De novo Design of SARS-CoV-2 Main Protease Inhibitors

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General Information

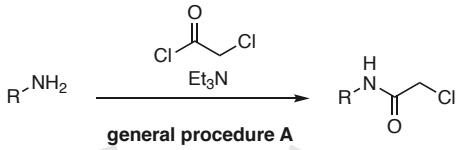
All reactions were carried out in dried glassware under an N_2 atmosphere. $Pd(Ph_3P)_4$ (Ark Pharm Inc., AK-25415) was suspended in dry MeOH, filtered, dried in vacuo and stored under N_2 in the dark. If not otherwise noted, all other starting materials were purchased from commercial sources and used without further purification. For water-free reactions, dry solvents from Acros Organics (ExtraDry, bottles equipped with AcroSeal) were used without further modification. For reactions containing water, analytical grade solvents were used without further modifications. Solvents for extractions and column chromatography were technical grade. Analytical thin layer column chromatography (TLC) was performed on pre-coated *Merck* silica gel 60 F_{254} plates (0.25 mm) and visualized by UV, VIS, $KMnO_4$ stain. For reactions requiring heat, magnetic stir plates were equipped with heating blocks provided by *IKA®* and the temperature reported is from inside the heating block, if not otherwise noted. Reactions performed in the microwave oven were run in a *Biotage® Initiator+*. Flash column chromatography was carried out with *Silicagel (Geduran ® 60 Å (40-63 µm), Merck KGaA)* using manual air pressure or a *Teledyne Isco Combiflash R_f+ UV* purification system. HPLC purification was performed on a *1260 Infinity Agilent Technologies* system (Windows 10, OpenLabs CDS Chemstation Software, two G1361A preparative pumps, G2260A autosampler (2400µL max. injection volume), G1170A column switching valve, G7115A diode array detector, G1364B fraction collector); with a semipreparative column Phenomenex Gemini 5 µm C18 (150 x 10 mm); mobile phase gradients of acetonitrile in water each containing 0.1% formic acid, 8mL/min flow rate and detection with a 0.3 mm preparative flow cell. Concentration *in vacuo* was performed by rotary evaporation to ~ 1 mbar at 40 °C and drying at high vacuum at 10^{-2} mbar and room temperature. ^1H NMR and ^{13}C NMR spectra were recorded on a *Bruker Ascend* 400 MHz equipped with a cryoprobe at 298 K and a *Bruker Avance* 400 MHz (NSF Award CHE-01162222) in $CDCl_3$ (DLM-7-100), $(CD_3)_2SO$ (DLM-10-25), $(CD_3)_2CO$ (DLM-9-25), CD_3OD (DLM-24-10) supplied by *Cambridge Isotope Laboratories*. Chemical shifts (δ) are reported in ppm relative to the solvent signal ($CDCl_3$ ^1H: 7.26 ppm, ^{13}C: 77.16 ppm; $(CD_3)_2SO$ ^1H: 2.50 ppm, ^{13}C: 39.5 ppm; $(CD_3)_2CO$ ^1H: 2.05 ppm, ^{13}C: 29.8 ppm; CD_3OD ^1H: 3.31 ppm, ^{13}C: 49.0 ppm). The multiplicities are reported in Hz as: s = singlet, br = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. IR spectra were measured from the neat compounds on an ATR *Nicolet 6700* FT-IR spectrometer and reported in cm^{-1}. The intensities of the bands are reported as: w = weak, m = medium, s = strong. Liquid chromatography mass spectrometry (LC-MS) analysis was performed on an *LCMS 1260 Infinity II Agilent Technologies* system (Windows 10, OpenLabs CDS Chemstation Software, *6120 Quadrupole LC/MS G7111B* quaternary pump, *G7129A Infinity II* vial sampler, *G7117C 1260 diode array detector*) equipped with an *LC Kinetex column* 2.6 µm C18 (50 x 3 mm) at room temperature. Runs were performed at a flow-rate of 1 mL/min with a run-time of 5 min. High-resolution mass spectrometry (HR-MS) was performed on an *Agilent 6224 TOF LC/MS* equipped with an ESI or APCI (noted for each compound individually). UV/Vis spectroscopy was performed on a *Varian Cary 60 UV-Visible* spectrometer and steady-state luminescence spectroscopy was performed on a *PTI QuantaMaster™ 400* instrument from Horiba Scientific of selected compounds at 10 µM concentration in aqueous PBS with 1% DMSO using Hellma fluorescence cells (111-QS, light path: 10 mm).

Virtual Screening Using ASINEX PPI Non-Macrocyclic Screening Library

The ASINEX PPI non-macrocyclic screening library, which consists of 11870 compounds, can be downloaded from (www.asinex.com/ppi/). RDKit[1,2] version 2019.09.1 was used to read the downloaded 2D SDF file and generate initial 3D ligand conformer, and then OpenBabel[3] version 2.4.1 was applied to generate maximum 10 conformers per ligand using genetic algorithm with the default options. Two main protease structures, one ligand-bound form (PDB: 6LU7, with an inhibitor N3 in the active site)[4] and an apo form (PDB: 6Y84, with unliganded active site), were used as target protein structures. Waters and ions were removed from the protein structures. Protein protonation state was calculated using PDB2PQR[5] with pH 7 condition. Docking pdbqt files for both the protein and ligand were prepared using AutoDockTools.[6] Smina docking suite[7] with the Lin_F9 scoring function (https://yzhang.hpc.nyu.edu/Lin_F9/) was used for protein-ligand docking. For each compound, its conformers were sequentially docked to the catalytic site of protein structures by flexible ligand docking. After docking, the highest predicted binding affinity of docked poses was chosen as the "docking score" for virtual screening. The ligand efficiency was calculated using the docking score divided by number of heavy atoms. Both the ligand efficiency and the docking score were used to select potential inhibitors for further evaluation. The virtual docking poses of compounds **6r**, **6v**, **21b**, **21c** and **28** in the protein structure 6Y84 are provided as separate pdb files.

Synthesis Procedures

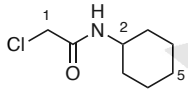
2-Chloroacetamide Syntheses 5a-d:



Scheme S1: Overview of the 2-chloroacetamide synthesis.

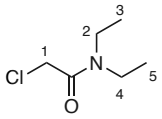
General Procedure A:
Prepared according to a modified literature procedure.[8] To a solution of amine (5.00 mmol) and Et_3N (0.830 mL, 6.00 mmol) in dry CH_2Cl_2 (10 mL) in a round-bottomed flask cooled with an ice bath was added dropwise chloroacetic chloride (6.00 mmol). The mixture was stirred for 10 minutes in the ice bath and then allowed to warm to room temperature over 1 hour. The mixture was treated with water (20 mL) and diluted with CH_2Cl_2 (20 mL). The organic layer was separated and washed with aq. 1.0 $molL^{-1}$ HCl (3 x 20 mL), aq. sat. $NaHCO_3$ (3 x 20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. If not otherwise mentioned, the crude product was used without further purification in the next step.

2-Chloro-*N*-cyclohexylacetamide (5a):



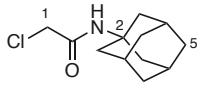
Prepared according to general procedure **A** using cyclohexylamine (3.50 mL, 30.2 mmol), Et_3N (5.00 mL, 36.3 mmol), CH_2Cl_2 (40 mL) and chloroacetic chloride (2.40 mL, 30.2 mmol) to afford product as a brown solid (4.55 g, 85%): $\mathbf{R_f}$ 0.79 (100% EtOAc); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 6.42 (1H, br, N*H*), 4.03 (2H, s, C1H_2), 3.72–3.87 (1H, m, C2H_1), 1.92 (2H, dt, ^3J 12.6, ^4J 4.0, C3H_2), 1.69–1.77 (2H, m, C4H_2), 1.59–1.67 (1H, m, C5H_1), 1.31–1.43 (2H, m, C4H_2), 1.14–1.27 (3H, m, C3H_2, *C5*H_1); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 165.0 (*C*=O), 48.8 (*C2*), 42.9 (*C1*), 33.0 (*C3*), 25.6 (*C4*), 24.9 (*C5*). Data in agreement with the literature.[8]

2-Chloro-*N*,*N*-diethylacetamide (5b):



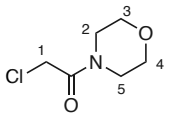
Prepared according to general procedure **A** using diethylamine (0.52 mL, 5.00 mmol), Et_3N (0.834 mL, 6.00 mmol), CH_2Cl_2 (7.0 mL) and chloroacetic chloride (0.480 mL, 6.00 mmol) to afford product as an orange liquid (748 mg, 100%): $\mathbf{R_f}$ 0.66 (100% EtOAc); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 4.06 (2H, s, C1H_2), 3.38 (4H, m, C2H_2, C4H_2), 1.24 (3H, t, ^3J 7.1, C3H_3), 1.14 (3H, t, ^3J 7.1, C5H_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 166.0 (*C*=O), 42.6 (*C2*), 41.2 (*C1*), 40.8 (*C4*), 14.5 (*C3*), 12.7 (*C5*). Data in agreement with the literature.[9]

***N*-Adamantanyl-2-chloroacetamide (5c):**



Prepared according to general procedure **A** using 1-adamantylamine (0.302 mg, 2.00 mmol), Et_3N (0.334 mL, 2.40 mmol) in dry CH_2Cl_2 (4.0 mL). The crude product was precipitated and washed with hexanes to afford product as an off-white solid (206 mg, 45%): $\mathbf{R_f}$ 0.55 (hexanes:EtOAc, 1:1, $KMnO_4$); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 6.21 (1H, br s, N*H*), 3.93 (2H, s, C1H_2), 2.09–2.12 (3H, m, 3 x C4*H*), 2.02–2.03 (6H, m, 3 x C3H_2), 1.69 (6H, t, ^4J 2.8, 3 x C5H_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 164.7 (*C*=O), 52.5 (*C2*), 43.1 (*C1*), 41.4 (*C3*), 36.4 (*C5*), 29.5 (*C4*). Data in agreement with the literature.[10]

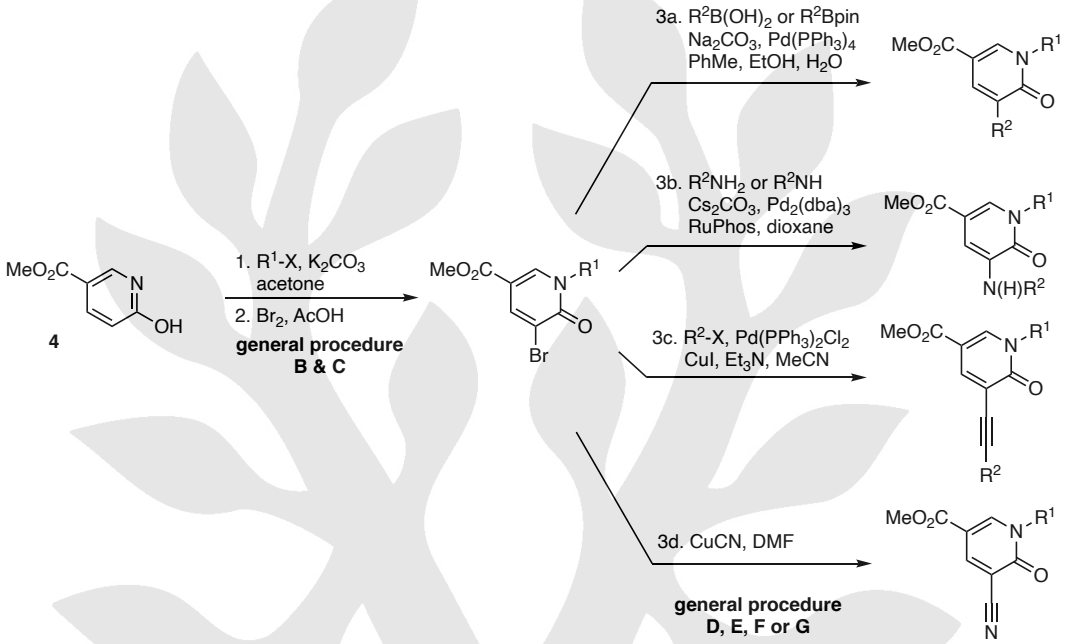
2-Chloro-1-morpholinoethan-1-one (5d):



Prepared according to general procedure **A** using morpholine (0.436 mL, 5.00 mmol), the crude material was subjected to column chromatography with eluent hexanes:CH_2Cl_2 1:1 to afford pure product as a yellowish oil (0.535 g, 65%): $\mathbf{R_f}$ 0.21 (hexanes:EtOAc, 1:1, UV/$KMnO_4$); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 4.06 (2H, s, C1H_2), 3.69–3.74 (4H, m,

C3H_2, C4H_2), 3.62–3.64 (2H, m, C2H_2), 3.52–3.54 (2H, m, C5H_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 165.4 (*C*=O), 66.8 (*C3*), 66.6 (*C4*), 46.9 (*C5*), 42.6 (*C2*), 40.7 (*C1*). Data in agreement with the literature.[11]

Pyridone Core Scaffold Syntheses 6a-v:



Scheme S2: Overview of the pyridone core structure assembly encompassing general procedures B-G.

General Procedure B:
To a mixture of a pyridone derivative (1.00 equiv.), K_2CO_3 (3.00 equiv.) in acetone (0.10 M based on pyridone derivative) was added an alkyl halide (1.00 or 1.40 equiv., specified individually) at room temperature and the mixture was stirred at 50 °C for an individually specified time. Worked-up by one of two methods:
Method 1: The mixture as concentrated in vacuo, treated with water (70 mL per mmol pyridone) and extracted with CH_2Cl_2 (3 x 70 mL per mmol pyridone). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo.
Method 2: The mixture was suspended by addition of hexanes (20 mL per mmol pyridone), filtered and washed with portionwise addition of hexanes (15 mL per mmol pyridone) and water (40 mL per mmol pyridone). The remaining solid was dried in vacuo.
In some cases, further purification either column chromatography or recrystallization were required to give clean *N*-alkylated compounds (individually specified).

General Procedure C:
Prepared according to a modified literature procedure.[12] To a solution of pyridone derivative (1.00 equiv.) in glacial acetic acid (4.0 mL per mmol pyridone) was added dropwise bromine (2.00 equiv.) at room temperature. The orange mixture was stirred at 60 °C for 4 hours. When cooled to room temperature the mixture was treated with aqueous saturated sodium thiosulfate (0.600 mL per mmol pyridone) and adjusted to pH 7 with aqueous saturated $NaHCO_3$ (6 mL per mmol pyridone). The suspension was filtered and washed extensively with water. The filter cake was dried in vacuo to give the desired brominated pyridone derivative.

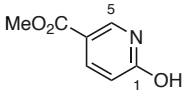
General Procedure D:
Prepared according to a modified literature procedure.[13] A mixture of bromopyridone (1.00 equiv.), arylboronic acid or arylboronic acid pinacol ester (2.50 equiv.), Na_2CO_3 (4.00 equiv.) and $Pd(PPh_3)_4$ (5.00-10.0 mol%) was evacuated for 5-10 minutes under high vacuum and backfilled with N_2. The mixture was treated with PhMe, EtOH and H_2O (8:3:1; 0.10 M) or for some reactions DMF (0.090 M) and the mixture was heated to 75 °C for an individually specified time in a pre-heated sand bath. The mixture was poured into water and rinsed with CH_2Cl_2 (both 30 mL per 0.10 mmol pyridone). The layers were separated, and the aqueous layer was extracted with fresh CH_2Cl_2 (2 x 30 mL per 0.10 mmol pyridone). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel with an individually specified eluent to give the desired products. Some of the products were additionally purified by recrystallization.

General Procedure E:
Prepared according to a modified literature procedure.[14] A deaerated mixture of bromo-pyridone (0.100 mmol), amine (0.150 mmol), Cs_2CO_3 (0.400 mmol), RuPhos (17.0 mol%), and $Pd_2(dba)_3$ (10 mol%) was treated with 1,4-dioxane (1.0 mL) and stirred for an individually specified time (18-20h) in a sand bath preheated to 110 °C. The mixture was filtrated through a plug of Celite, washed with CH_2Cl_2 and the filtrate was concentrated in vacuo. The residue was purified by column chromatography over silica gel with an individually specified eluent to give the desired products. Some of the products were additionally purified by recrystallization.

General Procedure F:
Prepared according to a modified literature procedure.[15] A deaerated solution of bromo-pyridone (0.100 mmol), CuI (20 mol%), $Pd(PPh_3)_2Cl_2$ (20 mol%) and triethylamine (0.200 mmol) in MeCN (1.0 mL) was treated with an alkynyl compound (0.120 mmol) and stirred for an individually specified time (5-20 h) in a sand bath preheated to 60 °C. The mixture was filtrated through a plug of Celite, washed with CH_2Cl_2 and the filtrate was concentrated in vacuo. The residue was purified by column chromatography over silica gel with an individually specified eluent to give the desired products. Some of the products were additionally purified by recrystallization.

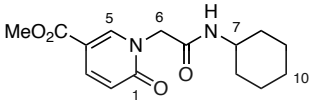
General Procedure G:
Prepared according to a modified literature procedure.[16] To a bromide substrate (1.00 equiv.) in dry DMF (2.0 mL per mmol substrate) was treated with CuCN (2.00 or 3.00 equiv.) at room temperature. The mixture was deareated by nitrogen or argon sparging for five minutes. The mixture was heated to 120 °C for 20 hours under a nitrogen atmosphere. EtOAc (20 mL per mmol substrate) was added to the mixture and was washed with water (3 x 10 mL per mmol substrate) and brine (2 x 10 mL per mmol substrate). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography over silica gel with an individually specified eluent gave the desired products. Some of the products were additionally purified by recrystallization.

Methyl 6-hydroxynicotinate (4):



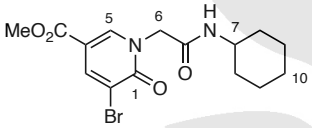
Prepared according to a modified literature procedure.[17] A suspension of 6-hydroxynicotinic acid (2.99 g, 21.5 mmol) in MeOH (43 mL) was treated drop wise with sulfuric acid (1.30 ml, 23.7 mmol), heated to reflux and stirred at this temperature for 18 hours. The mixture was cooled to room temperature and was concentrated in vacuo to a residual volume of ~10 ml. The solvent of the formed suspension was exchanged by water and the mixture was stirred for 1 hour at room temperature. The precipitated crystals were filtered, washed with water (2 x 20 ml) and dried in vacuo to give the product as an off-white solid (2.35 g, 71%): $\mathbf{R_f}$ 0.22 (EtOAc, 100%, UV/$KMnO_4$); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 13.05 (1H, br, O*H*), 8.21 (1H, d, ^4J 2.4, C5*H*), 8.01 (1H, dd, ^3J 9.6, ^4J 2.5, C3*H*), 6.58 (1H, d, ^3J 9.6, C2*H*), 3.87 (3H, s, OCH_3); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.6 (CO_2CH_3), 164.6 (*C1*), 141.1 (*C5*), 139.9 (*C3*), 119.7 (*C2*), 111.2 (*C4*), 52.3 (CO_2CH_3); **APCI-HRMS:** m/z calcd. for $[C_7H_8NO_3]^+$ 154.049 found 154.050 $[M+H]^+$. Data in agreement with the literature.[17]

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4'):



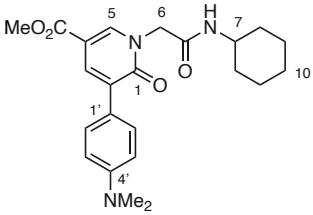
Prepared according to general procedure **B** and *Work-up Method 1* using methyl 6-hydroxynicotinate **(4)** (2.22 g, 14.5 mmol) and 2-chloro-*N*-cyclohexylacetamide (2.55 g, 14.5 mmol), acetone (145 mL), K_2CO_3 (6.00 g, 43.5 mmol). Stirred at 50 °C for 3 hours. Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate was obtained as a white solid without further purification (3.90 g, 92%): $\mathbf{R}_f$ 0.45 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3302m, 3036w, 2930m, 2853w, 1721m, 1663s, 1647s, 1609m, 1548m, 1449w, 1415w, 1346m, 1303s, 1261w, 1248m, 1202w, 1117m, 1105w, 982w, 993w, 930w, 892w, 840w, 799w, 774m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.29 (1H, d, ^4J 2.4, C5*H*), 7.91 (1H, dd, ^3J 9.5, ^4J 2.5, C3*H*), 6.58 (1H, d, ^3J 9.5,C2*H*), 6.40 (1H, d, ^3J 7.9, N*H*), 4.53 (2H, s, C6H_2), 3.86 (3H, *s*, OCH_3), 3.66–3.77 (1H, m, C7*H*), 1.82–1.91 (2H, m, 2 x C8*H*), 1.64–1.72 (2H, m, 2 x C9*H*), 1.54–1.63 (1H, m, C10*H*), 1.25–1.40 (2H, m, 2 x C9*H*), 1.11–1.23 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.2 (*C*=O), 164.5 (*C*=O), 162.8 (*C1*), 143.5 (*C5*), 139.7 (*C3*), 119.6 (*C2*), 110.7 (C*4*), 54.1 (*C6*), 52.3 (O*C*H$_3$), 48.8 (*C7*), 32.8 (*C8*), 25.5 (*C10*), 24.7 (C*9*); **APCI-HRMS:** m/z calcd. for $[C_{15}H_{21}N_2O_4]^+$ 293.1496 found 293.150 $[M+H]^+$.

Methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate:



Prepared according to general procedure **C** using methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate **(4')** (1.57 g, 5.37 mmol), bromine (0.550 mL, 10.7 mmol), acetic acid (21.5 mL). Methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate was obtained as a white solid (1.79 g, 90%): $\mathbf{R}_f$ 0.65 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3282w, 3077w, 2931w, 2855w, 2359w, 1715m, 1653s, 1560w, 1438w, 1331w, 1281m, 1227w, 1201w, 1145m, 1006w, 923w, 856w, 769w, 708w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.31 (1H, d, ^4J 2.3, C3*H*), 8.28 (1H, d, ^4J 2.3, C5*H*), 6.23 (1H, d, ^3J 8.1, N*H*), 4.57 (2H, s, C6H_2), 3.87 (3H, s, OCH_3), 3.66–3.77 (1H, m, C7*H*), 1.84–1.92 (2H, m, 2 x C8H), 1.64–1.74 (2H, m, 2 x C9*H*), 1.56–1.63 (m, 1H, C10*H*), 1.24–1.39 (m, 2H, 2 x C9*H*), 1.12–1.23 (3H, m, 2 x C8*H,* C10*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 164.6 (*C*=O), 163.6 (*C*=O), 159.3 (C*1*), 142.6 (*C5*), 141.4 (*C3*), 115.3 (*C2*), 110.7 (*C4*), 54.8 (*C6*), 52.6 (O*C*H$_3$), 49.1 (*C7*), 32.9 (*C8*), 25.5 (*C10*), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{15}H_{20}BrN_2O_4]^+$ 371.0601 found 371.0603 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6a):

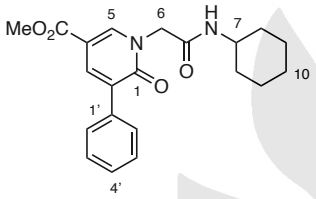


Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (50.0 mg, 0.140 mmol), *N,N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline* (83.2 mg, 0.340 mmol), Na_2CO_3, (57.1 mg, 0.540 mmol), $Pd(PPh_3)_4$ (15.6 mg, 0.0135 mmol) in PhMe:EtOH:H_2O (0.80:0.30:0.10 mL). Stirred at 75 °C for 1 hour. Column chromatography over silica gel with eluent 1:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) to 100% (EtOAc:CH_2Cl_2, 6:4) gives product as a yellow solid (50.9 mg, 91%): $\mathbf{R}_f$ 0.34 (hexanes:(EtOAc: CH_2Cl_2 6:4), 2:8; UV); **IR:** $\tilde{\nu}$ = 3279w, 3077w, 2923w, 2853w, 1708m, 1652w, 1608s, 1553m, 1522m, 1432m, 1357m, 1333m, 1307m, 1268m, 1250m, 1225s, 1204m, 1152m, 1113m, 1103m, 1011m, 967w, 946m, 918m, 882w, 867w, 816m, 789m, 764m, 707m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.21 (1H, d, ^4J 2.5, C5*H*), 8.01 (1H, d, ^4J 2.5, C3*H*), 7.60–7.64 (2H, m, 2 x C2'*H*), 6.74–6.79 (2H, m, 2 x C3'*H*), 6.52 (1H, d, *J* 8.2, CON*H*), 4.59 (2H, s, C6H_2), 3.87 (3H, s, CO_2CH_3), 3.64–3.77 (1H, m, C7*H*), 2.99 (6H, s, 2 x NCH_3), 1.79–1.91 (2H, m, 2 x C8*H*), 1.61–1.73 (2H, m, 2 x C9*H*), 1.52–1.61 (1H, m, C10*H*), 1.23–1.40 (2H, m, 2 x C9*H*), 1.08–1.22 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.7 (*C*ONH), 165.0 (*C*OCH$_3$), 162.3 (*C1*), 150.6 (*C4'*), 140.6 (*C5*), 135.1 (*C3*), 131.0 (*C2*), 129.5

(*C2'*), 123.5 (*C1'*), 112.1 (C3'), 110.8 (*C4*), 54.9 (*C6*), 52.3 (CO_2CH_3), 48.8 (*C7*), 40.6 ($N(CH_3)_2$), 32.8 (*C8*), 25.6 (*C10*), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{23}H_{30}N_3O_4]^+$ 412.2231 found 412.2230 $[M+H]^+$.

** Accessed with the borylation method described for benzimidazoles (see below) using 4-bromo-*N,N*-dimethylaniline (400 mg, 2.00 mmol). Column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 90:10 gives* N,N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (346 mg, 70%): **R_f** 0.69 (hexanes:EtOAc, 2:1, UV); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.68–7.70 (2H, m), 6.68–6.70 (2H, m), 2.99 (6H, s), 1.32 (12H, s); Data in agreement with literature.*[18]

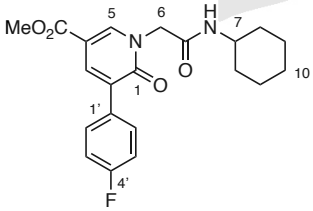
Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-5-phenyl-1,6-dihydropyridine-3-carboxylate (6b):



Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (10.0 mg, 0.0269 mmol), phenylboronic acid (3.90 mg, 0.0323 mmol), $PdCl_2(PPh_3)_2$ (1.40 mg, 0.00188 mmol), Na_2CO_3 (10.7 mg, 0.10 mmol) in PhMe:EtOH:H_2O (0.36:0.14:0.050 mL). Stirred at 75 °C for 5 hours. Column chromatography over silica gel with eluent 100% hexanes to 1:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) gives product as an off-white solid (7.90 mg, 80%): **R_f** 0.40 (hexanes:(EtOAc: CH_2Cl_2 6:4), 2:8; UV); **LC-MS** t_R=3.80 min. (5% to 100% MeCN in H_2O with 1% formic acid over 5 min.); **IR:** $\tilde{\nu}$ = 3295w, 3085w, 2929w, 2856w, 1704m, 1655s, 1557m, 1496w, 1451w, 1434w, 1424m, 1379w, 1333m, 1322m, 1305m, 1255m, 1222s, 1179w, 1151w, 1119m, 1006w, 969w, 952w, 920w, 884w, 871w, 843w, 825w, 794m, 771w, 759m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.30 (1H, d, ^4J 2.5, C5*H*), 8.07 (1H, d, ^4J 2.4, C3*H*), 7.65 (2H, d, *J* 7.4, 2 x C2'*H*), 7.33–7.45 (2H, m, 2 x C3'*H*), 6.50 (1H, d, *J* 8.1, C4'*H*), 4.61 (2H, s, C6H_2), 3.88 (3H, s, CO_2CH_3), 3.62–3.78 (1H, m, C7*H*), 1.77–1.93 (2H, m, 2 x C8*H*), 1.61– 1.74 (2H, m, 2 x C9*H*), 1.51–1.62 (1H, m, C10*H*), 1.24–1.37 (2H, m, 2 x C9*H*), 1.05–1.18 (3H, m, 2 x C8*H*, C10*H*). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.4 (*C*ONH), 164.7 (CO_2CH_3), 162.0 (*C1*), 142.4 (*C5*), 137.5 (*C3*), 135.8 (*C1'*), 130.8 (*C2*), 128.7 (C2'), 128.5 (**C4'*), 128.4 (**C3'*), 110.5 (*C4*), 54.5 (*C6*), 52.3 (CO_2CH_3), 48.9 (*C7*), 32.8 (*C8*), 25.5 (*C10*), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{21}H_{25}N_2O_4]^+$ 369.1809 found 369.1809 $[M+H]^+$.

** indistinguishable signals.*

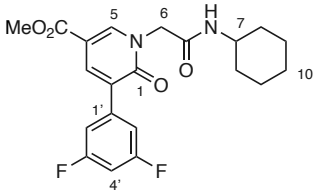
Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-fluorophenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6c):



Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (519 mg, 1.40 mmol), 4-fluorophenylboronic acid (490 mg, 3.50 mmol), Na_2CO_3, (594 mg, 5.60 mmol), $Pd(PPh_3)_4$ (80.9 mg, 0.0700 mmol), PhMe:H_2O:EtOH (8.7:1.2:3.4 mL). Stirred at 75 °C for 4 hours. Column chromatography over silica gel with eluent 9:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) to 100% (EtOAc:CH_2Cl_2, 6:4) and additional recrystallization from toluene gives product as an off-white solid (412 mg, 1.07 mmol, 76%): **R_f** = 0.39 (hexanes:(EtOAc:CH_2Cl_2 6:4), 2:8; UV); **IR:** $\tilde{\nu}$ = 3276w, 3078w, 2934w, 2854w, 1717m, 1649s, 1559m, 1509m, 1433m, 1363w, 1329m, 1299m, 1271m, 1250m, 1232s, 1222s, 1162m, 1126w, 1102m, 1026w, 1008m, 970w, 953w, 925w, 883w, 871w, 848m, 809m, 786w, 763m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.32 (1H, d, *J* 2.5, C5*H*), 8.06 (1H, d, *J* 2.4, C3*H*), 7.62–7.70 (2H, m, 2 x C2'*H*), 7.06–7.19 (2H, m, 2 x C3'*H*), 6.33 (1H, d, *J* 8.1, N*H*), 4.61 (2H, s, C6*H*), 3.91 (3H, s, CO_2CH_3), 3.67–3.82 (1H, m, C7*H*), 1.83–1.95 (2H, m, 2 x C8*H*), 1.66–1.77 (2H, m, 2 x C9*H*), 1.54–1.64 (2H, m, C10*H*), 1.30–1.43 (2H, m, 2 x C9*H*), 1.09–1.25 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.2 (*C*ONH), 164.6 (CO_2CH_3), 162.9 (d, $^1J_{CF}$ = 248, *C4'*), 161.9 (*C2*), 142.4 (*C5*), 137.2 (*C3*), 131.8 (d, $^4J_{CF}$ = 3.3, *C1'*), 130.5 (d, $^3J_{CF}$ = 8.1, *C2'*), 129.8 (*C1*), 115.5 (d. $^2J_{CF}$ = 22, *C3'*), 110.5 (*C4*), 54.5 (*C6*), 52.4 (CO_2CH_3), 49.0 (*C7*), 32.9 (*C8*), 25.5 (*C10*), 24.8 (*C9*). **^{19}F-NMR**

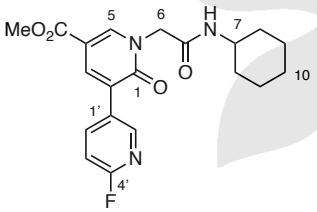
(377 MHz, $CDCl_3$): $\delta = -113.28$. **APCI-HRMS:** m/z calcd. for $[C_{21}H_{24}FN_2O_4]^+$ 387.1715 found: 387.1717 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(3,5-difluorophenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6d):



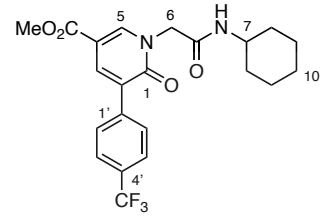
Prepared according to general procedure **E** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), 3,5-difluorophenylboronic acid (31.9 mg, 0.202 mmol), Cs_2CO_3, (34.3 mg, 0.323 mmol) $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), DMF (0.90 mL). Reaction was heated stepwise at 75 °C for 2 hours, 100 °C for 2 hours and at 115 °C for 18 hours. Column chromatography over silica gel with eluent 100% hexanes to 1:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) to 100% (EtOAc:CH_2Cl_2, 6:4) and additional recrystallization from toluene gives product as an off-white solid (5.70 mg, 17%): $\mathbf{R_f}$ 0.46 (hexanes:(EtOAc:CH_2Cl_2 6:4), 2:8; UV); **IR:** $\tilde{\nu} = 3283$w, 3081w, 2923w, 2850w, 1708m, 1652s, 1625m, 1590m, 1548m, 1477w, 1448m, 1438m, 1426w, 1409w, 1371w, 1338m, 1324m, 1306m, 1281m, 1252m, 1232s, 1207m, 1152w, 1120m, 1109m, 1093m, 1013m, 988m, 950m, 934w, 890m, 852m, 826m, 790m, 779w, 764m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.33 (1H, d, *J* 2.4, C5*H*), 8.09 (1H, d, *J* 2.4, C3*H*), 7.22–7.28 (2H, m, C2'*H*), 6.81 (1H, tt, $^3J_{HF}$ 8.8, $^4J_{HH}$ 2.4, C4'*H*), 6.25 (1H, d, *J* 7.9, N*H*), 4.60 (2H, s, C6H_2), 3.89 (3H, s, CO_2CH_3), 3.65–3.79 (1H, m, C7*H*), 1.82–1.96 (2H, m, 2 x C8*H*), 1.64–1.74 (2H, m, 2 x C9*H*), 1.53–1.62 (1H, m, C10*H*), 1.25–1.42 (2H, m, 2 x C9*H*), 1.07–1.21 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.8 (*C*ONH), 164.3 (*C*O_2CH$_3$), 162.8 (dd, $^1J_{CF}$ = 248, $^3J_{CF}$ 13.2, C3'), 161.5 (*C1*), 143.1 (*C5*), 138.5 (t, $^3J_{CF}$ 10.3, *C1'*), , 137.9 (*C3*), 128.1 (t, $^4J_{CF}$ 2.7 Hz, *C2*), 111.2–111.7 (m, *C2'*), 110.2 (*C4*), 103.7 (t, $^2J_{CF}$ 25.3, *C4'*), 54.2 (*C6*), 52.3 (CO_2CH_3), 48.9 (*C7*), 32.7 (*C8*), 25.4 (*C10*), 24.7 (*C9*); **^{19}F-NMR (377 MHz, $CDCl_3$):** δ = –109.9; **ESI-HRMS:** m/z calcd. for $[C_{42}H_{45}F_4N_4O_8]^+$ 809.3168 found 809.3200 $[2M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6'-fluoro-2-oxo-1,2-dihydro-[3,3'-bipyridine]-5-carboxylate (6e):



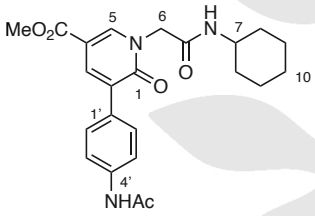
Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), (6-fluoropyridin-3-yl)boronic acid (28.5 mg, 0.200 mmol), Na_2CO_3, (34.3 mg, 0.320 mmol), $Pd(PPh_3)_4$ (4.70 mg, 0.00400 mmol), PhMe:H_2O:EtOH (0.50:0.70:0.20 mL). Stirred at 75 °C for 30 hours. Column chromatography over silica gel with eluent 100% hexanes to 2:8 hexanes:(EtOAc:CH_2Cl_2, 6:4) and additional recrystallization from toluene gives product as an off-white solid (20.0 mg, 64%): $\mathbf{R_f}$ 0.18 (hexanes:(EtOAc:CH_2Cl_2 6:4), 2:8; UV); **IR:** $\tilde{\nu} = 3271$w, 3088w, 2939w, 2855w, 1717m, 1650s, 1616m, 1590m, 1564m, 1484m, 1438m, 1428m, 1376w, 1363w, 1337w, 1315s, 1298m, 1263m, 1247s, 1224s, 1153w, 1122m, 1104m, 1021m, 1009m, 970w, 953w, 929m, 877w, 843m, 822m, 787m, 763s, 746m, 730m, 718m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.48 (1H, m, C5'*H*), 8.33 (1H, d, ^4J 2.5, C5*H*), 8.12–8.20 (1H, m, C2'*H*), 8.09 (1H, d, *J* 2.4, C3*H*), 6.99 (1H, dd, *J* 8.5, 3.0, C3'*H*), 6.22 (d, *J* 8.1, N*H*), 4.60 (2H, s, C6H_2), 3.89 (3H, s, CO_2CH_3), 3.67–3.80 (1H, m, C7*H*), 1.83–1.96 (2H, m, 2 x C8*H*), 1.63–1.74 (2H, m, 2 x C9*H*), 1.54–1.63 (1H, m, C10*H*), 1.27–1.41 (2H, m, 2 x C9*H*), 1.10–1.23 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (*C*ONH), 164.4 (*C*O_2CH$_3$), 163.4 (d, $^1J_{CF}$ 241, *C4'*), 161.5 (*C1*), 147.4 (d, $^3J_{CF}$ 15.1, *C5'*), 143.3 (*C5*), 141.5 (d, $^3J_{CF}$ 8.0, *C2'*), 137.6 (C3), 129.7 (d, $^4J_{CF}$ 4.7, *C1'*), 129.6, 126.4, 110.5 (*C4*), 109.1 ($^2J_{CF}$ 37.4, *C3'*), 54.3 (*C6*), 52.5 (CO_2CH_3), 49.1 (*C7*), 32.9 (*C8*), 25.5 (*C10*), 24.8 (*C9*); **^{19}F-NMR (377 MHz, $CDCl_3$):** δ = –68.3; **APCI-HRMS:** m/z calcd. for $C_{20}H_{23}FN_3O_4^+$ 388.1667 found 388.1673 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-5-(4-(trifluoromethyl)phenyl)-1,6-dihydropyridine-3-carboxylate (6f):



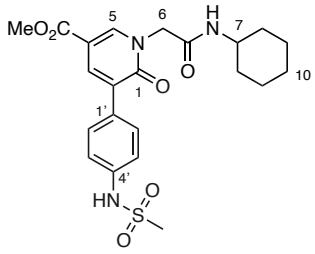
Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), 4-trifluoromethylboronic acid (38.4 mg, 0.200 mmol), Cs_2CO_3, (105 mg, 0.320 mmol), $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), DMF (0.80 mL). Stirred at 75 °C for 24 hours. Column chromatography over silica gel with eluent 100% hexanes to 2:8 hexanes:(EtOAc:CH_2Cl_2, 6:4) and additional recrystallization from toluene gives product as an off-white solid (6.10 mg, 17%): $\mathbf{R_f}$ 0.44 (hexanes:(EtOAc:CH_2Cl_2 6:4), 2:8; UV); **IR:** $\tilde{\nu}$ = 3293w, 3081w, 2930w, 2855w, 1709s, 1651s, 1626m, 1553s, 1433m, 1327s, 1308s, 1254s, 1230s, 1163s, 1110s, 1068s, 1013m, 968w, 954m, 940m, 923w, 892w, 870m, 846s, 820m, 789m, 766m, 730m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.34 (1H, d, *J* 2.4, C5*H*), 8.11 (1H, d, *J* 2.4, C3*H*), 7.79 (2H, d, *J* 8.2, C3'*H*), 7.68 (2H, d, *J* 8.2, C2'*H*), 6.25 (1H, d, *J* 8.0, N*H*), 4.60 (2H, s, C6H_2), 3.89 (3H, s, CO_2CH_3), 3.67–3.79 (1H, m, C7*H*), 1.88 (2H, dt, *J* 13, 4.0, 2 x C8*H*), 1.63–1.77 (2H, m, 2 x C9*H*), 1.54–1.63 (1H, m, C10*H*), 1.26–1.42 (2H, m, 2 x C9*H*), 1.12–1.21 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (*C*ONH), 164.3 (CO_2CH_3), 161.5 (*C1*), 143.0 (*C5*), 139.2 (*C1'*), 138.0 (*C3*), 130.2 ($^2J_{CF}$ 32.4, *C4'*), 129.2 (*C2*), 128.9 (2 x *C2'*), 125.3 (q, $^3J_{CF}$ 3.8, *C3'*), 124.2 ($^1J_{CF}$ 272, *C*F_3), 110.3 (*C4*), 54.3 (*C6*), 52.3 (CO_2CH_3), 48.9 (*C7*), 32.8 (*C8*), 25.4 (*C10*), 24.7 (*C9*); **^{19}F-NMR (377 MHz, $CDCl_3$):** δ = –62.7; **ESI-HRMS:** m/z calcd. $[C_{44}H_{46}F_6KN_4O_8]^+$ 911.2851 found 911.2866 $[2M+K]^+$.

Methyl 5-(4-acetamidophenyl)-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6g):



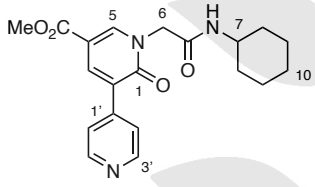
Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), (4-acetamidophenyl)pinacol borane (52.8 mg, 0.200 mmol), Na_2CO_3, (34.3 mg, 0.320 mmol), $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), PhMe:H_2O:EtOH (0.50:0.070:0.20 mL). Stirred at 75 °C for 4.5 hours. Column chromatography over silica gel with eluent 1:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) to 100% (EtOAc:CH_2Cl_2, 6:4) gives product as an off-white solid (24.4 mg, 71%): $\mathbf{R_f}$ 0.21 (CH_2Cl_2:MeOH, 95:5; UV); **IR:** $\tilde{\nu}$ = 3289w, 3081w, 2923w, 2851w, 2414w, 1711m, 1645s, 1606m, 1590m, 1553m, 1518m, 1436m, 1397m, 1371m, 1331m, 1307m, 1251m, 1227s, 1189m, 1116m, 1101m, 1009m, 965m, 930w, 874w, 840m, 818m, 788m, 765m, 724m; **^{1}H-NMR (400 MHz, CD_3OD):** δ = 8.42 (1H, d, ^4J 2.4, C5*H*), 8.07 (1H, d, ^4J 2.5, C3*H*), 7.63 (4H, s, 2 x C2'*H*, 2 x C3'*H*), 4.76 (2H, s, C6H_2), 3.90 (3H, s, CO_2CH_3), 3.64–3.74 (1H, m, C7*H*), 2.15 (3H, s, NHCH_3), 1.87–1.96 (2H, m, 2 x C8*H*), 1.74–1.82 (2H, m, 2 x C9*H*), 1.61–1.69 (1H, m, C10*H*), 1.18–1.45 (5H, m, 2 x C8*H*, 2 x C9*H*, C10*H*); **^{13}C-NMR (101 MHz, CD_3OD):** δ = 171.7 (NH*C*OCH_3), 167.9 (NH*C*O), 166.3 (CO_2CH_3), 163.4 (*C1*), 144.8 (*C5*), 140.0 (*C4'*), 137.9 (*C3*), 132.8 (*C1'*), 131.0 (*C2*), 130.1 (C2'), 120.6 (C3'), 111.2 (*C4*), 53.9 (*C6*), 52.6 (CO_2CH_3), 50.2 (*C7*), 33.7 (*C8*), 26.6 (*C10*), 26.1 (*C9*), 23.9 (NHCH_3 **APCI-HRMS:** m/z calcd. for $[C_{23}H_{28}N_3O_5]^+$ 426.2023 found 426.2025 $[M+H]^+$; **UV/Vis & Fluorescence Spectroscopy:** (in aqueous PBS, 1% DMSO): λ_{abs} 318 nm, ε_{abs} $1.1 \cdot 10^4$ M^{-1} cm; λ_{em}(exc 320) 420 nm.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-[3,4'-bipyridine]-5-carboxylate (6h):



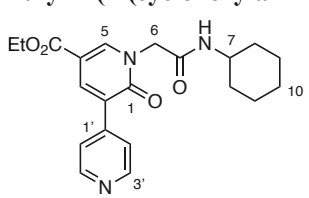
Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), (4-(methylsulfonamido)phenyl)boronic acid (43.4 mg, 0.202 mmol), Na_2CO_3, (34.3 mg, 0.320 mmol), $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), PhMe:H_2O:EtOH (0.50:0.070:0.20 mL). Stirred at 75 °C for 5 hours. Column chromatography over silica gel with eluent 100% (EtOAc:CH_2Cl_2, 6:4) to 97:3 (EtOAc:CH_2Cl_2, 6:4):MeOH and additional recrystallization from toluene gives product as a white solid (9.90 mg, 27%): $\mathbf{R}_f$ 0.50 ((CH_2Cl_2:EtOAc 6:4):MeOH, 95/5; UV); **IR:** $\tilde{\nu}$ = 3222w, 3076w, 2928w, 2851w, 2426w, 1713m, 1652s, 1607m, 1556w, 1512w, 1448m, 1432m, 1407w, 1332m, 1307m, 1251m, 1227s, 1196w. 1147s, 1117m, 1071w, 1014w, 990w, 980m, 968w, 931w, 842m, 806w, 789w, 764m, 734w, 725w; **^{1}H-NMR (400 MHz, $(CD_3)_2SO$):** δ = 9.85 (1H, s, N*H*SO_2CH_3), 8.48 (1H, d, ^4J 2.5, C5*H*), 7.91 (1H, d, ^4J 2.5, C3*H*), 7.65 (2H, d, *J* 8.56, 2 x C2'*H*), 7.23 (2H, d, *J* 8.56, 2 x C3'*H*), 4.71 (2H, s, 2 x C6*H*), 3.82 (3H, s, COC*H*$_3$), 3.53 (1H, td, *J* 10.3, 5.0, C7*H*), 3.01 (3H, s, SO_2CH_3), 1.63–1.79 (4H, m, 2 x C8*H*, 2 x C9*H*), 1.54 (1H, d, *J* 12.4, C10*H*), 1.09–1.37 (5H, m, 2 x C8*H*, 2 x C9*H*, C10*H*).
^{13}C-NMR (101 MHz, $(CD_3)_2SO$): δ = 165.1 (*C*ONH), 164.5 (*C*O_2CH_3), 160.5 (*C1*), 144.5 (*C5*), 138.1 (*C4'*), 135.4 (*C3*), 131.1 (*C1'*), 129.3 (*C2'*), 127.9 (*C2*), 119.0 (*C3'*), 107.7 (*C4*), 51.9 (*C6,* CO_2CH_3), 47.7 (*C7*), 39.3 (SO_2CH_3) 32.4 (*C8*), 25.2 (*C10*), 24.4 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{22}H_{28}N_3O_6S]^+$ 462.1693 found 462.1698 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-[3,4'-bipyridine]-5-carboxylate (6i):



Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (120 mg, 0.323 mmol), pyridine-4-boronic acid hydrate (114 mg, 0.808 mmol), Na_2CO_3, (137 mg, 1.29 mmol), $Pd(PPh_3)_4$ (18.7 mg, 0.0162 mmol), PhMe:H_2O:EtOH (2.0:0.30:0.80 mL). Stirred at 75 °C for 40 hours. Column chromatography over silica gel with eluent 1:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) to 100% (EtOAc:CH_2Cl_2, 6:4) and additional recrystallization from toluene gives product as an off-white solid (45.9 mg, 38%): $\mathbf{R}_f$ 0.27 ((CH_2Cl_2:EtOAc 6:4):MeOH, 95:5; UV); **IR:** $\tilde{\nu}$ = 3281w, 2933w, 2855w, 1716s, 1652s, 1596w, 1557m, 1440m, 1397w, 1332m, 1305w, 1255m, 1224w, 1193w, 1119w, 1104w, 997w, 937w, 891w, 833w, 816w, 787w, 768w, 729w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.63–8.70 (2H, m, 2 x C3'*H*), 8.36 (1H, d, ^4J 2.4, C5*H*), 8.18 (1H, d, ^4J 2.4, C3*H*), 7.61–7.65 (2H, m, 2 x C2'*H*), 6.23 (1H, d, *J* 8.1, N*H*), 4.60 (2H, s, C6*H*$_2$), 3.90 (3H, s, CO_2CH_3), 3.68–3.81 (1H, m, C7*H*), 1.84–1.94 (2H, m, 2 x C8*H*), 1.64–1.74 (2H, m, 2 x C9*H*), 1.55–1.64 (1H, m, C10*H*), 1.28–1.41 (2H, m, 2 x C9*H*), 1.10–1.23 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (*C*ONH), 164.4 (*C*O_2CH_3), 161.2 (C1), 150.1 (2 x *C3'*), 143.8 (*C5*), 143.3 (*C1'*), 138.5 (*C3*), 127.7 (*C2*), 123.0 (*C2'*), 110.4 (C4), 54.3 (*C6*), 52.5 (CO_2CH_3), 49.1 (*C7*), 32.9 (*C8*), 25.5 (C10), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{20}H_{24}N_3O_4]^+$ 370.1761 found 370.1762 $[M+H]^+$; **UV/Vis & Fluorescence Spectroscopy:** (in aqueous PBS, 1% DMSO): λ_{abs} 318 nm, ε_{abs} 0.86 $\cdot 10^4$ M^{-1} cm; λ_{em}(exc 320) 401 nm.

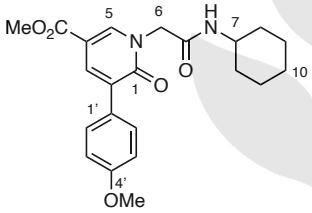
Ethyl 1-(2-(cyclohexylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-[3,4'-bipyridine]-5-carboxylate (6j):



To a solution of methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-[3,4'-bipyridine]-5-carboxylate (13.5 mg, 0.0380 mmol), in THF:H_2O (1:1, 1.5 mL) was added NaOH (15.2 mg, 0.380 mmol) at room temperature. The mixture was stirred at the same temperature for 1.5 hours. The mixture was filtered through a plug of Celite and the filtrate was concentrated in vacuo. The residue was dissolved in EtOH (0.38 mL) and treated with concentrated H_2SO_4 (20.0 µL, 0.380 mmol) at room temperature. The mixture was stirred at reflux for 20 hours, cooled to room temperature and adjusted to pH 10 using aqueous saturated $NaHCO_3$ followed by extraction with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered

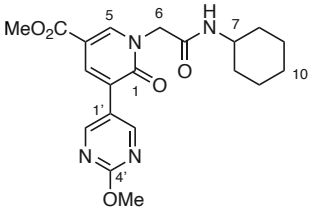
and concentrated in vacuo to give product as an off-white solid (7.00 mg, 48%); $\mathbf{R}_f$ 0.19 (EtOAc, 100%, UV/$KMnO_4$): **IR:** $\tilde{\nu}$ = 3398w, 2930m, 2854w, 2359w, 1715m, 1658s, 1596w, 1554m, 1432w, 1366w, 1325m, 1302m, 1253m, 1220m, 1107m, 1026w, 951w, 889w, 786w, 764w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.68 (2H, br s, C3'*H*), 8.36 (1H, d, ^4J 2.4, C5*H*), 8.19 (1H, d, ^4J 2.4, C3*H*), 7.66 (2H, d, ^3J 5.1, C2'*H*), 6.33 (1H, d, ^3J 8.0, N*H*), 4.62 (2H, s, C6H_2), 4.36 (2H, q, ^3J 7.1, OCH_2Me), 3.69–3.78 (1H, m, C7*H*), 1.85–1.93 (2H, m, 2 x C8*H*), 1.64–1.73 (2H, m, 2 x C9*H*), 1.55–1.63 (1H, m, C10*H*), 1.38 (3H, t, ^3J 7.2, OCH_2CH_3), 1.27–1.33 (2H, m, 2 x C9*H*), 1.11–1.22 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (*C*ONR), 163.9 (*C*O_2Et), 161.2 (*C1*), 149.8 (*C3'*), 143.80 (*C5)*, 143.6 (*C1'*), 138.7(*C3)*, 127.5 (*C2*), 123.1 (*C2'*), 110.7 (*C4*), 61.6 (O*Et*), 54.3 (*C6*), 49.1 (*C7*), 32.9 (*C8*), 25.5 (*C10*), 24.8 (*C9*), 14.5(O*Et*); **APCI-HRMS:** m/z calcd. for $[C_{21}H_{26}N_3O_4]^+$ 384.1918 found 384.1920 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6k):



Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), 4-methoxyphenylboronic acid (30.7 mg, 0.200 mmol), Na_2CO_3, (34.3 mg, 0.320 mmol), $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), PhMe:H_2O:EtOH (0.50:0.70:0.20 mL). Stirred at 75 °C for 2 hours. Column chromatography over silica gel with eluent 100% hexanes to 3:7 hexanes:(EtOAc:CH_2Cl_2, 6:4) and additional recrystallization from toluene gives product as a colorless solid (27.3 mg, 85%): $\mathbf{R}_f$ 0.36 (hexanes:(EtOAc:CH_2Cl_2 6:4), 2:8; UV); **IR:** $\tilde{\nu}$ = 3281w, 3080w, 2924w, 2853w, 1709m, 1652s, 1607m, 1556m, 1513m, 1431m, 1376w, 1334m, 1318m, 1305m, 1249s, 1224s, 1180m, 1153w, 1114m, 1026m, 1009m, 968w, 955w, 923w, 891w, 870w, 834m, 819m, 795w, 786w, 765m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.26 (1H, d, *J* 2.4, C5*H*), 8.02 (1H, d, *J* 2.5, C3*H*), 7.63 (2H, d, *J* 8.8, 2 x C3'*H*), 6.95 (2H, d, *J* 8.8, 2 x C2'*H*), 6.43 (1H, d, *J* 8.1, N*H*), 4.59 (2H, s, C6H_2), 3.88 (3H, s, CO_2CH_3), 3.84 (3H, s, OCH_3), 3.65–3.77 (1H, m, C7*H*), 1.86 (2H, dt, *J* 12, 4.0, 2 x C8*H*), 1.62–1.72 (2H, m, 2 x C9*H*), 1.53–1.58 (1H, m, C10*H*), 1.20–1.41 (2H, m, 2 x C9*H*), 0.95–1.22 (3H, m, 2 x C9*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.5 (*C*ONH), 164.8 (*C*O_2CH_3), 162.1 (*C1*), 159.9 (*C4'*), 141.6 (C5), 136.4 (C3), 130.5 (*C1'*), 129.9 (C3'), 128.2 (*C2*), 113.9 (C2'), 110.6 (*C4*), 55.5 (OCH_3), 54.7 (*C6*), 52.3 (CO_2CH_3), 48.9 (*C7*), 32.9 (*C*8), 25.5 (*C*10), 24.8 (*C*9); **ESI-HRMS:** m/z calcd. for $[C_{22}H_{27}N_2O_5]^+$ 399.1914 found 399.1933 $[M+H]^+$.

