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Synthesis of the Isonicotinoylnicotinamide Scaffolds of the Naturally Occurring Isoniazid−NAD(P) Adducts

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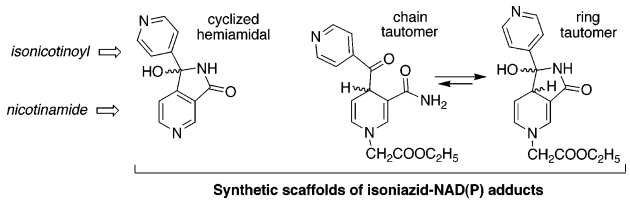

Synthetic scaffolds of isoniazid-NAD(P) adducts

The first syntheses of the 1-hydroxy-1-(pyridin-4-yl)-1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one heterocycle and the 3-aminocarbonyl-4-isonicotinoyl-1,4-dihydropyridine framework present in the isoniazid−NAD(P) adducts are described.

Tuberculosis (TB), a chronic disease caused by *Mycobacterium tuberculosis* (Mtb), is one of the leading causes of death from infectious origin in the world. The biggest threat is multidrug-resistant TB caused by strains resistant to at least isoniazid (INH) and rifampicin. Although isoniazid is an old and simple molecule used efficiently in the antitubercular therapy regimens, its molecular mechanism of action is still a matter of debate. The consensus opinion is that a Mtb catalase−peroxidase (KatG) oxidizes INH, a prodrug, to an isonicotinoyl radical, which then couples covalently to the NAD or NADP cofactor to give the 1,4-dihydropyridine type adducts (Scheme 1).[1] The resultant INH−NAD and INH−NADP adducts (4*S*)-enantiomers were found as strong inhibitors of InhA[2] and MabA[3] enzymes, respectively, two key reductases involved in the biosynthesis of mycolic acids, essential and specific constituents of the mycobacteria envelope.[4] Recently, Blanchard and co-workers reported that the INH−NADP adduct (4*R*)-enantiomer is also able to inhibit the dihydrofolate reductase (DHFR) of Mtb (Scheme 1).[5] Moreover, Tonge and collaborators described that the benzoylhydrazine−NAD adduct (BH−NAD) formed from the reaction of the activated benzoic acid hydrazide and NAD is also an inhibitor of InhA (Scheme 1).[6]

Thus, the great interest revealed by this category of biologically relevant molecules prompted us to investigate the possibilities for synthesis of the benzoyl- and isonicotinoylnicotinamide scaffolds. Recently, we have published the first chemical synthesis of 4-benzoylnicotinamide (**1**), the core structure of the BH−NAD adduct (Scheme 2). In fact, this compound exists exclusively under the ring hemiamidal form **2**.[7,8] No equilibrium between the ring (hemiamidal) and the chain (ketoamide) structure was observed. Further N-alkylation of **2** gave the pyridinium compound **3**, which could be regioselectively reduced to afford the 4-benzoyl-1,4-dihydronicotinamide derivative **4** (two epimers).[7,8] This good synthetic result encouraged us to prepare the unprecedented 4-isonicotinoylnicotinamide (**5**) and the 4-isonicotinoyl-1,4-dihydronicotinamide frameworks present in the naturally occurring INH−NAD(P) adducts **6**/**7** (Scheme 3). These compounds can be seen as potential pharmacophores for designing new antibiotic drugs. It is noteworthy that, despite the apparent simplicity of the 4-isonicotinoylnicotinamide, this molecule is still unknown in the literature. Moreover, synthesis and characterization of the 4-isonicotinoyl-1,4-dihydronicotinamide framework can be expected to be more complex than in the case of BH−NAD(P) analogues since the 4-benzoyl-1,4-dihydronicotinamide exists in only the chain ketoamide form (two epimers; Scheme 2), whereas the INH−NAD adduct exists, in solution, as a mixture of chain and ring tautomers, giving a total of six isomers (two epimers for **6** and four stereoisomers for **7**; Scheme 3).[9]

