



Supporting Information

Transition Metal-Free, Visible Light-Mediated Radical Cyclisation of Malonyl Radicals onto 5-Ring Heteroaromatics

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1 Experimental Details

1.1 General Experimental Details

Solvents and reagents

All reactions were performed using flame-dried reaction vessels under an atmosphere of argon unless stated otherwise. Anhydrous diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), acetonitrile (MeCN), tetrahydrofuran (THF), and toluene (PhMe) were obtained from solvent dispenser units having been passed through an activated alumina column under argon. Methanol was dried over 4 Å molecular sieves under argon. Oxalyl chloride and pyrrole were distilled in an S-bend immediately before use. *N*-Bromosuccinimide was recrystallised from boiling water before use. All other chemical reagents used were commercially available from Alfa Aesar, Fluorochem and Sigma-Aldrich and used as supplied.

Chromatography

Thin layer chromatography (TLC) was carried out using Merck aluminium-backed TLC Silica Gel 60 F254 pre-coated plates (particle size 0.2 mm). Plates were visualised by the quenching of fluorescence under ultraviolet light ($\lambda_{\text{max}} = 254$ nm) and by staining and heating with KMnO_4 or vanillin. Flash column chromatography was performed using Merck Geduran 60 silica gel (particle size 40–63 μm) with the solvent system given. All solvents used for chromatography purification were HPLC grade or equivalent and supplied by Sigma Aldrich.

NMR spectroscopy

^1H NMR and ^{13}C NMR spectra were recorded on Bruker AVIII HD 400 nanobay (400/101/377 MHz) and Bruker AVII 500 (500/126/471 MHz) spectrometers in deuterated solvents. ^{13}C spectra were recorded with broadband decoupling. Chemical shifts (δ_H , δ_C) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^1H NMR and 0.1 ppm for ^{13}C NMR. ^1H and ^{13}C NMR spectra were referenced relative to the solvent residual peak (CHCl_3). Peak assignments were made on the basis of chemical shifts, integrations, coupling constants, and comparison to known compounds, using COSY, HSQC, and HMBC experiments where appropriate. Multiplets are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or combinations thereof. Coupling constants (J) are reported to the nearest 0.5 Hz.

Mass spectrometry

High resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory mass-spec facilities using a Bruker MicroTOF spectrometer. The mass reported

is that containing the most abundant isotopes, with each value to 4 or 5 decimal places and within 5 ppm of the calculated mass. Mass to charge ratios (m/z) are reported in Daltons.

Reporting of compounds

Systematic names were generated by the computer programme ChemDrawTM according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). However, the numbering on the structures may not correspond to the systematic name. The NMR assignments follow the numbering system shown on the structures for straightforward comparison of data.

Handling of light-sensitive compounds

Light-sensitive iodomalonates were prepared and handled with the fumehood light turned off. Reaction vessels and flash column chromatography apparatus were covered in aluminium foil during use. Where possible a tinted NMR tube was used to record NMR spectra.

1.2 General Experimental Procedures

General Procedure A: Synthesis of iodomalonates

To a solution of the malonate (1.0 equiv.) in dry degassed ($3 \times$ freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) cooled to -78°C was added dropwise NaHMDS (1.0 M in THF, 1.2 equiv.) in the dark. The resulting solution was allowed to stir for 15 min at this temperature before the dropwise addition of *N*-iodosuccinimide (1.2 equiv.) in dry degassed ($3 \times$ freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) over 5 min. The mixture was then allowed to stir at room temperature for 5 h in the dark. After this time, the reaction mixture was diluted with water (20 mL/mmol of substrate) and extracted with EtOAc (3×30 mL/mmol of substrate). The combined organic layers were dried over MgSO_4 and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

General Procedure B: One-pot cyclisation of malonates

To a solution of the malonate (1.0 equiv.) in dry degassed ($3 \times$ freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) cooled to -78°C was added dropwise NaHMDS (1.0 M in THF, 1.2 equiv.) in the dark. The resulting solution was allowed to stir for 15 min at this temperature before the dropwise addition of *N*-iodosuccinimide (1.2 equiv.) in dry degassed ($3 \times$ freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) over 5 min. The mixture was then allowed to stir at room temperature for 5 h in the dark. After this time, TMP (2.0 equiv.) was added and the reaction mixture irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16–24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography.

General Procedure C: One-pot cyclisation of malonates for enolisable substrates

To a solution of the malonate (1.0 equiv.) and *N*-iodosuccinimide (1.2 equiv.) in dry degassed ($3 \times$ freeze/pump/thaw cycles) THF (10 mL/mmol of substrate) cooled to -78°C was added dropwise NaHMDS (1.0 M in THF, 1.1 equiv.) over 30 min in the dark. The resulting solution was allowed to warm up to room temperature and irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16–24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography.

General Procedure D: Sonogashira coupling

Pd(OAc)₂ (10 mol%) and XPhos (20 mol%) were dissolved in DMF (2.5 mL/mmol of substrate) and allowed to stir at room temperature under Ar for 30 min. To the resulting dark brown solution were added heterocyclic bromide (1.0 equiv.), dimethyl 2-(prop-2-yn-1-yl)malonate (1.2 equiv.), CuI (5 mol%), and DMF (7.5 mL/mmol of substrate). The reaction mixture was degassed (Ar bubbling for 10 min) and DBU (3.0 equiv.) added. The resulting solution was allowed to stir at 80 °C for 6 h. After this time, all volatiles were removed under a flow of N₂ and the crude mixture purified by flash-chromatography.

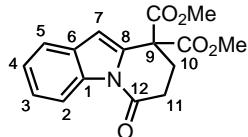
General Procedure E: Hydrogenation of Sonogashira coupling products

Pd (10% on activated carbon, 5 mol%) was added to an Ar purged solution of Sonogashira coupling product (1.0 equiv.) in dry MeOH (10 mL/mmol of substrate). The atmosphere was then replaced with hydrogen and the resulting mixture allowed to stir for 5 h at room temperature. After this time, the reaction was filtered through a Celite® pad, which was eluted with EtOAc. All volatiles were then removed *in vacuo* to give the desired product with no need for further purification.

1.3 Compound Synthesis and Characterisation

1.3.1 Cyclisation products

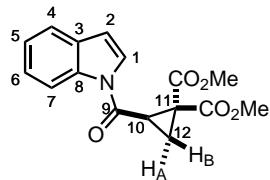
Dimethyl 6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate, 5



According to **General Procedure C**, using dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate **4** (303 mg, 1.00 mmol). Purification by flash-chromatography (5% to 15% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (284 mg, 0.94 mmol, 94%).

R_f 0.18 (20% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 8.48 (ddd, 1H, *J* = 8.0, 1.5, 1.0 Hz, C{2}–H), 7.53 (ddd, 1H, *J* = 7.5, 1.5, 1.0 Hz, C{5}–H), 7.36 (ddd, 1H, *J* = 8.0, 7.5, 1.5 Hz, C{3}–H), 7.29 (ddd, 1H, *J* = 7.5, 7.5, 1.5 Hz, C{4}–H), 6.70 (d, 1H, *J* = 1.0 Hz, C{7}–H), 3.85 (s, 6H, CO₂Me), 2.85–2.79 (m, H, C{11}–H), 2.73–2.67 (m, H, C{10}–H); **13C NMR** (101 MHz, CDCl₃) δ 169.0 (CO₂Me), 167.6 (C{12}), 135.3 (C{8}), 132.8 (C{1}), 129.1 (C{6}), 125.6 (C{3}), 124.5 (C{4}), 120.8 (C{5}), 116.8 (C{2}), 109.5 (C{7}), 55.5 (C{9}), 53.7 (CO₂Me), 30.9 (C{11}), 28.5 (C{10}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 302.0. C₁₆H₁₆NO₅⁺ requires 302.1. All data in accordance with literature.¹

Dimethyl 2-(1*H*-indole-1-carbonyl)cyclopropane-1,1-dicarboxylate, 6

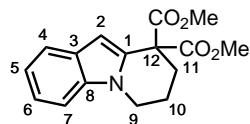


Isolated from the cyclisation of dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate **4** in variable yields.

R_f 0.32 (30% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 8.38 (d, 1H, *J* = 8.0 Hz, C{7}–H), 7.64 (d, 1H, *J* = 4.0 Hz, C{1}–H), 7.57 (d, 1H, *J* = 7.5 Hz, C{4}–H), 7.34 (dd, 1H, *J* = 8.0, 7.0 Hz, C{6}–H), 7.29 (dd, 1H, *J* = 7.5, 7.0 Hz, C{5}–H), 6.70 (d, 1H, *J* = 4.0 Hz, C{2}–H), 3.84 (s, 3H, CO₂Me), 3.67 (s, 3H, CO₂Me'), 3.25 (dd, 1H, *J* = 8.5, 7.0 Hz, C{10}–H), 2.34 (dd, 1H, *J* = 7.0, 5.0 Hz, H_B), 1.83 (dd, 1H, *J* = 8.5, 5.0 Hz, H_A); **13C NMR** (126 MHz, CDCl₃) δ 169.2 (C{9}), 166.4 (CO₂Me), 166.2 (CO₂Me'), 135.8 (C{3}), 130.6 (C{8}), 125.4 (C{6}), 124.9 (C{1}), 124.2 (C{5}), 121.1 (C{4}), 116.7 (C{7}), 110.1 (C{2}), 53.7 (CO₂Me), 53.3 (CO₂Me'), 37.7 (C{11}), 29.1 (C{10}), 20.1 (C{12}); **ν/cm⁻¹**(film) 2954w, 1735s, 1670m, 1319s, 1208m; **LRMS** (*m/z* +ESI): Found: [M+Na]⁺,

324.0. $C_{16}H_{15}NNaO_5^+$ requires 324.1.

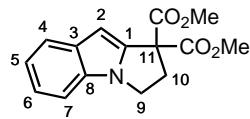
Dimethyl 7,8-dihydropyrido[1,2-*a*]indole-9,9(6*H*)-dicarboxylate, 10



According to **General Procedure B**, using dimethyl 2-(3-(1*H*-indol-1-yl)propyl)malonate **9** (48 mg, 0.17 mmol). Purification by flash-chromatography (20% EtOAc in PE₄₀₋₆₀) gave the *title compound* as a colourless oil (31 mg, 0.11 mmol, 64%).

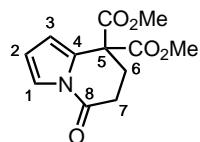
R_f 0.40 (30% EtOAc in PE₄₀₋₆₀, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.59 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{7}-H), 7.29 (ddd, 1H, *J* = 8.5, 1.0, 1.0 Hz, C{4}-H), 7.20 (ddd, 1H, *J* = 8.5, 7.0, 1.0 Hz, C{5}-H), 7.11 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{6}-H), 6.60 (d, 1H, *J* = 1.0 Hz, C{2}-H), 4.08 (t, 2H, *J* = 6.0 Hz, C{9}-H), 3.80 (s, 6H, CO₂Me), 2.58–2.50 (m, 2H, C{11}-H), 2.18–2.07 (m, 2H, C{10}-H); **13C NMR** (101 MHz, CDCl₃) δ 170.5 (CO₂Me), 136. (C{1}), 131. (C{8}), 127. (C{3}), 121.8 (C{5}), 120.9 (C{7}), 120.2 (C{6}), 109.2 (C{4}), 102.3 (C{2}), 56.3 (C{12}), 53.3 (CO₂Me), 42.0 (C{9}), 28.9 (C{11}), 20.0 (C{10}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 288.0. $C_{16}H_{18}NO_4^+$ requires 288.1. All data in accordance with literature.¹

Dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate, 12



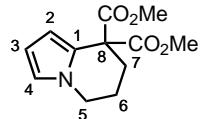
According to **General Procedure B**, using dimethyl 2-(2-(1*H*-indol-1-yl)ethyl)malonate (55 mg, 0.20 mmol) **11** (55 mg, 0.20 mmol). Purification by flash-chromatography (15% EtOAc in PE₄₀₋₆₀) gave the *title compound* as a colourless oil (40 mg, 0.14 mmol, 70%).

R_f 0.37 (30% EtOAc in PE₄₀₋₆₀, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.61 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{4}-H), 7.27 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{7}-H), 7.19 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{6}-H), 7.10 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{5}-H), 6.55 (d, 1H, *J* = 1.0 Hz, C{2}-H), 4.21 (t, 2H, *J* = 7.0 Hz, C{9}-H), 3.81 (s, 6H, CO₂Me), 3.19 (dd, 2H, *J* = 7.0, 6.5 Hz, C{10}-H); **13C NMR** (101 MHz, CDCl₃) δ 169.6 (CO₂Me), 139.0 (C{1}), 132.9 (C{8}), 132.6 (C{3}), 121.8 (C{6}), 121.5 (C{4}), 119.9 (C{5}), 109.9 (C{7}), 96.7 (C{2}), 58.9 (C{1}), 53.5 (CO₂Me), 42.7 (C{9}), 37.1 (C{10}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 274.1. $C_{15}H_{16}NO_4^+$ requires 274.1. All data in accordance with literature.¹

Dimethyl 5-oxo-6,7-dihydroindolizine-8,8(5*H*)-dicarboxylate, 14

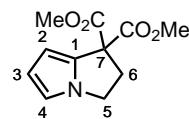
According to **General Procedure C**, using dimethyl 2-(3-oxo-3-(1*H*-pyrrol-1-yl)propyl)malonate **13** (52 mg, 0.20 mmol). Purification by flash-chromatography (20% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (42 mg, 0.17 mmol, 84%).

R_f 0.38 (30% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.44 (dd, 1H, *J* = 3.5, 1.5 Hz, C{1}–H), 6.35 (dd, 1H, *J* = 3.5, 1.5 Hz, C{3}–H), 6.29 (t, 1H, *J* = 3.5 Hz, C{2}–H), 3.81 (s, 6H, CO₂Me), 2.80–2.71 (m, 2H, C{7}–H), 2.66–2.58 (m, 2H, C{6}–H); **13C NMR** (101 MHz, CDCl₃) δ 169.3 (CO₂Me), 166.6 (C{8}), 127.7 (C{4}), 118. (C{1}), 113.6 (C{3}), 113.0 (C{2}), 54.5 (C{5}), 53.6 (CO₂Me), 30.0 (C{7}), 28.8 (C{6}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 252.0. C₁₂H₁₄NO₅⁺ requires 252.1. All data in accordance with literature.¹

Dimethyl 6,7-dihydroindolizine-8,8(5*H*)-dicarboxylate, 16

According to **General Procedure B**, using dimethyl 2-(3-(1*H*-pyrrol-1-yl)propyl)malonate **15** (45 mg, 0.19 mmol). Purification by flash-chromatography (15% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (35 mg, 0.15 mmol, 79%).

R_f 0.28 (20% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 6.60 (dd, 1H, *J* = 2.5, 1.5 Hz, C{4}–H), 6.23 (dd, 1H, *J* = 3.5, 1.5 Hz, C{2}–H), 6.17 (dd, 1H, *J* = 3.5, 2.5 Hz, C{3}–H), 3.95 (t, 2H, *J* = 6.0 Hz, C{5}–H), 3.76 (s, 6H, CO₂Me), 2.47–2.38 (m, 2H, C{7}–H), 2.06–1.96 (m, 2H, C{6}–H); **13C NMR** (126 MHz, CDCl₃) δ 171.1 (CO₂Me), 123.3 (C{1}), 120.6 (C{4}), 109.1 (C{2}), 108.3 (C{3}), 55.4 (C{8}), 53.1 (CO₂Me), 45.2 (C{5}), 29.2 (C{7}), 20.7 (C{6}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 238.0. C₁₂H₁₆NO₄⁺ requires 238.1. All data in accordance with literature.¹

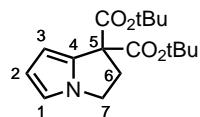
Dimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 18a

According to **General Procedure B**, using dimethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate **17a** (45 mg, 0.20 mmol). Purification by flash-chromatography (20% Et₂O in PE_{40–60}) afforded the

title compound as a colourless oil (35 mg, 0.16 mmol, 70%).

R_f 0.41 (50% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 6.64 (dd, 1H, *J* = 2.5, 1.5 Hz, C{4}–H), 6.26 (dd, 1H, *J* = 3.5, 2.5 Hz, C{3}–H), 6.15 (dd, 1H, *J* = 3.5, 1.5 Hz, C{2}–H), 4.08 (t, 2H, *J* = 7.0 Hz, C{5}–H), 3.77 (s, H, CO₂Me), 3.06 (t, 2H, *J* = 7.0 Hz, C{6}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 170.1 (CO₂Me), 132.2 (C{1}), 115.3 (C{4}), 113.2 (C{3}), 103.1 (C{2}), 58.6 (C{7}), 53.3 (CO₂Me), 45.0 (C{5}), 37.1 (C{6}); $\tilde{\nu}$ /cm⁻¹(film) 2955w, 1732s, 1267m, 1226m, 1098m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 224.09195. C₁₁H₁₄NO₄⁺ requires 224.09173.

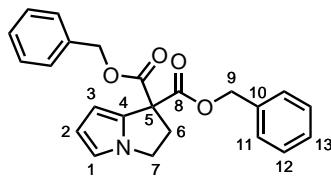
Di-*tert*-butyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 18b



According to **General Procedure B**, using di-*tert*-butyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate **17b** (61 mg, 0.20 mmol). Purification by flash-chromatography (5% to 7.5% EtOAc in PE_{40–60}) provided the *title compound* as a white powder (44.0 mg, 0.14 mmol, 72%).

R_f 0.40 (20% EtOAc in PE_{40–60}, purple in vanillin); **m.p.** 110–112 °C; **¹H NMR** (400 MHz, CDCl₃) δ 6.60 (dd, 1H, *J* = 2.5, 1.5 Hz, C{1}–H), 6.24 (dd, 1H, *J* = 3.5, 2.5 Hz, C{2}–H), 6.10 (dd, 1H, *J* = 3.5, 1.5 Hz, C{3}–H), 4.03 (t, 2H, *J* = 7.0 Hz, C{7}–H), 2.95 (t, 2H, *J* = 7.0 Hz, C{6}–H), 1.47 (s, 18H, CMe₃); **¹³C NMR** (126 MHz, CDCl₃) δ 168.8 (CO₂R), 133.3 (C{4}), 114.9 (C{1}), 113.0 (C{2}), 102.7 (C{3}), 82.0 (CMe₃), 60.4 (C{5}), 44.9 (C{7}), 36.4 (C{6}), 28.0 (CMe₃); $\tilde{\nu}$ /cm⁻¹(film) 2976w, 1726s, 1160m, 1100m, 715m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 308.1857. C₁₇H₂₆NO₄⁺ requires 308.1856.

Dibenzyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 18c

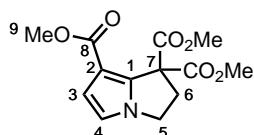


According to **General Procedure B**, using dibenzyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate **17c** (75 mg, 0.20 mmol). Purification by flash-chromatography (10% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (55.3 mg, 0.15 mmol, 75%).

R_f 0.28 (20% EtOAc in PE_{40–60}, orange in vanillin); **¹H NMR** (500 MHz, CDCl₃) δ 7.33–7.29 (m, 6H, C{12, 13}–H), 7.26–7.23 (m, 4H, C{11}–H), 6.63 (dd, 1H, *J* = 2.5, 1.5 Hz, C{1}–H), 6.25 (dd, 1H, *J* = 3.5, 2.5 Hz, C{2}–H), 6.14 (dd, 1H, *J* = 3.5, 1.5 Hz, C{3}–H), 5.19–5.11 (m, 4H, C{9}–H), 4.06 (t, 2H, *J* = 7.0 Hz, C{7}–H), 3.07 (t, 2H,

$J = 7.0$ Hz, C{6}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.3 (CO₂R), 135.4 (C{10}), 132.0 (C{4}), 128.7 (C{12}), 128.4 (C{13}), 128.1 (C{11}), 115.3 (C{1}), 113.3 (C{2}), 103.4 (C{3}), 67.7 (C{9}), 58.9 (C{5}), 45.0 (C{7}), 36.9 (C{6}); $\tilde{\nu}$ /cm⁻¹(film) 2980w, 1734s, 1263m, 1097m, 697w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 376.1543. C₂₃H₂₂NO₄⁺ requires 376.1543.

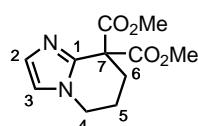
Trimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1,7-tricarboxylate, 20



According to **General Procedure B**, using dimethyl 2-(3-(methoxycarbonyl)-1*H*-pyrrol-1-yl)ethylmalonate **19** (57 mg, 0.20 mmol). Purification by flash-chromatography (35% EtOAc in pentane) provided the *title compound* as a pale yellow powder (40.4 mg, 0.14 mmol, 72% yield).

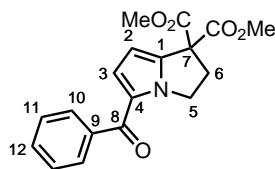
R_f 0.23 (40% EtOAc in PE_{40–60}, orange in vanillin); **m.p.** 94–97 °C; **¹H NMR** (500 MHz, CDCl₃) δ 6.67 (d, 1H, $J = 3.0$ Hz, C{3}–H), 6.59 (d, 1H, $J = 3.0$ Hz, C{4}–H), 4.05 (t, 2H, $J = 7.0$ Hz, C{5}–H), 3.76 (s, 6H, CO₂Me), 3.75 (s, 3H, C{9}–H), 3.20 (t, 2H, $J = 7.0$ Hz, C{6}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.6 (CO₂Me), 164.5 (C{8}), 137.6 (C{1}), 115.6 (C{4}), 115.0 (C{3}), 110.0 (C{2}), 60.1 (C{7}), 53.4 (CO₂Me), 51.0 (C{9}), 45.8 (C{5}), 39.1 (C{6}); $\tilde{\nu}$ /cm⁻¹(film) 2952w, 1750s, 1733m, 1436m, 1228m; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 304.0789. C₁₃H₁₅NNaO₆⁺ requires 304.0792.

Dimethyl 6,7-dihydroimidazo[1,2-*a*]pyridine-8,8(5*H*)-dicarboxylate, 24



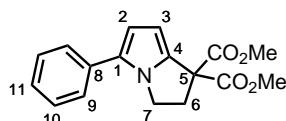
According to **General Procedure B**, using dimethyl 2-(3-(1*H*-imidazol-1-yl)propyl)malonate **23** (48 mg, 0.20 mmol) and NIS being added over 3 h at –78 °C. Purification by flash-chromatography (2.5% MeOH in CH₂Cl₂) gave the *title compound* as a colourless oil (21 mg, 0.088 mmol, 43%).

R_f 0.14 (EtOAc, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 7.11 (d, 1H, $J = 1.5$ Hz, C{2}–H), 6.86 (d, 1H, $J = 1.5$ Hz, C{3}–H), 4.01 (t, 2H, $J = 6.0$ Hz, C{4}–H), 3.81 (s, 6H, CO₂Me), 2.59–2.52 (m, 2H, C{6}–H), 2.06–1.97 (m, 2H, C{5}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.5 (CO₂Me), 139.7 (C{1}), 128.8 (C{2}), 119.2 (C{3}), 56.7 (C{7}), 53.6 (CO₂Me), 44.7 (C{4}), 29.5 (C{6}), 20.0 (C{5}); $\tilde{\nu}$ /cm⁻¹(film) 2956w, 1731s, 1436m, 1260m, 1114w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 239.10271. C₁₁H₁₅N₂O₄⁺ requires 239.10263.

Dimethyl 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22a

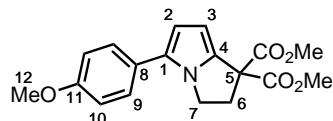
According to **General Procedure B**, using dimethyl 2-(2-benzoyl-1*H*-pyrrol-1-yl)ethylmalonate **21a** (66 mg, 0.20 mmol) (irradiation time = 48 h). Purification by flash-chromatography (10% to 25% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (52.8 mg, 0.16 mmol, 81% yield).

R_f 0.41 (40% EtOAc in PE_{40–60}, orange in vanillin); **1H NMR** (500 MHz, CDCl₃) δ 7.86–7.79 (m, 2H, C{10}–H), 7.57–7.50 (m, 1H, C{12}–H), 7.48–7.42 (m, 2H, C{11}–H), 6.84 (d, 1H, *J* = 4.0 Hz, C{3}–H), 6.27 (d, 1H, *J* = 4.0 Hz, C{2}–H), 4.55 (t, 2H, *J* = 7.0 Hz, C{5}–H), 3.81 (s, 6H, CO₂Me), 3.14 (t, 2H, *J* = 7.0 Hz, C{6}–H); **13C NMR** (126 MHz, CDCl₃) δ 185.4 (**C**{8}), 169.2 (CO₂Me), 140.4 (**C**{1}), 139.1 (**C**{9}), 131.7 (**C**{12}), 129.1 (**C**{10}), 128.3 (**C**{11}), 127.6 (**C**{4}), 124.7 (**C**{3}), 105.0 (**C**{2}), 58.9 (**C**{7}), 53.6 (CO₂Me), 47.1 (**C**{5}), 36.6 (**C**{6}); $\tilde{\nu}$ /cm^{−1}(film) 2955w, 1737s, 1625m, 1262s, 1099m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 328.1178. C₁₈H₁₈NO₅⁺ requires 328.1179.

Dimethyl 5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22b

According to **General Procedure B**, using dimethyl 2-(2-phenyl-1*H*-pyrrol-1-yl)ethylmalonate **21b** (60 mg, 0.20 mmol). Purification by flash-chromatography (15% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (50.1 mg, 0.17 mmol, 84%).

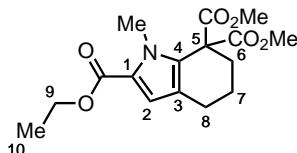
R_f 0.23 (20% EtOAc in PE_{40–60}, orange in vanillin); **1H NMR** (500 MHz, CDCl₃) δ 7.48–7.42 (m, 2H, C{9}–H), 7.39–7.33 (m, 2H, C{10}–H), 7.25–7.19 (m, 1H, C{11}–H), 6.45 (d, 1H, *J* = 3.5 Hz, C{2}–H), 6.25 (d, 1H, *J* = 3.5 Hz, C{3}–H), 4.26 (t, 2H, *J* = 7.0 Hz, C{7}–H), 3.80 (s, 6H, CO₂Me), 3.10 (t, 2H, *J* = 7.0 Hz, C{6}–H); **13C NMR** (126 MHz, CDCl₃) δ 170.0 (CO₂Me), 133.5 (**C**{4}), 133.1 (**C**{8}), 130.1 (**C**{1}), 128.8 (**C**{10}), 126.4 (**C**{11}), 126.0 (**C**{9}), 111.7 (**C**{2}), 104.2 (**C**{3}), 58.6 (**C**{5}), 53.4 (CO₂Me), 45.5 (**C**{7}), 37.0 (**C**{6}); $\tilde{\nu}$ /cm^{−1}(film) 2954w, 1735s, 1435m, 1247m, 755m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 300.1231. C₁₇H₁₈NO₄⁺ requires 300.1230.

Dimethyl 5-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22c

According to **General Procedure B**, using dimethyl 2-(2-(4-methoxyphenyl)-1*H*-pyrrol-1-yl)ethyl malonate **21c** (66 mg, 0.20 mmol). Purification by flash-chromatography (20% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (61.9 mg, 0.19 mmol, 94%).

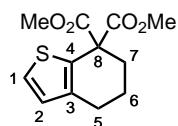
\mathbf{R}_f 0.16 (20% EtOAc in PE_{40–60}, red in vanillin); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ 7.40–7.34 (m, 2H, C{9}–H), 6.96–6.87 (m, 2H, C{10}–H), 6.34 (d, 1H, J = 3.5 Hz, C{2}–H), 6.22 (d, 1H, J = 3.5 Hz, C{3}–H), 4.20 (t, 2H, J = 7.0 Hz, C{7}–H), 3.83 (s, 3H, C{12}–H), 3.80 (s, 6H, CO_2Me), 3.09 (t, 2H, J = 7.0 Hz, C{6}–H); **$^{13}\text{C NMR}$** (126 MHz, CDCl_3) δ 170.1 (CO_2Me), 158.4 (C{11}), 132.7 (C{4}), 129.9 (C{1}), 127.5 (C{9}), 125.9 (C{8}), 114.3 (C{10}), 110.8 (C{2}), 104.0 (C{3}), 58.7 (C{5}), 55.4 (C{12}), 53.3 (CO_2Me), 45.2 (C{7}), 37.1 (C{6}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2955w, 1735s, 1556m, 1250s, 832w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 330.1335. $\text{C}_{18}\text{H}_{20}\text{NO}_5^+$ requires 330.1336.

2-Ethyl 7,7-dimethyl 1-methyl-1,4,5,6-tetrahydro-7*H*-indole-2,7,7-tricarboxylate, 34



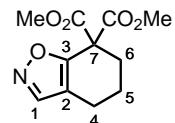
According to **General Procedure B**, using dimethyl 2-(3-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)propyl malonate **63** (50 mg, 0.15 mmol). Purification by flash-chromatography (40% Et₂O in PE_{40–60}) gave the *title compound* as a colourless oil (28 mg, 0.087 mmol, 58% yield).

\mathbf{R}_f 0.16 (33% Et₂O in PE_{40–60}, KMnO₄); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ 6.76 (s, 1H, C{2}–H), 4.26 (q, 2H, J = 7.0 Hz, C{9}–H), 3.78 (s, 6H, CO_2Me), 3.76 (s, 3H, N-Me), 2.55 (t, 2H, J = 6.5 Hz, C{8}–H), 2.43–2.35 (m, 2H, C{6}–H), 1.82–1.71 (m, 2H, C{7}–H), 1.32 (t, 3H, J = 7.0 Hz, C{10}–H); **$^{13}\text{C NMR}$** (126 MHz, CDCl_3) δ 170.9 (CO_2Me), 161.6 (CO_2Et), 130.4 (C{4}), 123.6 (C{1}), 120.2 (C{3}), 115.6 (C{2}), 59.9 (C{9}), 56.3 (C{5}), 53.3 (CO_2Me), 34.1 (N-Me), 33.9 (C{6}), 22.8 (C{8}), 20.9 (C{7}), 14.6 (C{10}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2980w, 1734s, 1700s, 1248s, 1086m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 346.1260. $\text{C}_{16}\text{H}_{21}\text{NNaO}_6^+$ requires 346.1261.

Dimethyl 5,6-dihydrobenzo[*b*]thiophene-7,7(4*H*)-dicarboxylate, 36

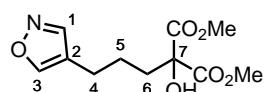
According to **General Procedure B**, using dimethyl 2-(thiophen-3-yl)propylmalonate **35** (51 mg, 0.20 mmol). Purification by flash-chromatography (20% Et₂O in PE_{40–60}) gave the *title compound* as a colourless oil (42.6 mg, 0.17 mmol, 85%).

R_f 0.22 (20% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.25 (d, 1H, *J* = 5.0 Hz, C{1}–H), 6.77 (d, 2H, *J* = 5.0 Hz, C{2}–H), 3.78 (s, 6H, CO₂Me), 2.67 (t, 2H, *J* = 6.5 Hz, C{5}–H), 2.45–2.39 (m, 2H, C{7}–H), 1.89–1.82 (m, 2H, C{6}–H); **13C NMR** (126 MHz, CDCl₃) δ 171.2 (CO₂Me), 138.9 (C{3}), 130.3 (C{4}), 127.1 (C{2}), 125.8 (C{1}), 56.9 (C{8}), 53.1 (CO₂Me), 31.5 (C{7}), 25.7 (C{5}), 20.0 (C{6}); $\tilde{\nu}$ /cm⁻¹(film) 2952w, 1736s, 1434m, 1240m, 1177m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 255.0687. C₁₂H₁₅O₅S⁺ requires 255.0686.

Dimethyl 5,6-dihydrobenzo[*d*]isoxazole-7,7(4*H*)-dicarboxylate, 30

TMP (68 μL, 0.40 mmol) was added to a solution of dimethyl 2-iodo-2-(3-(isoxazol-4-yl)propyl)malonate **29** (48 mg, 0.20 mmol) in THF (2.0 mL). The reaction mixture was then irradiated using a white 30 W CFL light (at 1.0 cm distance) for 24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography (30% to 33% Et₂O in PE_{40–60}) to give the *title compound* as a colourless oil (30 mg, 0.13 mmol, 63% yield).

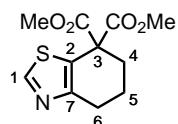
R_f 0.33 (50% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 8.13 (s, 1H, C{1}–H), 3.80 (s, 6H, CO₂Me), 2.52 (t, 2H, *J* = 6.0 Hz, C{4}–H), 2.48–2.41 (m, 2H, C{6}–H), 1.88–1.80 (m, 2H, C{5}–H); **13C NMR** (126 MHz, CDCl₃) δ 168.6 (CO₂Me), 161.1 (C{3}), 149.5 (C{1}), 115.4 (C{2}), 55.5 (C{7}), 53.6 (CO₂Me), 31.6 (C{6}), 20.3 (C{5}), 19.6 (C{4}); $\tilde{\nu}$ /cm⁻¹(film) 2980m, 1733s, 1436w, 1252m, 1158m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 240.08680. C₁₁H₁₄NO₅⁺ requires 240.08665.

Dimethyl 2-hydroxy-2-(3-(isoxazol-4-yl)propyl)malonate, 32

Isolated as a side product of the cyclisation reaction of dimethyl 2-(3-(isoxazol-4-yl)propyl)malonate **31** in variable yields.

¹H NMR (500 MHz, CDCl₃) δ 8.22 (s, 1H, C{3}–H), 8.14 (s, 1H, C{1}–H), 3.80 (s, 6H, CO₂Me), 2.50 (t, 2H, J = 7.5 Hz, C{4}–H), 2.10–2.03 (m, 2H, C{6}–H), 1.68–1.58 (m, 2H, C{5}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 170.9 (CO₂Me), 154.6 (C{3}), 150.3 (C{1}), 118.6 (C{2}), 78.9 (C{7}), 53.7 (CO₂Me), 34.2 (C{6}), 23.6 (C{5}), 22.0 (C{4}).

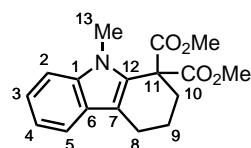
Dimethyl 5,6-dihydrobenzo[d]thiazole-7,7(4H)-dicarboxylate, **40**



According to **General Procedure B**, using dimethyl 2-(3-(thiazol-4-yl)propyl)malonate **39** (51 mg, 0.20 mmol) (irradiation time = 48 h). Purification by flash-chromatography (20% to 30% EtOAc in pentante) provided the *title compound* as a yellow oil (23.0 mg, 0.090 mmol, 46% yield).

R_f 0.31 (60% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 8.76 (s, 1H, C{1}–H), 3.77 (s, 6H, CO₂Me), 2.87 (t, 2H, J = 6.5 Hz, C{6}–H), 2.45–2.39 (m, 2H, C{4}–H), 2.01–1.90 (m, 2H, C{5}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 170.4 (CO₂Me), 154.1 (C{7}), 153.5 (C{1}), 124.9 (C{2}), 56.1 (C{3}), 53.4 (CO₂Me), 31.2 (C{4}), 26.9 (C{6}), 20.1 (C{5}); $\tilde{\nu}$ /cm⁻¹(film) 2954w, 1736s, 1244m, 1103w; **HRMS** (m/z +ESI): Found: [M+H]⁺, 256.0640. C₁₁H₁₄NO₄S⁺ requires 256.0638.

Dimethyl 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarboxylate, **48**

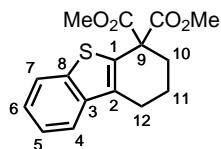


According to **General Procedure B**, using dimethyl 2-(3-(1-methyl-1*H*-indol-3-yl)propyl)malonate **47** (61 mg, 0.20 mmol). Purification by flash-chromatography (0% to 30% Et₂O in PE_{40–60}) provided the *title compound* as a colourless oil (53.1 mg, 0.18 mmol, 89%).

R_f 0.47 (50% Et₂O in PE_{40–60}, brown in vanillin); **¹H NMR** (500 MHz, CDCl₃) δ 7.52 (dt, 1H, J = 8.0, 1.0 Hz, C{5}–H), 7.30 (dt, 1H, J = 8.5, 1.0 Hz, C{2}–H), 7.27–7.23 (m, 1H, C{3}–H), 7.10 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{4}–H), 3.78 (s, 6H, CO₂Me), 3.65 (s, 3H, C{13}–H), 2.82 (t, 2H, J = 6.5 Hz, C{8}–H), 2.53–2.47 (m, 2H, C{10}–H), 1.99–1.88 (m, 2H, C{9}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 171.2 (CO₂Me), 137.9 (C{1}), 129.9 (C{12}), 126.1 (C{6}), 122.4 (C{3}), 119.1 (C{4}), 118.8 (C{5}), 112.7 (C{7}), 109.2 (C{2}), 56.2 (C{11}), 53.2 (CO₂Me), 33.9 (C{10}), 31.0 (C{13}), 21.0 (C{8}), 20.6 (C{9}); **LRMS** (m/z

+ESI): Found: $[M+Na]^+$, 324.0. $C_{17}H_{19}NNaO_4^+$ requires 324.1. All data in accordance with literature.²

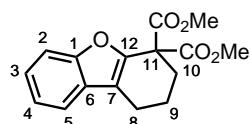
Dimethyl 2,3-dihydrodibenzo[*b,d*]thiophene-4,4(*1H*)-dicarboxylate, 50



According to **General Procedure B**, using dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)propyl)malonate **49** (61 mg, 0.20 mmol). Purification by flash-chromatography (20% Et₂O in PE_{40–60}) gave the *title compound* as an off-white solid (51.8 mg, 0.17 mmol, 85%).

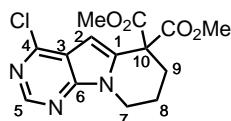
R_f 0.19 (20 % Et₂O in PE_{40–60}, KMnO₄); **m.p.** 138–140 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.81–7.75 (m, 1H, C{7}–H), 7.66–7.60 (m, 1H, C{4}–H), 7.38–7.30 (m, 2H, C{5, 6}–H), 3.81 (s, 6H, CO₂Me), 2.83 (t, 2H, *J* = 6.5 Hz, C{12}–H), 2.58–2.50 (m, 2H, C{10}–H), 2.02–1.94 (m, 2H, C{11}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 170.8 (CO₂Me), 139.8 (C{8}), 138.5 (C{3}), 133.6 (C{2}), 131.7 (C{1}), 125.0 (C{5}), 124.1 (C{6}), 122.3 (C{7}), 121.6 (C{4}), 57.5 (C{9}), 53.2 (CO₂Me), 31.7 (C{10}), 23.9 (C{12}), 19.4 (C{11}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2952w, 1735s, 1435m, 1247m, 754w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 305.0843. C₁₆H₁₇O₄S⁺ requires 305.0842.

Dimethyl 2,3-dihydrodibenzo[*b,d*]furan-4,4(*1H*)-dicarboxylate, 52



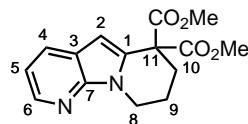
According to **General Procedure B**, using dimethyl 2-(3-(benzofuran-3-yl)propyl)malonate **51** (58 mg, 0.20 mmol). Purification by flash-chromatography (20% Et₂O in PE_{40–60}) gave the *title compound* as a yellow oil (40.0 mg, 0.14 mmol, 69%).

R_f 0.40 (50% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 7.50 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{2}–H), 7.47 (ddd, 1H, *J* = 7.5, 1.0, 1.0 Hz, C{5}–H), 7.29 (ddd, 1H, *J* = 8.0, 7.5, 1.0 Hz, C{3}–H), 7.23 (ddd, 1H, *J* = 7.5, 7.5, 1.0 Hz, C{4}–H), 3.81 (s, 6H, CO₂Me), 2.71 (t, 2H, *J* = 6.0 Hz, C{8}–H), 2.55–2.48 (m, 2H, C{10}–H), 1.97–1.90 (m, 2H, C{9}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 170.0 (CO₂Me), 154.9 (C{1}), 146.8 (C{12}), 127.6 (C{6}), 124.6 (C{3}), 122.5 (C{4}), 119.3 (C{5}), 117.0 (C{7}), 111.6 (C{2}), 56.1 (C{11}), 53.2 (CO₂Me), 31.9 (C{10}), 20.3 (C{8}), 20.0 (C{9}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2953w, 1734s, 1452m, 1253s, 748m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 289.1071. C₁₆H₁₇O₅⁺ requires 289.1071.

Dimethyl 4-chloro-8,9-dihydropyrimido[5,4-*b*]indolizine-6,6(7*H*)-dicarboxylate, 54

According to **General Procedure B**, using dimethyl 2-(3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propyl)malonate **53** (65 mg, 0.20 mmol). Purification by flash-chromatography (33% to 50% EtOAc in PE_{40–60}) provided the *title compound* as an off-white powder (57.7 mg, 0.18 mmol, 89%).

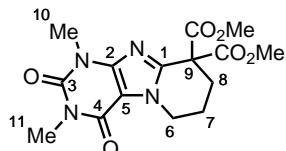
R_f 0.32 (50% EtOAc in PE_{40–60}, KMnO₄); **m.p.** 171–172 °C; **¹H NMR** (500 MHz, CDCl₃) δ 8.62 (s, 1H, C{5}–H), 6.71 (s, 1H, C{2}–H), 4.25 (t, 2H, *J* = 6.5 Hz, C{7}–H), 3.84 (s, 6H, CO₂Me), 2.59–2.53 (m, 2H, C{9}–H), 2.16–2.08 (m, 2H, C{8}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.3 (CO₂Me), 151.9 (C{4/6}), 150.7 (C{4/6}), 150.6 (C{5}), 133.4 (C{1}), 117.2 (C{3}), 100.0 (C{2}), 55.9 (C{10}), 53.6 (CO₂Me), 41.5 (C{7}), 28.5 (C{9}), 19.3 (C{8}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2957w, 1733s, 1432m, 1259s, 1180s; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 324.0747. C₁₄H₁₅³⁵ClN₃O₄⁺ requires 324.0746.

Dimethyl 8,9-dihydropyrido[3,2-*b*]indolizine-6,6(7*H*)-dicarboxylate, 56

According to **General Procedure B**, using dimethyl 2-(3-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propyl)malonate **55** (130 mg, 0.45 mmol). After 48 h of irradiation, the solvent was evaporated *in vacuo*. The resulting residue was diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 2 M aq. HCl (3 × 10 mL). These aqueous layers were combined, neutralised with 2 M NaOH to pH *ca.* 12, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na₂SO₄) and evaporated *in vacuo* to give the *title compound* as a white solid (106.9 mg, 0.37 mmol, 82%).

R_f 0.15 (33% EtOAc in PE_{40–60}, KMnO₄); **m.p.** 140–142 °C; **¹H NMR** (500 MHz, CDCl₃) δ 8.30 (dd, 1H, *J* = 4.5, 1.5 Hz, C{6}–H), 7.87 (dd, 1H, *J* = 8.0, 1.5 Hz, C{4}–H), 7.06 (dd, 1H, *J* = 8.0, 4.5 Hz, C{5}–H), 6.56 (s, 1H, C{2}–H), 4.26 (t, 2H, *J* = 6.0 Hz, C{8}–H), 3.81 (s, 6H, CO₂Me), 2.58–2.52 (m, 2H, C{10}–H), 2.15–2.07 (m, 2H, C{9}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 170.2 (CO₂Me), 147.6 (C{7}), 143.1 (C{6}), 131.8 (C{1}), 128.7 (C{4}), 120.3 (C{3}), 116.5 (C{5}), 100.4 (C{2}), 56.3 (C{11}), 53.5 (CO₂Me), 41.0 (C{8}), 28.9 (C{10}), 19.8 (C{9}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2954w, 1734s, 1434m, 1257m, 1064w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 289.1182. C₁₅H₁₇O₄N₂⁺ requires 289.1183.

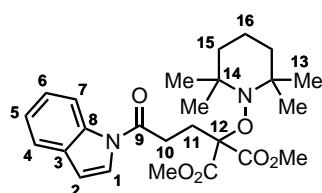
Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4,7,8-hexahydropyrido[2,1-*f*]purine-9,9(6*H*)- dicarboxylate, 58



According to **General Procedure B**, using dimethyl 2-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propyl) malonate **57** (70 mg, 0.20 mmol). Purification by flash-chromatography (30% to 70% EtOAc in PE_{40–60}) provided the *title compound*, together with some residual succinimide. It was then dissolved in EtOAc (10 mL) and washed with water (2 × 5 mL), and brine (10 mL). The organic layer was dried (Na₂SO₄) and evaporated *in vacuo* to give the *title compound* in pure form, as a white powder (48.0 mg, 0.14 mmol, 69%).

R_f 0.25 (80% EtOAc in PE_{40–60}, KMnO₄); **m.p.** 201–204 °C; **¹H NMR** (500 MHz, CDCl₃) δ 4.38 (t, 2H, *J* = 6.5 Hz, C{6}–H), 3.84 (s, 6H, CO₂Me), 3.57 (s, 3H, C{10}–H), 3.39 (s, 3H, C{11}–H), 2.62–2.56 (m, 2H, C{8}–H), 2.10–2.01 (m, 2H, C{7}–H), **¹³C NMR** (126 MHz, CDCl₃) δ 168.4 (CO₂Me), 155.3 (C{4}), 151.7 (C{3}), 148.2 (C{2}), 144.7 (C{1}), 107.4 (C{5}), 57.1 (C{9}), 53.7 (CO₂Me), 44.8 (C{6}), 30.1 (C{10}), 28.5 (C{8}), 27.9 (C{11}), 19.1 (C{7}); **ν/cm⁻¹**(film) 2956m, 1737m, 1704s, 1663s, 1262m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 351.1299. C₁₅H₁₈N₄O₆⁺ requires 351.1299.

Dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate, 64



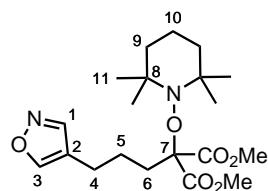
According to **General Procedure C**, using dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate **4** (45 mg, 0.15 mmol) with the addition of TEMPO (26 mg, 0.17 mmol) immediately before irradiation. Purification by flash-chromatography (5% to 20% Et₂O in PE_{40–60}) gave the *title compound* as a yellow oil (42.6 mg, 0.093 mmol, 62%).

R_f 0.52 (30% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 8.47 (d, 1H, *J* = 8.0 Hz, C{7}–H), 7.60 (d, 1H, *J* = 4.0 Hz, C{1}–H), 7.57 (ddd, 1H, *J* = 7.5, 1.0, 1.0 Hz, C{4}–H), 7.34 (ddd, 1H, *J* = 8.5, 7.5, 1.5 Hz, C{6}–H), 7.27 (ddd, 1H, *J* = 7.5, 1.0, 1.0 Hz, C{5}–H), 6.65 (dd, 1H, *J* = 4.0, 1.0 Hz, C{2}–H), 3.76 (s, 6H, CO₂Me), 3.22–3.13 (m, 2H, C{10}–H), 2.83–2.74 (m, 2H, C{11}–H), 1.66–1.38 (m, 6H, C{15, 16}–H), 1.23 (s, 6H,

$\text{C}\{13\}-\text{H}$), 1.15 (s, 6H, $\text{C}\{13'\}-\text{H}$). $\tilde{\nu}/\text{cm}^{-1}$ (film) 2935m, 1742s, 1708m, 1453m, 1208m; **HRMS** (m/z +ESI): Found: $[\text{M}+\text{H}]^+$, 459.2488. $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_6^+$ requires 459.2490.

Note: This compound quickly decomposed. ^{13}C NMR could not be obtained.

Dimethyl 2-(3-(isoxazol-4-yl)propyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate, 65

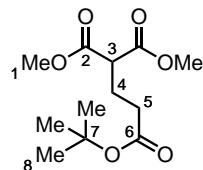


To a solution of iodomalonate **66** (50 mg, 0.14 mmol) in dry degassed THF (1.0 mL) were added TMP (51 μL) and TEMPO (26 mg, 0.15 mmol). The reaction mixture was irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography (0% to 30% Et_2O in PE_{40–60}) to give the *title compound* as a yellow oil (47.4 mg, 0.12 mmol, 88%).

R_f 0.32 (40% Et_2O in PE_{40–60}, KMnO_4); **^1H NMR** (400 MHz, CDCl_3) δ 8.24 (t, 1H, $J = 1.0$ Hz, $\text{C}\{1\}-\text{H}$), 8.15 (s, 1H, $\text{C}\{3\}-\text{H}$), 3.75 (s, 6H, CO_2Me), 2.50 (t, 2H, $J = 7.5$ Hz, $\text{C}\{4\}-\text{H}$), 2.32–2.13 (m, 2H, $\text{C}\{6\}-\text{H}$), 1.71–1.59 (m, 2H, $\text{C}\{5\}-\text{H}$), 1.58–1.52 (m, 1H, $\text{C}\{10\}-\text{H}$), 1.52–1.31 (m, 4H, $\text{C}\{9\}-\text{H}$), 1.30–1.22 (m, 1H, $\text{C}\{10'\}-\text{H}$), 1.18 (s, 6H, $\text{C}\{11\}-\text{H}$), 1.06 (s, 6H, $\text{C}\{11'\}-\text{H}$); **^{13}C NMR** (101 MHz, CDCl_3) δ 169.4 (CO_2Me), 154.1 (**C**{1}), 149.9 (**C**{3}), 118.3 (**C**{2}), 88.4 (**C**{7}), 60.6 (**C**{8}), 51.8 (CO_2Me), 40.8 (**C**{9}), 33.5 (**C**{6}), 33.0 (**C**{11}), 24.3 (**C**{5}), 22.0 (**C**{4}), 20.5 (**C**{11'}), 16.6 (**C**{10}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2936m, 1743s, 1364w, 1009w, 699w; **HRMS** (m/z +ESI): Found: $[\text{M}+\text{H}]^+$, 397.2338. $\text{C}_{20}\text{H}_{33}\text{N}_2\text{O}_6^+$ requires 397.2333.

1.3.2 Synthesis of cyclisation substrates

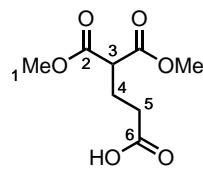
3-(*tert*-Butyl) 1,1-dimethyl propane-1,1,3-tricarboxylate, 67



According to the modified procedure of Katti,³ sodium hydride (60% w/w dispersion in mineral oil, 3.2 g, 80 mmol) was dissolved in THF (100 mL) and cooled to 0 °C before dimethyl malonate (9.1 mL, 80 mmol) was added dropwise over 10 min. The resulting mixture was allowed to stir for 20 min at 0 °C, *tert*-butyl acrylate (5.9 mL, 40 mmol) was added dropwise and the mixture allowed to stir for 16 h at room temperature. After this time, the reaction was cooled down to 0 °C, quenched with sat. aq. NH₄Cl (40 mL) and allowed to stir for 1 h. The resulting mixture was diluted with water (40 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and evaporated *in vacuo* to give a yellow oil. This was purified by vacuum distillation (30 °C to 150 °C, 1.32 mbar) and the fractions collected at 115 °C were re-purified by flash-chromatography (10% to 20% Et₂O in PE_{40–60}) to give the *title compound* as a colourless oil (4.69 g, 18.0 mmol, 45%).

R_f 0.50 (40% Et₂O in PE_{40–60}, KMnO₄); **b.p.** 115 °C (1.32 mbar); **¹H NMR** (400 MHz, CDCl₃) δ 3.74 (s, 6H, C{1}–H), 3.47 (t, 1H, J = 7.5 Hz, C{3}–H), 2.33–2.25 (m, 2H, C{5}–H), 2.21–2.13 (m, 2H, C{4}–H), 1.43 (s, 9H, C{8}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 171.8 (C{6}), 169.6 (C{2}), 80.8 (C{7}), 52.7 (C{1}), 50.7 (C{3}), 32.8 (C{5}), 28.2 (C{8}), 24.1 (C{4}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 283.1. C₁₂H₂₀NaO₆⁺ requires 283.1. All data in accordance with literature.³

5-Methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid, 68

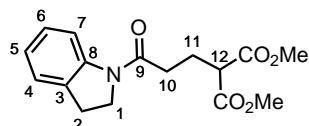


According to the modified procedure of Wu,⁴ trifluoroacetic acid (5.0 mL, 65 mmol) was added to a solution of 3-(*tert*-butyl) 1,1-dimethyl propane-1,1,3-tricarboxylate **67** (4.0 g, 15.3 mmol) in CH₂Cl₂ (30 mL). The resulting solution was allowed to stir for 16 h at room temperature. After this time, all volatiles were removed *in vacuo* to give the *title compound* as a yellow oil (3.00 g, 14.7 mmol, 96%).

R_f 0.05 (40% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 3.73 (s, 6H,

C{1}–H), 3.49 (t, 1H, J = 7.5 Hz, C{3}–H), 2.45 (t, 2H, J = 7.5 Hz, C{5}–H), 2.20 (dt, 2H, J = 8.0, 7.5 Hz, C{4}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.6 (C{6}), 169.4 (C{2}), 52.8 (C{1}), 50.4 (C{3}), 31.2 (C{5}), 23.5 (C{4}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 203.0. C₈H₁₁O₆⁺ requires 203.2. All data in accordance with literature.⁴

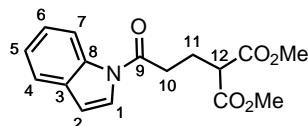
Dimethyl 2-(3-(indolin-1-yl)-3-oxopropyl)malonate, 69



According to the modified procedure of Kerr,¹ DMF (3 drops) and oxalyl chloride (0.65 mL, 7.16 mmol) were added to a solution of 5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid **68** (1.17 g, 5.73 mmol) in dry toluene (50 mL). The resulting solution was allowed to stir at room temperature for 30 min and was heated to 60 °C for 2 h. After this time, the mixture was allowed to cool down to room temperature and all volatiles were evaporated *in vacuo* to give a yellow oil (dimethyl 2-(3-chloro-3-oxopropyl)malonate) which was dissolved in CH₂Cl₂ (10 mL).

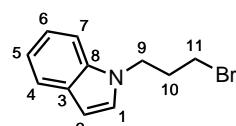
This solution was added dropwise to a solution of indoline (0.54 mL, 4.8 mmol) and triethylamine (1.0 mL, 7.2 mmol) in CH₂Cl₂ (10 mL) at 0 °C. The resulting mixture was allowed to stir at room temperature for 16 h. After this time, the mixture was poured into sat. aq. NH₄Cl (100 mL), and was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried (MgSO₄) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (50% EtOAc in PE_{40–60}) gave the *title compound* as a white solid (1.44 g, 4.72 mmol, 98%).

R_f 0.38 (50% EtOAc in PE_{40–60}, KMnO₄); **m.p.** 94–95 °C (lit.¹ 95–96 °C); **¹H NMR** (400 MHz, CDCl₃) δ 8.19 (d, 1H, J = 8.0 Hz, C{7}–H), 7.20–7.12 (m, 2H, C{4,6}–H), 6.98 (dd, 1H, J = 7.5, 7.5 Hz, C{5}–H), 3.98 (t, 2H, J = 8.5 Hz, C{1}–H), 3.73 (s, 6H, CO₂Me), 3.63 (t, 1H, J = 7.0 Hz, C{12}–H), 3.16 (t, 2H, J = 8.5 Hz, C{2}–H), 2.49 (t, 2H, J = 7.0 Hz, C{10}–H), 2.31 (dt, 2H, J = 7.0, 7.0 Hz, C{11}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 169.7 (9, CO₂Me), 143.0 (C{8}), 131.1 (C{3}), 127.6 (C{6}), 124.6 (C{4}), 123.7 (C{5}), 117.0 (C{7}), 52.6 (CO₂Me), 50.5 (C{12}), 47.9 (C{1}), 32.8 (C{10}), 28.0 (C{2}), 23.6 (C{11}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 328.0. C₁₆H₁₉NNaO₅⁺ requires 328.3. All data in accordance with literature.¹

Dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate, 4

According to the modified procedure of Kerr,¹ DDQ (1.29 g, 5.68 mmol) was added to a solution of dimethyl 2-(3-(indolin-1-yl)-3-oxopropyl)malonate **69** (1.44 g, 4.72 mmol) in dry toluene (23 mL) at room temperature. The reaction mixture was refluxed for 16 h. After this time, the reaction was allowed to cool to room temperature, diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (MgSO_4) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (30% EtOAc in PE_{40–60}) gave the *title compound* as an off-white solid (1.36 g, 4.48 mmol, 95%).

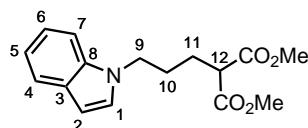
R_f 0.19 (20% EtOAc in PE_{40–60}, KMnO₄); **m.p.** 86–88 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.45 (d, 1H, *J* = 8.0 Hz, C{7}–H), 7.56 (ddd, 1H, *J* = 7.5, 1.5, 1.0 Hz, C{4}–H), 7.47 (d, 1H, *J* = 4.0 Hz, C{1}–H), 7.35 (ddd, 1H, *J* = 8.5, 7.0, 1.5 Hz, C{6}–H), 7.27 (td, 1H, *J* = 7.5, 1.0 Hz, C{5}–H), 6.65 (dd, 1H, *J* = 4.0, 1.0 Hz, C{2}–H), 3.77 (s, 6H, CO₂Me), 3.66 (t, 1H, *J* = 7.0 Hz, C{12}–H), 3.05 (t, 2H, *J* = 7.0 Hz, C{10}–H), 2.44 (dt, 2H, *J* = 7.0, 7.0 Hz, C{11}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 170.3 (C{9}), 169.6 (CO₂Me), 135.8 (C{8}), 130.5 (C{3}), 125.4 (C{6}), 124.6 (C{1}), 123.9 (C{5}), 121.0 (C{4}), 116.7 (C{7}), 109.6 (C{2}), 52.8 (CO₂Me), 50.4 (C{12}), 33.0 (C{10}), 23.7 (C{11}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 326.0. C₁₆H₁₇NNaO₅⁺ requires 326.1. All data in accordance with literature.¹

1-(3-Bromopropyl)-1*H*-indole, 70

According to the modified procedure of Barriault,⁵ a solution of indole (1.0 g, 8.5 mmol) in THF (5.0 mL) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 408 mg, 10.2 mmol) in THF (15 mL). The resulting solution was allowed to stir for 30 min at room temperature. After this time, 1,3-dibromopropane (1.7 mL, 17 mmol) was added and the solution stirred at room temperature for 16 h. The reaction mixture was then quenched by the addition of sat. aq. NH₄Cl (30 mL), the layers separated and the aqueous phase extracted with Et₂O (3 × 40 mL). The combined organic layers were dried (MgSO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (5% Et₂O in PE_{40–60}) gave the *title compound* as a colourless oil (172 mg, 0.722 mmol, 9%).

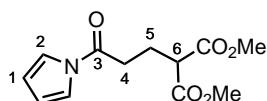
R_f 0.64 (30% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 7.64 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.38 (ddd, 1H, *J* = 8.5, 1.0, 1.0 Hz, C{7}–H), 7.22 (ddd, 1H, *J* = 8.5, 7.0, 1.0 Hz, C{6}–H), 7.15 (d, 1H, *J* = 3.0 Hz, C{1}–H), 7.12 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.51 (d, 1H, *J* = 3.0 Hz, C{2}–H), 4.34 (t, 2H, *J* = 6.5 Hz, C{9}–H), 3.31 (t, 2H, *J* = 6.0 Hz, C{11}–H), 2.36 (tt, 2H, *J* = 6.5, 6.0 Hz, C{10}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 136.0 (**C{8}**), 128.9 (**C{3}**), 128.2 (**C{1}**), 121.8 (**C{6}**), 121.3 (**C{4}**), 119.7 (**C{5}**), 109.4 (**C{7}**), 101.7 (**C{2}**), 44.1 (**C{9}**), 32.9 (**C{11}**), 30.7 (**C{10}**); **LRMS** (*m/z* +ESI): Found: [M]⁺, 237.0. C₁₁H₁₂⁷⁹BrN⁺ requires 237.0. All data in accordance with literature.⁶

Dimethyl 2-(3-(1*H*-indol-1-yl)propyl)malonate, 9



According to the modified procedure of Kerr,¹ dimethyl malonate (0.36 mL, 3.2 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 101 mg, 2.52 mmol) in DMF (5.0 mL) which was then allowed to stir for 30 min at room temperature. After this time, a solution of 1-(3-bromopropyl)-1*H*-indole **70** (150 mg, 0.63 mmol) in DMF (5.0 mL) was added dropwise and the resulting solution allowed to stir at room temperature for 16 h. The reaction mixture was then cooled to 0 °C before the dropwise addition of water (10 mL). The resulting mixture was extracted with Et₂O (3 × 20 mL) and the organic layers dried (MgSO₄) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (127 mg, 0.439 mmol, 70%).

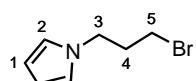
R_f 0.42 (30% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 7.63 (d, 1H, *J* = 8.0 Hz, C{4}–H), 7.32 (d, 1H, *J* = 8.5 Hz, C{7}–H), 7.21 (ddd, 1H, *J* = 8.5, 7.0, 1.0 Hz, C{6}–H), 7.13–7.06 (m, 2H, C{5}–H), 6.49 (d, 1H, *J* = 3.0 Hz, C{2}–H), 4.15 (t, 2H, *J* = 6.5 Hz, C{9}–H), 3.70 (s, 6H, CO₂Me), 3.34 (t, 1H, *J* = 7.0 Hz, C{12}–H), 2.00–1.84 (m, 4H, C{10, 11}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 169.6 (CO₂Me), 136.0 (**C{8}**), 128.8 (**C{3}**), 127.8 (**C{1}**), 121.7 (**C{6}**), 121.2 (**C{4}**), 119.5 (**C{5}**), 109.4 (**C{7}**), 101.5 (**C{2}**), 52.7 (CO₂Me), 51.3 (**C{12}**), 46.0 (**C{9}**), 28.0 (**C{10}**), 26.3 (**C{11}**); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 290.1. C₁₆H₂₀NO₄⁺ requires 290.2. All data in accordance with literature.¹

Dimethyl 2-(3-oxo-3-(1*H*-pyrrol-1-yl)propyl)malonate, 13

According to the modified procedure of Kerr,¹ DMF (3 drops) and oxalyl chloride (0.30 mL, 3.7 mmol) were added to a solution of 5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid **68** (600 mg, 2.94 mmol) in dry toluene (30 mL). The resulting solution was allowed to stir at room temperature for 30 min and was heated to 60 °C for 2 h. After this time, the mixture was allowed to cool down to room temperature and all volatiles were evaporated *in vacuo* to give a yellow oil (dimethyl 2-(3-chloro-3-oxopropyl)malonate) which was dissolved in THF (4.0 mL).

n-BuLi (2.5 M in hexanes, 0.98 mL, 2.4 mmol) was added dropwise to a solution of freshly distilled pyrrole (0.17 mL, 2.4 mmol) in THF (4.0 mL) at 0 °C. The reaction mixture was allowed to stir at this temperature for 20 min before being cooled down to –78 °C. The solution of dimethyl 2-(3-chloro-3-oxopropyl)malonate in THF was then added dropwise and the resulting mixture allowed to stir at room temperature for 16 h. After this time, the mixture was poured into sat. aq. NH₄Cl (20 mL) and extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (5% to 15% EtOAc in PE_{40–60}) gave the *title compound* as a yellow oil (168 mg, 0.663 mmol, 22%).

R_f 0.17 (15% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.30 (br, 2H, C{2}–H), 6.38–6.22 (t, 3H, *J* = 2.4 Hz, C{1}–H), 3.76 (s, 6H, CO₂Me), 3.60 (t, 1H, *J* = 7.0 Hz, C{6}–H), 2.96 (t, 2H, *J* = 7.0 Hz, C{4}–H), 2.38 (dt, 2H, *J* = 7.0, 7.0 Hz, C{5}–H); **13C NMR** (101 MHz, CDCl₃) δ 169.5 (3, CO₂Me), 119.1 (C{2}), 113.4 (C{1}), 52.8 (CO₂Me), 50.3 (C{6}), 31.8 (C{4}), 23.5 (C{5}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 276.0. C₁₂H₁₅NNaO₅⁺ requires 276.2. All data in accordance with literature.¹

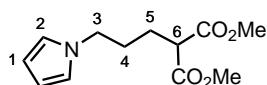
1-(3-Bromopropyl)-1*H*-pyrrole, 71

According to the modified procedure of Zhang,⁷ pyrrole (0.70 mL, 10 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 0.48 g, 12 mmol) in DMF (20 mL). The resulting solution was allowed to stir for 30 min at room temperature. After this time, 1,3-dibromopropane (2.0 mL, 20 mmol) was added and the solution stirred at room temperature for 16 h. The reaction mixture was then quenched with water (50 mL) and extracted with Et₂O (3 × 100 mL). The combined organic layers were dried (MgSO₄) and evap-

orated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (0% to 20% CH₂Cl₂ in PE_{40–60}) gave the *title compound* as a colourless oil (205 mg, 1.09 mmol, 11%).

R_f 0.44 (25% CH₂Cl₂ in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 6.68 (t, 2H, *J* = 2.0 Hz, C{2}–H), 6.16 (t, 2H, *J* = 2.0 Hz, C{1}–H), 4.08 (t, 2H, *J* = 6.5 Hz, C{3}–H), 3.31 (t, 2H, *J* = 6.0 Hz, C{5}–H), 2.26 (tt, 2H, *J* = 6.5, 6.0 Hz, C{4}–H); **13C NMR** (101 MHz, CDCl₃) δ 120.8 (C{2}), 108.6 (C{1}), 47.2 (C{3}), 34.3 (C{4}), 30.4 (C{5}); All data in accordance with literature.⁸

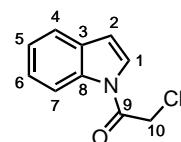
Dimethyl 2-(3-(1*H*-pyrrol-1-yl)propyl)malonate, 15



According to the modified procedure of Kerr,¹ dimethyl malonate (0.61 mL, 5.3 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 170 mg, 4.24 mmol) in DMF (8.0 mL) which was then allowed to stir for 30 min at room temperature. After this time, a solution of 1-(3-bromopropyl)-1*H*-pyrrole **71** (200 mg, 1.06 mmol) in DMF (8.0 mL) was added dropwise and the resulting solution allowed to stir at room temperature for 16 h. The reaction mixture was then cooled to 0 °C before the dropwise addition of water (10 mL). The resulting mixture was extracted with Et₂O (3 × 20 mL) and the organic layers dried (MgSO₄) and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (20% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (96.9 mg, 0.405 mmol, 39%).

R_f 0.27 (20% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 6.63 (t, 2H, *J* = 2.0 Hz, C{2}–H), 6.14 (t, 2H, *J* = 2.0 Hz, C{1}–H), 3.90 (t, 2H, *J* = 7.0 Hz, C{3}–H), 3.73 (s, 6H, CO₂Me), 3.33 (t, 1H, *J* = 7.5 Hz, C{6}–H), 1.95–1.85 (m, 2H, C{5}–H), 1.85–1.74 (m, 2H, C{4}–H); **13C NMR** (101 MHz, CDCl₃) δ 169.6 (CO₂Me), 120.6 (C{2}), 108.3 (C{1}), 52.7 (CO₂Me), 51.3 (C{6}), 49.2 (C{3}), 29.4 (C{4}), 26.2 (C{5}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 262.1. C₁₂H₁₇NNaO₄⁺ requires 262.1. All data in accordance with literature.¹

2-Chloro-1-(1*H*-indol-1-yl)ethan-1-one, 72

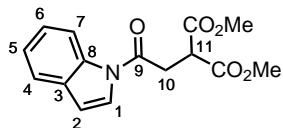


Experimental Details

According to the modified procedure of Winkler,⁹ chloroacetyl chloride (1.3 mL, 16 mmol) was added dropwise to a solution of indole (1.17 g, 10.0 mmol) in dry toluene (20 mL). The resulting solution was allowed to stir at 125 °C for 1 h. After this time, all volatiles were removed *in vacuo* and the resulting residue recrystallized in ethanol to give the title compound as a tan solid (939 mg, 4.85 mmol, 49%).

