# Supporting Information

## Cubanes in medicinal chemistry: synthesis of functionalized building blocks

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## General Analytical Information

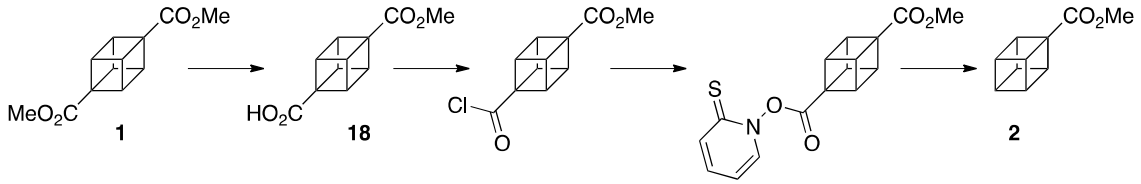
Nuclear Magnetic Resonance spectra were recorded on a Bruker 700 MHz or 400 MHz instrument at ambient temperature. All $^{1}H$ NMR spectra were measured in part per million (ppm) relative to the signals for residual chloroform ($CHCl_3$) in deuterated $CDCl_3$ (7.26 ppm), or the signals for tetramethylsilane (TMS) added into the deuterated chloroform (0 ppm). Data for $^{1}H$ NMR were reported as: chemical shift, multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, h = heptet, m = multiplet, br = broad), coupling constants, and integration. All $^{13}C$ NMR spectra were reported in ppm relative to $CDCl_3$ (77.16 ppm) or MeOD (49.00 ppm) unless otherwise stated, and were obtained with complete $^{1}H$ decoupling. IR spectra were reported on an Avatar 370 FT-IR Thermo Nicolet Spectrometer. High resolution mass spectra were obtained on a Thermo LTQ-FT/Accela/CTC/PDA instrument. Melting points were obtained on a Buchi B-545 capillary melting point apparatus. Cubane-1,4-dimethylester was purchased from Prof Philip Eaton, cubane and its derivatives can also be purchased from http://www.boronmolecular.com/Products/Cubanes. *Note: certain cubane derivatives including* ***4, 5*** *and the proceeding thioacetate did not give satisfactory HRMS data - the observed mass spectrometry data is, however, reported. The Boc-protected* ***16*** *and the t-butyl ester of* ***18*** *did not give molecular ions but did give satisfactory HRMS of fragment ions.*

## General Reagent Information

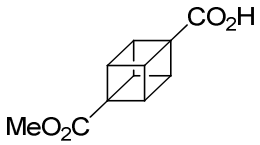
Unless otherwise noted, all chemicals were commercially available and were used as received without further purification. Dry solvents were used directly from Sigma-Aldrich Sure-Seal bottles.

## Experimental procedures and physical data

Compound **2** was prepared according to a modification of the literature route.[12]

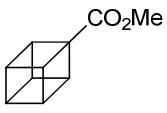



**4-(Methoxycarbonyl)cubane-1-carboxylic acid (18)**




To a solution of dimethyl-1,4-cubanedicarboxylate (10.00 g, 45.41 mmol) in THF (242 mL) was added a solution of sodium hydroxide in methanol (2.0 M, 22.70 mL, 45.41 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and redissolved in water (80 mL), and extracted with DCM (3 x 50 mL). The aqueous layer from the extraction was acidified with concentrated HCl to pH ~3, the white suspension formed was extracted with DCM (3 x 200 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 4-(methoxycarbonyl)cubane-1-carboxylic acid (9.00 g, 96 %) as a white solid. **m.p.:** 183-184 °C (lit.[3] 182-183 °C); **$^{1}H$ NMR** (400 MHz, $CDCl_3$, 30 °C) δ 4.28 (s, 6H), 3.72 (s, 3H). Data in accordance with the literature.[1]

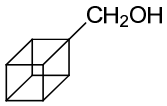
**Methyl cubane-1-carboxylate (2)**




To a solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (5.00 g, 24.25 mmol) in chloroform (230 mL), oxalyl chloride (13.34 mL, 26.7 mmol) was added dropwise followed by a catalytic amount of N,N-

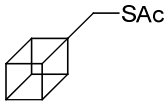
dimethylformamide (2 drops) and the reaction was stirred at room temperature for 3 hours. The crude mixture was then added dropwise to a solution of 1-hydroxypyridine-2-thione sodium salt (5.42 g, 36.4 mmol) and N,N-dimethylaminopyridine (0.29 g, 2.4 mmol) in chloroform (230 mL) and stirred at 60 °C for one hour. The reaction mixture was next pumped using a peristalitic pump (15 mL/min) *via* a flow system (assembled according to the procedure published by Booker-Millburn[4]) which was simultaneously irradiated with a medium pressure Hg vapour lamp. Heating and irradiation was discontinued after all the solution was pumped through. The solvent was removed under reduced pressure and the resulting residue was partitioned between $Et_2O$ (160 mL) and 1 N HCl (160 mL). The organic layer was further washed with 1 N HCl (2 x 100 mL), and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10% EtOAc in heptane) afforded methyl cubane-1-carboxylate (3.15 g, 80 %) as a white solid. **m.p.:** 51-54 °C (lit.[2] 51.2-52.9 °C); **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.28 - 4.21 (3H, m), 4.04 - 3.94 (4H, m), 3.69 (3H, s). Data in accordance with the literature.[1, 2]

**Cuban-1-ylmethanol (3)**



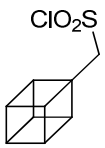

To a solution of methyl cubane-1-carboxylate (3.70 g, 22.8 mmol) in THF (43 mL) at 0 °C a solution of lithium borohydride (2.0 M, 13.70 mL, 27.38 mmol) in THF (43 mL) was added dropwise. The resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with $NH_4Cl$ (50 mL) extracted with EtOAc (3 x 50 mL), the organic layers were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 50% EtOAc in heptane). Pure fractions were evaporated to dryness to afford cuban-1-ylmethanol (2.95 g, 96 %) as a white solid. **m.p.:** 63-64 °C (lit.[5] 62-62.5°C); **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.07 – 4.01 (m, 1H), 3.96 – 3.86 (m, 6H), 3.75 (d, $J$ = 4.9 Hz, 2H), 1.22 (t, $J$ = 5.3 Hz, 1H). Data in accordance with the literature.[5]

**S-(Cuban-1-ylmethyl) ethanethioate**




To a well-stirred solution of triphenylphosphine (2.62 g, 9.99 mmol) in THF (10 mL) at 0 °C, diisopropyl azodicarboxylate (1.97 mL, 9.99 mmol) was added dropwise over a period of 10 minutes under nitrogen. The resulting mixture was stirred at room temperature for 30 minutes and a white precipitate resulted. Cuban-1-ylmethanol (0.67 g, 4.99 mmol) thioacetic acid (0.71 mL, 9.99 mmol) in THF (10 mL) was added dropwise at 0 °C over a period of 10 minutes under nitrogen. The resulting solution was stirred at 0 °C for 1 hour and at room temperature for another hour. A clear yellow solution resulted. The triphenylphosphine oxide was precipitated upon addition of EtOAc/hexane (50 mL, 1:10), removed by filtration, and washed with hexane. The combined filtrates were concentrated under reduced pressure and the crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane). Pure fractions were evaporated to dryness to afford S-(cuban-1-ylmethyl) ethanethioate (0.90 g, 94%) as a low melting white solid. **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.03 - 3.96 (m, 1H), 3.88 - 3.81 (m, 3H), 3.76 - 3.69 (m, 3H), 3.20 (s, 2H), 2.35 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 196.0, 56.7, 48.8, 48.6, 43.9, 32.5, 30.8; **HRMS** ($EI^+$) 115.0493 (100%); Calcd for $C_9H_9S^+$ $[M - CH_3CO]^+$ 149.0419, Found 149.0395 (5); **IR** (neat $cm^{-1}$): 2978, 2906, 1730, 1693, 1352, 1246, 1134, 1099, 995, 951, 920, 843, 636.

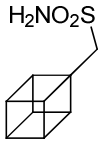
**Cuban-1-ylmethanesulfonylchloride (4)**




To a mixture of acetonitrile (46 mL) and hydrogen chloride in water (2.0 M, 6.13 mL, 12.27 mmol) at 10 °C, N-chlorosuccinimide (12.36 g, 92.57 mmol) was added followed by a dropwise addition of a solution of S-(cuban-1-ylmethyl) ethanethioate (4.45 g, 23.14 mmol) in acetonitrile (46 mL) over a period of 5 minute under nitrogen,

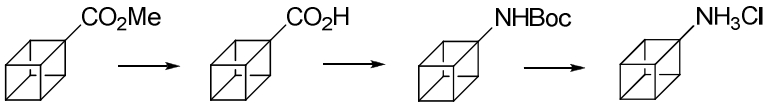
keeping the internal temperature below 20 °C. The resulting mixture was stirred at 20 °C for 20 minutes. The reaction mixture was diluted with $Et_2O$ (100 mL) and washed with 12% aqueous NaCl (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane). Pure fractions were evaporated to dryness to afford cuban-1-ylmethanesulfonyl chloride (5.01 g, 55%) as a white solid.
Small scale synthesis using S-(cuban-1-ylmethyl) ethanethioate (0.20 g, 1.04 mmol) gave (0.20 g, 89%) of the cuban-1-ylmethanesulfonyl chloride as a white solid. **m.p.:** 46.0-47.0 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.2 - 4.16 (m, 3H), 4.10 (s, 2H), 4.06 - 4.02 (m, 4H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 69.2, 51.9, 49.4, 48.3, 44.9; **HRMS** ($EI^+$) 115.0512 (100%); Calcd for $C_9H_9^+$ $[M - SO_2Cl]^+$ 117.0699, Found 117.0693 (10). **IR** (neat $cm^{-1}$): 3016, 2985, 2933, 1352, 1161, 1147, 839, 644.

**Cuban-1-yl methanesulfonamide (5)**



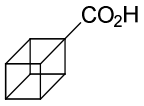

To a mixture of aqueous ammonia (28%, 0.044 mL, 2.31 mmol) in acetonitrile (1.5 mL) at 0 °C was added a solution of cuban-1-ylmethanesulfonyl chloride (50.0 mg, 0.23 mmol) in acetonitrile (1.5 mL) over a period of 5 minutes under nitrogen, keeping the internal temperature below 10 °C. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with brine and concentrated under reduced pressure. The crude cuban-1-ylmethanesulfonamide (40.0 mg, 88%) was sufficiently pure for further use. **m.p.:** 138.5-140.0 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.64 (s, 2H), 4.13 – 4.07 (m, 3H), 4.06 – 4.02 (m, 1H), 4.02 - 3.96 (m, 3H), 3.51 (s, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 58.3, 52.3, 49.1, 48.3, 44.8; **HRMS** ($EI^+$) 115.0516 (100%); Calcd for $C_9H_{10}N^+$ $[M– SO_2H]^+$ 132.0813, Found 132.0802 (5); **IR** (neat $cm^{-1}$): 3340, 3263, 2985, 1662, 1322, 1164, 1141, 964, 501.

The cubyl amine **6** was prepared according to the literature route[6]



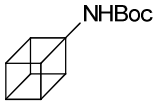

**2** **6**

**Cubanecarboxylic acid**



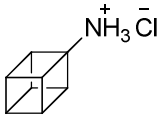

To a solution of methyl cubane-1-carboxylate (4.42 g, 27.25 mmol) in THF (182 mL) was added dropwise a solution of sodium hydroxide (2.73 g, 68.13 mmol) in MeOH (36 mL) at room temperature. The resulting mixture was stirred at room temperature for 12 hours and organic solvents were evaporated. Water (40 mL) was then added, and the mixture was extracted with $Et_2O$ (3 x 50 mL). The aqueous layer was acidified with concentrated HCl to pH ~3, and the so formed cloudy solution was extracted with DCM (3 x 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford cubane-1-carboxylic acid (4.04, 99%) as a white solid. **m.p.:** 123-125 °C (lit.[1] 124-125°C) **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.33 - 4.26 (3H, m), 4.07 – 3.97 (4H, m). Data in accordance with the literature.[1]

***tert*-Butyl cuban-1-ylcarbamate[6]**



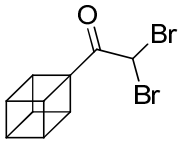

To a solution of triethylamine (0.53 mL, 4.05 mmol) and diphenyl phosphorylazide (0.80 mL, 3.71 mmol) in *tert*-butanol (10 mL) was added cubane-1-carboxylic acid (0.50 g, 3.37 mmol) and the reaction mixture was heated under reflux for 5 h. After starting material was consumed, the reaction was cooled down to room temperature and quenched with 1 M citric acid (10 mL). The layers were then separated and aqueous phase was extracted with chloroform (2 x 20 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($Na_2SO_4$) and evaporated. The crude product was purified by flash silica chromatography, (elution gradient 0 to 40% EtOAc in heptane). Pure fractions were evaporated to dryness to afford *tert*-butyl cuban-1-ylcarbamate (0.57 g, 77 %) as a white solid. **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 5.02 (s, 1H), 4.13 – 3.98 (m, 3H), 3.98 – 3.91 (m, 1H), 3.91 – 3.81 (m, 3H), 1.45 (s, 9H). Data in accordance with the literature.[6]

**Cubyl amine hydrochloride[6](6)**



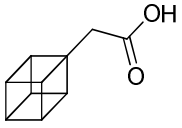

Through a suspension of *tert*-butyl cuban-1-ylcarbamate (2.80 g, 12.77 mmol) in MeOH (85 mL) at -60 °C, hydrochloric acid gas was bubbled until the mixture became homogeneous. The solution was then left to warm to room temperature and stirred for 20 hours. The solvent was removed under reduced pressure. The residue was washed with ice-cold ethanol. Cuban-1-amine hydrochloride (1.90 g, 96 %) was isolated as a white solid which was purified by crystallization from methanol/acetone. **m.p.:** 170 °C dec. (160 °C browned); **$^1$H NMR** (400 MHz, MeOD, 27 °C) δ 4.26 – 4.18 (3H, m), 4.09 – 3.99 (4H, m); **$^{13}$C NMR** (101 MHz, MeOD, 27 °C) δ 66.1, 51.7, 49.7, 44.2; **HRMS** ($ESI^+$) Calcd for $C_8H_{10}N$ $[M]^+$ 120.0808 (100%), Found 120.0807; **IR** (neat $cm^{-1}$): 3434, 3000, 2991, 2977, 2902, 2825, 2358, 1456, 1294, 1199, 1157, 837. Data in accordance with the literature.[6]

**2,2-Dibromo-1-(cuban-1-yl)ethanone (8)**




To a solution of methyl cubane-1-carboxylate (2.00 g, 12.33 mmol) in THF (42 mL) dibromomethane (1.56 mL, 22.20 mmol) was added. In a separate flask *n*-butyllithium (13.87 mL, 22.20 mmol) was added to a 2,2,6,6-tetramethylpiperidine (4.16 mL, 24.66 mmol) in THF (42 mL) cooled to -78 °C, over a period of 5 minutes under nitrogen. The yellow solution of lithium tetramethylpiperidide was added dropwise to the cubane dibromomethane solution. The resulting solution was stirred at -78 °C for 20 minutes. The reaction mixture was poured onto 2 M HCl (10 mL) and extracted with heptane (3 x 20 mL). The organic layers were dried ($MgSO_4$), filtered and evaporated to afford crude 2,2-dibromo-1-(cuban-1-yl)ethanone (3.89 g, 88%) as a yellow oil, which was sufficiently pure and could be used without further purification. **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 5.90 (s, 1H), 4.5 – 4.42 (m, 3H), 4.11 – 4.05 (m, 3H), 4.01 (ddd, $J$ = 4.9, 3.7, 2.3 Hz, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 194.0, 60.6, 52.1, 47.3, 45.4, 40.7; **HRMS** ($EI^+$) $C_8H_7^+$ 103.0513 (100%); Calcd for $C_{10}H_8OBr_2$ $[M]^+$ 301.8936, Found 301.8944 (3); **IR** (neat $cm^{-1}$): 2987, 1701, 1684, 1302, 1219, 1147, 1028, 885, 845, 732.

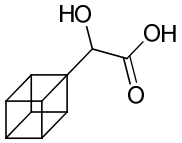
**2-(Cuban-1-yl)acetic acid[5] (7)**




To a solution of 2,2-dibromo-1-(cuban-1-yl)ethanone (0.50 g, 1.64 mmol) in THF (4 mL) was added lithium bis(trimethylsilyl)amide (1.0 M, 1.81 mL, 1.81 mmol) dropwise in THF (4 mL) cooled to -78 °C, over a period

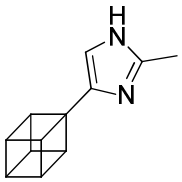
of 5 minutes under nitrogen. The resulting solution was stirred at -78 °C for 30 minutes and treated with *n*-butyllithium (2.16 mL, 3.45 mmol) and allowed to warm up to -50 over 20 min and to 0 °C over the next 20 min. The reaction mixture was then quenched with acidic methanol (12 mL) at 0 °C (acidic methanol was prepared by slow addition of acetyl chloride to ice-cooled dry methanol (1:5 ratio/vol)), diluted with $Et_2O$ (20 mL), and washed with $NaHCO_3$. The aqueous layer was re-extracted with $Et_2O$ (3 x 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a yellow solid. The crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane). Pure fractions were evaporated to dryness to afford 2-(cuban-1-yl)acetic acid (0.16 g, 60 %) as a white solid. **m.p.:** 139-141 °C (lit.[5] 141-142 °C); **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.08 – 3.99 (m, 1H), 3.95 – 3.90 (m, 3H), 3.90 – 3.85 (m, 3H), 2.74 – 2.63 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) 177.3, 54.2, 49.2, 48.5, 44.5, 38.2. Data in accordance with the literature.[5]

**2-(Cuban-1-yl)-2-hydroxyacetic acid (9)**



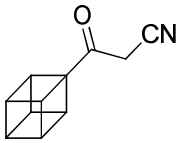

To a solution of 2,2-dibromo-1-(cuban-1-yl)ethanone (50.0 mg, 0.16 mmol) was slowly added 20% aqueous sodium hydroxide (0.82 mL, 1.64 mmol). The resulting solution was stirred at 0 °C for 20 minutes and at room temperature over night. The reaction mixture was then extracted with $Et_2O$ (3 x 5 mL) and the aqueous layer was acidified with concentrated HCl and extracted with DCM (3 x 10 mL). The organic phases were dried ($MgSO_4$), filtered and evaporated to afford yellow residue. The crude product was purified by flash silica chromatography, (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford 2-(cuban-1-yl)-2-hydroxyacetic acid (20.0 mg, 68%) as a white solid. **m.p.:** 114-115 °C; **$^1$H NMR** (400 MHz, DMSO, 27 °C) δ 4.06 (s, 1H), 3.99 – 3.93 (m, 1H), 3.92 – 3.87 (m, 3H), 3.87 – 3.81 (m, 3H); **$^{13}$C NMR** (101 MHz, DMSO, 27 °C) δ 173.5, 70.3, 58.1, 47.2, 46.6, 43.4; **HRMS** ($ESI^-$) Calcd for $C_{10}H_9O_3$ M-$H^+$ 177.0557 (100%), Found 177.0560; **IR** (neat $cm^{-1}$): 3525, 3448, 3413, 2977, 2364, 1685, 1257, 1172, 1041, 968.

**4-(Cuban-1-yl)-2-methyl-1H-imidazole (10)**



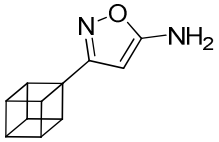

To a solution of 2,2-dibromo-1-(cuban-1-yl)ethanone (0.10 g, 0.33 mmol) in toluene (6 mL) at room temperarture, acetaldehyde (18.0 µL, 0.33 mmol) was added under nitrogen. The resulting solution was stirred at room temperature for 20 minutes and aqueous ammonium hydroxide (28%, 0.36 mL, 2.63 mmol) was added and the reaction mixture was heated at 70 °C for 10 hours. After cooling to room temperature TBME (10 mL) was added and the mixture was stirred for 20 min. The reaction mixture was then extracted with TBME (3 x 10 mL), the combined organic layers were washed with water to pH <8, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford 4-(cubane-1-yl)-2-methyl-1H-imidazole (20.0 mg, 33 %) as a light yellow solid. **m.p.:** 85-86 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 9.14 (br s, 1H), 6.62 (s, 1H), 4.12 – 4.05 (m, 3H), 4.05 – 4.01 (m, 1H), 3.98 – 3.92 (m, 3H), 2.39 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 144.8, 137.7, 115.9, 53.3, 51.0, 48.4, 44.7, 13.9; **HRMS** ($ESI^+$) Calcd for $C_{12}H_{13}N_2$ $[M+H]^+$ 185.1073 Found 185.1073 (100%); **IR** (neat $cm^{-1}$): 3157, 2975, 2921, 2358, 1633, 1413, 1216, 1114, 838, 754, 732.

**3-(Cuban-1-yl)-3-oxopropanenitrile (14)**



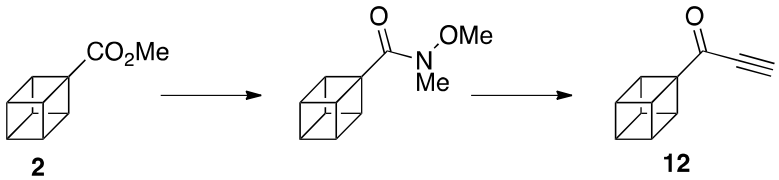
To a stirred solution of methyl cubane-1-carboxylate (0.50 g, 3.08 mmol) in acetonitrile (0.322 mL, 6.17 mmol) cooled to -78 °C, a freshly prepared solution of lithium diisopropylamide (3.55 mL, 7.09 mmol) ) in THF (10 mL) was added over a period of 10 minutes under nitrogen. The resulting solution was stirred at -78 °C for 20 minutes and warmed up to room temperature over 2 hours. The reaction mixture was quenched with 2 M HCl (2 mL), extracted with EtOAc (3 x 20 mL), the organic layers were dried ($MgSO_4$), filtered and evaporated to afford a yellow residue. The crude product was purified by flash silica chromatography (elution gradient 0 to 30 % EtOAc in heptane). Pure fractions were evaporated to dryness to afford 3-(cuban-1-yl)-3-oxopropanenitrile (0.46 g, 87 %) as a yellow solid which gradually turned dark brown. **m.p.:** 82 – 84 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.46 – 4.39 (m, 3H), 4.13 – 4.01 (m, 4H), 3.43 (s, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 194.8, 113.5, 63.6, 50.3, 47.9, 45.2, 27.9; **HRMS** ($EI^+$) Calcd for $C_{11}H_9NO$ $[M]^+$ 171.0684, Found 171.0681; **IR** (neat $cm^{-1}$): 3525, 2966, 2858, 2777, 2399, 1677, 1311, 1187, 964, 759.

**3-(Cuban-1-yl)isoxazol-5-amine (13a)**

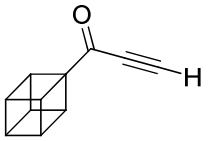



To a solution of 3-(cuban-1-yl)-3-oxopropanenitrile (0.100 g, 0.58 mmol) and sodium hydroxide (49.0 mg, 1.23 mmol) in water (1 mL), a solution of hydroxylamine sulfate (0.105 g, 0.64 mmol) in water (1 mL) was added at room temperature. The resulting solution was stirred at 100 °C for 2 hours. After cooling the reaction mixture was extracted with DCM (3 x 10 mL), the organic layers were dried ($Na_2SO_4$), filtered and evaporated to afford yellow solid. The crude product was purified by flash silica chromatography, elution gradient 0 to 30 % EtOAc in heptane. Pure fractions were evaporated to dryness to afford 3-(cuban-1-yl)-3-oxopropanenitrile (50.0 mg, 46 %) as a white solid. **m.p.:** 136 – 137 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.96 (s, 1H), 4.57 (br s, 2H), 4.21 – 4.14 (m, 3H), 4.07 – 3.97 (m, 4H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 168.7, 166.2, 77.6, 52.2, 50.5, 48.3, 45.3; **HRMS** ($ESI^+$) 115.0542 (100%) Calcd for $C_{11}H_{11}ON_2$ $[M+H]^+$ 187.0866, Found 187.0865 (35); **IR** (neat $cm^{-1}$): 3444, 3295, 3240, 3153, 2359, 1633, 1583, 1461, 966, 883, 837, 734.

Compound **12** was prepared from compound 2 according to the following route.



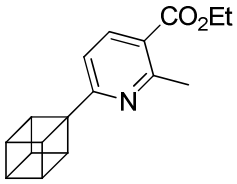

**1-(Cuban-1-yl)prop-2-yn-1-one (12)**




To a solution of N,O-dimethylhydroxylamine hydrochloride (1.35 g, 13.87 mmol) and methyl cubane-1-carboxylate (1.50 g, 9.25 mmol) in THF (22 mL) cooled to -40 °C, isopropylmagnesium chloride (2.0 M in THF, 9.25 mL, 18.50 mmol) was added over a period of 10 minutes under nitrogen. The resulting solution was stirred at -30 °C for 2 hours. The reaction mixture was quenched with saturated $NH_4Cl$ (20 mL), extracted with $Et_2O$ (3 x 20 mL), the organic layer was dried ($Na_2SO_4$), filtered and evaporated to afford N-methoxy-N-methylcubane-1-carboxamide (1.55 g, 88 %) as a white solid. **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) 4.27 (m. 3H), 4.03 – 3.96 (m, 4H), 3.70 (s, 3H), 3.18 (s, 3H), 3.70 (s, 3H). *n*-Butyllithium (0.90 mL, 1.44 mmol) was added to ethynyltrimethylsilane (0.20 mL, 1.44 mmol) in THF (5 mL) cooled to -78 °C, over a period of 5 minutes under nitrogen. The mixture was stirred for 10 min and then added dropwise to the N-methoxy-N-methylcubane-1-carboxamide (0.25 g, 1.31 mmol) solution in THF (5 mL) at -30 °C. The resulting solution was stirred at -30 °C for 20 minutes and allowed to warm up to room temperature over 2 hours. The reaction mixture was poured onto

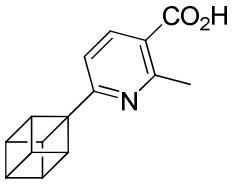
ice cold water (10 mL), extracted with heptane (3 x 20 mL), the organic layers were dried ($MgSO_4$), filtered and evaporated to afford a yellow residue. The crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane). Pure fractions were evaporated to dryness to afford 1-(cuban-1-yl)prop-2-yn-1-one (0.20 g, 98 %) as a white solid. **m.p.:** 69 – 70 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.44 – 4.35 (m, 3H), 4.06 – 3.98 (m, 4H), 3.23 (s, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 185.0, 79.8, 79.5, 64.2, 49.9, 48.4, 45.1; **HRMS** ($EI^+$) 128.0607 (100 %); Calcd for $C_{11}H_8O$ $[M]^+$ 156.0570, Found 156.0580 (12); **IR** (neat $cm^{-1}$): 3212, 2993, 2966, 2087, 1686, 1647, 1311, 1223, 1165, 987, 845, 748, 721.

**Ethyl 6-(cuban-1-yl)-2-methylnicotinate**



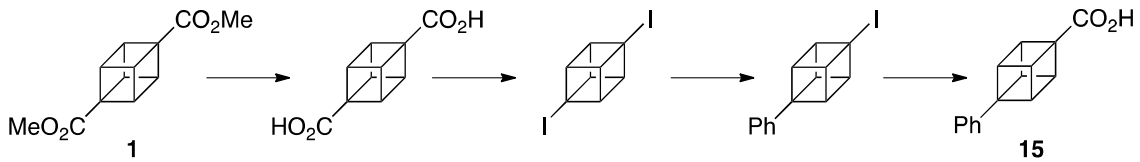

A solution of ethyl 3-aminobut-2-enoate (81.0 µL, 0.64 mmol) and 1-(cuban-1-yl)-3-prop-2-yn-1-one (0.10 g, 0.64 mmol) were dissolved in ethanol (3 mL) and sealed into a microwave tube. The reaction was heated to 60 °C for 2 hours in the microwave reactor and monitored by LCMS for the consumption of starting material. After starting material was fully consumed the temperature was increased to 100 °C and the reaction was stirred for 16 hours. Upon completion, solvent was evaporated and the crude product was purified by flash silica chromatography (elution gradient 0 to 20% EtOAc in heptane). Pure fractions were evaporated to dryness to afford ethyl 6-(cuban-1-yl)-2-methylnicotinate (0.132 g, 77 %) as a white solid. **m.p.:** 83 – 84 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.33 – 4.28 (m, 3H), 4.14 – 4.05 (m, 4H), 2.83 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 167.0, 164.9, 160.0, 138.7, 122.5, 116.9, 61.1, 60.7, 51.1, 48.5, 44.7, 25.4, 14.5; **HRMS** ($ESI^+$) 240.1017 (100%); Calcd for $C_{17}H_{18}O_2N$ $[M+H]^+$ 268.1332, Found 268.1333 (30); **IR** (neat $cm^{-1}$): 3525, 2977, 2939, 1701, 1585, 1554, 1434, 1381, 1281, 1173, 1138, 852, 783, 737.

**6-(Cuban-1-yl)-2-methylnicotinic acid (11)**

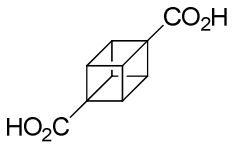



To a solution of ethyl 6-(cuban-1-yl)-2-methylnicotinate (70.0 mg, 0.26 mmol) in THF (2 mL) was added sodium hydroxide in MeOH (1.0 M, 0.77 mL, 0.79 mmol) at room temperature. After 12 hours at room temperature, the reaction mixture was evaporated to dryness, re-dissolved in DCM and neutralised with 2 M HCl. The crude mixture was extracted with DCM (3 x 10 mL), the organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford 6-(cuban-1-yl)-2-methylnicotinic acid (60.0 mg, 95 %) as a white solid. **m.p.:** 215 – 217 °C; **$^1$H NMR** (400 MHz, DMSO, 27 °C) δ 7.87 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 4.22 – 4.17 (m, 3H), 4.12 – 4.05 (m, 1H), 4.04 – 3.97 (m, 3H), 2.65 (s, 3H); **$^{13}$C NMR** (101 MHz, DMSO, 27 °C) δ 171.4, 158.7, 156.1, 136.9, 133.2, 115.9, 59.9, 49.9, 47.3, 43.4, 24.3; **HRMS** ($ESI^+$) 175.0629 (100%); Calcd for $C_{15}H_{14}O_2N$ $[M+H]^+$ 240.1019, Found 240.1020 (90); **IR** (neat $cm^{-1}$): 3484, 3336, 2979, 1587, 1564, 1513, 1394, 1213, 1103, 846, 798.

Compound 15 was prepared using a minor modification of the literature route.[1, 7, 8]

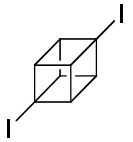


**Cubane-1,4-dicarboxylic acid[1] (18)**



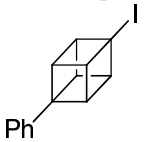

To a solution of dimethyl-1,4-cubanedicarboxylate (5.00 g, 22.7 mmol) in MeOH (123 mL) was added a solution of methanolic sodium hydroxide (2.0 M, 56.8 mmol, 28.4 mL) at room temperature. The resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and redissolved in water (50 mL), and extracted with DCM (3 x 30 mL). The aqueous layer from the extraction was acidified with concentrated HCl to pH ~1, the white suspension formed was filtered, washed with a small volume of water and thoroughly dried under reduced pressure to afford cubane-1,4-dicarboxylic acid (4.20 g, 96 %) as a white solid. **m.p.:** 224-226 °C dec (lit.[3] 225 °C dec.); **$^1$H NMR** (400 MHz, MeOD, 30 °C) δ 4.19 (6H, s). Data in accordance with the literature.

