A New Quadruply Bound Heterodimer DDAD·AADA and Investigations into the Association Process[‡]

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DDAD·AADA heterodimers based on the structures **8** and **9** have been synthesised and characterised. Solubility problems have been overcome through the introduction of a 2,6-dimethylphenyl substituent (**8c**), and association constants K_{ass} have been determined by ^{1}H NMR titrations. The K_{ass} values obtained could be confirmed by osmometry, as could the association constants for other heterodimers. The K_{ass} value increases when the acidity of participating N–H hydrogen atoms is enhanced.

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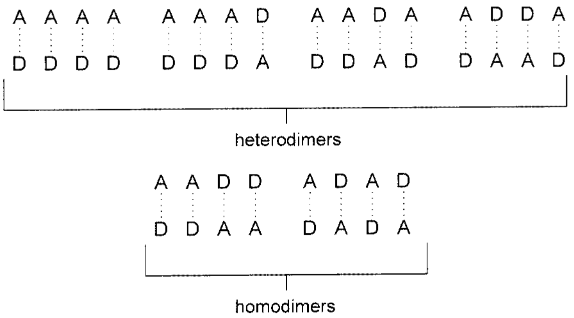
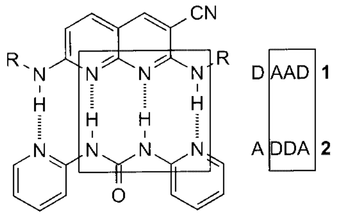
Introduction

Multiple hydrogen bonds are responsible for many recognition processes in nature, especially in nucleic acids.[1] While each base pair uses only two or three hydrogen bonds,[2] dimers with more than three hydrogen bonds have been used in supramolecular chemistry.[3–7] If four hydrogen bond acceptors A or hydrogen bond donors D are placed side by side, ten different arrays are possible.



These ten patterns may form dimers: four heterodimers and two homodimers. The homodimers (AADD)$_2$ and (ADAD)$_2$ have been used for supramolecular polymers.[8–10] While these dimers may exist once the molecule is synthesised, a heterodimer will only be formed when the respective partners are mixed. The first heterodimer with four hydrogen bonds, DAAD·ADDA (**1·2**), was reported in 1998.[11,12] A related pair is the heterodimer AADA·DDAD. In each half of this heterodimer, a subsequence – AAD and DAA, respectively – is identical to those in DAAD·ADDA (**1·2**),[11] as indicated in Scheme 1. The synthesis of this new pair and the determination of association constants is the goal of this work.



Scheme 1

Results and Discussion

Syntheses

The AADA Unit

AADA needs only one more hydrogen acceptor atom than the AAD subsequence (Scheme 1). A straightforward approach to such a pattern is the synthesis of an AAD unit such as **6** through a Friedländer condensation[13,14] and subsequent bridging of the two NH groups with a CO unit (Scheme 2).

The requisite aminopyridinecarbaldehyde **5** was synthesised by a literature procedure,[15] as were some of the cyanoacetamides **4**.[16,17] These acetamides had substituents at the amido nitrogen atom for two reasons: (i) a substitu-

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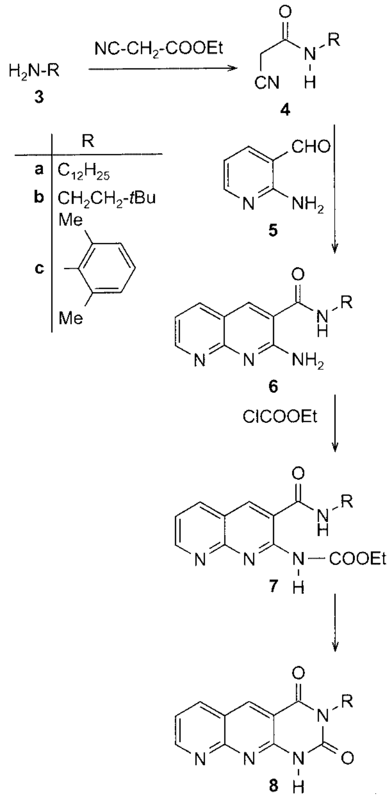


Scheme 2

ent on the imido nitrogen atom of the target **8** blocks the potentially competing ADA recognition site arising between the two C=O oxygen atoms, and (ii) many heterocycles including naphthyridines are known to be poorly soluble in common solvents,[18] and long and/or branched nonpolar groups usually confer some solubility on heterocyclic systems. Related tetraazaanthracenes have already been described in the literature.[19,20] Starting from barbituric acid or its doubly *N*-methylated derivative, a Friedländer condensation with **5** gives the desired heterocycle. In the products of this approach, however, either both nitrogen atoms are alkylated or both are non-alkylated, blocking the desired AADA domain or leaving the competing ADA pattern free, respectively.

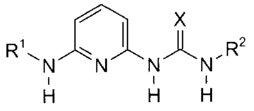
A first synthesis with the cyanacetamide **4a**,[16] accessible from commercially available amine **3a** and ethyl cyanoacetate, and the aminopyridinecarbaldehyde **5** afforded the naphthyridine **6a**. Use of trichloromethyl chloroformate (diphosgene) for the subsequent bridging with a CO unit gave only inseparable mixtures, as did heating with different derivatives of formic acid. The best procedure turned out to be the addition of ethyl chloroformate at low temperature, to give the urethane **7a**. After separation from by-products, application of heat resulted in condensation and the formation of **8a**. Heating of **7a** in pyridine at reflux for 3 d, followed by chromatography, yielded 64% of **8a**. When the neat solid **7a** was heated to 170 °C in vacuo (to remove the ethanol), 100% conversion could be achieved even within minutes. The AADA target **8a** is soluble to some extent in chloroform (up to about 5 mM). Higher concentrations were accessible by warming, but recrystallisation could be observed after a few minutes. When, however, approximately 1 equiv. of the complementary DDAD urea **9a** was added, warming achieved a homogeneous solution that was stable for weeks.

In an attempt to improve the solubility of the AADA target, compound **8b**, with a branched alkyl residue, was proposed. The required amine **3b** was synthesised from *tert*-butylacetyl chloride by known amidation[21] and reduction procedures.[22] Formation of the new cyanoacetamide **4b**, Friedländer condensation and formation of the urethane **7b** were carried out analogously to the procedures described above. Again, the condensation of **7b** to **8b** was effected by heating in pyridine or in the solid state. Unfortunately, the latter procedure resulted in lower purity and, due to the necessary recrystallisation, in a lower yield (60%) of **8b** than in the case of **8a**. The smaller yield may be caused by the higher melting point of the starting material **7b** (not below the conversion temperature of 170 °C). In contrast to expectations, **8b** had solubility no better than that of **8a**.

An alternative plan to increase the solubility of the AADA target involved the attachment of a 2,6-dimethylated aryl substituent directly onto the N-3 atom of the tetraazaanthracene part of **8**. This residue would be forced, due to the steric hindrance of the methyl groups, to maintain a twisted orientation with respect to the plane of the heterocycle, thus potentially disrupting dense packing of the molecules and, in consequence, favouring solution energy over crystal energies, which might be expected to result in a better solubility. Treatment of the dimethylaniline **3c** with ethyl cyanoacetate gave **4c**, then[17] known only as a by-product, in 21% yield. Friedländer condensation and treatment with ethyl chloroformate in the usual manner provided urethane **7c**. In this case, condensation to **8c** was achieved satisfactorily by heating neat solid **7c**, yielding 73% of product **8c** after recrystallisation of the solidified reaction cake. Compound **8c** was indeed much more soluble than its analogues **8a** and **8b** (about 200 mM solution in chloroform).

Counterpart DDAD

As the complementary counterpart of the AADA systems **8**, a DDAD unit was required. DDA subsequences are present in pyridyl ureas (see Scheme 1). Thus, treatment of 2,6-diaminopyridine with 1 equiv. of alkyl isocyanates gave compounds **9a** and **9b**, leaving the other amino group free as the solitary donor in the DDAD pattern. In one-step syntheses with commercially available starting materials, the ureas **9** could be isolated in only approximately 30% yield but in sufficient quantities.[23] To study the effects of substituents' size and donor acidity, a derivative of **9a** further acylated on the solitary donor site (**9c**) was synthesised in 73% yield by treatment of **9a** with acetic anhydride.[23] For the same reasons, a thio analogue of **9a** was prepared from butyl isothiocyanate and 2,6-diaminopyridine to give thiourea **9d** in 22% yield.