R_f 0.52 (50% Et₂O in PE_{40–60}, KMnO₄); **m.p.** 104–108 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.44 (d, 1H, *J* = 8.0 Hz, C{7}–H), 7.58 (d, 1H, *J* = 7.5 Hz, C{4}–H), 7.43 (d, 1H, *J* = 4.0 Hz, C{1}–H), 7.39 (ddd, 1H, *J* = 8.0, 7.5, 1.5 Hz, C{6}–H), 7.32 (ddd, 1H, *J* = 7.5, 7.5, 1.0 Hz, C{5}–H), 6.71 (dd, 1H, *J* = 4.0, 1.0 Hz, C{2}–H), 4.58 (s, 2H, C{10}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 164.1 (C{9}), 135.7 (C{8}), 130.3 (C{3}), 125.70 (C{5}), 124.4 (C{6}), 124.2 (C{1}), 121.1 (C{4}), 116.7 (C{7}), 110.6 (C{2}), 42.4 (C{10}); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 216.9. C₁₀H₈³⁵ClNNaO⁺ requires 216.6. All data in accordance with literature.¹⁰

Dimethyl 2-(2-(1*H*-indol-1-yl)-2-oxoethyl)malonate, 7

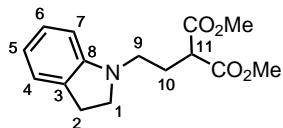


According to the modified procedure of Kerr,¹ dimethyl malonate (0.12 mL, 1.0 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 42 mg, 1.0 mmol) in THF (4.0 mL) which was then allowed to stir for 30 min at room temperature. After this time, a solution of 2-chloro-1-(1*H*-indol-1-yl)ethan-1-one **72** (100 mg, 0.52 mmol) in THF (1.0 mL) was added dropwise and the resulting solution allowed to stir at room temperature for 2 h. The reaction mixture was then quenched with water (10 mL) and extracted with Et₂O (3 × 20 mL). The organic layers were washed with brine (20 mL), dried (MgSO₄) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (30% Et₂O in PE_{40–60}) gave the *title compound* as a colourless oil (62 mg, 0.21 mmol, 41%).

R_f 0.28 (50% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 8.39 (d, 1H, *J* = 8.5 Hz, C{7}–H), 7.56 (ddd, 1H, *J* = 7.5, 1.5, 1.0 Hz, C{4}–H), 7.50 (d, 1H, *J* = 4.0 Hz, C{1}–H), 7.34 (ddd, 1H, *J* = 8.5, 7.0, 1.5 Hz, C{6}–H), 7.31–7.27 (m, 1H, C{5}–H), 6.68 (d, 1H, *J* = 4.0 Hz, C{2}–H), 4.16 (t, 1H, *J* = 7.0 Hz, C{11}–H), 3.82 (s, 6H, CO₂Me), 3.60 (d, 2H, *J* = 7.0 Hz, C{10}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 169.1 (CO₂Me), 130.5 (C{3}), 125.5 (C{5}), 124.4 (C{6}), 124.1 (C{1}), 121.1 (C{4}), 116.7 (C{7}), 110.1 (C{2}), 53.2 (CO₂Me), 47.3 (C{11}), 35.2 (C{10}), C{8} not observed; **ν/cm^{−1}**(film) 2955w, 1736s, 1704s, 1454m, 1317m, 753w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 290.10245. C₁₅H₁₆NO₅⁺

requires 290.10230.

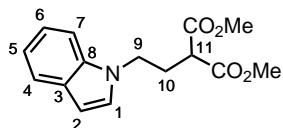
Dimethyl 2-(2-(indolin-1-yl)ethyl)malonate, 73



According to the modified procedure of Kerr,¹ indoline (0.21 mL, 1.9 mmol) and dimethyl cyclopropane-1,1-dicarboxylate (0.30 g, 1.9 mmol) were dissolved in toluene (4.0 mL) before the addition of ytterbium(III) trifluoromethanesulfonate hydrate (Yb 25–28% w/w, 59 mg, 0.10 mmol). The resulting solution was heated to reflux for 16 h. After this time, the yellow solution was allowed to cool down to room temperature and was partitioned between water (20 mL) and CH_2Cl_2 (30 mL). The phases were separated and the aqueous extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine, dried (MgSO_4) and evaporated *in vacuo* to give the *title compound* as a yellow oil (469 mg, 1.69 mmol, 89%).

\mathbf{R}_f 0.45 (30% EtOAc in PE_{40–60}, KMnO₄); ¹H NMR (400 MHz, CDCl_3) δ 7.09–7.02 (m, 2H, C{4,6}–H), 6.66 (ddd, 1H, J = 7.5, 7.5, 1.0 Hz, C{5}–H), 6.46 (d, 1H, J = 8.0 Hz, C{7}–H), 3.72 (s, 6H, CO_2Me), 3.57 (t, 1H, J = 7.5 Hz, C{11}–H), 3.33 (t, 2H, J = 8.5 Hz, C{1}–H), 3.13 (t, 2H, J = 7.0 Hz, C{9}–H); 2.95 (t, 2H, J = 8.5 Hz, C{2}–H); 2.23 (dt, 2H, J = 7.5, 7.0 Hz, C{10}–H); ¹³C NMR (101 MHz, CDCl_3) δ 169.9 (CO_2Me), 152.3 (C{8}), 130.1 (C{3}), 127.5 (C{6}), 124.6 (C{4}), 118.1 (C{5}), 107.3 (C{7}), 53.5 (C{1}), 52.7 (CO_2Me), 49.4 (C{11}), 47.5 (C{9}), 28.7 (C{2}), 27.1 (C{10}); LRMS (*m/z* +ESI): Found: [M+H]⁺, 278.1. $\text{C}_{15}\text{H}_{20}\text{NO}_4^+$ requires 278.1. All data in accordance with literature.¹

Dimethyl 2-(2-(1*H*-indol-1-yl)ethyl)malonate, 11

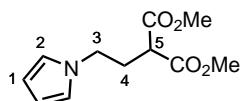


According to the modified procedure of Kerr,¹ DDQ (393 mg, 1.73 mmol) was added to a solution of dimethyl 2-(2-(indolin-1-yl)ethyl)malonate **73** (400 mg, 1.44 mmol) in dry toluene (7.0 mL) at room temperature. The reaction mixture was refluxed for 16 h. After this time, the reaction was allowed to cool to room temperature, diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO_4) and evaporated *in vacuo* to give a dark brown oil. Purification of the crude mixture by flash-chromatography (30% Et₂O in PE_{40–60}) gave the *title compound* as a colourless oil (237 mg, 0.861 mmol, 60%).

\mathbf{R}_f 0.24 (30% Et₂O in PE_{40–60}, KMnO₄); ¹H NMR (400 MHz, CDCl_3) δ 7.63 (ddd,

1H, $J = 8.0, 1.0, 1.0$ Hz, C{4}–H), 7.35 (ddd, 1H, $J = 8.0, 1.0, 1.0$ Hz, C{7}–H), 7.22 (ddd, 1H, $J = 8.0, 7.0, 1.0$ Hz, C{6}–H), 7.11 (ddd, 1H, $J = 8.0, 7.0, 1.0$ Hz, C{5}–H), 7.07 (d, 1H, $J = 3.0$ Hz, C{1}–H), 6.51 (dd, 1H, $J = 3.0, 1.0$ Hz, C{2}–H), 4.24 (t, 2H, $J = 7.0$ Hz, C{9}–H), 3.72 (s, 6H, CO₂Me), 3.32 (t, 1H, $J = 7.5$ Hz, C{11}–H), 2.45 (dt, 2H, $J = 7.5, 7.0$ Hz, C{10}–H); ¹³C NMR (101 MHz, CDCl₃) δ 169.3 (CO₂Me), 136.1 (C{8}), 128.8 (C{3}), 127.8 (C{1}), 121.8 (C{6}), 121.2 (C{4}), 119.7 (C{5}), 109.4 (C{7}), 101.9 (C{2}), 52.8 (CO₂Me), 48.9 (C{11}), 43.9 (C{9}), 29.4 (C{10}); LRMS (*m/z* +ESI): Found: [M+Na]⁺, 276.0. C₁₅H₁₈NO₄⁺ requires 276.1. All data in accordance with literature.¹¹

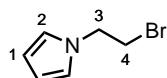
Dimethyl 2-(1*H*-pyrrol-1-yl)ethylmalonate, 17a



According to the modified procedure of Greenhouse,¹² pyrrole (0.10 mL, 1.5 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 60 mg, 24 mmol) in dry DMF (3.0 mL) and stirred for 30 min at room temperature. After this time, dimethyl cyclopropane-1,1-dicarboxylate (158 mg, 1.0 mmol) was added dropwise in DMF (1.0 mL). The resulting mixture was allowed to stir for 16 h at 60 °C. It was then quenched with sat. aq. NH₄Cl (15 mL) and extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), brine (20 mL), dried (MgSO₄) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (20% Et₂O in PE_{40–60}) afforded the *title compound* as a colourless oil (80 mg, 0.36 mmol, 36%).

R_f 0.17 (20% Et₂O in PE_{40–60}, KMnO₄); ¹H NMR (500 MHz, CDCl₃) δ 6.62 (t, 2H, $J = 2.0$ Hz, C{2}–H), 6.14 (t, 2H, $J = 2.0$ Hz, C{1}–H), 3.97 (t, 2H, $J = 7.0$ Hz, C{3}–H), 3.74 (s, 6H, CO₂Me), 3.28 (t, 1H, $J = 7.5$ Hz, C{5}–H), 2.35 (dt, 2H, $J = 7.5, 7.0$ Hz, C{4}–H); ¹³C NMR (126 MHz, CDCl₃) δ 169.4 (CO₂Me), 120.7 (C{2}), 108.7 (C{1}), 52.8 (CO₂Me), 48.7 (C{5}), 47.0 (C{3}); 30.8 (C{4}); $\tilde{\nu}$ /cm^{−1}(film) 2955w, 1731s, 1436m, 1154m, 727s; HRMS (*m/z* +ESI): Found: [M+H]⁺, 226.10759. C₁₁H₁₆NO₄⁺ requires 226.10848.

1-(2-Bromoethyl)-1*H*-pyrrole, 74



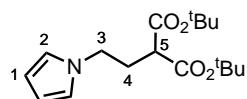
According to the modified procedure of Kandula,¹³ a mixture of 2-bromoethylamine hydrochloride (2.05 g, 10.0 mmol), NaOAc (820 mg, 10.0 mmol), H₂O (12 mL), acetic acid (4.0 mL), and 1,2-dichloroethane (12 mL) was heated to 80 °C before the addition of 2,5-dimethoxytetrahydrofuran (mixture of *cis* and *trans*, 1.3 mL, 10.0 mL). The resulting

Experimental Details

mixture was then allowed to stir at 90 °C for 1.5 h. After this time, the reaction was allowed to cool down and was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were dried (Na₂SO₄), and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (10% Et₂O in PE_{40–60}) provided the *title compound* as a colourless oil (1.05 g, 6.03 mmol, 60%).

R_f 0.59 (25% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 6.70 (t, 2H, *J* = 2.0 Hz, C{2}–H), 6.19 (t, 2H, *J* = 2.0 Hz, C{1}–H), 4.28 (t, 2H, *J* = 7.0 Hz, C{3}–H), 3.59 (t, 2H, *J* = 7.0 Hz, C{4}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 120.6 (**C{2}**), 108.8 (**C{1}**), 51.0 (**C{3}**), 31.0 (**C{4}**). All data in accordance with literature.¹³

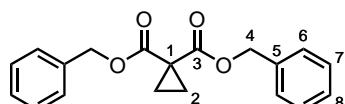
Di-*tert*-butyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 17b



According to the modified procedure of Browne,¹⁴ a mixture of 1-(2-bromoethyl)-1*H*-pyrrole **74** (174 mg, 1.0 mmol), di-*tert*-butyl malonate (0.17 mL, 0.75 mmol), and K₂CO₃ (138 mg, 1.0 mmol) in DMF (5.0 mL) was allowed to stir at 85 °C for 36 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (0% to 10% Et₂O in PE_{40–60}) provided the *title compound* as a colourless oil (75.1 mg, 0.24 mmol, 32%).

R_f 0.35 (10% acetone in PE_{40–60}, red in vanillin); **¹H NMR** (500 MHz, CDCl₃) δ 6.65 (t, 2H, *J* = 2.0 Hz, C{2}–H), 6.15 (t, 2H, *J* = 2.0 Hz, C{1}–H), 3.95 (t, 2H, *J* = 7.0 Hz, C{3}–H), 3.06 (t, 1H, *J* = 7.5 Hz, C{5}–H), 2.24 (tt, 2H, *J* = 7.5, 7.0 Hz, C{4}–H), 1.46 (s, 18H, CMe₃); **¹³C NMR** (126 MHz, CDCl₃) δ 168.3 (**CO₂R**), 120.6 (**C{2}**), 108.3 (**C{1}**), 81.8 (**CMe₃**), 50.9 (**C{5}**), 46.9 (**C{3}**), 30.6 (**C{4}**), 27.9 (**CMe₃**); **ν/cm⁻¹**(film) 2979m, 1725s, 1369m, 1140s, 724m; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 332.3314. C₁₇H₂₇NNaO₄⁺ requires 332.1832.

Dibenzyl cyclopropane-1,1-dicarboxylate, 75

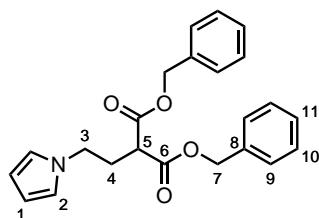


According to the modified procedure of Saruta,¹⁵ K₂CO₃ (6.9 g, 50 mmol) and 1,2-dibromoethane (1.20 mL, 15.0 mmol) were added to a solution of dibenzyl malonate (1.25 mL, 5.0 mmol) in DMF (14 mL). The resulting mixture was allowed to stir at room temperature for 16 h. After this time, the reaction was diluted with water (40 mL) and extracted with

EtOAc (3×20 mL). The combined organic layers were washed with brine (3×30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give the *title compound* as a colourless oil (968.4 mg, 3.12 mmol, 62%).

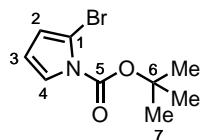
R_f 0.41 (30% Et₂O in PE_{40–60}, yellow in vanillin); **¹H NMR** (400 MHz, CDCl₃) δ 7.39–7.27 (m, 10H, C{6, 7, 8}–H), 5.16 (s, 4H, C{4}–H), 1.50 (s, 4H, C{2}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 169.7 (C{3}), 135.7 (C{5}), 128.7 (C{6/7/8}), 128.4 (C{6/7/8}), 128.2 (C{6/7/8}), 67.4 (C{4}), 28.4 (C{1}), 17.1 (C{2}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 333.0. C₁₉H₁₈NaO₄⁺ requires 333.1. All data in accordance with literature.¹⁵

Dibenzyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 17c



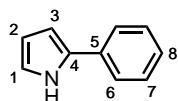
According to the modified procedure of Inaba,¹⁶ NaH (60% w/w dispersion in mineral oil, 96 mg, 2.4 mmol) was added to a solution of freshly distilled pyrrole (0.14 mL, 2.0 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) and allowed to stir at room temperature for 15 min. After this time, a solution of dibenzyl cyclopropane-1,1-dicarboxylate **75** (310 mg, 1.0 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) was added to the mixture, which was allowed to stir at 120 °C for 16 h. After this time, the reaction was quenched with water (1 mL) and filtered through a silica plug (eluted with EtOAc). All volatiles were evaporated *in vacuo*. The remaining oil was diluted with water (20 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (10% to 15% Et₂O in PE_{40–60}) provided the *title compound* as a colourless oil (138.5 mg, 0.37 mmol, 37%).

R_f 0.33 (30% Et₂O in PE_{40–60}, orange in vanillin); **¹H NMR** (500 MHz, CDCl₃) δ 7.36–7.31 (m, 6H, C{10, 11}–H), 7.31–7.27 (m, 4H, C{9}–H), 6.54 (t, 2H, *J* = 2.0 Hz, C{2}–H), 6.11 (t, 2H, *J* = 2.0 Hz, C{1}–H), 5.14 (s, 4H, C{7}–H), 3.91 (t, 2H, *J* = 7.0 Hz, C{3}–H), 3.35 (t, 1H, *J* = 7.5 Hz, C{5}–H), 2.37 (dt, 2H, *J* = 7.5, 7.0 Hz, C{4}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 168.6 (C{6}), 135.3 (C{8}), 128.8 (C{10}), 128.6 (C{11}), 128.4 (C{9}), 120.7 (C{2}), 108.6 (C{1}), 67.5 (C{7}), 49.1 (C{5}), 46.8 (C{3}), 30.7 (C{4}); **$\tilde{\nu}$ /cm^{−1}**(film) 2956w, 1731s, 1499w, 1150m, 729m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 378.1698. C₂₃H₂₃NO₄⁺ requires 378.1700.

***tert*-Butyl 2-bromo-1*H*-pyrrole-1-carboxylate, 76**

According to the modified procedure of Blagg,¹⁷ *N*-bromosuccinimide (1.78 g, 10.0 mmol) was added in 4 portions to a solution of freshly distilled pyrrole (0.70 mL, 10.0 mmol) in THF (27 mL) at -78 °C. The resulting green solution was kept at -20 °C for 2 h. The reaction mixture was then filtered through a cannula into a flask cooled to -78 °C. Triethyl amine (1.40 mL, 10.0 mmol) and 4-dimethylaminopyridine (61 mg, 0.50 mmol) were added, followed by a solution of di-*tert*-butyl dicarbonate (3.06 g, 14.0 mmol) in THF (5 mL). The resulting mixture was allowed to stir at room temperature for 16 h. After this time, all volatiles were evaporated *in vacuo*, and the residue obtained dissolved in EtOAc (40 mL), washed with water (3 × 30 mL), dried (Na₂SO₄), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (0% to 6% Et₂O in PE_{40–60}:NEt₃ 50:1) provided the *title compound* as a colourless oil (1.239 g, 5.03 mmol, 50%).

R_f 0.38 (5% EtOAc in PE_{40–60}, brown in vanillin); ¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, 1H, J = 3.5, 2.0 Hz, C{4}—H), 6.29 (dd, 1H, J = 3.5, 2.0 Hz, C{2}—H), 6.15 (t, 1H, J = 3.5 Hz, C{3}—H), 1.61 (s, 9H, C{7}—H); ¹³C NMR (101 MHz, CDCl₃) δ 148.1 (C{5}), 123.0 (C{4}), 117.2 (C{2}), 111.6 (C{3}), 100.3 (C{1}), 84.8 (C{6}), 27.8 (C{7}). All data in accordance with literature.¹⁷

2-Phenyl-1*H*-pyrrole, 77

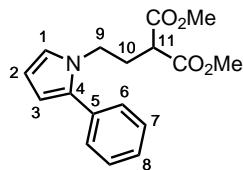
According to the modified procedure of Blagg:¹⁷

Step 1: K₂CO₃ (415 mg, 3.0 mmol) and phenylboronic acid (134 mg, 1.1 mmol) were added to a solution of *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **76** (246 mg, 1.0 mmol) in toluene (3.0 mL) in a microwave vial. EtOH (0.5 mL) and H₂O (0.5 mL) were then added to the mixture, which was degassed (Ar bubbling for 20 min). Pd(dppf)Cl₂ · CH₂Cl₂ (41 mg, 0.05 mmol) was then added, the vial sealed, and the reaction allowed to stir at 110 °C for 3 h. After this time, all volatiles were removed *in vacuo* and the resulting residue partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was re-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered through a short silica plug (eluted with EtOAc), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in MeOH/H₂O (3:1, 4.0 mL), and K₂CO₃ (415 mg, 3.0 mmol) added. The resulting dark brown mixture was allowed to stir at 75 °C for 16 h. After this time, volatiles were removed *in vacuo*, and the resulting residue was dissolved in water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na₂SO₄), and evaporated *in vacuo* to give a dark brown oil. Purification of the crude mixture by flash-chromatography (5% to 10% EtOAc in PE_{40–60}) provided the *title compound* as an off-white solid (77.2 mg, 0.54 mmol, 54% over 2 steps).

R_f 0.39 (20% EtOAc in PE_{40–60}, pink in vanillin); **m.p.** 125 (dec.) (lit.¹⁸ 130–132 °C); **¹H NMR** (400 MHz, CDCl₃) δ 8.43 (br, 1H, N—H), 7.54–7.43 (m, 2H, C{6}—H), 7.42–7.32 (m, 2H, C{7}—H), 7.25–7.17 (m, 1H, C{8}—H), 6.87 (ddd, 1H, *J* = 2.5, 2.5, 1.5 Hz, C{1}—H), 6.54 (ddd, 1H, *J* = 3.5, 2.5, 1.5 Hz, C{3}—H), 6.32 (ddd, 1H, *J* = 3.5, 2.5, 2.5 Hz, C{2}—H); **¹³C NMR** (101 MHz, CDCl₃) δ 132.9 (**C{4/5}**), 132.3 (**C{4/5}**), 129.0 (**C{7}**), 126.3 (**C{8}**), 124.0 (**C{6}**), 119.0 (**C{1}**), 110.3 (**C{2}**), 106.1 (**C{5}**); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 144.0. C₁₀H₁₀N⁺ requires 144.1. All data in accordance with literature.¹⁸

Dimethyl 2-(2-(2-phenyl-1*H*-pyrrol-1-yl)ethyl)malonate, 21b



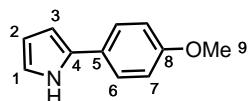
According to the modified procedure of Greenhouse,¹⁹ NaH (60% w/w dispersion in mineral oil, 22 mg, 0.55 mmol) was added to a solution of 2-phenyl-1*H*-pyrrole **77** (61 mg, 0.43 mmol) in DMF (2.5 mL) and allowed to stir for 30 min at room temperature. After this time, cyclopropane-1,1-dicarboxylate (0.14 mL, 1.0 mmol) was added, and the resulting solution allowed to stir at 60 °C for 16 h. It was then quenched with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na₂SO₄) and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (5% to 10% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (91.7 mg, 0.30 mmol, 70%).

R_f 0.15 (10% EtOAc in PE_{40–60}, red in vanillin); **¹H NMR** (400 MHz, CDCl₃) δ 7.42–7.33 (m, 4H, C{6,7}—H), 7.33–7.28 (m, 1H, C{8}—H), 6.74 (dd, 1H, *J* = 3.0, 1.5 Hz, C{1}—H), 6.22 (dd, 1H, *J* = 3.5, 3.0 Hz, C{2}—H), 6.18 (dd, 1H, *J* = 3.5, 1.5 Hz, C{3}—H), 4.04 (t, 2H, *J* = 7.0 Hz, C{9}—H), 3.63 (s, 6H, CO₂Me), 3.14 (t, 1H, *J* = 7.5 Hz, C{11}—H), 2.20 (dt, 2H, *J* = 7.5, 7.0 Hz, C{10}—H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.2 (**CO₂Me**), 134.6 (**C{4}**), 133.4 (**C{5}**), 129.1 (**C{6/7}**), 128.6 (**C{6/7}**), 127.2 (**C{8}**), 122.2 (**C{1}**), 109.4 (**C{3}**), 108.6 (**C{2}**), 52.7 (CO₂Me), 48.6 (**C{11}**), 44.6 (**C{9}**), 30.6 (**C{10}**); **HRMS** (*m/z*

+ESI): Found: [M+H]⁺, 302.1388. C₁₇H₂₀O₄N⁺ requires 302.1387.

Note: This compound proved unstable in CDCl₃, even when treated with basic alumina.

2-(4-Methoxyphenyl)-1*H*-pyrrole, 78



According to the modified procedure of Blagg:¹⁷

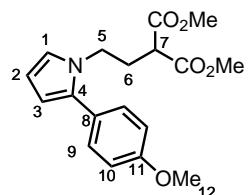
Step 1: K₂CO₃ (622 mg, 4.5 mmol) and 4-methoxyphenylboronic acid (251 mg, 1.65 mmol) were added to a solution of *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **76** (369 mg, 1.5 mmol) in toluene (4.5 mL) in a microwave vial. EtOH (0.75 mL) and H₂O (0.75 mL) were then added to the mixture, which was degassed (Ar bubbling for 20 min). Pd(dppf)Cl₂ · CH₂Cl₂ (61 mg, 0.075 mmol) was then added, the vial sealed, and the reaction allowed to stir at 110 °C for 6 h. After this time, all volatiles were removed *in vacuo* and the resulting residue partitioned between water (15 mL) and EtOAc (15 mL). The aqueous layer was re-extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na₂SO₄), filtered through a short silica plug (eluted with EtOAc), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in MeOH/H₂O (3:1, 6.0 mL), and K₂CO₃ (622 mg, 4.5 mmol) added. The resulting dark brown mixture was allowed to stir at 75 °C for 16 h. After this time, volatiles were removed *in vacuo*, and the resulting residue was dissolved in water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), and evaporated *in vacuo* to give a dark brown oil. Purification of the crude mixture by flash-chromatography (5% to 10% EtOAc in PE_{40–60}) provided the *title compound* as a grey solid (105.8 mg, 0.61 mmol, 41% over 2 steps).

R_f 0.17 (10% EtOAc in PE_{40–60}, red in vanillin); **m.p.** 138–142 °C (lit.²⁰ 147–148 °C)

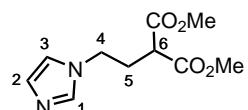
¹H NMR (400 MHz, CDCl₃) δ 8.34 (br, 1H, N–H), 7.44–7.37 (m, 2H, C{6}–H), 6.95–6.89 (m, 2H, C{7}–H), 6.83 (ddd, 1H, *J* = 2.5, 2.5, 1.5 Hz, C{1}–H), 6.41 (ddd, 1H, *J* = 3.5, 2.5, 1.5 Hz, C{3}–H), 6.28 (ddd, 1H, *J* = 3.5, 2.5, 2.5 Hz, C{2}–H), 3.83 (s, 3H, C{9}–H);

¹³C NMR (101 MHz, CDCl₃) δ 158.4 (**C{8}**), 132.3 (**C{4}**), 126.1 (**C{5}**), 125.4 (**C{6}**), 118.3 (**C{1}**), 114.5 (**C{7}**), 110.1 (**C{2}**), 105.0 (**C{3}**), 55.5 (**C{9}**); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 174.0. C₁₁H₁₂NO⁺ requires 174.1. All data in accordance with literature.²⁰

Dimethyl 2-(2-(4-methoxyphenyl)-1*H*-pyrrol-1-yl)ethyl)malonate, 21c

According to the modified procedure of Greenhouse,¹⁹ NaH (60% w/w dispersion in mineral oil, 48 mg, 1.2 mmol) was added to a solution of 2-(4-methoxyphenyl)-1*H*-pyrrole **78** (173 mg, 1.0 mmol) in DMF (5.0 mL) and allowed to stir for 30 min at room temperature. After this time, cyclopropane-1,1-dicarboxylate (0.28 mL, 2.0 mmol) was added, and the resulting solution allowed to stir at 60 °C for 16 h. It was then quenched with water (20 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (10% to 20% EtOAc in pentane) provided the *title compound* as a colourless oil (200.4 mg, 0.60 mmol, 60%).

R_f 0.40 (33% EtOAc in PE_{40–60}, red in vanillin); **¹H NMR** (500 MHz, CDCl_3) δ 7.30–7.26 (m, 2H, C{9}–H), 6.96–6.90 (m, 2H, C{10}–H), 6.71 (dd, 1H, *J* = 3.0, 2.0 Hz, C{1}–H), 6.20 (dd, 1H, *J* = 3.5, 3.0 Hz, C{2}–H), 6.11 (dd, 1H, *J* = 3.5, 2.0 Hz, C{3}–H), 3.99 (t, 2H, *J* = 7.0 Hz, C{5}–H), 3.84 (s, 3H, C{12}–H), 3.65 (s, 6H, CO₂Me), 3.15 (t, 1H, *J* = 7.5 Hz, C{7}–H), 2.19 (dt, 2H, *J* = 7.5, 7.5 Hz, C{6}–H); **¹³C NMR** (126 MHz, CDCl_3) δ 169.3 (CO₂Me), 159.0 (C{11}), 134.2 (C{4}), 130.5 (C{9}), 125.9 (C{8}), 121.6 (C{1}), 114.0 (C{10}), 108.9 (C{3}), 108.4 (C{2}), 55.4 (C{12}), 52.8 (CO₂Me), 48.7 (C{7}), 44.6 (C{5}), 44.6 (C{6}); **$\tilde{\nu}$ /cm^{−1}**(film) 2954w, 1733s, 1506m, 1249s, 837w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 332.1493. C₁₈H₂₂NO₅⁺ requires 332.1492.

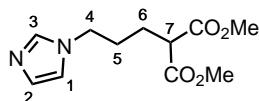
Dimethyl 2-(2-(1*H*-imidazol-1-yl)ethyl)malonate, 25

According to the modified procedure of Kerr,¹ imidazole (100 mg, 1.43 mmol) and ytterbium(III) trifluoromethanesulfonate hydrate (Yb 25–28% w/w, 30 mg, 0.05 mmol) were added to a solution of dimethyl cyclopropane-1,1-dicarboxylate (150 mg, 0.95 mmol) in toluene (4.0 mL). The resulting solution was allowed to stir at 125 °C for 16 h. After this time, the reaction mixture was allowed to cool down to room temperature, it was diluted with sat. aq. NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3×50 mL). The organic layers were combined, dried (MgSO₄) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture

by flash-chromatography (5% MeOH in CH₂Cl₂) gave the *title compound* as a colourless oil (105 mg, 0.437 mmol, 49%).

R_f 0.30 (5% MeOH in CH₂Cl₂, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.47 (s, 1H, C{5}—H), 7.07 (s, 1H, C{2}—H), 6.91 (s, 1H, C{3}—H), 4.04 (t, 2H, *J* = 7.0 Hz, C{4}—H), 3.74 (s, 6H, CO₂Me), 3.29 (t, 1H, *J* = 7.5 Hz, C{6}—H), 2.36 (dt, 2H, *J* = 7.5, 7.0 Hz, C{5}—H); **13C NMR** (126 MHz, CDCl₃) δ 169.0 (CO₂Me), 137.4 (C{1}), 130.0 (C{2}), 118.9 (C{3}), 53.0 (CO₂Me), 48.5 (C{6}), 44.5 (C{4}), 30.2 (C{5}); $\tilde{\nu}$ /cm⁻¹(film) 2956w, 1730s, 1437m, 1229m, 665w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 227.10280. C₁₀H₁₅N₂O₄⁺ requires 227.10263.

Dimethyl 2-(3-(1*H*-imidazol-1-yl)propyl)malonate, 23



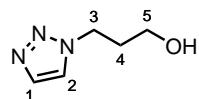
Step 1: According to the modified procedure of Zhang,⁷ 1,3-dibromopropane (1.0 mL, 10 mmol) and imidazole (0.34 g, 5.0 mmol) were added to a suspension of KOH (0.34 g, 6.0 mmol) in acetonitrile (2.5 mL) at 0 °C. The resulting mixture was allowed to stir for 3 h at 0 °C. After this time, the reaction was diluted with sat. aq. NaHCO₃ (40 mL) and extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were dried (MgSO₄), then diluted with DMF (10 mL) and evaporated *in vacuo* to give a colourless clear solution of 1-(3-bromopropyl)-1*H*-imidazole in DMF which was used with no further purification in the following step.

Step 2: Dimethyl malonate (2.9 mL, 25 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 1.0 g, 25 mmol) in dry DMF (40 mL) and stirred for 30 min at room temperature. After this time, the solution of 1-(3-bromopropyl)-1*H*-imidazole in DMF (10 mL) was added to the mixture, which was then allowed to stir for 16 h at room temperature. The reaction mixture was then cooled down to 0 °C, quenched with water (20 mL) and extracted with EtOAc (3 × 30mL)—these extracts were discarded. The aqueous layer was then extracted with CH₂Cl₂ (3 × 30mL), and the combined organic layers dried (MgSO₄) and evaporated *in vacuo* to give a clear oil. Purification of the crude mixture by flash-chromatography (3% MeOH in CH₂Cl₂) gave the *title compound* as a colourless oil (204 mg, 0.850 mmol, 17%).

R_f 0.14 3% MeOH in CH₂Cl₂, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.46 (br, 1H, C{3}—H), 7.04 (br, 1H, C{2}—H), 6.89 (br, 1H, C{1}—H), 3.94 (t, 2H, *J* = 7.0 Hz, C{4}—H), 3.71 (d, 6H, *J* = 1.0 Hz, CO₂Me), 3.33 (t, 1H, *J* = 7.0 Hz, C{7}—H), 1.95–1.75 (m, 4H, C{6}—H); **13C NMR** (101 MHz, CDCl₃) δ 169.4 (CO₂Me), 137.1 (C{3}), 129.7 (C{2}), 118.8 (C{1}), 52.8 (CO₂Me), 51.0 (C{7}), 46.6 (C{4}), 28.8 (C{5}), 25.8 (C{6});

$\tilde{\nu}/\text{cm}^{-1}$ (film) 2955w, 1729s, 1230m, 1154m, 665m; **HRMS** (m/z +ESI): Found: [M+H]⁺, 241.11819. C₁₁H₁₇N₂O₄⁺ requires 241.11828.

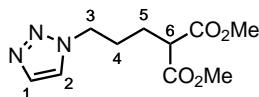
3-(1*H*-1,2,3-Triazol-1-yl)propan-1-ol , 79



According to the modified procedure of Sohn,²¹ K₂CO₃ (2.00 g, 14.5 mmol), KI (240 mg, 1.45 mmol) and 1,3-bromopropanol (1.0 mL, 10.8 mmol) were added to a solution of 1,2,3-triazole (500 mg, 7.25 mmol) in 1,4-dioxane (10 mL). The resulting mixture was allowed to stir at 100 °C for 4 h. After this time, the reaction mixture was allowed to cool down to room temperature, filtered and all volatiles evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (eluent: 5% MeOH in CH₂Cl₂; column size: Ø = 5 cm, L = 9 cm) gave the *title compound* as a colourless oil (401 mg, 3.15 mmol, 43%).

R_f 0.21 (10% MeOH in CH₂Cl₂, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.69 (d, 1H, *J* = 1.0 Hz, C{1}-H), 7.63 (d, 1H, *J* = 1.0 Hz, C{4}-H), 4.55 (t, 2H, *J* = 7.0 Hz, C{3}-H), 3.64 (t, 2H, *J* = 6.0 Hz, C{5}-H), 2.98 (s, 1H, O-H), 2.13 (tt, 2H, *J* = 7.0, 6.0 Hz, C{4}-H); **13C NMR** (101 MHz, CDCl₃) δ 133.7 (C{1}), 124.1 (C{2}), 58.7 (C{5}), 47.1 (C{3}), 32.8 (C{4}). All data in accordance with literature.²²

Dimethyl 2-(3-(1*H*-1,2,3-triazol-1-yl)propyl)malonate, 27



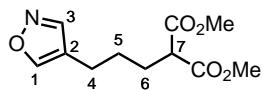
Step 1: According to the modified procedure of Itoh,²³ triethyl amine (0.37 mL, 2.7 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) were added dropwise to a solution of 3-(1*H*-1,2,3-triazol-1-yl)propan-1-ol **79** (225 mg, 1.77 mmol) in CH₂Cl₂ (8 mL) at 0 °C. The resulting mixture was allowed to stir for 1 h at room temperature. After this time, the reaction was quenched with 0.5 M aq. HCl (8 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated *in vacuo* to give a colourless oil, 3-(1*H*-1,2,3-triazol-1-yl)propyl methanesulfonate used in the next step without further purification.

Step 2: Dimethyl malonate (0.51 mL, 4.43 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 177 mg, 4.43 mmol) in DMF (8 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 3-(1*H*-1,2,3-triazol-1-yl)propyl methanesulfonate in THF (8 mL) was added dropwise to the mixture, which was then allowed to stir at 80 °C for 4 h. The reaction was then quenched with sat. aq. NH₄Cl (25 mL) and extracted with EtOAc (3 × 50 mL). The

combined organic layers were dried (MgSO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 80% EtOAc in PE_{40–60}; column size: $\varnothing = 3$ cm, L = 12 cm) gave the title compound as a colourless oil (196 mg, 0.81 mmol, 46%).

R_f 0.46 (EtOAc, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.70 (s, 1H, C{1}—H), 7.56 (s, 1H, C{2}—H), 4.41 (t, 2H, J = 7.0 Hz, C{3}—H), 3.73 (s, 6H, CO₂Me), 3.38 (t, 1H, J = 7.0 Hz, C{6}—H), 2.05–1.82 (m, 4H, C{4,5}—H); **13C NMR** (101 MHz, CDCl₃) δ 169.4 (CO₂Me), 134.0 (C{1}), 123.5 (C{2}), 52.8 (CO₂Me), 51.0 (C{6}), 49.7 (C{3}), 28.0 (C{4}), 25.8 (C{5}). **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 242.11364. C₁₀H₁₆O₄N₃⁺ requires 242.11353.

Dimethyl 2-(3-(isoxazol-4-yl)propyl)malonate, 31



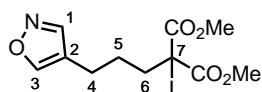
Step 1: According to the modified procedure of Itoh,²³ triethyl amine (0.37 mL, 2.7 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) were added dropwise to a solution of 3-(isoxazol-4-yl)propan-1-ol (250 mg, 1.97 mmol) in CH₂Cl₂ (8.0 mL) at 0 °C. The resulting mixture was allowed to stir for 25 min at room temperature. After this time, the reaction was quenched with 0.5 M aq. HCl (10 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (MgSO_4) and evaporated *in vacuo* to give a colourless oil, 3-(isoxazol-4-yl)propyl methanesulfonate, used in the next step without further purification.

Step 2: Dimethyl malonate (0.56 mL, 4.93 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 197 mg, 4.93 mmol) in DMF (8.0 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 3-(isoxazol-4-yl)propyl methanesulfonate in THF (8.0 mL) was added dropwise to the mixture, which was then allowed to stir at 80 °C for 2.5 h. The reaction was then quenched with sat. aq. NH₄Cl (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (MgSO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et₂O in PE_{40–60}; column size: $\varnothing = 3.5$ cm, L = 10 cm) gave the *title compound* as a colourless oil (224.2 mg, 0.93 mmol, 47%).

R_f 0.23 (40% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 8.22 (t, 1H, C{1}—H), 8.14 (s, 1H, C{3}—H), 3.73 (s, 6H, CO₂Me), 3.37 (t, 1H, J = 7.5 Hz, C{7}—H), 2.50 (t, 2H, J = 7.5 Hz, C{4}—H), 1.99–1.87 (m, 2H, C{6}—H), 1.68–1.54 (m, 2H, C{5}—H); **13C NMR** (101 MHz, CDCl₃) δ 169.7 (CO₂Me), 154.5 (C{1}), 150.2

(C{3}), 118.5 (C{2}), 52.7 (CO₂Me), 51.4 (C{7}), 28.3 (C{6}), 27.7 (C{5}), 21.9 (C{4}); $\tilde{\nu}$ /cm⁻¹(film) 2955w, 1731s, 1435m, 1148m, 851w; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 264.08419. C₁₁H₁₅O₅N²³Na⁺ requires 264.08424.

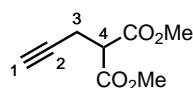
Dimethyl 2-iodo-2-(3-(isoxazol-4-yl)propyl)malonate, 29



The *title compound* was prepared from dimethyl 2-(3-(isoxazol-4-yl)propyl)malonate **31** (300 mg, 1.24 mmol) in accordance with **General Procedure A**. The crude residue was purified by flash-chromatography (eluent: 50% Et₂O in PE_{40–60}) to give the *title compound* as a yellow oil (344 mg, 0.94 mmol, 76% yield).

R_f 0.29 (50% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 8.25 (s, 1H, C{3}–H), 8.16 (s, 1H, C{1}–H), 3.80 (s, 6H, CO₂Me), 2.55 (t, 2H, *J* = 7.5 Hz, C{4}–H), 2.24–2.17 (m, 2H, C{6}–H), 1.73–1.63 (m, 2H, C{5}–H); **13C NMR** (126 MHz, CDCl₃) δ 168.7 (CO₂Me), 154.6 (C{3}), 150.2 (C{1}), 118.3 (C{2}), 54.2z (CO₂Me), 42.6 (C{7}), 39.6 (C{6}), 28.2 (C{5}), 21.7 (C{4}); $\tilde{\nu}$ /cm⁻¹(film) 2954w, 1732s, 1435m, 1249s, 1104m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 367.9989. C₁₁H₁₅INO₅⁺ requires 367.9989.

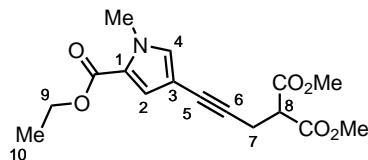
Dimethyl 2-(prop-2-yn-1-yl)malonate, 80



According to the modified procedure of Tang,²⁴ dimethyl malonate (1.7 mL, 15 mmol) and allyl bromide (1.1 mL, 10 mmol) were added to a suspension of K₂CO₃ in acetone (40 mL). The resulting mixture was allowed to stir at room temperature for 24 h. After this time, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (MgSO₄) and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (eluent: 5% MeOH in CH₂Cl₂; column size: Ø = 7 cm, L = 8 cm) gave the *title compound* as a colourless oil (1.06 g, 6.25 mmol, 63% yield).

R_f 0.52 (30% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 3.77 (s, 6H, CO₂Me), 3.61 (t, 1H, *J* = 8.0 Hz, C{4}–H), 2.79 (dd, 2H, *J* = 8.0, 3.0 Hz, C{3}–H), 2.02 (t, 1H, *J* = 3.0 Hz, C{1}–H); **13C NMR** (101 MHz, CDCl₃) δ 168.3 (CO₂Me), 79.8 (C{2}), 70.5 (C{1}), 52.8 (C{3}), 50.9 (CO₂Me), 18.5 (C{3}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 171.0. C₈H₁₁O₄⁺ requires 171.0. All data in accordance with literature.²⁴

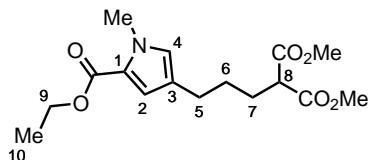
Dimethyl 2-(3-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)prop-2-yn-1-yl)malonate, 81



Prepared from ethyl 4-bromo-1-methyl-1*H*-pyrrole-2-carboxylate (116 mg, 0.50 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **80** (100 mg, 0.60 mmol) following **General Procedure D**. Purification of the crude mixture by flash-chromatography (eluent: 20% to 30% Et₂O in PE_{40–60}; column size: Ø = 4 cm, L = 8 cm) gave the *title compound* as a colourless oil (66 mg, 0.21 mmol, 41% yield).

R_f 0.17 (30% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 6.92 (d, 1H, *J* = 2.0 Hz, C{2}–H), 6.85 (d, 1H, *J* = 2.0 Hz, C{4}–H), 4.26 (q, 2H, *J* = 7.0 Hz, C{9}–H), 3.87 (s, 3H, N-Me), 3.77 (s, 6H, CO₂Me), 3.65 (t, 1H, *J* = 8.0 Hz, C{8}–H), 2.96 (d, 2H, *J* = 8.0 Hz, C{7}–H), 1.33 (t, 3H, *J* = 7.0 Hz, C{10}–H); **13C NMR** (126 MHz, CDCl₃) δ 168.7 (CO₂Me), 161.0 (CO₂Et), 132.3 (C{4}), 122.6 (C{1}), 120.6 (C{2}), 103.9 (C{3}), 83.8 (C{6}), 76.4 (C{5}), 60.2 (C{9}), 52.9 (CO₂Me), 51.5 (C{8}), 37.1 (N-Me), 19.7 (C{7}), 14.5 (C{10}); **ν/cm⁻¹**(film) 2956w, 1737s, 1702s, 1437m, 1101m; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 344.1104. C₁₆H₁₉NNaO₆⁺ requires 344.1105.

Dimethyl 2-(3-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)propyl) malonate, 63

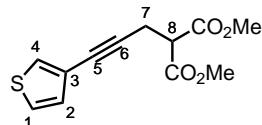


Prepared from dimethyl 2-(3-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)prop-2-yn-1-yl)malonate **81** (58 mg, 0.18 mmol) following **General Procedure E** to give the *title compound* as a brown oil (56 mg, 0.17 mmol, 94% yield).

R_f 0.35 (50% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 6.75 (d, 1H, *J* = 2.0 Hz, C{2}–H), 6.57 (d, 1H, *J* = 2.0 Hz, C{4}–H), 4.25 (q, 2H, *J* = 7.0 Hz, C{9}–H), 3.86 (s, 3H, N-Me), 3.73 (s, 6H, CO₂Me), 3.37 (t, 1H, *J* = 7.5 Hz, C{8}–H), 2.44 (t, 2H, *J* = 7.5 Hz, C{5}–H), 1.97–1.89 (m, 2H, C{7}–H), 1.61–1.52 (m, 2H, C{6}–H), 1.33 (t, 3H, *J* = 7.0 Hz, C{10}–H); **13C NMR** (126 MHz, CDCl₃) δ 170.0 (CO₂Me), 161.5 (CO₂Et), 127.7 (C{4}), 122.9 (C{3}), 122.4 (C{1}), 117.1 (C{2}), 59.8 (C{9}), 52.6 (CO₂Me), 51.7 (C{8}), 36.7 (N-Me), 28.8 (C{6}), 28.6 (C{7}), 26.3 (C{5}), 14.6 (C{10}); **ν/cm⁻¹**(film) 2954w, 1734s,

1697s, 1435m, 1097m; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 348.1418. C₁₆H₂₃NNaO₆⁺ requires 348.1418.

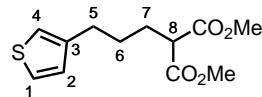
Dimethyl 2-(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate)-dicarboxylate, 82



Prepared from 3-bromothiophene (163 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **80** (204 mg, 1.20 mmol) following **General Procedure D**. Purification of the crude mixture by flash-chromatography (eluent: 20% Et₂O in PE_{40–60}; column size: Ø = 4 cm, L = 10 cm) gave the *title compound* as a yellow oil (140 mg, 0.56 mmol, 56%).

R_f 0.35 (33 % Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.36 (dd, 1H, *J* = 3.0, 1.0 Hz, C{4}–H), 7.22 (dd, 1H, *J* = 5.0, 3.0 Hz, C{1}–H), 7.04 (dd, 1H, *J* = 5.0, 1.0 Hz, C{2}–H), 3.78 (s, 6H, CO₂Me), 3.68 (t, 1H, *J* = 7.5 Hz, C{8}–H), 2.99 (d, 2H, *J* = 7.5 Hz, C{7}–H); **13C NMR** (126 MHz, CDCl₃) δ 168.6 (CO₂Me), 130.1 (C{2}), 128.6 (C{4}), 125.3 (C{1}), 122.2 (C{3}), 84.9 (C{6}), 77.7 (C{5}), 53.0 (CO₂Me), 51.3 (C{8}), 19.6 (C{7}); $\tilde{\nu}$ /cm⁻¹(film) 2954w, 1736s, 1436m, 1341m, 785m; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 275.0349. C₁₂H₁₂O₄NaS⁺ requires 275.0349.

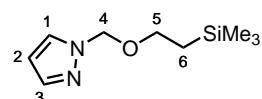
Dimethyl 2-(3-(thiophen-3-yl)propyl)malonate, 35



Prepared from dimethyl 2-(3-(thiophen-3-yl)propyl)malonate **82** (118 mg, 0.47 mmol) following **General Procedure E** to give the *title compound* as a yellow oil (112 mg, 0.44 mmol, 93%).

R_f 0.16 (20 % Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.24 (dd, 1H, *J* = 5.0, 3.0 Hz, C{1}–H), 6.95–6.93 (m, 1H, C{4}–H), 6.92 (dd, 1H, *J* = 5.0, 1.5 Hz, C{2}–H), 3.73 (s, 6H, CO₂Me), 3.38 (t, 1H, *J* = 7.5 Hz, C{8}–H), 2.66 (t, 2H, *J* = 7.5 Hz, C{5}–H), 1.99–1.91 (m, 2H, C{7}–H), 1.70–1.61 (m, 2H, C{6}–H); **13C NMR** (126 MHz, CDCl₃) δ 169.9 (CO₂Me), 142.0 (C{3}), 128.2 (C{2}), 125.5 (C{1}), 120.4 (C{4}), 52.7 (CO₂Me), 51.7 (C{8}), 29.9 (C{5}), 28.6 (C{7}), 28.3 (C{6}); $\tilde{\nu}$ /cm⁻¹(film) 2953w, 1734s, 1435m, 1154m, 776w; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 279.0663. C₁₂H₁₆O₄NaS⁺ requires 279.0662.

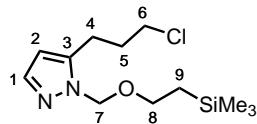
1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole, 83



According to the modified procedure of Cossy,²⁵ a solution of 1*H*-pyrazole (250 mg, 3.67 mmol) in THF (2.5 mL) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 220 mg, 5.5 mmol) in THF (2.5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h before the dropwise addition of 2-(trimethylsilyl)ethoxymethyl chloride (0.72 mL, 4.04 mmol) at 0 °C over 5 min. The reaction was allowed to stir at room temperature for 16 h. After this time, the mixture was cooled to 0 °C, quenched with water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 15% EtOAc in PE_{40–60}; column size: $\varnothing = 3$ cm, L = 11 cm) gave the *title compound* as a colourless oil (385 mg, 1.94 mmol, 53%).

\mathbf{R}_f 0.50 (15 % EtOAc in PE_{40–60}, red in vanillin); **1H NMR** (400 MHz, CDCl_3) δ 7.56 (dd, 1H, $J = 2.5, 0.5$ Hz, C{1}–H), 7.55 (dd, 1H, $J = 2.0, 0.5$ Hz, C{3}–H), 6.33 (dd, 1H, $J = 2.5, 2.0$ Hz, C{2}–H), 5.44 (s, 2H, $J = 6.0$ Hz, C{4}–H), 3.61–3.46 (m, 2H, C{5}–H), 0.96–0.78 (m, 2H, C{6}–H), −0.03 (s, 9H, Si(Me)₃); **13C NMR** (101 MHz, CDCl_3) δ 140.0 (C{3}), 129.5 (C{1}), 106.9 (C{2}), 80.2 (C{4}), 66.8 (C{5}), 17.9 (C{6}), −1.3 (Si(Me)₃); **LRMS** (*m/z* +ESI): Found: [M+Na]⁺, 221.0. $\text{C}_9\text{H}_{18}\text{N}_2\text{NaOSi}^+$ requires 221.1. All data in accordance with literature.²⁵

5-(3-Chloropropyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole, 84

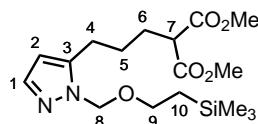


According to the modified procedure of Zhang,²⁶ *n*-BuLi (2.5 M in hexanes, 0.65 mL, 1.62 mmol) was added dropwise over 5 min to a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole **83** (230 mg, 1.16 mmol) in THF (9.0 mL) at −78 °C. The resulting solution was stirred at this temperature for 1.5 h, before the dropwise addition of 1-bromo-3-chloropropane (0.23 mL, 2.33 mmol). The mixture was then allowed to stir at room temperature for 16 h. After this time, the mixture was cooled to 0 °C, quenched with water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (MgSO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 20% Et₂O in PE_{40–60}; column size: $\varnothing = 3$ cm, L = 12 cm) gave the title compound as a colourless oil (110 mg, 0.40 mmol, 34%).

\mathbf{R}_f 0.26 (15% EtOAc in PE_{40–60}, vanillin); **1H NMR** (500 MHz, CDCl_3) δ 7.43 (d, 1H, $J = 2.0$ Hz, C{1}–H), 6.12 (d, 1H, $J = 2.0$ Hz, C{2}–H), 5.43 (s, 2H, C{7}–H), 3.58 (t, 2H, $J = 6.5$ Hz, C{6}–H), 3.56–3.51 (m, 2H, C{8}–H), 2.89 (t, 2H, $J = 7.5$ Hz, C{4}–H),

2.20–2.08 (m, 2H, C{5}–**H**), 0.95–0.81 (m, 2H, C{9}–**H**), –0.03 (s, 9H, Si(*Me*)₃); **¹³C NMR** (126 MHz, CDCl₃) δ 142.1 (**C{3}**), 139.1 (**C{1}**), 105.9 (**C{2}**), 77.9 (**C{7}**), 66.4 (**C{8}**), 44.1 (**C{6}**), 31.5 (**C{5}**), 22.5 (**C{4}**), 18.0 (**C{9}**), –1.3 (Si(*Me*)₃); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2955s, 1733m, 1248s, 1081s, 836s; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 275.13410. C₁₂H₂₄ON₂³⁵Cl²⁸Si⁺ requires 275.13409.

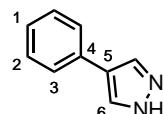
Dimethyl 2-(3-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)propyl)malonate, **43**



According to the modified procedure of Kerr,¹ dimethyl malonate (0.10 mL, 0.88 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 36 mg, 0.88 mmol) in DMF (1.7 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 5-(3-chloropropyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole **84** (95 mg, 0.35 mmol) in THF (1.7 mL) was added dropwise to the mixture, which was allowed to stir at 80 °C for 24 h. The reaction was then quenched with sat. aq. NH₄Cl (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (MgSO₄) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et₂O in PE_{40–60}; column size: Ø = 3 cm, L = 12 cm) gave the *title compound* as a colourless oil (81 mg, 0.22 mmol, 63%).

R_f 0.35 (67% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 7.40 (d, 1H, *J* = 2.0 Hz, C{1}–**H**), 6.09 (d, 1H, *J* = 2.0 Hz, C{2}–**H**), 5.40 (s, 2H, C{8}–**H**), 3.74 (s, 6H, CO₂*Me*), 3.55–3.47 (m, 2H, C{9}–**H**), 3.40 (t, 1H, *J* = 7.5 Hz, C{7}–**H**), 2.73 (t, 2H, *J* = 7.5 Hz, C{4}–**H**), 2.03–1.93 (m, 2H, C{6}–**H**), 1.78–1.66 (m, 2H, C{5}–**H**), 0.92–0.82 (m, 2H, C{10}–**H**), –0.04 (s, 9H, Si(*Me*)₃); **¹³C NMR** (126 MHz, CDCl₃) δ 169.8 (CO₂*Me*), 142.9 (**C{3}**), 139.0 (**C{1}**), 105.6 (**C{2}**), 77.9 (**C{8}**), 66.3 (**C{9}**), 52.7 (CO₂*Me*), 51.5 (**C{7}**), 28.5 (**C{6}**), 26.4 (**C{5}**), 24.9 (**C{4}**), 17.9 (**C{10}**), –1.3 (Si(*Me*)₃); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2953w, 1736s, 1436m, 1248m, 836w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 371.20005. C₁₇H₃₁O₅N₂²⁸Si⁺ requires 371.19968.

4-Phenyl-1*H*-pyrazole, **85**



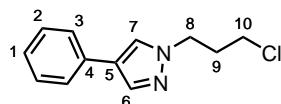
According to the modified procedure of Brooke:²⁷

Step 1: POCl₃ (2.0 mL, 21.4 mmol) was added to dry DMF (4.5 mL) over 30 min. The resulting mixture was then allowed to stir at room temperature for 1 h before the addition of phenyl acetic acid (1.0 g, 7.3 mmol). The reaction was then allowed to stir at 85 °C for 3 h. After this time, the reaction mixture was allowed to cool down and was poured onto ice (10 mL). Once stirred at room temperature for 30 min, NaBF₄ (1.5 g in 1.5 mL H₂O) was added, and the resulting yellow solid filtered. It was then washed with cold water (2 mL) and dried *in vacuo*.

Step 2: The aforementioned solid was added to NaOH (0.60 g in 10 mL H₂O) at 50 °C and the resulting mixture stirred until no solid remained. The solution was then neutralised with 10% w/w HCl to pH *ca.* 5 before the dropwise addition of hydrazine hydrate (50-60% w/w, 1.6 mL, 25.5 mmol). The resulting mixture was allowed to stir for 16 h. After this time, a white solid had formed, which was filtered off and dried *in vacuo* to give the *title compound* as a white crystalline solid (399 mg, 2.78 mmol, 38%).

R_f 0.22 (50 % EtOAc in PE_{40–60}, UV); **¹H NMR** (400 MHz, DMSO-d⁶) δ 8.05 (br, 2H, C{6}-H), 7.63–7.56 (m, 2H, C{3}-H), 7.38–7.29 (m, 2H, C{2}-H), 7.22–7.13 (m, 1H, C{1}-H); **¹³C NMR** (101 MHz, DMSO-d⁶) δ 132.8 (C{4}), 128.7 (C{2}), 125.8 (C{1}), 125.0 (C{3, 6}), 121.1 (C{5}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 145.0. C₉H₉N₂⁺ requires 145.1. All data in accordance with literature.²⁷

1-(3-chloropropyl)-4-phenyl-1*H*-pyrazole, 86

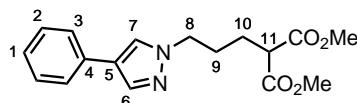


According to the modified procedure of Chen,²⁸ a mixture of 4-phenyl-1*H*-pyrazole **85** (144 mg, 1.00 mmol), 1-bromo-3-chloropropane (0.20 mL, 2.0 mmol) and caesium carbonate (391 mg, 1.20 mmol) was allowed to stir at 80 °C for 1.5 h. After this time, the reaction was allowed to cool to room temperature and poured into water (30 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL), washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (40% to 60% Et₂O in PE_{40–60}) gave the *title compound* as a colourless oil (160 mg, 0.72 mmol, 72%).

R_f 0.50 (50% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 7.80 (d, 1H, *J* = 1.0 Hz, C{6}-H), 7.68 (d, 1H, *J* = 1.0 Hz, C{7}-H), 7.51–7.45 (m, 2H, C{3}-H), 7.41–7.32 (m, 2H, C{2}-H), 7.26–7.19 (m, 1H, C{1}-H), 4.35 (t, 2H, *J* = 6.5 Hz, C{8}-H), 3.51 (t, 2H, *J* = 6.0 Hz, C{10}-H), 2.36 (tt, 2H, *J* = 6.5, 6.0 Hz, C{9}-H); **¹³C NMR** (126 MHz, CDCl₃) δ 137.4 (C{6}), 132.6 (C{4}), 129.0 (C{2}), 126.9 (C{7}), 126.6 (C{1}),

125.6 (**C{3}**), 123.1 (**C{5}**), 48.9 (**C{8}**), 41.8 (**C{10}**), 32.8 (**C{9}**); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2956w, 1607m, 954m, 760s, 695s; **HRMS** (m/z +ESI): Found: $[\text{M}+\text{H}]^+$, 221.0842. $\text{C}_{12}\text{H}_{14}\text{N}_2^{35}\text{Cl}^+$ requires 221.0840.

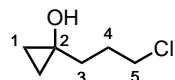
Dimethyl 2-(3-(4-phenyl-1*H*-pyrazol-1-yl)propyl)malonate, 45



According to the modified procedure of Browne,¹⁴ a mixture of 1-(3-chloropropyl)-4-phenyl-1*H*-pyrazole **86** (132 mg, 0.60 mmol), dimethyl malonate (0.27 mL, 2.4 mmol), and K_2CO_3 (332 mg, 2.4 mmol) in DMF (5.0 mL) was allowed to stir at 85 °C for 15 h. After this time, the solvent was evaporated under a flow of N_2 and the resulting residue partitioned between water (20 mL) and EtOAc (40 mL). The layers were separated and the aqueous re-extracted with EtOAc (2 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (30% to 40% EtOAc in PE_{40–60}) gave the *title compound* as a white solid (130 mg, 0.41 mmol, 68%).

R_f 0.31 (50% EtOAc in PE_{40–60}, KMnO_4); **m.p.** 66–67 °C; **¹H NMR** (500 MHz, CDCl_3) δ 7.77 (d, 1H, *J* = 1.0 Hz, C{6}–H), 7.63 (d, 1H, *J* = 1.0 Hz, C{7}–H), 7.50–7.44 (m, 2H, C{3}–H), 7.39–7.32 (m, 2H, C{2}–H), 7.25–7.18 (m, 1H, C{1}–H), 4.21–4.13 (m, 2H, C{8}–H), 3.73 (s, 6H, CO₂Me), 3.43–3.36 (m, 1H, C{11}–H), 2.01–1.89 (m, 4H, C{9, 10}–H); **¹³C NMR** (126 MHz, CDCl_3) δ 169.4 (CO₂Me), 136.9 (C{6}), 132.6 (C{4}), 128.8 (C{2}), 126.4 (C{1}), 126.0 (C{7}), 125.5 (C{3}), 123.0 (C{5}), 52.6 (CO₂Me), 51.8 (C{8}), 51.1 (C{11}), 28.0 (C{9}), 25.9 (C{10}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2954w, 1733s, 1608m, 1436m, 762m; **HRMS** (m/z +ESI): Found: $[\text{M}+\text{H}]^+$, 317.1497. $\text{C}_{17}\text{H}_{21}\text{O}_4\text{N}_2^+$ requires 317.1496.

1-(3-Chloropropyl)cyclopropan-1-ol, 87

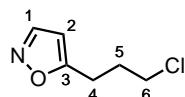


According to the modified procedure of Kananovich,²⁹ titanium(IV) isopropoxide (0.20 mL, 0.66 mmol) was added to a solution of ethyl 4-chlorobutanoate (1.00 g, 6.64 mmol) in Et₂O (13 mL). Ethyl magnesium bromide (1 M in Et₂O, 16.3 mL, 16.3 mmol) was added dropwise over 2.5 h at room temperature; the reaction was then allowed to stir for 1 h at the same temperature. After this time, the mixture was cooled down to 0 °C, quenched with 10% w/w aq. H₂SO₄ (13 mL) and extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (25 mL), dried (MgSO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et₂O in PE_{40–60};

column size: $\emptyset = 5$ cm, $L = 5.5$ cm) gave the *title compound* as a colourless oil (878.3 mg, 6.53 mmol, 98%).

R_f 0.33 (50% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 3.64 (t, 2H, $J = 6.5$ Hz, C{5}—H), 2.09–1.96 (m, 2H, C{4}—H), 1.85 (br, 1H, O—H), 1.74–1.61 (m, 2H, C{3}—H), 0.80–0.73 (m, 2H, C{1}—H), 0.52–0.44 (m, 2H, C{1'}—H); **13C NMR** (101 MHz, CDCl₃) δ 55.2 (C{2}), 45.2 (C{5}), 35.6 (C{3}), 29.4 (C{4}), 13.8 (C{1}). All data in accordance with literature.²⁹

5-(3-Chloropropyl)isoxazole, 88

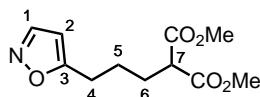


Step 1: According to the modified procedure of Kulinkovich,³⁰ isoamyl nitrite (0.80 mL, 5.96 mmol) was added to a solution of 1-(3-chloropropyl)cyclopropan-1-ol (200 mg, 1.49 mmol) in toluene (0.25 mL) at 0 °C. The reaction was allowed to stir at 0 °C for 2 h and then at room temperature for 87 h. After this time, all volatiles were evaporated *in vacuo* and the resulting oil used in the next step with no further purification.

Step 2: The aforementioned oil was dissolved in methanol (2.5 mL) and allowed to stir at 80 °C for 48 h. After this time, all volatiles were evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (eluent: 50% Et₂O in PE_{40–60}; column size: $\emptyset = 3.5$ cm, $L = 10$ cm) gave the *title compound* as a colourless oil (129.3 mg, 0.89 mmol, 60%).

R_f 0.69 (50% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 8.16 (s, 1H, C{1}—H), 6.04 (s, 1H, C{2}—H), 3.57 (t, 2H, $J = 6.5$ Hz, C{6}—H), 2.98 (t, 2H, $J = 7.5$ Hz, C{4}—H), 2.22–2.13 (m, 2H, C{5}—H); **13C NMR** (101 MHz, CDCl₃) δ 171.0 (C{3}), 150.3 (C{1}), 100.7 (C{2}), 43.6 (C{6}), 30.2 (C{5}), 23.8 (C{4}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 146.0. C₆H₉³⁵ClNO⁺ requires 146.0. All data in accordance with literature.³⁰

Dimethyl 2-(3-(isoxazol-5-yl)propyl)malonate, 37

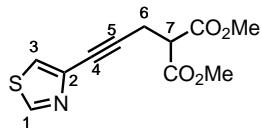


According to the modified procedure of Kerr,¹ dimethyl malonate (0.20 mL, 1.70 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 68 mg, 1.70 mmol) in DMF (3.5 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 5-(3-chloropropyl)isoxazole **88** (100 mg, 0.68 mmol) in THF (3.5 mL) was added dropwise to the mixture, which was then

allowed to stir at 80 °C for 16 h. The reaction was then quenched with sat. aq. NH₄Cl (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 50 mL) dried (MgSO₄) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 20% EtOAc in PE_{40–60}; column size: Ø = 3 cm, L = 9 cm) gave the *title compound* as a colourless oil (18.5 mg, 0.077 mmol, 11%).

R_f 0.56 (50% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 8.14 (d, 1H, *J* = 2.0 Hz, C{1}–H), 6.01 (dd, 1H, *J* = 2.0, 1.0 Hz, C{2}–H), 3.74 (s, 6H, CO₂Me), 3.39 (t, 1H, *J* = 7.5 Hz, C{7}–H), 2.81 (t, 2H, *J* = 7.5 Hz, C{4}–H), 2.01–1.93 (m, 2H, C{6}–H), 1.80–1.69 (m, 2H, C{5}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 171.9 (C{4}), 169.6 (CO₂Me), 150.4 (C{1}), 100.4 (C{2}), 52.8 (CO₂Me), 51.4 (C{7}), 28.3 (C{6}), 26.3 (C{4}), 25.4 (C{5}); $\tilde{\nu}$ /cm⁻¹(film) 2958w, 1731s, 1594w, 1435m, 1154s; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 264.08416. C₁₁H₁₅O₅N²³Na⁺ requires 264.08424.

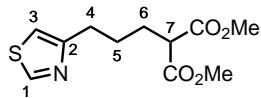
Dimethyl 2-(3-(thiazol-4-yl)prop-2-yn-1-yl)malonate, 89



Prepared from 4-bromothiazole (164 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **80** (204 mg, 1.20 mmol) following **General Procedure D**. Purification of the crude mixture by flash-chromatography (5% to 25% acetone in PE_{40–60}) gave the *title compound* as a yellow oil (124 mg, 0.49 mmol, 49%).

R_f 0.39 (40% acetone in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 8.73 (d, 1H, *J* = 2.0 Hz, C{1}–H), 7.42 (d, 1H, *J* = 2.0 Hz, C{3}–H), 3.79 (s, 6H, CO₂Me), 3.72 (t, 1H, *J* = 7.5 Hz, C{7}–H), 3.04 (d, 2H, *J* = 7.5 Hz, C{6}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 168.4 (CO₂Me), 152.4 (C{1}), 138.4 (C{2}), 122.1 (C{3}), 86.1 (C{5}), 76.5 (C{4}), 53.1 (CO₂Me), 50.9 (C{6}), 19.5 (C{7}); $\tilde{\nu}$ /cm⁻¹(film) 2955w, 1736s, 1436m, 1240m, 1158w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 254.0483. C₁₁H₁₂O₄NS⁺ requires 254.0482.

Dimethyl 2-(3-(thiazol-4-yl)propyl)malonate, 39

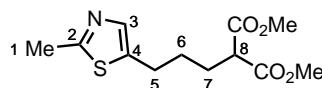


Prepared from dimethyl 2-(3-(thiophen-3-yl)propyl)malonate **89** (92.8 mg, 0.37 mmol) following **General Procedure E** (reaction time = 24 h) to give the *title compound* as a yellow oil (87.7 mg, 0.34 mmol, 92%).

R_f 0.14 (20% Et₂O in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 8.79 (d, 1H,

$J = 2.0$ Hz, C{1}–H), 7.00 (s, 1H, C{3}–H), 3.73 (s, 6H, CO₂Me), 3.40 (t, 1H, $J = 7.5$ Hz, C{7}–H), 2.88 (t, 2H, $J = 7.5$ Hz, C{4}–H), 2.00–1.93 (m, 2H, C{6}–H), 1.83–1.74 (m, 2H, C{5}–H); ¹³C NMR (126 MHz, CDCl₃) δ 169.9 (CO₂Me), 157.0 (C{2}), 152.7 (C{1}), 113.5 (C{3}), 52.7 (CO₂Me), 51.6 (C{7}), 30.8 (C{4}), 28.4 (C{6}), 27.0 (C{5}); $\tilde{\nu}$ /cm⁻¹(film) 2954w, 1733s, 1436m, 1150m, 731w; HRMS (*m/z* +ESI): Found: [M+H]⁺, 258.0796. C₁₁H₁₆O₄NS⁺ requires 258.0795.

