Facile, Regioselective Syntheses of *N*-Alkylated 2,3-Diaminopyridines and Imidazo[4,5-*b*]pyridines

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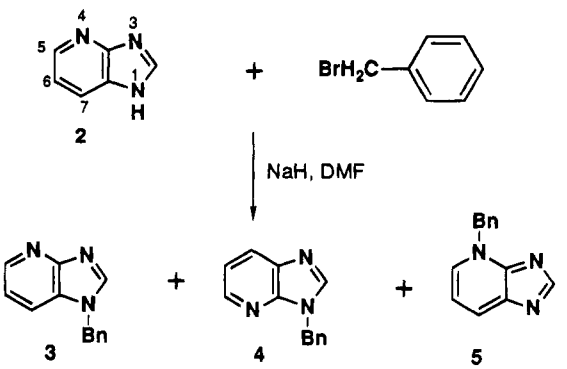
Useful strategies are reported for the differentiation and selective synthetic manipulations of amino groups at the 2- and 3-positions of pyridines. It has been found that 2,3-diaminopyridine reacts with aldehydes under reductive amination conditions to give predominantly the *N*-3 alkylated products, which have been used for the regioselective synthesis of *N*-1 substituted imidazo[4,5-*b*]-pyridines. Investigations using 2-formamido-3-aminopyridine (**13**), synthesized in two steps from 2-amino-3-nitropyridine, show it to be a versatile intermediate for the regioselective synthesis of either *N*-1 or *N*-3 substituted imidazo[4,5-*b*]pyridines, depending upon the conditions employed. The reductive amination of aldehydes with **13** using borane–pyridine in acetic acid affords the *N*-1 substituted imidazo[4,5-*b*]pyridines in one step, whereas reaction of **13** with alkyl halides in the presence of a suitable base (e.g., cesium carbonate) yields the *N*-3 substituted imidazo[4,5-*b*]-pyridines. The generality of this synthetic methodology is noted.

Introduction

Imidazo[4,5-*b*]pyridines and 2,3-diaminopyridines are useful precursors for the synthesis of a variety of medicinal agents. The heterocycles derived from these intermediates have recently been evaluated as antagonists of various biological receptors, including angiotensin II[1] and platelet activating factor (PAF).[2] Substituted imidazo[4,5-*b*]pyridines have also been tested for their potential as anticancer,[3] inotropic,[4] and selective antihistamine (H_1)[5] agents. Despite the importance of these intermediates, the methodologies available[1–5] for the regioselective syntheses of their *N*-alkylated derivatives are generally target specific and restrictive in their scope.[6]

During the course of our investigations[2] into the synthesis of imidazo[4,5-*b*]pyridine-derived antagonists of PAF, we were faced with the problem of developing a regioselective synthesis of 1-alkyl-1*H*-imidazo[4,5-*b*]pyridines, and this paper describes our regioselective syntheses of both 1-alkyl-1*H*- and 3-alkyl-3*H*-imidazo-[4,5-*b*]pyridines.

Scheme 1



Results and Discussion

The reaction of imidazopyridine (**2**) with benzyl bromide in the presence of a suitable base (sodium hydride, DMF) afforded a mixture of all three possible *N*-alkylated products (**3**, **4**, **5**; Scheme 1), of which the desired 1-alkyl derivative **3** was produced in the least amount (**3/4/5** = 1/3.6/1.6, 72% combined yield). This method involved a successful but tedious chromatographic separation of the regioisomers and thus was not attractive for large scale preparation. An alternate approach based on regioselective alkylation of the appropriate diaminopyridine followed by cyclization to form an imidazole ring was explored.[14]

Because of its greater basicity,[10] we anticipated that the 3-amino group in 2,3-diaminopyridine (**1**) would favor the selective formation of a Schiff base. Indeed, the conversion of **1** to **7a**, with or without the isolation of intermediate Schiff base,[15] proceeded regioselectively to give **7a** in 84 and 89% yield, respectively, (Scheme 2). Byproducts **8a** (4%) and **9** (2%) were also isolated in minor amounts.

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(1) (a) Chen, S. T.; Dost, G. (Merck) U. S. Pat. 5 132 216, 1992. (b) Roberts, D. A.; Russel, S. T.; Ratcliffe, A. H.; Gibson, K. H.; Wood, R. (ICI). Eur. Pat. 399 731, 1990.

(2) (a) Weier, R. M.; Khanna, I. K.; Stealey, M. A.; Julien, J. (Searle). U. S. Pat. 5 262 426, 1993. (b) Weier, R. M.; Khanna, I. K.; Lentz, K.; Stealey, M. A.; Julien, J. (Searle) U. S. Pat. 5 359 073, 1994.

(3) (a) Temple, C., Jr.; Rose, J. D.; Comber, R. N.; Rener, G. A. *J. Med. Chem.* **1987**, *30*, 1746. (b) Temple, C., Jr.; Smith, B. H.; Elliott, R. D.; Montgomery, J. A. *J. Med. Chem.* **1973**, *16*, 292.

(4) (a) Barraclough, P.; Black, J. W.; Cambridge, D.; Collard, D.; Firmin, D.; Gerskowitch, V. P.; Glen, R. C.; Giles, H.; Hill, A. P.; Hull, R. A. D.; Iyer, R.; King, W. R.; Kneen, C. O.; Lindon, J. C.; Nobbs, M. S.; Randall, P.; Shah, G. P.; Smith, S.; Vine, S. J.; Whiting, M. V.; Williams, J. M. *J. Med. Chem.* **1990**, *33*, 2231. (b) Barraclough, P.; Beams, R. M.; Black, J. W.; Cambridge, D.; Collard, D.; Demaine, D. A.; Firmin, D.; Gerskowitch, V. P.; Glen, R. C.; Giles, H.; Hill, A. P.; Hull, R. A. D.; Iyer, R.; King, W. R.; Livingstone, D. J.; Nobbs, M. S.; Randall, P., Shah, G. P.; Vine, S. J.; Whiting, M. V. *Eur. J. Med. Chem.* **1990**, *25*, 467.

(5) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1943.

