

**189. 2,3-Dihydrospiro[1*H*-4- and 5-azabenzimidazole-2,1'-cyclohexane]
(= Spiro[cyclohexane-1,2'(3'*H*)-1'*H*-imidazo[4,5-*b*]pyridine] and
Spiro[cyclohexane-1,2'(3'*H*)-1'*H*-imidazo[4,5-*c*]pyridine]):
Reactions with Nucleophiles**

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Dedicated to *Rolf Huisgen* on the occasion of his 75th birthday

(16. V. 94)

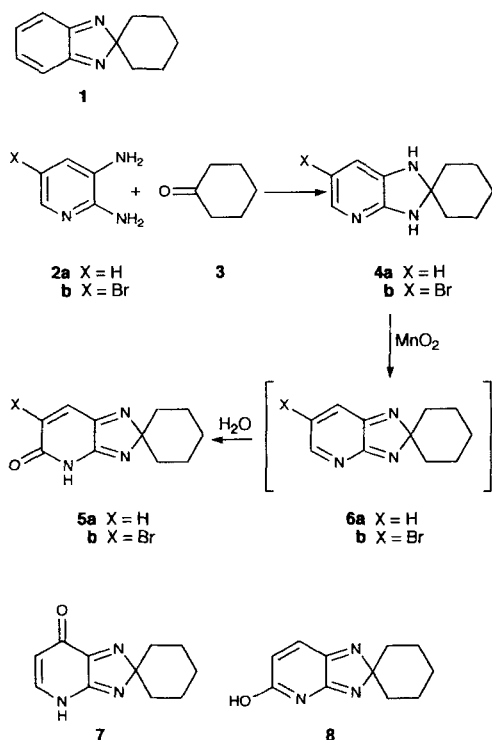
The readily available title compounds **4a** and **24** react with N-, O-, S-, and C-nucleophiles in presence of MnO₂ to give the corresponding mono- or disubstituted 2*H*-azabenzimidazoles (= azaisobenzimidazoles), *e.g.*, **11–18** and **26a–h**, respectively, or 2,3-dihydro-1*H*-azabenzimidazoles (= dihydro-azabenzimidazoles) such as **9** and **10** and **27** and **28**, respectively, by a 1,4- or 1,6-*Michael* addition (*Schemes 2* and *4*). The bromo-dihydro-1*H*-azabenzimidazole **4b** lost the Br-atom when treated with piperidine or morpholine yielding the corresponding disubstituted 2*H*-azabenzimidazole **21** (*Scheme 3*). Reductive ring opening of the substituted spiro compounds leads to mono- and disubstituted diaminopyridines which are intermediates for fused pyridine ring systems with substituents often not available by conventional routes and of potential pharmaceutical interest (see **32–37**). *E.g.*, starting from **4a**, a three-step synthesis of the analgesic flupirtine maleate (= ethyl {2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate maleate = *Katadolon*®; **39**) and of its non-fluorinated derivative *D-7195* is described. Its analogue **40** was similarly made from the spiro compound **24**.

Introduction. – Spiro[2*H*-benzimidazole-2,1'-cyclohexanes], *e.g.* **1**, were shown to be versatile synthons for introducing nucleophilic substituents into aromatic molecules [1] and for preparing new fused heterocycles after reductive hydrolysis [2] [3]. It was of obvious interest to apply this chemistry to the structurally related 2,3-dihydrospiro[1*H*-azabenzimidazole-2,1'-cyclohexanes] **4a** and **24**, available from the 2,3- and 3,4-diaminopyridines (**2a** and **22**), respectively. Moreover, new pyridine chemistry would be of potential interest to biochemistry and pharmaceutical chemistry.

Results. – *Reactions of 2,3-Diaminopyridine (2a).* Amine **2a** readily underwent condensation with cyclohexanone (**3**) under reflux to give the expected 2,3-dihydro-1*H*-4-azabenzimidazole **4a** (*Scheme 1*). Oxidation of **4a** with MnO₂ or other oxidizing agents in an inert solvent (THF) led invariably to the pyridinone **5a** and not to **6a** as expected. This is most likely due to the instability of the intermediate 2*H*-azabenzimidazole **6a** which, by a 1,4-*Michael* addition of adventitious H₂O followed by oxidation, led to formation of the stable **5a**.

The structural assignment of **5a** was made by ¹³{¹H}-NOE difference spectra (*cf. Fig.*). Selective irradiation of the protons *H*–C(6') and *H*–C(7') caused a clear NOE in each case excluding structure **7** and possible tautomeric forms. Irradiation of the exchangeable proton led to two NOE's of comparable intensity. This confirms structure **5a** with the exchangeable proton in a central position relative to C(3a') and C(5').

Scheme 1



A recent note on the preparation of 6-substituted 2,3-diaminopyridines [4] reports the formation of the pyridinol derivative **8**, when the spiro compound **4a** is treated with MnO_2 which we could not confirm. Following closely the literature procedure, we obtained a pure compound which was in all analytical details identical with our **5a**. Our conclusion is further supported by the absence of any by-products and of a tautomeric equilibrium on varying solvent and temperature. Attempts at producing the desired 2*H*-azabenzimidazole **6a** as an intermediate failed in spite of exploring different oxidizing agents (DDQ , PbO_2 , HgO , $\text{Ph}_3\text{C}(\text{BF}_4)$, KMnO_4 , tetracyanoethylene, $(\text{COCl})_2/\text{DMSO}$, or **1**).

To achieve introduction of a nucleophile into **4a**, we had to employ a different strategy, namely to use a competition reaction between the reagent and MnO_2 , *i.e.* to oxidize the dihydro compound **4a** in the presence of an excess of nucleophile. This method prevented pyridinone formation in favour of the required substitution products, *i.e.*, of the mono- and disubstituted 2,3-dihydro-1*H*-4-azabenzimidazoles **9** and **10** and 2*H*-4-azabenzimidazoles (= 4-azaisobenzimidazoles) **11–18** (Scheme 2, Table 1). The examples demonstrate the use of N-, S-, O-, and C-nucleophiles. With tetracyanoethylene (= ethylenetetracarbonitrile), the propanedinitrile **19** was formed without addition of MnO_2 as the reagent acted as oxidizing agent. The loss of =C(CN)_2 occurred by a sequence analogous to that reported by us for the reaction of 2*H*-benzimidazole **1** with this reagent [5]. It is noteworthy that the reactions proceeded at room temperature and heating lead to decomposition of the products. The phenyl/sulfonyl-substituted deriva-

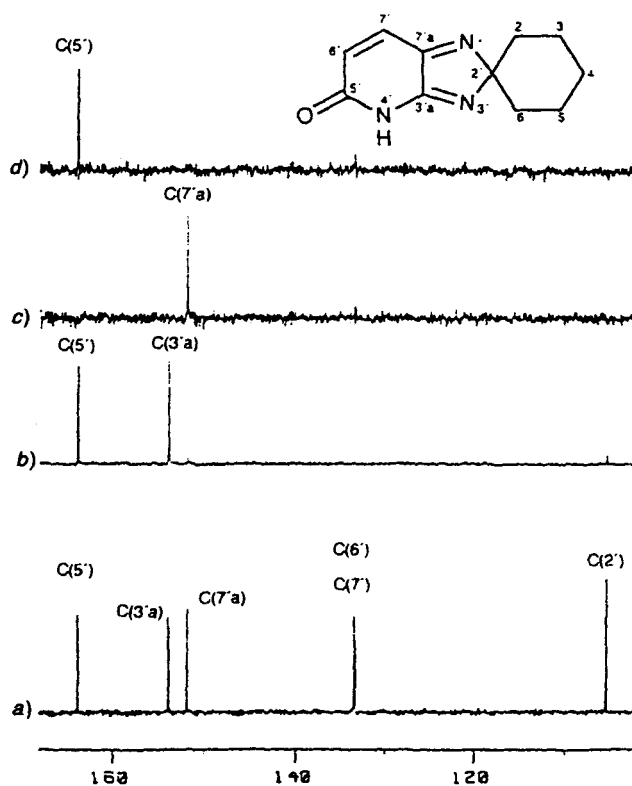


Figure. ^{13}C -NMR Spectra (62.89 MHz; Bruker WM 250) in CDCl_3 for compound 5a: a) ^1H -noise-decoupled spectrum; b) c) d) $^{13}\text{C}\{^1\text{H}\}$ -NOE difference spectra obtained by selective irradiation of $\text{H}-\text{N}(4')$, of $\text{H}-\text{C}(7')$, and of $\text{H}-\text{C}(6')$, respectively

tives **9** and **10** were obtained in the dihydro form owing to the reducing properties of the reagent. Intermediacy of **6a** in all these nucleophilic additions is supported by the fact that without MnO_2 , no reaction between **4a** and the nucleophile occurred which is also valid for the formation of **10** from **9**.

Scheme 2

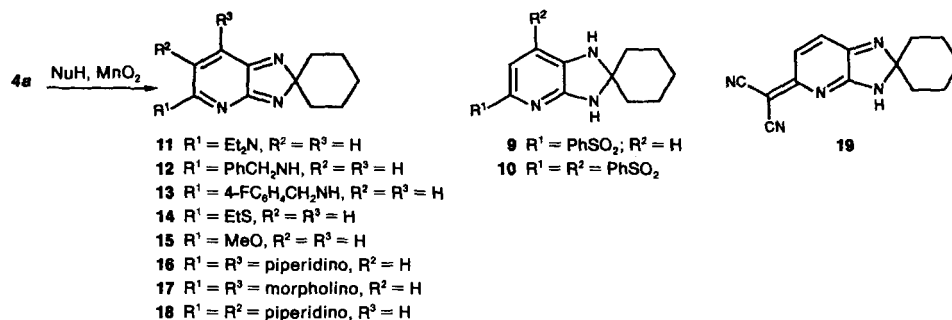


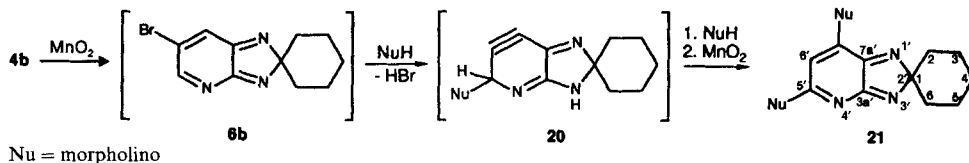
Table 1. Reaction of **4a** with Nucleophiles at Room Temperature: Conditions and Products

Nucleophile ^{a)}	Solvent	Time	Product (yield [%])	M.p. [°]
Et ₃ NH	THF	140 h	11 (16)	62
PhCH ₂ NH ₂	THF	18 h	12 (45)	198
4-FC ₆ H ₄ CH ₂ NH ₂	THF	18 h	13 (53)	189
EtSH	MeOH	4 h	14 (28)	134
MeOH	—	70 h	15 (25)	128
Piperidine	EtOH or THF ^{b)}	6.5 h or 21 h ^{b)}	16 (5), 18 (10) or 16 (23) ^{b)}	165 and 156, resp.
Morpholine ^{b)}	THF	63 h	17 (57)	226
NaOS(O)Ph ^{c)}	EtOH/H ₂ O 3:1	45 min	9 (35), 10 (24)	86–88 and 146, resp.
(CN) ₂ C=C(CN) ₂	THF	10 min	19 (25)	258

^{a)} Molar ratio nucleophile/**4a** 20:1.^{b)} Starting material **4b** instead of **4a**.^{c)} Reaction at 0°.

Reactions of 2,3-Diamino-5-bromopyridine (2b). It was of interest to use the bromo compound **2b** [6] to study the influence of the bulky Br-atom on the substitution pattern. Condensation with cyclohexanone (**3**) led to **4b** as expected (*Scheme 1*). A surprising result was obtained by reacting **4b** with N-nucleophiles (morpholine or piperidine) under conditions of the competition reaction (*cf.* above). The Br-atom was eliminated with formation of the disubstituted 2*H*-azabenzimidazole **21**. A plausible explanation to account for the loss of the Br-atom is the operation of a *cine*-mechanism [7] (*Scheme 3*): The unstable intermediate **6b** formed by oxidation adds the nucleophile by a 1,4-addition followed by loss of HBr to give the dihydro pyridine **20**. Addition of another molecule of nucleophile across the triple bond followed by oxidation leads to **21**.

Scheme 3

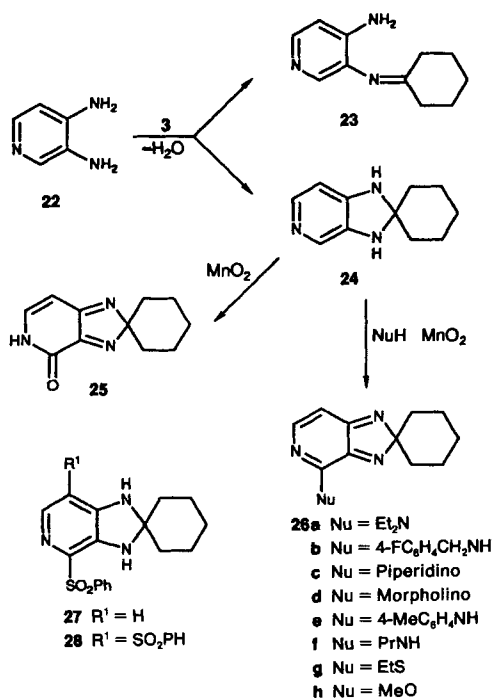


The possibility of a direct attack on the Br-atom by the amine (protodebromination) [8] requires a polyhalogenated system and can, therefore, be discounted.

