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5-Substituted 1*H*-pyrrolo[3,2-*b*]pyridines as inhibitors of gastric acid secretion☆

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Abstract—A series of novel 1*H*-pyrrolo[3,2-*b*]pyridines was prepared relying on a copper iodide catalyzed cyclization of 2-prop-1-ynylpyridin-3-amines. A structure–activity relationship was established focusing on the influence of the substitution pattern in position 1, 3, and 5 of the heterocycle on anti-secretory activity, lipophilicity, and pK_a value. Some of the compounds proved to be potent inhibitors of the gastric acid pump.

1. Introduction

Gastroesophageal reflux disease (GERD), the backward flow of the stomach's contents into the oesophagus, is a digestive condition that affects 20% of the American population and often becomes manifested in heartburn, which is characterized by burning pain that radiates through chest, neck, and throat.[1,2] Peptic ulcer disease, estimated to affect 14.5 million people in the United States, is a chronic inflammation of the stomach and duodenum and responsible for a large economic burden. The formation of a peptic ulcer is favoured by two factors, the hypersecretion of acid and a weakened resistance of the protective mucous coating of the stomach and duodenum.[3,4] The inhibition of acid secretion and the neutralization of formed acid constitute effective approaches for the treatment of both diseases.[1,3] A whole series of compounds, which inhibit gastric acid secretion by blockade of the gastric proton pump enzyme (H^+/K^+-ATPase), are known. The compounds designated as proton pump inhibitors (PPIs), for example omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or tenatoprazole, bind irreversibly to the H^+/K^+-ATPase and have been available as therapeutics for a long time. A new class of compounds designated as acid pump antagonists (APAs) or as potassium competitive acid blockers (P-CABs) bind reversibly to the H^+/K^+-ATPase. Although PPIs are considered as the gold standard for the treatment of acid-related diseases, P-CABs might offer some therapeutic advantages such as better symptom control and faster healing.[5,6]

Over the past two decades, one important approach for the identification of potent P-CABs relied on the structural class of substituted imidazo[1,2-*a*]pyridines. The inhibitor **1** depicted in Figure 1 constitutes a representative example for P-CABs that are based on the imidazo[1,2-*a*]pyridine scaffold.[7,8] The presence of a 8-[(2,6-dimethylbenzyl)amino] group is characteristic for such 'open-chain' P-CAB inhibitors. 'Open chain' inhibitors of the gastric proton pump are distinguished from 'tricyclic' inhibitors, like e.g. Soraprazan (Fig. 1), by the absence of a tether that connects the heterocyclic scaffold (7-position of the imidazo[1,2-*a*]pyridine system) with the benzylic position of the CH_2aryl-substituent. The presence of two substituents in the ortho-positions of the phenyl ring enforces a pitched orientation of the heterocyclic moiety and the aromatic ring, which is considered to be an important feature for potent inhibition of the gastric proton pump enzyme. Despite the focus on the imidazo[1,2-*a*]pyridine system, the synthesis of structurally related heterocyclic systems has also been reported.[9] The imidazo[1,2-*a*]pyrazine **2** (Fig. 1) is a potent inhibitor of the gastric proton pump enzyme (H^+/K^+-ATPase) with an IC_{50} value of 0.16 μM ($pIC_{50} = 6.8$).[9] We were interested in the question whether further P-CABs could be identified, which pos-

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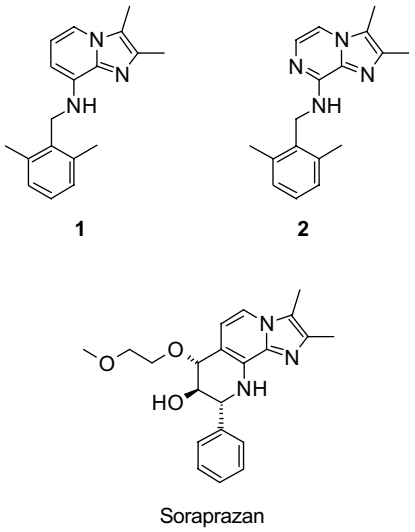


Figure 1.

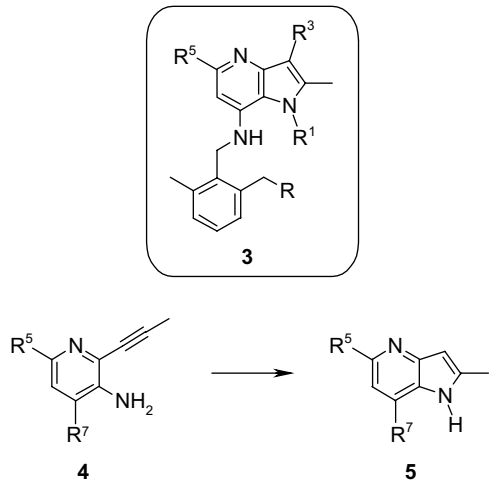


Figure 2.

sess a heterocyclic core different from the well-known imidazo[1,2-*a*]pyridine system.

In the course of the identification of suitable heterocyclic scaffolds, special attention has to be paid to their physicochemical properties, namely, their pK_a value. The pK_a value of a potassium competitive acid blocker is an important parameter for two reasons. First, it determines the concentration of the protonated species in the parietal cell, which is the active form for inhibition of H^+/K^+-ATPase.[10] Second, the parietal cell is distinguished from other compartments by its low pH value of approximately 3. Hence, P-CABs with low pK_a values are accumulated in a selective manner and possible interactions with enzymes that are expressed in other cells are prevented, which should translate in an improved safety profile.[6]

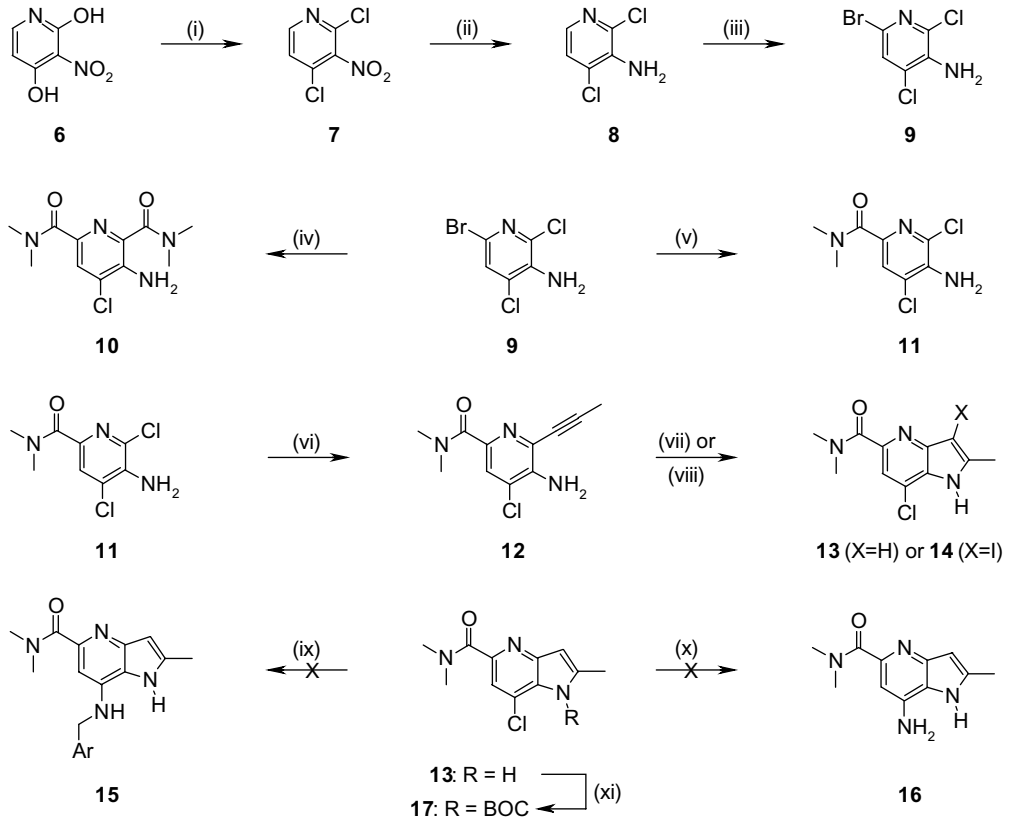
We considered 1*H*-pyrrolo[3,2-*b*]pyridines of the general formula **3** as interesting scaffolds for the development of novel P-CABs (Fig. 2).[11] Depending on the choice of the substituents R^1, R^3, and R^5, the basicity of the core system could be modulated over a wide range. Several approaches for the preparation and functionalization of 4-azaindoles have been disclosed in the literature including the transformation of 2-chloro-3-nitropyridines with carbon nucleophiles,[12] the conversion of 3-nitropyridines with Grignard reagents[13] and the oxidation/cyclization of *o*-hydroxyaminostyrylpyridines with DDQ.[14] In the present communication, the synthesis of the target compounds relied on the elaboration of highly substituted 2-prop-1-ynylpyridin-3-amines **4** which were then transformed into 1*H*-pyrrolo[3,2-*b*]pyridines **5** by copper iodide catalyzed cyclization (Fig. 2).[15,16]

2. Results and discussion

2.1. Synthesis of 1*H*-pyrrolo[3,2-*b*]pyridines

In a first approach, 2,4-dihydroxy-3-nitropyridine (**6**) was used as starting material for the synthesis of the tetrasubstituted pyridine **12** (Scheme 1). After displacement of the hydroxyl functions with chlorine atoms, the obtained 2,4-dichloro-3-nitropyridine (**7**) was reduced with tin chloride.[15] Subsequent bromination of 2,4-dichloro-pyridin-3-ylamine (**8**) afforded key intermediate **9**.[15] Regioselective amidocarbonylation of 6-bromo-2,4-dichloro-pyridin-3-ylamine (**9**) was feasible by control of the reaction temperature.[17] Heating a solution of pyridine **9**, palladium acetate (10 mol%), triphenylphosphine, dimethylamine and triethylamine in THF under a pressure of 6 bar carbon monoxide for 4 h at 70 °C afforded carboxamide **11** in 83% yield. On the other hand, when the reaction mixture was heated to 100 °C, displacement of both, the 2-chloro and 6-bromo atoms, occurred and dicarboxamide **10** was isolated in 59% yield. Finally, 2-prop-1-ynylpyridin-3-amine **12** was secured by Sonogashira reaction of 2,4-dichloropyridine **11** with propyne. In this palladium-catalyzed cross-coupling reaction, the more reactive 2-chloro atom was replaced in a regioselective manner. The 1*H*-pyrrolo[3,2-*b*]pyridine scaffold was obtained by copper iodide mediated cyclization of 2-prop-1-ynylpyridin-3-ylamine **12**. Depending on the amount of copper iodide employed, either 1*H*-pyrrolo[3,2-*b*]pyridine **13** or its 3-iodo-substituted analogue **14** was isolated. With the key intermediate **13** in hand, it was envisaged to complete the synthesis by nucleophilic substitution of the remaining chlorine atom. Unfortunately, the 7-amino-substituted 1*H*-pyrrolo[3,2-*b*]pyridine **15** was not accessible by heating a mixture of **13** and 1-(2-ethyl-6-methylphenyl)-methanamine[18] under microwave-assisted conditions.[19] In the same manner, attempts to prepare 7-amino-1*H*-pyrrolo[3,2-*b*]pyridine **16** using either ammonia or sodium amide as nucleophile were not successful. Experiments aiming at the nucleophilic substitution of the 7-chloro atom with 1-(2-ethyl-6-methylphenyl)-methanamine or ammonia were also conducted with the BOC-protected derivative **17**. However, only cleavage of the BOC group affording 4-azaindole **13** was observed.

We then focused our attention on an alternative approach for the preparation of the 1*H*-pyrrolo[3,2-*b*]pyr-

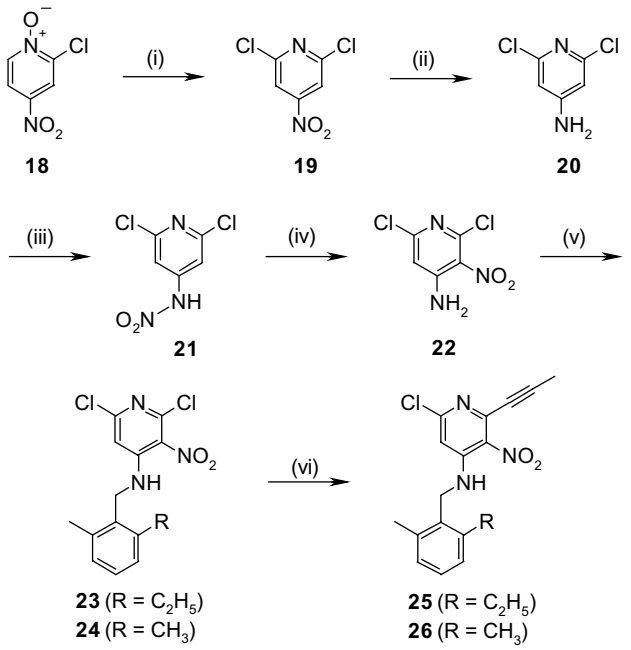


Scheme 1. Reagents and conditions: (i) $POCl_3$, 110 °C, 4 h, 62%; (ii) $SnCl_2$-$2H_2O$, HCl (conc.), Et_2O, rt, 2 h, 92%; (iii) NBS, DMF, 0 °C to rt, 3 h, 80%; (iv) $Pd(OAc)_2$, PPh_3, $HNMe_2$ (solution in THF), NEt_3, 6 bar CO, THF, 100 °C, 4 h, 59%; (v) $Pd(OAc)_2$, PPh_3, $HNMe_2$ (solution in THF), NEt_3, 6 bar CO, THF, 70 °C, 4 h, 83%; (vi) $Pd(PPh_3)_2Cl_2$, CuI, propyne, Et_3N, autoclave, 80 °C, 16.5 h, 71%, (vii) CuI (catalytic), DMF, 110 °C, 2 h, 63%; (viii) CuI (stoichiometric), DMF, 110 °C, 5.5 h, 65%; (ix) 1-(2-ethyl-6-methylphenyl)-methanamine, CH_3CN, DMF, NMP, toluene, or without solvent, microwave heating, 180 °C, no conversion or decomposition; (x) NH_3 or $NaNH_2$, dioxane or toluene, microwave or conventional heating, 120–160 °C, no conversion; (xi) BOC_2O, 4-DMAP, THF, CH_2Cl_2, rt, 18 h, 81%.