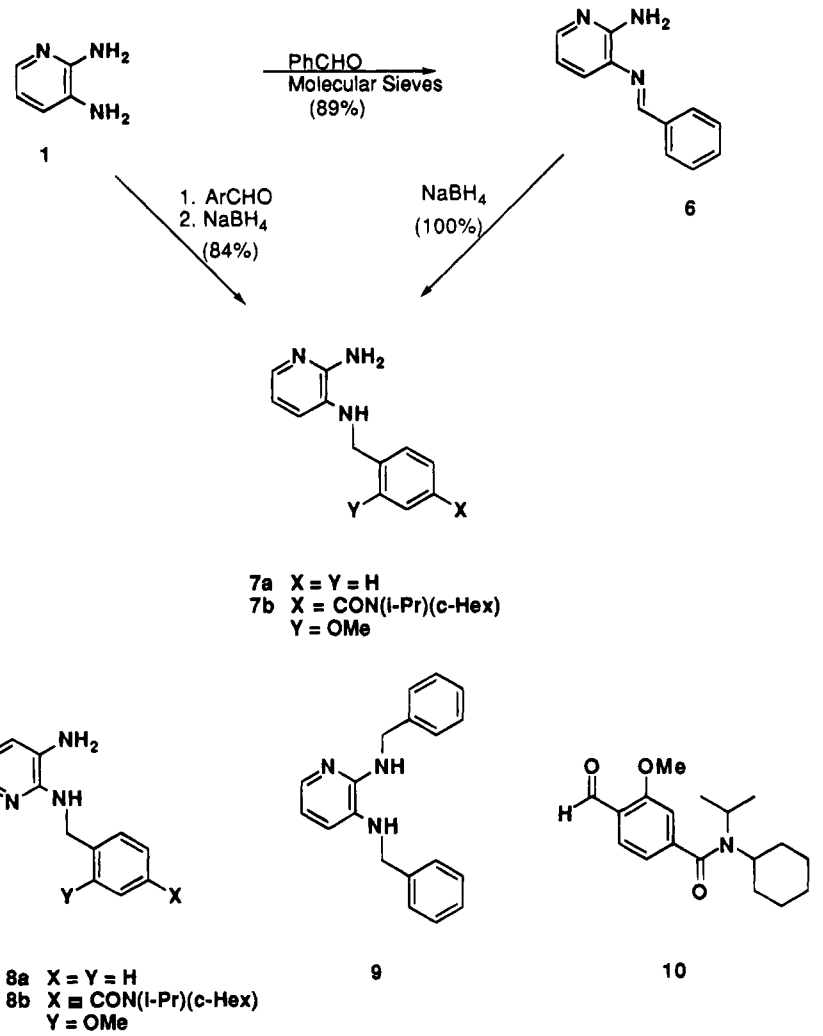
(6) Of the regioselective syntheses of *N*-alkylated imidazo[4,5-*b*]-pyridines and 2,3-diaminopyridines reported in literature, the preparation of 2-(alkylamino)-3-aminopyridines seems the simplest as these can be easily prepared by starting with 2-chloro-3-nitropyridines. Robison, M. M.; Switzerland, R.; Finch, N. (Ciba-Geigy); U. S. Pat. 3 719 683, 1973; see also ref 5.

(7) Faure, A. (Laboratoires U. P. S. A.); French Pat. 8363, 1971.

(8) Pelter, A.; Rosser, R. M. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 717.

0022-3263/95/1960-0960$09.00/0

Scheme 2



When the substituted aldehyde **10**[11] was employed in this sequence, formation of 3-alkylated product **7b** was favored again (**7b**/**8b** = 83/17). The overall chemical yield in this reaction was, however, lower (**7b** + **8b** = 36%) as compared to the unsubstituted benzaldehyde, possibly due to deactivation of the aldehyde carbonyl by the *o*-OMe substituent.

The intermediate **7a** was cyclized with triethyl orthoformate (90 °C, 18 h), using *p*-toluenesulfonic acid as catalyst, to give the desired *N*-1-benzylated imidazopyridine[9] (**3**) in 91% yield.

Regioselective Synthesis of 1-Alkyl-1*H*-imidazo[4,5-*b*]pyridines. A process for the regioselective synthesis of *N*-1-alkylimidazopyridines using the substrate **13**, with a built-in cyclizing group, was explored. This approach was based on the hypothesis that the 3-amino group in **13** would react with an aldehyde (RCHO) more efficiently (to give e.g., **14**) than with the formamido group to give imidazopyridine **2**. The synthesis of the target intermediate **13** was accomplished in a two-step sequence as shown in Scheme 3, starting from commercially available 2-amino-3-nitropyridine, by formylation (Ac_2O, HCO_2H; 100%) followed by reduction (Raney nickel, H_2; 78%).

(9) The regiochemistry of *N*-alkylation in substituted imidazo[4,5-*b*]pyridines was determined by NMR spectroscopy using Overhauser (NOE difference and NOESY) experiments. The results of these experiments on the diaminopyridine compounds (**7a** and **7b**), however, gave inconclusive results, possibly due to modulation of the Overhauser effects by their chemical exchange phenomena. The structures of **7a** and **7b** were unambiguously established by their chemical cyclization to the imidazo[4,5-*b*]pyridine derivatives, followed by comparison of the analytical and spectral properties of the resultant products with those of the authentic standards synthesized by independent routes.[13] All other compounds reported in this paper gave satisfactory NMR results consistent with their indicated structures. The details of the apparent ambiguity associated with the structural assignments of **7a** and **7b** using NMR Overhauser techniques is being investigated in more detail and will be communicated separately.

(10) For pK_a studies on 2,3-diaminopyridines, see (a) Bellobono, I. R.; Favini, G. *J. Chem. Soc. (B)* **1971**, 2034. (b) Bryson, J. *J. Am. Chem. Soc.* **1960**, *82*, 4871.

(11) Substituted benzaldehydes **10** and **16**, the intermediates used in our PAF program, were initially prepared from the corresponding benzyl bromides by direct oxidation using trimethylamine *N*-oxide in DMSO. However, this transformation could not be scaled up very well and we routinely preferred to use the three-step sequence involving (a) displacement of the substituted benzyl bromide with acetate (NaOAc, DMF) (b) hydrolysis (aqueous K_2CO_3) of the ester, and (c) oxidation (PCC) to the desired aldehyde. The synthesis of substituted benzyl bromides has been reported: Khanna, I. K.; Nosal, R.; Weier, R. M. (Searle). U. S. Patent 4 914 108 and 5 019 581; *Chem. Abstr.* **1990**, *112*, 235299z.

(12) No attempts have been made to optimize the yields.

(13) As described in the Experimental Section, compound **3** was synthesized by reacting **1** with benzyl bromide using NaH as base. Similarly, **3** was also synthesized from **7a** by heating with triethyl orthoformate.