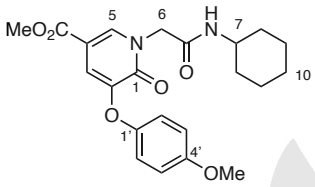
Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(2-methoxypyrimidin-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6l):



Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), 2-methoxypyrimidine-5-boronic acid (31.1 mg, 0.200 mmol), Na_2CO_3, (34.3 mg, 0.320 mmol), $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), PhMe:H_2O:EtOH (0.50:0.70:0.20 mL). Stirred at 75 °C for 4 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to CH_2Cl_2:MeOH 9:1 and additional recrystallization from toluene gives product as an off-white solid (19.8 mg, 61%): $\mathbf{R}_f$ 0.37 (CH_2Cl_2:MeOH, 95:5; UV); **IR:** $\tilde{\nu}$ = 3230w, 3086w, 2995w, 2934w, 2853w, 1724m, 1672m, 1647s, 1617m, 1590m, 1574m, 1551m, 1478s, 1453m, 1433m, 1417m, 1408m, 1365w, 1328s, 1305s, 1293s, 1262m, 1220s, 1151w, 1123m, 1046m, 1028m, 1014m, 969w, 954w, 933m, 890m, 882m, 846w, 832w, 817w, 801m, 788s, 762s, 721m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.86 (1H, s, 2 x C2'*H*), 8.32 (1H, d, *J* 2.4, C5*H*), 8.08 (1H, d, *J* 2.4, C3*H*), 6.22 (1H, br, N*H*), 4.60 (1H, s, C6H_2), 4.06 (3H, s, C4'OCH_3), 3.90 (3H, s, CO_2CH_3), 3.67–3.80 (1H, m, C7*H*), 1.89 (2H, dt, *J* 12, 3.9, 2 x C8*H*), 1.64–1.72 (2H, m, 2 x C9*H*), 1.54–1.64 (1H, m, C10*H*), 1.26–1.42 (2H, m, 2 x C9*H*), 1.09–1.23 (3H, m, 2 x C8*H*, C10*H*);

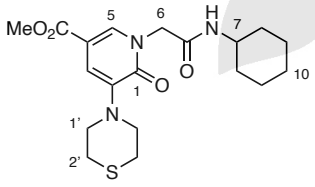
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.3 (*C4'*), 164.9 (*C*ONH), 164.4 (CO_2CH_3), 161.5 (*C1*), 158.8 (*C2'*), 143.2 (*C5*), 136.7 (*C3*), 124.7 (*C2*), 123.4 (*C1'*), 110.5 (*C4*), 55.3 (C4'OCH_3), 54.4 (*C6*), 52.5 (CO_2CH_3), 49.1 (*C7*), 32.9 (*C8*), 25.5 (*C10*), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{20}H_{25}N_4O_5]^+$ 401.1819 found 401.1823 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenoxy)-6-oxo-1,6-dihydropyridine-3-carboxylate (6m):



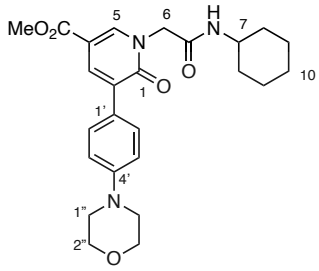
Prepared according to a modified literature procedure.[19] An oven-dried screw cap test tube was charged with 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), CuI (2.00 mg, 0.0100 mmol), 2-picolinic acid (2.50 mg, 0.0200 mmol), 4-methoxyphenol (15.0 mg, 0.120 mmol) and K_3PO_4 (42.5 mg, 0.200 mmol), evacuated and backfilled with argon three times. DMSO (1.0 mL) was added to the mixture and the tube was placed in a preheated oil bath at 90 ºC. The reaction mixture was stirred vigorously for 48 hours, cooled to room, treated with water (1.0 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered over celite and concentrated in vacuo. The residue was purified by column chromatography over silica gel with eluent hexanes 100% to hexanes:EtOAc 75:25 to 50:50 to give the product as a white solid (4.00 mg, 10%): **R_f** 0.22 (hexanes:EtOAc, 1:2, UV); **IR:** $\tilde{\nu}$ = 3297w, 2924m, 2852w, 2360w, 2340w, 1720m, 1658s, 1552m, 1504s, 1442m, 1303m, 1228s, 1198m, 1103w, 1036m, 923w, 891w, 826w, 764w; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ = 8.05 (1H, d, ^4J 2.2, C5*H*), 7.19 (1H, d, ^4J 2.2, C3*H*), 6.94–7.05 (2H, m, 2 x C3'*H*), 6.86–6.93 (2H, m, 2 x C2'*H*), 6.40 (1H, d, ^3J 9.5, N*H*), 4.60 (2H, s, C6H_2), 3.81 (3H, s, OCH_3), 3.80 (3H, s, CO_2Me), 3.67–3.77 (1, m, C7*H*), 1.84–1.91 (2H, m, 2 x C8*H*), 1.64–1.74 (2H, m, 2 x C9*H*), 1.58–1.63 (1H, m, C10*H*), 1.28–1.40 (2H, m, 2 x C9*H*), 1.11–1.22 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.2 (*C*ONR), 164.5 (CO_2Me), 158.6 (*C1*), 156.8 (*C4'*), 148.4 (*C1'*), 148.1 (*C2*), 136.4 (*C5*), 121.0 (*C3'*), 118.9 (*C3*), 115.2 (*C2'*), 109.7 (*C4*), 55.8 (OCH_3), 54.2 (*C6*), 52.4 (CO_2Me), 49.0 (*C7*), 32.8 (*C8*), 25.6 (*C10*), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{22}H_{27}N_2O_6]^+$ 415.1864 found 415.1864 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-5-thiomorpholino-1,6-dihydropyridine-3-carboxylate (6n):



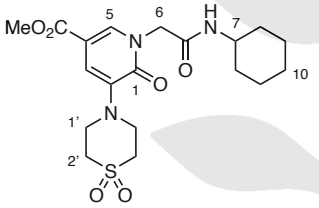
Prepared according to general procedure **E** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), thiomorpholine (15.0 µL, 0.150 mmol), Cs_2CO_3 (130 mg, 0.400 mmol), RuPhos (7.90 mg, 0.0170 mmol), $Pd_2(dba)_3$ (9.20 mg, 0.0100 mmol), 1,4-dioxane (1.0 mL). Stirred at 110 °C for 18 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a pale yellow solid (16.0 mg, 41%): **R_f** 0.63 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3291w, 3089w, 2927m, 2853w, 2359w, 1708m, 1654s, 1619m, 1554m, 1440m, 1306m, 1292m, 1274m, 1234m, 1216m, 1195m, 1115w, 1081w, 1007w, 954w, 765w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.99 (1H, d, ^4J 2.2, C5*H*), 7.24 (1H, d, ^4J 2.2, C3*H*), 6.21 (1H, d, ^3J 8.0, N*H*), 4.52 (2H, s, C6H_2), 3.85 (3H, s, OCH_3), 3.71 (1H, m, C7*H*), 3.36–3.41 (4H, m, 2 x C1'H_2), 2.78–2.85 (4H, m, 2 x C2'H_2), 1.83–1.90 (2H, m, C8H_2), 1.63–1.72 (2H, m, C9H_2), 1.55–1.62 (1H, m, C10*H*), 1.23–1.40 (2H, m, C9H_2), 1.09–1.21 (3H, m, C8H_2, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.4 (*C*ONR), 165.1 (CO_2Me), 159.7 (C*1*), 142.0 (C*2*), 136.0 (C*5*), 121.0 (C*3*), 110.3 (C*4*), 54.1 (C*6*), 52.3 (OCH_3), 51.74 (C*1'*), 48.9 (C*7*), 32.9 (*C8*), 27.7 (*C2'*), 25.5 (*C10*), 24.8 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{19}H_{28}N_3O_4S]^+$ 394.1795 found 394.1803 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-morpholinophenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6o):



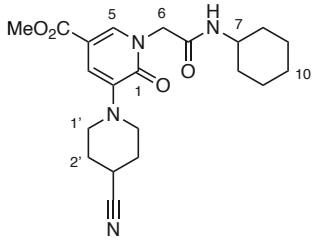
Prepared according to general procedure **D** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (30.0 mg, 0.0808 mmol), 4-morpholinophenylboronic acid (41.8 mg, 0.200 mmol), Na_2CO_3, (34.3 mg, 0.320 mmol), $Pd(PPh_3)_4$ (9.30 mg, 0.00810 mmol), PhMe:H_2O:EtOH (0.50:0.70:0.20 mL). Stirred at 75 °C for 2 hours. Column chromatography over silica gel with eluent 1:1 hexanes:(EtOAc:CH_2Cl_2, 6:4) to 100% EtOAc:CH_2Cl_2, 6:4 and additional recrystallization from EtOAc gives product as an off-white solid (30.9 mg, 84%): $\mathbf{R}_f$ 0.11 (Hexanes:(EtOAc:CH_2Cl_2, 6:4), 2:8; UV); **IR:** $\tilde{\nu}$ = 3285w, 3079w, 2928w, 2852w, 1709m, 1655s, 1608m, 1556m, 1516m, 1434m, 1375w, 1332m, 1306m, 1254m, 1225s, 1119m, 1070w, 1052w, 1030w, 1007w, 955w, 928m, 891w, 869w, 816m, 788w, 764m, 713w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.24 (1H, d, ^3J 2.5, C5*H*), 8.03 (1H, d, ^3J 2.4, C3*H*), 7.64 (2H, d, ^2J 8.8, 2 x C2'*H*), 6.95 (2H, d, ^2J 8.8, 2 x C3'*H*), 6.43 (1H, d, ^2J 8.1, N*H*), 4.59 (2H, s, C6H_2), 3.85–3.92 (7H, m, CO_2CH_3, 2 x C2"H_2), 3.65–3.80 (1H, m, C7*H*), 3.15–3.27 (4H, m, 2 x C1"H_2), 1.86 (2H, dt, *J* 12, 4.0, 2 x C8*H*), 1.60–1.74 (2H, m, 2 x C9*H*), 1.56–1.62 (1H, m, C10*H*), 1.27–1.41 (2H, m, 2 x C9*H*), 1.09–1.22 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.5 (*C*ONH), 164.9 (*C*O_2CH_3), 162.2 (*C1*), 151.3(*C4'*), 141.3 (*C5*), 135.9 (*C3*), 130.5 (C2), 129.6 (*C2'*), 126.9 (C1'), 115.1 (*C3'*), 110.7 (*C4*), 67.0 (*C2"*), 54.8 (*C6*), 52.3 (CO_2CH_3), 49.0 (*C1"*), 48.9 (*C7*), 32.9 (*C8*), 25.6 (*C10*), 24.8 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{25}H_{32}N_3O_5]^+$ 454.2336 found 454.2346 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(1,1-dioxidothiomorpholino)-6-oxo-1,6-dihydropyridine-3-carboxylate (6p):



Prepared according to general procedure **E** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), thiomorpholine-*S*,*S*-dioxide (20.3 mg, 0.150 mmol), Cs_2CO_3 (130 mg, 0.400 mmol), RuPhos (7.90 mg, 0.0170 mmol), $Pd_2(dba)_3$ (9.20 mg, 0.010 mmol), 1,4-dioxane (1.0 mL). Stirred at 110 °C for 18 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a pale yellow solid (21.0 mg, 49%): $\mathbf{R}_f$ 0.39 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3307w, 2927w, 2852w, 1711s, 1652s, 1621m, 1550m, 1429w, 1385w, 1346w, 1319s, 1302m, 1276s, 1240s, 1218m, 1187m, 1125s, 1083w, 1040m, 1010w, 951w, 888w, 867w, 817w, 786w, 764w, 723w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.03 (1H, d, ^4J 2.2, C5*H*), 7.30 (1H, d, ^4J 2.2, C3*H*), 6.02 (1H, d, ^3J 8.0, N*H*), 4.53 (2H, s, C6H_2), 3.86 (3H, s, OCH_3), 3.71–3.78 (1H, m, C7*H*), 3.66–3.71 (4H, m, 2 x C1'H_2), 3.18–3.23 (4H, m, 2 x C2'H_2), 1.86–1.93 (2H, m, 2 x C8*H*), 1.66–1.73 (2H, m, 2 x C9*H*), 1.60–1.64 (1H, m, C10*H*), 1.25–1.41 (2H, m, 2 x C9*H*), 1.10–1.22 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (*C*ONR), 164.7 (*C*O_2Me), 159.3 (*C1*), 139.6 (C*2*), 136.9 (C*5*), 121.9 (C*3*), 110.1 (C*4*), 54.0 (*C6*), 52.4 (*C1'*), 51.8 (O*C*H_3), 49.0 (*C7*), 47.7 (*C2'*), 32.9 (*C8*), 25.5 (*C10)*, 24.8 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{19}H_{28}N_3O_6S]^+$ 426.1693 found 426.1696 $[M+H]^+$.

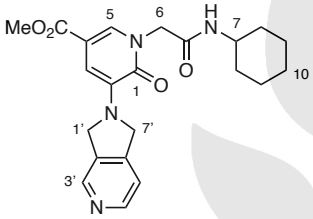
Methyl 5-(4-cyanopiperidin-1-yl)-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6q):



Prepared according to general procedure **E** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), piperidine-4-carbonitrile (17.0 µL, 0.150 mmol), Cs_2CO_3 (130 mg, 0.400 mmol), RuPhos (7.90 mg, 0.0170 mmol), $Pd_2(dba)_3$ (9.20 mg, 0.0100 mmol), 1,4-dioxane (1.0 mL). Stirred at 110 °C for 20 hours. Column chromatography over silica gel with eluent 100% hexanes to 2:8 hexanes:EtOAc gives product as a pale yellow solid (18.0 mg, 45%): $\mathbf{R}_f$ 0.53 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3307w, 2931m, 2854w, 2239w, 1716s, 1648s, 1612s, 1549m, 1439s, 1388m, 1346m, 1302s, 1285s, 1253s, 1215m, 1150w, 1114m, 1077m, 1040m, 1013w, 928w, 891w, 787w,

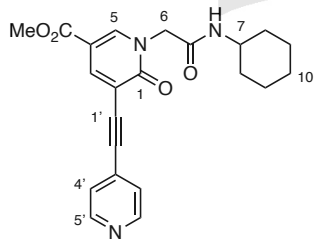
763w, 733m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.00 (1H, d, ^4J 2.2, C5*H*), 7.25 (1H, d, ^4J 2.2, C3*H*), 6.15 (1H, d, ^3J 8.1, N*H*), 4.52 (2H, s, C6H_2), 3.85 (3H, s, OCH_3), 3.66–3.77 (1H, m, C7*H*), 3.31–3.38 (2H, m, C1'H_2), 3.03–3.11 (2H, m, C1'H_2), 2.80–2.87 (1H, m, C3'*H*), 2.00–2.15 (4H, m, 2 x C2'H_2), 1.83–1.91 (2H, m, 2 x C8*H*), 1.65–1.72 (2H, m, 2 x C9*H*), 1.56–1.64 (1H, m, C10*H*), 1.26–1.39 (2H, m, 2 x C9*H*), 1.10–1.21 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.3 (*C*ONR), 165.0 (*C*O_2Me), 159.6 (*C1*), 141.2 (*C2*), 136.2 (*C5*), 121.4 (*C3*), 120.9 (*C*N), 110.3 (*C4*), 54.2 (*C6*), 52.3 (O*C*H_3), 48.9 (*C7*), 47.7 (*C1'*), 32.9 (*C8*), 28.6 (*C2'*), 26.2 (*C3'*), 25.5 (*C10)*, 24.8 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{21}H_{29}N_4O_4]^+$ 401.2183 found 401.2186 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6r):



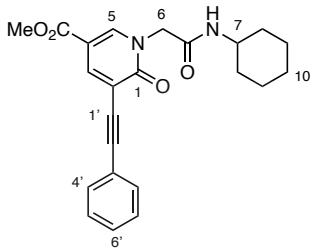
Prepared according to general procedure **E** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), 2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine (18.0 mg, 0.150 mmol), Cs_2CO_3 (130 mg, 0.400 mmol), RuPhos (7.90 mg, 0.0170 mmol), $Pd_2(dba)_3$ (9.20 mg, 0.0100 mmol), 1,4-dioxane (1.0 mL). Stirred at 110 °C for 18 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH and additional recrystallization from toluene gives product as an orange solid (12.0 mg, 29%): **R_f** 0.15 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3284w, 2926w, 2854w, 1714m, 1652s, 1612w, 1552m, 1440m, 1360m, 1269m, 1086w, 932w, 819w, 778w, 761w, 732w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.61 (1H, s, C3'*H*), 8.53 (1H, d, ^3J 5.0, C4'*H*), 7.78 (1H, d, ^4J 2.1, C5*H*), 7.28 (1H, d, ^3J 5.3, C5'*H*), 6.86 (1H, d, ^4J 2.1, C3*H*), 6.32 (1H, d, ^3J 8.1, N*H*), 4.98 (4H, d, ^3J 6.4, C1'H_2, C7'H_2), 4.53 (2H, s, C6H_2), 3.86 (3H, s, OCH_3), 3.64–3.80 (1H, m, C7*H*), 1.84–1.93 (2H, m, 2 x C8*H*), 1.63–1.71 (2H, m, 2 x C9*H*), 1.54–1.63 (1H, m, C10*H*), 1.26–1.40 (2H, m, 2 x C9*H*), 1.11–1.24 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.7 (*C*ONR), 165.4 (*C*O_2Me), 159.2 (*C1*), 148.3(*C4'*), 147.1 (*C2'*), 144.2 (*C3'*), 137.6 (*C2*), 133.9 (*C6'*), 131.9 (*C5*), 117.8 (*C5'*), 112.4 (*C3*), 111.5 (*C4*), 55.5 (*C1'*), 54.6 (*C6*), 53.9 (*C7'*), 52.2 (O*C*H_3), 48.8 (*C7*), 32.9 (*C8*), 25.6 (*C10)*, 24.8 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{22}H_{27}N_4O_4]^+$ 411.2027 found 411.2029 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-5-(pyridin-4-ylethynyl)-1,6-dihydropyridine-3-carboxylate (6s):



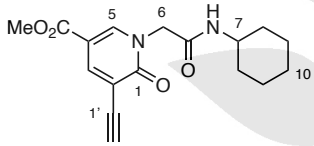
Prepared according to general procedure **F** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), 4-ethynylpyridine (17.3 mg, 0.120 mmol), CuI (1.00 mg, 0.00500 mmol), $Pd(PPh_3)_2Cl_2$ (3.50 mg, 0.00500 mmol), Et_3N (28.0 µL, 0.200 mmol), MeCN (1.0 mL). Stirred at 60 °C for 20 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a yellow solid (14.0 mg, 36%): **R_f** 0.26 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3283w, 3057w, 2926w, 2852w, 2360w, 1717w, 1683w, 1653s, 1620w, 1595w, 1551w, 1491w, 1442w, 1427m, 1395w, 1338w, 1269w, 1234w, 1195w, 1164w, 1109w, 1005w, 924w, 823w, 793w, 778w, 764w, 723w; **^{1}H-NMR (400 MHz, CD_3OD):** δ = 8.54–8.58 (2H, m, 2 x C5'*H*), 8.52 (1H, d, ^4J 2.5, C5*H*), 8.29 (1H, d, ^4J 2.4, C3*H*), 7.52–7.60 (2H, m, 2 x C4'*H*), 4.75 (2H, s, C6H_2), 3.89 (3H, s, OCH_3), 3.63–3.72 (1H, m, C7*H*), 1.87–1.93 (2H, m, 2 x C8*H*), 1.73–1.81 (2H, m, 2 x C9*H*), 1.61–1.68 (1H, m, C10*H*), 1.30–1.43 (2H, m, 2 x C9*H*), 1.18–1.27 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, CD_3OD):** δ = 167.3 (*C*ONR), 165.3 (*C*O_2Me), 163.2 (*C1*), 150.3 (*C6'*), 147.0 (*C5*), 144.7 (*C3*), 133.2 (*C3'*), 127.2 (*C4'*), 114.3 (*C2*), 111.3 (*C4*), 92.3 (*C2'*), 90.1 (*C1'*), 54.0 (*C6*), 52.8 (O*C*H_3), 50.2 (*C7*), 33.7 (*C8*), 26.6 (*C10)*, 26.0 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{22}H_{24}N_3O_4]^+$ 393.1761 found 393.1762 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-5-(phenylethynyl)-1,6-dihydropyridine-3-carboxylate (6t):



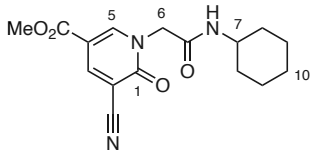
Prepared according to general procedure **F** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), phenylacetylene (13.0 µL, 0.120 mmol), CuI (1.00 mg, 0.0200 mmol), $Pd(PPh_3)_2Cl_2$ (3.50 mg, 0.0200 mmol), Et_3N (28.0 µL, 0.200 mmol), MeCN (1.0 mL). Stirred at 60 °C for 20 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH and additional recrystallization from toluene gives product as a yellow solid (31.2 mg, 80%); $\mathbf{R}_f$ 0.76 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3307w, 3077w, 2929w, 2853w, 1720m, 1650s, 1616m, 1549m, 1489w, 1439m, 1393w, 1332m, 1263s, 1220m, 1162m, 1106m, 1005m, 921w, 890w, 790w, 778w, 757m, 734w, 716w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.29 (1H, d, ^4J 2.5, C5*H*), 8.18 (1H, d, ^4J 2.4, C3*H*), 7.50–7.62 (2H, m, 2 x C4'*H*), 7.31–7.37 (3H, m, 2 x C5'*H,* C6'*H*), 6.33 (1H, d, ^3J 8.1, N*H*), 4.58 (2H, s, C6H_2), 3.88 (3H, s, OCH_3), 3.66–3.77 (1H, m, C7*H*), 1.85–1.92 (2H, m, 2 x C8*H*), 1.65–1.74 (2H, m, 2 x C9*H*), 1.57–1.63 (1H, m, C10*H*), 1.24–1.39 (2H, m, 2 x C9*H*), 1.10–1.23 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (*C*ONR), 164.8 (*C*O_2Me), 161.8 (*C1*), 142.8 (*C5*), 142.1 (*C3*), 132.0 (*C4'*), 128.9 (*C6'*), 128.5 (*C5'*), 122.7 (*C3'*), 115.6 (*C2*), 110.5 (*C4*), 95.62 (*C2'*), 84.14 (*C1'*), 54.2 (*C6*), 52.5 (O*C*H_3), 49.1 (*C7*), 32.9 (*C8*), 25.5 (*C10)*, 24.9 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{23}H_{25}N_2O_4]^+$ 393.1809 found 393.1800 $[M+H]^+$.

Methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-ethynyl-6-oxo-1,6-dihydropyridine-3-carboxylate (6u):



Prepared according to general procedure **F** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), TMS-acetylene (17.0 µL, 0.120 mmol), CuI (1.00 mg, 0.00500 mmol), $Pd(PPh_3)_2Cl_2$ (3.50 mg, 0.00500 mmol), Et_3N (28.0 µL, 0.200 mmol), MeCN (1.0 mL). Stirred at 60 °C for 18 hours. The mixture was filtered over a plug of Celite and the filtrate was concentrated in vacuo. The residue was dissolved in THF (0.50 mL) and treated with *tetra-n*-butylammonium fluoride (1 mol L^{-1} in THF, 0.100 mL) at 0 °C. The mixture was stirred at that temperature for 4 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a pale white solid (6.50 mg, 20%): $\mathbf{R}_f$ 0.42 (hexanes:EtOAc, 1:2, UV, $KMnO_4$); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.30 (1H, d, ^4J 2.4, C5*H*), 8.17 (1H, d, ^4J 2.4, C3*H*), 6.25 (1H, d, ^3J 8.0, N*H*), 4.54 (2H, s, C6H_2), 3.87 (3H, s, OCH_3), 3.65–3.77 (1H, m, C7*H*), 3.35 (1H, s, C2'*H*), 1.84–1.91 (2H, m, 2 x C8*H*), 1.65–1.73 (2H, m, 2 x C9*H*), 1.57–1.63 (1H, m, C10*H*), 1.27–1.38 (2H, m, 2 x C9*H*), 1.10–1.23 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.7 (*C*ONR), 163.9 (*C*O_2Me), 162.0 (*C1*), 143.5 (*C3*), 143.4 (*C5*), 114.3 (*C2*), 110.3 (*C4*), 83.5 (*C2'*), 78.1 (*C1'*), 54.3 (*C6*), 52.5 (O*C*H_3), 49.1 (*C7*), 32.9 (*C8*), 25.5 (*C10)*, 24.8 (*C9)*.

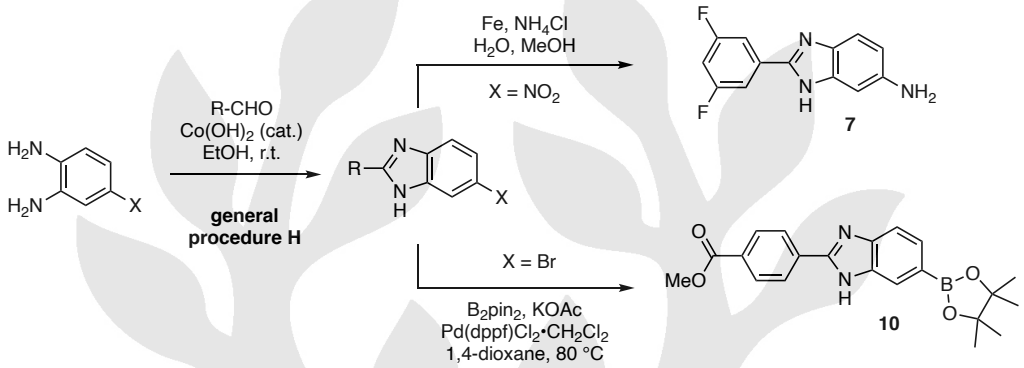
Methyl 5-cyano-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (6v):



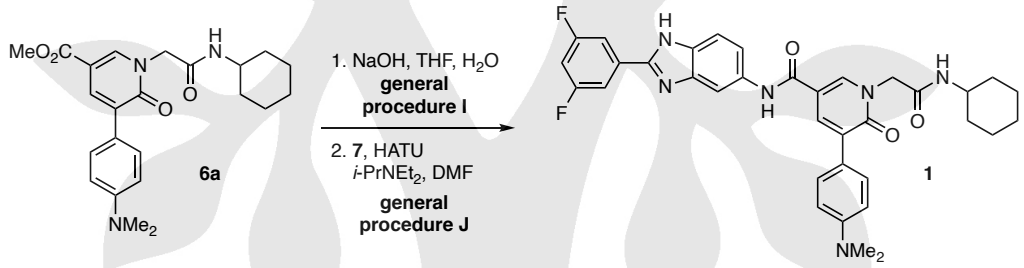
Prepared according to general procedure **G** using methyl 5-bromo-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (37.1 mg, 0.100 mmol), CuCN (18.0 mg, 0.200 mmol), DMF (1.0 mL). Stirred at 120 °C for 20 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH and additional recrystallization from toluene gives product as a white solid (17.0 mg, 55%): $\mathbf{R}_f$ 0.65 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3326w, 3076w, 2932w, 2854w, 2361w, 2232m, 1723w, 1659s, 1546m, 1442w, 1325w, 1297w, 1210w, 1042m, 1009w, 1001w, 953w, 891w, 783w, 766w, 734w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.50 (1H, d, ^4J 2.5, C5*H*), 8.39 (1H, d, ^4J 2.5, C3*H*), 6.15 (1H, d, ^3J 8.0, N*H*), 4.60 (2H, s, C6H_2), 3.90 (3H, s, OCH_3), 3.63–3.80 (1H, m, C7*H*), 1.85–1.93 (2H, m, 2 x C8*H*), 1.67–1.74 (2H, m, 2 x C9*H*), 1.57–1.64 (1H, m, C10*H*), 1.27–1.39 (2H, m, 2 x C9*H*), 1.12–1.24 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 163.7 (*C*ONR), 162.9 (*C*O_2Me), 159.6 (*C1*), 147.9 (*C5*), 147.1 (*C3*), 114.5 (*C2*), 110.0 (*C4*), 104.8 (*C*N), 53.4 (*C6*), 52.9 (O*C*H_3), 49.4 (*C7*), 32.9 (*C8*),

25.5 (*C10)*, 24.8 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{16}H_{20}N_3O_4]^+$ 318.1448 found 318.1450 $[M+H]^+$.

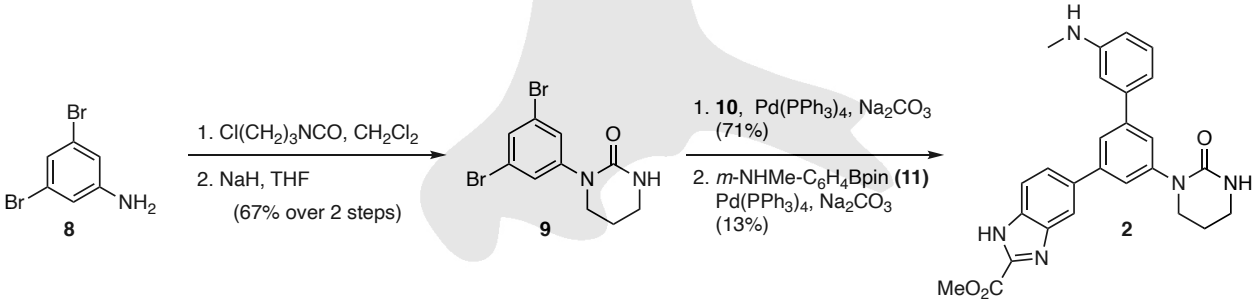
Assembly of the Initial Benzimidazole Scaffolds 1 & 2:



Scheme S6: Synthesis of the amino- and Bpin-benzimidazole building blocks.



Scheme S7: Assembly of benzimidazole scaffold **1**.



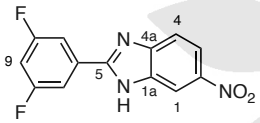
Scheme S8: Assembly of benzimidazole scaffold **2**.

General Procedure H:
Prepared according to a modified literature procedure.[20] To a suspension of 4-nitrobenzene-1,2-diamine *or* 4-bromobenzene-1,2-diamine (1.00 equiv.) and $Co(OH)_2$ (10.0 mol%) in EtOH (3.0 mL/mmol diamine) vigorously stirred in a container open to air atmosphere was added an aryl aldehyde (1.10 *or* 1.20 equiv.) at r.t. over an individually specified time period. The mixture was filtered over a plug of Celite using solvent EtOH or CH_2Cl_2 and the filtrate was concentrated in vacuo and purified with individually specified technics to give 6-nitro-2-aryl-1*H*-benzo[*d*]imidazoles *or* 6-bromo-2-aryl-1*H*-benzo[*d*]imidazoles *or* 6-bromo-2-aryl-2,3-dihydro-1*H*-benzo[*d*]imidazoles *or* 2-(3,5-difluorophenyl)-6-nitro-1*H*-benzo[*d*]imidazoles.

General Procedure I:
Prepared according to a modified literature procedure.[21] To a solution of the ester (1.00 equiv.) in THF and water at room temperature was added sodium hydroxide (4.0-10 equiv.). The reaction mixture was stirred at an individually specified temperature and for an individually specified time. The mixture was diluted with water, adjusted to pH 2-3 with aqueous 1 M HCl and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give the corresponding carboxylic acid, which was used without further purification in the next step.

General Procedure J:
To a mixture of carboxylic acid (1.00 equiv), HATU (1.50 equiv), *N,N*-diisopropylethylamine (5.00 equiv) in dry DMF (10-14 mL per mmol carboxylic acid) at room temperature was added a secondary *or* primary amine (1.20 equiv). The mixture was stirred at room temperature for an individually specified time, poured into aqueous 10% LiCl (50 mL per mmol acid) and extracted with EtOAc (80 mL per mmol acid). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel with an individually specified eluent to give the desired amide.

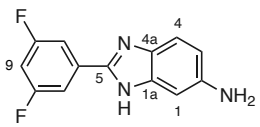
2-(3,5-Difluorophenyl)-6-nitro-1*H*-benzo[*d*]imidazole:



Prepared according to general procedure **H** using 4-nitrobenzene-1,2-diamine (500 mg, 3.27 mmol), $Co(OH)_2$ (30.3 mg, 0.330 mmol) in EtOH (10 mL) and 3.5-difluorobenzaldehyde (557 mg, 3.92 mmol, 1.20 equiv.) was added in one portion. The mixture was stirred vigorously at room temperature for 5 hours. Column chromatography over silica gel with eluent hexanes:EtOAc 9:1 to 1:1 gives product as a yellow solid (851 mg, 95%): $\mathbf{R}_f$ 0.18 (hexanes:EtOAc, 9:1, UV); **IR:** $\tilde{\nu}$ = 3487w, 3374w, 3090w, 2361w, 1629m, 1616m, 1591s, 1484m, 1450w, 1329s, 1314s, 1272m, 1219w, 1196w, 1156w, 1116m, 1097w, 1002w, 984w, 900w, 859w, 832w, 815w, 747w, 735w, 711w; **^{1}H-NMR (400 MHz, $(CD_3)_2CO$):** δ = 8.94 (1H, s, N*H*), 8.12 (1H, d, ^4J 2.4, C1*H*), 7.99 (1H, dd, ^3J 9.0, ^4J 2.5, C3*H*), 7.77 (2H, dt, $^3J_{HF}$ 6.7, ^4J 2.1, 2 x C7*H*), 7.21 (1H, tt, $^3J_{HF}$ 9.0, ^4J 2.4, C9*H*), 6.90 (1H, d, ^3J 9.0, C4*H*); **^{13}C-NMR (101 MHz, $(CD_3)_2CO$)** δ = 163.2 (dd, $^1J_{CF}$ 147, $^3J_{CF}$ 12.5, *C8*), 157.0 (t, J_{CF} 3.4)*****, 150.8, 140.1 (m)*, 137.4, 133.4 (m)*, 124.6 (*C3*), 113.2 (*C4*)*, 113.1 (*C1*), 111.9, 111.6 (m, 2 x *C7*)*, 106.3 (t, $^2J_{CF}$ 26.3, *C9*); **^{19}F-NMR (377 MHz, $CDCl_3$):** δ = –110.9.

** spectrum shows a mixture of tautomers and long-range C–F-couplings are observed.*

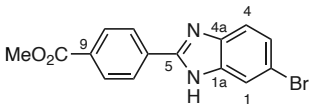
2-(3,5-Difluorophenyl)-1*H*-benzo[*d*]imidazolamine (7):



Prepared according to a modified literature procedure.[22] To a suspension of 2-(3,5-difluorophenyl)-6-nitro-1*H*-benzo[*d*]imidazole (82.6 mg, 0.300 mmol), and NH_4Cl (192.6 mg, 12.00 mmol) in MeOH/H_2O (1:1, 5.0 mL) was added iron powder (100.5 mg, 1.80 mmol) and the mixture was stirred at 90 °C for 1 hour. The mixture was cooled to room temperature, filtered over Celite using EtOAc. The filtrate was concentrated in vacuo and purified by column chromatography over silica gel with eluent hexanes 100%

to hexanes:acetone 40:60 to give the desired 2-(3,5-difluorophenyl)-1*H*-benzo[*d*]imidazolamine **(7)** as a beige-brown solid (34.5 mg, 47%): $\mathbf{R}_f$ 0.58 (CH_2Cl_2:MeOH, 9:1, UV/$KMnO_4$); **^{1}H-NMR (400 MHz, $(CD_3)_2CO$):** δ = 7.73 (2H, dq, ^3J 6.7, ^3J 4.6, ^4J 3.4), 7.37 (1H, d, ^3J 8.3), 7.03–7.09 (1H, m), 6.80 (1H, s), 6.69 (1H, dd, ^3J 8.6, ^4J 2.1), 4.65 (1H, br).

Methyl 4-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)benzoate:

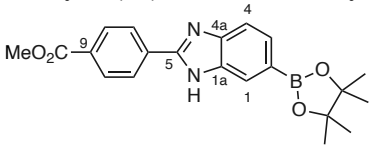


Prepared according to general procedure **H**. A solution of methyl 4-formylbenzoate (0.361 g, 2.20 mmol) in EtOH (6.0 mL) was added dropwise over 4 hours to a mixture of 4-bromobenzene-1,2-diamine* (374 mg, 2.00 mmol) and $Co(OH)_2$ (18.6 mg, 10 mol%), in EtOH (6.0 mL). The mixture was filtered and concentrated in vacuo. Suspending the crude product in cold EtOH and filtration gave methyl 4-(((2-amino-4-bromophenyl)imino)methyl)benzoate as a yellow solid (571 mg, 86%): $\mathbf{R}_f$ 0.54 (hexanes:EtOAc, 2:1, UV); **^{1}H-NMR (400 MHz, $(CD_3)_2SO$):** δ = 8.76 (1H, s, C5*H*), 8.12–8.14 (2H, m, 2 x C7*H*), 8.05–8.07 (2H, m, 2 x C8*H*), 7.13 (1H, d, ^3J 8.4, C4*H*), 6.90 (1H, d, ^4J 2.2, C1*H*), 6.68 (1H, dd, ^3J 8.4, ^4J 2.2, C3*H*), 5.59 (2H, br, 2 x N*H*), 3.89 (3H, s, CO_2CH_3); **^{13}C-NMR (101 MHz, $(CD_3)_2SO$):** δ = 165.9 (CO_2Me), 155.8 (*C5*), 146.1 (*C1a*), 140.5 (*C6*), 133.7 (*C4a*), 131.3 (*C9*), 129.4 (*C8*), 128.8 (*C7*), 120.9 (*C2*), 118.8 (*C4*), 118.2 (*C3*), 116.6 (*C1*), 52.3 (CO_2CH_3); **APCI-HRMS:** m/z calcd. for $[C_{15}H_{14}BrN_2O_2]^+$ 333.0233 found 333.0245 $[M+H]^+$.

Methyl 4-(((2-amino-4-bromophenyl)imino)methyl)benzoate (598 mg, 1.80 mmol) was treated with glacial acetic acid (4.00 mL) and stirred at 80 °C for 1 hour. The brown solution was cooled to room temperature and methyl 4-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)benzoate was suspended with water, filtered. The filtercake was washed portionwise with hexanes:toluene (4:2) to give product as a beige solid (313 mg, 47%): $\mathbf{R}_f$ 0.22 (hexanes:EtOAc, 2:1, UV); **^{1}H-NMR (400 MHz, $(CD_3)_2SO$):** δ = 13.34 (1H, br, N*H*), 8.30–8.32 (2H, m, 2 x C8*H*), 8.12–8.14 (2H, m, C7*H*), 7.73–7.90 (1H, m, C1*H*), 7.54–7.65 (1H, m, C4*H*), 7.38 (1H, br, C3*H*), 3.90 (3H, s, CO_2CH_3) *in ^{1}H-NMR, benzimidazole signals of both tautomers overlap*; Data in agreement with literature.[23]

**Older batches of 4-bromobenzene-1,2-diamine, often black solids, led directly to the benzimidazole. After filtration over a plug of Celite and concentration in vacuo, column chromatography with eluent hexanes 100% to hexanes:EtOAc 95:5 to 90:10 to 80:20 gave 6-bromo-2-phenyl-1H-benzo[d]imidazole as a brown solid (417 mg, 63%).*

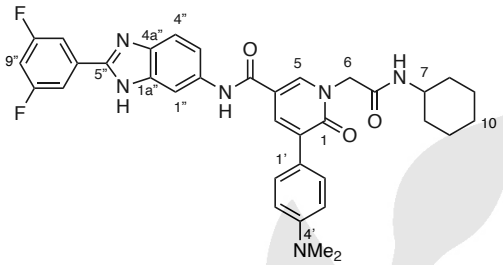
Methyl 4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)benzoate (10):



6-Bromo-2-phenyl-1*H*-benzo[*d*]imidazole (310 mg, 0.936 mmol), bis(pinacolato)diboron (262 mg, 1.03 mmol), potassium acetate (276 mg, 2.81 mmol) and 1,1-bis(diphenyl-phosphino)ferrocene-palladium(II)dichloride CH_2Cl_2 complex (38.2 mg, 5.00 mol%) were combined with 1,4-dioxane (3.3 mL) in a microwave vial. The mixture was deareated by nitrogen sparging for five minutes and stirred at 100 °C in a microwave oven for 10 hours. The mixture was filtered over a plug of Celite and the filtrate was concentrated in vacuo, column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 90:10 to 80:20 to 75:25 gave 2-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole **(10)** as a beige solid (202 mg, 57%): $\mathbf{R}_f$ 0.42 (hexanes:EtOAc, 1:1); **IR:** $\tilde{\nu}$ = 2977w, 1722m, 1613w, 1435w, 1414w, 1354s, 1317w, 1274s, 1192w, 1143m, 1109m, 1066w, 1018w, 964w, 858m, 821w, 778w, 747w; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ = 8.15 (4H, s, 2 x C7*H*, 2 x C8*H*), 8.10–8.12 (1H, m, arom*H*), 7.75–7.77 (1H, m, arom*H*), 7.70–7.71 (1H, m, C3*H*), 3.95 (3H, s, CO_2CH_3), 1.38 (12H, s, 4 x CH_3) *in ^{1}H-NMR*

benzimidazole signals of both tautomers overlap; **APCI-HRMS:** m/z calcd. for $[C_{21}H_{24}BN_2O_4]^+$ 379.1824 found 379.1827 $[M+H]^+$.

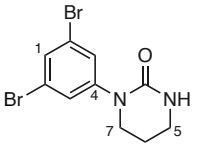
1-(2-(Cyclohexylamino)-2-oxoethyl)-*N*-(2-(3,5-difluorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)-5-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (1):



Prepared according to general procedure **I** using methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (10.3 mg, 0.0250 umol, 1.00 equiv.), THF (0.50 mL), water (0.50 mL) and NaOH (3.00 mg, 0.0750 mmol, 3.00 equiv.). Stirred at 40 °C for 2 hours. 1-(2-(Cyclohexylamino)-2-oxoethyl)-5-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid. **LC-MS:** (5-100% MeCN in H_2O over 5 min, 0.1% formic acid): t_{Ret} = 2.6 min.

Prepared according to general procedure **J** using 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (16.0 mg, 0.0403 mmol), HATU (23.0 mg, 0.0604 mmol) *N,N*-diisopropylethylamine (0.0320 mL, 0.180 mmol, 4.56 equiv.), DMF (2.8 mL), and 2-(3,5-difluorophenyl)-1*H*-benzo[*d*]imidazolamine (14.8 mg, 0.0604 mmol, 1.50 equiv.). Stirred at room temperature for 16 hours. The crude product was filtered over a plug of silica gel and chromatographed over a semi-preparative column using eluent 30% to 45% MeCN in H_2O (with constant 0.1% formic acid) in 8 minutes and 100% MeCN (with 0.1% formic acid) for 3 min, ($t_{R,Prod}$: 9.26, 9.58 min) to yield product as a brown solid (9.6 mg, 38% over two steps):
^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.58 (1H, s, N*H*), 8.24–8.36 (2H, m, C5*H*, N*H*), 8.08 (1H, d, *J* 2.4, C3*H*), 7.76–7.87 (2H, m, 2 x C7"*H*), 7.69 (2H, d, ^2J 8.4, 2 x C2'*H*), 7.55–7.61 (1H, m, C1"*H*), 7.41–7.51 (2H, m, C3"*H*, C4"*H*), 7.09–7.19 (1H, m, C9"*H*), 6.75 (2H, d, ^2J 8.4, 2 x C3'*H*), 4.75 (2H, s, C6H_2), 3.67–3.80 (1H, m, C7*H*), 2.97 (6H, s, 2 x NCH_3), 1.82–1.96 (2H, m, 2 x C8*H*), 1.67–1.78 (2H, m, 2 x C9*H*), 1.54–1.62 (1H, m, C10*H*), 1.15–1.40 (5H, m, 2 x C8*H*, 2 x C9*H*, C10*H*); **ESI-HRMS:** m/z calcd. for $[C_{35}H_{35}F_2N_6O_3]^+$ calcd. 625.2733 found 625.2718 $[M+H]^+$.

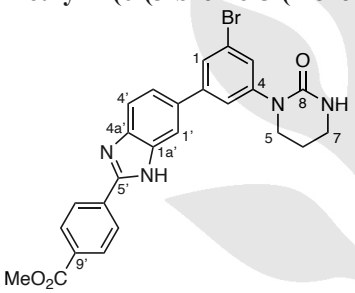
1-(3,5-Dibromophenyl)tetrahydropyrimidin-2(1*H*)-one (9):



Prepared according to a modified literature procedure.[24] To a solution of 3,5-dibromoaniline **(8)** (1.00 g, 4.00 mmol) in CH_2Cl_2 (16 mL) in an ice bath was added dropwise 3-chloropropyl isocyanate (0.450 mL, 4.40 mmol). The icebath was removed and the mixture was allowed to warm to room temperature over 24 hours. The mixture was concentrated in vacuo. The resulting residue was suspended in hexanes and filtered to give 1-(2-chloroethyl)-3-(3,5-dibromophenyl)urea as a white solid (1.05 g, 71%): **R_f** 0.44 (hexanes:EtOAc, 1:1, UV); **IR:** $\tilde{\nu}$ = 3305m, 3085w, 2966w, 2865w, 1633s, 1570s, 1555s, 1478w, 1439w, 1407m, 1322w, 1292w, 1255m, 1230w, 1101w, 1076w, 1036w, 982w, 922w, 872w, 843m, 779w, 762w, 740m; **^{1}H-NMR (400 MHz, $(CD_3)_2SO$):** δ = 8.85 (1H, br, N*H*), 7.64–7.65 (2H, m, 2 x C3*H*), 7.29–7.30 (1H, m, C1*H*), 6.47 (1H, t, ^3J 5.7, N*H*C5H$_2$), 3.66 (2H, t, ^3J 6.5, C7H_2), 3.20 (2H, dd, ^3J 12, ^3J 6.4, C5H_2), 1.85–1.92 (2H, m, C6H_2); **^{13}C-NMR (101 MHz, $(CD_3)_2SO$)** δ = 154.7 (*C*O), 143.4 (*C4*), 125.3 (*C1*), 122.3 (*C2*), 118.9 (*C3*), 43.0 (*C7*), 36.7 (*C5*), 32.5 (*C6*); **APCI-HRMS:** m/z calcd. for $[C_{10}H_{12}Br_2ClN_2O]^+$ 368.8999 found 368.8994 $[M+H]^+$.

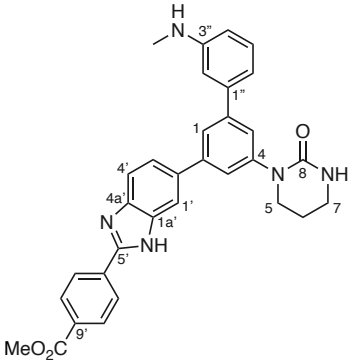
A solution of 1-(2-chloroethyl)-3-(3,5-dibromophenyl)urea (1.05 g, 2.83 mmol) in dry THF (11 mL) was cooled in an ice bath and treated portionwise with NaH (60% dispersion in mineral oil, 340 mg, 8.50 mmol). The mixture was continued to stir in the ice bath for 30 minutes and allowed to warm to room temperature over 21 hours. The mixture was treated portionwise with water (50 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Column chromatography with eluent hexanes 100% to hexanes:EtOAc 3:1 to 1:1 to 1:3 gave 1-(3,5-dibromophenyl)tetrahydropyrimidin-2(1*H*)-one **(9)** as a beige solid (898 mg, 95%): $\mathbf{R}_f$ 0.29 (100% EtOAc); **IR:** $\tilde{\nu}$ = 3307w, 3229w, 3079w, 2921w, 1667s, 1580m, 1548m, 1483m, 1436s, 1412s, 1382w, 1355w, 1312s, 1225m, 1168m, 1127w, 1092w, 1026w, 1003w, 985w, 937w, 890w, 869w, 845m, 740s; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.45 (3H, s, C1*H*, 2 x C3*H*), 5.28 (1H, br, N*H*), 3.66 (2H, t, ^3J 5.7, C7H_2), 3.42 (2H, t, ^3J 5.9, C5H_2), 2.09 (2H, q, ^3J 5.8, C6H_2); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 155.0 (*C*=O), 145.6 (*C4*), 130.9 (*C1*) 127.2 (*C3*), 122.6 (*C2*), 48.5 (*C7*), 40.8 (*C5*), 22.4 (*C6*); **APCI-HRMS:** m/z calcd. for $[C_{10}H_{11}Br_2N_2O]^+$ 332.9233 found 332.9228 $[M+H]^+$.

Methyl 4-(6-(3-bromo-5-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)benzoate:



A deaerated mixture of 1-(3,5-dibromophenyl)tetrahydropyrimidin-2(1*H*)-one **(9)** (100 mg, 0.300 mmol), 2-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole (75.6 mg, 0.200 mmol), Na_2CO_3 (106 mg, 1.00 mmol) and $Pd(PPh_3)_4$ (6.90 mg, 3.0 mol%) in MeCN (1.3 mL) and water (0.20 mL) was heated in the microwave oven at 75 °C for 10 hours. The mixture was treated with water (50 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 1:1 to 1:3 to 100% EtOAc gave product as an off-white solid (72.1 mg, 71%): $\mathbf{R}_f$ 0.12 (100% EtOAc, UV); **IR:** $\tilde{\nu}$ = 3317w, 2924m, 2360w, 2342w, 1701s, 1629w, 1614w, 1592w, 1563w, 1498s, 1443m, 1384w, 1349w, 1278s, 1221w, 1170w, 1111m, 1019w, 996w, 951w, 930w, 859w, 851m, 779w, 750w; **^{1}H-NMR (400 MHz, $(CD_3)_2SO$):** δ = 13.3 (1H, d, ^4J 4.9, N*H*), 8.33–8.36 (2H, m, 2 x C7'*H*), 8.14–8.16 (2H, m, 2 x C8'*H*), 7.75–7.79 (1H, m, $C_{arom}H$), 7.58–7.65 (3H, m, 3 x $C_{arom}H$), 7.51–7.56 (2H, m, 2 x $C_{arom}H$), 6.76 (1H, d, ^3J 2.6, C8ON*H*), 3.91 (3H, s, CO_2CH_3), 3.73–3.76 (2H, m, C5H_2), 3.23–3.27 (2H, m, C7H_2), 1.95–2.01 (2H, m, C6H_2); **APCI-HRMS:** m/z calcd. for $[C_{25}H_{22}BrN_4O_3]^+$ 505.0870 found 505.0897 $[M+H]^+$.

Methyl 4-(6-(3'-(methylamino)-5-(2-oxotetrahydropyrimidin-1(2*H*)-yl)-[1,1'-biphenyl]-3-yl)-1*H*-benzo[*d*]imidazol-2-yl)benzoate (1):

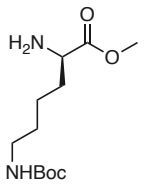


A deaerated mixture of methyl 4-(6-(3-bromo-5-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)benzoate* (35.4 mg, 0.0700 mmol), *N*-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (32.6 mg, 0.140 mmol), Na_2CO_3 (37.1 mg, 0.350 mmol) and $Pd(PPh_3)_4$ (2.40 mg, 3.0 mol%) in MeCN (0.467 mL) and water (0.070 mL) was heated in the microwave oven at 90 °C for 10 hours. The mixture was treated with water (15 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography over silica gel with eluent 100% CH_2Cl_2 to CH_2Cl_2:MeOH 98:2 to 96:4 to 92:8. Product containing fractions were combined and recrystallized from acetone to give product as an off-white solid (5.00 mg, 13%): $\mathbf{R}_f$ 0.46 (CH_2Cl_2:MeOH, 9:1, UV); **IR:** $\tilde{\nu}$ = 3048m, 2966w, 1724m, 1638s, 1597s, 1518m, 1499m, 1428m, 1347w, 1311m, 1274s, 1226w, 1184w, 1155w, 1110m, 1018w, 989w, 960w, 940w, 865m, 804m, 771s, 755w; **^{1}H-NMR (400 MHz, $(CD_3)_2SO$):** δ = 13.2 (1H, s, N*H*), 8.34–8.36 (2H, m, 2 x C7'*H*), 8.14–8.16 (2H, m, 2 x C8'*H*), 7.79 (1H, br, $C_{arom}H$), 7.57–7.67 (4H, m, 4

x C$_{arom}$*H*), 7.47 (1H, br, C$_{arom}$*H*), 7.18–7.22 (1H, m, C5"*H*), 6.89–6.90 (1H, m, C6"*H*), 6.86 (1H, br, C2"*H*), 6.64 (1H, br, C8ON*H*), 6.56–6.58 (1H, m, C4"*H*), 5.74 (1H, br, MeN*H*), 3.91 (3H, s, CO_2CH_3), 3.77–3.80 (2H, m, C5H_2), 3.27–3.30 (2H, m, C7H_2), 2.75 (3H, d, ^3J 4.7, NHCH_3), 1.99–2.04 (2H, m, C6H_2); **APCI-HRMS:** m/z calcd. for $[C_{32}H_{30}N_5O_3]^+$ 532.2343 found 532.2345 $[M+H]^+$. ** Accessed with the borylation method described for benzimidazoles (see above) using 3-bromo-*N*-methylaniline (744 mg, 4.00 mmol) to yield after column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 90:10 N-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (834 mg, 89%):* **R$_f$** 0.57 (hexanes:EtOAc, 2:1, UV); ***^{1}H-NMR (400 MHz, CDCl$_3$):*** *δ = 7.18–7.24 (2H, m), 7.09 (1H, d, ^4J 2.0), 6.75–6.78 (1H, m), 4.29 (1H, br, NH), 2.86 (3H, s, CH$_3$), 1.34 (12H, s, 4 x CH$_3$);* ***^{13}C-NMR (101 MHz, CDCl$_3$):*** *δ = 148.4, 128.8, 124.4, 119.1, 115.9, 83.8, 31.3, 25.0;* Data in agreement with literature.[25]

D-Phg-D-Lys Peptide 3 Synthesis:

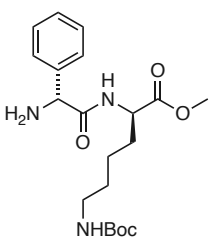
Methyl N^6-(*tert*-butoxycarbonyl)-*D*-lysinate (13):



To a solution of *N*(ε)-Boc-*N*(α)-Fmoc-D-lysine (**12**) (5.00 g, 10.7 mmol, 1.00 equiv) in anhydrous acetonitrile (60 mL) at 0 °C was added EDCI (2.25 g, 11.7 mmol, 1.10 equiv) and HOBt (1.80 g, 11.7 mmol, 1.10 equiv). The mixture was stirred for 5 minutes at the same temperature, MeOH (25 mL, 58 equiv.) was added and the mixture was allowed to warm to room temperature over 2 hours. After additional 3 hours at room temperature, LC-MS analysis indicated complete conversion of **12**. The mixture was concentrated in vacuo and the residue was treated with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with aqueous saturated sodium chloride solution (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude methyl ester (white foam) obtained was directly subjected to Fmoc-deprotection without further purification.

To a solution of the methyl ester in acetonitrile (110 mL) was added piperidine (4.00 mL, 40.4 mmol, 3.79 equiv.) at room temperature. After stirring for 12 hours at room temperature LC-MS analysis indicated complete conversion of the methyl ester. The mixture was concentrated in vacuo and the residue was subjected to column chromatography over silica gel using eluent CH_2Cl_2 100% to CH_2Cl_2:MeOH 95:5 to afford product **13** as a colorless oil (2.35 g, 85 %): **R$_f$** 0.28 (CH_2Cl_2:MeOH, 9:1, ninhydrin); **LC-MS** t$_R$ = 2.283 min (5-100% MeCN in H_2O with 0.1% formic acid); **IR:** $\tilde{\nu}$ = 3376w, 2936m, 2869w, 1735s, 1697s, 1526m, 1456m, 1392w, 1274m, 1251m, 1172s, 1051w, 999w; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 4.55 (1H, s), 3.71 (3H, d, *J* 1.3), 3.43 (1H, dd, *J* 7.5, 5.4), 3.11 (2H, q, *J* 6.7), 1.68–1.79 (1H, m), 1.46–1.61 (5H, m), 1.43 (9H, s); **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 176.6, 156.1, 79.2, 54.5, 52.1, 40.5, 34.6, 29.9, 28.5, 23.0; **ESI-HRMS:** m/z calcd. for $[C_{12}H_{25}N_2O_4]^+$ 261.1809 found 261.1809 $[M+H]^+$.

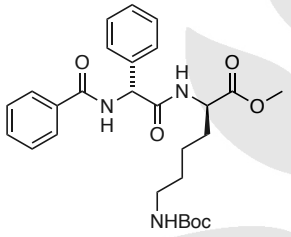
Methyl N^2-((*R*)-2-amino-2-phenylacetyl)-N^6-(*tert*-butoxycarbonyl)-*D*-lysinate (15):



To a solution of *N*(α)-Fmoc-D-phenylglycine **(14)** (2.75 g, 7.36 mmol, 1.00 equiv.) in anhydrous MeCN(40 mL) at 0 °C was added EDCI (1.56 g, 8.11 mmol, 1.10 equiv.) and HOBt (1.24 g, 8.11 mmol, 1.10 equiv.). After 5 minutes at that temperature the mixture was treated with a solution of *N*(ε)-Boc-D-lysine methyl ester **(13)** (1.92 g, 7.38 mmol 1.00 equiv.) in acetonitrile (6.0 mL and 2 x 1.0 mL for rinsing) and the mixture was allowed to warm to room temperature over the course of 2 hours. Stirring was continued for additional 2 hours, when LC-MS analysis indicated complete conversion of **13**. The mixture was concentrated in vacuo and the residue was treated with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with aqueous saturated sodium chloride solution

(30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was dissolved in acetonitrile (70 mL) and treated with piperidine (3.00 mL, 30.3 mmol, 4.12 equiv.) at room temperature. After stirring for 3 hours at room temperature, LC-MS-analysis indicated complete Fmoc-deprotection. The mixture was concentrated in vacuo and the residue was subjected to column chromatography over silica gel using eluent CH_2Cl_2 100% to CH_2Cl_2:MeOH 92:8 to afford peptide **15** as a colorless oil (2.46 g, 85 %): $\mathbf{R_f}$ 0.46 (CH_2Cl_2:MeOH, 9:1, ninhydrin); **LC-MS:** t_R = 2.812 min (5-100% MeCN in H_2O with 0.1% formic acid); **IR:** $\tilde{\nu}$ = 3299w, 2973m, 1678s, 1528m, 1452m, 1393m, 1366m, 1251m, 1172m, 1066m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.41–7.46 (2H, m), 7.32–7.38 (2H, m), 7.25–7.31 (1H, m), 4.52 (1H, s), 4.41 (1H, dd, *J* 8.8, 5.2), 3.62 (3H, s), 3.00 (2H, t, *J* 6.8), 1.84 (1H, dtd, *J* 13, 7.9, 7.5, 5.2), 1.72 (1H, tt, *J* 14, 7.8), 1.44 (11H, m), 1.36 (2H, ddt, *J* 10, 7.3, 3.7); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 175.7, 173.8, 158.5, 142.2, 129.6, 128.8, 128.0, 79.8, 60.0, 53.7, 52.6, 41.0, 32.2, 30.4, 28.8, 24.0; **ESI-HRMS:** m/z calcd. for $[C_{20}H_{32}N_3O_5]^+$ 394.2336 found 394.2332 $[M+H]^+$.

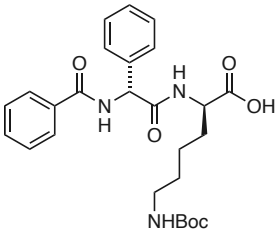
Methyl N^2-((*R*)-2-benzamido-2-phenylacetyl)-N^6-(*tert*-butoxycarbonyl)-*D*-lysinate:



To a solution of peptide **15** (215 mg, 0.546 mmol, 1.00 equiv.) and benzoic acid (73.4 mg, 0.601 mmol, 1.10 equiv.) in anhydrous DMF (5.0 mL) at 0 °C was added EDCI (210 mg, 1.09 mmol, 2.00 equiv.), HOBt (148 mg, 1.09 mmol, 2.00 equiv.) and DMAP (0.672 mg, 0.00550 mmol, 10 mol%). The mixture was allowed to warm to room temperature over 2 hours and stirring was continued for additional 3 hours, when LC-MS analysis indicated complete conversion of **15**. The mixture was concentrated in vacuo and the residue was treated with water (5.0 mL) and extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layers were washed with aqueous saturated sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was subjected to column chromatography over silica gel using eluent CH_2Cl_2 100% to CH_2Cl_2:MeOH 95:5, affording the desired amide as a colorless oil (142 mg, 52%): **LC-MS:** t_R = 3.987 min (5-100% MeCN in H_2O with 0.1% formic acid); **IR:** $\tilde{\nu}$ = 3854w, 3676w, 2988m, 2970m, 2926m, 2362s, 2341s, 1734w, 1717w, 1700w, 1684w, 1559w, 1540w, 1507w, 1457w, 1395w, 1066m, 1057m; **^{1}H-NMR (400 MHz, CD_3OD):** δ = 7.84–7.89 (2H, m), 7.51–7.57 (3H, m), 7.46 (2H, dd, *J* 8.3, 6.9), 7.31–7.41 (3H, m), 6.59 (1H, t, *J* 5.9), 5.78 (1H, s), 4.45 (1H, dd, *J* 9.0, 5.1), 3.62 (3H, s), 3.00–3.07 (2H, m), 1.87 (1H, dtd, *J* 15, 7.6, 5.3), 1.74 (1H, qd, *J* 8.9, 5.1), 1.39–1.51 (13H, m);* **^{13}C NMR (101 MHz, CD_3OD):** δ = 173.7, 172.6, 169.8, 158.6, 138.4, 135.2, 132.9, 129.7, 129.6, 129.3, 128.9, 128.6, 79.8, 58.9, 54.0, 52.6, 41.1, 32.1, 30.4, 28.8, 24.1;* **ESI-HRMS:** m/z calcd. for $[C_{27}H_{36}N_3O_6]^+$ 498.2599 found 498.2590 $[M+H]^+$.

** NMR sample contains residual amounts of DMF.*

N^2-((*R*)-2-benzamido-2-phenylacetyl)-N^6-(*tert*-butoxycarbonyl)-*D*-lysine (16):

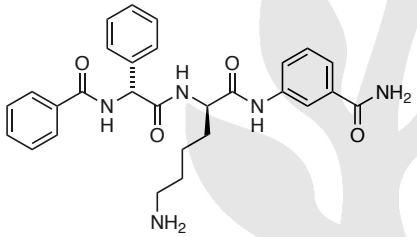


A solution of methyl N^2-((*R*)-2-benzamido-2-phenylacetyl)-N^6-(*tert*-butoxycarbonyl)-D-lysinate (142 mg, 0.285 mmol, 1.00 equiv.) in MeOH (2.0 mL) at 0 °C was treated with aqueous sodium hydroxide solution (2 M, 2.00 mL, 4.00 mmol., 14 equiv.) and the mixture was allowed to warm to room temperature over 3 hours, when LC-MS analysis indicated complete conversion of the starting material. Methanol was removed under reduced pressure and the remaining aqueous residue was diluted further with water. The mixture was cooled in an ice bath, and the pH was adjusted to 2 by dropwise addition of aqueous hydrochloric acid solution (1 M), which caused a white precipitate to form. The aqueous suspension was extracted with ethyl acetate (4 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was subjected to column chromatography over silica gel using eluent CH_2Cl_2 100% to CH_2Cl_2:MeOH 80:20 to afford carboxylic acid **16** as a white solid (120 mg, 87%, inseparable 8:2 mixture of diastereomers/rotamers): $\mathbf{R_f}$ 0.11 (CH_2Cl_2:MeOH, 9:1, UV/CAM); **LC-MS:**

t_R = 3.676 min (5-100% MeCN in H_2O with 0.1% formic acid); **IR:** $\tilde{\nu}$ = 3854w, 3676w, 2988m, 2972m, 2901m, 2361s, 2341s, 1559w, 1394w, 1066s, 1057s; **^{1}H-NMR (400 MHz, CD_3OD):** δ = 7.86 (2H, m), 7.52–7.57 (3H, m), 7.46 (2H, m), 7.30–7.42 (3H, m), 5.79 (1H, s), 4.43 (1H, t, *J* 4.4), 2.84–3.06 (2H, m), 1.56–1.93 (2H, m), 1.42 (9H, s), 1.14–1.38 (4H, m);* **^{13}C NMR (101 MHz, CD_3OD):** δ = 175.1, 172.5, 169.6, 158.5, 139.3, 135.2, 132.9, 129.8, 129.6, 129.4, 128.8, 128.6, 79.9, 59.0, 53.6, 41.1, 32.2, 30.2, 28.8, 24.0;** **ESI-HRMS:** m/z calcd. for $[C_{26}H_{33}N_3NaO_6]^+$ 506.2262 found 506.2257 $[M+H]^+$.

