Formal Nucleophilic Substitution of Bromocyclopropanes with Amides en route to Conformationally Constrained β-Amino Acid Derivatives

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SUPPORTING INFORMATION

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General Information

NMR spectra were recorded on a Bruker Avance DPX-400 instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or Bruker Avance AV-III 500 with a dual carbon/proton (CPDUL) cryoprobe at room temperature unless specified otherwise. ^{13}C NMR spectra were registered with broad-band decoupling. (+) and (-) represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. Column chromatography was carried out employing silica gel (Selecto Scientific, 63-200 μm). Pre-coated silica gel plates (Merck Kieselgel 60 F-254) were used for thin-layer chromatography. GC analyses were performed on a Shimadzu GC-2010 gas chromatograph equipped with an AOC-20i auto-injector and an AOC-20S auto-sampler tray (150 vials). 30 m x 0.25 mm x 0.25 μm capillary column, SHR5XLB, polydimethyl-siloxane, 5% Ph was employed. Helium (99.96%), additionally purified by passing consecutively through a CRS oxygen/moisture/hydrocarbon trap (#202839) and VICI oxygen/moisture trap (P100-1), was used as a carrier gas. Hydrogen gas was used as FID fuel; zero-grade air and zero-grade nitrogen were used as an oxidant and make-up gas, respectively, for the FID. All these gases were purified by passing through CRS #202839 traps. The following GC oven program was employed: 50 ^{o}C (isotherm, 2 min) – (ramp 20 ^{o}C/min) – 275 ^{o}C (isotherm). IR spectra were recorded on a Shimadzu FT-IR 8400S instrument. High resolution mass-spectra were obtained using a LCT Premier (Micromass Technologies) instrument using electrospray ionization and time of flight detection techniques. Relative configurations of bromocyclopropane starting materials and diamide product **6ab** were assigned based on comparative analysis of the chemical shifts and the coupling constants for four protons at cyclopropyl rings as described in the Supporting Information for our previous report.[1] Configuration of diamide **6bw** was determined by single crystal X-ray diffraction. ^{1}H NMR spectra of diamides **6ap** and **6aw** obtained as described in the experimental section, contained unidentified minor impurities, which integrated within 95% purity threshold. The purity of all other diamide products was assessed to exceed 97%.

Anhydrous ether, dichloromethane and tetrahydrofuran were obtained by passing degassed HPLC-grade commercially available solvents consecutively through two columns with activated alumina (Innovative Technology). Preparative procedures for synthesis of starting bromocyclopropanes (**5a-d**) and secondary amide pronucleophiles (**4b-f, 4h-y**) are provided below. 18-Crown-6 ether was dried in the vacuum desiccator over P_2O_5. All other chemicals were purchased from Sigma-Aldrich, Acros Organics, or TCI America, and used as received.

All manipulations with powdered KOH and 18-crown-6 ether were conducted under inert atmosphere (<8 ppm residual oxygen and moisture) using a combination of glovebox and standard Schlenk techniques. After quench the reaction mixtures and compounds were treated on air. All the obtained materials were moisture and oxygen stable at ambient temperatures.

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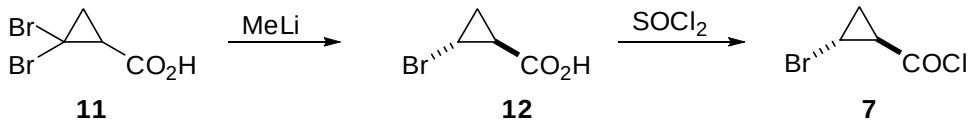
(1) Alnasleh B. K.; Sherrill, W. M.; Rubina, M.; Banning, J.; Rubin, M. *J. Am. Chem. Soc.* **2009**, *131*, 6906.

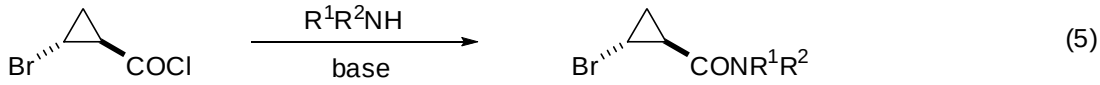
Preparation of Starting Materials

Synthesis of Bromocyclopropanes



11 **12** **7** (4)

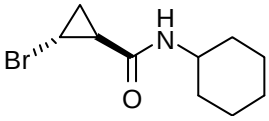
(1*S**,2*R**)-2-Bromocyclopropanecarbonyl chloride (**7**): Flame-dried 3000 mL three neck round bottom flask was charged with solution of 2,2-dibromocyclopropanecarboxylic acid (**11**) (27.0 g, 111 mmol) in anhydrous ether (1300 mL) under nitrogen atmosphere. The mixture was vigorously stirred (500-650 rpm) at -20 ^{o}C, and methyl lithium solution (1.6M in ether, 95 mL, 152 mmol, 1.37 equiv) was added dropwise. For safety reasons it is essential to add methyl lithium directly to a solution rather than draining along the flask wall to minimize the amount of solid precipitate, which might ignite during the following work up. An aliquot of solution (1 mL) was withdrawn from the flask with a syringe, quenched consecutively with brine (2-3 drops) and 5% aqueous HCl (2-3 drops) in 10 mL test tube. The aqueous layer was saturated with NaCl, and extracted with EtOAc (3 x 0.5 mL). The combined organic phases collected with Pasteur pipet were dried with $MgSO_4$ and concentrated. The conversion was measured based on ^{1}H NMR analysis of this probe, and additional amount of MeLi necessary to complete the transformation was assessed (35 mL, 56 mmol). The mixture was quenched at -20 ^{o}C by adding brine (100 mL) and 5% aqueous HCl (100 mL). (It is essential to perform the quenching at low temperature and to maintain inert atmosphere to avoid ignition of the mixture). The mixture was allowed to warm up to rt, then aqueous layer was saturated with NaCl. Ethereal layer was separated, and then aqueous phase was extracted with EtOAc (6 x 100 mL). Combined organic phases were dried with $MgSO_4$, filtered and concentrated. The oily residue was distilled in vacuum (bp 71 ^{o}C at 3 torr) to provide (1*S**,2*R**)-2-bromocyclopropanecarboxylic acid (**12**) as a colorless oil, which solidified upon standing. Yield 8.79 g (53.3 mmol, 48%). This material was charged into a 25 mL round bottomed flask equipped and thionyl chloride (11.5 g, 110 mmol) was added. The mixture was stirred at room temperature overnight, then an excess of thionyl chloride was distilled off, and the residue was fractionated in vacuum to obtain the title compound as clear oil, bp 56 ^{o}C at 15 torr. Yield 9.19 g (50.1 mmol, 94%).



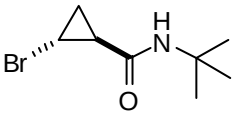
(5)

12

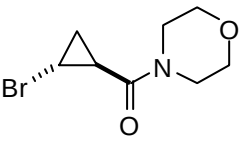
5a: R^1 = *t*-Bu, R^2 = H
5b: R^1R^2 = -$(CH_2)_2O(CH_2)_2$-
5c: R^1R^2 = -$(CH_2)_5$-
5d: R^1 = Cy, R^2 = H
5e: R^1 = Me, R^2 = OMe



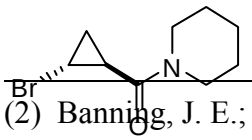
(1*S**,2*R**)-2-bromo-*N*-cyclohexylcyclopropanecarboxamide (**5d**) (typical procedure): To a stirred solution of cyclohexylamine (1.87 mL, 1.62 g, 16.4 mmol, 3 equiv.) in dry THF (30 mL) was added *trans*-2-bromocyclopropanecarbonyl chloride **7** (1.0 g, 5.5 mmol). The mixture was stirred for 1 hr at room temperature, and then the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed consecutively with 10% aqueous HCl (3 x 20 mL) and 4N aqueous NaOH (5 mL), dried with $MgSO_4$, filtered and concentrated. The obtained colorless crystalline material (mp 102-105 ^oC) was pure enough to be used for the following transformations without additional purification. Yield 1.26 g (5.12 mmol, 94%). ^1H NMR (500.13 MHz, CD_3OD) δ ppm 3.62 (tt, *J* = 10.7 Hz, 3.7 Hz, 1H), 3.14 (ddd, *J* = 7.9 Hz, 4.7 Hz, 3.2 Hz, 1H), 1.99 (ddd, *J* = 9.1 Hz, 6.0 Hz, 3.2 Hz, 1H), 1.90-1.80 (m, 2H), 1.79-1.72 (m, 2H), 1.67-1.61 (m, 1H), 1.49 (dt, *J* = 7.6 Hz, 6.0 Hz, 1H), 1.40-1.30 (m, 2H), 1.28-1.16 (m, 4H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.7, 50.2 (+), 34.0 (-), 33.9 (-), 26.8 (-), 26.24 (-, 2C), 26.18 (+), 19.3 (+), 17.8 (-); FTIR (NaCl, film, cm^{-1}): 3292, 2932, 2854, 1634, 1553, 1450, 1393, 1211, 1024, 945, 981, 843; HRMS (TOF ES): found 246.0483, calculated for $C_{10}H_{17}BrNO$ (M+H) 246.0494 (4.5 ppm).



(1*S**,2*R**)-2-Bromo-*N*-tert-butylcyclopropanecarboxamide (**5a**): The reaction was performed according to the typical procedure, employing acyl chloride **7** (1.0 g, 5.5 mmol) and *tert*-butylamine (1.72 mL, 1.20 g, 16.4 mmol) to produce the title compound as a colorless solid, yield 1.13 g (5.12 mmol, 93%). The physical and spectral properties of this material were identical to those reported previously.[1]



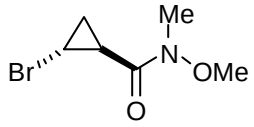
((1*S**,2*R**)-2-Bromocyclopropyl)(morpholino)methanone (**5b**): The reaction was performed according to the typical procedure, employing acyl chloride **7** (1.0 g, 5.5 mmol) and morpholine (1.42 mL, 1.43 g, 16.4 mmol) to produce the title compound as a colorless solid, yield 1.16 g (4.95 mmol, 90%). The physical and spectral properties of this material were identical to those reported previously.[2]



((1*S**,2*R**)-2-Bromocyclopropyl)(piperidin-1-yl)methanone (**5c**):

(2) Banning, J. E.; Prosser, A. R.; Rubin, M. *Org. Lett.* **2010**, *12*, 1488.

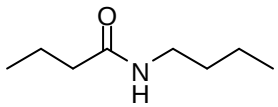
The reaction was performed according to the typical procedure, employing acyl chloride **7** (1.0 g, 5.5 mmol) and piperdine (1.64 mL, 1.40 g , 16.4 mmol) to produce the title compound as a colorless oil, yield 1.20 g (5.18 mmol, 95%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 3.63-3.59 (m, 2H), 3.57-3.53 (m, 2H), 3.22 (ddd, *J* = 9.5 Hz, 6.0 Hz, 3.2 Hz, 1H), 1.70-1.61 (m, 5H), 1.57-1.52 (m, 2H), 2.18 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.2 Hz, 1H), 1.31 (ddd, *J* = 9.5 Hz, 6.0 Hz, 4.7 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.1, 46.8 (-), 43.4 (-), 26.6 (-), 25.4 (-), 24.5 (-), 22.6 (+), 19.6 (+), 17.5 (-); FTIR (NaCl, film, cm^{-1}): 2935, 2854, 1634, 1445, 1367, 1354, 1254, 1223, 1138, 1024, 955, 926, 852; HRMS (TOF ES): found 232.0327, calculated for $C_9H_{15}BrNO$ (M+H) 232.0337 (4.3 ppm).



(1*S**,2*R**)-2-Bromo-*N*-methoxy-*N*-methylcyclopropanecarboxamide (**5e**): To a solution of carboxylic acid **12** (3.27 g, 19.82 mmol) in dry CH_2Cl_2 (60 mL) was added 1,1-carbonyldiimidazole (3.86 g, 23.8 mmol, 1.20 equiv) at 0 °C, and the resulting mixture was stirred for 30 min. Then *N*,*O*-dimethylhydroxylamine hydrochloride (4.50 g, 46.5 mmol, 2.35 equiv) was added; the resulting suspension was stirred for 24 hrs at room temperature, then filtered. The filter cake was washed with DCM. The filtrate was washed with water, brine, dried with $MgSO_4$, filtered, and concentrated in vacuum to give 3.41 g (16.4 mmol, 83%) of Weinreb amide **5e** as an yellow oil. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 3.80 (s, 3H), 3.24 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.2 Hz, 1H), 3.22 (s, 3H), 2.59 (br. s, 1H), 1.65 (dt, *J* = 7.6 Hz, 6.0 Hz, 1H), 1.39 (ddd, *J* = 9.5 Hz, 5.7 Hz, 4.7 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 171.1, 61.9 (+), 32.5 (+), 21.2 (+), 19.9 (+), 18.0 (-); FTIR (teflon, film, cm^{-1}): 3501, 3082, 3069, 3003, 2966, 2937, 2901, 1655, 1475, 1462, 1421, 1391, 1327, 1207, 1177, 1153, 1105, 1016, 997, 943, 760, 727, 609, 582, 507, 440; HRMS (TOF ES): found 207.9974, calculated for $C_6H_{11}BrNO_2$ (M+H) 207.9973 (0.5 ppm).

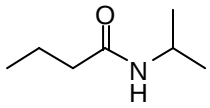
Synthesis of Pro-nucleophiles:

N-methylacetamide (**4a**) and *N*-methylbenzamide (**4g**) were commercially available and used as recieved.

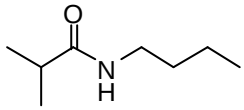


N-Butylbutyramide (**4b**) (typical procedure): To a stirred solution of *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) in 1M aqueous NaOH (50 mL, 50 mmol, 2.36 equiv) was added butyryl chloride (4.19 mL, 4.33 g, 40.6 mmol, 1.67 equiv). The mixture was stirred for 2 hrs at room temperature, then aqueous layer was saturated with brine and extracted with EtOAc (3 x 25 mL). Combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuum. The residue was distilled in vacuum employing Kugelröhr apparatus to afford the title compound as colorless amorphous solid. Yield 3.08 g (21.5 mmol, 88%). Physical and spectral properties of this material were identical

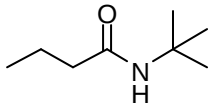
to those previously reported in literature. [3]



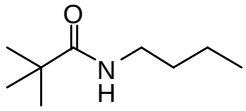
N-Isopropylbutyramide (**4c**): This compound was prepared according to a typical procedure starting from isopropylamine (2.09 mL, 1.44 g, 24.4 mmol) and butyryl chloride (4.19 mL, 4.33 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 2.52 g (19.5 mmol, 80%). Physical and spectral properties of this material were identical to those previously reported in literature.[4]



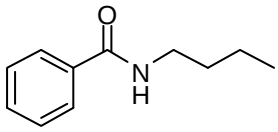
N-Butylisobutyramide (**4d**): This compound was prepared according to a typical procedure starting from *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) and isobutyryl chloride (4.26 mL, 4.33 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 2.65 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature.[5]



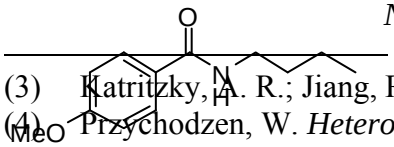
N-*tert*-Butylbutyramide (**4e**): This compound was prepared according to a typical procedure starting from *t*-butylamine (2.56 mL, 1.78 g, 24.4 mmol) and butyryl chloride (4.19 mL, 4.33 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 2.94 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature. [6]



N-Butylpivalamide (**4f**): This compound was prepared according to a typical procedure starting from *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) and pivaloyl chloride (5.00 mL, 4.90 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 3.23 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature.[5]



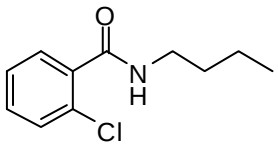
N-Butylbenzamide (**4h**): This compound was prepared according to a typical procedure starting from *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) and benzoyl chloride (4.71 mL, 5.71 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 3.63 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature.[7]



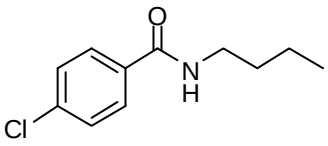
N-Butyl-4-methoxybenzamide (**4i**): To a stirred solution of

(3) Katritzky, A. R.; Jiang, R.; Sommen, G. L.; Singh, S. K. *ARKIVOC* **2004**, 44.
(4) Przychodzen, W. *Heteroatom Chem.* **2006**, *17*, 676.
(5) Steffel, L. R.; Cashman, T. J.; Reutershan, M. H.; Linton, B. R. *J. Am. Chem. Soc.* **2007**, *129*, 12956.
(6) Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Eur. J. Org. Chem.* **2009**, 430.
(7) (a) Zhang, M.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2004**, *69*, 8340. (b) Comerford, J. W.; Clark, J. H.; Macquarrie, D. J.; Breeden, S. W. *Chem. Commun.* **2009**, 2562.

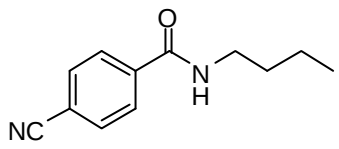
dicyclohexyl carbodiimide (1.36 g, 6.57 mmol), DMAP (0.04 g, 0.33 mmol), and *p*-anisic acid (1.03 g, 6.57 mmol) in dry CH_2Cl_2 (15 mL) was added dry *n*-butylamine (0.82 mL, 600 mg, 8.21 mmol). The mixture was stirred for 36 hrs at 30 ^oC, then quenched with 5N aqueous NaOH (25 mL) and extracted with ether (4 x 15 mL). Combined organic phases were dried with $MgSO_4$, and concentrated. Flash column chromatography afforded the title compound as colorless solid. Yield 721 mg (3.48 mmol, 53%). Physical and spectral properties of this material were identical to those previously reported in literature.[8]



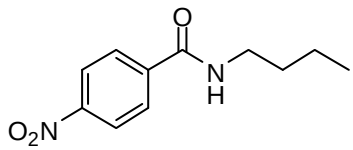
N-Butyl-2-chlorobenzamide (**4j**): was obtained from o-chlorobenzoic acid (1.00 g, 6.57 mmol) according to a protocol, described for preparation of amide **4i**. Yield 760 mg (3.61 mmol, 55%). Physical and spectral properties of this material were identical to those previously reported in literature.[9]



N-Butyl-4-chlorobenzamide (**4k**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 4-chlorobenzoyl chloride (547 μL, 753 mg, 4.30 mmol) as colorless crystalline solid, mp 62-64 ^oC. Yield 865 mg (4.09 mmol, 95%); ^1H NMR (500.13 MHz, CD_3OD) δ ppm 7.79 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 3.37 (t, *J* = 7.3 Hz, 2H), 1.60 (quin, *J* = 7.3 Hz, 2H), 1.41 (sxt, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 169.3, 138.7, 134.7, 130.1 (+, 2C), 129.8 (+, 2C), 41.0 (-), 32.8 (-), 21.4 (-), 14.3 (+); FTIR (NaCl, film, cm^{-1}): 3323, 2962, 2932, 2870, 2359, 2341, 1632, 1547, 1472, 843, 654; HRMS (TOF ES): found 229.1109, calculated for $C_{11}H_{14}ClN_2O$ (M+NH_4) 229.1108 (0.4 ppm).



N-Butyl-4-cyanobenzamide (**4l**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 4-cyanobenzoyl chloride (712 mg, 4.30 mmol) as colorless crystalline solid, mp 45-50 ^oC. Yield 834 mg (4.13 mmol, 96%); ^1H NMR (500.13 MHz, CD_3OD) δ ppm 7.94 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 3.39 (t, *J* = 7.1 Hz, 2H), 1.61 (quin, *J* = 7.3 Hz, 2H), 1.41 (sxt, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.5, 140.2, 133.7 (+, 2C), 129.3 (+, 2C), 119.2, 116.1, 41.1 (-), 32.7 (-), 21.3 (-), 14.3 (+); FTIR (NaCl, film, cm^{-1}): 3319, 2959, 2934, 2872, 2231, 1643, 1549, 1499, 1306, 858; HRMS (TOF ES): found 209.1274, calculated for $C_{12}H_{14}N_2OLi$ (M+Li) 209.1266 (3.8 ppm).

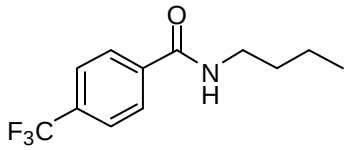


N-Butyl-4-nitrobenzamide (**4m**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 4-nitrobenzoyl chloride (522 μL, 798 mg, 4.30 mmol) as colorless crystalline solid, mp 135-140 ^oC.

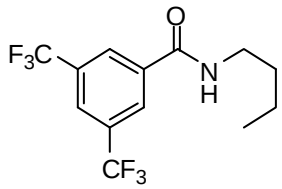
(8) (a) Wu, X.; Larhed, M. *Org. Lett.* **2005**, 7, 3327. (b) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, 3619.

(9) Shapiro, S. L.; Parrino, V. A.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 3728.

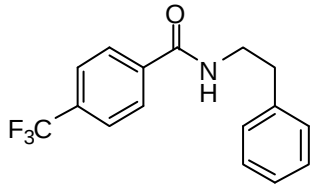
Yield 668 mg (3.01 mmol, 70%); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.30 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 6.14 (br. s, 1H), 3.50 (td, *J* = 7.3 Hz, 5.8 Hz, 2H), 1.68-1.59 (m, 2H), 1.49-1.40 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{1}H NMR (125.76 MHz, CD_3OD) δ ppm 178.3, 151.1, 141.8, 129.8 (+, 2C), 124.8 (+, 2C), 41.1 (-), 32.7 (-), 21.3(-), 14.3 (+); FTIR (NaCl, film, cm^{-1}): 3304, 2955, 2932, 1643, 1601, 1526, 1346, 868, 841, 719; HRMS (TOF ES): found 245.0901, calculated for $C_{11}H_{14}N_2O_3Na$ (M+Na) 245.0902 (0.4 ppm).



N-Butyl-4-(trifluoromethyl)benzamide (**4n**) To a solution of 4-(trifuluoromethyl)benzoic acid (2.89 g, 13.0 mmol) in dry CH_2Cl_2 (50 mL) was added 1,1-carbonyldiimidazole (2.53 g, 15.6 mmol, 1.20 equiv). The resulting suspension was stirred for 30 min at 0 °C, and then *n*-butylamine (3.03 mL, 2.23 g, 30.5 mmol, 2.35 equiv) was added dropwise. The mixture was stirred at room temperature overnight, then filtered. The filter cake was washed with CH_2Cl_2, the filtrate was washed consecutively with water and brine, dried with MgSO4, filtered and concentrated. Crude material was filtered through a short plug of Silica gel, eluting with EtOAc to afford the title material as a colorless oil. Yield 3.00 g (12.2 mmol, 94%). This material was identical to the one previously described in literature.[10]



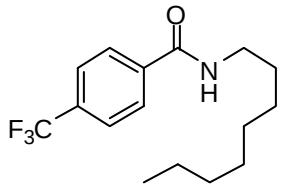
N-Butyl-3,5-bis(trifluoromethyl)benzamide (**4o**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 61-63 °C. Yield 1.28 g (4.09 mmol, 95%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.42 (s, 2H), 8.15 (s, 1H), 3.42 (t, *J* = 6.8 Hz, 2H), 1.63 (qnt, *J* = 6.9 Hz, 2H), 1.43 (sxt, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.7, 138.4, 133.2 (q, $^2J_{CF}$ =33.6 Hz, 2C), 129.1 (+, 2C), 126.0 (+), 124.7 (q, $^1J_{CF}$ =271.6 Hz, 2C), 41.2 (-), 32.6 (-), 21.4 (-), 14.3 (+); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3319, 3092, 2964, 2937, 1649, 1556, 1381, 1335, 1182, 1134, 908, 845, 702, 681; HRMS (TOF ES): found 336.0809, calculated for $C_{13}H_{13}F_6NONa$ (M+Na) 336.0799 (3.0 ppm).



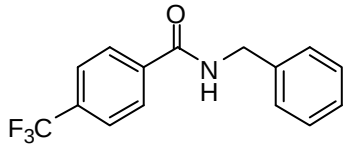
N-Phenethyl-4-(trifluoromethyl)benzamide (**4p**): was obtained according to a typical procedure from phenethylamine (1.36 mL, 1.31 g, 10.8 mmol, 2.5 equiv.) and and 4-(trifluoro-methyl)benzoyl chloride (640 μL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 140-142 °C. Yield 1.15 g (3.91 mmol, 91%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.92 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.31-7.25 (m, 4H), 7.22-7.18 (m, 1H), 3.62 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.9, 140.7, 139.7, 134.1 (q, $^2J_{CF}$ =32.7 Hz), 130.1 (+, 2C), 129.7 (+, 2C), 129.1 (+, 2C), 127.6 (+), 126.7 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^1J_{CF}$ =271.5 Hz), 42.9 (-), 36.6 (-); ^{19}F

(10) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327.

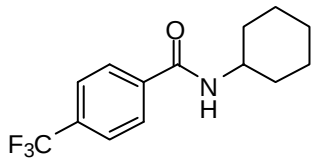
NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3319, 1641, 1549, 1337, 1165, 1155, 1111, 1072, 858, 748, 700, 685; HRMS (TOF ES): found 316.0923, calculated for $C_{16}H_{14}F_3NONa$ (M+Na) 316.0925 (0.6 ppm).



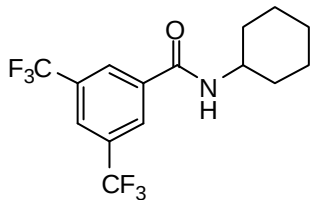
N-Octyl-4-(trifluoromethyl)benzamide (**4q**): was obtained according to a typical procedure from *n*-octylamine (1.79 mL, 1.40 g, 10.8 mmol, 2.5 equiv.) and 4-(trifluoromethyl)benzoyl chloride (640 μL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 49-53 °C. Yield 1.24 g (4.13 mmol, 96%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.97 (d, J = 7.9 Hz, 2H), 7.74 (d, J = 7.9 Hz, 2H), 3.38 (t, J = 7.2 Hz, 2H), 1.62 (quint, J = 7.3 Hz, 2H), 1.41-1.25 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.8, 139.7, 134.1 (q, $^2J_{CF}$ = 32.6 Hz), 129.2 (+, 2C), 126.6 (+, 2C), 125.4 (q, $^1J_{CF}$ = 271.3 Hz), 41.3 (-), 33.1 (-), 30.6 (-, 2C), 28.3 (-), 23.8 (-), 14.6 (-), 14.5 (+); FTIR (NaCl, film, cm^{-1}): 3339, 2920, 2849, 2957, 1541, 1468, 1335, 1169, 1130, 1107, 1074, 1018, 860, 773; HRMS (TOF ES): found 308.1801, calculated for $C_{16}H_{22}F_3NOLi$ (M+Li) 308.1814 (4.2 ppm).



N-Benzyl-4-(trifluoromethyl)benzamide (**4r**): was obtained according to a typical procedure from benzylamine (1.18 mL, 1.16 g, 10.8 mmol) and and 4-(trifluoromethyl)benzoyl chloride (640 μL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 149-151 °C. Yield 1.12 g (4.00 mmol, 93%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.02 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.38-7.31 (m, 4H), 7.28-7.24 (m, 1H), 4.59 (s, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.7, 139.9, 139.4, 134.1 (q, $^2J_{CF}$ = 31.8 Hz), 129.6 (+, 2C), 129.1 (+, 2C), 128.6 (+, 2C), 128.3 (+), 126.6 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.3 (q, $^1J_{CF}$ = 271.6 Hz), 44.7 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3329, 3053, 2986, 1643, 1547, 1421, 1265, 1167, 1157, 1124, 862, 739; HRMS (TOF ES): found 302.0783, calculated for $C_{15}H_{12}F_3NONa$ (M+Na) 302.0769 (4.6 ppm).

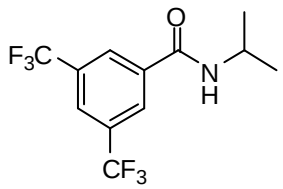


N-Cyclohexyl-4-(trifluoromethyl)benzamide (**4s**): was obtained according to a typical procedure from cyclohexyl-amine (1.23 mL, 1.07 g, 10.8 mmol) and and 4-(trifluoro-methyl)benzoyl chloride (640 μL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 167-170 °C. Yield 1.10 g (4.04 mmol, 94%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.96 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 3.87 (tt, J = 11.0 Hz, 4.1 Hz, 1H), 1.99-1.94 (m, 2H), 1.85-1.80 (m, 2H), 1.72-1.67 (m, 1H), 1.47-1.32 (m, 4H), 1.28-1.18 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.1, 139.9, 133.9 (q, $^2J_{CF}$ = 32.7 Hz), 129.1 (+), 126.4 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.3 (q, $^1J_{CF}$ = 271.5 Hz), 50.8 (+), 33.7 (-, 2C), 26.6 (-), 26.4 (-, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3312, 2941, 2908, 1634, 1545, 1325, 1161, 1124, 1065, 856; HRMS (TOF ES): found 272.1269, calculated for $C_{14}H_{17}F_3NO$ (M+H) 272.1262 (2.6 ppm).

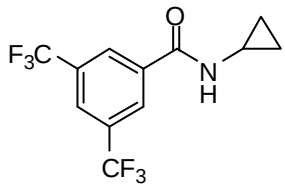


N-Cyclohexyl-3,5-bis(trifluoromethyl)benzamide (**4t**): was obtained according to a typical procedure from

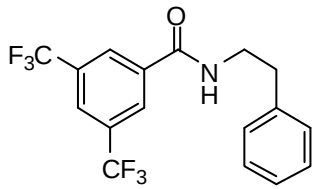
cyclohexylamine (1.23 mL, 1.07 g, 10.8 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 150-152 ^{o}C.. Yield 1.37 g (4.04 mmol, 94%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.42 (s, 2H), 8.14 (s, 1H), 3.92-3.87 (m, 1H), 2.00-1.96 (m, 2H), 1.86-1.81 (m, 2H), 1.47-1.34 (m, 4H), 1.29-1.19 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.0, 138.6, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.2 (q, $^{3}J_{CF}$ =3.3 Hz, +, 2C), 125.9 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.8 (q, $^{1}J_{CF}$ = 272.5 Hz, 2C), 51.2 (+), 33.7 (-, 2C), 26.8 (-), 26.6 (-, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3416, 2937, 2858, 1643, 1553, 1279, 1182, 1134, 908, 702, 681; HRMS (TOF ES): found 362.0958, calculated for $C_{15}H_{15}F_6NONa$ (M+Na) 362.0956 (0.6 ppm).



N-Isopropyl-3,5-bis(trifluoromethyl)benzamide (**4u**): was obtained according to a typical procedure from isopropylamine (924 μL, 638 mg, 10.8 mmol) and 3,5-bis(trifluoromethyl)-benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 108-111 ^{o}C.. Yield 1.22 g (4.09 mmol, 95%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.43 (s, 2H), 8.14 (s, 1H), 4.24 (spt, *J* = 6.6 Hz, 1H), 1.28 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 165.9, 138.6, 133.2 (q, $^{2}J_{CF}$ = 33.5 Hz, 2C), 129.2 (q, $^{3}J_{CF}$ =3.6 Hz, +, 2C), 125.9 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.8 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 43.8 (+), 22.5 (+, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3339, 2986, 1641, 1556, 1452, 1369, 1344, 1279, 1134, 910, 741, 700, 681; HRMS (TOF ES): found 322.0640, calculated for $C_{12}H_{11}F_6NONa$ (M+Na) 322.0643 (0.9 ppm).

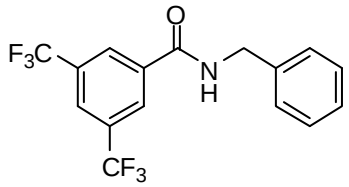


N-Cyclopropyl-3,5-bis(trifluoromethyl)benzamide (**4v**): was obtained according to a typical procedure from cyclopropylamine (748 μL, 617 mg, 10.8 mmol) and 3,5-bis(trifluoromethyl)-benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 90-94 ^{o}C. Yield 1.12 g (3.78 mmol, 88%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.41 (s, 2H), 8.14 (s, 1H), 2.91 (tt, *J* = 7.4 Hz, 3.8 Hz, 1H), 0.87 - 0.80 (m, 2H), 0.72-0.66 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.2, 138.1, 133.2 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.1 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 126.1 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 24.4 (+), 6.6 (-, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.6 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3315, 3086, 3022, 2448, 1641, 1545, 1448, 1375, 1354, 1277, 1136, 908, 698, 681; HRMS (TOF ES): found 297.0589, calculated for $C_{12}H_9F_6NO$ (M^{+}) 297.0588 (0.3 ppm).

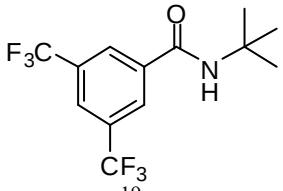


N-Phenethyl-3,5-bis(trifluoromethyl)benzamide (**4w**), (typical procedure): To a stirred solution of phenethylamine (1.36 mL, 1.31 g, 10.8 mmol, 2.5 equiv.) in dry THF (30 mL) was added 3,5-bis(trifluoromethyl)benzoyl chloride (780 μL, 1.19 g, 4.30 mmol). The mixture was stirred for 1 hr at room temperature, than the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). Organic layer was separated and washed consecutively with 10% aqueous HCL (3 x 20 mL) and 4N

aqueous NaOH (5 mL), dried with $MgSO_4$, filtered and concentrated. The obtained crystalline material (colorless crystalline solid, mp 44-47 ^oC) was pure enough to be used for the following transformation without additional purification. Yield 1.44 g (4.00 mmol, 93%). ^1H NMR (500.13 MHz, CD_3OD) δ ppm 8.35 (s, 2H), 8.15 (s, 1H), 7.31-7.25 (m, 4H), 7.22-7.19 (m, 1H), 3.64 (t, J = 7.4 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H),; ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.8, 140.6, 138.4, 133.2 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 130.1 (+, 2C), 129.7 (+, 2C), 129.1 (q, $^3J_{CF}$ = 2.7 Hz, +, 2C), 127.6 (+), 126.1 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^1J_{CF}$ = 272.5 Hz, 2C), 43.0 (-), 36.5 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3313, 3089, 1647, 1555, 1383, 1279, 1184, 1134, 908, 700, 681; HRMS (TOF ES): found 384.0793, calculated for $C_{17}H_{13}F_6NONa$ (M+Na) 313.0901 (1.6 ppm).

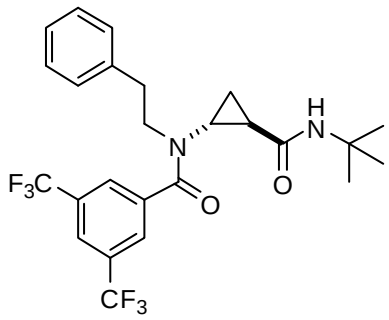


N-Benzyl-3,5-bis(trifluoromethyl)benzamide (**4x**): was obtained according to a typical procedure from benzylamine (1.18 mL, 1.16 g, 10.8 mmol) and 3,5-bis(trifluoromethyl)-benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 92-95 ^oC. Yield 1.45 g (4.17 mmol, 97%); ^1H NMR (500.13 MHz, CD_3OD) δ ppm 8.46 (s, 2H), 8.17 (s, 1H), 7.39-7.32 (m, 4H), 7.28-7.24 (m, 1H), 4.61 (s, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.7, 139.8, 138.2, 133.3 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 129.8 (+, 2C), 129.2 (q, $^3J_{CF}$ = 2.7 Hz, +, 2C), 128.9 (+, 2C), 128.5 (+), 126.2 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^1J_{CF}$ = 271.6 Hz, 2C), 45.0 (-); FTIR (NaCl, film, cm^{-1}): 3292, 3090, 3069, 1647, 1553, 1454, 1381, 1279, 1184, 1136, 908, 698; HRMS (TOF ES): found 370.0645, calculated for $C_{16}H_{11}F_6NONa$ (M+Na) 370.0643 (0.5 ppm).

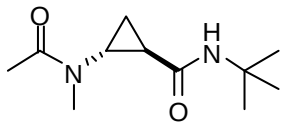


N-tert-Butyl-3,5-bis(trifluoromethyl)benzamide: (**4y**): ^1H NMR (500.13 MHz, CD_3OD) δ ppm 8.34 (s, 2H), 8.11 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 166.9, 139.8, 133.0 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 129.2 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.6 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.8 (q, $^1J_{CF}$ = 271.6 Hz, 2C), 53.4, 28.9 (+, 3C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.6 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3317, 3072, 1645, 1547, 1448, 1364, 1302, 1275, 1144, 1130, 906, 845, 702; HRMS (TOF ES): found 313.0896, calculated for $C_{13}H_{23}F_6NO$ (M^+) 313.0901 (1.6 ppm).

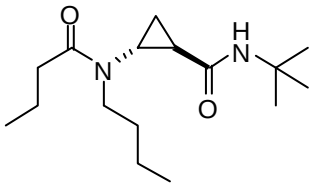
Synthesis of cyclopropyl diamides



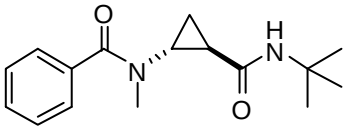
N-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-phenethyl-3,5-bis(trifluoromethyl)benzamide (**6aw**): (Typical procedure) An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **5a** (110 mg, 0.5 mmol, 1.0 equiv), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), KOH (98 mg, 1.75 mmol, 3.5 equiv), *N*-Phenethyl-3,5-bis(trifluoromethyl)benzamide (**4w**) (290 mg, 1.0 mmol, 2.0 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then the reaction mixture was filtered into a 100 mL round bottom flask, both the reaction vessel and filter were rinsed consecutively with DCM (15 mL) and EtOAc (15 mL), which were combined with filtrate. Silica gel (2.0 g) was added to a filtrate, and then the solvent was removed by rotary evaporation. The residue absorbed onto silica gel was loaded on the top of the column packed with silica gel, which was eluted with hexane/EtOAc 1:1 to obtain two fractions. The less polar fraction (R_f 0.54) was identified as non-reacted benzamide **4w**, and the more polar one (R_f 0.23) as the title product, white amorphous solid. Yield 236 mg (94%, 0.47 mmol). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.02 (s, 1H), 7.64 (s, 2H), 7.38-7.32 (m, 4H), 7.28-7.25 (m, 1H), 4.11 (ddd, *J* = 13.7 Hz, 7.3 Hz, 6.0 Hz, 1H), 3.70 (ddd, *J* = 13.7 Hz, 6.9 Hz, 6.0 Hz, 1H), 3.10-3.07 (m, 2H), 2.84 (br. s, 1H), 1.61-1.55 (m, 1H), 1.12 (s, 9H), 1.06-1.01 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.9, 171.0, 141.2, 140.1, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 130.3 (+, 2C), 129.9 (+, 2C), 128.6 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 128.0 (+), 124.5 (q, $^{1}J_{CF}$ = 272.5 Hz), 124.6 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 52.0, 48.4 (-), 39.3 (+), 34.6 (-), 28.9 (+, 3C), 28.4 (+), 17.1 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3342, 3065, 3030, 2970, 2934, 1651, 1545, 1456, 1366, 1281, 1178, 1140, 905, 741, 702, 681; HRMS (TOF ES): found 501.1964, calculated for $C_{25}H_{27}F_6N_2O_2$ (M+H) 501.1977 (2.6 ppm).



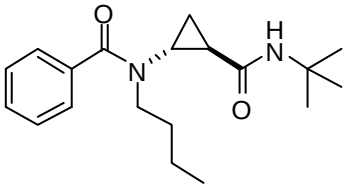
(1*R**,2*R**)-*N*-*tert*-butyl-2-(*N*-methylacetamido)cyclopropanecarboxamide (**6aa**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-methylacetamide (**4a**) (73.1 mg, 1.00 mmol). The excess of *N*-methylacetamide was distilled out in vacuum. Flash column chromatography on Silica gel afforded the title compound as a viscous oil, R_f 0.31 (hexane-EtOAc 1:3). Yield 106 mg (0.44 mmol, 88%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 5.98 (br. s, 1H), 3.10 (br. s, 1H), 2.87 (s, 3H), 2.15 (s, 3H), 1.64 (br. s, 1H), 1.45 (br, sm 1H), 1.35 (s, 9H), 1.17-1.12 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 173.2, 169.2, 51.5, 38.9 (+), 33.5 (+), 28.8 (+, 3C), 26.2 (+), 22.3 (+), 16.0 (-); FTIR (NaCl, film, cm^{-1}): 3299, 2964, 2930, 1645, 1556, 1454, 1253, 1111, 960; HRMS (TOF ES): found 213.1609, calculated for $C_{11}H_{21}N_2O_2$ (M+H) 213.1603 (2.8 ppm).



(1*R**,2*R**)-*N*-*tert*-Butyl-2-(*N*-butylbutyramido)cyclopropanecarboxamide (**6ab**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butylbutyramide (**4b**) (143 mg, 1.00 mmol). The excess of *N*-butylbutyramide was distilled out in vacuum (Kugelrhor oven temperature 110 ^{o}C at 0.05 torr for 4 hrs) to afford to produce the title compound as a viscous oil, which did not require further purification. Yield 71 mg (0.25 mmol, 51%). ^{1}H NMR (500.13 MHz, DMSO-d_6 at 370 K) δ ppm 7.85 (br. s, 1H), 3.36 (ddd, *J* = 13.9 Hz, 7.3 Hz, 6.6 Hz, 1H), 3.14 (ddd, *J* = 13.6 Hz, 7.9 Hz, 6.0 Hz, 1H), 2.74 (ddd, *J* = 7.6 Hz, 4.7 Hz, 2.8 Hz, 1H), 2.43 (ddd, *J* = 15.5 Hz, 8.5 Hz, 6.9 Hz, 1H), 2.30 (dt, J = 15.5 Hz, 7.8 Hz, 1H), 1.90 (ddd, *J* = 8.8 Hz, 6.0 Hz, 2.8 Hz, 1H), 1.54-1.47 (m, 2H), 1.41-1.34 (m, 2H), 1.26 (s, 9H), 1.24-1.13 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, DMSO-d_6 at 370 K) δ ppm 173.9, 169.1, 54.8 (-), 50.1, 44.0 (-), 36.1 (+), 35.4 (-), 29.6 (-), 28.5 (+), 25.5 (+), 19.5 (-), 17.9 (-), 14.3 (-), 13.7 (+), 13.6 (+); FTIR (NaCl, film, cm^{-1}): 3323, 2962, 2932, 1639, 1549, 1456, 1402, 1259, 1094, 912; HRMS (TOF ES): found 370.0645, calculated for $C_{16}H_{11}F_6NONa$ (M+Na) 370.0643 (0.5 ppm).

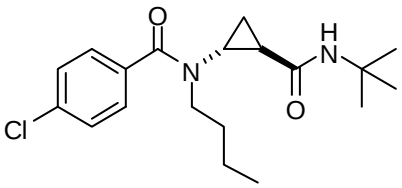


N-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-methylbenzamide (**6ag**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-methylbenzamide (**4g**) (135 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.28) was identified as non-reacted *N*-methylbenzamide, and the more polar one (R_f 0.14) as the title compound, colorless crystalline solid, mp 108-111 ^{o}C. Yield 103 mg (0.375 mmol, 75%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.52-7.40 (m, 5H), 4.57 (br. s, 1H), 3.11 (br. s, 3H), 1.63 (br. s, 1H), 1.34-1.25 (br. m, 2H), 1.20 (br. s, 9H), 0.92 (br. m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 172.3, 168.6, 137.4, 129.7 (+), 128.4 (+, 2C), 127.2 (+, 2C), 51.1, 39.4 (br, +), 35.0 (br, +), 28.7 (+, 3C), 27.6 (+), 15.0 (br, -); FTIR (NaCl, film, cm^{-1}): 3325, 2966, 2928, 1632, 1547, 1447, 1389, 1074, 704; HRMS (TOF ES): found 275.1764, calculated for $C_{16}H_{23}N_2O_2$ (M+H) 275.1760 (1.5 ppm).

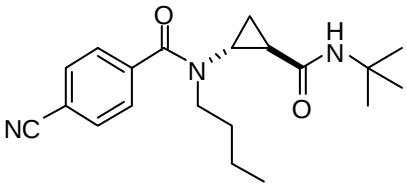


N-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)benzamide (**6ah**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butylbenzamide (**4h**) (177 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.61) was identified as non-reacted *N*-butylbenzamide, and the more polar one (R_f 0.39) as the title compound, colorless crystalline solid, mp 95-97 ^{o}C. Yield 115 mg (0.365 mmol, 73%). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ ppm 7.44-7.36 (m, 5H), 7.27 (br. s, 1H), 3.50-3.36 (br. m, 2H), 2.89 (br. s, 1H), 1.69 (br. s, 1H), 1.61-1.54 (br. m, 2H), 1.40-1.29 (br. m, 2H), 1.15 (br. s, 9H), 0.95-0.79 (br. m, 5H); ^{13}C NMR (125.76 MHz, DMSO-d_6) δ ppm 171.3, 168.6, 137.5, 129.1 (+), 128.0 (+, 2C), 126.7 (+, 2C), 49.9, 44.9 (br., -), 37.4 (br., +), 29.3 (-), 28.4 (+, 3C), 25.7 (br., +), 19.5 (-), 15.8 (br., -),

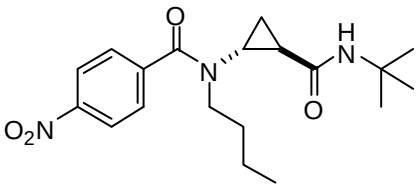
13.6 (+); FTIR (NaCl, film, cm^{-1}): 3325, 292, 2930, 2872, 1626, 1547, 1448, 1400, 1053, 791, 729, 702; HRMS (TOF ES): found 317.2245, calculated for $C_{19}H_{29}N_2O_2$ (M+H) 317.2229 (5.0 ppm).



N-Butyl-N-((1*R*,2*R*)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-chlorobenzamide (**6ak**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butyl-4-chlorobenzamide (**4k**) (212 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.44) was identified as non-reacted benzamide **tp0116B**, and the more polar one (R_f 0.20) as the title compound, a colorless crystalline solid, mp 162-164 ^oC. Yield 142 mg (0.41 mmol, 81%). ^1H NMR (500.13 MHz, CD_3OD) δ ppm 7.44 (s, 4H), 3.85 (br. s, 1H), 3.27 (ddd, *J* = 13.7 Hz, 7.7 Hz, 5.7 Hz, 1H), 3.11 (br. s, 1H), 1.76-1.66 (m, 2H), 1.53 (br. s, 1H), 1.48-1.42 (m, 2H), 1.20 (s, 9H), 1.14 (br. s, 1H), 1.07 (br. s, 1H), 1.01 (br. s, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.9, 171.5, 137.3, 136.9, 130.1 (+, 2C), 129.9 (+, 2C), 52.0, 47.4 (-), 39.5 (+), 31.0 (-), 28.9 (+, 3C), 21.3 (-), 16.6 (-), 14.3 (+); FTIR (NaCl, film, cm^{-1}): 3333, 3065, 3053, 2966, 2932, 1668, 1630, 1553, 1435, 1418, 1315, 1256, 1225, 1209, 1090, 843, 756, 636; HRMS (TOF ES): found 373.1644, calculated for $C_{19}H_{27}ClN_2O_2Na$ (M+Na) 373.1659 (4.0 ppm).

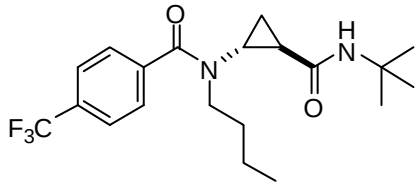


N-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-cyanobenzamide (**6al**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butyl-4-cyanobenzamide (**4l**) (202 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:2) afforded two fractions. The less polar one (R_f 0.73) was identified as non-reacted benzamide **4l**, and the more polar one (R_f 0.47) as the title compound, a colorless crystalline solid, mp 136-140 ^oC. yield 136 mg (0.40 mmol, 80%). ^1H NMR (500.13 MHz, CD_3OD) δ ppm 7.81 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.23 (br. s, 1H), 3.86-3.79 (m, 1H), 3.34-3.28 (m, 1H), 3.09 (br. s, 1H), 1.78-1.66 (m, 2H), 1.53 (br. s, 1H), 1.49-1.42 (m, 2H), 1.19 (s, 9H), 1.14-1.04 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.0, 171.4, 143.2, 133.8 (+, 2C), 129.0 (+, 2C), 119.4, 114.7, 52.1, 47.4 (-), 39.3 (+), 30.9 (-), 29.0 (+, 3C), 28.7 (+), 21.3 (-), 16.7 (-), 14.3 (+); FTIR (NaCl, film, cm^{-1}): 3339, 2962, 2932, 2230, 1634, 1547, 1418, 1398, 1310, 1258, 1275, 1225, 1207, 1107, 849, 764, 737; HRMS (TOF ES): found 342.2169, calculated for $C_{20}H_{28}N_3O_2$ (M+H) 342.2182 (3.8 ppm).