Dimethyl 2-(3-(2-methylthiazol-5-yl)propyl)malonate, 41



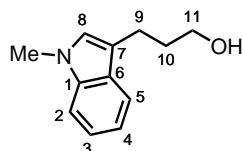
Step 1: According to the modified procedure of Kaufman,³¹ *n*-BuLi (2.5 M in hexanes, 2.7 mL, 6.8 mmol) was added dropwise to a solution of 2-methylthiazole (520 mg, 5.24 mmol) in THF (50 mL) at -78 °C. The resulting solution was allowed to stir at this temperature for 1 h before the addition of 1-bromo-3-chloropropane (1.0 mL, 11 mmol). The reaction was then allowed to warm up to room temperature and stirred for 16 h. After this time, the reaction mixture was quenched with water (6 mL) and all volatiles were evaporated *in vacuo*. The resulting oil was partitioned between water (30 mL) and EtOAc (50 mL), the layers separated and the aqueous re-extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (MgSO₄) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et₂O in PE_{40–60}; column size: Ø = 3.5 cm, L = 14 cm) gave a mixture of regioisomers of the desired 5-(3-chloropropyl)-2-methylthiazole, which was used in the next step without further purification (477.4 mg).

Step 2: According to the modified procedure of Kerr,³¹ dimethyl malonate (0.24 mL, 2.13 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 85 mg, 2.13 mmol) in DMF (4.0 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 5-(3-chloropropyl)-2-methylthiazole (150 mg, 0.85 mmol) in THF (4.0 mL) was added dropwise to the mixture, which was then allowed to stir at 80 °C for 24 h. The reaction was then quenched with sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (MgSO₄) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 50% to 60% Et₂O in PE_{40–60}; column size: Ø = 3 cm, L = 12 cm) gave the *title compound* as a colourless oil (101.4 mg, 0.37 mmol, 33%).

R_f 0.24 (50% Et₂O in PE_{40–60}, KMnO₄); ¹H NMR (500 MHz, CDCl₃) δ 7.28 (t, 1H, $J = 1.0$ Hz, C{3}–H), 3.74 (s, 6H, CO₂Me), 3.37 (t, 1H, $J = 7.5$ Hz, C{8}–H), 2.80 (t,

2H, $J = 7.5$ Hz, C{5}–H), 2.64 (s, 3H, C{1}–H), 2.00–1.90 (m, 2H, C{7}–H), 1.71–1.61 (m, 2H, C{6}–H); **^{13}C NMR** (126 MHz, CDCl_3) δ 169.7 (CO_2Me), 164.7 (C{2}), 139.3 (C{3}), 138.1 (C{4}), 52.7 (CO_2Me), 51.5 (C{8}), 29.3 (C{6}), 28.2 (C{7}), 26.8 (C{5}), 19.4 (C{1}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2955w, 1732s, 1436m, 1157s, 638w; **HRMS** (m/z +ESI): Found: [M+H]⁺, 272.09506. $\text{C}_{12}\text{H}_{18}\text{O}_4\text{N}^{32}\text{S}^+$ requires 272.09511.

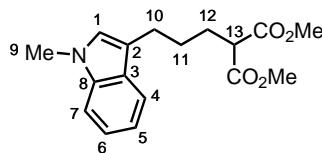
3-(1-Methyl-1*H*-indol-3-yl)propan-1-ol, 90



Step 1: According to the modified procedure of Franzén,³² acrolein (0.20 mL, 3.0 mmol) and *N*-methyl indole (0.56 mL, 4.50 mL) were added to a solution of tritylium tetrafluoroborate (10 mg, 0.030 mmol) in CH_2Cl_2 (10 mL). The resulting pale yellow solution was allowed to stir at room temperature for 16 h, by which time it had turned pink. This solution was then passed through a short silica plug, which was eluted with CH_2Cl_2 . All volatiles were evaporated *in vacuo* to give 3-(1-methyl-1*H*-indol-3-yl)propanal as a colourless oil, which was used in the next step without further purification.

Step 2: According to the modified procedure of Oestreich,³³ crude 3-(1-methyl-1*H*-indol-3-yl) propanal (all the previous crude) was dissolved in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1, 5.2 mL) and cooled to 0 °C. NaBH_4 (136 mg, 3.60 mmol) was added in 2 portions over 10 min. The resulting mixture was allowed to stir for 10 min at the same temperature before being quenched with 1.0 M aq. HCl (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (33% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (401.9 mg, 2.12 mmol, 71%).

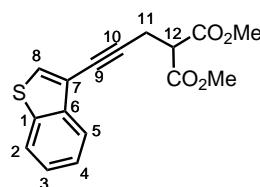
R_f 0.17 (33% EtOAc in PE_{40–60}, KMnO_4); **^1H NMR** (400 MHz, CDCl_3) δ 7.61 (ddd, 1H, $J = 8.0, 1.0, 1.0$ Hz, C{5}–H), 7.30 (ddd, 1H, $J = 8.0, 1.0, 1.0$ Hz, C{2}–H), 7.23 (ddd, 1H, $J = 8.0, 7.0, 1.0$ Hz, C{3}–H), 7.11 (ddd, 1H, $J = 8.0, 7.0, 1.0$ Hz, C{4}–H), 6.86 (s, 1H, C{8}–H), 3.75 (s, 3H, NMe), 3.73 (t, 2H, $J = 6.5$ Hz, C{11}–H), 2.86 (t, 2H, $J = 7.5$ Hz, C{9}–H), 1.99 (tt, 2H, $J = 7.5, 6.5$ Hz, C{10}–H); **^{13}C NMR** (101 MHz, CDCl_3) δ 137.1 (C{1}), 127.9 (C{6}), 126.1 (C{8}), 121.5 (C{3}), 119.0 (C{5}), 118.6 (C{4}), 114.4 (C{7}), 109.1 (C{2}), 62.7 (C{11}), 33.2 (C{10}), 32.5 (N–Me), 21.3 (C{9}); **LRMS** (m/z +ESI): Found: [M+H]⁺, 190.0. $\text{C}_{15}\text{H}_{17}\text{O}_4\text{N}_2^+$ requires 190.1. All data in accordance with literature.³³

Dimethyl 2-(3-(1-methyl-1*H*-indol-3-yl)propyl)malonate, 47

Step 1: Triethyl amine (0.21 mL, 1.5 mmol) and methanesulfonyl chloride (0.10 mL, 1.2 mmol) were added dropwise to a solution of 3-(1-methyl-1*H*-indol-3-yl)propan-1-ol) **90** (189 mg, 1.0 mmol) at 0 °C. The resulting solution was allowed to stir at room temperature for 1 h. After this time, it was quenched with sat. aq. NaHCO₃ (30 mL), and the mixture extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), and evaporated *in vacuo* to give 3-(1-methyl-1*H*-indol-3-yl)propyl methanesulfonate as a yellow oil.

Step 2: Crude 3-(1-methyl-1*H*-indol-3-yl)propyl methanesulfonate (all the previous crude) was dissolved in DMF (6.5 mL), before the addition of K₂CO₃ (553 mg, 4.0 mmol) and dimethyl malonate (0.46 mL, 4.0 mmol). The resulting mixture was stirred at 85 °C for 16 h. After this time, the reaction was diluted with water (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% to 50% Et₂O in PE_{40–60}) provided the *title compound* as a colourless oil (111.2 mg, 0.37 mmol, 37% over 2 steps).

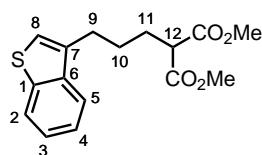
R_f 0.33 (50% Et₂O in PE_{40–60}, red in vanillin); **¹H NMR** (500 MHz, CDCl₃) δ 7.56 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.28 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.21 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.09 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.84 (s, 1H, C{1}–H), 3.74 (s, 3H, C{9}–H), 3.72 (s, 6H, CO₂Me), 3.41 (t, 1H, *J* = 7.5 Hz, C{13}–H), 2.78 (t, 2H, *J* = 7.5 Hz, C{10}–H), 2.06–1.97 (m, 2H, C{12}–H), 1.78–1.69 (m, 2H, C{11}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.9 (CO₂Me), 137.0 (C{8}), 127.7 (C{3}), 126.2 (C{1}), 121.5 (C{6}), 118.9 (C{4}), 118.6 (C{5}), 114.3 (C{2}), 109.1 (C{7}), 52.5 (CO₂Me), 51.6 (C{13}), 32.6 (C{9}), 28.7 (C{12}), 28.0 (C{11}), 24.7 (C{10}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 304.2. C₁₇H₂₂NO₄⁺ requires 304.2. All data in accordance with literature.³⁴

Dimethyl 2-(3-(benzo[b]thiophen-3-yl)prop-2-yn-1-yl)malonate, 91

Prepared from 3-bromobenzothiophene (213 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **80** (204 mg, 1.20 mmol) following **General Procedure D**. Purification of the crude mixture by flash-chromatography (eluent: 16% Et₂O in PE_{40–60}; column size: Ø = 4 cm, L = 10 cm) gave the *title compound* as a yellow oil (147 mg, 0.49 mmol, 49%).

R_f 0.33 (33 % Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.88 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{5}–H), 7.83 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{2}–H), 7.53 (s, 1H, C{8}–H), 7.43 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{4}–H), 7.38 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{3}–H), 3.81 (s, 6H, CO₂Me), 3.77 (t, 1H, *J* = 7.5 Hz, C{12}–H), 3.12 (d, 2H, *J* = 7.5 Hz, C{11}–H); **13C NMR** (126 MHz, CDCl₃) δ 168.6 (CO₂Me), 139.5 (C{1}), 138.9 (C{6}), 129.7 (C{8}), 125.1 (C{3}), 124.8 (C{4}), 123.0 (C{5}), 122.7 (C{2}), 118.3 (C{7}), 87.9 (C{10}), 76.4 (C{9}), 53.0 (CO₂Me), 51.4 (C{12}), 19.8 (C{11}); $\tilde{\nu}$ /cm⁻¹(film) 2954w, 1737s, 1435m, 1159m, 760w; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 325.0505. C₁₆H₁₄O₄NaS⁺ requires 325.0505.

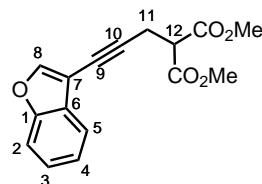
Dimethyl 2-(3-(benzo[b]thiophen-3-yl)propyl)malonate, **49**



Prepared from dimethyl 2-(3-(thiophen-3-yl)propyl)malonate **91** (124 mg, 0.41 mmol) following **General Procedure E** to give the *title compound* as a yellow oil (122 mg, 0.40 mmol, 97%).

R_f 0.14 (20 % Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.85 (d, 1H, *J* = 8.0 Hz, C{2}–H), 7.72 (d, 1H, *J* = 8.0 Hz, C{5}–H), 7.38 (ddd, 1H, *J* = 8.0, 7.5, 1.5 Hz, C{4}–H), 7.34 (ddd, 1H, *J* = 7.5, 7.0, 1.5 Hz, C{3}–H), 7.11 (s, 1H, C{8}–H), 3.73 (s, 6H, CO₂Me), 3.42 (t, 1H, *J* = 7.5 Hz, C{12}–H), 2.88 (t, 2H, *J* = 7.5 Hz, C{9}–H), 2.08–1.99 (m, 2H, C{11}–H), 1.84–1.73 (m, 2H, C{10}–H); **13C NMR** (126 MHz, CDCl₃) δ 169.9 (CO₂Me), 140.6 (C{1}), 139.0 (C{6}), 136.0 (C{7}), 124.3 (C{3}), 124.0 (C{4}), 123.0 (C{2}), 121.7 (C{5}), 121.5 (C{8}), 52.7 (CO₂Me), 51.7 (C{12}), 28.8 (C{11}), 28.3 (C{9}), 26.9 (C{10}); $\tilde{\nu}$ /cm⁻¹(film) 2952w, 1732s, 1434m, 1149m, 762w; **HRMS** (*m/z* +ESI): Found: [M+Na]⁺, 329.0818. C₁₆H₁₈O₄NaS⁺ requires 329.0818.

Dimethyl 2-(3-(benzofuran-3-yl)prop-2-yn-1-yl)malonate, **92**

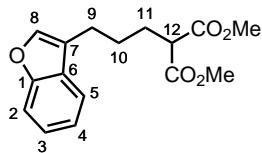


Experimental Details

Prepared from 3-bromobenzofuran (197 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **80** (204 mg, 1.20 mmol) following **General Procedure D**. Purification of the crude mixture by flash-chromatography (eluent: 10% to 25% Et₂O in PE_{40–60}; column size: Ø = 4 cm, L = 10 cm) gave the *title compound* as a yellow oil (94 mg, 0.33 mmol, 33%).

R_f 0.19 (20% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (400 MHz, CDCl₃) δ 7.73 (s, 1H, C{8}–H), 7.62 (d, 1H, *J* = 7.0 Hz, C{5}–H), 7.47 (d, 1H, *J* = 8.5 Hz, C{2}–H), 7.36–7.25 (m, 2H, C{3, 4}–H), 3.80 (s, 6H, CO₂Me), 3.74 (t, 1H, *J* = 7.5 Hz, C{12}–H), 3.09 (d, 2H, *J* = 7.5 Hz, C{11}–H); **13C NMR** (126 MHz, CDCl₃) δ 168.5 (CO₂Me), 154.6 (C{1}), 147.5 (C{8}), 127.9 (C{6}), 125.2 (C{3}), 123.4 (C{4}), 120.5 (C{5}), 111.7 (C{2}), 104.4 (C{7}), 90.1 (C{10}), 72.1 (C{9}), 53.0 (CO₂Me), 51.4 (C{12}), 19.9 (C{11}); $\tilde{\nu}$ /cm⁻¹(film) 2955w, 1737s, 1435m, 1089w, 749m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 287.0916. C₁₆H₁₅O₅⁺ requires 287.0914.

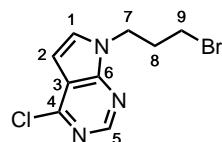
Dimethyl 2-(3-(benzofuran-3-yl)propyl)malonate, **51**



Prepared from dimethyl 2-(3-(benzofuran-3-yl)prop-2-yn-1-yl)malonate **92** (94 mg, 0.33 mmol) following **General Procedure E** to give the *title compound* as a colourless oil (81 mg, 0.28 mmol, 85%).

R_f 0.40 (50% Et₂O in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.53 (d, 1H, *J* = 8.0 Hz, C{2}–H), 7.46 (d, 1H, *J* = 8.0 Hz, C{5}–H), 7.42 (s, 1H, C{8}–H), 7.28 (dd, 1H, *J* = 8.0, 7.5 Hz, C{4}–H), 7.23 (dd, 1H, *J* = 8.0, 7.5 Hz, C{3}–H), 3.73 (s, 6H, CO₂Me), 3.41 (t, 1H, C{12}–H), 2.71 (t, 2H, C{9}–H), 2.06 – 1.97 (m, 2H, C{11}–H), 1.80 – 1.71 (m, 2H, C{10}–H); **13C NMR** (126 MHz, CDCl₃) δ 169.9 (CO₂Me), 155.5 (C{1}), 141.3 (C{8}), 128.2 (C{6}), 124.3 (C{4}), 122.4 (C{3}), 119.7 (C{7}), 119.7 (C{2}), 111.6 (C{5}), 52.6 (CO₂Me), 51.6 (C{12}), 28.7 (C{11}), 26.8 (C{10}), 23.4 (C{9}); $\tilde{\nu}$ /cm⁻¹(film) 2953w, 1733s, 1453m, 1153s, 748m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 291.1227. C₁₆H₁₉O₅⁺ requires 291.1227.

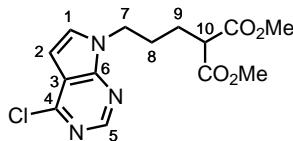
7-(3-Bromopropyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine, **93**



According to the modified procedure of Raić-Malić,³⁵ K₂CO₃ (829 mg, 6.0 mmol) was added to a solution of 6-chloro-7-deazapurine (768 mg, 5.0 mmol) in DMF (16 mL). The resulting mixture was allowed to stir at room temperature for 1 h before the addition of 1,3-dibromopropane (1.0 mL, 10.0 mmol). It was then allowed to stir for 16 h at the same temperature. After this time, all volatiles were evaporated under a flow of N₂. Purification of the crude mixture by flash-chromatography (10% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (858.4 mg, 3.13 mmol, 63%).

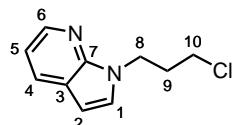
R_f 0.42 (33% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 8.60 (s, 1H, C{5}–H), 7.29 (d, 1H, *J* = 3.5 Hz, C{1}–H), 6.58 (d, 1H, *J* = 3.5 Hz, C{2}–H), 4.44 (t, 2H, *J* = 6.5 Hz, C{7}–H), 3.31 (t, 2H, *J* = 6.5 Hz, C{9}–H), 2.40 (tt, 2H, *J* = 6.5 Hz, C{8}–H); **13C NMR** (126 MHz, CDCl₃) δ 152.2 (C{4}), 150.9 (C{6}), 150.7 (C{5}), 129.6 (C{1}), 117.7 (C{3}), 99.6 (C{2}), 43.5 (C{7}), 32.4 (C{8}), 29.8 (C{9}); $\tilde{\nu}$ /cm⁻¹(film) 2947w, 1587s, 1351s, 923s, 726s; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 273.9742. C₉H₁₀N₃⁷⁹Br³⁵Cl⁺ requires 273.9741.

Dimethyl 2-(3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propyl)malonate, 53



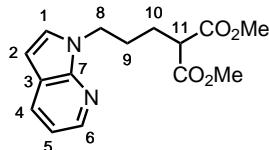
According to the modified procedure of Browne,¹⁴ a mixture of 7-(3-bromopropyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **93** (275 mg, 1.0 mmol), dimethyl malonate (0.46 mL, 4.0 mmol), and K₂CO₃ (553 mg, 4.0 mmol) in DMF (5.0 mL) was allowed to stir at 55 °C for 15 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (30% to 40% EtOAc in PE_{40–60}) provided the *title compound* as a pink oil (254.6 mg, 0.78 mmol, 78%).

R_f 0.29 (33% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 8.63 (s, 1H, C{5}–H), 7.25 (d, 1H, *J* = 3.5 Hz, C{1}–H), 6.62 (d, 1H, *J* = 3.5 Hz, C{2}–H), 4.30 (t, 2H, *J* = 6.5 Hz, C{7}–H), 3.71 (s, 6H, CO₂Me), 3.41 (t, 1H, *J* = 7.0 Hz, C{10}–H), 1.97–1.84 (m, 4H, C{8, 9}–H); **13C NMR** (126 MHz, CDCl₃) δ 169.3 (CO₂Me), 152.0 (C{4}), 150.9 (C{6}), 150.4 (C{5}), 129.1 (C{1}), 117.5 (C{3}), 99.8 (C{2}), 52.6 (CO₂Me), 50.8 (C{10}), 44.6 (C{7}), 27.8 (C{8}), 25.8 (C{9}); $\tilde{\nu}$ /cm⁻¹(film) 2954w, 1733s, 1352m, 1234m, 927w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 326.0904. C₁₄H₁₇³⁵ClN₃O₄⁺ requires 326.0902.

1-(3-chloropropyl)-1*H*-pyrrolo[2,3-*b*]pyridine, 94

According to the modified procedure of Aoki,³⁶ NaH (60% w/w dispersion in mineral oil, 800 mg, 20.0 mmol) was added to a solution of 7-azaindole (473 mg, 4.00 mmol) in DMF (6 mL) at 0 °C under argon. The resulting mixture was allowed to stir at room temperature for 30 min before the addition of 1-bromo-3-chloropropane (1.2 mL, 12 mmol). The reaction mixture was allowed to stir at room temperature for 15 h. After this time, it was quenched with water (20 mL) and extracted with Et₂O (3 × 40 mL). The combined organic layers were dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% to 40% EtOAc in PE_{40–60}) gave the *title compound* as a colourless oil (514 mg, 2.64 mmol, 66%).

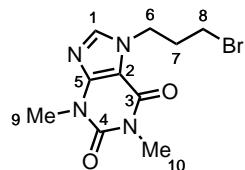
R_f 0.37 (33 % EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (400 MHz, CDCl₃) δ 8.31 (dd, 1H, *J* = 4.5, 1.5 Hz, C{6}–H), 7.91 (dd, 1H, *J* = 8.0, 1.5 Hz, C{4}–H), 7.26 (d, 1H, *J* = 3.5 Hz, C{1}–H), 7.07 (dd, 1H, *J* = 8.0, 4.5 Hz, C{5}–H), 6.46 (d, 1H, *J* = 3.5 Hz, C{2}–H), 4.49 (t, 2H, *J* = 6.5 Hz, C{8}–H), 3.49 (t, 2H, *J* = 6.5 Hz, C{10}–H), 2.36 (tt, 2H, *J* = 6.5 Hz, C{9}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 147.5 (C{7}), 143.0 (C{6}), 129.0 (C{4}), 128.6 (C{1}), 120.9 (C{3}), 115.9 (C{5}), 99.7 (C{2}), 42.2 (C{10}), 41.9 (C{8}), 32.8 (C{9}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 195.0. C₁₀H₁₂³⁵ClN₂⁺ requires 195.1. All data in accordance with literature.³⁶

Dimethyl 2-(3-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propyl)malonate, 55

According to the modified procedure of Browne,¹⁴ a mixture of 1-(3-chloropropyl)-1*H*-pyrrolo[2,3-*b*]pyridine **94** (195 mg, 1.0 mmol), dimethyl malonate (0.46 mL, 4.0 mmol), and K₂CO₃ (553 mg, 4.0 mmol) in DMF (8.0 mL) was allowed to stir at 85 °C for 16 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 2 M aq. HCl (3 × 10 mL). These extracts were then basified with 2 M aq. NaOH to pH *ca.* 10, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na₂SO₄), and evaporated *in vacuo* to give the *title compound* as a red oil (116.9 mg, 0.40 mmol, 40%).

R_f 0.19 (33% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 8.30 (dd, 1H, *J* = 4.5, 1.5 Hz, C{6}–H), 7.91 (dd, 1H, *J* = 8.0, 1.5 Hz, C{4}–H), 7.21 (d, 1H, *J* = 3.5 Hz, C{1}–H), 7.05 (dd, 1H, *J* = 8.0, 4.5 Hz, C{5}–H), 6.46 (d, 1H, *J* = 3.5 Hz, C{2}–H), 4.38–4.28 (m, 2H, C{8}–H), 3.70 (s, 6H, CO₂Me), 3.46–3.35 (m, 1H, C{11}–H), 1.99–1.88 (m, 4H, C{9, 10}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.6 (CO₂Me), 147.3 (C{7}), 142.6 (C{6}), 129.0 (C{4}), 127.9 (C{1}), 120.7 (C{3}), 115.7 (C{5}), 99.7 (C{2}), 52.6 (CO₂Me), 51.1 (C{11}), 44.1 (C{8}), 28.0 (C{9/10}), 26.0 (C{9/10}); **ν/cm⁻¹**(film) 2955w, 1734s, 1428m, 1234m, 776w; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 291.1341. C₁₅H₁₉N₂O₄⁺ requires 291.1339.

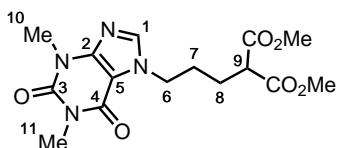
7-(3-Bromopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione, 95



According to the modified procedure of Firouzabadi,³⁷ K₂CO₃ (1.38 g, 10.0 mmol) and 1,3-dibromopropane (1.0 mL, 10.0 mmol) were added to a solution of theophylline (900 mg, 5.0 mmol) in DMF (25 mL). The resulting mixture was allowed to stir for 16 h. After this time, the reaction was diluted with water (40 mL) and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo* to give a white solid. Recrystallisation from hot ethanol provided the *title compound* as a white powder (530.9 mg, 1.77 mmol, 35%).

R_f 0.31 (EtOAc, KMnO₄); **m.p.** 132–134 °C (lit.³⁸ 132 °C); **¹H NMR** (400 MHz, DMSO-d⁶) δ 8.07 (s, 1H, C{1}–H), 4.35 (t, 2H, *J* = 7.0 Hz, C{6}–H), 3.46 (t, 2H, *J* = 6.5 Hz, C{8}–H), 3.42 (s, 3H, C{9}–H), 3.22 (s, 3H, C{10}–H), 2.35 (tt, 2H, *J* = 7.0, 6.5 Hz, C{7}–H); **¹³C NMR** (101 MHz, DMSO-d⁶) δ 154.3 (C{3}), 150.9 (C{4}), 148.5 (C{5}), 142.5 (C{1}), 106.0 (C{2}), 44.9 (C{6}), 32.7 (C{7}), 30.7 (C{8}), 29.4 (C{9}), 27.5 (C{10}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 303.0. C₁₀H₁₄⁸¹BrN₄O₂⁺ requires 303.0. All data in accordance with literature.³⁷

Dimethyl 2-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propyl)malonate, 57

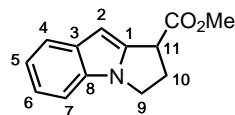


According to the modified procedure of Browne,¹⁴ a mixture of 7-(3-bromopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **95** (301 mg, 1.0 mmol), dimethyl malonate (0.46 mL, 4.0 mmol), and K₂CO₃ (553 mg, 4.0 mmol) in DMF (5.0 mL) was allowed to stir at 55 °C for 15 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (33% to 60% acetone in PE_{40–60}) gave the *title compound* as a white powder (251.6 mg, 0.71 mmol, 71%).

R_f 0.27 (EtOAc, KMnO₄); **m.p.** 108–110 °C; **¹H NMR** (500 MHz, CDCl₃) δ 7.55 (s, 1H, C{1}–H), 4.30 (t, 2H, *J* = 6.5 Hz, C{6}–H), 3.72 (s, 6H, CO₂Me), 3.58 (s, 3H, C{10}–H), 3.40 (s, 3H, C{11}–H), 3.39 (t, 1H, *J* = 7.0 Hz, C{9}–H), 1.99–1.85 (m, 4H, C{7, 8}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 169.3 (CO₂Me), 155.1 (C{4}), 151.7 (C{3}), 149.0 (C{2}), 140.9 (C{1}), 106.9 (C{5}), 52.7 (CO₂Me), 50.8 (C{9}), 46.7 (C{8}), 29.8 (C{10}), 28.5 (C{7}), 28.0 (C{11}), 25.4 (C{8}); **ν/cm^{−1}**(film) 2955w, 1733m, 1702s, 1657s, 1234m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 353.1458. C₁₅H₂₁N₄O₆⁺ requires 353.1456.

1.3.3 Product derivatisation

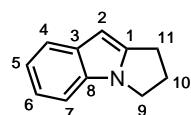
Methyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1-carboxylate, 59



Lithium chloride (84 mg, 2.0 mmol) was added to a solution of dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate **12** (110 mg, 0.40 mmol) in DMF/H₂O (100:1, 2.0 mL) at room temperature. The resulting solution was allowed to stir at 150 °C for 2 h. After this time, the reaction mixture was partitioned between Et₂O (15 mL) and water (10 mL). The layers were separated and the aqueous re-extracted with Et₂O (2 × 10 mL). The organic layers were combined, washed with water (4 × 10 mL), dried (Na₂SO₄) and evaporated to give a colourless oil. Purification of the crude mixture by flash-chromatography (5% to 25% EtOAc in pentane) provided the *title compound* as a colourless oil (73.2 mg, 0.34 mmol, 85%).

R_f 0.40 (20% EtOAc in PE_{40–60}, KMnO₄); **1H NMR** (500 MHz, CDCl₃) δ 7.57 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.25 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.15 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.08 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.35 (dd, 1H, *J* = 1.0, 1.0 Hz, C{2}–H), 4.29–4.18 (m, 2H, C{9, 11}–H), 4.10 (ddd, 1H, *J* = 9.5, 8.5, 5.0 Hz, C{9'}–H), 3.76 (s, 3H, CO₂Me), 3.00 (dddd, 1H, *J* = 13.0, 8.5, 5.0, 5.0 Hz, C{10}–H), 2.83 (dddd, 1H, *J* = 13.0, 8.5, 8.5, 6.0 Hz, C{10'}–H); **13C NMR** (126 MHz, CDCl₃) δ 172.3 (CO₂Me), 140.9 (C{1}), 132.9 (C{3}), 132.9 (C{8}), 121.2 (C{6}), 121.0 (C{4}), 119.6 (C{5}), 109.8 (C{7}), 94.4 (C{2}), 52.7 (CO₂Me), 43.2 (C{9}), 42.5 (C{11}), 31.5 (C{10}); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2951w, 1738s, 1457w, 1207m, 745m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 216.1021. C₁₃H₁₄O₂N⁺ requires 216.1019.

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole, 60

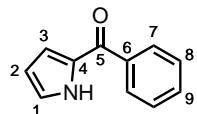


Lithium chloride (64 mg, 1.5 mmol) was added to a solution of dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate **12** (41 mg, 0.15 mmol) in DMF/H₂O (100:1, 1.5 mL) at room temperature. The resulting solution was allowed to stir at 150 °C for 18 h. After this time, the reaction mixture was partitioned between Et₂O (10 mL) and water (10 mL). The layers were separated and the aqueous re-extracted with Et₂O (2 × 10 mL). The organic layers were combined, washed with water (4 × 10 mL), dried (Na₂SO₄) and evaporated to give the *title compound* as a colourless oil (21.2 mg, 0.13 mmol, 89%).

R_f 0.58 (20% EtOAc in PE_{40–60}, KMnO₄); **¹H NMR** (500 MHz, CDCl₃) δ 7.57 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.26 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.14 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.08 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.19 (dt, 1H, *J* = 1.0, 1.0 Hz, C{2}–H), 4.08 (t, 2H, *J* = 7.0 Hz, C{9}–H), 3.04 (t, 2H, *J* = 7.5 Hz, C{11}–H), 2.63 (tt, 2H, *J* = 7.5, 7.0 Hz, C{10}–H); **¹³C NMR** (126 MHz, CDCl₃) δ 144.7 (C{1}), 133.4 (C{3/8}), 132.8 (C{3/8}), 120.4 (C{4}), 120.2 (C{6}), 119.2 (C{5}), 109.5 (C{7}), 92.4 (C{2}), 43.7 (C{9}), 28.0 (C{10}), 24.4 (C{11}); **ν/cm⁻¹**(film) 2951w, 1738s, 1479m, 1207m, 771m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 216.1021. C₁₃H₁₄O₂N⁺ requires 216.1019.

1.3.4 Synthesis of ketorolac

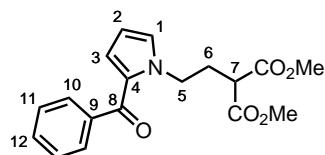
Phenyl(1*H*-pyrrol-2-yl)methanone, 62



According to the modified procedure of Booker-Milburn,³⁹ morpholino(phenyl)methanone (574 mg, 3.0 mmol) was added to freshly distilled POCl₃ (0.60 mL, 6.5 mmol) and the resulting mixture was allowed to stir at 35 °C until full dissolution. The resulting colourless solution was then allowed to stir at room temperature for 5 h, before a solution of freshly distilled pyrrole (0.14 mL, 2.0 mmol) in CH₂Cl₂ (8 mL) was added rapidly. The reaction was allowed to stir at the same temperature for 16 h. After this time, the reaction was carefully neutralised with sat. aq. NaHCO₃ (20 mL), and allowed to stir for 15 min at room temperature, then for 3 h at 55 °C. The mixture was then allowed to cool down, the layers separated, and the aqueous extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% EtOAc in PE_{40–60}) provided the *title compound* as a white solid (338.7 mg, 1.98 mmol, 98%).

R_f 0.56 (50% EtOAc in PE_{40–60}, brown in vanillin); **m.p.** 78–80 °C (lit.³⁹ 78–81 °C)
¹H NMR (500 MHz, CDCl₃) δ 9.89 (br, 1H, N–H), 7.98–7.84 (m, 2H, C{7}–H), 7.62–7.53 (m, 1H, C{9}–H), 7.53–7.45 (m, 2H, C{8}–H), 7.16 (ddd, 1H, *J* = 2.5, 2.5, 1.5 Hz, C{1}–H), 6.90 (ddd, 1H, *J* = 4.0, 2.5, 1.5 Hz, C{3}–H), 6.35 (ddd, 1H, *J* = 4.0, 2.5, 2.5 Hz, C{2}–H);
¹³C NMR (126 MHz, CDCl₃) δ 184.8 (C{5}), 138.3 (C{6}), 131.8 (C{9}), 131.1 (C{4}), 129.0 (C{7}), 128.3 (C{8}), 125.3 (C{1}), 119.5 (C{3}), 111.0 (C{2}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 172.0. C₁₁H₁₀NO⁺ requires 172.1. All data in accordance with literature.³⁹

Dimethyl 2-(2-(2-benzoyl-1*H*-pyrrol-1-yl)ethyl)malonate, 21a



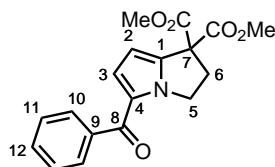
Step 1: According to the modified procedure of Lautens,⁴⁰ KOH (1.41 g, 25.0 mmol) was added to a solution of phenyl(1*H*-pyrrol-2-yl)methanone **62** (430 mg, 2.50 mmol) in DMSO (6.25 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 1 h, before the addition of 1,2-dibromoethane (4.3 mL, 50 mmol). The reaction was then allowed to stir for 1 h. After this time, the reaction mixture was diluted with water (40 mL) and extracted

with EtOAc (3×30 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in DMF (14 mL) before the addition of dimethyl malonate (0.95 mL, 8.3 mmol) and K_2CO_3 (1.15 g, 8.3 mmol). The resulting mixture was allowed to stir at 60 °C for 2 h and 20 min. After this time, the mixture was diluted with water (50 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (15% to 25% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (219.2 mg, 0.67 mmol, 32% over 2 steps).

\mathbf{R}_f 0.28 (30% EtOAc in PE_{40–60}, orange in vanillin); **^1H NMR** (500 MHz, CDCl_3) δ 7.80–7.74 (m, 2H, C{10}–H), 7.56–7.51 (m, 1H, C{12}–H), 7.47–7.42 (m, 2H, C{11}–H), 6.97 (dd, 1H, $J = 2.5, 1.5$ Hz, C{1}–H), 6.74 (dd, 1H, $J = 4.0, 1.5$ Hz, C{3}–H), 6.18 (dd, 1H, $J = 4.0, 2.5$ Hz, C{2}–H), 4.50 (t, 2H, $J = 7.0$ Hz, C{5}–H), 3.73 (s, 6H, CO_2Me), 3.40 (t, 1H, $J = 7.0$ Hz, C{7}–H), 2.45 (dt, 2H, $J = 7.0, 7.0$ Hz, C{6}–H); **^{13}C NMR** (126 MHz, CDCl_3) δ 186.2 (C{8}), 169.5 (CO_2Me), 140.1 (C{9}), 131.5 (C{12}), 131.0 (C{1}), 130.0 (C{4}), 129.3 (C{10}), 128.2 (C{11}), 123.8 (C{3}), 108.8 (C{2}), 52.8 (CO_2Me), 48.9 (C{7}), 47.0 (C{5}), 30.7 (C{6}); **LRMS** (*m/z* +ESI): Found: [M+H]⁺, 352.0. $\text{C}_{18}\text{H}_{19}\text{NNaO}_5^+$ requires 352.1. All data in accordance with literature.⁴¹

Dimethyl 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22a

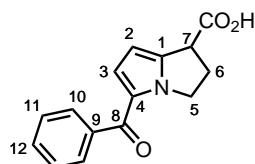


According to **General Procedure B**, using dimethyl 2-(2-(2-benzoyl-1*H*-pyrrol-1-yl)ethyl)malonate **21a** (66 mg, 0.20 mmol) (irradiation time = 48 h). Purification by flash-chromatography (10% to 25% EtOAc in PE_{40–60}) provided the *title compound* as a colourless oil (52.8 mg, 0.16 mmol, 81% yield).

\mathbf{R}_f 0.41 (40% EtOAc in PE_{40–60}, orange in vanillin); **^1H NMR** (500 MHz, CDCl_3) δ 7.86–7.79 (m, 2H, C{10}–H), 7.57–7.50 (m, 1H, C{12}–H), 7.48–7.42 (m, 2H, C{11}–H), 6.84 (d, 1H, $J = 4.0$ Hz, C{3}–H), 6.27 (d, 1H, $J = 4.0$ Hz, C{2}–H), 4.55 (t, 2H, $J = 7.0$ Hz, C{5}–H), 3.81 (s, 6H, CO_2Me), 3.14 (t, 2H, $J = 7.0$ Hz, C{6}–H); **^{13}C NMR** (126 MHz, CDCl_3) δ 185.4 (C{8}), 169.2 (CO_2Me), 140.4 (C{1}), 139.1 (C{9}), 131.7 (C{12}), 129.1 (C{10}), 128.3 (C{11}), 127.6 (C{4}), 124.7 (C{3}), 105.0 (C{2}), 58.9 (C{7}), 53.6

(CO₂*Me*), 47.1 (**C{5}**), 36.6 (**C{6}**); $\tilde{\nu}/\text{cm}^{-1}$ (film) 2955w, 1737s, 1625m, 1262s, 1099m; **HRMS** (*m/z* +ESI): Found: [M+H]⁺, 328.1178. C₁₈H₁₈NO₅⁺ requires 328.1179.

5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, 2



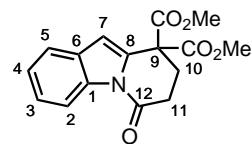
According to the modified procedure of Muchowski,⁴² 1 M aq. NaOH (0.12 mL, 0.12 mmol) was added to a solution of dimethyl 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate **96** (20 mg, 0.061 mmol) in MeOH (2.0 mL). The resulting solution was allowed to stir at room temperature for 16 h. After this time, all volatiles were removed *in vacuo* and the resulting residue was dissolved in water (5 mL). This solution was washed with EtOAc (2 × 5 mL), and then acidified with 2 M aq. HCl to pH *ca.* 2. The acidic aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na₂SO₄) and evaporated *in vacuo* to give the *title compound* as a white solid (13.5 mg, 0.053 mmol, 87%).

R_f 0.05 (40% EtOAc in PE_{40–60}, KMnO₄); **m.p.** 159–160 °C (lit.⁴³ 160–161 °C); **¹H NMR** (400 MHz, CDCl₃) δ 7.87–7.75 (m, 2H, C{10}–H), 7.58–7.49 (m, 1H, C{12}–H), 7.49–7.39 (m, 2H, C{11}–H), 6.84 (d, 1H, *J* = 4.0 Hz, C{3}–H), 6.15 (d, 1H, *J* = 4.0 Hz, C{2}–H), 4.58 (ddd, 1H, *J* = 12.0, 8.5, 6.0 Hz, C{5}–H), 4.47 (ddd, 1H, *J* = 12.0, 8.5, 6.0 Hz, C{5'}–H), 4.11 (dd, 1H, *J* = 9.0, 5.5 Hz, C{7}–H), 3.02–2.74 (m, 2H, C{6}–H); **¹³C NMR** (101 MHz, CDCl₃) δ 185.3 (**C{8}**), 176.8 (CO₂H), 141.9 (**C{1}**), 139.2 (**C{9}**), 131.6 (**C{12}**), 129.1 (**C{10}**), 128.3 (**C{11}**), 127.4 (**C{4}**), 125.3 (**C{3}**), 103.6 (**C{2}**), 47.7 (**C{5}**), 42.5 (**C{7}**), 31.1 (**C{6}**); $\tilde{\nu}/\text{cm}^{-1}$ (film) 3000br (CO₂H), 1739s, 1712s, 1270s, 723s; **HRMS** (*m/z* +ESI): Found: [M–H][–], 254.0832. C₁₅H₁₂NO₃[–] requires 254.0823. All data in accordance with literature.⁴⁴

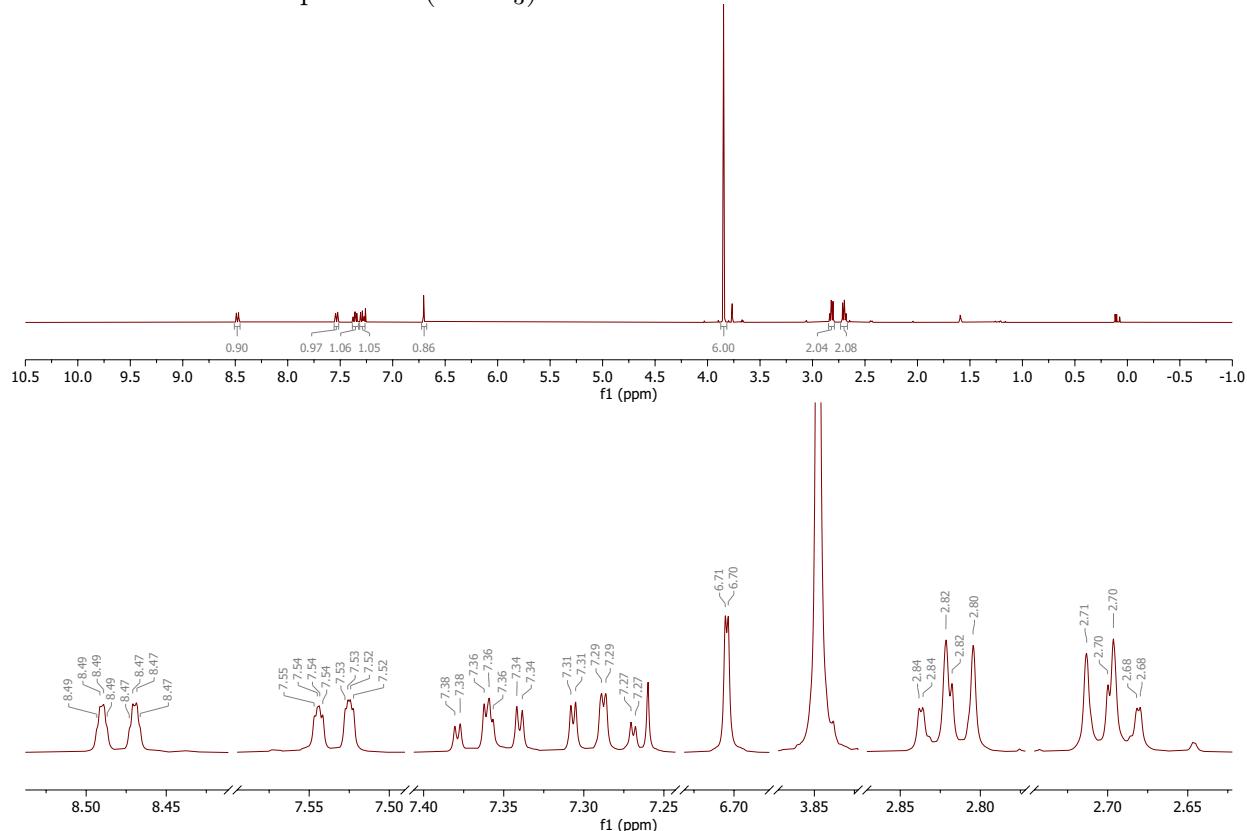
1.4 NMR Spectra

1.4.1 Cyclisation products

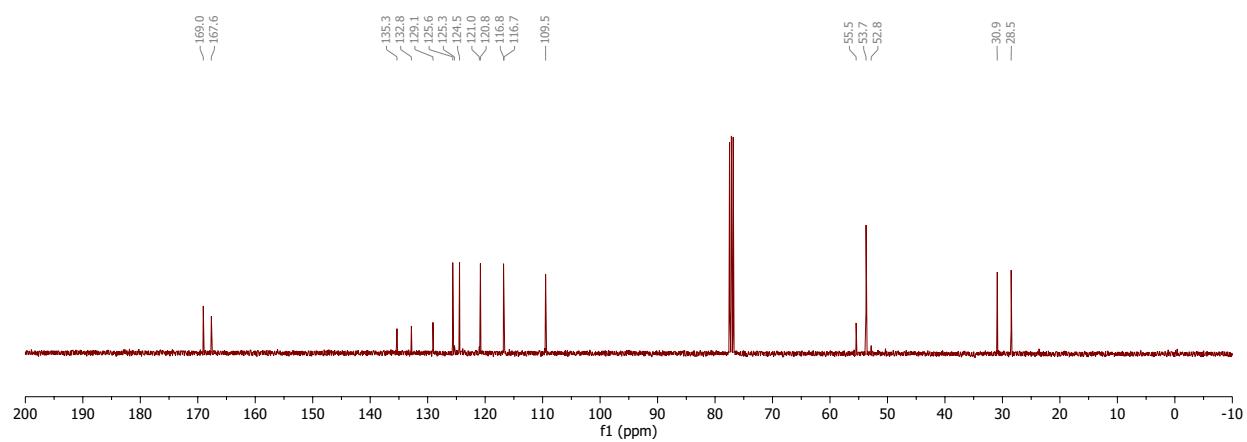
Dimethyl 6-oxo-7,8-dihydropyrido[1,2-*a*]indole-9,9(6*H*)-dicarboxylate, 5

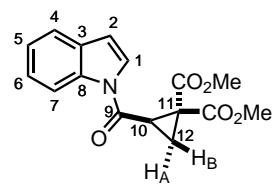
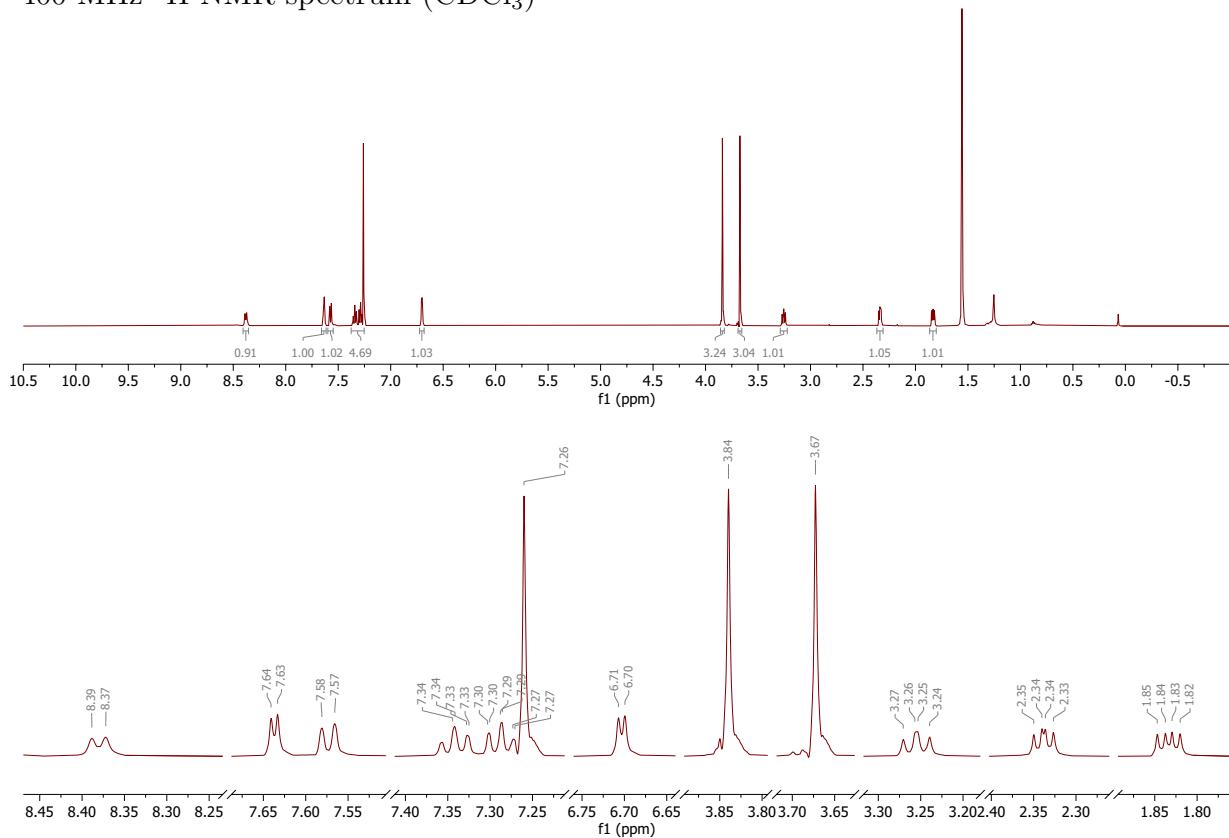
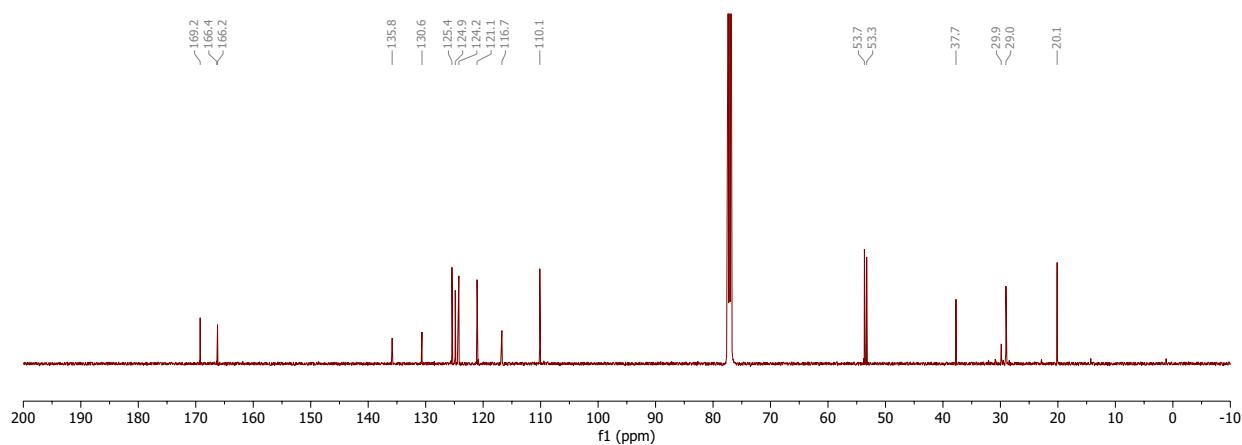


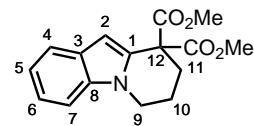
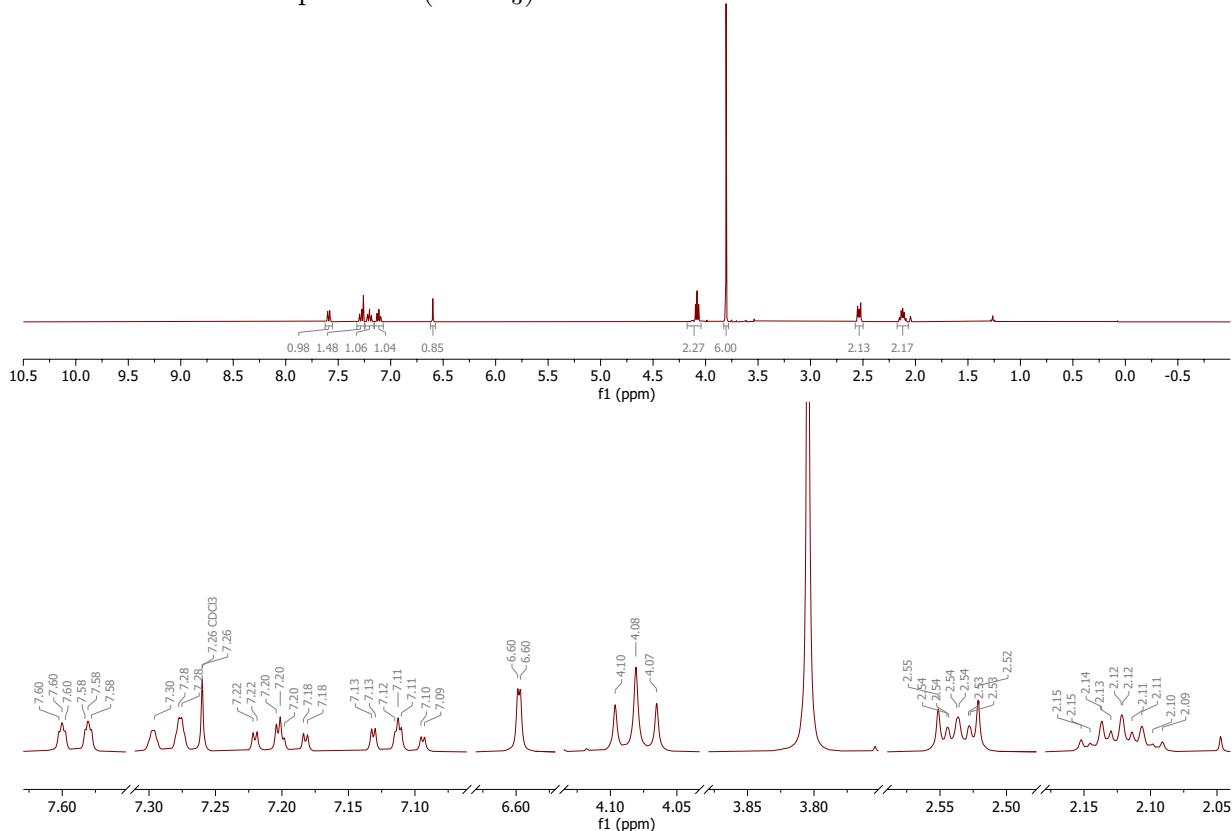
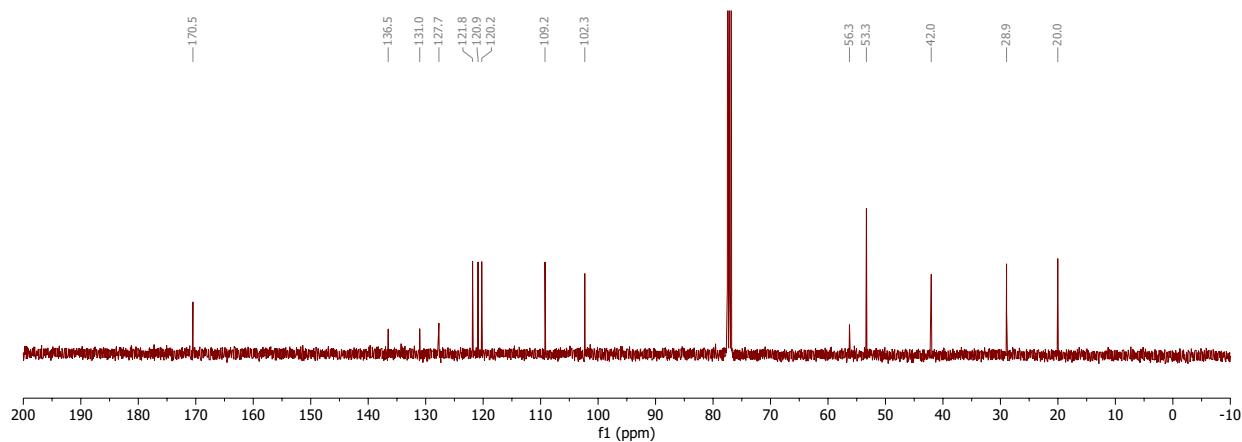
400 MHz ^1H NMR spectrum (CDCl_3)

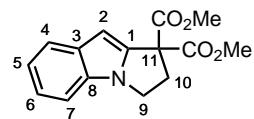
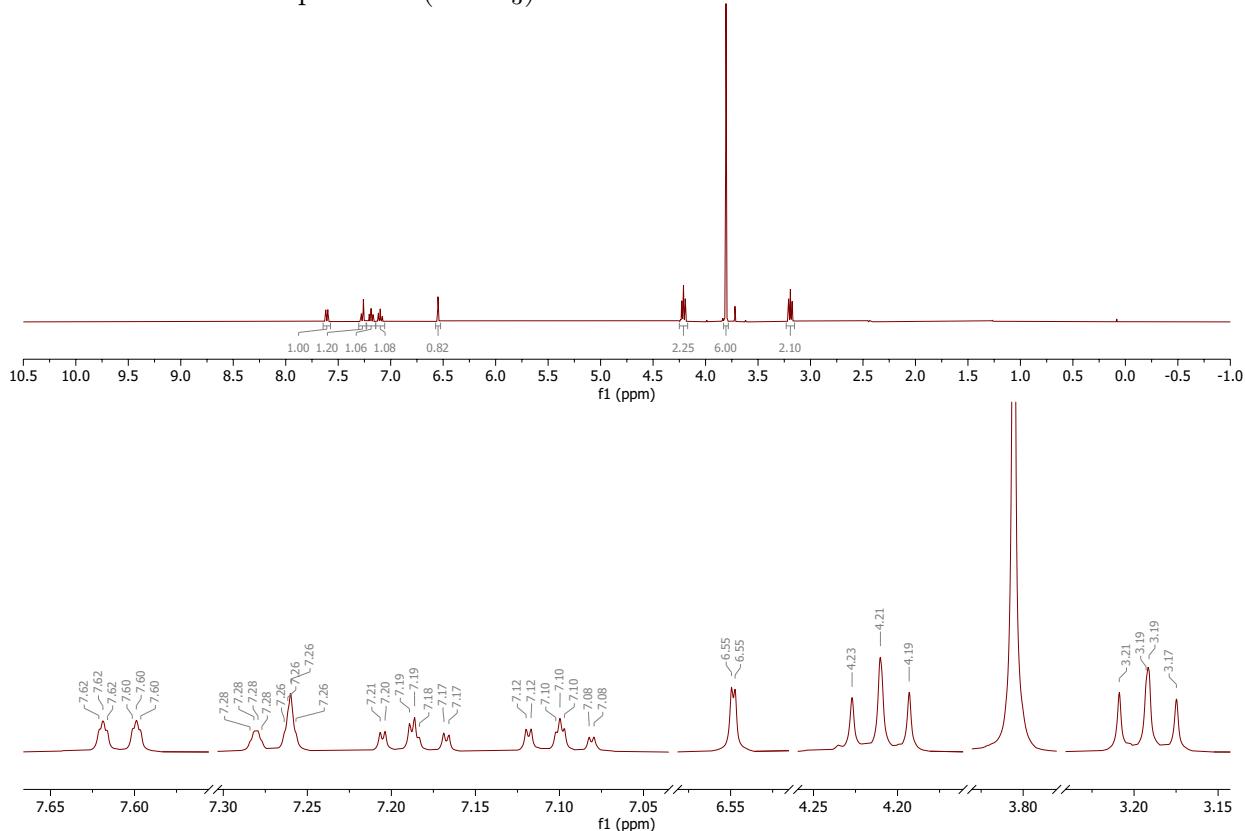
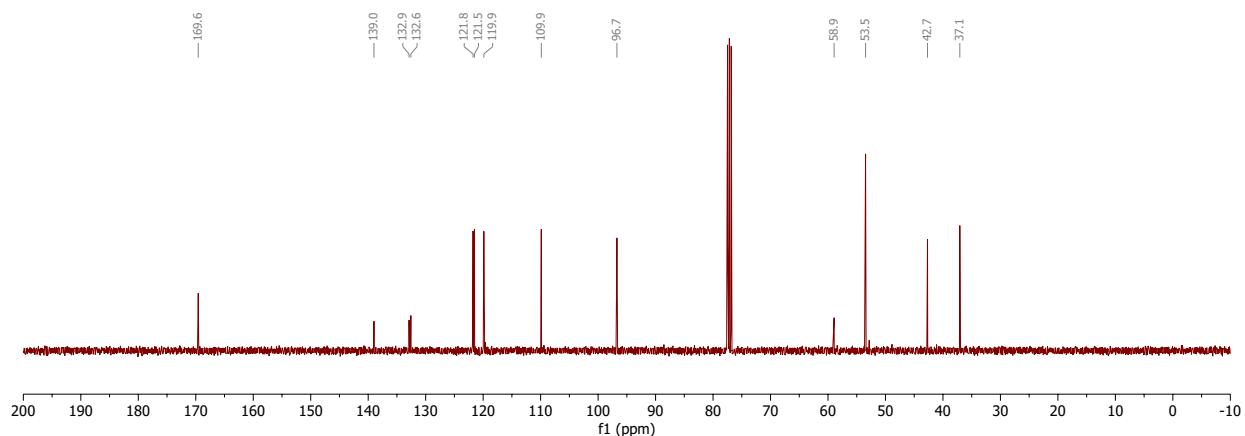


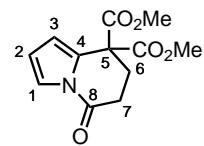
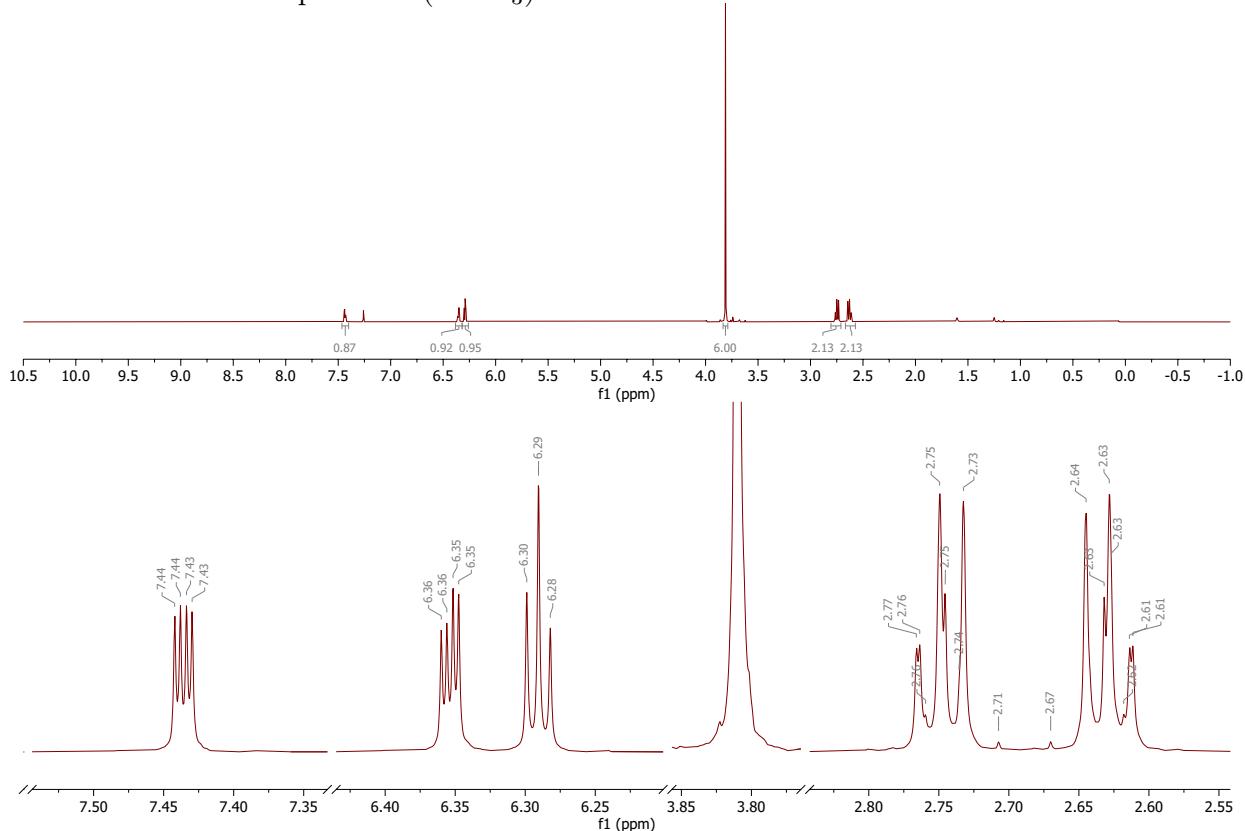
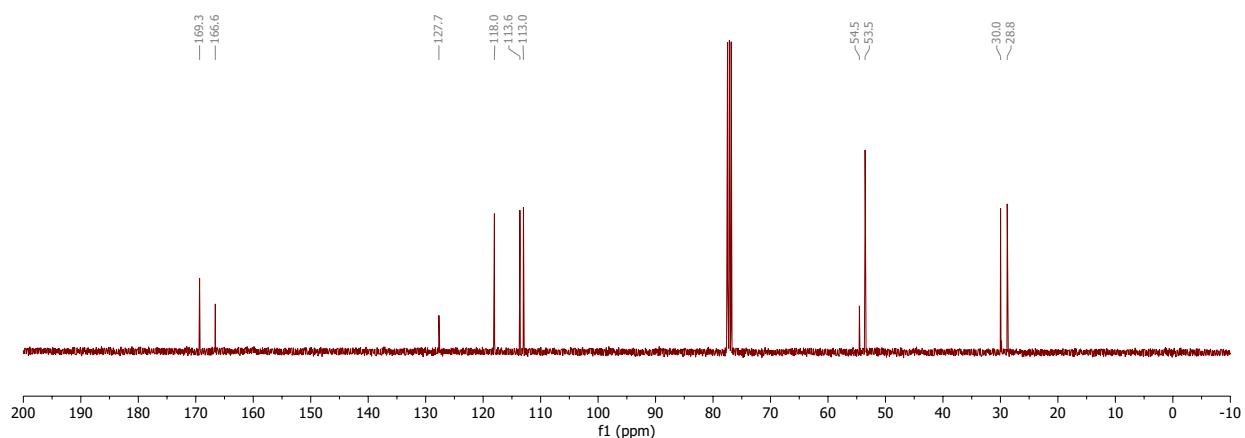
101 MHz ^{13}C NMR spectrum (CDCl_3)

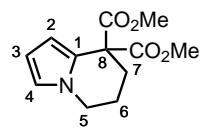
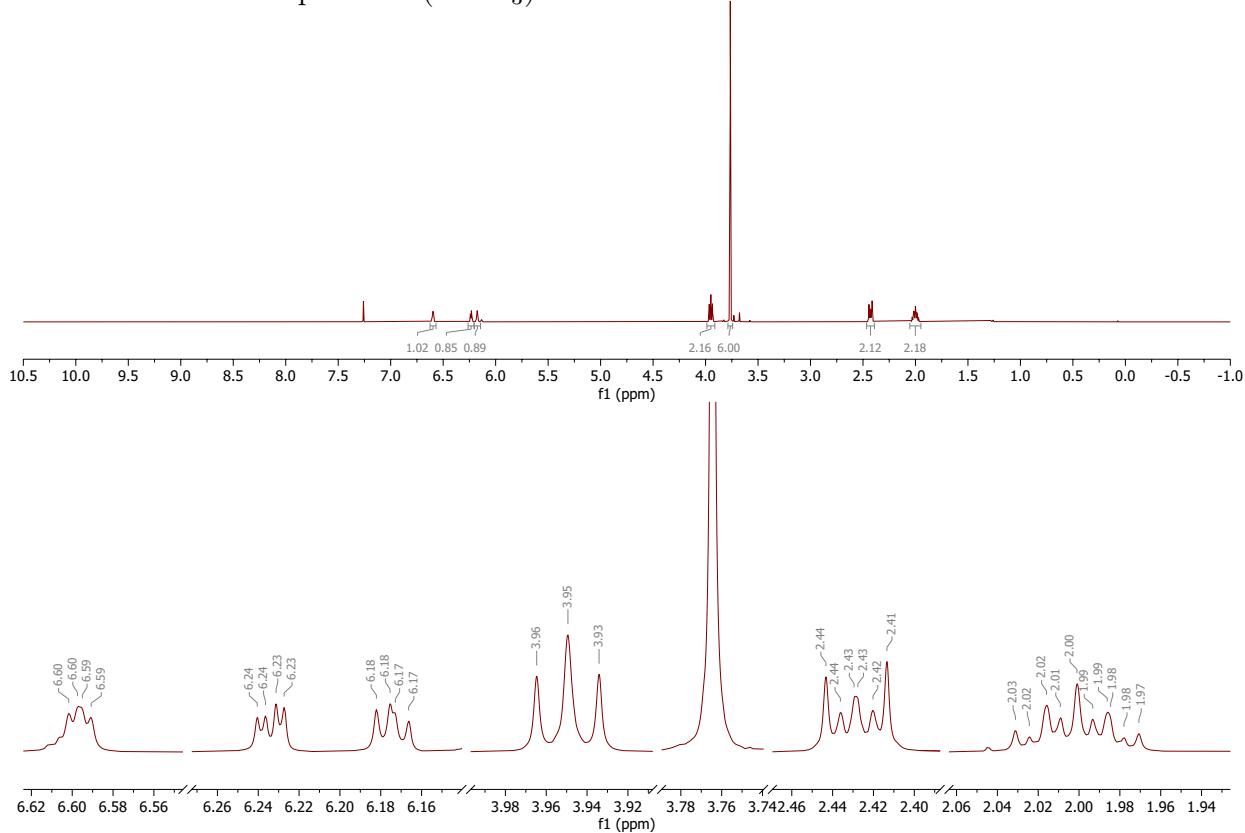
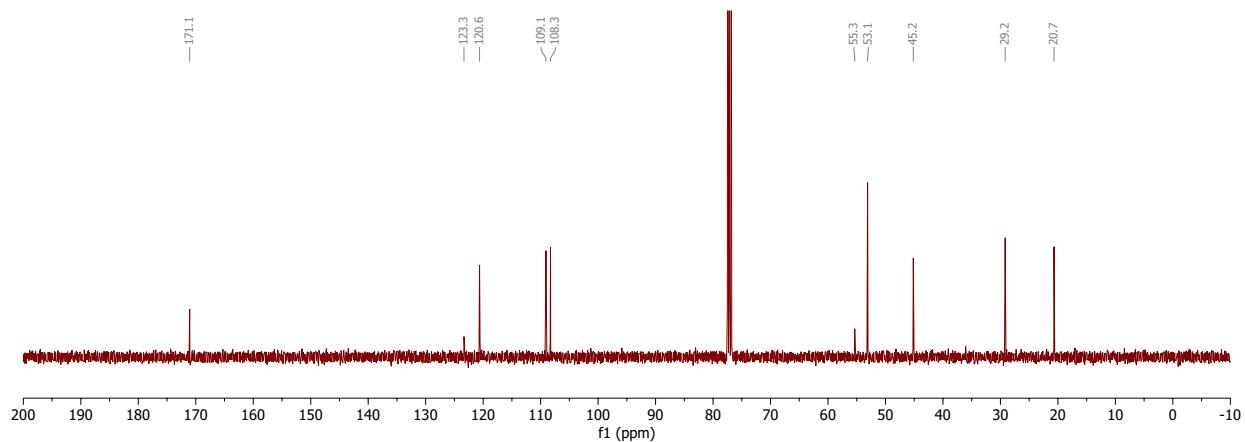


