Synthesis of indolo-quinonediimine derivatives by the thermolysis of 5-(1-benzotriazolyl)-substituted spiro[2*H*-benzimidazole-2,1'-cyclohexane]

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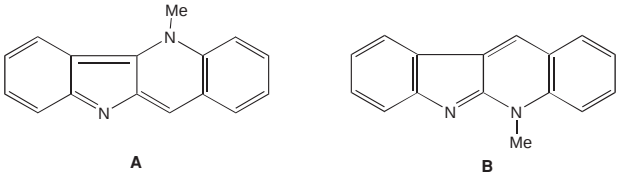
Nucleophilic introduction of the 1H-benzotriazole ring into spiro[2H-benzimidazole-2,1'-cyclohexane] and spiro[2H-imidazo[4,5-b]pyridine-2,1'-cyclohexane], followed by Graebe-Ullmann thermolysis, and also the reduction and formic acid cyclization of five spiro[cyclohexane-1,2'-2'H-imidazo[4,5-b]pyridine] derivatives to give 5-substituted 1H-imidazo[4',5':5,6]pyrido[1,2-a]benzimidazoles, are described.

Keywords: oxidative nucleophilic substitution, indoloquinonediimine, isobenzimidazoles; fused imidazoles, pyridines, indoles, ring expansion

Both cryptolepine (A) and cryptoteckipeine (B) have been found in the indoloquinoline alkaloids of the West African plant *Cryptolepis sanguinolenta*. Cryptolepine is currently under investigation as a lead compound, showing promising antiplasmodial and cytotoxic antitumor properties.[1] The increasing interest in this field prompts us to find new ways to synthesise analogues with indolo-fused systems.



The 2,3-dihydrobenzimidazole-2-spirocyclohexane (**2**), obtained by reaction of 1,2-diaminobenzene **1** with cyclohexanone, both in hot water and dioxane as solvent,[2] when oxidised by manganese dioxide gives the highly stable spiro[2*H*-benzimidazole-2,1'-cyclohexane] (**3**), an isobenzimidazole.[3,4] This stable quinonediimine system undergoes a nucleophilic substitution with benzotriazole, followed by manganese dioxide oxidation, to give compound **4** by Michael-type addition.[5,6] The benzotriazole attacks the unsubstituted isobenzimidazole **3** at C(5) to generate the product **4** in the presence of both Hünig's base and MnO_2. In the next step, thermolysis of the 5-mono-substituted compound **4** in refluxing toluene in the presence of Hünig's base, a Graebe-Ullmann type cyclisation occurs,[7] followed (or accompanied) by rearrangement of the spiro-ring system, forming the fused benzimidazole (**7**). First formed is likely to be an intermediate zwitterion **5** and then structure **6**, which should aromatise to generate compound **7**. These reactions are outlined in Scheme 1.

In order to test the synthetic potential of this path for preparing further heterocycles of pharmaceutical interest, 5-(benzotriazol-1-yl)-spiro[2*H*-imidazo[4,5-*b*]pyridine-2,1'-cyclohexane] (**8**) was heated in refluxing toluene in the presence of Hünig's base. In this case no rearrangement of the spirocyclohexane ring occurred; the product was spiro[(2*H*-imidazo[4',5'-2,3] pyrido[1,2-*a*]benzimidazole)-2,1'-cyclohexane] (**10**),[6] formed, presumably, through the zwitterion **9**. This product is reduced by sodium dithionite in aqueous tetrahydrofuran to give pyrido [1,2-*a*]benzimidazole-1,2-diamine (**11**), a key intermediate for further syntheses of materials promising antiplasmodial and antitumor cytotoxic activities. Treatment of compound **11** with a mixture of water and formic acid under reflux led to 1*H*-imidazo [4',5':5,6]pyrido[1,2-*a*]benzimidazole (12), a tetraazacyclopenta[*c*]fluorene. These reactions are illustrated in Scheme 2.