The 4-isonicotinoyl-1,4-dihydronicotinamide framework present in INH−NAD(P) adducts (**6**/**7**) can theoretically be obtained by following the same strategy as that for the preparation of compound **4** (Scheme 2); a chemoselective alkylation of the pyridinic nitrogen of nicotinamide in **5** followed by reduction of the pyridinium intermediate would afford the desired 1,4-dihydropyridine compound. Therefore, in a first step, various methods were examined to prepare the 4-isonicotinoylnicotinamide compound **5**. The approach using 4-pyridinyllithium generated from 4-bromopyridine and BuLi to arylate **8** (Scheme 4) was unsuccessful, probably because of the difficult formation and/or the instability of the 4-pyridinyllithium. Therefore, we tried the same reaction using 3-bromopyridine, which is a synthetic equivalent of 4-halopyridine, via subsequent removal of the bromine atom[10] (Scheme 4). The reaction provided a 1:3

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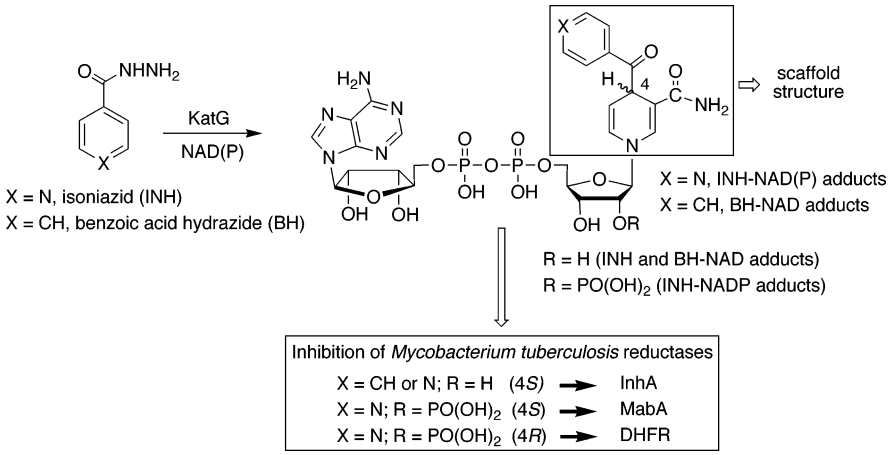
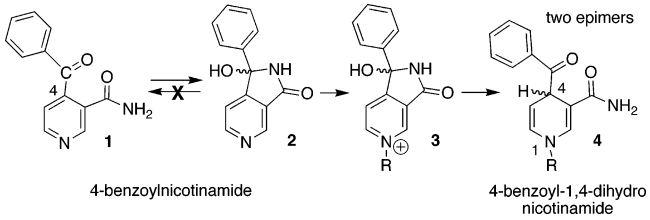
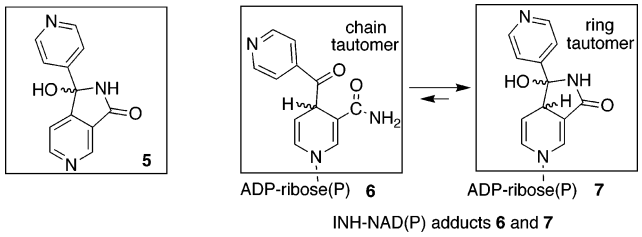
SCHEME 1. Formation of INH− and BH−NAD(P) Adducts in *Mycobacterium tuberculosis*



SCHEME 2. Benzoylnicotinamide and Benzoyldihydronicotinamide Scaffolds[7,8]



SCHEME 3. Isonicotinoylnicotinamide (Ring Tautomer) and Isonicotinoyldihydronicotinamide Scaffolds



mixture of meta/para[11] regioisomers in a 10% yield. The pure para product **9** was obtained by recrystallization in acetone (5% yield). The low efficiency of this reaction could be explained by the significant amounts of 4-*N*,*N*-diisopropylaminopyridine (*m*/*z* 179 [$M^+ + 1$]) and 4-(3-bromopyridinyl)-3-bromopyridine (*m*/*z* 315 [$M^+ + 1$]) formed as byproducts. The subsequent removal of the bromine atom of **9** by a metal−halogen exchange reaction (BuLi) notably afforded, for the first time, the pyridinyl derivative **5**. However, the low yield for the preparation of the intermediate **9** makes this approach not suitable to prepare the isonicotinoylnicotinamide scaffold.

