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SYNTHESIS OF 8-HYDROXYIMIDAZO[1,2-*a*]PYRIDINE-2-CARBOXYLIC ACID AND ITS DERIVATIVES

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Abstract – Two new imidazo[1,2-*a*]pyridines, 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylic acid (**4**) and ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (**6**) were prepared *via* cyclization of 2-aminopyridin-3-ol (**1**) with bromopyruvic acid (**2**) and ethyl bromopyruvate (**3**), respectively. 8-Hydroxyimidazo[1,2-*a*]-pyridine-2-carboxylic acid (**4**) was successfully coupled with various amino acid derivatives *via* its active ester intermediate into the corresponding amides **22-27**. *O*-protected ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate **11** was transformed into its hydrazide **13**, acyl azide **14**, and amide **15** derivatives.

INTRODUCTION

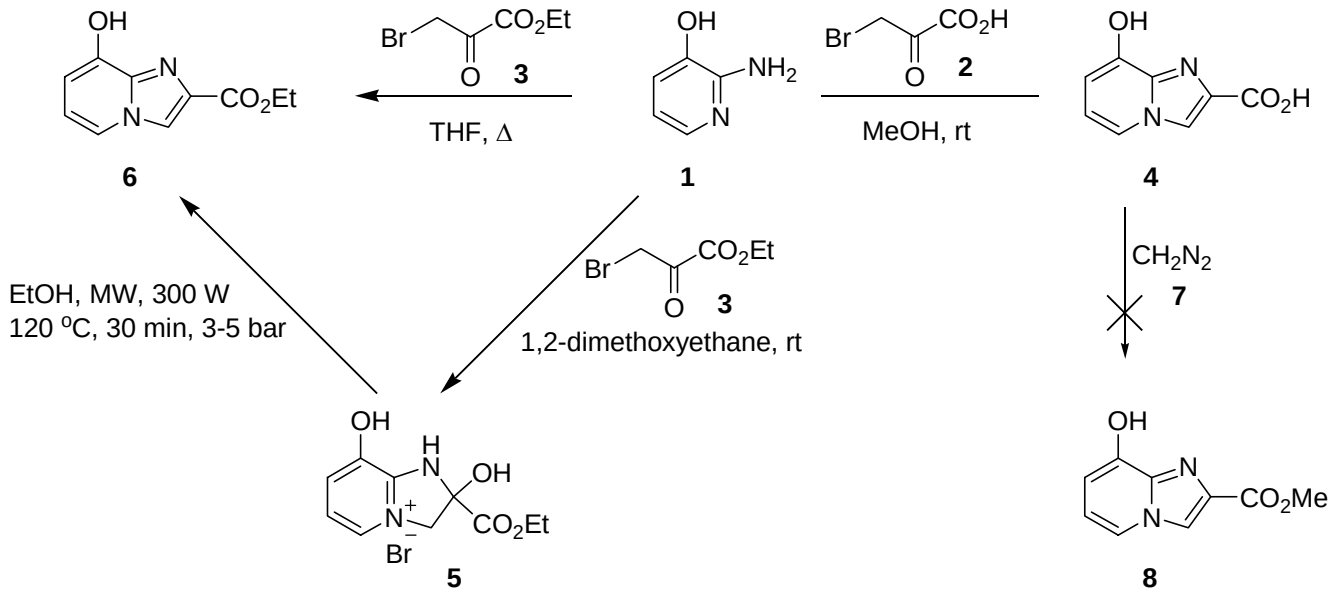
Numerous reactions resulting in the formation of the imidazo[1,2-*a*]pyridine ring system have been reported. The majority of imidazo[1,2-*a*]pyridines have been prepared by the reaction of a variety of 2-aminopyridines with α-halocarbonyl compounds, usually a ketone or aldehyde. Other methods include cyclizations of 2-aminopyridines with α-dioxo compounds, including α-oxocarboxylic acids derivatives, 1,5-dipolar cyclization, and a number of other reactions which either appear to lack generality for this ring systems, or in which only poor yields have been obtained.[1,2,3] Recently, a regioselective synthesis of substituted imidazonaphthyridines, azacarbolines and cyclazines[4] and vinyl substituted imidazo-[1,2-*a*]pyridines[5] have been reported.

Imidazo[1,2-*a*]pyridine system has been extensively investigated mainly because of important biological applications, such as antibacterial,[6] antifungal,[7] antiviral,[8] cardiotonic,[9] acetylcholinesterase inhibitors,[10] DNA binding ligands targeting drug-resistant bacteria,[11] and phosphodiesterase 5 inhibiting activity.[12]

Mur ligases play an essential role in the intracellular biosynthesis of bacterial peptidoglycan, the main component of the bacterial cell wall.[13] The critical biological function as well as an active site amenable for small molecule inhibition as revealed by crystallographic structures[14] make Mur ligases an attractive target for the discovery of novel antibacterial agents.[14,15] In this paper, we report the synthesis of 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylic acid derivatives as potential inhibitors of Mur ligases.

RESULTS AND DISCUSSION

The starting compounds 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylic acid (**4**) and ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (**6**) were prepared in 39% and 38% yield, respectively, by cyclocondensation of 2-aminopyridin-3-ol (**1**) with bromopyruvic acid (**2**) and ethyl bromopyruvate (**3**), respectively.[11] The formation of compound **6** proceeds *via* the intermediate **5**, which was isolated when the cyclization of **1** with ethyl bromopyruvate (**3**) was carried out in 1,2-dimethoxyethane at room temperature. Treatment of intermediate **5** in ethanol under microwave irradiation at 120 °C gave cyclocondensation product **6**. Attempted formation of methyl ester of **4**, compound **8**, with excess of diazomethane (**7**) performed in different solvents (ethanol, CH_2Cl_2, Et_2O) failed completely probably due to the zwitterionic nature of compound **4**. The unreacted starting compound **4** was successfully recovered (Scheme 1).