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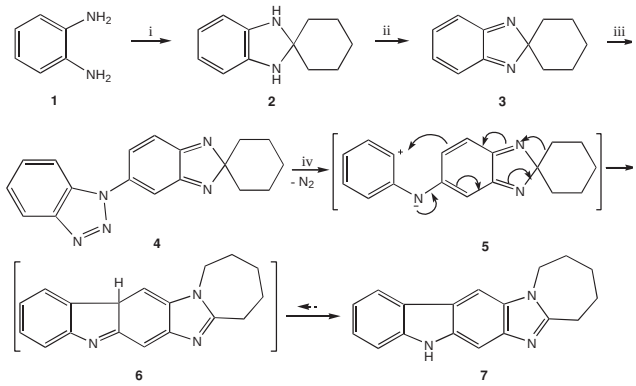
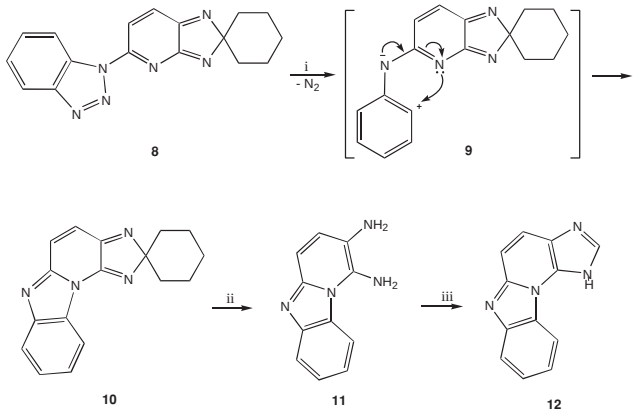
To identify saturated and unsaturated C-atoms in the structures, distortionless enhancement by polarization transfer (DEPT) experiments were performed.

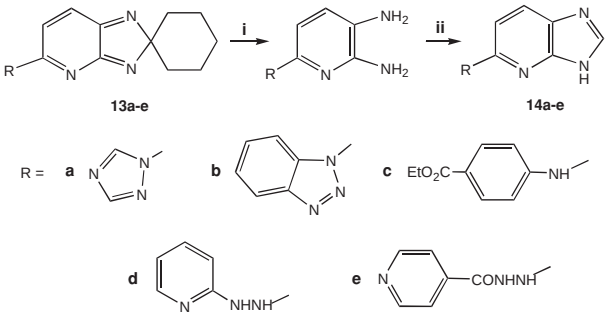
In analogy to compound **12**, five novel 5-substituted imidazo-pyridines (**14a-e**) were synthesised. The reactions are shown in Scheme 3.



Scheme 1 (i) Cyclohexanone, dioxan, reflux temperature; (ii) THF, MnO_2, 12 rt; (iii) THF, *N*-ethyldiisopropylamine, benzotriazole, MnO_2, 14h, r.t; (iv) toluene, *N*-ethyldiisopropylamine, 12 h reflux.



Scheme 2 Cyclisation and reduction of 5-(1-benzotriazolyl)-spiro[2*H*-imidazo[4,5-*b*]pyridine-2,1'-cyclohexane] (8). (i) Toluene, *N*-ethyldiisopropylamine, reflux, 18 h; (ii) H_2O, THF, sodium dithionite, 30 minutes r.t; (iii) formic acid, H_2O, reflux, 4 h.

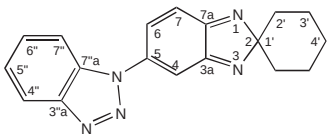


Scheme 3 Reduction and recyclisation of spiro-compounds (i) H_2O, THF, sodium dithionite, 30 minutes r.t; (ii) formic acid, H_2O, reflux, 4 h.