In order to find a more efficient synthetic strategy to **5**, we examined another methodology previously developed by us to prepare the phenyl analogue **2**.[8] This approach was based on a direct ortho-metalation of *N*,*N*-diisopropylnicotinamide (**10**), followed by a reaction with *N*,*N*-dimethylbenzamide as the benzoylation agent. In the case of preparation of the pyridinyl analogue **5**, the *N*,*N*-dimethylisonicotinamide is not easily available; therefore, we investigated other electrophilic agents (*N*,*N*-diethylisonicotinamide,[12] isonicotinaldehyde, 4-cyanopyridine, and isonicotinoyl chloride), but in all of the cases, the experiences were disappointing. More satisfactory results were obtained in experiments involving the Weinreb amide **12** as the aroylation agent (Scheme 4). Treatment of **10** with LDA in ether at −78 °C, followed by addition of **12**, gave the condensed product **13** in a 39% yield. Afterward, reduction of the ketoamide **13** by $NaBH_4$ afforded the alcohol−amide **14**. Successive treatments of **14** by formic acid, NH_3/MeOH, aq HCl/air, and $SOCl_2$/aq NH_3 (according to methodology described in ref 8) successfully provided **5** in a 77% yield. The overall yield for the conversion of **10** into **5** was 29%.

As shown previously[8] for the corresponding phenyl derivative **2** (Scheme 2), compounds **9** and **5** were unambiguously confirmed by ^{13}C NMR (C7 at 85.4 and 86.3 ppm, respectively) to exist only under a ring hemiamidal structure (azaisoindolinone), which might serve as a masked synthon of the ketoamide moiety for further syntheses in the 1,4-dihydronicotinamide series.

In a second part of this work, we tried to prepare the isonicotinoyl-1,4-dihydronicotinamide scaffolds present in the INH−NAD(P) adducts (Scheme 3) following the strategy depicted in Scheme 2 for synthesis of BH−NAD analogues. The N-alkylation of **5**, carried out with ethyl bromoacetate, did not lead to the expected compound **15** (through alkylation on the nitrogen of the nicotinamide moiety, Scheme 4) but, in contrast, took place preferentially on the pyridine ring to give a monoalkylated derivative[14] (^1H NMR: δ H2 9.11, H6 8.82, H5 7.57, H12 9.00, H11 8.34 ppm) along with a bisalkylated derivative[15] on both the pyridine and the nicotinamide rings (^1H NMR: δ H2 9.58, H6 9.27, H5 8.43, H12 9.09, H11 8.47 ppm). As a consequence of this unsuccessful synthetic route, we turned our attention to the study of direct preparation of the dihydropyridine derivatives **17**/**18** by a biomimetic approach.[9,13] It serves to activate INH by a chemical procedure able to mimic the mycobacterial catalase−peroxidase activity (KatG). It is known that the catalase−peroxidase KatG can catalyze the conversion of Mn^{II} into Mn^{III} and, then, that Mn^{III}, acting as a

(11) Meta and para refer to the position of the carbonyl group that undergoes nucleophilic attack.

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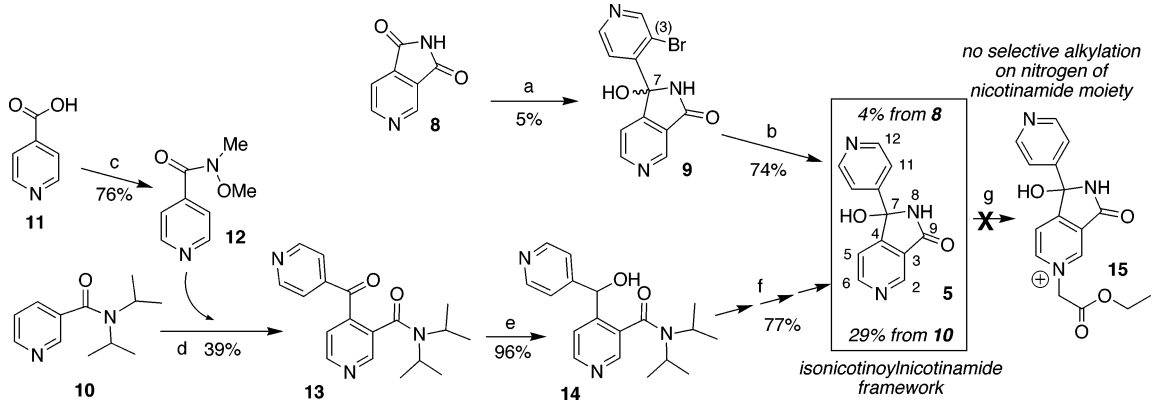
(14) 1-[2-(Ethyloxy)-2-oxoethyl]-4-[1-hydroxy-3-oxo-1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridin-1-yl]pyridin-1-ium bromide.