(14) Pertinent to this approach, there is a report[7] illustrating the conversion of 2-chloro-3-aminopyridine to 2-anilino-3-aminopyridine derivatives. An attempted displacement reaction of 2-chloro-3-aminopyridine and 2-chloro-3-(benzylamino)pyridine with ammonia under forcing conditions (200 °C, approximately 3000 psi, NH_3, 1-methyl-2-pyrrolidinone, steel autoclave) did not prove successful in our hands and therefore was not pursued.

Scheme 3

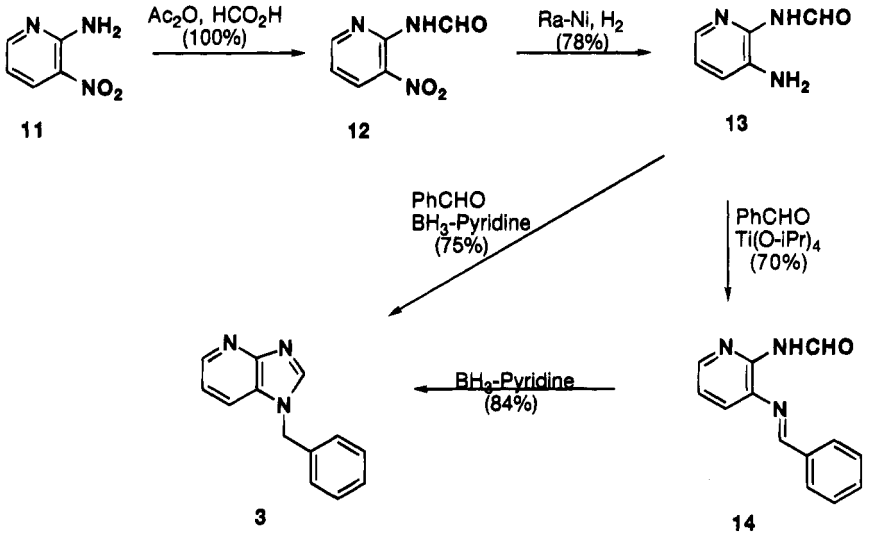
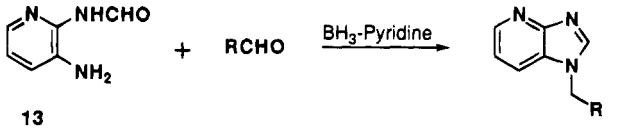
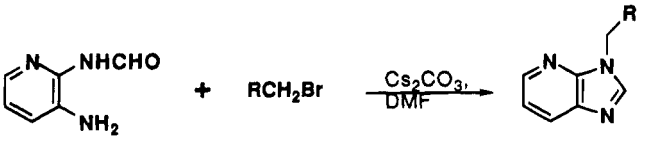


Table 1. Regioselective Synthesis of 1-Alkyl-1*H*-imidazo[4,5-*b*]pyridines



example	RCHO	product (str no.)	yield[12] (%)
1	PhCHO	**3**	75
2	4-Br-PhCHO	**17**	56
3	4-NO_2-PhCHO	**18**	77
4	2-OMe-PhCHO	**19**	88
5	$CH_3CH_2CH_2CHO$	**20**	59
6	**16**	**21**	74

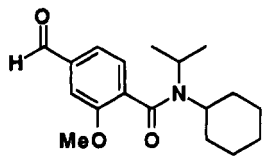
Table 2. Regioselective Synthesis of 3-Alkyl-3*H*-imidazo[4,5-*b*]pyridines



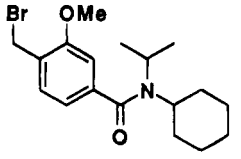
example	RCH_2Br	product (str no.)	yield[12] (%)
1	$PhCH_2Br$	**4**	77
2	4-Br-$PhCH_2Br$	**22**	49
3	4-NO_2-$PhCH_2Br$	**23**	64
4	$CH_3CH_2CH_2CH_2Br$	**24**	45
5	**26**	**25**	48

The reaction of 3-amino-2-formamidopyridine (**13**) with benzaldehyde under a variety of conditions proceeded very sluggishly and gave 40–70% conversion (Scheme 3). The best results were obtained by treating **13** with benzaldehyde (20 °C, 20 h) in the presence of a Lewis acid [Ti(O-*i*Pr)$_4$] to give **14** in 70% yield. Conversion of **14** to imidazopyridine **3** required reduction of the imine and cyclization of the resulting amino group with the *N*-formyl group. A superior method for this conversion evolved from the use of borane–pyridine.[8] Reaction of **14** with borane–pyridine complex in 1:1 CH_2Cl_2:AcOH at 20 °C for 3 h resulted in a one-pot reduction and cyclization to give **3** in an overall isolated yield of 84% (Scheme 3). Additional experimentation produced an even more advantageous one-pot three-step procedure. Thus, the reaction of **13** with benzaldehyde in the presence of borane–pyridine (CH_2Cl_2/AcOH, 20 °C, 3 h) afforded **3** in 75% overall isolated yield.

This reaction appears to be general, as shown by the examples in Table 1. The reaction conditions used are mild and are well tolerated by a variety of groups including halogen, methoxy, and nitro. Neither an electron-donating (such as 2-OMe, example 4) nor an electron-withdrawing group (such as 4-NO_2, example 3) adversely influences yield. It may also be used with aliphatic aldehydes, since *n*-butyraldehyde reacts to give **20** in 59% yield (example 5). In contrast to the process discussed above (e.g., the synthesis of **7b**, Scheme 2), the presence of a methoxy group ortho to the aldehydic function did not cause a lower yield of the imidazopyridine **19** (example 4, Table 1). This methodology was also successful with the highly substituted benzaldehyde **16**[11] and gave the desired 1*H*-imidazopyridine **21** in 74% yield.