Reactions of 3,4-Diaminopyridine (22). Condensation of amine **22** with cyclohexanone (**3**) below 100° led to the *Schiff's* base **23** which on reflux was converted into the required dihydro-1*H*-azabenzimidazole **24** (*Scheme 4*). This is in contrast to the direct formation of the isomeric **4a** even when the reaction was carried out under mild conditions. As oxidation of **24** (MnO₂) led to pyridinone **25**, we again used the strategy of a competition reaction for introducing nucleophiles. *Table 2* gives examples of N-, S-, and O-nucleophiles yielding mono-substituted 2*H*-5-azabenzimidazoles **26a–h** by *Michael* addition. Only sodium benzenesulfinate gave again the mono- and disubstituted products **27** and **28** in the dihydro form.

Comparison of the Reactivity of 2a and 22. Condensation with cyclohexanone (**3**) and subsequent oxidation led to analogous results, except for the isolable *Schiff's* base **23** in

Scheme 4

Table 2. Reaction of **24** with Nucleophiles at Room Temperature: Conditions and Products

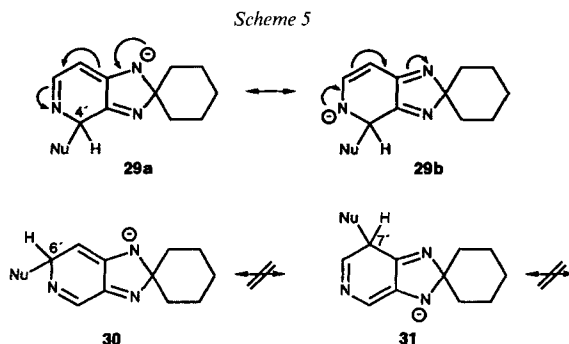
Nucleophile ^{a)}	Solvent	Time	Product (yield [%])	M.p. [°]
Et ₃ NH	THF	1 h	26a (29)	70
4-FC ₆ H ₄ CH ₂ NH ₂	THF	1 h	b (53)	104
Piperidine	THF	1 h	c (60)	72
Morpholine	THF	1 h	d (65)	154
4-MeC ₆ H ₄ NH ₂	THF	1 h	e (12)	148
PrNH ₂	THF	1 h	f (50)	59–62
EtSH	THF	1 h	g (9)	97
MeOH	–	20 h	h (25)	86
NaOS(O)Ph	EtOH/H ₂ O 6:1	2 h	27 (31), 28 (14)	214 and 219–220, resp.

^{a)} Molar ratio nucleophile/**24** 1:1.

the case of **22**. However, results in the competition reaction with N-nucleophiles differ: With **24** (derived from **22**), 1 equiv. of nucleophile led to the required product **26** within 1 h at room temperature (Table 2). With **4a** (derived from **2a**), variation of solvent and reaction time influenced the outcome: A 20:1 excess of nucleophile led to the optimum result avoiding pyridinone formation; depending on the nucleophile, mono- or disubstitution occurred (Table 1).

While disubstitution occurred readily in **4a** by 1,4- or 1,6-*Michael* additions, in the case of **24**, only monosubstitution to **26** by 1,6-addition was observed, except for the very

reactive S-nucleophile PhSO_2Na . The substitution pattern obtained from **24** is best accounted for by the extended conjugation in the transition state $[\text{N}=\text{C}=\text{C}=\text{N}^-]$ of the 1,6-addition ($\mathbf{29a} \leftrightarrow \mathbf{29b}$), in contrast to that of a 1,4(or 1,3)-addition (**30** or **31**; Scheme 5).



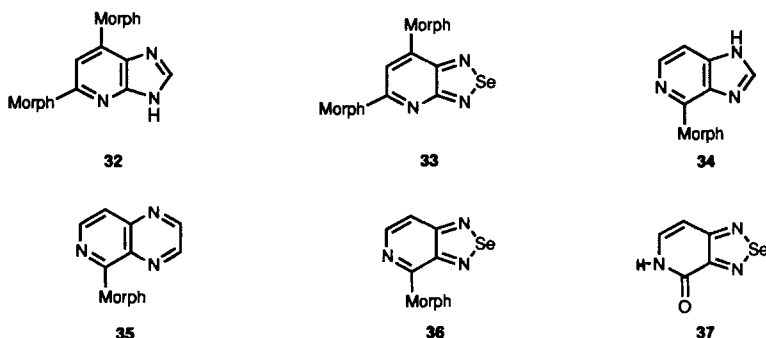
The O-nucleophile MeOH yielded the corresponding MeO-substituted *2H*-azabenzimidazoles **15** ($\text{R}^1 = \text{MeO}$) or **26h** ($\text{Nu} = \text{MeO}$), while EtOH gave only the pyridinones **5a** or **25**.

It is of interest to compare the reactivity with nucleophiles of the *2H*-benzimidazoles **1** [1] with that of the *2H*-azabenzimidazoles derived from **4a** and **24**. The former can yield mono-, di-, or even polysubstituted derivatives [1] [9] depending on reaction conditions, while the aza analogues **4a** and **24** yield addition products (4-h refluxing and equimolar reagents **22** and **3**). It is striking that $(i\text{-Pr})_2\text{NH}$ so far produced exclusively the pyridinones **5a** and **25** from the corresponding spiro derivatives **4a** and **24**, possibly because of its bulky character leading to lone-pair repulsion. By contrast it can be readily introduced into **1** [2].

Synthetic Applications of 2,3-Dihydro-1H-4 and 5-azabenzimidazoles 4a and 24, Respectively. The dimorpholino-substituted *2H*-4-azabenzimidazole **17** ($\text{R}^1 = \text{R}^3 = \text{morpholino}$; obtained from **4a**) was ring-opened in an aqueous solution of sodium dithionite at room temperature yielding an unstable tetraamino-substituted pyridine which was cyclised *in situ* with formic acid or with SeO_2 to give the expected *3H*-imidazo[4,5-*b*]-pyridine **32** or the selenadiazolo[3,4-*b*]pyridine **33**, respectively. The synthetic advantage of this procedure lies in the convenient preparation of fused pyridinoheterocycles with nucleophilic substituents, especially the imidazopyridines (*e.g.* **32**) being of current pharmaceutical interest [10]. Conventional methods for introducing nucleophiles into such systems make use of displacement reactions [11]. The imidazopyridine **32** exists only in the *3H*-tautomeric form. The usual 1,3-tautomerism found in imidazoles [12] appears to be prevented, possibly owing to strong H-bonding between $\text{H}-\text{N}(3)$ and the pyridine N-atom. The structure followed from $^{13}\text{C}\{^1\text{H}\}$ -NOE difference spectra (irradiation of $\text{NH} \rightarrow$ clear NOE for C(3a), but not for C(3a) and C(7a) as expected in the case of tautomerism) and the IR spectrum (3150 and 3130 cm^{-1} (sharp, NH, intramolecular H-bond)).

Conversions of the monomorpholino-substituted *2H*-5-azabenzimidazole **26d** (obtained from **24**) into fused heterocycles were carried out by a procedure analogous to the

one described above for **17**. The intermediate triamino-substituted pyridine was directly cyclised because of its instability to give the heterocycles **34–37**. Ring closure of this intermediate with SeO_2 occurred only under reflux yielding also the pyridinone **37** as a by-product, in contrast to the cyclisation to **33** which was effected at room temperature. In contrast to **32**, the imidazopyridine **34** exists in the *1H*-tautomeric form. This follows from a homonuclear NOE experiment which established the position of the exchangeable NH as being central to H–C(2) and H–C(7) (irradiation of H–N(1)→NOE's for H–C(2) and H–C(7)). In the absence of an intramolecular H-bond in the *1H*-form **34**, it is reasonable to assume that intermolecular association is responsible for holding the conformation, as supported by broad IR absorption at $3200\text{--}2580\text{ cm}^{-1}$ [13].

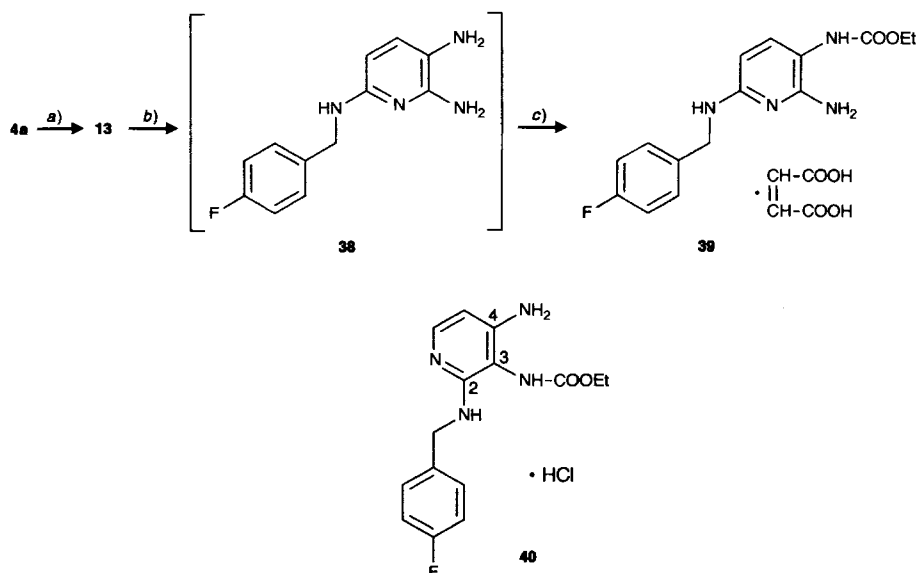


We also undertook a target synthesis of flupirtine maleate, *i.e.*, ethyl {2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate maleate (**39**), a novel analgesic developed by *Asta Medica AG*, Frankfurt/Main, and called *Katadolon*[®] [14–16]. The reported synthesis used 2,6-dichloro-3-nitropyridine as a starting material [14] [17] replacing the reactive Cl-atom at C(6) by (4-fluorobenzyl)amine or by benzylamine leading to **39** or *D-7175* (see **39**, H instead of F, HCl instead of $(\text{CHCOOH})_2$; and anticonvulsant), respectively. As **39** is derived from a 2,3,6-triamino-substituted pyridine, an alternative synthesis based on our experience with 2,3-dihydro-1*H*-4-azabenzimidazole **4a** suggested itself (*Scheme 6*). Under moderate conditions of the above discussed competition reaction, the 2*H*-azabenzimidazole **13** was obtained. Reductive hydrolysis with $\text{Na}_2\text{S}_2\text{O}_4$ led to the unstable triamino-substituted pyridine **38**, and reaction with ethyl chloroformate and then with maleic acid gave the required crystalline maleate **39**. The yields were not optimized.

An advantage of the transformation of the type **4a** → **39** over the reported method [14] [18] is the simple reduction ($\text{Na}_2\text{S}_2\text{O}_4$) instead of catalytic hydrogenation and above all its better versatility. Indeed, the closely related anticonvulsant *D-7175* (see **39**, H instead of F) [18] was similarly prepared *via* **12** using benzylamine instead of (4-fluorobenzyl)amine in step *a* of *Scheme 6*.

We also used the 2,3-dihydro-1*H*-5-azabenzimidazole **24** (*Scheme 4*) as starting material to prepare the flupirtine analogue **40** (*Scheme 6*) *via* 2*H*-azabenzimidazole **26b**. Again the 3- NH_2 group of the intermediate 2,3,4-triamino-substituted pyridine reacted with ethyl chloroformate, as shown by a $^{13}\text{C}\{^1\text{H}\}$ -NOE difference spectrum of **40** (irradiation of NHCOOEt →NOE's at 154.4 (NHCOOEt) and 98.8 ppm (C(3); *i.e.*, signal at high field due to the *m*-position rel. to N(1)); ^{13}C -NMR: 154.7 (C(4)) and 149.9 ppm (C(2))).

Scheme 6



a) (4-Fluorobenzyl)amine, MnO_2 . b) $\text{Na}_2\text{S}_2\text{O}_4$. c) ClCOOEt ; NH_3 ; maleic acid.

Moreover, the ready formation of the *Schiff's* base **23** from 3,4-diamine **22** and cyclohexanone (**3**; Scheme 4) confirms the preferential reactivity of the 3- NH_2 group in this diamine [19]. It is noteworthy that the flupirtine analogue **40**, unlike **39**, shows no fluorescence. Further structural elaboration of these compounds is of considerable interest in view of the parent system displaying pronounced pharmacological action.

