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A simple approach to multifunctionalized N1-alkylated 7-amino-6-azaoxindole derivatives using their in situ stabilized tautomer form

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ABSTRACT

A simple approach for the synthesis of multifunctionalized N1-alkyl 7-amino-6-azaoxindole derivatives was developed and investigated. Formation of 5-amino- and 7-amino-6-aza-2-oxindoles **12a** and **13a**, respectively, was achieved using an intramolecular reductive cyclization as a key step. Subsequent alkylation of the pyrrole N1 atom in **12a** led to the desired N1-alkylated compounds **22a**–**24** comprising different functionalities. Alkylation of 5-amino-substituted regioisomer **13a** under the same conditions as used for **12a** did not resulted in N1-alkylated products. To find a plausible explanation for the observed differences in reactivity, we investigated the possible tautomers of **12a** and **13a** and the distribution of their neutral and ionized forms in a gas phase. The relevant physicochemical properties of compounds **12a** and **23** were determined.

1. Introduction

Azaindoles represent a growing class of condensed heterobicycles that display a wide range of significant biological and pharmacological properties.[1,2] In contrast to indoles, there are relatively few examples of natural products such as variolin[3] and grossularine[4] alkaloids comprising an azaindole core. However, the most azaindoles are synthetic products or a fragment of synthetic analogues of naturally occurring alkaloids.[5] Due to their physicochemical features,[6] azaindoles are frequently exploited as bioisosteres of indoles and purines,[7] and belong to the so-called 'privileged structures' in drug development.[2,8,9] The azaindole nucleus shows better solubility in water than the indole scaffold due to the sp^2-hybridized nitrogen of the pyridine moiety by providing an additional position for protonation and salt formation.[7] Structurally, azaindoles **c**onsist of a fused [5,6]-membered ring system, which arises from the different condensation of the π-electron-deficient pyridine ring and the π-electron-rich pyrrole ring resulting in 4-, 5-, 6- or 7-azaindole (pyrrolopyridine) scaffolds **1**–**4**, respectively, differ in the location of the pyridine nitrogen atom (Fig. 1, panel A). Furthermore, the ring fusion in **1**–**4** is consistent with the specific arrangement of the substitution pattern and variety of biological activities of their N1-substituted analogues **5**–**8** (Fig. 1, panel B). For example, N1-3,4-difluorobenzoyl-benzamido-substituted 4-azaindole NTZ-2130 (**5**) has been recently discovered as a promising monoamine oxidase B (MAO-B) inhibitor for neuroprotective treatment of Parkinson's disease (PD).[10] The N1-methyl-1-morpholin-4-ylmethanone-substituted 5-azaindole GSK554418A (**6**) has been identified as a potent cannabinoid receptor type 2 (CB_2) agonist for the therapy of chronic pain.[11] An example for advanced drug development represents the N1-phosphonooxymethyl prodrug BMS-663749 (**7**) comprising 6-azaindole core. This compound was profiled as an effective HIV-1 attachment inhibitor in a variety of preclinical in vitro and in vivo models.[12] Furthermore, highly functionalized 7-azaindole **8** was reported as peroxisome proliferator-activated receptor gamma (PPARγ) modulator for potential treatment of type 2 diabetes (T2DM).[13]

As a result of the versatile biological and physicochemical properties of azaindoles, several methodologies for their synthesis including heterocyclisations,[7,9,14] and organometallic-promoted heteroannulations[15] have been developed. The large number of these methods has been deduced from the classical synthetic strategies used for the formation of indole ring systems.[7,9,14,16] However, the most common synthetic procedures were applied for the construction of 7-azaindole derivatives,[7b,14,17] whereas considerably few have been developed for the synthesis of highly functionalized 6-azaindole analogues.[7b,17]

An explanation for this fact could be the unfavorable electron-deficient constitution of the pyridine ring caused by an altered π-electron delocalization during the heterocyclization step to form

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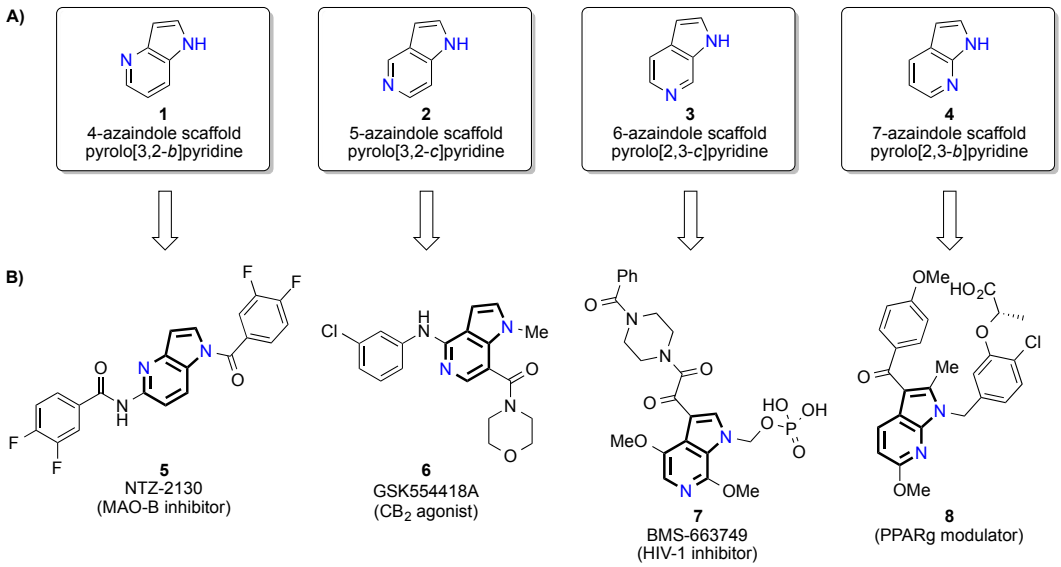

Fig. 1. Structures of azaindole scaffolds **1**–**4** (**A**) and biologically active compounds **5**–**8** with a 4-, 5-, 6- and 7-azaindole core (**B**).

the pyrrolo[2,3-*c*]pyridine ring system.[7b] Hence, many conventional indole synthesis methods are not effective or have limited application for the preparation of 6-azaindole scaffold.[7b]

In this contribution, a facile approach for the synthesis of drug-like 5-amino- and 7-amino-6-azaoxindole derivatives **13a** and **12a** using reductive cyclization as a key step has been recently developed.[18] When starting from the commercially available 2-amino-4-chloropyridine (**9**) both, 5-amino- or 7-amino-2-hydroxy[2,3-*c*]pyridine (**12a** or **13a**) are easily accessible in a regioselective manner depending on the substitution pattern of the corresponding 3-nitro- or 5-nitro-substituted 4-chloropyridine-2-amine precursors **10** or **11**, respectively (Fig. 2). Consequently, we were interested in the feasible formation of N1-substituted 6-azaindoles containing an amino group, either in the 5- or 7-position of the pyrrolo[2,3-*c*]pyridine framework, respectively. In either case the favored structures would consist a hydrogen bond donor (HBD, free NH_2 group) and an adjacent hydrogen bond acceptor (HBA, pyridine nitrogen atom) in a highly functionalized pyrrolo[2,3-*c*]pyridine ring system. Such structures may be considered as adrenomimetics interacting with many important drug targets such as protein kinases[19] and *ecto*-nucleotidases.[20] Moreover, N1-alkylated 5-amino- and 7-amino-6-azaindole derivatives may act as precursors for further modifications allowing the introduction of diverse substitution pattern, e.g., substitution at the pyridine nitrogen, CO_2Et and/or the amino group.

To continuously explore the substitution of the nitrogen N1, we performed series of N-alkylation reactions with a variety of residues (R) in the very last step. While the regioselective N-alkylation of **12a** led to the formation of the desired N1-alkyl 7-amino-6-azaoxindole derivative **14**, synthesis of its 5-amino-substituted isomer **13a** failed due to the unfavorable tautomer forms under the same reaction conditions (Fig. 2).

In this article we summarize an investigation of the influence of the amino function and the reaction conditions on the regioselective N1-alkylation of 7-amino- and 5-amino-6-azaoxindole derivatives **12a** and **13a**. To explain the completely different accessibility for substitution of the nitrogen atom N1 and preferences of N1 versus N6 alkylation, we systematically studied the possible tautomer forms of structures **12** and **13** by considering the energetics of the neutral and ionized species during the alkylation step.

2. Results and discussion

The synthesis of the 5- and 7-amino-substituted 6-azaoxindoles **12a** and **13a** was achieved following an adapted and optimized reaction sequence.[18,21] The advantage of this three-steps synthesis consists in the avoiding of protection of the amino function, which allows a regioselective formation of the desired products **12a** and

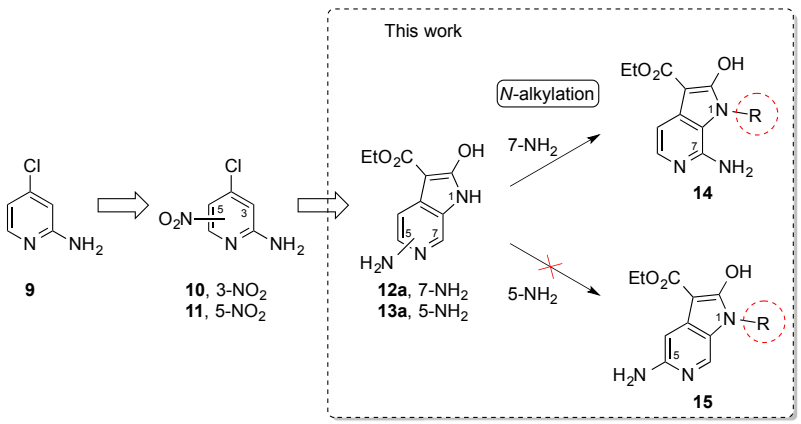

Fig. 2. Feasible synthetic approach to multifunctionalized N1-alkylated 7-amino-6-aza-2-oxindole derivatives.