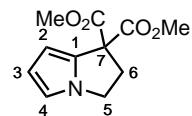
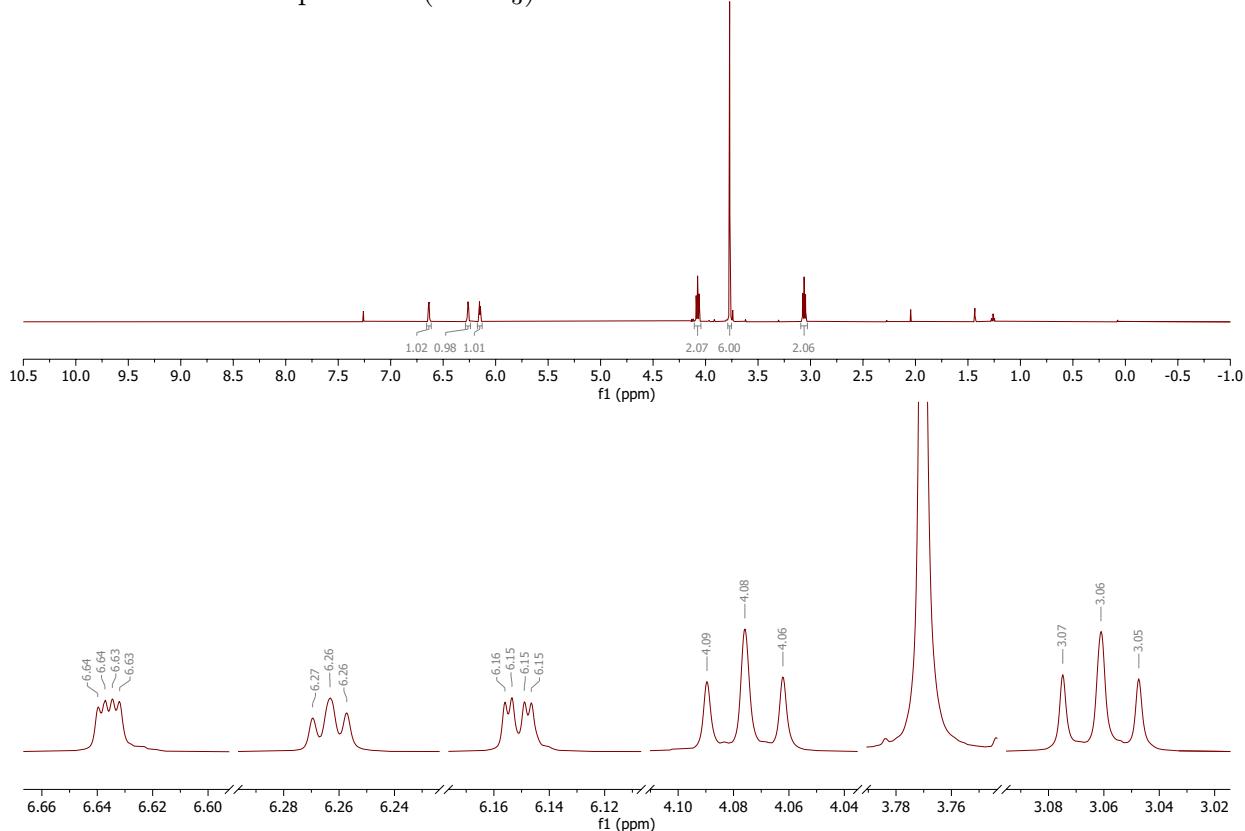
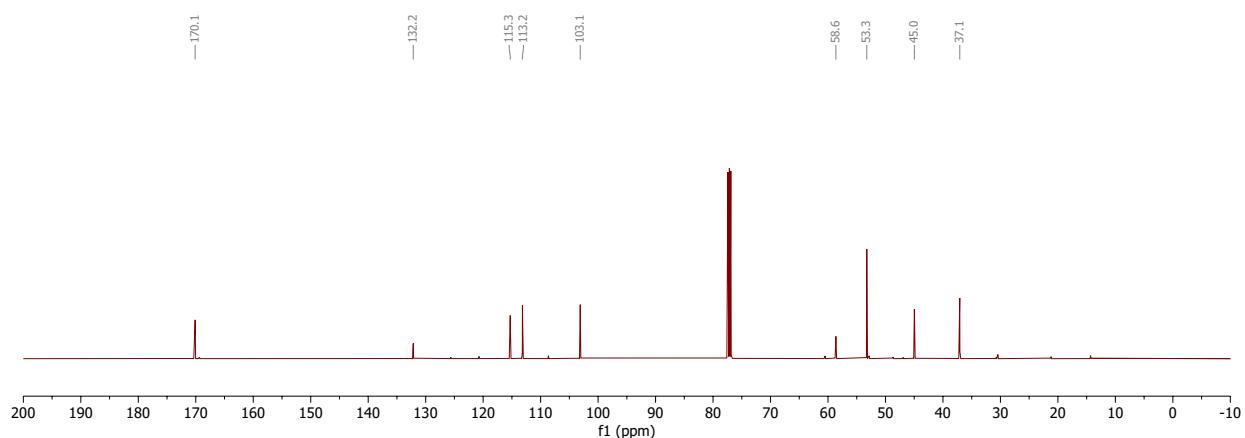
Dimethyl 2-(1*H*-indole-1-carbonyl)cyclopropane-1,1-dicarboxylate, 6400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

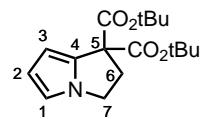
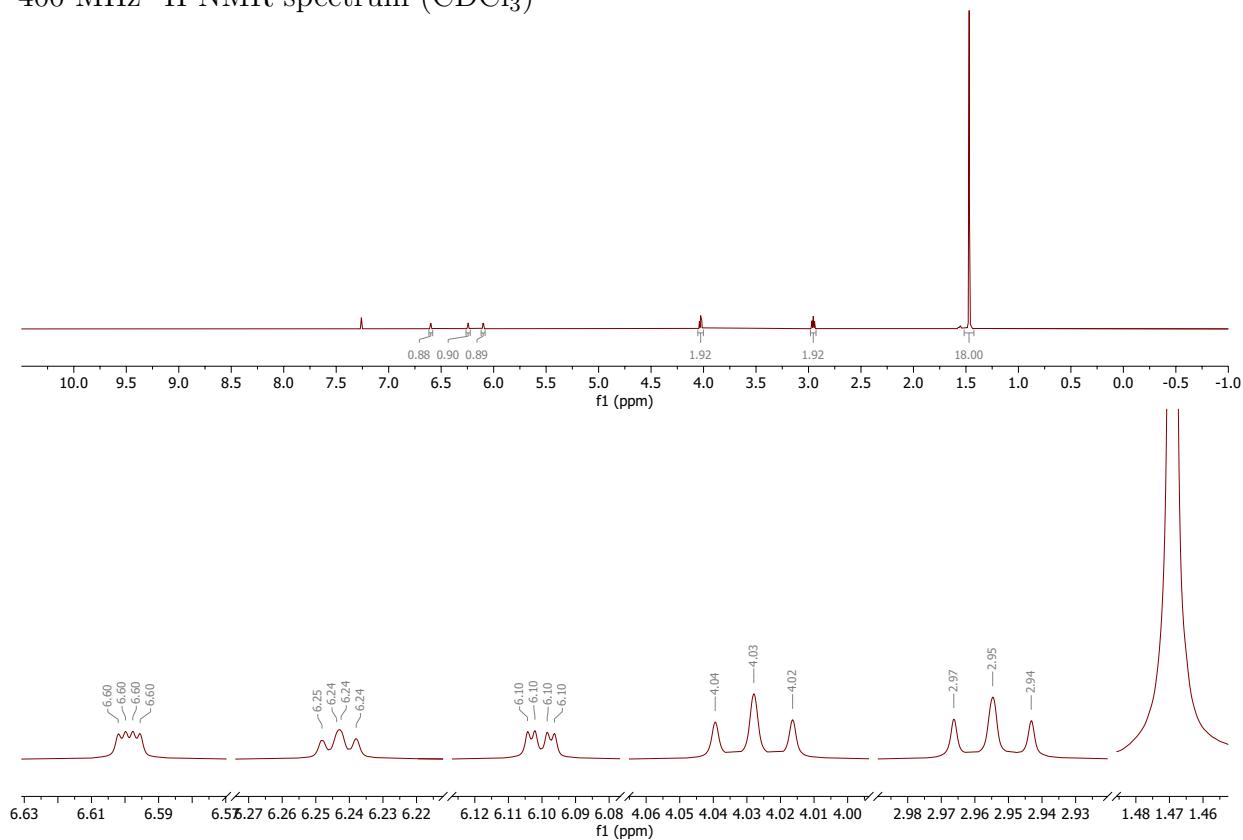
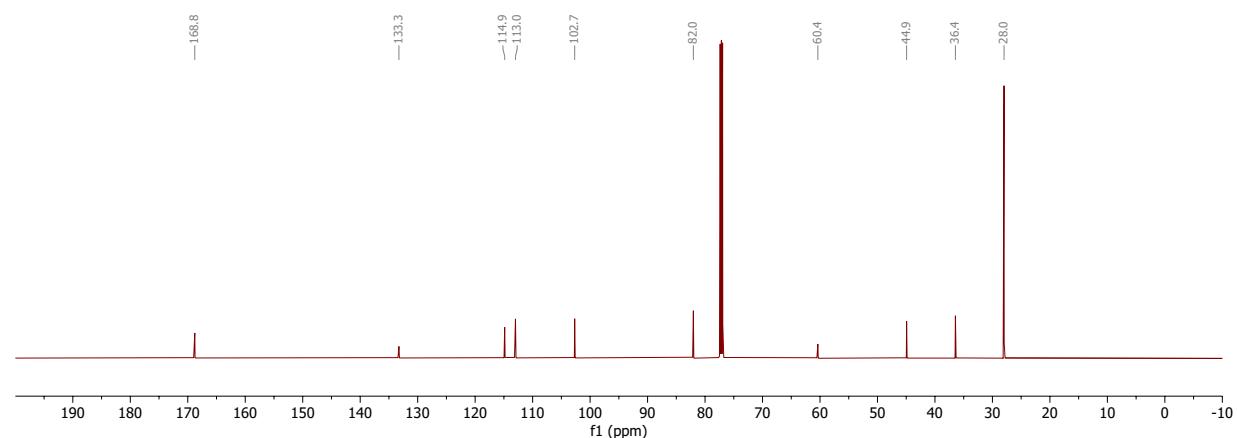
Dimethyl 7,8-dihydropyrido[1,2-*a*]indole-9,9(6*H*)-dicarboxylate, 10400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate, 12400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

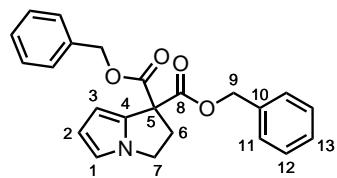
Dimethyl 5-oxo-6,7-dihydroindolizine-8,8(5*H*)-dicarboxylate, 14400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 6,7-dihydroindolizine-8,8(5*H*)-dicarboxylate, 16400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

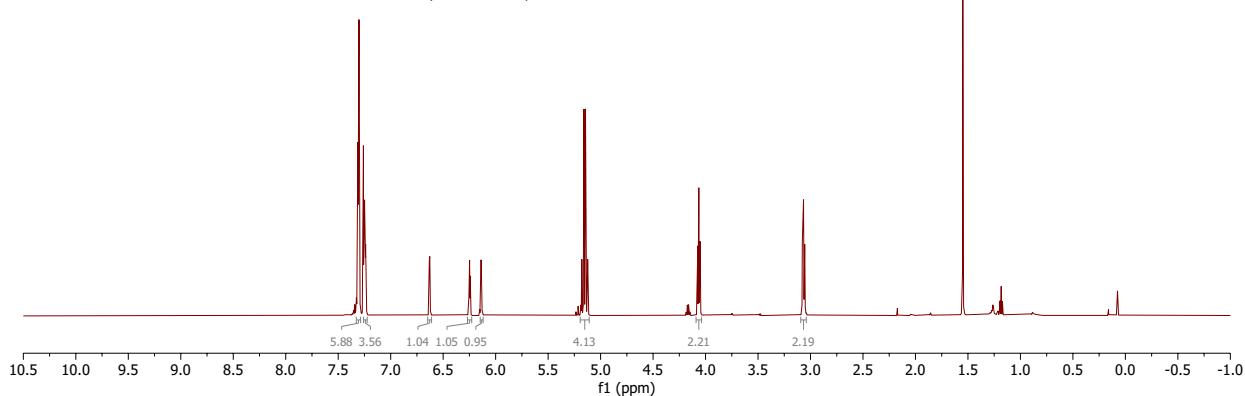
Dimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 18a500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

Di-*tert*-butyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 18b400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

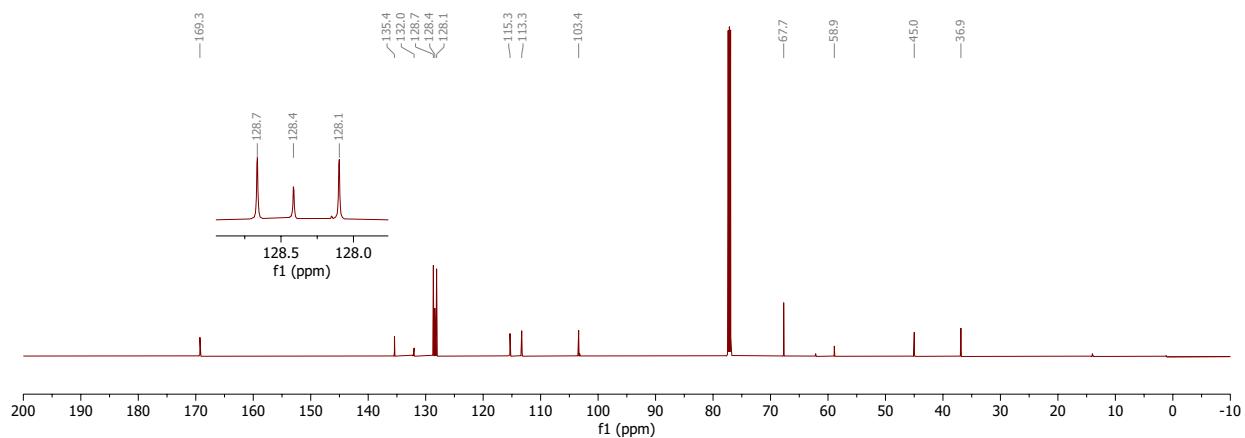
Dibenzyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 18c

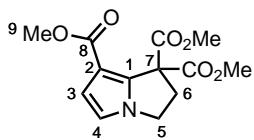
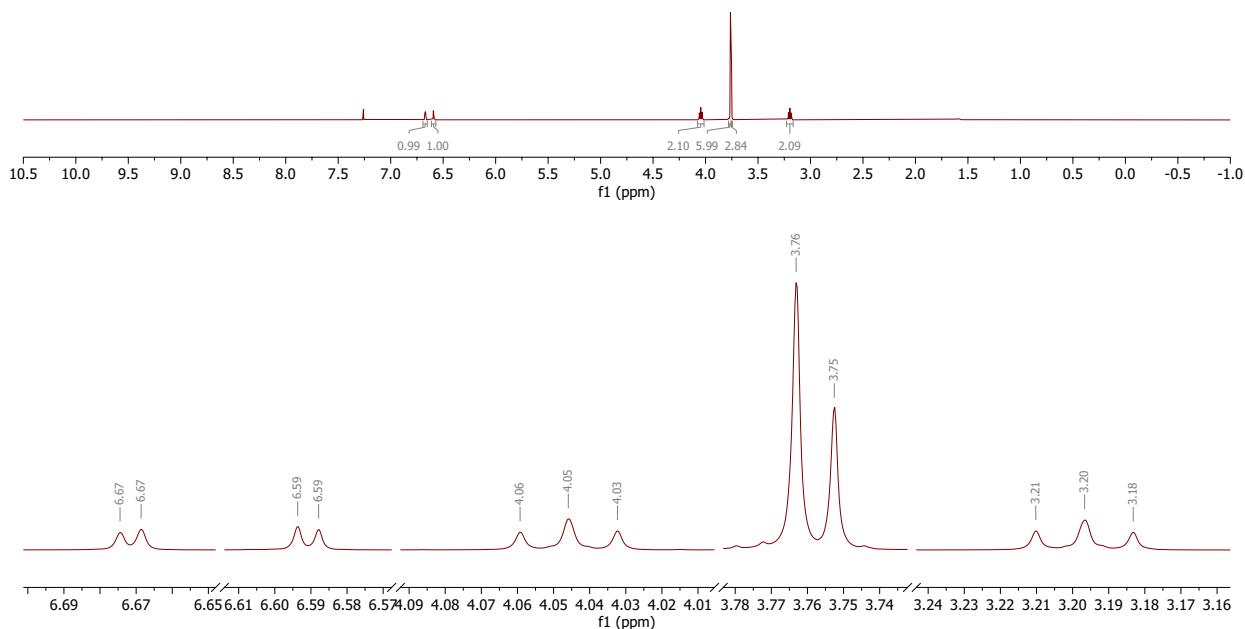
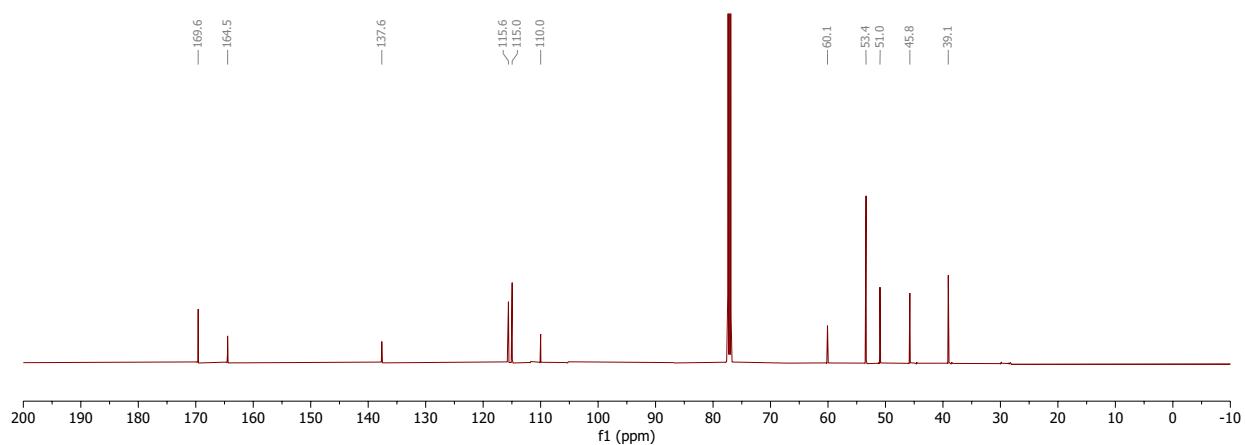


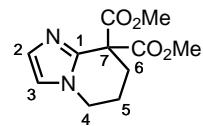
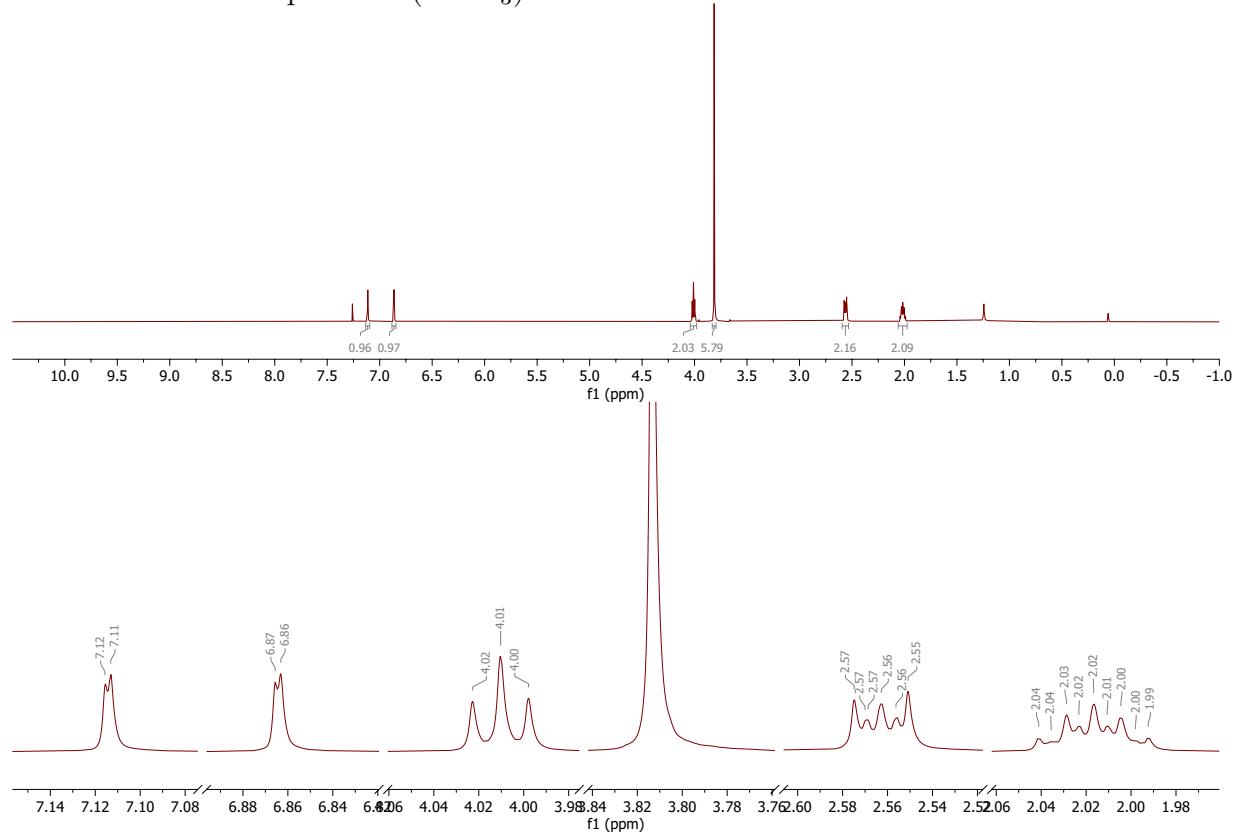
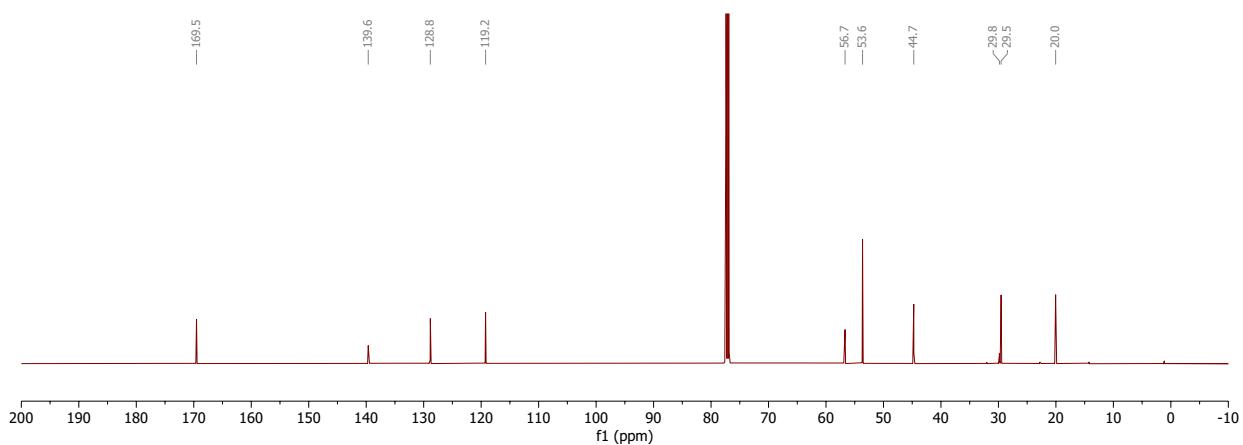
400 MHz ^1H NMR spectrum (CDCl_3)

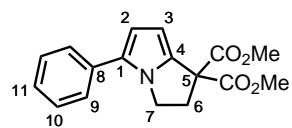


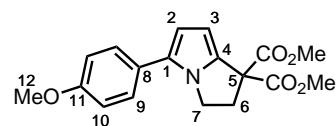
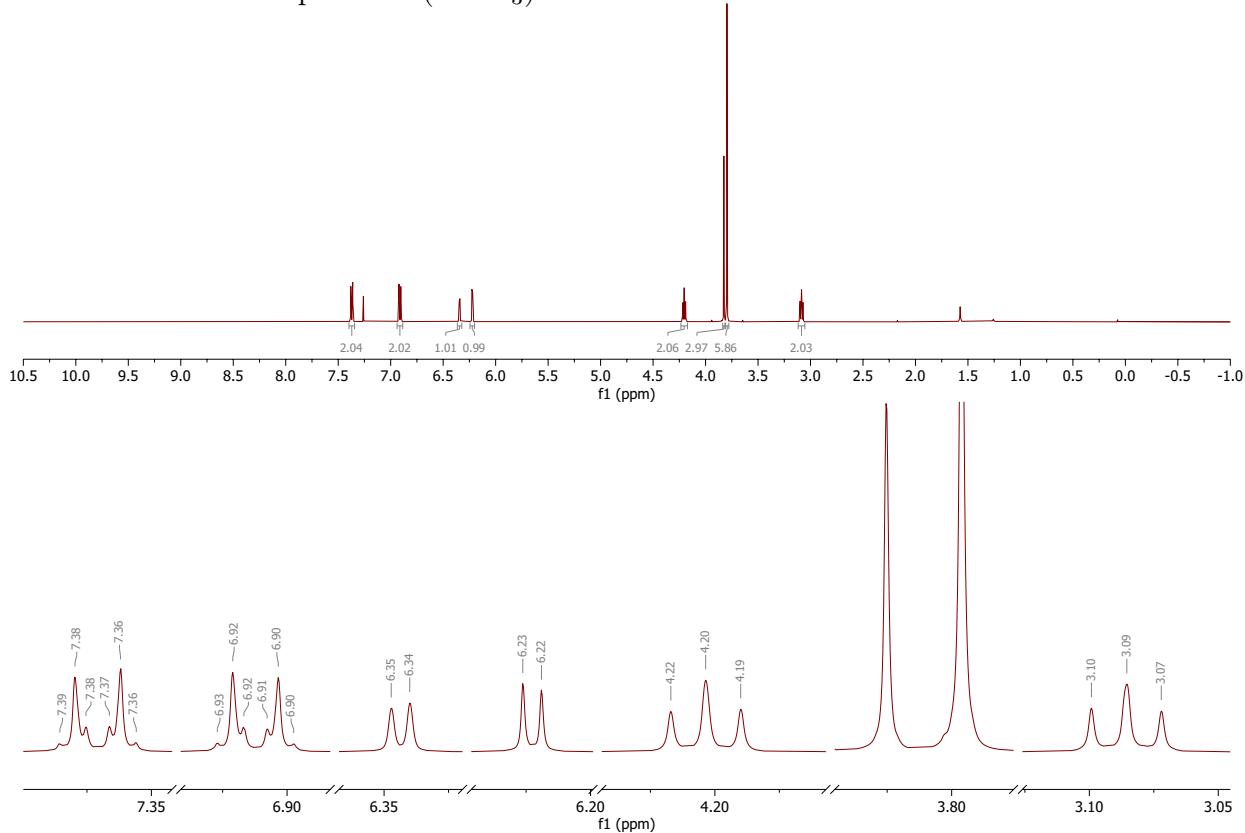
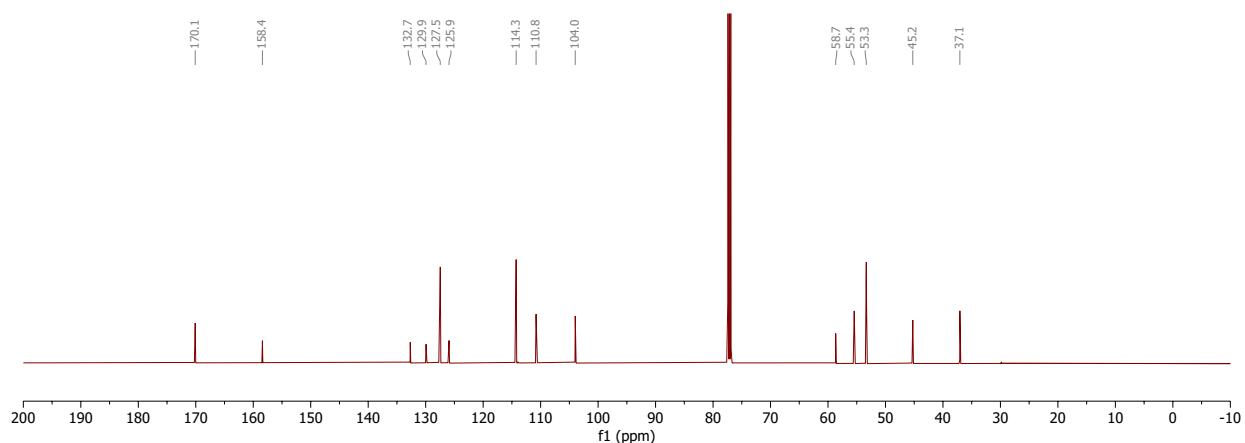
101 MHz ^{13}C NMR spectrum (CDCl_3)



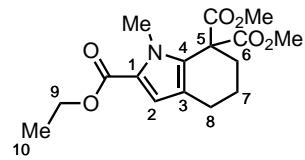
Trimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1,7-tricarboxylate, 20500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

Dimethyl 6,7-dihydroimidazo[1,2-*a*]pyridine-8,8(5*H*)-dicarboxylate, 24500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

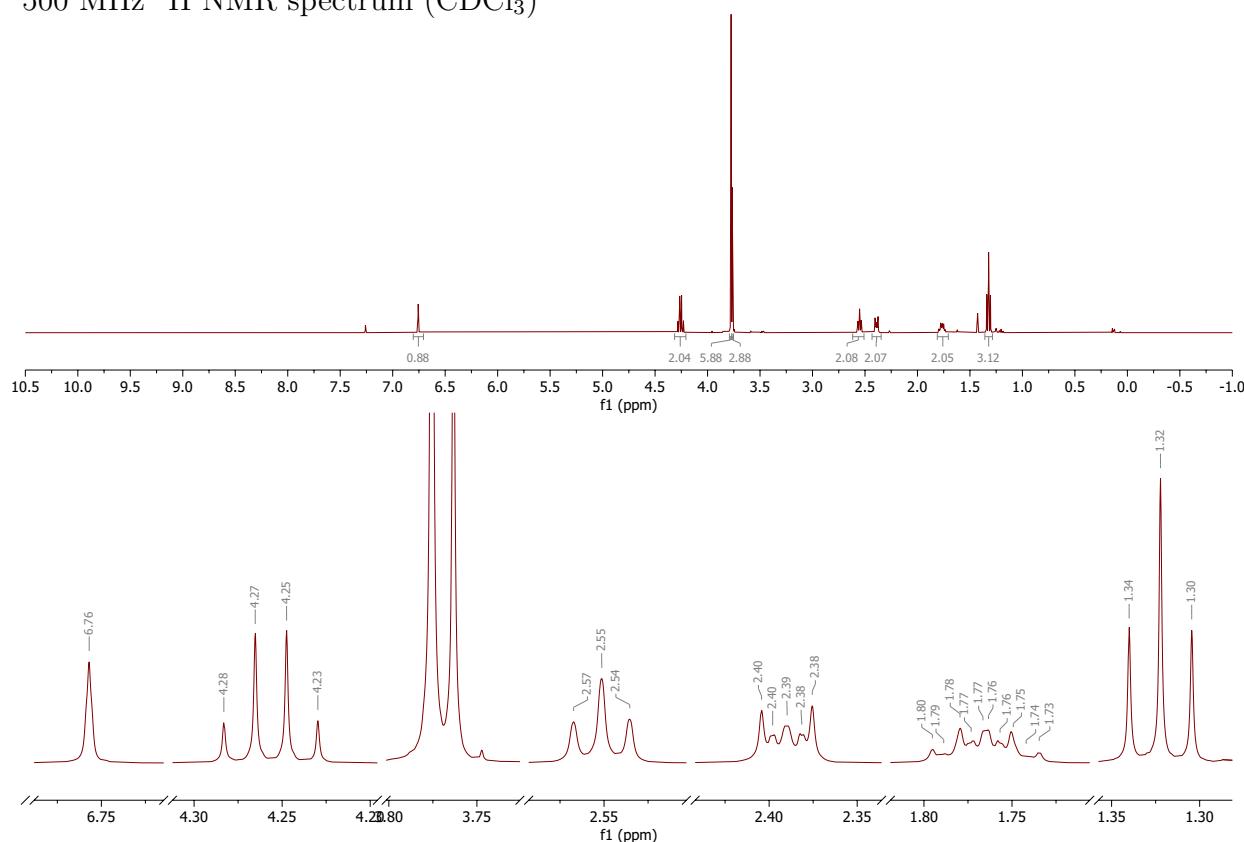
Dimethyl 5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22b

Dimethyl 5-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22c500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

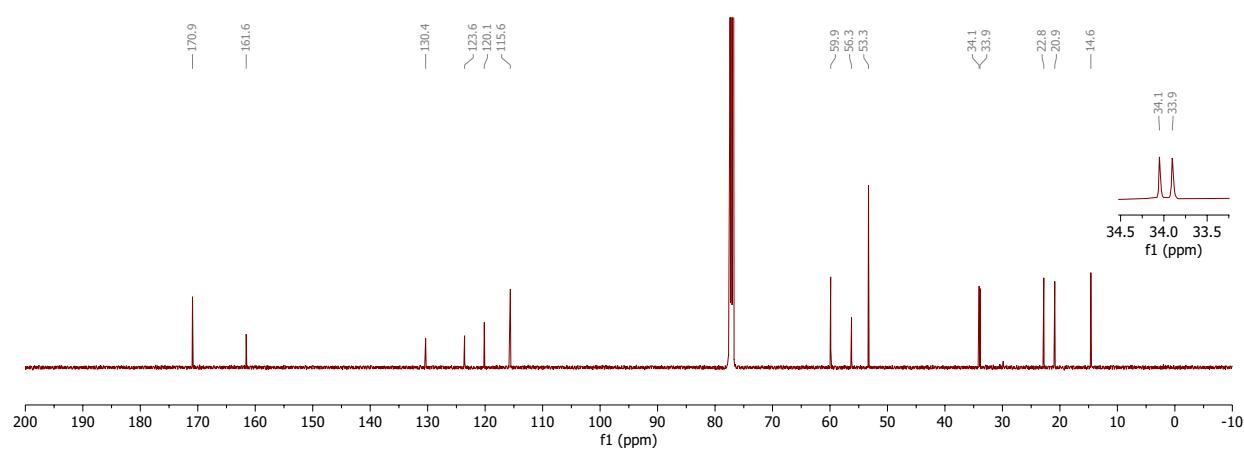
2-Ethyl 7,7-dimethyl 1-methyl-1,4,5,6-tetrahydro-7*H*-indole-2,7,7- tricarboxylate, 34



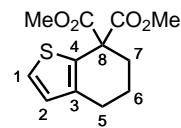
500 MHz ^1H NMR spectrum (CDCl_3)



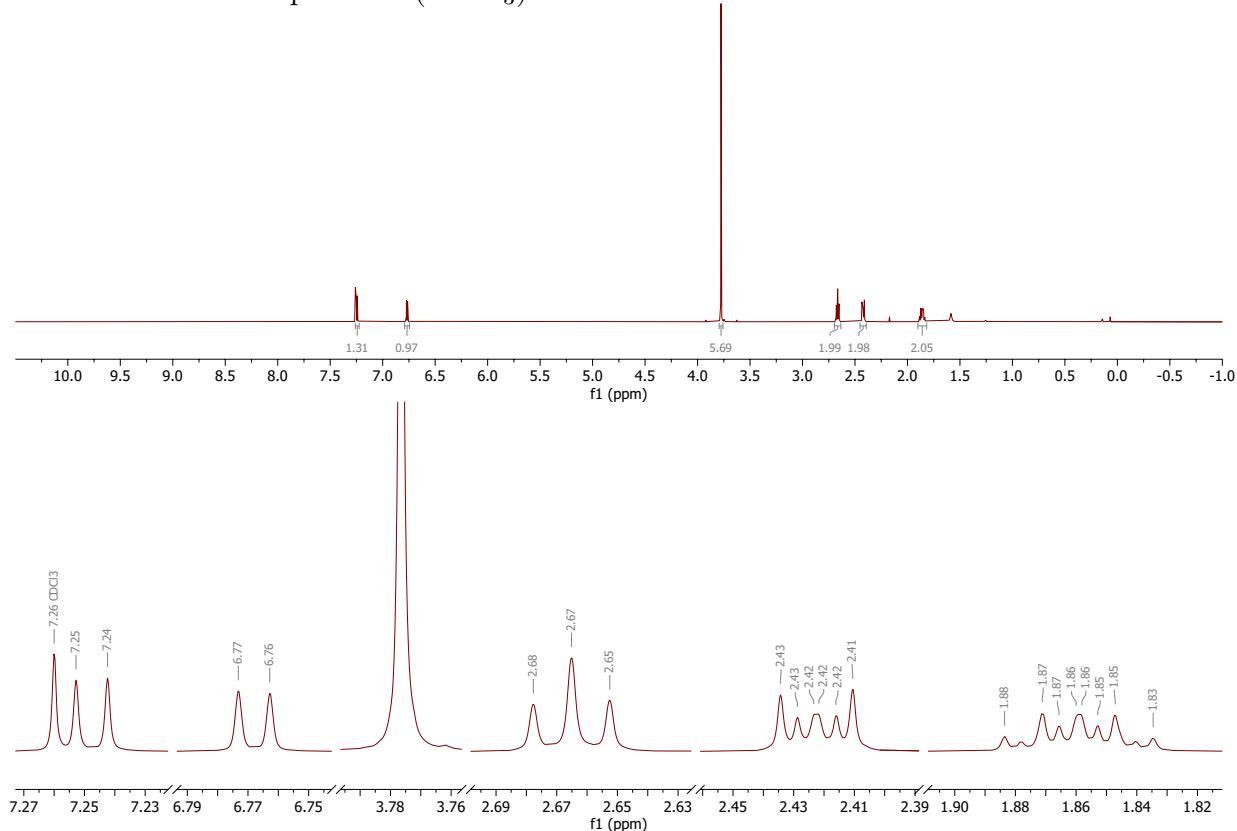
126 MHz ^{13}C NMR spectrum (CDCl_3)



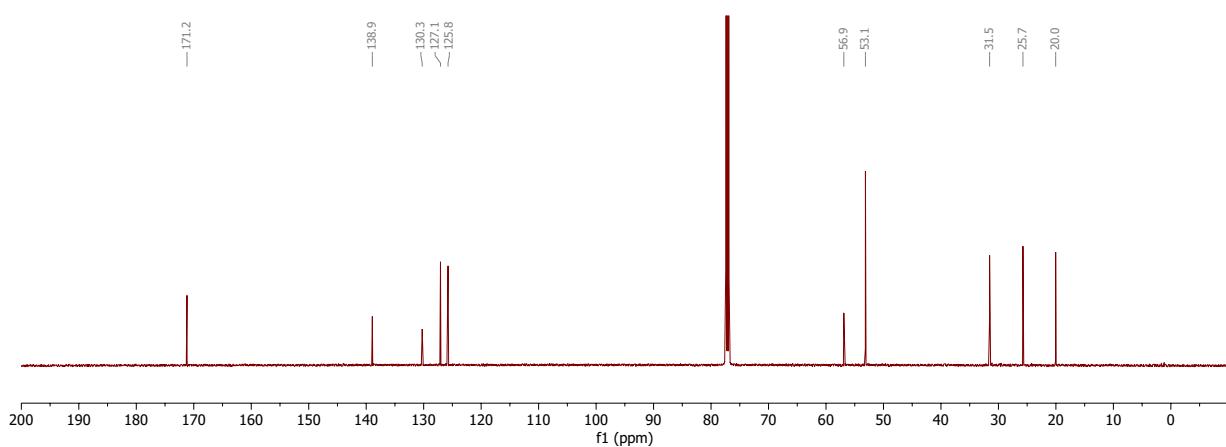
Dimethyl 5,6-dihydrobenzo[*b*]thiophene-7,7(4*H*)-dicarboxylate, 36

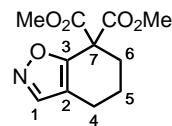
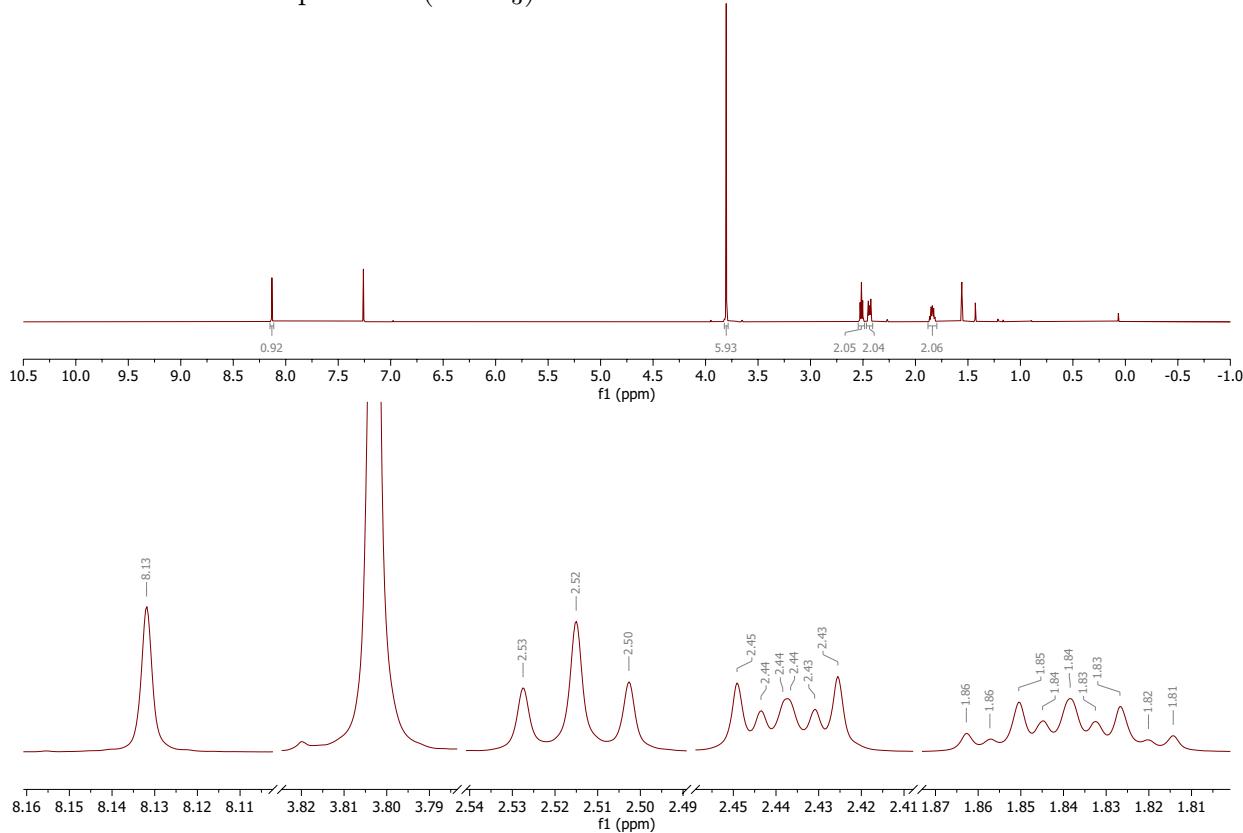
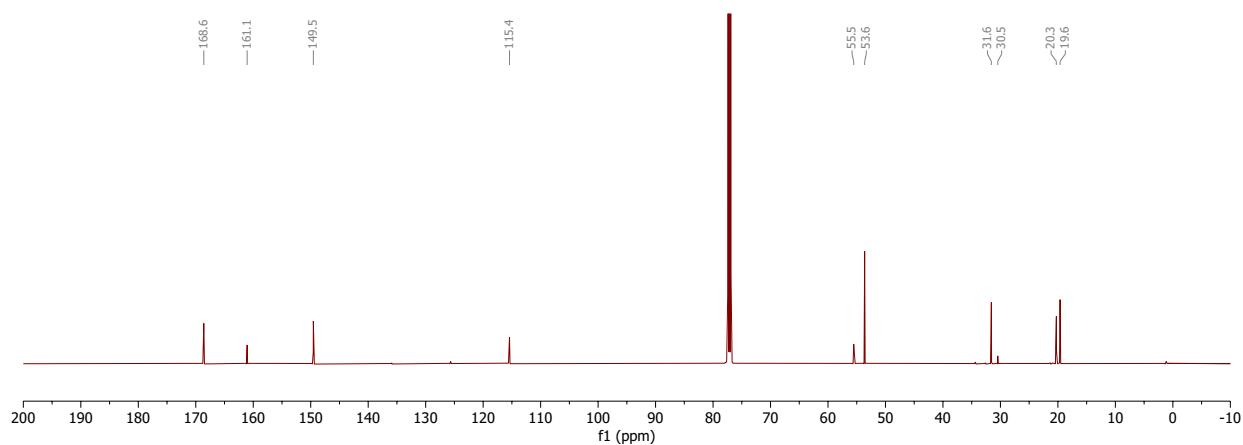


500 MHz ^1H NMR spectrum (CDCl_3)

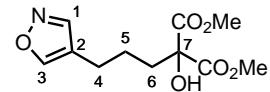


126 MHz ^{13}C NMR spectrum (CDCl_3)

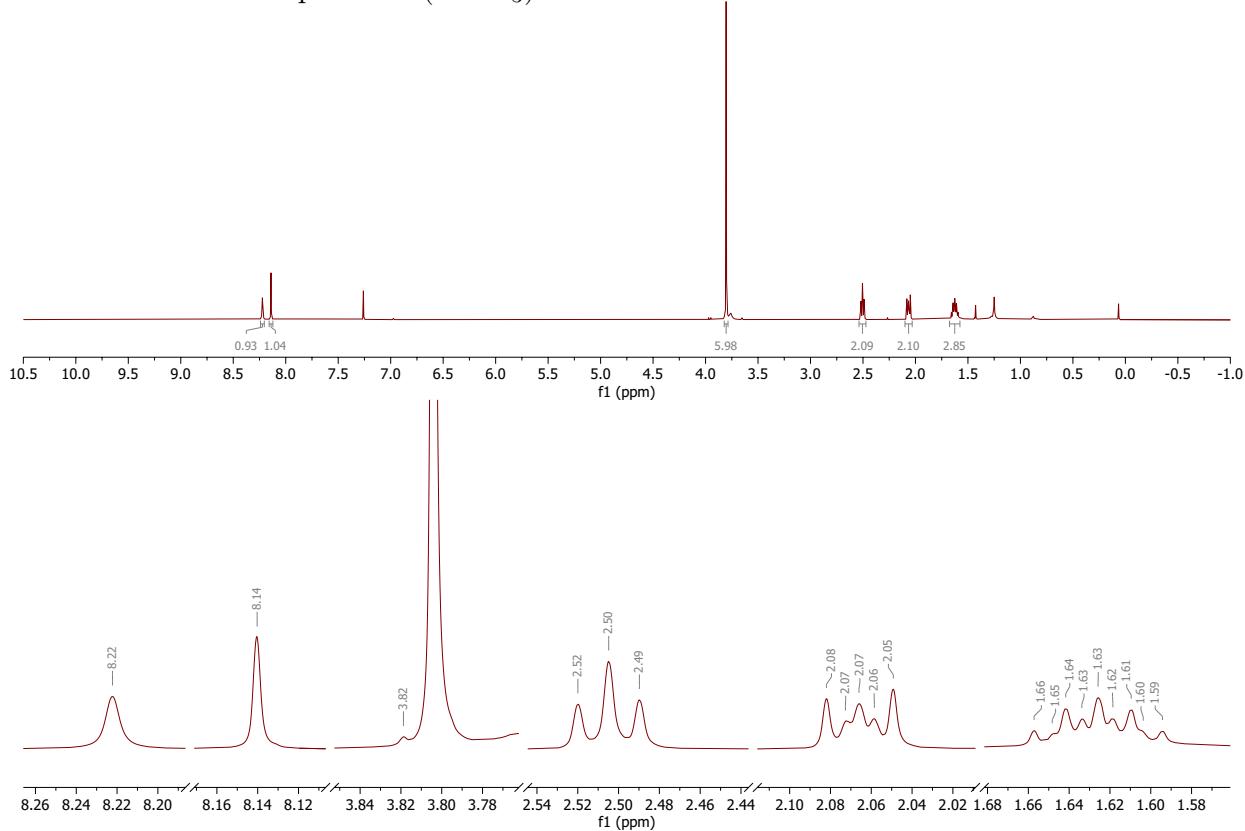


Dimethyl 5,6-dihydrobenzo[*d*]isoxazole-7,7(4*H*)-dicarboxylate, 30500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

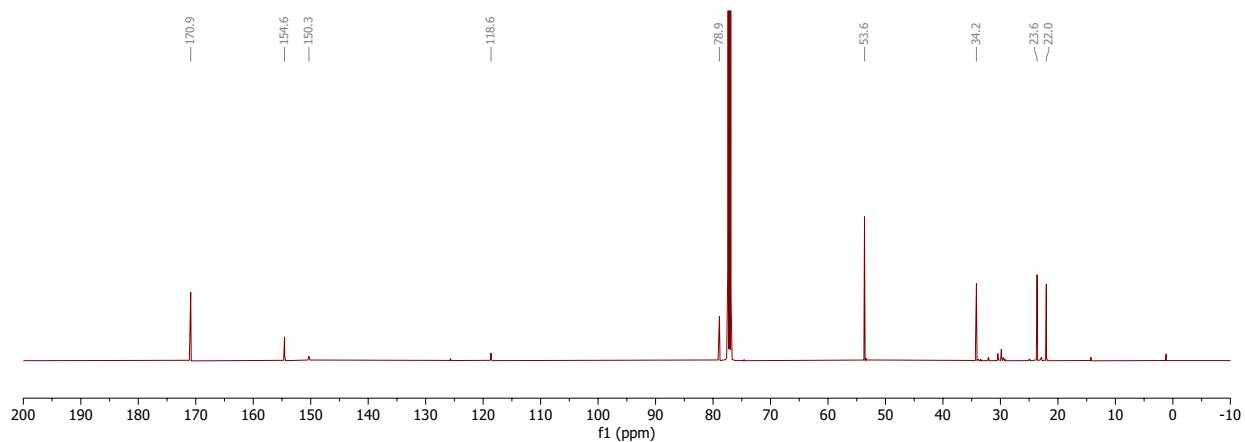
Dimethyl 2-hydroxy-2-(3-(isoxazol-4-yl)propyl)malonate, 32

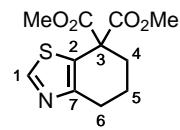
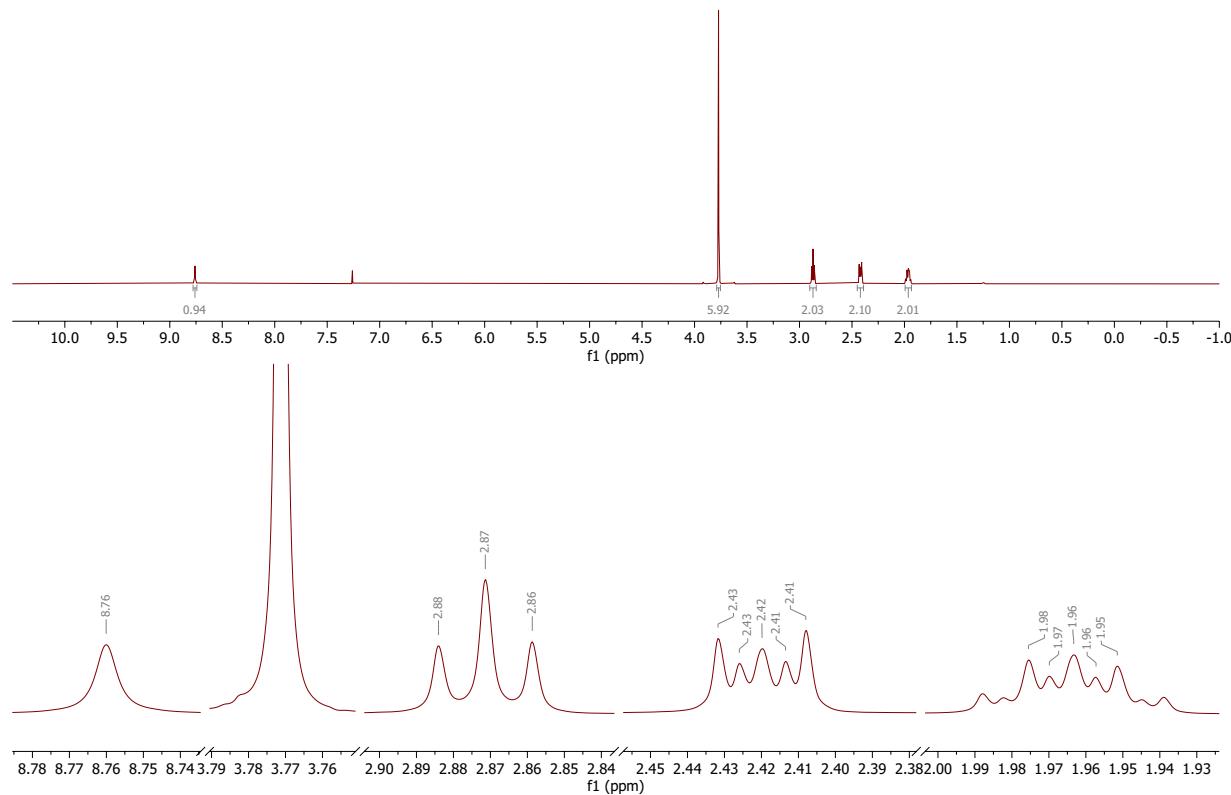
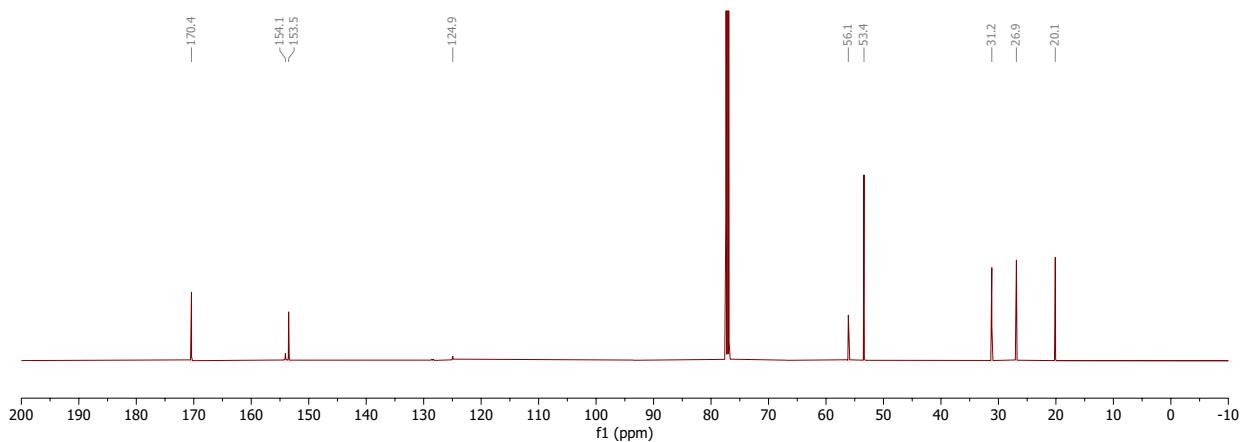


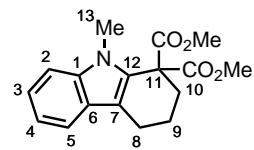
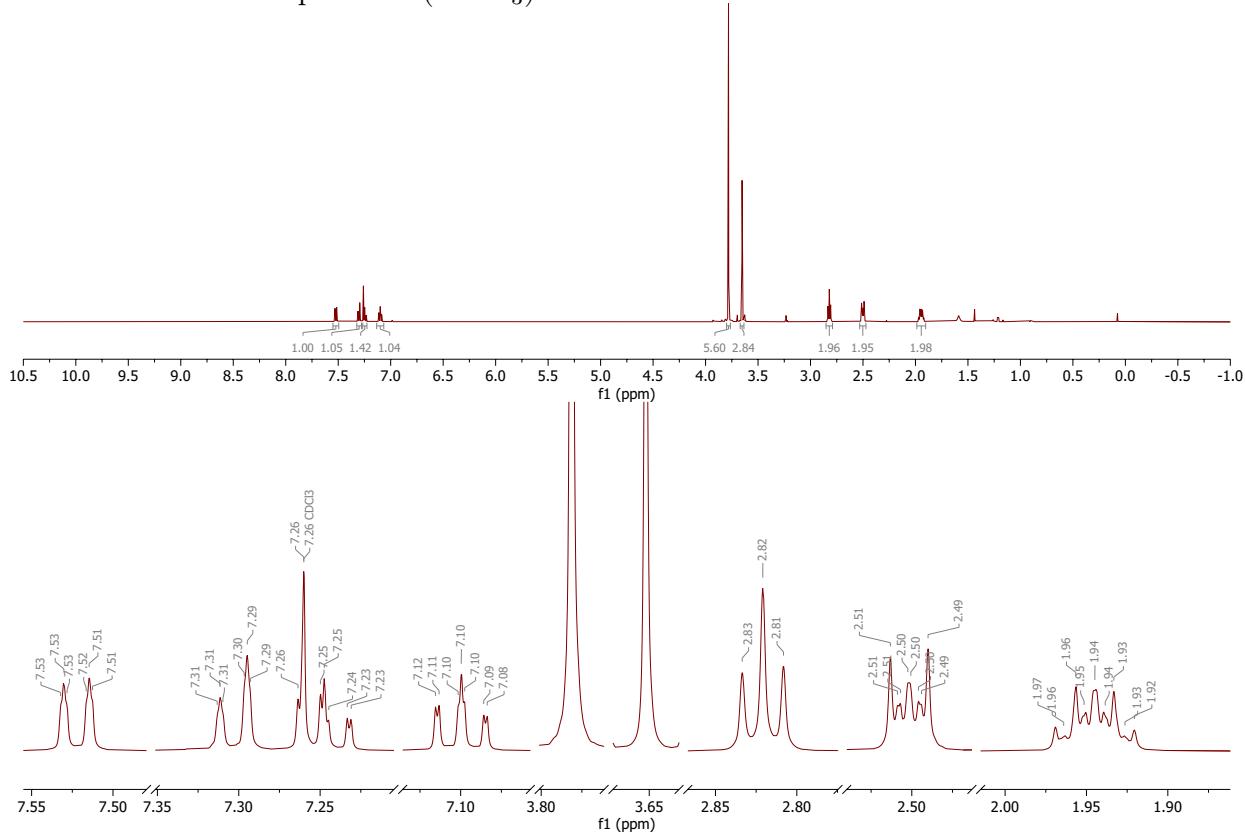
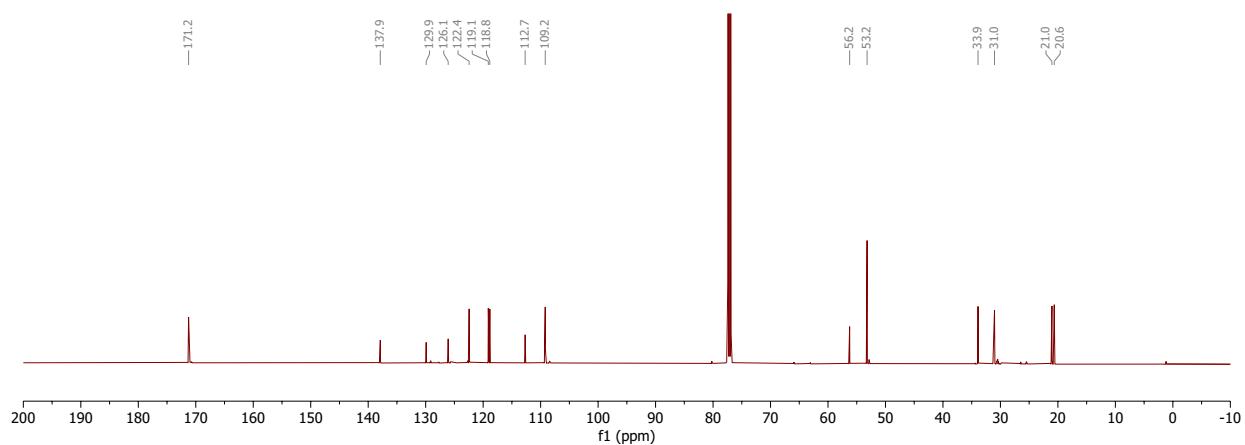
500 MHz ^1H NMR spectrum (CDCl_3)



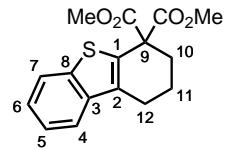
126 MHz ^{13}C NMR spectrum (CDCl_3)



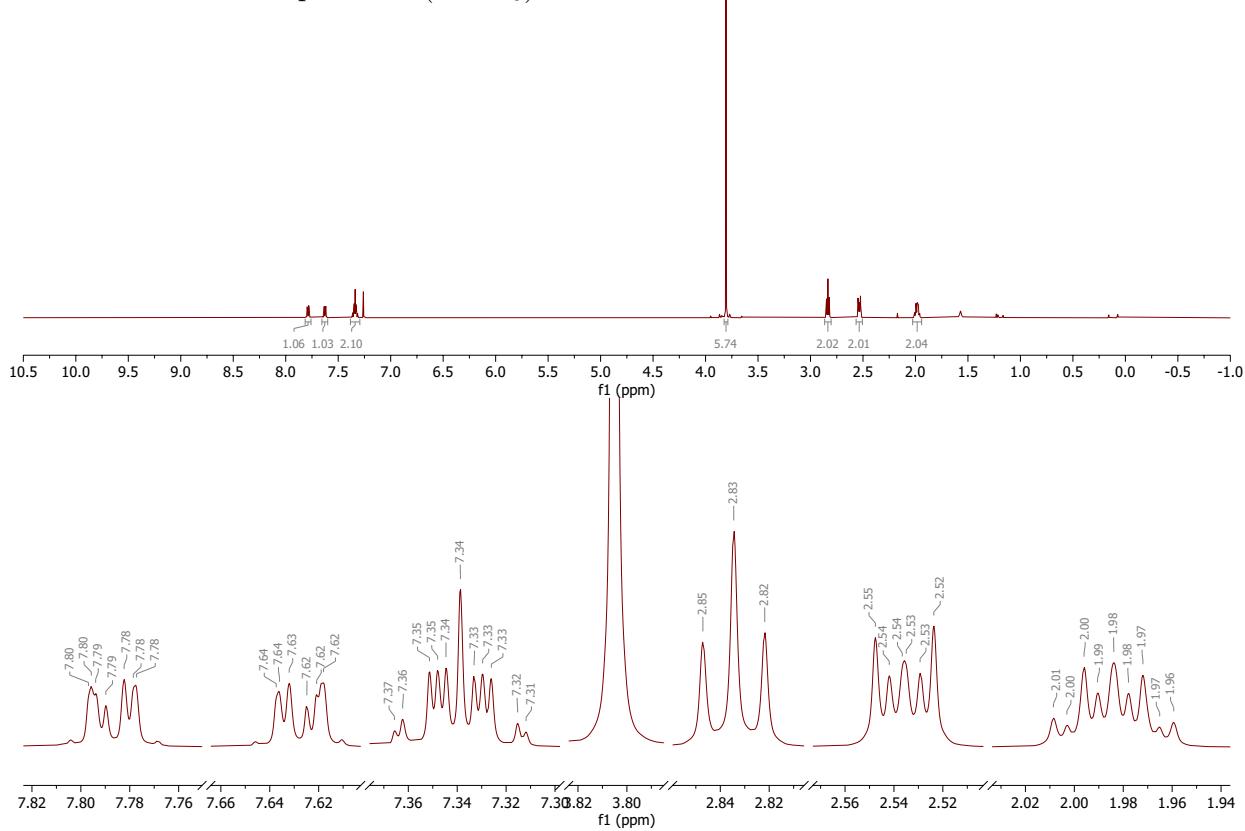
Dimethyl 5,6-dihydrobenzo[*d*]thiazole-7,7(4*H*)-dicarboxylate, 40500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

Dimethyl 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarboxylate, 48500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

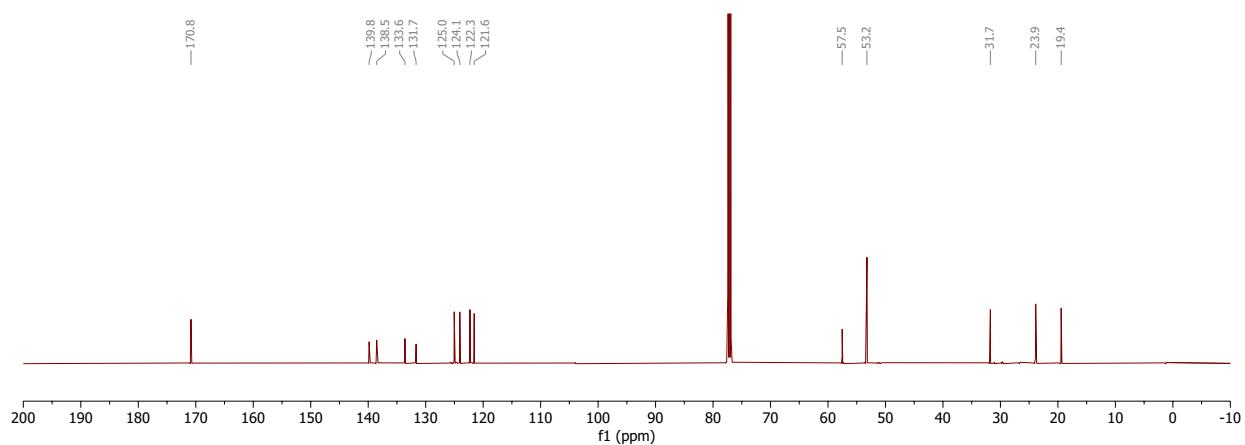
Dimethyl 2,3-dihydrodibenzo[*b,d*]thiophene-4,4(1*H*)-dicarboxylate, 50