Experimental

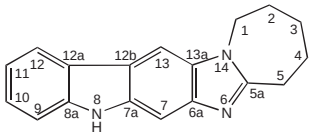
Melting points were determined using a Reichert hot stage microscope. Infrared spectra were measured with a Perkin-Elmer spectrophotometer 283 on potassium bromide discs. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker WM-250 (^{1}H: 250.13 MHz, ^{13}C: 62.89 MHz) or a Varian XL 300 (^{1}H: 299.95 MHz, ^{13}C: 75.43 MHz) spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and coupling constants *J* are given in Hz. DEPT-Technique (Distortionless Enhancement by Polarization Transfer) experiments were carried out to confirm the assignments. Electron impact mass spectra were obtained on a Varian MAT 311A instrument. High resolution mass spectra (HRMS) were obtained on the same instrument. The CHN elemental analyses were carried out on an automatic microanalyser, Foss-Heraeus Vario EL (Heraeus). Column chromatography was performed using silica gel 60 (0.063–0.2 mm / 70–230 mesh ASTM) or Al_2O_3. TLC (thin layer chromatography) was carried out on percolated plastic sheets POLYGRAM ALOX N/UV_{254} or POLYGRAM SIL G/UV_{254} using *n*-hexane – ethyl acetate or ethyl acetate – ethanol as eluent. The spots were visualised by UV light at 254 and 366 nm.

5-(Benzotriazol-1-yl)-isobenzimidazole-2,1'-spirocyclohexane (**4**):



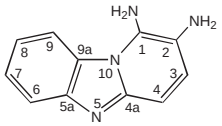
Benzotriazole (1.3 g, 10.9 mmol) and MnO_2 (2.6 g, 30.0 mmol) were added to isobenzimidazole **3** (1.0 g, 5.4 mmol) in tetrahydrofuran (100 ml). After 14 h stirring at room temperature the reaction mixture was filtered. The filtrate was evaporated to dryness and the residue was purified on a column (basified AlOX, ethyl acetate : *n*-hexane 1 : 1) affording compound **4** (0.8 g, 2.6 mmol., 49%), m.p. 185–189 °C. IR: ν_{max} (cm^{-1}) 3085 (Aryl-H), 2940 (CH_2), 1680 (C=N), 1595 (C=C). ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 8.4 (1H, d, *J* = 8.3 Hz, 4"-H), 8.2 (1H, d, *J* = 8.2 Hz, 7"-H), 8.1 (1H, d, *J* = 10.3 Hz, 6-H), 8.0 (1H, s, 4-H), 7.8 (1H, dd, *J* = 8.3, 6.6 Hz, 6"-H), 7.6 (1H, d, *J* = 10.3 Hz, 7-H), 7.4 (1H, dd, *J* = 8.3, 6.6 Hz, 5"-H), 1.8–1.3 (10H, m, H-2'-4'); δ ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 167.0 (C-7a), 163.7 (C-3a), 146.4 (C-3"a), 141.0 (C-5), 137.1 (C-7), 130.1 (C-7"a), 127.5 (C-6"), 124.4 (C-5"), 122.0 (C-6), 119.7 (C-4"), 110.3 (C-7"), 107.5 (C-4), 82.2 (C-2/1'), 43.3 (C-2'), 25.0 (C-4'), 24.0 (C-3'). MS: *m/z* (%) 303 (8) [M]$^+$, 277 (80), 186 (16), 118 (36), 106 (16), 54 (21), 42 (5). Anal. Calcd. for $C_{18}H_{17}N_5$ (303.37): C 71.27; H 5.65; N 23.08. Found: C 71.17; H 5.59; N 23.21 %.

1,2,3,4,5,8-Hexahydroazepino[1',2':1,2]imidazo[4,5-b]carbazole (**7**)