We thank Mrs. U. Hertle for ^1H - and ^{13}C -NMR spectra, H. Rudy and P. Weyrich for MS and CHN analyses, Dr. B. Kutscher and Dr. P. Emig (Asta Medica AG) for useful discussions and gifts of chemicals as well as Dr. E. F. V. Scriven (Reilly and Tar, Indianapolis) for generous gifts of pyridines. Support of this work by BASF AG, Bayer AG, and Hoechst AG with generous gifts of chemicals is acknowledged. We are also grateful to ICN Biomedicals GmbH (Eschwege) for gifts of silica gel and to the Verband der Chemischen Industrie – Fonds der Chemie, and Deutsche Forschungsgemeinschaft for donation of chemicals.

Experimental Part

General. Activated MnO_2 was purchased from Fluka (CAS No. [1313-13-9]). Column chromatography (CC): silica gel 60 (Merck). M.p.: Reichert melting-point microscope, uncorrected. UV Spectra: Carl-Zeiss-DMR-4 spectrometer; λ (log ϵ) in nm. IR Spectra: Perkin-Elmer-325 spectrometer. NMR Spectra: Bruker WM 250 (250 MHz for ^1H and 62.89 MHz for ^{13}C) and Varian XL-300 (300 MHz for ^1H and 75.43 MHz for ^{13}C); δ values relative to Me_4Si . MS: Varian MAT-311-A (80 eV).

Spiro[cyclohexane-1,2'-(3'H)-1'-H-imidazo[4,5-b]pyridine] (4a). A soln. of 2,3-diaminopyridine (**2a**; 16.0 g, 147 μmol) and cyclohexanone (**3**; 14.4 g, 147 μmol) in *i*-PrOH (1 l) is heated under reflux for 71 h. After $2/3$ of the solvent is evaporated, recrystallisation of the solid residue from EtOH (99%) gives pure **4a** (11.45 g, 41.8%). Silvery platelets. M.p. 214° ([20]: 212 – 214°). UV (MeCN): 203 (3.964), 264 (3.122), 312 (3.344). IR (KBr): 3390, 3180 (NH); 3060 (Aryl-H); 2940, 2860 (C-H); 1620, 1600, 1500, 1450 (C=C, C=N); 1430. ^1H -NMR (250.13 MHz, CDCl_3): 7.35 (dd, $^3J = 5.5$, $^4J = 1.5$, H-C(5')); 6.50 (dd, $^3J = 7.5$, $^4J = 1.5$, H-C(7')); 6.37 (dd, $^3J = 7.5$, 5.5,

H–C(6'')); 5.41 (s, NH); 3.95 (s, NH); 1.92–1.30 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 154.6 (s, C(3'a)); 134.1 (s, C(5'')); 133.2 (s, C(7'a)); 112.2 (s, C(6'')); 107.2 (s, C(7'')); 7.77 (s, C(2'')); 39.5 (s, C(2), C(6)); 24.6 (s, C(4)); 21.9 (s, C(3), C(5)). MS: 189 (42, M⁺), 146 (100, [C₈H₈N₃]⁺). Anal. calc. for C₁₁H₁₅N₃ (189.26): C 69.80, H 7.99, N 22.21; found: C 70.04, H 8.09, N 22.17.

6'-Bromospiro[cyclohexane-1,2'-(3'H)-1'-H-imidazo[4,5-b]pyridine] (4b). As described for **4a**, from 2,3-diamino-5-bromopyridine [6] (**2b**; 5.6 g, 29.8 mmol), **3** (2.9 g, 30 mmol), and i-PrOH (350 ml; 24 h). Recrystallisation from CHCl₃ yields **4b** (3.75 g, 47%). Powder of an orange lustre. M.p. 194°. UV (MeCN): 208 (4.267), 274 (3.573), 330 (3.971). IR (KBr): 3340, 3195, 3160 (NH); 3075 (Aryl-H); 2920, 2860 (C–H); 1615, 1495, 1450 (C=C, C=N); 1370. ¹H-NMR (250.13 MHz, (D₆)DMSO): 7.31 (s, NH); 6.98 (d, ⁴J = 1.98, H–C(5'')); 6.66 (s, NH); 6.18 (d, ⁴J = 1.98, H–C(7'')); 1.87–1.17 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 153.5 (s, C(3'a)); 135.3 (s, C(7'a)); 133.1 (s, C(5'')); 108.3 (s, C(7'')); 106.6 (s, C(6'')); 79.0 (s, C(2'')); 39.5 (s, C(2), C(6)); 24.5 (s, C(4)); 21.9 (s, C(3), C(5)). MS: 267 (26, M⁺), 224 (100, [C₈H₇BrN₃]⁺). Anal. calc. for C₁₁H₁₄BrN₃ (268.15): C 49.27, H 5.26, N 15.67; found: C 49.17, H 5.36, N 15.64.

Spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-b]pyridine]-5'-(4'H)-one (5a). To a soln. of **4a** (1.0 g, 5.3 mmol) in dry THF (80 ml) MnO₂ (4.6 g, 53 mmol) is added and the mixture stirred at r.t. for 2 h. After filtration and evaporation, the crude residual is recrystallised from MeOH: **5a** (0.35 g, 32.5%). M.p. 184° ([21]: 184°). UV (MeCN): 255 (4.338), 425 (2.614). IR (KBr): 3300–2600 (band due to aggregation); 1740–1660 (C=O); 1605, 1445 (C=C, C=N); 1325. ¹H-NMR (250.13 MHz, CDCl₃): 8.35 (s, NH); 7.53 (d, ³J = 9.75, H–C(7'')); 6.70 (d, ³J = 9.75, H–C(6'')); 2.04–1.60 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃): 163.7 (s, C(5'')); 153.8 (s, C(3'a)); 151.9 (s, C(7'a)); 133.4 (s, C(6'), C(7'')); 105.5 (s, C(2'')); 34.4 (s, C(2), C(6)); 25.4 (s, C(4)); 24.0 (s, C(3), C(5)). MS: 203 (100, M⁺). Anal. calc. for C₁₁H₁₃N₃O (203.24): C 65.00, H 6.45, N 20.68; found: C 65.04, H 6.67, N 20.47.

6'-Bromospiro[cyclohexane-1,2'-2'-H-imidazo[4,5-b]pyridine]-5'-(4'H)-one (5b). As described for **5a**, from **4b** (0.3 g, 1.1 mmol) and MnO₂ (0.96 g, 11 mmol) in CHCl₃ (150 ml; 3 h): **5b** (0.1 g, 31.8%). Brown needles. M.p. 227° (dec.). UV (MeCN): 211 (3.898), 256 (3.942), 273 (3.942), 327 (3.491). IR (KBr): 3500–3350 (NH); 3030 (Aryl-H); 2940, 2860 (C–H); 1705 (C=O); 1620, 1595, 1505, 1455 (C=C, C=N); 1390. ¹H-NMR (250.13 MHz, (D₆)DMSO): 12.10 (s, NH); 8.29 (s, H–C(7'')); 1.93–1.27 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 158.9 (s, C(5'')); 153.1 (s, C(3'a)); 151.8 (s, C(7'a)); 134.9 (s, C(7'')); 131.0 (s, C(6'')); 104.1 (s, C(2'')); 33.6 (s, C(2), C(6)); 25.0 (s, C(4)); 23.8 (s, C(3), C(5)). MS: 281 (100, M⁺). Anal. calc. for C₁₁H₁₂BrN₃O (282.14): C 46.83, H 4.29, N 14.89; found: C 46.80, H 4.36, N 14.78.

5'-(Diethylamino)spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-b]pyridine] (11). To **4a** (0.35 g, 1.85 mmol) in dry THF (60 ml), Et₃NH (2.7 g, 37 mmol) and MnO₂ (1.6 g, 18.5 mmol) are added and stirred at r.t. for 140 h. After filtration and evaporation, the residue oil is chromatographed twice (silica gel, 1. AcOEt/MeOH 5:2, 2. CHCl₃/MeOH 20:1). Recrystallisation from petroleum ether (40–60°) provides **11** (78.4 mg, 16.2%). Yellow crystals. M.p. 62°. UV (MeCN): 274 (4.054), 293 (4.030), 390 (3.733). IR (KBr): 3050 (Aryl-H); 2930, 2850 (C–H); 1630, 1600, 1505–1430 (C=C, C=N); 1355. ¹H-NMR (250.13 MHz, CDCl₃): 7.46 (d, ³J = 10.26, H–C(7'')); 6.97 (d, ³J = 10.26, H–C(6'')); 3.96–3.43 (br. 2 MeCH₂); 2.14–1.46 (m, C₆H₁₀); 1.27 (t, 2 MeCH₃). ¹³C-NMR (62.89 MHz, CDCl₃): 161.7 (s, C(3'a)); 159.8 (s, C(5'')); 153.7 (s, C(7'a)); 133.1 (s, C(7'')); 123.6 (s, C(6'')); 102.4 (s, C(2'')); 43.7 (s, 2 MeCH₂); 34.2 (s, C(2), C(6)); 25.7 (s, C(4)); 24.5 (s, C(3), C(5)); 15.1 (s, MeCH₂); 13.0 (s, MeCH₂). MS: 258 (64, M⁺), 79 (100). Anal. calc. for C₁₅H₂₂N₄ (258.35): C 69.73, H 8.58, N 21.69; found: C 69.18, H 8.65, N 21.28.

5'-(Ethylthio)spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-b]pyridine] (14). As described for **11**, from **4a** (1.0 g, 5.3 mmol) in MeOH (100 ml), EtSH (0.656 g, 10.58 mmol) MnO₂ (4.6 g, 52.9 mmol; 4 h). CC (silica gel, AcOEt) and recrystallisation from hexane yield **14** (362 mg, 27.8%). Yellow crystals. M.p. 134°. UV (MeCN): 301 (4.054), 350 (3.810). IR (KBr): 3065 (Aryl-H); 2940, 2860 (C–H); 1625, 1580, 1485, 1450, 1410 (C=C, C=N); 1265. ¹H-NMR (250.13 MHz, (D₆)DMSO): 7.60 (d, ³J = 10.63, H–C(7'')); 7.03 (d, ³J = 10.63, H–C(6'')); 3.22 (q, MeCH₂); 1.92–1.41 (m, C₆H₁₀); 1.35 (t, MeCH₃). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 174.9 (s, C(5'')); 159.4 (s, C(3'a)); 154.2 (s, C(7'a)); 131.3 (s, C(6'), C(7'')); 103.2 (s, C(2'')); 32.9 (s, C(2), C(6)); 25.1 (s, C(4)); 24.3 (s, MeCH₂); 24.0 (s, C(3), C(5)); 13.8 (s, MeCH₂). MS: 247 (32, M⁺), 96 (100). Anal. calc. for C₁₃H₁₇N₃S (247.35): C 63.12, H 6.93, N 16.99; found: C 63.18, H 6.93, N 16.92.

5'-Methoxyspiro[cyclohexane-1,2'-2'-H-imidazo[4,5-b]pyridine] (15). As described for **11**, from **4a** (0.4 g, 2.12 mmol) in MeOH (40 ml) and MnO₂ (1.84 g, 21.2 mmol; 70 h). Recrystallisation from Et₂O provides pure **15** (115.2 mg, 25%). Brown-yellow crystals. M.p. 128°. UV (MeCN): 254 (4.050), 263 (4.016), 305 (3.283). IR (KBr): 3050, 3020 (Aryl-H); 2925, 2860 (C–H); 1630, 1605, 1525, 1445, 1405 (C=C, C=N); 1310 (C–O–C). ¹H-NMR (300 MHz, CDCl₃): 7.53 (d, ³J = 9.99, H–C(7'')); 6.72 (d, ³J = 9.99, H–C(6'')); 4.17 (s, MeO); 2.25–1.40 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃): 169.4 (s, C(5'')); 160.4 (s, C(3'a)); 154.1 (s, C(7'a)); 134.5 (s, C(7'')); 127.4 (s, C(6'')); 104.6 (s, C(2'')); 55.2 (s, MeO); 33.4 (s, C(2), C(6)); 25.6 (s, C(4)); 24.4 (s, C(3), C(5)). MS: 217 (91, M⁺), 80 (100). Anal. calc. for C₁₂H₁₅N₃O (217.26): C 66.34, H 6.96, N 19.34; found: C 66.31, H 6.93, N 19.18.

5',7'-Di(piperidin-1-yl)spiro[cyclohexane-1,2'-2'H-imidazo[4,5-b]pyridine] (16). Method A: As described for **18**. The 2nd orange band provides pure compound. Recrystallisation from Et₂O yields **16** (77 mg, 4.6%). Yellow-orange-crystals.