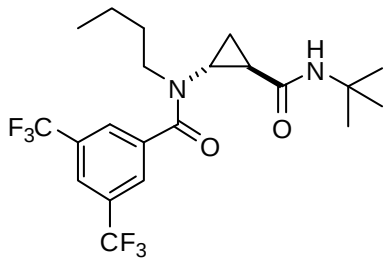


N-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-nitrobenzamide (**6am**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butyl-4-nitrobenzamide (**4m**) (222 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent

hexane/EtOAc 1:2) afforded two fractions. The less polar one (R_f 0.77) was identified as non-reacted benzamide **4m**, and the more polar one (R_f 0.36) as the title compound, yellowish crystalline solid, mp 143-145 °C. Yield 145 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.32 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 4.61 (br. s, 1H), 3.86 (ddd, *J* = 14.2 Hz, 7.6 Hz, 6.6 Hz, 1H), 3.10 (br. s, 1H), 1.78-1.70 (m, 2H), 1.54 (br. s, 1H), 1.50-1.44 (m, 2H), 1.35-1.25 (m, 3H), 1.10 (s, 9H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 172.8, 171.3, 149.9, 144.9, 129.4 (+, 2C), 125.1 (+, 2C), 51.9, 47.4 (-), 39.3 (+), 30.9 (-), 29.1 (+), 28.9 (+, 3C), 21.3 (-), 16.6 (-), 14.3 (+); FTIR (NaCl, film, cm^{-1}): 3335, 2961, 2928, 1634, 1524, 1456, 1348, 1312, 1259, 1105, 864, 735; HRMS (TOF ES): found 362.2068, calculated for $C_{19}H_{28}N_3O_4$ (M+H) 362.2080 (3.3 ppm).

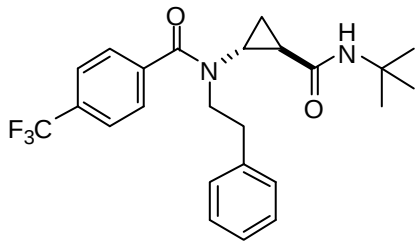


N-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-(trifluoromethyl)benzamide (**6an**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butyl(*p*-triflouromethyl)benzamide (**4n**) (245 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.60) was identified as non-reacted benzamide **4n**, and the more polar one (R_f 0.22) as the title compound, colorless crystalline solid, mp 158-161 °C. Yield 163.5 mg (0.425 mmol, 85%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.74 (d, *J* = 7.9 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 2H), 4.04 (br. s, 1H), 3.06 (br. s, 1H), 1.96-1.84 (m, 4H), 1.75-1.70 (m, 2H), 1.60 (br. s, 1H), 1.44-1.29 (m, 3H), 1.19 (s, 9H), 1.07-1.02 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.5, 171.9, 143.0, 132.6 (q, $^2J_{CF}$ = 32.1 Hz), 129.1 (+, 2C), 126.7 (q, $^3J_{CF}$ = 3.7 Hz, +, 2C), 125.5 (q, $^1J_{CF}$ = 271.3 Hz), 52.1, 52.0 (-), 32.5 (+), 32.2 (-), 28.9 (+, 3C), 27.44 (+), 27.38 (-), 27.0 (-), 17.5 (br, +); ^{19}F NMR (376.50 MHz, $CDCl_3$) δ ppm -62.6 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3335, 2928, 2854, 1628, 1549, 1323, 1167, 1130, 1067, 854, 737, 652, 592; HRMS (TOF ES): found 407.1941, calculated for $C_{20}H_{27}F_3N_2O_2Na$ (M+Na) 407.1922 (4.7 ppm).

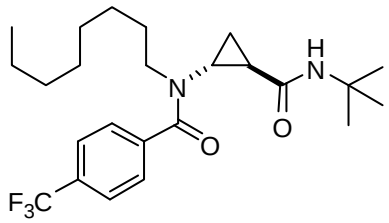


N-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzamide (**6ao**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butyl-3,5-bis(triflouromethyl)benzamide (**4o**) (313 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:2) afforded two fractions. The less polar one (R_f 0.75) was identified as non-reacted benzamide **4o**, and the more polar one (R_f 0.38) as the title compound, a colorless amorphous solid. Yield 180 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.08 (s, 1H), 8.05 (s, 2H), 3.76-3.69 (m, 1H), 3.46-3.39 (m, 1H), 3.18 (br. s, 1H), 1.80-1.68 (m, 2H), 1.62 (br. s, 1H), 1.50-1.42 (m, 2H), 1.14 (s, 9H), 1.11-1.05 (m, 2H), 1.05-0.99 (m, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.6, 171.2, 141.4, 133.2 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 128.8 (+, 2C), 124.6 (+), 124.6 (q, $^1J_{CF}$ =272.5 Hz), 52.0, 47.6 (-), 39.2 (+), 30.9 (-), 28.9 (+, 3C), 28.4 (+), 21.4 (-), 17.3 (-), 14.3 (+); ^{19}F NMR

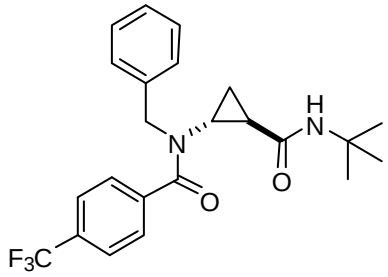
(376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3344, 2966, 2933, 2876, 1643, 1545, 1456, 1427, 1398, 1366, 1279, 1171, 1140, 903, 681; HRMS (TOF ES): found 475.1818, calculated for $C_{21}H_{26}F_6N_2O_2Na$ (M+Na) 475.1796 (4.6 ppm).



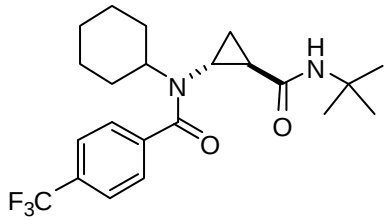
N-((1*R**,2R*)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-phenethyl-4-(trifluoromethyl)benzamide (**6ap**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-phenethyl-(*p*-triflouromethyl)-benzamide (**4p**) (293 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.68) was identified as non-reacted benzamide **4p**, and the more polar one (R_f 0.36) as the title compound, a colorless crystalline solid, mp 146-147 °C. Yield 178 mg (0.41 mmol, 82%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.70 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.37-7.33 (m, 3H) 7.28-7.24 (m, 2H), 4.10 (ddd, *J* = 13.3 Hz, 7.3 Hz, 6.6 Hz, 1H), 3.65 (ddd, *J* = 13.3 Hz, 6.6 Hz, 6.3 Hz, 1H), 3.10-3.03 (m, 2H), 2.91 (br. s, 1H), 1.56 (br. s, 1H), 1.15 (s, 9H), 1.08-0.96 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.5, 171.3, 142.3, 140.2, 132.6 (q, $^2J_{CF}$ = 31.8 Hz), 130.2 (+, 2C), 129.8 (+, 2C), 128.8 (+, 2C), 127.9 (+), 126.7 (+, 2C), 125.4 (q, $^1J_{CF}$ = 271.6 Hz), 51.9, 49.2 (-), 39.5 (+), 34.8 (-), 28.9 (+, 3C), 28.5 (+), 16.8 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.2 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3337, 2970, 1639, 1547, 1454, 1420, 1325, 1167, 1130, 1067, 851, 741, 700; HRMS (TOF ES): found 433.2113, calculated for $C_{24}H_{28}F_3N_2O_2$ (M+H) 433.2103 (2.3 ppm).



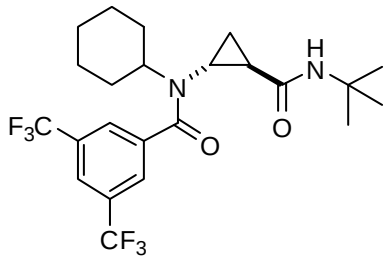
N-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-octyl-4-(trifluoromethyl)benzamide (**6aq**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-octyl-4-(triflouromethyl)benzamide (**4q**) (301 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The less polar one (R_f 0.57) was identified as non-reacted benzamide **4q**, and the more polar one (R_f 0.15) as the title compound, a colorless amorphous solid. Yield 187 mg (0.43 mmol, 85%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.75 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.31 (br. s, 1H), 3.83-3.77 (m, 1H), 3.38-3.32 (m, 1H), 3.14 (br. s, 1H), 1.79-1.69 (m, 2H), 1.60 (br. s, 1H), 1.45-1.29 (m, 10H), 1.16 (s, 9H), 1.12-1.04 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.3, 171.5, 142.5, 132.6 (q, $^2J_{CF}$ = 32.7 Hz), 128.9 (+, 2C), 126.8 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^1J_{CF}$ = 271.6 Hz), 52.1, 47.7 (-), 39.2 (+), 33.2 (-), 30.5 (-, 2C), 28.9 (+, 3C), 28.8 (-), 28.5 (+), 28.2 (-), 23.9 (-), 16.9 (-), 14.6 (+); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.2 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3337, 2961, 2930, 2856, 1632, 1547, 1456, 1421, 1402, 1325, 1258, 1227, 1167, 1130, 851, 613; HRMS (TOF ES): found 463.2533, calculated for $C_{24}H_{35}F_3N_2O_2Na$ (M+Na) 463.2548 (3.2 ppm).



N-Benzyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-(trifluoromethyl)benzamide (**6ar**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-benzyl-4-(triflouromethyl)benzamide (**4r**) (279 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The less polar one (R_f 0.40) was identified as non-reacted benzamide **4r**, and the more polar one (R_f 0.13) as the title compound, a colorless crystalline solid, mp 163-167 ^{o}C. Yield 168 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.77 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.42-7.36 (m, 4H), 7.34-7.30 (m, 1H), 4.88 (d, *J* = 14.2 Hz, 1H), 4.73 (d, *J* = 14.2 Hz, 1H), 2.96 (br. s, 1H), 1.67 (br. s, 1H), 1.15 (s, 9H), 1.02 (br. s, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.4, 171.4, 142.1, 138.6, 132.8 (q, $^{2}J_{CF}$ = 32.7 Hz), 130.1 (+, 2C), 129.3 (+, 2C), 128.9 (+, 2C), 128.9 (+), 126.8 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^{1}J_{CF}$ = 271.6 Hz), 52.0, 51.3 (-), 39.4 (+), 28.9 (+, 3C), 28.1 (+), 17.1 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.3 (s, 3F); FTIR (NaCl, film, cm^{-1}): 2979, 2934, 1636, 1454, 1418, 1325, 1169, 1130, 1067, 851, 702; HRMS (TOF ES): found 419.1926, calculated for $C_{23}H_{26}F_3N_2O_2$ (M+H) 419.1946 (4.8 ppm).

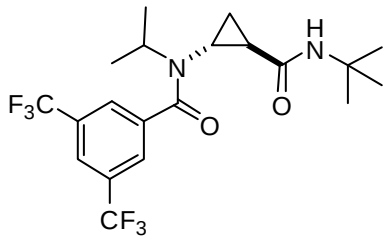


N-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-cyclohexyl-4-(trifluoromethyl)benzamide (**6as**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and N-cyclohexyl-4-(triflouromethyl)benzamide (**4s**) (271 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The less polar one (R_f 0.58) was identified as non-reacted benzamide **4s**, and the more polar one (R_f 0.21) as the title compound, a colorless crystalline solid, mp 160-163 ^{o}C. Yield 92 mg (0.225 mmol, 45%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 4.06 (br. s, 1H), 3.07 (br. s, 1H), 1.99-1.83 (m, 6H), 1.78-1.69 (m, 2H), 1.60 (br. s, 1H), 1.46-1.36 (m, 2H), 1.18 (s, 9H), 1.10-1.00 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.4, 171.9, 142.9, 132.6 (q, $^{2}J_{CF}$ = 31.8 Hz), 129.1 (+, 2C), 126.7 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^{1}J_{CF}$ = 271.6 Hz), 60.6 (+), 52.0, 37.2 (+), 32.5 (-), 32.1 (-), 28.9 (+, 3C), 27.7 (+), 27.44 (-), 27.38 (-), 27.0 (-), 17.5 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.3 (s, 3F); FTIR (NaCl, film, cm^{-1}): 3337, 2934, 2858, 1628, 1547, 1454, 1418, 1323, 1167, 1130, 1067, 854, 735; HRMS (TOF ES): found 417.2343, calculated for $C_{22}H_{29}F_3N_2O_2Li$ (M+Li) 417.2341 (0.5 ppm).

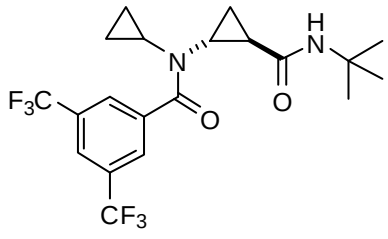


N-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-cyclohexyl-3,5-bis(trifluoromethyl)benzamide (**6at**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-cyclohexyl-3.5-bis(triflouromethyl)-benzamide (**4t**) (339 mg, 1.00 mmol). Flash column

chromatography on Silica gel (eluent hexane/EtOAc 5:1) afforded two fractions. The less polar one (R_f 0.58) was identified as non-reacted benzamide **4t**, and the more polar one (R_f 0.19) as the title compound, a colorless crystalline solid, mp 140-141 ^{o}C. Yield 198 mg (0.42 mmol, 83%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.07 (s, 3H), 4.02 (br. s, 1H), 3.09 (br. s, 1H), 2.03-1.98 (m, 2H), 1.94-1.84 (m, 3H), 1.76-1.70 (m, 2H), 1.66 (br. s, 1H), 1.18 (s, 9H), 1.06-0.99 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ ppm 171.7, 171.5, 141.8, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.0 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 124.5 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 272.5 Hz), 60.9 (+), 52.1, 37.2 (+), 32.3 (-), 32.1 (-), 29.0 (+), 28.0 (+), 27.39 (-), 27.36 (-), 27.0 (-), 17.7 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3337, 2935, 2856, 1630, 1547, 1356, 1281, 1184, 1138, 905, 683; HRMS (TOF ES): found 479.2122, calculated for $C_{23}H_{29}F_6N_2O_2$ (M+H) 479.2133 (2.3 ppm).

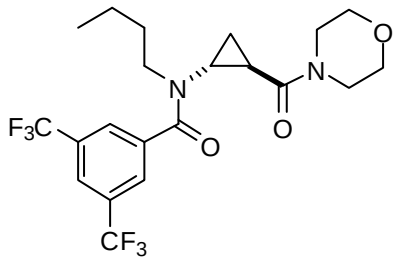


N-((1*R**,2*R**)-2-(tert-butylcarbamoyl)cyclopropyl)-*N*-isopropyl-3,5-bis(trifluoromethyl)benzamide (**6au**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-isopropyl-3,5-bis(triflouromethyl)benzamide (**4u**) (299 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/ EtOAc 3:1) afforded two fractions. The less polar one (R_f 0.58) was identified as non-reacted benzamide **4u**, and the more polar one (R_f 0.19) as the title compound, a colorless amorphous solid. Yield 134 mg (0.31 mmol, 61%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.09 (s, 2H), 8.07 (s, 1H), 4.38 (br. s, 1H), 3.10 (br. s, 1H), 1.70-1.65 (m, 1H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 9H), 1.06-1.02 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.8, 171.5, 141.8, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.0 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 124.6 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 52.4 (+), 52.1, 37.1 (+), 29.0 (+, 3C), 27.7 (+), 21.3 (+), 21.0 (+), 17.4 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3342, 2976, 2937, 2494, 1634, 1427, 1346, 1281, 1184, 1140, 905, 681; HRMS (TOF ES): found 461.1618, calculated for $C_{20}H_{24}F_6N_2O_2Na$ (M+Na) 461.1640 (4.8 ppm).

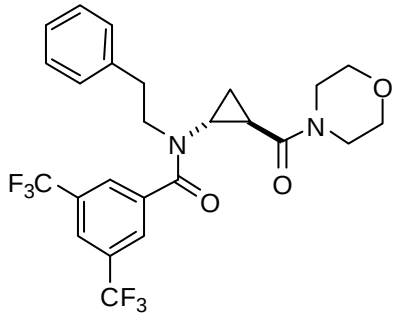


N-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-cyclopropyl-3,5-bis(trifluoromethyl)benzamide (**6av**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-cyclopropyl-3.5-bis(triflouromethyl)-benzamide (**4v**) (297 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/ EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.51) was identified as non-reacted benzamide **4v**, and the more polar one (R_f 0.21) as the title compound, a colorless crystalline solid, mp 148-151 ^{o}C. Yield 129 mg (0.30 mmol, 59%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.14 (s, 2H), 8.09 (s, 1H), 7.42 (br. s, 1H), 3.10 (br. s, 1H), 2.79 (br. s, 1H), 1.78 (br. s, 1H), 1.45-1.04 (m, 11H), 0.96-0.62 (m, 4H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.1, 171.8, 140.8, 132.9 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.3 (+, 2C), 124.8 (+), 124.5 (q, $^{1}J_{CF}$ = 272.5 Hz, 2C), 52.0, 51.9 (+), 39.4 (br. s, +), 31.4 (br. s, +),

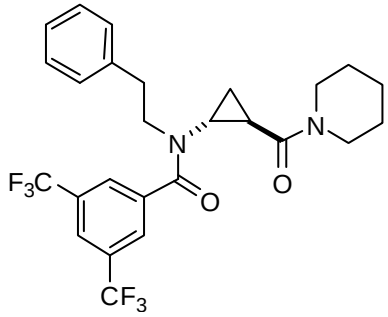
28.9 (+, 3C), 16.7 (br. s, -), 9.3 (br. s, -, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3340, 2966, 2933, 1651, 1545, 1458, 1424, 1364, 1281, 1173, 1140, 905, 681; HRMS (TOF ES): found 437.1661, calculated for $C_{20}H_{23}F_6N_2O_2$ (M+H) 437.1664 (0.7 ppm).



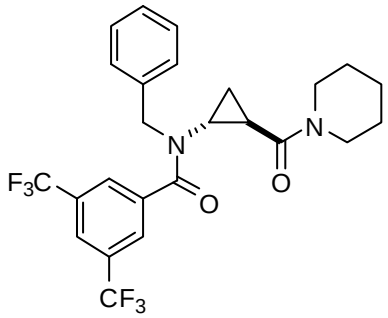
N-Butyl-*N*-((1*R**,2*R**)-2-(morpholine-4-carbonyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzamide (**6bo**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5b** (117 mg, 0.50 mmol) and *N*-butyl-3,5-bis(triflouromethyl)-benzamide (**4o**) (313 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R_f 0.72) was identified as non-reacted benzamide **4o**, and the more polar one (R_f 0.13) as the title compound, a white solid mp 69-71 ^{o}C. Yield 171.7 mg (0.37 mmol, 74%); ^{1}H NMR (400.13 MHz, CD_3OD) δ ppm 8.14 (s, 1H) 8.10 (s, 2H), 3.84 (br. s, 1H), 3.56-3.33 (m, 8H), 3.15 (br. s, 1H), 3.04 (br. s, 1H), 2.08 (br. s, 1H), 1.83-1.68 (m, 2H), 1.53-1.14 (5H), 1.05-0.98 (m, 3H), 0.80 (br. s, 1H); ^{13}C NMR (100.67 MHz, CD_3OD) δ ppm 170.7, 170.6, 141.0, 133.0 (q, $^2J_{CF}$ = 32.3 Hz, 2C), 129.2 (+, 2C), 124.7 (spt, $^3J_{CF}$ = 3.7 Hz, +), 124.6 (q, $^1J_{CF}$ = 272.2 Hz, 2C), 67.7 (-), 67.6 (-), 48.1 (-), 47.0 (-), 43.7 (-), 40.5 (+), 30.9 (-), 24.4 (+), 21.4 (-), 18.8 (-), 14.3 (+); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm^{-1}): 2962, 2932, 2862, 1645, 1464, 1448, 1425, 1362, 1281, 1184, 1171, 1136, 1119, 905, 849, 757, 704, 681; HRMS (TOF ES): found 466.1698, calculated for $C_{21}H_{24}F_6N_2O_3$ (M^+) 466.1691 (1.5 ppm).



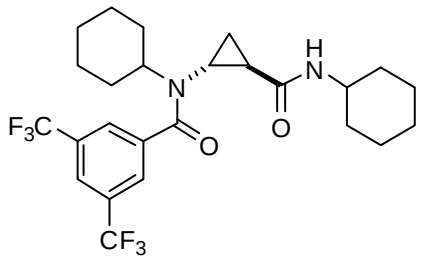
N-((1*R**,2*R**)-2-(Morpholine-4-carbonyl)cyclopropyl)-*N*-phenethyl-3,5-bis(trifluoromethyl)benzamide (**6bw**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5b** (117 mg, 0.50 mmol) and *N*-phenethyl-3,5-bis(triflouromethyl)-benzamide (**4w**) (313 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R_f 0.69) was identified as non-reacted benzamide **4w**, and the more polar one (R_f 0.10) as the title compound, a colorless viscous oil. Yield 195 mg (0.38 mmol, 76%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.10 (s, 1H), 7.79 (s, 2H), 7.39-7.32 (m, 4H), 7.28-7.23 (m, 1H), 4.15 (dt, *J* = 13.2 Hz, 6.6 Hz, 1H), 3.73-3.63 (m, 3H), 3.53-3.41 (m, 5H), 3.16-3.01 (m, 4H), 2.02 (br. s, 1H), 1.20-1.15 (m, 1H), 1.13-1.08 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.1, 170.5, 140.9, 140.2, 133.0 (q, $^2J_{CF}$ = 33.6 Hz), 130.4 (+, 2C), 129.9 (+, 2C), 129.1 (+, 2C), 128.0 (+), 124.7 (+, 2C), 124.6 (q, $^1J_{CF}$ = 271.6 Hz), 67.8 (-), 67.6 (-), 49.3 (-), 47.0 (-), 43.7 (-), 40.8 (+), 34.6 (-), 24.4 (+), 18.9 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); FTIR (NaCl, film, cm^{-1}): 2924, 2890, 1645, 1456, 1423, 1366, 1280, 1236, 1177, 1136, 905, 752, 702; HRMS (TOF ES): found 515.1765, calculated for $C_{25}H_{25}F_6N_2O_3$ (M+H) 515.1769 (0.8 ppm);



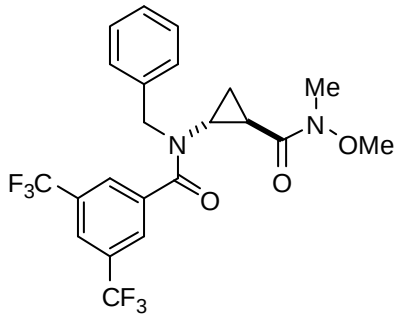
N-Phenethyl-*N*-((1*R**,2*R**)-2-(piperidine-1-carbonyl)-cyclopropyl)-3,5-bis(trifluoromethyl)benzamide (**6cw**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5c** (115 mg, 0.50 mmol) and *N*-phenethyl-3,5-bis(triflouromethyl)-benzamide (**4w**) (313 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R_f 0.69) was identified as non-reacted benzamide **4w**, and the more polar one (R_f 0.21) as the title compound, a colorless viscous oil. Yield 195 mg (0.38 mmol, 76%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.07 (s, 1H), 7.80 (s, 2H), 7.40-7.33 (m, 4H), 7.29-7.24 (m, 1H), 4.16 (ddd, *J* = 12.9 Hz, 6.6 Hz, 6.3 Hz, 1H), 3.72-3.64 (m, 1H), 3.56-3.49 (m, 1H), 3.16-2.98 (m, 4H), 2.06-2.00 (m, 1H), 1.75-1.50 (m, 4H), 1.44-1.33 (m, 4H), 1.18-1.12 (m, 1H), 1.10-1.05 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.2, 169.8, 140.9, 140.2, 132.9 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 130.3 (+, 2C), 129.8 (+, 2C), 129.0 (+, 2C), 128.0 (+), 124.6 (+), 124.6 (q, $^1J_{CF}$ = 272.5 Hz, 2C), 49.3 (-), 47.7 (-), 44.5 (-), 40.6 (+), 34.6 (-), 27.8 (-), 26.6 (-), 25.5 (-), 24.5 (+), 18.6 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); HRMS (TOF ES): found 519.2058, calculated for $C_{26}H_{26}F_6N_2O_2Li$ (M+Li) 519.2059 (0.2 ppm);



N-Benzyl-*N*-((1*R**,2*R**)-2-(piperidine-1-carbonyl)cyclo-propyl)-3,5-bis(trifluoromethyl)benzamide (**6cx**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5c** (116 mg, 0.50 mmol) and *N*-benzyl-3,5-bis(triflouromethyl)benzamide (**4x**) (347 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/ EtOAc 1:1) afforded two fractions. The less polar one (R_f 0.61) was identified as non-reacted benzamide **4x**, and the more polar one (R_f 0.21) as the title compound, a colorless viscous oil. Yield 170 mg (0.34 mmol, 68%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.12 (s, 3H), 7.44-7.35 (m, 4H), 7.35-7.29 (m, 1H), 5.06 (d, *J* = 14.5 Hz, 1H), 4.58 (d, *J* = 14.5 Hz, 1H), 3.49 (dt, J = 13.2 Hz, 5.0 Hz, 1H), 3.22 (br. s, 1H), 3.07 (br. s, 1H), 2.93 (br. s, 1H), 2.07 (br. s, 1H), 1.63-1.49 (m, 3H), 1.40-1.27 (m, 4H), 1.14 (br. s, 1H), 1.03 (br. s, 1H); ^{13}C NMR (126 MHz, MeOD) δ ppm 171.1, 169.9, 140.6, 138.6, 133.0 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 130.1 (+, 4C), 129.2 (+, 2C), 128.9 (+), 124.8 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.6 (q, $^1J_{CF}$ = 272.5 Hz, 2C), 52.0 (-), 47.6 (-), 44.5 (-), 40.6 (+), 27.8 (-), 26.6 (-), 25.5 (-), 24.1 (+), 18.5 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3088, 3064, 3032, 3009, 2941, 2858, 1643, 1452, 1364, 1281, 1184,1138, 905, 849, 700, 681; HRMS (TOF ES): found 499.1817, calculated for $C_{25}H_{25}F_6N_2O_2$ (M+H) 499.1820 (0.6 ppm).



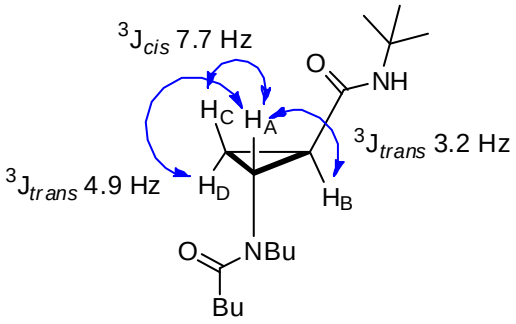
N-Cyclohexyl-*N*-((1*R**,2*R**)-2-(cyclohexylcarbamoyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzamide (**6dt**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5d** (123 mg, 0.50 mmol) and *N*-cyclohexyl-3,5-bis(triflouromethyl)-benzamide (**4t**) (339 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R_f 0.78) was identified as non-reacted benzamide **4t**, and the more polar one (R_f 0.31) as the title compound, a colorless viscous oil. Yield 166 mg (0.33 mmol, 66%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.09 (s, 2H), 8.06 (s, 1H), 4.06 (br. s, 1H), 3.48-3.41 (m, 1H), 3.19 (br. s, 1H), 2.04-1.97 (m, 1H), 1.93-1.84 (m, 3H), 1.76-1.58 (m, 9H), 1.46-1.00 (m, 11H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.4 (2C), 141.5, 133.0 (q, $^2J_{CF}$ = 34.5 Hz, 2C), 129.2 (s, +, 2C), 124.7 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^1J_{CF}$ = 271.6 Hz, 2C), 60.8 (+), 49.9 (+), 37.3 (+), 33.93 (-), 33.85 (-), 32.4 (-), 32.1 (-), 27.5 (br. s., +), 27.39 (-), 27.36 (-), 27.0 (-), 26.7 (-), 26.2 (-), 26.1 (-), 18.0 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); FTIR (NaCl, film, cm^{-1}): 3302, 2933, 2856, 1632, 1547, 1454, 1427, 1352, 1278, 1182, 1138, 905, 681; HRMS (TOF ES): found 505.2287, calculated for $C_{25}H_{31}F_6N_2O_2$ (M+H) 505.2290 (0.6 ppm).



N-Benzyl-N-((1*R**,2*R**)-2-(methoxy(methyl)carbamoyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzamide (**6ex**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5e** (104 mg, 0.50 mmol) and *N*-benzyl-3,5-bis(trifluoromethyl)benzamide (**4x**) (347 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R_f 0.61) was identified as non-reacted benzamide **4x**, and the more polar one (R_f 0.31) as the title compound, a yelowish viscous oil. ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.09 (s, 3H), 7.45-7.38 (m, 4H), 7.35-7.31 (m, 1H), 5.03 (d, *J* = 14.5 Hz, 1H), 4.63 (d, *J* = 14.5 Hz, 1H), 3.45 (br. s, 3H), 3.17 (br. s, 1H), 2.93 (br. s, 3H), 2.26 (br. s, 1H), 1.28-1.21 (m, 1H), 1.11 (br. s, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 172.1, 171.3, 140.6, 138.5, 133.2 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 130.1 (+, 2C), 129.3 (+, 2C), 129.0 (q, $^3J_{CF}$ = 2.7 Hz, +, 2C), 129.0 (+), 124.8 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.6 (q, $^1J_{CF}$ = 271.6 Hz, 2C), 62.2 (+), 51.9 (-), 40.8 (+), 32.4 (+), 23.6 (+), 18.3 (-); FTIR (teflon, film, cm^{-1}): 2939, 1651, 1620, 1441, 1418, 1364, 1279, 1207, 1184, 1150, 1138, 1109, 1003, 905, 756, 700, 681; HRMS (TOF ES): found 475.1457, calculated for $C_{22}H_{21}F_6N_2O_3$ (M+H) 475.1456 (0.2 ppm);

Assignment of Relative Configurations by ^{1}H NMR

The relative configuration of compound **6ab** was assigned based on analysis of the coupling constants in the multiplet at 2.75 ppm. Albeit severe broadening of the resonance lines complicated the analysis, careful optimization of the sample temperature allowed for obtaining of an acceptable resolution in DMSO-d6 at 370 K (97 ^{o}C). Further improvement of the line resolution was achieved by applying Lorentzian-Gaussian Windows Function (LB = -1, GF = 0.5) prior to the Fourier Transform. Coupling constant values were determined by multiplete simulation using ACD/SpecManager 11.01 (Figure 1). The observation of two *trans*-^{3}J coupling constants (3.15 Hz, 4.89 Hz) and only one *cis*-^3J coupling constant (7.72 Hz) allowed for unambiguous assignment of the *trans*-configuration to product **6ab**.



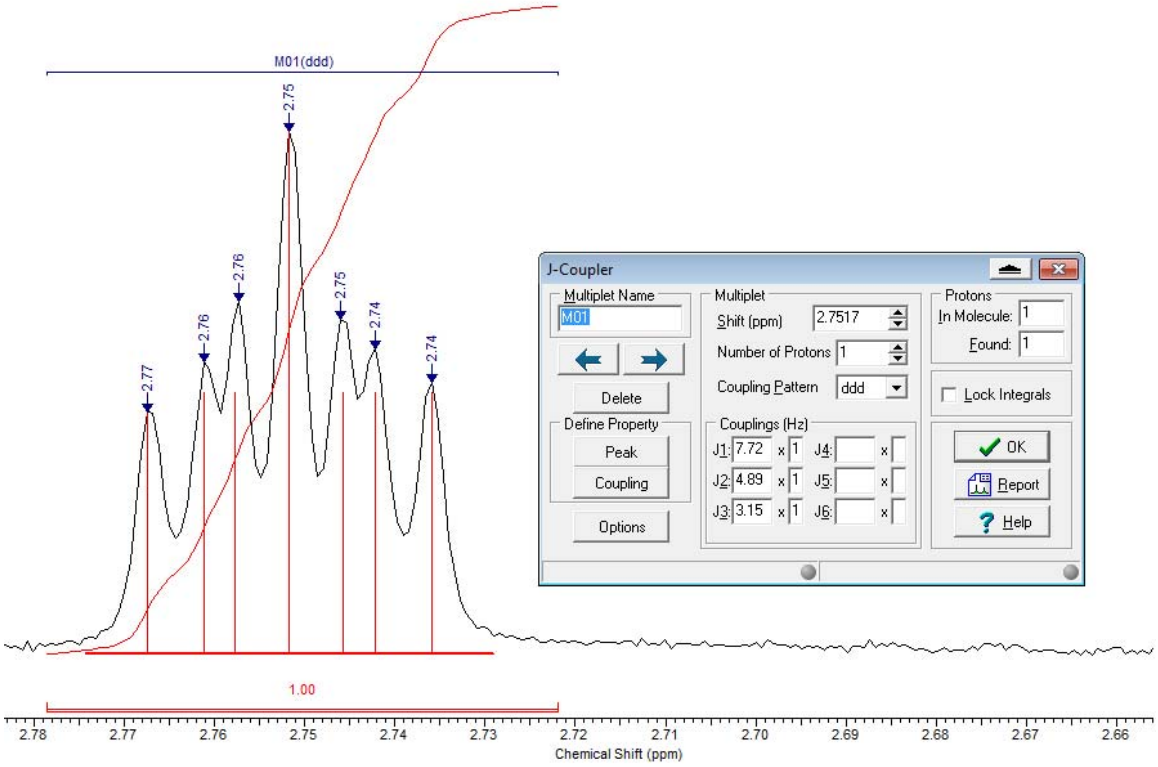


Figure 1. Analysis of coupling constants in ^{1}H NMR signal of proton A in compound **6ab**.

Crystallographic Data

Colorless parallelepiped-shaped crystals of $C_{25}H_{24}F_6N_2O_3$ are, at 100(2) K, monoclinic, space group $P2_1/c$ – C_{2h}^5 (No. 14)[11] with a = 15.679(9) Å, b = 16.496(10) Å, c = 8.969(5) Å, β = 95.185(11)°, V = 2310(2) Å^3 and Z = 4 molecules {dcalcd = 1.479 g/cm^3; μ_a(MoKα) = 0.130 mm^{-1}}. A full hemisphere of diffracted intensities (1850 10-second frames with a ω scan width of 0.30°) was measured for a 2-domain specimen using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System.[12] The second domain accounted for 41% of the crystal volume and was rotated by 180° about the a axis of the unit cell for the major domain. X-rays were provided by a fine-focus sealed x-ray tube operated at 50 kV and 30 mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 3072 reflections. A total of 3875 unique integrated reflection intensities having 2θ((MoKα)< 50.00° and a coverage which was 95.1% complete were produced using the Bruker program SAINT;[13] 27.4% of the reflections had two twin components and the rest had just one. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.914 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package.[14] The final structural model took the 2-domain twinning into account and incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were included in the structural model as idealized atoms (assuming *sp*^{2}- or *sp*^{3}-hybridization of the carbon atoms and C-H bond lengths of 0.95 – 1.00 Å). The isotropic thermal parameters of all hydrogen atoms were fixed at values 1.2 times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. A total of 326 parameters were refined using no restraints, 3875 data and weights of $w = 1/[\sigma^2(F^2) + (0.1314P)^2 + 1.8112P]$, where $P = [F_o^2 + 2F_c^2]/3$. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.089 for 2972 independent absorption-corrected "observed" reflections having 2θ(MoKα) < 50.00° and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.113 and wR_2(weighted, based on F^2) = 0.244 for 3875 independent absorption-corrected reflections having 2θ(MoKα) < 50.00°. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.85 and -0.61 e$^-$/Å^3, respectively.

Table 1. Atomic coordinates (Å) and equivalent isotopic factors (Å^2) for diamide **6bw**.

(11) International Tables for Crystallography, Vol A, 4th ed., Kluwer: Boston (1996).

(12) Data Collection: SMART Software Reference Manual (1998). Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373, USA.

(13) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

(14) (a) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373, USA. (b) International Tables for Crystallography, Vol C, Tables 4.2.4.2, 4.2.6.8, and 6.1.1.4, Kluwer: Boston (1995).

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
F1	0.03357(15)	0.29620(15)	0.3107(5)	0.0911(12)
F2	0.1009(3)	0.30901(18)	0.1232(4)	0.1169(16)
F3	0.16018(15)	0.25784(14)	0.3149(4)	0.0724(9)
F4	0.00448(19)	0.60552(18)	0.1745(3)	0.0730(9)
F5	-0.0232(2)	0.60032(19)	0.3928(4)	0.0831(10)
F6	0.07646(18)	0.67539(14)	0.3336(6)	0.144(2)
O1	0.13519(14)	0.55382(14)	-0.2558(3)	0.0315(6)
O2	0.28798(15)	0.72017(13)	0.1247(3)	0.0357(6)
O3	0.35411(14)	0.44771(14)	0.6035(3)	0.0333(6)
N1	0.37900(16)	0.56393(16)	0.4826(3)	0.0264(6)
N2	0.22643(19)	0.61286(16)	0.0056(3)	0.0313(7)
C1	0.3620(2)	0.62182(19)	0.3643(4)	0.0270(7)
H1	0.3336	0.6733	0.3918	0.032
C2	0.4281(2)	0.6297(2)	0.2565(4)	0.0310(8)
H2A	0.4780	0.5928	0.2687	0.037
H2B	0.4407	0.6847	0.2203	0.037
C3	0.3419(2)	0.59320(19)	0.2052(4)	0.0260(7)
H3	0.3391	0.5335	0.1866	0.031
C4	0.2827(2)	0.64657(19)	0.1094(4)	0.0273(7)
C5	0.2018(2)	0.52773(19)	-0.0082(4)	0.0298(7)
H5A	0.1467	0.5193	0.0353	0.036
H5B	0.2457	0.4937	0.0479	0.036
C6	0.1930(2)	0.5029(2)	-0.1699(4)	0.0304(7)
H6A	0.2498	0.5054	-0.2098	0.036
H6B	0.1725	0.4462	-0.1782	0.036
C7	0.1646(2)	0.6352(2)	-0.2485(4)	0.0327(8)
H7A	0.1248	0.6698	-0.3124	0.039
H7B	0.2218	0.6383	-0.2870	0.039
C8	0.1702(2)	0.6655(2)	-0.0902(4)	0.0376(9)
H8A	0.1929	0.7215	-0.0861	0.045
H8B	0.1124	0.6663	-0.0541	0.045
C9	0.4561(2)	0.5791(2)	0.5853(4)	0.0306(8)
H9A	0.5004	0.6052	0.5295	0.037
H9B	0.4794	0.5267	0.6248	0.037
C10	0.4368(2)	0.6329(2)	0.7147(4)	0.0296(8)
H10A	0.4129	0.6852	0.6760	0.035
H10B	0.3937	0.6065	0.7727	0.035
C11	0.51772(19)	0.64782(18)	0.8143(3)	0.0234(7)
C12	0.5330(2)	0.60544(19)	0.9452(4)	0.0285(7)
H12	0.4911	0.5686	0.9746	0.034
C13	0.6087(2)	0.6156(2)	1.0351(4)	0.0351(8)
H13	0.6188	0.5859	1.1257	0.042
C14	0.6698(2)	0.6696(2)	0.9919(4)	0.0375(9)
H14	0.7224	0.6762	1.0521	0.045
C15	0.6545(2)	0.7131(2)	0.8635(4)	0.0347(8)
H15	0.6957	0.7510	0.8354	0.042
C16	0.5793(2)	0.7021(2)	0.7741(4)	0.0296(7)
H16	0.5694	0.7321	0.6838	0.036
C17	0.3309(2)	0.49846(19)	0.5094(3)	0.0249(7)
C18	0.24389(19)	0.48842(19)	0.4250(3)	0.0237(7)
C19	0.2176(2)	0.41142(19)	0.3843(4)	0.0268(7)
H19	0.2561	0.3672	0.4017	0.032
C20	0.1365(2)	0.39775(19)	0.3190(4)	0.0254(7)
C21	0.0784(2)	0.46126(19)	0.2954(3)	0.0263(7)
H21	0.0220	0.4516	0.2509	0.032
C22	0.10391(19)	0.5380(2)	0.3375(3)	0.0263(7)
C23	0.18691(19)	0.55252(19)	0.4007(3)	0.0240(7)
H23	0.2045	0.6061	0.4272	0.029
C24	0.1083(2)	0.3150(2)	0.2666(5)	0.0400(9)
C25	0.0431(2)	0.6063(2)	0.3113(4)	0.0326(8)

Acknowledgment. The authors thank the National Science Foundation (grant CHE-

0079282) and the University of Kansas for funds to purchase the X-ray instrument and computers.

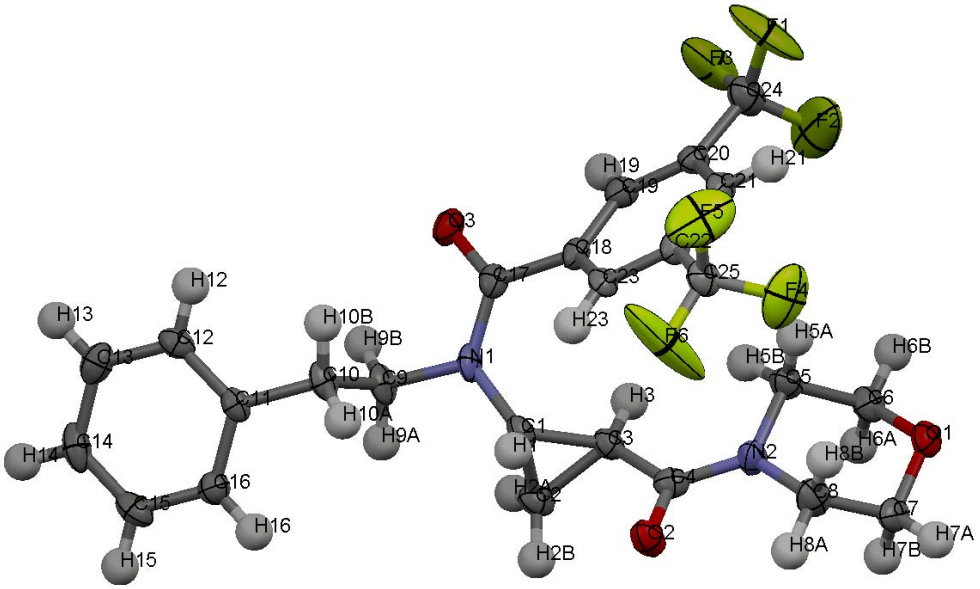


Figure 2. ORTEP drawing of diamide **6bw** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown.

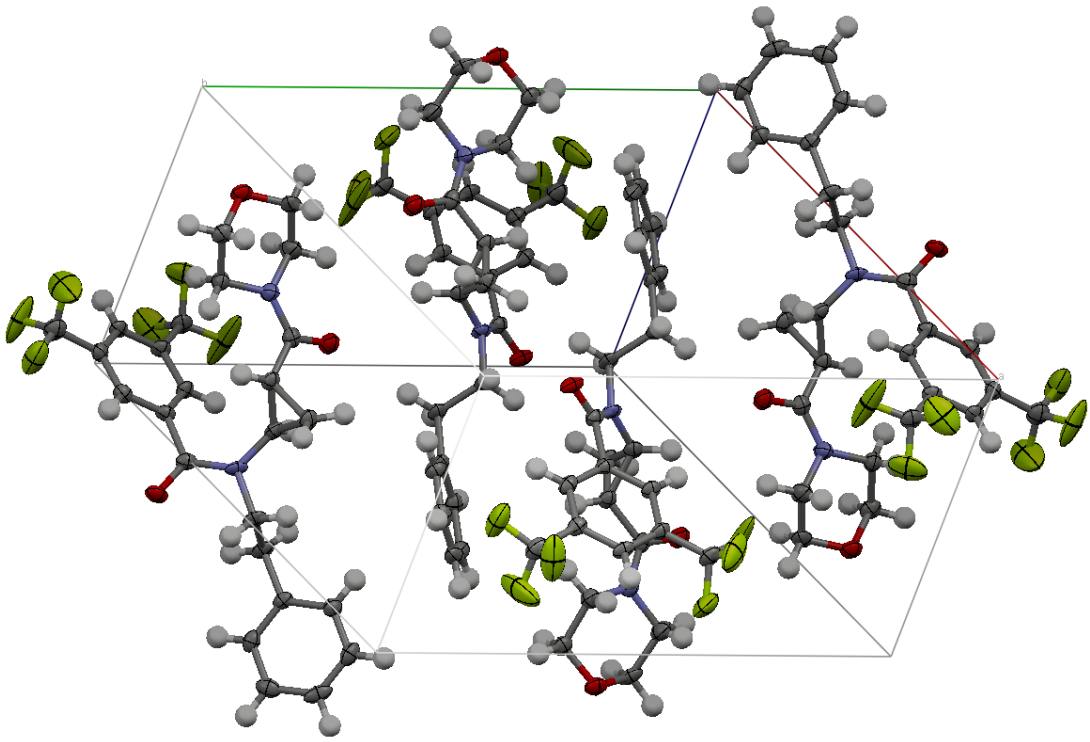
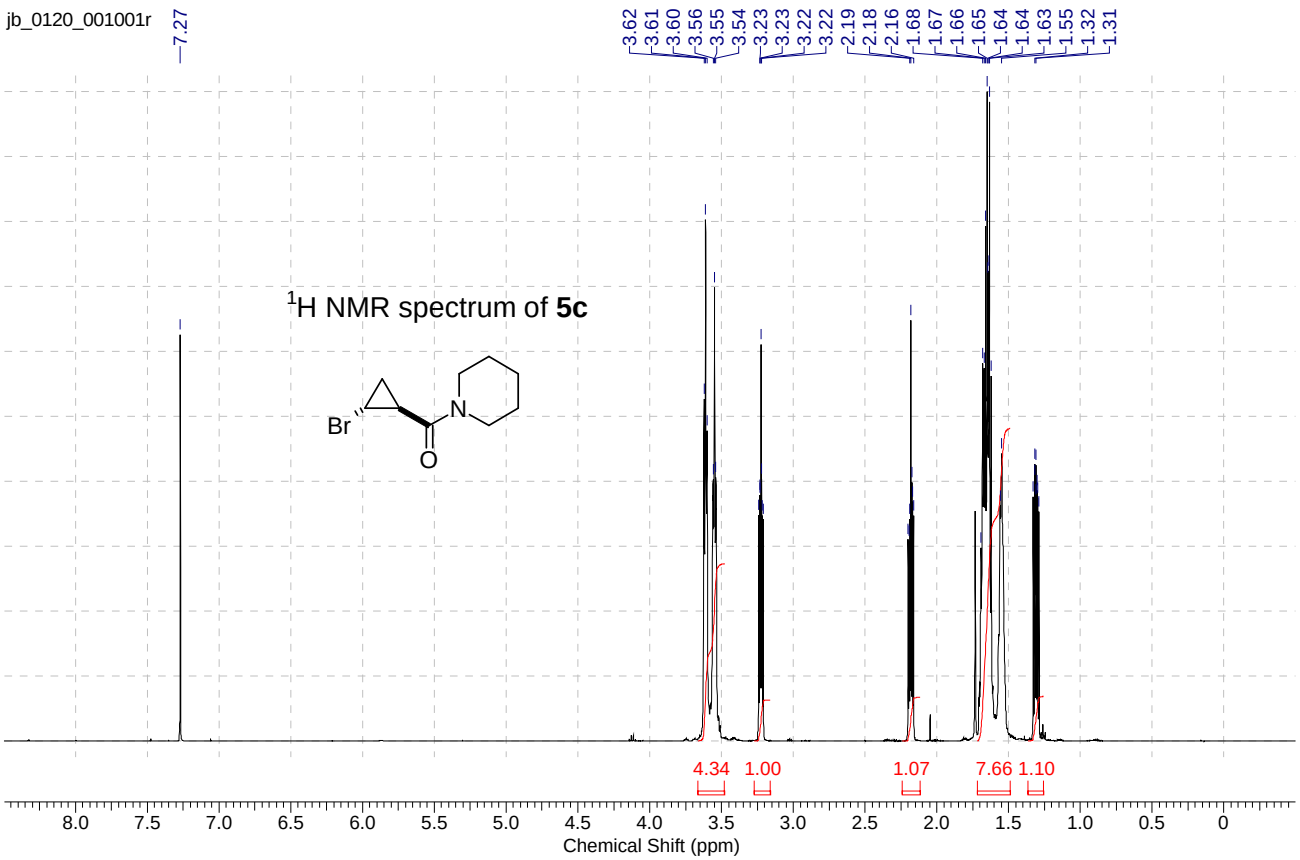
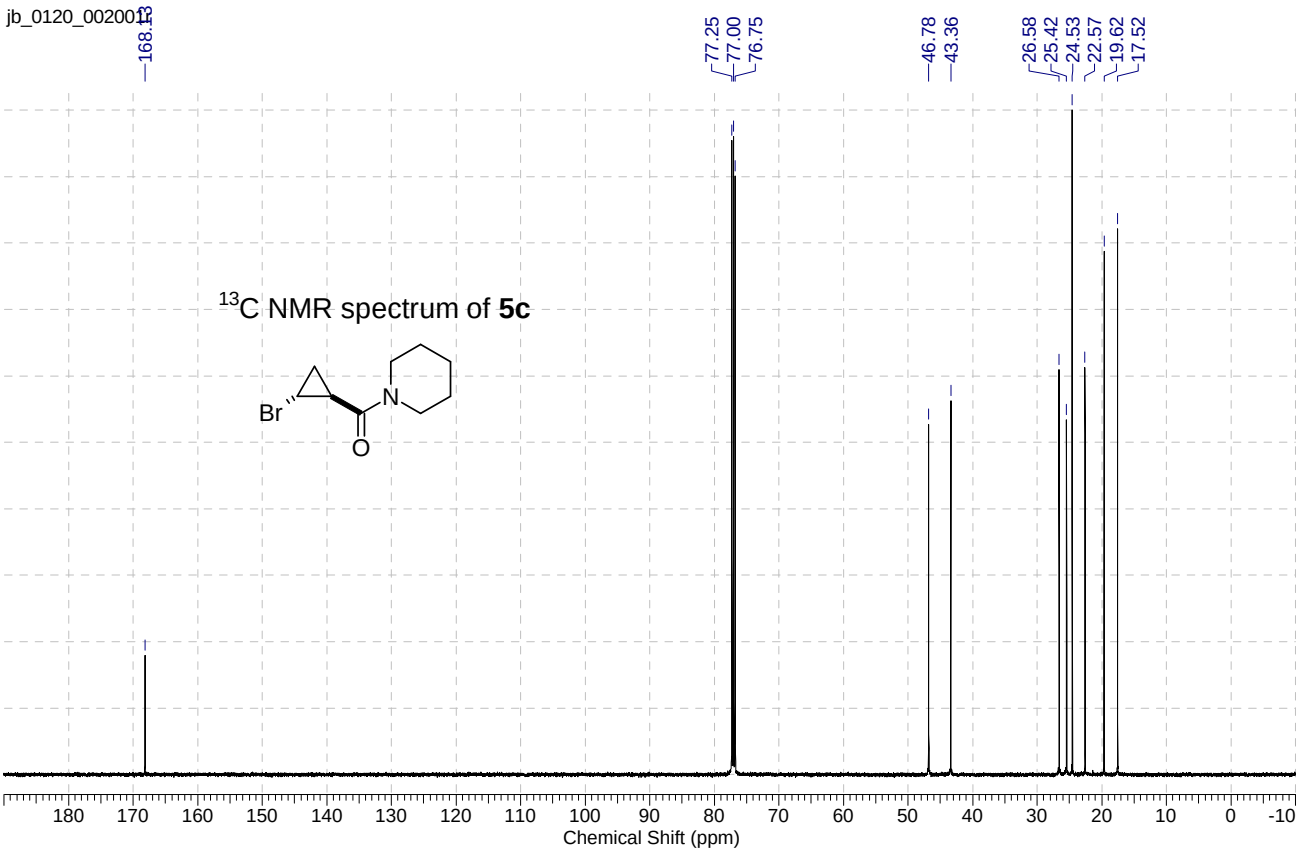


Figure 3. Packing of diamide **6bw** molecules in the crystalline lattice cell.