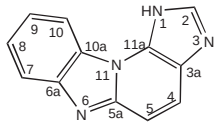
To 5-(benzotriazol-1-yl)-isobenzimidazole-2,1'-spirocyclohexane (**4**) (303 mg, 1.0 mmol) in toluene (50 ml), Hünig's base (*N*-ethyldiisopropylamine) (0.5 ml) was added and the mixture was refluxed for 12 h. The solution was evaporated to dryness and the residue was purified by column chromatography (AlOX, ethyl acetate : *n*-hexane 1:1) affording the product **7** (40 mg, 14%), mp. > 230 °C. IR: ν_{max} (cm^{-1}), 3150 (N–H), 3058 (Aryl-H), 2985 (CH_2), 1695 (C=N), 1611 (C=C). ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 8.2–7.3 (m, 6H, H-7, 9-12, 13), 4.3–4.15 (m, 2H, H-1), 3.2–3.1 (m, 2H, H-5), 2.0–1.7 (m, 6H, H2-4); ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 159.0 (C-5a), 146.0 (C-8a), 142.4 (C-6a), 135.0 (C-13a), 132.1 (C-7a), 131.0 (C-10), 125.3–122.1 (m, C-9, 11, 12, 12a, 12b), 113.4 (C-7, C-13), 92.0 (C-1), 56.2 (C-5), 42.8 (C-2), 27.9 (C-4), 24.4 (C-3). MS: *m/z* (%) 276 (23) [M+1]$^+$, 275 (100) [M]$^+$, 246 (26), 220 (25), 192 (7), 41 (8); HRMS: Calcd. for $C_{18}H_{17}N_3$: 275.1422, found: 275.1422. Anal. Calcd. for $C_{18}H_{17}N_3 \cdot H_2O$ (293.37): C 73.70, H 6.53, N 14.32. Found: C 73.92, H 6.83, N 14.72 %.

Pyrido[1,2-a]benzimidazole-1,2-diamine (**11**):



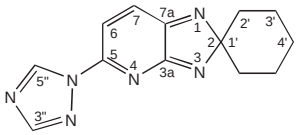
To spiro[(2*H*-imidazo[4,5:2,3]pyrido[1,2-*a*]benzimidazole)-2,1'-cyclohexane] (**8**) [6] (0.5 g, 1.8 mmol) in tetrahydrofuran (20 ml) was added sodium dithionite (0.95 g, 5.4 mmol in H_2O (10 ml) and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and were filtered. The filtrate was evaporated to dryness. The residue was purified on column (silica gel, ethyl acetate : ethanol 1:2) affording the diamine **11** (0.1 g, 0.5 mmol, 28%), m.p. 168 °C. IR: ν_{max} (cm^{-1}) 3185 (N–H_2), 3089 (Aryl-H), 1685 (C=N), 1605 (C=C). ^{1}H NMR (250.13 MHz, CD_3OD): δ 8.83 (1H, d, *J* = 8.6 Hz, H-6), 8.53 (4H, m, 2NH_2), 8.2 (1H, d, *J* = 10.2 Hz, H-3), 8.15 (1H, d, *J* = 10.2, H-4), 8.10 (1H, d, *J* = 8.2 Hz, H-9), 7.7 (1H, dd, *J* = 8.2, 6.5 Hz, H-8), 7.5 (1H, dd, *J* = 8.5, 6.5 Hz, H-7); ^{13}C NMR (62.89 MHz, CD_3OD): δ 161.8 (C-5a), 152.0 (C-1), 146.1 (C-4a), 132.0 (C-6), 129.8 (C-9a), 128.5 (C-2), 125.0 (C-7), 120.0 (C-8), 118.6 (C-3), 114.8 (C-9), 109.0 (C-4); (180° DEPT): δ 132.0 (C-6), 125.0 (C-7), 120.0 (C-8), 118.6 (C-3), 114.8 (C-9), 109.0 (C-4). MS: *m/z* (%) 199 (23) [M+1]$^+$, 168 (12), 118 (16), 108 (16), 78 (6), 54 (21), 42 (5). Anal: Calcd. for $C_{11}H_{10}N_4$ (198.23): C 66.60, H 5.08, N 28.26. Found: C 66.81, H 5.10, N 29.06 %.

