Electronic Supplementary Information

A Protocol for Amide Bond Formation with Electron Deficient Amines and Sterically Hindered Substrates

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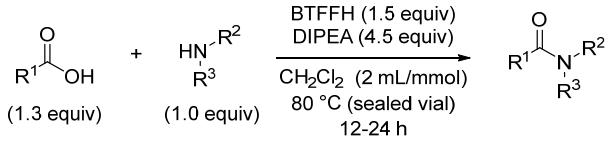
General Information

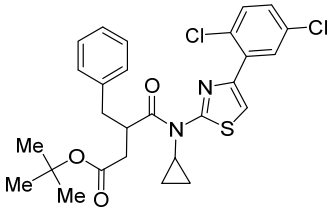
All commercial starting materials and solvents were used as received without further purification. DMF and CH_2Cl_2 were dried over 4 Å sieves. DIPEA was dried over 3 Å sieves. Microwave chemistry was performed in a Biotage Initiator+ EU microwave reactor. Purification by flash chromatography was carried out using silica gel 60 (0.040-0.063 mm, Merck). TLC analysis was performed on silica gel 60 F_{254} plates. ^{1}H and ^{13}C NMR spectra were calibrated relative to TMS internal standard or residual solvent peak (^{1}H NMR: 7.26 ppm for $CDCl_3$, 2.50 ppm for DMSO-d_6; ^{13}C NMR: 77.16 ppm for $CDCl_3$, 39.52 ppm for DMSO-d_6). Abbreviations: ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were obtained on Thermo Finnigan TSQ 700 using electrospray ionization (ESI). Melting point ranges were determined on a Standford Research Systems MPA100 using a ramp rate of 1 ^{o}C/min. HPLC analysis was performed using a Dionex 120 C18 column (5 μm, 4.6 mm X 150 mm) or a Gemini C18 column (5 μm, 4.6 mm X 150 mm) with 10% acetonitrile in water (0-1 min), 10-100% acetonitrile in water (1-10 min), 100% acetonitrile (11-15 min) both solvents containing 0.05% trifluoroacetic acid or 0.10% formic acid as modifier, with a flow of 1 mL/min and UV detection at 254 nm.

General Procedure for Amide Coupling

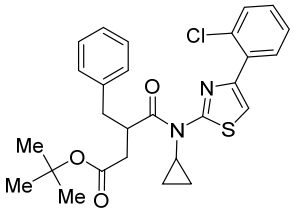


A dry microwave (thick walled Biotage 0.5-2 mL) vial was added carboxylic acid (1.3 equiv) and BTFFH (1.5 equiv) in dry CH_2Cl_2 (2 mL/mmol) under argon. DIPEA (4.5 equiv) was subsequently added and the reaction was stirred under argon for 30 min. The amine (1.0 equiv) was added and the vial was sealed and heated in an oil bath at 80 °C overnight (12 h unless otherwise noted) (CAUTION: Heating CH_2Cl_2 over its boiling point causes overpressure in the reactor). The reaction mixture was cooled to room temperature and diluted with water and extracted with EtOAc (×3). The collected organic phases were combined and washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography.

Procedures and Compound Characterization

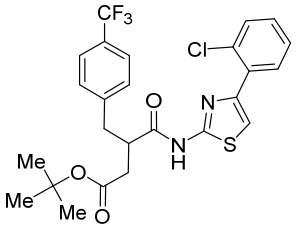


***tert*-Butyl 3-benzyl-4-(cyclopropyl(4-(2,5-dichlorophenyl)-thiazol-2-yl)amino)-4-oxobutanoate (1).** The title compound was synthesized from 2-benzyl-4-(*tert*-butoxy)-4-oxobutanoic acid (171 mg, 0.65 mmol) and *N*-cyclopropyl-4-(2,5-dichlorophenyl)thiazol-2-amine (143 mg, 0.50 mmol) according to the General Procedure, yielding a white amorphous solid (220 mg, 83%) after purification by flash chromatography (EtOAc:petroleum ether, 1:9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.6 Hz, 1H), 7.62 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.28–7.15 (m, 6H), 4.27–4.06 (m, 1H), 3.11–3.04 (m, 1H), 2.95–2.81 (m, 2H), 2.76–2.67 (m, 1H), 2.46–2.39 (m, 1H), 1.38 (s, 9H), 1.32–1.20 (m, 3H), 0.85–0.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 171.2, 159.5, 144.6, 138.1, 134.9, 132.7, 131.6, 131.1, 130.1, 129.0, 128.7, 128.4, 126.9, 115.1, 81.0, 41.7, 38.8, 37.6, 29.9, 28.0, 11.6, 11.3; HRMS (ESI) calcd for $C_{27}H_{28}Cl_2N_2O_3S$ ($M+H^+$): 531.1270, found: 531.1248.

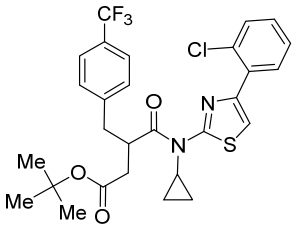


***tert*-Butyl 3-benzyl-4-(cyclopropyl(4-(2-chlorophenyl)-thiazol-2-yl)amino)-4-oxobutanoate (2).** The title compound was synthesized from 2-benzyl-4-(*tert*-butoxy)-4-oxobutanoic acid (172 mg, 0.65 mmol) and *N*-cyclopropyl-4-(2-chlorophenyl)thiazol-2-amine (290 mg, 1.16 mmol) according to the General Procedure with 16 hours reaction time, yielding a white amorphous solid (258 mg, 80%) after purification by flash chromatography (EtOAc:petroleum ether, 1:9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.54 (s, 1H), 7.45 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.35–7.30 (m, 1H), 7.29–7.19 (m, 4H), 7.18–7.13 (m, 2H), 4.17 (ap br s, 1H), 3.09 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.98–2.89 (m, 1H), 2.84 (dd, *J* = 16.6, 9.7 Hz, 1H), 2.71 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.41 (dd, *J* = 16.7, 4.8 Hz, 1H), 1.38 (s, 9H), 1.28–1.24 (m, 3H), 0.84–0.81 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 171.4, 138.4, 132.2, 131.5, 130.6, 129.2, 128.8, 128.7, 127.02, 126.99, 81.1, 41.9,

38.9, 37.7, 30.2, 28.2, 11.5; HRMS (ESI) calcd for $C_{27}H_{29}ClN_2NaO_3S$ ($M+Na^+$): 519.1480, found: 519.1471.

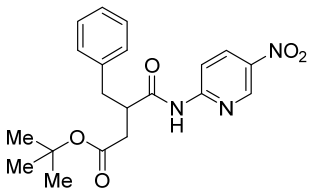


***tert*-Butyl 4-((4-(2-chlorophenyl)thiazol-2-yl)amino)-4-oxo-3-(4-(trifluoromethyl)benzyl)-butanoate (3).** The title compound was synthesized from 4-(*tert*-butoxy)-4-oxo-2-(4-(trifluoromethyl)benzyl)butanoic acid (217 mg, 0.65 mmol) and 4-(2-chlorophenyl)thiazol-2-amine (106 mg, 0.50 mmol) according to the General Procedure with 16 hours reaction time, yielding an orange solid (227 mg, 86%) after purification by flash chromatography (EtOAc:petroleum ether, 0:10→1:9): mp 138.7–140.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.81 (dd, J = 7.6, 1.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.59 (s, 1H), 7.55 (dd, J = 7.8, 1.2 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.46–7.35 (m, 2H), 3.33–3.24 (m, 1H), 3.09–3.01 (m, 1H), 2.87–2.78 (m, 1H), 2.66 (dd, J = 16.6, 10.4 Hz, 1H), 2.29 (dd, J = 16.5, 4.2 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 170.2, 157.0, 145.6, 143.4 (q, J_{CF} = 1.2 Hz), 133.12, 131.08, 131.0, 130.4, 129.9, 129.3, 127.3, 127.2 (q, J_{CF} = 31.5 Hz), 124.4 (q, J_{CF} = 272.1 Hz), 125.2 (q, J_{CF} = 3.6 Hz), 112.8, 80.2, 43.0, 37.4, 36.1, 27.6; HRMS (ESI) calcd for $C_{25}H_{25}ClF_3N_2O_3S$ ($M+H^+$): 525.1221, found: 525.1219.

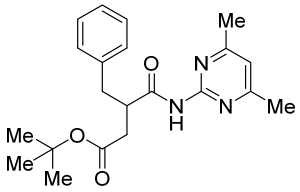


***tert*-Butyl 4-((4-(2-chlorophenyl)thiazol-2-yl)(cyclopropyl)-amino)-4-oxo-3-(4-(trifluoro-methyl)benzyl)butanoate (4).** The title compound was synthesized from 4-(*tert*-butoxy)-4-oxo-2-(4-(trifluoromethyl)benzyl)butanoic acid (217 mg, 0.65 mmol) and *N*-cyclopropyl-4-(2-chlorophenyl)thiazol-2-amine (127 mg, 0.50 mmol) according to the General Procedure with 16 hours reaction time, yielding a white solid (240 mg, 85%) after purification by flash chromatography (EtOAc:petroleum ether, 1:9): mp 113.1–117.5 °C; ^{1}H NMR (400 MHz, DMSO-

d$_6$) δ 7.90 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.72 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.55 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48–7.34 (m, 4H), 4.14 (ap br s, 1H), 3.18–3.03 (m, 2H), 2.89–2.69 (m, 2H), 2.37 (dd, *J* = 16.6, 4.1 Hz, 1H), 1.30 (s, 9H), 1.28–1.12 (m, 3H), 0.88–0.76 (m, 1H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 176.1, 170.6, 143.1, 133.2, 131.3, 131.0, 130.4, 130.1, 129.3, 127.4 (q, J_{CF} = 31.7 Hz), 127.3, 125.3 (q, J_{CF} = 3.6 Hz), 124.3 (q, J_{CF} = 272.0 Hz), 80.4, 40.7, 37.1, 36.9, 29.8, 27.6, 11.2, 10.9; HRMS (ESI) calcd for $C_{28}H_{28}ClF_3N_2NaO_3S$ (M+Na$^+$): 587.1353, found: 587.1337.

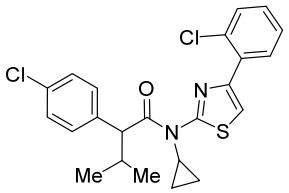


***tert*-Butyl-3-benzyl-4-((5-nitropyridin-2-ylamino)-4-oxobutanoate (5).** The title compound was synthesized from 2-benzyl-4-(*tert*-butoxy)-4-oxobutanoic acid (138 mg, 0.52 mmol) and 2-amino-5-nitropyridine (56 mg, 0.40 mmol) according to the General Procedure with 24 h reaction time, yielding a light yellow solid (126 mg, 81%) after purification by flash chromatography (EtOAc:petroleum ether, 1:4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 2.6 Hz, 1H), 8.56 (s, 1H), 8.45 (dd, *J* = 9.2, 2.6 Hz, 1H), 8.36 (d, *J* = 9.2 Hz, 1H), 7.30–7.23 (m, 2H), 7.23–7.14 (m, 3H), 3.11–3.01 (m, 2H), 2.86–2.74 (m, 2H), 2.53–2.45 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 171.5, 155.0, 144.7, 140.5, 138.0, 133.9, 128.9, 128.8, 127.0, 112.8, 81.7, 46.3, 38.2, 37.4, 28.0; HRMS (ESI) calcd for $C_{20}H_{23}N_3NaO_5$ (M+Na$^+$): 408.1535, found: 408.1511.

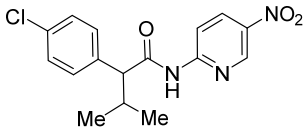


***tert*-Butyl 3-benzyl-4-((4,6-dimethylpyrimidin-2-yl)amino)-4-oxobutanoate (6).** The title compound was synthesized from 2-benzyl-4-(*tert*-butoxy)-4-oxobutanoic acid (139 mg, 0.53 mmol) and 4,6-dimethylpyrimidin-2-amine (50 mg, 0.41 mmol) according to the General Procedure with 24 h reaction time, yielding a pale yellow solid (118 mg, 79%) after purification by flash chromatography (EtOAc:petroleum ether, 1:2→1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.30–7.24 (m, 4H), 7.22–7.15 (m, 1H), 6.72 (s, 1H), 4.05–3.74 (m, 1H), 3.21 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.82 (dd, *J* = 17.0, 9.9 Hz, 1H), 2.68 (dd, *J* = 13.6, 9.1 Hz, 1H), 2.43 (s, 6H), 2.39–2.28 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 171.8, 168.3, 157.0, 138.9, 129.3, 128.5,

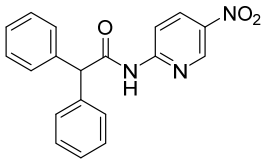
126.6, 115.5, 80.9, 44.2, 37.9, 36.7, 28.1, 24.0; HRMS (ESI) calcd for $C_{21}H_{27}N_3NaO_3$ ($M+Na^+$): 392.1945, found: 392.1956.



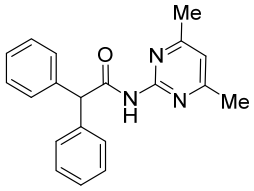
***N*-(4-(2-Chlorophenyl)thiazol-2-yl)-*N*-cyclopropyl-3-methyl-2-phenylbutanamide (7).** The title compound was synthesized from 2-(4-chlorophenyl)-3-methylbutanoic acid (139 mg, 0.65 mmol) and 4-(2-chlorophenyl)-*N*-cyclopropylthiazol-2-amine (125 mg, 0.50 mmol) according to the General Procedure, yielding a white solid (195 mg, 88%) after purification by flash chromatography (EtOAc:petroleum ether, 1:9): mp 121.2–122.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.7, 1.8 Hz, 1H), 7.54 (s, 1H), 7.44 (dd, J = 7.9, 1.3 Hz, 1H), 7.33–7.21 (m, 6H), 4.19 (d, J = 9.3 Hz, 1H), 3.11–3.04 (m, 1H), 2.52–2.40 (m, 1H), 1.36–1.25 (m, 2H), 1.06 (d, J = 6.5 Hz, 3H), 0.97–0.87 (m, 2H), 0.73 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 136.4, 133.3, 132.1, 131.3, 130.6, 130.1, 128.8, 128.7, 126.9, 57.2, 33.5, 30.3, 21.9, 20.4, 12.1; HRMS (ESI) calcd for $C_{23}H_{22}Cl_2N_2NaOS$ ($M+Na^+$): 467.0723, found: 467.0741.



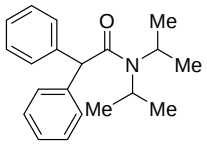
2-(4-Chlorophenyl)-3-methyl-*N*-(5-nitropyridin-2-yl)butanamide (8). The title compound was synthesized from 2-(4-chlorophenyl)-3-methylbutanoic acid (138 mg, 0.65 mmol) and 2-amino-5-nitropyridine (69 mg, 0.50 mmol) according to the General Procedure with a reaction time of 24 h, yielding a white solid (101 mg, 61%) after purification by flash chromatography (EtOAc:petroleum ether, 1:8): R_f = 0.16 (EtOAc:petroleum ether 1:8); mp 108.2–110.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 2.6 Hz, 1H), 8.47 (dd, J = 9.2, 2.6 Hz, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.17 (br s, 1H), 7.35–7.28 (m, 4H), 3.06 (d, J = 10.1 Hz, 1H), 2.56–2.40 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 155.1, 144.8, 140.8, 136.3, 134.2, 134.0, 129.7, 129.3, 113.0, 62.6, 31.8, 21.7, 20.3; HRMS (ESI) calcd for $C_{16}H_{17}ClN_3O_3$ ($M+H^+$): 334.0953, found: 334.0956.



***N*-(5-Nitropyridin-2-yl)-2,2-diphenylacetamide (9).** The title compound was synthesized from 2,2-diphenylacetic acid (111 mg, 0.52 mmol) and 2-amino-5-nitropyridine (56 mg, 0.40 mmol) according to the General Procedure with 24 h reaction time, yielding a brown solid (**9**) (125 mg, 93%) after purification by flash chromatography (EtOAc:petroleum ether,1:4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 0.9 Hz, 1H), 8.56–8.41 (m, 3H), 7.56–7.00 (m, 10H), 5.13 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 155.0, 144.6, 140.7, 137.8, 134.1, 129.1, 128.9, 127.9, 112.9, 60.1; HRMS (ESI) calcd for $C_{19}H_{16}N_3O_3$ ($M+H^+$): 334.1192, found: 334.1174.

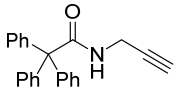


***N*-(4,6-Dimethylpyrimidin-2-yl)-2,2-diphenylacetamide (10).** The title compound was synthesized from 2,2-diphenylacetic acid (138 mg, 0.65 mmol) and 4,6-dimethylpyrimidin-2-amine (61 mg, 0.50 mmol) according to the General Procedure, yielding a pale yellow solid (139 mg, 88%) after purification by flash chromatography (EtOAc:petroleum ether, 1:5): mp 157.4–160.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.39–7.34 (m, 4H), 7.33-7.28 (m, 4H), 7.27-7.21 (m, 2H), 6.69 (s, 1H), 5.83 (br s, 1H), 2.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 156.9, 139.0, 129.2, 128.6, 127.2, 115.7, 23.9; HRMS (ESI) calcd for $C_{20}H_{19}N_3NaO$ ($M+Na^+$): 340.1420, found: 340.1435.

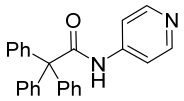


***N,N*-Diisopropyl-2,2-diphenylacetamide (11).**[1] The title compound was synthesized from 2,2-diphenylacetic acid (104 mg, 0.49 mmol) and diisopropylamine (90 μL, 0.66 mmol) according to the General Procedure, yielding a pale yellow solid (102 mg, 71%) after purification by flash chromatography (EtOAc:petroleum ether, 1:5): mp 51.2–52.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ

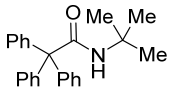
7.38–7.15 (m, 10H), 5.12 (s, 1H), 4.09 (hept, J = 6.6 Hz, 1H), 3.40 (ap br s, 1H), 1.43 (d, J = 6.6 Hz, 6H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 140.3, 129.2, 128.5, 126.9, 56.6, 49.0, 46.2, 20.7, 20.6; HRMS (ESI) calcd for $C_{19}H_{26}NO$ ($M+H^+$): 296.2009, found: 296.2022



2,2,2-Triphenyl-*N*-(prop-2-yn-1-yl)acetamide (12). The title compound was synthesized from 2,2,2-triphenylacetic acid (184 mg, 0.637 mmol) and propargylamine (31 μL, 0.490 mmol) according to the General Procedure with 24 h reaction time, yielding a white solid (123 mg, 77%) after purification by flash chromatography (EtOAc:petroleum ether, 1:9): mp 121.7–124.5 °C; HRMS (ESI) calcd for $C_{23}H_{19}NNaO$ ($M+Na^+$): 348.1364, found: 348.1361. NMR spectra in agreement with previously published data.[2]

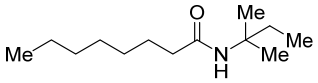


2,2,2-Triphenyl-*N*-(pyridin-4-yl)acetamide (13). The title compound was synthesized from 2,2,2-triphenylacetic acid (188 mg, 0.65 mmol) and 4-aminopyridine (47 mg, 0.50 mmol) according to the General Procedure. After purification by flash chromatography (EtOAc:petroleum ether,1:5 → 1:1), the residue containing the product was dissolved in a minimal amount of EtOAc and added drop wise to a vial of petroleum ether with stirring, leading to precipitation of a white compound that was isolated by filtration, washed with petroleum ether and dried (100 mg, 55%): HRMS (ESI) calcd for $C_{25}H_{20}N_2O$ ($M+H^+$): 365.1648, found: 365.1656. NMR spectra in agreement with previously published data.[3]

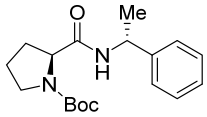


***N*-(*tert*-Butyl)-2,2,2-triphenylacetamide (14).**[1] The title compound was synthesized from 2,2,2-triphenylacetic acid (190 mg, 0.66 mmol) and *tert*-butylamine (53 μL, 0.50 mmol) according to the General Procedure with 24 h reaction time), yielding a white solid (127 mg, 73%) after purification by flash chromatography (EtOAc:petroleum ether, 1:9): mp 125.8–127.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–6.83 (m, 15H), 5.50 (s, 1H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1,

143.7, 130.6, 127.8, 126.8, 68.1, 51.7, 28.5; HRMS (ESI) calcd for $C_{24}H_{25}NNaO$ ($M+Na^+$): 366.1834, found: 366.1840.