Method B: As described for **11**, from **4b** (0.33 g, 1.24 mmol) in dry THF (66 ml) piperidine (2.11 g, 24.8 mmol), and MnO₂ (1.08 g, 12.4 mmol); 21 h; careful evaporation). CC (silica gel, CHCl₃/MeOH 8:1) and recrystallisation from Et₂O give **16** (101.5 mg, 23.4%). Yellow-orange crystals. M.p. 165°. UV (MeCN): 223 (4.373), 362 (4.108). IR (KBr): 2940, 2860 (C–H); 1620, 1575, 1495, 1440 (C=C, C=N); 1345. ¹H-NMR (250.13 MHz, CDCl₃): 5.73 (s, H–C(6'')); 3.83–3.67 (m, 4 CH₂); 2.10–1.39 (m, 6 CH₂, C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃): 163.6 (s, C(5') or C(3'a)); 163.5 (s, C(5') or C(3'a)); 153.0 (s, C(7'a)); 149.3 (s, C(7'')); 100.8 (s, C(2'')); 92.9 (s, C(6'')); 49.1 (s, 2 CH₂); 46.8 (s, 2 CH₂); 34.7 (s, C(2), C(6)); 26.4 (s, 2 CH₂); 25.9 (s, C(4)); 25.3 (s, 2 CH₂); 24.8 (s, CH₂); 24.6 (s, C(3), C(5)); 24.5 (s, CH₂). MS: 353 (100, M⁺). Anal. calc. for C₂₁H₃₁N₅ (353.51): 71.35, H 8.84, N 19.81; found: C 71.20, H 8.90, N 19.54.

5',7'-Di(morpholin-4-yl)spiro[cyclohexane-1,2'-2'H-imidazo[4,5-b]pyridine] (17). As described for **11**, from **4b** (6.0 g, 22.4 mmol) in dry THF (1200 ml), morpholine (39.2 g, 450 mmol), and MnO₂ (19.6 g, 225 mmol; 63 h). CC (silica gel, AcOEt/MeOH 5:2) and recrystallisation from Et₂O give **17** (4.55 g, 56.6%). Yellow-orange crystals. M.p. 226°. UV (MeCN): 216 (4.344), 350 (4.041). IR (KBr): 3020 (Aryl-H); 2940, 2850 (C–H); 1620, 1575, 1485, 1440 (C=C, C=N); 1350, 1120 (C–O–C). ¹H-NMR (250.13 MHz, CDCl₃): 5.66 (s, H–C(6'')); 4.24–3.55 (m, 8 CH₂); 2.18–1.34 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃): 163.4 (s, C(5'')); 162.6 (s, C(3'a)); 152.4 (s, C(7'a)); 149.2 (s, C(7'')); 101.5 (s, C(2'')); 92.5 (s, C(6'')); 66.6 (s, 2 CH₂O); 66.1 (s, 2 CH₂OCH₂); 47.6 (s, 2 CH₂N); 45.6 (s, 2 CH₂N); 34.2 (s, C(2), C(6)); 25.6 (s, C(4'')); 24.3 (s, C(3), C(5)). MS: 357 (83, M⁺), 299 (100). Anal. calc. for C₁₉H₂₇N₅O₂ (357.44): C 63.84, H 7.62, N 19.59; found: C 63.60, H 7.81, N 19.32.

5',6'-Di(piperidin-1-yl)spiro[cyclohexane-1,2'-2'H-imidazo[4,5-b]pyridine] (18). As described for **11**, from **4a** (0.9 g, 4.76 mmol) in EtOH (240 ml), piperidine (8.28 g, 95.2 mmol), and MnO₂ (4.2 g, 47.6 mmol; 6.5 h). CC (silica gel, CHCl₃/MeOH 8:1) gives a 1st, yellow band which provides pure product. Recrystallisation from Et₂O yields **18** (0.17 g, 10.1%). Yellow crystals. M.p. 156°. UV (MeCN): 208 (4.226), 350 (4.085). IR (KBr): 2930, 2860 (C–H); 1535, 1495, 1445 (C=C, C=N); 1365. ¹H-NMR (250.13 MHz, CDCl₃): 6.64 (s, H–C(7'')); 3.98–3.82 (m, 2 CH₂); 3.14–2.83 (m, 2 CH₂); 2.07–1.36 (m, 6 CH₂, C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃): 162.0 (s, C(3'a) or C(5'')); 159.7 (s, C(3'a) or C(5'')); 155.4 (s, C(7'a) or C(6'')); 149.2 (s, C(7'a) or C(6'')); 111.7 (s, C(7'')); 102.0 (s, C(2'')); 51.2 (s, 2 CH₂); 49.4 (s, 2 CH₂); 34.1 (s, C(2), C(6)); 26.1 (s, 2 CH₂ or C(3), C(5)); 25.6 (s, CH₂ or C(4)); 25.4 (s, 2 CH₂ or C(3), C(5)); 24.5 (s, CH₂ or C(4)); 24.4 (s, 2 CH₂ or C(3), C(5)); 23.8 (s, CH₂ or C(4)). MS: 353 (100, M⁺). Anal. calc. for C₂₁H₃₁N₅ (353.51): C 71.35, H 8.84, N 19.81; found: C 71.26, H 9.06, N 20.09.

5'-(Phenylsulfonyl)spiro[cyclohexane-1,2'-(3'H)-1'H-imidazo[4,5-b]pyridine] (9). To a soln. of **4a** (0.7 g, 3.7 mmol) in EtOH (210 ml), a soln. of sodium benzenesulfinate (1.22 g, 7.4 mmol) in H₂O (70 ml), MnO₂ (3.2 g, 37 mmol), and AcOH (0.6 ml, 10.6 mmol) AcOH are added. The suspension is stirred at 0° for 45 min, the solid filtered off, and the filtrate evaporated. The solid is chromatographed twice (silica gel, 1. AcOEt, 2. CHCl₃/MeOH 20:1) and the more polar fraction (2nd band recrystallised from MeOH): colourless powder of **9** (426 mg, 35%). M.p. 86–88°. UV (MeCN): 216 (4.221), 335 (4.078). IR (KBr): 3370 (NH); 2940, 2870 (C–H); 1625, 1595, 1510, 1450 (C=C, C=N); 1300 (SO₂); 1150 (SO₂). ¹H-NMR (250.13 MHz, (D₆)DMSO): 7.98 (s, NH); 7.85–7.79 (m, 2 H, Ph); 7.68–7.54 (m, 3 H, Ph); 7.51 (s, NH); 7.13 (d, ³J = 7.17, H–C(6'')); 6.16 (d, ³J = 7.17, H–C(7'')); 1.69–1.28 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 154.0 (s, C(3'a)); 141.2 (s, SO₂C); 140.1 (s, C(5'')); 137.2 (s, C(7'a)); 132.7 (s, 1 C, Ph); 129.0 (s, 2 C, Ph); 127.4 (s, 2 C, Ph); 115.4 (s, C(6'')); 102.4 (s, C(7'')); 79.0 (s, C(2'')); 39.7 (s, C(2), C(6)); 24.4 (s, C(4)); 21.7 (s, C(3), C(5)). MS: 329 (40, M⁺), 286 (100, [C₁₄H₁₂N₃O₂S]⁺). Anal. calc. for C₁₇H₁₉N₃O₂S (329.40): C 61.98, H 5.81, N 12.76, S 9.73; found: C 62.00, H 5.76, N 12.91, S 9.79.

5',7'-Bis(phenylsulfonyl)spiro[cyclohexane-1,2'-(3'H)-1'H-imidazo[4,5-b]pyridine] (10). As described for **9**, from **4a** (0.7 g, 3.7 mmol) in EtOH (210 ml), sodium benzenesulfinate (12.2 g, 74.2 mmol) in H₂O (70 ml), MnO₂ (3.2 g, 37 mmol), and AcOH (0.6 ml, 10.6 mmol). The 1st band of the CC leads, after recrystallisation from MeOH, to **10** (420 mg, 24.3%). Colourless powder. M.p. 146°. UV (MeCN): 220 (4.346), 328 (3.972), 355 (4.013). IR (KBr): 3360 (NH); 2950, 2870 (C–H); 1610, 1530, 1450 (C=C, C=N); 1305, 1150 (SO₂). ¹H-NMR (250.13 MHz, (D₆)DMSO): 9.20 (s, NH); 8.80 (s, NH); 8.14–7.95 (m, 2 H, Ph); 7.90–7.52 (m, 8 H, Ph); 7.24 (s, H–C(6'')); 2.02–1.33 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 155.5 (s, C(3'a)); 141.1 (s, SO₂C); 140.3 (s, C(5'')); 139.9 (s, SO₂C); 135.2 (s, C(7'a)); 133.9 (s, 1 C, Ph); 133.3 (s, 1 C, Ph); 129.8 (s, 2 C, Ph); 129.3 (s, 2 C, Ph); 127.7 (s, 2 C, Ph); 126.4 (s, 2 C, Ph); 110.4 (s, C(6'')); 109.6 (s, C(6'')); 81.4 (s, C(2'')); 38.5 (s, C(2), C(6)); 24.2 (s, C(4)); 21.6 (s, C(3), C(5)). MS: 469 (30, M⁺), 426 (100, [C₂₀H₁₆N₃O₄S₂]⁺). Anal. calc. for C₂₃H₂₃N₃O₄S₂ (469.56): C 58.83, H 4.94, N 8.95, S 13.65; found: C 58.75, H 4.80, N 8.64, S 13.47.

2-{Spiro[cyclohexane-1,2'-(5'H)-3'H-imidazo[4,5-b]pyridine]-5'-ylidene}propanedinitrile (19). To **4a** (1.0 g, 5.3 mmol) in dry THF (167 ml) at 0°, a soln. of (CN)₂C=C(CN)₂ (0.68 g, 5.3 mmol) in THF (30 ml) is added and

stirred for 10 min. After evaporation, CC (silica gel, AcOEt) and recrystallisation from Et₂O give **19** (330.8 mg, 24.9%). Brown powder. M.p. 258°. UV (MeCN): 251 (3.903), 305 (3.891), 433 (4.184). IR (KBr): 3260–3080 (NH); 3030 (Aryl-H); 2940, 2860 (C–H); 2210 (CN); 1640, 1595, 1495 (C=C, C=N); 1440. ¹H-NMR (250.13 MHz, (D₆)DMSO): 12.30 (s, NH); 7.48 (d, ³J = 10.47, H–C(7'')); 7.32 (d, ³J = 10.47, H–C(6'')); 1.95–1.43 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 168.5 (s, C(5'')); 157.2 (s, C(3'a)); 153.2 (s, C(7'a)); 130.8 (s, C(7') or C(6'')); 129.1 (s, C(7') or C(6'')); 115.4 (s, =C–CN); 115.0 (s, =C–CN); 93.5 (s, C(2'')); 66.9 (s, =C–CN); 34.5 (s, C(2), C(6)); 24.2 (s, C(4)); 22.5 (s, C(3), C(5)). MS: 251 (77, M⁺), 61 (100). HR-MS (peak matching): 251.1172 ([C₁₄H₁₃N₃]⁺, calc. 251.1171). Elemental analysis: unsatisfactory due to instability of **19**.

5',7'-Dimorpholinospiro[cyclohexane-1,2'-2'H-imidazo[4,5-b]pyridine] (**21**). A soln. of **4b** (6 g, 22.4 mmol) in 1200 ml of dried THF, morpholin (39.2 g, 450 mmol) and MnO₂ (19.6 g, 225 mmol) is added and stirred 63 h at r.t. After filtration and careful evaporation of solvent, the residue is purified by SC (silica gel, AcOEt/MeOH 5:2). Its recrystallisation from Et₂O provides yellow-to-orange crystals of **21** (4.55 g, 56.6%). M.p. 226°. UV (MeCN): 216 (4.344), 350 (4.041). IR (KBr): 3020 (Aryl-H); 2940, 2850 (C–H); 1620, 1575, 1485, 1440 (C=C, C=N); 1350, 1260, 1230, 1120 (C–O–C); 1005, 905. ¹H-NMR (250.13 MHz): 5.66 (s, H–C(6'')); 4.24–3.55 (m, 2 morpholino-H, 8 CH₂); 2.18–1.34 (m, C₆H₁₀). MS: 358 (16, [M + 1]⁺); 357 (83, M⁺), 328 (13, [C₁₇H₂₂N₅O₂]⁺), 327 (57, [C₁₈H₂₃N₅O]⁺), 326 (19, [C₁₈H₂₄N₅O]⁺), 314 (8, [C₁₆H₂₀N₅O₂]⁺), 312 (16, [C₁₇H₂₂N₅O]⁺), 271 (9, [C₁₅H₁₉N₄O]⁺). Anal. calc. for C₁₉H₂₇N₅O₂ (357.44): C 63.84, H 7.62, N 19.59; found: C 63.60, H 7.81, N 19.32.