1H-Imidazo[4',5':5,6]pyrido[1,2-a]benzimidazole (**12**):



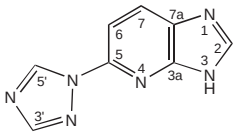
To pyrido[1,2-*a*]benzimidazole-1,2-diamine (**11**) (80 mg, 0.4 mmol) in 1N HCl (10 ml), formic acid (1 ml) was added and the mixture was refluxed for 4 h. The reaction mixture was first neutralised with 1N NaOH and then extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. The residue was purified on column (silica gel, ethyl acetate : ethanol 1 : 2) affording **12** (50 mg, 0.24 mmol, 60%) m.p. 195 °C. IR: ν_{max} (cm^{-1}) 3155 (N-H), 3079 (Aryl-H), 1675 (C=N), 1600 (C=C). ^{1}H NMR (250.13 MHz, CD_3OD): δ 8.6 (1H, d, *J* = 8.4 Hz, H-10), 8.5 (1H, s, N-H), 8.15 (1H, s, H-2), 7.83 (1H, d, *J* = 8.7 Hz, H-4), 7.8 (1H, d, *J* = 8.5 Hz, H-7), 7.54 (1H, dd, *J* = 8.4, 6.5 Hz, H-9), 7.43 (1H, dd, *J* = 8.4, 6.5 Hz, H-8), 7.4 (1H, d, *J* = 8.7 Hz, H-5); ^{13}C NMR (62.89 MHz, CD_3OD): δ 149.0 (C-6a), 144.0 (C-5a), 141.0 (C-10a), 140.0 (C-2), 129.0 (C-11a), 126.8 (C-8), 123.1 (C-9), 121.1 (C-4), 120.0 (C-3a), 119.0 (C-7), 115.7 (C-5), 111.0 (C-10); (180° DEPT); δ 140.0 (C-2), 126.7 (C-8), 123.1 (C-9), 121.1 (C-4), 119.0 (C-7), 115.7 (C-5), 111.0 (C-10). MS: *m/z* (%) 209 (3) [M+1]$^+$, 208 (100) [M]$^+$, 198 (12), 168 (26), 93 (18), 77 (6), 64 (2), 52 (5). HRMS: Calcd. for $C_{17}H_{16}N_4$: 208.0748. Found: 208.0744. Anal. Calcd. for $C_{12}H_8N_4 \cdot H_2O$ (226.24): C 63.71; H 4.46; N 24.76. Found: C 63.83; H 4.75; N 24.96 %.

5-(1,2,4-Triazol-1-yl)-spiro[2H-imidazo[4,5-b]pyridine-2,1'-cyclohexane] (**13a**):



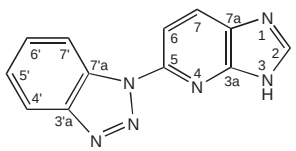
To 2,3-dihydrospiro[(2*H*-imidazo[4,5-*b*]pyridine)-2,1'-cyclohexane] (189 mg, 1 mmol) in ethanol (50 ml) were added 1,2,4-triazole (69.0 mg) and MnO_2 (0.5 g, 5.44 mmol) and the mixture was stirred for 24 h at room temperature. After filtration and evaporation to dryness, the residue was purified on column chromatography (Al_2O_3, ethyl acetate / *n*-hexane 1:1) affording 5-(1,2,4-triazol-1-yl)spiro[2*H*-imidazo[4,5-*b*]pyridine-2,1'-cyclohexane] (104 mg, 0.41 mmol, 41%), mp 146 °C. IR: ν_{max} (cm^{-1}), 3026 (Aryl-H), 2935 ($(CH_2)_5$), 1696 (N–C=N), 1640 (C=N), 1605 (C=C). ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 9.4 (1H, s, 3''-H), 8.2 (1H, s, 5''-H), 7.5 (1H, d, *J* = 10.0 Hz, 7-H), 6.7 (1H, d, *J* = 10.0 Hz, 6-H), 2.1-1.5 (10H, m, H-2'-4'); ^{13}C NMR (90.56 MHz, $CDCl_3$): δ 163.7 (C-5), 153.9 (C-3''), 153.7 (C-3a), 151.8 (C-7a), 137.4 (C-5''), 133.3 (C-7), 124.1 (C-6), 106.7 (C-2/1'), 34.3 (C-2'), 25.5 (C-4'), 24.0 (C-3'). MS: *m/z* (%) 255 (3) $[M+1]^+$, 254 (20) $[M]^+$, 203 (100), 174 (18), 148 (25), 81 (34), 41 (19); HRMS: Calcd. for $C_{17}H_{16}N_4$: 254.1280. Found: 254.1280. Anal: Calcd. for $C_{13}H_{14}N_6$ (254.30): C 61.40; H 5.55; N 33.05. Found: C 61.81; H 5.71; N 33.41 %.

