.1 Hz, 2H, $CH_2CH_2NMe_2$), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.09 (s, 2H, CH_2 Ph), 6.74 (d, J = 8.5 Hz, 1H, H-5′), 6.90–6.92 (m, 2H, H-2′, H-6′), 7.27 (t, J = 7.6 Hz, 1H, H-8), 7.49 (d, J = 6.8 Hz, 1H, H-7), 7.61 (d, J = 8.1 Hz, 1H, H-9), 8.55 (s, 1H, H-3), 8.99 (s, 1H, H-10), 10.70 (br t, J = 5.3 Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.2 ($ArCH_3$), 37.4 ($CH_2CH_2NMe_2$), 45.2 [$N(CH_3)_2$], 51.9 (CH_2Ph), 55.6 (OCH_3), 55.7 (OCH_3), 58.6 ($CH_2CH_2NMe_2$), 109.6 (C-4), 111.1 (CH, C-5′), 111.5 (CH, C-6′), 119.1 (C-10a), 120.9 (CH, C-2′), 125.4 (C-9a), 126.2 (CH, C-8), 126.9 (CH, C-9), 128.2 (C-1′), 132.4 (CH, C-7), 135.5 (C-6), 139.5 (CH, C-10), 142.3 (CH, C-3), 147.6 (C-5a), 148.2 (C-4a), 148.9 (C-4′), 149.1 (C-3′), 162.1 (C-1), 164.1 (CONH). Anal. Calcd for $C_{27}H_{30}N_4O_4$: C, 68.3; H, 6.4; N, 11.8. Found: C, 68.5; H, 6.s6; N, 11.8%.

4.46. *N*-[2-(Dimethylamino)ethyl]-2-[2-(3,4-dimethoxyphenyl)ethyl]-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]-naphthyridine-4-carboxamide (2k)

From acid **5k**, with a reflux time of 48 h and a recharge with an equal amount of CDI after 24 h, and obtained as a yellow solid (81%), mp 113–114 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.26 [s, 6H, $N(CH_3)_2$], 2.58 (t, J = 6.5 Hz, 2H, $CH_2CH_2NMe_2$), 2.77 (s, 3H, $ArCH_3$), 2.98–3.04 (m, 2H, CH_2CH_2Ph), 3.67 (q, J = 6.1 Hz, 2H, $CH_2CH_2NMe_2$), 3.79 (s, 6H, $2\times OCH_3$), 4.20–4.25 (m, 2H, CH_2CH_2Ph), 6.72–6.75 (m, 3H, H-2′, H-5′, H-6′), 7.41 (t, J = 7.6 Hz, 1H, H-8), 7.64 (d, J = 6.8 Hz, 1H, H-7), 7.77 (d, J = 8.2 Hz, 1H, H-9), 8.51 (s, 1H, H-3), 9.15 (s, 1H, H-10), 10.83 (br t, J = 5.3 Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.4 ($ArCH_3$), 34.9 (CH_2CH_2Ph), 37.5 ($CH_2CH_2NMe_2$), 45.4 [$N(CH_3)_2$], 51.2 (CH_2CH_2Ph), 55.8 ($2\times OCH_3$), 58.7 ($CH_2CH_2NMe_2$), 109.5 (C-4), 111.4 (CH, Ar), 111.9 (CH, Ar), 119.3 (C-10a), 120.7 (CH, Ar), 125.7 (C-9a), 126.5 (CH, C-8), 127.2 (CH, C-9), 129.8 (C, Ar), 132.7 (CH, C-7), 135.8 (C-6), 139.7 (CH, C-10), 142.7 (CH, C-3), 147.8 (C, Ar), 148.0 (C-5a), 148.6 (C-4a), 149.0 (C, Ar), 162.2 (C-1), 164.3 (CONH). Anal. Calcd for $C_{28}H_{32}N_4O_4$: C, 68.8; H, 6.6; N, 11.5. Found: C, 68.7; H, 6.9; N, 11.5%.

