ELECTRONIC SUPPORTING INFORMATION

Efficient Ugi-3CR / aza Diels-Alder / Pommeranz-Fritsch Protocol Towards Novel Aza-analogues of (±)-Nuevamine, (±)-Lennoxamine and Magallanesine: A Diversity Oriented Synthesis Approach

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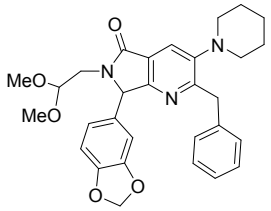
General information, instrumentation and chemicals

^{1}H and ^{13}C NMR spectra were acquired on either, Bruker Advance III (500 or 400 MHz) spectrometers. The solvent was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). Internal reference for ^{1}H NMR spectra is respect to TMS at 0.0 ppm. Internal reference for ^{13}C NMR spectra is respect to $CDCl_3$ at 77.0 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). IR spectra were acquired on a Perkin Elmer Spectrum 2000 and Perkin Elmer Spectrum 100. The absorbance peaks are reported in reciprocal centimeters (ν/cm^{-1}). High resolution mass spectra were acquired on either, Jeol SX-102A (FAB+) or Bruker Maxis Impact (ESI+) spectrometers. HRMS samples were ionized by either, FAB+ or ESI+ and recorded via the TOF method. Microwave assisted reactions were performed on a CEM Discover™ Synthesis Unit in close vessel mode. Reaction progress was monitored by TLC on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures of Hexanes with AcOEt (v/v) as mobile phase. The chromatography on silica-gel preparative plates was done on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light (254 or 365 nm). All starting materials were purchased from Sigma-Aldrich and were used without further purification. The solvents were distilled and dried according to standard procedures.

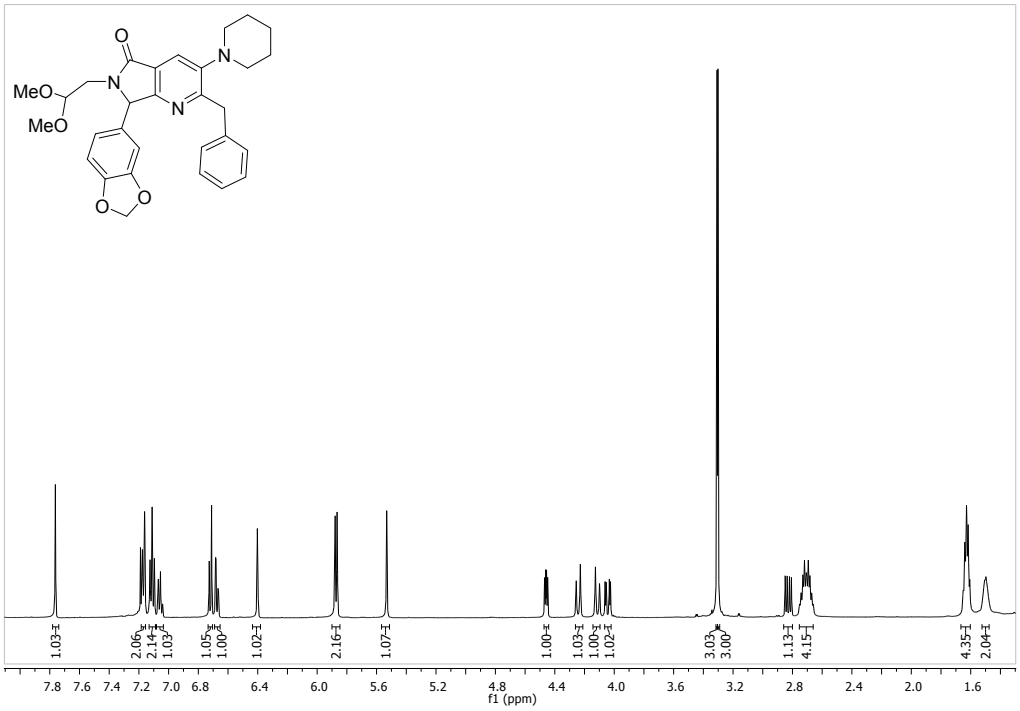
Synthesis and characterization of the pyrrolo[3,4-*b*]pyridin-5-ones 16a-d

General Procedure 1 - Step 1 (GP1-S1): 2,2-dimethoxyethan-1-amine (1.00 equiv.) and the corresponding aldehyde (1.00 equiv.) were placed in a 10 mL sealed CEM Discover™ MW reaction tube and diluted in dry PhMe (1.0 mL). Then, the mixture was MW-heated (65 °C, 55 W) for 20 minutes, and $Sc(OTf)_3$ (0.03 equiv.) was added. The mixture was MW-heated (65 °C, 55 W) for 15 minutes, and the corresponding isocyanide (1.20 equiv.) was added. The mixture was MW-heated (80 °C, 65 W) for 30 minutes, and maleic anhydride (1.40 equiv.) was added. Finally, the reaction mixture was MW-heated (80 °C, 65 W) for 30 minutes, cooled at room temperature and the solvent was removed until dryness. The crude was dissolved in CH_2Cl_2 (5.6 mL) and washed with a concentrated aq. solution of $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL). The organic layer was dried with Na_2SO_4, filtered using celite-pad and the solvent was removed until dryness. The crude was purified by silica gel column chromatography using mixtures of Hexanes/EtOAc as mobile phase. Finally, the product was re-purified on silica-gel preparative plates 20x20 cm using mixtures of Hexanes/EtOAc as mobile phase to afford the corresponding pyrrolo[3,4-*b*]pyridin-5-ones **16a-d.**

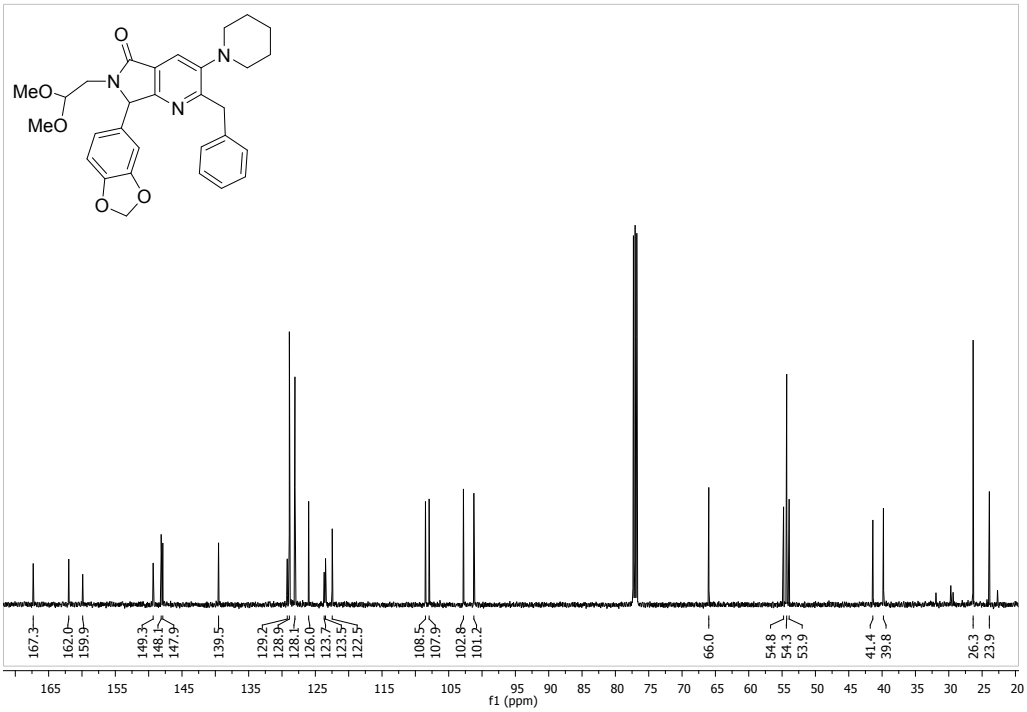
7-(benzo[*d*][1,3]dioxol-5-yl)-2-benzyl-6-(2,2-dimethoxyethyl)-3-(piperidin-1-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**16a**)



According to ***GP1-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), piperonal (103.0 mg, 0.685 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-3-phenyl-1-(piperidin-1-yl)propan-1-one (203.0 mg, 0.838 mmol) and maleic anhydride (94.0 mg, 0.959 mmol) were reacted together in PhMe (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **16a** (232.8 mg, 66%) as yellow gum; R_f = 0.47 (Hexanes/AcOEt, 2/1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (s, 1H), 7.19 – 7.15 (m, 2H), 7.13 – 7.09 (m, 2H), 7.08 – 7.04 (m, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.67 (dd, J = 8.0, 1.6 Hz, 1H), 6.40 (d, J = 1.5 Hz, 1H), 5.87 (d, J = 6.5 Hz, 2H), 5.53 (s, 1H), 4.46 (dd, J = 6.6, 3.8 Hz, 1H), 4.24 (d, J = 13.7 Hz, 1H), 4.11 (d, J = 13.7 Hz, 1H), 4.04 (dd, J = 14.4, 3.8 Hz, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 2.83 (dd, J = 14.4, 6.6 Hz, 1H), 2.76 – 2.66 (m, 4H), 1.66 – 1.60 (m, 4H), 1.53 – 1.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 167.3, 162.0, 159.9, 149.3, 148.1, 147.9, 139.5, 129.2, 128.9, 128.1, 126.0, 123.7, 123.5, 122.5, 108.5, 107.9, 102.8, 101.2, 66.0, 54.8, 54.3, 53.9, 41.4, 39.8, 26.3, 23.9. HRMS: m/z calcd. for: $C_{30}H_{34}N_3O_5^+$ = 516.2993, found: 516.2996.

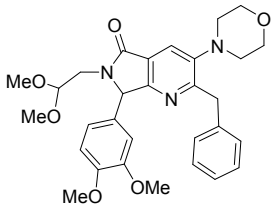


^{1}H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16a**

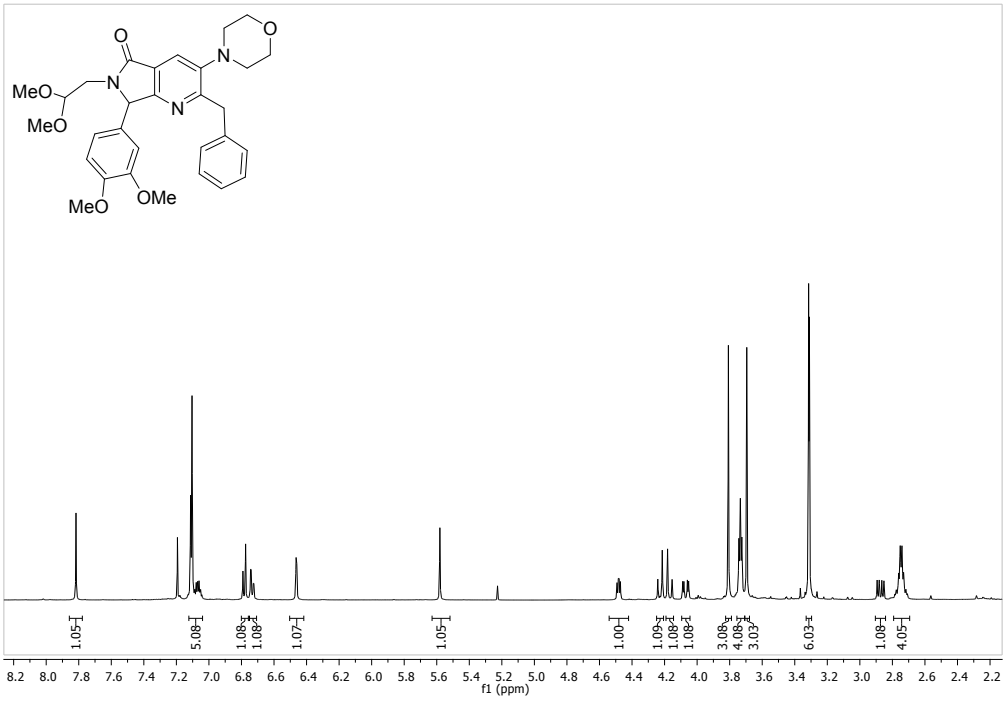


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16a**

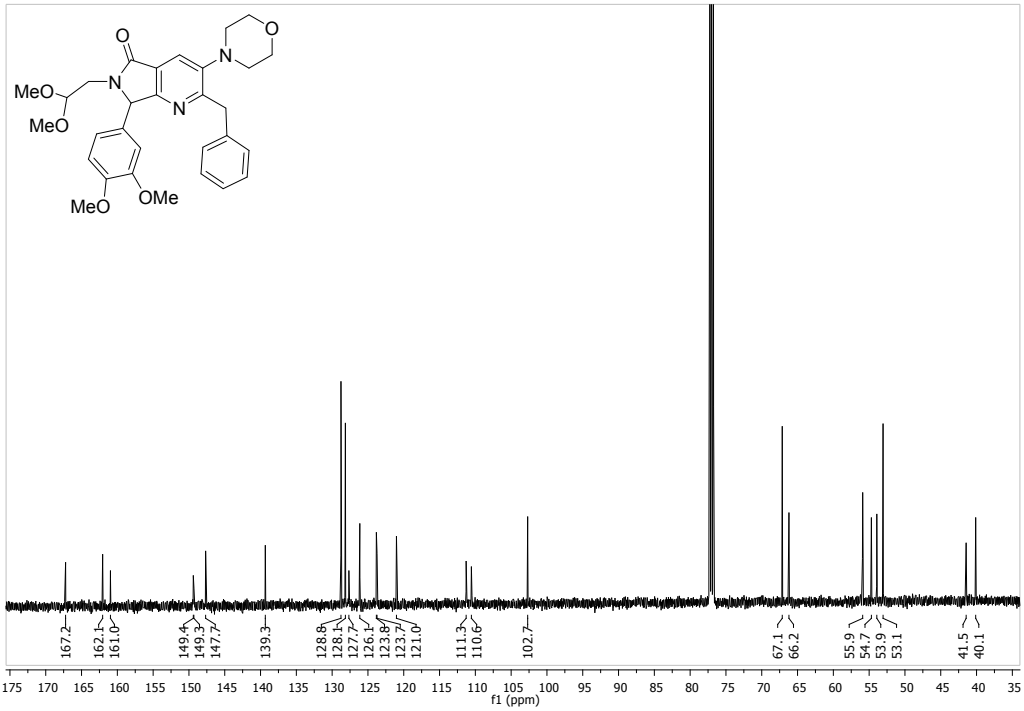
2-benzyl-6-(2,2-dimethoxyethyl)-7-(3,4-dimethoxyphenyl)-3-morpholino-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**16b**)



According to ***GP1-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), 3,4-dimethoxybenzaldehyde (113.7 mg, 0.685 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (200.6 mg, 0.822 mmol) and maleic anhydride (94.0 gm, 0.959 mmol) were reacted together in PhMe (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **16b** (160.6 mg, 44%) as yellow gum; R_f = 0.21 (AcOEt/Hexanes, 2/1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.23–7.10 (m, 5H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.82–6.78 (m, 1H), 6.53 (d, *J* = 1.9 Hz, 1H), 5.65 (s, 1H), 4.57–4.53 (m, 1H), 4.30 (d, *J* = 13.9 Hz, 1H), 4.24 (d, *J* = 13.9 Hz, 1H), 4.14 (dd, *J* = 14.4, 3.8 Hz, 1H), 3.88 (s, 3H), 3.83–3.79 (m, 4H), 3.77 (s, 3H), 3.40–3.36 (m, 6H), 2.95 (dd, *J* = 14.4, 6.5 Hz, 1H), 2.87–2.78 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 167.2, 162.1, 161.0, 149.4, 149.3, 147.7, 139.3, 128.8, 128.1, 127.7, 126.1, 123.8, 123.7, 121.0, 111.3, 110.6, 102.7, 67.1, 66.2, 55.9 (2), 54.7, 53.9, 53.1, 41.5, 40.1; HRMS: m/z calcd. for: $C_{30}H_{36}N_3O_6$ = 534.2599, found: 534.2574.

