Electronic Supplementary Material (ESI) for Chemical Communications

Intramolecular arylation of amino acid enolates

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SUPPORTING INFORMATION

CONTENTS

General Information

Nuclear Magnetic Resonance (NMR) spectra (^{1}H NMR and ^{13}C NMR) were recorded on either Bruker Ultrashield 300, 400 or 500 MHz spectrometers. The residual solvent peak for $CDCl_3$, CD_3OD, D_2O and $(CD_3)_2SO$ were used as internal standards when assigning NMR spectra (δ_H: $CDCl_3$ 7.26 ppm; δ_C: $CDCl_3$ 77.16 ppm; δ_H: CD_3OD 3.31 ppm; δ_C: CD_3OD 49.00 ppm; δ_H: D_2O 4.79 ppm; δ_H: $(CD_3)_2SO$ 2.50 ppm; δ_C: $(CD_3)_2SO$ 39.52 ppm). Chemical shifts, δ, are quoted in parts per million (ppm) downfield of trimethylsilane. Coupling constants (*J*) are reported to the nearest 0.1 Hz. The splitting patterns for the spectra assignment are abbreviated to: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), septet (sept.), multiplet (m), broad (br.) and some as a combination of these.

Low and high resolution mass spectra were recorded mainly by staff at the University of Manchester. ESI were recorded on a Micromass Platform II or Waters QTOF; GCMS were recorded on Agilent 5975C Triple Axis GCMS; high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP mass spectrometer or Waters QTOF. A small number of HRMS were recorded at the EPSRC National Facility Swansea using the LTQ Orbitrap XL.

Infrared spectra were recorded on a Thermo Scientific iD5 ATR, FT-IR spectrometer, using a Universal ATR accessory for sampling, with absorption of most relevance quoted as ν in cm^{-1}. Capillary melting points were determined on a Stuart Scientific melting point SMP 10 apparatus.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram SIL G/UV254). Visualisation was *via* UV light (at 254 nm) or by staining with phosphomolybdic acid or 'Seebach' dip (2.50 g phosphomolybdic acid hydrate, 1.00 g Cerium (IV) sulphate tetrahydrate, 3.20 mL conc. H_2SO_4, 90.50 mL H_2O) then heating. Flash column chromatography used chromatography grade silica, 60 Å particle size, 40-63 microns from Aldrich and compounds were loaded as saturated solutions in the correct solvents.

Optical rotation measurements were taken on an AA-100 polarimeter using a cell with a pathlength of 0.25 dm at 20-21 ^{o}C with the solvent and concentration (g/100 mL) stated.

All reactions were performed under a nitrogen atmosphere in flame-dried apparatus. All reagents and chemicals were bought from chemical suppliers and used without further purification (unless stated). Tetrahydrofuran (THF) was distilled under nitrogen from sodium wire using benzophenone as an indicator. Diisopropylamine (DiPA) and dichloromethane (DCM) were obtained by distillation from calcium hydride under nitrogen. Diethylether was collected under inert conditions from an Innovative Technologies PureSolve PS-MP-5 solvent purification system. All solvents were removed under

vacuum using a rotary evaporator. Pet.Ether indicates fractions of petroleum ether boiling at 40-60 °C. Lithium chloride (LiCl) was dried in the oven and used directly. Acetone/dry ice cooling baths were used to obtain -78 °C, acetonitrile/dry ice cooling baths were used to obtain -40 °C and other temperatures were reached using a Thermo Scientific Haake Immersion Cooler EK90.

The ReactIR *i*C10, made by Mettler Toledo was used for the *in situ* IR experiments. It was fitted with a K6 conduit, that is a silicon tipped 16mm probe, and uses an MCT detector. The data was collected using *i*C IR software (version 4.1.882) as supplied by Mettler Toledo. Nitrogen purge of the probe was used throughout the experiment and this was subtracted from all spectra as the background. Further to this, solvent spectra at the appropriate temperature for each experiment were taken and this was also subtracted from the data. Each spectrum represents 256 scans measured at a spectral resolution of 8 cm^{-1} although provides data points approximately every 4 cm^{-1}.

General Procedures

Procedure 1: *Carbamoyl chloride formation from methylaniline*

To a solution of triphosgene (0.5 eq) in anhydrous DCM (0.4 M) at -78 °C were added pyridine (1.0 eq), followed by *N*-methylaniline (1.0 eq) in anhydrous DCM (16.0 M). After 10 minutes the reaction mixture was warmed to room temperature, stirred for three hours and quenched with 1.0 M HCl. The organic layer was separated and the aqueous layer was extracted with DCM three times. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used without further purification.

Procedure 2: *Nitrile urea formation from carbamoyl chloride*

To a solution of 2-aminopropanonitrile hydrochloride (1.5 eq) in anhydrous 1,2-DCE (0.3 M) was added triethylamine (2.5 eq). To the resulting mixture was added carbamoyl chloride (1.0 eq) and DMAP (catalytic amount). The reaction was heated at 65 °C and left until TLC analysis showed the reaction was complete. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with 1.0 M HCl, then brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 3: *Methylation of nitrile ureas*

A solution of urea (1.0 eq) in anhydrous DMF (0.1 M) was cooled to 0 °C and sodium hydride (60% solution, 2.0 eq) was added. The resulting mixture was stirred for fifteen minutes, before adding methyl iodide (3.0 eq). The reaction was then stirred for one hour at 0 °C. The resulting mixture was diluted with ethyl acetate, quenched by the addition of ice and 1.0 M NaOH. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 4: *Imino hydantoin formation from methylated nitrile urea*

To a solution of urea (1.0 eq) in anhydrous THF (0.1 M) at -78 °C was added dropwise *s* BuLi (1.3 M solution in hexane, 2.0 eq). The reaction mixture was stirred for one hour then quenched with MeOH and saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 5: *Hydantoin formation from imino hydantoin*

A stirred mixture of imine (1.0 eq), HCl (12.0 M, 60.0 eq) and ethanol (0.2 M) was refluxed for twenty hours. The resulting mixture was diluted with water and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 6a: *Urea formation from carbamoyl chloride*

Amine·HCl (1.1 eq), anhydrous 1,2-DCE (0.2-0.6 M) and Et_3N (2.3 eq) were combined and stirred for ten minutes at room temperature. To this solution was added the carbamoyl chloride (1.0 eq) and DMAP (catalytic amount). The reaction mixture was then heated to reflux and left until TLC analysis showed the reaction was complete. The reaction mixture was cooled to room temperature then quenched with saturated aqueous $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with 1.0 M HCl and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 6b: *Urea formation from carbamoyl chloride*

Amine.HCl (1.0 eq) was added to a stirred solution of carbamoyl chloride (1.0 eq) dissolved in anhydrous 1,2-DCE (0.1-0.5 M). Et_3N (1.2 eq) and DMAP (catalytic amount) were then added and the resulting mixture was refluxed for two hours. The mixture was then diluted with DCM and quenched with water. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 7: *Methylation of ureas*

Urea (1.0 eq) was dissolved in anhydrous DMF (0.1-0.4 M) and methyl iodide (3.0 eq) was added. The solution was cooled to 0 °C before sodium hydride (2.0 eq, (60% suspension)) was added. The reaction was allowed to warm to room temperature, monitored by TLC and worked up when complete. The reaction mixture was quenched with water and basified before being extracted three times with diethyl ether. The combined organic layers were washed twice with water, once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 8: *Removal of tert-butyl group (TFA deprotection)*

Urea (1.0 eq) was dissolved in anhydrous DCM (0.5-0.7 M) and TFA (0.5-0.7 M) was added dropwise. The reaction mixture was left to stir at room temperature and monitored by TLC. When the reaction was complete, the reaction mixture was diluted with DCM (three times starting amount) and washed with water three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 9: *Removal of benzyl group (hydrogenation)*

Urea ester (1.0 eq) was dissolved in methanol (0.2 M) and nitrogen was bubbled through the solution. 10% palladium on carbon (10% by weight) was added to the reaction mixture and the reaction was placed under a hydrogen atmosphere through use of a balloon. The reaction mixture was left to stir at room temperature and monitored by TLC. When the reaction was complete the solution was filtered over celite, washed through with ethyl acetate and concentrated *in vacuo*. The crude product was used without any further purification.

Procedure 10: *Removal of methyl ester group (saponification)*

Urea (1.0 eq) was dissolved in 2:1 THF:H_2O (0.03 M) and LiOH (50.0 eq) was added. The resulting mixture was stirred for twenty hours at 45 °C. The reaction mixture was diluted with ethyl acetate and 1.0 M HCl was added until pH = 2. The organic layer was then separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 11: *Rearrangement to hydantoin*

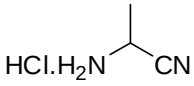
To urea acid (1.0 eq) was added anhydrous LiCl (3.0 eq) and anhydrous THF (0.1 M (overall)). The reaction mixture was cooled to -78 ^{o}C. In a separate flask LDA was prepared; anhydrous THF (0.1 M (overall)) and DiPA (3.0 eq) were cooled to 0 ^{o}C, *n*BuLi (3.0 eq) was added dropwise and stirred for ten minutes. The LDA was added dropwise to the reaction mixture and a colour change was observed. The reaction mixture was left to stir at -78 ^{o}C for five minutes before the reaction mixture was allowed to warm to room temperature and stir for three hours. The reaction mixture was quenched *via* dropwise addition of 1.0 M HCl and stirred for fifteen to thirty minutes ensuring the pH was acidic. The reaction mixture was extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Stereochemistry of the amino acid derivatives 6

Although the products **5** of the rearrangement are all racemic, for convenience compounds **6** were made from L-amino acids, apart from **6i** (from Gly) and **6j** (from (±)-allylglycine). During the synthesis, alanine derivatives **6a-6d**, **6g**, **6h** underwent partial racemisation (ca. 60% ee). All other carboxylic acids **6** remained enantiomerically pure by HPLC.

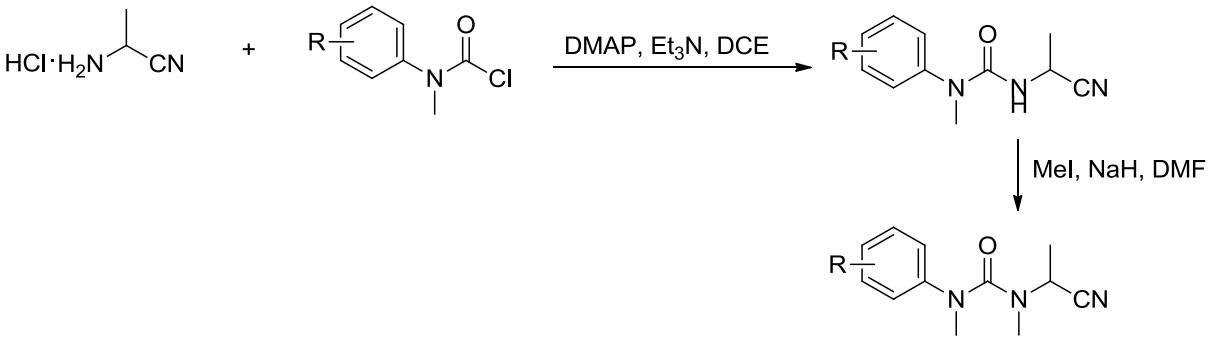
Experimental Procedures and Characterisation Data

Synthesis of 2-aminopropanonitrile hydrochloride[1]

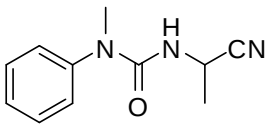


A solution of lactonitrile (6.00 mL, 83.70 mmol, 1.0 eq), NH_4Cl (1.56 g, 29.20 mmol, 0.4 eq) in ammonium hydroxide (34.00 mL) was stirred at room temperature for two hours. The product was extracted with DCM three times, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Diethyl ether (50.00 mL) was added to the resulting amine, the solution was cooled to 0 °C and HCl (2.0 M, 38.50 mL, 0.08 mmol) was added. The mixture was stirred for ten minutes. The suspension formed was filtered *in vacuo*, washed with diethyl ether and air dried to yield 2-aminopropanonitrile hydrochloride as a white solid (1.32 g, 12.38 mmol, 15%). **^{1}H NMR** (300 MHz, CD_3OD): δ_H = 9.12 (2H, br. s, N*H*$_2$), 4.59 (1H, q, *J* = 7.0, C*H*CH$_3$), 1.66 (3H, d, *J* = 7.0, CHC*H*$_3$).

Synthesis of Urea Nitriles:



Synthesis of 1a:

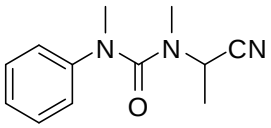


3-(1-Cyanoethyl)-1-methyl-1-phenylurea (S1a)

Following general procedure **2**, *N*-methyl-*N*-phenylcarbamoyl chloride (440 mg, 2.60 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of 2-aminopropanonitrile hydrochloride (417 mg, 3.91 mmol) and Et_3N (0.91 mL, 6.51 mmol) in DCE (8.70 mL). The reaction was complete after twenty hours heating at 65 °C. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a solid (257

[1] M. Paventi and J. T. Edward, *Canadian Journal of Chemistry*, 1987, **65**, 282.

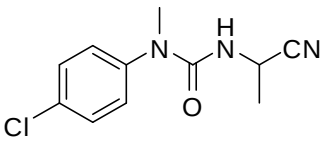
mg, 1.26 mmol, 49%). **S1a**: **mp**: 115-117 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.49-7.43 (2H, m, Ph*H*), 7.40-7.34 (1H, m, Ph*H*), 7.27–7.24 (2H, m, Ph*H*), 4.85 (1H, dq, *J* = 8.4, 7.3, NHC*H*CH_3), 4.50 (1H, d, *J* = 7.3, N*H*CH), 3.28 (3H, s, NCH_3), 1.43 (3H, d, *J* = 7.3 ,CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 155.2 (*C*=O), 142.3 (Ar*C*N), 130.4 (2xAr), 128.1 (Ar), 127.3 (2xAr), 120.0 (*C*≡N), 37.5 (*C*H), 37.4 (N*C*H_3), 19.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3357 (NH), 2942 (C-H), 2353 (C≡N), 1649 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$ 204.1134, found 204.1131.



3-(1-Cyanoethyl)-1,3-dimethyl-1-phenylurea (1a)

Following general procedure **3**, methyl iodide (0.15 mL, 2.36 mmol) and sodium hydride (63 mg, 1.58 mmol) were added to urea **S1a** (160 mg, 0.79 mmol) in DMF (7.00 mL). The reaction was complete after one hour at 0 °C. The title compound was yielded as a yellow oil without further purification (130 mg, 0.60 mmol, 76%). **1a**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.40-7.35 (2H, m, Ph*H*), 7.21-7.16 (1H, m, Ph*H*), 7.11-7.08 (2H, m, Ph*H*), 5.22 (1H, q, *J* = 7.3, C*H*CH_3), 3.24 (3H, s, NCH_3), 2.51 (3H, s, NCH_3), 1.42 (3H, d, *J* = 7.3, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 161.0 (*C*=O), 145.9 (Ar*C*N), 130.0 (2xAr), 125.7 (Ar), 124.7 (2xAr), 118.6 (*C*≡N), 44.2 (*C*H), 40.3 (N*C*H_3), 32.4 (N*C*H_3), 17.1 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2936 (C-H), 2360 (C≡N), 1645 (C=O urea); HRMS (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3ONa$ $[M+Na]^+$ 240.1107, found 240.1110.

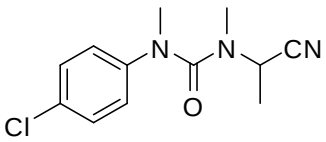
Synthesis of 1b:



1-(4-Chlorophenyl)-3-(1-cyanoethyl)-1-methylurea (S1b)

Following general procedure **1**, to a solution of triphosgene (417 mg, 1.41 mmol) in DCM (4.00 mL) at -78 °C was added pyridine (0.25 mL, 3.06 mmol), followed by 4-chloro-*N*-methylaniline (433 mg, 3.06 mmol) in DCM (0.17 mL). The crude product was used in the next reaction without further purification.

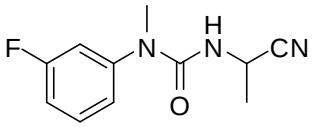
Following general procedure **2**, *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (3.06 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of 2-aminopropanonitrile hydrochloride (396 mg, 3.71 mmol) and Et_3N (0.86 mL, 6.19 mmol) in DCE (10.20 mL). The reaction was complete after twenty hours heating at 65 °C. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a solid (451 mg, 1.89 mmol, 62% over two steps). **S1b**: **mp**: 146-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.49-7.37 (2H, m, Ar*H*), 7.23-7.16 (2H, m, Ar*H*), 4.83 (1H, dq, *J* = 8.3, 7.3, NHC*H*CH_3), 4.47 (1H, br. d, *J* = 8.2, N*H*CH), 3.25 (3H, s, NCH_3), 1.45 (3H, d, *J* = 7.3, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 155.2 (*C*=O), 140.9 (Ar*C*N), 134.0 (Ar*C*Cl), 130.7 (2xAr), 128.8 (2xAr), 120.2 (*C*≡N), 37.7 (*C*H), 37.6 (N*C*H_3), 19.9 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3305 (NH), 3072, 2990, 2943, 2881 (C-H), 2246 (C≡N), 1648 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{12}N_3OClNa$ $[M+Na]^+$ 260.0561, found 260.0569.



1-(4-Chlorophenyl)-3-(1-cyanoethyl)-1,3-dimethylurea (1b)

Following general procedure **3**, methyl iodide (0.24 mL, 3.79 mmol) and sodium hydride (126 mg, 3.16 mmol) were added to urea **S1b** (300 mg, 1.26 mmol) in DMF (3.20 mL). The reaction was complete after one hour at 0 °C. The title compound was yielded as a yellow oil without further purification (224 mg, 0.89 mmol, 71%). **1b**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.32-7.29 (2H, d, *J* = 8.7, Ar*H*), 7.03-7.00 (2H, d, *J* = 8.7, Ar*H*), 5.15 (1H, q, *J* = 7.2, C*H*CH_3), 3.18 (3H, s, NCH_3), 2.49 (3H, s, NCH_3), 1.45 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 160.5 (*C*=O), 144.2 (Ar*C*N), 130.8 (Ar*C*Cl), 129.8 (2xAr), 125.6 (2xAr), 118.4 (*C*≡N), 44.0 (*C*H), 39.9 (N*C*H_3), 32.4 (N*C*H_3), 19.9 (CH_3); **IR (film, cm^{-1})**: ν_{max} = 3080 2990, 2942, 2880 (C-H), 2242 (C≡N), 1648 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}N_3OClNa$ $[M+Na]^+$ 274.0718, found 274.0721.

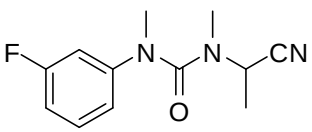
Synthesis of 1c:



3-(1-Cyanoethyl)-1-(3-fluorophenyl)-1-methylurea (S1c)

Following general procedure **1**, to a solution of triphosgene (377 mg, 1.27 mmol) in DCM (3.63 mL) at -78 °C was added pyridine (0.22 mL, 2.76 mmol), followed by 3-fluoro-*N*-methylaniline (345 mg, 2.76 mmol) in DCM (0.17 mL). The crude product was used in the next reaction without purification.

Following general procedure **2**, *N*-(3-fluorophenyl)-*N*-methylcarbamoyl chloride (2.76 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of 2-aminopropanonitrile hydrochloride (427 mg, 4.01 mmol) and Et_3N (0.93 mL, 6.68 mmol) in DCE (9.20 mL). The reaction was complete after twenty hours heating at 65 °C. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a solid (317 mg, 1.43 mmol, 52% over two steps). **S1c**: **mp**: 96-98 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.50-7.32 (1H, m, Ar*H*), 7.11-6.84 (3H, m, Ar*H*), 4.86-4.62 (2H, m, NHC*H*CH_3 and N*H*CH), 3.24 (3H, s, NCH_3), 1.43 (3H, d, *J* = 7.3, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 163.3 (d, $^{1}J_{C\text{-}F}$ = 249.6, Ar*C*F), 155.0 (*C*=O), 143.9 (d, $^{3}J_{C\text{-}F}$ = 9.3, Ar*C*N), 131.5 (d, $^{3}J_{C\text{-}F}$ = 9.3, Ar), 122.9 (d, $^{4}J_{C\text{-}F}$ = 3.2, Ar), 120.0 (*C*≡N), 115.1 (d, $^{2}J_{C\text{-}F}$ = 20.9, Ar), 114.6 (d, $^{2}J_{C\text{-}F}$ = 22.0, Ar), 37.7 (*C*H), 37.5 (N*C*H_3), 19.7 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3318 (NH), 3068, 2992, 2943, 2880 (C-H), 2242 (C≡N), 1651 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{12}N_3OFNa$ $[M+H]^+$ 244.0857, found 244.0857.

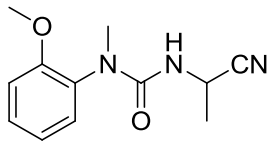


3-(1-Cyanoethyl)-1-(3-fluorophenyl)-1,3-dimethylurea (1c)

Following general procedure **3**, methyl iodide (0.27 mL, 4.30 mmol) and sodium hydride (143 mg, 3.58 mmol) were added to urea **S1c** (317 mg, 1.43 mmol) in DMF (3.60 mL). The reaction was complete after one hour at 0 °C. The title compound was yielded as a yellow oil without further purification (158 mg, 0.67 mmol, 47%). **1c**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.36-7.20 (1H, m, Ar*H*), 6.93-6.72 (3H, m, Ar*H*), 5.18 (1H, q, *J* = 7.2, C*H*CH_3), 3.21 (3H, s, NCH_3), 2.53 (3H, s, NCH_3), 1.43 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz,

$CDCl_3$): δ_C = 163.4 (d, $^1J_{C\text{-}F}$ = 247.9, Ar*C*F), 160.5 (*C*=O), 147.3 (d, $^3J_{C\text{-}F}$ = 9.6, Ar*C*N), 131.0 (d, $^3J_{C\text{-}F}$ = 9.4, Ar), 119.8 (d, $^4J_{C\text{-}F}$ = 3.1, Ar), 118.4 (*C*≡N), 112.5 (d, $^2J_{C\text{-}F}$ = 21.0, Ar), 111.6 (d, $^2J_{C\text{-}F}$ = 23.3, Ar), 44.2 (*C*H), 39.9 (N*C*H_3), 32.5 (N*C*H_3), 17.1 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3069, 2993, 2947 (C-H), 2241 (C≡N), 1652 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3OF$ $[M+H]^+$ 236.1194, found 236.1193.

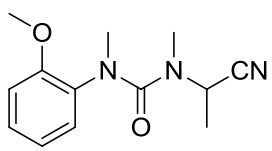
Synthesis of 1d:



3-(1-Cyanoethyl)-1-(2-methoxyphenyl)-1-methylurea (S1d)

Following general procedure **1**, to a solution of triphosgene (369 mg, 1.24 mmol) in DCM (3.55 mL) at -78 °C was added pyridine (0.22 mL, 2.70 mmol), followed by methyl *N*-methylanthranilate (370 mg, 2.70 mmol) in DCM (0.17 mL). The crude product was used in the next reaction without purification.

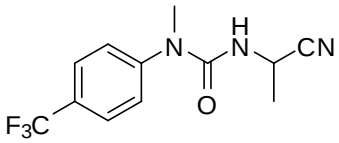
Following general procedure **2**, *N*-(2-methoxyphenyl)-*N*-methylcarbamoyl chloride (2.70 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of 2-aminopropanonitrile hydrochloride (320 mg, 3.01 mmol) and Et_3N (0.70 mL, 5.00 mmol) in DCE (9.00 mL). The reaction was complete after twenty hours heating at 65 °C. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as an oil (138 mg, 0.59 mmol, 22% over two steps). **S1d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.37-7.28 (1H, m, Ar*H*), 7.19-7.13 (1H, m, Ar*H*), 7.04-6.93 (2H, m, Ar*H*) 4.79 (1H, dq, *J* = 8.6, 7.3, NHC*H*CH_3), 4.53 (1H, br. d, *J* = 8.6, N*H*CH), 3.82 (3H, s, OCH_3), 3.12 (3H, s, NCH_3), 1.36 (3H, d, *J* = 7.3, CHCH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 155.9 (Ar*C*OMe), 155.4 (*C*=O), 130.1 (Ar*C*N), 129.9 (Ar), 129.6 (Ar), 121.5 (Ar), 120.2 (*C*≡N), 112.5 (Ar), 55.6 (O*C*H_3), 37.5 (*C*H), 36.4 (N*C*H_3), 19.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3322 (NH), 3080, 2942, 2839 (C-H), 2241 (C≡N), 1650 (C=O urea), 1239, 1024 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3O_2Na$ $[M+Na]^+$ 256.1057, found 256.1057.



3-(1-Cyanoethyl)-1-(2-methoxyphenyl)-1,3-dimethylurea (1d)

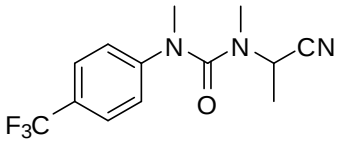
Following general procedure **3**, methyl iodide (0.11 mL, 1.77 mmol) and sodium hydride (59 mg, 1.48 mmol) were added to urea **S1d** (138 mg, 0.59 mmol) in DMF (1.50 mL). The reaction was complete after one hour at 0 °C. The title compound was yielded as a yellow oil without further purification (100 mg, 0.41 mmol, 69%). **1d**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.39-7.23 (1H, m, Ar*H*), 7.18-6.92 (3H, m, Ar*H*), 5.24 (1H, q, *J* = 7.3, C*H*CH_3), 3.95 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 2.51 (3H, s, NCH_3), 1.43 (3H, d, *J* = 7.3, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 161.6 (Ar*C*OMe), 154.1 (*C*=O), 133.8 (Ar*C*N), 128.1 (Ar), 127.7 (Ar), 121.5 (Ar), 118.8 (*C*≡N), 112.0 (Ar), 55.7 (O*C*H_3), 44.1 (*C*H), 38.7 (N*C*H_3), 31.8 (N*C*H_3), 17.2 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3066, 2988, 2942, 2839 (C-H), 2237 (C≡N), 1645 (C=O urea), 1238, 1024 (C-O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{17}N_3O_2Na$ $[M+H]^+$ 270.1213, found 270.1214.

Synthesis of 1e:



3-(1-Cyanoethyl)-1-methyl-1-[4-(trifluoromethyl)phenyl]urea (S1e)

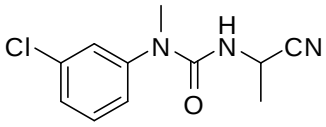
Following general procedure **1**, to a solution of triphosgene (364 mg, 1.23 mmol) in DCM (3.52 mL) at -78 °C was added pyridine (0.22 mL, 2.67 mmol), followed by 4-(trifluoromethyl)-*N*-methylaniline (467 mg, 2.67 mmol) in DCM (0.17 mL). The crude product was used in the next reaction without purification. Following general procedure **2**, *N*-methyl-*N*-[4-(trifluoromethyl)phenyl]carbamoyl chloride (2.67 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of 2-aminopropanonitrile hydrochloride (404 mg, 3.79 mmol) and Et_3N (0.88 mL, 6.31 mmol) in DCE (8.90 mL). The reaction was complete after twenty hours heating at 65 °C. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a solid (385 mg, 1.42 mmol, 53% over two steps). **S1e: mp**: 154-156 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.73-7.70 (2H, d, *J* = 8.4, Ar*H*), 7.40-7.37 (2H, d, *J* = 8.3, Ar*H*), 4.83 (1H, dq, *J* = 8.2, 7.3, NHC*H*CH$_3$), 4.66 (1H, br. d, *J* = 8.2, N*H*CH), 3.30 (3H, s, NC*H*$_3$), 1.47 (3H, d, *J* = 7.3, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 154.9 (*C*=O), 145.8 (Ar*C*N), 129.8 (q, $^2J_{C\text{-}F}$ = 33.1, Ar*C*CF$_3$), 127.5 (q, $^3J_{C\text{-}F}$ = 3.7, 2xAr), 127.4 (2xAr), 123.7 (q, $^1J_{C\text{-}F}$ = 273.2, *C*F), 119.9 (*C*≡N), 37.8 (*C*H), 37.5 (NCH$_3$), 19.8 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3319 (NH), 3069, 2993, 2945, 2884 (C-H), 2243 (C≡N), 1653 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{12}N_3OF_3Na$ $[M+Na]^+$ 294.0825, found 294.0830.



3-(1-Cyanoethyl)-1,3-dimethyl-1-[4-(trifluoromethyl)phenyl]urea (1e)

Following general procedure **3**, methyl iodide (0.27 mL, 4.26 mmol) and sodium hydride (142 mg, 3.55 mmol) were added to urea **S1e** (385 mg, 1.42 mmol) in DMF (3.60 mL). The reaction was complete after one hour at 0 ^{o}C. The title compound was yielded as a yellow oil without further purification (222 mg, 0.78 mmol, 55%). **1e**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.62 (2H, d, *J* = 8.6, Ar*H*), 7.18 (2H, d, *J* = 8.6, Ar*H*), 5.23 (1H, q, *J* = 7.3, C*H*CH$_3$), 3.27 (3H, s, NC*H*$_3$), 2.54 (3H, s, NC*H*$_3$), 1.47 (3H, d, *J* = 7.3, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 160.4 (*C*=O), 148.8 (Ar*C*N), 127.1 (q, $^2J_{C\text{-}F}$ = 32.9, Ar*C*CF$_3$), 127.0 (q, $^3J_{C\text{-}F}$ = 3.7, 2xAr), 123.9 (q, $^1J_{C\text{-}F}$ = 271.8, *C*F), 123.7 (2xAr), 118.3 (*C*≡N), 44.1 (*C*H), 39.6 (NCH$_3$), 32.6 (NCH$_3$), 17.0 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3065, 2948 (C-H), 2361 (C≡N), 1656 (C=O urea); **HRMS** (EI): *m/z* calcd for $C_{13}H_{14}N_3OF_3$ $[M]^{\cdot+}$ 285.1083, found 285.1071.

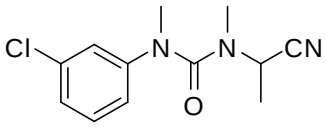
Synthesis of 1f:



1-(3-Chlorophenyl)-3-(1-cyanoethyl)-1-methylurea (S1f)

Following general procedure **1**, to a solution of triphosgene (344 mg, 1.28 mmol) in DCM (9.30 mL) at -78 °C was added pyridine (0.22 mL, 2.78 mmol), followed by *N*-methyl-3-chloroaniline (393 mg, 2.78 mmol) in DCM (0.17 mL). The crude product was used in the next reaction without purification.

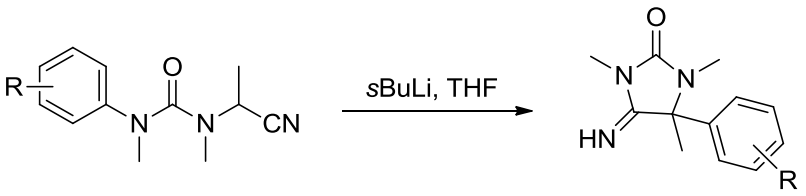
Following general procedure **2**, *N*-(3-chlorophenyl)-*N*-methylcarbamoyl chloride (2.78 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of 2-aminopropanonitrile hydrochloride (396 mg, 3.71 mmol) and Et_3N (0.86 mL, 6.19 mmol) in DCE (9.30 mL). The reaction was complete after twenty hours heating at 65 °C. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a solid (324 mg, 1.36 mmol, 49% over two steps). **S1f**: **mp**: 94-96 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.45-7.07 (4H, m, Ar*H*), 4.80 (1H, dq, *J* = 8.2, 7.3, NHC*H*CH_3), 4.70 (1H, br. d, *J* = 8.2, N*H*CH), 3.25 (3H, s, NCH_3, N*H*CH), 1.46 (3H, d, *J* = 7.1, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 155.0 (*C*=O), 143.6 (Ar*C*N), 135.7 (Ar*C*Cl), 131.3 (Ar), 128.3 (Ar), 127.7 (Ar), 125.6 (Ar), 120.0 (*C*≡N), 37.7 (*C*H), 37.6 (NCH_3), 19.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3316 (NH), 3066, 2991, 2942, 2879 (C-H), 2244 (C≡N), 1650 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{12}N_3OClNa$ $[M+Na]^+$ 260.0561, found 260.0562.



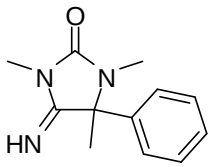
1-(3-Chlorophenyl)-3-(1-cyanoethyl)-1,3-dimethylurea (1f)

Following general procedure **3**, methyl iodide (0.25 mL, 3.93 mmol) and sodium hydride (131 mg, 3.24 mmol) were added to urea **S1f** (311 mg, 1.31 mmol) in DMF (3.30 mL). The reaction was complete after one hour at 0 °C. The title compound was yielded as a yellow oil without further purification (208 mg, 0.83 mmol, 63%). **1f**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.33-7.21 (1H, m, Ar*H*), 7.19-7.05 (2H, m, Ar*H*), 7.01-6.91 (1H, m, Ar*H*), 5.19 (1H, q, *J* = 7.3, C*H*CH_3), 3.22 (3H, s, NCH_3), 2.54 (3H, s, NCH_3), 1.44 (3H, d, *J* = 7.3, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 160.5 (*C*=O), 146.9 (Ar*C*N), 135.4 (Ar*C*Cl), 130.8 (Ar), 125.7 (Ar), 124.5 (Ar), 122.3 (Ar), 118.4 (*C*≡N), 44.2 (*C*H), 39.9 (NCH_3), 32.5 (NCH_3), 17.1 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3066, 2946 (C-H), 2239 (C≡N), 1651 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}N_3OClNa$ $[M+Na]^+$ 274.0718, found 274.0715.

Synthesis of Iminohydantoins:



Synthesis of 2a:

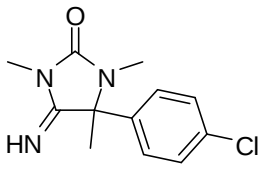


5-Imino-1,3,4-trimethyl-4-phenylimidazolidin-2-one (2a)

Following general procedure **4**, to a solution of urea nitrile **1a** (100 mg, 0.46 mmol) in THF (4.60 mL) at -78 °C was added dropwise *s*BuLi (0.71 mL, 0.92 mmol, 1.3 M in hexanes). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (85 mg, 0.39 mmol, 85%). **2a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.42-7.38 (2H, m, Ph*H*), 7.37-7.33 (1H, m, Ph*H*), 7.29-7.26 (2H, m, Ph*H*), 6.68 (1H, br. s, N*H*), 3.11 (3H, s, NCH_3), 2.73 (3H, s, NCH_3), 1.79 (3H, s, CCH_3); **^{13}C {^{1}H}**

NMR (100 MHz, $CDCl_3$): δ_C = 169.8 (*C*=N), 156.9 (C=O), 138.2 (Ar*C*), 129.3 (2xAr), 128.9 (Ar), 126.1 (2xAr), 66.0 (N*C*C=NH), 25.9 (N*C*H_3), 25.4 (N*C*H_3), 21.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2924 (C-H), 1733 (C=O urea), 1675 (C=N); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3O$ $[M+H]^+$ 218.1289, found 218.1289.

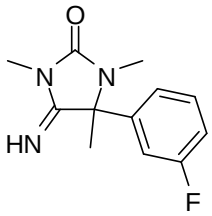
Synthesis of 2b:



4-(4-Chlorophenyl)-5-imino-1,3,4-trimethylimidazolidin-2-one (2b)

Following general procedure **4**, to a solution of urea nitrile **1b** (117 mg, 0.46 mmol) in THF (4.60 mL) at -78 °C was added dropwise *s*BuLi (0.72 mL, 0.92 mmol, 1.3 M in hexanes). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (115 mg, 0.45 mmol, 98%). **2b**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.40-7.32 (2H, m, Ar*H*), 7.24-7.11 (2H, m, Ar*H*), 6.68 (1H, br. s, N*H*), 3.07 (3H, s, NC*H*$_3$), 2.70 (3H, s, NC*H*$_3$), 1.78 (3H, s, CC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 168.6 (*C*=N), 156.6 (*C*=O), 136.9 (Ar*C*), 134.9 (Ar*C*), 129.4 (2xAr), 127.6 (2xAr), 65.5 (N*C*C=NH), 25.8 (N*C*H_3), 25.3 (N*C*H_3), 21.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3274 (NH), 3065, 2935 (C-H), 1731 (C=O urea), 1654 (C=N); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}N_3OClNa$ $[M+Na]^+$ 274.0718, found 274.0715.

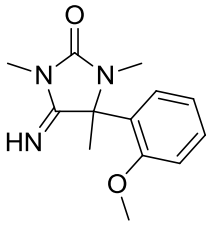
Synthesis of 2c:



4-(3-Fluorophenyl)-5-imino-1,3,4-trimethylimidazolidin-2-one (2c)

Following general procedure **4**, to a solution of urea nitrile **1c** (117 mg, 0.50 mmol) in THF (5.00 mL) at -78 °C was added dropwise *s*BuLi (0.77 mL, 1.00 mmol, 1.3 M in hexanes). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (101 mg, 0.43 mmol, 86%). **2c**: **mp**: 123-125 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.44-7.30 (1H, m, Ar*H*), 7.13-6.91 (3H, m, Ar*H*), 6.69 (1H, br. s, N*H*), 3.09 (3H, s, NC*H*$_3$), 2.73 (3H, s, NC*H*$_3$), 1.77 (3H, s, CC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 168.5 (*C*=N), 163.3 (d, $^1J_{C\text{-}F}$ = 247.8, Ar*C*F), 156.7 (*C*=O), 141.0 (d, $^3J_{C\text{-}F}$ = 5.5, Ar*C*), 130.9 (d, $^3J_{C\text{-}F}$ = 8.2, Ar), 121.8 (d, $^4J_{C\text{-}F}$ = 2.8, Ar), 115.9 (d, $^2J_{C\text{-}F}$ = 21.2, Ar), 113.6 (d, $^2J_{C\text{-}F}$ = 22.8, Ar), 65.6 (N*C*C=NH), 25.8 (*C*H_3), 25.4 (N*C*H_3), 21.9 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3278 (NH), 3070, 2978, 2943 (C-H), 1731 (C=O urea), 1653 (C=N); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3OF$ $[M+H]^+$ 236.1194, found 236.1194

Synthesis of 2d:

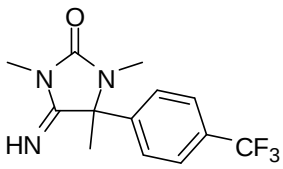


5-Imino-4-(2-methoxyphenyl)-1,3,4-trimethylimidazolidin-2-one (2d)

Following general procedure **4**, to a solution of urea nitrile **1d** (92 mg, 0.37 mmol) in THF (3.70 mL) at -78 °C was added dropwise *s*BuLi (0.57 mL, 0.74 mmol, 1.3

M in hexanes). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (70 mg, 0.28 mmol, 76%). **2d**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.46-7.28 (2H, m, Ar*H*), 6.97 (1H, t, *J* = 7.6, Ar*H*), 6.86 (1H, d, *J* = 8.1, Ar*H*), 6.44 (1H, br. s, N*H*) 3.69 (3H, s, OCH_3), 3.11 (3H, s, NCH_3), 2.52 (3H, s, NCH_3), 1.71 (3H, s, CCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 170.6 (*C*=N), 158.1 (Ar*C*OMe), 157.4 (*C*=O), 130.7 (Ar), 128.7 (Ar), 125.2 (Ar*C*), 120.5 (Ar), 111.8 (Ar), 64.1 (N*C*C=NH), 56.0 (O*C*H_3), 25.7 (N*C*H_3), 25.3 (N*C*H_3), 22.9 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3271 (NH), 3085, 2935, 2839 (C-H), 1730 (C=O urea), 1653 (C=N), 1251, 1016 (C-O); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{18}N_3O_2$ $[M+H]^+$ 248.1398, found 248.1389.

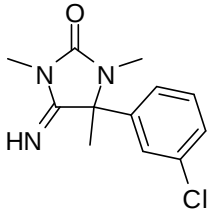
Synthesis of 2e:



5-Imino-1,3,4-trimethyl-4-[4-(trifluoromethyl)phenyl]imidazolidin-2-one (2e)

Following general procedure **4**, to a solution of urea nitrile **1e** (110 mg, 0.39 mmol) in THF (3.90 mL) at -78 °C was added dropwise *s*BuLi (0.59 mL, 0.77 mmol, 1.3 M in hexanes). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (107 mg, 0.38 mmol, 97%). **2e**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.65 (2H, d, *J* = 8.3, Ar*H*), 7.40 (2H, d, *J* = 8.2, Ar*H*), 6.50 (1H, br. s, N*H*), 3.07 (3H, s, NCH_3), 2.73 (3H, s, NCH_3), 1.81 (3H, s, CCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 168.0 (*C*=N), 156.7 (*C*=O), 142.4 (Ar*C*), 131.0 (q, $^2J_{C\text{-}F}$ = 32.6, Ar*C*CF_3), 126.7 (2xAr), 126.3 (q, $^3J_{C\text{-}F}$ = 3.6, 2xAr), 123.8 (q, $^1J_{C\text{-}F}$ = 272.3, *C*F), 65.7 (N*C*C=NH), 25.8 (N*C*H_3), 25.4 (N*C*H_3), 21.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3276 (NH), 3073, 2940 (C-H), 1733 (C=O urea), 1653 (C=N); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{15}N_3OF_3$ $[M+H]^+$ 286.1162, found 286.1174.

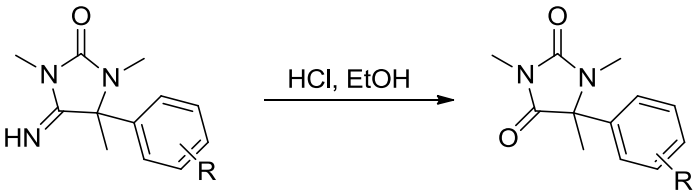
Synthesis of 2f:



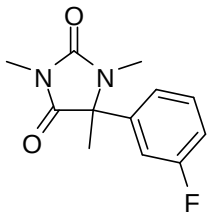
4-(3-Chlorophenyl)-5-imino-1,3,4-trimethylimidazolidin-2-one (2f)

Following general procedure **4**, to a solution of urea nitrile **1f** (130 mg, 0.52 mmol) in THF (5.20 mL) at -78 °C was added dropwise *s*BuLi (0.79 mL, 1.03 mmol, 1.3 M in hexanes). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (111 mg, 0.44 mmol, 85%). **2f**: **mp**: 131-133 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.41-7.10 (4H, m, Ar*H*), 6.68 (1H, br. s, N*H*), 3.11 (3H, s, NCH_3), 2.74 (3H, s, NCH_3), 1.78 (3H, s, CCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 168.6 (*C*=N), 156.7 (*C*=O), 140.4 (Ar*C*), 135.3 (Ar*C*), 130.5 (Ar), 129.0 (Ar), 126.5 (Ar), 124.4 (Ar), 65.6 (N*C*C=NH), 25.8 (N*C*H_3), 25.4 (N*C*H_3), 21.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3273 (NH), 3083, 2977, 2942 (C-H), 1731 (C=O urea), 1652 (C=N); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3OCl$ $[M+H]^+$ 252.0898, found 252.0909.

Synthesis of hydantoins:



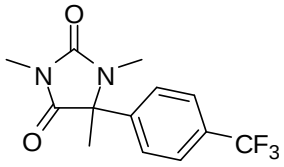
Synthesis of 5c:



5-(3-Fluorophenyl)-1,3,5-trimethylimidazolidin-2,4-one (5c)

Following general procedure **5**, to a solution of imino hydantoin **2c** (96 mg, 0.41 mmol) in ethanol (2.36 mL) was added 12.0 M HCl (0.79 mL). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (54 mg, 0.23 mmol, 56%). **5c**: $\mathbf{R_f}$ (2:1 Pet.Ether:EtOAc) 0.34; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.46-7.28 (1H, m, Ar*H*), 7.13-6.87 (3H, m, Ar*H*), 3.04 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 1.78 (3H, s, CCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.5 (*C*=O), 163.3 (d, $^1J_{C\text{-}F}$ = 247.4, Ar*C*F), 156.3 (*C*=O), 139.1 (d, $^3J_{C\text{-}F}$ = 6.8, Ar*C*C), 130.8 (d, $^3J_{C\text{-}F}$ = 8.2, Ar), 121.7 (d, $^4J_{C\text{-}F}$ = 2.9, Ar), 115.9 (d, $^2J_{C\text{-}F}$ = 21.0, Ar), 113.5 (d, $^2J_{C\text{-}F}$ = 23.1, Ar), 65.5 (d, $^4J_{C\text{-}F}$ = 1.7, N*C*C=O), 25.5 (N*C*H$_3$), 25.3 (N*C*H$_3$), 20.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3072, 2939 (C-H), 1770 (C=O amide), 1706 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}O_2N_2F$ $[M+H]^+$ 237.1034, found 237.1029.

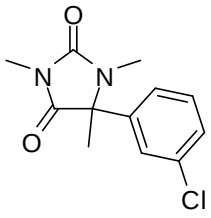
Synthesis of 5e:



1,3,5-Trimethyl-5-[4-(trifluoromethyl)phenyl]imidazolidin-2,4-one (5e)

Following general procedure **5**, to a solution of imino hydantoin **2e** (80 mg, 0.28 mmol) in ethanol (1.63 mL) was added 12.0 M HCl (0.54 mL). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (40 mg, 0.14 mmol, 50%). **5e**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.67 (2H, d, *J* = 8.3, Ar*H*), 7.42 (2H, d, *J* = 8.2, Ar*H*), 3.05 (3H, s, NCH_3), 2.88 (3H, s, NCH_3), 1.84 (3H, s, CCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.0 (*C*=O), 156.3 (*C*=O), 140.6 (Ar*C*), 131.1 (q, $^2J_{C\text{-}F}$ = 32.8, Ar*C*CF$_3$), 126.6 (2xAr), 126.3 (q, $^3J_{C\text{-}F}$ = 3.7, 2xAr), 123.9 (q, $^1J_{C\text{-}F}$ = 272.3, *C*F), 66.7 (N*C*C=O), 25.7 (N*C*H$_3$), 25.4 (N*C*H$_3$), 20.6 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3067, 2942 (C-H), 1774 (C=O amide), 1707 (C=O urea); **HRMS** (FTMS+pNSI): *m/z* calcd for $C_{13}H_{14}F_3O_2N_2$ $[M+H]^+$ 287.1002, found 287.1005.

Synthesis of 5f:

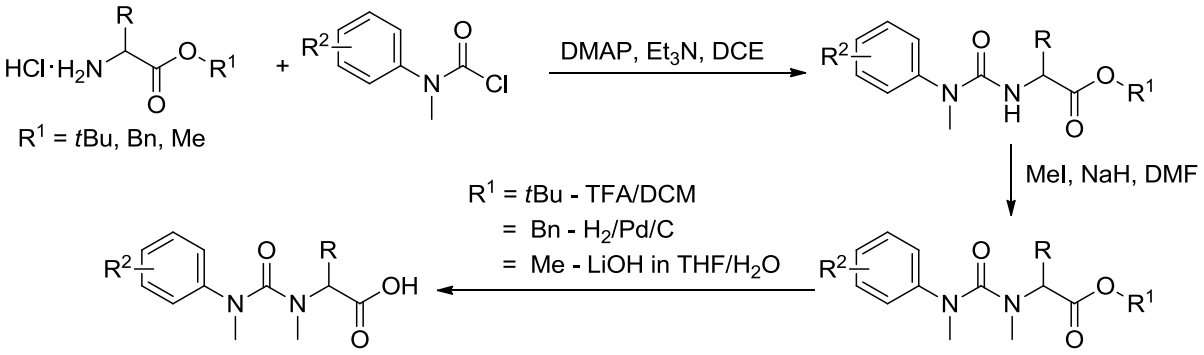


5-(3-Chlorophenyl)-1,3,5-trimethylimidazolidin-2,4-one (5f)

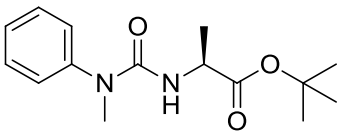
Following general procedure **5**, to a solution of imino hydantoin **2f** (98 mg, 0.39 mmol) in ethanol (2.25 mL) was added 12.0 M HCl (0.75 mL). Purification by

flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (50 mg, 0.20 mmol, 51%). **5f**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.43-6.98 (4H, m, Ar*H*), 2.99 (3H, s, NCH_3), 2.79 (3H, s, NCH_3), 1.73 (3H, s, CCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.4 (*C*=O), 156.3 (*C*=O), 138.6 (Ar*C*), 135.3 (Ar*C*), 130.5 (Ar), 129.0 (Ar), 126.4 (Ar), 124.3 (Ar), 66.4 (N*C*C=O), 25.5 (N*C*H$_3$), 25.3 (N*C*H$_3$), 20.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3065, 2934 (C-H), 1770 (C=O amide), 1707 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{20}O_3N_2NaS$ $[M+Na]^+$ 253.0738, found 253.0744.

Synthesis of Urea Acids:

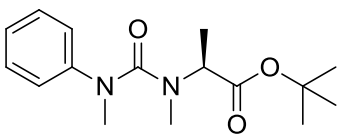


Synthesis of 6aAla:



(*S*)-*tert*-Butyl 2-(3-methyl-3-phenylureido)propanoate (S2a)

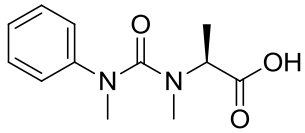
Following general procedure **6a**, *N*-methyl-*N*-phenylcarbamoyl chloride (3.49 g, 20.58 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (4.00 g, 22.08 mmol) and Et_3N (6.59 mL, 47.30 mmol) in DCE (0.5 M). The reaction was complete after twenty hours heating at reflux. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (5.42 g, 19.47 mmol, 95%). **S2a: R_f** (4:1 Pet.Ether:EtOAc) 0.29; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.40-7.34 (2H, m, Ph*H*), 7.26-7.20 (3H, m, Ph*H*), 4.82 (1H, br. d, *J* = 7.0, N*H*CH), 4.33 (1H, quin., *J* = 7.0, NHC*H*CH$_3$), 3.21 (3H, s, NCH_3), 1.34 (9H, s, OC(CH_3)$_3$), 1.21 (3H, d, *J* = 7.0, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.9 (C=O), 156.4 (C=O), 143.3 (Ar*C*N), 130.0 (2xAr), 127.2 (Ar), 127.2 (2xAr), 81.4 (*C*(CH$_3$)$_3$), 49.9 (NH*C*HCH$_3$), 37.1 (N*C*H$_3$), 28.0 (C(*C*H$_3$)$_3$), 19.2 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3343 (NH), 2978, 2934, 2879 (C-H), 1731 (C=O ester), 1664 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{22}O_3N_2Na$ $[M+Na]^+$ 301.1523, found 301.1516.



(*S*)-*tert*-Butyl 2-(1,3-dimethyl-3-phenylureido)propanoate (S3a)

Following a similar method to general procedure **7**, sodium hydride (1.94 g, 48.75 mmol, 2.5 eq., 60% suspension) was added to urea **S2a**

(5.42 g, 19.50 mmol) in DMF (0.4 M). After thirty minutes methyl iodide (3.64 mL, 58.50 mmol) was added. The reaction was left at 0 °C for one hour before warming to room temperature. The reaction was complete after twenty two hours at room temperature. Purification by flash column chromatography (SiO_2, 9:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (4.27 g, 14.61 mmol, 75%). **S3a: R_f** (1:1 Pet.Ether:EtOAc) 0.69; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.34-7.30 (2H, m, Ph*H*), 7.16-7.08 (3H, m, Ph*H*), 4.66 (1H, q, *J* = 7.0, NC*H*CH_3), 3.23 (3H, s, NCH_3), 2.45 (3H, s, NCH_3), 1.45 (9H, s, OC(CH_3)$_3$), 1.27 (3H, d, *J* = 7.0, CHCH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.3 (C=O), 161.6 (C=O), 146.7 (Ar*C*N), 129.4 (2xAr), 124.4 (Ar), 124.0 (2xAr), 81.2 (*C*(CH$_3$)$_3$), 55.7 (N*C*HCH$_3$), 39.8 (N*C*H$_3$), 32.5 (N*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 14.3 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2976, 2926, 2872, 2854 (C-H), 1732 (C=O ester), 1649 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{24}O_3N_2Na$ $[M+Na]^+$ 315.1680 found 315.1667.

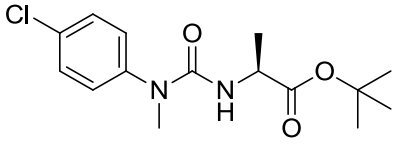


(*S*)-2-(1,3-Dimethyl-3-phenylureido)propanoic acid (6a)

Following general procedure **8**, anhydrous DCM (20.00 mL) and TFA (20.00 mL) were added to urea **S3a** (4.27 g, 14.62 mmol). The reaction was complete after four hours. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc to 100% EtOAc) yielded the title compound as a white solid (1.97 g, 8.33 mmol, 57%). **6a: mp**: 104-107 °C; **R_f** (1:1 Pet.Ether:EtOAc) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.40-7.37 (2H, m, Ph*H*), 7.23-7.20 (1H, m, Ph*H*), 7.15-7.13 (2H, m, Ph*H*), 4.48 (1H, q, *J* = 7.2, NC*H*CH_3), 3.33 (3H, s, NCH_3), 2.35 (3H, s, NCH_3), 1.35 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 174.7 (C=O), 162.8 (C=O), 145.5 (Ar*C*N), 129.5 (2xAr), 125.2 (Ar), 124.3 (2xAr), 55.5 (N*C*HCH$_3$), 39.7 (N*C*H$_3$), 33.5 (N*C*H$_3$), 13.9 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2982 (OH broad), 2938 (C-H), 1710 (C=O acid), 1644 (C=O urea); **HRMS**: (ESI$^+$) *m/z* calcd for $C_{12}H_{16}O_3N_2$ $[M+H]^+$ 237.1234, found 237.1239.

Enantiomerically enriched; HPLC: *er* 80:20, Chiral AD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 262 nm, t_R = 19 (major), 22 (minor) min.

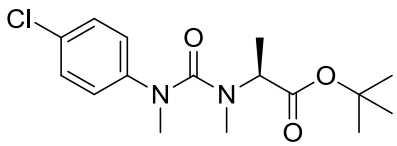
<u>Synthesis of 6bAla:</u>



(*S*)-*tert*-Butyl 2-(3-(4-chlorophenyl)-3-methylureido)propanoate (S2b)

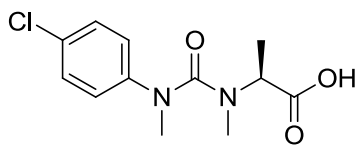
Following general procedure **6a**, *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (510 mg, 2.50 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (500 mg, 2.75 mmol) and Et_3N (0.80 mL, 5.76 mmol) in DCE (0.5 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a brown oil without further purification (776 mg, 2.48 mmol, 99%). **S2b: R_f** (1:1 Pet.Ether:EtOAc) 0.66; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.41-7.38 (2H, m, Ar*H*), 7.26-7.23 (2H, m, Ar*H*), 4.86 (1H, br. d, *J* = 7.0, N*H*CH), 4.39

(1H, quin., *J* = 7.0, NHC*H*CH$_3$), 3.25 (3H, s, NC*H*$_3$), 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.28 (3H, d, *J* = 7.0, CHC*H*$_3$).



(*S*)-*tert*-Butyl 2-(3-(4-chlorophenyl)-1,3-dimethylureido)propanoate (S3b)

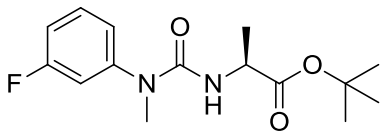
Following general procedure **7**, methyl iodide (0.46 mL, 7.40 mmol) and sodium hydride (118 mg, 4.94 mmol) were added to urea **S2b** (772 mg, 2.47 mmol) in DMF (0.3 M). The reaction was complete after three hours at room temperature. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (363 mg, 1.11 mmol, 45%). **S3b: R$_f$** (1:1 Pet.Ether:EtOAc) 0.80; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.31-7.26 (2H, m, Ar*H*), 7.11-7.06 (2H, m, Ar*H*), 4.62 (1H, q, *J* = 7.2, C*H*CH$_3$), 3.20 (3H, s, NC*H*$_3$), 2.48 (3H, s, NC*H*$_3$), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.30 (3H, d, *J* = 7.2, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 171.1 (C=O), 161.3 (C=O), 145.1 (Ar*C*N), 129.6 (Ar*C*Cl), 129.4 (2xAr), 124.9 (2xAr), 81.2 (*C*(CH$_3$)$_3$), 55.7 (*C*HCH$_3$), 39.7 (N*C*H$_3$), 32.6 (N*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 14.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2978, 2935 (C-H), 1732 (C=O ester), 1651 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{23}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 349.1289 found 349.1289.



(*S*)-2-(3-(4-Chlorophenyl)-1,3-dimethylureido)propanoic acid (6b)

Following a similar method to general procedure **8**, anhydrous DCM (2.10 mL) and TFA (2.10 mL) were added to urea **S3b** (343 mg, 1.05 mmol). The reaction was complete after two hours. Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc to 95:5 EtOAc:MeOH) yielded the title compound as a yellow oil (137 mg, 0.51 mmol, 48%). **6b: R$_f$** (1:1 Pet.Ether:EtOAc) 0.37; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 9.17 (1H, br. s, COO*H*), 7.34-7.31 (2H, m, Ar*H*), 7.10-7.07 (2H, m, Ar*H*), 4.52 (1H, q, *J* = 7.2, C*H*CH$_3$), 3.26 (3H, s, NC*H*$_3$), 2.43 (3H, s, NC*H*$_3$), 1.35 (3H, d, *J* = 7.2, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.4 (C=O), 163.0 (C=O), 144.0 (Ar*C*N), 130.8 (Ar*C*Cl), 129.7 (2xAr), 125.6 (2xAr), 55.8 (*C*HCH$_3$), 39.7 (N*C*H$_3$), 33.8 (N*C*H$_3$), 13.9 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2981 (OH broad), 2938 (C-H), 1733 (C=O acid), 1644 (C=O urea); **HRMS**: (ESI$^+$) *m/z* calcd for $C_{12}H_{15}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 293.0663, found 293.0670.

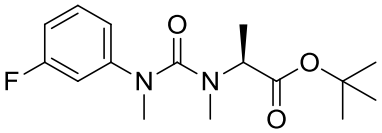
<u>Synthesis of 6cAla:</u>



(*S*)-*tert*-Butyl 2-(3-(3-fluorophenyl)-3-methylureido)propanoate (S2c)

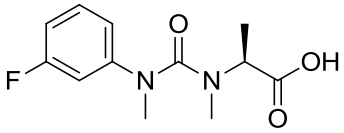
Following general procedure **6a**, *N*-(3-fluorophenyl)-*N*-methylcarbamoyl chloride (469 mg, 2.50 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (500 mg, 2.75 mmol) and Et$_3$N (0.80 mL, 5.76 mmol) in DCE (0.5 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a brown oil without further purification (735 mg, 2.48 mmol, 99%). **S2c: R$_f$**

(1:1 Pet.Ether:EtOAc) 0.63; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.43-7.35 (1H, m, Ar*H*), 7.12-7.09 (1H, m, Ar*H*), 7.05-6.97 (2H, m, Ar*H*), 4.97 (1H, br. d, *J* = 7.2, N*H*CH), 4.40 (1H, quin., *J* = 7.2, NHC*H*CH_3), 3.27 (3H, s, NCH_3), 1.43 (9H, s, C(CH_3)$_3$), 1.30 (3H, d, *J* = 7.0, CHCH_3).



(*S*)-*tert*-Butyl 2-(3-(3-fluorophenyl)-1,3-dimethylureido)propanoate (S3c)

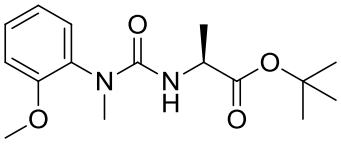
Following general procedure **7**, methyl iodide (0.46 mL, 7.44 mmol) and sodium hydride (198 mg, 4.96 mmol) were added to urea **S2c** (735 mg, 2.48 mmol) in DMF (0.3 M). The reaction was complete after three hours at room temperature. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (393 mg, 1.27 mmol, 51%). **S3c: R_f** (4:1 Pet.Ether:EtOAc) 0.29; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.29-7.24 (1H, m, Ar*H*), 6.93-6.91 (1H, m, Ar*H*), 6.88-6.85 (1H, m, Ar*H*), 6.81-6.77 (1H, m, Ar*H*), 4.63 (1H, q, *J* = 7.0, C*H*CH_3), 3.22 (3H, s, NCH_3), 2.52 (3H, s, NCH_3), 1.46 (9H, s, C(CH_3)$_3$), 1.31 (3H, d, *J* = 7.5, CHCH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.1 (C=O), 163.3 (d, $^1J_{C\text{-}F}$ = 244.6, Ar*C*F), 161.0 (C=O), 148.1 (d, $^3J_{C\text{-}F}$ = 9.8, Ar*C*N), 130.4 (d, $^3J_{C\text{-}F}$ = 9.4, Ar), 118.7 (d, $^4J_{C\text{-}F}$ = 2.8, Ar), 110.9 (d, $^2J_{C\text{-}F}$ = 21.0, Ar), 110.4 (d, $^2J_{C\text{-}F}$ = 23.4, Ar), 81.4 (*C*(CH$_3$)$_3$), 55.7 (*C*HCH$_3$), 39.4 (NCH$_3$), 32.5 (NCH$_3$), 28.0 (C(*C*H$_3$)$_3$), 14.2 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2979, 2937 (C-H), 1733 (C=O ester), 1655 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{23}O_3N_2FNa$ $[M+Na]^+$ 333.1585 found 333.1574.



(*S*)-2-(3-(3-Fluorophenyl)-1,3-dimethylureido)propanoic acid (6c)

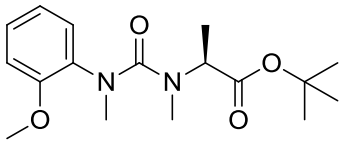
Following a similar method to general procedure **8**, anhydrous DCM (2.50 mL) and TFA (2.50 mL) were added to urea **S3c** (390 mg, 1.26 mmol). The reaction was complete after two hours. Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc to 95:5 EtOAc:MeOH) yielded the title compound as a pale yellow oil (163 mg, 0.64 mmol, 51%). **6c: R_f** (1:1 Pet.Ether:EtOAc) 0.34; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 9.73 (1H, br. s, COO*H*), 7.36-7.28 (1H, m, Ar*H*), 6.95-6.85 (3H, m, Ar*H*), 4.55 (1H, q, *J* = 7.2, C*H*CH_3), 3.29 (3H, s, NCH_3), 2.46 (3H, s, NCH_3), 1.38 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.1 (C=O), 163.3 (d, $^1J_{C\text{-}F}$ = 246.0, Ar*C*F), 162.9 (C=O), 146.8 (d, $^3J_{C\text{-}F}$ = 10.0, Ar*C*N), 130.7 (d, $^3J_{C\text{-}F}$ = 9.2, Ar), 119.6 (d, $^4J_{C\text{-}F}$ = 3.0, Ar), 112.2 (d, $^2J_{C\text{-}F}$ = 20.9, Ar), 111.3 (d, $^2J_{C\text{-}F}$ = 23.3, Ar), 55.8 (*C*HCH$_3$), 39.5 (NCH$_3$), 33.8 (NCH$_3$), 13.8 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2927 (OH broad), 2854 (C-H), 1736 (C=O acid), 1644 (C=O urea); **HRMS**: (FTMS + p APCI) *m/z* calcd for $C_{12}H_{16}O_3N_2F$ $[M+H]^+$ 255.1139, found 255.1136.

Synthesis of 6dAla:



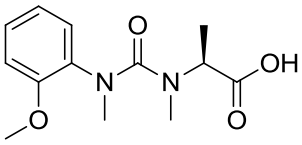
(*S*)-*tert*-Butyl 2-(3-(2-methoxyphenyl)-3-methylureido)propanoate (S2d)

Following general procedure **6a**, *N*-(2-methoxyphenyl)-*N*-methylcarbamoyl chloride (500 mg, 2.50 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (500 mg, 2.75 mmol) and Et_3N (0.80 mL, 5.76 mmol) in DCE (0.5 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a brown oil without further purification (768 mg, 2.49 mmol, 90%). **S2d: R_f** (2:1 Pet.Ether:EtOAc) 0.53; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.35-7.29 (1H, m, Ar*H*), 7.27-7.25 (1H, m, Ar*H*), 7.01-6.97 (2H, m, Ar*H*), 4.78 (1H, br. d, *J* = 7.5, N*H*CH), 4.40 (1H, quin., *J* = 7.2, NHC*H*CH_3), 3.83 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 1.40 (9H, s, C(CH_3)$_3$), 1.25 (3H, d, *J* = 7.2, CHCH_3).



(*S*)-*tert*-Butyl 2-(3-(2-methoxyphenyl)-1,3-dimethylureido)propanoate (S3d)

Following general procedure **7**, methyl iodide (0.45 mL, 7.18 mmol) and sodium hydride (191 mg, 4.79 mmol) were added to urea **S2d** (738 mg, 2.39 mmol) in DMF (0.3 M). The reaction was complete after three hours at room temperature. Purification by flash column chromatography (SiO_2, 7:2 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (671 mg, 2.08 mmol, 87%). **S3d: R_f** (1:1 Pet.Ether:EtOAc) 0.63; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.22-7.17 (1H, m, Ar*H*), 7.11-7.08 (1H, m, Ar*H*), 6.94-6.88 (2H, m, Ar*H*), 4.63 (1H, q, *J* = 7.2, C*H*CH_3), 3.88 (3H, s, OCH_3), 3.06 (3H, s, NCH_3), 2.34 (3H, s, NCH_3), 1.41 (9H, s, C(CH_3)$_3$), 1.21 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 171.6 (C=O), 162.2 (C=O), 153.9 (Ar*C*OMe), 134.8 (Ar*C*N), 127.6 (Ar), 127.2 (Ar) 121.1 (Ar), 111.8 (Ar), 80.9 (*C*(CH$_3$)$_3$), 55.4 (*C*HCH$_3$ and OCH_3), 38.3 (NCH_3), 31.7 (NCH_3), 28.1 (C(*C*H$_3$)$_3$), 14.4 (CH*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2977, 2936 (C-H), 1731 (C=O ester), 1645 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{26}O_4N_2Na$ $[M+Na]^+$ 345.1785 found 345.1787.

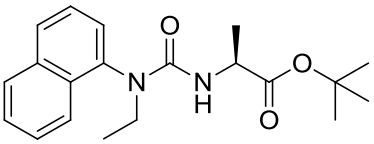


(*S*)-2-(3-(2-Methoxyphenyl)-1,3-dimethylureido)propanoic acid (6d)

Following a similar method to general procedure **8**, anhydrous DCM (4.20 mL) and TFA (4.20 mL) were added to urea **S3d** (671 mg, 2.08 mmol). The reaction was complete after two hours. Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc to 95:5 EtOAc:MeOH) yielded the title compound as a pale yellow oil (147 mg, 0.55 mmol, 27%). **6d: R_f** (1:1 Pet.Ether:EtOAc) 0.31; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 12.30 (1H, br. s, COO*H*), 7.28-7.25 (1H, m, Ar*H*), 7.10-7.08 (1H, m, Ar*H*), 6.98-6.95 (2H, m, Ar*H*), 4.40 (1H, q, *J* = 7.0, C*H*CH_3), 3.87 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 2.29 (3H, s, NCH_3), 1.28 (3H, d, *J* = 7.5, CHCH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.2 (C=O), 165.2 (C=O), 153.9 (Ar*C*OMe), 132.8 (Ar*C*N), 128.4 (Ar), 127.6 (Ar) 121.3 (Ar), 112.0 (Ar),

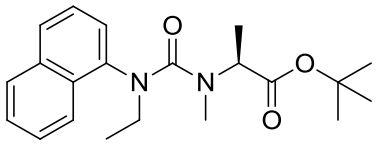
56.2 (*C*HCH$_3$), 55.6 (O*C*H$_3$), 38.4 (N*C*H$_3$), 33.4 (N*C*H$_3$), 13.6 (CH*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2978 (OH broad), 2939 (C-H), 1733 (C=O acid), 1635 (C=O urea); **HRMS**: (ESI$^+$) *m/z* calcd for $C_{13}H_{18}O_4N_2Na$ $[M+Na]^+$ 289.1159, found 289.1156.

Synthesis of 6gAla:



(*S*)-*tert*-Butyl 2-(3-ethyl-3-(naphthalen-1-yl)ureido)propanoate (S2g)

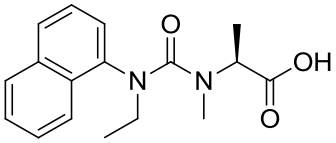
Following a similar method to general procedure **6a**, *N*-ethyl-*N*-(1-naphthalen-1-yl)carbamoyl chloride (708 mg, 3.30 mmol, 1.1 eq) and DMAP (catalytic amount) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (500 mg, 2.75 mmol, 1.0 eq) and Et_3N (0.88 mL, 6.33 mmol) in DCE (0.5 M). The reaction was complete after twenty hours heating at reflux. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) yielded the title compound as a rose-coloured oil (933 mg, 2.73 mmol, 99%). **S2g: R$_f$** (1:1 Pet.Ether:EtOAc) 0.71; **^{1}H NMR** (500 MHz, $CDCl_3$) (0.6:0.4 rotamers): δ_H = 7.96-7.88 (3H, m, Napht*H*), 7.57-7.50 (3H, m, Napht*H*), 7.48-7.47 (0.60H, m, Napht*H*), 7.41-7.39 (0.40H, m, Napht*H*), 4.57 (0.60H, br. d, *J* = 8.0, N*H*CH), 4.46 (0.40H, br. d, *J* = 7.0, N*H*CH), 4.40 (0.60H, quin., *J* = 7.5, NHC*H*CH$_3$), 4.34 (0.40H, quin., *J* = 7.5, NHC*H*CH$_3$), 4.21-4.10 (1H, m, C*H$_A$*H$_B$CH$_3$), 3.54-3.33 (1H, m, CH$_A$*H$_B$*CH$_3$), 1.38 (5.40H, s, C(C*H*$_3$)$_3$), 1.27 (3.60H, s, C(C*H*$_3$)$_3$), 1.20 (1.20H, d, *J* = 7.0, CHC*H*$_3$), 1.13 (3H, t, *J* = 7.3, CH$_2$C*H*$_3$), 1.12 (1.80H, d, *J* = 7.0, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 172.9 (*C*=O$_{maj}$), 172.4 (*C*=O$_{min}$), 156.5 (*C*=O), 137.2 (Napht*C*N), 135.0 (Napht*C*), 131.1 (Napht*C*$_{min}$), 131.0 (Napht*C*$_{maj}$), 128.8 (Napht$_{maj}$), 128.7 (Napht$_{min}$), 128.5 (Napht$_{maj}$), 128.4 (Napht$_{min}$), 127.5 (Napht$_{maj}$), 127.3 (Napht$_{min}$), 127.2 (Napht$_{min}$), 127.0 (Napht$_{maj}$), 126.7 (Napht$_{min}$), 126.6 (Napht$_{maj}$), 126.0 (Napht$_{maj}$), 125.8 (Napht$_{min}$), 123.2 (Napht$_{min}$), 123.0 (Napht$_{maj}$), 81.2 (*C*(CH$_3$)$_{3maj}$), 81.0 (*C*(CH$_3$)$_{3min}$), 50.0 (*C*HCH$_{3min}$), 49.7 (*C*HCH$_{3maj}$), 44.0 (*C*H$_2$CH$_3$), 27.9 (C(*C*H$_3$)$_{3maj}$), 27.8 (C(*C*H$_3$)$_{3min}$), 19.1 (CH*C*H$_3$), 14.1 (CH$_2$*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3421 (NH), 3050, 2976, 2933, 2873 (C-H), 1731 (C=O ester), 1660 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{26}O_3N_2Na$ $[M+Na]^+$ 365.1836 found 365.1835.



(*S*)-*tert*-Butyl 2-(3-ethyl-1-methyl-3-(naphthalen-1-yl)ureido)propanoate (S3g)

Following general procedure **7**, methyl iodide (0.51 mL, 8.15 mmol) and sodium hydride (217 mg, 5.43 mmol) were added to urea **S2g** (930 mg, 2.72 mmol) in DMF (0.3 M). The reaction was complete after three hours at room temperature. Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (727 mg, 2.04 mmol, 75%). **S3g: R$_f$** (1:1 Pet.Ether:EtOAc) 0.80; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.02 (1H, d, *J* = 8.5, Napht*H*), 7.89 (1H, d, *J* = 7.5, Napht*H*), 7.75 (1H, d, *J* = 8.0, Napht*H*), 7.57-7.50 (2H, m, Napht*H*), 7.42 (1H, t, *J* = 8.0, Napht*H*), 7.27-7.25 (1H, m, Napht*H*), 4.60 (1H, q, *J* = 7.0, C*H*CH$_3$), 3.72-3.61 (2H, m, C*H*$_2$CH$_3$), 2.24 (3H, s, NC*H*$_3$), 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.18 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$),

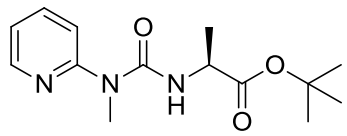
1.14 (3H, d, *J* = 7.5, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 171.6 (*C*=O), 162.1 (*C*=O), 140.8 (Naphth*C*N), 134.8 (Naphth*C*), 129.9 (Naphth*C*), 128.7 (Napht), 126.8 (Napht), 126.7 (Napht), 126.2 (Napht), 125.6 (Napht), 124.9 (Napht), 123.0 (Napht), 80.9 (*C*(CH$_3$)$_3$), 55.6 (*C*HCH$_3$), 46.8 (*C*H$_2$CH$_3$), 32.1 (NCH$_3$), 28.0 (C(*C*H$_3$)$_3$), 14.3 (CH*C*H$_3$), 13.4 (CH$_2$*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3050, 2977, 2934, 2873 (C-H), 1731 (C=O ester), 1644 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{28}O_3N_2Na$ $[M+Na]^+$ 379.1992, found 379.2004.