4.47. *N*-[2-(Dimethylamino)ethyl]-6-methyl-2-(pyridin-2-yl)methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2l)

From acid **5l**, with a reflux time of 48 h and a recharge with an equal amount of CDI after 24 h, and obtained as a bright yellow solid (75%), mp 183–184 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.25 [s, 6H, $N(CH_3)_2$], 2.57 (t, J = 6.4 Hz, 2H, $CH_2CH_2NMe_2$), 2.67 (s, 3H, $ArCH_3$), 3.66 (q, J = 6.1 Hz, CH_2, $CH_2CH_2NMe_2$), 5.30 (s, 2H, CH_2Pyr), 7.10 (dd, J = 7.0, 5.2 Hz, 1H, H-5′), 7.26–7.33 (m, 2H, H-3′, H-8), 7.52–7.59 (m, 2H, H-4′, H-7), 7.64 (d, J = 8.2 Hz, 1H, H-9), 8.46 (d, J = 4.4 Hz, 1H, H-6′), 8.66 (s, 1H, H-3), 9.02 (s, 1H, H-10), 10.79 (br t, J = 5.1 Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.3 ($ArCH_3$), 37.3 ($CH_2CH_2NMe_2$), 45.2 [$N(CH_3)_2$], 53.7 (CH_2Pyr), 58.6 ($CH_2CH_2NMe_2$), 109.6 (C-4), 119.1 (C-10a), 122.1 (CH, C-3′), 122.7 (CH, C-5′), 125.5 (C-9a), 126.4 (CH, C-8), 127.0 (CH, C-9), 132.6 (CH, C-7), 135.6 (C-6), 136.7 (CH, C-4′), 139.6 (CH, C-10), 143.4 (CH, C-3), 147.7 (C-5a), 148.5 (C-4a), 149.6 (CH, C-6′), 155.0 (C-2′), 162.2 (C-1), 164.3 (CONH). Anal. Calcd for $C_{24}H_{25}N_5O_2$: C, 69.4; H, 6.1; N, 16.9. Found: C, 69.1; H, 6.2; N, 16.8%.

4.48. *N*-[2-(Dimethylamino)ethyl]-6-methyl-1-oxo-2-[3-(2-oxopyrrolidin-1-yl)propyl]-1,2-dihydrobenzo[*b*][1,6]-naphthyridine-4-carboxamide (2m)

From acid **5m**, with a reflux time of 24 h, and obtained as a yellow solid (89%), mp 170–171 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 1.96–2.06 (m, 4H), 2.25 [s, 6H, $N(CH_3)_2$], 2.35 (t, J = 8.1 Hz, 2H), 2.58 (t, J = 6.5 Hz, 2H), 2.75 (s, 3H, $ArCH_3$), 3.35–3.42 (m, 4H), 3.66 (q, J = 5.9 Hz, 2H), 4.00–4.05 (m, 2H), 7.41 (dd, J = 7.3, 7.9 Hz, 1H, H-8), 7.64 (d, J = 6.9 Hz, 1H, H-7), 7.76 (d, J = 8.1 Hz, 1H, H-9), 8.52 (s, 1H, H-3), 9.13 (s, 1H, H-10), 10.85 (br t, J = 3.5 Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 17.6 (CH_2), 18.0 ($ArCH_3$), 26.6 (CH_2), 30.5 (CH_2), 37.2 (CH_2), 39.5 (CH_2), 45.0 [$N(CH_3)_2$], 46.6 (CH_2), 47.1 (CH_2), 58.3 (CH_2), 109.3 (C-4), 118.8 (C-10a), 125.3 (C-9a), 126.2 (CH, C-8), 126.8 (CH, C-9), 132.4 (CH, C-7), 135.4 (C-6), 139.2 (CH, C-10), 142.2 (CH, C-3), 147.6 (C-5a), 148.1 (C-4a), 161.8 (C-1), 163.9 (CONH), 174.8 (C-2′). Anal. Calcd for $C_{25}H_{31}N_5O_3$: C, 66.8; H, 7.0; N, 15.6. Found: C, 66.3; H, 7.1; N, 15.7%.