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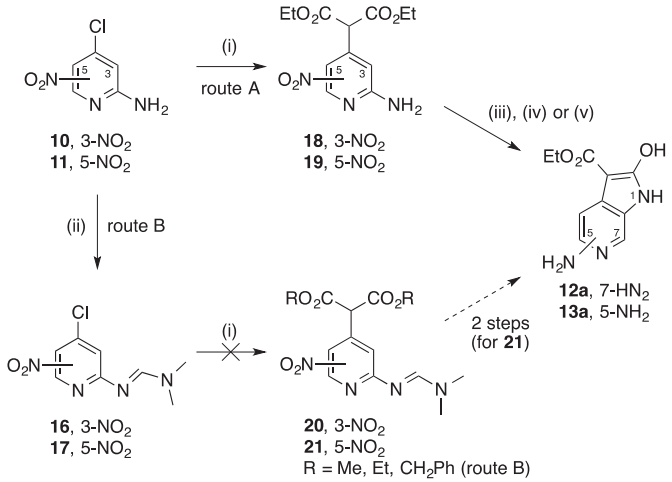
13a and their hydrochloride salts in high yields and purity even in large scale (route A, Scheme 1).



Scheme 1. Synthesis of 5- and 7-amino-6-azaoxindole derivatives **12a** and **13a** (for route A, see Ref. 18). Reagents and conditions: (i) NaH (3.6–4.2 equiv), malonic acid diethyl ester (3.6–4.0 equiv), DMF, 40–55 °C, 40–50 min (for **18**) and 3–4 h (for **19**); Yield 87% (**18**) and 84% (**19**);[21a] (ii) DMF–DMA (1.0 mL per 1.0 mmol), MeOH/THF (2:1), 75 °C, 16 h (for **10**) and 20 h (for **11**); Yield 87% (**16**) and 68% (**17**); (iii) 1) Zn dust (20.0 equiv), AcOH–H_2O (3:1), rt, 15 min (for **12a**) and 20 min (for **13a**), 2) NH_4OH (25%), rt, 5–20 min (method 1); Yield 78% (**12a**) and 96% (**13a**); (iv) 1) H_2 (40 psi), Pd/C (10%), EtOH, rt, 90 min, 2) HCl (18%), rt, over night (method 2); Yield 42% (**12a**) and 94% (**13a**); (v) 1) $SnCl_2 \cdot 2H_2O$ (10.0 equiv), EtOH, 30 °C, 2 h, 2) NH_4OH (25%), rt, 30 min (method 3); Yield 62% (**12a**).

Introduction of a nitro group at the 3- and 5-position of 2-amino-4-chloropyridine (**9**) afforded a mixture of the respective 3- and 5-nitro-substituted regioisomers **10** and **11** (LC/ESI-MS product ratio, **10**:**11**=1.3:1) via 2-nitraminopyridine rearrangement.[18,22] Separation and isolation of the regioisomers was performed following a modified three-step purification procedure (for details, see Supplementary data).[22b]

Compounds **18** and **19** were obtained in 87 and 84% yield, respectively, by a condensation of **10** and **11** with diethyl malonate in the presence of sodium hydride as a base in DMF.[18,21a] Equally high yields were obtained when the addition of **10** or **11** to the malonic ester proceeds at a reaction temperature not higher than 52–55 °C. The conversion of 3-substituted pyridine was completed in shorter reaction times than the condensation of its 5-substituted analogue (40 min for **10** to **18** cf. 4 h for **11** to **19**). This fact could be explained by the faster mesomeric destabilization of the reactive intermediate **10** following by a rapid tautomeric stabilization of **18** under basic conditions. The X-ray structures of **18** and **19** provide insight into their structural features (Fig. 3).[23] Both form dimers connected by N–H···N hydrogen bonds (Fig. S3, Supplementary data). Compound **18** contains two independent molecules in the asymmetric unit and shows a second H-bond intramolecular to an oxygen atom of the *ortho*-nitro group. It reveals two rotamers A and B, differing in the orientation of both ethyl groups (Fig. S4, Supplementary data). The 5-amino-substituted derivative **19** contains a second H-bond intermolecular to an oxygen atom of a CO_2Et group of a neighboring molecule and shows only one molecule per asymmetric unit. The importance of the free amino function for the stabilization of the in situ formed tautomers during the whole synthetic approach was demonstrated by reaction of **10** and **11** with DMF-DMA in methanol towards the corresponding amino-protected compounds **16** and **17**, respectively (route B, Scheme 1).[24] However, their further condensation with various malonic esters (R=Me, Et, CH_2Ph) failed to produce **20** and **21**, respectively, probably due to the rigid structure of the reactive intermediates **16** and **17**. Therefore, an alternative three-step conversion of **17** towards 5-amino-6-azaoxindole derivative **13a** via protection of the amino group was not feasible.[25]

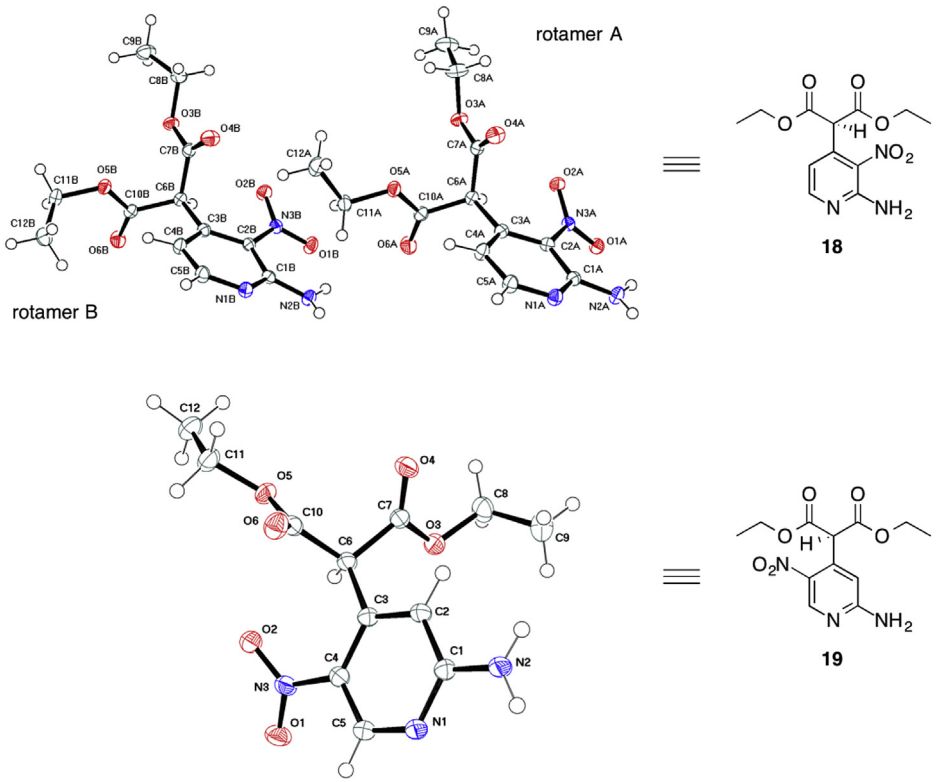


Fig. 3. X-ray crystal structures of **18** and **19**. The thermal ellipsoids are drawn at 50% probability level.

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Subsequently, the desired 7-amino- and 5-amino-6-azaoxindoles **12a** and **13a** were obtained by selective reduction of the nitro group in **18** and **19** followed by an intramolecular heterocyclization.[18] This key step of the synthesis of amino-substituted 6-azaoxindole derivatives was performed applying different reaction conditions, e.g., variation of the solvent, the reaction time, and the amount of the reducing agent that was used (Table 1). We found that fast reactions and highest yields of **12a** (78%) and **13a** (96%) were obtained when the reductive cyclization was conducted as an one-pot reaction with a large excess of zinc dust (20.0 equiv) in AcOH/H_2O (3:1) followed by addition of 25% aqueous ammonia for a reaction time of 20–40 min at room temperature (method 1).[18] Compound **13a** was obtained in equally high yield (94%) when the reductive step was performed in a Parr hydrogenator at 40 psi using catalytic amount of palladium on charcoal (10%) in ethanol as a solvent and subsequent heterocyclization by treatment of the diamino intermediate with 18% hydrochloric acid (method 2).[18] However, the reductive cyclization proceeds slower with reaction times of up to 15 h. The proposed mechanism for the formation of **13a** using Pd/C catalyst is illustrated in Fig. S5 (see Supplementary data). There was no improvement towards the yield of **12a** (20%) when applying method 2.[26] We observed that the isolation of the products was difficult under these conditions. Depending of the reaction conditions the synthesis of amino-substituted 6-azaoxindoles is more complex when comparing with their unsubstituted analogues due to the formation of different tautomers and the basicity of the free amino group. Thus, neutralization of the reaction mixture to pH 6–7 after completed reaction is required in order to obtain the products in high yields and purity. With the aim to further improve the yield of **12a**, conversion of **18** with a large excess of $SnCl_2 \cdot H_2O$ (20.0 equiv) in ethanol under ultrasonic irradiation[27] at 30–35 °C was conducted (method 3). Though, no significant improvement for the formation of **12a** (62% cf. 78% isolated yield by method 1) was observed, even when the cyclization step was performed at 70 °C.