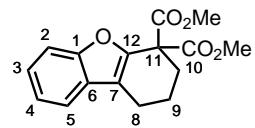
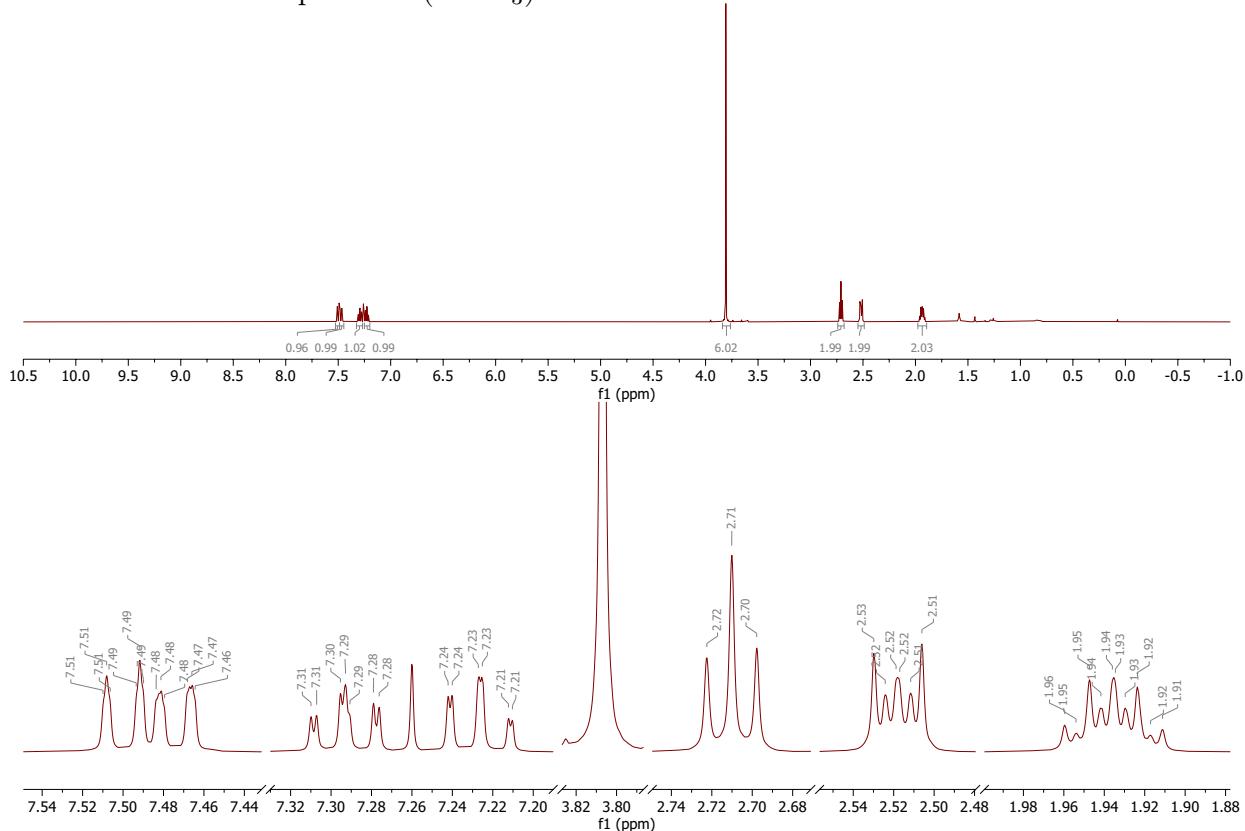
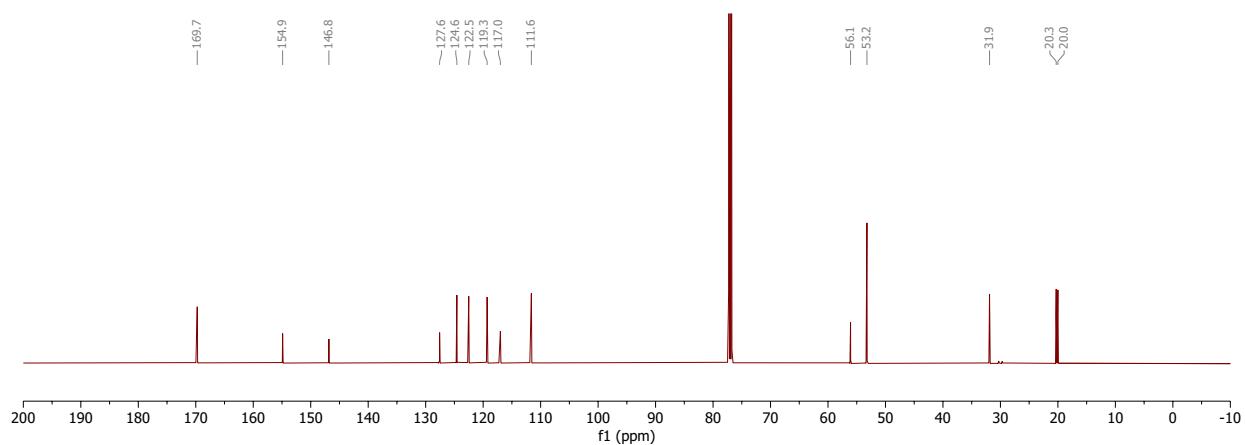


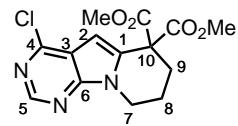
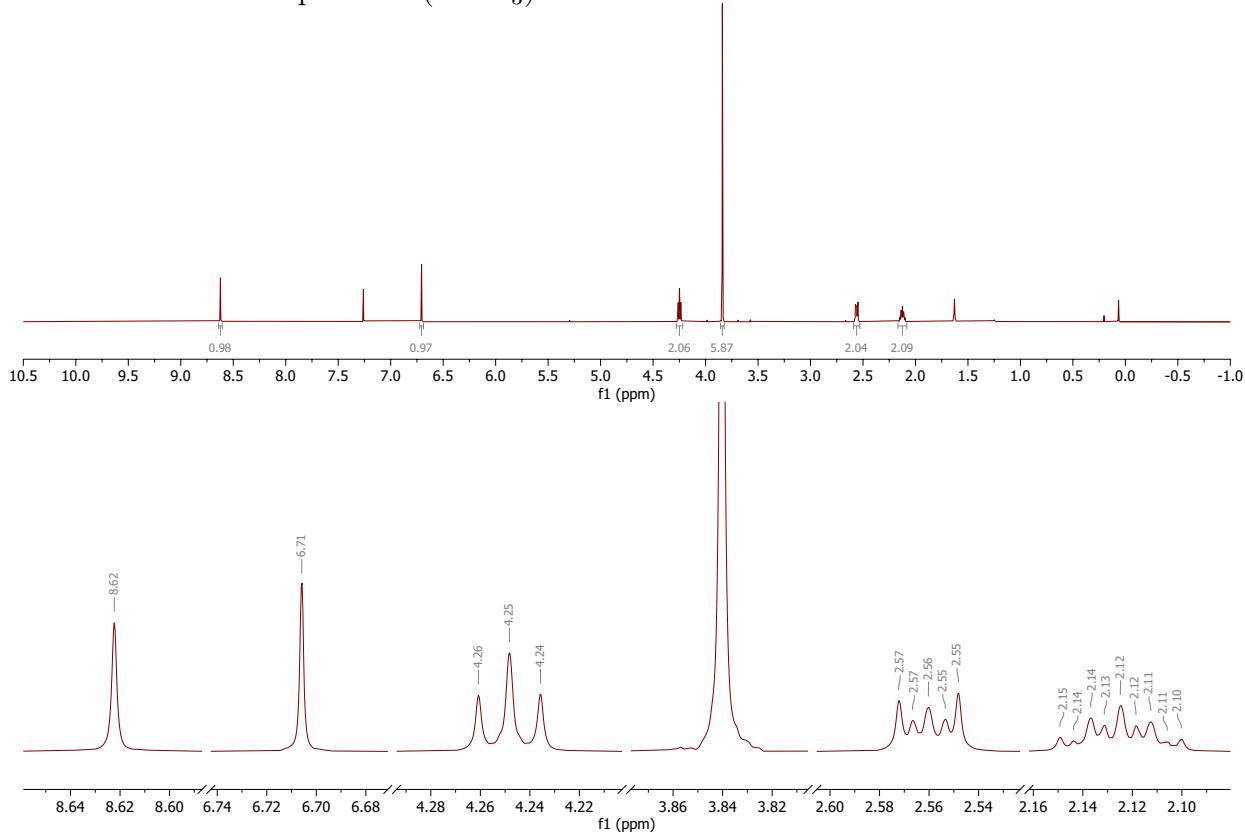
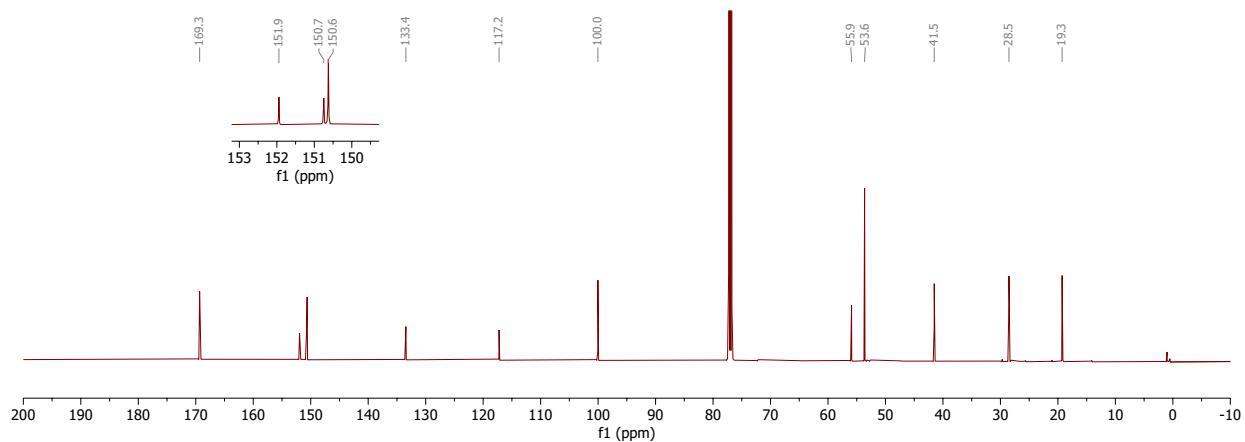
500 MHz ^1H NMR spectrum (CDCl_3)

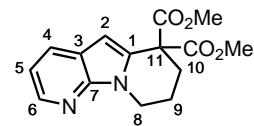
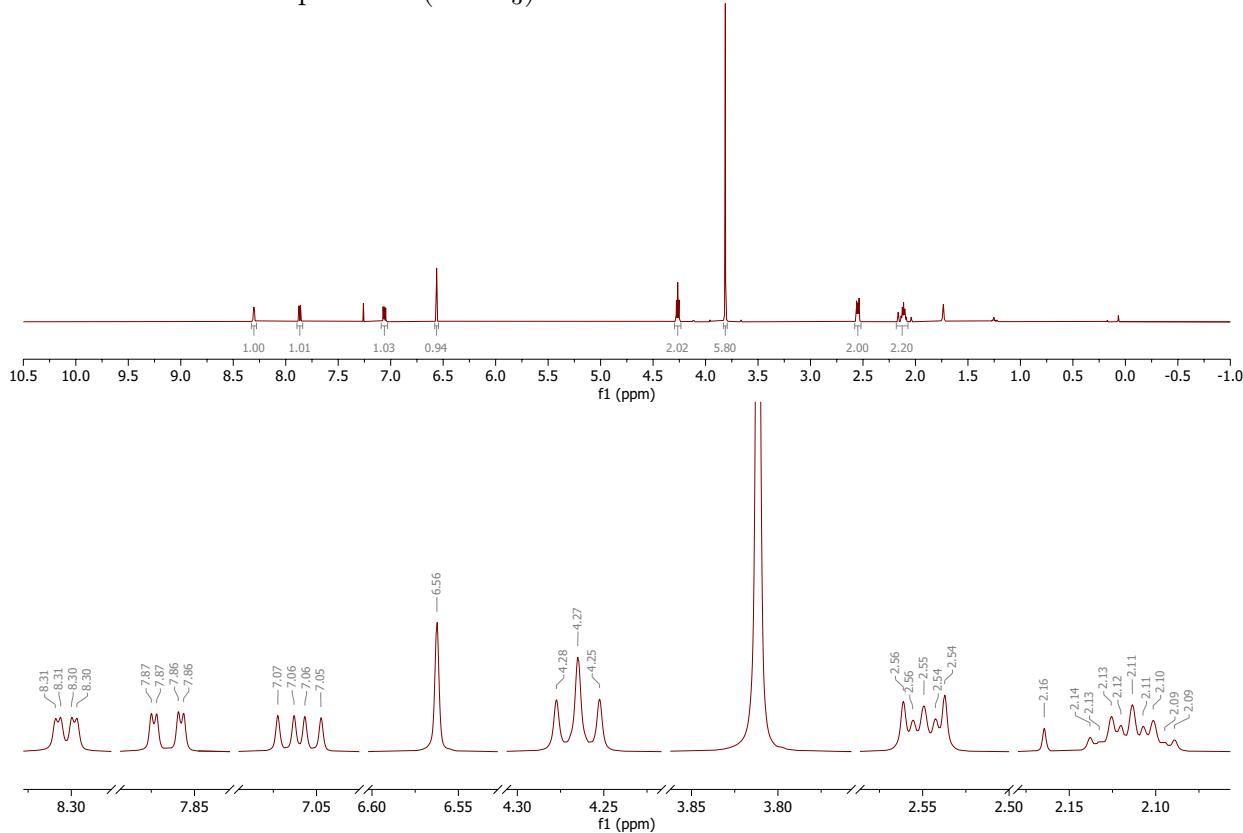
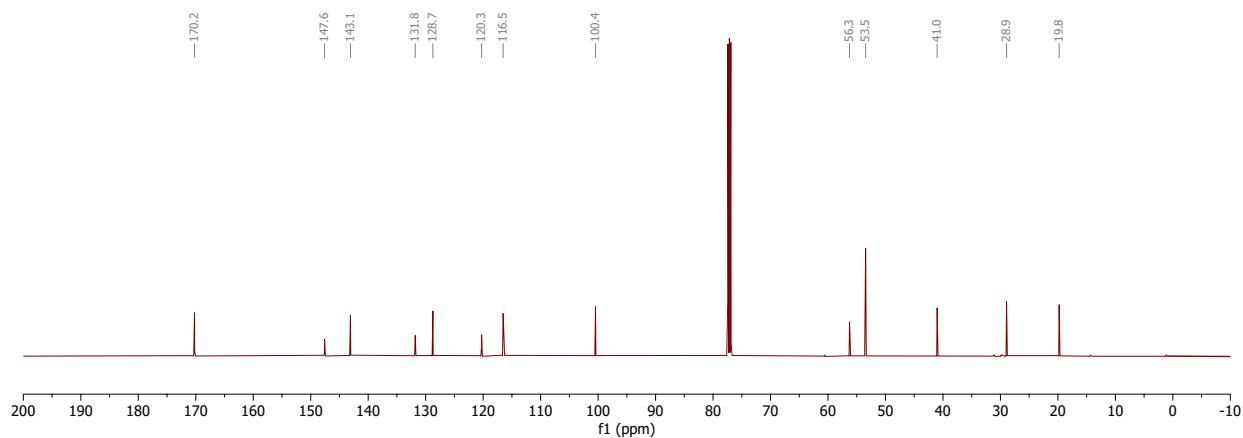


126 MHz ^{13}C NMR spectrum (CDCl_3)

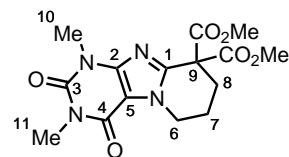
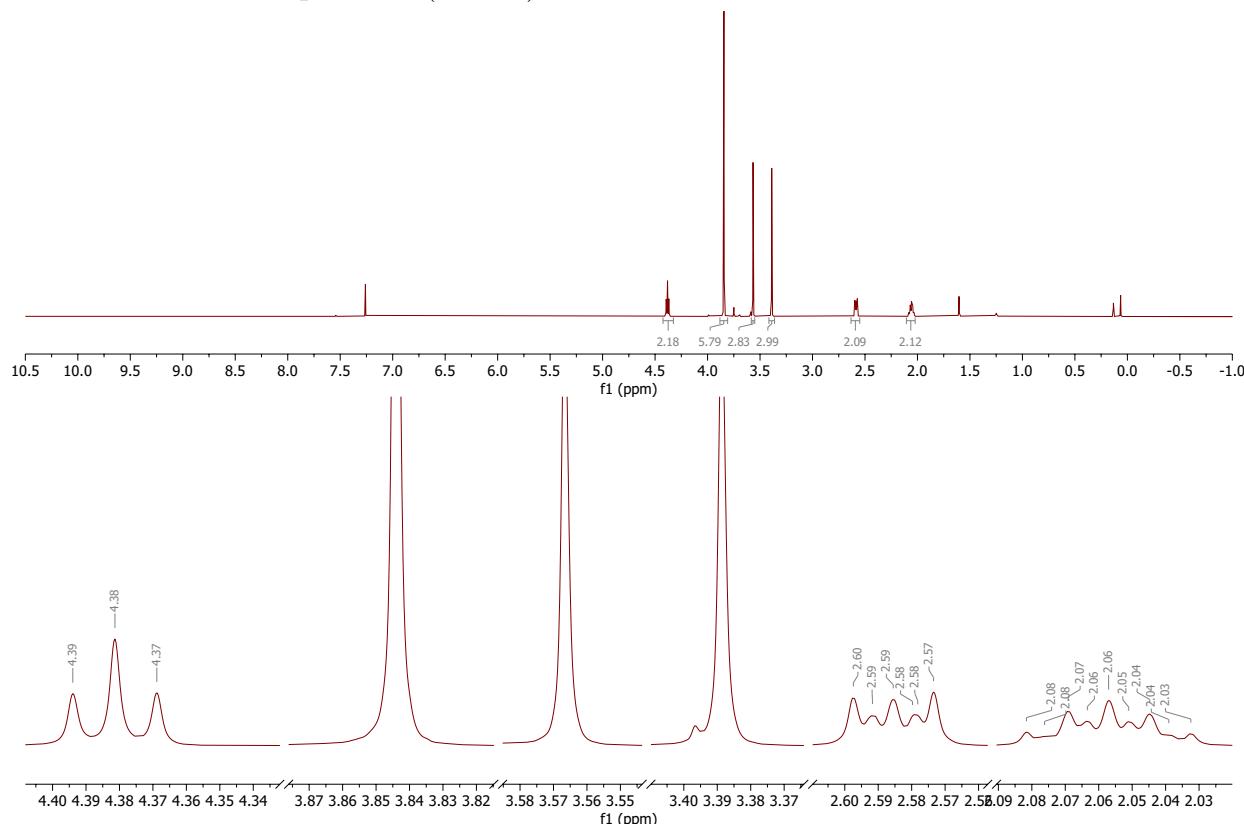
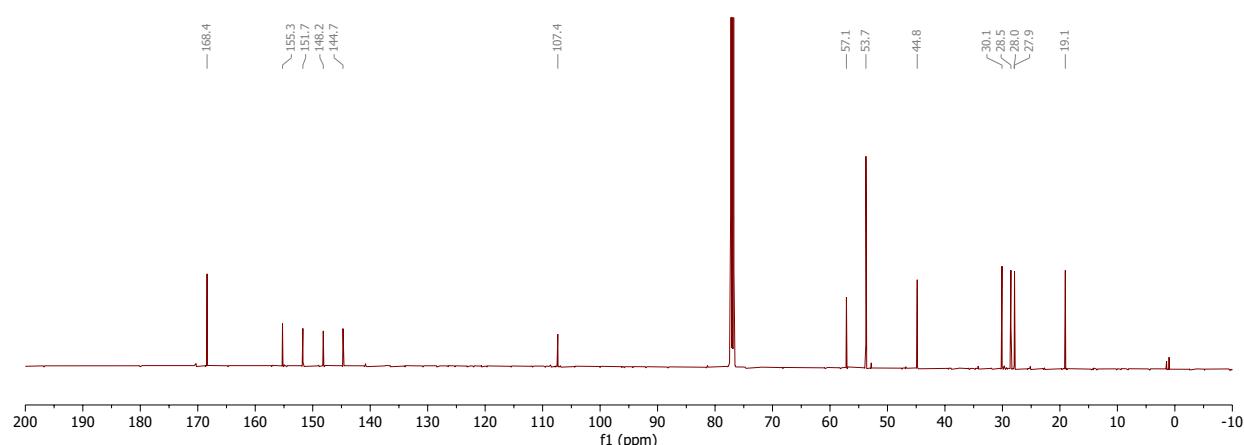


Dimethyl 2,3-dihydrodibenzo[*b,d*]furan-4,4(1*H*)-dicarboxylate, 52500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

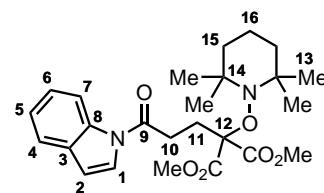
Dimethyl 4-chloro-8,9-dihydropyrimido[5,4-*b*]indolizine-6,6(7*H*)-dicarboxylate, 54500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

Dimethyl 8,9-dihydropyrido[3,2-*b*]indolizine-6,6(7*H*)-dicarboxylate, 56500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

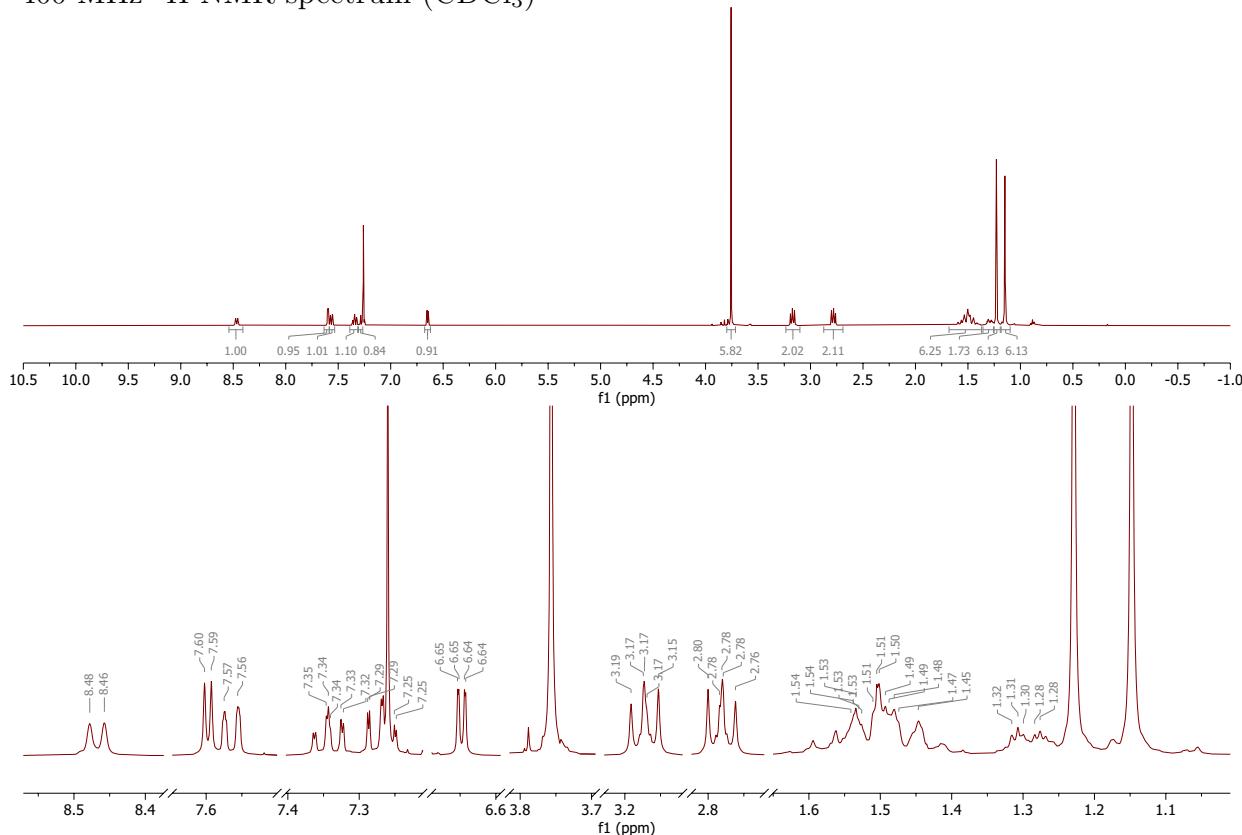
Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4,7,8-hexahydropyrido[2,1-*f*]purine-9,9(6*H*)- dicarboxylate, 58

500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

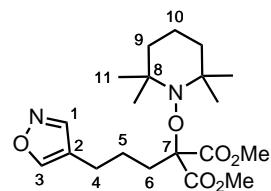
Dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate, 64



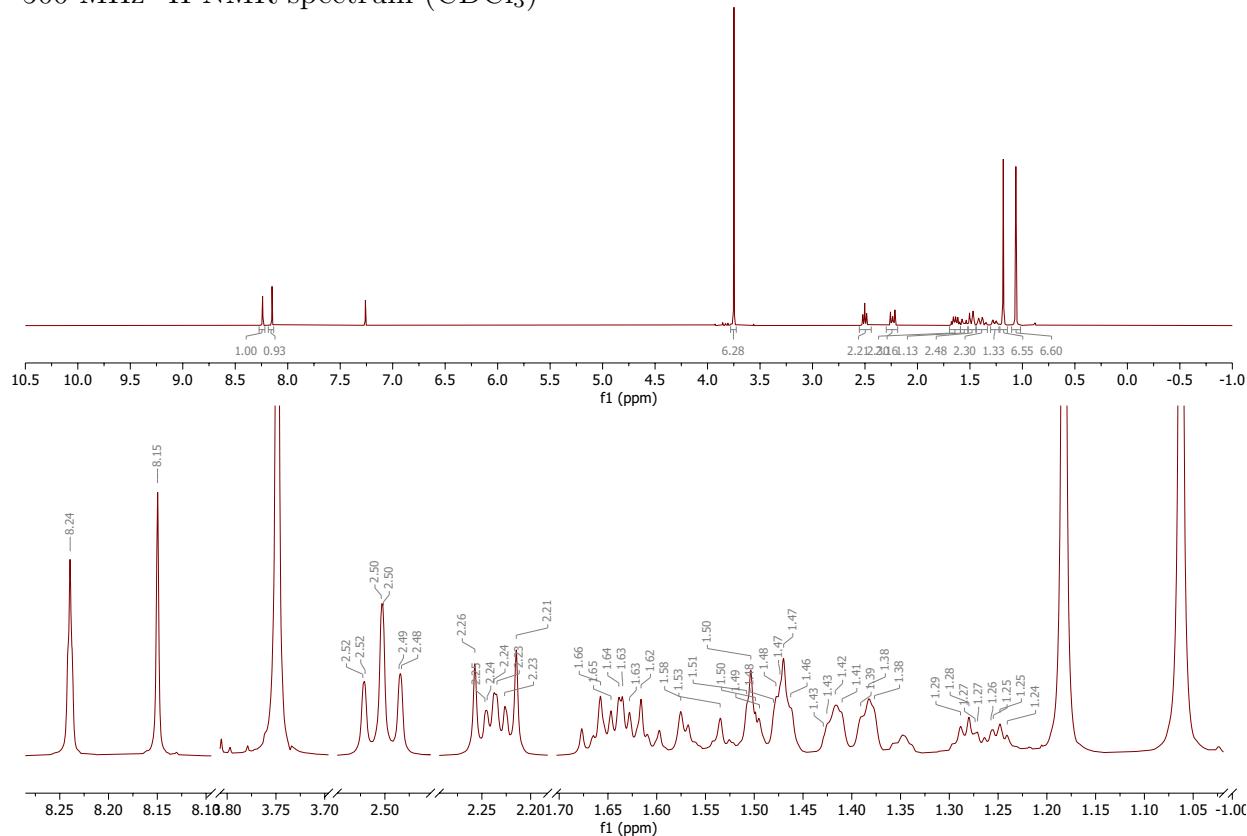
400 MHz ^1H NMR spectrum (CDCl_3)



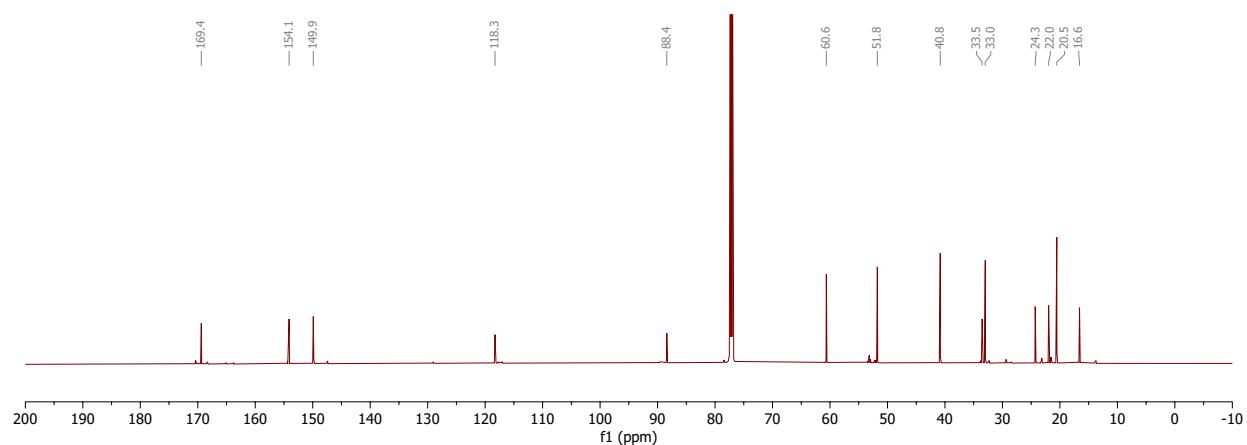
Dimethyl 2-(3-(isoxazol-4-yl)propyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate, 65



500 MHz ^1H NMR spectrum (CDCl_3)

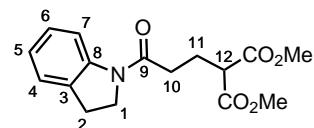


126 MHz ^{13}C NMR spectrum (CDCl_3)

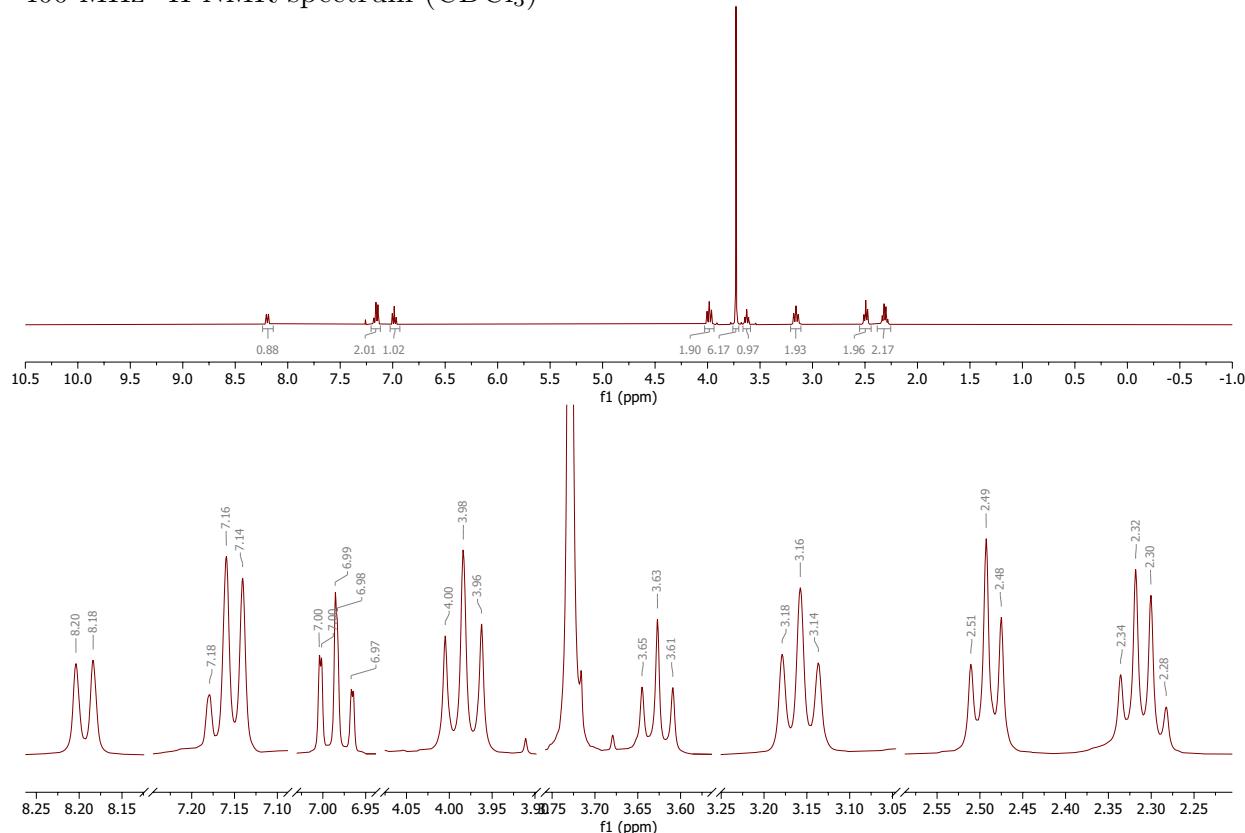


1.4.2 Cyclisation substrates and other novel compounds

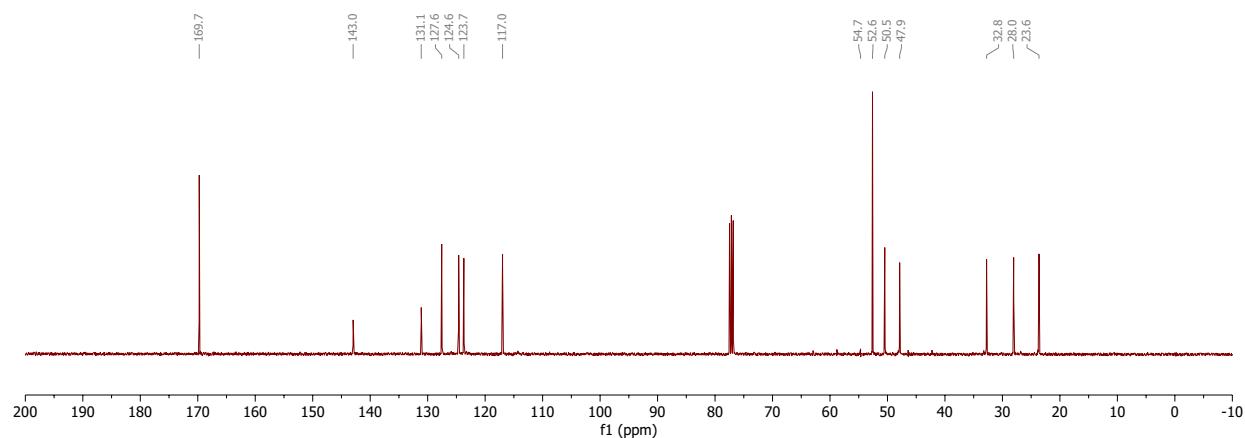
Dimethyl 2-(3-(indolin-1-yl)-3-oxopropyl)malonate, 69

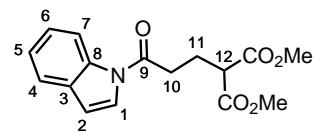
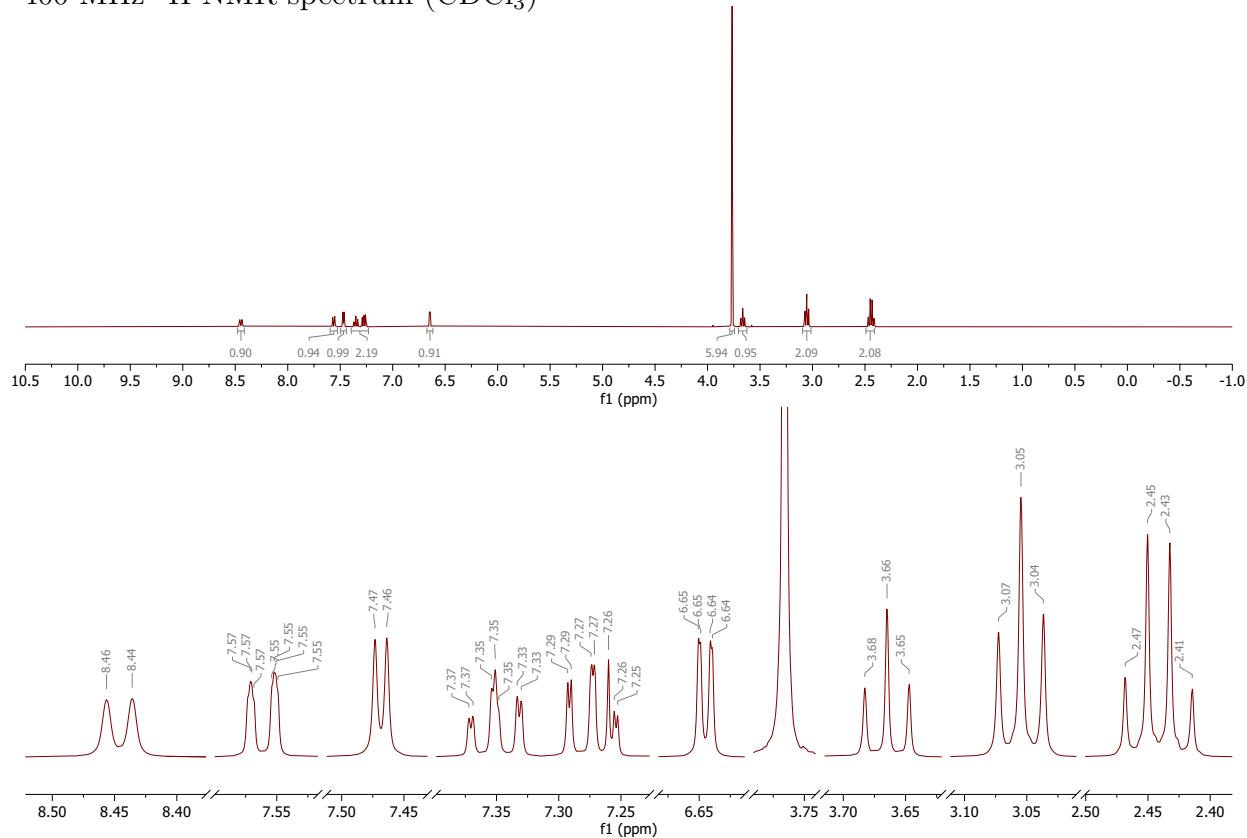
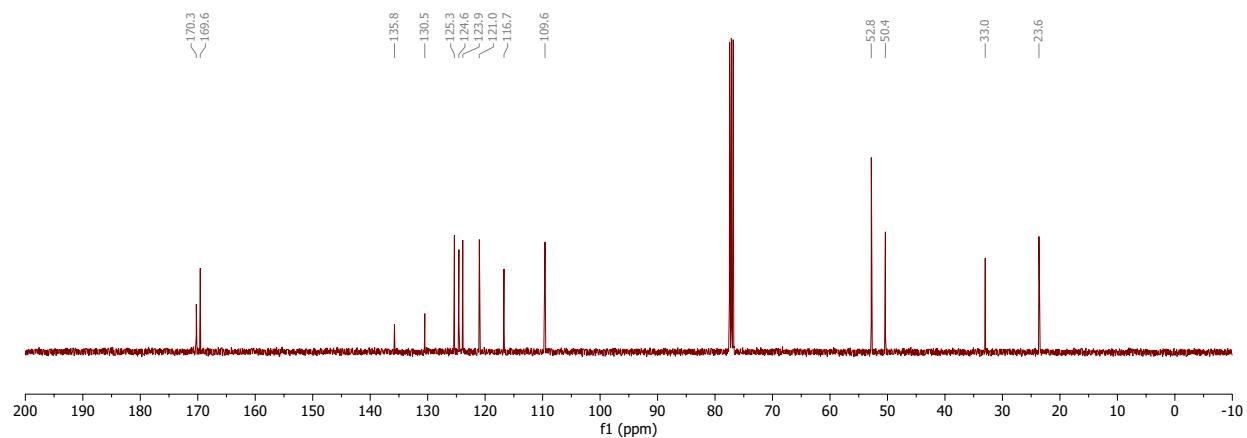


400 MHz ^1H NMR spectrum (CDCl_3)

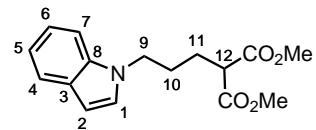


101 MHz ^{13}C NMR spectrum (CDCl_3)

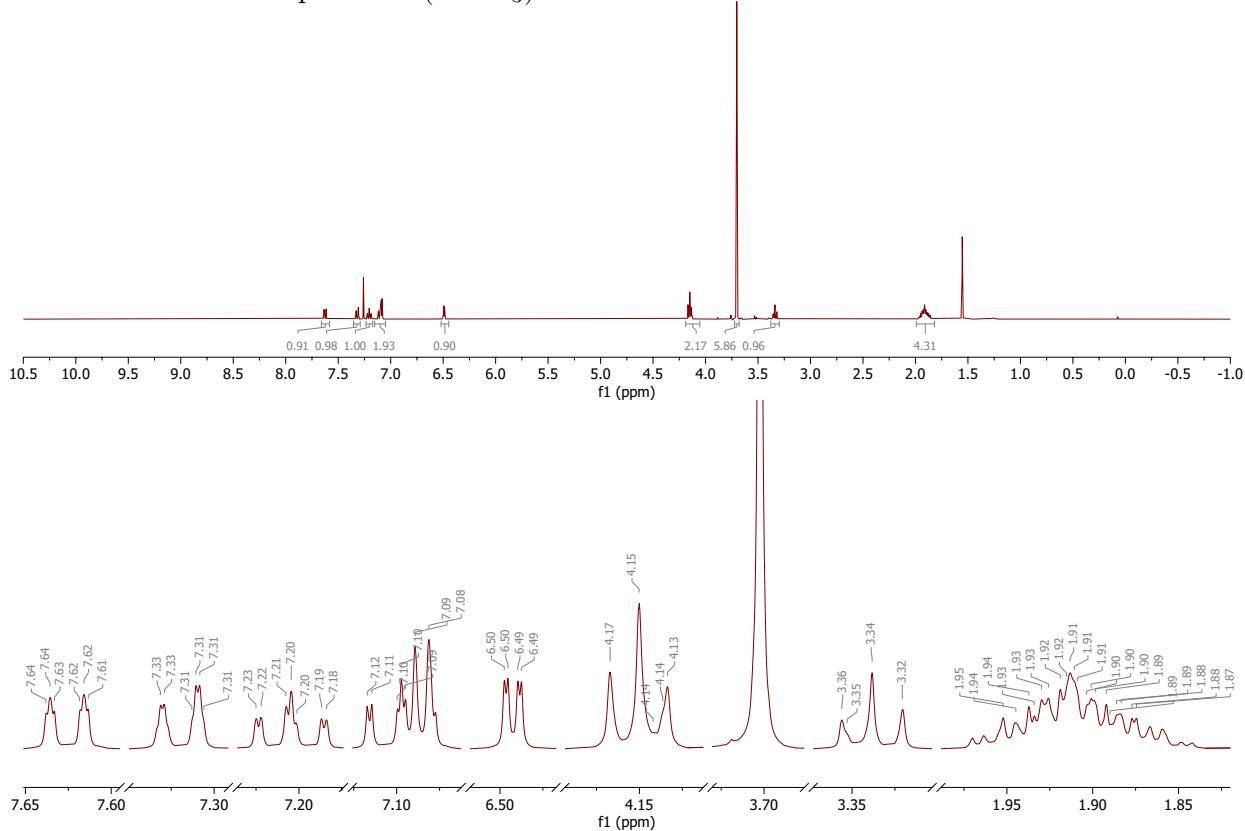


Dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate, 4400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

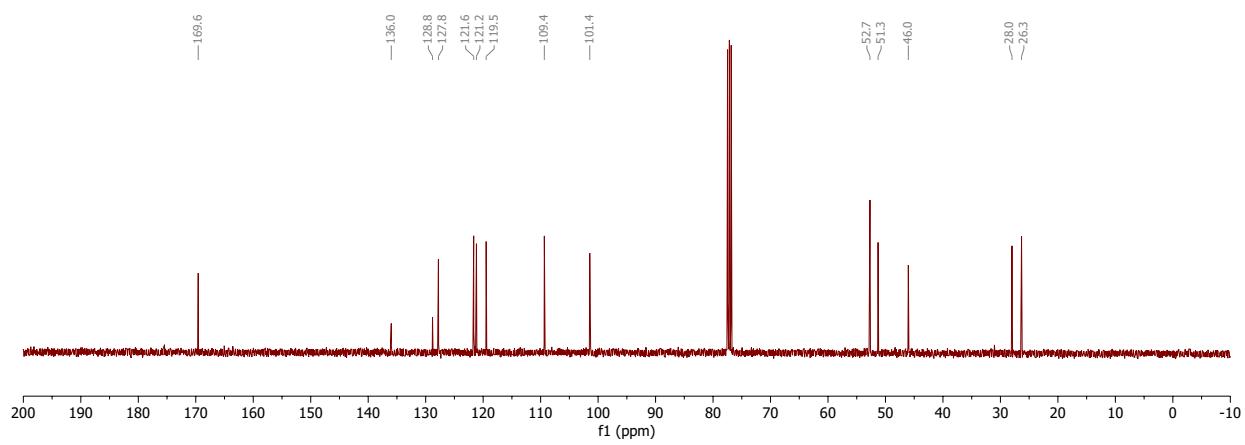
Dimethyl 2-(3-(1*H*-indol-1-yl)propyl)malonate, 9

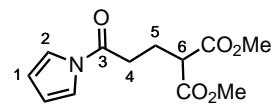
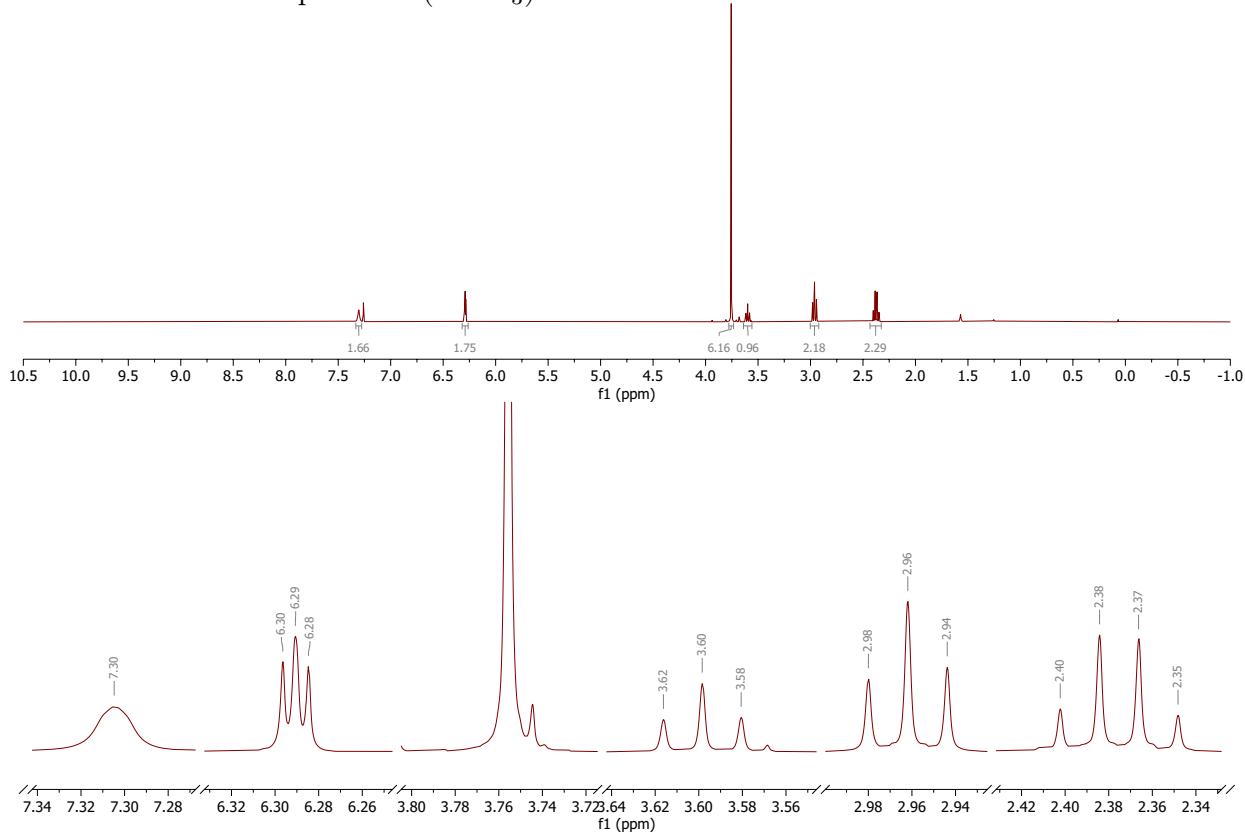
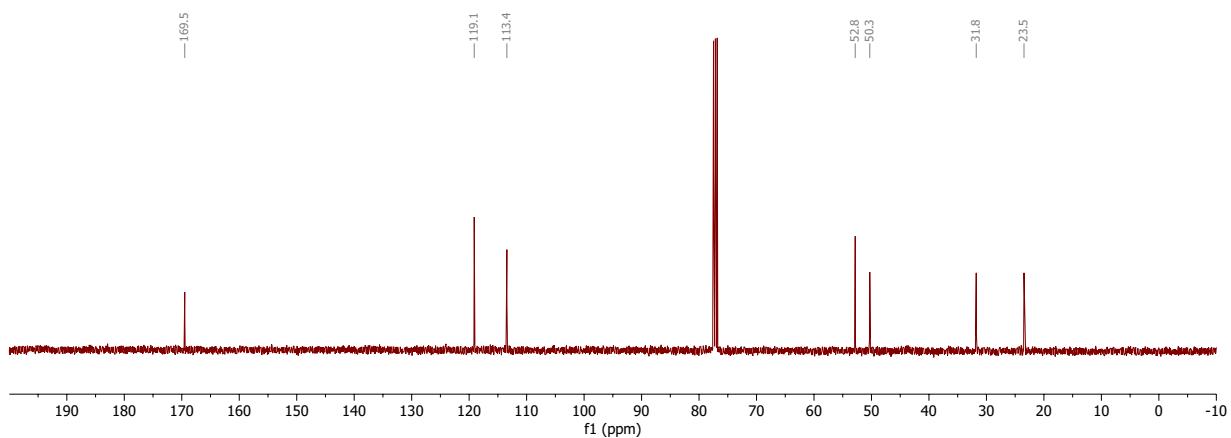


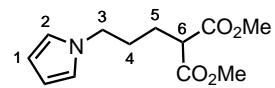
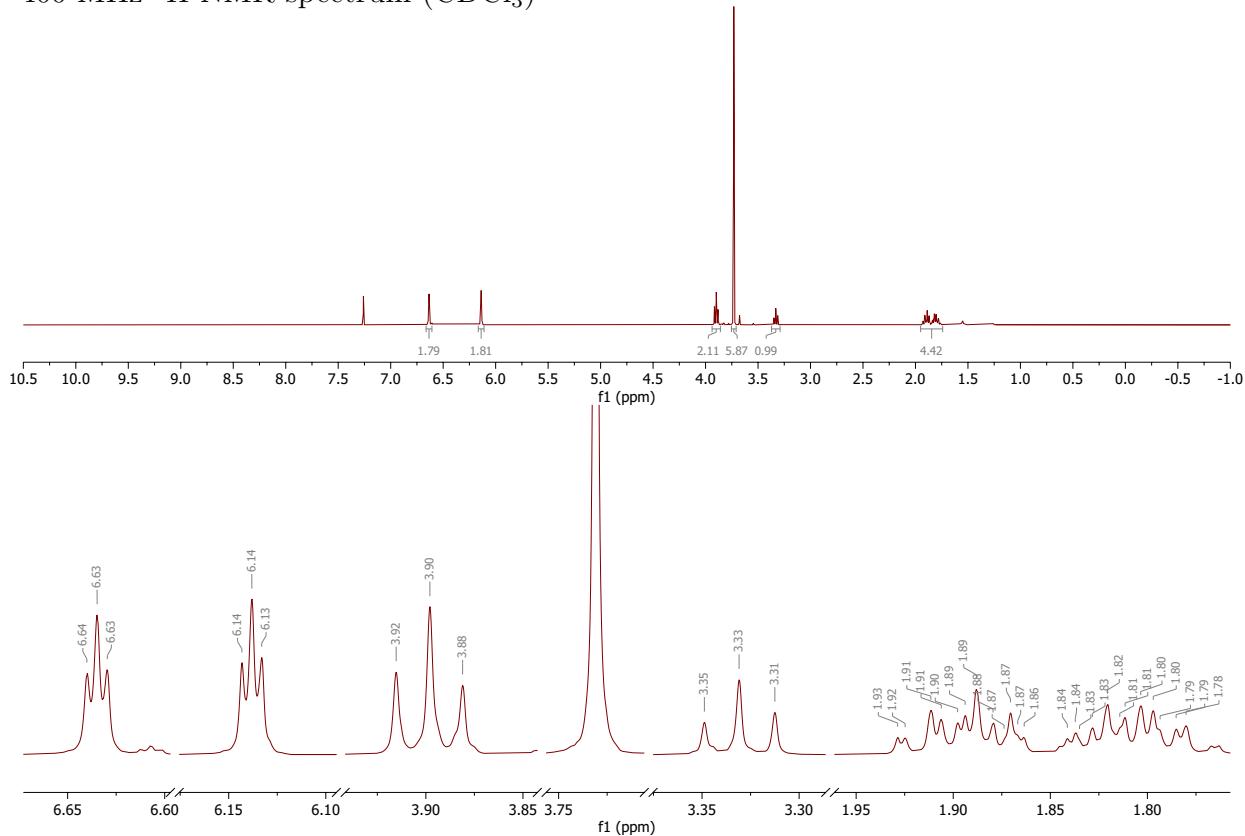
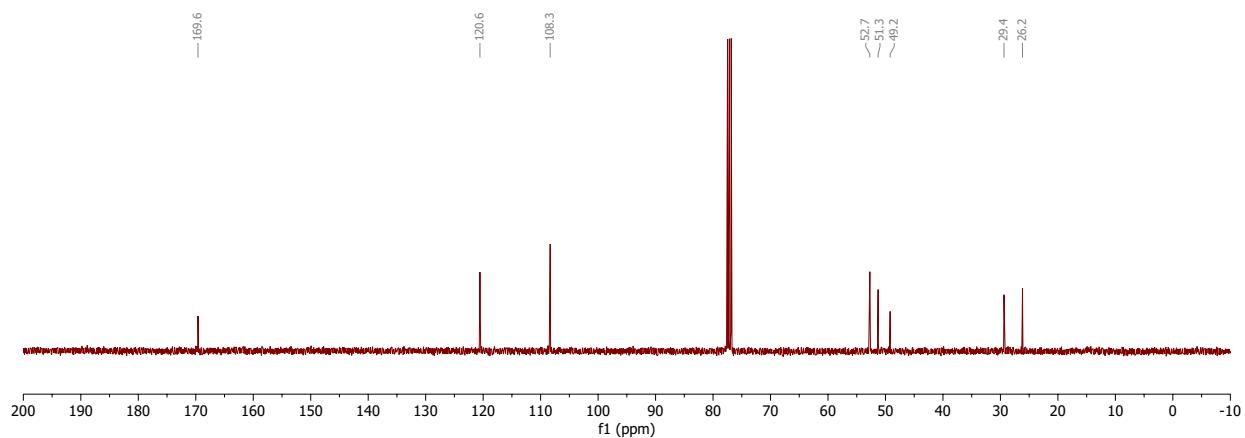
400 MHz ^1H NMR spectrum (CDCl_3)

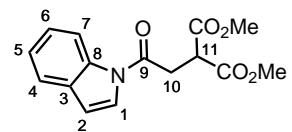
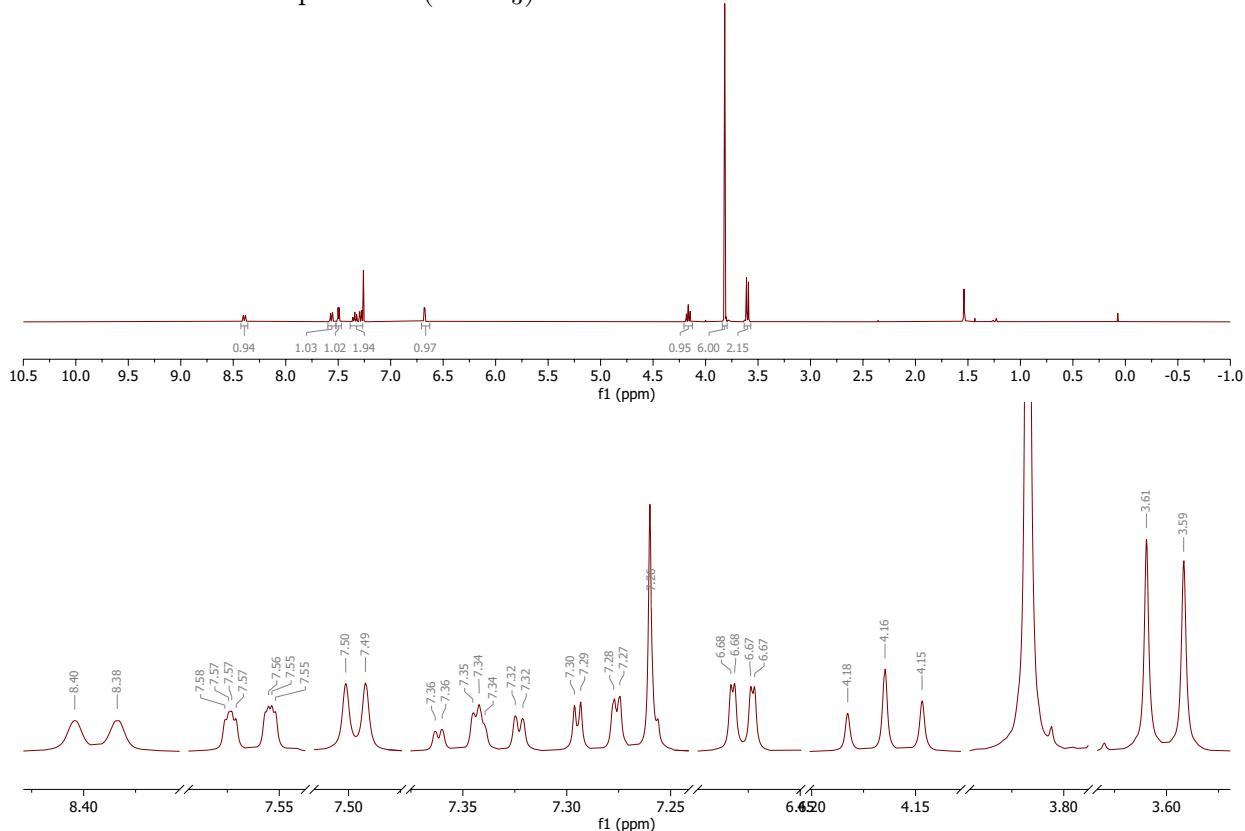
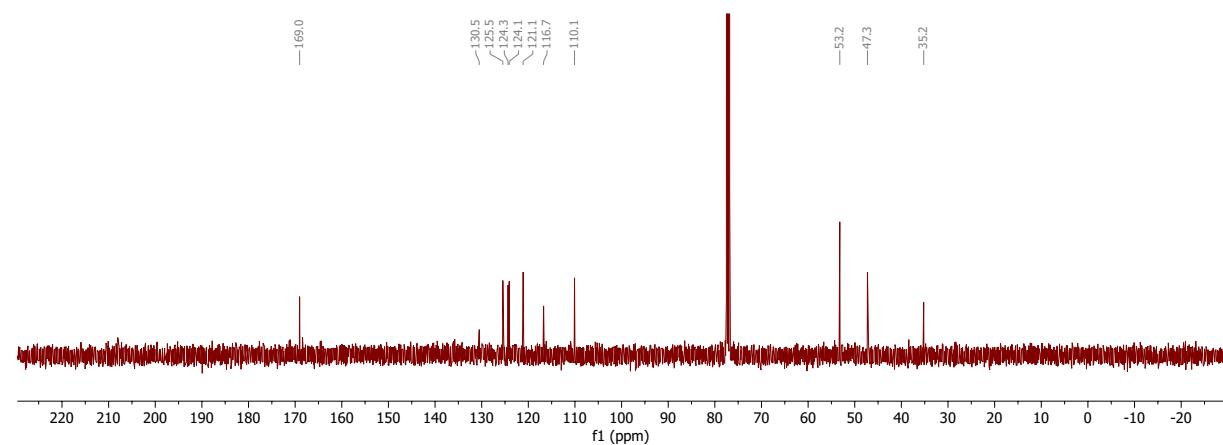


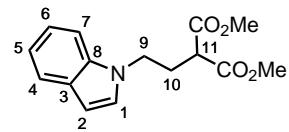
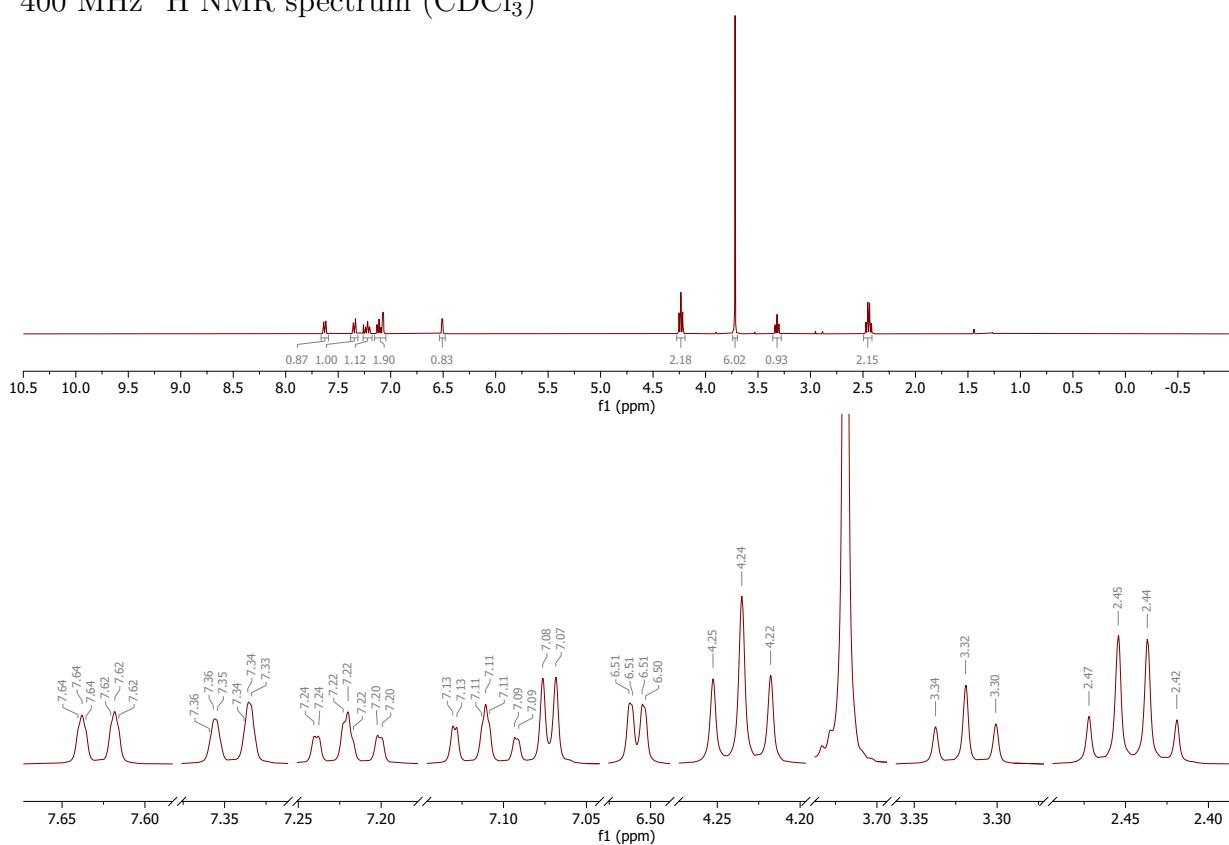
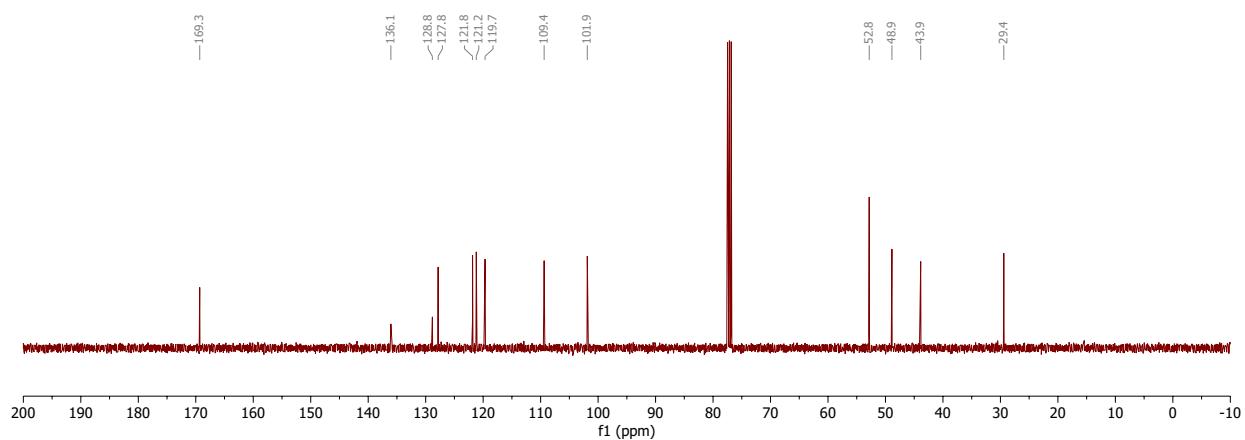
101 MHz ^{13}C NMR spectrum (CDCl_3)