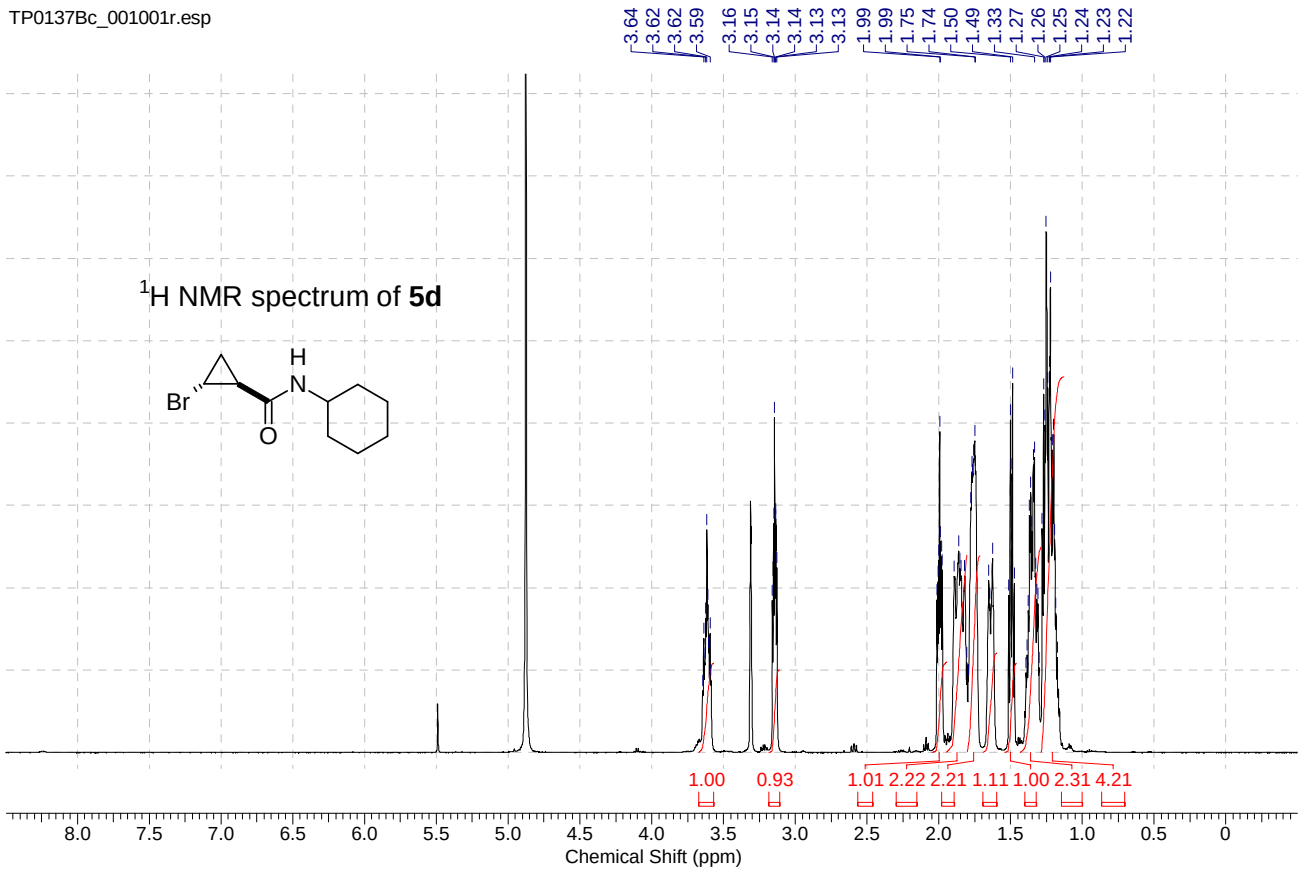


^{1}H NMR spectrum of **5c**



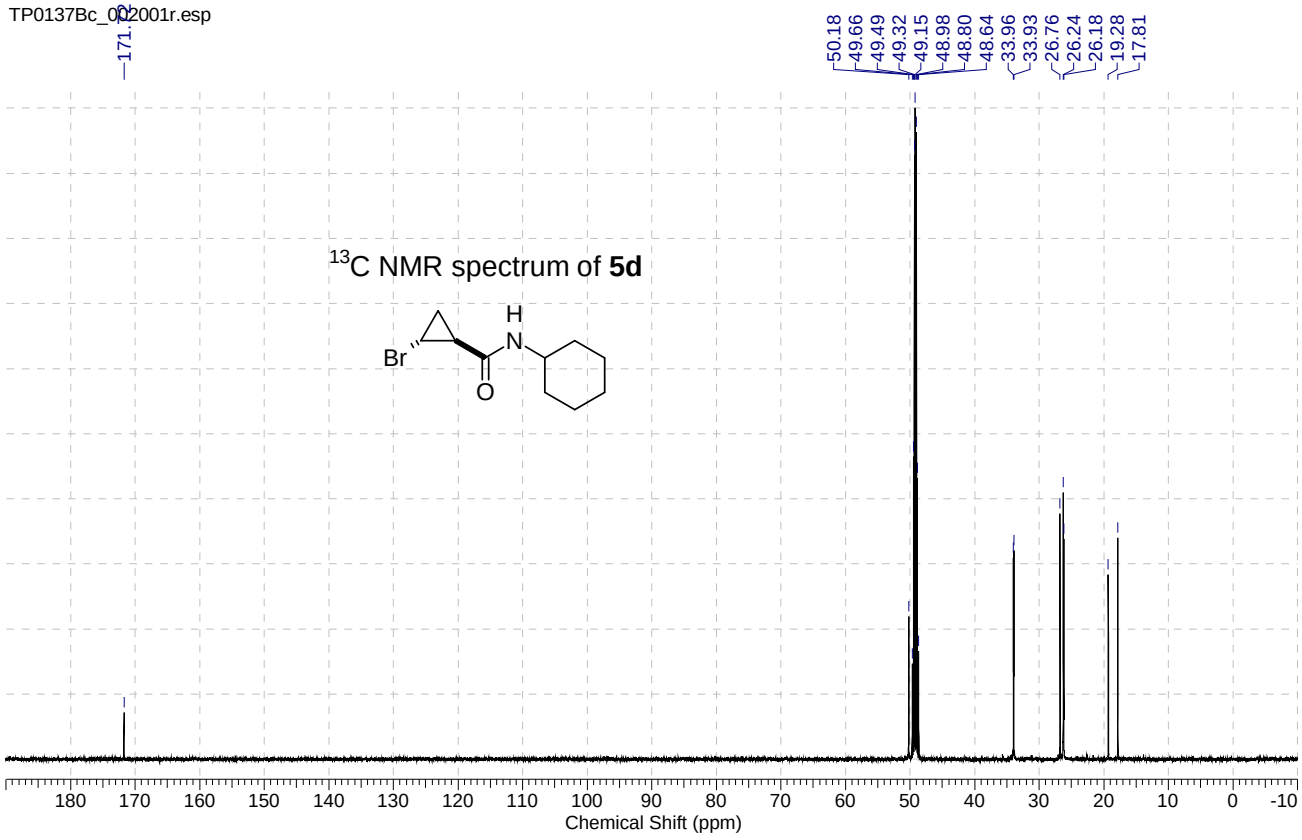
^{13}C NMR spectrum of **5c**

TP0137Bc_001001r.esp

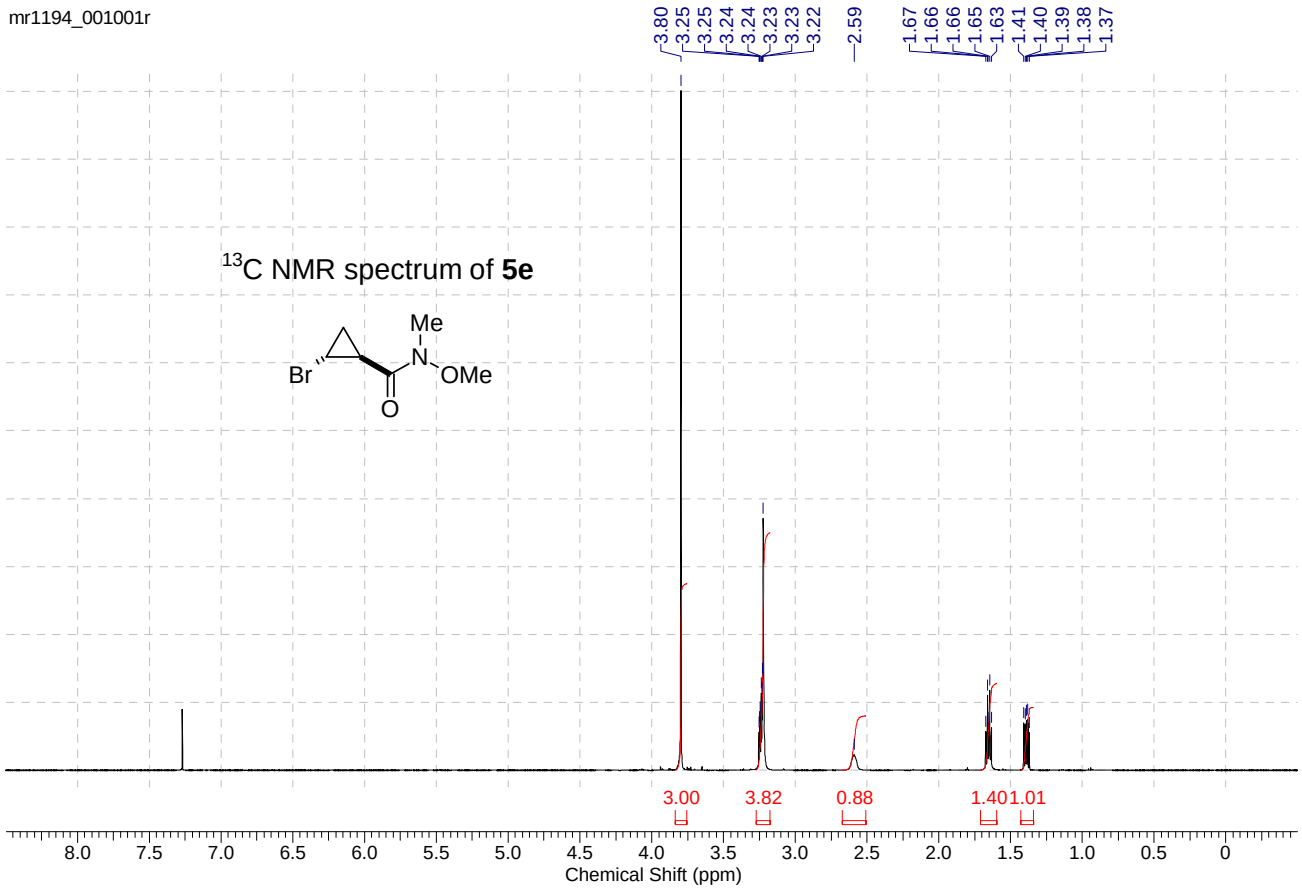


^{1}H NMR spectrum of **5d**

TP0137Bc_002001r.esp



^{13}C NMR spectrum of **5d**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3.25
3.24
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3.22
2.59
1.67
1.66
1.66
1.65
1.63
1.41
1.40
1.39
1.38
1.37
^{13}C NMR spectrum of **5e**
Me
N
Br
OMe
O
3.00
3.82
0.88
1.40
1.01
8.0
7.5
7.0
6.5
6.0
5.5
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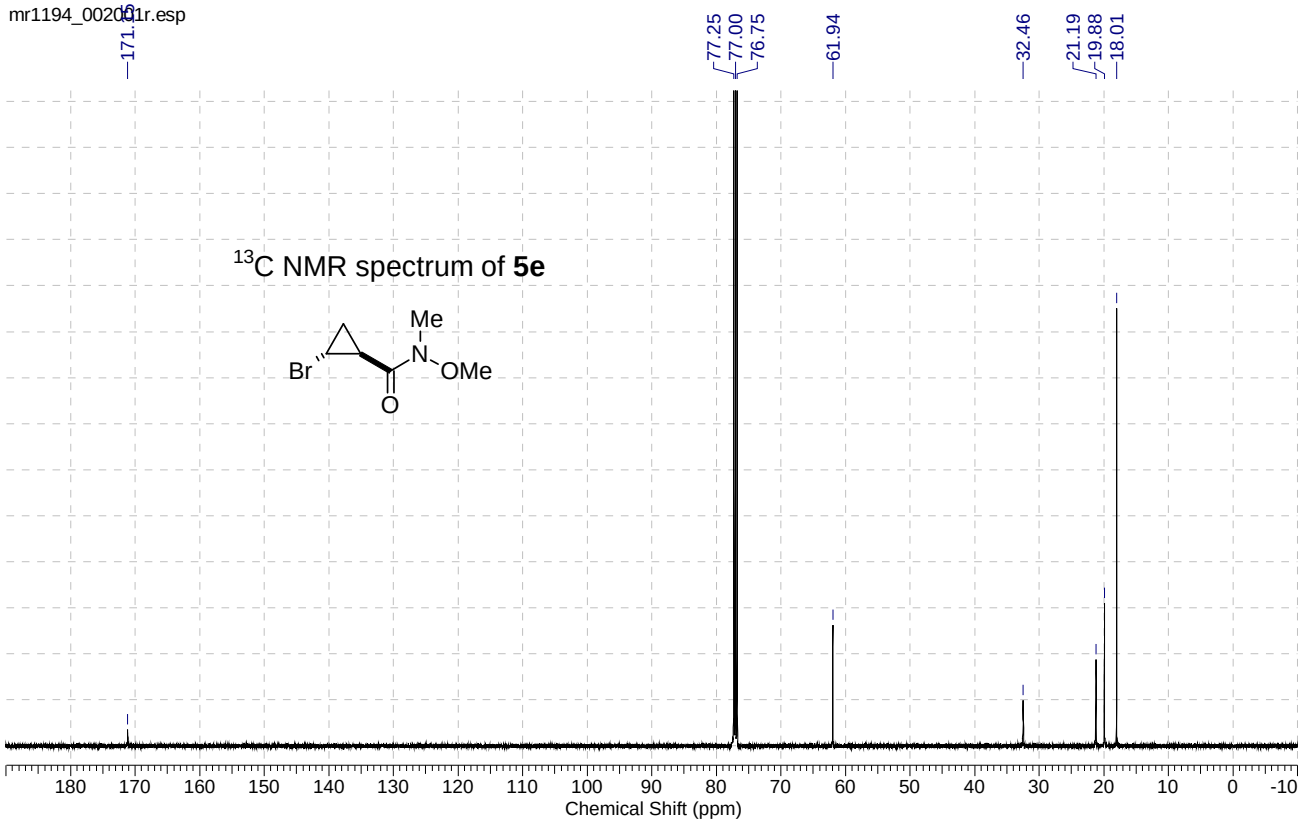
0
Chemical Shift (ppm)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^{13}C NMR spectrum of **5e**
Me
N
Br
OMe
O
180
170
160
150
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120
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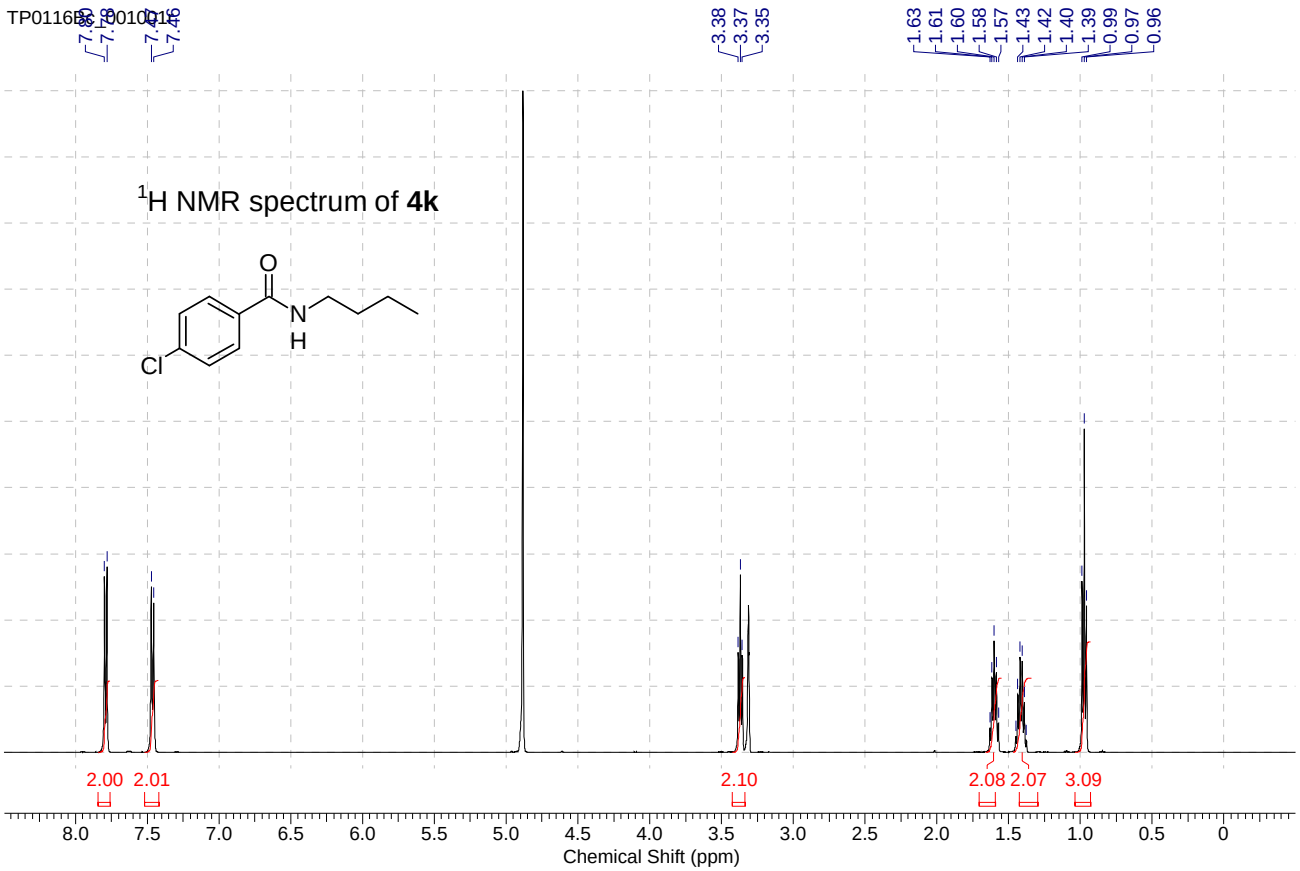
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)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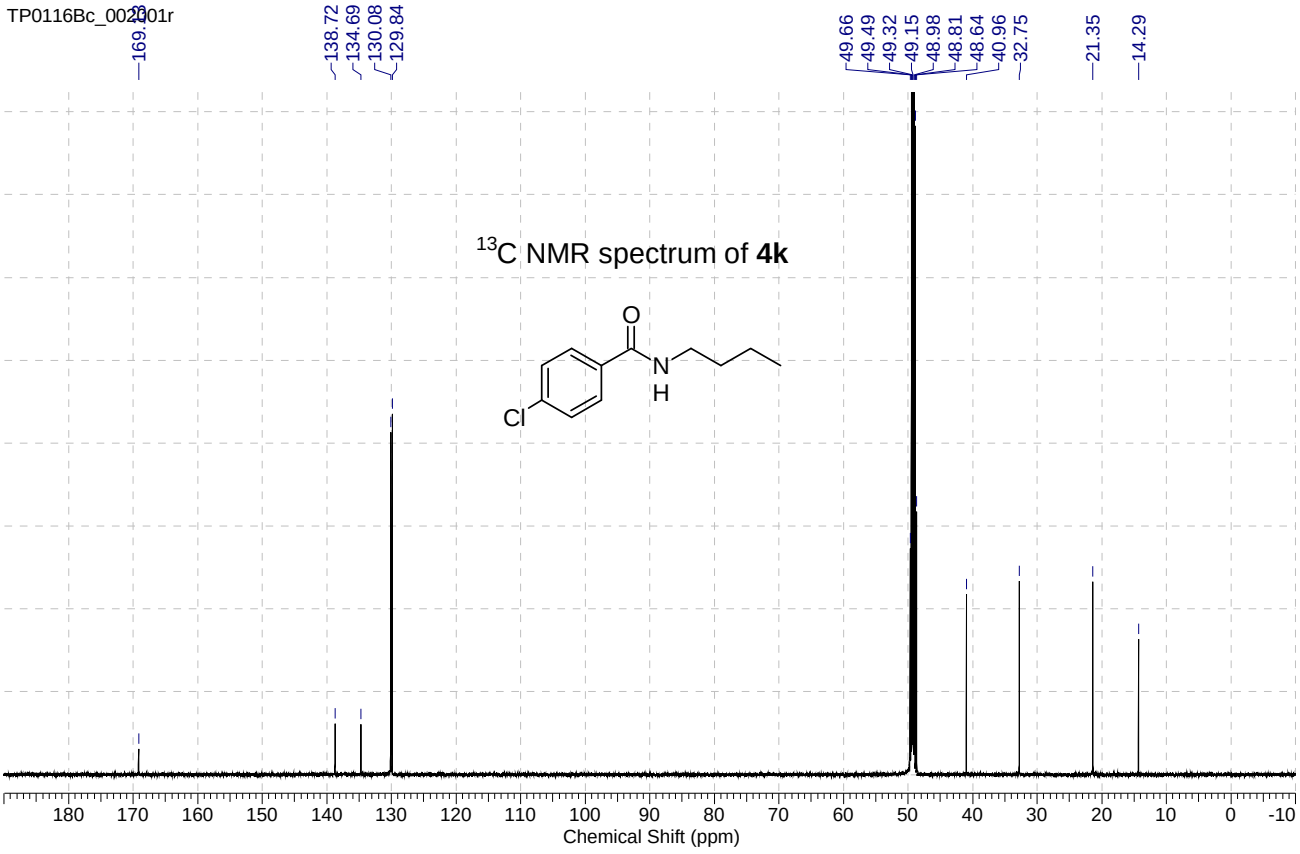
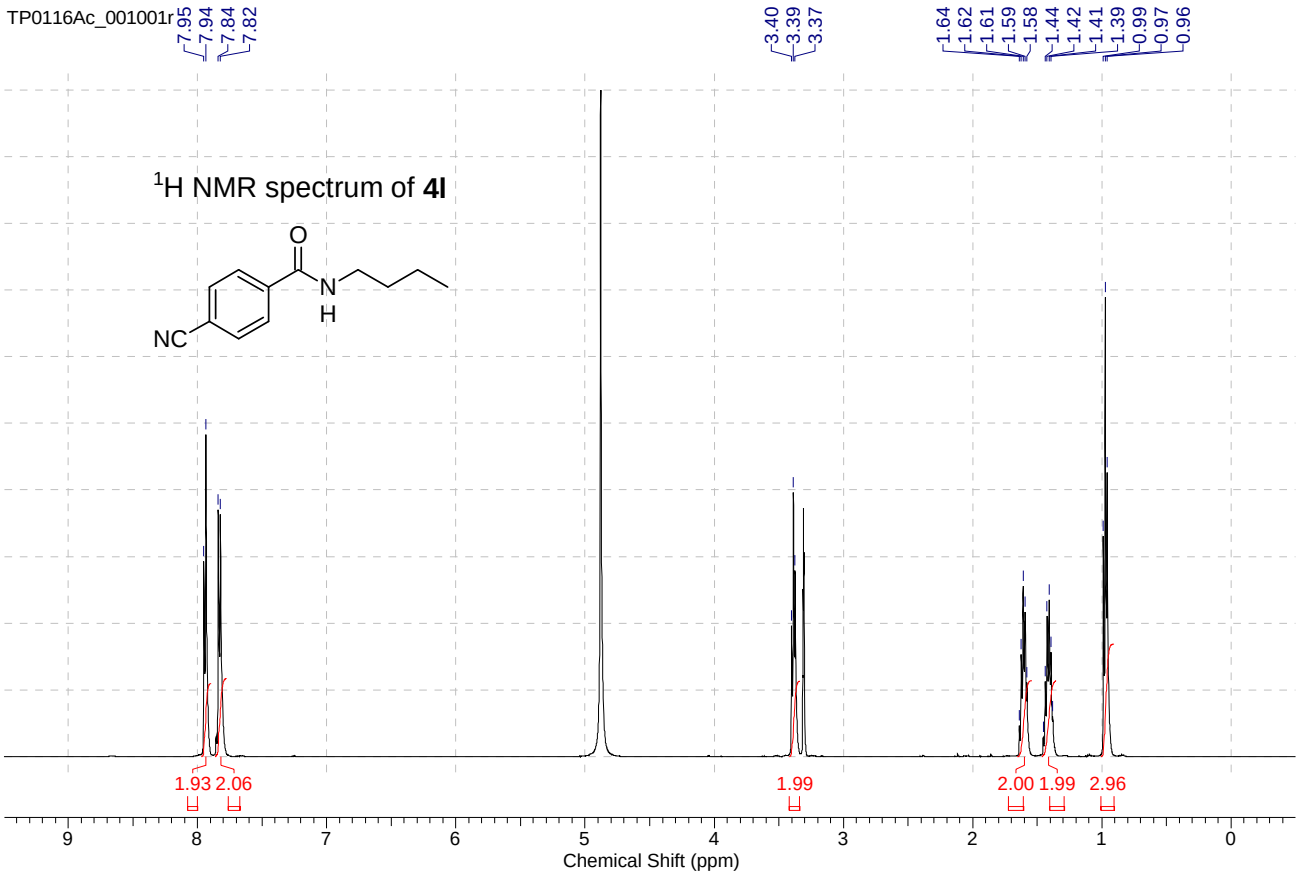
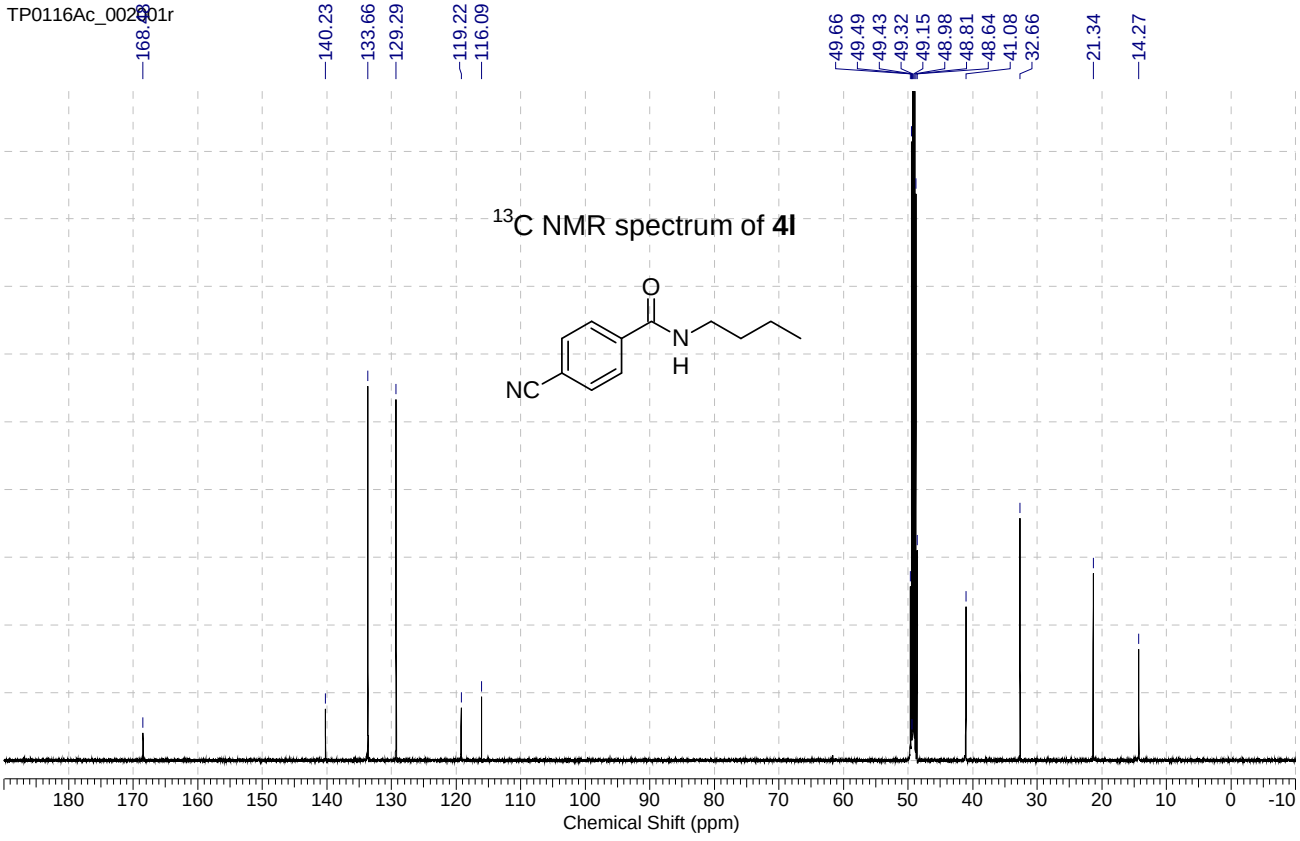
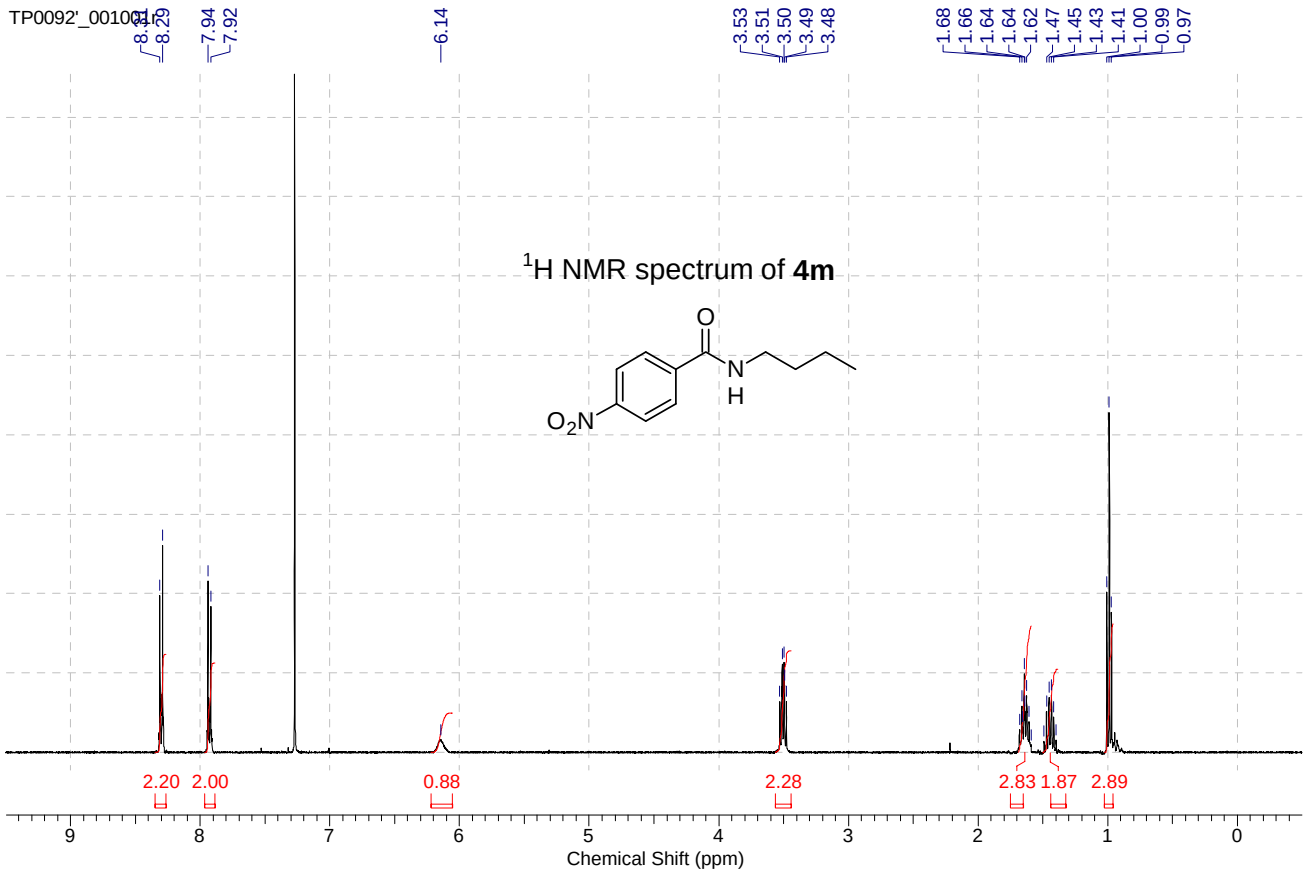
7.98
7.97
7.46
7.45
3.38
3.37
3.35
1.63
1.61
1.60
1.58
1.57
1.43
1.42
1.40
1.39
0.99
0.97
0.96
^{1}H NMR spectrum of **4k**
O
N
H
Cl
2.00
2.01
2.10
2.08
2.07
3.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

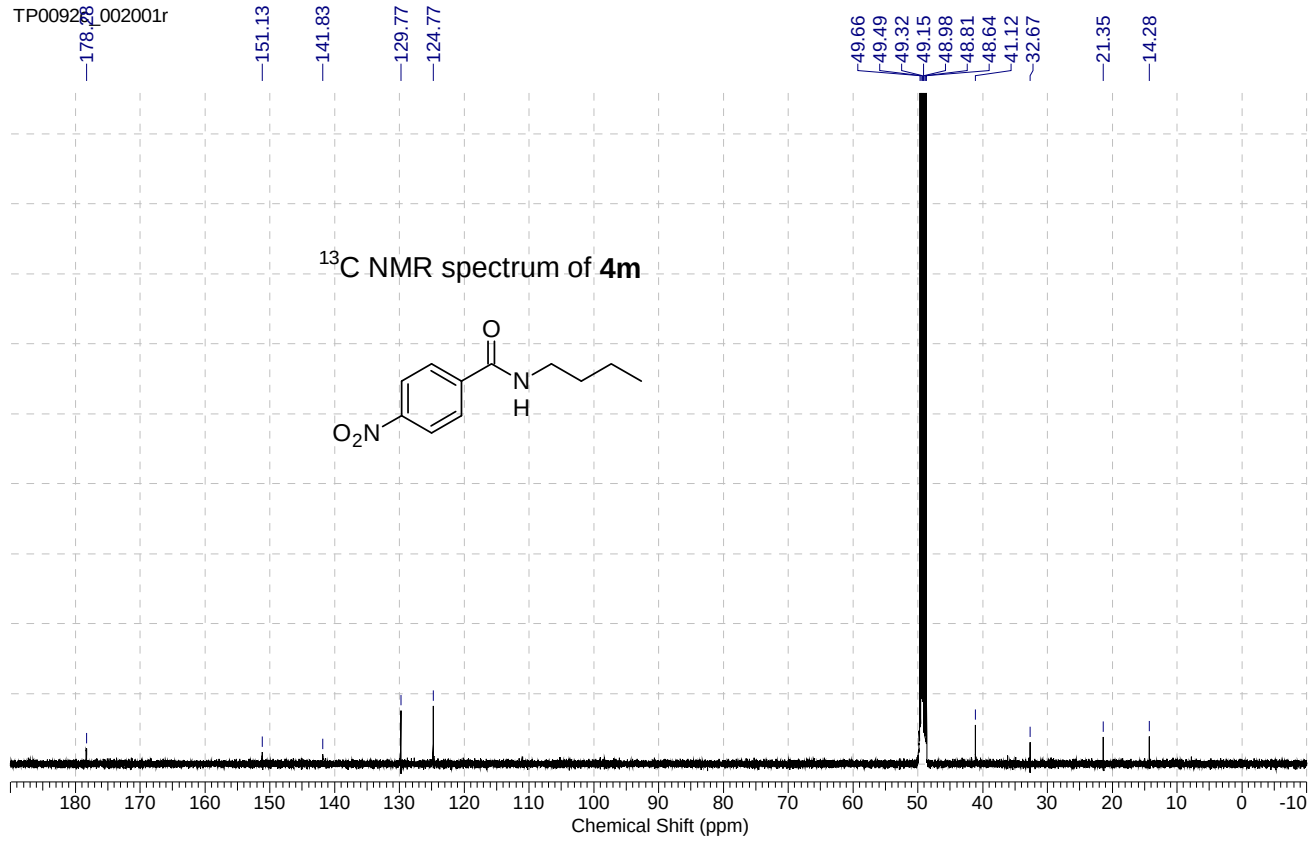

TP0116Bc_002001r
169.70
138.72
134.69
130.08
129.84
49.66
49.49
49.32
49.15
48.98
48.81
48.64
40.96
32.75
21.35
14.29
^{13}C NMR spectrum of **4k**
O
N
H
Cl
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


TP0116Ac_001001r
7.95
7.94
7.84
7.82
3.40
3.39
3.37
1.64
1.62
1.61
1.59
1.58
1.44
1.42
1.41
1.39
0.99
0.97
0.96
1H NMR spectrum of 4l
O
N
H
NC
1.93
2.06
1.99
2.00
1.99
2.96
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

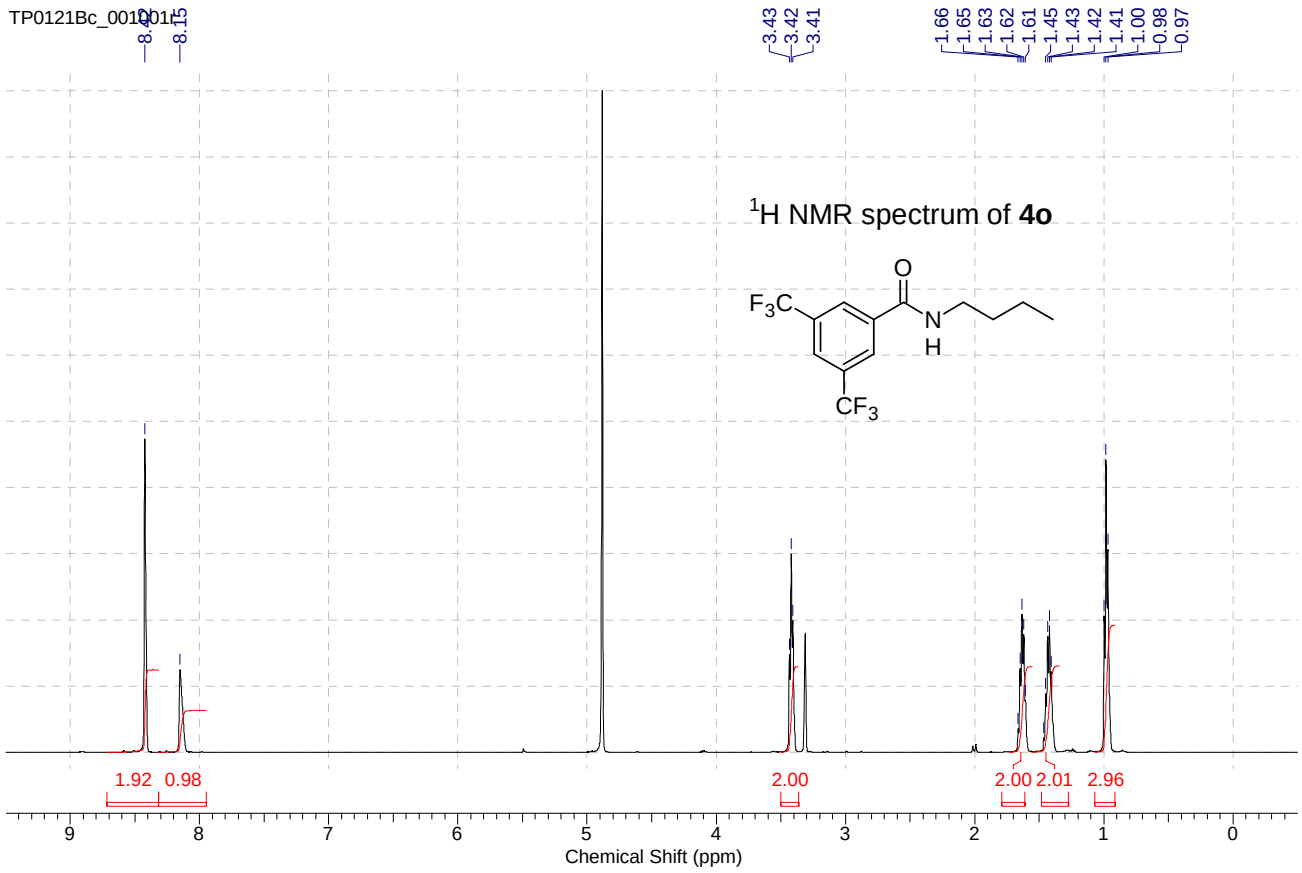

TP0116Ac_002001r
168.48
140.23
133.66
129.29
119.22
116.09
49.66
49.49
49.43
49.32
49.15
48.98
48.81
48.64
41.08
32.66
21.34
14.27
13C NMR spectrum of 4l
O
N
H
NC
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