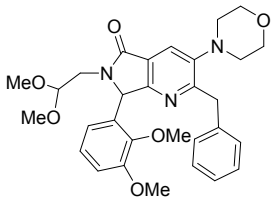


^{1}H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16b**

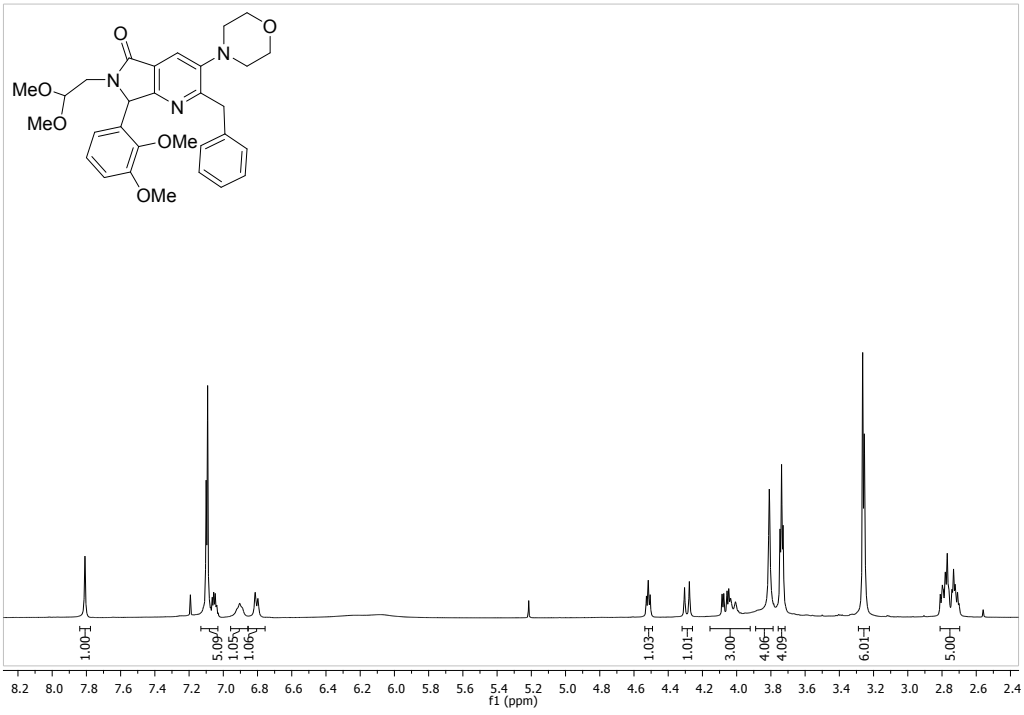


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16b**

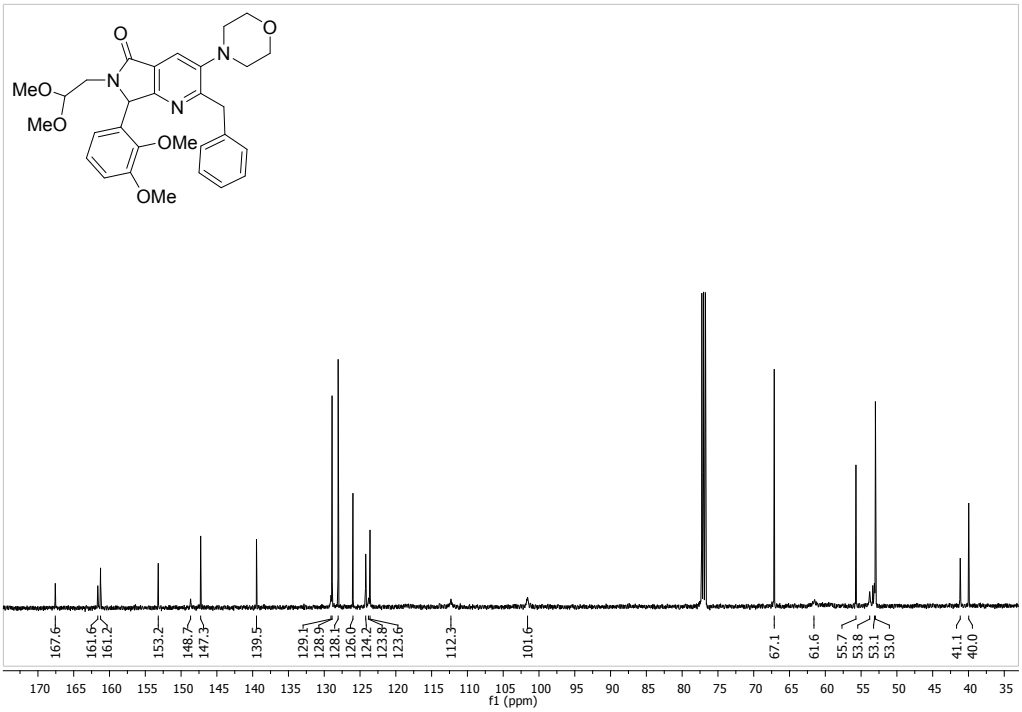
2-benzyl-6-(2,2-dimethoxyethyl)-7-(2,3-dimethoxyphenyl)-3-morpholino-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridin-5-one (**16c**)



According to ***GP1-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), 2,3-dimethoxybenzaldehyde (113.7 mg, 0.685 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (200.6 mg, 0.822 mmol) and maleic anhydride (94.0 gm, 0.959 mmol) were reacted together in PhMe (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **16c** (163.3 mg, 45%) as yellow gum; R_f = 0.39 (AcOEt/Hexanes, 2/1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (s, 1H), 7.13–7.03 (m, 5H), 6.96–6.86 (m, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 4.54–4.49 (m, 1H), 4.29 (d, *J* = 14.1 Hz, 1H), 4.14–3.92 (m, 3H), 3.89–3.79 (m, 4H), 3.76–3.71 (m, 4H), 3.29–3.23 (m, 6H), 2.81–2.70 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 167.6, 161.6, 161.2, 153.2, 148.7, 147.3, 139.5, 129.1, 128.9, 126.0, 124.2, 123.8, 123.6, 112.3, 101.6, 112.3, 101.6, 67.1, 61.4, 61.6, 55.7, 53.8, 53.1, 53.0, 41.1, 40.0; HRMS: m/z calcd. for: $C_{30}H_{36}N_3O_6$ = 534.2599, found: 534.2549.

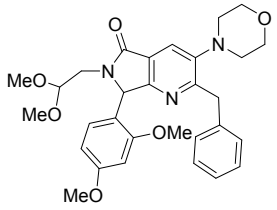


^{1}H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16c**

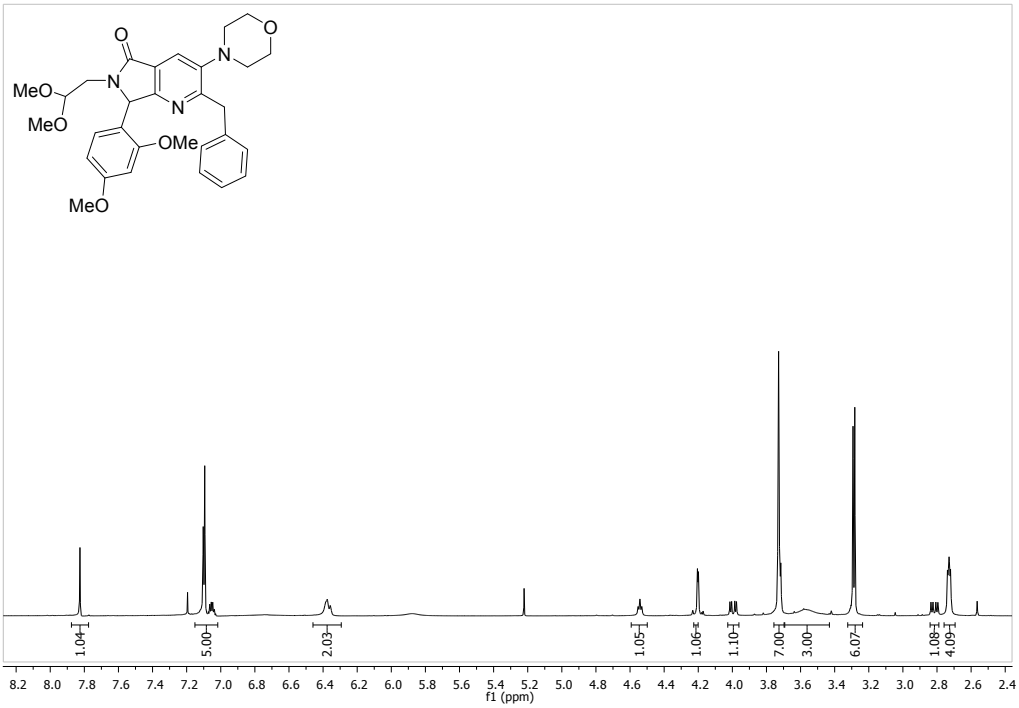


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16c**

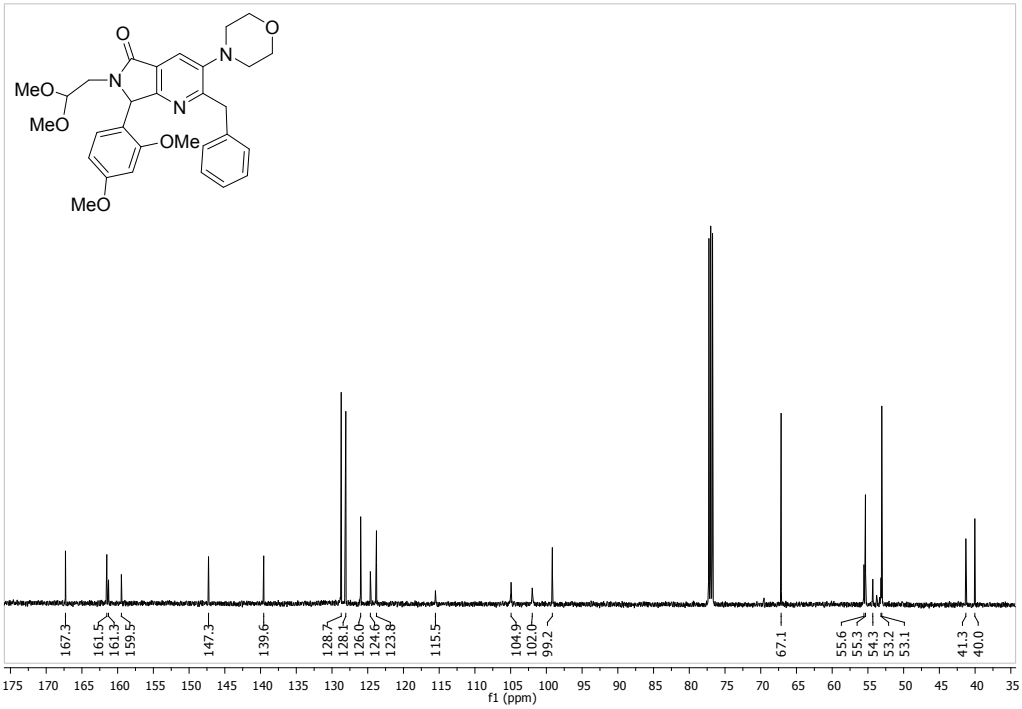
2-benzyl-6-(2,2-dimethoxyethyl)-7-(2,4-dimethoxyphenyl)-3-morpholino-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**16d**)



According to ***GP1-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), 2,4-dimethoxybenzaldehyde (113.7 mg, 0.685 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (200.6 mg, 0.822 mmol) and maleic anhydride (94.0 gm, 0.959 mmol) were reacted together in PhMe (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **16d** (171.6 mg, 47%) as yellow gum; R_f = 0.30 (AcOEt/Hexanes, 2/1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 7.15–7.03 (m, 5H), 6.37 (d, *J* = 8.7 Hz, 2H), 4.59–4.50 (m, 1H), 4.25–4.20 (m, 2H), 3.99 (dd, *J* = 14.4, 5.0 Hz, 1H), 3.76–3.70 (m, 7H), 3.69–3.44 (m, 3H), 3.32–3.23 (m, 6H), 2.82 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.76–2.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 167.3, 161.5, 161.3, 159.5, 147.3, 139.6, 128.7, 128.1, 126.0, 124.6, 123.8, 115.5, 104.9, 102.0, 99.2, 67.1, 55.6, 55.3, 54.3, 53.2, 53.1, 41.3, 40.0; HRMS: m/z calcd. for: $C_{30}H_{36}N_3O_6$ = 534.2599, found: 534.2577.



^{1}H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16d**

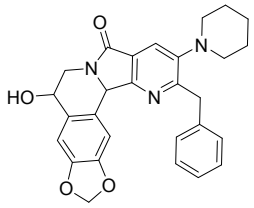


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **16d**

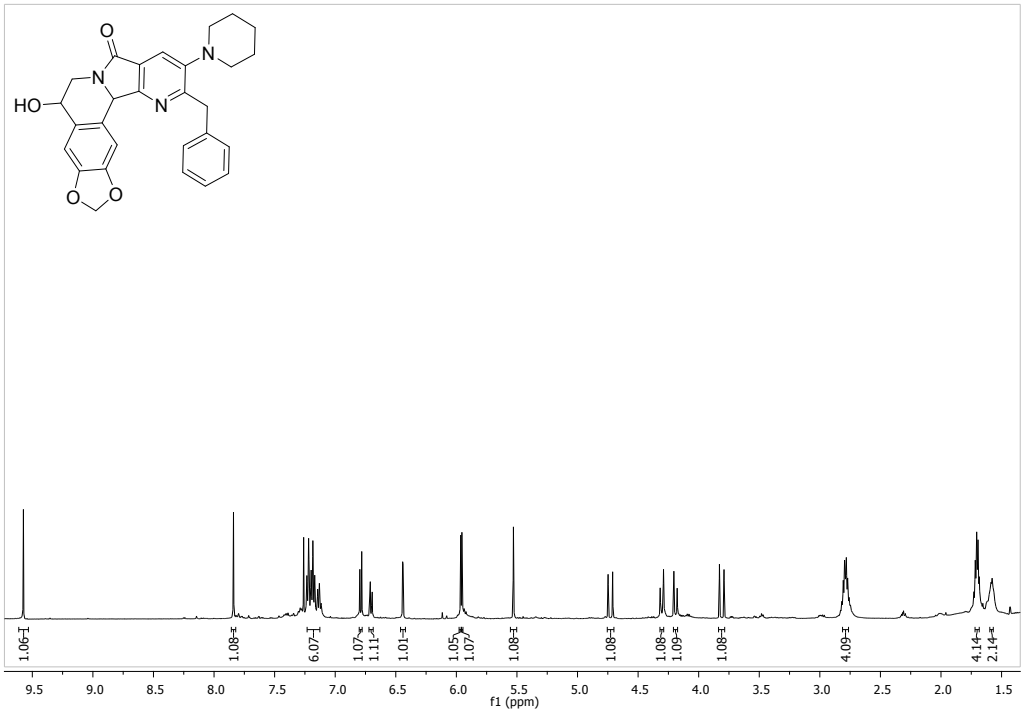
Synthesis and characterization of the (±)-Nuevamine Aza-Analogues 4a-d

General Procedure - Step 2 (GP1-S2): A solution of the corresponding pyrrolo[3,4-*b*]pyridin-5-one **16a-d** (1.00 equiv.) in dioxane/HCl [6 N],1/2, v/v (3.0 mL) was placed in a 10 mL round bottom flask. The mixture was stirred overnight in dark at room temperature under N_2 atmosphere. The reaction mixture was neutralized by a concentrated aq. solution of $NaHCO_3$ (3 x 25 mL) and extracted with EtOAc (3 x 25 mL). The organic layer was washed with brine (3 × 15 mL). Finally, it was dried with Na_2SO_4, and the solvent was evaporated to dryness. The crude was purified on a silica-gel preparative plate (20 x 20 cm) using mixtures of hexanes–EtOAc as mobile phase to afford the corresponding (±)-Nuevamine Aza-Analogs **4a-d**.

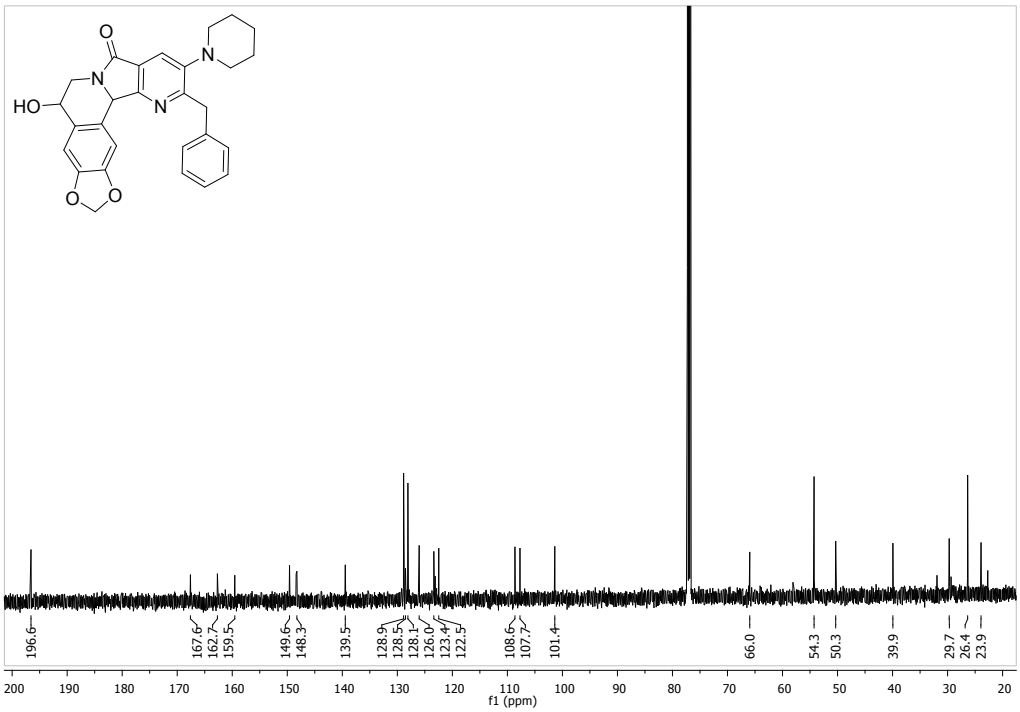
11-benzyl-5-hydroxy-10-(piperidin-1-yl)-5,12*b*-dihydro-[1,3]dioxolo[4,5-*g*]pyrido[2',3':3,4]pyrrolo[2,1-*a*]isoquinolin-8(6*H*)-one (**4a**)



According to ***GP1-S2***, pyrrolo[3,4-*b*]pyridin-5-one **16a** (55.0 mg, 0.107 mmol) was dissolved in dioxane/HCl [6 N],1/2, v/v (3.0 mL) and stirred overnight to afford the (±)-Nuevamine Aza-analogue **4a** (32.1 mg, 64%) as orange gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.84 (s, 1H), 7.23 (d, *J* = 7.1 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.44 (s, 1H), 5.96 (d, *J* = 6.0 Hz, 2H), 5.53 (s, 1H), 4.73 (d, *J* = 18.9 Hz, 1H), 4.30 (d, *J* = 13.7 Hz, 1H), 4.19 (d, *J* = 13.7 Hz, 1H), 3.81 (d, *J* = 18.9 Hz, 1H), 2.83–2.74 (m, 4H), 1.71 (m, 4H), 1.61–1.55 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 196.6, 167.6, 162.7, 159.5, 149.6, 148.4, 139.5, 128.9, 128.5, 128.1, 126.0, 123.4, 122.5, 108.6, 107.7, 101.4, 66.0, 54.3, 50.3, 39.9, 29.7, 26.4, 23.9; HRMS: m/z calcd. for: $C_{28}H_{28}N_3O_4$ = 470.2074, found: 470.2043.