9

	R1	R2	X
a	H	Bu	O
b	H	cHex	O
c	Ac	Bu	O
d	H	Bu	S

Complex Formation Studies

^{1}H NMR Titrations

The association of AADA units with their DDAD complements was mainly investigated by ^{1}H NMR titration. Association constants K_{ass} were calculated from the shifts of selected host NMR signals on addition of increasing amounts of a guest, by the fitting of a function containing K_{ass} as a variable parameter to the experimental data.[24] Because of the limited solubilities of the tetraazaanthracenes **8a** and **8b**, compounds **8** were usually chosen as hosts and the ureas **9** as the guests, added in up to about a twentyfold excess. The data are collected in Table 1.

Table 1. Association constants K_{ass} [M^{-1}] of tetraazaanthracenes **8a−c** and ureas **9a−d** as determined by ^{1}H NMR titration of hosts **8** with guests **9** in $CDCl_3$ at 25°C

	9a	**9b**[a]	**9c**	**9d**[a]
8a	115		[b]	
8b	100	85	[b]	59
8c	120		590[c]	

[a] Because of the similarity of the results for the titrations of **8a−c** with **9a**, these titrations were only performed with **8b**. [b] No determination was possible, due to the limited solubility of both components. [c] Because of the poor solubility of **9c**, this titration was performed inversely: the tetraazaanthracene **8c** was added to a given solution of the urea **9c**.

All AADA systems **8** exhibited similar association constants K_{ass} of about 110 M^{-1} with the butyl-substituted DDAD unit **9a**. The sterically more demanding cyclohexyl substituent in **9b** lowered K_{ass} slightly to 85 M^{-1}. Comparison of these results with those known for other quadruple hydrogen bonding systems such as DAAD·ADDA (**1·2**)[11] (K_{ass} = 2000 M^{-1}) or self complementary AADD[25,26] (K_{ass} about 10^6 M^{-1}) shows that the association between **8** and **9** is rather weak.

This could most probably be due to an intramolecular hydrogen bond (see Figure 1); such a hydrogen bond has been found in analogous 2-azaheterocycle-substituted ureas.[27−30] The new conformation produced by the intramolecular hydrogen bond conceals the DDAD pattern. The energetic cost of breaking this bond and exposing the recognition site is met at the expense of complex stability. Such an intramolecular bond was already suspected to lie behind the relatively low association constant K_{ass} of the DAAD·ADDA couple **1·2**; the ^{1}H NMR spectrum of the ADDA urea **2** in fact reveals its high mobility. In forming this bond the molecule becomes unsymmetrical, and the signals of the pyridyl H atoms should split, and this effect should be greatest on the 3-H signal, due to its varying distance from the carbonyl group. There are two identical intramolecular bonds for such a symmetrical dipyridylurea, and obviously there is a fast interconversion between them, because the 3-H signals are not split, but extremely broadened (distinguishable from the baseline only by integration).

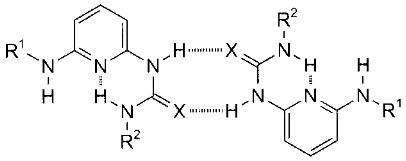


Figure 1. 2-Pyridylureas may form intramolecular hydrogen bonds; such an intramolecular hydrogen bond was found in the crystal structure for *N,N'*-bis(6-methyl-2-pyridyl)urea;[26] the new conformation allows the ureas to form $(AD)_2$ dimers

In contrast, the ^{1}H NMR spectra of the asymmetric ureas **9a**, **9b**, and **9d** each show one set of sharp signals for the pyridyl moieties. The presence of the intramolecular hydrogen bond was shown by a dilution experiment: the NMR signal of the NH proton next to the alkyl group (the one involved in the internal hydrogen bond) virtually does not change its chemical shift at $\delta \approx 9$ ppm when the sample is diluted by a factor of twenty, because this bond is formed in a *uni*molecular (concentration-independent) process. The other NH proton is to some extent involved in self-complementary AD recognition (Figure 1). As this is a *bi*molecular process, the association decreases upon dilution, and the NMR signal shifts upfield from $\delta = 8.1$ to 6.5 ppm.

Ureas **9** are thus fixed to a certain extent[31] in the cyclic conformation, which has to be broken for recognition of the DDAD pattern. In fact, during the ^{1}H NMR titration of AADA units **8** with DDAD units **9**, the 3-H signals of all ureas **9** were broadened and had positions downfield relative to the spectrum of pure **9** as long as **8** was still in excess. As the amount of **9** was increased, the 3-H signal shifted further and further upfield and sharpened, finally to resemble the spectrum of neat **9**. Obviously, the "stretched" conformation of **9**, almost absent in the pure solution, is stabilized by hydrogen bonding to **8** because it provides the complementary AADA pattern.[32]

For further study of the effects of substituents' size and donor acidity, thiourea **9d**, analogous to **9a**, was titrated with the complementary **8b**. The NH protons of a thiourea are more acidic[33,34] (thought to be better hydrogen bond donors), so heteromolecular association might be stronger.

On the other hand, though, the intramolecular hydrogen bond would be stronger as well, possibly disfavouring the stretched form. The association constant turned out to be 59 M^{-1}, and the NH signal from the intramolecular hydrogen bond in a neat sample of **9d** had (and kept upon dilution) a position even further downfield than that in **9a**. Obviously, the cyclic form is more stable for the thio compound than for its oxygen analogue. As well as the increased acidity of the NH hydrogen atom, the greater steric hindrance of the bigger sulfur atom and the pyridine moiety in the stretched conformation may also be responsible.

The opposite effect was observed with an analogue of **9a** acetylated on the solitary amino group (**9c**). The bigger acetyl residue next to the recognition-pattern motif might sterically hamper association, but acetylation, on the other hand, acidifies the NH proton and thus could stabilize the heterodimer. Furthermore, the amido group withdraws electron density from the pyridine ring and should thus weaken the intramolecular hydrogen bond. In fact, the association constant was determined to be 590 M^{-1}, so electronic effects outweighed steric ones. In this titration, the less soluble urea **9c** was treated with increasing amounts of the highly soluble tetraazaanthracene **8c**, and the unfolding of the urea during the titration again became obvious. The NMR signals of the pyridine 3-H and 5-H protons in **9c** started out at δ = 6.45 and 7.65 ppm, respectively. With increasing amounts of **8c**, the proportion of stretched **9c** grew. In this conformation, 3-H and 5-H have fairly similar environments, each with equal distances to a carbonyl group, and indeed their ^{1}H NMR signals finally reached δ = 7.75 and 7.73 ppm, respectively.

Vapour Pressure Osmometry

Vapour Pressure Osmometry (VPO), usually applied to pure substances, was chosen as an alternative means of investigating association. Osmotic pressure is a colligative property and reveals the weighted *average* molecular mass M_{obs} of *all* species present in the sample solution. If a 1:1 mixture of two substances is measured and a 1:1 association model presumed, the highest possible concentration for each species equals c_0, while their actual concentrations depend on the degree of association (α). M_{obs} is calculated from the total mass concentration ($c_0 \cdot M_{\text{ass}}$), divided by the actual molar concentration of each species. Equation (1) is thus obtained, and can be transformed into Equation (2).

$$\mathrm{M}_{\text{obs}} = \frac{c_0 \mathrm{M}_{\text{ass}}}{2c_0(1-\alpha) + c_0\alpha} \tag{1}$$

$$\alpha = \frac{2\mathrm{M}_{\text{obs}} - \mathrm{M}_{\text{ass}}}{\mathrm{M}_{\text{obs}}} \tag{2}$$

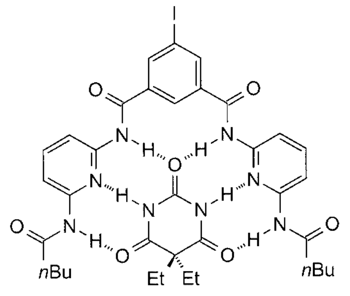
On the other hand, the K_{ass} values derived from the ^{1}H NMR titrations are related to the degree of *dissociation* (δ) by Equation (3), with c_0 being the initial concentration of the presumed complex on hypothetical total association.[35]

$$\frac{1}{K_{\text{ass}}} = \frac{\delta^2 \cdot c_0}{1-\delta} \tag{3}$$

From the concentrations used in the osmometric experiments for Equation (3) and by application of Equation (4), the degrees of association α_{NMR} can be compared to those derived from the osmometric experiments (α_{osmo}) with Equation (2).

$$\alpha = 1 - \delta \tag{4}$$

Besides the new heterodimer **8a·9a**, the known couple DAAD·ADDA (**1·2**) and another, bent, pair **10·11**[36] were investigated by osmometry (see Table 2). ^{1}H NMR titrations were usually performed at 25 °C, but the vapour pressure osmometer available had a fixed operating temperature of 36.5 °C, which of course decreases association. The couples **8a·9a** and **1·2** were therefore also titrated in the NMR at 36.5 °C to provide an idea of the magnitude of this decrease. The third couple had rather high α values anyway and was not titrated again. With allowance for a relative error of about ±10% for both methods, the values obtained by NMR titrations and by VPO correlate quite well.