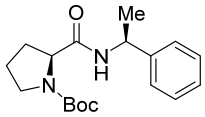


***N*-(*tert*-Pentyl)octanamide (15).** The title compound was synthesized from octanoic acid (105 µL, 0.66 mmol) and 2-methylbutan-2-amine (60 µL, 0.51 mmol) according to the General Procedure, yielding a colorless oil (99 mg, 91%) after purification by flash chromatography (EtOAc:petroleum ether, 1:8): R_f = 0.14 (EtOAc:petroleum ether 1:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (br s, 1H), 2.08 (t, *J* = 7.6 Hz, 2H), 1.72 (q, *J* = 7.5 Hz, 2H), 1.63–1.54 (m, 2H), 1.32–1.23 (m, 14H), 0.90–0.79 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 53.9, 37.9, 32.8, 31.9, 29.4, 29.2, 26.7, 26.0, 22.8, 14.2, 8.5. NMR spectra in agreement with previously published data.[4] HRMS (ESI) calcd for $C_{13}H_{28}NO$ ($M+H^+$): 214.2165, found: 214.2169.

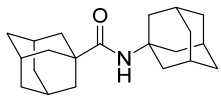


***tert*-Butyl (2*S*)-2-(((1*R*)-1-phenylethyl)carbamoyl)pyrrolidine-1-carboxylate (16).** The title compound was synthesized from (*S*)-*N*-Boc-proline (141 mg, 0.65 mmol) and (*R*)-1-phenylethanamine (64 µL, 0.50 mmol) according to the General Procedure with 24 h reaction time, yielding a white solid (154 mg, 96%) after purification by flash chromatography (EtOAc:petroleum ether, 3:7): ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C) *δ* 7.84 (d, *J* = 6.3 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 4.92 (ap p, *J* = 7.1 Hz, 1H), 4.11 (ap d, *J* = 6.3 Hz, 1H), 3.40–3.34 (m, 1H), 3.33–3.26 (m, 1H); 2.13–2.02 (m, 1H), 1.86–1.65 (m, 3H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6, 25 °C) δ 171.3, 153.2, 144.4, 128.0, 126.5, 126.0, 78.2, 59.5, 47.5, 46.4, 31.1, 28.0, 27.8, 23.0, 22.0; HRMS (ESI) calcd for $C_{18}H_{26}N_2NaO_3$ ($M+Na^+$): 341.1841, found: 341.1844. NMR spectra in agreement with previously published data.[5] The title compound **16** was deprotected by treatment with TFA in CH_2Cl_2 as described previously[6] to provide (*S*)-*N*-((*R*)-1-phenylethyl)pyrrolidine-2-carboxamide. (^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.38–7.21 (m, 5H), 5.14–5.05 (m, 1H), 3.77 (dd, *J* = 9.1, 5.2 Hz, 1H), 3.01 (dt, *J* = 10.2, 6.8 Hz, 1H), 2.87 (dt, *J* = 10.2, 6.3 Hz, 1H), 2.19–2.00 (m, 2H), 1.95–1.84 (m, 1H), 1.74–1.62 (m, 2H), 1.48 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 143.8,

128.6, 127.1, 125.9, 60.6, 47.9, 47.3, 30.7, 26.2, 22.3; in agreement with previously published data[6]), and determined to >99% de by comparison with deprotected **17**.

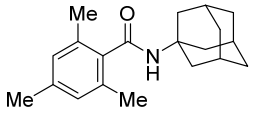


***tert*-Butyl (*S*)-2-(((*S*)-1-phenylethyl)carbamoyl)pyrrolidine-1-carboxylate (17).** The title compound was synthesized from (*S*)-*N*-Boc-proline (141 mg, 0.65 mmol) and *(S)*-1-phenylethanamine (65 µL, 0.51 mmol) according to the General Procedure with 24 h reaction time, yielding a white solid (156 mg, 97%) after purification by flash chromatography (EtOAc:petroleum ether, 3:7): ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C) δ 7.87 (d, J = 6.6 Hz, 1H), 7.31–7.26 (m, 4H), 7.19 (ddd, J = 8.4, 5.7, 2.6 Hz, 1H), 4.98–4.92 (m, 1H), 4.12 (dd, J = 8.4, 2.9 Hz, 1H), 3.39–3.33 (m, 1H), 3.33–3.26 (m, 1H), 2.14–2.01 (m, 1H), 1.83–1.70 (m, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6, 25 °C) δ 171.4, 171.0, 153.5, 153.3, 144.7, 128.1, 126.5, 126.4, 125.8, 125.6, 78.4, 78.2, 59.5, 59.4, 47.4, 46.6, 46.4, 30.9, 29.9, 28.1, 27.9, 23.8, 23.1, 22.4, 22.1; HRMS (ESI) $C_{18}H_{26}N_2NaO_3$ ($M+Na^+$): 341.1841, found: 341.1835. NMR spectra in agreement with previously published data.[5] The title compound **17** was deprotected by treatment with TFA in CH_2Cl_2 as described previously[6] to provide (*S*)-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide. (^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.39–7.21 (m, 5H), 5.10 (dd, J = 8.6, 6.9 Hz, 1H), 3.71 (dd, J = 9.1, 5.3 Hz, 1H), 3.01 (dt, J = 10.2, 6.8 Hz, 1H), 2.91 (dt, J = 10.2, 6.3 Hz, 1H), 2.21–2.08 (m, 1H), 2.01–1.87 (m, 2H), 1.77–1.66 (m, 2H), 1.47 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 143.5, 128.6, 127.2, 126.2, 60.6, 47.9, 47.3, 30.8, 26.2, 22.2; in agreement with previously published data[6]), and determined to >99% de by comparison with deprotected **16**.

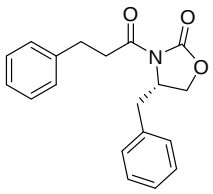


***N*-(Adamantan-1-yl)adamantane-1-carboxamide (18).** The title compound was synthesized from adamantane-1-carboxylic acid (90 mg, 0.50 mmol) and 1-adamantylamine (99 mg, 0.65 mmol) according to the General Procedure with a reaction time of 22 hours, yielding a white solid (122 mg, 78%) after a combination of crystallization in acetone and purification by flash chromatography

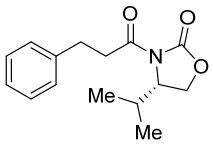
(EtOAc:petroleum ether, 1:5): mp >250 °C; HRMS (ESI) calcd for $C_{21}H_{32}NO$ ($M+H^+$): 314.2478, found: 314.2476. NMR spectra in agreement with previously published data.[7]



***N*-(Adamantan-1-yl)-2,4,6-trimethylbenzamide (19).** The title compound was synthesized from 2,4,6-trimethylbenzoic acid (82 mg, 0.50 mmol) and 1-adamantylamine (99 mg, 0.65 mmol) according to the General Procedure with a reaction time of 24 hours, yielding a white solid (73 mg, 50%) after purification by flash chromatography (EtOAc:petroleum ether, 1:5): mp 231.6–233.0 °C; HRMS (ESI) calcd for $C_{20}H_{28}NO$ ($M+H^+$): 298.2165, found: 298.2175. NMR spectra in agreement with previously published data.[8]



(*S*)-4-Benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one (20). The title compound was synthesized from 3-phenylpropanoic acid (108 mg, 0.72 mmol) and (*S*)-4-benzyloxazolidin-2-one (175 mg, 0.99 mmol) according to the General Procedure, but with less DIPEA (3 equiv), yielding a white solid (200 mg, 90%) after purification by flash chromatography (EtOAc:petroleum ether, 1:4): t_R = 12.42 min. NMR spectra in agreement with previously published data.[9]



(*S*)-4-Isopropyl-3-(3-phenylpropanoyl)oxazolidin-2-one (21). The title compound was synthesized from 3-phenylpropanoic acid (107 mg, 0.71 mmol) and (*S*)-4-isopropyloxazolidin-2-one (129 mg, 1.00 mmol) according to the General Procedure with a reaction time of 19 hours, yielding a pale yellow solid (160 mg, 86%) after purification by flash chromatography (EtOAc:petroleum ether, 1:3): t_R = 12.23 min; mp 60.8–62.2 °C; HRMS (ESI) calcd for $C_{15}H_{19}NNaO_3$ ($M+Na^+$): 284.1257, found: 284.1245. NMR spectra in agreement with previously published data.[10]

(1) Fang, J. B.; Sanghi, R.; Kohn, J.; Goldman, A. S. *Inorg. Chim. Acta* **2004**, *357*, 2415.

(2) Kizjakina, K.; Bryson, J. M.; Grandinetti, G.; Reineke, T. M. *Biomaterials* **2012**, *33*, 1851.

(3) Faler, C. A.; Joullié, M. M. *Tetrahedron Lett.* **2006**, *47*, 7229.

(4) Orliac, A.; Gomez Pardo, D.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013**, *15*, 902.

(5) Gryko, D.; Lipinski, R. *Eur. J. Org. Chem.* **2006**, 3864.

(6) Kelleher, F.; Kelly, S.; Watts, J.; McKee, V. *Tetrahedron* **2010**, *66*, 3525.

(7) Wagner, C. E.; Mohler, M. L.; Kang, G. S.; Miller, D. D.; Geisert, E. E.; Chang, Y.-A.; Fleischer, E. B.; Shea, K. J. *J. Med. Chem.* **2003**, *46*, 2823.

(8) Schäfer, G.; Matthey, C.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 9173.

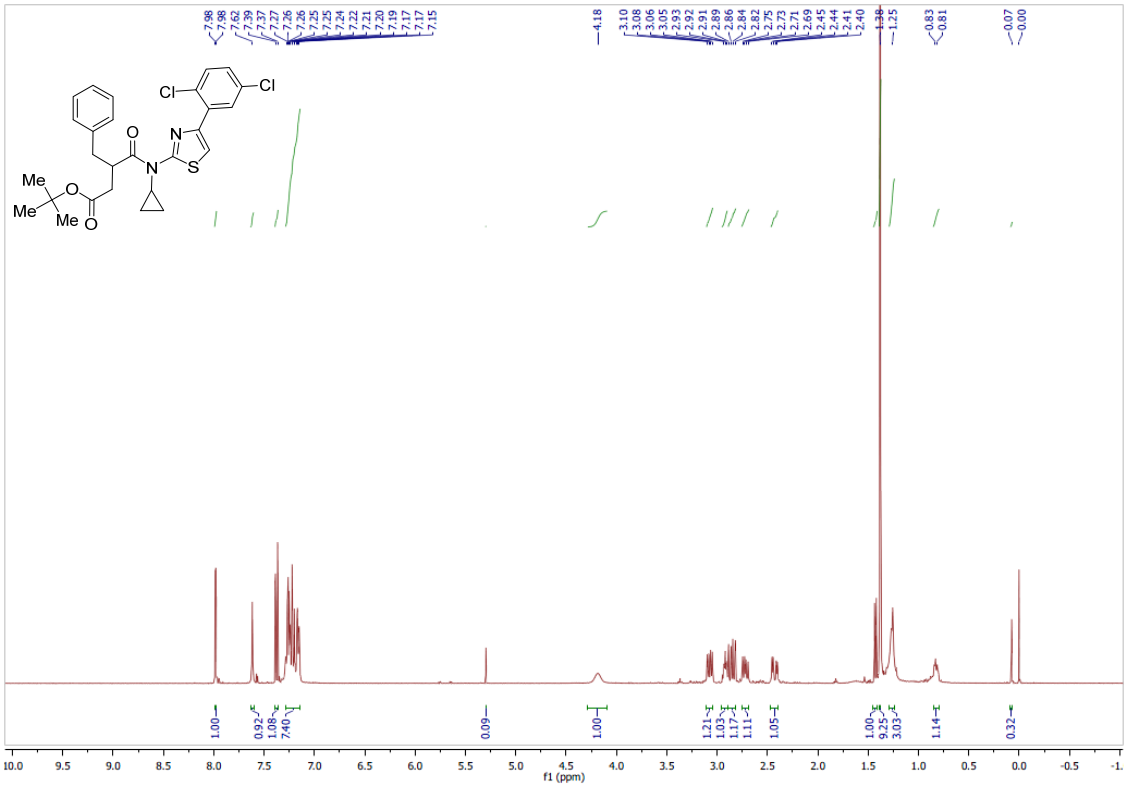
(9) Heitsch, H.; Henning, R.; Kleemann, H. W.; Linz, W.; Nickel, W. U.; Ruppert, D.; Urbach, H.; Wagner, A. *J. Med. Chem.* **1993**, *36*, 2788.

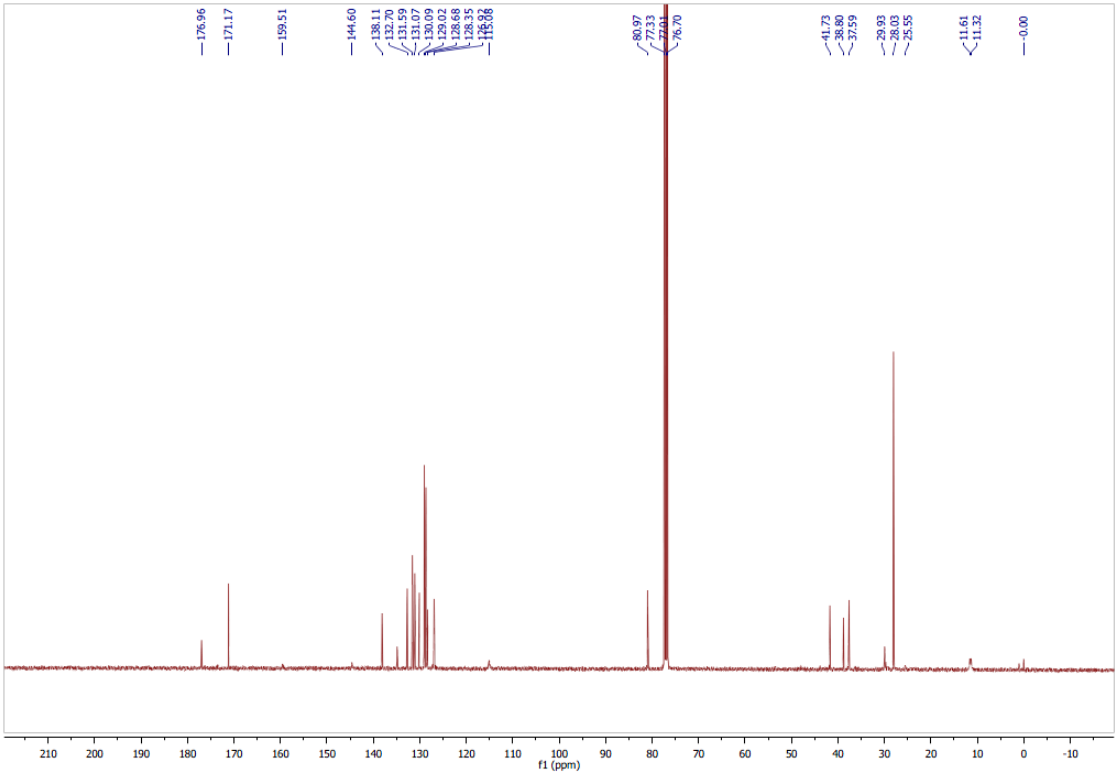
(10) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830.

NMR Spectra

tert-Butyl 3-benzyl-4-(cyclopropyl(4-(2,5-dichlorophenyl)-thiazol-2-yl)amino)-4-oxobutanoate

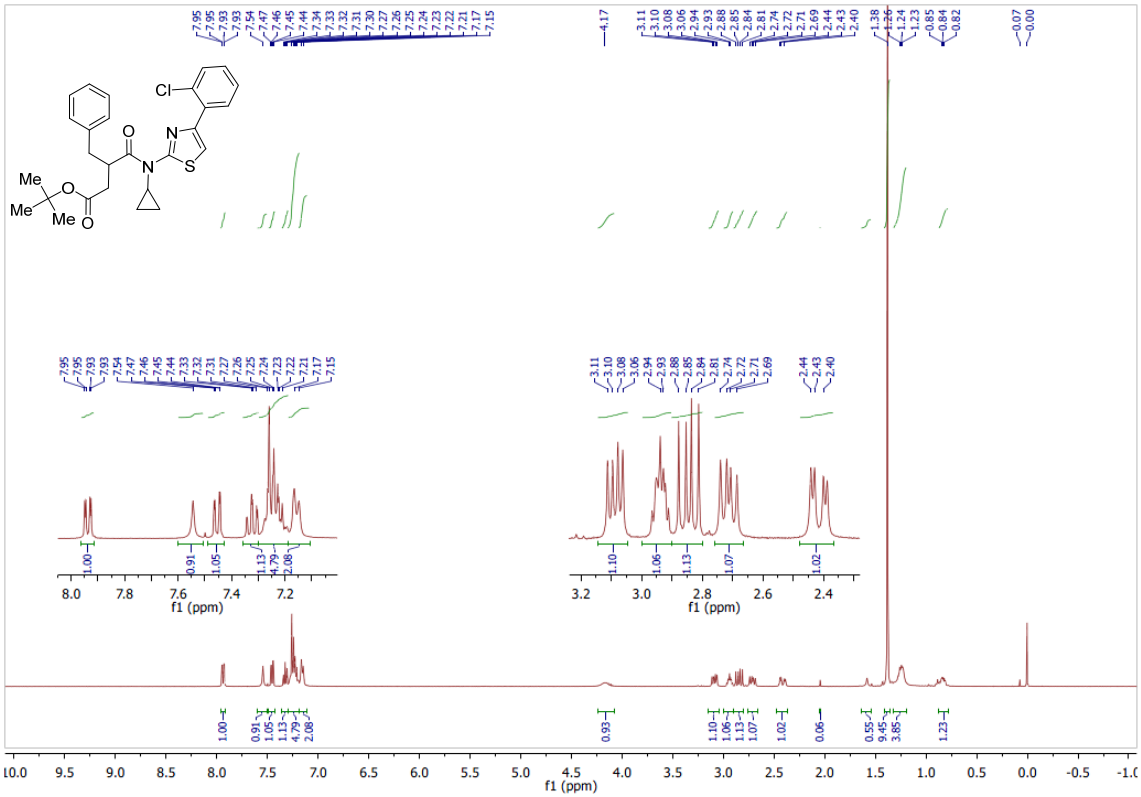
(1) ^{1}H NMR (400 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$)