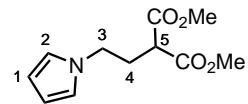
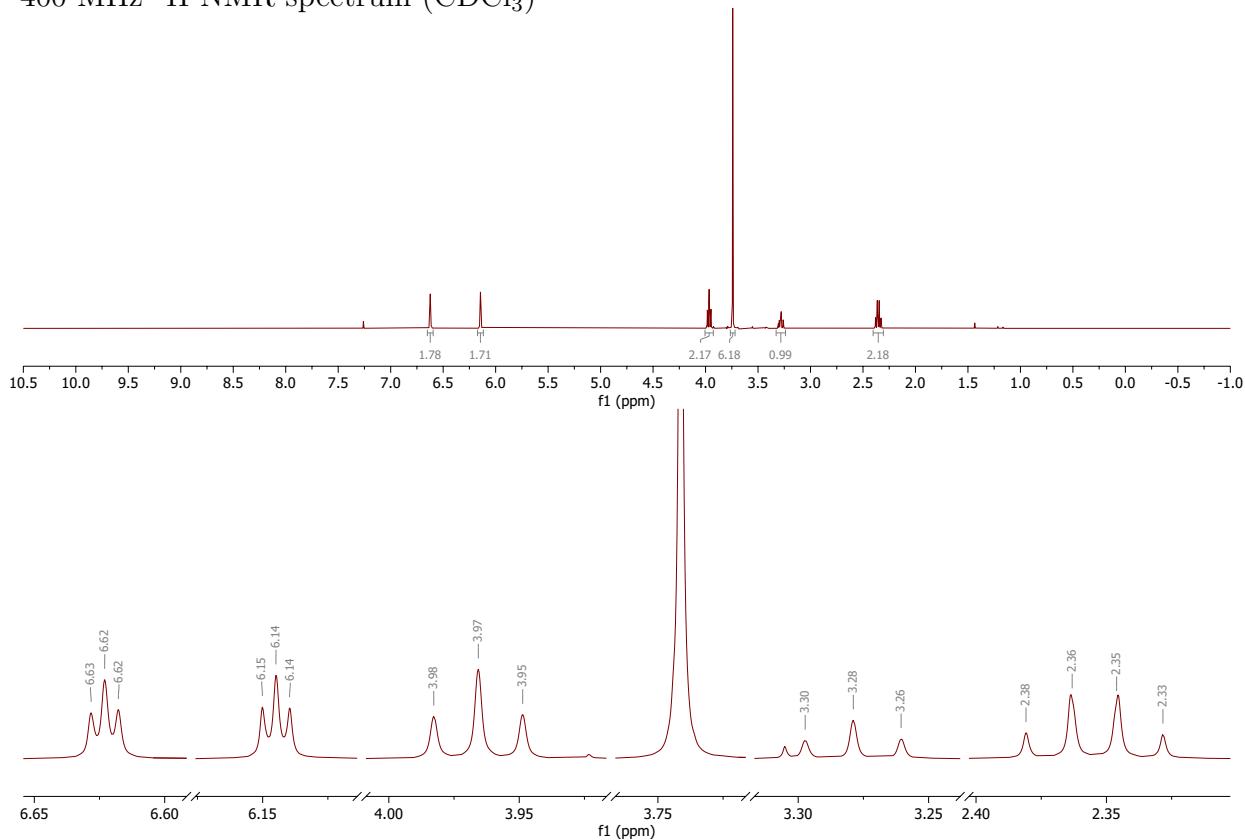
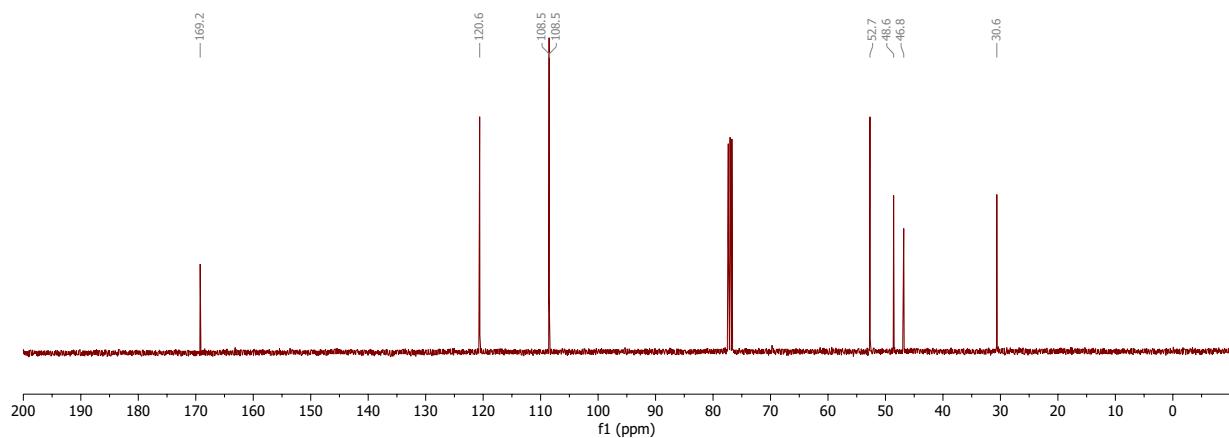


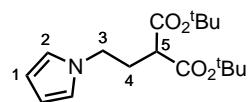
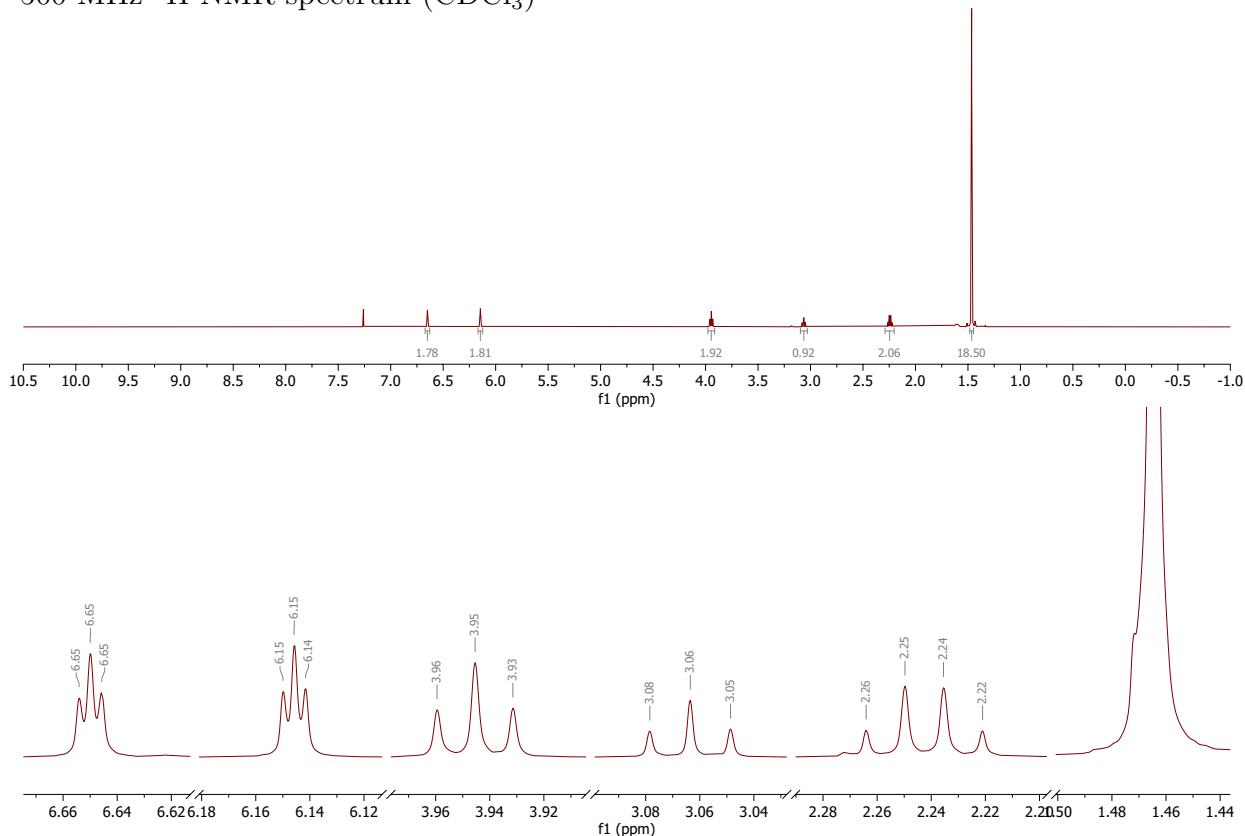
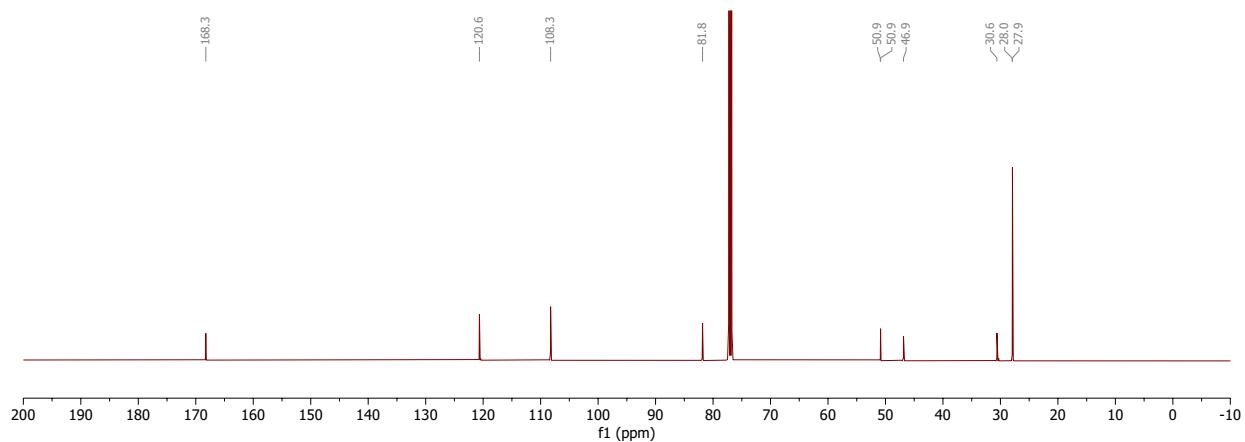
Dimethyl 2-(3-oxo-3-(1*H*-pyrrol-1-yl)propyl)malonate, 13400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

Dimethyl 2-(3-(1*H*-pyrrol-1-yl)propyl)malonate, 15400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

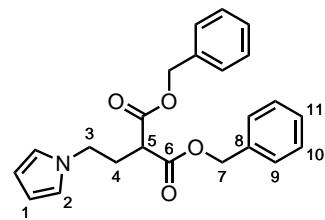
Dimethyl 2-(2-(1*H*-indol-1-yl)-2-oxoethyl)malonate, 7400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 2-(2-(1*H*-indol-1-yl)ethyl)malonate, 11400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

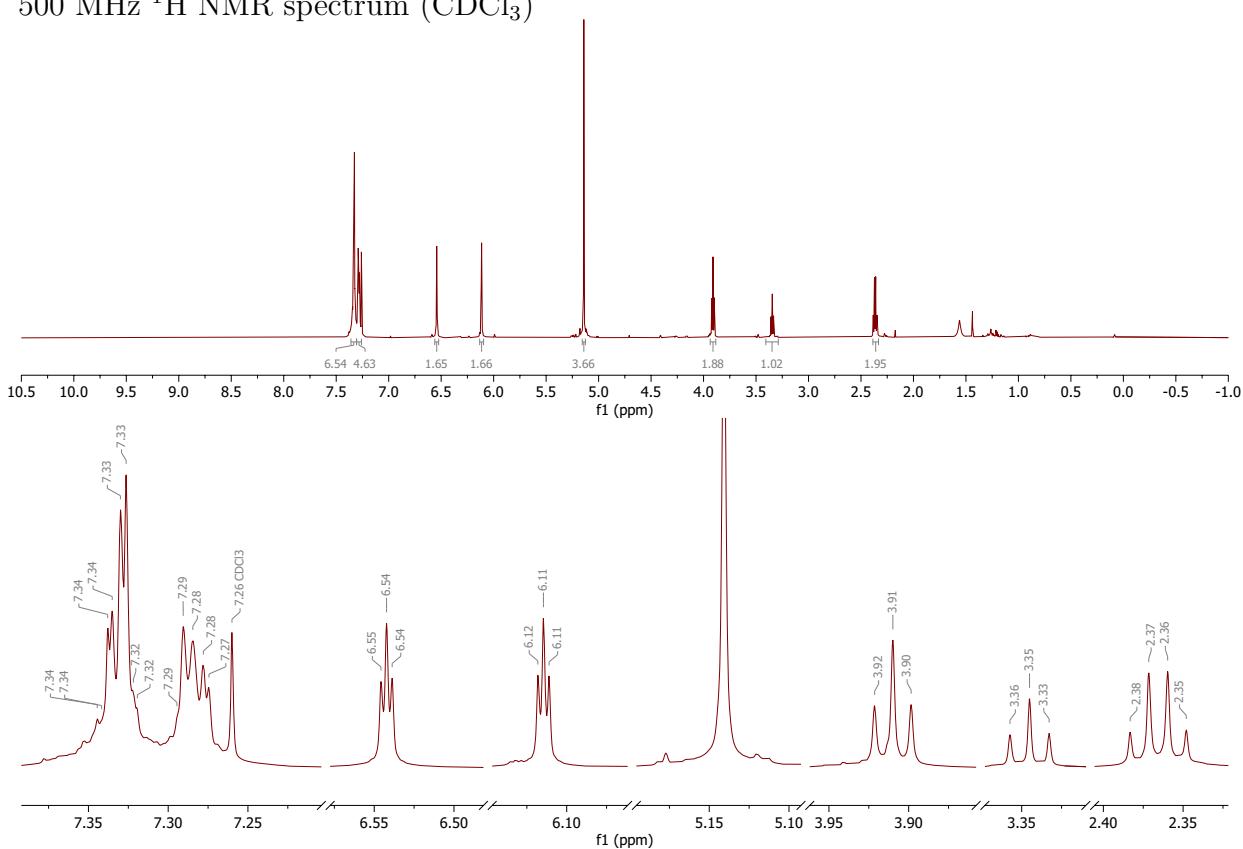
Dimethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 17a400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

Di-*tert*-butyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 17b500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

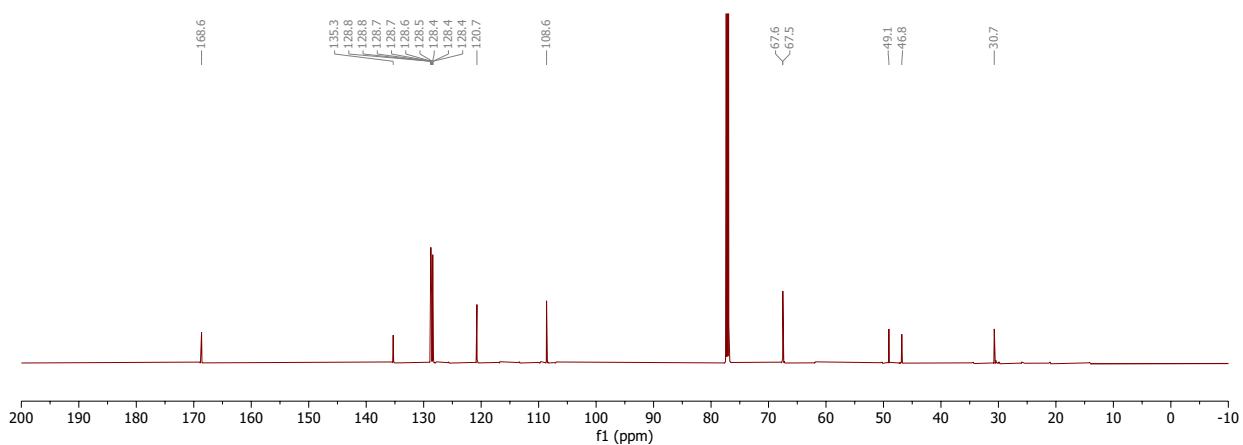
Dibenzyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 17c

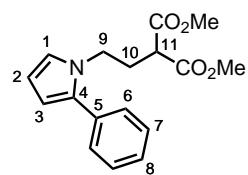
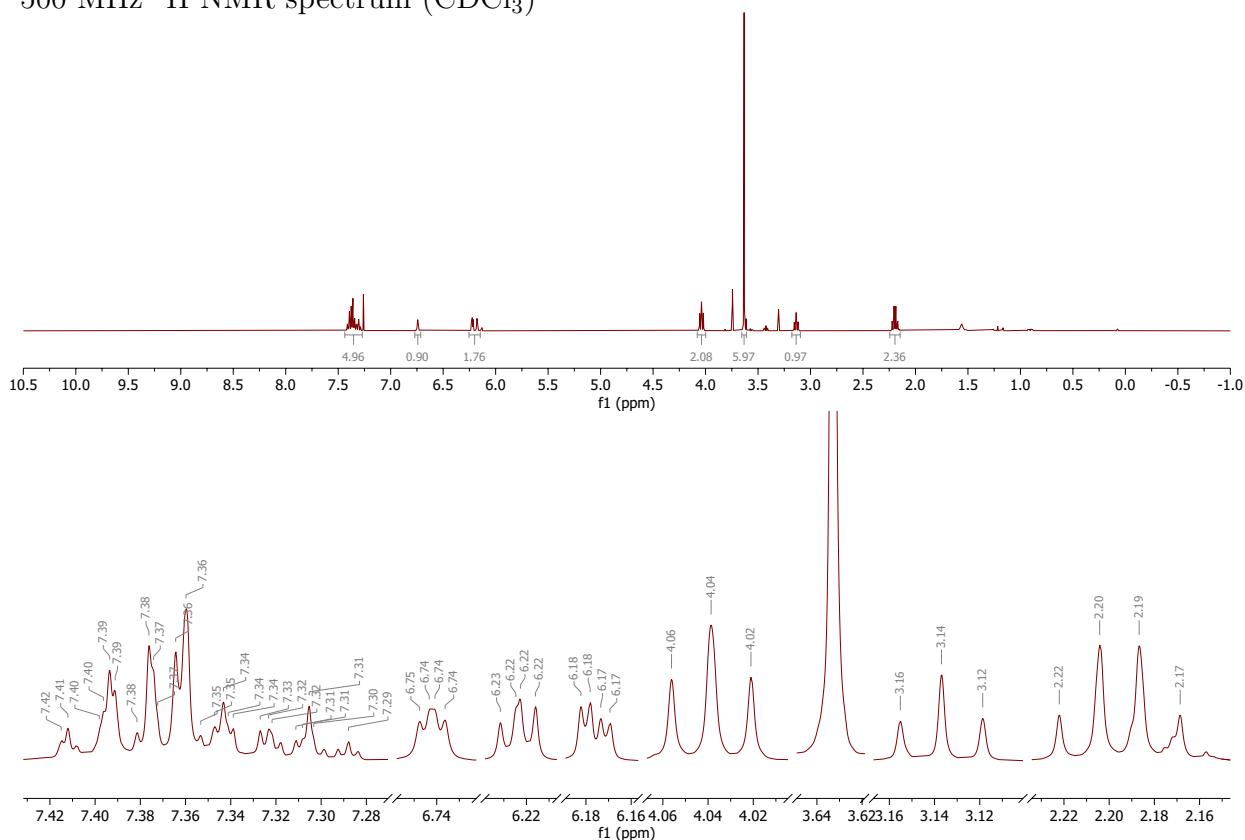


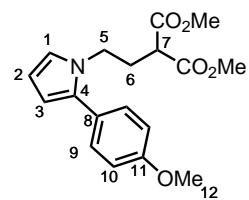
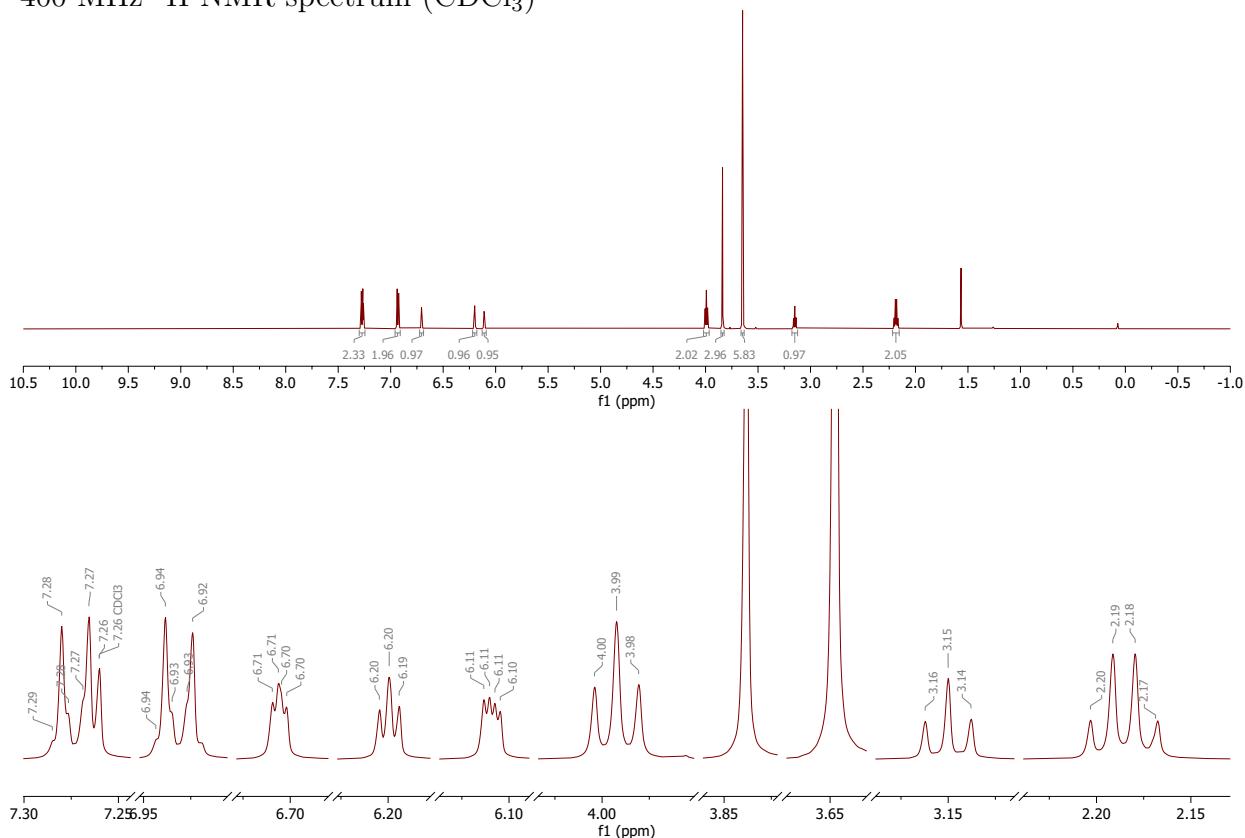
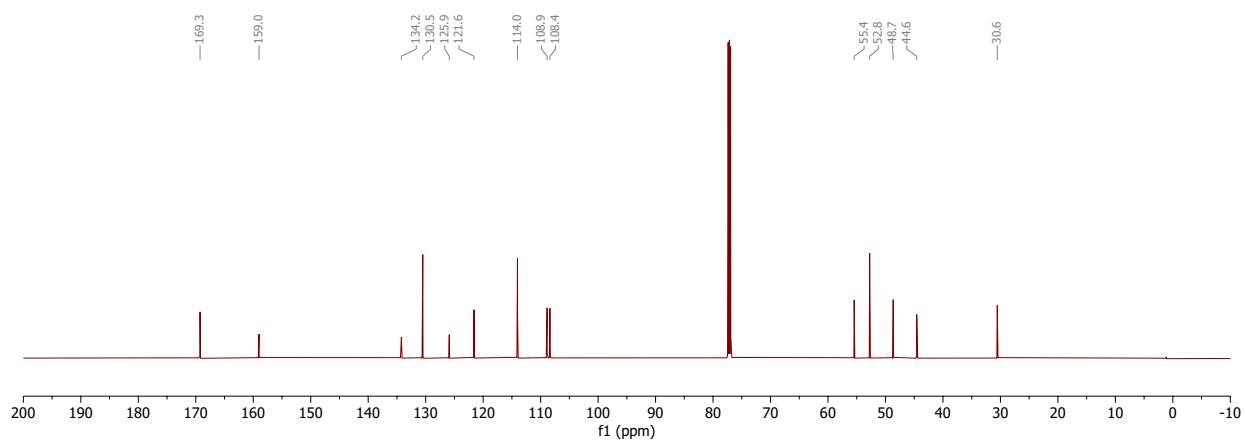
500 MHz ^1H NMR spectrum (CDCl_3)

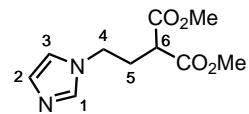
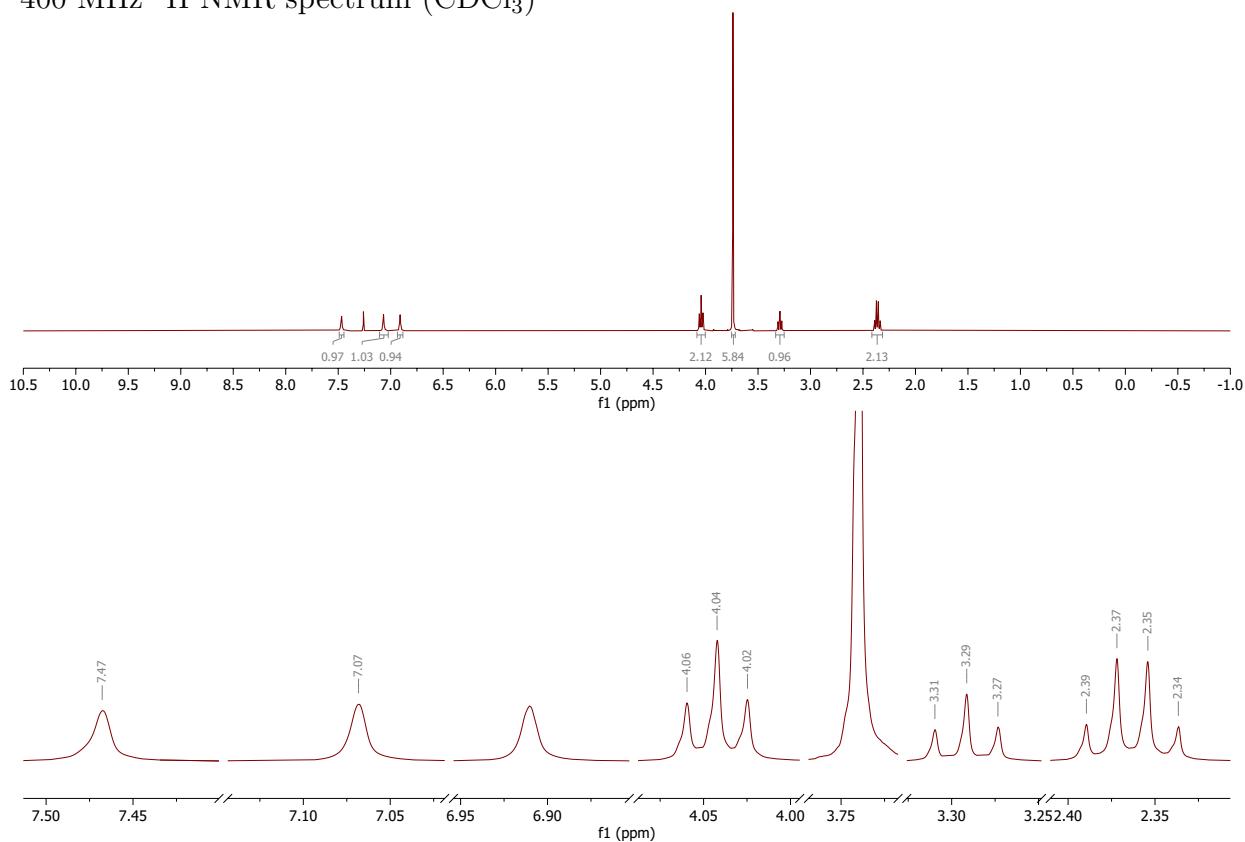
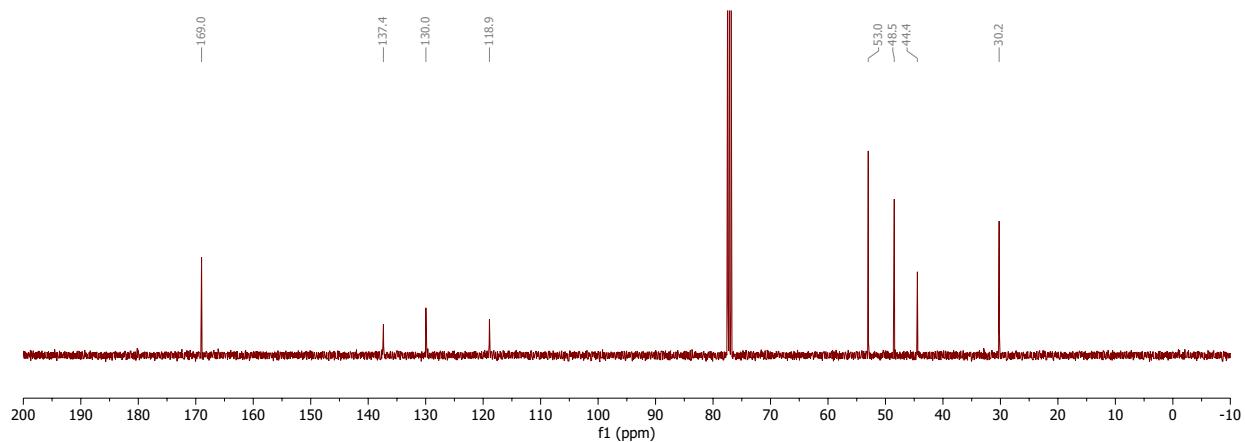


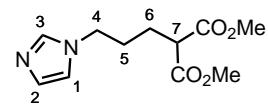
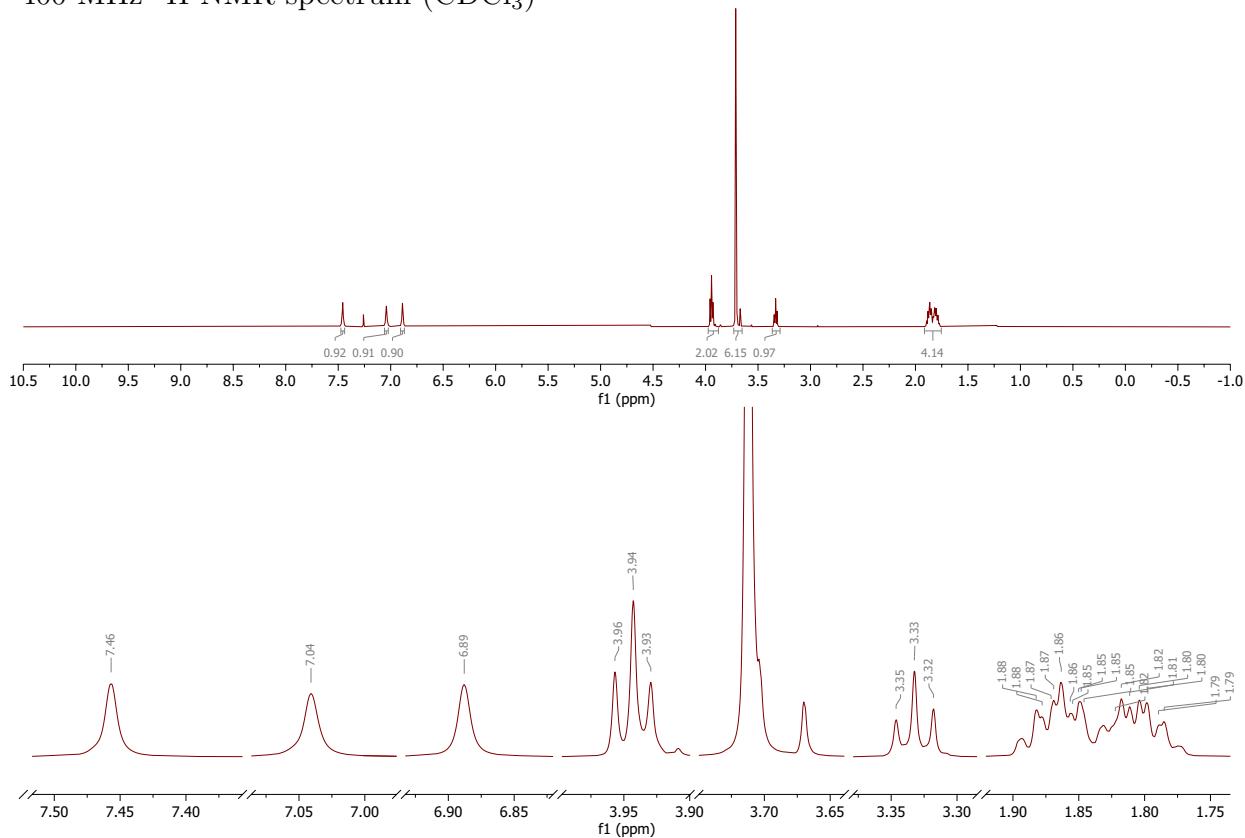
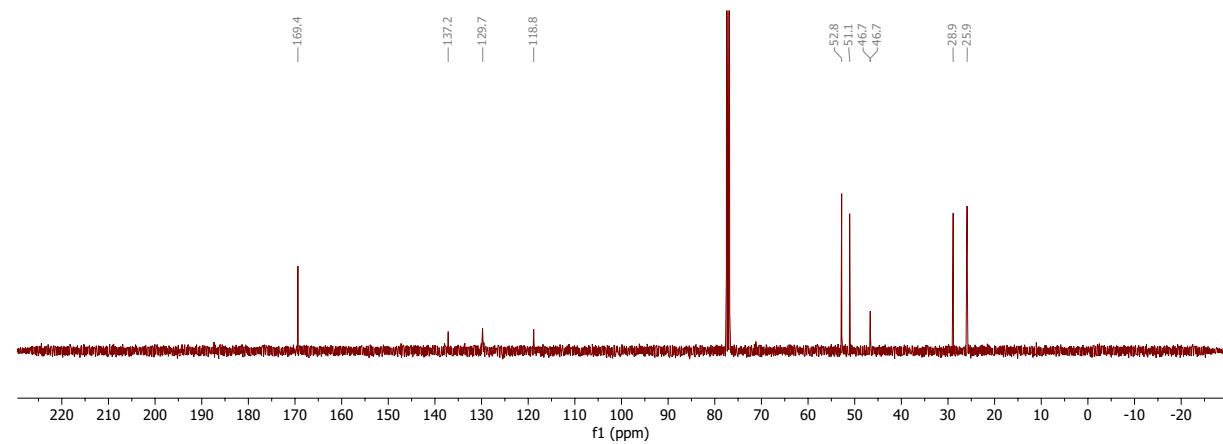
126 MHz ^{13}C NMR spectrum (CDCl_3)

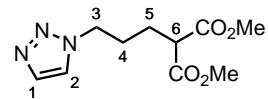
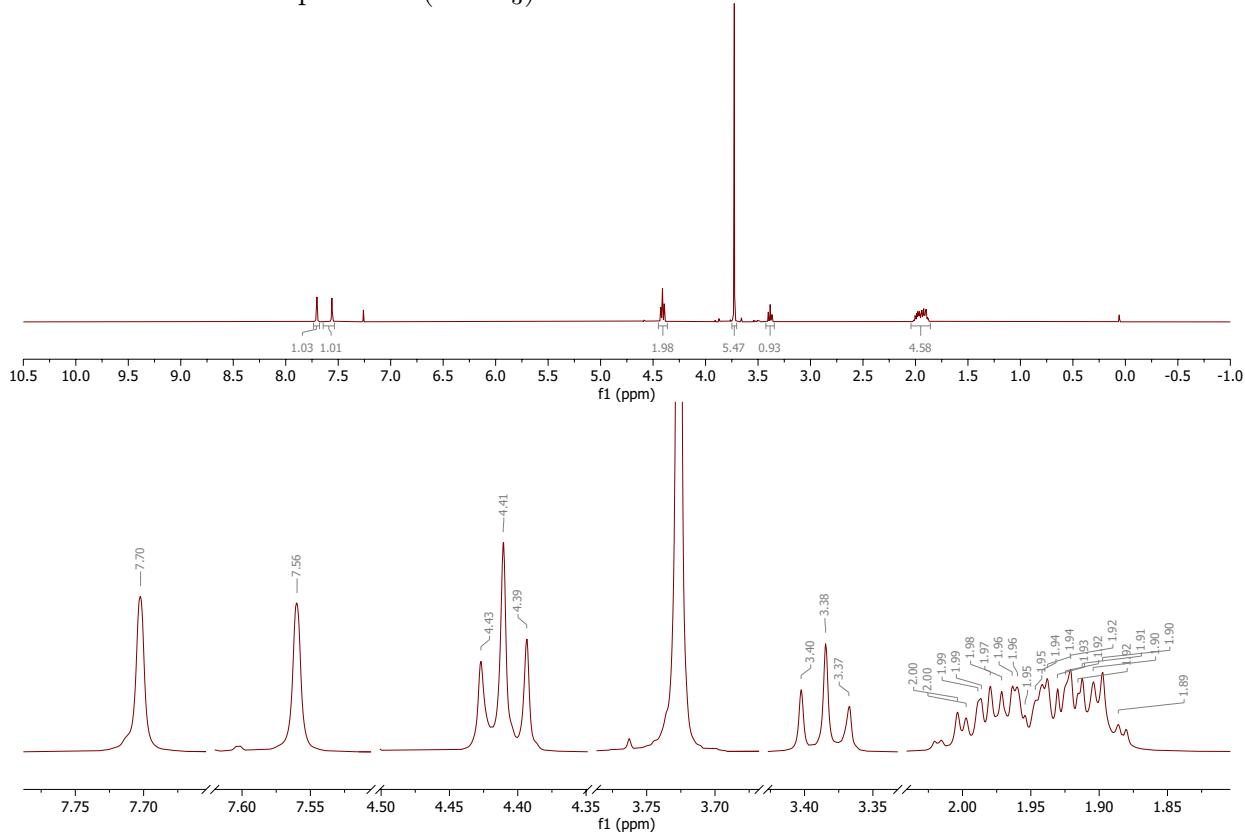
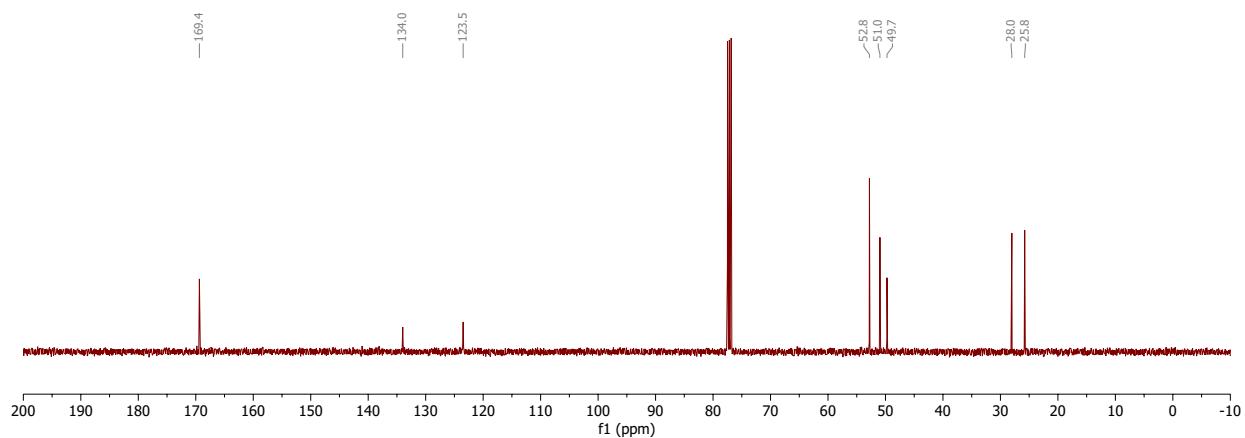


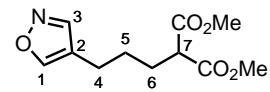
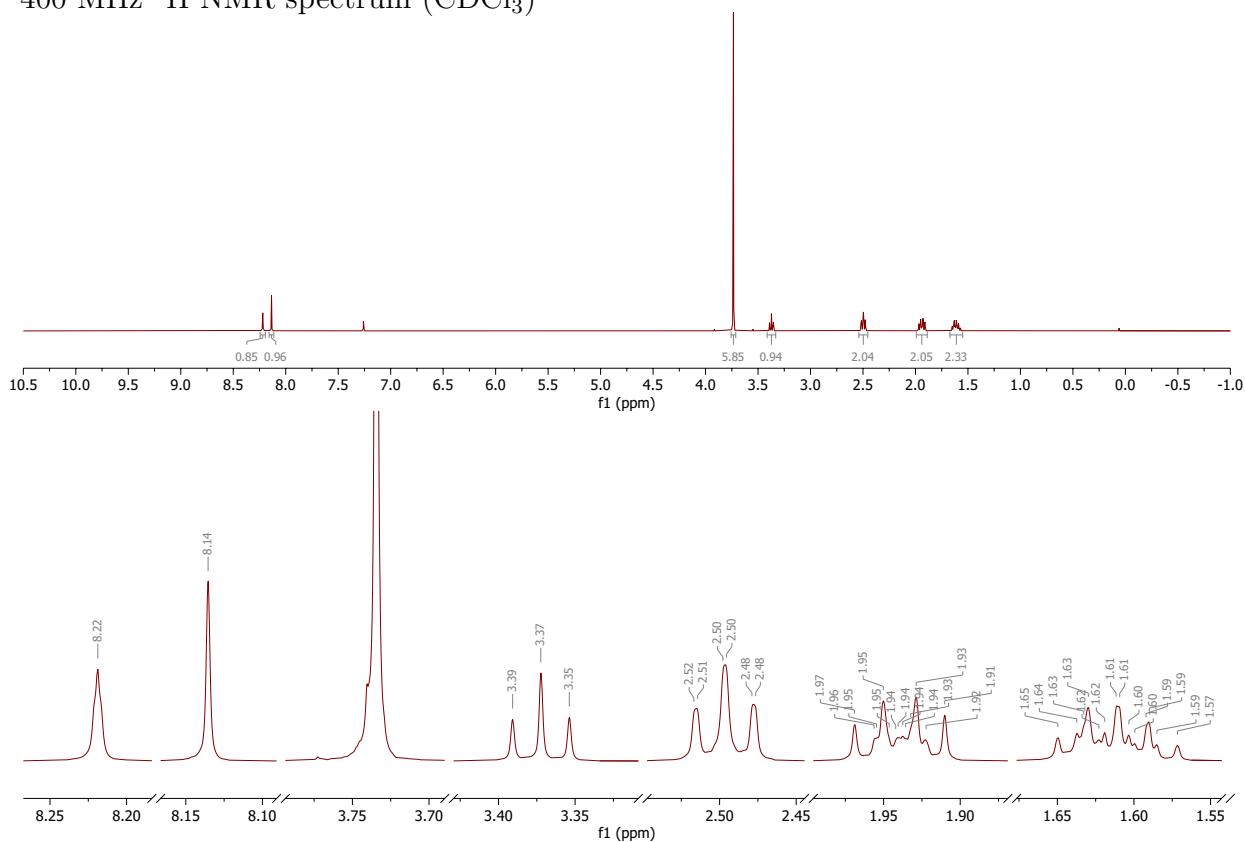
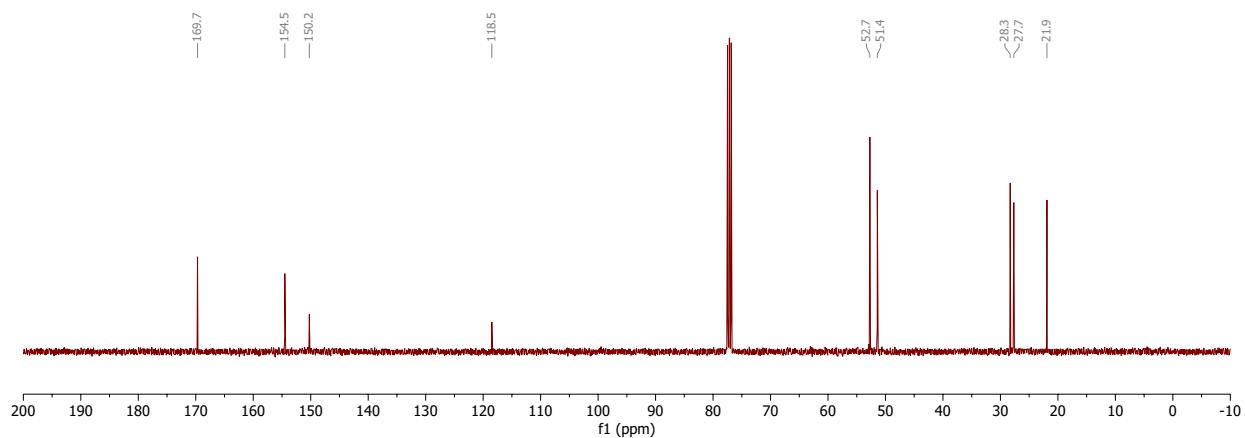
Dimethyl 2-(2-(2-phenyl-1*H*-pyrrol-1-yl)ethyl)malonate, 21b500 MHz ¹H NMR spectrum (CDCl₃)

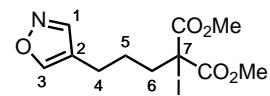
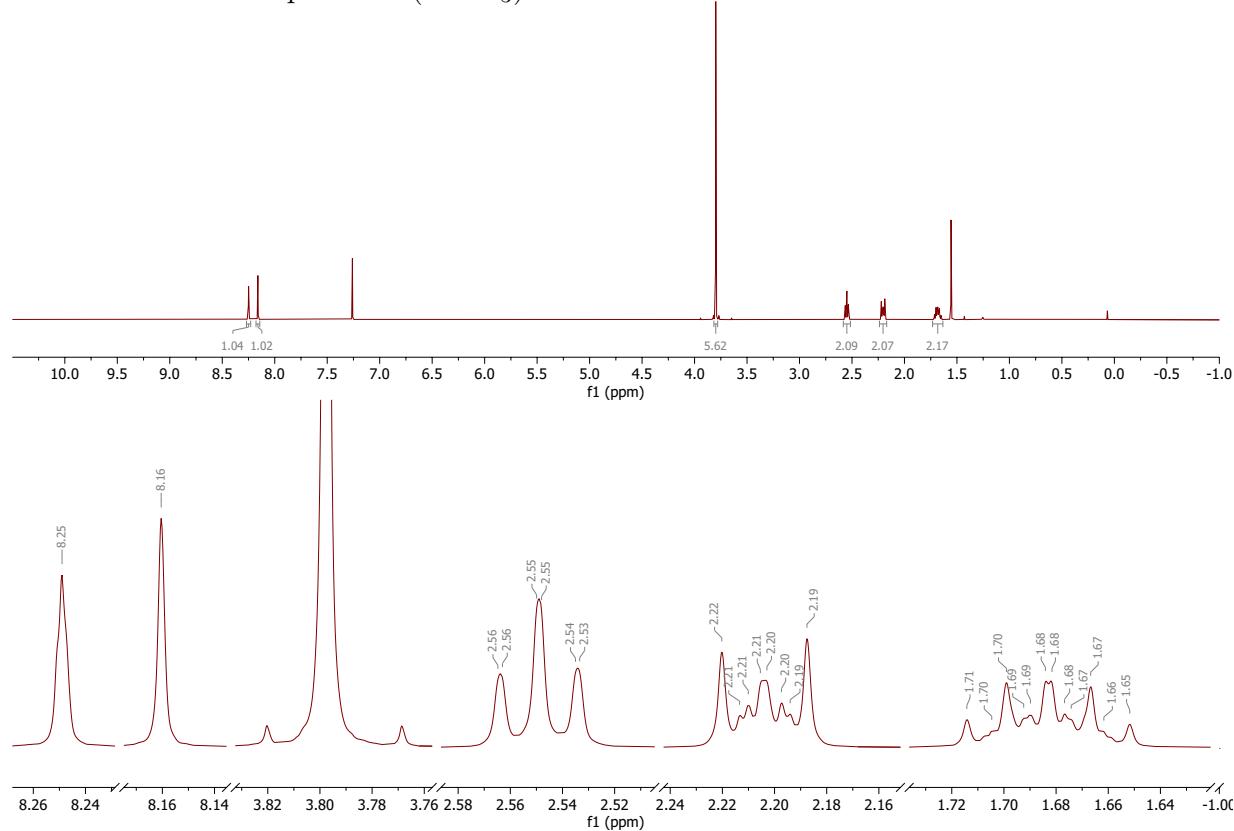
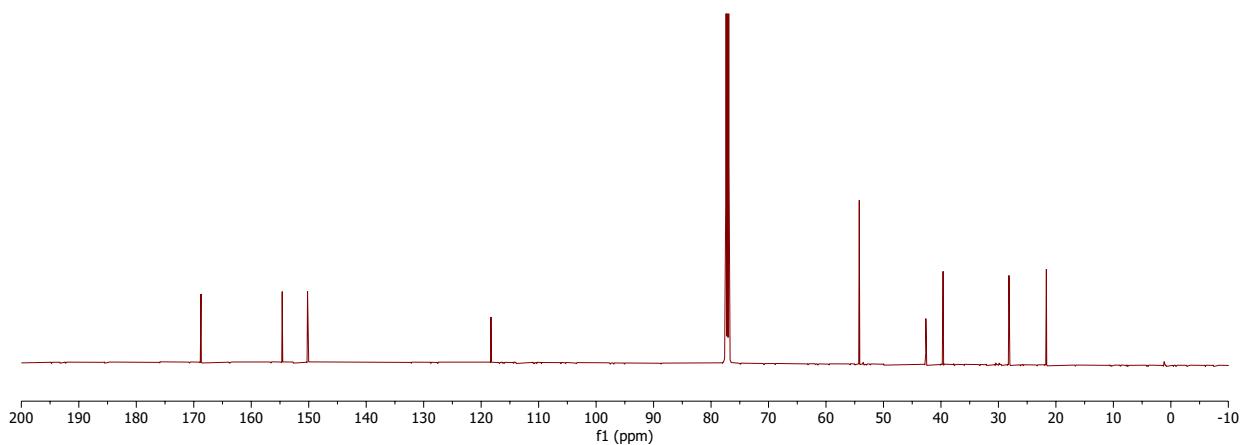
Dimethyl 2-(2-(4-methoxyphenyl)-1*H*-pyrrol-1-yl)ethyl)malonate, 21c400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

Dimethyl 2-(2-(1*H*-imidazol-1-yl)ethyl)malonate, 25400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

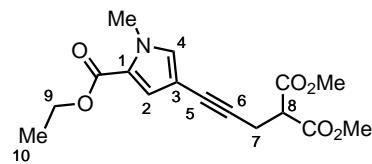
Dimethyl 2-(3-(1*H*-imidazol-1-yl)propyl)malonate, 23400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

Dimethyl 2-(3-(1*H*-1,2,3-triazol-1-yl)propyl)malonate, 27400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

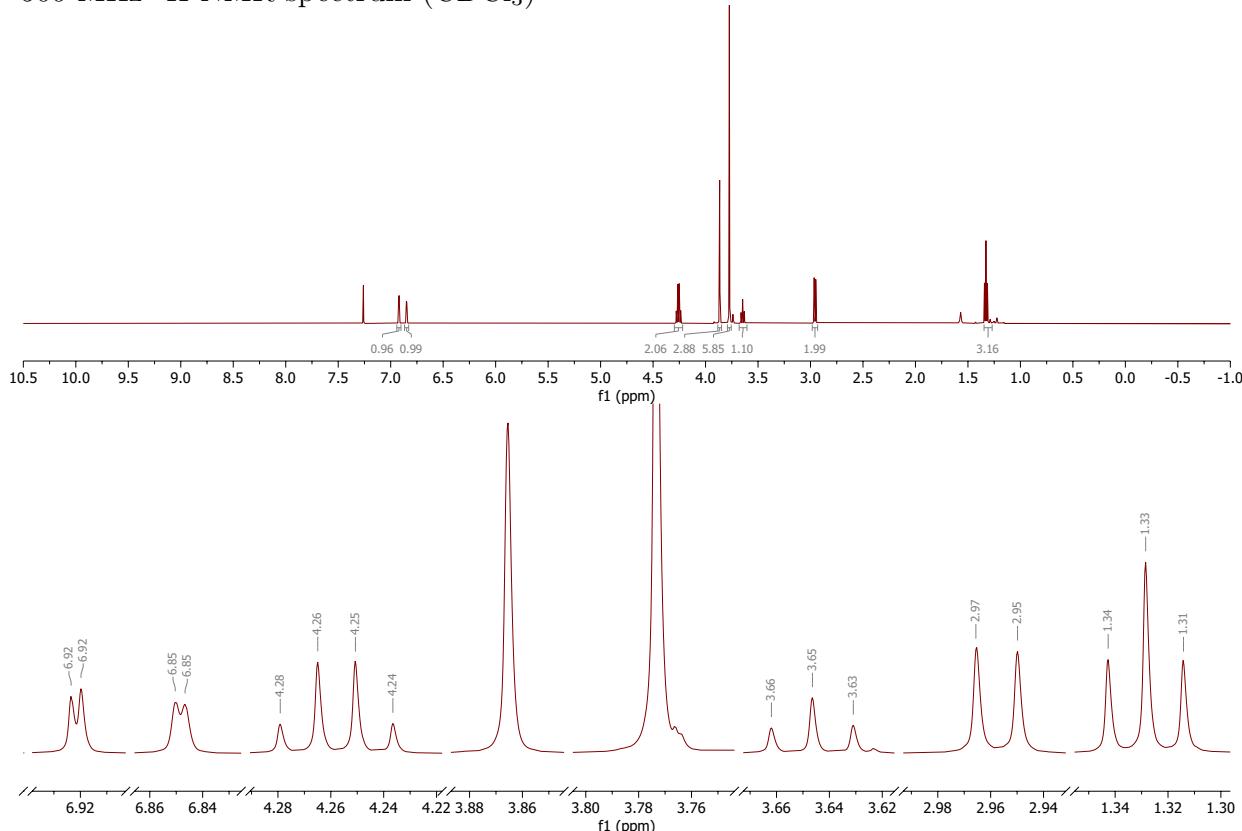
Dimethyl 2-(3-(isoxazol-4-yl)propyl)malonate, 31400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 2-iodo-2-(3-(isoxazol-4-yl)propyl)malonate, 29500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

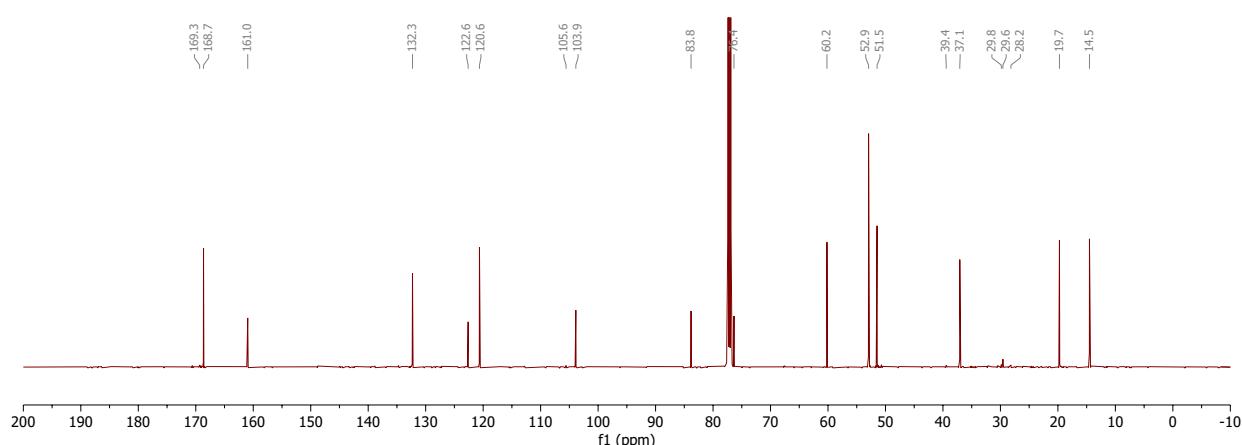
**Dimethyl 2-(3-(5-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)prop-2-yn-1-yl)malonate,
81**

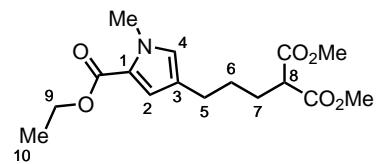
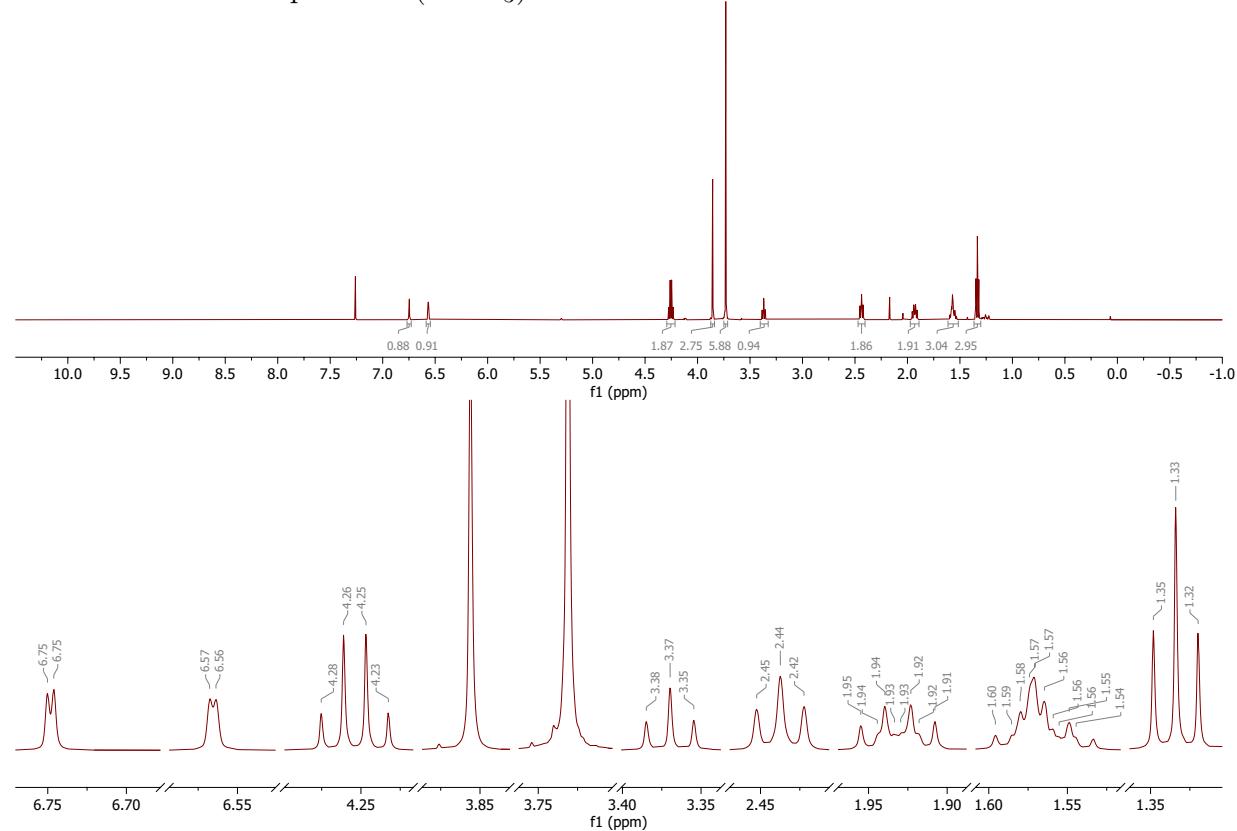
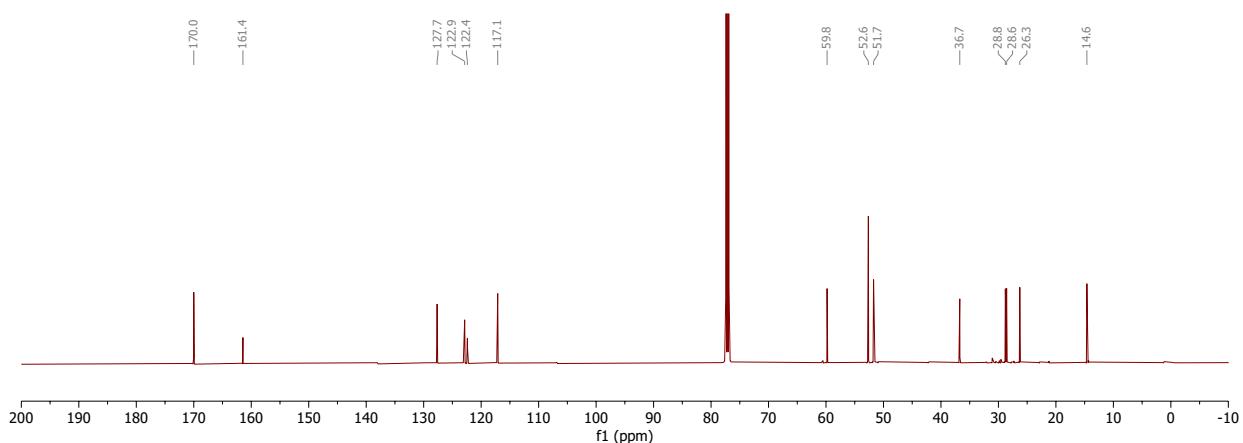


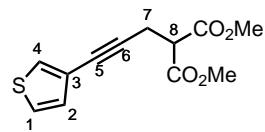
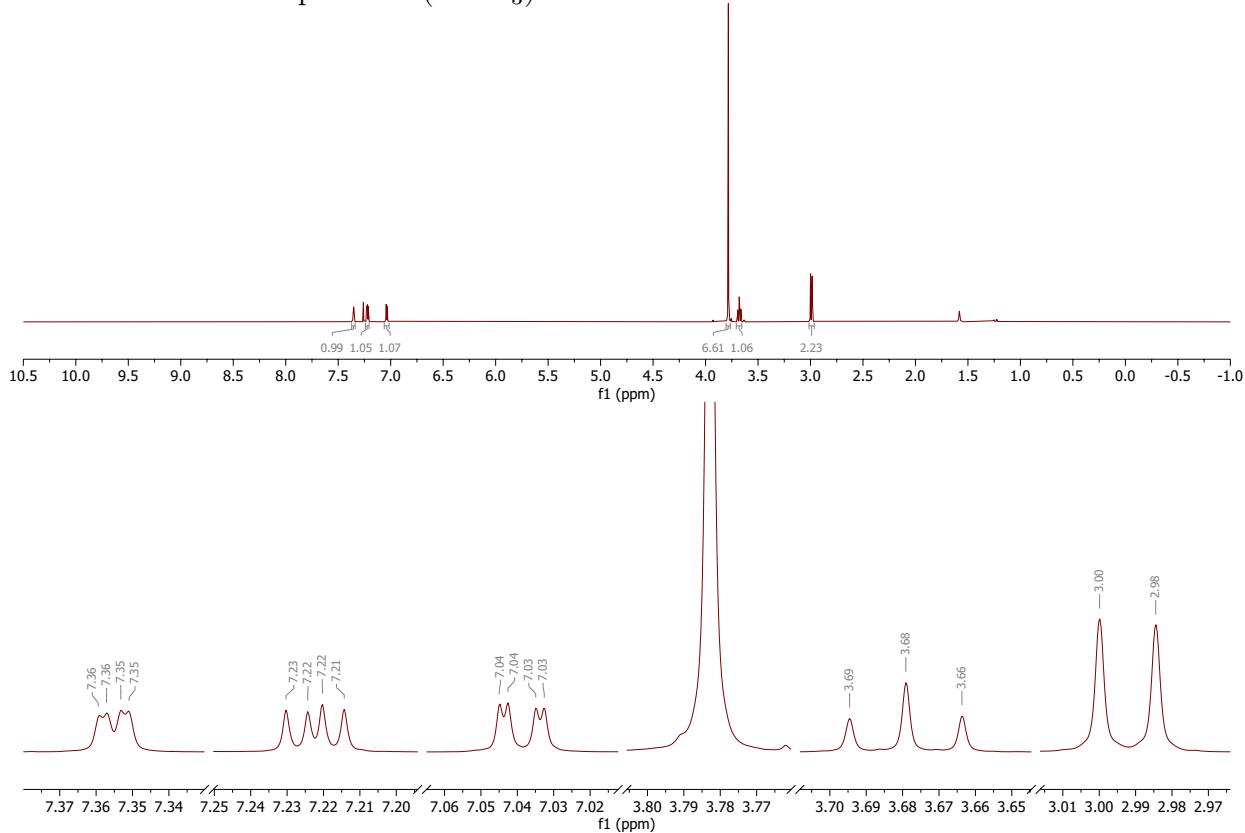
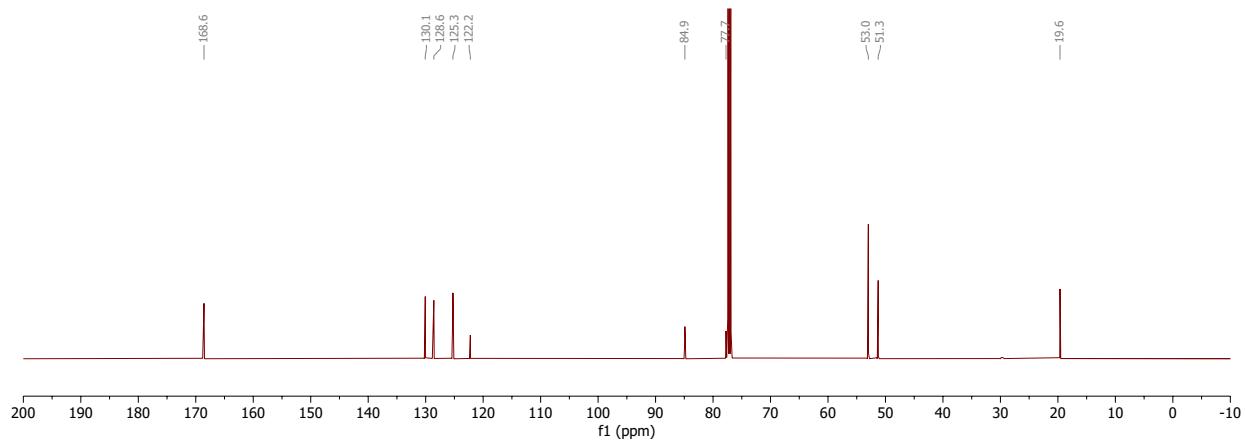
500 MHz ^1H NMR spectrum (CDCl_3)

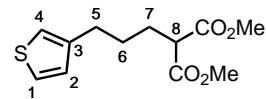
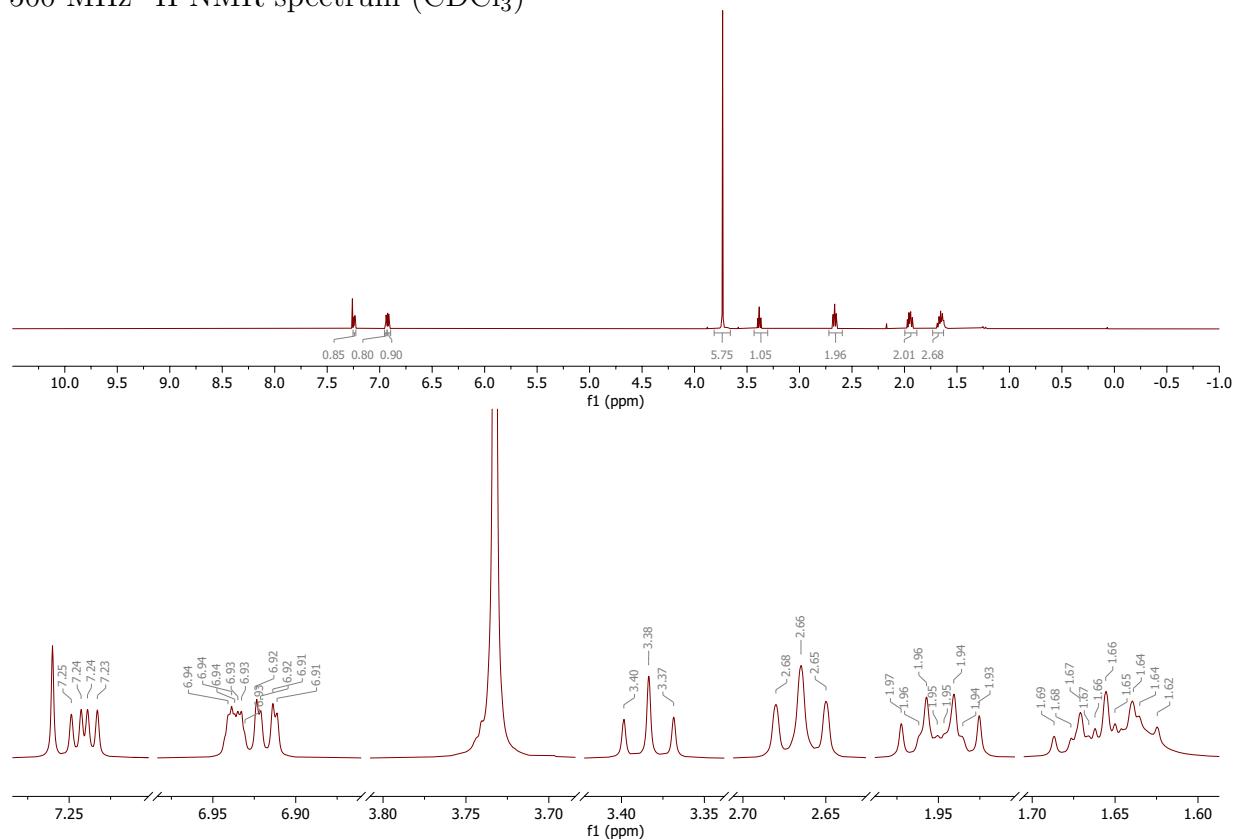
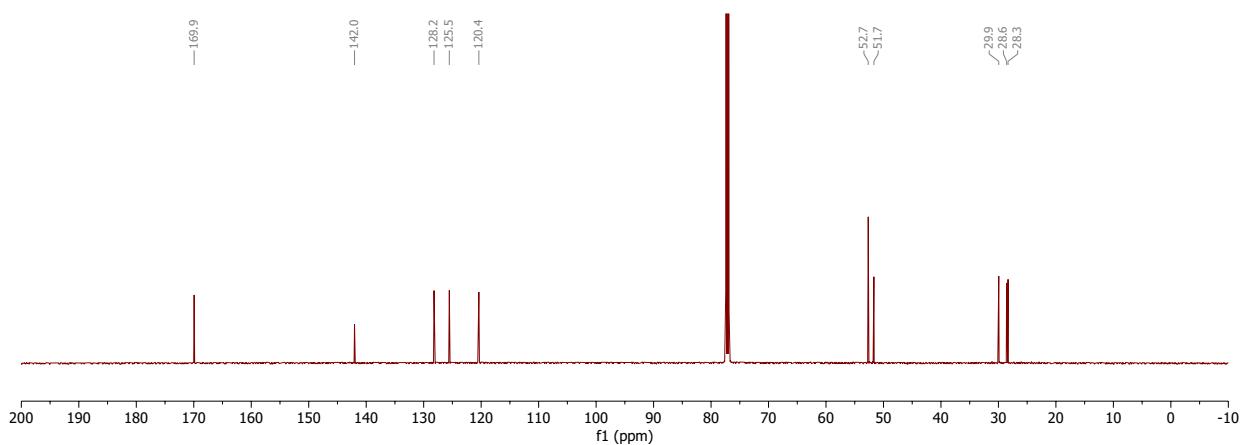