**1,4-Diidodocubane[7]**



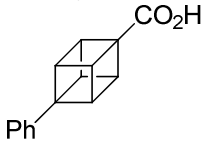

To a stirred suspension of (cubane-1,4-dicarboxylic acid (5.0 g, 26.0 mmol) in anhydrous benzene (100 mL) were added iodobenzene diacetate (26.0 g, 80.7 mmol) and iodine (21.1 g, 83.3 mmol) at room temperature. The resulting purple mixture was heated under reflux for 6 hours. The solution was cooled and washed with aqueous saturated $Na_2SO_3$ (2 x 50 mL), water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to give a crude mixture. Trituration with cold hexane dissolved away the iodobenzene and left pure iodocubane as a white solid. Flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane) of the iodobenzene phase afforded more of the iodocubane, giving in total 1,4-diiodocubane (6.35 g, 69 %) as a white solid. **m.p.:** 225 °C dec (lit.[9] 226-227 °C dec.);**$^1$H NMR** (400 MHz, $CDCl_3$, 30 °C) δ 4.40 (6H, s). Data in accordance with the literature.[7]

**1-Iodo-4-phenylcubane[7]**




To a stirred solution of bromobenzene (2.10 mL, 19.4 mmol) in diethyl ether (135 mL) was added *tert*-butyllithium (24.20 mL, 38.8 mmol) dropwise at -78 °C. The resulting pale yellow solution was allowed to reach room temperature and was then cooled to 0 °C. Solid, powdered ,4-diiodocubane (4.60 g, 12.9 mmol) was added all at once. The cooling bath was removed and the mixture stirred for 40 min at room temperature. The resulting yellow homogenous solution was cooled to -20 °C and quenched with MeOH. The reaction mixture was diluted with $Et_2O$ (50 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, (elution gradient 0 to 10% EtOAc in heptane.) Pure fractions were evaporated to dryness to afford 1-iodo-4-phenylcubane (3.50 g, 88 %) as a white solid. **m.p.:** 86-87 °C (lit.[7] 85-86 °C); **$^1$H NMR** (400 MHz, $CDCl_3$, 30 °C) δ 7.36 (m, 2H), 7.23 – 7.15 (m, 3H), 4.32 (s, 6H). Data in accordance with the literature.[7]

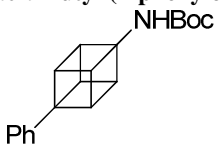
**4-Phenylcubane-1-carboxylic acid[8] (15)**




To a solution of *tert*-butyllithium (8.98 mL, 14.4 mmol) in diethyl ether (20 mL) at -78 °C was added suspension of 1-iodo-4-phenylcubane (2.00 g, 6.53 mmol) in diethyl ether (76 mL), dropwise under nitrogen. The resulting

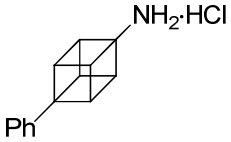
solution was stirred at -78 °C for 10 minutes and warmed up to 0 °C and stirred for 30 minutes. After re-cooling to -78 °C solid carbon dioxide was added at once and the reaction was stirred for 1 h at -78 °C and gradually warmed up to room temperture over 12 hours. The reaction mixture was diluted with 2 M HCl (50 mL) and extracted with chloroform (3 x 100 mL). The organic layer was dried ($Na_2SO_4$), filtered and evaporated to afford crude product. The precipitate was collected by filtration, washed with heptane (50 mL) and dried under vacuum to afford 4-phenylcubane-1-carboxylic acid (1.30 g, 89 %) as a white solid, which was used without further purification. **m.p.:** 180-181 °C (lit.[8] 178-179 °C); **$^1$H NMR** (400 MHz, $CDCl_3$, 30 °C) δ 7.42 - 7.31 (m, 2H), 7.25-7.14 (m, 3H), 4.34-4.25(m, 3H), 4.23-4.09 (m, 3H). Data in accordance with the literature.[8]

***tert*-Butyl (4-phenylcuban-1-yl)carbamate**



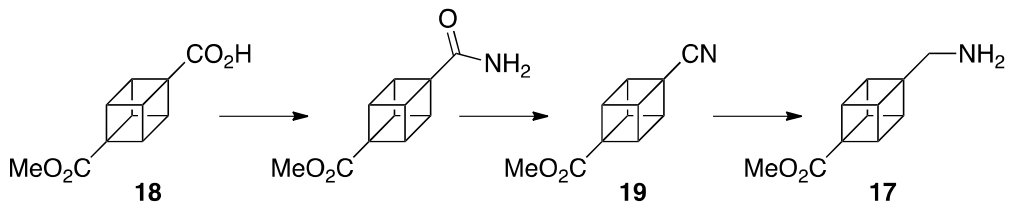

To a solution of 4-phenylcubane-1-carboxylic acid (1.16 g, 5.15 mmol) and triethylamine (0.81 mL, 6.18 mmol) in *tert*-butanol (15 mL) was added diphenyl phosphorylazide (1.22 mL, 5.67 mmol) and the reaction mixture was heated under reflux for 6 h. The solution was then cooled down and quenched with 1 M citric acid (20 mL). The mixture was separated and the aqueous layer was extracted with chloroform (2 x 20 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried ($Na_2SO_4$) and solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography (elution gradient 10 to 40% EtOAc in heptan)e. Pure fractions were evaporated to dryness to afford *tert*-butyl (4-phenylcuban-1-yl)carbamate (1.20 g, 79 %) as a white solid. **m.p.:** 145 – 147 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 30 °C) δ 7.38 – 7.32 (m, 2H), 7.23 – 7.18 (m, 3H), 5.16 (br s, 1H), 4.03 (br s, 6H), 1.48 (br s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 30 °C) δ 143.0, 130.2, 128.5, 126.0, 124.8, 67.3, 60.5, 49.3, 46.3, 28.53; **HRMS** (ESI$^+$) 196.1124 (100%); Calcd for $C_{15}H_{14}O_2N$ $[M+H-C_4H_8]^+$ 240.1019, Found 240.1023 (40); **IR** (neat $cm^{-1}$): 3246, 3119, 2984, 2363, 2147, 1713, 1489, 1364, 1207, 1165, 1093, 918, 750.

**4-Phenylcuban-1-aminehydrochloride (16)**

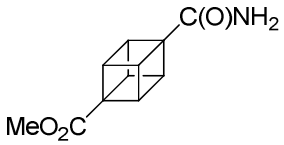



Hydrogen chloride gas was bubbled through a suspension of *tert*-butyl (4-phenylcuban-1-yl)carbamate (3.00 g, 10.15 mmol) in MeOH (200 mL) at -60 °C until the mixture became homogeneous. The solution was then left to warm to room temperature. The methanol was removed under reduced pressure. The residue was filtered and washed with ice-cold ethanol. 4-Phenylcuban-1-amine hydrochloride (1.20 g, 61 %) was isolated as an off-white solid. Small scale synthesis using (50.0 mg, 0.17 mmol) of *tert*-butyl (4-phenylcuban-1-yl)carbamate gave (40.0 mg, 99%) of 4-phenylcuban-1-amine hydrochloride. **m.p.:** 175-178 °C; **$^1$H NMR** (700 MHz, MeOD, 30 °C) δ 7.36 – 7.33 (m, 2H), 7.22 – 7.18 (m, 3H), 4.24 – 4.21 (m, 3H), 4.15 – 4.13 (m, 3H); **$^{13}$C NMR** (176 MHz, MeOD, 30 °C) δ 142.8, 129.6, 127.5, 125.6, 66.9, 62.4, 48.2, 47.8. **HRMS** (ESI$^+$) 178.0779 (100%) Calcd for $C_{14}H_{14}N$ $M^+$ 196.1121, Found 196.1124 (70%); **IR** (neat $cm^{-1}$): 3406, 2985, 2146, 1489, 1221, 1162, 1083, 918, 750.

Compound **17** was prepared from compound 18 according to a literature procedure.[10]

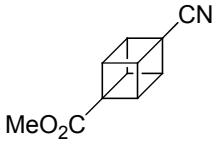



**Methyl 4-carbamoylcubane-1-carboxylate[10]**



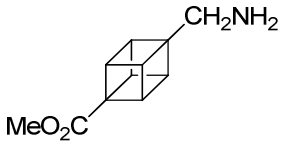

To a solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (3.00 g, 14.6 mmol) in THF (35 mL) at -10 °C was added dropwise a solution of triethylamine (2.23 mL, 16.0 mmol) in THF (10 mL) at -10 °C and a solution of ethyl chloroformate (1.53 mL, 16.0 mmol). The resulting mixture was stirred at for 10 min and ammonia in THF (0.5 M, 364.0 mL, 0.146 mol) was added. The reaction mixture was then stirred at room temperature over night and washed with water (100 mL), 2 M HCl (100 mL), $NaHCO_3$ (100 mL), the organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude methyl 4-carbamoylcubane-1-carboxylate (2.40 g, 80 %) as a white solid. **m.p.:** 235-240 °C dec. (lit.[11] 232-237 °C dec.); **$^1$H NMR** (400 MHz, DMSO, 30 °C) δ 7.24 (s, 1H), 6.92 (s, 1H), 4.10 (s, 6H), 3.62 (s, 3H). Data in accordance with the literature.[10]

**Methyl 4-cyanocubane-1-carboxylate[10] (19)**



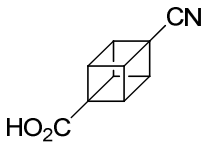

To a solution of methyl 4-carbamoylcubane-1-carboxylate (1.20 g, 5.85 mmol) in 1,2-dichloroethane (42 mL) at room temperature was added dropwise phosphorus oxychloride (2.73 mL, 29.2 mmol). The resulting mixture was heated under reflux for 30 min and then 5% sodium bicarbonate was added slowly. The layers were separated and the organic phase was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and evaporated to give crude product, which was purified by flash silica chromatography (elution gradient 0 to 50% EtOAc in heptane). Pure fractions were evaporated to dryness to afford methyl 4-cyanocubane-1-carboxylate (1.10 g, 99.5 %) as a white solid. **m.p.:** 146-148 °C (lit.[12] 145.5-147 °C); **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.40 - 4.19 (m, 6H), 3.67 (s, 3H). Data in accordance with the literature.[10]

**Methyl 4-(aminomethyl)cubane-1-carboxylate[10] (17)**




A solution of methyl 4-cyanocubane-1-carboxylate (0.40 g, 2.13 mmol) and hydrogen chloride (36.0 µL, 0.213 mmol) in MeOH (70 mL) was hydrogenated in the H-Cube hydrogenation cell using a 30 mm $PtO_2$ cartridge, at 50 °C with a flow rate of 1 mL/min under 50 psi. The solution was concentrated to provide methyl 4-(aminomethyl)cubane-1-carboxylate (0.40 g, 98 %) as a white solid. **m.p.:** 240 °C dec. (lit.[12] 245-255 °C); **$^1$H NMR** (400 MHz, MeOD, 27 °C) δ 4.19 – 4.12 (m, 3H), 4.03 – 3.95 (m, 3H), 3.35 (s, 3H), 3.20 (s, 2H); **$^{13}$C NMR** (101 MHz, MeOD, 27 °C) δ 173.9, 57.7, 56.6, 49.8, 47.4, 46.2, 42.14; **HRMS** ($ESI^+$) Calcd for $C_{11}H_{14}O_2N$ $[M+H]^+$ 192.1019, Found 192.1018 (100%). Data in accordance with the literature.[10]

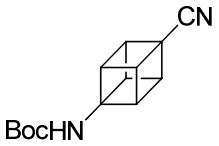
**4-Cyanocubane-1-carboxylic acid[10]**




To a solution of methyl 4-cyanocubane-1-carboxylate (0.40 g, 2.14 mmol) in absolute boiling ethanol (21 mL) was added dropwise a solution of sodium hydroxide (0.11 g, 2.78 mmol) in $H_2O$ (2.0 mL). The resulting mixture was heated under reflux for 2 h and stirred at room temperature over night. The reaction mixture was evaporated to dryness and redissolved in water (20 mL), the solution was filtered, cooled and acidified with 6 N HCl. The precipitated acid was extracted with EtOAc (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and

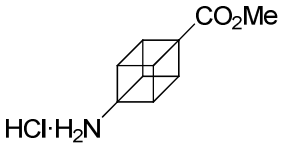
evaporated to afford 4-cyanocubane-1-carboxylic acid (0.33 g, 89 %) as a white solid. **m.p.:** 200-201 °C (lit.[12] 196-202 °C); **$^1$H NMR** (400 MHz, MeOD, 27 °C) δ 4.35 – 4.24 (6H, m). Data in accordance with the literature.[10]

***tert*-Butyl (4-cyanocuban-1-yl)carbamate (20)**



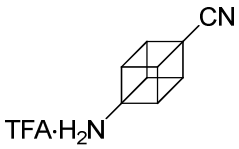

To a solution of 4-cyanocubane-1-carboxylic acid (0.10 g, 0.58 mmol) and triethylamine (90.0 µL, 0.690 mmol) in *tert*-butanol (1.70 mL) was added diphenyl phosphorylazide (0.14 mL, 0.64 mmol) and the reaction mixture was heated under reflux for 5 hours. Upon completion the reaction was allowed to reach room temperature and 1 M citric acid (5 mL) was added followed by chloroform (10 mL). The layers were separated and the aqueous layer was extracted with chloroform (2 x 10 mL). The combined organic phase was washed with water (10 mL) and brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography (elution gradient 10 to 40% EtOAc in heptane). Pure fractions were evaporated to dryness to afford *tert*-butyl (4-cyanocuban-1-yl)carbamate (0.13 g, 95 %) as a white solid. **m.p.:** 202 – 203 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 30 °C) δ 5.02 (br s, 1H), 4.21 (br s, 3H), 4.15 (br s, 3H), 1.45 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 30 °C) δ 153.9, 119.1, 80.3, 66.2, 51.3, 45.2, 40.2, 28.5; **HRMS** ($EI^+$) 41.0407 (100%); Calcd for $C_9H_7N_2$ $[M\text{-}C_4H_8O\text{-}CO]^+$ 143.0604, Found 144.0602 (10); **IR** (neat $cm^{-1}$): 3412, 3242, 3117, 2989, 2218, 1699, 1362, 1338, 1163, 1057, 839, 779.

**4-(Methoxycarbonyl)cubane-1-amine hydrochloride (22)**



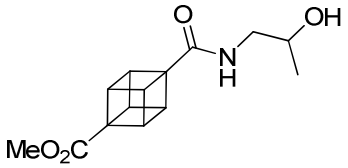

Through a suspension of *tert*-butyl (4-cyanocuban-1-yl)carbamate (0.45 g, 1.84 mmol) in MeOH (12 mL) at -60 °C hydrochloric acid gas was bubbled for 1 hour until the mixture became homogeneous. The solution was then left to warm to room temperature and methanol was removed under reduced pressure. The residue was washed with ice-cold ether to give methyl 4-(methoxycarbonyl)cubane-1-amine hydrochloride (0.31 g, 79 %) as off-white solid. **m.p.:** 195 – 197 °C dec. (190 °C browned); **$^1$H NMR** (400 MHz, DMSO, 30 °C) δ 7.27 (br s, 2H), 4.12 – 4.07 (m, 6H), 3.63 (s, 3H); **$^{13}$C NMR** (176 MHz, DMSO, 30 °C) δ 171.0, 64.2, 55.3, 51.2, 47.7, 44.4; **HRMS** ($ESI^+$) Calcd for $C_{10}H_{12}NO_2$ $M^+$ 178.0863, Found 178.0861 (100%); **IR** (neat $cm^{-1}$): 3525, 3001, 2866, 2816, 2415, 1728, 1709, 1547, 1300, 1176, 1095, 964, 833.

**4-Aminocubane-1-carbonitrile trifluoroacetic acid salt (21)**



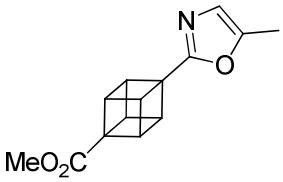

A solution of trifluoroacetic acid (10% in DCM) (11.02 mL) was added to *tert*-butyl (4-cyanocuban-1-yl)carbamate (0.28 g, 1.15 mmol) at room temperature. The resulting solution was stirred at RT for 2 hours. The reaction mixture was concentrated and diluted with DCM (15 mL), and washed sequentially with saturated $NaHCO_3$ (15 mL), and saturated brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. **$^1$H NMR** (400 MHz, $CDCl_3$, 30 °C) δ 4.13 – 4.07 (3H, m), 3.92 – 3.84 (3H, m); **HRMS** ($ESI^+$) Calcd for $C_9H_9N_2$ $M^+$: Calc. 145.0760, Found 145.0759 (100%).

**Methyl 4-((2-hydroxypropyl)carbamoyl)cubane-1-carboxylate (24)**



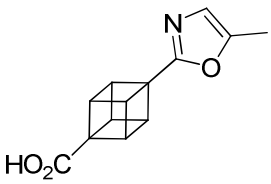
A solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (9.50 g, 46.07 mmol), 1-hydroxybenzotriazole hydrate (7.06 g, 46.07 mmol), and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (17.66 g, 92.15 mmol) in DCM (197 mL) was stirred at 0 °C for 30 minutes, and 1-amino-2-propanol (3.56 mL, 46.07 mmol) was added. The resulting mixture was stirred at 0 °C for 2 hours and at room temperature over night. The reaction mixture was quenched with water (100 mL), extracted with DCM (3 x 100 mL), the combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford a crude white residue. The crude product was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford methyl 4-((2-hydroxypropyl)carbamoyl)cubane-1-carboxylate (9.25 g, 76 %) as a white solid. **m.p.:** 138 – 139 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 6.18 (t, *J* = 5.1 Hz, 1H), 4.26 – 4.11 (m, 6H), 3.95 – 3.83 (m, 1H), 3.69 (s, 3H), 3.44 (ddd, *J* = 13.9, 6.6, 3.0 Hz, 1H), 3.16 (d, *J* = 3.6 Hz, 1H), 3.10 (ddd, *J* = 13.9, 7.8, 5.1 Hz, 1H), 1.17 (d, *J* = 6.3 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 174.4, 172.1, 67.4, 57.8, 55.9, 51.8, 47.1, 46.9, 46.8, 21.1; **HRMS** ($ESI^+$) Calcd for $C_{14}H_{18}O_4N$ $[M + H]^+$ 264.1230, Found 264.1231 (100%); **IR** (neat $cm^{-1}$): 3527, 2394, 1710, 1630, 1170, 1041, 966.

**Methyl 4-(5-methyloxazol-2-yl)cubane-1-carboxylate**



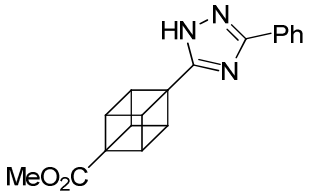
Dess-Martin periodinane (16.32 g, 38.48 mmol) was added portionwise to methyl 4-((2-hydroxypropyl)carbamoyl)cubane-1-carboxylate (9.21 g, 34.98 mmol) in DCM (327 mL) at room temperature. The resulting solution was stirred at room temperature for 30 minutes. The reaction mixture was diluted with $Et_2O$ (100 mL) and poured into saturated $NaHCO_3$ (100 mL) containing sodium thiosulfate (38.74 g, 0.245 mol). The resulting suspension was stirred vigorously for 10 minutes, before separating the layers. The organic layer was washed with water (100 mL), dried ($Na_2SO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford methyl 4-((2-oxopropyl)carbamoyl)cubane-1-carboxylate (6.20 g, 68 %) as a white solid. **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) ) δ 6.25 (s, 1H), 4.25 – 4.19 (m, 6H), 4.18 (d, *J* = 4.6 Hz, 2H), 3.70 (s, 3H), 2.21 (s, 3H). To a solution of methyl 4-((2-oxopropyl)carbamoyl)cubane-1-carboxylate (5.60 g, 21.43 mmol) in dichloroethane (65 mL) at room temperature was added dropwise phosphorus oxychloride (100 mL, 1.072 mol). The resulting mixture was heated under reflux for 90 minutes. After cooling to 0 °C, the reaction was carefully quenched with 2 M NaOH (100 mL) and DCM was added. The layers were separated and the organic phase was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to give crude product, which was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford methyl 4-(5-methyloxazol-2-yl)cubane-1-carboxylate (4.95 g, 95 %) as a white solid. **m.p.:** 62 – 63 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 6.68 (d, *J* = 1.2 Hz, 1H), 4.37 – 4.23 (m, 6H), 3.73 (s, 3H), 2.30 (d, *J* = 1.2 Hz, 3H); **$^{13}$C NMR** δ (101 MHz, $CDCl_3$, 27 °C) δ 172.3, 162.2, 148.8, 123.1, 56.1, 52.6, 51.8, 48.0, 47.2, 11.1; **HRMS** ($ESI^+$) 184.0757 (100%); Calcd for $C_{14}H_{14}O_3N$ $[M+H]^+$ 244.0968, Found 244.0968 (15); **IR** (neat $cm^{-1}$): 3529, 2997, 2407, 1720, 1435, 1319, 1215, 1169, 1088, 964.

**4-(5-Methyloxazol-2-yl)cubane-1-carboxylic acid (23)**



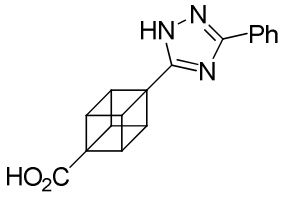
To a solution of methyl 4-(5-methyloxazol-2-yl)cubane-1-carboxylate (4.95 g, 20.35 mmol) in THF (68 mL) at room temperature, sodium hydroxide (1.22 g, 30.52 mmol) in MeOH (14 mL) was added over a period of 20 minutes. The resulting suspension was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and redissolved in water (50 mL), and extracted with heptane (50 mL). The aqueous layer was acidified with concentrated HCl to pH ~4 and extracted with DCM (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford 4-(5-methyloxazol-2-yl)cubane-1-carboxylic acid (3.78 g, 81 %) as a white solid. **m.p.:** 175 – 177 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 6.71 (d, *J* = 1.2 Hz, 1H), 4.35 (s, 6H), 2.30 (d, *J* = 1.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 176.4, 162.4, 148.9, 122.7, 56.1, 52.5, 48.0, 47.2, 11.0; **HRMS** ($ESI^+$) 184.0756 (100%); Calcd for $C_{13}H_{12}O_3N$ $[M+H]^+$ 230.0812, Found 230.0812; **IR** (neat $cm^{-1}$): 3583, 3525, 3448, 3097, 3004, 2943, 2773, 2399, 1689, 1554, 1292, 1169, 1041, 968.

**Methyl 4-(3-phenyl-1H-1,2,4-triazol-5-yl)cubane-1-carboxylate (25)**



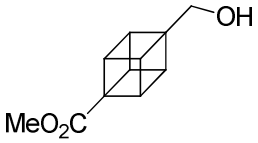

To a stirred solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (0.20 g, 0.97 mmol), 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.44 g, 1.16 mmol) and benzamidine (0.14 g, 1.16 mmol) in DCM (4 mL) at room temperature was added DIPEA (0.51 mL, 2.91 mmol) under nitrogen. The resulting solution was stirred at room temperature for 3 hours. Upon consumption of the starting material, as indicated by TLC, hydrazine hydrochloride (0.10 g, 1.45 mmol) and acetic acid (56.0 µL, 0.97 mmol) were added to the reaction mixture which then was heated under reflux for 5 h. After consumption of intermediate the reaction mixture was diluted with EtOAc and extracted once with saturated $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford methyl 4-(3-phenyl-1H-1,2,4-triazol-5-yl)cubane-1-carboxylate (0.12 g, 41%) as a white solid. **m.p.:** 180 – 182 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 8.03 – 7.97 (m, 2H), 7.46 – 7.39 (m, 3H), 4.37 – 4.33 (m, 3H), 4.33 – 4.27 (m, 3H), 3.73 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 172.4, 160.9, 159.7, 129.9, 129.7, 128.9, 126.7, 56.1, 52.4, 51.8, 48.3, 47.3; **HRMS** ($ESI^+$) Calcd for $C_{18}H_{16}O_2N_3$ $[M+H]^+$ 306.1243, Found 306.1240 (100%); **IR** (neat $cm^{-1}$): 3446, 3001, 2983, 2359, 2332, 1697, 1333, 1267, 1223, 1159, 930, 843.

**4-(3-Phenyl-1H-1,2,4-triazol-5-yl)cubane-1-carboxylic acid (26)**



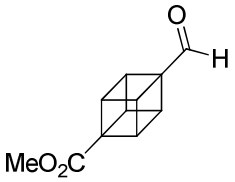

To a solution of methyl 4-(3-phenyl-1H-1,2,4-triazol-5-yl)cubane-1-carboxylate (0.10 g, 0.33 mmol) in THF (3 mL) was added dropwise a solution of sodium hydroxide in methanol (0.98 mL, 0.98 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was evaporated to dryness, redissolved in water (10 mL), and extracted with DCM (3 x 10 mL). The aqueous layer was carefully acidified with concentrated HCl to pH ~4. The white precipitate so formed was filtered and dried under reduced pressure to give 4-(3-phenyl-1H-1,2,4-triazol-5-yl)cubane-1-carboxylic acid (98.0 mg, 100 %) as a white solid. **m.p.:** 162 – 163 °C; **$^1$H NMR** (700 MHz, DMSO, 30 °C) δ 13.81 (s, 1H), 12.34 (s, 1H), 8.00 (d, *J*=7.3, 2H), 7.5 – 7.36 (m, 3H), 4.32 – 4.20 (m, 6H); **$^{13}$C NMR** (176 MHz, DMSO, 30°C) δ 172.4, 161.2, 156.5, 131.4, 128.6, 125.8, 55.6, 48.5, 47.2, 46.1; **HRMS** ($ESI^+$) Calcd for $C_{17}H_{14}O_2N_3$ $[M+H]^+$ 292.1081, Found 292.1081 (100%); **IR** (neat $cm^{-1}$): 3441, 2993, 2758, 1682, 1566, 1470, 1435, 1400, 1265, 1192, 930, 737.

**Methyl 4-(hydroxymethyl)cubane-1-carboxylate[13]**



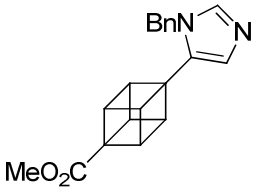

To a solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (0.20 g, 0.97 mmol) in THF (10 mL) at -10 °C was added dropwise a solution of triethylamine (0.15 mL, 1.07 mmol) in THF (2 mL) and ethyl chloroformate (0.10 mL, 1.07 mmol). The resulting mixture was stirred at -10 °C for 30 min and sodium borohydride (81.0 mg, 2.13 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 6 hours, when a further aliquot of sodium borohydride (81.0 mg, 2.13 mmol) was added and the stirring continued overnight. The reaction mixture was quenched with saturated $NH_4Cl$ (5 mL), extracted with $Et_2O$ (3 x 10 mL), the organic layer was dried ($Na_2SO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 50% EtOAc in heptane). Pure fractions were evaporated to dryness to afford methyl 4-(hydroxymethyl)cubane-1-carboxylate (0.15 g, 80 %) as a colourless solid. **m.p.:** 87-89 °C (lit.[11] 86-90 °C); **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.18 – 4.10 (m, 3H), 3.94 – 3.83 (m, 3H), 3.77 (s, 2H), 3.70 (s, 3H). Data in accordance with the literature.[13]

**Methyl 4-formylcubane-1-carboxylate[13] (27)**




Dess-Martin periodinane (1.43 g, 3.38 mmol) was added portionwise to methyl 4-(hydroxymethyl)cubane-1-carboxylate (0.59 g, 3.07 mmol) in DCM (29 mL) at room temperature. The resulting solution was stirred at room temperature for 30 minutes. The reaction mixture was diluted with $Et_2O$ (20 mL) and poured into saturated $NaHCO_3$ (20 mL) containing sodium thiosulfate (3.4 g, 21.5 mmol). The resulting suspension was stirred vigourously for 10 minutes, before separating the layers. The organic layer was washed with water (20 mL), dried ($Na_2SO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 50% EtOAc in heptane). Pure fractions were evaporated to dryness to afford methyl 4-formylcubane-1-carboxylate (0.525 g, 90 %) as a colourless solid. **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 9.75 (s, 1H), 4.41 – 4.33 (m, 3H), 4.30 - 4.23 (m, 3H), 3.72 (s, 3H). Data in accordance with the literature.[13]

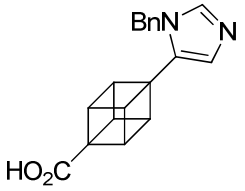
**Methyl 4-(1-benzyl-1H-imidazol-5-yl)cubane-1-carboxylate**




A solution of methyl 4-formylcubane-1-carboxylate (50.0 mg, 0.26 mmol) and benzylamine (63.0 µL, 0.58 mmol) in DMF (1 mL) was stirred at ambient temperature for 2 hours. Upon consumption of starting material, as indicated by TLC, 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (34.0 mg, 0.17 mmol) and potassium carbonate (36.0 mg, 0.26 mmol) were added. The solution was stirred at 25 °C, over a period of 16 hours. The reaction mixture was diluted with EtOAc and poured onto water (10 mL). The organic layer was washed with water (1 x 15 mL), saturated $NaHCO_3$ (1 x 15 mL) and dried ($Na_2SO_4$), filtered and evaporated to afford white solid. The crude product was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford methyl 4-(1-benzyl-1H-imidazol-5-yl)cubane-1-carboxylate (22.0 mg, 27 %) as a lightly yellow solid. **m.p.:** 136 – 137 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 7.53 (d, *J* = 1.0 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.04 (dd, *J* = 5.5, 2.4 Hz, 2H), 6.82 (d, *J* = 1.0 Hz, 1H), 5.04 (s, 2H), 4.13 – 4.08 (m, 3H), 3.90 – 3.84 (m, 3H), 3.69 (s, 3H); **$^{13}$C NMR** δ (101 MHz, $CDCl_3$, 27 °C) 172.4, 139.2, 136.6, 131.7, 129.1, 128.4, 126.9, 126.6, 55.8, 52.2, 51.7, 49.5, 48.2, 46.5; **HRMS** ($ESI^+$) Calcd for $C_{20}H_{19}O_2N_2$

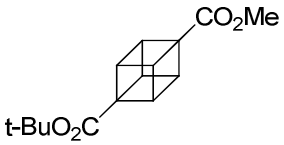
$[M+H]^+$ 319.1441, Found 319.1440 (100%); **IR** (neat $cm^{-1}$): 3448, 2991, 2951, 2359, 2341, 1720, 1435, 1323, 1217, 1090, 723.

**4-(1-Benzyl-1H-imidazol-5-yl)cubane-1-carboxylic acid (28)**



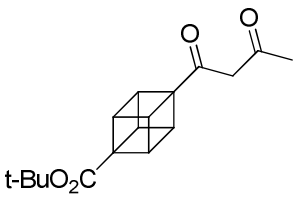

To a solution of methyl 4-(1-benzyl-1H-imidazol-5-yl)cubane-1-carboxylate (10.0 mg, 0.03 mmol) in THF (0.20 mL) was added sodium hydroxide in MeOH (1.0 M, 94.0 µL, 0.09 mmol). The reaction mixture was stirred over night at room temperature. The reaction mixture was evaporated to dryness and re-dissolved in DCM (2 mL), quenched with 2 M HCl, extracted with DCM (3 x 10 mL), the organic layers were dried ($Na_2SO_4$), filtered and evaporated to afford lightly yellow solid. The crude product was purified by trituration with cold ether to afford 4-(1-benzyl-1H-imidazol-5-yl)cubane-1-carboxylic acid (8.0 mg, 84%) as a lightly yellow solid. **m.p.:** 148 – 150 °C; **$^1$H NMR** (400 MHz, MeOD, 27 °C) δ 7.70 (s, 1H), 7.39 - 7.25 (m, 3H), 7.09 (d, *J* = 7.1 Hz, 2H), 6.75 (s, 1H), 5.17 (s, 2H), 4.02 – 3.95 (m, 3H), 3.82 – 3.74 (m, 3H).; **$^{13}$C NMR** (176 MHz, MeOD, 27 °C) δ 181.3, 140.2, 138.5, 134.3, 129.9, 129.0, 127.7, 126.0, 60.6, 50.2, 49.8, 48.6, 47.9.; **HRMS** ($ESI^+$) Calcd for $C_{19}H_{17}O_2N_2$ $[M+H]^+$ 305.1285, Found 305.1291; **IR** (neat $cm^{-1}$): 3448, 3334, 2991, 2950, 2358, 2341, 1720, 1634, 1323, 1199, 1111, 922, 819.

**1-*tert*-Butyl 4-methyl cubane-1,4-dicarboxylate**




To a stirred solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (0.50 g, 2.42 mmol), di-*tert*-butyl dicarbonate (1.06 g, 4.85 mmol) in *tert*-butanol (24 mL) at room temperature, 4-dimethylaminopyridine(2.96 mg, 0.02 mmol) was added under nitrogen. The resulting solution was stirred at room temperature for 12 hours. Upon consumption of starting material, solvent was evaporated and the crude product was purified by flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane). Pure fractions were evaporated to dryness to afford 1-*tert*-butyl 4-methyl cubane-1,4-dicarboxylate (0.42 g, 66.0 %) as a white solid. **m.p.:** 69 -70 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.24 – 4.18 (m, 3H), 4.18 – 4.12 (m, 3H), 3.71 (s, 3H), 1.46 (s, 9H); **$^{13}$C NMR** (176 MHz, $CDCl_3$, 30 °C) δ 171.9, 102.1, 80.4, 57.5, 53.6, 48.6, 46.9, 28.3, 12.3; **HRMS** ($EI^+$) Calcd for $C_{14}H_{15}O_3$ $[M-CH_3O]^+$ 231.1016, Found 231.1007; **IR** (neat $cm^{-1}$): 2978, 2935, 1701, 1454, 1327, 1230, 1203, 1146, 1092, 845, 725.

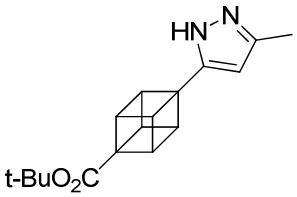
***tert*-Butyl 4-(3-oxobutanoyl)cubane-1-carboxylate (30)**




A solution of 1-*tert*-butyl 4-methyl cubane-1,4-dicarboxylate (0.36 g, 1.37 mmol) in THF (4 mL) was added to a freshly prepared solution of lithium diisopropylamide (1.51 mL, 3.02 mmol) and propan-2-one (0.20 mL, 2.74 mmol) in THF (4 mL) cooled to -78 °C, over a period of 10 minutes under nitrogen. The resulting solution was stirred at -78 °C for 20 minutes and warmed up to room temperature over 2 hours. The reaction mixture was

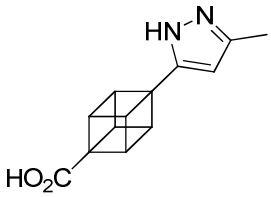
quenched with 2M HCl, extracted with EtOAc (3 x 20 mL), the organic layers were dried ($MgSO_4$), filtered and evaporated to afford yellow residue. The crude product was purified by flash silica chromatography, elution gradient 0 to 50 % EtOAc in heptane. Pure fractions were evaporated to dryness to afford *tert*-butyl 4-(3-oxobutanoyl)cubane-1-carboxylate (0.16 g, 42 %) as an off-white solid. **m.p.:** 75 – 77 °C; contains enol **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 5.43 (s, 1H), 4.11 (s, 6H), 2.04 (s, 3H), 1.41 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 194.1, 188.8, 171.3, 97.4, 80.6, 59.1, 57.3, 47.3, 46.9, 28.3, 25.9; **HRMS** ($EI^+$) 232.0759 (100%); Calcd for $C_{17}H_{20}O_4$ $[M]^+$ 288.1356, Found 288.1355 (5); **IR** (neat $cm^{-1}$): 3514, 2985, 2931, 1713, 1597, 1369, 1331, 1227, 1161, 1092, 840.

***tert*-Butyl 4-(3-methyl-1H-pyrazol-5-yl)cubane-1-carboxylate**



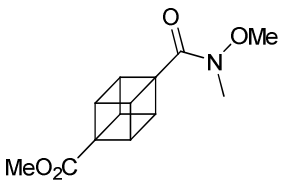

To a solution of *tert*-butyl 4-(3-oxobutanoyl)cubane-1-carboxylate (0.13 g, 0.47 mmol) in ethanol (2 mL) and THF (1 mL) was added acetic acid (0.54 mL, 9.36 mmol). The reaction mixture was stirred for 5 minutes at room temperature, when hydrazine hydrate (0.23 mL, 4.68 mmol) was added and temperature was increased to 70 °C. After 10 minutes the reaction mixture was cooled down and quenched with 2 M NaOH (2 mL), extracted with EtOAc (3 x 10 mL), the combined organic layer was dried ($Na_2SO_4$), filtered and evaporated to afford *tert*-butyl 4-(3-methyl-1H-pyrazol-5-yl)cubane-1-carboxylate (0.12 g, 90%) as a lightly yellow solid. **m.p.:** 128 – 129 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 5.90 (s, 1H), 4.22 – 4.15 (m, 3H), 4.15 – 4.06 (m, 3H), 2.29 (s, 3H), 1.48 (s, 9H); **$^{13}$C NMR** (176 MHz, $CDCl_3$, 30 °C) δ 171.9, 144.5, 150.0, 102.0, 80.4, 57.4, 53.6, 48.6, 46.8, 28.3, 12.3; **HRMS** ($ESI^+$) Calcd for $C_{17}H_{21}O_2N_2$ $[M+H]^+$ 285.1598, Found 285.1598 (100%); **IR** (neat $cm^{-1}$): 3529, 2982, 2928, 2866, 2411, 1709, 1581, 1335, 1254, 1169, 1092, 968, 840.