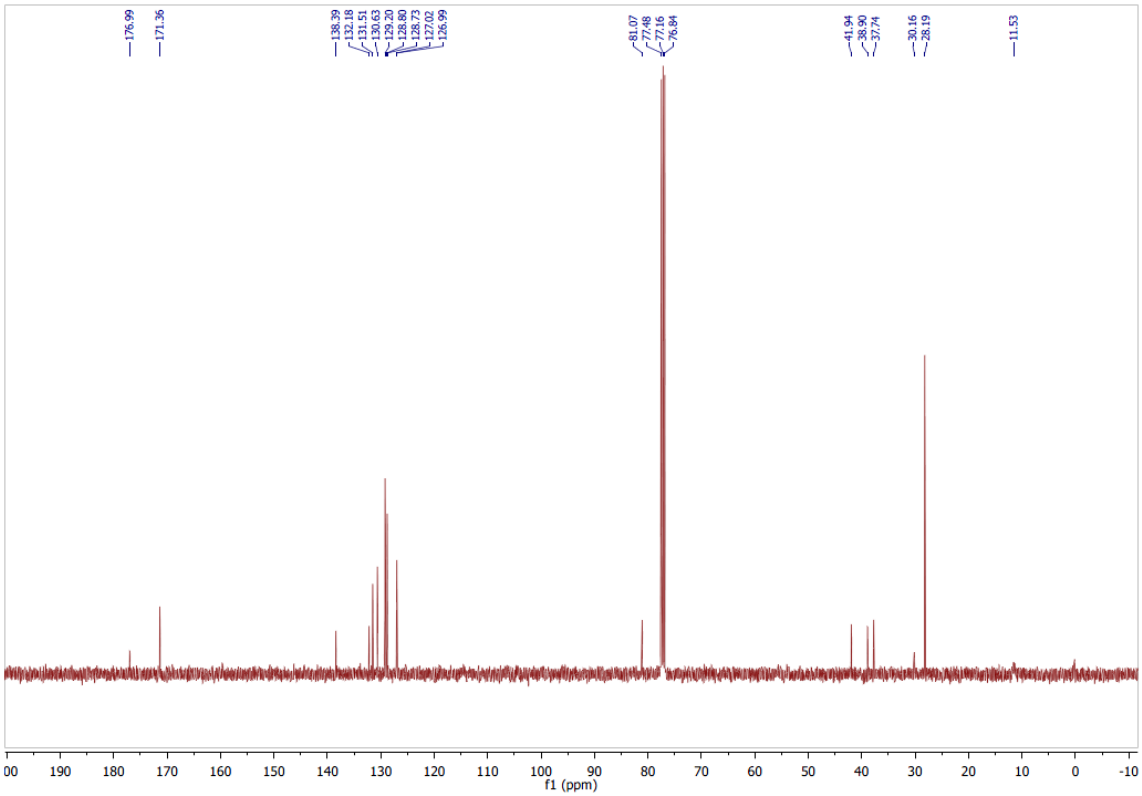




***tert*-Butyl 3-benzyl-4-(cyclopropyl(4-(2-chlorophenyl)-thiazol-2-yl)amino)-4-oxobutanoate (2)**

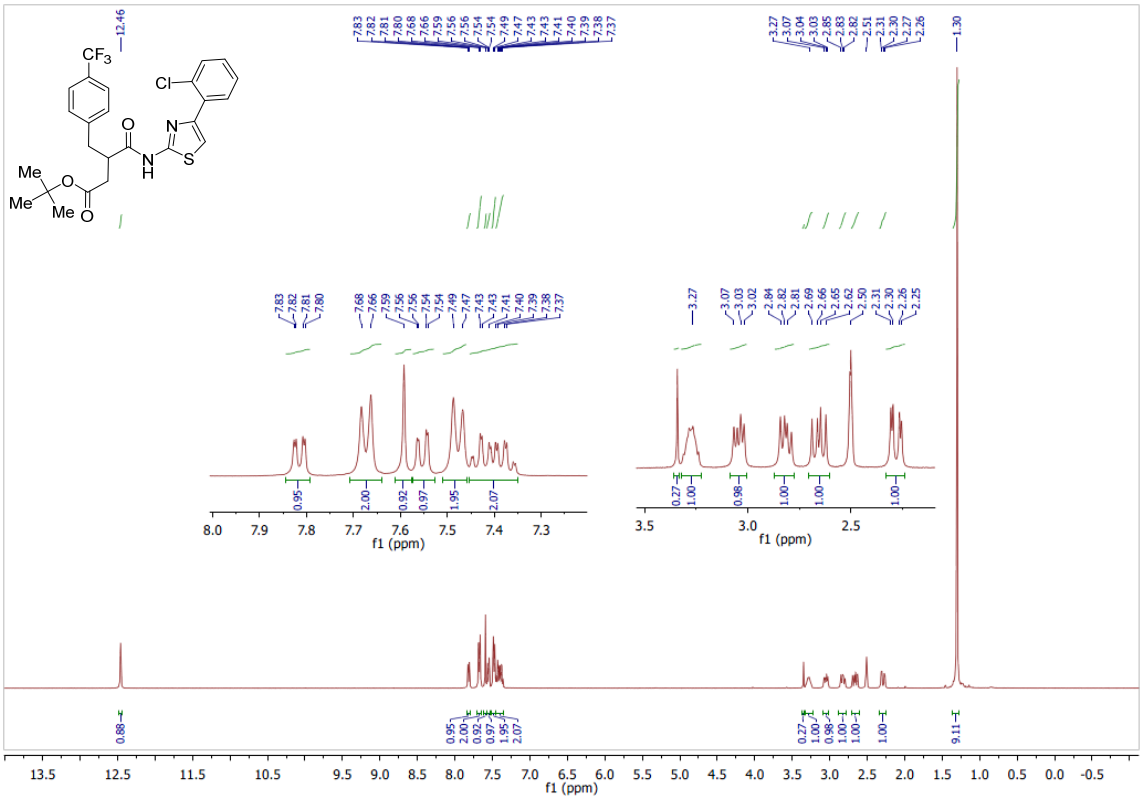
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

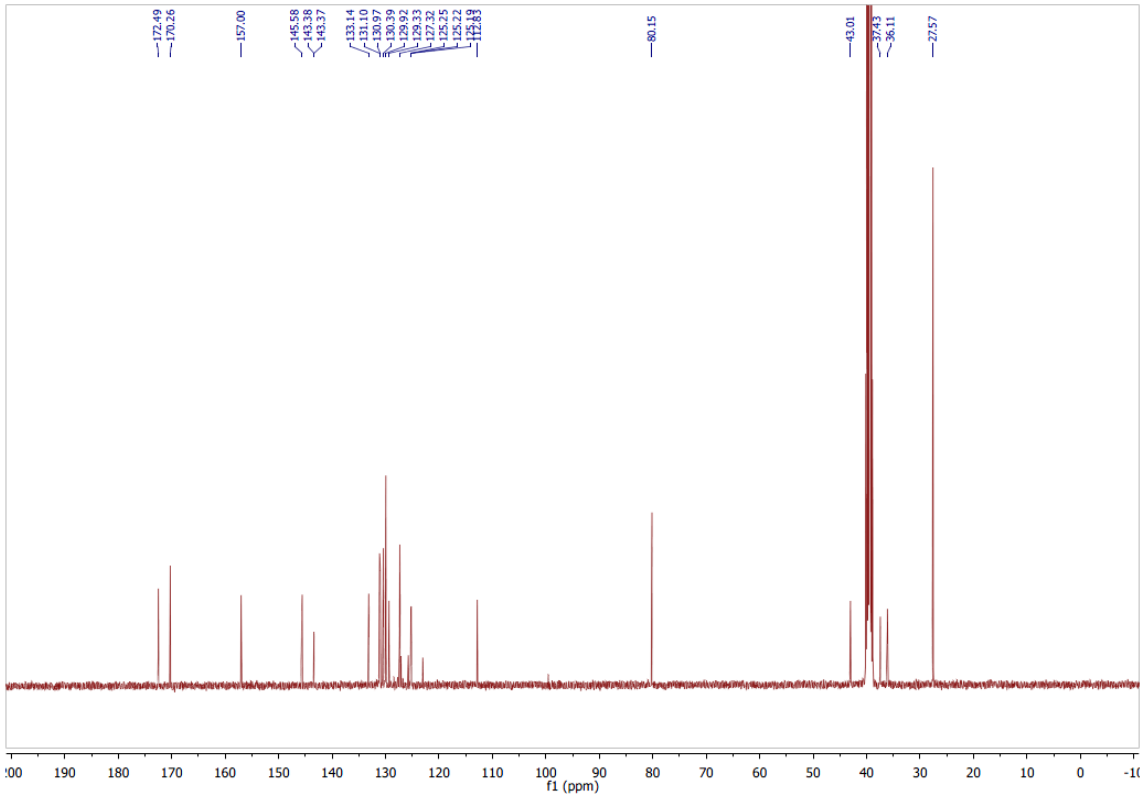




tert-Butyl 4-((4-(2-chlorophenyl)thiazol-2-yl)amino)-4-oxo-3-(4-(trifluoromethyl)benzyl)-butanoate (3)

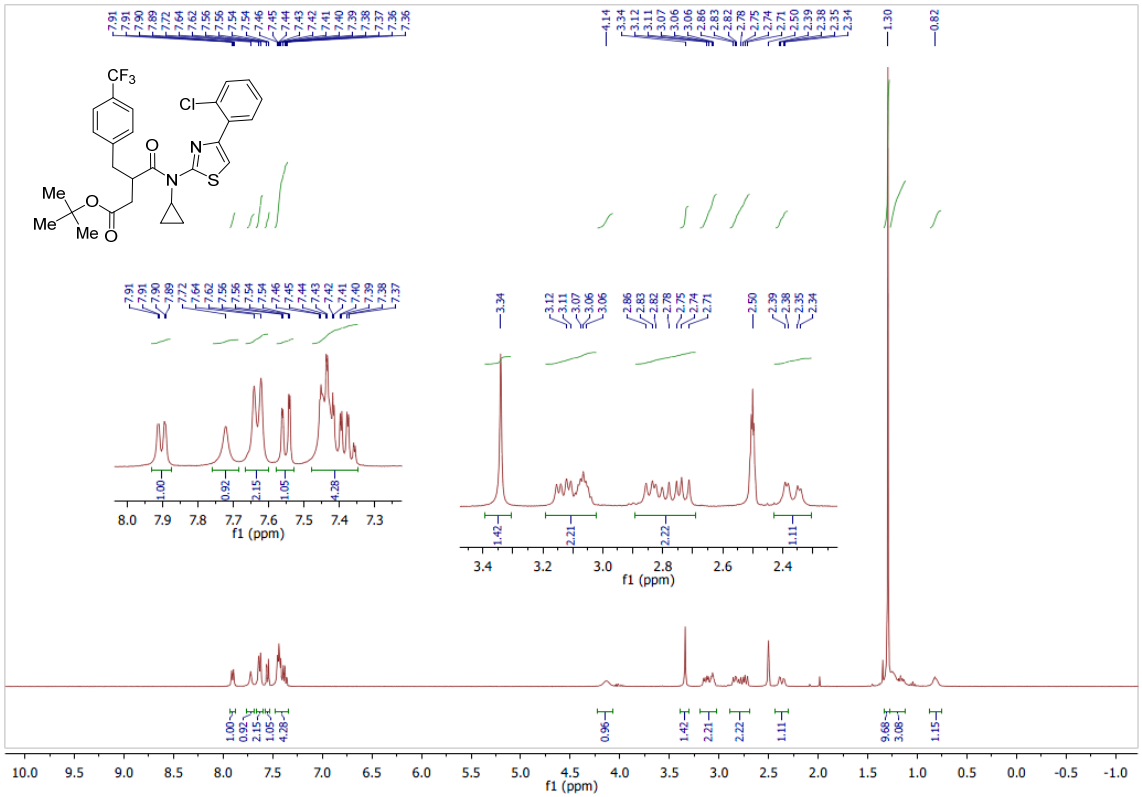
^{1}H NMR (400 MHz, DMSO-d_6); ^{13}C NMR (101 MHz, DMSO-d_6)

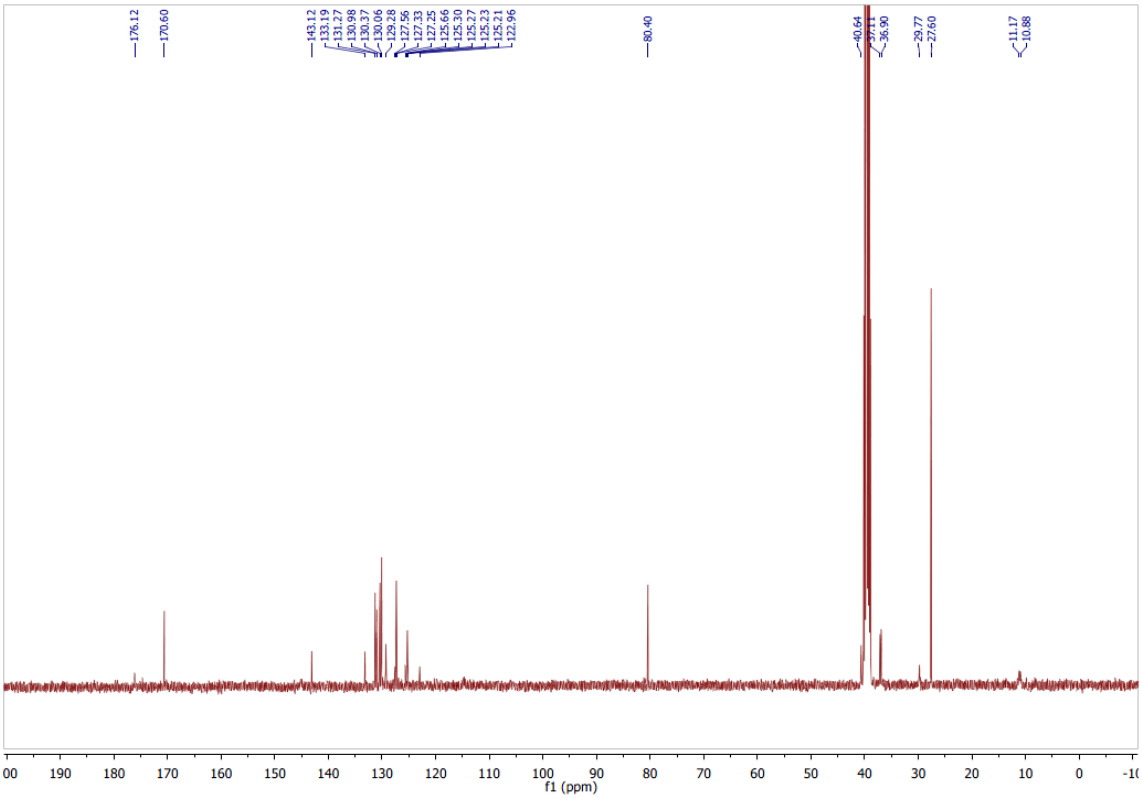




***tert*-Butyl 4-((4-(2-chlorophenyl)thiazol-2-yl)(cyclopropyl)-amino)-4-oxo-3-(4-(trifluoro-methyl)benzyl)butanoate (4)**

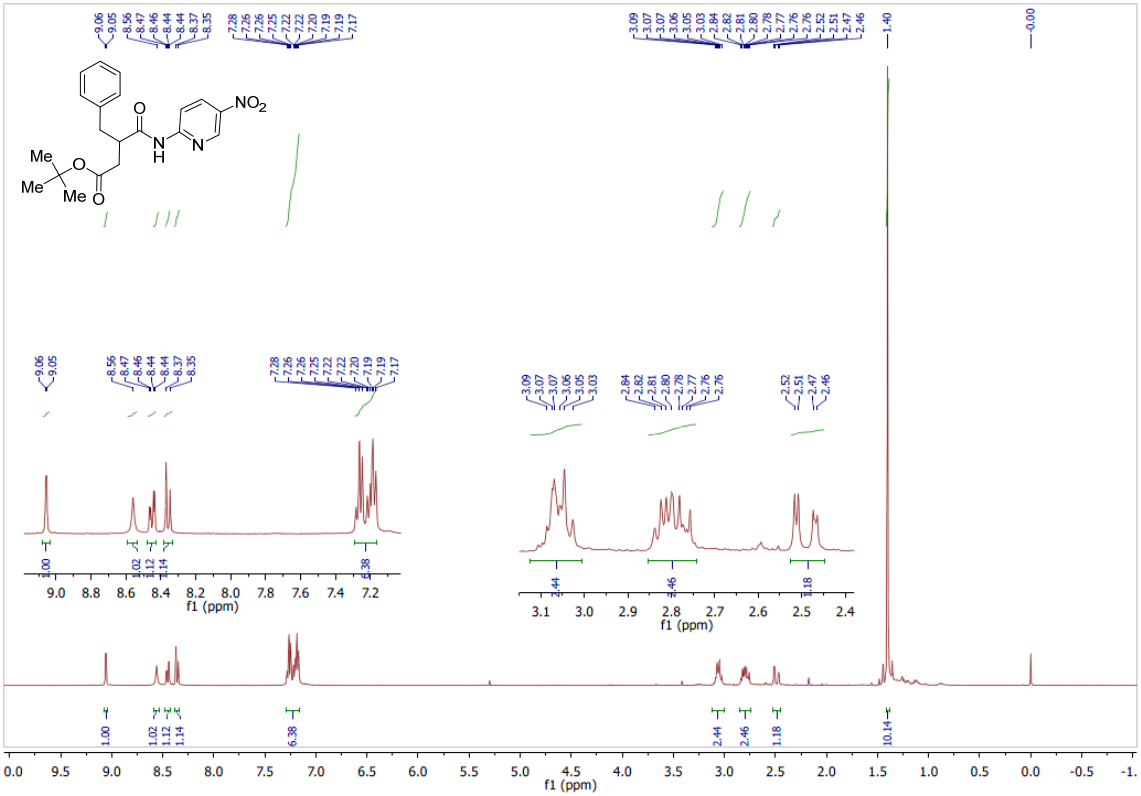
^{1}H NMR (400 MHz, DMSO-d_6); ^{13}C NMR (101 MHz, DMSO-d_6)

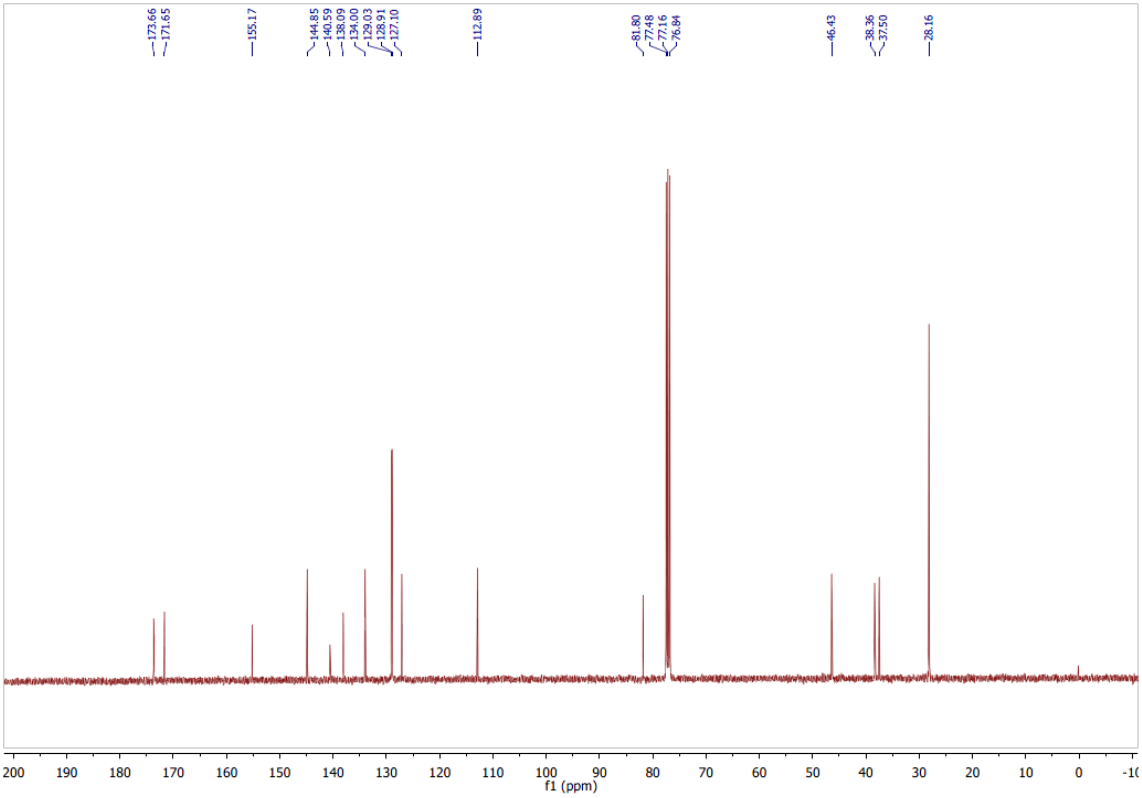




tert-Butyl-3-benzyl-4-((5-nitropyridin-2-ylamino)-4-oxobutanoate (5)