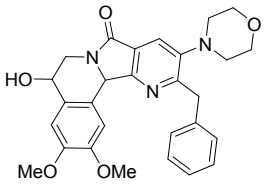


^{1}H NMR spectra of the (±)-Nuevamine Aza-analogue **4a**

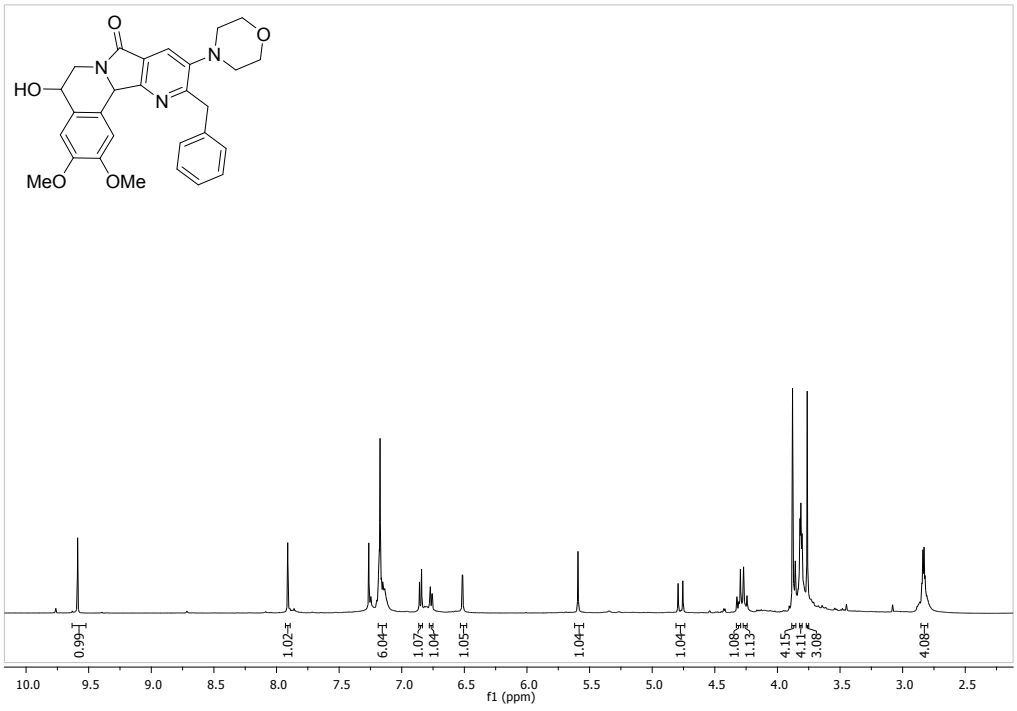


^{13}C NMR spectra of the (±)-Nuevamine Aza-analogue **4a**

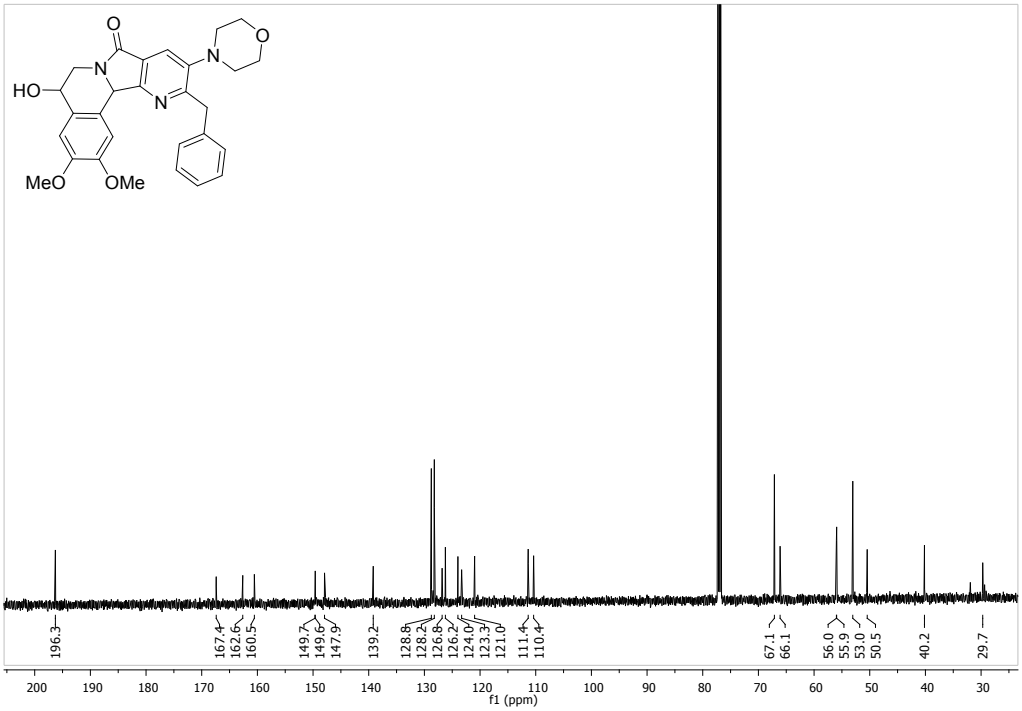
11-benzyl-5-hydroxy-2,3-dimethoxy-10-morpholino-5,12*b*-dihydropyrido[2',3':3,4] pyrrolo[2,1-*a*]isoquinolin-8(6*H*)-one (**4b**)



According to ***GP1-S2***, pyrrolo[3,4-*b*]pyridin-5-one **16b** (60.0 mg, 0.112 mmol) was dissolved in dioxane/HCl [6 N],1/2, v/v (3.0 mL) and stirred overnight to afford the (±)-Nuevamine Aza-analogue **4b** (46.4 mg, 85%) as orange gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.59 (s, 1H), 7.91 (s, 1H), 7.21–7.13 (m, 6H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.78–6.75 (m, 1H), 6.51 (d, *J* = 1.9 Hz, 1H), 5.59 (s, 1H), 4.77 (d, *J* = 12.9 Hz, 1H), 4.31 (d, *J* = 13.9 Hz, 1H), 4.26 (d, *J* = 13.8 Hz, 1H), 3.90–3.73 (m, 11H), 2.89–2.79 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 196.3, 167.4, 162.6, 160.5, 149.7, 149.6, 147.9, 139.2, 128.8, 128.2, 126.8, 126.2, 124.0, 123.3, 121.0, 111.4, 110.4, 67.1, 66.1, 56.0, 55.9, 53.1, 50.5, 40.2, 29.7; HRMS: m/z calcd. for: $C_{28}H_{30}N_3O_5$ = 488.2180, found: 488.2166.

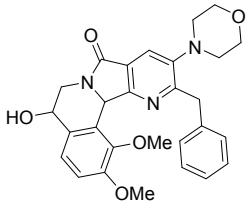


^{1}H NMR spectra of the (±)-Nuevamine Aza-analogue **4b**

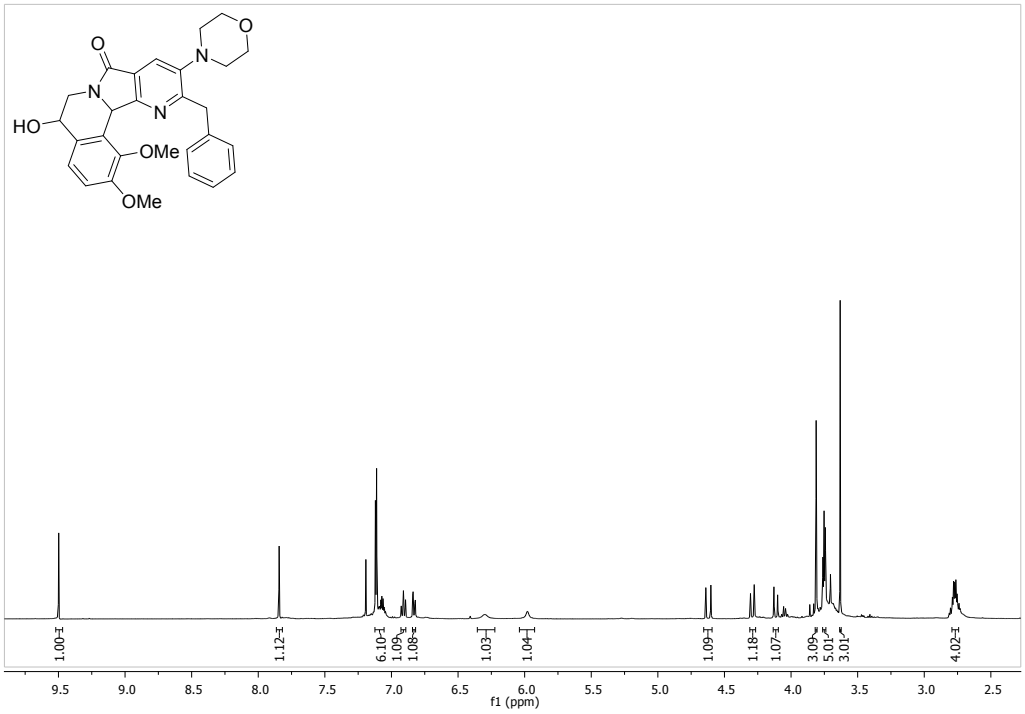


^{13}C NMR spectra of the (±)-Nuevamine Aza-analogue **4b**

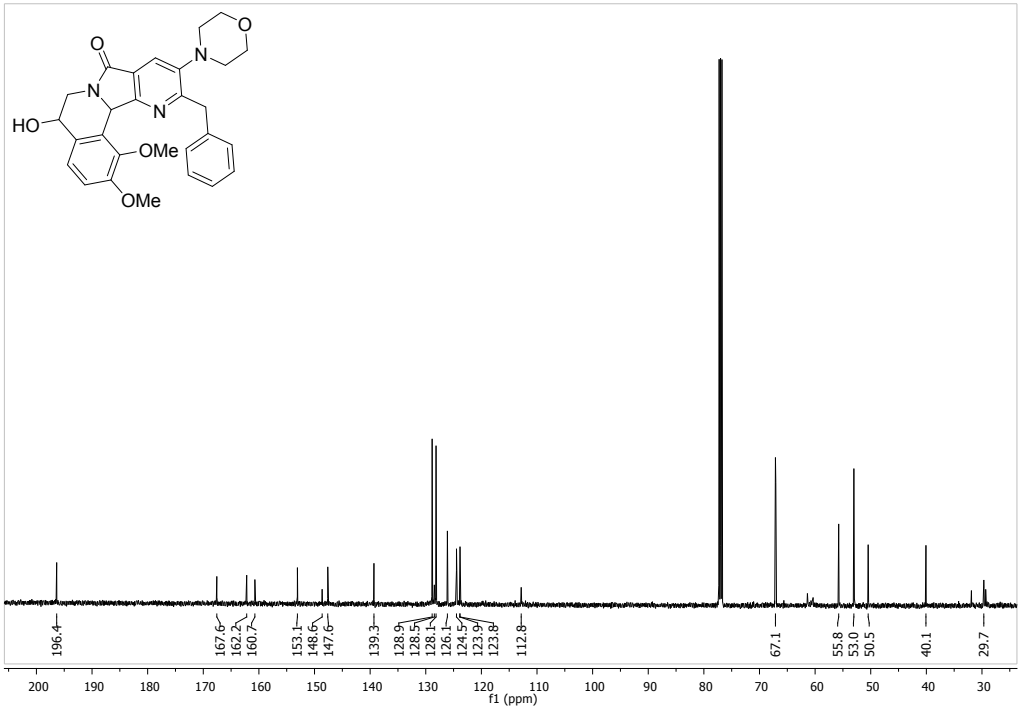
11-benzyl-5-hydroxy-1,2-dimethoxy-10-morpholino-5,12*b*-dihydropyrido[2',3':3,4]pyrrolo[2,1-*a*]isoquinolin-8(6*H*)-one (**4c**)



According to ***GP1-S2***, pyrrolo[3,4-*b*]pyridin-5-one **16c** (50.0 mg, 0.094 mmol) was dissolved in dioxane/HCl [6 N],1/2, v/v (3.0 mL) and stirred overnight to afford the (±)-Nuevamine Aza-analogue **4c** (33.4 mg, 73%) as orange gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.50 (s, 1H), 7.84 (s, 1H), 7.14–7.02 (m, 5H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.84–6.82 (m, 1H), 6.30 (s, 1H), 5.98 (s, 1H), 4.62 (d, *J* = 18.8 Hz, 1H), 4.29 (d, *J* = 14.0 Hz, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.77–3.74 (m, 5H), 3.63 (s, 3H), 2.83–2.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 196.4, 167.6, 162.2, 160.7, 153.1, 148.6, 147.6, 139.3, 128.9, 128.5 128.1 (2), 126.1, 124.5, 123.9, 123.8, 112.8, 67.1 (2), 55.8, 53.0, 50.5, 40.1, 29.7; HRMS: m/z calcd. for: $C_{28}H_{30}N_3O_5$ = 488.2180, found: 488.2147.

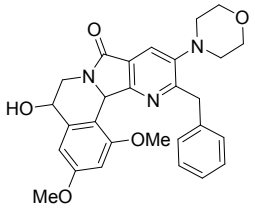


^{1}H NMR spectra of the (±)-Nuevamine Aza-analogue **4c**

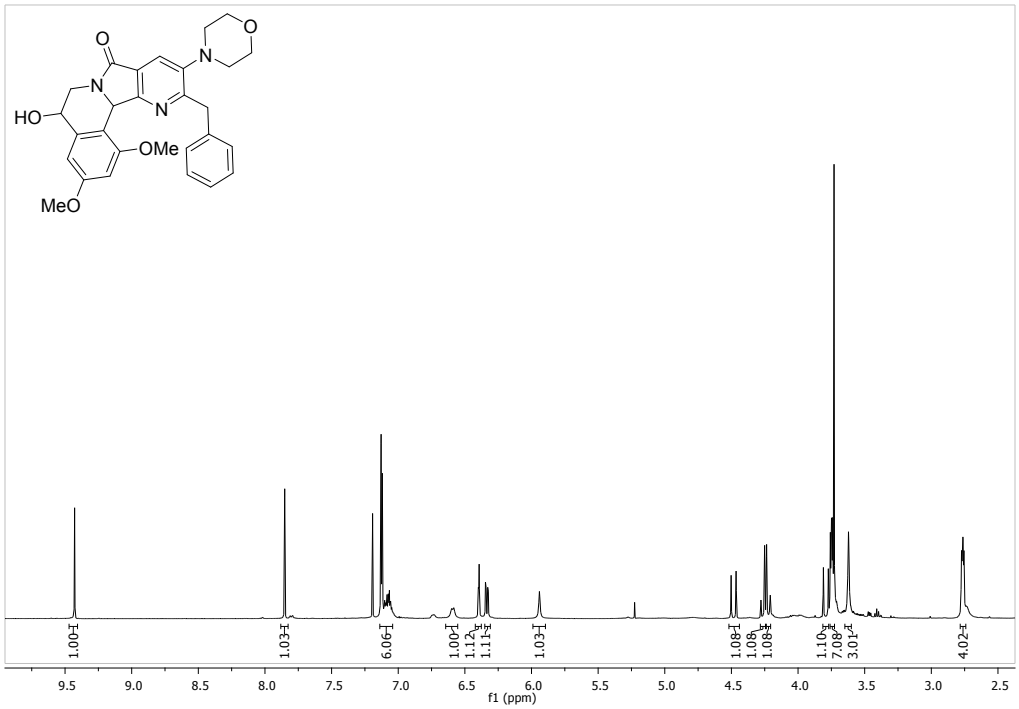


^{13}C NMR spectra of the (±)-Nuevamine Aza-analogue **4c**

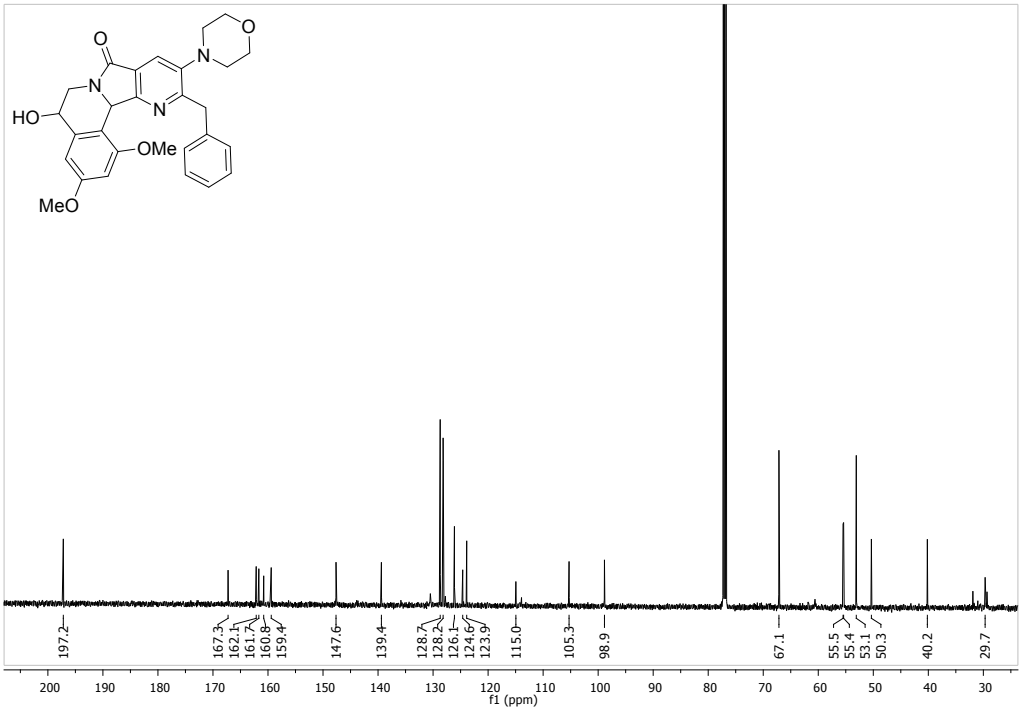
11-benzyl-5-hydroxy-1,3-dimethoxy-10-morpholino-5,12*b*-dihydropyrido[2',3':3,4]pyrrolo[2,1-*a*]isoquinolin-8(6*H*)-one (**4d**)



According to ***GP1-S2***, pyrrolo[3,4-*b*]pyridin-5-one **16d** (50.0 mg, 0.094 mmol) was dissolved in dioxane/HCl [6 N],1/2, v/v (3.0 mL) and stirred overnight to afford the (±)-Nuevamine Aza-analogue **4d** (29.3 mg, 64%) as orange gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.43 (s, 1H), 7.85 (s, 1H), 7.16–7.02 (m, 6H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.35–6.31 (m, 1H), 5.94 (s, 1H), 4.48 (d, *J* = 18.6 Hz, 1H), 4.26 (d, *J* = 13.8 Hz, 1H), 4.22 (d, *J* = 13.8 Hz, 1H), 3.79 (d, *J* = 18.6 Hz, 1H), 3.76–3.72 (m, 7H), 3.62 (s, 3H), 2.83–2.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.2, 167.3, 162.1, 161.7, 160.8, 159.4, 147.6, 139.4, 128.7, 128.2, 126.1, 124.6, 123.9, 115.0, 105.0, 98.9, 67.1, 55.5, 55.4, 53.1, 50.3, 40.2, 29.7; HRMS: m/z calcd. for: $C_{28}H_{30}N_3O_5$ = 488.2180, found: 488.2174.