** Reported as combined integrals of both diastereomers.*
*** Signals of main diastereomer are reported.*

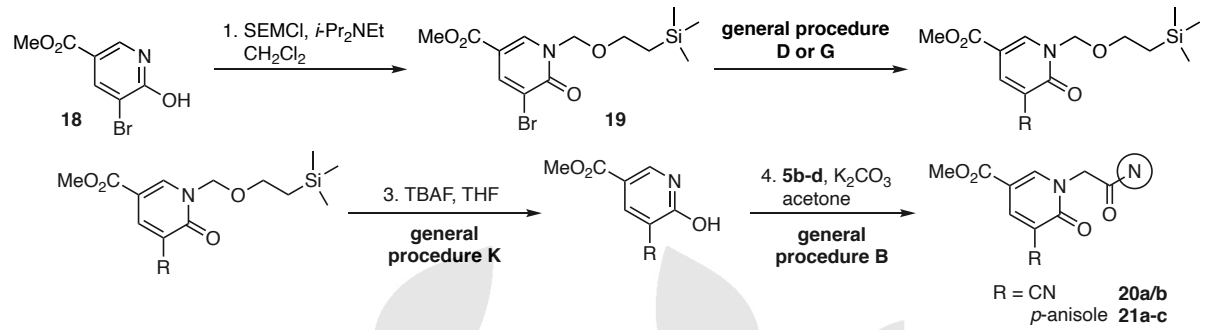
_N_-((_R_)-2-(((_R_)-6-amino-1-((3-carbamoylphenyl)amino)-1-oxohexan-2-yl)amino)-2-oxo-1-phenylethyl)benzamide (3):



To a solution of carboxylic acid **16** (10.0 mg, 0.0207 mmol, 1.00 equiv.) and *m*-aminobenzamide (3.10 mg, 0.0227 mmol, 1.10 equiv.) in anhydrous MeCN (0.50 mL) at 0 °C was added EDCI (4.40 mg, 0.0227 mmol, 1.10 equiv.), HOBt (3.50 mg, 0.0227 mmol, 1.10 equiv.) and DMAP (0.300 mg, 0.00210 mmol, 10 mol%). The mixture was allowed to warm to room temperature over 2 hours and was continued to stir at that temperature for 3 hours, when LC-MS analysis indicated complete conversion of **16**. The mixture was concentrated in vacuo and the residue was treated with water (2.0 mL) and extracted with CH_2Cl_2 (3 x 2.0 mL). The combined organic layers were washed with aqueous saturated sodium chloride solution (2.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in HCl in dioxane (4 M, 0.500 mL, 2.00 mmol) at room temperature and stirred at that temperature for 30 minutes, when LC-MS analysis indicated complete Boc-deprotection. The mixture was concentrated in vacuo and the residue was purified by reverse phase HPLC (semiprep column, 8 ml/min flow rate, 12% to 20% MeCN in water over 8 minutes, then 100% MeCN for 3 minutes, t_R = 4.359 min) affording tripeptide **16** as a pale yellow solid (3.6 mg, 35%, inseparable 3:2-mixture of diastereomers): **LC-MS:** t_R = 2.322 min (5-100% MeCN in H_2O with 0.1% formic acid); **IR:** $\tilde{\nu}$ = 3301w, 2921w, 2852w, 2361s, 2340s, 1734w, 1663s, 1647s, 1608s, 1570s, 1541m, 1473m, 1375w, 1250w; **^{1}H-NMR (400 MHz, CD_3OD):** δ = 8.55 (1H, s), 8.21 (1H, t, *J* 2.0), 7.86–7.91 (1H, m), 7.73–7.82 (2H, m), 7.50–7.64 (3H, m), 7.40 (4H, m), 6.83 (2H, d, *J* 8.9, 2.8), 5.55–5.68 (1H, m), 4.51 (1H, m), 2.68–2.95 (2H, m), 1.21–2.07 (6H, m);* **^{13}C NMR (101 MHz, CD_3OD):** δ = 173.7, 172.4, 170.1, 162.5, 139.8, 138.0, 135.9, 130.9, 130.7, 129.9, 129.8, 129.2, 129.0, 125.5, 124.9, 124.4, 121.1, 116.2, 60.5, 54.8, 40.5, 31.9, 28.1, 23.6;** **ESI-HRMS:** m/z calcd. for $[C_{28}H_{31}N_5O_4]^+$ 502.2449 found 502.2441 $[M+H]^+$.

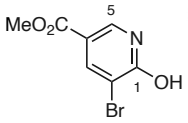
** Reported as combined integrals of both diastereomers.*
*** Signals of main diastereomer are reported.*

Acetamide Optimizations to 20a/b, 21a-c:



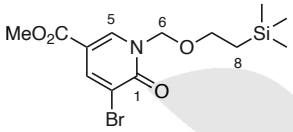
Scheme S3: General strategy to facilitate diverse *N*-substitution on the pyridone core.

Methyl 5-bromo-6-hydroxynicotinate (18):



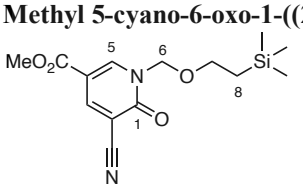
Prepared according to general procedure **C** using methyl 6-hydroxynicotinate (1.69 g, 11.0 mmol) to give product as a pale yellow solid (1.86 g, 73%): $\mathbf{R}_f$ 0.14 (hexanes:EtOAc, 1:1, UV); **^{1}H-NMR (400 MHz, (CD_3)$_2$SO):** δ = 12.69 (1H, br, O*H*), 8.18 (1H, d, ^4J 2.4, C3*H*), 8.10 (1H, br, C5*H*), 3.78 (3H, s, CH_3); **^{13}C NMR (101 MHz, (CD_3)$_2$SO):** δ = 163.4 (*C*O_2Me), 158.5 (*C1*), 140.7 (*C3*), 140.0 (*C5*), 114.8 (*C2*), 108.9 (*C4*), 52.1 (*C*H_3); Data in agreement with literature.[12]

Methyl 5-bromo-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate (19):



Prepared according to a modified literature procedure.[26] To a mixture of methyl 5-bromo-6-hydroxynicotinate **(18)** (1.85 g, 7.97 mmol) in dry CH_2Cl_2 (17 mL) and *N*,*N*-diisopropylethylamine (1.80 mL, 10.4 mmol) in an ice bath was added dropwise 2-(trimethylsilyl)ethoxymethyl chloride (1.70 mL, 9.57 mmol) to keep the inside temperature at 8±2 °C. The mixture was allowed to warm to room temperature over 18 hours and treated with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Column chromatography over silica gel with eluent hexanes 100% to hexanes:Et_2O 95:5 to 90:10 gave product (1.68 g, 58%): $\mathbf{R}_f$ 0.32 (hexanes:EtOAc, 2:1, UV); **IR:** $\tilde{\nu}$ = 3062w, 2957w, 2895w, 1720m, 1654s, 1615m, 1529w, 1452w, 1438m, 1418w, 1401w, 1377w, 1329w, 1279s, 1249m, 1199m, 1182w, 1134w, 1090s, 1061m, 1034w, 969w, 925m, 906m, 834s, 771m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.30 (1H, d, ^4J 2.3, C5*H*), 8.27 (1H, d, ^4J 2.3, C3*H*), 5.41 (2H, s, C6H_2), 3.88 (3H, s, CO_2CH_3), 3.64–3.68 (2H, m, C7H_2), 0.95–0.99 (2H, m, C8H_2), 0.01 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 163.8 (*C*O_2Me), 159.1 (*C1*), 140.8 (*C3*), 140.2 (*C5*), 116.1 (*C2*), 110.5 (*C4*), 78.6 (*C6*), 68.4 (*C7*), 52.5 (CO_2CH_3), 18.2 (*C8*), –1.3 (Si(*C*H_3)$_3$); **APCI-HRMS:** m/z calcd. for $[C_{13}H_{21}BrNO_4Si]^+$ 362.0418 found 362.0424 $[M+H]^+$.

Methyl 5-cyano-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate:



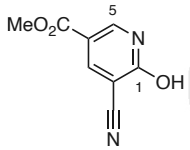
Prepared according to general procedure **G** using methyl 5-bromo-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate **(19)** (435 mg, 1.20 mmol) and CuCN (215 mg, 2.40 mmol) in DMF (2.4 mL). Column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 95:5 to 90:10 to 85:15 gave product as a white solid (268 mg, 72%): $\mathbf{R}_f$ 0.45 (hexanes:EtOAc, 1:1, UV); **IR:** $\tilde{\nu}$ = 2954w, 2232w, 1725m, 1673s, 1624w, 1547m, 1442m, 1295s, 1250m, 1205m, 1169w, 1095m, 989w, 939w, 910w, 860m, 837m, 778w, 764w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.52–8.54 (1H, m, C5*H*), 8.36–8.38 (1H, m, C3*H*),

5.40 (2H, s, C6H_2), 3.91 (3H, s, CO_2CH_3), 3.65–3.69 (2H, m, C7H_2), 0.96–1.00 (2H, m, C8H_2), 0.01 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 163.1 (CO_2CH_3), 159.5 (*C1*), 146.8 (*C3*), 145.0 (*C5*), 114.6 (*C*N), 109.9 (*C4*), 105.5 (*C2*), 78.0 (*C6*), 68.9 (*C7*), 52.9 (CO_2CH_3), 18.2 (*C8*), 1.30 (Si(CH_3)$_3$).

General Procedure K:

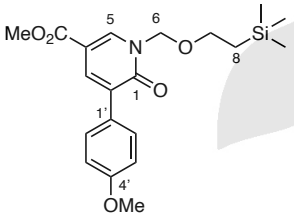
Prepared according to a modified literature procedure.[26] To a solution of N-SEM protected pyridones (1.00 equiv) in dry THF (10 mL per mmol substrate) at room temperature was added *tetra-n*-butylammonium fluoride (1 mol L^{-1} in THF, 2.20 equiv) in one portion. The mixture was heated to 65 °C and stirred for an individually specified time. The mixture was treated with water (20 mL per mmol substrate) and extracted with CH_2Cl_2 (3 x 20 mL per mmol substrate). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography over silica gel gave the unprotected pyridones (individually specified).

Methyl 5-cyano-6-hydroxynicotinate:



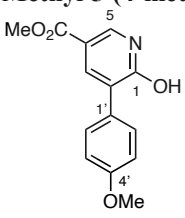
Prepared according to general procedure **K** using methyl 5-cyano-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate (256 mg, 0.830 mmol), *tetra-n*-butylammonium fluoride (1 mol L^{-1} in THF, 1.80 mL) and THF (8.3 mL) stirred at 65 °C for 2 hours. Column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 75:25 to 50:50 to 25:75 to 100% EtOAc to EtOAc:acetone 80:20 to 50:50 100% acetone. Product containing fractions were concentrated in vacuo, suspended in *i*-PrOH:hexanes (7:3) and filtered to give product as a beige solid (84.0 mg, 57%): **R_f** 0.28 (100% EtOAc, UV); **IR:** $\tilde{\nu}$ = 3073m, 2875m, 2239m, 1718s, 1654s, 1620m, 1567m, 1495w, 1433m, 1345s, 1292s, 1246s, 1223s, 1191m, 1136m, 1090m, 1000w, 976m, 911m, 834w, 777s, 757m; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ = 13.15 (1H, br, O*H*), 8.47 (1H, s, C3*H*), 8.36 (1H, s, C5*H*), 3.80 (3H, s, CO_2CH_3); **^{13}C-NMR (101 MHz, $CDCl_3$)** δ = 163.1 (CO_2Me), 160.0 (*C1*), 147.7 (*C3*), 145.7 (*C5*), 115.5 (*C*N), 108.4 (*C4*), 103.3 (*C2*), 52.2 (CO_2CH_3); **APCI-HRMS:** m/z calcd. for $[C_8H_7N_2O_3]^+$ 179.0451 found 179.0456 $[M+H]^+$.

Methyl 5-(4-methoxyphenyl)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate:



Prepared according to general procedure **D** using methyl 5-bromo-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate **(19)** (420 mg, 1.16 mmol), 4-methoxyphenylboronic acid (440 mg, 2.90 mmol), Na_2CO_3 (492 mg, 4.64 mmol), $Pd(PPh_3)_4$ (67.0 mg, 0.0580 mmol, *5.00 mol%*) in PhMe:EtOH:H_2O (7.2 mL, 2.9 mL, 1.0 mL) at 75 °C for 3 hours. Column chromatography over silica gel using 100% hexanes to hexanes:Et_2O 95:5 to 90:10 to 85:15 to 80:20 gives product (506 mg, directly used in the next step): **R_f** 0.32 (hexanes:EtOAc, 2:1, UV); **IR:** $\tilde{\nu}$ = 2953w, 1720m, 1655s, 1557w, 1511w, 1439w, 1316w, 1303m, 1247s, 1179w, 1095m, 1032w, 982w, 915w, 861w, 835m, 787w, 763w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.29 (1H, d, ^4J 2.5, C5*H*), 7.98 (1H, d, ^4J 2.5, C3*H*), 7.64–7.68 (2H, m, 2 x C2'*H*), 6.93–6.97 (2H, m, 2 x C3'*H*), 5.44 (2H, s, C6H_2), 3.89 (3H, s, CO_2CH_3), 3.84 (3H, s, OCH_3), 3.67–3.71 (2H, m, C7H_2), 0.96–1.01 (2H, m, C8H_2), 0.01 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.1 (CO_2CH_3), 162.0 (*C1*), 159.8 (*C4'*), 139.6 (*C5*), 135.7 (*C3*), 130.8 (*C1'*), 130.0 (*C2'*), 128.3 (*C2*), 113.8 (*C3'*), 110.1 (*C4*), 77.7 (*C6*), 68.0 (*C7*), 55.5 (OCH_3), 52.3 (CO_2CH_3), 18.2 (*C8*), –1.3 (Si(CH_3)$_3$); **APCI-HRMS:** m/z calcd. for $[C_{20}H_{28}NO_5Si]^+$ 390.1731 found 390.1730 $[M+H]^+$.

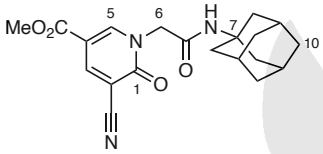
Methyl 5-(4-methoxyphenyl)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate:



Prepared according to general procedure **K** using methyl 5-(4-methoxyphenyl)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate (499 mg, 1.28 mmol), *tetra-n*-butylammonium fluoride (1 mol L^{-1} in THF, 2.80 mL) and THF (13 mL) stirred at 65 °C for 3 hours. Column chromatography over silica gel using eluent 100% hexanes to hexanes:EtOAc 90:10 to 80:20 to 70:30 to 60:40 to 50:50

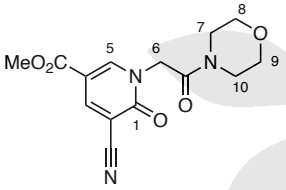
gives product as an off-white solid (105 mg, 32% over two steps): $\mathbf{R}_f$ 0.28 (hexanes:EtOAc, 1:2, UV); **IR:** $\tilde{\nu}$ = 2919m, 2850w, 1720m, 1644s, 1609m, 1575w, 1514m, 1437m, 1397w, 1316m, 1303m, 1250s, 1182w, 1114m, 1039w, 969w, 886w, 836w, 761w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 12.48 (1H, br, O*H*), 8.15 (1H, s, C5*H*), 8.10 (1H, s, C3*H*), 7.69 (2H, d, 2 x C2'*H*), 6.98 (2H, d, ^3J 8.3, 2 x C3'*H*), 3.88 (3H, s, CO_2CH_3), 3.86 (3H, s, OCH_3); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.9 (CO_2CH_3), 159.9 (*C4'*), 137.9 (*C5*), 137.6 (*C3*), 129.9 (*C2'*), 127.9 (*C1'*), 114.0 (*C3'*), 111.4 (*C4*), 55.5 (OCH_3), 52.3 (CO_2CH_3); **APCI-HRMS:** m/z calcd. for $[C_{14}H_{14}NO_4]^+$ 260.0917 found 260.0916 $[M+H]^+$.

Methyl 1-(2-((adamantan-1-yl)amino)-2-oxoethyl)-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxylate (20a):



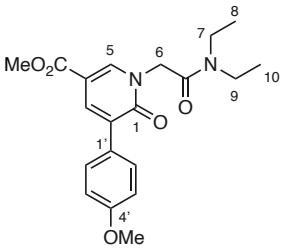
Prepared according to general procedure **B** and *Work-up Method 2* using methyl 5-cyano-6-hydroxynicotinate (17.8 mg, 0.100 mmol) and *N*-adamantanyl-2-chloroacetamide **(5c)** (31.9 mg, 0.140 mmol), acetone (1.0 mL), K_2CO_3 (41.5 mg, 0.300 mmol). Stirred at 50 °C for 18 hours. The product was obtained as an off-white solid without further purification (12.5 mg, 34%): $\mathbf{R}_f$ 0.45 (hexanes:EtOAc, 1:2, UV); **IR:** $\tilde{\nu}$ = 3301w, 3075w, 2917m, 2850w, 2235w, 1717w, 1676s, 1659s, 1543m, 1444w, 1408w, 1362w, 1326m, 1295m, 1214m, 1104w, 1009w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.45 (1H, d, ^4J 2.4, C5*H*), 8.38 (1H, d, ^4J 2.4, C3*H*), 5.76 (1H, br, N*H*), 4.53 (2H, s, C6H_2), 3.89 (3H, s, CO_2CH_3), 2.08 (3H, br, 3 x C9*H*), 1.99 (6H, d, ^4J 2.5, 3 x C8H_2), 1.66–1.68 (6H, m, 3 x C10H_2); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 163.4 (*C*ONR), 163.0 (CO_2Me), 159.5 (*C1*), 147.9 (*C5*), 147.0 (*C3*), 114.6 (*C*N), 109.8 (*C4*), 104.8 (*C2*), 53.6 (*C6*), 53.4 (C7), 52.8 (CO_2CH_3), 41.5 (*C8*), 36.3 (*C10*), 29.5 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{20}H_{24}N_3O_4]^+$ 370.1761 found 370.1764 $[M+H]^+$.

Methyl 5-cyano-1-(2-morpholino-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (20b):



Prepared according to general procedure **B** and *Work-up Method 2* using methyl 5-cyano-6-hydroxynicotinate (17.8 mg, 0.100 mmol) and 2-chloro-1-morpholinoethan-1-one **(5d)** (5(22.9 mg, 0.140 mmol), acetone (1.0 mL), K_2CO_3 (41.5 mg, 0.300 mmol). Stirred at 50 °C for 18 hours. The product was obtained as a beige solid without further purification (15.2 mg, 50%): $\mathbf{R}_f$ 0.07 (hexanes:EtOAc, 1:2); **IR:** $\tilde{\nu}$ = 2922w, 2855w, 2233w, 1722m, 1661s, 1547m, 1441m, 1327m, 1298s, 1274w, 1236m, 1210s, 1112m, 1068w, 1040w, 1000w, 979w, 916w, 807w, 771w; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ = 8.38 (2H, s, C3*H*, C5*H*), 4.83 (2H, s, C6H_2), 3.89 (3H, s, CO_2CH_3), 3.78–3.80 (2H, m, C9H_2), 3.71–3.74 (2H, m, C8H_2), 3.59–3.66 (4H, m, C7H, C10H); **^{13}C-NMR (101 MHz, $CDCl_3$)** δ = 163.4 (*C*ONR), 162.9 (CO_2Me), 159.2 (*C1*), 148.1 (*C5*), 146.9 (*C3*), 114.4 (*C*N), 109.6 (*C4*), 104.7 (*C2*), 66.6 (C8), 66.4 (C9), 52.7 (CO_2CH_3), 49.6 (*C6*), 45.8 (*C7*), 42.9 (*C10*); **APCI-HRMS:** m/z calcd. for $[C_{14}H_{16}N_3O_5]^+$ 306.1084 found 306.1084 $[M+H]^+$.

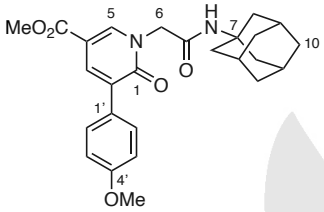
Methyl 1-(2-(diethylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (21a):



Prepared according to general procedure **B** and *Work-up Method 2* using methyl 5-(4-methoxyphenyl)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate (25.9 mg, 0.100 mmol) and 2-chloro-*N*,*N*-diethylacetamide **(5b)** (20.9 mg, 0.140 mmol), acetone (1.0 mL), K_2CO_3 (41.5 mg, 0.300 mmol). Stirred at 50 °C for 3 hours. Column chromatography over silica gel with eluent hexanes 100% to hexanes:EtOAc 90:10 to 70:30 gave product as an off-white solid (17.2 g, 46%): $\mathbf{R}_f$ 0.25 (hexanes:EtOAc, 1:2, UV); **IR:** $\tilde{\nu}$ = 2953w, 1717m, 1651s, 1608m, 1557w, 1512w, 1439m, 1393w, 1322w, 1304m, 1251s, 1222m, 1180w, 1146w, 1114w, 1031w, 944w, 871w, 837w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 8.19 (1H, d, ^4J 2.5, C5*H*), 8.00 (1H, d, ^4J 2.5, C3*H*), 7.61–7.64 (2H, m, 2 x C2'*H*), 6.91–6.94 (2H, m, 2 x C3'*H*), 4.82 (2H, s, C6H_2), 3.86 (3H, s, CO_2CH_3), 3.82 (3H, s, OCH_3), 3.39–3.49 (4H, m, C7H_2, C9H_2), 1.32 (3H, t, ^3J 7.2,

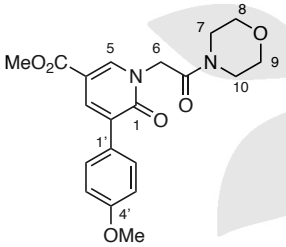
C8H_3), 1.15 (3H, t, ^4J 7.2, C10H_3); **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 165.1 (*C*ONEt$_2$), 165.0 (*C*O$_2$Me), 161.6 (*C1*), 159.5 (*C4'*), 142.6 (*C5*), 135.9 (*C3*), 130.0 (*C2*), 129.9 (*C2'*), 128.4 (*C1'*), 113.6 (*C3'*), 109.6 (*C4*), 55.3 (O*C*H$_3$), 52.0 (CO$_2$*C*H$_3$), 50.0 (*C6*), 41.9 (*C7*), 41.2 (*C9*), 14.5 (*C8*), 13.0 (*C10*); **APCI-HRMS:** m/z calcd. for $[C_{20}H_{25}N_2O_5]^+$ 373.1758 found 373.1758 $[M+H]^+$.

Methyl 1-(2-((adamantan-1-yl)amino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (21b):



Prepared according to general procedure **B** and *Work-up Method 2* using methyl 5-(4-methoxyphenyl)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate (25.9 mg, 0.100 mmol) and *N*-adamantanyl-2-chloroacetamide **(5c)** (31.9 mg, 0.140 mmol), acetone (1.0 mL), K_2CO_3 (41.5 mg, 0.300 mmol). Stirred at 50 °C for 3 hours. Column chromatography over silica gel with eluent hexanes 100% to hexanes:EtOAc 90:10 to 70:30 gave product as a white solid (23.7 mg, 53%): **R$_f$** 0.22 (hexanes:EtOAc, 1:1, UV); **IR:** $\tilde{\nu}$ = 3311w, 2907m, 2850w, 2248w, 1717w, 1645s, 1607m, 1556m, 1512m, 1439m, 1392w, 1360w, 1321m, 1304m, 1247s, 1217m, 1179w, 1113w, 1033w, 910w, 872w, 836w, 730m; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 8.24 (1H, d, ^4J 2.4, C5*H*), 8.02 (1H, d, ^4J 2.4, C3*H*), 7.63–7.65 (2H, m, 2 x C2'*H*), 6.94–6.96 (2H, m, 2 x C3'*H*), 6.06 (1H, br, N*H*), 4.53 (2H, s, C6H_2), 3.87 (3H, s, CO$_2$CH_3), 3.84 (3H, s, O*C*H$_3$), 2.06 (3H, br, 3 x C9*H*), 1.97 (6H, d, ^4J 2.4, 3 x C8H_2), 1.64–1.66 (6H, m, 3 x C10H_2); **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 165.2 (*C*ONR), 164.9 (*C*O$_2$Me), 162.0 (*C1*), 159.8 (*C4'*), 141.8 (*C5*), 136.3 (*C3*), 130.4 (*C2*), 130.0 (*C2'*), 128.3 (*C1'*), 113.9 (*C3'*), 110.3 (*C4*), 55.5 (O*C*H$_3$), 55.0 (*C6*), 52.8 (*C7*), 52.3 (CO$_2$*C*H$_3$), 41.5 (*C8*), 36.4 (*C10*), 29.5 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{26}H_{31}N_2O_5]^+$ 451.2227 found 451.2208 $[M+H]^+$.

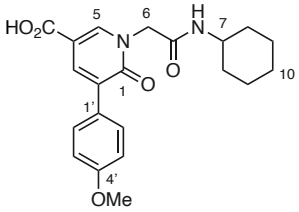
Methyl 5-(4-methoxyphenyl)-1-(2-morpholino-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (21c):



Prepared according to general procedure **B** and *Work-up Method 2* using methyl 5-(4-methoxyphenyl)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridine-3-carboxylate (25.9 mg, 0.100 mmol) and 2-chloro-1-morpholinoethan-1-one **(5d)** (22.9 mg, 0.140 mmol), acetone (1.0 mL), K_2CO_3 (41.5 mg, 0.300 mmol). Stirred at 50 °C for 4 hours. Column chromatography over silica gel with eluent hexanes 100% to hexanes:EtOAc 75:25 to 50:50 to 20:80 gave as a white solid (28.3 mg, 73%): **R$_f$** 0.24 (100% EtOAc, UV); **IR:** $\tilde{\nu}$ = 2924w, 2855w, 1717m, 1650s, 1608m, 1558w, 1512w, 1439m, 1321m, 1304m, 1249s, 1223m, 1180w, 1113m, 1037w, 961w, 910w, 872w, 838w, 763w, 730w; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 8.18 (1H, d, ^4J 2.5, C5*H*), 8.02 (1H, d, ^4J 2.5, C3*H*), 7.62–7.65 (2H, m, 2 x C2'*H*), 6.92–6.95 (2H, m, 2 x C3'*H*), 4.83 (2H, s, C6H_2), 3.87 (3H, s, CO$_2$CH_3), 3.83 (3H, s, OCH_3), 3.77 (2H, t, ^3J 4.5, C8H_2), 3.72 (2H, t, ^3J 4.5, C9H_2), 3.63–3.67 (4H, m, C7H_2, C10H_2); **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 165.0 (*C*O$_2$Me), 164.9 (*C*ONR), 161.7 (*C1*), 159.8 (*C4'*), 142.3 (*C5*), 136.1 (*C3*), 130.3 (*C2*), 130.0 (*C2'*), 128.3 (*C1'*), 113.8 (*C3'*), 110.1 (*C4*), 66.9 (*C9*), 66.7 (*C8*), 55.5 (O*C*H$_3$), 52.3 (CO$_2$*C*H$_3$), 49.9 (*C6*), 46.0 (*C7*), 42.8 (*C10*); **APCI-HRMS:** m/z calcd. for $[C_{20}H_{23}N_2O_6]^+$ 387.1551 found 387.1547 $[M+H]^+$.

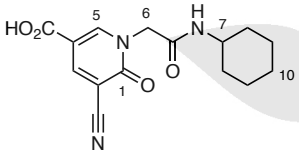
Additional Pyridone Amides 23a-c, 24a/b:

1-(2-(Cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (22a):



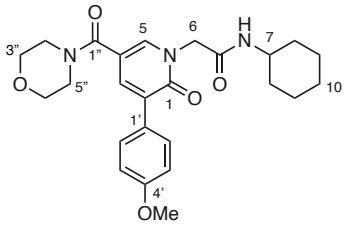
Prepared according to general procedure **I** using methyl 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (100 mg, 0.250 mmol), THF (4.8 ml), water (4.8 ml) and NaOH (102 mg, 2.55 mmol, 10 equiv). Stirred at room temperature for 19 hours. The product was obtained as a light beige solid (98.0 mg, quant.): **IR:** $\tilde{\nu}$ =2933w, 2853w, 2412w, 1691m, 1643s, 1606s, 1573w, 1554m, 1513m, 1441s, 1416m, 1347w, 1317m, 1305m, 1256s, 1223m, 1180s, 1156m, 1117m, 1097m, 1022m, 946m, 894w, 868m, 834m, 809m, 785w, 766m, 749w; **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 8.36 (1H, d, *J* 2.4, C5*H*), 8.04 (1H, d, *J* 2.4, C3*H*), 7.57–7.64 (2H, m, 2 x *C2'*H), 6.94–7.01 (2H, m, 2 x *C3'*H), 4.75 (2H, s, C6*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 3.64–3.67 (1H, m, C7*H*), 1.86–1.96 (2H, m, 2 x C8*H*), 1.73–1.82 (2H, m, 2 x C9*H*), 1.61–1.70 (1H, m, C10*H*), 1.16–1.44 (5H, m, 2 x C9*H*, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, CD$_3$OD):** δ = 168.0 (*C*ONH), 167.8 (*C*O$_2$H), 163.6 (*C1*), 161.1 (*C4'*), 144.4 (*C5*), 138.0 (*C3*), 131.1 (*C2*), 130.9 (*C2'*), 129.7 (C1'), 114.6 (*C3'*), 112.2 (*C4*), 55.7 (O*C*H$_3$), 54.0 (*C6*), 50.2 (*C7*), 33.7 (*C8*), 26.6 (*C10*), 26.1 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{21}H_{25}N_2O_5]^+$ calcd. 385.1758 found 385.1763 $[M+H]^+$.

5-Cyano-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (22b):



Prepared according to general procedure **I** using methyl 5-cyano-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (63.5 mg, 0.200 mmol), THF (1.0 mL), water (1.0 mL) and NaOH (32.0 mg, 0.800 mmol, 4.0 equiv). Stirred at 40 °C for 3 hours. The product was obtained as a pink solid (37.0 mg, 61%): **IR:** $\tilde{\nu}$ = 3402m, 2919s, 2850s, 2359w, 2327w, 1718s, 1670s, 1547w, 1439w, 1377w, 1262m, 1185w, 1090w, 950w, 799w, 781w, 720w; **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 8.66 (1H, d, ^{4}*J* 2.4, C5*H*), 8.50 (1H, d, ^{4}*J* 2.4, C3*H*), 4.75 (2H, s, C6*H*$_2$), 3.59–3.70 (1H, m, C7*H*), 1.85–1.93 (2H, m, 2 x C8*H*), 1.71–1.81 (2H, m, 2 x C9*H*), 1.57–1.66 (1H, m, C10*H*), 1.34–1.43 (2H, m, 2 x C9*H*), 1.12–1.24 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, CD$_3$OD):** δ = 167.0 (*C*ONR), 165.5 (*C*O$_2$H), 161.5 (*C1*), 150.7 (*C5*), 148.8 (*C3*), 115.9 (*C2*), 111.6 (*C4*), 104.7 (*C*N), 53.7 (*C6*), 50.29 (*C7*), 33.6 (*C8*), 26.6 (*C10*), 26.0 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{15}H_{18}N_3O_4]^+$ 304.1292 found 304.1298 $[M+H]^+$.

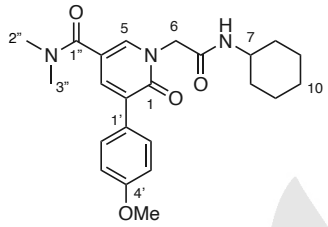
***N*-Cyclohexyl-2-(3-(4-methoxyphenyl)-5-(morpholine-4-carbonyl)-2-oxopyridin-1(2*H*)-yl)acetamide (23a):**



Prepared according to general procedure **J** using 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropy-ridine-3-carboxylic acid **(22a)** (23.1 mg, 0.0600 mmol), HATU (34.2 mg, 0.0900 mmol), *N,N*-diisopropylethylamine (0.052 mL, 0.300 mmol), DMF (0.86 mL) and morpholine (6.30 mg, 0.0720 mmol). Stirred at room temperature for 18 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 98:2 CH_2Cl_2:MeOH gives product as an off-white solid (6.60 mg, 24%): **R$_f$** 0.34 (CH_2Cl_2:MeOH, 95:5, UV); **IR:** $\tilde{\nu}$ = 3552w, 3297w, 2923m, 2852m, 2418w, 1647s, 1602s, 1572m, 1551m, 1509m, 1452s, 1429s, 1366m, 1339m, 1308m, 1300m, 1288m, 1276m, 1251s, 1232s, 1195m, 1177m, 1149m, 1103s, 1064m, 1028s, 979m, 961m, 943m, 932m, 894m, 860m, 835s, 816m, 796m, 744m; **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 7.86 (1H, d, *J* 2.5, C5*H*), 7.68 (1H, d, *J* 2.4, C3*H*), 7.59–7.64 (2H, m, 2 x C2'*H*), 6.93–7.00 (2H, m, C3'*H*), 4.74 (2H, s, C6*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 3.73 (8H, s, C2"*H*$_2$, C3"*H*$_2$, C4"*H*$_2$, C5"*H*$_2$), 3.64–3.73 (1H, m, C7*H*), 1.86–1.96 (2H, m, 2 x C8*H*), 1.74–1.85 (2H, m, 2 x C9*H*), 1.65 (1H, dp, *J* 12, 3.5, C10*H*), 1.16–1.47 (5H, m, 2 x C8*H,* 2 x C9*H*, C10*H*); **^{13}C-NMR (101 MHz, CD$_3$OD):** δ = 168.9 (*C1"*), 168.1 (*C*ONH), 163.0 (*C1*), 161.2 (*C4'*), 140.7 (*C5*), 138.0 (*C3*), 131.8 (*C2*), 131.0 (*C2'*), 129.6 (*C1'*), 115.1 (*C4*), 114.7

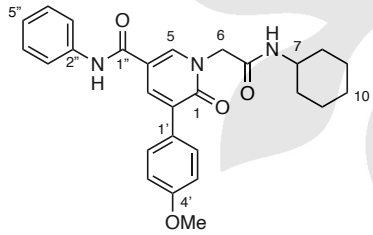
(*C3'*), 67.8 (*C2"*, *C3"*, *C4"*, *C5"*), 55.7 (O*C*H$_3$), 53.4 (*C6*), 50.2 (*C7*), 33.7 (*C8*), 26.6 (*C10*), 26.1 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{25}H_{32}N_3O_5]^+$ calcd. 454.2336 found 454.2342 $[M+H]^+$.

1-(2-(Cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (23b):



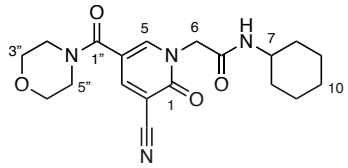
Prepared according to general procedure **J** using 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropy-ridine-3-carboxylic acid **(22a)** (23.1 mg, 0.0600 mmol), HATU (34.2 mg, 0.0900 mmol), *N,N*-diisopropylethylamine (0.052 mL, 0.300 mmol), DMF (0.86 mL), dimethylamine (0.036 mL, 0.0720 mmol). Stirred at room temperature for 3 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 98:2 CH_2Cl_2:MeOH and additional recrystallization from EtOH gives product as an off-white solid (16.9 mg, 68%): $\mathbf{R}_f$ 0.33 (95:5 CH_2Cl_2:MeOH, UV); **IR:** $\tilde{\nu}$ = 2928w, 2852w, 2401w, 1676m, 1652m, 1616s, 1605s, 1551m, 1497m, 1450s, 1413m, 1400m, 1380m, 1341w, 1302m, 1249s, 1235m, 1207m, 1176s, 1108m, 1036m, 981w, 944w, 924w, 903w, 891m, 865w, 849s, 826m, 793m, 767w, 754w; **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 7.82 (1H, d, *J* 2.5, C5*H*), 7.70–7.76 (2H, m, 2 x C2'*H*), 7.67 (1H, d, *J* 2.5, C3*H*), 7.32 (1H, d, *J* 7.8, N*H*), 6.91–6.97 (2H, m, 2 x C3'*H*), 4.70 (2H, s, C6*H*), 3.82 (3H, s, OC*H*$_3$), 3.63–3.74 (1H, m, C7*H*), 3.09 (6H, s, C2"*H*$_3$, C3"*H*$_3$), 1.82–1.91 (2H, m, 2 x C8*H*), 1.66–1.76 (2H, m, 2 x C9*H*), 1.55–1.63 (1H, m, C10*H*), 1.12–1.39 (5H, m, 2 x C8*H*, 2 x C9*H*, C10*H*); **^{13}C-NMR (101 MHz, CD$_3$OD):** δ = 168.2 (*C1"*), 166.5 (*C*ONH), 161.4 (*C1*), 160.4 (*C4'*), 140.5 (*C5*), 136.9 (*C3*), 130.6 (2 x *C3'*), 129.9 (*C1'*), 129.8 (*C2*), 114.5 (*C4*), 114.1 (*C2'*), 55.5 (O*C*H$_3$), 52.6 (C6), 49.3 (*C7*), 33.5 (*C8*), 26.3 (*C10*), 25.6 (*C9*), *signals for C2" and C3" were not found*; **APCI-HRMS:** m/z calcd. for $[C_{23}H_{30}N_3O_4]^+$ $[M+H]^+$ calcd. 412.2231 found 412.2235.

1-(2-(Cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (23c):



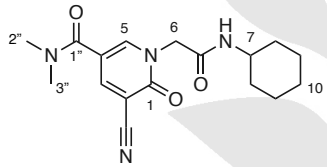
Prepared according to general procedure **J** using 1-(2-(cyclohexylamino)-2-oxoethyl)-5-(4-methoxyphenyl)-6-oxo-1,6-dihydropy-ridine-3-carboxylic acid **(22a)** (23.1 mg, 0.0600 mmol), HATU (34.2 mg, 0.0900 mmol), *N,N*-diisopropylethylamine (0.052 mL, 0.300 mmol), DMF (0.86 ml), and aniline (6.70 mg, 0.0720 mmol). Stirred at room temperature for 3 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 98:2 CH_2Cl_2:MeOH and additional recrystallization from toluene gives product as an off-white solid (16.1 mg, 58%): $\mathbf{R}_f$ 0.25 (Hexanes:(EtOAc:CH_2Cl_2, 6:4), 2:8; UV); **IR:** $\tilde{\nu}$ = 2928w, 2852w, 2384w, 1669w, 1635s, 1601s, 1554m, 1499s, 1465s, 1423m, 1403s, 1376s, 1330m, 1302m, 1287m, 1248s, 1213m, 1192m, 1151m, 1105m, 1015m, 976w, 949m, 914m, 885m, 835s, 796m, 786m, 755s, 731m, 715m; **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 8.34 (1H, d, *J* 2.6, C5*H*), 8.15 (1H, d, *J* 2.6, C3*H*), 7.63–7.70 (4H, m, 2 x C2'*H*, 2 x C3"*H*), 7.34–7.41 (2H, m, 2 x C4"*H*), 7.13–7.19 (1H, m, C5"*H*), 6.96–7.02 (2H, m, 2 x C3'*H*), 4.77 (2H, s, C6*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 3.63–3.81 (1H, m, C7*H*), 1.89–1.97 (2H, m, 2 x C8*H*), 1.74–1.83 (2H, m, 2 x C9*H*), 1.61–1.71 (1H, m, C10*H*), 1.18–1.49 (5H, m, 2 x C8*H*, 2 x C9*H*, C10*H*); **^{13}C-NMR (101 MHz, CD$_3$OD):** δ = 168.0 (*C*ONH), 165.3 (*C1"*), 163.4 (*C1*), 161.2 (*C4'*), 141.9 (*C5*), 139.7 (*C2"*), 136.9 (*C3*), 131.2 (*C2*), 131.0 (*C2'*), 129.8 (*C4"*), 129.8 (*C1'*), 125.6 (*C5"*), 122.2 (*C3"*), 115.6 (*C4*), 114.6 (*C3'*), 55.7 (*C*H$_3$), 54.1 (*C6*), 50.2 (*C7*), 33.7 (*C8*), 26.6 (*C10*), 26.1 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{27}H_{30}N_3O_4]^+$ calcd. 460.2231 found 460.2231 $[M+H]^+$.

2-(3-Cyano-5-(morpholine-4-carbonyl)-2-oxopyridin-1(2*H*)-yl)-*N*-cyclohexylacetamide (24a):



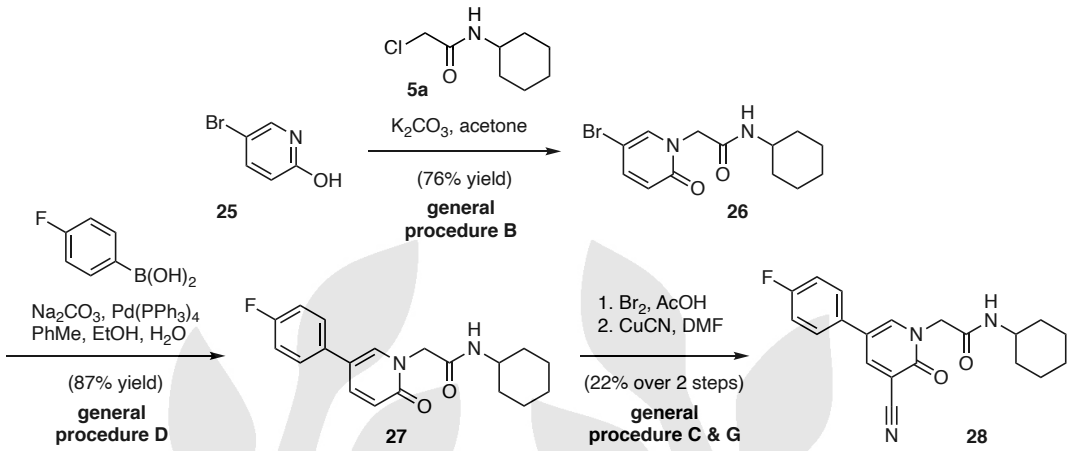
Prepared according to general procedure **J** using 5-cyano-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **(22b)** (11.0 mg, 0.036 mmol), HATU (20.7 mg, 0.0540 mmol), *N,N*-diisopropylethylamine (23.4 mg, 0.181 mmol), DMF (0.35 mL) and morpholine (3.80 mg, 0.0440 mmol). Stirred at room temperature for 3h. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a white solid (6.00 mg, 44%): $\mathbf{R_f}$ 0.14 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3374w, 3071w, 2930w, 2853w, 2230w, 1656s, 1628s, 1541m, 1498w, 1390w, 1275w, 1242w, 1097w, 955w, 939w, 892w, 879w, 843w, 775w, 758w, 727w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.90 (2H, s, C3*H*, C5*H*), 6.26 (1H, d, ^3J 8.1, N*H*), 4.60 (2H, s, C6H_2), 3.70–3.76 (5H, m, 2 x C3'*H*, 2 x C5'*H*, C7*H*), 3.64–3.69 (4H, m, 2 x C3'*H*, 2 x C5'*H*), 1.84–1.93 (2H, m, 2 x C8*H*), 1.67–1.76 (2H, m, 2 x C9*H*), 1.60–1.66 (1H, m, C10*H*), 1.27–1.40 (2H, m, 2 x C9*H*), 1.11–1.26 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 164.8 (*C1'*), 164.1 (*C*ONR), 159.2 (*C1*), 146.9 (*C3*), 145.5 (*C5*), 114.8 (*C2*), 113.4 (*C4*), 104.8 (*C*N), 66.9 (*C3', C5'*), 52.5 (*C6*), 49.4 (*C7*), 32.9 (*C8*), 25.5 (*C10)*, 24.9 (*C9)*; **APCI-HRMS:** m/z calcd. for $[C_{19}H_{25}N_4O_4]^+$ 373.1870 found 373.1874 $[M+H]^+$.

5-Cyano-1-(2-(cyclohexylamino)-2-oxoethyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (24b):



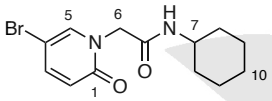
Prepared according to general procedure **J** using 5-cyano-1-(2-(cyclohexylamino)-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **(22b)** (27.0 mg, 0.089 mmol), HATU (50.8 mg, 0.134 mmol), *N,N*-diisopropylethylamine (57.5 mg, 0.445 mmol), DMF (0.90 mL) and dimethylamine (4.80 mg, 0.107 mmol). Stirred at room temperature for 3 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a white solid (16.0 mg, 54%): $\mathbf{R_f}$ 0.11 (EtOAc, 100%, UV/$KMnO_4$); **IR:** $\tilde{\nu}$ = 3374w, 3071w, 2930w, 2853w, 2230w, 1656s, 1628s, 1541m, 1498w, 1390w, 1275w, 1242w, 1097w, 955w, 939w, 892w, 879w, 843w, 775w, 758w, 727w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.98–8.02 (2H, m, C3*H*, C5*H*), 6.20 (1H, d, ^3J 8.0, N*H*), 4.59 (2H, s, C6H_2), 3.67–3.79 (1H, m, C7*H*), 3.10 (6H, s, 3 x C2'*H*, 3 x C3'*H*), 1.86–1.94 (2H, m, 2 x C8*H*), 1.67–1.76 (2H, m, 2 x C9*H*), 1.59–1.65 (1H, m, C10*H*), 1.27–1.37 (2H, m, 2 x C9*H*), 1.13–1.24 (3H, m, 2 x C8*H,* C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.7 (*C1'*), 164.2 (*C*ONR), 159.2 (*C1*), 147.0 (*C3*), 145.3 (*C5*), 114.9 (*C2*), 114.4 (*C4*), 104.5 (*C*N), 52.6 (*C6*), 49.4 (*C7*), 32.9 (*C8*), 25.5 (*C10)*, 24.9 (*C9), signals for C2" and C3" were not found*; **APCI-HRMS:** m/z calcd. for $[C_{17}H_{23}N_4O_3]^+$ 331.1765 found 331.1769 $[M+H]^+$.

Assembly of the Arene/Nitrile Derivative 28:



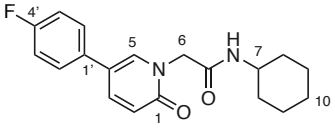
Scheme S5: Overview of the assembly of an arene/nitrile derivative.

2-(5-Bromo-2-oxopyridin-1(2*H*)-yl)-*N*-cyclohexylacetamide (26):



Prepared according to general procedure **B** using 5-bromo-2-hydroxypyridine **(25)** (522 mg, 3.00 mmol) and 2-chloro-*N*-cyclohexylacetamide **(5a)** (738 mg, 4.20 mmol), acetone (30 mL), K_2CO_3 (1244 mg, 9.00 mmol). Stirred at 50 °C for 18 hours. The suspension was treated with hexanes (50 mL), filtered and washed portionwisely with water (100 mL). The remaining solid was dried and recrystallized from acetone/hexanes to give product as an off-white solid (716 mg, 76%): $\mathbf{R}_f$ 0.31 (hexanes:EtOAc, 1:2); **IR:** $\tilde{\nu}$ = 3298m, 3074w, 2928m, 2855w, 1657s, 1587s, 1554m, 1525m, 1420w, 1378w, 1254w, 1170w, 962w, 886w, 828m; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.56 (1H, d, ^4J 2.6, C5*H*), 7.41 (1H, dd, ^3J 9.7, ^4J 2.7, C3*H*), 6.62 (1H, d, ^3J 5.8, N*H*), 6.52 (1H, d, ^3J 9.7, C2*H*), 4.45 (2H, s, C6H_2), 3.65–3.74 (1H, m, C7*H*), 1.83–1.87 (2H, m, 2 x C8*H*), 1.65–1.71 (2H, m, 2 x C9*H*), 1.54–1.61 (1H, m, C10*H*), 1.28–1.39 (2H, m, 2 x C9*H*), 1.11–1.21 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 165.6 (*C*ONR); 161.4 (*C1*), 143.7 (*C3*), 138.1 (*C5*), 121.9 (*C2*), 99.0 (*C4*), 54.0 (*C6*), 48.8 (*C7*), 32.8 (*C8*), 25.6 (*C10*), 24.7 (*C9*); **APCI-HRMS:** m/z calcd. for $[C_{13}H_{18}BrN_2O_2]^+$ 315.0526 found 315.0529 $[M+H]^+$.

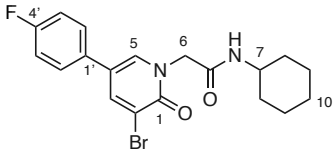
***N*-Cyclohexyl-2-(5-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl)acetamide (27):**



Prepared according to general procedure **D** using 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)-*N*-cyclohexylacetamide **(26)** (94.0 mg, 0.300 mmol), 4-fluorophenylboronic acid (105 mg, 0.750 mmol), Na_2CO_3 (127 mg, 1.20 mmol), $Pd(PPh_3)_4$ (17.3 mg, 0.0150 mmol, *5.00 mol%*) in PhMe:EtOH:H_2O (1.9 mL, 0.74 mL, 0.26 mL). Stirred at 75 °C for 3 hours. Purification by precipitation from hexanes gives product as a white solid (85.3 mg, 87%): $\mathbf{R}_f$ 0.26 (hexanes:EtOAc, 1:2, UV); **IR:** $\tilde{\nu}$ = 3280w, 2928w, 2855w, 1676m, 1660m, 1648s, 1606m, 1561w, 1534w, 1512m, 1448w, 1398w, 1301w, 1271w, 1232m, 1163w, 1093w, 955w, 823s, 726w; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.64 (1H, dd, ^3J 9.4, ^4J 2.6, C3*H*), 7.59 (1H, d, ^4J 2.4, C5*H*), 7.36–7.40 (2H, m, 2 x C2'*H*), 7.09–7.13 (2H, m, 2 x C3'*H*), 6.82 (1H, d, ^3J 6.7, N*H*), 6.71 (1H, d, ^3J 9.4, C2*H*), 4.57 (2H, s, C6H_2), 3.67–3.76 (1H, m, C7*H*), 1.85–1.89 (2H, m, 2 x C8*H*), 1.66–1.71 (2H, m, 2 x C9*H*), 1.55–1.60 (1H, m, C10*H*), 1.28–1.36 (2H, m, 2 x C9*H*), 1.14–1.24 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 166.1 (*C*ONR), 162.6 ($^1J_{CF}$ 247, *C4'*), 162.2 (*C1*), 140.4 (*C3*), 135.4 (*C5*), 132.3 ($^4J_{CF}$ 3.7, *C1'*), 127.8 ($^3J_{CF}$ 8.1, *C2'*), 120.9 (*C2*),

120.5 (*C4*), 116.2 ($^2J_{CF}$ 22, *C3'*), 54.6 (*C6*), 48.7 (*C7*), 32.8 (*C8*), 25.6 (*C10*), 24.7 (*C9*); **^{19}F-NMR (377 MHz, CDCl$_3$):** δ = –114.66; **APCI-HRMS:** m/z calcd. for $[C_{19}H_{22}FN_2O_2]^+$ 329.1660 found 329.1660 $[M+H]^+$.

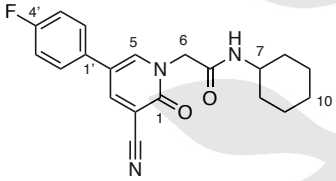
2-(3-Bromo-5-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-cyclohexylacetamide:



Prepared according to general procedure **C** using *N*-cyclohexyl-2-(5-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl)acetamide **(27)** (32.8 mg, 0.100 mmol), bromine (8.00 µL, 0.150 mmol), acetic acid (1.0 mL). Stirred at 60 °C for 18 hours. Column chromatography over silica gel with eluent 100% hexanes to hexanes:EtOAc 90:10 to 75:25 to 60:40 to 50:50 gives product (27 mg, 66%): **R$_f$** 0.30 (hexanes:EtOAc, 1:1, UV); **IR:** $\tilde{\nu}$ = 3309m, 2928w, 2856w, 1654s, 1608s, 1541m, 1515s, 1438w, 1423w, 1391w, 1272w, 1230m, 1167w, 1131w, 908w, 889w, 840m, 817w, 766w, 732w; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 8.03 (1H, d, ^4J 2.4, C3*H*), 7.64 (1H, d, ^4J 2.3, C5*H*), 7.36–7.39 (2H, m, 2 x C2'*H*), 7.09–7.13 (2H, m, 2 x C3'*H*), 6.73 (1H, d, ^3J 8.1, N*H*), 4.63 (2H, s, C6*H*$_2$), 3.67–3.76 (1H, m, C7*H*), 1.85–1.89 (2H, m, 2 x C8*H*), 1.67–1.72 (2H, m, 2 x C9*H*), 1.56–1.61 (1H, m, C10*H*), 1.28–1.38 (2H, m, 2 x C9*H*), 1.15–1.24 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 165.5 (*C*ONR), 162.8 ($^1J_{CF}$ 248, *C4'*), 158.6 (*C1*), 142.3 (*C3*), 135.1 (*C5*), 131.3 ($^4J_{CF}$ 3.3, *C1'*), 128.0 ($^3J_{CF}$ 8.8, *C2'*), 120.6 (*C4*), 116.3 ($^2J_{CF}$ 21, *C3'*), 55.0 (*C6*), 49.0 (*C7*), 32.8 (*C8*), 25.5 (*C10*), 24.8 (*C9*); **^{19}F-NMR (377 MHz, CDCl$_3$):** δ = – 13.99; **APCI-HRMS:** m/z calcd. for $[C_{19}H_{21}BrFN_2O_2]^+$ 407.0765 found 407.0767 $[M+H]^+$.