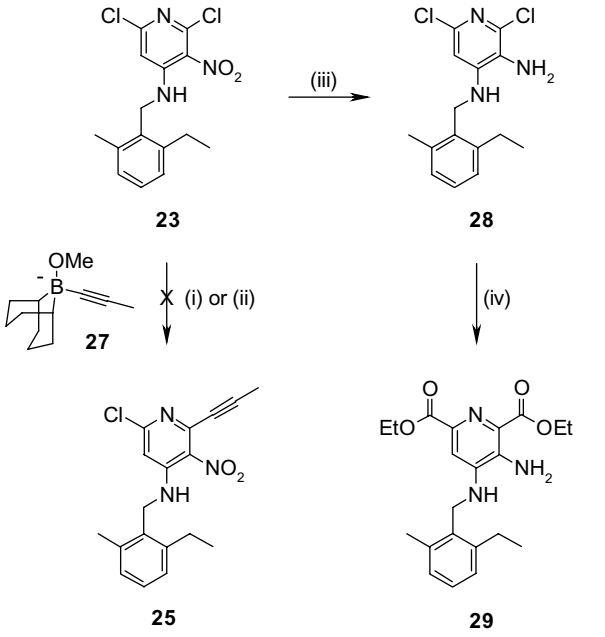
idine scaffold (Scheme 2). Following a four-step procedure published in the literature, the tetrasubstituted pyridine **22** was obtained in 57% overall yield from 2-chloro-4-nitropyridine-*N*-oxide (**18**):[20] Starting material **18** was converted into 2,6-dichloro-pyridin-4-ylamine (**20**) by treatment with phosphorus oxychloride to afford **19** and subsequent nucleophilic substitution of the nitro function. Nitration of 2,6-dichloro-pyridin-4-ylamine (**20**) was followed by acid-catalyzed rearrangement of the nitro group furnishing 2,6-dichloro-3-nitro-pyridin-4-ylamine (**22**). Transformation of pyridinylamine **22** with 2-ethyl-6-methyl-benzyl chloride proceeded smoothly and the corresponding N-alkylated derivative **23** was secured in 77% yield. Introduction of the propynyl substituent was accomplished by Stille reaction of 2,6-dichloro-3-nitropyridine (**23**) with tributyl(1-propynyl)tin. The cross-coupling proceeded in a regioselective manner with replacement of the more reactive 2-chloro atom affording pyridine **25**.

Although the tin organyles could be removed completely by chromatography and crystallization at the stage of compound **30** (Scheme 4), attempts were made to replace the Stille coupling with another Palladium-catalyzed cross-coupling reaction (Scheme 3). First, borate complex **27** was formed from prop-1-ynyllithium and 9-OMe-9-BBN and used as coupling partner for chloropyridine **23** as described by Fürstner and Seidel[21a] and Soderquist et al.[21b] However, either no conversion or decomposition of the starting material **23** was observed. Second, the propynylation of 3-nitro-2-chloropyridine **23** by Sonogashira reaction was examined. Under reaction conditions similar to those reported for the preparation of 2-propynyl-pyridin-3-ylamine **12** (Scheme 1), complete conversion of the starting material **23** was observed. However, no defined product could be isolated. As a further possibility to accomplish selective substitution of one chloro atom, we investigated the alkoxycarbonylation of 2,6-dichloropyridin-3-ylamine **28**, which was obtained by reduction of the 3-nitro analogue **23** with tin chloride.[17] However, under the drastic conditions required for this cross-coupling reaction (16 bar carbon monoxide, 150 °C, 6 h) only dicarboxylate **29** was isolated in low yield (Scheme 3).

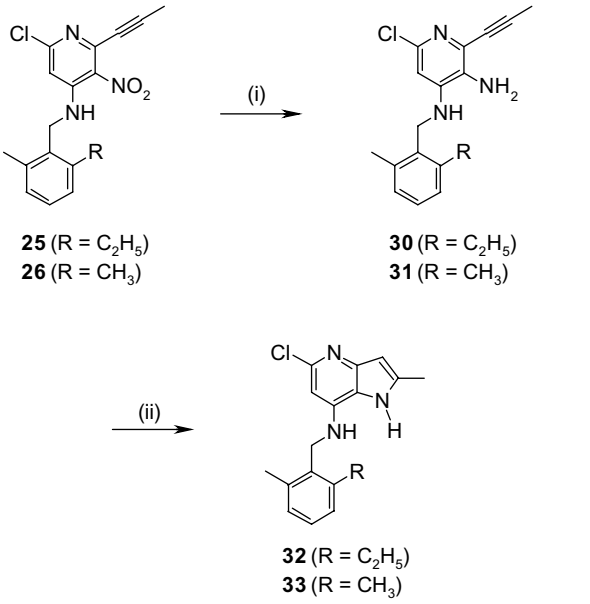
The synthesis of the 1*H*-pyrrolo[3,2-*b*]pyridine scaffold was completed by copper iodide mediated cyclization of 2-prop-1-ynylpyridin-3-amine **30**, which in turn was obtained by reduction of the corresponding nitro precursor **25** (Scheme 4). The cyclization was examined with respect to the stoichiometry of copper iodide and



Scheme 2. Reagents and conditions: (i) $POCl_3$, 110 °C, 2.5 h, 70%; (ii) NH_3, THF, autoclave, 95 °C, 4 h, 82%; (iii) H_2SO_4, HNO_3, 0 °C, 2 h, 100%; (iv) H_2SO_4, 100 °C, 1 h, 100%; (v) NaH, THF, 10–15 °C, 1 h, then addition of a prestirred mixture (rt, 1 h) of 2-ethyl-6-methyl-benzyl chloride or 2,6-dimethyl-benzyl chloride and NaI, 0–10 °C, 1 h, **23**: 77%, **24**: 79%; (vi) $Bu_3Sn(C_3H_3)$, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, 50 °C, 3 h, **25**: 76%, **26**: 84%.



Scheme 3. Reagents and conditions: (i) Preparation of **27**: (1) propyne, *n*-BuLi, THF; (2) 9-OMe-9-BBN, −60 °C; attempted cross-coupling: $PdCl_2$(dppf), **23**, rt (no conversion), Δ (decomposition); (ii) $Pd(PPh_3)_2Cl_2$, CuI, propyne, Et_3N, autoclave, 80 °C, 16.5 h, full conversion (mixture of uncharacterized products); (iii) $SnCl_2$-2 H_2O, HCl, Et_2O, rt, 2 h, 55%; (iv) $Pd(OAc)_2$, DPPP, K_2CO_3, 16 bar CO, EtOH, DMF, 150 °C, 16 h, 18%, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, DPPP = 1,3-bis(diphenylphosphino)propane.

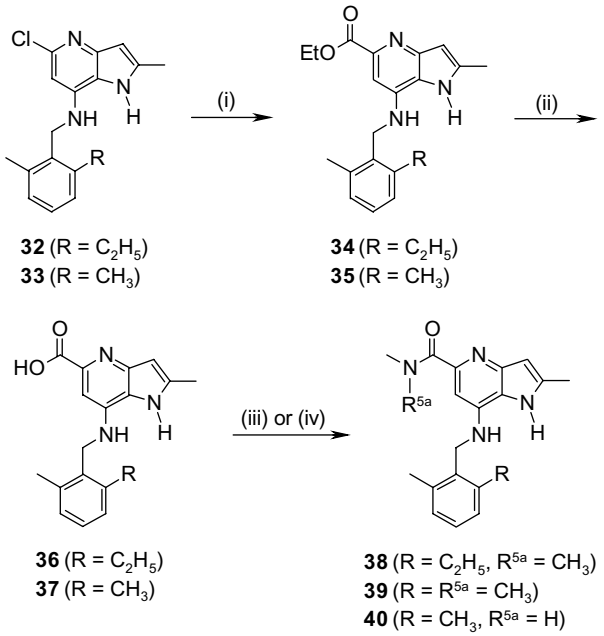


Scheme 4. Reagents and conditions: (i) $SnCl_2$-2 H_2O, HCl, Et_2O, rt, 1 h, **30**: 96%, **31**: 78%; (ii) CuI, DMF, 80 °C, 1 h, then quenching with 0.1 M Na_2SO_3, **32**: 91%, **33**: 92%.

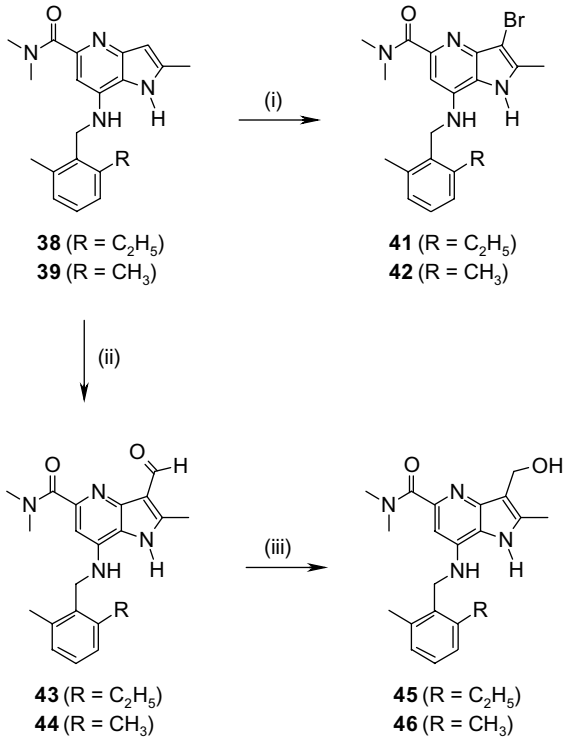
the reaction temperature. At least 0.2 equivalents of copper iodide was required for complete transformation of the starting material **30** at 80 °C. The reaction could be conducted at 50, 80 or 110 °C with reaction periods of 3, 1.5 or 0.5 h, respectively. The 1*H*-pyrrolo[3,2-*b*]pyridine **32** was isolated in 91% yield. The formation of the 3-iodo analogue of **32** as possible by-product could be avoided by reductive work-up (quenching with 0.1 M sodium sulfite solution).[22]

In summary, 4-azaindole **32** was prepared in 8 steps with an overall yield of 29%. All transformations were amenable to scale up using 13–70 g of the corresponding starting material. The structurally related 1*H*-pyrrolo[3,2-*b*]pyridine **33**, which possesses a 7-(2,6-dimethyl-benzylamino) substituent rather than a 7-(2-ethyl-6-methyl-benzylamino) residue, was prepared in an analogous manner (see Schemes 2 and 4) and was obtained in 27% overall yield.

Having completed the synthesis of the heterocyclic scaffold, functionalization of the 3- and 5-position of the 1*H*-pyrrolo[3,2-*b*]pyridine moiety had to be elaborated next. For the introduction of a 5-carboxamide substituent, alkoxycarbonylation using the palladium acetate/1,3-bis(diphenylphosphino)propane catalyst system was investigated (Scheme 5). Applying a pressure of 15 bar of carbon monoxide, sluggish conversion was observed at a temperature of 150 °C. At a temperature of 195 °C, full conversion was achieved within 16 h and ethyl carboxylate **34** was isolated in 48% yield. A significant reduction of the reaction time was achieved when the reaction mixture was subjected to a carbon monoxide pressure of 30 bar. After heating the reaction mixture at a temperature of 190 °C for 3 h, ethyl carboxylate **34** was isolated in 68% yield.[23] After saponification of the ester group, carboxamide **38** was pre-



Scheme 5. Reagents and conditions: (i) $Pd(OAc)_2$, DPPP, K_2CO_3, EtOH, DMF, 30–35 bar CO, 190–200 °C, 3 h, **34**: 68%, **35**: 69%; (ii) KOH, MeOH, H_2O, 50–60 °C, 1.5–2 h, **36**: 79%, **37**: 71%; (iii) **38**: (1) TBTU, CH_2Cl_2/DMF, 50 °C, 1 h; (2) Me_2NH in THF, rt, 1 h, 76%; **39**: (1) TBTU, DMF, 60 °C, 1.5 h; (2) Me_2NH in THF, 60 °C, 2 h, 66%; **40**: (1) TBTU, DMF, 60 °C, 1 h; (2) $MeNH_2$ in EtOH, 60 °C, 2 h, rt, 16 h, 45%.

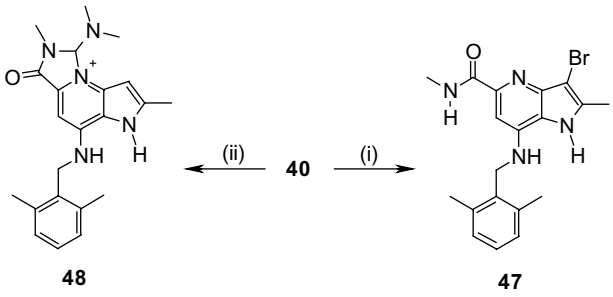


Scheme 6. Reagents and conditions: (i) NBS, DMF, 0 °C, 0.5 h, **41**: 81%, **42**: 71%; (ii) **43**: $POCl_3$/DMF, rt, 1.5 d, 58%, **44**: $POCl_3$, DMF, 80 °C, 100 min, 43%; (iii) **45**: $NaBH_4$, EtOH, rt, 1.5 h, 72%, **46**: $NaBH_4$, EtOH, rt to 50 °C, 1 h, 74%.

pared by TBTU-mediated coupling of the obtained carboxylic acid **36** with dimethylamine.[24] In the same manner, the analogous 1*H*-pyrrolo[3,2-*b*]pyridines **39** and **40** were prepared from their 5-chloro precursor **33** applying the reaction sequence depicted in Scheme 5.

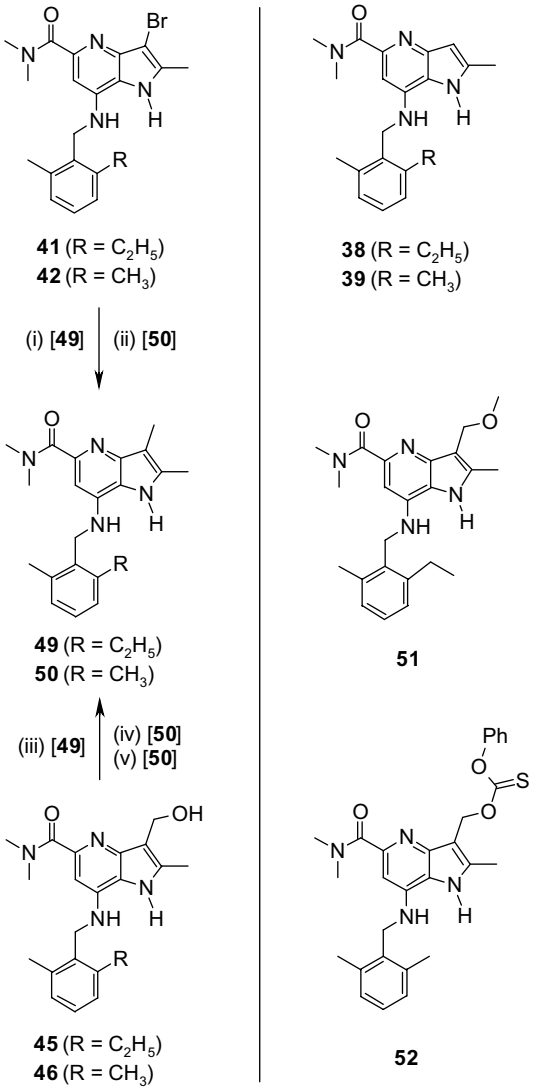
Introduction of a substituent in 3-position of the *N*,*N*-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxamides **38** and **39** was accomplished either by transformation with *N*-bromosuccinimide yielding bromides **41** and **42** or by Vilsmeier formylation furnishing aldehydes **43** and **44** (Scheme 6). Subsequently, aldehydes **43** and **44** were reduced to the corresponding alcohols **45** and **46** using sodium borohydride as reducing agent.