^{1}H NMR spectra of the (±)-Nuevamine Aza-analogue **4d**

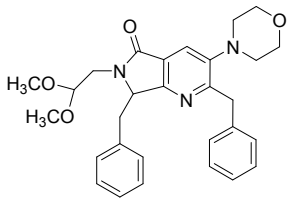


^{13}C NMR spectra of the (±)-Nuevamine Aza-analogue **4d**

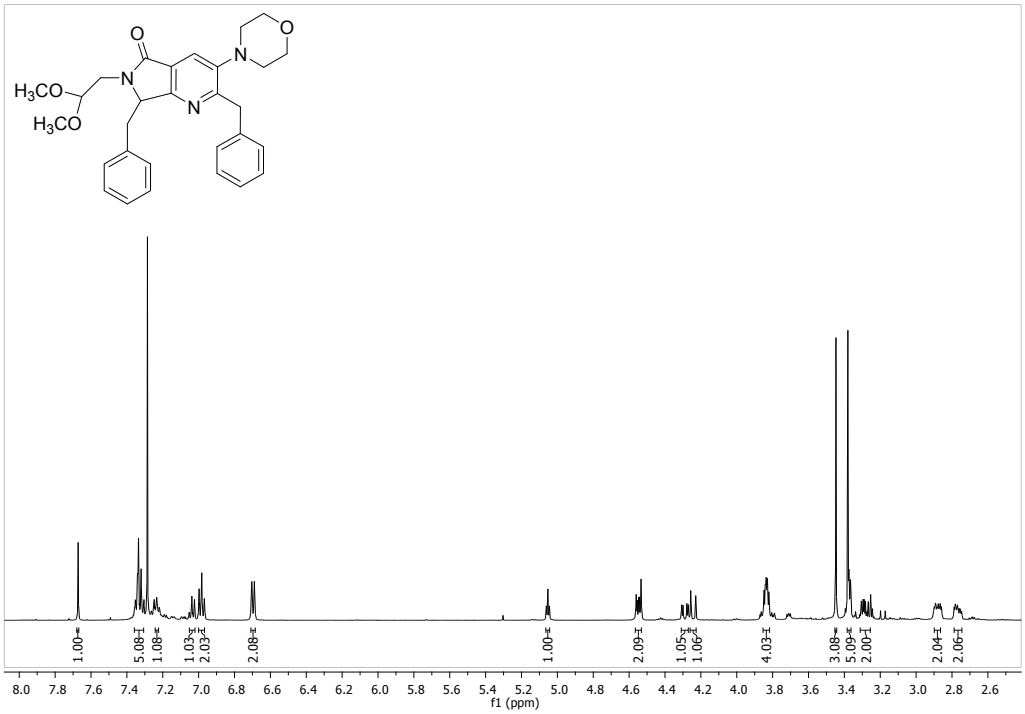
Synthesis and characterization of the pyrrolo[3,4-*b*]pyridin-5-ones 23a-c

General Procedure 2 - Step 1 *(**GP2-S1**):* 2,2-dimethoxyethan-1-amine (1.00 equiv.) and the corresponding aldehyde (1.20 equiv.) were placed in a 10 mL sealed CEM Discover™ MW reaction tube and diluted in dry PhH (2.0 mL). Then, the mixture was MW-heated (65 °C, 100 W) for 12 minutes, and $Sc(OTf)_3$ (0.03 equiv.) was added. The mixture was MW-heated (65 °C, 100 W) for 12 minutes, and the corresponding isocyanide (1.20 equiv.) was added. The mixture was MW-heated (80 °C, 100 W) for 15 minutes, and maleic anhydride (1.40 equiv.) was added. Finally, the reaction mixture was MW-heated (70 °C, 100 W) for 30 minutes, cooled at room temperature and the solvent was removed until dryness. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with a concentrated aq. solution of $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL). The organic layer was dried with Na_2SO_4, filtered using celite-pad and the solvent was removed until dryness. The crude was purified by silica gel column chromatography using mixtures of Hexanes/EtOAc as mobile phase to afford the corresponding pyrrolo[3,4-*b*]pyridin-5-ones **23a-c**.

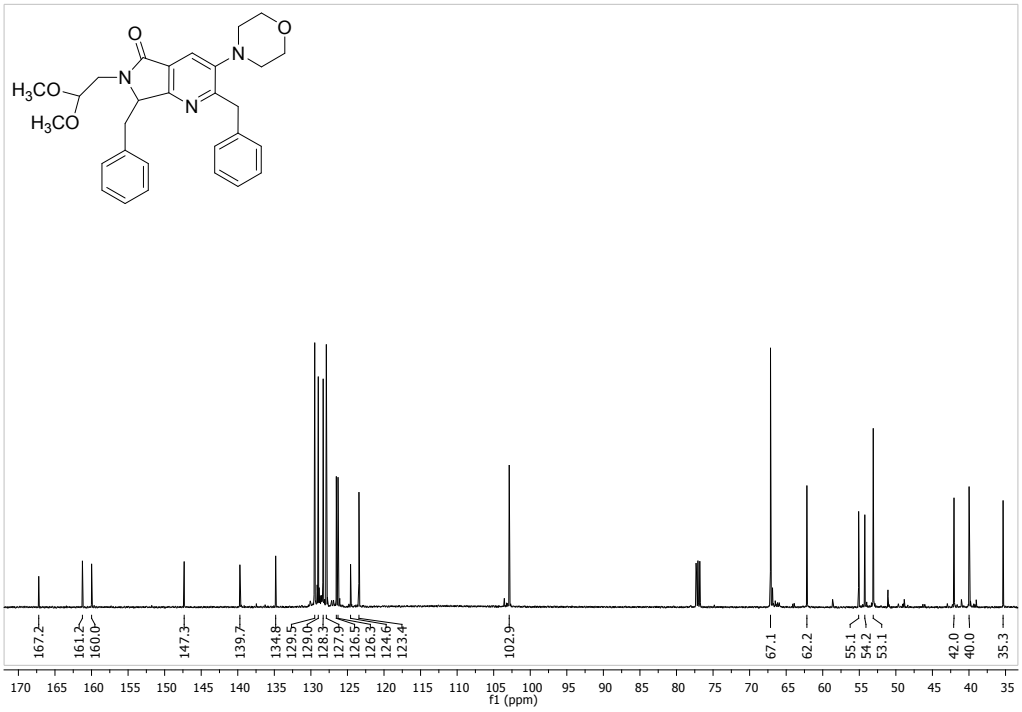
2,7-dibenzyl-6,7-dihydro-6-(2,2-dimethoxyethyl)-3-morpholinopyrrolo[3,4-*b*]pyridin-5-one (**23a**)



According to ***GP2-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), phenylacetaldehyde (98.6 mg, 0.822 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (200.5 mg, 0.822 mmol) and maleic anhydride (93.9 mg, 0.959 mmol) were reacted together in PhMe (2.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **23a** (133.4 mg, 40%) as yellow oil; R_f = 0.47 (Hexanes/AcOEt, 2/1, v/v); FT-IR (cm^{-1}) ν_{max} 1683, 1122, 1053, 700; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.36–7.30 (m, 5H), 7.27–7.22 (m, 1H), 7.06–7.02 (m, 1H), 6.99–6.96 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 5.05–5.04 (m, 1H), 4.56–4.53 (m, 2H), 4.29 (dd, *J* = 14.4, 3.7 Hz, 1H), 4.24 (d, *J* = 13.8 Hz, 1H), 3.88–3.83 (m, 4H), 3.44 (s, 3H), 3.39–3.36 (m, 5H), 3.31–3.24 (m, 2H), 2.91–2.85 (m, 2H), 2.79–2.74 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 167.2, 161.2, 160.0, 147.3, 139.7, 134.8, 129.5, 129.0, 128.3, 127.9, 126.5, 126.3, 124.6, 123.4, 102.9, 67.1, 62.2, 55.1, 54.4, 53.1, 42.0, 40.0, 35.3; HRMS: m/z calcd. for: $C_{29}H_{33}N_3O_4$ = 487.2471, found: 487.2515.

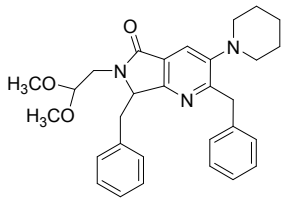


^1H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **23a**

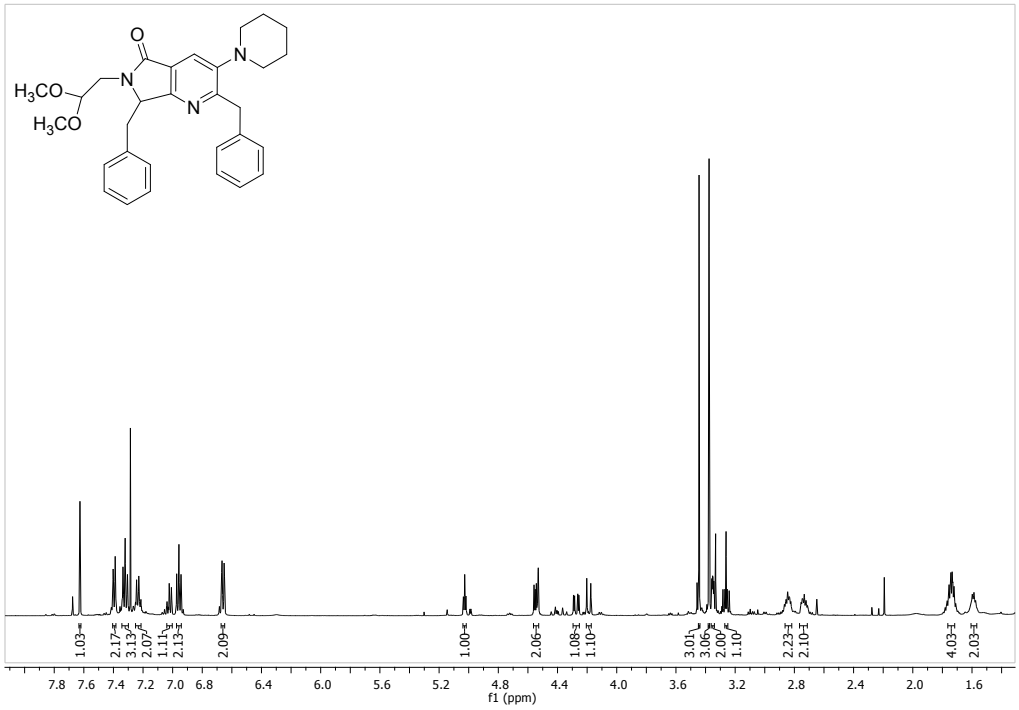


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **23a**

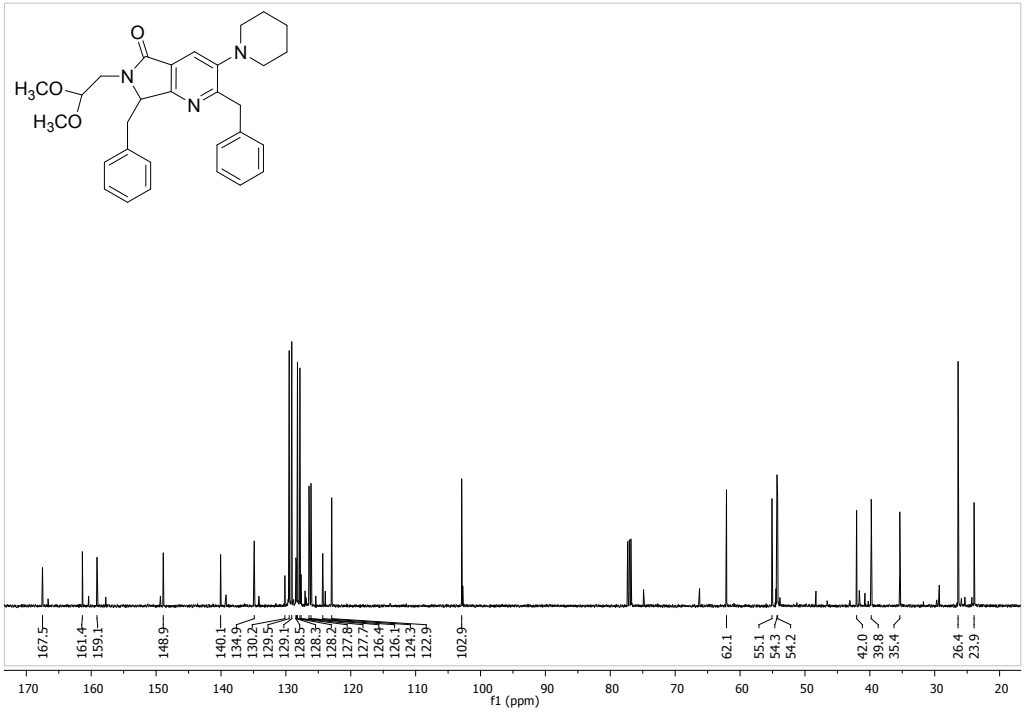
2,7-dibenzyl-6,7-dihydro-6-(2,2-dimethoxyethyl)-3-(piperidin-1-il)pyrrolo[3,4-*b*]pyridin-5-one (**23b**)



According to ***GP2-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), phenylacetaldehyde (98.6 mg, 0.822 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-3-phenyl-1-(piperidin-1-yl)propan-1-one (198.9 mg, 0.822 mmol) and maleic anhydride (93.9 mg, 0.959 mmol) were reacted together in PhMe (2.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **23b** (56.5 mg, 17%) as yellow oil; R_f = 0.45 (Hexanes/AcOEt, 2/1, v/v); FT-IR (cm^{-1}) ν_{max} 1690, 1599, 1440, 1259, 1113, 1068; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (s, 1H), 7.41–7.38 (m, 2H), 7.35–7.30 (m, 3H), 7.25–7.21 (m, 2H), 7.04–7.00 (m, 1H), 6.98–6.93 (m, 2H), 6.68–6.65 (m, 2H), 5.03 (t, *J* = 4.3 Hz, 1H), 4.56–4.53 (m, 2H), 4.27 (dd, *J* = 14.3, 3.7 Hz, 1H), 4.19 (d, *J* = 13.6 Hz, 1H), 3.45 (s, 3H), 3.38 (s, 3H), 3.36–3.34 (m, 2H), 3.29–3.24 (m, 1H), 2.87–2.79 (m, 2H), 2.76–2.71 (m, 2H), 1.78–1.70 (m, 4H), 1.62–1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.5, 161.4, 159.1, 148.9, 140.1, 134.9, 130.2, 129.5, 129.1, 128.5, 128.3, 128.2, 127.8, 127.7, 126.4, 126.1, 124.3, 122.9, 102.9, 62.1, 55.1, 54.3, 54.2, 42.0, 39.8, 35.4, 26.4, 23.9.

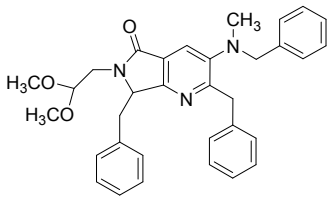


^{1}H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **23b**

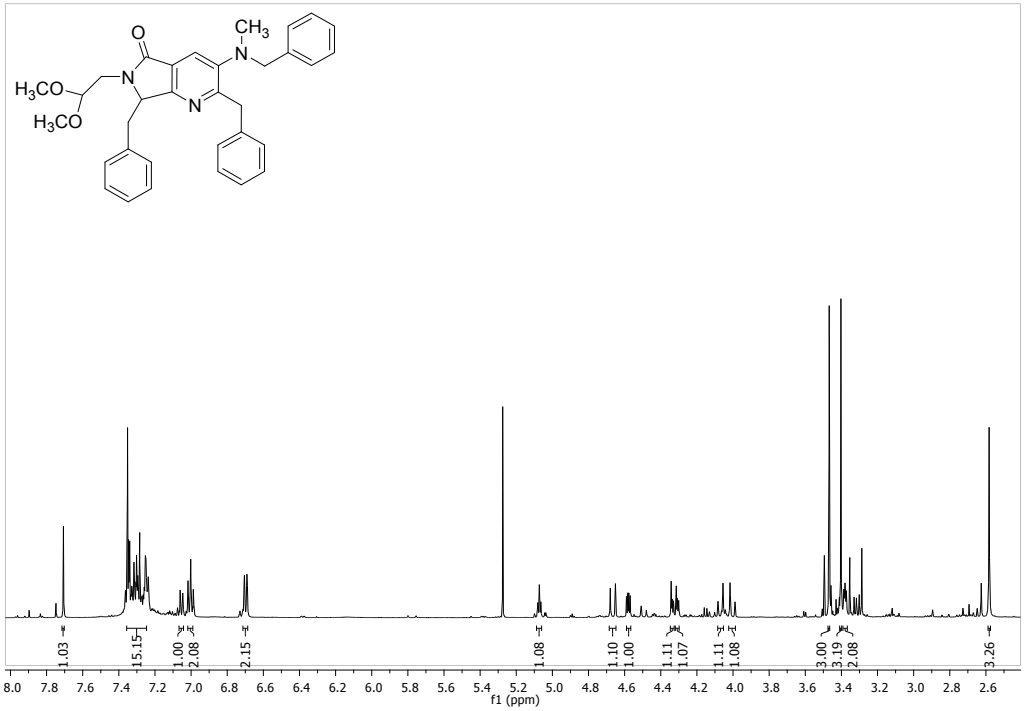


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **23b**

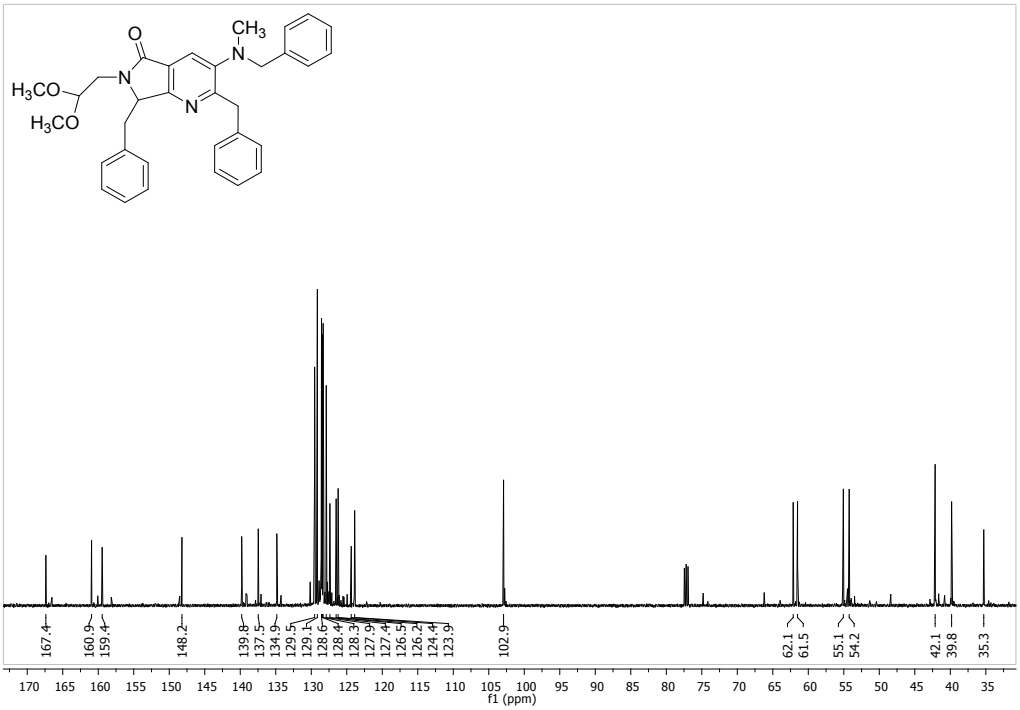
3-(*N*-benzyl-*N*-methylamino)-2,7-dibenzyl-6,7-dihydro-6-(2,2-dimethoxyethyl)pyrrolo[3,4-*b*]piridin-5-one (**23c**)



According to ***GP2-S1***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), phenylacetaldehyde (98.6 mg, 0.822 mmol), scandium triflate (10.1 mg, 0.021 mmol), N-benzyl-2-isocyano-N-methyl-3-phenylpropanamide (228.5 mg, 0.822 mmol) and maleic anhydride (93.9 mg, 0.959 mmol) were reacted together in PhMe (2.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **23c** (128.4 mg, 36%) as yellow oil; R_f = 0.42 (Hexanes/AcOEt, 2/1, v/v); FT-IR (cm^{-1}) ν_{max} 1688, 1446, 1259, 1121, 1026; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.37–7.23 (m, 15 H), 7.07–7.04 (m, 1H), 7.02–6.98 (m, 2H), 6.72–6.98 (m, 2H), 5.07 (t, *J* = 4.3 Hz, 1H), 4.67 (d, *J* = 14.2 Hz, 1H), 4.58 (dd, *J* = 6.6, 3.8 Hz, 1H), 4.35–4.33 (m, 1H), 4.32–4.30 (m, 1H), 4.07 (d, *J* = 13.9 Hz, 1H), 4.00 (d, *J* = 13.9 Hz, 1H), 3.47 (s, 3H), 3.40 (s, 3H), 3.39–3.37 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.4, 160.9, 159.4, 148.2, 139.8, 137.5, 134.9, 129.5, 129.1, 128.6, 128.4, 128.3, 127.9, 127.4, 126.5, 126.2, 124.4, 123.9, 102.9, 62.1, 61.5, 55.1, 54.2, 42.1, 39.8, 35.3.