16



26

Regioselective Synthesis of 3-Alkyl-3*H*-imidazo[4,5-*b*]pyridines. 2-Formamido-3-aminopyridine (**13**) also served as the key intermediate in the regioselective synthesis of 3-alkylimidazopyridines. The greater acidity of the amide proton at position 2 relative to the amino protons at position 3 permitted regioselective alkylation at the formamido nitrogen with appropriate alkyl halides. Thus, the reaction of **13** with benzyl bromide in the presence of a non-nucleophilic base (DMF, Cs_2CO_3, 20 °C, 18 h) proceeded as a one-pot process involving regioselective alkylation and cyclization to give **4** in an isolated yield of 77% (Table 2). This reaction is also general, as illustrated by the examples in Table 2. The reaction of **13** with the 4-bromo- and 4-nitrobenzyl bromide gave **22** and **23** in 49 and 64% yields, respectively. The reaction of **13** with 1-bromobutane gave predominantly the *N*-3 alkylated product **24**. This procedure was then applied to synthesize **25**, another of

(15) For formation of imines using molecular sieves, see (a) Bonnett, R.; Emerson, T. R. *J. Chem. Soc.* **1965**, 4508. (b) Kyba, E. P. *Org. Prep. Proc. Int.* **1970**, *2*, 149.

our target PAF antagonists.[2] Reaction of **13** with substituted benzyl bromide **26** gave the 3*H*-imidazopyridine **25** in 48% yield.

In summary, we have utilized the fundamental differences in the reactivity of amino groups (or derivatives) at positions 2 and 3 of diaminopyridines for short, practical and highly regioselective syntheses of substituted 2,3-diaminopyridines and their cyclized products imidazo[4,5-*b*]pyridines. The intermediate 2-formamido-3-aminopyridine (**13**) is particularly versatile because of its ability to generate predominantly either *N*-1 or *N*-3-alkylated imidazopyridines, depending upon the conditions used (Tables 1 & 2). We believe that the processes described here have fairly general applications and can be utilized for the regioselective syntheses of other heterocyclic systems, including those derived from 3,4-diaminopyridines or substituted 1,2-phenylenediamines.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$, DMSO-d_6, or MeOH-d_4 (Merck Isotopes) solution in 5-mm o.d. tubes (Wilmad-535) at 20 °C and were collected on either a General Electric QE-300, a Varian VXR-400, or a Varian VXR-500 spectrometer at 300, 400, or 500 MHz for ^1H (75, 100, or 125 MHz for ^{13}C). Nuclear Overhauser effect (NOE) difference spectra and two-dimensional NMR spectra were determined on the VXR-400. The chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$ ppm) and expressed in ppm. Infrared spectra were recorded using a Perkin-Elmer Model 681 grating spectrophotometer in $CHCl_3$ solutions or using KBr pellets; frequencies are expressed in cm^{-1}. Melting points were determined on a Thomas Hoover capillary melting point apparatus. DSC measurements were performed on a Dupont Model 912 Dual DSC system and run under nitrogen. Mass spectra were obtained on either a Finnigan-MAT Model 4500 or a Finnigan-MAT 8430 system. Microanalyses (C,H,N) were performed by the Microanalytical Group of the Physical Methodology Department, G. D. Searle & Co.

2,3-Diaminopyridine, 2-amino-3-nitropyridine, borane–pyridine complex, substituted benzyl bromides, substituted benzaldehydes and butyraldehyde, unless otherwise specified, were all commercial products. Solvents used were reagent grade or were dried using conventional procedures. The reactions were routinely carried out under an inert atmosphere unless otherwise indicated. Analytical chromatography was performed on EM Reagents 0.25 mm silica gel 60-F plates. Preparative chromatographic separations were carried out on Merck silica gel 60 (230–400 mesh).

1-(Phenylmethyl)-1*H*-imidazo[4,5-*b*]pyridine (3), 3-(Phenylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (4), and 4-(Phenylmethyl)-4*H*-imidazo[4,5-*b*]pyridine (5) from 1*H*-Imidazo[4,5-*b*]pyridine (2). To a stirred solution of **2** (357 mg, 3.0 mmol) in *N*,*N*-dimethylformamide (15 mL) was added sodium hydride (144 mg, 60% dispersion in mineral oil, 3.6 mmol). After stirring for 30 min, benzyl bromide (430 μL, 3.6 mmol) was added over 10 min. The reaction mixture was stirred under argon at 25 °C. After 3 h, the reaction was quenched by adding acetic acid (0.5 mL), and the solvent was removed under reduced pressure at <45 °C. The concentrated mixture was diluted with methylene chloride and washed with aqueous potassium carbonate and brine. After drying ($MgSO_4$) and filtration, the organic solvent was removed. The crude mixture (1.69 g) was chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give the following products in the order of elution.

4 (265 mg, 42%): mp (DSC) 83 °C; IR (KBr) 3440, 3060, 1600, 1450, 1410; ^1H NMR ($CDCl_3$) δ 8.43 (dd, J = 4.9, 1.4 Hz, 1H), 8.08 (dd, J = 8.0, 1.4 Hz, 1H), 8.03 (s, 1H), 7.28–7.40 (complex band, 5H), 7.26 (dd, J = 8.0, 4.9 Hz, 1H), 5.48 (s, 2H); MS (DCI, NH_3–PCI) 210 (MH^+). Anal. Calcd for $C_{13}H_{11}N_3 \cdot 0.2\ H_2O$: C, 73.36; H, 5.40; N, 19.74. Found: C, 73.37; H, 5.31; N, 19.74.

3 (75 mg, 12%): mp (DSC) 119 °C; IR (KBr) 3400, 3050, 1600, 1490, 1410; ^1H NMR ($CDCl_3$) δ 8.56 (dd, J = 4.7, 1.5 Hz, 1H), 8.17 (s, 1H), 7.57 (dd, J = 8.1, 1.5 Hz, 1H), 7.30–7.40 (complex band, 3H), 7.13–7.21 (complex band, 2H), 7.16 (dd, J = 8.1, 4.8 Hz, 1H), 5.37 (s, 2H); MS (EI) 209 (M^+). Anal. Calcd for $C_{13}H_{11}N_3 \cdot 0.2\ H_2O$: C, 73.36; H, 5.40; N, 19.74. Found: C, 73.68; H, 5.46; N, 19.71.

5 (115 mg, 18%): IR (KBr) 2960, 1625, 1580, 1400; ^1H NMR ($CDCl_3$) δ 8.49 (s, 1H), 8.23 (dd, J = 7.7, 0.8 Hz, 1H), 7.70 (dd, J = 6.4, 0.8 Hz, 1H), 7.30–7.40 (complex band, 5H), 7.07 (dd, J = 7.7, 6.4 Hz, 1H), 5.86 (s, 2H); MS (DCI, NH_3–PCI) 210 (MH^+). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.19; H, 5.38; N, 19.99.