3-(Cyclohexylideneamino)pyridine-4-amine (**23**). A soln. of 3,4-diaminopyridine (0.5 g, 4.59 mmol; **22**) and **3** (0.9 g, 9.17 mmol) in MeOH (10 ml) is heated under reflux for 26 h and then carefully evaporated. After dissolving the residue in pentane, a crude solid is obtained on cooling at –20°. Its recrystallisation from Et₂O provides **23** (118.0 mg, 13.5%). Salmon-coloured crystals which become discoloured rapidly when exposed to air. M.p. 143°. UV (MeCN): 211 (4.375), 280 (3.398). IR (KBr): 3340, 3180 (NH₂); 3020 (Aryl-H); 2940, 2860 (C–H); 1655, 1585, 1500 (C=C, C=N); 1270. ¹H-NMR (250.13 MHz, CDCl₃): 7.98 (d, ³J = 5.90, H–C(6)); 7.67 (s, H–C(2)); 6.57 (d, ³J = 5.90, H–C(5)); 4.26 (s, NH₂); 2.52 (t, 2 H–C(6'')); 2.28 (t, 2 H–C(2'')); 1.95–1.59 (m, 2 H–C(3'), 2 H–C(4'), 2 H–C(5')). ¹³C-NMR (62.89 MHz, CDCl₃): 179.1 (s, C(1'')); 145.8 (s, C(6)); 144.9 (s, C(4)); 139.7 (s, C(2)); 132.3 (s, C(3)); 109.1 (s, C(5)); 39.6 (s, C(6'')); 31.2 (s, C(2'')); 28.0 (s, C(3') or C(5'')); 27.7 (s, C(3') or C(5'')); 25.6 (s, C(4')). MS: 189 (38, M⁺), 146 (100, [C₈H₉N₃]⁺). Anal. calc. for C₁₁H₁₅N₃ (189.26): C 69.25, H 8.12, N 22.43.

Spiro[cyclohexane-1,2'(3'H)-1'-H-imidazo[4,5-c]pyridine] (**24**). A soln. of **22** (4.0 g, 36.7 mmol) in **3** (36.0 g, 367 mmol) is heated under reflux for 4 h and then allowed to cool. On addition of Et₂O (70 ml), crude **24** is precipitated which crystallises from toluene as colourless needles (3.25 g, 46.9%). M.p. 186°. UV (MeCN): 216 (4.262), 300 (3.465). IR (KBr): 3400, 3240, 3200 (NH); 3040 (Aryl-H); 2920, 2860 (C–H); 1670, 1605, 1500, 1475, 1460, 1430 (C=C, C=N). ¹H-NMR (250.13 MHz, (D₆)DMSO): 7.51 (d, ³J = 5.60, H–C(6'')); 7.33 (s, H–C(4'')); 6.80 (s, H–N(1'')); 6.16 (d, ³J = 5.60, H–C(7'')); 5.87 (s, H–N(3'')); 1.66–1.23 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 147.0 (s, C(7'a)); 141.2 (s, C(6'')); 137.2 (s, C(3'a)); 125.6 (s, C(4'')); 101.3 (s, C(7'')); 81.3 (s, C(2'')); 39.6 (s, C(2), C(6)); 25.1 (s, C(4)); 22.8 (s, C(3), C(5)). MS: 189 (37, M⁺), 146 (100, [C₈H₉N₃]⁺). Anal. calc. for C₁₁H₁₅N₃ (189.26): C 69.80, H 7.99, N 22.21; found: C 69.67, H 7.99, N 22.21.

Spiro[cyclohexane-1,2'-2'H-imidazo[4,5-c]pyridine]-4'(5'H)-one (**25**). *Method A*: As described for **5a**, from **24** (1.2 g, 6.34 mmol), dry THF (200 ml), and MnO₂ (8.8 g, 101 mmol; 17 h). CC (silica gel, MeOH/AcOH 500:1) provides a 1st band of pure product which is recrystallised from benzene/hexane 1:1: lemon-coloured powder (250 mg, 19.4%).

Method B: To a soln. of **24** (0.35 g, 1.85 mmol) in EtOH (20 ml), a soln. of Na (0.1 g, 4.35 mmol) in dry EtOH (40 ml) is added and the mixture stirred at r.t. for 2 h. After evaporation, CC (silica gel, AcOEt/MeOH 5:2) and recrystallisation from benzene/hexane 1:1 yield **25** (184 mg, 49%). Lemon-coloured powder. M.p. 226°. UV (MeCN): 262 (2.914). IR (KBr): 3600–3030 (band due to aggregation); 2940, 2860 (C–H); 1710 (C=O); 1655–1525, 1410 (C=C, C=N); 1260. ¹H-NMR (250.13 MHz, (D₆)DMSO): 7.62 (s, NH); 7.10 (m, H,D-exchange → d, ³J = 7.25, H–C(6'')); 6.17 (d, ³J = 7.25, H–C(7'')); 1.89–1.43 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 159.53 (s, C(7'a) or C(4'')); 159.45 (s, C(7'a) or C(4'')); 155.7 (s, C(3'a)); 137.8 (s, C(6'')); 107.7 (s, C(2'')); 100.4 (s, C(7'')); 32.8 (s, C(2), C(6)); 25.0 (s, C(4)); 23.9 (s, C(3), C(5)). MS: 203 (100, M⁺). Anal. calc. for C₁₁H₁₃N₃O (203.24): C 65.00, H 6.45, N 20.68; found: C 65.22, H 6.53, N 20.61.

4'-(Diethylamino)spiro[cyclohexane-1,2'-2'H-imidazo[4,5-c]pyridine] (**26a**). As described for **11**, from **24** (0.7 g, 3.7 mmol) in dry THF (245 ml), Et₂NH (0.275 g, 3.7 mmol), and MnO₂ (5.2 g, 59.2 mmol; 1 h). CC (silica gel, AcOEt) and recrystallisation from hexane give **26a** (276 mg, 29%). Red platelets. M.p. 70°. UV (MeCN): 234 (4.303), 466 (3.783). IR (KBr): 2940, 2860 (C–H); 1620, 1540, 1520, 1440 (C=C, C=N); 1360. ¹H-NMR (250.13 MHz, CDCl₃): 7.50 (d, ³J = 5.79, H–C(6'')); 6.28 (d, ³J = 5.79, H–C(7'')); 4.38–3.52 (br., 2 MeCH₂); 2.10–1.40 (m, C₆H₁₀); 1.28 (t, 2 MeCH₂). ¹³C-NMR (62.89 MHz, CDCl₃): 159.7 (s, C(7'a)); 154.1 (s, C(4'')); 153.5 (s, C(3'a));

149.8 (s, C(6')); 106.7 (s, C(2')); 103.7 (s, C(7')); 44.6 (s, 2 MeCH₂); 33.4 (s, C(2), C(6)); 25.7 (s, C(4)); 24.7 (s, C(3), C(5)); signal for 2 MeCH₂ not distinguishable because of extreme broadening. MS: 258 (32, M⁺), 229 (100, [C₁₃H₁₇N₄]⁺). Anal. calc. for C₁₅H₂₂N₄ (258.35): C 69.73, H 8.58, N 21.69; found: C 69.57, H 8.59, N 21.55.

4'-(Piperidin-1-yl)spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-c]pyridine] (**26c**). As described for **11**, from **24** (0.3 g, 1.59 mmol) in dry THF (55 ml), piperidine (0.135 g, 1.59 mmol), and MnO₂ (2.2 g, 25.3 mmol; 1 h). CC (silica gel, AcOEt) and recrystallisation from MeOH provides **26c** (256.5 mg, 60%). Red platelets. M.p. 72°. UV (MeCN): 231 (4.283), 467 (3.763). IR (KBr): 3040, 3020 (Aryl-H); 2940, 2860 (C-H); 1620, 1540, 1510, 1430 (C=C, C=N); 1370. ¹H-NMR (250.13 MHz, CDCl₃): 7.48 (d, ³J = 6.77, H-C(6')); 6.30 (d, ³J = 6.77, H-C(7')); 4.56–4.00 (m, 2 CH₂); 2.10–1.43 (m, 3 CH₂C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃, 300 K): 159.8 (s, C(7'a)); 154.2 (s, C(4')); 153.9 (s, C(3'a)); 149.4 (s, C(6')); 106.5 (s, C(2')); 104.2 (s, C(7')); 32.7 (s, C(2), C(6)); 26.3 (only pip. signal); 25.2 (s, C(4)); 24.4 (s, C(3), C(5)). ¹³C-NMR (233 K): single pip. signals at 48.5 (s, CH₂N); 46.1 (s, CH₂N); 26.7 (s, CH₂); 25.6 (s, CH₂); 24.3 (s, CH₂). MS: 270 (88, M⁺), 227 (100, [C₁₆H₂₂N₄] (270.39): C 71.08, H 8.20, N 20.72; found: C 71.19, H 8.20, N 20.61.

4'-(Morpholin-4-yl)spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-c]pyridine] (**26d**). As described for **11**, from **24** (4.26 g, 22.5 mmol) in dry THF (1490 ml), morpholine (1.96 g, 22.5 mmol), and MnO₂ (31.4 g, 361 mmol; 1 h). CC (silica gel, AcOEt) and recrystallisation from MeOH yield red needles of **26d** (3.98 g, 65%). M.p. 154°. UV (MeCN): 234 (4.004), 460 (3.501). IR (KBr): 3030 (Aryl-H); 2940, 2860 (C-H); 1625, 1535, 1505, 1440 (C=C, C=N); 1120 (C-O-C). ¹H-NMR (250.13 MHz, CDCl₃): 7.47 (d, ³J = 7.04, H-C(6')); 6.37 (d, ³J = 7.04, H-C(7')); 4.72–4.00 (m, 2 CH₂O); 4.00–3.58 (m, 2 CH₂N); 2.10–1.34 (m, C₆H₁₀). ¹³C-NMR (62.89 MHz, CDCl₃, 300 K): 159.4 (s, C(7'a)); 154.0 (s, C(4')); 153.4 (s, C(3'a)); 148.7 (s, C(6')); 107.2 (s, C(2')); 105.6 (s, C(7')); 67.0 (s, 2 CH₂O); 47.7 (s, (at 233 K), CH₂N); 44.2 (s, (at 233 K), CH₂N); 33.2 (s, C(2), C(6)); 25.6 (s, C(4)); 24.6 (s, C(3), C(5)). MS: 272 (54, M⁺), 241 (100, [C₁₄H₁₇N₄]⁺). Anal. calc. for C₁₅H₂₀N₄O (272.34): C 66.15, H 7.40, N 20.57; found: C 66.21, H 7.27, N 20.43.

4'-[(4-Methylphenyl)amino]spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-c]pyridine] (**26e**). As described for **11**, from **24** (0.242 g, 1.28 mmol) in dry THF (105 ml), 4-methylbenzenamine (0.137 g, 1.28 mmol), and MnO₂ (2.22 g, 25.52 mmol; 1 h). The oil is chromatographed twice (silica gel, 1. AcOEt, 2. AcOEt/petroleum ether (40–60°) 4:1): **26e** (45 mg, 12%). Dark red crystals. M.p. 148°. UV (MeCN): 228 (4.218), 420 (3.836). IR (KBr): 3280 (NH); 3020 (Aryl-H); 2940, 2860 (C-H); 1650, 1625, 1600, 1550, 1505 (C=C, C=N). ¹H-NMR (300 MHz, CDCl₃): 8.02 (s, NH); 7.73 (d, ³J = 7.76, 2 H, Ph); 7.59 (d, ³J = 7.06, H-C(6')); 7.18 (d, ³J = 7.76, 2 H, Ph); 6.48 (d, ³J = 7.06, H-C(7')); 2.35 (s, Me); 2.10–1.40 (m, C₆H₁₀). ¹³C-NMR (75.43 MHz, CDCl₃): 158.1 (s, C(7'a)); 152.6 (s, C(4')); 151.6 (s, C(3'a)); 149.2 (s, C(6')); 135.6 (s, 1 C, Ph); 133.8 (s, 1 C, Ph); 129.4 (s, 2 C, Ph); 120.3 (s, 2 C, Ph); 108.3 (s, C(2')); 107.2 (s, C(7')); 33.1 (s, C(2), C(6)); 25.6 (s, C(4)); 24.7 (s, C(3), C(5)); 20.9 (s, Me). MS: 292 (78, M⁺), 291 (100, [M – 1]⁺). Anal. calc. for C₁₈H₂₀N₄ (292.37): C 73.94, H 6.90, N 19.16; found: C 73.88, H 6.95, N 18.64.

4'-(Propylamino)spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-c]pyridine] (**26f**). As described for **11**, from **24** (0.7 g, 3.7 mmol) in dry THF (245 ml), PrNH₂ (0.22 g, 3.7 mmol), and MnO₂ (5.2 g, 59.2 mmol; 1 h). CC (silica gel, AcOEt) and recrystallisation from hexane lead to **26f** (450 mg, 49.7%). Orange-red crystals. M.p. 59–62°. UV (MeCN): 223 (4.231), 434 (3.670). IR (KBr): 3340–3200 (NH); 3080 (Aryl-H); 2940, 2860 (C-H); 1635, 1570, 1500 (C=C, C=N). ¹H-NMR (250.13 MHz, CDCl₃): 7.50 (d, ³J = 7.17, H-C(6')); 6.37–6.23 (br, NH); 6.34 (d, ³J = 7.17, H-C(7')); 3.63–3.40 (m, MeCH₂CH₂N); 2.18–1.46 (m, MeCH₂CH₂N, C₆H₁₀); 1.04 (t, MeCH₂CH₂N). ¹³C-NMR (62.89 MHz, CDCl₃): 158.6 (s, C(7'a)); 154.9 (s, C(4')); 152.5 (s, C(3'a)); 150.0 (s, C(6')); 108.1 (s, C(2')); 105.2 (s, C(7')); 42.8 (s, MeCH₂CH₂N); 33.0 (s, C(2), C(6)); 25.5 (s, C(4)); 24.5 (s, C(3), C(5)); 22.3 (s, MeCH₂CH₂N); 11.5 (s, MeCH₂CH₂N). MS: 244 (22, M⁺), 215 (100, [C₁₄H₂₀N₄] (244.33): C 68.82, H 8.25, N 22.93; found: C 68.59, H 8.22, N 22.79.