^1H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **23c**

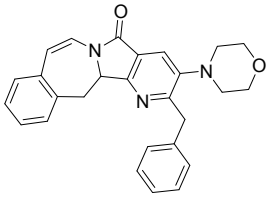


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **23c**

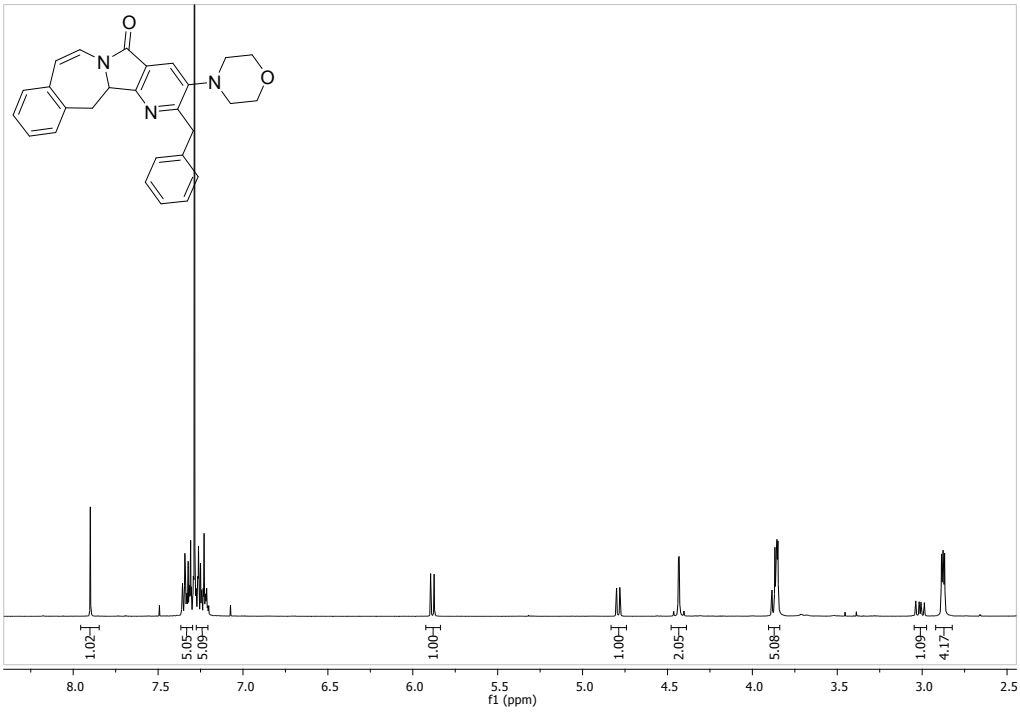
Synthesis and characterization of the (±)-Lennoxamine Aza-Analogues 5a-d

General procedure 2 - Step 2 (GP2-S2): A solution of the corresponding pyrrolo[3,4-*b*]pyridin-5-one **23a-e** (1.00 equiv.) in CH_3COOH/H_2SO_4, 1/2, v/v (3.0 mL) was placed in a 10 mL round bottom flask. The mixture was stirred at room temperature for 24 hours. The reaction mixture was neutralized by a concentrated aq. solution of $NaHCO_3$ (3 x 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was washed with brine (3 × 15 mL). Finally, it was dried with Na_2SO_4, and the solvent was evaporated to dryness. The crude was purified on a silica-gel preparative plate (20 x 20 cm) using mixtures of hexanes–EtOAc as mobile phase to afford the corresponding (±)-Lennoxamine Aza-Analogues **5a-e**.

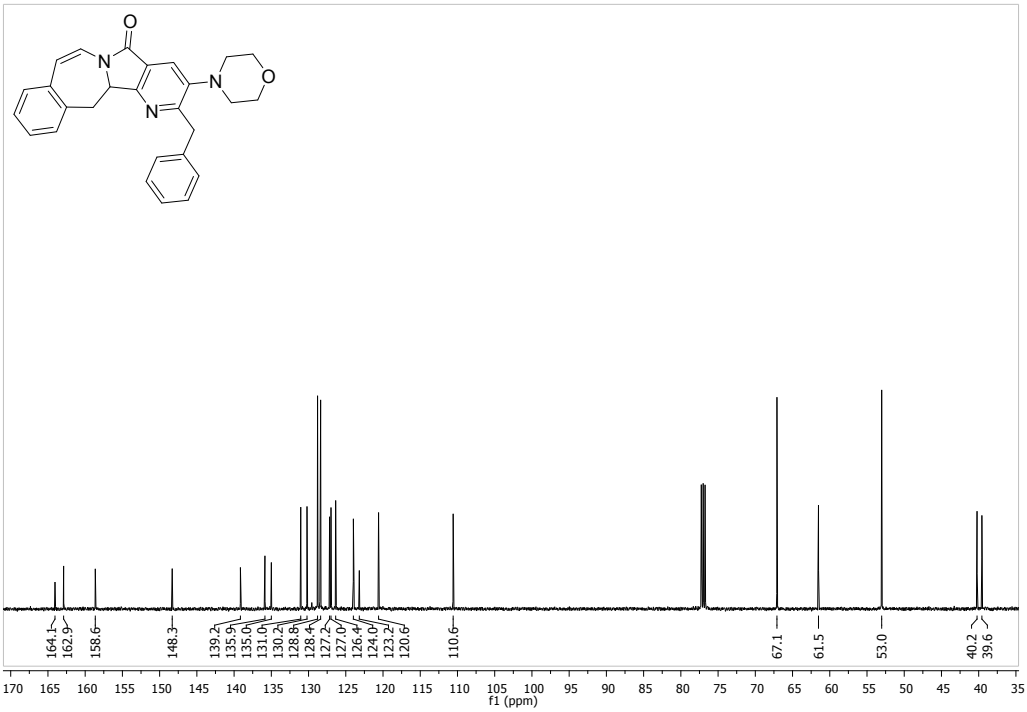
2-benzyl-3-morpholino-13,13*a*-dihydro-5*H*-benzo[*d*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azepin-5-one (**5a**)



According to ***GP2-S2***, pyrrolo[3,4-*b*]pyridin-5-one **23a** (45.0 mg, 0.092 mmol) was dissolved in CH_3COOH/H_2SO_4, 1/2, v/v (3.0 mL) and stirred for 24 hours to afford the (±)-Lennoxamine Aza-analogue **5a** (11.7 mg, 30%) as yellow solid; mp = 110 ºC; R_f = 0.40 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 1710, 1637, 1440, 1358, 1107, 740; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.37–7.30 (m, 5H), 7.27–7.20 (m, 5H), 5.88 (d, *J* = 10.3 Hz, 1H), 4.79 (d, 1H, *J* = 9.4 Hz), 4.48–4.39 (m, 2H), 4.48–4.39 (m, 5H), 3.00 (dd, 1H, *J* = 15.3, 9.9 Hz), 2.92–2,82 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.1, 162.9, 158.6, 148.3, 139.2, 135.9, 135.0, 131.0, 130.2, 128.8, 128.4, 127.2, 127.0, 126.4, 124.0, 123.2, 120.6, 110.6, 67.1, 61.5, 53.0, 40.2, 39.6.

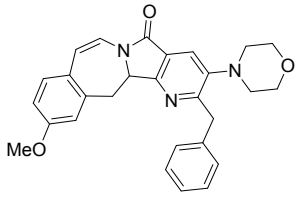


^{1}H NMR spectra of the (±)-Lennoxamine Aza-analogue **5a**

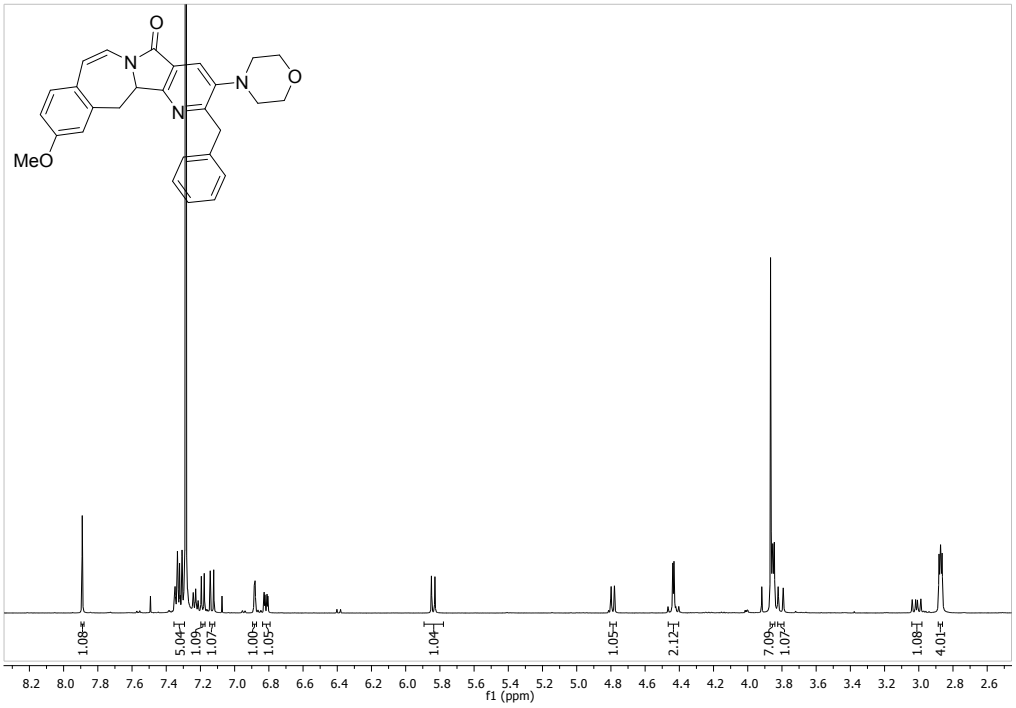


^{13}C NMR spectra of the (±)-Lennoxamine Aza-analogue **5a**

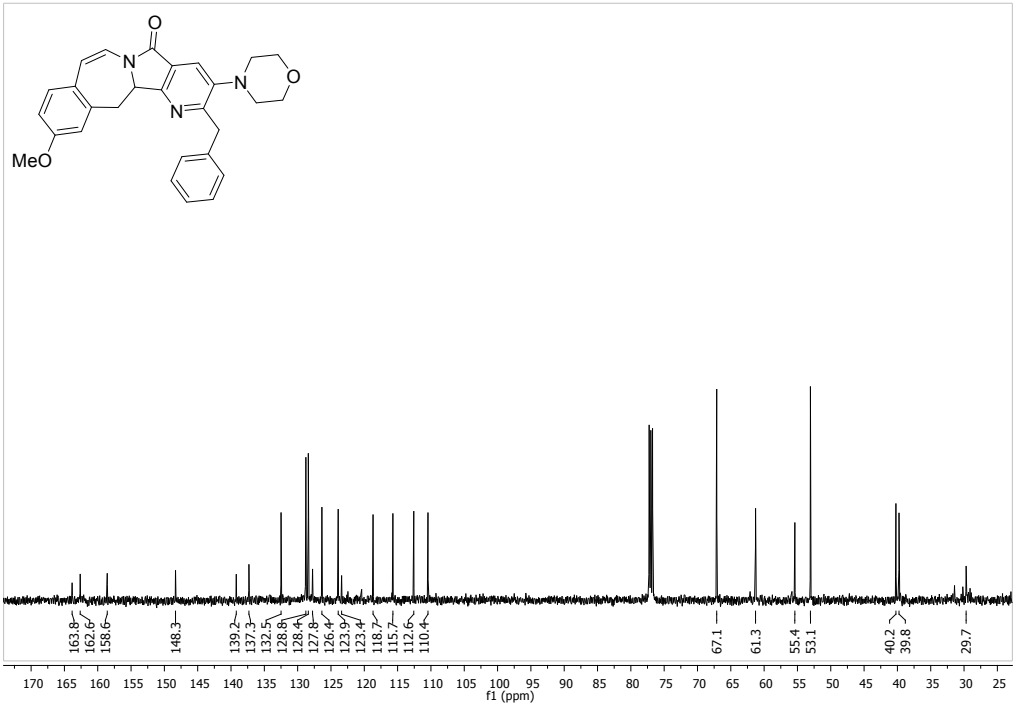
2-benzyl-11-methoxy-3-morpholino-13,13*a*-dihydro-5*H*-benzo[*d*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azepin-5-one (**5b**)



According to ***GP2-S2***, pyrrolo[3,4-*b*]pyridin-5-one **23b** (50.0 mg, 0.096 mmol) was dissolved in CH_3COOH/H_2SO_4, 1/2, v/v (3.0 mL) and stirred for 24 hours to afford the (±)-Lennoxamine Aza-analogue **5b** (32.2 mg, 74%) as yellow solid; mp = 130 °C; R_f = 0.42 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 1678, 1438, 1250, 1060, 1024, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.39–7.29 (m, 5H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 10.2 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.84 (d, *J* = 10.3 Hz, 1H), 4.79 (d, *J* = 9.5 Hz, 1H), 4.47–4.40 (m, 2H), 3.88–3.84 (m, 7H), 3.81 (d, *J* = 14.9 Hz, 1H), 3.01 (dd, *J* = 15.3, 10.0 Hz, 1H), 2.89–2.86 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.8, 162.6, 158.6 (2), 148.3, 139.2, 137.3, 132.5, 128.8, 128.4, 127.8, 126.4, 123.9, 123.4, 118.7, 115.7, 112.6, 110.4, 67.1, 61.3, 55.4, 53.1, 40.2, 39.8, 29.7; HRMS: m/z calcd. for: $C_{28}H_{27}N_3O_3$ = 453.1848, found: 453.2052.