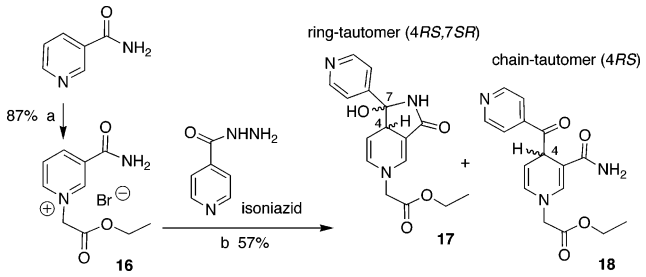
(15) 5-[2-(Ethyloxy)-2-oxoethyl]-1-[1-(2-(ethyloxy)-2-oxoethyl)pyridinium-4-yl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-5-ium dibromide.

SCHEME 4. Synthesis of the Isonicotinoylnicotinamide Framework 5 from 3,4-Pyridinedicarboximide (8) and from Diisopropylnicotinamide (10) using Weinreb Amide (12) as the Aroylation Agent[a]



[a] Reagents: (a) 3-Br-pyridine/LDA/THF; (b) BuLi/THF; (c) *N*,*O*-dimethylhydroxylaminehydrochloride/1-hydroxybenzotriazole/1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride/TEA/CH_3CN; (d) LDA/ether; (e) $NaBH_4$/ethanol; (f) (i) HCOOH, heat, (ii) NH_3/MeOH, (iii) HCl, air oxidation, (iv) $SOCl_2/NH_3$ aq/acetone; (g) $BrCH_2COOEt$/THF.

SCHEME 5. Synthesis of the Isonicotinoyldihydronicotinamide Analogues 17/18 of the INH−NAD(P) Adducts[a]



[a] Reagents: (a) $BrCH_2COOEt$/THF/heat; (b) $Mn(H_2P_2O_7)_3$/buffer.

mediator, can oxidize INH. Therefore, direct activation of INH by a stoichiometric amount of manganese pyrophosphate (a stable form of Mn^{III} with a suitable redox potential in aqueous solution) in the presence of the appropriate pyridinium salt **16** (obtained, in turn, by reaction of nicotinamide with ethyl bromoacetate, yield 87%) successfully afforded a 57% yield of the targeted 1,4-dihydropyridines **17**/**18** (Scheme 5). The purity of this equilibrated mixture was estimated to be about 90% by HPLC analysis. Compounds **17**/**18** represent simplified analogues of the naturally occurring INH−NAD(P) adducts, and it is interesting to note that, as reported previously for these adducts,[9] the 1,4-dihydropyridines **17**/**18** were found, in solution, as an equilibrated mixture of ring (65−85%) and chain (15−35%) tautomers. Minor chain tautomer **18** was identified by its ^1H NMR spectrum, while full description of the ^1H and ^{13}C NMR spectra is given for the ring tautomer **17**, mainly present under the trans configuration (4*RS*,7*SR*). The assignment of the structure **17** is strongly supported by the shielded H4 resonance (3.52 ppm) with respect to the one in the minor chain tautomer **18** (4.96 ppm), by the characteristic chemical shift of the tetrahedral C7 (88.5 ppm), by the strong ^3J correlation between H8 and C4 observed in the $^1H-^{13}C$ HMQC−LR spectrum, and by data previously published for the INH−NAD(P) adducts.[9] In UV spectra, these compounds showed one maximum of absorption at 330 nm, characteristic of the presence of the dihydropyridine moiety.