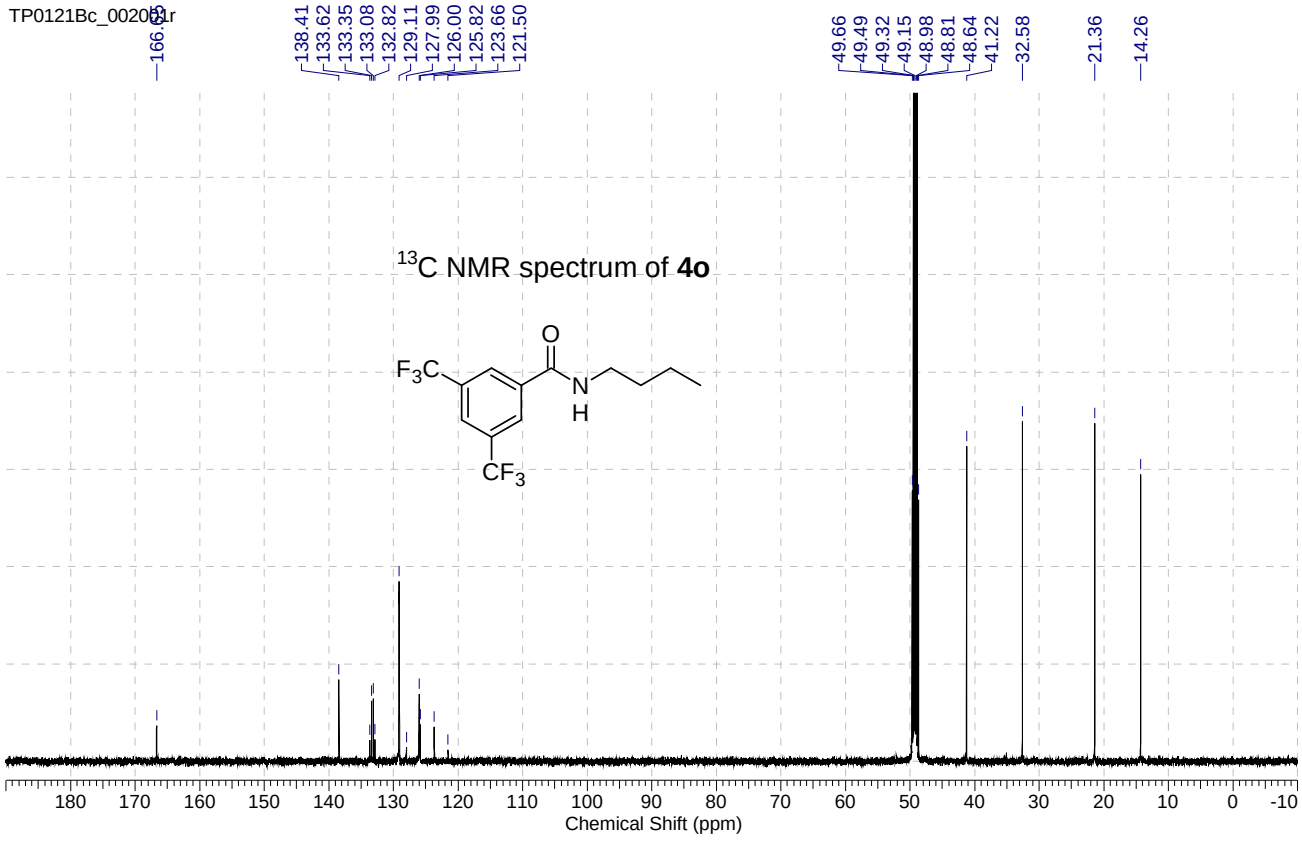


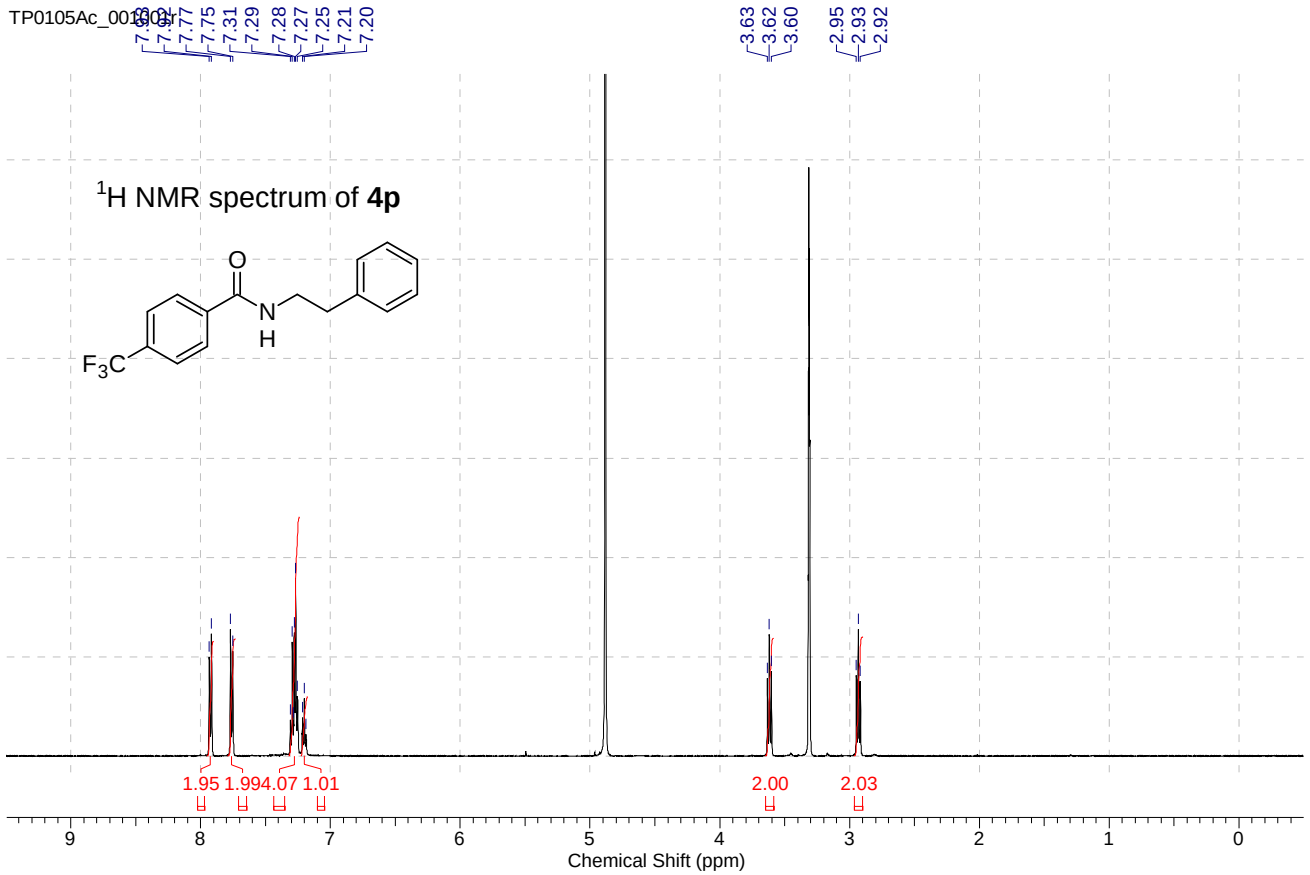
^{1}H NMR spectrum of **4m**

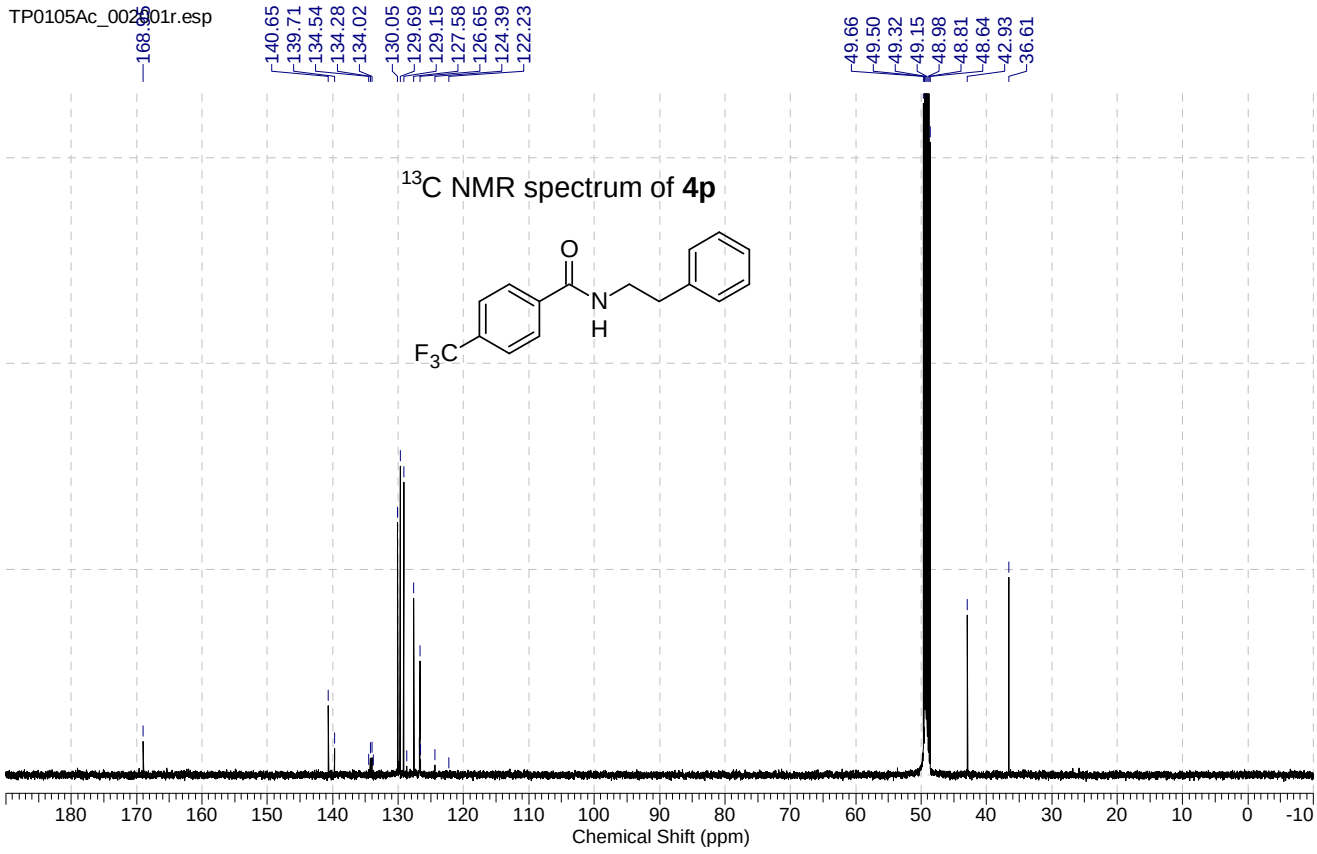


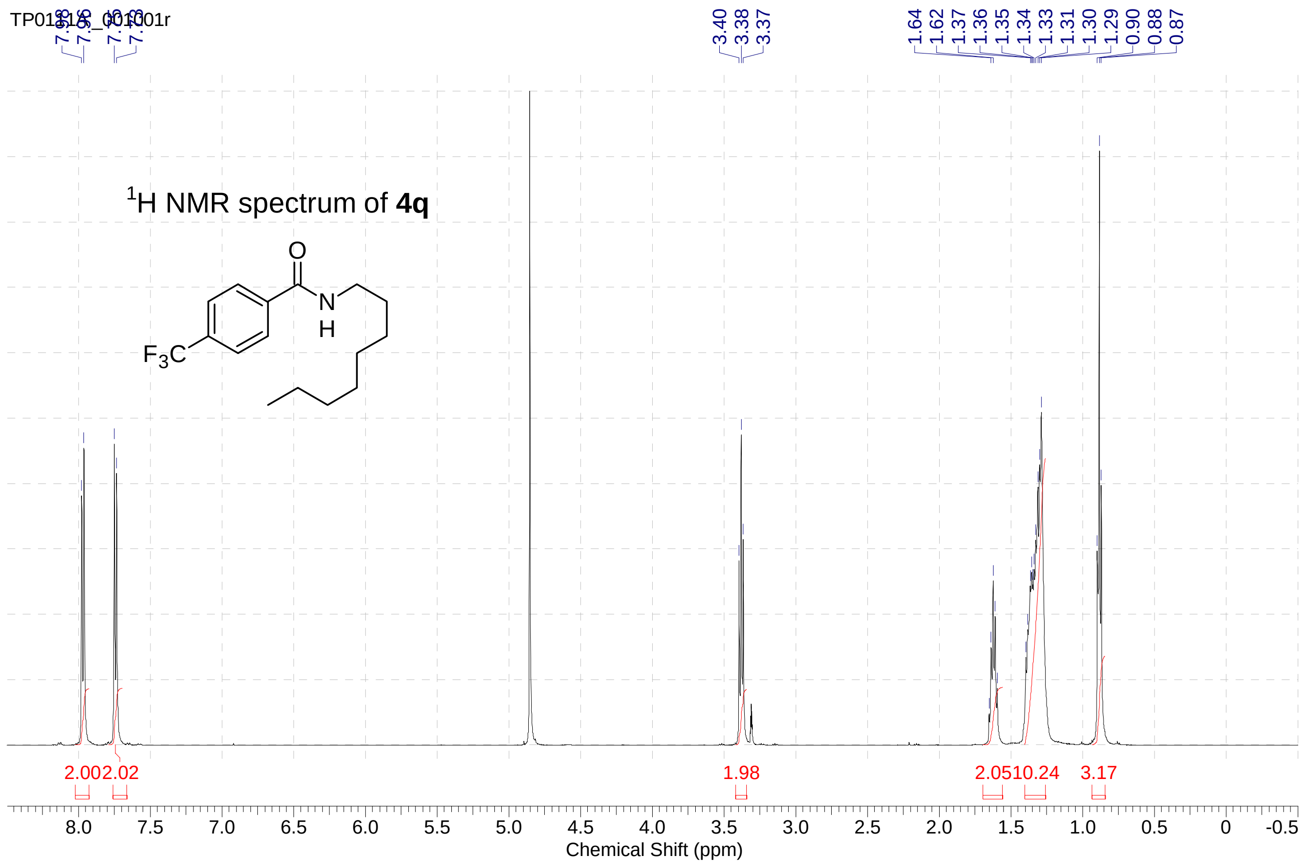
^{13}C NMR spectrum of **4m**


TP0121Bc_001001r
8.44
8.15
3.43
3.42
3.41
1.66
1.65
1.63
1.62
1.61
1.45
1.43
1.42
1.41
1.00
0.98
0.97
1H NMR spectrum of 4o
F3C
O
N
H
CF3
1.92
0.98
2.00
2.00
2.01
2.96
Chemical Shift (ppm)

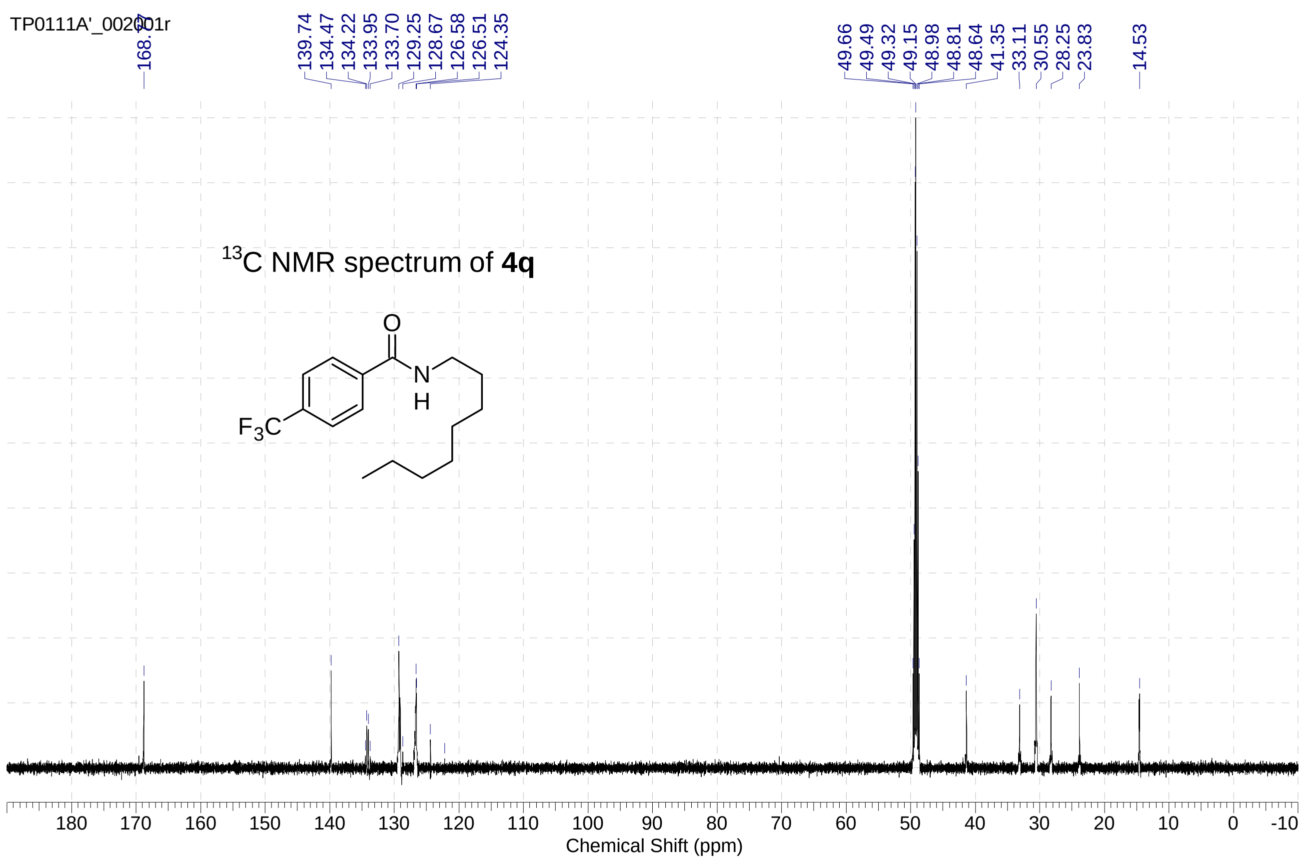

TP0121Bc_002001r
166.63
138.41
133.62
133.35
133.08
132.82
129.11
127.99
126.00
125.82
123.66
121.50
49.66
49.49
49.32
49.15
48.98
48.81
48.64
41.22
32.58
21.36
14.26
13C NMR spectrum of 4o
F3C
O
N
H
CF3
Chemical Shift (ppm)


TP0105Ac_001001
7.80
7.77
7.75
7.31
7.29
7.28
7.27
7.25
7.21
7.20
3.63
3.62
3.60
2.95
2.93
2.92
1H NMR spectrum of 4p
O
N
H
F3C
1.95
1.99
4.07
1.01
2.00
2.03
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

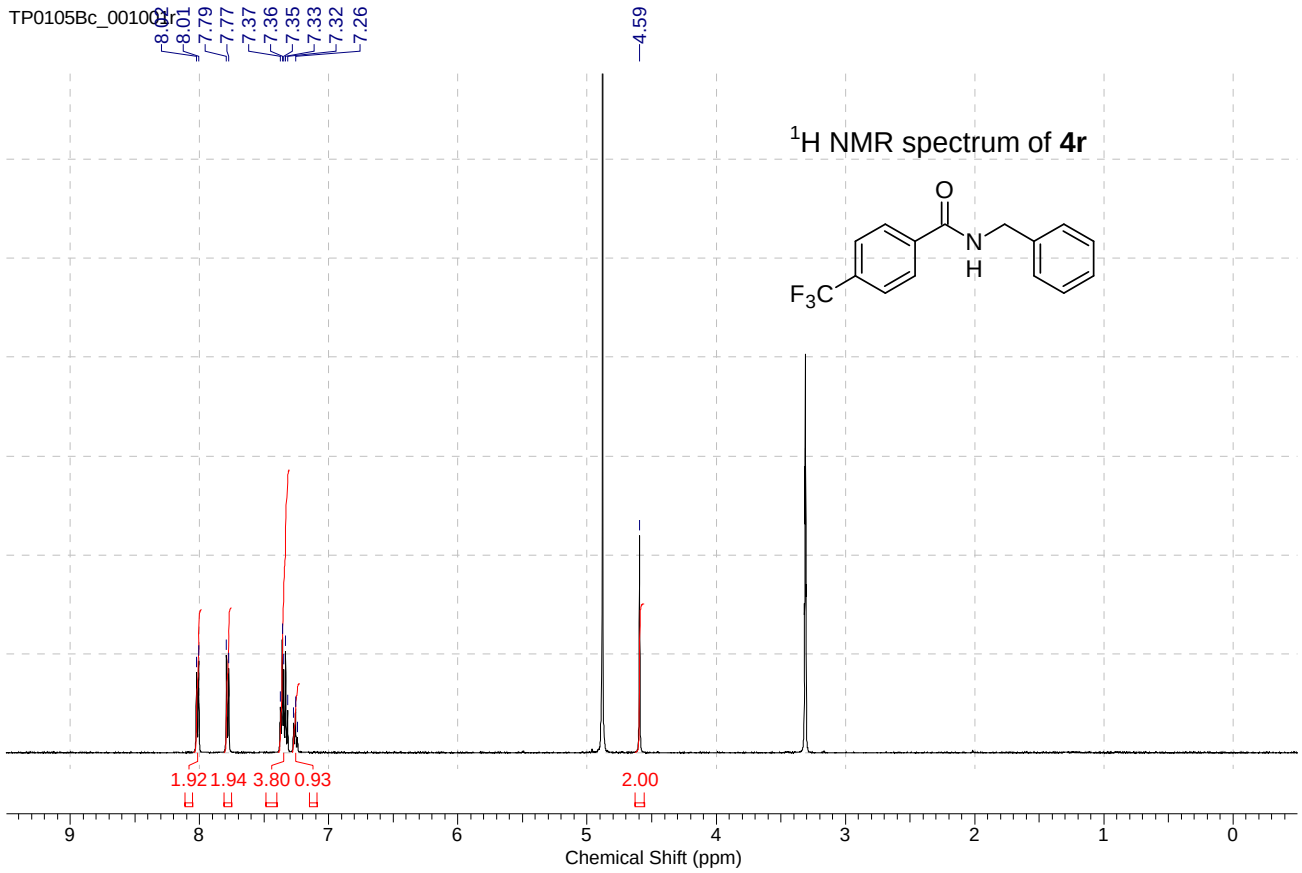

TP0105Ac_002001r.esp
168.80
140.65
139.71
134.54
134.28
134.02
130.05
129.69
129.15
127.58
126.65
124.39
122.23
49.66
49.50
49.32
49.15
48.98
48.81
48.64
42.93
36.61
13C NMR spectrum of 4p
O
N
H
F3C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

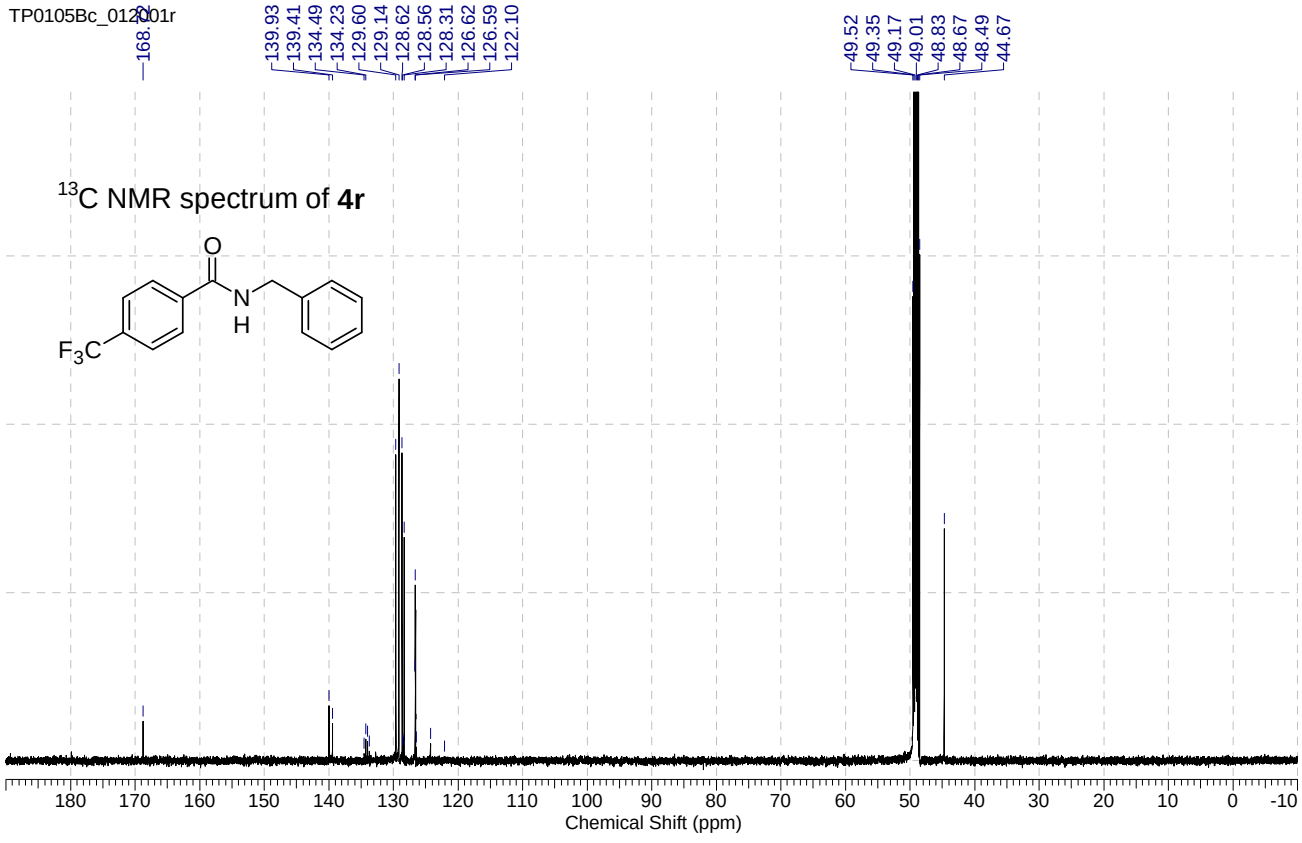


TP0111A'_001001r
3.40 3.38 3.37
1.64 1.62 1.37 1.36 1.35 1.34 1.33 1.31 1.30 1.29 0.90 0.88 0.87
1H NMR spectrum of 4q
O
N
H
F3C
2.00 2.02
1.98
2.05 10.24
3.17
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)



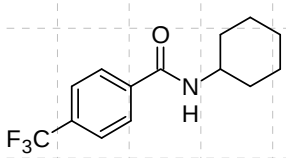
TP0111A'_002001r
139.74 134.47 134.22 133.95 133.70 129.25 128.67 126.58 126.51 124.35
49.66 49.49 49.32 49.15 48.98 48.81 48.64 41.35 33.11 30.55 28.25 23.83
14.53
13C NMR spectrum of 4q
O
N
H
F3C
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TP0105Bc_001001r
8.03
8.01
7.79
7.77
7.37
7.36
7.35
7.33
7.32
7.26
4.59
1H NMR spectrum of 4r
O
N
H
F3C
1.92
1.94
3.80
0.93
2.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

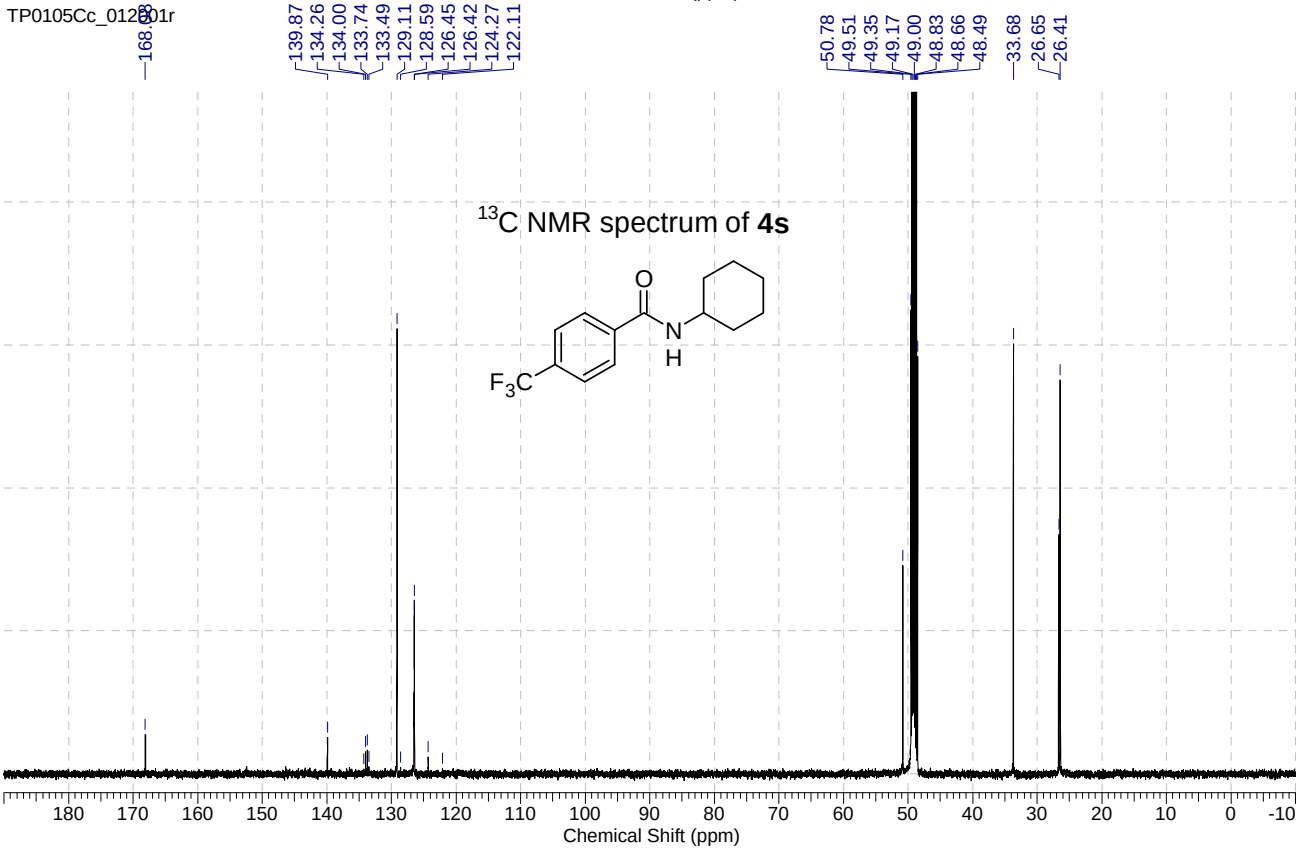

TP0105Bc_012001r
168.
139.93
139.41
134.49
134.23
129.60
129.14
128.62
128.56
128.31
126.62
126.59
122.10
49.52
49.35
49.17
49.01
48.83
48.67
48.49
44.67
13C NMR spectrum of 4r
O
N
H
F3C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

TP0105Cc_001001r

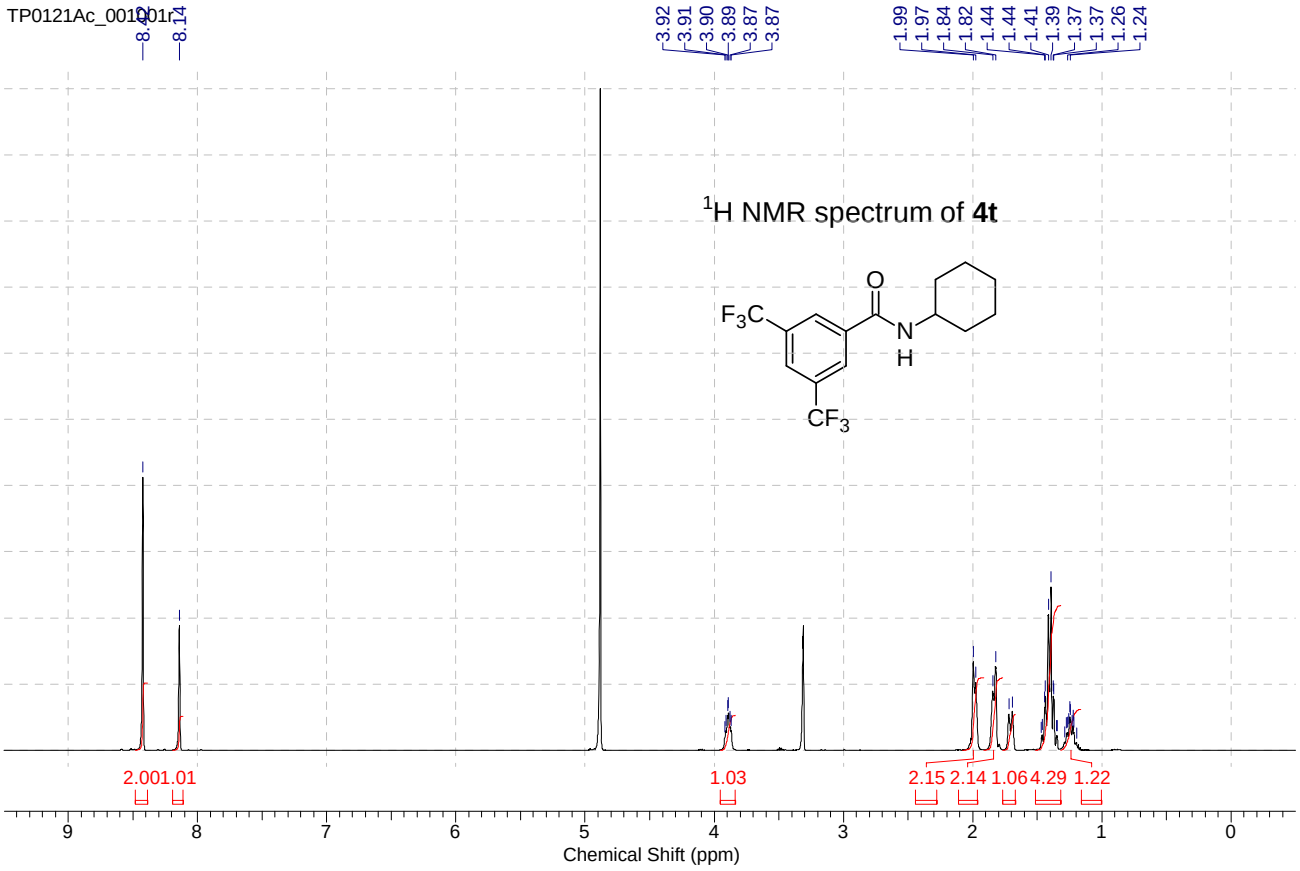
^{1}H NMR spectrum of **4s**

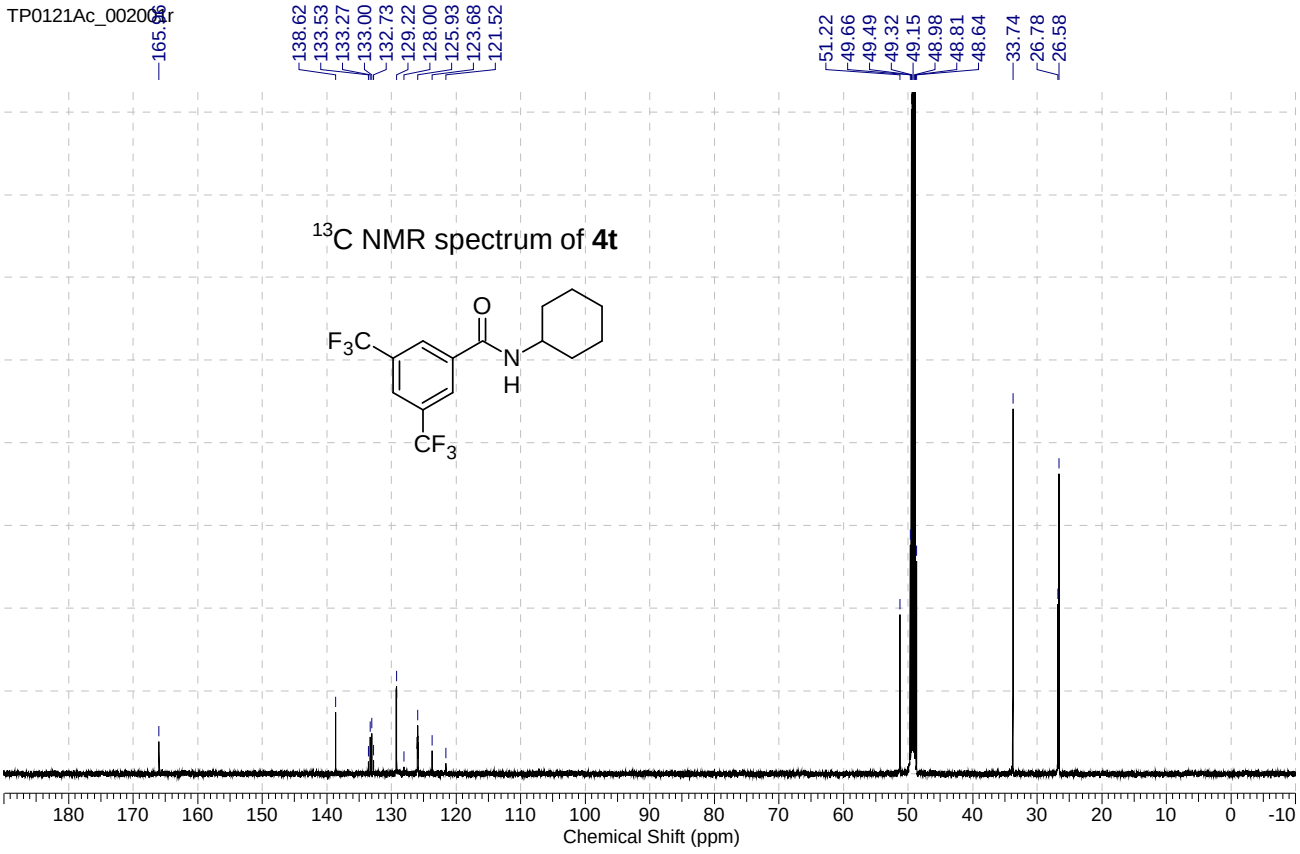


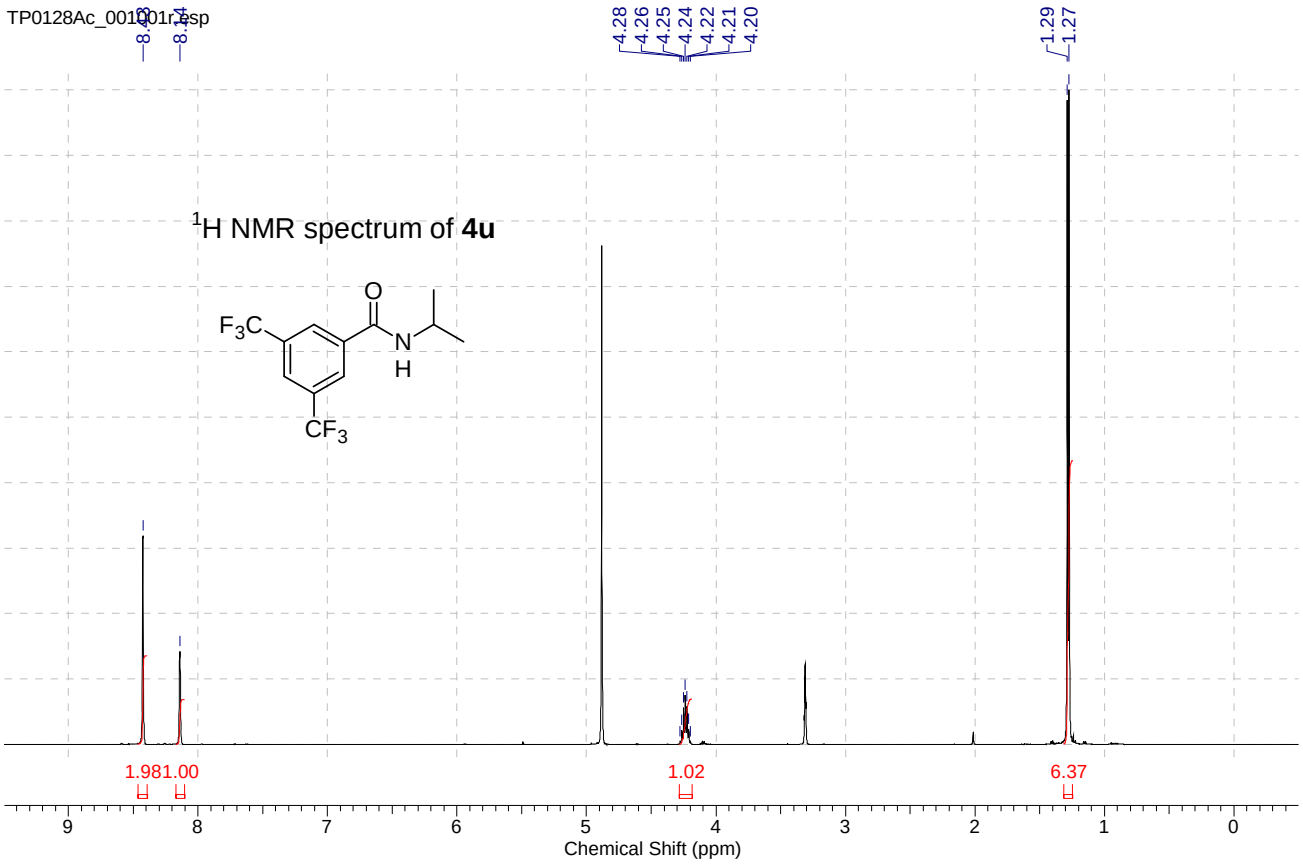
TP0105Cc_012001r



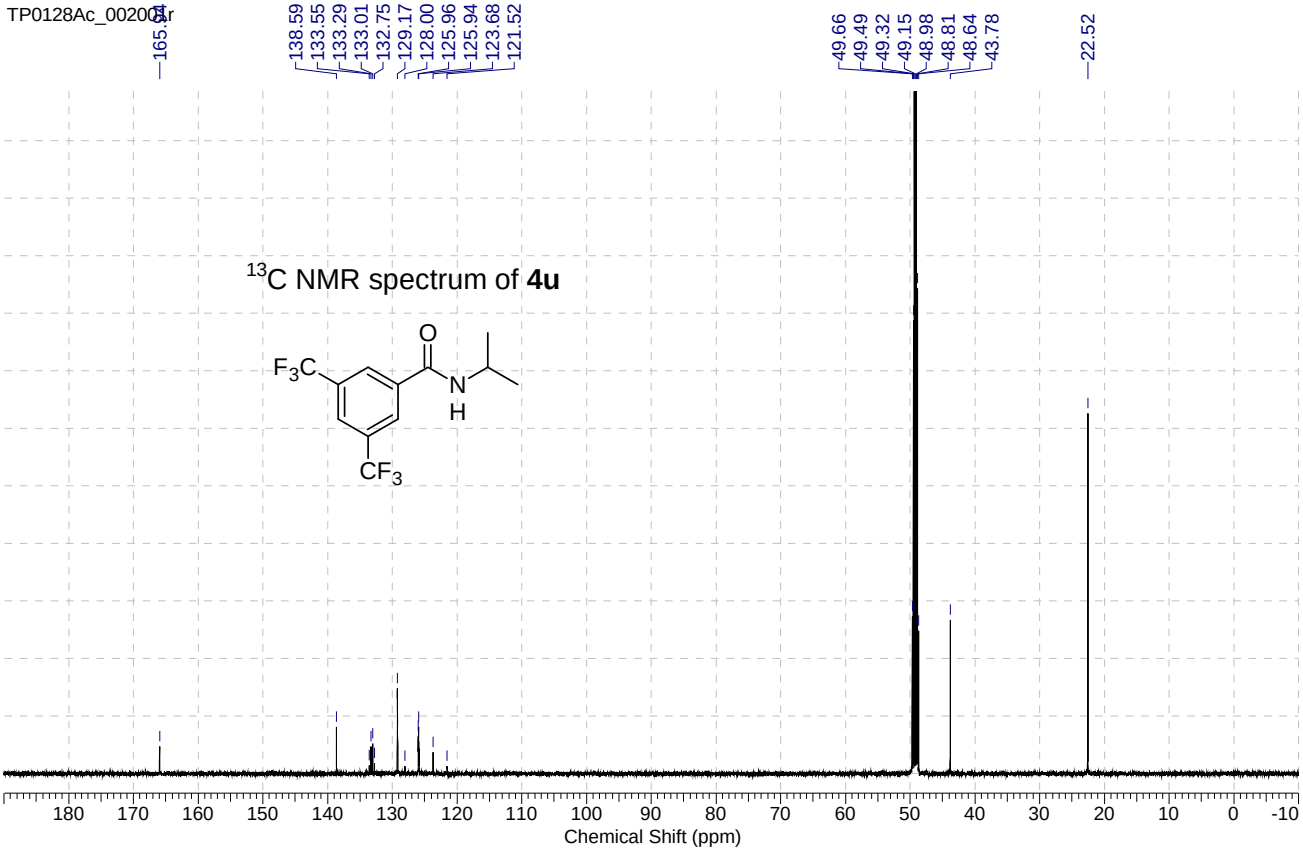
^{13}C NMR spectrum of **4s**


TP0121Ac_001001r
8.44
8.14
3.92
3.91
3.90
3.89
3.87
3.87
1.99
1.97
1.84
1.82
1.44
1.44
1.41
1.39
1.37
1.37
1.26
1.24
^{1}H NMR spectrum of **4t**
O
F_3C
N
H
CF_3
2.00
1.01
1.03
2.15
2.14
1.06
4.29
1.22
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

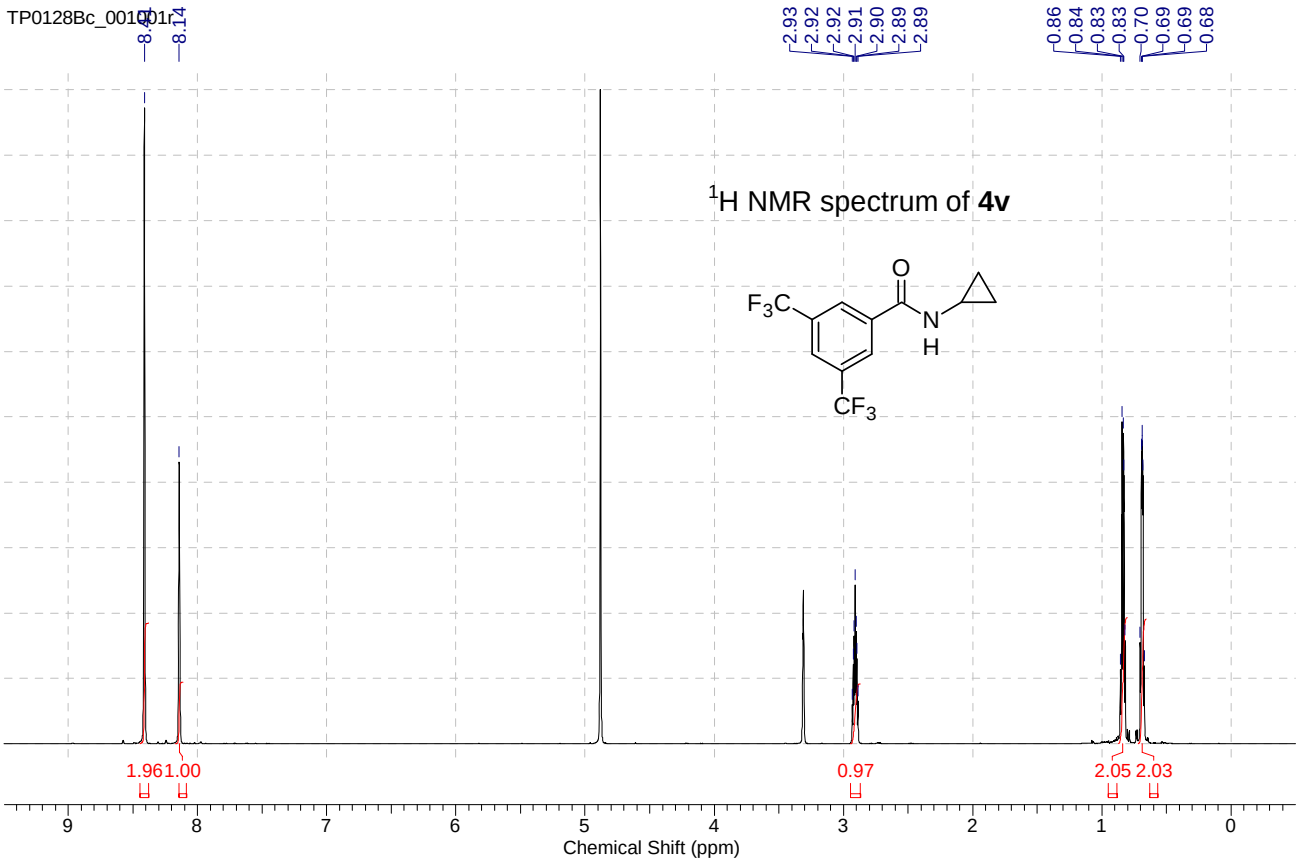

TP0121Ac_002001r
165.18
138.62
133.53
133.27
133.00
132.73
129.22
128.00
125.93
123.68
121.52
51.22
49.66
49.49
49.32
49.15
48.98
48.81
48.64
33.74
26.78
26.58
^{13}C NMR spectrum of **4t**
O
F_3C
N
H
CF_3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