In the same manner, *N*-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxamide **40** was transformed with *N*-bromosuccinimide or phosphorus oxychloride/DMF, respectively (Scheme 7). Whereas the 3-bromo derivative **47** was isolated in 44% yield, the corresponding 3-carbaldehyde was not accessible. In lieu thereof, electrophilic attack of the Vilsmeier reagent occurred at the pyridine ring and the 3-oxo-1,2,3,6-tetrahydroimidazo[1,5-*a*]pyrrolo[2,3-*e*]pyridin-9-ium ion **48** was obtained in 51% yield.



Scheme 7. Reagents and conditions: (i) NBS, DMF, 0 °C, 0.5 h, 44%; (ii) $POCl_3$, DMF, 80 °C, 70 min, 51%.

In the beginning, two strategies for the synthesis of the 3-methyl-substituted 1*H*-pyrrolo[3,2-*b*]pyridine **49** were pursued (Scheme 8). The first strategy relied on the Suzuki coupling of bromo derivative **41** with trimethylboroxine.[25] The reaction proved to be feasible using Palladium catalyst SK-CC01-A and microwave-assisted heating.[26] However, in all experiments the cross-coupling was accompanied by dehalogenation of starting material **41** and mixtures of 3-methyl-1*H*-pyrrolo[3,2-*b*]pyridine **49** along with its 3-unsubstituted analogue **38** were isolated. Therefore, the reduction of 3-hydroxymethyl derivative **45** by catalytic hydrogenation was investigated as alternative approach:[27] Using methanol as solvent, transformation of starting material **45** was accomplished under harsh conditions (50 bar hydrogen, 50 °C, 28 h) only. An inseparable mixture of 3-methyl-1*H*-pyrrolo[3,2-*b*]pyridine **49** along with its 3-methoxymethyl analogue **51** was isolated. When the hydrogenation was conducted in acetic acid rather than in methanol, the reduction of the 3-hydroxymethyl derivative **45** proceeded under milder conditions (10 bar hydrogen, 50 °C, 4 h). Although purification of the



Scheme 8. Reagents and conditions: (i) SK-CC01-A, trimethylboroxine, Cs_2CO_3, 1,4-dioxane, 150 °C, MW, 2× 16 min, 82% (mixture of **49** and **38**, ratio 7:3); (ii) SK-CC01-A, $ZnMe_2$ in toluene, MW, 1,4-dioxane, 150 °C, 1 h, 70% (mixture of **50**, **39** and **42**, ratio 57:20:23); (iii) variant 1: Pd/C, 50 bar H_2, MeOH, 50 °C, 28 h, 38% (mixture of **49** and **51**), variant 2: Pd/C, 10 bar H_2, HOAc, 50 °C, 4 h, 46% **49**; (iv) *O*-phenyl chlorothionoformate, pyridine, DMAP, CH_2Cl_2, rt or 40 °C, 2 h, then AIBN, H_3PO_2, NEt_3, 1,4-dioxane, water, 100 °C, 1 h, 15% **50**; (v) Et_3SiH, TFA, rt, 3 h, 63% **50**.

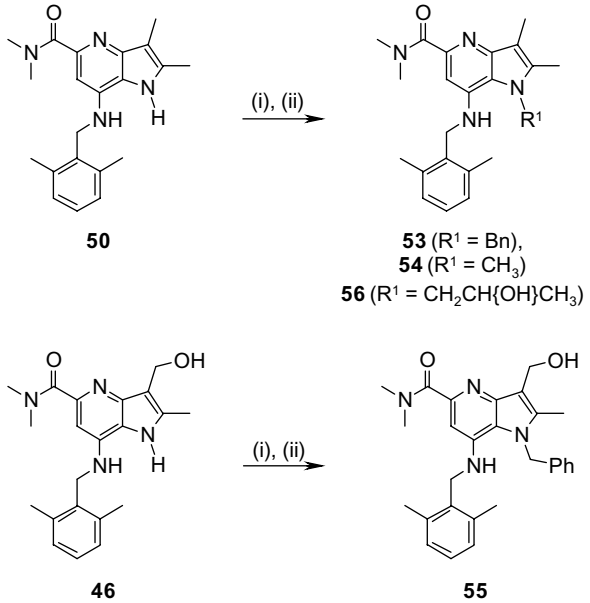
crude product turned out to be tedious, target compound **49** was isolated in 46% yield.

Since neither of the two approaches for the synthesis of the 2,3-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine **49** turned out satisfactory, three further methods were investigated for the synthesis of the analogous 4-azaindole **50** (Scheme 8): (1) Incomplete conversion was achieved in the Negishi coupling of 3-bromo-1*H*-pyrrolo[3,2-*b*]pyridine **42** with dimethylzinc and a mixture of the desired product **50**, its 3-H analogue **39** and untransformed starting material **42** was isolated.[26,28] (2) In an alternative approach, 3-hydroxymethyl-1*H*-pyrrolo[3,2-*b*]pyridine **46** was transformed into the corresponding *O*-phenyl thiocarbonate **52**, which in turn was reduced by addition of hypophosphoric acid and AIBN.[29] This afforded the 3-methyl derivative **50** albeit in low yield. (3) Finally, the reduction of alcohol **46** with an excess of triethylsilane was identified as an efficient method to secure 3-methyl-1*H*-pyrrolo[3,2-*b*]pyridine **50**.[30] If pure trifluoroacetic acid was used as solvent, the reaction proceeded smoothly at room temperature and the 3-methyl derivative **50** was isolated in good yield.[30] However, if mixtures of dichloromethane and trifluoroacetic acid were used, long reaction times were required and the target compound **50** was isolated in low yield only.

The 1*H*-pyrrolo[3,2-*b*]pyridine scaffold exhibits ambident reactivity, e.g. the treatment of 4-azaindoles with alkyl halides can result in N-1- or N-4-alkylation.[31] According to the literature, in the presence of a base, N-1-alkylation is favoured.[31] Indeed, deprotonation of 1*H*-pyrrolo[3,2-*b*]pyridine **50** with sodium hydride and subsequent transformation with benzyl bromide or methyl iodide afforded the corresponding N-1-alkylated derivatives **53** and **54** in moderate yield (Scheme 9). N-Benzylation of the 3-hydroxymethyl analogue **46** was also feasible applying similar reaction conditions and the corresponding 4-azaindole **55** was isolated in 48% yield. Epoxides can also be used as electrophiles for N-1-alkylation. Transformation of 4-azaindole **50** with 2-methyloxirane afforded the corresponding N-1-alkylated 1*H*-pyrrolo[3,2-*b*]pyridine **56** in 10% yield.

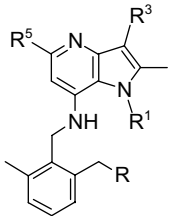
2.2. Inhibitory activity and physicochemical properties of 1*H*-pyrrolo[3,2-*b*]pyridines

The inhibitory and cellular activity of 1*H*-pyrrolo[3,2-*b*]pyridines **38**–**42**, **45**–**47**, **49**–**50** and **53**–**56** was evaluated in a competitive binding assay against H^+/K^+-ATPase from hog gastric mucosa and by determi-



Scheme 9. Reagents and conditions: (i) NaH, DMF, 0 °C to rt, 1 h; (ii) **53**: BnBr, DMF, rt, 1 h, 38%; **54**: MeI, rt, 2 h, 33%; **55**: BnBr, DMF, rt, 1 h, 48%; **56**: 2-methyloxirane, DMF, MW, 100 °C, 2× 2 h, 10%.

Table 1. Inhibitory activity and physicochemical properties of 1*H*-pyrrolo[3,2-*b*]pyridines **38**–**42**, **45**–**47**, **49**–**50** and **53**–**56**



Compound	R^1	R^3	R^5	R	H^+/K^+-ATPase $-\log IC_{50}$	Gastric glands $-\log IC_{50}$	pK_a	log *D* (pH 7.4)
38	H	H	$CONMe_2$	CH_3	5.9	5.5	7.39	4.10
39	H	H	$CONMe_2$	H	6.1	5.6	7.30	3.62
40	H	H	CONHMe	H	5.5	5.8	7.33	2.96
41	H	Br	$CONMe_2$	CH_3	5.0	5.0	5.84	>4.80[a]
42	H	Br	$CONMe_2$	H	5.0	5.5	6.02	>4.80[a]
45	H	CH_2OH	$CONMe_2$	CH_3	5.7	4.3	7.07	3.27
46	H	CH_2OH	$CONMe_2$	H	5.6	4.2	7.20	2.95
47	H	Br	CONHMe	H	<4	5.3	5.64	—[b]
49	H	CH_3	$CONMe_2$	CH_3	6.6	6.6	7.57	4.60
50	H	CH_3	$CONMe_2$	H	6.9	6.6	7.56	4.04
53	CH_2Ph	CH_3	$CONMe_2$	H	5.1	6.0	6.86	5.20
54	CH_3	CH_3	$CONMe_2$	H	4.6	4.8	7.13	3.53
55	CH_2Ph	CH_2OH	$CONMe_2$	H	4.6	5.0	6.52	3.87
56		CH_3	$CONMe_2$	H	4.8	5.4	7.19	3.40

[a] Limit of quantitation of employed method (see Section 4).
[b] log *D* value not determined due to insufficient solubility of compound **47** in 1-octanol.

nation of acid formation in gastric glands. Additionally, the lipophilicity and pK_a values of all target compounds were determined. The results are summarized in Table 1.

The figures reported in Table 1 clearly demonstrate that the pK_a values of the obtained 1*H*-pyrrolo[3,2-*b*]pyridines are in the same range as those reported for the corresponding imidazo[1,2-*a*]pyridines.[32] In light of this, the goal to synthesize P-CABs with rather low basicity that would accumulate in a selective manner was attained. Furthermore, the physicochemical properties can be fine-tuned by modification of the residues R^1, R^3, R^5, and the substitution pattern of the 7-benzylamino residue. For example, replacement of the 2-ethyl-6-methyl-benzyl residue (**38**, **45**, and **49**) versus a 2,6-dimethylbenzyl substituent (**39**, **46**, and **50**) comes along with a significant reduction of lipophilicity ($\Delta\log D \sim 0.5$). The lipophilicity can be decreased further ($\Delta\log D \sim 0.7$) by replacement of the dimethylcarboxamide residue R^5 (**39**) with a methylcarboxamide substituent (**40**). The pK_a value can be influenced by the character of the residue R^3. With respect to the corresponding parent compounds (**38** and **39**), the presence of a 3-methyl substituent (**49** and **50**) causes a slight increase of the pK_a value ($\Delta pK_a \sim 0.2$), whereas 3-hydroxymethyl substitution (**45** and **46**) results in a decrease of the pK_a value ($\Delta pK_a \sim 0.2$). The 3-bromo derivatives **41** and **42** possess significantly lower pK_a values than the corresponding parent compounds **38** and **39** ($\Delta pK_a \sim 1.4$). The pK_a value can also be lowered by N-1-alkylation. The magnitude of the effect depends on the character of the N-1 substituent and seems to be more pronounced for *N*-benzyl (**53** vs. **50** and **55** vs. **46**, $\Delta pK_a \sim 0.7$) than for *N*-methyl and *N*-{2-hydroxypropyl} (**54** and **56** vs. **50**, $\Delta pK_a \sim 0.4$). Based on the assumption that potassium-competitive acid blockers should preferentially possess log *D* values in the range of 2–3, the 3-hydroxymethyl-substituted 1*H*-pyrrolo[3,2-*b*]pyridine **46** combines a favourable log *D* value of 2.95 with an adequately low pK_a value of 7.20. On this account, the alcohol **46** constitutes the most interesting inhibitor from a physicochemical point of view.

On the other hand, high affinity to the gastric proton pump enzyme is observed only if R^3 is a methyl group or a hydrogen atom. If R^3 represents a hydroxymethyl group, compounds with modest inhibitory activity of H^+/K^+-ATPase and with weak potency as inhibitors of acid secretion from gastric glands are obtained. N-1-alkylation results in a significant decrease of affinity towards the enzyme (**53**–**56**). With the exception of the 3-hydroxymethyl derivatives **45** and **46**, there is a good correlation between the strength of inhibition of H^+/K^+-ATPase and the amount of reduction of acid secretion from gastric glands. From a pharmacological point of view, the 3-methyl-substituted 1*H*-pyrrolo[3,2-*b*]pyridines **49** and **50** show the most potent in vitro activity and are the most promising candidates for further development as potassium-competitive acid blockers.

3. Conclusions

In summary, a series of novel 1*H*-pyrrolo[3,2-*b*]pyridines was prepared relying on a copper iodide mediated cyclization of 2-prop-1-ynylpyridin-3-amines. The possibility to fine-tune the physicochemical properties of the target compounds by modification of the residues R^1, R^3, R^5, and the substitution pattern of the 7-benzylamino residue was demonstrated. It was shown that the imidazo[1,2-*a*]pyridine scaffold does not constitute an indispensable structural element of potent P-CABs: the 1*H*-pyrrolo[3,2-*b*]pyridines **49** and **50** are potent inhibitors of the gastric proton pump enzyme and promising candidates for further development as potassium-competitive acid blockers.

4. Experimental

4.1. Chemistry

4.1.1. General. All chemicals were purchased from the major chemical suppliers as highest purity grade and used without any further purification. The progress of the reaction was monitored on Macherey-Nagel HPTLC plates Nano-SIL 20 UV_{254} (0.20 mm layer, nano silica gel 60 with fluorescence indicator UV_{254}) using dichloromethane/methanol as solvent system. Column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM) with the solvent mixtures specified in the corresponding experiment. Spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm). Melting points (mp) were taken in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker DRX 200 FT-NMR spectrometer at a frequency of 200.1 MHz or a Bruker AV 400 FT-NMR spectrometer at a frequency of 400.1 MHz. $CDCl_3$ or DMSO-d_6 was used as solvent. The chemical shifts were reported as parts per million (δ ppm) with tetramethylsilane (TMS) as an internal standard. High resolution mass spectra were obtained on a Bruker Daltonics MicroTOF Focus instrument using electrospray ionisation (ESI positive). Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer.

4.1.2. 2,4-Dichloro-3-nitropyridine (7). A suspension of 2,4-dihydroxy-3-nitropyridine (**6**) (25.0 g, 160 mmol) in phosphorus oxychloride (250 ml) was heated at 110 °C for 4 h. The dark solution was concentrated to a volume of approximately 60 ml. With caution (exothermic reaction), the residue was added portionwise to ice-water (200 ml). The aqueous phase was extracted with ethyl acetate (4× 80 ml). The combined organic phases were washed with water (3× 100 ml), dried over sodium sulfate and concentrated under reduced pressure. The dark residue (30 g) was purified by column chromatography (silica gel, eluant: dichloromethane). Evaporation of the corresponding fractions afforded 19.0 g of 2,4-dichloro-3-nitropyridine (**7**) (colourless solid, 62% yield): mp 62–63 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 8.04 (d, 1H), 8.69 (d, 1H).