(*S*)-2-(3-Ethyl-1-methyl-3-(naphthalen-1-yl)ureido)propanoic acid (6g)

Following a similar method to general procedure **8**, anhydrous DCM (3.90 mL) and TFA (3.90 mL) were added to urea **S3g** (700 mg, 1.96 mmol). The reaction was complete after one hour. The reaction mixture was concentrated *in vacuo* to give a pale brown solid. Purification by suspension in diethyl ether, filtration and washing with a small volume of cold diethyl ether yielded the title compound as a white solid (486 mg, 1.62 mmol, 82%). **6g: mp** 166-171 ^{o}C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.37; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ_H = 12.46 (1H, s, COO*H*), 8.00 (1H, d, *J* = 8.0, Napht*H*), 7.94 (1H, d, *J* = 8.0, Napht*H*), 7.85 (1H, d, *J* = 8.5, Napht*H*), 7.61 (1H, t, *J* = 7.3, Napht*H*), 7.56 (1H, t, *J* = 7.3, Napht*H*), 7.50 (1H, t, *J* = 7.8, Napht*H*), 7.28 (1H, d, *J* = 7.0, Napht*H*), 4.41 (1H, q, *J* = 7.0, C*H*CH$_3$), 3.61-3.46 (2H, m, C*H*$_2$CH$_3$), 2.14 (3H, s, NC*H*$_3$), 1.06-1.04 (6H, m, CH$_2$C*H*$_3$ and CHC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $(CD_3)_2SO$): δ_C = 173.4 (*C*=O), 161.2 (*C*=O), 140.3 (Naphth*C*N), 134.4 (Naphth*C*), 129.3 (Naphth*C*), 128.7 (Napht), 126.9 (Napht), 126.7 (Napht), 126.3 (Napht), 125.9 (Napht), 124.7 (Napht), 122.5 (Napht), 54.6 (*C*HCH$_3$), 46.2 (*C*H$_2$CH$_3$), 32.5 (NCH$_3$), 14.3 (CH*C*H$_3$), 13.1 (CH$_2$*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3051, 2983, 2937, 2875 (C-H), 1737 (C=O acid), 1640 (C=O urea); **HRMS**: (ESI$^+$) *m/z* calcd for $C_{17}H_{20}O_3N_2Na$ $[M+Na]^+$ 323.1366, found 323.1359.

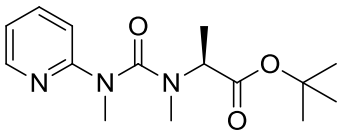
Synthesis of 6hAla:



(*S*)-*tert*-Butyl 2-{[methyl(pyridin-2-yl)carbamoyl]amino}propanoate (S2h)

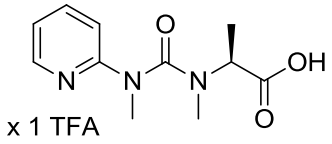
Following general procedure **6b**, L-alanine *tert*-butyl ester hydrochloride (882 mg, 4.86 mmol) was added to a pre-stirred solution of *N*-methyl-*N*-(pyridin-2-yl)carbamoyl chloride (827 mg, 4.86 mmol) in DCE (9.70 mL). To this solution was added Et_3N (0.80 mL, 5.74 mmol) and DMAP (catalytic amount). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (1.14 g, 4.08 mmol, 84%). **S2h: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.29 (1H, d, *J* = 6.8, Ar*H*), 7.87 (1H, br. d, *J* = 4.7, Ar*H*), 7.27 (1H, m, Ar*H*), 6.53 (2H, m, Ar*H* and N*H*CH), 4.07 (1H, quin., *J* = 7.0, NHC*H*CH$_3$), 2.92 (3H, s, NC*H*$_3$), 1.07 (9H, s, C(C*H*$_3$)$_3$), 1.05 (3H, d, *J* = 7.0, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.2 (*C*=O), 155.4 (*C*=O), 155.2 (Ar*C*N), 145.4 (Ar), 138.3 (Ar), 116.6 (Ar), 111.1 (Ar), 88.4 (O*C*(CH$_3$)$_3$), 49.9 (*C*HCH$_3$), 32.1 (NCH$_3$), 27.5 (OC(*C*H$_3$)$_3$), 18.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2977 (C-H), 1732 (C=O

ester), 1666 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{21}O_3N_3Na$ $[M+Na]^+$ 302.1475, found 302.1471.



(*S*)-*tert*-Butyl 2-{methyl[methyl(pyridin-2-yl)carbamoyl]amino} propanoate (S3h)

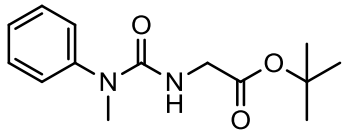
Following a similar method to general procedure **7**, sodium hydride (324 mg, 8.10 mmol) was added to urea **S2h** (1.13 g, 4.05 mmol) in DMF (10.00 mL). After fifteen minutes methyl iodide (0.75 mL, 12.15 mmol) was added. The reaction was complete after one hour at 0 ^oC. The reaction was diluted with ethyl acetate and quenched by addition of ice water. The aqueous layer was extracted twice with ethyl acetate and the organic layer washed with brine. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (986 mg, 3.36 mmol, 83%). **S3h: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.08 (1H, dt, *J* = 4.9, 0.8, Ar*H*), 7.33 (1H, m, Ar*H*), 6.86 (1H, d, *J* = 8.3, Ar*H*), 6.64 (1H, m, Ar*H*), 4.44 (1H, q, *J* = 7.2, NC*H*CH_3), 3.09 (3H, s, NCH_3), 2.45 (3H, s, NCH_3), 1.23 (9H, s, C(CH_3)$_3$), 1.16 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 170.5 (*C*=O), 160.5 (*C*=O), 156.6 (Ar*C*N), 147.9 (Ar), 137.2 (Ar), 117.0 (Ar), 114.1 (Ar), 81.1 (O*C*(CH$_3$)$_3$), 55.5 (*C*H), 35.3 (N*C*H$_3$), 32.1 (N*C*H$_3$), 27.7 (OC(*C*H$_3$)$_3$), 14.1 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2978 (C-H), 1731 (C=O ester), 1656 (C=O urea). **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{23}N_3O_3Na$ $[M+Na]^+$ 316.1637, found 316.1646



(*S*)-2-{Methyl[methyl(pyridin-2-yl)carbamoyl]amino}propanoic acid (6h)

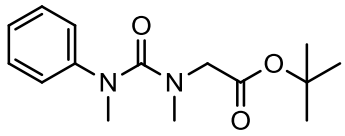
Following a similar method to general procedure **8**, anhydrous DCM (4.00 mL) and TFA (1.00 mL) were added to urea **S3h** (112 mg, 0.38 mmol). The reaction was complete after two hours. Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 9:1 EtOAc:MeOH) yielded the title compound as its trifluoroacetic salt (77 mg, 0.32 mmol, 85%). **6h: ^{1}H NMR** (300 MHz, CD_3OD): δ_H = 8.26 (1H, br. d, *J* = 5.0, Ar*H*), 7.82 (1H, ddd, *J* = 8.3, 5.0, 1.7, Ar*H*), 7.21 (1H, d, *J* = 8.3, Ar*H*), 7.07 (1H, m, Ar*H*), 4.65 (1H, q, *J* = 7.2, NC*H*CH_3), 3.27 (3H, s, NCH_3), 2.71 (3H, s, NCH_3), 1.43 (3H, d, *J* = 7.2, CHCH_3); **^{13}C {^{1}H} NMR** (75 MHz, CD_3OD): δ_C = 174.8 (*C*=O), 161.8 (*C*=O), 156.9 (Ar*C*N), 146.6 (Ar), 141.7 (Ar), 119.2 (Ar), 116.5 (Ar), 56.7 (*C*H), 36.5 (N*C*H$_3$), 33.4 (N*C*H$_3$), 14.7 (*C*H$_3$). **^{19}F NMR** (400 MHz CD_3OD): δ_F = -76.9; **IR (film, cm^{-1})**: ν_{max} = 2979 (C-H), 1731 (C=O acid), 1659 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{15}N_3O_3Na$ $[M+Na]^+$ 260.0998, found 260.1006.

Synthesis of 6iGly:



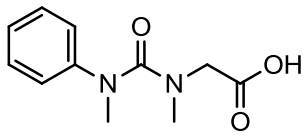
***tert*-Butyl 2-(3-methyl-3-phenylureido)acetate (S2i)**

Following general procedure **6a**, *N*-methyl-*N*-phenylcarbamoyl chloride (473 mg, 2.79 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of glycine *tert*-butyl ester hydrochloride (500 mg, 2.98 mmol) and Et_3N (0.89 mL, 6.41 mmol) in DCE (0.3 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a yellow oil without further purification (736 mg, 2.79 mmol, >99%). **S2i: R_f** (4:1 Pet.Ether:EtOAc) 0.15; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.46-7.41 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 4.79 (1H, br. s, N*H*CH), 3.86 (2H, d, *J* = 4.8, NHCH_2), 3.28 (3H, s, NCH_3), 1.43 (9H, s, OC(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.0 (C=O), 156.8 (C=O), 143.0 (Ar*C*N), 130.0 (2xAr), 127.4 (Ar), 127.3 (2xAr), 81.7 (*C*(CH$_3$)$_3$), 43.3 (NH*C*H$_2$), 37.3 (N*C*H$_3$), 28.0 (C(*C*H$_3$)$_3$); **IR (film, cm^{-1})**: ν_{max} = 3370 (NH), 2977 (C-H), 1740 (C=O ester), 1657 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{20}O_3N_2Na$ $[M+Na]^+$ 287.1367, found 287.1377.



***tert*-Butyl 2-(1,3-dimethyl-3-phenylureido)acetate (S3i)**

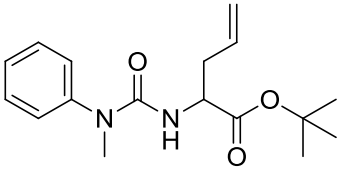
Following general procedure **7**, methyl iodide (0.52 mL, 8.36 mmol) and sodium hydride (223 mg, 5.58 mmol) were added to urea **S2i** (736 mg, 2.79 mmol) in DMF (0.2 M). The reaction was complete after two hours at 0 °C. The reaction mixture was quenched with methanol and saturated aqueous NH_4Cl solution. The title compound was yielded as a yellow oil without further purification (775 mg, 2.79 mmol, > 99%). **S3i: R_f** (2:1 Pet.Ether:EtOAc) 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.36-7.31 (2H, m, Ph*H*), 7.20-7.17 (2H, m, Ph*H*), 7.13-7.09 (1H, m, Ph*H*), 3.85 (2H, s, NCH_2), 3.23 (3H, s, NCH_3), 2.60 (3H, s, NCH_3), 1.45 (9H, s, OC(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 169.0 (C=O), 161.5 (C=O), 146.4 (Ar*C*N), 129.5 (2xAr), 124.6 (Ar), 124.2 (2xAr), 81.5 (*C*(CH$_3$)$_3$), 52.5 (N*C*H$_2$), 40.0 (N*C*H$_3$), 37.9 (N*C*H$_3$) , 28.1 (C(*C*H$_3$)$_3$); **IR (film, cm^{-1})**: ν_{max} = 2927 (C-H), 1740 (C=O ester), 1650 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{22}O_3N_2Na$ $[M+Na]^+$ 301.1523, found 301.1521.



2-(1,3-Dimethyl-3-phenylureido)acetic acid (6i)

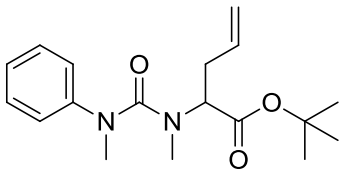
Following general procedure **8**, anhydrous DCM (5.00 mL) and TFA (5.00 mL) were added to urea **S3i** (769 mg, 2.77 mmol). The reaction was complete after five hours. Purification by removal of grease through washing with pentane over a silica plug and extraction with ethyl acetate yielded the title compound as a white solid (369 mg, 1.66 mmol, 60%). **6i: mp** 104-107 °C; **R_f** (2:1 Pet.Ether:EtOAc) 0.06; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H =11.01 (1H, br. s, COO*H*), 7.34-7.30 (2H, m, Ph*H*), 7.18-7.10 (3H, m, Ph*H*), 3.95 (2H, s, NCH_2), 3.23 (3H, s, NCH_3), 2.56 (3H, s, NCH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.1 (C=O), 162.1 (C=O), 145.6 (Ar*C*N), 129.5 (2xAr), 125.1 (Ar), 124.4 (2xAr), 51.8 (N*C*H$_2$), 40.0 (N*C*H$_3$), 38.0 (N*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2931 (OH broad), 2931 (C-H), 1736 (C=O acid), 1592 (C=O urea); **HRMS** (ESI$^-$): *m/z* calcd for $C_{11}H_{13}O_3N_2$ $[M-H]^-$ 221.0931, found 221.0921.

Synthesis of 6jPrg:



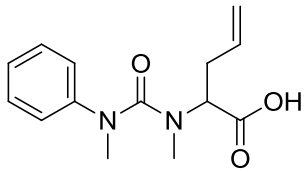
***tert*-Butyl 2-(3-methyl-3-phenylureido)pent-4-enoate (S2j)**

Following a similar method to general procedure **6a**, *N*-methyl-*N*-phenylcarbamoyl chloride (726 mg, 4.27 mmol, 1.1 eq) and DMAP (catalytic amount) were added to a pre-stirred solution of DL-2-allylglycine *tert*-butyl ester (666 mg, 3.89 mmol, 1.0 eq) and Et_3N (0.70 mL, 5.06 mmol, 1.3 eq) in DCE (0.5 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a brown oil without further purification (1.05 g, 3.43 mmol, 88%). **S2j: R_f** (1:1 Pet.Ether:EtOAc) 0.69; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.43-7.40 (2H, m, Ph*H*), 7.31-7.28 (3H, m, Ph*H*), 5.59 (1H, ddt, *J* = 17.4, 10.2, 7.2, CH_2CH=CH_2), 5.00-4.95 (2H, m, CH=CH_2), 4.86 (1H, br. d, *J* = 7.7, N*H*), 4.47 (1H, dt, *J* = 7.9, 5.7, NHC*H*CH_2), 3.27 (3H, s, NCH_3), 2.50-2.45 (1H, m, $CHCH_AH_BCH$), 2.42-2.36 (1H, m, $CHCH_AH_BCH$), 1.42 (9H, s, $C(CH_3)_3$).



***tert*-Butyl 2-(1,3-dimethyl-3-phenylureido)pent-4-enoate (S3j)**

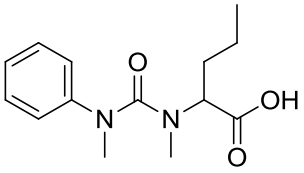
Following general procedure **7**, methyl iodide (0.64 mL, 10.30 mmol) and sodium hydride (275 mg, 6.87 mmol) were added to urea **S2j** (1.05 g, 3.43 mmol) in DMF (0.3 M). The reaction was complete after three hours at room temperature. Purification by flash column chromatography (SiO_2, 9:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (750 mg, 2.35 mmol, 69%). **S3j: R_f** (1:1 Pet.Ether:EtOAc) 0.80; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.33-7.28 (2H, m, Ph*H*), 7.14-7.08 (3H, m, Ph*H*), 5.80-5.67 (1H, m, CH_2CH=CH_2), 5.10-5.04 (2H, m, CH=CH_2), 4.69 (1H, dd, *J* = 9.9, 5.7, C*H*CH_2), 3.22 (3H, s, NCH_3), 2.69-2.60 (1H, m, $CHCH_AH_BCH$), 2.47 (3H, s, NCH_3), 2.40-2.29 (1H, m, $CHCH_AH_BCH$), 1.44 (9H, s, $C(CH_3)_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 170.5 (C=O), 162.0 (C=O), 146.5 (Ar*C*N), 134.6 (Ar), 129.3 (2xAr), 124.5 (*C*H=CH_2), 124.2 (2xAr), 117.4 (CH=*C*H_2), 81.4 (*C*$(CH_3)_3$), 59.6 (*C*HCH_2CH), 40.0 (N*C*H_3), 33.6 (CH*C*H_2CH), 32.9 (N*C*H_3), 28.1 ($C(CH_3)_3$); **IR (film, cm^{-1})**: ν_{max} = 2978, 2932 (C-H), 1731 (C=O ester), 1649 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{26}O_3N_2Na$ $[M+Na]^+$ 341.1836 found 341.1845.



2-(1,3-Dimethyl-3-phenylureido)pent-4-enoic acid (S3j')

Following a similar method to general procedure **8**, anhydrous DCM (4.70 mL) and TFA (4.70 mL) were added to urea **S3j** (750 mg, 2.35 mmol). The reaction was complete after two hours. Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc to 95:5 EtOAc:MeOH) yielded the title compound as a pale yellow oil (445 mg, 1.70 mmol, 72%). **S3j': R_f** (1:1 Pet.Ether:EtOAc) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.38-7.33 (2H, m, Ph*H*), 7.23-7.19 (1H, m, Ph*H*), 7.16-7.13 (3H, m, Ph*H*), 5.71 (1H, dddd, *J* = 16.4, 10.8, 8.0, 5.6, CH_2CH=CH_2), 5.16-5.15 (1H, m, CH=CH_AH_B), 5.13-5.10 (1H, m, CH=CH_AH_B), 4.46 (1H, dd, *J* = 10.8, 5.6, C*H*CH_2), 3.34 (3H, s, NCH_3), 2.68-2.60 (1H, m, $CHCH_AH_BCH$), 2.35 (3H, s, NCH_3), 2.51-2.43 (1H, m, $CHCH_AH_BCH$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.8 (C=O), 164.6 (C=O), 144.4 (Ar*C*N),

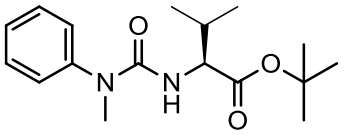
133.7 (Ar), 129.6 (2xAr), 126.1 (*C*H=CH_2), 125.1 (2xAr), 118.4 (CH=*C*H_2), 60.4 (*C*HCH_2CH), 39.9 (N*C*H_3), 34.0 (CH*C*H_2CH), 32.2 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3008 (OH broad), 2978, 2940 (C-H), 1731 (C=O acid), 1642 (C=O urea); **HRMS**: (ESI$^+$) *m/z* calcd for $C_{14}H_{19}O_3N_2$ $[M+H]^+$ 263.1390, found 263.1387.



2-(1,3-Dimethyl-3-phenylureido)pentanoic acid (6j)

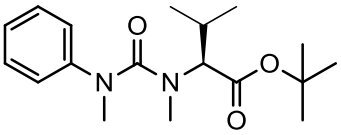
Urea **6bb** (243 mg, 0.93 mmol, 2.5 eq) was dissolved in methanol (0.1 M) and nitrogen was bubbled through the solution. 10% Palladium on carbon (40 mg, 0.38 mmol, 10% by weight, 1.0 eq) was added to the reaction mixture and the reaction was placed under a hydrogen atmosphere through use of a balloon. The reaction was left to stir for twenty hours. The solution was filtered over celite, washed through with dichloromethane and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc to 95:5 EtOAc:MeOH) yielded the title compound as a pale yellow oil (227 mg, 0.86 mmol, 93%). **6j: R_f** (1:1 Pet.Ether:EtOAc) 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.38-7.35 (2H, m, Ph*H*), 7.21-7.18 (1H, m, Ph*H*), 7.14-7.12 (2H, m, Ph*H*), 4.38 (1H, dd, *J* = 10.0, 6.0, C*H*CH_2), 3.29 (3H, s, NCH_3), 2.37 (3H, s, NCH_3), 1.88-1.81 (1H, m, CHCH_AH$_B$$CH_2$), 1.67-1.59 (1H, m, CHC$H_A$$H_B$$CH_2$), 1.31-1.26 (2H, m, C$H_2$$CH_3$), 0.94 (3H, t, *J* = 7.0, CH_2CH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.4 (C=O), 164.3 (C=O), 145.1 (Ar*C*N), 129.7 (2xAr), 125.9 (Ar), 124.9 (2xAr), 59.9 (*C*HCH_2), 40.0 (N*C*H_3), 33.7 (N*C*H_3), 30.1 (CH*C*H_2), 19.4 (*C*$H_2$$CH_3$), 13.6 (*C*$H_3$); **IR (film, cm^{-1})**: ν_{max} = 3006 (OH broad), 2959, 2933, 2873 (C-H), 1731 (C=O acid), 1642 (C=O urea); **HRMS**: (EI): *m/z* calcd for $C_{14}H_{20}O_3N_2$ $[M]^{\cdot+}$ 284.1468, found 284.1461.

Synthesis of 6kVal:



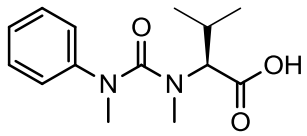
(*S*)-*tert*-Butyl 3-methyl-2-(3-methyl-3-phenylureido)butanoate (S2k)

Following general procedure **6a**, *N*-methyl-*N*-phenylcarbamoyl chloride (378 mg, 2.23 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-valine *tert*-butyl ester hydrochloride (500 mg, 2.38 mmol) and Et_3N (0.71 mL, 5.12 mmol) in DCE (0.2 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a yellow oil without further purification (647 mg, 2.11 mmol, 95%). **S2k: R_f** (4:1 Pet.Ether:EtOAc) 0.23; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.47-7.41 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 4.81 (1H, br. d, *J* = 8.4, N*H*CH), 4.34 (1H, dd, *J* = 8.7, 4.5, NHC*H*CH), 3.28 (3H, s, NCH_3), 2.11-2.00 (1H, m, C*H*$(CH_3)_2$), 1.42 (9H, s, OC(CH_3)$_3$), 0.89 (3H, d, *J* = 6.9, CH(CH_3)$_2$), 0.71 (3H, d, *J* = 6.9, CH(CH_3)$_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 171.8 (C=O), 156.9 (C=O), 143.3 (Ar*C*N), 130.0 (2xAr), 127.3 (Ar), 127.2 (2xAr), 81.4 (*C*$(CH_3)_3$), 58.7 (N*C*H), 37.2 (N*C*H_3), 31.5 (*C*H$(CH_3)_2$), 28.3 (C(*C*H_3)$_3$), 27.6 (CH(*C*H_3)$_2$), 17.4 (CH(*C*H_3)$_2$); **IR (film, cm^{-1})**: ν_{max} = 3428 (NH), 2966, 2933, 2874 (C-H), 1728 (C=O ester), 1670 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{26}O_3N_2Na$ $[M+Na]^+$ 329.1836 found 329.1834.



(*S*)-*tert*-Butyl 2-(1,3-dimethyl-3-phenylureido)-3-methylbutanoate (S3k)

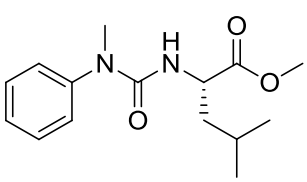
Following a similar method to general procedure **7**, sodium hydride (206 mg, 5.15 mmol, 2.5 eq, 60% suspension) was added to urea **S2k** (630 mg, 2.06 mmol) in DMF (0.2 M). After twenty minutes methyl iodide (0.38 mL, 6.18 mmol) was added. The reaction was left at 0 °C for one hour before warming to room temperature. The reaction was complete after one hour at room temperature. The reaction was quenched with water. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (610 mg, 1.91 mmol, 93%). **S3k: mp**: 72-74 °C, **R_f** (4:1 Pet.Ether:EtOAc) 0.49; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.33-7.29 (2H, m, Ph*H*), 7.13-7.08 (3H, m, Ph*H*), 4.27 (1H, d, *J* = 10.4, NC*H*CH), 3.20 (3H, s, NCH_3), 2.49 (3H, s, NCH_3), 2.14-2.01 (1H, m, C*H*$(CH_3)_2$), 1.45 (9H, s, OC(CH_3)$_3$), 0.96 (3H, d, *J* = 6.8, CH(CH_3)$_2$), 0.85 (3H, d, *J* = 6.8, CH(CH_3)$_2$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 170.8 (C=O), 162.6 (C=O), 146.7 (Ar*C*N), 129.4 (2xAr), 124.6 (Ar), 124.4 (2xAr), 81.1 (*C*$(CH_3)_3$), 65.3 (N*C*HCO$_2$C$(CH_3)_3$), 40.2 (N*C*H_3), 32.3 (N*C*H_3), 28.1 (C(*C*H_3)$_3$), 27.6 (*C*H$(CH_3)_2$), 19.8 (CH(*C*H_3)$_2$), 19.3 (CH(*C*H_3)$_2$); **IR (film, cm^{-1})**: ν_{max} = 2970, 2933, 2875 (C-H), 1728 (C=O ester), 1651 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{28}O_3N_2Na$ $[M+Na]^+$ 343.1993 found 343.1998.



(*S*)-2-(1,3-Dimethyl-3-phenylureido)-3-methylbutanoic acid (6k)

Following general procedure **8**, anhydrous DCM (2.50 mL) and TFA (2.50 mL) were added to urea **S3k** (400 mg, 1.25 mmol). The reaction was complete after two hours. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc to 100% EtOAc) yielded the title compound as a pale yellow oil (304 mg, 1.15 mmol, 92%). **6k: R_f** (1:1 Pet.Ether:EtOAc) 0.27; $[\alpha]_D^{20}$ = –207.4 (*c* = 1.5 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.89 (1H, br. s, COO*H*), 7.39-7.34 (2H, m, Ph*H*), 7.23-7.13 (3H, m, Ph*H*), 3.91 (1H, d, *J* = 10.8 , NC*H*CH), 3.29 (3H, s, NCH_3), 2.36 (3H, s, NCH_3), 2.22-2.10 (1H, m, C*H*$(CH_3)_2$), 1.01 (3H, d, *J* = 6.3, CH(CH_3)$_2$), 0.84 (3H, d, *J* = 6.6, CH(CH_3)$_2$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.4 (C=O), 164.7 (C=O), 144.6 (Ar*C*N), 129.7 (2xAr), 126.3 (Ar), 125.4 (2xAr), 67.3 (N*C*H), 40.2 (N*C*H_3), 34.1 (N*C*H_3), 26.6 (*C*H$(CH_3)_2$), 20.3 (CH(*C*H_3)$_2$), 19.5 (CH(*C*H_3)$_2$); **IR (film, cm^{-1})**: ν_{max} = 2965 (OH broad), 2965, 2931, 2875 (C-H), 1726 (C=O acid), 1639 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{21}O_3N_2$ $[M+H]^+$ 265.1547 found 265.1548.

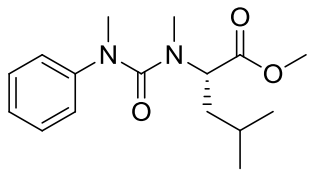
Synthesis of 6lLeu:



(*S*)-Methyl 4-methyl-2-{[methyl(phenyl)carbamoyl]amino}pentanoate (S2l)

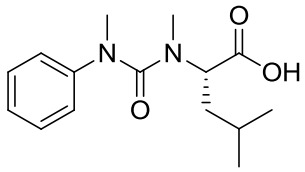
Following general procedure **6b**, L-leucine methyl ester hydrochloride (510 mg, 2.82 mmol) was added to a pre-stirred solution of *N*-methyl-*N*-phenylcarbamoyl chloride (475 mg, 2.82 mmol) in DCE (10.00 mL). To this solution was added Et_3N

(0.96 mL, 6.88 mmol, 2.4 eq) and DMAP (catalytic amount). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (708 mg, 2.54 mmol, 90%). **S2l:** **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.43-7.28 (2H, m, Ph*H*), 7.23-7.14 (3H, m, Ph*H*), 4.64 (1H, br. d, *J* = 7.9, N*H*CH), 4.48-4.26 (1H, m, NHC*H*CH_2), 3.59 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 1.71-1.08 (3H, m, CHCH_2CH and CH_2C*H*$(CH_3)_2$), 0.89-0.63 (6H, m, CH(CH_3)$_2$).



(*S*)-Methyl 4-methyl-2-{methyl[methyl(phenyl)carbamoyl]amino} pentanoate (S3l)

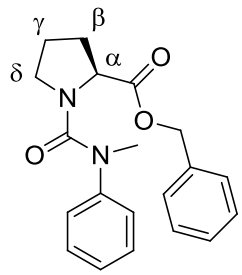
Following a similar method to general procedure **7**, sodium hydride (203 mg, 5.09 mmol) was added to urea **S2l** (708 mg, 2.54 mmol) in DMF (10.00 mL). After fifteen minutes methyl iodide (0.47 mL, 7.62 mmol) was added. The reaction was complete after one hour at 0 °C. The reaction was diluted with ethyl acetate and quenched by addition of ice water. The aqueous layer was extracted twice with ethyl acetate and the organic layer washed with brine. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (519 mg, 1.78 mmol, 70%). **S3l:** **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.37-7.17 (2H, m, Ph*H*), 7.12-6.96 (3H, m, Ph*H*), 4.65 (1H, t, *J* = 8.1, NC*H*CH_2), 3.55 (3H, s, OCH_3), 3.13 (3H, s, NCH_3), 2.42 (3H, s, NCH_3), 1.66-1.22 (3H, m, CHCH_2CH and CH_2C*H*$(CH_3)_2$), 0.88 (3H, d, *J* = 6.4, CH(CH_3)$_2$), 0.82 (3H, d, *J* = 6.5, CH(CH_3)$_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.1 (*C*=O), 162.5 (*C*=O), 146.7 (Ar*C*N), 129.6 (2xAr), 125.0 (Ar), 124.1 (2xAr), 57.4 (N*C*H), 51.9 (O*C*H_3), 40.3 (N*C*H_3), 38.2 (*C*H_2), 32.8 (N*C*H_3), 25.2 (*C*H), 23.3 (*C*H_3), 21.4 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2954 (C-H), 1742 (C=O ester), 1646 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{24}N_2O_3Na$ $[M+Na]^+$ 315.1679, found 315.1685.



(*S*)-4-Methyl-2-{methyl[methyl(phenyl)carbamoyl]amino}pentanoic acid (6l)

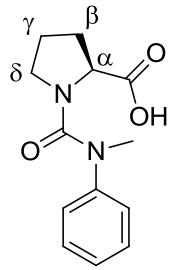
Following general procedure **10**, urea **S3l** (334 mg, 1.14 mmol) was dissolved in 2:1 THF:H_2O (32.10 mL) and LiOH (1.37 g, 57.00 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:3 Pet.Ether:EtOAc) yielded the title compound as an oil (187 mg, 0.67 mmol, 59%). **6l:** $[\alpha]_D^{20}$ = –48.5 (*c* = 1.7 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 12.23 (1H, br. s, COO*H*), 7.44-7.33 (2H, m, Ph*H*), 7.28-7.19 (1H, m, Ph*H*), 7.16-7.08 (2H, m, Ph*H*), 4.40 (1H, t, *J* = 7.9, NC*H*CH_2), 3.33 (3H, s, NCH_3), 2.33 (3H, s, NCH_3), 1.64 (2H, m, CHCH_2CH), 1.52-1.39 (1H, m, CHCH_2C*H*$(CH_3)_2$), 0.96 (3H, d, *J* = 6.6, CH(CH_3)$_2$), 0.93 (3H, d, *J* = 6.5, CH(CH_3)$_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.7 (*C*=O), 165.0 (*C*=O), 144.9 (Ar*C*N), 129.9 (2xAr), 126.4 (Ar), 125.2 (2xAr), 58.7 (N*C*H), 40.2 (N*C*H_3), 36.7 (*C*H_2), 34.2 (N*C*H_3), 24.6 (*C*H), 23.2 (*C*H_3), 21.8 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2956 (C-H), 2584 (OH broad), 1735 (C=O acid), 1593 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{22}O_3N_2Na$ $[M+Na]^+$ 301.1523, found 301.1519.

Synthesis of 6mPro:



(*S*)-Benzyl 1-(methyl(phenyl)carbamoyl)pyrrolidine-2-carboxylate (S2m)

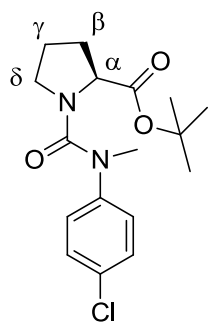
Following general procedure **6a**, *N*-methyl-*N*-phenylcarbamoyl chloride (983 mg, 5.80 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (1.50 g, 6.21 mmol) and Et_3N (1.86 mL, 13.35 mmol) in DCE (0.6 M). The reaction was complete after twenty hours heating at reflux. The title compound was yielded as a yellow oil without further purification (1.96 g, 5.80 mmol, >99%). **S2m: R_f** (1:1 Pet.Ether:EtOAc) 0.5; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.49-7.43 (5H, m, Ph*H*), 7.37-7.30 (4H, m, Ph*H*), 7.24-7.18 (1H, m, Ph*H*), 5.33 (1H, d, *J* = 12.3, OCH_AH$_B$Ph), 5.26 (1H, d, *J* = 12.3, OCH$_A$$H_B$Ph), 4.68-4.63 (1H, m, NC*H*CO(α)), 3.32 (3H, s, NCH_3), 3.09-3.02 (1H, m, NCH_2(δ)), 2.81-2.73 (1H, m, NCH_2(δ)), 2.30-2.20 (1H, m, CH_2(β)), 1.89-1.72 (3H, m, CH_2CH_2(β +2γ)); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.0 (C=O), 159.3 (C=O), 145.8 (Ar*C*N), 135.9 (Ar*C*), 129.4 (2xAr), 128.6 (2xAr), 128.3 (3xAr), 125.4 (2xAr), 125.0 (Ar), 66.7 (O*C*H$_2$Ph), 60.4 (N*C*HCO(α)), 49.0 (N*C*H$_2$(δ)), 39.6 (N*C*H$_3$), 29.4 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2925, 2877 (C-H), 1742 (C=O ester), 1641 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{22}O_3N_2Na$ $[M+Na]^+$ 361.1523, found 361.1519.



(*S*)-1-(Methyl(phenyl)carbamoyl)pyrrolidine-2-carboxylic acid (6m)

Following general procedure **9**, urea ester **S2m** (1.47 g, 4.35 mmol) was dissolved in methanol (20.00 mL) and palladium on carbon (150 mg, 10% by weight) was added. The reaction was complete in twenty hours. The title compound was yielded as a white solid without further purification (1.00 g, 4.03 mmol, 93%). **6m: mp** 158-160 ^{o}C; **R_f** (1:1 Pet.Ether:EtOAc) 0.1; $[\alpha]_D^{20}$ = –122.0 (*c* = 0.2 in $CHCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.39-7.35 (2H, m, Ph*H*), 7.24-7.18 (3H, m, Ph*H*), 4.53 (1H, dd, *J* = 7.2, 4.8, NC*H*CO(α)), 3.28 (3H, s, NCH_3), 2.76-2.70 (1H, m, NCH_2(δ)), 2.67-2.61 (1H, m, NCH_2(δ)), 2.26-2.18 (1H, m, CH_2(β)), 1.94-1.86 (1H, m, CH_2(β)), 1.83-1.72 (1H, m, CH_2(γ)), 1.71-1.61 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.2 (C=O), 160.7 (C=O), 144.9 (Ar*C*N), 129.7 (2xAr), 126.0 (Ar), 125.7 (2xAr), 61.0 (N*C*HCO(α)), 49.2 (N*C*H$_2$(δ)), 40.3 (N*C*H$_3$), 28.1 (*C*H$_2$(β)), 25.2 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 3002 (OH broad), 2976, 2948, 2876 (C-H), 1721 (C=O acid), 1644 (C=O urea); **HRMS** (ESI$^-$): *m/z* calcd for $C_{13}H_{15}O_3N_2$ $[M-H]^-$ 247.1088, found 247.1088.

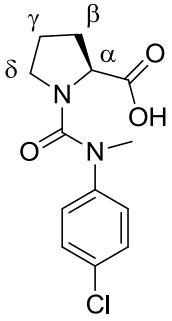
Synthesis of 6nPro:



(*S*)-*tert*-Butyl 1-((4-chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (S2n)

Following a similar method to general procedure **6a**, *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (530 mg, 2.60 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-proline *tert*-butyl ester (446 mg, 2.60

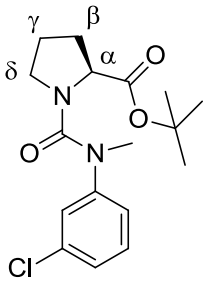
mmol, 1.0 eq) and Et_3N (0.47 mL, 3.38 mmol, 1.3 eq) in DCE (0.5 M). The reaction mixture was heated to 45 °C and was complete after twenty hours heating at temperature. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (792 mg, 2.34 mmol, 90%). **S2n: mp** 115-117 °C; $\mathbf{R_f}$ (4:1 Pet.Ether:EtOAc) 0.16; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.31-7.22 (4H, m, Ar*H*), 4.37-4.32 (1H, m, NC*H*CO(α)), 3.20 (3H, d, *J* = 1.5, NCH_3), 3.03-2.97 (1H, m, NCH_2(δ)), 2.77-2.69 (1H, m, NCH_2(δ)), 2.22-2.09 (1H, m, CH_2(β)), 1.77-1.62 (3H, m, CH_2CH_2(β +2γ)), 1.48 (9H, d, *J* = 1.8, OC(CH_3)$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.0 (C=O), 158.9 (C=O), 144.5 (Ar*C*N), 129.8 (Ar*C*Cl), 129.3 (2xAr), 126.1 (2xAr), 80.9 (O*C*(CH$_3$)$_3$), 60.8 (N*C*HCO(α)), 49.0 (N*C*H$_2$(δ)), 39.2 (N*C*H$_3$), 29.5 (*C*H$_2$(β)), 28.0 (OC(*C*H$_3$)$_3$), 25.2 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2976, 2877 (C-H), 1735 (C=O ester), 1645 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{23}O_3N_2{}^{35}ClNa$ $[M+Na]^+$ 361.1289, found 361.1289.



(*S*)-1-((4-Chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (6n)

Following general procedure **8**, anhydrous DCM (3.00 mL) and TFA (3.00 mL) were added to urea **S2n** (611 mg, 1.81 mmol). The reaction was complete after four hours. The title compound was yielded as a pale yellow solid without further purification (413 mg, 1.45 mmol, 81%). **6n: mp** 150-152 °C; $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.08; $[\alpha]_D^{20}$ = +104.7 (*c* = 1.2 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 9.90 (1H, br. s, COO*H*), 7.34-7.30 (2H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 4.54-4.50 (1H, m, NC*H*CO(α)), 3.24 (3H, s, NCH_3), 2.89-2.84 (1H, m, NCH_2(δ)), 2.74-2.68 (1H, m, NCH_2(δ)), 2.18-2.09 (1H, m, CH_2(β)), 1.99-1.90 (1H, m, CH_2(β)), 1.86-1.78 (1H, m, CH_2(γ)), 1.76-1.65 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.7 (C=O), 159.9 (C=O), 143.8 (Ar*C*N), 130.9 (Ar*C*Cl), 129.6 (2xAr), 126.8 (2xAr), 60.6 (N*C*HCO(α)), 49.3 (N*C*H$_2$(δ)), 39.9 (N*C*H$_3$), 28.7 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2976 (OH broad), 2976, 2879 (C-H), 1737 (C=O acid), 1606 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{15}O_3N_2{}^{35}ClNa$ $[M+Na]^+$ 305.0663, found 305.0663.

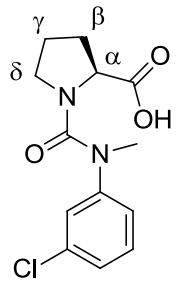
Synthesis of 6oPro:



(*S*)-*tert*-Butyl 1-((3-chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (S2o)

Following a similar method general procedure **6a**, *N*-(3-chlorophenyl)-*N*-methylcarbamoyl chloride (498 mg, 2.44 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-proline *tert*-butyl ester (418 mg, 2.44 mmol, 1.0 eq) and Et_3N (0.44 mL, 3.17 mmol, 1.3 eq) in DCE (0.5 M). The reaction mixture was heated to 45 °C and was complete after twenty hours heating at temperature. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (753 mg, 2.22 mmol, 91%). **S2o: $\mathbf{R_f}$** (4:1 Pet.Ether:EtOAc) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.30-7.23 (3H, m, Ar*H*), 7.11-7.09 (1H, m, Ar*H*), 4.37-4.34 (1H, m,

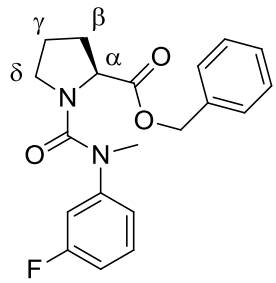
NC*H*CO(α)), 3.24 (3H, s, NCH_3), 3.06-3.01 (1H, m, NCH_2(δ)), 2.84-2.78 (1H, m, NCH_2(δ)), 2.23-2.14 (1H, m, CH_2(β)), 1.83-1.67 (3H, m, CH_2CH_2(β +2γ)), 1.51 (9H, s, OC(CH_3)$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 171.9 (C=O), 158.7 (C=O), 147.1 (Ar*C*N), 134.6 (Ar*C*Cl), 130.2 (Ar), 124.5 (Ar), 124.4 (Ar), 122.7 (Ar), 81.0 (O*C*(CH$_3$)$_3$), 60.9 (N*C*HCO(α)), 49.1 (NCH$_2$(δ)), 39.1 (N*C*H$_3$), 29.5 (*C*H$_2$(β)), 28.0 (OC(*C*H$_3$)$_3$), 25.2 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2977, 2877 (C-H), 1736 (C=O ester), 1649 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{23}O_3N_2{}^{35}ClNa$ $[M+Na]^+$ 361.1289, found 361.1289.



(*S*)-1-((3-Chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (6o)

Following general procedure **8**, anhydrous DCM (3.00 mL) and TFA (3.00 mL) were added to urea **S2o** (688 mg, 2.04 mmol). The reaction was complete after two hours. The title compound was yielded as a off-white solid without further purification (514 mg, 1.82 mmol, 89%). **6o: mp** 132-134 °C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.08; $[\alpha]_D^{20}$ = +100.9 (*c* = 1.3 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 10.92 (1H, br. s, COO*H*), 7.29-7.25 (2H, m, Ar*H*), 7.22-7.19 (1H, m, Ar*H*), 7.14-7.11 (1H, m, Ar*H*), 4.56-4.52 (1H, m, NC*H*CO(α)), 3.24 (3H, s, NCH_3), 2.95-2.90 (1H, m, NCH_2(δ)), 2.75-2.69 (1H, m, NCH_2(δ)), 2.22-2.14 (1H, m, CH_2(β)), 1.96-1.87 (1H, m, CH_2(β)), 1.86-1.77 (1H, m, CH_2(γ)), 1.77-1.66 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 176.2 (C=O), 159.5 (C=O), 146.5 (Ar*C*N), 134.8 (Ar*C*Cl), 130.4 (Ar), 125.3 (2xAr), 123.5 (Ar), 60.4 (N*C*HCO(α)), 49.2 (N*C*H$_2$(δ)), 39.6 (N*C*H$_3$), 28.9 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2976 (OH broad), 2976, 2879 (C-H), 1738 (C=O acid), 1610 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{15}O_3N_2{}^{35}ClNa$ $[M+Na]^+$ 305.0663, found 305.0659.

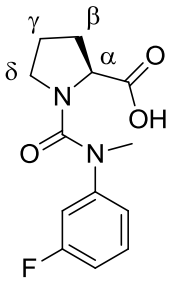
Synthesis of 6pPro:



(*S*)-Benzyl 1-((3-fluorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (S2p)

Following general procedure **6a**, *N*-(3-fluorophenyl)-*N*-methylcarbamoyl chloride (362 mg, 1.93 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and Et_3N (0.62 mL, 4.45 mmol) in DCE (0.4 M). The reaction was complete after twenty hours heating at reflux. Purification by flash column chromatography (SiO_2, 4:1 to 3:2 Pet.Ether:EtOAc) yielded the title compound as a yellow oil (649 mg, 1.82 mmol, 94%). **S2p: R$_f$** (4:1 Pet.Ether:EtOAc) 0.13; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.38-7.31 (5H, m, Ph*H*), 7.21 (1H, dt, *J* = 6.4, 8.0, FAr*H*), 7.02 (1H, ddd, *J* = 8.0, 2.0, 0.8, FAr*H*), 6.97 (1H, dt, *J* = 10.4, 2.4, FAr*H*), 6.81 (1H, tdd, *J* = 8.0, 2.8, 0.8, FAr*H*), 5.23 (1H, d, *J* = 12.4, OCH_AH$_B$Ph), 5.17 (1H, d, *J* = 12.4, OCH$_A$*H$_B$*Ph), 4.58-4.54 (1H, m, NC*H*CO(α)), 3.22 (3H, s, NCH_3), 3.04-2.99 (1H, m, NCH_2(δ)), 2.80-2.73 (1H, m, NCH_2(δ)), 2.26-2.16 (1H, m, CH_2(β)), 1.82-1.66 (3H, m, CH_2CH_2(β +2γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.7 (C=O), 163.1 (d, $^1J_{C\text{-}F}$ = 245.0, Ar*C*F), 158.8 (C=O), 147.3

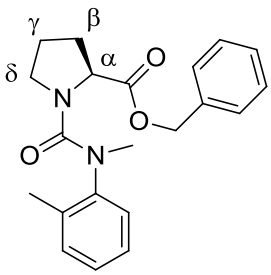
(Ar*C*N), 135.7 (Ar*C*), 130.3 (d, $^{3}J_{C\text{-}F}$ = 9.2, FAr), 128.5 (2xAr), 128.3 (Ar), 128.2 (2xAr), 120.4 (d, $^{4}J_{C\text{-}F}$ = 3.0, FAr), 112.0 (d, $^{2}J_{C\text{-}F}$ = 30.0, FAr), 111.5 (d, $^{2}J_{C\text{-}F}$ = 20.0, FAr), 66.7 (O*C*H$_2$Ph), 60.3 (N*C*HCO(α)), 49.0 (N*C*H$_2$(δ)), 39.2 (N*C*H$_3$), 29.4 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 3064, 2953, 2879 (C-H), 1741 (C=O ester), 1645 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{21}O_3N_2FNa$ $[M+Na]^+$ 379.1433, found 379.1436.



(*S*)-1-((3-Fluorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (6p)

Following general procedure **9**, urea ester **S2p** (602 mg, 1.69 mmol) was dissolved in methanol (10.00 mL) and palladium on carbon (60 mg, 10% by weight) was added. The reaction was complete after twenty hours. The title compound was yielded as a white solid without further purification (435 mg, 1.64 mmol, 97%). **6p: mp** 143-145 °C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.18; $[\alpha]_D^{20}$ = +92.4 (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.32 (1H, dt, *J* = 6.8, 8.0, Ar*H*), 7.03 (1H, ddd, *J* = 8.0, 2.0, 0.8, Ar*H*), 6.98 (1H, dt, *J* = 10.0, 2.0, Ar*H*), 6.90 (1H, tdd, *J* = 8.0, 2.4, 0.8, Ar*H*), 4.57-4.53 (1H, m, NC*H*CO(α)), 3.27 (3H, s, NC*H*$_3$), 2.86-2.74 (2H, m, NC*H*$_2$(δ)), 2.15-2.01 (2H, m, C*H*$_2$(β)), 1.87-1.78 (1H, m, C*H*$_2$(γ)), 1.76-1.66 (1H, m, C*H*$_2$(γ)); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 175.3 (C=O), 163.2 (d, $^{1}J_{C\text{-}F}$ = 245.9, Ar*C*F), 159.9 (C=O), 146.8 (d, $^{3}J_{C\text{-}F}$ = 9.8, Ar*C*N), 130.6 (d, $^{3}J_{C\text{-}F}$ = 9.3, Ar), 120.9 (d, $^{4}J_{C\text{-}F}$ = 3.0, Ar), 112.6 (d, $^{2}J_{C\text{-}F}$ = 12.2, Ar), 112.3 (d, $^{2}J_{C\text{-}F}$ = 10.4, Ar), 60.7 (N*C*HCO(α)), 49.2 (N*C*H$_2$(δ)), 39.8 (N*C*H$_3$), 28.6 (*C*H$_2$(β)), 25.3 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2976 (OH broad), 2976, 2881 (C-H), 1740 (C=O acid), 1589 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{16}O_3N_2F$ $[M+H]^+$ 267.1140, found 267.1135.

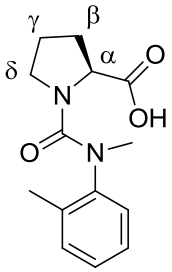
Synthesis of 6qPro:



(*S*)-Benzyl 1-(methyl(2-methylphenyl)carbamoyl)pyrrolidine-2-carboxylate (S2q)

Following general procedure **6a**, *N*-methyl-*N*-(2-methylphenyl)carbamoyl chloride (355 mg, 1.93 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and Et_3N (0.62 mL, 4.45 mmol) in DCE (0.4 M). The reaction was complete after twenty hours heating at reflux. Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (654 mg, 1.85 mmol, 96%). **S2q: R$_f$** (7:3 Pet.Ether:EtOAc) 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.37-7.30 (5H, m, Ph*H*), 7.22-7.20 (1H, m, MeAr*H*), 7.17-7.08 (3H, m, MeAr*H*), 5.23 (1H, d, *J* = 12.4, OC*H*$_A$H$_B$Ph), 5.12 (1H, d, *J* = 12.4, OCH$_A$*H*$_B$Ph), 4.53-4.49 (1H, m, NC*H*CO(α)), 3.08 (3H, s, NC*H*$_3$), 2.76-2.70 (1H, m, NC*H*$_2$(δ)), 2.55-2.50 (1H, m, NC*H*$_2$(δ)), 2.28 (3H, s, C*H*$_3$) 2.13-2.03 (1H, m, C*H*$_2$(β)), 1.77-1.62 (3H, m, C*H*$_2$C*H*$_2$(β +2γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.0 (C=O), 159.5 (C=O), 144.1 (Ar*C*N + Ar*C*), 135.9 (Ar*C*), 131.1 (MeAr), 128.5 (2xAr), 128.1 (2xAr + MeAr), 127.9 (Ar), 127.1 (MeAr),

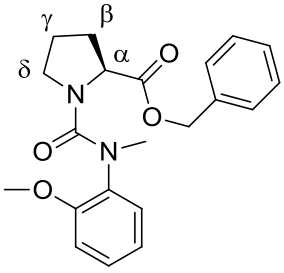
126.7 (MeAr), 66.6 (O*C*H$_2$Ph), 60.7 (N*C*HCO(α)), 48.0 (NCH$_2$(δ)), 38.6 (NCH$_3$), 29.2 (*C*H$_2$(β)), 25.2 (*C*H$_2$(γ)), 17.7 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3029, 2957, 2880 (C-H), 1742 (C=O ester), 1638 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{25}O_3N_2$ [M+H]$^+$ 353.1860, found 353.1867.



(*S*)-1-(Methyl(2-methylphenyl)carbamoyl)pyrrolidine-2-carboxylic acid (6q)

Following general procedure **9**, urea ester **S2q** (617 mg, 1.75 mmol) was dissolved in methanol (10.00 mL) and palladium on carbon (62 mg, 10% by weight) was added. The reaction was complete after twenty hours. The title compound was yielded as a white solid without further purification (454 mg, 1.73 mmol, 99%). **6q: mp** 152-154 °C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.14; $[\alpha]_D^{20}$ = –120.0 (*c* = 1.0 in CHCl$_3$); **^{1}H NMR** (400 MHz, CDCl$_3$): δ_H = 10.50 (1H, br. s, COO*H*), 7.24-7.17 (4H, m, Ar*H*), 4.51-4.47 (1H, m, NC*H*CO(α)), 3.14 (3H, s, NC*H*$_3$), 2.62-2.56 (1H, m, NC*H*$_2$(δ)), 2.52-2.46 (1H, m, NC*H*$_2$(δ)), 2.27 (3H, s, CH$_3$) 2.13-2.06 (1H, m, C*H*$_2$(β)), 2.94-2.86 (1H, m, C*H*$_2$(β)), 1.81-1.71 (1H, m, C*H*$_2$(γ)), 1.69-1.59 (1H, m, C*H*$_2$(γ)); **^{13}C {^{1}H} NMR** (100 MHz, CDCl$_3$): δ_C = 174.7 (C=O), 160.5 (C=O), 143.2 (Ar*C*N), 135.0 (Ar*C*), 131.3 (Ar), 127.8 (Ar), 127.3 (Ar), 127.2 (Ar), 61.3 (N*C*HCO(α)), 48.2 (NCH$_2$(δ)), 39.2 (NCH$_3$), 28.0 (*C*H$_2$(β)), 25.2 (*C*H$_2$(γ)), 17.6 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2971 (OH broad), 2971, 2881 (C-H), 1740 (C=O acid), 1576 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_3N_2Na$ [M+Na]$^+$ 285.1210, found 285.1222.

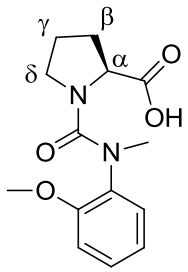
Synthesis of 6rPro:



(*S*)-Benzyl 1-((2-methoxyphenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (S2r)

Following general procedure **6a**, *N*-(2-methoxyphenyl)-*N*-methylcarbamoyl chloride (385 mg, 1.93 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and Et$_3$N (0.62 mL, 4.45 mmol) in DCE (0.4 M). The reaction was complete after twenty hours heating at reflux. Purification by flash column chromatography (SiO$_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (694 mg, 1.88 mmol, 98%). **S2r: R$_f$** (1:1 Pet.Ether:EtOAc) 0.35; **^{1}H NMR** (400 MHz, CDCl$_3$): δ_H = 7.38-7.30 (5H, m, Ph*H*), 7.21-7.17 (2H, m, OMeAr*H*), 6.91 (1H, dd, *J* = 8.8, 1.2, OMeAr*H*), 6.84 (1H, td, *J* = 7.6, 1.2, OMeAr*H*), 5.21 (1H, d, *J* = 12.4, OC*H*$_A$H$_B$Ph), 5.12 (1H, d, *J* = 12.4, OCH$_A$*H*$_B$Ph), 4.53-4.50 (1H, m, NC*H*CO(α)), 3.87 (3H, s, OC*H*$_3$), 3.08 (3H, s, NC*H*$_3$), 2.90-2.84 (1H, m, NC*H*$_2$(δ)), 2.58-2.52 (1H, m, NC*H*$_2$(δ)), 2.14-2.09 (1H, m, C*H*$_2$(β)), 1.76-1.63 (3H, m, C*H*$_2$C*H*$_2$(β +2γ)); **^{13}C {^{1}H} NMR** (100 MHz, CDCl$_3$): δ_C = 173.0 (C=O), 159.7 (C=O), 154.3 (Ar*C*OMe), 135.9 (Ar*C*N), 133.8 (Ar*C*), 128.6 (Ar), 128.5 (2xAr), 128.1 (3xAr), 127.5 (Ar), 121.1 (Ar), 111.5 (Ar), 66.5 (O*C*H$_2$Ph), 60.4 (N*C*HCO(α)), 55.4 (O*C*H$_3$), 48.0 (NCH$_2$(δ)), 37.7 (N*C*H$_3$), 29.5 (*C*H$_2$(β)), 25.3 (*C*H$_2$(γ)); **IR**

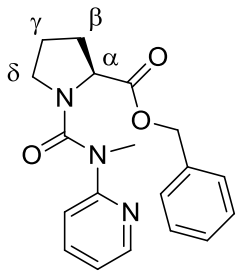
(film, cm^{-1}): ν_{max} = 2957, 2880 (C-H), 1743 (C=O ester), 1639 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{25}O_4N_2$ $[M+H]^+$ 369.1809, found 369.1800.



(*S*)-1-((2-Methoxyphenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (6r)

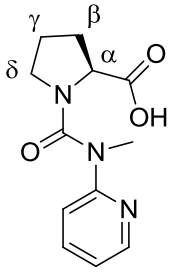
Following general procedure **9**, urea ester **S2r** (678 mg, 1.84 mmol) was dissolved in methanol (10.00 mL) and palladium on carbon (70 mg, 10% by weight) was added. The reaction was complete after twenty hours. The title compound was yielded as a white solid without further purification (511 mg, 1.84 mmol, >99%). **6r: mp** 136-138 °C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.21; $[\alpha]_D^{20}$ = –105.5 (*c* = 1.1 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 11.50 (1H, br. s, COO*H*), 7.27-7.23 (1H, m, Ar*H*), 7.20-7.18 (1H, m, Ar*H*) 6.98-6.93 (2H, m, Ar*H*), 4.53-4.50 (1H, m, NC*H*CO(α)), 3.87 (3H, s, OCH_3), 3.15 (3H, s, NCH_3), 2.66-2.55 (2H, m, NCH_2(δ)), 2.25-2.17 (1H, m, CH_2(β)), 1.89-1.80 (1H, m, CH_2(β)), 1.77-1.68 (1H, m, CH_2(γ)), 1.68-1.59 (1H, m, CH_2 (γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.6 (C=O), 161.4 (C=O), 154.4 (Ar*C*OMe), 132.8 (Ar*C*N), 128.5 (Ar), 128.4 (Ar), 121.4 (Ar), 111.9 (Ar), 61.3 (N*C*HCO(α)), 55.8 (O*C*H$_3$) 48.5 (NCH$_2$(δ)), 39.0 (N*C*H$_3$), 27.7 (*C*H$_2$(β)), 25.2 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2969 (OH broad), 2969, 2881 (C-H), 1740 (C=O acid), 1593 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{19}O_4N_2$ $[M+H]^+$ 279.1340, found 279.1343.

Synthesis of 6sPro:



(*S*)-Benzyl 1-[methyl(pyridin-2-yl)carbamoyl]pyrrolidine-2-carboxylate (S2s)

Following general procedure **6b**, L-proline benzyl ester hydrochloride (392 mg, 1.62 mmol) was added to a pre-stirred solution of *N*-methyl-*N*-(pyridin-2-yl)carbamoyl chloride (276 mg, 1.62 mmol) in DCE (3.24 mL). To this solution was added Et_3N (0.29 mL, 2.11 mmol) and DMAP (catalytic amount). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (478 mg, 1.41 mmol, 87%). **S2s: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.21 (1H, dd, *J* = 4.8, 1.0, Ar*H*), 7.35 (1H, m, Ar*H*), 7.22-7.15 (6H, m, Ar*H*), 6.67 (1H, dd, *J* = 6.8, 5.3, Ar*H*), 5.08 (1H, d, *J* = 12.3, OCH_AH$_B$Ph), 5.02 (1H, d, *J* = 12.3, OCH$_A$$H_B$Ph), 4.51 (1H, m, NC*H*CO(α)), 3.21 (3H, s, NCH_3), 3.04-2.99 (1H, m, NCH_2(δ)), 2.85-2.81 (1H, m, NCH_2(δ)), 2.16-2.09 (1H, m, CH_2(β)), 1.72-1.56 (3H, m, CH_2CH_2(β +2γ)); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.5 (*C*=O), 158.3 (Ar*C*N), 156.6 (*C*=O), 148.2 (Ar*C*CH$_2$), 137.6 (Ar), 135.5 (Ar), 128.4 (2xAr), 128.1 (Ar), 128.0 (2xAr), 118.0 (Ar), 116.6 (Ar), 66.6 (O*C*H$_2$Ph), 59.9 (N*C*HCO(α)), 48.7 (NCH$_2$(δ)), 35.5 (N*C*H$_3$), 29.4 (*C*H$_2$(β)), 25.1 (*C*H$_2$(γ)); **IR (film, cm^{-1})**: ν_{max} = 2977 (C-H), 1735 (C=O ester), 1667 (C=O urea). **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{21}N_3O_3Na$ $[M+Na]^+$ 362.1481, found 362.1464.

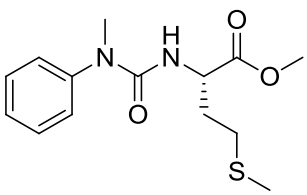


(*S*)-1-[Methyl(pyridin-2-yl)carbamoyl]pyrrolidine-2-carboxylic acid (6s)

Urea **S2s** (68 mg, 0.20 mmol) was dissolved in ethyl acetate and Et_3N (0.06 mL, 0.40 mmol). Palladium on carbon (10 mol%) was added to this solution and the resulting mixture was placed under a hydrogen atmosphere through use of a balloon. The reaction was complete after one hour at room temperature. The reaction mixture was diluted with ethyl acetate and methanol and filtered over celite. The filtrate was concentrated under *in vacuo* to yield the title compound as an oil without further purfication (50 mg, 0.20 mmol, >99%). **6s:** $[\alpha]_D^{20}$ = –285.3 (*c* = 0.3 in $CHCl_3$); **^{1}H NMR** (300 MHz, CD_3OD): δ_H = 12.34 (1H, br. s, COO*H*), 8.34 (1H, dd, *J* = 2.0, 5.0, Ar*H*), 7.79-7.68 (1H, m, Ar*H*), 7.14 (1H, d, *J* = 8.3, Ar*H*), 7.01 (1H, dd, *J* = 5.1, 6.7, Ar*H*), 4.75 (1H, dd, *J* = 6.2, 8.3, NC*H*CO(α)), 3.31 (3H, s, NCH_3), 3.36-3.14 (1H, m, NCH_2(δ)), 2.97-2.80 (1H, m, NCH_2(δ)), 2.40-2.22 (1H, m, CH_2(β)), 2.14-1.98 (1H, m, CH_2(β)), 1.80 (2H, quin., *J* = 6.9, CH_2CH_2(2γ)); **^{13}C {^{1}H} NMR** (100 MHz, CD_3OD): δ_C = 174.7 (*C*=O), 158.6 (*C*=O), 157.0 (Ar*C*N), 147.7 (Ar), 139.5 (Ar), 118.6 (Ar), 115.3 (Ar), 60.2 (N*C*H), 48.8 (N*C*H$_2$), 36.2 (N*C*H$_3$), 29.8 (*C*H$_2$), 25.1 (*C*H$_2$); **IR (film, cm^{-1})**: ν_{max} = 2980 (C-H), 1731 (C=O acid), 1643 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_3O_3Na$ $[M+Na]^+$ 272.0999, found 272.1006.

Triethylamine was added to quench the carboxylic acid forming in the reaction and thus avoid pyridine hydrogenation.[2,3]

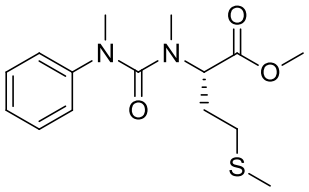
Synthesis of 6tMet:



(*S*)-Methyl 2-{[methyl(phenyl)carbamoyl]amino}-4-(methylsulfanyl) butanoate (S2t)

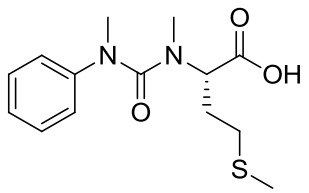
Following general procedure **6b**, L-methionine methyl ester hydrochloride (400 mg, 2.00 mmol) was added to a pre-stirred solution of *N*-methyl-*N*-phenylcarbamoyl chloride (338 mg, 2.00 mmol) in DCE (6.50 mL). To this solution was added Et_3N (0.84 mL, 6.00 mmol, 3.0 eq) and DMAP (catalytic amount). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (583 mg, 1.96 mmol, 98%). **S2t: ^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.37-7.31 (2H, m, Ph*H*), 7.22-7.15 (3H, m, Ph*H*), 4.96 (1H, br. d, *J* = 8.1, N*H*CH), 4.50 (1H, dt, *J* = 4.9, 8.0, NHC*H*CH$_2$), 3.59 (3H, s, OCH_3), 3.15 (3H, s, NCH_3), 2.36-2.28 (2H, m, CH$_2$CH_2S), 2.01-1.86 (1H, m, CHCH_AH$_B$CH$_2$), 1.90 (3H, s, SCH_3), 1.78-1.68 (1H, m, CHCH$_A$$H_BCH_2$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 173.1 (*C*=O), 156.5 (*C*=O), 142.7 (Ar*C*N), 129.8 (2xAr), 127.3 (Ar), 127.0 (2xAr), 52.7 (N*C*H), 52.1 (O*C*H$_3$), 37.0 (N*C*H$_3$), 31.4 (*C*H$_2$), 29.9 (*C*H$_2$), 15.1 (S*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3346 (NH), 2951, 2916 (C-H), 1740 (C=O ester), 1661 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{20}O_3N_2NaS$ $[M+Na]^+$ 319.1087, found 319.1086.

[2] F. Glorius, *Org. Biomol. Chem.*, 2005, **3**, 4171.
[3] C. Cheng, J. Xu, R. Zhu, L. Xing, X. Wang and Y. Hu, *Tetrahedron*, 2009, **65** (41), 8538.



(*S*)-Methyl 2-{methyl[methyl(phenyl)carbamoyl]amino}-4-(methylsulfanyl)butanoate (S3t)

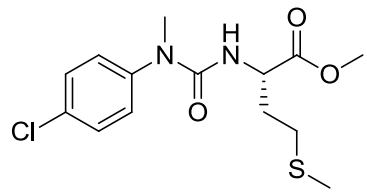
Following a similar method to general procedure **7**, sodium hydride (157 mg, 3.92 mmol) was added to urea **S2t** (583 mg, 1.96 mmol) in DMF (10.00 mL). After fifteen minutes methyl iodide (0.37 mL, 5.88 mmol) was added. The reaction was complete after one hour at 0 ^{o}C. The reaction was diluted with ethyl acetate and quenched by addition of ice water. The aqueous layer was extracted twice with ethyl acetate and the organic layer washed with brine. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (414 mg, 1.33 mmol, 68%). **S3t: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.36-7.20 (2H, m, Ph*H*), 7.18-7.01 (3H, m, Ph*H*), 4.71 (1H, dd, *J* = 10.1, 5.1, NC*H*CH_2), 3.65 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 2.49-2.29 (2H, m, CH_2CH_2S), 2.46 (3H, s, NCH_3), 2.26-2.12 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.06 (3H, s, SC$H_3$), 2.00-1.78 (1H, m, $CHCH_AH_BCH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.0 (*C*=O), 162.1 (*C*=O), 146.3 (Ar*C*N), 129.3 (2xAr), 124.9 (Ar), 124.6 (2xAr), 58.1 (N*C*H), 51.9 (O*C*H_3), 40.0 (N*C*H_3), 33.2 (N*C*H_3), 30.8 (CH_2), 28.4 (CH_2), 15.1 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2950, 2916 (C-H), 1740 (C=O ester), 1644 (C=O urea); **HRMS** (ESI^{+}): *m/z* calcd for $C_{15}H_{22}O_3N_2NaS$ $[M+Na]^+$ 333.1243, found 333.1251.



(*S*)-2-{Methyl[methyl(phenyl)carbamoyl]amino}-4-(methylsulfanyl) butanoic acid (6t)

Following general procedure **10**, urea **S3t** (170 mg, 0.55 mmol) was dissolved in 2:1 THF:H_2O (15.50 mL) and LiOH (656 mg, 27.38 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:3 Pet.Ether:EtOAc) yielded the title compound as an oil (121 mg, 0.41 mmol, 74%). **6t:** $[\alpha]_D^{20}$ = –94.7 (*c* = 1.3 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.97 (1H, br. s, COO*H*), 7.42-7.30 (2H, m, Ph*H*), 7.24-7.10 (3H, m, Ph*H*), 4.63 (1H, dd, *J* = 9.9, 5.4, NC*H*CH_2), 3.28 (3H, s, NCH_3), 2.54-2.31 (2H, m, CH_2CH_2S), 2.37 (3H, s, NCH_3), 2.27-2.13 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.09 (3H, s, SC$H_3$), 2.01-1.80 (1H, m, $CHCH_AH_BCH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.7 (*C*=O), 164.4 (*C*=O), 145.3 (Ar*C*N), 129.9 (2xAr), 126.2 (Ar), 125.3 (2xAr), 58.6 (N*C*H), 40.2 (N*C*H_3), 34.0 (N*C*H_3), 30.5 (CH_2), 27.4 (CH_2), 15.3 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2917 (C-H), 2587 (OH broad), 1736 (C=O acid), 1592 (C=O urea).); **HRMS** (ESI^{+}): *m/z* calcd for $C_{14}H_{20}O_3N_2NaS$ $[M+Na]^+$ 319.1087, found 319.1090.

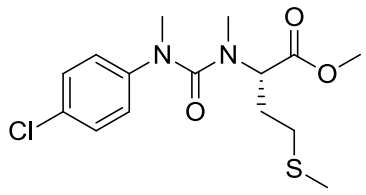
<u>Synthesis of 6uMet:</u>



(*S*)-Methyl 2-{[(4-chlorophenyl)(methyl)carbamoyl]amino}-4-(methylsulfanyl)butanoate (S2u)

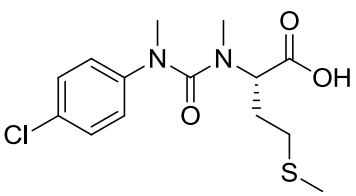
Following general procedure **6a**, *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (500 mg, 2.45 mmol) and DMAP

(catalytic amount) were added to a pre-stirred solution of L-methionine methyl ester hydrochloride (734 mg, 3.68 mmol, 1.5 eq) and Et_3N (0.85 mL, 6.13 mmol, 2.5 eq) in DCE (8.00 mL). The reaction was complete after twenty hours at 65 °C. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (626 mg, 1.89 mmol, 77%). **S2u: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.42 (2H, d, *J* = 8.7, Ar*H*), 7.25 (2H, d, *J* = 8.7, Ar*H*), 5.03 (1H, br. d, *J* = 7.9, N*H*CH), 4.83 (1H, ddd, *J* = 15.7, 7.9, 4.8, NHC*H*CH_2), 3.73 (3H, s, OCH_3), 3.25 (3H, s, NCH_3), 2.45 (2H, dd, *J* = 7.4, 7.0, CH_2CH_2S), 2.14-1.98 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.04 (3H, s, SC$H_3$), 1.87 (1H, ddt, *J* = 14.2, 7.2, 7.2, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.5 (*C*=O), 156.6 (*C*=O), 141.7 (Ar*C*N), 133.3 (Ar*C*Cl), 130.4 (2xAr), 128.8 (2xAr), 53.2 (N*C*H), 52.5 (O*C*H_3), 37.4 (N*C*H_3), 31.8 (*C*H_2), 30.3 (*C*H_2), 15.6 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3342 (NH), 2950, 2916 (C-H), 1738 (C=O ester), 1657 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{19}N_2O_3{}^{35}ClSNa$ $[M+Na]^+$ 353.0697, found 353.0689.



(*S*)-Methyl 2-{[(4-chlorophenyl)(methyl) carbamoyl](methyl)amino} -4-(methylsulfanyl)butanoate (S3u)

Following general procedure **7**, methyl iodide (0.36 mL, 5.68 mmol) and sodium hydride (189 mg, 4.73 mmol) were added to urea **S2u** (626 mg, 1.89 mmol) in DMF (4.70 mL). The reaction was complete after one hour at 0 °C. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (316 mg, 0.92 mmol, 49%). **S3u: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.30 (2H, d, *J* = 8.7, Ar*H*), 7.08 (2H, d, *J* = 8.7, Ar*H*), 4.72 (1H, dd, *J* = 10.1, 5.1, NC*H*CH_2), 3.69 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 2.55-2.33 (2H, m, CH_2CH_2S), 2.51 (3H, s, NCH_3), 2.29-2.13 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.10 (3H, s, SC$H_3$), 2.02-1.82 (1H, m, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.2 (*C*=O), 162.1 (*C*=O), 145.1 (Ar*C*N), 130.5 (Ar*C*Cl), 129.7 (2xAr), 126.0 (2xAr), 58.4 (N*C*H), 52.2 (O*C*H_3), 40.2 (N*C*H_3), 33.5 (N*C*H_3), 31.1 (*C*H_2), 28.7 (*C*H_2), 15.5 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2950, 2916 (C-H), 1740 (C=O ester), 1647 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{21}N_2O_3{}^{35}ClNa$ $[M+Na]^+$ 367.0854, found 367.0867.

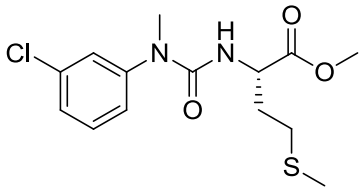


(*S*)-2-{[(4-Chlorophenyl)(methyl) carbamoyl](methyl)amino}-4-(methylsulfanyl)butanoic acid (6u)

Following general procedure **10**, urea **S3u** (316 mg, 0.92 mmol) was dissolved in 2:1 THF:H_2O (27.50 mL) and LiOH (1.10 g, 45.82 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (220 mg, 0.66 mmol, 72%). **6u:** $[\alpha]_D^{21}$**=** –99.4 (*c* = 1.3 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.84 (1H, br. s, COO*H*), 7.33 (2H, d, *J* = 8.7, Ar*H*), 7.10 (2H, d, *J* = 8.7, Ar*H*), 4.63 (1H, dd, *J* = 9.4, 5.2, NC*H*CH_2), 3.25 (3H, s, NCH_3), 2.55-2.29 (2H, m, CH_2CH_2S), 2.43 (3H, s, NCH_3), 2.29-2.14 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.09 (3H, s, SC$H_3$), 2.00-1.83 (1H, m, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz,

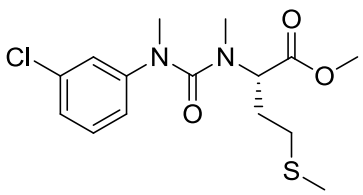
$CDCl_3$): δ_C = 173.7 (*C*=O), 163.9 (*C*=O), 144.0 (Ar*C*N), 131.5 (Ar*C*Cl), 130.0 (2xAr), 126.4 (2xAr), 58.5 (N*C*H), 40.1 (N*C*H_3), 34.1 (N*C*H_3), 30.7 (*C*H_2), 27.5 (*C*H_2), 15.3 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2969 (OH broad), 2914 (C-H), 1733 (C=O acid), 1589 (C=O urea); **HRMS** (ESI^+): *m/z* calcd for $C_{14}H_{19}N_2O_3{}^{35}ClSNa$ $[M+Na]^+$ 353.0697, found 353.0698.