**4-(3-Methyl-1H-pyrazol-5-yl)cubane-1-carboxylic acid (29)**



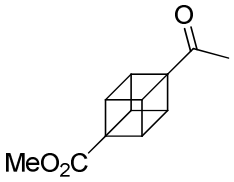

To a solution of (*tert*-butyl 4-(3-methyl-1H-pyrazol-5-yl)cubane-1-carboxylate (0.10 g, 0.35 mmol) in DCM (3.0 mL) was added dropwise trifluoroacetic acid (0.70 mL) at room temperature and the resulting mixture was stirred for 1 hour. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), washed sequentially with saturated $NaHCO_3$ (10 mL), and saturated brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford 4-(3-methyl-1H-pyrazol-5-yl)cubane-1-carboxylic acid (60.0 mg, 75 %). **m.p.:** 225 – 227 °C dec. (220 °C browned); **$^1$H NMR** (400 MHz, DMSO, 27 °C) δ 5.79 (s, 1H), 3.91 (s, 6H), 2.14 (s, 3H); **$^{13}$C NMR** (101 MHz, DMSO, 27°C) δ 175.9, 100.8, 58.8, 52.7, 47.3, 46.0, 12.1; **HRMS** ($ESI^+$) Calcd for $C_{13}H_{13}O_2N_2$ $[M+H]^+$ 229.0972, Found 229.0972 (100%); **IR** (neat $cm^{-1}$): 3390, 3263, 2985, 1682, 1539, 1419, 1203, 1138, 841, 802.

**Methyl 4-(methoxy(methyl)carbamoyl)cubane-1-carboxylate**



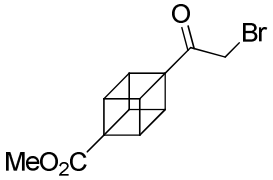
To a solution of 4-(methoxycarbonyl)cubane-1-carboxylic acid (6.50 g, 31.5 mmol), N,O-dimethylhydroxylamine hydrochloride (3.38 g, 34.7 mmol) and 4-dimethylaminopyridine (4.24 g, 34.7 mmol) in THF (158 mL) at 0 °C, *N*-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride EDC (7.55 g, 39.4 mmol) was added in one portion. The resulting solution was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed sequentially with water (100 mL), and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford methyl 4-(methoxy(methyl)carbamoyl)cubane-1-carboxylate (6.40 g, 81 %) as a white solid. **m.p.:** 130 – 132 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.28 – 4.23 (m, 3H), 4.23 – 4.18 (m, 3H), 3.71 (s, 3H), 3.71 (s, 3H), 3.19 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 172.4, 61.8, 55.50 51.7, 47.4, 47.2.; **HRMS** ($ESI^+$) Calcd for $C_{13}H_{16}NO_4$ $[M+H]^+$ 250.1074, Found 250.1077; **IR** (neat $cm^{-1}$): 3529, 3001, 2754, 2399, 1666, 1639, 1169, 1041, 968.

**Methyl 4-acetylcubane-1-carboxylate (32)**



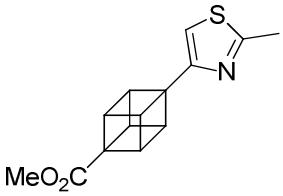

To a solution of methyl 4-(methoxy(methyl)carbamoyl)cubane-1-carboxylate (5.60 g, 22.4 mmol) in THF (200 mL) cooled to -20 °C, methylmagnesium bromide (9.73 mL, 29.2 mmol) was added over a period of 10 minutes under nitrogen. The resulting solution was stirred at -30 °C for 2 hours. The reaction mixture was quenched with water (100 mL), extracted with $Et_2O$ (3 x 100 mL), the organic layers were dried ($Na_2SO_4$), filtered and evaporated to afford a yellow solid. Purification by flash silica chromatography (elution gradient 0 to 10% EtOAc in heptane) afforded methyl 4-acetylcubane-1-carboxylate (3.40 g, 73 %) as a white solid. **m.p.:** 78 – 79 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.28 – 4.23 (m, 3H), 4.23 – 4.19 (m, 3H), 3.71 (s, 3H), 2.13 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 205.9, 171.9 63.6, 56.2, 51.8, 47.3, 46.7, 25.0; **HRMS** ($EI^+$) Calcd for $C_{12}H_{12}O_3$ $[M]^+$ 204.0786, Found 204.0782; **IR** (neat $cm^{-1}$): 3525, 3448, 3001, 2951, 1728, 1686, 1439, 1331, 1223, 1200, 1095, 937, 910, 837.

**Methyl 4-(2-bromoacetyl)cubane-1-carboxylate (31)**



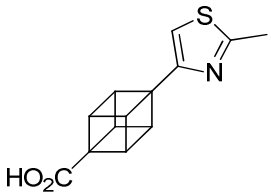

To a solution of methyl 4-acetylcubane-1-carboxylate (4.76 g, 23.3 mmol) and N-ethyl-N-isopropylpropan-2-amine (6.09 mL, 34.9 mmol) in DCM (126 mL) cooled to -78 °C, trimethylsilyl trifluoromethanesulfonate (5.06 mL, 27.9 mmol) was added over a period of 5 minutes under nitrogen. The resulting solution was stirred at -78 °C for 2 hours. The reaction mixture was quenched with saturated $NaHCO_3$ (15 mL), extracted with DCM (3 x 40 mL), the organic layers were dried ($Na_2SO_4$), filtered and evaporated to afford lightly yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$, 27°C) δ 4.20 (d, *J* = 1.0 Hz, 1H), 4.13 – 4.09 (m, 3H), 4.06 (d, *J* = 1.0 Hz, 1H), 3.98 – 3.93 (m, 3H), 3.71 (s, 3H), 0.21 (s, 9H); 1-bromopyrrolidine-2,5-dione (4.53 g, 25.5 mmol) was added to freshly prepared TMS-ether (6.4 g, 23.2 mmol) and sodium hydrogencarbonate (2.92 g, 34.7 mmol) in THF (463 mL) cooled to -78 °C under nitrogen. The resulting solution was stirred at -78 °C for 2 hours. The reaction mixture was quenched with saturated $NaHCO_3$ (15 mL), extracted with $Et_2O$ (3 x 20 mL), the organic layers were dried ($Na_2SO_4$), filtered and evaporated to afford methyl 4-(2-bromoacetyl)cubane-1-carboxylate (6.30, 96%) as a white solid. **m.p.:** 126 – 127 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 4.39 – 4.33 (m, 3H), 4.29 – 4.23 (m, 3H), 3.93 (s, 2H), 3.72 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 199.5, 171.9, 62.4, 55.6, 51.8, 48.6, 47.2, 31.6; **HRMS** ($EI^+$) 133.0539 (100%); Calcd for $C_{12}H_{11}BrO_3$ $[M]^+$ 281.9886, Found 281.9884 (50); **IR** (neat $cm^{-1}$): 2993, 2947, 2850, 1713, 1331, 1219, 1196, 964, 841, 737.

**Methyl 4-(2-methylthiazol-4-yl)cubane-1-carboxylate**



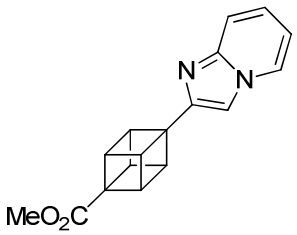
To a solution of (methyl 4-(2-bromoacetyl)cubane-1-carboxylate (5.00 g, 17.7 mmol) in methanol (177 mL) was added ethanethioamide (1.33 g, 17.7 mmol) at 20 °C under nitrogen. The resulting solution was stirred at 70 °C for 2 hours. Upon consumption of the starting material the solvent was evaporated and the mixture was redisolved in EtOAc. Formed precipitate was filtered, re-dissolved in DCM (100 mL) and washed with saturated $NaHCO_3$ (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford pure product methyl 4-(2-methylthiazol-4-yl)cubane-1-carboxylate (4.50 g, 98%) as a white solid. **m.p.:** 170-173 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 7.04 (s, 1H), 4.47 – 4.42 (m, 3H), 4.41 (d, *J* = 4.4 Hz, 3H), 3.71 (s, 3H), 3.19 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 172.7, 171.9, 149.7, 113.6, 55.9, 52.8, 51.8, 49.1, 47.3, 16.5; **HRMS** ($ESI^+$) Calcd for $C_{14}H_{14}NO_2S$ $[M+H]^+$ 260.07398, Found 260.07397 (100%); **IR** (neat $cm^{-1}$): 3456, 2993, 2982, 2661, 2611, 2523, 1720, 1597, 1319, 1230, 1084, 887.

**4-(2-Methylthiazol-4-yl)cubane-1-carboxylic acid (34)**



To a solution of methyl 4-(2-methylthiazol-4-yl)cubane-1-carboxylate (4.30 g, 16.6 mmol) in THF (116 mL) was added dropwise a solution of sodium hydroxide in methanol (49.7 mL, 49.7 mmol) at room temperature. The resulting mixture was stirred at room temperature over night. The reaction mixture was evaporated to dryness and redissolved in water (50 mL), and extracted with DCM (3 x 50 mL). The aqueous layer was acidified with concentrated HCl to pH ~4. The white suspension soformed was filtered off and the solid was dried to afford the desired product 4-(2-methylthiazol-4-yl)cubane-1-carboxylic acid (4.00 g, 98 %) as a white solid. **m.p.:** 200 – 202 °C dec. (195 °C browned); **$^1$H NMR** (400 MHz, DMSO, 27 °C) δ 12.31 (s, 1H), 7.18 (s, 1H), 4.18 – 4.12 (m, 3H), 4.12 – 4.06 (m, 3H), 2.63 (s, 3H); **$^{13}$C NMR** (101 MHz, DMSO, 27°C) δ 172.7, 165.9, 155.8, 113.1, 56.3, 55.8, 47.5, 45.5, 18.8; **HRMS** ($ESI^-$) Calcd for $C_{13}H_{10}NO_2S$ $M-H^+$ 244.0438, Found 244.0422; **IR** (neat $cm^{-1}$): 3525, 2966, 2777, 2399, 1678, 1311, 1246, 1180, 964, 760.

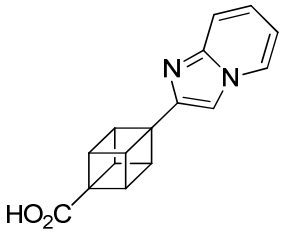
**Methyl 4-(imidazo[1,2-a]pyridin-2-yl)cubane-1-carboxylate**



To a methyl 4-(2-bromoacetyl)cubane-1-carboxylate (0.10 g, 0.353 mmol) in methanol (3 mL) was added pyridin-2-amine (33.0 mg, 0.353 mmol) at room temperature under nitrogen. The resulting solution was stirred at 60 °C for 4 hours. Upon consumption of the starting material, as indicated by TLC, solvent was evaporated and the mixture was re-dissolved in DCM, and applied to silica column chromatography (elution gradient 0 to 10% MeOH in DCM). Pure fractions were evaporated to dryness to afford methyl 4-(imidazo[1,2-a]pyridin-2-yl)cubane-1-carboxylate (70.0 mg, 71 %) as an off yellow solid. **m.p.:** 141 – 143 °C; **$^1$H NMR** (400 MHz, $CDCl_3$, 27 °C) δ 8.06 (d, *J* = 6.7 Hz, 1H), 7.57 (d, *J* = 9.1 Hz, 1H), 7.37 (s, 1H), 7.14 (ddd, *J* = 9.0, 6.8, 1.1 Hz, 1H), 6.74 (t, *J* = 6.8 Hz, 1H), 4.34 – 4.28 (m, 3H), 4.28 – 4.21 (m, 3H), 3.74 (s, 3H); **$^{13}$C NMR** (101 MHz,

$CDCl_3$, 27 °C) δ 172.9, 147.5, 146.2, 125.6, 124.6, 117.4, 112.2, 108.6, 56.4, 55.2, 51.7, 48.6, 46.9; **HRMS** ($ESI^+$) Calcd for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ 279.1128, Found 279.1129 (100%); **IR** (neat $cm^{-1}$): 3583, 2939, 2827, 2403, 1666, 1173, 1041, 964, 906.

**4-(Imidazo[1,2-a]pyridin-2-yl)cubane-1-carboxylic acid (33)**




To a solution of (2r,3R,4s,5S)-methyl 4-(imidazo[1,2-a]pyridin-2-yl)cubane-1-carboxylate (70.0 mg, 0.25 mmol) in THF (2 mL) was added dropwise a solution of sodium hydroxide in methanol (0.75 mL, 0.75 mmol) at room temperature. The resulting mixture was stirred at room temperature over night. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), concentrated HCl was then added to pH ~4 and the layers were separated. The organic layer was extracted with DCM (3 x 10 mL). The combined organic layers was dried ($MgSO_4$), filtered and evaporated to afford desired product 4-(3-phenyl-1H-1,2,4-triazol-5-yl)cubane-1-carboxylic acid (98.0 mg, 100 %) as a white solid. **m.p.:** 223 – 225 °C dec. (220 °C browned); **$^1$H NMR** (400 MHz, DMSO, 27°C) δ 15.16 (s, 1H), 12.45 (s, 1H), 8.89 – 8.78 (m, 1H), 8.27 (s, 1H), 7.91 (d, *J* = 5.8 Hz, 2H), 7.46 (td, *J* = 6.4, 6.2, 2.4 Hz, 1H), 4.35 – 4.27 (m, 3H), 4.27 – 4.21 (m, 3H); **$^{13}$C NMR** (101 MHz, DMSO, 27°C) δ 172.2, 139.7, 136.6, 132.9, 128.9, 116.8, 111.8, 111.2, 55.7, 50.3, 47.5, 46.2; **HRMS** ($ESI^+$) Calcd for $C_{16}H_{13}N_2O_2$ $[M+H]^+$ 265.0972, Found 265.09722 (100%); **IR** (neat $cm^{-1}$): 3417, 2835, 2735, 2658, 1716, 1655, 1531, 1281, 1200, 1169, 1080, 760, 633.

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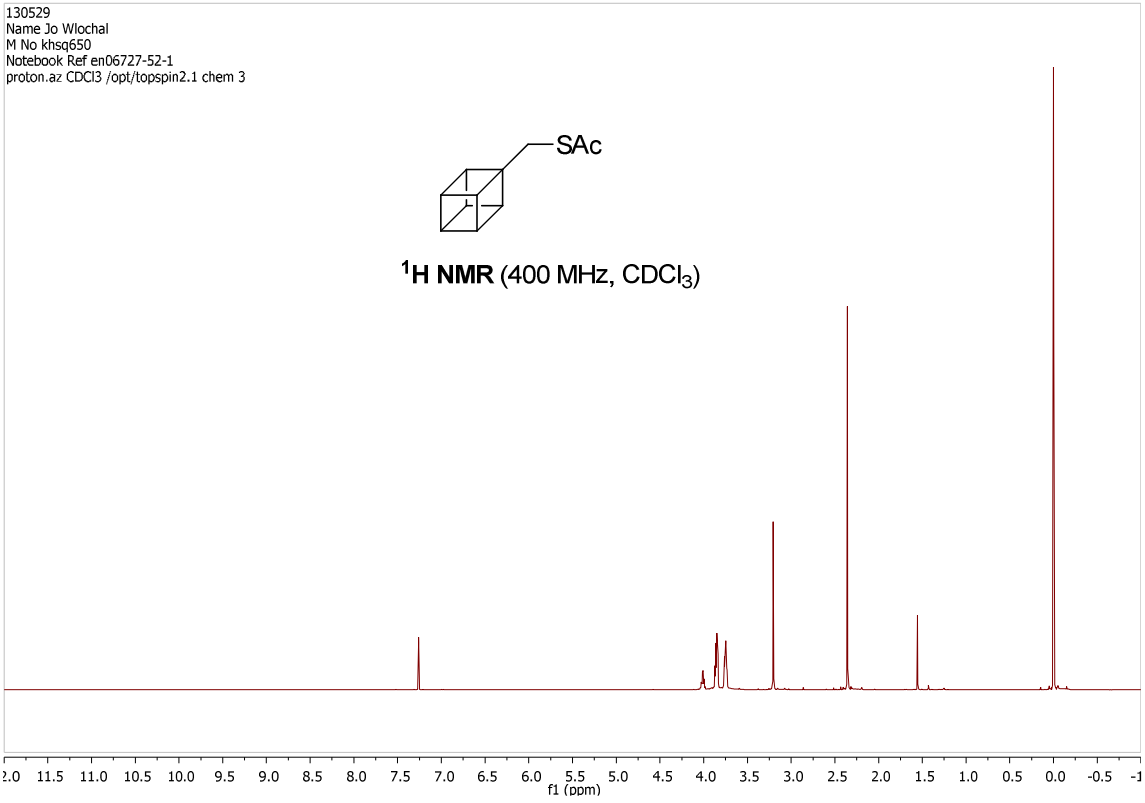
Spectra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M No khsq650
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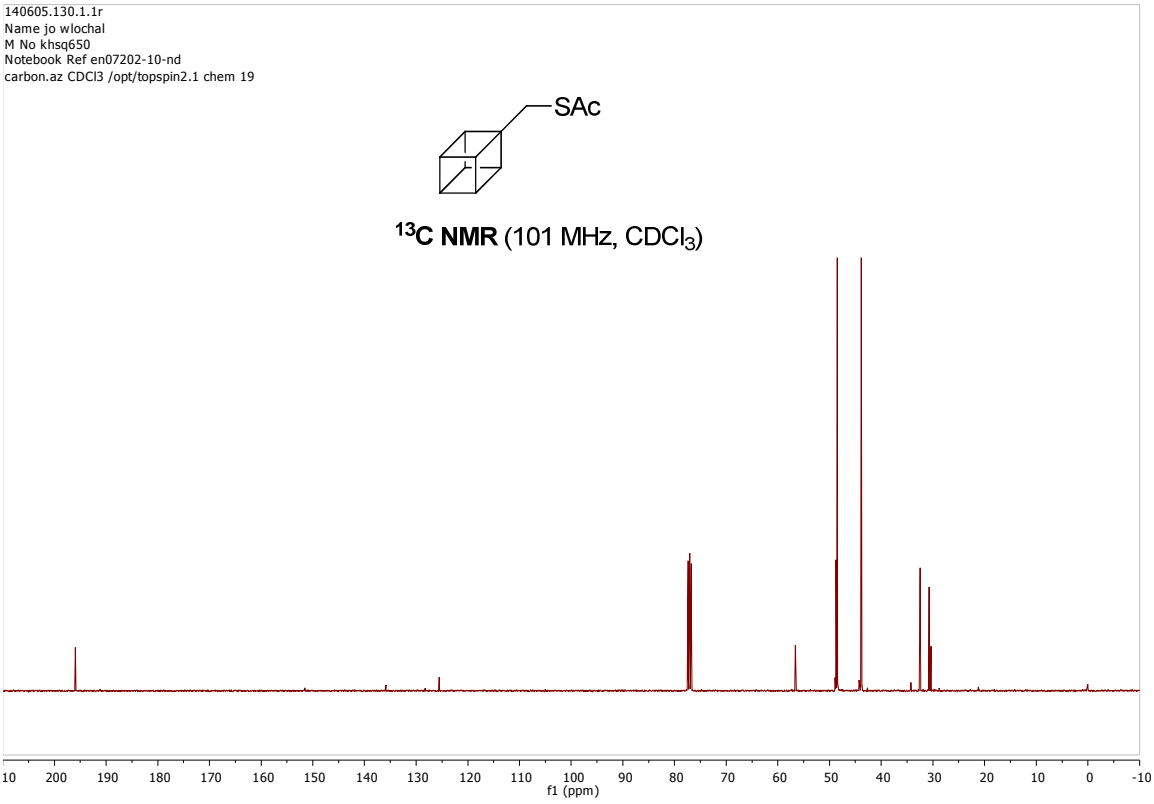
f1 (ppm)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Name jo wlochal
M No khsq650
Notebook Ref en07202-10-nd
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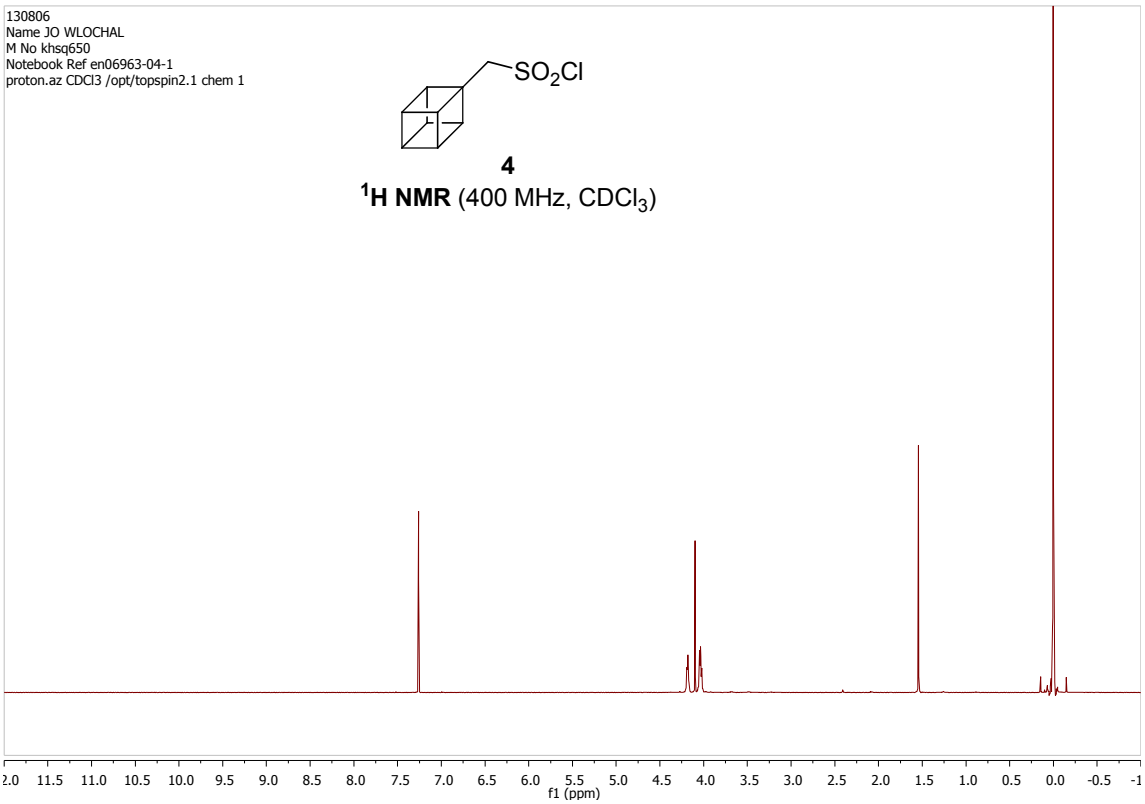
$^{13}$C NMR (101 MHz, CDCl$_3$)
f1 (ppm)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M No khsq650
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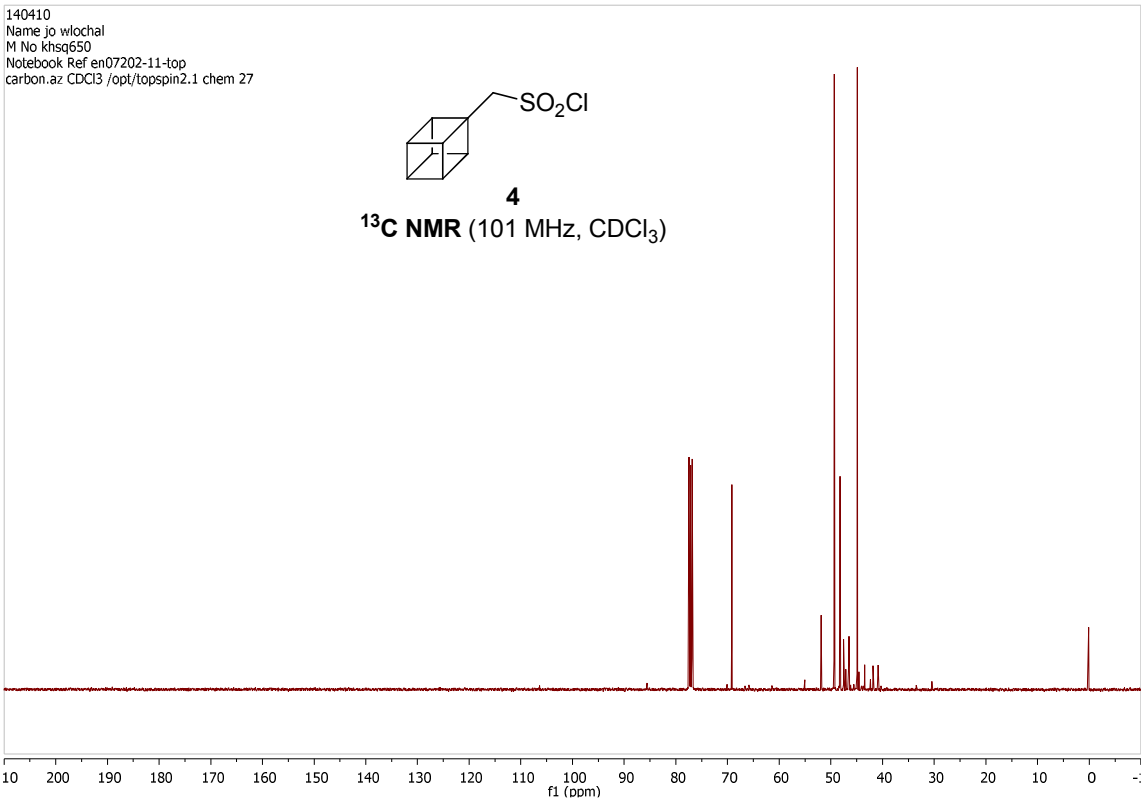
1H NMR (400 MHz, CDCl3)
f1 (ppm)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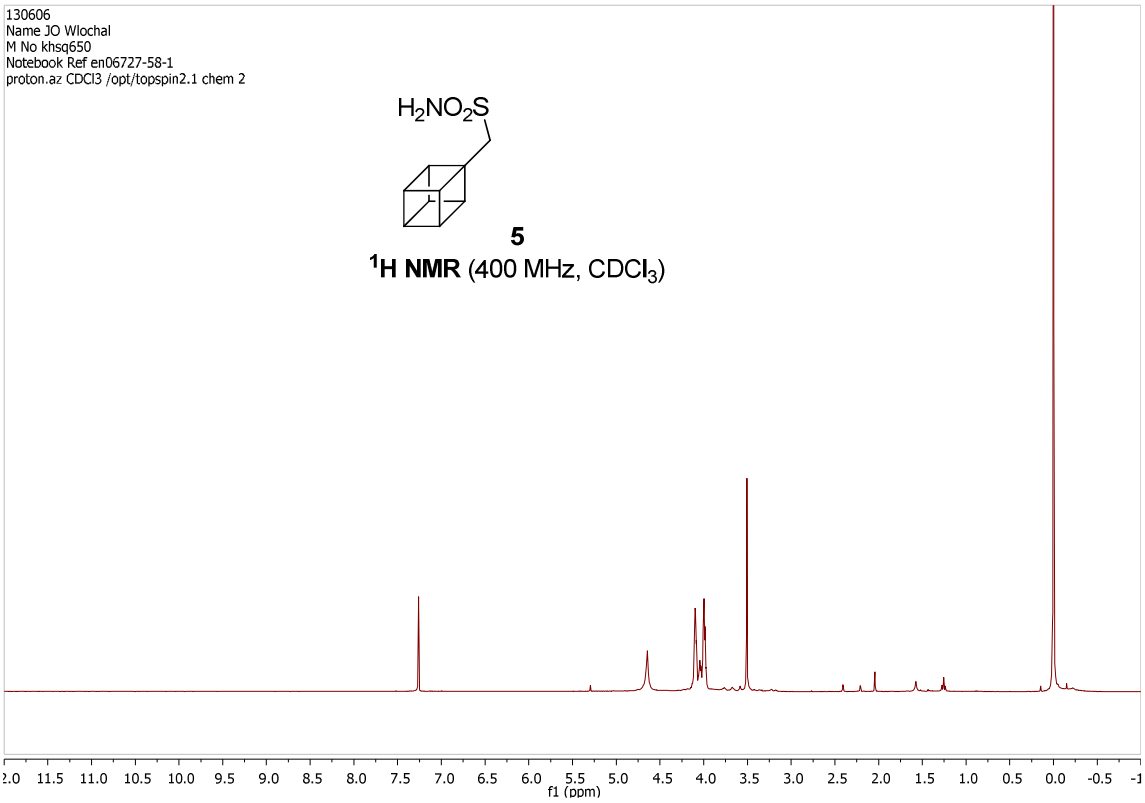
f1 (ppm)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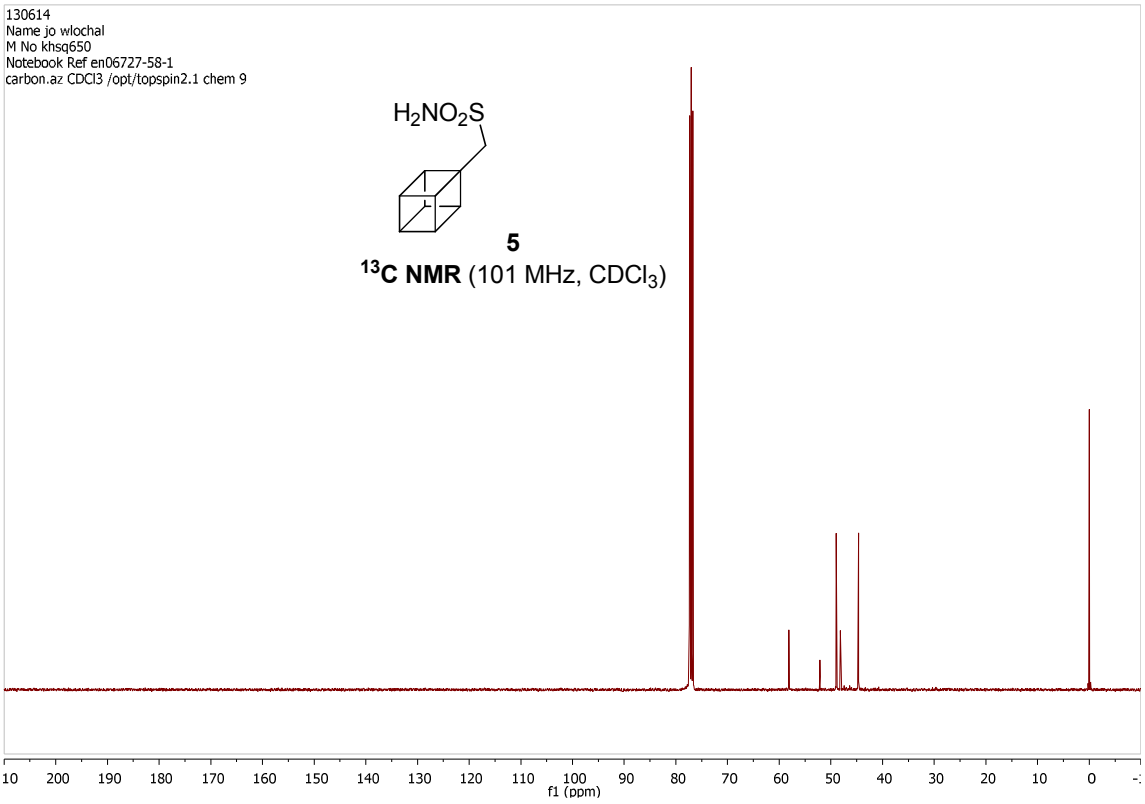
5
$^1$H NMR (400 MHz, $CDCl_3$)
f1 (ppm)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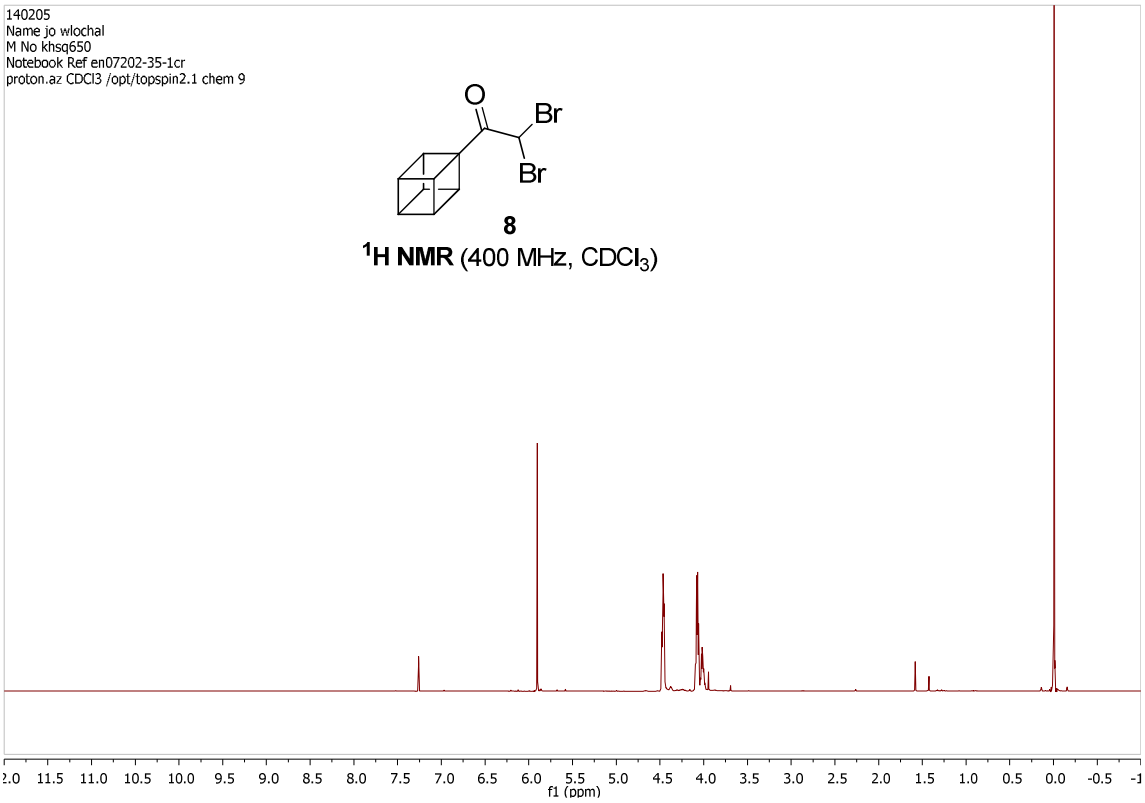
f1 (ppm)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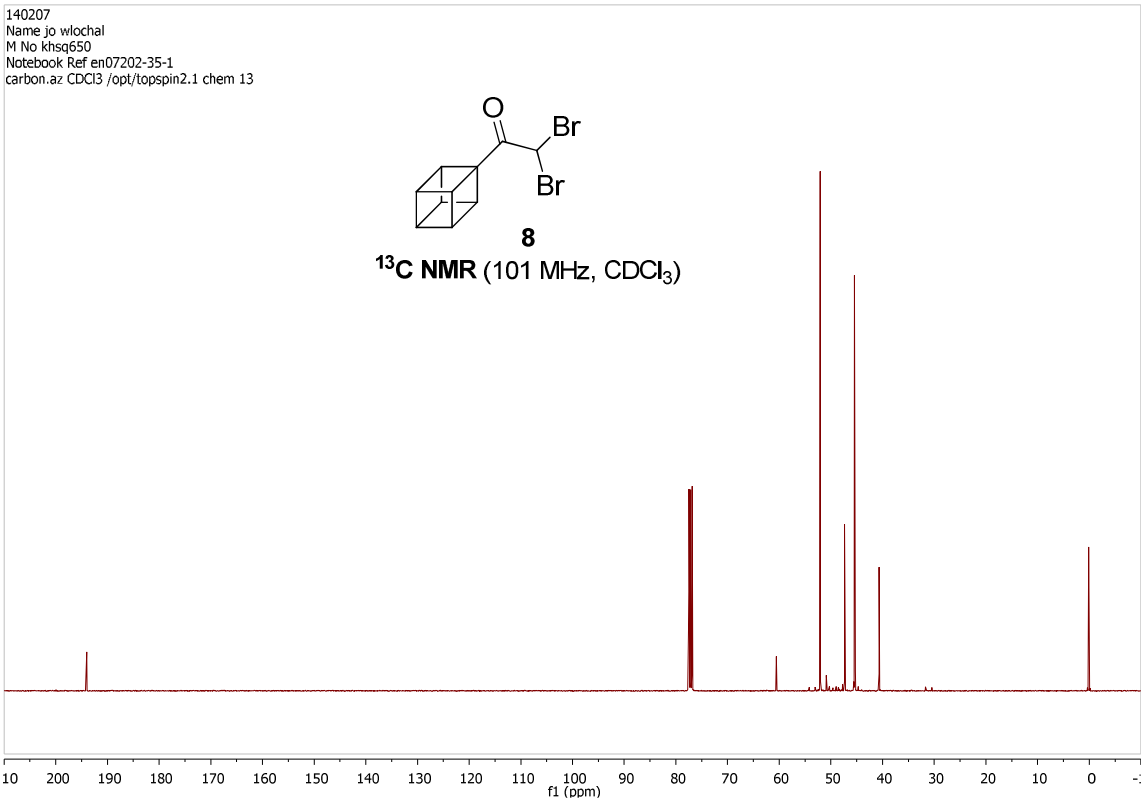
1H NMR (400 MHz, CDCl3)
f1 (ppm)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Br
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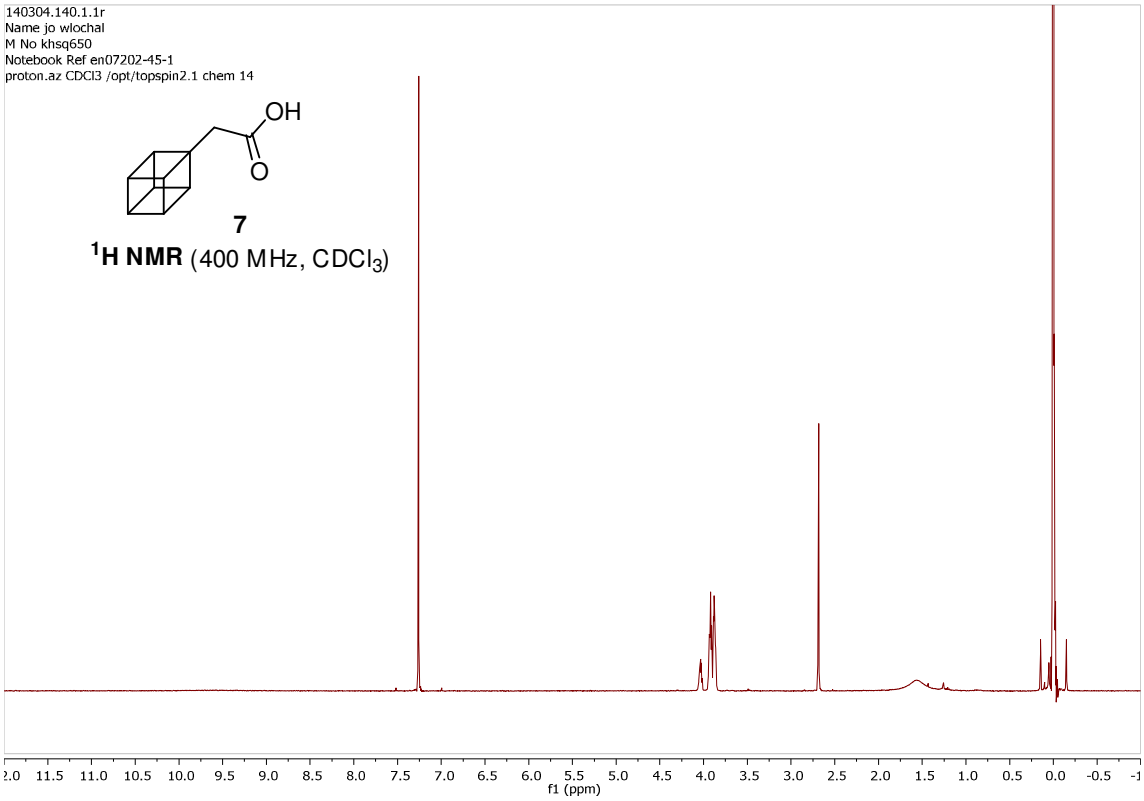
f1 (ppm)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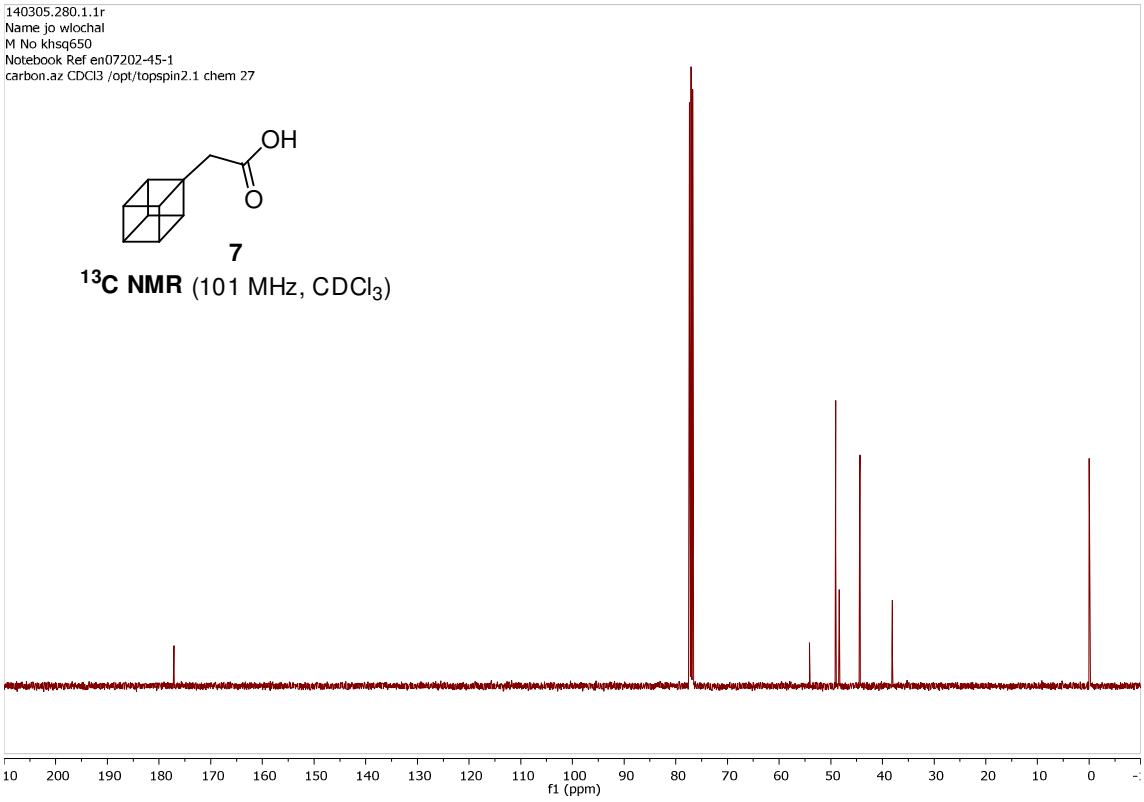
O
7
1H NMR (400 MHz, CDCl3)
f1 (ppm)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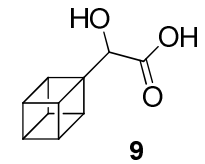
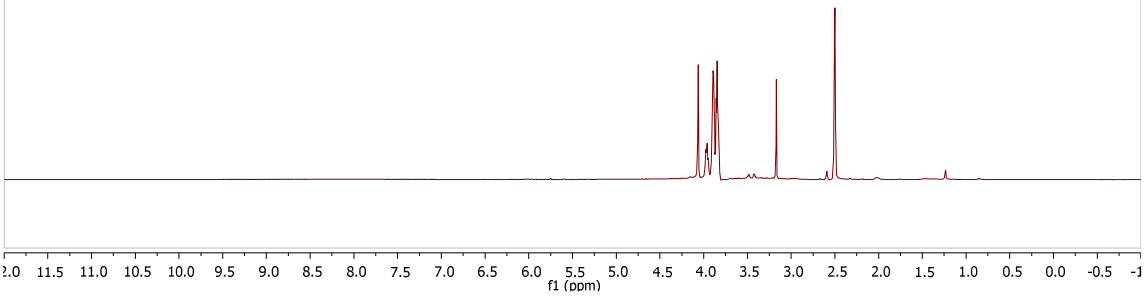
OH
O
7
13C NMR (101 MHz, CDCl3)
f1 (ppm)