In summary, we have developed two routes for accessing the unprecedented azaindolinone **5** (stable form of the 4-isonicotinoylnicotinamide). The most convenient one is based on an ortho-metalation−electrophilic substitution sequence using a Weinreb amide as the aroylation agent (overall yield from *N*,*N*-diisopropylnicotinamide is 29%). Since the chemoselective alkylation of the pyridinic nitrogen of the nicotinamide moiety of **5** has not been possible, access to the 1,4-dihydronicotinamide scaffold through a reduction step could not be envisioned by this route. Therefore, the biomimetic approach, previously used to prepare INH−NAD adducts, has been expanded to the preparation of the truncated dihydropyridine analogues **17**/**18**, and this method presently represents the best way to prepare the 4-isonicotinoyl-1,4-dihydronicotinamide framework. These scaffolds are directly derived from the structure of the isoniazid−NAD(P) adducts that are considered as the biologically relevant effectors of the antibiotic activity of isoniazid. The synthesis of new potential inhibitors of Mtb reductases inspired from these scaffolds is currently in progress in our laboratory.

Experimental Section

1-Hydroxy-1-(pyridin-4-yl)-1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one (5), Prepared from 9. To a solution of **9** (93 mg, 3.0 mmol) in dry THF (6 mL), under argon at −78 °C, was added butyllithium (0.6 mL, 1.5 M in cyclohexane, 9.1 mmol) dropwise, and the mixture was allowed to warm to room temperature over 4 h. Water was added, and the solvent was evaporated under vacuum. The crude was purified by silica gel column chromatography (CH_2Cl_2/MeOH 95:5 to 90:10) to give a white powder (61 mg, 74%): mp 223−224 °C; IR (KBr, ν_{max}/cm^{-1}) 3256, 3062, 1715, 1644, 1606, 1536; ^1H NMR (250 MHz, DMSO-d_6) δ 9.65 (s br, 1H), 8.91 (s, 1H), 8.75 (d, J = 5.0 Hz, 1H), 8.58 (d, J = 5.9 Hz, 2H), 7.51 (s, 1H), 7.48−7.43 (m, 3H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 167.0 (Cq), 157.3 (Cq), 153.1 (CH), 149.9 (2 × CH), 149.2 (Cq), 144.7 (CH), 126.1 (Cq), 120.5 (2 × CH), 117.8 (CH), 86.3 (Cq); MS (ESI, positive mode) *m*/*z* 477 ($2M + Na^+$), 250 ($M + Na^+$), 228 ($M + H^+$); HRMS (ESI) calcd for $C_{12}H_{10}N_3O_2$, 228.0773; found, 228.0771.

1-Hydroxy-1-(pyridin-4-yl)-1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one (5), Prepared from 14. A solution of **14** (200 mg, 0.64 mmol) in formic acid (24 mL) was refluxed for 24 h, and the solvent was evaporated. Water (10 mL) was added to the residue, and it was extracted with dichloromethane, and the organic phase was washed with saturated $NaHCO_3$ solution. Combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude, without further purification, was stirred at room

temperature with a NH_3/MeOH solution (24 mL) for 2 days; after evaporation of the solvent, the residue was dissolved in $SOCl_2$ (8 mL) and refluxed for 2 h. The reaction mixture was concentrated, dissolved in dichloromethane, and the solvent was removed in vacuum. The last operation was done twice. The paste obtained was dissolved in acetone (8 mL), and then aqueous ammonia solution (6 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, diluted with water (10 mL), and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 100:0 to 95:5) to give the hemiamidal **5** (145 mg, 77%). The analytical data obtained were identical to those described for **5** prepared from **9**.