4.49. *N*-[2-(Dimethylamino)ethyl]-2-(4-boronophenyl)-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2v)

From acid **5ee**, carried out under nitrogen, with a reflux time of 48 h and a recharge with an equal amount of CDI after 24 h. When the amination reaction was complete, the volatiles were removed at reduced pressure with heat (~0.3 mmHg, 100 °C, 20 min) and residual *N*,*N*-dimethylethylenediamine was removed by azeotropic distillation with toluene (×3). The residue was then boiled in toluene and, while hot, decanted from a brown oil. The toluene was removed at reduced pressure, and the residue was crystallized from acetonitrile to give the intermediate *N*-[2-(dimethylamino)ethyl]-6-methyl-1-oxo-2-[4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-phenyl]1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide as a yellow solid (74%), mp 139–141 °C. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 12H, $4\times CH_3$), 2.31 [s, 6H, $N(CH_3)_2$], 2.64 (t, J = 6.5 Hz, 2H, $CH_2CH_2NMe_2$), 2.81 (s, 3H, $ArCH_3$), 3.72 (q, J = 6.1 Hz, 2H, $CH_2CH_2NMe_2$), 7.42–7.48 (m, 3H, H-8, H-2′, H-6), 7.69 (d, J = 6.9 Hz, 1H, H-7), 7.80 (d, J = 8.1 Hz, 1H, H-9), 7.95 (d, J = 8.3 Hz, 2H, H-3′, H-5′), 8.68 (s, 1H,

H-3), 9.23 (s, 1H, H-10), 10.98 (br t, $J = 5.4$ Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.2 ($ArCH_3$), 24.5 ($4 \times CH_3$), 37.2 ($CH_2CH_2NMe_2$), 45.0 [$N(CH_3)_2$], 58.3 ($CH_2CH_2NMe_2$), 83.8 ($2 \times C$), 109.7 (C-4), 119.4 (C-10a), 125.5 ($2 \times CH$, C-2′, C-6′), 125.7 (C-9a), 126.4 (CH, C-8), 127.0 (CH, C-9), 132.7 (CH, C-7), 135.6 ($2 \times CH$, C-3′, C-5′), 140.1 (CH, C-10), 142.0 (C-1′), 142.8 (CH, C-3), 147.8 (C-5a), 148.4 (C-4a), 161.7 (C-1), 164.1 (CONH). C-6 and C-4′ were not observed.

Water (5 mL) was added to a solution of this compound (0.12 g, 0.23 mmol) in methanol (5 mL), and the whole was heated at reflux for 30 min. The volume was then reduced to ca. 2 mL at reduced pressure, water was added, and the solid was filtered, washed with water, and recrystallized from ethanol to give the boronic acid **2v** as a yellow solid (0.05 g, 49%), mp 242–244 °C. ^{1}H NMR (DMSO-d_6): δ 2.23 [s, 6H, $N(CH_3)_2$], 2.56 (t, $J = 5.8$ Hz, 2H, $CH_2CH_2NMe_2$), 2.82 (s, 3H, $ArCH_3$), 3.59 (q, $J = 5.7$ Hz, 2H, $CH_2CH_2NMe_2$), 7.52 (d, $J = 8.0$ Hz, 2H, H-3′, H-5′), 7.59 (t, $J = 7.5$ Hz, 1H, H-8), 7.86 (d, $J = 6.7$ Hz, 1H, H-7), 7.95 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 8.14 (d, $J = 8.0$ Hz, 1H, H-9), 8.23 [s, 2H, $B(OH)_2$], 8.43 (s, 1H, H-3), 9.39 (s, 1H, H-10), 10.76 (br t, $J = 4.8$ Hz, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ 17.8 ($ArCH_3$), 37.1 ($CH_2CH_2NMe_2$), 45.1 [$N(CH_3)_2$], 58.5 ($CH_2CH_2NMe_2$), 109.2 (C-4), 119.5 (C-10a), 125.7 (C-9a), 125.8 (C-2′, C-6′), 126.8 (CH, C-8), 127.6 (CH, C-9), 133.2 (CH, C-7), 135.1 (C-3′, C-5′), 135.3 (C-6), 140.1 (CH, C-10), 141.8 (C-1′), 143.2 (CH, C-3), 147.4 (C-5a), 148.4 (C-4a), 161.3 (C-1), 163.2 (CONH). C-4′ was not observed. Anal. Calcd for $C_{24}H_{25}BN_4O_4 \cdot 0.25H_2O$: C, 64.2; H, 5.7; N, 12.3. Found: C, 64.4; H, 5.9; N, 12.5%.