***N*³-(Phenylmethylene)-2,3-pyridinediamine (6).** To a suspension of 2,3-diaminopyridine **1** (1.1 g, 10 mmol) in THF (100 mL), dried molecular sieves (5 g, 4Å) and benzaldehyde (1.2 mL, 12 mmol) were added. After refluxing for 4 h, the mixture was cooled to room temperature and stirred for 18 h. The reaction mixture was filtered and the residue washed with methylene chloride (150 mL). The combined organic filtrates were concentrated and dried under vaccuum. The crude dried product (2.2 g) was chromatographed (silica gel; ethyl acetate/acetone 98/2) to give **6** (1.75 g, 89%): mp (DSC) 129 °C; IR (KBr) 3460, 3300, 1610, 1570, 1460,1450; ^1H NMR ($CDCl_3$) δ 8.51 (s, 1H), 7.98 (dd, J = 5, 2 Hz, 1H), 7.90 (m, 2H), 7.42–7.54 (complex band, 3H), 7.23 (dd, J = 8, 2 Hz, 1H), 6.67 (dd, J = 8, 5 Hz, 1H), 5.09 (broad s, 2H); MS (DCI, NH_3–PCI) 198 (MH^+). Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C, 72.94; H, 5.64; N, 21.10.

***N*³-(Phenylmethyl)-2,3-pyridinediamine (7a) from 6.** Compound **6** (1.0 g, 5.08 mmol) was dissolved in ethanol (50 mL) and treated with sodium borohydride (1 g). After refluxing for 20 h, the reaction mixture was cooled to room temperature and quenched with water (200 mL). The aqueous solution was extracted with methylene chloride (2 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to give **7a** (1.04 g, 100%): mp (DSC) 133 °C; IR (KBr) 3440, 3360, 1640, 1575, 1515, 1440; ^1H NMR ($CDCl_3$) δ 7.61 (dd, J = 5.1, 1.5 Hz, 1H), 7.27–7.40 (complex band, 5H), 6.80 (dd, J = 7.7, 1.5 Hz, 1H), 6.67 (dd, J = 7.7, 5.1 Hz, 1H), 4.29 (d, J = 5.0 Hz, 2H), 4.23 (broad s, 2H), 3.61 (broad s, 1H); MS (EI) 199 (M^+). Anal. Calcd for $C_{12}H_{13}N_3 \cdot 0.1H_2O$: C, 71.69; H, 6.62; N, 20.90. Found: C, 71.89; H, 6.57; N, 21.00.

***N*³-(Phenylmethyl)-2,3-pyridinediamine (7a), *N*²-(phenylmethyl)-2,3-pyridinediamine (8a), and *N*,*N*′-bis(phenylmethyl)-2,3-pyridinediamine (9) from 1.** To a suspension of 2,3-diaminopyridine (1.65 g, 15 mmol) in benzene (120 mL) were added dried molecular sieves (5 g, 4 Å) and benzaldehyde (1.85 mL, 18 mmol). After refluxing for 3 h, the mixture was cooled to room temperature and stirred for 20 h. The reaction was filtered and the residue washed with ether. The combined organic filtrates were concentrated and dried under vaccuum. The crude dried product (2.9 g) was dissolved in ethanol (150 mL) and treated with sodium borohydride (4 g). After refluxing for 18 h, the reaction mixture was cooled to room temperature and quenched with water (100 mL). The aqueous solution was extracted with methylene chloride (2 × 250 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product (3.13 g) was chromatographed (silica gel; ethyl acetate/acetone 98/2) to give **9** (82 mg, 2%), **8a** (120 mg, 4%), and **7a** (2.5 g, 84%), respectively:

7a was found to be identical in analytical and spectral properties to the product obtained above.

8a: mp (DSC) 87 °C; IR (KBr) 3420, 3400, 3340, 1630, 1580, 1500; ^1H NMR ($CDCl_3$) δ 7.72 (dd, J = 6.2, 0.9 Hz, 1H), 7.30–7.41 (complex band, 5H), 6.91 (broad d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.9, 6.2 Hz, 1H), 5.46 (broad s, 2H), 4.31 (d, J = 5.4 Hz, 2H), 3.52 (broad t, J = 5 Hz, 1H); MS (EI) 199 (M^+). Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.09. Found: C, 72.01; H, 6.81; N, 20.95.

9: mp (DSC) 76 °C; IR (KBr) 3300, 1610, 1580, 1525, 1500, 1460, 1445; ^1H NMR ($CDCl_3$) δ 7.74 (dd, J = 5.0, 1.5 Hz, 1H), 7.38 (complex d, J = 7 Hz, 4H), 7.23–7.37 (complex band, 8H), 6.79 (dd, J = 7.6, 1.5 Hz, 1 H), 6.61 (dd, J = 7.6, 5.0 Hz,1H), 4.61 (d, J = 4.8 Hz, 2H), 4.34 (broad t, J = 4.8 Hz, 1H), 4.24 (s, 2H), 3.38 (broad s, 1H); MS (EI) 289 (M^+). Anal. Calcd for

$C_{19}H_{19}N_3 \cdot 0.1H_2O$: C, 78.37; H, 6.65; N, 14.43. Found: C, 78.19; H, 6.65; N, 14.43.

4-[{(2-Amino-3-pyridinyl)amino}methyl]-*N*-cyclohexyl-3-methoxy-*N*-(1-methylethyl)benzamide (7b) and 4-[{(3-Amino-2-pyridinyl)amino}methyl]-*N*-cyclohexyl-3-methoxy-*N*-(1-methylethyl)benzamide (8b) from 1. To a suspension of 2,3-diaminopyridine (550 mg, 5.0 mmol) in dry tetrahydrofuran (200 mL) were added dried molecular sieves (5 g, 4 Å) and the aldehyde **10** (1.82 g, 6 mmol). After refluxing for 4 h, the mixture was cooled to room temperature and stirred for 18 h. The reaction was filtered and the residue washed with more ether (200 mL). The combined organic filtrates were concentrated and dried under vaccuum. The crude dried product (1.4 g) was dissolved in ethanol (200 mL) and treated with sodium borohydride (1.4 g). After refluxing for 20 h, the reaction mixture was cooled to room temperature and quenched with water (200 mL). The aqueous solution was extracted with methylene chloride (2 × 300), dried ($MgSO_4$), and concentrated. The crude product (1.18 g) was chromatographed (silica gel, methylene chloride/methanol/ammonium hydroxide 90/10/1) to give **8b** (113 mg, 6%) and **7b** (598 mg, 30%), respectively:

8b: IR ($CHCl_3$) 3603, 3422, 2966, 2856, 1613, 1576, 1495, 1404; ^{1}H NMR ($CDCl_3$) δ 7.77 (dd, J = 5.0, 1.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 6.86 (dd, J = 7.5, 1.5 Hz, 1H), 6.85 (d, J = 1.5 Hz, 1H), 6.82 (dd, J = 7.5, 1.5 Hz, 1H), 6.53 (dd, J = 7.5, 5.0 Hz, 1H), 4.69 (s, 1H), 4.64 (s, 2H), 3.87, 3.88 (s, 3H), 2.9–3.8 (very broad signals, 4H), 0.9–2.8 (complex band, broad signals, 16H); MS (EI) 396 (M^+).