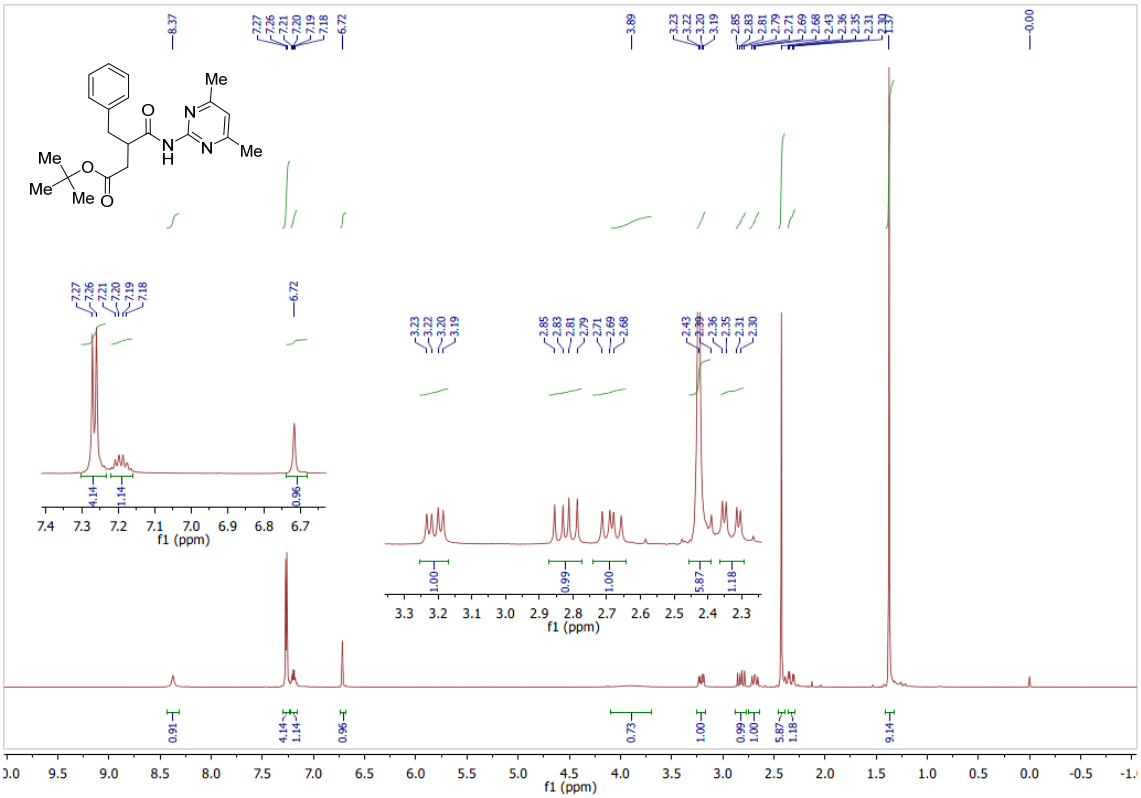
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

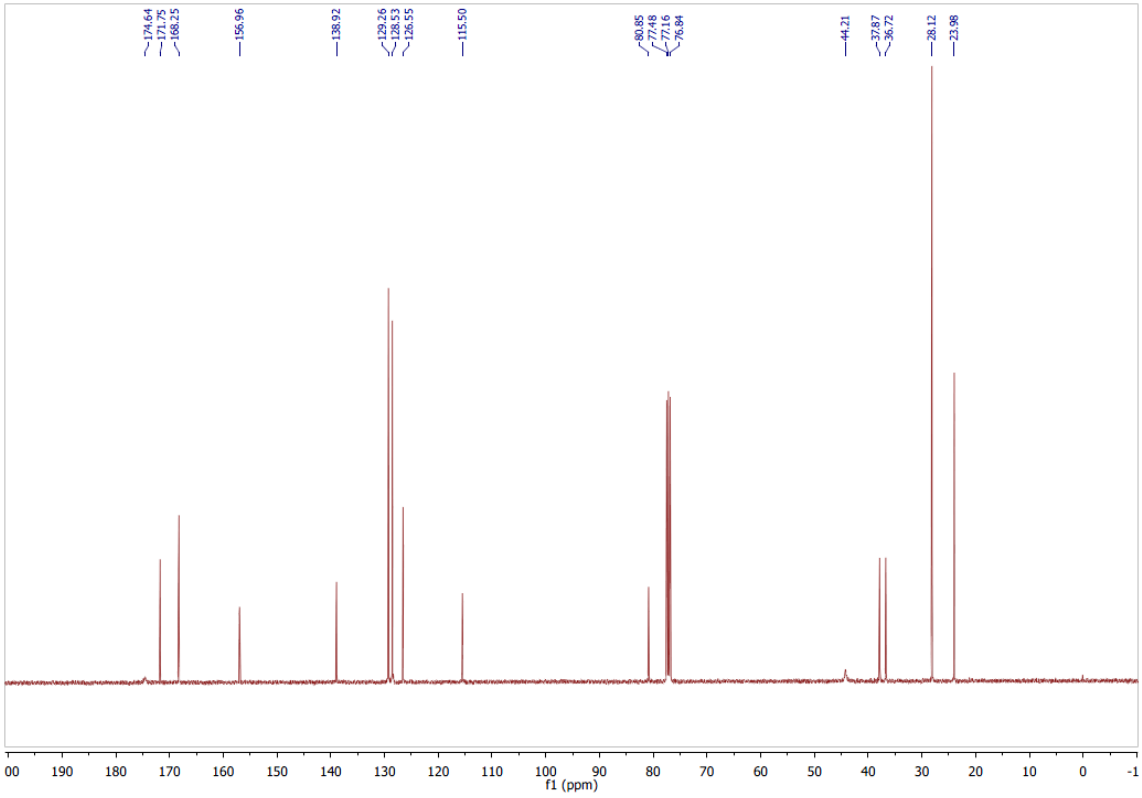




tert-Butyl 3-benzyl-4-((4,6-dimethylpyrimidin-2-yl)amino)-4-oxobutanoate (6)

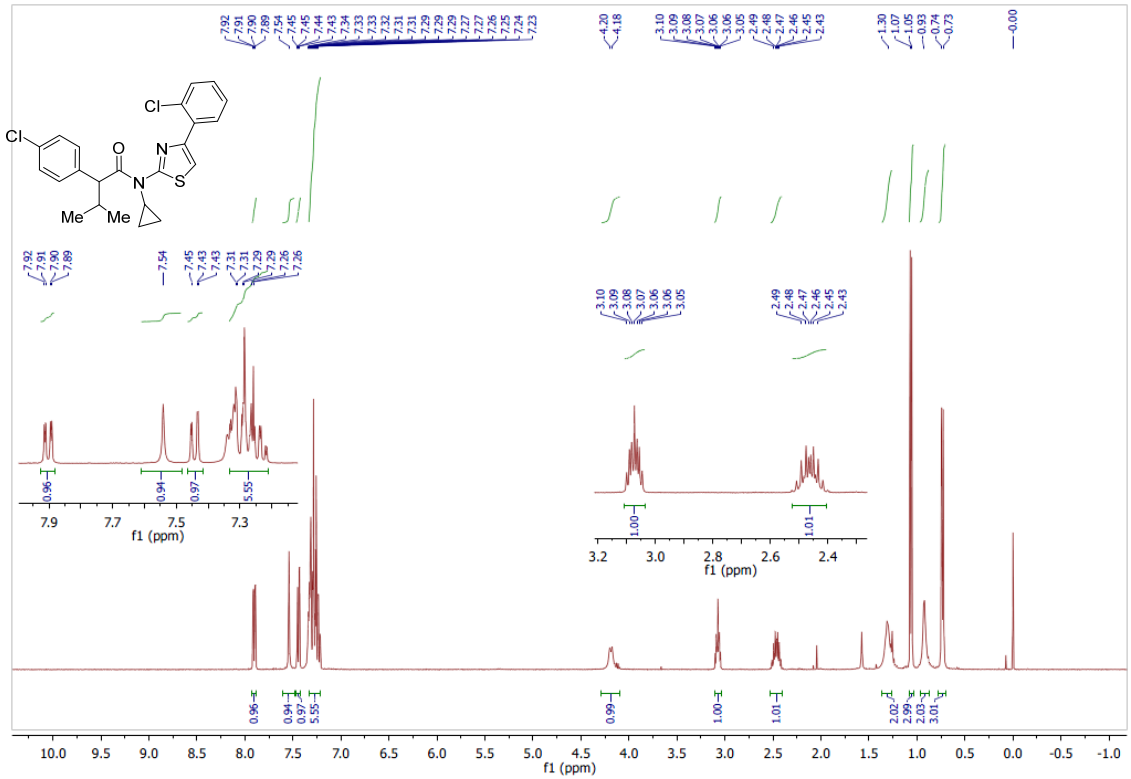
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

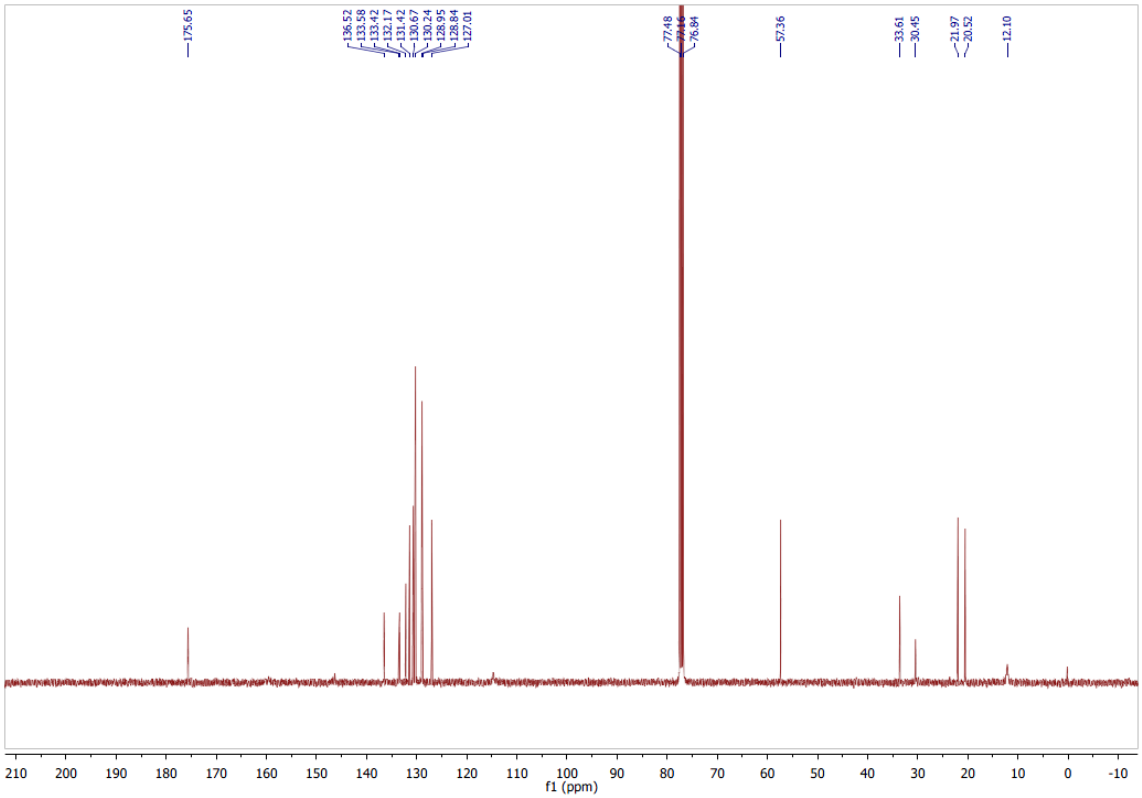




_N_-(4-(2-Chlorophenyl)thiazol-2-yl)-_N_-cyclopropyl-3-methyl-2-phenylbutanamide (7)

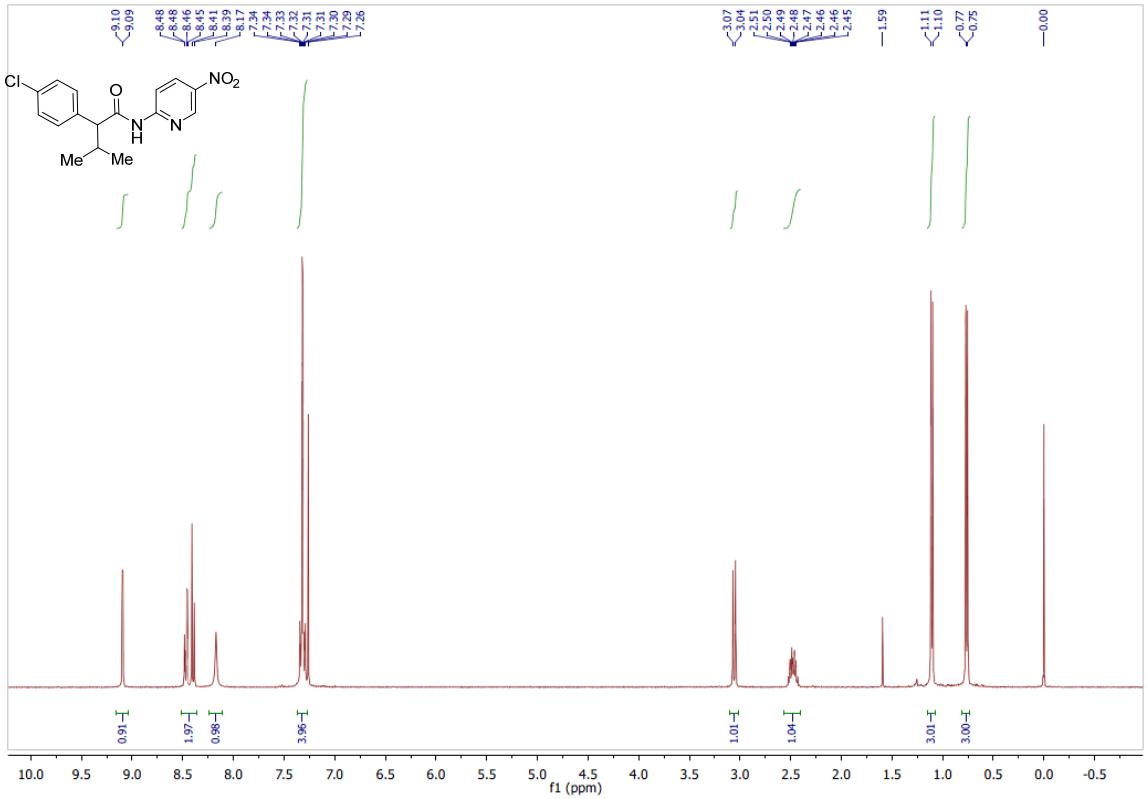
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

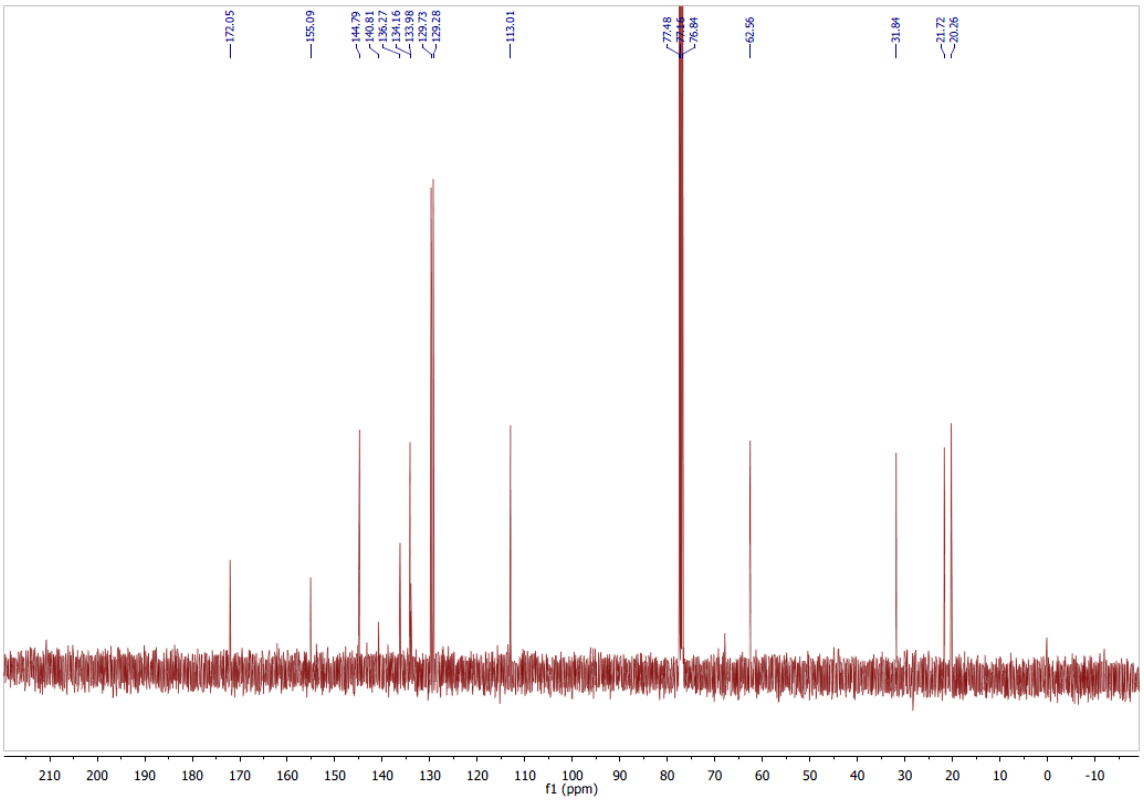




2-(4-Chlorophenyl)-3-methyl-*N*-(5-nitropyridin-2-yl)butanamide (8)