4.1.3. 2,4-Dichloropyridin-3-ylamine (8). 2,4-Dichloro-3-nitropyridine (**7**) (18.0 g, 93.3 mmol) was dissolved in diethyl ether (100 ml) and a solution of tin(II) chloride dihydrate (210 g, 931 mmol) in concentrated hydrochloric acid (220 ml) was added over a period of 2 h. After complete addition, the white suspension was stirred for 2 h at room temperature and for 1 h at 0 °C. The precipitate was collected by filtration and washed with water (20 ml). A suspension of the residue in water (300 ml) and ethyl acetate (100 ml) was treated with ammonia solution (25% in water) until a pH value of 7 was obtained. Stirring was continued for several minutes and the aqueous phase was extracted with ethyl acetate (2× 80 ml). The combined organic phases were washed with saturated sodium chloride solution (2× 50 ml), dried over sodium sulfate and concentrated in vacuo. This afforded 14.0 g of 2,4-dichloropyridin-3-ylamine (**8**) (colourless solid, 92% yield): mp 68–70 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 5.79 (bs, 2H), 7.35 (d, 1H), 7.58 (d, 1H).

4.1.4. 6-Bromo-2,4-dichloropyridin-3-ylamine (9). 2,4-Dichloropyridin-3-ylamine (**8**) (13.5 g, 82.8 mmol) was dissolved in DMF (430 ml) and a solution of *N*-bromosuccinimide (17.8 g, 100.0 mmol) in DMF (200 ml) was added over a period of 3 h at 0 °C. After complete addition, the yellow solution was stirred for 15 min at 0 °C and for 3 h at room temperature. The reaction mixture was quenched with ice-water (1500 ml) and ethyl acetate (300 ml) and stirring was continued for several minutes. The phases were separated and the aqueous phase was extracted with ethyl acetate (3× 100 ml). The combined organic phases were washed with sodium chloride solution (2× 50 ml) and water (2× 80 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, eluant: petroleum ether/ethyl acetate = 1:1 (v/v)]. Evaporation of the corresponding fractions afforded 6-bromo-2,4-dichloropyridin-3-ylamine **9** in 80% yield (16 g of a colourless solid): mp 84–85 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 6.03 (bs, 2H), 7.66 (s, 1H).

4.1.5. 3-Amino-4-chloro-pyridine-2,6-dicarboxylic acid bis-dimethylamide (10). In an autoclave, a mixture of 6-bromo-2,4-dichloropyridin-3-ylamine (**9**) (5.0 g, 20.7 mmol), dimethylamine (2 M solution in THF, 50.0 ml, 100 mmol), palladium acetate (0.5 g, 2.2 mmol), triphenylphosphine (4.0 g, 15.3 mmol), triethylamine (7.0 ml, 5.1 g, 50.2 mmol), and THF (50 ml) was heated under a pressure of carbon monoxide (6 bar) for 4 h at 100 °C. The suspension was cooled to room temperature and poured on a mixture of saturated ammonium chloride solution (100 ml) and ethyl acetate (100 ml). The biphasic mixture was stirred for several minutes, the phases were separated, and the aqueous phase was extracted with ethyl acetate (5× 30 ml). The combined organic phases were dried over sodium sulfate and evaporated to dryness. The residue (12 g of a brown liquid) was purified by column chromatography (silica gel, eluant: ethyl acetate) and subsequent slurrying in diethyl ether (80 ml). The bis-carboxamide **10** was isolated in 59% yield (3.3 g of a colourless solid): mp 164–166 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.90,

2.96, 3.01, 3.04 (4 s, 12H), 5.98 (bs, 2H), 7.59 (s, 1H); Anal. Calcd for $C_{11}H_{15}ClN_4O_2$: C, 48.80; H, 5.58; N, 20.70; Cl, 13.10. Found: C, 49.01; H, 5.58; N, 20.47; Cl, 12.93; HRMS (ESI) *m/z* $C_{11}H_{16}ClN_4O_2$ $[M+H]^+$ calcd: 271.0956. Found: 271.0945.

4.1.6. 5-Amino-4,6-dichloro-pyridine-2-carboxylic acid dimethylamide (11). In an autoclave, a mixture of 6-bromo-2,4-dichloropyridin-3-ylamine (**9**) (5.0 g, 20.7 mmol), dimethylamine (2 M solution in THF, 50.0 ml, 100 mmol), palladium acetate (0.5 g, 2.2 mmol), triphenylphosphine (4.0 g, 15.3 mmol), triethylamine (7.0 ml, 5.1 g, 50.2 mmol) and THF (25 ml) was heated under a pressure of carbon monoxide (6 bar) for 4 h at 70 °C. The suspension was cooled to room temperature and poured on a mixture of saturated ammonium chloride solution (50 ml) and ethyl acetate (80 ml). The biphasic mixture was stirred for several minutes, the phases were separated, and the aqueous phase was extracted with ethyl acetate (3× 30 ml). The combined organic phases were washed with saturated ammonium chloride solution (2× 30 ml) and water (2× 50 ml), dried over sodium sulfate and evaporated to dryness. The residue (13 g of a brown liquid) was purified by column chromatography [silica gel, eluant: petroleum ether/ethyl acetate = 1:1 (v/v)]. The carboxamide **11** was isolated in 83% yield (4.1 g of a colourless solid): mp 164–166 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.10 (s, 3H), 3.21 (s, 3H), 4.70 (bs, 2H), 7.70 (s, 1H); Anal. Calcd for $C_8H_9Cl_2N_3O$: C, 41.05; H, 3.88; N, 17.95. Found: C, 41.41; H, 3.95; N, 17.49.

4.1.7. 5-Amino-4-chloro-6-prop-1-ynyl-pyridine-2-carboxylic acid dimethylamide (12). A suspension of 4,6-dichloropyridine **11** (2.61 g, 11.2 mmol) in triethylamine (50 ml) was degassed with argon. At a temperature of −30 °C, freshly condensed propyne (6.4 ml, 4.5 g, 0.11 mmol), bis(triphenylphosphine)palladium(II) dichloride (402 mg, 0.57 mmol) and copper(I) iodide (109 mg, 0.57 mmol) were added. The autoclave was closed tightly and heated to 80 °C. After a period of 16.5 h, the autoclave was cooled to room temperature and the heterogenic mixture was poured on ethyl acetate (150 ml) and saturated ammonium chloride solution (75 ml). The autoclave was washed with dichloromethane (80 ml). The aqueous phase was extracted with ethyl acetate (2× 75 ml). The combined organic phases were washed with saturated ammonium chloride solution (75 ml) and water (75 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue (2.5 g of a brown solid) was purified by column chromatography [100 g of silica gel, eluant: ethyl acetate/petroleum ether = 7:3 (v/v)]. Evaporation of the corresponding fractions afforded the title compound **12** (1.90 g of an ochre solid, 71% yield): mp 170–171 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.14 (s, 3H), 2.95, 3.04 (2 s, 6H), 6.00 (bs, 2H), 7.48 (s, 1H); Anal. Calcd for $C_{11}H_{12}ClN_3O$: C, 55.59; H, 5.09; N, 17.68; Cl, 14.92. Found: C, 55.23; H, 5.10; N, 17.40; Cl, 14.65.

4.1.8. 7-Chloro-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (13). In a flame-dried flask filled with argon, 2-prop-1-ynyl-pyridin-3-ylamine **12** (11.1 g, 46.7 mmol) was dissolved in DMF (600 ml) and copper(I) iodide (1.77 g, 9.3 mmol) was added. The reaction mixture was stirred at 110 °C for 2 h and poured on a mixture of ice-water (1 L) and dichloromethane (500 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 100 ml). The combined organic phases were washed with water (100 ml), dried over sodium sulfate, and the solvent was evaporated. The residue (12 g of a brown oil) was purified by column chromatography [600 g of silica gel, eluant: petroleum ether/ethyl acetate = 3:7 (v/v), then ethyl acetate/methanol = 1:1 (v/v)]. Evaporation of the corresponding fractions afforded 7.0 g of 1*H*-pyrrolo[3,2-*b*]pyridine **13** (63% yield): mp 226–227 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.52 (s, 3H), 3.15 (s, 6H), 6.46 (s, 1H), 7.44 (s, 1H), 8.75 (bs, 1H); HRMS (ESI) *m/z* $C_{11}H_{13}ClN_3O$ $[M+H]^+$ calcd 238.0742. Found: 238.0742.

4.1.9. 7-Chloro-3-iodo-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (14). In a flame-dried flask filled with argon, 2-prop-1-ynyl-pyridin-3-ylamine **12** (200 mg, 0.84 mmol) was dissolved in DMF (15 ml) and copper(I) iodide (160 mg, 0.84 mmol) was added. The reaction mixture was stirred for 4 h at 110 °C. Another portion of copper(I) iodide (32 mg, 0.17 mmol) was added and the reaction was continued for 1.5 h at 110 °C. The reaction mixture was poured on a mixture of water (25 ml) and dichloromethane (50 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were washed with water (50 ml) and saturated sodium chloride solution (50 ml), dried over sodium sulfate, and the solvent was evaporated. The residue (273 mg of a dark-brown solid) was purified by column chromatography [15 g of silica gel, eluant: petroleum ether/ethyl acetate = 1:1 (v/v)]. Evaporation of the corresponding fractions afforded 197 mg of 3-iodo-1*H*-pyrrolo[3,2-*b*]pyridine **14** (65% yield): mp 225–226 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.59 (s, 3H), 3.17 (s, 3H), 3.28 (s, 3H), 7.65 (s, 1H), 8.75 (bs, 1H); HRMS (ESI) *m/z* $C_{11}H_{12}ClIN_3O$ $[M+H]^+$ calcd: 363.9708. Found: 363.9697.

4.1.10. 7-Chloro-5-dimethylcarbamoyl-2-methyl-pyrrolo-[3,2-*b*]pyridine-1-carboxylic acid *tert*-butyl ester (17). A solution of 1*H*-pyrrolo[3,2-*b*]pyridine **13** (178 mg, 0.75 mmol) in THF (8 ml) and dichloromethane (8 ml) was treated with di-*tert*-butyl dicarbonate (180 mg, 0.82 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol). The clear solution was stirred for 2.5 h at room temperature. More di-*tert*-butyl dicarbonate (45 mg, 0.21 mmol) was added and the reaction was continued for 15.5 h at room temperature. The reaction was quenched by addition of saturated sodium bicarbonate solution (10 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 20 ml). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography [15 g of silica gel, eluant: petroleum ether/ethyl acetate = 3:7 (v/v)]. Evaporation of the corresponding fractions afforded the 1-BOC-derivative **17** (205 mg, 81% yield): mp

85–86 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.66 (s, 9H), 2.58 (s, 3H), 3.13, 3.15 (2 s, 6H), 6.50 (s, 1H), 7.52 (s, 1H); HRMS (ESI) *m/z* $C_{16}H_{21}ClN_3O_3$ $[M+H]^+$ calcd: 338.1266. Found: 338.1251.

4.1.11. 2,6-Dichloro-4-nitropyridine (19). A suspension of 2-chloro-4-nitro-pyridine-*N*-oxide (**18**) (50.0 g, 286 mmol) in phosphorus oxychloride (280 ml) was heated for 2.5 h at 110 °C. Phosphorus oxychloride was removed by distillation and the residue was poured on ice-water (800 ml). At a temperature of 0 °C, a pH value of 8 was adjusted by addition of 6 N sodium hydroxide solution and stirring was continued for 15 min. A beige precipitate was formed, which was collected by filtration. 2,6-Dichloro-4-nitropyridine (**19**) was isolated in 70% yield (38.5 g of a beige solid): mp 92–93 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.01 (s, 2H).

4.1.12. 2,6-Dichloropyridin-4-ylamine (20). In an autoclave, a mixture of 2,6-dichloro-4-nitropyridine (**19**) (19.0 g, 98.5 mmol), ammonia solution (25% in water, 55 ml) and THF (250 ml) was heated at 95 °C for 4 h. The reaction mixture was concentrated (removal of THF). At a temperature of 0 °C, ice-water (250 ml) was added and stirring was continued for 1 h. The title compound **20** was collected by filtration (13.2 g, 82% yield): mp 156–157 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.38 (bs, 2H), 6.48 (s, 2H).

4.1.13. 2,6-Dichloro-4-nitroamino-pyridine (21). Portions of 2,6-dichloropyridin-4-ylamine (**20**) (50.0 g, 307 mmol) were dissolved in concentrated sulfuric acid (320 ml). The rate of addition was adjusted so that an internal temperature of 10 °C was not exceeded. The mixture was cooled to −5 °C and nitric acid (90%, 150 ml) was added over a period of 40 min so that an internal temperature of below 0 °C was maintained. The reaction was continued for 2 h at 0 °C and the reaction mixture was poured on ice-water (2.5 L, mechanical stirring). A colourless suspension was formed which was stirred for 30 min at 0 °C and filtered. At room temperature, the filter cake was suspended in water (1 L) and stirring was continued for 15 min. The title compound was isolated by filtration and dried in vacuo (50 mbar, 17 h, 50 °C). A colourless solid was obtained (67.0 g of **21**, quantitative yield): mp 106–109 °C (literature: mp 114–115 °C);[20] ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 7.48 (s, 2H), NH signal not visible.

4.1.14. 2,6-Dichloro-3-nitro-pyridin-4-ylamine (22). Portions of 2,6-dichloro-4-nitroamino-pyridine (**21**) (67.0 g, 322 mmol) were dissolved in concentrated sulfuric acid (320 ml). The rate of addition was adjusted so that an internal temperature of 40 °C was not exceeded. The reaction mixture was heated to 100 °C. After a period of 1 h, a yellow solution was obtained which was poured on ice-water (3 L). A pH value of 9.5 was adjusted by addition of 6 N sodium hydroxide solution (approximately 1.9 L). A colourless suspension was formed which was stirred for 30 min at room temperature. The precipitate was collected by filtration, suspended in water (4 L) and stirring was continued for 30 min at room temperature. The title compound was isolated by filtration and was dried in vacuo (50 mbar, 17 h, 50 °C). A colourless solid was obtained (75.3 g of **22**, quantitative yield): mp 137–140 °C (literature: mp 142–143 °C);[20] ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 6.88 (s, 1H), 7.64 (bs, 2H).