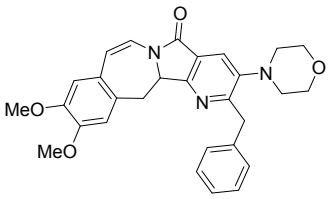


^{1}H NMR spectra of the (±)-Lennoxamine Aza-analogue **5b**

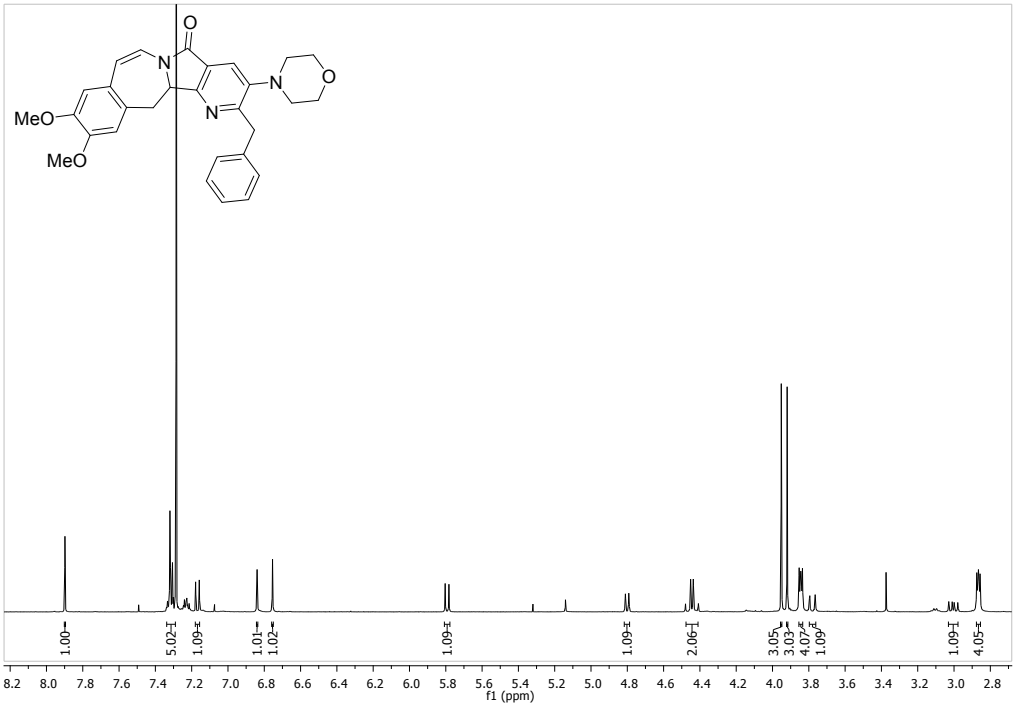


^{13}C NMR spectra of the (±)-Lennoxamine Aza-analogue **5b**

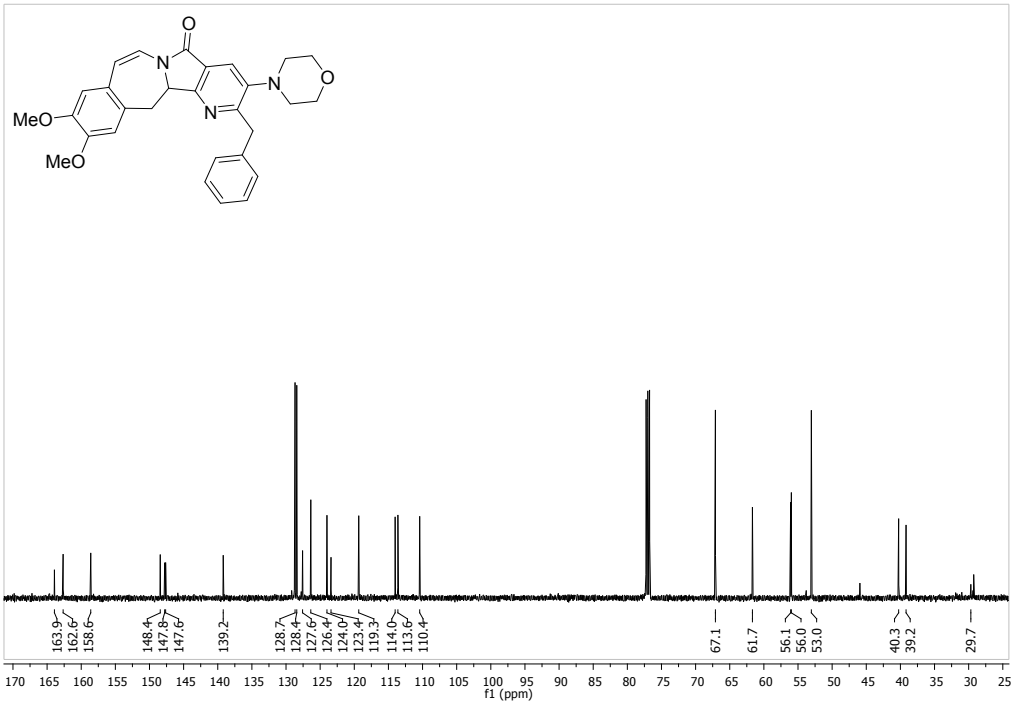
2-benzyl-10,11-dimethoxy-3-morpholino-13,13*a*-dihydro-5*H*-benzo[*d*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azepin-5-one (**5c**)



According to ***GP2-S2***, pyrrolo[3,4-*b*]pyridin-5-one **23c** (50.0 mg, 0.091 mmol) was dissolved in CH_3COOH/H_2SO_4, 1/2, v/v (3.0 mL) and stirred for 24 hours to afford the (±)-Lennoxamine Aza-analogue of **5c** (22.0 mg, 50%) as yellow solid; mp = 140 °C; R_f = 0.44 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 1708, 1440, 1350, 1105, 739; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.90 (s, 1H), 7.36–7.26 (m, 5H), 7.17 (d, *J* = 10.1 Hz, 1H), 6.84 (s, 1H), 6.75 (s, 1H), 5.79 (d, *J* = 10.3 Hz, 1H), 4.80 (d, *J* = 9.3 Hz, 1H), 4.44 (q, *J* = 14.0 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.88–3.83 (m, 4H), 3.78 (d, *J* = 14.7 Hz, 1H), 3.00 (dd, *J* = 15.1, 9.7 Hz, 1H), 2.89–2.84 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.9, 162.6, 158.6, 148.4, 147.8, 147.6, 139.2, 128.7, 128.4, 127.6, 126.4, 124.0, 123.4, 119.3, 114.0, 113.6, 110.4, 67.1, 61.7, 56.1, 56.0, 53.0, 40.3, 39.2, 29.7; HRMS: m/z calcd. for: $C_{29}H_{29}N_3O_4$ = 453.1848, found: 453.2052.

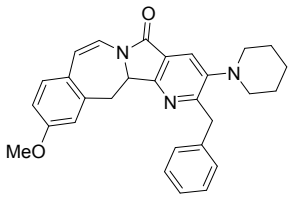


^1H NMR spectra of the (±)-Lennoxamine Aza-analogue **5c**

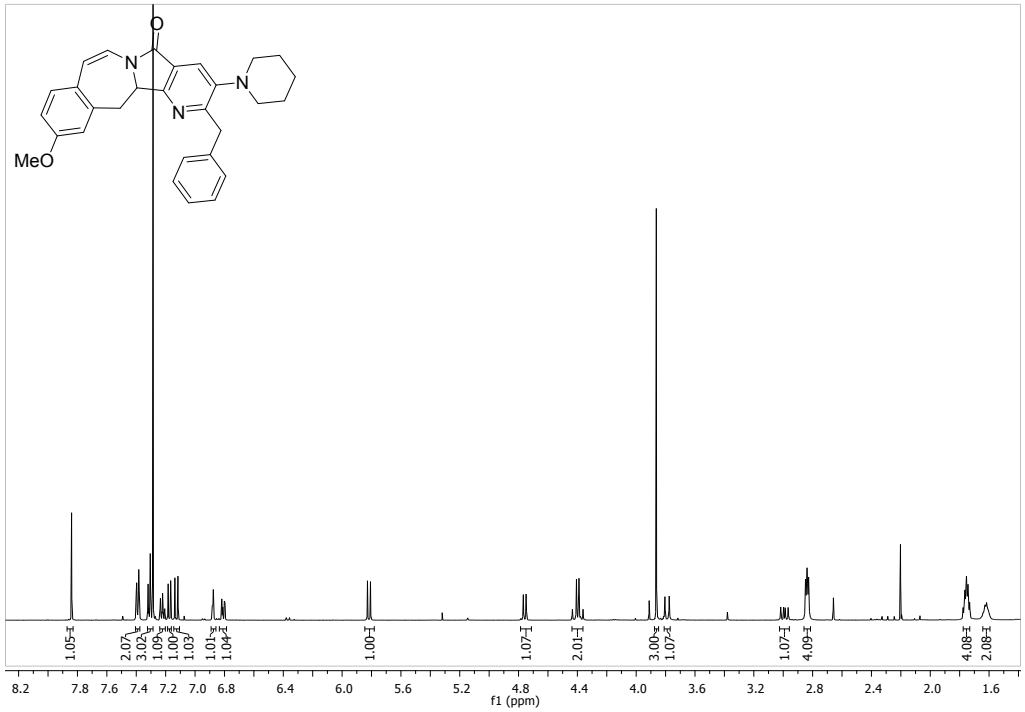


^{13}C NMR spectra of the (±)-Lennoxamine Aza-analogue **5c**

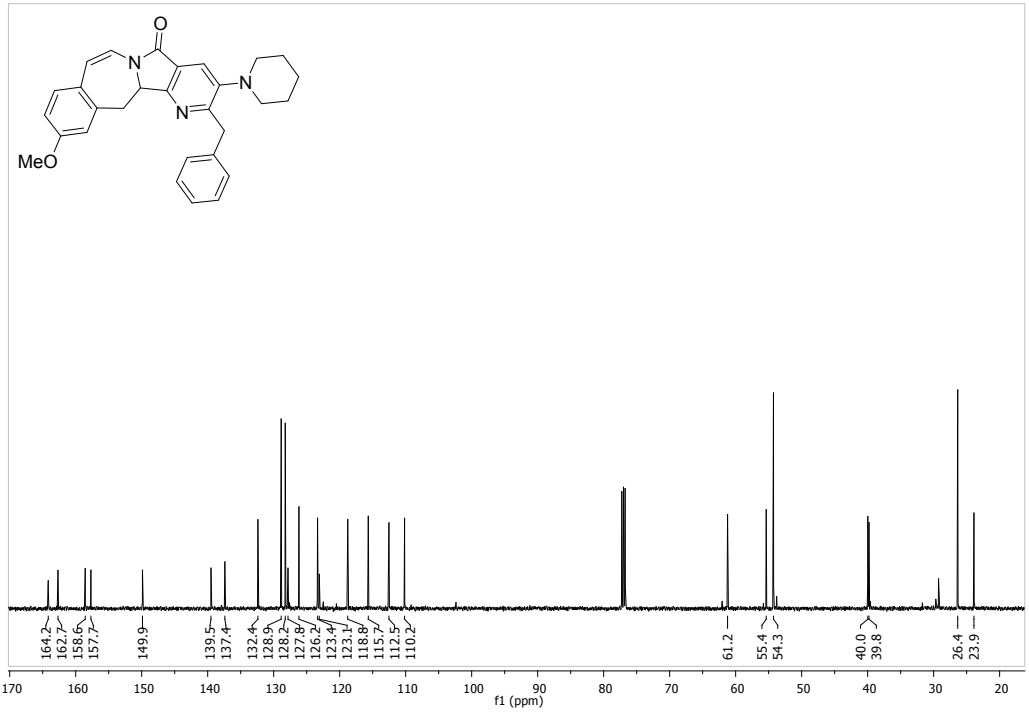
2-benzyl-11-methoxy-3-(piperidin-1-yl)-13,13*a*-dihydro-5*H*-benzo[*d*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azepin-5-one (**5d**)



According to ***GP2-S2***, pyrrolo[3,4-*b*]pyridin-5-one **23d** (50.0 mg, 0.097 mmol) was dissolved in CH_3COOH/H_2SO_4, 1/2, v/v (3.0 mL) and stirred for 24 hours to afford the (±)-Lennoxamine Aza-analogue **5d** (28.0 mg, 64%) as yellow solid; mp = 108 °C; R_f = 0.40 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 1688, 1440, 1260, 1111, 1064, 729; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (s, 1H), 7.41–7.38 (m, 2H), 7.32–7.28 (m, 3H), 7.24–7.20 (m, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 10.4 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.82 (d, *J* = 10.2 Hz, 1H), 4.76 (d, *J* = 9.4 Hz, 1H), 4.40 (q, *J* = 13.9 Hz, 2H), 3.86 (s, 3H), 3.79 (d, *J* = 14.6 Hz, 1H), 2.99 (dd, *J* = 15.3, 10.0 Hz, 1H), 2.85–2.82 (m, 4H), 1.79–1.72 (m, 4H), 1.65–1.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.2, 162.7, 158.6, 157.7, 149.9, 139.5, 137.4, 132.4, 128.9, 128.2, 127.8, 126.2, 123.4, 123.1, 118.8, 115.7, 112.5, 110.2, 61.2, 55.4, 54.3, 40.0, 39.8, 26.4, 23.9. HRMS: m/z calcd. for: $C_{29}H_{29}N_3O_2$ = 451.2819, found: 451.2260.

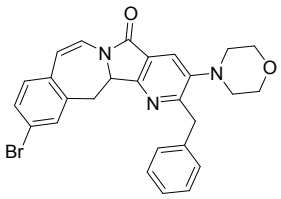


^{1}H NMR spectra of the (±)-Lennoxamine Aza-analogue **5d**

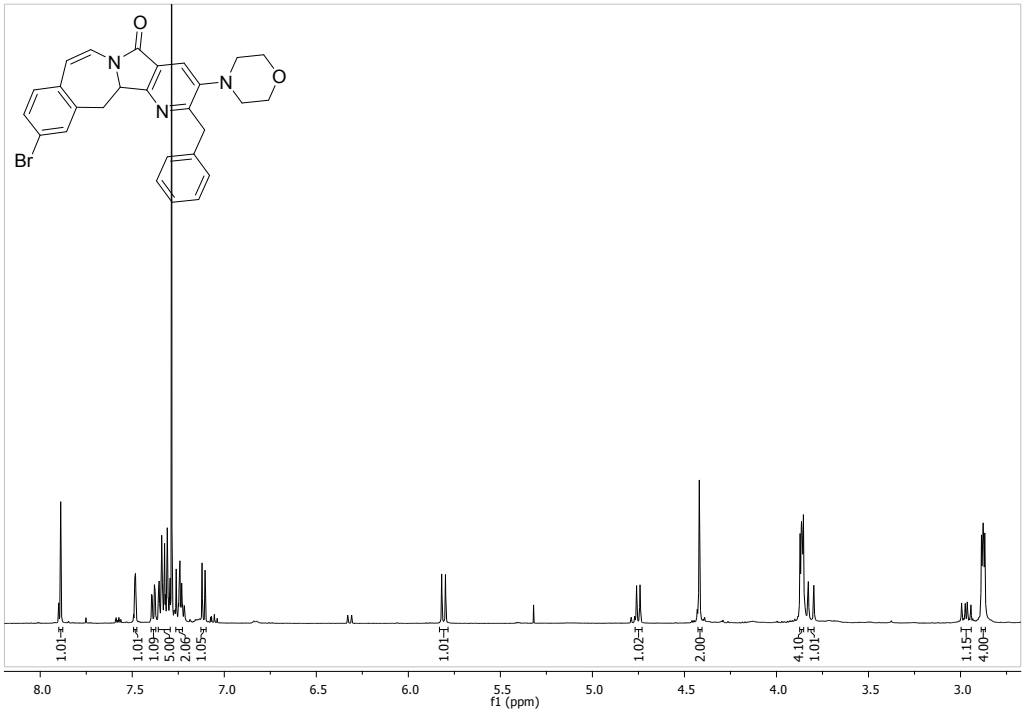


^{13}C NMR spectra of the (±)-Lennoxamine Aza-analogue **5d**

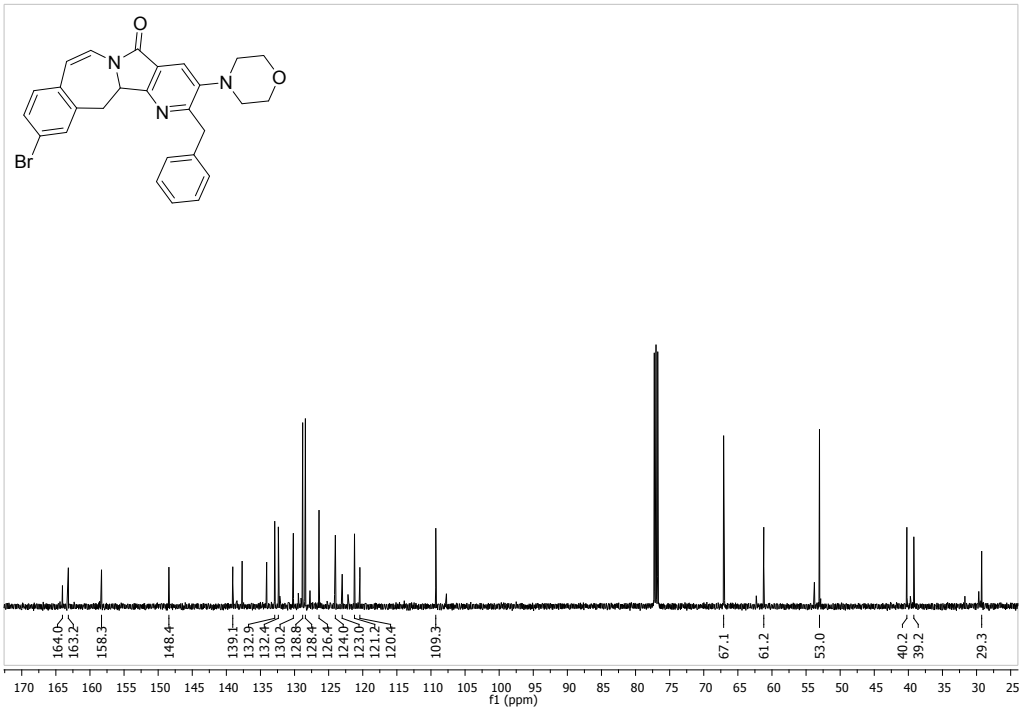
2-benzyl-11-bromo-3-morpholino-13,13*a*-dihydro-5*H*-benzo[*d*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azepin-5-one (**5e**)



According to ***GP2-S2***, pyrrolo[3,4-*b*]pyridin-5-one **23e** (50.0 mg, 0.088 mmol) was dissolved in CH_3COOH/H_2SO_4, 1/2, v/v (3.0 mL) and stirred for 24 hours to afford the (±)-Lennoxamine Aza-analogue **5e** (13.3 mg, 30%) as yellow solid; mp = 112 °C; R_f = 0.40 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 1719, 1445, 1340, 1104, 748; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.39 (ddd, *J* = 8.2, 2.1, 0.7 Hz, 1H), 7.36–7.29 (m, 5H), 7.26–7.21 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 5.81 (d, *J* = 10.3 Hz, 1H), 4.75 (d, *J* = 9.4 Hz, 1H), 4.42 (s, 2H), 3.86 (m, 4H), 3.81 (d, *J* = 14.9 Hz, 1H), 2.97 (dd, *J* = 15.4, 9.9 Hz, 1H), 2.90–2.83 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.0, 163.2, 158.3, 148.4, 139.1, 132.9, 132.4, 130.2, 128.8, 128.4, 126.4, 124.0, 123.0, 121.2, 120.4, 109.3, 67.1, 61.2, 53.0, 40.2, 39.2, 29.3; HRMS: m/z calcd. for: $C_{27}H_{24}BrN_3O_2$ = 501.1070, found: 501.1052.