Scheme 1. Synthesis of starting compounds **4** and **6**

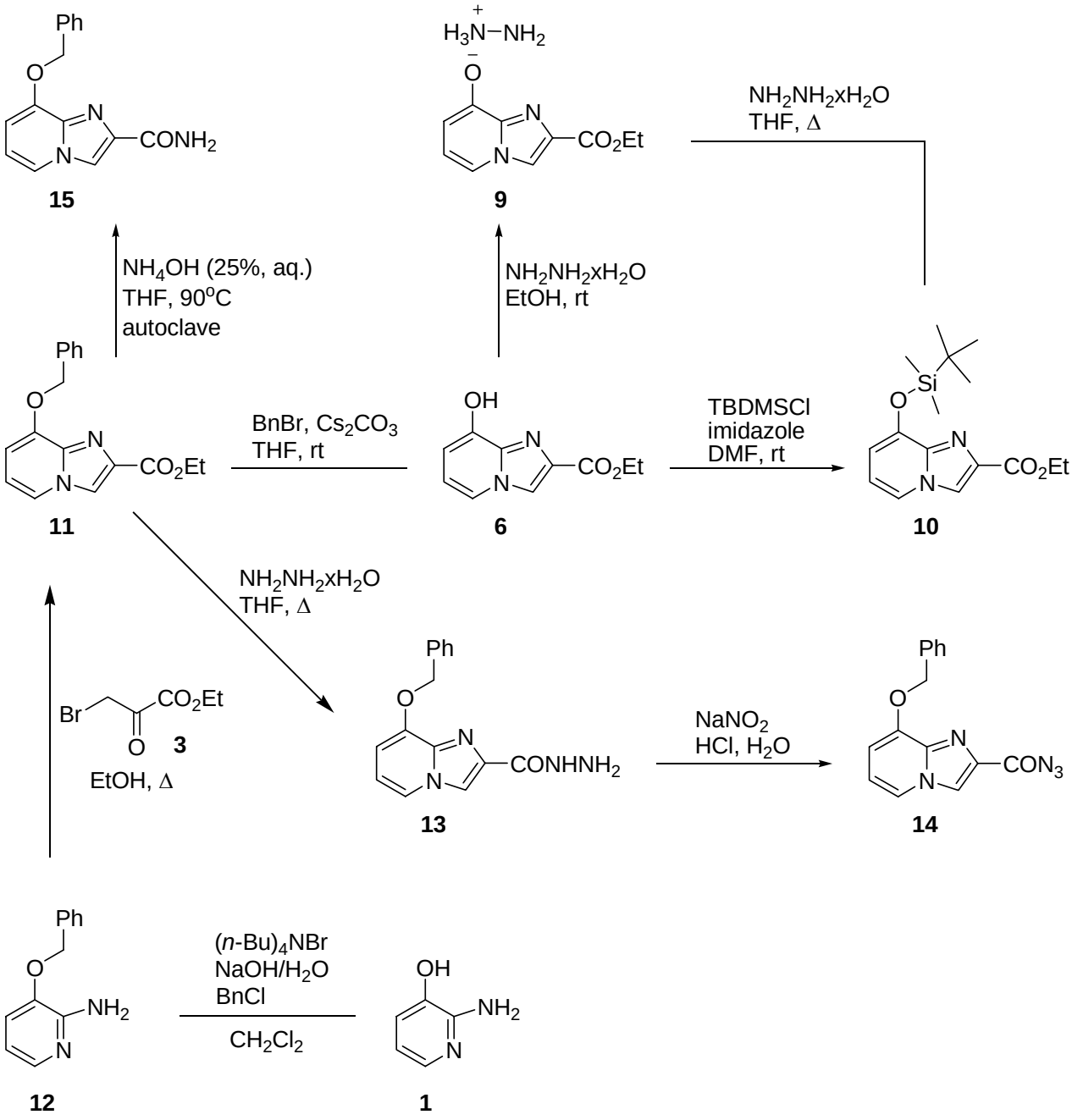
Next, synthesis of the corresponding hydrazide from ester **6** was attempted. Reaction of **6** with two equivalents of hydrazine monohydrate in ethanol at room temperature gave hydrazinium salt **9** due to the

acidic nature of hydroxy group in position 8. Reactions of **6** with large excess of hydrazine monohydrate at room temperature gave again hydrazinium salt **9**, whereas the same reaction at elevated temperature led to the inseparable mixture of products. In order to prevent the formation of undesired hydrazinium salt **9** and other similar salts, the 8-hydroxy group was protected. Treatment of **6** with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole gave TBDMS-protected compound **10**,[16] while Cs_2CO_3 catalyzed reaction of **6** with benzylbromide in THF furnished benzyl protected compound **11**.[17] Alternatively, cyclization of *O*-benzylated 2-aminopyridin-3-ol **12**, prepared from **1** following the modiefied literature procedure,[18] with ethyl bromopyruvate (**3**) gave **11** in 27% overall yield. Compound **11** prepared *via* the sequence **1→6→11** was obtained in 21% overall yield. Reaction of compound **10** with basic hydrazine monohydrate in THF induced the TBDMS deprotection and formation of the undesired hydrazinium salt **9**. On the other hand, treatment of **11** with a large excess of hydrazine monohydrate in refluxing THF yielded the desired hydrazide **13**.[19] Diazotization of hydrazide **13** gave acyl azide **14**.[4] Finally, preparation of the amide **15** was undertaken. Reactions of **11** in liquid ammonia, $CHCl_3/NH_3$(g), and ethanol/NH_3(g) failed to give the desired product **15**. Reaction of **11** in the mixture of NH_4OH (25% aq)/THF at room temperature for several days gave **15** in 28% conversion. On the other hand, the same reaction in an avtoclave at elevated temperature (90 °C) gave amide **15** in full conversion (Scheme 2).

Hydroxy acid **4** was used as the starting compound in the coupling reactions with amine **16** and amino acid derivatives **17-21** to form the corresponding amidation products. Coupling of acid **4** with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) as activating agent failed to give the desired amides. On the other hand, activation of **4** with bis(pentafluorophenyl) carbonate (BPC) in the presence of Et_3N followed by the addition of amine **16** or amino acid derivatives **17-21** gave the corresponding amides **22-27**.[20] Using the BPC activation for the coupling of **4** with different heteroaromatic amines failed completely. Hydrolysis of esters **23-25** with NaOH in a mixture of MeOH/H_2O proceeded smoothly to the acids **28-30**, respectively (Scheme 3, Table 1).[21]

STRUCTURE DETERMINATION

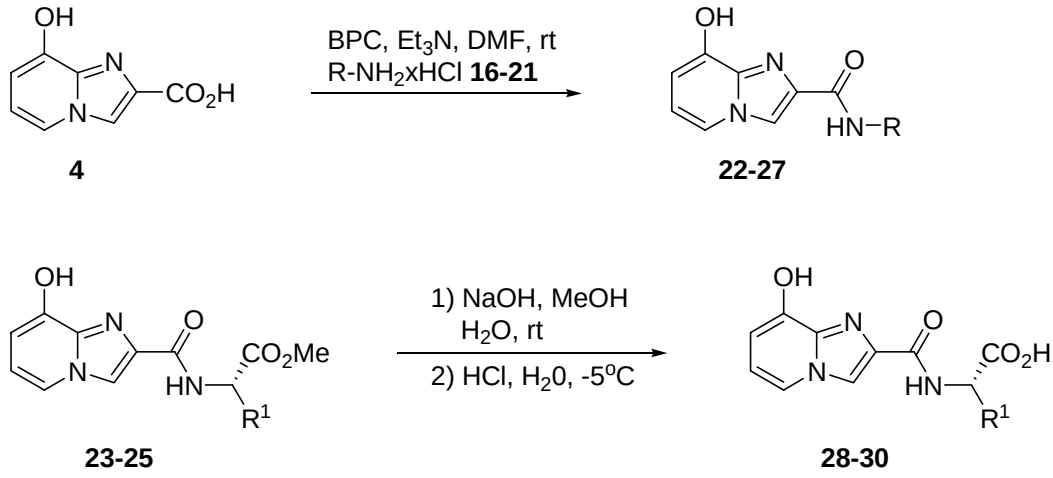
The structures of compounds **4-6**, **9-11**, **13-15**, **22-27**, and **28-30** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, NOESY spectroscopy, MS) and by elemental analyses for C, H, and N. Compounds **4-6**, **9**, **14**, **22**, **23**, **27**, **28**, and **30** were not prepared in analytically pure form. Identities of compounds **4**, **6**, **9**, **14**, **22**, **23**, **27**, **28**, and **30** were confirmed by ^{13}C NMR and/or EI–HRMS. Compounds **5** and **9** were characterized only by ^{1}H NMR.