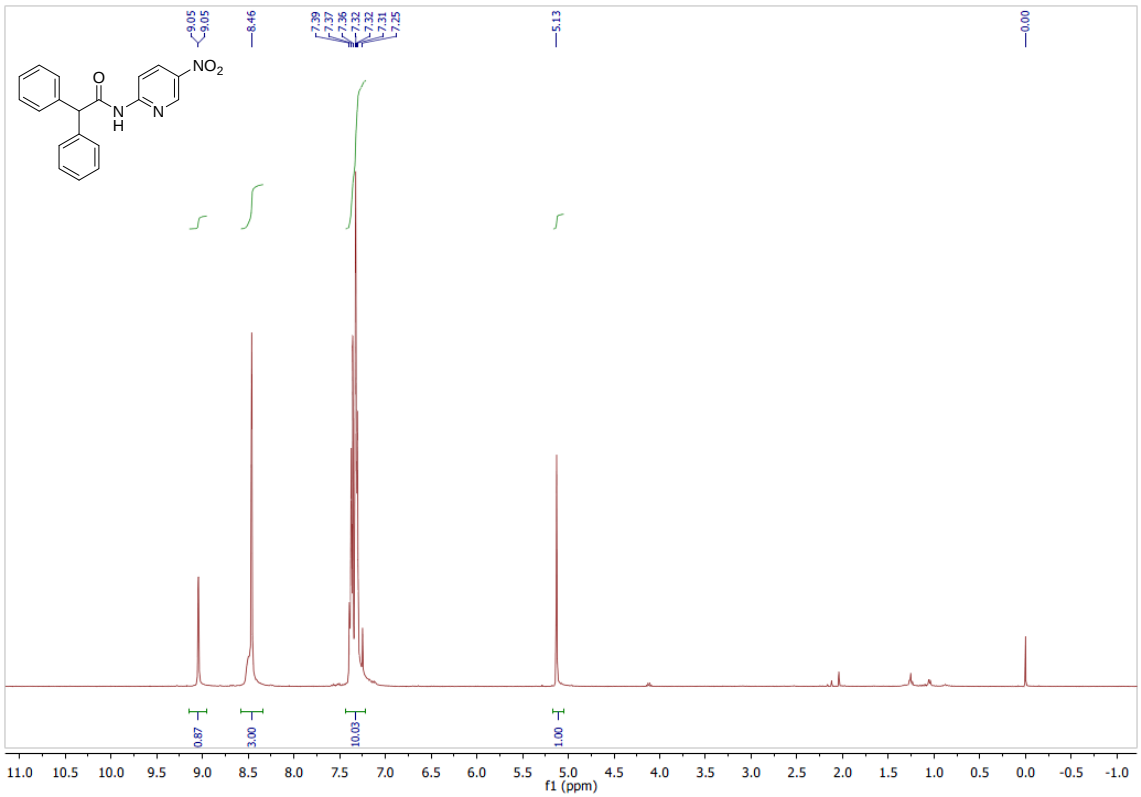
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

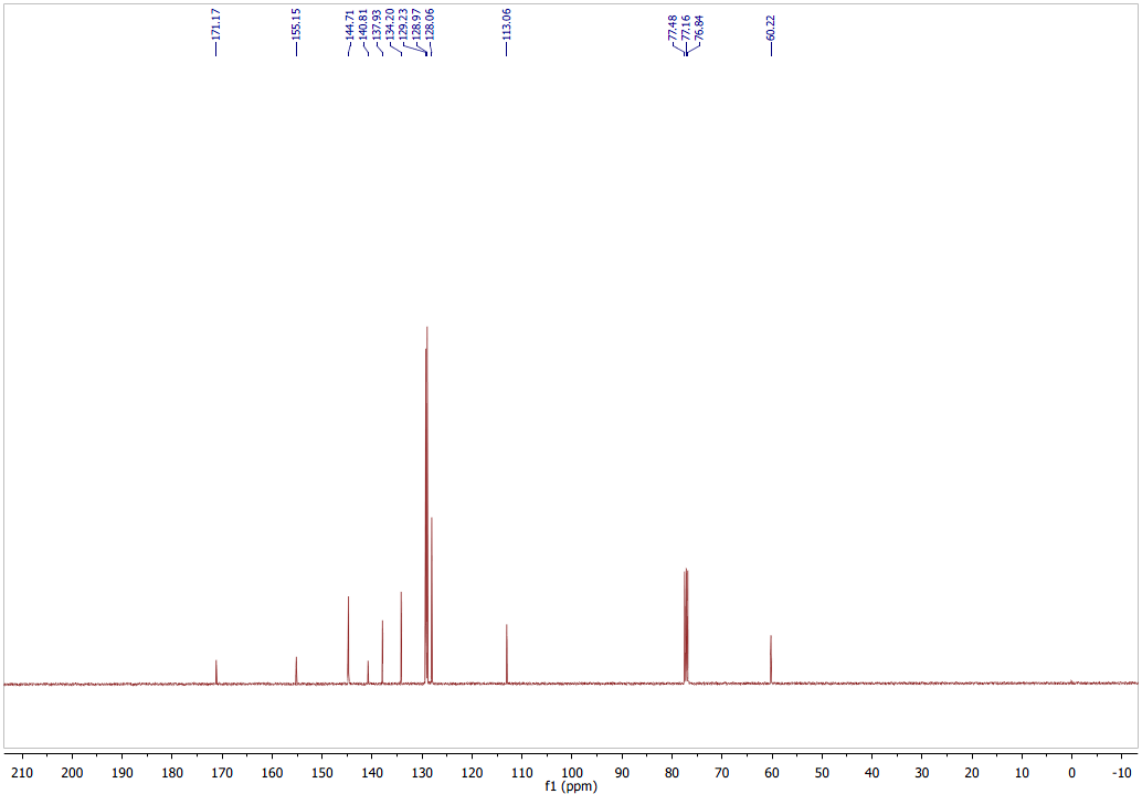




***N*-(5-Nitropyridin-2-yl)-2,2-diphenylacetamide (9)**

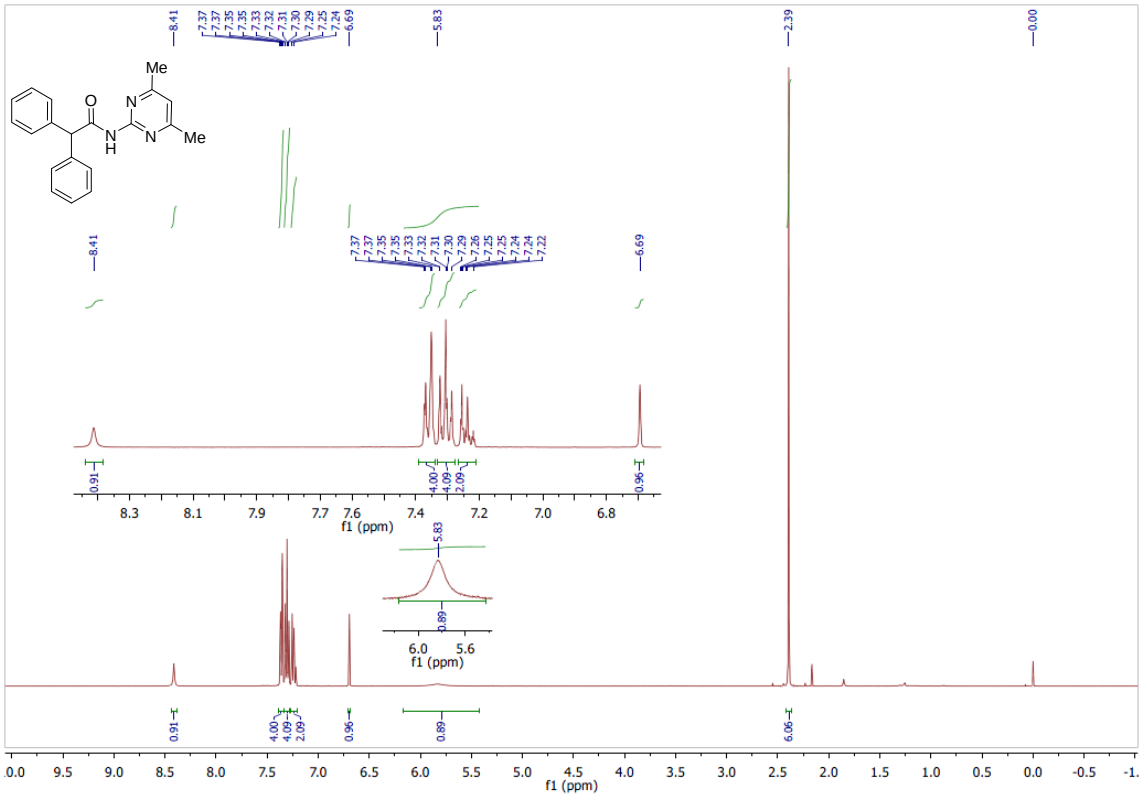
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

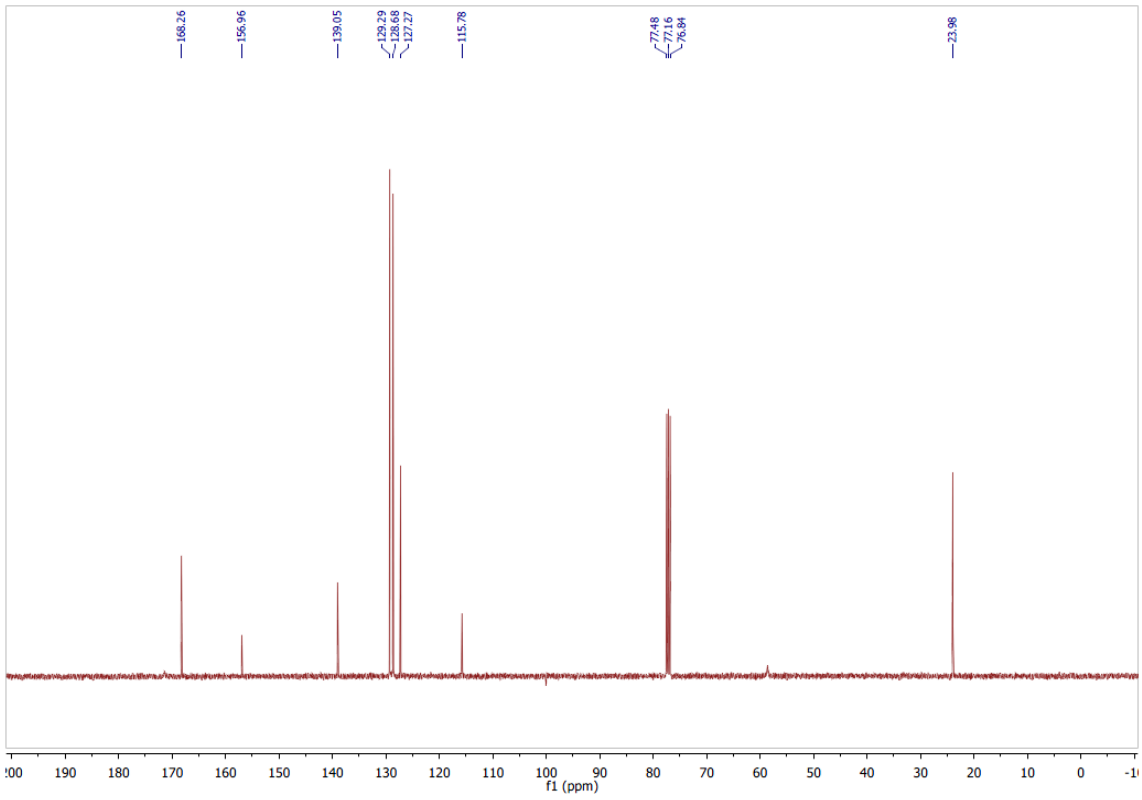




N-(4,6-Dimethylpyrimidin-2-yl)-2,2-diphenylacetamide (10)

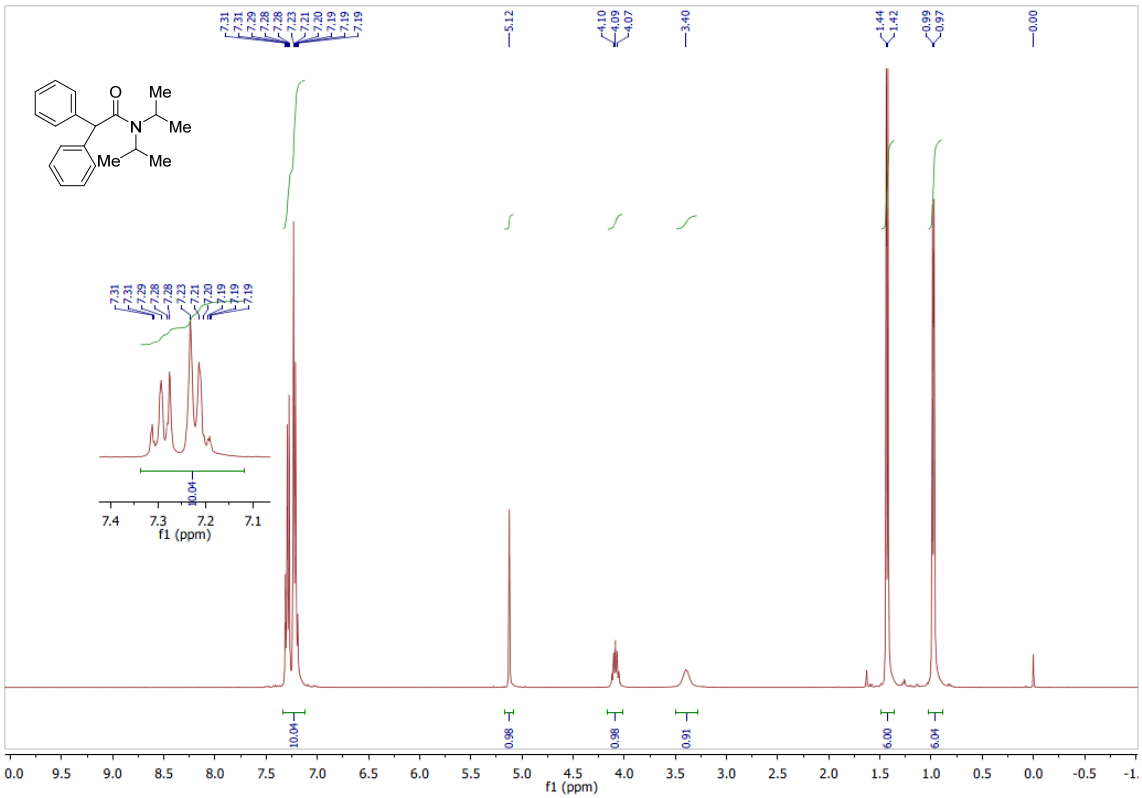
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

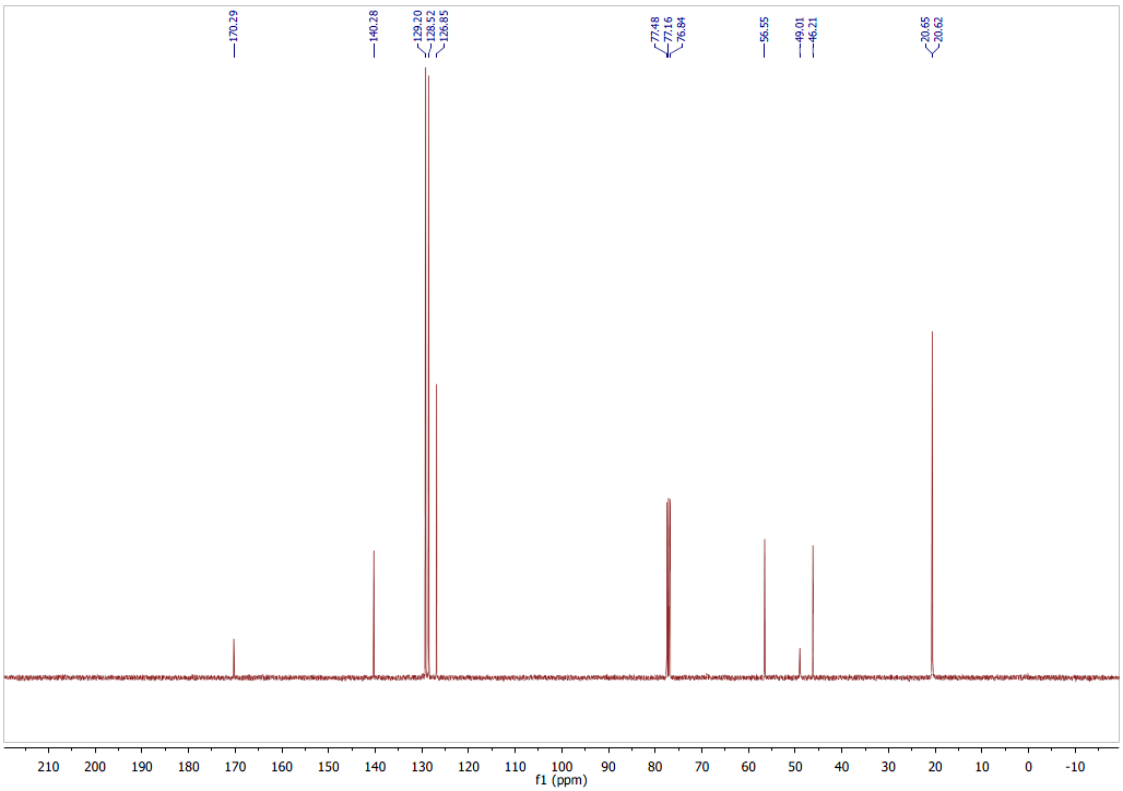




N,N-Diisopropyl-2,2-diphenylacetamide (11)

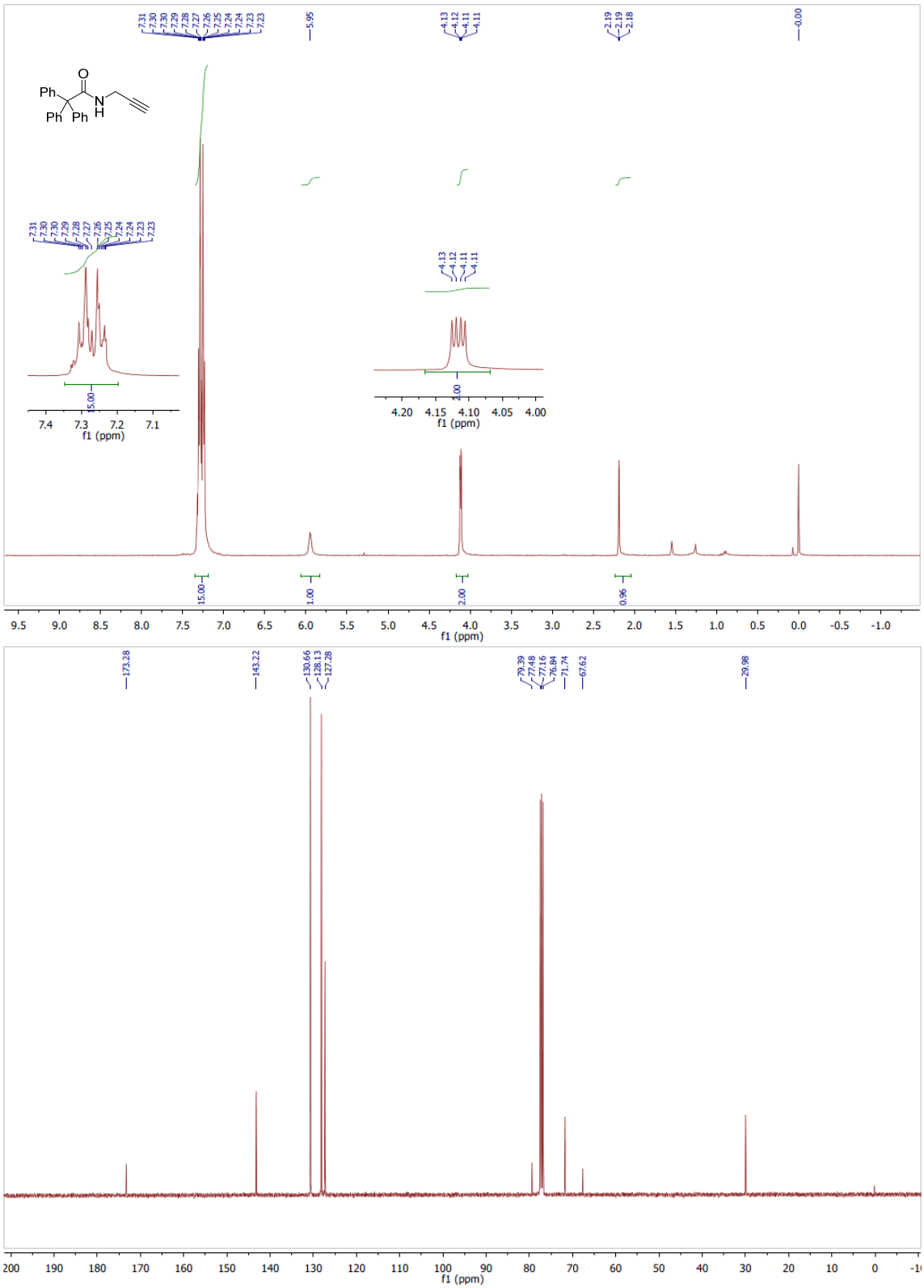
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)