In general, regioselective N1-alkylation was performed with 1.0–1.5 equiv of the corresponding alkyl halides in DMF as a solvent under basic reaction conditions.[28] First, N1-substitution experiments were conducted by reaction of 7-amino-substituted 6-azaoxindole **12a** with methyl methanesulfonate (MMS, **25**),[28b] methyl iodide (**26**), benzyl bromide (**27**), and 2-bromo-*N*-phenethylacetamide (**28**)[29] as alkylation reagents. Substitution of the thermodynamically preferred N1-position of **12a** with **25** and **26** was achieved using potassium carbonate (1.1–1.25 equiv) as a base at room temperature (method 1) affording *N*-methylated compound **22a** in moderate to good yields (Table 2, entries 1–4). The reaction shows strong dependency of the amount of base and alkyl halide that was used. The best yield (78%) was achieved when using **25** (1.35 equiv) as methylation reagent in the presence of 1.25 equiv of potassium carbonate (entry 3), whereas shorter reaction time of 6 h was observed by methylation with methyl iodide (1.1 equiv) leading to the formation of **22a** in 52% isolated yield (entry 4). Alkylation of **12a** with benzyl bromide was performed under different conditions yielding *N*-benzylated product **23** in poor to high yields (Table 2, entries 6–8). In the presence of sodium hydride (1.1 equiv) at room temperature (method 2) the product was isolated in 36% yield (entry 6). In this case when an excess of benzyl bromide (1.5 equiv) was used, traces of bis-alkylated products were detected by LC/ESI-MS analysis after a reaction time of up to 6 h. Moderate yield of **23** (53%) was achieved when using method 1, however, the alkylation took longer (entry 7). A significant improvement was observed when the conversion was performed with stoichiometric amount of **27** using both, sodium hydride (1.1 equiv) and K_2CO_3 (1.1 equiv) as bases starting the reaction at 0 °C with gradually increasing to room temperature for 6 h (method 3). Following this

Table 1
Methods and reaction conditions for the synthesis of **12a** and **13a**

Entry	Starting compd.	Reducing agent	Solvent	Cyclization	Method[b]	Time (min)	Product	Yield (%)[a]
1	**18** (3-NO_2)	Zn (5.0 equiv)	AcOH–H_2O (3:1)	NH_4OH (25%), H_2O, rt	1	135	**12a**	65
2	**18** (3-NO_2)	Zn (10.0 equiv)	AcOH–H_2O (3:1)	NH_4OH (25%), H_2O, rt	1	50	**12a**	74
3	**18** (3-NO_2)	Zn (20.0 equiv)	AcOH–H_2O (3:1)	NH_4OH (25%), H_2O, rt	1	20	**12a**	78
4	**18** (3-NO_2)	H_2 (40 psi), Pd/C (10%)[c]	EtOH	HCl (18%), EtOH, rt	2	420	**12a**[e]	20
5	**18** (3-NO_2)	$SnCl_2 \cdot 2H_2O$ (5.0 equiv)[d]	EtOH	HCl (18%), NH_4OH (25%), H_2O, 70 °C	3	150	**12a**	48
6	**18** (3-NO_2)	$SnCl_2 \cdot 2H_2O$ (10.0 equiv)[d]	EtOH	NH_4OH (25%), H_2O, 30 °C[c]	3	150	**12a**	62
7	**19** (5-NO_2)	Zn (20.0 equiv)	AcOH–H_2O (3:1)	NH_4OH (25%), H_2O, rt	1	40	**13a**	96
8	**19** (5-NO_2)	H_2 (40 psi), Pd/C (10%)	EtOH	HCl (18%), EtOH, rt	2	900	**13a**	94

[a] Isolated yields, unless otherwise noted.
[b] Ref. 18 for method 1 and 2.
[c] Hydrogenation was carried out in a Parr apparatus.
[d] Under ultrasonic irradiation.
[e] Product isolated as a hydrochloride salt.

Pure products **12a** and **13a** were isolated after repeated recrystallization from different solvent mixtures. Structure determination was carried out by NMR and LC/ESI-MS analysis. Depending on the reaction conditions 6-azaoxindoles may exist as a mixture of their keto and enol forms. However, based on NMR spectral data in DMSO-d_6 only the hydroxy tautomer of both products was identified. The reason could be the stabilizing effect of the ester group at the 3-position of **12a** and **13a**.[18] An autoxidation of the enol form was not detected (ESI-MS *m/z* 220 $[M-H]^-$/222 $[M+H]^+$ for **12a** and **13a**).[21c]

Following the proposed strategy for the formation of N1-substituted amino-6-azaoxindole derivatives (**14** or **15**) possessing an ester group at 3-position, we used compounds **12a** and **13a** as starting materials in series of N-alkylation experiments. Different attempts were performed in order to access the desired N1-substituted products and to optimize the reaction conditions. Consequently, reaction time, temperature, type, and the amount of bases and reagents were varied (Table 2).

In general, regioselective N1-alkylation was performed with 1.0–1.5 equiv of the corresponding alkyl halides in DMF as a solvent under basic reaction conditions.[28] First, N1-substitution experiments were conducted by reaction of 7-amino-substituted 6-azaoxindole **12a** with methyl methanesulfonate (MMS, **25**),[28b] methyl iodide (**26**), benzyl bromide (**27**), and 2-bromo-*N*-phenethylacetamide (**28**)[29] as alkylation reagents. Substitution of the thermodynamically preferred N1-position of **12a** with **25** and **26** was achieved using potassium carbonate (1.1–1.25 equiv) as a base at room temperature (method 1) affording *N*-methylated compound **22a** in moderate to good yields (Table 2, entries 1–4). The reaction shows strong dependency of the amount of base and alkyl halide that was used. The best yield (78%) was achieved when using **25** (1.35 equiv) as methylation reagent in the presence of 1.25 equiv of potassium carbonate (entry 3), whereas shorter reaction time of 6 h was observed by methylation with methyl iodide (1.1 equiv) leading to the formation of **22a** in 52% isolated yield (entry 4). Alkylation of **12a** with benzyl bromide was performed under different conditions yielding *N*-benzylated product **23** in poor to high yields (Table 2, entries 6–8). In the presence of sodium hydride (1.1 equiv) at room temperature (method 2) the product was isolated in 36% yield (entry 6). In this case when an excess of benzyl bromide (1.5 equiv) was used, traces of bis-alkylated products were detected by LC/ESI-MS analysis after a reaction time of up to 6 h. Moderate yield of **23** (53%) was achieved when using method 1, however, the alkylation took longer (entry 7). A significant improvement was observed when the conversion was performed with stoichiometric amount of **27** using both, sodium hydride (1.1 equiv) and K_2CO_3 (1.1 equiv) as bases starting the reaction at 0 °C with gradually increasing to room temperature for 6 h (method 3). Following this method, compound **23** was isolated in 96% yield (entry 8). Conversion of **12a** with 2-bromo-*N*-phenethylacetamide (**28**) was performed using method 1 and 3 with major modifications (Table 2, entries 10–13). In this case, we found that the alkylation with **28** requires higher reaction temperatures of about 80 °C than the reaction with the above used alkylation reagents. The desired *N*-alkylated product **24** was obtained in poor to moderate yields (31–51%) when the alkylation was performed using method 1 at room temperature (entries 10–12). An increasing of the reaction temperature to 70 °C was required. There was an improvement towards the yield of **24** (51%) when the thermodynamic substitution took longer requiring a reaction time of up to 72 h (entry 12). Fast reaction and highest yield of **24** (73%) was obtained by

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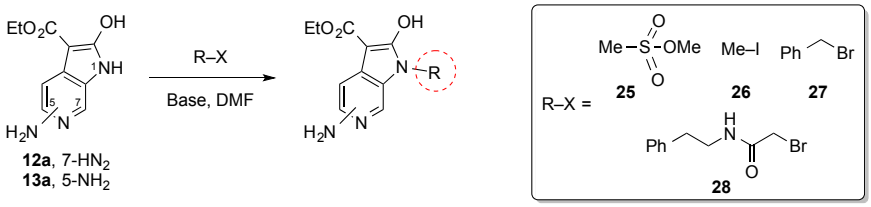
Table 2
N-alkylation of amino-6-azaoxindoles **12a** and **13a**



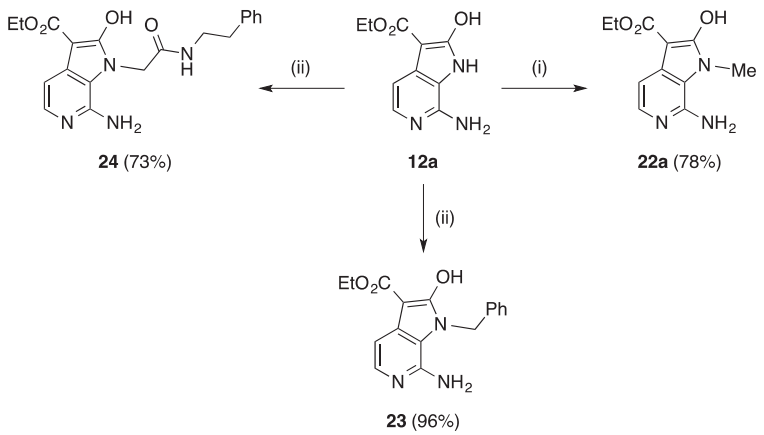
12a, 7-HN_2
13a, 5-NH_2

Entry	Starting compd.	R–X (equiv)	Base (equiv)	Temp (°C)	Method	Time (h)	Product	Yield (%)[a]
1	**12a** (7-NH_2)	**25** (1.1)	K_2CO_3 (1.1)	rt	1	19	**22a**	49
2	**12a** (7-NH_2)	**25** (1.3)	K_2CO_3 (1.2)	rt	1	24	**22a**	74
3	**12a** (7-NH_2)	**25** (1.35)	K_2CO_3 (1.25)	rt	1	11	**22a**	78
4	**12a** (7-NH_2)	**26** (1.1)	K_2CO_3 (1.2)	rt	1	6	**22a**	52
5	**13a** (5-NH_2)	**26** (1.1)	K_2CO_3 (1.1)	rt	1	24	—	NR[b]
6	**12a** (7-NH_2)	**27** (1.5)	NaH (1.1)	rt	2	6	**23**	36[c]
7	**12a** (7-NH_2)	**27** (1.1)	K_2CO_3 (1.1)	rt	1	29	**23**	53
8	**12a** (7-NH_2)	**27** (1.0)	NaH (1.1) K_2CO_3 (1.1)	0→rt	3	6	**23**	96
9	**13a** (5-NH_2)	**27** (1.2)	NaH (1.1) K_2CO_3 (1.1)	0→rt	3	12	—	NR
10	**12a** (7-NH_2)	**28** (1.1)	K_2CO_3 (1.1)	rt→65	1	24	**24**	31
11	**12a** (7-NH_2)	**28** (1.2)	K_2CO_3 (1.2)	rt→65	1	48	**24**	38
12	**12a** (7-NH_2)	**28** (1.2)	K_2CO_3 (1.2)	rt→70	1	72	**24**	51
13	**12a** (7-NH_2)	**28** (1.2)	NaH (1.1) K_2CO_3 (1.1)	0→rt→70	3	12	**24**	73
14	**13a** (5-NH_2)	**28** (1.2)	K_2CO_3 (2.5)	rt	1	4	—	NR
15	**13a** (5-NH_2)	**28** (2.0)	NaH (1:1) K_2CO_3 (1.1)	0→rt→80	3	192	—	NR