4.50. *N*-[2-(Dimethylamino)ethyl]-7-methoxy-2-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2w)

From acid **5w**, with a reflux time of 96 h and a recharge with an equal amount of CDI after 48 h, and obtained as a yellow solid (80%), mp 213–215 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.50 [s, 6H, $N(CH_3)_2$], 2.78 (t, $J = 6.0$ Hz, 2H, $CH_2CH_2NMe_2$), 3.67 (s, 3H, NCH_3), 3.77 (q, $J = 5.8$ Hz, 2H, $CH_2CH_2NMe_2$), 4.02 (s, 3H, $ArOCH_3$), 7.22 (dd, $J = 9.1$, 2.2 Hz, 1H, H-8), 7.43 (d, $J = 2.2$ Hz, 1H, H-6), 7.85 (d, $J = 9.1$ Hz, 1H, H-9), 8.53 (s, 1H, H-3), 9.14 (s, 1H, H-10), 11.36 (br s, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 36.8 ($CH_2CH_2NMe_2$, NCH_3), 45.0 [$N(CH_3)_2$], 55.6 ($ArOCH_3$), 57.7 ($CH_2CH_2NMe_2$), 105.3 (CH, C-6), 108.8 (C-4), 117.3 (C-10a), 120.9 (CH, C-8), 121.4 (C-9a), 130.0 (CH, C-9), 138.3 (CH, C-10), 143.1 (CH, C-3), 149.7 (C-4a), 150.9 (C-5*a*), 162.5 (C-1), 163.4 (C-7), 164.4 (CONH). Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.4; H, 6.3; N, 15.8. Found: C, 64.4; H, 6.5; N, 15.6%.

4.51. *N*-[2-(Dimethylamino)ethyl]-2-[((2-(dimethylamino)ethyl)amino)carbonyloxy]ethyl-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (8a)