Synthesis of 6vMet:



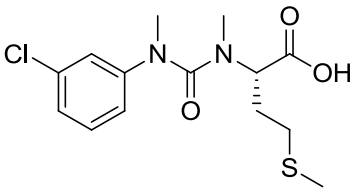
(*S*)-Methyl 2-{[(3-chlorophenyl)(methyl) carbamoyl]amino}-4-(methylsulfanyl)butanoate (S2v)

Following general procedure **6a**, *N*-(3-chlorophenyl)-*N*-methylcarbamoyl chloride (500 mg, 2.45 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-methionine methyl ester hydrochloride (734 mg, 3.68 mmol, 1.5 eq) and Et_3N (0.85 mL, 6.13 mmol, 2.5 eq) in DCE (8.00 mL). The reaction was complete after twenty hours at 65 °C. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (614 mg, 1.81 mmol, 76%). **S2v: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.45-7.13 (4H, m, Ar*H*), 5.12 (1H, br. d, *J* = 7.9, N*H*CH), 4.83 (1H, ddd, *J* = 12.6, 7.8, 4.8, NHC*H*CH_2), 3.73 (3H, s, OCH_3), 3.26 (3H, s, NCH_3), 2.45 (2H, dt, *J* = 1.3, 6.5, CH_2CH_2S), 2.15-1.98 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.04 (3H, s, SC$H_3$), 1.87 (1H, ddt, *J* = 14.3, 7.4, 7.4, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.4 (*C*=O), 156.5 (*C*=O), 144.4 (Ar*C*N), 135.5 (Ar*C*Cl), 131.1 (Ar), 127.8 (Ar), 127.6 (Ar), 125.5 (Ar), 53.3 (N*C*H), 52.6 (O*C*H_3), 37.4 (N*C*H_3), 31.7 (*C*H_2), 30.3 (*C*H_2), 15.6 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3329 (NH), 2950, 2916 (C-H), 1739 (C=O ester), 1659 (C=O urea); **HRMS** (ESI^+): *m/z* calcd for $C_{14}H_{19}N_2O_3{}^{35}ClSNa$ $[M+Na]^+$ 353.0697, found 353.0710.



(*S*)-Methyl 2-{[(3-chlorophenyl)(methyl) carbamoyl](methyl)amino}-4-(methylsulfanyl)butanoate (S3v)

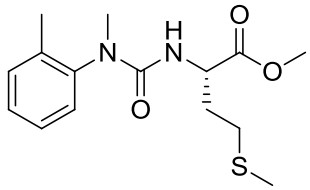
Following general procedure **7**, methyl iodide (0.31 mL, 5.03 mmol) and sodium hydride (168 mg, 4.19 mmol) were added to urea **S2v** (555 mg, 1.67 mmol) in DMF (4.20 mL). The reaction was complete after one hour at 0 °C. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (150 mg, 0.43 mmol, 26%). **S3v: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.37-7.21 (1H, m, Ar*H*), 7.18-6.99 (3H, m, Ar*H*), 4.76 (1H, dd, *J* = 10.1, 5.1, NC*H*CH_2), 3.72 (3H, s, OCH_3), 3.21 (3H, s, NCH_3), 2.54-2.41 (2H, m, CH_2CH_2S), 2.52 (3H, s, NCH_3), 2.34-2.15 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.12 (3H, s, SC$H_3$), 2.04-1.86 (1H, m, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.1 (*C*=O), 161.8 (*C*=O), 147.7 (Ar*C*N), 135.0 (Ar*C*Cl), 130.6 (Ar), 125.0 (Ar), 124.5 (Ar), 122.4 (Ar), 58.4 (N*C*H), 52.3 (O*C*H_3), 39.9 (N*C*H_3), 33.5 (N*C*H_3), 31.1 (*C*H_2), 28.6 (*C*H_2), 15.5 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2950, 2917 (C-H), 1740 (C=O ester), 1649 (C=O urea); **HRMS** (ESI^+): *m/z* calcd for $C_{15}H_{21}N_2O_3{}^{35}ClSNa$ $[M+Na]^+$ 367.0854, found 367.0868.



(*S*)-2-{[(3-Chlorophenyl)(methyl) carbamoyl](methyl)amino}-4-(methylsulfanyl)butanoic acid (6v)

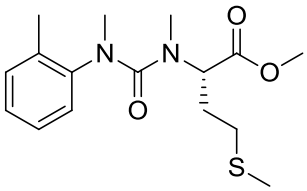
Following general procedure **10**, urea **S3v** (150 mg, 0.43 mmol) was dissolved in 2:1 THF:H_2O (13.00 mL) and LiOH (520 mg, 21.70 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (80 mg, 0.24 mmol, 56%). **6v:** $[\alpha]_D^{21} = -101.3$ (*c* = 1.2 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.72 (1H, br. s, COO*H*), 7.37-7.24 (1H, m, Ar*H*), 7.21-7.11 (2H, m, Ar*H*), 7.11-6.99 (1H, m, Ar*H*), 4.67 (1H, dd, *J* = 9.9, 5.4, NC*H*CH_2), 3.28 (3H, s, NCH_3), 2.58-2.35 (2H, m, CH_2CH_2S), 2.46 (3H, s, NCH_3), 2.32-2.15 (1H, m, CHCH_AH$_B$$CH_2$), 2.12 (3H, s, SC$H_3$), 2.05-1.84 (1H, m, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.9 (*C*=O), 163.6 (*C*=O), 146.6 (Ar*C*N), 135.2 (Ar*C*Cl), 130.8 (Ar), 125.9 (Ar), 125.0 (Ar), 122.8 (Ar), 58.5 (N*C*H), 39.9 (N*C*H_3), 34.0 (N*C*H_3), 30.7 (*C*H_2), 27.6 (*C*H_2), 15.4 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2971 (OH broad), 2940, 2912 (C-H), 1734 (C=O acid), 1589 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{19}N_2O_3{}^{35}ClSNa$ $[M+Na]^+$ 353.0697, found 353.0685.

Synthesis of 6wMet:



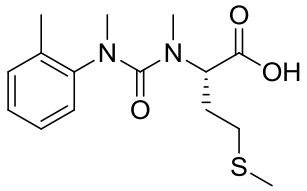
(*S*)-Methyl 2-{[methyl(2-methylphenyl)carbamoyl]amino}-4-(methylsulfanyl)butanoate (S2w)

Following general procedure **6a**, *N*-methyl-*N*-(2-methylphenyl)carbamoyl chloride (500 mg, 2.72 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-methionine methyl ester hydrochloride (815 mg, 4.08 mmol, 1.5 eq) and Et_3N (0.95 mL, 6.81 mmol, 2.5 eq) in DCE (8.80 mL). The reaction was complete after twenty hours at 65 °C. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (646 mg, 2.08 mmol, 77%). **S2w: ^{1}H NMR** (300 MHz, $CDCl_3$) (1:1 rotamers): δ_H = 7.36-7.09 (4H, m, Ar*H*), 4.82-4.69 (1H, m, N*H*CH), 4.65-4.53 (1H, m, NHC*H*CH_2), 3.69 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 2.42 (2H, br. t, *J* = 7.9, CH_2CH_2S), 2.31 (1.5H, s, ArCH_3), 2.25 (1.5H, s, ArCH_3), 2.00 (1.5H, s, SCH_3), 2.12-1.93 (1H, m, CHCH_AH$_B$$CH_2$), 1.99 (1.5H, s, SC$H_3$), 1.87 (1H, ddt, *J* = 14.4, 7.5, 7.5, CHC$H_A$$H_B$$CH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.5 (*C*=O_{rot1}), 172.3 (*C*=O_{rot2}), 156.9 (*C*=O_{rot1}), 156.8 (*C*=O_{rot2}), 141.0 (Ar*C*N), 132.0 (Ar*C*Me_{rot1}), 131.8 (Ar*C*Me_{rot2}), 128.8 (3xAr$_{rot2}$), 128.7 (3xAr$_{rot1}$), 128.1 (Ar$_{rot1}$), 127.9 (Ar$_{rot2}$), 53.0 (N*C*H), 52.4 (O*C*H_3), 36.1 (N*C*H_3), 32.2 (*C*H_{2rot1}), 31.7 (*C*H_{2rot2}), 30.3 (*C*H_2), 17.5 (Ph*C*H_{3rot1}), 17.4 (Ph*C*H_{3rot2}), 15.5 (S*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3334 (NH), 2950, 2916 (C-H), 1739 (C=O ester), 1661 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{22}N_2O_3SNa$ $[M+Na]^+$ 333.1243, found 333.1241.



(*S*)-Methyl 2-{methyl[methyl(2-methylphenyl)carbamoyl]amino}-4-(methylsulfanyl)butanoate (S3w)

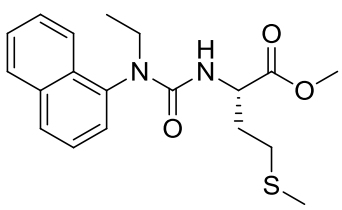
Following general procedure **7**, methyl iodide (0.34 mL, 6.24 mmol) and sodium hydride (208 mg, 5.20 mmol) were added to urea **S2w** (646 mg, 2.08 mmol) in DMF (5.20 mL). The reaction was complete after one hour at 0 °C. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (190 mg, 0.59 mmol, 28%). **S3w: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.28-7.12 (3H, m, Ar*H*), 7.08-7.00 (1H, m, Ar*H*), 4.70 (1H, dd, *J* = 10.3, 5.0, NC*H*CH_2), 3.65 (3H, s, OCH_3), 3.05 (3H, s, NCH_3), 2.47-2.24 (2H, m, $CH_2C\mathit{H}_2S$), 2.38 (3H, s, NCH_3), 2.31 (3H, s, ArCH_3), 2.23-2.08 (1H, m, CHCH_AH$_B$CH$_2$), 2.03 (3H, s, SCH_3), 1.93-1.77 (1H, m, CHCH$_A$$H_BCH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.4 (*C*=O), 163.1 (*C*=O), 144.9 (Ar*C*N), 134.7 (Ar*C*Me), 131.7 (Ar), 127.3 (Ar), 127.1 (Ar), 126.9 (Ar), 58.5 (N*C*H), 52.1 (O*C*H$_3$), 39.2 (N*C*H$_3$), 32.6 (N*C*H$_3$), 31.0 (*C*H$_2$), 28.9 (*C*H$_2$), 17.9 (Ar*C*H$_3$), 15.5 (S*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2950, 2917 (C-H), 1741 (C=O ester), 1645 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{24}N_2O_3SNa$ [M+Na]$^+$ 347.1400, found 347.1392.



(*S*)-2-{Methyl[methyl(2-methylphenyl)carbamoyl]amino}-4-(methylsulfanyl)butanoic acid (6w)

Following general procedure **10**, urea **S3w** (190 mg, 0.59 mmol) was dissolved in 2:1 THF:H_2O (16.60 mL) and LiOH (701 mg, 29.28 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (145 mg, 0.47 mmol, 79%). **6w:** $[\alpha]_D^{21}$ = –14.0 (*c* = 1.4 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.90 (1H, br. s, COO*H*), 7.31-7.17 (3H, m, Ar*H*), 7.11-6.99 (1H, m, Ar*H*), 4.60 (1H, dd, *J* = 9.0, 6.0, NC*H*CH_2), 3.14 (3H, s, NCH_3), 2.45-2.08 (3H, m, $CH_2C\mathit{H}_2S$ and CHCH_AH$_B$CH$_2$), 2.28 (3H, s, NCH_3), 2.27 (3H, s, ArCH_3), 2.07 (3H, s, SCH_3), 1.92-1.74 (1H, m, CHCH$_A$$H_BCH_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.9 (*C*=O), 165.5 (*C*=O), 143.4 (Ar*C*N), 134.4 (Ar*C*Me), 131.9 (Ar), 127.7 (Ar), 127.5 (Ar), 127.2 (Ar), 58.6 (N*C*H), 39.1 (N*C*H$_3$), 33.1 (N*C*H$_3$), 30.4 (*C*H$_2$), 27.2 (*C*H$_2$), 17.9 (Ar*C*H$_3$), 15.3 (S*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2969 (OH broad), 2913 (C-H), 1734 (C=O acid), 1594 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{22}N_2O_3SNa$ [M+Na]$^+$ 333.1243, found 333.1246.

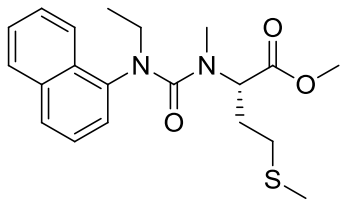
Synthesis of 6xMet:



(*S*)-Methyl 2-{ethyl[(naphtalen-1-yl)carbamoyl]amino}-4-(methylsulfanyl)butanoate (S2x)

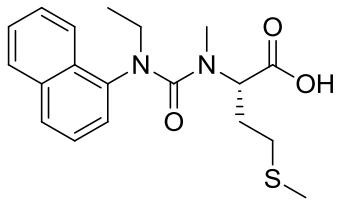
Following general procedure **6a**, *N*-ethyl-*N*-(naphthalen-1-yl)carbamoyl chloride (700 mg, 3.00 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of L-methionine methyl ester hydrochloride (718 mg, 3.59 mmol, 1.5 eq) and Et_3N (1.04 mL, 7.49 mmol, 2.5 eq) in DCE

(10.00 mL). The reaction was complete after twenty hours at 65 °C. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (846 mg, 2.44 mmol, 82%). **S2x: ^{1}H NMR** (300 MHz, $CDCl_3$) (1:0.8 rotamers): δ_H = 7.99-7.78 (3H, m, Napht*H*), 7.68-7.34 (4H, m, Napht*H*), 4.77 (0.42H, br. d, *J* = 8.2, N*H*CH), 4.67-4.50 (1H, m, NHC*H*CH_2), 4.66 (0.58H, br. d, *J* = 8.0, N*H*CH), 4.14 (1H, dq, *J* = 20.8, 7.1, C$H_A$$H_B$$CH_3$), 3.67 (1.6H, s, OC$H_3$), 3.59 (1.4H, s, OC$H_3$), 3.52 (1H, m, $CH_A$$H_B$$CH_3$), 2.44-1.56 (4H, m, CHC$H_2$$CH_2$ and CH_2CH_2S), 1.92 (1.3H, s, SCH_3), 1.78 (1.7H, s, SCH_3), 1.13 (3H, t, *J* = 7.0, CH_2CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.5 (*C*=O_{maj}), 173.1 (*C*=O_{min}), 157.0 (*C*=O_{min}), 156.9 (*C*=O_{maj}), 137.1 (Napht*C*N_{maj}), 137.1 (Napht*C*N_{min}), 135.2 (Napht*C*$_{min}$), 135.2 (Napht*C*$_{maj}$), 131.2 (Napht*C*$_{maj/min}$), 129.1 (Napht$_{maj/min}$), 128.8 (Napht$_{maj}$), 128.6 (Napht$_{min}$), 127.6 (Napht$_{maj}$), 127.5 (Napht$_{min}$), 127.3 (Napht$_{min}$), 127.3 (Napht$_{maj}$), 127.0 (Napht$_{min}$), 126.9 (Napht$_{maj}$), 126.2 (Napht$_{maj}$), 125.9 (Napht$_{min}$), 123.3 (Napht$_{min}$), 123.0 (Napht$_{maj}$), 53.2 (N*C*H$_{min}$), 52.8 (N*C*H$_{maj}$), 52.4 (O*C*H$_{3maj}$), 52.2 (O*C*H$_{3min}$), 44.2 (N*C*H$_{2min}$), 44.2 (N*C*H$_{2maj}$), 31.7 (*C*H$_{2maj}$), 31.5 (*C*H$_{2min}$), 30.3 (*C*H$_{2min}$), 30.0 (*C*H$_{2maj}$), 15.5 (S*C*H$_{3min}$), 15.3 (S*C*H$_{3maj}$), 14.3 (*C*H$_{3maj}$), 14.2 (*C*H$_{3min}$); **IR (film, cm^{-1})**: ν_{max} = 3355 (NH), 2951 (C-H), 1740 (C=O ester), 1655 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{24}N_2O_3SNa$ [M+Na]$^+$ 383.1400, found 383.1396.



(*S*)-Methyl 2-{[ethyl(naphtalen-1-yl)carbamoyl](methylamino}-4-(methylsulfanyl)butanoate (S3x)

Following general procedure **7**, methyl iodide (0.39 mL, 6.30 mmol) and sodium hydride (210 mg, 5.25 mmol) were added to urea **S2x** (758 mg, 2.10 mmol) in DMF (5.25 mL). The reaction was complete after one hour at 0 °C. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (630 mg, 1.68 mmol, 80%). **S3x: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.01 (1H, br. d, *J* = 7.8, Napht*H*), 7.87 (1H, dd, *J* = 7.0, 1.6, Napht*H*), 7.75 (1H, d, *J* = 18.2, Napht*H*), 7.58-7.46 (2H, m, Napht*H*), 7.41 (1H, t, *J* = 7.9, Napht*H*), 7.23 (1H, br. d, *J* = 7.8, Napht*H*), 3.69 (1H, dd, *J* = 10.5, 4.8, NC*H*CH_2), 3.84-3.85 (2H, m, NC$H_2$$CH_3$), 3.63 (3H, s, OC$H_3$), 2.39-1.91 (3H, m, CHC$H_A$$H_B$$CH_2$ and CH_2CH_2S), 2.25 (3H, s, NCH_3), 2.00 (3H, s, SCH_3), 1.82-1.65 (1H, m, CHC$H_A$$H_B$$CH_2$), 1.15 (3H, t, *J* = 7.0, CH_2CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.3 (*C*=O), 162.9 (*C*=O), 140.4 (Napht*C*N), 134.9 (Napht*C*), 130.0 (Napht*C*), 128.7 (Napht), 127.2 (Napht), 126.9 (Napht), 126.4 (Napht), 125.5 (Napht), 125.3 (Napht), 123.0 (Napht), 58.4 (N*C*H), 51.9 (O*C*H$_3$), 46.9 (N*C*H$_2$), 33.0 (N*C*H$_3$), 30.9 (*C*H$_2$), 28.6 (*C*H$_2$), 15.5 (S*C*H$_3$), 13.3 (CH$_3$); **IR (film, cm^{-1})**: ν_{max} = 2949, 2916 (C-H), 1740 (C=O ester), 1641 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{26}N_2O_3SNa$ [M+Na]$^+$ 397.1556, found 397.1561.

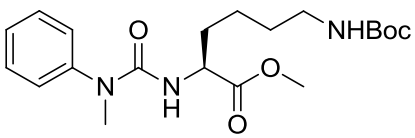


(*S*)-2-{[Ethyl(naphtalen-1-yl)carbamoyl](methyl)amino}-4-(methylsulfanyl)butanoic acid (6x)

Following general procedure **10**, urea **S3x** (450 mg, 1.20 mmol) was dissolved in 2:1 THF/H_2O (36.00 mL) and LiOH (1.44 g, 60.08 mmol)

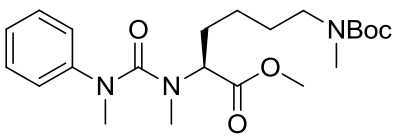
was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (368 mg, 1.03 mmol, 86%). **6x:** $[\alpha]_D^{21} = -24.3$ (*c* = 1.3 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.73 (1H, br. s, COO*H*), 8.07-7.71 (3H, m, Napht*H*), 7.67-7.05 (4H, m, Napht*H*), 4.65 (1H, br. s, NC*H*CH_2), 3.93 (1H, br. s, NC$H_A$$H_B$$CH_3$), 3.48 (1H, br. s, NC$H_A$$H_B$$CH_3$), 2.46-1.63 (7H, m, CHC$H_2$$CH_2$S, CH_2CH_2S and CH_3), 2.13 (3H, s, CH_3), 1.18 (3H, t, *J* = 7.0, CH_2CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.0 (*C*=O), 165.4 (*C*=O), 138.8 (Napht*C*N), 134.9 (Napht*C*), 129.7 (Napht*C*), 129.0 (Napht), 128.2 (Napht), 127.5 (Napht), 126.7 (Napht), 125.7 (Napht), 125.6 (Napht), 122.5 (Napht), 58.3 (N*C*H), 46.8 (NCH_2), 33.2 (NCH_3), 30.3 (CH_2), 27.0 (CH_2), 15.3 (SCH_3), 13.2 (CH_3); **IR (film, cm^{-1})**: ν_{max} = 3047 (OH broad), 2968, 2916 (C-H), 1735 (C=O acid), 1591 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{24}N_2O_3SNa$ $[M+Na]^+$ 383.1400; found 383.1414.

Synthesis of 6yLys:



(*S*)-Methyl 6-{[(tert-butoxy)carbonyl]amino}-2-{[methyl(phenyl) carbamoyl]amino}hexanoate (S2y)

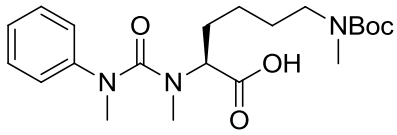
Following general procedure **6b**, *N*-Boc-L-lysine methyl ester hydrochloride (378 mg, 1.27 mmol) was added to a pre-stirred solution of *N*-methyl-*N*-phenyl carbamoyl chloride (215 mg, 1.27 mmol) in DCE (10.00 mL). To this solution was added Et_3N (0.51 mL, 3.81 mmol, 3.0 eq) and DMAP (catalytic amount). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (465 mg, 1.18 mmol, 93%). **S2y: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.32-7.27 (2H, m, Ph*H*), 7.18-7.13 (3H, m, Ph*H*), 4.92 (1H, m, CH_2N*H*), 4.71 (1H, d, *J* = 8.1, N*H*CH), 4.33 (1H, dt, *J* = 5.1, 8.1, NHC*H*), 3.53 (3H, s, OCH_3), 3.11 (3H, s, NCH_3), 2.93-2.87 (2H, m, CH_2), 1.66-1.55 (1H, m, C$H_A$$H_B$), 1.43-1.21 (3H, m, $CH_A$$H_B$ and CH_2), 1.27 (9H, s, C(CH_3)$_3$), 1.11 (2H, m, CH_2); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.6 (*C*=O), 156.2 (*C*=O), 155.9 (*C*=O), 142.8 (Ar*C*N), 129.9 (2xAr), 127.3 (Ar), 127.0 (2xAr), 78.5 (O*C*(CH$_3$)$_3$), 53.1 (OCH_3), 51.9 (N*C*H), 37.0 (NCH_2), 32.1 (NCH_3), 31.4 (CH_2), 29.2 (CH_2), 28.2 (OC(*C*H$_3$)$_3$), 22.4 (CH_2); **IR (film, cm^{-1})**: ν_{max} = 3338 (NH), 2933 (C-H), 1739 (C=O ester), 1697 (C=O Boc), 1655 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{32}O_5N_3$ $[M+H]^+$ 394.2336, found 394.2340.



(*S*)-Methyl 6-{[(tert-butoxy)carbonyl](methyl)amino}-2-{methyl [methyl(phenyl)carbamoyl]amino}hexanoate (S3y)

Following a similar method to general procedure **7**, sodium hydride (188 mg, 4.72 mmol, 4.0 eq) was added to urea **S2y** (465 mg, 1.18 mmol) in DMF (10.00 mL). After fifteen minutes methyl iodide (0.43 mL, 7.08 mmol, 6.0 eq) was added. The reaction was complete after one hour at 0 °C. The reaction was diluted with ethyl acetate and quenched by addition of ice water. The aqueous layer was extracted twice with ethyl acetate and the organic layer washed with brine. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title

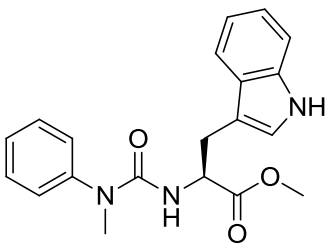
compound as an oil (438 mg, 1.04 mmol, 88%). **S3y: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.28-7.23 (2H, m, Ph*H*), 7.04-7.01 (3H, m, Ph*H*), 4.55 (dd, 1H, *J* = 10.4, 5.3, C*H*CH_2), 3.57 (3H, s, OCH_3), 3.12 (3H, s, NCH_3), 3.12 (2H, m, CH_2), 2.74 (3H, s, NCH_3), 2.38 (3H, s, NCH_3), 1.84-1.75 (1H, m, CH_AH$_B$), 1.59-1.39 (3H, m, CH$_A$$H_B$ and CH_2), 1.35 (s, 9H, C(CH_3)$_3$), 1.19-1.14 (2H, m, CH_2); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.4 (*C*=O), 162.2 (*C*=O), 155.6 (*C*=O), 146.3 (Ar*C*N), 129.3 (2xAr), 124.8 (Ar), 124.5 (2xAr), 79.0 (O*C*(CH$_3$)$_3$), 58.8 (O*C*H$_3$), 51.7 (N*C*H), 40.0 (N*C*H$_2$), 39.9 (N*C*H$_3$), 32.6 (NCH$_3$), 31.4 (N*C*H$_3$), 28.7 (*C*H$_2$), 28.3 (OC(*C*H$_3$)$_3$), 23.5 (*C*H$_2$), 22.5 (*C*H$_2$); **IR (film, cm^{-1})**: ν_{max} = 2932 (C-H), 1741 (C=O ester), 1688 (C=O Boc), 1644 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{36}O_5N_3$ $[M+H]^+$ 422.2649, found 422.2645.



(*S*)-6-{[(*tert*-Butoxy)carbonyl](methyl)amino}-2-{methyl[methyl (phenyl)carbamoyl]amino}hexanoic acid (6y)

Following a similar method to general procedure **10**, urea **S3y** (160 mg, 0.38 mmol) was dissolved in 2:1 THF:H_2O (15.00 mL) and LiOH (455 mg, 19.00 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. The reaction mixture was diluted with ethyl acetate and 5% $KHSO_4$ was added. The organic layer was separated and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were washed with brine. Purification by flash column chromatography (SiO_2, 1:3 Pet.Ether:EtOAc) yielded the title compound as an oil (139 mg, 0.34 mmol, 90%). **6y:** $[\alpha]_D^{20}$ **=** –20.4 (*c* = 1.8 in $CHCl_3$); **^{1}H NMR** (300 MHz, CD_3OD): δ_H = 7.48-7.32 (2H, m, Ph*H*), 7.27-7.11 (3H, m, Ph*H*), 4.68-4.46 (1H, m, NC*H*CH_2), 3.44-3.13 (2H, m, CH_2), 3.19 (3H, s, NCH_3), 3.12 (2H, m, CH_2), 2.50 (3H, s, NCH_3), 2.43 (3H, s, NCH_3), 2.08-1.09 (6H, m, CH_2CH_2CH_2), 1.46 (s, 9H, C(CH_3)$_3$); **^{13}C {^{1}H} NMR** (75 MHz, CD_3OD): δ_C = 173.4 (*C*=O), 164.4 (*C*=O), 157.5 (*C*=O), 147.5 (Ar*C*N), 130.7 (2xAr), 126.4 (Ar), 125.8 (2xAr), 74.1 (O*C*(CH$_3$)$_3$), 60.3 (N*C*H), 43.8 (N*C*H$_2$), 40.5 (N*C*H$_3$), 34.4 (N*C*H$_3$), 33.6 (*C*H$_2$), 29.8 (*C*H$_2$), 28.8 (C(*C*H$_3$)$_3$), 24.8 (*C*H$_2$); **IR (film, cm^{-1})**: ν_{max} = 2942 (OH broad), 2923 (C-H), 1736 (C=O acid), 1689 (C=O Boc), 1645 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{34}N_3O_5$ $[M+H]^+$ 408.2491, found 408.2493.

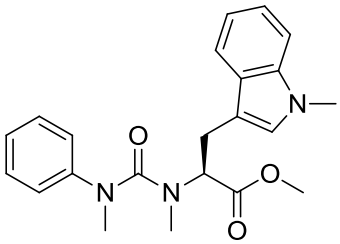
Synthesis of 6zTrp:



(*S*)-Methyl 3-(1H-indol-3-yl)-2-{[methyl(phenyl)carbamoyl]amino} propanoate (S2z)

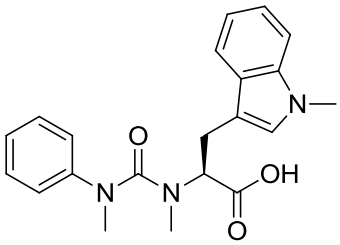
Following general procedure **6b**, L-tryptophane methyl ester hydrochloride (350 mg, 1.37 mmol) was added to a pre-stirred solution of *N*-methyl-*N*-phenylcarbamoyl chloride (233 mg, 1.37 mmol) in DCE (2.74 mL). To this solution was added Et_3N (0.25 mL, 1.78 mmol, 1.3 eq) and DMAP (catalytic amount). Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (438 mg, 1.25 mmol, 91%). **S2z: ^{1}H NMR** (300

MHz, $CDCl_3$): δ_H = 9.06 (1H, br. s, N*H*), 7.43 (1H, d, *J* = 7.9, Ar*H*), 7.34 (1H, d, *J* = 8.1, Ar*H*), 7.27-7.15 (4H, m, Ar*H*), 7.08-7.03 (3H, m, Ar*H*), 6.73 (1H, br. s, Ar*H*), 4.96 (1H, d, *J* = 7.5, N*H*CH), 4.83 (1H, m, NHC*H*CH_2), 3.66 (3H, s, OCH_3), 3.32-3.16 (2H, m, CHCH_2), 3.25 (3H, s, NCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.5 (*C*=O), 156.8 (*C*=O), 142.6 (Ar*C*), 136.3 (Ar*C*), 129.8 (2xAr), 127.4 (Ar*C*), 127.3 (Ar), 126.9 (2xAr), 122.9 (Ar*C*), 121.8 (Ar), 119.4 (Ar), 118.3 (Ar), 111.4 (Ar), 109.4 (Ar), 54.5 (O*C*H_3), 52.2 (N*C*H), 37.1 (N*C*H_3), 27.6 (*C*H_2); **IR (film, cm^{-1})**: ν_{max} = 3271 (NH), 3007 (C-H), 1738 (C=O ester), 1644 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{22}N_3O_3$ $[M+H]^+$ 352.1661, found 352.1650.



(*S*)-Methyl 3-(1-methyl-1H-indol-3-yl)-2-{methyl[methyl(phenyl) carbamoyl]amino}propanoate (S3z)

Following a similar method to general procedure **7**, sodium hydride (190 mg, 4.80 mmol, 4.0 eq) was added to urea **S2z** (420 mg, 1.20 mmol) in DMF (10.00 mL). After fifteen minutes methyl iodide (0.44 mL, 7.20 mmol, 6.0 eq) was added. The reaction was complete after one hour at 0 ^oC. The reaction was diluted with ethyl acetate and quenched by addition of ice water. The aqueous layer was extracted twice with ethyl acetate and the organic layer washed with brine. Purification by flash column chromatography (SiO_2, 1:1 Pet.Ether:EtOAc) yielded the title compound as an oil (328 mg, 0.86 mmol, 72%). **S3z: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.63 (1H, d, *J* = 7.7, Ar*H*), 7.36-7.25 (2H, m, Ar*H*), 7.17-7.12 (1H, m, Ar*H*), 6.97-6.95 (3H, m, Ar*H*), 6.91 (1H, s, Ar*H*), 6.64-6.60 (2H, m, Ar*H*), 5.17 (1H, dd, *J* = 10.8, 5.4, C*H*CH_2), 3.75 (6H, s, NCH_3 and OCH_3), 3.45 (1H, dd, *J* = 15.1, 5.3, CHC$H_A$$H_B$), 3.17 (1H, dd, *J* = 15.1, 10.9, CHC$H_A$$H_B$), 3.10 (3H, s, NC$H_3$), 2.51 (3H, s, NC$H_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.3 (*C*=O), 161.8 (*C*=O), 146.0 (Ar*C*), 137.0 (Ar*C*), 129.0 (2xAr), 127.7 (Ar*C*), 127.3 (2xAr), 124.2 (Ar), 123.7 (Ar*C*), 121.7 (Ar), 119.1 (Ar), 118.8 (Ar), 110.0 (Ar), 109.2 (Ar), 59.9 (O*C*H_3), 52.0 (N*C*H), 39.6 (N*C*H_3), 33.5 (N*C*H_3), 32.7 (N*C*H_3), 25.1 (*C*H_2); **IR (film, cm^{-1})**: ν_{max} = 2949 (C-H), 1740 (C=O ester), 1639 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{25}N_2O_3Na$ $[M+Na]^+$ 402.1777, found 402.1789.

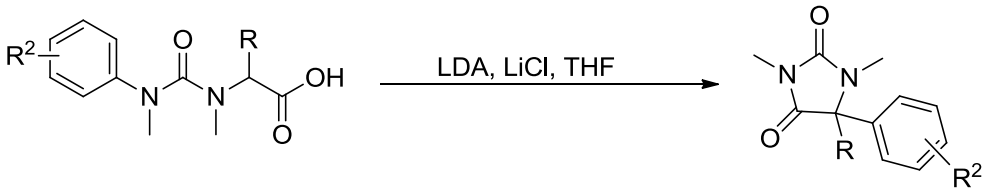


(*S*)-3-(1-Methyl-1H-indol-3-yl)-2-{methyl[methyl(phenyl)carbamoyl] amino}propanoic acid (6z)

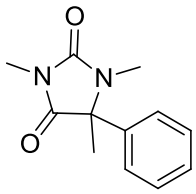
Following general procedure **10**, urea **S3z** (239 mg, 0.63 mmol) was dissolved in 2:1 THF:H_2O (15.00 mL) and LiOH (754 mg, 31.50 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. Purification by flash column chromatography (SiO_2, 1:3 Pet.Ether:EtOAc) yielded the title compound as an oil (182 mg, 0.50 mmol, 79%). **6z:** $[\alpha]_D^{20}$ = –128.0 (*c* = 0.6 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 11.3 (1H, br. s, COO*H*), 7.6 (1H, d, *J* = 7.9, Ar*H*), 7.40 (1H, d, *J* = 8.1, Ar*H*), 7.30 (1H, t, *J* = 7.3, Ar*H*), 7.16 (1H, t, *J* = 7.17, Ar*H*), 7.00-6.88 (4H, m, Ar*H*), 6.49 (2H, d, *J* = 7.4, Ar*H*), 5.03 (1H, dd, *J* = 11.0, 5.4, NC*H*CH_2), 3.80 (3H, s, NCH_3),

3.46-3.39 (1H, dd, *J* = 15.4, 5.3, CHC*H*$_A$CH$_B$), 3.30-3.25 (1H, m, CHCH$_A$C*H*$_B$), 3.20 (3H, s, NC*H*$_3$), 2.42 (3H, s, NC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.1 (*C*=O), 163.5 (*C*=O), 144.7 (Ar*C*), 137.0 (Ar*C*), 129.1 (2xAr), 127.6 (Ar*C*), 127.6 (Ar), 125.0 (Ar*C*), 124.1 (2xAr), 121.9 (Ar), 119.3 (Ar), 118.7 (Ar), 109.6 (Ar), 109.3 (Ar), 60.8 (N*C*H), 39.7 (N*C*H$_3$), 34.3 (N*C*H$_3$), 32.7 (N*C*H$_3$), 24.3 (*C*H$_2$); **IR (film, cm^{-1})**: ν_{max} = 2929 (C-H), 1733 (C=O acid), 1592 (C=O urea); **HRMS** (ESI$^+$): *m/z*: calcd for $C_{21}H_{23}N_3O_3Na$ $[M+Na]^+$ 388.1624, found 388.1632.

Synthesis of hydantoins:



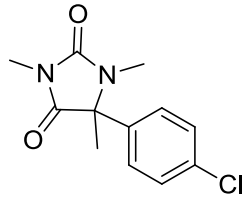
Synthesis of 5aAla:



1,3,5-Trimethyl-5-phenylimidazolidine-2,4-dione (5a)

Following general procedure **11**, LiCl (276 mg, 6.52 mmol) and THF (17.00 mL) were added to urea acid **6a** (513 mg, 2.17 mmol). LDA was prepared with DiPA (0.91 mL, 6.52 mmol), THF (5.00 mL) and *n*BuLi (2.61 mL, 6.52 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow solid (422 mg, 1.93 mmol, 89%). **5a: mp** 81-83 ^{o}C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.44; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.42-7.32 (3H, m, Ph*H*), 7.29-7.26 (2H, m, Ph*H*), 3.06 (3H, s, NC*H*$_3$), 2.84 (3H, s, NC*H*$_3$), 1.81 (3H, s, CC*H*$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.0 (C=O), 156.3 (C=O), 136.3 (Ar*C*), 129.1 (2xAr), 128.7 (Ar), 125.9 (2xAr), 66.7 (*C*CH$_3$), 25.3 (N*C*H$_3$), 25.1 (N*C*H$_3$), 20.2 (C*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2939 (C-H), 1770 (C=O amide), 1704 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}O_2N_2$ $[M+Na]^+$ 241.0948, found 241.0948.

Synthesis of 5bAla:

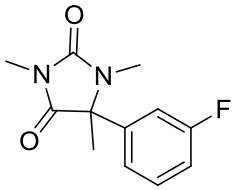


5-(4-Chlorophenyl)-1,3,5-trimethylimidazolidine-2,4-dione (5b)

Following general procedure **11**, LiCl (63 mg, 1.50 mmol) and THF (2.5 mL) were added to urea acid **6b** (135 mg, 0.50 mmol). LDA was prepared with DiPA (0.21 mL, 1.50 mmol), THF (2.5 mL) and *n*BuLi (0.60 mL, 1.50 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow before becoming brown upon warming to room temperature. Purification by flash column chromatography (SiO_2, 7:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow solid (98 mg, 0.39 mmol, 78%). **5b: mp** 96-101 ^{o}C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.51; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.36-7.34 (2H, m, Ar*H*), 7.22-7.19 (2H, m, Ar*H*), 3.03 (3H, s, NC*H*$_3$), 2.82 (3H, s, NC*H*$_3$), 1.77 (3H, s, CC*H*$_3$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 174.4 (C=O), 156.1 (C=O), 134.9 (Ar*C*), 134.8 (Ar*C*Cl), 129.2 (2xAr), 127.3

(2xAr), 66.2 (*C*CH$_3$), 25.3 (NCH$_3$), 25.1 (NCH$_3$), 20.3 (CCH$_3$); **IR (film, cm^{-1})**: ν_{max} = 3061, 2939 (C-H), 1770 (C=O amide), 1704 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{13}O_2N_2{}^{35}ClNa$ $[M+Na]^+$ 275.0558, found 275.0558.

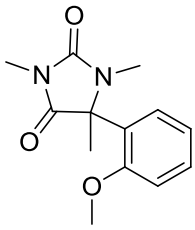
Synthesis of 5cAla:



5-(3-Fluorophenyl)-1,3,5-trimethylimidazolidine-2,4-dione (5c)

Following general procedure **11**, LiCl (44 mg, 1.04 mmol) and THF (1.75 mL) were added to urea acid **6c** (86 mg, 0.35 mmol). LDA was prepared with DiPA (0.15 mL, 1.04 mmol), THF (1.75 mL) and *n*BuLi (0.52 mL, 1.04 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned yellow before becoming brown upon warming to room temperature. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as a yellow oil (56 mg, 0.24 mmol, 70%). **5c**: **R$_f$** (2:1 Pet.Ether:EtOAc) 0.34; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.46-7.28 (1H, m, Ar*H*), 7.13-6.87 (3H, m, Ar*H*), 3.04 (3H, s, NC*H*$_3$), 2.84 (3H, s, NC*H*$_3$), 1.78 (3H, s, CC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.5 (*C*=O), 163.3 (d, $^1J_{C\text{-}F}$ = 247.4, Ar*C*F), 156.3 (*C*=O), 139.1 (d, $^3J_{C\text{-}F}$ = 6.8, Ar*C*C), 130.8 (d, $^3J_{C\text{-}F}$ = 8.2, Ar), 121.7 (d, $^4J_{C\text{-}F}$ = 2.9, Ar), 115.9 (d, $^2J_{C\text{-}F}$ = 21.0, Ar), 113.5 (d, $^2J_{C\text{-}F}$ = 23.1, Ar), 65.5 (d, $^4J_{C\text{-}F}$ = 1.7, N*C*C=O), 25.5 (NCH$_3$), 25.3 (NCH$_3$), 20.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3072, 2939 (C-H), 1770 (C=O amide), 1706 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}O_2N_2F$ $[M+H]^+$ 237.1034, found 237.1029.

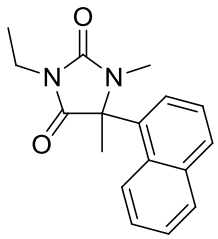
Synthesis of 5dAla:



5-(2-Methoxyphenyl)-1,3,5-trimethylimidazolidine-2,4-dione (5d)

Following general procedure **11**, LiCl (50 mg, 1.17 mmol) and THF (2.00 mL) were added to urea acid **6d** (104 mg, 0.39 mmol). LDA was prepared with DiPA (0.16 mL, 1.17 mmol), THF (2.00 mL) and *n*BuLi (0.58 mL, 1.17 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned yellow before becoming brown upon warming to room temperature. Purification by flash column chromatography (SiO_2, 2:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (73 mg, 0.29 mmol, 75%). **5d: mp** 136-137 ^{o}C; **R$_f$** (1:1 Pet.Ether:EtOAc) 0.40; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.42-7.31 (2H, m, Ar*H*), 7.05-6.99 (1H, m, Ar*H*), 6.90-6.87 (1H, m, Ar*H*), 3.73 (3H, s, OC*H*$_3$), 3.13 (3H, s, NC*H*$_3$), 2.59 (3H, s, NC*H*$_3$), 1.76 (3H, s, CC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 176.6 (C=O), 157.4 (C=O), 156.5 (Ar*C*OMe) 130.5 (Ar), 128.6 (Ar), 123.6 (Ar*C*), 120.7 (Ar), 111.3 (Ar), 64.2 (*C*CH$_3$), 55.9 (OCH$_3$), 24.8 (2xNCH$_3$), 20.5 (CCH$_3$); **IR (film, cm^{-1})**: ν_{max} = 3074, 2941 (C-H), 1768 (C=O amide), 1701 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{17}O_3N_2$ $[M+H]^+$ 249.1234, found 249.1237.

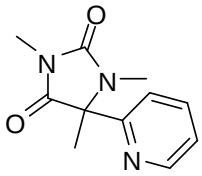
Synthesis of 5gAla:



3-Ethyl-1,5-dimethyl-5-(naphthalen-1-yl)imidazolidine-2,4-dione (5g)

Following general procedure **11**, LiCl (64 mg, 1.50 mmol) and THF (7.50 mL) were added to urea acid **6g** (150 mg, 0.50 mmol). LDA was prepared with DiPA (0.21 mL, 1.50 mmol), THF (2.50 mL) and *n*BuLi (0.60 mL, 1.50 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow before becoming orange upon warming to room temperature. Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (129 mg, 0.46 mmol, 91%). **5g: mp** 119-123 °C; **R_f** (1:1 Pet.Ether:EtOAc) 0.49; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.89-7.86 (2H, m, Napht*H*), 7.67-7.65 (1H, m, Napht*H*), 7.50-7.43 (4H, m, Napht*H*), 3.79 (2H, q, *J* = 7.2, C*H*$_2$CH$_3$), 2.61 (3H, s, NC*H*$_3$), 1.96 (3H, s, CC*H*$_3$), 1.38 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 175.5 (C=O), 155.4 (C=O), 134.3 (Napht*C*), 131.0 (Napht*C*), 130.7 (Napht), 130.0 (Napht*C*), 129.5 (Napht), 127.8 (Napht), 127.0 (Napht), 125.8 (Napht), 124.7 (Napht), 122.5 (Napht), 66.5 (*C*CH$_3$), 34.1 (*C*H$_2$CH$_3$), 24.9 (NCH$_3$), 23.4 (C*C*H$_3$), 13.2 (CH$_2$*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3053, 2977, 2938, 2878 (C-H), 1765 (C=O amide), 1702 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{19}O_2N_2$ $[M+H]^+$ 283.1452, found 283.1444.

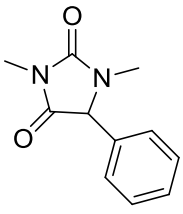
Synthesis of 5hAla:



1,3,5-Trimethyl-5-(pyridin-2-yl)imidazolidin-2,4-dione (5h)

Following general procedure **11**, LiCl (13 mg, 0.30 mmol) and THF (0.50 mL) were added to urea acid **6h** (27 mg, 0.10 mmol). LDA was prepared with DiPA (0.04 mL, 0.30 mmol), THF (0.27 mL) and *n*BuLi (0.12 mL, 0.30 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 1:2 Hexane:EtOAc) yielded the title compound as an oil (13 mg, 0.06 mmol, 78%). **5h: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.56 (1H, dt, *J* = 4.8, 0.8, Ar*H*), 7.67 (1H, td, *J* = 7.8, 1.8, Ar*H*), 7.27 (1H, d, *J* = 8.1, Ar*H*), 7.19 (1H, m, Ar*H*), 3.02 (3H, s, NC*H*$_3$), 2.74 (3H, s, NC*H*$_3$), 1.79 (3H, s, C*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.4 (*C*=O), 156.5 (*C*=O), 155.4 (Ar*C*), 149.8 (Ar), 137.2 (Ar), 123.4 (Ar), 120.9 (Ar), 68.3 (NC*C*=O), 25.5 (NCH$_3$), 25.2 (NCH$_3$), 19.1 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2934 (C-H), 1770 (C=O amide), 1704 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{14}N_3O_2$ $[M+H]^+$ 220.1074, found 220.1081.

Synthesis of 5iGly:

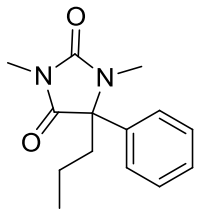


1,3-Dimethyl-5-phenylimidazolidine-2,4-dione (5i)

Following general procedure **11**, LiCl (67 mg, 1.57 mmol) and THF (4.20 mL) were added to urea acid **6i** (116 mg, 0.52 mmol). LDA was prepared with DiPA (0.22 mL, 1.57 mmol), THF (1.00 mL) and *n*BuLi (1.30 mL, 1.57 mmol, 1.2 M in hexanes). Upon addition of LDA the reaction mixture turned pale yellow and with warming to room temperature turned orange. Purification by flash column chromatography (SiO_2, 3:2

Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (85 mg, 0.42 mmol, 80%). **5i: R_f** (3:2 Pet.Ether:EtOAc) 0.41; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.45-7.34 (3H, m, Ph*H*), 7.26-7.23 (2H, m, Ph*H*), 4.79 (1H, s, NC*H*C=O), 3.06 (3H, s, NCH_3), 2.89 (3H, s, NCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 171.3 (C=O), 156.9 (C=O), 132.5 (Ar*C*), 129.3 (3xAr), 127.2 (2xAr), 65.9 (N*C*H), 28.1 (N*C*H_3), 25.1 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2918 (C-H), 1770 (C=O amide), 1702 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{12}O_2N_2Na$ $[M+Na]^+$ 227.0791, found 227.0796. Matches literature data.[4]

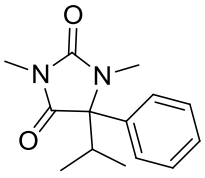
Synthesis of 5jPrg:



1,3-Dimethyl-5-phenyl-5-propylimidazolidine-2,4-dione (5j)

Following general procedure **11**, LiCl (48 mg, 1.12 mmol) and THF (2.00 mL) were added to urea acid **6j** (99 mg, 0.37 mmol). LDA was prepared with DiPA (0.16 mL, 1.12 mmol), THF (2.00 mL) and *n*BuLi (0.45 mL, 1.12 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow before becoming brown upon warming to room temperature. Purification by flash column chromatography (SiO_2, 3:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow solid (72 mg, 0.29 mmol, 78%). **5j: mp** 99-101 °C; **R_f** (1:1 Pet.Ether:EtOAc) 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.37-7.34 (2H, m, Ph*H*), 7.31-7.28 (1H, m, Ph*H*), 7.26-7.25 (2H, m, Ph*H*), 3.01 (3H, s, NCH_3), 2.79 (3H, s, NCH_3), 2.47 (1H, ddd, *J* = 16.0, 11.5, 4.5, CH_AH$_B$CH$_2$), 1.92 (1H, ddd, *J* = 16.5, 12.0, 4.5, CH$_A$$H_BCH_2$), 1.26-1.09 (2H, m, CH$_2CH_2CH_3$), 0.99 (H, t, *J* = 7.0, CH$_2$CH_3); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 174.3 (C=O), 156.7 (C=O), 136.3 (Ar*C*), 129.0 (2xAr), 128.5 (Ar), 125.8 (2xAr), 70.2 (*C*CH$_2$), 34.7 (C*C*H$_2$), 25.4 (N*C*H$_3$), 24.9 (N*C*H$_3$), 16.7 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2959, 2931, 2873 (C-H), 1782 (C=O acid), 1716 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_2N_2Na$ $[M+Na]^+$ 269.1260, found 269.1267.

Synthesis of 5kVal:



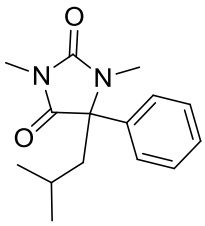
5-Isopropyl-1,3-dimethyl-5-phenylimidazolidine-2,4-dione (5k)

Following general procedure **11**, LiCl (28 mg, 0.65 mmol) and THF (1.20 mL) were added to urea acid **6k** (57 mg, 0.22 mmol). LDA was prepared with DiPA (0.09 mL, 0.65 mmol), THF (1.00 mL) and *n*BuLi (0.26 mL, 0.65 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (28 mg, 0.11 mmol, 53%). **5k: R_f** (3:2 Pet.Ether:EtOAc) 0.55; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.44-7.31 (3H, m, Ph*H*), 7.29-7.26 (2H, m, Ph*H*), 3.04 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 2.99-2.90 (1H, m, C*H*(CH$_3$)$_2$), 1.02 (3H, d, *J* = 5.4, CH(CH_3)$_2$), 0.99 (3H, d, *J* = 6.0, CH(CH_3)$_2$); **^{13}C {^{1}H} NMR** (100

[4] D. R. Anderson, N. C. Faibish and P. Beak, *J. Am. Chem. Soc.*, 1999, **121**, 7553.

MHz, $CDCl_3$): δ_C = 174.3 (C=O), 156.9 (C=O), 135.2 (Ar*C*), 129.1 (2xAr), 128.4 (Ar), 126.7 (2xAr), 73.8 (N*C*C=O), 32.0 (*C*H(CH_3)$_2$), 27.6 (N*C*H$_3$), 24.9 (N*C*H$_3$), 17.1 (CH(*C*H$_3$)$_2$), 16.7 (CH(*C*H$_3$)$_2$); **IR (film, cm^{-1})**: ν_{max} = 2969 (C-H), 1768 (C=O amide), 1704 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_2N_2Na$ $[M+Na]^+$ 269.1261, found 269.1262.

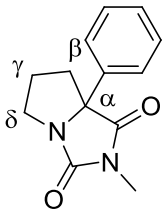
Synthesis of 5lLeu:



5-Isobutyl-1,3-dimethyl-5-phenylimidazolidine-2,4-dione (5l)

Following general procedure **11**, LiCl (13 mg, 0.30 mmol) and THF (0.50 mL) were added to urea acid **6l** (29 mg, 0.10 mmol). LDA was prepared with DiPA (0.04 mL, 0.30 mmol), THF (0.27 mL) and *n*BuLi (0.12 mL, 0.30 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 1:2 Hexane:EtOAc) yielded the title compound as an oil (17 mg, 0.07 mmol, 64%). **5l: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.34-7.25 (3H, m, Ph*H*), 7.21-7.18 (2H, m, Ph*H*), 2.98 (3H, s, NC*H*$_3$), 2.77 (3H, s, NC*H*$_3$), 2.42 (1H, dd, *J* = 14.7, 8.1, C*H*$_A$H$_B$), 1.91 (1H, dd, *J* = 14.7, 4.2, CH$_A$*H*$_B$), 1.57-1.51 (1H, m, C*H*(CH$_3$)$_2$), 0.92 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 0.83 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.5 (*C*=O), 156.9 (*C*=O), 137.2 (Ar*C*), 129.1 (2xAr), 128.6 (Ar), 125.7 (2xAr), 69.8 (N*C*C=O), 41.3 (*C*H$_2$), 25.9 (N*C*H$_3$), 25.1 (N*C*H$_3$), 24.4 (*C*H$_3$), 24.1 (*C*H$_3$), 22.8 (*C*H); **IR (film, cm^{-1})**: ν_{max} = 2925 (C-H), 1771 (C=O amide), 1708 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{20}N_2O_2Na$ $[M+Na]^+$ 283.1413, found 283.1417.

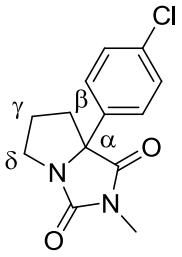
Synthesis of 5mPro:



2-Methyl-7a-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (5m)

Following general procedure **11**, LiCl (66 mg, 1.56 mmol) and THF (3.20 mL) were added to urea acid **6m** (129 mg, 0.52 mmol). LDA was prepared with DiPA (0.22 mL, 1.56 mmol), THF (2.00 mL) and *n*BuLi (0.78 mL, 1.56 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned yellow and with warming to room temperature turned orange. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (84 mg, 0.36 mmol, 70%). **5m: R$_f$** (7:3 Pet.Ether:EtOAc) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.59-7.56 (2H, m, Ph*H*), 7.41-7.31 (3H, m, Ph*H*), 3.86-3.79 (1H, m, NC*H*$_2$(δ)), 3.43-3.37 (1H, m, NC*H*$_2$(δ)), 2.97 (3H, s, NC*H*$_3$), 2.42-2.34 (1H, m, C*H*$_2$(β)), 2.16-2.07 (2H, m, C*H*$_2$(β) + C*H*$_2$(γ)), 1.96-1.84 (1H, m, C*H*$_2$(γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 174.5 (C=O), 160.2 (C=O), 137.4 (Ar*C*), 128.6 (2xAr), 128.3 (Ar), 125.7 (2xAr), 74.5 (C(α)), 45.0 (N*C*H$_2$(δ)), 36.1 (*C*H$_2$(β)), 26.0 (*C*H$_2$(γ)), 25.2 (N*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2952, 2899 (C-H), 1771 (C=O amide), 1705 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2Na$ $[M+Na]^+$ 253.0948, found 253.0951.

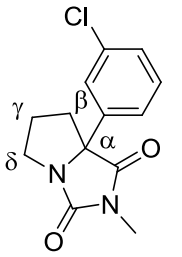
Synthesis of 5nPro:



7a-(4-Chlorophenyl)-2-methyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (5n)

Following general procedure **11**, LiCl (22 mg, 0.53 mmol) and THF (1.00 mL) were added to urea acid **6n** (50 mg, 0.18 mmol). LDA was prepared with DiPA (0.07 mL, 0.53 mmol), THF (0.80 mL) and *n*BuLi (0.26 mL, 0.53 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned bright yellow. Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as white solid (34 mg, 0.13 mmol, 72%). **5n: R_f** (7:3 Pet.Ether:EtOAc) 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.53-7.49 (2H, m, Ar*H*), 7.37-7.34 (2H, m, Ar*H*), 3.85-3.78 (1H, m, NCH_2(δ)), 3.41-3.35 (1H, m, NCH_2(δ)), 2.97 (3H, s, NCH_3), 2.36-2.28 (1H, m, CH_2(β)), 2.17-2.08 (2H, m, CH_2(β) + CH_2(γ)), 1.96-1.81 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 174.1 (C=O), 160.1 (C=O), 136.0 (Ar*C*), 134.5 (Ar*C*Cl), 128.8 (2xAr), 127.2 (2xAr), 74.1 (C(α)), 45.2 (NCH_2(δ)), 36.2 (*C*H_2(β)), 26.0 (*C*H_2(γ)), 25.3 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2952, 2900 (C-H), 1772 (C=O amide), 1705 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2{}^{35}Cl$ $[M+H]^+$ 265.0738, found 265.0728.

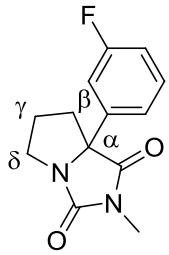
Synthesis of 5oPro:



7a-(3-Chlorophenyl)-2-methyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (5o)

Following general procedure **11**, LiCl (22 mg, 0.53 mmol) and THF (1.00 mL) were added to urea acid **6o** (50 mg, 0.18 mmol). LDA was prepared with DiPA (0.07 mL, 0.53 mmol), THF (0.80 mL) and *n*BuLi (0.26 mL, 0.53 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned bright yellow. Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale pink oil (31 mg, 0.12 mmol, 65%). **5o: R_f** (7:3 Pet.Ether:EtOAc) 0.30; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.59-7.55 (1H, m, Ar*H*), 7.49-7.44 (1H, m, Ar*H*), 7.39-7.29 (2H, m, Ar*H*), 3.87-3.78 (1H, m, NCH_2(δ)), 3.44-3.36 (1H, m, NCH_2(δ)), 2.98 (3H, s, NCH_3), 2.41-2.29 (1H, m, CH_2(β)), 2.18-2.07 (2H, m, CH_2(β) + CH_2(γ)), 1.99-1.82 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 173.9 (C=O), 160.1 (C=O), 139.5 (Ar*C*), 134.6 (Ar*C*Cl), 130.0 (Ar), 128.6 (Ar), 126.0 (Ar), 124.1 (Ar), 74.2 (C(α)), 45.2 (NCH_2(δ)), 36.2 (*C*H_2(β)), 26.0 (*C*H_2(γ)), 25.3 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2952, 2900 (C-H), 1773 (C=O amide), 1705 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2{}^{35}Cl$ $[M+H]^+$ 265.0738, found 265.0733.

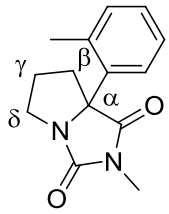
Synthesis of 5pPro:



7a-(3-Fluorophenyl)-2-methyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (5p)

Following general procedure **11**, LiCl (48 mg, 1.13 mmol) and THF (1.80 mL) were added to urea acid **6p** (100 mg, 0.38 mmol). LDA was prepared with DiPA (0.16 mL, 1.13 mmol), THF (2.00 mL) and *n*BuLi (0.56 mL, 1.13 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned bright yellow. Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (52 mg, 0.21 mmol, 55%). **5p: R_f** (7:3 Pet.Ether:EtOAc) 0.27; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.38-7.33 (2H, m, Ar*H*), 7.30-7.28 (1H, m, Ar*H*), 7.04-7.00 (1H, m, Ar*H*) 3.86-3.80 (1H, m, NCH_2(δ)), 3.42-3.37 (1H, m, NCH_2(δ)), 2.98 (3H, s, NCH_3), 2.36-2.31 (1H, m, CH_2(β)), 2.16-2.09 (2H, m, CH_2(β) + CH_2(γ)), 1.95-1.85 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 174.0 (C=O), 162.9 (d, $^1J_{C\text{-}F}$ = 245.5, Ar*C*F), 160.1 (C=O), 140.1 (d, $^3J_{C\text{-}F}$ = 7.3, Ar*C*), 130.2 (d, $^3J_{C\text{-}F}$ = 8.1, Ar), 121.4 (d, $^4J_{C\text{-}F}$ = 3.0, Ar), 115.3 (d, $^2J_{C\text{-}F}$ = 20.9, Ar), 113.1 (d, $^2J_{C\text{-}F}$ = 22.9, Ar), 74.5 (C(α)), 45.2 (N*C*H_2(δ)), 36.3 (*C*H_2(β)), 26.0 (*C*H_2(γ)), 25.3 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2953 (C-H), 1774 (C=O amide), 1707 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2F$ $[M+H]^+$ 249.1034, found 249.1045.

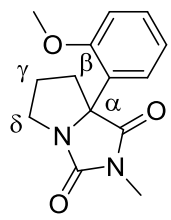
Synthesis of 5qPro:



2-Methyl-7a-(2-methylphenyl)tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (5q)

Following general procedure **11**, LiCl (24 mg, 0.57 mmol) and THF (1.00 mL) were added to urea acid **6q** (50 mg, 0.19 mmol). LDA was prepared with DiPA (0.08 mL, 0.57 mmol), THF (0.90 mL) and *n*BuLi (0.29 mL, 0.57 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned orange/brown. Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (28 mg, 0.12 mmol, 60%). **5q: R_f** (7:3 Pet.Ether:EtOAc) 0.34; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.51-7.49 (1H, m, Ar*H*), 7.26-7.21 (2H, m, Ar*H*), 7.18-7.15 (1H, m, Ar*H*), 3.95-3.90 (1H, m, NCH_2(δ)), 3.22-3.16 (1H, m, NCH_2(δ)), 2.98 (3H, s, NCH_3), 2.68 (ArCH_3) 2.66-2.61 (1H, m, CH_2(β)), 2.28-2.22 (1H, m, CH_2(β)), 2.10-2.02 (1H, m, CH_2(γ)), 1.95-1.86 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 174.7 (C=O), 159.8 (C=O), 136.9 (Ar*C*), 135.4 (Ar*C*), 133.0 (Ar), 128.5 (Ar), 126.1 (Ar), 125.9 (Ar), 75.1 (C(α)), 44.3 (N*C*H_2(δ)), 34.6 (*C*H_2(β)), 26.5 (*C*H_2(γ)), 25.2 (N*C*H_3), 21.5 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2952 (C-H), 1771 (C=O amide), 1706 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{16}O_2N_2Na$ $[M+Na]^+$ 267.1104, found 267.1101.

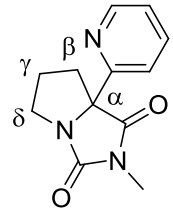
Synthesis of 5rPro:



7a-(2-Methoxyphenyl)-2-methyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (5r)

Following general procedure **11**, LiCl (69 mg, 1.62 mmol) and THF (3.40 mL) were added to urea acid **6r** (150 mg, 0.54 mmol). LDA was prepared with DiPA (0.23 mL, 1.62 mmol), THF (2.00 mL) and *n*BuLi (0.81 mL, 1.62 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned orange/brown. Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (106 mg, 0.41 mmol, 75%). **5r: mp** 148-150 ^oC; $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.18; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.36-7.31 (2H, m, Ar*H*), 6.97-6.93 (2H, m, Ar*H*), 3.85-3.80 (1H, m, NCH_2(δ)), 3.82 (3H, s, OCH_3) 3.18-3.13 (1H, m, NCH_2(δ)), 3.03 (3H, s, NCH_3), 2.85 (1H, ddd, *J* = 13.5, 7.0, 2.5, *C*H_2(β)), 2.22-2.14 (1H, m, CH_2(γ)) 2.12-2.05 (1H, m, CH_2(γ)), 1.95-1.88 (1H, m, *C*H_2(β)); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 175.1 (C=O), 160.5 (C=O), 158.2 (Ar*C*OMe) 130.2 (Ar), 127.3 (Ar), 124.5 (Ar*C*), 120.5 (Ar), 112.5 (Ar), 72.9 (*C*(α)), 56.0 (O*C*H_3), 44.2 (N*C*H_2(δ)), 31.7 (*C*H_2(β)), 26.7 (*C*H_2(γ)), 25.1 (N*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2949, 2839 (C-H), 1770 (C=O amide), 1703 (C=O urea); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{16}O_3N_2Na$ $[M+Na]^+$ 283.1053, found 283.1042.

Synthesis of 5sPro:

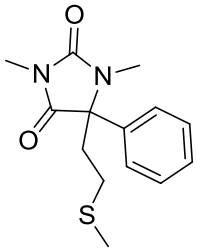


2-Methyl-7a-(pyridin-2-yl)-hexahydro-1H-pyrrolo[1,2-c]imidazolidin-1,3-dione (5s)

Following a similar method to general procedure **11**, LiCl (58 mg, 1.38 mmol) and THF (4.00 mL) were added to urea acid **6s** (117 mg, 0.46 mmol). LDA was prepared with DiPA (0.19 mL, 1.38 mmol), THF (0.60 mL) and *n*BuLi (0.55 mL, 1.38 mmol, 2.5 M in hexanes). The reaction mixture was quenched with methanol and stirred for ten minutes. The solvent was removed *in vacuo* and the crude product re-dissolved in methanol (3.00 mL) and conc. H_2SO_4 (0.10 mL) added. The resulting mixture was stirred for eighteen hours at room temperature. The reaction was then diluted with ethyl acetate and saturated aqueous $NaHCO_3$ solution was added until pH = 8. The basic organic layer was separated and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% EtOAc) yielded the title compound as a colourless oil (71 mg, 0.31 mmol, 67%). **5s: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.65-8.62 (1H, m, Ar*H*), 7.65 (1H, td, *J* = 7.7, 1.9, Ar*H*), 7.50 (1H, d, *J* = 7.7, Ar*H*), 7.21-7.17 (1H, m, Ar*H*), 3.88-3.74 (1H, m, NCH_2(δ)), 3.32-3.25 (1H, m, NCH_2(δ)), 2.95 (3H, s, NCH_3), 2.87-2.83 (1H, m, CH_2(β)), 2.09-2.01 (2H, m, CH_2(β) + CH_2(γ)), 1.98-1.75 (1H, m, CH_2(γ)); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.3 (*C*=O), 160.4 (*C*=O), 155.7 (Ar*C*), 150.0 (Ar), 136.9 (Ar), 123.2 (Ar), 120.4 (Ar), 76.1 (N*C*C=O), 45.2 (N*C*H_2), 33.8 (*C*H_2), 26.2 (N*C*H_3), 24.4 (*C*H_2); **IR (film, cm^{-1})**: ν_{max} = 2954 (C-H),

1772 (C=O amide), 1708 (C=O urea); **HRMS** (ESI^+): *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1085, found 232.1081.

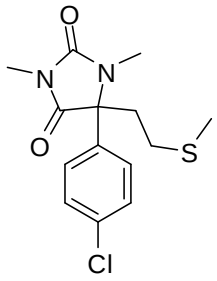
Synthesis of 5tMet:



1,3-Dimethyl-5-(2-(methylthio)ethyl)-5-phenylimidazolidine-2,4-dione (5t)

Following general procedure **11**, LiCl (14 mg, 0.36 mmol) and THF (1.00 mL) were added to urea acid **6t** (37 mg, 0.12 mmol). LDA was prepared with DiPA (0.51 mL, 0.36 mmol), THF (0.20 mL) and *n*BuLi (0.14 mL, 0.36 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 1:2 Hexane:EtOAc) yielded the title compound as an oil (24 mg, 0.09 mmol, 72%). **5t: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.36-7.28 (3H, m, Ph*H*), 7.22-7.18 (2H, m, Ph*H*), 2.99 (3H, s, NCH_3), 2.81-2.76 (1H, m, $CH_2CH_AH_BS$), 2.78 (3H, s, NCH_3), 2.30-2.17 (3H, m, $CH_2CH_AH_BS$ and CH_2CH_2), 2.07 (3H, s, SCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.7 (*C*=O), 153.7 (*C*=O), 135.8 (Ar*C*), 129.2 (2xAr), 128.9 (Ar), 125.8 (2xAr), 69.8 (N*C*C=O), 32.2 (CH_2), 28.1 (CH_2), 25.6 (NCH_3), 25.2 (NCH_3), 15.7 (SCH_3); **IR (film, cm^{-1})**: ν_{max} = 2917 (C-H), 1714 (C=O amide), 1644 (C=O urea). **HRMS** (EI): *m/z* calcd for $C_{11}H_{11}N_2O_2$ $[M-SC_3H_7]^{\cdot+}$ 203.0815, found 203.0806.

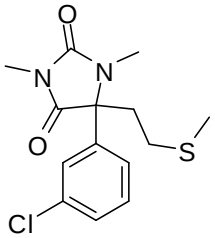
Synthesis of 5uMet:



5-(4-Chlorophenyl)-1,3-dimethyl-5-[2-(methylsulfanyl)ethyl] imidazolidin-2,4-dione (5u)

Following general procedure **11**, LiCl (41 mg, 0.97 mmol) and THF (2.50 mL) were added to urea acid **6u** (100 mg, 0.30 mmol). LDA was prepared with DiPA (0.14 mL, 0.97 mmol), THF (0.50 mL) and *n*BuLi (0.39 mL, 0.97 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (73 mg, 0.23 mmol, 78%). **5u: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.38 (2H, d, *J* = 8.7, Ar*H*), 7.21 (2H, d, *J* = 8.7, Ar*H*), 3.04 (3H, s, NCH_3), 2.88-2.75 (1H, m, $CH_2CH_AH_BS$), 2.84 (3H, s, NCH_3), 2.47-2.17 (3H, m, CH_2CH_2 and $CH_2CH_AH_BS$), 2.12 (3H, s, SCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.4 (*C*=O), 156.7 (*C*=O), 135.2 (Ar*C*), 134.6 (Ar*C*), 129.6 (2xAr), 127.4 (2xAr), 69.5 (N*C*C=O), 32.5 (CH_2), 28.1 (CH_2), 25.8 (NCH_3), 25.4 (NCH_3), 15.9 (SCH_3); **IR (film, cm^{-1})**: ν_{max} = 2916 (C-H), 1769 (C=O amide), 1706 (C=O urea); **HRMS** (EI): *m/z* calcd for $C_{11}H_{11}N_2O_2{}^{35}Cl$ $[M-SC_3H_6]^{\cdot+}$ 238.0504, found 238.0509.

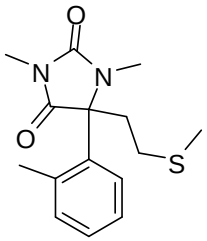
Synthesis of 5vMet:



5-(3-Chlorophenyl)-1,3-dimethyl-5-[2-(methylsulfanyl)ethyl] imidazolidin-2,4-dione (5v)

Following general procedure **11**, LiCl (28 mg, 0.65 mmol) and THF (1.70 mL) were added to urea acid **6v** (68 mg, 0.21 mmol). LDA was prepared with DiPA (0.09 mL, 0.65 mmol), THF (0.40 mL) and *n*BuLi (0.26 mL, 0.65 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (41 mg, 0.13 mmol, 64%). **5v: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.29-7.22 (2H, m, Ar*H*), 7.13 (1H, br. s, Ar*H*), 7.11-7.02 (1H, m, Ar*H*), 2.97 (3H, s, NCH_3), 2.82-2.67 (1H, m, $CH_2CH_AH_BS$), 2.77 (3H, s, NCH_3), 2.36-2.08 (3H, m, CH_2CH_2 and $CH_2CH_AH_BS$), 2.05 (3H, s, SCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.2 (*C*=O), 156.7 (*C*=O), 138.1 (Ar*C*), 135.5 (Ar*C*), 130.7 (Ar), 129.3 (Ar), 126.4 (Ar), 124.2 (Ar), 69.6 (N*C*C=O), 34.5 (CH_2), 28.1 (CH_2), 25.9 (NCH_3), 25.5 (NCH_3), 15.9 (SCH_3); **IR (film, cm^{-1})**: ν_{max} = 2917 (C-H), 1770 (C=O amide), 1707 (C=O urea). **HRMS** (EI): *m/z* calcd for $C_{11}H_{11}N_2O_2{}^{35}Cl$ [M-SC_3H_6]$^{\cdot+}$ 238.0504, found 238.0502.

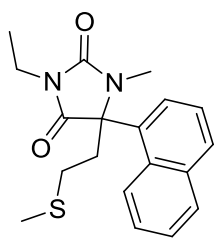
Synthesis of 5wMet:



1,3-Dimethyl-5-(2-methylphenyl)-5-[2-(methylsulfanyl)ethyl] imidazolidin-2,4-dione (5w)

Following general procedure **11**, LiCl (44 mg, 1.03 mmol) and THF (2.70 mL) were added to urea acid **6w** (100 mg, 0.32 mmol). LDA was prepared with DiPA (0.15 mL, 1.03 mmol), THF (0.50 mL) and *n*BuLi (0.41 mL, 1.03 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow. Purification by flash column chromatography (SiO_2, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (50 mg, 0.17 mmol, 53%). **5w: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.52-7.38 (1H, m, Ar*H*), 7.29-7.24 (2H, m, Ar*H*), 7.20-7.08 (1H, m, Ar*H*), 3.10 (3H, s, NCH_3), 2.81-2.66 (1H, m, $CH_2CH_AH_BS$), 2.62 (3H, s, NCH_3), 2.57-2.21 (3H, m, CH_2CH_2 and $CH_2CH_AH_BS$), 2.14 (3H, s, ArCH_3), 2.05 (3H, s, SCH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.2 (*C*=O), 156.4 (*C*=O), 137.1 (Ar*C*), 133.1 (Ar), 132.9 (Ar*C*), 129.4 (Ar), 128.1 (Ar), 126.7 (Ar), 69.1 (N*C*C=O), 34.2 (CH_2), 27.7 (CH_2), 25.1 (NCH_3), 24.9 (NCH_3), 19.9 (ArCH_3), 16.0 (SCH_3); **IR (film, cm^{-1})**: ν_{max} = 2933, 2916 (C-H), 1767 (C=O amide), 1704 (C=O urea). **HRMS** (EI): *m/z* calcd for $C_{12}H_{14}N_2O_2$ [M-SC_3H_6]$^{\cdot+}$ 218.1050, found 218.1049.