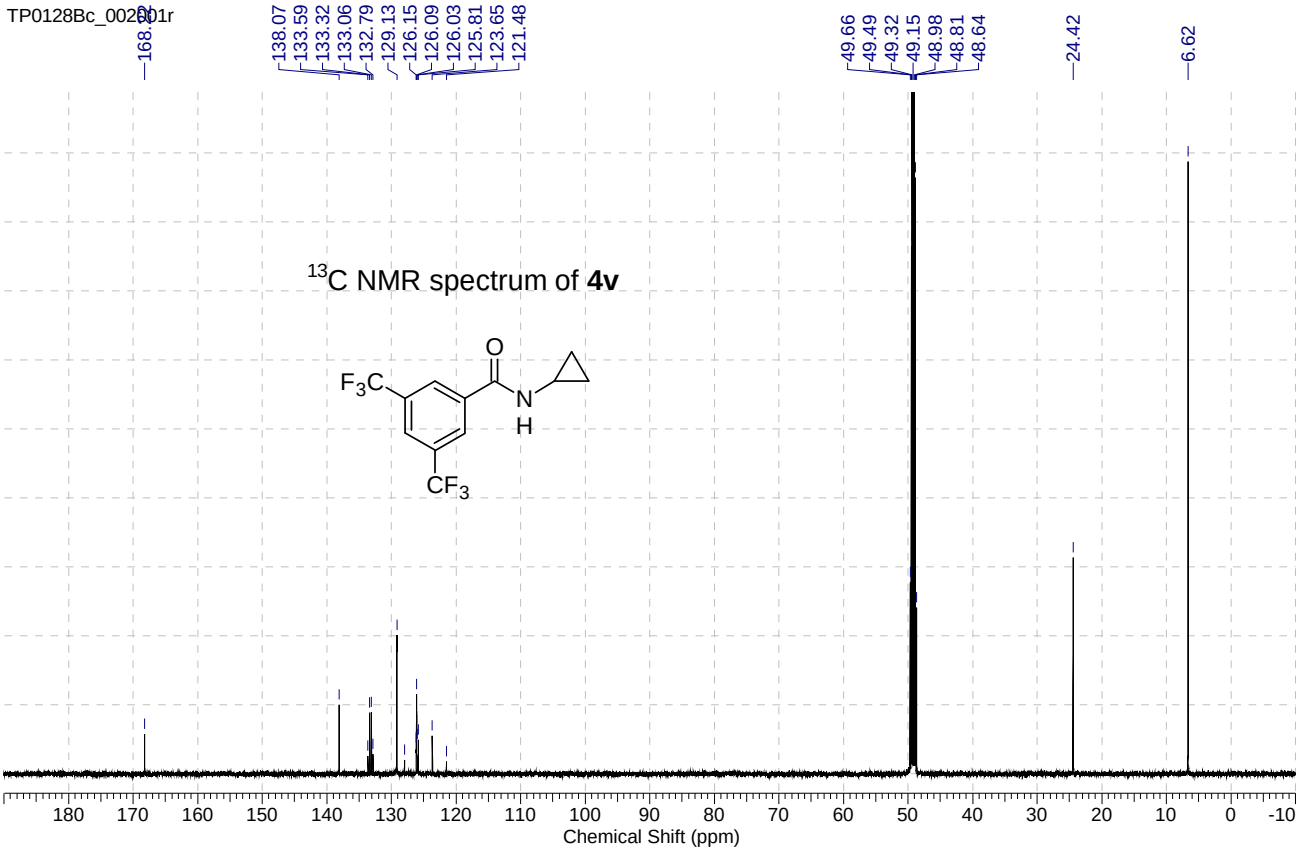


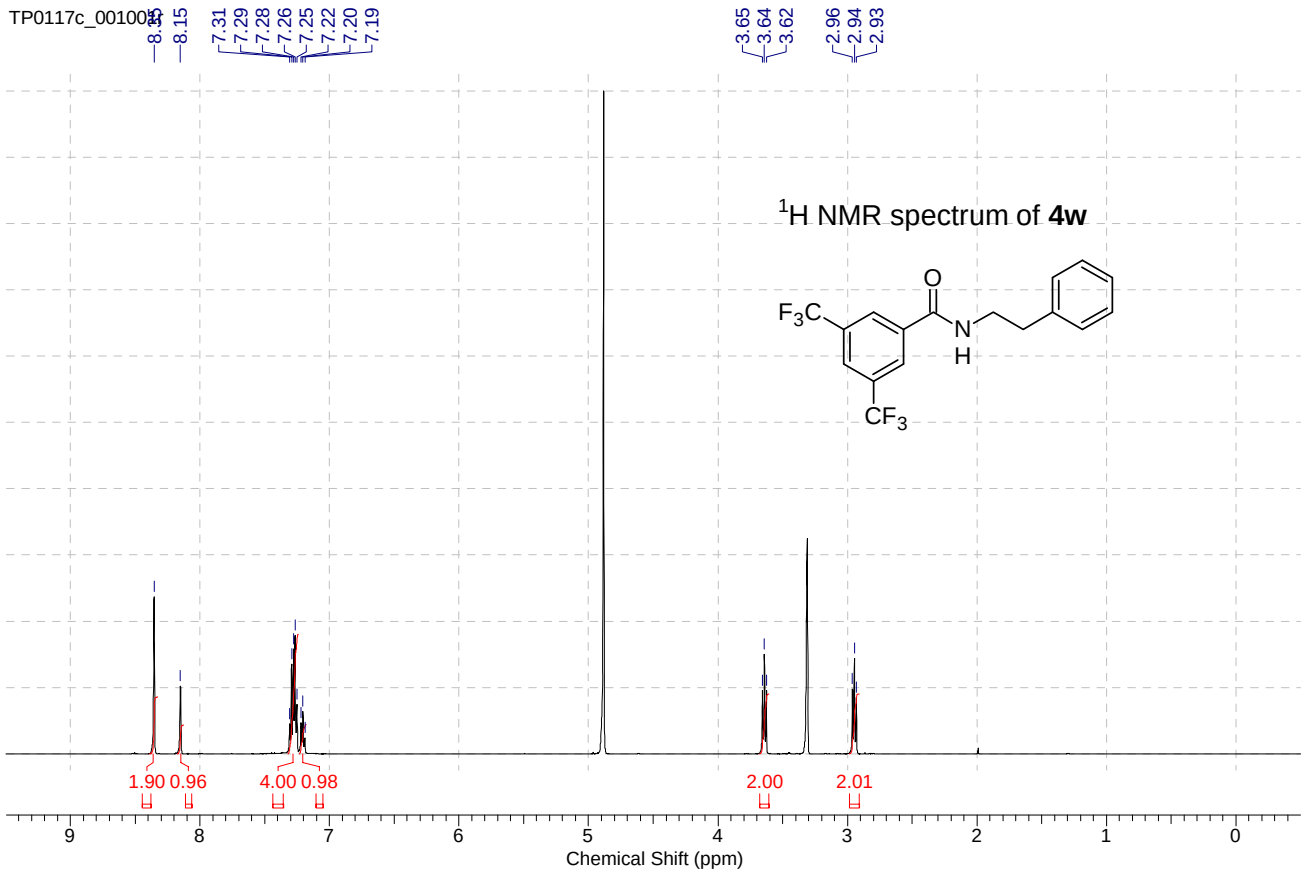
^{1}H NMR spectrum of **4u**

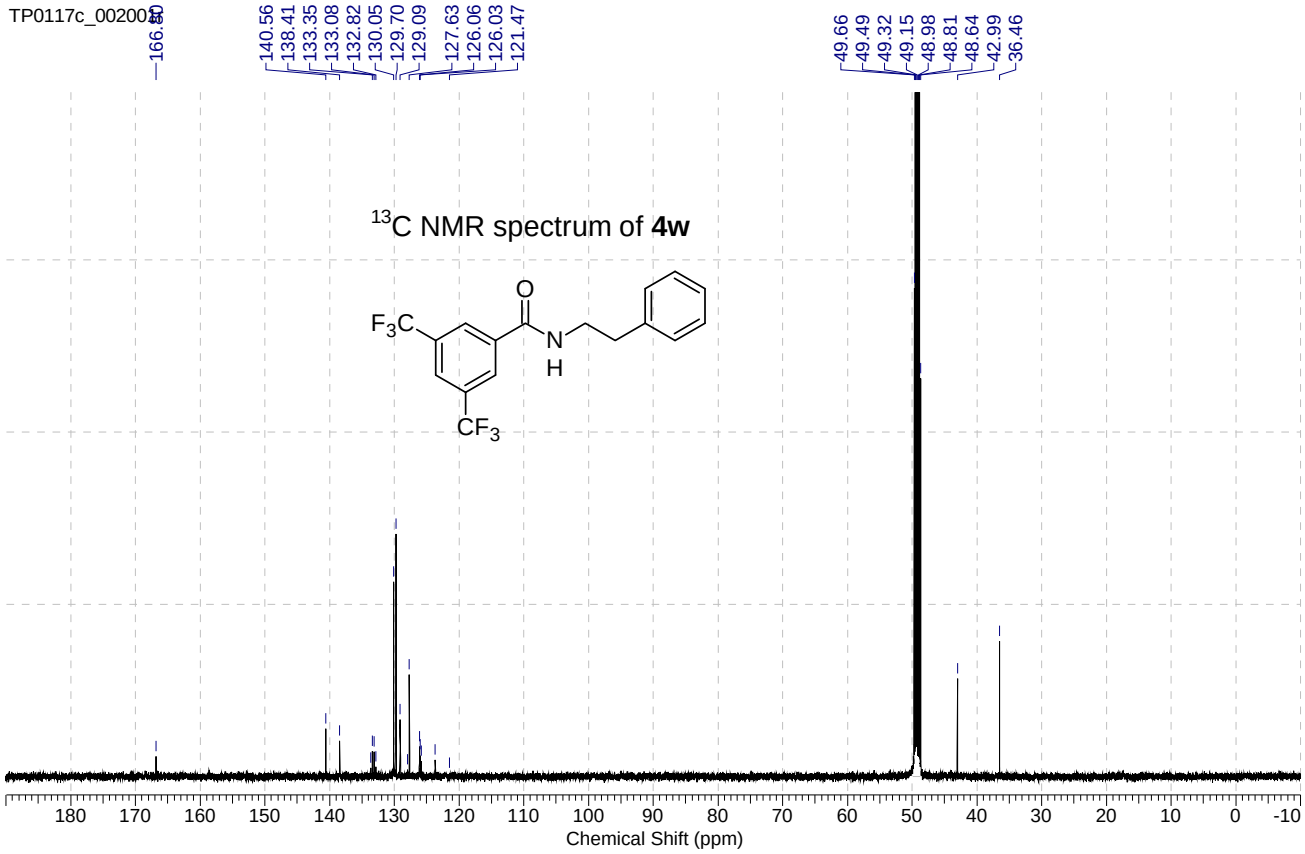


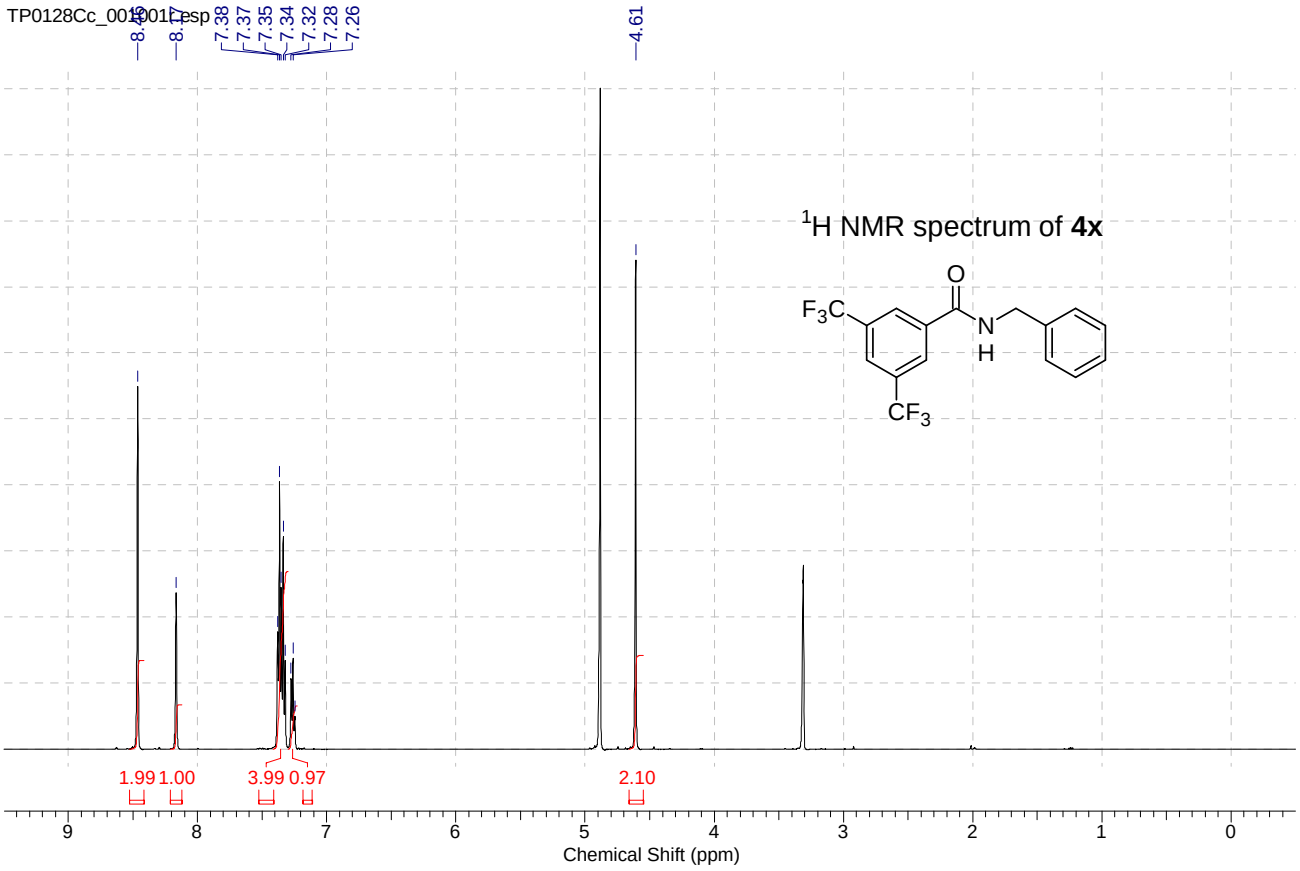
^{13}C NMR spectrum of **4u**


TP0128Bc_001_01r
8.14
2.93
2.92
2.92
2.91
2.90
2.89
2.89
0.86
0.84
0.83
0.83
0.70
0.69
0.69
0.68
^{1}H NMR spectrum of **4v**
O
F_3C
N
H
CF_3
1.96
1.00
0.97
2.05
2.03
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

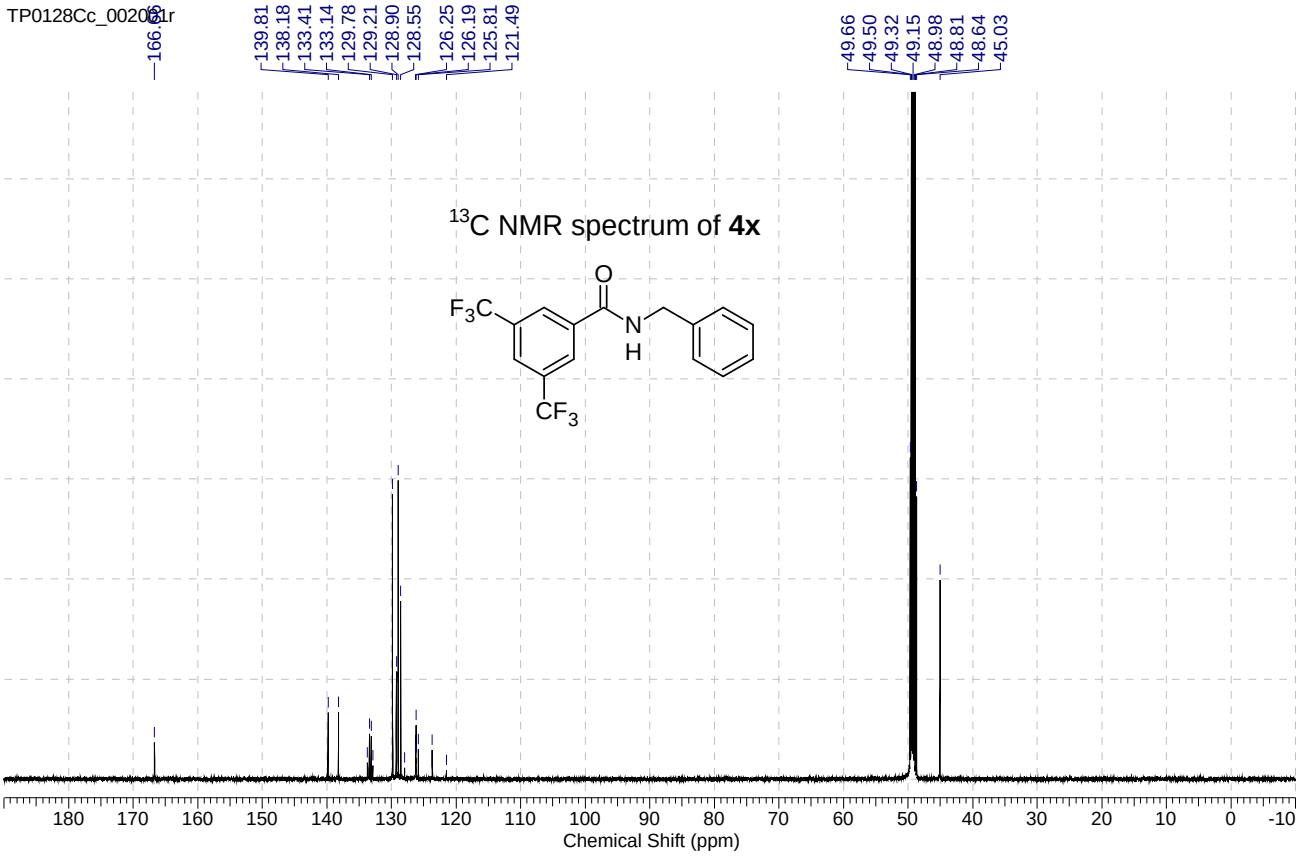

TP0128Bc_002_01r
168.80
138.07
133.59
133.32
133.06
132.79
129.13
126.15
126.09
126.03
125.81
123.65
121.48
49.66
49.49
49.32
49.15
48.98
48.81
48.64
24.42
6.62
^{13}C NMR spectrum of **4v**
O
F_3C
N
H
CF_3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


TP0117c_001004
8.17
8.15
7.31
7.29
7.28
7.26
7.25
7.22
7.20
7.19
3.65
3.64
3.62
2.96
2.94
2.93
1H NMR spectrum of 4w
O
F3C
N
H
CF3
1.90
0.96
4.00
0.98
2.00
2.01
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

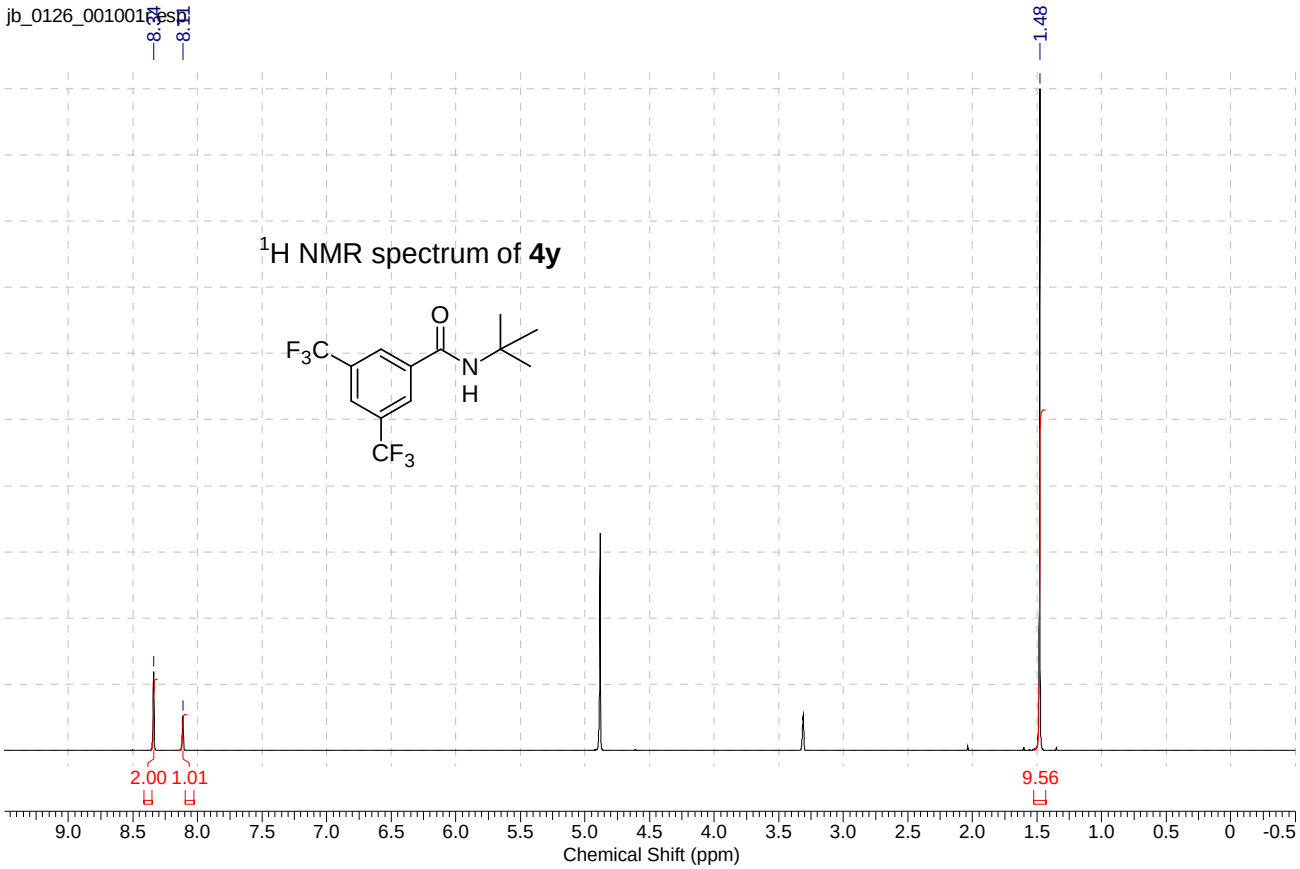

TP0117c_002004
166.80
140.56
138.41
133.35
133.08
132.82
130.05
129.70
129.09
127.63
126.06
126.03
121.47
49.66
49.49
49.32
49.15
48.98
48.81
48.64
42.99
36.46
13C NMR spectrum of 4w
O
F3C
N
H
CF3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

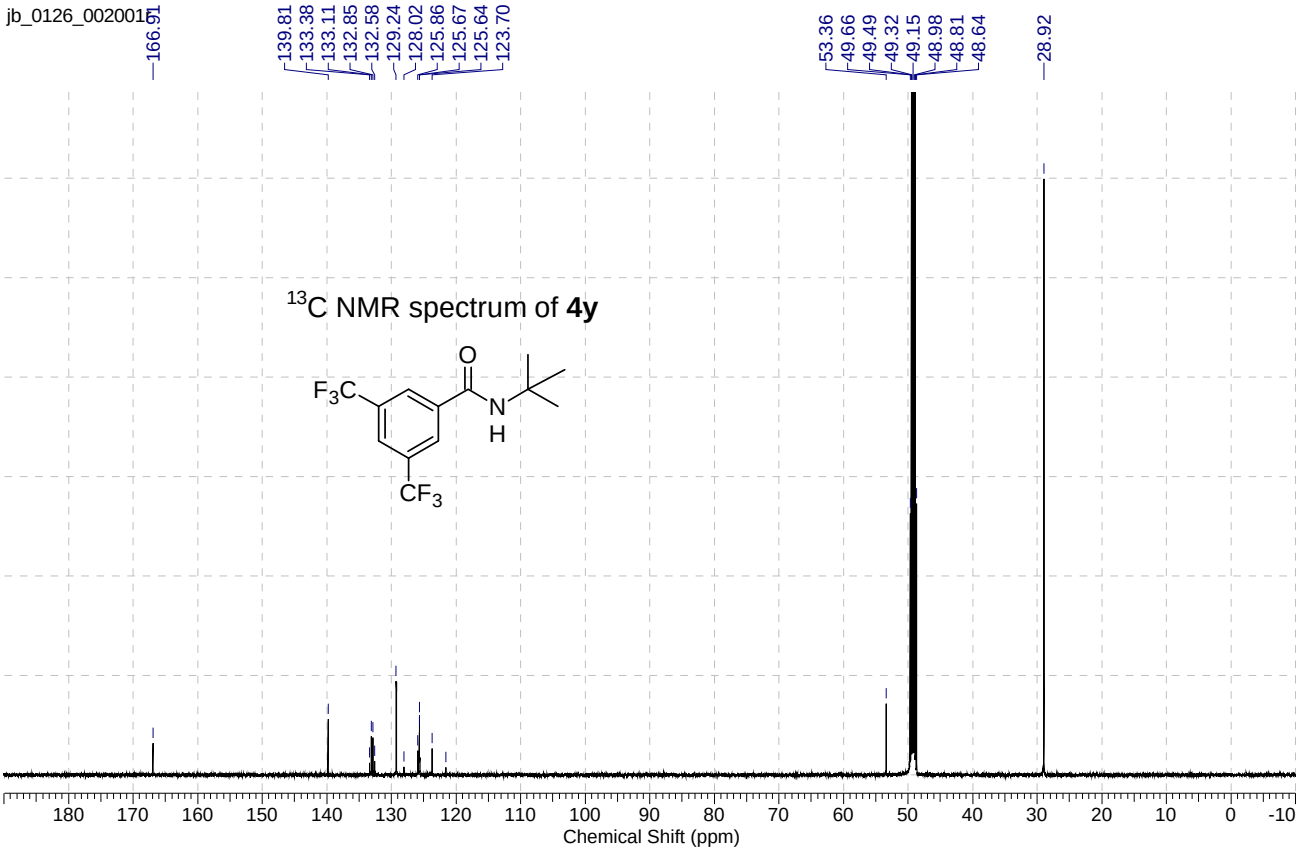


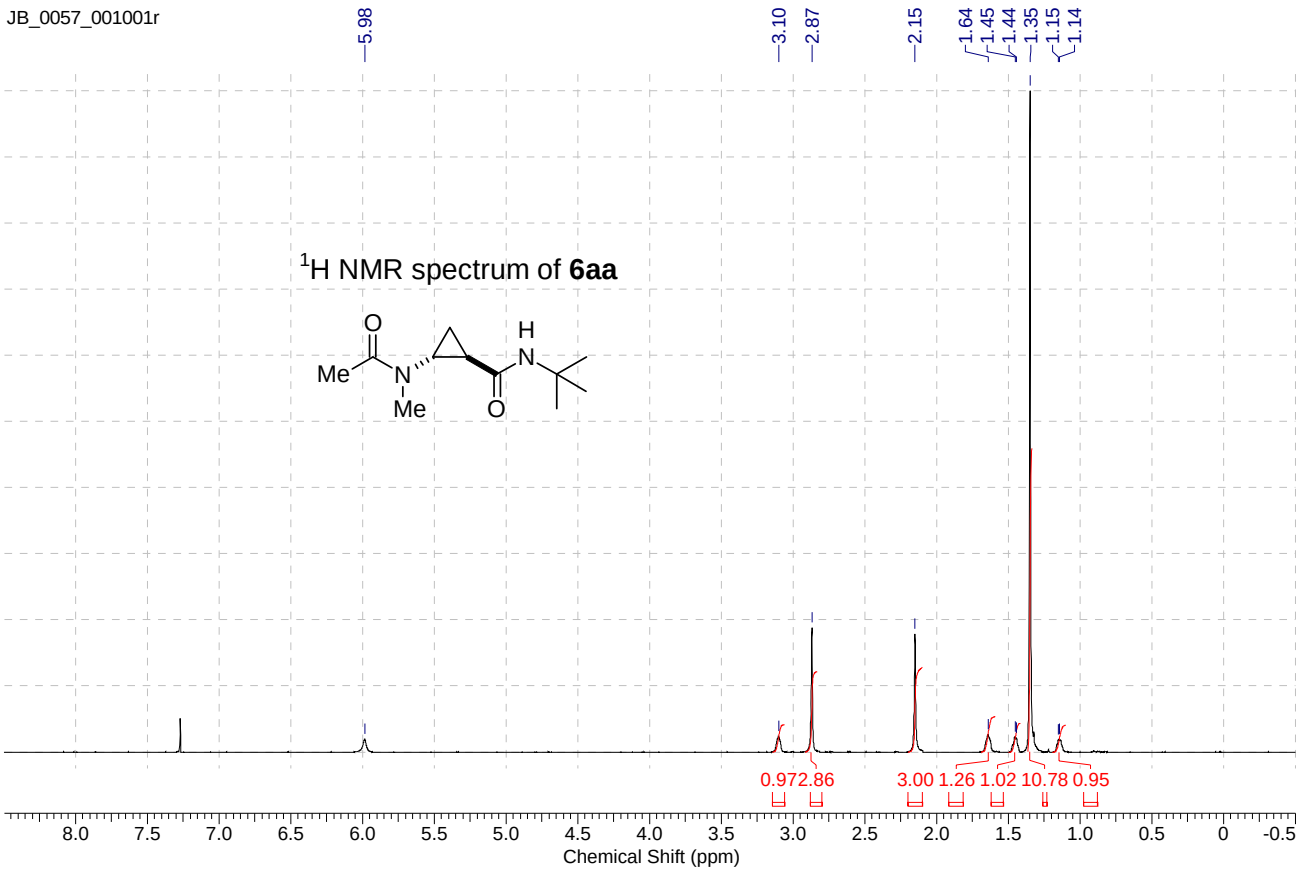
^{1}H NMR spectrum of **4x**



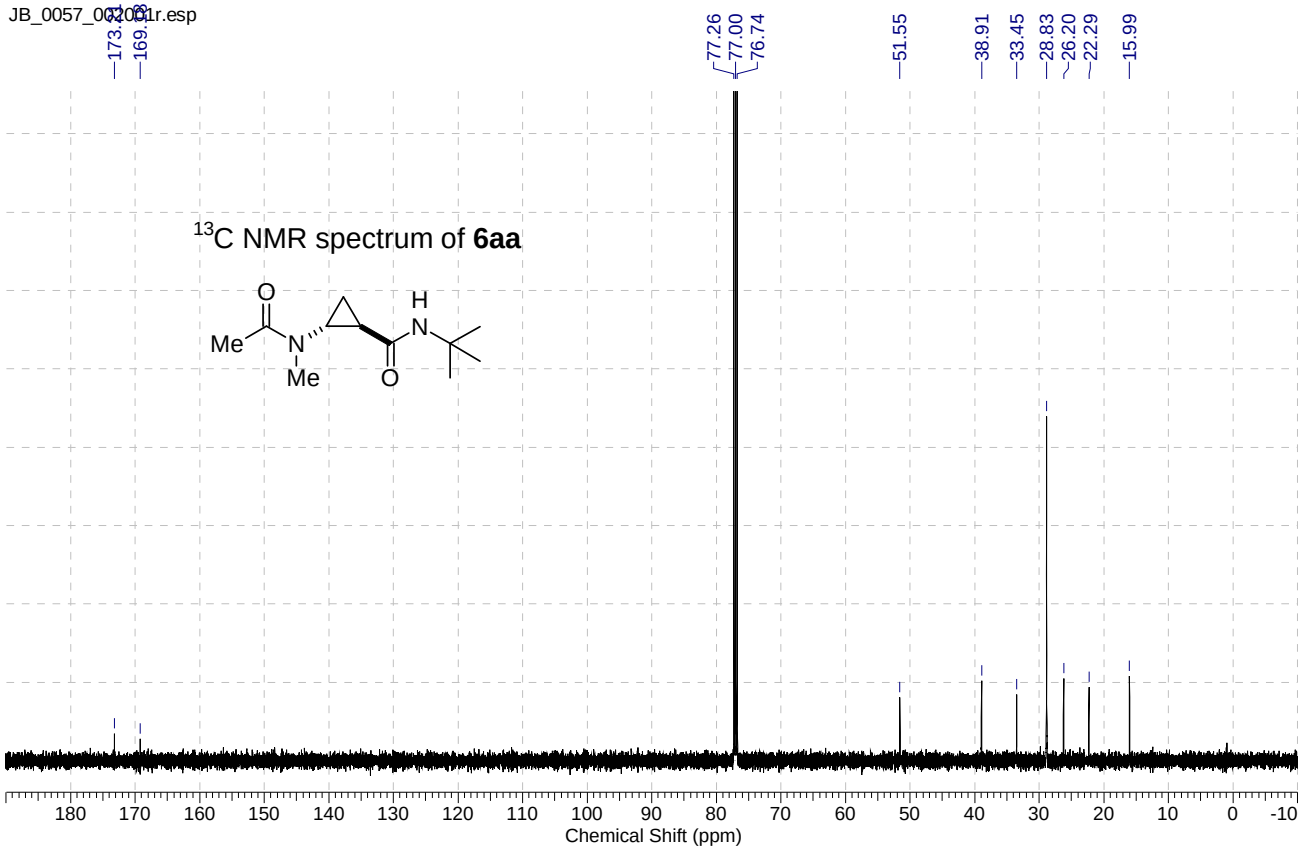
^{13}C NMR spectrum of **4x**


jb_0126_001001esp
8.24
8.11
1.48
^{1}H NMR spectrum of **4y**
O
F_3C
N
H
CF_3
2.00
1.01
9.56
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

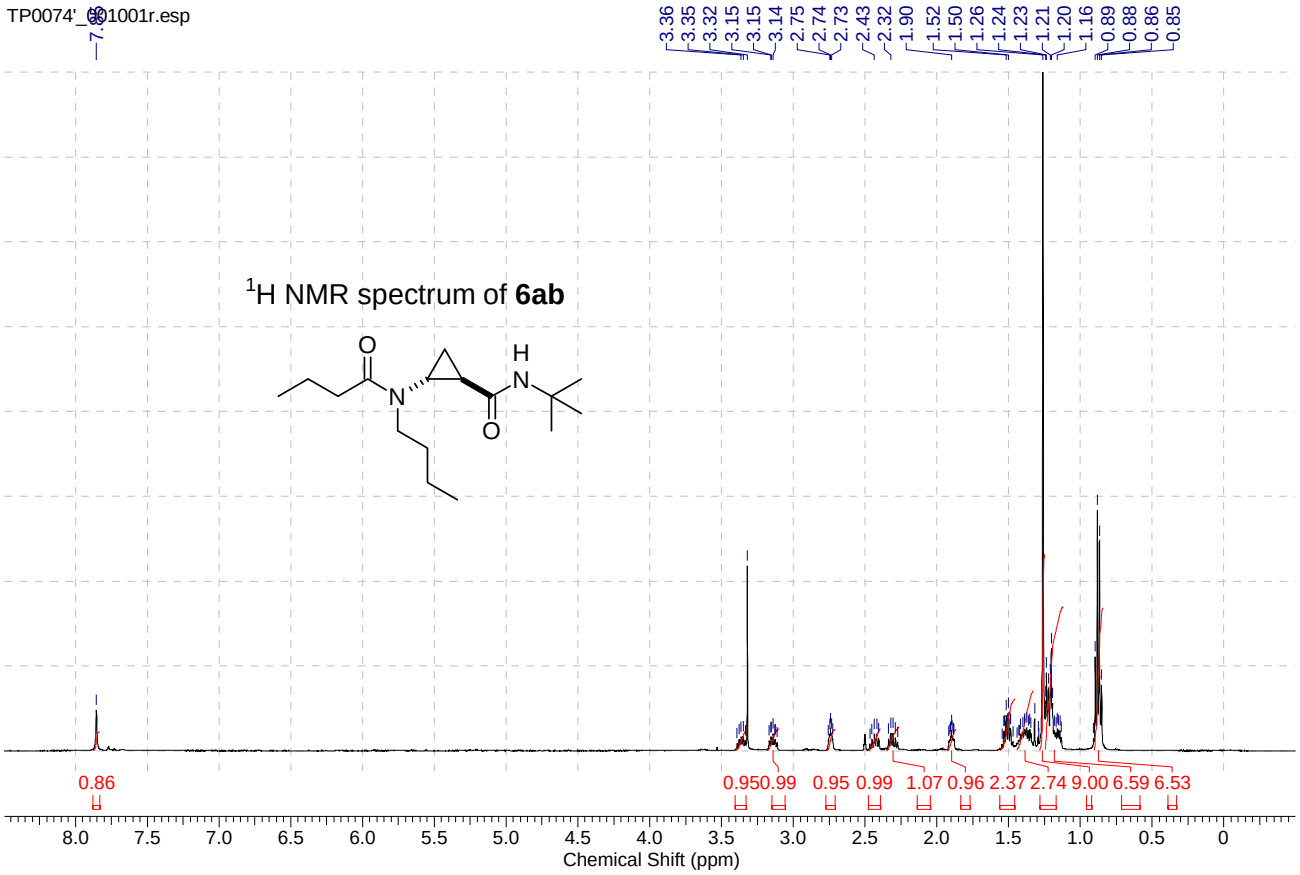

jb_0126_002001
166.91
139.81
133.38
133.11
132.85
132.58
129.24
128.02
125.86
125.67
125.64
123.70
53.36
49.66
49.49
49.32
49.15
48.98
48.81
48.64
28.92
^{13}C NMR spectrum of **4y**
O
F_3C
N
H
CF_3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

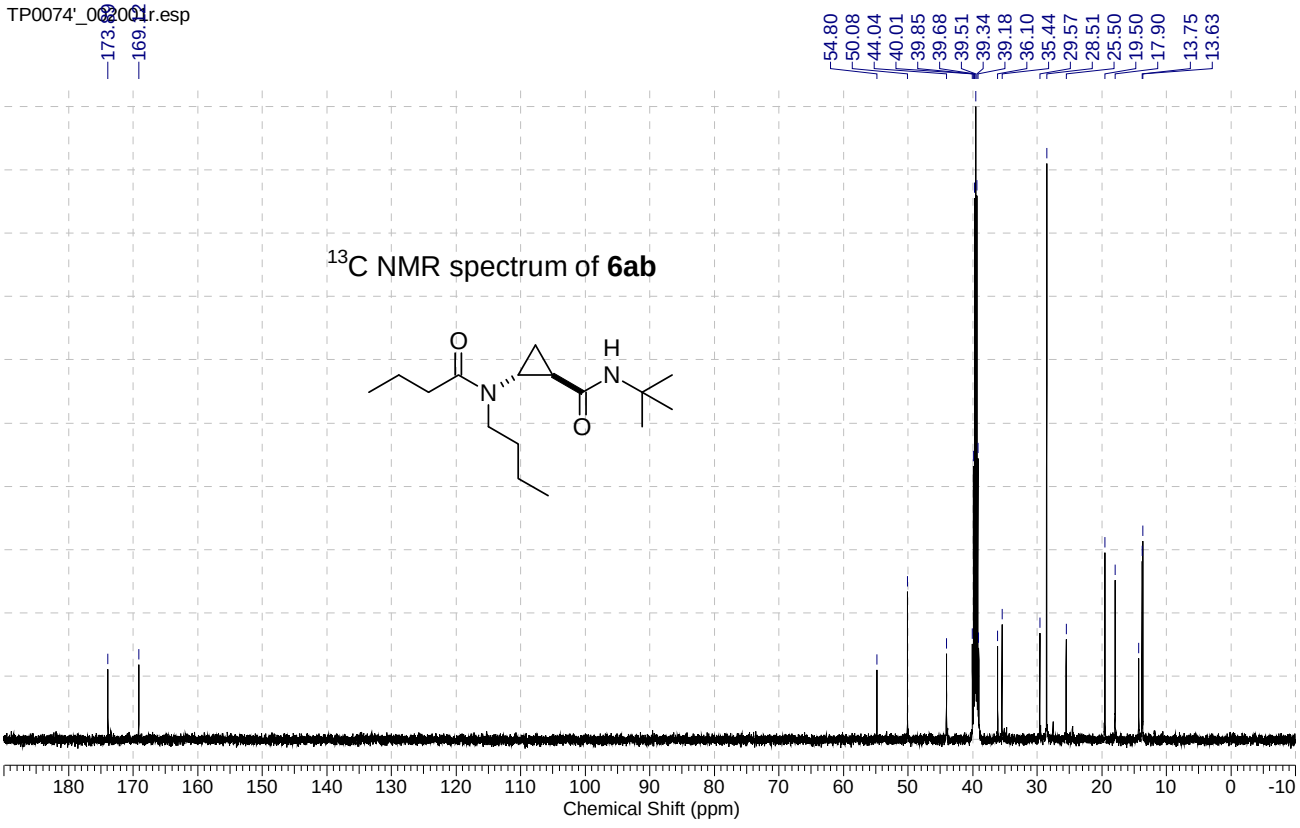


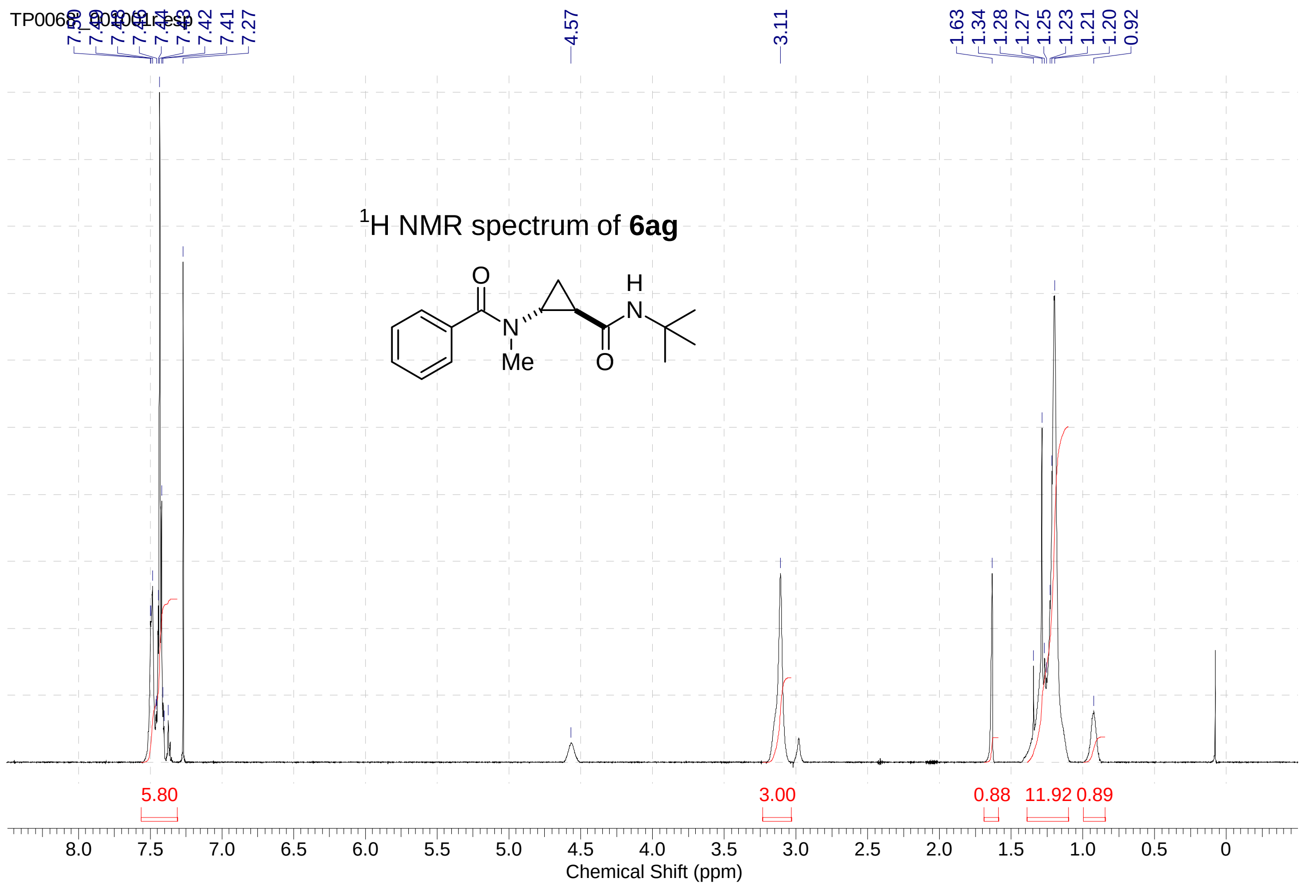
^{1}H NMR spectrum of **6aa**

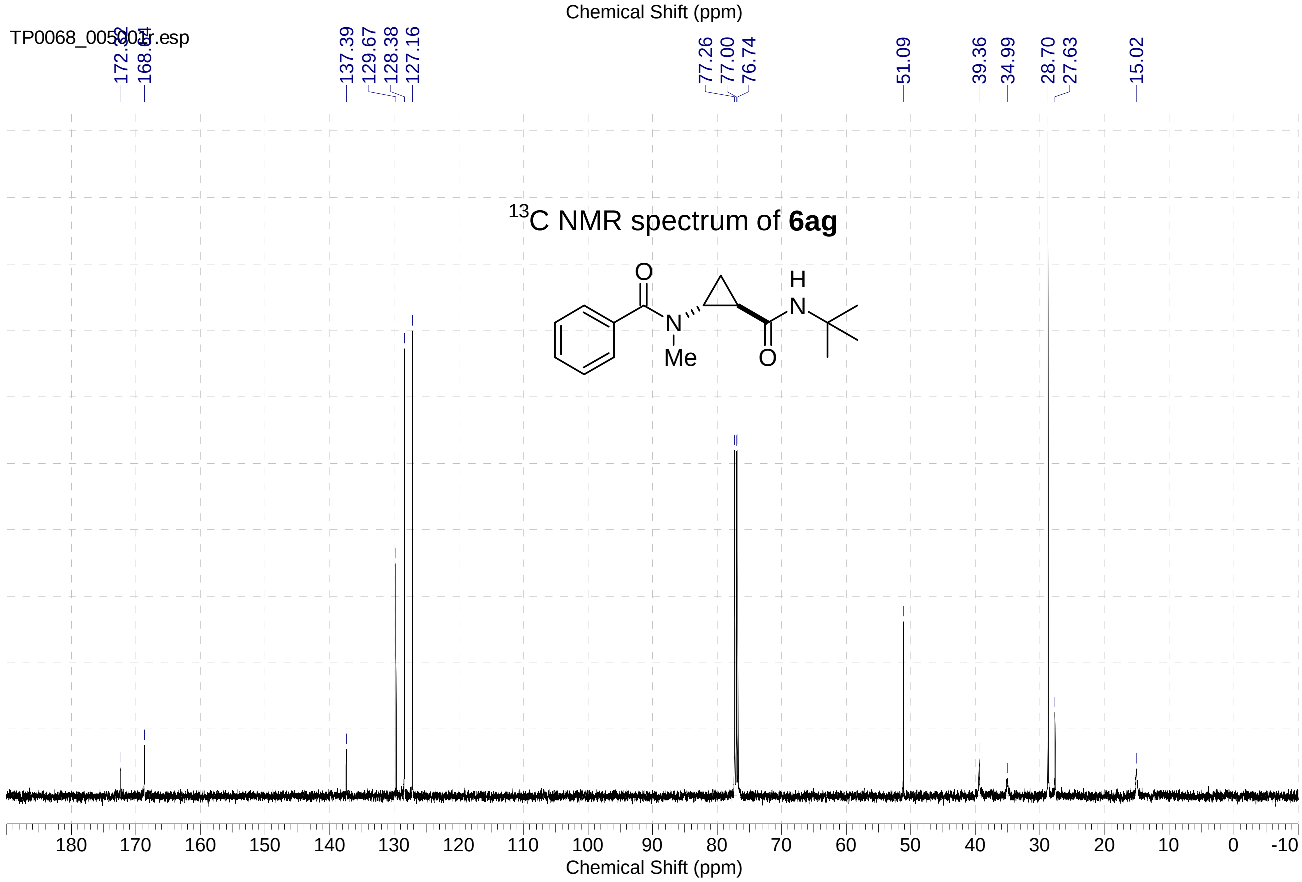


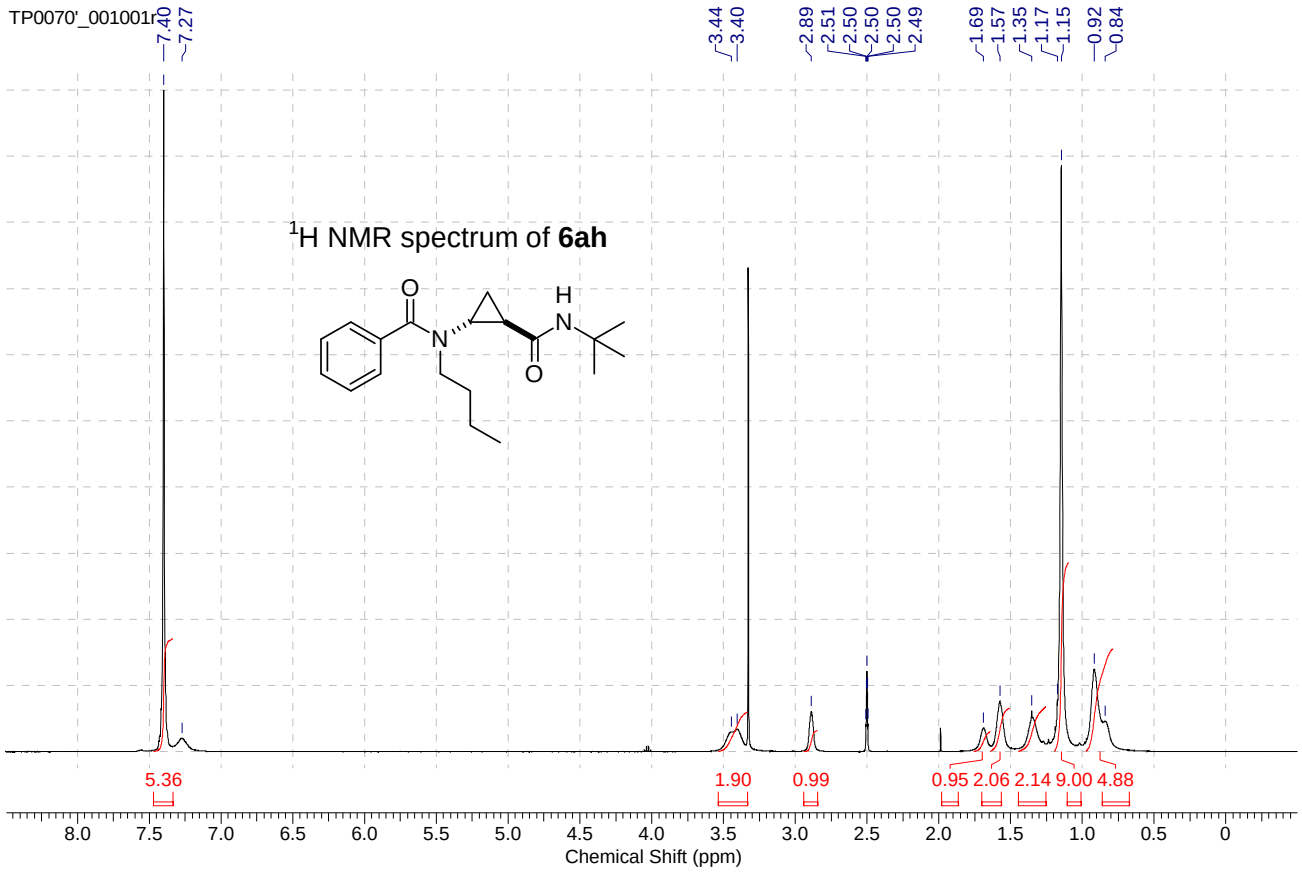
^{13}C NMR spectrum of **6aa**


TP0074'_001001r.esp
3.36
3.35
3.32
3.15
3.15
3.14
2.75
2.74
2.73
2.43
2.32
1.90
1.52
1.50
1.26
1.24
1.23
1.21
1.20
1.16
0.89
0.88
0.86
0.85
^{1}H NMR spectrum of **6ab**
O
N
H
N
O
0.86
0.95 0.99 0.95 0.99 1.07 0.96 2.37 2.74 9.00 6.59 6.53
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