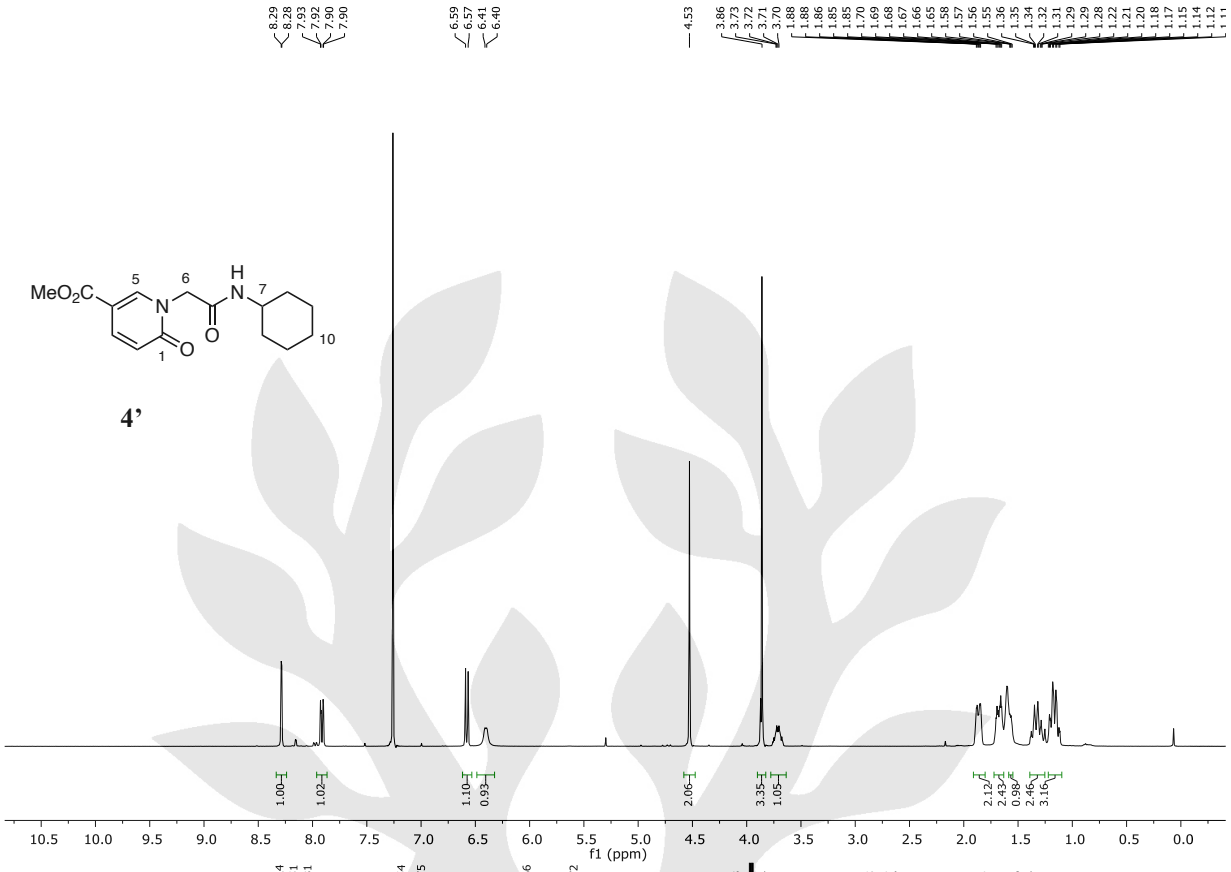
** NMR sample contains residual amounts of AcOH.*

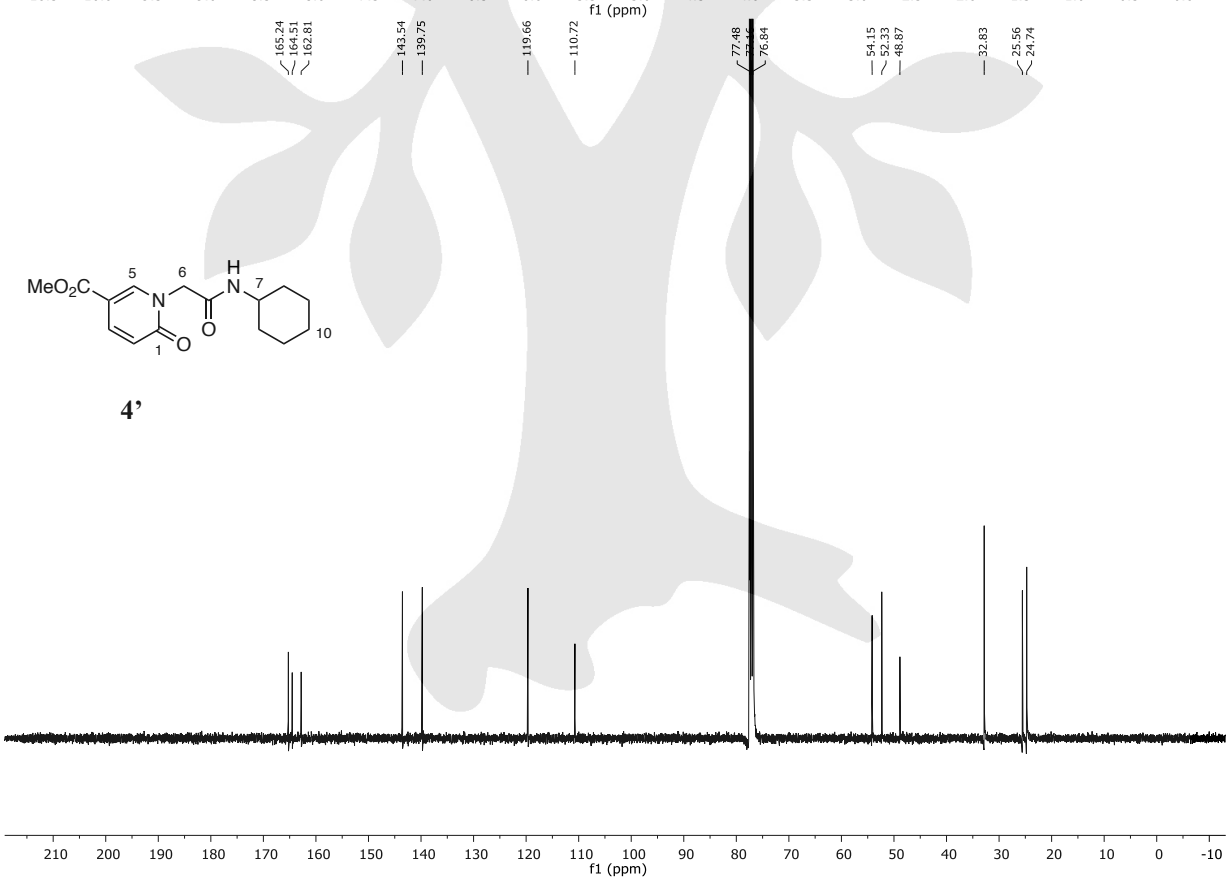
2-(3-Cyano-5-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-cyclohexylacetamide (28):

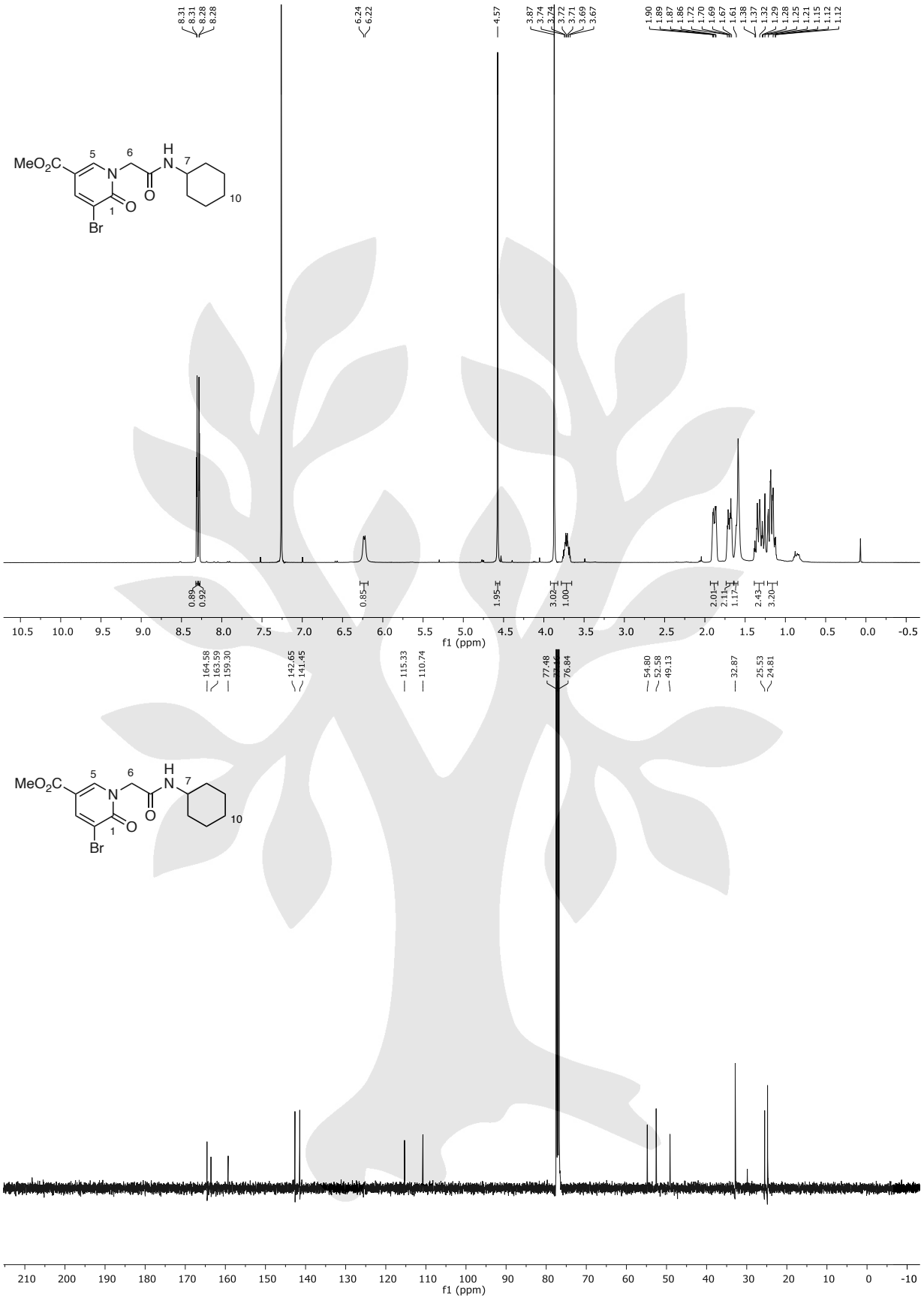


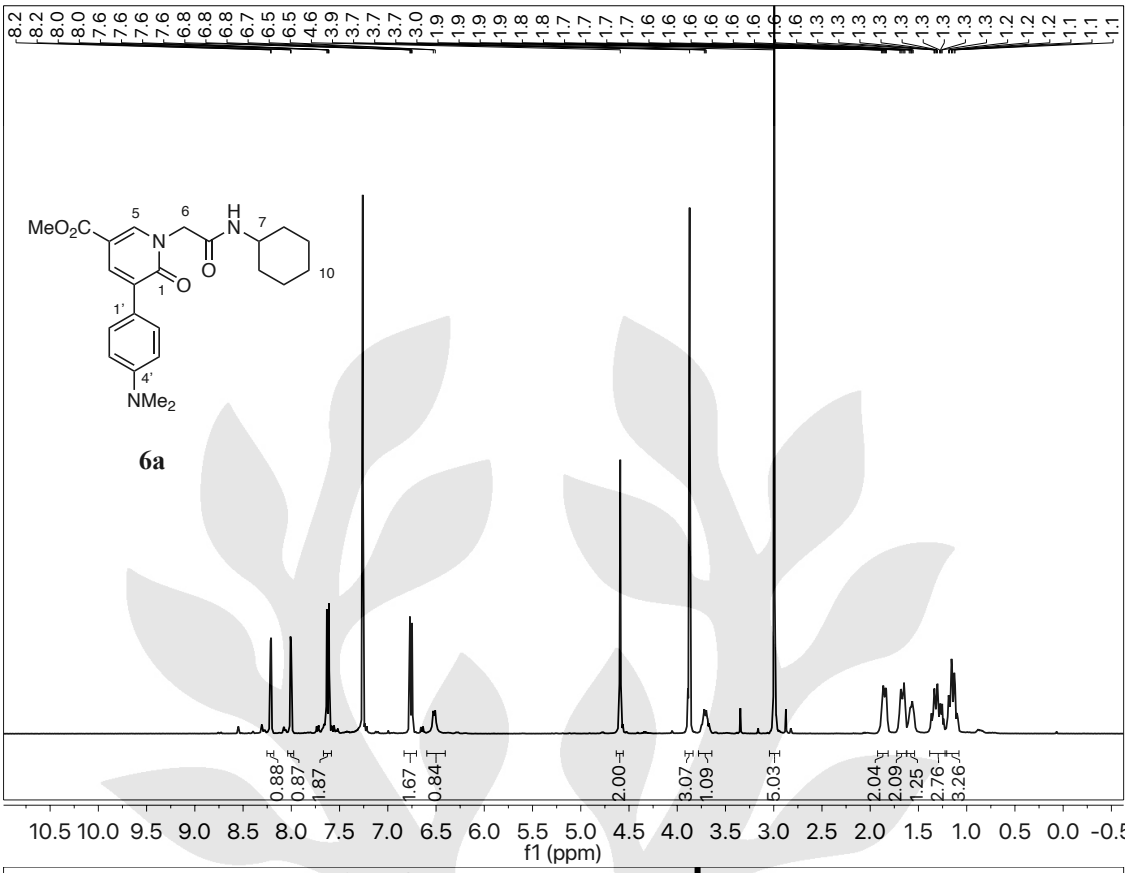
Prepared according to general procedure **G** using 2-(3-bromo-5-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-cyclohexylacetamide (12.7 mg, 0.030 mmol) CuCN (8.40 mg, 0.0900 mmol), DMF (0.30 mL). Stirred at 120 °C for 20 hours. Column chromatography over silica gel with eluent 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH gives product as a white solid (3.70 mg, 34%): **R$_f$** 0.21 (hexanes:EtOAc, 1:1, UV); **IR:** $\tilde{\nu}$ = 3315w, 2925w, 2856w, 2364w, 2331w, 2230w, 2166w, 2027w, 1681m, 1654s, 1604m, 1548m, 1517s, 1452w, 1400w, 1348w, 1297w, 1272w, 1238w, 1167w, 1094w, 1085w, 1014w, 953w, 910w, 831m, 780w, 731w; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 8.07 (1H, d, ^4J 2.6, C3*H*), 7.87 (1H, d, ^4J 2.7, C5*H*), 7.34–7.41 (2H, m, 2 x C2'*H*), 7.11–7.19 (2H, m, 2 x C3'*H*), 6.40 (1H, d, ^3J 7.9, N*H*), 4.62 (2H, s, C6*H*$_2$), 3.67–3.77 (1H, m, C7*H*), 1.85–1.94 (2H, m, 2 x C8*H*), 1.67–1.72 (2H, m, 2 x C9*H*), 1.58–1.64 (1H, m, C10*H*), 1.28–1.40 (2H, m, 2 x C9*H*), 1.13–1.26 (3H, m, 2 x C8*H*, C10*H*); **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 164.5 (*C*ONR), 163.0 ($^1J_{CF}$ 248, *C4'*), 159.2 (*C1*), 147.2 (*C3*), 141.0 (*C5*), 130.5 ($^4J_{CF}$ 3.4, *C1'*), 128.1 ($^3J_{CF}$ 8.3, *C2'*), 119.9 (*C4*), 116.6 ($^2J_{CF}$ 22, *C3'*), 105.6 (*CN*), 53.7 (*C6*), 49.3 (*C7*), 32.9 (*C8*), 25.5 (*C10*), 24.8 (*C9*); **^{19}F-NMR (377 MHz, CDCl$_3$):** δ = –113.03; **APCI-HRMS:** m/z calcd. for $[C_{20}H_{21}FN_3O_2]^+$ 354.1612 found 354.1609 $[M+H]^+$.

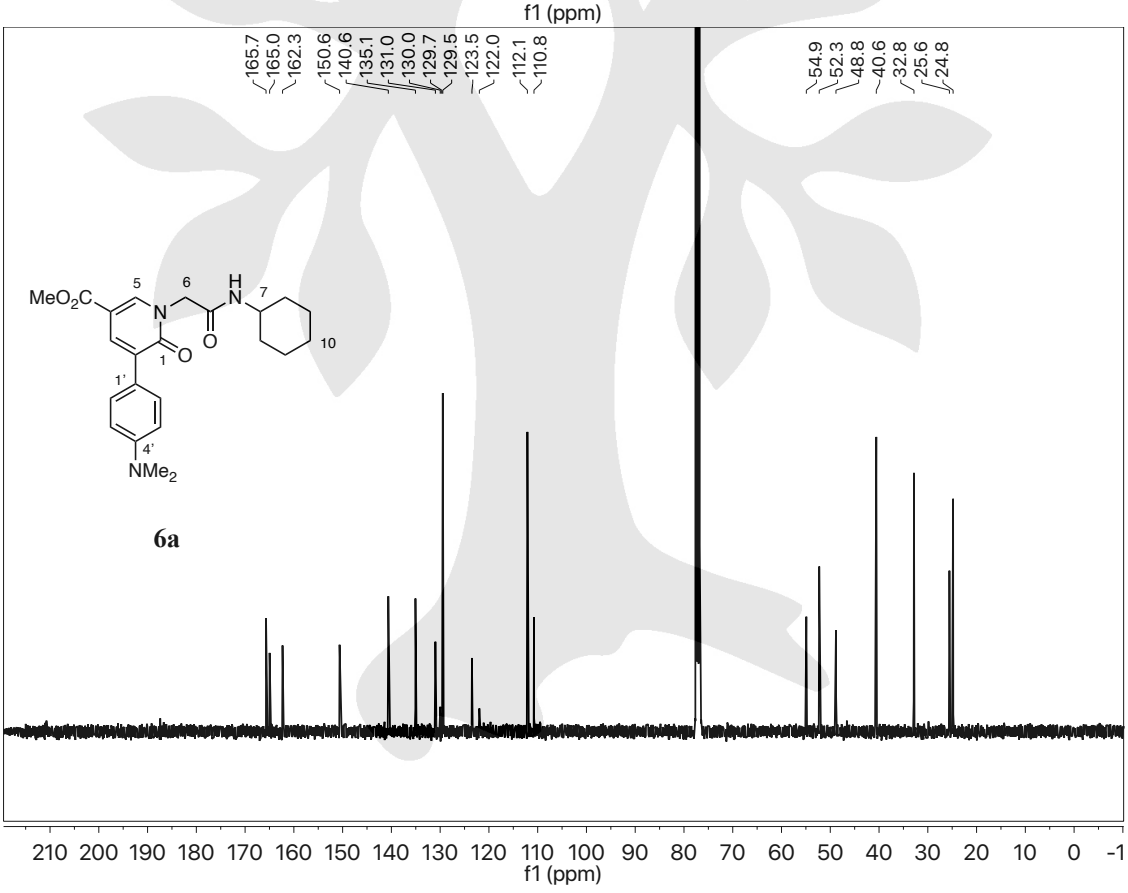
NMR Data:

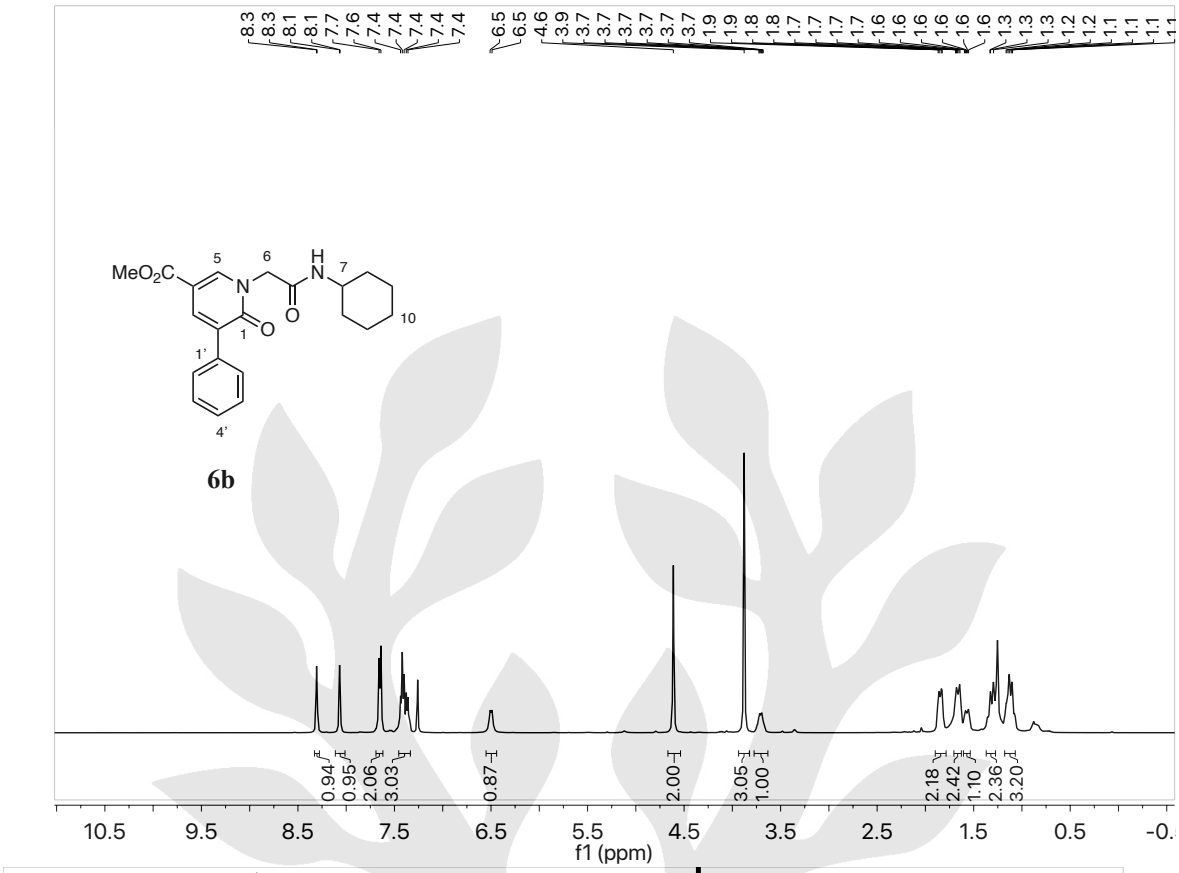


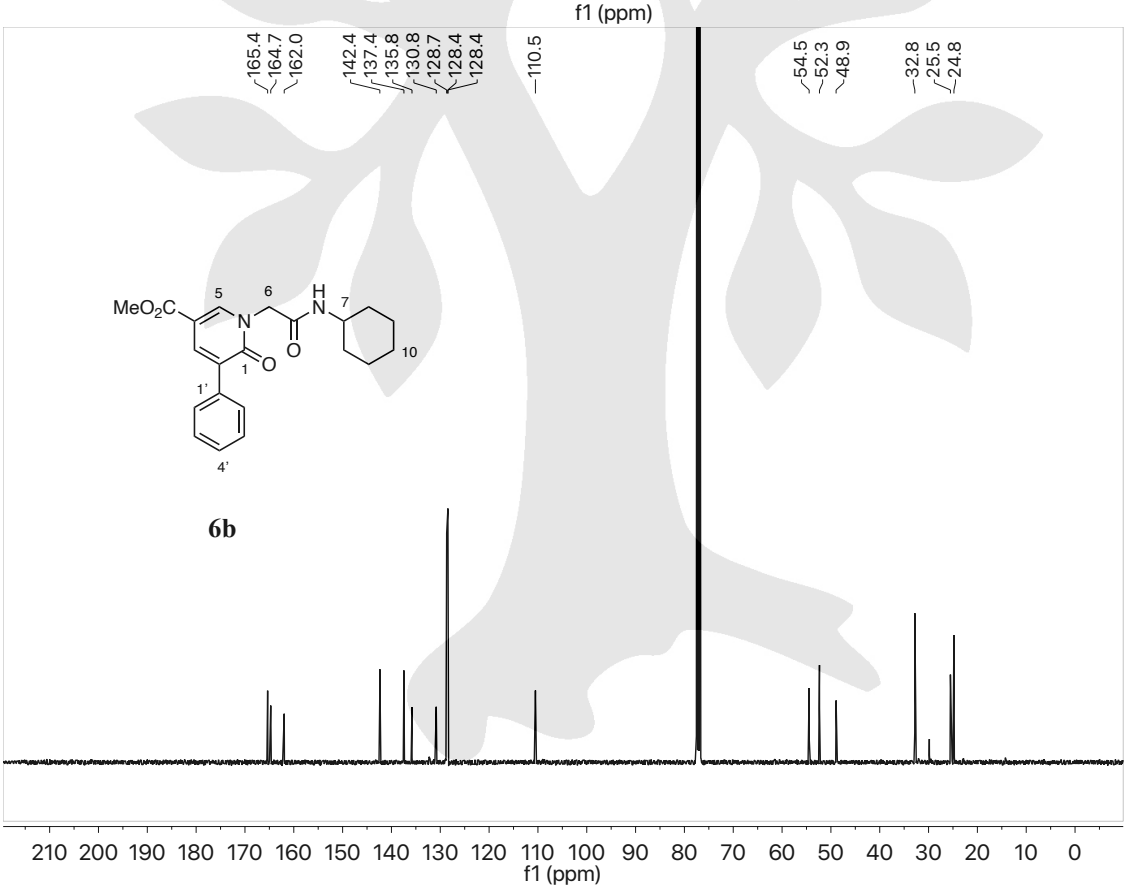


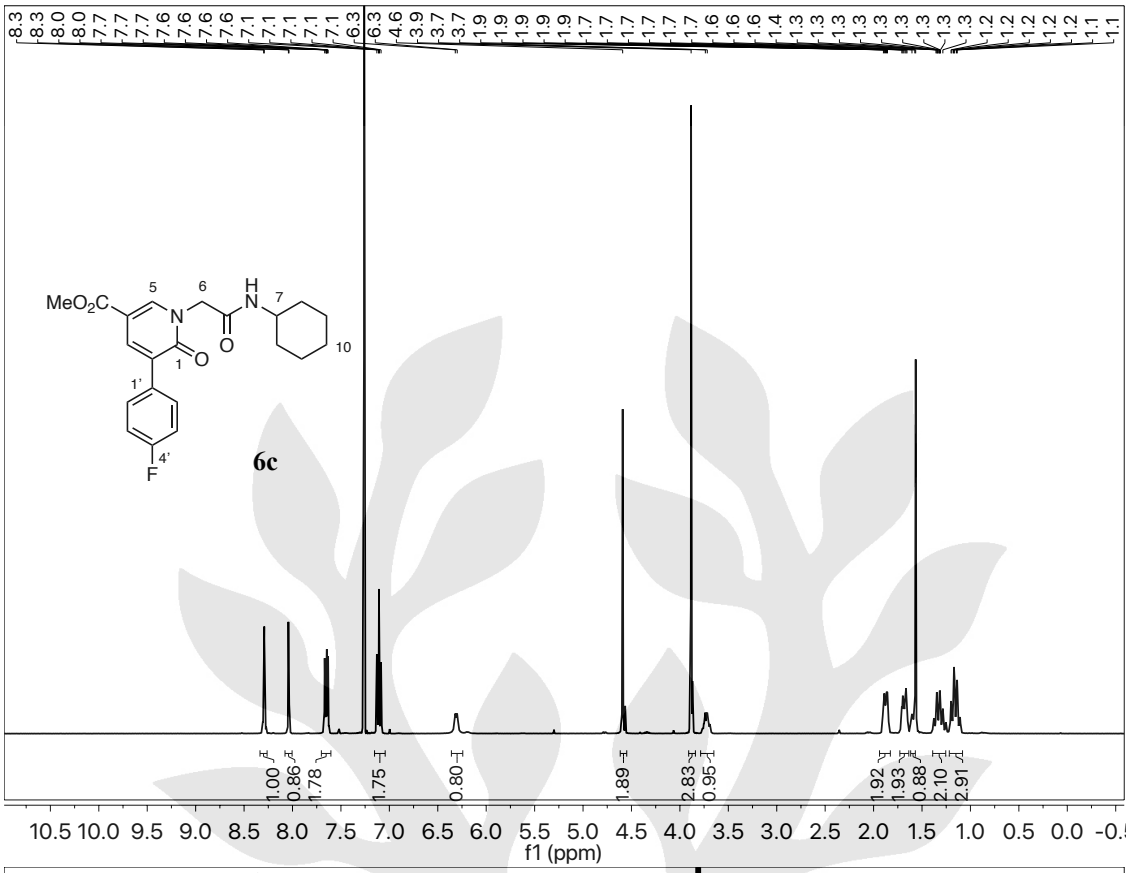


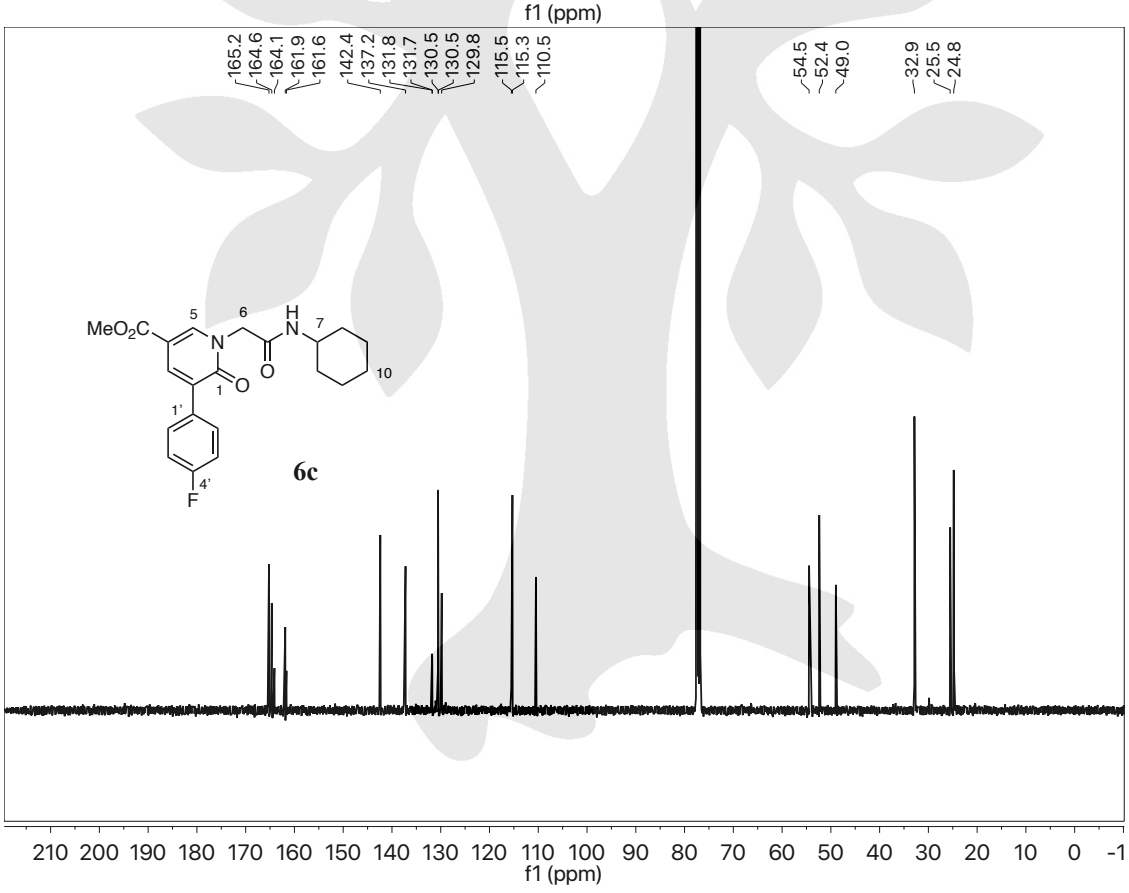


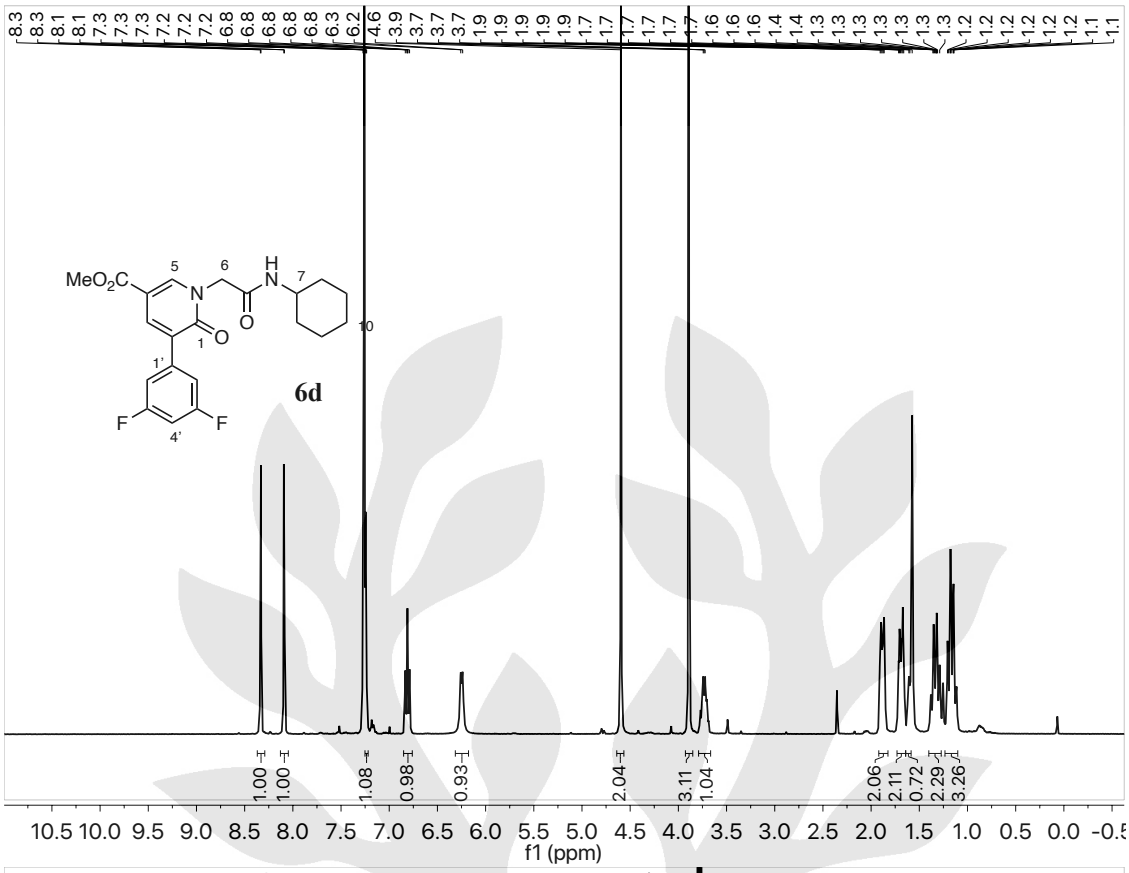


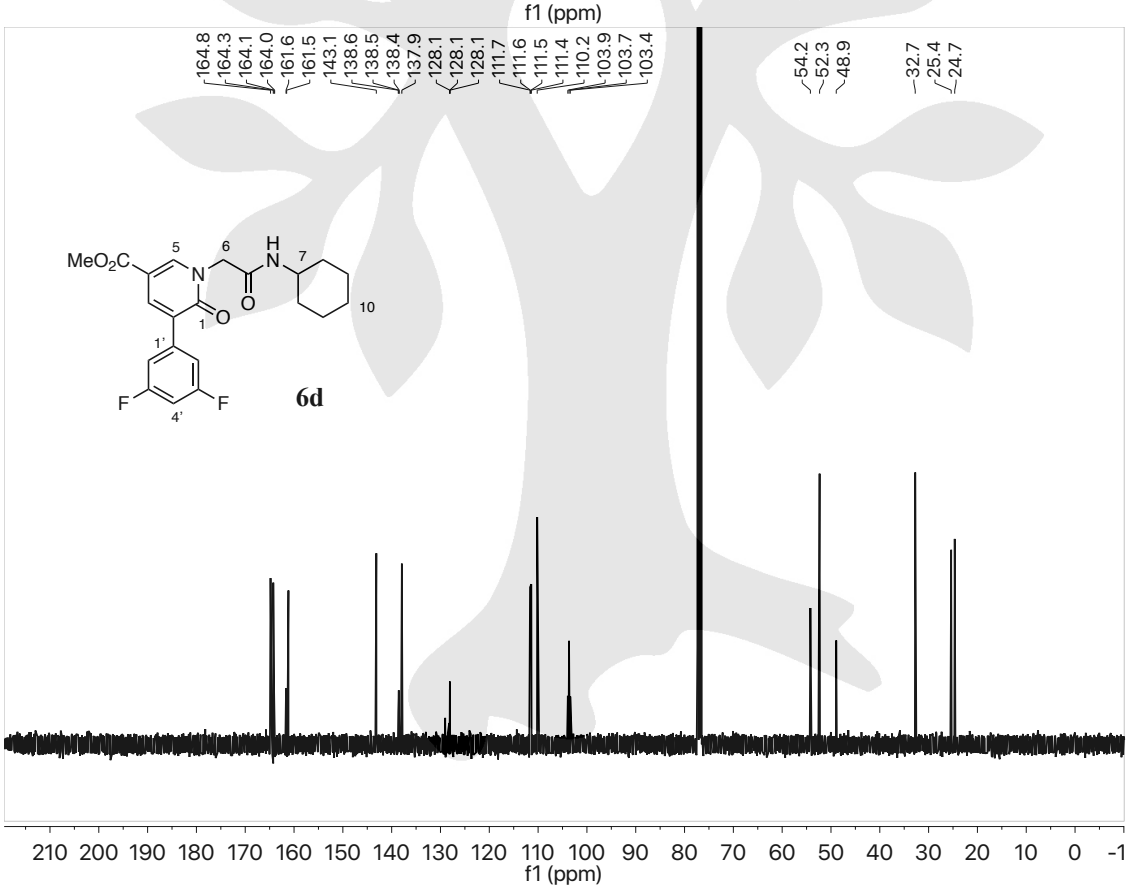


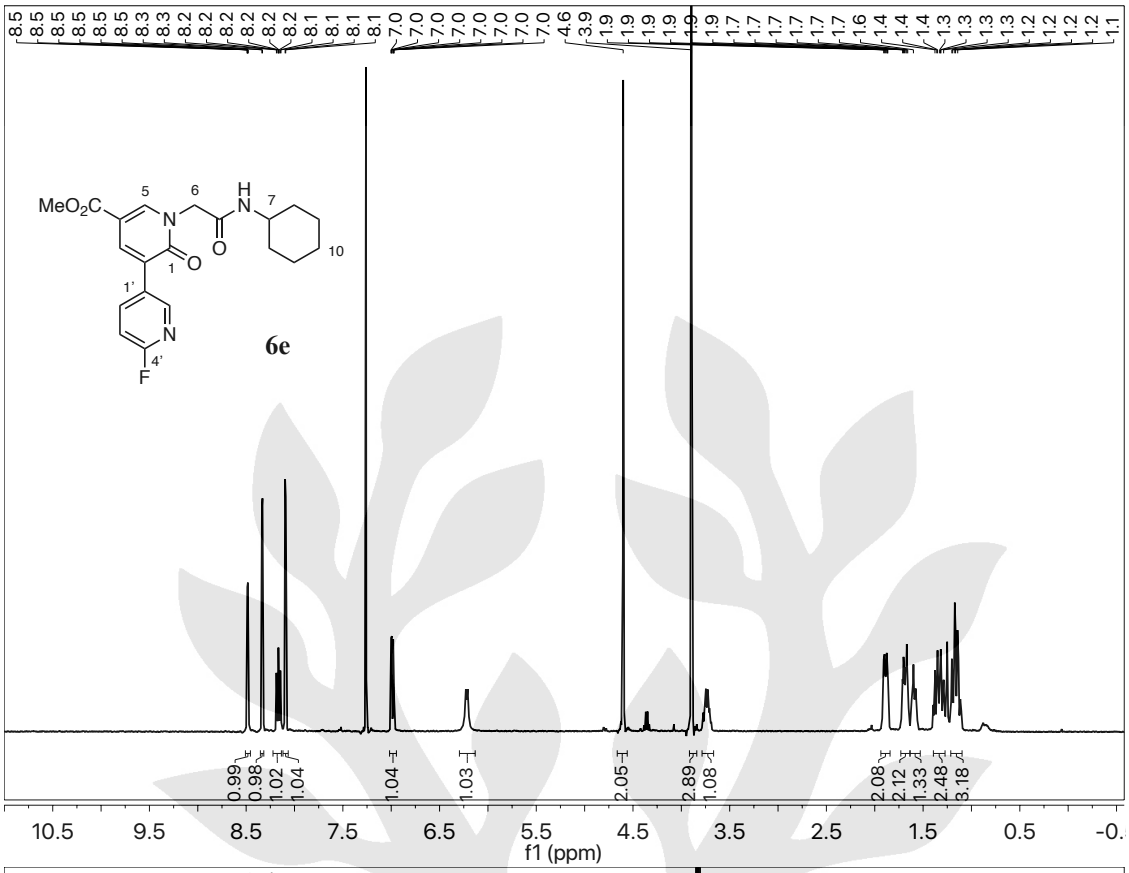


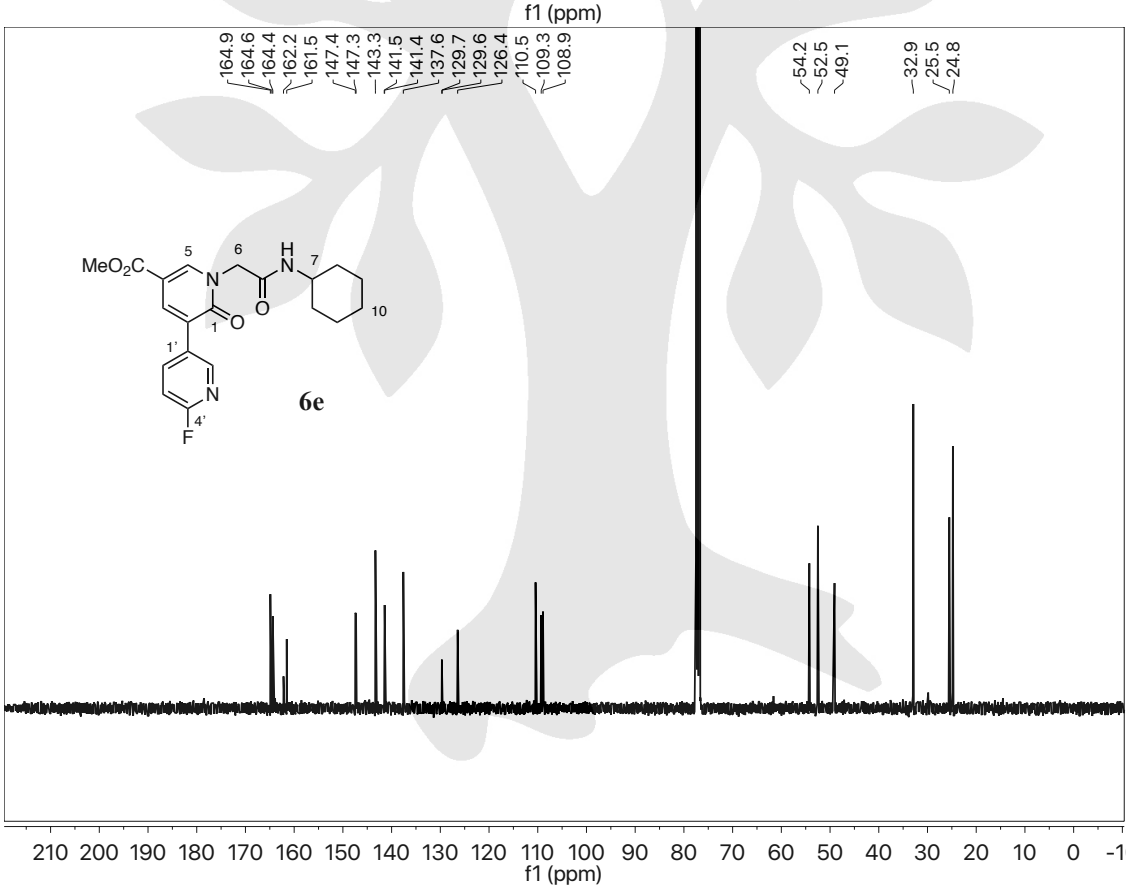


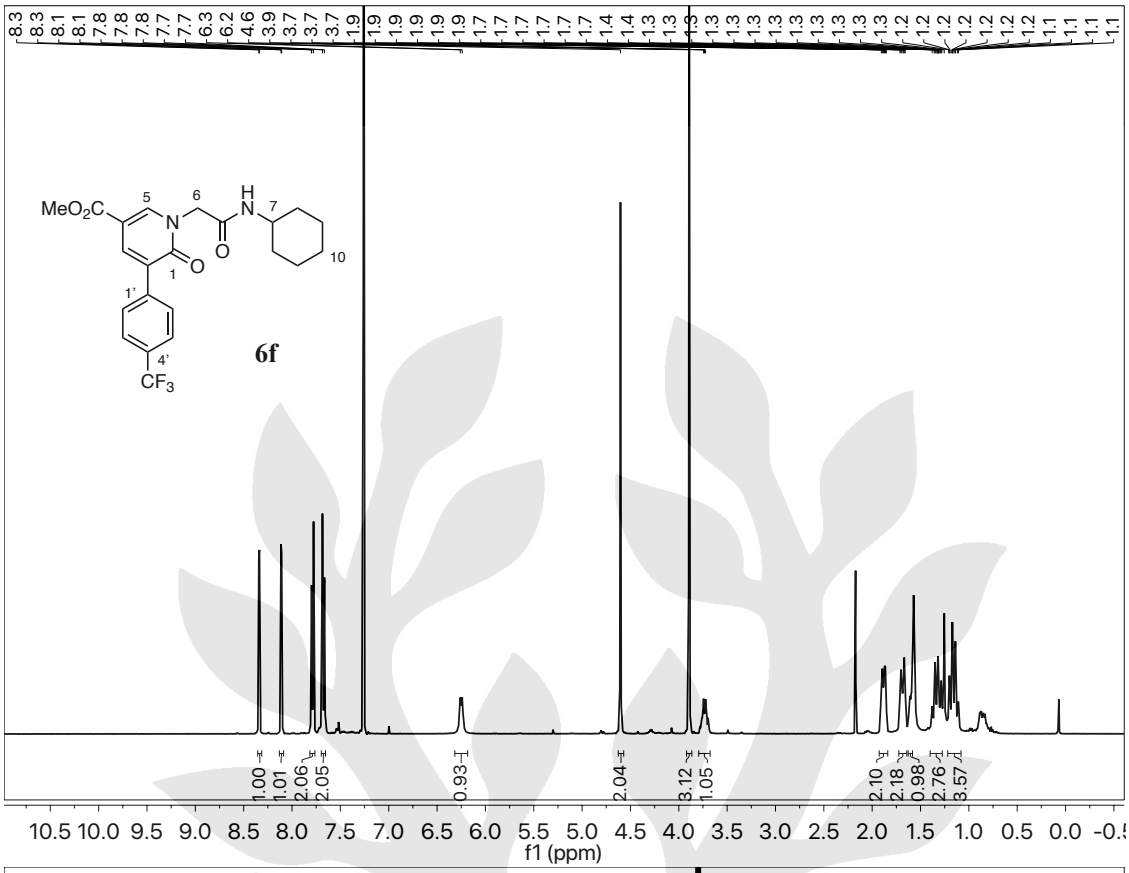


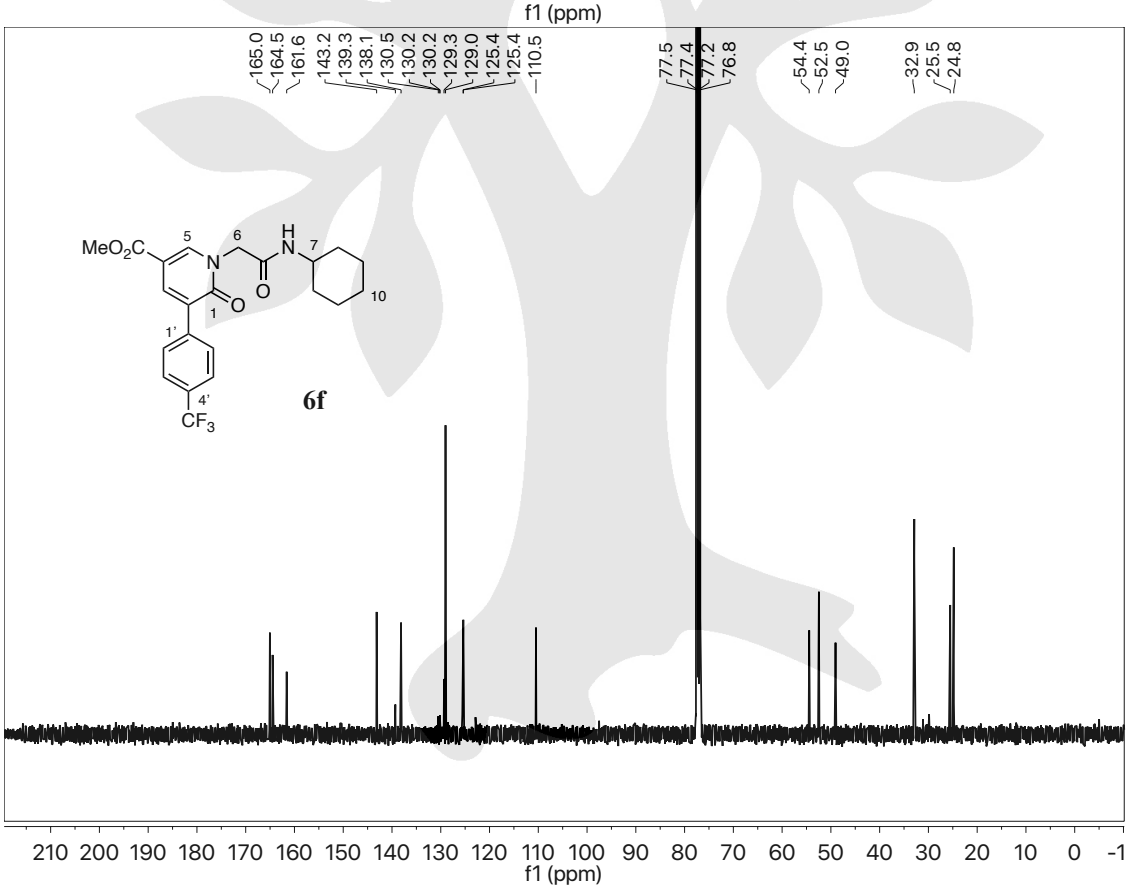


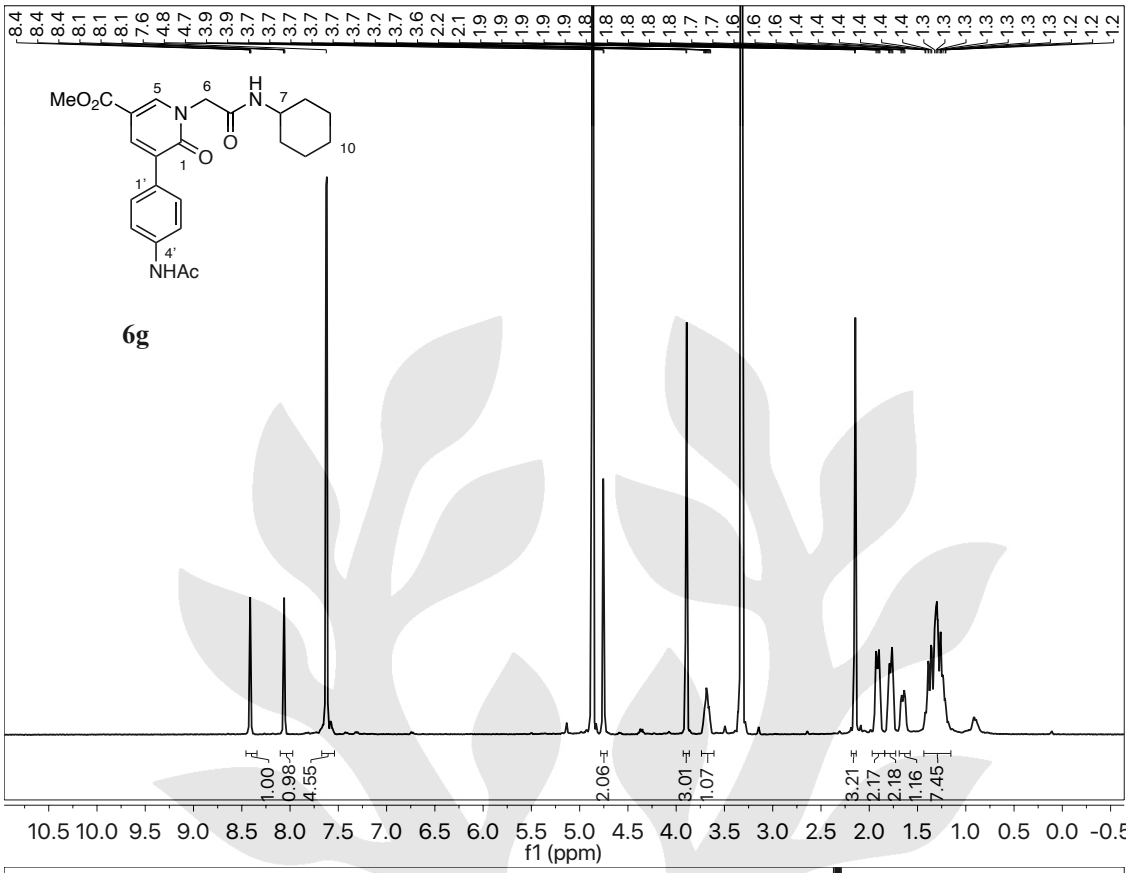


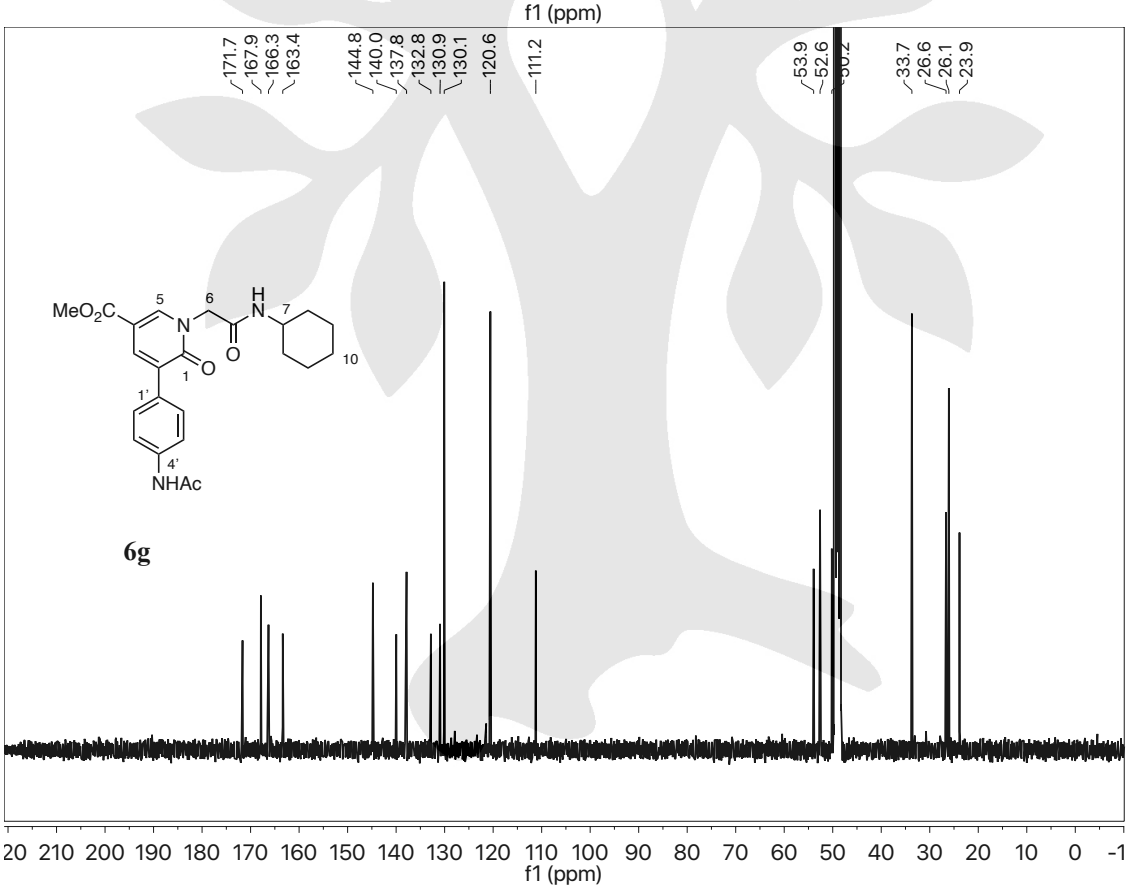


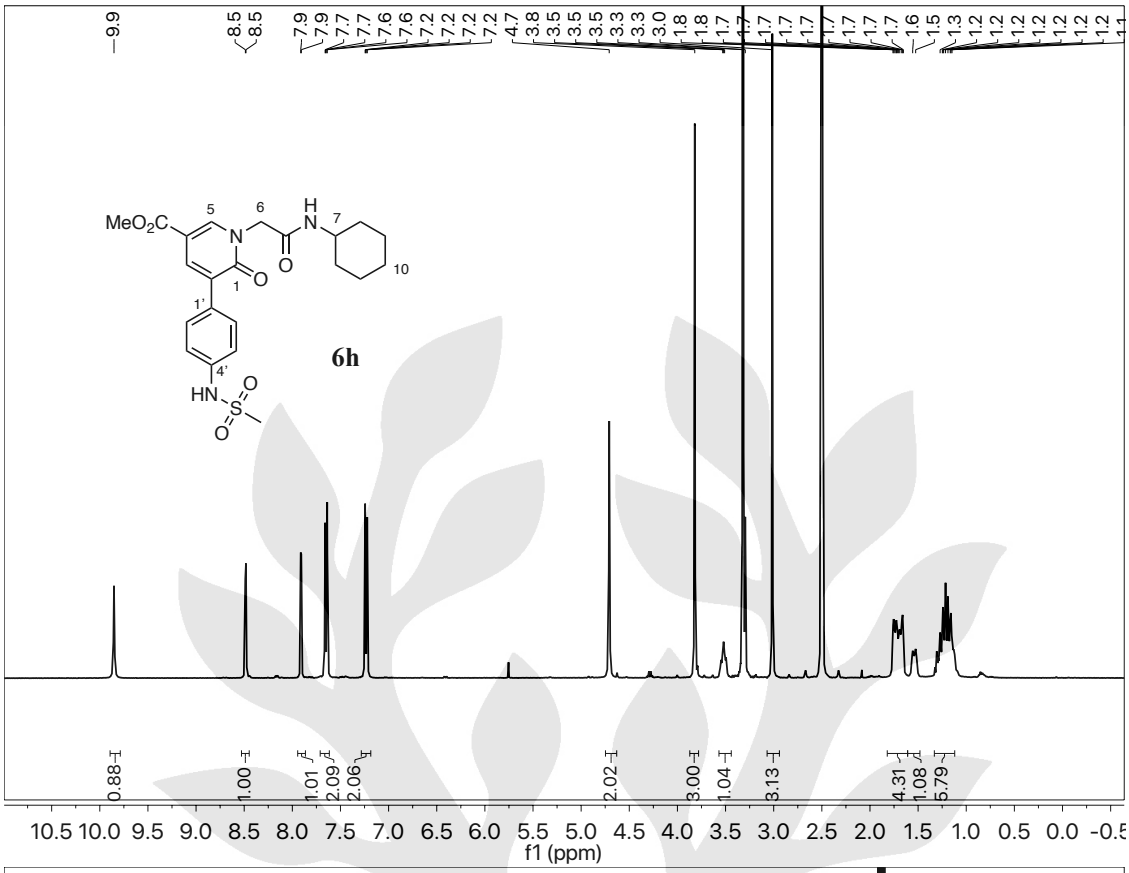


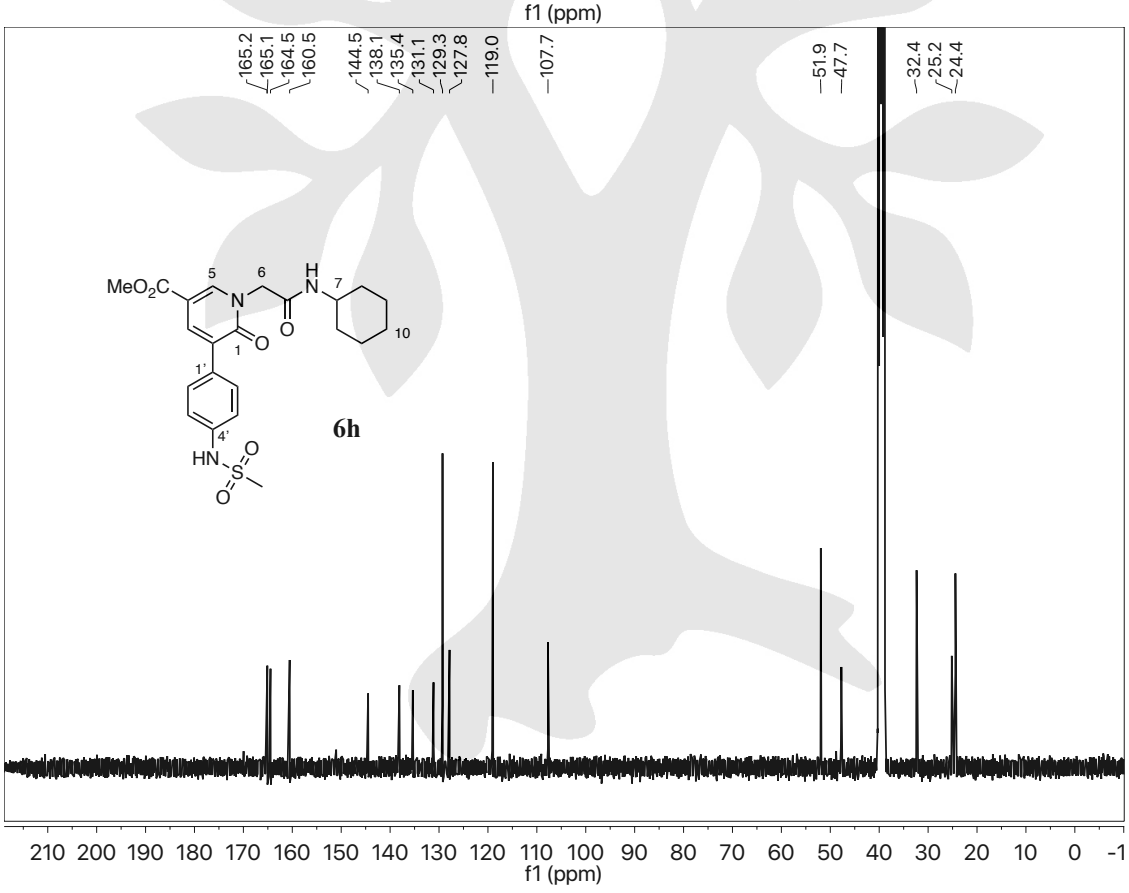


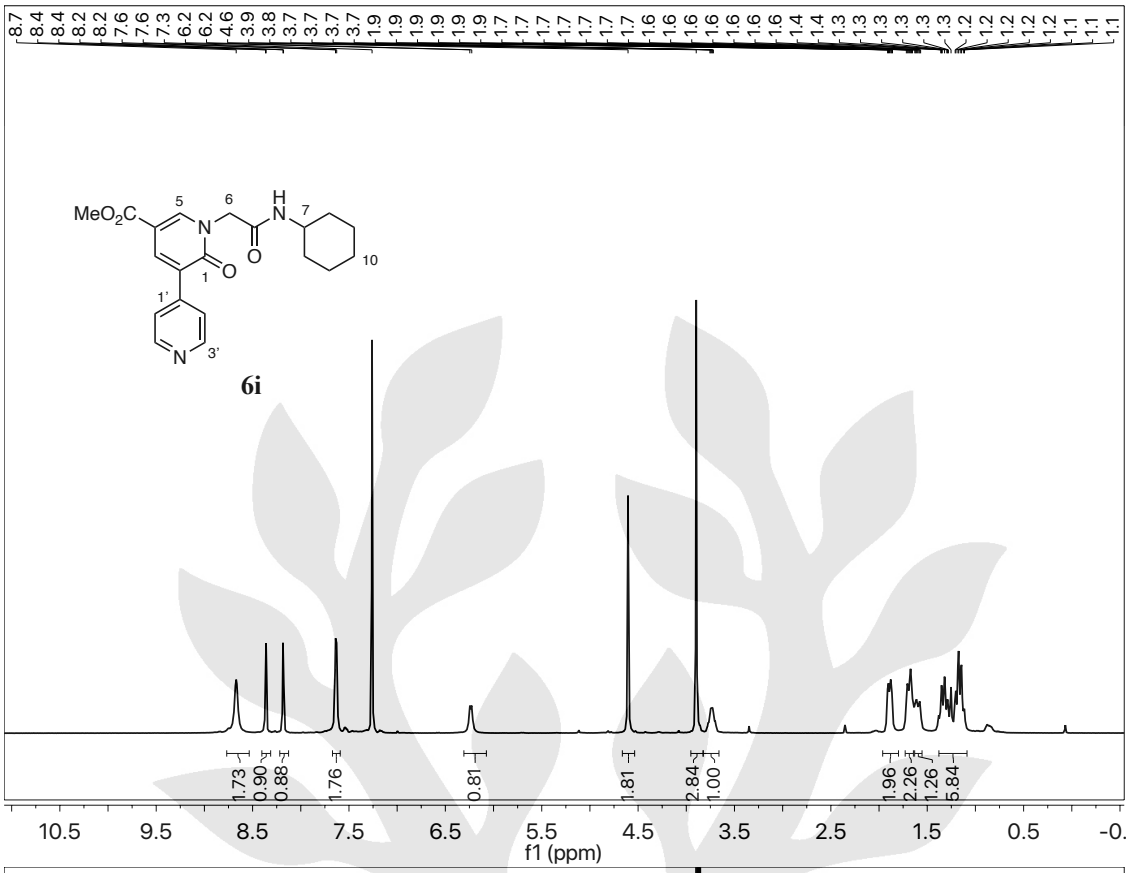


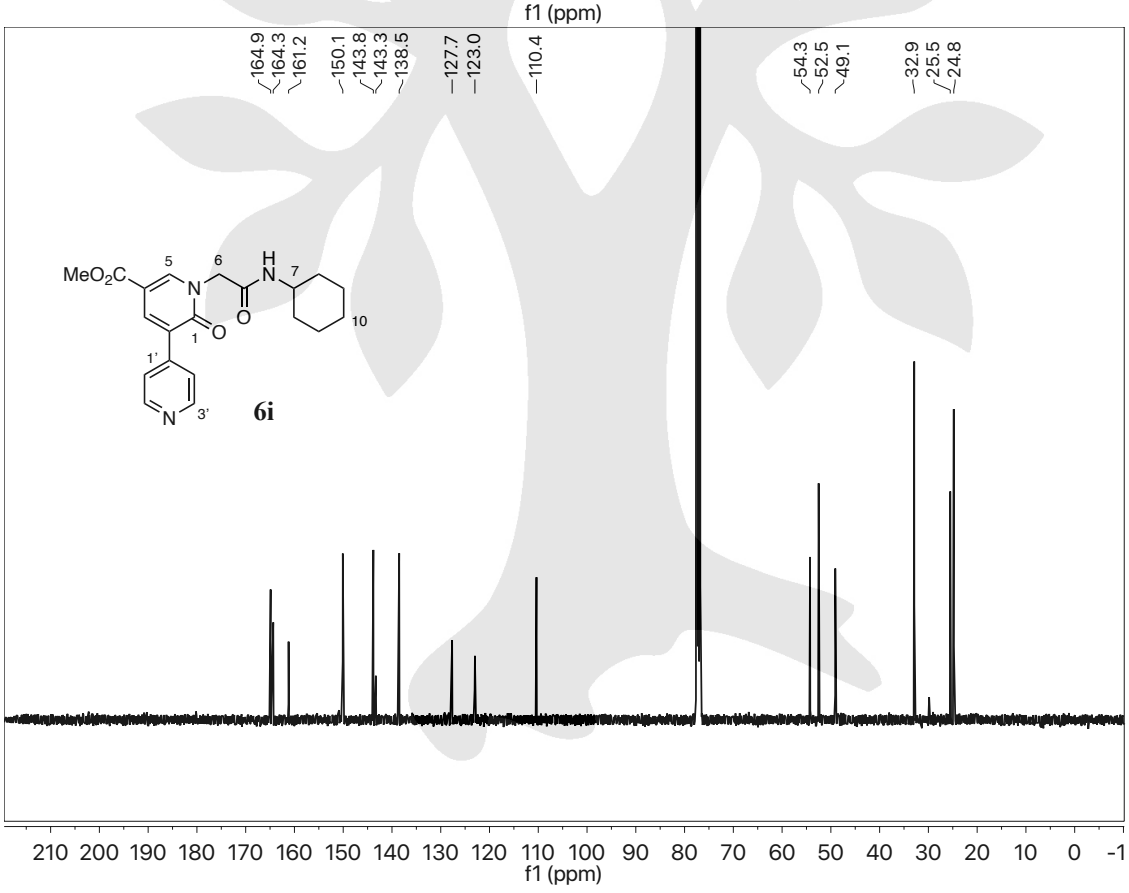


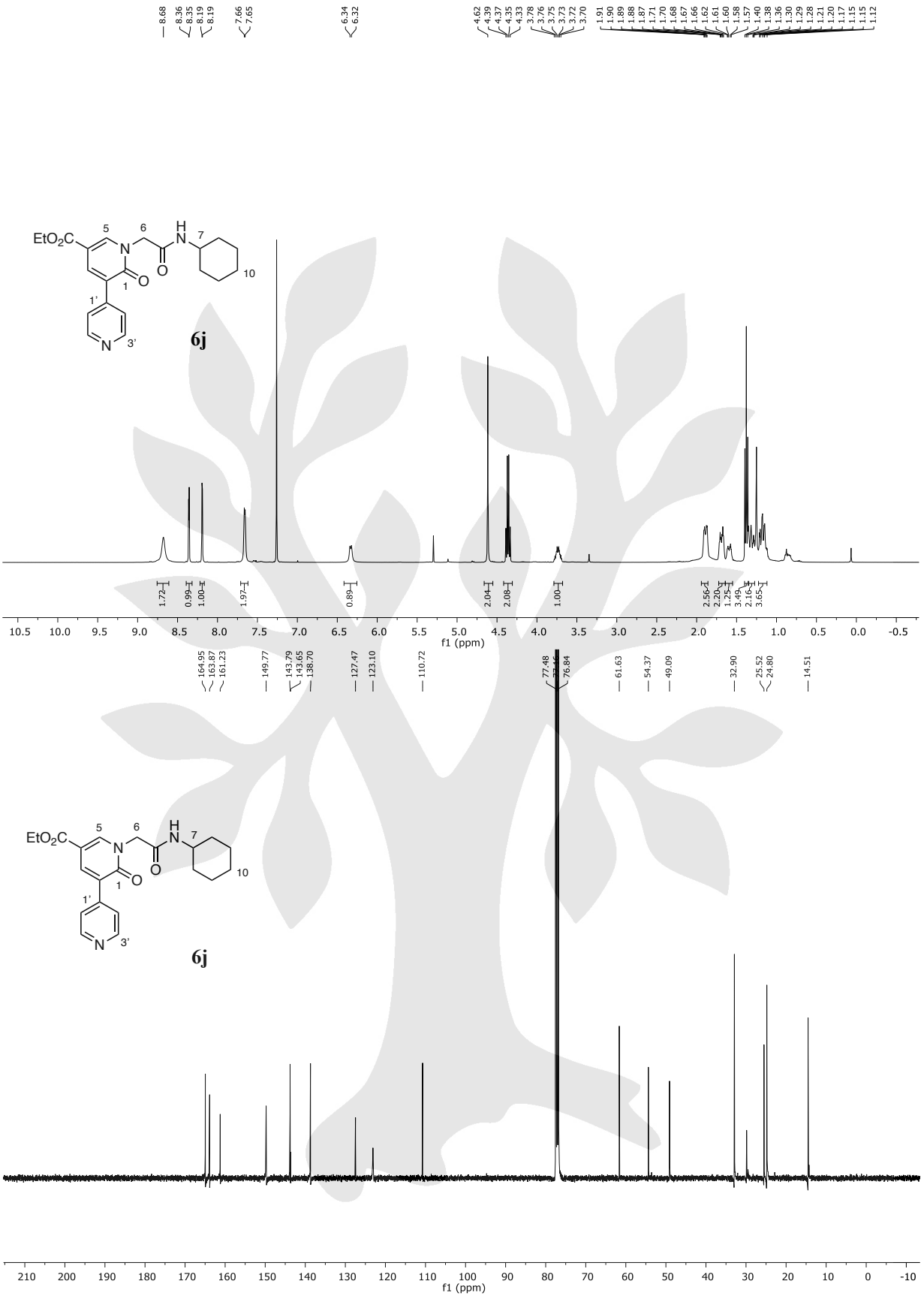


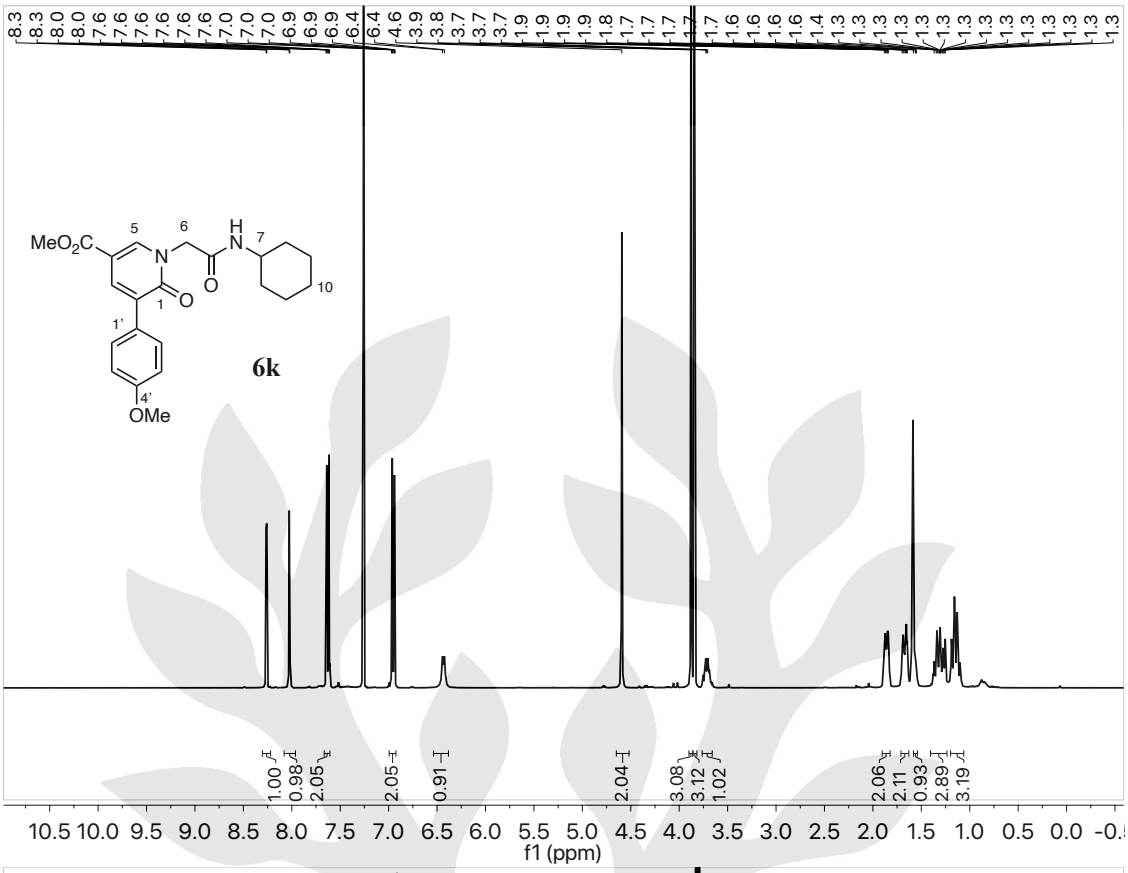


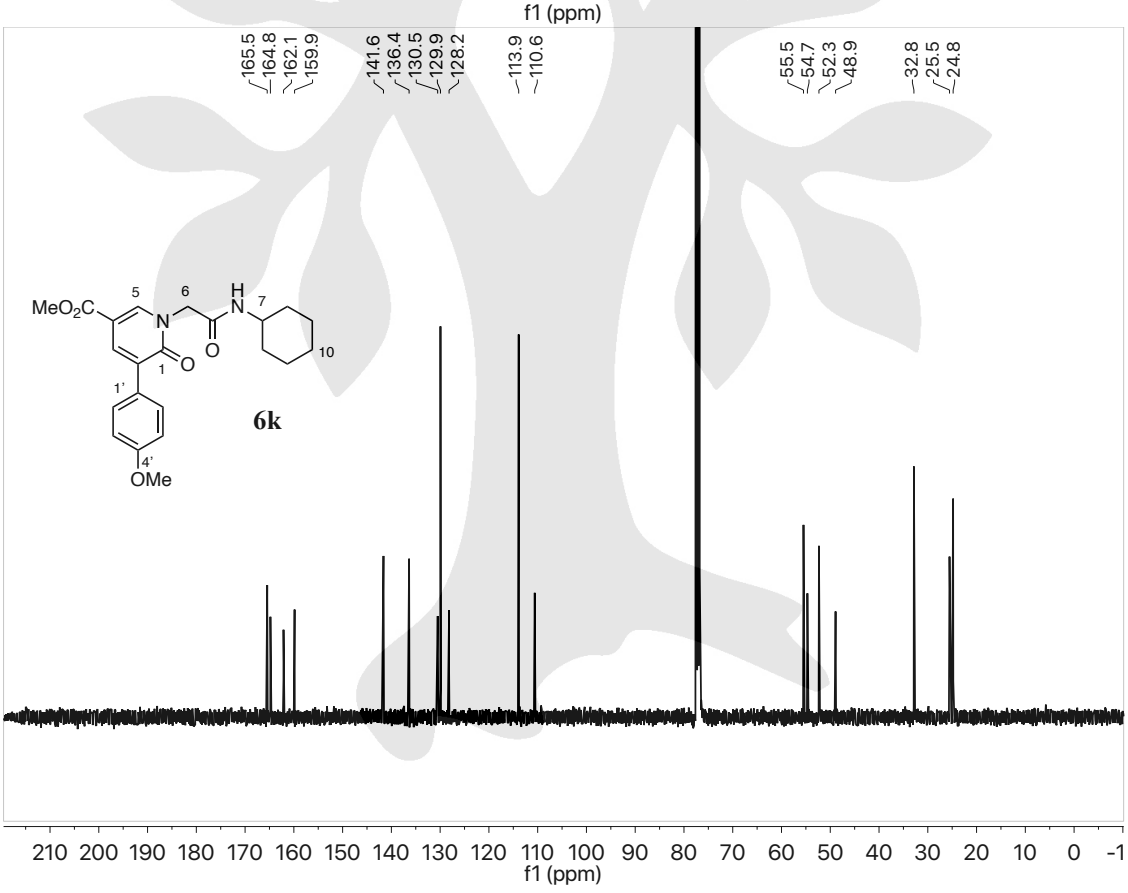


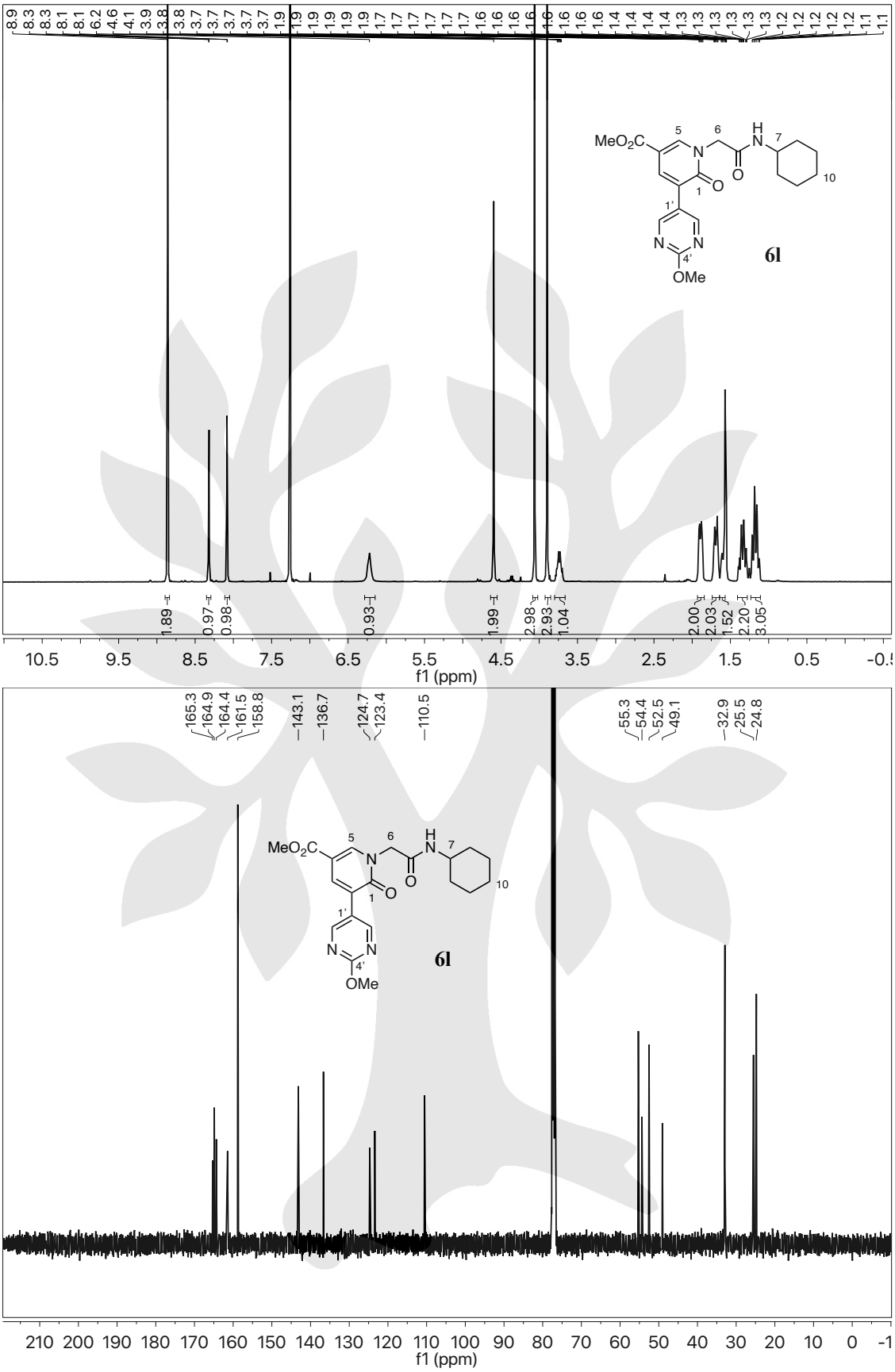


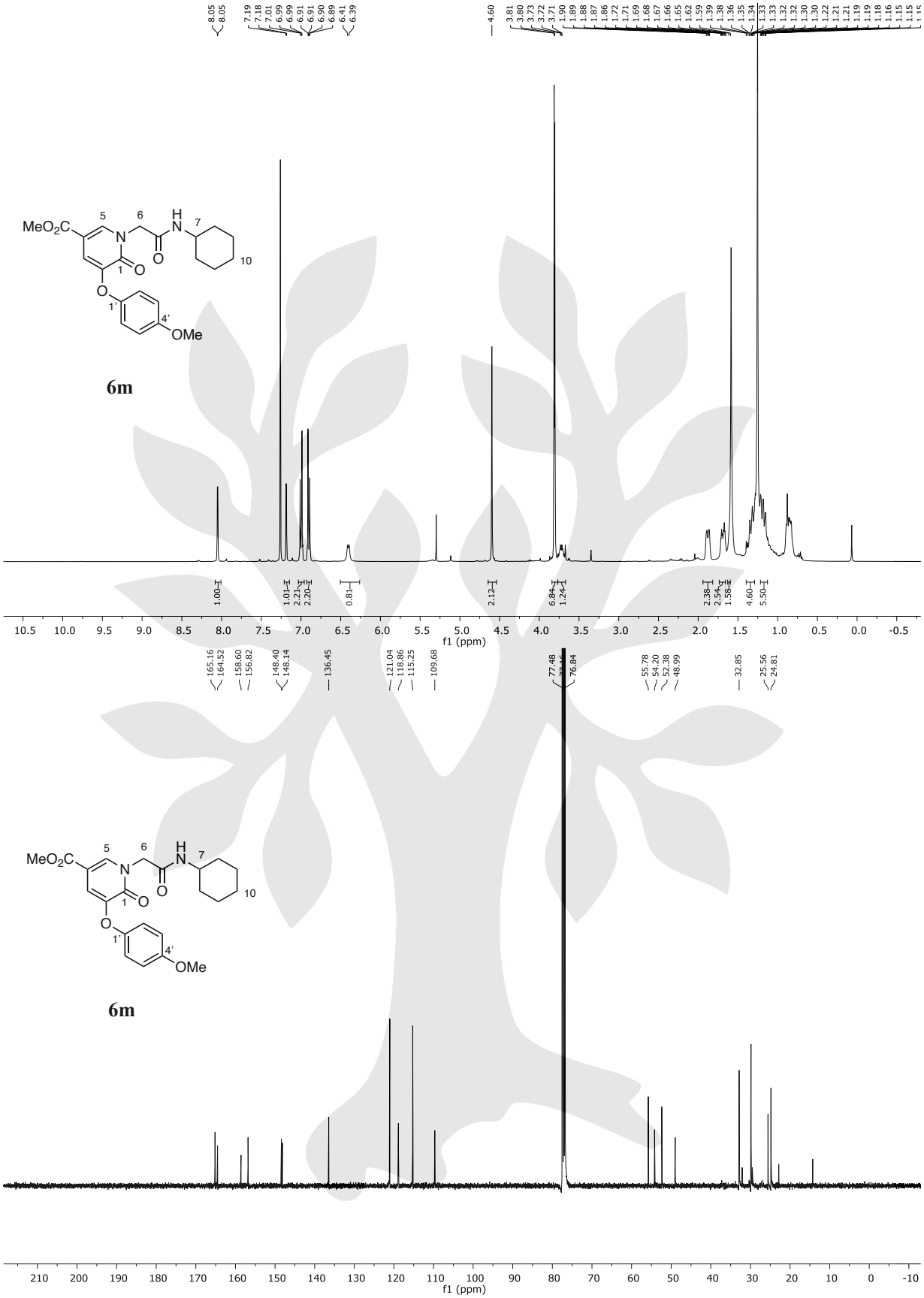


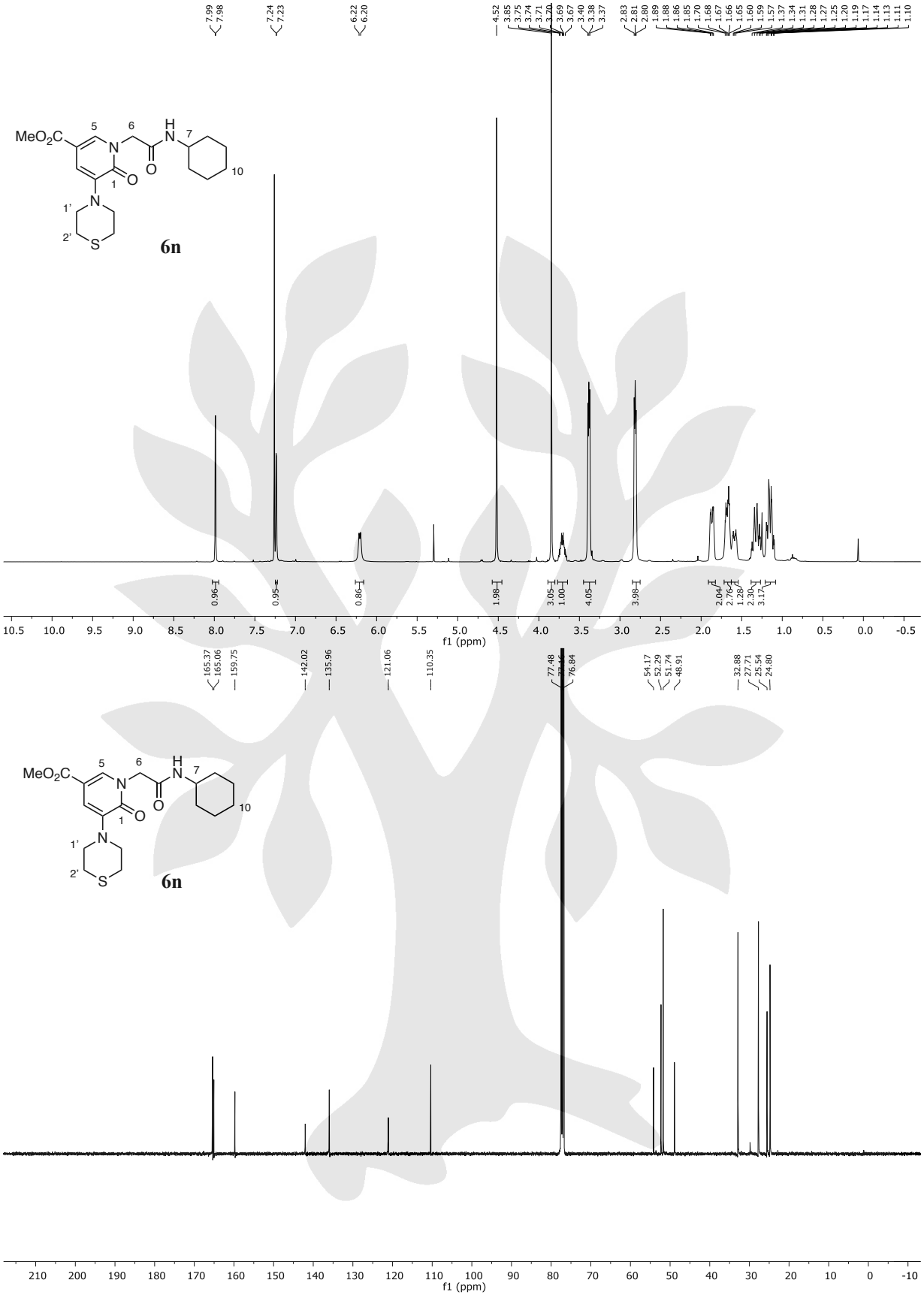


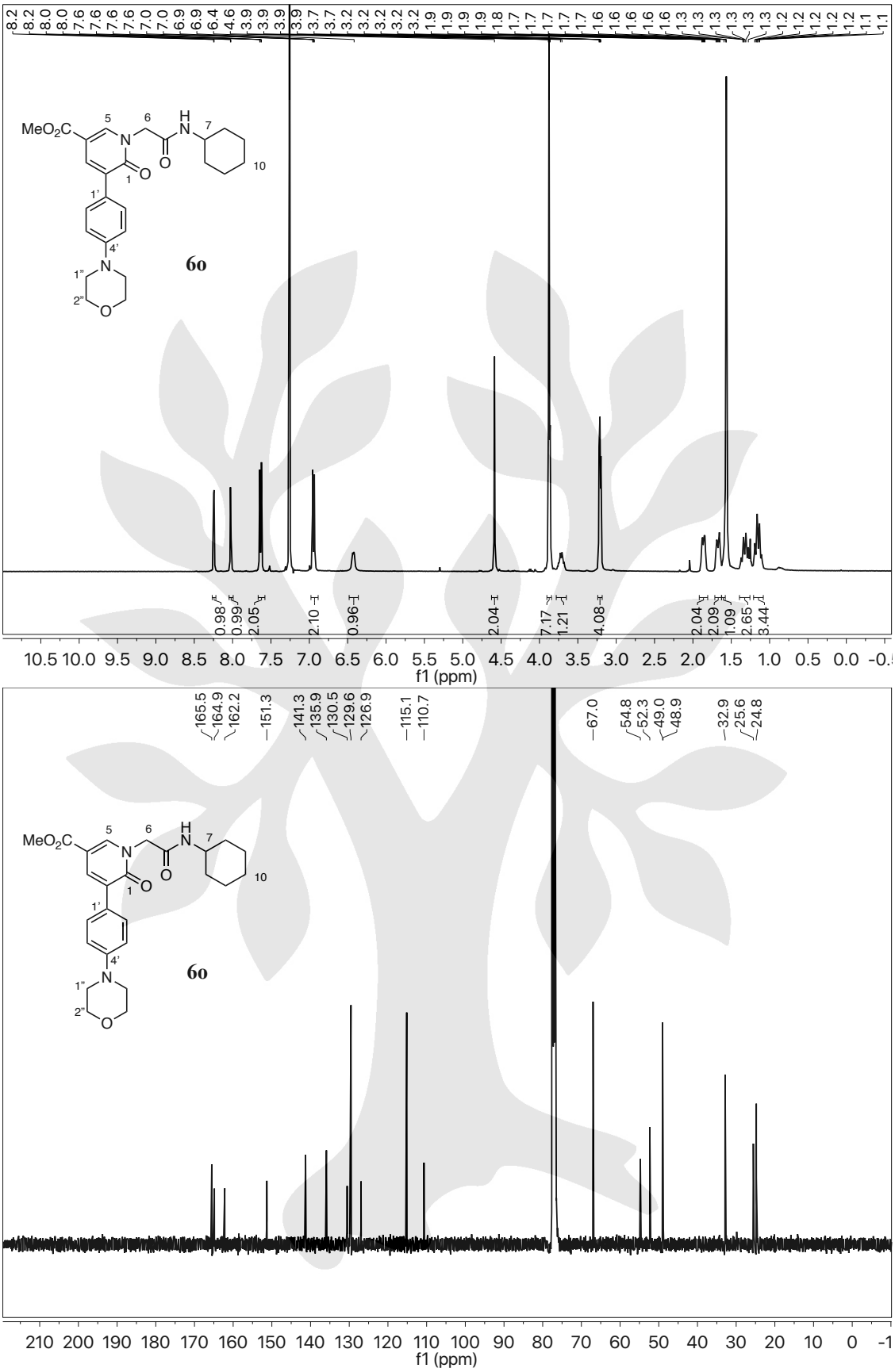


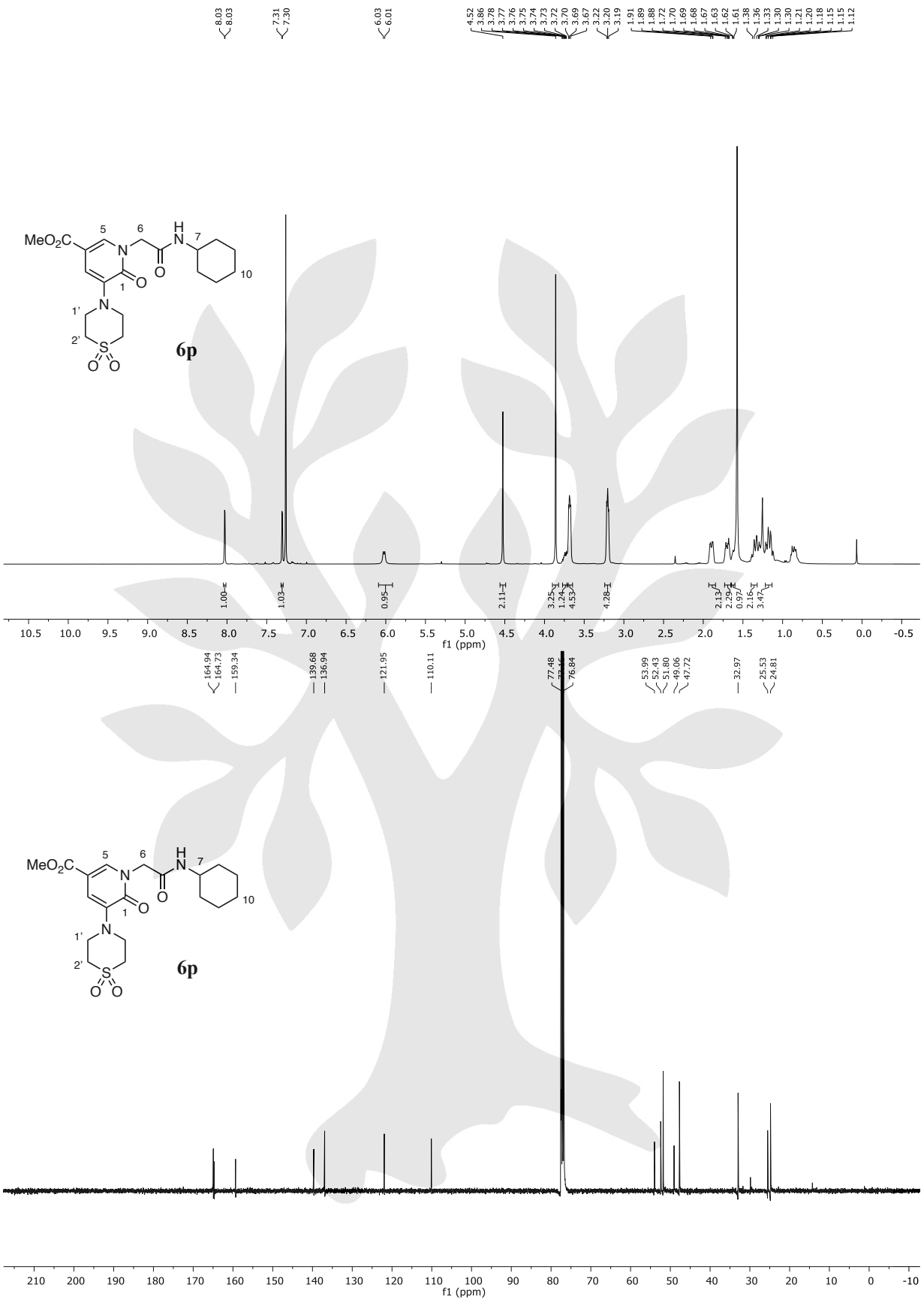


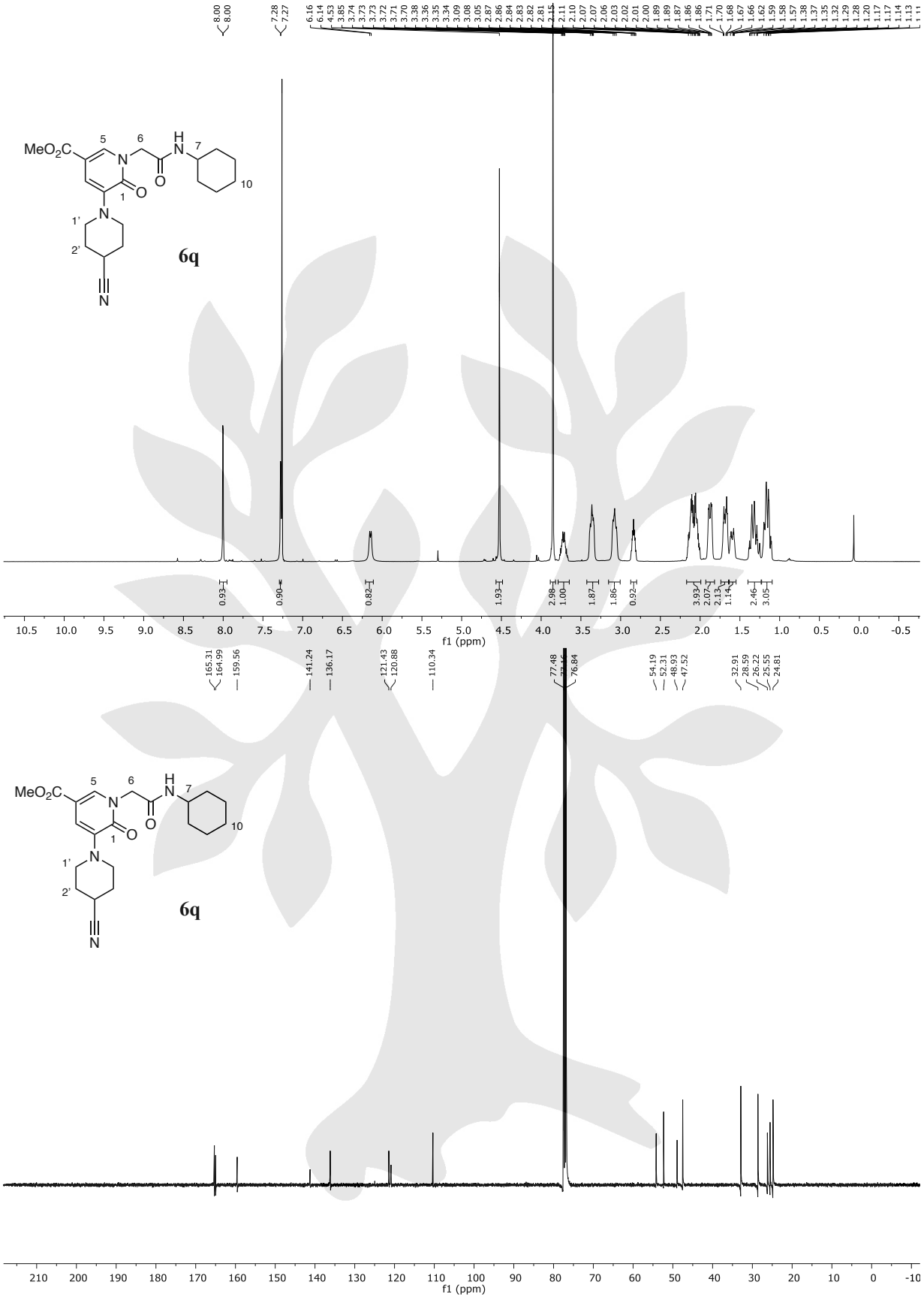


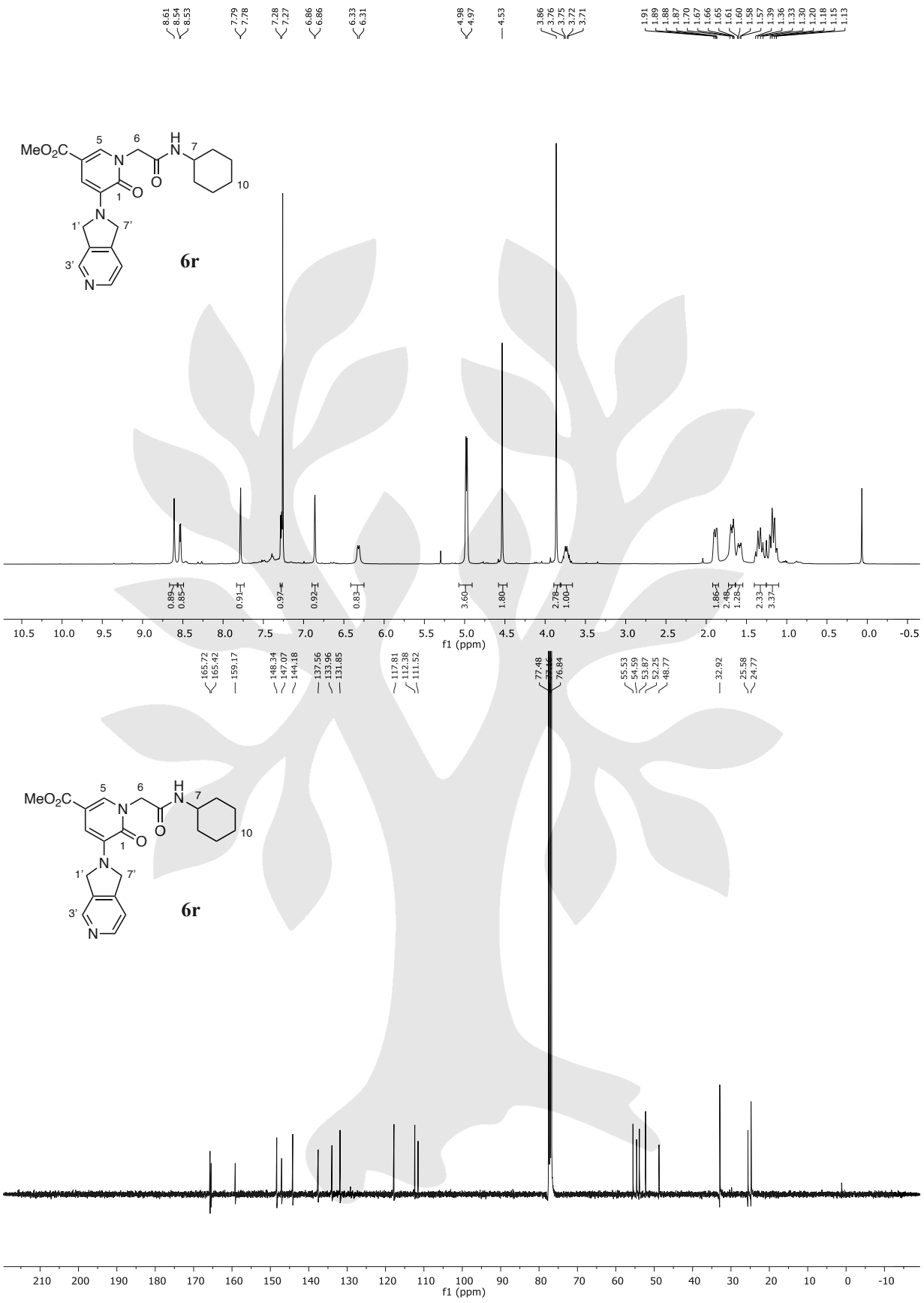


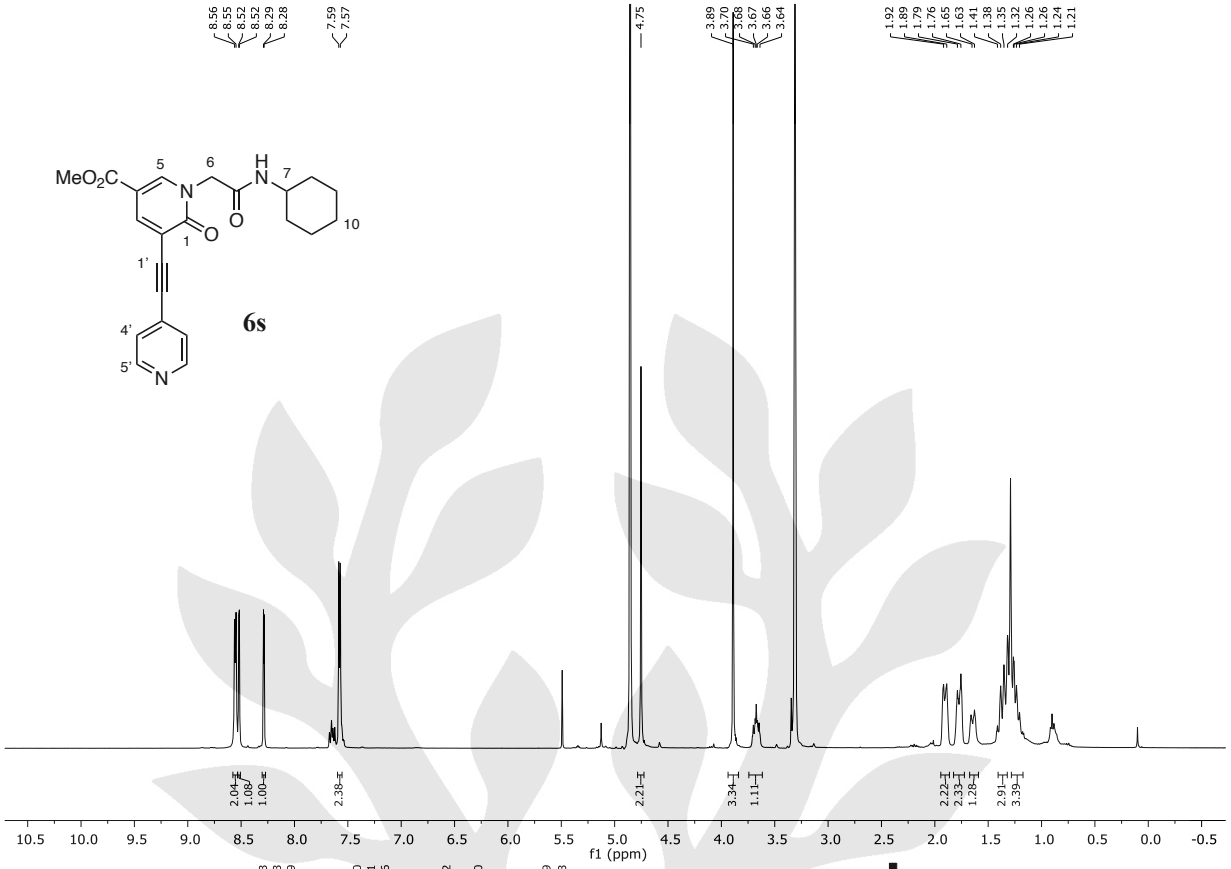


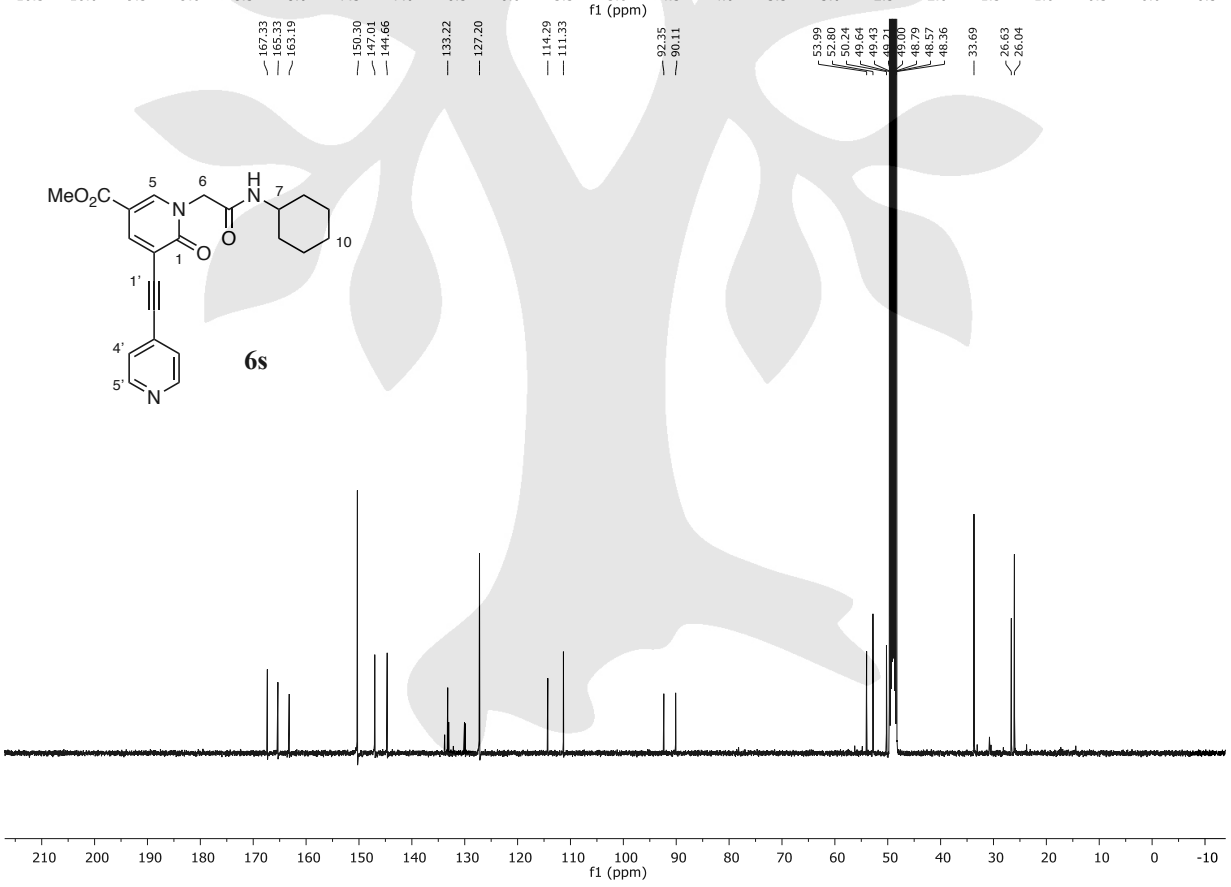


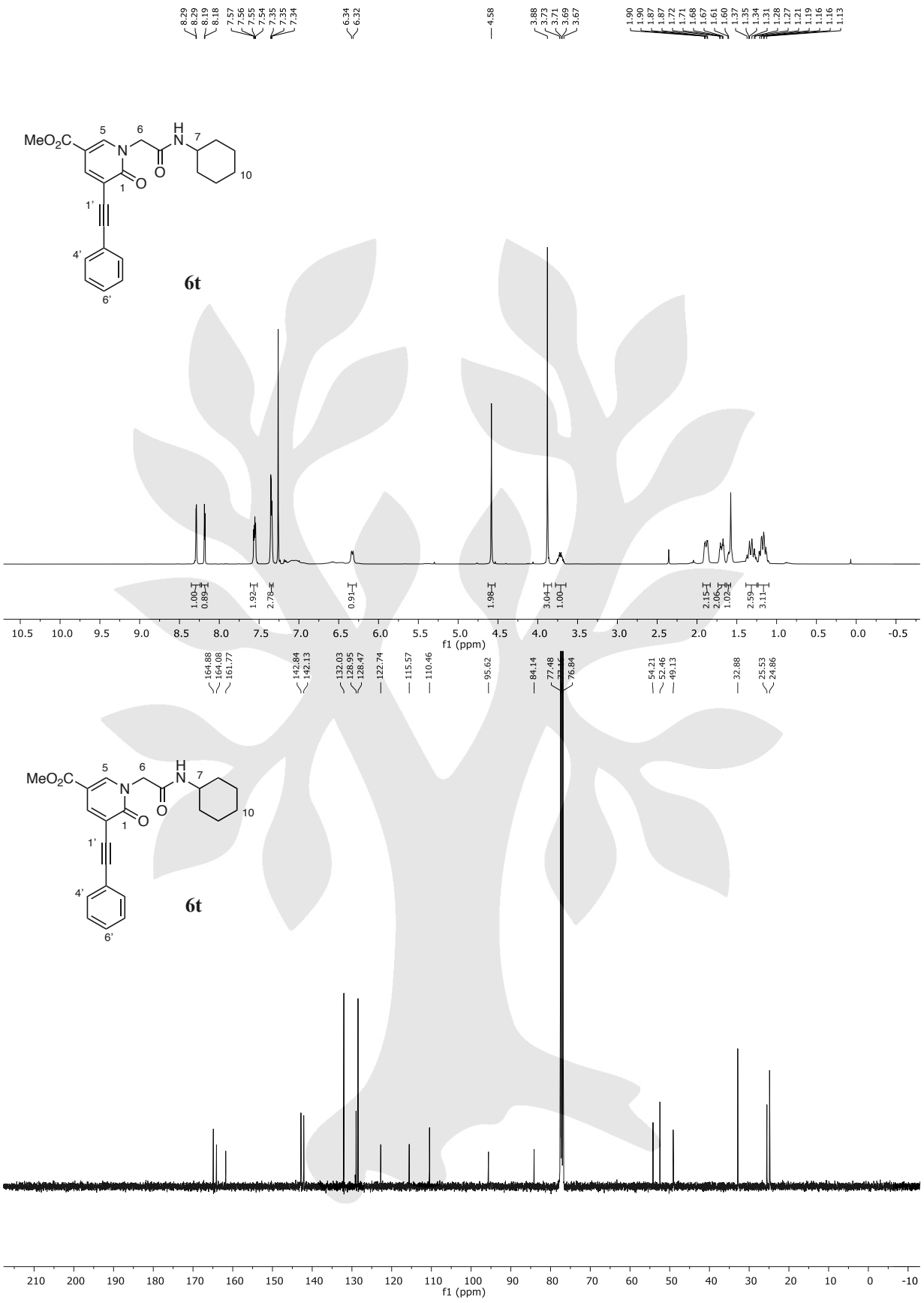












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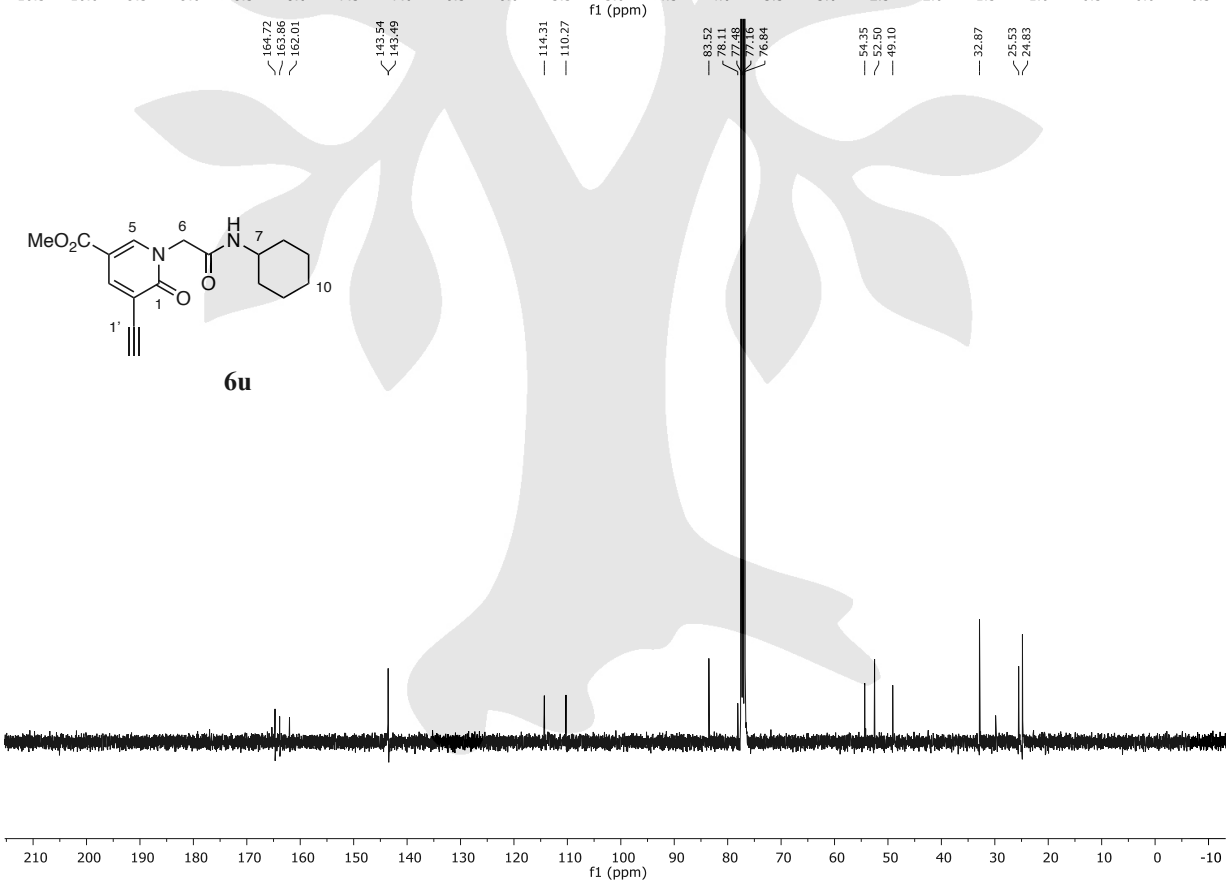

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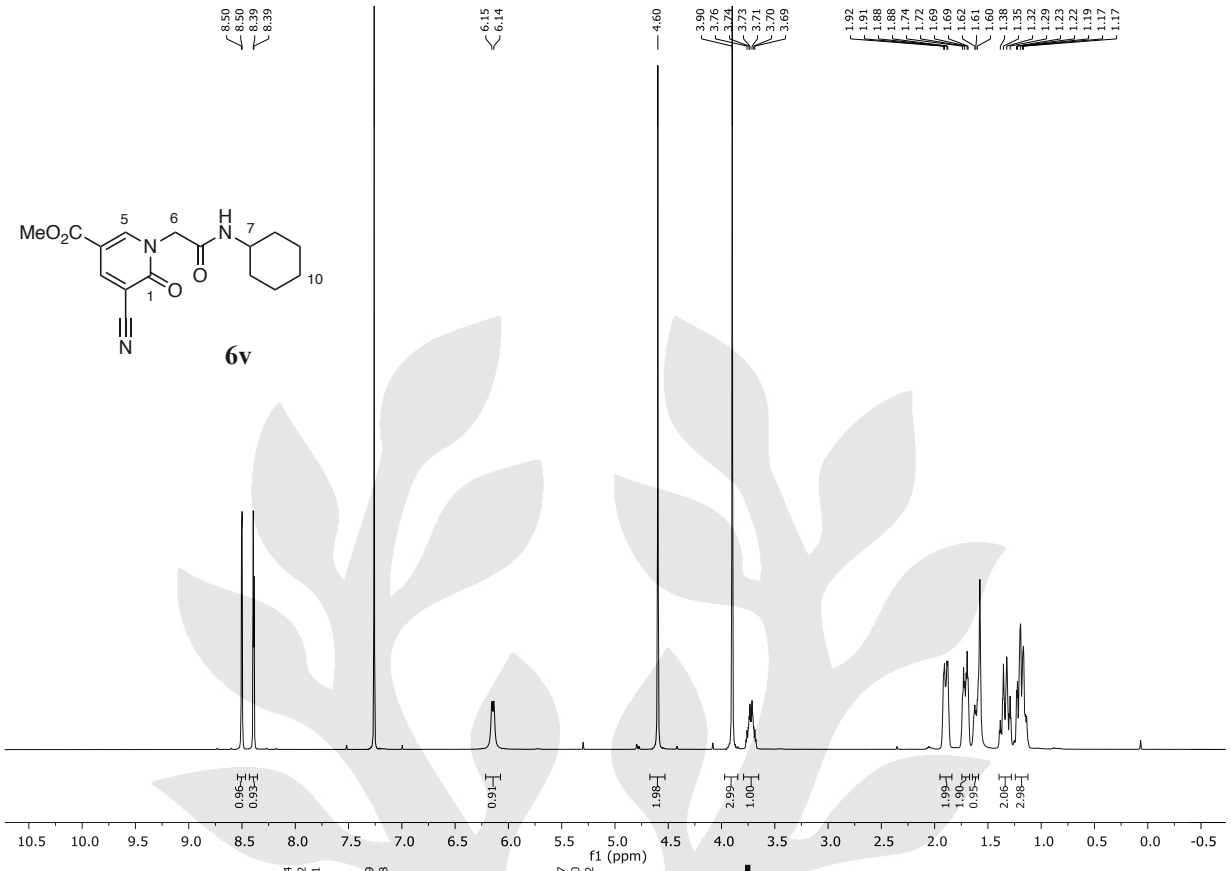