From acid **5g**, with a reflux time of 48 h, and obtained as a yellow solid (63%), mp 75–76 °C (from toluene ×3). ^{1}H NMR ($CDCl_3$): δ 2.17 [s, 6H, $N(CH_3)_2$], 2.28 [s, 6H, $N(CH_3)_2$], 2.34 (t, $J = 6.0$ Hz, 2H, $CH_2CH_2NMe_2$), 2.60 (t, $J = 6.5$ Hz, 2H, $CH_2CH_2NMe_2$), 2.81 (s, 3H, $ArCH_3$), 3.19 (q, $J = 5.8$ Hz, 2H, $CH_2CH_2NMe_2$), 3.69 (q, $J = 6.2$ Hz, 2H, $CH_2CH_2NMe_2$), 4.30–4.32 (m, 2H, CH_2CH_2OCO), 4.39–4.43 (m, 2H, CH_2CH_2OCO), 5.82 (br s, 1H, CONH), 7.47 (t, $J = 7.6$ Hz, 1H, H-8), 7.70 (d, $J = 6.8$ Hz, 1H, H-7), 7.83 (d, $J = 8.1$ Hz, 1H, H-9), 8.58 (s, 1H, H-3), 9.23 (s, 1H, H-10), 10.99 (br s, 1H, CONH-4). ^{13}C NMR ($CDCl_3$): δ 18.2 ($ArCH_3$), 37.3 ($CH_2CH_2NMe_2$), 38.1 ($CH_2CH_2NMe_2$), 44.8 [$N(CH_3)_2$], 45.1 [$N(CH_3)_2$], 48.8 (CH_2CH_2OCO), 58.0 ($CH_2CH_2NMe_2$), 58.5 ($CH_2CH_2NMe_2$), 61.9 (CH_2CH_2OCO), 109.0 (C-4), 119.0 (C-10a), 125.6 (C-9a), 126.3 (CH, C-8), 127.0 (CH, C-9), 132.6 (CH, C-7), 135.5 (C-6), 139.7 (CH, C-10), 143.4 (CH, C-3), 147.9 (C-5a), 148.4 (C-4a), 155.6 (CONH), 162.1 (C-1), 164.4 (CONH). HRMS (EI) calcd for $C_{25}H_{34}N_6O_4$ [M^+]: 482.2643. Found: 482.2626.

4.52. *N*-[2-(Dimethylamino)ethyl]-2-[*N*-(((2-(dimethylamino)ethyl)amino)carbonyl)-1*H*-indol-3-yl]ethyl-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (8b)

From acid **5n**, with a reflux time of 48 h and a recharge with an equal amount of CDI after 24 h, and obtained as a yellow solid (62%), mp 182–185 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.27 [s, 12H, $2 \times N(CH_3)_2$], 2.52–2.61 (m, 4H, $2 \times CH_2CH_2NMe_2$), 2.77 (s, 3H, $ArCH_3$), 3.18 (t, $J = 7.7$ Hz, 2H, CH_2CH_2Indole), 3.50 (q, $J = 5.4$ Hz, 2H, $CH_2CH_2NMe_2$-1′), 3.68 (q, $J = 6.0$ Hz, 2H, $CH_2CH_2NMe_2$-4), 4.32 (t, $J = 7.7$ Hz, 2H, CH_2CH_2Indole), 6.60 (br t, $J = 4.1$ Hz, 1H, CONH-1′), 7.18 (t, $J = 7.4$ Hz, 1H, H-5′), 7.27 (t, $J = 7.8$ Hz, 1H, H-6′), 7.39–7.44 (m, 2H, H-2′, H-8), 7.64–7.66 (m, 2H, H-4′, H-7), 7.77 (d, $J = 8.2$ Hz, 1H, H-9), 8.09 (d, $J = 8.2$ Hz, 1H, H-7′), 8.55 (s, 1H, H-3), 9.17 (s, 1H, H-10), 10.87 (br t, $J = 5.2$ Hz, 1H, CONH-4). ^{13}C NMR ($CDCl_3$): δ 18.4 (ArCH3), 24.8 (CH_2CH_2Indole), 37.6 ($CH_2CH_2NMe_2$-4), 37.9 ($CH_2CH_2NMe_2$-1′), 45.0 [$N(CH_3)_2$], 45.4 [$N(CH_3)_2$], 49.7 (CH_2CH_2Indole), 57.7 ($CH_2CH_2NMe_2$-1′), 58.7 ($CH_2CH_2NMe_2$-4), 109.5 (C-4), 114.4 (CH, C-7′), 115.8 (CONH-1′), 118.8 (CH, C-4′), 119.3 (C-10a), 121.98 (CH, C-2′), 122.03 (CH, C-5′), 124.4 (CH, C-6′), 125.8 (C-9a), 126.5 (CH, C-8), 127.2 (CH, C-9), 129.5 (C, C-3a′), 132.8 (CH, C-7), 135.6 (C-7a′), 135.8 (C-6), 139.7 (CH, C-10), 142.7 (CH, C-3), 148.0 (C-5a), 148.5 (C-4a), 152.0 (C-3′), 162.2 (C-1), 164.4 (CONH-4). Anal. Calcd for $C_{33}H_{39}N_7O_3 \cdot 0.5H_2O$: C, 67.1; H, 6.8; N, 16.6. Found: C, 67.2; H, 6.7; N, 16.6%.