Synthesis of 5xMet:

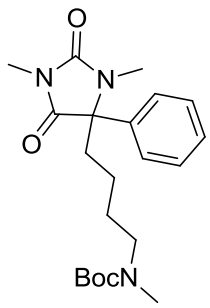


3-Ethyl-1-methyl-5-[2-(methylsulfanyl)ethyl]-5-(naphthalen-1-yl) imidazolidin-2,4-dione (5x)

Following general procedure **11**, LiCl (39 mg, 0.91 mmol) and THF (1.80 mL) were added to urea acid **6x** (103 mg, 0.28 mmol). LDA was prepared with

DiPA (0.12 mL, 0.91 mmol), THF (1.00 mL) and *n*BuLi (0.37 mL, 0.91 mmol, 2.5 M in hexanes). The title compound was yielded as a pale yellow oil without further purification (95 mg, 0.28 mmol, >99%). **5x: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.95-7.79 (2H, m, Napht*H*), 7.77-7.66 (1H, m, Napht*H*), 7.59-7.35 (4H, m, Napht*H*), 3.79 (2H, q, *J* = 7.2, NCH_2CH$_3$), 2.89 (1H, ddd, *J* = 13.3, 9.3, 7.4, CH_AH$_B$S), 2.71-2.54 (1H, m, CH$_A$$H_B$S), 2.63 (3H, s, NC$H_3$), 2.48-2.36 (2H, m, CHC$H_2CH_2$), 2.18 (3H, s, SC$H_3$), 1.37 (3H, t, *J* = 7.2, CH$_2$CH_3) ; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.0 (*C*=O), 156.2 (*C*=O), 134.7 (Napht*C*), 131.4 (Napht*C*), 131.1 (Napht), 130.1 (Napht*C*), 129.9 (Napht), 127.6 (Napht), 127.4 (Napht), 126.1 (Napht), 125.0 (Napht), 122.4 (Napht), 69.2 (N*C*C=O), 35.3 (*C*H$_2$), 34.4 (*C*H$_2$), 27.8 (*C*H$_2$), 25.4 (N*C*H$_3$), 16.1 (S*C*H$_3$), 13.5 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2973, 2918 (C-H), 1765 (C=O amide), 1706 (C=O urea). **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{22}N_2O_2SNa$ $[M+Na]^+$ 365.1294; found 365.1287.

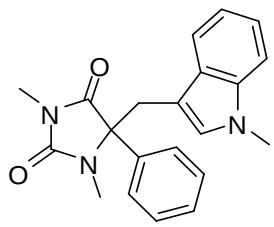
Synthesis of 5yLys:



***tert*-Butyl N-[4-(1,3-dimethyl-2,5-dioxo-4-phenylimidazolidin-4-yl)butyl]-N-methylcarbamate (5y)**

Following general procedure **11**, LiCl (16 mg, 0.37 mmol) and THF (1.00 mL) were added to urea acid **6y** (50 mg, 0.12 mmol). LDA was prepared with DiPA (0.52 mL, 0.37 mmol), THF (0.22 mL) and *n*BuLi (0.15 mL, 0.37 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 1:2 Hexane:EtOAc) yielded the title compound as an oil (39 mg, 0.10 mmol, 83%). **5y: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.34-7.25 (3H, m, Ph*H*), 7.22-7.19 (2H, m, Ph*H*), 3.31-3.10 (3H, m, CH_AH$_B$ and CH_2), 2.97 (3H, s, NCH_3), 2.75 (6H, s, 2xNCH_3), 2.45 (1H, m, CH$_A$$H_B$), 1.57-1.46 (2H, m, C$H_2$), 1.37 (s, 9H, C(C$H_3$)$_3$), 1.22-1.02 (2H, m, C$H_2$); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$): δ_C = 174.3 (*C*=O), 156.7 (*C*=O), 155.7 (*C*=O), 136.2 (Ar*C*), 129.1 (2xAr), 128.7 (Ar), 125.9 (2xAr), 79.3 (O*C*(CH$_3$)$_3$), 70.2 (N*C*C=O), 34.0 (N*C*H$_2$), 31.5 (*C*H$_2$), 28.4 (OC(*C*H$_3$)$_3$), 25.5 (2xN*C*H$_3$), 25.0 (N*C*H$_3$), 22.6 (*C*H$_2$), 14.1 (*C*H$_2$); **IR (film, cm^{-1})**: ν_{max} = 2929 (C-H), 1710 (C=O amide), 1690 (C=O urea). **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{31}N_3O_4Na$ $[M+H]^+$ 412.2201, found 412.2207.

Synthesis of 5zTrp:

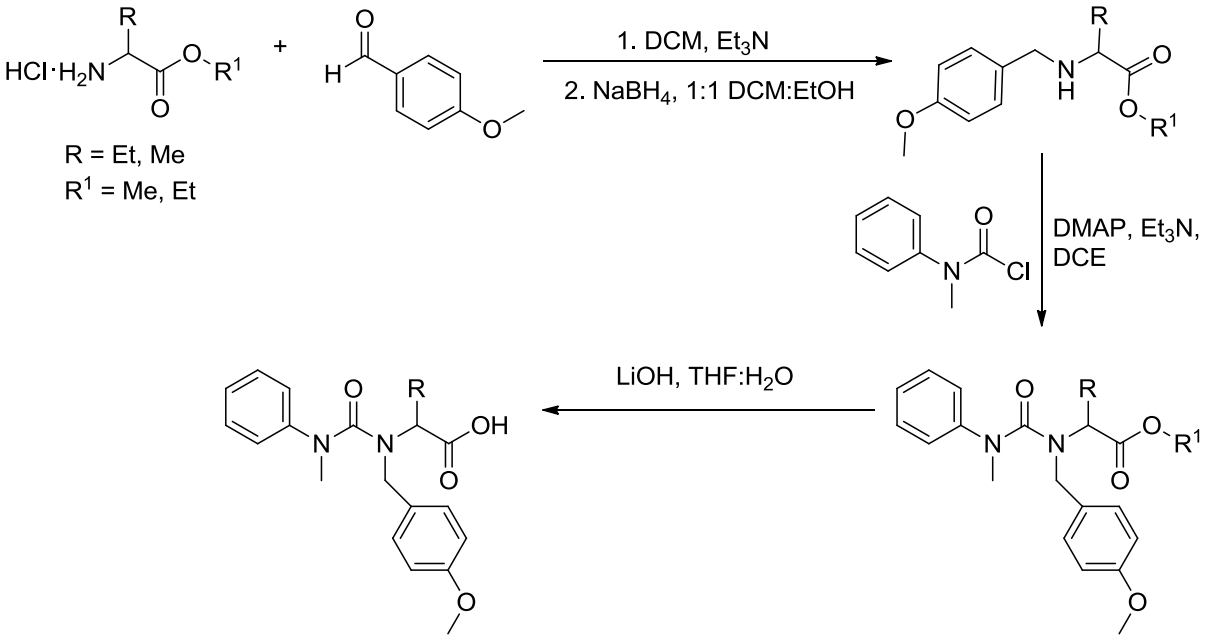


1,3-Dimethyl-5-[(1-methyl-1H-indol-3-yl)methyl]-5-phenylimidazolidin-2,4-dione (5z)

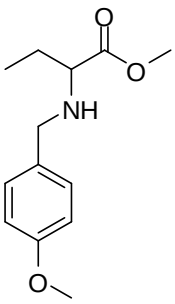
Following general procedure **11**, LiCl (16 mg, 0.37 mmol) and THF (1.00 mL) were added to urea acid **6z** (45 mg, 0.12 mmol). LDA was prepared with DiPA (0.52 mL, 0.37 mmol), THF (0.24 mL) and *n*BuLi (0.15 mL, 0.37 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 1:2 Hexane:EtOAc) yielded the title compound as an oil (22 mg, 0.06 mmol, 52%) and starting material (7 mg, 0.02 mmol, 15%). **5z: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.51 (1H, d, *J* = 7.9, Ar*H*), 7.39-7.30 (5H, m, Ar*H*),

7.21-7.10 (2H, m, Ar*H*), 7.05-7.00 (1H, m, Ar*H*), 6.74 (1H, s, Ar), 4.01 (1H, d, *J* = 14.8, C*H*), 3.65 (3H, s, NC*H*$_3$), 3.37 (1H, d, *J* = 14.8, C*H*), 2.81 (3H, s, NC*H*$_3$), 2.68 (3H, s, NC*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.7 (*C*=O), 156.8 (*C*=O), 136.6 (Ar*C*), 136.3 (Ar*C*), 129.2 (2xAr), 128.8 (Ar*C*), 127.8 (Ar), 127.6 (Ar*C*), 126.4 (2xAr), 121.8 (Ar), 119.2 (Ar), 118.8 (Ar), 109.3 (Ar), 106.3 (Ar), 71.1 (N*C*C=O), 32.8 (*C*H$_2$), 28.7 (N*C*H$_3$), 26.2 (N*C*H$_3$), 24.8 (N*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2924 (C-H), 1767 (C=O amide), 1703 (C=O urea). **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{22}N_3O_2$ $[M+H]^+$ 348.1708, found 348.1707.

Synthesis of PMB protected Urea Acids:



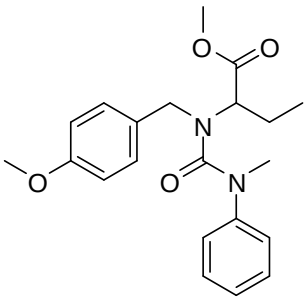
Synthesis of 14a:



Methyl-2-{[(4-methoxyphenyl)methyl]amino}butanoate (S4a)

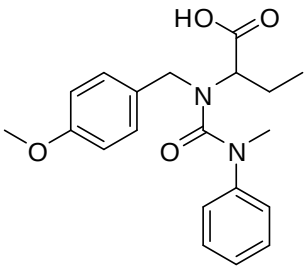
To a solution of methyl-DL-α-aminobutyrate hydrochloride (10.00 g, 65.10 mmol, 1.2 eq) and molecular sieves (3 Å), in anhydrous DCM (108.50 mL, 0.5 M), was added Et_3N (13.60 mL, 97.65 mmol, 1.8 eq). The reaction mixture was stirred for ten minutes before *p*-anisaldehyde (6.60 mL, 54.25 mmol, 1.0 eq) was added. The reaction was stirred for eighteen hours at room temperature. The mixture was filtered and concentrated *in vacuo*. The crude residue was dissolved in 1:1 DCM:EtOH (108.00 mL), cooled to 0 °C and $NaBH_4$ (3.27 g, 86.40 mmol, 1.6 eq) was added. The reaction was warmed to room temperature and stirred for eighteen hours. The reaction mixture was cooled to 0 °C, a solution of conc. HCl was added, then a solution of NaOH (5.0 M) to pH = 12. The aqueous layer was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1 Pet. Ether:EtOAc + 1% Et_3N) yielded the title compound as an oil (13.60 g, 48.88 mmol, 91%). **S4a: ^{1}H NMR** (300 MHz,

$CDCl_3$): δ_H = 7.25 (2H, d, *J* = 8.6, Ar*H*), 6.86 (2H, *J* = 8.6, Ar*H*), 3.79 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.67 (2H, AB pattern, *J* = 12.6, Δυ = 48.8, CH_2NH), 3.22 (1H, t, *J* = 7.4, C*H*CH_2), 1.84 (1H, br. s, N*H*CH), 1.76-1.56 (2H, m, CHCH_2CH_3), 0.92 (3H, t, *J* = 7.1, CH_2CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 176.0 (*C*=O), 158.9 (Ar*C*OMe), 132.1 (Ar*C*), 129.6 (2xAr), 113.9 (2xAr), 62.0 (N*C*H), 55.4 (O*C*H_3), 51.7 (O*C*H_3), 51.6 (N*C*H_2), 26.7 (*C*H_2), 10.3 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 3330 (NH), 2952 (C-H), 1732 (C=O ester), 1245 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$ 260.1257, found 260.1249.



Methyl-2-{[(4-methoxyphenyl)methyl][methyl(phenyl)carbamoyl] amino}butanoate (S5a)

Following general procedure **6a**, *N*-methyl-*N*-phenylcarbamoyl chloride (6.88 g, 40.56 mmol) and DMAP (catalytic amount) were added to a pre-stirred solution of **S4a** (10.30 g, 43.40 mmol) and Et_3N (7.35 mL, 52.74 mmol) in DCE (101.00 mL). The reaction was complete after twenty hours. Purification by flash column chromatography (SiO_2, 2:1 Pet. Ether:EtOAc) yielded the title compound as an oil (4.13 g, 11.16 mmol, 28%). **S5a: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.36-7.27 (2H, m, Ph*H*), 7.19-7.11 (1H, m, Ph*H*), 7.10-7.00 (4H, m, Ph*H* + Ar*H*), 6.84-6.76 (2H, m, Ar*H*), 4.12 (2H, AB pattern, *J* = 15.1, Δυ = 35.9, CH_2N), 4.10 (1H, t, *J* = 7.1, C*H*CH_2), 3.79 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.13 (3H, s, NCH_3), 1.90 (1H, dquin., *J* = 14.5, 7.4, CHCH_2CH_3), 1.60 (1H, dq, *J* = 14.9, 7.5, CHCH_2CH_3), 0.77 (3H, t, *J* = 7.4, CH_2CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 172.5 (*C*=O), 162.4 (*C*=O), 158.8 (Ar*C*OMe), 146.3 (Ar*C*N), 130.2 (Ar*C*), 129.6 (2xAr), 129.5 (2xAr), 125.1 (Ar), 125.1 (2xAr), 113.6 (2xAr), 61.8 (N*C*H), 55.4 (O*C*H_3), 51.9 (O*C*H_3), 49.5 (N*C*H_2), 40.0 (N*C*H_3), 23.5 (*C*H_2), 11.4 (*C*H_3); **IR (film, cm^{-1})**: ν_{max} = 2951 (C-H), 1739 (C=O ester), 1651 (C=O urea), 1245 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{26}N_2O_4Na$ $[M+Na]^+$ 393.1785, found 393.1782.

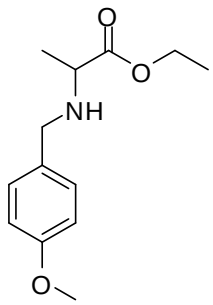


2-{[(4-Methoxyphenyl)methyl][methyl(phenyl)carbamoyl]amino} butanoic acid (14a)

Following general procedure **10**, urea **S5a** (3.10 g, 8.37 mmol) was dissolved in 2:1 THF:H_2O (285.00 mL) and LiOH (10.02 g, 418.38 mmol) was added. The resulting mixture was stirred for twenty hours at 45 °C. The title compound was yielded as a yellow oil without further purification (2.93 g, 8.22 mmol, 98%). **14a: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.01 (1H, br. s, COO*H*), 7.45-7.33 (2H, m, Ph*H*), 7.28-7.19 (1H, m, Ph*H*), 7.15-7.06 (2H, m, Ph*H*), 6.91-6.83 (2H, m, Ar*H*), 6.80-6.72 (2H, m, Ar*H*), 3.90 (2H, AB pattern, *J* = 15.4, Δυ = 57.1, CH_2N), 3.89-3.80 (1H, m, C*H*CH_2), 3.76 (3H, s, OCH_3), 3.25 (3H, s, NCH_3), 2.10 (1H, dquin., *J* = 15.0, 7.5, CHCH_2CH_3), 1.79 (1H, dquin., *J* = 14.9, 7.4, CHCH_2CH_3), 0.94 (3H, t, *J* = 7.4, CH_2CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 173.0 (*C*=O), 164.3 (*C*=O), 159.3 (Ar*C*OMe), 144.7 (Ar*C*N), 129.9 (2xAr), 129.2 (2xAr), 128.0 (Ar*C*), 126.4 (Ar), 125.1 (2xAr), 114.0 (2xAr), 64.2 (N*C*H), 55.3 (O*C*H_3), 52.0 (N*C*H_2),

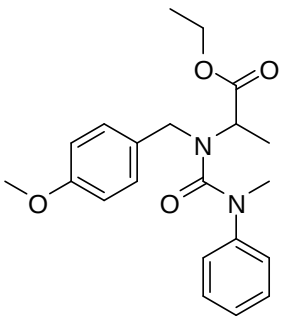
40.1 (N*C*H$_3$), 22.3 (*C*H$_2$), 11.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2967, 2935 (C-H), 2549 (OH broad), 1733 (C=O acid), 1650 (C=O urea), 1245 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{24}N_2O_4Na$ $[M+Na]^+$ 379.1628, found 379.1628.

Synthesis of 14b:



Ethyl-2-{[(4-methoxyphenyl)methyl]amino}propanoate (S4b)

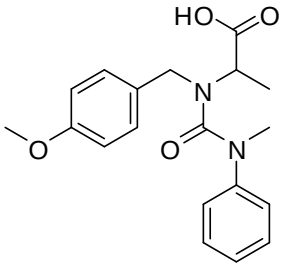
To a solution of L-alanine ethyl ester hydrochloride (9.39 g, 61.14 mmol, 1.2 eq) and molecular sieves (3 Å), in anhydrous DCM (101.90 mL, 0.5 M), was added Et$_3$N (12.78 mL, 91.72 mmol, 1.8 eq). The reaction mixture was stirred for ten minutes before *p*-anisaldehyde (6.20 mL, 50.95 mmol, 1.0 eq) was added. The reaction was stirred for eighteen hours at room temperature. The mixture was filtered and the organic layer was concentrated *in vacuo*. The crude residue was dissolved in 1:1 DCM:EtOH (102.00 mL), cooled to 0 °C and $NaBH_4$ (3.08 g, 81.52 mmol, 1.6 eq) was added. The reaction was warmed to room temperature and stirred for eighteen hours. The reaction mixture was cooled to 0 °C, a solution of conc. HCl was added, then a solution of NaOH (5.0 M) to pH = 12. The aqueous layer was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1 Pet. Ether:EtOAc + 1% Et$_3$N) yielded the title compound as an oil (10.50 g, 44.25 mmol, 87%). **S4b: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.30-7.19 (2H, m, Ar*H*), 6.90-6.81 (2H, m, Ar*H*), 4.19 (2H, q, *J* = 7.1, C*H*$_2$CH$_3$), 3.79 (3H, s, OC*H*$_3$), 3.68 (2H, AB pattern, *J* = 12.4, Δυ = 34.2, C*H*$_2$NH), 3.35 (1H, q, *J* = 7.0, C*H*CH$_3$), 2.16 (1H, br. s, N*H*CH), 1.32 (3H, d, *J* = 7.0, CHC*H*$_3$), 1.29 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 175.7 (*C*=O), 159.0 (Ar*C*OMe), 131.7 (Ar*C*), 129.7 (2xAr), 114.0 (2xAr), 60.9 (O*C*H$_2$), 55.9 (N*C*H), 55.4 (O*C*H$_3$), 51.4 (N*C*H$_2$), 19.1 (*C*H$_3$), 14.4 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3327 (NH), 2978, 2935, 2906 (C-H), 1728 (C=O ester), 1245 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{20}NO_3$ $[M+H]^+$ 238.1438, found 238.1442.



Ethyl-2-{[(4-methoxyphenyl)methyl][methyl(phenyl)carbamoyl]amino} propanoate (S5b)

Following general procedure **6a**, *N*-methyl-*N*-phenyl carbamoyl chloride (7.00 g, 41.40 mmol, 1.0 eq) and DMAP (catalytic amount) were added to a pre-stirred solution of **S4b** (10.50 g, 44.25 mmol, 1.1 eq) and Et$_3$N (8.00 mL, 57.50 mmol, 1.4 eq) in DCE (103.80 mL). The reaction was complete after twenty hours. The title compound was yielded as a yellow oil without further purification (9.40 g, 25.37 mmol, 57%). **S5b: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 7.35-7.24 (2H, m, Ph*H*), 7.16-7.06 (3H, m, Ph*H*), 7.00-6.92 (2H, m, Ar*H*), 6.82-6.73 (2H, m, Ar*H*), 4.24 (1H, q, *J* = 7.0, C*H*CH$_3$), 4.14 (2H, dq, *J* = 0.9, 7.1, C*H*$_2$CH$_3$), 4.08 (2H, AB pattern, *J* = 15.7, Δυ = 81.2, C*H*$_2$N), 3.76 (3H, s, OC*H*$_3$), 3.11 (3H, s, NC*H*$_3$), 1.32 (3H, d, *J* = 6.9, CHC*H*$_3$), 1.27 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 172.4 (*C*=O), 161.8 (*C*=O), 158.7 (Ar*C*OMe),

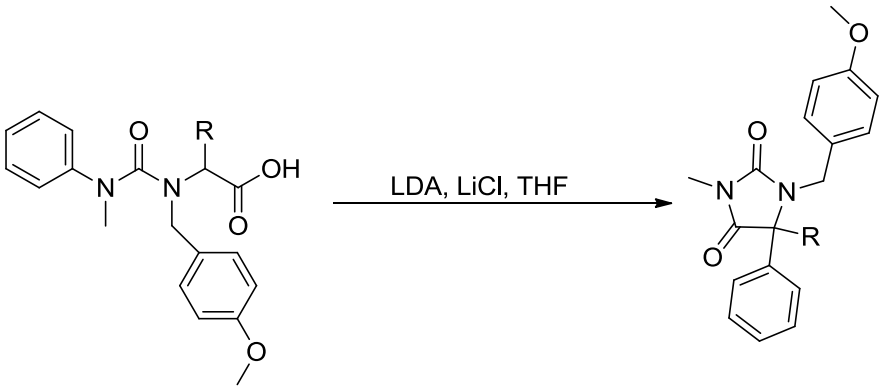
146.1 (Ar*C*N), 130.0 (Ar*C*), 129.4 (2xAr), 128.7 (2xAr), 125.1 (Ar), 124.6 (2xAr), 113.6 (2xAr), 61.0 (O*C*H$_2$), 55.9 (N*C*H), 55.2 (O*C*H$_3$), 50.1 (N*C*H$_2$), 39.8 (N*C*H$_3$), 15.1 (*C*H$_3$), 14.3 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2938 (C-H), 1736 (C=O ester), 1650 (C=O urea), 1244 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{26}N_2O_4Na$ [M+Na]$^+$ 393.1785, found 393.1792.



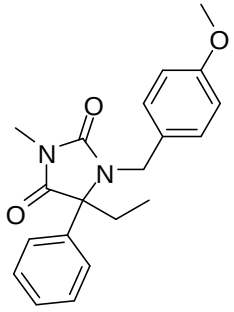
2-{[(4-Methoxyphenyl)methyl][methyl(phenyl)carbamoyl]amino} propanoic acid (14b)

Following general procedure **10**, urea **S5b** (9.40 g, 25.37 mmol) was dissolved in 2:1 THF:H$_2$O (0.85 L) and LiOH (30.40 g, 1.27 mol) was added. The resulting mixture was stirred for twenty hours at 45 °C. The title compound was yielded as an oil without further purification (8.35 g, 24.39 mmol, 98%). **14b: ^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 10.60 (1H, br. s, COO*H*), 7.42-7.31 (2H, m, Ph*H*), 7.24-7.09 (3H, m, Ph*H*), 6.99-6.85 (2H, m, Ar*H*), 6.82-6.73 (2H, m, Ar*H*), 4.07 (1H, q, *J* = 7.1, C*H*CH$_3$), 3.98 (2H, AB pattern, *J* = 15.5, Δυ = 100.2, C*H*$_2$N), 3.76 (3H, s, OC*H*$_3$), 3.23 (3H, s, NC*H*$_3$), 1.44 (3H, d, *J* = 7.2, CHC*H*$_3$); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$): δ_C = 175.0 (*C*=O), 163.3 (*C*=O), 159.0 (Ar*C*OMe), 145.3 (Ar*C*N), 129.7 (2xAr), 129.0 (2xAr), 128.7 (Ar*C*), 125.8 (Ar), 124.8 (2xAr), 113.9 (2xAr), 57.4 (N*C*H), 55.3 (O*C*H$_3$), 51.5 (N*C*H$_2$), 39.8 (N*C*H$_3$), 14.9 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2907 (OH broad), 2937 (C-H), 1721 (C=O acid), 1651 (C=O urea), 1246 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{22}N_2O_4Na$ [M+Na]$^+$ 365.1472, found 365.1479.

Synthesis of PMB protected hydantoins:



Synthesis of 15a:

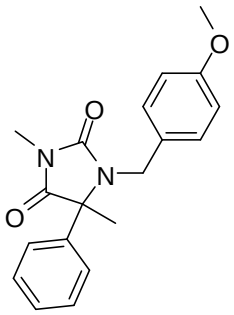


5-Ethyl-1-[(4-methoxyphenyl)methyl]-3-methyl-5-phenylimidazolidine-2,4-dione (15a)

Following general procedure **11**, LiCl (84 mg, 1.97 mmol) and THF (6.00 mL) were added to urea acid **14a** (234 mg, 0.66 mmol). LDA was prepared with DiPA (0.28 mL, 1.97 mmol), THF (0.60 mL) and *n*BuLi (0.79 mL, 1.97 mmol, 2.5 M in hexanes). Purification by flash column chromatography (SiO_2, 2:1

Pet.Ether:EtOAc) yielded the title compound as an oil (107 mg, 0.32 mmol, 48%). **15a: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.41-6.96 (7H, m, Ph*H* + Ar*H*), 6.78-6.63 (2H, m, Ar*H*), 4.22 (2H, AB pattern, *J* = 15.4, Δυ = 333.6, CH_2N), 3.72 (3H, s, OCH_3), 3.07 (3H, s, NCH_3), 2.45-2.28 (1H, m, CH_2CH$_3$), 1.95-1.76 (1H, m, CH_2CH$_3$), 0.51 (3H, t, *J* = 15.4, CH$_2$CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.6 (*C*=O), 159.3 (Ar*C*OMe), 157.6 (*C*=O), 136.6 (Ar*C*), 130.5 (2xAr), 129.3 (Ar*C*), 129.2 (2xAr), 128.9 (Ar), 126.7 (2xAr), 113.9 (2xAr), 72.1 (N*C*C=O), 55.4 (O*C*H$_3$), 44.1 (N*C*H$_2$), 25.8 (*C*H$_2$), 25.1 (N*C*H$_3$), 7.5 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2969, 2936 (C-H), 1767 (C=O amide), 1704 (C=O urea), 1245 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{22}N_2O_3Na$ [M+Na]$^+$ 361.1523, found 361.1520.

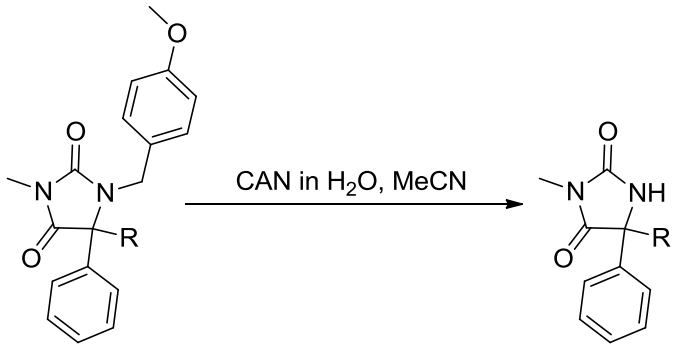
Synthesis of 15b:



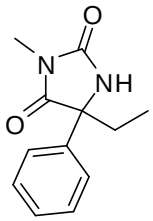
1-[(4-Methoxyphenyl)methyl]-3,5-dimethyl-5-phenylimidazolidine-2,4-dione (15b)

Following general procedure **11**, LiCl (18 mg, 0.43 mmol) and THF (1.00 mL) were added to urea acid **14b** (49 mg, 0.14 mmol). LDA was prepared with DiPA (0.06 mL, 0.43 mmol), THF (0.40 mL) and *n*BuLi (0.25 mL, 0.43 mmol, 1.75 M in hexanes). Purification by flash column chromatography (SiO_2, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (32 mg, 0.10 mmol, 69%). **15b: R$_f$** (1:1 Pet.Ether:EtOAc) 0.49; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.34-7.06 (5H, m, Ph*H*), 7.02-7.00 (2H, m, Ar*H*), 6.69-6.66 (2H, m, Ar*H*), 4.23 (2H, AB pattern, *J* = 15.4, Δυ = 333.6, CH_2N), 3.67 (3H, s, OCH_3), 3.01 (3H, s, NCH_3), 1.47 (3H, s, CH_3C); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 175.3 (*C*=O), 159.2 (Ar*C*OMe), 156.9 (*C*=O), 136.6 (Ar*C*), 129.8 (2xAr), 129.7 (Ar*C*), 129.3 (2xAr), 128.9 (Ar), 126.4 (2xAr), 114.0 (2xAr), 67.7 (N*C*C=O), 55.4 (O*C*H$_3$), 43.9 (N*C*H$_2$), 25.4 (N*C*H$_3$), 21.6 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 2983 (C-H), 1769 (C=O amide), 1705 (C=O urea), 1245 (C-O ether); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{20}N_2O_3Na$ [M+Na]$^+$ 347.1366, found 347.1354.

Synthesis of deprotected hydantoins:



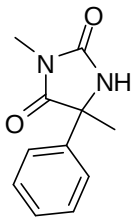
Synthesis of 16a:



5-Ethyl-3-methyl-5-phenylimidazolidine-2,4-dione (16a)[5]

To a solution of hydantoin **15a** (35 mg, 0.10 mmol, 1.0 eq) in acetonitrile (1.03 mL, 0.1 M) at 0 °C, a solution of CAN (Ceric Ammonium Nitrate) (226 mg, 0.41 mmol, 4.0 eq) in water (0.52 mL, 0.8 M) was added dropwise. The reaction mixture was stirred for one hour at 0 °C. The solution was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc) yielded the title compound as an oil (21 mg, 0.09 mmol, 96%). **16a: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.60-7.51 (2H, m, Ph*H*), 7.44-7.28 (3H, m, Ph*H*), 6.80 (1H, br. s, N*H*), 3.01 (3H, s, NCH_3), 2.24 (1H, dq, *J* = 14.5, 7.3, CH_2CH$_3$), 2.12 (1H, dq, *J* = 14.5, 7.4, CH_2CH$_3$), 0.90 (3H, t, *J* = 7.4, CH$_2$CH_3); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 174.9 (*C*=O), 157.5 (*C*=O), 137.8 (Ar*C*), 128.8 (2xAr), 128.4 (Ar), 125.4 (2xAr), 67.9 (N*C*C=O), 32.1 (*C*H$_2$), 24.7 (N*C*H$_3$), 8.1 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3288 (NH), 2970 (C-H), 1775 (C=O amide), 1706 (C=O urea).

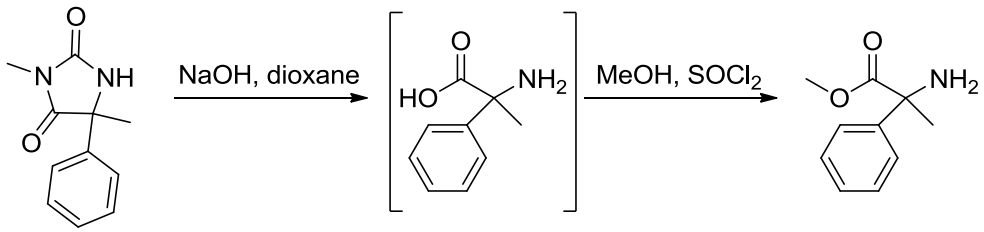
Synthesis of 16b:



3,5-Dimethyl-5-phenylimidazolidine-2,4-dione (16b)[6]

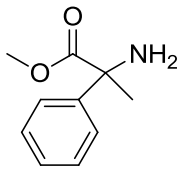
To a solution of hydantoin **15b** (47 mg, 0.15 mmol, 1.0 eq) in acetonitrile (1.45 mL, 0.1 M) at 0 °C, a solution of CAN (318 mg, 0.58 mmol, 4.0 eq) in water (0.72 mL, 0.8 M) was added dropwise. The reaction mixture was stirred for one hour at 0 °C. The solution was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1 Pet.Ether:EtOAc + 1% Et_3N) yielded the title compound as a solid (25 mg, 0.12 mmol, 84%). **16b: mp**: 136-138 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.56-7.47 (2H, m, Ph*H*), 7.44-7.30 (3H, m, Ph*H*), 6.23 (1H, br. s, N*H*), 3.03 (3H, s, NCH_3), 1.84 (3H, s, CH_3C); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 175.4 (*C*=O), 157.0 (*C*=O), 138.7 (Ar*C*), 129.1 (2xAr), 128.7 (Ar), 125.3 (2xAr), 63.9 (N*C*C=O), 25.8 (*C*H$_3$), 25.0 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3291 (NH), 2981 (C-H), 1780 (C=O amide), 1710 (C=O urea).

Synthesis of amino ester:



[5]M. D. Rosa and A. J. Freyer, *J. Heterocyclic Chem.*, 1995, **32**, 1661.
[6]M. E. Koscho and W. H. Pirkle, *Tetrahedron: Asymmetry*, 2005, **16**, 3345.

Synthesis of 18:



Methyl 2-amino-2-phenylpropanoate (18)

To hydantoin **16b** (392 mg, 1.92 mmol, 1.0 eq) in water (8.00 mL, 0.2 M) was added aqueous NaOH (8.00 mL, 2.0 M) and dioxane (1.60 mL, 1.2 M). The resulting mixture was heated to reflux. After twenty four hours the reaction mixture was cooled to room temperature, diluted with water (10.00 mL), and acidified with conc. HCl. The mixture was concentrated *in vacuo*. The crude residue was dissolved in methanol (12.40 mL), cooled to 0 °C and thionyl chloride (0.56 mL, 7.68 mmol, 4.0 eq) was added dropwise. The reaction was heated to reflux for twenty hours. The reaction mixture was cooled to room temperature, the solution was filtered and concentrated *in vacuo*. The title compound was yielded as an oil without further purification (326 mg, 1.82 mmol, 95%). **18: ^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 9.43 (2H, br. s, N*H*$_2$), 7.80-7.13 (5H, m, Ph*H*), 3.75 (3H, s, OC*H*$_3$), 2.07 (3H, s, C*H*$_3$C); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$): δ_C = 170.3 (*C*=O), 135.7 (Ar*C*), 129.5 (Ar), 129.3 (2xAr), 126.0 (2xAr), 62.5 (N*C*C=O), 54.1 (O*C*H$_3$), 22.5 (*C*H$_3$); **IR (film, cm^{-1})**: ν_{max} = 3393 (NH), 2951 (C-H), 1746 (C=O ester). **HRMS** (EI): *m/z* calcd for $C_9H_{10}N_1O_2$ $[M\text{-}CH_3]^{\cdot+}$ 164.0706, found 164.0708.

Optimisation of the rearrangement of 6a

Preliminary optimisation work was carried out prior to the ReactIR studies to investigate the behaviour of *N*'-phenyl-*N,N'*-dimethylurea derivative of alanine **6a** upon treatment with base.

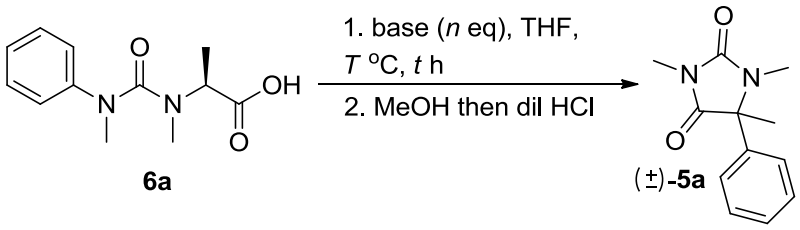


Table S1. Optimisation of the transformation of **6a** to **5a**

entry	base, *n* equiv	conditions (*T* °C, *t* h)	remaining **6a**; % racemisation[a]	**5a**, % yield
1	*sec*-BuLi, 3	–78 °C, 1 h	–[b]	0
2	LDA, 3	–78 °C, 1 h	15	18[c]
3	LDA, 3	–40 °C, 1 h	31	43[c]
4	LDA, 3	–15 °C, 1 h	62	86[c]
5	LDA, 3	0 °C, 2 h	9	83[c]
6	LDA, 3[d]	0 °C, 1 h	64	59[c]
7	LiTMP, 3	0 °C, 2 h	–[b]	50[c]
8	$LiNEt_2$, 3	0 °C, 2 h	–[b]	75[c]
9	LDA, 7	0 °C, 2 h	–[b]	90[c]
10	LDA, 3	–78-20 °C, 20 h	–[b]	96[c]
11	LDA, 3 + LiCl, 3[e]	–78-20 °C, 3 h	–[b]	98[c], 89[f]

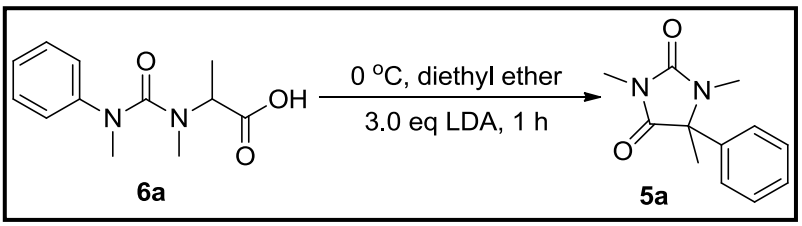
[a] 100- (100 x [ee of recovered **6a**] / [ee of starting **6a** (= ca. 60%)]); [b]not determined. [c]NMR yield. [d]Et_2O as solvent. [e]Similar result with 10 eq LiCl. [f]Isolated yield (0.5 g scale).

Treatment of **6a** with an excess of *sec*-BuLi at –78 °C led only to decomposition (entry 1), but encouragingly using LDA as the base generated some of the racemic hydantoin **5a** (entry 2), presumably by formation of the enolate dianion, aryl migration to the enolate, and cyclization. Although the yield was low (entry 2), lack of racemisation of the remaining starting material suggested that this was due to slow formation of the enolate. Raising the temperature increased both the yield of **5a** and the extent of starting material racemisation (entries 3, 4), indicating that both deprotonation and rearrangement were increasing in rate. At 0 °C, a drop in the extent of racemisation suggested that the yield, though good (83%), was again limited by incomplete deprotonation (entry 5). Using ether as solvent or other lithium amide bases (entries 6-8) gave no improvement, but adding a large excess of LDA (entry 9) or raising the temperature further to 20 °C (entry 10) increased the yield above 90%. Reasoning that coordination of reaction intermediates by Li^+ might facilitate rearrangement, LiCl was added to the reaction mixture resulting in almost quantitative conversion to **5a** (entry 11) which was isolated in 89% yield.

In situ ReactIR Data

In order to explore in more detail the mechanism of the intramolecular enolate arylation, the rearrangement of **6a** to **5a** was followed by *in situ* infra-red spectroscopy (ReactIR). The result in table S1, entry 6, suggested that in Et_2O at 0 °C both deprotonation by LDA and rearrangement would occur at rates slow enough to allow observation of any intermediates. Rearrangements of **6a** were carried out in diethyl ether and in THF and followed by ReactIR. The slower rate of reaction in diethyl ether allowed for a more detailed observation of reaction intermediates.

Reaction carried out in diethyl ether



Anhydrous diethyl ether (8.00 mL) was added to a 100 mL three-necked flask equipped with a stirrer bar and ReactIR probe under nitrogen. The solution was cooled to 0 °C using an ice bath, and left to stabilise, after which time an IR solvent background spectrum was taken. Urea acid **6a** (250 mg, 1.06 mmol, 1.0 eq) was added *via* one of the three necks, followed by anhydrous diethyl ether (6.00 mL) to wash the substrate into the flask and dissolve the urea acid **6a**. The reaction mixture was warmed to room temperature and left to stir for 30 min, whilst all the urea acid **6a** dissolved. The reaction mixture was a pale orange solution. In a separate flask LDA was prepared; anhydrous diethyl ether (4.00 mL) and DiPA (0.45 mL, 3.18 mmol, 3.0 eq) were cooled to 0 °C, *n*BuLi (1.38 mL, 3.18 mmol, 2.3 M in hexanes, 3.0 eq) was added dropwise and stirred for 30 min. The three-necked flask was cooled to 0 °C and an IR reactant background spectrum was taken. The LDA was added dropwise to the reaction mixture over 10 min and the reaction mixture became cloudy. The reaction mixture was left to stir for 1 h at 0 °C and was quenched by a dropwise addition of methanol. The reaction mixture was allowed to warm to room temperature and the ReactIR probe was removed. The reaction mixture was acidified with 1.0 M HCl and the product was extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. NMR analysis of the crude reaction mixture confirmed the presence of hydantoin **5a**, along with unreacted **6a** (1:3 **6a:5a**)

Throughout the experiment IR spectra were recorded continuously at varying time intervals. An IR spectrum was initially recorded every minute, with **6a** in diethyl ether at 0 °C. The frequency of recording IR spectra was increased to every 15 seconds during the LDA addition and for 10 minutes after the addition was complete. The frequency was then reduced to every 45 seconds for the remainder of the 1 h hold at 0 °C and finally the frequency was increased to every 15 seconds during

the methanol quench of the reaction. **Figures S1-S3** show the changes observed in the portion of the IR spectrum centred on the carbonyl absorptions during the course of the reaction.

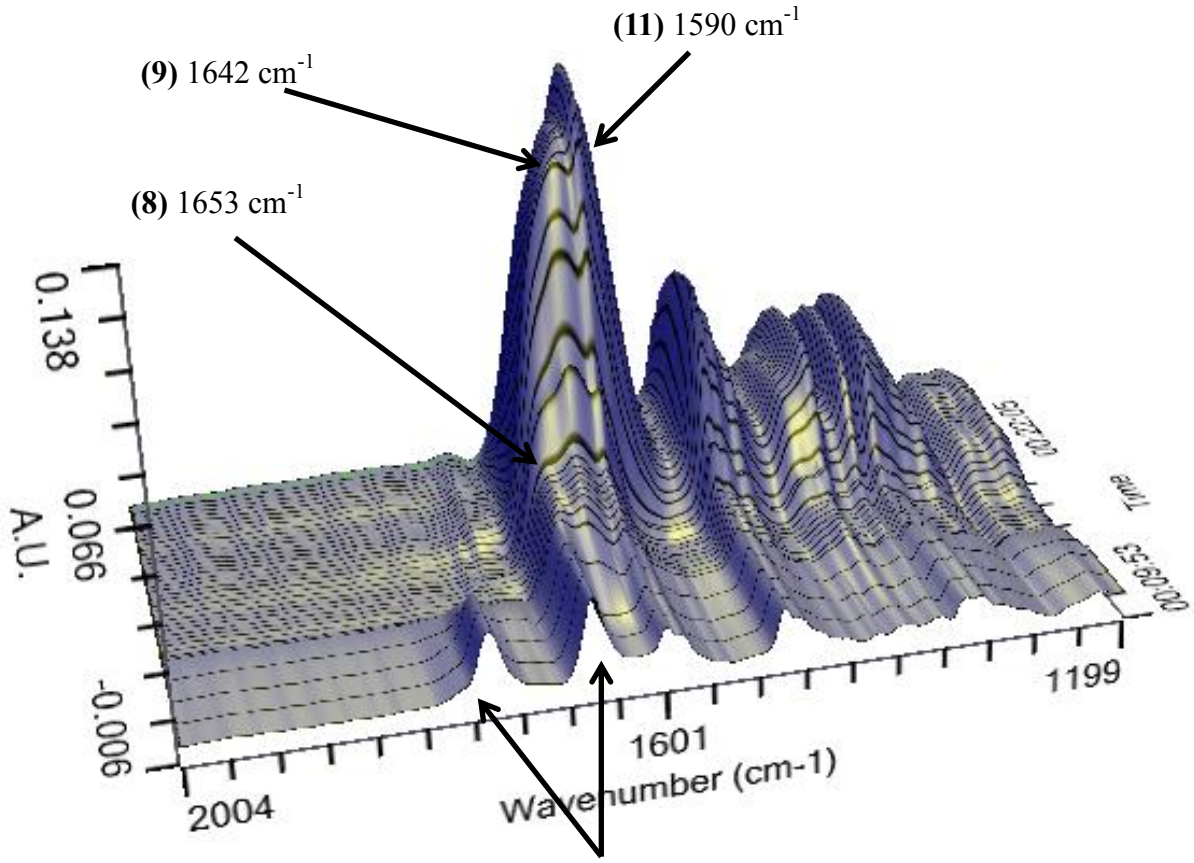


Figure S1: 3D-ReactIR trace for **6a** in diethyl ether at 0 °C during the addition of LDA over 10 min.

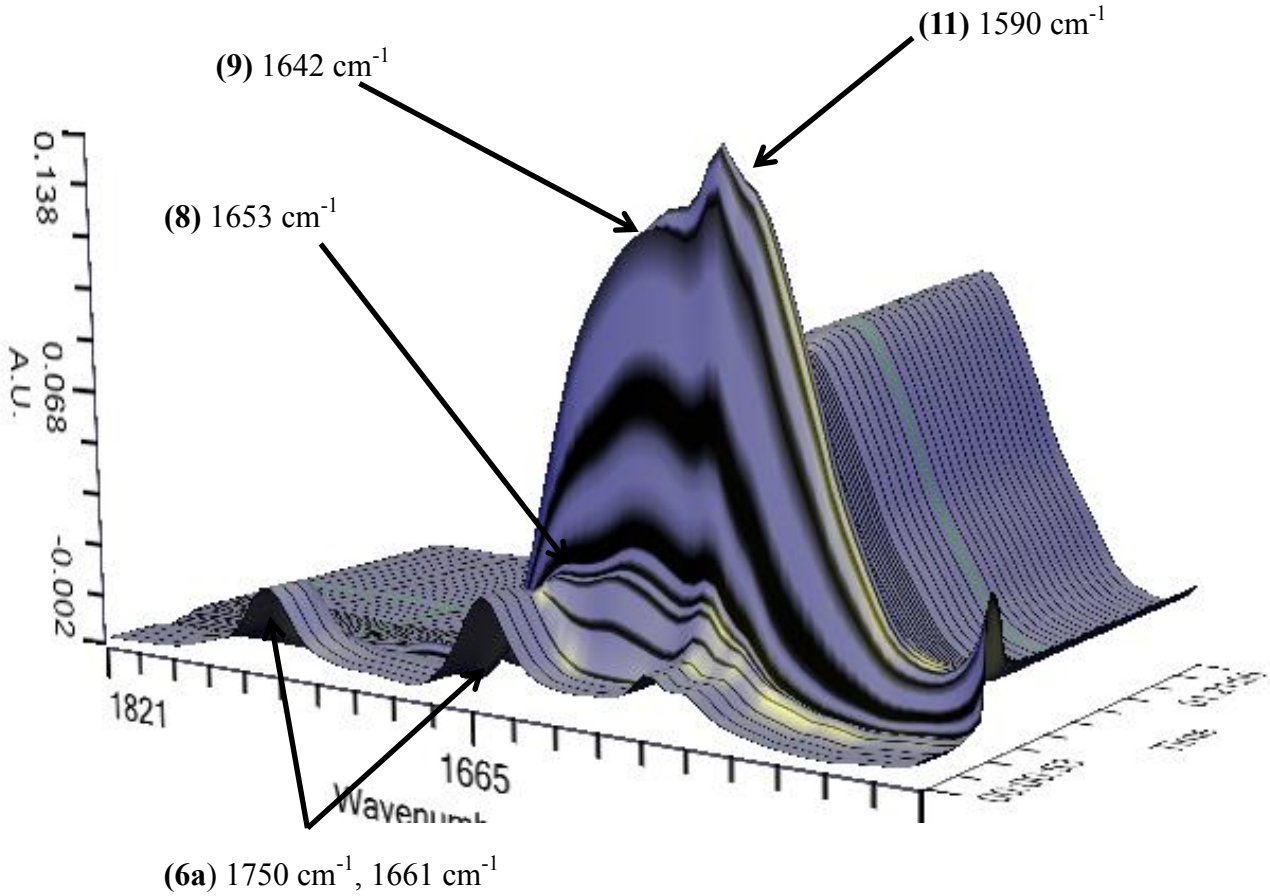


Figure S2: 3D-ReactIR trace for **6a** in diethyl ether at 0 °C during the addition of LDA over 10 min and through the 1 h reaction period at 0 °C.

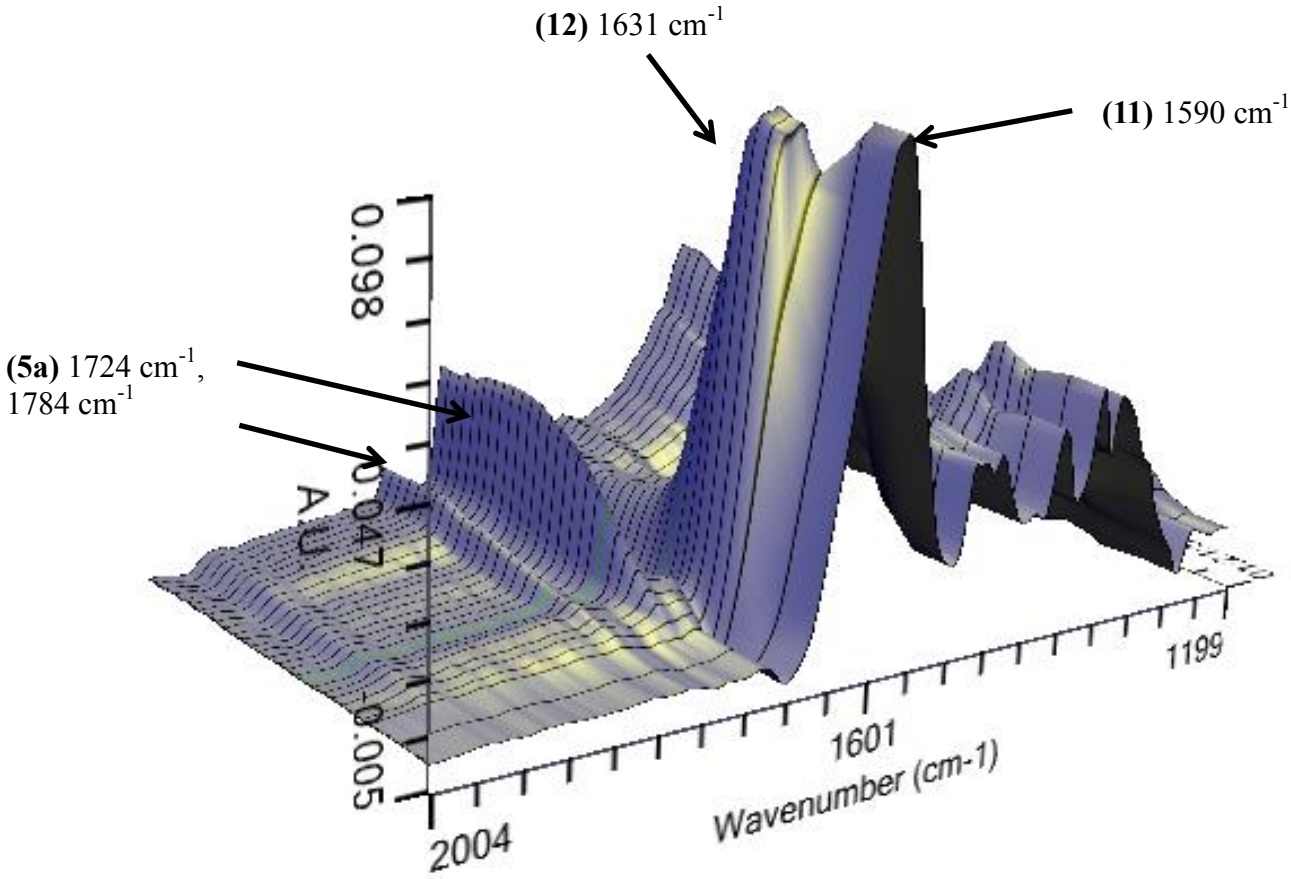


Figure S3: 3D-ReactIR trace from the end of the 1 h reaction period at 0 °C through the quench with methanol.

Using the IR data acquired over different time periods of the reaction, difference spectra allow successive reaction intermediates to be identified by shifts in the C=O stretching frequencies. The spectra shown in **Figure S4, S5, S6** and **S7** have the spectrum of **6a** subtracted. The spectra shown in **Figure S4** also have the spectrum of **11** (taken at the end of the 1 h reaction period) subtracted.

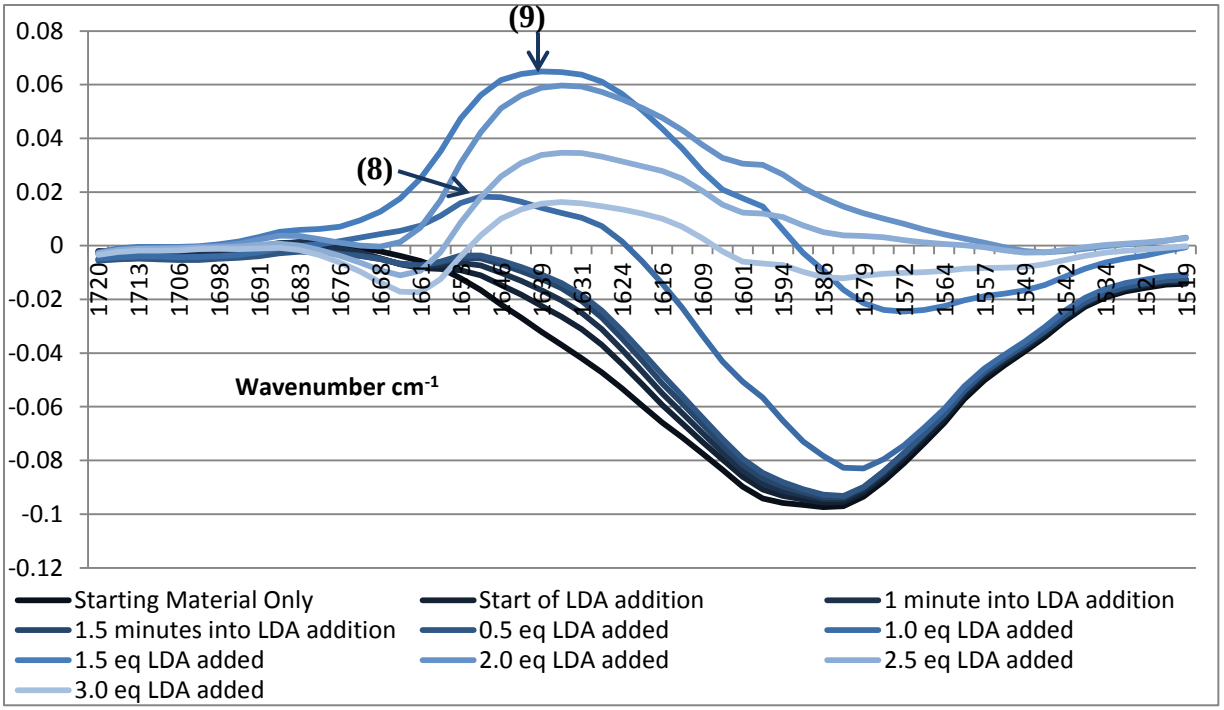


Figure S4: IR difference spectra for the period during the addition of 3.0 eq LDA over 10 min at 0 °C.

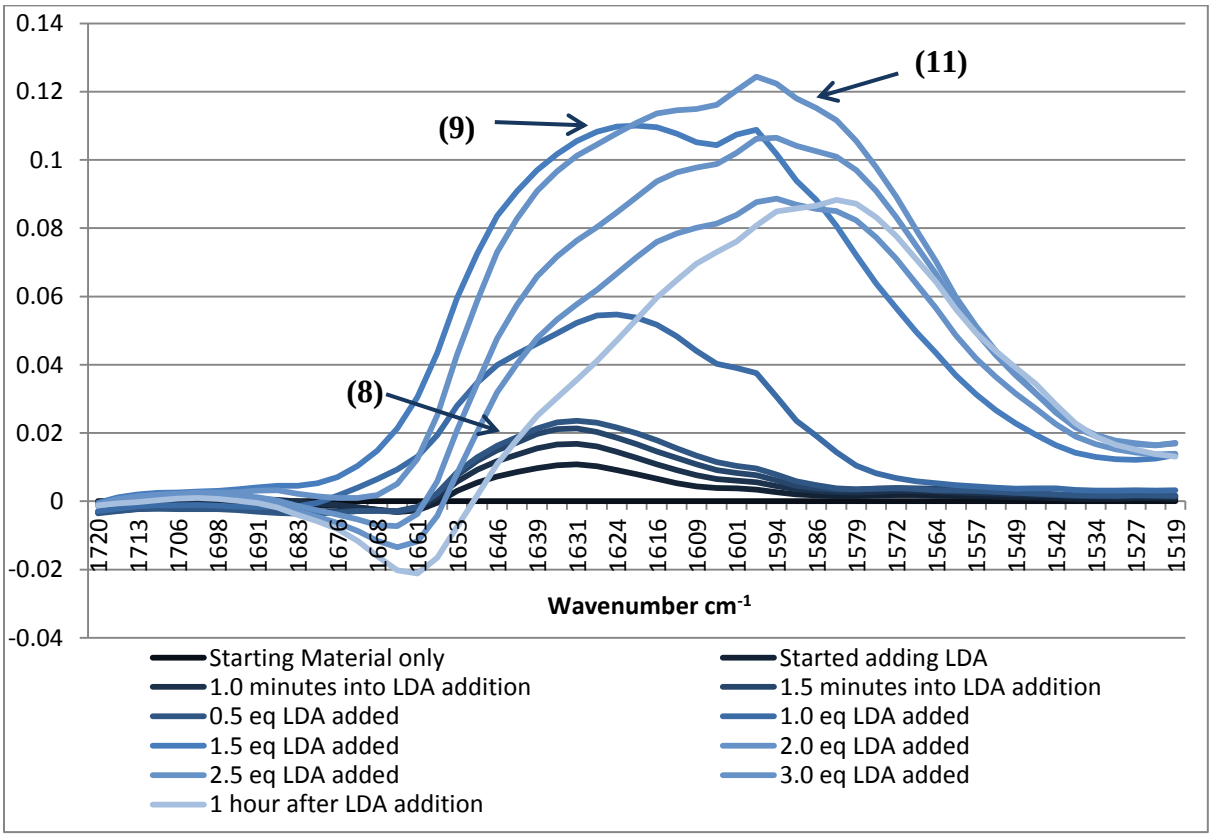


Figure S5: IR difference spectra for the period during the addition of 3.0 eq LDA over 10 min at 0 °C and the 1 h reaction period at 0 °C.

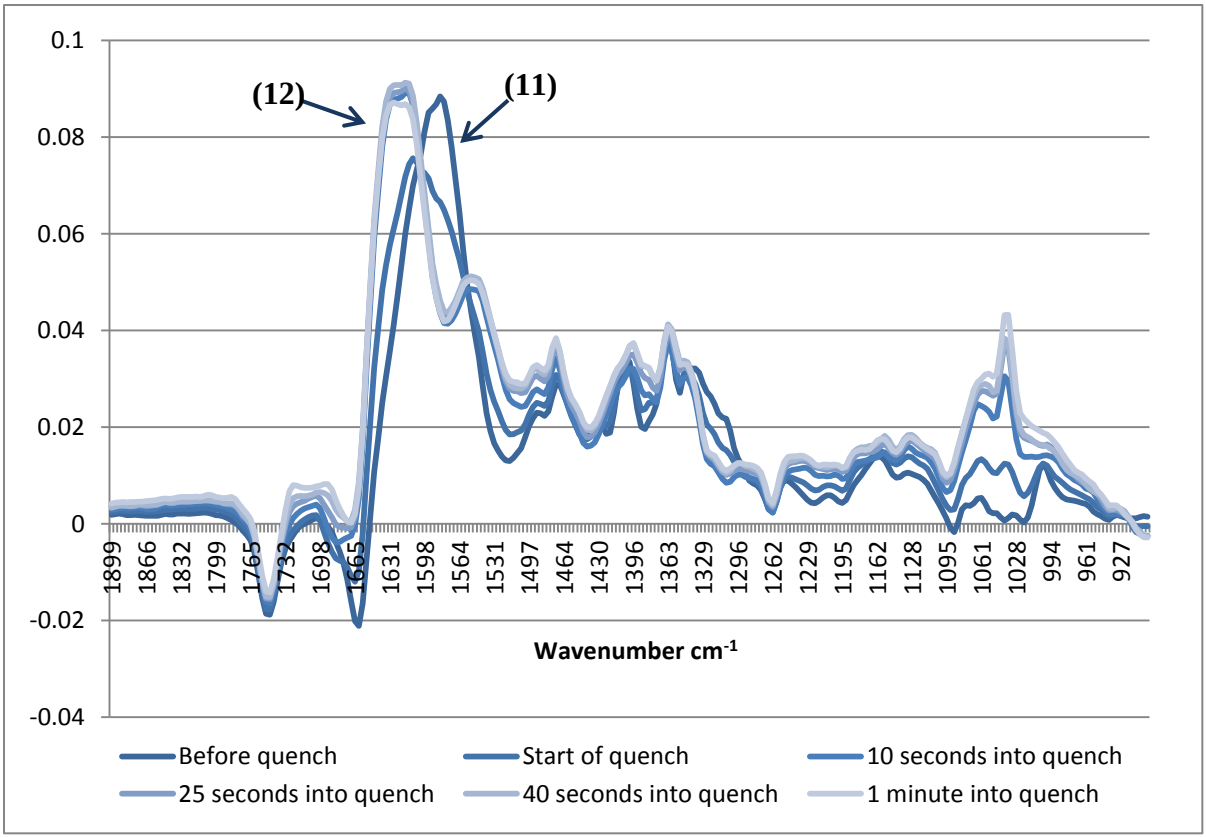


Figure S6: IR difference spectra for the period after the 1 h reaction period at 0 °C and during the first minute of the quench with methanol.

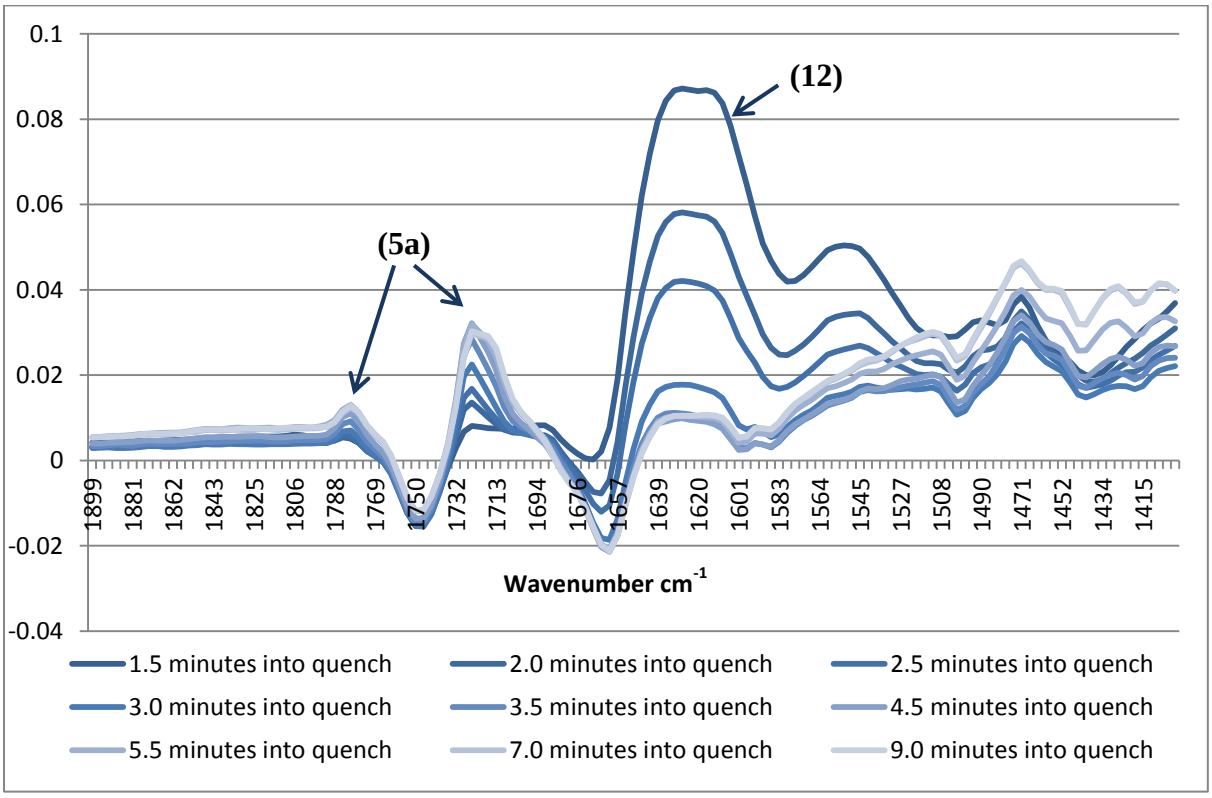


Figure S7: IR difference spectra for the period 1.5 min into the methanol addition until the end of the quench (9.0 min).

The difference spectra at a specific times during the reaction allows estimation of the C=O stretching frequencies of the proposed species formed successively in the reaction mixture. The spectra shown in **Figure S9, S10, S11, S12** and **S13** have the spectrum of **6a** subtracted. The spectra shown in **Figures S9** and **S10** also have the spectrum of **11** (taken at the end of the 1 h reaction period) subtracted.

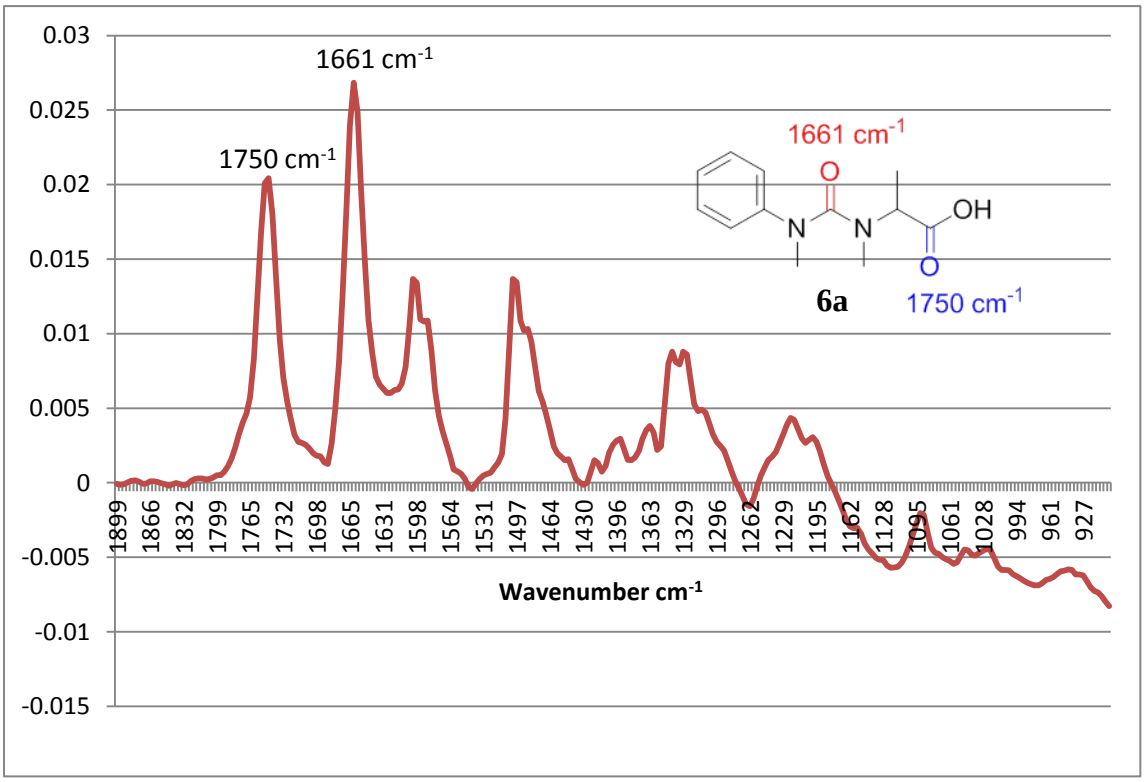


Figure S8: Starting material **6a** in diethyl ether at 0 °C prior to the addition of LDA.

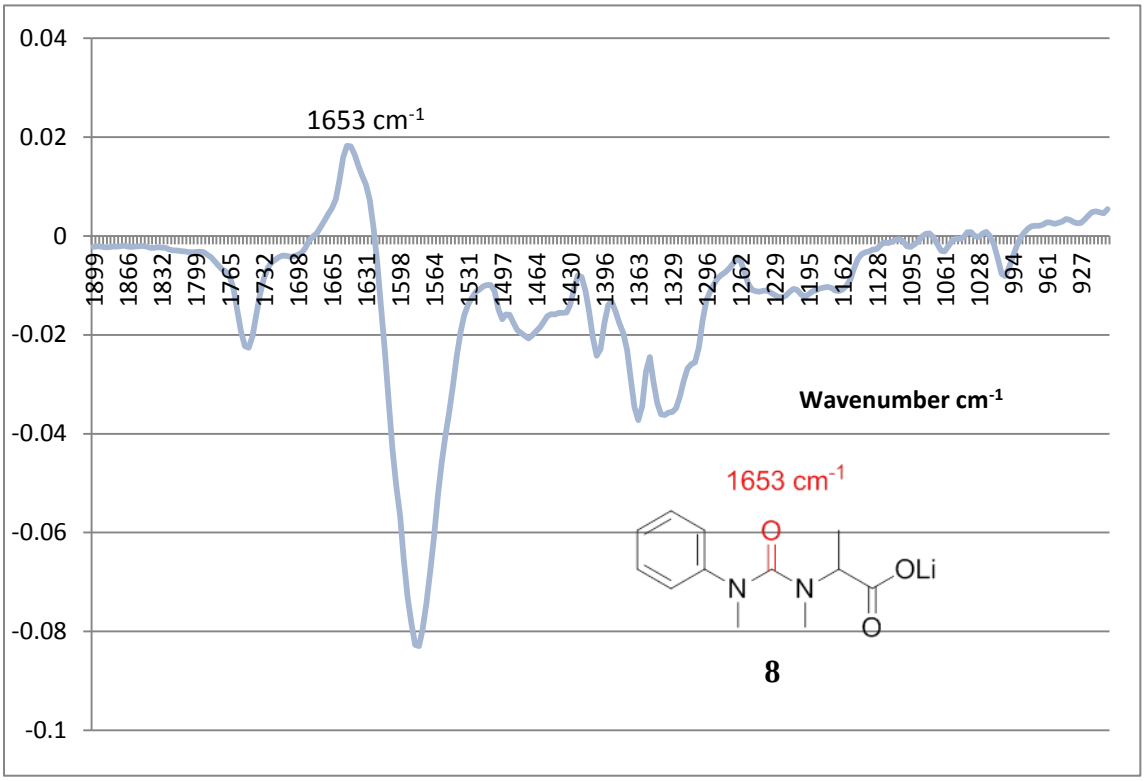


Figure S9: IR difference spectrum after addition of *ca.* 1.0 eq LDA.

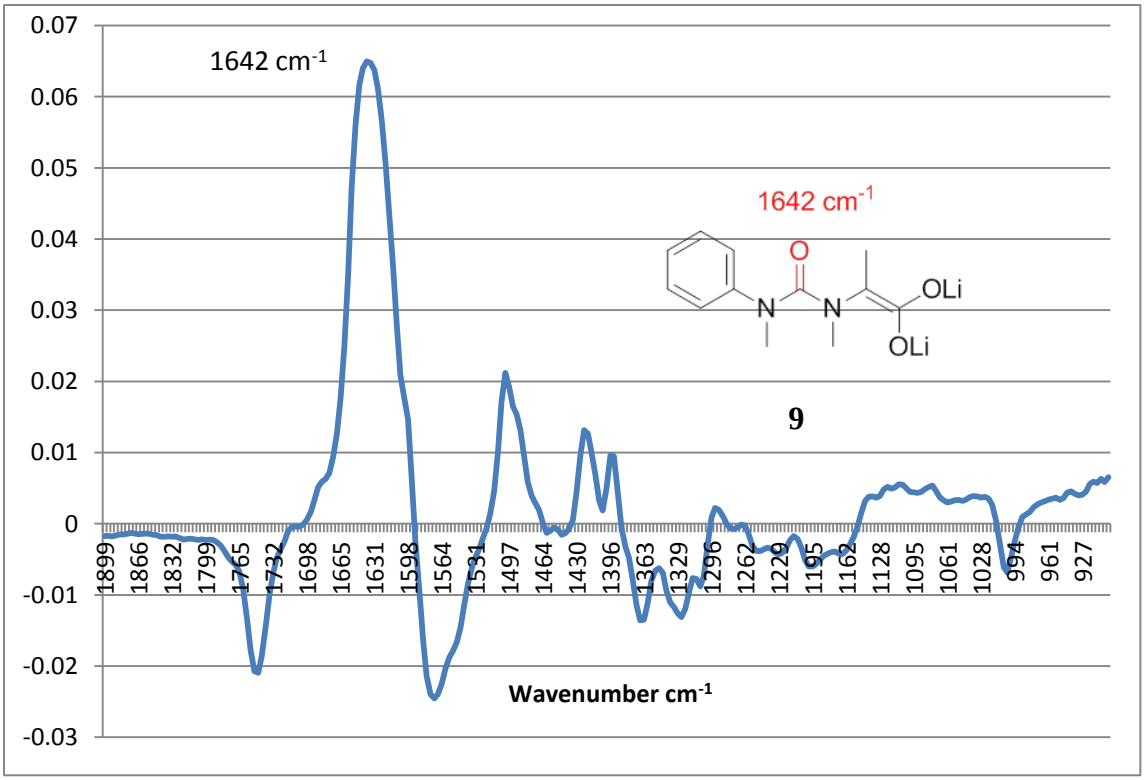


Figure S10: IR difference spectrum after addition of *ca.* 1.5 eq LDA had been added.