4'-(Ethylthio)spiro[cyclohexane-1,2'-2'-H-imidazo[4,5-c]pyridine] (**26g**). As described for **11**, from **24** (0.3 g, 1.59 mmol) in dry THF (105 ml), EtSH (0.099 g, 1.59 mmol), and MnO₂ (2.22 g, 25.52 mmol; 1 h). CC (25 cm, silica gel, AcOEt) followed by careful evaporation provide orange crystals of pure **26g** (36.2 mg, 9.2%). M.p. 97°. UV (MeCN): 408 (3.558). IR (KBr): 2920, 2850 (C-H); 1705, 1620, 1460 (C=C, C=N). ¹H-NMR (250.13 MHz, CDCl₃): 7.72 (d, ³J = 6.45, H-C(6')); 6.77 (d, ³J = 6.45, H-C(7')); 3.25 (q, MeCH₂); 2.10–1.60 (m, C₆H₁₀); 1.44 (t, MeCH₂). ¹³C-NMR (62.89 MHz, CDCl₃): 166.6 (s, C(4')); 157.7 (s, C(7'a)); 154.1 (s, C(3'a)); 146.2 (s, C(6')); 111.8 (s, C(7')); 108.9 (s, C(2')); 32.5 (s, C(2), C(6)); 25.5 (s, C(4)); 24.5 (s, C(3), C(5)); 23.8 (s, MeCH₂); 13.8 (s, MeCH₂). MS: 247 (45, M⁺), 214 (100, [C₁₃H₁₆N₃]⁺). Anal. calc. for C₁₃H₁₇N₃S (247.35): C 63.12, H 6.93, N 16.99; found: C 62.96, H 6.89, N 16.75.

4'-Methoxyspiro[cyclohexane-1,2'-2'-H-imidazo[4,5-c]pyridine] (**26h**). A mixture of **24** (0.4 g, 2.12 mmol) and MnO₂ (1.84 g, 21.2 mmol) in MeOH (40 ml) is stirred at r.t. for 20 h. After filtration and evaporation, recrystallisation from Et₂O provides **26h** (115 mg, 25%). Ochreous crystals. M.p. 86°. UV (MeCN): 362 (3.479). IR (KBr): 3030 (Aryl-H); 2960, 2840 (C-H); 1630, 1530, 1455 (C=C, C=N); 1310 (C-O-C). ¹H-NMR (300 MHz, CDCl₃):

7.53 (*d*, $^3J = 7.71$ H–C(6'')); 6.73 (*d*, $^3J = 7.71$, H–C(7'')); 4.10 (*s*, MeO); 2.25–1.50 (*m*, C₆H₁₀). ¹³C-NMR (75.43 MHz, CDCl₃): 160.6 (*s*, C(4') or C(7'a)); 159.0 (*s*, C(4') or C(7'a)); 151.3 (*s*, C(3'a)); 146.0 (*s*, C(6'')); 111.6 (*s*, C(7'')); 109.5 (*s*, C(2'')); 54.6 (*s*, MeO); 32.6 (*s*, C(2), C(6)); 25.4 (*s*, C(4)); 24.4 (*s*, C(3), C(5)). MS: 217 (60, *M*⁺), 216 (100, *M* – 1)⁺. Anal. calc. for C₁₂H₁₅N₃O (217.26): C 66.34, H 6.96, N 19.34; found: C 66.28, H 6.87, N 19.08.

4'-(Phenylsulfonyl)spiro[cyclohexane-1,2'-(3'H)-1'-H-imidazo[4,5-c]pyridine] (27). As described for 9, from 24 (0.6 g, 3.17 mmol), EtOH (180 ml), sodium benzenesulfinate (10.48 g, 63.2 mmol), H₂O (30 ml), MnO₂ (2.76 g, 31.7 mmol), and AcOH (0.4 ml, 6.93 mmol, 2 h r.t.). The residue is suspended in H₂O, the aq. layer extracted with CHCl₃, the combined org. phase evaporated and the residue chromatographed (silica gel, AcOEt/petroleum ether (40–60°) 20:1). The 2nd, yellow-fluorescent band furnishes, after recrystallisation from MeOH, 27 (325 mg, 31.2%). Colourless needles. M.p. 214°. UV (MeCN): 223 (4.417), 247 (4.104), 345 (3.933). IR (KBr): 3440, 3360 (NH); 3060 (Aryl-H); 2940, 2860 (C–H); 1615, 1505, 1455 (C=C, C=H); 1310, 1300, 1275 (SO₂); 1140 (SO₂). ¹H-NMR (250.13 MHz, (D₆)DMSO): 8.04–7.93 (*m*, 2 H, Ph); 7.87 (*s*, NH); 7.78–7.55 (*m*, 3 H, Ph); 7.45 (*d*, $^3J = 5.26$, H–C(6'')); 6.96 (*s*, NH); 6.13 (*d*, $^3J = 5.26$, H–C(7'')); 1.96–1.34 (*m*, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 148.4 (*s*, C(7'a)); 141.3 (*s*, SO₂C); 140.6 (*s*, C(6'')); 136.5 (*s*, C(3'a)); 133.1 (*s*, 1 C, Ph); 129.1 (*s*, 2 C, Ph); 127.8 (*s*, C(4'')); 127.0 (*s*, 2 C, Ph); 100.0 (*s*, C(7'')); 81.9 (*s*, C(2'')); 38.9 (*s*, C(2), C(6)); 24.3 (*s*, C(4)); 22.1 (*s*, C(3), C(5)). MS: 329 (32, *M*⁺), 286 (100, [C₁₄H₁₂N₃O₂S]⁺). Anal. calc. for C₁₇H₁₉N₃O₂S (329.40): C 61.98, H 5.81, N 12.76; found: C 62.13, H 5.93, N 12.62.

4',7'-Bis(phenylsulfonyl)spiro[cyclohexane-1,2'-(3'H)-1'-H-imidazo[4,5-c]pyridine] (28). As described for 9, from 24 (0.6 g, 3.17 mmol), EtOH (180 ml), sodium benzenesulfinate (10.48 g, 63.2 mmol), H₂O (30 ml), MnO₂ (2.76 g, 31.7 mmol), and AcOH (0.4 ml, 6.93 mmol; 2 h r.t.). Workup as described for 27. The 1st band gives, after recrystallisation from MeOH, pure 28 (0.2 g, 13.6%). Pale yellow powder. M.p. 219–220°. UV (MeCN): 217 (4.391), 254 (4.158), 353 (3.819). IR (KBr): 3380 (NH); 2930, 2860 (C–H); 1605, 1510, 1450 (C=C, C=N); 1305, 1145 (SO₂). ¹H-NMR (250.13 MHz, (D₆)DMSO): 8.54 (*s*, H–N(1'')); 8.08–7.99 (*m*, 2 H, Ph); 7.96–7.84 (*m*, 2 H, Ph); 7.73 (*s*, H–C(6'')); 7.71–7.53 (*m*, 6 H, Ph); 7.32 (*s*, H–N(3'')); 1.93–1.24 (*m*, C₆H₁₀). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 146.0 (*s*, C(7'a)); 141.3 (*s*, SO₂C); 140.0 (*s*, SO₂C); 137.5 (*s*, C(6'')); 137.0 (*s*, C(3'a)); 133.7 (*s*, 1 C, Ph); 133.5 (*s*, 1 C, Ph); 129.5 (*s*, 2 C, Ph); 129.2 (*s*, 2 C, Ph); 128.3 (*s*, C(4'')); 127.2 (*s*, 2 C, Ph); 126.4 (*s*, 2 C, Ph); 110.6 (*s*, C(7'')); 84.4 (*s*, C(2'')); 38.2 (*s*, C(2), C(6)); 24.0 (*s*, C(4)); 21.7 (*s*, C(3), C(5)). MS: 469 (36, *M*⁺), 426 (100, [C₂₀H₁₆N₃O₄S₂]⁺). Anal. calc. for C₂₃H₂₃N₃O₄S₂ (469.56): C 58.83, H 4.94, N 8.95; found: C 58.58, H 4.92, N 8.75.

5,7-Di(morpholin-4-yl)-3H-imidazo[4,5-b]pyridine (32). To a soln. of 17 (1.0 g, 2.8 mmol) in THF/H₂O 4:3 (350 ml), Na₂S₂O₄ (3.9 g, 22.4 mmol) is added (immediately orange→yellow). The mixture is stirred at r.t. for 1 h and then made alkaline with K₂CO₃ (pH 10). The unstable tetraaminopyridine is extracted with AcOEt, the combined org. phase carefully evaporated, and the residual oil immediately dissolved in aq. conc. HCl soln./H₂O 2:3 (20 ml). After addition of HCOOH (20 ml), the soln. is heated at 100° (oil bath) for 3 h and then allowed to cool. The diluted (40 ml of H₂O) and alkaline soln. (Na₂CO₃, pH 9–10) is again extracted with AcOEt followed by evaporation. Recrystallisation from AcOEt provides a light grey powder of 32 (37.4 mg, 4.6% rel. to 17), which is finally washed with hexane. M.p. 227°. UV (MeCN): 212 (4.550), 242 (4.570), 267 (4.373). IR (KBr): 3150, 3130 (NH); 3010 (Aryl-H); 2960, 2860 (C–H); 1615, 1580, 1445 (C=C, C=N); 1120 (C–O–C). ¹H-NMR (300 MHz, (D₆)DMSO): 12.35 (*s*, H–N(3)); 7.80 (*s*, H–C(2)); 5.93 (*s*, H–C(6)); 4.05–3.23 (*m*, 8 CH₂). ¹³C-NMR (75.43 MHz, (D₆)DMSO): 157.8 (*s*, C(5)); 148.7 (*s*, C(7)); 147.2 (*s*, C(3a)); 135.5 (*s*, C(2)); 118.8 (*s*, C(7a)); 85.9 (*s*, C(6)); 66.1 (*s*, 2 CH₂O); 66.0 (*s*, 2 CH₂O); 47.7 (*s*, 2 CH₂N); 46.4 (*s*, 2 CH₂N). MS: 289 (100, *M*⁺). Anal. calc. for C₁₄H₁₉N₅O₂ (289.32): C 58.12, H 6.62, N 24.20; found: C 58.21, H 6.60, N 24.01.

5,7-Di(morpholin-4-yl)-2,1,3-selenadiazolo[3,4-b]pyridine (33). As described for 32, 17 (1.0 g, 2.8 mmol) in THF/H₂O 4:3 (350 ml) is reduced with Na₂S₂O₄ (3.9 g, 22.4 mmol). The combined org. phase is carefully evaporated and the unstable tetraaminopyridine dissolved in EtOH (10 ml) to which a freshly prepared and filtered soln. of SeO₂ (310.8 mg, 2.8 mmol) in H₂O (3 ml) is added (brown→red). After 1 h stirring at r.t., the mixture is diluted with H₂O (40 ml) and basified (K₂CO₃, pH 10), the aq. layer extracted with AcOEt and the org. phase evaporated: lemon yellow needles of 33 (167.7 mg, 16.9% rel. to 17) which are recrystallised from MeOH. M.p. 259–261°. UV (MeCN): 236 (4.413), 284 (3.448), 377 (4.177). IR (KBr): 3000 (Aryl-H); 2960, 2860 (C–H); 1585, 1500, 1445 (C=C, C=N); 1110 (C–O–C). ¹H-NMR (250.13 MHz, (D₆)DMSO): 6.28 (*s*, H–C(6)); 3.95–3.60 (*m*, 8 CH₂). ¹³C-NMR (75.43 MHz, (D₆)DMSO): 165.1 (*s*, C(5)); 160.7 (*s*, C(3a)); 149.5 (*s*, C(7a)); 146.6 (*s*, C(7)); 93.1 (*s*, C(6)); 65.9 (*s*, 2 CH₂O); 65.7 (*s*, 2 CH₂O); 48.7 (*s*, 2 CH₂N); 45.2 (*s*, 2 CH₂N). MS: 355 (100, *M*⁺(⁸⁰Se)). Anal. calc. for C₁₃H₁₇N₅O₂Se (354.26): C 44.07, H 4.84, N 19.77; found: C 44.26, H 5.00, N 19.55.