[a] Isolated yields, unless otherwise noted.
[b] NR=no reaction, partly formation of by-products or recovery of starting material.
[c] Product accompanied with <9% of bis-alkylated product.

applying method 3 with gradually increasing of the reaction temperature from 0 to 70 °C for 12 h (entry 13).

The regioselectivity of the N1-alkylation of ethyl 7-amino-2-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylate **12a** was further confirmed by re-synthesis of **22a**–**24** in large scale under optimized conditions resulting in 85% yield in overage (Scheme 2). Overall, in all these transformations, we did not find a non-selective formation of pyridine N6-alkylated and/or bis-alkylated products. The final products **22a**–**24** were isolated after recrystallization from methanol/EtOAc/petroleum ether mixtures in high purity and characterized by different NMR techniques and LC/ESI-MS analysis. The NMR spectral data in DMSO-d_6 reveal that only the hydroxy tautomers of the N1-alkylated products **22a**–**24** are present. ^{1}H NMR analysis of **22a** in deuterated methanol was used to provide the existence of the 2-OH- and 7-NH_2–hydrogen atoms by proton exchange at 298 K (see Supplementary data). This observation excludes the formation of a 2-methoxy derivative. Compare to its precursor **12a**, the ^{1}H signal for the 2-OH group in N1-methylated product **22a** is shifted from about 12 to 10 ppm, whereas no significant changes could be observed for the 7-NH_2 protons (6.91 ppm for **12a** vs. 6.97 ppm for **22a**). The coupling constant between C-4 and C-5 methine protons 4-H and H-5 of the pyridine moiety in both compounds remains almost unchanged ($^3J_{4H-5H}$ ~ 6.6–6.9), indicating of a non-substituted pyridine nitrogen atom. In the case of an N6-methylation of **12a**, a shifting of the hydrogen atoms at pyridine C-4 and C-5 positions as well as the 7-NH_2-group would be observed. Analysis of the ^{13}C and DEPT spectra of compound **22a** confirms its preferable N1-substitution.



Scheme 2. Synthesis of *N*-alkylated 7-amino-6-azaoxindoles **22a**–**24** using the optimized reaction conditions: (i) Entry 3 for **22a** (method 1); (ii) Entry 8 and 13 for **23** and **24** (method 2). Isolated yields refer to **12a**.

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Next, similar alkylation experiments were performed with 5-amino-substituted 6-azaoxindole derivative **13a** (Table 2, entries 5, 9, 14, and 15) using the same alkyl halides and reaction conditions as applied for **12a**. In Table 2 are outlined only a few representative examples of these reactions. To achieve the corresponding *N*-alkylated products of **13a**, several attempts were performed. However, the experiments were not successful to produce the desired structures. Furthermore, in the most cases a large amount of the starting material was recovered and, depending on the reaction time, side processes such as dimerization and tautomerization took place (ESI-MS analysis).

In order to find a plausible explanation of this observation and to validate our hypothesis on the preferable N1-substitution for 7-NH_2- versus 5-NH_2-substituted 6-azaoxindoles, theoretical calculations on the neutral and the charged (deprotonated) tautomer forms of **12a** and **13a** in a gas phase were performed.

The possible tautomers of **12** and **13** are sketched in Figs. S6 and S7, and the relative energies are collected in Tables S3 and S4, respectively. Comparing the most stable tautomeric forms for **12** and **13** and their isomers (Fig. 4) it could be concluded that there is almost no difference in the tautomeric behavior of **12** (panel A) and **13** (panel B) in a neutral state. In both cases, the **a** tautomer is strongly stabilized and the most of the stable tautomers exhibit a proton at N1, which does not allow a direct alkylation. At the same time, the stability of these forms (**a**, **b**, **i**, and **c**), and their isomers mostly related to the rotation of the CO_2Et group, clearly indicates that the OH proton in **a** is easily movable one and would be the first to be lost during a deprotonation, giving an anion with an engaged N1 position.

The deprotonation under basic conditions (pH>10) substantially changes the tautomeric picture (Fig. 5). As seen, the most stable deprotonated forms ($\mathbf{a}^-$ and $\mathbf{f}^-$) in both **12** and **13** are very similar. The structure $\mathbf{a}^-$ allows alkylation only at N6, while the $\mathbf{f}^-$ tautomer gives such an option at both nitrogen atoms. However, there is a substantial difference. In the case of **12**, the $\mathbf{12f}^-$ anion is slightly more stable allowing potential alkylation at N1, while $\mathbf{13a}^-$ form is strongly dominating in the case of **13**, giving no option for N1 attack. This theoretical prediction matches very well the observed experimental results. Returning back to $\mathbf{12f}^-$, where both nitrogens are available for alkylation, the total atomic charge of N1 is −0.194 against −0.176 at N6, which could give an idea about the preferable obtainment of the N1-alkylated product (see Tables S5 and S6, Supplementary data). Furthermore, the analysis of the tautomerism of **22** shows that it exists exclusively as **22a**, i.e., preference for N1- versus N6-methylation of **12a** (see Fig. S8 and S9, Table S7, Supplementary data).

Summarizing our findings, we can conclude that (i) compounds **12** and **13** exist in their more stable enol form (tautomer **a**), (ii) deprotonation of N1 proton in the 5-amino-substituted compound **13a** is energetically unfavorable when comparing to its 7-amino-substituted analogue **12a**, i.e., the only deprotonated $\mathbf{12f}^-$ form is accessible for an N1-alkylation (cf. $\mathbf{12f}^-$ and $\mathbf{13f}^-$, Fig. 5), (iii) the nitrogen N1 is preferable for an electrophilic substitution rather than N6, (iv) the N-alkylation reaction of **12a** proceeds via formation of stable enol intermediates (enolate anion and/or conjugate base), (v) the N1-substitution (reaction time, temperature, amount of base and reagent) depends on the substitutions pattern of the alkylation reagent that is used, e.g., length and functionalities of the side chain, and (vi) in the case that the N-alkylation takes longer than expected, additionally amount of the corresponding base should be added to the reaction to ensure the stabilization of the in situ formed anion $\mathbf{12f}^-$.

A decarboxylation of **24** to obtain the dealkoxycarbonylated derivative **25** was attempted with a view to provide an indirect evidence for the favorable N1-substitution of **12a**. The reaction was conducted in analogy to a method described by Krapcho[30] using an excess of lithium chloride (2.0 equiv) in DMSO/water (1:1) under thermal conditions (Scheme 3). However, no significant conversion of the starting material towards **25** was observed even by a reaction time of up to 18 h. In this case, we observed formation of by-products when the reaction took place longer. We assume that under these conditions the initially formed anion at 2-position of **24** rapidly undergoes in situ tautomerization to form the stable β-keto anion **I** (Scheme 3). Similarly, conversion of **24** under acidic conditions, e.g., in the presence of 18% aqueous hydrochloric acid in refluxing water was not successful to obtain **25** by saponification and subsequent decarboxylation.[31] Moreover, **24** was recovered from the reaction mixture in form of its hydrochloride salt.

Finally, in order to access the physicochemical properties and to evaluate the drug-likeness of 7-amino-2-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridines, we determined water solubility and $\log D_{7.4}$ values for compound **12a** and its N1-alkylated derivative **23** as representatives of this class of 6-azaindoles. Additionally, the p*K*a and logP values,[32] and the HBA/HBD counts[33] for these compounds were calculated (for more details, see Table S8, Supplementary data). Water solubility at physiological pH of 7.4 was found to be 3 μg/mL (13.6 μM) for **12a**. The N1-benzylated compound **23** displayed much better solubility of 20 μg/mL (64.2 μM) at pH 7.4, which is a sufficient range for further development of peroral active drugs. The logD values (octanol-buffer at pH 7.4, rt) were determined to be 0.08 (**12a**) and 1.50 (**23**), respectively, indicating that the nitrogen N1 atom of the pyrrolo[2,3-*c*]pyridine core is important for introducing of lipophilicity. The $\log D_{7.4}$ value for **23** is in the preferable range for predictive oral bioavailability.[34]

Furthermore, the lipophilic character of the N1-substituted 6-azaoxindoles can be fine-tuned for the purpose to obtain brain penetrable CNS active drugs, e.g., by introducing of suitable substituents in the *meta*- and/or *para*-position of the benzyl residue of **23**. The p*K*a values were evaluated to be 4.8 (acid)/10.2 (base) for **12a** and 4.7 (acid)/10.2 (base) for **23**, respectively. Both compounds displayed similar pH profile with two p*K*a values revealing of their almost amphoteric character (see Fig. S10, Supplementary data). Thus, the molecules will be uncharged in the physiologically relevant pH range of 6–8. The obtained data indicate that both, the pyridine nitrogen N6 and the nitrogen N1 of the pyrrolo[2,3-*c*]pyridine core can be protonated under physiological conditions in the stomach (at pH<5). As aforementioned, under basic conditions (pH>10), the compounds can be deprotonated due to the hydroxy group at C2. The basicity of N1 in **12a** can be modulated by an alkylation with a broad diversity of suitable substituents. In addition, it appears to be indispensable to determine the physicochemical properties of 6-azaindole derivatives, especially for their N1-unsubstituted analogues at different physiologically relevant pH ranges.