7b: mp (DSC) 197 °C; IR (KBr) 3374, 2930, 2855, 1610, 1576, 1502, 1404; ^{1}H NMR ($CDCl_3$) δ 7.59 (dd, J = 5.0, 1.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 1.4 Hz, 1H), 6.82 (dd, J = 7.5, 1.4 Hz, 1H), 6.79 (dd, J = 7.7, 1.5 Hz, 1H), 6.65 (dd, J = 7.7, 5.0 Hz, 1H), 4.30 (broad s, 2H), 4.28 (s, 2H), 3.87 (s, 3H), 3.80 (broad s, 1H), 3.60 (very broad m, 1H), 3.35, 3.07 (very broad m, 1H), 2.60 (broad m, 1H), 0.9–2.2 (complex band, broad signals, 15H); MS (EI) 396 (M^+). Anal. Calcd for $C_{23}H_{32}N_4O_2 \cdot 0.75H_2O$: C, 67.37; H, 8.37; N, 13.66. Found C, 67.20; H, 8.03; N, 13.57.

1-(Phenylmethyl)-1*H*-imidazo[4,5-*b*]pyridine (3) from (7a). To a solution of **7a** (800 mg, 4 mmol) in *N*,*N*-dimethylacetamide (2 mL) were added triethyl orthoformate (10 mL) and *p*-toluenesulfonic acid (30 mg). The mixture was heated at 90–95 °C. After 18 h, the solvent was removed under reduced pressure and the residue dissolved in methylene chloride. The organic solution was washed with aqueous potassium carbonate, dried ($MgSO_4$), and concentrated. The crude (830 mg) was chromatographed (silica gel; methylene chloride/methanol/ammonium hydroxide 95/5/0.5) to give **3** (730 mg, 91%), identical to the product reported above.

***N*-(3-Nitro-2-pyridinyl)formamide (12).** A solution of acetic anhydride (102 mL) and formic acid (43 mL) was heated at 60 °C for 3 h. The reaction was cooled to 20 °C and 2-amino-3-nitropyridine (6.95 g, 0.05 mol) was added over 15 min. After stirring at room temperature for 72 h, the solvents were removed under reduced pressure at <45 °C and the product obtained, **12** (8.5 g, 100%), was used in the next step without further purification: mp (DSC) 143 °C; IR (KBr) 3300, 1705, 1600, 1575, 1515, 1470,1445; ^{1}H NMR ($CDCl_3$) δ 10.14 (broad s, $w(1/2)$ = 28 Hz, 1H), 9.77 (d, J = 9.6 Hz, 1H), 8.58 (complex band, 2H), 7.24 (m, 1H); MS (EI) 289 (M^+). Anal. Calcd for $C_6H_5N_3O_3$: C, 43.12; H, 3.02; N, 25.14. Found: C, 42.78; H, 2.92; N, 25.20.

***N*-(3-Amino-2-pyridinyl)formamide (13).** To a solution of **12** (4.49 g, 0.027 mol) in distilled tetrahydrofuran (130 mL) in a Parr bottle was added Raney-nickel in methanol (6 mL). The reaction mixture was flushed with nitrogen and hydrogen several times and then maintained under hydrogen at a delivery pressure of 5 psi. After stirring at 20–25 °C for approximately 4 h, the reaction was vented and purged with nitrogen. The contents of the reaction were filtered and concentrated to remove the solvent. The crude product (4.5 g) was chromatographed (silica gel, ethyl acetate/acetone 98/2) to give **13** (2.88 g, 78%): DSC (mp) 153 °C; IR (KBr) 3430, 3220, 1695, 1645, 1590, 1495, 1470, 1445; ^{1}H NMR (DMSO-d_6) δ 9.91 (broad s, 1H), 9.15 (broad s, 1H), 7.54 (d, J = 5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.91 (dd, J = 7.5, 5.0 Hz, 1H), 5.23 (s, 2H). Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.53; H, 5.18; N, 30.43.

***N*-[{3-(Phenylmethylene)amino}-2-pyridinyl]formamide (14).** To a clear solution of **13** (272 mg, 2.0 mmol) and benzaldehyde (360 μL, 3.0 mmol) in THF (20 mL) was added $Ti(O\text{-}iPr)_4$ (600 μL, 2 mmol) over 10 min. The reaction mixture was stirred at room temperature for 28 h and then concentrated to remove the solvent. The residue was chromatographed using silica gel (hexane/ethyl acetate 6/4) to give pure **14** (315 mg, 70%): mp (DSC) 118 °C; IR (KBr) 3380, 1690, 1620, 1590, 1575, 1480, 1455; ^{1}H NMR ($CDCl_3$) δ 9.57 (d, J = 10.8 Hz, 1H), 8.63 (broad d, J = 11 Hz, 1H), 8.59 (s, 1H), 8.17 (dd, J = 4.9, 1.5 Hz, 1H), 7.93 (dd, J = 8.1, 1.6 Hz, 2 H), 7.49–7.58 (complex band, 3 H), 7.49 (dd, J = 7.9, 1.5 Hz, 1H), 7.09 (dd, J = 7.9, 4.9 Hz, 1H); MS (EI) 225 (M^+). Anal. Calcd for $C_6H_5N_3O_3$: C, 43.12; H, 3.02; N, 25.14. Found: C, 42.78; H, 2.92; N, 25.20.

1-(Phenylmethyl)-1*H*-imidazo[4,5-*b*]pyridine (3) from (14). To a clear solution of **14** (75 mg, 0.33 mmol) in methylene chloride (2 mL) and acetic acid (2 mL) was added borane–pyridine complex (35 μL, 0.33 mmol). After stirring for 3 h, the reaction mixture was quenched by adding 5 N HCl (2 mL) and stirred for 5 min. The reaction mixture was neutralized to pH 7 using aqueous ammonium hydroxide and extracted with methylene chloride. The organic layer was separated, dried over $MgSO_4$, and filtered. After concentration, the crude residue (71 mg) was chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 93/7/0.7) to give pure **3** (58 mg, 84%) identical in properties to the product reported above.