Scheme 2. Transformations of compound **6**

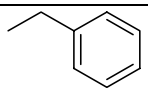
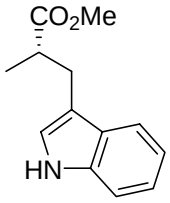
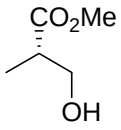
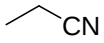
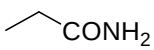
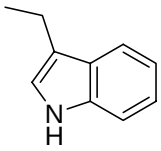
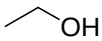
X-Ray structure analysis for compound 15

Single crystal X-ray diffraction data of compound **15** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[22] DENZO and SCALEPACK[23] were used for indexing and scaling of the data and the structure was solved by means of SIR97.[24] Refinement was done using Xtal3.4[25] program package. Crystal structure was refined on *F* values using the full-matrix least-squares procedure.



Scheme 3. Synthesis of coupling products **22-27** and methyl ester hydrolysis products **28-30**

Table 1. Selected experimental data for compounds **22-30**

Reaction	R	R^1	Yield (%)
4→22			
4→23			42
4→24			48
4→25			40
4→26			40
4→27			27
23→28			75
24→29			53
25→30		H	63

The non-hydrogen atoms were refined anisotropically, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[26] weighting scheme was used. ORTEP-III[27] drawings of the content of asymmetric units of amide **15** showing the atom-labeling scheme is presented in Figure 1.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 670122. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

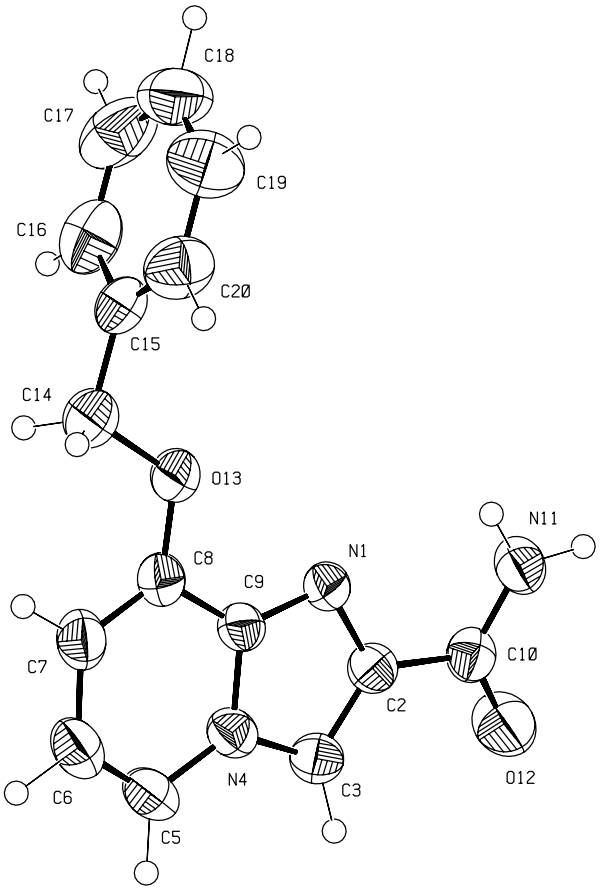


Figure 1. The asymmetric unit of compound **15**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO–d_6 and $CDCl_3$, with TMS as the internal standard, as solvents (δ in ppm, *J* in Hz). All NMR experiments were carried out

at 302 K. Optical rotations were measured on a Perkin-Elmer 241MC Polarimeter. Mass spectra were recorded on an AutoSpecQ spectrometer and Q-TOF Premier spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (ν in cm^{-1}). Microanalyses were performed on a Perkin-Elmer Series II CHN Analyser 2400. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm).

8-Hydroxyimidazo[1,2-*a*]pyridine-2-carboxylic acid (4) A suspension of 2-aminopyridin-3-ol (**1**) (2.2 g, 20 mmol) in anhydrous MeOH (50 mL) was treated with bromopyruvic acid (**2**) (3.34 mL, 20 mmol) at rt and the resulting mixture was stirred at rt for 24 h. The resulting precipitate was collected by filtration to give **4**. 39% yield (1.39 g) of a greyish-white solid; mp >350 °C. ^{1}H NMR (DMSO-d_6) δ: 6.53 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.78 (1H, t, J = 7.2 Hz, Ar); 8.05 (1H, dd, J = 0.9; 6.9 Hz, Ar); 8.44 (1H, s, Ar); 10.57 (1H, br s, OH). *m*/*z* (EI) = 178 (M^+); *m*/*z* (HRMS) Found: 178.038000 (M^+); $C_{10}H_{10}N_2O_3$ requires: *m*/*z* = 178.037842. *Anal.* Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 52.73; H, 3.78; N, 13.23. ν_{max} (KBr) 3446, 3134, 3038, 2934, 1861, 1790, 1645, 1567, 1418, 1393, 1321, 1296, 1234, 1139, 1106, 1060, 1035, 897, 828, 781, 734, 623, 577, 532 cm^{-1}.