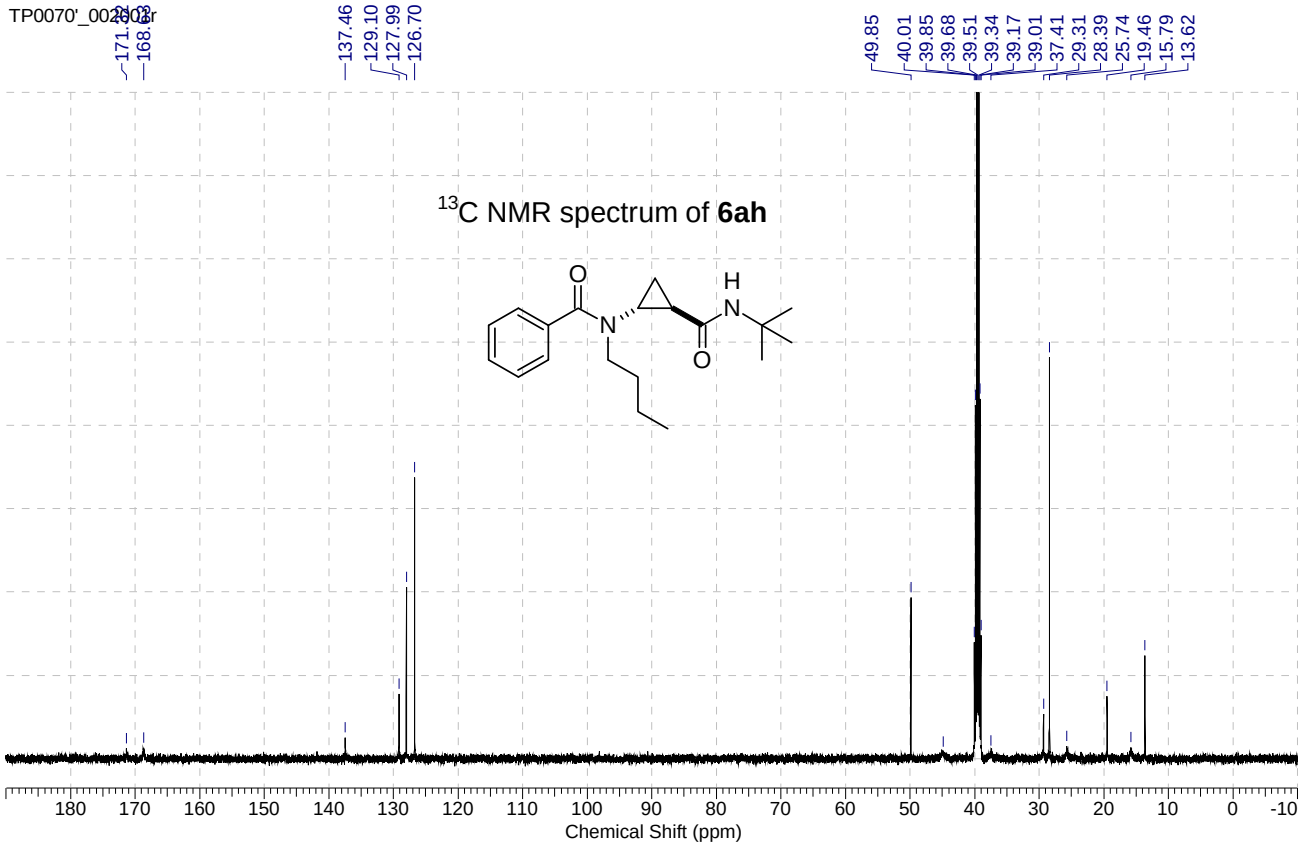

TP0074'_002001r.esp
54.80
50.08
44.04
40.01
39.85
39.68
39.51
39.34
39.18
36.10
35.44
29.57
28.51
25.50
19.50
17.90
13.75
13.63
^{13}C NMR spectrum of **6ab**
O
N
H
N
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TP0068_001001r.esp
7.42
7.41
7.27
4.57
3.11
1.63
1.34
1.28
1.27
1.25
1.23
1.21
1.20
0.92
^{1}H NMR spectrum of **6ag**
O
H
N
N
Me
O
5.80
3.00
0.88
11.92
0.89
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

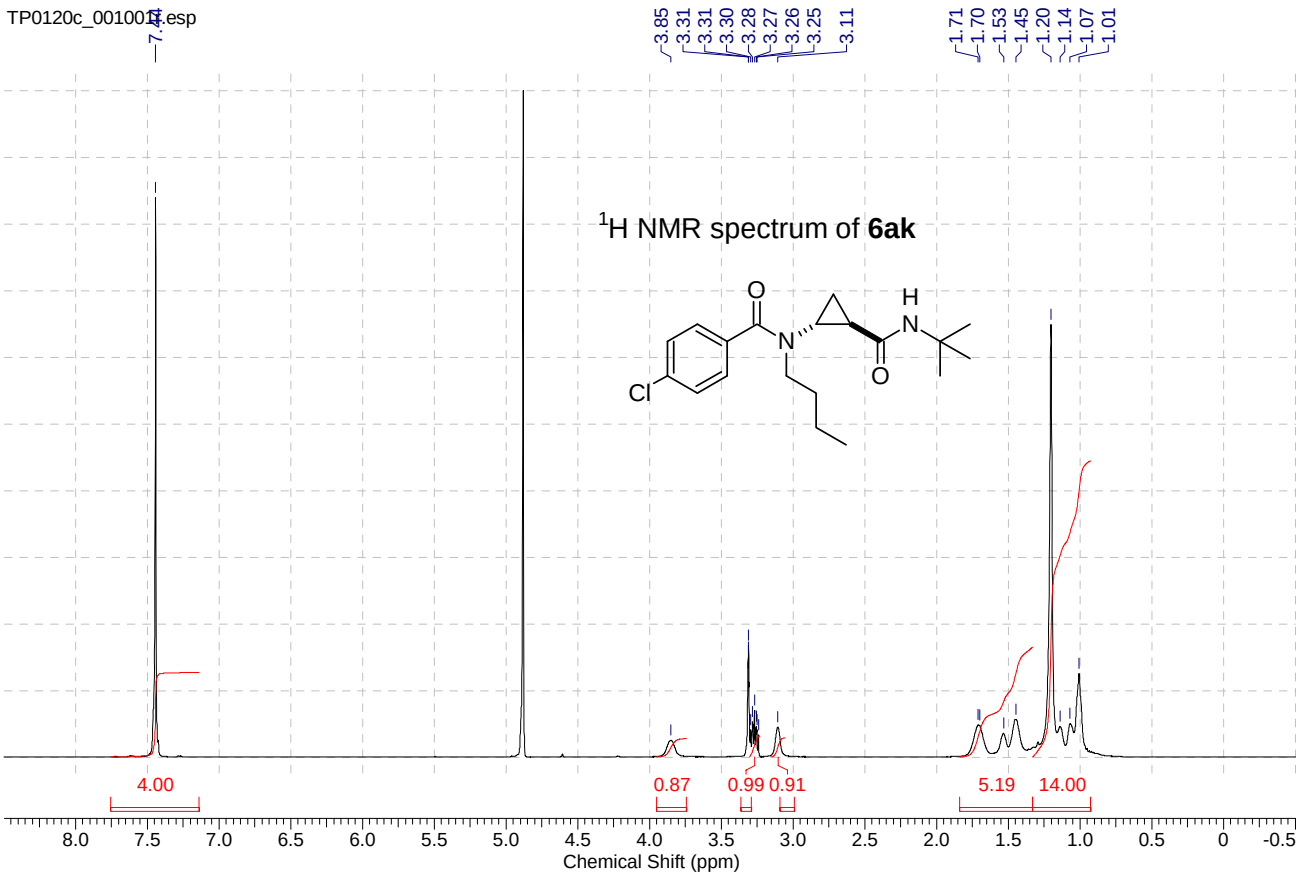

TP0068_005001r.esp
168.04
137.39
129.67
128.38
127.16
77.26
77.00
76.74
51.09
39.36
34.99
28.70
27.63
15.02
^{13}C NMR spectrum of **6ag**
O
H
N
N
Me
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

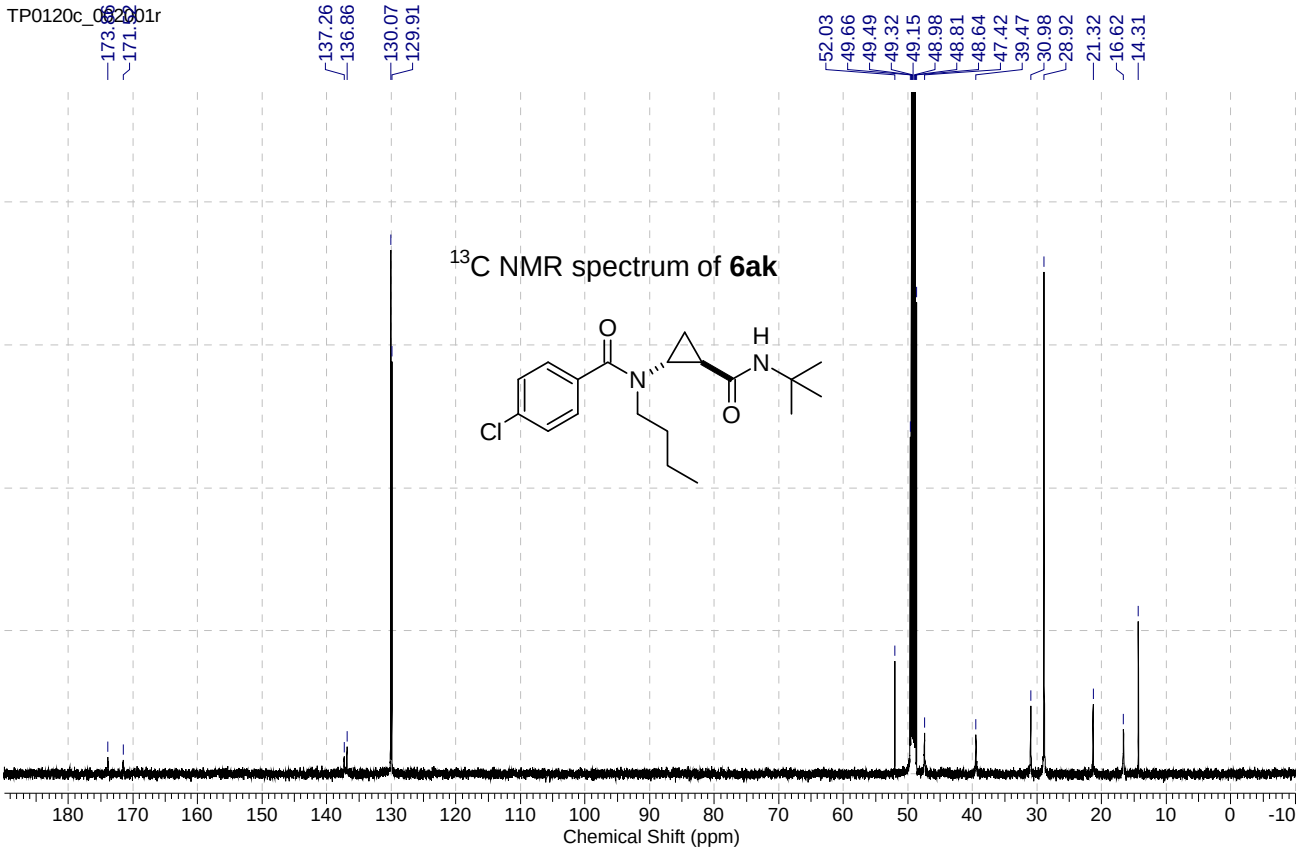


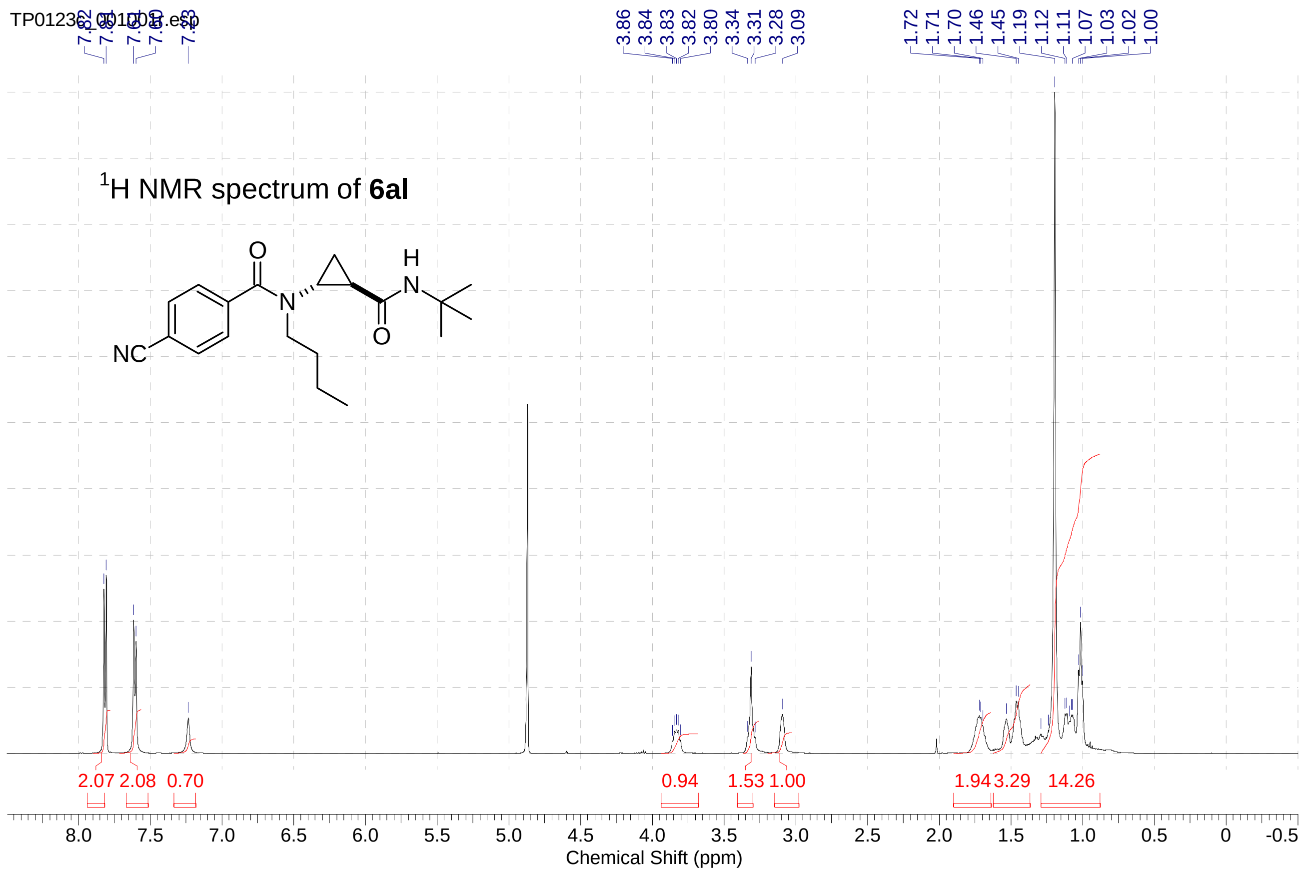
^{1}H NMR spectrum of **6ah**



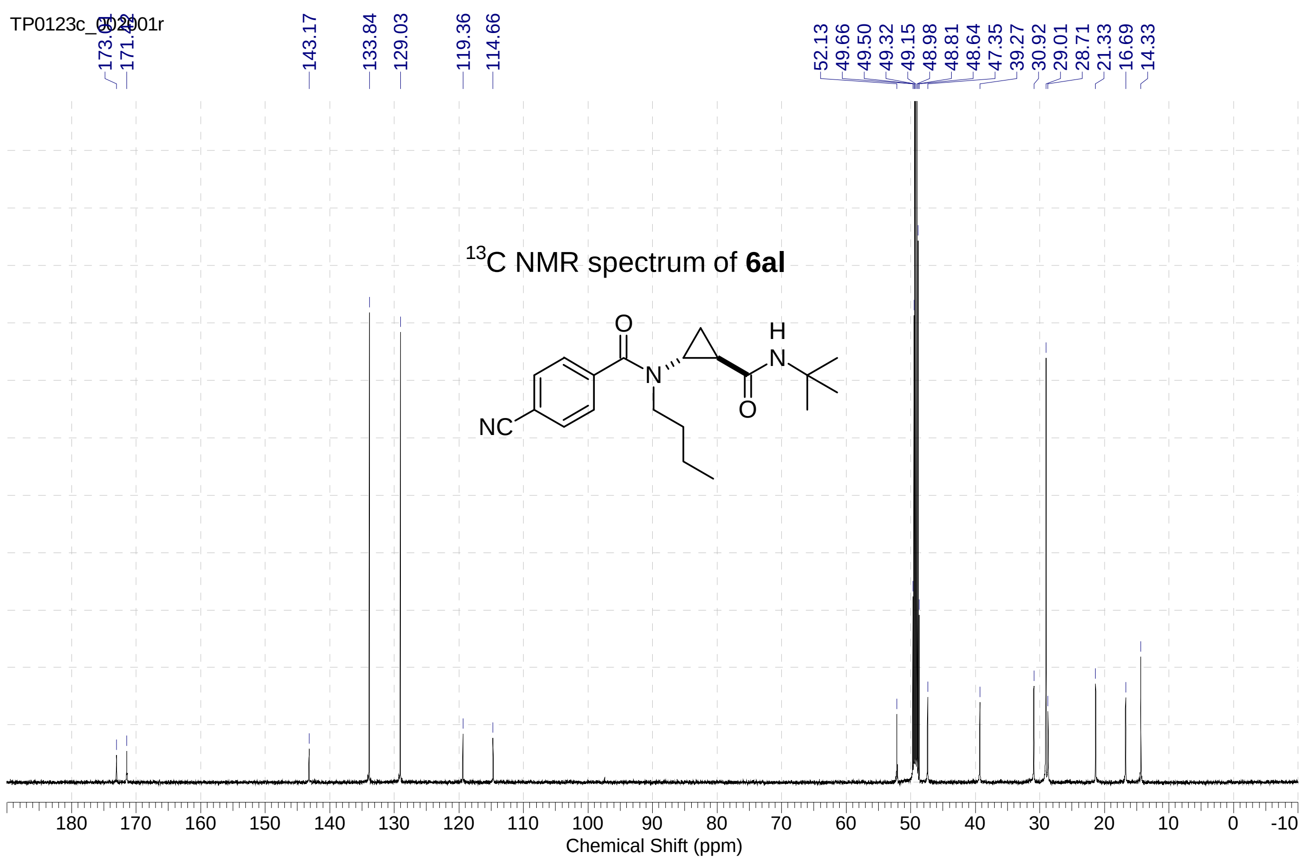
^{13}C NMR spectrum of **6ah**


TP0120c_0010001.esp
7.41
3.85
3.31
3.31
3.30
3.28
3.27
3.26
3.25
3.11
1.71
1.70
1.53
1.45
1.20
1.14
1.07
1.01
^{1}H NMR spectrum of **6ak**
O
H
N
N
O
Cl
4.00
0.87
0.99
0.91
5.19
14.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

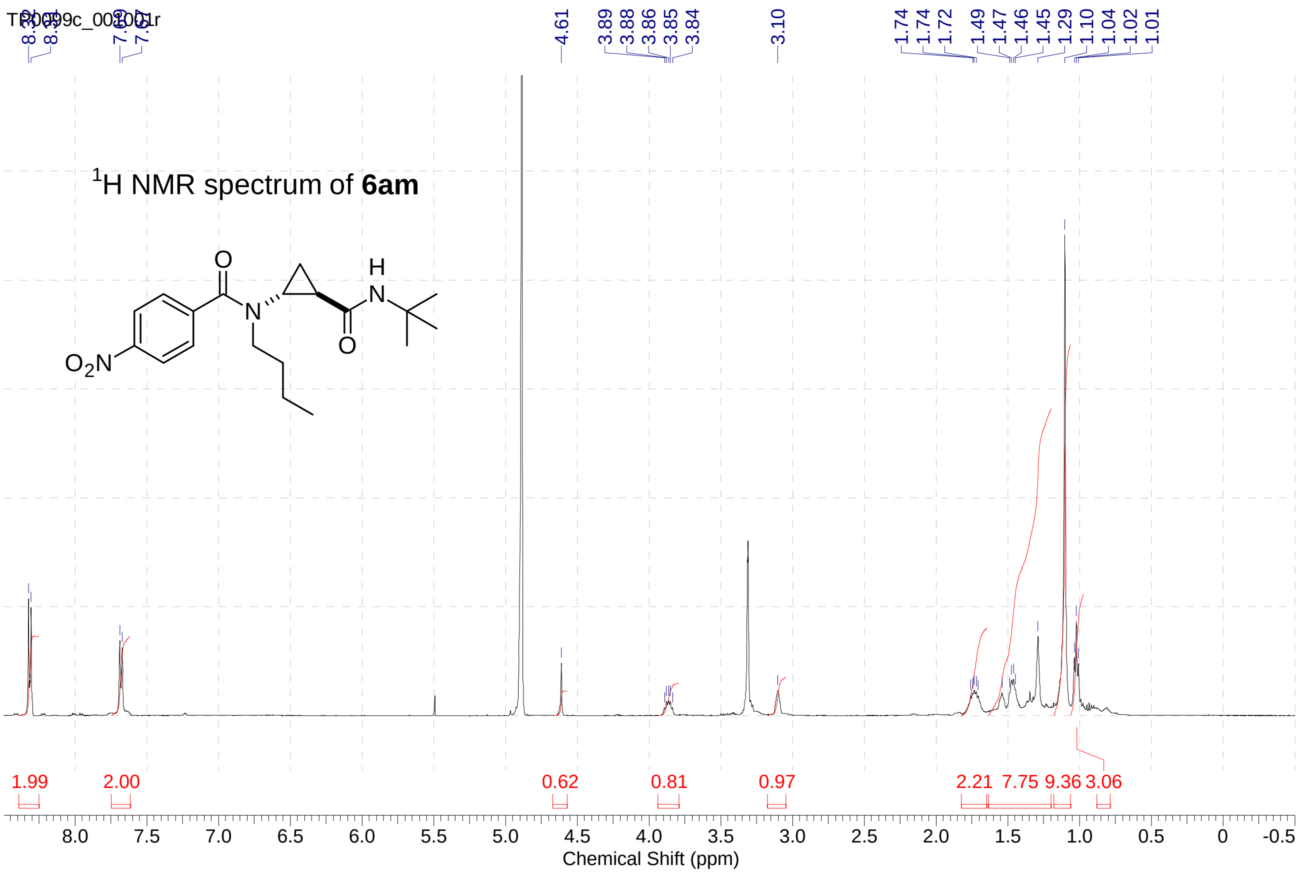

TP0120c_0010001r
173.26
171.01
137.26
136.86
130.07
129.91
52.03
49.66
49.49
49.32
49.15
48.98
48.81
48.64
47.42
39.47
30.98
28.92
21.32
16.62
14.31
^{13}C NMR spectrum of **6ak**
O
H
N
N
O
Cl
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

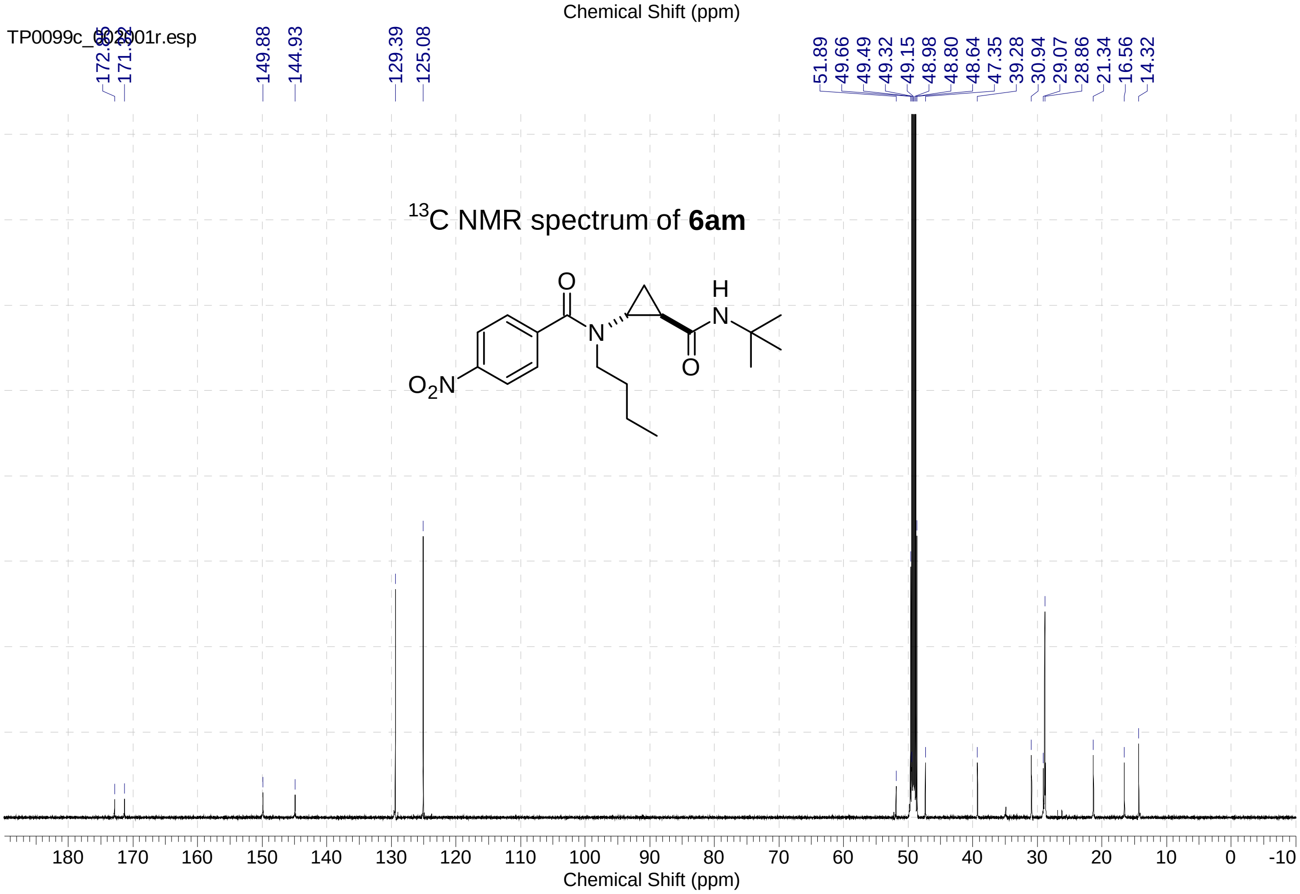


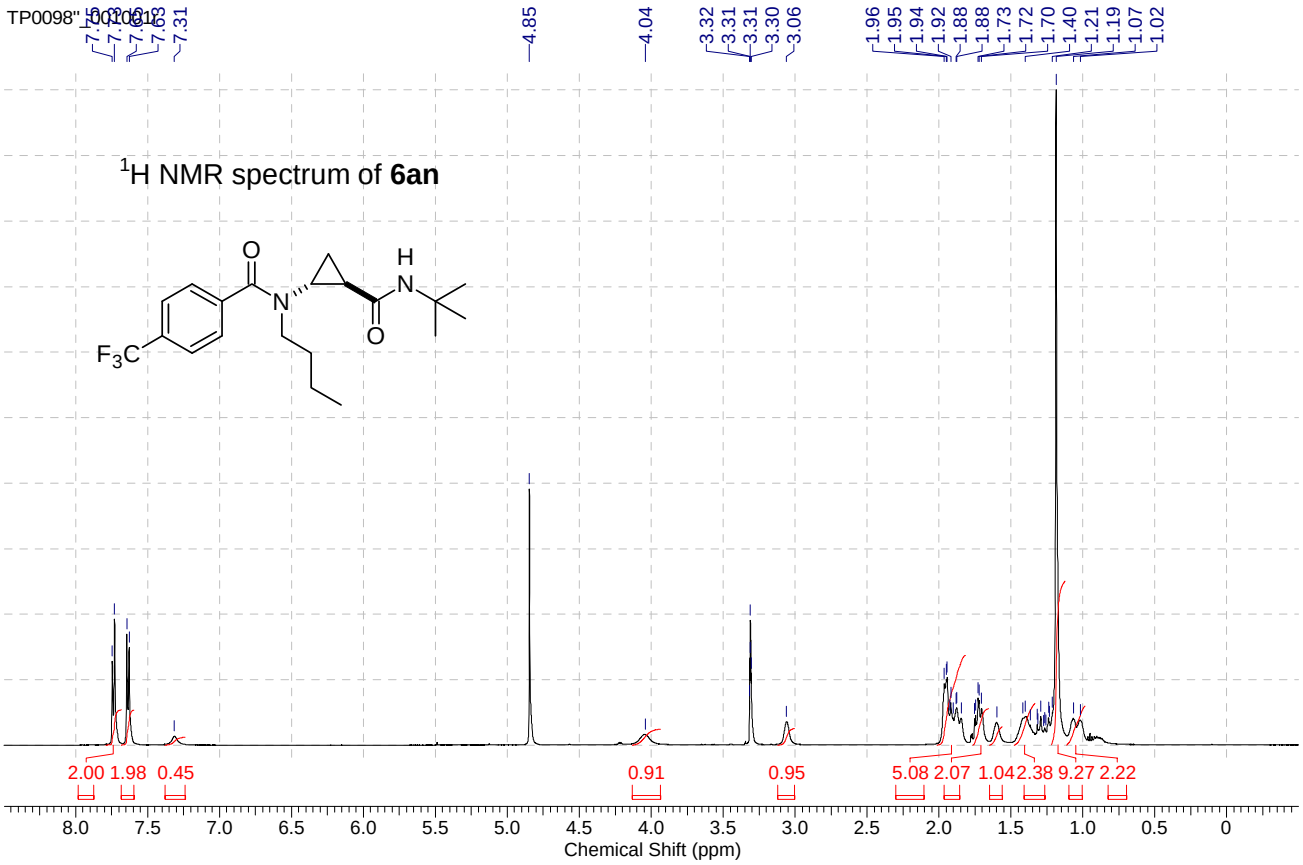
1H NMR spectrum of 6al
NC
O
N
H
N
O
3.86 3.84 3.83 3.82 3.80 3.34 3.31 3.28 3.09
1.72 1.71 1.70 1.46 1.45 1.19 1.12 1.11 1.07 1.03 1.02 1.00
2.07 2.08 0.70
0.94
1.53 1.00
1.94 3.29
14.26
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

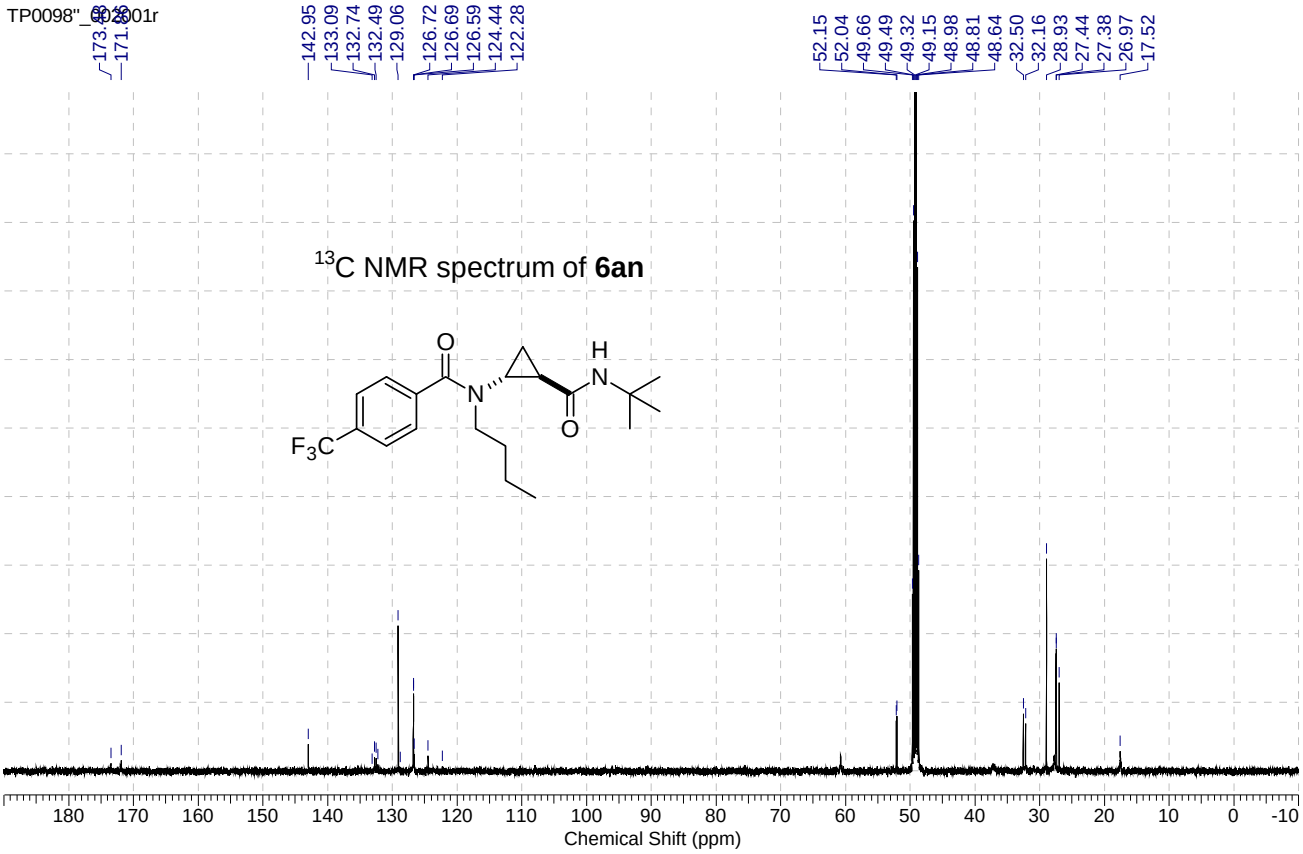


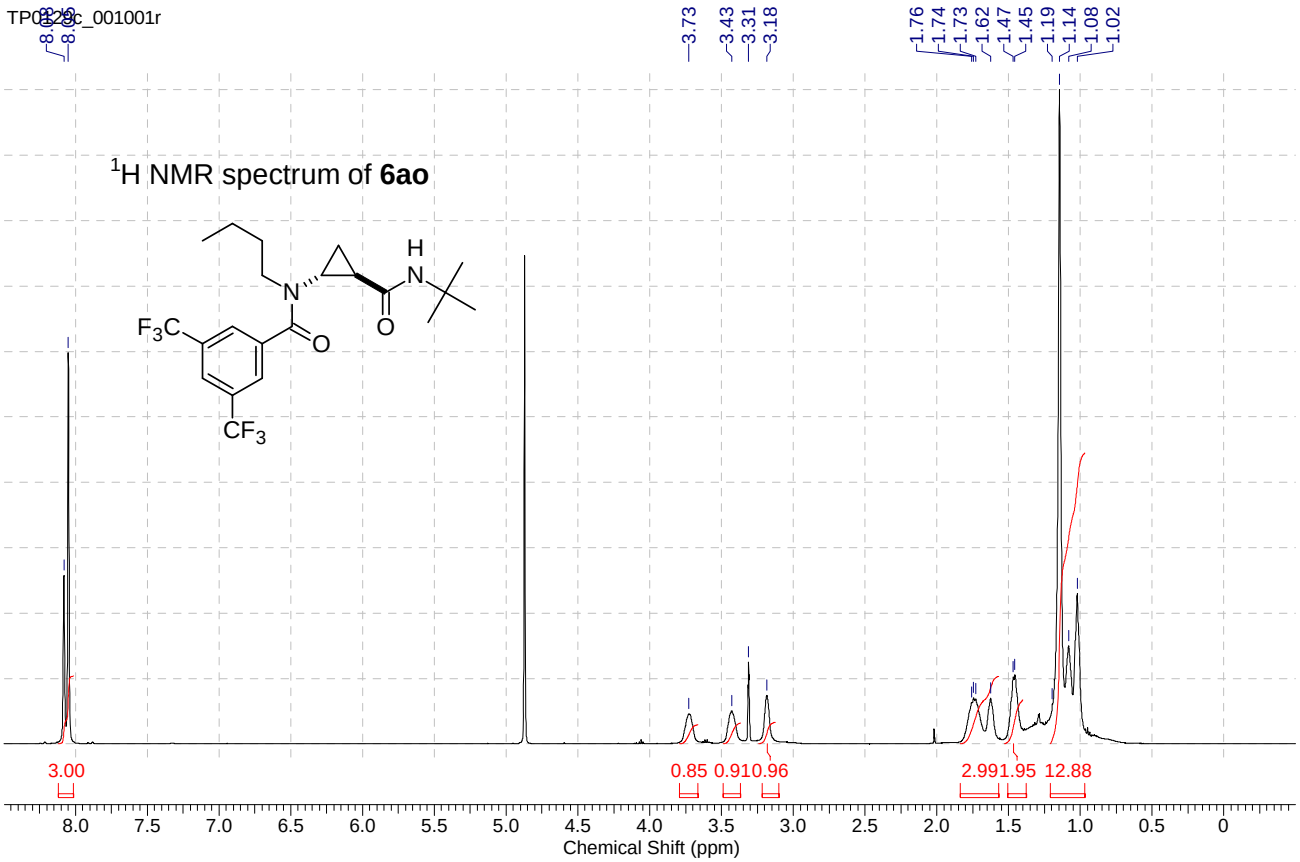
TP0123c_002001r
143.17 133.84 129.03 119.36 114.66
52.13 49.66 49.50 49.32 49.15 48.98 48.81 48.64 47.35 39.27 30.92 29.01 28.71 21.33 16.69 14.33
13C NMR spectrum of 6al
NC
O
N
H
N
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

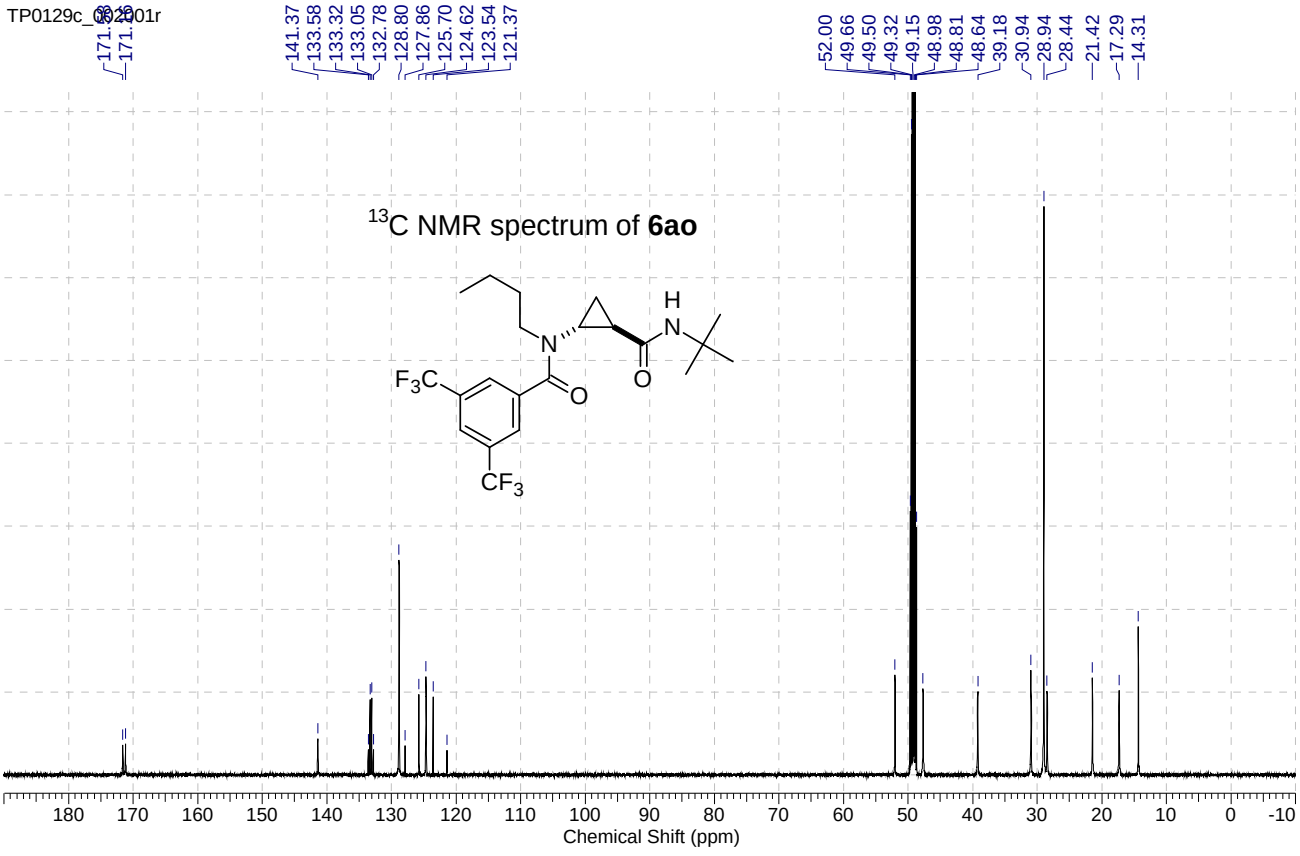

TP0099c_001001r
[1]H NMR spectrum of 6am
Chemical Shift (ppm)

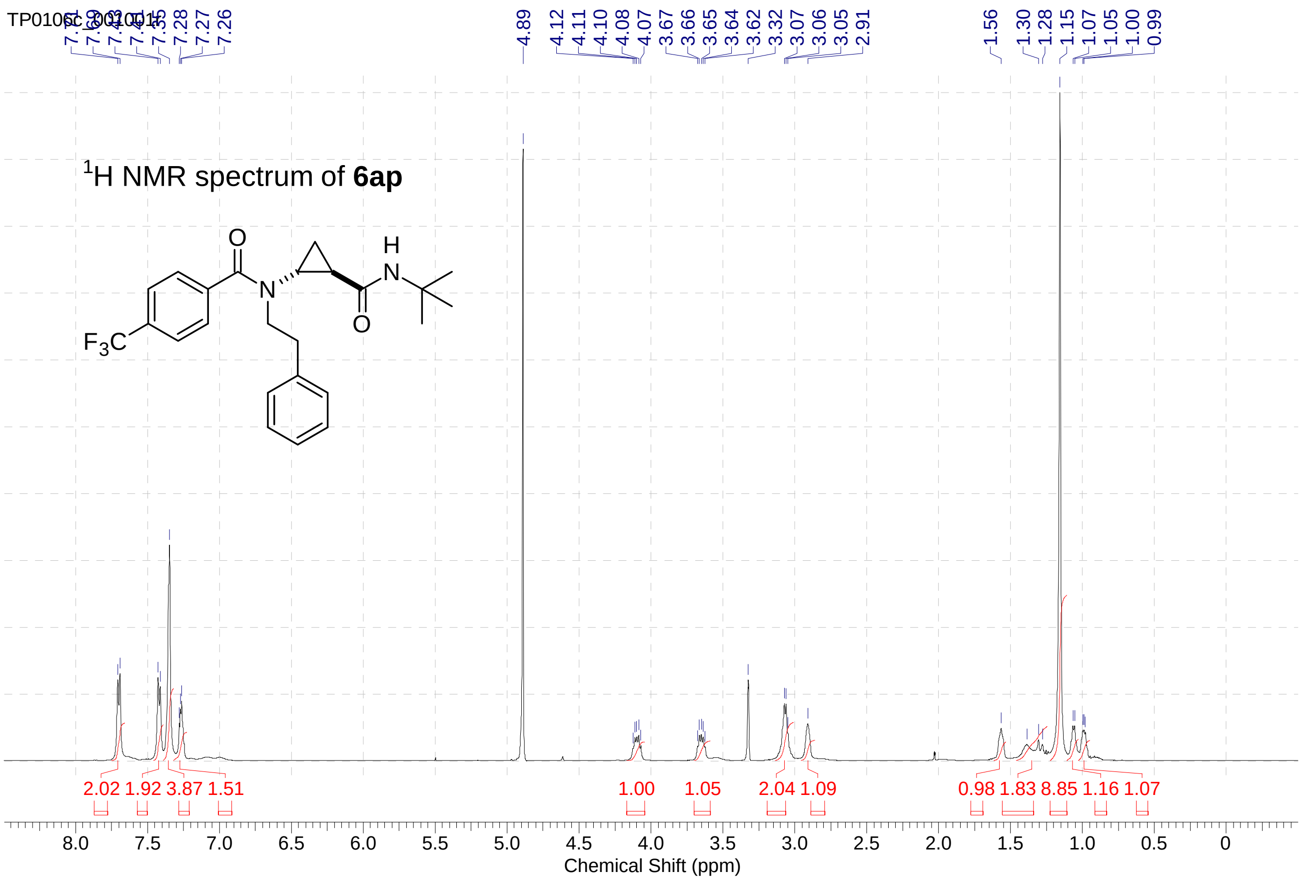

TP0099c_002001r.esp
[13]C NMR spectrum of 6am
Chemical Shift (ppm)

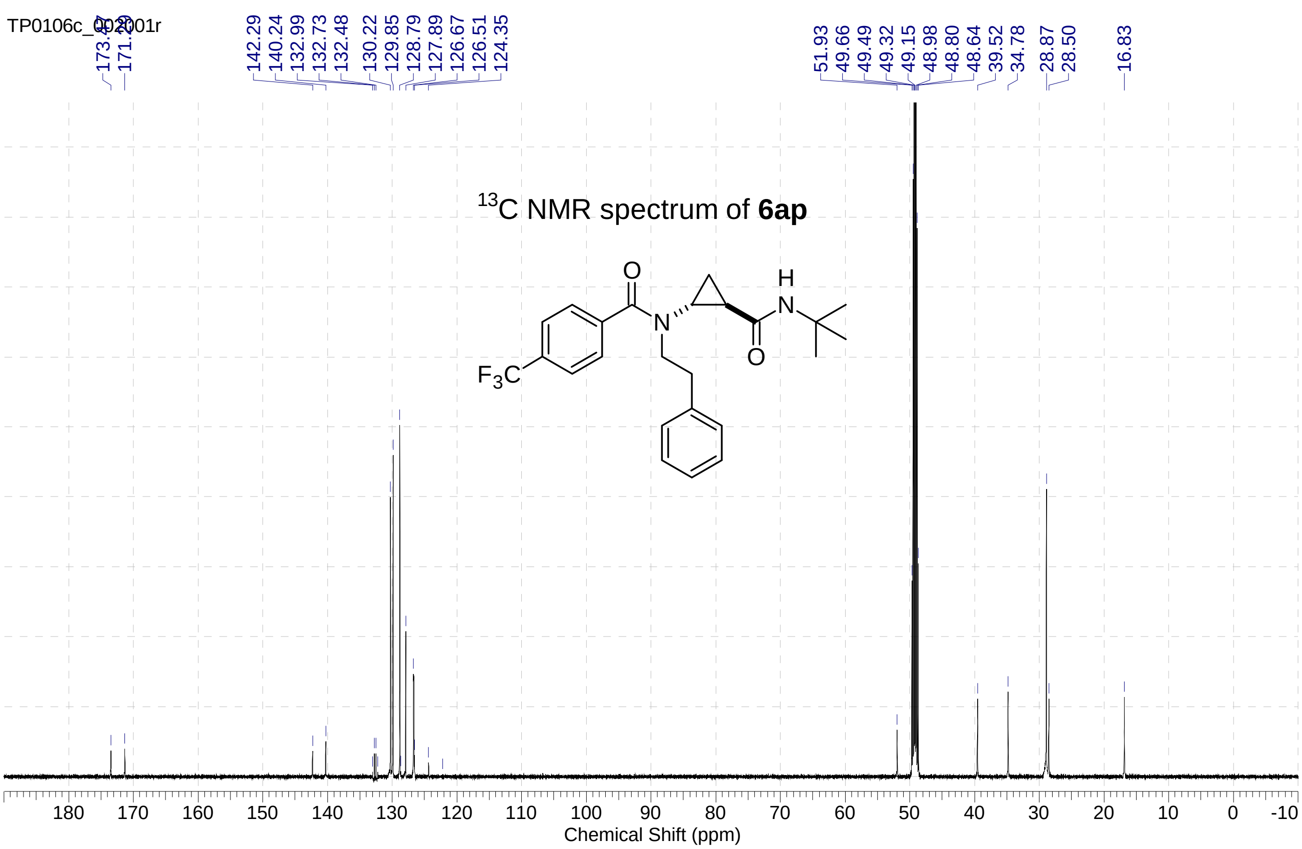

^{1}H NMR spectrum of **6an**
Chemical Shift (ppm)

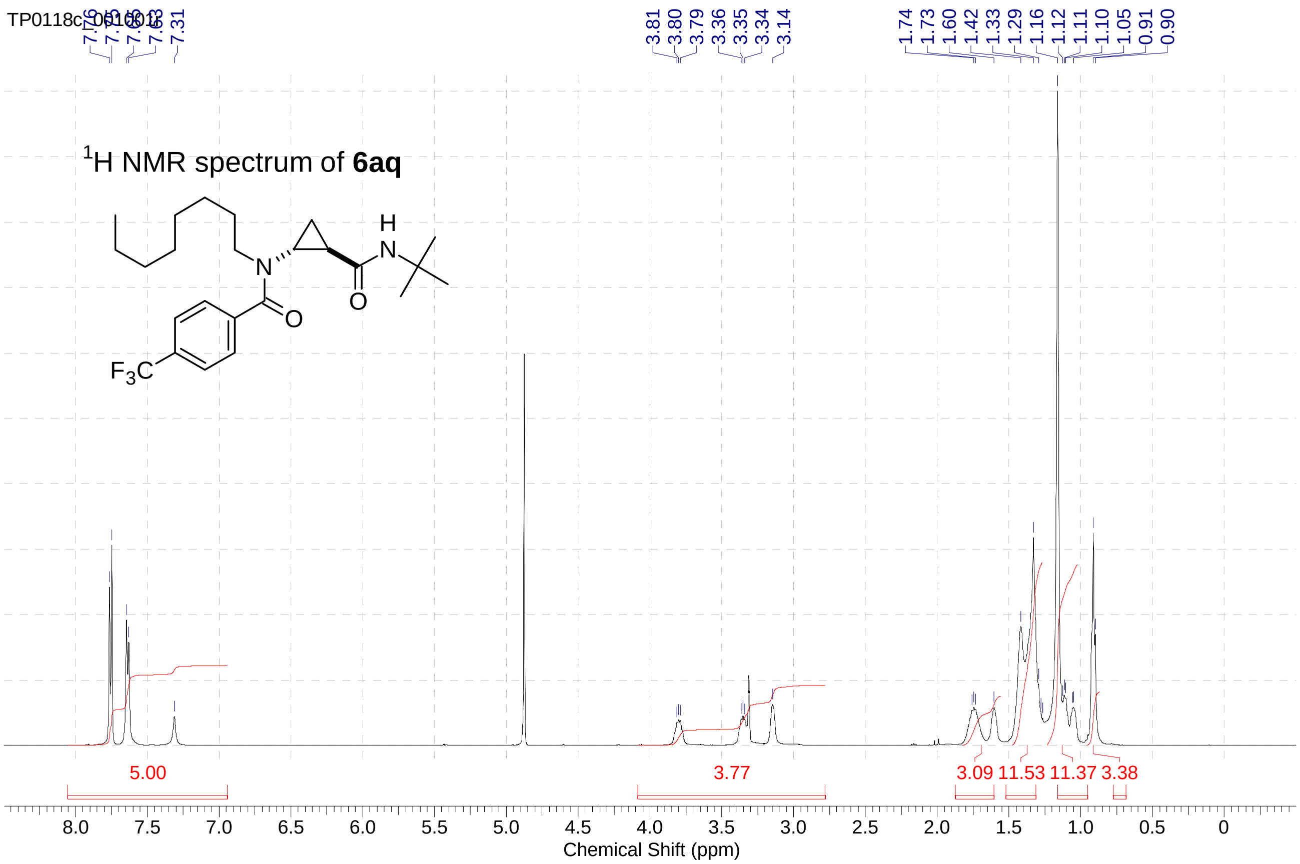

^{13}C NMR spectrum of **6an**
Chemical Shift (ppm)