4.1.15. (2,6-Dichloro-3-nitro-pyridin-4-yl)-(2-ethyl-6-methyl-benzyl)-amine (23). In a flame-dried flask filled with nitrogen, sodium hydride (5.2 g, 60 wt% in paraffin, 130 mmol) was suspended in dry THF (120 ml). A solution of 2,6-dichloro-3-nitropyridin-4-ylamine (**22**) (22.4 g, 108 mmol) in dry THF (200 ml) was added dropwise so that a temperature of 10–15 °C was maintained in the flask. A red solution was obtained which was stirred for 1 h. A second flask was filled with nitrogen, charged with a solution of 2-ethyl-6-methylbenzyl chloride (20.0 g, 118 mmol) in dry THF (120 ml) and sodium iodide (17.7 g, 118 mmol) was added. A yellow suspension was obtained which was stirred for 1 h and then slowly added to the content of the first flask so that a temperature of 10 °C was not exceeded. The reaction mixture was stirred for 1 h at 0 °C, poured on ice-water (1.2 L) and extracted with ethyl acetate (2× 400 ml, 2× 200 ml). The organic phases were dried over sodium sulfate and concentrated to a volume of 600 ml. Silica gel (100 g) was added and the remaining solvent was removed in vacuo. A flash column filled with 1.2 kg of silica gel was charged with the residue and the title compound was eluted with petroleum ether/ethyl acetate 15:1 (v/v). A colourless solid (26.3 g of **23**, 77% yield) was obtained which was pure according to ^{1}H NMR spectroscopy: mp 128–129 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.22 (t, 3H), 2.35 (s, 3H), 2.67 (q, 2H), 4.36 (d, 2H), 6.23 (bt, 1H), 6.86 (s, 1H), 7.19 (m_c, 3H); Anal. Calcd for $C_{15}H_{15}Cl_2N_3O_2$: C, 52.96; H, 4.44; N, 12.35; Cl, 20.84. Found: C, 52.93; H, 4.47; N, 12.39; Cl, 21.00.

4.1.16. (2,6-Dichloro-3-nitro-pyridin-4-yl)-(2,6-dimethyl-benzyl)-amine (24). In a flame-dried flask filled with nitrogen, sodium hydride (4.8 g, 60 wt% in paraffin, 120 mmol) was suspended in dry THF (110 ml). The grey suspension was cooled to 0 °C and a solution of 2,6-dichloro-3-nitropyridin-4-ylamine (**22**) (25.0 g of crude product, 120 mmol) in dry THF (180 ml) was added dropwise so that a temperature of 10–15 °C was maintained in the flask. A red solution was obtained which was stirred for 1 h at 0 °C. A second flask was filled with nitrogen, charged with a solution of 2,6-dimethylbenzyl chloride (17.0 g, 110 mmol) in dry THF (110 ml), and sodium iodide (16.5 g, 110 mmol) was added. A colourless suspension was obtained which was stirred for 1 h at room temperature and then slowly added to the content of the first flask so that a temperature of 5 °C was not exceeded. The reaction mixture was stirred for 1 h at 0 °C, poured on ice-water (1.5 L), and extracted with ethyl acetate (3× 250 ml). The organic phases were dried over sodium sulfate and concentrated to a volume of 400 ml. Silica gel (100 g) was added and the remaining solvent was removed in vacuo. A flash column filled with 1 kg of silica gel was charged with the residue and the title compound was

eluted with petroleum ether/ethyl acetate [15:1 (v/v), then 10:1 (v/v)]. The title compound **24** was obtained as a yellow solid (30.8 g, 79% yield), pure according to ^{1}H NMR spectroscopy: mp 173–174 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.29 (s, 6H), 4.38 (d, 2H), 7.08 (m_c, 3H), 7.20 (s, 1H), 7.72 (bt, 1H); Anal. Calcd for $C_{14}H_{13}Cl_2N_3O_2$: C, 51.55; H, 4.02; N, 12.88; Cl, 21.74. Found: C, 51.30; H, 4.01; N, 13.14; Cl, 21.77.

4.1.17. (6-Chloro-3-nitro-2-prop-1-ynyl-pyridin-4-yl)-(2-ethyl-6-methyl-benzyl)-amine (25). In a flame-dried flask filled with argon, a solution of 2,6-dichloro-pyridine **23** (10.0 g, 29 mmol) in dry 1,4-dioxane (30 ml) was treated with tri-*n*-butyl-1-propynylstannane (9.9 ml, 10.7 g, 33 mmol) and bis(triphenylphosphine)palladium(II) dichloride (1.00 g, 1.4 mmol). The reaction mixture was heated to 50 °C, kept at this temperature for 3 h and evaporated in the presence of silica gel (60 g). A flash column filled with 500 g of silica gel was charged with the residue. After the organotin compounds had been removed by elution with petroleum ether (1 L), the title compound was eluted with petroleum ether/ethyl acetate = 10:1 (v/v). Orange crystals of **25** (7.7 g, 76% yield) were isolated. As indicated by the ^{1}H NMR spectrum, organotin compounds were removed almost completely in the course of the work-up/purification: mp 133 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.22 (t, 3H), 2.13 (s, 3H), 2.35 (s, 3H), 2.67 (q, 2 H), 4.35 (d, 2H), 6.82 (s, 1H), 6.92 (bt, 1H), 7.19 (m_c, 3 H); HRMS (ESI) *m/z* $C_{18}H_{19}ClN_3O_2$ $[M+H]^+$ calcd: 344.1160. Found: 344.1149.

4.1.18. (6-Chloro-3-nitro-2-prop-1-ynyl-pyridin-4-yl)-(2,6-dimethyl-benzyl)-amine (26). In a flame-dried flask filled with argon, 2,6-dichloro-pyridine **24** (38.0 g, 117 mmol) and bis(triphenylphosphine)palladium(II) dichloride (4.10 g, 5.8 mmol) were dissolved in dry 1,4-dioxane (120 ml) and tri-*n*-butyl-1-propynylstannane (37.2 ml, 40.3 g, 122 mmol) was added. The reaction mixture was heated to 50 °C and was kept at this temperature for 3 h. More bis(triphenylphosphine)palladium(II) dichloride (0.50 g, 0.7 mmol) and tri-*n*-butyl-1-propynylstannane (0.9 ml, 1.0 g, 3 mmol) were added and the reaction was continued for 1.5 h at 50 °C. The brown solution was evaporated in the presence of silica gel (80 g). A flash column filled with 1 kg of silica gel was charged with the residue. After the organotin compounds had been removed by elution with petroleum ether (2 L), the title compound was eluted with petroleum ether/ethyl acetate = 10:1 (v/v) and ethyl acetate. Evaporation of the corresponding fractions furnished two batches of the title compound **26**: a beige solid (22.3 g, 58% yield) and a brown oil (19 g). The second batch was further purified by column chromatography [500 g of silica gel, eluant: petroleum ether/ethyl acetate = 5:1 (v/v)]. A beige solid (9.9 g of **26**, 26% yield) was isolated. The amount of organotin compounds present in the two batches (13 mol %/4 mol %) was determined by ^{1}H NMR spectroscopy: mp (second batch): 146–148 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.08 (s, 3 H), 2.30 (s, 6H), 4.37 (d, 2H), 7.11 (m_c, 4H), 7.37 (bt, 1 H), signals of tri-*n*-butylstannane at δ = 0.88 (t), 1.15 (m_c), 1.31 (m_c), 1.61 (m_c); Anal. Calcd for $C_{17}H_{16}ClN_3O_2$: C, 61,92; H, 4.89; N, 12.74; Cl, 10.75. Found: C, 61.24; H, 5.04; N, 12.07; Cl, 10.67.

4.1.19. 2,6-Dichloro-N^4-(2-ethyl-6-methyl-benzyl)-pyridine-3,4-diamine (28). Nitropyridine **23** (8.0 g, 23.5 mmol) was suspended in diethyl ether (100 ml) and a suspension of tin(II) chloride dihydrate (53.0 g, 235 mmol) in concentrated hydrochloric acid (54 ml) was added over a period of 30 min. The reaction mixture was stirred for 2 h at room temperature and poured on water (200 ml) and ethyl acetate (100 ml). A pH value of 8 was adjusted by addition of 6 N sodium hydroxide solution. The biphasic suspension was filtered over Celite 545 and the Celite pad was washed with ethyl acetate (200 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2× 100 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. This afforded aminopyridine **28** in 55% yield (4.0 g of a colourless solid): mp 240 °C; ^{1}H NMR ($CDCl_3$ + MeOD, 200 MHz): δ = 1.23 (t, 3H), 2.37 (s, 3H), 2.69 (q, 2H), 4.26 (s, 2H), 6.60 (s, 1H), 7.18 (m_c, 3H); HRMS (ESI) *m/z* $C_{15}H_{18}Cl_2N_3$ $[M+H]^+$ calcd: 310.087. Found: 310.087.

4.1.20. 3-Amino-4-(2-ethyl-6-methyl-benzylamino)-pyridine-2,6-dicarboxylic acid diethyl ester (29). In an autoclave, a mixture of 2,6-dichloropyridine **28** (500 mg, 1.61 mmol), palladium acetate (18 mg, 0.08 mmol), potassium carbonate (333 mg, 2.4 mmol), 1,3-bis(diphenylphosphino)propane (23 mg, 0.06 mmol), ethanol (100 ml), and DMF was heated under a pressure of carbon monoxide (16 bar) for 16 h at 150 °C. The reaction mixture was cooled to room temperature, filtered and evaporated to dryness. The crude product was purified by column chromatography [silica gel, eluant: petroleum ether/ethyl acetate = 1:1 (v/v)] and subsequent slurrying in diethyl ether (10 ml). The diester **29** was isolated in 18% yield (110 mg of a colourless solid): mp 198 °C; ^{1}H NMR ($CDCl_3$ + MeOD, 200 MHz): δ = 1.23 (t, 3H), 1.47 (t, 6H), 2.43 (s, 3H), 2.76 (q, 2H), 4.49 (m_c, 6H), 7.17 (m_c, 4 H); HRMS (ESI) *m/z* $C_{21}H_{28}N_3O_4$ $[M+H]^+$ calcd: 386.207. Found: 386.206.

4.1.21. 6-Chloro-N^4-(2-ethyl-6-methyl-benzyl)-2-prop-1-ynyl-pyridine-3,4-diamine (30). A solution of 3-nitropyridine **25** (10.0 g, 29 mmol) in diethyl ether (140 ml) was treated with a solution of tin(II) chloride (66.0 g, 293 mmol) in concentrated hydrochloric acid (34.4 ml). The rate of the addition was adjusted so that gentle boiling of the etherous solution was maintained; approximately 15 min was required for complete addition of the reagent. The reaction mixture was stirred for 1 h at room temperature, poured on a mixture of ice-water (1 L) and ethyl acetate (500 ml), and the pH value of the biphasic mixture was adjusted to 10 by addition of 6 N sodium hydroxide solution. The suspension was filtered over Celite 545, the filter cake was washed with ethyl acetate (400 ml), and the phases of the obtained filtrate were separated. The aqueous phase was extracted with ethyl acetate (2× 200 ml). The combined organic phases were dried over sodium sulfate and evaporated to dryness yielding 5.38 g of 3-amino-pyridine **30** (beige

solid, 59% yield). Further 3.4 g of the title compound **30** (colourless solid, 37% yield) was obtained by continuous extraction of the Celite residue with ethyl acetate (1 L) using a Soxhlet apparatus (15 h) and subsequent concentration in vacuo: mp 218 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.23 (t, 3H), 2.11 (s, 3H), 2.37 (s, 3 H), 2.69 (q, 2H), 3.48 (bs, 2H), 3.88 (bt, 1H), 4.24 (d, 2H), 6.59 (s, 1H), 7.18 (m_c, 3H); Anal. Calcd for $C_{18}H_{20}ClN_3$: C, 68.89; H, 6.42; N, 13.39; Cl, 11.30. Found: C, 68.76; H, 6.43; N, 13.40; Cl, 11.16.

4.1.22. 6-Chloro-N^4-(2,6-dimethyl-benzyl)-2-prop-1-ynyl-pyridine-3,4-diamine (31). A solution of 3-nitropyridine **26** (10.0 g, 30 mmol) in diethyl ether (140 ml) was treated with a solution of tin(II) chloride dihydrate (69.0 g, 306 mmol) in concentrated hydrochloric acid (36.0 ml). The rate of the addition was adjusted so that gentle boiling of the etherous solution was maintained; approximately 15 min was required for complete addition of the reagent. The reaction mixture was stirred for 1 h at room temperature, poured on a mixture of ice-water (1 L) and ethyl acetate (500 ml), and the pH value of the biphasic mixture was adjusted to 10 by addition of 6 N sodium hydroxide solution. The suspension was filtered over Celite 545, the filter cake was washed with ethyl acetate (2× 150 ml), and the phases of the obtained filtrate were separated. The aqueous phase was extracted with ethyl acetate (2× 150 ml). The combined organic phases were dried over sodium sulfate and evaporated to dryness. The brown solid residue (3.78 g) was treated with hot diethyl ether (15 ml). The suspension was allowed to cool to room temperature, diluted with more diethyl ether (40 ml), and stirring was continued for 1 h at 0 °C. Pyridin-3-ylamine **31** was isolated by filtration (2.0 g of yellow crystals, 22% yield). The Celite residue was continuously extracted with a mixture of ethyl acetate/methanol = 9:1 (v/v) [1 L] using a Soxhlet apparatus. After a period of 15 h, the solvent was evaporated. The yellow solid residue (7.0 g) was suspended in boiling chloroform (300 ml). The hot suspension was stirred for 1 h at reflux and was filtered rapidly. Concentration of the filtrate afforded a second batch of the title compound **31** (5.14 g of a yellow solid, 56% yield). Both batches contained only traces of organotin impurities (as confirmed by ^{1}H NMR spectroscopy): mp 272–274 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.09 (s, 3H), 2.31 (2s, 6H), 4.19 (d, 2H), 5.09 (bs, 2H), 5.74 (bt, 1H), 6.50 (s, 1H), 7.12 (m_c, 3H); HRMS (ESI) *m/z* $C_{17}H_{19}ClN_3$ $[M+H]^+$ calcd: 300.126. Found: 300.125.

4.1.23. (5-Chloro-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-7-yl)-(2-ethyl-6-methyl-benzyl)-amine (32). In a flame-dried flask filled with argon, 2-prop-1-ynyl-pyridinyl-3-amine **30** (10.0 g, 32 mmol) was dissolved in dry DMF (80 ml) which had been degassed with argon. Copper(I) iodide (1.20 g, 6.3 mmol) was added and the reaction mixture was heated to 80 °C using an oil-bath which had been pre-heated to this temperature. After a reaction time of 1 h, the hot dark-brown reaction mixture was poured on a mixture of a 0.1 M sodium sulfite solution (160 ml) and ice (100 g). A beige suspension was obtained which was stirred for 1 h at 0 °C. The precipitate was removed by filtration, washed with 100 ml portions of water and methanol/water = 1:4 (v/v), and dried in vacuo. This afforded 10.7 g of the 1*H*-pyrrolo[3,2-*b*]pyridine **32**. The beige solid was pure according to ^{1}H NMR spectroscopy and contained approximately 15% of inorganic salts (as determined by elemental analysis, 91% yield): mp 296 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 2.33, 2.35 (2s, 6H), 2.68 (q, 2H), 4.31 (d, 2H), 6.08 (bs, 1H), 6.18 (bt, 1H), 6.43 (bs, 1H), 7.20 (m_c, 3H), 10.80 (bs, 1H); Anal. Calcd for $C_{18}H_{20}N_3Cl$: C, 68.89; H, 6.42; N, 13.39. Found: C, 59.63; H, 5.86; N, 11.30; HRMS (ESI) *m/z* $C_{18}H_{21}ClN_3$ $[M+H]^+$ calcd: 314.142. Found: 314.141.