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Interpretation

Table 2 provides a comparison between the new AADA·DDAD heterodimer (**8a·9a**) and the DAAD·ADDA pair (**1·2**). Surprisingly, there is a large difference in K_{ass}, of a factor of 20, although the association is through four hydrogen bonds in each pair. Even when secondary hydrogen bond interactions[37,38] between neighbouring hydrogen bonds are considered, the K_{ass} values should be similar because the numbers of positive and negative secondary interactions are alike in both pairs (one and two, respectively). One of the partners is a pyridyl urea in each pair. An intramolecular hydrogen bond therefore has to be cleaved in both cases before the quadruple hydrogen bond can be formed. Again though, this cannot cause the twentyfold difference in the association constants K_{ass} between **1·2** and any of the three heterodimers **8a−c·9a** (see Table 1).

When the association between **8c** and **9c** is compared to that between **8c** and **9a**, however (see Table 1), an increase of K_{ass} by a factor of five is observed. The only difference between **9a** and **9c** is the fact that the lateral NH_2 group in

Table 2. Degrees of association α for different heterodimers (at 1:1 stoichiometry), determined at 36.5 °C by osmometry by application of Equation (2) (α_{osmo}) and by ^{1}H NMR titration by application of Equations (3) and (4) (α_{NMR}) at the temperatures given; c_0 in Equation (3) was taken from the osmometric experiments ($2 \cdot 10^{-2}$ mol·L^{-1})

Couple	K_{ass} [M^{-1}] (25 °C)	(36.5 °C)	α_{NMR} (25 °C)	(36.5 °C)	α_{osmo} (36.5 °C)	M_{obs} [g·mol^{-1}]
AADA·DDAD (**8a·9a**)	115	76	0.53	0.45	0.49	392
DAAD·ADDA (**1·2**)	2000	580	0.85	0.74	0.73	448
10·11[35]	60000	[a]	0.97	[a]	0.90	753

[a] These values were not determined at 36.5 °C because of the large analytical effort required and the α values being rather high anyway.

9a is acylated in **9c**. The acidity of the amide NH group is thus increased relative to that of an amine, suggesting that this enhanced polarisation is the cause of the larger binding constants. In the DAAD·ADDA pair (**1·2**), each NH group is adjacent to a carbonyl group, either in an amide or in a urea substructure. In the AADA·DDAD heterodimers **8·9a−b**, however, only three NH groups are next to a carbonyl group, one NH group being part of a less acidic NH$_2$ group. Acidification of this NH group by acylation (**9c** instead of **9a** or **9b**) increases the binding constant by a factor of five. In this case, the K_{ass} values for the DAAD·ADDA and the AADA·DDAD pairs deviate only by a factor of three.

Tables 1 and 2 again show that prediction of an association constant K_{ass} for binding by several hydrogen bonds cannot be based on the number of hydrogen bonds alone,[5] and that the acidity and basicity of hydrogen bond donors and acceptors may have a strong influence on complex stability.[39,40]

Experimental Section

General Remarks: Commercially available starting materials were used as received. Melting points were measured with a Büchi (< 250 °C) or with an Electrothermal Melting Point Apparatus (< 380 °C) and are not corrected. ^{1}H NMR spectra were obtained with Bruker AC 200, AM 300, or DRX 500 machines, IR spectra were run with a Perkin−Elmer Paragon 1000, mass spectra with a Finnigan MAT 8230 or MAT 8200. Elemental analyses were obtained with a Perkin−Elmer Elemental Analyzer 240 or an Elementaranalysen GmbH VarioEL machine. GC analysis was performed with a Varian 3400, equipped with an FID. ^{1}H NMR titrations were performed in CDCl$_3$ with a Bruker DRX 500, starting with approximately $5 \cdot 10^{-3}$ M of one component. For K_{ass} = 400, the choice of this concentration gives 50% complexation at 1:1 stoichiometry. The partner was added in small aliquots in such a way that several data points could be measured in the vicinity of a 1:1 stoichiometry. Vapour pressure osmometry (concentration: $2 \cdot 10^{-2}$ mol·L^{-1}) was performed with a Mechrolab 301 A vapour pressure osmometer at 36.5 °C with benzil as a standard.

3,3-Dimethylbutanamide: In a three-necked flask with thermometer and mechanical stirrer, *tert*-butylacetyl chloride (25.0 mL, 179 mmol) was added dropwise to concd. ammonia (250 mL), with the temperature being maintained below 12 °C by use of an ice/salt bath. After the mixture had been stirred for a further 90 min, the precipitated solid (4.71 g) was filtered off and the filtrate was concentrated to dryness. The residue was heated for 10 min with ethyl acetate (150 mL) and was filtered hot. This extraction was repeated twice. After the combined solutions had been kept for 3 d at −18 °C, a colourless solid (6.11 g) had formed, and this was filtered off. On concentration of the filtrate, further colourless crystals (2.99 g) precipitated. Total yield: 13.8 g (70%; ref.[21] 82%), m.p. 126−129 °C (all batches; ref.[21] 132 °C). IR (KBr): $\tilde{\nu}$ = 3396, 3197 cm^{-1} (N−H), 2955, 2869 (aliph. C−H), 1661, 1628 (C=O). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.05 ppm [s, 9 H, C(CH_3)$_3$], 2.09 (s, 2 H, CH_2), 5.50 (br. s, 1 H, *cis*-NH), 5.95 (br. s, 1 H, *trans*-NH). MS (EI, 70 eV): *m*/*z* (%) = 115 (40) [M]$^+$, 100 (100) [M − NH]$^+$. MS (CI, isobutane): *m*/*z* (%) = 116 (100) [M + 1]$^+$.

3,3-Dimethylbut-1-ylamine (3b): 3,3-Dimethylbutanamide (13.8 g, 120 mmol), dissolved in dry THF (300 mL), was added dropwise under nitrogen to a suspension of lithium aluminium hydride (5.46 g, 144 mmol) in dry THF (80 mL) over a period of 2 h. The mixture was heated to 50−55 °C for 17 h. It was cooled with ice and hydrolysed with water until gas evolution had ceased. The precipitate was dissolved with 2 N sulfuric acid. The organic layer was separated and concentrated in vacuo. Water was added and the mixture was extracted four times with diethyl ether (80 mL). Solid sodium hydroxide was added to the combined water layer until the pH was basic. After extraction with diethyl ether (five times 50 mL), the organic layer was dried with sodium sulfate, the solvent was removed in vacuo, and the residue was purified by distillation to yield a colourless oil (6.2 g, 51%), b.p. 115 °C (ref.[22] 112.8−112.9 °C). IR (KBr): $\tilde{\nu}$ = 3283 cm^{-1} (N−H), 2954, 2867 (aliph. C−H). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.89 ppm [s, 9 H, C(CH_3)$_3$], 1.28 (s, 2 H, NH_2), 1.37 (m$_c$, 2 H, NH$_2$CH$_2$CH_2), 2.69 (m$_c$, 2 H, NH$_2$CH_2). MS (EI, 70 eV): *m*/*z* (%) = 101 (18) [M]$^+$, 71 (100). MS (CI, isobutane): *m*/*z* (%) = 102 (100) [M + 1]$^+$.