On the basis of above experimental data and the tautomer calculations, further chemoselective transformations of highly functionalized 6-azaoxindole derivatives can be achieved under basic conditions,[35] whereas treatment with selected inorganic and/or organic acids leads to salts formation. Moreover, 7-amino-2-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine **14** can be substituted with a variety of residues (R^1, R^2 and/or R^3). Depending on the target molecules, one- or two-step modification of **14** are possible, e.g., by reduction of the ester group at 3-position (route A), amide coupling reaction at 7-position (route B) or combination of both (route C) to achieve highly functionalized 6-azaindoles **26**, **27** or **28**, respectively (Fig. 6).

3. Conclusion

In summary, we have demonstrated that multifunctionalized N1-alkyl-7-amino-6-azaoxindole derivatives with drug-like properties can be successfully achieved by applying of a simple

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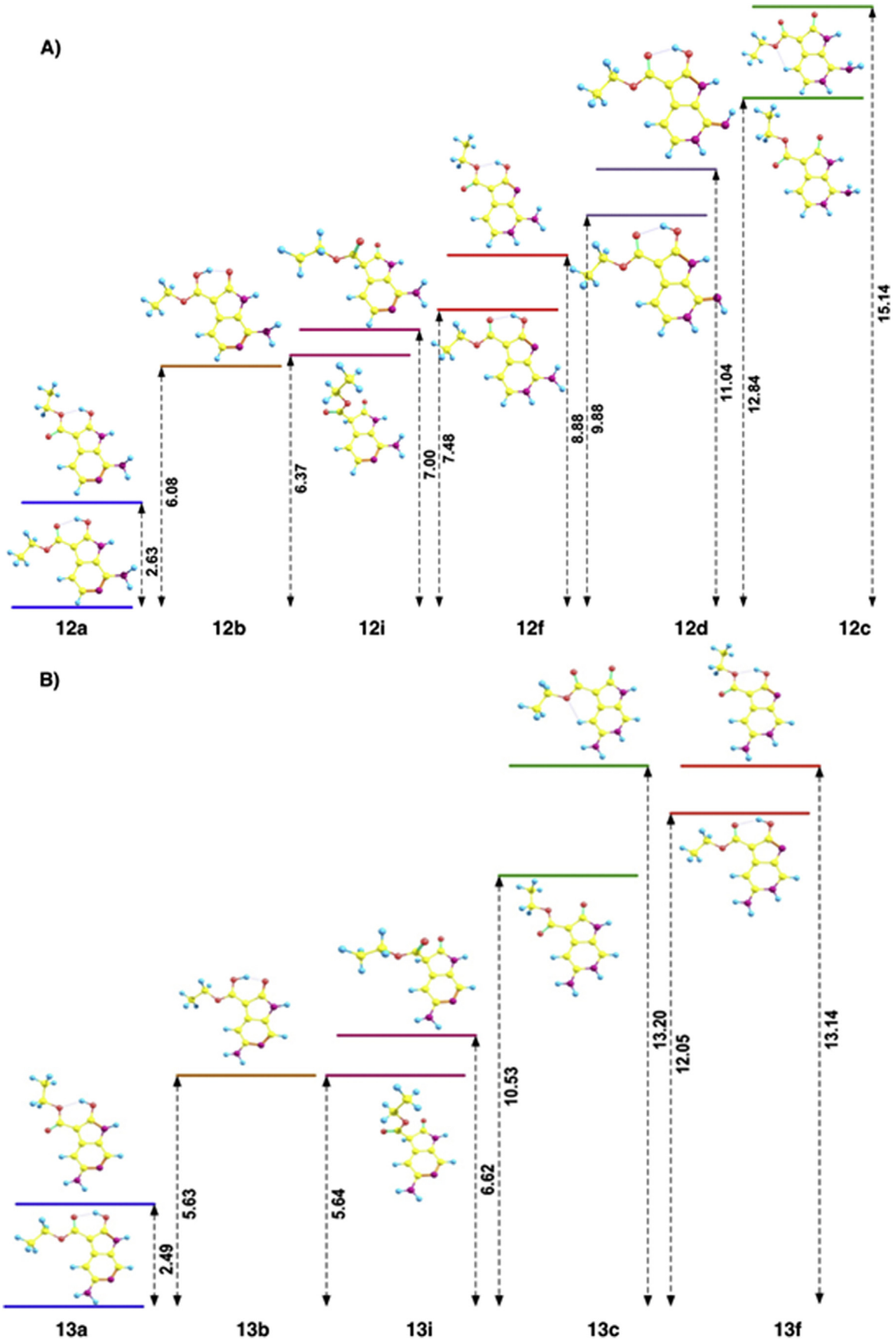

Fig. 4. Relative energies (in kcal/mol units) of the most stable tautomers and isomers of **12** (panel **A**) and **13** (panel **B**) in a gas phase (M06-2X/TZVP).

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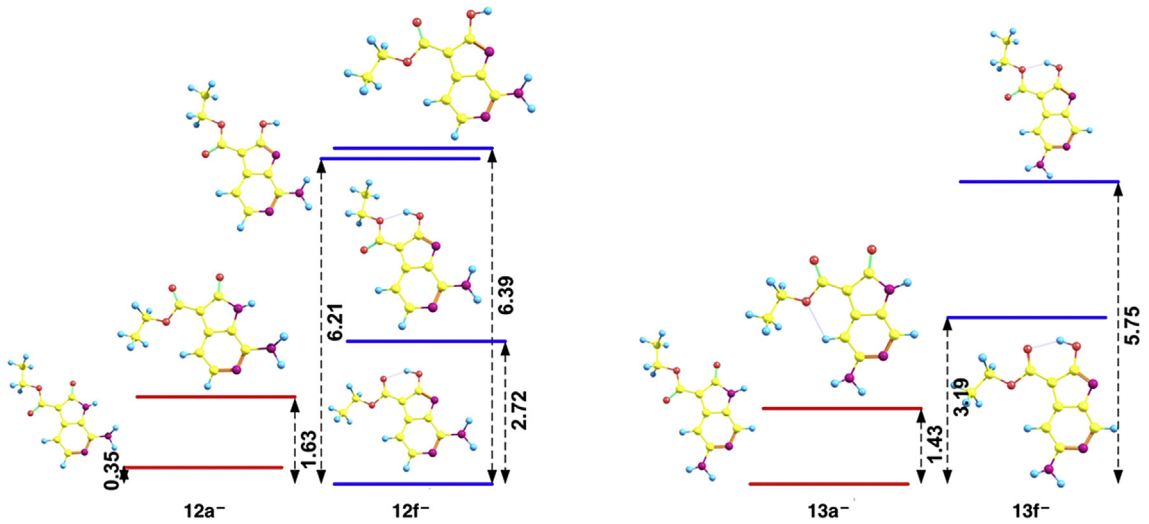
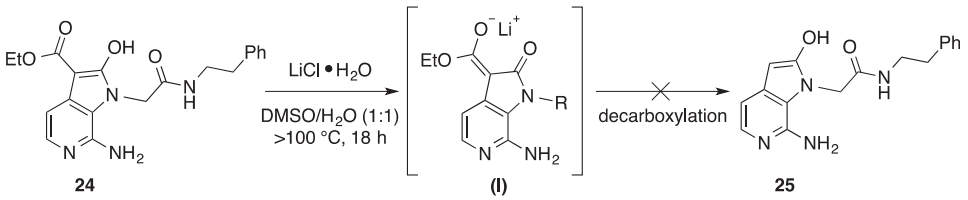


Fig. 5. Relative energies (in kcal/mol units) of the most stable deprotonation forms of **12** (left) and **13** (right) in a gas phase (M06-2X/TZVP). The relative energies of the remaining forms are more than 10 kcal/mol higher.



Scheme 3. Attempted decarboxylation of **24**.

four-step synthetic approach. The convergent sequence includes reductive cyclization as a key step leading to the regioselective formation of the 5-amino- and 7-amino-substituted 6-azaoxindoles **12a** and **13a**. The subsequent N1-alkylation of **12a** was conducted under various basic conditions providing high tolerance of sensitive functionalities and high yields of the desired *N*-alkylated amino-6-azaoxindoles **22a**–**24**. The synthetic procedure was optimized for all steps and will enable simple scale-up in large scale. The N1-substitution of the amino-substituted 6-azaoxindoles showed strong dependency on the position of the amino group, i.e., preference for 7-NH_2- versus 5-NH_2-substitution. An additional evidence for the proposed hypothesis was obtained by means of quantum chemical calculations of the tautomers of **12**, **13** and **22** in their ionized and neutral forms. The experimentally determined and calculated physicochemical properties of the representative compound **23** indicate of drug-like features in case of N1-alkylation of 7-amino-6-azaindole derivatives. Regioselective alkylation in the final step allows the introduction of broad structural modifications and an easy access to compound libraries that can be applied for drug design and development.