4.1.24. (5-Chloro-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-7-yl)-(2,6-dimethyl-benzyl)-amine (33). In a flame-dried flask filled with argon, 2-prop-1-ynyl-pyridinyl-3-amine **31** (10.0 g, 33 mmol) was dissolved in dry DMF (80 ml) which had been degassed with argon. Copper(I) iodide (1.27 g, 6.7 mmol) was added and the reaction mixture was heated to 80 °C using an oil-bath which had been pre-heated to this temperature. After a reaction time of 1 h, the hot dark-brown reaction mixture was poured on a mixture of a 0.1 M sodium sulfite solution (160 ml) and ice (100 g). A beige suspension was obtained which was stirred for 1 h at 0 °C. The precipitate was removed by filtration and dried in vacuo (50 mbar, 60 °C, 12 h). This afforded 9.2 g of the 1*H*-pyrrolo[3,2-*b*]pyridine **33** (92% yield). The sample contained approximately 13% of inorganic salts (as determined by elemental analysis): mp 310–312 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.33, 2.35 (2s, 9H), 4.32 (dd, 2H), 6.09 (bs, 1H), 6.20 (bt, 1H), 6.41 (bs, 1H), 7.16 (m_c, 3H), 10.77 (bs, 1H); Anal. Calcd for $C_{17}H_{18}ClN_3$: C, 68.11; H, 6.05; N, 14.02. Found: C, 59.39; H, 5.51; N, 12.14; HRMS (ESI) *m/z* $C_{17}H_{19}ClN_3$ $[M+H]^+$ calcd: 300.126. Found: 300.126.

4.1.25. Ethyl [7-(2-ethyl-6-methyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate] (34). A solution of 5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine **32** (10.5 g containing approximately 15 wt% of inorganic salts, 28 mmol) in ethanol (800 ml) and DMF (200 ml) was treated with palladium(II) acetate (1.13 g, 5.0 mmol), 1,3-bis(diphenylphosphino)propane (2.35 g, 5.7 mmol) and potassium carbonate (6.9 g, 5.0 mmol). The reaction mixture was transferred into a 2 L autoclave and a carbon monoxide pressure of 15 bar was applied. The reaction mixture was heated until—after a period of 1.5 h—a temperature of 190 °C and a carbon monoxide pressure of 30 bar was reached. It was kept for 3 h at this temperature and then cooled to room temperature over a period of 1 h. The pressure was released, the reaction mixture was concentrated until most of the ethanol had been removed and then diluted with water (600 ml) and dichloromethane (600 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 100 ml). The organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography [300 g of silica gel, eluant: ethyl acetate, then ethyl acetate/methanol = 5:1 (v/v)]. The ethyl carboxylate **34** (8.75 g) was isolated as a pale

brown, sticky solid which contained approximately 20 wt% of DMF (as judged from the corresponding ^{1}H NMR spectrum). A suspension of the solid in diethyl ether (100 ml) and methanol (10 ml) was stirred for 30 min at room temperature. After removal of the solvent and drying in vacuo, a beige solid (6.8 g, 68% yield) was obtained; the pure title compound **34** as judged from the ^{1}H NMR spectrum: mp 274–275 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 1.34 (t, 3H), 2.36, 2.37 (2s, 6H), 2.70 (q, 2H), 4.32, 4.38 (q, d, 4H), 6.07 (bt, 1H), 6.23 (s, 1H), 7.20 (m_c, 4 H), 10.94 (s, 1H); HRMS (ESI) *m/z* $C_{21}H_{26}N_3O_2$ $[M+H]^+$ calcd: 352.2020. Found: 352.2011.

4.1.26. Ethyl [7-(2,6-dimethyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylate] (35). A solution of 5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine **33** (18.9 g, 63 mmol) in ethanol (1900 ml) and DMF (475 ml) was treated with palladium(II) acetate (2.15 g, 9.6 mmol), 1,3-bis(diphenylphosphino)propane (4.47 g, 10.8 mmol) and potassium carbonate (13.2 g, 9.6 mmol). The reaction mixture was transferred into a 10 L autoclave and a carbon monoxide pressure of 18 bar was applied. The reaction mixture was heated until—after a period of 1 h—a temperature of 200 °C and a carbon monoxide pressure of 35 bar was reached. It was kept for 3 h at this temperature and then cooled to room temperature over a period of 0.5 h. The pressure was released, the reaction mixture was concentrated until most of the ethanol had been removed and then diluted with water (800 ml) and dichloromethane (500 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 100 ml). The organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product, a brown oil, was dissolved in methanol (100 ml) and silica gel (50 g) was added. The solvent was evaporated and the residue was placed on top of a column packed with 1 kg of silica gel. The title compound was eluted with mixtures of dichloromethane/methanol [30:1 (v/v), then 8:2 (v/v)]. After evaporation of the corresponding fractions, two batches of ethyl carboxylate **35** were isolated: 11.42 g of beige crystals (44% corrected yield) and 5.35 g of light-brown crystals (25% yield). The first batch contained approximately 18 wt% of DMF (as judged from the corresponding ^{1}H NMR spectrum): mp 254 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.34 (t, 3H), 2.37 (s, 9H), 4.32, 4.39 (q, d, 4H), 6.13 (bt, 1H), 6.23 (s, 1H), 7.16 (m_c, 4 H), 10.95 (bs, 1H); HRMS (ESI) *m/z* $C_{20}H_{24}N_3O_2$ $[M+H]^+$ calcd: 338.186. Found: 338.185.

4.1.27. 7-(2-Ethyl-6-methyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid hydrochloride (36). Ethyl carboxylate **34** (1.55 g, 4.4 mmol) was dissolved in methanol (30 ml) and water (3 ml). Crushed potassium hydroxide (493 mg, 8.80 mmol) was added and the reaction mixture was stirred for 1 h at 50 °C. Another 250 mg (4.46 mmol) of crushed potassium hydroxide was added and the reaction was continued for an additional hour at 50 °C. The reaction mixture was concentrated under reduced pressure and the residue was treated with water (20 ml) and 2 N hydrochloric acid until a pH value of 6 was obtained. After addition of methanol (20 ml) a colourless precipitate was formed. The pH value was re-adjusted to 6 and the suspension was stirred for 1 h at 0 °C. The solid was isolated by filtration and dried in vacuo yielding 1.26 g of the pure carboxylic acid **36** (79% yield): mp 325 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 2.37, 2.43 (2s, 6H), 2.72 (q, 2H), 4.60 (d, 2H), 6.36 (s, 1H), 7.22 (m_c, 4H), 7.71 (bt, 1H), 11.94 (s, 1H), 2 exchangeable protons not visible; Anal. Calcd for $C_{19}H_{22}ClN_3O_2$: C, 63.42; H, 6.16; N, 11.68. Found: C, 64.23; H, 6.19; N, 11.38.

4.1.28. 7-(2,6-Dimethyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid hydrochloride (37). Ethyl carboxylate **35** (11.0 g, 33 mmol) was dissolved in methanol (210 ml) and water (21 ml). Crushed potassium hydroxide (7.3 g, 130 mmol) was added and the reaction mixture was stirred for 1.5 h at 60 °C. Most of the methanol (150 ml) was removed under reduced pressure. The reaction mixture was diluted with water (90 ml) and 6 N hydrochloric acid was added until a pH value of 6 was obtained. A suspension was formed, which was stirred for 30 min at 0 °C. The solid was isolated by filtration and dried in vacuo (50 mbar, 50 °C, 18 h) yielding 8.05 g of the pure carboxylic acid **37** (71% yield): mp 235–237 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.38, 2.44 (2s, 9H), 4.62 (d, 2H), 6.36 (s, 1H), 7.20 (m_c, 3H), 7.31 (s, 1H), 7.96 (bt, 1H), 12.25 (s, 1H), 2 exchangeable protons not visible; HRMS (ESI) *m/z* $C_{18}H_{20}N_3O_2$ $[M+H]^+$ calcd: 310.155. Found: 310.154.

4.1.29. 7-(2-Ethyl-6-methyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (38). In a flask filled with argon, a suspension of carboxylic acid **36** (1.00 g, 2.8 mmol) in dichloromethane (100 ml) and DMF (25 ml) was treated with TBTU (1.10 g, 3.4 mmol). The yellow reaction mixture was refluxed for 1 h and dimethylamine (1.90 ml of a 2 M solution in THF, 3.8 ml) was added. The reaction was continued for 1 h at room temperature and the yellow solution was extracted with water (2× 50 ml). The aqueous phase was extracted with dichloromethane (20 ml), the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. A solid residue was obtained which was washed with ethyl acetate (20 ml). In order to remove benzotriazole impurities, the solid was suspended in dichloromethane (50 ml) and water (50 ml) and a pH value of 10 was adjusted by addition of 2 N sodium hydroxide solution. After addition of methanol (5 ml) two clear phases were obtained which were separated. The aqueous phase was extracted with dichloromethane (3× 50 ml). The combined organic phases were dried over sodium sulfate and the solvent was removed in vacuo. The title compound (740 mg, 76% yield) was obtained as a beige solid, pure according to ^{1}H NMR spectroscopy: mp 292-293 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.18 (t, 3H), 2.35, 2.36 (2s, 6H), 2.70 (q, 2H), 3.00, 3.01 (2s, 6H), 4.32 (d, 2H), 5.95 (bt, 1H), 6.12 (s, 1H), 6.55 (s, 1H), 7.20 (m_c, 3H), 10.74 (s, 1H); HRMS (ESI) *m/z* $C_{21}H_{27}N_4O$ $[M+H]^+$ calcd: 351.2179. Found: 351.2174.

4.1.30. 7-(2,6-Dimethyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (39). A suspension of carboxylic acid **37** (11.0 g, 32 mmol) and TBTU (20.4 g, 64 mmol) in dry DMF (260 ml) was heated for 1.5 h at 60 °C. After addition of a 2 M solution of dimethylamine in THF (158 ml, 316 mmol) the reaction mixture was heated for 1 h at 60 °C. Another portion of TBTU (2.0 g, 6 mmol) and dimethylamine solution (2 M in THF, 50 ml, 100 mmol) were added. The reaction was continued for 1 h at 60 °C and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of dichloromethane (400 ml) and saturated sodium bicarbonate solution (400 ml). A pH value of 10 was adjusted by addition of 6 N sodium hydroxide solution. The mixture was diluted with methanol (50 ml) and the phases were separated. The aqueous phase was extracted with a mixture of dichloromethane and methanol [1:1 (v/v), 2× 100 ml]. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography [150 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. After evaporation of the fractions that contained the pure title compound **39** (according to TLC analysis), 4.7 g of solid material was obtained. The solid was suspended in ethyl acetate and 2.0 g (19% yield) of the pure carboxamide **39** was isolated by filtration. The chromatography fractions that contained the title compound along with impurities were combined with the filtrate and the solvent was evaporated. The residue was purified by column chromatography [200 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v) then 10:1 (v/v)]. This afforded another 5.0 g of the pure title compound **39** (47% yield, total yield: 66%): mp 299 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.36 (s, 9H), 2.99, 3.00 (2s, 6H), 4.32 (d, 2H), 5.93 (bt, 1H), 6.11 (s, 1H), 6.55 (s, 1H), 7.15 (m_c, 3H), 10.70 (bs, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{25}N_4O$ $[M+H]^+$ calcd: 337.202. Found: 337.201.

4.1.31. 7-(2,6-Dimethyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid methylamide (40). A suspension of carboxylic acid **37** (5.0 g, 16 mmol) and TBTU (10.4 g, 32 mmol) in dry DMF (140 ml) was heated for 1 h at 60 °C. After addition of a 8 M solution of methylamine in ethanol (21 ml, 168 mmol) the reaction mixture was heated for 1 h at 60 °C. Another portion of TBTU (2.0 g, 6 mmol) and methylamine solution (8 M in ethanol, 10 ml, 80 mmol) were added. The reaction was continued for 1 h at 60 °C and for 16 h at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in a mixture of dichloromethane (300 ml) and saturated sodium bicarbonate solution (300 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product (a brown oil) was purified by column chromatography [200 g of silica gel, eluant: dichloromethane/methanol = 20:1 to 10:1 (v/v)]. Evaporation of the corresponding fractions afforded the title compound **40**: 2.34 g of a beige solid (45% yield): mp 272–274 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.37 (s, 9H), 2.82 (d, 3H), 4.39 (d, 2H), 6.02 (bt, 1H), 6.18 (s, 1H), 7.16 (m_c, 4H), 8.51 (bq, 1H), 10.80 (bs, 1H); Anal. Calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38. Found: C, 70.37; H, 6.94; N, 17.38.

4.1.32. 3-Bromo-7-(2-ethyl-6-methyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (41). In a flask filled with argon, 1*H*-pyrrolo[3,2-*b*]pyridine **38** (150 mg, 0.43 mmol) was dissolved in dry DMF (10 ml). The solution was cooled to 0 °C, *N*-bromosuccinimide (84 mg, 0.47 mmol, dissolved in 2 ml of DMF) was added over a period of 10 min, and the reaction was continued for 30 min at 0 °C. Dichloromethane (30 ml) and saturated sodium carbonate solution (30 ml) were added to the reaction mixture, the phases were separated, and the aqueous phase was extracted with dichloromethane (2× 10 ml). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography [30 g of silica gel, eluant: ethyl acetate/petroleum ether = 8:2 (v/v), then ethyl acetate/methanol = 10:1 (v/v)] and treatment with a mixture of ethyl acetate (2 ml) and diethyl ether (5 ml). After the suspension had been stirred for 15 min, 3-bromo-1*H*-pyrrolo[3,2-*b*]pyridine **41** was collected by filtration and dried in vacuo (150 mg, 81% yield); mp 307 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 2.35 (s, 6H), 2.69 (q, 2H), 3.02 (s, 6H), 4.34 (d, 2H), 6.07 (bt, 1H), 6.63 (s, 1H), 7.20 (m_c, 3H), 11.17 (s, 1H); Anal. Calcd for $C_{21}H_{25}BrN_4O$: C, 58.75; H, 5.87; N, 13.05; Br, 18.61. Found: C, 58.19; H, 5.92; N, 12.80; Br, 18.36.

4.1.33. 3-Bromo-7-(2,6-dimethyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (42). In a flask filled with argon, 1*H*-pyrrolo[3,2-*b*]pyridine **39** (2.00 g, 5.9 mmol) was dissolved in dry DMF (100 ml). The solution was cooled to 0 °C, *N*-bromosuccinimide (1.16 g, 6.5 mmol, dissolved in 20 ml of DMF) was added over a period of 20 min, and the reaction was continued for 30 min at 0 °C. The reaction solution was poured on a mixture of dichloromethane (100 ml) and saturated sodium carbonate solution (200 ml). After addition of methanol (30 ml) the phases were separated. The aqueous phase was extracted with a mixture of dichloromethane and methanol [7:3 (v/v), 2× 20 ml]. The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (2.5 g) was purified by column chromatography [100 g of silica gel, eluant: ethyl acetate/petroleum ether = 8:2 (v/v), then ethyl acetate/ methanol = 8:2 and 1:1 (v/v)] and subsequent treatment with a hot mixture of ethyl acetate (50 ml) and methanol (0.2 ml). After the suspension had been stirred for 1 h, 3-bromo-1*H*-pyrrolo[3,2-*b*]pyridine **42** was collected by filtration and dried in vacuo (1.75 g, 71% yield); mp 284 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.35 (s, 9 H), 3.02 (s, 6H), 4.34 (d, 2H), 6.07 (bt, 1H), 6.62 (s, 1H), 7.16 (m_c, 3H), 11.17 (bs, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{24}BrN_4O$ $[M+H]^+$ calcd: 415.113. Found: 415.113.