***N*-Dodecylcyanoacetamide (4a):** *n*-Dodecylamine (**3a**, 6.13 g, 33.1 mmol) was dissolved in ethyl cyanoacetate (23.0 mL, 216 mmol) by slight warming. After 1 h at room temp., a precipitate started to form. After 17 h, this was filtered off, washed with ethanol and diethyl ether and recrystallised from ethanol to yield a colourless solid (4.40 g). Concentration of the mother liquor and recrystallisation of the residue from ethanol gave further product (1.41 g). Total yield: 5.81 g (69%, ref.[16] 95%), m.p. 82−83 °C (both batches, ref.[16] 90.5 °C). IR (KBr): $\tilde{\nu}$ = 3298 cm^{-1} (N−H), 2916, 2849 (aliph. C−H), 2261 (C≡N), 1652, 1560 (C=O). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.88 ppm (t, *J* = 6.9 Hz, 3 H, CH_3), 1.2−1.4 [m, 18 H, (CH_2)$_9$CH$_3$], 1.54 (m$_c$, 2 H, NHCH$_2$CH_2), 3.30 (dt, J_1 = 7.2 Hz, J_2 = 5.7 Hz, 2 H, NHCH_2), 3.37 (s, 2 H, CNCH_2), 6.15 (br. s, 1 H, NH). MS (EI, 70 eV): *m*/*z* (%) = 252 (5) [M]$^+$, 212 (100) [M − CNCH$_2$]$^+$. MS (CI, isobutane): *m*/*z* (%) = 253 (100) [M + 1]$^+$.

***N*-(3,3-Dimethylbutyl)cyanoacetamide (4b):** 3,3-Dimethylbut-1-ylamine (**3b**, 6.2 g, 61 mmol) was added with ice-cooling to ethyl cyanoacetate (10 mL, 94 mmol). After 17 h at room temp., colourless crystals (4.1 g) had formed, and these were filtered off. After the filtrate had stood in the open flask for several days, further product (2.4 g) had precipitated from the filtrate. The batches were dried in vacuo over silica gel, each for 5 d. Because of its excellent solubility in any solvent tested, the substance was not washed or recrystallised; GC analysis showed high purity anyway. Total yield: 6.57 g (64%), m.p. 92−93 °C (both batches). IR (KBr): $\tilde{\nu}$ = 3290, 3109 $\mathrm{cm^{-1}}$ (N−H), 2960, 2865 (aliph. C−H), 2255 (C≡N), 1659, 1571 (C=O). ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 0.94 ppm [s, 9 H, $\mathrm{C(C\mathit{H}_3)_3}$], 1.46 ($\mathrm{m_c}$, 2 H, $\mathrm{NHCH_2C\mathit{H}_2}$), 3.32 ($\mathrm{m_c}$, 2 H, $\mathrm{NHC\mathit{H}_2}$), 3.37 (s, 2 H, $\mathrm{CNC\mathit{H}_2}$), 6.17 (br. s, 1 H, N*H*). MS (EI, 70 eV): *m/z* (%) = 168 (9) $[\mathrm{M}]^+$, 153 (12) $[\mathrm{M - CH_3}]^+$, 128 (14) $[\mathrm{M - CNCH_2}]^+$, 97 (30) $[\mathrm{M - CH_2C(CH_3)_3}]^+$, 69 (100) $[\mathrm{CNCH_2CHO}]^+$. MS (CI, isobutane): *m/z* (%) = 169 (100) $[\mathrm{M + 1}]^+$. HR-MS: calcd. for $\mathrm{C_9H_{16}N_2O}$ 168.12627, found 168.12610 (diff.: 1.0 ppm); calcd. for $\mathrm{C_8{}^{13}CH_{16}N_2O}$ 169.12962, found 169.12950 (diff.: 0.7 ppm). GC (OPTIMA 1, 25 m, 5 min at 60, 10°C/min until 250°C, 15 min at 250°C): t_R = 13.95 min, 96%.

***N*-(2,6-Dimethylphenyl)cyanoacetamide (4c):** 2,6-Dimethylaniline (**3c**, 17.4 mL, 140 mmol) and ethyl cyanoacetate (20.0 mL, 18.7 mmol) were stirred under nitrogen at room temp. for 16 h. The precipitate was filtered off and washed with ethanol. The solid was heated under reflux in ethanol (100 mL) for 6 h. After cooling, it was filtered off and dried in vacuo to provide slightly purple crystals (5.5 g, 21%, ref.[17] 3%), m.p. 203−209 °C (ref.[17] 180 °C). IR (KBr): $\tilde{\nu}$ = 3252 $\mathrm{cm^{-1}}$ (N−H), 3045 (arom. C−H), 2985, 2927 (aliph. C−H), 2258 (C≡N), 1661 (C=O), 1543, 1472 (arom.). ^{1}H NMR (300 MHz, $[\mathrm{D_6}]$DMSO): δ = 2.14 ppm (s, 6 H, $\mathrm{C\mathit{H}_3}$), 3.92 (s, 2 H, $\mathrm{C\mathit{H}_2}$), 7.04−7.14 (m, 3 H, Ar′-*H*), 9.66 (br. s, 1 H, N*H*). MS (EI, 70 eV): *m/z* (%) = 188 (64) $[\mathrm{M}]^+$, 148 (100) $[\mathrm{M - H_2CCN}]^+$, 120 (36) $[\mathrm{M - COH_2CCN}]^+$. MS (CI, isobutane): *m/z* (%) = 189 (100) $[\mathrm{M + 1}]^+$.

2-Aminopyridine-3-carbaldehyde (5): A mixture of ammonium sulfamate (52.0 g, 450 mmol) and nicotinamide (36.5 g, 300 mmol) was heated at 150 °C (in a molten state) under nitrogen. Over 8 h, the temperature was raised to 200 °C and maintained for another hour. After cooling, the solid was suspended in water (80 mL). Concd. ammonia was added until the suspension was basic. After the mixture had been stirred for 1 h, the remaining solid was filtered off and washed with diethyl ether. It was dissolved in 2 N hydrochloric acid and heated under reflux under nitrogen for 4 h. On neutralisation of the cooled solution with solid sodium hydrogencarbonate, a precipitate formed. The mixture was extracted eight times with diethyl ether (80 mL). The combined organic layers were dried with sodium sulfate and the solvent was evaporated to yield a yellow solid (4.0 g, 11%; ref.: 58%[15] or 25%[15a]) sufficiently pure for further synthesis, m.p. 94−96 °C (ref.:[15] 99 °C). IR (KBr): $\tilde{\nu}$ = 3413, 3132 $\mathrm{cm^{-1}}$ (N−H), 2747 (CHO), 1644 (C=O), 1553, 1450 (arom.). ^{1}H NMR (300 MHz, $[\mathrm{D_6}]$DMSO): δ = 6.74 ppm (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1 H, 5-*H*), 7.55 (br. s, 2 H, $\mathrm{N\mathit{H}_2}$), 8.00 (dd, J_1 = 7.6 Hz, J_2 = 2 Hz, 1 H, 4-*H*), 8.24 (dd, J_1 = 4.8 Hz, J_2 = 2 Hz, 1 H, 6-*H*), 9.85 (s, 1 H, C*H*O). MS (EI, 70 eV): *m/z* (%) = 122 (100) $[\mathrm{M}]^+$, 94 (70) $[\mathrm{M - CO}]^+$, 67 (22) $[\mathrm{M - CO - HCN}]^+$. MS (CI, isobutane): *m/z* (%) = 123 (100) $[\mathrm{M + 1}]^+$.