2-(Ethoxycarbonyl)-2,8-dihydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (5) A suspension of 2-aminopyridin-3-ol (**1**) (0.55 g, 5 mmol) in 1,2-dimethoxyethane (25 mL) was treated with ethyl bromopyruvate (**3**) (0.975 g, 5 mmol) at rt. After stirring at rt for 5-10 min the suspension completely dissolved. The reaction mixture was stirred at rt for 18 h. The resulting precipitate was collected by filtration, suspended in MeCN (15 mL) and stirred at rt for 15 min. The suspension was collected by filtration to give **5**. 34% yield (0.550 g) of a white solid; mp 138-141 °C. ^{1}H NMR (DMSO-d_6) δ: 1.27 (3H, t, J = 7.2 Hz, COOEt); 4.24 (2H, q, J = 7.2 Hz, COOEt); 4.68 (1H, d, J = 14.1 Hz, 1H of CH_2); 5.08 (1H, d, J = 14.1 Hz, 1H of CH_2); 6.96 (1H, dd, J = 6.3; 7.8 Hz, Ar); 7.37 (1H, d, J = 7.5 Hz, Ar); 7.80 (1H, br s); 7.83 (1H, d, J = 6.6 Hz, Ar); 10.45 (1H, br s, OH); 11.50 (1H, br s). *Anal.* Calcd for $C_{10}H_{13}BrN_2O_4$: C, 39.36; H, 4.29; N, 9.18. Found: C, 39.90; H, 4.53; N, 8.00. ν_{max} (KBr) 3344, 3190, 3011, 2946, 1926, 1869, 1743 (C=O), 1656, 1596, 1560, 1428, 1395, 1296, 1273, 1206, 1138, 1104, 1055, 1016, 921, 808, 785, 735 cm^{-1}.

Ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (6)

Procedure A: A suspension of 2-(ethoxycarbonyl)-2,8-dihydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]-pyridin-4-ium bromide (**5**) (0.153 g, 0.5 mmol) in EtOH (2 mL) was irradiated in a laboratory microwave oven (P = 300 W, T = 120 °C, P = 3–5 bar) for 30 min. Volatile components were evaporated *in vacuo* and the residue was purified by CC (ethyl acetate/ethanol, 10:1). Fractions containing the product were combined and evaporated *in vacuo* to give **6**. 38% yield (0.040 g) of a greyish-white solid.

Procedure B: A suspension of 2-aminopyridin-3-ol (**1**) (5.858 g, 53.2 mmol) in anhydrous THF (120 mL) was treated with ethyl bromopyruvate (**3**) (6.65 mL, 53 mmol) at rt and heated at reflux for 40 h. Volatile components were evaporated *in vacuo*, CH_2Cl_2 (200 mL) was added to the residue and the mixture was washed with saturated aqueous sodium bicarbonate solution (100 mL). Aqueous phase was additionally extracted twice with CH_2Cl_2 (50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by CC (AcOEt/petroleum ether, 3:2 for elution of nonpolar impurities followed by AcOEt for elution of the product **6**). Fractions containing the product were combined and evaporated *in vacuo* to give **6**. 38% yield (4.200 g) of a greyish-white solid; mp 100-130 °C. ^{1}H NMR (DMSO-d_6) δ: 1.32 (3H, t, J = 7.2 Hz, COOEt); 4.32 (2H, q, J = 7.2 Hz, COOEt); 6.55 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.80 (1H, deg t, J = 6.6; 7.5 Hz, Ar); 8.06 (1H, dd, J = 0.9; 6.9 Hz, Ar); 8.52 (1H, s, Ar); 10.59 (1H, br s, OH). ^{13}C NMR (DMSO-d_6) δ: 15.1, 61.0, 106.4, 115.2, 119.5, 119.7, 135.4, 140.9, 147.7, 163.6. *m/z* (EI) = 206 (M^+); *m/z* (HRMS) Found: 206.069850 (M^+); $C_{10}H_{10}N_2O_3$ requires: *m/z* = 206.069142. *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 56.21; H, 4.79; N, 12.14. ν_{max} (KBr) 3144, 3115, 2976, 2928, 2541, 1709 (C=O), 1550, 1489, 1475, 1451, 1401, 1384, 1340, 1298, 1256, 1239, 1177, 1137, 1113, 1094, 1030, 991, 926, 909, 869, 840, 817, 779, 758, 740, 729, 714 cm^{-1}.

Hydrazinium 2-(ethoxycarbonyl)imidazo[1,2-*a*]pyridin-8-olate (9)

Procedure A: A solution of ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (**6**) (0.103 g, 0.5 mmol) in anhydrous EtOH (2 mL) was treated with hydrazine monohydrate (0.049 mL, 1 mmol) and stirred at rt for 48 h. The resulting white precipitate was collected by filtration and washed with ethanol (2 mL) and Et_2O (5 mL) to give **9**. 67% yield (0.080 g) of a greyish-white solid.

Procedure B: A solution of ethyl 8-(*tert*-butyldimethylsilyloxy)imidazo[1,2-*a*]pyridine-2-carboxylate (**10**) (0.091 g, 0.28 mmol) in anhydrous THF (2 mL) was treated with hydrazine monohydrate (0.016 mL, 0.33 mmol) at rt and heated at reflux for 5 h. The resulting precipitate was collected by filtration and washed with EtOH (2 mL) and Et_2O (5 mL) to give **9**. 43% yield (0.029 g) of a greyish-white solid. Melting point: 157-163 °C. ^{1}H NMR (DMSO-d_6) δ: 1.32 (3H, t, J = 7.2 Hz, COOEt); 4.31 (2H, q, J = 7.2 Hz, COOEt); 4.51 (5H, br s, $NH_2NH_3^+$); 6.47 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.77 (1H, deg t, J = 6.9; 7.2 Hz, Ar); 7.98 (1H, dd, J = 0.9; 6.6 Hz, Ar); 8.49 (1H, s, Ar). *Anal.* Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 53.24; H, 5.44; N, 19.03. ν_{max} (KBr) 3446, 3140, 1721 (C=O), 1552, 1525, 1490, 1399, 1387, 1318, 1305, 1226, 1176, 1130, 1030, 985, 775, 734 cm^{-1}.

Ethyl 8-(*tert*-butyldimethylsilyloxy)imidazo[1,2-*a*]pyridine-2-carboxylate (10) A solution of ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (**6**) (0.279 g, 1.35 mmol), *tert*-butyldimethylsilyl chloride (0.408 g, 2.71 mmol), and imidazole (0.368 g, 5.40 mmol) in DMF (5 mL) was stirred at rt for

24 h. The reaction mixture was poured into water (200 mL) and extracted with petroleum ether (4x50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by CC (ethyl acetate/petroleum ether, 1:3). Fractions containing the product were combined and evaporated *in vacuo* to give **10**. 78% yield (0.251 g) of a white solid; mp 85-90 °C. ^{1}H NMR ($CDCl_3$) δ: 0.33 (6H, s, 2xMe); 1.05 (9H, s, *t*-Bu); 1.41 (3H, t, *J* = 7.2 Hz, COOEt); 4.41 (2H, q, *J* = 7.2 Hz, COOEt); 6.57 (1H, dd, *J* = 0.9; 7.2 Hz, Ar); 6.70 (1H, deg t, *J* = 6.9; 7.2 Hz, Ar); 7.78 (1H, dd, *J* = 0.9; 6.6 Hz, Ar); 8.13 (1H, s, Ar). ^{13}C NMR ($CDCl_3$) δ: -4.2, 14.4, 18.7, 25.9, 60.9, 111.0, 114.0, 117.8, 119.6, 136.2, 142.6, 146.4, 163.5. *Anal.* Calcd for $C_{16}H_{24}N_2O_3Si$: C, 59.97; H, 7.55; N, 8.74. Found: C, 59.81; H, 7.70; N, 8.62. ν_{max} (KBr) 3462, 3144, 3107, 2956, 2855, 1715 (C=O), 1550, 1473, 1383, 1361, 1343, 1309, 1273, 1252, 1217, 1187, 1114, 1100, 1054, 1031, 976, 905, 839, 824, 794, 779, 757, 741, 695 cm^{-1}.