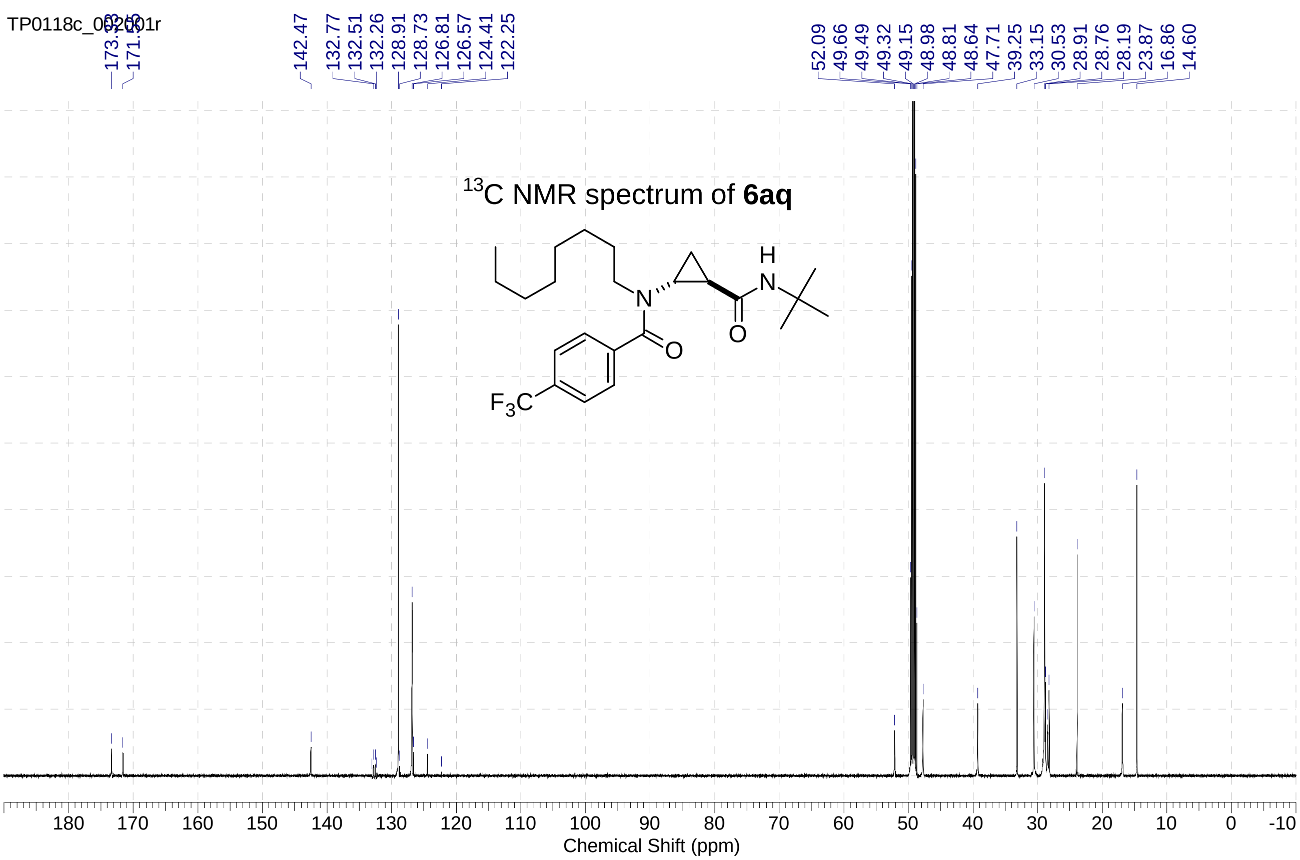

TP0129c_001001r
8.06
8.04
3.73
3.43
3.31
3.18
1.76
1.74
1.73
1.62
1.47
1.45
1.19
1.14
1.08
1.02
^{1}H NMR spectrum of **6ao**
H
N
N
O
O
F_3C
CF_3
3.00
0.85
0.91
0.96
2.99
1.95
12.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

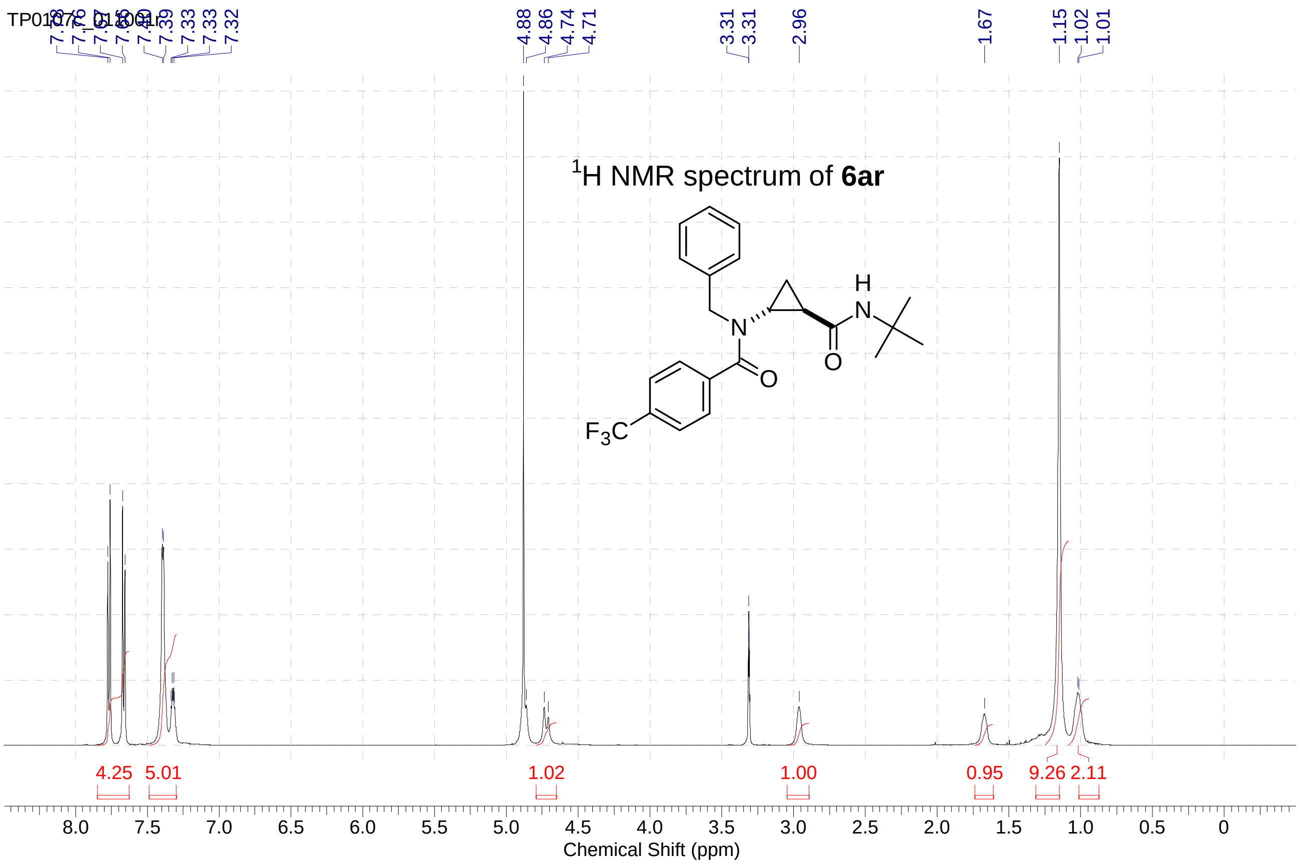

TP0129c_002001r
171.37
171.29
141.37
133.58
133.32
133.05
132.78
128.80
127.86
125.70
124.62
123.54
121.37
52.00
49.66
49.50
49.32
49.15
48.98
48.81
48.64
39.18
30.94
28.94
28.44
21.42
17.29
14.31
^{13}C NMR spectrum of **6ao**
H
N
N
O
O
F_3C
CF_3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

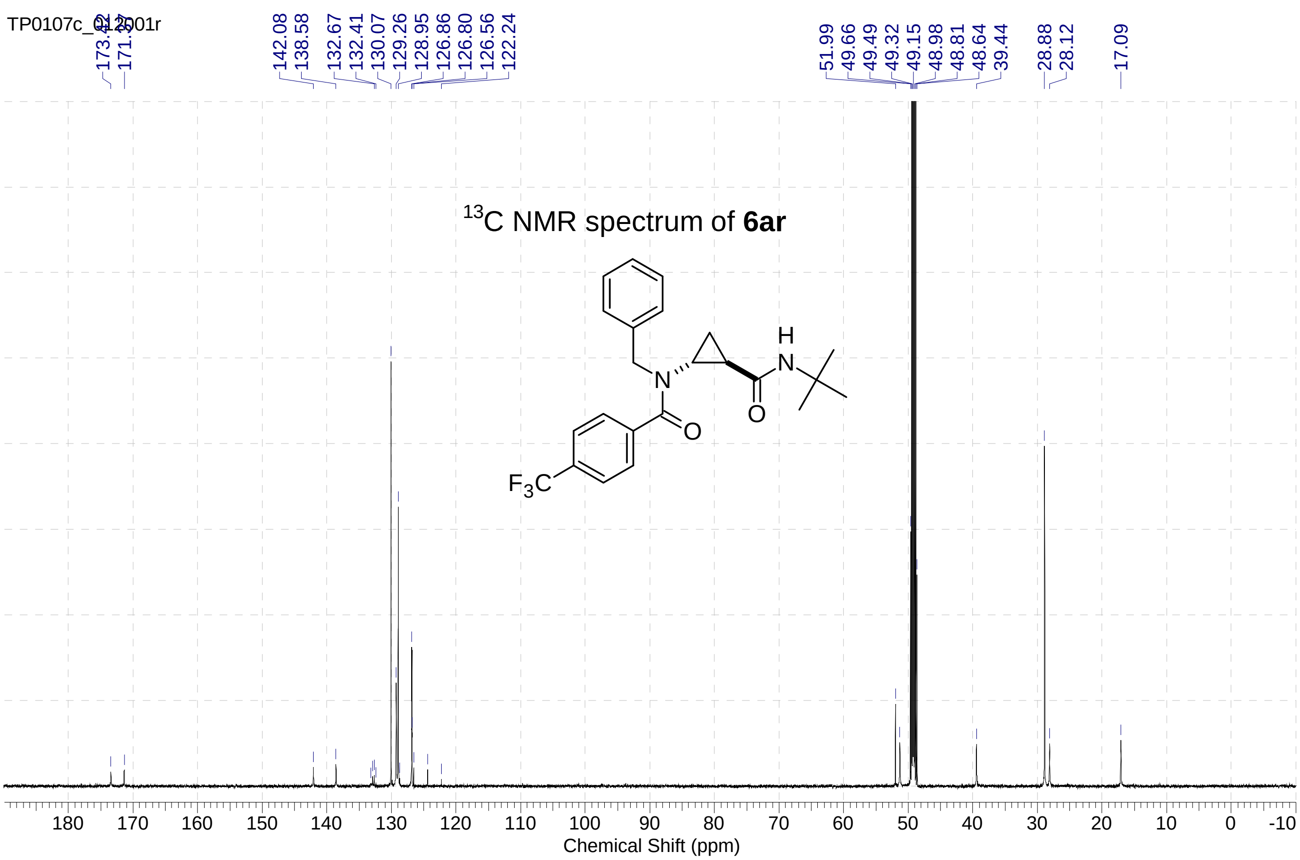

TP0106c_001001r
1H NMR spectrum of 6ap
F3C
Chemical Shift (ppm)

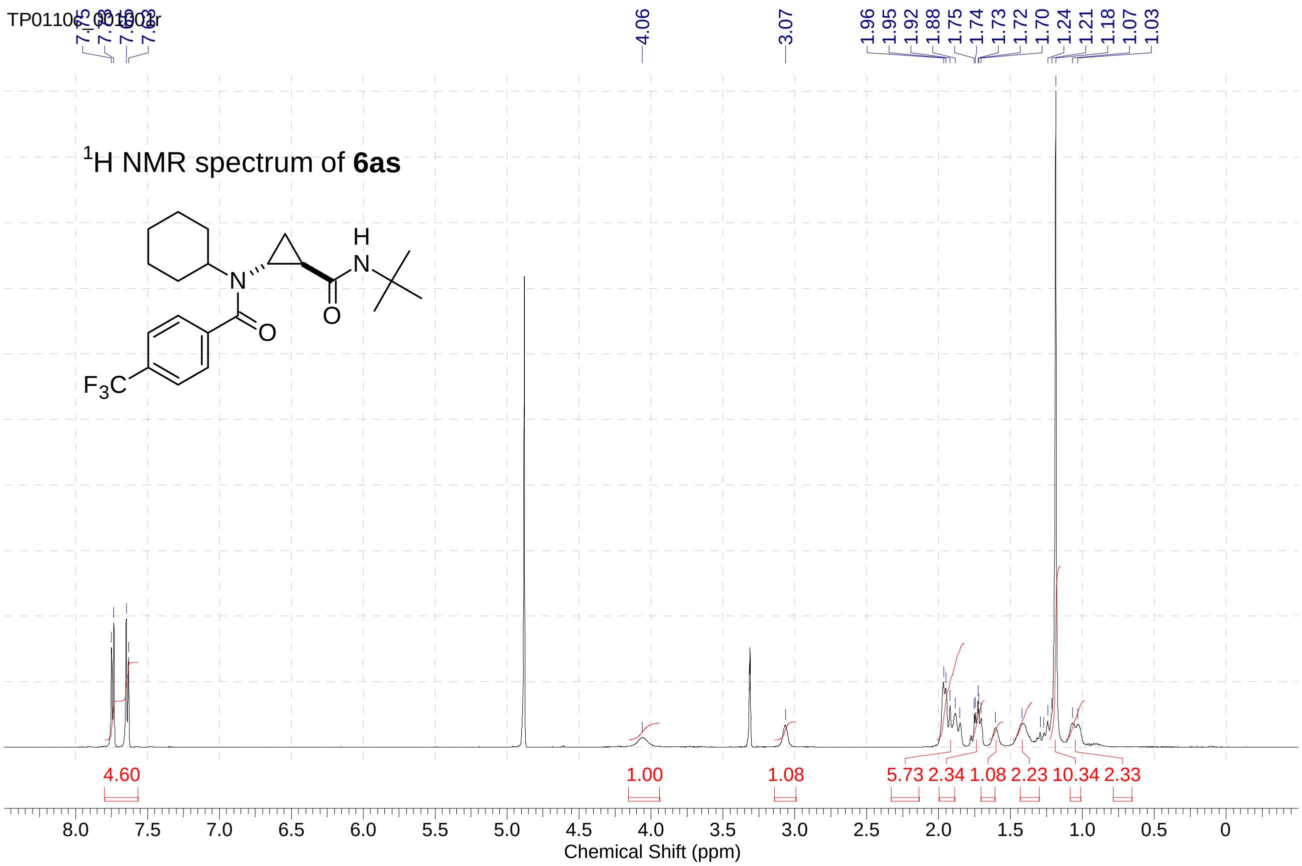

TP0106c_002001r
13C NMR spectrum of 6ap
F3C
Chemical Shift (ppm)

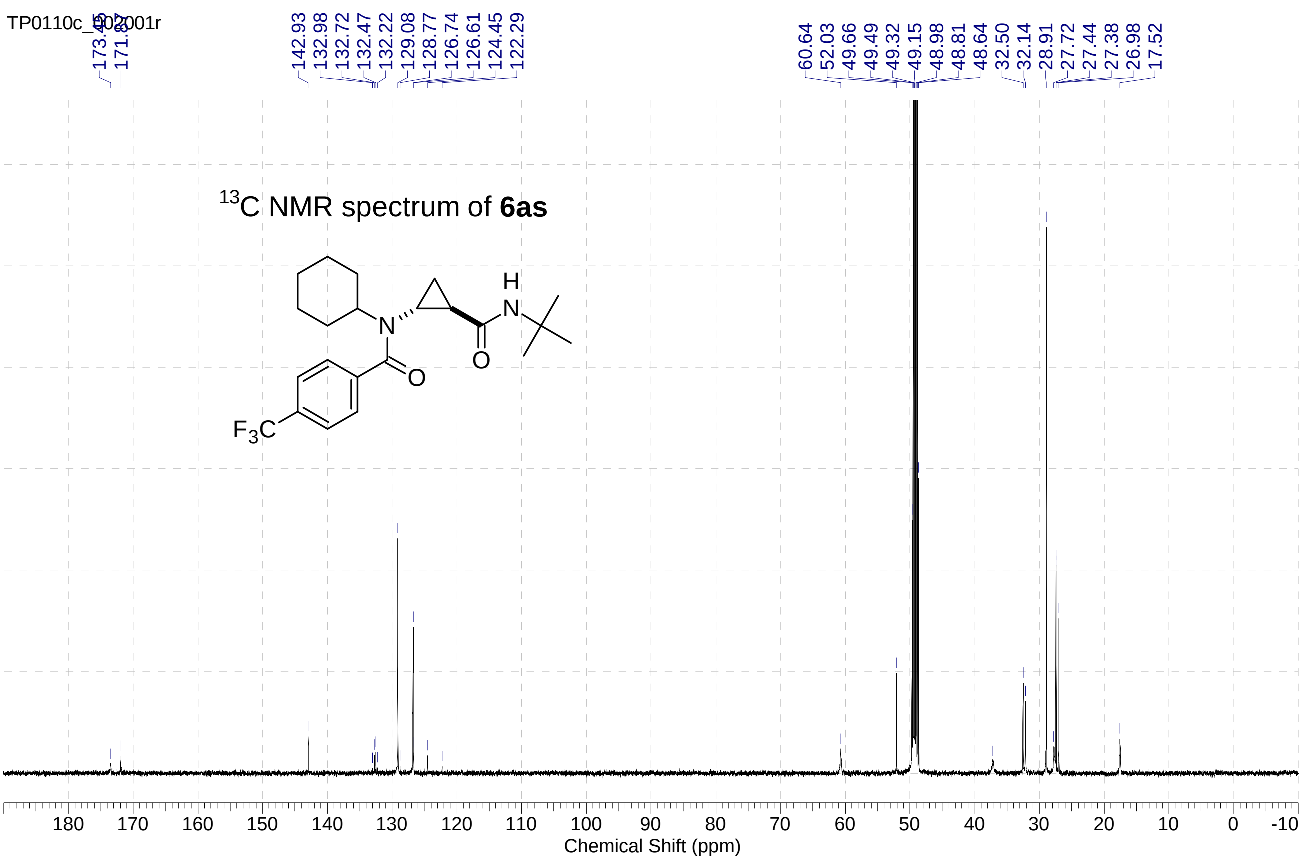

TP0118c_0...
7.31
3.81
3.80
3.79
3.36
3.35
3.34
3.14
1.74
1.73
1.60
1.42
1.33
1.29
1.16
1.12
1.11
1.10
1.05
0.91
0.90
¹H NMR spectrum of 6aq
F3C
N
H
N
O
O
5.00
3.77
3.09
11.53
11.37
3.38
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

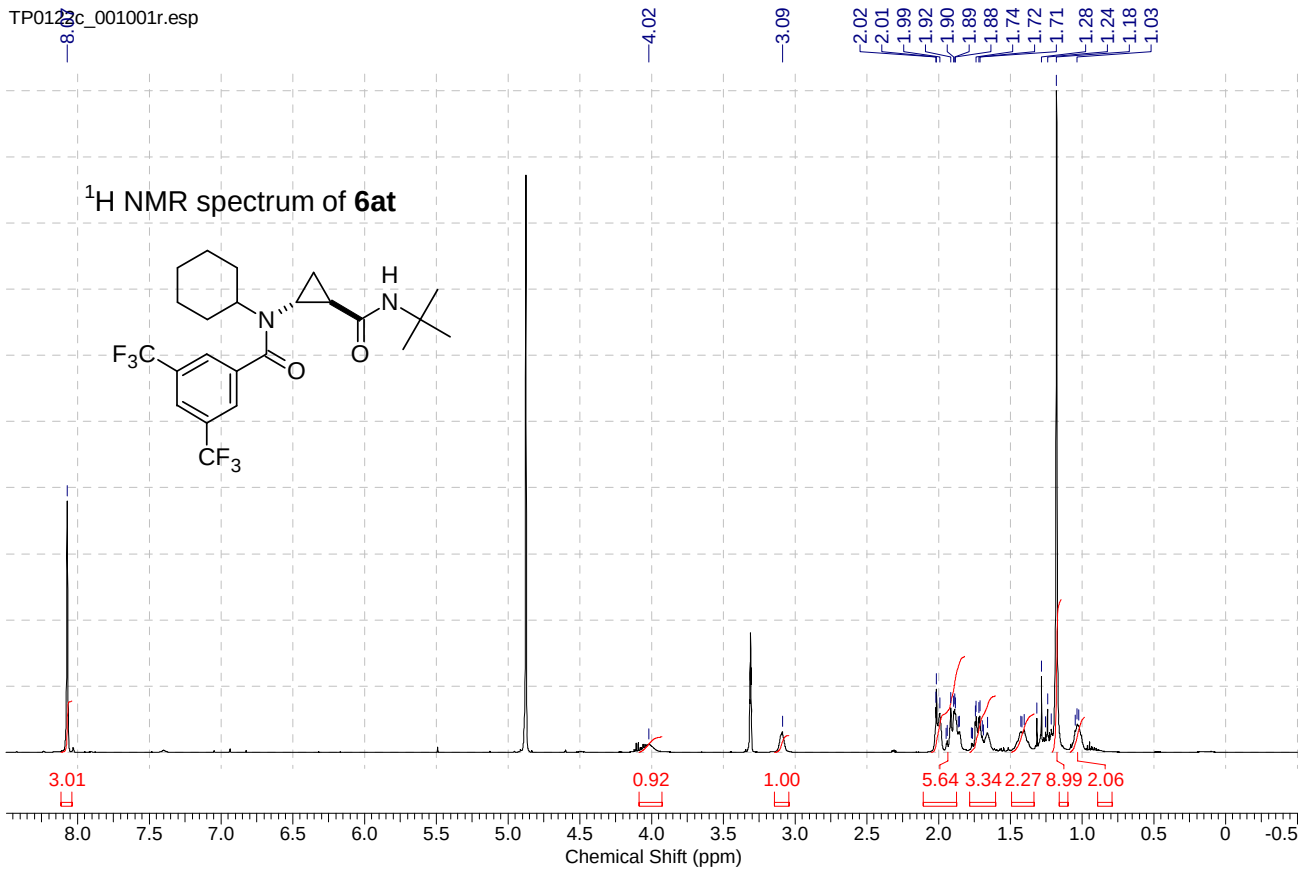

TP0118c_0...01r
142.47
132.77
132.51
132.26
128.91
128.73
126.81
126.57
124.41
122.25
52.09
49.66
49.49
49.32
49.15
48.98
48.81
48.64
47.71
39.25
33.15
30.53
28.91
28.76
28.19
23.87
16.86
14.60
¹³C NMR spectrum of 6aq
F3C
N
H
N
O
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

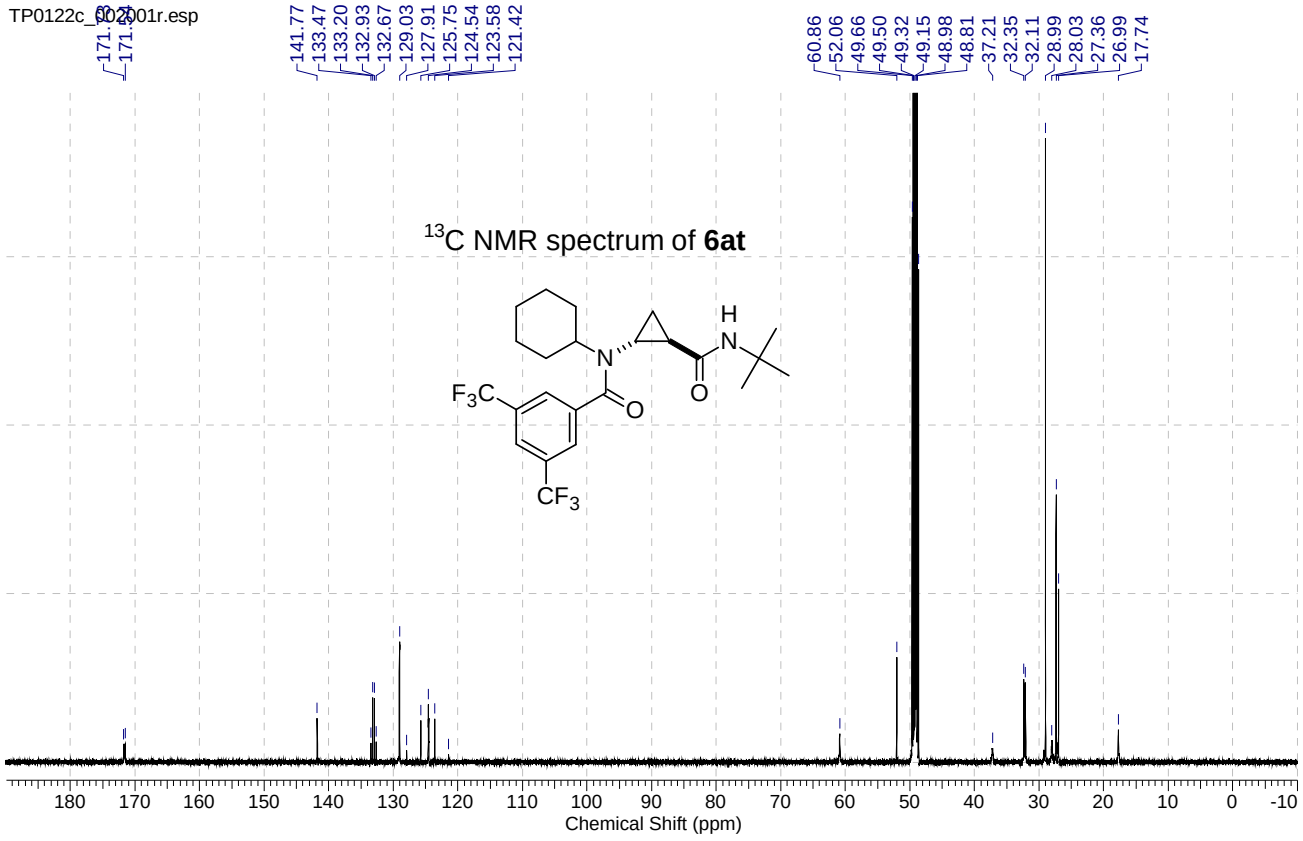

TP0107c_012001r
1H NMR spectrum of 6ar
F3C
Chemical Shift (ppm)

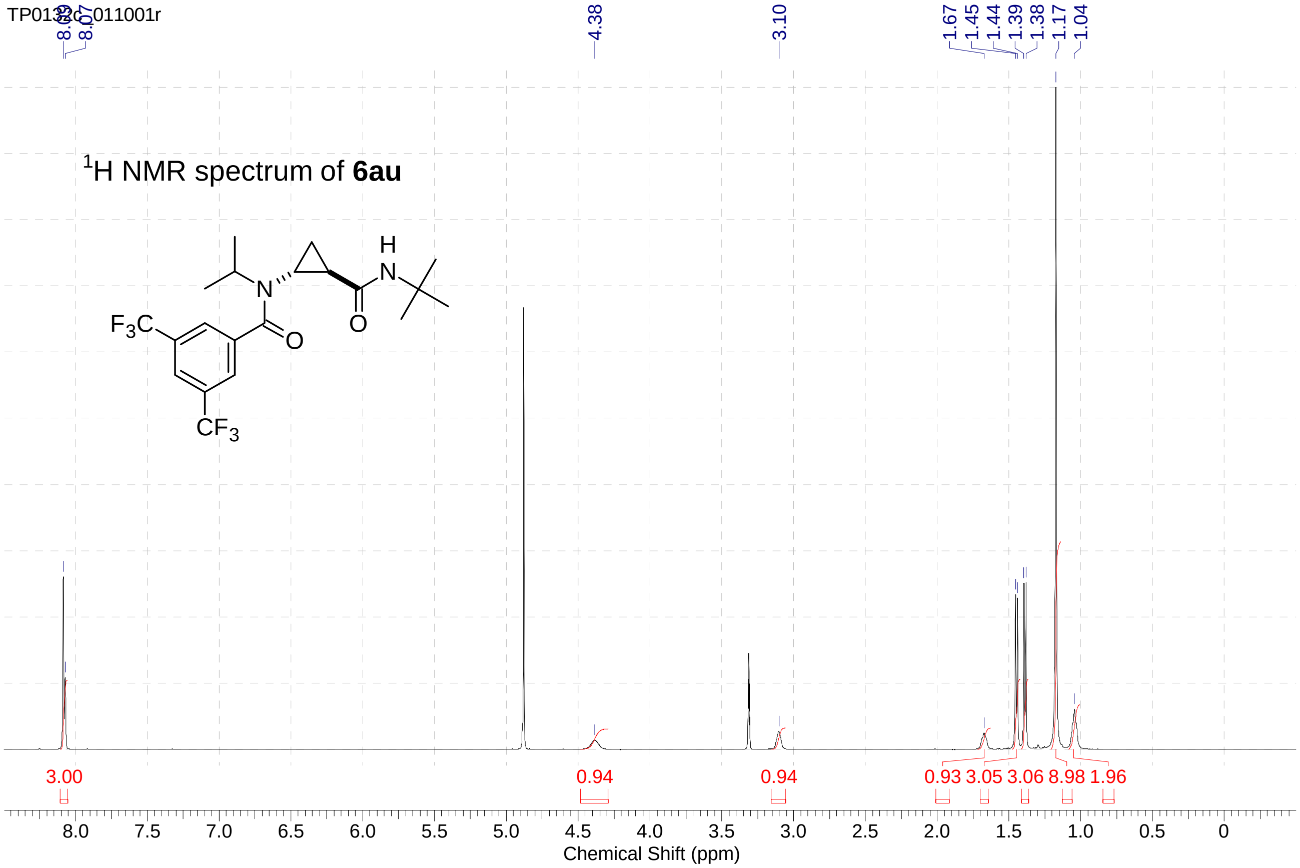

TP0107c_012001r
13C NMR spectrum of 6ar
F3C
Chemical Shift (ppm)

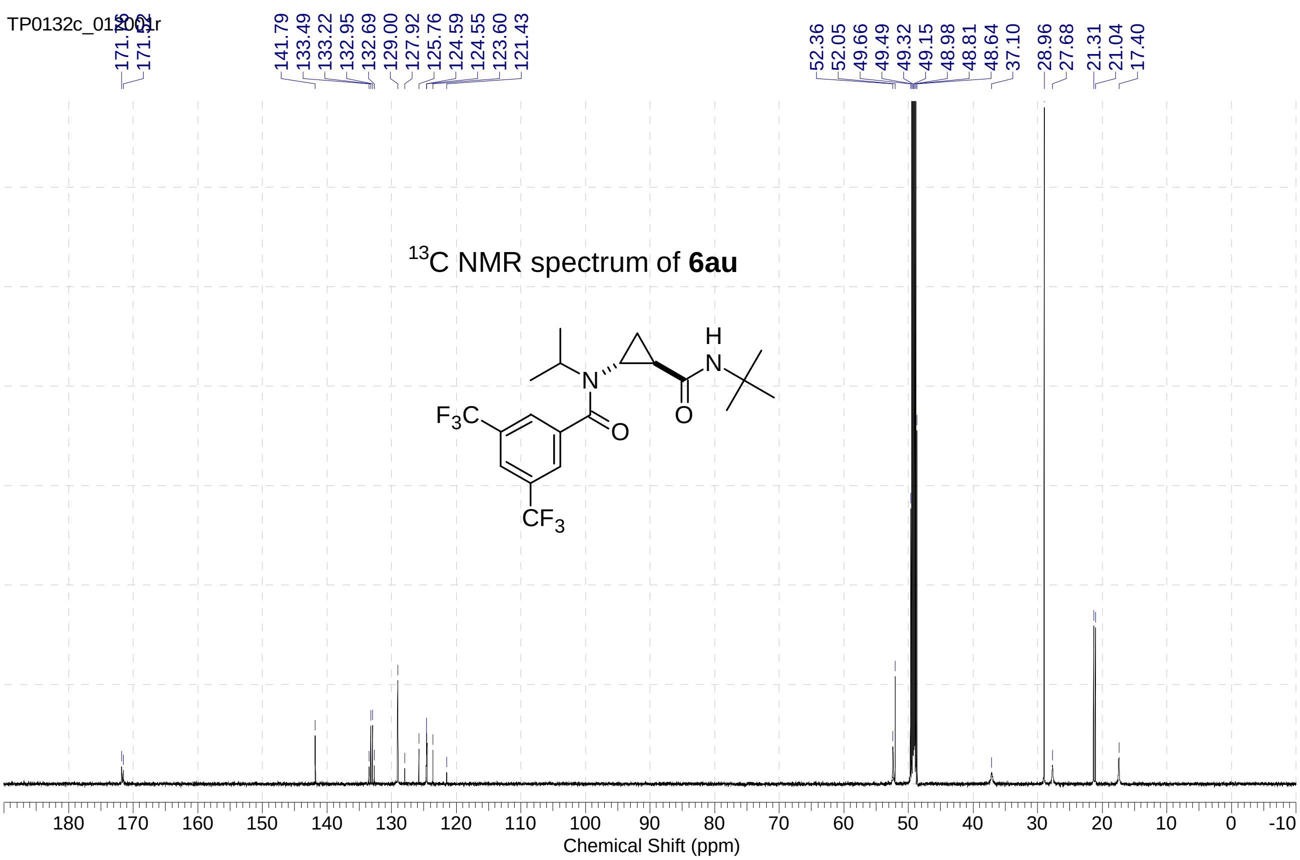

TP0110c_001001r
1H NMR spectrum of 6as
F3C
N
O
H
N
O
4.06
3.07
1.96
1.95
1.92
1.88
1.75
1.74
1.73
1.72
1.70
1.24
1.21
1.18
1.07
1.03
4.60
1.00
1.08
5.73 2.34 1.08 2.23 10.34 2.33
Chemical Shift (ppm)

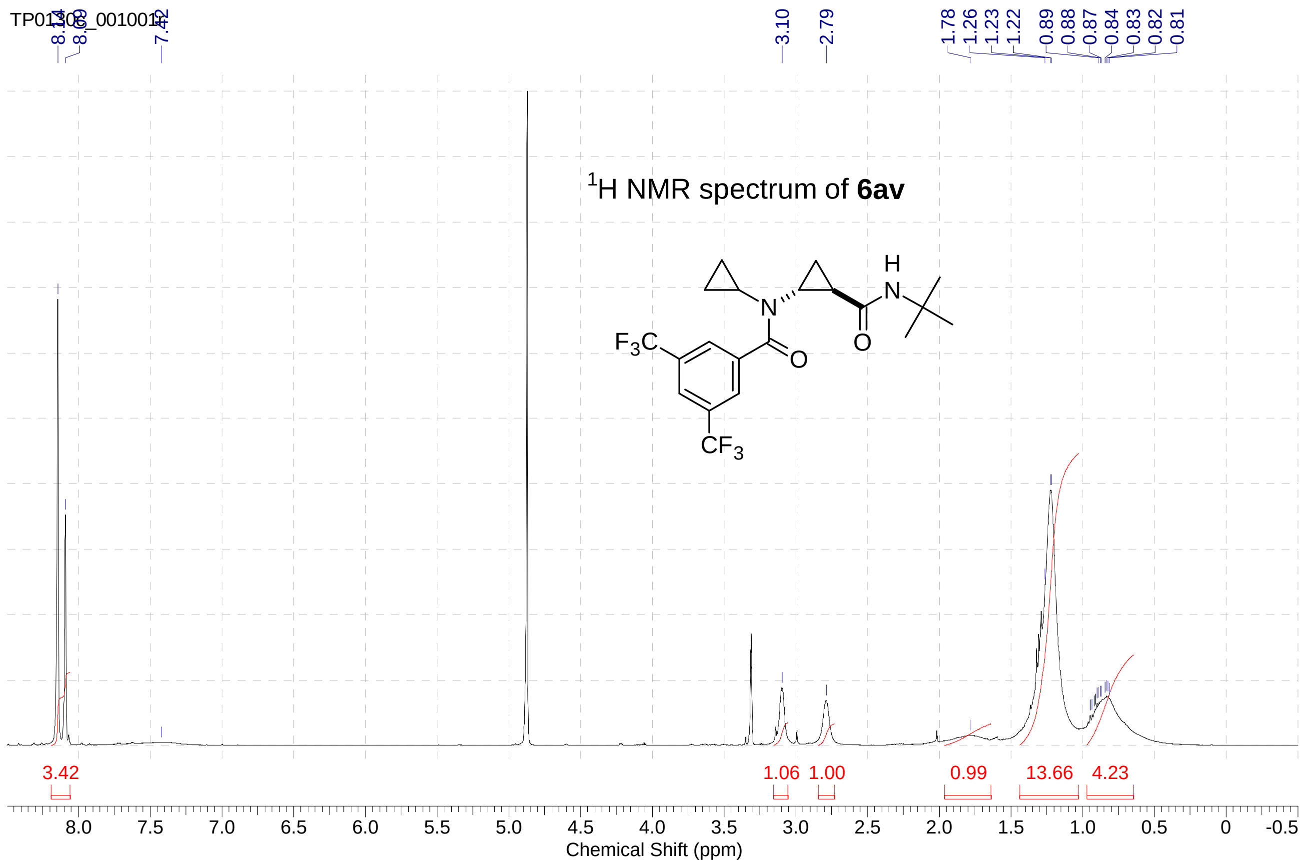

TP0110c_002001r
13C NMR spectrum of 6as
F3C
N
O
H
N
O
142.93
132.98
132.72
132.47
132.22
129.08
128.77
126.74
126.61
124.45
122.29
60.64
52.03
49.66
49.49
49.32
49.15
48.98
48.81
48.64
32.50
32.14
28.91
27.72
27.44
27.38
26.98
17.52
Chemical Shift (ppm)

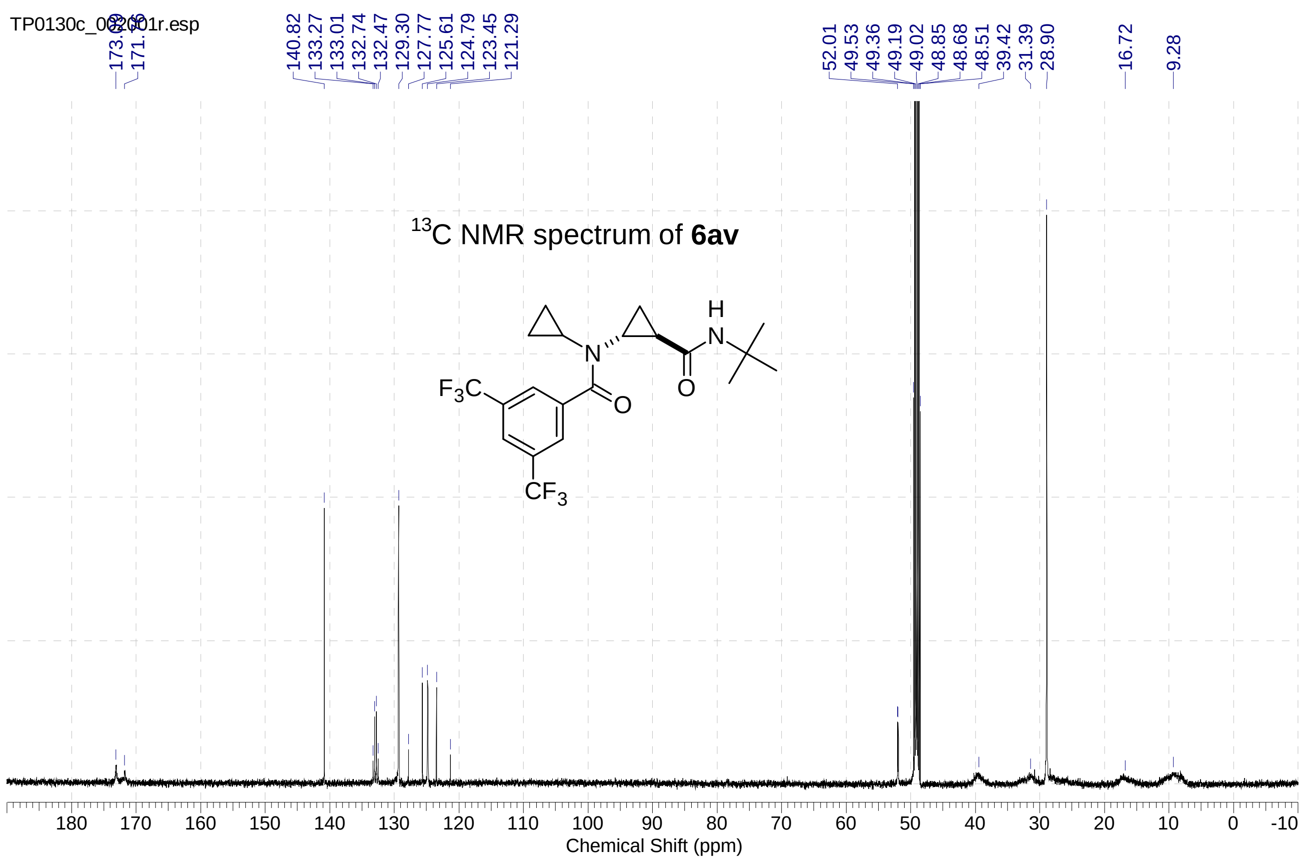

TP0122c_001001r.esp
8.01
4.02
3.09
2.02
2.01
1.99
1.92
1.90
1.89
1.88
1.74
1.72
1.71
1.28
1.24
1.18
1.03
^{1}H NMR spectrum of **6at**
H
N
N
O
F_3C
CF_3
3.01
0.92
1.00
5.64
3.34
2.27
8.99
2.06
Chemical Shift (ppm)

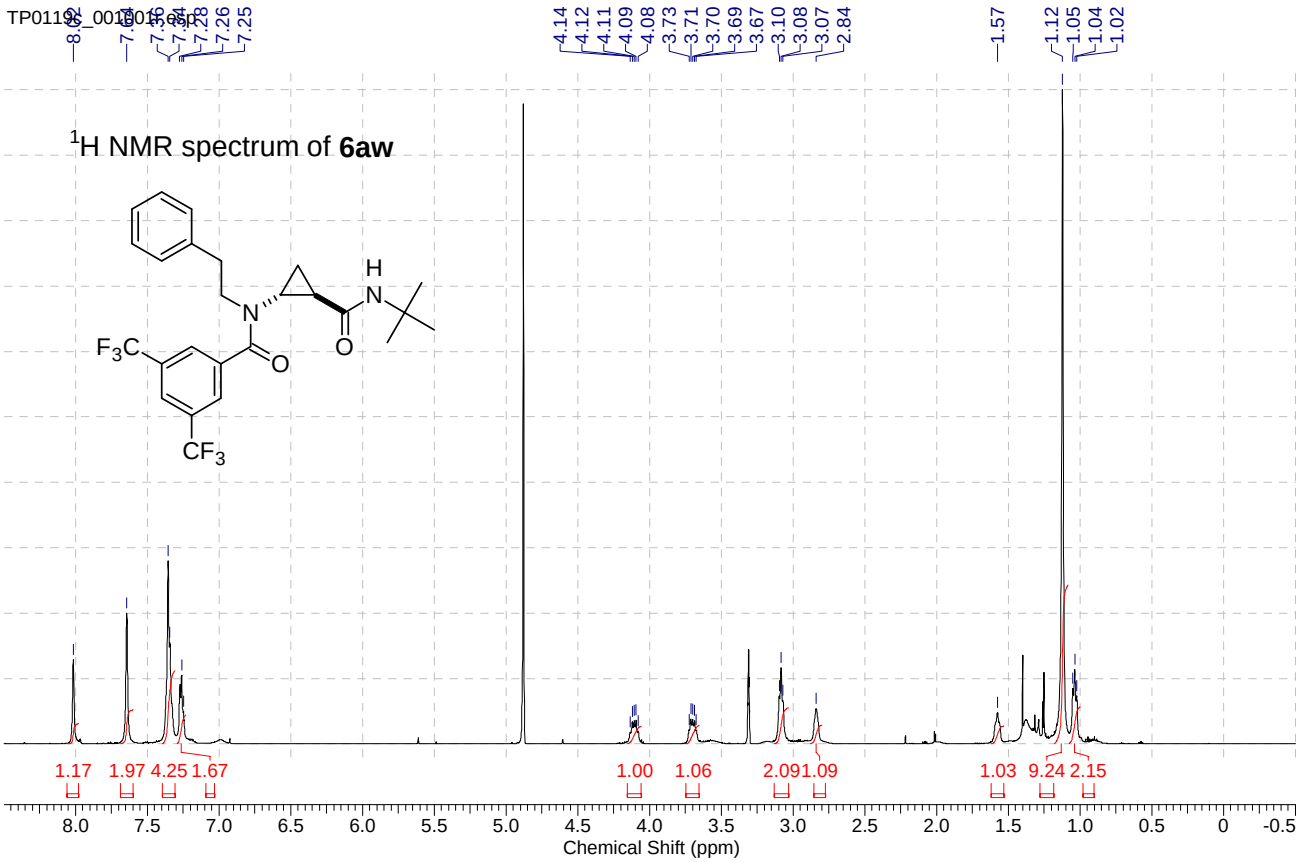

TP0122c_002001r.esp
171.20
171.17
141.77
133.47
133.20
132.93
132.67
129.03
127.91
125.75
124.54
123.58
121.42
60.86
52.06
49.66
49.50
49.32
49.15
48.98
48.81
37.21
32.35
32.11
28.99
28.03
27.36
26.99
17.74
^{13}C NMR spectrum of **6at**
H
N
N
O
F_3C
CF_3
Chemical Shift (ppm)

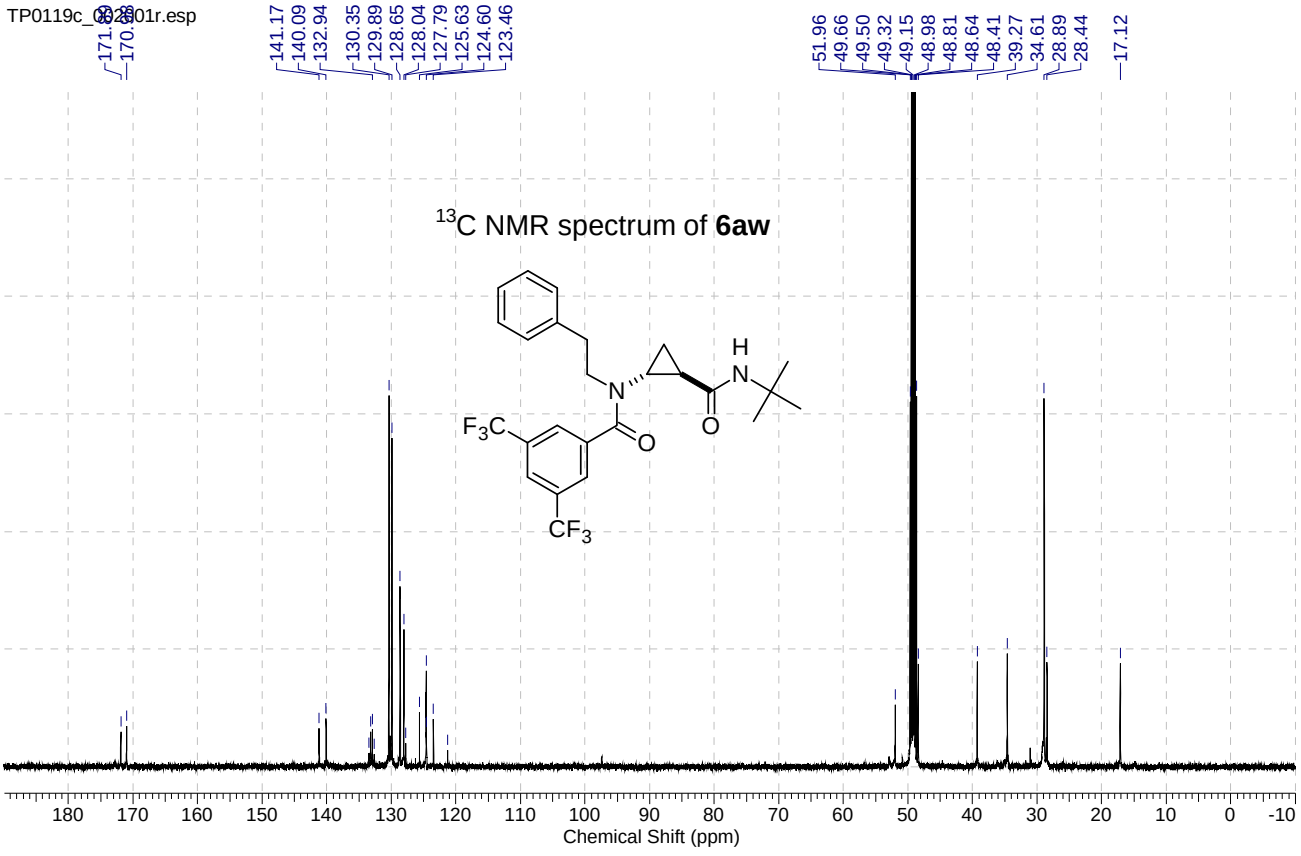

TP0132c_011001r
8.09
8.07
4.38
3.10
1.67
1.45
1.44
1.39
1.38
1.17
1.04
[1]H NMR spectrum of **6au**
F3C
CF3
N
O
H
N
O
3.00
0.94
0.94
0.93
3.05
3.06
8.98
1.96
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