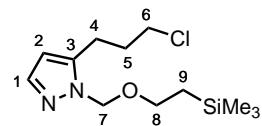
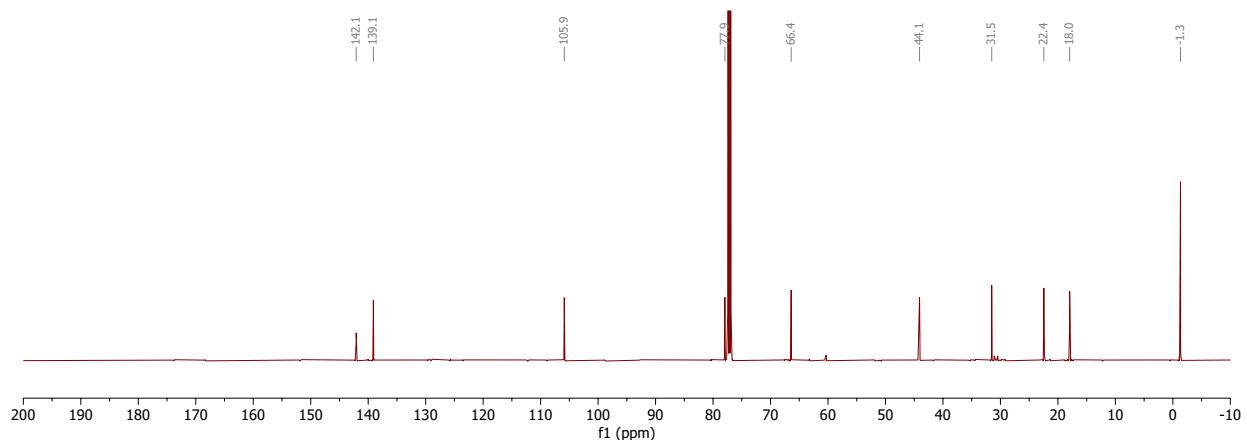
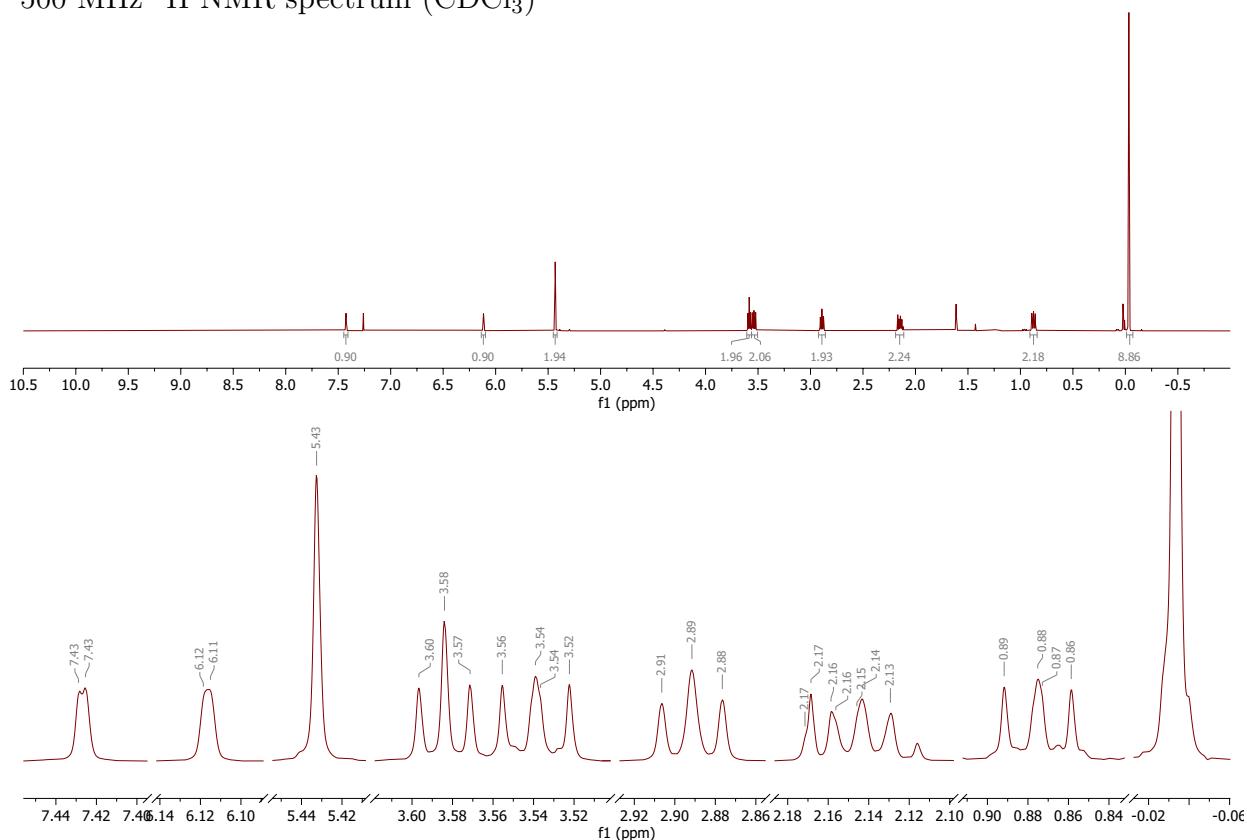
126 MHz ^{13}C NMR spectrum (CDCl_3)



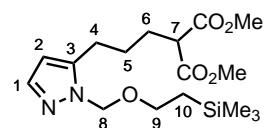
Dimethyl 2-(3-(5-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)propyl) malonate, 63500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 2-(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate, 82500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

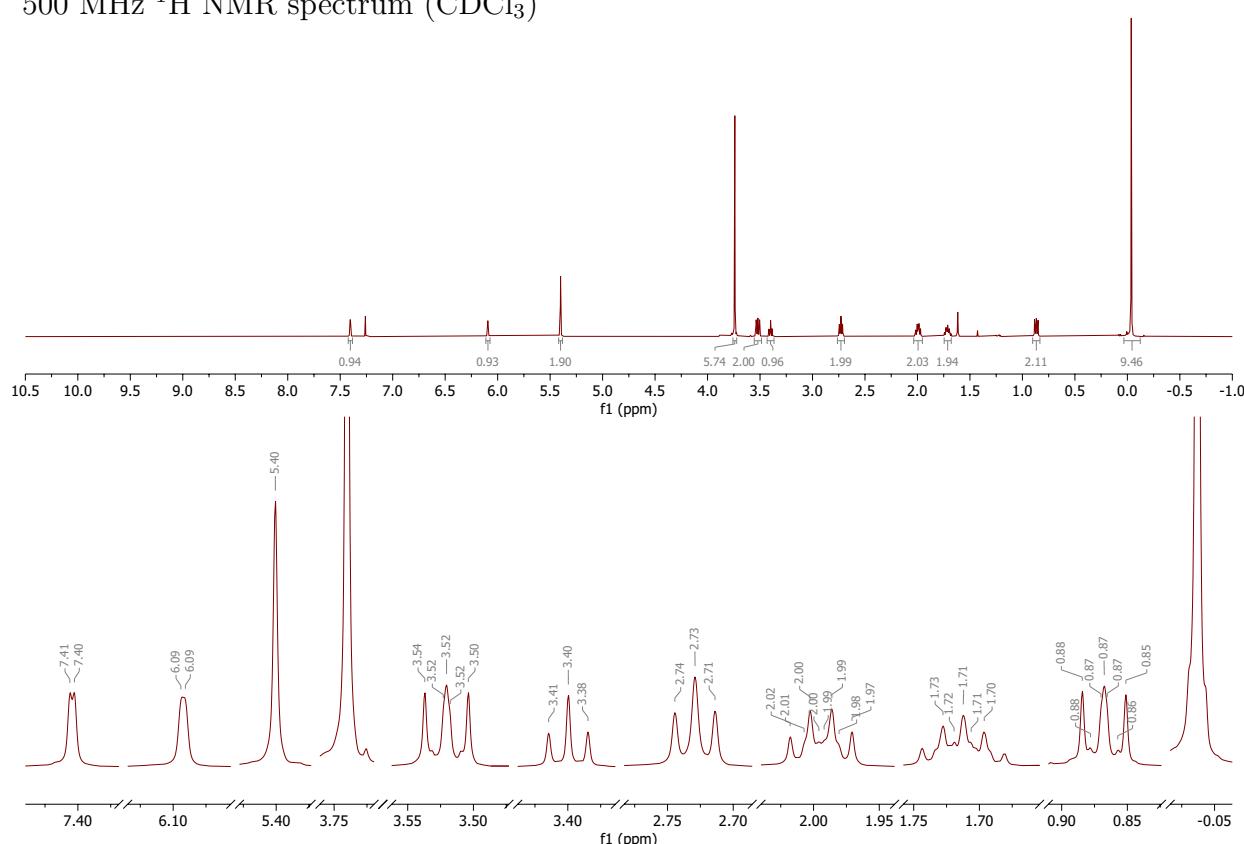
Dimethyl 2-(3-(thiophen-3-yl)propyl)malonate, 35500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

5-(3-Chloropropyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole, 84500 MHz ^1H NMR spectrum (CDCl_3)

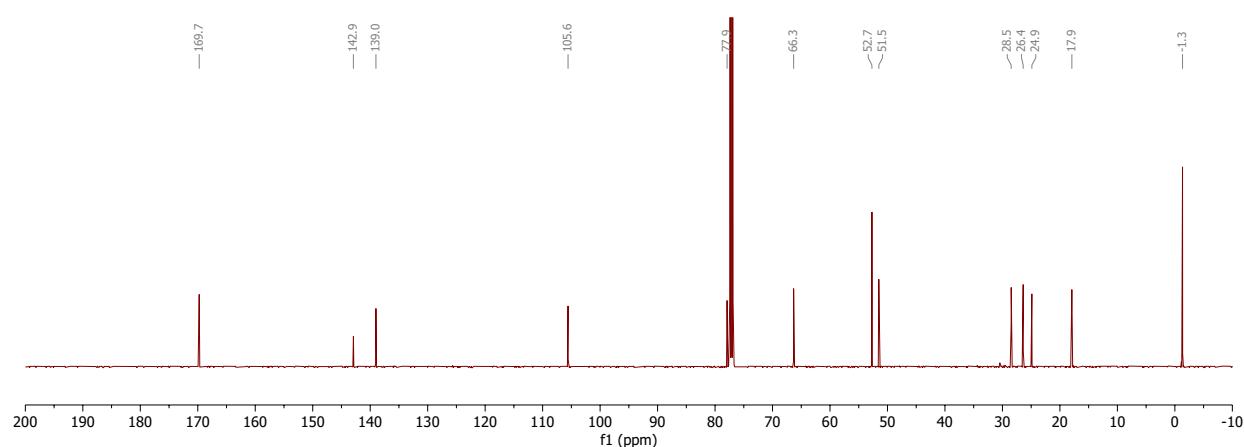
Dimethyl 2-(3-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)propyl)malonate, 43

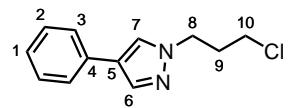
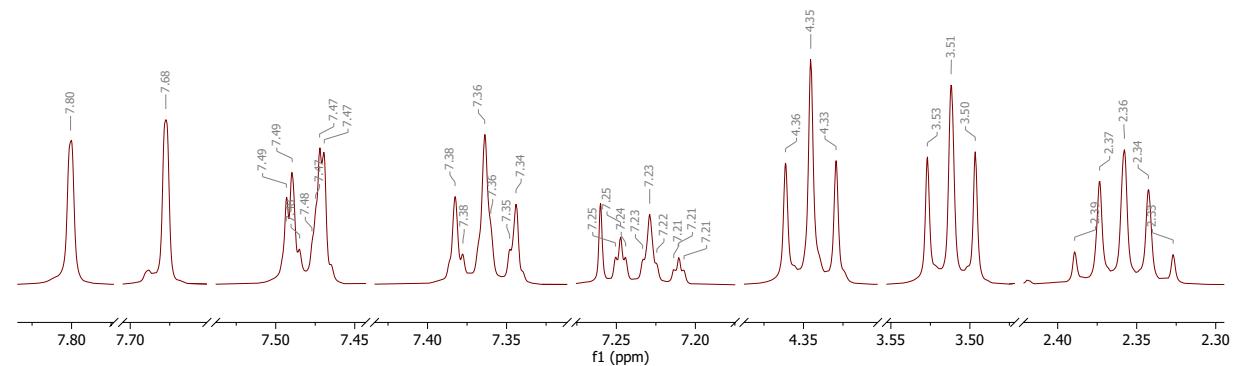
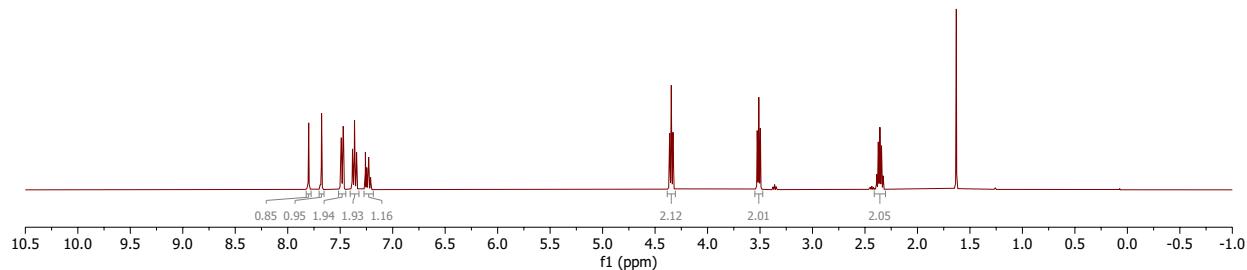
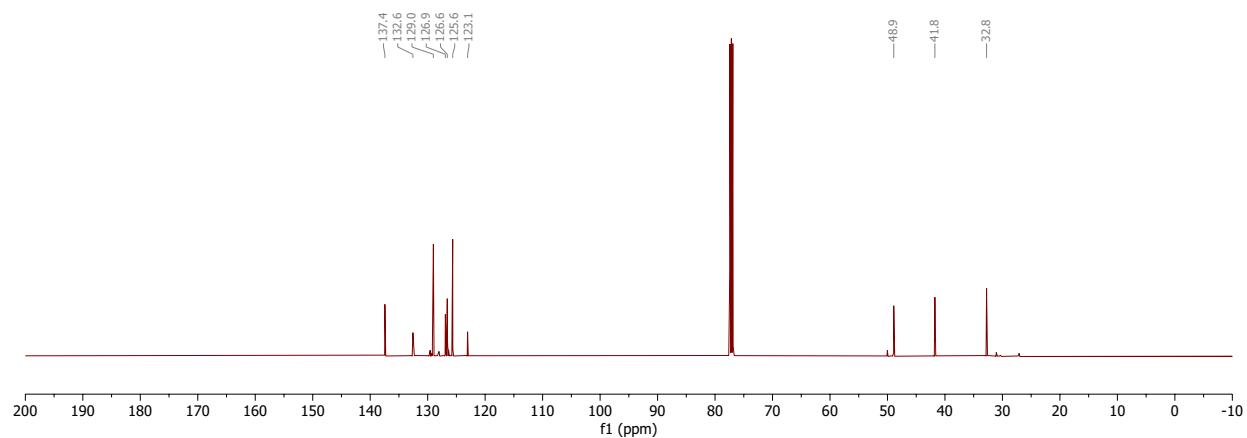


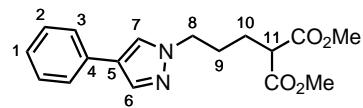
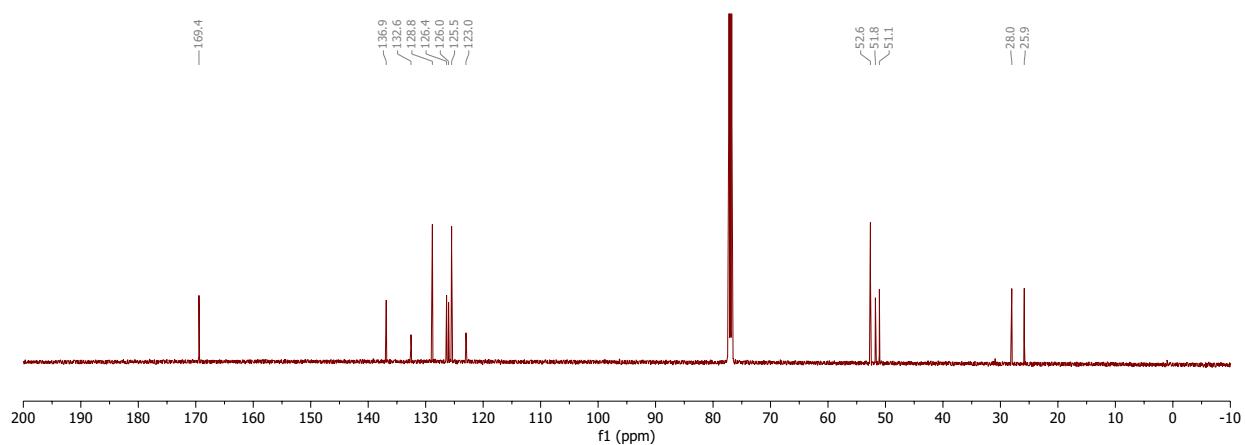
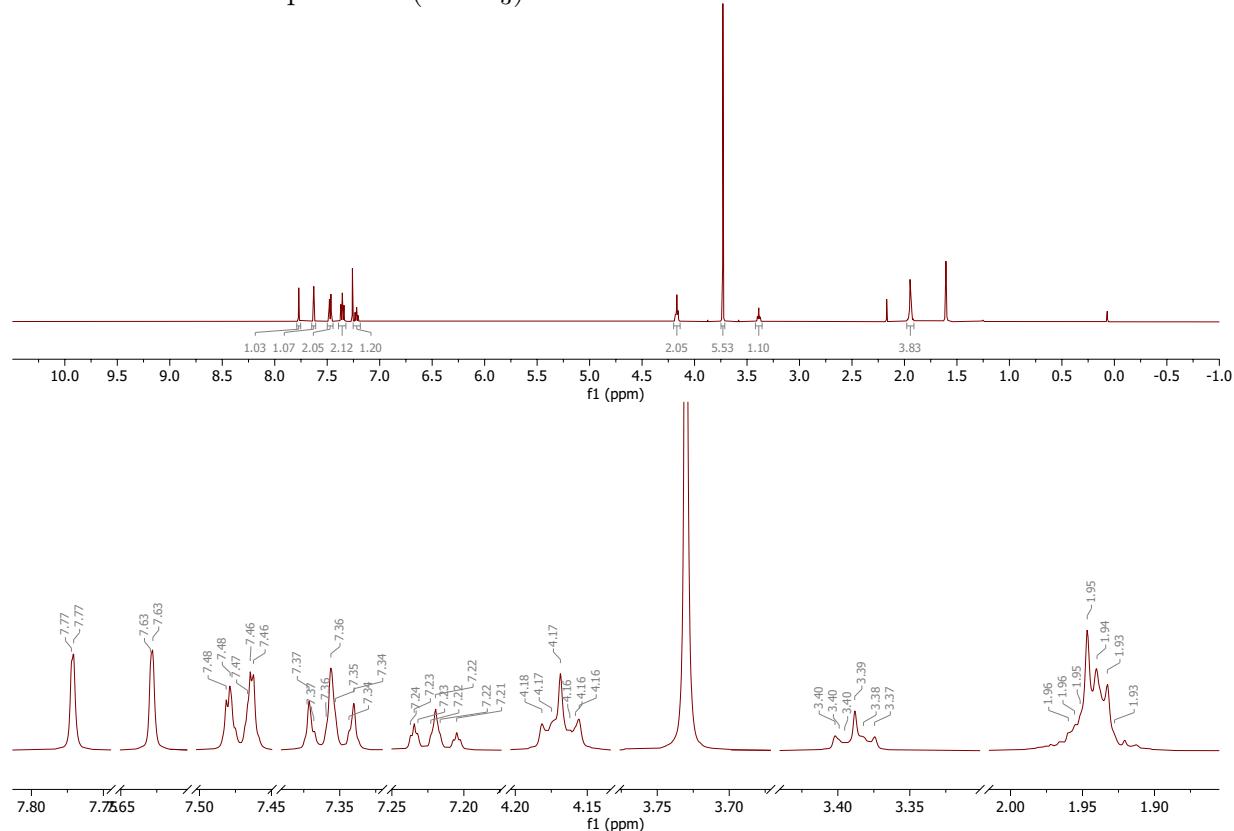
500 MHz ^1H NMR spectrum (CDCl_3)



126 MHz ^{13}C NMR spectrum (CDCl_3)

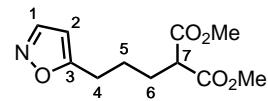


1-(3-chloropropyl)-4-phenyl-1*H*-pyrazole, 86400 MHz ^1H NMR spectrum (CDCl_3)101 MHz ^{13}C NMR spectrum (CDCl_3)

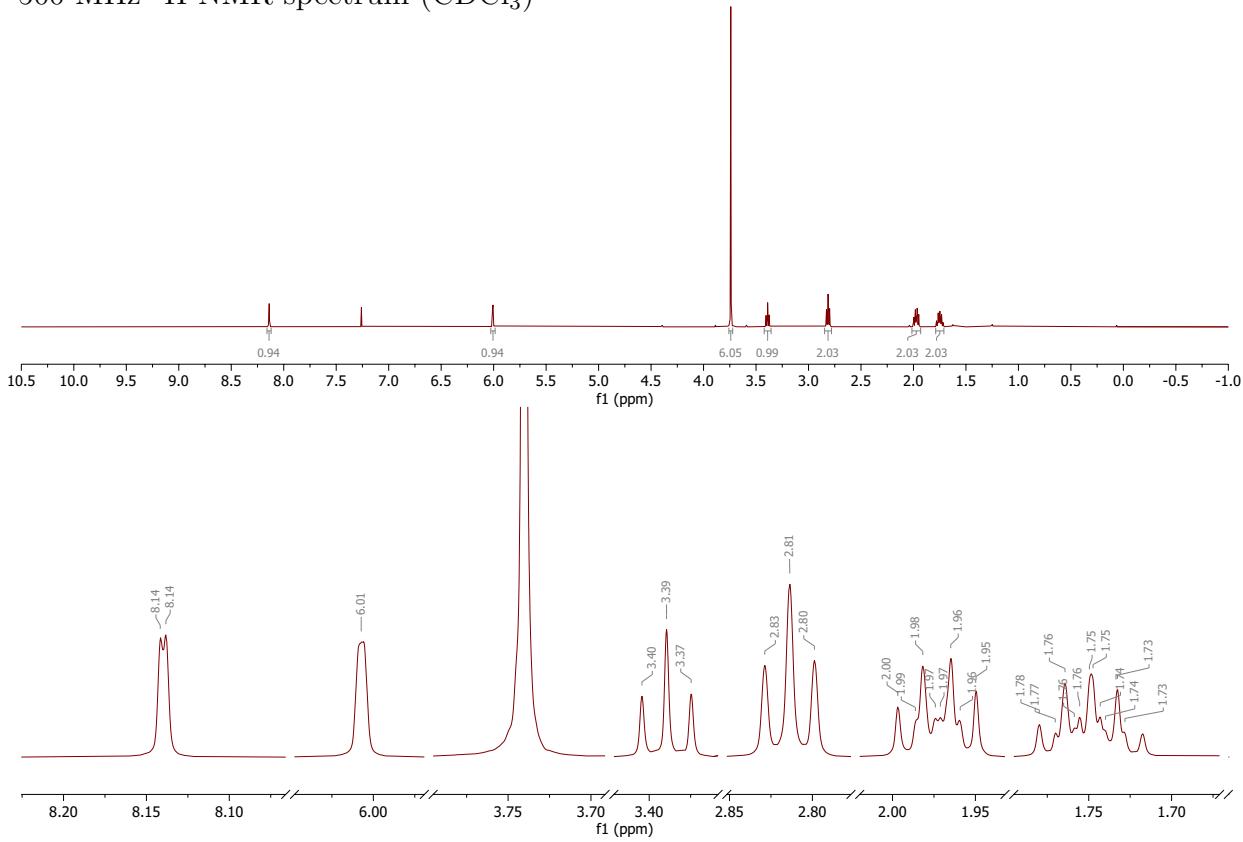
Dimethyl 2-(3-(4-phenyl-1*H*-pyrazol-1-yl)propyl)malonate, 45500 MHz ^1H NMR spectrum (CDCl_3)

Experimental Details

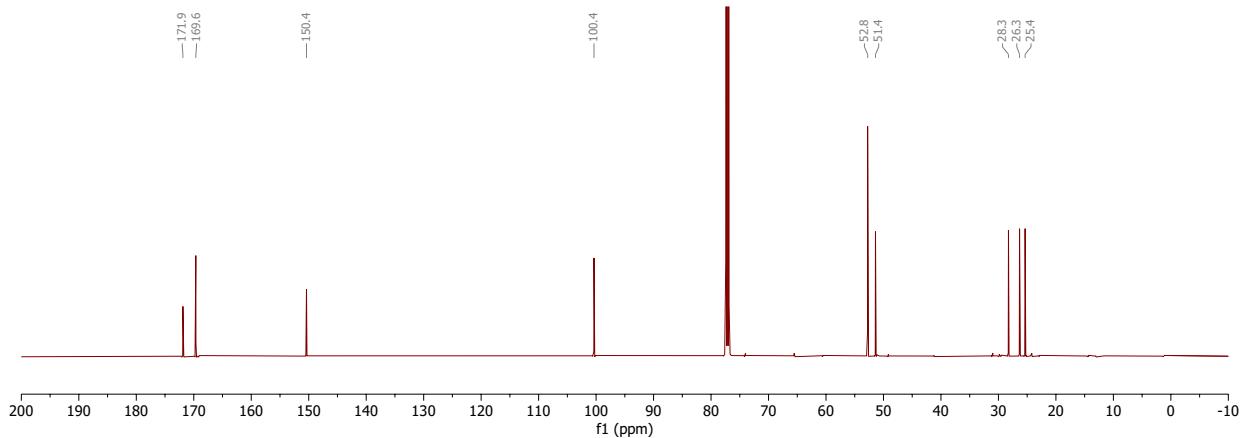
Dimethyl 2-(3-(isoxazol-5-yl)propyl)malonate, 37

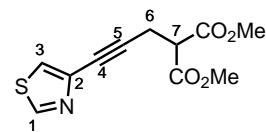
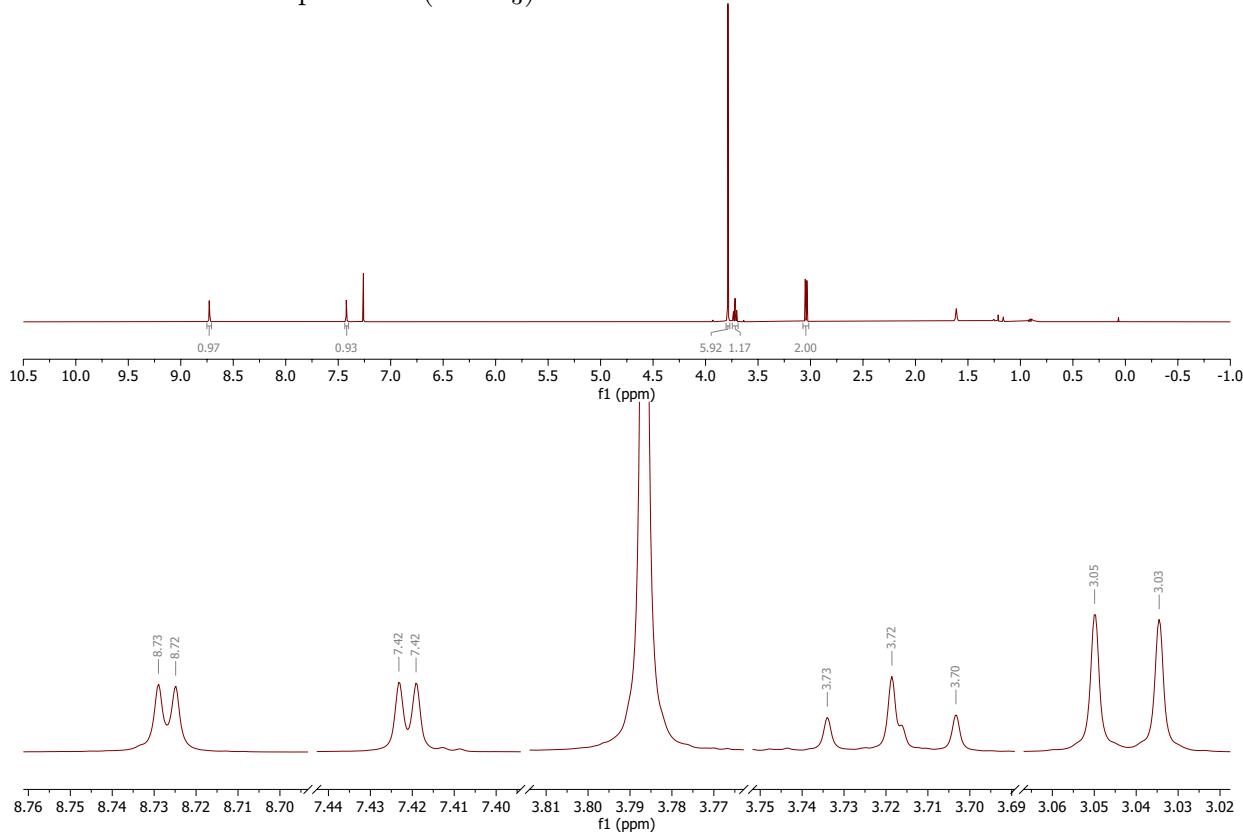
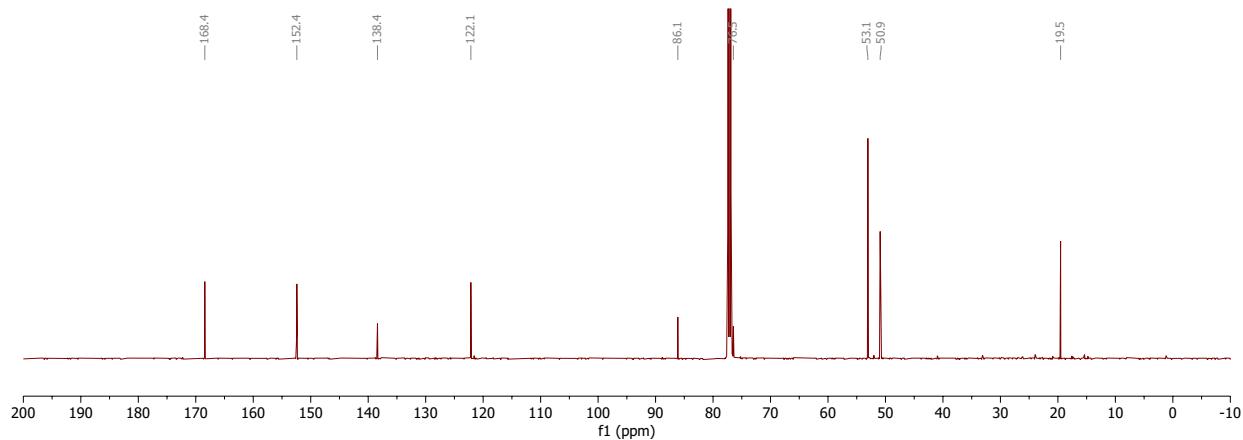


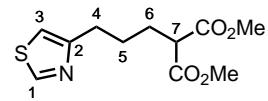
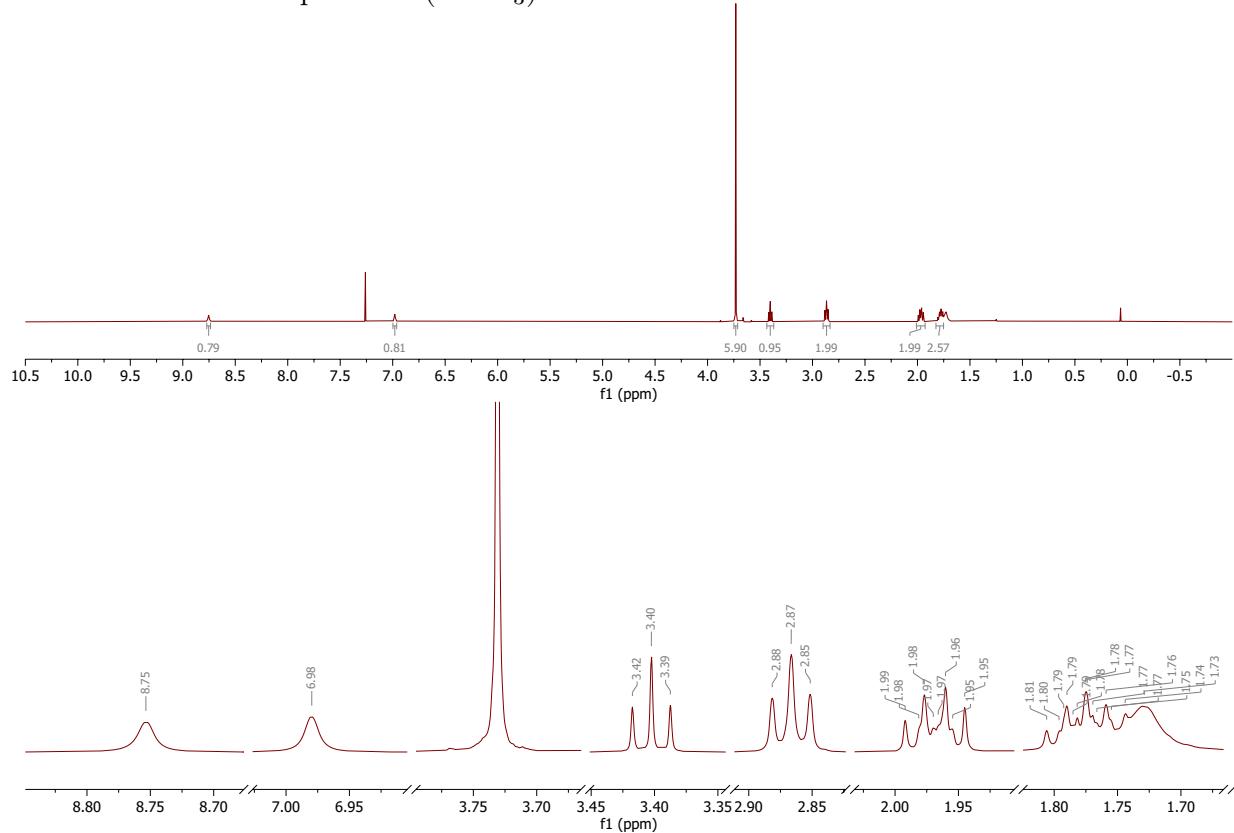
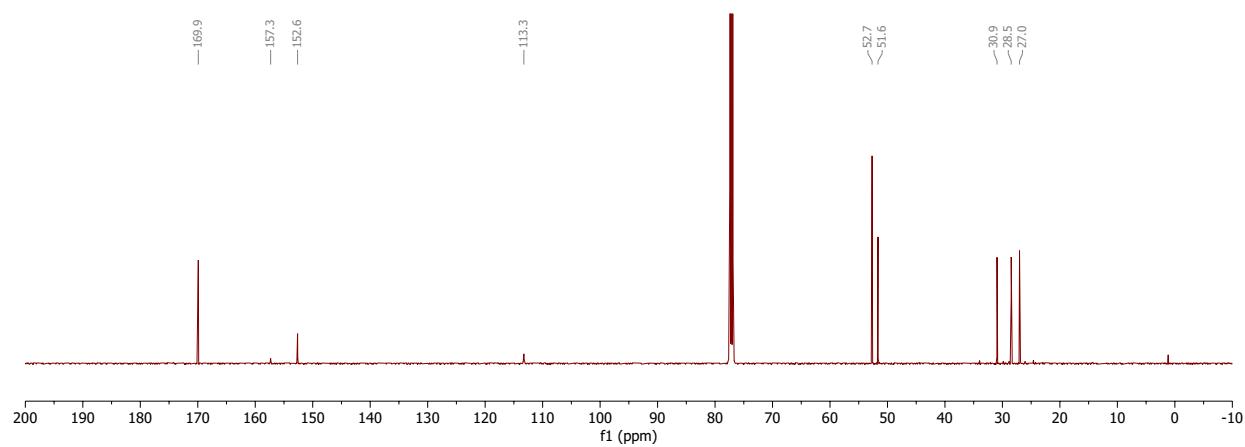
500 MHz ^1H NMR spectrum (CDCl_3)

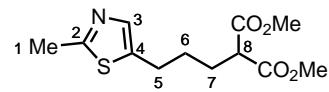
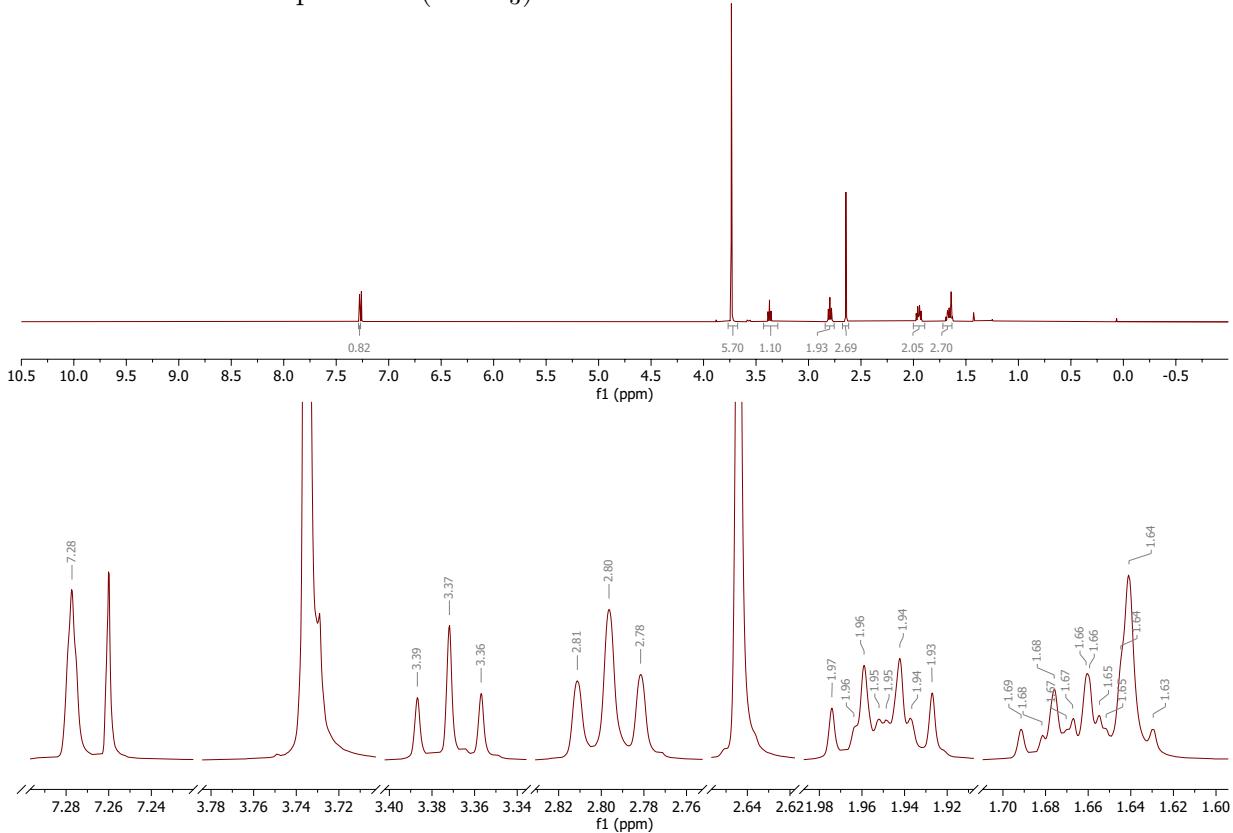
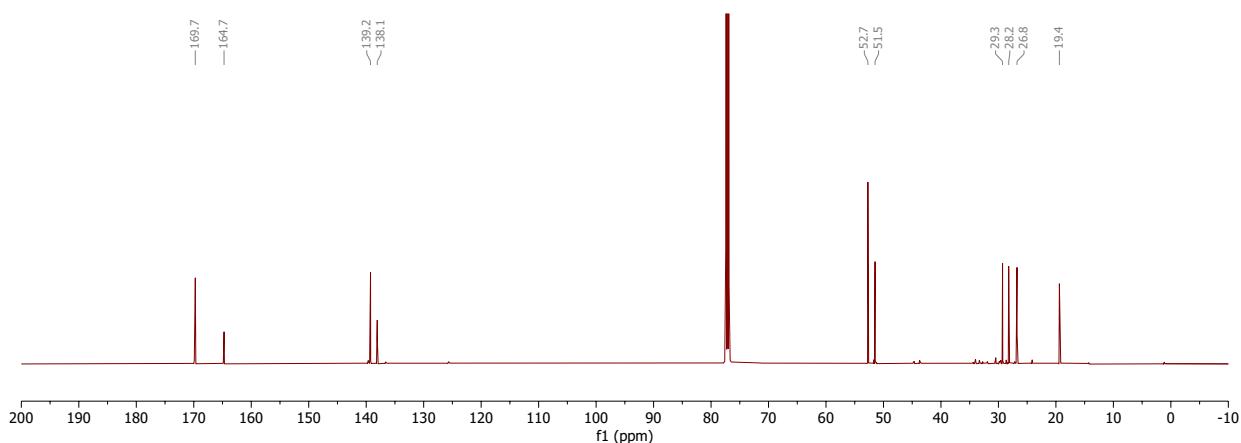


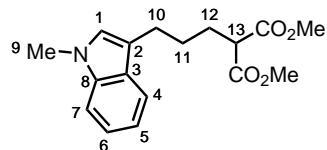
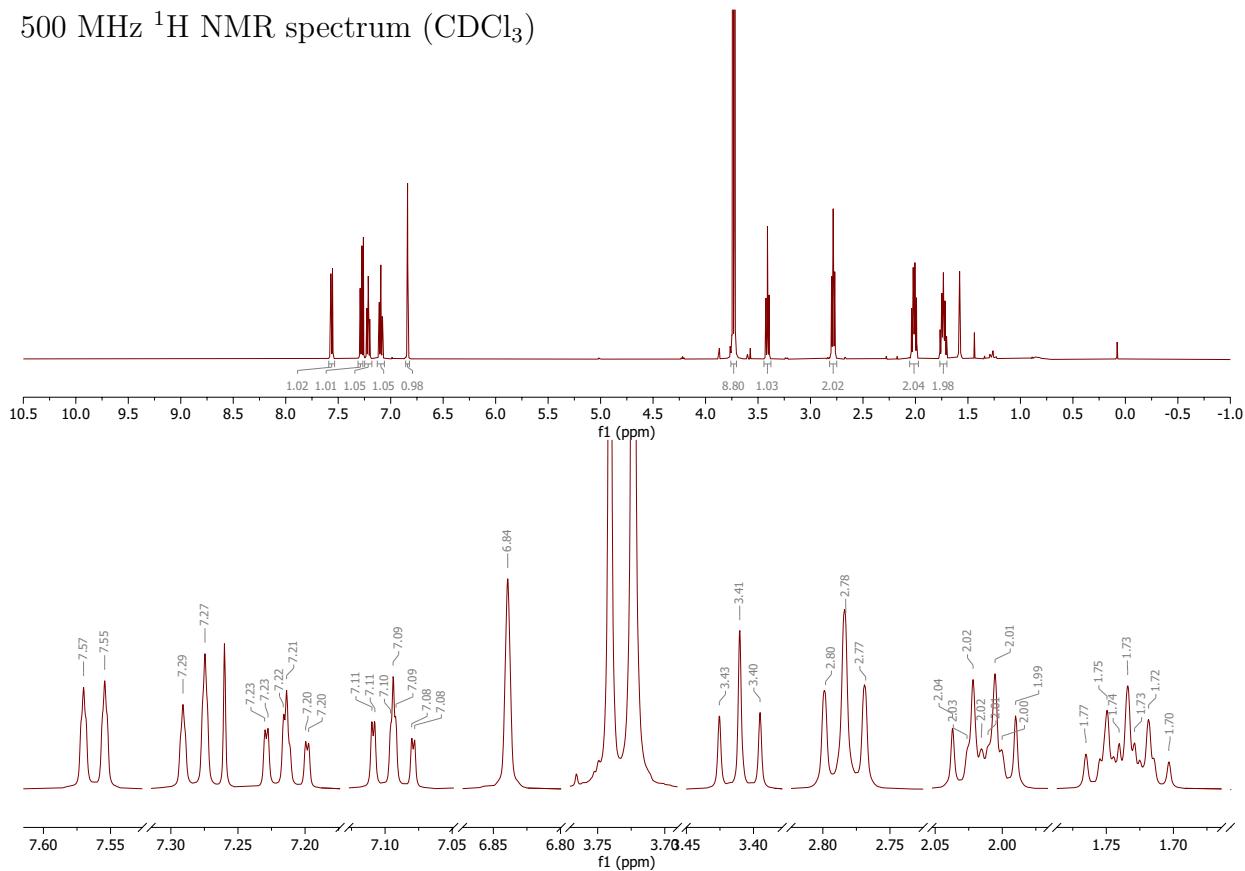
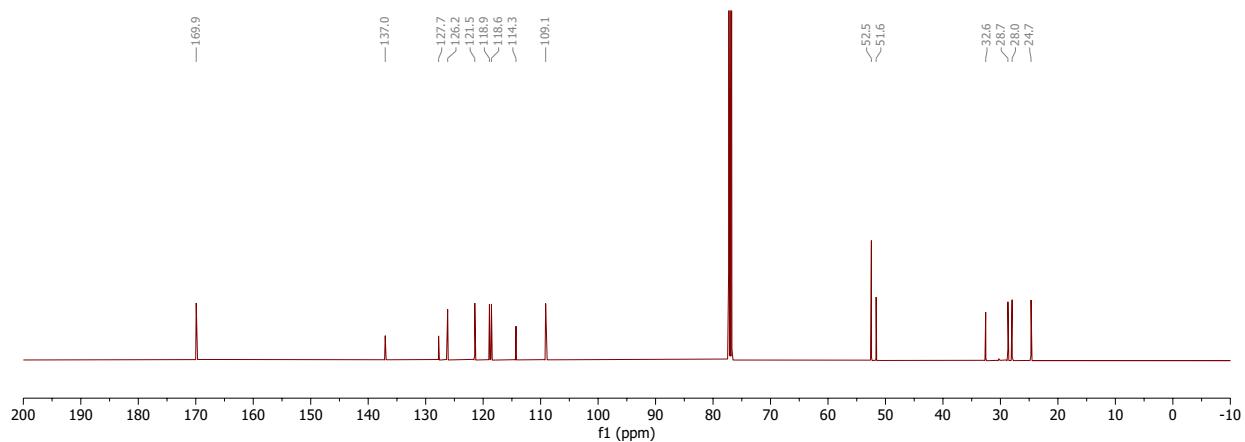
126 MHz ^{13}C NMR spectrum (CDCl_3)

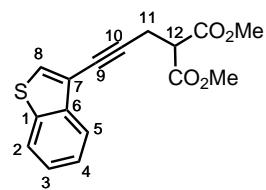
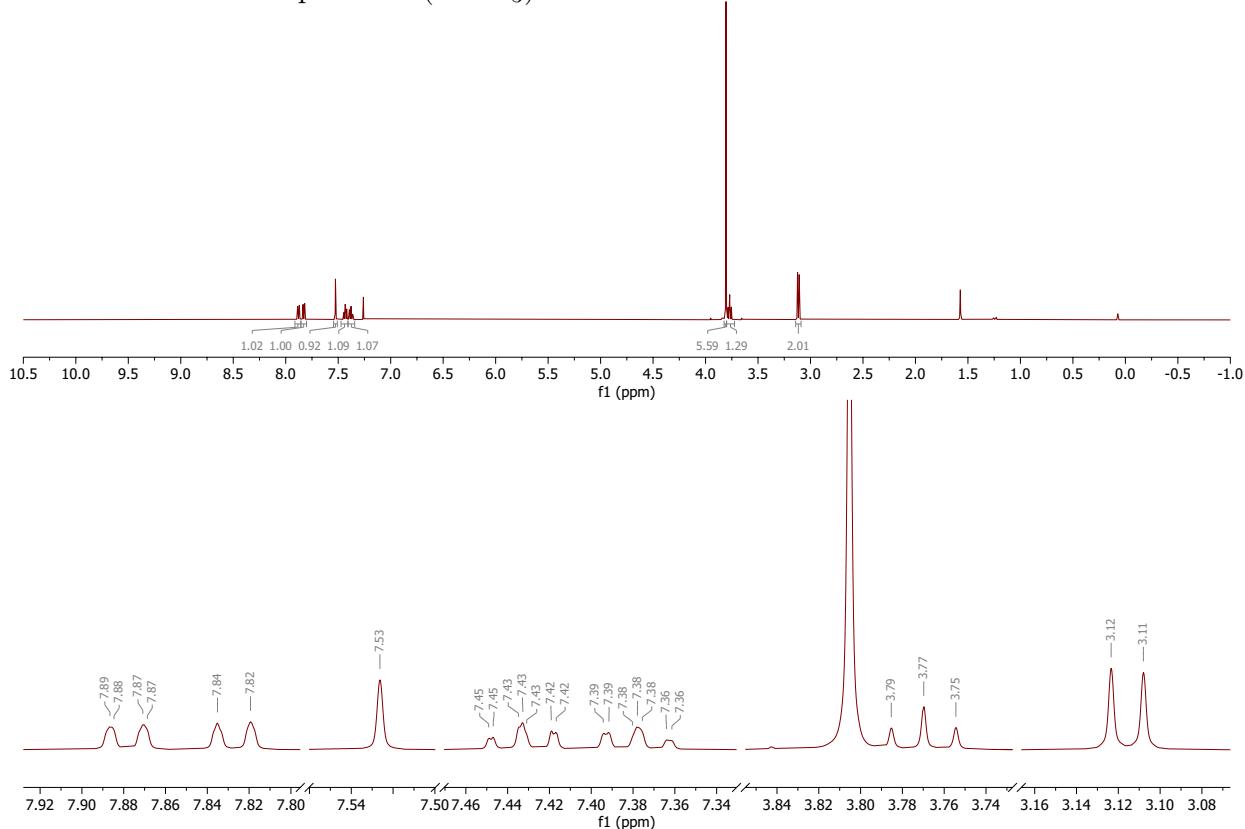
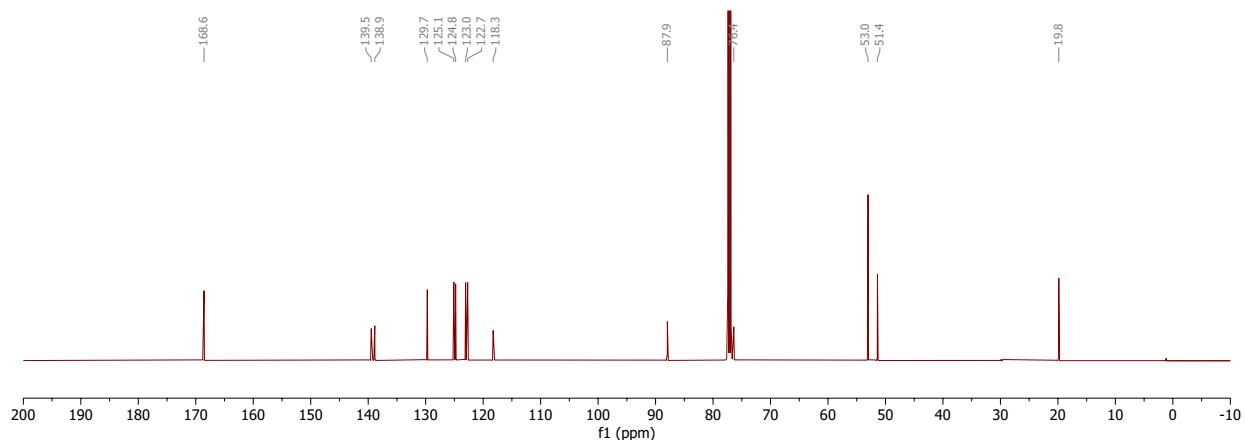


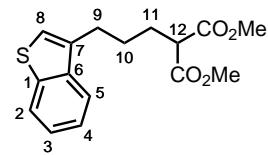
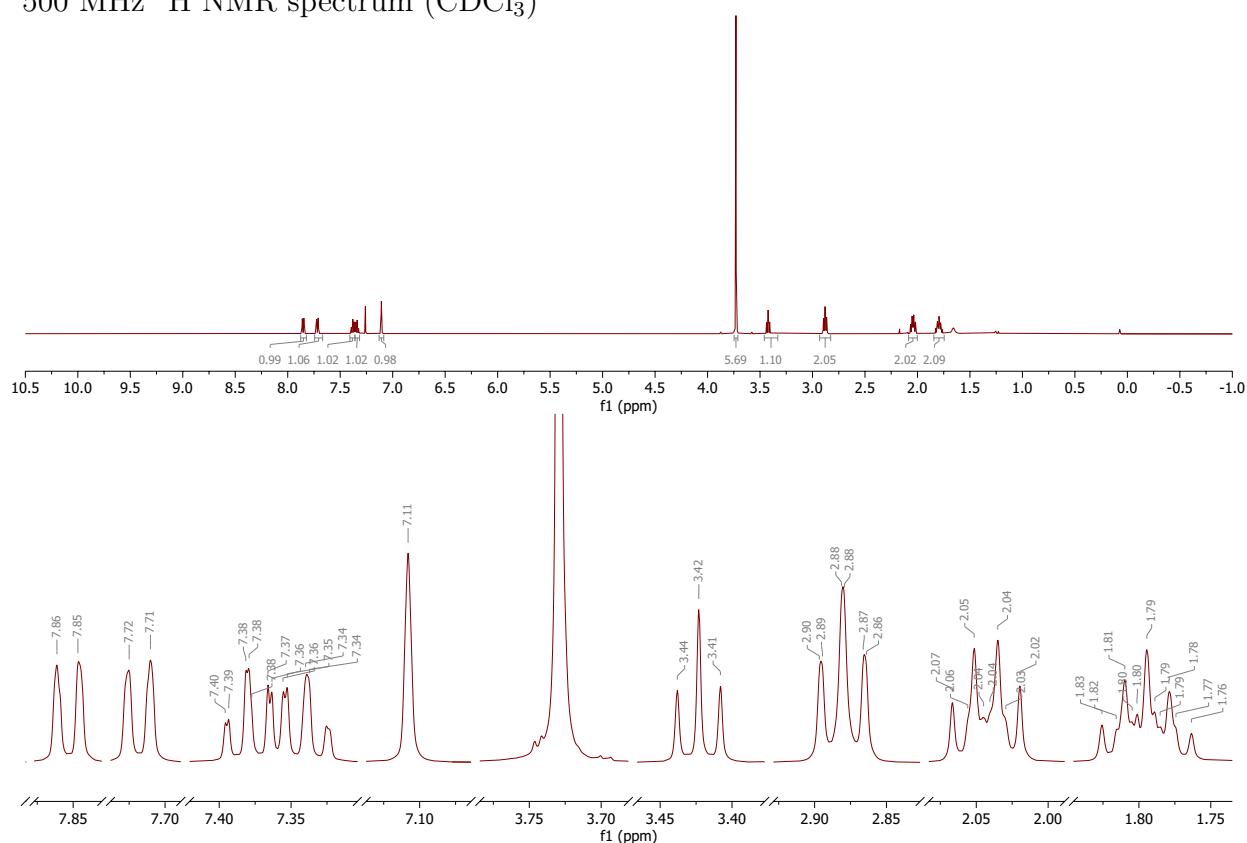
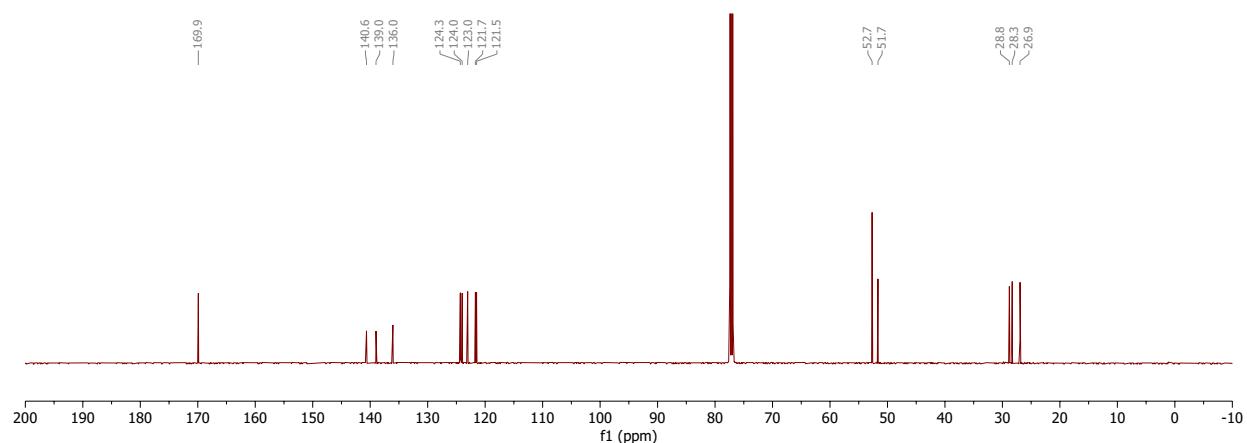
Dimethyl 2-(3-(thiazol-4-yl)prop-2-yn-1-yl)malonate, 89500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

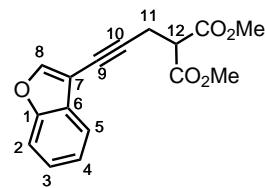
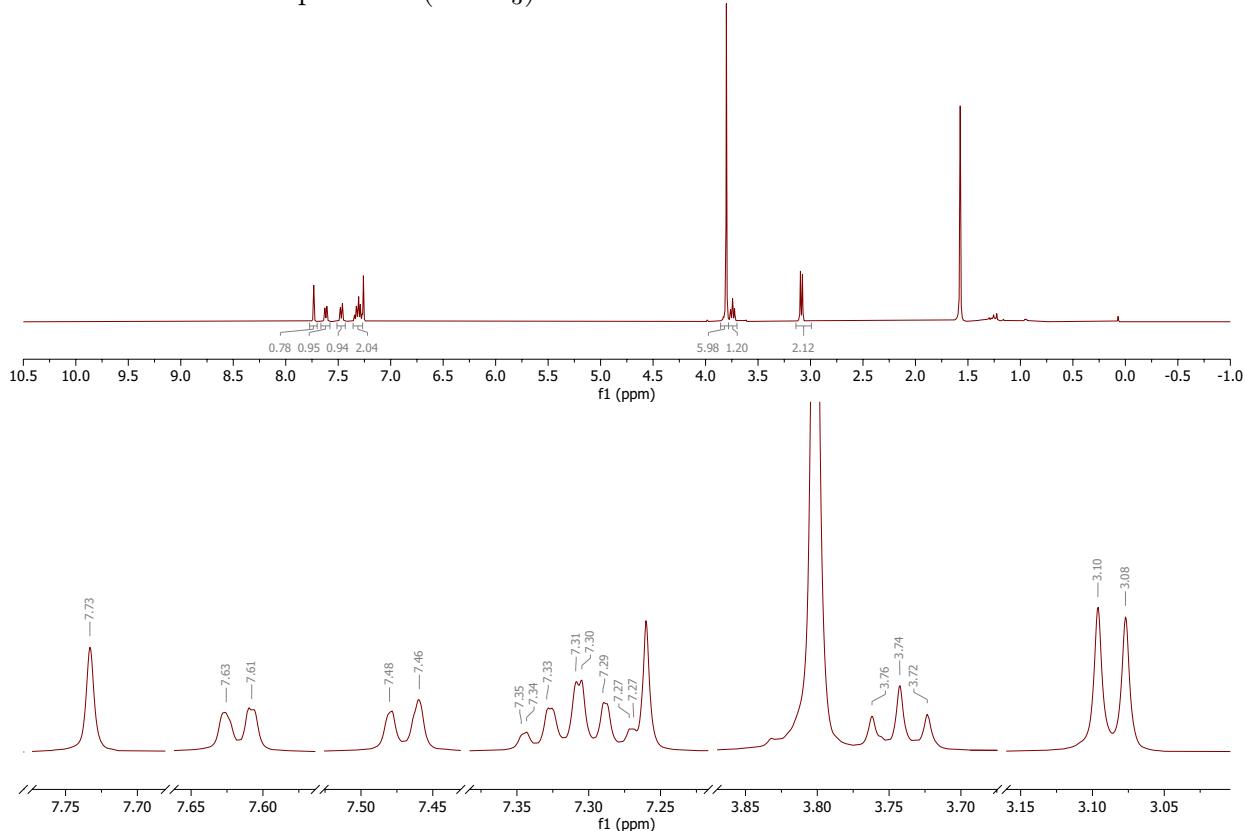
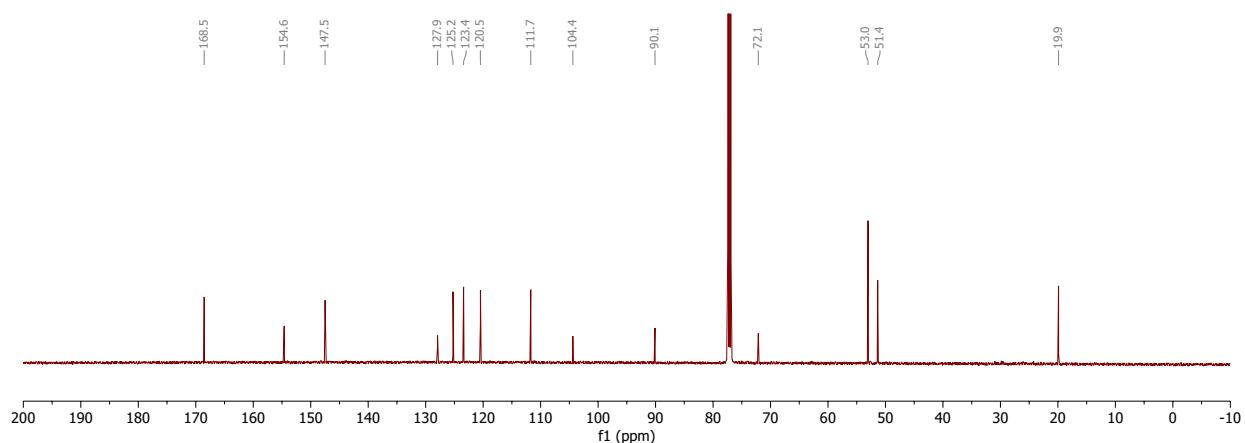
Dimethyl 2-(3-(thiazol-4-yl)propyl)malonate, 39500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

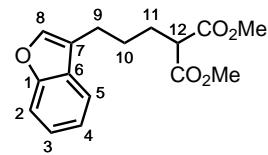
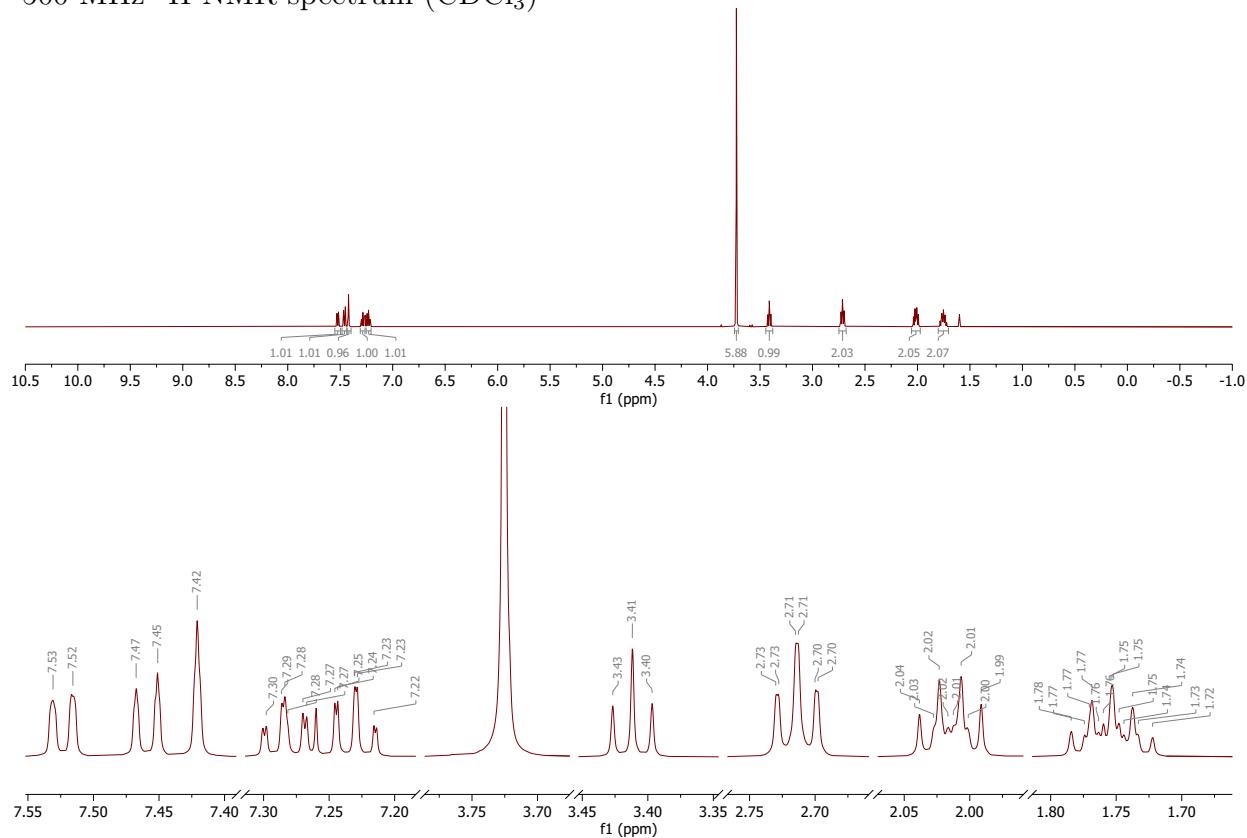
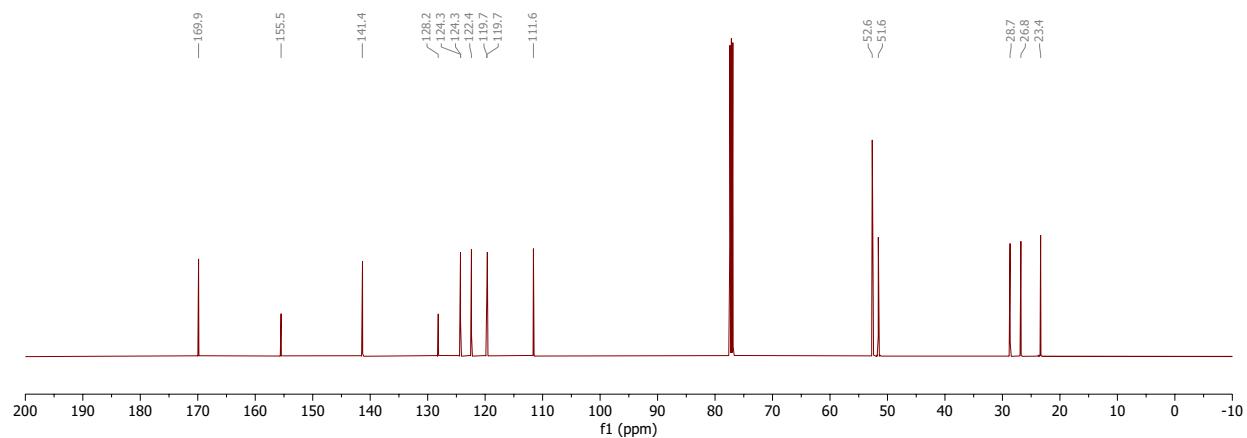
Dimethyl 2-(3-(2-methylthiazol-5-yl)propyl)malonate, 41500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