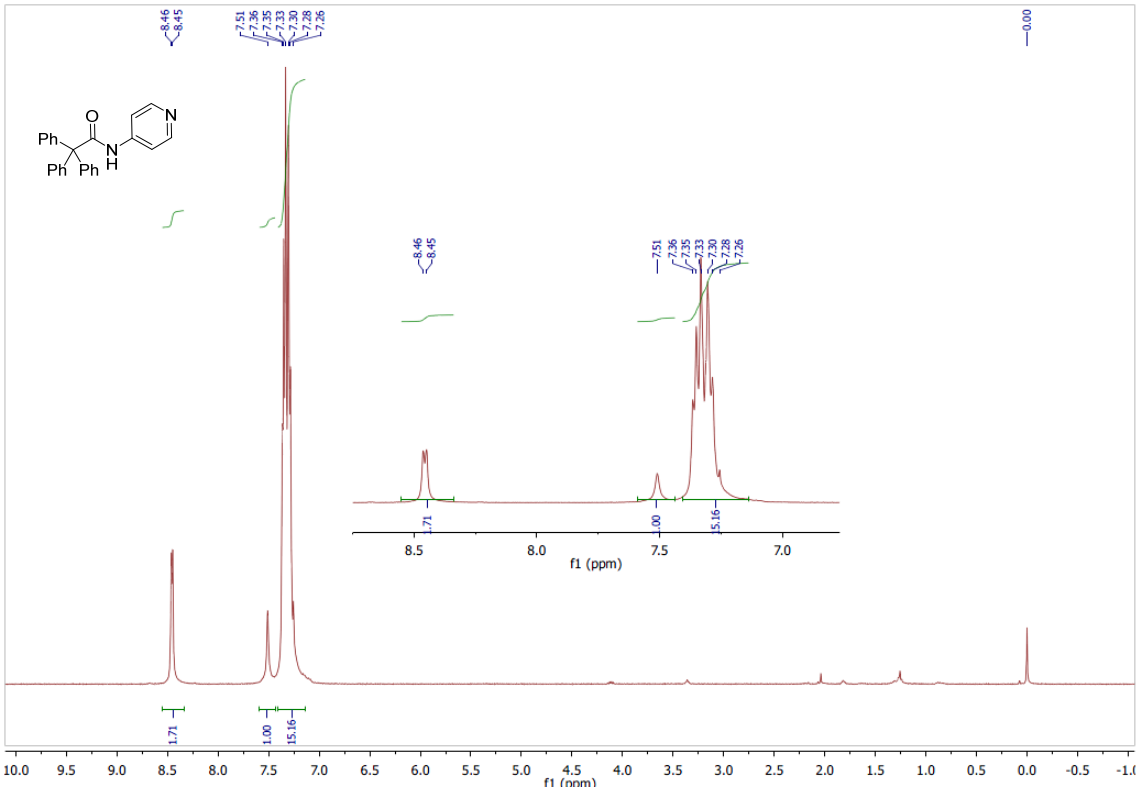
2,2,2-Triphenyl-*N*-(prop-2-yn-1-yl)acetamide (12)

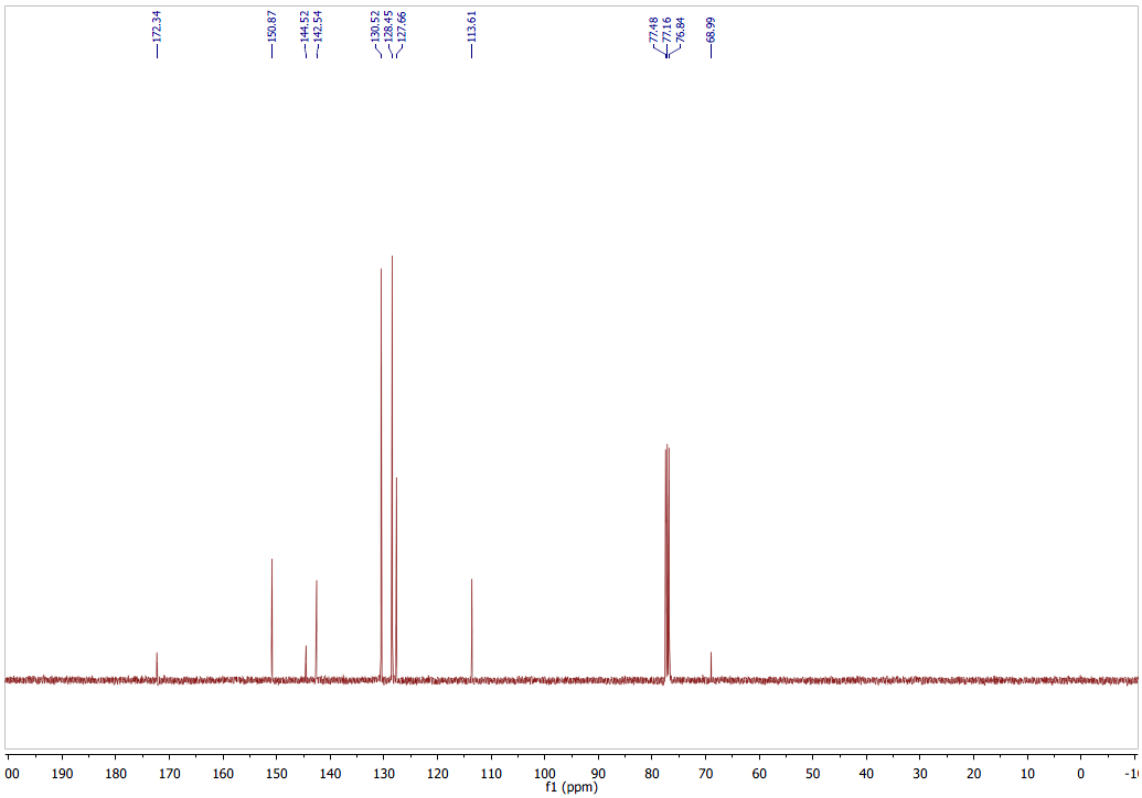
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)



2,2,2-Triphenyl-*N*-(pyridin-4-yl)acetamide (13)

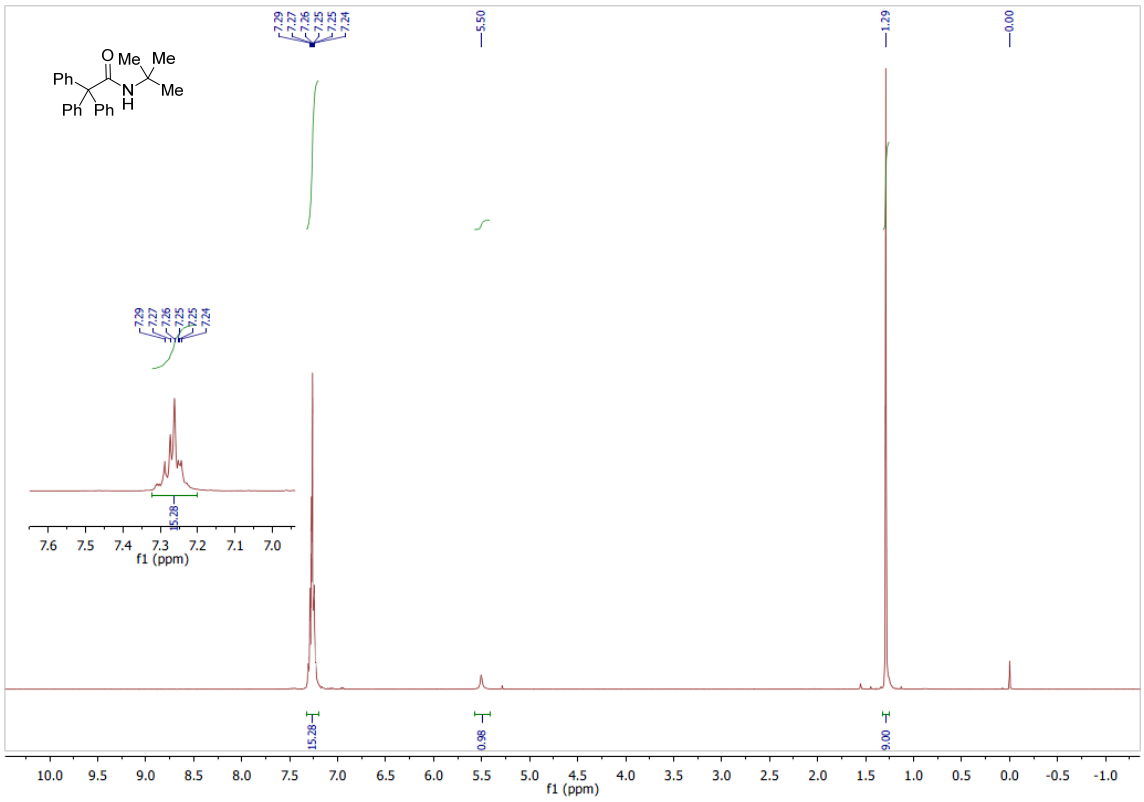
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

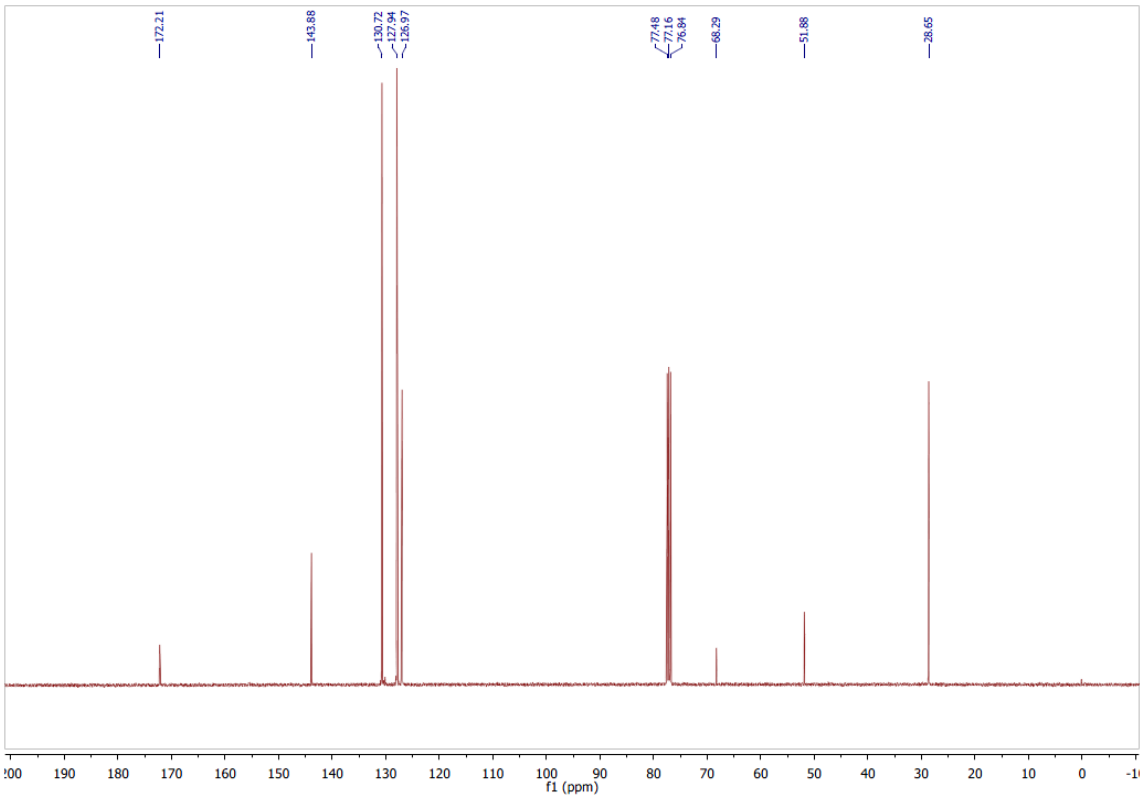




N-(*tert*-Butyl)-2,2,2-triphenylacetamide (14)

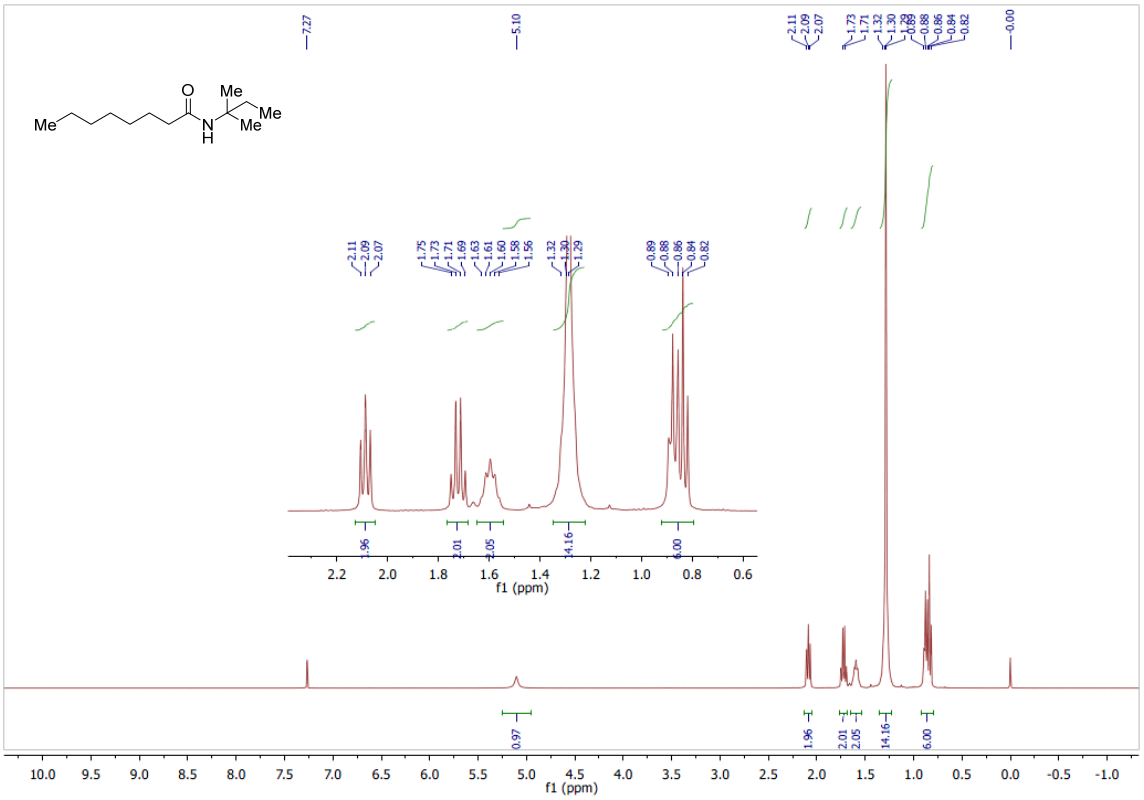
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

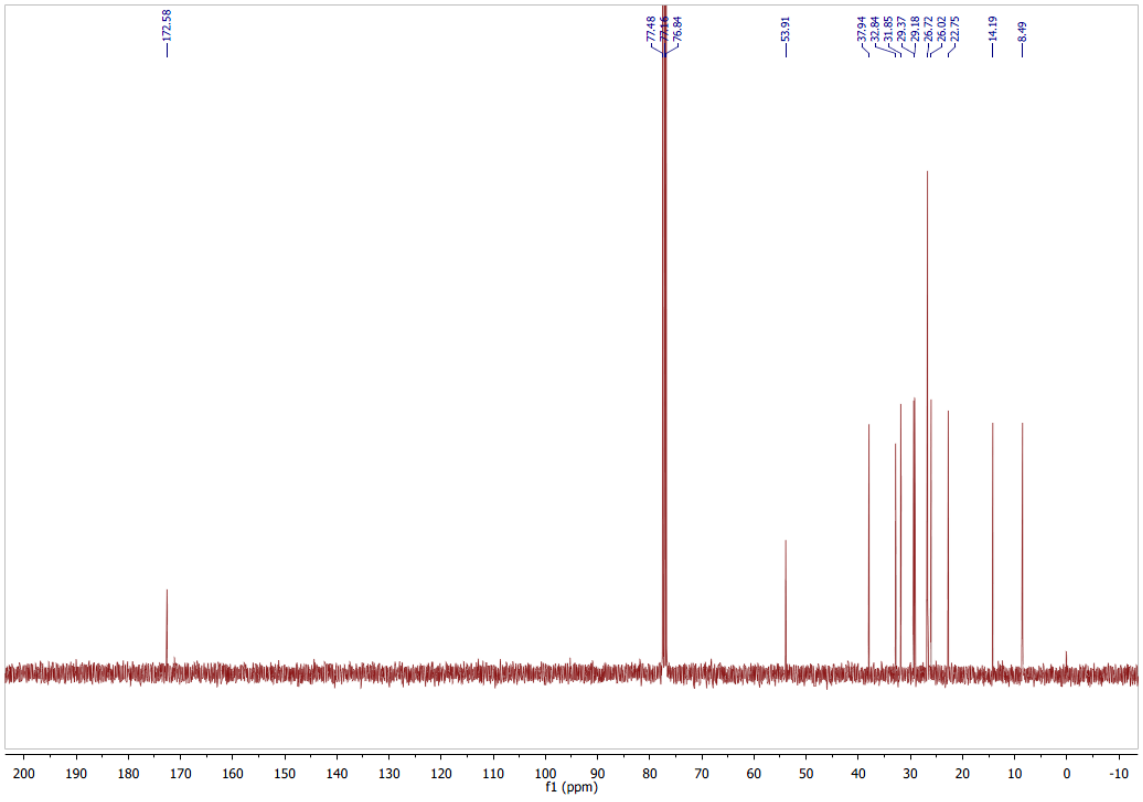




N-(*tert*-Pentyl)octanamide (15)

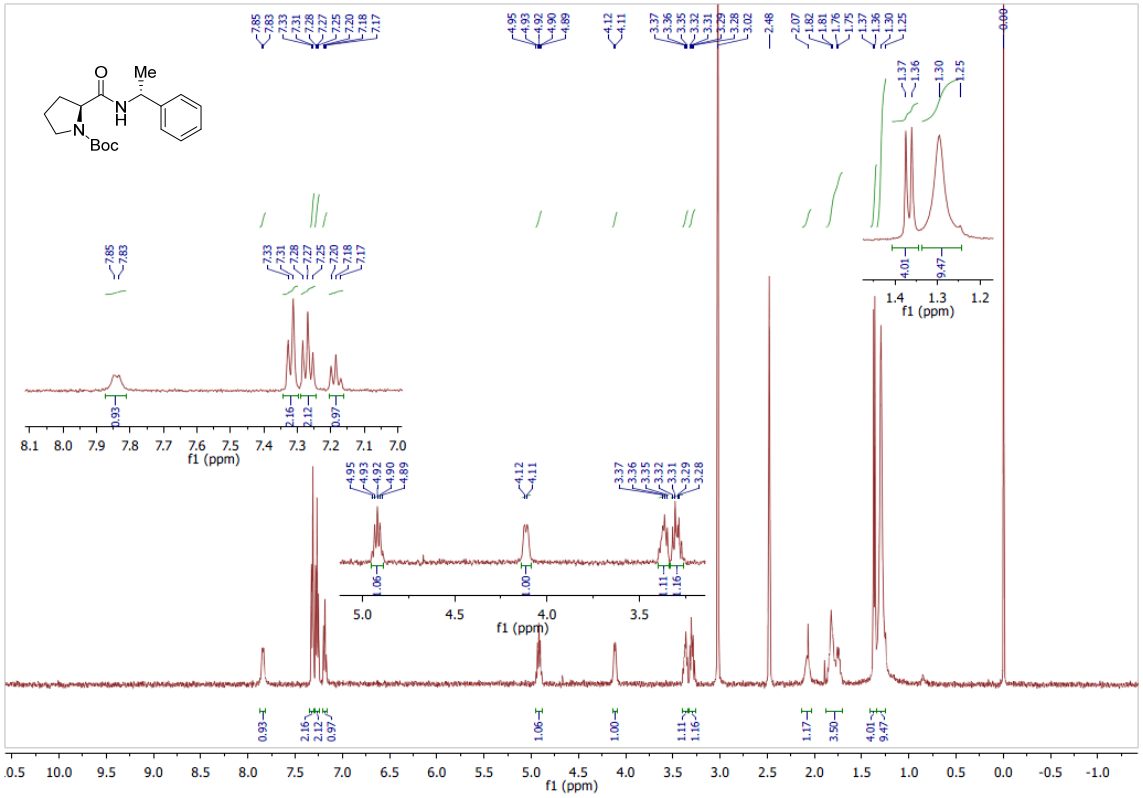
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