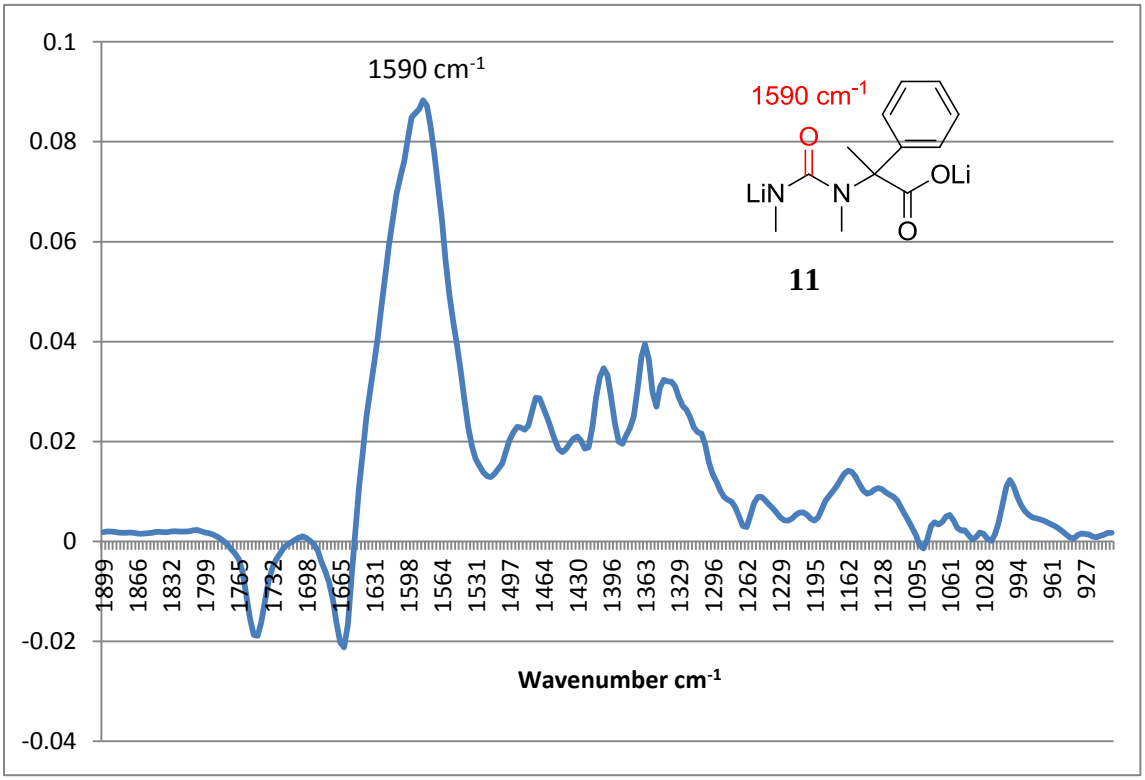


Figure S11: IR difference spectrum after 1 h reaction time at 0 °C.

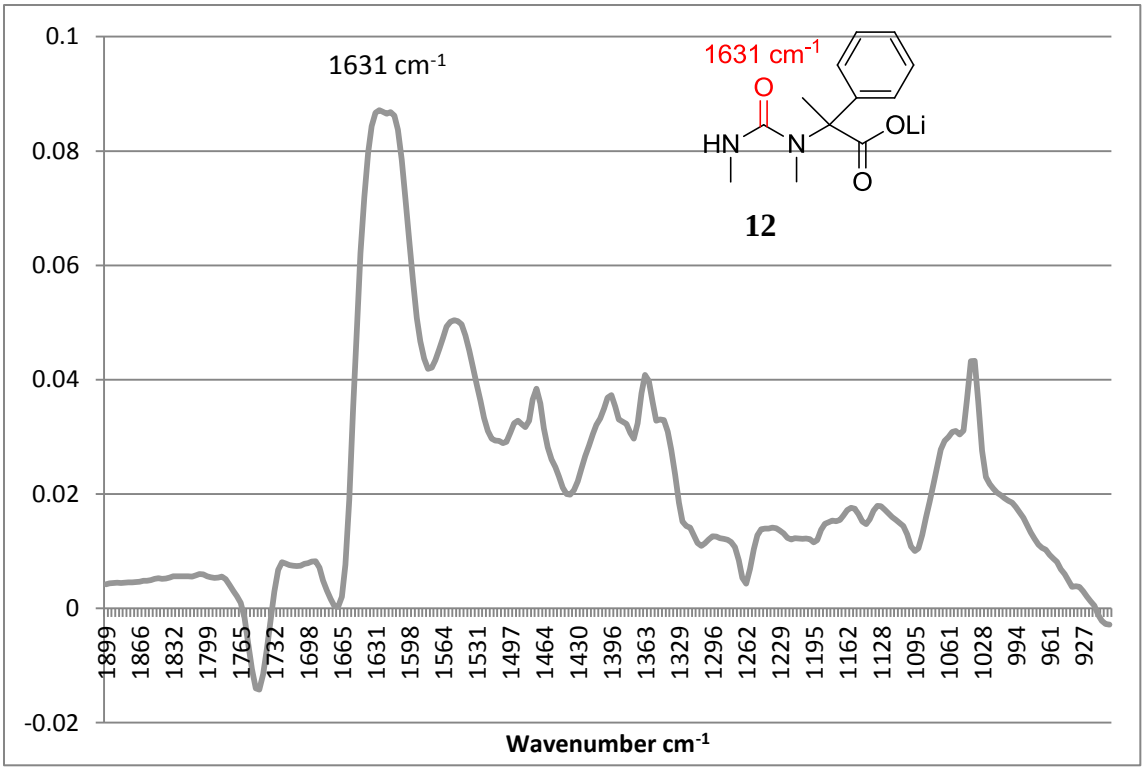


Figure S12: IR difference spectrum 1 min after the start of the quench with methanol.

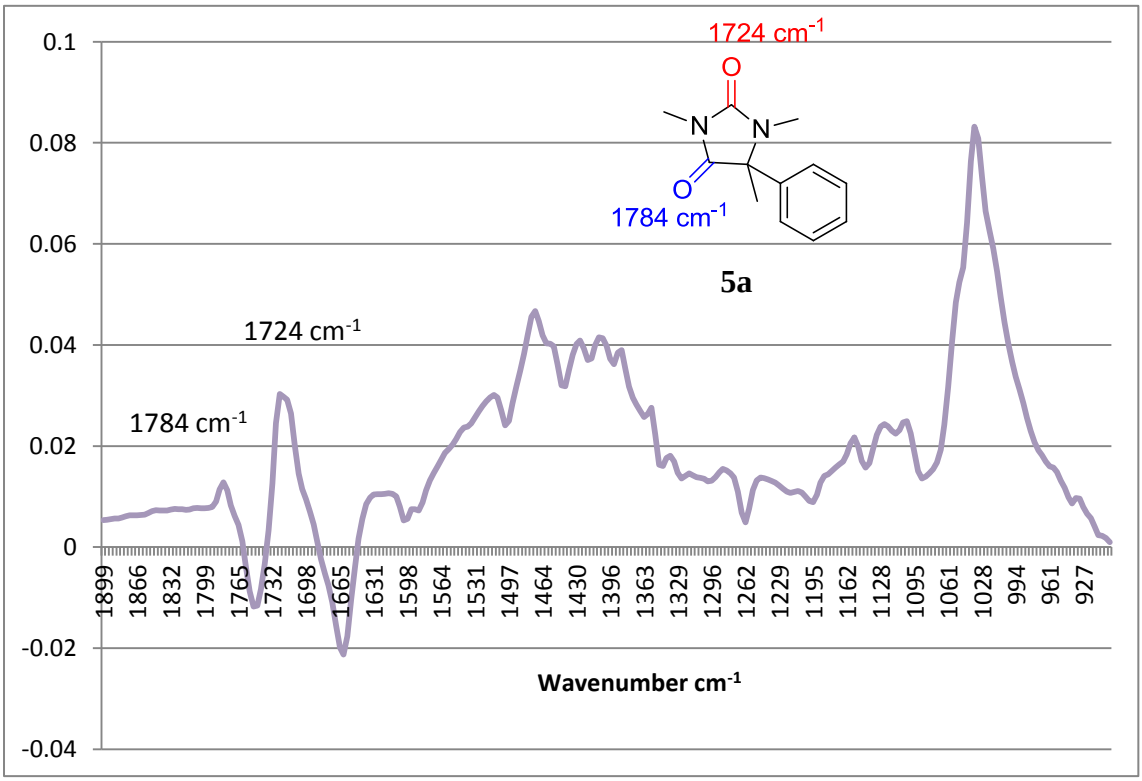


Figure S13: IR difference spectrum 9 min after the quench with methanol.

For the urea starting material **6a** in diethyl ether at 0 °C, the two absorptions at 1750 cm^{-1} and 1661 cm^{-1} were assigned to $\nu_{C=O}$ for the carboxylic acid and urea respectively (**Figure S8**). Upon addition of the first equivalent of LDA there was immediate loss of the absorption at 1750 cm^{-1} corresponding to the carbonyl of the carboxylic acid, suggesting formation of a carboxylate anion. A change from the starting material **6a** was further indicated by a small shift in the urea carbonyl absorption at 1661 cm^{-1} to 1653 cm^{-1} which we assign to the carboxylate **8** (**Figure S9**).

During the addition of the remaining LDA, the 1653 cm^{-1} absorption disappeared and an absorption appeared at a lower wavenumber of 1642 cm^{-1}. A carboxylic acid carbonyl absorption was still absent. This new stretching frequency was assigned to enolate **9** (**Figure S10**). This species predominated between the addition of one and two equivalents of LDA (**Figure S4**).

Towards the end of the LDA addition there was a decay in the intensity of the absorption at 1653 cm^{-1} assigned to enolate **9**, but at the same time a new absorption at 1590 cm^{-1} grew (**Figure S1, S2 and S5**). This significant shift in the carbonyl stretching frequency to a lower wavenumber is consistent with formation of the deprotonated urea and we assign this absorption to the urea function of dianion **11** (**Figure S11**). A negative charge on the nitrogen donating into the adjacent carbonyl group is expected to weaken the carbonyl stretching frequency significantly, and the shift to a wavenumber of 1550-1600 cm^{-1} is consistent with data reported for related anionic ureas.[7,8] Throughout the addition the absorption assigned to enolate **9** reduced and the absorption assigned to dianion **11** increased.

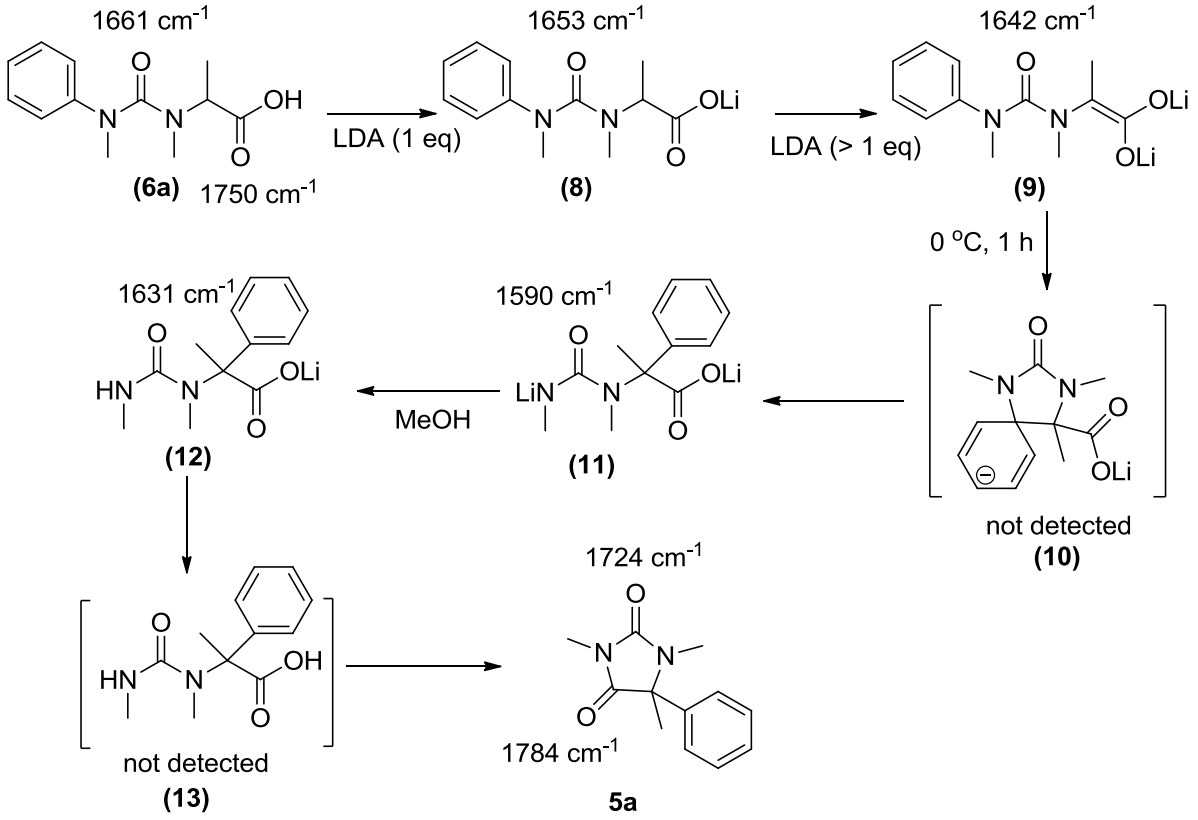
The reaction was left at 0 °C for 1 hour, during which time the peak for dianion **11** remained constant (**Figure S2** and **S5**). At no point during the reaction was a higher frequency carbonyl absorption observed that would be expected for a 5-membered-ring cyclic intermediate **10**. If such an intermediate is formed it does not accumulate to any significant concentration during the reaction.

After one hour at 0 °C the reaction was quenched through dropwise addition of methanol, and immediately the absorption at 1590 cm^{-1} assigned to the dianion **11** shifted back to a higher wavenumber, reappearing at 1631 cm^{-1}. This is consistent with reprotonation of the anionic urea. No absorbance appeared with a stretching frequency indicative of a carboxylic acid C=O. We assign the peak at 1631 cm^{-1} to a rearranged carboxylate species **12**. No intermediate with both the nitrogen and carboxylate protonated **(13)** was observed (**Figure S3**, **S6** and **S12**). Species **12** was present for the

[7] J. Lefranc, A. M. Fournier, G. Mingat, S. Herbert, T. Marcelli and J. Clayden, *J. Am. Chem. Soc.*, 2012, **134** (17), 7286.
[8] D. M. Grainger, A. Campbell Smith, M. A. Vincent, I. H. Hillier, A. E. H. Wheatley and J. Clayden, *Eur. J. Org. Chem.*, 2012, **4**, 731.

first minute and a half of the quench, after which time the absorption at 1631 cm^{-1} decreased in intensity and finally disappeared.

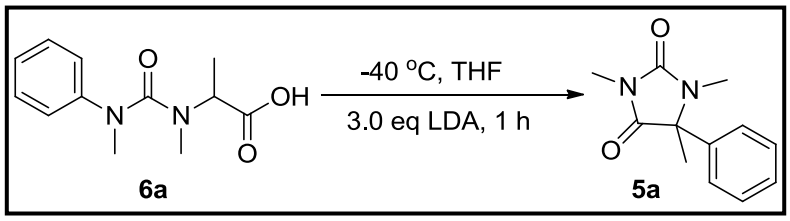
Approximately one minute into the quench two new absorptions appeared, at 1724 cm^{-1} and 1784 cm^{-1}, which correspond to $\nu_{C=O}$ for **5a** (**Figure S3, S7** and **S13**). The IR data for an isolated sample of hydantoin **5a**, obtained in the solid state, gave stretching frequencies of 1704 cm^{-1} and 1770 cm^{-1}. No carboxylic acid C=O absorption was evident before the cyclisation to give hydantoin **5a** suggesting the hydantoin must form even under basic conditions; directly from the carboxylate (**Scheme S1**).



Scheme S1: The six successive reaction species identified on the pathway from **6a** to **5a** in diethyl ether.

Reaction carried out in THF

The reaction was carried in THF to establish whether the same ReactIR trace was observed for the intermediates **8**, **9** and **11** during the LDA addition as in the experiment in diethyl ether. It was necessary to carry the reaction out at -40 °C in THF to slow the reaction enough to observe the reaction intermediates.



Anhydrous THF (8.00 mL) was added to a 100 mL three-necked flask equipped with a stirrer bar and ReactIR probe under nitrogen. The solution was cooled to -40 °C using an acetonitrile/dry ice bath and left to stabilise. An IR solvent background spectrum was taken. Urea acid **6a** (250 mg, 1.06 mmol, 1.0 eq) was added through one of the three necks and an IR reactant background spectrum was taken. The reaction mixture was warmed to room temperature to allow the urea acid **6a** to dissolve. Once homogeneous the reaction mixture was cooled to -40 °C. In a separate flask LDA was prepared; anhydrous THF (4.00 mL) and DiPA (0.45 mL, 3.18 mmol, 3.0 eq) were cooled to 0 °C, *n*BuLi (1.38 mL, 3.18 mmol, 2.3 M in hexanes, 3.0 eq) was added dropwise and the mixture was stirred for 30 min. The LDA was added very slowly dropwise to the reaction mixture over 25 min (1.0 eq with 5 min wait, 2.0 eq with 5 min wait and 3.0 eq). The reaction mixture was left to stir for 1 h at -40 °C and was quenched by a dropwise addition of methanol. The reaction mixture was allowed to warm to room temperature and the ReactIR probe was removed. The reaction mixture was acidified with 1.0 M HCl and the product extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. NMR analysis confirmed the hydantoin **5a** was present at the end of the reaction (1:1 **6a**:**5a**).

Throughout the experiment IR spectra were recorded continuously at varying time intervals. An IR spectrum was recorded every 15 seconds from the start of the experiment until 7 minutes after the LDA addition was complete. After this time the frequency of recording IR spectra was decreased to every 45 seconds. When the methanol was added to quench the reaction the frequency was increased to recording spectra every 15 seconds.

Figure S14 shows a difference spectrum constructed using the IR data acquired over the 25 min LDA addition at -40 °C (one equivalent added at a time), subtracting the spectrum of **6a** to allow clearer identification of new species.

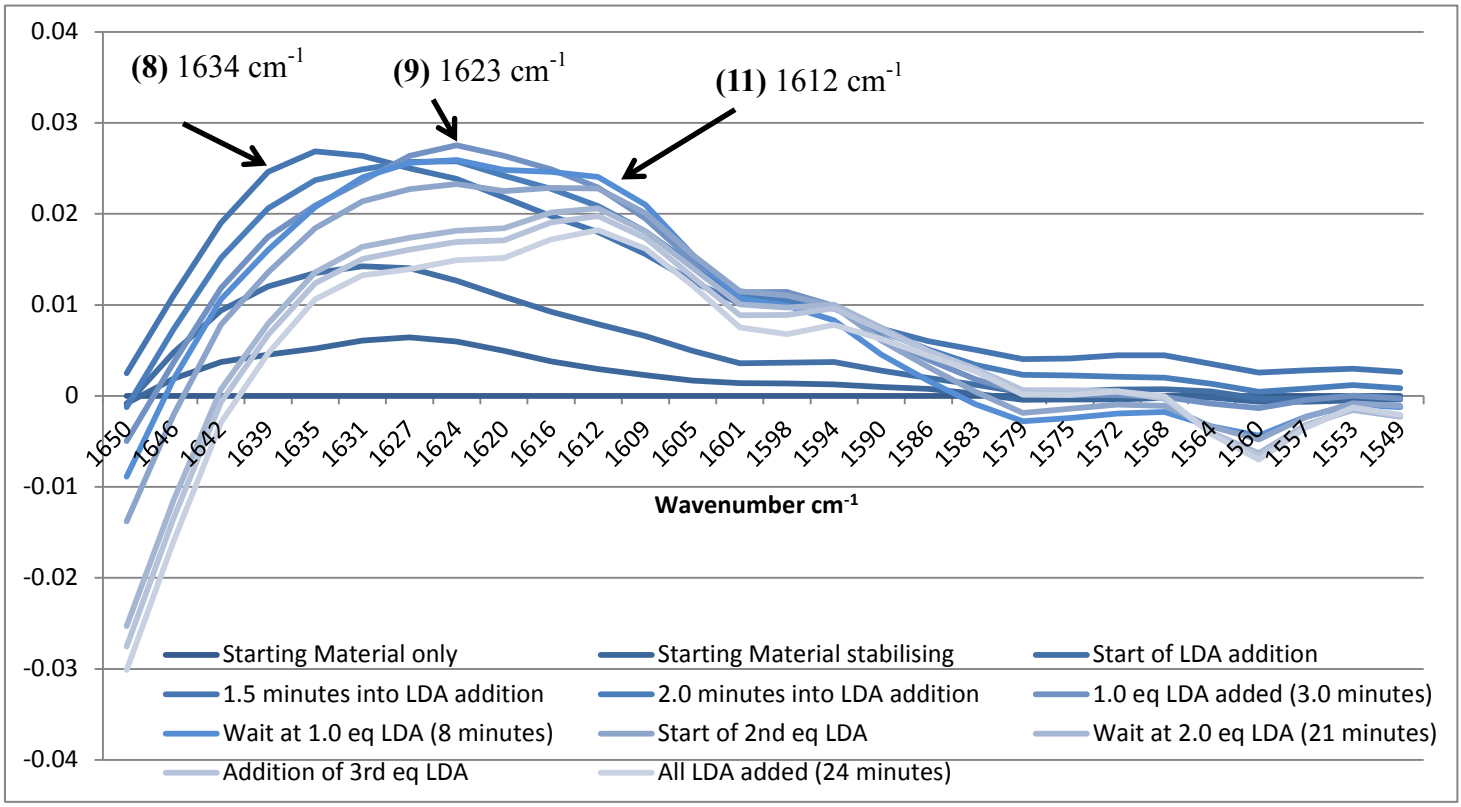
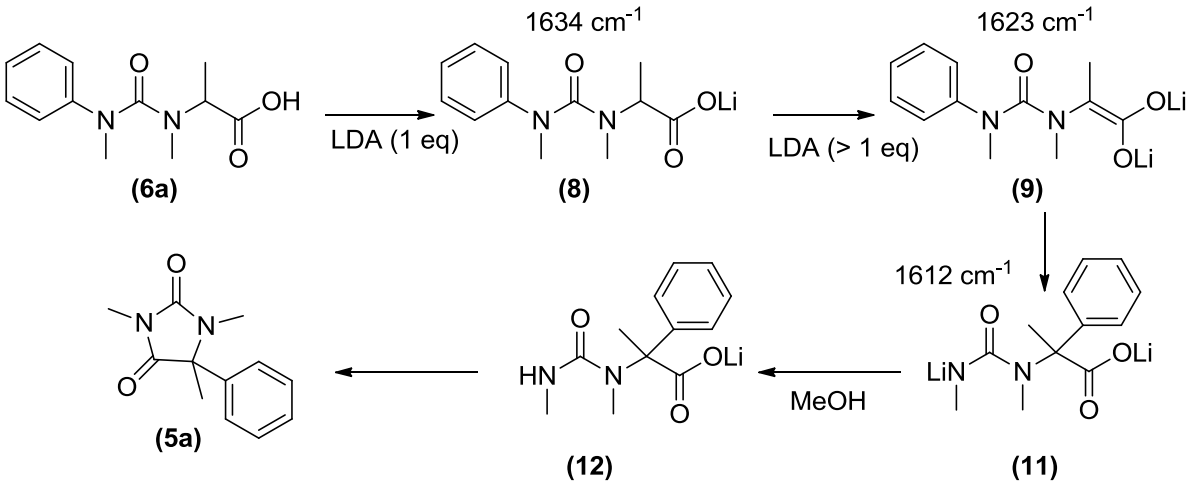


Figure S14: IR difference spectrum for the 25 min addition of LDA to **6a** at -40 °C.

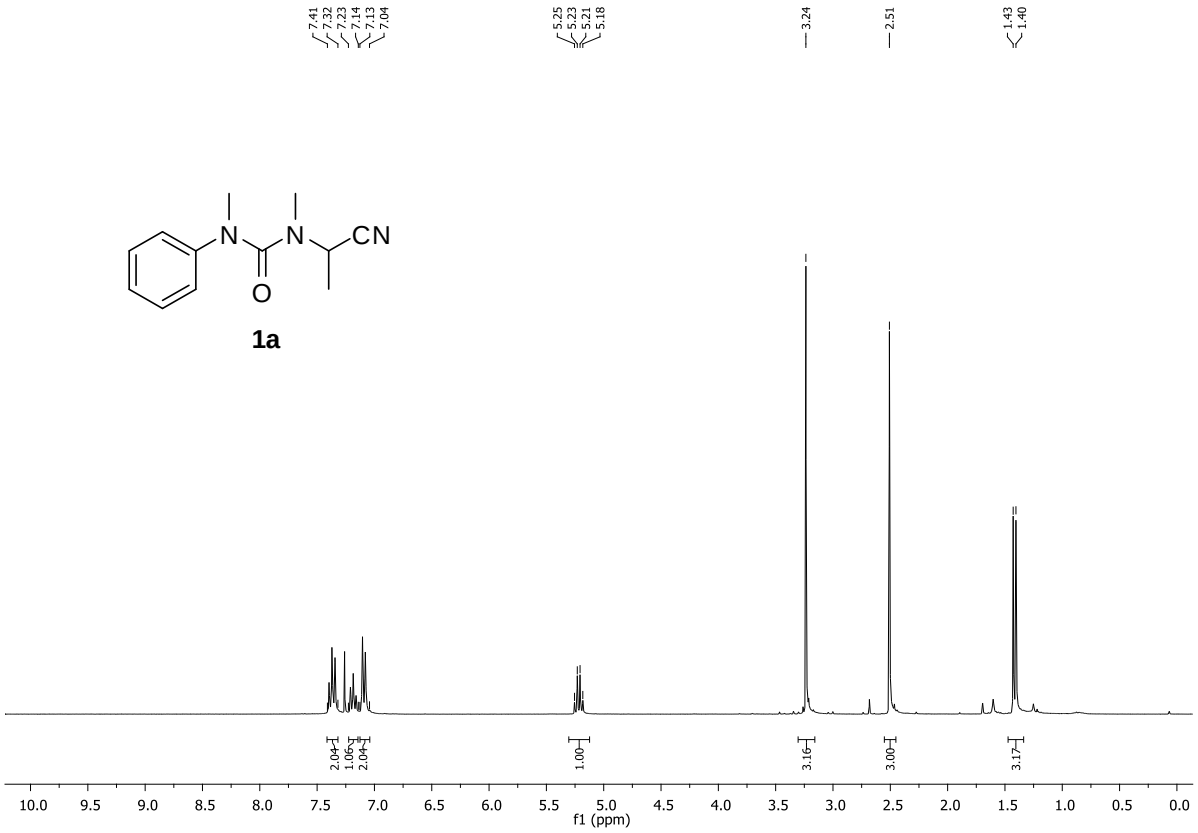
The LDA was added over 25 min, and as soon as one drop of LDA was added an absorption at 1634 cm^{-1} was observed, which we assign to the carboxylate **8**. At the end of the addition of the first equivalent and during the 5 min wait the enolate **9** started to form and continued to form throughout the addition of the second equivalent of LDA, with the absorption at 1623 cm^{-1} appearing and the absorption at 1634 cm^{-1} reducing in intesity. Finally, between the addition of the second and the third equivalents, a third absorption was observed at 1612 cm^{-1}, which was assigned to **11**. Throughout the addition the carbonyl absorption for **8** increases then reduces in intensity as the carbonyl absorption for **9** increases. At the end of the addition the carbonyl absorption for **9** reduces and the carbonyl peak for **11** becomes predominant (**Figure S14**).

The same pattern was observed in the diethyl ether ReactIR experiments, confirming the reaction undergoes the same pathway in both diethyl ether and THF. The values of the stretching frequencies are different due to the two different solvents but the same general shifts in the carbonyl stretching frequencies were consistent with a corresponding series of reaction intermediates (**Scheme S2**).

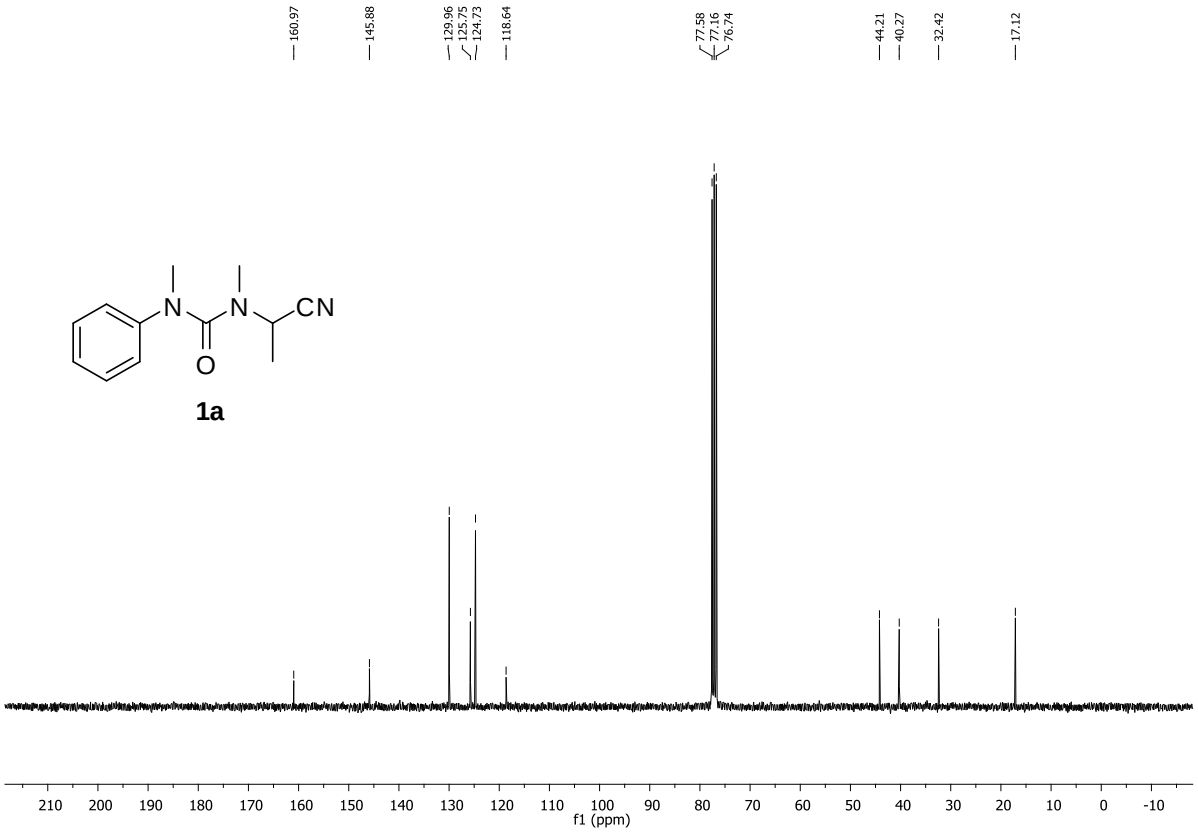


Scheme S2: The observed reaction species on the pathway from **6a** to **5a** in THF.

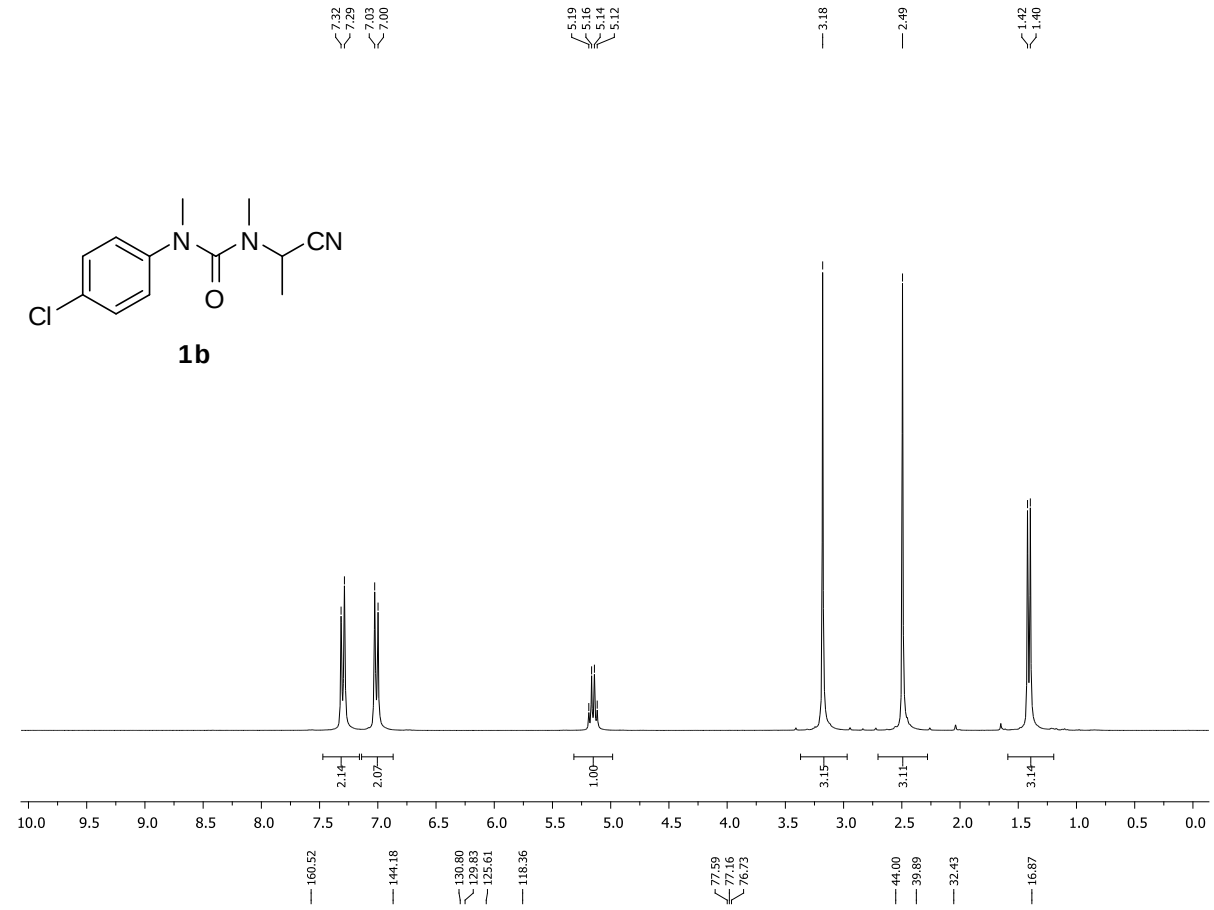
^{1}H and ^{13}C NMR Spectra



1a



1a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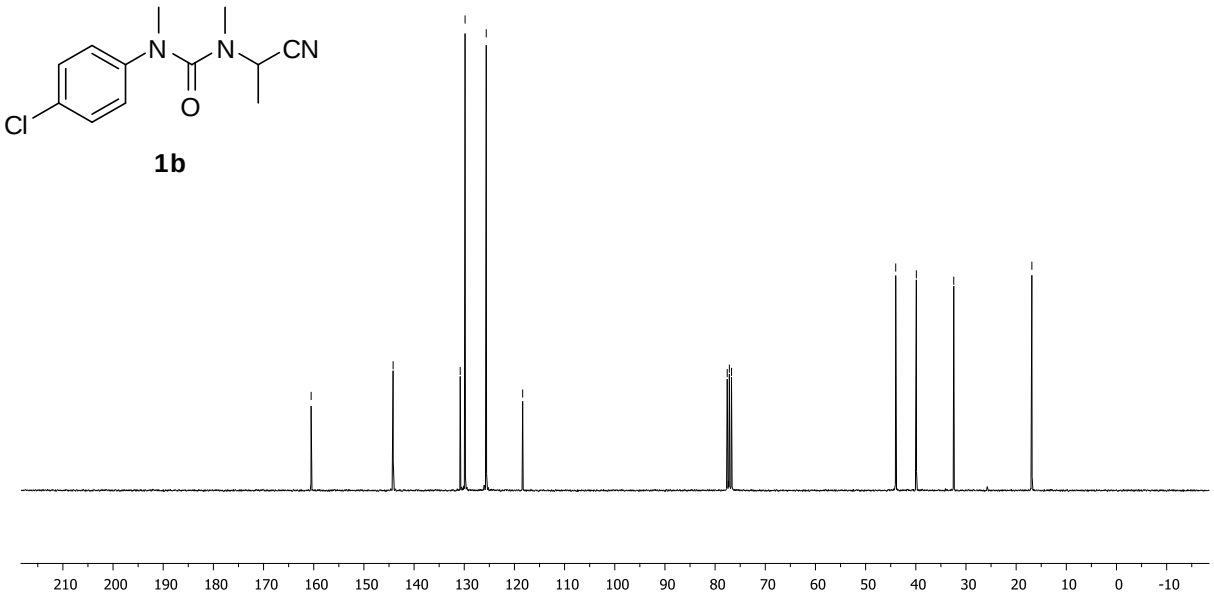
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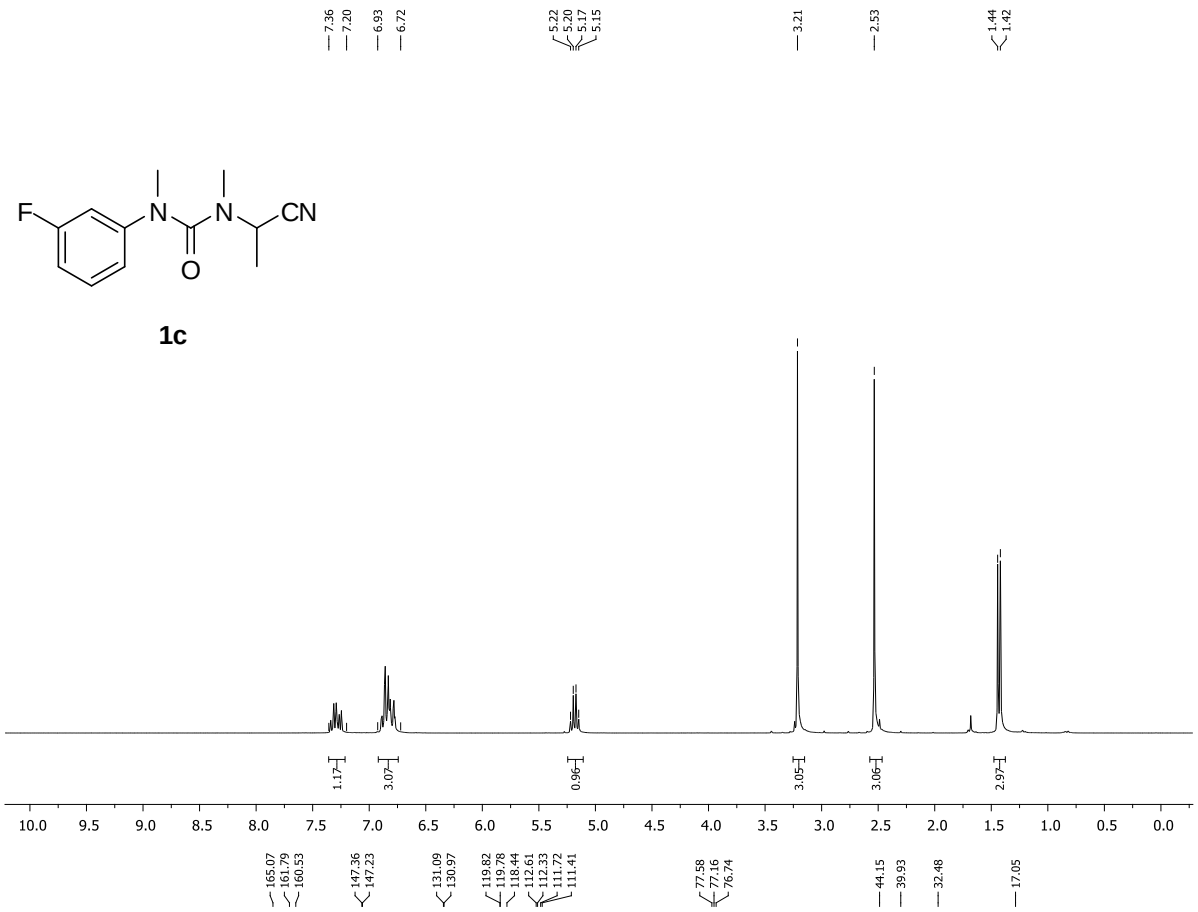
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6.72
5.22
5.20
5.17
5.15
3.21
2.53
1.44
1.42
F
N
N
CN
O
1.17
3.07
0.96
3.05
3.06
2.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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1.5
1.0
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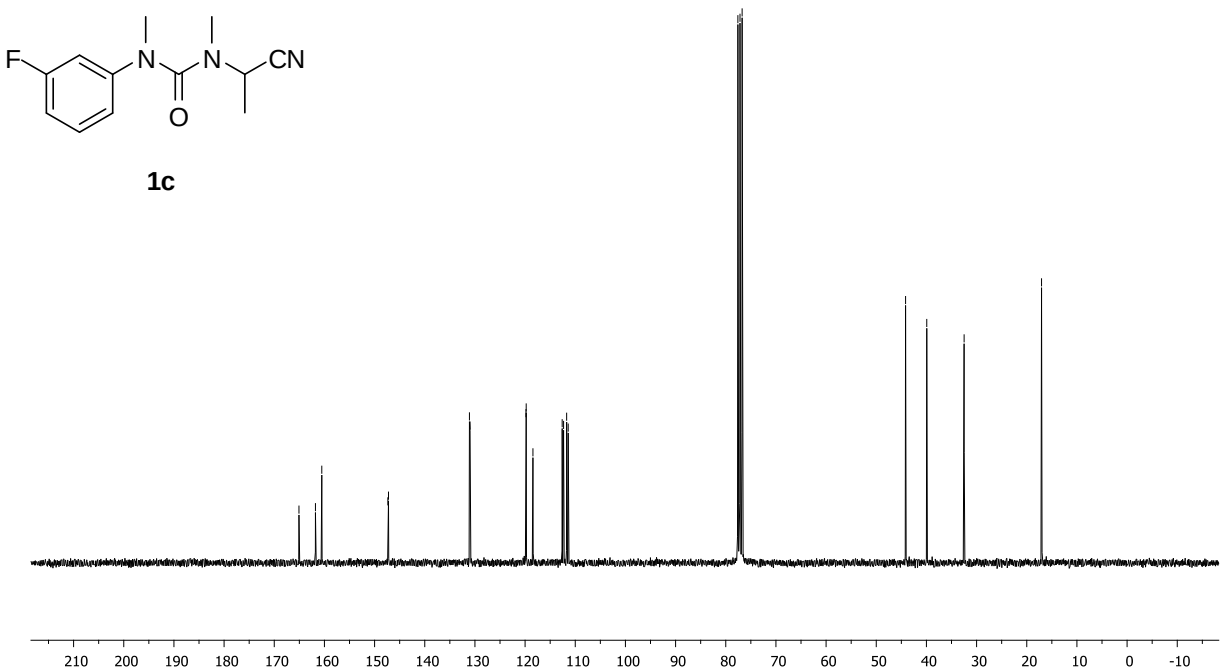
0.0

1c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161.79
160.53
147.36
147.23
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130.97
119.82
119.78
118.44
112.61
112.33
111.72
111.41
77.58
77.16
76.74
44.15
39.93
32.48
17.05
F
N
N
CN
O
210
200
190
180
170
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50
40
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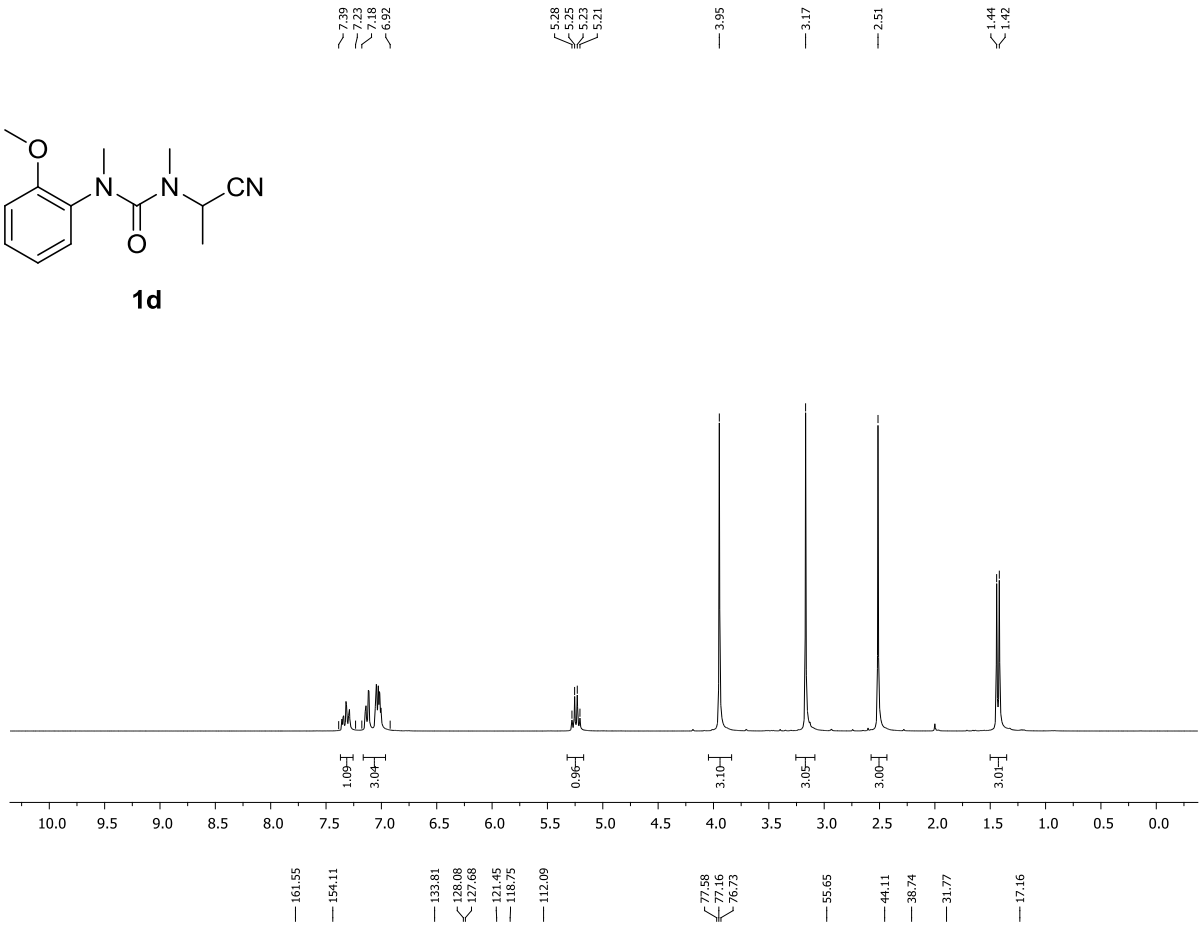
0
-10

1c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6.92
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5.25
5.23
5.21
3.95
3.17
2.51
1.44
1.42
O
N
N
CN
O
1d
1.09
3.04
0.96
3.10
3.05
3.00
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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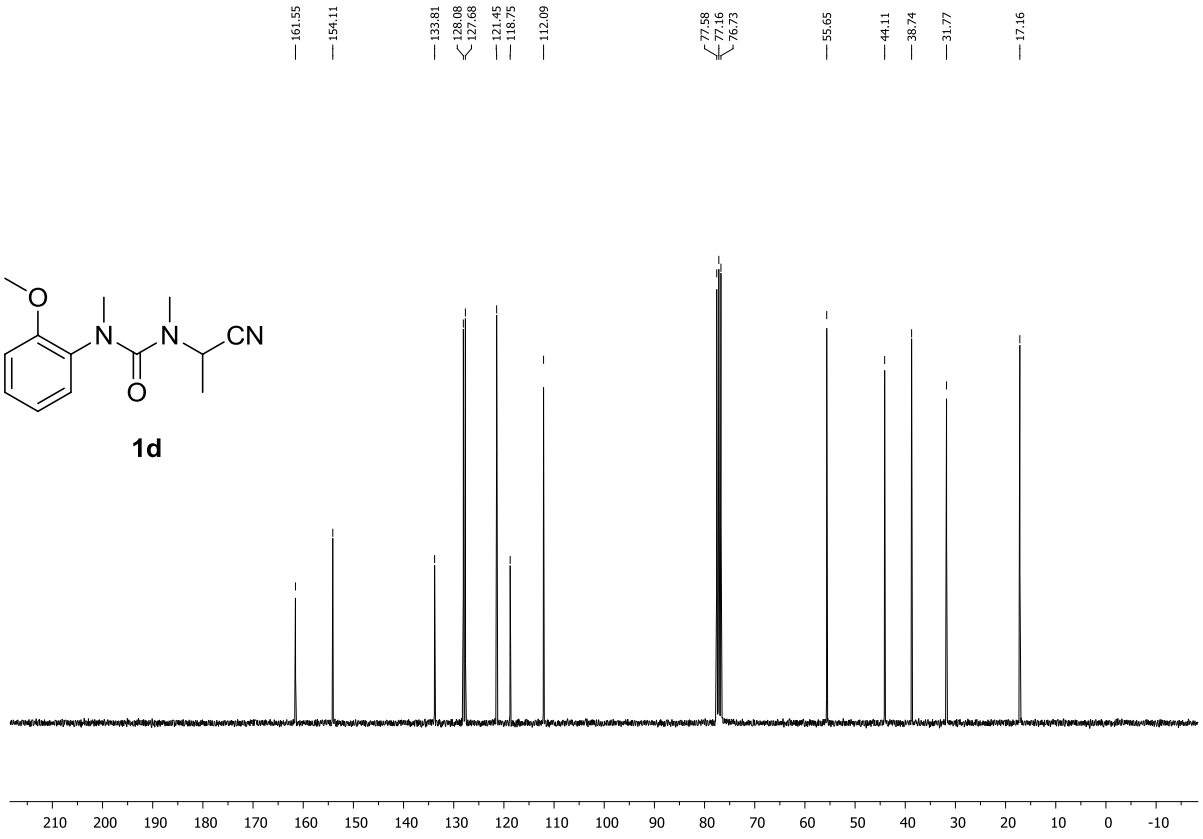
0.0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121.45
118.75
112.09
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77.16
76.73
55.65
44.11
38.74
31.77
17.16
O
N
N
CN
O
1d
210
200
190
180
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140
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120
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100
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80
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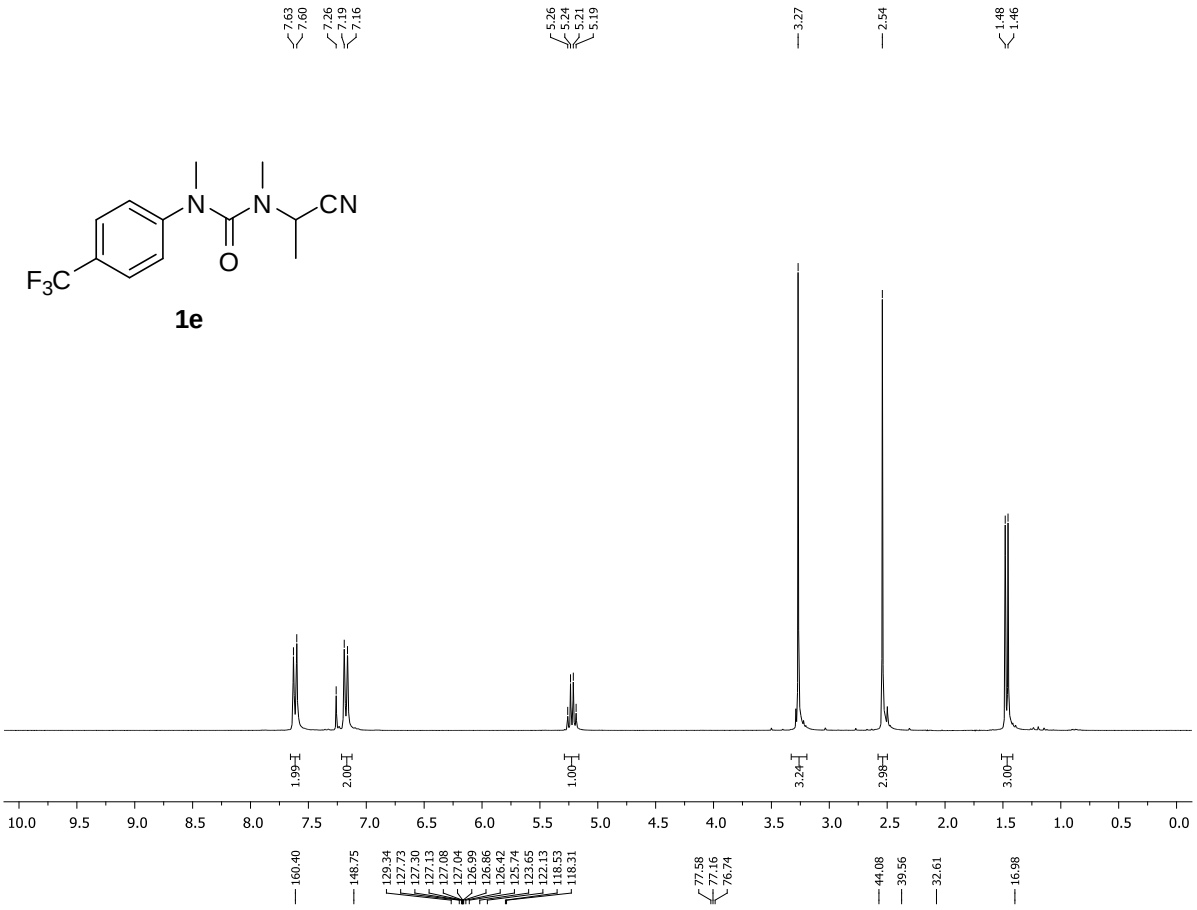
0
-10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7.26
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5.26
5.24
5.21
5.19
3.27
2.54
1.48
1.46
N
N
CN
O
F3C
1e
1.99
2.00
1.00
3.24
2.98
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
160.40
148.75
129.34
127.73
127.30
127.13
127.08
127.04
126.99
126.86
126.42
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118.53
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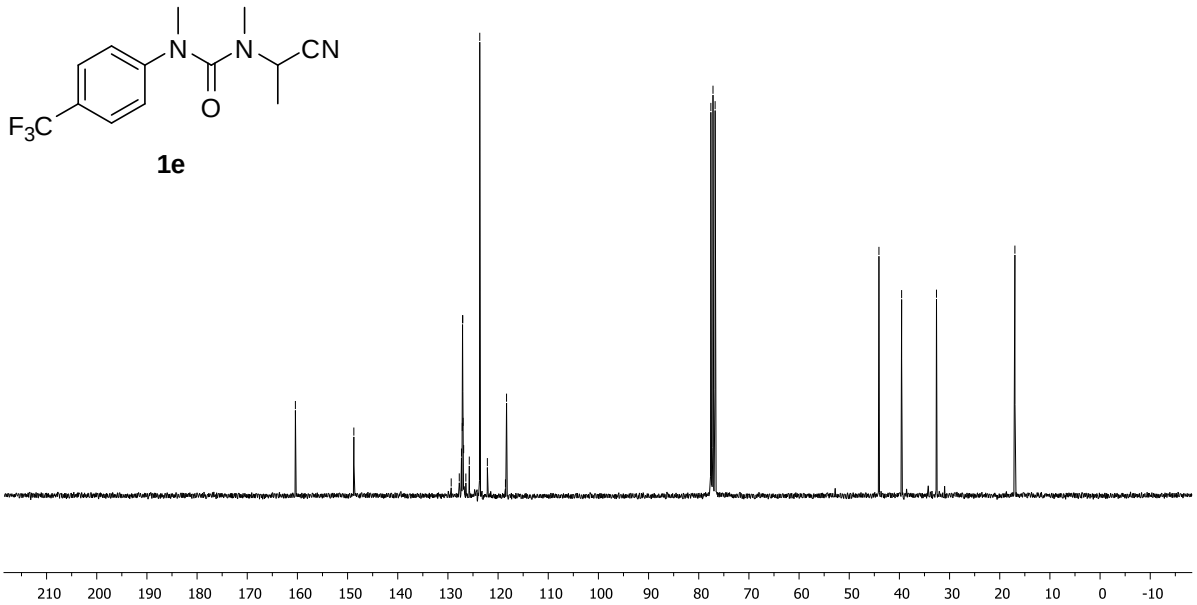
77.58
77.16
76.74
44.08
39.56
32.61
16.98


N
N
CN
O
F3C
1e
210
200
190
180
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160
150
140
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120
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100
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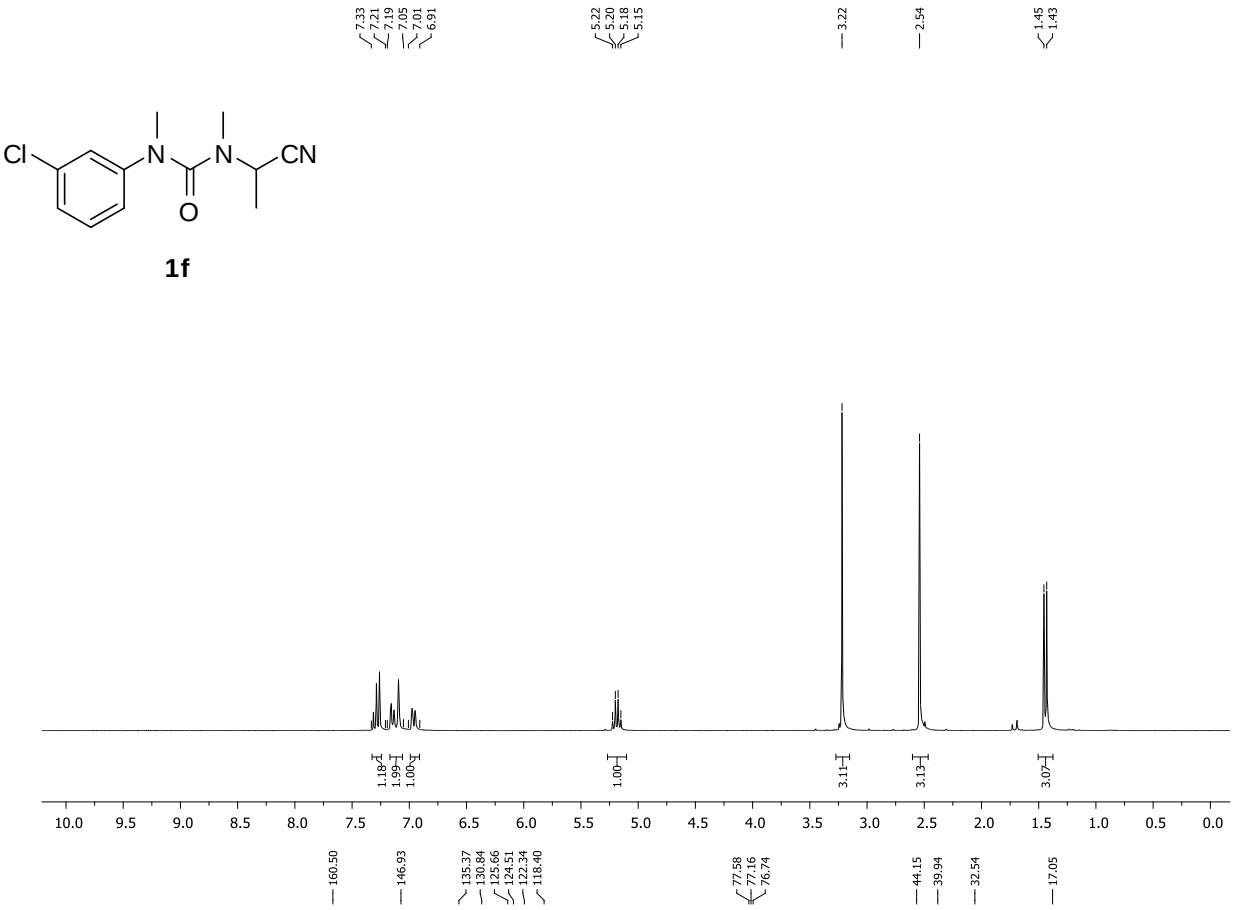
80
70
60
50
40
30
20
10
0
-10


7.33
7.21
7.19
7.05
7.01
6.91
5.22
5.20
5.18
5.15
3.22
2.54
1.45
1.43
Cl
N
N
CN
O
1f
1.18
1.99
1.00
1.00
3.11
3.13
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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3.0
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2.0
1.5
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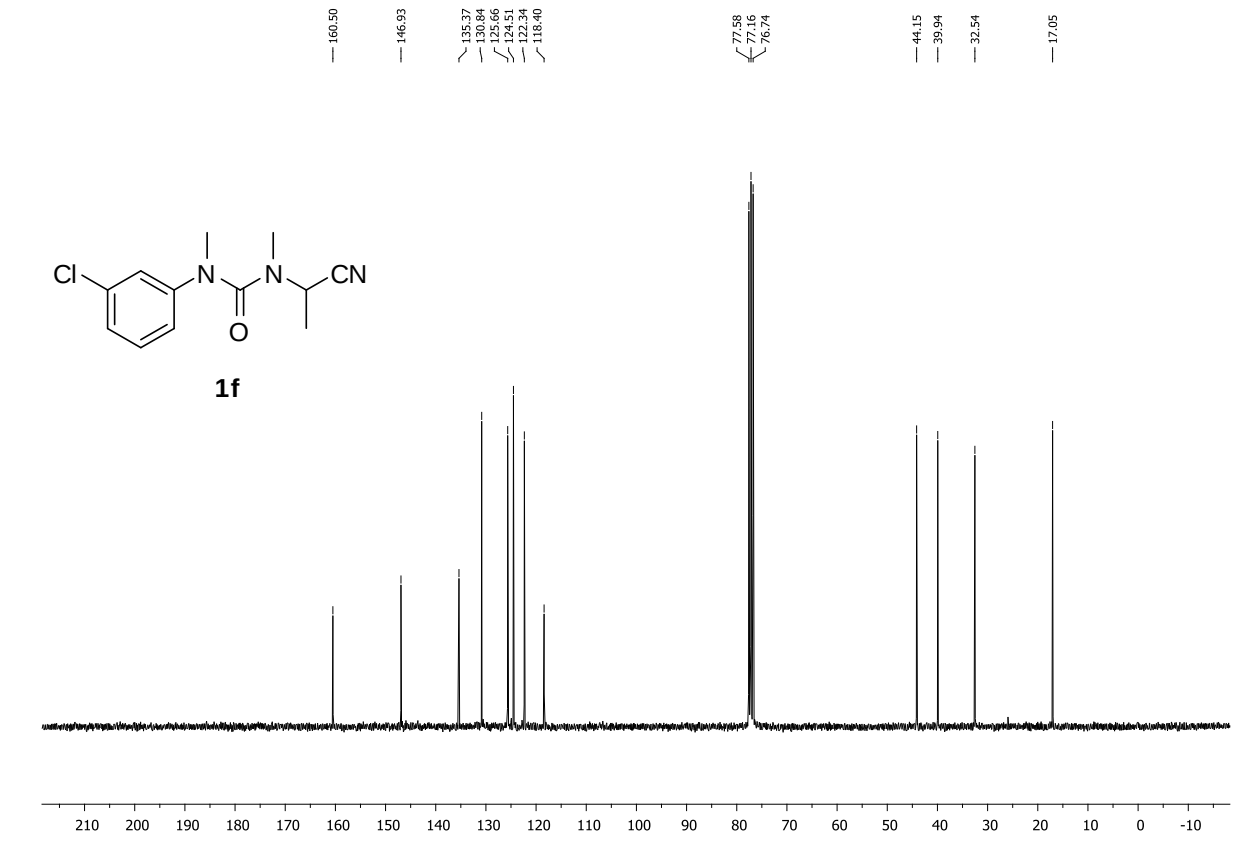
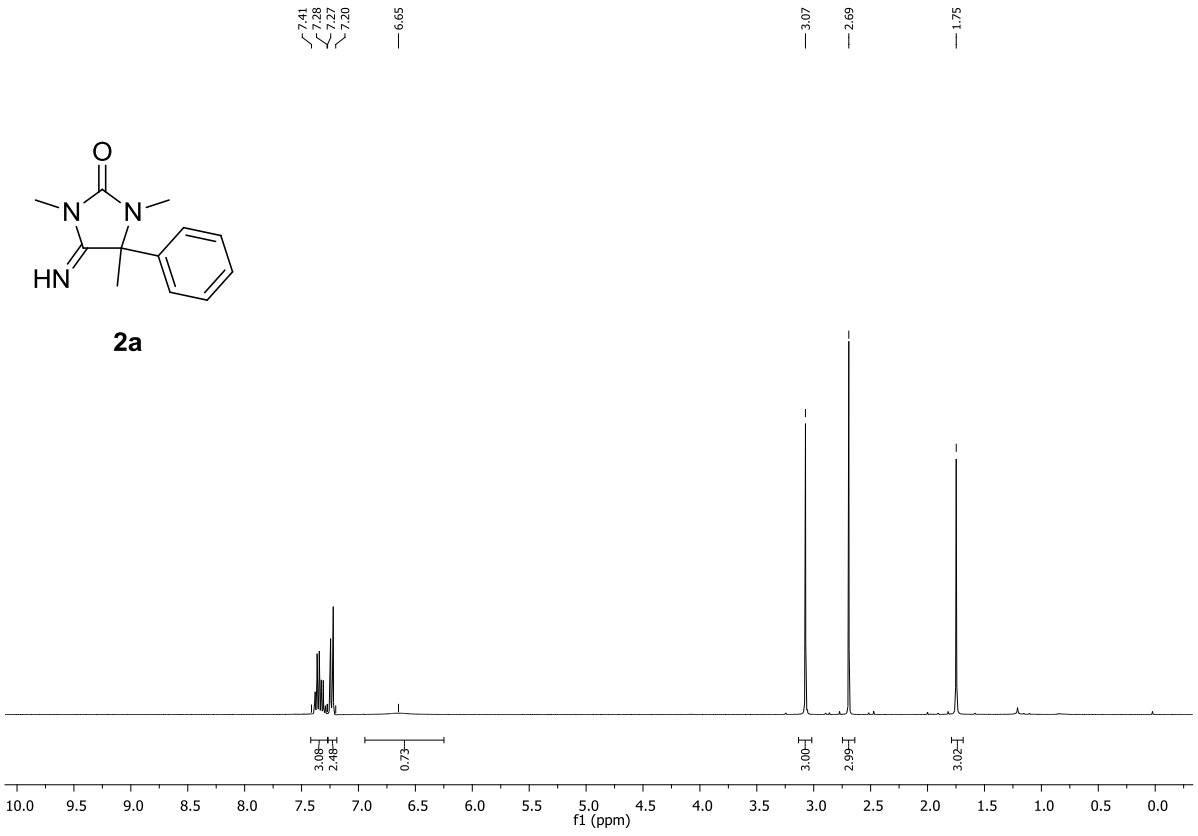
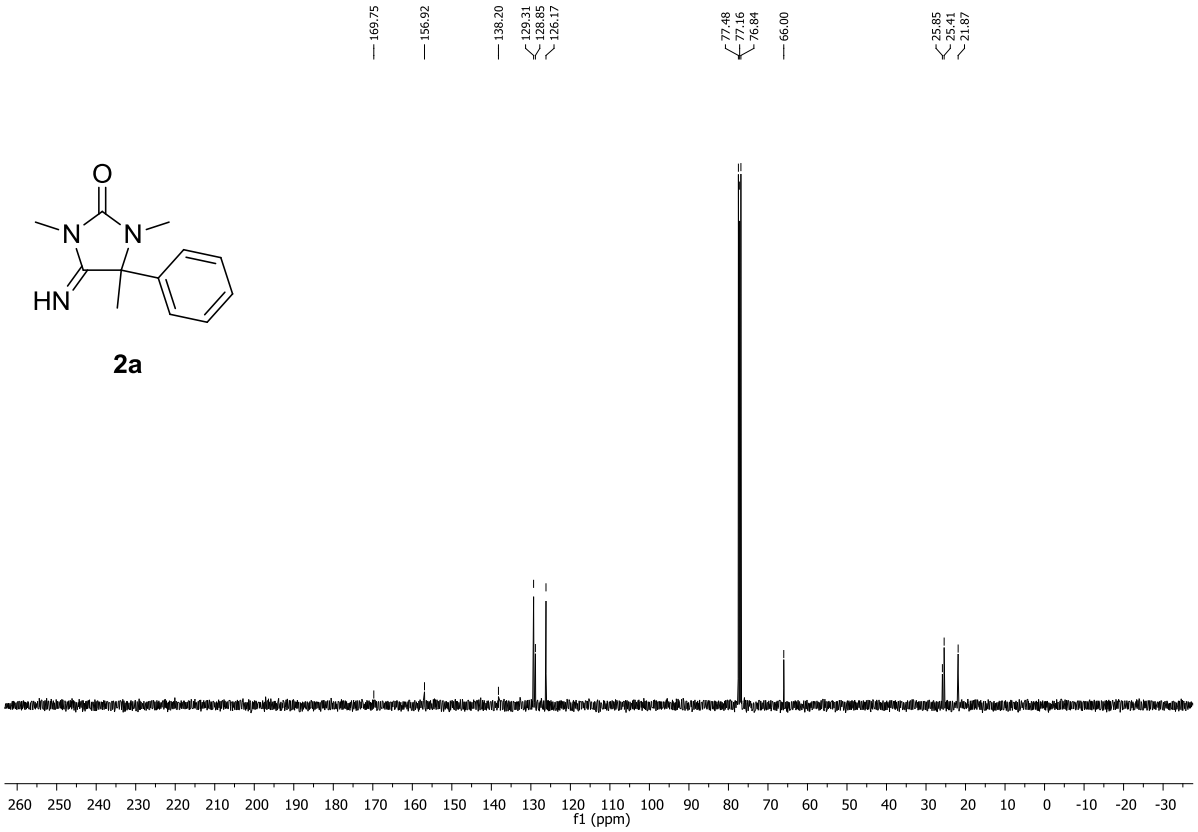
0.5
0.0

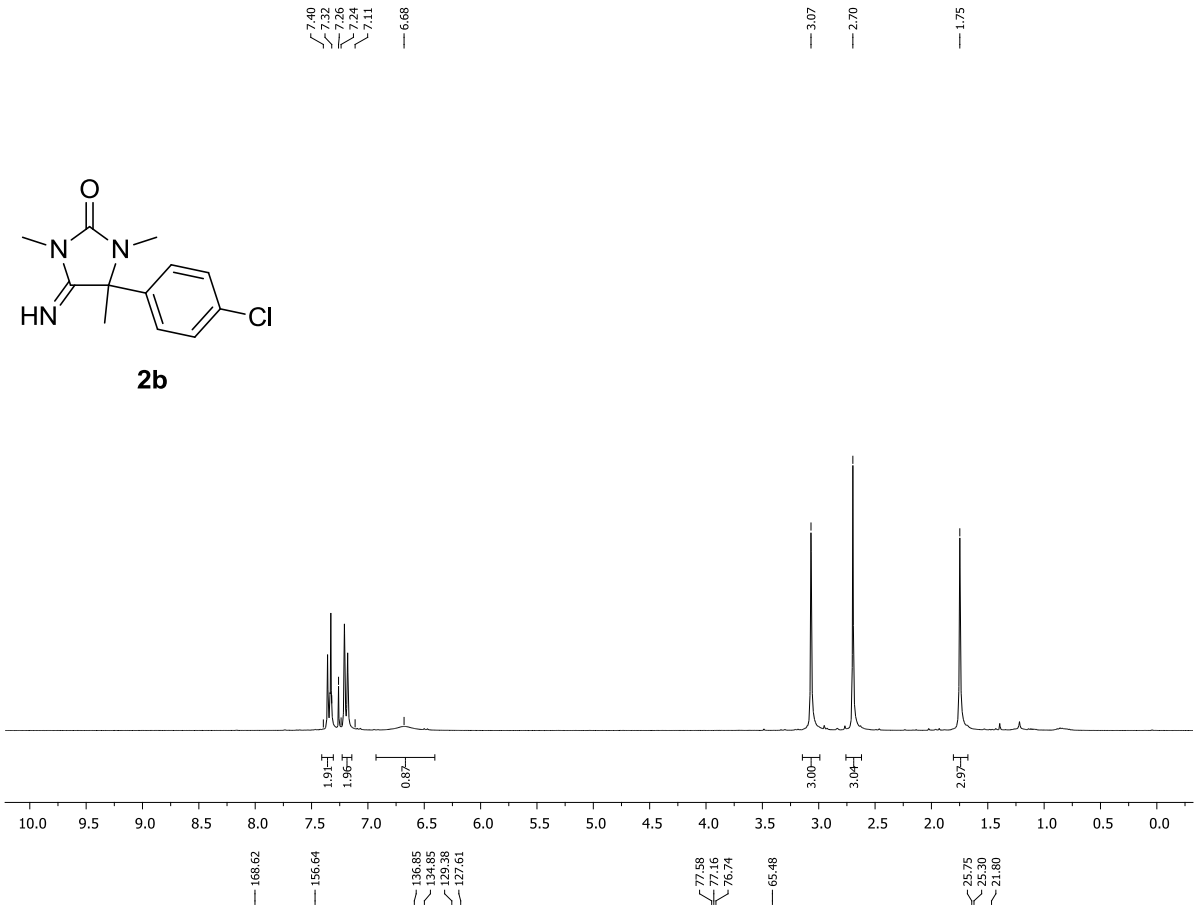

160.50
146.93
135.37
130.84
125.66
124.51
122.34
118.40
77.58
77.16
76.74
44.15
39.94
32.54
17.05
Cl
N
N
CN
O
1f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