2-Amino-3-[(dodecylamino)carbonyl]-1,8-naphthyridine (6a): 2-Aminopyridine-3-carbaldehyde (**5**, 1.00 g, 8.19 mmol), *N*-dodecylcyanoacetamide (**4a**, 2.08 g, 8.24 mmol) and piperidine (3.2 mL, 33 mmol) were heated at reflux in dry ethanol (50 mL) under nitrogen for 2 d. On cooling to 8 °C for 1 d, a yellow precipitate formed and was filtered off, washed with ethanol and dried in vacuo. The ^{1}H NMR spectrum showed no impurities. Yield: 2.43 g (83%), m.p. 141−143 °C. IR (KBr): $\tilde{\nu}$ = 3393 $\mathrm{cm^{-1}}$ (N−H), 3094 (arom. C−H), 2920, 2847 (aliph. C−H), 1642, 1557, 1517 (C=O). ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$): δ = 0.88 ppm (t, *J* = 7.0 Hz, 3 H, $\mathrm{C\mathit{H}_3}$), 1.2−1.4 (m, 18 H, $\mathrm{[C\mathit{H}_2]_9CH_3}$), 1.6−1.7 (m, 2 H, $\mathrm{NHCH_2C\mathit{H}_2}$), 3.46 (td, J_t = 7.3 Hz, J_d = 5.9 Hz, 2 H, $\mathrm{NHC\mathit{H}_2}$), 6.56 (br. s, 1 H, N*H*), 6.65 (br. s, 2 H, $\mathrm{N\mathit{H}_2}$), 7.14 (dd, J_1 = 7.9 Hz, J_2 = 4.4 Hz, 1 H, Ar-6-*H*), 7.89 (dd, J_1 = 7.9 Hz, J_2 = 2.0 Hz, 1 H, Ar-5-*H*), 8.08 (s, 1 H, Ar-4-*H*), 8.84 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1 H, Ar-7-*H*). MS (EI, 70 eV): *m/z* (%) = 356 (27) $[\mathrm{M}]^+$, 172 (100) $[\mathrm{M - NHC_{12}H_{25}}]^+$, 145 (93) $[\mathrm{M - NHC_{12}H_{25} - HCN}]^+$. MS (CI, isobutane): *m/z* (%) = 357 (100) $[\mathrm{M + 1}]^+$. HR-MS: calcd. for $\mathrm{C_{21}H_{32}N_4O}$ 356.25760, found 356.25740 (diff.: −0.6 ppm); calcd. $\mathrm{C_{20}{}^{13}CH_{32}N_4O}$ for 357.26096, found 357.26100 (diff.: 0.9 ppm).

2-Amino-3-{[(3,3-dimethylbutyl)amino]carbonyl}-1,8-naphthyridine (6b): 2-Aminopyridine-3-carbaldehyde (**5**, 3.50 g, 28.7 mmol), *N*-(3,3-dimethylbutyl)cyanoacetamide (**4b**, 4.78 g, 28.4 mmol) and piperidine (10.0 mL, 101 mmol) were heated at reflux in dry ethanol (80 mL) under nitrogen for 55 h. On cooling to 8 °C for 3 d, a yellow precipitate formed and was filtered off, washed with ethanol and dried in vacuo. The ^{1}H NMR spectrum showed no impurities. Yield: 5.60 g (72%), m.p. 202−205 °C. IR (KBr): $\tilde{\nu}$ = 3364 $\mathrm{cm^{-1}}$ (N−H), 3054 (arom. C−H), 2959, 2849 (aliph. C−H), 1648, 1557, 1528 (C=O). ^{1}H NMR (300 MHz, $[\mathrm{D_6}]$DMSO): δ = 0.94 ppm [s, 9 H, $\mathrm{C(C\mathit{H}_3)_3}$], 1.48 ($\mathrm{m_c}$, 2 H, $\mathrm{NHCH_2C\mathit{H}_2}$), 3.33 ($\mathrm{m_c}$, 2 H, $\mathrm{NHC\mathit{H}_2}$), 7.22 (dd, J_1 = 7.9 Hz, J_2 = 4.4 Hz, 1 H, Ar-6-*H*), 7.47 (br. s, 2 H, $\mathrm{N\mathit{H}_2}$), 8.12 (dd, J_1 = 7.9 Hz, J_2 = 2.0 Hz, 1 H, Ar-5-*H*), 8.40 (s, 1 H, Ar-4-*H*), 8.73 and 8.75 (2 br. s, 1 H, *cis/trans*-N*H*), 8.78 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1 H, Ar-7-*H*). MS (EI, 70 eV): *m/z* (%) = 272 (34) $[\mathrm{M}]^+$, 215 (19) $[\mathrm{M - C(CH_3)_3}]^+$, 172 (100) $[\mathrm{M - NH(CH_2)_2C(CH_3)_3}]^+$, 145 (36) $[\mathrm{M - NH(CH_2)_2C(CH_3)_3 - HCN}]^+$. MS (CI, isobutane): *m/z* (%) = 273 (100) $[\mathrm{M + 1}]^+$. HR-MS: calcd. for $\mathrm{C_{15}H_{20}N_4O}$ 272.16370, found 272.16280 (diff.: −3.0 ppm); calcd. for $\mathrm{C_{14}{}^{13}CH_{20}N_4O}$ 273.16705, found 273.16670 (diff.: −1.3 ppm).

2-Amino-3-{[(2,6-dimethylphenyl)amino]carbonyl}-1,8-naphthyridine (6c): 2-Aminopyridine-3-carbaldehyde (**5**, 1.84 g, 15.1 mmol), *N*-(2,6-dimethylphenyl)cyanoacetamide (**4c**, 2.88 g, 15.3 mmol) and piperidine (2.0 mL, 20 mmol) were heated at reflux in dry ethanol (100 mL) under nitrogen for 22 h. On cooling to −18 °C for 18 h, a yellow precipitate formed and was filtered off, washed with ethanol and dried in vacuo. The ^{1}H NMR spectrum showed no impurities. Yield: 2.39 g (54%), m.p. 280−290 °C (gas evolution, decomp.). IR (KBr): $\tilde{\nu}$ = 3416, 3243, 3146 $\mathrm{cm^{-1}}$ (N−H), 1654, 1557, 1516 (C=O), 1472 (arom.). ^{1}H NMR (300 MHz, $[\mathrm{D_6}]$DMSO): δ = 2.24 ppm (s, 6 H, $\mathrm{C\mathit{H}_3}$), 7.15 (s, 3 H, Ar′-*H*), 7.28 (dd, J_1 = 7.9 Hz, J_2 = 4.4 Hz, 1 H, Ar-6-*H*), 7.39 (br. s, 2 H, $\mathrm{N\mathit{H}_2}$), 8.23 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H, Ar-5-*H*), 8.69 (s, 1 H, Ar-4-*H*), 8.82 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1 H, Ar-7-*H*), 10.12 (br. s, 0.5 H, N*H*). MS (EI, 70 eV): *m/z* (%) = 292 (39) $[\mathrm{M}]^+$, 172 (100) $[\mathrm{M - NHC_6H_3(CH_3)_2}]^+$, 144 (30) $[\mathrm{M - CONHC_6H_3(CH_3)_2}]^+$, 117 (26) $[\mathrm{M - CONHC_6H_3(CH_3)_2 - HCN}]^+$. MS (CI, isobutane): *m/z* (%) = 293 (100) $[\mathrm{M + 1}]^+$. HR-MS: calcd. for $\mathrm{C_{17}H_{16}N_4O}$ 292.13242, found 292.13230 (diff.: 0.4 ppm); calcd. for $\mathrm{C_{16}{}^{13}CH_{16}N_4O}$ 293.13577, found 293.13570 (diff.: 0.1 ppm).