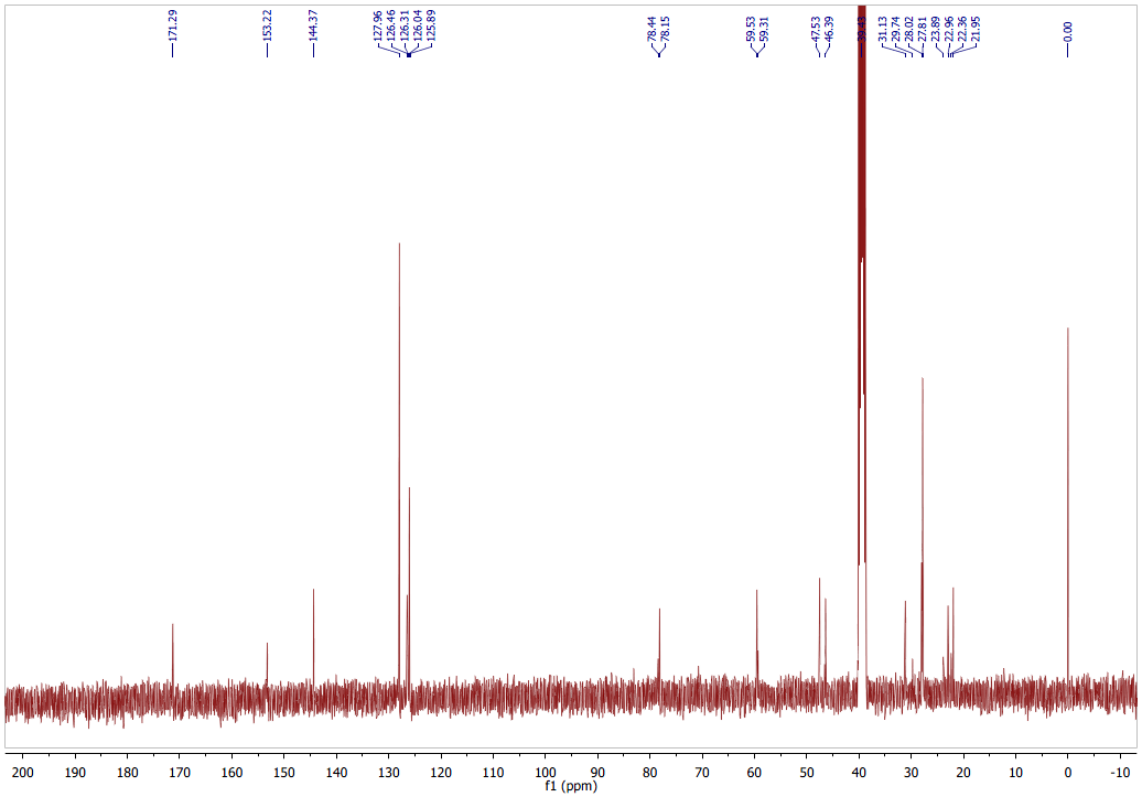




***tert*-Butyl (2*S*)-2-(((1*R*)-1-phenylethyl)carbamoyl)pyrrolidine-1-carboxylate (16)**

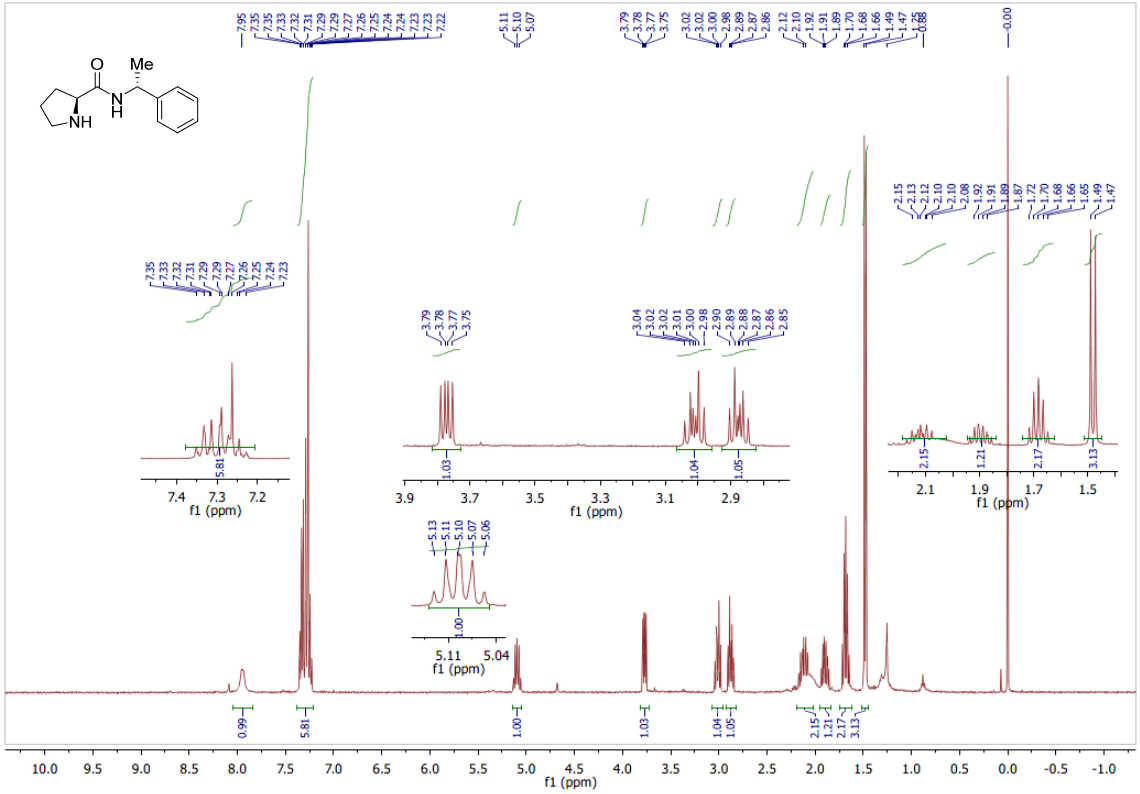
^{1}H NMR (500 MHz, DMSO-d_6, 80 °C); ^{13}C NMR (101 MHz, DMSO-d_6, 25 °C)

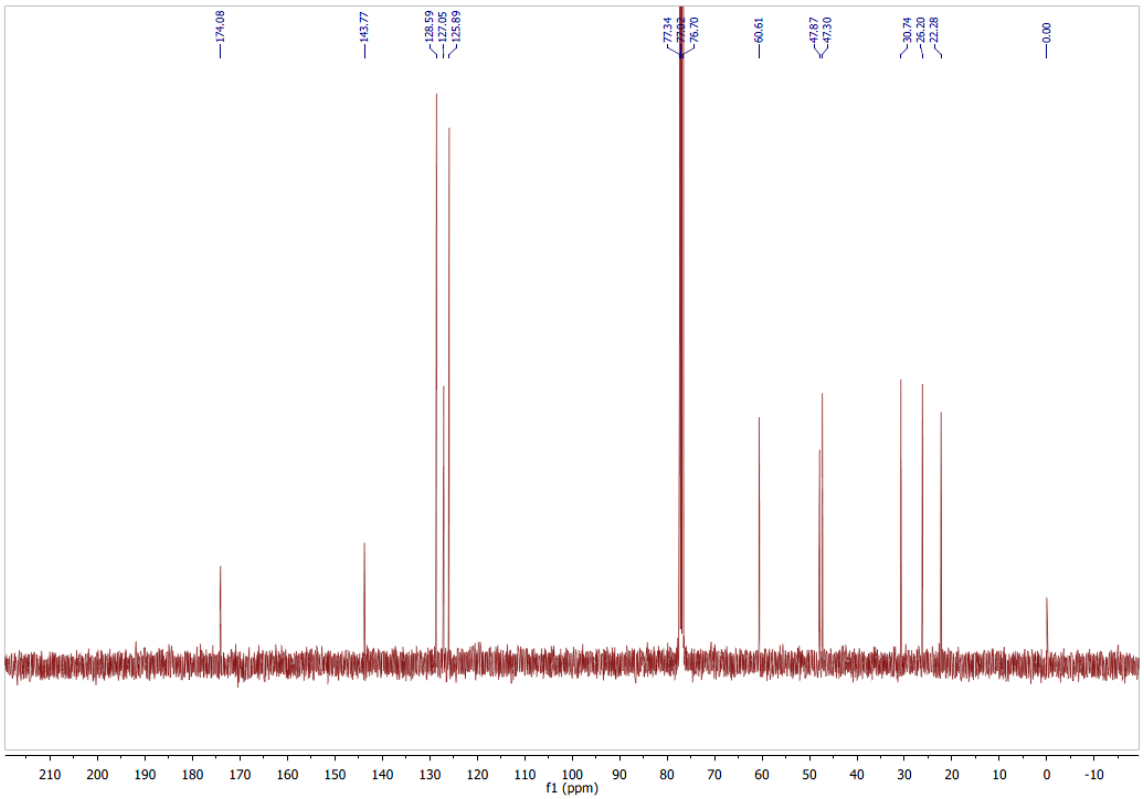




(*S*)-*N*-((*R*)-1-Phenylethyl)pyrrolidine-2-carboxamide (deprotected 16)

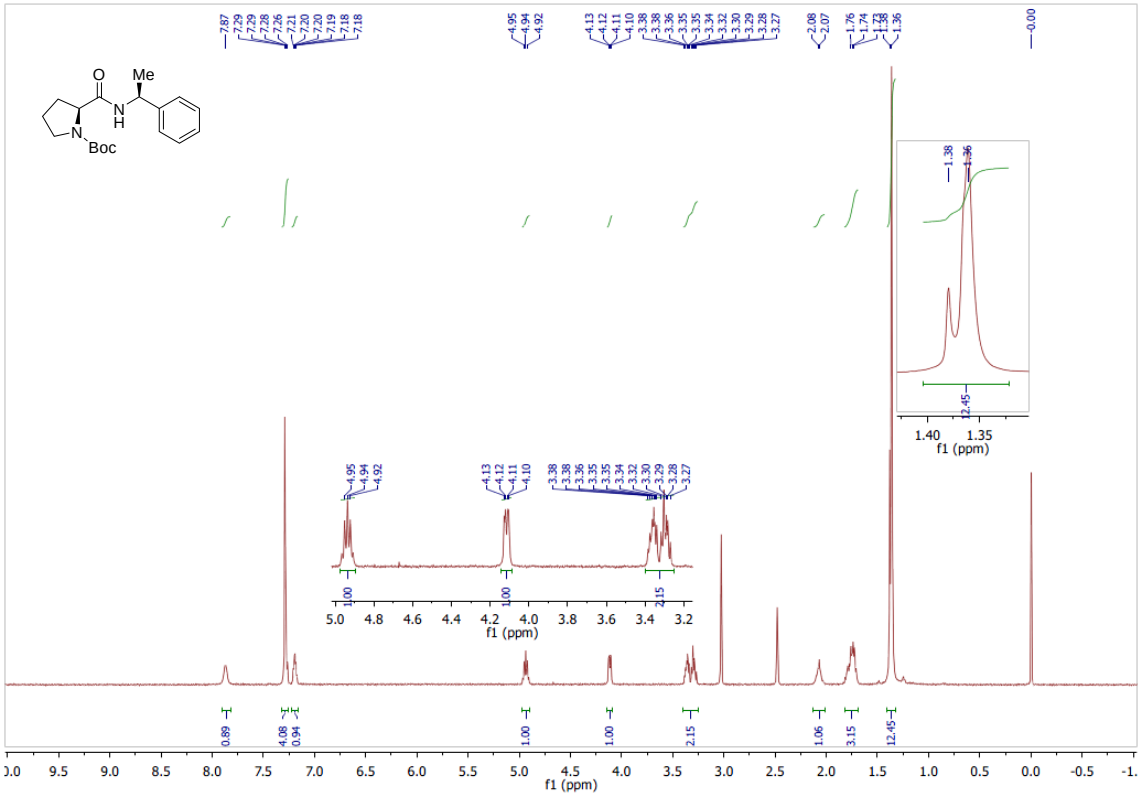
^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

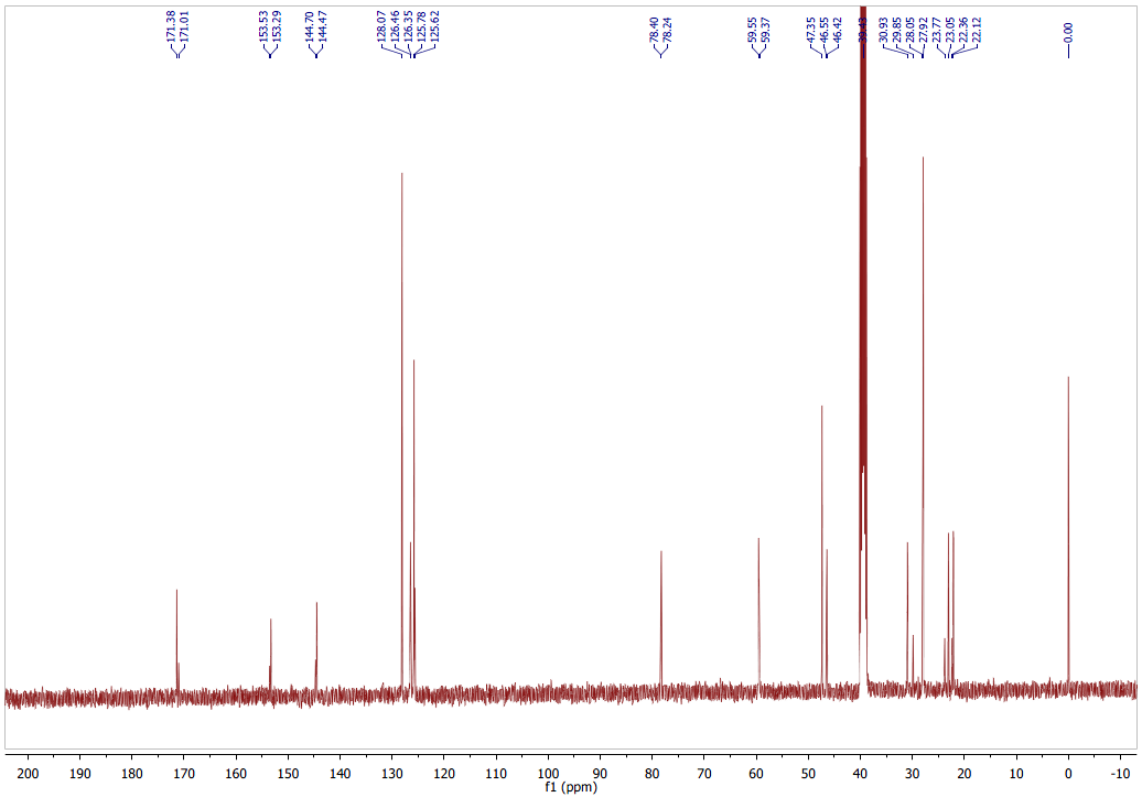




tert-Butyl (_S_)-2-(((_S_)-1-phenylethyl)carbamoyl)pyrrolidine-1-carboxylate (17)

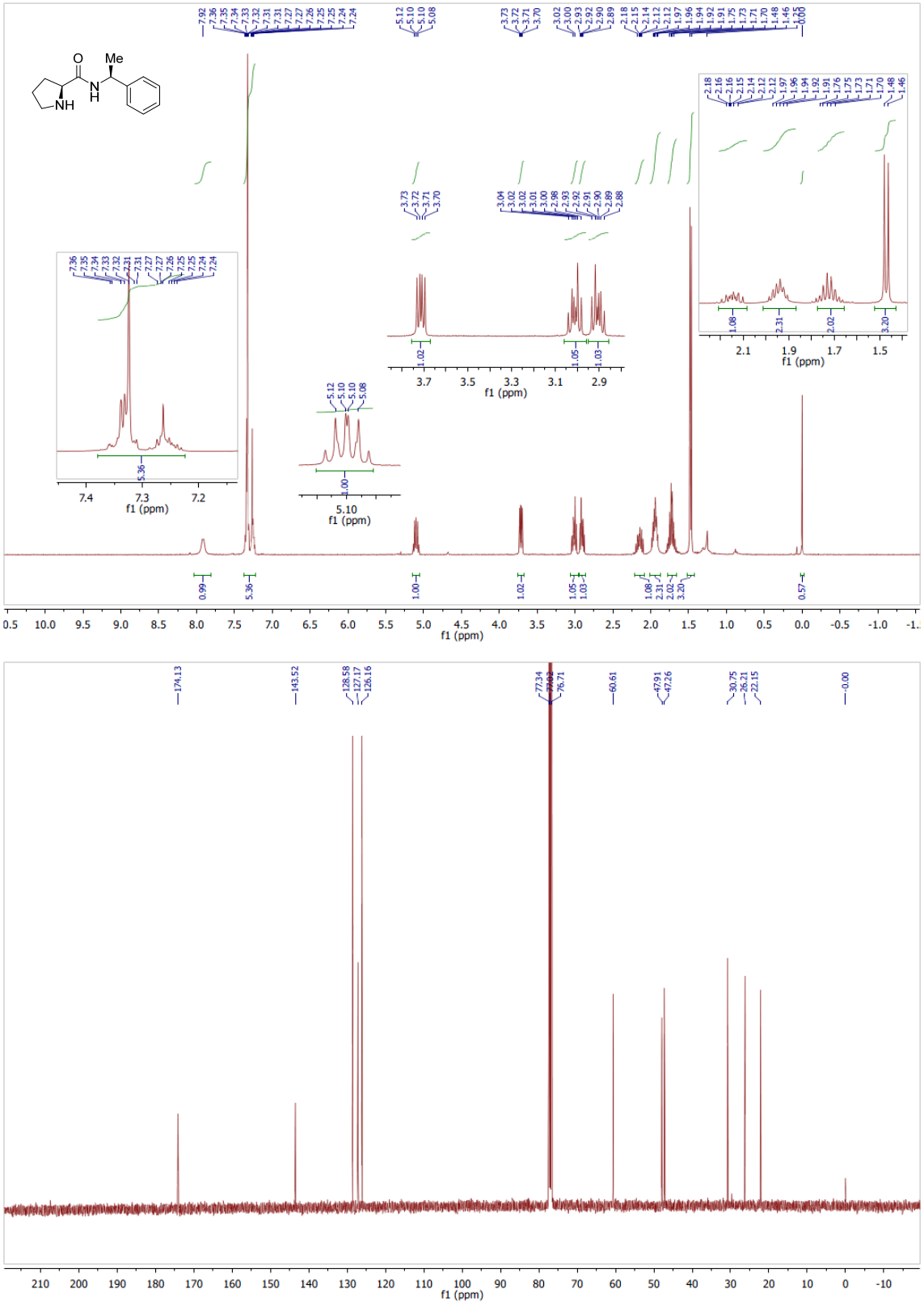
^{1}H NMR (500 MHz, DMSO-d_6, 80 °C); ^{13}C NMR (101 MHz, DMSO-d_6, 25 °C)