140305
Name jo wlochal
M No khsq650
Notebook Ref en07202-32-1
proton.az DMSO /opt/topspin2.1 chem 26




**9**

**$^{1}$H NMR** (400 MHz, DMSO)



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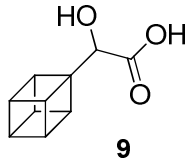
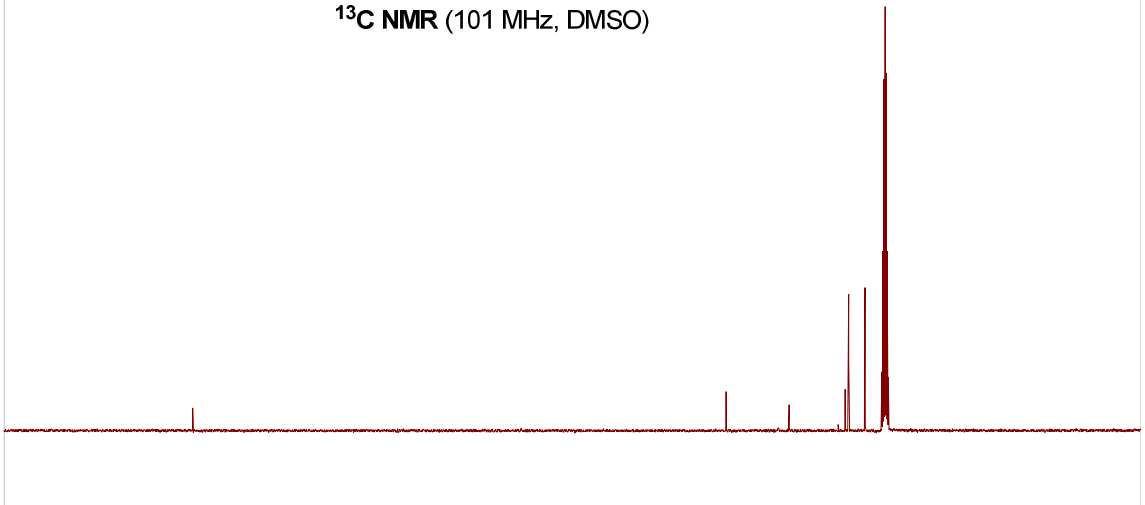
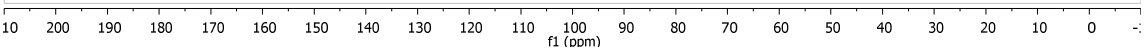
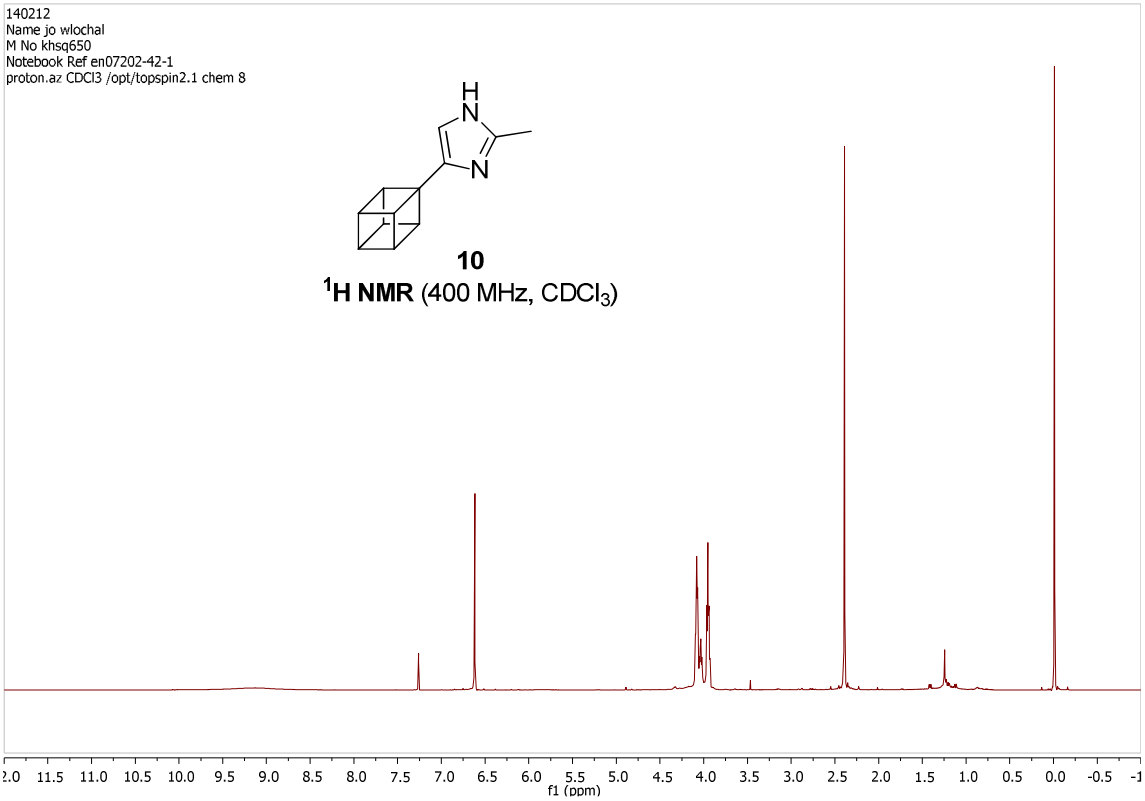