1-(Phenylmethyl)-1*H*-imidazo[4,5-*b*]pyridine (3) from (13). To a clear solution of **13** (408 mg, 3.0 mmol) and benzaldehyde (540 μL, 4.5 mmol) in methylene chloride (4 mL) and acetic acid (4 mL) at room temperature was added borane–pyridine complex (300 μL, 3 mmol). After stirring for 2 h, the reaction mixture was neutralized to pH 7 using aqueous ammonium hydroxide and extracted with methylene chloride. The organic layer was separated, dried over $MgSO_4$, and filtered. After concentration, the crude residue (880 mg) was chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give pure **3** (472 mg, 75%) identical in properties to the product reported above.

1-[(4-Bromophenyl)methyl]-1*H*-imidazo[4,5-*b*]-pyridine (17). Compound **17** was prepared from **13** (275 mg, 2.0 mmol), 4-bromobenzaldehyde (553 mg, 3.0 mmol), and borane–pyridine complex (200 μL, 2.0 mmol) using the procedure described above for compound **3**. After stirring for 3 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 95/5/0.5) to give pure **17** (324 mg, 56%): DSC (mp) 189 °C; IR (KBr) 3935, 3434, 2975, 1612, 1593, 1495; ^{1}H NMR ($CDCl_3$) δ 8.56 (dd, J = 5, 1.5 Hz, 1H), 8.18 (s, 1H), 7.54 (dd, J = 8, 1.5 Hz, 1H), 7.47 (d, J = 8 Hz, 2H), 7.17 (dd, 8, 5 Hz, 1H), 7.05 (d, J = 8 Hz, 2H), 5.34 (s, 2H); MS (EI) 287/289 (M^+). Anal. Calcd for $C_{13}H_{10}N_3Br$: C, 54.19; H, 3.50; N, 14.58. Found: C, 53.83; H, 3.63; N, 14.38.

1-[(4-Nitrophenyl)methyl]-1*H*-imidazo[4,5-*b*]-pyridine (18). Compound **18** was prepared from **13** (275 mg, 2.0 mmol), 4-nitrobenzaldehyde (455 mg, 3.0 mmol), and borane–pyridine complex (200 μL, 2.0 mmol) using the procedure described above for compound **3**. After stirring for 2 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give pure **18** (394 mg, 77%): DSC (mp) 197 °C; IR (KBr) 3980, 3746, 2943, 1613, 1518, 1489; ^{1}H NMR ($CDCl_3$) δ 8.62 (dd, J = 5, 1.5 Hz, 1H), 8.25 (s, 1H), 8.21 (d, J = 8 Hz, 2H), 7.53 (dd, J = 8, 1.5 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.22 (dd, 8, 5 Hz, 1H), 5.53 (s, 2H); MS (EI) 254 (M^+). Anal. Calcd for $C_{13}H_{10}N_4O_2 \cdot 0.2\ H_2O$: C, 60.56; H, 4.07; N, 21.73. Found: C, 60.58; H, 4.06; N, 21.40.

1-[(2-Methoxyphenyl)methyl]-1*H*-imidazo[4,5-*b*]pyridine (19). Compound **19** was prepared from **13** (275 mg, 2.0 mmol), *o*-anisaldehyde (410 μL, 3.0 mmol), and borane–pyridine complex (200 μL, 2.0 mmol) using the procedure described above for compound **3**. After stirring for 3 h, the reaction mixture was worked up and the crude product

chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give pure **19** (420 mg, 88%): DSC (mp) 135 °C; IR (KBr) 3435, 3049, 2993, 1612, 1603, 1589, 1479, 1454; ^1H NMR ($CDCl_3$) δ 8.52 (dd, J = 5, 1.5 Hz, 1H), 8.19 (s, 1H), 7.71 (dd, J = 8, 1.5 Hz, 1H), 7.32 (td, J = 8, 1.5 Hz, 1H), 7.17 (dd, J = 8, 5 Hz, 1H), 7.12 (dd, J = 8, 1.5 Hz, 1H), 6.92 (t, J = 8 Hz, 1H), 6.90 (t, J = 8 Hz, 1H), 5.34 (s, 2H); MS (EI) 239 (M^+). Anal. Calcd for $C_{14}H_{13}N_3O \cdot 0.1H_2O$: C, 69.75; H, 5.52; N, 17.43. Found: C, 69.71; H, 5.42; N, 17.21.

1-Butyl-1*H*-imidazo[4,5-*b*]pyridine (20). Compound **20** was prepared from **13** (408 mg, 3 mmol), butyraldehyde (410 μL, 4.5 mmol), and borane-pyridine complex (300 μL, 3 mmol) using the procedure described above for compound **3**. After stirring for 4 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give **20** (312 mg, 59%): IR (KBr) 2985, 1610, 1495, 1480, 1420; ^1H NMR ($CDCl_3$) δ 8.55 (dd, J = 4.7, 1.5 Hz, 1H), 8.11 (s, 1H), 7.75 (dd, J = 8.1, 1.5 Hz, 1H), 7.22 (dd, J = 8.1, 4.7 Hz, 1H), 4.19 (t, J = 7.1 Hz, 2H), 1.86 (p, J = 7.1 Hz, 2H), 1.34 (h, J = 7.1 Hz, 2H), 0.94 (t, J = 7.1 Hz, 3H); MS (EI) 175 (M^+). Anal. Calcd for $C_{10}H_{13}N_3 \cdot 0.1\ H_2O$: C, 67.85; H, 7.52; N, 23.74. Found: C, 67.73; H, 7.48; N, 23.64.