3-[(Dodecylamino)carbonyl]-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (7a): Ethyl chloroformate (900 µl, 9.49 mmol) was added slowly by syringe, at 0 °C and under nitrogen, to a solution of 2-amino-3-[(dodecylamino)carbonyl]-1,8-naphthyridine (**6a**, 158 mg, 443 µmol) in dry pyridine (13 mL). The mixture was allowed to warm to room temp. while stirring for 17 h. The volatile components were distilled off in vacuo. The solid residue was dissolved in chloroform and the same volume of water was added. The water layer was extracted three times with chloroform (10 mL). The combined organic layers were dried with sodium sulfate and concentrated to dryness. Chromatography (silica gel, dichloromethane/methanol, 6:1, $R_f = 0.64$) yielded a pale yellow solid, which was recrystallised from *n*-hexane and a little methanol to give an almost colourless powder (115 mg, 61%), m.p. 104−106 °C (the sample solidifies at 160 °C and remelts at 244−246 °C, corresponding to the m.p. of the next desired product **8a**). IR (KBr): $\tilde{\nu}$ = 3454 cm^{-1} (N−H), 2915, 2850 (aliph. C−H), 1675, 1629, 1594, 1540 (C=O), 1272 (C−O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 ppm [t, J = 6.9 Hz, 3 H, $(CH_2)_{11}CH_3$], 1.2−1.5 [m, 18 H, $(CH_2)_9CH_3$], 1.38 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.67 (m_c, 2 H, $NHCH_2CH_2$), 3.50 (td, J_t = 6.8 Hz, J_d = 5.4 Hz, 2 H, $NHCH_2$), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2), 7.38 (dd, J_1 = 7.9 Hz, J_2 = 4.7 Hz, 1 H, Ar-6-*H*), 8.12 (ddd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, J_3 = 0.7 Hz, 1 H, Ar-5-*H*), 8.73 (dd, J_1 = 4.7 Hz, J_2 = 1.8 Hz, 1 H, Ar-7-*H*), 9.12 (s, 1 H, Ar-4-*H*), 11.03 (br. t, J = 5.5 Hz, 1 H, $NHCH_2$), 14.21 (br. s, 1 H, ArN*H*). MS: The substance obviously reacts to give the next desired product **8a** upon vaporization in the mass spectrometer, and so no HR-MS could be obtained. MS (EI, 70 eV): *m/z* (%) = 382 (92) $[M_{\mathbf{8a}}]^+$, 215 (100) $[M_{\mathbf{8a}} - C_{12}H_{23}]^+$. MS (CI, isobutane): *m/z* (%) = 383 (100) $[M_{\mathbf{8a}} + 1]^+$.

3-{[(3,3-Dimethylbutyl)amino]carbonyl}-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (7b): Ethyl chloroformate (900 µl, 9.49 mmol) was treated with 2-amino-3-{[(3,3-dimethylbutyl)amino]carbonyl}-1,8-naphthyridine (**6b**, 159 mg, 587 µmol). Synthesis and workup were carried out analogously to those used in the preparation of 3-[(dodecylamino)carbonyl]-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7a**). Chromatography (R_f = 0.57) and crystallisation yielded a yellow solid (169 mg, 84%), m.p. > 160 °C, the sample sinters and turns brown, m.p. 325−334 °C, corresponding to the m.p. of the next desired product **8b**. IR (KBr): $\tilde{\nu}$ = 3498, 3354 cm^{-1} (N−H), 3067 (arom. C−H), 2956, 2866 (aliph. C−H), 1743, 1654, 1611, 1515 (C=O), 1247, 1206 (C−O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 ppm [s, 9 H, $C(CH_3)_3$], 1.39 (t, J = 7.4 Hz, 3 H, OCH_2CH_3), 1.61 (m_c, 2 H, $NHCH_2CH_2$), 3.51 (m_c, 2 H, $NHCH_2$), 4.28 (q, J = 7.4 Hz, 2 H, OCH_2), 7.37 (dd, J_1 = 7.9 Hz, J_2 = 4.7 Hz, 1 H, Ar-6-*H*), 8.12 (dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz, 1 H, Ar-5-*H*), 8.72 (dd, J_1 = 4.7 Hz, J_2 = 1.9 Hz, 1 H, Ar-7-*H*), 9.11 (s, 1 H, Ar-4-*H*), 10.90 (br. t, J = 4.8 Hz, 1 H, $NHCH_2$), 14.16 (br. s, 1 H, ArN*H*). MS: Like **7a**, **7b** partially reacts to form **8b** upon vaporization in the mass spectrometer; peaks of both species are detected simultaneously. MS (EI, 70 eV): *m/z* (%) = 344 (12) $[M_{\mathbf{7b}}]^+$, 329 (10) $[M_{\mathbf{7b}} - CH_3]^+$, 298 (39) $[M_{\mathbf{8b}}]^+$, 287 (18) $[M_{\mathbf{7b}} - C(CH_3)_3]^+$, 273 (33) $[M_{\mathbf{7b}} - CH_2C(CH_3)_3]^+$, 215 (100) $[M_{\mathbf{8b}} - C(CH_3)_3 - CN]^+$. MS (CI, isobutane): *m/z* (%) = 345 (49) $[M_{\mathbf{7b}} + 1]^+$, 299 (100) $[M_{\mathbf{8b}} + 1]^+$. HR-MS: calcd. for $C_{18}H_{24}N_4O_3$ 344.18484, found 344.18300 (diff.: −5.3 ppm); calcd. for $C_{17}{}^{13}CH_{24}N_4O_3$ 345.18820, found 345.18730 (diff.: −2.6 ppm).

3-{[(2,6-Dimethylphenyl)amino]carbonyl}-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (7c): Ethyl chloroformate (1.20 mL, 12.7 mmol) was treated with 2-amino-3-{[(2,6-dimethylphenyl)amino]carbonyl}-1,8-naphthyridine (**6c**, 199 mg, 682 µmol). Synthesis and workup were carried out analogously to those used for the preparation of 3-[(dodecylamino)carbonyl]-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7a**). Chromatography (R_f = 0.70) yielded a yellow solid (179 mg, 72%), m.p. 158−162 °C (gas evolution). IR (KBr): $\tilde{\nu}$ = 3448 cm^{-1} (N−H), 3044 (arom. C−H), 2992 (aliph. C−H), 1741, 1682, 1624 (C=O), 1535, 1474 (arom.), 1220 (C−O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 ppm (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.33 (s, 6 H, CH_3), 4.26 (q, J = 7.1 Hz, 2 H, OCH_2), 7.14 (s, 3 H, Ar′-*H*), 7.40 (dd, J_1 = 7.9 Hz, J_2 = 4.7 Hz, 1 H, Ar-6-*H*), 8.14 (dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz, 1 H, Ar-5-*H*), 8.76 (dd, J_1 = 4.7 Hz, J_2 = 1.9 Hz, 1 H, Ar-7-*H*), 9.22 (s, 1 H, Ar-4-*H*), 12.66 (br. s, 1 H, Ar′-N*H*), 14.24 (br. s, 1 H, ArN*H*). MS: Like **7a**, **7c** partially reacts to give **8c** upon vaporization in the mass spectrometer; peaks of both species are detected simultaneously. MS (EI, 70 eV): *m/z* (%) = 364 (14) $[M_{\mathbf{7c}}]^+$, 318 (100) $[M_{\mathbf{8c}}]^+$, 301 (34) $[M_{\mathbf{8c}} - NH_3]^+$, 198 (65) $[M_{\mathbf{7c}} - (CH_3)_2C_6H_3NH - H_5C_2OH]^+$. MS (CI, isobutane): *m/z* (%) = 365 (8) $[M_{\mathbf{7c}} + 1]^+$, 319 (100) $[M_{\mathbf{8c}} + 1]^+$. HR-MS: calcd. for $C_{20}H_{20}N_4O_3$ 364.15353, found 364.15320 (diff.: 0.9 ppm); calcd. for $C_{19}{}^{13}CH_{20}N_4O_3$ 365.15689, found 365.15680 (diff.: 0.2 ppm).

3-Dodecylpyrimido[4,5-*b*]-1,8-naphthyridine-2,4(1*H*,3*H*)-dione (8a). Method A: A solution of 3-[(dodecylamino)carbonyl]-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7a**, 235 mg, 548 µmol) in dry pyridine (10 mL) was heated under reflux under argon for 2 d. The volatile components were distilled off in vacuo. The solid residue was dissolved in chloroform (5 mL) and the same volume of water was added. The water layer was extracted three times with chloroform (5 mL each). The combined organic layers were dried with sodium sulfate and concentrated to dryness. Chromatography (silica gel, dichloromethane/methanol, 6:1, R_f = 0.74) yielded a yellow solid (134 mg, 64%) that was pure by ^{1}H NMR spectroscopy. For elemental analysis, a sample was recrystallised from *n*-hexane and a little methanol, m.p. 243−246 °C (decomp.). **Method B:** 3-[(Dodecylamino)carbonyl]-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7a**, 58.9 mg, 137 µmol) was heated to 170 °C in vacuo (approximately 15 mbar), kept at that temperature for 5 min and cooled, also in vacuo. The yellow solid residue (52.6 mg, 100%) was identical to that obtained by Method A, m.p. 241−244 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 2919, 2849 cm^{-1} (aliph. C−H), 1729, 1665, 1634 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 ppm (t, J = 6.9 Hz, 3 H, CH_3), 1.2−1.4 (m, 18 H, $[CH_2]_9CH_3$), 1.7−1.75 (m, 2 H, NCH_2CH_2), 4.09 (m_c, 2 H, NCH_2), 7.53 (dd, J_1 = 8.2 Hz, J_2 = 4.3 Hz, 1 H, Ar-7-*H*), 8.34 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1 H, Ar-6-*H*), 9.05 (s, 1 H, Ar-5-*H*, 9.18 (br. s, 0.6 H, N*H*), 9.21 (dd, J_1 = 4.3 Hz, J_2 = 2.0 Hz, 1 H, Ar-8-*H*). MS (EI, 70 eV): *m/z* (%) = 382 (12) $[M]^+$, 215 (29) $[M - C_{12}H_{23}]^+$, 110 (100). MS (CI, isobutane): *m/z* (%) = 383 (100) $[M + 1]^+$. HR-MS: calcd. for $C_{22}H_{30}N_4O_2$ 382.23688, found 382.23660 (diff.: −0.7 ppm); calcd. for $C_{21}{}^{13}CH_{30}N_4O_2$ 383.24023, found 383.24010 (diff.: −0.3 ppm). $C_{22}H_{30}N_4O_2$ (382.5): calcd. C 69.08, H 7.81, N 14.65; found C 69.02, H 7.70, N 14.44.