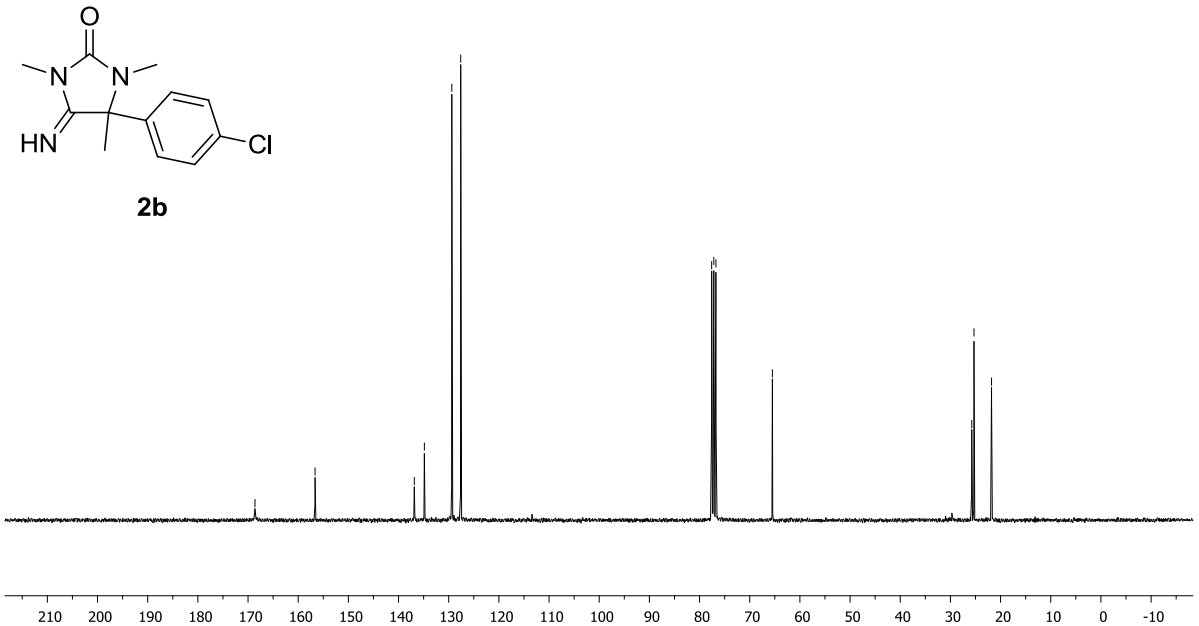


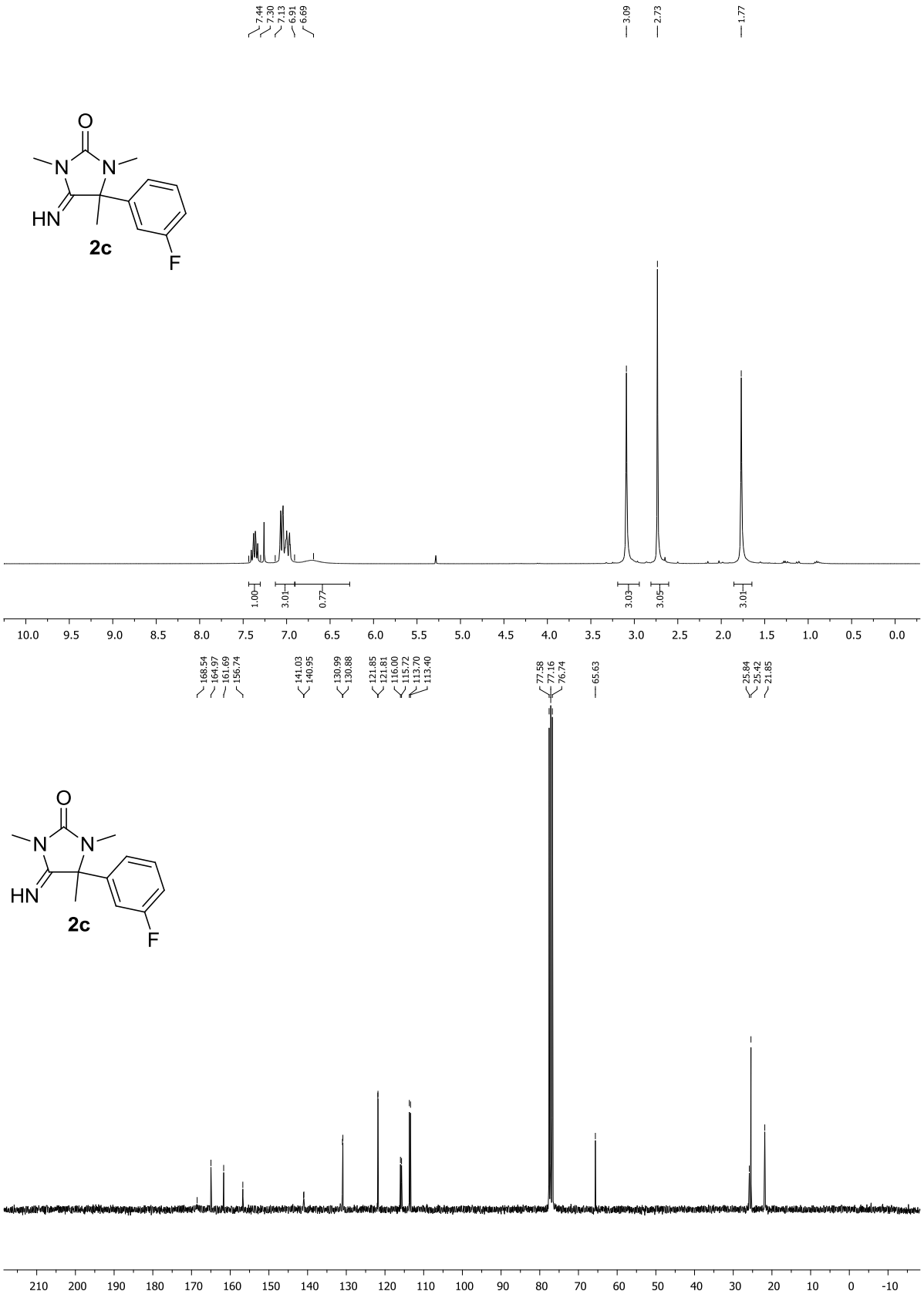
2a



2a






7.44
7.30
7.13
6.91
6.69
3.09
2.73
1.77
2c
1.00
3.01
0.77
3.03
3.05
3.01
168.54
164.97
161.69
156.74
141.03
140.95
130.99
130.88
121.85
121.81
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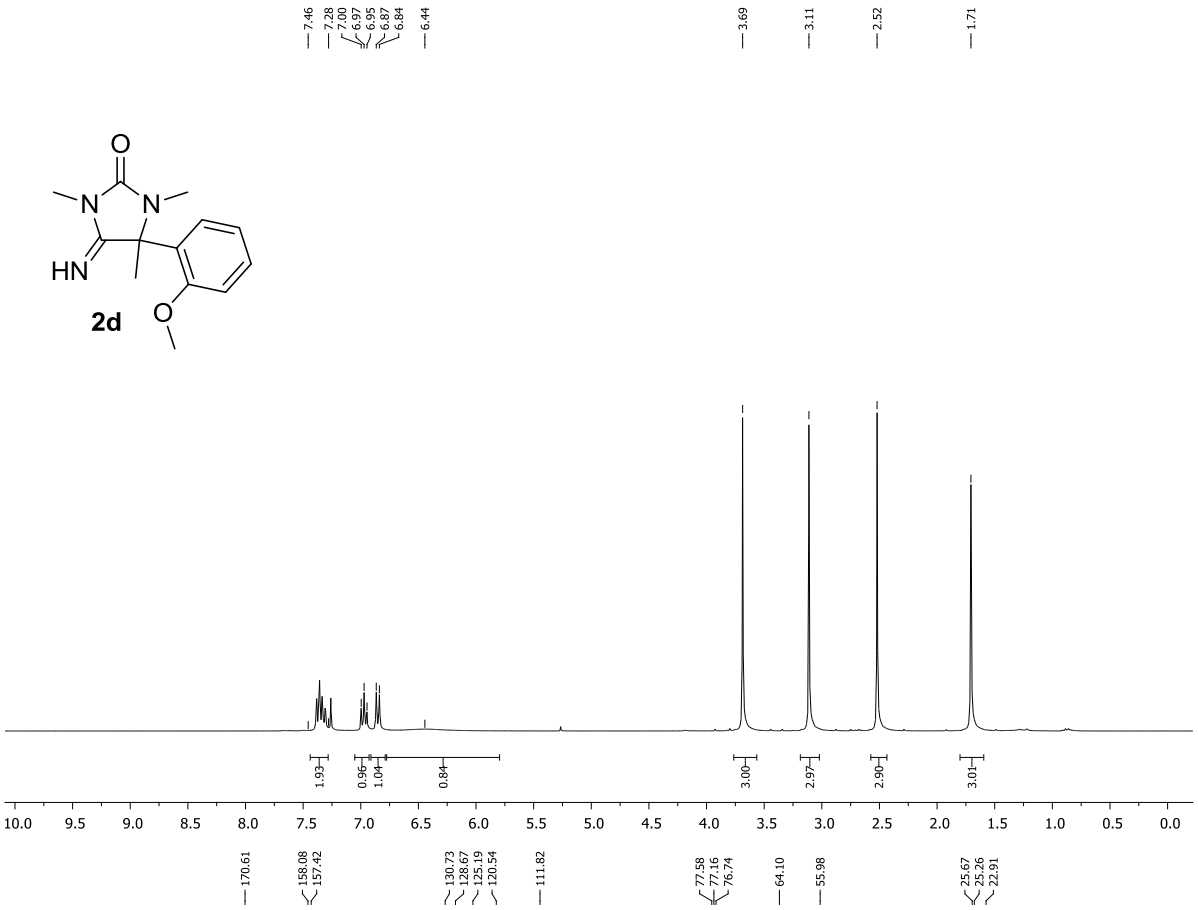
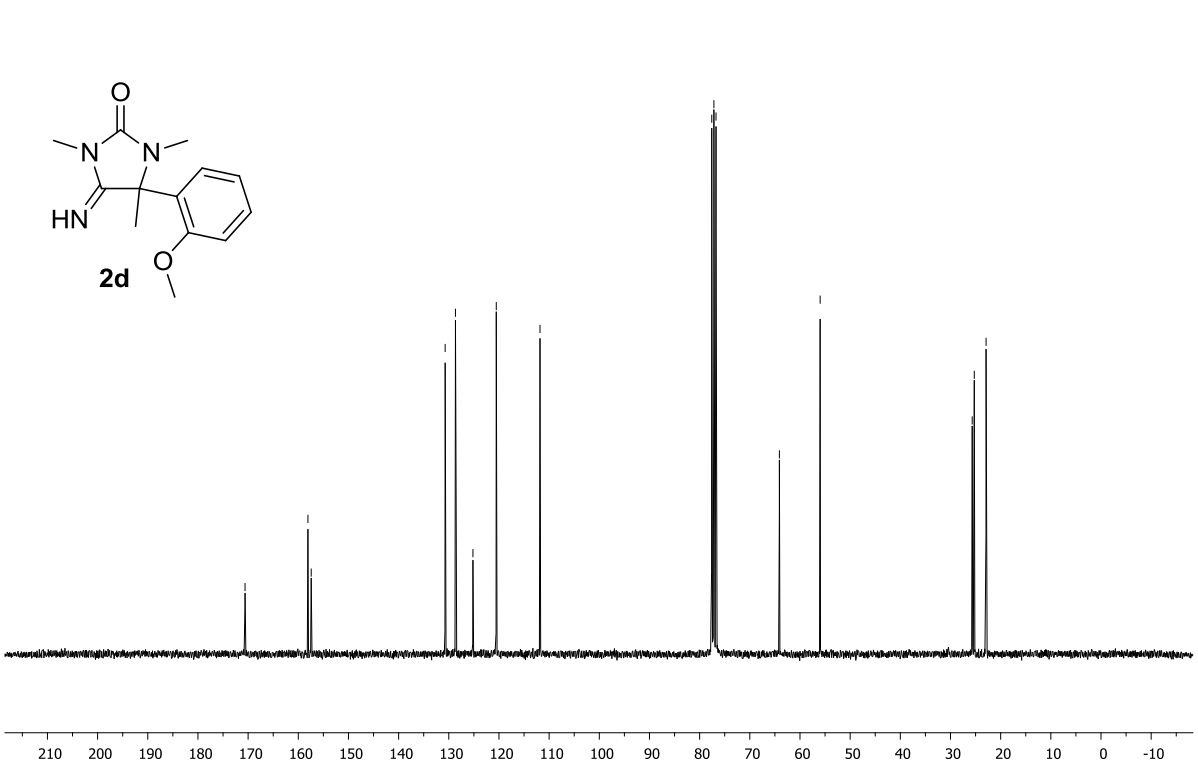
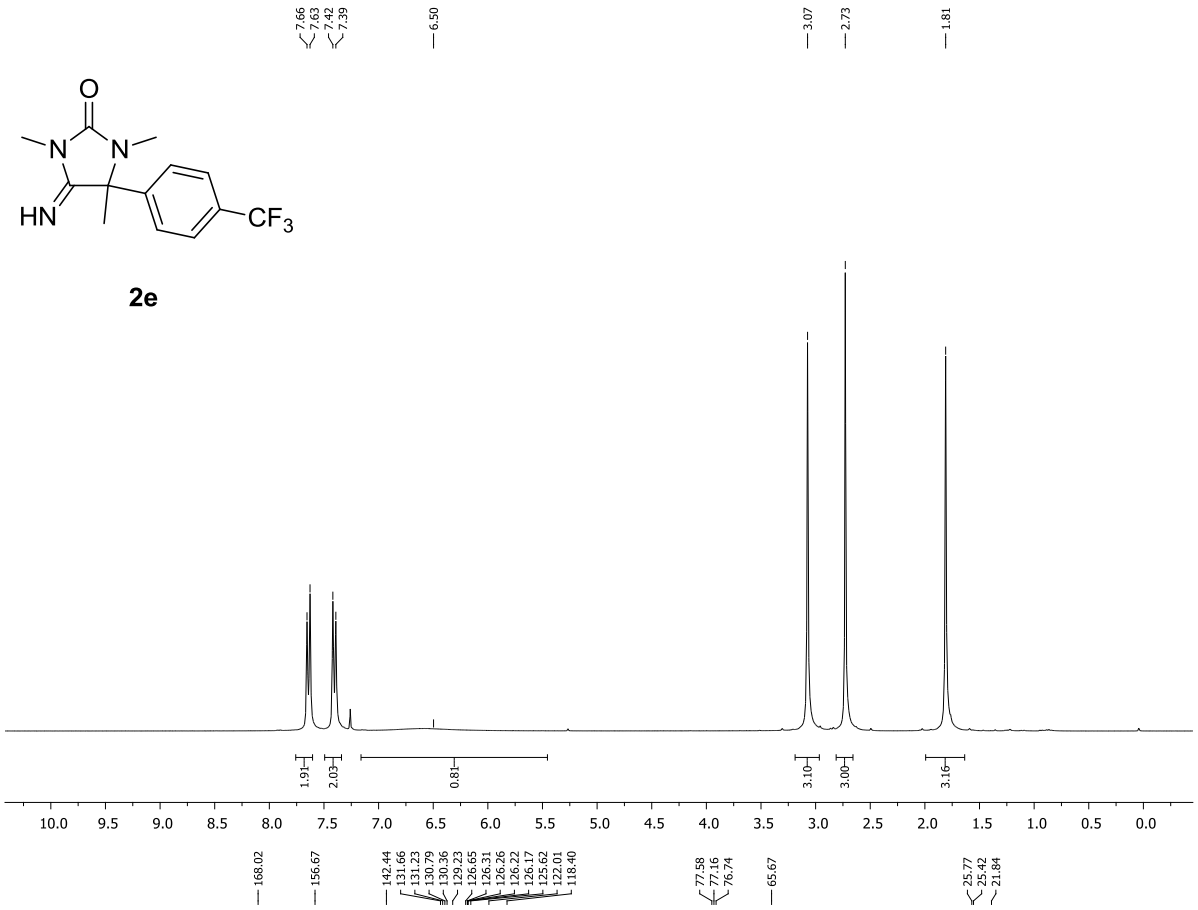
76.74
65.63
25.84
25.42
21.85
2c


7.46
7.28
7.00
6.97
6.95
6.87
6.84
6.44
3.69
3.11
2.52
1.71
2d
1.93
0.96
1.04
0.84
3.00
2.97
2.90
3.01
10.0 9.5 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


170.61
158.08
157.42
130.73
128.67
125.19
120.54
111.82
77.58
77.16
76.74
64.10
55.98
25.67
25.26
22.91
2d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10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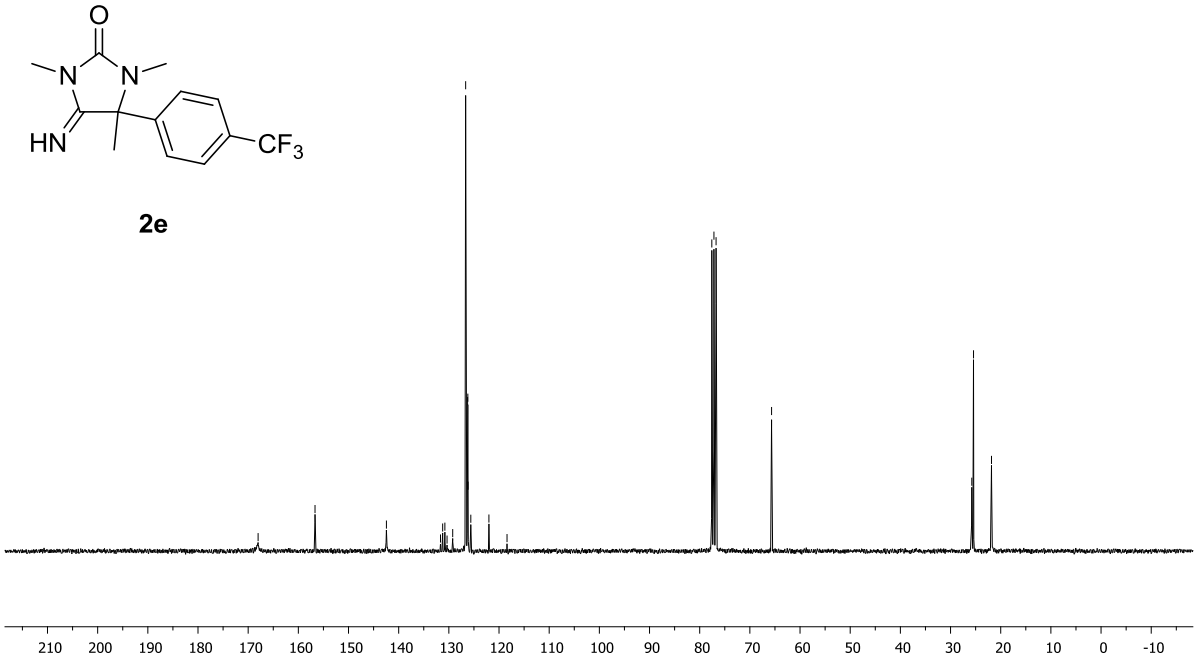
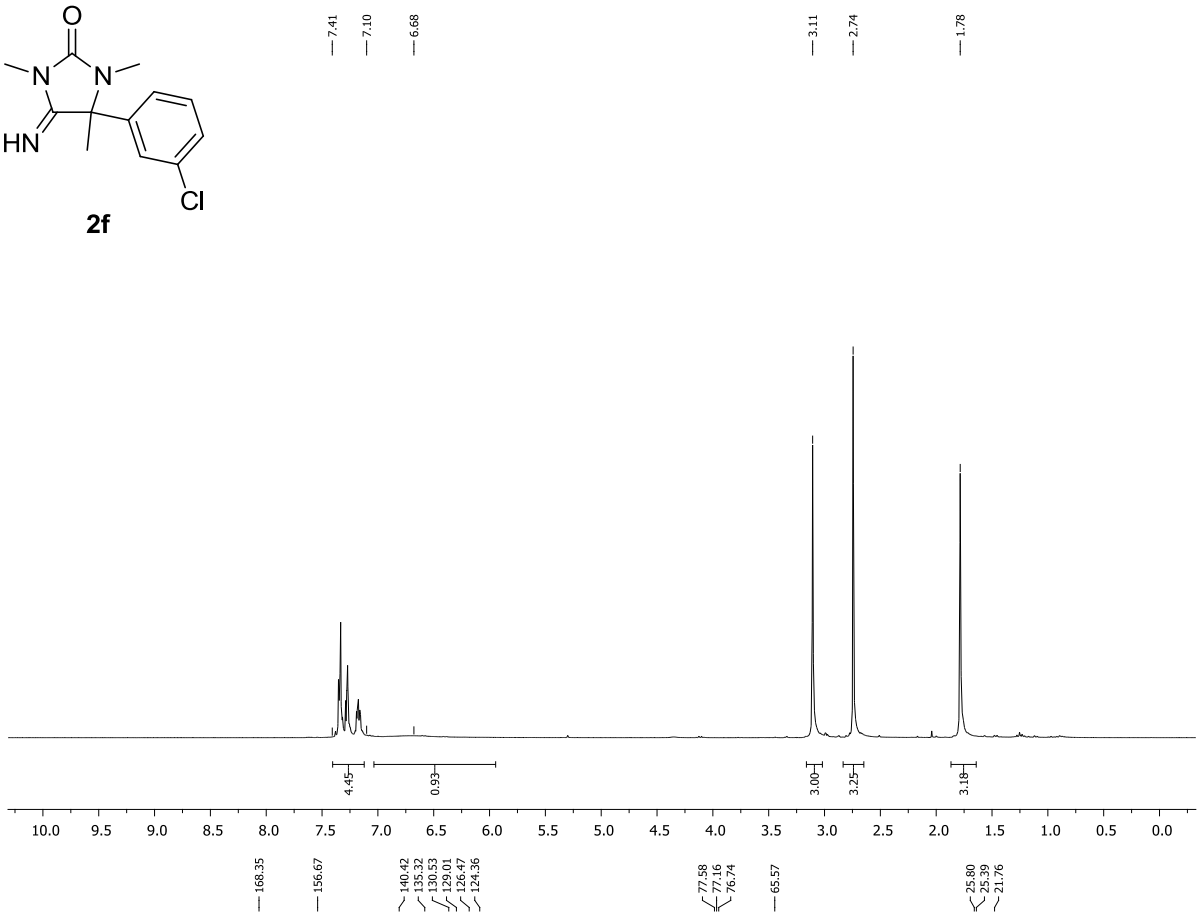
7.63
7.42
7.39
6.50
3.07
2.73
1.81
O
N
N
HN
CF3
1.91
2.03
0.81
3.10
3.00
3.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
168.02
156.67
142.44
131.66
131.23
130.79
130.36
129.23
126.65
126.31
126.26
126.22
126.17
125.62
122.01
118.40
77.58
77.16
76.74
65.67
25.77
25.42
21.84

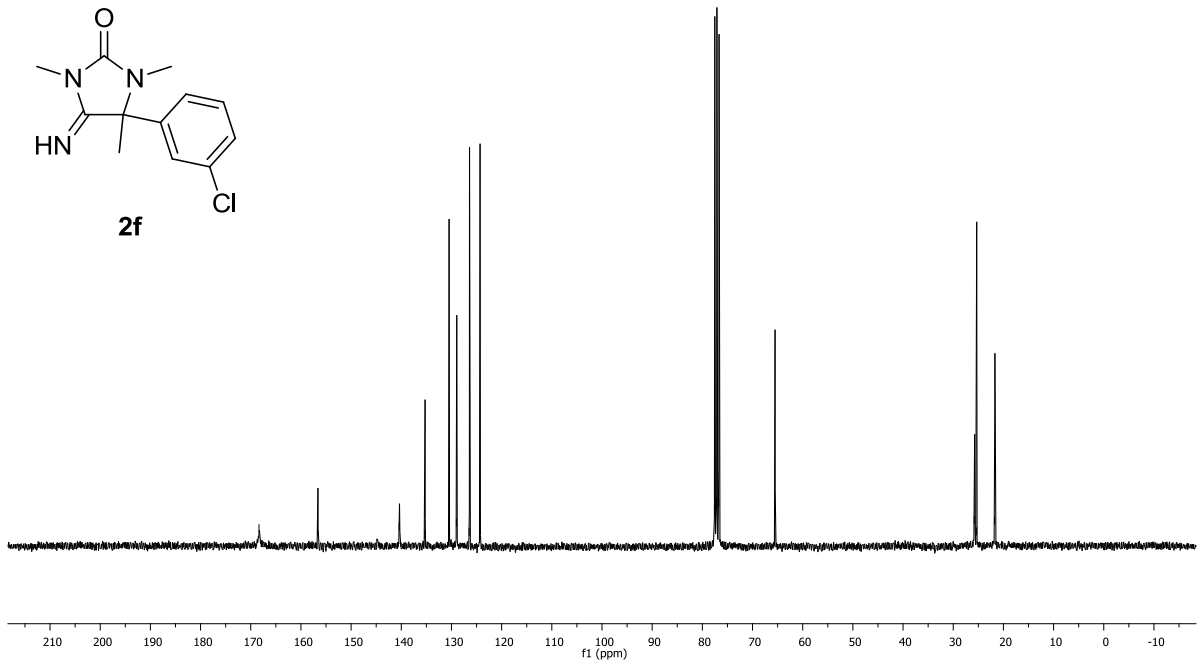
2e


O
N
N
HN
CF3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

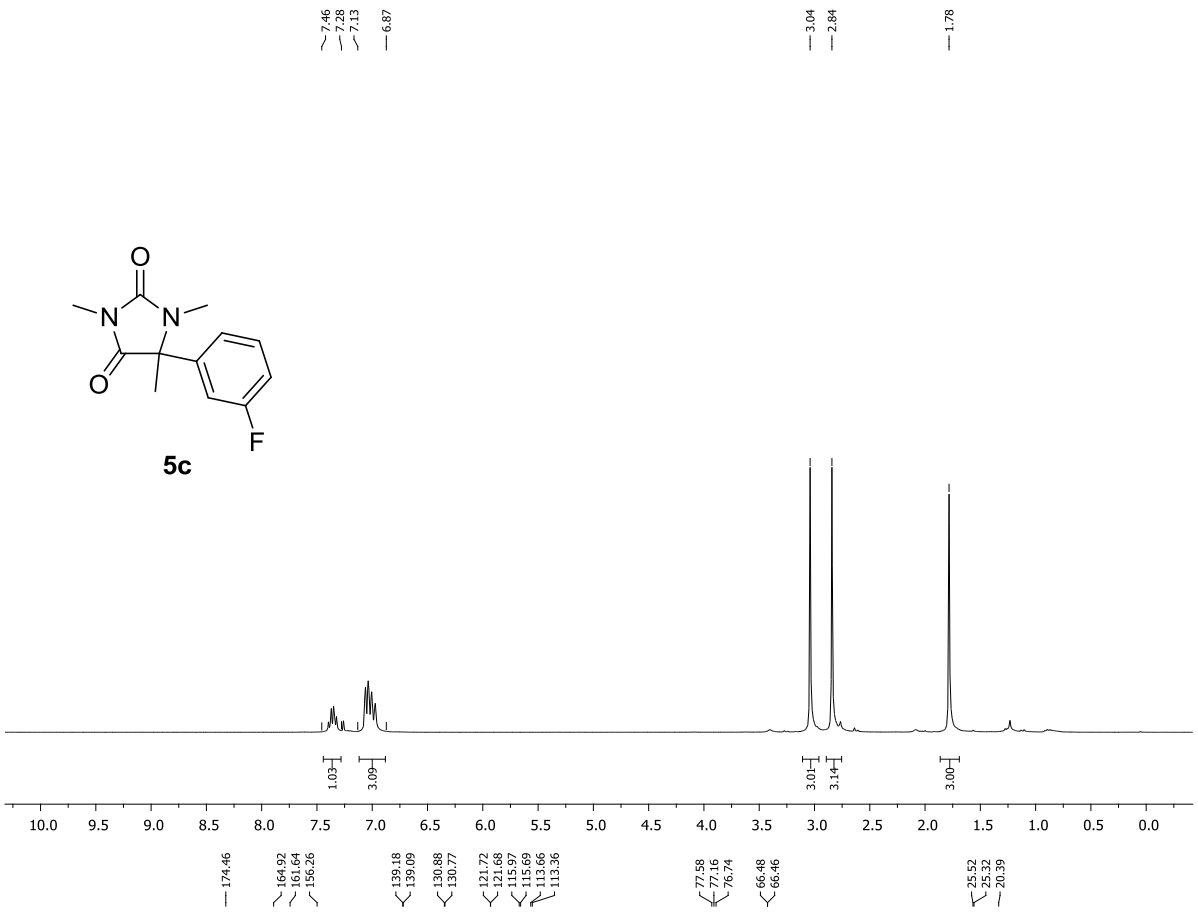
2e

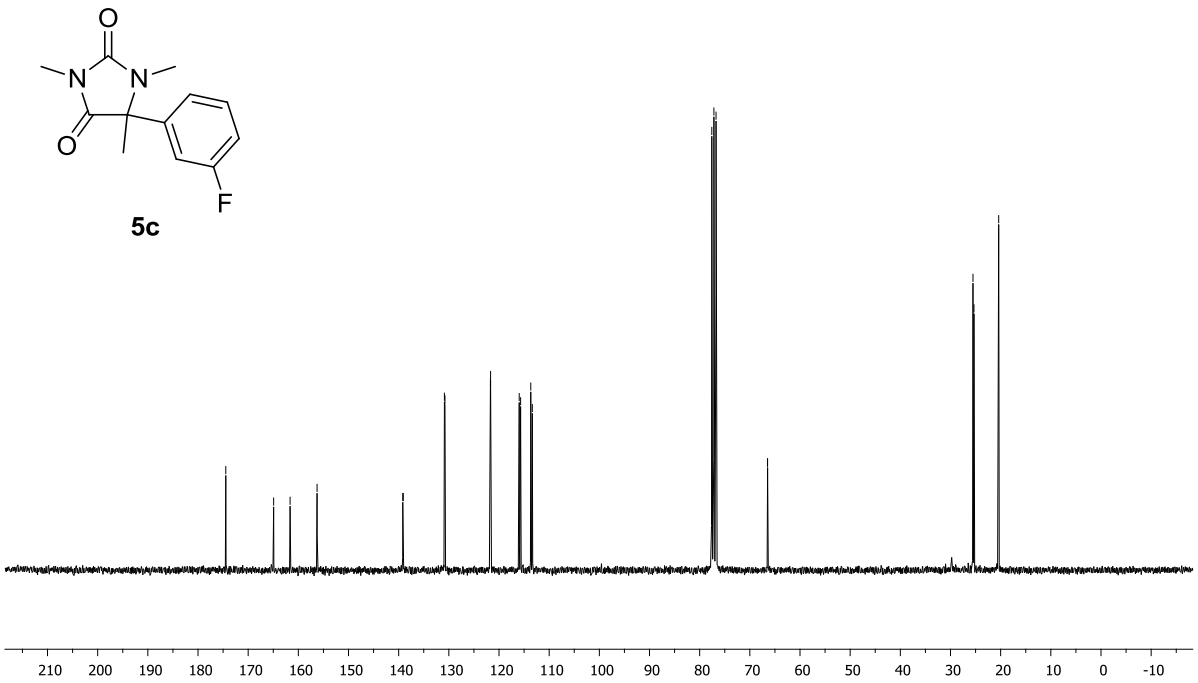

7.41
7.10
6.68
3.11
2.74
1.78
4.45
0.93
3.00
3.25
3.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

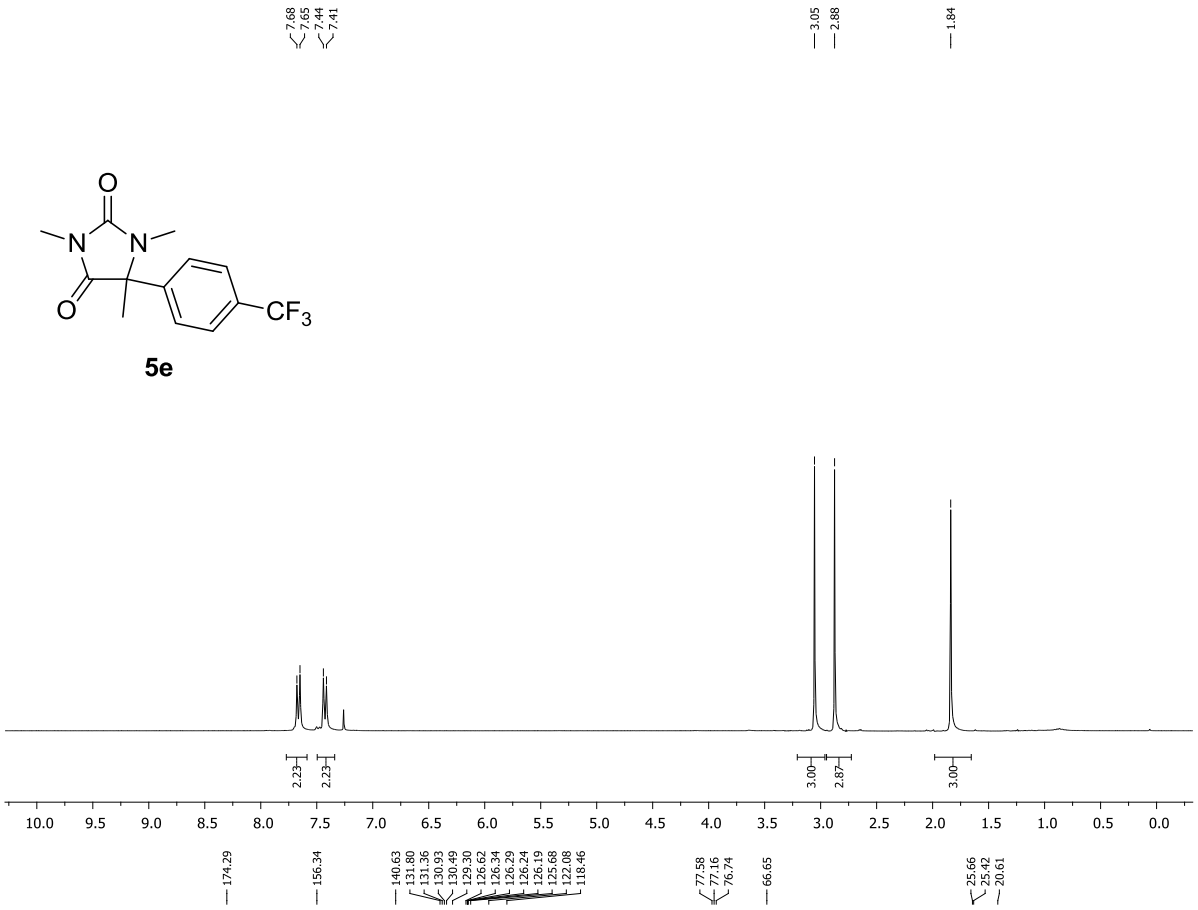
2f

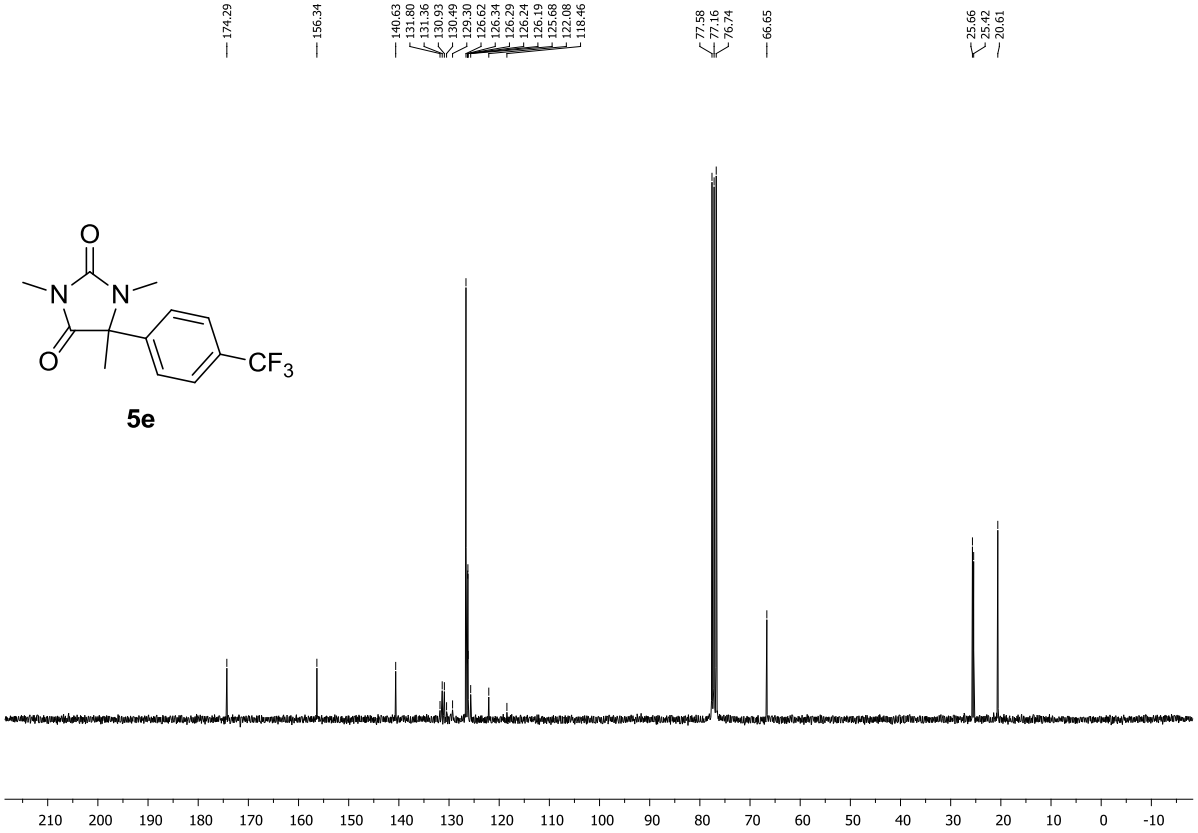

168.35
156.67
140.42
135.32
130.53
129.01
126.47
124.36
77.58
77.16
76.74
65.57
25.80
25.39
21.76
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

2f

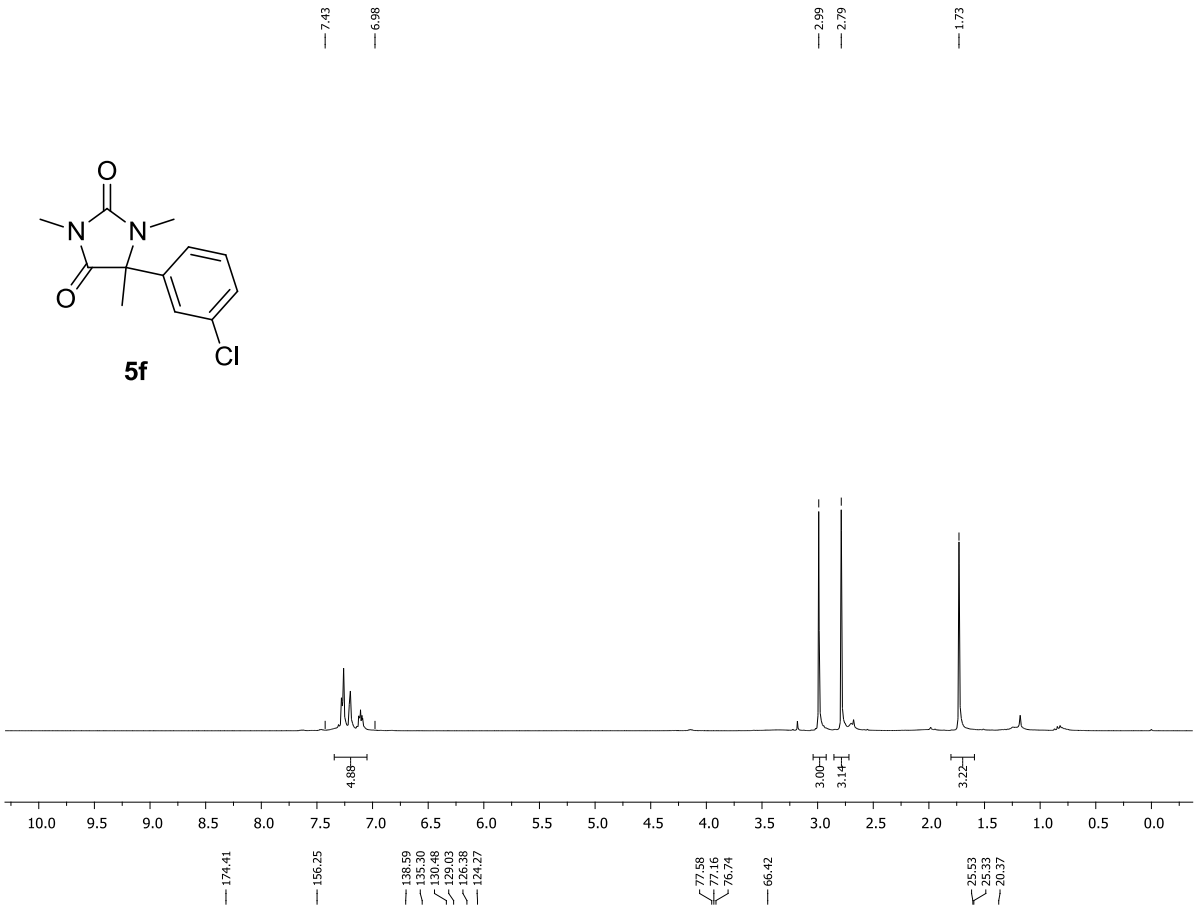

7.46
7.28
7.13
6.87
3.04
2.84
1.78
5c
1.03
3.09
3.01
3.14
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

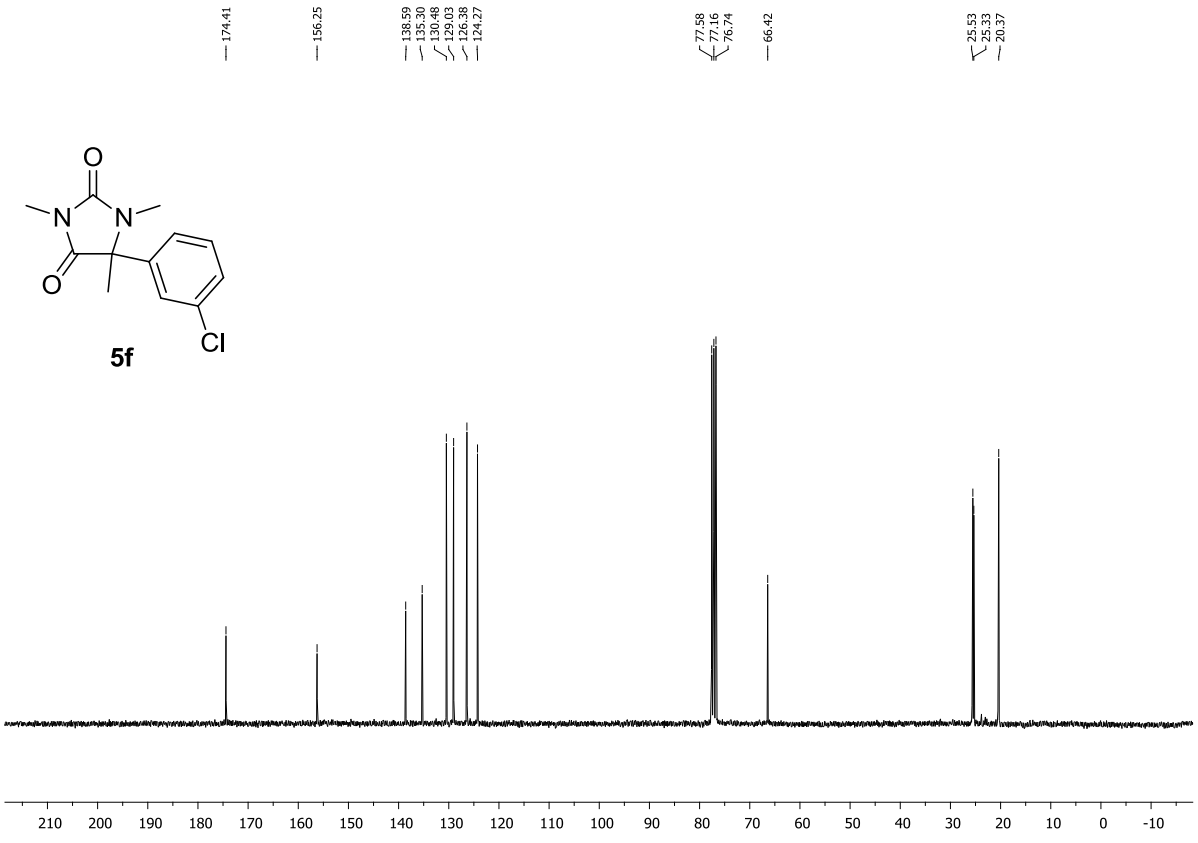

174.46
164.92
161.64
156.26
139.18
139.09
130.88
130.77
121.72
121.68
115.97
115.69
113.66
113.36
77.58
77.16
76.74
66.48
66.46
25.52
25.32
20.39
5c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

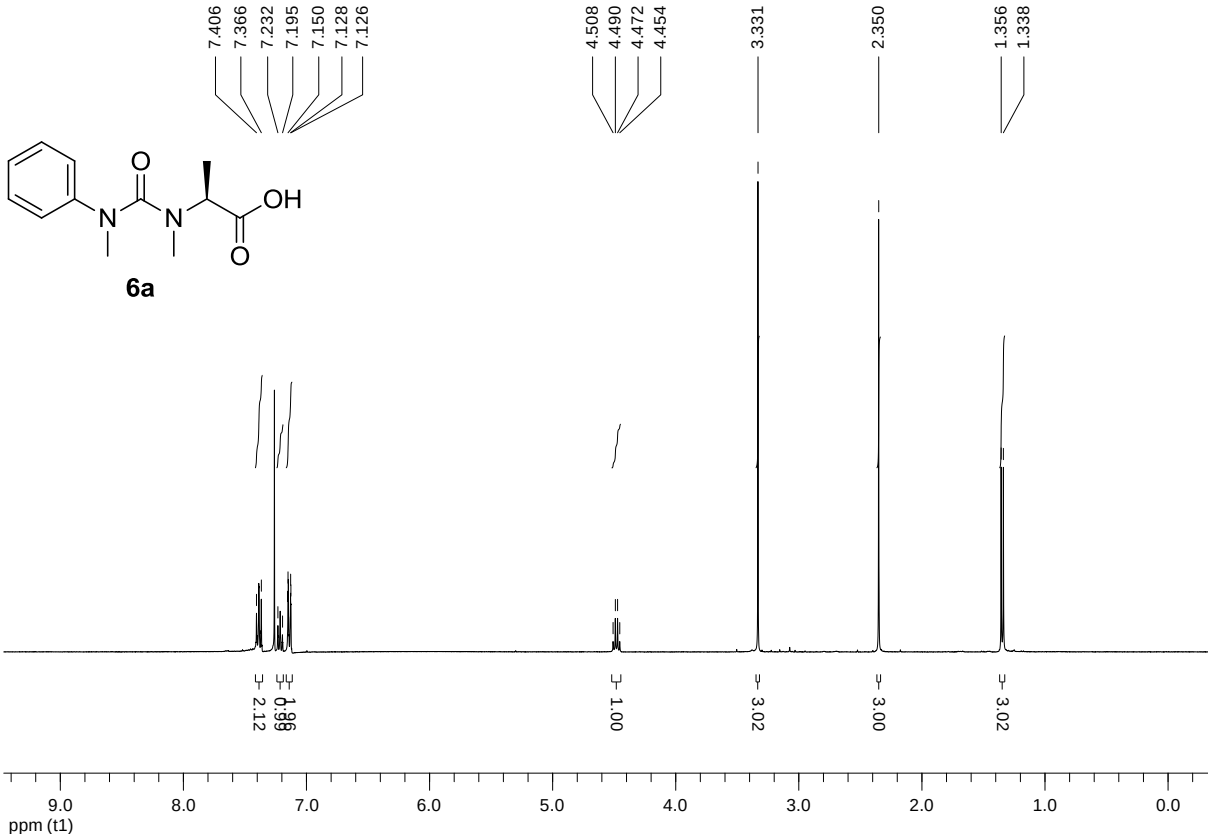

7.68
7.65
7.44
7.41
3.05
2.88
1.84
O
N
N
O
CF3
5e
2.23
2.23
3.00
2.87
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

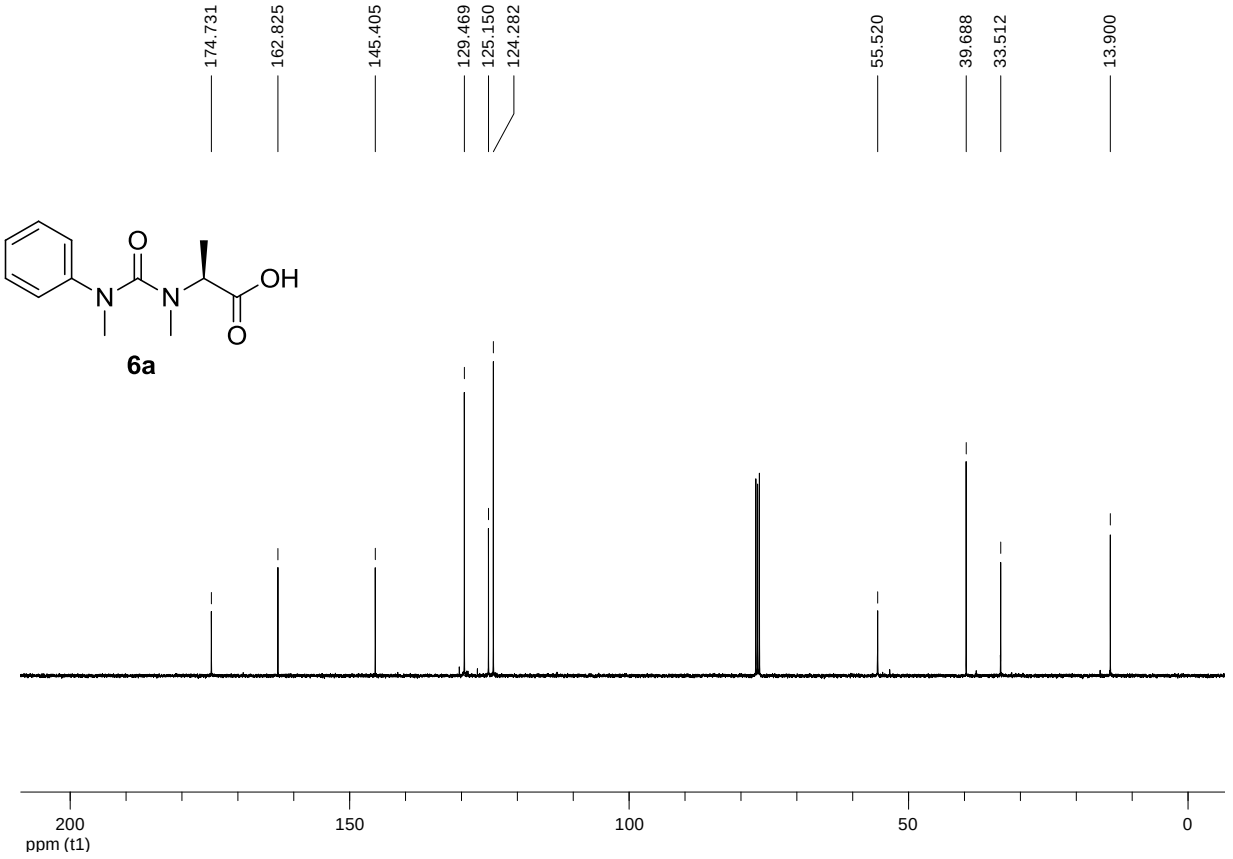

174.29
156.34
140.63
131.80
131.36
130.93
130.49
129.30
126.62
126.34
126.29
126.24
126.19
125.68
122.08
118.46
77.58
77.16
76.74
66.65
25.66
25.42
20.61

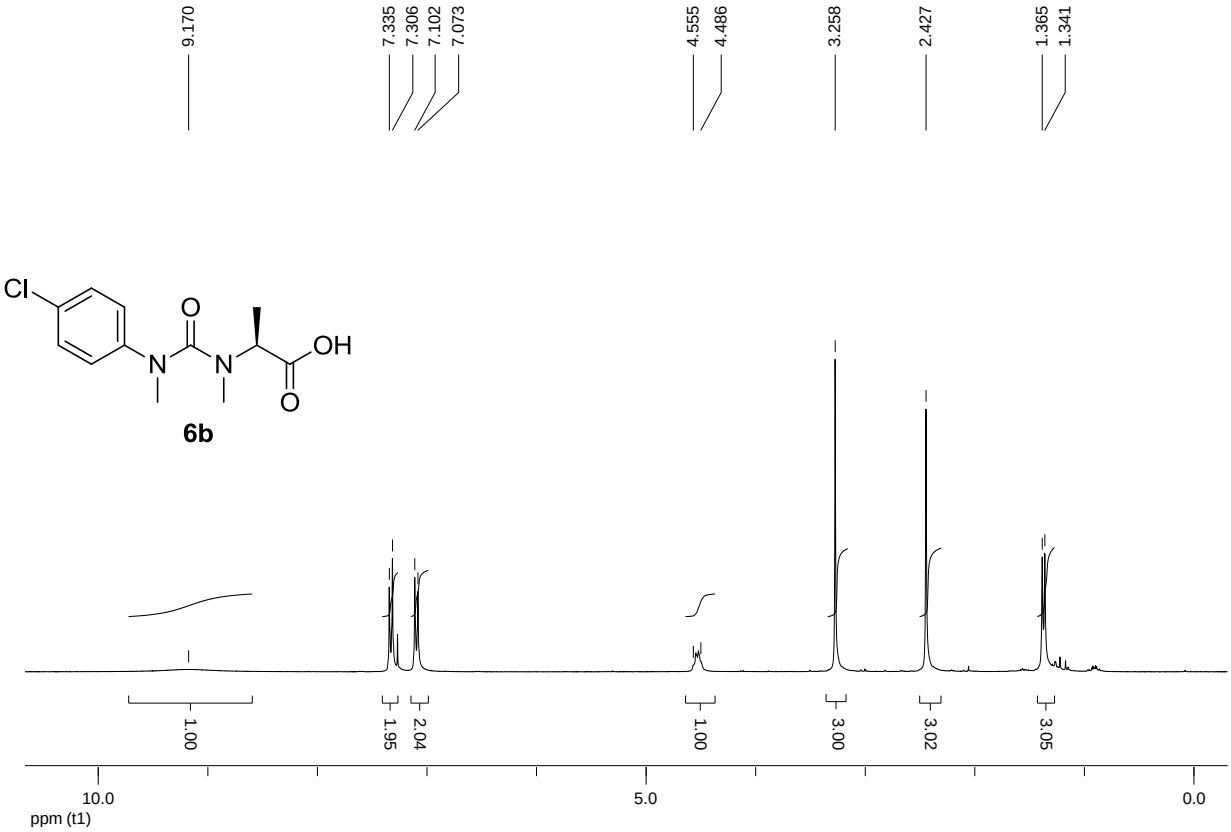
O
N
N
O
CF3
5e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

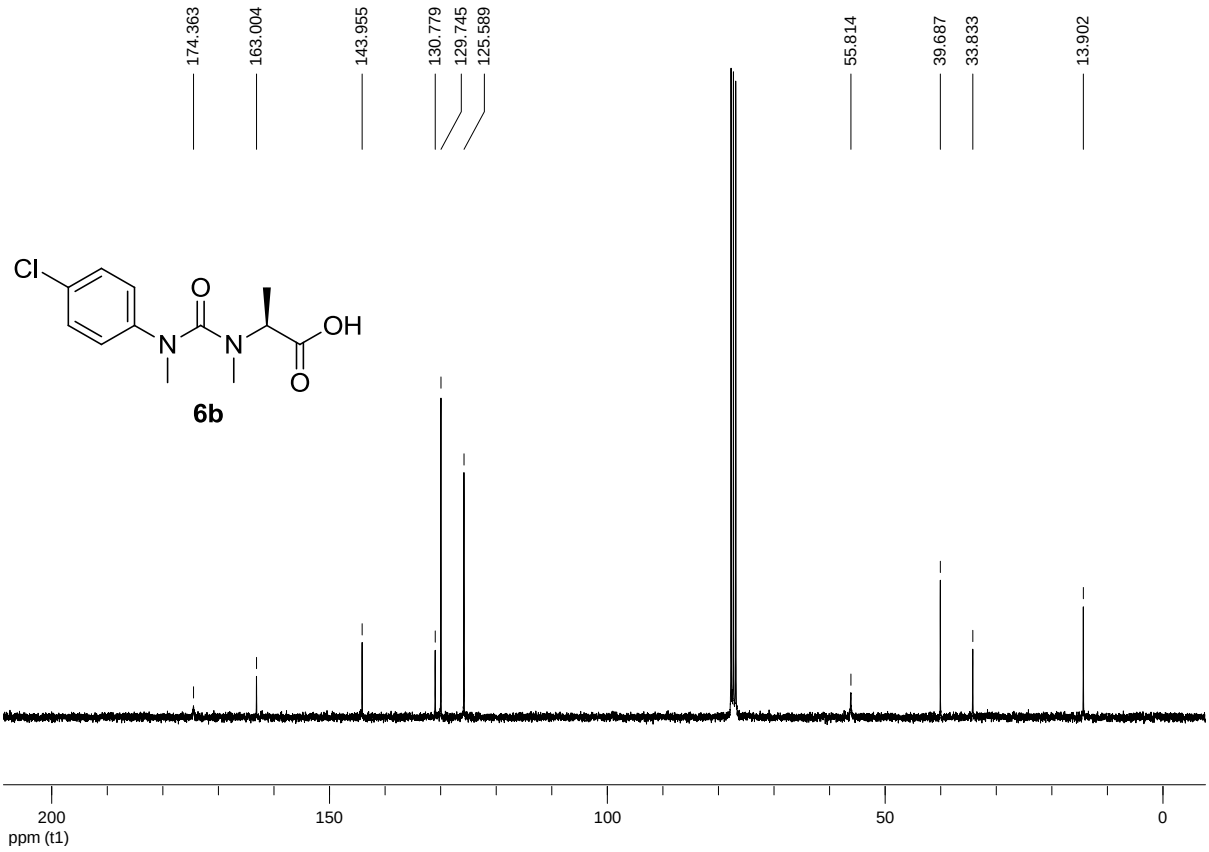

7.43
6.98
2.99
2.79
1.73
5f
4.88
3.00
3.14
3.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

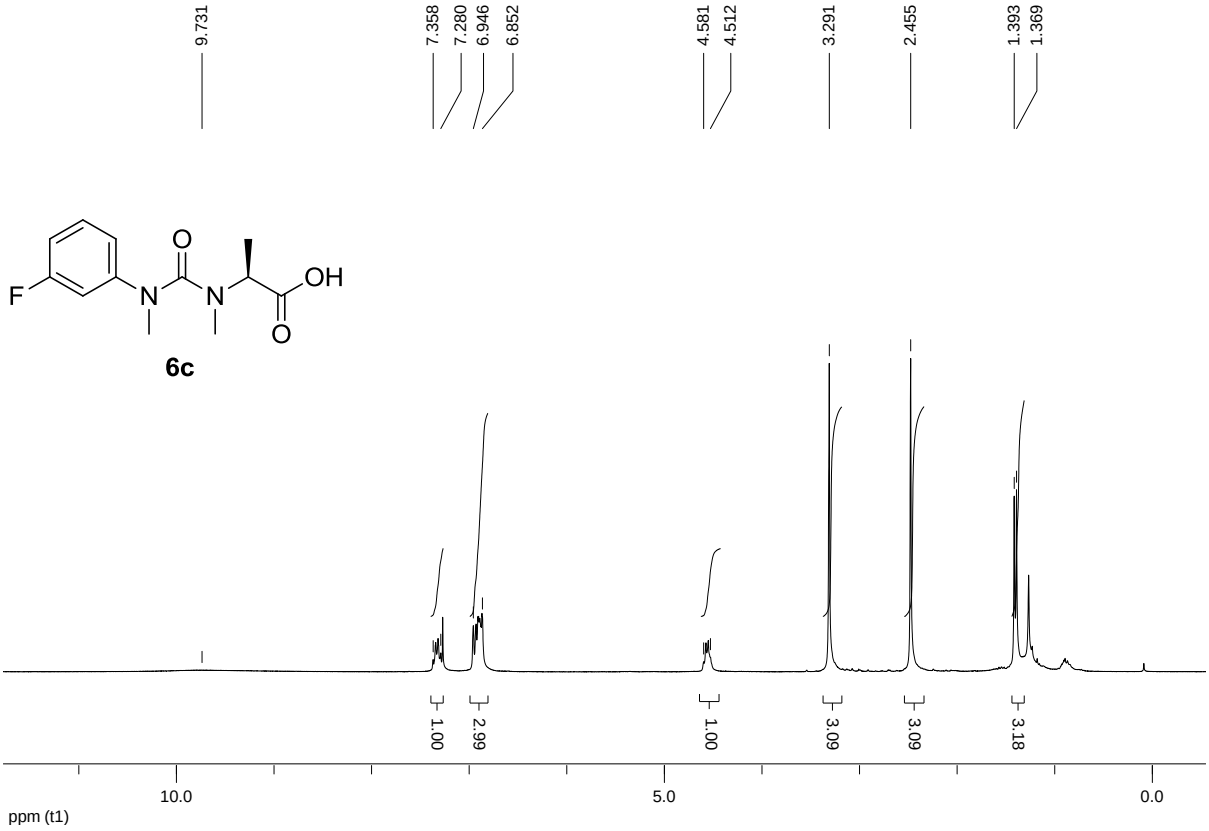

174.41
156.25
138.59
135.30
130.48
129.03
126.38
124.27
77.58
77.16
76.74
66.42
25.53
25.33
20.37
5f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

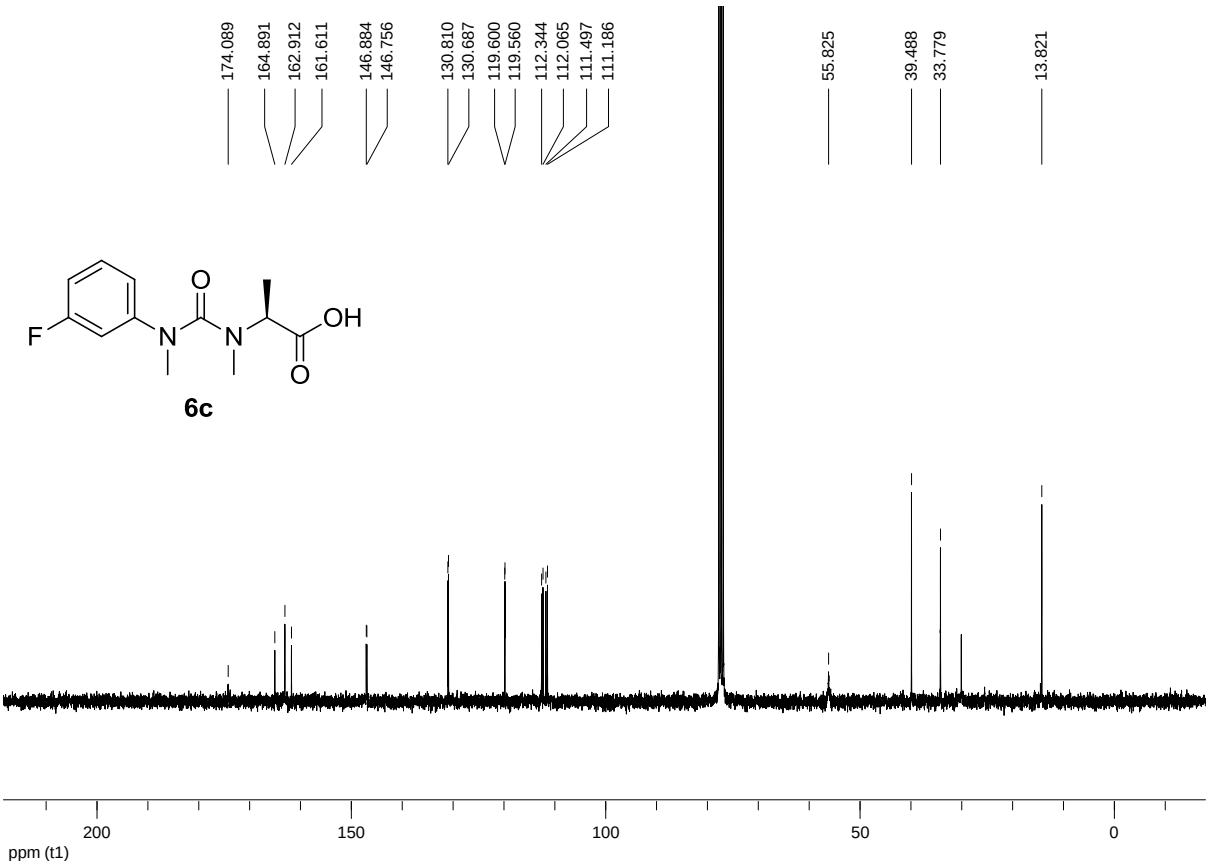

7.406
7.366
7.232
7.195
7.150
7.128
7.126
4.508
4.490
4.472
4.454
3.331
2.350
1.356
1.338
O
N
N
OH
O
6a
2.12
1.98
1.00
3.02
3.00
3.02
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

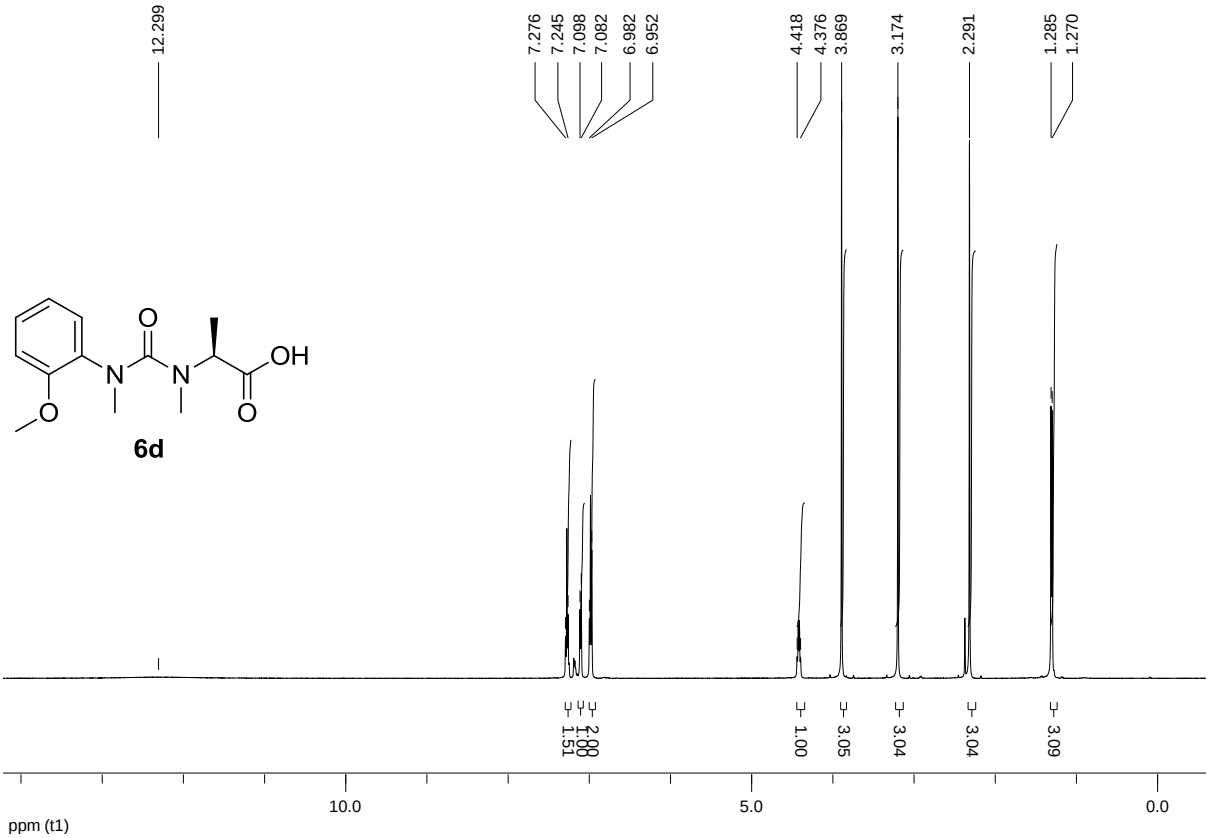

174.731
162.825
145.405
129.469
125.150
124.282
55.520
39.688
33.512
13.900
O
N
N
OH
O
6a
200
150
100
50
0
ppm (t1)

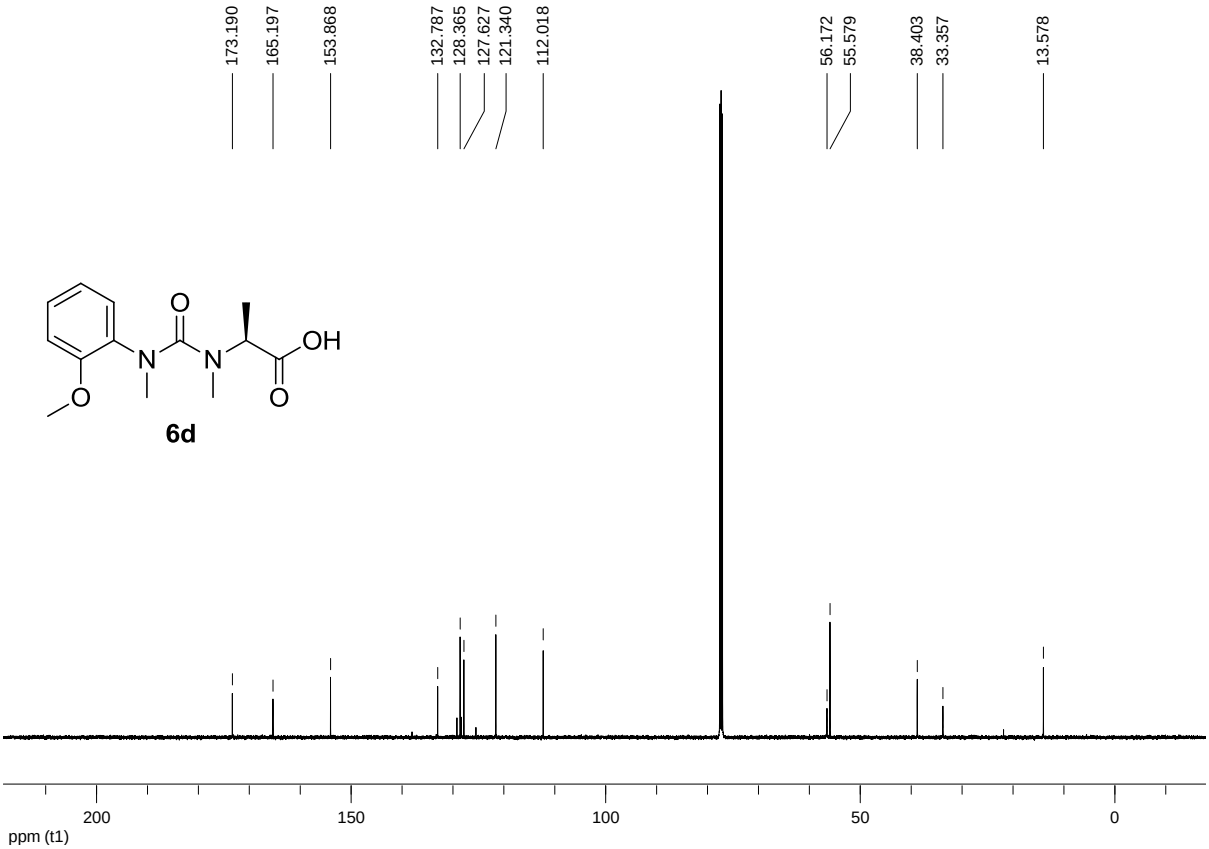

9.170
7.335
7.306
7.102
7.073
4.555
4.486
3.258
2.427
1.365
1.341
Cl
O
N
N
OH
O
6b
1.00
1.95
2.04
1.00
3.00
3.02
3.05
10.0
5.0
0.0
ppm (t1)

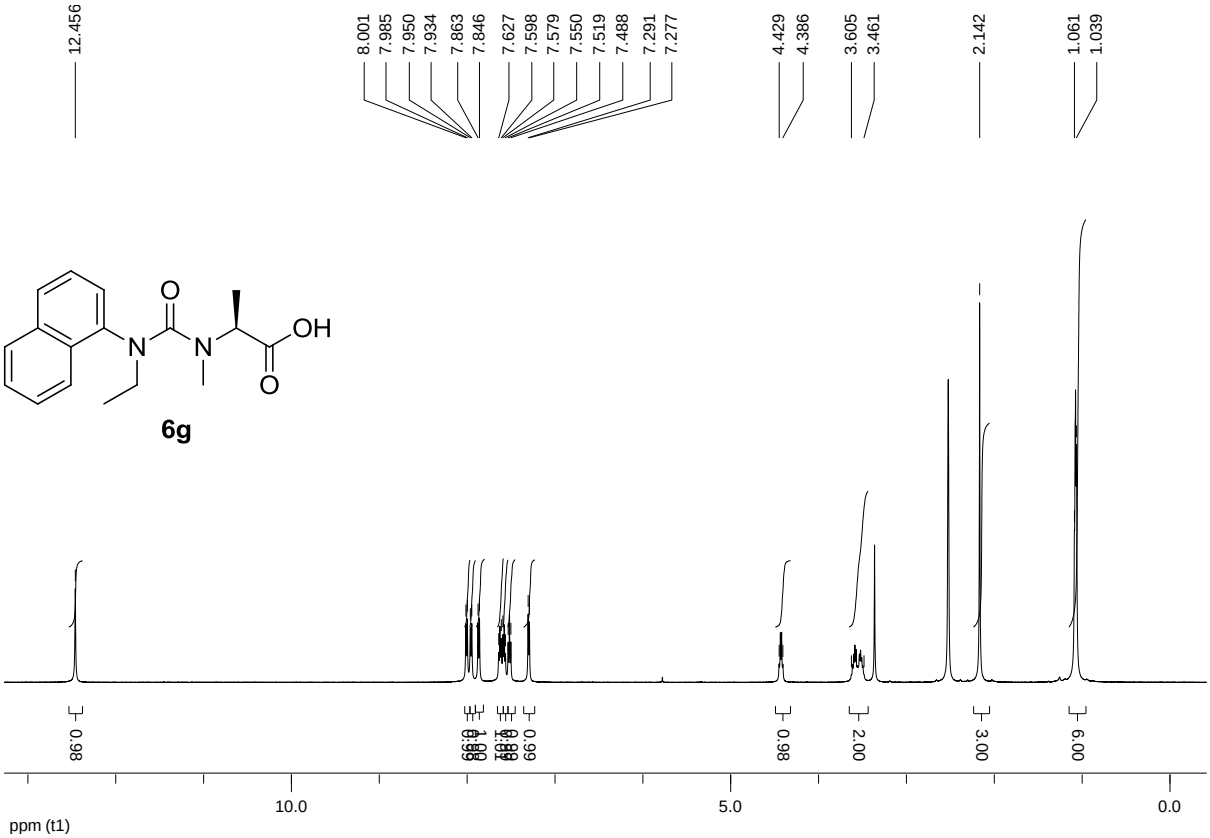

174.363
163.004
143.955
130.779
129.745
125.589
55.814
39.687
33.833
13.902
Cl
O
N
N
OH
O
6b
200
150
100
50
0
ppm (t1)