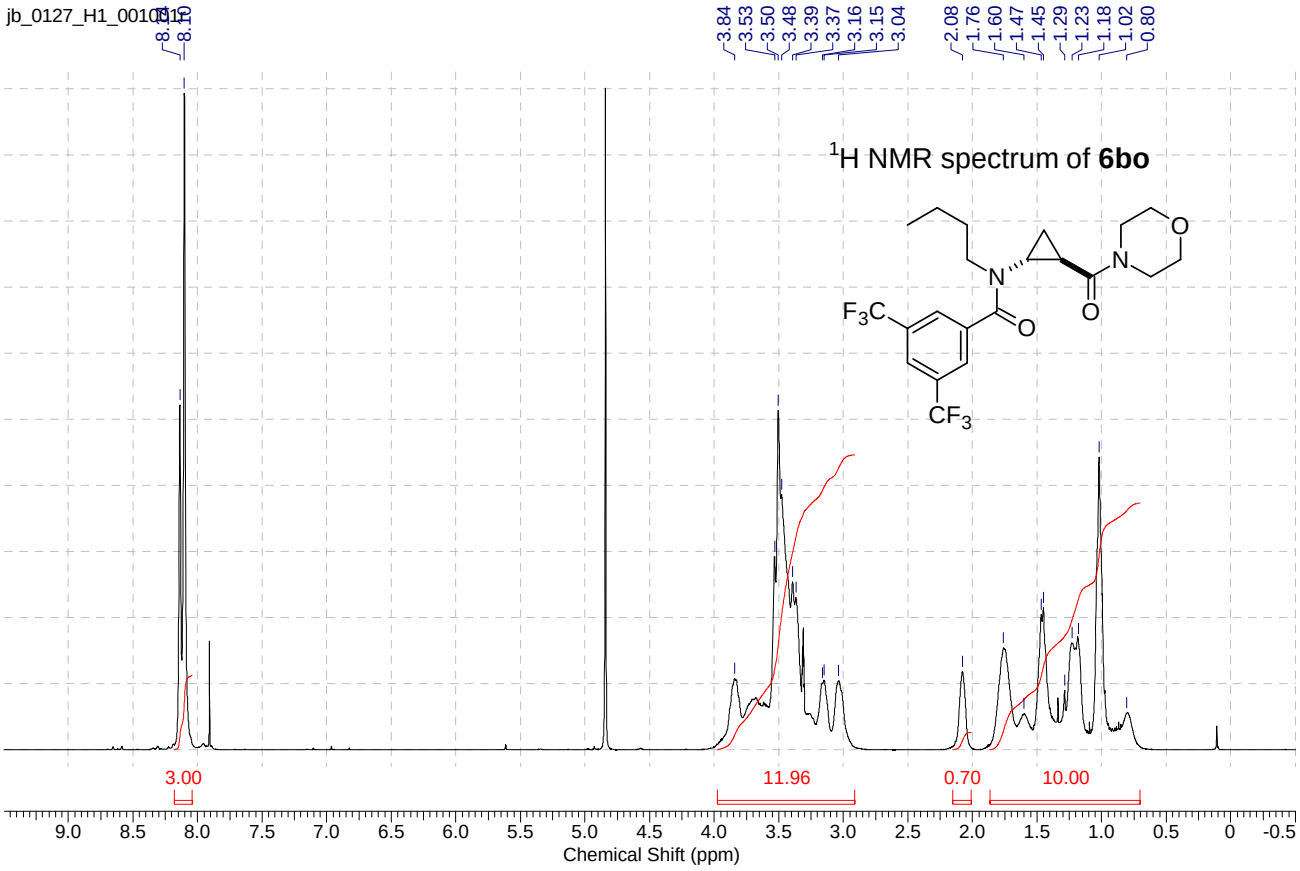

TP0132c_012001r
171.58
171.52
141.79
133.49
133.22
132.95
132.69
129.00
127.92
125.76
124.59
124.55
123.60
121.43
52.36
52.05
49.66
49.49
49.32
49.15
48.98
48.81
48.64
37.10
28.96
27.68
21.31
21.04
17.40
[13]C NMR spectrum of **6au**
F3C
CF3
N
O
H
N
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

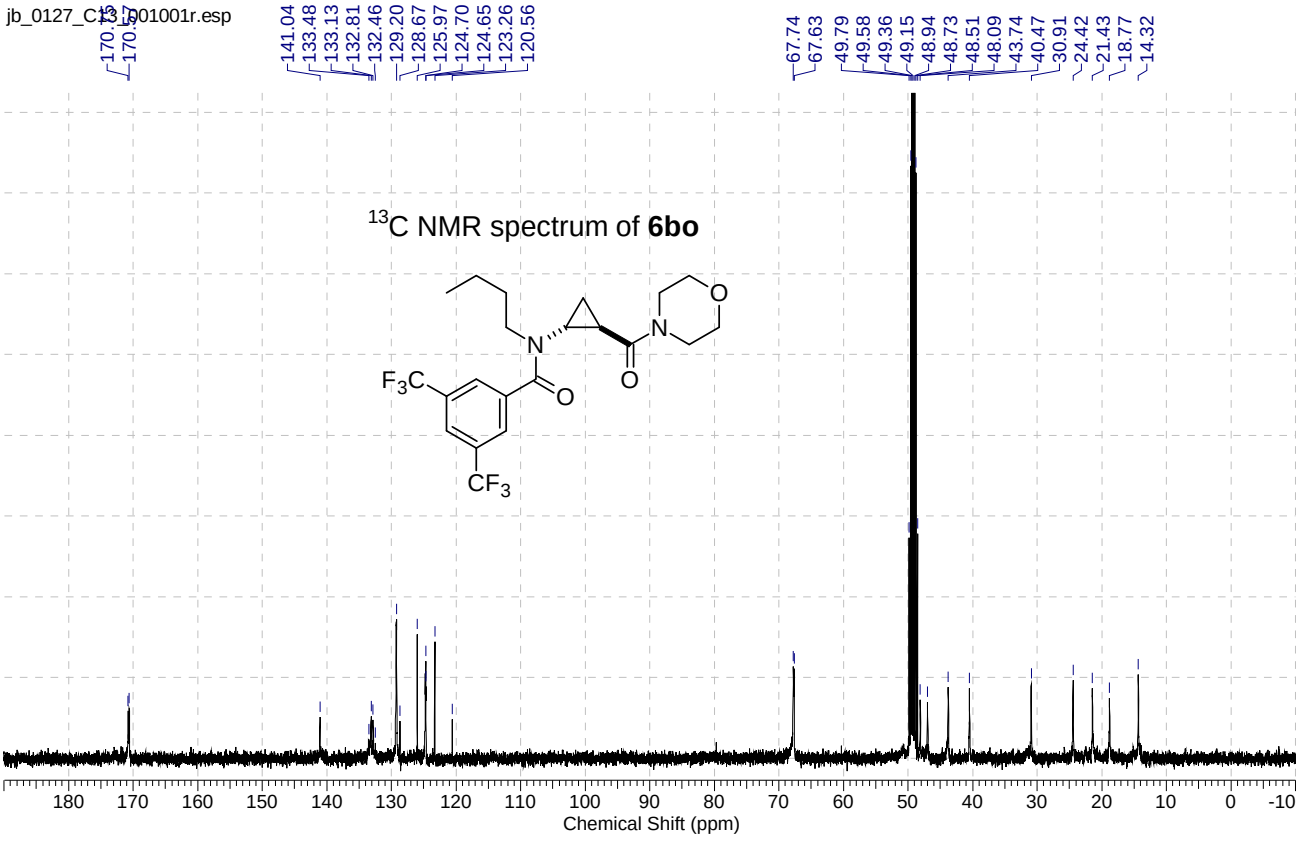

1H NMR spectrum of 6av
3.10
2.79
1.78
1.26
1.23
1.22
0.89
0.88
0.87
0.84
0.83
0.82
0.81
7.42
3.42
1.06 1.00
0.99
13.66
4.23
F3C
CF3
N
O
H
N
O
Chemical Shift (ppm)

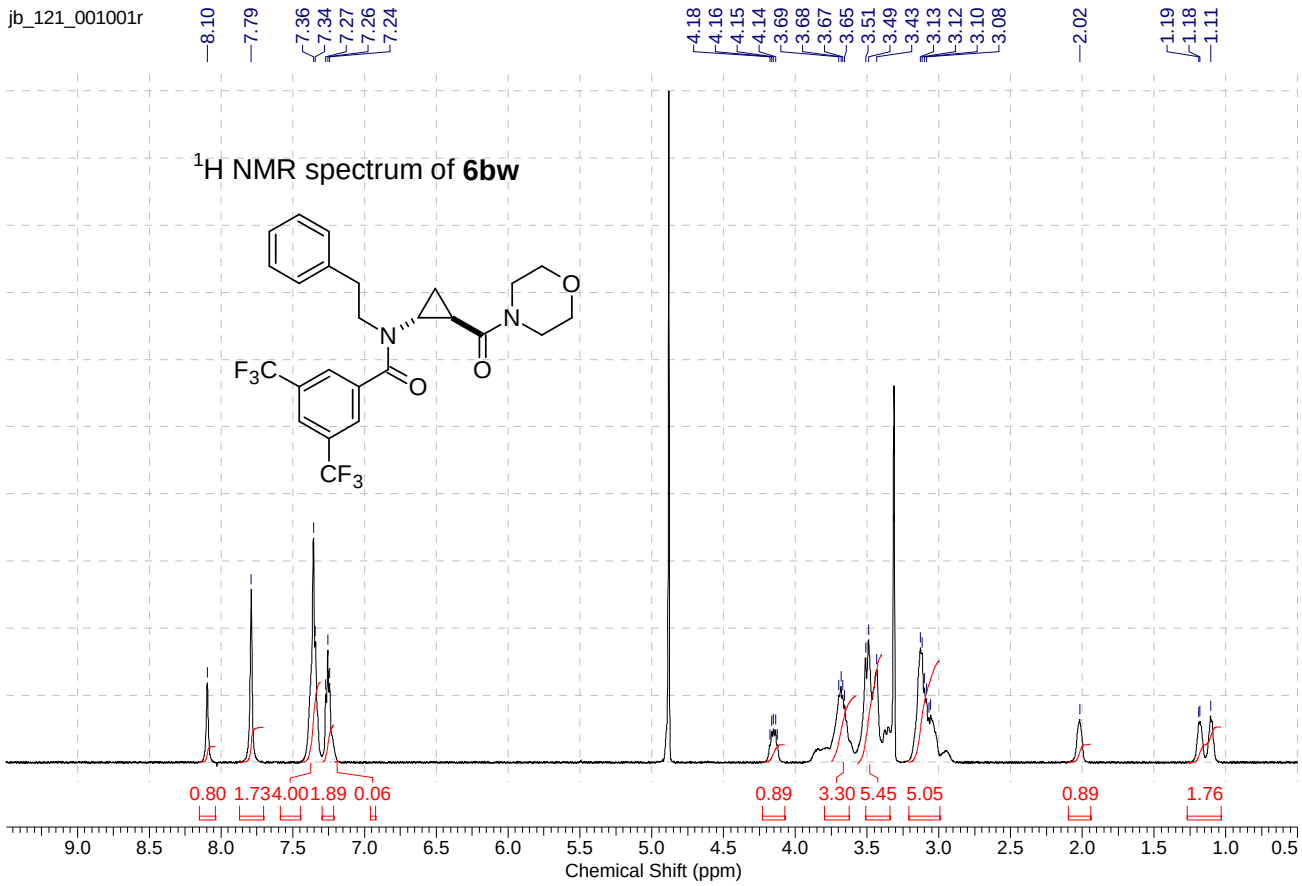

TP0130c_002001r.esp
13C NMR spectrum of 6av
140.82
133.27
133.01
132.74
132.47
129.30
127.77
125.61
124.79
123.45
121.29
52.01
49.53
49.36
49.19
49.02
48.85
48.68
48.51
39.42
31.39
28.90
16.72
9.28
F3C
CF3
N
O
H
N
O
Chemical Shift (ppm)


^{1}H NMR spectrum of **6aw**
Chemical Shift (ppm)

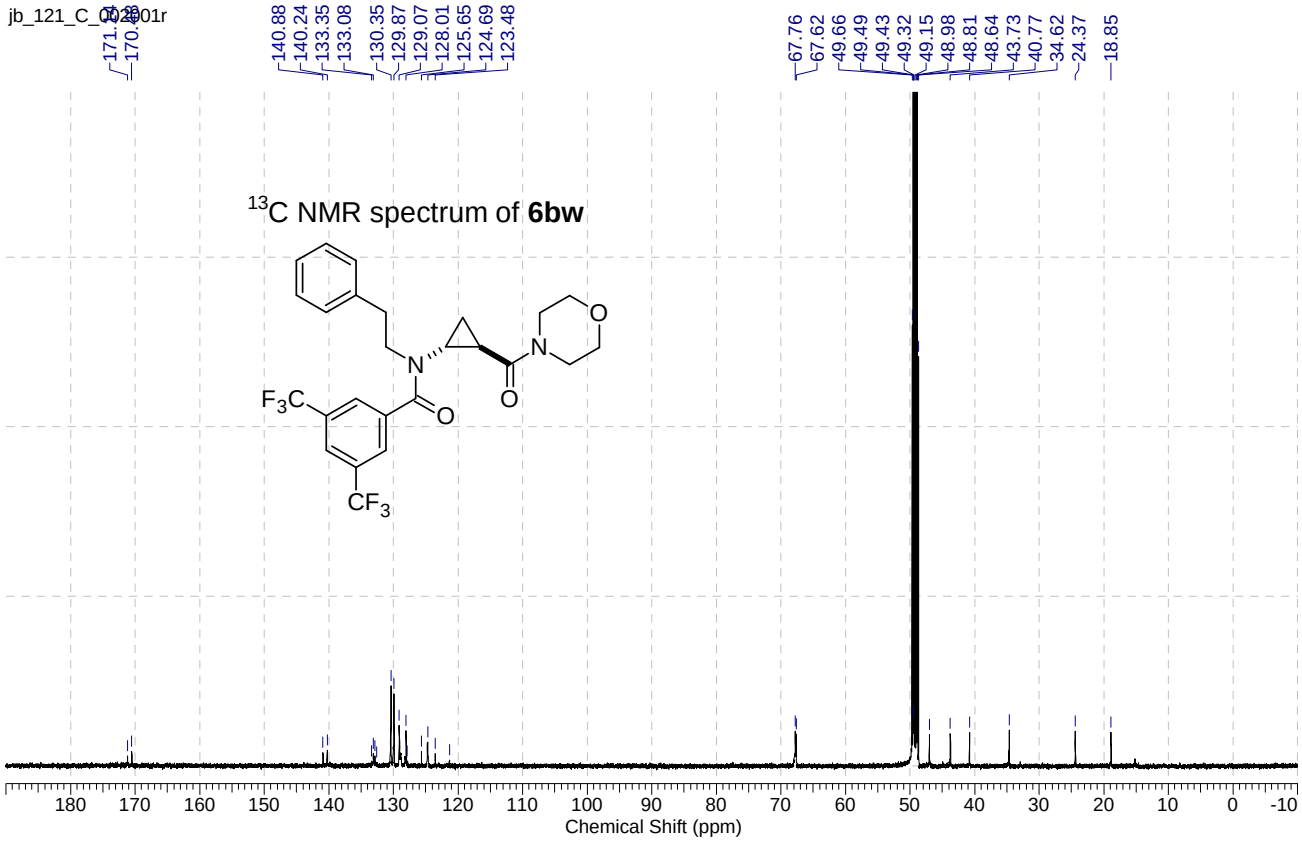

^{13}C NMR spectrum of **6aw**
Chemical Shift (ppm)


jb_0127_H1_001001r
8.12
8.10
3.84
3.53
3.50
3.48
3.39
3.37
3.16
3.15
3.04
2.08
1.76
1.60
1.47
1.45
1.29
1.23
1.18
1.02
0.80
^{1}H NMR spectrum of **6bo**
F3C
CF3
O
N
3.00
11.96
0.70
10.00
Chemical Shift (ppm)

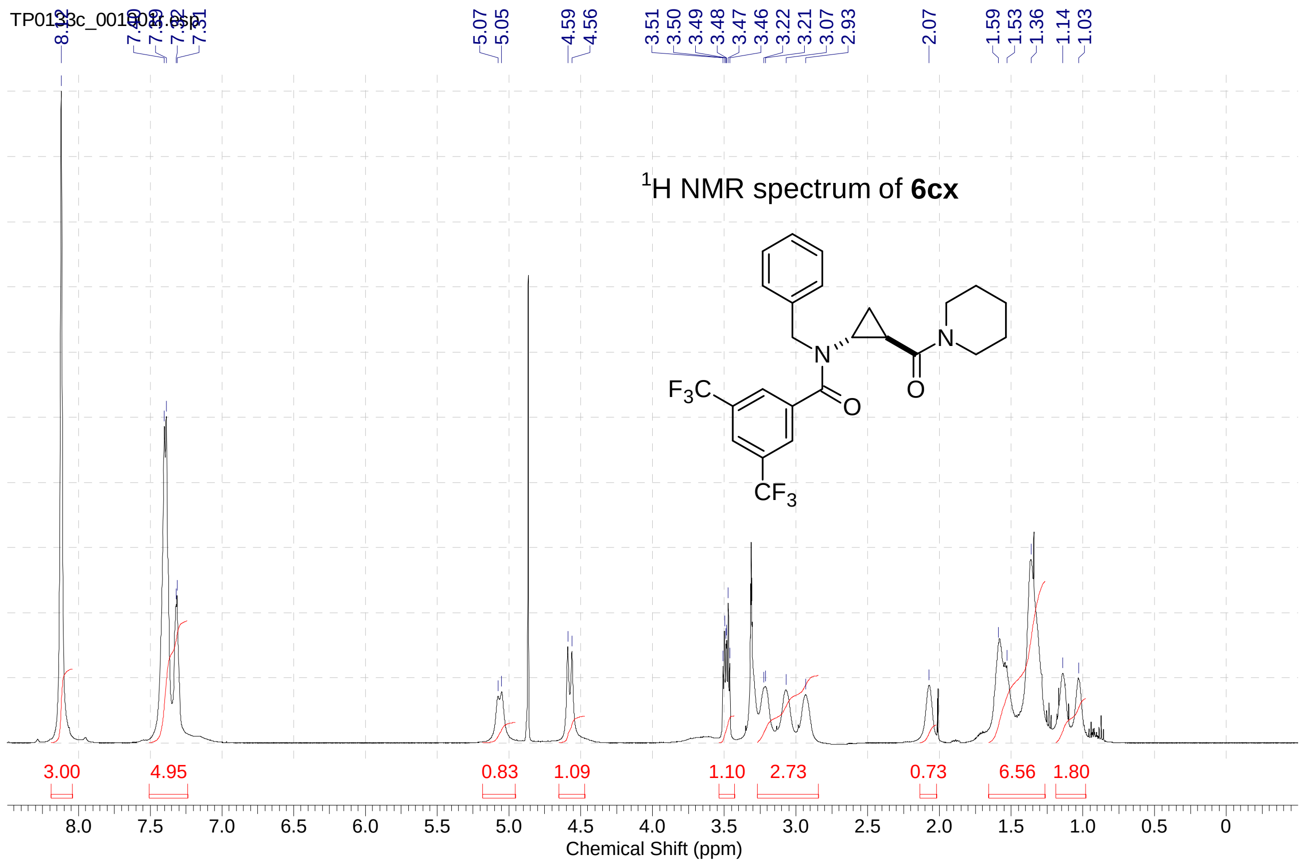

jb_0127_C13_001001r.esp
170.17
170.15
141.04
133.48
133.13
132.81
132.46
129.20
128.67
125.97
124.70
124.65
123.26
120.56
67.74
67.63
49.79
49.58
49.36
49.15
48.94
48.73
48.51
48.09
43.74
40.47
30.91
24.42
21.43
18.77
14.32
^{13}C NMR spectrum of **6bo**
F3C
CF3
O
N
Chemical Shift (ppm)

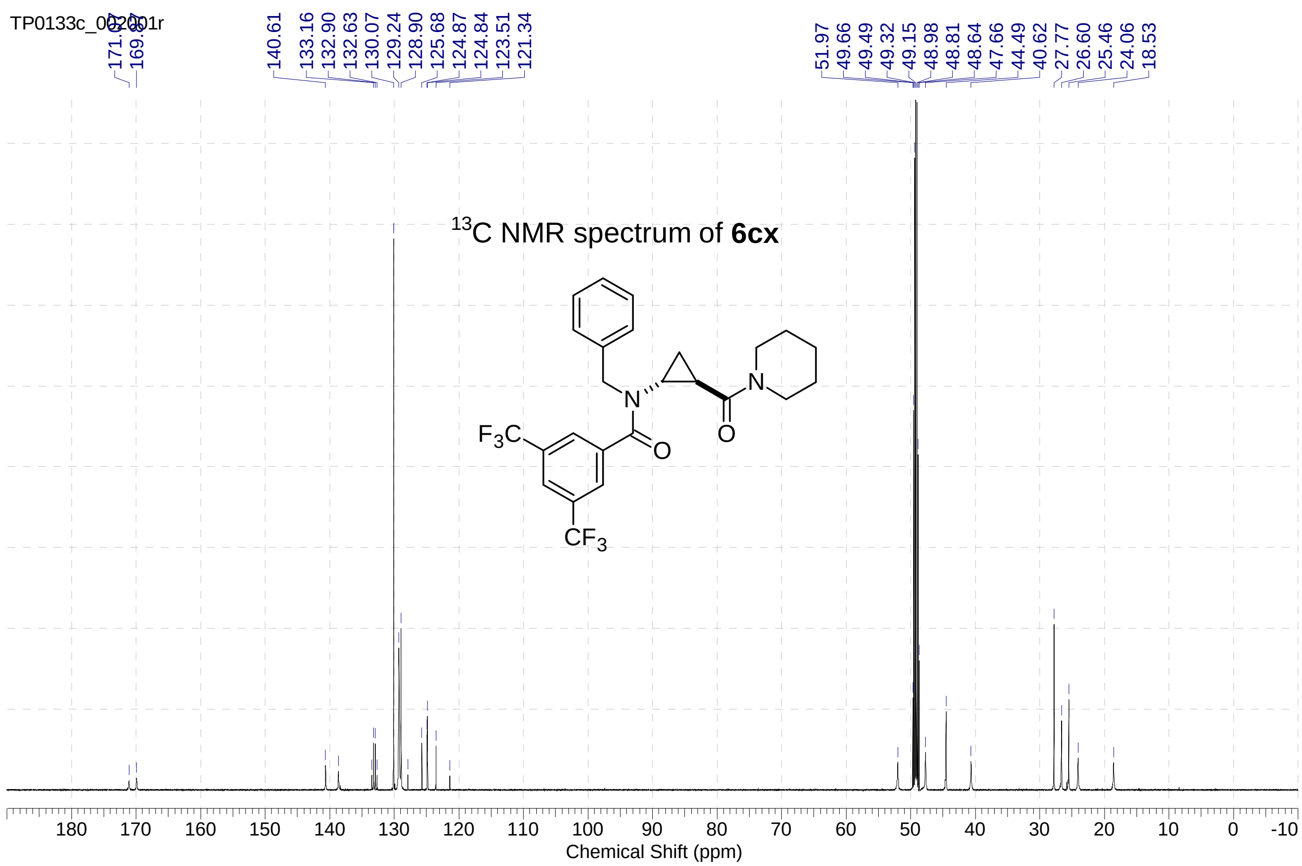


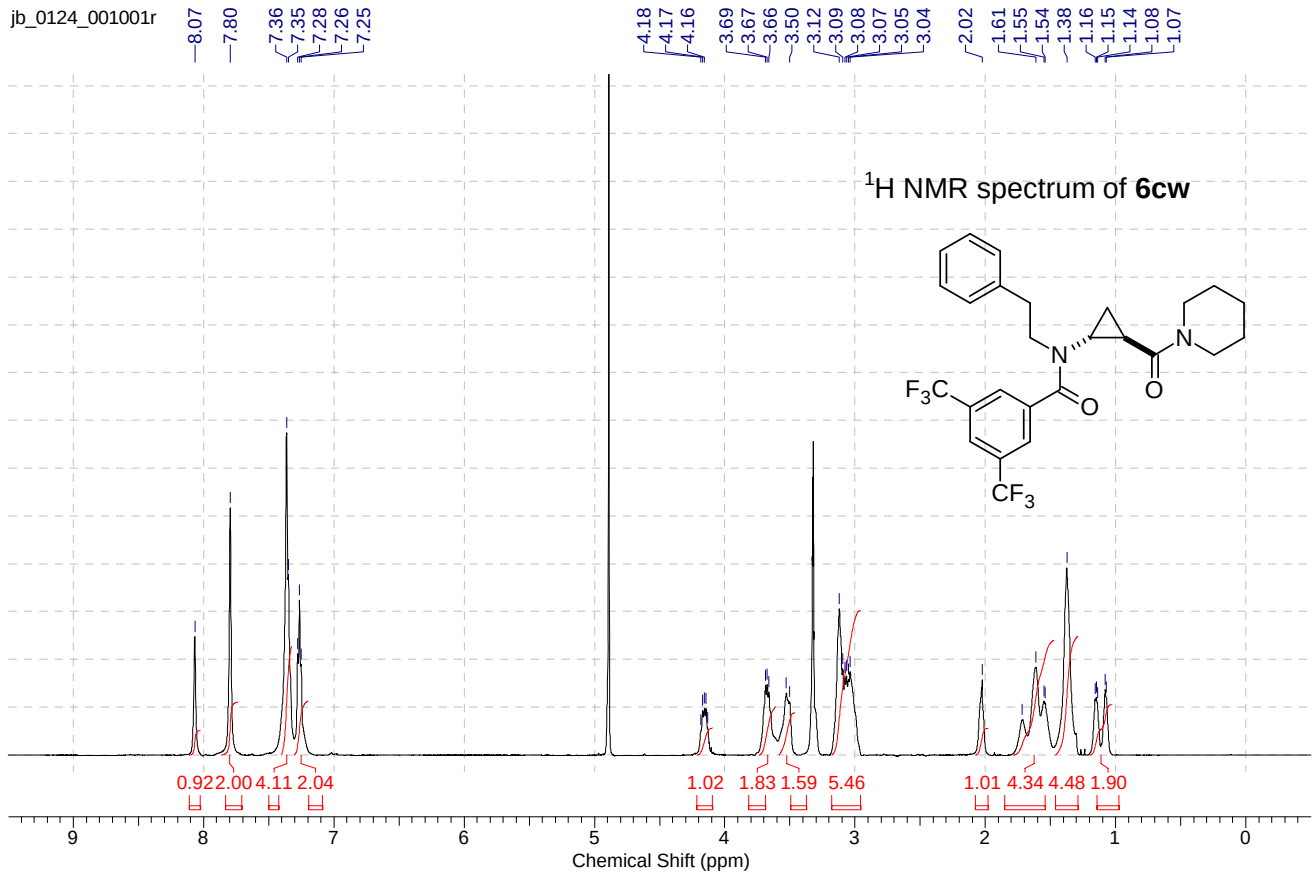
^{1}H NMR spectrum of **6bw**



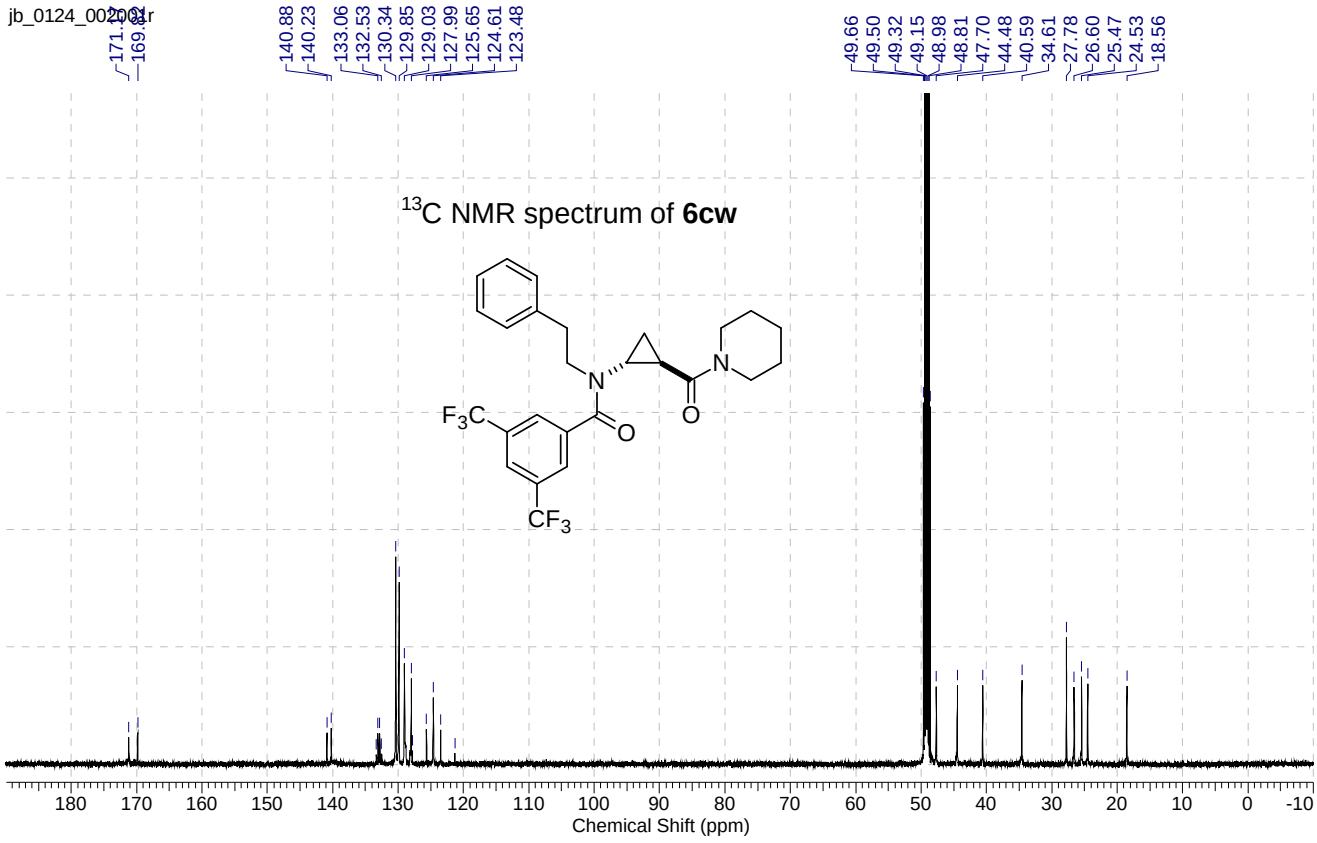
^{13}C NMR spectrum of **6bw**


TP0133c_001001r.esp
8.12
7.40
7.39
7.32
7.31
5.07
5.05
4.59
4.56
3.51
3.50
3.49
3.48
3.47
3.46
3.22
3.21
3.07
2.93
2.07
1.59
1.53
1.36
1.14
1.03
1H NMR spectrum of 6cx
F3C
N
O
N
O
CF3
3.00
4.95
0.83
1.09
1.10
2.73
0.73
6.56
1.80
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

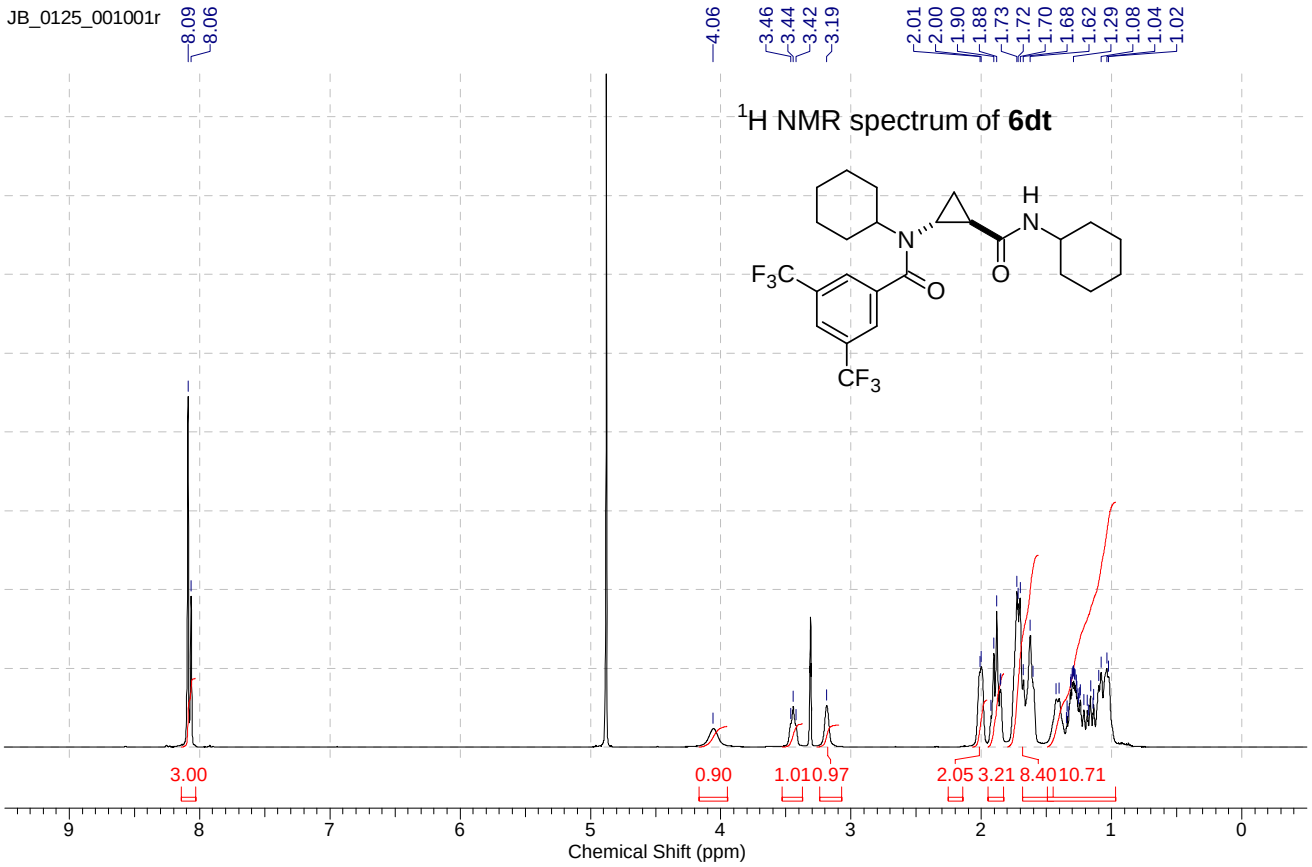

TP0133c_002001r
171.07
169.97
140.61
133.16
132.90
132.63
130.07
129.24
128.90
125.68
124.87
124.84
123.51
121.34
51.97
49.66
49.49
49.32
49.15
48.98
48.81
48.64
47.66
44.49
40.62
27.77
26.60
25.46
24.06
18.53
13C NMR spectrum of 6cx
F3C
N
O
N
O
CF3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

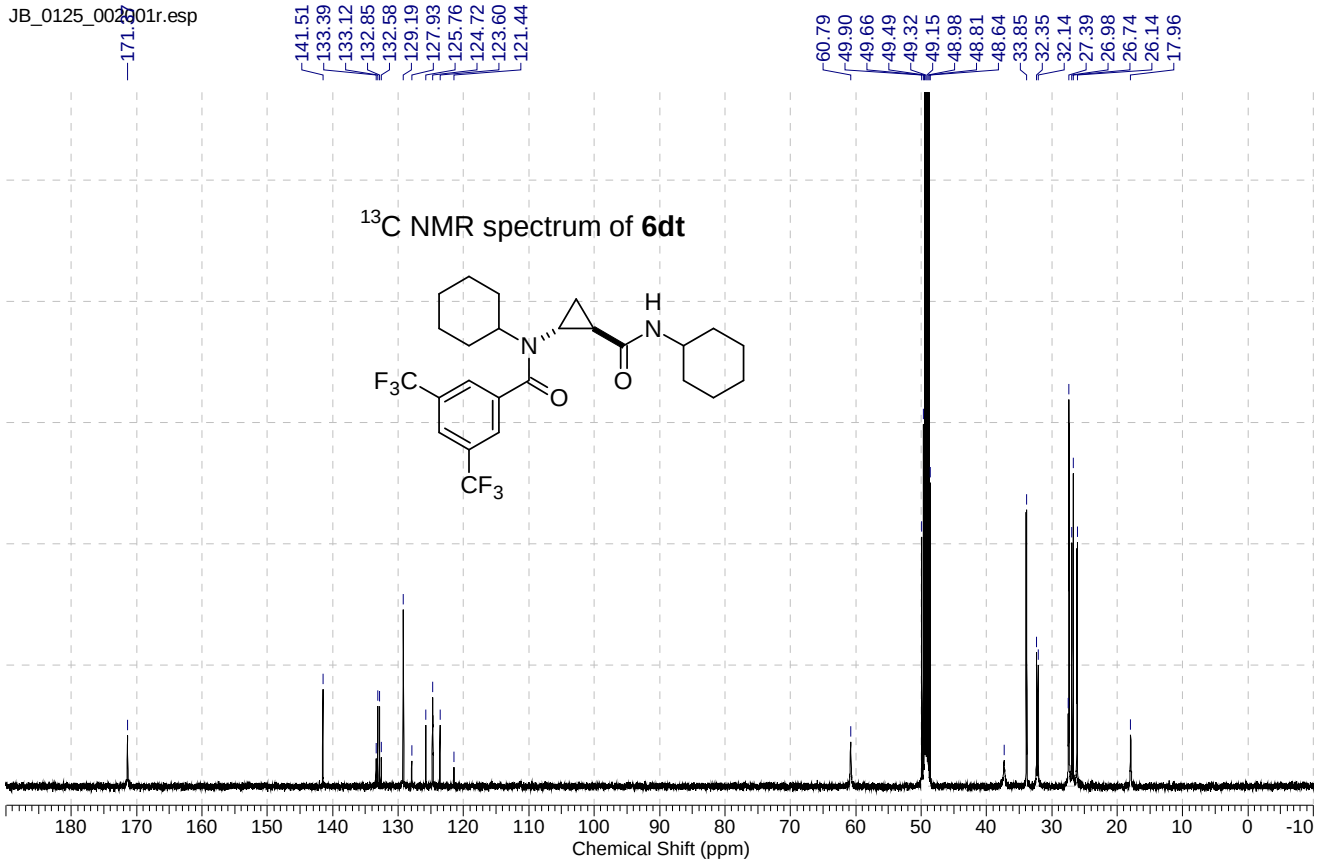


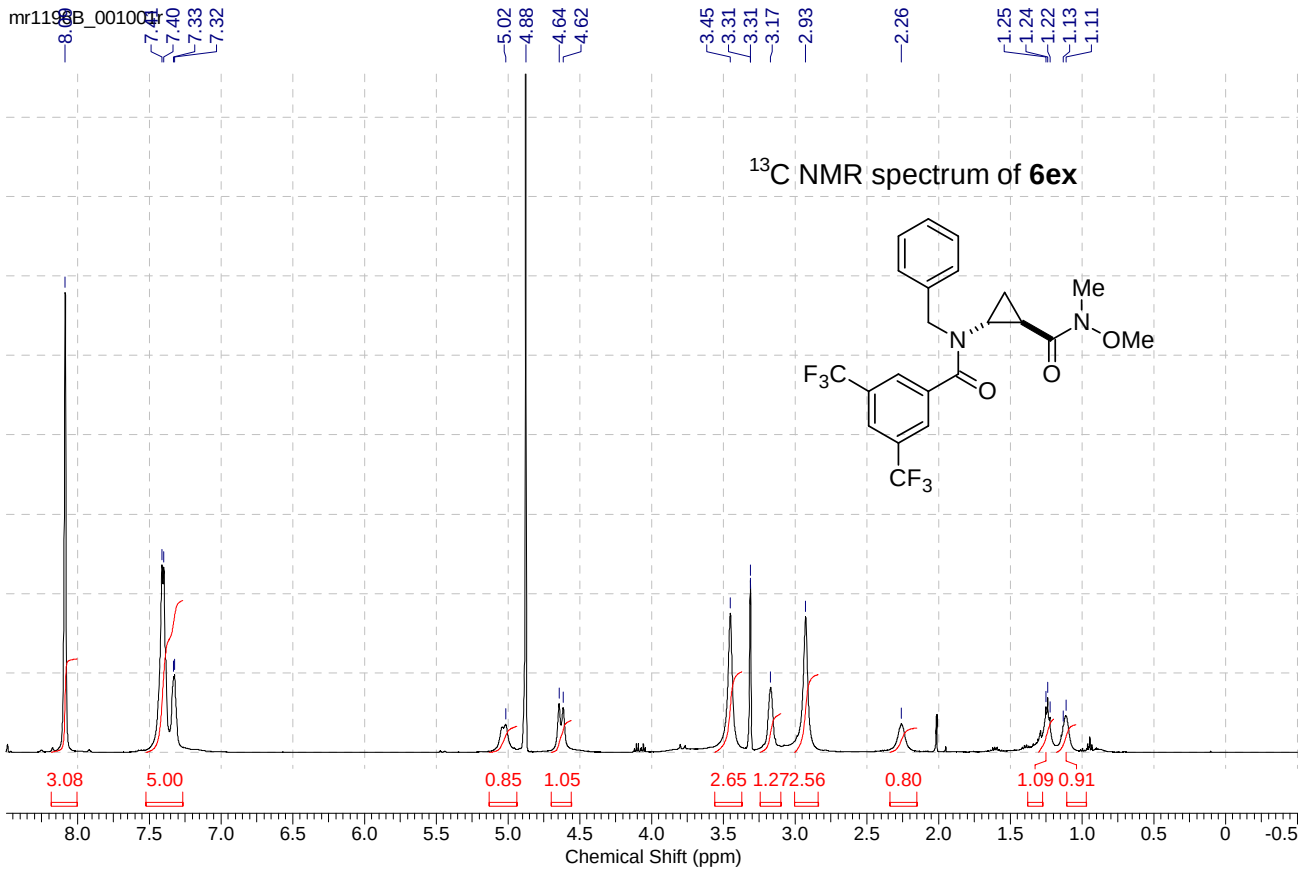
^{1}H NMR spectrum of **6cw**

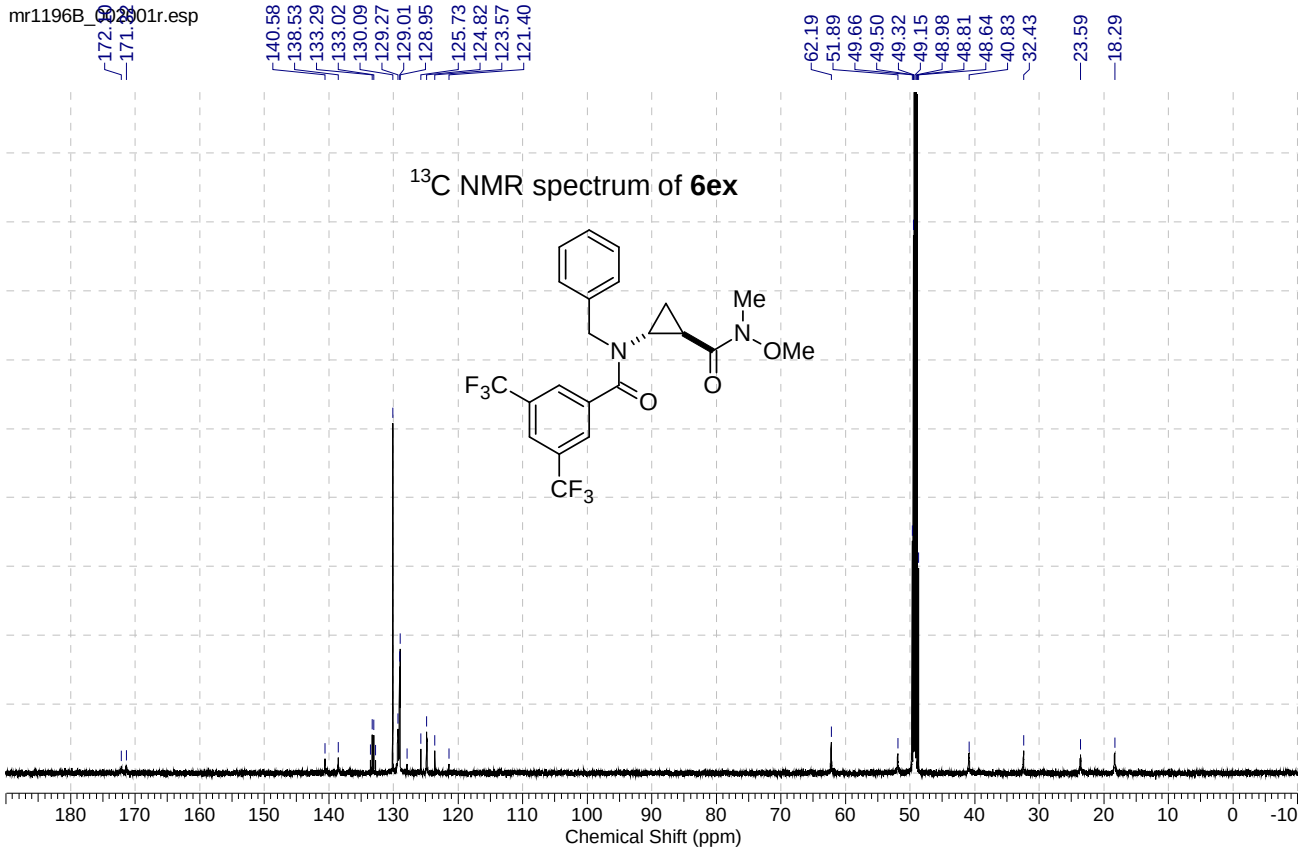


^{13}C NMR spectrum of **6cw**


JB_0125_001001r
8.09
8.06
4.06
3.46
3.44
3.42
3.19
2.01
2.00
1.90
1.88
1.73
1.72
1.70
1.68
1.62
1.29
1.08
1.04
1.02
^{1}H NMR spectrum of **6dt**
H
N
N
O
F_3C
O
CF_3
3.00
0.90
1.01
0.97
2.05
3.21
8.40
10.71
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JB_0125_002001r.esp
171.44
141.51
133.39
133.12
132.85
132.58
129.19
127.93
125.76
124.72
123.60
121.44
60.79
49.90
49.66
49.49
49.32
49.15
48.98
48.81
48.64
33.85
32.35
32.14
27.39
26.98
26.74
26.14
17.96
^{13}C NMR spectrum of **6dt**
H
N
N
O
F_3C
O
CF_3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


mr1196B_001001r
8.08
7.41
7.40
7.33
7.32
5.02
4.88
4.64
4.62
3.45
3.31
3.31
3.17
2.93
2.26
1.25
1.24
1.22
1.13
1.11
^{13}C NMR spectrum of **6ex**
Me
N
OMe
O
N
O
F_3C
CF_3
3.08
5.00
0.85
1.05
2.65
1.27
2.56
0.80
1.09
0.91
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


mr1196B_002001r.esp
172.28
171.66
140.58
138.53
133.29
133.02
130.09
129.27
129.01
128.95
125.73
124.82
123.57
121.40
62.19
51.89
49.66
49.50
49.32
49.15
48.98
48.81
48.64
40.83
32.43
23.59
18.29
^{13}C NMR spectrum of **6ex**
Me
N
OMe
O
N
O
F_3C
CF_3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)