**9**

**$^{13}$C NMR** (101 MHz, DMSO)



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M No khsq650
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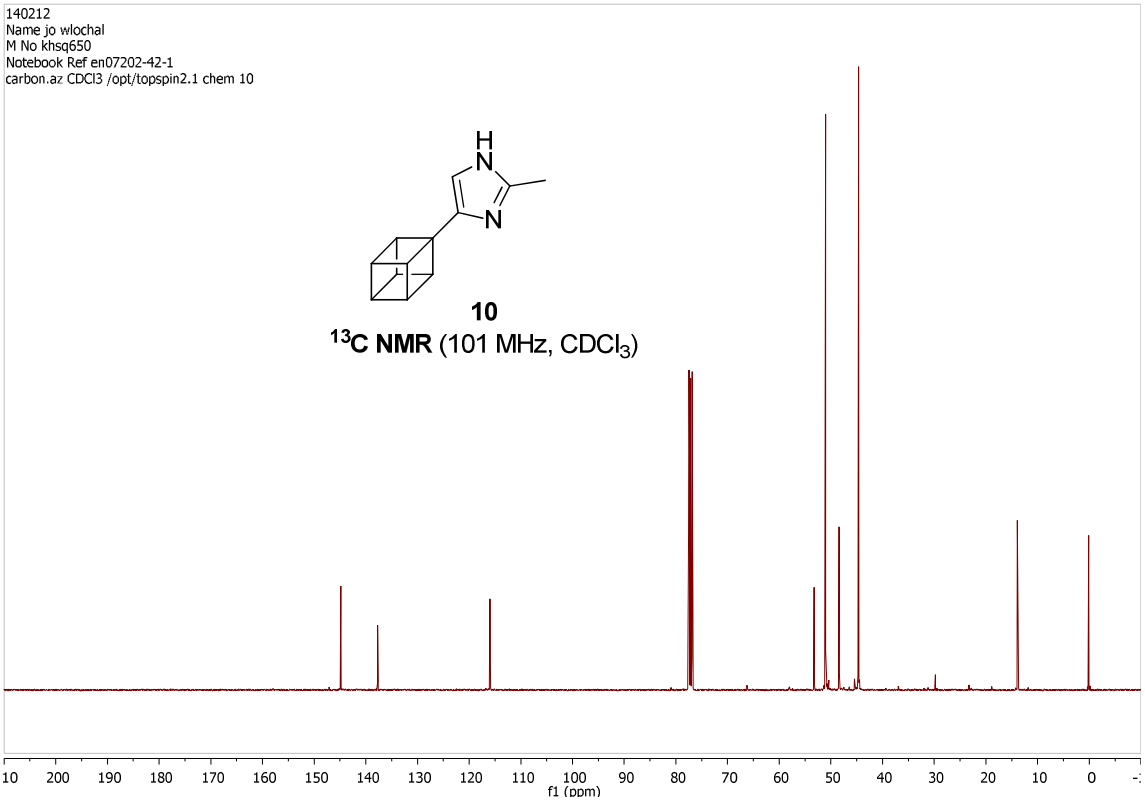
N
N
10
1H NMR (400 MHz, CDCl3)
f1 (ppm)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Name jo wlochal
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N
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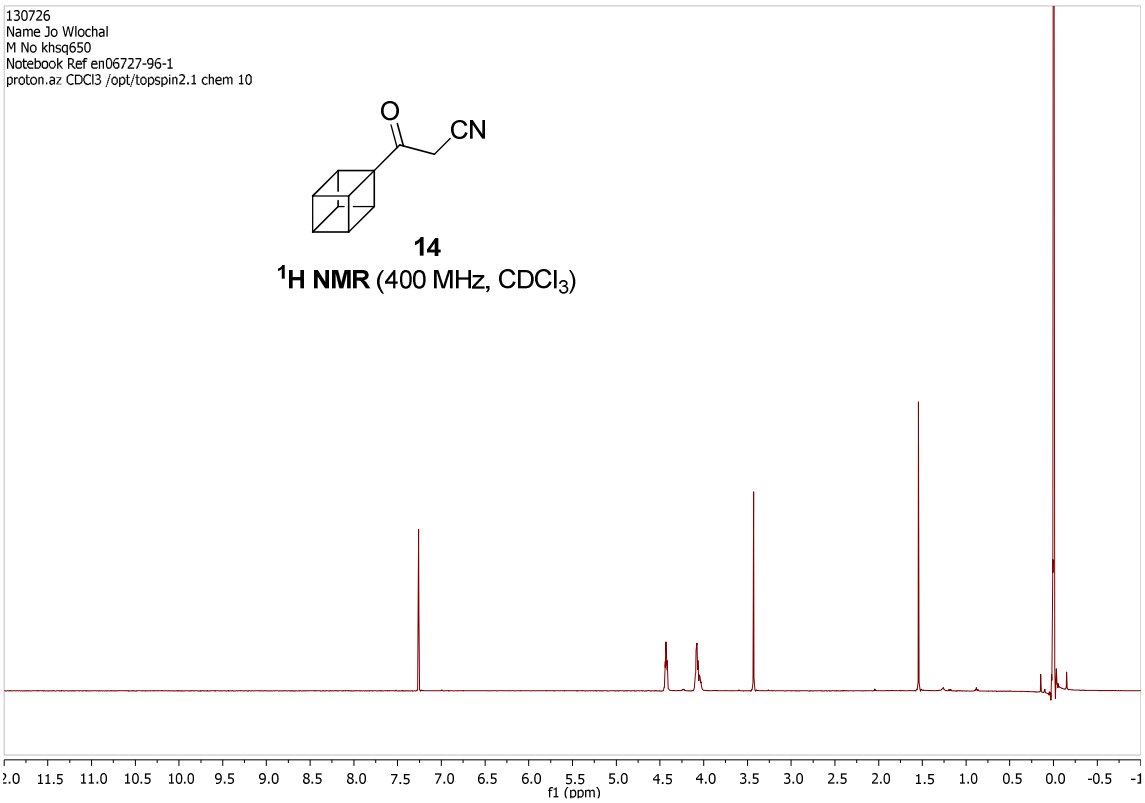
13C NMR (101 MHz, CDCl3)
f1 (ppm)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M No khsq650
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CN
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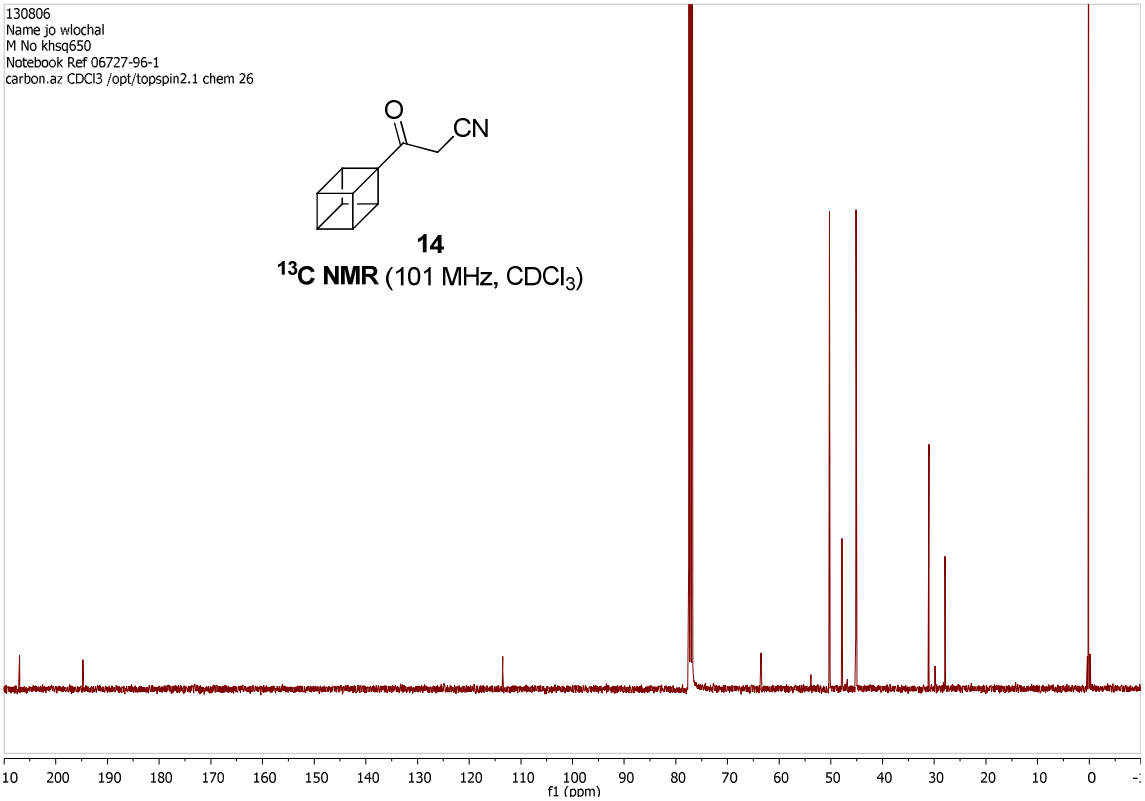
1H NMR (400 MHz, CDCl3)
f1 (ppm)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M No khsq650
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O
CN
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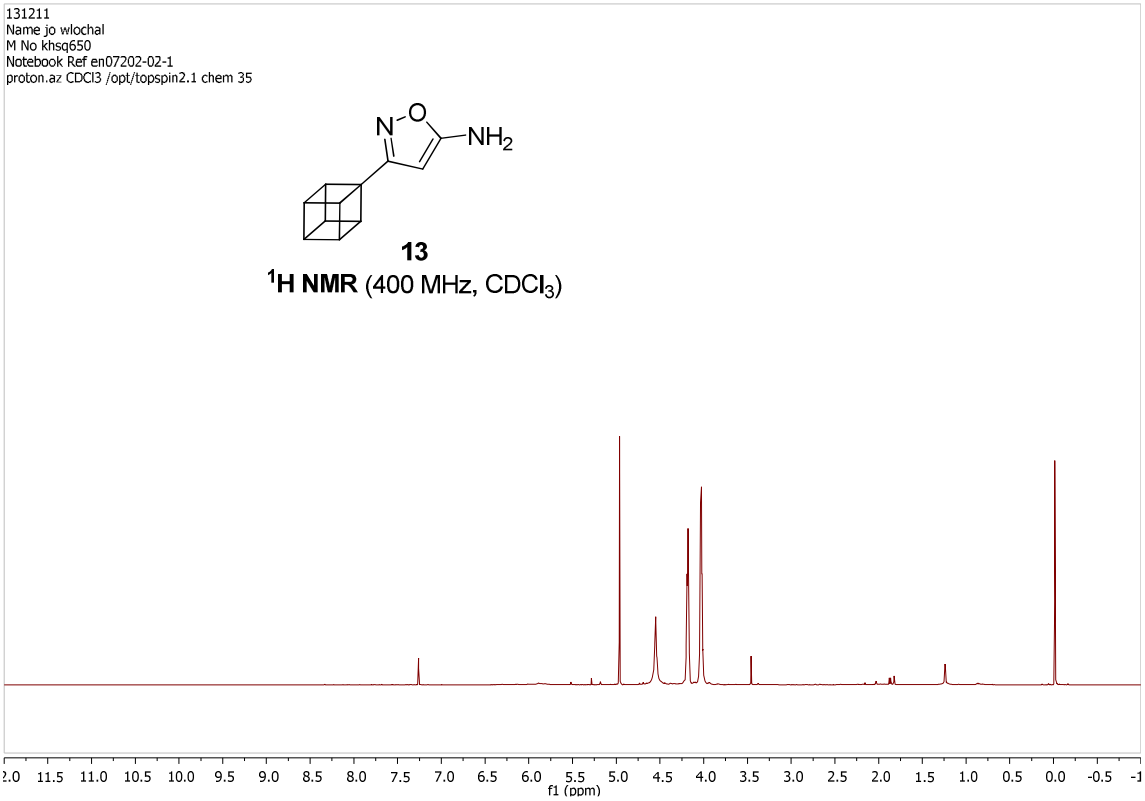
f1 (ppm)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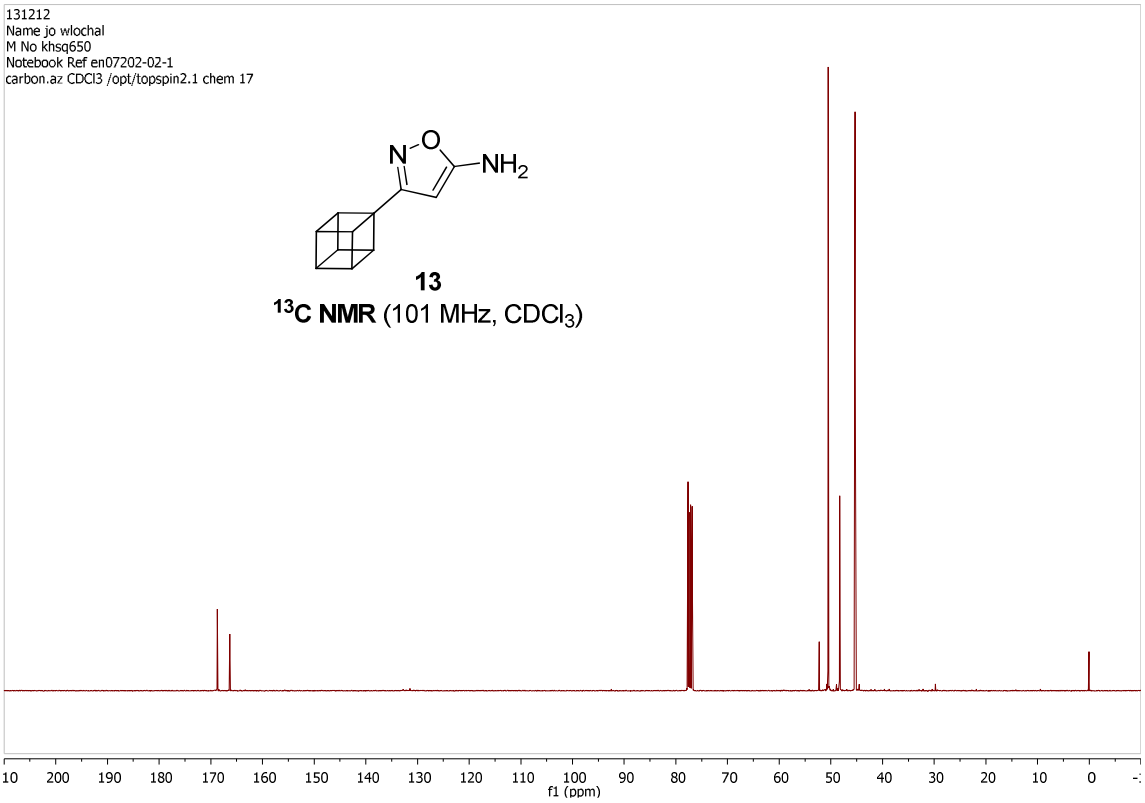
O
NH2
13
1H NMR (400 MHz, CDCl3)
f1 (ppm)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O
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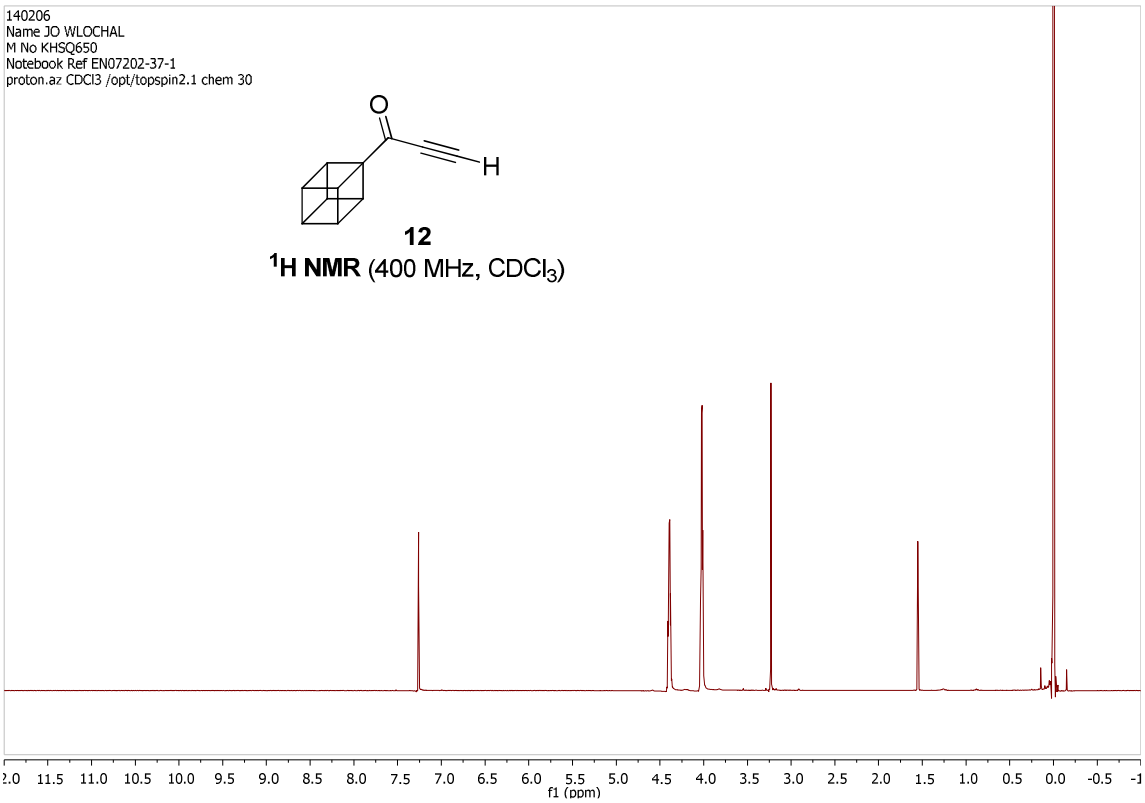
13
13C NMR (101 MHz, CDCl3)
f1 (ppm)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M No KHSQ650
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O
H
12
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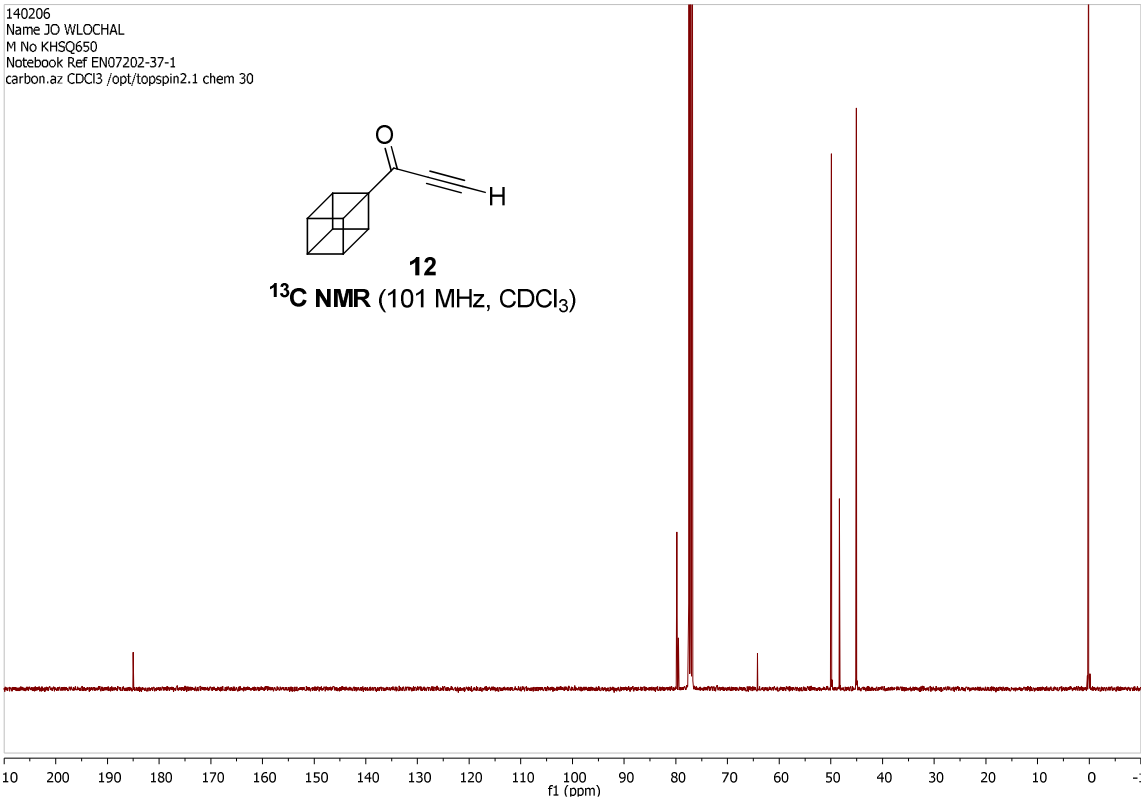
f1 (ppm)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O
H
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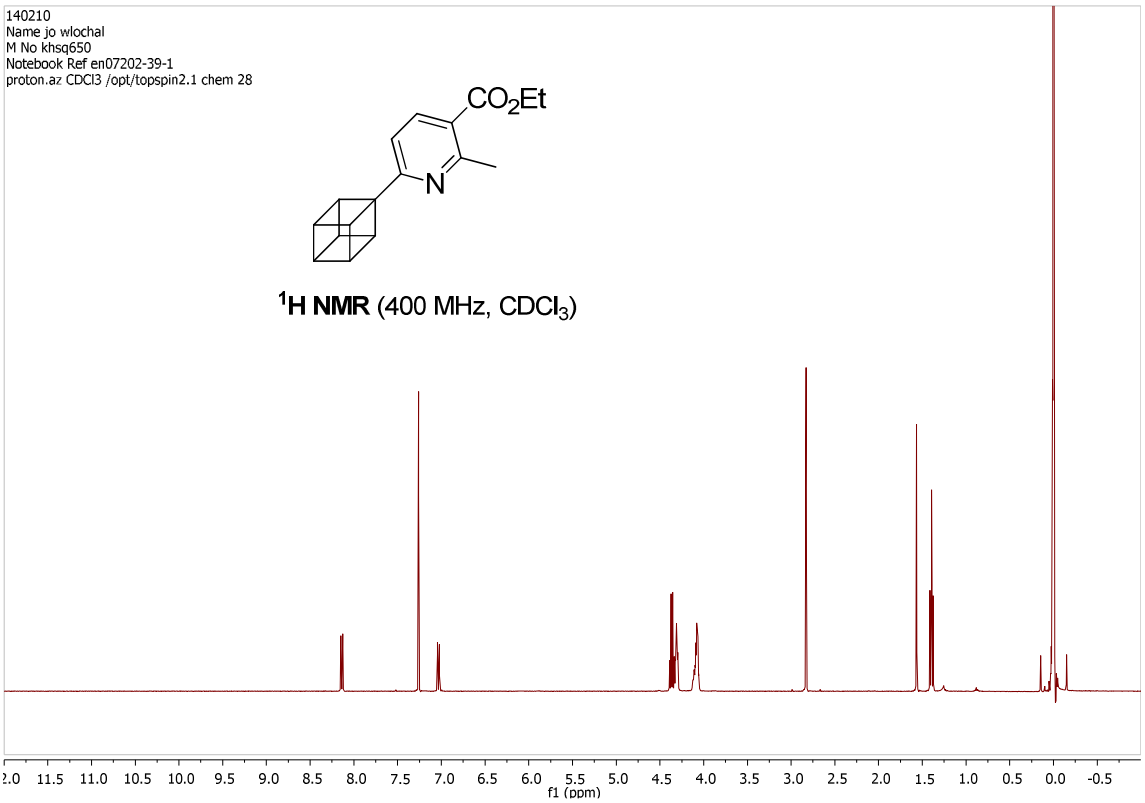
13C NMR (101 MHz, CDCl3)
f1 (ppm)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M No khsq650
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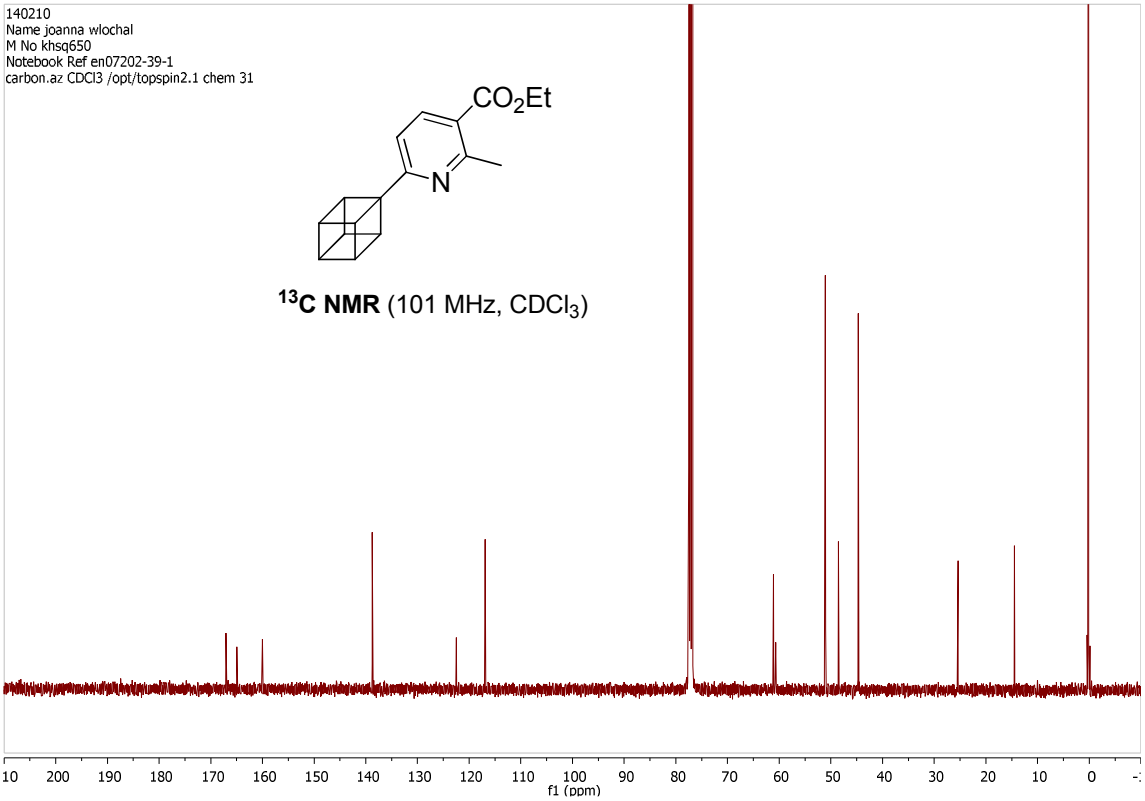
1H NMR (400 MHz, CDCl3)
f1 (ppm)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M No khsq650
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CO2Et
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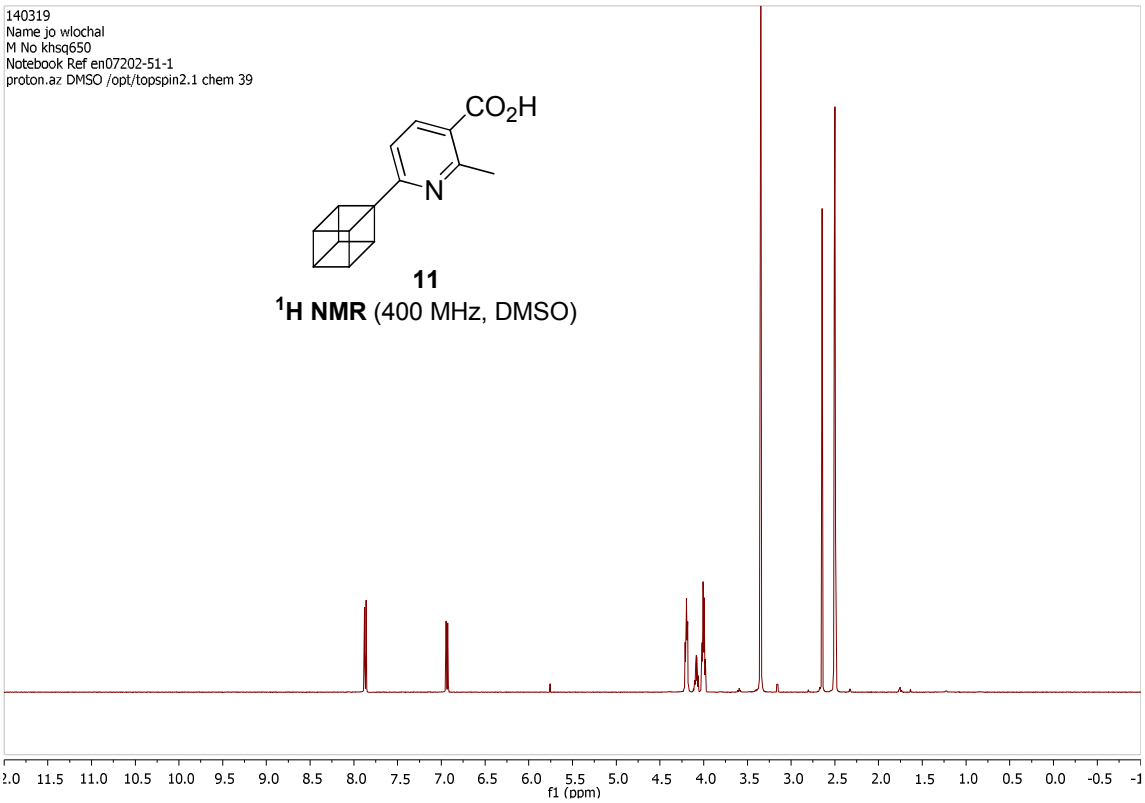
13C NMR (101 MHz, CDCl3)
f1 (ppm)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CO2H
N
11
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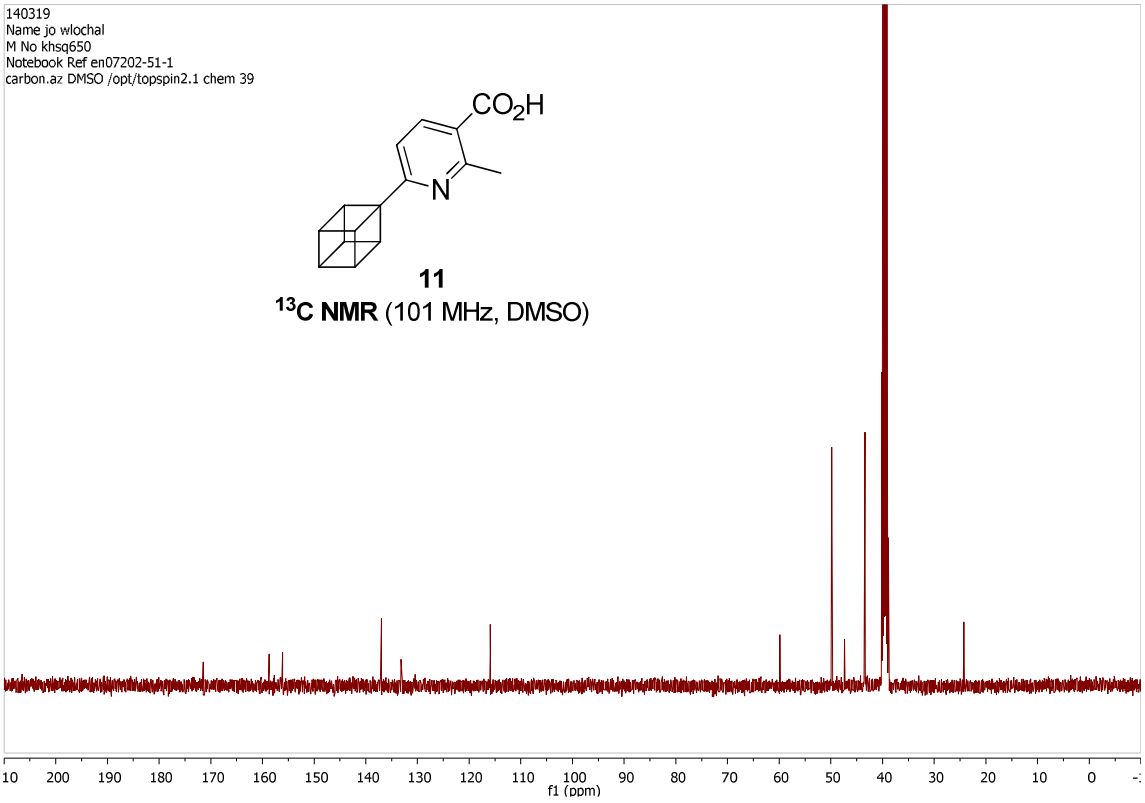
f1 (ppm)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CO2H
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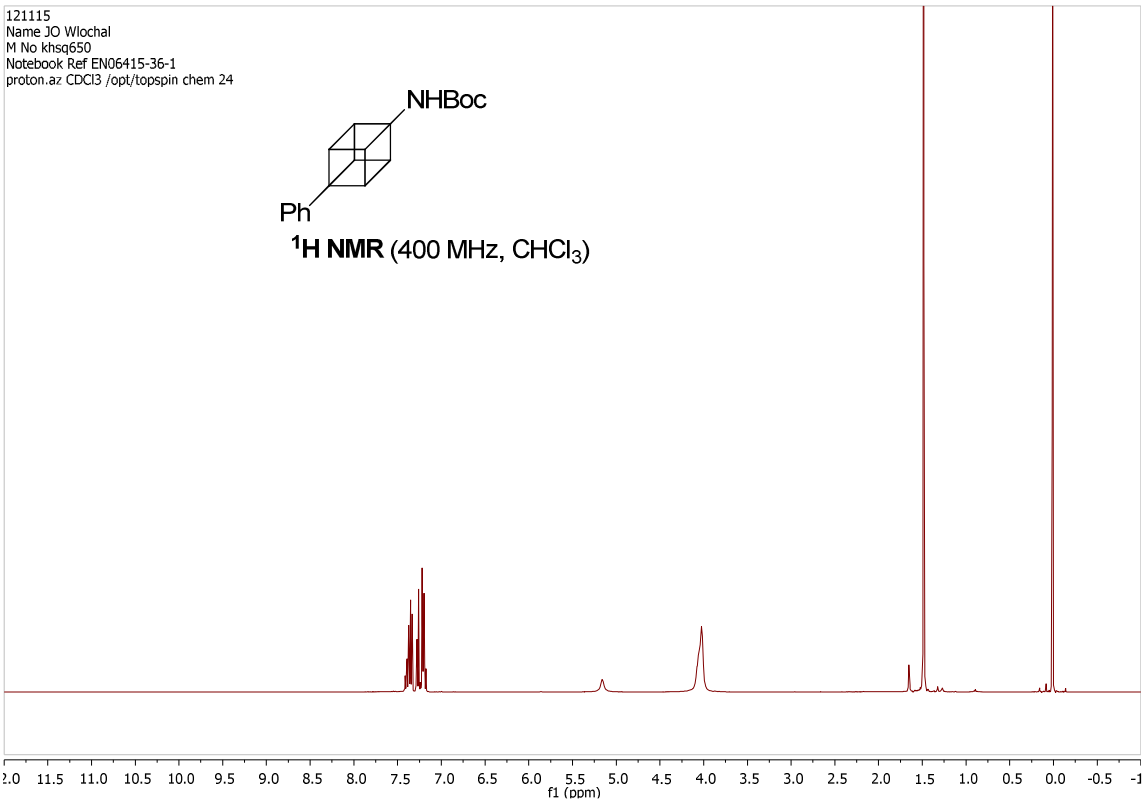
f1 (ppm)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Ph
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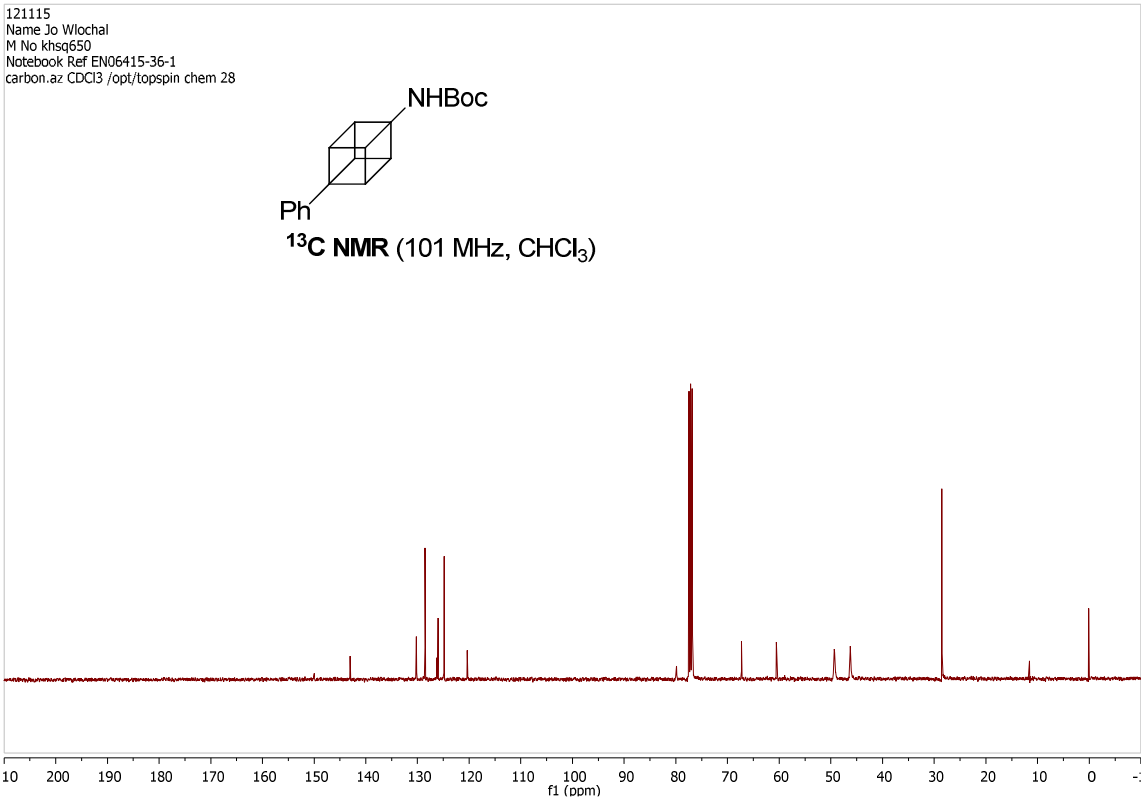
f1 (ppm)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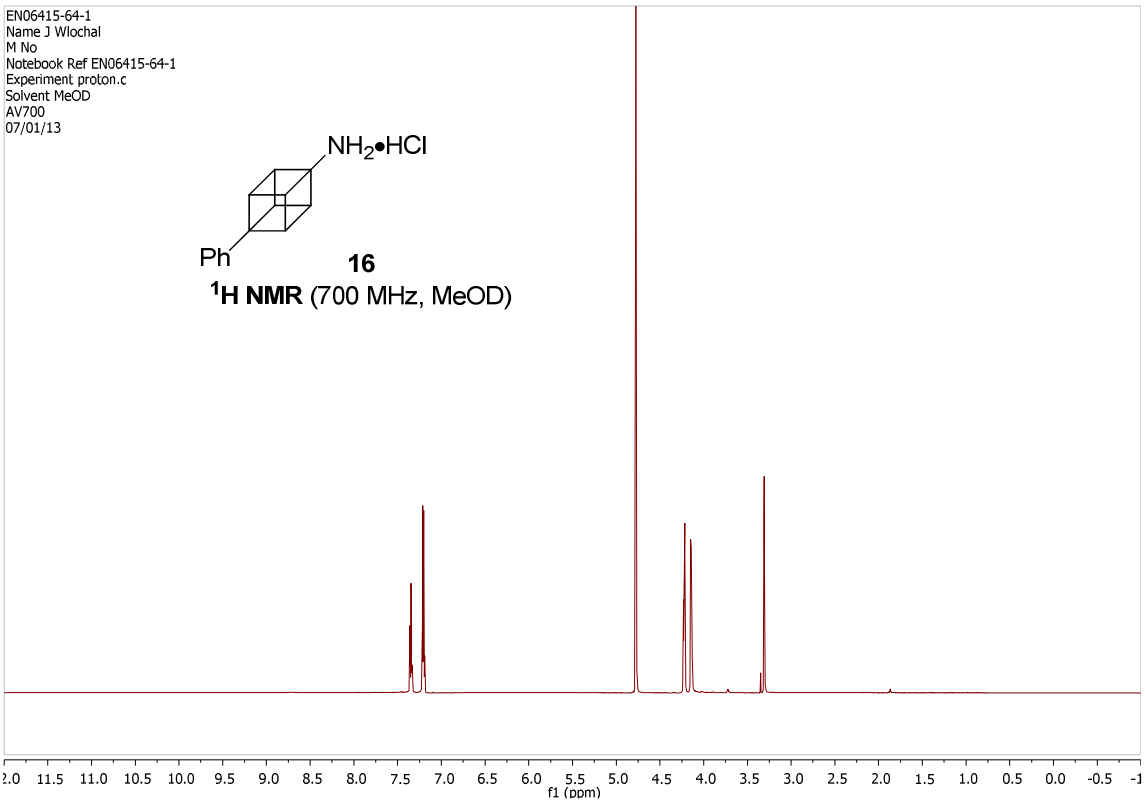
13C NMR (101 MHz, CHCl3)
f1 (ppm)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Notebook Ref EN06415-64-1
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AV700
07/01/13
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Ph
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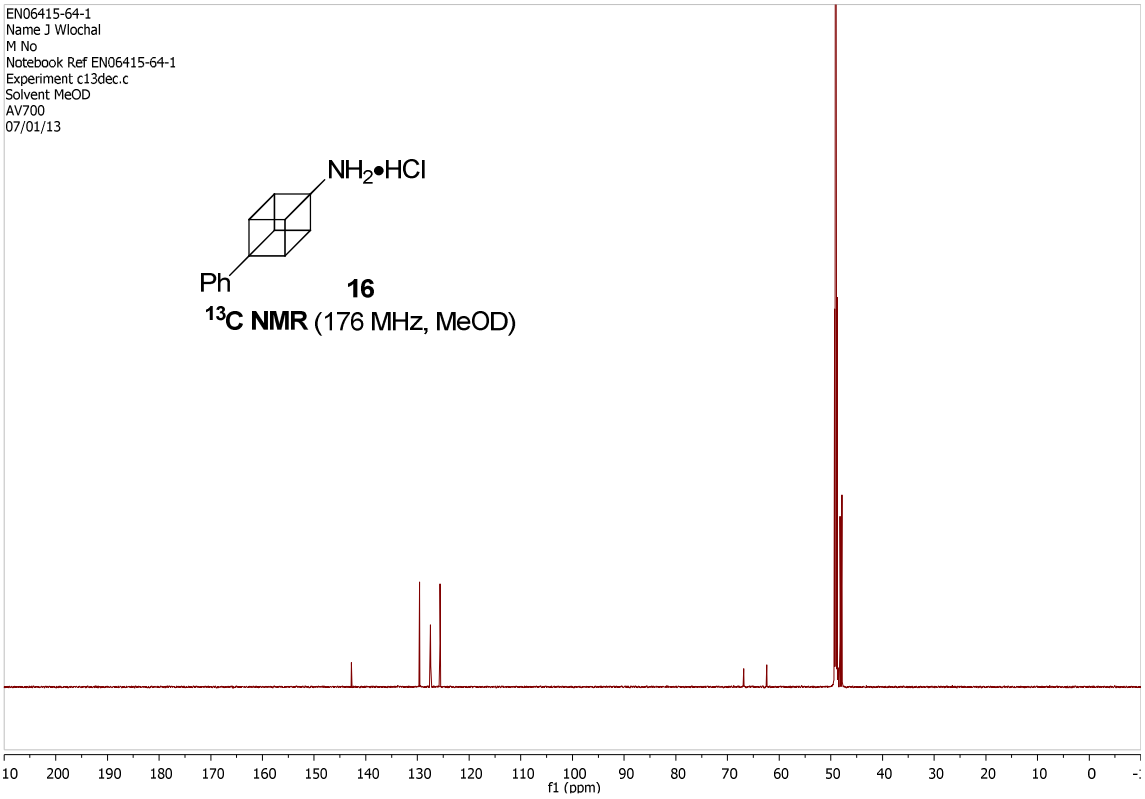
f1 (ppm)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Notebook Ref EN06415-64-1
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AV700
07/01/13
NH2•HCl
Ph
16
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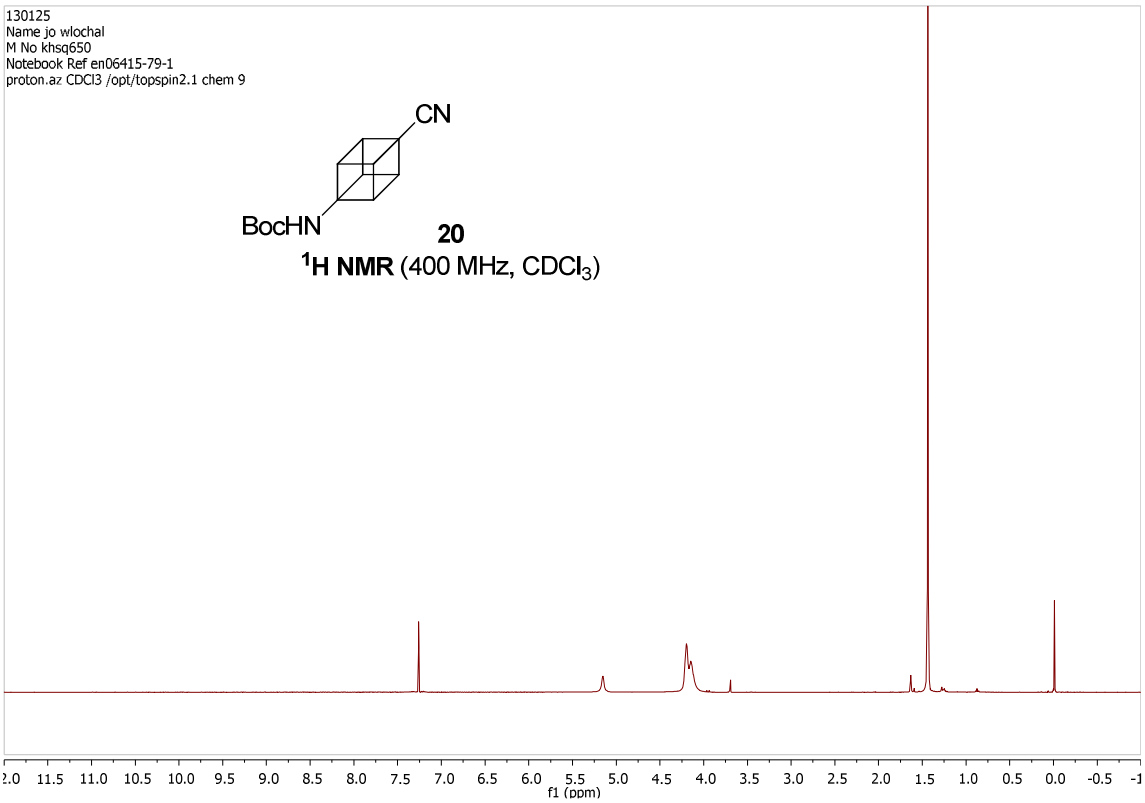
f1 (ppm)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M No khsq650
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BocHN
20
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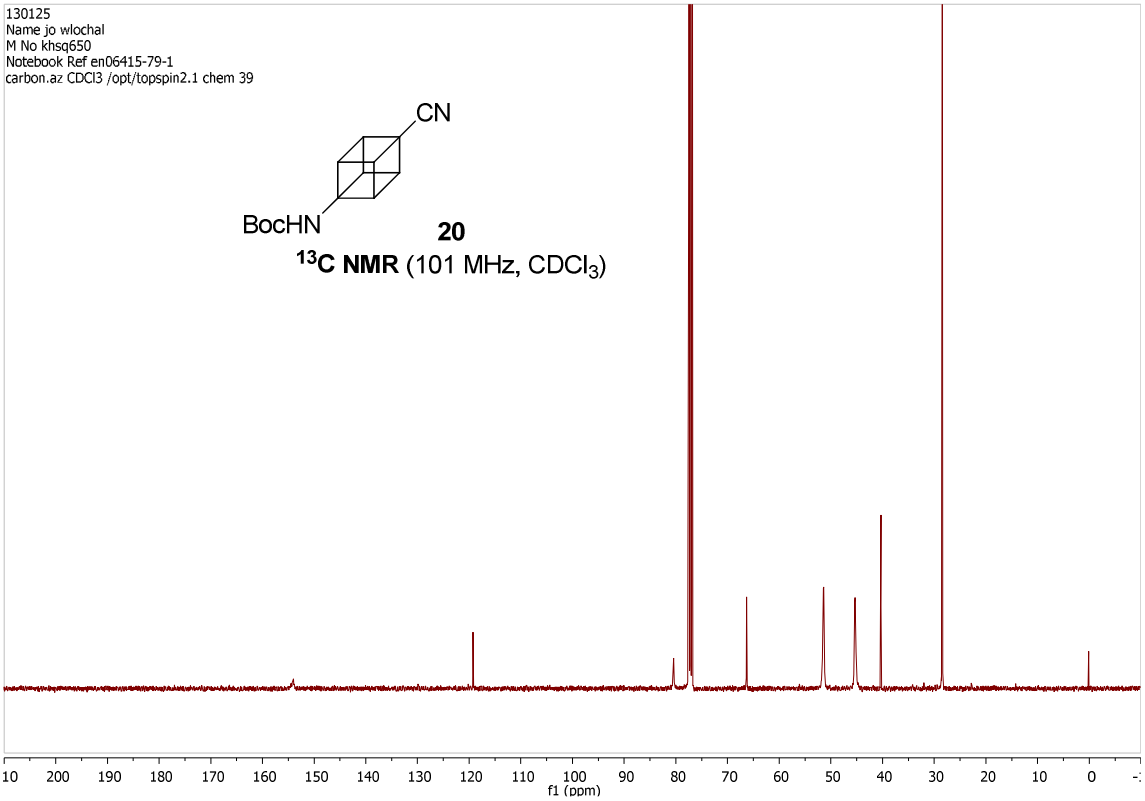
f1 (ppm)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BocHN
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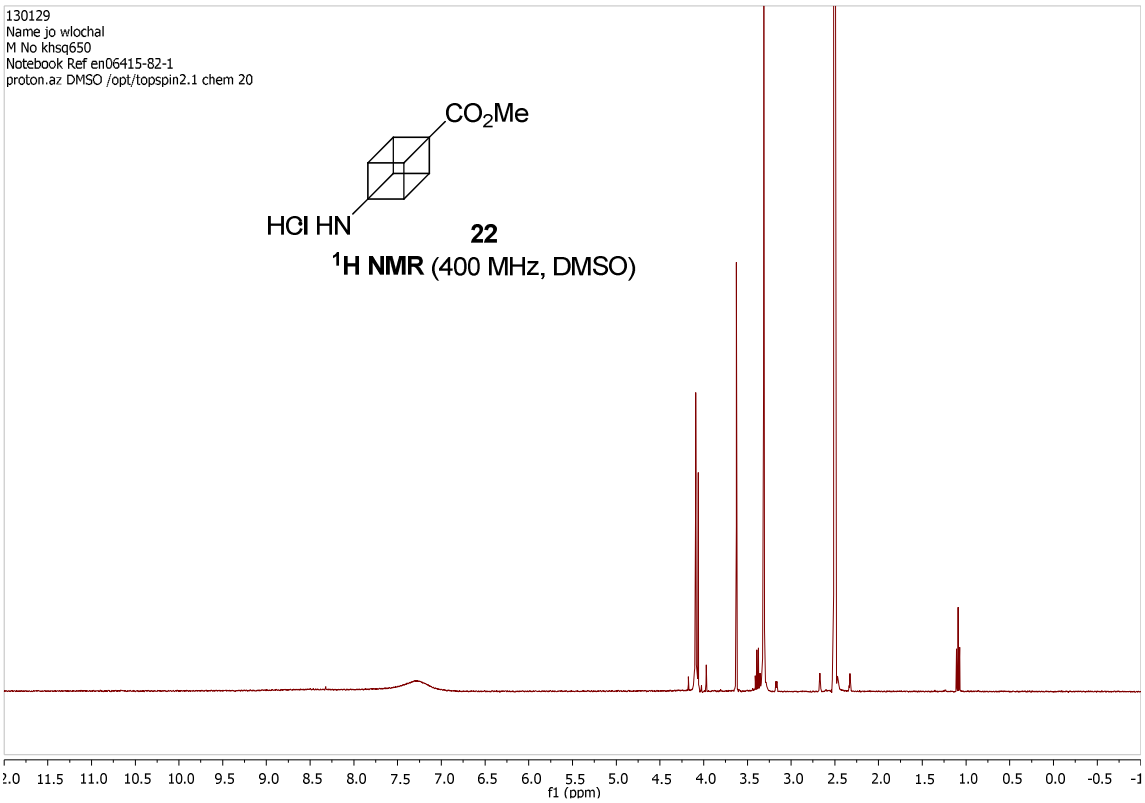
f1 (ppm)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HCl HN
22
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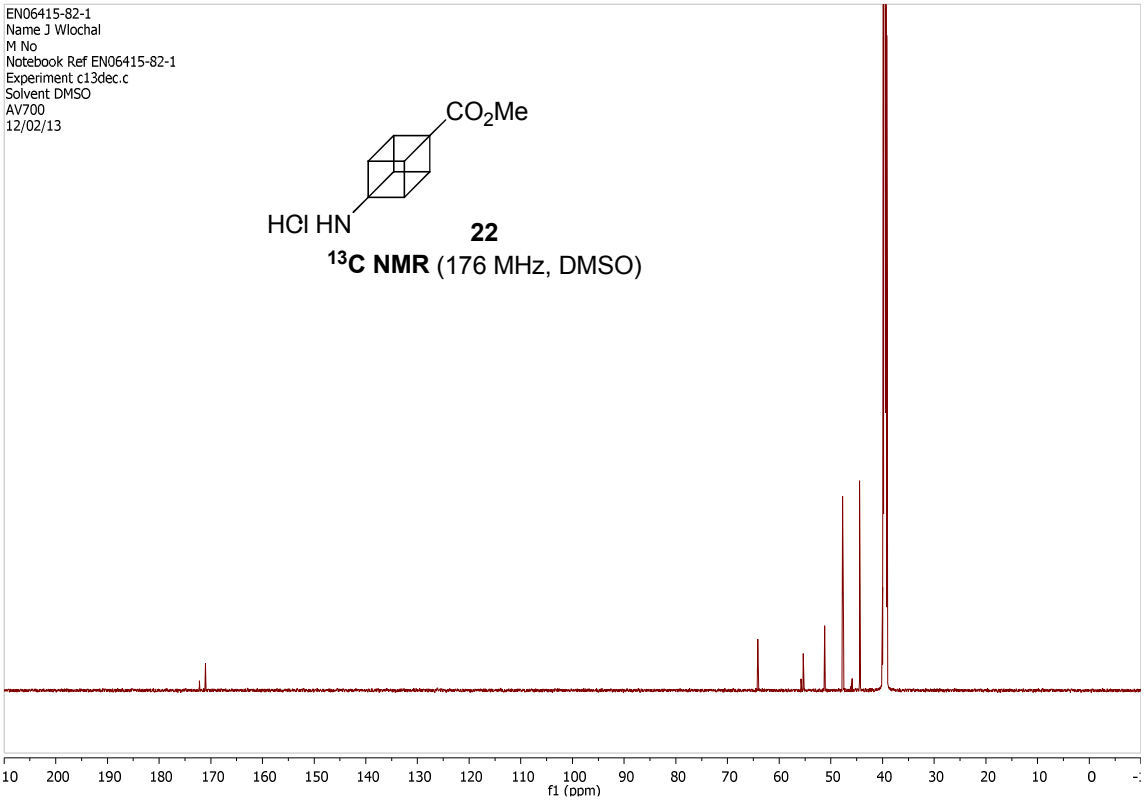
f1 (ppm)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M No
Notebook Ref EN06415-82-1
Experiment c13dec.c
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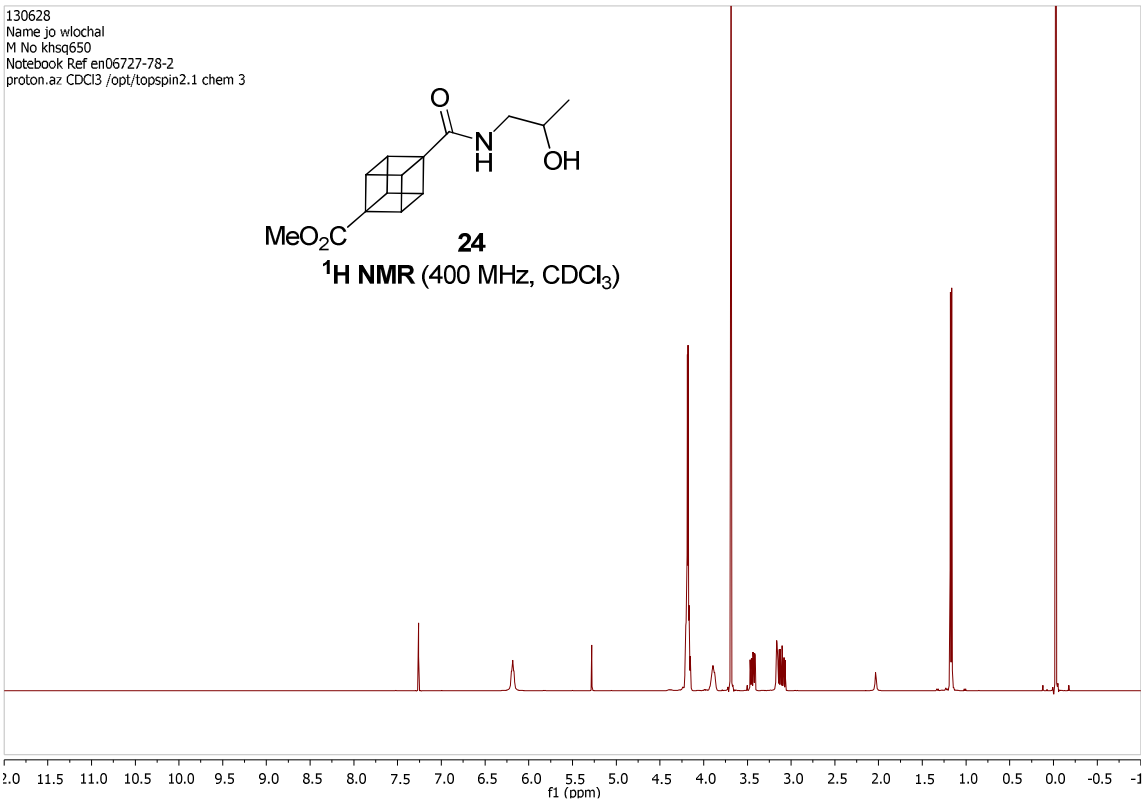
AV700
12/02/13
CO2Me
HCl HN
22
13C NMR (176 MHz, DMSO)
f1 (ppm)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Notebook Ref en06727-78-2
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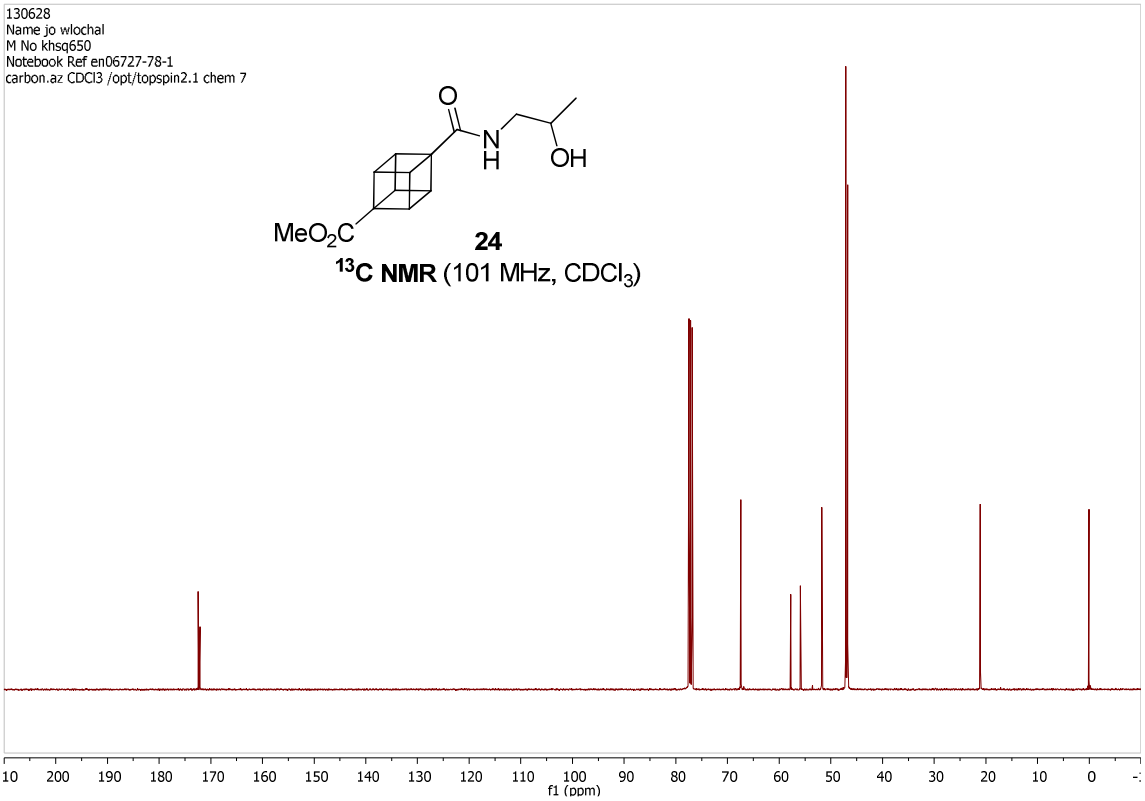
MeO2C
24
1H NMR (400 MHz, CDCl3)
f1 (ppm)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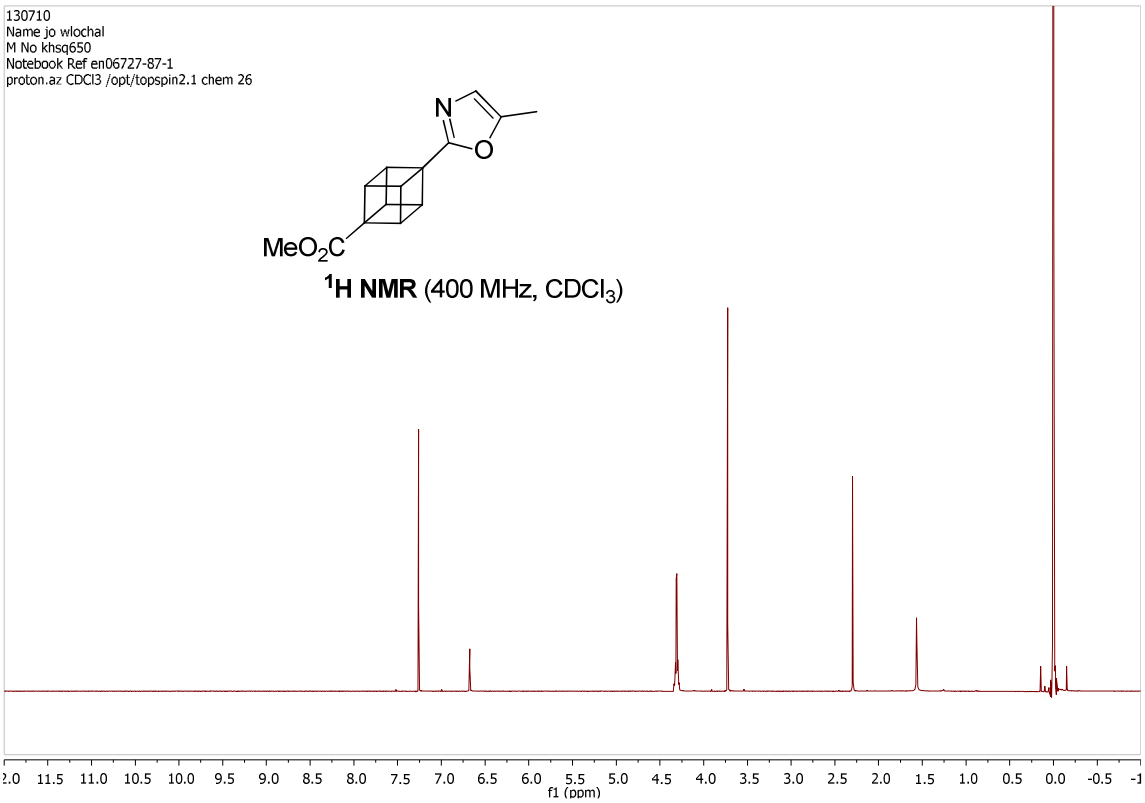
OH
MeO2C
24
13C NMR (101 MHz, CDCl3)
f1 (ppm)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Name jo wlochal
M No khsq650
Notebook Ref en06727-87-1
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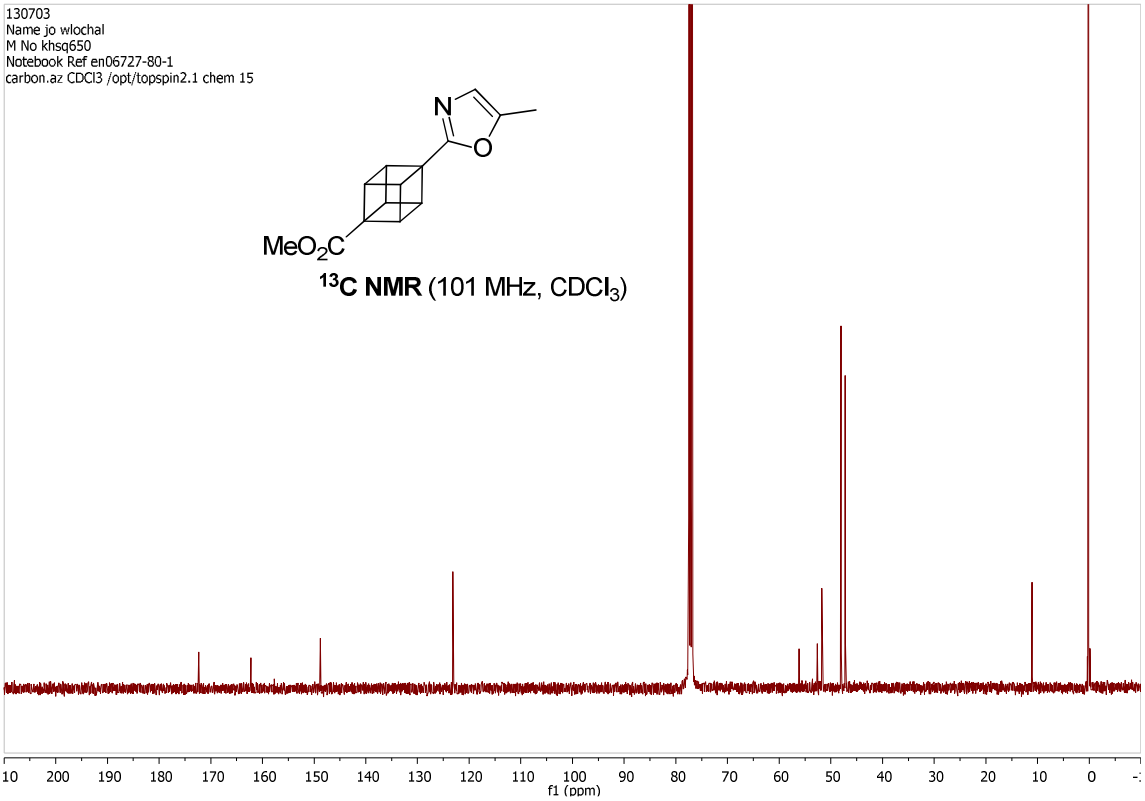
O
MeO2C
1H NMR (400 MHz, CDCl3)
f1 (ppm)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M No khsq650
Notebook Ref en06727-80-1
carbon.az CDCl3 /opt/topspin2.1 chem 15
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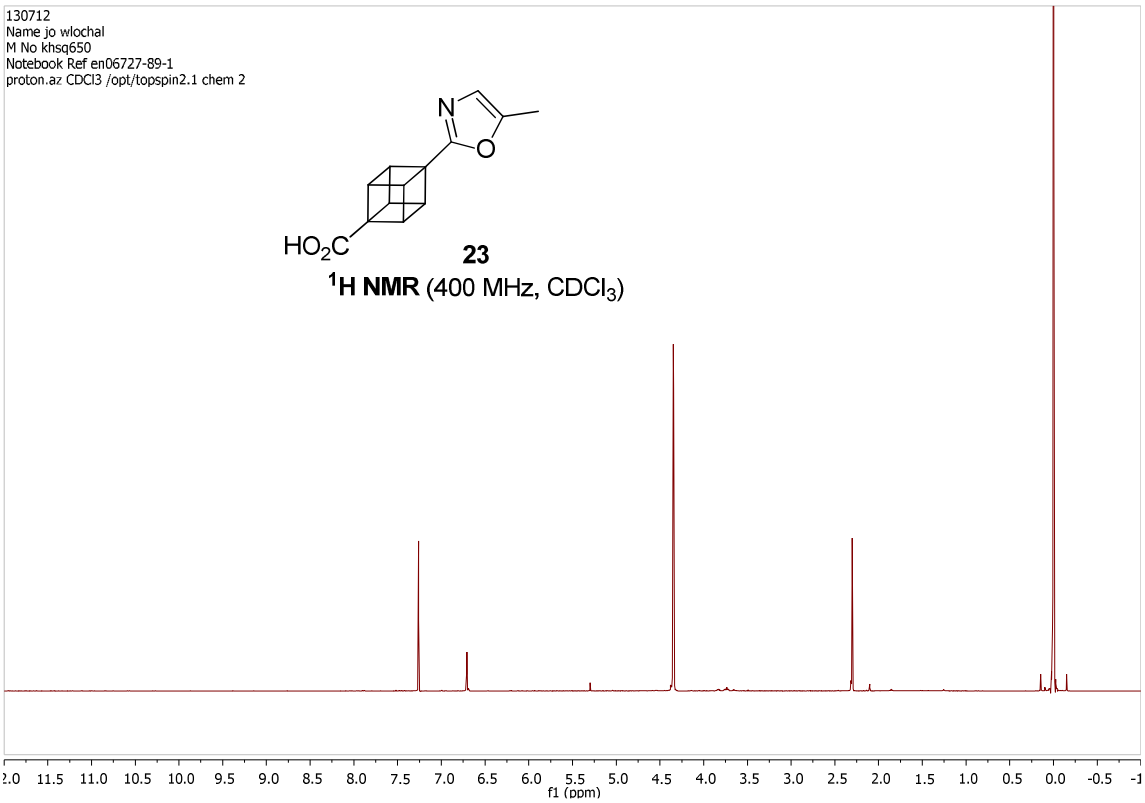
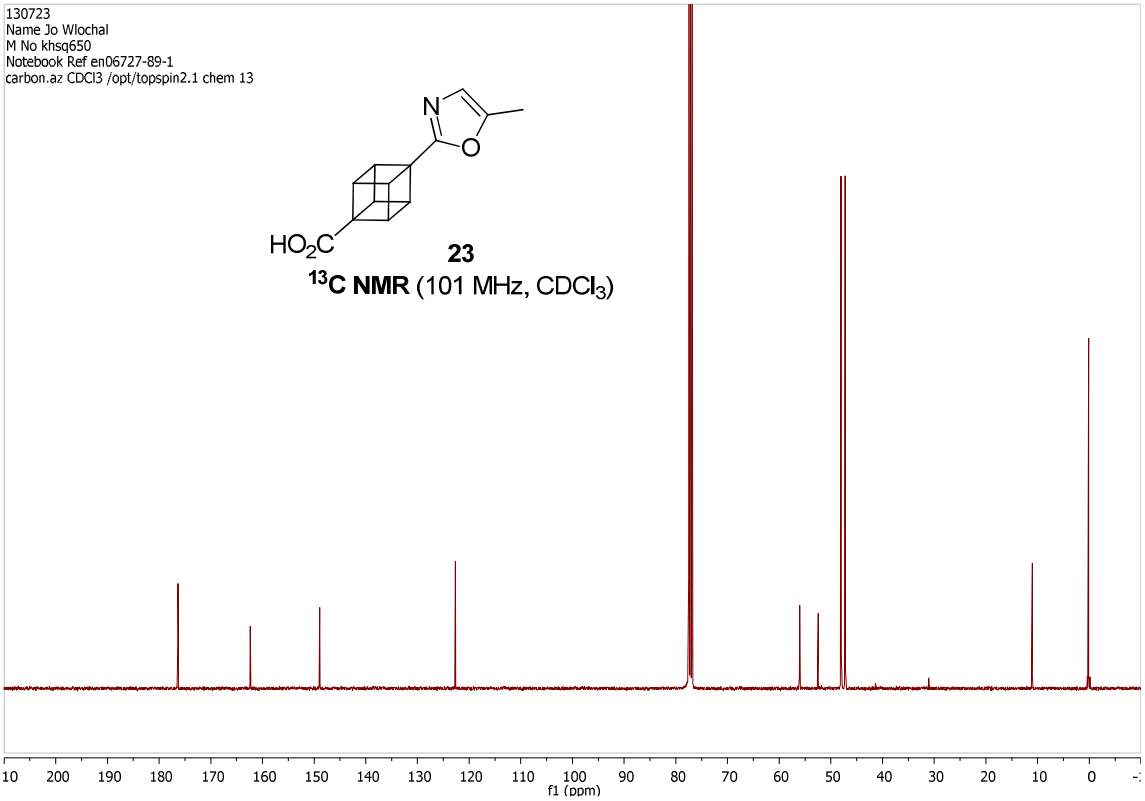
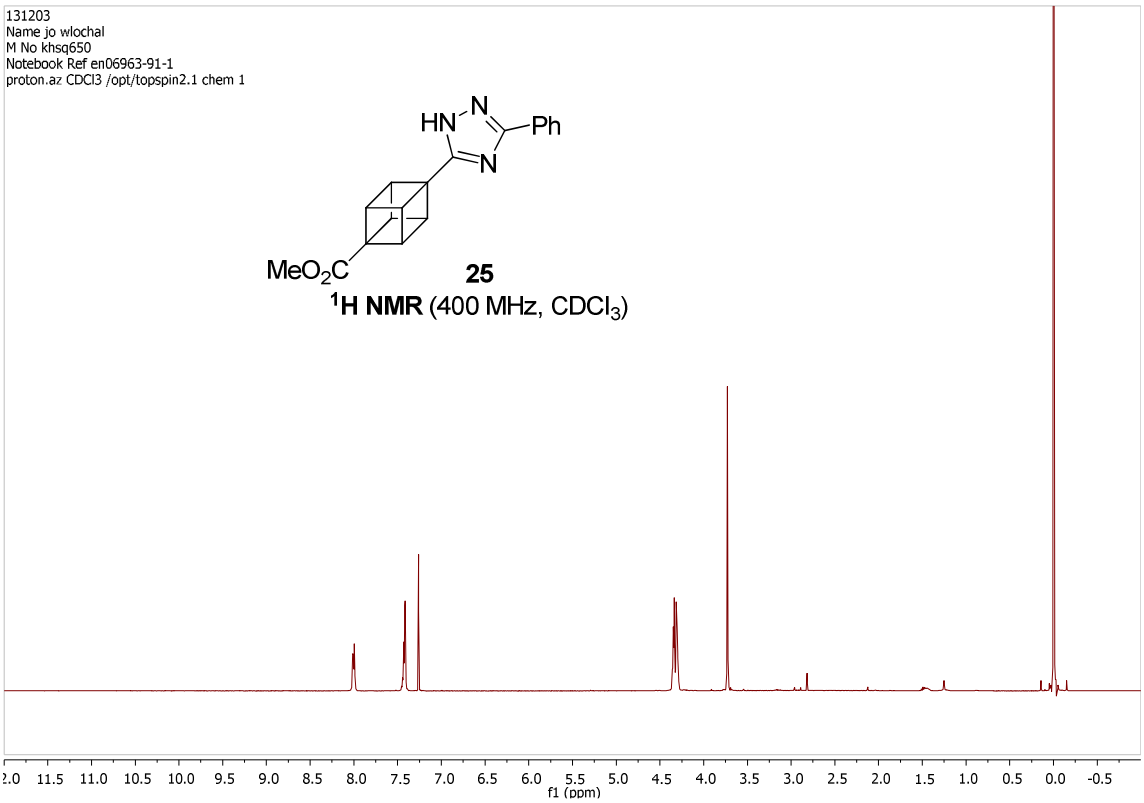
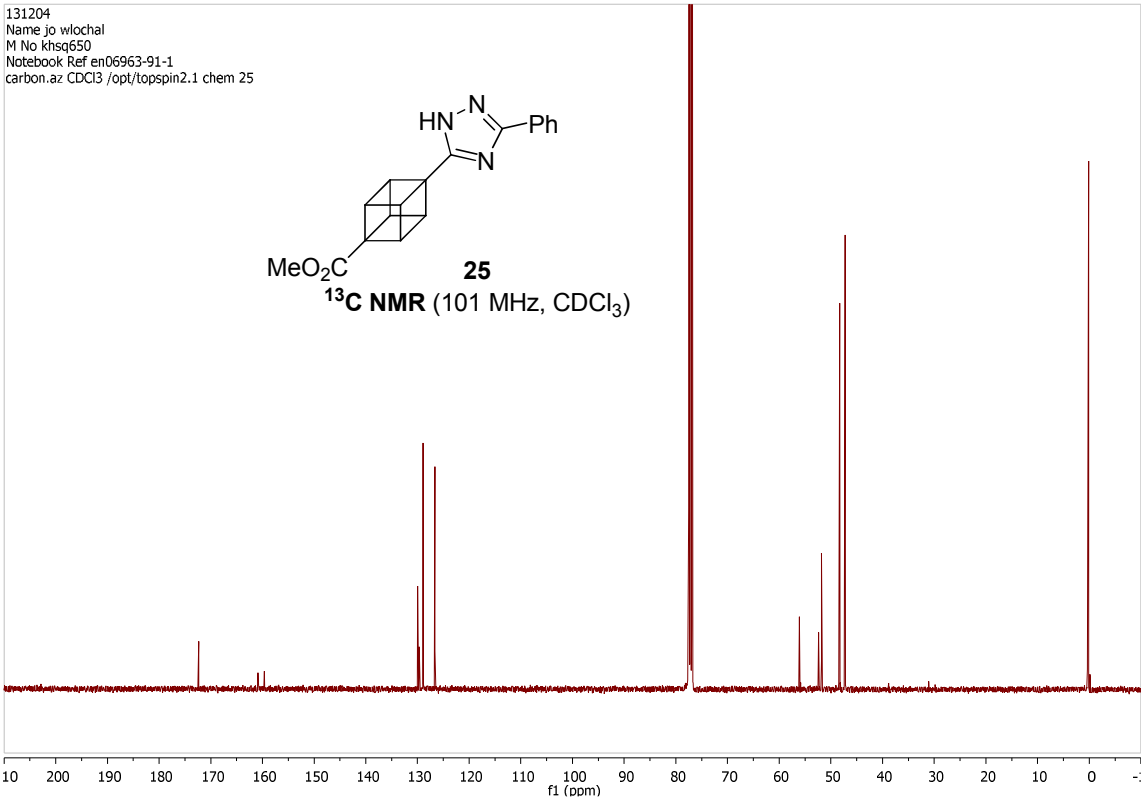
O
MeO2C
13C NMR (101 MHz, CDCl3)
f1 (ppm)