^1H NMR spectra of the (±)-Lennoxamine Aza-analogue **5e**

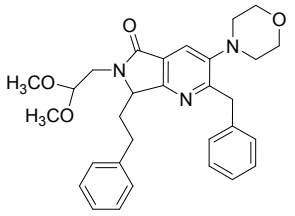


^{13}C NMR spectra of the (±)-Lennoxamine Aza-analogue **5e**

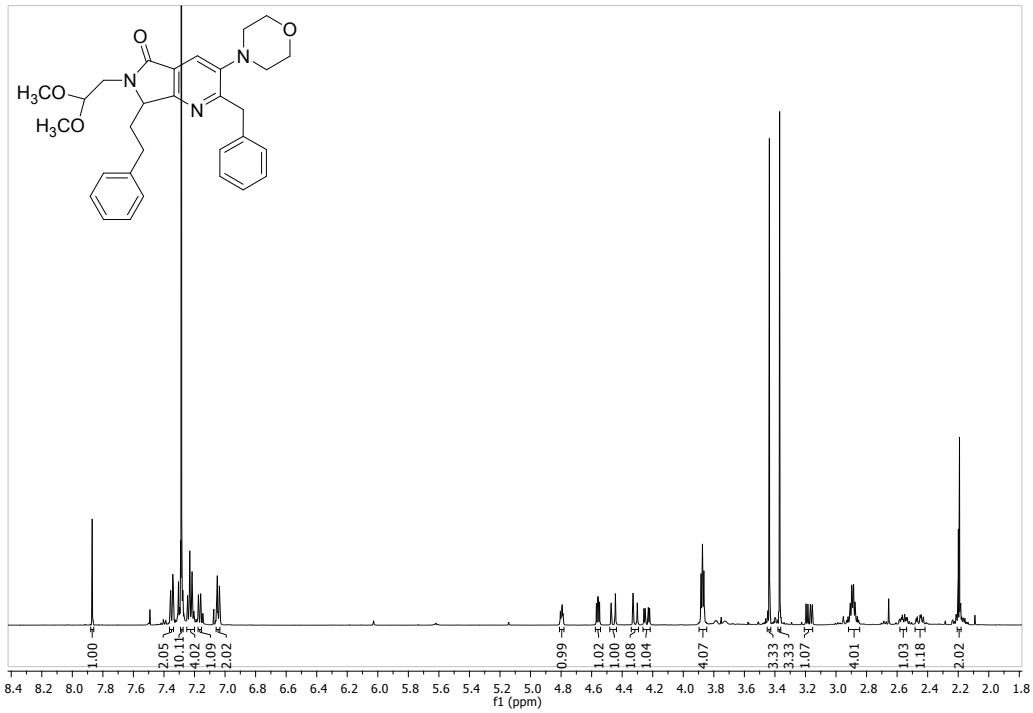
Synthesis and characterization of the pyrrolo[3,4-*b*]pyridine-5-one 24a

General procedure 3 - ***Step 1*** *(**GP3-S1**):* 2,2-dimethoxyethan-1-amine (1.00 equiv.) and the corresponding aldehyde (0.9 equiv.) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube and diluted in dry PhMe (1.0 mL). Then, the mixture was MW-heated (65 °C, 55 W) for 15 minutes, and $Sc(OTf)_3$ (0.03 equiv.) was added. The mixture was MW-heated (65 °C, 55 W) for 10 minutes, and the corresponding isocyanide (1.20 equiv.) was added. The mixture was MW-heated (85 °C, 65 W) for 15 minutes, and maleic anhydride (1.20 equiv.) was added. Finally, the reaction mixture was MW-heated (65 °C, 65 W) for 15 minutes, cooled at room temperature and the solvent was removed until dryness. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with a concentrated aq. solution of $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL). The organic layer was dried with Na_2SO_4, filtered using celite-pad and the solvent was removed until dryness. The crude was purified by silica-gel column chromatography using mixtures of Hexanes with EtOAc as mobile phase to afford the corresponding pyrrolo[3,4-*b*]pyridine-5-one **24a**.

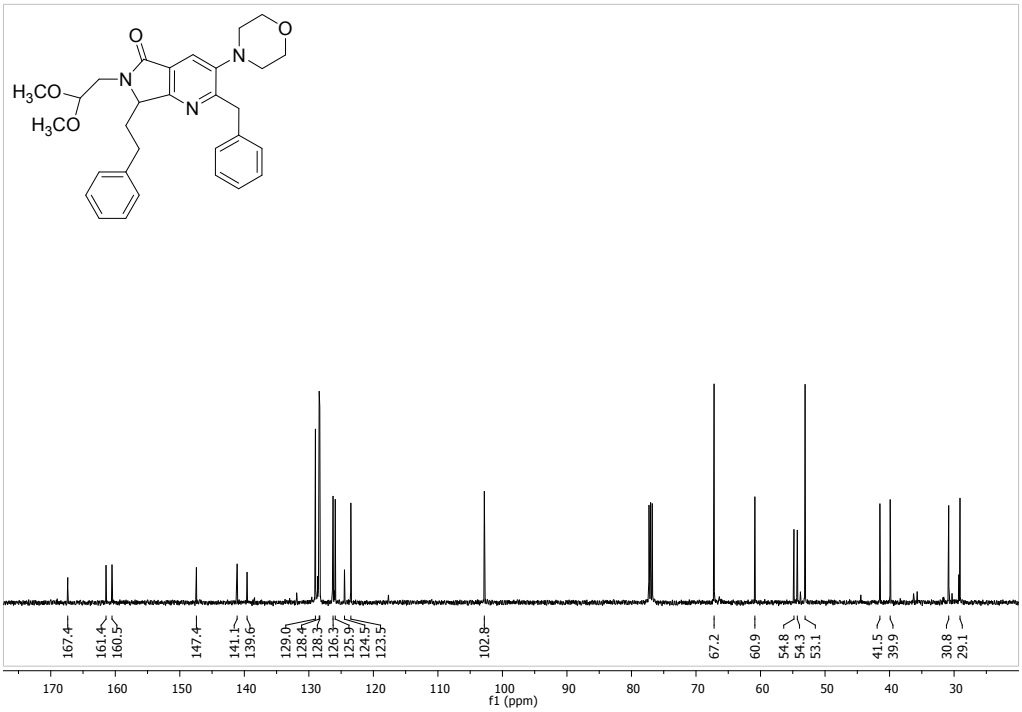
2-benzyl-6-(2,2-dimethoxyethyl)-3-morpholino-7-phenethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**24a**)



According to ***GP3-S1***, 2,2-dimethoxyethan-1-amine (250.0 μL, 0.230 mmol), hydrocinnamaldehyde (270.0 μL, 0.206 mmol), scandium triflate (3.4 mg, 0.006 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (67.0 mg, 0.270 mmol), and maleic anhydride (22.0 mg, 0.270 mmol) were reacted together in dry PhMe (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-5-one **24a** (51.8 mg, 45%) as a yellow oil; FT-IR (cm^{-1}) ν_{max} 2922, 2853, 1708, 1444 cm^{-1}; R_f = 0.53 (Hex/AcOEt, 3/1, v/v); ^1H RMN (500 MHz, $CDCl_3$) δ: 7.87 (s, 1H), 7.37–7.33 (m, 2H), 7.31–7.28 (m, 10H), 7.25–7.20 (m, 4H), 7.18–7.14 (m, 1H), 7.06–7.02 (m, 2H), 4.81–4.78 (m,1H), 4.56 (dd, *J* = 6.2, 4.1 Hz, 1H), 4.46 (d, *J* = 14.1 Hz, 1H), 4.32 (d, *J* = 14.1 Hz, 1H), 4.24 (dd, *J* = 14.4, 3.8 Hz, 1H), 3.89–3.86 (m, 4H), 3.44 (s, 3H), 3.37 (s, 1H), 3.18 (dd, *J* = 14.4, 6.2 Hz, 1H), 2.92–2.85 (m, 4H), 2.59–2.53 (m, 1H), 2.48–2.42 (m, 1H), 2.22–2.17 (m, 2H); ^{13}C RMN (126 MHz, $CDCl_3$) δ: 167.4, 161.4, 160.5, 147.4, 141.1, 139.6, 129.0, 128.4, 128.3, 125.9, 124.5, 123.5, 102.8, 67.2, 60.9, 54.8, 54.3, 53.1, 41.5, 39.9, 30.8, 29.1; HRMS: m/z calcd. for: $C_{30}H_{35}N_3O_4$ = 502.2628, found 502.2677.



^1H NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **24a**

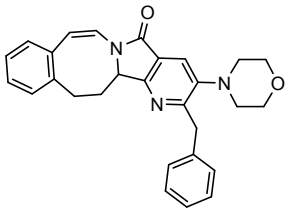


^{13}C NMR spectra of the pyrrolo[3,4-*b*]pyridin-5-one **24a**

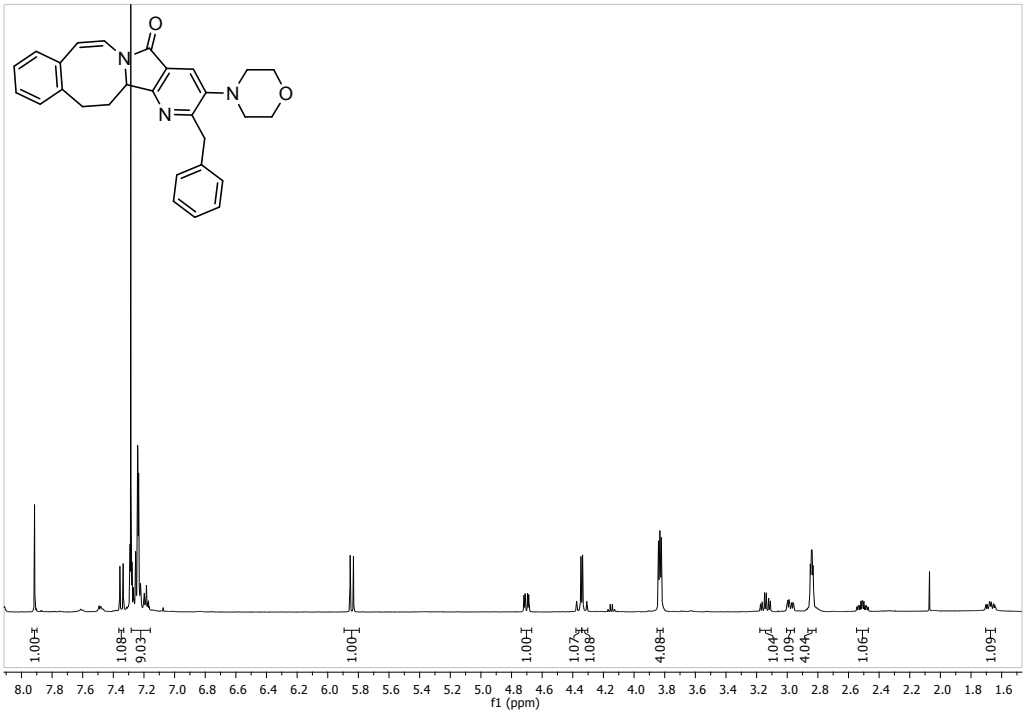
Synthesis and characterization of the Magallanesine Aza-Analogues 6a-d

General procedure 3 - ONE POT (GP3-OP): 2,2-dimethoxyethan-1-amine (0.90 equiv.) and the corresponding aldehyde (1.00 equiv.) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube and diluted in dry PhMe (1.0 mL). Then, the mixture was MW-heated (65 °C, 55 W) for 15 minutes, and $Sc(OTf)_3$ (0.03 equiv.) was added. The mixture was MW-heated (65 °C, 55 W) for 10 minutes, and the corresponding isocyanide (1.20 equiv.) was added. The mixture was MW-heated (85 °C, 65 W) for 15 minutes, and maleic anhydride (1.20 equiv.) was added. Finally, the reaction mixture was MW-heated (65 °C, 65 W) for 15 minutes, cooled at room temperature and the solvent was removed until dryness. Then, the crude was diluted in CH_3COOH/H_2SO_4, 1/1, v/v (3.0 mL) and stirred overnight at room temperature. The reaction mixture was neutralized by a concentrated aq. solution of $NaHCO_3$ (3 x 25 mL) and extracted with EtOAc (3 x 25 mL). Organic layer was washed with water brine (3 x 25 mL). Finally, it was dried with Na_2SO_4 and the solvent was evaporated to dryness. The crude was purified by silica gel column chromatography using mixtures of Hexanes–EtOAc to afford the corresponding Magallanesine Aza-Analogues **6a-e**.

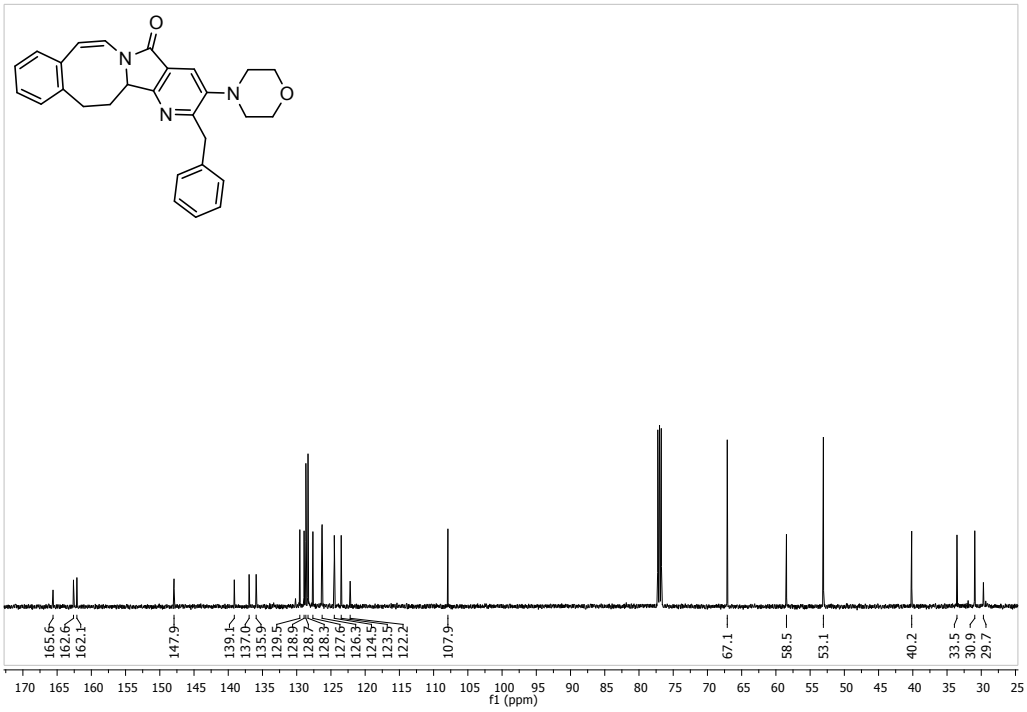
(*Z*)-2-benzyl-3-morpholino-14,14*a*-dihydrobenzo[*e*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azocin-5(13*H*)-one (**6a**)



According to ***GP3-OP***, 2,2-dimethoxyethan-1-amine (25.0 μL, 0.230 mmol), hydrocinnamaldehyde (33.0 μL, 0.255 mmol), scandium triflate (3.0 mg, 0.007 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (74.0 mg, 0.306 mmol), and maleic anhydride (30.0 g, 0.306 mmol) were reacted together in PhMe (1.0 mL) to afford the Magallanesine Aza-analogues **6a** (38.0 g, 15%) as orange gum; R_f = 0.40 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 2922, 2853, 1708, 1444; ^1H RMN (500 MHz, $CDCl_3$) δ: 7.92 (s, 1H), 7.35 (d, *J* = 10.7 Hz, 1H), 7.28–7.16 (m, 9H), 5.84 (d, *J* = 10.7 Hz, 1H), 4.70 (dd, *J* = 11.5, 3.5 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 4.32 (d, *J* = 14.0 Hz, 1H), 3.86–3.79 (m, 4H), 3.18–3.10 (m, 1H), 3.01–2.95 (m, 1H), 2.88–2.78 (m, 4H), 2.55–2.47 (m, 1H), 1.71–1.64 (m, 1H); ^{13}C RMN (126 MHz, $CDCl_3$) δ: 165.6, 162.6, 162.1, 147.9, 139.1, 137.0, 135.9, 129.5, 128.9, 128.7, 128.3, 127.6, 126.3 (2), 124.5, 123.5, 122.2, 107.9, 67.1, 58.5, 53.1, 40.2, 33.5, 30.9, 29.7; HRMS: m/z calcd. for: $C_{28}H_{27}N_3O_2$ = 438.2182, found: 438.2190.