1-(3-Bromopyridin-4-yl)-1-hydroxy-1,2-dihydro-3*H*-pyrrolo-[3,4-*c*]pyridin-3-one (9). To a solution of 3,4-pyridinedicarboximide **8** (1.0 g, 6,8 mmol) and 3-bromopyridine (1.4 mL, 14.9 mmol) in dry THF (60 mL), under argon at −95 °C, was added lithium diisopropylamide (8.1 mL, 2.0 M in THF/*n*-heptane, 16.2 mmol) dropwise. The mixture was stirred at −80 °C for 1 h and then allowed to warm to room temperature over 4 h. Water was added, and the solvent was evaporated under vacuum. The brown paste was purified by silica gel column chromatography (CH_2Cl_2/MeOH 100:0 to 80:20). The yellow solid was recrystallized in acetone to give the hemiamidal **9** as a white solid (100 mg, 5%): mp 229−239 °C (decomposition); IR (KBr, ν_{max}/cm^{-1}) 3178, 3075, 2801, 1959, 1708, 1612; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.43 (s br, 1H), 8.92 (d, J = 1.0 Hz, 1H), 8.75 (d, J = 5.0 Hz, 1H), 8.69 (d, J = 5.1 Hz, 1H), 8.64 (s, 1H), 8.17 (d, J = 5.0 Hz, 1H), 7.57 (s br, 1H), 7.28 (dd, J = 1.0 and 5.0 Hz, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 168.0 (Cq), 155.7 (Cq), 153.2 (CH), 153.1 (CH), 148.9 (CH), 146.3 (Cq), 144.3 (CH), 128.4 (Cq), 124.6 (CH), 118.6 (Cq), 117.5 (CH), 85.4 (Cq); MS (ESI, positive mode) *m*/*z* 329 (M + Na^+), 307 (M + H^+), 288 (M + H^+ − H_2O); HRMS (ESI) calcd for $C_{12}H_8BrN_3O_2$, 305.9878; found, 305.9872.

4-Isonicotinoyl-*N*,*N*-diisopropylnicotinamide (13). To a solution of *N*,*N*-diisopropylnicotinamide (**10**) (1.0 g, 4.85 mmol) in ether (125 mL) at −78 °C was added lithium diisopropylamide (3.64 mL, 2.0 M in THF/*n*-heptane, 7.28 mmol) dropwise. After 15 min stirring, a solution of *N*-methyl-*N*-methoxy isonicotinamide (**12**) (886 mg, 5.34 mmol) in ether (10 mL) was added dropwise at −78 °C, and the mixture was allowed to warm to room temperature over 3 h. Water was added to quench the reaction, and the mixture was concentrated in vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 100:0 to 95:5) to afford **13** (590 mg, 39%): IR (KBr, ν_{max}/cm^{-1}) 3418, 3012, 2967, 2931, 1688, 1629, 1582, 1556; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.74 (dd, J = 4.3 and 1.7 Hz, 2H), 8.68 (d, J = 5.0 Hz, 1H), 8.60 (s, 1H), 7.53 (dd, J = 4.5 and 1.5 Hz, 2H), 7.26 (d, J = 4.9 Hz, 1H), 3.79 (m, 1H), 3.42 (m, 1H), 1.32 (d, J = 6.7 Hz, 6H), 1.18 (d, J = 6.5 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.3 (Cq), 167.0 (Cq), 150.8 (2 × CH), 149.7 (CH), 147.1 (CH), 143.0 (Cq), 141.9 (Cq), 133.8 (Cq), 122.7 (2 × CH), 122.3 (CH), 51.9 (CH), 46.3 (CH), 20.6 (2 × CH_3), 20.1 (2 × CH_3); MS (DCI, NH_3) *m*/*z* 329 (M + NH_4^+), 312 (M + H^+).