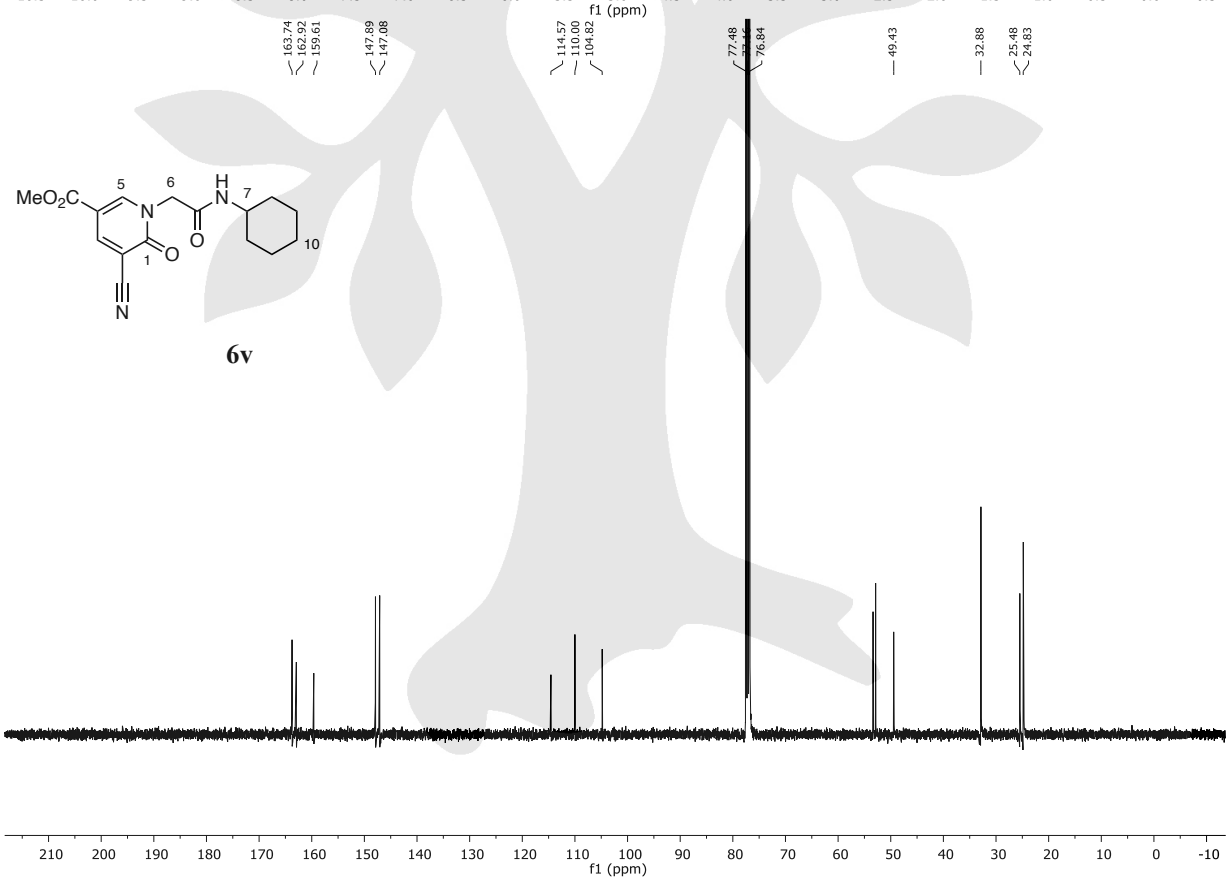

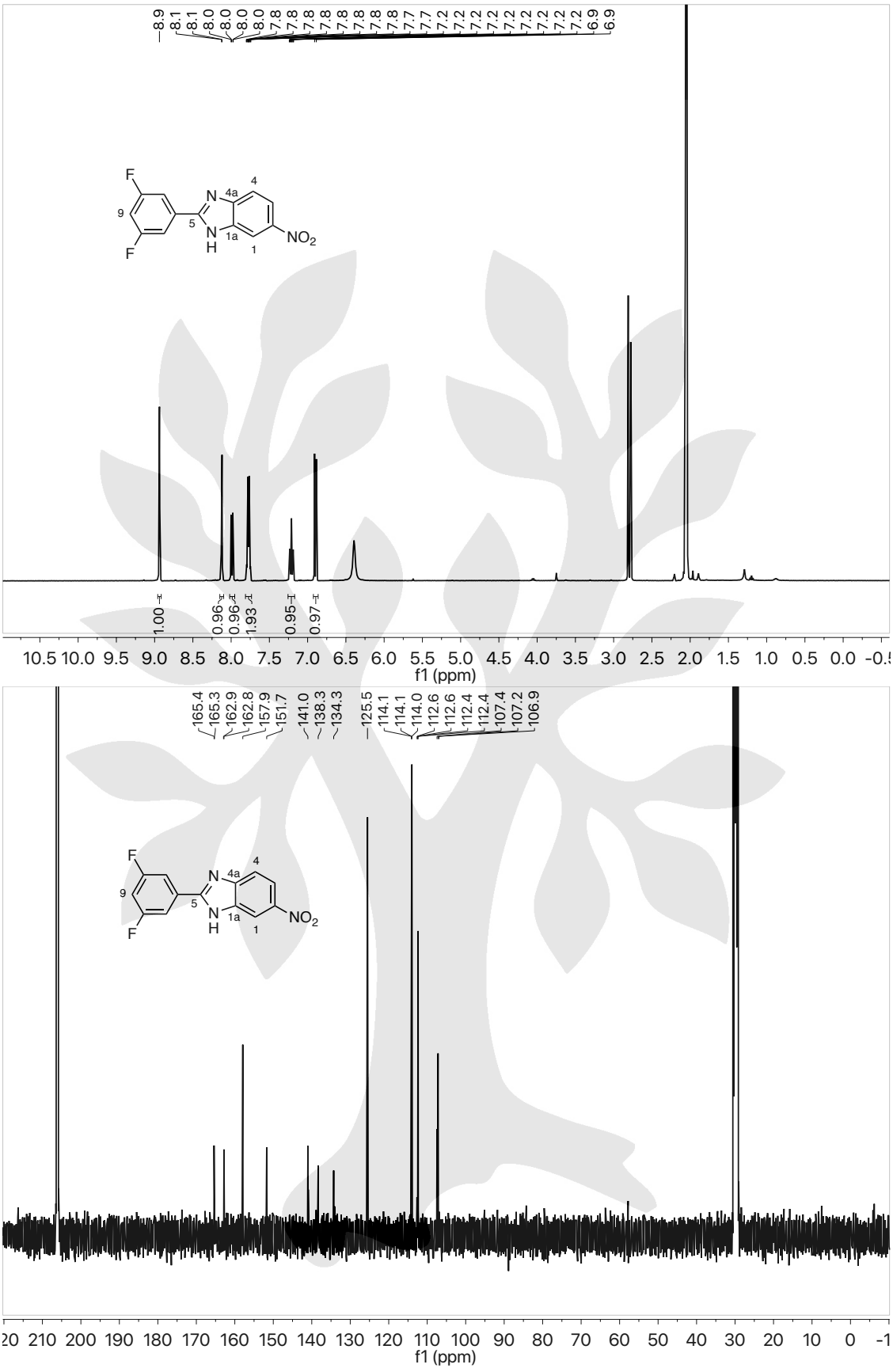

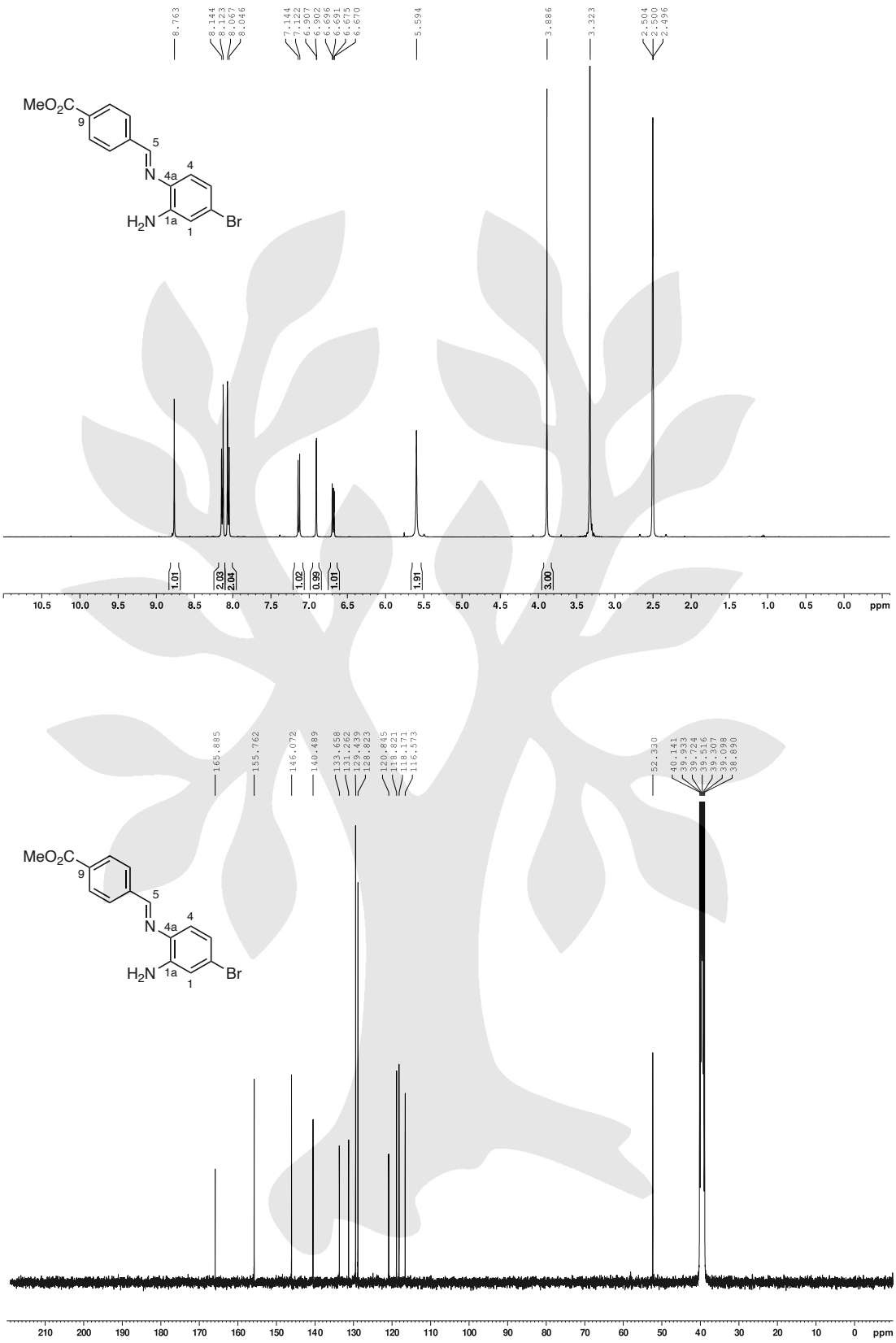

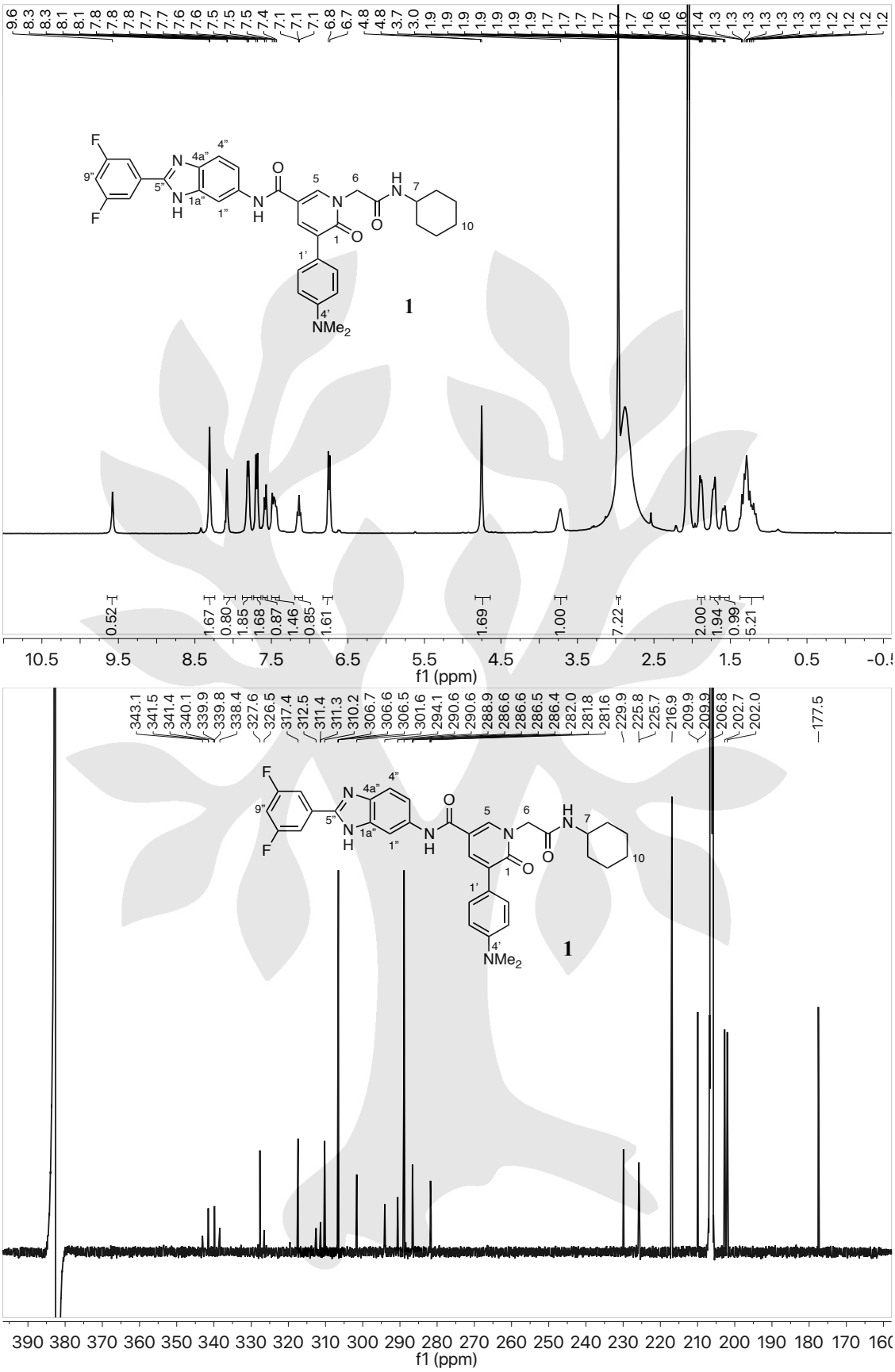

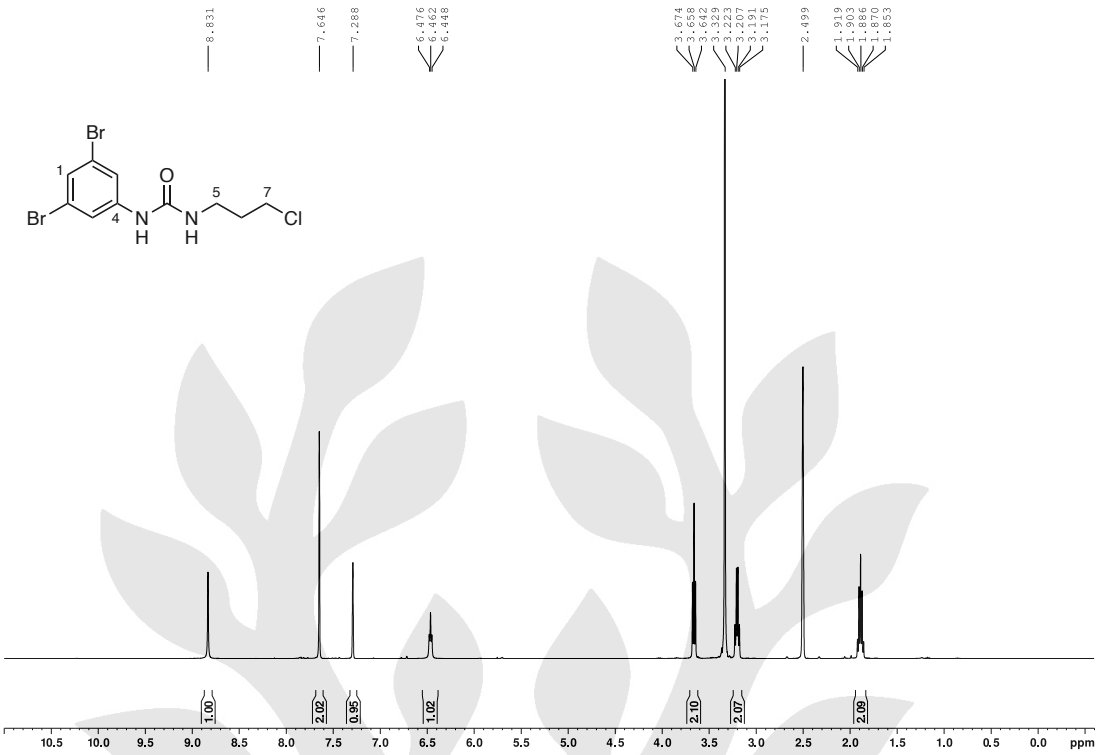

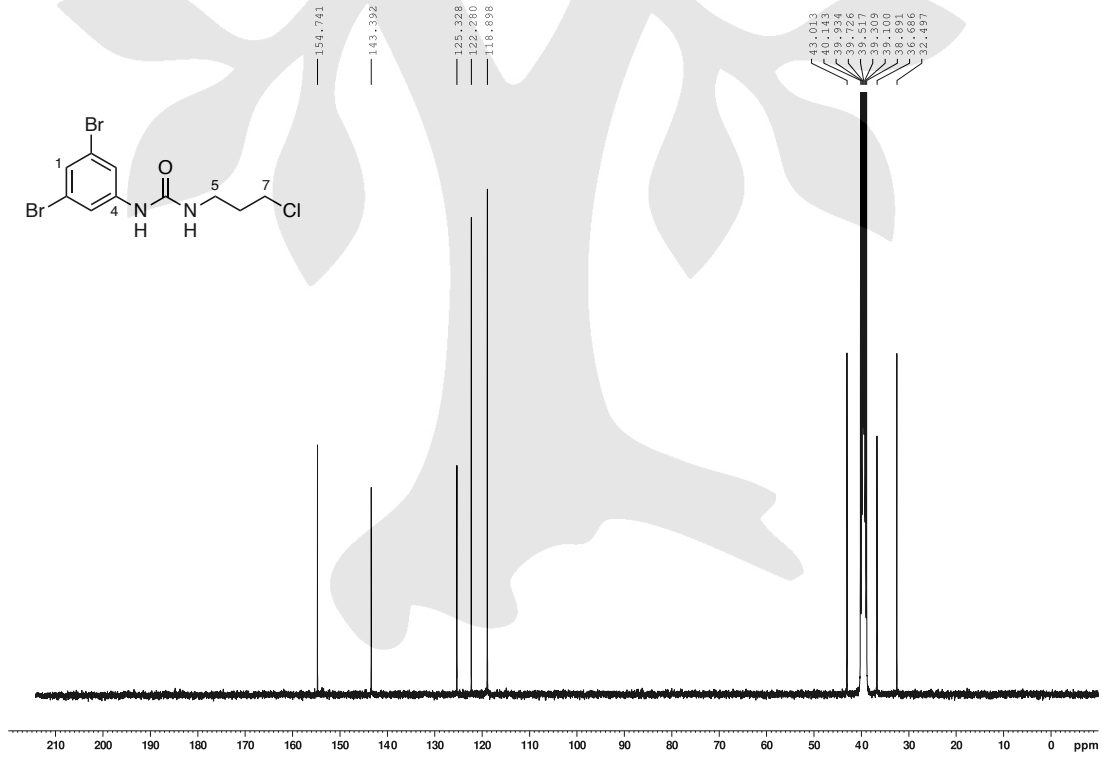

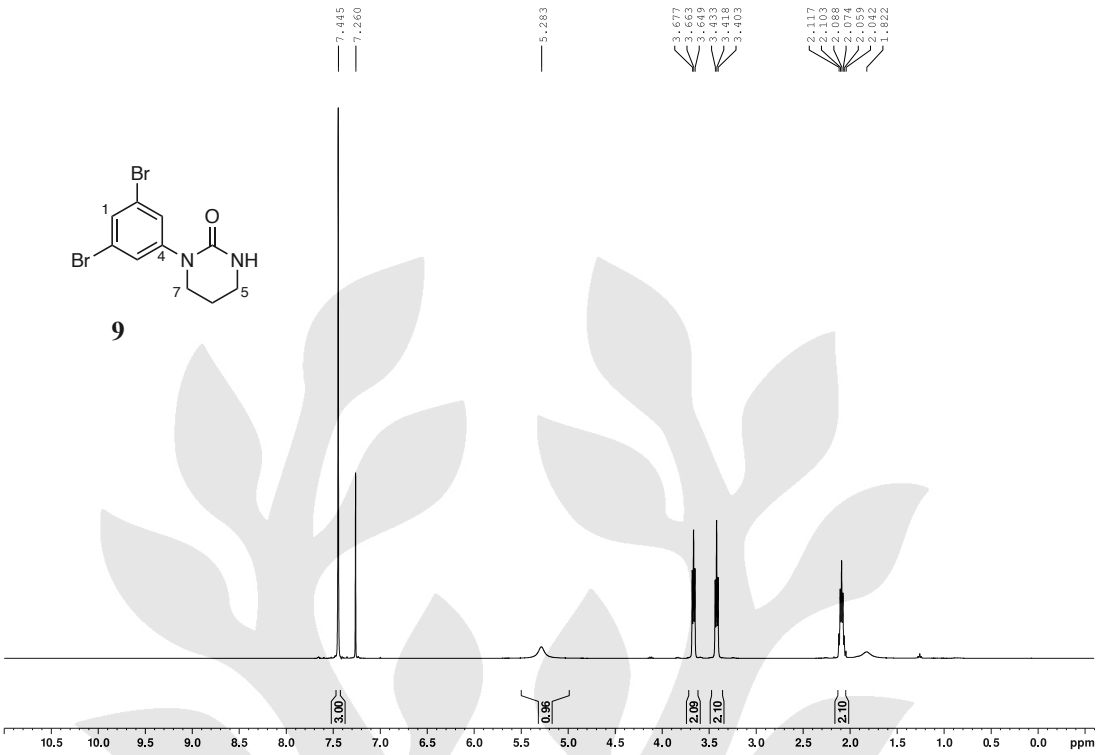

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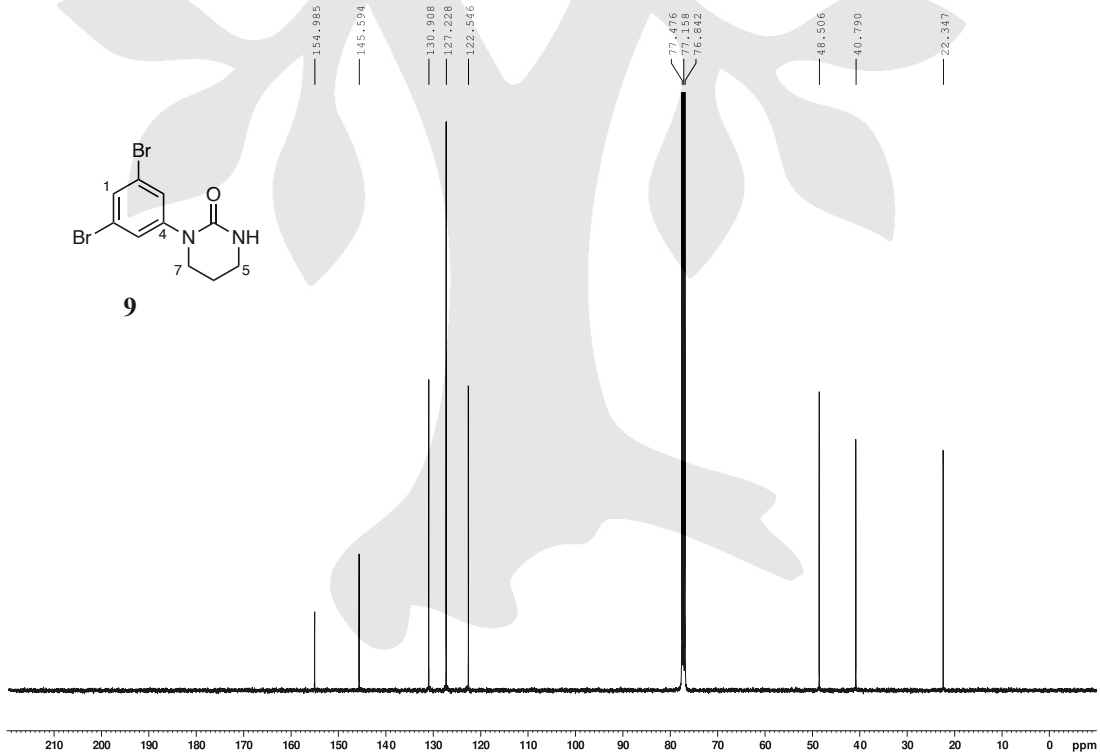

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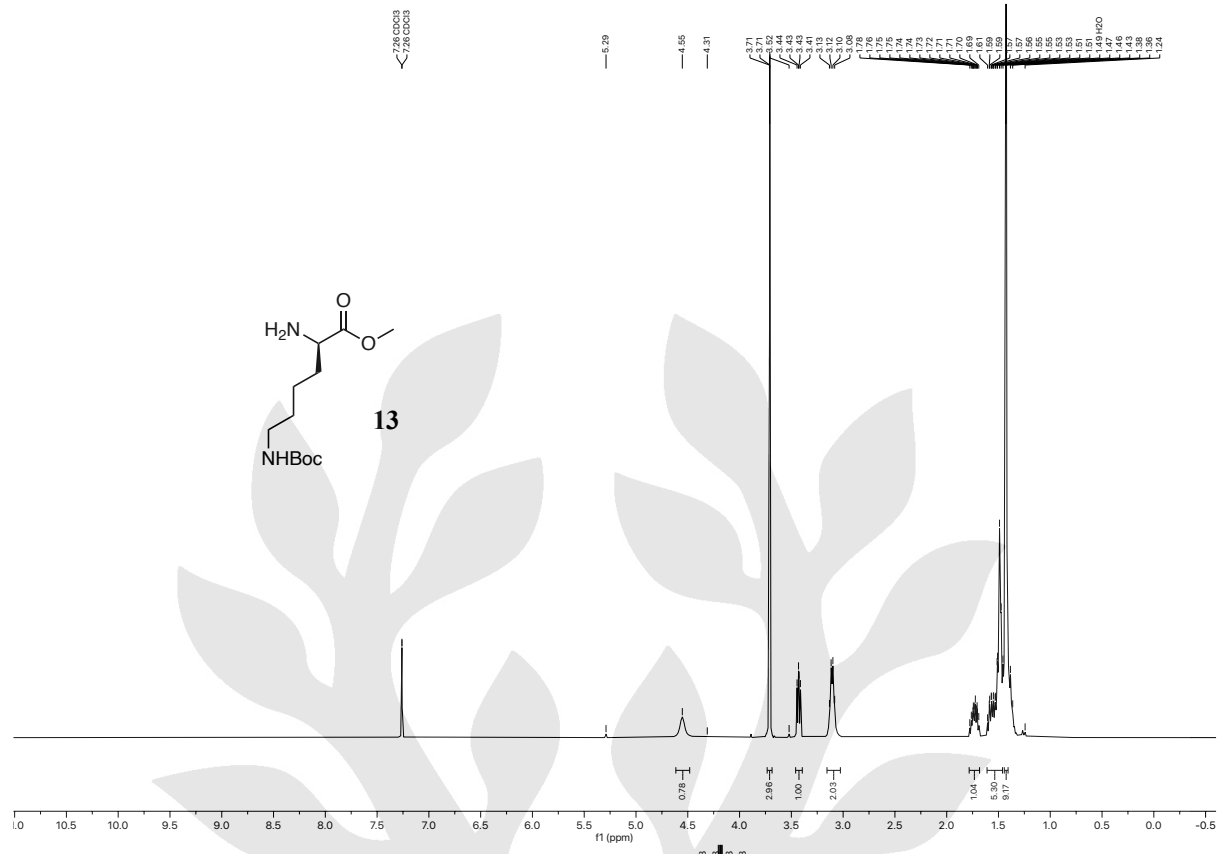