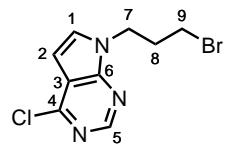
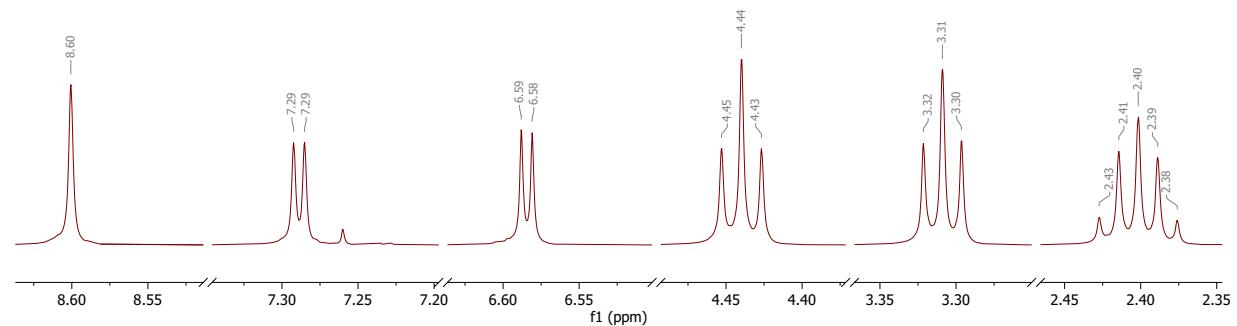
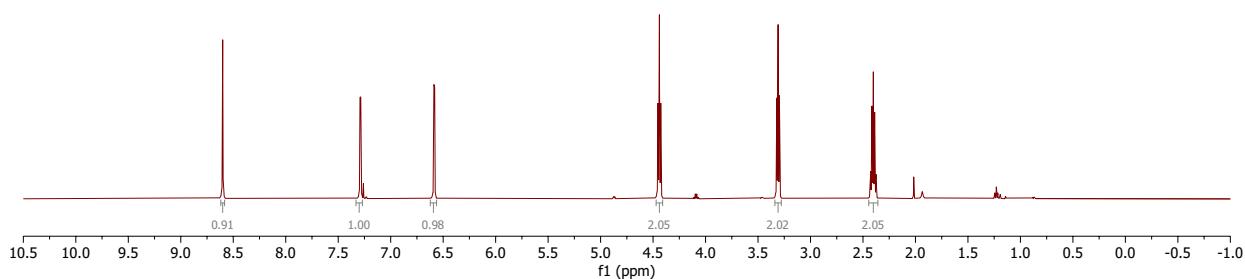
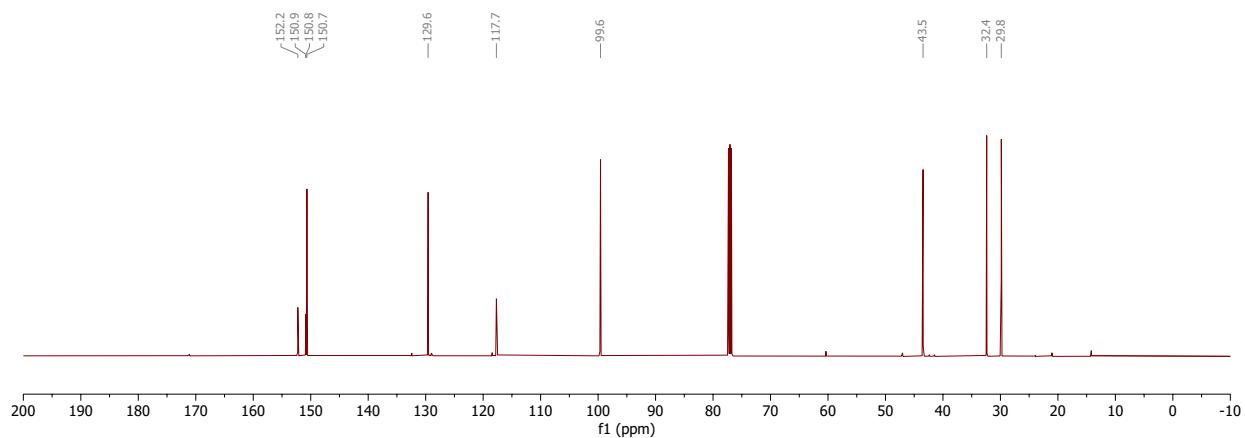
Dimethyl 2-(3-(1-methyl-1*H*-indol-3-yl)propyl)malonate, 47500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)prop-2-yn-1-yl)malonate, 91500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

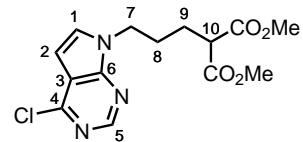
Dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)propyl)malonate, 49500 MHz ¹H NMR spectrum (CDCl₃)126 MHz ¹³C NMR spectrum (CDCl₃)

Dimethyl 2-(3-(benzofuran-3-yl)prop-2-yn-1-yl)malonate, 92400 MHz ¹H NMR spectrum (CDCl₃)101 MHz ¹³C NMR spectrum (CDCl₃)

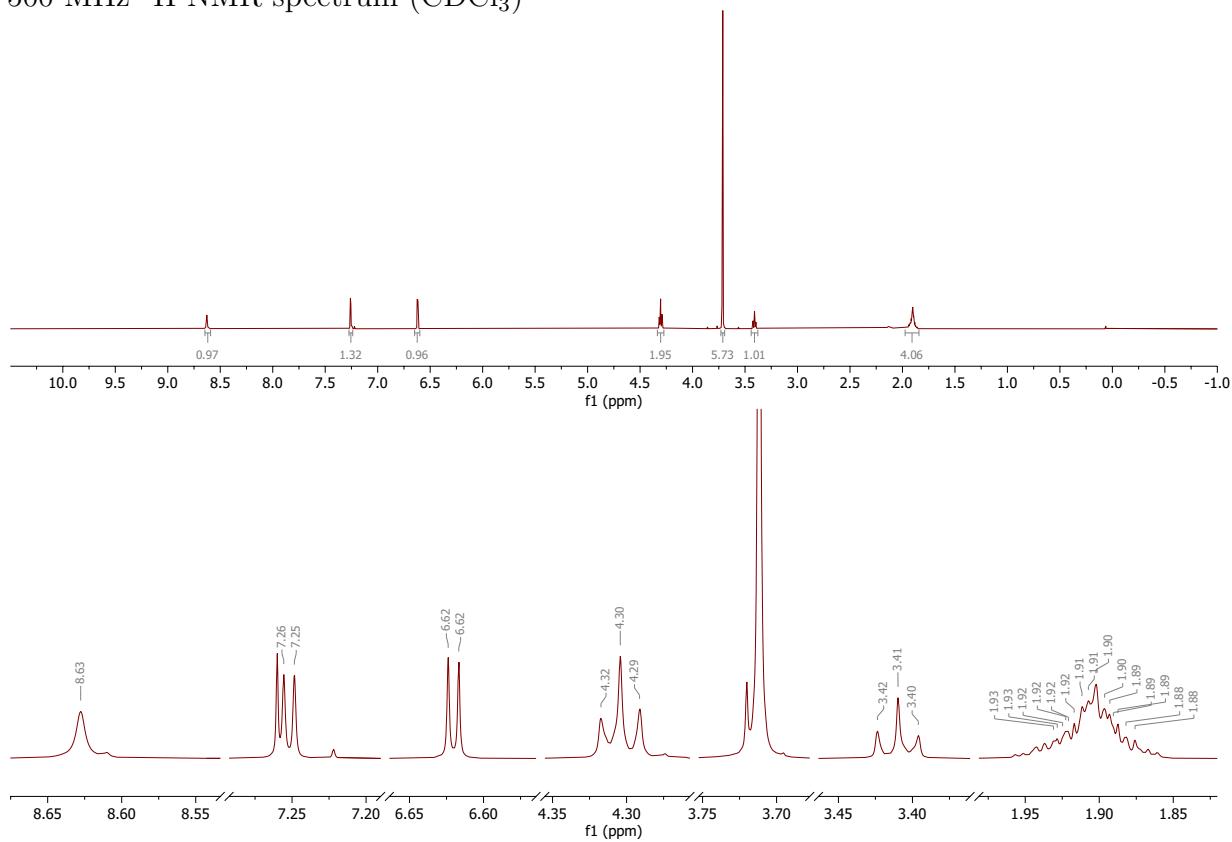
Dimethyl 2-(3-(benzofuran-3-yl)propyl)malonate, 51500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

7-(3-Bromopropyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine, 93500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

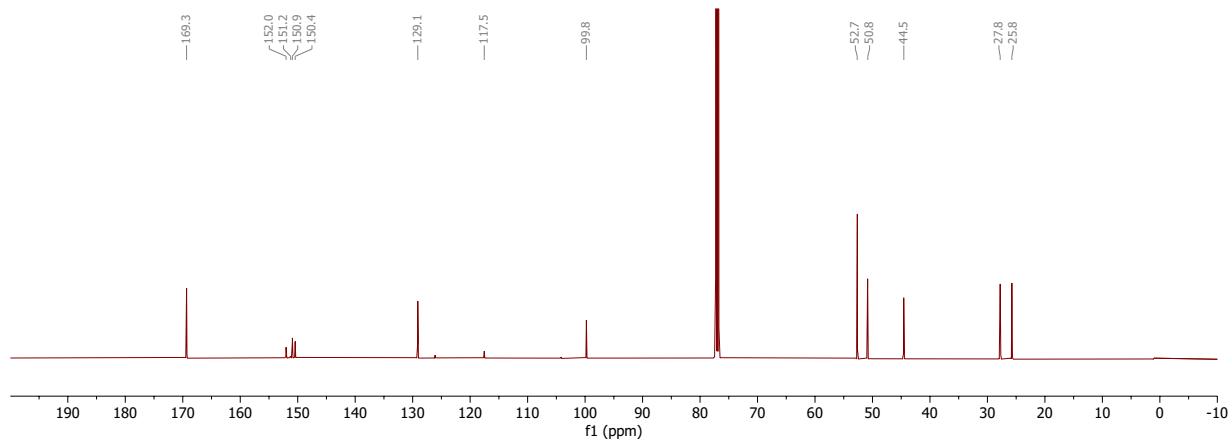
Dimethyl 2-(3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propyl)malonate, 53

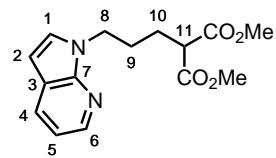
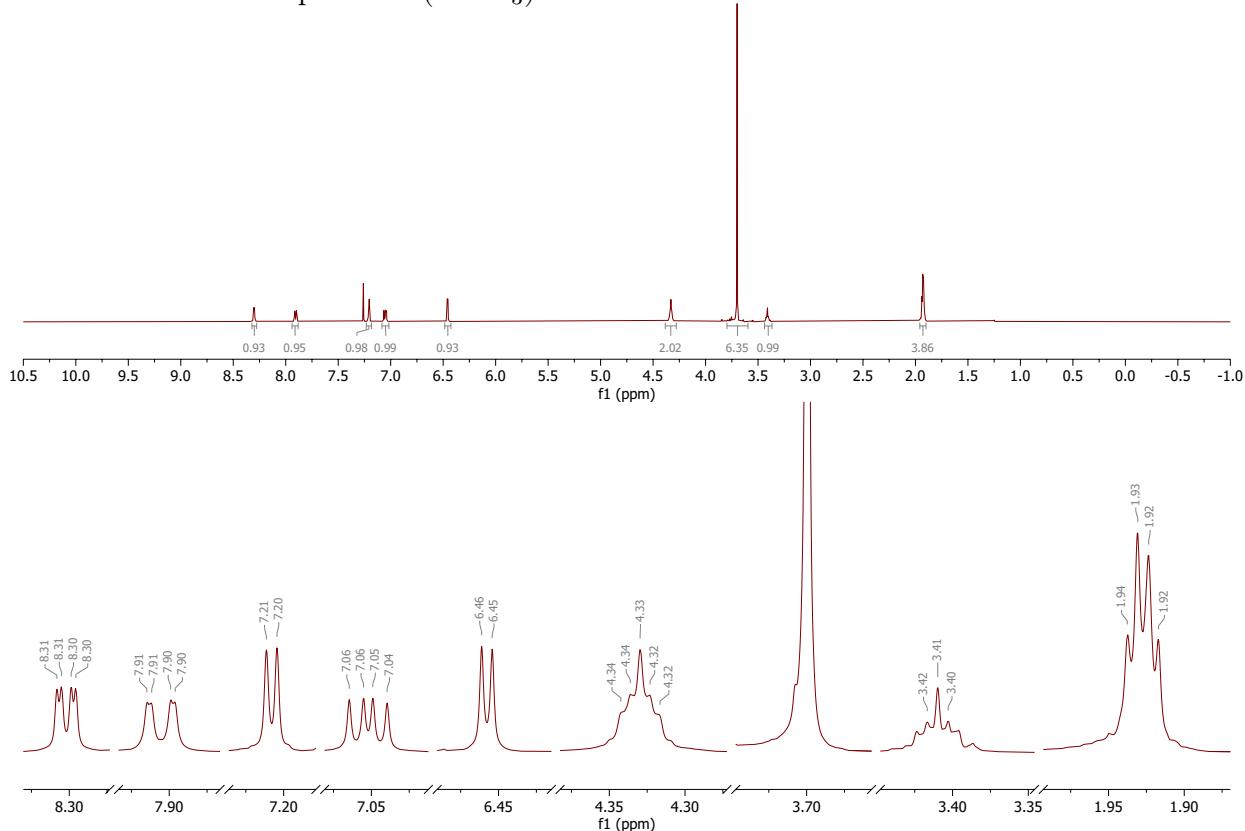
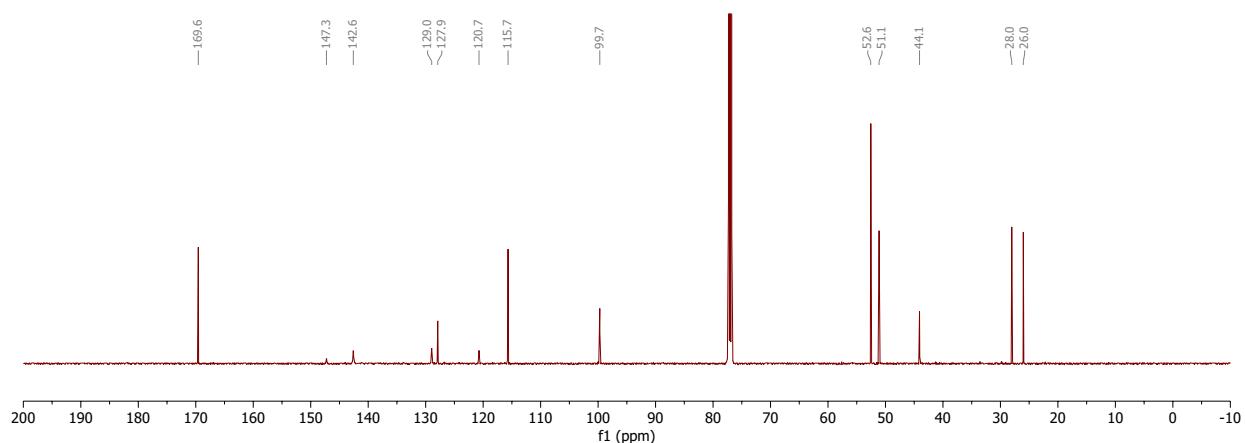


500 MHz ^1H NMR spectrum (CDCl_3)

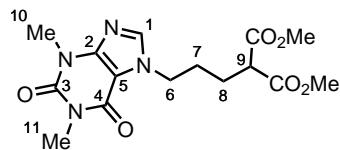


126 MHz ^{13}C NMR spectrum (CDCl_3)

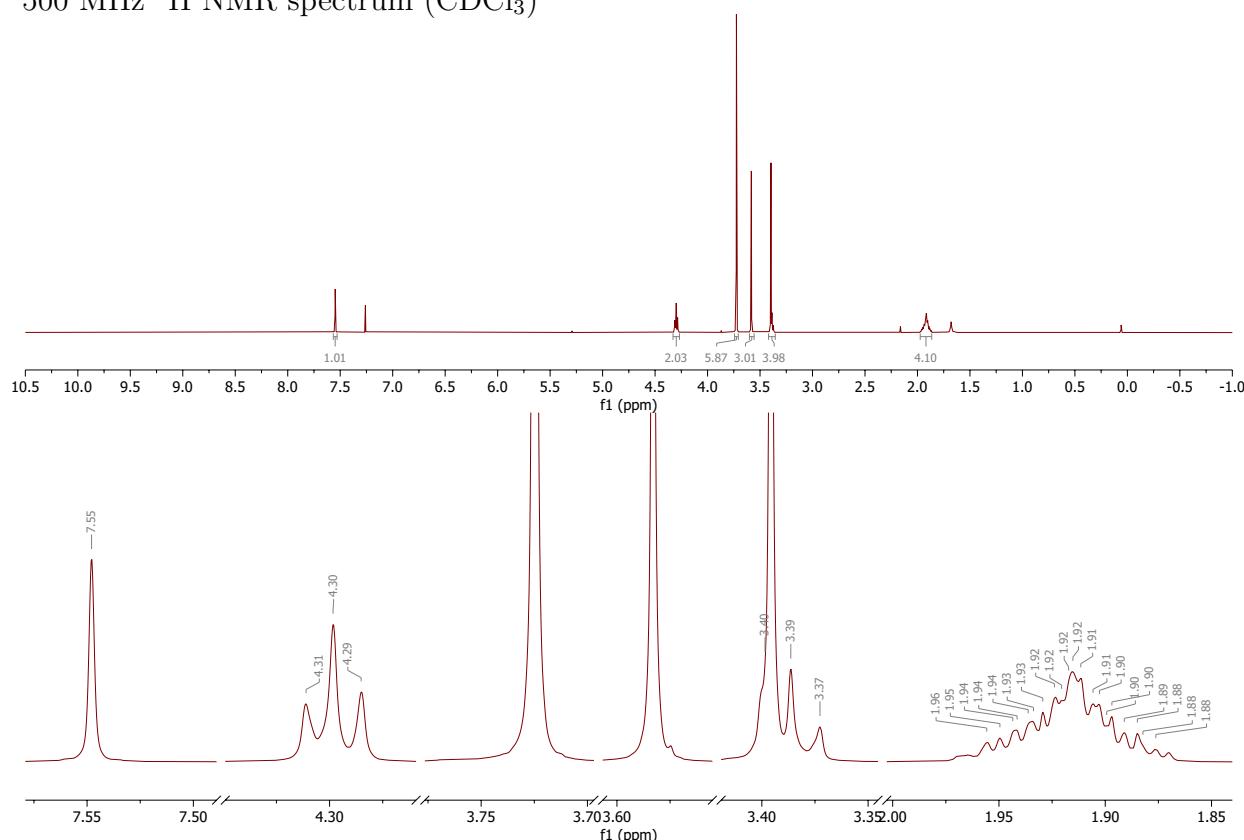


Dimethyl 2-(3-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propyl)malonate, 55500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

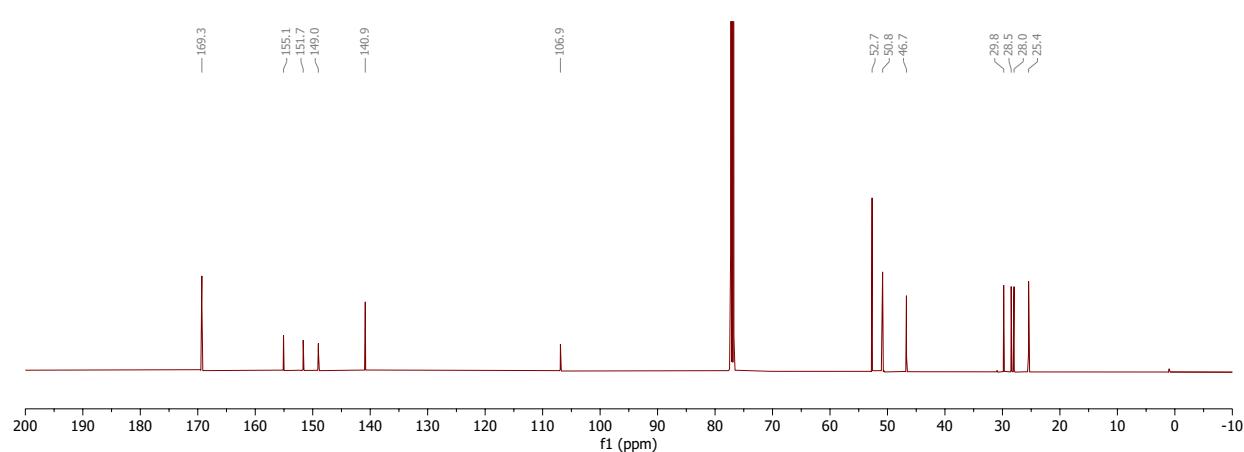
Dimethyl 2-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propyl)malonate, 57



500 MHz ¹H NMR spectrum (CDCl₃)

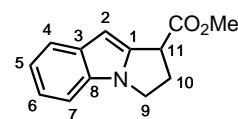


126 MHz ¹³C NMR spectrum (CDCl₃)

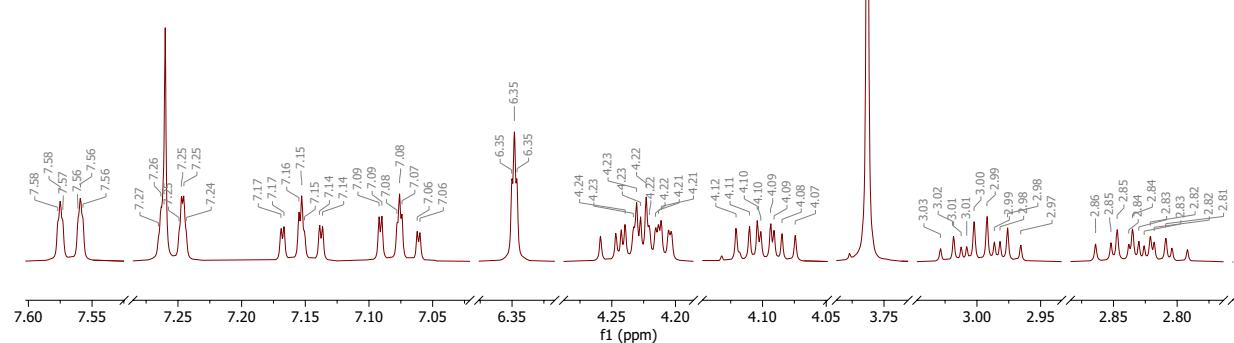
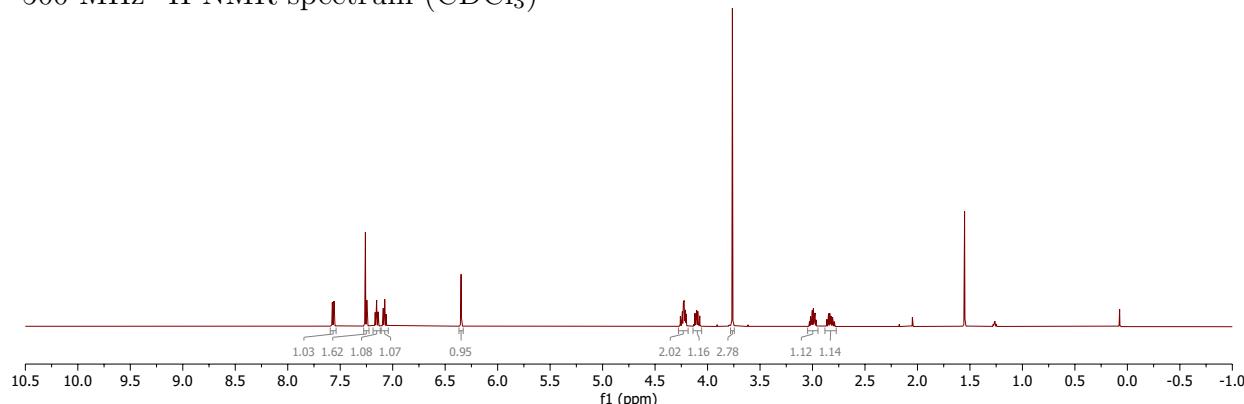


1.4.3 Product derivatisation

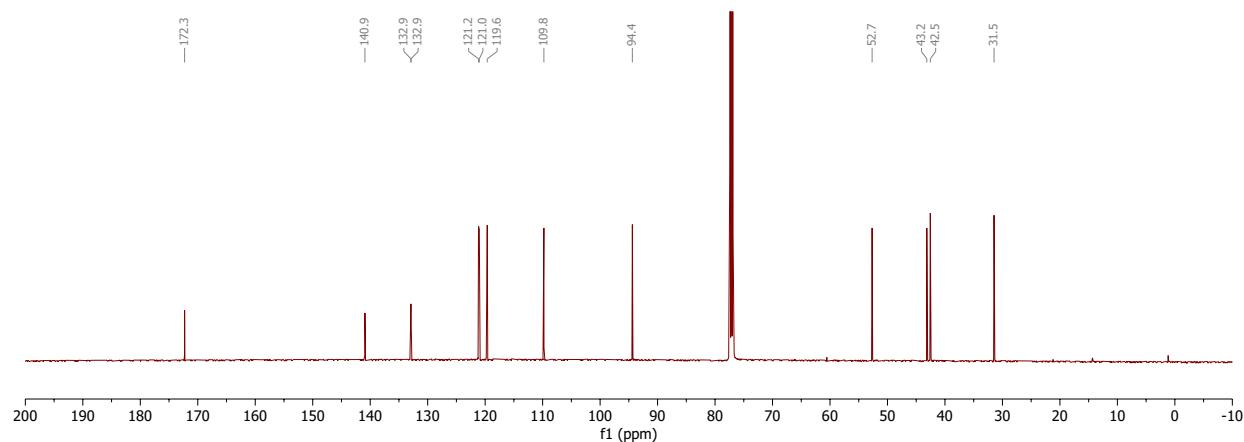
Methyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1-carboxylate, 59

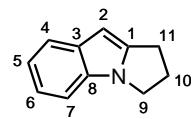
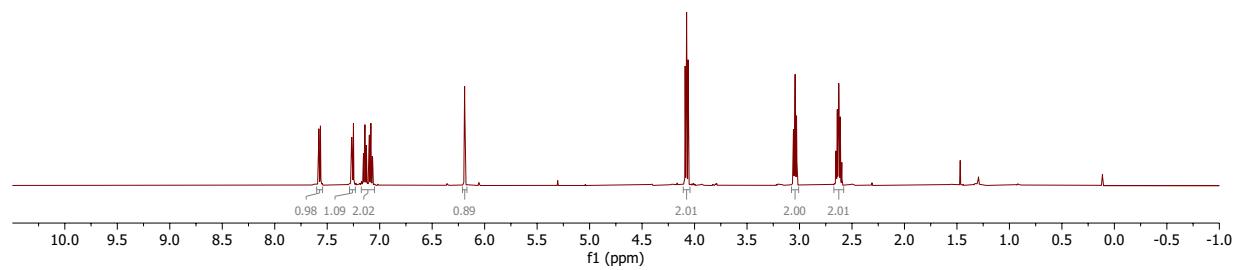
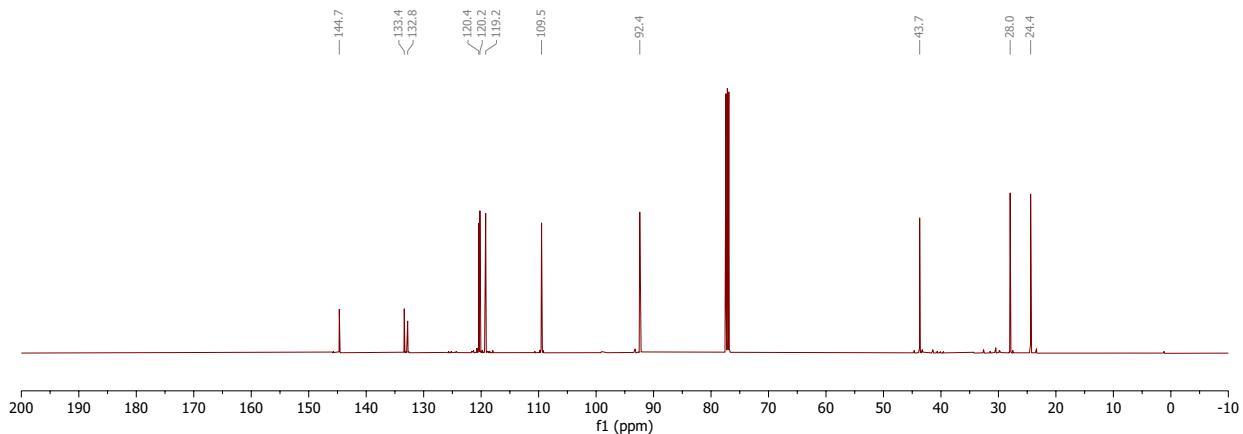


500 MHz ^1H NMR spectrum (CDCl_3)



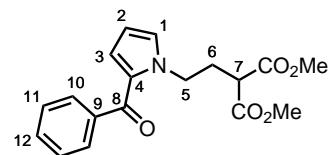
126 MHz ^{13}C NMR spectrum (CDCl_3)



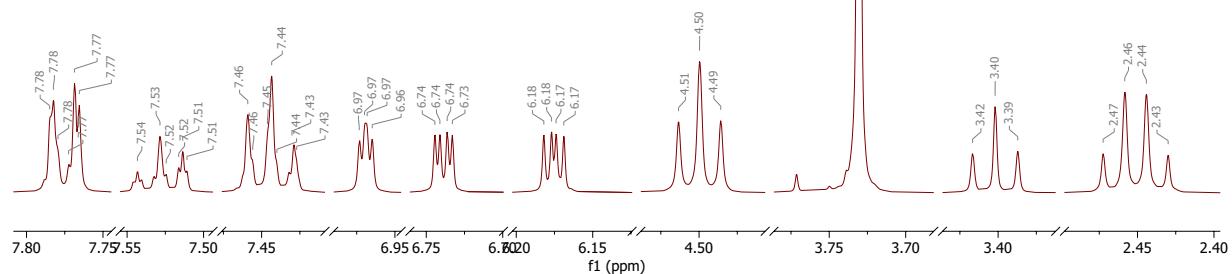
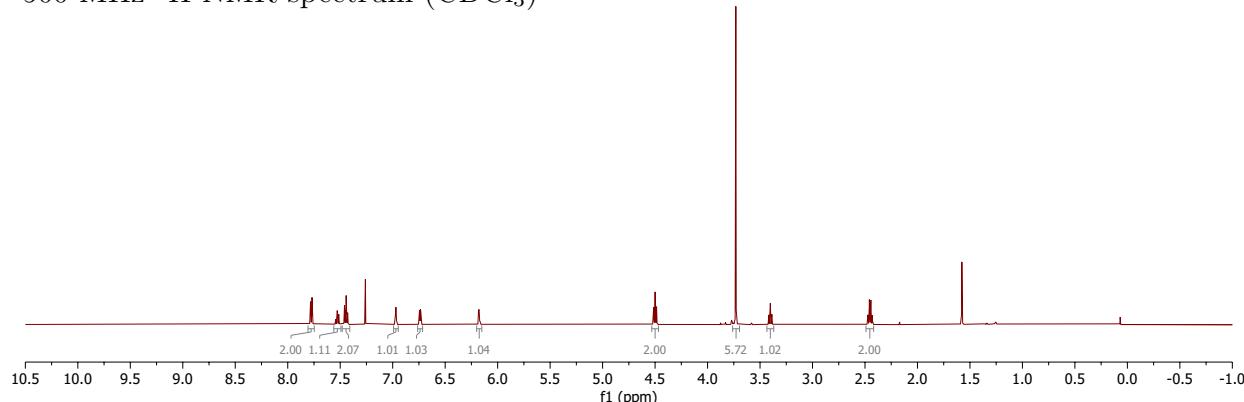
2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole, 60500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

1.4.4 Synthesis of ketorolac

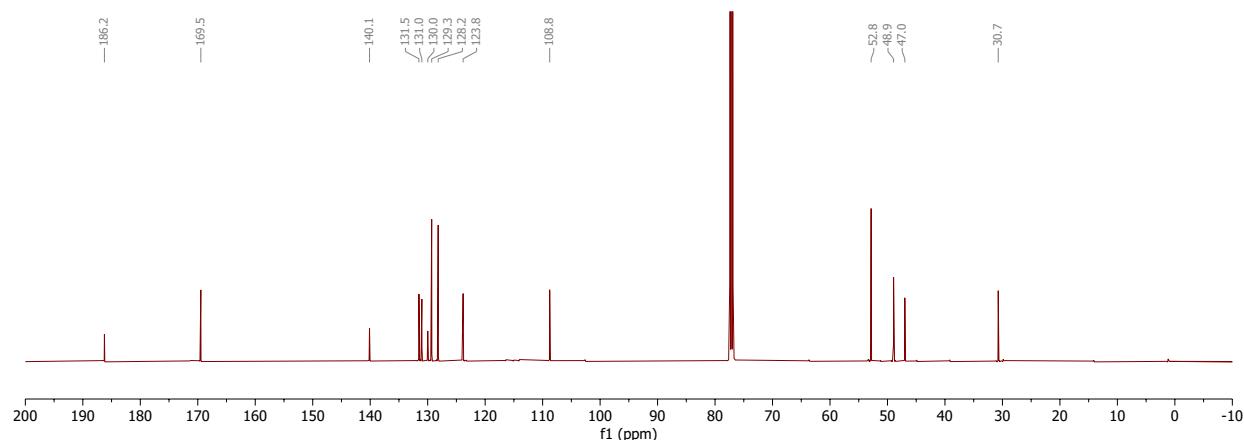
Dimethyl 2-(2-(2-benzoyl-1*H*-pyrrol-1-yl)ethyl)malonate, 21a

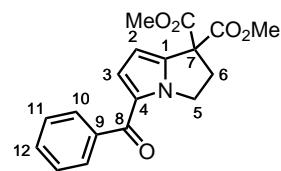
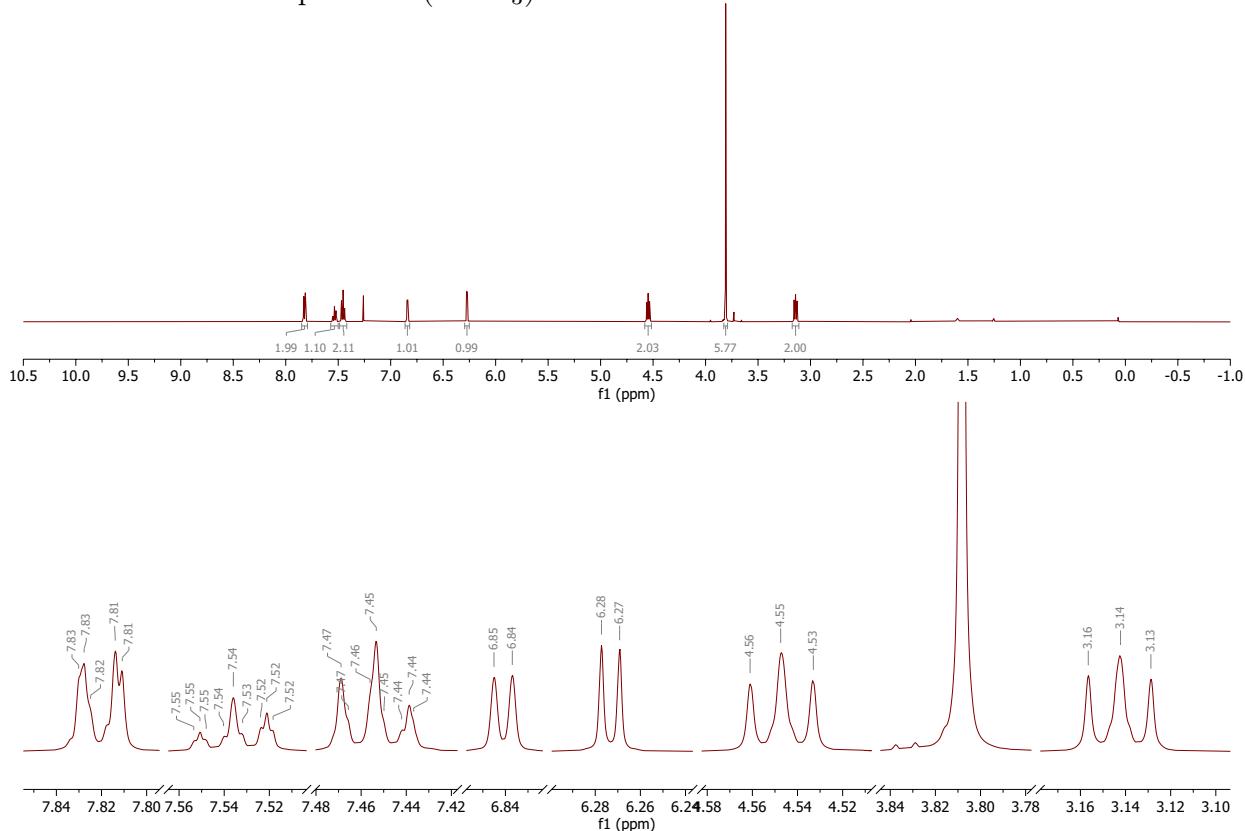
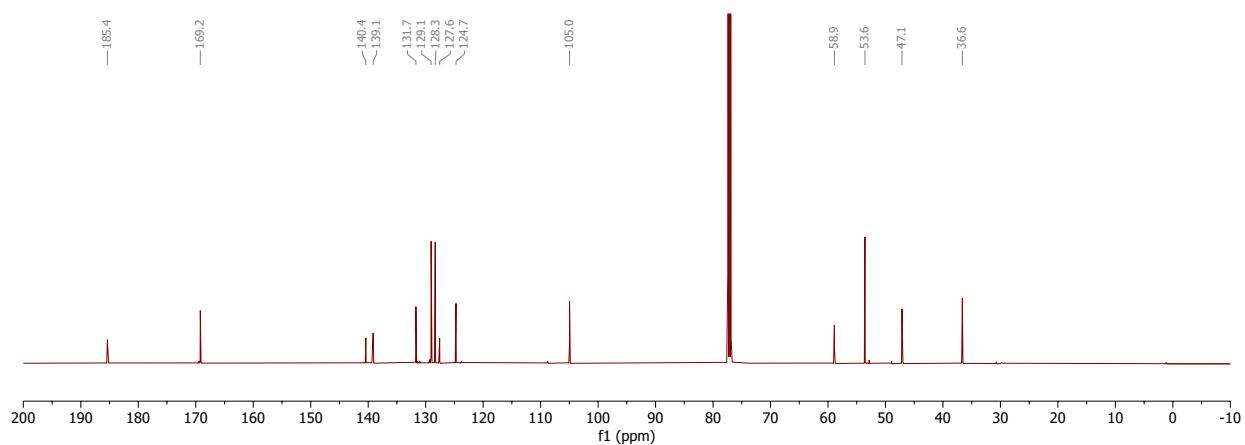


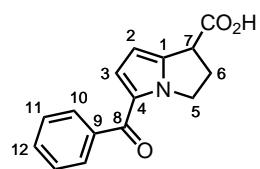
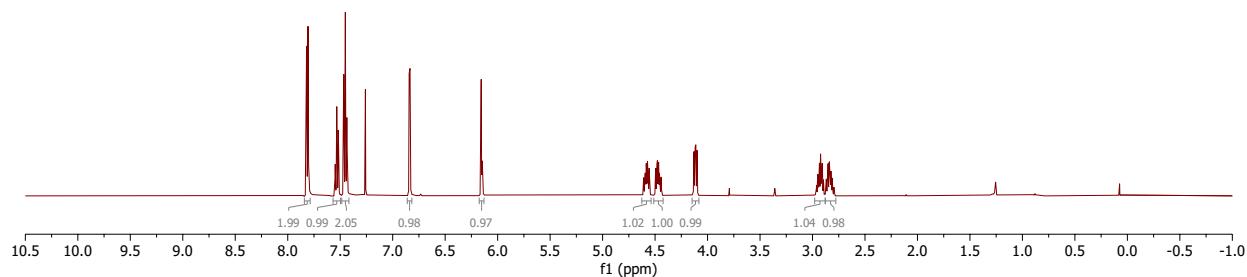
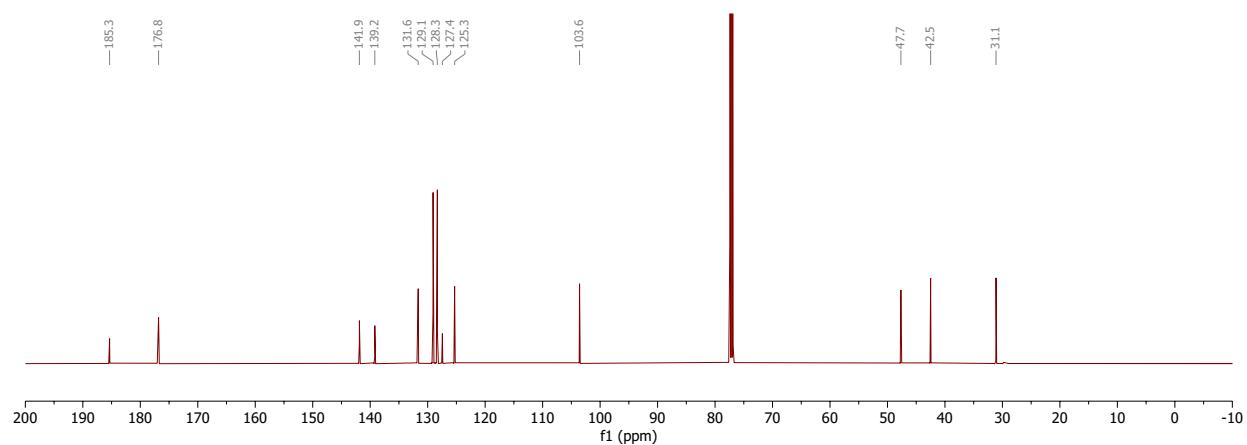
500 MHz ^1H NMR spectrum (CDCl_3)



126 MHz ^{13}C NMR spectrum (CDCl_3)



Dimethyl 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 22a500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, 2500 MHz ^1H NMR spectrum (CDCl_3)126 MHz ^{13}C NMR spectrum (CDCl_3)

2 Appendices

2.1 Cyclisation reaction set-up



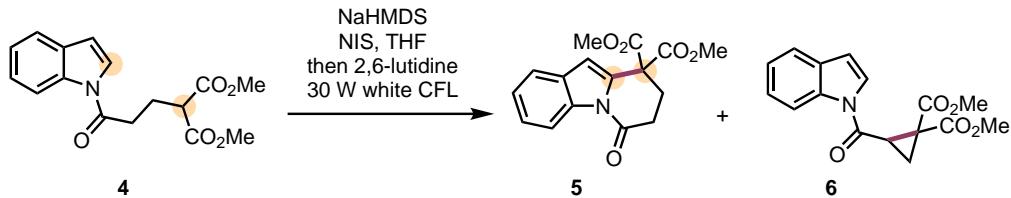
Reaction set-up for the cyclisation of indole **11** on 55 mg scale (0.20 mmol).



Reaction set-up for the cyclisation of indole **11** on 1.0 g scale (3.6 mmol).

2.2 Optimisation tables

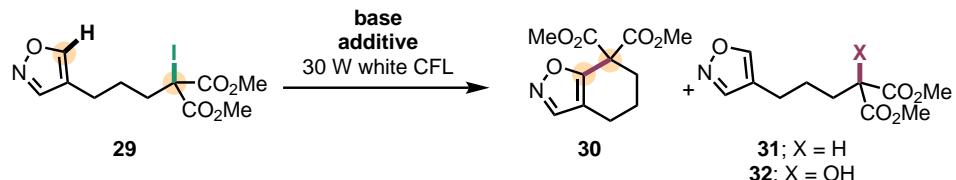
Conditions screen for the cyclisation of indole 4



Entry	Deviation from above	Yield 5/% ^a	Yield 6/% ^a
1	—	51	30
2	LiHMDS instead of NaHMDS	38	58
3	KHMDS instead of NaHMDS	12	0
4	NaH instead of NaHMDS	39	8
5	tBuOK instead of NaHMDS	37	<5
6	No 2,6-lutidine	58	28
7 ^{b,f}	No 2,6-lutidine	94^e	<5
8 ^{b,g}	No 2,6-lutidine	94 ^e	<5
9 ^{b,c}	No 2,6-lutidine, MeCN instead of THF	52	9
10 ^b	No 2,6-lutidine, 2-MeTHF instead of THF	65	8
11 ^{b,d}	No 2,6-lutidine, 1,4-dioxane instead of THF	76	<5
12 ^b	No 2,6-lutidine, Et ₂ O instead of THF	60	5
13 ^b	No 2,6-lutidine, toluene instead of THF	33	<5
14 ^b	No 2,6-lutidine, CH ₂ Cl ₂ instead of THF	88	<5
15 ^b	No light	0	0
16	NCS instead of NIS	0	13
17	NBS instead of NIS	0	51
18 ^b	1.1 equiv. TEMPO added	0	0

Table 2.1. Summary of the optimisation of the cyclisation of indole 4. Reagents and conditions: 4 (0.05 mmol), NaHMDS (1.2 equiv.), NIS (1.2 equiv.), THF (0.1 M), 2,6-lutidine (1.2 equiv.), 30 W white CFL, RT, 18–24 h. ^a Calculated yield by ¹H NMR using (1,3,5-trimethoxybenzene) as internal standard; ^b NaHMDS added over 30 min at –78 °C; ^c NaHMDS added over 30 min at –40 °C; ^d NaHMDS added over 30 min at 0 °C; ^e Isolated yield; ^f Reaction performed on a 0.20 mmol scale; ^g Reaction performed on a 1.0 mmol scale.

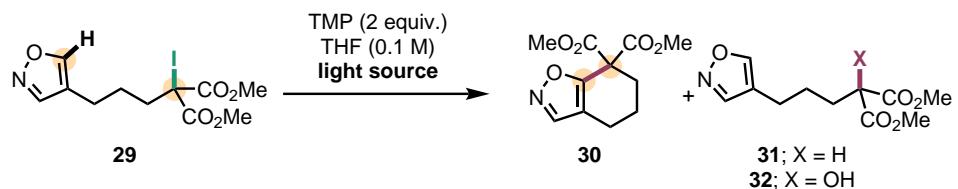
Base and additive screen for the cyclisation of iodomalonate 29



Entry	Base	Additive	Yield 30/% ^a	Yield 31/% ^a	Yield 32/% ^a
1	—	—	11	7	8
2 ^b	—	—	0	0	43
3	2,6-lutidine	—	17	11	22
4	K ₂ CO ₃	—	49	12	0
5	DABCO	—	27	0	79
6	PMP	—	27	25	41
7	NEt ₃	—	4	91	0
8	DBU	—	0	100	0
9	pyridine	—	6	0	94
10	quinuclidine	—	17	37	0
11	TMEDA	—	16	11	73
12	TMP	—	66	12	13
13	TMP^c	—	66	3	29
14	TMP ^d	—	45	0	58
15	TMP	Cu(OTf) ₂	8	0	12
16	TMP	Cu(OTf) ₂ , bpy	0	0	34
17	TMP	Cu(OTf) ₂ , bpy ^e	0	5	22
18	TMP	BF ₃ · Et ₂ O	25	64	11
19	TMP	MgBr ₂ · Et ₂ O	8	51	0
20	TMP	Sc(OTf) ₃	29	71	0
21	TMP	LiOTf	79	21	0
22 ^f	TMP	—	63 ^g	na	na

Table 2.2. Base and additive screen for the cyclisation of iodomalonate **29**. Reagents and conditions: **29** (0.05 mmol), base (1.2 equiv.), additive (1.2 equiv.), THF (0.1 M), 30 W white CFL, RT, 18–24 h. ^a Calculated yield by ¹H NMR using (1,3,5-trimethoxybenzene) as internal standard; ^b Reaction carried out under air; ^c Reaction with 2.0 eq. TMP; ^d Reaction with 4.0 eq. TMP; ^e Reaction with 2.4 equiv. bpy; ^f Reaction carried out on a 0.20 mmol scale; ^g Isolated yield.

Light source screen for the cyclisation of iodomalonate 29



Entry	Light source	Yield 30/% ^a	Yield 31/% ^a	Yield 32/% ^a
1	30 W white CFL	66	3	29
2	43 W 370 nm LED	48	14	0
3	45 W 427 nm LED	55	16	0
4	44 W 525 nm LED	55	16	12

Table 2.3. Light source screen for the cyclisation of iodomalonate 29. Reagents and conditions: 29 (0.05 mmol), TMP (2.0 equiv.), THF (0.1 M), irradiation, RT–35 °C, 18–24 h. ^a Calculated yield by ¹H NMR using (1,3,5-trimethoxybenzene) as internal standard.

2.3 UV/Vis Spectroscopy

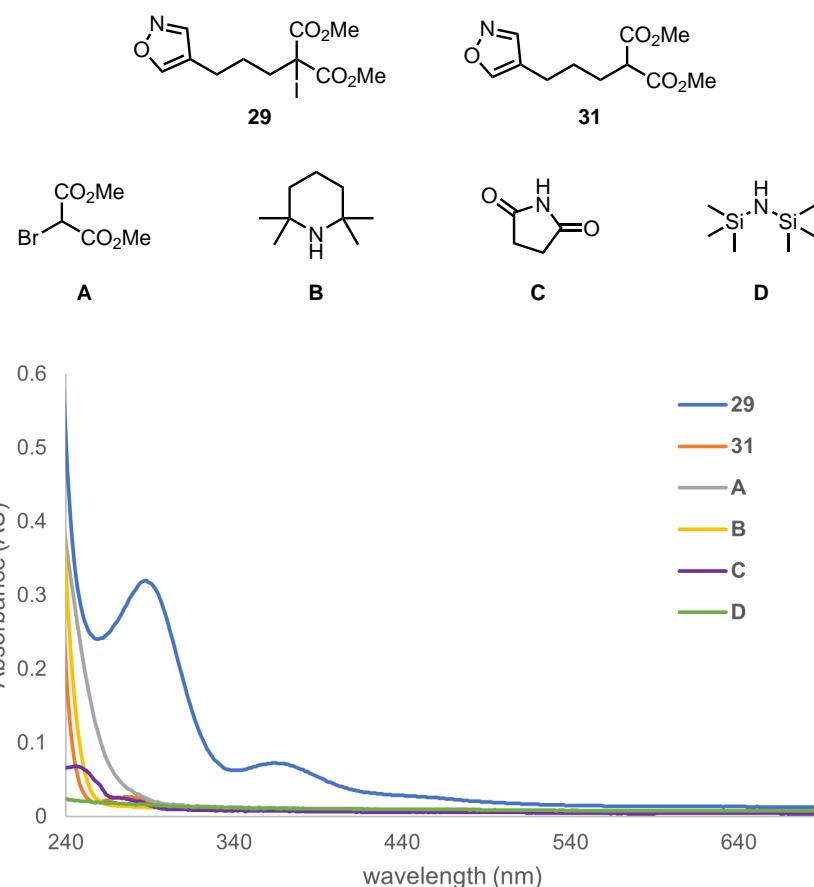


Figure 2.1. UV-VIS spectra of iodomalonate **29**, malonate **31**, bromomalonate **A**, TMP (**B**), succinimide (**C**), and HMDS (**D**) (5 mM in THF).

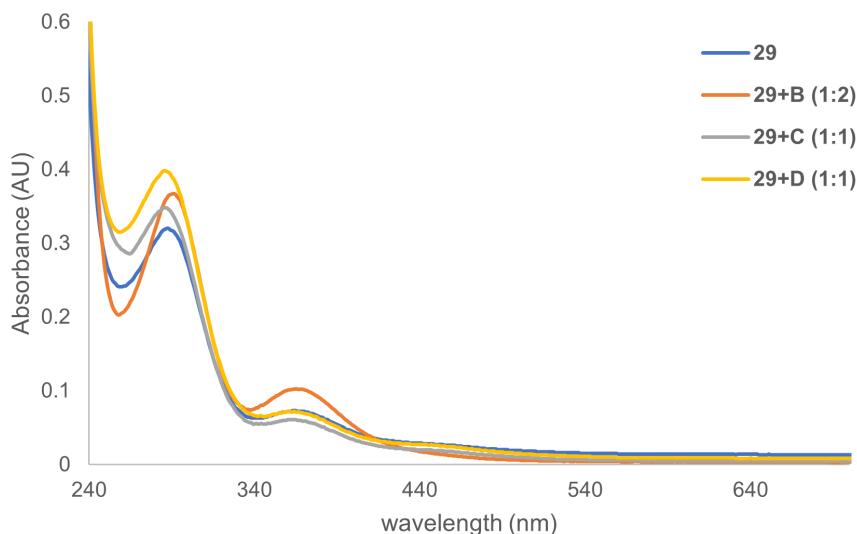
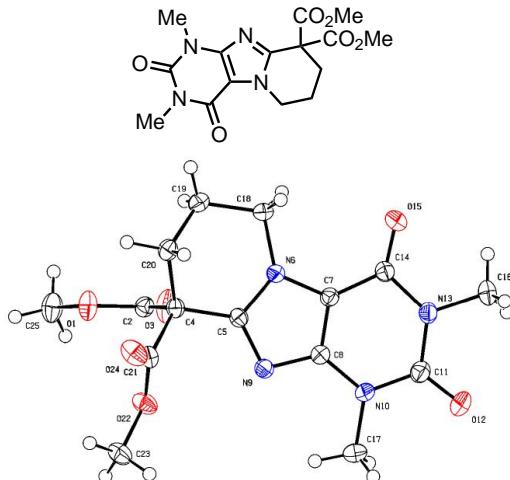


Figure 2.2. UV-VIS spectra of iodomalonate **29**, and mixtures of iodomalonate **29** with TMP (**B**), succinimide (**C**), and HMDS (**D**) (5 mM in THF).

2.4 Crystallographic data

Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4,7,8-hexahydropyrido[2,1-*f*] purine-9,9(6*H*)- dicarboxylate 58 (CCDC 2097518)



Crystal data

$C_{15}H_{18}N_4O_6$	$F(000) = 1472$
$M_r = 350.33$	$D_x = 1.481 \text{ Mg m}^{-3}$
Monoclinic, $I2/a$	Melting point: not measured K
Hall symbol: $-I\ 2ya$	$\text{Cu } K\alpha$ radiation, $\lambda = 1.54180 \text{ \AA}$
$a = 2.7979 (3) \text{ \AA}$	Cell parameters from 5642 reflections
$b = 19.0627 (4) \text{ \AA}$	$\theta = 4.176.4^\circ$
$c = 14.1683 (3) \text{ \AA}$	$\mu = 0.99 \text{ mm}^{-1}$
$\beta = 114.602 (3)^\circ$	$T = 150 \text{ K}$
$V = 3142.76 (14) \text{ \AA}^3$	Block, colourless
$Z = 8$	$0.29 \times 0.25 \times 0.19 \text{ mm}$

Data collection

Oxford Diffraction SuperNova diffractometer

3064 reflections with $I > 2.0\sigma I$

Focussing mirrors monochromator, ω scans

Absorption correction: multi-scan CrysAlis PRO (Rigaku Oxford Diffraction, 2017)

$R_{int} = 0.018$	$k = -23 \rightarrow 22$
$\theta_{max} = 76.9^\circ, \theta_{min} = 4.1^\circ$	7490 measured reflections
$h = -15 \rightarrow 15$	$l = -14 \rightarrow 17$
$T_{min} = 0.78, T_{max} = 0.83$	3264 independent reflections

Refinement

Refinement on F^2	Primary atom site location: other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.038$	H-atom parameters constrained
$wR(F^2) = 0.105$	Method = modified Sheldrick
$S = 1.02$	$(\Delta/\sigma)_{max} = 0.0003$
3264 reflections	$\Delta\rho_{max} = 0.31 \text{ e } \text{\AA}^{-3}$
226 parameters	$\Delta\rho_{min} = -0.27 \text{ e } \text{\AA}^{-3}$
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2) for compound 58

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{iso} * / U_{eq}$
O1	0.25631 (8)	0.44739 (6)	0.19559 (7)	0.0311
C2	0.34905 (10)	0.41085 (6)	0.20562 (9)	0.0229
O3	0.36707 (9)	0.38784 (6)	0.13549 (7)	0.0379
C4	0.43032 (10)	0.40414 (6)	0.32135 (9)	0.0208
C5	0.52709 (10)	0.35431 (6)	0.33517 (8)	0.0193
N6	0.63121 (9)	0.37891 (5)	0.34754 (8)	0.0200
C7	0.70014 (10)	0.32069 (6)	0.36114 (9)	0.0203
C8	0.63102 (10)	0.26448 (6)	0.35489 (8)	0.0200
N9	0.52318 (9)	0.28434 (5)	0.33912 (8)	0.0212
N10	0.67129 (9)	0.19674 (6)	0.36408 (8)	0.0246
C11	0.78467 (12)	0.18484 (7)	0.38263 (10)	0.0255
O12	0.82315 (9)	0.12558 (5)	0.39022 (9)	0.0376
N13	0.85373 (9)	0.24379 (6)	0.39305 (8)	0.0233
C14	0.81890 (10)	0.31459 (6)	0.38243 (9)	0.0226
O15	0.88605 (8)	0.36240 (5)	0.39210 (9)	0.0352
C16	0.97567 (11)	0.22986 (8)	0.41947 (11)	0.03
C17	0.59481 (13)	0.13647 (7)	0.34608 (12)	0.033
C18	0.66615 (11)	0.45223 (6)	0.34542 (11)	0.0259
C19	0.56262 (11)	0.50035 (7)	0.31619 (10)	0.0269
C20	0.48270 (11)	0.47628 (7)	0.36516 (10)	0.0253
C21	0.35820 (10)	0.37621 (7)	0.37728 (9)	0.0223
O22	0.29370 (8)	0.32270 (5)	0.32375 (7)	0.0294
C23	0.21912 (12)	0.29075 (8)	0.36481 (11)	0.0301
O24	0.35862 (9)	0.40028 (6)	0.45522 (7)	0.033
C25	0.16764 (12)	0.45537 (8)	0.09132 (10)	0.0347
H161	1.0067	0.2689	0.4024	0.0487*

H162	1.0152	0.2188	0.4905	0.0465*
H163	0.9781	0.1914	0.3786	0.0471*
H171	0.6199	0.1074	0.408	0.0515*
H172	0.5192	0.1521	0.3331	0.0506*
H173	0.5932	0.1094	0.2892	0.0518*
H181	0.7246	0.4626	0.4156	0.0308*
H182	0.701	0.4549	0.2953	0.0303*
H191	0.5877	0.5462	0.338	0.0329*
H192	0.5202	0.5016	0.2403	0.0315*
H201	0.5249	0.4705	0.4394	0.0305*
H202	0.4194	0.5096	0.3509	0.0309*
H231	0.1591	0.2689	0.3063	0.0440*
H232	0.1885	0.3257	0.396	0.0443*
H233	0.2622	0.2568	0.4165	0.0441*
H251	0.1014	0.4705	0.0982	0.0552*
H252	0.194	0.4887	0.0582	0.0538*
H253	0.1534	0.4119	0.0544	0.0534*

Atomic displacement parameters (\AA^2) for compound 58

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0262 (5)	0.0407 (5)	0.0235 (4)	0.0123 (4)	0.0075 (4)	-0.0031 (4)
C2	0.0238 (6)	0.0226 (6)	0.0239 (6)	0.0027 (4)	0.0116 (5)	0.0003 (4)
O3	0.0397 (6)	0.0524 (7)	0.0237 (5)	0.0194 (5)	0.0153 (4)	0.0024 (4)
C4	0.0209 (5)	0.0216 (6)	0.0223 (5)	0.0018 (4)	0.0114 (4)	-0.0013 (4)
C5	0.0191 (5)	0.0212 (6)	0.0187 (5)	-0.0003 (4)	0.0091 (4)	-0.0009 (4)
N6	0.0196 (5)	0.0185 (5)	0.0234 (5)	-0.0002 (4)	0.0106 (4)	0.0003 (4)
C7	0.0209 (6)	0.0193 (6)	0.0211 (5)	0.0007 (4)	0.0091 (4)	-0.0001 (4)
C8	0.0209 (5)	0.0199 (6)	0.0191 (5)	0.0001 (4)	0.0082 (4)	-0.0004 (4)
N9	0.0208 (5)	0.0208 (5)	0.0226 (5)	-0.0007 (4)	0.0097 (4)	-0.0011 (4)
N10	0.0236 (5)	0.0176 (5)	0.0315 (5)	-0.0004 (4)	0.0105 (4)	-0.0009 (4)
C11	0.0260 (6)	0.0226 (6)	0.0273 (6)	0.0028 (5)	0.0105 (5)	-0.0004 (5)
O12	0.0355 (5)	0.0240 (5)	0.0531 (6)	0.0082 (4)	0.0183 (5)	0.0017 (4)
N13	0.0204 (5)	0.0238 (5)	0.0260 (5)	0.0030 (4)	0.0098 (4)	-0.0002 (4)
C14	0.0208 (6)	0.0238 (6)	0.0237 (5)	0.0005 (4)	0.0096 (5)	-0.0006 (4)
O15	0.0233 (5)	0.0281 (5)	0.0554 (6)	-0.0037 (4)	0.0177 (4)	0.0009 (4)
C16	0.0220 (6)	0.0339 (7)	0.0355 (7)	0.0060 (5)	0.0133 (5)	0.0004 (5)
C17	0.0314 (7)	0.0198 (6)	0.0469 (8)	-0.0048 (5)	0.0155 (6)	-0.0019 (5)
C18	0.0249 (6)	0.0181 (6)	0.0367 (7)	-0.0022 (5)	0.0148 (5)	0.0012 (5)
C19	0.0287 (6)	0.0184 (6)	0.0362 (6)	0.0004 (5)	0.0159 (5)	0.0001 (5)
C20	0.0264 (6)	0.0218 (6)	0.0303 (6)	0.0012 (5)	0.0143 (5)	-0.0047 (5)
C21	0.0184 (5)	0.0268 (6)	0.0220 (5)	0.0029 (4)	0.0088 (4)	0.0005 (4)

O22	0.0298 (5)	0.0338 (5)	0.0316 (5)	-0.0080 (4)	0.0196 (4)	-0.0076 (4)
C23	0.0268 (6)	0.0352 (7)	0.0331 (6)	-0.0059 (5)	0.0174 (5)	-0.0030 (5)
O24	0.0322 (5)	0.0456 (6)	0.0265 (5)	-0.0076 (4)	0.0175 (4)	-0.0093 (4)
C25	0.0297 (7)	0.0426 (8)	0.0256 (6)	0.0108 (6)	0.0054 (5)	-0.0007 (5)

Geometric parameters (\AA , $^\circ$) for compound 58

O1–C2	1.3317 (15)	C16–H162	0.943
O1–C25	1.4482 (15)	C16–H163	0.943
C2–O3	1.1931 (16)	C17–H171	0.973
C2–C4	1.5385 (16)	C17–H172	0.954
C4–C5	1.5074 (16)	C17–H173	0.95
C4–C20	1.5426 (16)	C18–C19	1.5203 (17)
C4–C21	1.5402 (16)	C18–H181	0.984
C5–N6	1.3534 (15)	C18–H182	0.984
C5–N9	1.3369 (16)	C19–C20	1.5261 (17)
N6–C7	1.3805 (15)	C19–H191	0.938
N6–C18	1.4715 (15)	C19–H192	0.983
C7–C8	1.3686 (16)	C20–H201	0.969
C7–C14	1.4257 (17)	C20–H202	0.982
C8–N9	1.3569 (15)	C21–O22	1.3326 (15)
C8–N10	1.3762 (15)	C21–O24	1.1937 (15)
N10–C11	1.3814 (16)	O22–C23	1.4431 (15)
N10–C17	1.4614 (16)	C23–H231	0.959
C11–O12	1.2191 (16)	C23–H232	0.968
C11–N13	1.3989 (17)	C23–H233	0.961
N13–C14	1.4097 (16)	C25–H251	0.937
N13–C16	1.4695 (15)	C25–H252	0.933
C14–O15	1.2207 (16)	C25–H253	0.956
C16–H161	0.923		
C2–O1–C25	116.67 (10)	N10–C17–H171	110.2
O1–C2–O3	125.18 (12)	N10–C17–H172	109.9
O1–C2–C4	109.53 (10)	H171–C17–H172	106.2
O3–C2–C4	125.28 (11)	N10–C17–H173	110.5
C2–C4–C5	110.20 (9)	H171–C17–H173	109.8
C2–C4–C20	110.02 (10)	H172–C17–H173	110.2
C5–C4–C20	108.27 (10)	N6–C18–C19	109.93 (10)
C2–C4–C21	107.05 (9)	N6–C18–H181	106.3
C5–C4–C21	110.57 (10)	C19–C18–H181	111.3
C20–C4–C21	110.75 (10)	N6–C18–H182	107.2
C4–C5–N6	120.66 (10)	C19–C18–H182	112.2
C4–C5–N9	126.23 (10)	H181–C18–H182	109.7

N6–C5–N9	113.10 (10)	C18–C19–C20	111.58 (10)
C5–N6–C7	106.08 (10)	C18–C19–H191	109.4
C5–N6–C18	128.14 (10)	C20–C19–H191	109.4
C7–N6–C18	125.77 (10)	C18–C19–H192	109.5
N6–C7–C8	105.20 (10)	C20–C19–H192	109.6
N6–C7–C14	131.15 (11)	H191–C19–H192	107.2
C8–C7–C14	123.59 (11)	C4–C20–C19	110.26 (10)
C7–C8–N9	112.20 (11)	C4–C20–H201	106.8
C7–C8–N10	121.46 (11)	C19–C20–H201	110.6
N9–C8–N10	126.33 (11)	C4–C20–H202	108.1
C8–N9–C5	103.42 (10)	C19–C20–H202	111.4
C8–N10–C11	119.63 (10)	H201–C20–H202	109.6
C8–N10–C17	121.60 (11)	C4–C21–O22	109.49 (10)
C11–N10–C17	118.57 (11)	C4–C21–O24	124.77 (12)
N10–C11–O12	121.51 (12)	O22–C21–O24	125.72 (12)
N10–C11–N13	117.11 (11)	C21–O22–C23	116.78 (10)
O12–C11–N13	121.38 (12)	O22–C23–H231	105.1
C11–N13–C14	126.86 (11)	O22–C23–H232	110.7
C11–N13–C16	116.05 (11)	H231–C23–H232	111.3
C14–N13–C16	117.08 (11)	O22–C23–H233	109
C7–C14–N13	111.26 (10)	H231–C23–H233	111.4
C7–C14–O15	126.98 (12)	H232–C23–H233	109.2
N13–C14–O15	121.75 (11)	O1–C25–H251	106.6
N13–C16–H161	108.4	O1–C25–H252	106.9
N13–C16–H162	110.7	H251–C25–H252	112
H161–C16–H162	111.2	O1–C25–H253	110.9
N13–C16–H163	106.7	H251–C25–H253	110.4
H161–C16–H163	109.8	H252–C25–H253	110
H162–C16–H163	110		

Hydrogen-bond geometry (\AA , $^\circ$) for compound 58

D–H \cdots A	D–H	H \cdots A	D \cdots A	D–H \cdots A
C16–H163 \cdots O3 ⁱ	0.94	2.56	3.3161 (19)	137
C20–H202 \cdots O1 ⁱⁱ	0.98	2.59	3.3949 (19)	140
C23–H231 \cdots N9 ⁱⁱⁱ	0.96	2.59	3.5430 (19)	171

Symmetry codes: (i) $-x + 3/2, -y + 1/2, -z + 1/2$, (ii) $x - 1/2, -y + 1, z$, (iii) $-x + 1/2, -y + 1/2, -z + 1/2$.

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