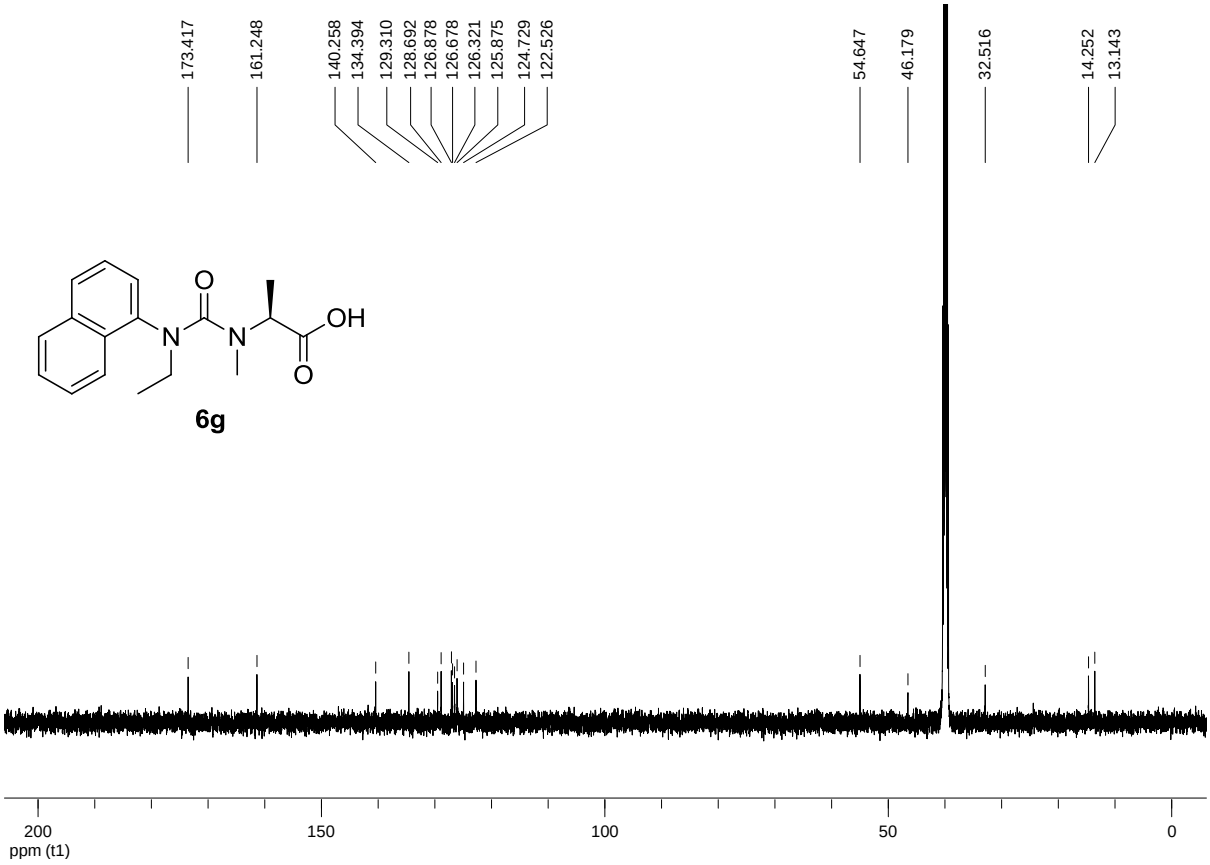

9.731
7.358
7.280
6.946
6.852
4.581
4.512
3.291
2.455
1.393
1.369
F
N
O
N
OH
O
6c
1.00
2.99
1.00
3.09
3.09
3.18
10.0
5.0
0.0
ppm (t1)

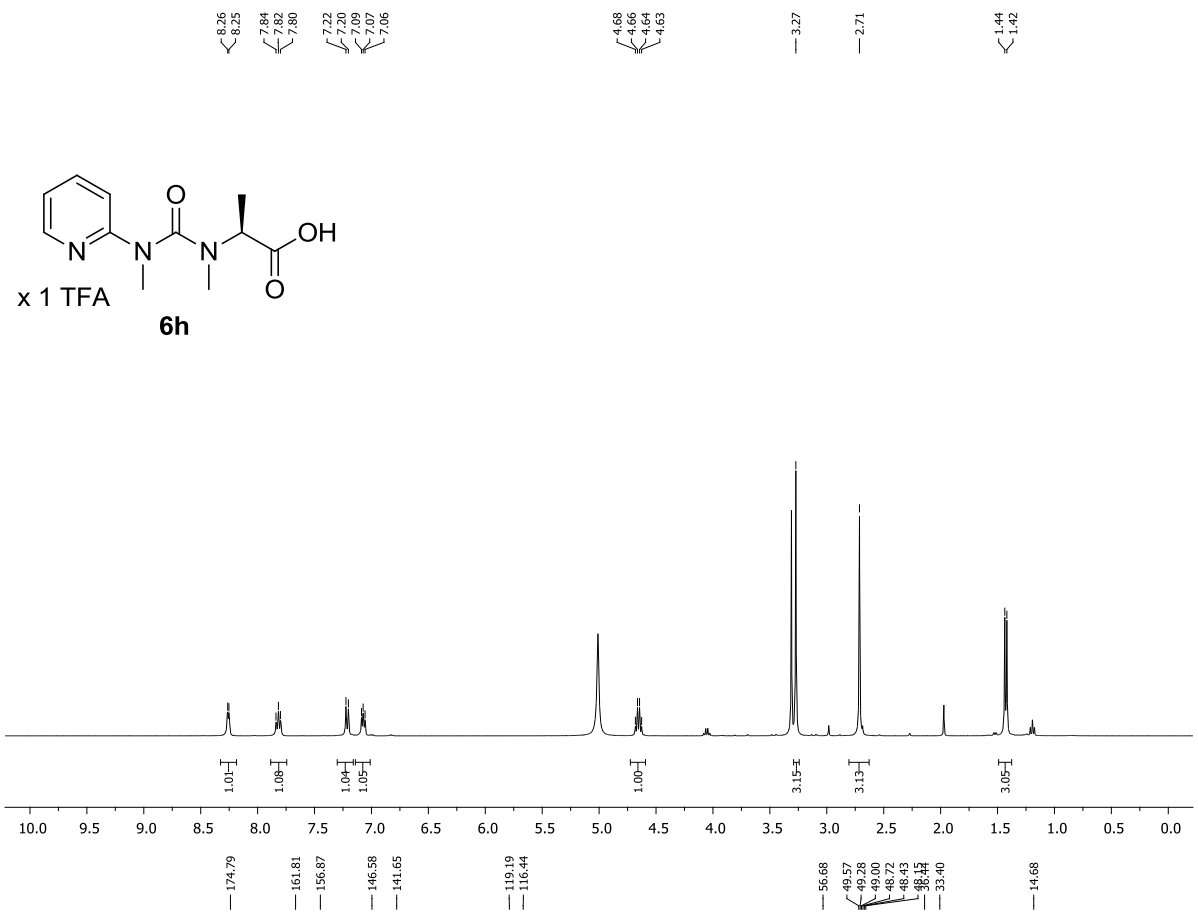

174.089
164.891
162.912
161.611
146.884
146.756
130.810
130.687
119.600
119.560
112.344
112.065
111.497
111.186
55.825
39.488
33.779
13.821
F
N
O
N
OH
O
6c
200
150
100
50
0
ppm (t1)

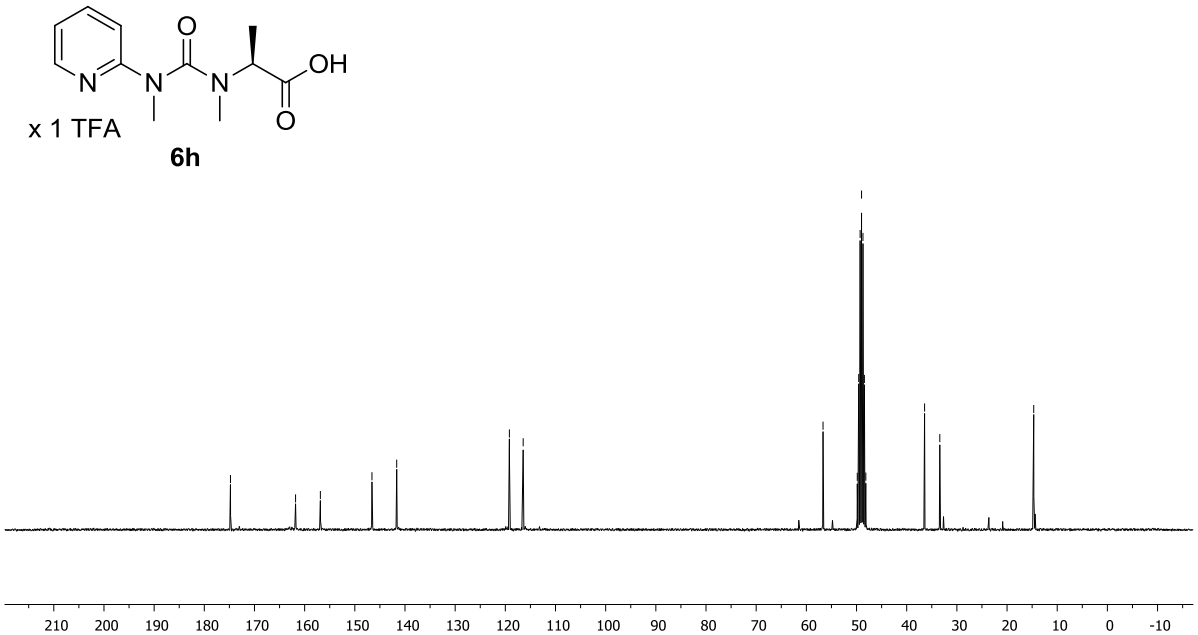

12.299
7.276
7.245
7.098
7.082
6.982
6.952
4.418
4.376
3.869
3.174
2.291
1.285
1.270
1.51
2.00
1.00
3.05
3.04
3.04
3.09
10.0
5.0
0.0
ppm (t1)
O
N
N
OH
O
O
6d


173.190
165.197
153.868
132.787
128.365
127.627
121.340
112.018
56.172
55.579
38.403
33.357
13.578
200
150
100
50
0
ppm (t1)
O
N
N
OH
O
O
6d

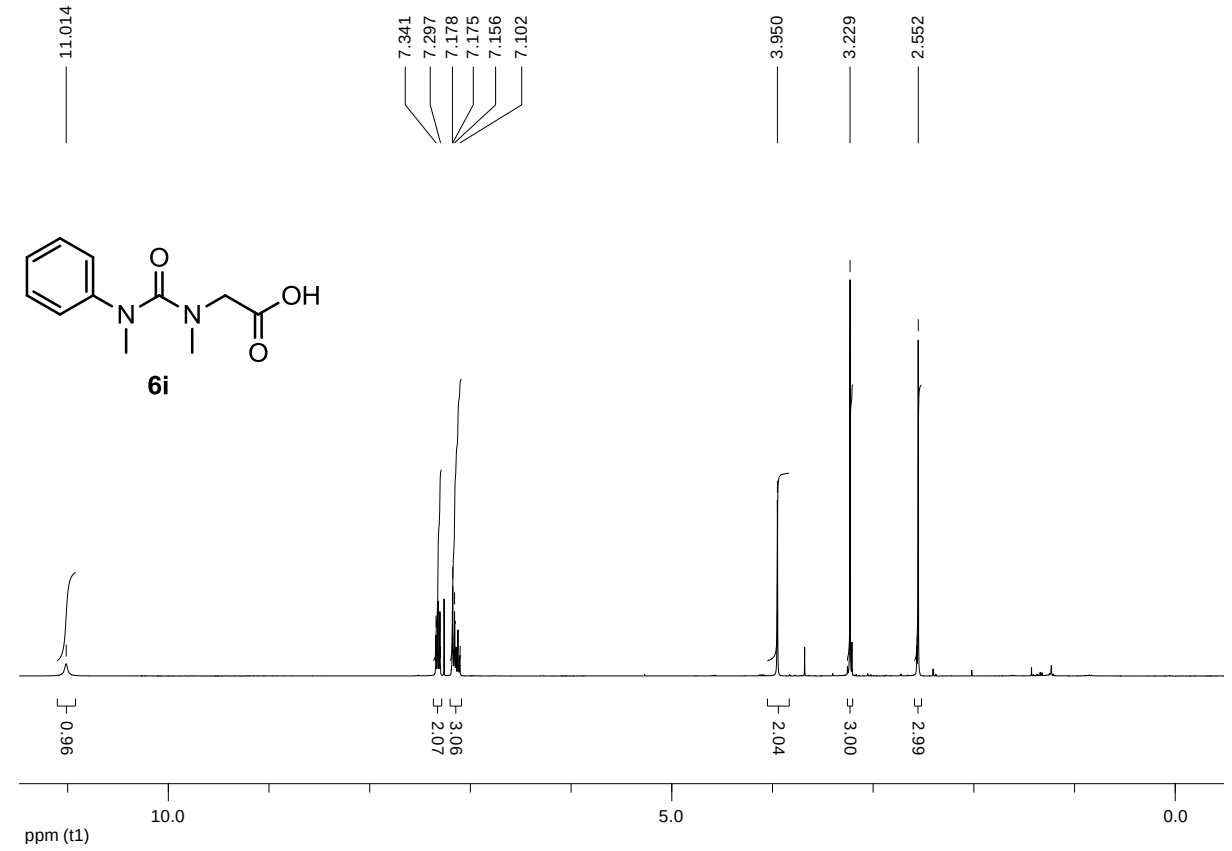

12.456
8.001
7.985
7.950
7.934
7.863
7.846
7.627
7.598
7.579
7.550
7.519
7.488
7.291
7.277
4.429
4.386
3.605
3.461
2.142
1.061
1.039
O
N
N
OH
O
6g
0.98
0.99
0.98
2.00
3.00
6.00
10.0
5.0
0.0
ppm (t1)

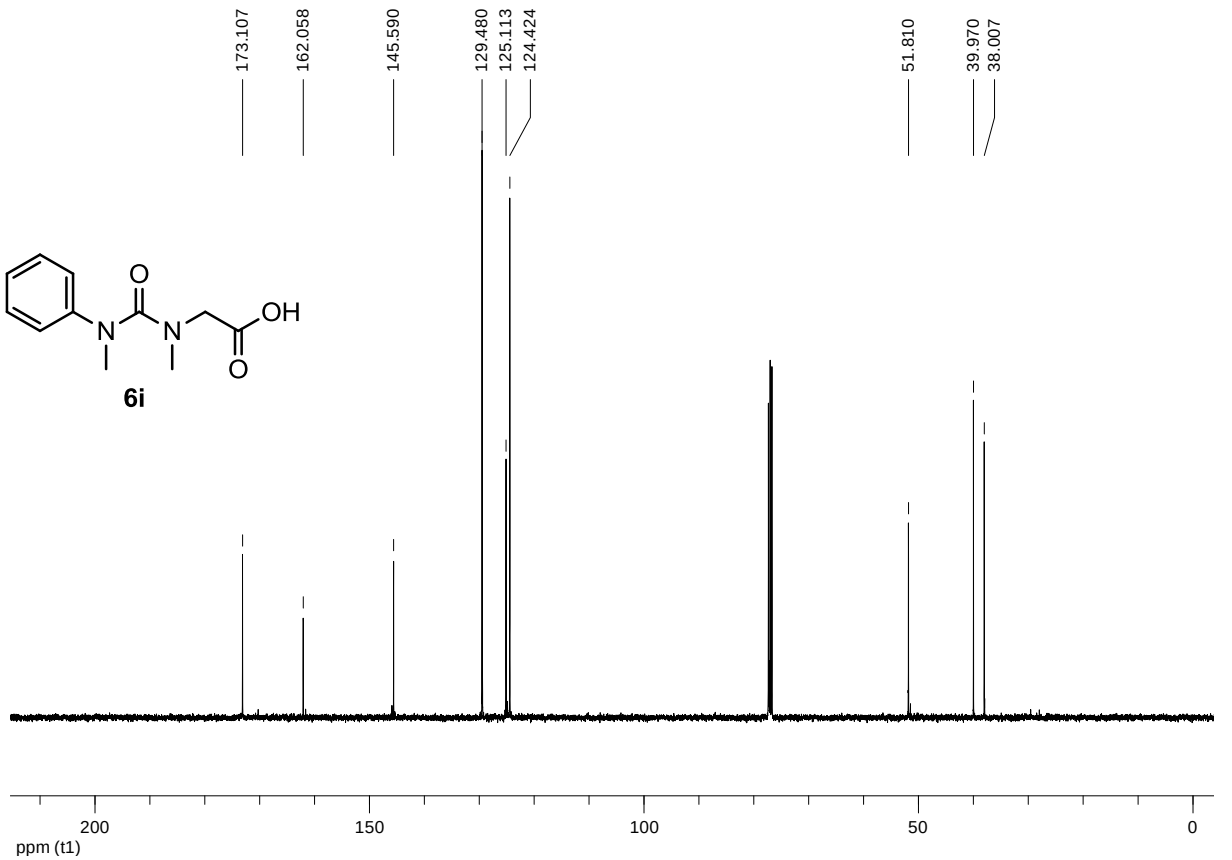

173.417
161.248
140.258
134.394
129.310
128.692
126.878
126.678
126.321
125.875
124.729
122.526
54.647
46.179
32.516
14.252
13.143
O
N
N
OH
O
6g
200
150
100
50
0
ppm (t1)

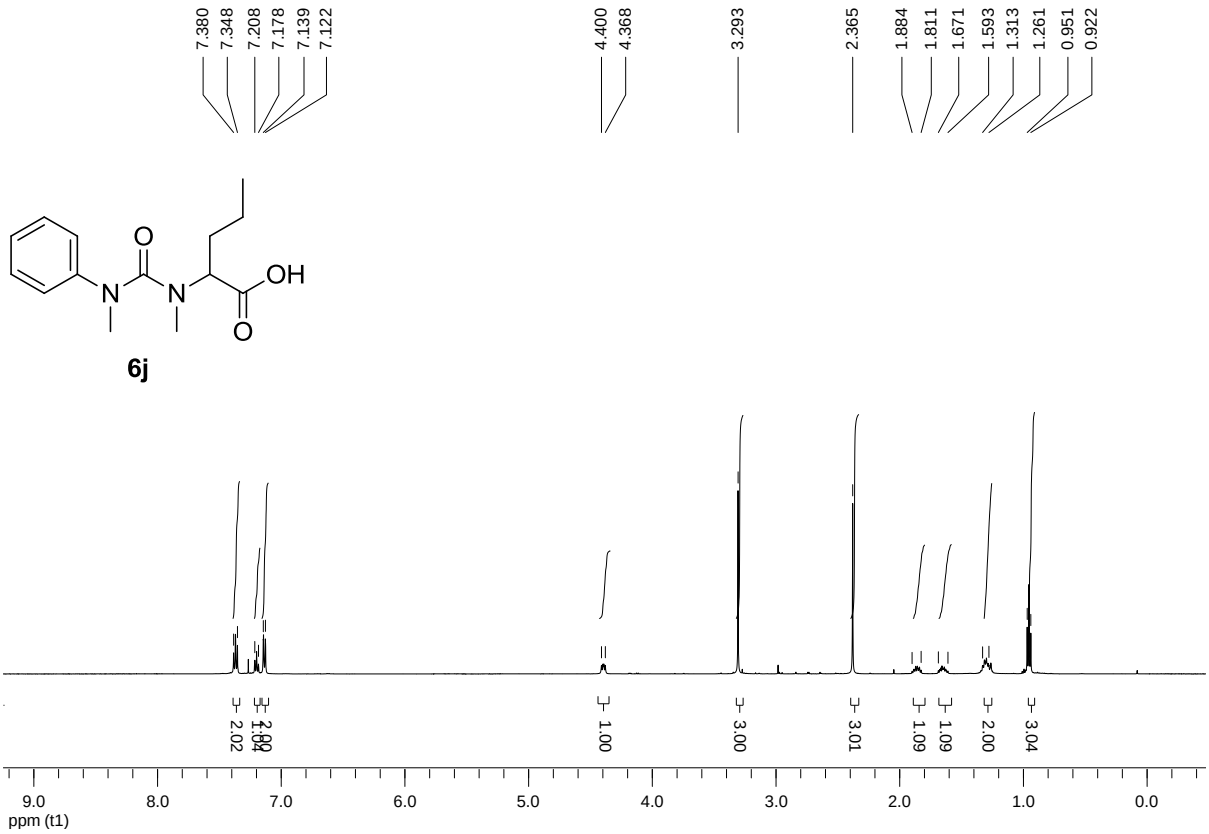

8.26
8.25
7.84
7.82
7.80
7.22
7.20
7.09
7.07
7.06
4.68
4.66
4.64
4.63
3.27
2.71
1.44
1.42
OH
O
N
N
N
O
x 1 TFA
6h
1.01
1.08
1.04
1.05
1.00
3.15
3.13
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
174.79
161.81
156.87
146.58
141.65
119.19
116.44
56.68
49.57
49.28
49.00
48.72
48.43
33.40
14.68


OH
O
N
N
N
O
x 1 TFA
6h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

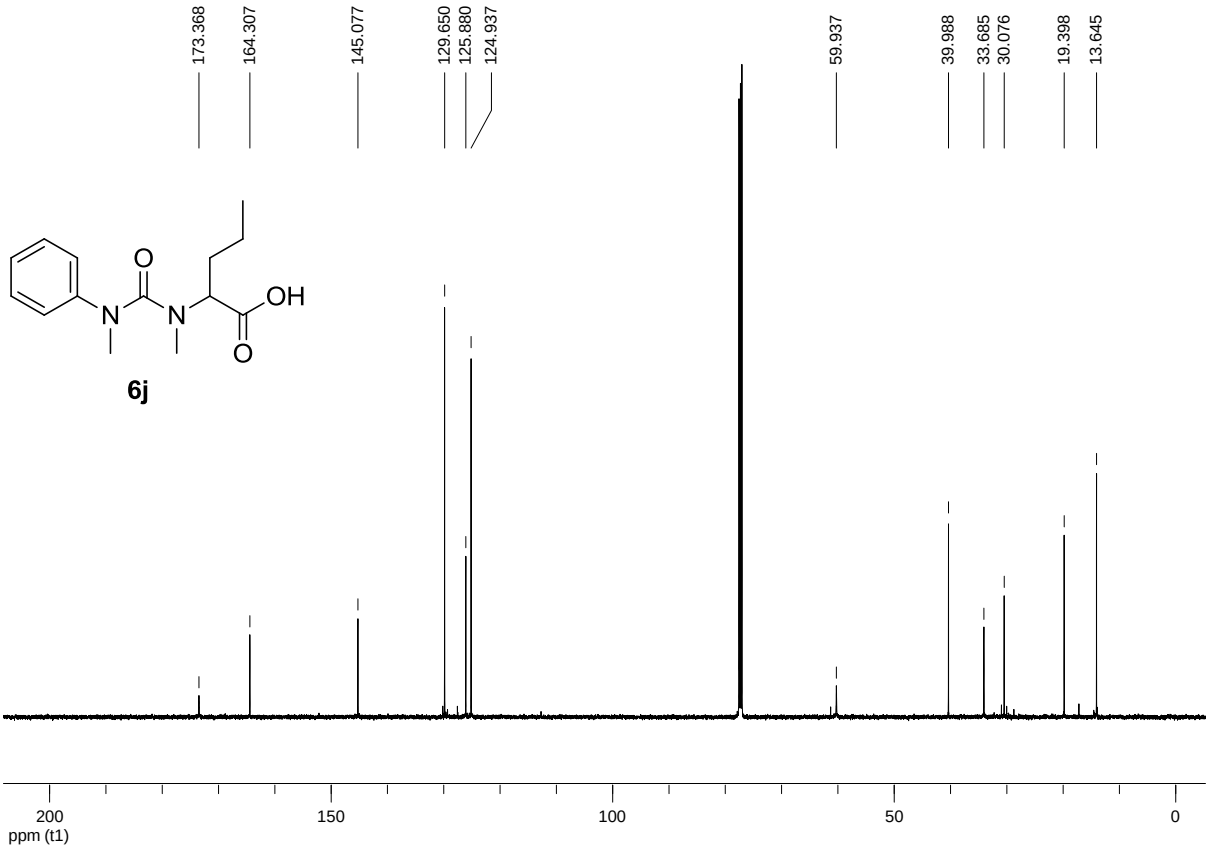
6h


11.014
7.341
7.297
7.178
7.175
7.156
7.102
3.950
3.229
2.552
O
N
N
OH
O
6i
0.96
2.07
3.06
2.04
3.00
2.99
10.0
5.0
0.0
ppm (t1)

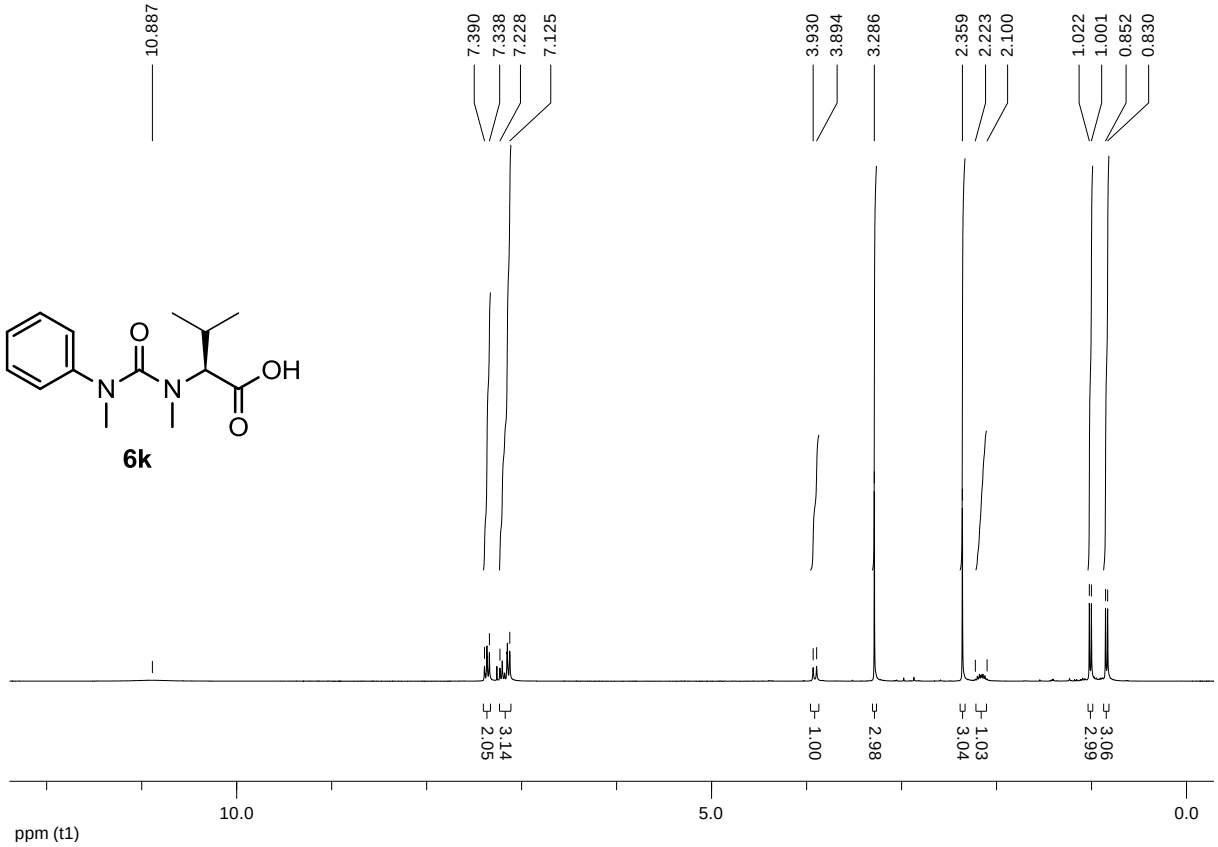

173.107
162.058
145.590
129.480
125.113
124.424
51.810
39.970
38.007
O
N
N
OH
O
6i
200
150
100
50
0
ppm (t1)

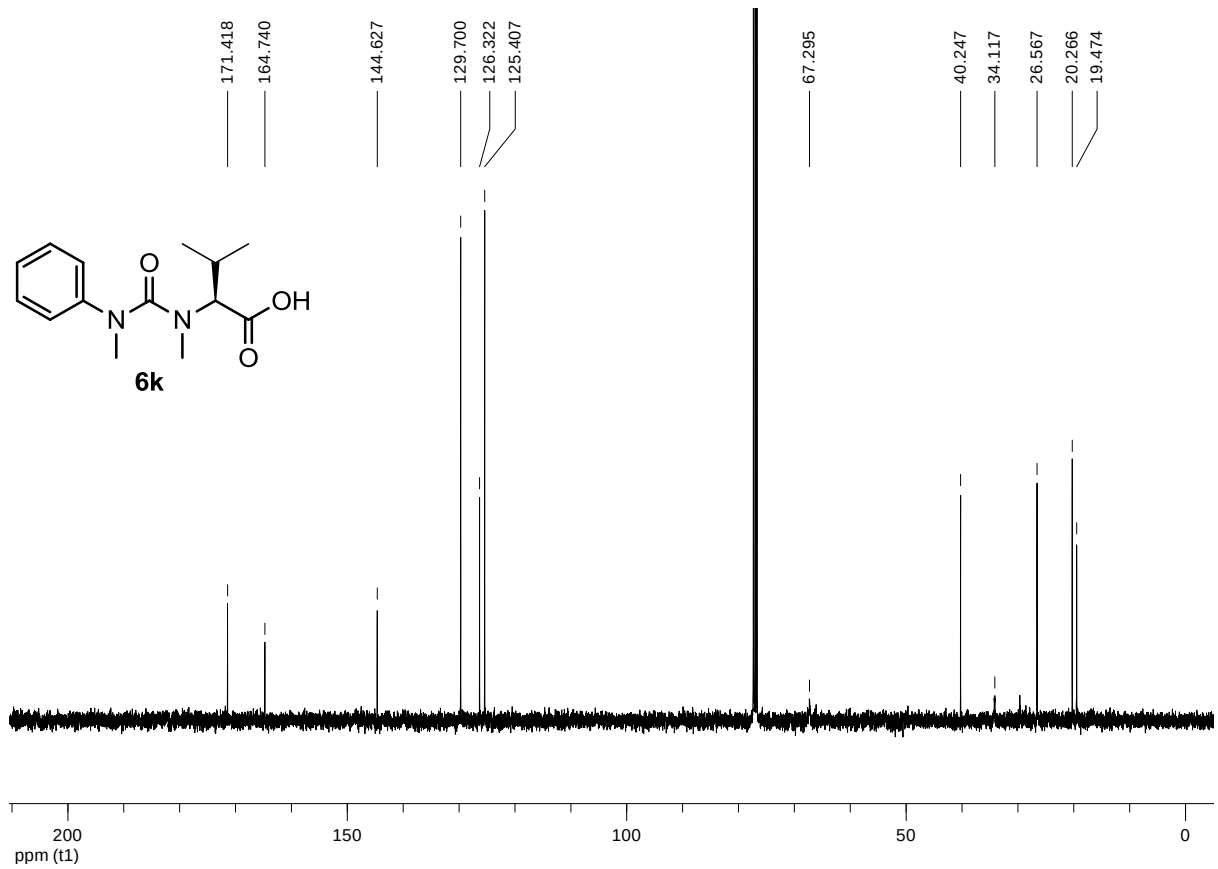

7.380
7.348
7.208
7.178
7.139
7.122
4.400
4.368
3.293
2.365
1.884
1.811
1.671
1.593
1.313
1.261
0.951
0.922
O
N
N
OH
O
2.02
2.04
1.00
3.00
3.01
1.09
1.09
2.00
3.04
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

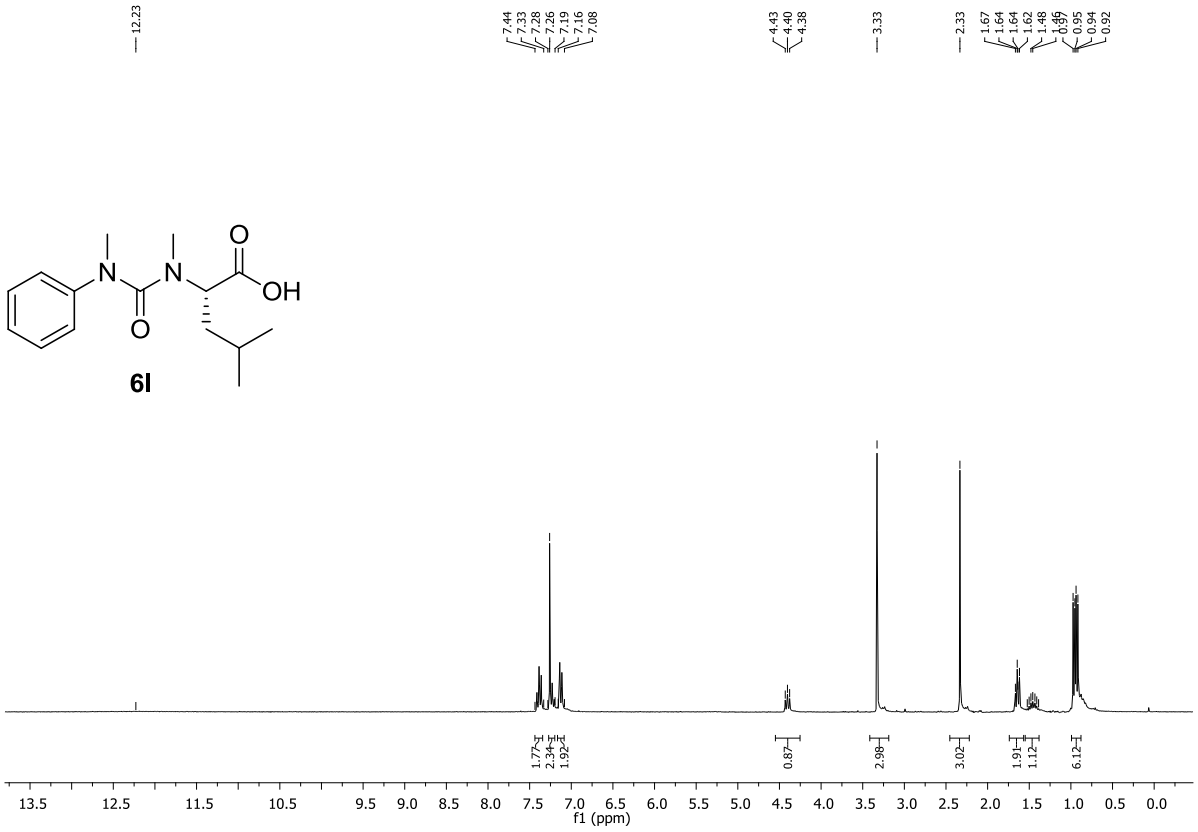
6j

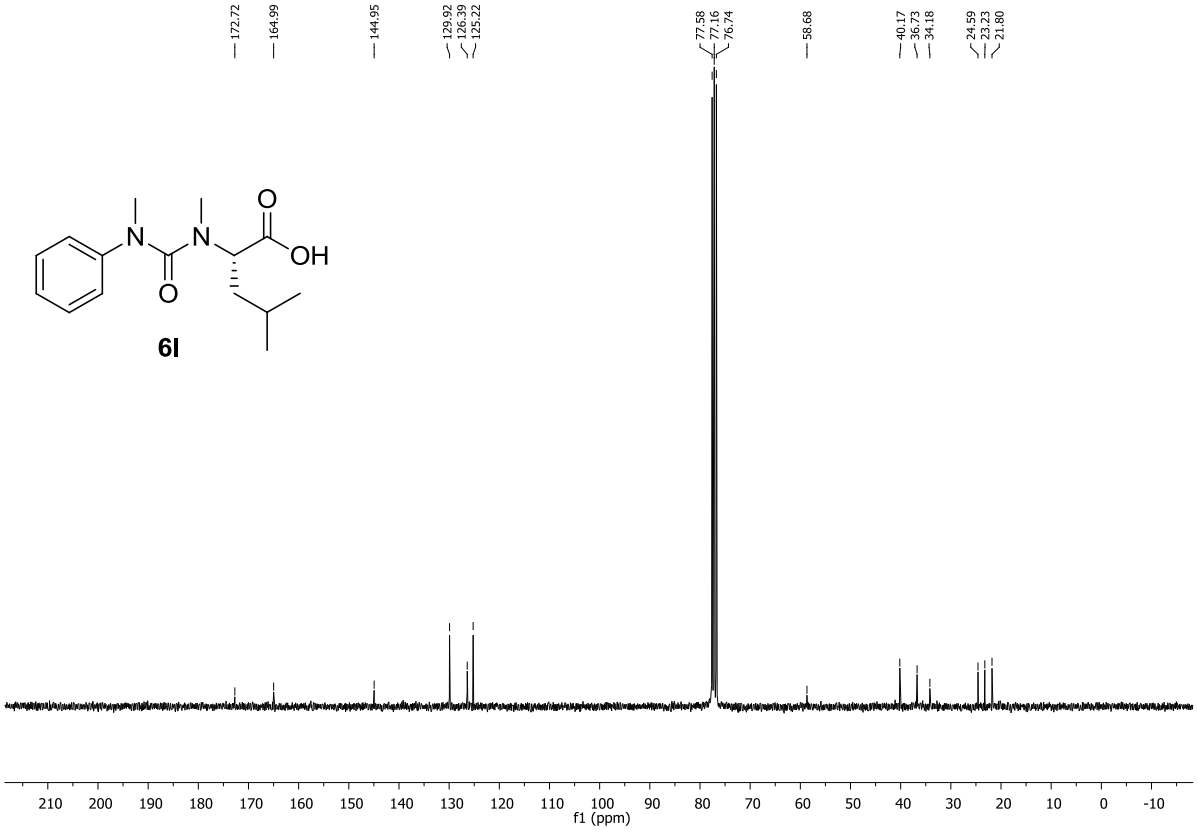

173.368
164.307
145.077
129.650
125.880
124.937
59.937
39.988
33.685
30.076
19.398
13.645
O
N
N
OH
O
200
150
100
50
0
ppm (t1)

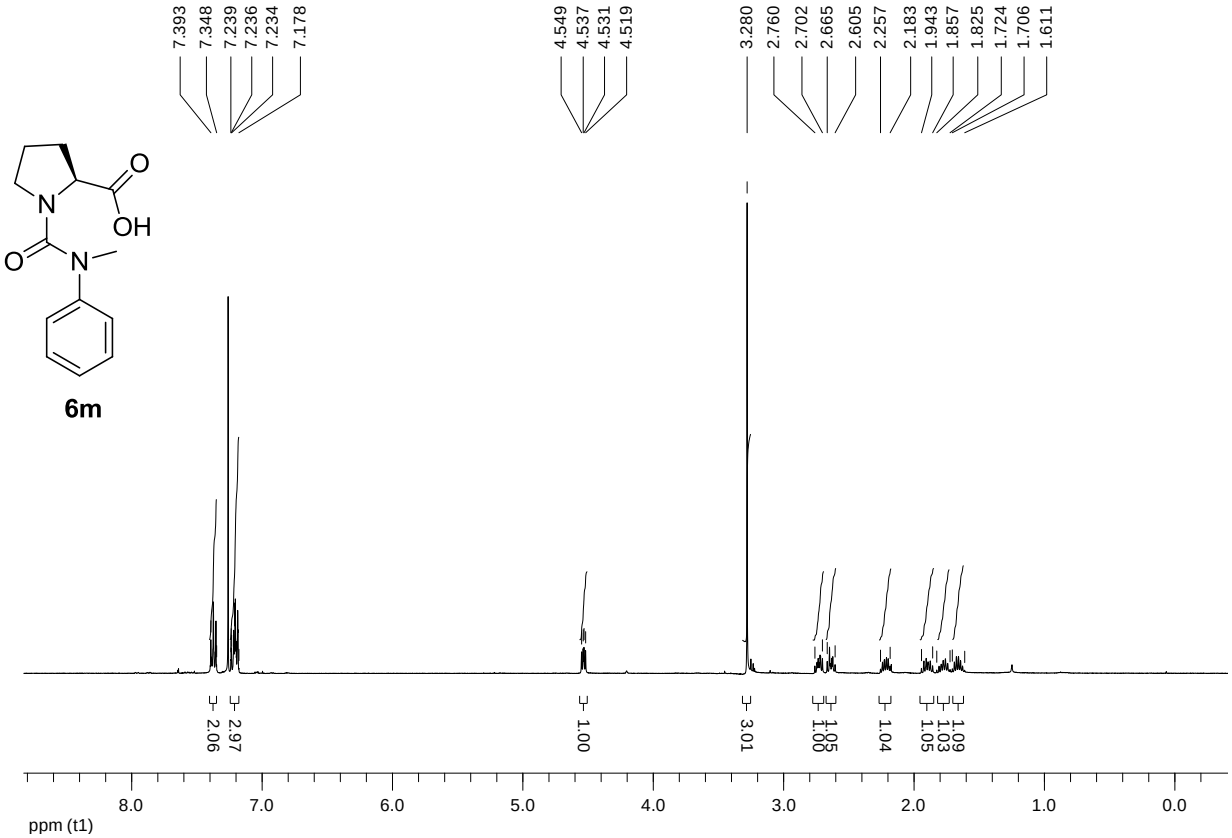
6j

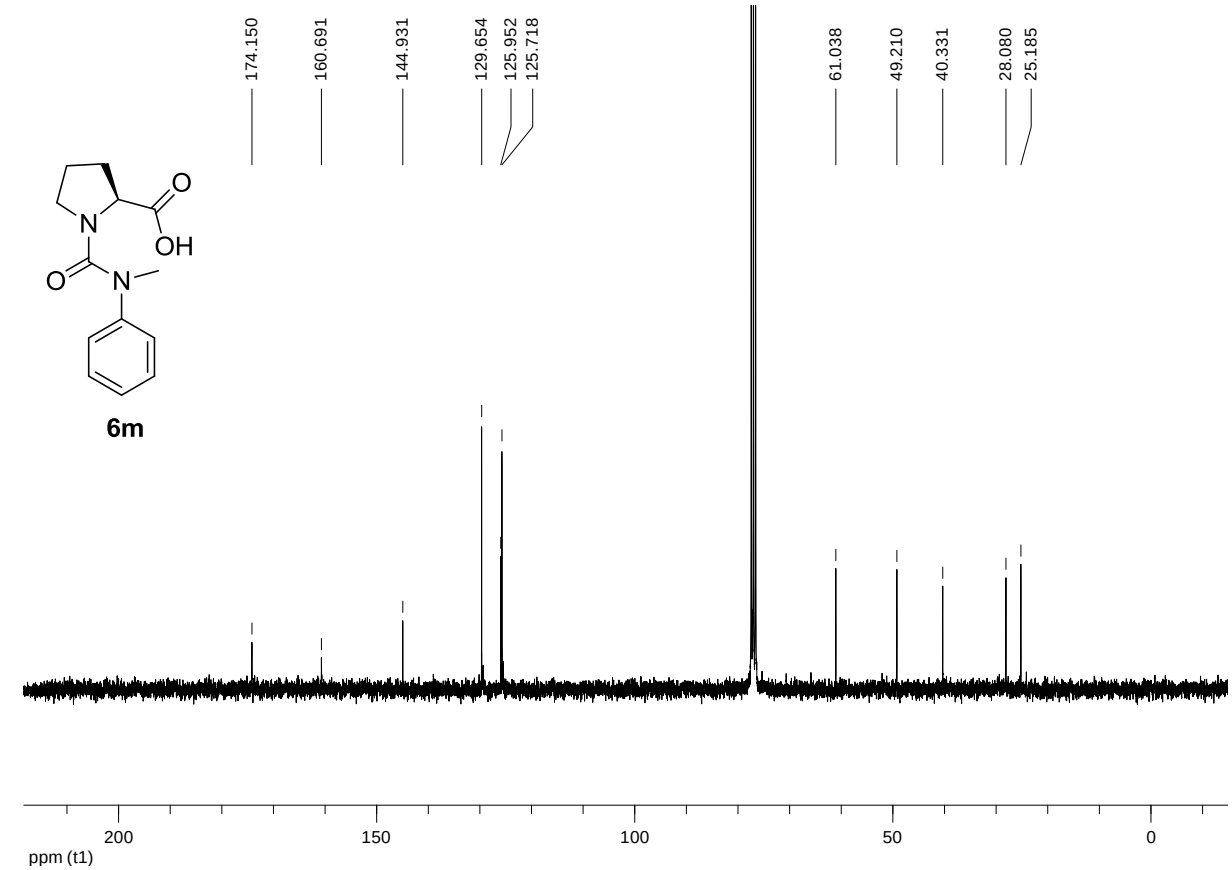

10.887
7.390
7.338
7.228
7.125
3.930
3.894
3.286
2.359
2.223
2.100
1.022
1.001
0.852
0.830
2.05
3.14
1.00
2.98
3.04
1.03
3.06
2.99
10.0
5.0
0.0
ppm (t1)
6k

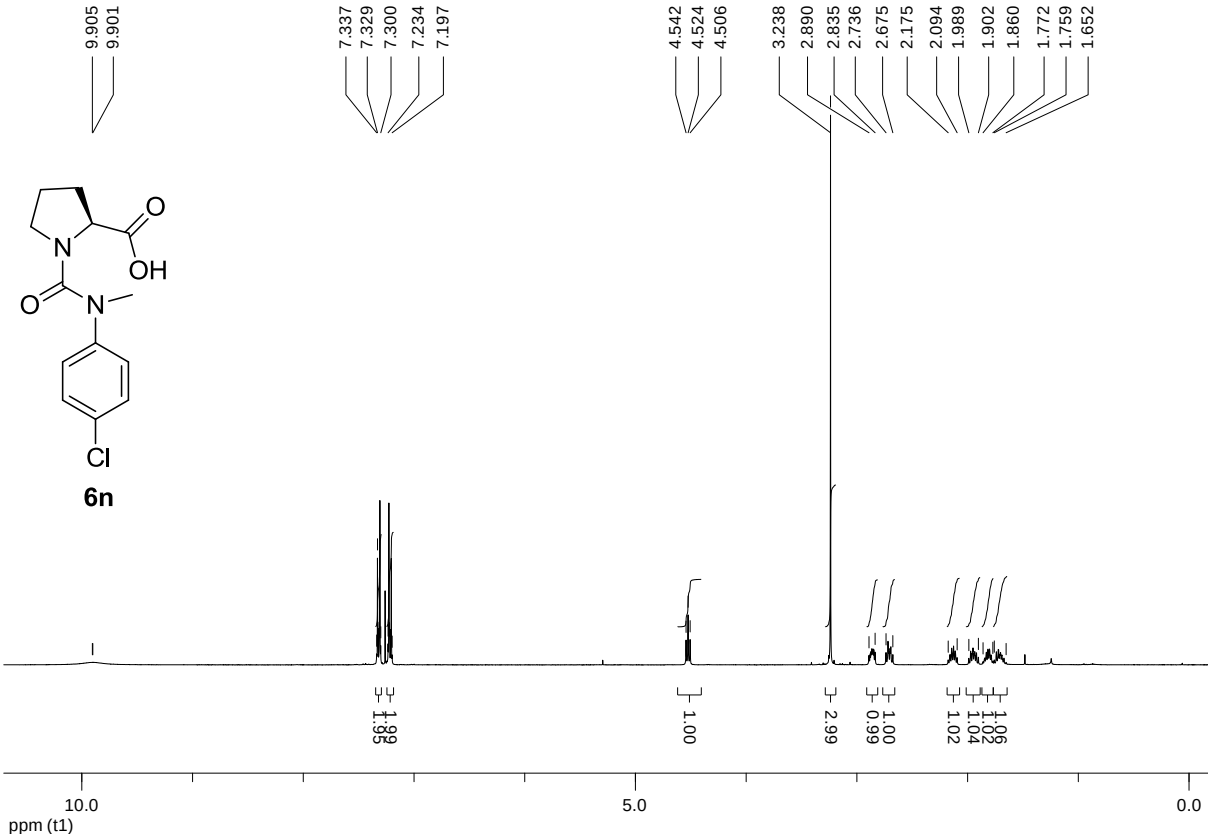

171.418
164.740
144.627
129.700
126.322
125.407
67.295
40.247
34.117
26.567
20.266
19.474
200
150
100
50
0
ppm (t1)
6k

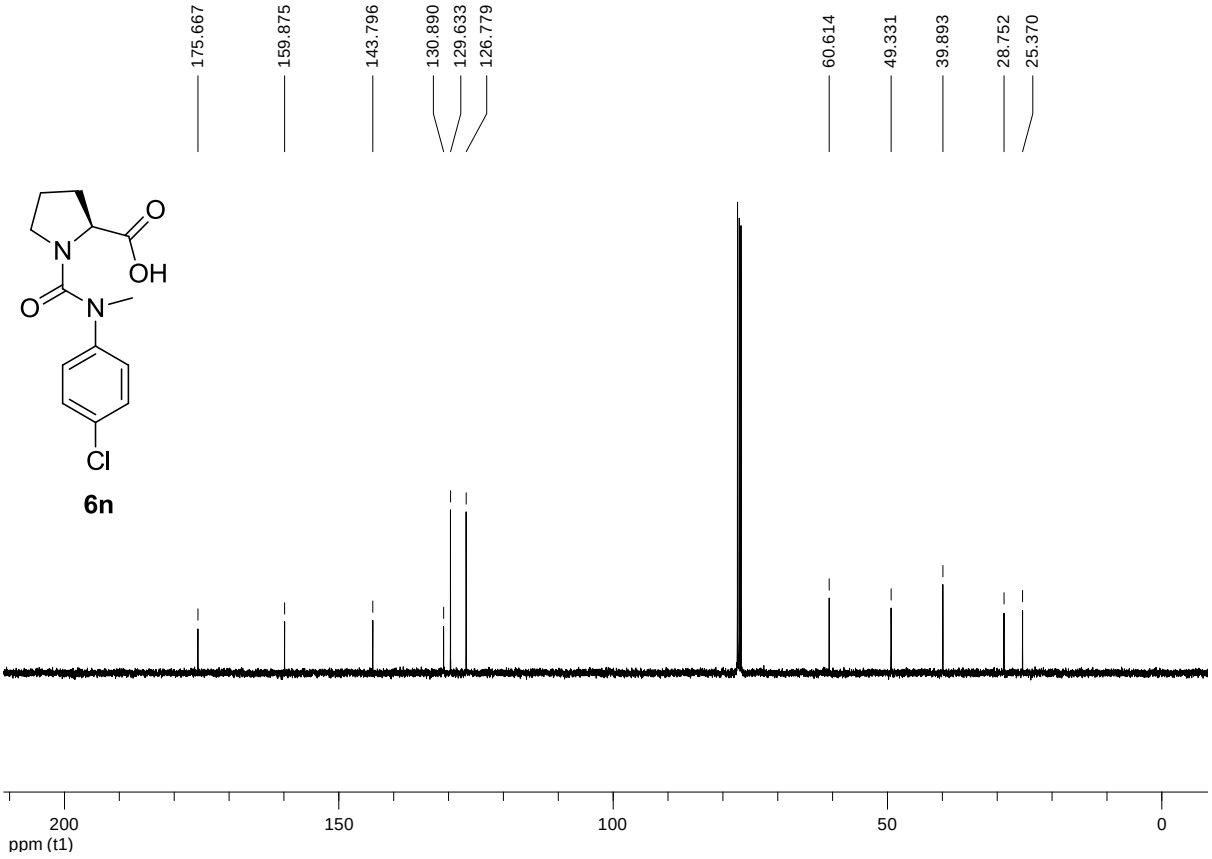

12.23
7.44
7.33
7.28
7.26
7.19
7.16
7.08
4.43
4.40
4.38
3.33
2.33
1.67
1.64
1.64
1.62
1.48
0.97
0.95
0.94
0.92
O
N
N
OH
O
6l
1.77
2.34
1.92
0.87
2.98
3.02
1.91
1.12
6.12
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.72
164.99
144.95
129.92
126.39
125.22
77.58
77.16
76.74
58.68
40.17
36.73
34.18
24.59
23.23
21.80
O
N
N
OH
O
6l
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.393
7.348
7.239
7.236
7.234
7.178
4.549
4.537
4.531
4.519
3.280
2.760
2.702
2.665
2.605
2.257
2.183
1.943
1.857
1.825
1.724
1.706
1.611
O
N
OH
O
N
6m
2.06
2.97
1.00
3.01
1.00
1.05
1.04
1.05
1.03
1.09
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


174.150
160.691
144.931
129.654
125.952
125.718
61.038
49.210
40.331
28.080
25.185
O
N
OH
O
N
6m
200
150
100
50
0
ppm (t1)


9.905
9.901
7.337
7.329
7.300
7.234
7.197
4.542
4.524
4.506
3.238
2.890
2.835
2.736
2.675
2.175
2.094
1.989
1.902
1.860
1.772
1.759
1.652
O
N
OH
O
N
Cl
6n
1.95
1.96
1.00
2.99
0.99
1.00
1.02
1.04
1.02
1.00
10.0
5.0
0.0
ppm (t1)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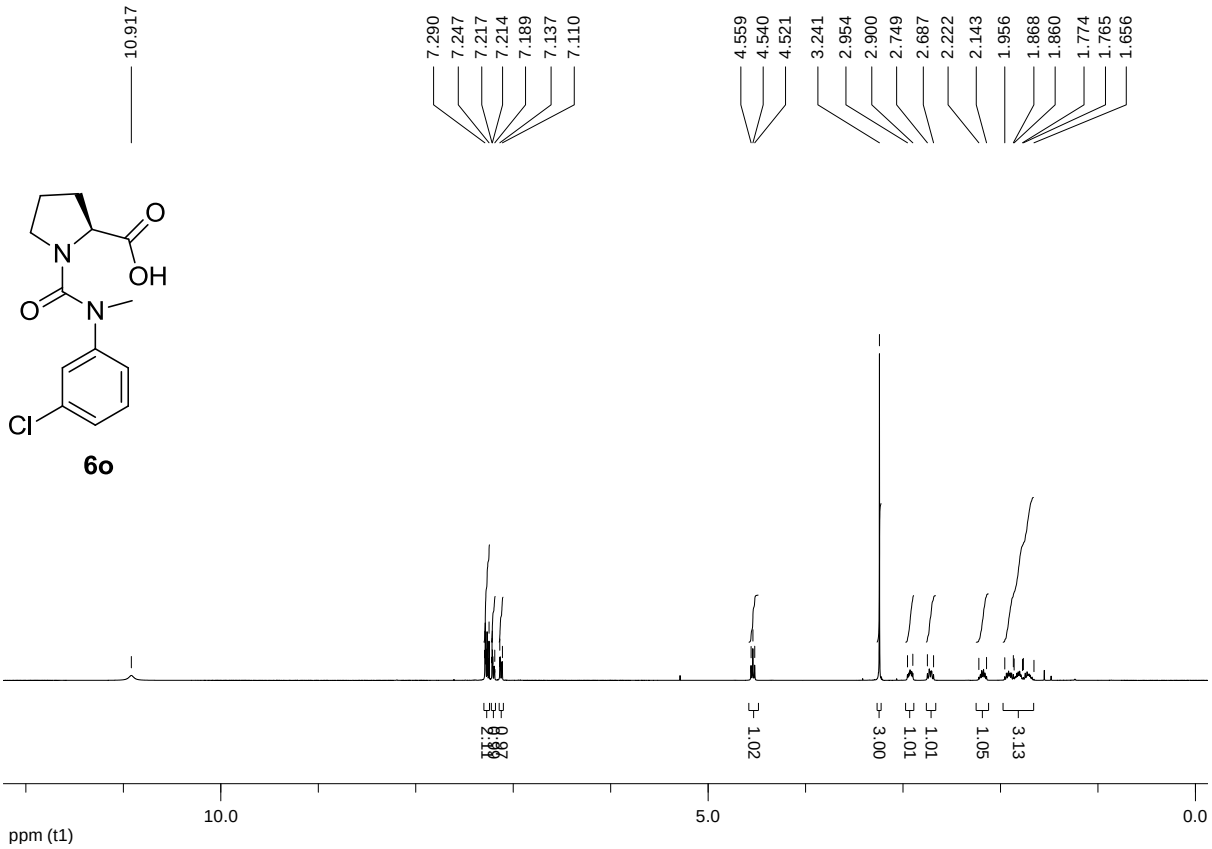
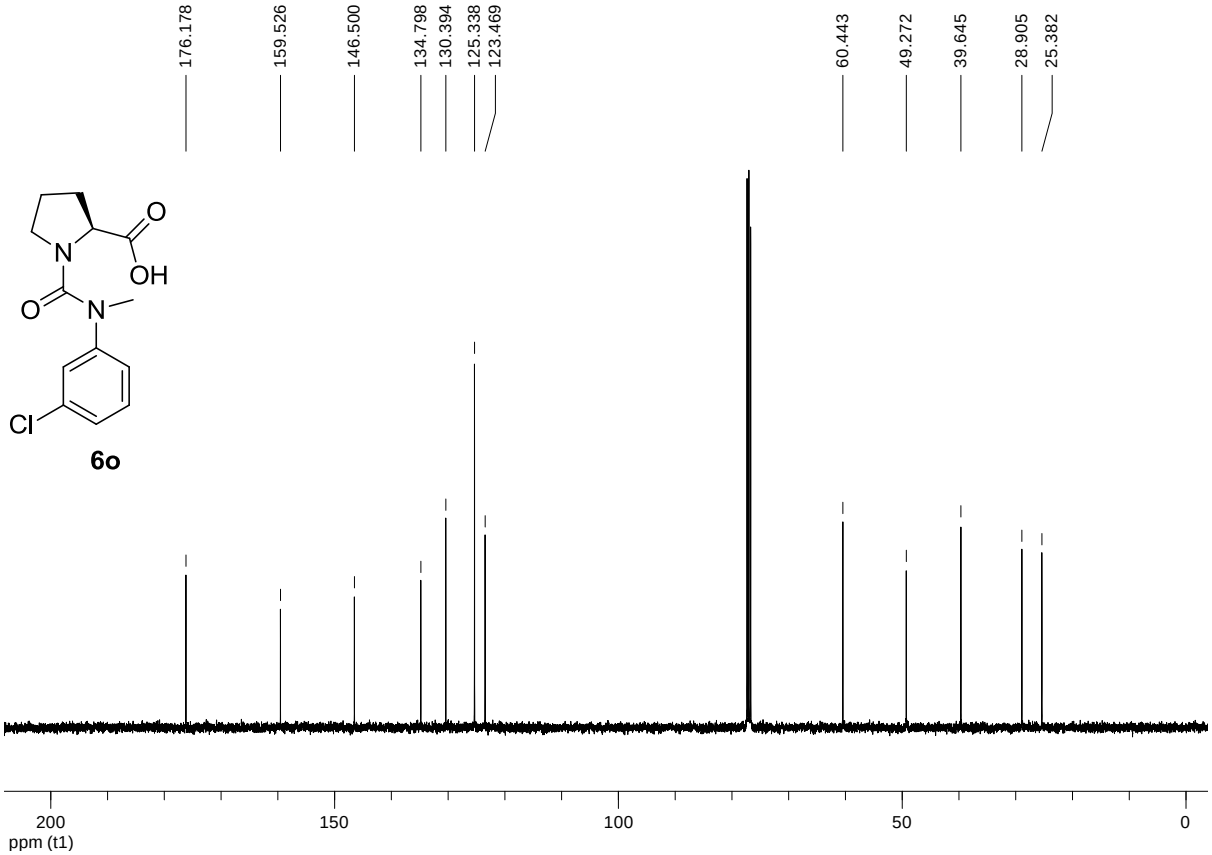
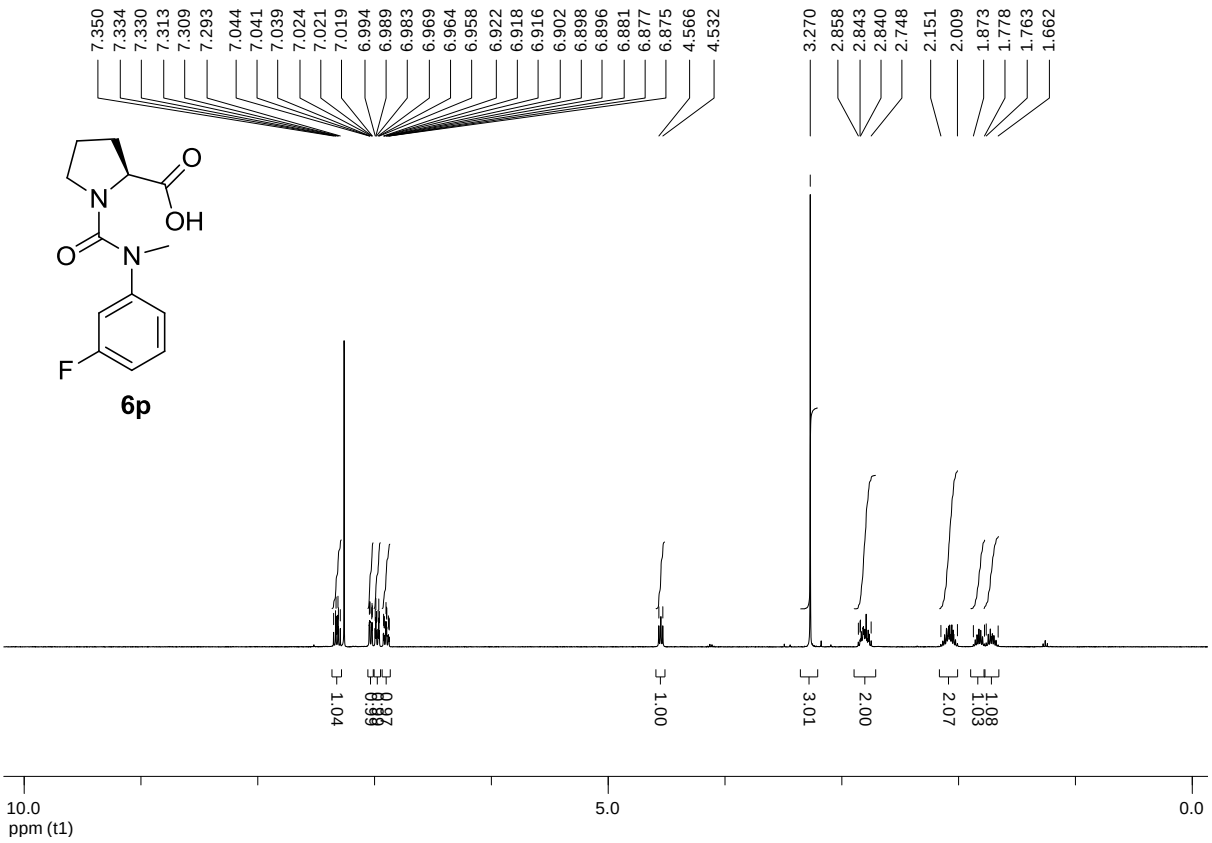
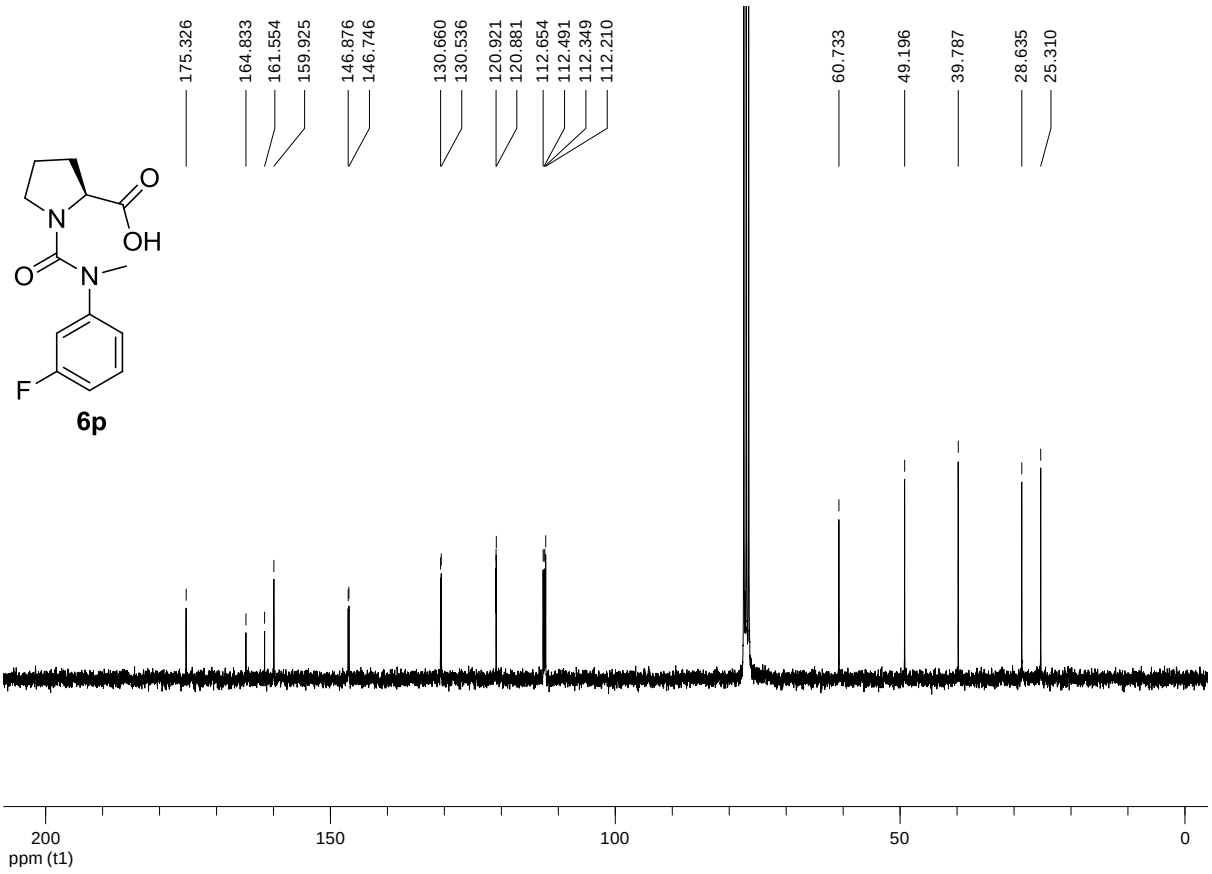
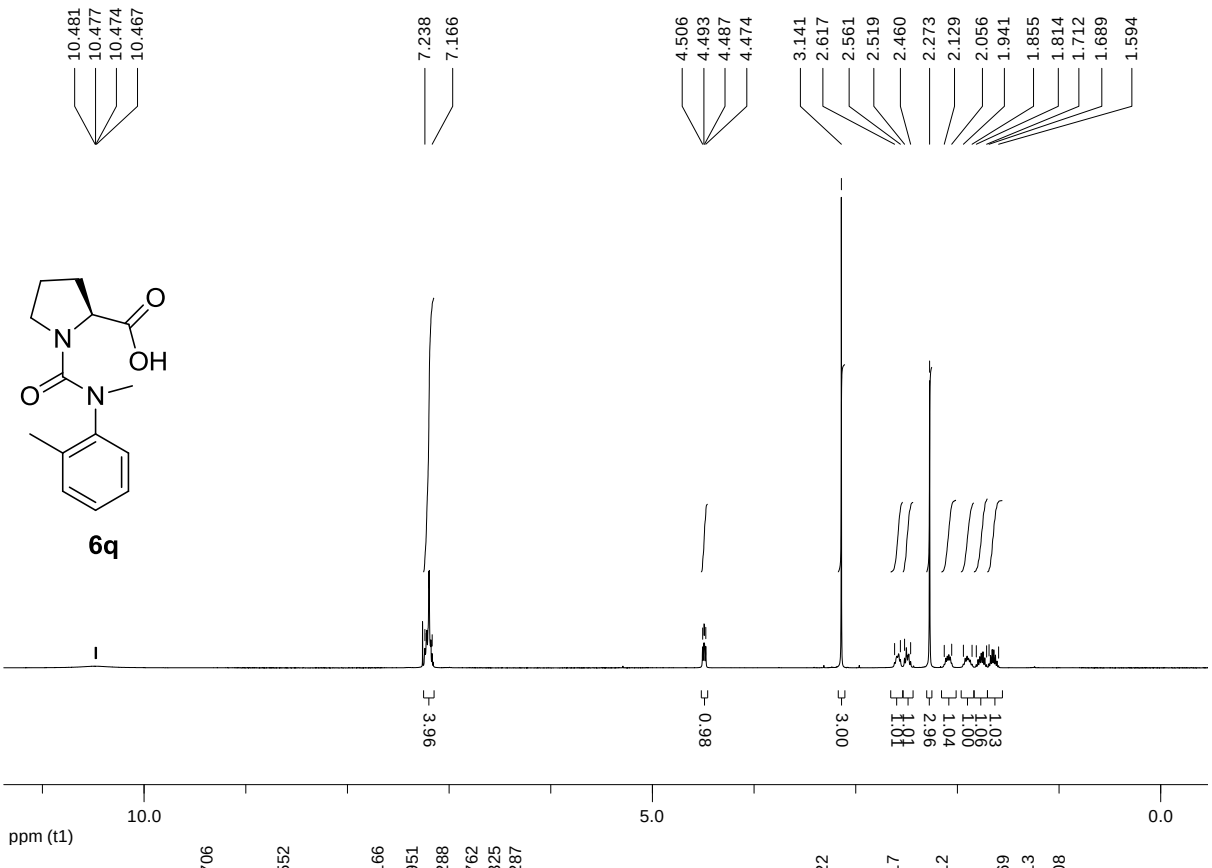
159.875
143.796
130.890
129.633
126.779
60.614
49.331
39.893
28.752
25.370
O
N
OH
O
N
Cl
6n
200
150
100
50
0
ppm (t1)

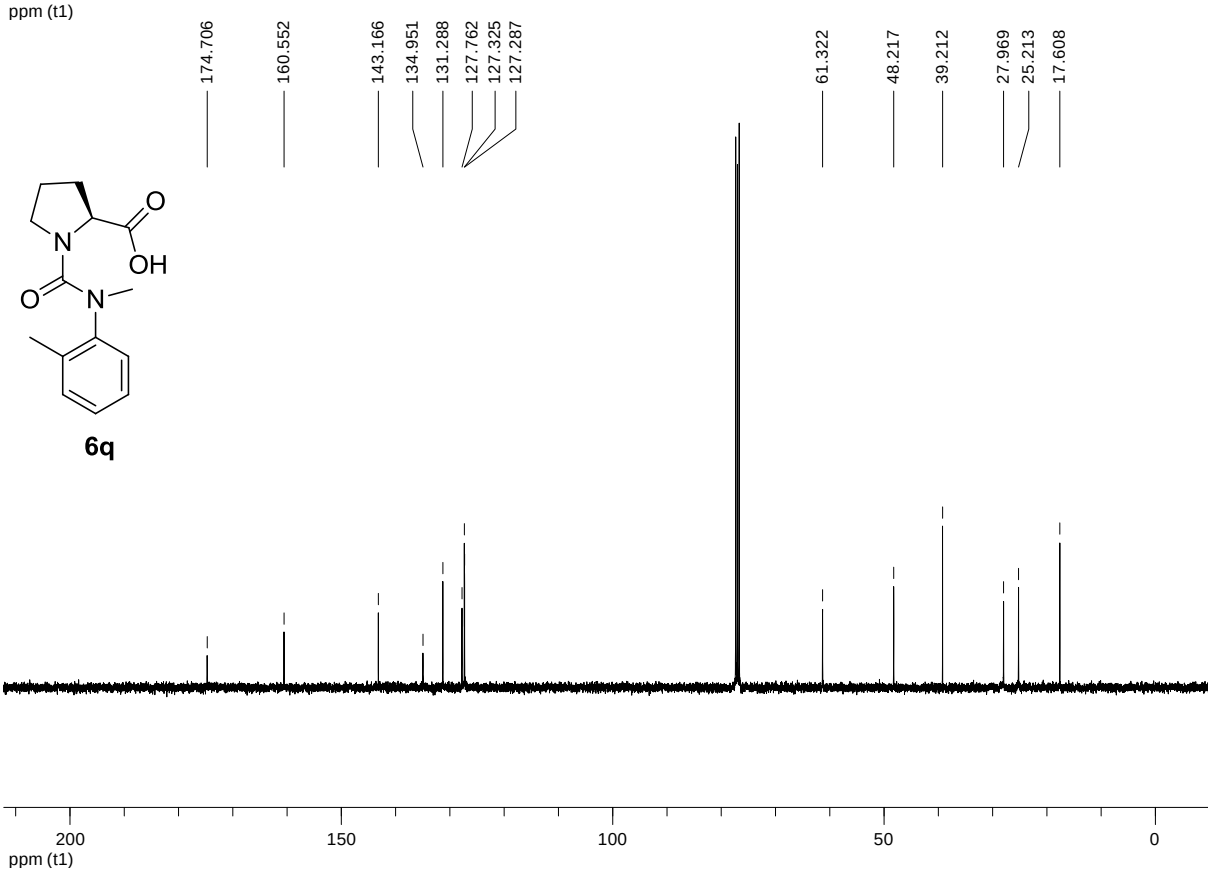

10.917
7.290
7.247
7.217
7.214
7.189
7.137
7.110
4.559
4.540
4.521
3.241
2.954
2.900
2.749
2.687
2.222
2.143
1.956
1.868
1.860
1.774
1.765
1.656
O
N
OH
O
N
Cl
6o
1.02
3.00
1.01
1.01
1.05
3.13
10.0
5.0
0.0
ppm (t1)