Ethyl 8-(benzyloxy)imidazo[1,2-*a*]pyridine-2-carboxylate (11)

Procedure A: A mixture of ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (**6**) (0.104 g, 0.5 mmol), Cs_2CO_3 (0.326 g, 1 mmol), and benzyl bromide (118 µl, 1 mmol) in THF (5 mL) was stirred at rt for 24 h. Volatile components were evaporated in *vacuo* and the residue was suspended in CH_2Cl_2 (70 mL) and washed with $NaHSO_4$ (aq sat) (50 mL) and water (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in *vacuo*. The residue was purified by CC (AcOEt/petroleum ether, 2:1). Fractions containing the product were combined and evaporated *in vacuo* to give **11**. The product **11** was recrystallized from the mixture of AcOEt /*n*-heptane. 55% yield (0.082 g) of a white solid; mp 158-165 °C. ^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, *J* = 7.2 Hz, COOEt); 4.45 (2H, q, *J* = 7.2 Hz, COOEt); 5.34 (2H, s, CH_2); 6.48 (1H, br d, *J* = 7.2 Hz, Ar); 6.68 (1H, deg t, *J* = 6.9; 7.5 Hz, Ar); 7.31-7.40 (3H, m, 3H of Ph); 7.46-7.50 (2H, m, 2H of Ph); 7.74 (1H, dd, *J* = 0.9; 6.9 Hz, Ar); 8.15 (1H, s, Ar). ^{13}C NMR ($CDCl_3$) δ: 14.4, 61.0, 70.8, 103.6, 113.8, 118.0, 119.0, 127.4, 128.1, 128.6, 135.9, 136.3, 140.2, 148.7, 163.2. *m/z* (EI) = 296 (M^+); *m/z* (HRMS) Found: 296.116650 (M^+); $C_{17}H_{16}N_2O_3$ requires: *m/z* = 296.116093. *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.70; H, 5.33; N, 9.39. ν_{max} (KBr) 3447, 3147, 3108, 1717 (C=O), 1543, 1481, 1438, 1398, 1383, 1350, 1296, 1264, 1212, 1182, 1130, 1105, 1067, 1021, 978, 791, 762, 748, 736, 701 cm^{-1}.

Procedure B: A solution of 3-(benzyloxy)pyridin-2-amine (**12**) (0.400g, 2.0 mmol) in anhydrous EtOH (10 mL) was treated with ethyl bromopyruvate (**3**) (0.39g, 2.0 mmol) and stirred under reflux for 2h. Volatile components were evaporated in *vacuo*, the oily residue was crystallized by addition of water (20 mL), and collected by filtration to give raw product **11**. The raw product **11** was dissolved in hot EtOH (3 mL) and precipitated by addition of water (20 mL). The resulting precipitate was collected by filtration to give pure **11**. 55% yield (0.326 g) of a white solid.

3-(Benzyloxy)pyridin-2-amine (12)[18] To a suspension of 2-amino-3-hydroxypyridine (2.2 g, 20 mmol) in CH_2Cl_2 were added $(n\text{-Bu})_4NBr$ (0.07 g, 0.22 mmol) and aqueous NaOH (10 mL, 40%). After a minute of stirring, the suspension dissolved and benzyl chloride (2.9 g, 21.4 mmol) was added. The reaction mixture was stirred for 16 h at rt. The organic phase was separated and the aqueous phase was diluted with water (10 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in *vacuo* to give crude **12**. Crude **12** was purified by recrystallization from EtOH. 49% yield (1.963 g) of a yellow solid; mp 89-91 °C, lit.[18] mp 97-99 °C. ^{1}H NMR ($CDCl_3$) δ: 4.70 (2H, s, NH_2); 5.09 (2H, s, CH_2); 6.6 (1H, dd, J = 5.1; 7.8 Hz, Ar); 6.98 (1H, dd, J = 1.2; 7.8 Hz, Ar); 7.34-7.46 (5H, m, Ph); 7.70 (1H, dd, J = 1.3; 5.1 Hz, Ar).

8-(Benzyloxy)imidazo[1,2-*a*]pyridine-2-carbohydrazide (13) A mixture of ethyl 8-(benzyloxy)imidazo[1,2-*a*]pyridine-2-carboxylate (**11**) (0.297 g, 1.0 mmol), and hydrazine monohydrate (1.5 mL) in THF (7 mL) was refluxed for 5 h. The reaction mixture was cooled to rt, Et_2O (15 mL) was added and the resulting precipitate was collected by filtration and washed with Et_2O (10 mL). The collected raw product was suspended in cooled water (50 mL, 5 °C) stirred for 10 minutes and the suspension was collected by filtration and washed with cooled water (100 mL, 5 °C) to give **13**. 78% yield (0.220 g) of a white solid; mp 185-187 °C. ^{1}H NMR (DMSO-d_6) δ: 4.42 (2H, br s, NH_2); 5.31 (2H, s, CH_2); 6.80-6.88 (2H, m, 2H of Ar); 7.34-7.47 (3H, m, 3H of Ph); 7.50-7.54 (2H, m, 2H of Ph); 8.18 (1H, dd, J = 1.2; 6.0 Hz, Ar); 8.34 (1H, s, Ar); 9.49 (1H, br s; NH). ^{13}C NMR (DMSO-d_6) δ: 70.1, 103.9, 112.9, 115.4, 120.2, 128.2, 128.3, 128.5, 136.2, 138.1, 138.7, 147.6, 161.1. *m*/*z* (EI) = 282 (M^+); *m*/*z* (HRMS) Found: 282.112200 (M^+); $C_{15}H_{14}N_4O_2$ requires: *m*/*z* = 282.111676. *Anal.* Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.67; H, 4.96; N, 19.80. ν_{max} (KBr) 3416, 3333, 3143, 1646 (C=O), 1576, 1563, 1546, 1480, 1456, 1444, 1400, 1387, 1343, 1310, 1267, 1102, 1068, 997, 974, 941, 913, 865, 767, 760, 731, 696 cm^{-1}.