4.1.34. 7-(2-Ethyl-6-methyl-benzylamino)-3-formyl-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (43). A flask filled with argon was charged with dry DMF (7 ml) and phosphorus oxychloride (660 μl, 1.10 g, 7.2 mmol) was added at a temperature of 0 °C. The solution was stirred for 1 h at room temperature and then added at 0 °C to a solution of 1*H*-pyrrolo[3,2-*b*]pyridine **38** (1.00 g, 2.9 mmol) in dry DMF (10 ml). The reaction mixture was stirred for 20 h at room temperature and more Vilsmeier reagent (prepared from 660 μl of phosphorus oxychloride and 7 ml of dry DMF as described above) was added at 0 °C. The reaction was continued for 16 h at room temperature and quenched by addition of ice-water (50 ml). Dichloromethane (100 ml) and saturated sodium bicarbonate solution (50 ml) were added and a pH value of 8 was adjusted with 2 N sodium hydroxide solution. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 30 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue (1.2 g of a yellow oil) was purified by column chromatography [60 g of silica gel, eluant: ethyl acetate/methanol = 10:1 (v/v)]. Evaporation of the corresponding fractions afforded the pure aldehyde **43** (620 mg of yellow crystals, 58% yield): ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 2.36 (s, 3H), 2.63, 2.70 (s, q, 5H), 3.02 (s, 6H), 4.35 (d, 2H), 6.25 (bt, 1H), 6.70 (s, 1H), 7.20 (m_c, 3 H), 10.26 (s, 1H), 11.91 (bs, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{27}N_4O_2$ $[M+H]^+$ calcd: 379.2129. Found: 379.2108.

4.1.35. 7-(2,6-Dimethyl-benzylamino)-3-formyl-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-dimethylamide (44). In a flask filled with argon, phosphorus oxychloride (0.72 ml, 1.21 g, 7.9 mmol) was added to a suspension of 1*H*-pyrrolo[3,2-*b*]pyridine **39** (1.30 g, 3.9 mmol) in dry DMF (8 ml). The reaction mixture was heated to 80 °C for 1 h. After addition of another portion of phosphorus oxychloride (0.10 ml, 0.17 g, 1.1 mmol) the reaction was continued for 40 min at 80 °C. The brown solution was added slowly to an ice-cold mixture of sodium bicarbonate solution (600 ml) and dichloromethane (200 ml). The biphasic mixture was stirred for 20 min. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were dried over sodium sulfate and the solvent was evaporated. Dichloromethane (5 ml) and diethyl ether (10 ml) were added to a solution of the crude product in DMF (3 ml). The resulting suspension was stirred for 30 min at room temperature and the precipitate was isolated by filtration. This afforded the pure aldehyde **44** (600 mg, 43% yield). Note: It is also possible to omit the crystallization step and to subject the crude product (which contains about 60 wt% of the title compound) to the reduction step described in procedure 4.1.37: ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.36 (s, 6H), 2.63 (s, 3H), 3.02 (s, 6H), 4.35 (d, 2H), 6.15 (bt, 1H), 6.70 (s, 1H), 7.17 (m_c, 3H), 10.26 (s, 1H), 11.72 (bs, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{25}N_4O_2$ $[M+H]^+$ calcd: 365.197. Found: 365.196.

4.1.36. 7-(2-Ethyl-6-methyl-benzylamino)-3-hydroxymethyl-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (45). In a flask filled with argon, sodium borohydride (70 mg, 1.85 mmol) was added to a suspension of aldehyde **43** (1.40 g, 3.7 mmol) in dry ethanol (120 ml). The reaction mixture was stirred for 30 min at room temperature and then treated with another portion of sodium borohydride (70 mg, 1.85 mmol). Stirring was continued for 1 h at room temperature. The solution was concentrated to a volume of 60 ml. Dichloromethane (100 ml) and saturated ammonium chloride solution (80 ml) were added. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 40 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude title compound (1.35 g) was purified by column chromatography [200 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v) then 8:2 (v/v)]. Evaporation of the corresponding fractions afforded 1.01 g of the pure alcohol **45** (72% yield): mp 280 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 2.36 (s, 6H), 2.69 (q, 2H), 3.02, 3.04 (2s, 6 H), 4.35, 4.42 (d, bt, 3H), 4.58 (d, 2H), 6.10 (bs, 1H), 6.60 (s, 1 H), 7.20 (m_c, 3H), 10.77 (bs, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{29}N_4O_2$ $[M+H]^+$ calcd: 381.229. Found: 381.227.

4.1.37. 7-(2,6-Dimethyl-benzylamino)-3-hydroxymethyl-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (46). In a flask filled with argon, sodium borohydride (120 mg, 3.17 mmol) was added to a suspension of aldehyde **44** (580 mg, 1.59 mmol) in dry ethanol (12 ml). The reaction mixture was heated to 50 °C for 5 min and then stirred for 1 h at room temperature. The solution was poured on a mixture of dichloromethane (100 ml) and saturated ammonium chloride solution (200 ml). The biphasic mixture was stirred for 20 min at room temperature. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 20 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was suspended in a mixture of dichloromethane (10 ml) and diethyl ether (20 ml). The suspension was stirred for 30 min at room temperature. The pure alcohol **46** was isolated by filtration and was dried in vacuo (430 mg of a colourless solid, 74% yield): mp 301 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.36 (s, 9H), 3.02, 3.03 (2s, 6H), 4.35 (d, 2H), 4.47 (bt, 1H), 4.57 (bd, 2H), 6.11 (bs, 1H), 6.61 (s, 1H), 7.16 (m_c, 3H), 10.77 (bs, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{27}N_4O_2$ $[M+H]^+$ calcd: 367.213. Found: 367.212.

4.1.38. 3-Bromo-7-(2,6-dimethyl-benzylamino)-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid methylamide (47). At a temperature of 0 °C, 1*H*-pyrrolo[3,2-*b*]pyridine **40** (400 mg, 1.24 mmol) was dissolved in DMF (25 ml) and a solution of *N*-bromosuccinimide (243 mg, 1.37 mmol) in DMF (2 ml) was slowly added. The reaction mixture was stirred for 0.5 h at 0 °C and poured on saturated sodium bicarbonate solution (100 ml) and dichloromethane (100 ml). The phases were separated and the aqueous phase was extracted with

dichloromethane (2× 10 ml). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product (520 mg of a yellow oil) was purified by column chromatography [30 g of silica gel, eluant: petroleum ether/ethyl acetate = 1:1 (v/v), then ethyl acetate/methanol = 7:3 (v/v)]. Evaporation of the corresponding fractions afforded a yellow solid (300 mg), which was slurried in a mixture of ethyl acetate (15 ml) and diethyl ether (15 ml). After a period of 48 h, the bromo derivative **47** was isolated by filtration (217 mg of a colourless solid, 44% yield): mp 290-291 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.36 (s, 9H), 2.87 (d, 3H), 4.40 (d, 2H), 6.12 (t, 1H), 7.15 (m_c, 3H), 7.23 (s, 1H), 8.31 (q, 1H), 11.20 (s, 1H); HRMS (ESI) *m/z* $C_{19}H_{22}BrN_4O$ $[M+H]^+$ calcd: 401.097. Found: 401.097.

4.1.39. 1-(Dimethylamino)-5-[(2,6-dimethylbenzylamino)-2,7-dimethyl-3-oxo-1,2,3,6-tetrahydroimidazo[1,5-*a*]-pyrrolo[2,3-*e*]pyridin-9-ium chloride (48). Phosphorus oxychloride (1.5 ml, 2.5 g, 16.1 mmol) was added to a solution of 1*H*-pyrrolo[3,2-*b*]pyridine **40** (2.6 g, 8.1 mmol) in DMF (20 ml). The reaction mixture was stirred for 70 min at 80 °C and slowly added to a mixture of ice (100 g), saturated sodium bicarbonate solution (200 ml) and dichloromethane (100 ml). The pH value was adjusted to a value of 8–9 by addition of 6 N sodium hydroxide solution. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. A solution of the crude product (2.5 g) in ethanol (50 ml) was treated with sodium borohydride (540 mg, 14.3 mmol). According to TLC analysis, no reaction occurred within a period of 1 h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (200 ml) and dichloromethane (200 ml) and a pH value of 6.5 was adjusted by addition of 2 N hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (2.4 g of a yellow foam) was purified by crystallization from ethyl acetate (20 ml), methanol (2 ml) and diethyl ether (10 ml). After a period of 16 h, the title compound was collected by filtration (1.55 g of a colourless solid, 51% yield): mp 140 °C (decomp.); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.38 (s, 6H), 2.49 (s, 9 H, overlay with DMSO), 3.09 (s, 3H), 4.71 (bs, 2H), 6.44 (s, 1H), 6.72 (s, 1H), 7.17 (m_c, 3H), 7.31 (s, 1H), 8.39 (bs, 1H), 12.72 (bs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, 90 °C): δ 12.94, 18.95, 26.59, 36.13, 41.54, 90.91, 91.79, 94.31, 117.98, 127.39, 127.66, 131.37, 131.71, 135.60, 137.16, 142.78, 144.54, 158.16; HRMS (ESI) *m/z* $C_{22}H_{28}N_5O$ $[M+H]^+$ calcd: 378.2288. Found: 378.2275.

4.1.40. 7-(2-Ethyl-6-methyl-benzylamino)-2,3-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (49)

4.1.40.1. Catalytic hydrogenation of the 3-hydroxymethyl precursor 45. A solution of alcohol **45** (200 mg, 0.52 mmol) in acetic acid (70 ml) was treated with palladium on charcoal (10 wt%, 40 mg). A hydrogen pressure of 10 bar was applied and the reaction mixture was stirred for 3.5 h at room temperature and for 4 h at 50 °C. The hydrogenation catalyst was removed by filtration and the filtrate was concentrated to a volume of 3 ml. Dichloromethane (50 ml) and methanol (20 ml) were added and a pH value of 8 was adjusted with 2 N sodium hydroxide solution. The phases were separated and the aqueous phase was extracted two times with a mixture of dichloromethane (20 ml) and methanol (2 ml). The combined organic phases were evaporated to dryness and the residue (200 mg of a yellow oil) was purified by column chromatography [70 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. The pure title compound **49** (87 mg, 46% yield) was isolated in the form of a colourless solid: mp 260–262 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.17 (t, 3H), 2.13 (s, 3H), 2.29 (s, 3H), 2.35 (s, 3H), 2.69 (q, 2H), 3.02, 3.03 (2s, 6H), 4.36 (d, 2H), 6.17 (bs, 1H), 6.62 (s, 1H), 7.20 (m_c, 3H), 10.70 (bs, 1H).

4.1.40.2. Cross-coupling of the 3-bromo precursor 41. Four microwave reaction vessels were charged each with a suspension of 3-bromo-1*H*-pyrrolo[3,2-*b*]pyridine **41** (188 mg, 0.44 mmol) in dry dioxane (4 ml). After addition of trimethylboroxine (165 mg, 183 µl, 1.31 mmol), cesium carbonate (430 mg, 1.32 mmol) and chloro-[2′-(dimethylamino)-2-biphenylyl]-(dinorbornylphosphine)-palladium (CAS 359803-53-5, 13 mg, 23 µmol), each vessel was sealed and heated to 150 °C in a microwave oven. After a period of 16 min, more catalyst (13 mg, 23 µmol) was added and the reaction mixture was continued for another 16 min. The reaction mixtures were combined and diluted with saturated ammonium chloride solution (100 ml) and dichloromethane (100 ml). A pH value of 7 was adjusted by addition of 3 N hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were dried over sodium sulfate and evaporated to dryness. The crude product (890 mg) was purified by column chromatography [120 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions furnished 514 mg of a mixture of the title compound **49** (70 weight %, 57% yield) with its 3-H-analogue **38** (30 weight %, 25% yield). The mixture was separated by preparative HPLC and the pure title compound **49** was isolated: HRMS (ESI) *m/z* $C_{22}H_{29}N_4O$ $[M+H]^+$ calcd: 365.2336. Found: 365.2328.

4.1.41. 7-(2,6-Dimethyl-benzylamino)-2,3-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (50)

4.1.41.1. Reduction of the 3-hydroxymethyl precursor 46 with triethylsilane. At room temperature, triethylsilane (6.8 ml, 5.0 g, 43 mmol) was added dropwise to a solution of alcohol **46** (1.00 g, 2.7 mmol) in trifluoroacetic acid (15 ml). The solution was stirred for 2 h at room temperature (gas evolution was observed) and more triethylsilane (2.3 ml, 1.7 g, 14 mmol) was added. After a period of 1 h, the reaction was poured on a mixture of ice (100 g) and dichloromethane (50 ml). At a temperature of 0 °C, a pH value of 8 was adjusted by addition

of 6 N sodium hydroxide solution. Addition of dichloromethane (50 ml) and methanol (20 ml) afforded a clear biphasic mixture. The phases were separated and the aqueous phase was extracted with a mixture of dichloromethane and methanol [5:1 (v/v), 2× 60 ml]. The combined organic phases were dried over sodium sulfate and evaporated to dryness. The solid residue was suspended in hot ethyl acetate (50 ml). Over a period of 1 h, the suspension was allowed to cool to room temperature. The precipitate was isolated by filtration and washed with ethyl acetate (15 ml) and diethyl ether (15 ml). A colourless solid was obtained (630 mg), which was co-evaporated with a mixture of dichloromethane and methanol [6:1 (v/v), 35 ml] and then dried in vacuo. This afforded the pure title compound **50** (600 mg, 63% yield): mp 319 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.12 (s, 3H), 2.28 (s, 3H), 2.35 (s, 6H), 3.01, 3.04 (2s, 6H), 4.32 (d, 2H), 5.83 (bt, 1H), 6.55 (s, 1H), 7.15 (m_c, 3H), 10.45 (bs, 1H); HRMS (ESI) *m/z* $C_{21}H_{27}N_4O$ $[M+H]^+$ calcd: 351.218. Found: 351.217.