3-(3,3-Dimethylbutyl)pyrimido[4,5-*b*]-1,8-naphthyridine-2,4(1*H*,3*H*)-dione (8b). Method A: 3-{[(3,3-Dimethylbutyl)amino]carbonyl}-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7b**, 243 mg, 706 µmol) was heated at reflux in dry pyridine (8 mL) under argon for 3 d. The workup was performed analogously to that used for the preparation of 3-Dodecylpyrimido[4,5-*b*]-1,8-naphthyridine-2,4(1*H*,3*H*)-dione (**8a**, Method A). After chromatography (R_f = 0.66) and crystallisation, a yellow solid (81.7 mg, 39%) was obtained, m.p. 335−343 °C (decomp.). **Method B:** 3-{[(3,3-Dimethylbutyl)amino]carbonyl}-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7b**, 77.6 mg, 225 µmol) was heated to 170 °C in vacuo (approximately 15 mbar), kept at that temperature for 5 min and cooled, also in vacuo. The remaining brown solid was recrystallised from hexanes/methanol/chloroform (approximately 1:6:6), yielding a rose-coloured powder (64.5 mg, 60%) identical to that obtained from Method A, m.p. 340−345 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1} (N−H), 2956, 2853 (aliph. C−H), 1728, 1662, 1628 (C=O), 1244 (*tert*-butyl). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 ppm [s, 9 H, $C(CH_3)_3$], 1.61 (m_c, 2 H, NCH_2CH_2), 4.12 (m_c, 2 H, NCH_2), 7.53 (dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz, 1 H, Ar-7-*H*), 8.34 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1 H, Ar-6-*H*), 8.90 (br. s, 0.6 H, N*H*), 9.03 (s, 1 H, Ar-5-*H*), 9.21 (dd, J_1 = 4.2 Hz, J_2 = 2.0 Hz, 1 H, Ar-8-*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2 [q, C(CH_3)$_3$], 29.7 [s, *C*(CH_3)$_3$], 38.5 (t, NCH_2CH_2), 40.9 (t, NCH_2), 111.5 (s, Ar-5a-*C*), 119.9 (s, Ar-9a-*C*), 121.7 (d, Ar-7-*C*), 138.7 (d, Ar-6-*C*), 141.8 (d, Ar-5-*C*), 149.8 (s, Ar-4a-*C*), 157.2 (d, Ar-8-*C*), 160.8 (s, Ar-10a-*C*), the Ar-2-C and Ar-4-C signals were not detected due to the small amount sampled. MS (EI, 70 eV): *m/z* (%) = 298 (42) $[M]^+$, 241 (34) $[M - C(CH_3)_3]^+$, 215 (100) $[M - C(CH_3)_3 - CN]^+$. MS (CI, isobutane): *m/z* (%) = 299 (100) $[M + 1]^+$. HR-MS: calcd. for $C_{16}H_{18}N_4O_2$ 298.14297, found 298.14338 (diff.: 1.4 ppm); calcd. for $C_{15}{}^{13}CH_{18}N_4O_2$ 299.14633, found 299.14685 (diff.: 1.7 ppm). $C_{16}H_{18}N_4O_2$ (298.3): calcd. C 64.41, H 6.08, N 18.78; found C 64.24, H 6.08, N 18.54.

3-(2,6-Dimethylphenyl)pyrimido[4,5-*b*]-1,8-naphthyridine-2,4(1*H*,3*H*)-dione (8c): 3-{[(2,6-Dimethylphenyl)amino]carbonyl}-2-[(ethoxycarbonyl)amino]-1,8-naphthyridine (**7c**, 61.3 mg, 168 μmol) was heated to 170 °C in vacuo (approximately 15 mbar), kept at that temperature until gas evolution from the molten material had ceased (approximately 15 min) and cooled, also in vacuo. The remaining brown solid was recrystallised from hexanes/methanol/chloroform (approximately 1:2:1), yielding pale brown crystals (39.2 mg, 73%), m.p. 150−157 °C (gas evolution). IR (KBr): ṽ = 3392 cm^{-1} (N−H), 3035 (arom. C−H), 2812 (aliph. C−H), 1730, 1674, 1624 (C=O), 1578, 1499 (arom.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 ppm (s, 6 H, C*H*$_3$), 7.20−7.35 (m, 3 H, Ar′-*H*), 7.55 (dd, J_1 = 8.1 Hz, J_2 = 4.3 Hz, 1 H, Ar-7-*H*), 8.38 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1 H, Ar-6-*H*), 9.14 (s, 1 H, Ar-5-*H*), 9.31 (dd, J_1 = 4.3 Hz, J_2 = 2.0 Hz, 1 H, Ar-8-*H*), 10.80 (br. s, 0.8 H, N*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.7 ppm (q, *C*H$_3$), 111.6 (s, Ar-5a-*C*), 120.0 (s, Ar-9a-*C*), 121.7 (d, Ar-7-*C*), 128.7 (d, Ar′-3,5-*C*), 129.3 (d, Ar′-4-*C*), 132.7 (s, Ar′-2,6-*C*), 135.8 (s, Ar′-1-*C*), 138.8 (d, Ar-6-*C*), 142.2 (d, Ar-5-*C*), 149.6 (s, Ar-4-*C*), 151.2 (s, Ar-4a-*C*), 157.3 (d, Ar-8-*C*), 157.6 (s, Ar-10a-*C*), 160.5 (s, Ar-2-*C*). MS (EI, 70 eV): *m/z* (%) = 318 (100) $[M]^+$, 301 (38) $[M - NH_3]^+$, 172 (36) $[M - (CH_3)_2C_6H_3 - N - HCN]^+$. MS (CI, isobutane): *m/z* (%) = 319 (100) $[M + 1]^+$. HR-MS: calcd. for $C_{18}H_{14}N_4O_2$ 318.11166, found 318.11189 (diff.: −0.7 ppm); calcd. for $C_{17}{}^{13}CH_{14}N_4O_2$ 319.11502, found 319.11497 (diff.: 0.2 ppm). $C_{18}H_{14}N_4O_2$ (318.3): calcd. C 67.92, H 4.43, N 17.60; found C 67.87, H 4.53, N 16.97. Purity (HPLC, RP-18, CH_2Cl_2/MeOH 5:1): 99.2%.