***N*-Cyclohexyl-4-(1*H*-imidazo[4,5-*b*]pyridin-1-ylmethyl)-2-methoxy-*N*-(1-methylethyl)benzamide (21).** Compound **21** was prepared from **13** (1.53 g, 11.2 mmol), **16** (5.0 g, 16.5 mmol), and borane-pyridine complex (1.1 mL, 11 mmol) using the procedure described above for compound **3**. After stirring for 2 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give pure **21** (3.38 g, 74%) as a white crystalline solid: mp (capillary) 193–95 °C; IR (KBr) 3430, 2940, 1630, 1610, 1495, 1440, 1415; ^1H NMR (CD_3OD) δ 8.60 (s, 1H), 8.44, 8.43 (dd, J = 5.0, 1.4 Hz, 1H), 7.98, 7.92 (dd, J = 8.1, 1.4 Hz, 1H), 7.30 (m, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.07 (broad s, 1H), 6.91 (broad d, J = 7.6 Hz, 1H), 5.58, 5.56 (s, 2H), 3.79 (s, 3H), 3.62 (heptet, J = 6 Hz, 1H), 3.12, 3.09 (tt, J = 12.0, 3.5 Hz, 1H), 2.56 (m, 1H), 0.77–1.85 (m, 16H). Anal. Calcd for $C_{24}H_{30}N_4O_2$: C, 70.91; H, 7.44; N, 13.78 Found: C, 70.71; H, 7.51; N, 13.75.

3-(Phenylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (4) from 13. To a solution of **13** (300 mg, 2.2 mmol) in DMF (10 mL), cesium carbonate (1.58 g, 4.84 mmol), and benzyl bromide (260 μL, 2.2 mmol) were added. After stirring at room temperature for 20 h, the reaction mixture was filtered and the residue washed with methylene chloride. The filtrates were combined and the solvent removed under reduced pressure. The crude residue (720 mg) was chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give **4** (348 mg, 77%) identical in properties to the product reported above.

3-[(4-Bromophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (22). Compound **22** was prepared from **13** (275 mg, 2.0 mmol), cesium carbonate (1.43 g, 4.4 mmol), and 4-bromobenzyl bromide (750 mg, 3.0 mmol) in DMF (10 mL) using the procedure described above for compound **4**. After stirring for 20 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 95/5/0.5) to give **22** (280 mg, 49%): DSC (mp) 128 °C; IR (KBr) 3834, 3630, 2974, 1655, 1637, 1597; ^1H NMR ($CDCl_3$) δ 8.42 (dd, J = 5, 1.5 Hz, 1H), 8.09 (dd, J = 8, 1.5 Hz, 1H), 8.03 (s, 1H), 7.46 (d, J = 8 Hz, 2H), 7.27 (dd, J = 8, 5 Hz, 1H), 7.18 (d, J = 8 Hz, 2H), 5.43 (s, 2H); MS (EI) 287/289 (M^+). Anal. Calcd for $C_{13}H_{10}N_3Br$: C, 54.19; H, 3.50; N, 14.58. Found: C, 53.94; H, 3.75; N, 14.19.

3-[(4-Nitrophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (23). Compound **23** was prepared from **13** (275 mg, 2.0 mmol), cesium carbonate (1.43 g, 4.4 mmol), and 4-nitrobenzyl bromide (650 mg, 3.0 mmol) in DMF (10 mL) using the procedure described above for compound **4**. After stirring for 20 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; ethyl acetate/acetone 98/2) to give **23** (324 mg, 64%): DSC (mp) 125 °C; IR (KBr) 3966, 3676, 3072, 1599, 1585, 1500; ^1H NMR ($CDCl_3$) δ 8.42 (dd, J = 5, 1.5 Hz, 1H), 8.19 (d, J = 8 Hz, 2H), 8.12 (dd, J = 8, 1.5 Hz, 1H), 8.10 (s, 1H), 7.44 (d, J = 8 Hz, 2H), 7.30 (dd, J = 8, 5 Hz, 1H), 5.60 (s, 2H); MS (CI, NH_3–PCI) 254 (MH^+). Anal. Calcd for $C_{13}H_{10}N_4O_2 \cdot 0.25\ H_2O$: C, 60.34; H, 4.09; N, 21.65. Found: C, 60.51; H, 4.19; N, 21.43.

3-Butyl-3*H*-imidazo[4,5-*b*]pyridine (24). Compound **24** was prepared from **13** (275 mg, 2.0 mmol), cesium carbonate (1.43 g, 4.4 mmol), and 1-bromobutane (325 μL, 3.0 mmol) in DMF (10 mL) using the procedure described above for compound **4**. After stirring for 20 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; ethyl acetate/acetone 98/2) to give **24** (230 mg, 45%): IR (KBr) 3667, 3348, 3061, 2936, 1601, 1585, 1501, 1460, 1410; ^1H NMR ($CDCl_3$) δ 8.40 (dd, J = 5, 1.5 Hz, 1H), 8.07 (dd, J = 8, 1.5 Hz, 1H), 8.03 (s, 1H), 7.22 (dd, J = 8, 5 Hz, 1H), 4.29 (t, J = 7 Hz, 2H), 1.91 (p, J = 7 Hz, 2H), 1.38 (h, J = 7 Hz, 2H), 0.95 (t, J = 7 Hz, 3H); MS (EI) 175 (M^+). Anal. Calcd for $C_{10}H_{13}N_3 \cdot 0.25\ H_2O$: C, 66.83; H, 7.57; N, 23.38. Found: C, 66.60; H, 7.55; N, 23.26.

***N*-Cyclohexyl-4-(3*H*-imidazo[4,5-*b*]pyridin-3-ylmethyl)-3-methoxy-*N*-(1-methylethyl)benzamide (25).** Compound **25** was prepared from **13** (300 mg, 2.2 mmol), cesium carbonate (1.58 g, 4.84 mmol), and **26** (803 mg, 2.2 mmol) in DMF (10 mL) using the procedure described above for compound **4**. After stirring for 20 h, the reaction mixture was worked up and the crude product chromatographed (silica gel; CH_2Cl_2/MeOH/NH_4OH 90/10/1) to give **25** (430 mg, 48%): mp (DSC) 198 °C; IR (KBr) 3430, 2920, 1610, 1500, 1460, 1410; ^1H NMR ($CDCl_3$) δ 8.43 (dd, J = 5, 2 Hz, 1H), 8.14 (s, 1H), 8.08 (dd, J = 8, 2 Hz, 1H), 7.25 (dd, J = 8, 5 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 6.88 (d, J = 1 Hz, 1H), 6.82 (dd, J = 8, 1 Hz, 1H), 5.49 (s, 2H), 3.90 (s, 3H), 3.35 (very broad m, 1H), 3.00 (very broad m, 1H), 2.60 (very broad m, 1H), 2.2–0.8 (complex band, broad signals, 15H); MS (DCI, NH_3–PCI) 407 (MH^+). Anal. Calcd for $C_{24}H_{30}N_4O_2 \cdot 0.4H_2O$: C, 69.67; H, 7.50; N, 13.54. Found C, 69.49; H, 7.38; N, 13.37.

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