4.53. *N*-[2-(Dimethylamino)ethyl]-2-hydroxyethyl-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2g)

To the carbamate **8a** (0.55 g, 1.49 mmol) in ethanol (25 mL) was added 10% sodium hydroxide (20 mL), and the whole was heated under reflux for 1 h, then cooled on ice, adjusted to pH ~ 8 with concentrated hydrochloric acid, and evaporated to dryness at reduced

pressure. The residual solid was boiled in acetonitrile, the mixture was filtered while hot, and the filtrate was taken to dryness at reduced pressure to give an orange solid (0.26 g). This solid was dissolved in a little warm ethanol and added to a bed of silica. This was eluted with a little ethanol, then with ethanol/triethylamine (25:1). The ethanol/triethylamine eluate was taken to dryness at reduced pressure. The residual solid (0.17 g) was dissolved in a little chloroform, filtered through a bed of basic alumina, washed with chloroform, and then eluted with methanol. The methanol eluate was evaporated to dryness under reduced pressure to give a yellow solid (0.12 g), which was recrystallized twice from dichloromethane to give the amide **2g** as a yellow solid (0.10 g, 24%), mp 174–180 °C. ^{1}H NMR ($CDCl_3$): δ 2.27 [s, 6H, $N(CH_3)_2$], 2.43 (s, 3H, $ArCH_3$), 2.54 (t, $J = 6.4$ Hz, 2H, $CH_2CH_2NMe_2$), 3.55 (q, $J = 6.0$ Hz, 2H, $CH_2CH_2NMe_2$), 4.03–4.06 (m, 2H, CH_2CH_2OH), 4.20–4.23 (m, 2H, CH_2CH_2OH), 7.34 (t, $J = 7.5$ Hz, 1H, H-8), 7.50 (d, $J = 6.7$ Hz, 1H, H-7), 7.63 (d, $J = 8.1$ Hz, 1H, H-9), 8.56 (s, 1H, H-3), 8.96 (s, 1H, H-10), 10.67 (br t, $J = 5.0$ Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 17.9 ($ArCH_3$), 37.0 ($CH_2CH_2NMe_2$), 45.0 [$N(CH_3)_2$], 52.3 (CH_2CH_2OH), 58.1 ($CH_2CH_2NMe_2$), 60.2 (CH_2CH_2OH), 108.2 (C-4), 118.7 (C-10a), 125.1 (C-9a), 126.1 (CH, C-8), 126.8 (CH, C-9), 132.3 (CH, C-7), 135.3 (C-6), 139.0 (CH, C-10), 143.9 (CH, C-3), 147.3 (C-5a), 147.9 (C-4a), 162.4 (C-1), 164.3 (CONH). HRMS (LSI) calcd for $C_{20}H_{25}N_4O_3$ [$(M+H)^+$]: 369.1928. Found: 369.1940.