8-(Benzyloxy)imidazo[1,2-*a*]pyridine-2-carbonyl azide (14) To a suspension of 8-(benzyloxy)imidazo[1,2-*a*]pyridine-2-carbohydrazide (**13**) (0.282 g, 1.0 mmol) in water (10 mL) was added hydrochloric acid (37%, 0.20 mL, ~2 mmol) at rt. The resulting mixture was cooled to 0 °C and aqueous $NaNO_2$ (0.5 M, 5 mL, 2.5 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 1.5 h. The resulting white precipitate was collected by filtration and washed with water (30 mL). The filtrate was suspended in CH_2Cl_2 (150 mL) and washed with $NaHCO_3$ (aq sat) (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in *vacuo*. The residue was dissolved in a minimal amount of CH_2Cl_2 and precipitated by addition of *n*-heptane. The resulting precipitate was collected by filtration to give **14**. 51% yield (0.150 g) of a grayish-white solid; mp 125-140 °C (decomposition with extrusion of N_2). ^{1}H NMR (DMSO-d_6) δ: 5.30 (2H, s, CH_2); 6.84-6.96

(2H, m, 2H of Ar); 7.37-7.46 (3H, m, 3H of Ph); 7.50-7.54 (2H, m, 2H of Ph); 8.19 (1H, dd, J = 0.9; 6.6 Hz, Ar); 8.67 (1H, s, Ar). ^{13}C NMR (DMSO-d_6) δ: 70.1, 104.4, 114.1, 120.2, 120.3, 128.0, 128.2, 128.5, 135.1, 136.1, 140.0, 147.8, 167.6. *m/z* (EI) = 293 (M^+); *m/z* (HRMS) Found: 293.091600 (M^+); $C_{15}H_{11}N_5O_2$ requires: *m/z* = 293.091275. *Anal.* Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.25; H, 3.81; N, 22.90. ν_{max} (KBr) 3448, 2158 (N_3), 1693 (C=O), 1543, 1478, 1454, 1435, 1383, 1353, 1292, 1263, 1186, 1104, 1064, 1049, 976, 949, 845, 801, 781, 760, 739, 701 cm^{-1}.

8-(Benzyloxy)imidazo[1,2-*a*]pyridine-2-carboxamide (15) A mixture of ethyl 8-(benzyloxy)imidazo[1,2-*a*]pyridine-2-carboxylate (**11**) (0.593 g, 2.0 mmol), NH_4OH (aq, 25%) (15 mL), and THF (10 mL) was heated in an autoclave for 48 h. The reaction mixture was cooled to rt, the excess NH_3 and THF were evaporated on a heating plate, the residue was cooled to rt, and the resulting precipitate was collected by filtration and washed with water (10 mL) to give **15**. 80% yield (0.428 g) of a white solid; mp 230-234 °C. ^{1}H NMR (DMSO-d_6) δ: 5.30 (2H, s, CH_2); 6.79-6.88 (2H, m, 2H of Ar); 7.30 (1H, br s, 1H of NH_2); 7.34-7.46 (3H, m, 3H of Ph); 7.50-7.54 (2H, m, 2H of Ph); 7.68 (1H, br s, 1H of NH_2); 8.18 (1H, dd, J = 1.2; 6.3 Hz, Ar); 8.32 (1H, s, Ar). ^{13}C NMR (DMSO-d_6) δ: 70.1, 103.7, 113.0, 115.8, 120.2, 128.2, 128.4, 128.5, 136.1, 138.5, 139.2, 147.6, 164.2. *m/z* (EI) = 267 (M^+); *m/z* (HRMS) Found: 267.101000 (M^+); $C_{15}H_{13}N_3O_2$ requires: *m/z* = 267.100777. *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.38; H, 4.85; N, 15.58. ν_{max} (KBr) 3468, 3285, 1661, 1583, 1544, 1455, 1400, 1384, 1357, 1316, 1276, 1187, 1101, 974, 918, 784, 746 cm^{-1}.

General Procedure for Amidation of 8-Hydroxyimidazo[1,2-*a*]pyridine-2-carboxylic acid (4) with BPC as the Activating Reagent.

Triethylamine (0.280 mL, 2 mmol) was added to a suspension of 8-hydroxyimidazo-[1,2-*a*]pyridine-2-carboxylic acid (**4**) (0.356 g, 2 mmol) in anhydrous dimethylformamide (10 mL), and the mixture was stirred at rt for 10 min. Bis(pentafluorophenyl) carbonate (BPC) (0.946 g, 2.4 mmol) was added and the mixture was stirred at rt for 12 h. Then, amine hydrochloride **16-21** (2 mmol) and triethylamine (0.560 ml, 4.0 mmol) was added and the mixture was stirred at rt for 12 h. Reaction mixture was evaporated *in vacuo* (0.1 Torr/ 60 °C) to remove all volatile components and the residue was purified by CC. Compounds **22-26** were prepared in this manner. In the case of compound **27**, the residue was suspended in MeOH (11 mL) and stirred at rt for 12 h. The suspension was collected by filtration, the filtrate suspended in MeOH/$CHCl_3$ (MeOH/$CHCl_3$ = 10 mL/5 mL), and stirred at rt for 12 h. The suspension was collected by filtration and washed with Et_2O (15 ml) to give pure **27**.

***N*-Benzyl-8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamide (22)** Benzylamine hydrochloride (**16**) (0.287 g); CC (first elution of nonpolar impurities with AcOEt/petroleum ether = 5:1, followed by elution

of the product **22** with ethyl acetate); 35% yield (0.188 g) of a white solid; mp 199-202 °C. ^{1}H NMR (DMSO-d_6) δ: 4.48 (2H, d, J = 6.3 Hz, CH_2); 6.55 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.76 (1H, dd, J = 6.9; 7.4 Hz, Ar); 7.23-7.36 (1H, m, Ar); 8.07 (1H, dd, J = 0.9; 6.7 Hz, Ar); 8.33 (1H, s, Ar); 8.68 (1H, t, J = 6.3 Hz, CONH); 10.50 (1H, br s, Ar-OH). ^{13}C NMR (DMSO-d_6) δ: 42.1, 105.1, 113.7, 115.4, 118.7, 126.7, 127.4, 128.2, 138.6, 139.2, 139.8, 146.8, 162.2. *m/z* (EI) = 267 (M^+); *m/z* (HRMS) Found: 267.101230 (M^+); $C_{15}H_{13}N_3O_2$ requires: *m/z* = 267.100777. *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.11; H, 4.76; N, 15.50. ν_{max} (KBr) 3420, 3026, 2926, 1651 (C=O), 1609, 1575, 1545, 1493, 1447, 1401, 1364, 1346, 1298, 1248, 1232, 1055, 890, 726 cm^{-1}.