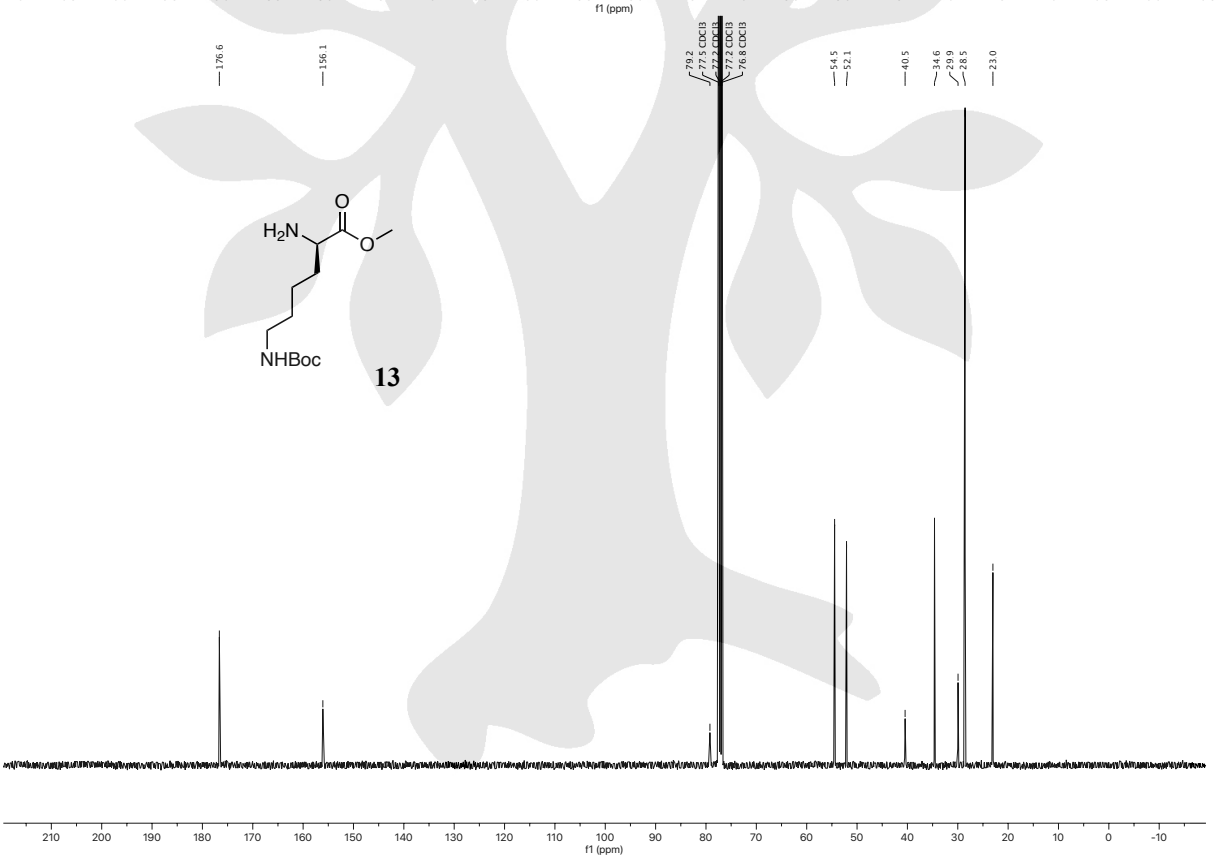

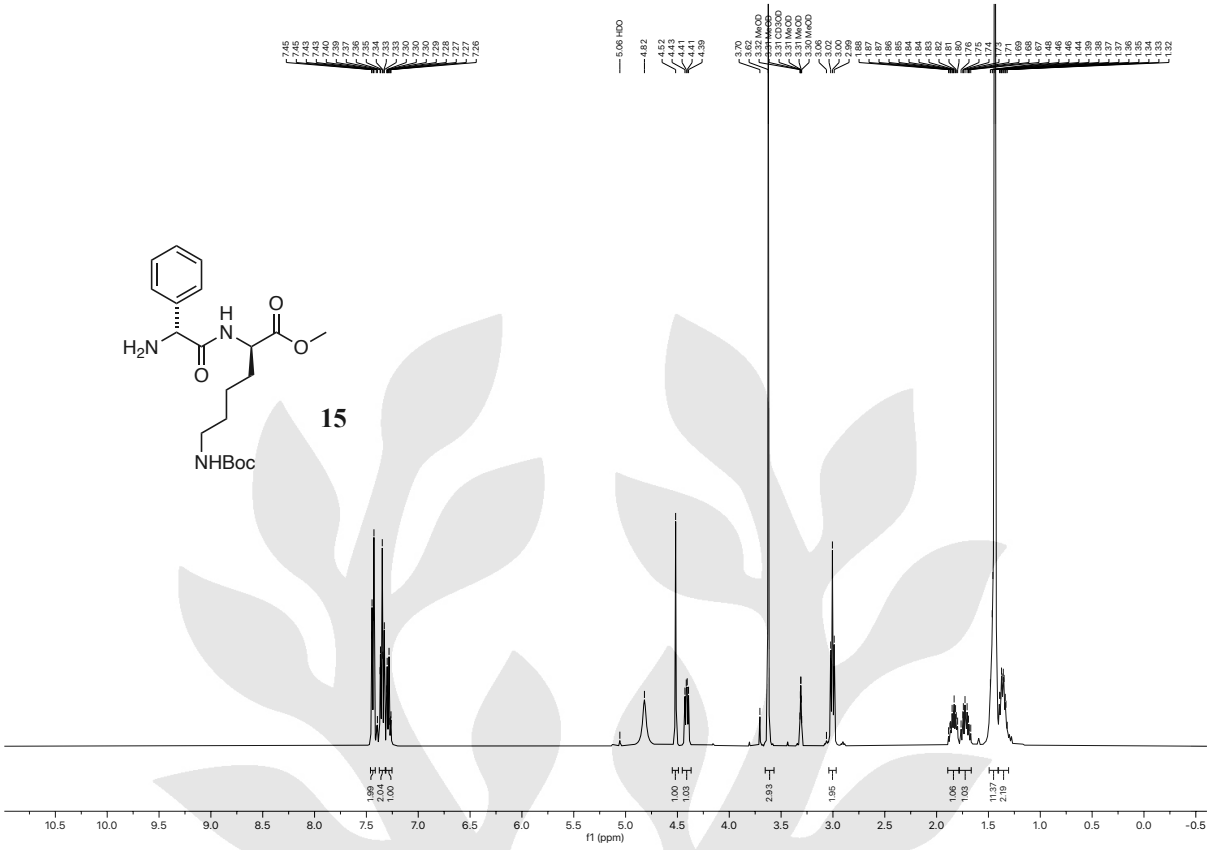

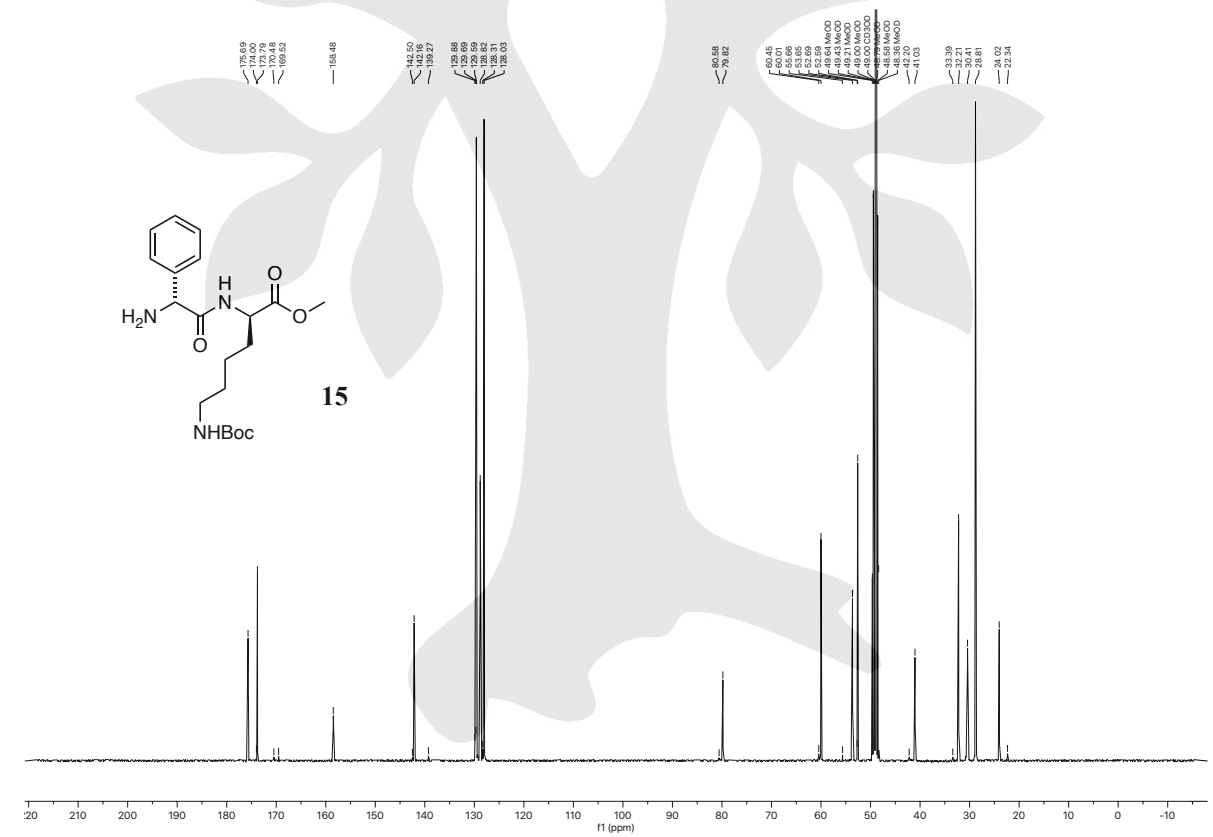

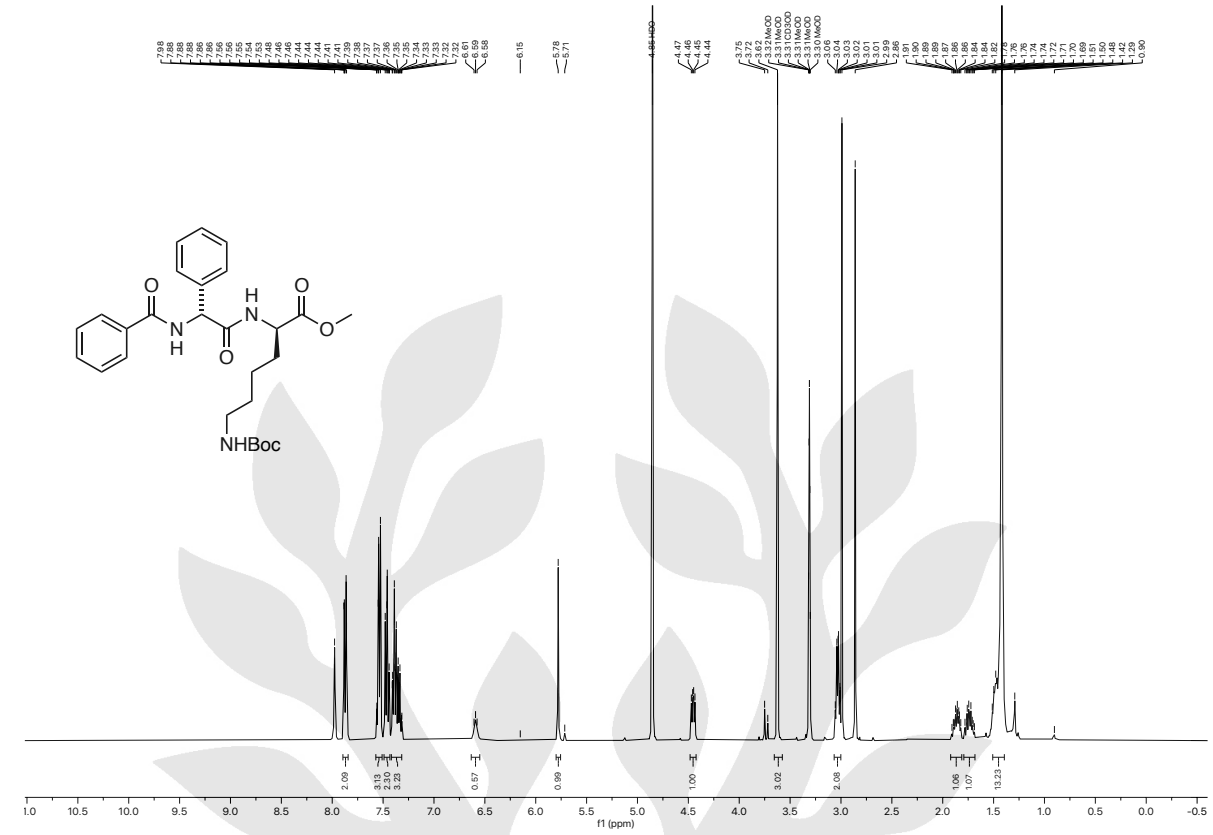

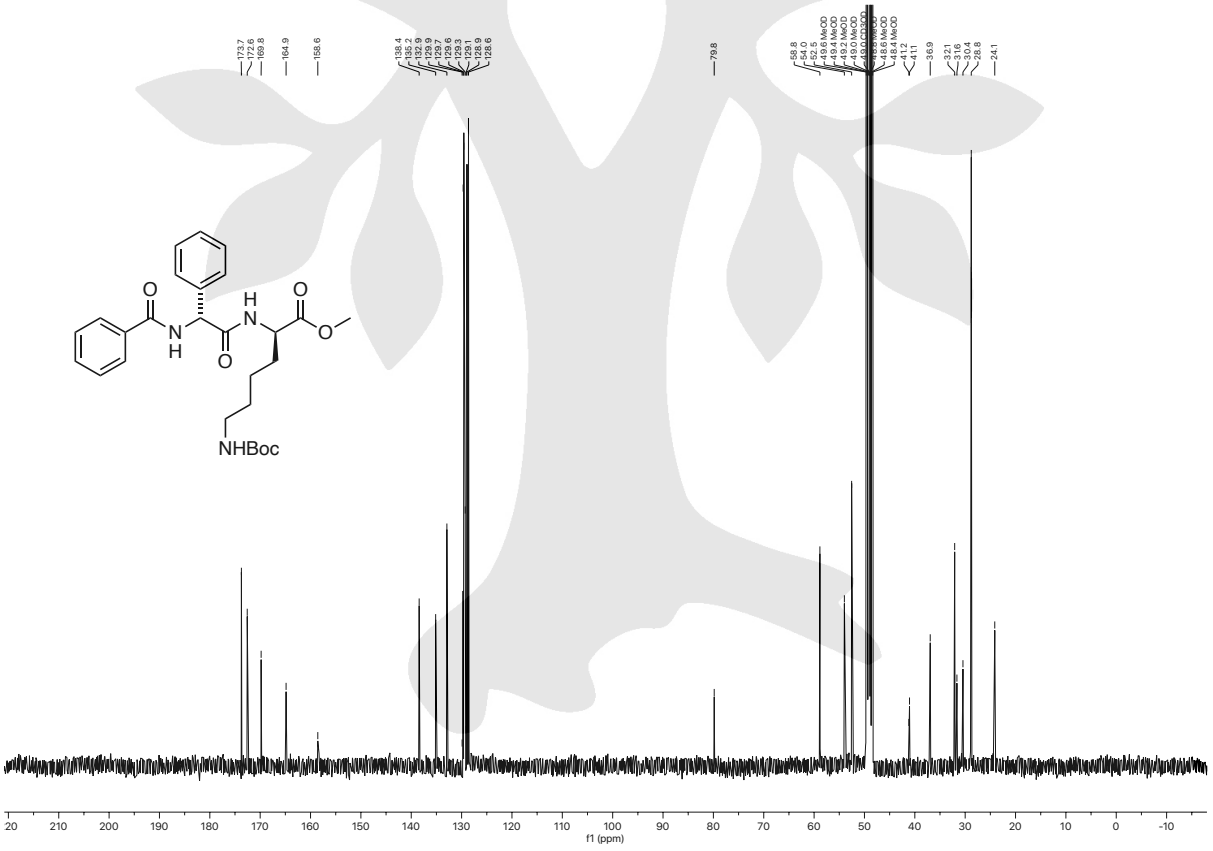

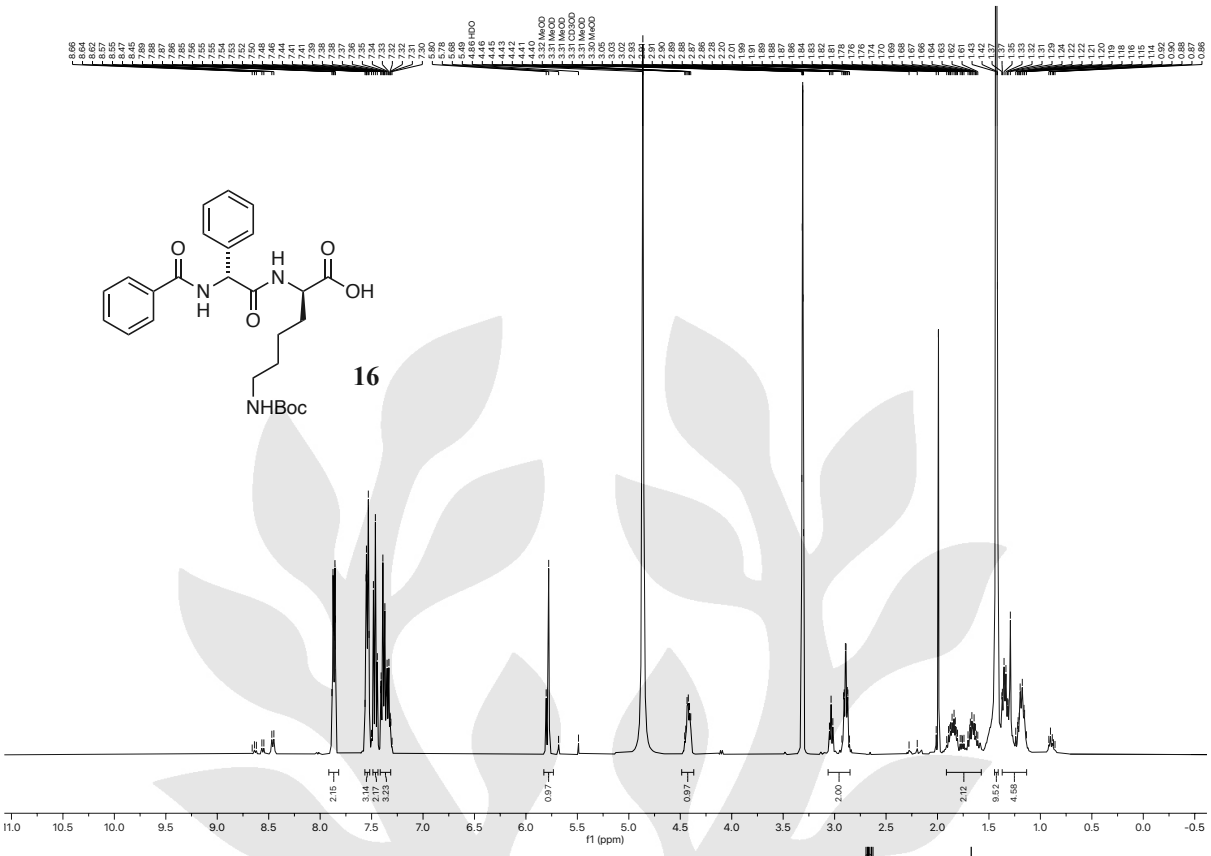

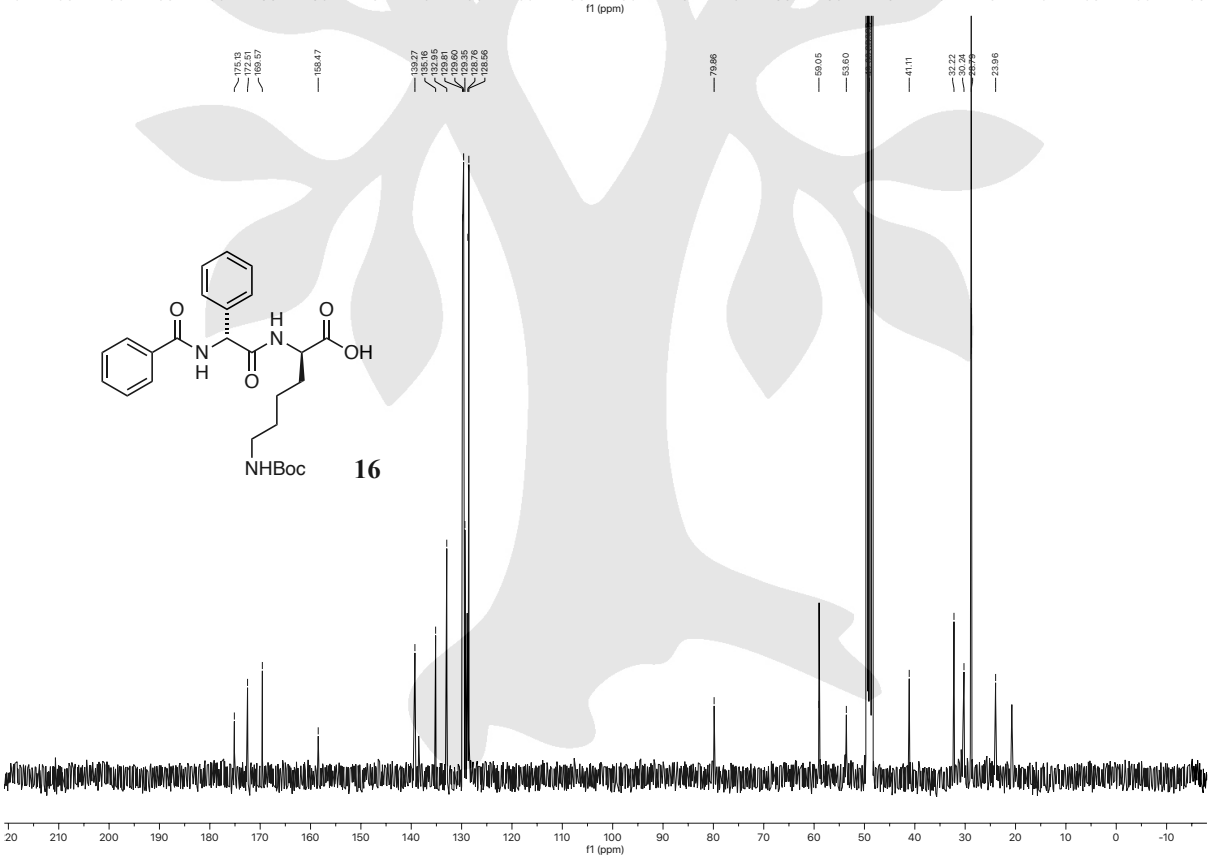

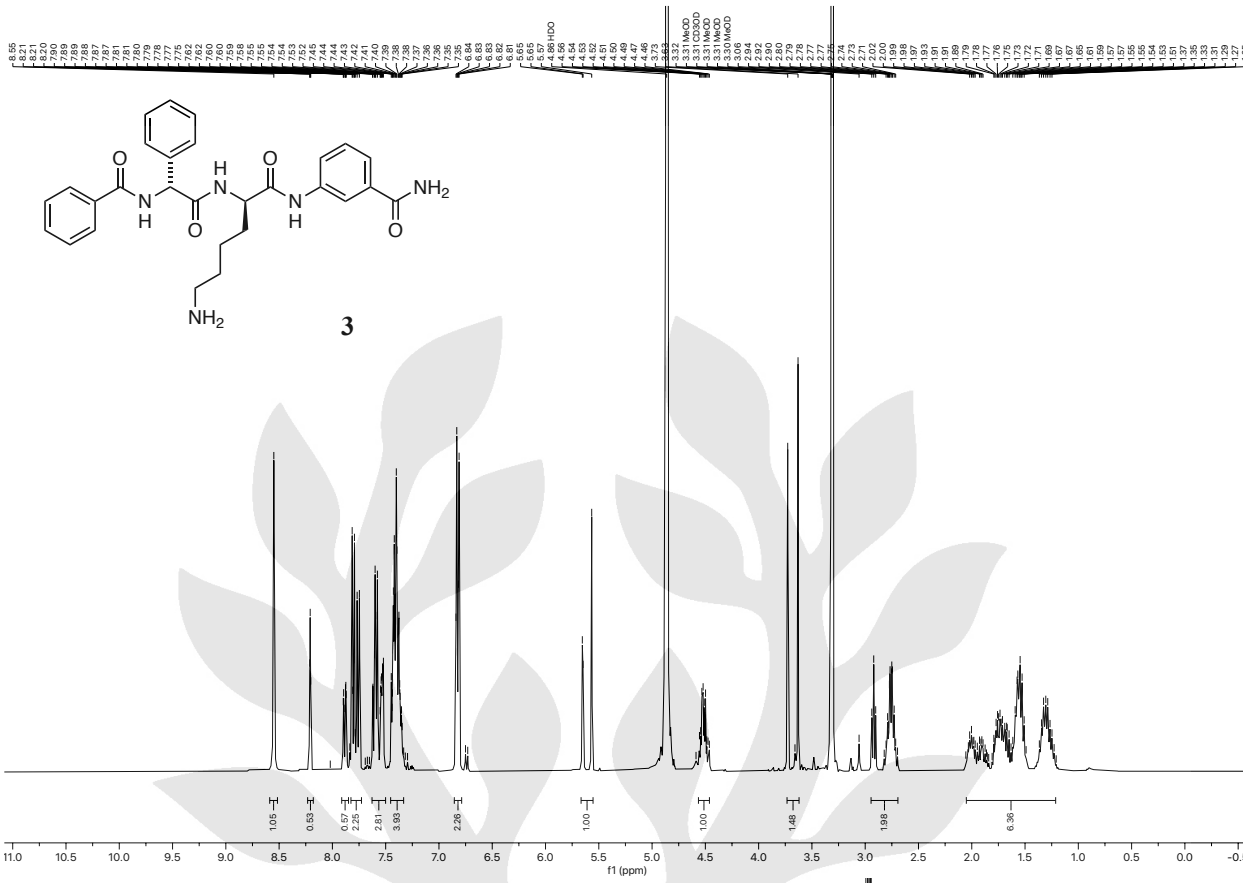

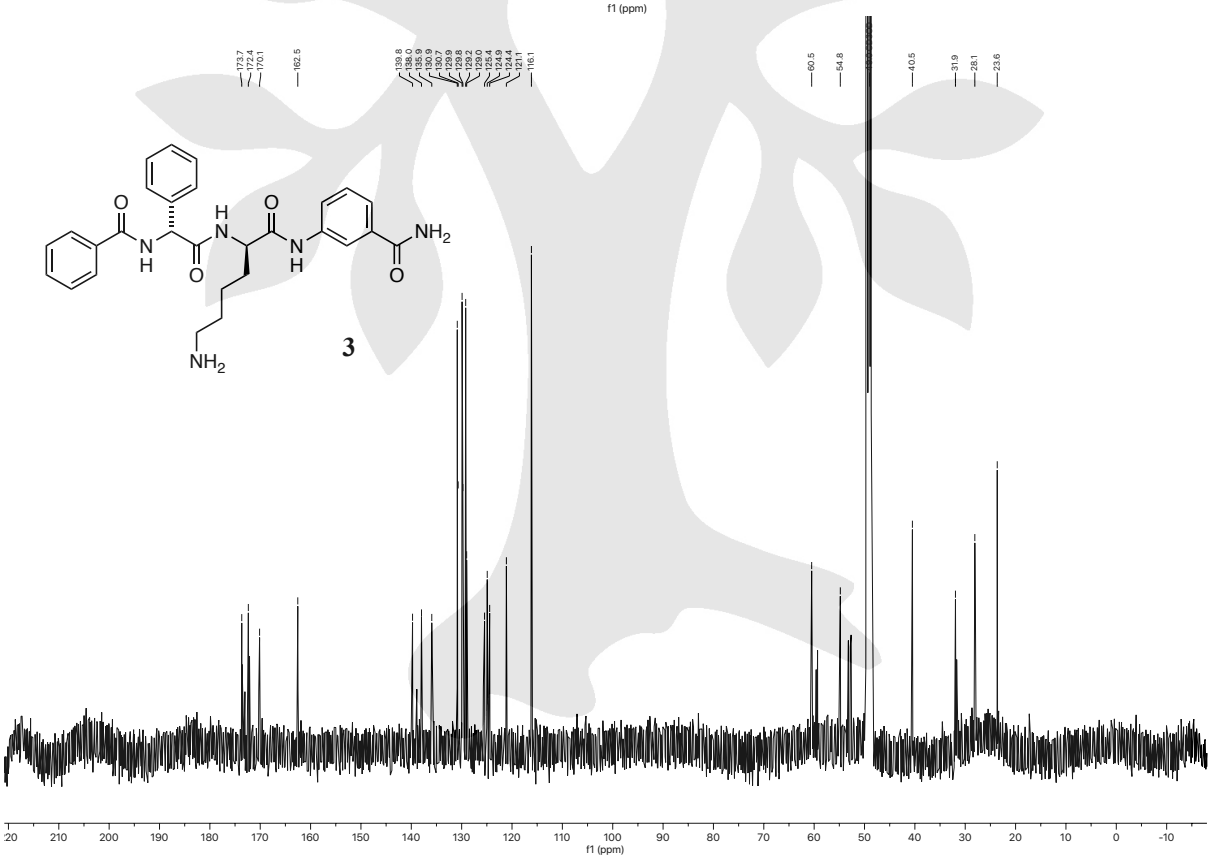

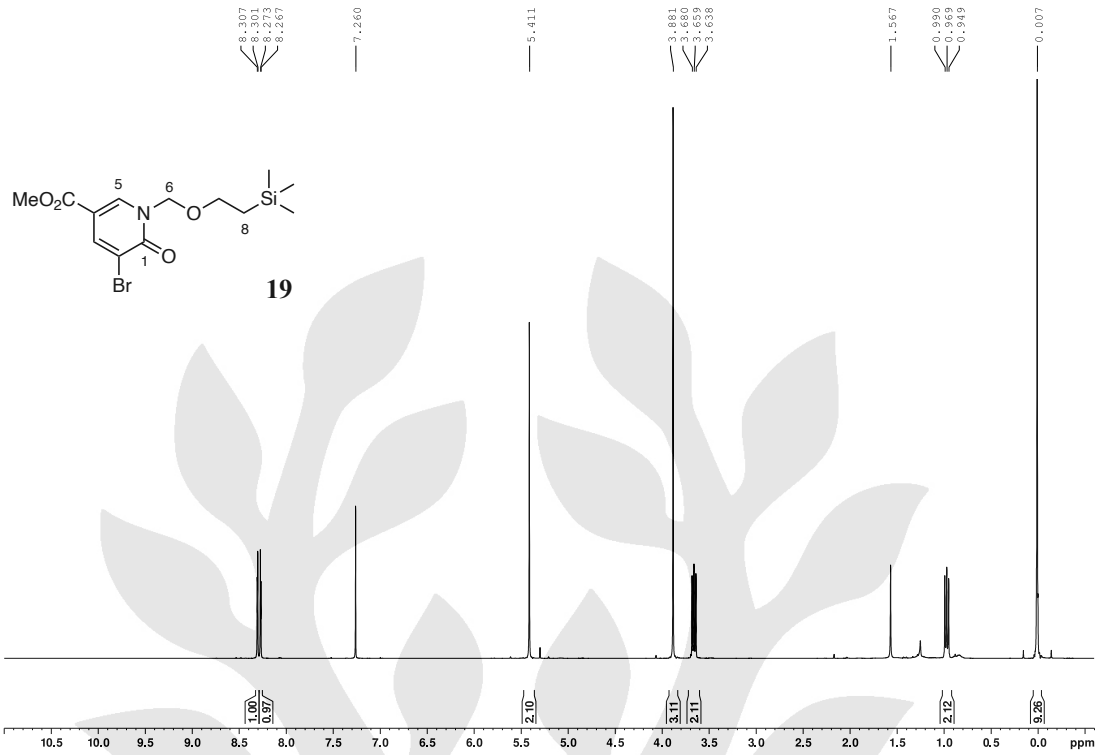

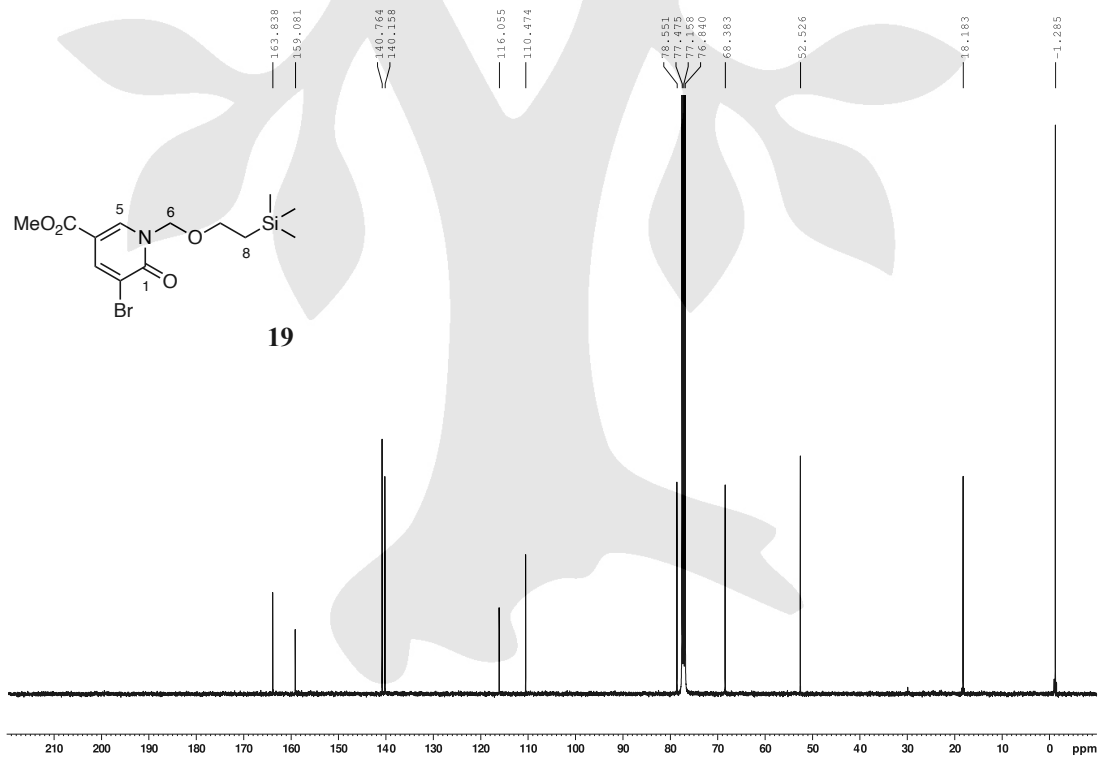

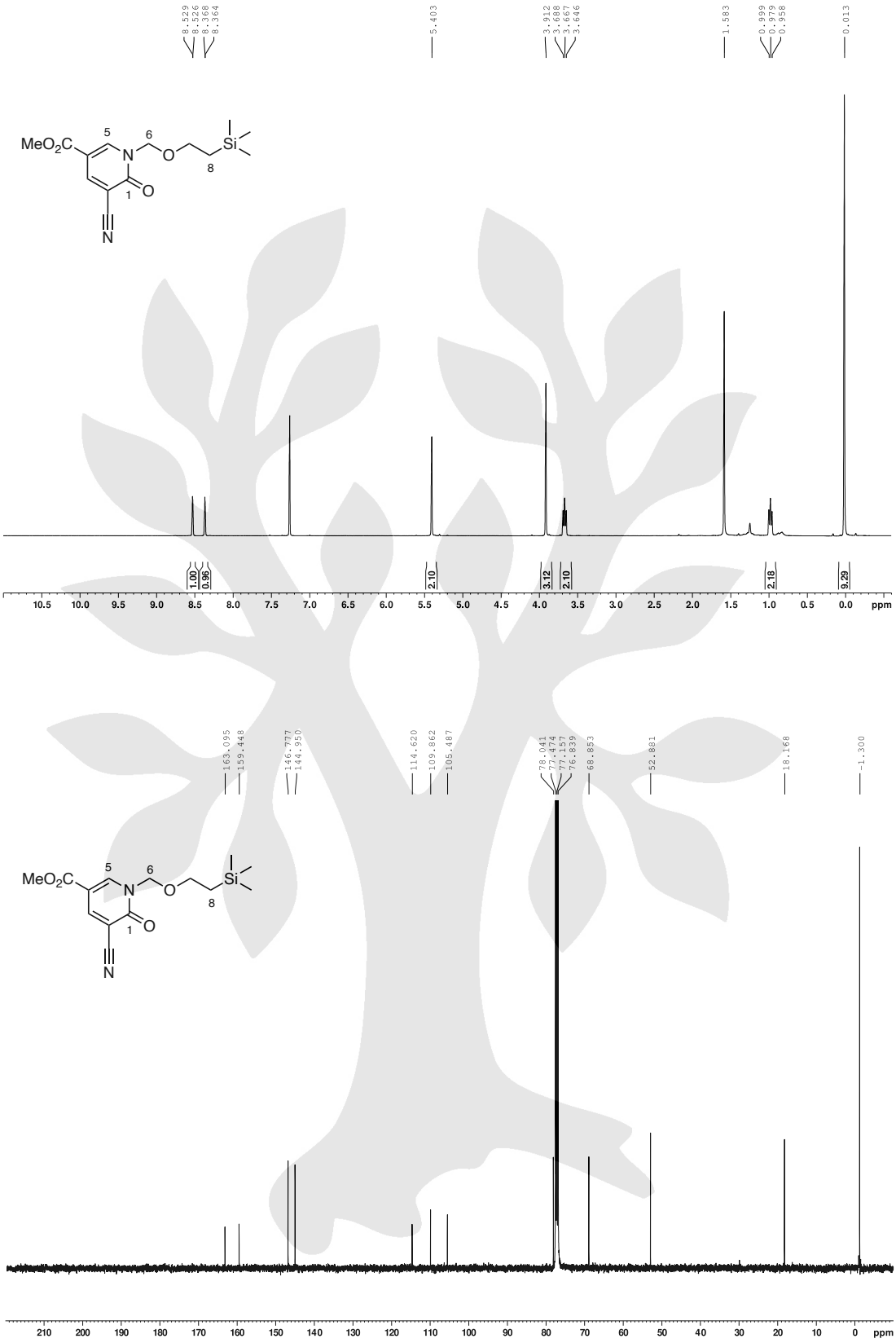

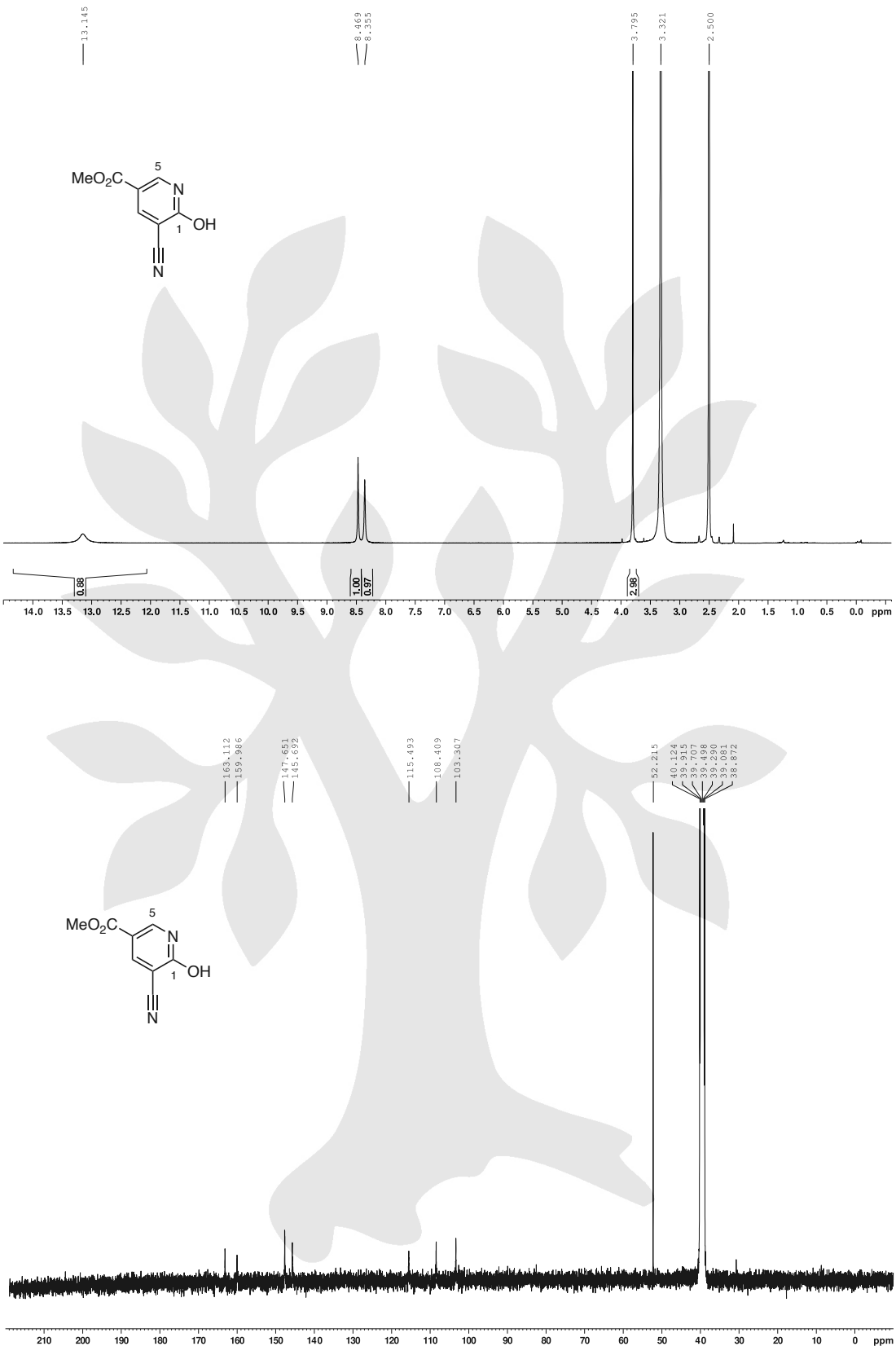

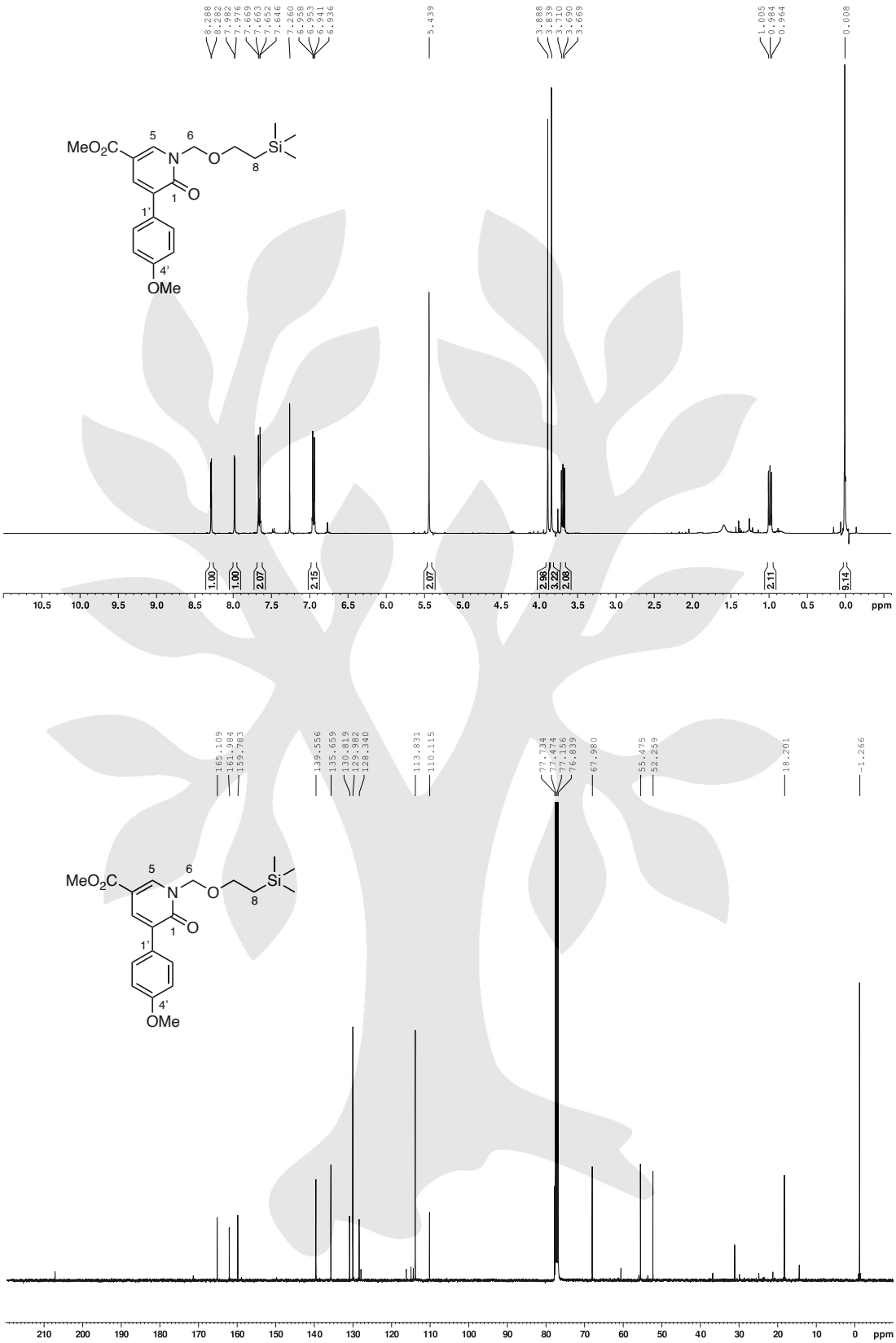

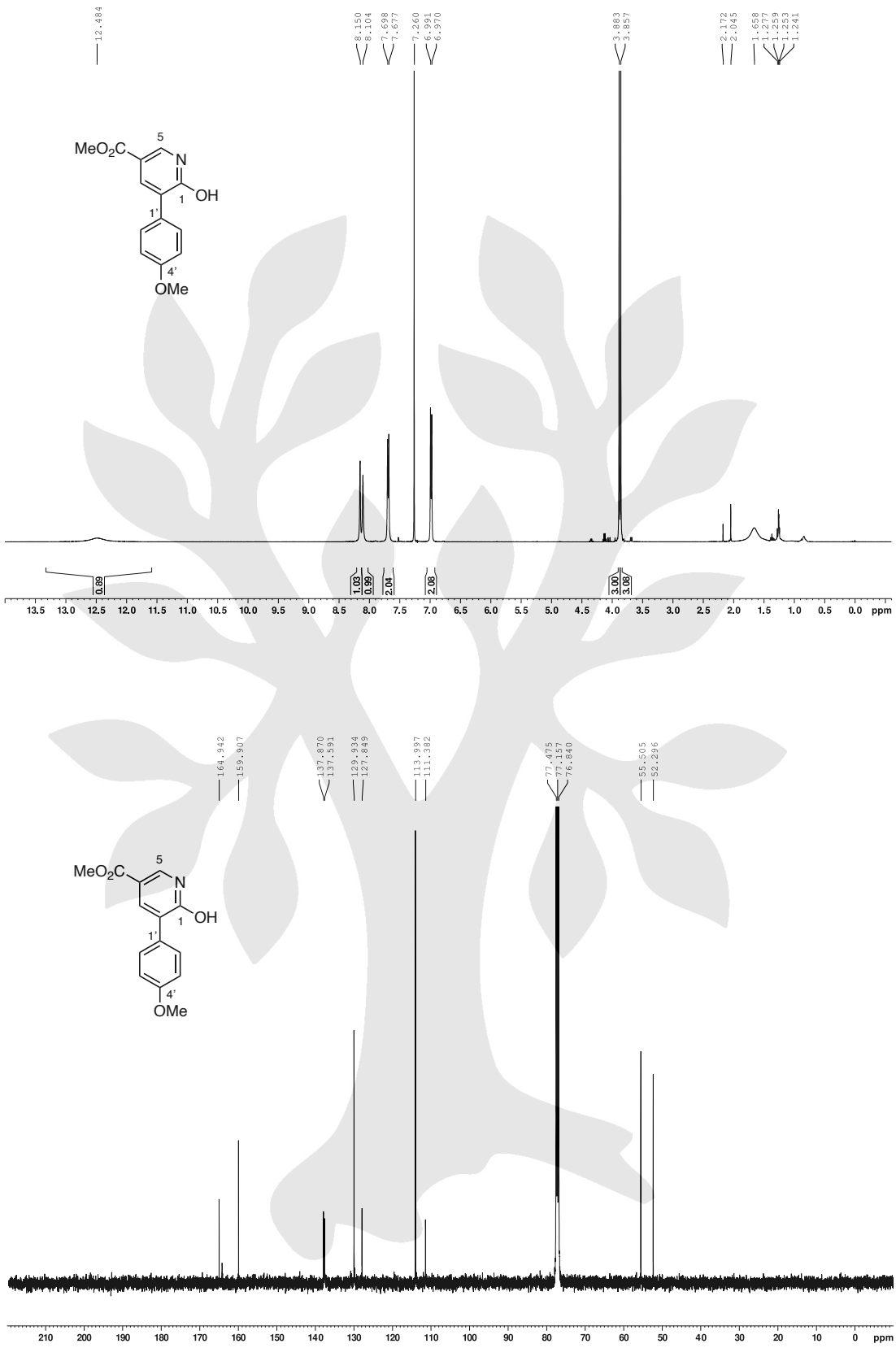

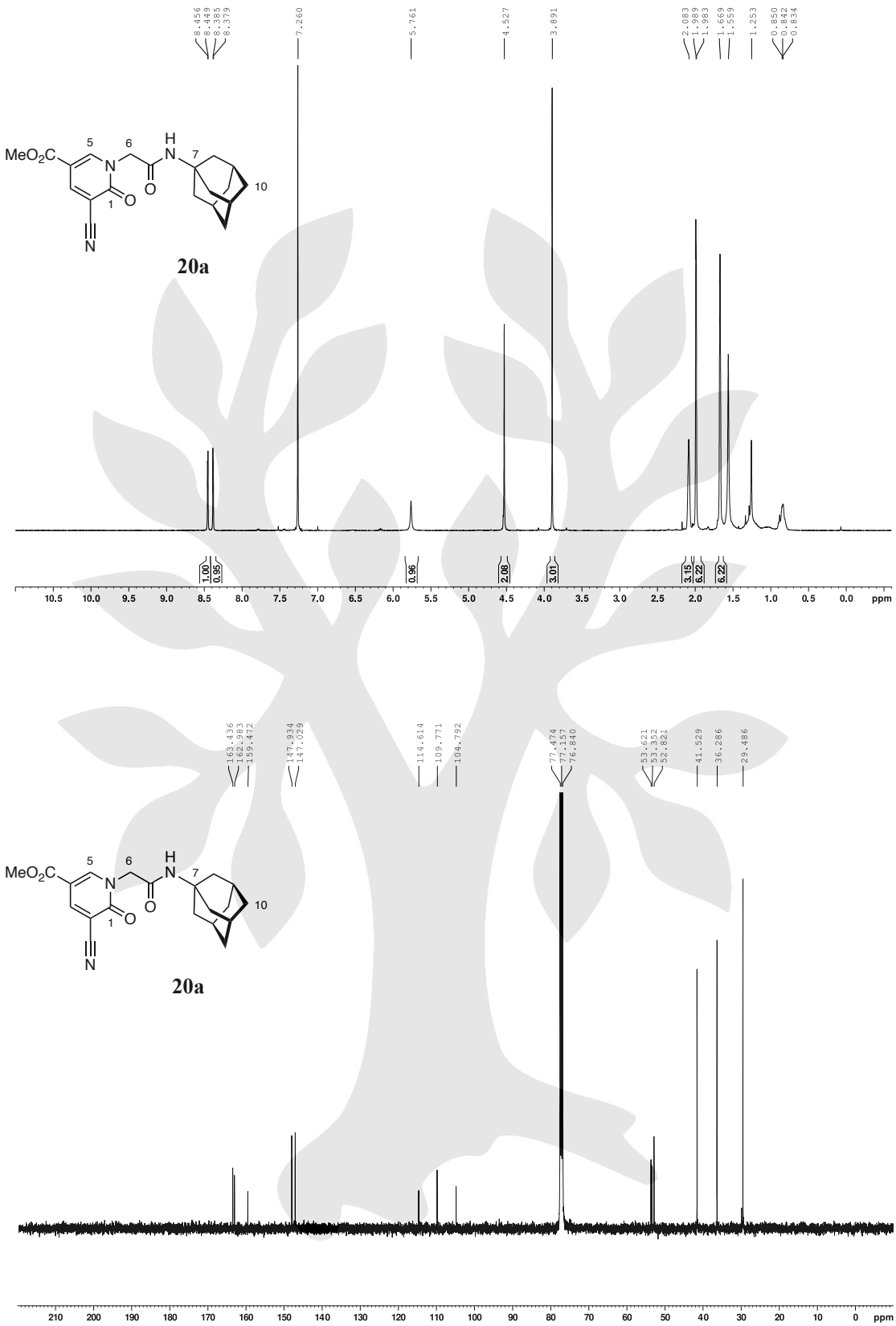

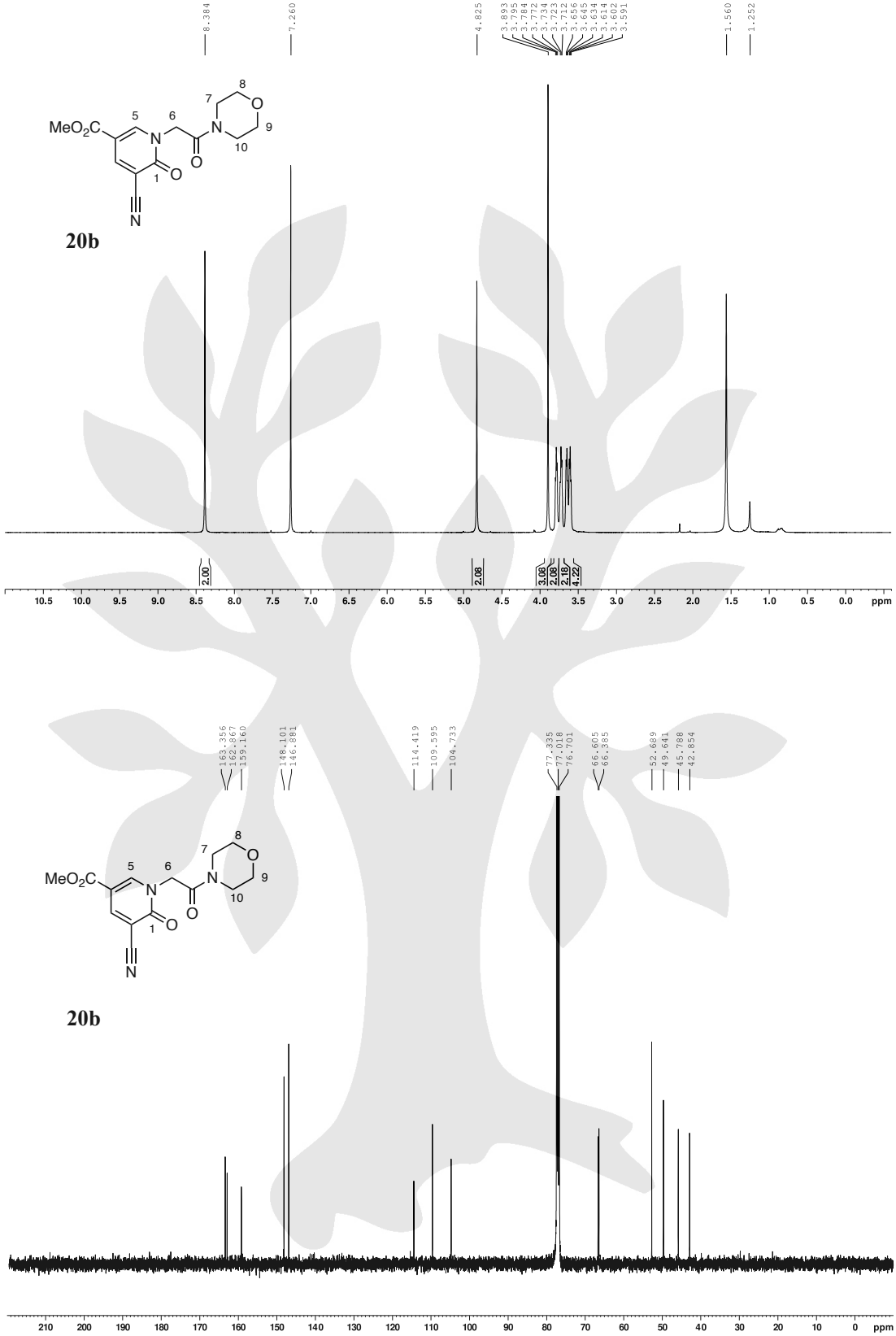

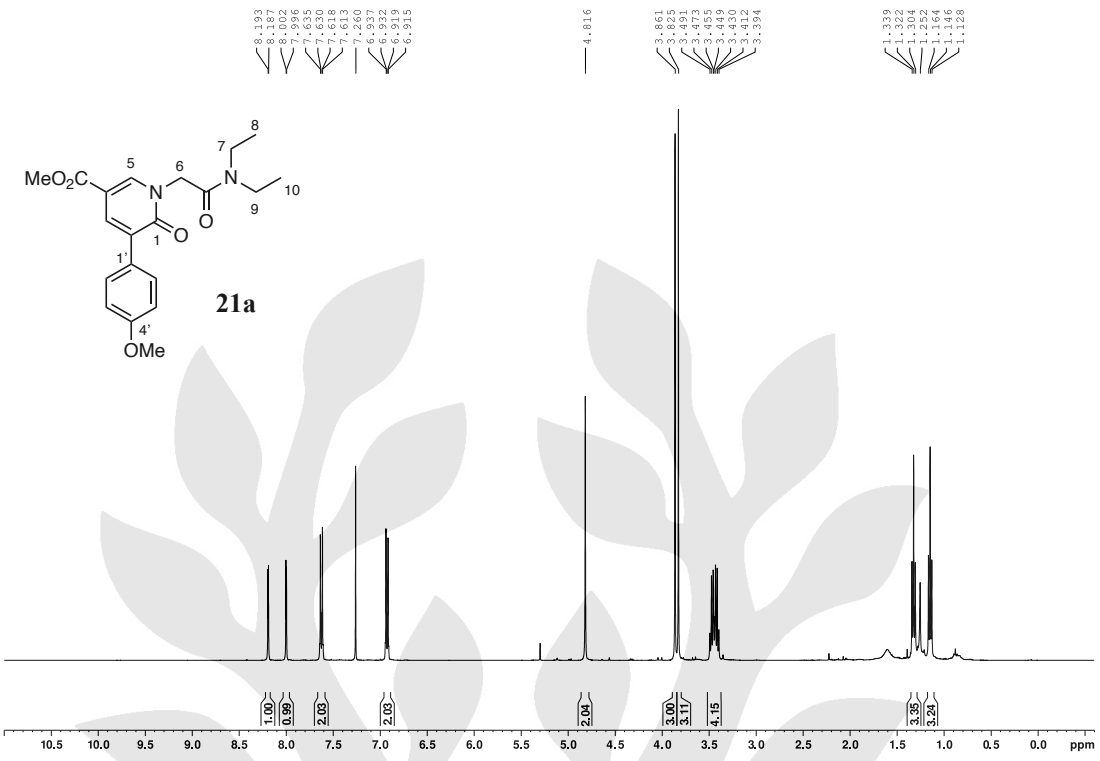

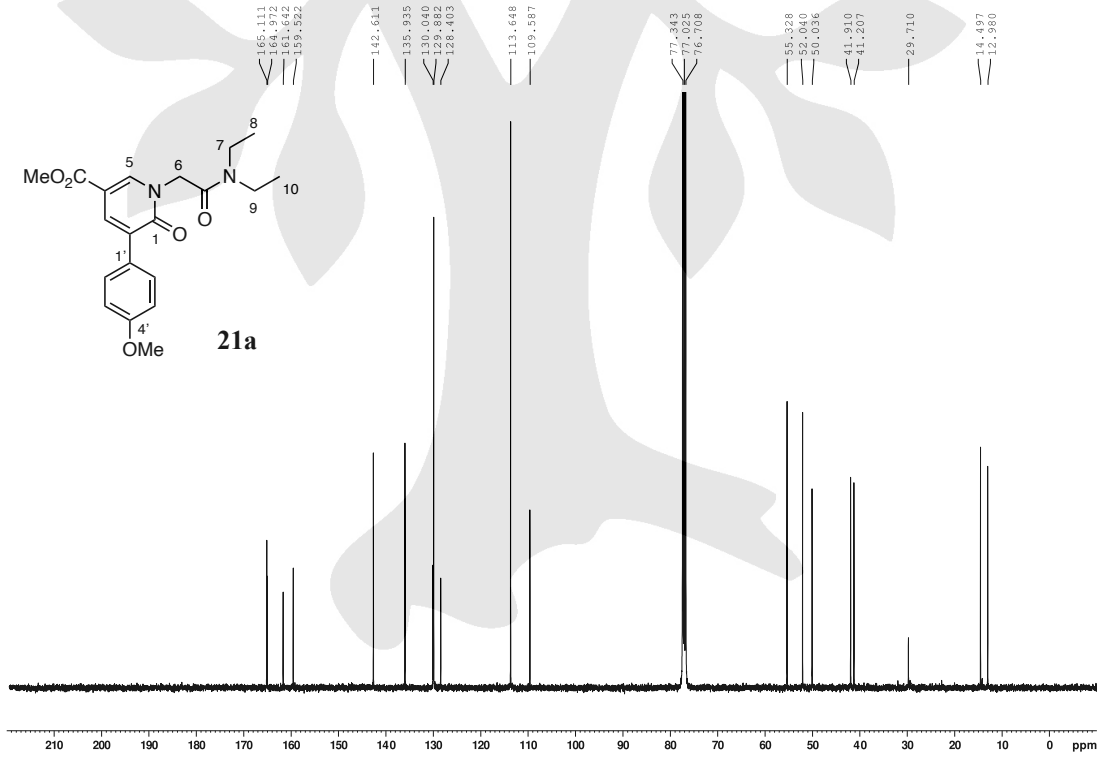

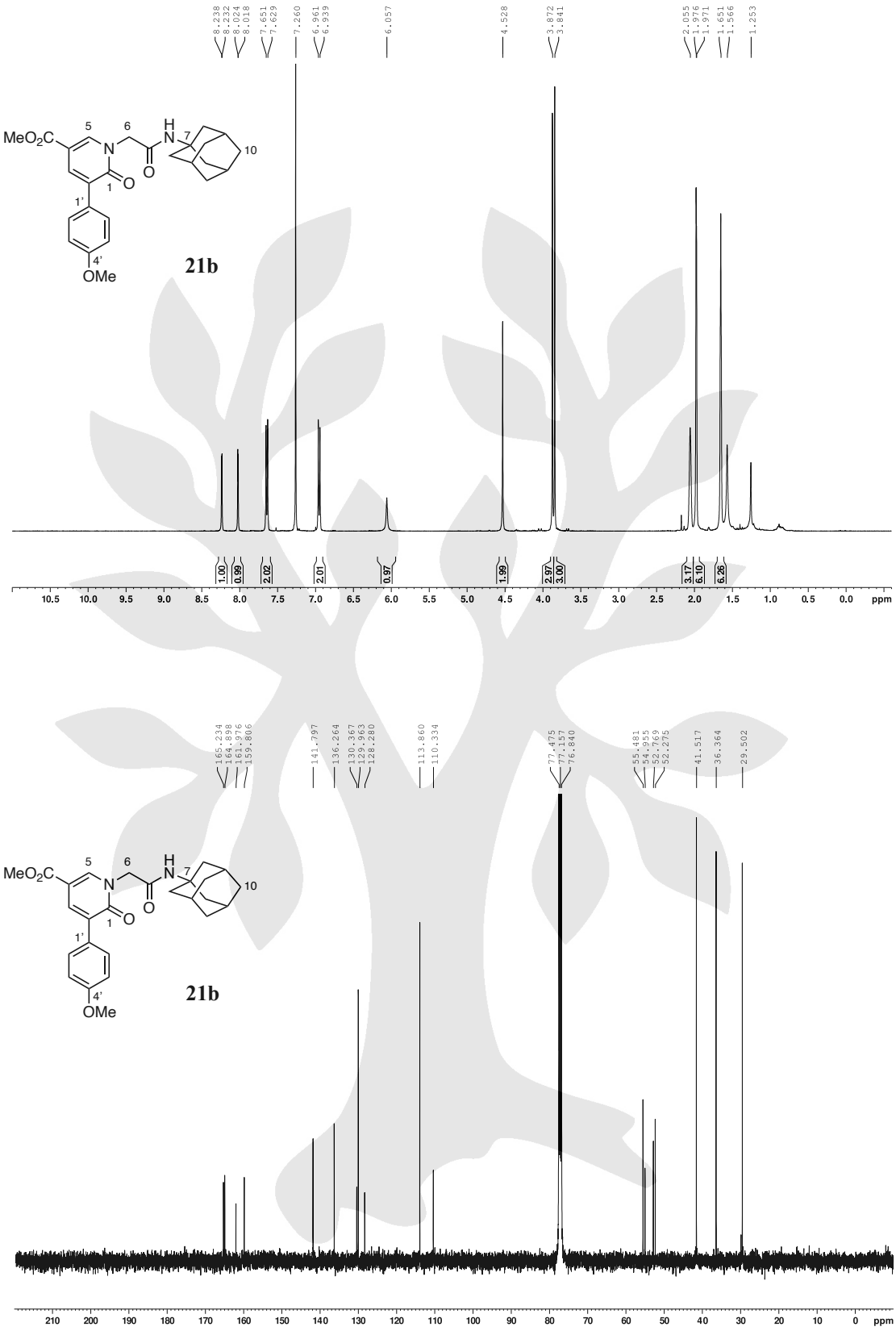

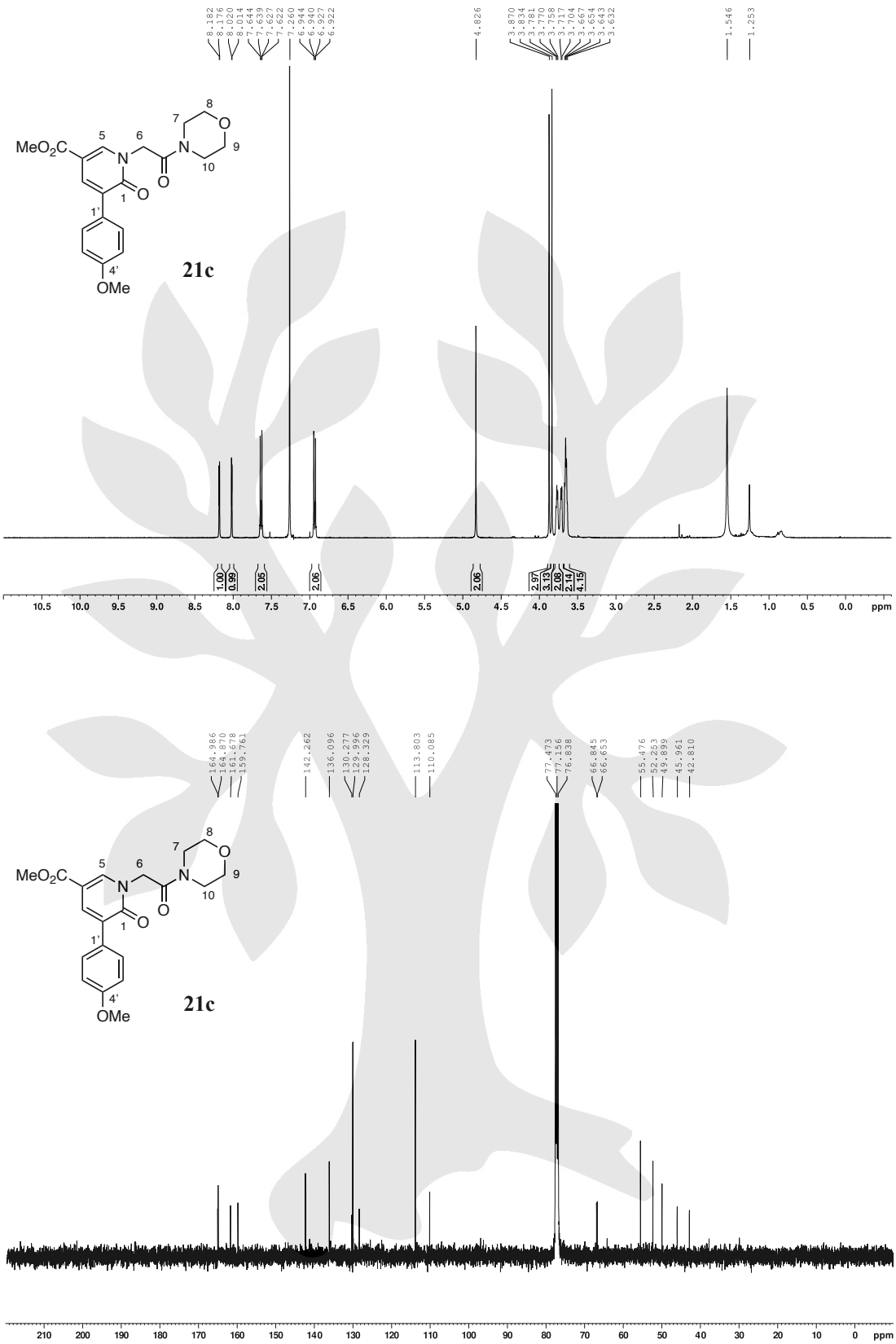

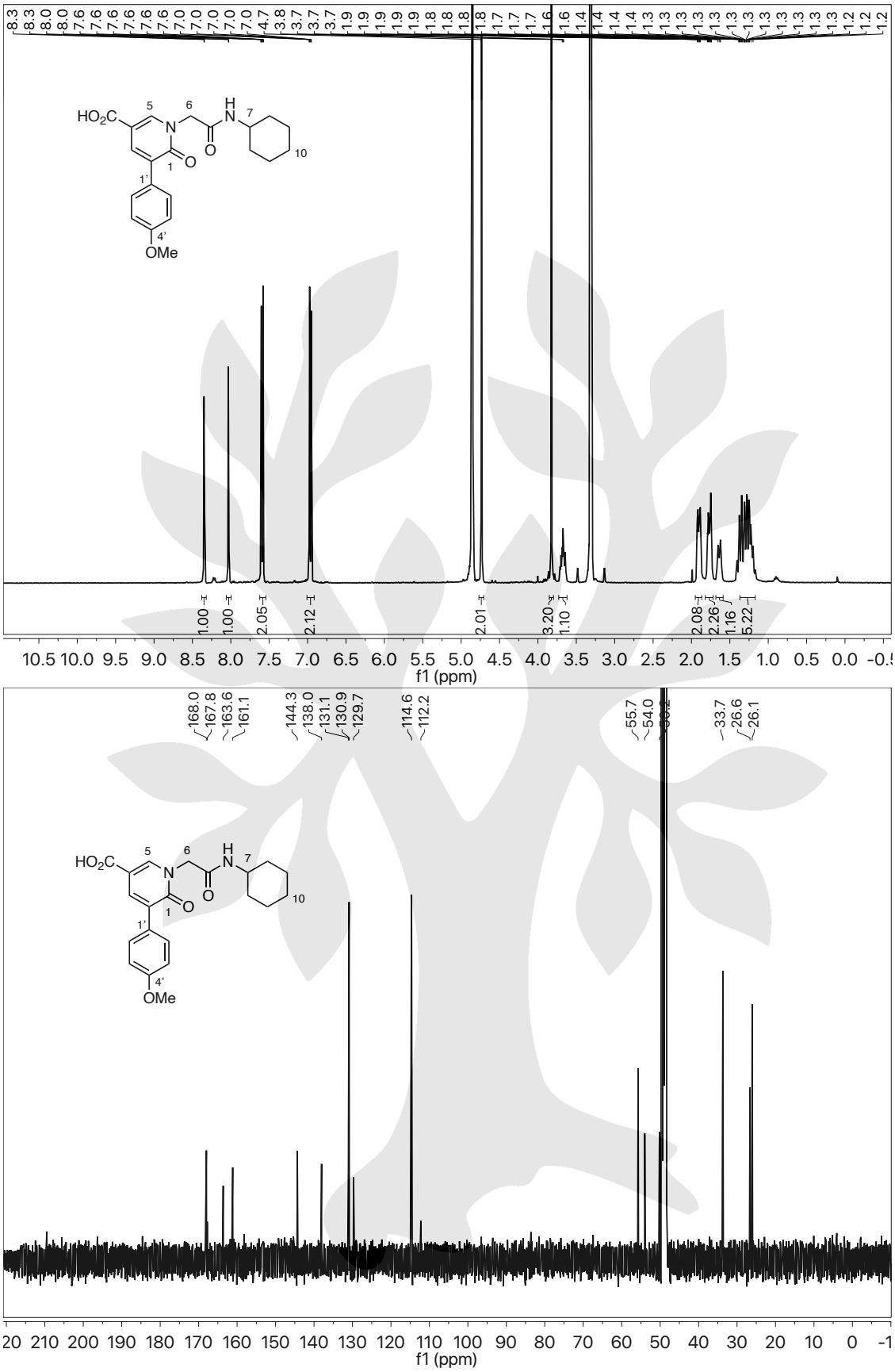

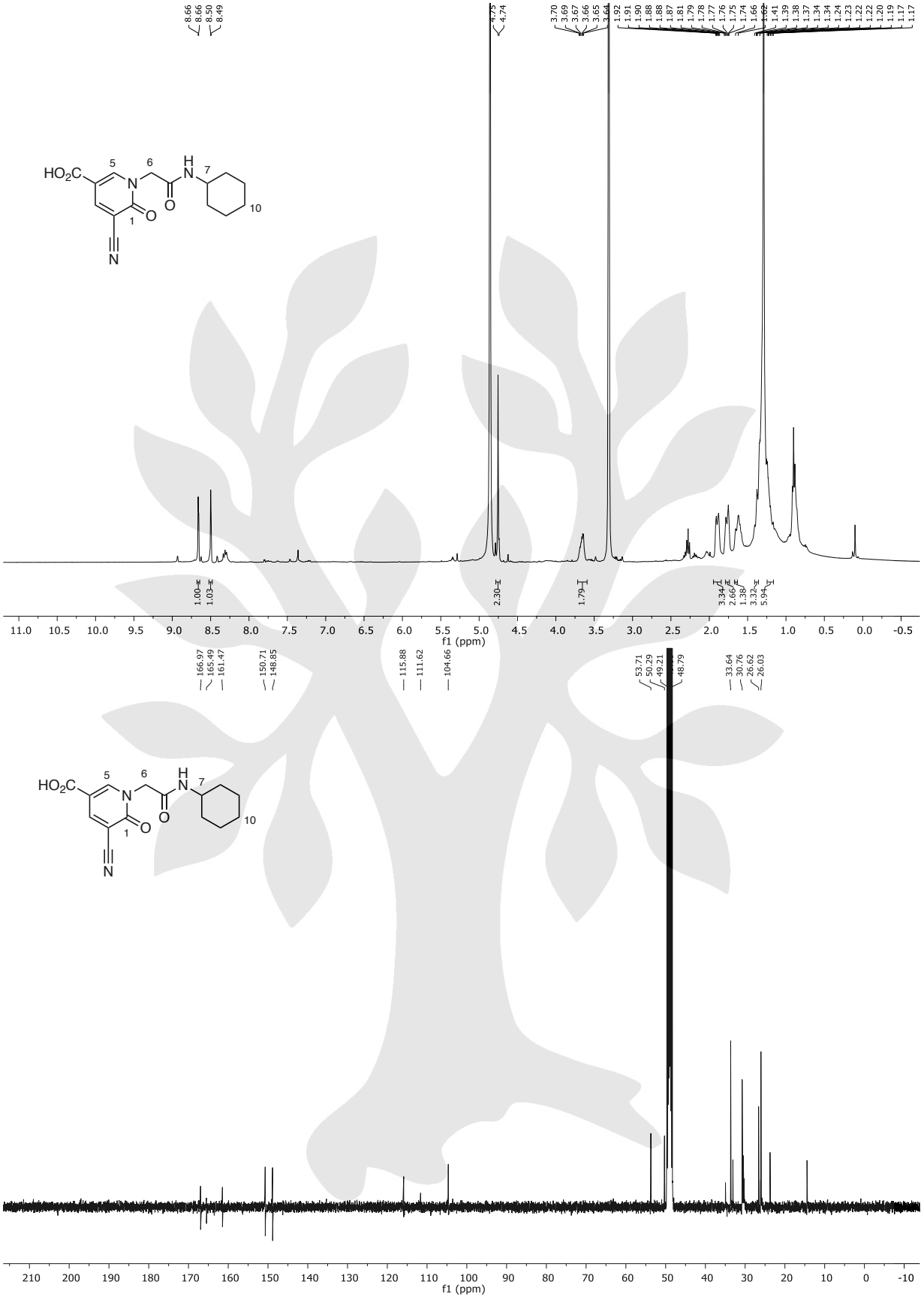

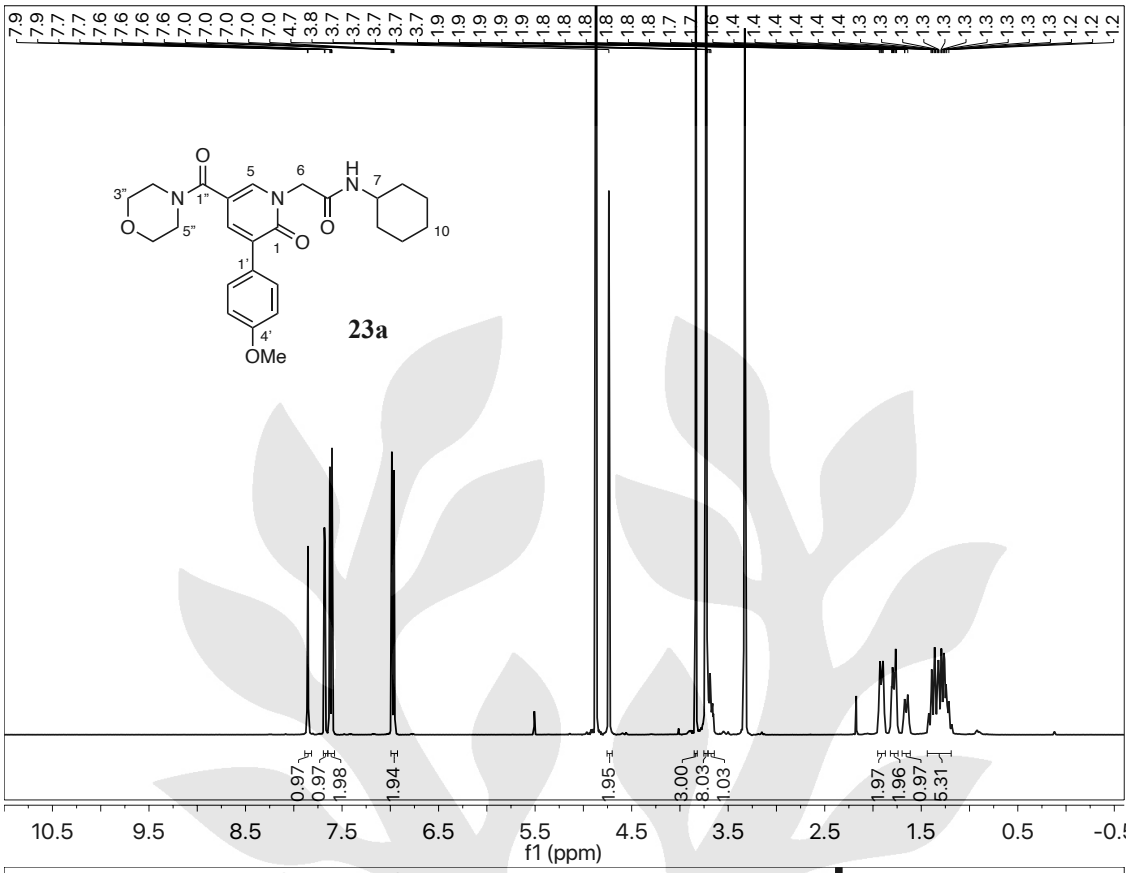

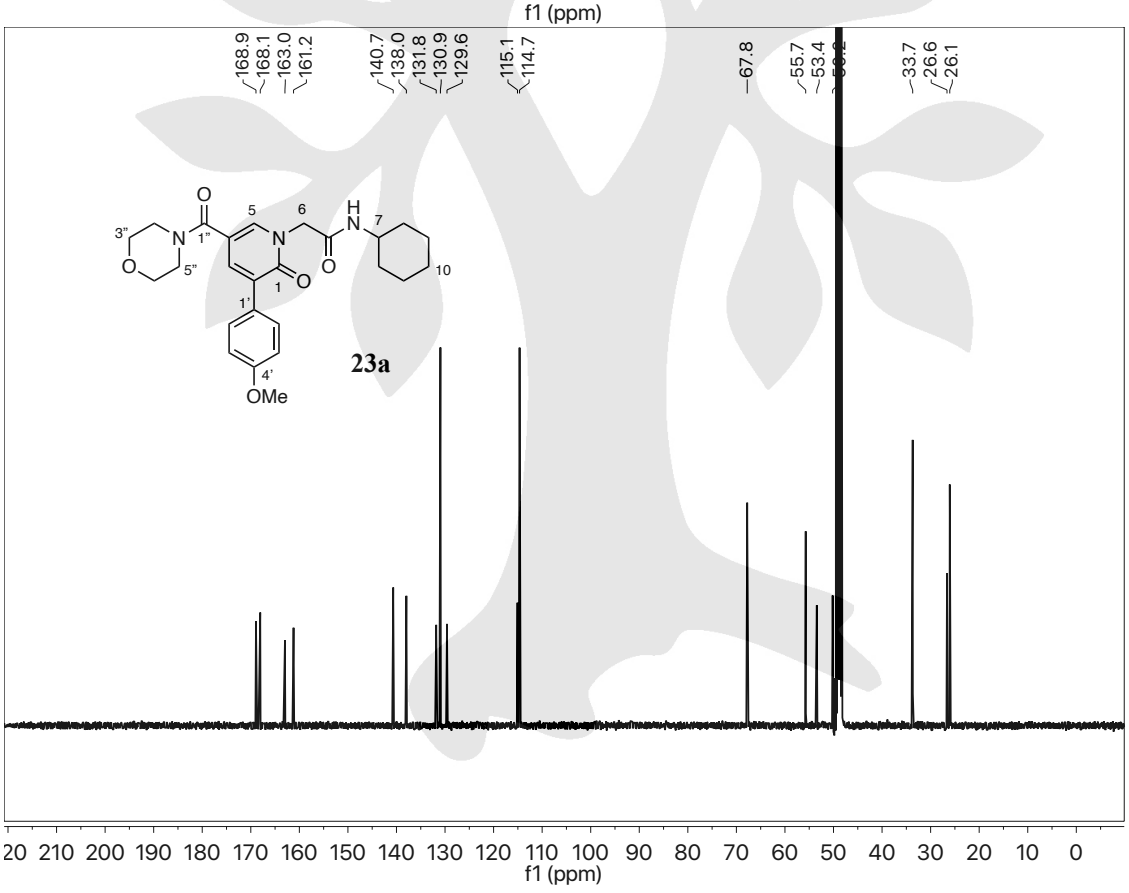

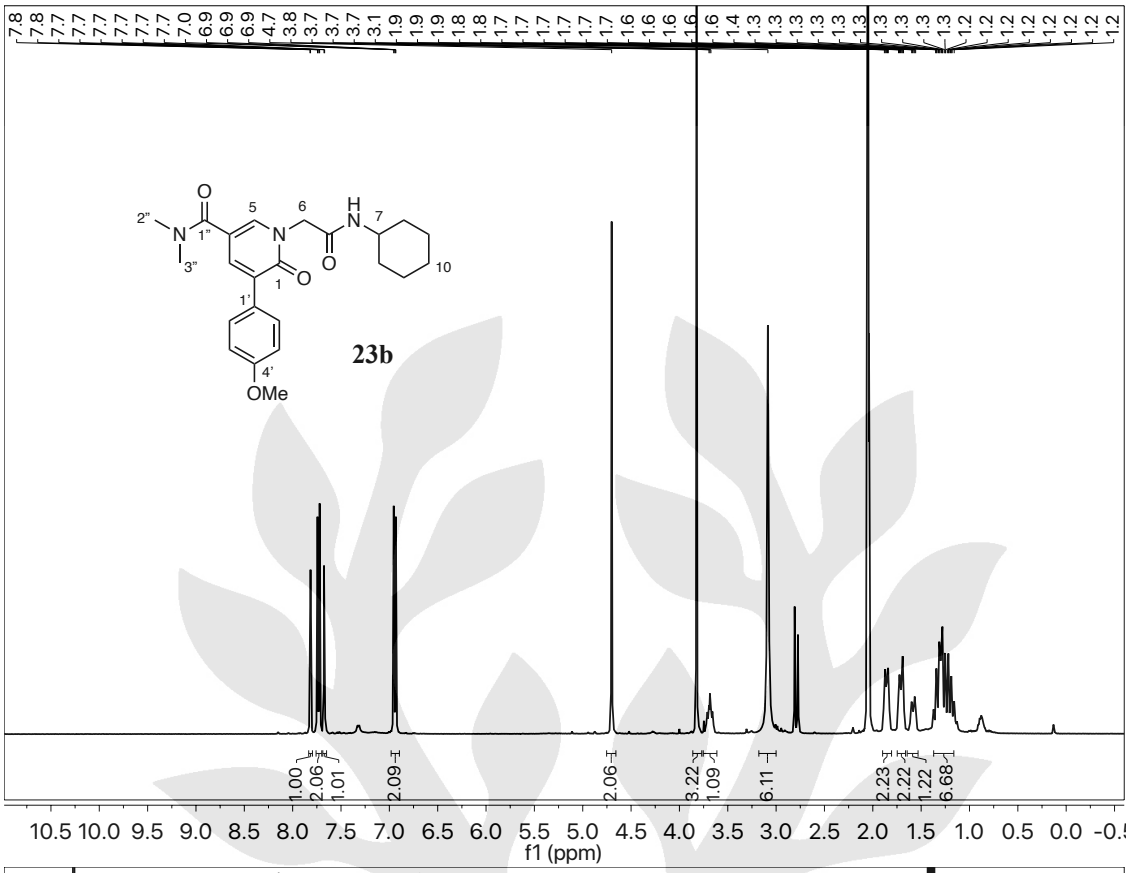

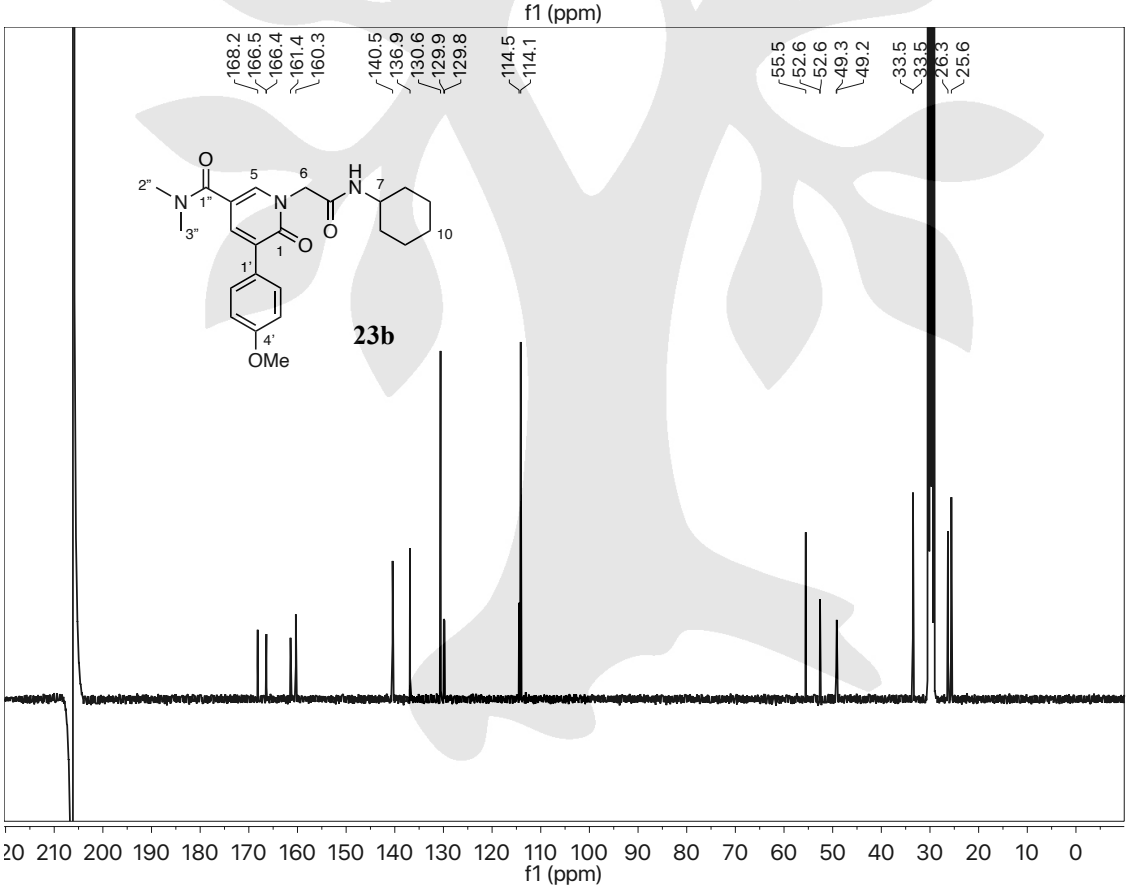

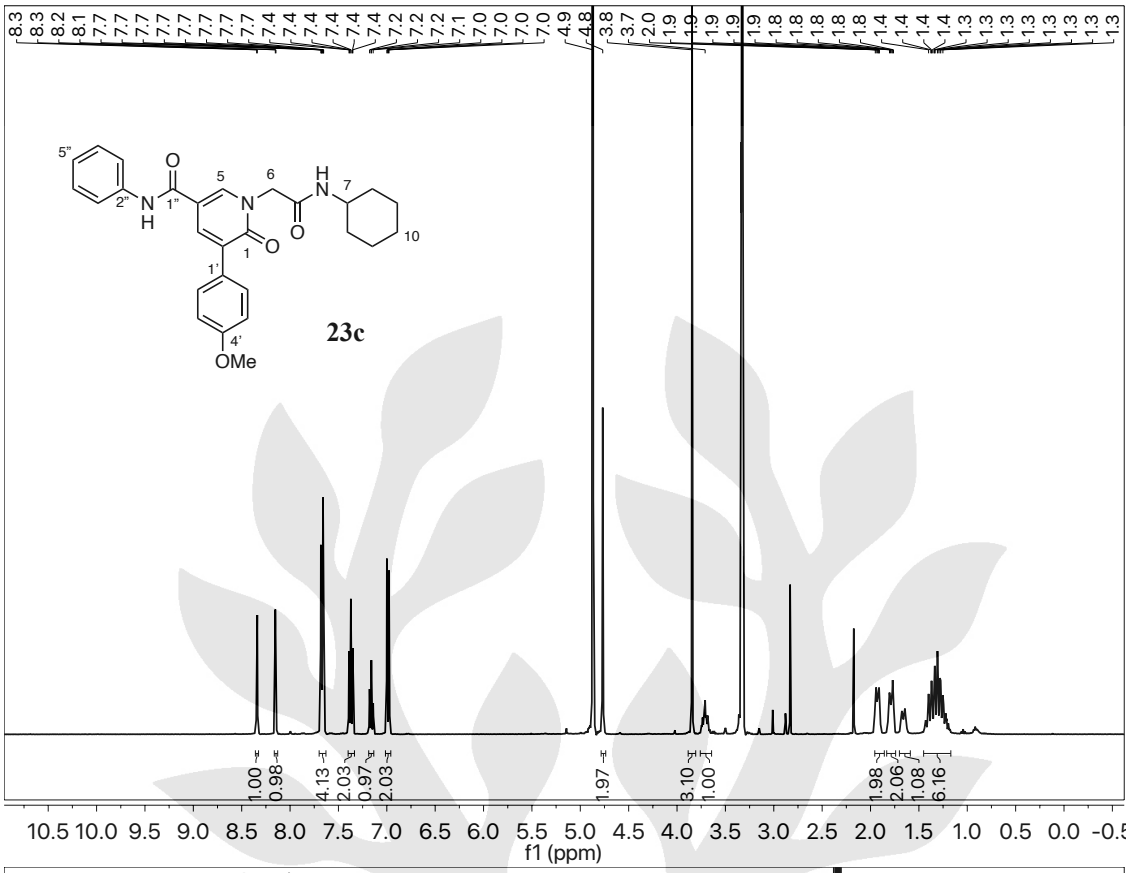

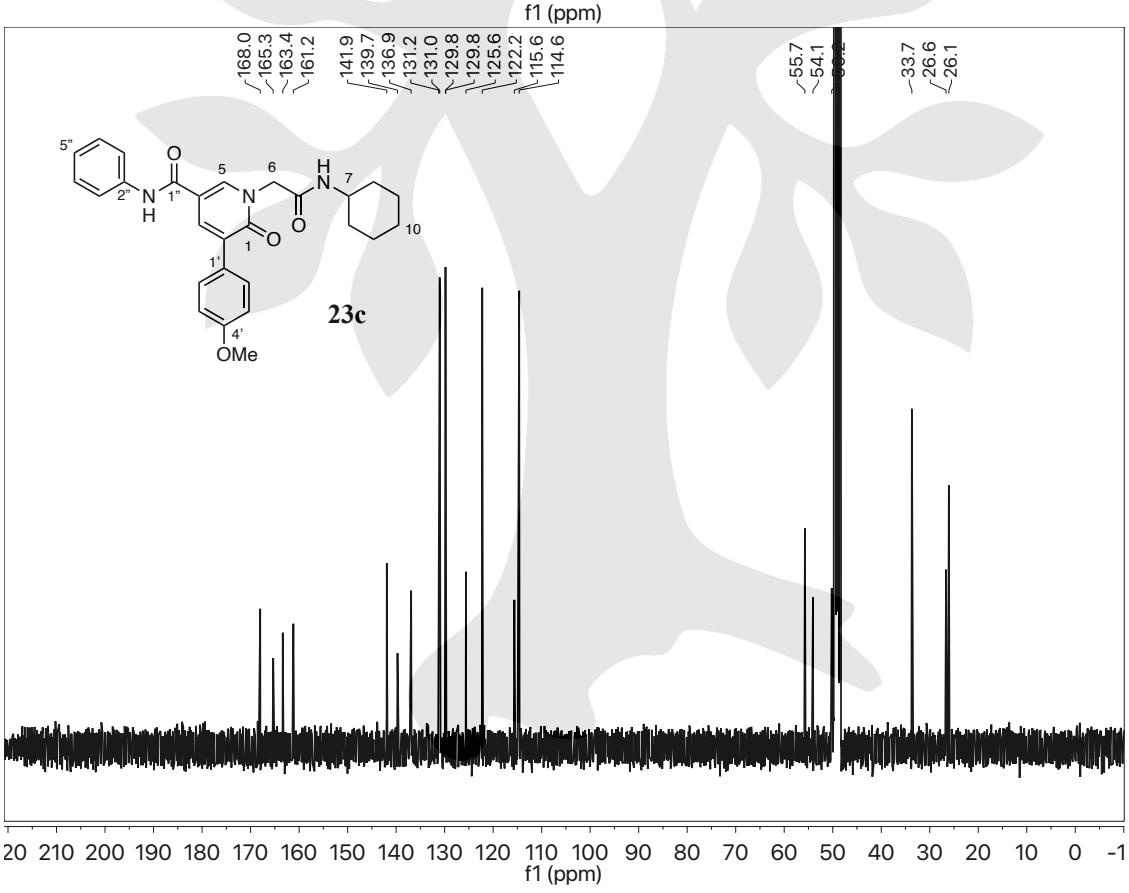

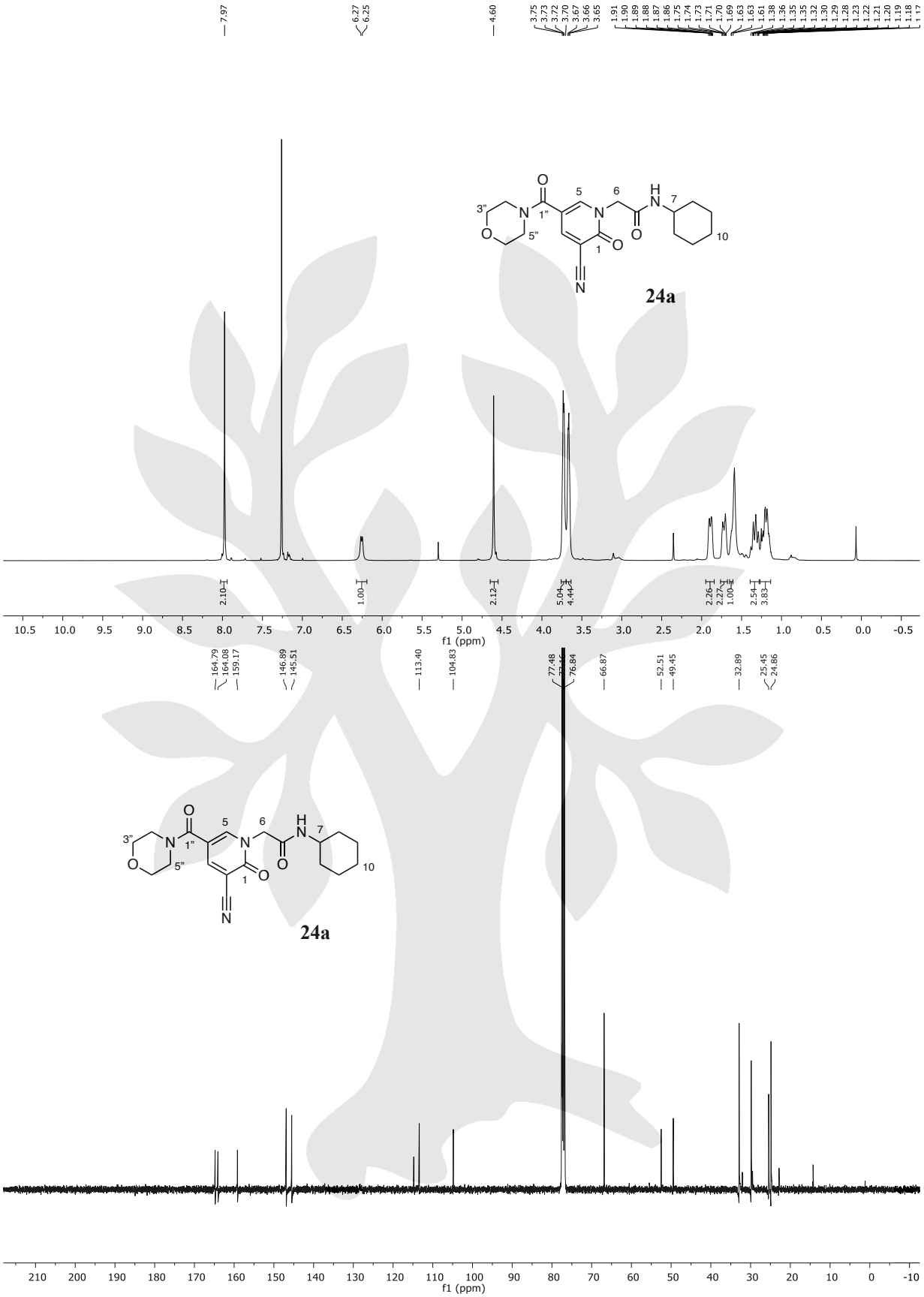

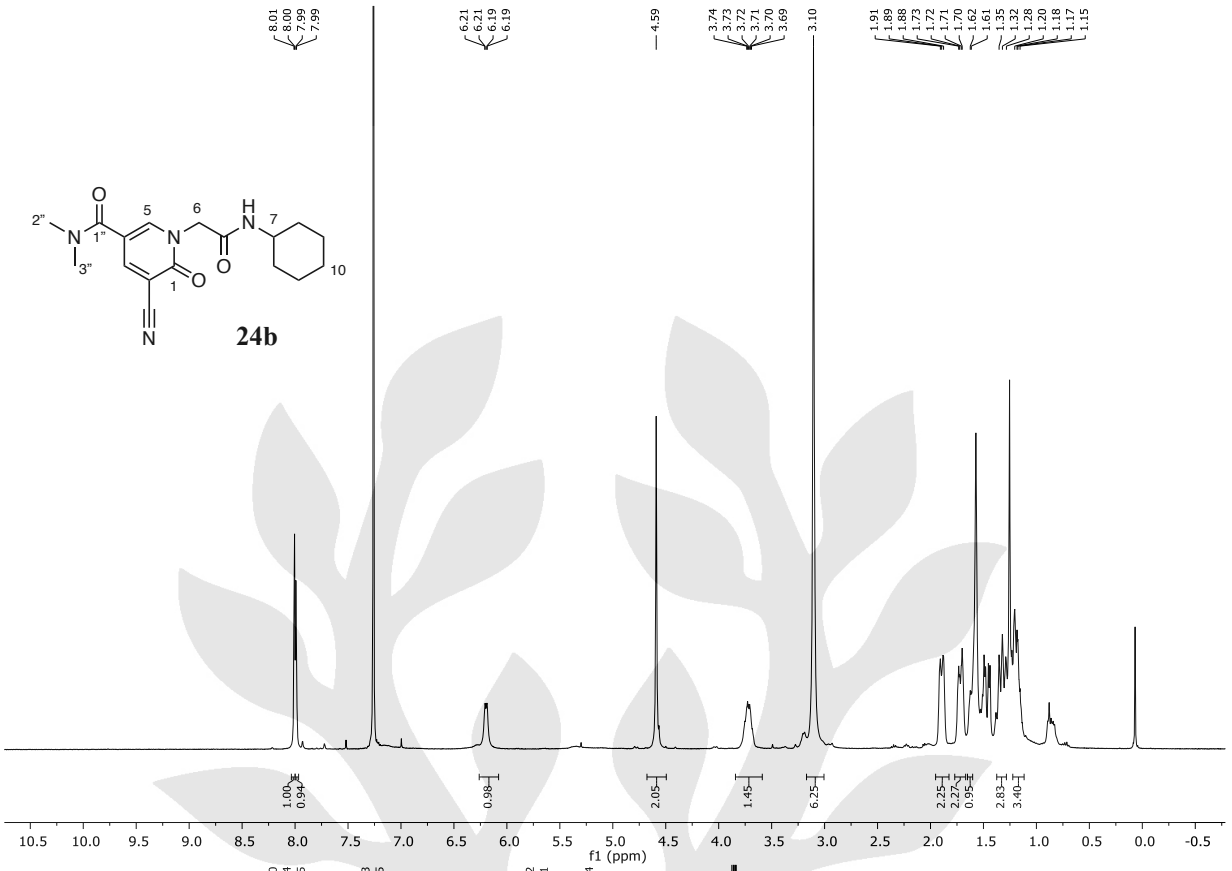

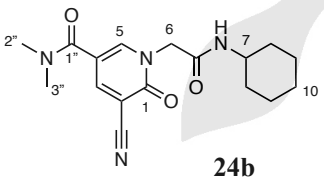

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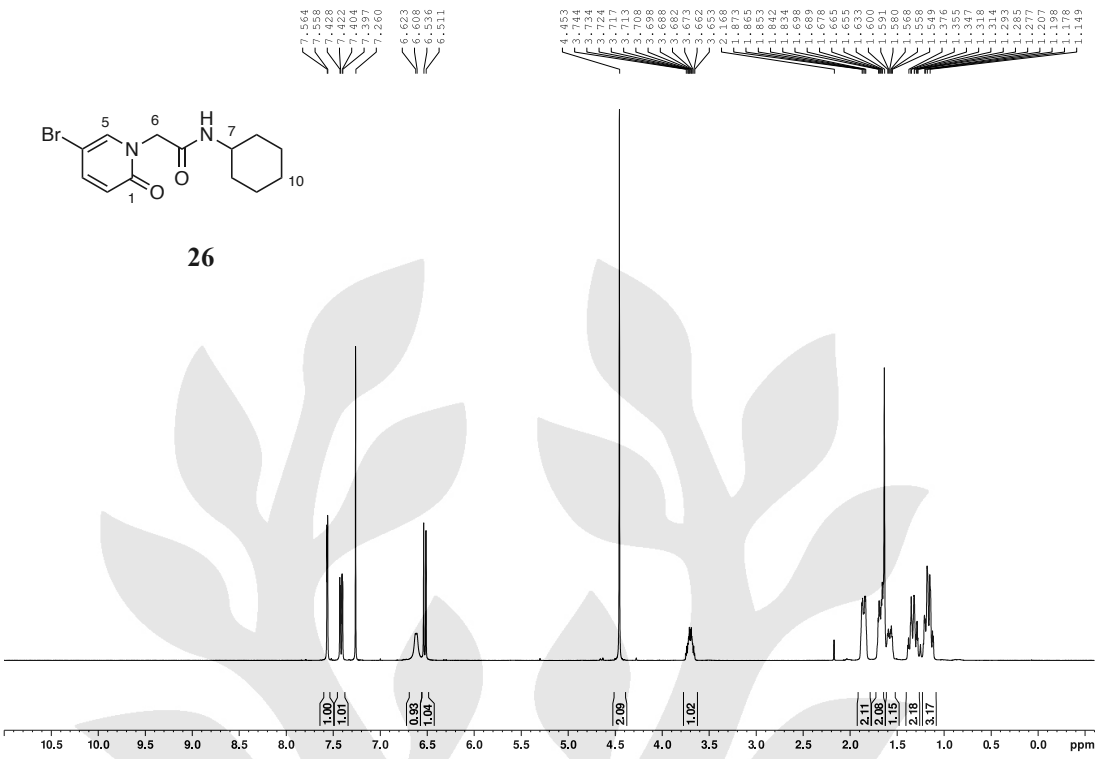

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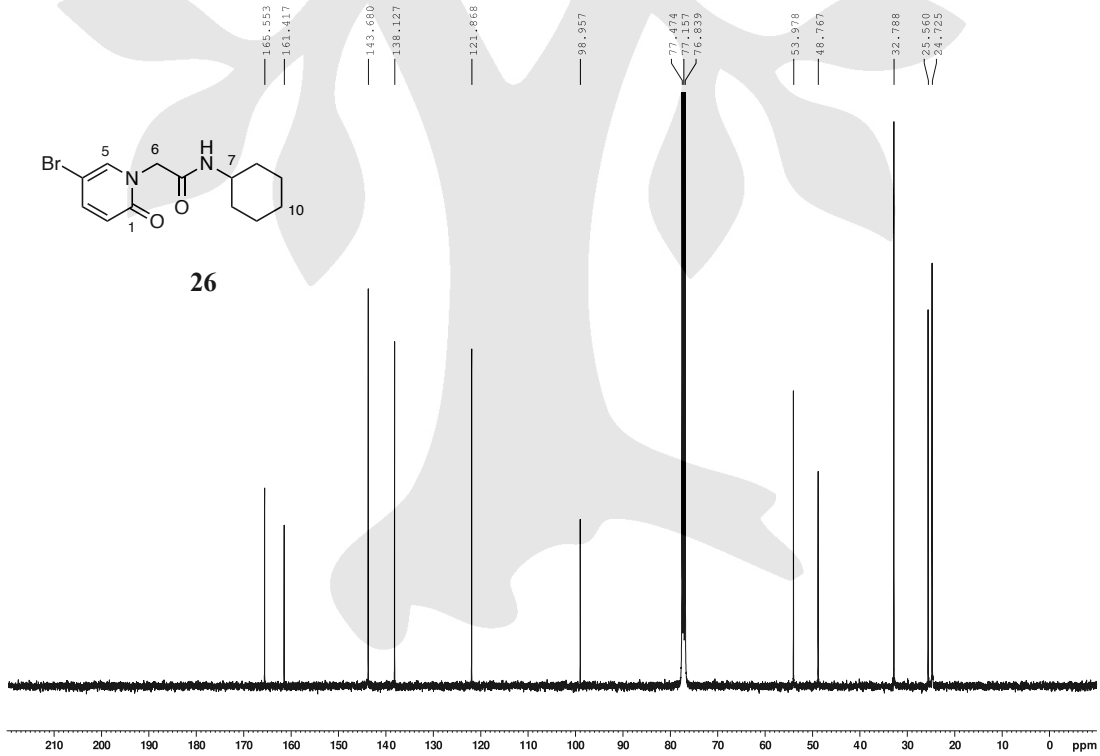

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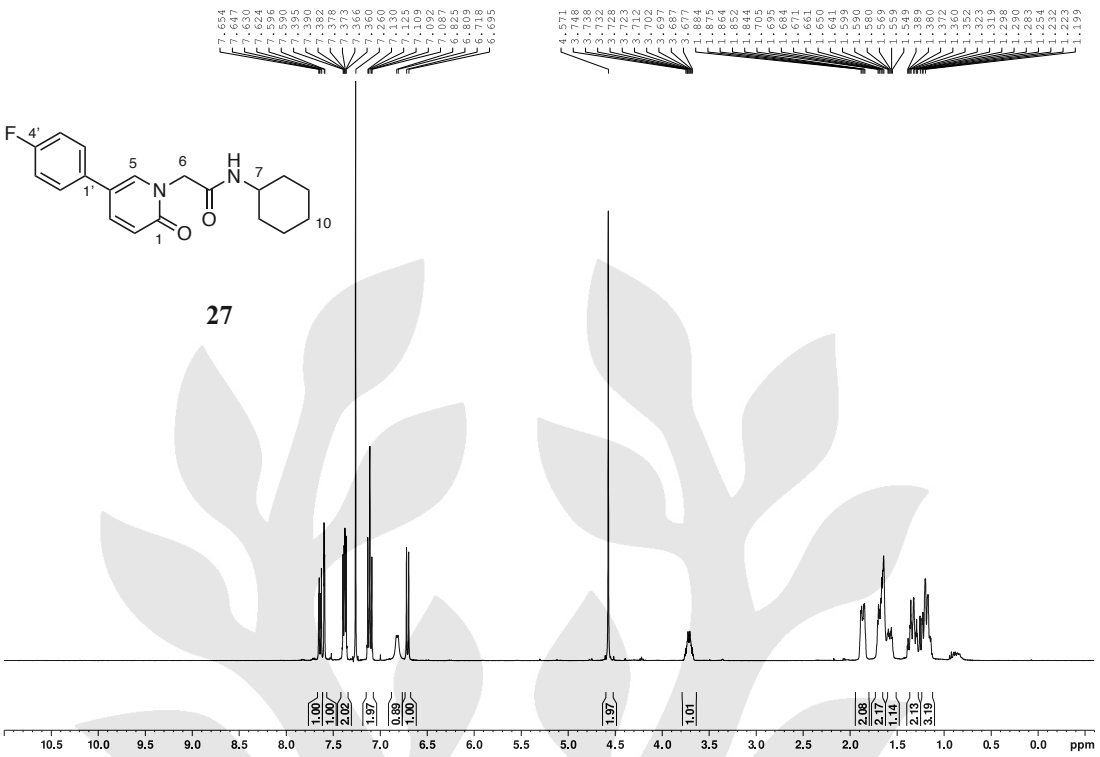

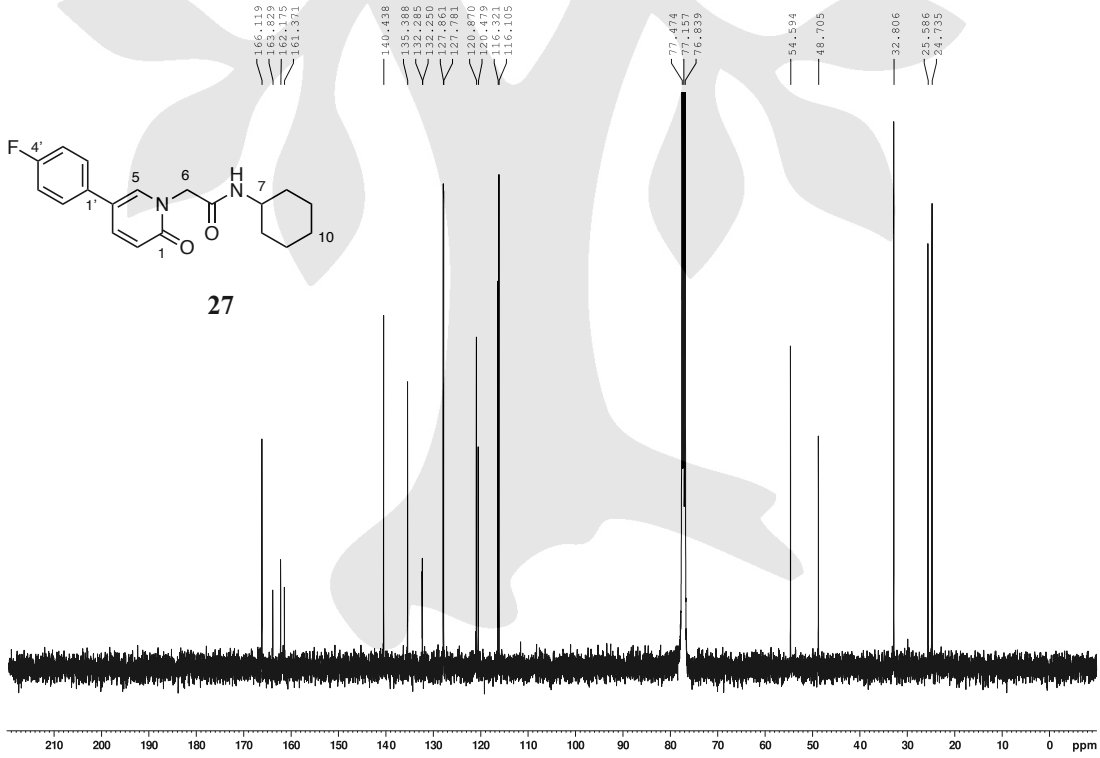

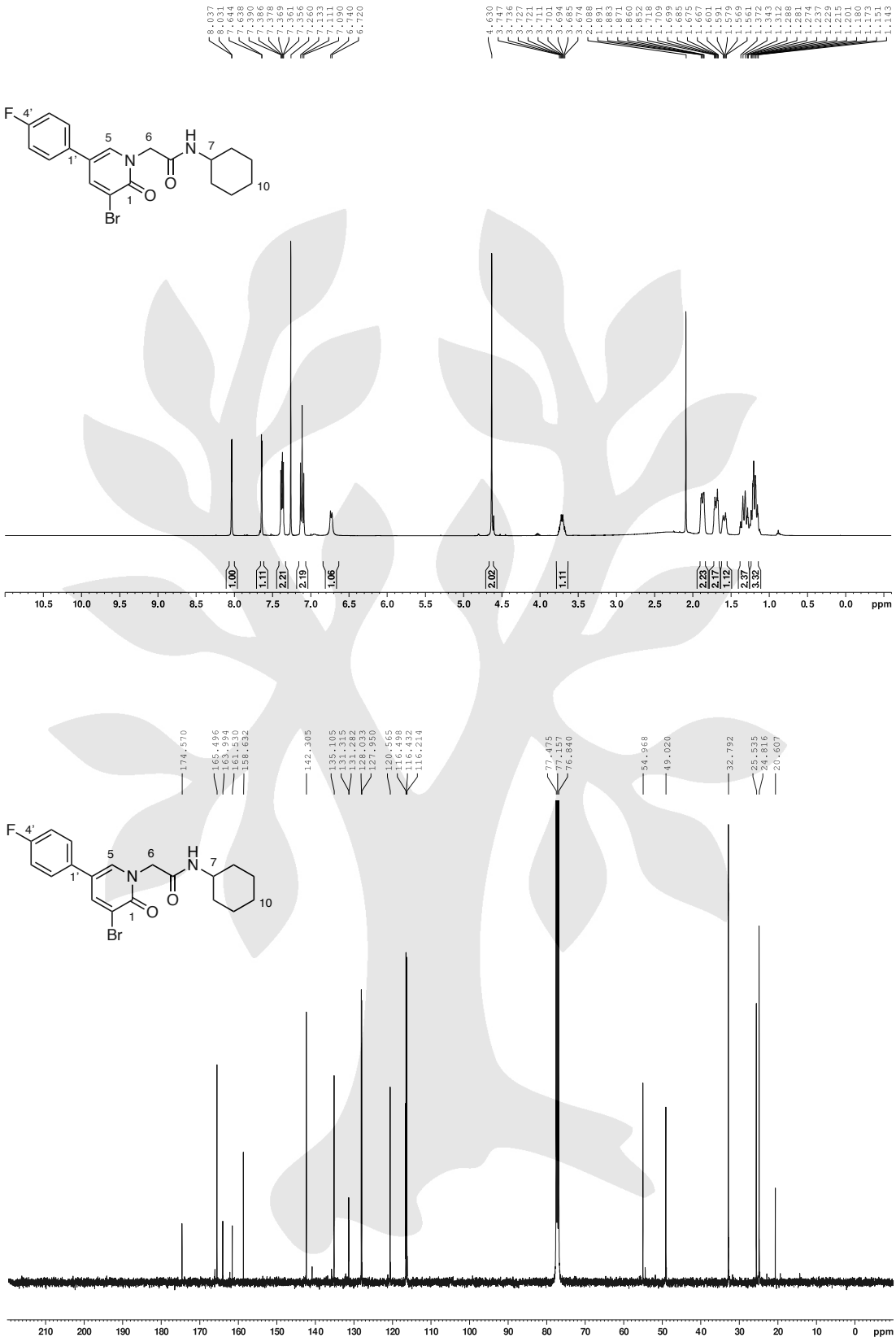

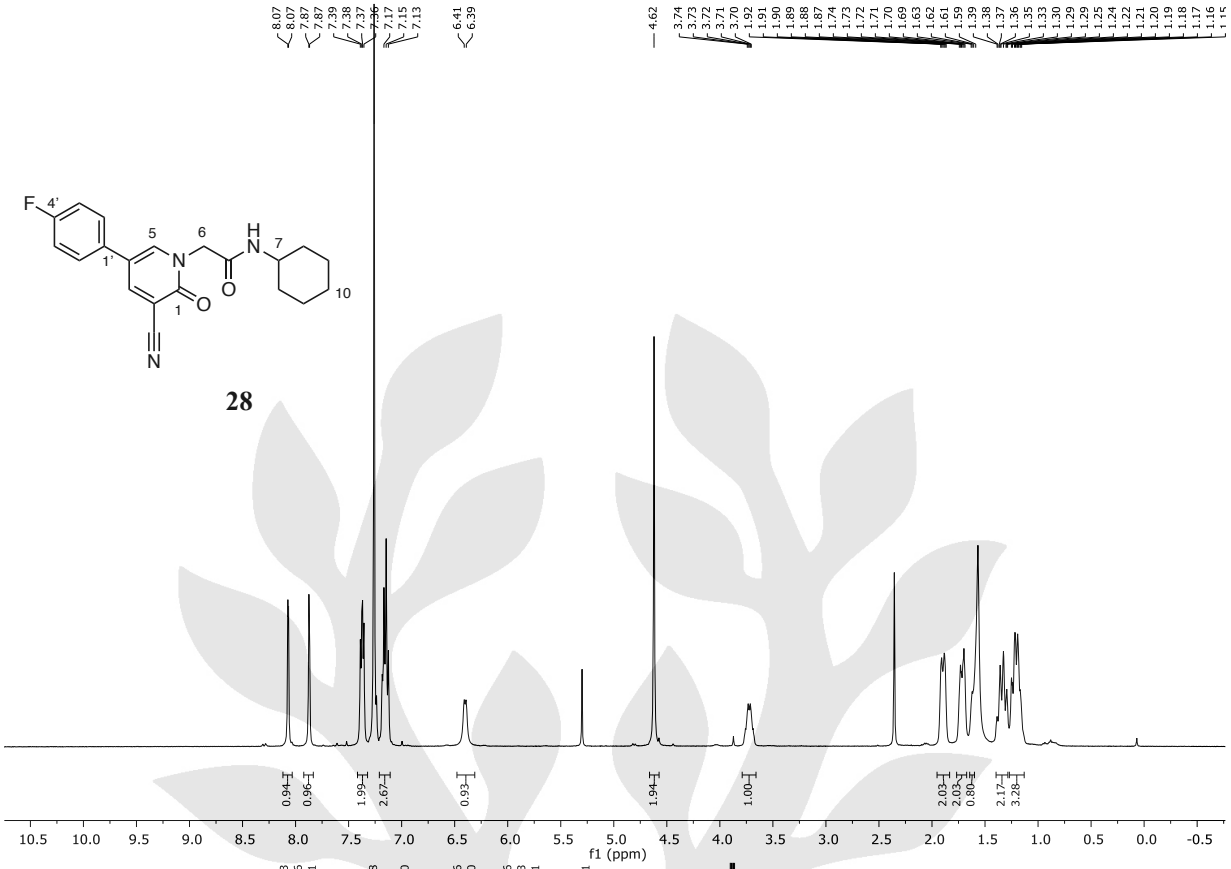

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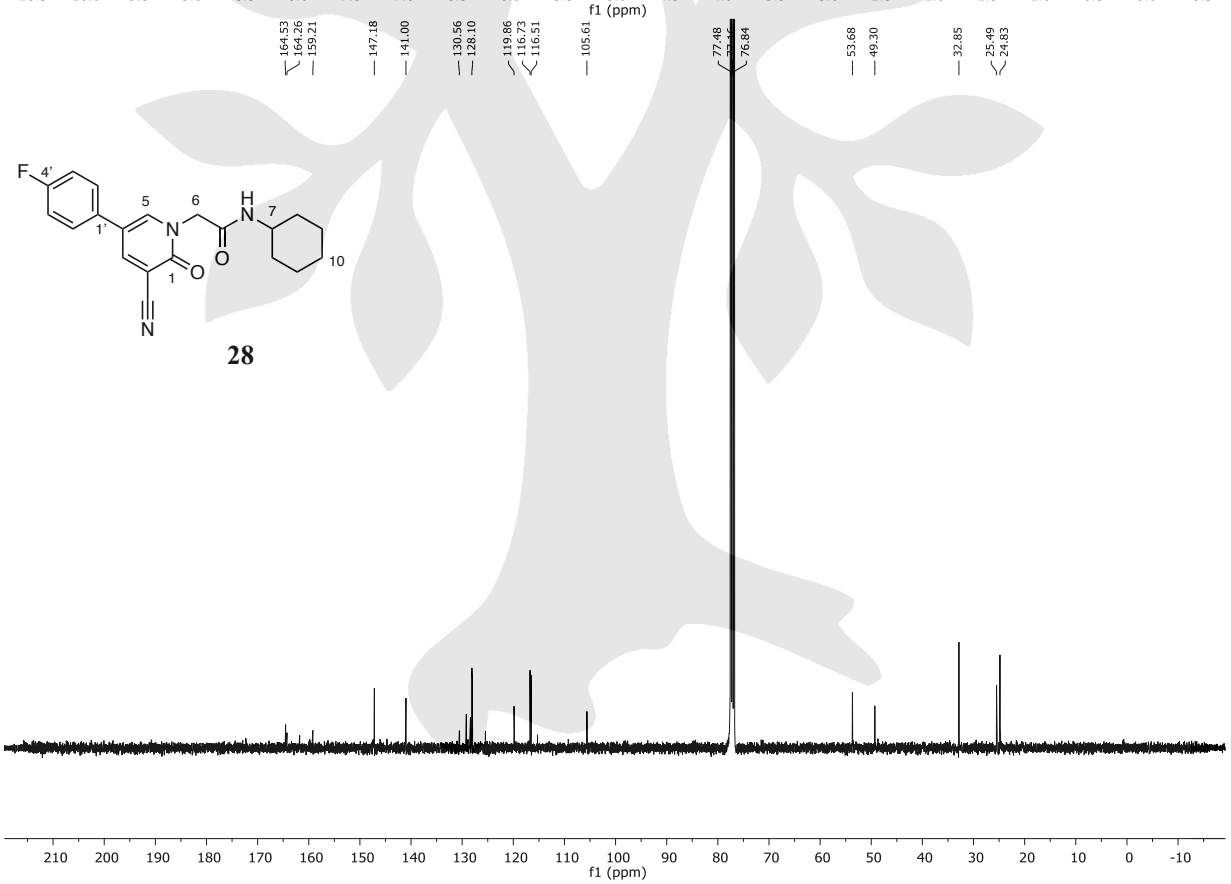
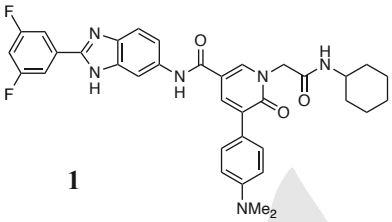


28

SARS-CoV-2 M^{Pro} Activity Assay:

The purification of the M^{Pro} protein and the activity assay were performed as previously published.[27]
The recorded dose response curves and the resulting IC_{50} values are reported below:



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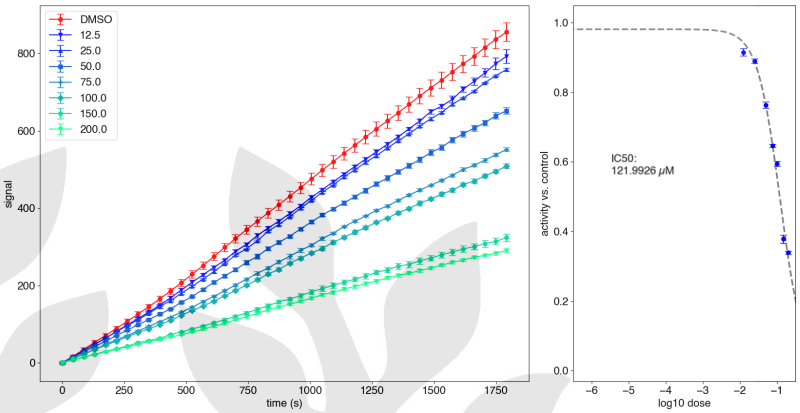

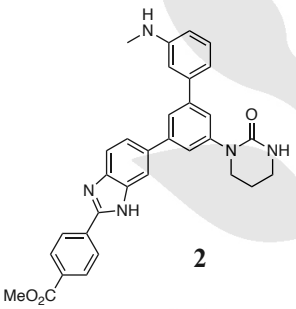

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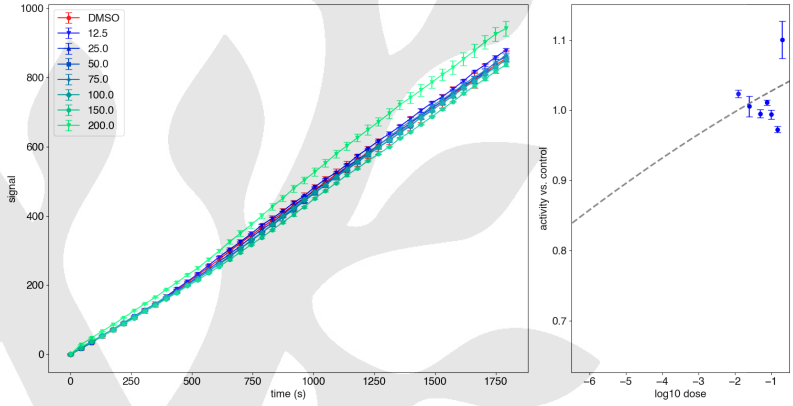

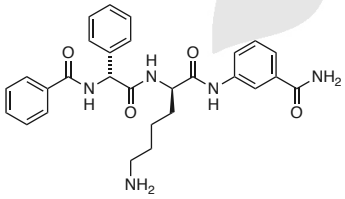

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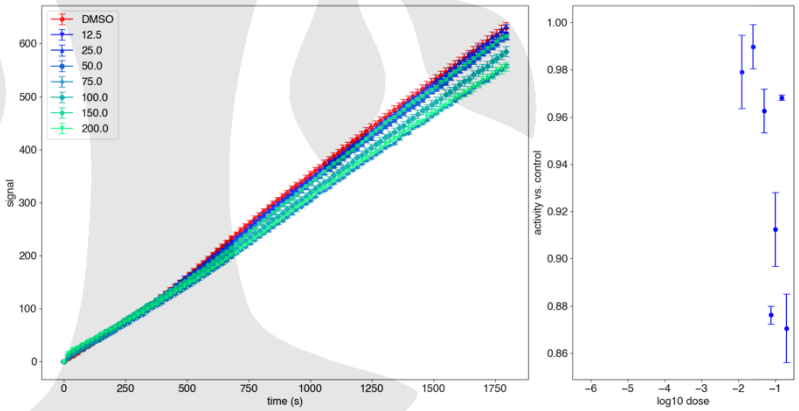

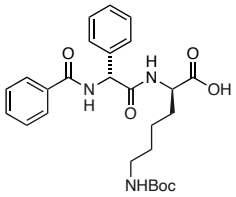

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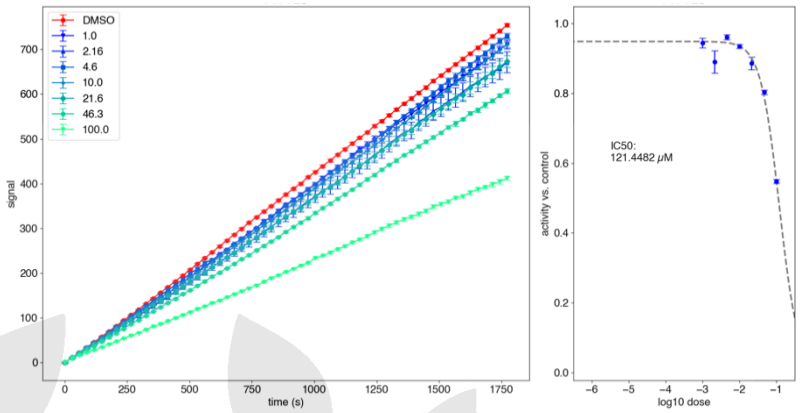

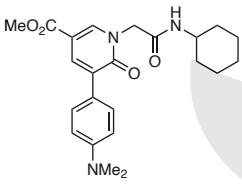