4.54. *N*-[2-(Dimethylamino)ethyl]-2-[2-(1*H*-indol-3-yl)ethyl]-6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (2n)

To a hot solution of the bisamide **8b** (0.58 g, 1.00 mmol) in ethanol (10 mL) was added 10% sodium hydroxide (10 mL), and the whole was heated at reflux for 40 min. The reaction mixture was then evaporated to dryness under reduced pressure, water was added, and the solid was filtered and washed with water to give **2n** as a gold solid (0.42 g, 90%), mp 105–107 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$): δ 2.31 [s, 6H, $N(CH_3)_2$], 2.64 (t, $J = 6.4$ Hz, 2H, $CH_2CH_2NMe_2$), 2.82 (s, 3H, $ArCH_3$), 3.21 (t, $J = 7.7$ Hz, 2H, CH_2CH_2Indole), 3.73 (q, $J = 6.1$ Hz, 2H, $CH_2CH_2NMe_2$), 4.30 (t, $J = 7.8$ Hz, 2H, CH_2CH_2Indole), 6.99 (d, $J = 2.0$ Hz, 1H, H-2′), 7.06–7.14 (m, 2H, H-5′, H-6), 7.30 (d, $J = 7.7$ Hz, 1H, H-7′), 7.46 (t, $J = 7.6$ Hz, 1H, H-8), 7.66–7.70 (m, 2H, H-4′, H-7), 7.82 (d, $J = 8.2$ Hz, 1H, H-9), 8.51 (s, 1H, H-3), 8.62 (br s, 1H, NH-1′), 9.24 (s, 1H, H-10), 10.98 (br t, $J = 5.3$ Hz, 1H, CONH). ^{13}C NMR ($CDCl_3$): δ 18.2 ($ArCH_3$), 24.8 (CH_2CH_2Indole), 37.2 ($CH_2CH_2NMe_2$), 45.0 [$N(CH_3)_2$], 50.2 (CH_2CH_2Indole), 58.4 ($CH_2CH_2NMe_2$), 109.0 (C), 110.9 (CH, C-7′), 111.1 (C), 118.2 (CH, C-4′), 119.2 (CH, C-5′), 121.7 (CH, C-6′), 122.0 (CH, C-2), 125.6 (C-9a), 126.2 (CH, C-8), 126.8 (C-3a′), 127.0 (CH, C-9), 132.5 (CH, C-7), 135.5 (C-6), 136.0 (C-7a′), 139.5 (CH, C-3), 142.7 (CH, C-10), 147.8 (C-5a), 148.4 (C-4a), 162.1 (C-1), 164.4 (CONH). C-3′ was not observed. HRMS (EI) calcd for $C_{28}H_{29}N_5O_2$ [M^+]: 467.2323. Found: 467.2314.

4.55. In vitro cytotoxicity assays

Murine P388 leukemia cells, Lewis lung carcinoma cells (LLTC), and human Jurkat leukemia cells (JL_C), together with their amsacrine and doxorubicin-resistant derivatives (JL_A and JL_D, respectively), were obtained and cultured as described.[13] Growth inhibition assays were performed by culturing cells at 4.5×10^3 (P388), and 10^3 (LLTC) per well in microculture plates (150 mL per well) for 3 (P388) or 4 days in the presence of drug. Cell growth was determined by [3H]TdR uptake (P388)[14] or the sulforhodamine assay.[15] Independent assays were performed at least in duplicate.

4.56. In vivo tumor assays

Colon 38 tumors were grown subcutaneously from 1 mm^3 fragments implanted in one flank of BDF1 mice (anesthetized with pentobarbitone 90 mg/kg). When tumors reached a diameter of approximately 4–6 mm (7–8 days), mice were divided into control and drug treatment groups (five mice/group), with similar average tumor volumes in each group. Drugs were administered as solutions of the hydrochloride salts in distilled water, injected intraperitoneally in a volume of 0.01 mL/g body weight, using either single dose or intermittent (q4d × 3) schedules. The mice were monitored closely and tumor diameters were measured with callipers three times a week. Tumor volumes were calculated as $0.52 \times a^2 \times b$, where a and b are the minor and major tumor axes and data plotted on a semi-logarithmic graph as mean tumor volumes (±SEM) versus time after treatment. The growth delay was calculated as the time taken for tumors to reach a mean volume 4-fold higher than their pre-treatment volume.

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