(*S*)-Methyl 2-(8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamido)-3-(1*H*-indol-3-yl)propanoate (23) L-Tryptophan methyl ester hydrochloride (**17**) (0.510 g); CC (AcOEt); 42% yield (0.320 g) of a yellowish-white solid; mp 108-115 °C; $[\alpha]_{589}^{18}$ +183.9 (*c* 0.17, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ: 3.34 (2H, CH_2); 3.65 (3H, s, COOMe); 4.84-4.91 (1H, m, CH); 6.55 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.75-6.80 (1H, m, Ar); 6.93-6.98 (1H, m, Ar); 7.03-7.08 (1H, m, Ar); 7.14 (1H, d, J = 2.4 Hz, Ar); 7.33 (1H, d, J = 7.8 Hz, Ar); 7.50 (1H, d, J = 7.8 Hz, Ar); 8.06 (1H, dd, J = 0.9; 6.6 Hz, Ar); 8.17 (1H, d, J = 8.1 Hz, CONH); 8.34 (1H, s, Ar); 10.53 (1H, br s, Ar-OH); 10.87 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ: 27.2, 52.2, 52.7, 107.2, 108.8, 111.5, 114.8, 116.3, 118.0, 118.6, 119.2, 122.0, 122.4, 127.1, 136.3, 137.7, 139.7, 145.6, 162.4, 172.9. *m/z* (EI) = 378 (M^+); *m/z* (HRMS) Found: 378.133520 (M^+); $C_{20}H_{18}N_4O_4$ requires: *m/z* = 378.132805. *Anal.* Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81. Found: C, 60.71; H, 4.80; N, 13.61. ν_{max} (KBr) 3387, 1739 (C=O), 1648 (C=O), 1572, 1518, 1483, 1457, 1438, 1400, 1356, 1346, 1295, 1215, 1179, 1091, 739 cm^{-1}.

(*S*)-Methyl 3-hydroxy-2-(8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamido)propanoate (24) L-Serine methyl ester hydrochloride (**18**) (0.311 g); CC (AcOEt/MeOH = 20:1); 48% yield (0.272 g) of a pink-orange solid; mp 210-215 °C; $[\alpha]_{589}^{18}$ +40.7 (*c* 0.16, $CHCl_3$/MeOH = 5:1). ^{1}H NMR (DMSO-d_6) δ: 3.68 (3H, s, COOMe); 3.75 (1H, br d, J = 11.4 Hz, H_α of CH_2); 3.91 (1H, br d, J = 10.8 Hz, H_β of CH_2); 4.60-4.65 (1H, m, CH); 5.33 (1H, br s, Ser-OH); 6.58 (1H, d, J = 7.5 Hz, Ar); 6.79 (1H, deg t, J = 6.9; 7.2 Hz, Ar); 8.08 (1H, d, J = 6.6 Hz, Ar); 8.18 (1H, d, J = 8.4 Hz, CONH); 8.37 (1H, s, Ar); 10.57 (1H, br s, Ar-OH). ^{13}C NMR (DMSO-d_6) δ: 52.1, 54.1, 61.5, 105.4, 113.9, 115.7, 118.7, 137.8, 139.3, 146.8, 162.0, 171.0. *m/z* (EI) = 279 (M^+); *m/z* (HRMS) Found: 279.086250 (M^+); $C_{12}H_{13}N_3O_5$ requires: *m/z* = 279.085521. *Anal.* Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.34; H, 4.80; N, 14.82. ν_{max} (KBr) 3346, 3159, 3128, 3089, 1744 (C=O), 1645 (C=O), 1576, 1557, 1535, 1491, 1464, 1438, 1403, 1330, 1301, 1248, 1233, 1213, 1184, 1154, 1097, 1051, 1042, 1002, 732 cm^{-1}.

Methyl 2-(8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamido)acetate (25) Glycine methyl ester hydrochloride (**19**) (0.251 g); CC (AcOEt); 40% yield (0.200 g) of a white solid; mp 175-178 °C. ^{1}H NMR (DMSO-d_6) δ: 3.66 (3H, s, COOMe); 4.06 (2H, d, J = 6.3 Hz, CH_2); 6.57 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.77 (1H, deg t, J = 6.6; 7.5 Hz, Ar); 8.07 (1H, dd, J = 0.9; 6.6 Hz, Ar); 8.34 (1H, s, Ar); 8.54 (1H, br t, J = 6.0 Hz, CONH); 10.55 (1H, br s, Ar-OH). ^{13}C NMR (DMSO-d_6) δ: 40.6, 51.7, 105.2, 113.7, 115.5, 118.8, 138.1, 139.3, 146.8, 162.6, 170.4. *m/z* (EI) = 249 (M^+); *m/z* (HRMS) Found: 249.075660 (M^+); $C_{11}H_{11}N_3O_4$ requires: *m/z* = 249.074956. *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.81; H, 4.57; N, 16.65. ν_{max} (KBr) 3379, 3132, 1725 (C=O), 1650 (C=O), 1581, 1556, 1527, 1493, 1465, 1434, 1422, 1405, 1344, 1295, 1267, 1249, 1238, 1181, 1091, 1051, 1030, 1000, 954, 893, 852, 772, 735 cm^{-1}.

***N*-(Cyanomethyl)-8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamide (26)** Aminoacetonitrile hydrochloride (**20**) (0.185 g); CC (AcOEt); 40% yield (0.176 g) of a greyish-white solid; mp 250-255 °C. ^{1}H NMR (DMSO-d_6) δ: 4.27 (2H, d, J = 6.0 Hz, CH_2); 6.58 (1H, d, J = 7.5 Hz, Ar); 6.79 (1H, deg t, J = 6.9; 7.2 Hz, Ar); 8.08 (1H, d, J = 6.6 Hz, Ar); 8.41 (1H, s, Ar); 8.98 (1H, br deg t, J = 5.4; 5.7 Hz, CONH); 10.60 (1H, br s, Ar-OH). *m/z* (EI) = 216 (M^+); *m/z* (HRMS) Found: 216.065320 (M^+); $C_{10}H_8N_4O_2$ requires: *m/z* = 216.064726. *Anal.* Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.91. Found: C, 55.49; H, 3.75; N, 25.61. ν_{max} (KBr) 3377, 3161, 3121, 1677 (C=O), 1578, 1560, 1517, 1485, 1400, 1387, 1378, 1301, 1280, 1236, 1213, 956, 773, 735 cm^{-1}.