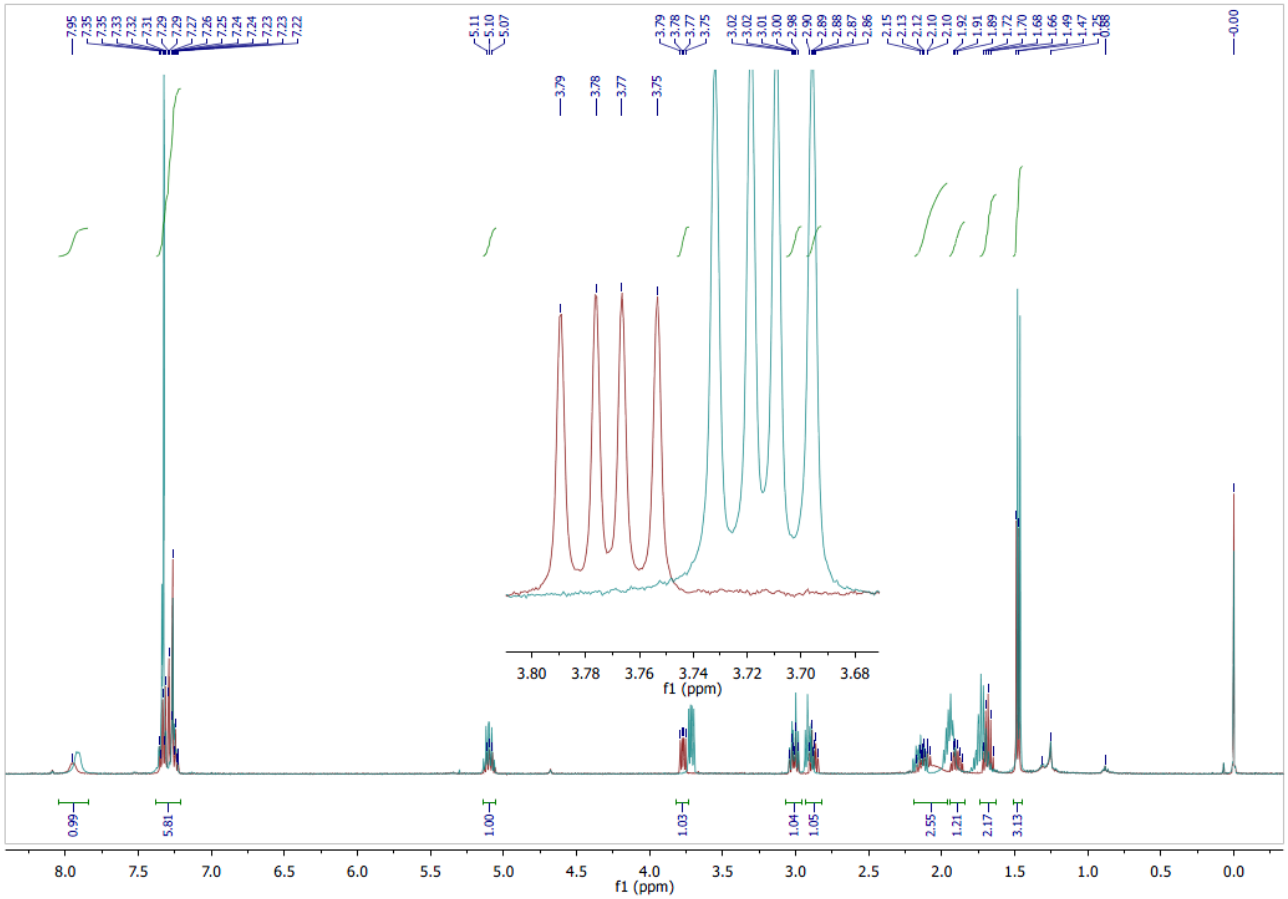


(*S*)-*N*-((*S*)-1- Phenylethyl)pyrrolidine-2-carboxamide (deprotected 17)

^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

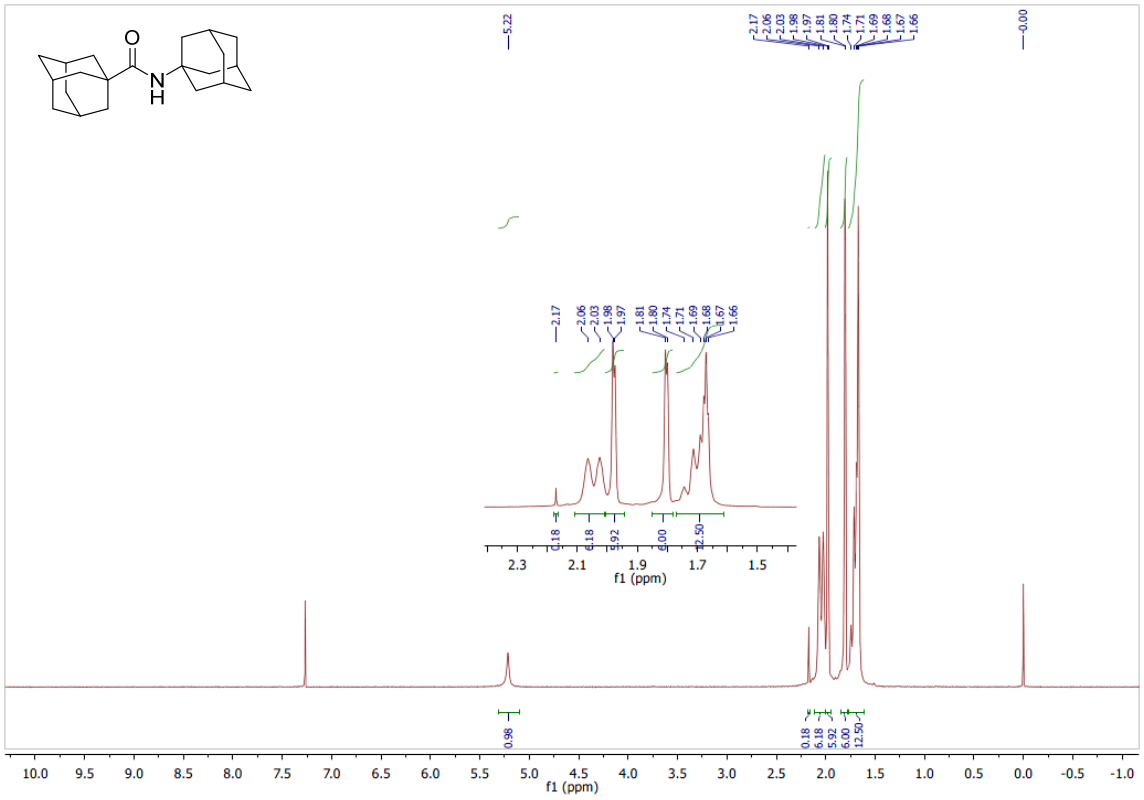


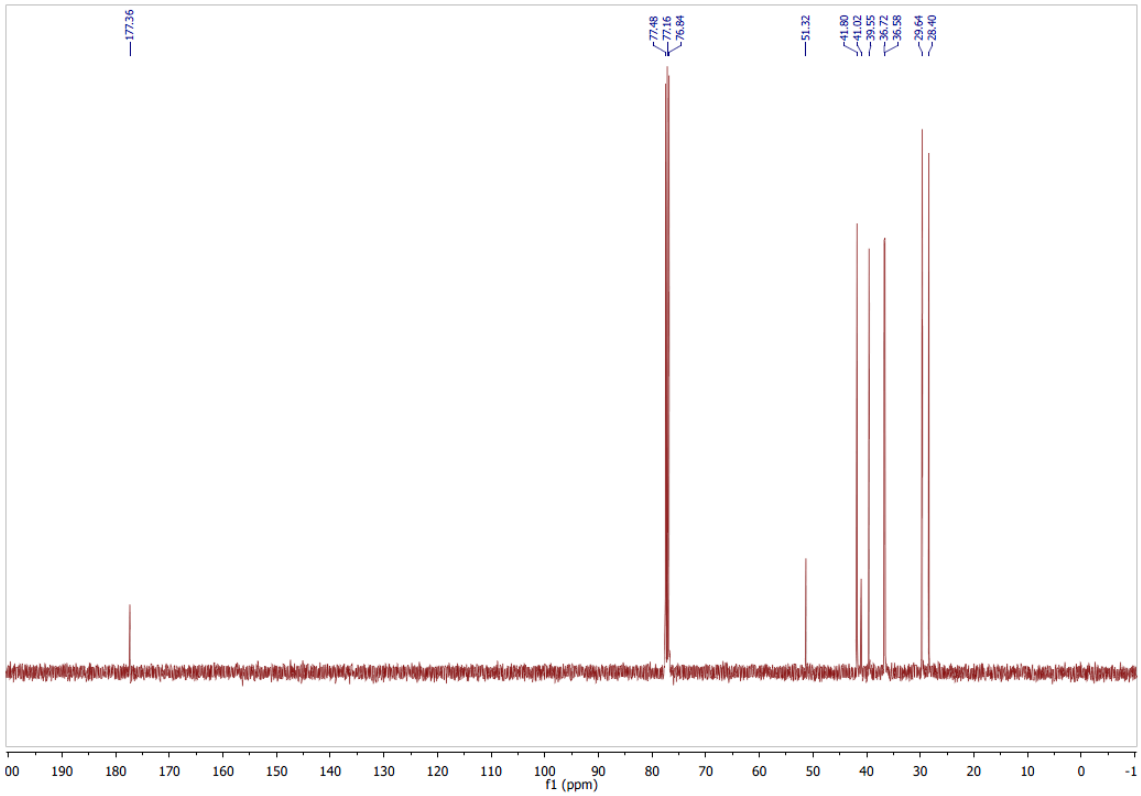
Overlay of ^{1}H NMR spectra for deprotected **16** and **17**



N-(Adamantan-1-yl)adamantane-1-carboxamide (18)

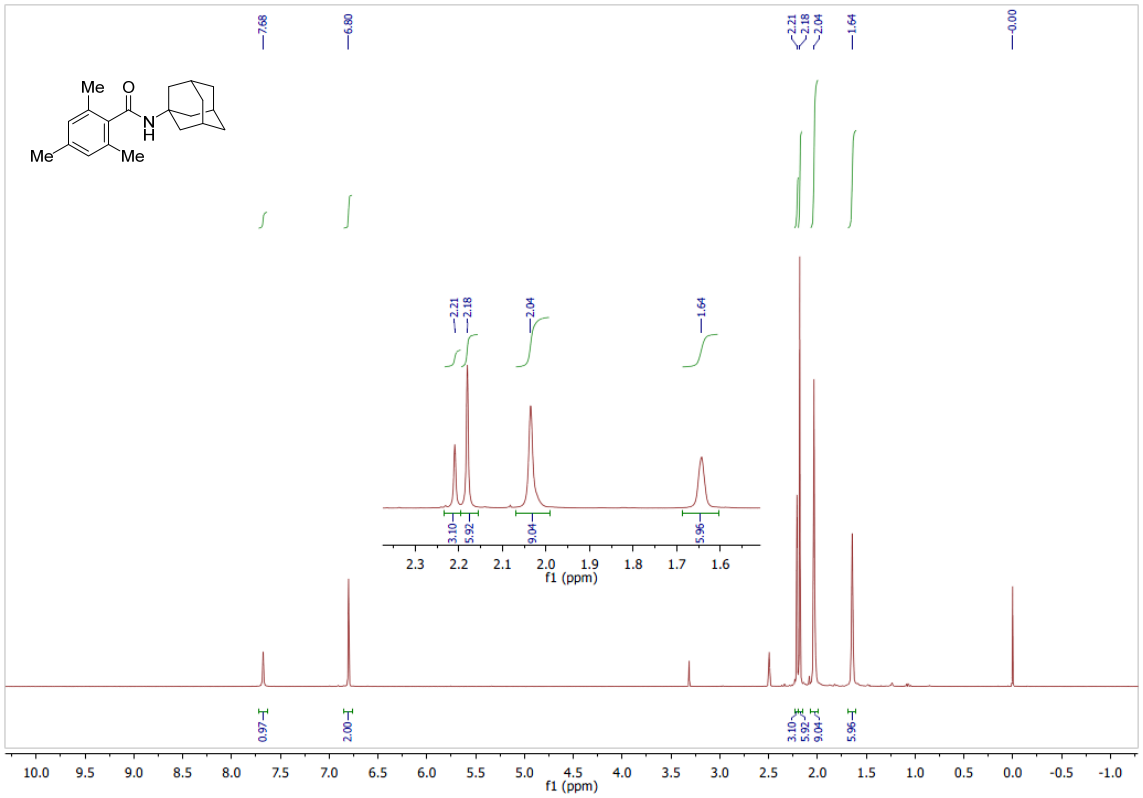
^{1}H NMR (400 MHz, DMSO-d_6); ^{13}C NMR (101 MHz, DMSO-d_6)

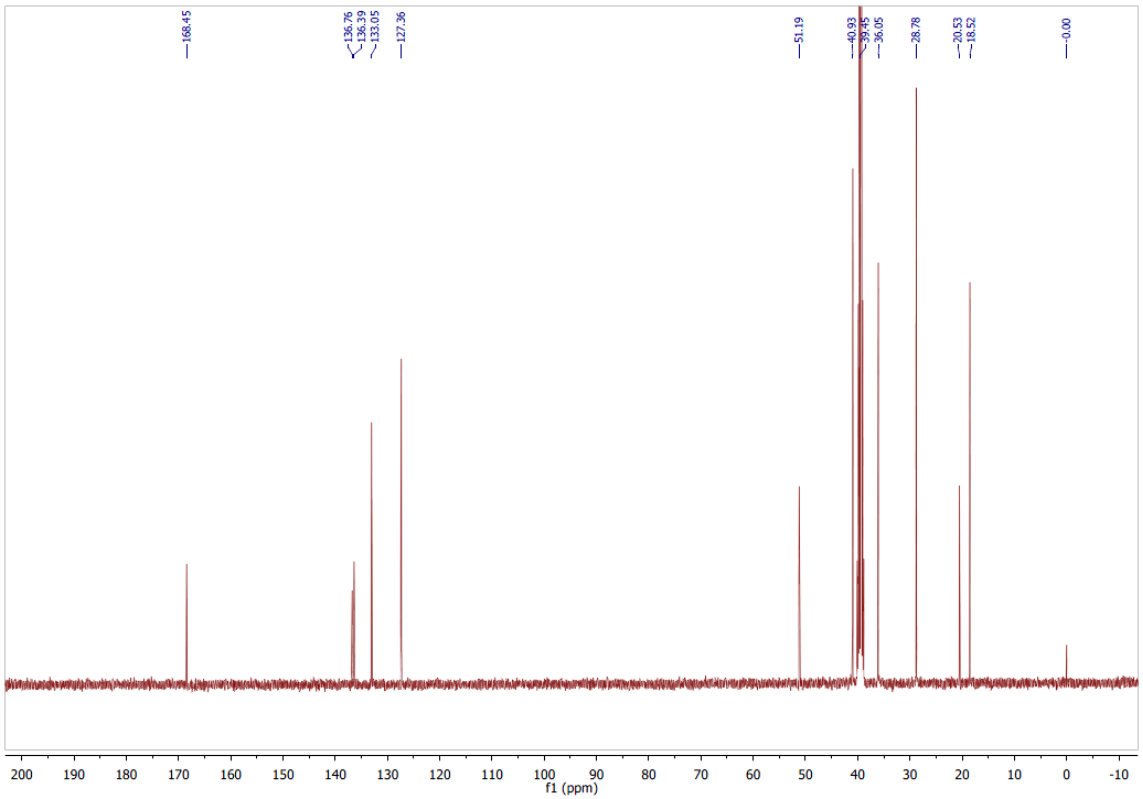




N-(Adamantan-1-yl)-2,4,6-trimethylbenzamide (19)

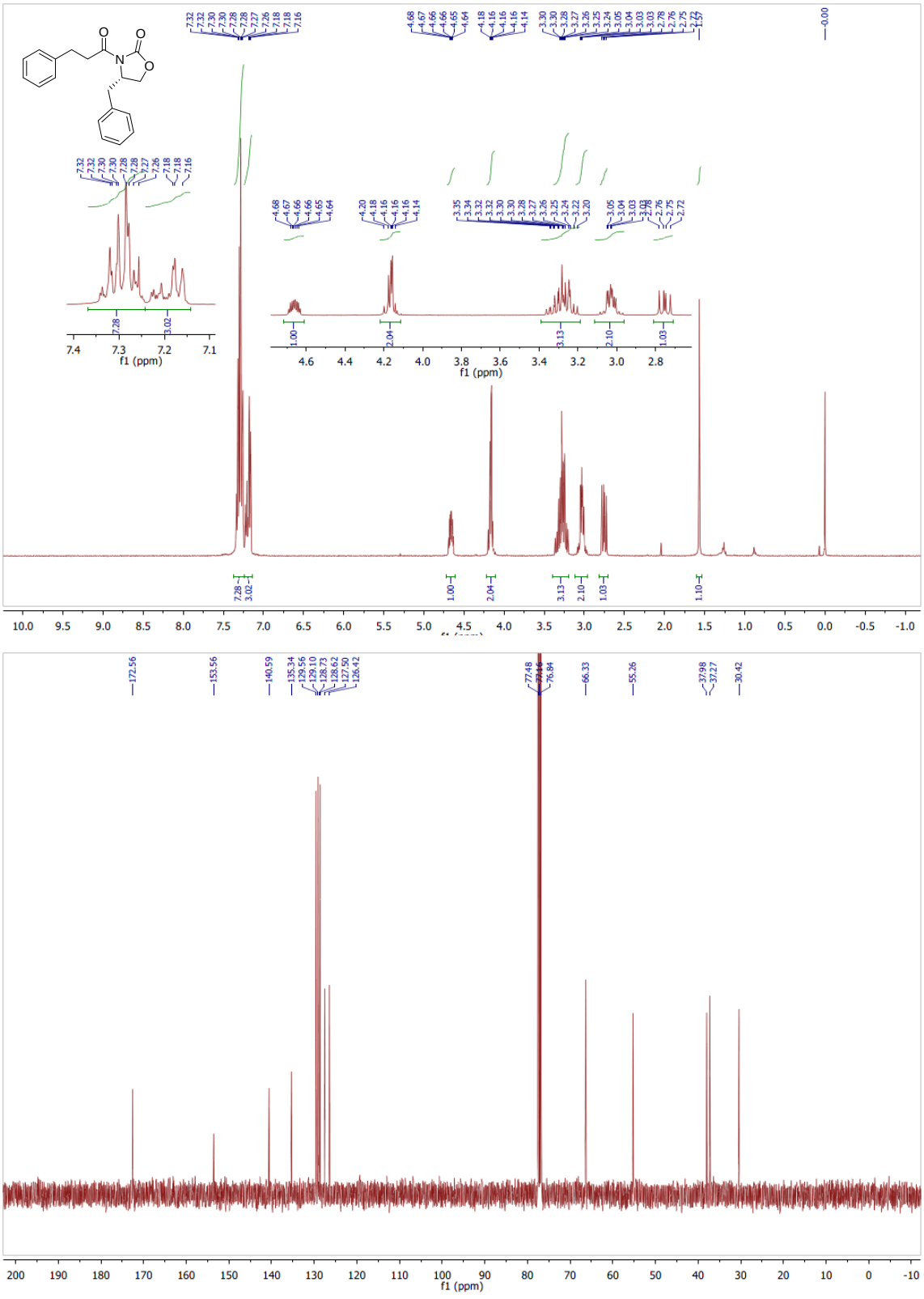
^{1}H NMR (400 MHz, DMSO-d_6); ^{13}C NMR (101 MHz, DMSO-d_6)





(*S*)-4-Benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one (20)

^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)



(*S*)-4-Isopropyl-3-(3-phenylpropanoyl)oxazolidin-2-one (21)

^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$)