***N*-(6-Amino-2-pyridyl)-*N*′-(*n*-butyl)urea (9a):** A suspension of 2,6-diaminopyridine (1.00 g, 9.16 mmol) in dry toluene (50 mL) was stirred under nitrogen at 50 °C for 1 h, after which *n*-butyl isocyanate (1.0 mL, 9.2 mmol) was added and the mixture was heated at reflux for 2 h. The clear solution was concentrated to dryness. The residue was dissolved in dichloromethane/methanol (9:1) and purified by chromatography (silica gel with the same eluent). The fraction eluting with R_f = 0.5 was concentrated to dryness and crystallised from cyclohexane/ethanol (2:1). On vacuum filtration of the colourless solid, further product precipitated from the mother liquor and was also filtered off. Total yield: 559 mg (29%), m.p. 132−135 °C. IR (KBr): ṽ = 3484, 3328, 3205 cm^{-1} (N−H), 2956, 2863 (aliph. C−H), 1678, 1624, 1597, 1564 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 ppm (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.35−1.5 (m, 2 H, C*H*$_2$CH$_3$), 1.5−1.65 (m, 2 H, C*H*$_2$CH$_2$CH$_3$), 3.37 (td, J_t = 6.9 Hz, J_d = 5.6 Hz, 2 H, NHC*H*$_2$), 4.33 (br. s, 2 H, N*H*$_2$), 6.06 (dd, J_1 = 8.0 Hz, J_2 = 0.7 Hz, 1 H, Ar-3-*H*), 6.15 (dd, J_1 = 7.9 Hz, J_2 = 0.7 Hz, 1 H, Ar-5-*H*), 7.32 (t, *J* = 7.9 Hz, 1 H, Ar-4-*H*), 8.13 (br. s, 1 H, Ar-N*H*), 9.13 (br. t, lateral maxima only visible as shoulders, 1 H, N*H*CH$_2$). MS (EI, 70 eV): *m/z* (%) = 208 (14) $[M]^+$, 109 (100) $[M - H_9C_4NCO]^+$. MS (CI, isobutane): *m/z* (%) = 209 (58) $[M + 1]^+$, 173 (100). HR-MS: calcd. for $C_{10}H_{16}N_4O$ 208.13242, found 208.13230 (diff.: −0.6 ppm); calcd. for $C_9{}^{13}CH_{16}N_4O$ 209.13577, found 209.13570 (diff.: −0.3 ppm). $C_{10}H_{16}N_4O$ (208.3): calcd. C 57.67, H 7.74, N 26.90; found C 57.79, H 7.66, N 26.71.

***N*-(6-Amino-2-pyridyl)-*N*′-cyclohexylurea (9b):** 2,6-Diaminopyridine (4.40 g, 40.4 mmol) was dissolved in dry toluene (25 mL) under nitrogen. Freshly distilled cyclohexyl isocyanate (1.30 g, 10.5 mmol) was added and the mixture was heated to reflux for 2 h. After cooling to room temperature, excess 2,6-diaminopyridine was filtered off and the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane and filtered through silica gel (1 × 3 cm), R_f = 0.72. Evaporation of the solvent and recrystallisation from toluene gave colourless needles (630 mg, 27%), m.p. 164−165 °C. IR (KBr): ṽ = 3441, 3339, 3254 cm^{-1} (N−H), 2934, 2852 (aliph. C−H), 1663 (C=O), 1606, 1583, 1500 (arom.), 1537 (N−H), 1458 (C−H). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.2−2.1 ppm (m, 10 H, C*H*$_2$), 3.7−3.9 (m, 1 H, C*H*), 4.30 (br. s, 2 H, N*H*$_2$), 6.06 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 6.13 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.32 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 7.89 (br. s, 1 H, N*H*), 9.15 (d, *J* = 7.6 Hz, 1 H, N*H*). MS (EI, 70 eV): *m/z* (%) = 234 (8) $[M]^+$, 109 (100) $[(NH_2)_2C_5H_3N]^+$. MS (CI/isobutane): *m/z* (%) = 235 (100) $[M + 1]^+$. $C_{12}H_{18}N_4O$ (234.3): calcd. C 61.52, H 7.74, N 23.91; found C 61.47, H 7.76, N 23.89.

***N*-(6-Acetamido-2-pyridyl)-*N*′-(*n*-butyl)urea (9c):** Triethylamine (50.5 mg, 500 μmol) was added under nitrogen to a solution of *N*-(6-amino-2-pyridyl)-*N*′-(*n*-butyl)urea (**9a**, 100 mg, 481 μmol) in dry dichloromethane (5 mL). Dry acetic anhydride (49.1 mg, 481 μmol) was then added at 0 °C. After stirring for 1 h at 0 °C and standing for 15 h, the mixture was hydrolysed with ice/water (20 mL). The water layer was extracted with dichloromethane (four times 20 mL). The combined organic layers were dried with sodium sulfate, and the solvent was evaporated in vacuo. Recrystallisation first from toluene/ethanol (10:1) and then from toluene gave a colourless solid (87.6 mg, 73%), m.p. 158−160 °C. IR (KBr): ṽ = 3250, 3173, 3076 cm^{-1} (N−H), 2957, 2928, 2870 (aliph. C−H), 1689, 1670 (C=O), 1594 (arom.), 1555 (N−H), 1449 (C−H). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 0.89 ppm (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.2−1.5 (m, 4 H, C*H*$_2$), 2.10 (s, 3 H, C*H*$_3$), 3.19 (m$_c$, 2 H, C*H*$_2$), 6.76 (d, *J* = 7.9 Hz, 1 H, Ar*H*), 7.40 (d, *J* = 7.9 Hz, 1 H, Ar*H*), 7.58 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 8.68 (m$_c$, 1 H, N*H*), 9.09 (br. s, 1 H, N*H*), 10.23 (br. s, 1 H, N*H*). MS (EI, 70 eV): *m/z* (%) = 250 (70) $[M]^+$, 109 (100) $[(NH_2)_2C_5H_3N]^+$. MS (CI/isobutane): *m/z* (%) = 251 (100) $[M + 1]^+$. $C_{12}H_{18}N_4O_2$ (250.3): calcd. C 57.58, H 7.25, N 22.38; found C 57.34, H 7.19, N 22.20.

***N*-(6-Amino-2-pyridyl)-*N*′-(*n*-butyl)thiourea (9d):** A suspension of 2,6-diaminopyridine (1.00 g, 9.16 mmol) and *n*-butyl thioisocyanate (1.0 mL, 9.2 mmol) in dry toluene (50 mL) was stirred under nitrogen at 50 °C for 30 min and then heated under reflux for 3 h. The clear solution was concentrated to dryness. The residue was dissolved in chloroform and water (20 mL each) and the phases were separated. The organic layer was dried with sodium sulfate, concentrated and purified by chromatography (silica gel, dichloromethane/methanol, 10:1). The fraction eluting with R_f = 0.5 was concentrated to dryness and crystallised from hexanes/ethanol to give large, colourless needles (451 mg, 22%), m.p. 129−131 °C. IR (KBr): ṽ = 3458, 3331, 3207 cm^{-1} (N−H), 2959, 2863 (aliph. C−H), 1618, 1587, 1562. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 ppm (t, *J* = 7.3 Hz, 3 H, C*H*$_3$), 1.4−1.55 (m, 2 H, C*H*$_2$CH$_3$), 1.65−1.75 (m, 2 H, C*H*$_2$CH$_2$CH$_3$), 3.37 (dt, J_1 = 7.1 Hz, J_2 = 5.3 Hz, 2 H, NHC*H*$_2$), 4.33 (br. s, 2 H, N*H*$_2$), 4.37 (br. s, 2 H, N*H*$_2$), 6.06 (dd, J_1 = 7.9 Hz, J_2 = 0.7 Hz, 1 H, Ar-3-*H*), 6.15 (dd,

J_1 = 8.0 Hz, J_2 = 0.7 Hz, 1 H, Ar-5-*H*), 7.32 (t, J = 8.0 Hz, 1 H, Ar-4-*H*), 8.32 (br. s, 1 H, Ar-N*H*), 11.39 (br. t, lateral maxima only visible as shoulders, 1 H, N*H*CH$_2$). MS (EI, 70 eV): *m*/*z* (%) = 224 (60) $[M]^+$, 152 (35) $[M - H_9C_4NH]^+$, 109 (100) $[M - H_9C_4NCS]^+$. MS (CI, isobutane): *m*/*z* (%) = 225 (100) $[M + 1]^+$. HR-MS: calcd. for $C_{10}H_{16}N_4S$ 224.10957, found 224.11050 (diff.: −4.1 ppm); calcd. for $C_9{}^{13}CH_{16}N_4S$ 225.11293, found 225.11340 (diff.: 2.1 ppm). $C_{10}H_{16}N_4S$ (224.3)[41]: calcd. C 53.54, H 7.19, N 24.97, S 14.29; found C 54.15, H 8.01, N 24.39, S 13.31.

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