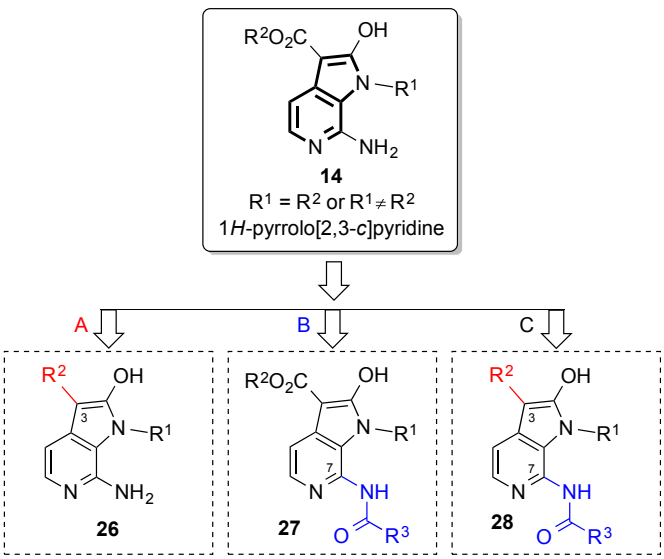


Fig. 6. Possible functionalizations of N1-alkylated 7-amino-6-aza-2-oxindoles.

4. Experimental section

4.1. General information

All commercially available anhydrous solvents, reagent grade solvents for chromatography, reagents and starting materials used were obtained from various producers and used in reactions as received without further purification or drying. Dry *N*,*N*-dimethylformamide (DMF. 99.8% extra dry over molecular sieves, AcroSeal, Acros) was used throughout the synthesis. Thin layer chromatography (TLC) was performed on pre-coated Merck 60F_{254} silica gel plates using UV light (λ=254 nm light source). Preparative column chromatography was performed on Acros Organics silica gel 60 Å (0.060–0.200 mm). Hydrogenation was achieved by using a Hogen GC hydrogen generator (Proton Energy System, Inc.). Sonication was performed in a Sonorex Super RK 100/H ultrasonic cleaning bath at a frequency of 35 kHz, a nominal power of 80 W and a bath temperature at 30 °C with explosion of the reactions to air in standard glassware or glass sample vials. Solvents were removed in vacuo on a Büchi Rotavapor R-100 or R-300. Mass spectra were

recorded on an API 2000 mass spectrometer (electron spray ion source ESI, Applied Biosystems) coupled with an Agilent 1100 HPLC system. NMR spectra were recorded on a Bruker AV 500 MHz NMR spectrometer at 500 MHz (^{1}H), or 125 MHz (^{13}C, DEPT) at 303 or 298 *K* on samples dissolved in an appropriate deuterated solvent (DMSO-d_6 or CD_3OD). Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak in the respective spectra: DMSO-d_6 δ 2.50 (^{1}H) and 39.51 (^{13}C); CD_3OD δ 3.31 (^{1}H) and 49.00 (^{13}C). Coupling constants (*J* values) are reported in Hertz (Hz); spin multiplicities are indicated by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), quartet (q), dq (doublet of quartets), and m (multiplet). Melting points are uncorrected and were obtained on a Büchi MP B-454 apparatus using open capillary tubes.

4.2. Optimized scale-up procedure for the preparation of 4-chloro-3-/5-nitropyridin-2-amines (10 and 11)

The compounds were prepared as described in the literature with major modifications.[22b] To a solution of 4-chloropyridin-2-amine **9** (2.60 g, 0.02 mol) in sulfuric acid (96%, 40 mL) was slowly added fuming nitric acid (20 mL) under intensively stirring at 0 °C over a period of 6 h. The reaction mixture was allowed to stay at 0–5 °C for 3 days and then poured into ice water (120 g). The mixture was adjusted to pH 3–5 with ammonium hydroxide (25%, 160 mL) and the yellow precipitate filtered, washed with cooled water, and dried at room temperature to give 4-chloro-2-nitraminopyridine intermediate (3.46 g, 99%) as yellow crystals; mp 204–205 °C. The crude nitramine (2.73 g, 0.016 mol) was carefully dissolved in small portions into cooled sulfuric acid (96%, 54 mL) under constant stirring. The solution was allowed to warm to room temperature and stirred for further 3 h. After that, the reaction mixture was poured into ice water (60 g) and adjusted to pH 6–7 with ammonium hydroxide (25%, 150 mL) until a yellow crystalline precipitate was formed. The cooled product (mixture of 3- and 5-nitro isomers) was filtered under normal pressure, dried at room temperature over night, and washed several times with ethyl acetate (170 mL) until the color of the crystalline precipitate had turned to a slight yellow. The residue left after filtration was dissolved in ethanol (100 mL), boiled for 15 min, filtered to remove the insoluble precipitate, and recrystallized from dichloromethane/petroleum ether (50%, 50 mL) to give the pure product **11** (Fraction 1). The combined ethyl acetate layers were evaporated to dryness and purified by repeated column chromatography on silica gel using 50% dichloromethane/ethyl acetate as eluent. Chromatographically purified products were additionally recrystallized from dichloromethane/petroleum ether (50%, each 50 mL), evaporated, and dried at 70 °C to give pure product **10** (Fractions 2 and 4) and **11** (Fraction 3, for details, see Supplementary data, Fig. S2).

*4.2.1. 4-Chloro-3-nitropyridin-2-amine (**10**).*[22b] Slight yellow needles (1.47 g, 42% over two steps); mp 176–177 °C; R_f (50% CH_2Cl_2/EtOAc) 0.69; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 6.85 (1H, d, *J*=5.36 Hz, H-5), 7.21 (2H, br s, NH_2), 8.11 (1H, d, *J*=5.36 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 113.2 (C5), 129.5 (C3), 136.0 (C4), 152.1 (C6), 152.8 (C2); LC/ESI-MS calcd for $C_5H_4ClN_3O_2$ *m/z* 173.0, found 171.9 $[M-H]^-$, 174.9 $[M+H]^+$.

*4.2.2. 4-Chloro-5-nitropyridin-2-amine (**11**).*[22b] Yellow crystals (1.05 g, 30% over two steps); mp 260–261 °C; R_f (50% CH_2Cl_2/EtOAc) 0.48; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 6.58 (1H, s, H-3), 7.59 (2H, br s, NH_2), 8.79 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 108.4 (C3), 133.5 (C5), 137.1 (C4), 149.7 (C6), 162.7 (C2); LC/ESI-MS calcd for $C_5H_4ClN_3O_2$ *m/z* 173.0, found 171.9 $[M-H]^-$.

4.3. Preparation of amidines 16 and 17

The compounds were prepared as described in the literature with minor modifications.[24] To a solution of the corresponding 4-chloro-nitropyridin-2-amine (**10** or **11**, 1.0 mmol) in methanol (10 mL per 1.0 mmol starting material) and dimethylformamide (1.0 mL) was added dimethylformamide dimethyl acetal (DMF-DMA, 1.0 mL) and heated to 75 °C. After a reaction time of 16–20 h, the solvent was evaporated and the residue was stirred under water–petroleum ether (50%, 10 mL) until full crystallization. The product was filtered under reduced pressure, washed with petroleum ether (3×10 mL), and dried at 70 °C to afford amidine **16** or **17**.

*4.3.1. (E)-N′-(4-Chloro-3-nitropyridin-2-yl)-N,N-dimethylform-amide (**16**).*[24] Yellow crystals (194.9 mg, 87%); mp 121–123 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.96 (3H, s, NMe_2), 3.14 (3H, s, NMe_2), 7.21 (1H, d, *J*=5.36 Hz, H-5), 8.28 (1H, d, *J*=5.67 Hz, H-6), 8.61 (1H, s, N*H*=NMe_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.5, 40.7, 116.8, 133.6, 138.9, 150.1, 154.6, 156.9; LC/ESI-MS calcd for $C_8H_9ClN_4O_2$ *m/z* 228.1, found 228.9 $[M+H]^+$.

*4.3.2. (E)-N′-(4-Chloro-5-nitropyridin-2-yl)-N,N-dimethylform-amide (**17**).*[24] Yellow crystals (180.2 mg, 68%); mp 144–145 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.08 (3H, s, NMe_2), 3.18 (3H, s, NMe_2), 6.99 (1H, s, H-3), 8.69 (1H, s, N*H*=NMe_2), 8.91 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.9, 40.9, 118.2, 137.1, 147.6, 158.0, 165.8; LC/ESI-MS calcd for $C_8H_9ClN_4O_2$ *m/z* 228.1, found 229.1 $[M+H]^-$.

4.4. Preparation of compounds 18 and 19

The compounds were prepared in analogy to a published procedure.[18,21a] A suspension of sodium hydride (60%, 1.5 mmol) in mineral oil was washed with *n*-hexane (3×10 mL), the solvent was pipetted out and traces were removed under reduced pressure, and the remaining material was suspended in dry DMF (5 mL) under argon atmosphere. The mixture was cooled to 0–5 °C and a solution of malonic acid dialkyl ester (1.0 mmol) in dry DMF (0.5 mL) was added dropwise. During malonate addition the temperature was not allowed to rise about 40 °C. When the hydrogen evolution ceased (about 5–10 min) the reaction was allowed to warm to 50 °C and stirred for further 30 min at the same temperature, after which a solution of the corresponding 4-chloro-nitropyridine-2-amine (**10** or **11**, 0.5 mmol) in DMF (1 mL) was added dropwise while the temperature kept below 50–55 °C. The mixture was stirred for specified time at this temperature. After the starting material was consumed as monitored by TLC control (90% dichloromethane/methanol), the reaction mixture was evaporated under reduced pressure, the residue diluted with ice water (5 mL), and neutralized carefully with hydrochloric acid (2.0 N, 2 mL). The formed precipitate was filtered and washed with ice water (3×5 mL). The crude product was purified by column chromatography on silica gel using 50% dichloromethane/ethyl acetate as eluent to afford the corresponding condensed product **18** or **19**.