130712
Name jo wlochal
M No khsq650
Notebook Ref en06727-89-1
proton.az CDCl3 /opt/topspin2.1 chem 2
N
O
HO2C
23
1H NMR (400 MHz, CDCl3)
f1 (ppm)


130723
Name Jo Wlochal
M No khsq650
Notebook Ref en06727-89-1
carbon.az CDCl3 /opt/topspin2.1 chem 13
N
O
HO2C
23
13C NMR (101 MHz, CDCl3)
f1 (ppm)


131203
Name jo wlochal
M No khsq650
Notebook Ref en06963-91-1
proton.az CDCl3 /opt/topspin2.1 chem 1
HN
N
Ph
N
MeO2C
25
1H NMR (400 MHz, CDCl3)
f1 (ppm)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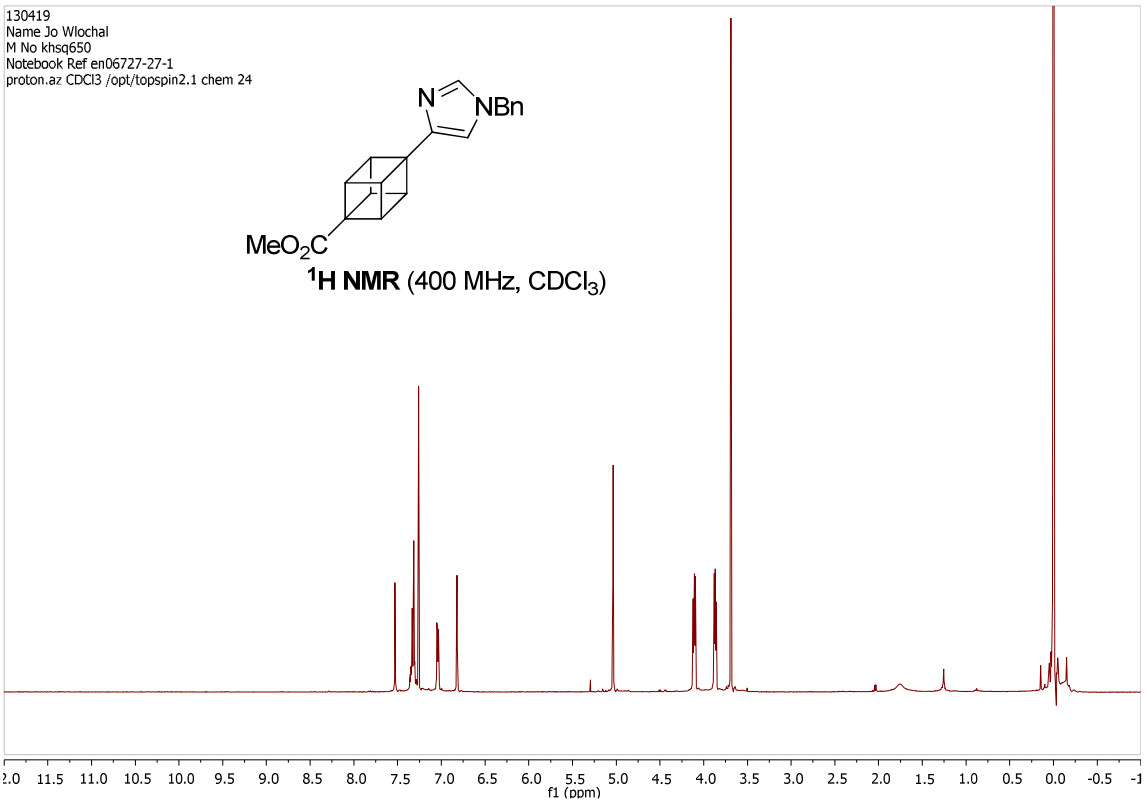
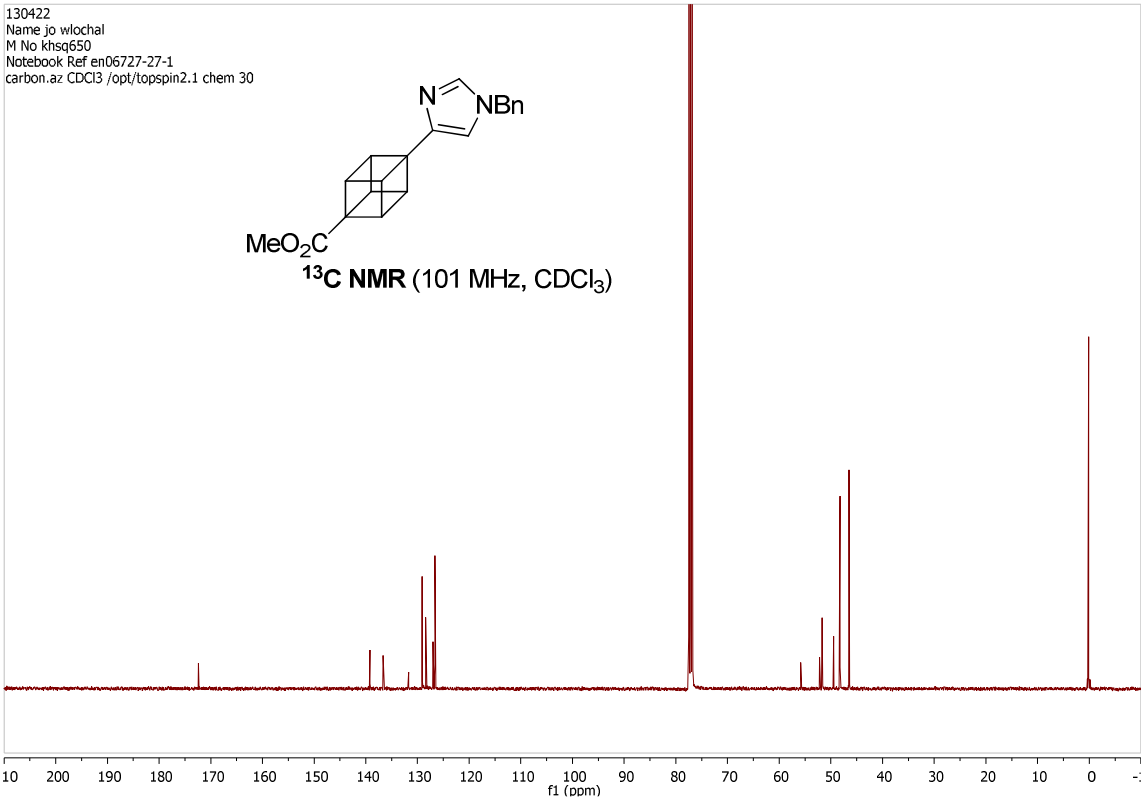
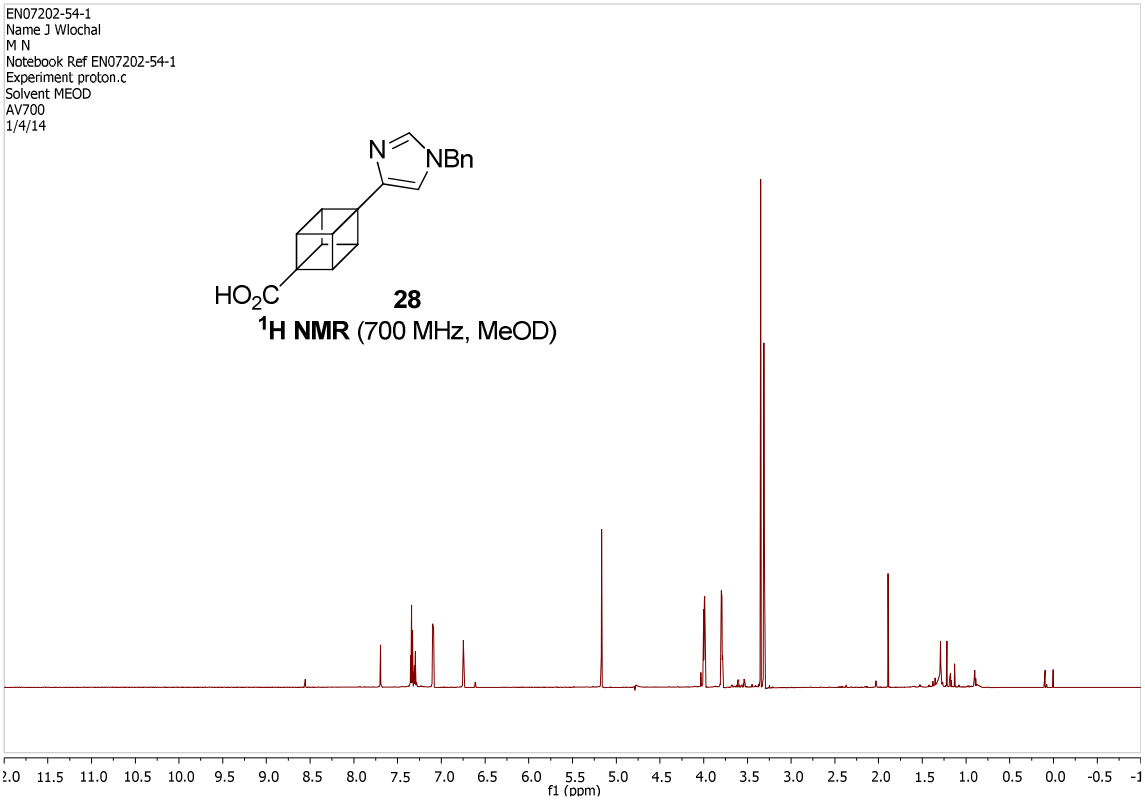
Name jo wlochal
M No khsq650
Notebook Ref en06963-91-1
carbon.az CDCl3 /opt/topspin2.1 chem 25
HN
N
Ph
N
MeO2C
25
13C NMR (101 MHz, CDCl3)
f1 (ppm)