2-(Morpholin-4-yl)-pyridine-3,4-diamine. To a soln. of 26d (0.5 g, 1.85 mmol) in MeOH/H₂O 5:1 (150 ml), Na₂S₂O₄ (8.0 g, 46.25 mmol) is added (→colourless) and stirred at r.t. for 30 min. After addition of a sat. aq. soln. of NaHSO₃ (5.0 g, 48.1 mmol), stirring is continued for another 2 h. The residue obtained on evaporation is suspended in CHCl₃ (70 ml), the product extracted into CHCl₃ under reflux, the mixture filtered, the filtrate

concentrated to $\frac{1}{3}$, and hexane (40 ml) added. The white precipitate is isolated and washed with hexane yielding colourless crystals (98 mg, 27.3%) which quickly darken on exposure to air. M.p. 183°. UV (MeCN): 226 (4.374), 290 (3.744). IR (KBr): 3420, 3360, 3230 (NH₂); 1655, 1595, 1500, 1450 (C=C, C=N); 1115, 1110 (C–O–C). ¹H-NMR (250.13 MHz, (D₆)DMSO): 7.32 (*d*, ³*J* = 5.25, H–C(6)); 6.30 (*d*, ³*J* = 5.25, H–C(5)); 5.29 (*s*, NH₂); 4.09 (*s*, NH₂); 3.80–3.67 (*m*, 2 CH₂O); 2.95–2.82 (*m*, 2 CH₂N). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 149.3 (*s*, C(2)); 141.7 (*s*, C(4)); 136.5 (*s*, C(6)); 121.1 (*s*, C(3)); 106.7 (*s*, C(5)); 66.5 (*s*, CH₂O); 49.3 (*s*, 2 CH₂N). MS: 194 (81, *M*⁺), 135 (100). HR-MS (peak matching): 194.1164 [(C₉H₁₄N₄O)]⁺, calc. 194.1168). Elemental analysis: unsatisfactory due to instability of product.

4-(Morpholin-4-yl)-1H-imidazo[4,5-*c*]pyridine (**34**). A soln. of **26d** (0.275 g, 1.01 mmol) in MeOH/H₂O 5:1 (84 ml) undergoes hydrolysis on addition of Na₂S₂O₄ (4.4 g, 25.29 mmol). The crude triaminopyridine is dissolved in conc. HCl soln./H₂O 2:3 (10 ml) and, after addition of HCOOH (10 ml), heated on the oil bath (100°) for 3 h and finally allowed to cool. The diluted (30 ml of H₂O) and basified soln. (Na₂CO₃, pH 10) is extracted with CHCl₃, the extract evaporated, and the residue recrystallised: **34** (62 mg, 29.7% rel. to **26d**). Brown crystals. M.p. 209°. UV (MeCN): 208 (4.290), 275 (4.180). IR (KBr): 3200–2580 (band due to aggregation); 1600, 1485, 1460 (C=C, C=N); 1120, 1110 (C–O–C). ¹H-NMR (250.13 MHz, (D₆)DMSO): 13.00–12.27 (br., H–N(1)); 8.12 (*s*, H–C(2)); 7.82 (*d*, ³*J* = 5.56, H–C(6)); 6.92 (*d*, ³*J* = 5.56, H–C(7)); 4.18–3.84 (*m*, 2 CH₂O); 3.84–3.60 (*m*, 2 CH₂N). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 151.1 (*s*, C(4)); 139.4 (*s*, C(6)); 139.1 (*s*, C(7a)); 138.9 (*s*, C(2)); 127.7 (*s*, C(3a)); 99.3 (*s*, C(7)); 66.3 (*s*, 2 CH₂O); 46.5 (*s*, 2 CH₂N). MS: 204 (56, *M*⁺), 119 (100, [C₆H₅N₃])⁺. Anal. calc. for C₁₀H₁₂N₄O (204.23): C 58.81, H 5.93, N 27.43; found: C 58.82, H 6.00, N 27.38.

5-(Morpholin-4-yl)pyrido[3,4-*b*]pyrazine (**35**). As described for **32**, **26d** (0.3 g, 1.1 mmol) in THF/H₂O 8:7 (150 ml) is reduced by Na₂S₂O₄ (1.84 g, 10.56 mmol). The residue of the evaporated org. layer is dissolved in THF/H₂O 2:1 (30 ml) and the resulting mixture treated with CHO–CHO·NaHSO₃ (0.7 g, 2.46 mmol) in H₂O (20 ml). The mixture is stirred at 50–60° (H₂O bath) for 20 h and then allowed to cool. The alkaline soln. (K₂CO₃, pH 9–10) is extracted with AcOEt, the org. phase dried (MgSO₄) and evaporated, and the residual oil subjected to CC (50 cm, silica gel, AcOEt). Recrystallisation from Et₂O yields **35** (44 mg, 18.5% rel. to **26d**). Lemon-coloured, long needles. M.p. 121°. UV (MeCN): 252 (4.233), 387 (3.670). IR (KBr): 3030 (Aryl-H); 2970, 2860 (C–H); 1570, 1455 (C=C, C=N); 1120 (C–O–C). ¹H-NMR (250.13 MHz, CDCl₃): 8.88 (*d*, ³*J* = 1.53, H–C(2) or H–C(3)); 8.72 (*d*, ³*J* = 1.53, H–C(2) or H–C(3)); 8.30 (*d*, ³*J* = 5.76, H–C(7)); 7.32 (*d*, ³*J* = 5.76, H–C(8)); 4.24–4.00 (*m*, 2 CH₂O); 4.00–3.78 (*m*, 2 CH₂N). ¹³C-NMR (62.89 MHz, CDCl₃): 158.5 (*s*, C(5)); 148.2 (*s*, C(8a)); 147.7 (*s*, C(2) or C(3)); 145.6 (*s*, C(2) or C(3)); 141.4 (*s*, C(7)); 131.7 (*s*, C(4a)); 113.6 (*s*, C(8)); 67.1 (*s*, 2 CH₂O); 49.7 (*s*, 2 CH₂N). MS: 216 (100, *M*⁺). Anal. calc. for C₁₁H₁₂N₄O (216.23): C 61.10, H 5.59, N 25.91; found: C 61.21, H 5.71, N 25.65.

4-(Morpholin-4-yl)-2,1,3-selenadiazolo[3,4-*c*]pyridine (**36**). As described for **32**, **26d** (1.0 g, 3.68 mmol) in THF/H₂O 13:10 (460 ml) is reduced by Na₂S₂O₄ (5.14 g, 29.44 mmol). The combined org. phase is evaporated, the residue dissolved in EtOH (50 ml) and a freshly prepared and filtered soln. of SeO₂ (0.409 g, 3.68 mmol) in H₂O (4 ml) added. The mixture is refluxed for 2 h, allowed to cool, and, after addition of H₂O/AcOEt 1:1 (240 ml), made alkaline (K₂CO₃, pH 10). Extraction with AcOEt, evaporation of the org. layer, and recrystallisation of the residue from MeOH gives pure **36** (320 mg, 32.3% rel. to **26d**). Orange platelets. M.p. 126°. UV (MeCN): 250 (4.094), 310 (3.813), 443 (3.699). IR (KBr): 2980, 2860 (C–H); 1565, 1520, 1485, 1445 (C=C, C=N); 1110 (C–O–C). ¹H-NMR (300 MHz, (D₆)DMSO): 7.82 (*d*, ³*J* = 6.35, H–C(6)); 7.00 (*d*, ³*J* = 6.35, H–C(7)); 4.43–4.05 (*m*, 2 CH₂O); 3.97–3.66 (*m*, 2 CH₂N). ¹³C-NMR (75.43 MHz, (D₆)DMSO): 162.6 (*s*, C(7a)); 152.4 (*s*, C(4)); 149.4 (*s*, C(3a)); 143.5 (*s*, C(6)); 107.4 (*s*, C(7)); 66.1 (*s*, 2 CH₂O); 47.2 (*s*, 2 CH₂N). MS: 270 (100, *M*⁺(⁸⁰Se)). Anal. calc. for C₉H₁₀N₄OSe (269.16): C 40.16, H 3.74, N 20.82; found: C 40.34, H 4.07, N 20.71.

2,1,3-Selenadiazolo[3,4-*c*]pyridine-4(5H)-one (**37**). As described for **36**, from **26d** (1.0 g) in THF/H₂O 13:10 Na₂S₂O₄, and SeO₂. The evaporated org. layer is chromatographed (50 cm, silica gel, AcOEt). The 1st orange band containing the main product **36** is rejected; the residue of the 2nd, weakly fluorescent band is recrystallised from MeOH to provide ochreous crystals of **37** (40 mg, 5.4% based on **26d**). M.p. 279–281°. UV (MeCN): 244 (3.853), 282 (3.411), 363 (3.609). IR (KBr): 3520–3360 (NH); 3190; 3070 (Aryl-H); 2950 (C–H); 1730 (C=O); 1650; 1330. ¹H-NMR (250.13 MHz, (D₆)DMSO): 11.30 (*s*, H–N(5)); 7.30 (*d*, ³*J* = 7.94, H–C(6)); 6.60 (*d*, ³*J* = 7.94, H–C(7)). ¹³C-NMR (62.89 MHz, (D₆)DMSO): 162.4 (*s*, C(7a) or C(4) or C(3a)); 157.6 (*s*, C(7a) or C(4) or C(3a)); 154.2 (*s*, C(7a) or C(4) or C(3a)); 132.5 (*s*, C(6)); 102.0 (*s*, C(7)). MS: 201 (100, *M*⁺(⁸⁰Se)). HR-MS (peak matching): 200.9442 [(C₇H₅N₃OSe)]⁺, calc. 200.9441). Elemental analysis: unsatisfactory due to instability of **37**.

5'-[(4-Fluorobenzyl)amino]spiro[cyclohexane-1,2'-2'H-imidazo[4,5-*b*]pyridine] (**13**). As described for **11**, from **4a** (1.31 g, 6.9 mmol) in dry THF (260 ml), 4-fluorobenzylamine (17.47 g, 139.8 mmol), and MnO₂ (6.03 g, 69 mmol; 18 h r.t.). CC (silica gel, AcOEt/MeOH 5:2) and recrystallisation from AcOEt give ochreous crystals of **13** (1.13 g, 52.8%) which are finally washed with hexane. M.p. 189°. UV (MeCN): 202 (4.409), 266 (4.166), 274 (4.143), 353 (3.663). IR (KBr): 3220 (NH); 3050 (Aryl-H); 2930, 2850 (C–H); 1630, 1610, 1510 (C=C, C=N); 1430,

1220 (C–F). $^1\text{H-NMR}$ (250.13 MHz, $(\text{D}_6)\text{DMSO}$): 8.79 (*t*, NH); 7.48 (*d*, $^3J = 10.00$, H–C(7')); 7.47–7.35 (*m*, 2 H, $\text{FC}_6\text{H}_4\text{CH}_2$); 7.28–7.14 (*m*, 2 H, $\text{FC}_6\text{H}_4\text{CH}_2$); 6.88 (*d*, $^3J = 10.00$, H–C(6')); 4.62 (*d*, $^3J = 5.31$, 2 H, $\text{FC}_6\text{H}_4\text{CH}_2$); 1.90–1.30 (*m*, C_6H_{10}). $^{13}\text{C-NMR}$ (62.89 MHz, $(\text{D}_6)\text{DMSO}$): 161.3 (*d*, $^1J = 243.1$, C_p of $\text{FC}_6\text{H}_4\text{CH}_2$); 161.1 (*s*, C(3'a)); 160.6 (*s*, C(5')); 154.0 (*s*, C(7'a)); 134.5 (*d*, $^4J = 3.1$, C_{para} of $\text{FC}_6\text{H}_4\text{CH}_2$); 131.9 (*s*, C(7')); 129.7 (*d*, $^3J = 8.6$, 2 C_o of $\text{FC}_6\text{H}_4\text{CH}_2$); 128.8 (*s*, C(6')); 115.1 (*d*, $^2J = 21.1$, 2 C_m of $\text{FC}_6\text{H}_4\text{CH}_2$); 101.4 (*s*, C(2)); 43.3 (*s*, $\text{FC}_6\text{H}_4\text{CH}_2$); 34.0 (*s*, C(2), C(6)); 25.3 (*s*, C(4)); 24.0 (*s*, C(3), C(5)). MS: 310 (100, M^+). Anal. calc. for $\text{C}_{18}\text{H}_{19}\text{FN}_4$ (310.36): C 69.66, H 6.17, N 18.05; found: C 69.53, H 6.26, N 18.05.