*4.4.1. Diethyl 2-(2-amino-3-nitropyridin-4-yl)malonate (**18**).*[18] Yellow crystals (240.3 mg, 87%); mp 117–118 °C; R_f (50% CH_2Cl_2/EtOAc) 0.77; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.17 (6H, t, *J*=7.25 Hz, 2×OCH_2CH_3), 4.17 (4H, dq, *J*=1.58, 7.25 Hz, 2×OCH_2CH_3), 5.20 (1H, s, C*H*), 6.58 (1H, d, *J*=5.36 Hz, H-5), 7.50 (2H, s, NH_2), 8.27 (1H, d, *J*=4.73 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.9 (2×OCH_2CH_3), 55.1 (*C*H), 66.9 (2×OCH_2CH_3), 114.3, 128.2, 139.4, 153.8, 153.9, 166.3; LC/ESI-MS calcd for $C_{12}H_{15}N_3O_6$ *m/z* 297.3, found 296.0 $[M-H]^-$, 298.3 $[M+H]^+$.

*4.4.2. Diethyl 2-(2-amino-5-nitropyridin-4-yl)malonate (**19**).*[18] Yellow crystals (231.7 mg, 84%); mp 151–152 °C; R_f (50% CH_2Cl_2/EtOAc) 0.81; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.18 (6H, t, *J*=7.25 Hz, 2×OCH_2CH_3),

4.18 (4H, dq, J=2.83, 7.25 Hz, 2×OCH_2CH$_3$), 5.35 (1H, s, CH), 6.34 (1H, s, H-3), 7.60 (2H, s, NH_2), 8.84 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.0 (2×OCH$_2$CH$_3$), 55.2 (CH), 61.8 (2×OCH$_2$CH$_3$), 108.3, 134.1, 138.8, 149.2, 162.9, 166.4; LC/ESI-MS calcd for $C_{12}H_{15}N_3O_6$ m/z 297.3, found 296.3 [M−H]$^-$, 298.4 [M+H]$^+$.

4.5. Procedures for reductive cyclization of 18 and 19

4.5.1. Method 1 using Zn/AcOH.[18] To a stirred suspension of the corresponding diethyl malonate **18** or **19** (1.0 mmol) in glacial acetic acid and water (4 mL, 3:1) was added zinc dust in small portions (20.0 mmol). The mixture was stirred at room temperature until a clear solution was formed and then filtered under reduced pressure to remove the zinc residue. The filtrate was evaporated to dryness, diluted with water (10 mL) and treated dropwise with aqueous ammonia (25%) until an alkaline pH was reached. The resulting mixture was stirred at room temperature for 5–10 min and the formed precipitate was filtered under reduced pressure, washed with water (2×10 mL), petroleum ether (2×10 mL), and dried at 70 °C to obtain pure products **12a** or **13a** as free amines. Alternatively, the work-up was performed by extraction of the alkaline solution with *n*-butanol (3×10 mL). Then, the combined organic extracts were washed with water (3×10 mL), dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residue was recrystallized from ethyl acetate/petroleum ether and/or methanol mixtures (4:1 or 3:1:1, 15 mL).

4.5.2. Method 2 using H_2–Pd/C.[18] A mixture of the corresponding diethyl malonate **18** or **19** (1.0 mmol) in absolute ethanol (5 mL) was treated with palladium on charcoal (10 mol-%). The mixture was subjected to hydrogenation using a Parr hydrogenator (40 psi) at room temperature in the presence of molecular sieve (3 Å) until complete reduction of the staring material was detected. The reaction was monitored by TLC analysis (50% ethyl acetate/dichloromethane). After complete reaction, the mixture was filtered through Celite pad and the filtrate was evaporated to dryness. The dark-red residue was treated with hydrochloric acid (2 N) and stirred at room temperature for respective time (TLC control: 100% methanol). When the reaction was complete, the reaction mixture was concentrated under reduced pressure, treated with saturated sodiumhydrogencarbonate solution (10 mL, pH>8), and extracted with *n*-butanol (3×10 mL). The combined organic layers were washed with water (3×10 mL), dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residue was diluted with ethyl acetate/petroleum ether (20%, 20 mL) and stirred at room temperature for 10 min. The formed slight green precipitate was recrystallized from dichloromethane/petroleum ether (50%, 20 mL) to afford **12a** or **13a** as white or off-white solids. For the preparation of the corresponding hydrochloride of **12a**, the work-up procedure after complete cyclization is not necessary.

4.5.3. Method 3 using $SnCl_2 \cdot 2H_2O$.[27] To a stirred solution of **18** (1.0 mmol) in ethanol (5 mL) was added tin(II) chloride dihydrate (10.0 mmol). The reaction mixture was then irradiated using ultrasonic bath for appropriate time at 30–35 °C. The reaction was monitored by TLC analysis (50% ethyl acetate/dichloromethane). After complete reaction, the solution was evaporated to dryness under reduced pressure and the residue was dissolved in water (5 mL). The resulting mixture was made strong alkaline with aqueous ammonia (25%, 5 mL) and then stirred at room temperature or under ice bath cooling until full precipitation. The precipitate was collected by filtration under reduced pressure, washed with water (3×5 mL) and dried at 70 °C. The residue was recrystallized from dichloromethane/petroleum ether (50%, 20 mL) to afford **12a** or **13a** as a white or off-white solid. Products were obtained with small amounts of impurities (LC-MS analysis). Alternatively, the work-up procedure was performed as described for method 1 with small modifications.

*4.5.4. Ethyl 7-amino-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate (**12a**).*[18] Preparation according to method 1 afforded **12a** as a white solid (401.3 mg, 95%); mp 302–303 °C (dec); R_f (100% MeOH) 0.29; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.25 (3H, t, J=6.94 Hz, OCH$_2$CH_3), 4.13 (2H, q, J=6.63 Hz, OCH_2CH$_3$), 6.91 (2H, br s, NH_2), 7.05 (1H, d, J=6.62 Hz, H-4), 7.31 (1H, d, J=6.62 Hz, H-5), 10.3 (1H, s, NH), 11.7 (1H, br s, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.9 (OCH$_2$CH$_3$), 57.5 (OCH$_2$CH$_3$), 87.7, 104.5, 110.0, 126.0, 135.7, 137.9, 164.9, 166.5 (CO_2Et); ^{13}C-DEPT NMR (125 MHz, DMSO-d_6) δ_C: 14.9 (OCH$_2$CH_3), 57.5 (OCH_2CH$_3$), 104.5 (C4), 125.8 (C5); LC/ESI-MS calcd for $C_{10}H_{11}N_3O_3$ m/z 221.1, found 220.1 [M−H]$^-$, 222.3 [M+H]$^+$.

*4.5.5. Ethyl 7-amino-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate hydrochloride (**12a**·**HCl**).* Following method 2, the hydrochloride salt of **12a** was obtained as a white solid (18.2 mg, 20%); mp 383–385 °C (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.30 (3H, t, J=6.94 Hz, OCH$_2$CH_3), 4.25 (2H, q, J=7.25 Hz, OCH_2CH$_3$), 7.21 (1H, d, J=6.93 Hz, H-4), 7.52 (1H, d, J=6.94 Hz, H-5), 7.85 (2H, br s, NH_2), 12.48 (1H, br s, OH), 12.88 (1H, br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.6 (OCH$_2$CH$_3$), 59.3 (OCH$_2$CH$_3$), 89.4, 105.4, 110.5, 127.4, 134.4, 141.0, 159.1, 163.6 (CO_2Et); LC/ESI-MS calcd for $C_{10}H_{11}N_3O_3$ m/z 221.1, found 222.3 [M+H]$^+$.

*4.5.6. Ethyl 5-amino-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate (**13a**).*[18] Preparation according to method 2 afforded **13a** as an off-white solid (228.8 mg, 96%); mp 328–330 °C (dec); R_f (100% MeOH) 0.18; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.27 (3H, t, J=7.25 Hz, OCH$_2$CH_3), 4.10 (2H, q, J=7.25 Hz, OCH_2CH$_3$), 4.65 (2H, br s, NH_2), 6.43 (1H, s, H-4), 7.23 (1H, s, H-7), 9.13 (1H, s, NH), 11.1 (1H, s, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 15.2 (OCH$_2$CH$_3$), 56.9 (OCH$_2$CH$_3$), 95.9, 112.9, 114.1, 123.9, 137.1, 152.8, 159.7, 166.9 (CO_2Et); LC/ESI-MS calcd for $C_{10}H_{11}N_3O_3$ m/z 221.1, found 219.9 [M−H]$^-$, 222.3 [M+H]$^+$.

4.6. Procedures for alkylation of 18

4.6.1. Method 1 using K_2CO_3. A suspension of ethyl 7-amino-2-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylate (**12a**, 1.0 mmol) and potassium carbonate (1.20–1.25 mmol) in dry DMF was treated with a solution of the corresponding alkylating reagent (**25**–**28**, 1.1–1.7 mmol) in dry DMF (1 mL). The mixture was stirred at room temperature for the appropriate period of time, or at 75–80 °C (for alkylation with 2-bromo-*N*-phenethylacetamide **28**), respectively, until complete conversion (TLC control: 90% dichloromethane/methanol). After all of the starting material was dissipated, the reaction mixture was evaporated to dryness under reduced pressure, hydrolyzed with water (10 mL) and neutralized with hydrochloric acid (2 N). The precipitate was filtered, washed with water (3×10 mL), dried at 70 °C over night, and recrystallized from methanol/ethyl acetate/petroleum ether (1:1:3) to afford products **22a**–**24** as free amines.

4.6.2. Method 2 using NaH–K_2CO_3. A suspension of sodium hydride (60%, 1.1 mmol) in mineral oil was washed with *n*-hexane (3×10 mL) under argon atmosphere, the solvent was pipetted out and traces were removed under reduced pressure. The remaining material was placed in a dry apparatus under argon atmosphere, anhydrous DMF (5 mL) was added dropwise and the resulting suspension was stirred at room temperature for 10 min until the hydrogen evolution ceased. The reaction mixture was cooled to −2 to 0 °C with ice/acetone bath and a solution of the appropriate alkylating reagent (**27** or **28**, 1.0 mmol) in dry DMF (2 mL) was added through a septum over 10–15 min. The reaction mixture was

stirred at −2 to 0 °C for 30 min, then allowed to warm slowly to room temperature and intensively stirred for 3–4 h. After the mixture had been stirred for a definite time, potassium carbonate (1.1 mmol) was added and the system was further stirred at ambient temperature until full conversion of the starting material. The reaction was monitored either by TLC (90%, dichloromethane/methanol) or by LC-MS analysis. The work-up procedure was performed as described for method 1 yielding compounds **23** or **24** as brownish solids.