130419
Name Jo Wlochal
M No khsq650
Notebook Ref en06727-27-1
proton.az CDCl3 /opt/topspin2.1 chem 24
N
NBn
MeO2C
1H NMR (400 MHz, CDCl3)
f1 (ppm)


130422
Name jo wlochal
M No khsq650
Notebook Ref en06727-27-1
carbon.az CDCl3 /opt/topspin2.1 chem 30
N
NBn
MeO2C
13C NMR (101 MHz, CDCl3)
f1 (ppm)


EN07202-54-1
Name J Wlochal
M N
Notebook Ref EN07202-54-1
Experiment proton.c
Solvent MEOD
AV700
1/4/14
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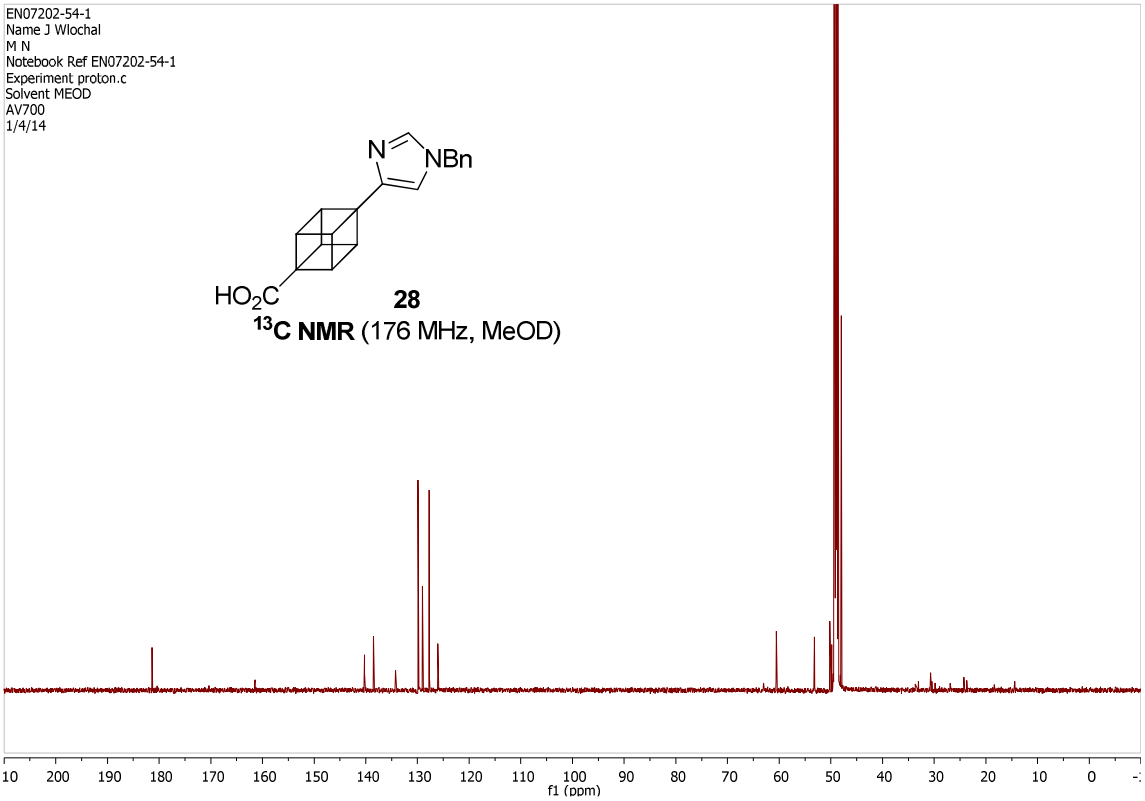
NBn
HO2C
28
1H NMR (700 MHz, MeOD)
f1 (ppm)


EN07202-54-1
Name J Wlochal
M N
Notebook Ref EN07202-54-1
Experiment proton.c
Solvent MEOD
AV700
1/4/14
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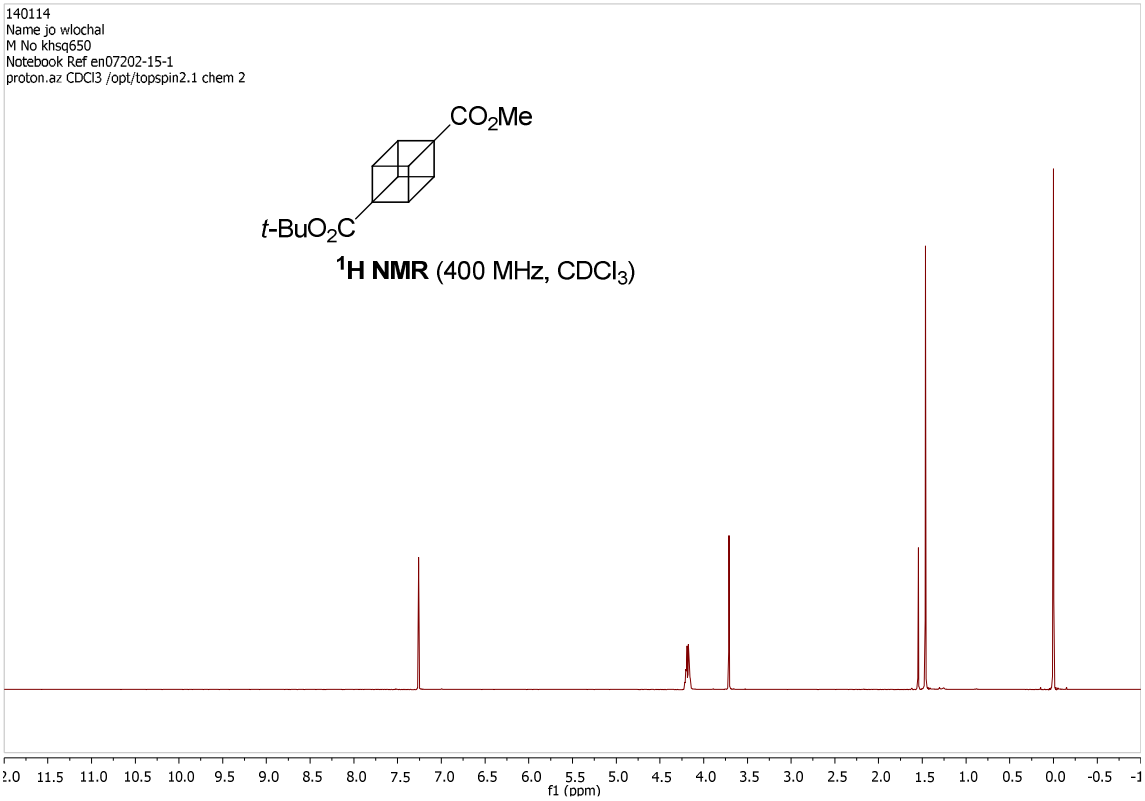
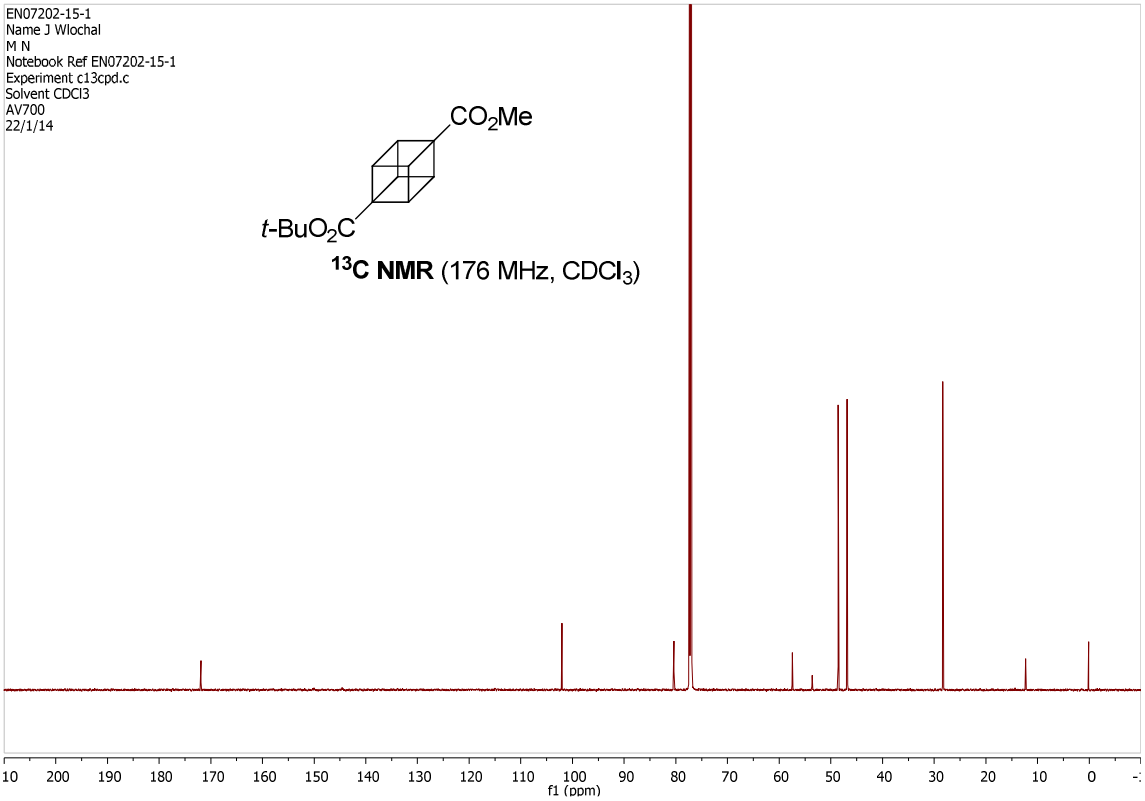
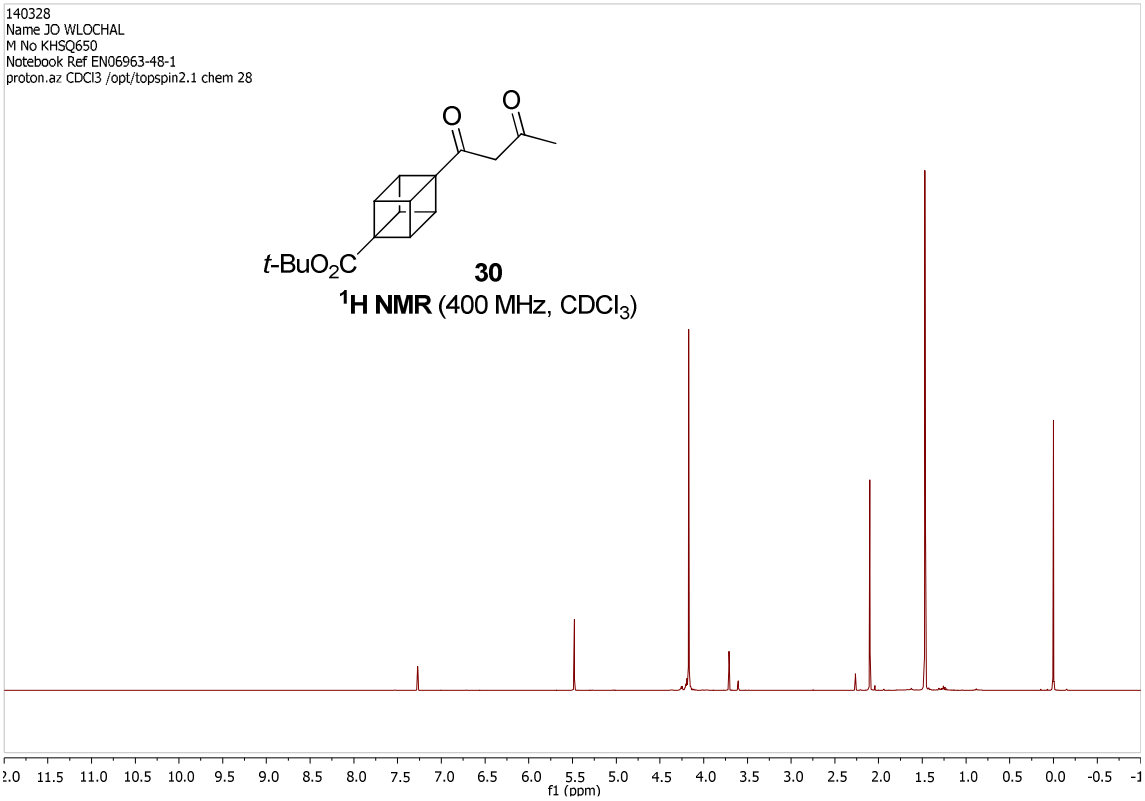
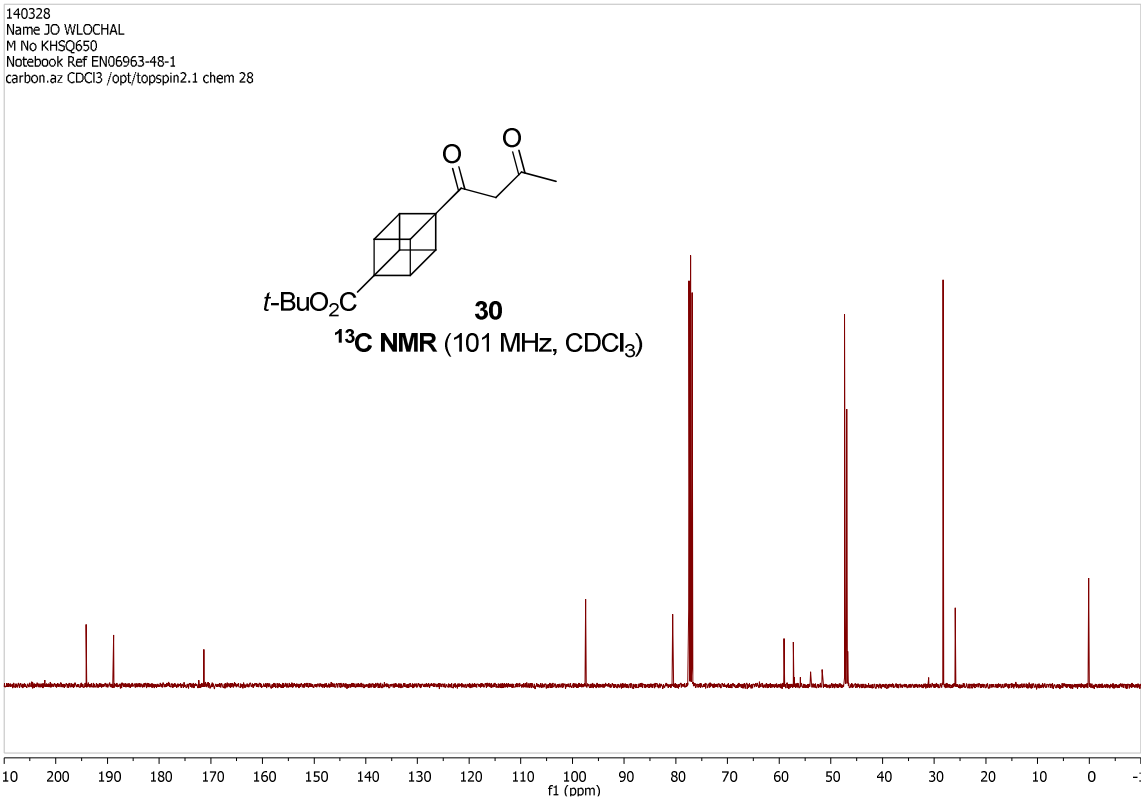
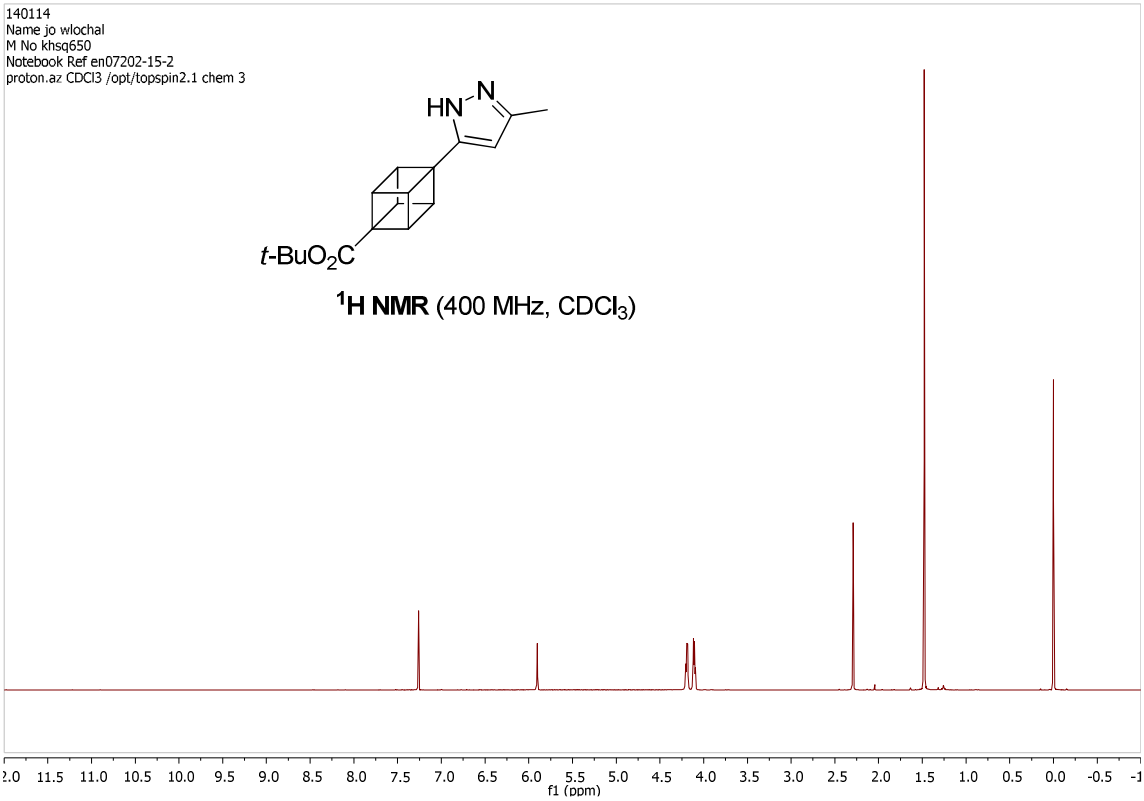
NBn
HO2C
28
13C NMR (176 MHz, MeOD)
f1 (ppm)


140114
Name jo wlochal
M No khsq650
Notebook Ref en07202-15-1
proton.az CDCl3 /opt/topspin2.1 chem 2
CO2Me
t-BuO2C
1H NMR (400 MHz, CDCl3)
f1 (ppm)


EN07202-15-1
Name J Wlochal
M N
Notebook Ref EN07202-15-1
Experiment c13cpd.c
Solvent CDCl3
AV700
22/1/14
CO2Me
t-BuO2C
13C NMR (176 MHz, CDCl3)
f1 (ppm)


140328
Name JO WLOCHAL
M No KHSQ650
Notebook Ref EN06963-48-1
proton.az CDCl3 /opt/topspin2.1 chem 28
O
O
t-BuO2C
30
1H NMR (400 MHz, CDCl3)
f1 (ppm)


140328
Name JO WLOCHAL
M No KHSQ650
Notebook Ref EN06963-48-1
carbon.az CDCl3 /opt/topspin2.1 chem 28
O
O
t-BuO2C
30
13C NMR (101 MHz, CDCl3)
f1 (ppm)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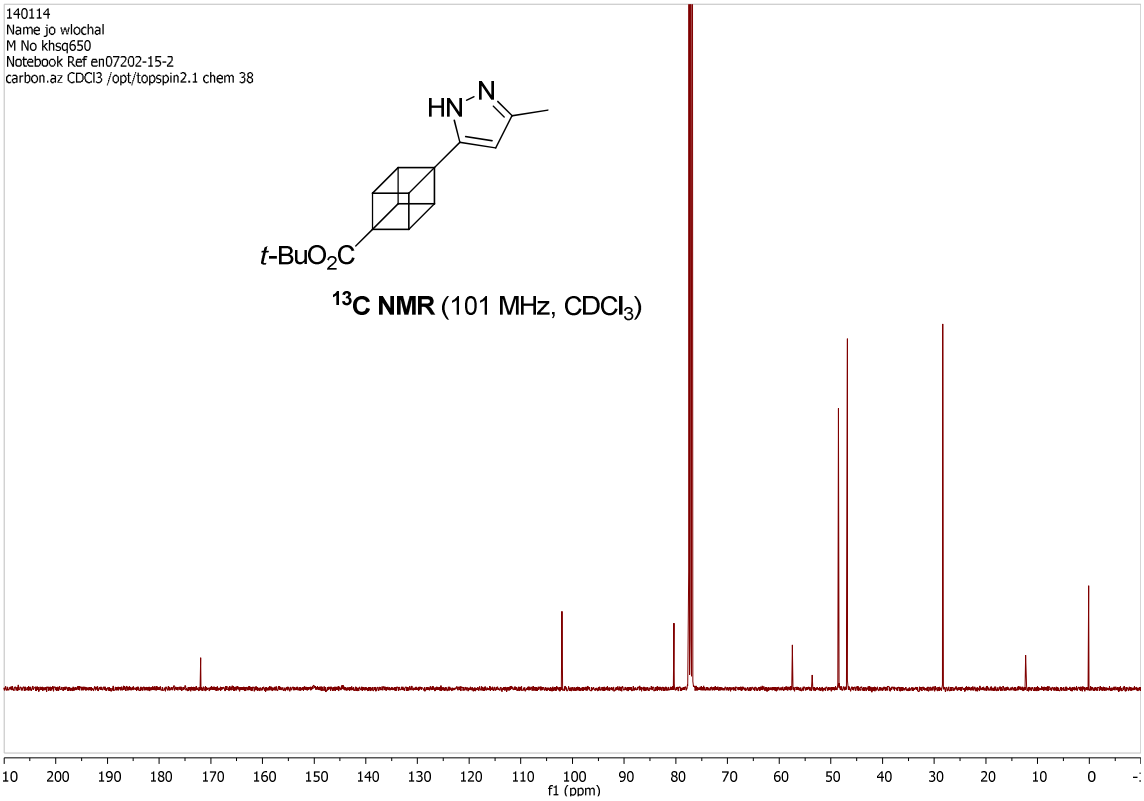
Name jo wlochal
M No khsq650
Notebook Ref en07202-15-2
proton.az CDCl3 /opt/topspin2.1 chem 3
HN
N
t-BuO2C
1H NMR (400 MHz, CDCl3)
f1 (ppm)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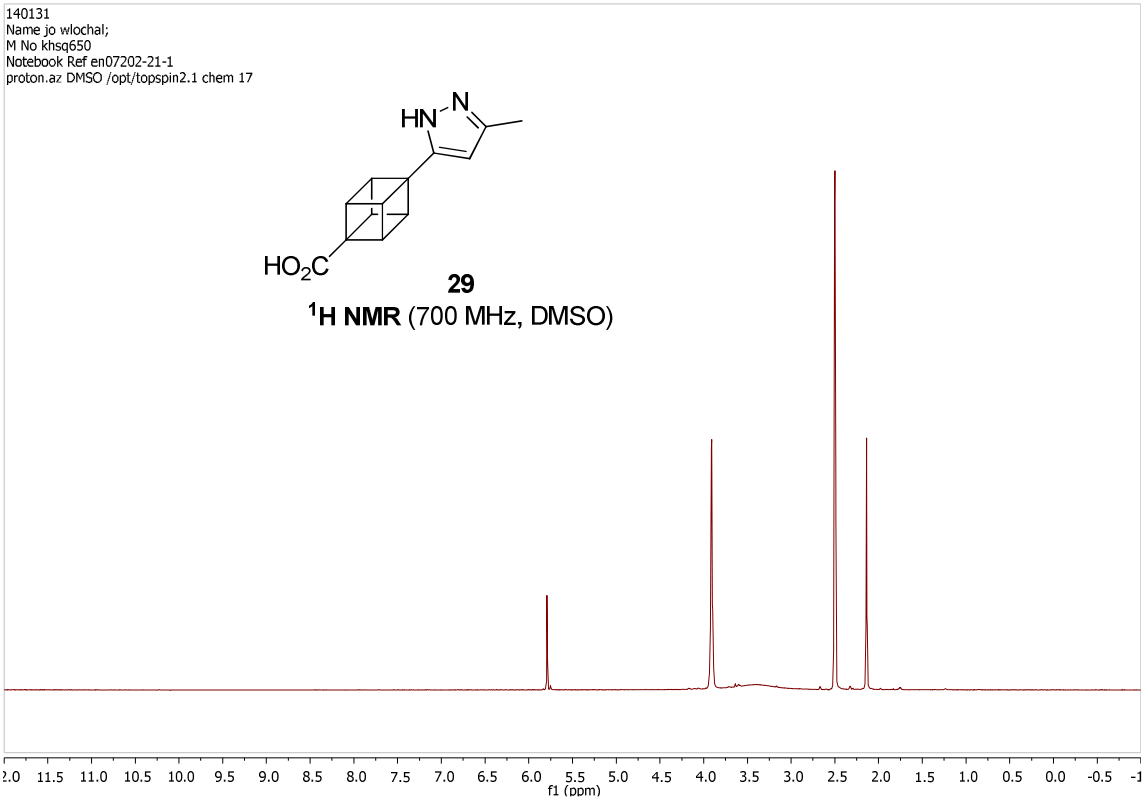
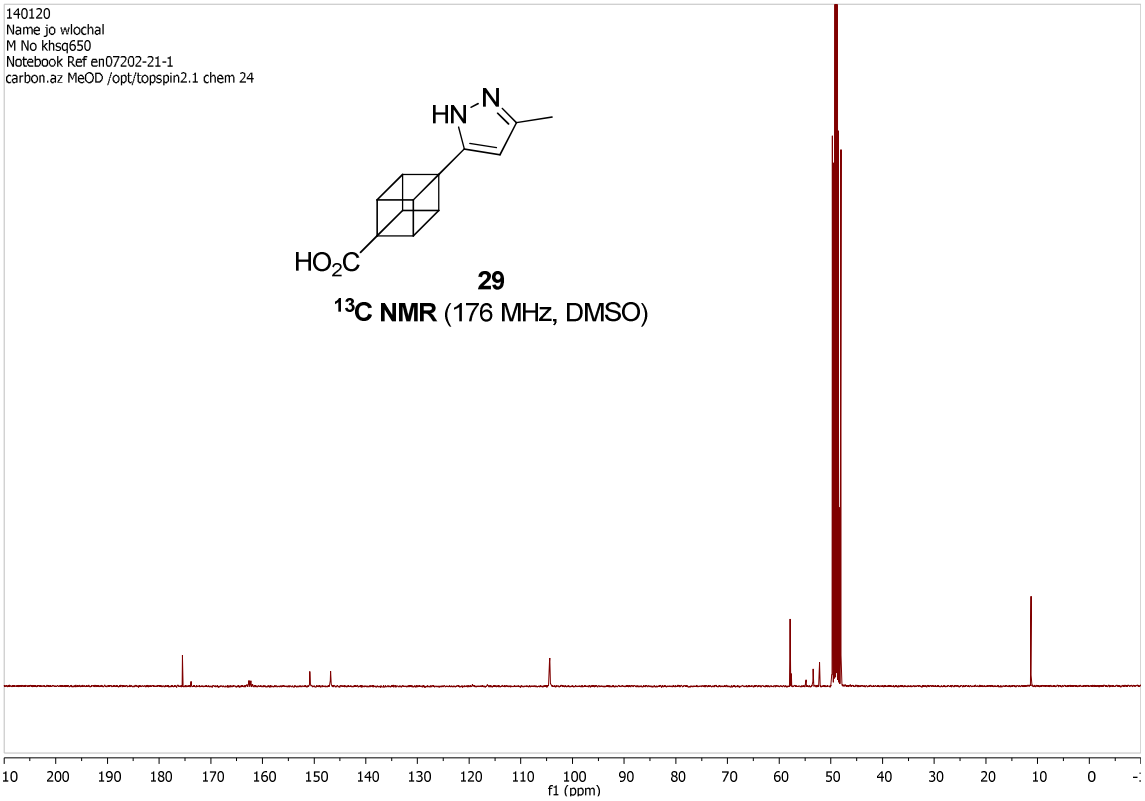
Name jo wlochal
M No khsq650
Notebook Ref en07202-15-2
carbon.az CDCl3 /opt/topspin2.1 chem 38
HN
N
t-BuO2C
13C NMR (101 MHz, CDCl3)
f1 (ppm)