4-[Hydroxy(pyridin-4-yl)methyl]-*N*,*N*-diisopropylnicotinmide (14). To a solution of the ketoamide **13** (170 mg, 0.55 mmol) in ethanol (27 mL) was added $NaBH_4$ (131 mg, 2.7 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere for 1.5 h, and then acetone (2.0 mL) and water (15 mL) were added. The reaction mixture was extracted with dichloromethane, and the organic phase was dried over Na_2SO_4, filtered, and concentrated in a vacuum to give the alcohol−amide **14** as a mixture of two diastereoisomers (rotamers) (154 mg, 90%): IR (KBr, ν_{max}/cm^{-1}) 3057, 2982, 2967, 2359, 2341, 1622, 1604, 1582, 1558; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.63 (d, J = 4.9 Hz, 1H), 8.54−8.47 (m, 5H), 8.42 (s, 1H), 8.38 (s, J = 5.9 Hz, 1H), 7.40 (d, J = 4.9 Hz, 1H), 7.30−7.20 (m, 5H), 5.94 (s, 1H), 5.64 (s, 1H), 3.64 (m, 1H), 3.46 (m, 2H), 3.31 (m, 1H), 1.50 (d, J = 6.6 Hz, 6H), 1.40 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3 H), 0.51 (d, J = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.8 (Cq), 168.2 (Cq), 151.7 (Cq), 151.0 (CH), 150.5 (Cq), 149.9 (CH), 149.6 (4 × CH), 147.6 (CH), 145.9 (CH), 132.2 (Cq), 131.8 (Cq), 125.1 (CH), 122.4 (CH + Cq), 122.1 (Cq), 121.2 (4 × CH), 74.6 (CH), 70.5 (CH), 51.6 (2 × CH), 46.6 (2 × CH), 20.6, 20.3, 20.0 (8 × CH_3); MS (EI) *m*/*z* 313 (M^+), 270 (M^+ − $CH(CH_3)_2$), 252 (M^+ − $CH(CH_3)_2$ − H_2O).

Preparation of the Mixture of Ethyl[1-hydroxy-3-oxo-1-(pyridin-4-yl)-1,2,5,7a-tetrahydro-3*H*-pyrrolo[3,4-*c*]pyridin-5-yl]acetate 17 and Ethyl(3-aminocarbonyl-4-isonicotinoyl-1,4-dihydropyridin-1-yl)acetate 18. The reaction medium (100 mM phosphate buffer, pH 7.5, 15 mL final volume) containing INH (2 mM), **16** (2 mM), and Mn^{III} pyrophosphate (4 mM) was stirred at room temperature for 20 min. The reaction mixture was chromatographed through a Sep Pak Vac20 cc (5 g) C_{18} cartridge with a 4 mM NH_4OAc aqueous solution. Then, careful washing with water, followed by elution with acetonitrile, and concentration to dryness under vacuum afforded the desired compound as an unstable mixture of ring (**17**) and chain (**18**) structures in 57% yield (65−85% of the ring tautomer): ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.77 (s br, 2H, chain form), 8.54 (s br, 2H, ring form), 8.09 (s, 1H, NH, ring form), 7.86 (d, J = 5.9 Hz, 2H, chain form), 7.50 (d, J = 4.1 Hz, 2H, ring form), 7.21 (d, J = 1.1 Hz, 1H, chain form), 6.83 (s, 1H, ring form), 6.33 (s, 1H, OH, ring form), 6.11 (d, J = 7.8 Hz, 1H, chain form), 6.03 (d, J = 7.8 Hz, 1H, ring form), 4.96, (dd, J = 4.5 and 1.0 Hz, 1H, chain form), 4.64 (dd, J = 7.8 and 4.5 Hz, 1H, chain form), 4.52 (dd, J = 7.6 and 1.4 Hz, 1H, ring form), 4.22−4.03 (m, 2 × 2H + 2 × 2H, chain + ring form), 3.52 (d, J = 1.7 Hz, 1H, ring form), 1.19 (m, 2 × 3H, chain + ring form); ^{13}C NMR (125 MHz, DMSO-d_6; the pics assignment could be done only for the ring tautomer **17**) δ 171.3 (Cq), 170.3 (Cq), 153.8 (Cq), 149.9 (2 × CH), 133.7 (CH), 133.0 (CH), 121.2 (2 × CH), 101.7 (Cq), 96.9 (CH), 88.5 (Cq), 61.1 (CH_2), 53.7 (CH_2), 46.5 (CH), 14.3 (CH_3); MS (FAB, MMBA) *m*/*z* 316 (M + H^+); UV (CH_3CN) λ_{max} 330 nm.

Supporting Information Available: The general experimental methods are provided, and preparation of compounds **12** and **16** is described. A compound characterization checklist and copies of a ^{1}H NMR spectrum and/or a proton-decoupled ^{13}C NMR spectrum for each new compound, along with two-dimensional ^{1}H−^{13}C HSQC ^1J and ^{1}H−^{13}C HMBC ^3J correlations for the mixture of compounds **17**/**18**, are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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