4.1.41.2. Deoxigenation of the 3-hydroxymethyl precursor 46 via activation with *O*-phenyl chlorothionoformate. A suspension of alcohol **46** (200 mg, 0.55 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol) and pyridine (90 µl, 88 mg, 1.11 mmol) in dichloromethane (5 ml) was treated with *O*-phenyl chlorothionoformate (129 µl, 165 mg, 0.96 mmol). A red solution was obtained which was warmed to 40 °C for 30 min. Equal amounts of all reagents (20 mg of 4-dimethylaminopyridine, 90 µl of pyridine, 129 µl of *O*-phenyl chlorothionoformate) were added and the reaction was continued for 1.5 h at room temperature. The reaction mixture was poured on saturated ammonium chloride solution (50 ml) and the biphasic mixture was extracted with dichloromethane (3× 10 ml). The combined organic phases were dried over sodium sulfate and evaporated to dryness. This afforded the crude intermediate **52** (520 mg). After addition of dioxane (4 ml), triethylamine (0.28 ml, 0.20 g, 2.0 mmol) and hypophosphorus acid (0.22 ml, 50% in water), the reaction mixture was warmed to 100 °C and treated with 2,2′-azobis(2-methylpropionitrile) [66 mg, 0.40 mmol]. After a period of 1 h, the reaction was poured on saturated sodium bicarbonate solution (50 ml) and extracted with dichloromethane (3× 15 ml). The combined organic phases were dried over sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography [20 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions afforded the pure title compound **50** (30 mg, 15% yield): mp 315 °C.

4.1.42. 1-Benzyl-7-(2,6-dimethyl-benzylamino)-2,3-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (53). Under an argon atmosphere at 0 °C, a solution of 1*H*-pyrrolo[3,2-*b*]pyridine **50** (200 mg, 0.57 mmol) in dry DMF (7 ml) was treated with sodium hydride (60 wt% in oil, 25 mg, 0.63 mmol). The solution was stirred for 1 h at room temperature, cooled to 0 °C and benzyl bromide (75 µl, 108 mg, 0.63 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and poured on a mixture of saturated ammonium chloride solution (40 ml) and dichloromethane (40 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 5 ml). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography [20 g of silica gel, eluant: dichloromethane/methanol = 40:1 (v/v)]. Evaporation of the corresponding fractions afforded a yellow oil, which solidified upon treatment with diethyl ether. A suspension of the yellow solid in ethyl acetate (0.2 ml) and diisopropyl ether (2 ml) was stirred for 20 min at room temperature. The 1-benzyl derivative **53** (95 mg, 38% yield) was isolated by filtration: mp 203 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.04 (s, 6 H), 2.21 (s, 3H), 2.29 (s, 3H), 3.01 (s, 3H), 3.07 (s, 3H), 4.09 (d, 2H), 4.70 (bt, 1H), 5.38 (s, 2H), 6.62 (m_c, 3H), 6.98 (m_c, 2H), 7.13 (m_c, 4H); HRMS (ESI) *m/z* $C_{28}H_{33}N_4O$ $[M+H]^+$ calcd: 441.2649. Found: 441.2640.

4.1.43. 7-(2,6-Dimethyl-benzylamino)-1,2,3-trimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (54). Under an argon atmosphere at 0 °C, a solution of 1*H*-pyrrolo[3,2-*b*]pyridine **50** (200 mg, 0.57 mmol) in dry DMF (7 ml) was treated with sodium hydride (60 wt% in oil, 25 mg, 0.63 mmol). The solution was stirred for 1 h at room temperature, cooled to 0 °C and methyl iodide (53 µl, 120 mg, 0.85 mmol) was added. The reaction mixture was stirred for 2 h at room temperature and poured on a mixture of water (50 ml) and dichloromethane (50 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 20 ml). The combined organic phases were diluted with methanol (10 ml), dried over sodium sulfate and concentrated in vacuo. The residue (an orange oil) was purified by column chromatography [30 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions afforded a yellow oil (170 mg), which solidified upon treatment with diethyl ether. A suspension of the yellow solid in ethyl acetate/petroleum ether [1:1 (v/v), 2 ml] was stirred for 30 min at room temperature. The title compound **54** (33 mg, 16% yield) was isolated by filtration. Evaporation of the filtrate afforded 94 mg of a yellow oil, which was purified by column chromatography [silica gel, eluant: ethyl acetate, then ethyl acetate/methanol = 9:1 (v/v)] and subsequent treatment with diisopropyl ether (1 ml). This afforded another 36 mg of the 1-methyl derivative **54** (17% yield): mp 203 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.14 (s, 3H), 2.28 (s, 3H), 2.39 (s, 6H), 3.00 (s, 3H), 3.05 (s, 3H), 3.76 (s, 3H), 4.26 (d, 2H), 5.48 (bt, 1H), 6.64 (s, 1H), 7.10 (m_c, 3H); HRMS (ESI) *m/z* $C_{22}H_{29}N_4O$ $[M+H]^+$ calcd: 365.2336. Found: 365.2324.

4.1.44. 1-Benzyl-7-(2,6-dimethyl-benzylamino)-3-hydroxymethyl-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (55). Under an argon atmosphere at 0 °C, 1*H*-pyrrolo[3,2-*b*]pyridine **46** (100 mg, 0.27 mmol) was added to a suspension of sodium hydride (60 wt% in oil, 11 mg, 0.28 mmol) in dry THF (3 ml). The mixture was stirred for 40 min at 0 °C and evaporated to dryness. The residue was suspended in dry DMF (3 ml) and benzyl bromide (43 ml, 62 mg,

0.36 mmol) was added. The reaction mixture (a clear solution) was stirred for 1 h at room temperature and poured on a mixture of saturated sodium bicarbonate solution (5 ml), water (50 ml) and dichloromethane (50 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 10 ml). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The residue (130 mg) was purified by column chromatography [20 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. The 1-benzyl derivative **55** (59 mg, 48% yield) was isolated in 90% purity (as judged from the corresponding ^{1}H NMR spectrum) and could be purified further by crystallization (room temperature, 20 h) from ethyl acetate/acetic acid [20:1 (v/v), 1 ml]. The precipitate was isolated by filtration and dried in vacuo. This afforded 23 mg of the pure 1-benzyl derivative **55** (18% yield): mp 97 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.04 (s, 6H), 2.37 (s, 3H), 3.01 (s, 3H), 3.07 (s, 3H), 4.09 (d, 2H), 4.51 (t, 1H), 4.68 (m_c, 3H), 5.41 (s, 2H), 6.63 (m_c, 3 H), 6.99 (m_c, 2H), 7.14 (m_c, 4H); HRMS (ESI) *m/z* $C_{28}H_{33}N_4O_2$ $[M+H]^+$ calcd: 457.2598. Found: 457.2587.

4.1.45. 7-(2,6-Dimethyl-benzylamino)-1-(2-hydroxy-propyl)-2,3-dimethyl-1*H*-pyrrolo[3,2-*b*]pyridine-5-carboxylic acid dimethylamide (56). At a temperature of 0 °C, sodium hydride (60 wt% in oil, 28 mg, 0.70 mmol) was added to a solution of 1*H*-pyrrolo[3,2-*b*]pyridine **50** (200 mg, 0.56 mmol) in DMF (4 ml). After a period of 1 h at room temperature, 1,2-epoxypropane (60 µl, 50 mg, 0.86 mmol) was added. Under microwave irradiation, the reaction mixture was heated for 2 h at 100 °C. At a temperature of 0 °C, more sodium hydride (60 wt% in oil, 14 mg, 0.35 mmol) was added and the solution was stirred for 45 min at room temperature. After addition of 1,2-epoxypropane (60 µl, 50 mg, 0.86 mmol), microwave heating (100 °C) was continued for 2 h. The reaction mixture was poured on saturated ammonium chloride solution (100 ml) and dichloromethane (50 ml). The phases were separated. The aqueous phase was extracted with dichloromethane (2× 10 ml). The combined organic phases were dried over sodium sulfate and the solvent was evaporated. The crude product (230 mg of a brown foam) was purified by column chromatography [20 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions and subsequent crystallization from diethyl ether (1 ml) afforded the title compound **56** (24 mg, 10% yield): mp 261 °C, ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.83 (d, 3 H), 2.15 (s, 3H), 2.27 (s, 3H), 2.35 (s, 6H), 3.01 (s, 3H), 3.07 (s, 3H), 3.83 (bs, 1H), 3.99 (m_c, 2H), 4.20 (m_c, 2H), 5.61 (bs, 1H), 6.40 (d, 1H), 6.65 (s, 1H), 7.10 (m_c, 3H); HRMS (ESI) *m/z* $C_{24}H_{33}N_4O_2$ $[M+H]^+$ Calcd: 409.2598. Found: 409.260.

4.2. Biochemistry

4.2.1. Determination of inhibitory activity in a competitive binding assay against H^+/K^+-ATPase from hog gastric mucosa. Given data are mean IC_{50} values from 2 to 3 independent determinations. The malachite green assay modified from Yoda, A. and Hokin, L. E. (*Biochem. Biophys. Res. Commun.* **1970**, *40*, 880–886) was used for the determination of H^+/K^+-ATPase IC_{50}: Lanzetta, P. A.; Alvarez, L. J.; Reinach, P. S.; Candia, O. A. *Anal. Biochem*. **1979**, *100*, 95–97. Pipes [piperazine-1,4-bis(2-ethanesulfonic acid)], sucrose, nigericin, Na–ATP and malachite green were purchased from Sigma–Aldrich, tris [tris(hydroxymethyl)aminomethane], KCl and ammoniumheptamolybdate tetrahydrate from Merck, and $MgCl_2$ from Fluka. Final assay concentrations: 4 mM Pipes/8 mM tris buffer, pH 7.4, 0.25 M sucrose, 1 mM KCl, 1 mM $MgCl_2$, 0.5 to 1 µg/100 µl nigericin (1:1 ratio with enzyme), 0.5 to 1 µg/100 µl enzyme (dependent on K^+-stimulated, specific activity) and 1 mM Na–ATP (high grade), reaction volume: 101 µl. Preparation of malachite green reagent: 2 parts of malachite green stock solution (1.2 M in H_2O, protected from light and used within 12 weeks) were mixed with 1 part of ammoniumheptamolybdate tetrahydrate stock solution (42 g/l in 4 N HCl) and kept for 30 min at room temperature prior to use. A pipes/tris buffer based solution with sucrose and $MgCl_2$ was prepared. Nigericin and enzyme were added to reach the final concentrations mentioned above. Eighty microliters per well of this mixture was placed into 96-well flat-bottomed plates (clear, polystyrol, Greiner bio-one). Ten microliters per well of KCl (1 mM final) was used for stimulation of the H^+/K^+-ATPase activity. Test substances were dissolved as 10 mM solutions in 100% DMSO. 1 µl of substance solution was added in dilutions ranging from 1×10^{-4} to 1×10^{-9} M (final). The enzymatic reaction was started by addition of 10 µl ATP (1 mM final). The assay was incubated for 30 min at room temperature. The reaction was stopped by addition of 150 µl of malachite green reagent and incubated for another 15 min prior to photometric reading of the plate at 680 nm in a PowerWave HT Microplate spectral photometer (BioTek). The results were analyzed with GraphPad Prism software (Version 4.02) to calculate IC_{50} values by sigmoidal curve fitting. 'Enzyme' refers to H^+/K^+-ATPase-containing vesicles prepared from hog gastric mucosa as described in Rabon, E. C.; Im, W. B.; Sachs, G. *Methods Enzymol*. **1988**, *157*, 649–654.

4.2.2. ^{14}C-dimethylaminopyridine accumulation in intact gastric glands. Gastric acid secretion is stimulated by gastrin, histamine and acetylcholine via the receptors on the parietal or the enterochromaffin-like cell. These physiologic stimuli influence the intracellular cyclic AMP and Ca^{2+} levels, thus leading to relocation and activation of H^+/K^+-ATPase. Instead of the physiologic agonists, the membrane-permeant dibutyryl-cyclic AMP was used to stimulate receptor-independent acid secretion in isolated gastric glands. Accumulation of the weak base ^{14}C-dimethylaminopyridine (^{14}C-AP) in the acidic compartment of the canaliculi serves as an indirect measure of acid secretion and forms the basis of measurement of acid secretion in this in vitro model of the mammalian stomach. Intact gastric glands were prepared from anaesthetized New Zealand rabbits (weight 2–3 kg) by high-pressure perfusion of the stomach, separation of the fundic mucosa and subsequent collagenase digestion of fragments of the mucosa (Berglindh, T; Helander, H. F.; Obrink, K. J. *Acta Physiol. Scand.*

1976, *97*, 401–414; Berglindh, T.; Obrink, K. J. *Acta Physiol. Scand.* **1976**, *96*, 150–159). After the gastric glands were washed several times, they were suspended in Krebs-Henseleit solution containing 2 mg/ml rabbit serum albumin and 2 mg/ml glucose. Glands were incubated for 30 min at 37°C in a shaker bath (200 osc/min) in the presence of 0.125 μM ^{14}C-AP (113 μCi/μmol) at pH 7.4. Glands were stimulated with 1 mM dibutyryl cAMP in absence or presence of the corresponding inhibitor (concentration range 3 nM–100 μM). The reaction was stopped by centrifugation (10 s at 20,000*g*). After centrifugation, the accumulation of ^{14}C-AP in the glands was calculated as follows: radioactivity was measured in an aliquot of the supernatant (200 μl) and in the precipitate after dissolution in 1 ml of 1 N NaOH. In order to calculate the amount of protein, the Eppendorf tubes were weighed empty, with protein (wet weight) and with freeze-dried protein (dry weight). This ratio of supernatant and pellet protein radioactivity was used to calculate the accumulation of ^{14}C-AP in the glands. The inhibitor concentration required to achieve 50% inhibition (IC_{50}) of ^{14}C-AP accumulation was determined by fitting the equation for the expected inhibition pattern to the data points.

4.3. Physical chemistry

4.3.1. General. The determination of dissociation constants (pK_a) and lipophilicity [log *P*, log *D*(pH 7.4)] was performed on a Sirius GL pK_a analyzer specifically designed for pH-metric pK_a and 1-octanol/water partition coefficient measurements (Sirius Analytical Instruments Ltd., Forest Row, UK).

4.3.2. Determination of dissociation constants. The pK_a values of the investigated compounds were determined by potentiometric co-solvent titrations in 0.15 mol/l KCl solutions in the range of pH 2.0–11.0 at 25 °C using methanol as co-solvent in varying portions and 0.5 mol/l KOH and HCl as titrants, respectively. Linear extrapolation to 0% co-solvent-content was performed by the Yasuda-Shedlovsky plot method implemented in the software RefinementPro 2 from SIRIUS (Avdeef, A.; Box, K. J.; Comer, J. E. A., Gilges, M.; Hadley, M.; Hibbert, C.; Patterson, W.; Tam, K. Y. *J. Pharm. Biomed. Anal.* **1999**, *20*, 631–641).

4.3.3. Determination of distribution coefficients. The distribution coefficients between 1-octanol and aqueous KCl solution were determined at 25 °C by potentiometric titrations in the range of pH 2.0–pH 11.0. The titrations were performed in mixtures of 0.15 mol/l KCl solution and water saturated 1-octanol with varying 1-octanol portions using 0.5 mol/l KOH and HCl as titrants, respectively. The log *D* values in dependence of pH were obtained by least squares fitting of the experimental data to a theoretical function of the distribution coefficient *D* (RefinementPro2): Comer, J.; Tam, K.; *Lipophilicity profiles: Theory and Measurement, in Pharmakokinetic Optimization in Drug Research: Biological, Physicochemical and Computational Strategies*, Editors: Testa, B.; van de Waterbeemd, H.; Folkers, G.; Guy, R.; VHCA: Zurich, 2001, 275–304.

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