*4.6.3. Ethyl 7-amino-2-hydroxy-1-methyl-1H-pyrrolo[2,3-c]pyridine-3-carboxylate (**22a**).* This compound was produced by method 1: **12a** (222.2 mg, 1.0 mmol) was treated with methyl methanesulfonate (MMS, 127.5 mg, 1.22 mmol) to afford **22a** as a pale brown solid (183.5 mg, 78%); mp 280–281 °C (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.24 (3H, t, J=6.94 Hz, OCH$_2$C*H*$_3$), 3.70 (3H, s, NMe), 4.12 (2H, q, J=7.25 Hz, OC*H*$_2$CH$_3$), 6.97 (2H, br s, N*H*$_2$), 7.03 (1H, d, J=6.94 Hz, H-4), 7.42 (1H, d, J=6.94 Hz, H-5), 10.08 (1H, br s, O*H*); ^{1}H NMR (500 MHz, CD$_3$OD) δ_H: 1.44 (3H, t, J=6.94 Hz, OCH$_2$C*H*$_3$), 3.92 (3H, s, NMe), 4.42 (2H, q, J=7.25 Hz, OC*H*$_2$CH$_3$), 7.32 (1H, d, J=6.93 Hz, H-4), 7.61 (1H, d, J=6.94 Hz, H-5); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.9 (OCH$_2$*C*H$_3$), 34.3 (NMe, signal overlapped with the residual signal from DMSO-d_6), 57.7 (O*C*H$_2$CH$_3$), 87.7, 105.2, 111.2, 131.3, 136.2, 136.6, 164.8; ^{13}C NMR (125 MHz, CD$_3$OD) δ_C: 15.1 (OCH$_2$*C*H$_3$), 41.3 (NMe), 61.6 (O*C*H$_2$CH$_3$), 90.8, 108.2, 113.1, 134.1, 135.0, 143.4, 162.6, 166.7 (*C*O$_2$Et); ^{13}C-DEPT NMR (125 MHz, CD$_3$OD) δ_C: 15.1 (OCH$_2$*C*H$_3$), 41.1 (NMe), 61.6 (O*C*H$_2$CH$_3$), 108.2 (C4), 134.1 (C5); LC/ESI-MS calcd for $C_{11}H_{13}N_3O_3$ *m/z* 235.1, found 234.4 [M−H]$^-$, 236.3 [M+H]$^+$.

*4.6.4. Ethyl 7-amino-1-benzyl-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate (**23**).* This compound was produced by method 2: **12a** (100.0 mg, 0.45 mmol) was treated with benzyl bromide (**27**, 77.0 mg, 0.45 mmol) to afford **22a** as a brown solid (135 mg, 96%); mp 287–289 °C (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.21 (3H, t, J=7.25 Hz, OCH$_2$C*H*$_3$), 4.07 (2H, q, J=7.25 Hz, OC*H*$_2$CH$_3$), 5.36 (2H, s, C*H*$_2$Ph), 6.70 (2H, br s, N*H*$_2$), 7.11 (1H, d, J=6.94 Hz, H-4), 7.16 (2H, d, J=7.25 Hz, Ar), 7.30 (1H, d, J=7.25 Hz, Ar), 7.36 (2H, t, J=6.94 Hz, Ar), 7.48 (1H, d, J=6.94 Hz, H-5), 9.63 (1H, s, O*H*); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.9 (OCH$_2$*C*H$_3$), 53.9 (*C*H$_2$Ph), 57.3 (O*C*H$_2$CH$_3$), 88.1, 105.5, 111.3, 126.6 (2×C, Ar), 127.9, 128.8 (2×C, Ar), 130.0 (Ar), 134.7, 135.8, 137.9, 164.6, 166.2 (*C*O$_2$Et); LC/ESI-MS calcd for $C_{17}H_{17}N_3O_3$ *m/z* 311.1, found 310.1 [M−H]$^-$, 312.5 [M+H]$^+$.

*4.6.5. Ethyl 7-amino-2-hydroxy-1-(2-oxo-2-phenethylamino) ethyl-1H-pyrrolo[2,3-c]pyridine-3-carboxylate (**24**).* This compound was produced by method 2: **12a** (110.0 mg, 0.5 mmol) was treated with 2-bromo-*N*-phenethylacetamide (**28**, 145.0 mg, 0.45 mmol) to afford **24** as a brown solid (135 mg, 96%); mp 191–193 °C (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.23 (3H, t, J=6.94 Hz, OCH$_2$C*H*$_3$), 2.73 (2H, t, J=7.57 Hz, CH$_2$C*H*$_2$Ph), 3.38 (2H, q, J=6.51 Hz, C*H*$_2$CH$_2$Ph), 4.08 (2H, q, J=6.94 Hz, OC*H*$_2$CH$_3$), 4.77 (2H, s, C*H*$_2$), 6.54 (2H, br s, N*H*$_2$), 7.05 (1H, d, J=6.94 Hz, H-4), 7.15–7.35 (6H, m, Ar, H-5), 8.27 (1H, t, J=5.68 Hz, CON*H*), 9.61 (1H, s, O*H*); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.9 (OCH$_2$*C*H$_3$), 35.1 (*C*H$_2$), 40.7, 53.5, 57.3 (O*C*H$_2$CH$_3$), 88.1, 105.2, 111.4, 126.3, 128.5 (2×C, Ar), 128.8 (2×C, Ar), 131.5, 135.2, 137.9, 139.3, 164.7, 165.7 (*C*O$_2$Et), 166.3 (*C*ONH); LC/ESI-MS calcd for $C_{20}H_{22}N_4O_4$ *m/z* 382.2, found 381.3 [M−H]$^-$, 383.1 [M+H]$^+$.

*4.6.6. Ethyl 7-amino-2-hydroxy-1-(2-oxo-2-phenethylamino) ethyl-1H-pyrrolo[2,3-c]pyridine-3-carboxylate hydrochloride (**24·2HCl**).* This compound was produced by method 2 following by a conversion with hydrochloric acid. The free amine **24** (50.0 mg, 0.13 mmol) was refluxed with hydrochloric acid (2 N, 10 mL) for 3 h. Then, the reaction mixture was cooled with ice/acetone bath and the formed precipitate was filtered, washed with petroleum ether (3×10 mL) to yield 52.1 mg (87%) of a brown solid of the corresponding hydrochloride salt; mp>303 °C (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.31 (3H, t, J=6.93 Hz, OCH$_2$C*H*$_3$), 2.75 (2H, t, J=7.88 Hz, CH$_2$C*H*$_2$Ph), 3.34 (2H, q, J=6.31 Hz, C*H*$_2$CH$_2$Ph), 4.27 (2H, q, J=6.93 Hz, OC*H*$_2$CH$_3$), 4.93 (2H, s, C*H*$_2$), 7.17–7.24 (4H, m, Ar, H-4), 7.28 (2H, d, J=7.56 Hz, Ar), 7.53 (1H, d, J=6.94 Hz, H-5), 8.23 (2H, br s, N*H*$_2$), 8.42 (1H, t, J=5.36 Hz, CON*H*), 12.58 (1H, s, O*H*); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.6 (OCH$_2$*C*H$_3$), 35.1, 40.8, 54.0 (*C*H$_2$), 40.7, 53.5, 57.5 (O*C*H$_2$CH$_3$), 88.1, 105.2, 111.4, 126.3, 128.5 (2×C, Ar), 128.7 (2×C, Ar), 133.1, 133.2, 139.3, 141.9, 159.1, 163.4 (*C*ONH), 164.9 (*C*O$_2$Et); LC/ESI-MS calcd for $C_{20}H_{22}N_4O_4$ *m/z* 382.2, found 381.1 [M−H]$^-$, 383.3 [M+H]$^+$.

4.7. General procedure for the preparation of hydrochlorides

The corresponding free amine (1.0 mmol) was suspended in hydrochloric acid (1 N, 5 mL, 5.0 mmol) and stirred under reflux for 3–5 h. Stirring was continued for further 3 h in which the mixture was allowed to cool down to room temperature. The obtained slight colored solution was evaporated to dryness. The residue was treated with petroleum ether (20 mL) and stirred for 10 min under ice bath cooling. The mixture was allowed to stay at 0–5 °C over night. The formed precipitate was filtered under atmospheric pressure, washed with petroleum ether (3×10 mL) and dried at 70 °C to obtain pure hydrochloride salts.

4.8. Theoretical calculations

Quantum-chemical calculations were performed using the Gaussian 09 D.01 program suite.[36] The M06-2X functional[37] was used with TZVP basis set.[38] This fitted hybrid *meta*-GGA functional with 54% HF exchange is specially developed to describe main-group thermochemistry and non-covalent interactions, showing very good results in prediction of the position of the tautomeric equilibrium compounds possessing intramolecular hydrogen bond.[39] All structures were optimized in ground state without restrictions, using tight optimization criteria and ultrafine grid in the computation of two-electron integrals and their derivatives. The true minima were verified by performing frequency calculations.

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Supplementary data

Supplementary data (synthetic and purification schemes for compounds **10** and **11**, proposed mechanism for the formation of **13a**, all possible tautomeric forms for structures **12**, **13** and **22**, physicochemical properties of **12a** and **23**, X-ray data of **18** and **19**, and NMR spectra of selected compounds) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.08.055.

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