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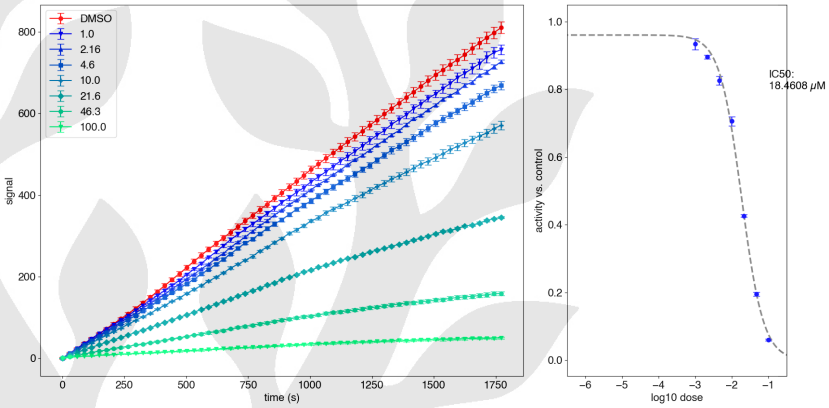

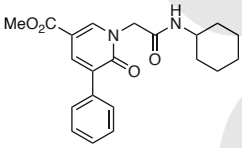

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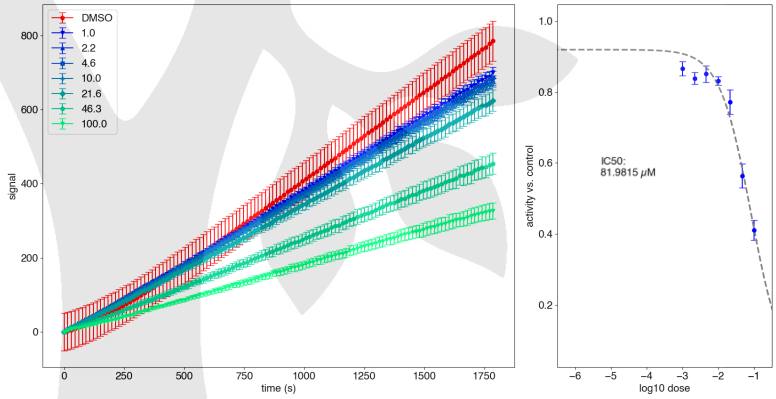

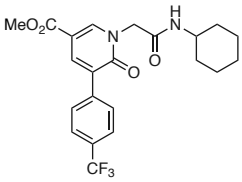

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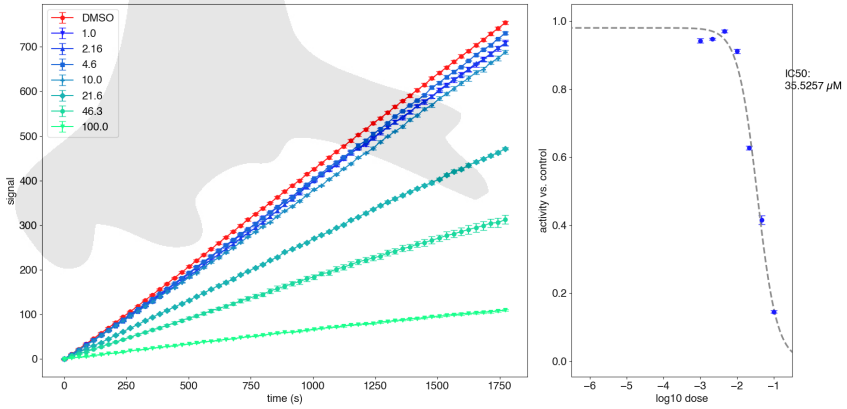

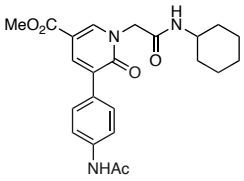

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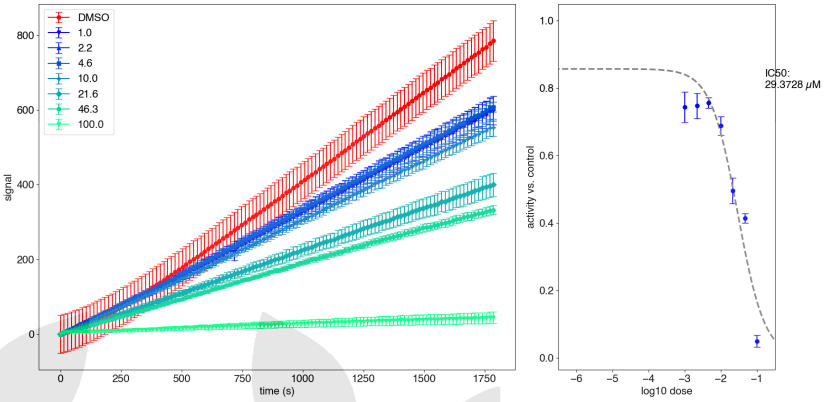

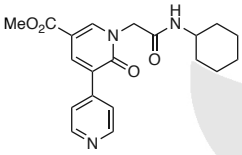

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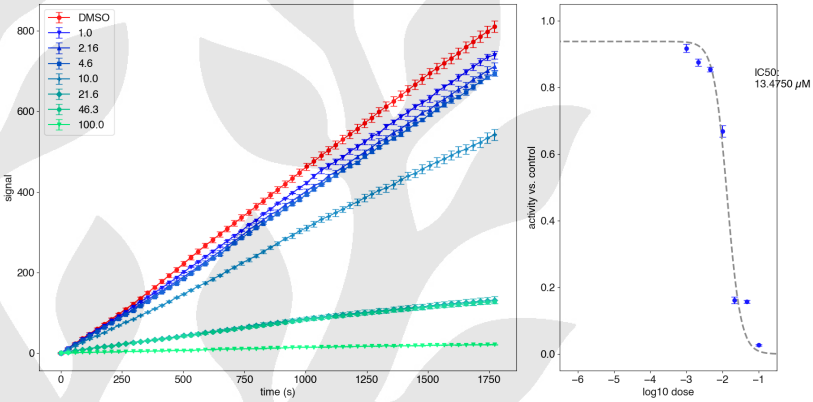

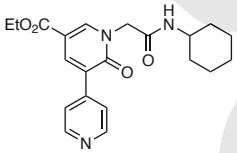

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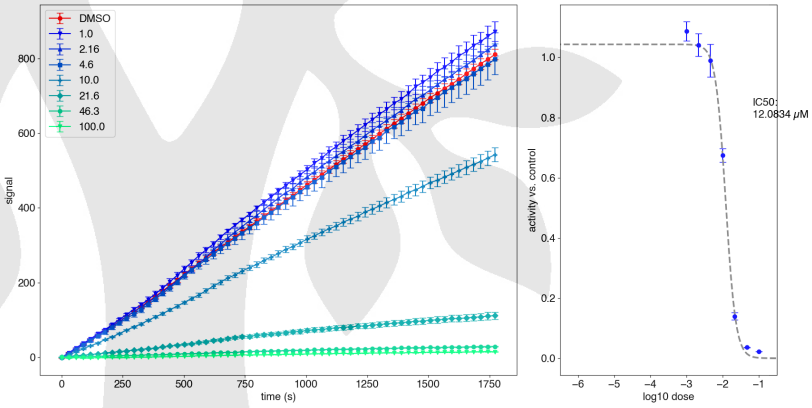

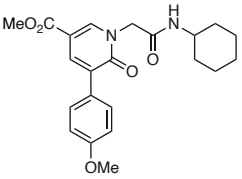

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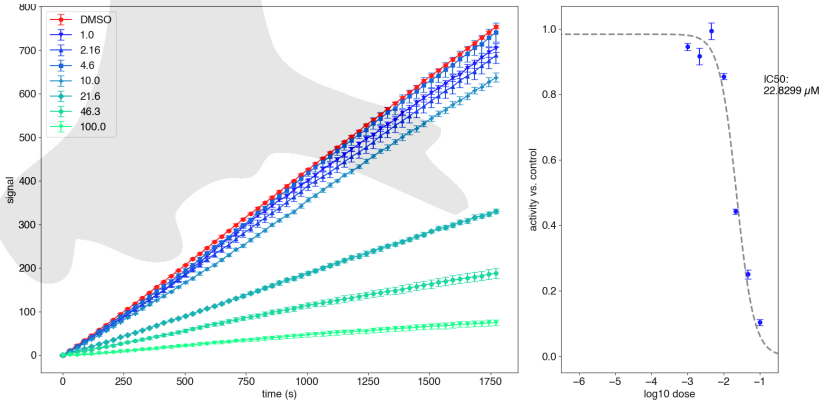

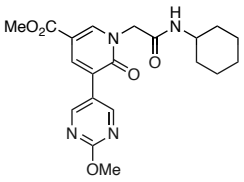

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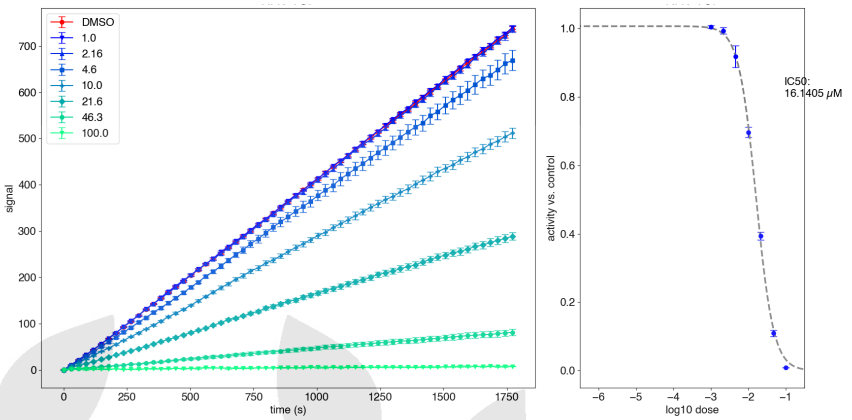

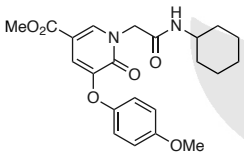

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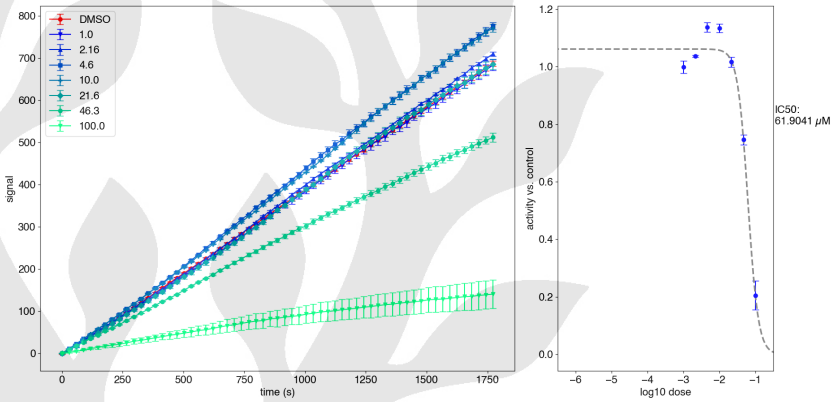

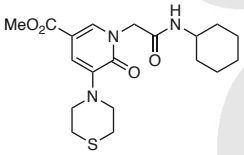

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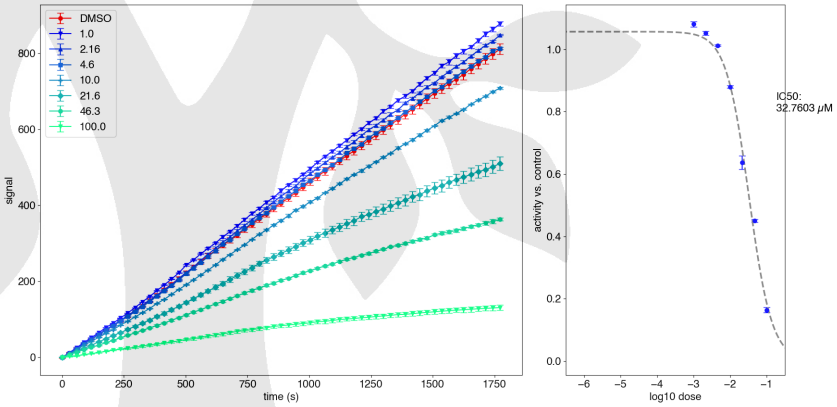

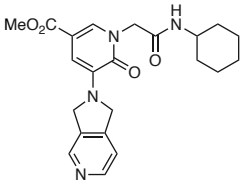

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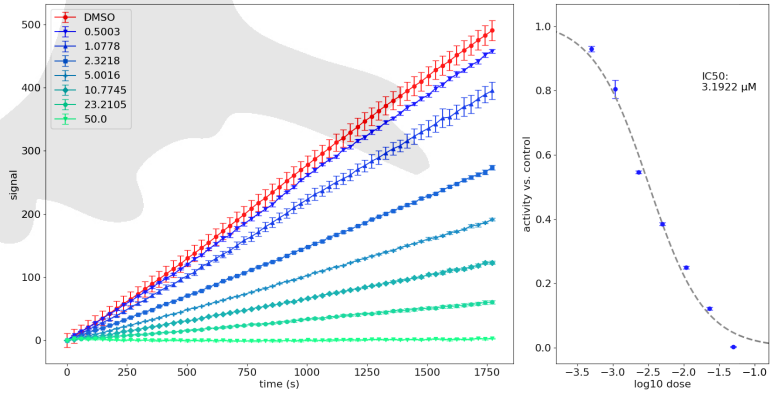

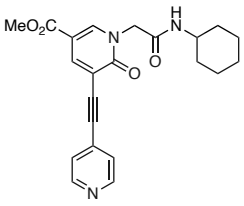

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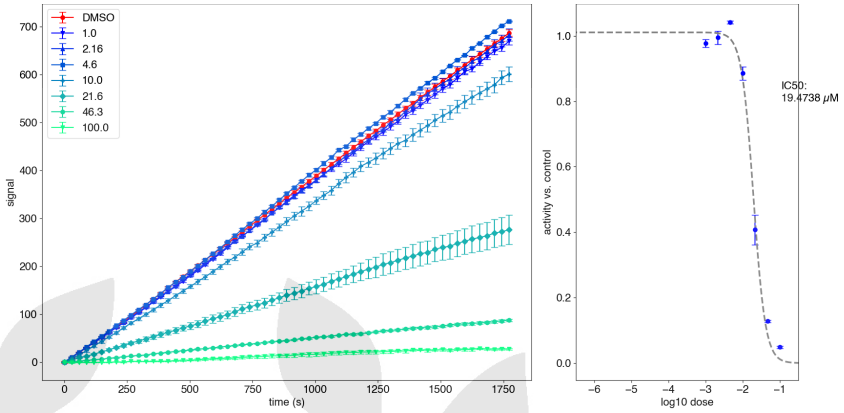

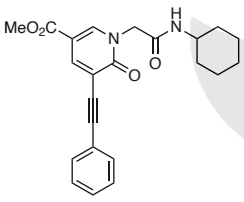

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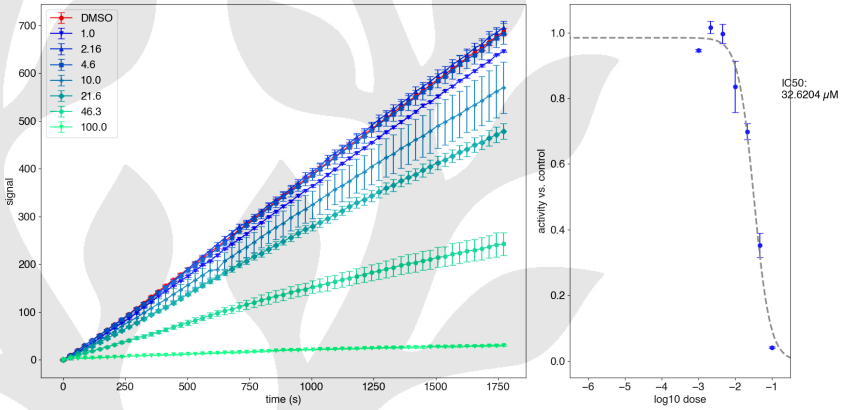

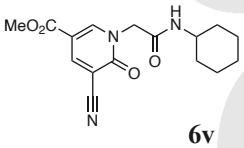

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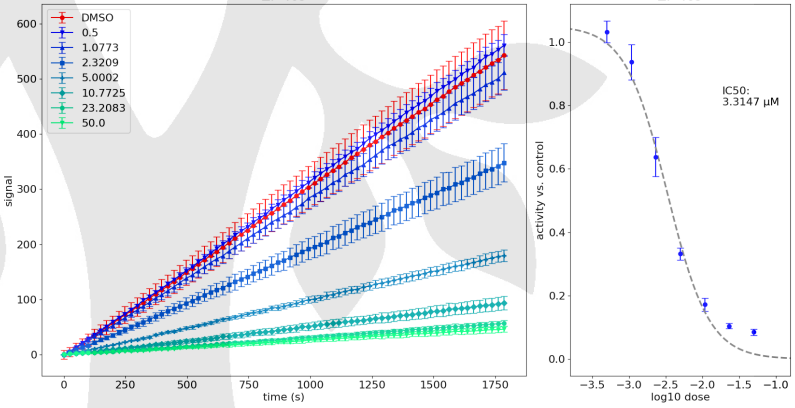

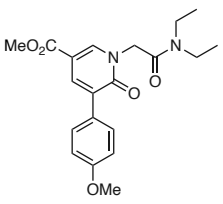

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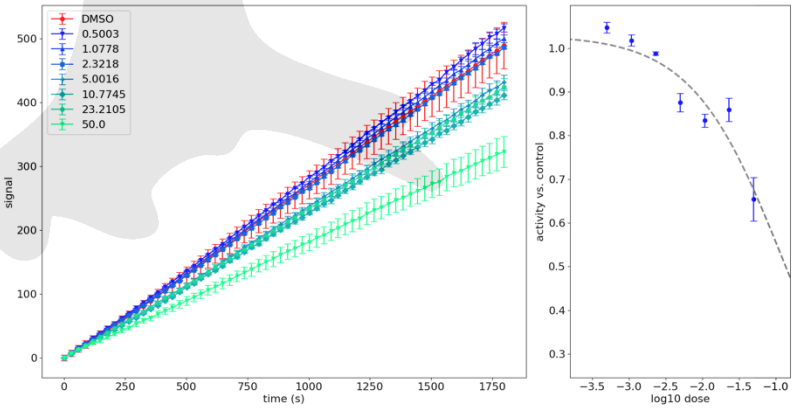

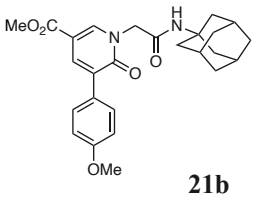

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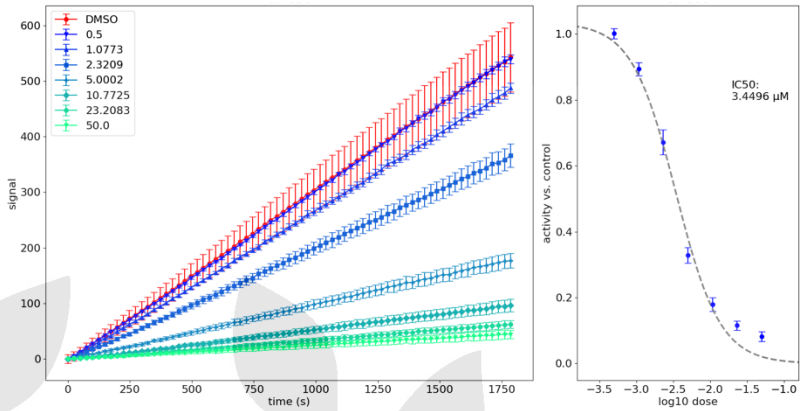

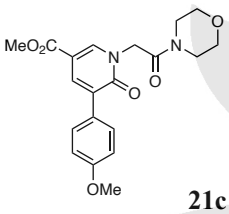

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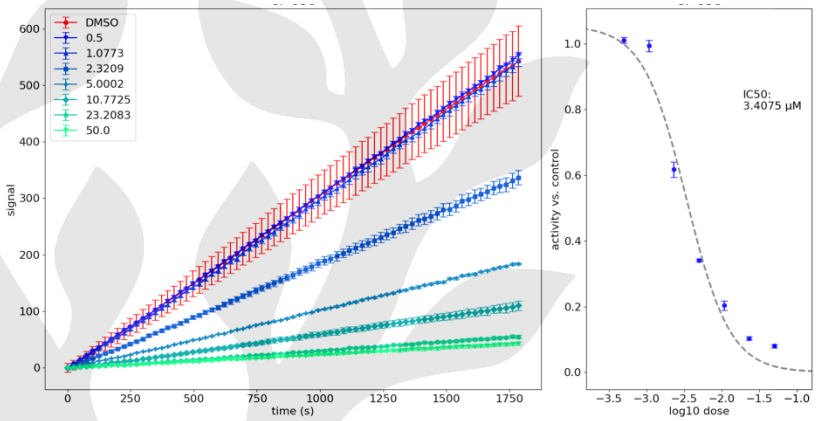

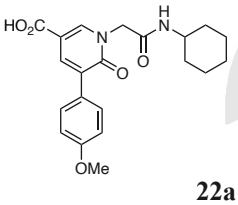

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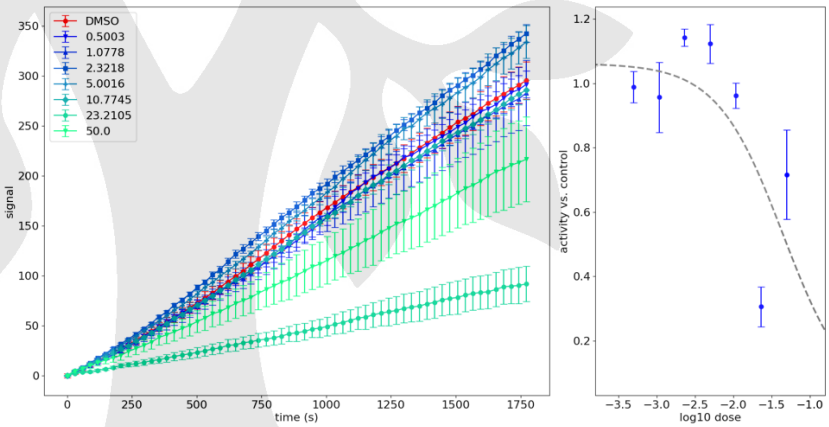

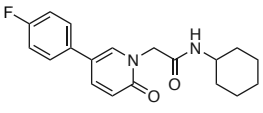

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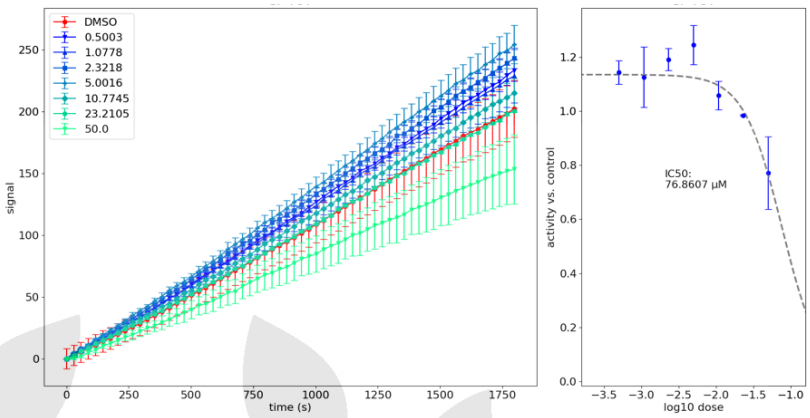

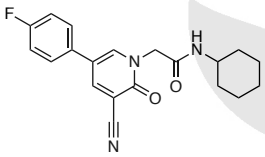

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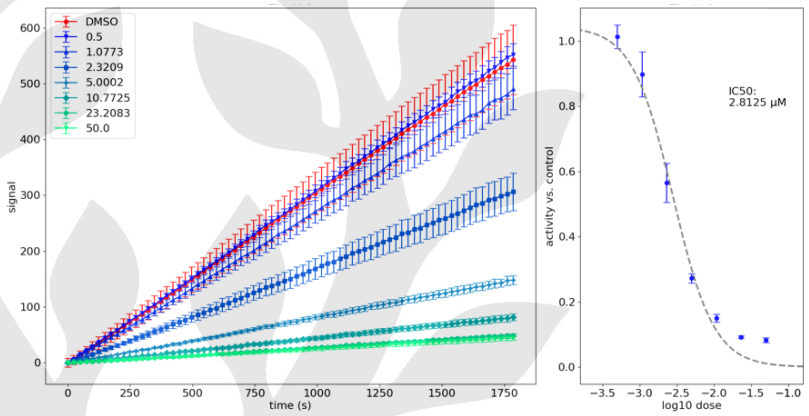

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