5-(1,2,4-Triazol-1-yl)-3H-imidazo[4,5-b]pyridine (**14a**):



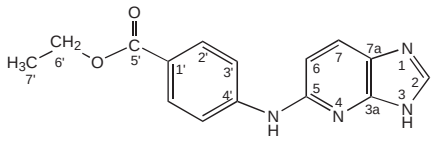
To 5-(1,2,4-triazol-1-yl)-spiro[(2*H*-imidazo[4,5-*b*]pyridine)-2,1'-cyclohexane] (0.1 g, 0.37 mmol) in tetrahydrofuran (10 ml) was added sodium dithionite (0.2 g, 1.2 mmol) in H_2O (5 ml) and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and were filtered. The filtrate was evaporated to dryness. To the unpurified residue 1N-HCl (10 ml) and 1 ml formic acid were added and the mixture was refluxed for 4 h. The reaction mixture was first neutralised with 1N-NaOH and then extracted with ethyl acetate (3 × 30 ml). The combined extracts were dried over Na_2SO_4 and were filtered. The filtrate was evaporated to dryness. The residue was purified on column (silica gel, ethyl acetate : ethanol 1 : 1) affording 5-(1,2,4-triazol-1-yl)-3*H*-imidazo[4,5-*b*]pyridine (34 mg, 0.12 mmol, 49%), m.p. > 230°C. IR: ν_{max} (cm^{-1}) 3165 (N–H), 3059 (Aryl-H), 1674 (N–C=N), 1665 (C=N), 1604 (C=C). ^{1}H NMR (250.13 MHz, CD_3OD): δ 9.4 (1H, s, H-3'), 8.4 (1H, br, N–H), 8.37 (1H, s, H-5'), 8.3 (1H, s, H-2), 8.15 (1H, d, *J* = 9.4 Hz, H-7), 8.1 (1H, d, *J* = 9.4, H-6); ^{13}C NMR (62.89 MHz, CD_3OD): δ 159.0 (C-7), 154.1 (C-5'), 151.0 (C-3a), 142.1 (C-3'), 129.9 (C-7a), 128.8 (C-7), 103.1 (C-6). MS: *m/z* (%) 187 (5) $[M+1]^+$, 186 (30) $[M]^+$, 118 (45), 108 (26). Anal: Calcd. for $C_8H_6N_6$ (186.18): C 51.61; H 3.25; N 45.14. Found: C 51.60; H 3.30; N 45.10 %.

5-(Benzotriazol-1-yl)-3H-imidazo[4,5-b]pyridine (**14b**):



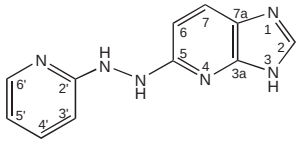
To 5-(benzotriazol-1-yl)spiro[(2*H*-imidazo[4,5-*b*]pyridine)-2,1'-cyclohexane](**13b**)[6] (0.3 g, 1.0 mmol) in THF (10 ml) was added sodium dithionite (0.8 g, 4.8 mmol) in H_2O (5 ml), and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. To the unpurified residue 1N HCl (10 ml) and formic acid (1 ml) were added and the mixture was refluxed for 4 h. After cooling to room temperature the reaction mixture was neutralised with 1N NaOH and then extracted with ethyl acetate (3 × 30 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness and the residue was purified on column (silica gel, ethyl acetate : ethanol 1 : 1), affording 5-(benzotriazol-1-yl)-3*H*-imidazo[4,5-*b*]pyridine (**14b**) (102 mg, 0.43 mmol, 43%), m.p. 148 °C. IR: ν_{max} (cm^{-1}) 3155 (N-H), 3069 (Aryl-H), 1678 (N–C=N), 1669 (C=N), 1607 (C=C). ^{1}H NMR (250.13 MHz, CD_3OD): δ 8.3–8.1 (4H, m, H-2,6,7,7'), 7.7–7.4 (3H, m, H-4',5',6'); ^{13}C NMR (62.89 MHz, CD_3OD): δ 154.2 (C-5), 150.1 (C-3a), 146.0 (C-3'a), 142.1 (C-2), 129.4 (C-7'a), 128.6 (C-7a), 128.0 (C-7), 126.5 (C-6'), 124.3 (C-5'), 120.0 (C-4'), 111.1 (C-7'), 103.12 (C-6); MS: *m/z* (%) 237 (8) $[M+1]^+$, 236 (30) $[M]^+$, 208 (47), 118 (36), 108 (10). Anal. Calcd. for $C_{12}H_8N_6 \cdot H_2O$ (236.24): C 61.01; H 3.41; N 35.57. Found: C 56.68; H 3.95; N 33.06 %.