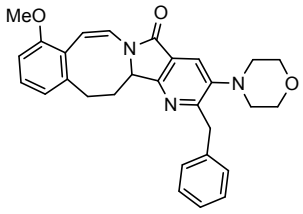


^1H NMR spectra of the Magallanesine Aza-analogue **6a**

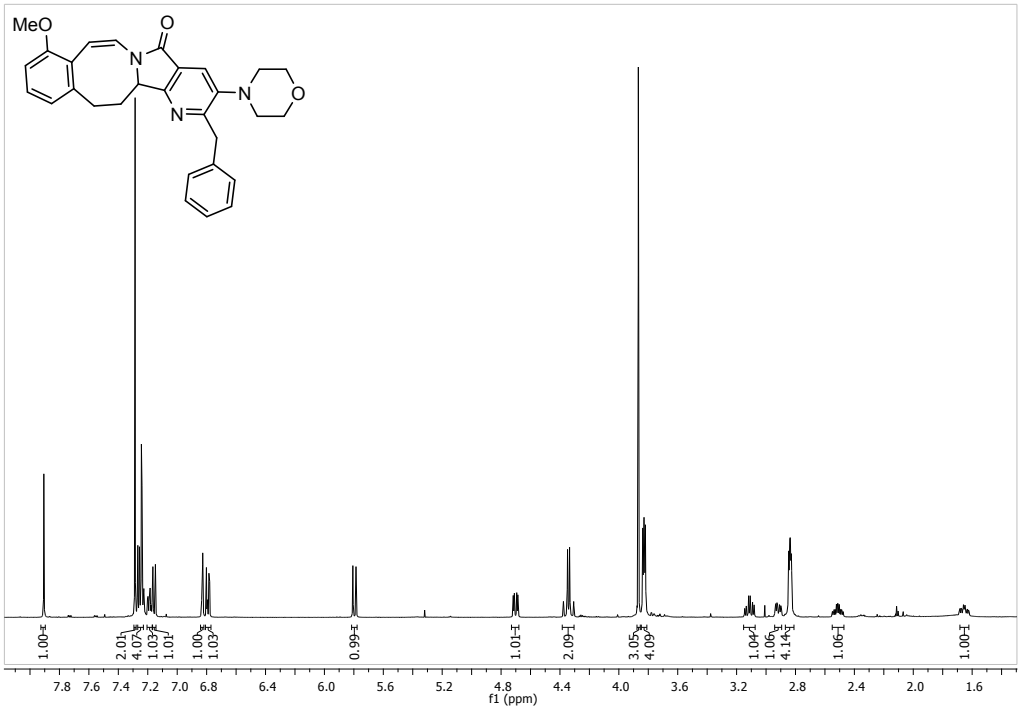


^{13}C NMR spectra of the Magallanesine Aza-analogue **6a**

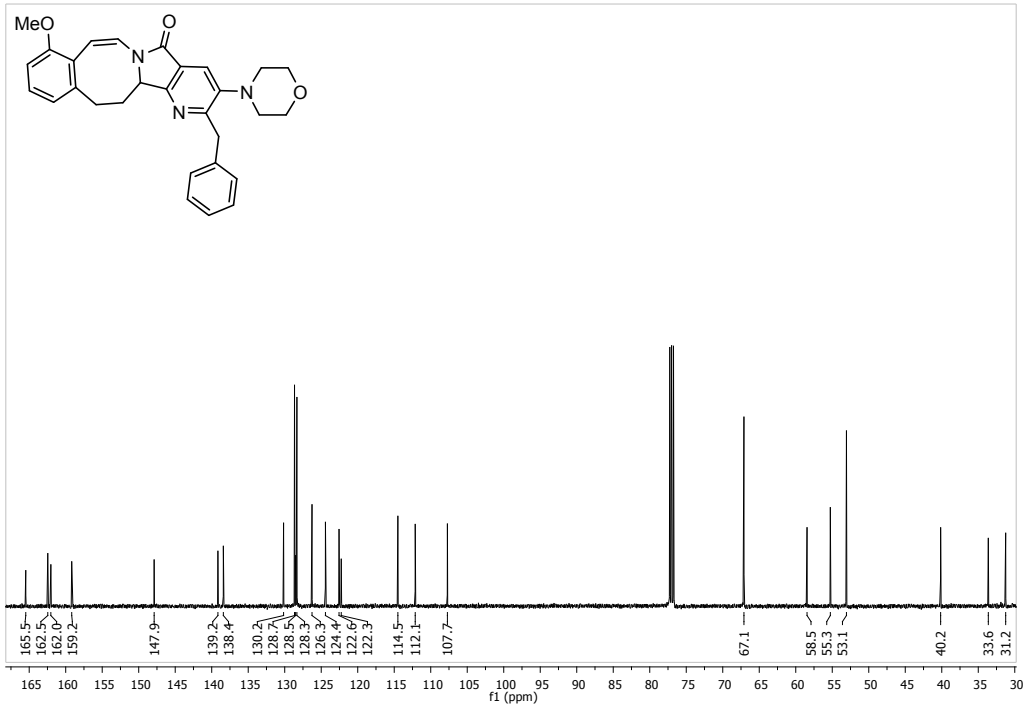
(*Z*)-2-benzyl-9-methoxy-3-morpholino-14,14*a*-dihydrobenzo[*e*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azocin-5(13*H*)-one (**6b**)



According to ***GP3-OP***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), 3-methoxyhydrocinnamaldehyde (116.0 mg, 0.699 mmol), scandium triflate (11.0 mg, 0.0021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (204.0 mg, 0.838 mmol), and maleic anhydride (96.0 mg, 0.978 mmol) were reacted together in PhMe (1.0 mL) to afford the Magallanesine Aza-analogue **6b** (32.0 mg, 20%) as orange gum; R_f = 0.35 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 2922, 2853, 1708, 1444; ^{1}H RMN (500 MHz, $CDCl_3$) δ: 7.92 (s, 1H), 7.29–7.28 (m, 2H), 7.27–7.22 (m, 4H), 7.20–7.17 (m, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.80 (d, *J* = 9.8 Hz, 1H), 4.70 (dd, *J* = 11.8, 3.8 Hz, 1H), 4.34 (q, *J* = 14.1 Hz, 1H), 3.87 (s, 3H), 3.84–3.81 (m, 4H), 3.16–3.07 (m, 1H), 2.94–2.89 (m, 1H), 2.85–2.81 (m, 4H), 2.55–2.47 (m, 1H), 1.69–1.61 (m, 1H); ^{13}C RMN (126 MHz, $CDCl_3$) δ: 165.6, 162.5, 162.0, 159.2, 147.9, 139.2, 138.4, 130.2, 128.7, 128.5, 128.3, 126.3, 124.4, 122.6, 122.3, 114.5, 112.1, 107.7, 67.1, 58.5, 55.3, 53.1, 40.2, 33.6, 31.2; HRMS: m/z calcd. for: $C_{28}H_{27}N_3O_2$ = 438.2182, found: 438.2190.

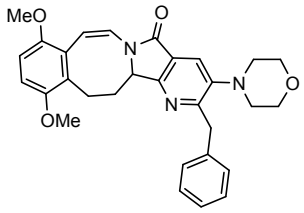


^{1}H NMR spectra of the Magallanesine Aza-analogue **6b**

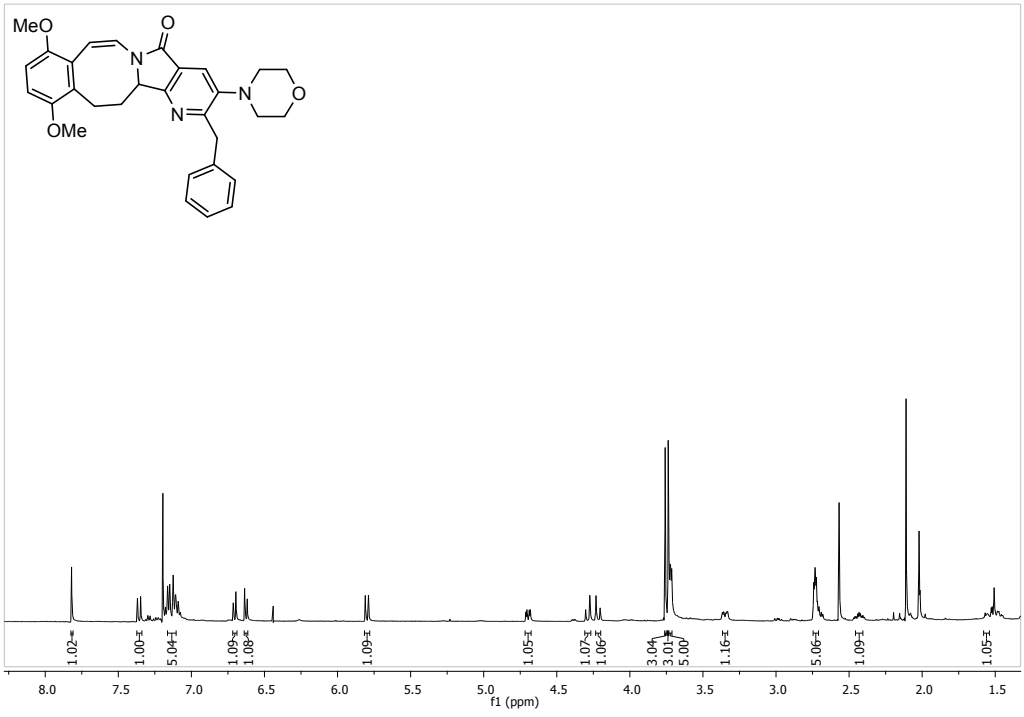


^{13}C NMR spectra of the Magallanesine Aza-analogue **6b**

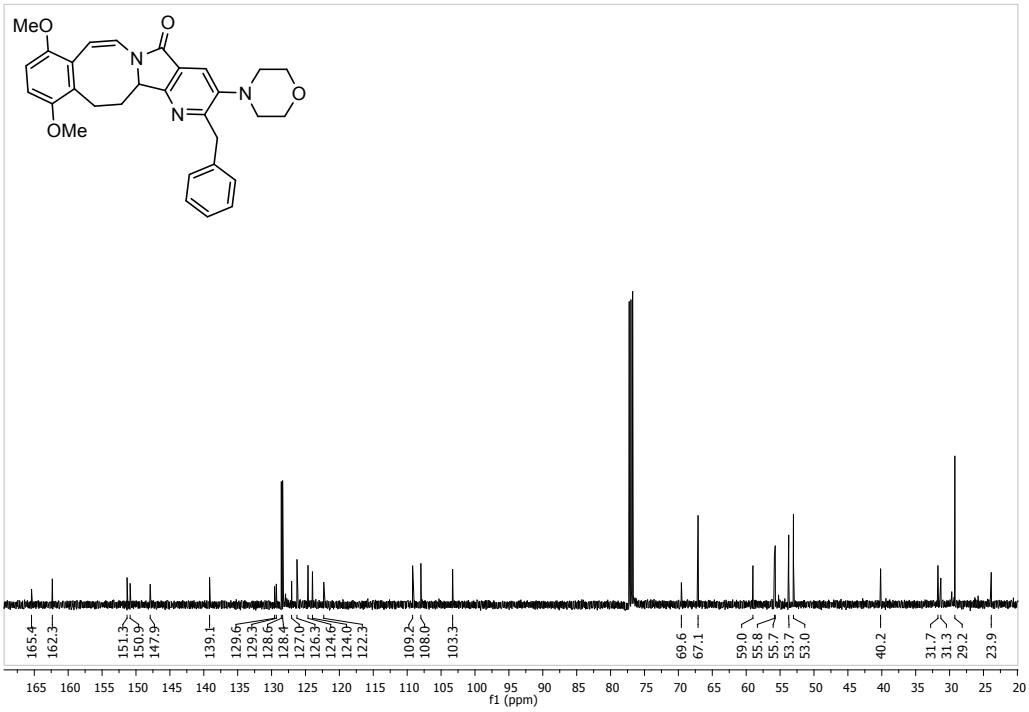
(*Z*)-2-benzyl-9,12-dimethoxy-3-morpholino-14,14*a*-dihydrobenzo[*e*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azocin-5(13*H*)-one (**6c**)



According to ***GP3-OP***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), 2,5-dimethoxyhydrocinnamaldehyde (116.0 mg, 0.699 mmol), scandium triflate (11.0 mg, 0.021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (204.0 mg, 0.838 mmol), and maleic anhydride (96.0 mg, 0.978 mmol) were reacted together in PhMe (1.0 mL) to afford the Magallanesine Aza-Analogue **6c** (32.0 mg, 17%) as orange gum; R_f = 0.30 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 2925, 2854, 1707, 1445 2925, 2854, 1707, 1445; ^{1}H RMN (500 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.36 (d, *J* = 10.8 Hz, 1H), 7.16–7.10 (m, 5H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 5.80 (d, *J* = 10.8 Hz, 1H), 4.70 (dd, *J* = 11.8, 3.9 Hz, 1H), 4.29 (d, *J* = 14.1 Hz, 1H), 4.22 (d, *J* = 14.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79–3.77 (m, 5H), 3.44–3.38 (m, 1H), 2.81–2.74 (m, 5H), 2.47–2.39 (m, 1H), 1.57–1.51 (m, 1H); ^{13}C RMN (126 MHz, $CDCl_3$) δ: 165.4, 162.3 (2), 151.3, 150.9, 147.9, 139.1, 129.6, 129.3, 128.6, 128.4, 127.0, 126.3 (2), 124.6, 124.0, 122.3, 109.2, 108.0, 103.3, 69.6, 67.1, 59.0, 55.8, 55.7, 53.7, 53.0, 40.2, 31.7, 31.3, 29.2, 23.9; HRMS: m/z calcd. for: $C_{30}H_{31}N_3O_4$ = 496.2362, found 496.2359.

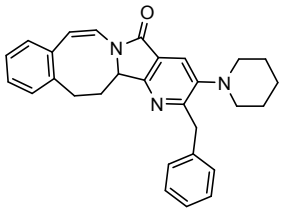


^{1}H NMR spectra of the Magallanesine Aza-analogue **6c**

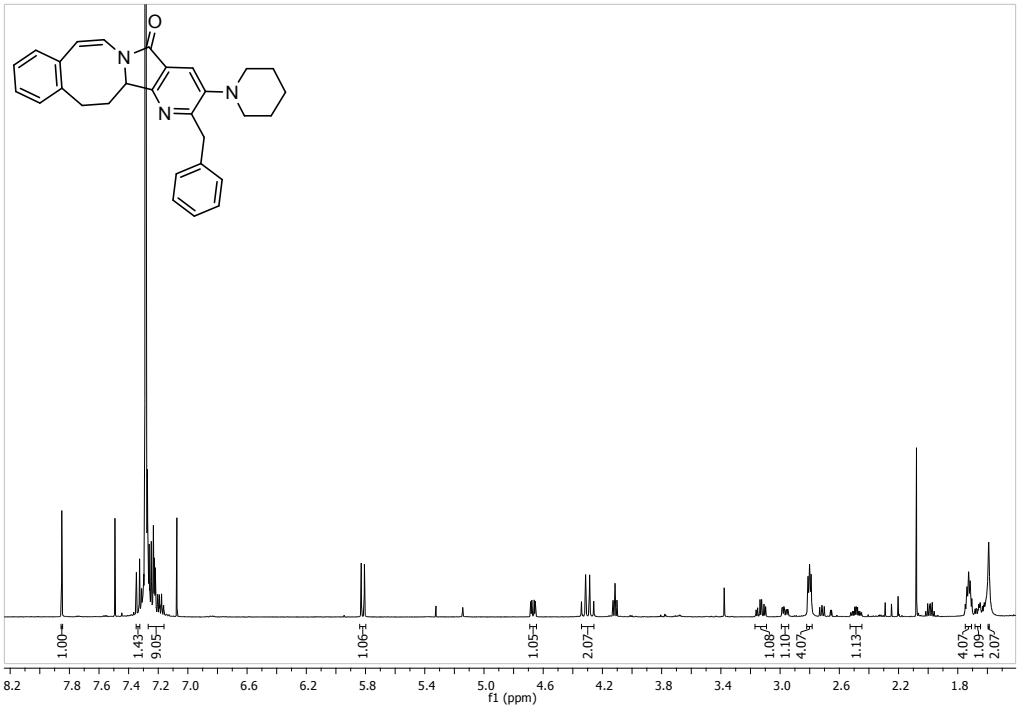


^{13}C NMR spectra of the Magallanesine Aza-analogue **6c**

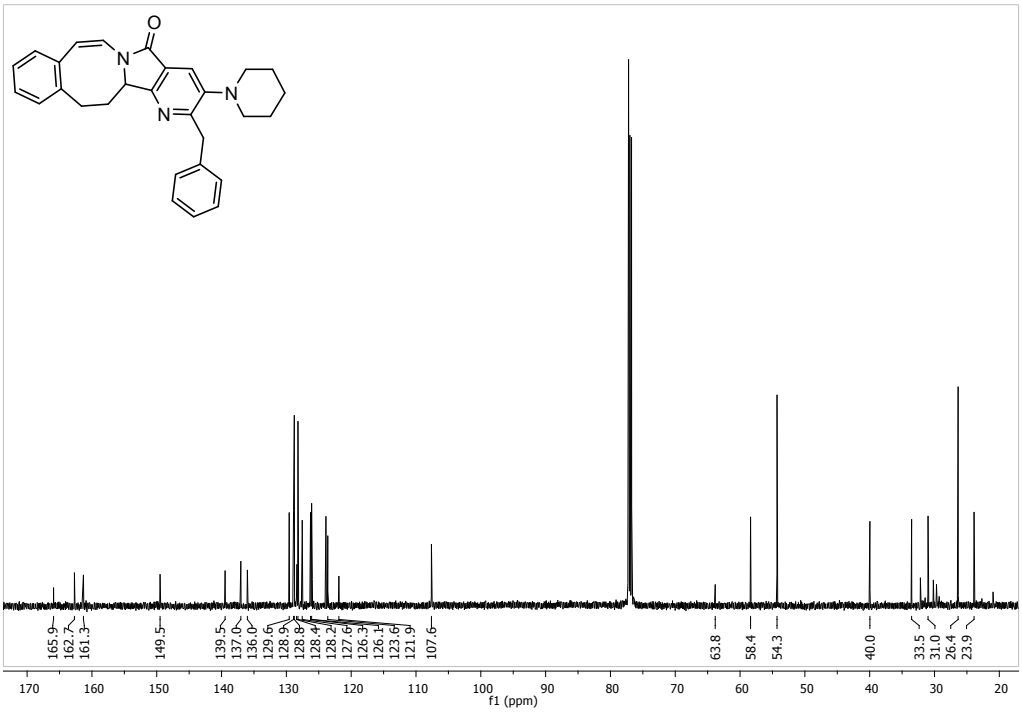
(*Z*)-2-benzyl-3-(piperidin-1-yl)-14,14*a*-dihydrobenzo[*e*]pyrido[2',3':3,4]pyrrolo[1,2-*a*]azocin-5(13*H*)-one (**6d**)



According to ***GP3-OP***, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), hydrocinnamaldehyde (116.0 g, 0.699 mmol), scandium triflate (11.0 mg, 0.021 mmol), 2-isocyano-1-piperidino-3-phenylpropan-1-one (204.0 mg, 0.838 mmol), and maleic anhydride (96.0 mg, 0.978 mmol) were reacted together in PhMe (1.0 mL) to afford the Magallanesine Aza-analogue **6d** (32.0 g, 14%) as orange gum; R_f = 0.47 (AcOEt/Hexanes, 3/1, v/v); FT-IR (cm^{-1}) ν_{max} 2928, 2851, 1712, 1443; ^{1}H RMN (500 MHz, $CDCl_3$) δ: 7.85 (s, 1H), 7.33 (d, *J* = 10.8 Hz, 1H), 7.31–7.16 (m, 9H), 5.82 (d, *J* = 10.7 Hz, 1H), 4.67 (dd, *J* = 11.9, 3.8 Hz, 1H), 4.30 (q, *J* = 13.8 Hz, 1H), 3.13 (td, *J* = 13.4, 5.4 Hz, 1H), 2.97 (ddd, *J* = 13.2, 6.0, 1.9 Hz, 1H), 2.82–2.78 (m, 4H), 2.53–2.43 (m, 1H), 1.75–1.70 (m, 4H), 1.69–1.63 (m, 1H), 1.61–1.58 (m, 2H); ^{13}C RMN (126 MHz, $CDCl_3$) δ: 165.9, 162.7, 161.3, 149.5, 139.5, 137.0, 136.0, 129.6, 128.9, 128.8, 128.4 (2), 128.2, 127.6, 126.3, 126.1, 123.6, 121.9, 107.6, 63.8, 58.4, 54.3, 40.0, 33.5, 31.0, 26.4, 23.9; HRMS: m/z calcd. for: $C_{29}H_{29}N_3O$ = 466.2256, found: 466.2245.



^{1}H NMR spectra of the Magallanesine Aza-analogue **6d**



^{13}C NMR spectra of the Magallanesine Aza-analogue **6d**