Ethyl {2-Amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate Maleate (**39**). As described for **32**, **13** (0.5 g, 1.61 mmol) in THF/ H_2O 4:3 (175 ml) is reductively hydrolysed by $\text{Na}_2\text{S}_2\text{O}_4$ (2.4 g, 13.68 mmol). The combined org. phase is carefully concentrated to 5 ml and the unstable intermediate directly chromatographed (25 cm, silica gel, AcOEt/MeOH 5:2). The main fraction is dried (MgSO_4), again concentrated to 5 ml, and immediately dissolved in dry THF (10 ml). Slowly a soln. of ClCOOEt (216 mg, 2 mmol) in dry THF (5 ml) is added at r.t. (→turquoise soln. and precipitate). After evaporation, the residue is dissolved in MeOH (5 ml) and 25% aq. NH_3 soln. (20 ml) added. The aq. soln. is extracted with AcOEt and to the extract a soln. of maleic acid (0.175 g, 1.5 mmol) in AcOEt/MeOH 7:2 (9 ml) added (deep violet→turquoise). At -20° , a fine, sandy, light blue precipitate is formed which is recrystallised from *i*-PrOH: pure **39** (216 mg, 31.7% rel. to **13**). Colourless crystals. M.p. 170 and 177° (2 modifications). UV (MeCN): 248 (4.046), 319 (3.864), 343 (3.826). IR (KBr): 3450, 3330, 3250 (NH, NH_2); 2980 (C–H); 1730–1710 (C=O); 1655, 1620, 1575, 1510 (C=C, C=N); 1360, 1250 (C–O–C); 1230 (C–F). $^1\text{H-NMR}$ (300 MHz, $(\text{D}_6)\text{DMSO}$): 8.35 (*s*, NHCOOEt); 7.54–7.00 (*m*, $\text{FC}_6\text{H}_4\text{CH}_2$, H–C(4)); 6.15 (*s*, $\text{HC}=\text{CH}$); 5.79 (*d*, $^3J = 8.25$, H–C(5)); 4.39 (*s*, 2 H, FC_6CH_2); 4.03 (*q*, MeCH_2); 1.21 (*t*, MeCH_2); signals for 5 exchangeable H's not distinguishable because of extreme broadening. $^{13}\text{C-NMR}$ (62.89 MHz, $(\text{D}_6)\text{DMSO}$): 166.8 (*s*, 2 COOH); 161.1 (*d*, $^1J = 242.4$, C_p of $\text{FC}_6\text{H}_4\text{CH}_2$); 155.0 (*s*, C(2)); 152.5 (*s*, C(6) or NHCOOEt); 151.0 (*s*, C(6) or NHCOOEt); 139.1 (*s*, C(4)); 135.4 (*s*, C_{para} of $\text{FC}_6\text{H}_4\text{CH}_2$); 132.8 (*s*, $\text{HC}=\text{CH}$); 129.1 (*d*, $^3J = 7.4$, 2 C_o of $\text{FC}_6\text{H}_4\text{CH}_2$); 115.0 (*d*, $^2J = 21.0$, 2 C_m of $\text{FC}_6\text{H}_4\text{CH}_2$); 106.8 (*s*, C(3)); 94.1 (*s*, C(5)); 60.1 (*s*, MeCH_2); 44.0 (*s*, $\text{FC}_6\text{H}_4\text{CH}_2$); 14.4 (*s*, MeCH_2). MS: 304 (78, $[\text{C}_{15}\text{H}_{17}\text{FN}_4\text{O}_2]^+$), 109 (100, $[\text{C}_7\text{H}_6\text{F}]^+$). Anal. calc. for $\text{C}_{15}\text{H}_{17}\text{FN}_4\text{O}_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ (420.39): C 54.28, H 5.03, N 13.33; found: C 54.29, H 5.07, N 13.24.

5'-(Benzylamino)spiro[cyclohexane-1,2'-2H-imidazo[4,5-b]pyridine] (**12**). As described for **11**, from **4a** (1.31 g, 6.9 mmol) in dry THF (260 ml), PhCH_2NH_2 (14.85 g, 138 mmol), and MnO_2 (6.03 g, 69 mmol; 18 h r.t.). Recrystallisation from AcOEt gives yellow crystals of **12** (0.9 g, 44.6%). M.p. 198° . UV (MeCN): 266 (4.186), 275 (4.164), 352 (3.690). IR (KBr): 3230 (NH); 3030 (Aryl-H); 2930, 2860 (C–H); 1640, 1615, 1530–1480 (C=C, C=N); 1455. $^1\text{H-NMR}$ (250.13 MHz, $(\text{D}_6)\text{DMSO}$): 8.78 (br., NH); 7.47 (*d*, $^3J = 9.32$, H–C(7')); 7.43–7.20 (*m*, PhCH_2); 6.88 (*d*, $^3J = 9.32$, H–C(6')); 4.63 (*d*, $^3J = 4.97$, PhCH_2); 1.90–1.32 (*m*, C_6H_{10}). $^{13}\text{C-NMR}$ (62.89 MHz, CDCl_3): 161.7 (*s*, C(3'a)); 160.8 (*s*, C(5')); 154.1 (*s*, C(7'a)); 137.4 (*s*, 1 C, Ph); 132.1 (*s*, C(7')); 128.7 (*s*, C(6')); 128.6 (*s*, 2 C, Ph); 128.1 (*s*, 2 C, Ph); 127.6 (*s*, 1 C, Ph); 102.4 (*s*, C(2')); 45.5 (*s*, PhCH_2); 34.1 (*s*, C(2), C(6)); 25.5 (*s*, C(4)); 24.3 (*s*, C(3), C(5)). MS: 292 (100, M^+). Anal. calc. for $\text{C}_{18}\text{H}_{20}\text{N}_4$ (292.37): C 73.94, H 6.90, N 19.16; found: C 73.52, H 6.95, N 18.95.

Ethyl [2-Amino-6-(benzylamino)pyridin-3-yl]carbamate Hydrochloride (*D*-7175; see **39**, H instead of F, HCl instead of $(\text{CHCOOH})_2$). As described for **39**, from **12** (0.44 g, 1.5 mmol) in THF/ H_2O 4:3 (175 ml), $\text{Na}_2\text{S}_2\text{O}_4$ (2.1 g, 12.04 mmol), and ClCOOEt (216 mg, 2 mmol). After evaporation of the THF, recrystallisation from *i*-PrOH yields *D*-7175 (62.9 mg, 13% rel. to **12**). Light-brown crystals. M.p. 195° . UV (MeCN): 242 (3.642), 338 (3.678). IR (KBr): 3320, 3170 (NH, NH_2); 2990, 2930 (C–H); 1695 (C=O); 1660, 1640, 1610, 1525 (C=C, C=N); 1260 (C–O–C). $^1\text{H-NMR}$ (300 MHz, $(\text{D}_6)\text{DMSO}$): 13.40 (*s*, $\text{NH}^+(\text{pyr.})$); 8.28 (*s*, NHCOOEt); 8.18 (br., PhCH_2NH); 7.80–7.20 (*m*, Ph_2CH_2 , H–C(4), NH_2); 5.95 (*d*, 3J not measurable, H–C(5)); 4.60 (*d*, 3J not measurable, PhCH_2); 4.07 (*q*, MeCH_2); 1.20 (*t*, MeCH_2). $^{13}\text{C-NMR}$ (62.89 MHz, $(\text{D}_6)\text{DMSO}$): 154.9 (*s*, C(2)); 149.1 (*s*, C(6) or NHCOOEt); 149.0 (*s*, C(6) or NHCOOEt); 142.7 (*s*, C(4)); 137.4 (*s*, 1 C, Ph); 128.4 (*s*, 2 C, Ph); 127.4 (*s*, 2 C, Ph); 127.3 (*s*, 1 C, Ph); 106.3 (*s*, C(3)); 93.7 (*s*, C(5)); 60.4 (*s*, MeCH_2); 45.2 (*s*, PhCH_2); 14.4 (*s*, MeCH_2). MS: 286 (83, $[\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2]^+$), 91 (100, $[\text{C}_7\text{H}_7]^+$). Anal. calc. for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2 \cdot \text{HCl}$ (322.79): C 55.81, H 5.93, N 17.35; found: C 55.64, H 5.87, N 17.25.

4'-[(4-Fluorobenzyl)amino]spiro[cyclohexane-1,2'-2'H-imidazo[4,5-c]pyridine] (**26b**). As described for **11**, from **24** (1.31 g, 6.9 mmol) in dry THF (400 ml), (4-fluorobenzyl)amine (0.868 g, 6.9 mmol), and MnO_2 (12 g, 137.9 mmol; 1 h). CC (silica gel, AcOEt) and recrystallisation from hexane give **26b** (1.13 g, 52.8%). Orange crystals. M.p. 104° . UV (MeCN): 218 (4.219), 423 (3.657). IR (KBr): 3290 (NH); 3070 (Aryl-H); 2930, 2860 (C–H); 1640, 1580, 1570, 1505 (C=C, C=N); 1290; 1220 (C–F). $^1\text{H-NMR}$ (250.13 MHz, CDCl_3): 7.53 (*d*, $^3J = 6.25$, H–C(6')); 7.47–7.32 (*m*, 2 H, $\text{FC}_6\text{H}_4\text{CH}_2$); 7.17–7.00 (*m*, 2 H, $\text{FC}_6\text{H}_4\text{CH}_2$); 6.64–6.36 (br., NH); 6.41 (*d*, $^3J = 6.25$, H–C(7')); 4.72 (*s*, 2 H, $\text{FC}_6\text{H}_4\text{CH}_2$); 2.06–1.50 (*m*, C_6H_{10}). $^{13}\text{C-NMR}$ (62.89 MHz, CDCl_3): 162.4 (*d*, $^1J = 247.0$, C_p of $\text{FC}_6\text{H}_4\text{CH}_2$); 158.5 (*s*, C(7'a)); 154.6 (*s*, C(4')); 152.3 (*s*, C(3'a)); 149.6 (*s*, C(6')); 133.3 (*d*, $^4J = 3.1$, C_{para} of

$\text{FC}_6\text{H}_4\text{CH}_2$); 129.9 (d , $^3J = 8.4$, 2 C_o of $\text{FC}_6\text{H}_4\text{CH}_2$); 115.7 (d , $^2J = 21.7$, 2 C_m of $\text{FC}_6\text{H}_4\text{CH}_2$); 108.5 (s , C(2')); 106.1 (s , C(7')); 44.4 (s , $\text{FC}_6\text{H}_4\text{CH}_2$); 33.1 (s , C(2), C(6)); 25.5 (s , C(4)); 24.6 (s , C(3), C(5)). MS: 310 (97, M^+), 187 (100, $[\text{C}_{11}\text{H}_{13}\text{N}_2]^+$). Anal. calc. for $\text{C}_{18}\text{H}_{19}\text{FN}_4$ (310.36): C 69.66, H 6.17, N 18.05; found: C 69.53, H 6.37, N 18.02.

Ethyl {4-Amino-2-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate Hydrochloride (40). As described for **32**, **26b** (0.462 g, 1.49 mmol) in THF/H₂O 108:78 (186 ml) is reductively hydrolysed with $\text{Na}_2\text{S}_2\text{O}_4$ (2.08 g, 11.93 mmol). The extract is concentrated and chromatographed (25 cm, silica gel, AcOEt/MeOH 5:2) and the solid thus obtained dissolved in dry THF (5 ml). A soln. of ClCOOEt (216 mg, 2 mmol) in dry THF (5 ml) is slowly added ($\rightarrow$ cloudy, then brown and viscous precipitate). Evaporation and recrystallisation of the residue from i-PrOH give **40** (92 mg, 18.2% rel. to **26b**). Colourless crystals. M.p. 155°. UV (MeCN): 276 (3.904). IR (KBr): 3480–2920 (band due to aggregation); 1715 (C=O); 1660, 2615, 1450 (C=C, C=N); 1380; 1250 (C–O–C); 1225 (C–F). ¹H-NMR (300 MHz, (D₆)DMSO): 12.54 (s , NH⁺(pyr.)); 8.27 (s , NHCOOEt); 7.95 (br., $\text{FC}_6\text{H}_4\text{CH}_2\text{NH}$); 7.61–6.91 (m , $\text{FC}_6\text{H}_4\text{CH}_2$, H–C(6), NH₂); 6.34 (d , $^3J = 7.00$, H–C(5)); 4.68 (d , $^3J = 5.92$, $\text{FC}_6\text{H}_4\text{CH}_2$); 4.10 (q , MeCH_2); 1.28 (t , MeCH_2). ¹³C-NMR (75.43 MHz, (D₆)DMSO): 161.0 (d , $^1J = 242.3$, C_p of $\text{FC}_6\text{H}_4\text{CH}_2$); 154.7 (s , C(4) or C(2)); 154.4 (s , NHCOOEt); 149.9 (s , C(4) or C(2)); 133.8 (s , $C_{p,so}$ of $\text{FC}_6\text{H}_4\text{CH}_2$); 133.4 (s , C(6)); 128.7 (d , $^3J = 7.9$, 2 C_o of $\text{FC}_6\text{H}_4\text{CH}_2$); 114.7 (d , $^2J = 21.4$, 2 C_m of $\text{FC}_6\text{H}_4\text{CH}_2$); 102.9 (s , C(5)); 98.9 (s , C(3)); 60.5 (s , MeCH_2); 43.2 (s , $\text{FC}_6\text{H}_4\text{CH}_2$); 14.3 (s , MeCH_2). MS: 304 (76, $[\text{C}_{15}\text{H}_{17}\text{FN}_4\text{O}_2]^+$), 109 (100, $[\text{C}_7\text{H}_6\text{F}]^+$). HR-MS (peak matching): 304.1337 ($[\text{C}_{15}\text{H}_{17}\text{FN}_4\text{O}_2 \cdot \text{HCl}]^+$, calc. 304.1336). Elemental analysis: unsatisfactory due to instability of **40**.

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