***N*-(2-Amino-2-oxoethyl)-8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamide (27)** Glycinamide hydrochloride (**21**) (0.221 g); 27% yield (0.130 g) of a grey solid; mp 230-235 °C. ^{1}H NMR (DMSO-d_6) δ: 3.90 (2H, d, J = 5.4 Hz, CH_2); 6.56 (1H, dd, J = 0.9; 7.5 Hz, Ar); 6.77 (1H, deg t, J = 6.9; 7.2 Hz, Ar); 7.12 (1H, br s, 1H of $CONH_2$); 7.45 (1H, br s, 1H of $CONH_2$); 8.07 (1H, dd, J = 0.9; 6.6 Hz, Ar); 8.17 (1H, br t, J = 5.4 Hz, CONH); 8.33 (1H, s, Ar); 10.57 (1H, br s, Ar-OH). ^{1}H NMR (DMSO-d_6 + D_2O) δ: 3.93 (2H, s, CH_2); 6.62 (1H, d, J = 7.5 Hz, Ar); 6.82 (1H, deg t, J = 6.9; 7.2 Hz, Ar); 8.10 (1H, d, J = 6.6 Hz, Ar); 8.36 (1H, s, Ar). *m/z* (EI) = 234 (M^+); *m/z* (HRMS) Found: 234.075860 (M^+); $C_{10}H_{10}N_4O_3$ requires: *m/z* = 234.075290. *Anal.* Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 49.36; H, 4.46; N, 24.19. ν_{max} (KBr) 3373, 3191, 1670 (C=O), 1649 (C=O), 1640, 1577, 1556, 1523, 1487, 1455, 1429, 1404, 1297, 1267, 1247, 1094, 773, 737 cm^{-1}.

General Procedure for the Methyl Ester Hydrolysis of Compounds 23-25.

NaOH (1 M in H_2O, 1.5 mL) was added to a suspension of compound **23-25** (0.65 mmol) in MeOH (3 mL) and the resulting solution was stirred at rt for 24 h. The reaction mixture was cooled to -5 °C followed by addition of HCl (1 M in H_2O, 1.5 mL) and H_2O (2 mL, 4 °C). The reaction mixture was

stirred at -5 °C for 1 h. The resulting precipitate was collected by filtration and washed with H_2O (5 mL, 4 °C). Compounds **28-30** were prepared in this manner.

(*S*)-2-(8-Hydroxyimidazo[1,2-*a*]pyridine-2-carboxamido)-3-(1*H*-indol-3-yl)propanoic acid (28) Prepared from compound **23** (0.246 g); 75% yield (0.178 g) of a white solid; mp 178-185 °C; $[\alpha]_{589}^{21}$ +20.2 (*c* 0.25, DMSO). ^{1}H NMR (DMSO-d_6) δ: 3.31-3.34 (2H,m, CH_2); 4.78-4.85 (1H, m, CH); 6.59 (1H, d, *J* = 6.9 Hz, Ar); 6.80 (1H, t, *J* = 6.9; 7.2 Hz, Ar); 6.91-6.96 (1H, m, Ar); 7.02-7.07 (1H, m, Ar); 7.12 (1H, d, *J* = 2.4 Hz, Ar); 7.32 (1H, d, *J* = 7.8 Hz, Ar); 7.53 (1H, d, *J* = 8.1 Hz, Ar); 8.07-8.10 (2H, m, CONH, 1H of Ar); 8.37 (1H, s, Ar); 10.61 (1H, br s, Ar-OH); 10.86 (1H, br s, NH); 12.97 (1H, br s, COOH). ^{13}C NMR (DMSO-d_6) δ: 27.3, 52.5, 106.1, 109.4, 111.4, 114.2, 115.7, 118.3, 118.5, 118.8, 121.0, 123.7, 127.4, 136.1, 137.3, 138.9, 146.5, 161.5, 173.2. *m/z* (EI) = 364 (M^+); *m/z* (HRMS) Found: 364.118000 (M^+); $C_{19}H_{16}N_4O_4$ requires: *m/z* = 364.117155. *Anal.* Calcd for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43; N, 15.38. Found: C, 59.19; H, 4.60; N, 14.40. ν_{max} (KBr) 3406, 3125, 1653, 1577, 1520, 1488, 1458, 1400, 1340, 1300, 1230, 1094, 734 cm^{-1}.

(*S*)-3-Hydroxy-2-(8-hydroxyimidazo[1,2-*a*]pyridine-2-carboxamido)propanoic acid (29) Prepared from compound **24** (0.182 g); 53% yield (0.092 g) of a brownish-white solid; mp 255-258 °C; $[\alpha]_{589}^{21}$ +37.8 (*c* 0.16, DMSO). ^{1}H NMR (DMSO-d_6) δ: 3.75 (1H, dd, *J* = 3.4; 10.9 Hz, H_α of CH_2); 3.91 (1H, dd, *J* = 3.8; 10.9 Hz, H_β of CH_2); 4.50-4.55 (1H, m, CH); 5.27 (1H, br s, OH); 6.56-6.59 (1H, m, Ar); 6.79 (1H, deg t, *J* = 6.8; 7.5 Hz, Ar); 8.06-8.12 (2H, m, CONH, 1H of Ar); 8.37 (1H, s, Ar); 10.62 (1H, br s, Ar-OH); 12.71 (1H, br s, COOH). ^{13}C NMR (DMSO-d_6) δ: 54.1, 61.6, 105.5, 113.9, 115.6, 118.8, 138.0, 139.3, 146.7, 161.9, 172.0. *m/z* (EI) = 266 (MH^+); *m/z* (HRMS) Found: 266.0772 (MH^+); $C_{11}H_{12}N_3O_5$ requires: *m/z* = 266.0777. *Anal.* Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.75; H, 4.39; N, 15.55. ν_{max} (KBr) 3437, 3312, 3118, 2452, 1630, 1578, 1508, 1463, 1430, 1338, 1293, 1247, 1231, 1112, 1056, 1041, 953, 788, 739 cm^{-1}.

2-(8-Hydroxyimidazo[1,2-*a*]pyridine-2-carboxamido)acetic acid (30) Prepared from compound **25** (0.162 g); 63% yield (0.097 g) of a brownish-white solid; mp 293-300 °C. ^{1}H NMR (DMSO-d_6) δ: 3.98 (2H, d, *J* = 5.7 Hz, CH_2); 6.56 (1H, dd, *J* = 0.9; 7.5 Hz, Ar); 6.77 (1H, deg t, *J* = 6.6; 7.5 Hz, Ar); 8.07 (1H, dd, *J* = 0.9; 6.6 Hz, Ar); 8.34 (1H, s, Ar); 8.35 (1H, br t, *J* = 6.0 Hz, CONH); 10.55 (1H, br s, Ar-OH); 12.62 (1H, br s, COOH). ^{13}C NMR (DMSO-d_6) δ: 40.7, 105.3, 113.8, 115.5, 118.8, 138.2, 139.3, 146.8, 162.5, 171.3. *m/z* (EI) = 236 (MH^+); *m/z* (HRMS) Found: 236.0660 (MH^+); $C_{10}H_{10}N_3O_4$ requires: *m/z* = 236.0671. *Anal.* Calcd for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 49.40; H, 4.45; N, 17.15. ν_{max} (KBr) 3481, 3316, 3118, 2451, 1633, 1578, 1508, 1451, 1423, 1338, 1306, 1286, 1237, 1094, 946, 838, 789, 739 cm^{-1}.

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