4-(3H-Imidazo[4,5-b]pyridin-5-ylamino)-benzoic acid ethyl ester (**14c**):



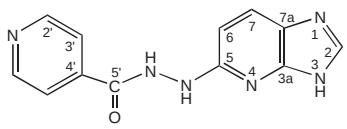
To 4-spiro[2,1'-cyclohexane-2*H*-imidazo[4,5-*b*]-pyridin-5ylamino] benzoic acid ethyl ester (**13c**)[6] (0.2 g 0.6 mmol) in THF (10 ml) was added sodium dithionite (0.8 g, 4.8 mmol) in H_2O (5 ml) and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. To the unpurified residue 1N HCl (10 ml) and formic acid (1 ml) were added and the mixture was refluxed for 4 h. After cooling to room temperature the reaction mixture was neutralised with 1N NaOH and then extracted with ethyl acetate (3 × 30 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. The residue was purified on column (silica gel, ethyl acetate : ethanol 1 : 1) affording 4-(3*H*-imidazo[4,5-*b*]pyridin-5-ylamino)-benzoic acid ethyl ester (**14c**) (55 mg, 0.19 mmol, 32%), m.p. 210 °C. IR: ν_{max} (cm^{-1}) 3171 (N–H), 3089 (Aryl-H), 1705 (COOEt, N–C=N), 1663 (C=N), 1609 (C=C); ^{1}H NMR (250.13 MHz, CD_3OD): δ 8.3 (1H, s, H-2), 8.0 (1H, d, *J* = 9.3 Hz, H-7), 7.5 (2H, d, *J* = 8.5 Hz, H-2'), 7.4 (2H, *J* = 8.5 Hz, H-3'), 7.3 (1H, *J* = 9.3 Hz, H-6), 4.3 (2H, q, *J* = 7.2 Hz, H-6'), 1.51 (3H, t, *J* = 7.2 Hz, H-7'); ^{13}C NMR (62.89 MHz, CD_3OD): δ 164.9 (C-5'), 152.1 (C-5), 146.1 (C-3a), 142.0 (C-2), 141.1 (C-4'), 127.5 (C-3'), 127.0 (C-2'), 126.7 (C-7a), 126.2 (C-1'), 124.1 (C-7), 120.0 (C-6), 62.1 (C-6'), 15.1 (C-7'). MS: *m/z* (%) 283 (17) $[M+1]^+$, 282 (81) $[M]^+$, 237 (47), 209 (26), 132 (7), 116 (12). Anal. Calcd. for $C_{15}H_{14}N_4O_2$ (282.30): C 63.82; H 5.00; N 19.85. Found: C 64.04; H 5.25; N 20.16 %.