140131
Name jo wlochal;
M No khsq650
Notebook Ref en07202-21-1
proton.az DMSO /opt/topspin2.1 chem 17
HN
N
HO2C
29
1H NMR (700 MHz, DMSO)
f1 (ppm)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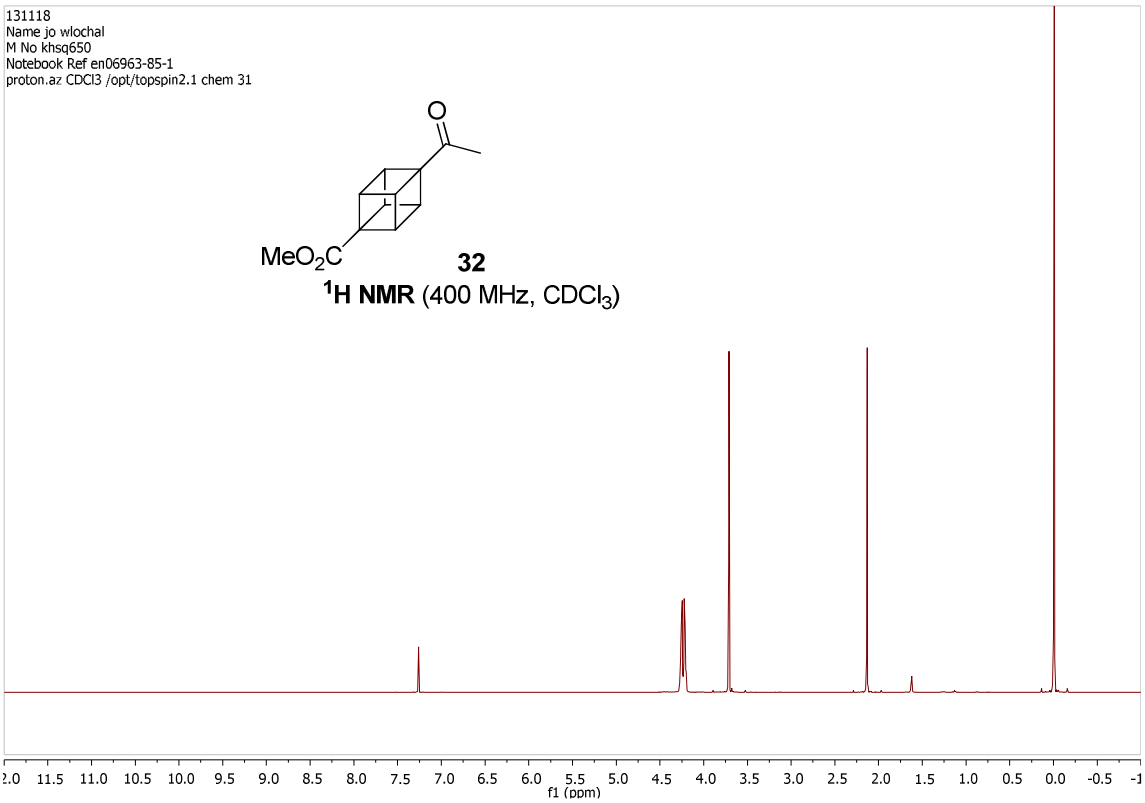
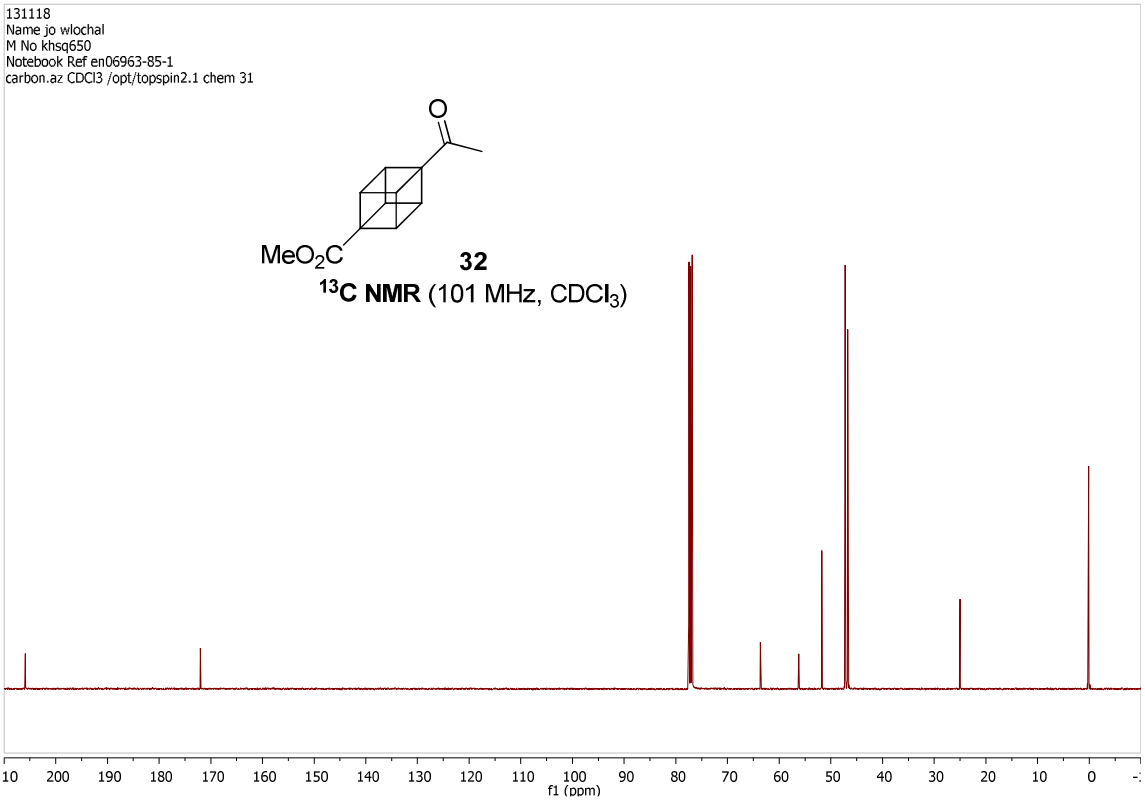
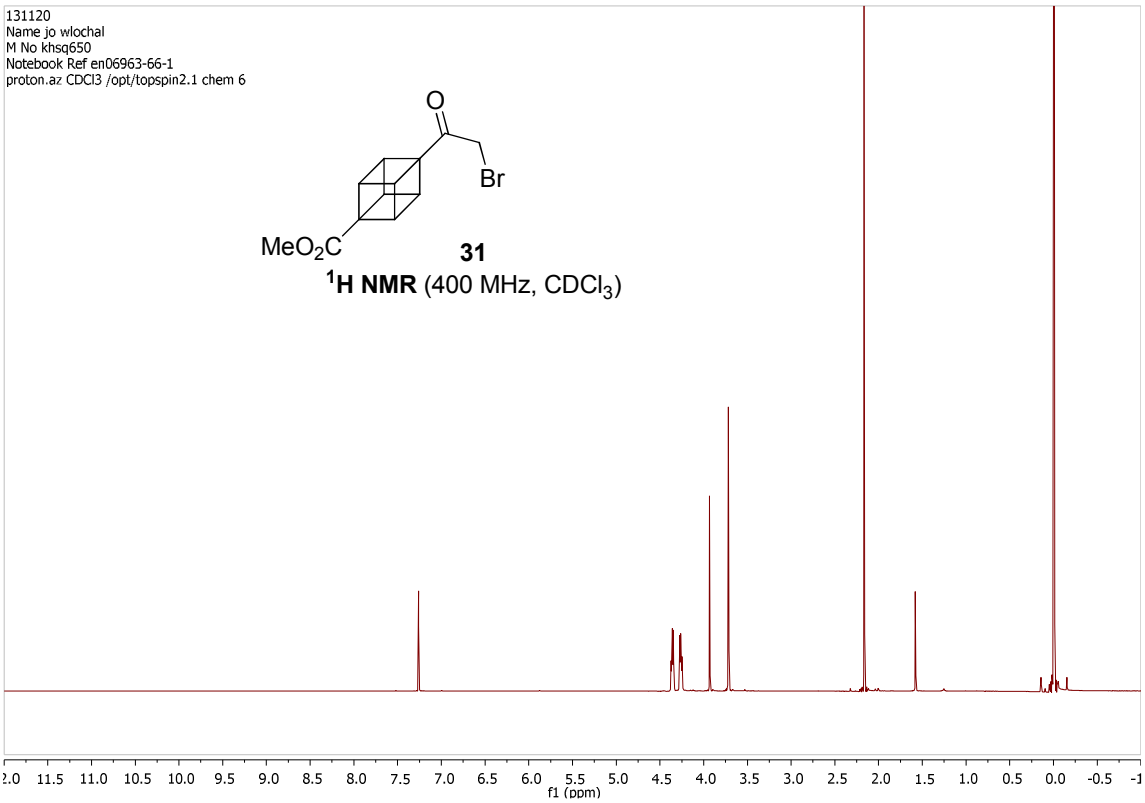
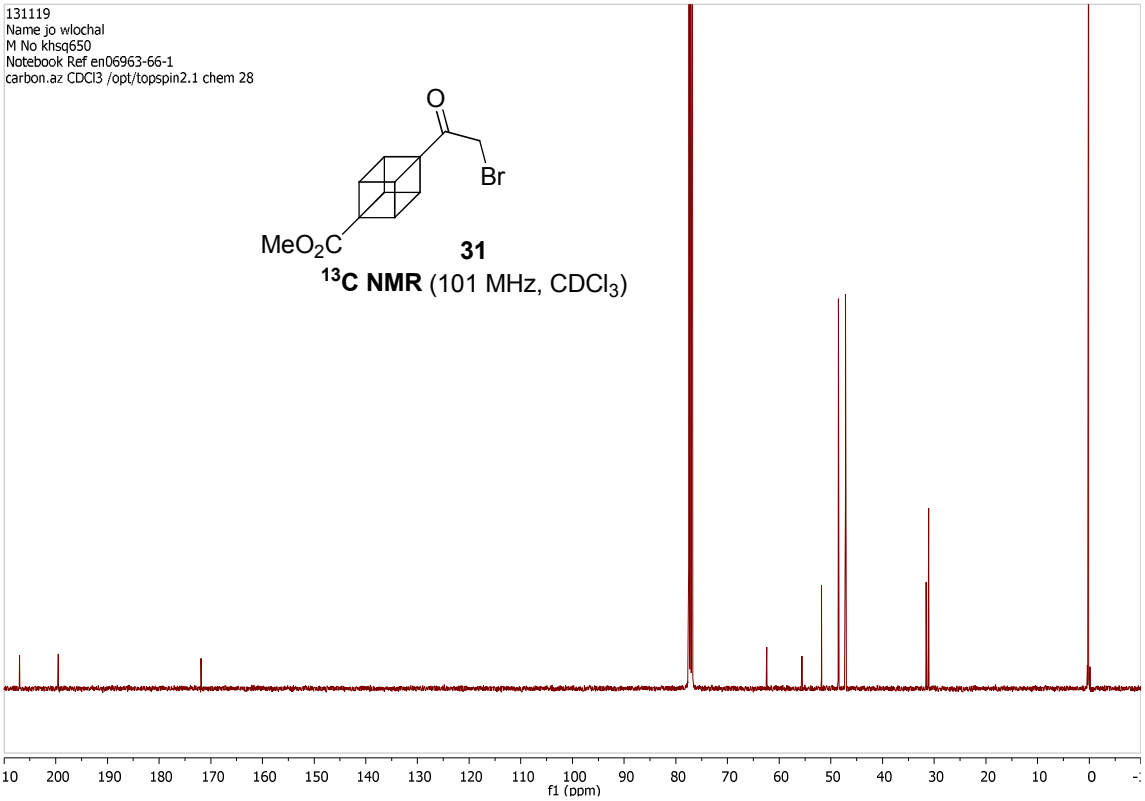
Name jo wlochal
M No khsq650
Notebook Ref en07202-21-1
carbon.az MeOD /opt/topspin2.1 chem 24
HN
N
HO2C
29
13C NMR (176 MHz, DMSO)
f1 (ppm)


131118
Name jo wlochal
M No khsq650
Notebook Ref en06963-85-1
proton.az CDCl3 /opt/topspin2.1 chem 31
O
MeO2C
32
1H NMR (400 MHz, CDCl3)
f1 (ppm)


131118
Name jo wlochal
M No khsq650
Notebook Ref en06963-85-1
carbon.az CDCl3 /opt/topspin2.1 chem 31
O
MeO2C
32
13C NMR (101 MHz, CDCl3)
f1 (ppm)


131120
Name jo wlochal
M No khsq650
Notebook Ref en06963-66-1
proton.az CDCl3 /opt/topspin2.1 chem 6
O
Br
MeO2C
31
1H NMR (400 MHz, CDCl3)
f1 (ppm)


131119
Name jo wlochal
M No khsq650
Notebook Ref en06963-66-1
carbon.az CDCl3 /opt/topspin2.1 chem 28
O
Br
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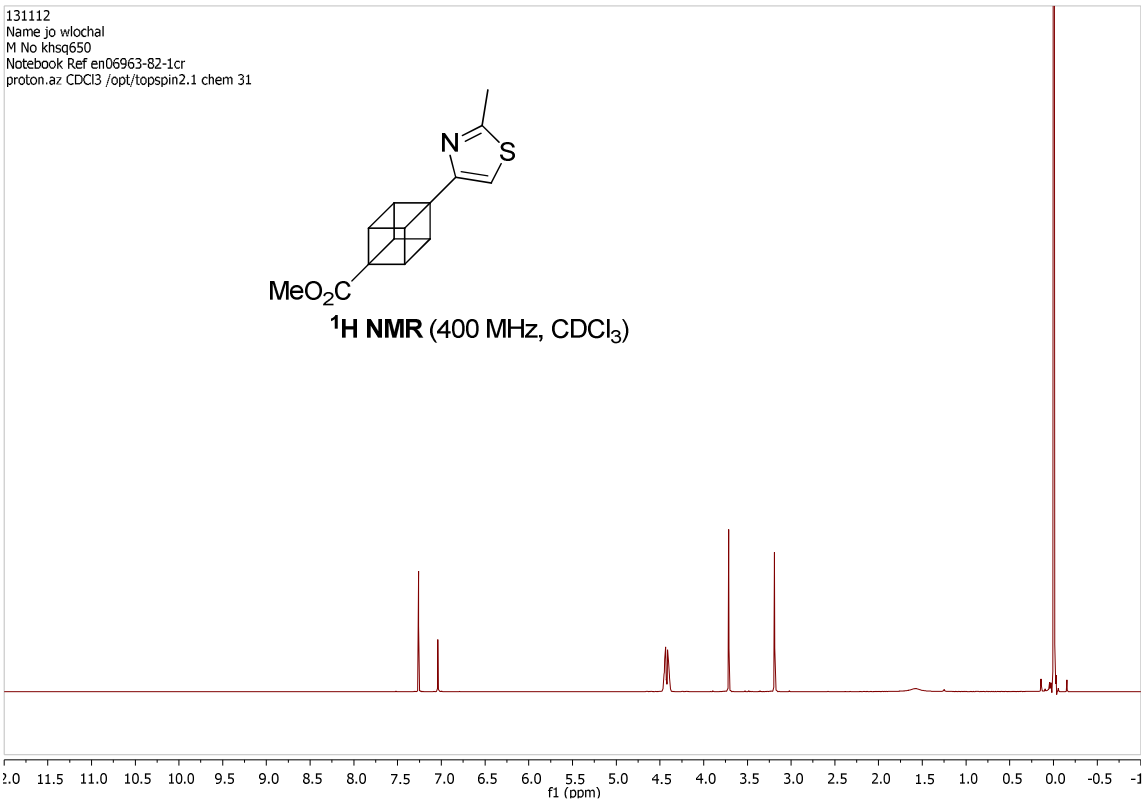
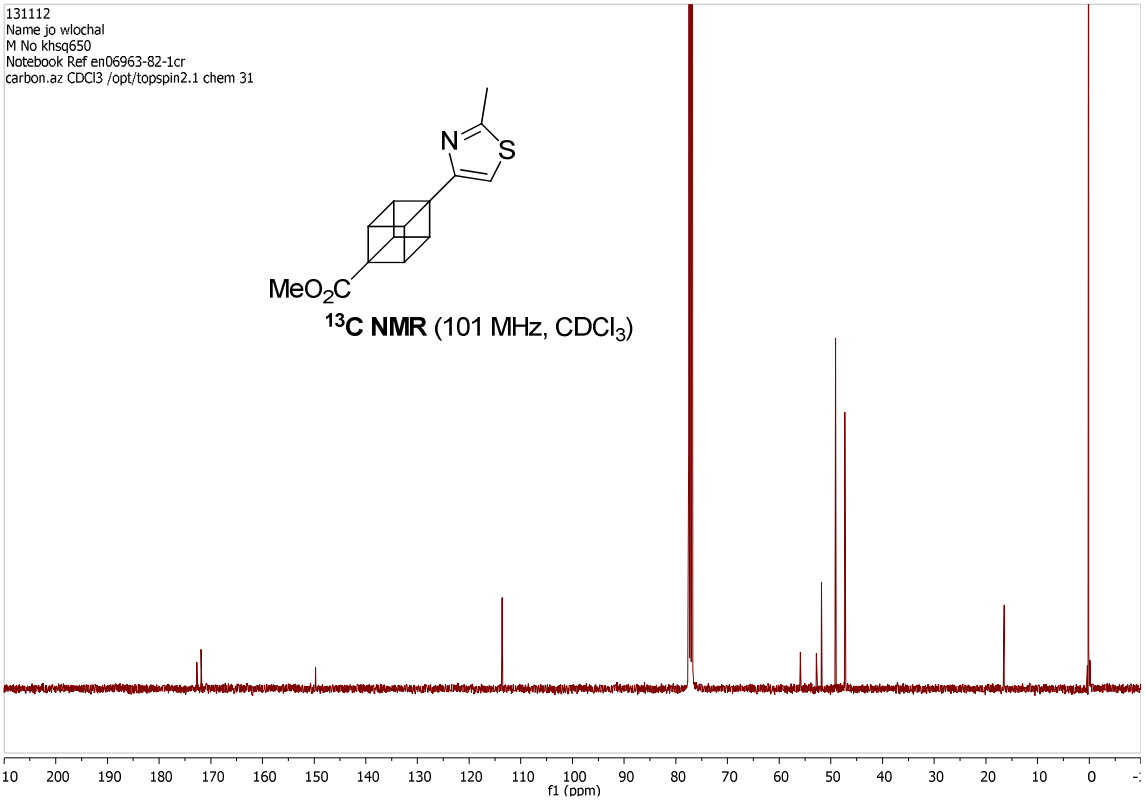
31
13C NMR (101 MHz, CDCl3)
f1 (ppm)


131112
Name jo wlochal
M No khsq650
Notebook Ref en06963-82-1cr
proton.az CDCl3 /opt/topspin2.1 chem 31
N
S
MeO2C
1H NMR (400 MHz, CDCl3)
f1 (ppm)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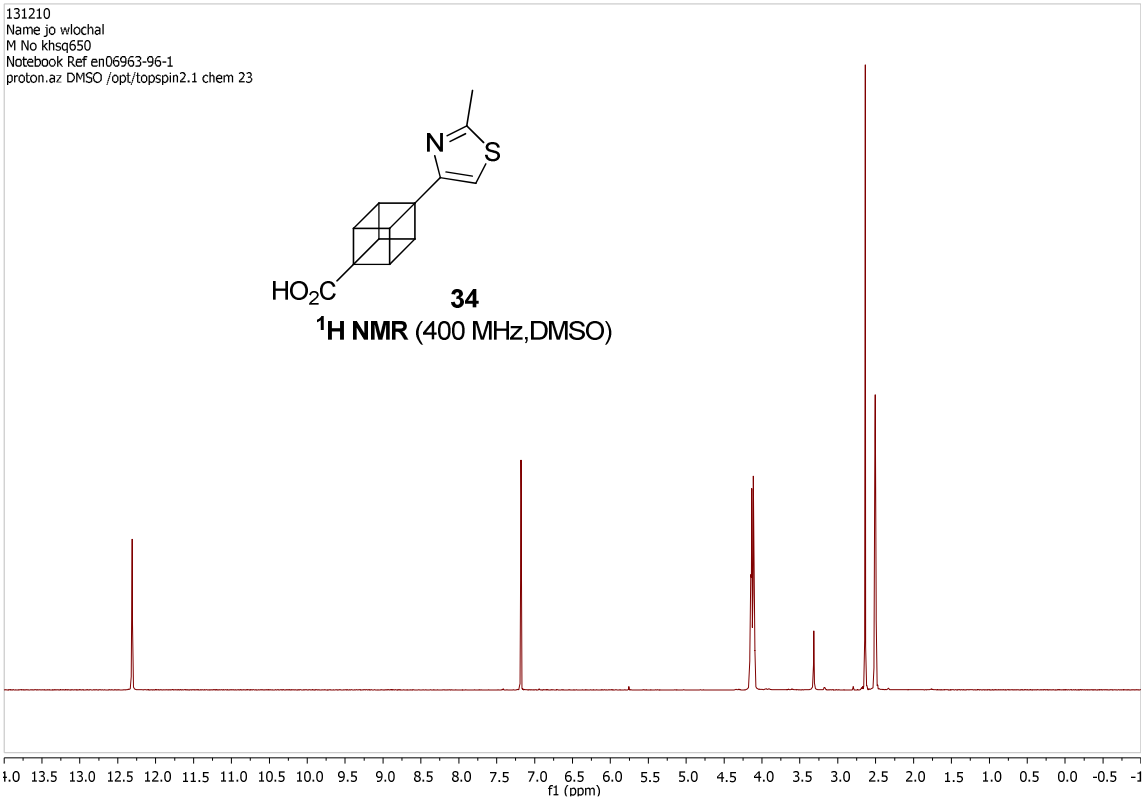
Name jo wlochal
M No khsq650
Notebook Ref en06963-82-1cr
carbon.az CDCl3 /opt/topspin2.1 chem 31
N
S
MeO2C
13C NMR (101 MHz, CDCl3)
f1 (ppm)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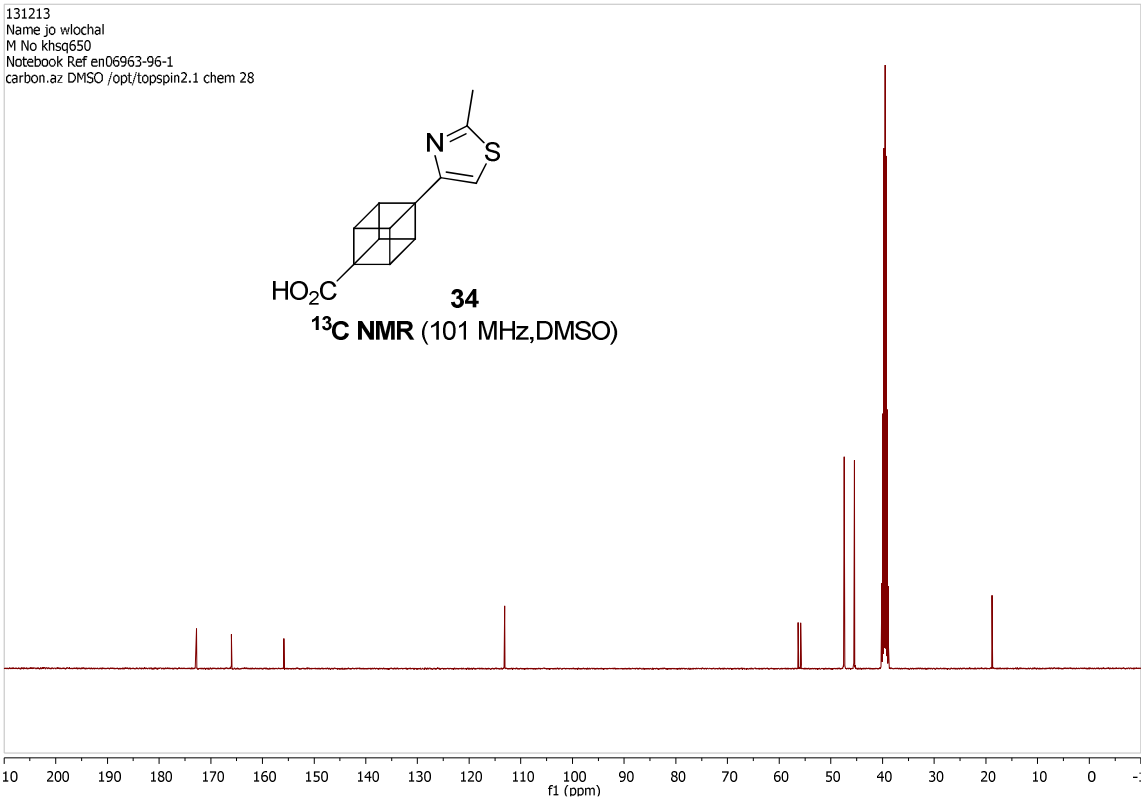
Name jo wlochal
M No khsq650
Notebook Ref en06963-96-1
proton.az DMSO /opt/topspin2.1 chem 23
N
S
HO2C
34
1H NMR (400 MHz,DMSO)
f1 (ppm)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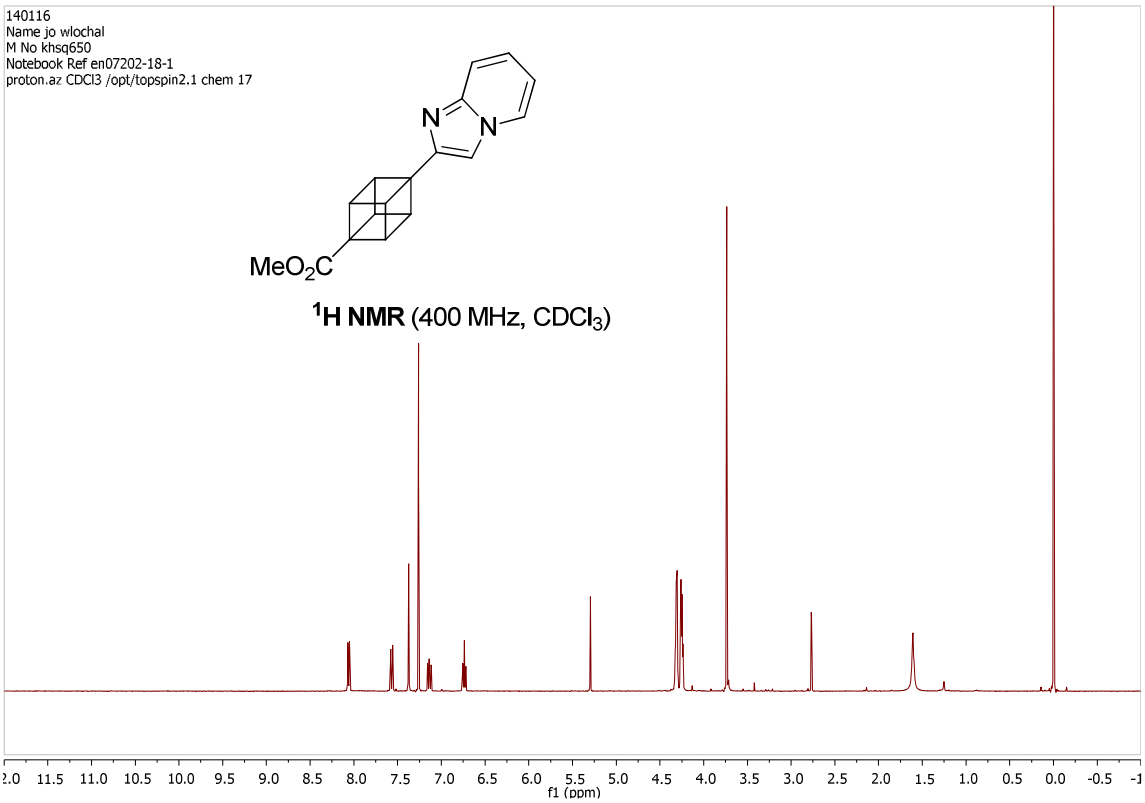
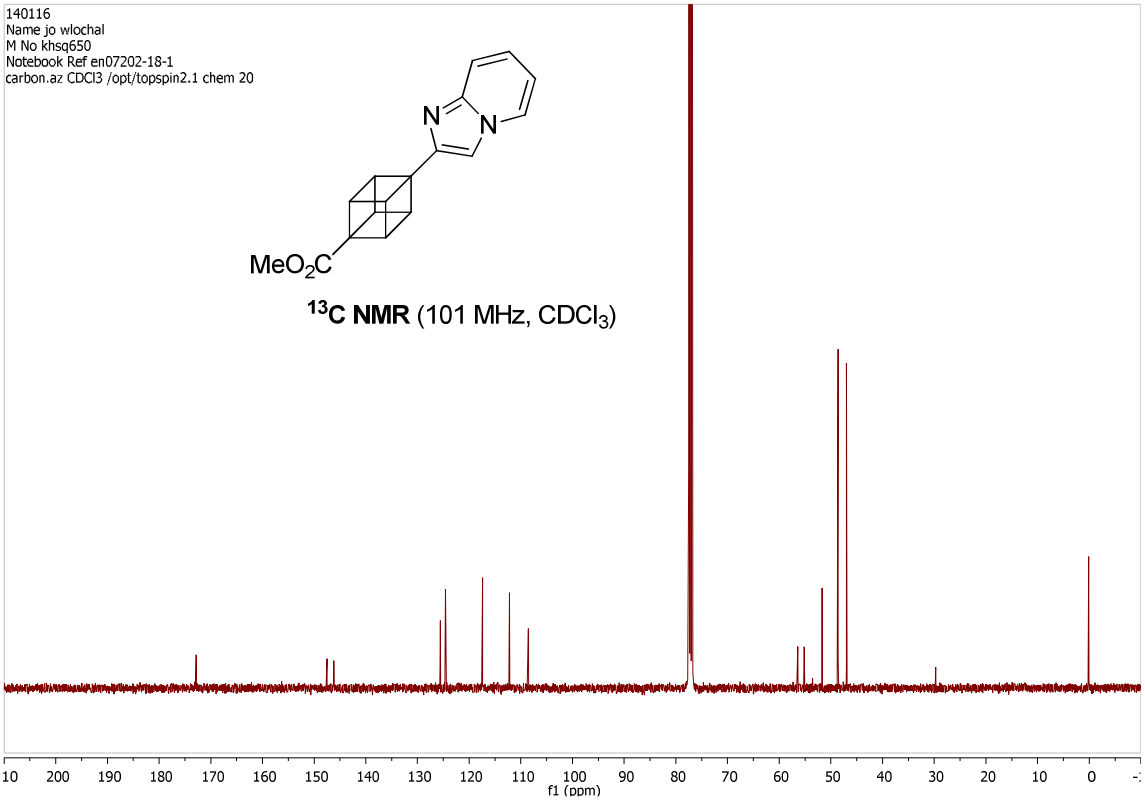
Name jo wlochal
M No khsq650
Notebook Ref en06963-96-1
carbon.az DMSO /opt/topspin2.1 chem 28
N
S
HO2C
34
13C NMR (101 MHz,DMSO)
f1 (ppm)


140116
Name jo wlochal
M No khsq650
Notebook Ref en07202-18-1
proton.az CDCl3 /opt/topspin2.1 chem 17
N
N
MeO2C
1H NMR (400 MHz, CDCl3)
f1 (ppm)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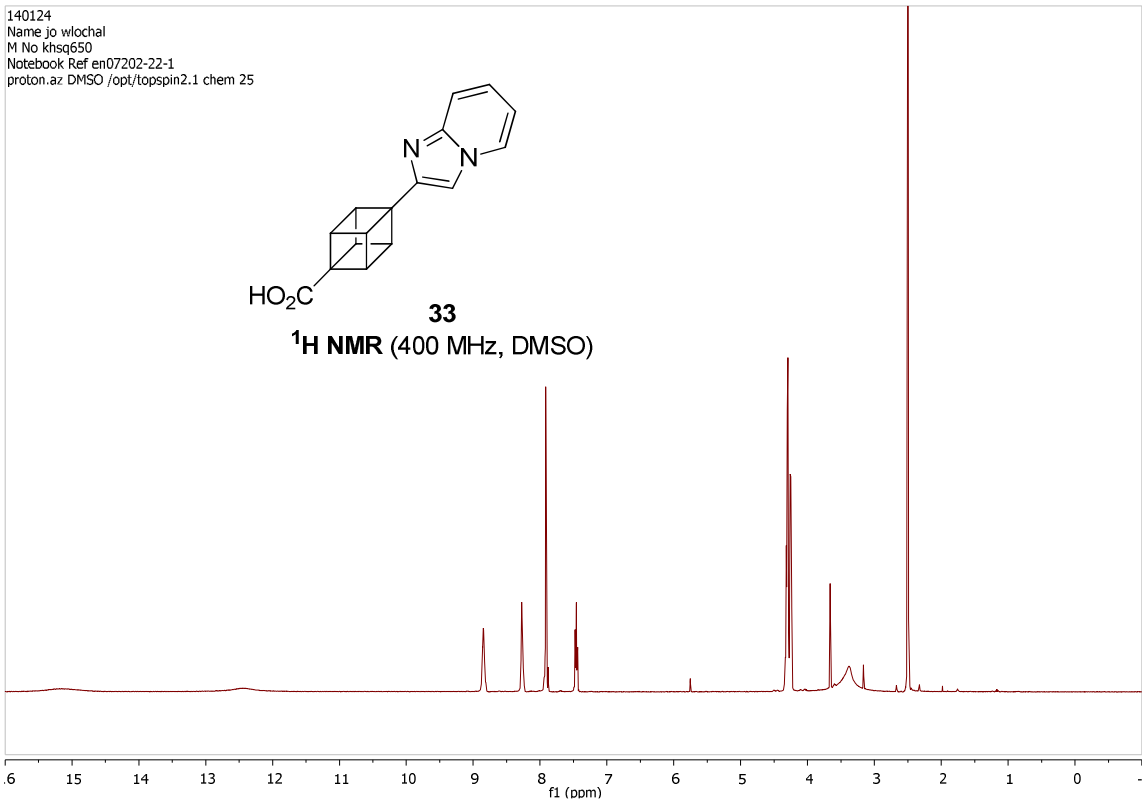
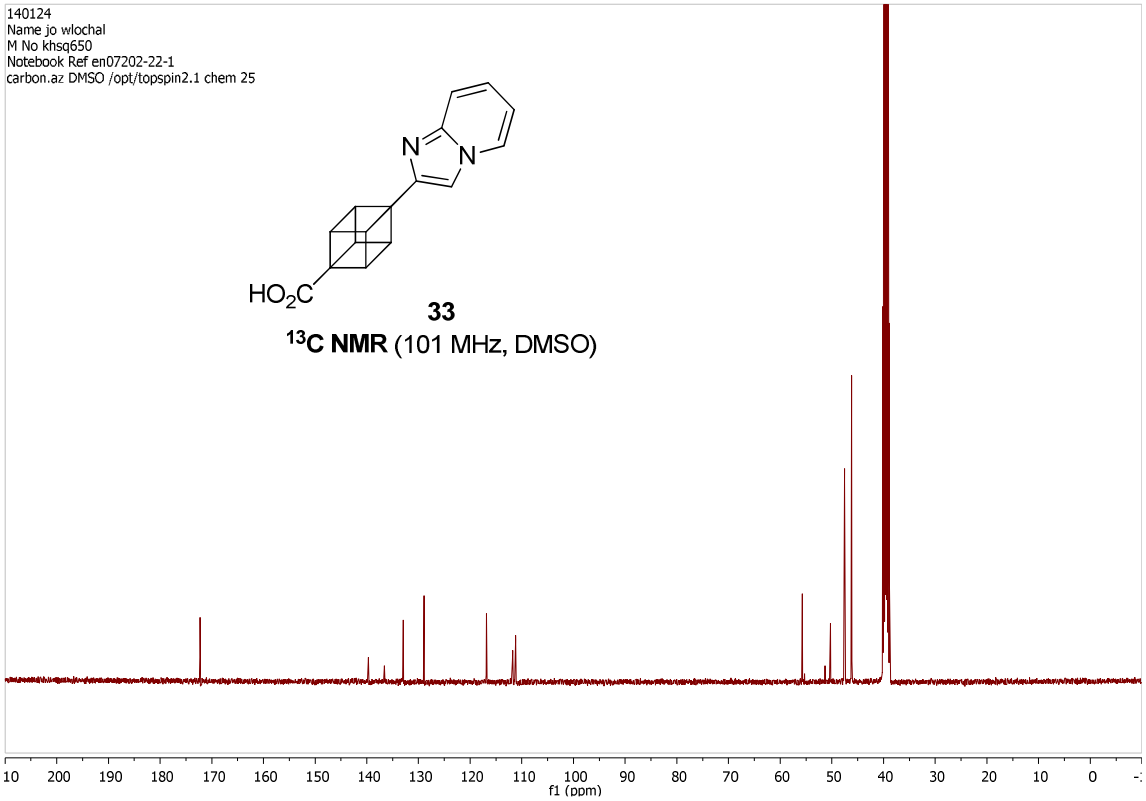
Name jo wlochal
M No khsq650
Notebook Ref en07202-18-1
carbon.az CDCl3 /opt/topspin2.1 chem 20
N
N
MeO2C
13C NMR (101 MHz, CDCl3)
f1 (ppm)


140124
Name jo wlochal
M No khsq650
Notebook Ref en07202-22-1
proton.az DMSO /opt/topspin2.1 chem 25
N
N
HO2C
33
1H NMR (400 MHz, DMSO)
f1 (ppm)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Name jo wlochal
M No khsq650
Notebook Ref en07202-22-1
carbon.az DMSO /opt/topspin2.1 chem 25
N
N
HO2C
33
13C NMR (101 MHz, DMSO)
f1 (ppm)