N-(3H-Imidazo[4,5-b]pyridin-5-yl)-N'-(pyridin-2-yl)-hydrazine (**14d**):



To *N*-spiro[2,1'-cyclohexane-2*H*-imidazo[4,5-b]pyridin-5-yl]-*N*'-(pyridin-2-yl)-hydrazine (**13d**)[6] (0.1 g, 0.34 mmol) in THF (10 ml) was added sodium dithionite (0.23 g, 1.4 mmol) in H_2O (5 ml) and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and were filtered. The filtrate was evaporated to dryness. To the unpurified residue 1N HCl (10 ml) and formic acid (1 ml) were added and the mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture was neutralised with 1N NaOH and then extracted with ethyl acetate (3 × 30 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. The residue was purified on column (silica gel, ethyl acetate : ethanol 1:1) affording *N*-(3*H*-imidazo[4,5-*b*]pyridine-5-yl)-*N*'-(pyridin-2-yl)-hydrazine (25 mg, 0.11 mmol, 32%) m.p. 142 °C. IR: ν_{max} (cm^{-1}) 3181 (N–H), 3081 (Aryl-H), 1697 (N–C=N), 1673 (C=N), 1602 (C=C); ^{1}H NMR (250.13 MHz, CD_3OD): δ 10.1 (3H, br, 3'N–H), 8.3 (1H, s, 2-H), 8.2–8.0 (2H, m), 7.5–7.1 (3H, m), 6.4–6.3 (1H, m); ^{13}C NMR (62.89 MHz, CD_3OD): δ 150.9 (C-5), 149.6 (C-2'), 148.1 (C-3a), 147.0 (C-6'), 142.4 (C-2), 137.9 (C-4'), 126.9 (C-7a), 126.5 (C-7), 116.9 (C-5'), 111.1 (C-3'), 99.5 (C-6). MS: *m/z* (%) 227 (27) $[M+1]^+$, 226 (100) $[M]^+$, 118 (41), 116 (12), 41 (9). Anal. Calcd. for $C_{11}H_{10}N_6 \cdot H_2O$ (226.24): C 58.4; H 4.45; N 37.15. Found: C 54.09; H 4.94; N 34.41 %.

Isonicotinic acid N'-(3H-imidazo[4,5-b]pyridin-5-yl)-hydrazide (**14e**):



To isonicotinic acid *N*'-spiro-[2,1'-cyclohexan-2*H*-imidazo[4,5-*b*] pyridin-5-yl]-hydrazide (**13e**)[6] (0.2 g, 0.8 mmol) in THF (10 ml) was added sodium dithionite (0.5 g, 3.1 mmol) in H_2O (5 ml) and the

mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. To the unpurified residue 1N HCl (10 ml) and formic acid (1 m were added and the mixture was refluxed for 4 h. After cooling to room temperature the reaction mixture was neutralised with 1N NaOH and then extracted with ethyl acetate (3 × 30 ml). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness and the residue was purified on column (silica gel, ethyl acetate : ethanol 1:1) affording isonicotinic acid *N'*-(3*H*-imidazo [4,5-*b*]pyridin-5-yl)-hydrazide (**14e**) (25 mg, 0.11 mmol, 32%) m.p. 222 °C. IR: ν_{max} (cm^{-1}) 3171 (N–H), 3081 (Aryl-H), 1697 (N–C=N), 1673 (C=N), 1667 (NC=O), 1603 (C=C); ^{1}H NMR (250.13 MHz, CD_3OD): δ 10.1 (3H, br, 3'N-H), 8.7 (2H, d, *J* = 5.2 Hz, H-2'), 8.2–8.0 (2H, d, *J* = 5.5 Hz, H-3'), 8.1 (1H, s, H-2), 7.9 (1H, d, *J* = 9.1 Hz, H-7), 7.2 (1H, d, *J* = 9.1 Hz, H-6); ^{13}C NMR (62.89 MHz, CD_3OD): δ 170.9 (C-5'), 160.6 (C-5), 150.1 (C-2'), 147.5 (C-3a), 142.6 (C-4'), 142.0 (C-7), 125.9 (C-2), 125.5 (C-7a), 122.0 (C-3'), 99.1 (C-6). MS: *m/z* (%) 255 (17) $[M+1]^+$, 254 (100) $[M]^+$, 244 (42), 167 (22), 139 (9), 109 (7), 79 (9), 29 (5). Anal: Calcd. for $C_{12}H_{10}N_6O{\cdot}H_2O$ (254.25): C 56.59; H 3.96; N 33.05. Found: C 52.94; H 4.44; N 30.87 %.

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