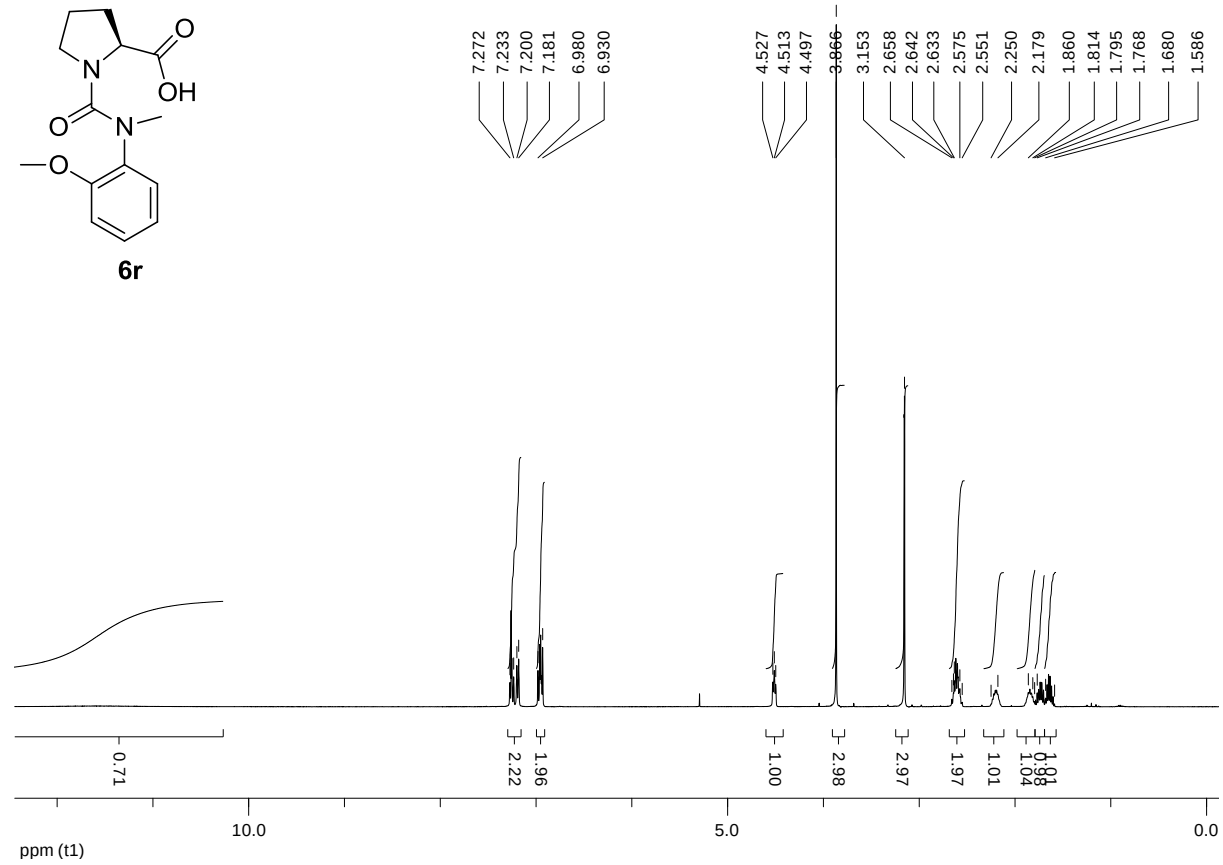

176.178
159.526
146.500
134.798
130.394
125.338
123.469
60.443
49.272
39.645
28.905
25.382
O
N
OH
O
N
Cl
6o
200
150
100
50
0
ppm (t1)

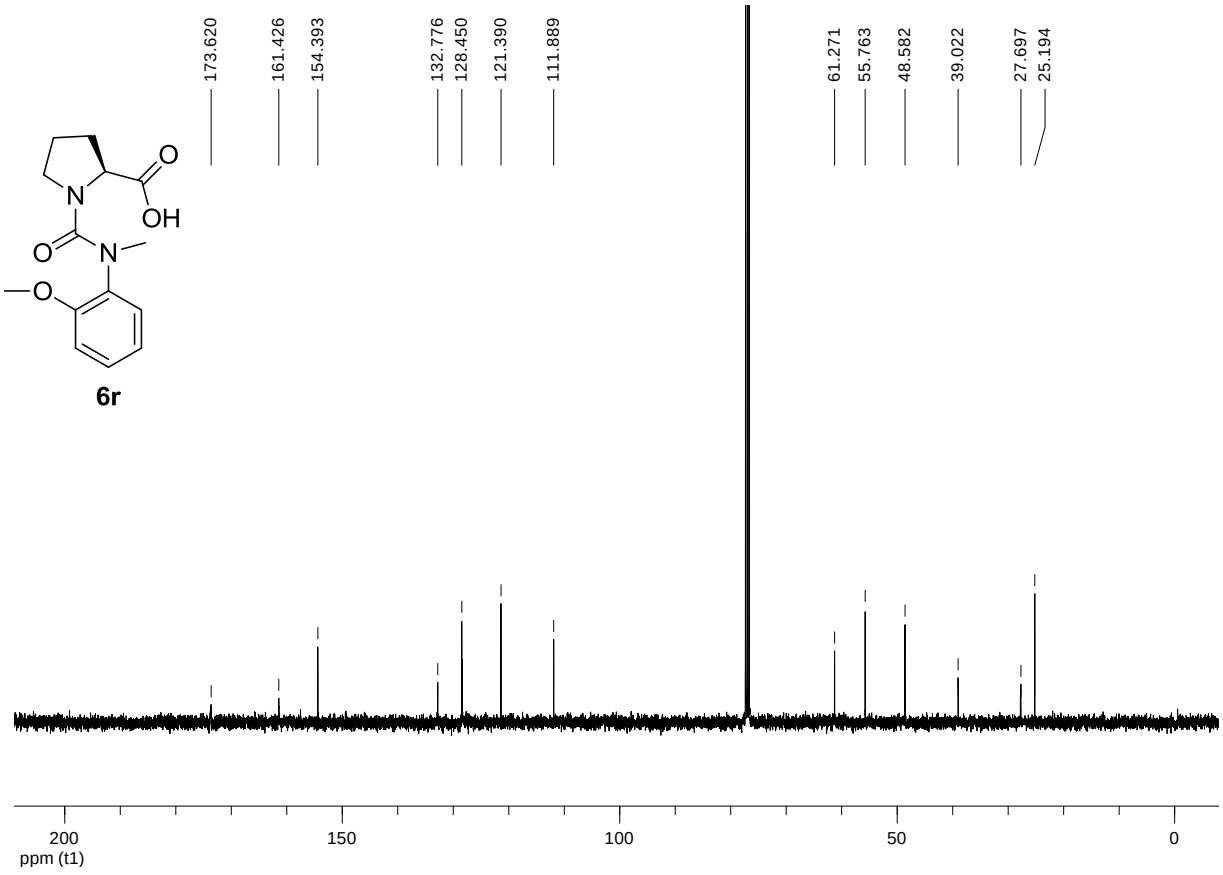

7.350
7.334
7.330
7.313
7.309
7.293
7.044
7.041
7.039
7.024
7.021
7.019
6.994
6.989
6.983
6.969
6.964
6.958
6.922
6.918
6.916
6.902
6.898
6.896
6.881
6.877
6.875
4.566
4.532
3.270
2.858
2.843
2.840
2.748
2.151
2.009
1.873
1.778
1.763
1.662
O
OH
N
O
N
F
6p
1.04
1.00
3.01
2.00
2.07
1.08
1.03
10.0
5.0
0.0
ppm (t1)

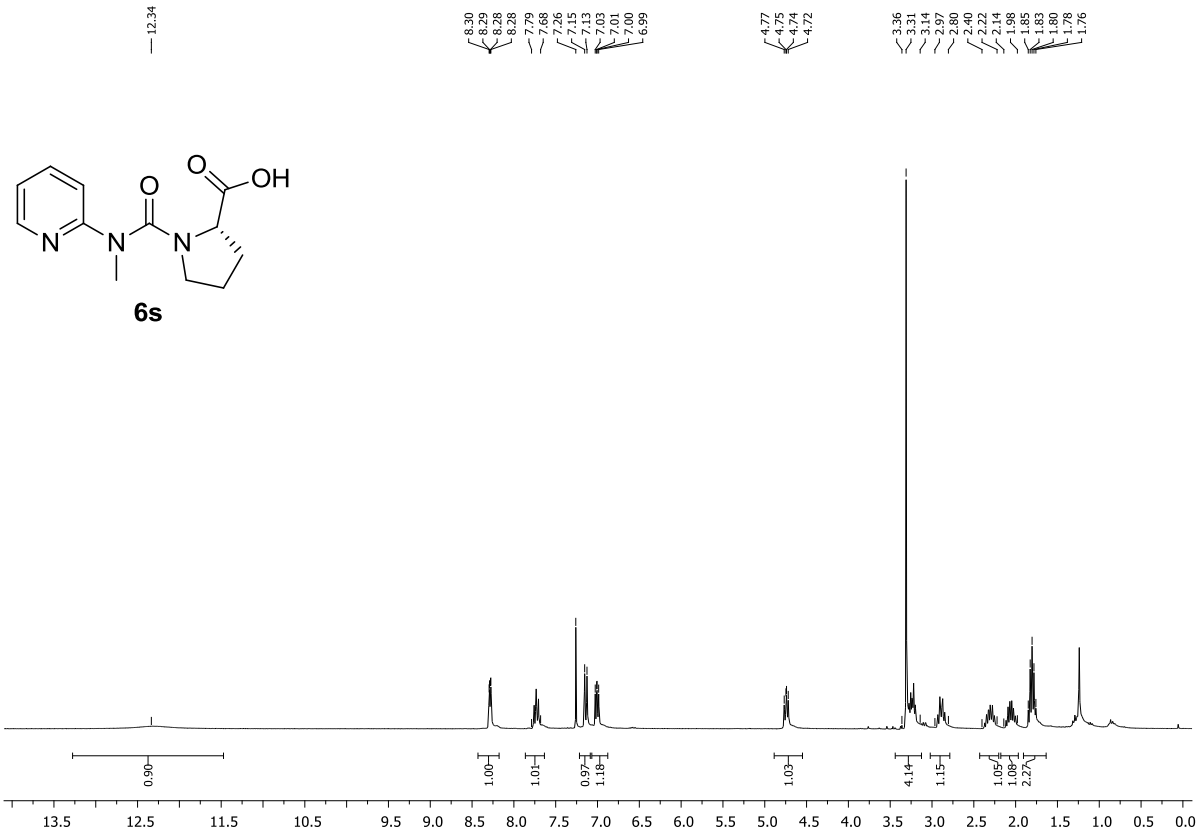

175.326
164.833
161.554
159.925
146.876
146.746
130.660
130.536
120.921
120.881
112.654
112.491
112.349
112.210
60.733
49.196
39.787
28.635
25.310
O
OH
N
O
N
F
6p
200
150
100
50
0
ppm (t1)


10.481
10.477
10.474
10.467
7.238
7.166
4.506
4.493
4.487
4.474
3.141
2.617
2.561
2.519
2.460
2.273
2.129
2.056
1.941
1.855
1.814
1.712
1.689
1.594
O
N
OH
O
N
6q
3.96
0.98
3.00
1.01
1.01
2.96
1.04
1.00
1.06
1.03
10.0
5.0
0.0
ppm (t1)


174.706
160.552
143.166
134.951
131.288
127.762
127.325
127.287
61.322
48.217
39.212
27.969
25.213
17.608
O
N
OH
O
N
6q
200
150
100
50
0
ppm (t1)


6r
7.272
7.233
7.200
7.181
6.980
6.930
4.527
4.513
4.497
3.866
3.153
2.658
2.642
2.633
2.575
2.551
2.250
2.179
1.860
1.814
1.795
1.768
1.680
1.586
0.71
2.22
1.96
1.00
2.98
2.97
1.97
1.01
1.04
1.01
1.01
10.0
5.0
0.0
ppm (t1)


6r
173.620
161.426
154.393
132.776
128.450
121.390
111.889
61.271
55.763
48.582
39.022
27.697
25.194
200
150
100
50
0
ppm (t1)


12.34
8.30
8.29
8.28
8.28
7.79
7.68
7.26
7.15
7.13
7.03
7.01
7.00
6.99
4.77
4.75
4.74
4.72
3.36
3.31
3.14
2.97
2.80
2.40
2.22
2.14
1.98
1.85
1.83
1.80
1.78
1.76
O
OH
N
N
N
6s
0.90
1.00
1.01
0.97
1.18
1.03
4.14
1.15
1.05
1.08
2.27
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
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3.0
2.5
2.0
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1.0
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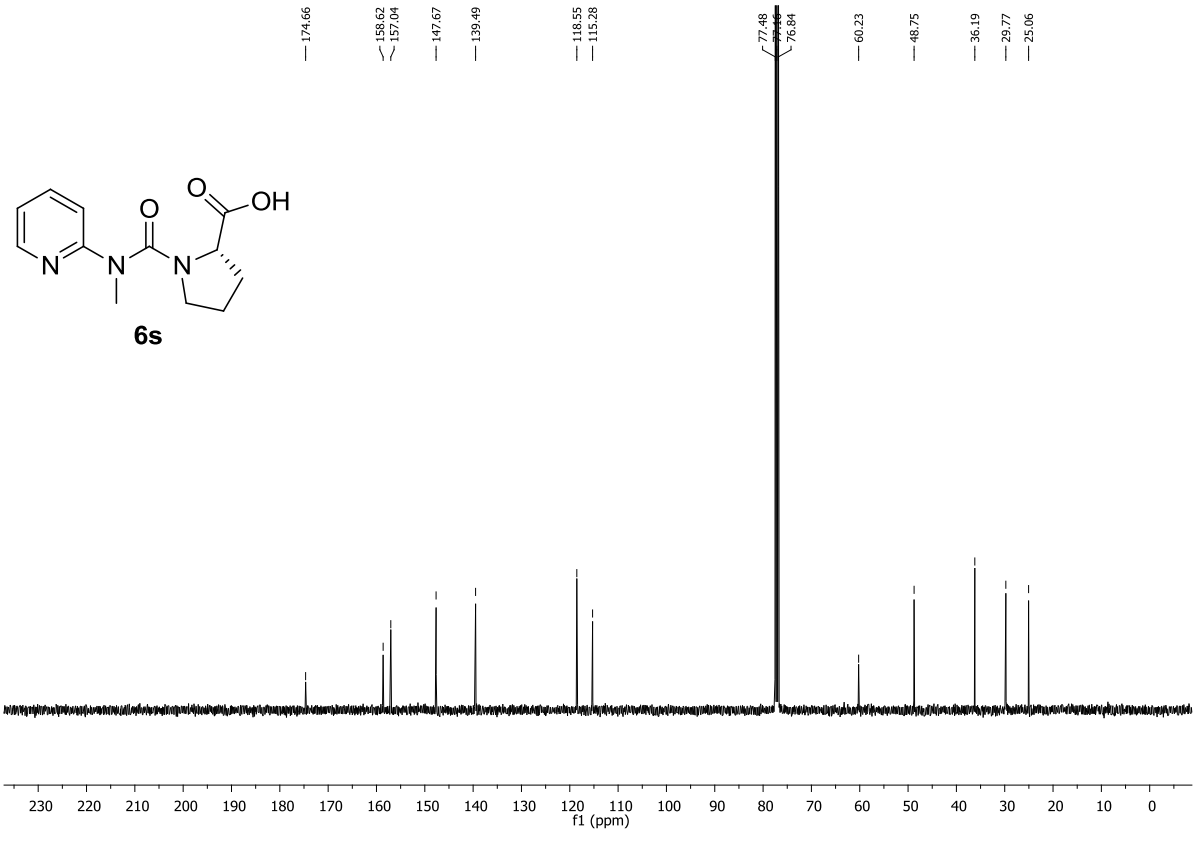
0.0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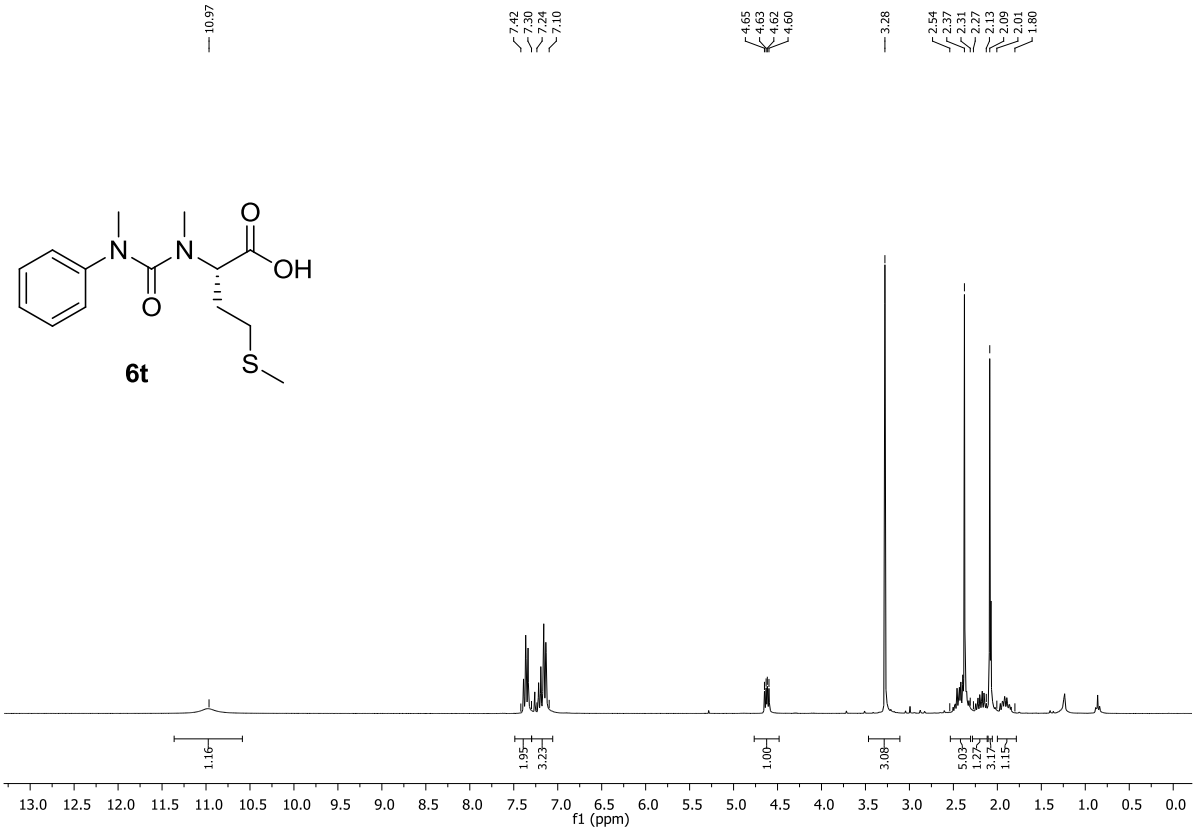
158.62
157.04
147.67
139.49
118.55
115.28
77.48
77.16
76.84
60.23
48.75
36.19
29.77
25.06
O
OH
N
N
N
6s
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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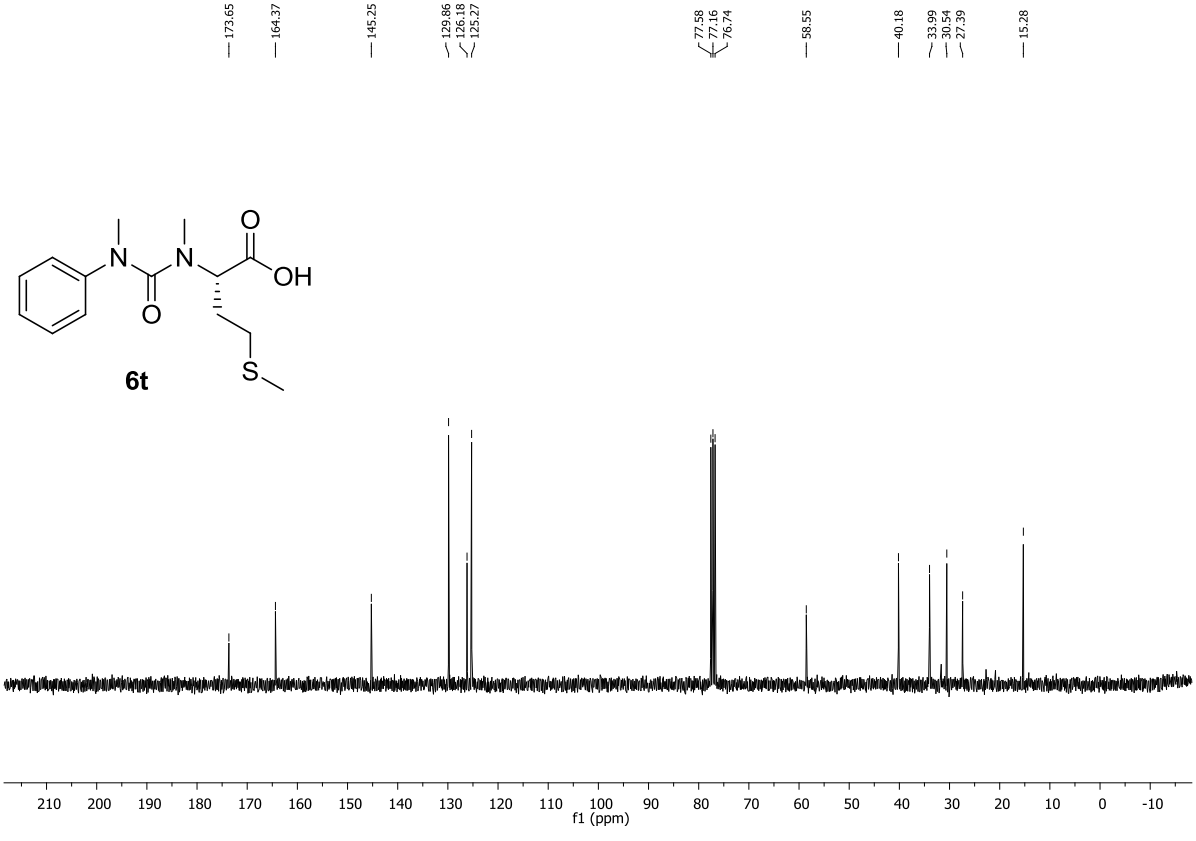
7.30
7.24
7.10
4.65
4.63
4.62
4.60
3.28
2.54
2.37
2.31
2.27
2.13
2.09
2.01
1.80
O
N
N
O
OH
S
6t
1.16
1.95
3.23
1.00
3.08
5.03
1.27
3.17
1.15
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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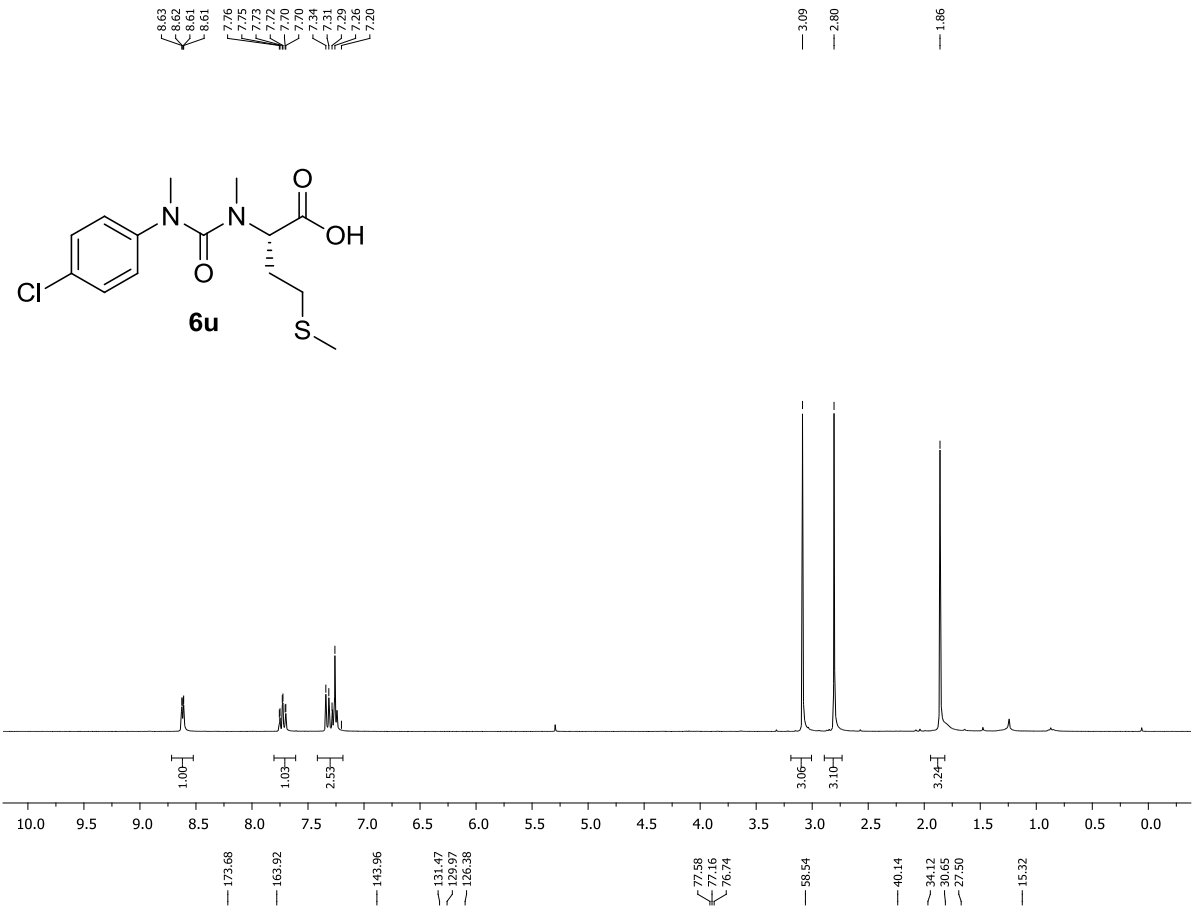
164.37
145.25
129.86
126.18
125.27
77.58
77.16
76.74
58.55
40.18
33.99
30.54
27.39
15.28
O
N
N
O
OH
S
6t
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.63
8.62
8.61
8.61
7.76
7.75
7.73
7.72
7.70
7.70
7.34
7.31
7.29
7.26
7.20
3.09
2.80
1.86
Cl
N
N
O
O
OH
S
6u
1.00
1.03
2.53
3.06
3.10
3.24
10.0
9.5
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
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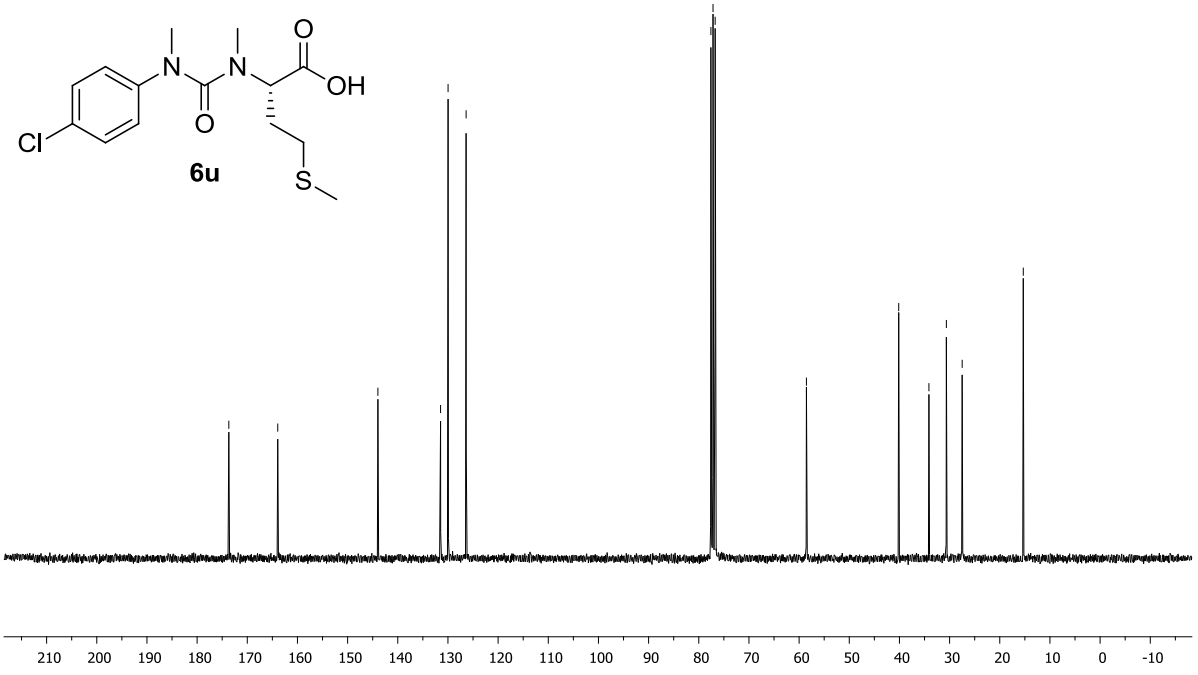
0.0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163.92
143.96
131.47
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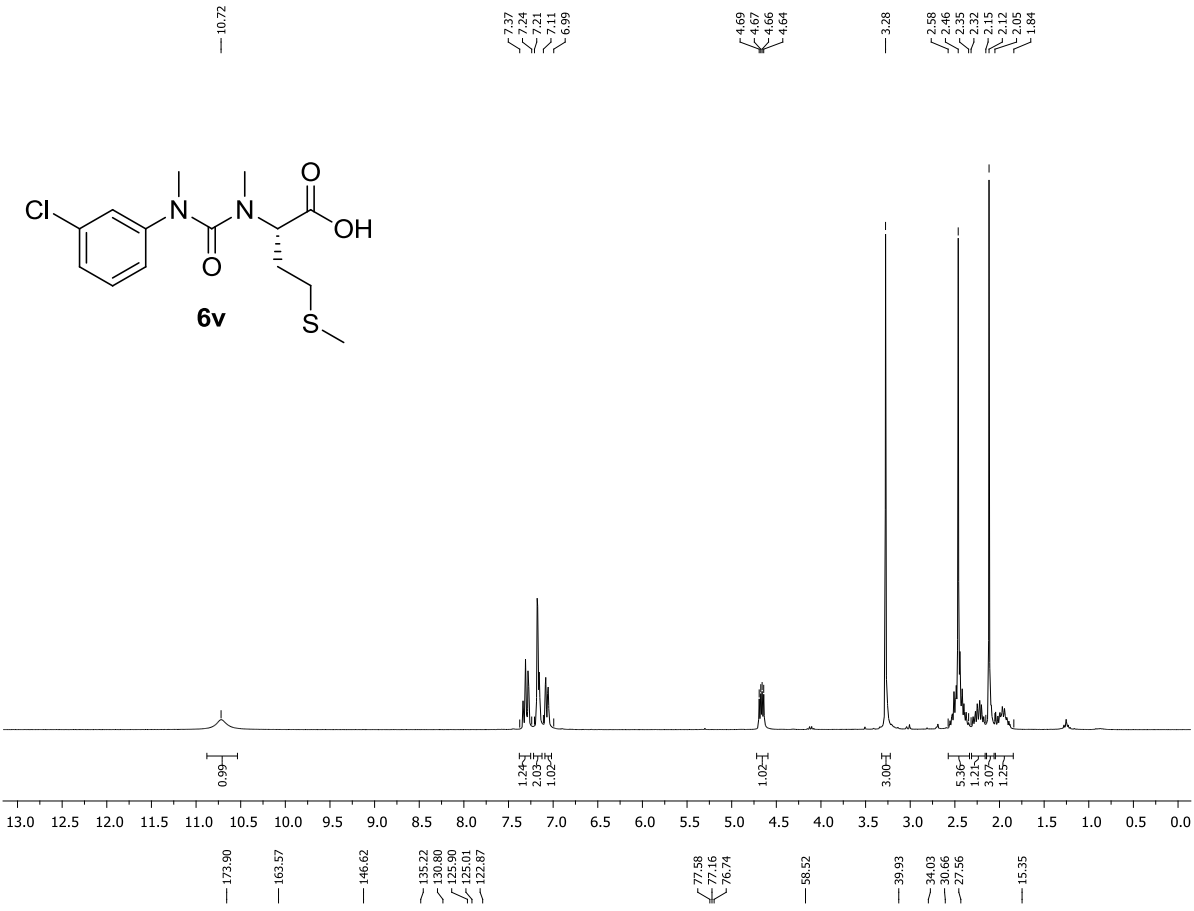
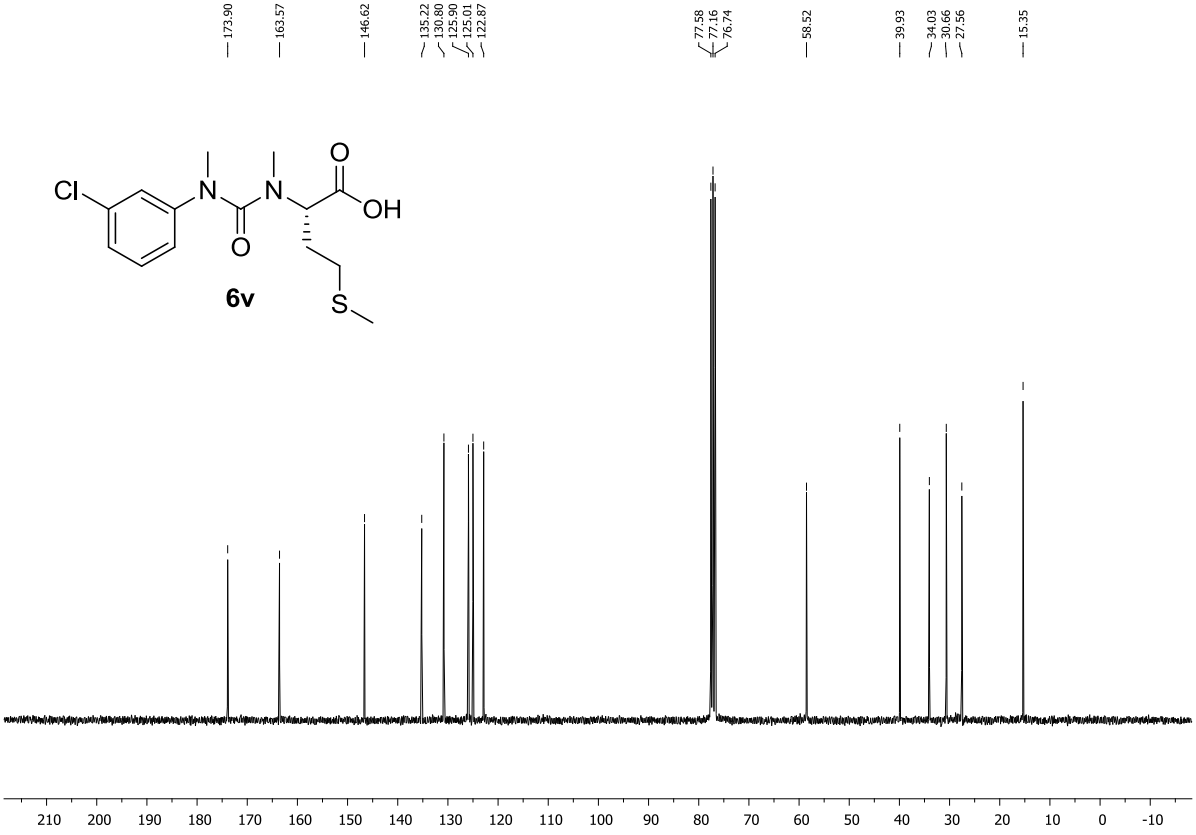
126.38
77.58
77.16
76.74
58.54
40.14
34.12
30.65
27.50
15.32
Cl
N
N
O
O
OH
S
6u
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


10.72
7.37
7.24
7.21
7.11
6.99
4.69
4.67
4.66
4.64
3.28
2.58
2.46
2.35
2.32
2.15
2.12
2.05
1.84
Cl
N
N
O
O
OH
S
6v
0.99
1.24
2.03
1.02
1.02
3.00
5.36
1.21
3.07
1.25
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 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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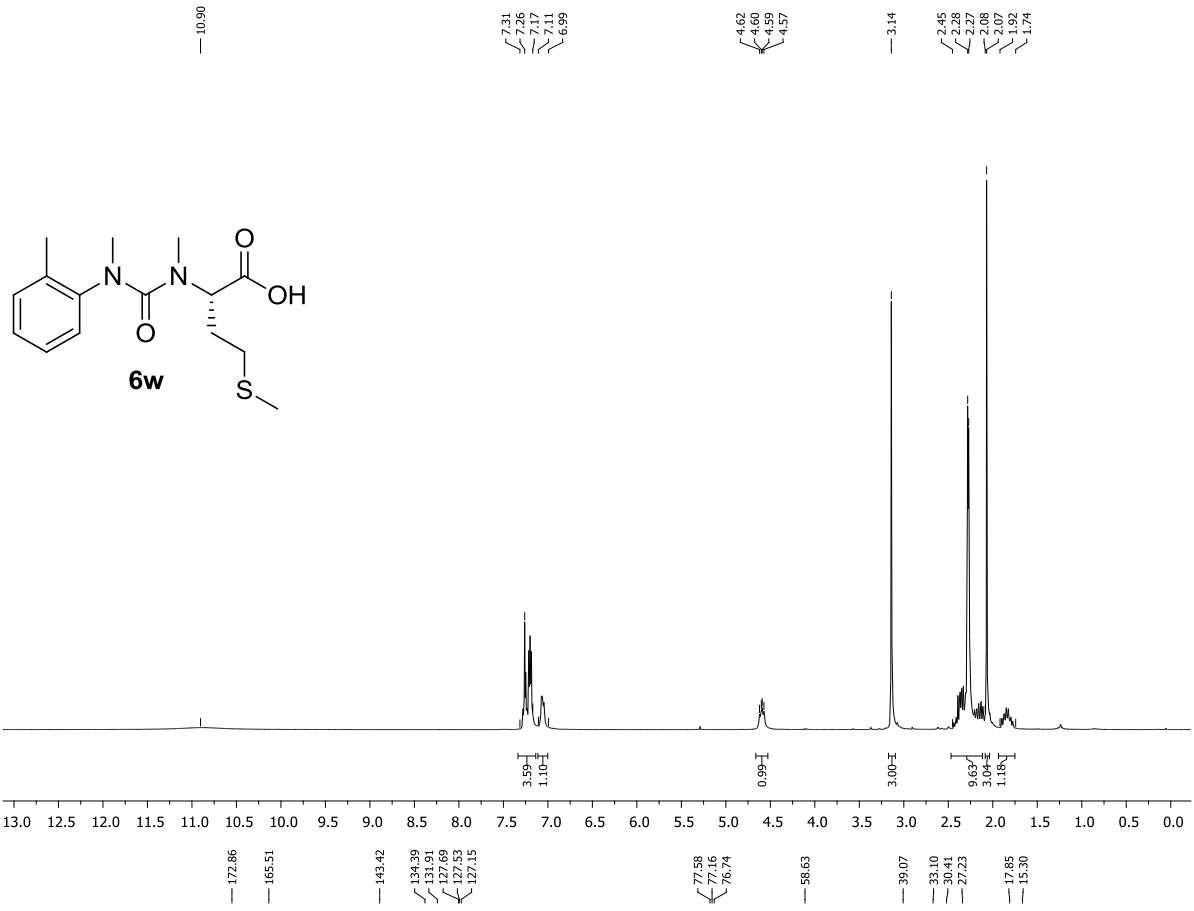
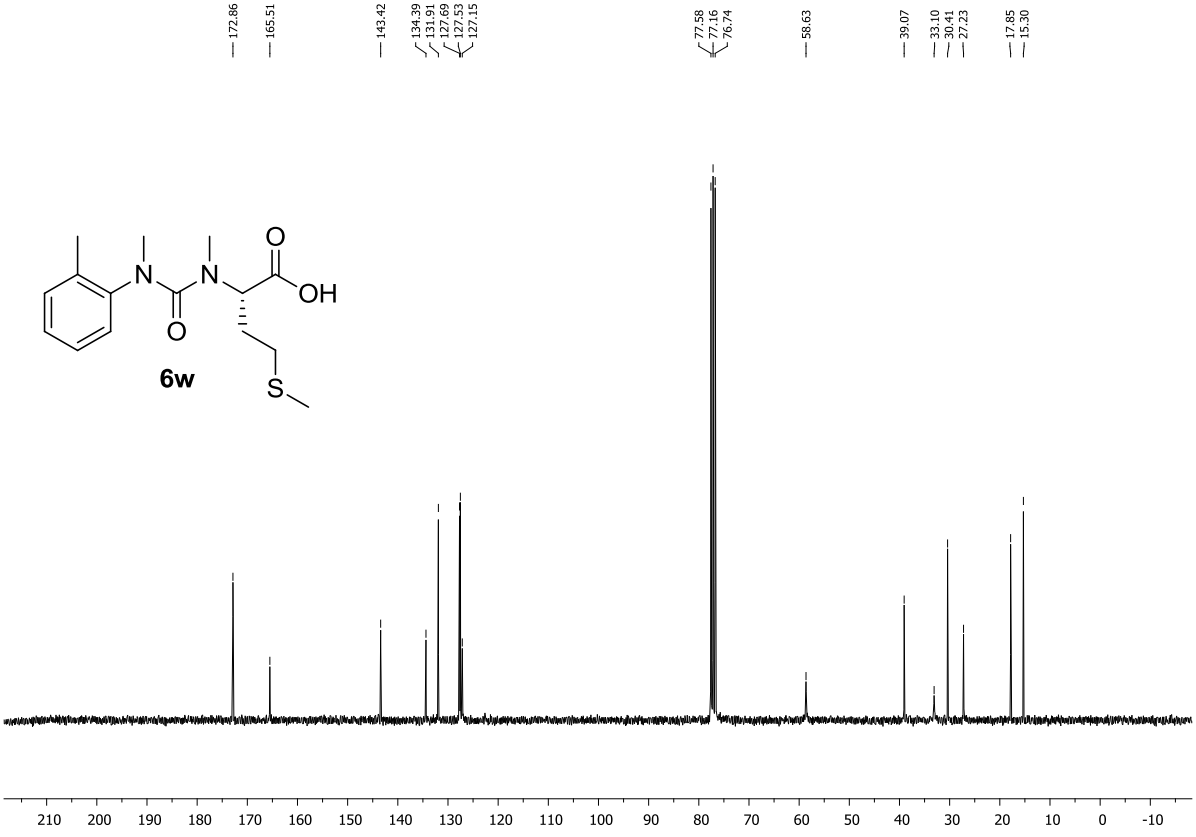
163.57
146.62
135.22
130.80
125.90
125.01
122.87
77.58
77.16
76.74
58.52
39.93
34.03
30.66
27.56
15.35
Cl
N
N
O
O
OH
S
6v
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


10.90
7.31
7.26
7.17
7.11
6.99
4.62
4.60
4.59
4.57
3.14
2.45
2.28
2.27
2.08
2.07
1.92
1.74
6w
3.59
1.10
0.99
3.00
9.63
3.04
1.18
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 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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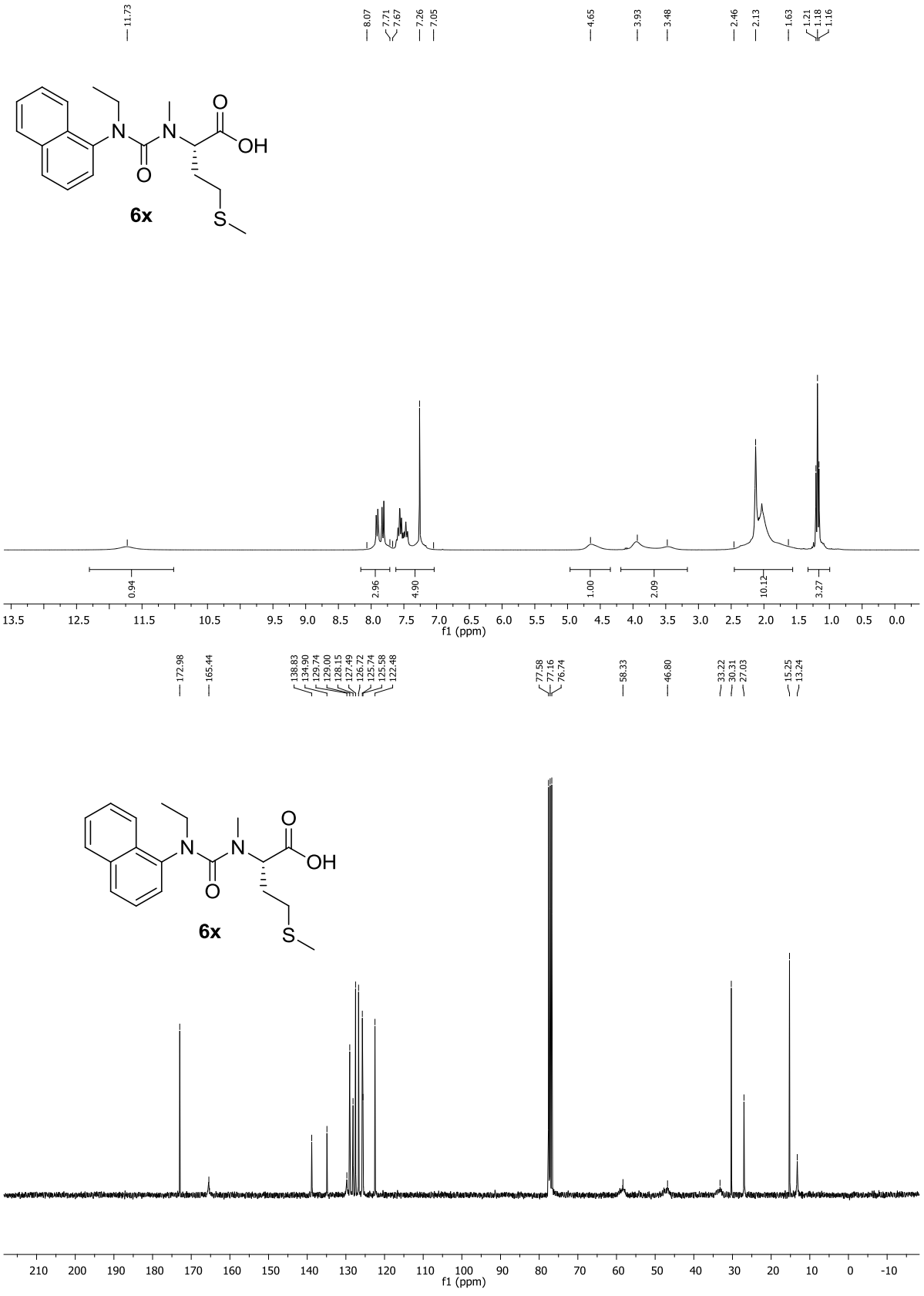
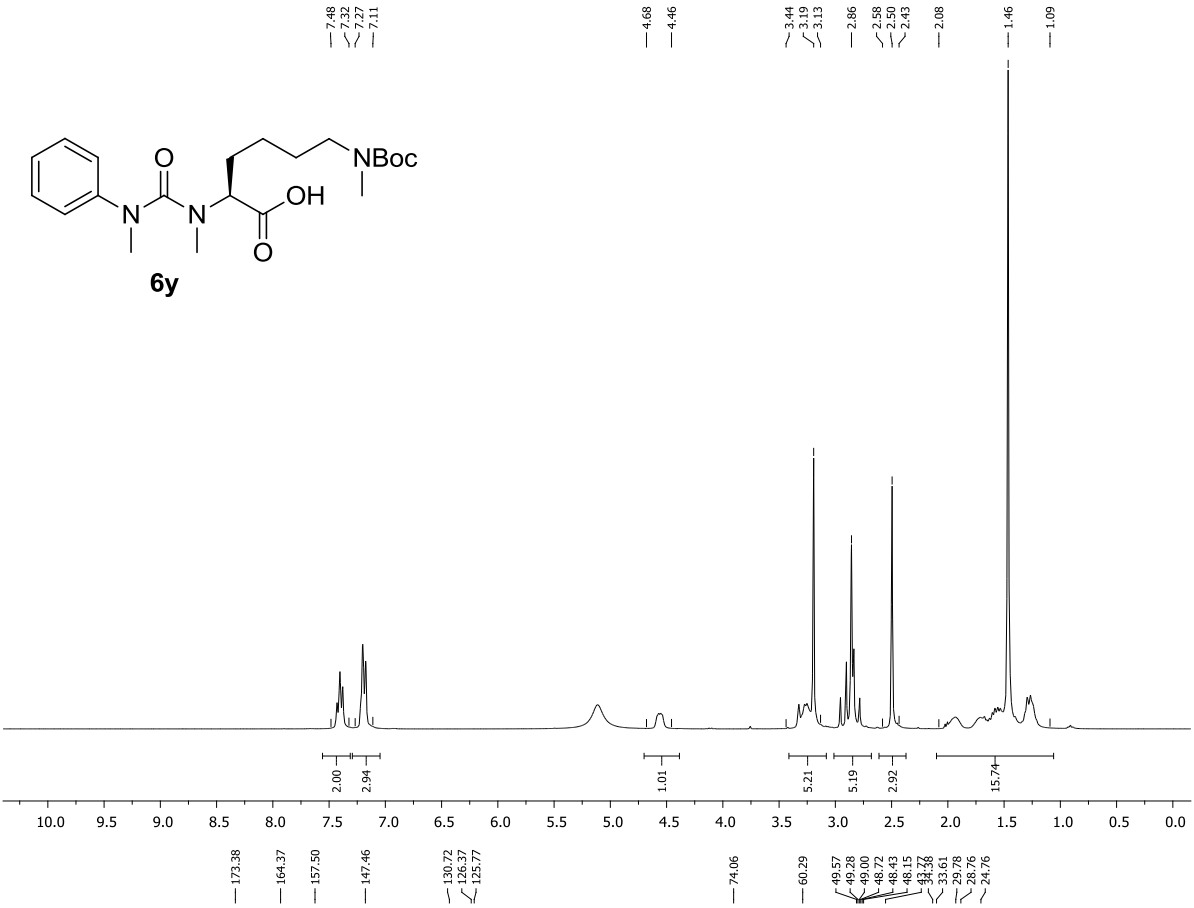
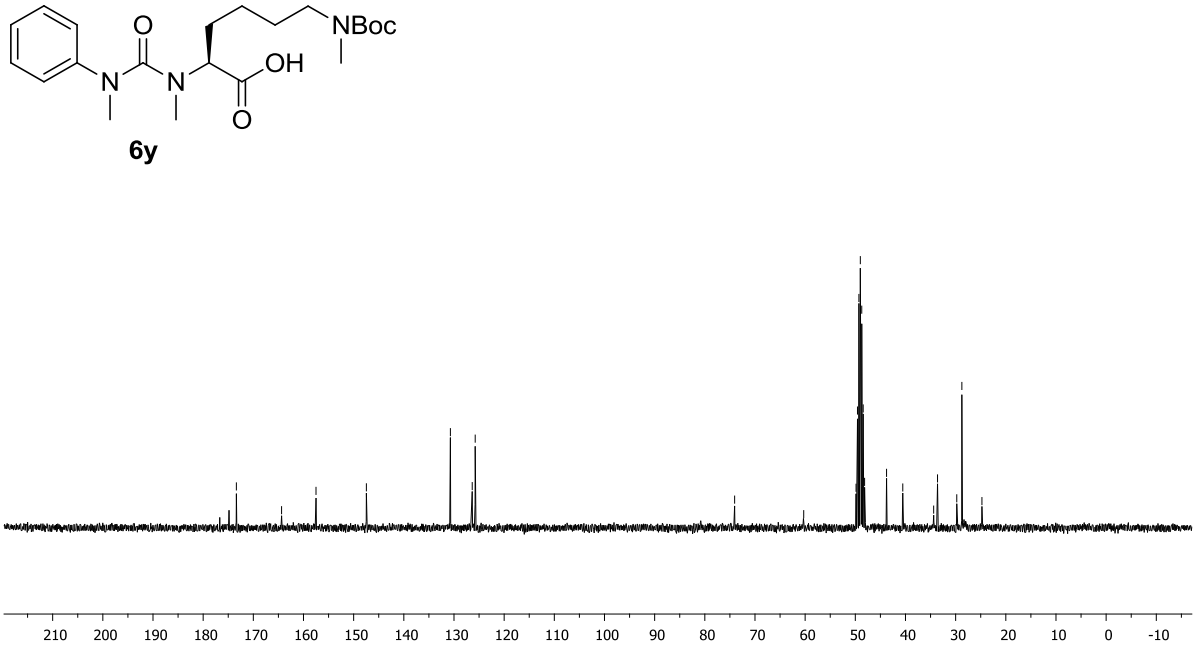
165.51
143.42
134.39
131.91
127.69
127.53
127.15
77.58
77.16
76.74
58.63
39.07
33.10
30.41
27.23
17.85
15.30
6w
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


11.73
8.07
7.71
7.67
7.26
7.05
4.65
3.93
3.48
2.46
2.13
1.63
1.21
1.18
1.16
N
N
O
O
OH
S
6x
0.94
2.96
4.90
1.00
2.09
10.12
3.27
f1 (ppm)
172.98
165.44
138.83
134.90
129.74
129.00
128.15
127.49
126.72
125.74
125.58
122.48
77.58
77.16
76.74
58.33
46.80
33.22
30.31
27.03
15.25
13.24
f1 (ppm)


7.48
7.32
7.27
7.11
4.68
4.46
3.44
3.19
3.13
2.86
2.58
2.50
2.43
2.08
1.46
1.09
NBoc
OH
O
N
N
O
2.00
2.94
1.01
5.21
5.19
2.92
15.74
10.0
9.5
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

6y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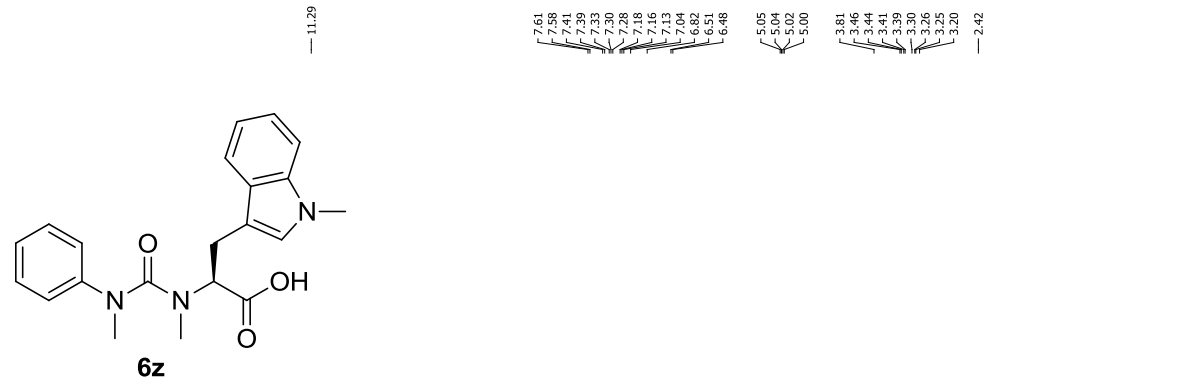
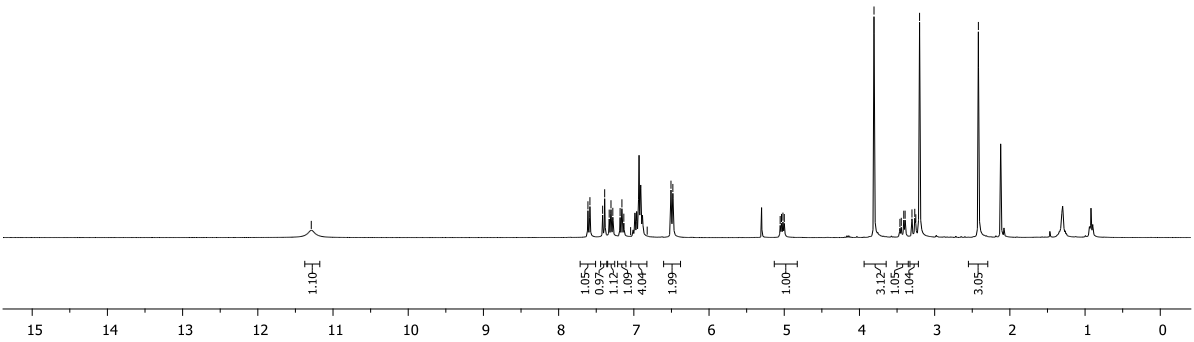
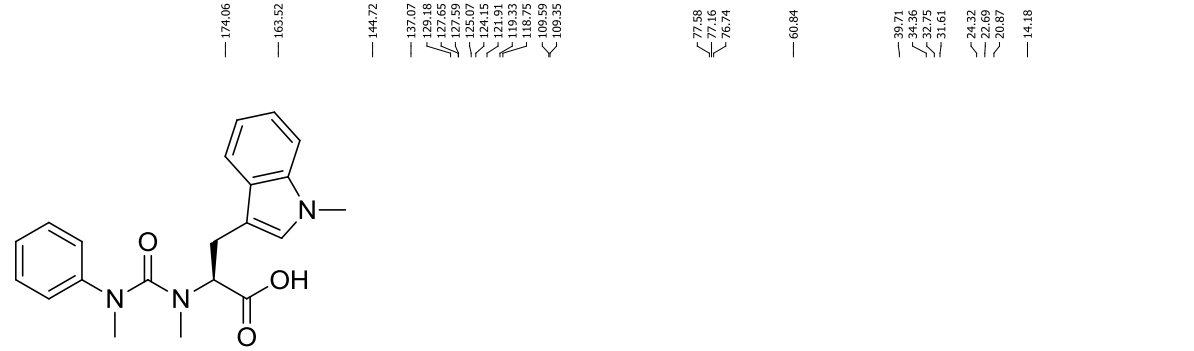
164.37
157.50
147.46
130.72
126.37
125.77
74.06
60.29
49.57
49.28
49.00
48.72
48.43
48.15
34.37
34.18
33.61
29.78
28.76
24.76
NBoc
OH
O
N
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

6y


11.29
7.61
7.58
7.41
7.39
7.33
7.30
7.28
7.18
7.16
7.13
7.04
6.82
6.51
6.48
5.05
5.04
5.02
5.00
3.81
3.46
3.44
3.41
3.39
3.30
3.26
3.25
3.20
2.42
N
O
N
N
OH
O

6z


1.10
1.05
0.97
1.12
1.09
4.04
1.99
1.00
3.12
1.05
1.04
3.05
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0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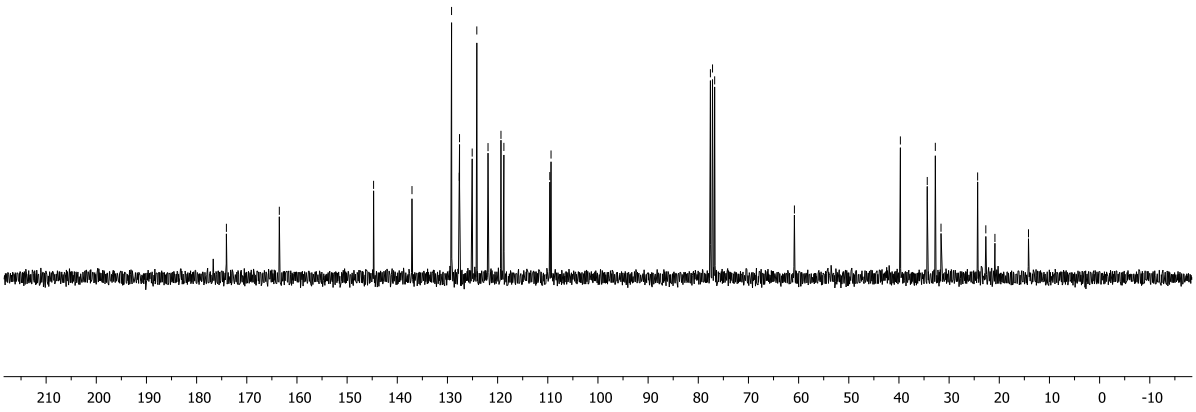
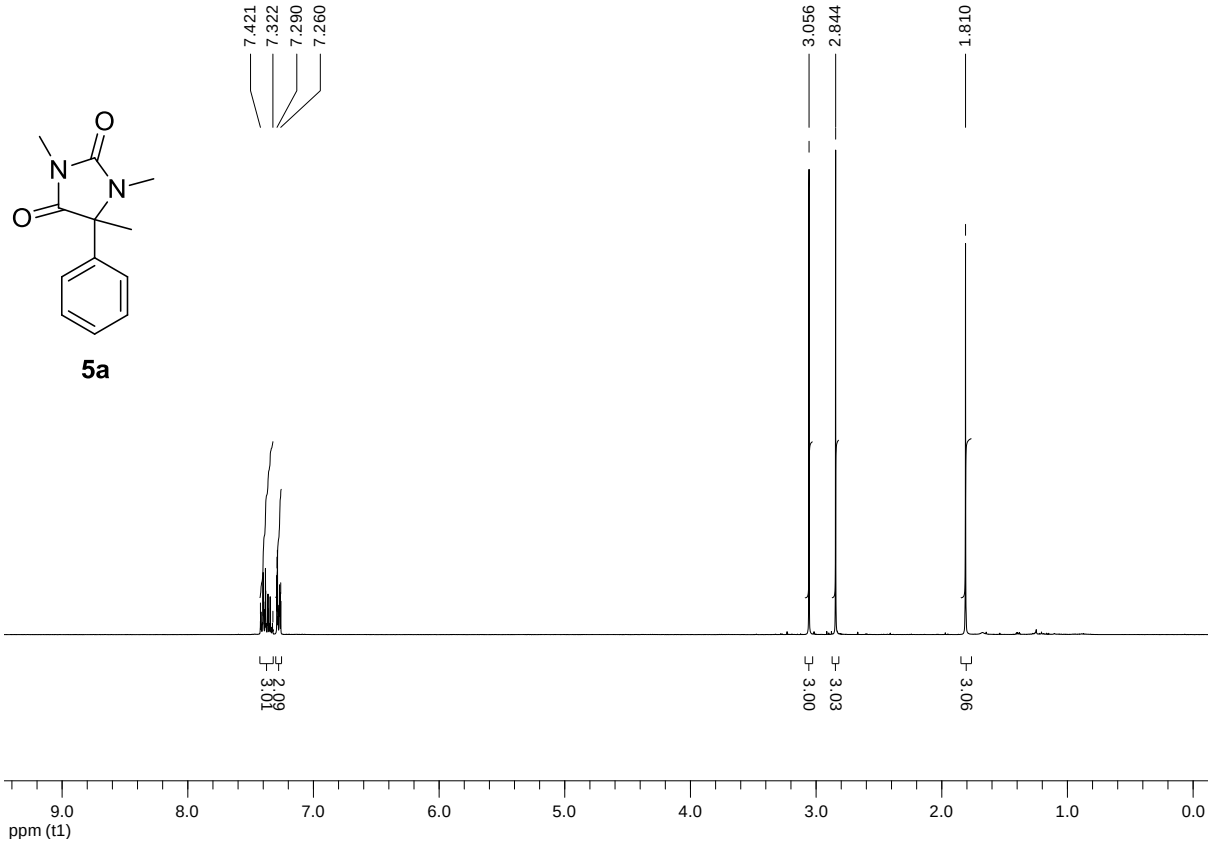
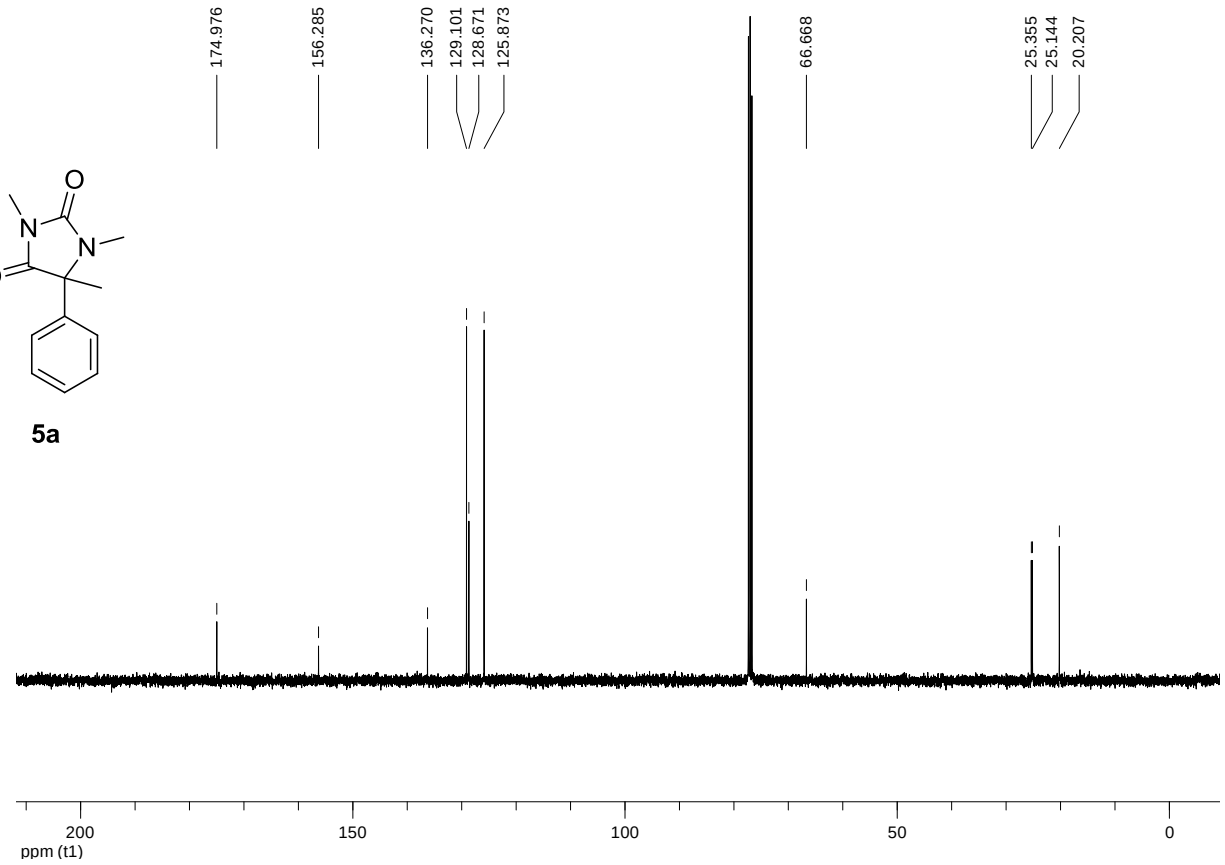
163.52
144.72
137.07
129.18
127.65
127.59
125.07
124.15
121.91
119.33
118.75
109.59
109.35
77.58
77.16
76.74
60.84
39.71
34.36
32.75
31.61
24.32
22.69
20.87
14.18
N
O
N
N
OH
O

6z

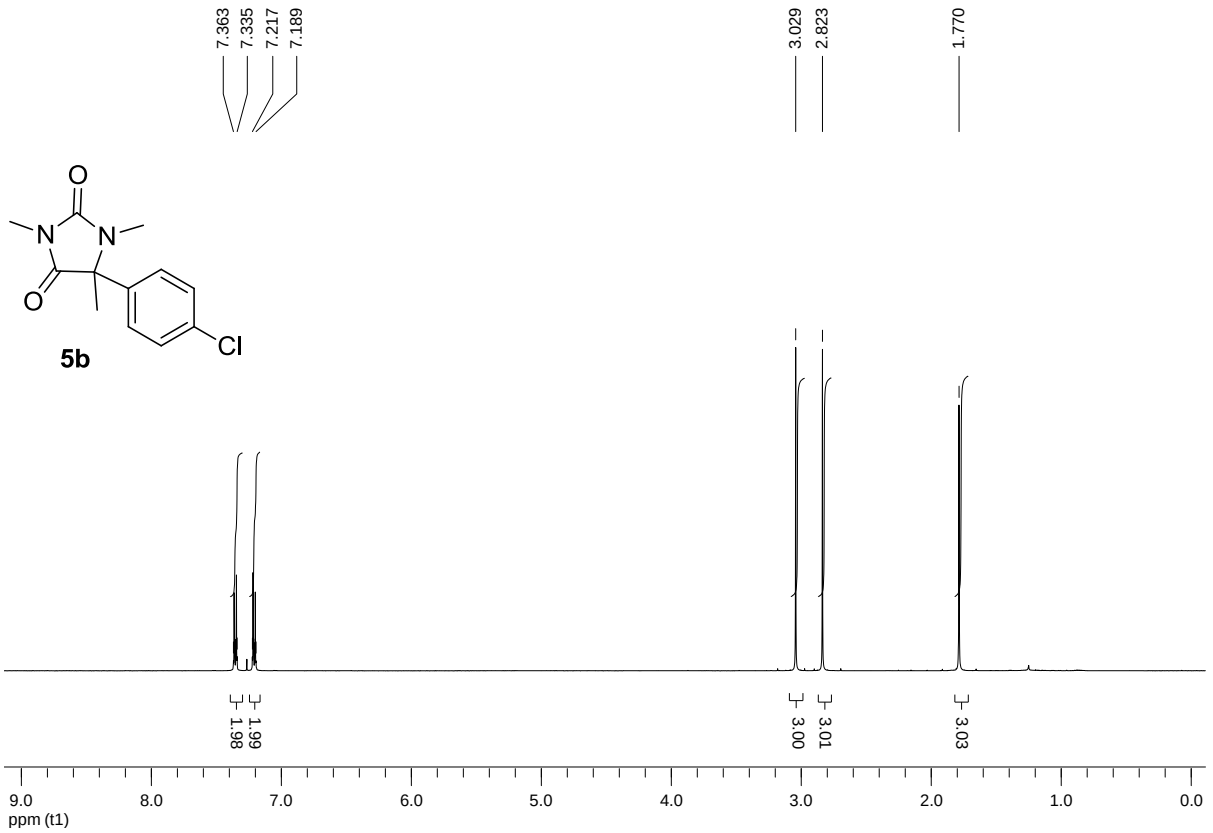

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

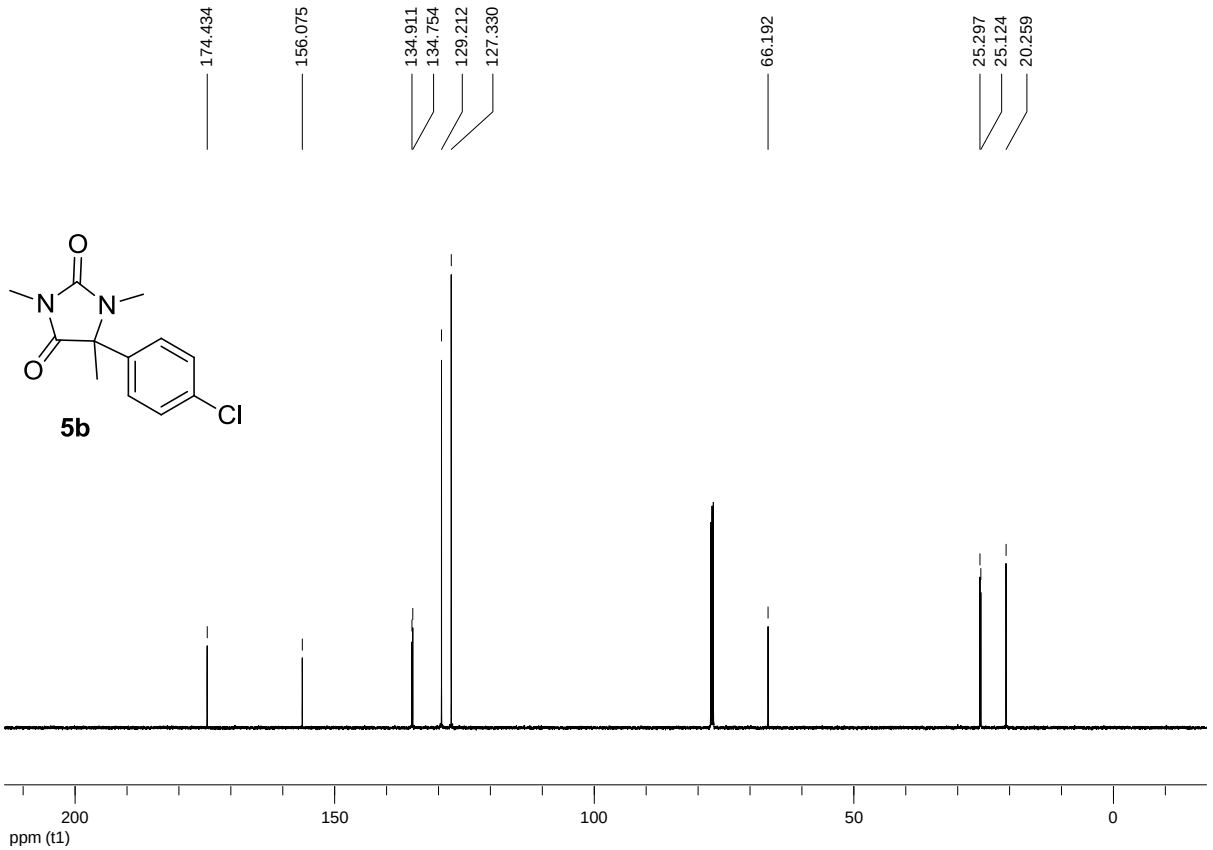

7.421
7.322
7.290
7.260
3.056
2.844
1.810
2.09
2.01
3.00
3.03
3.06
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

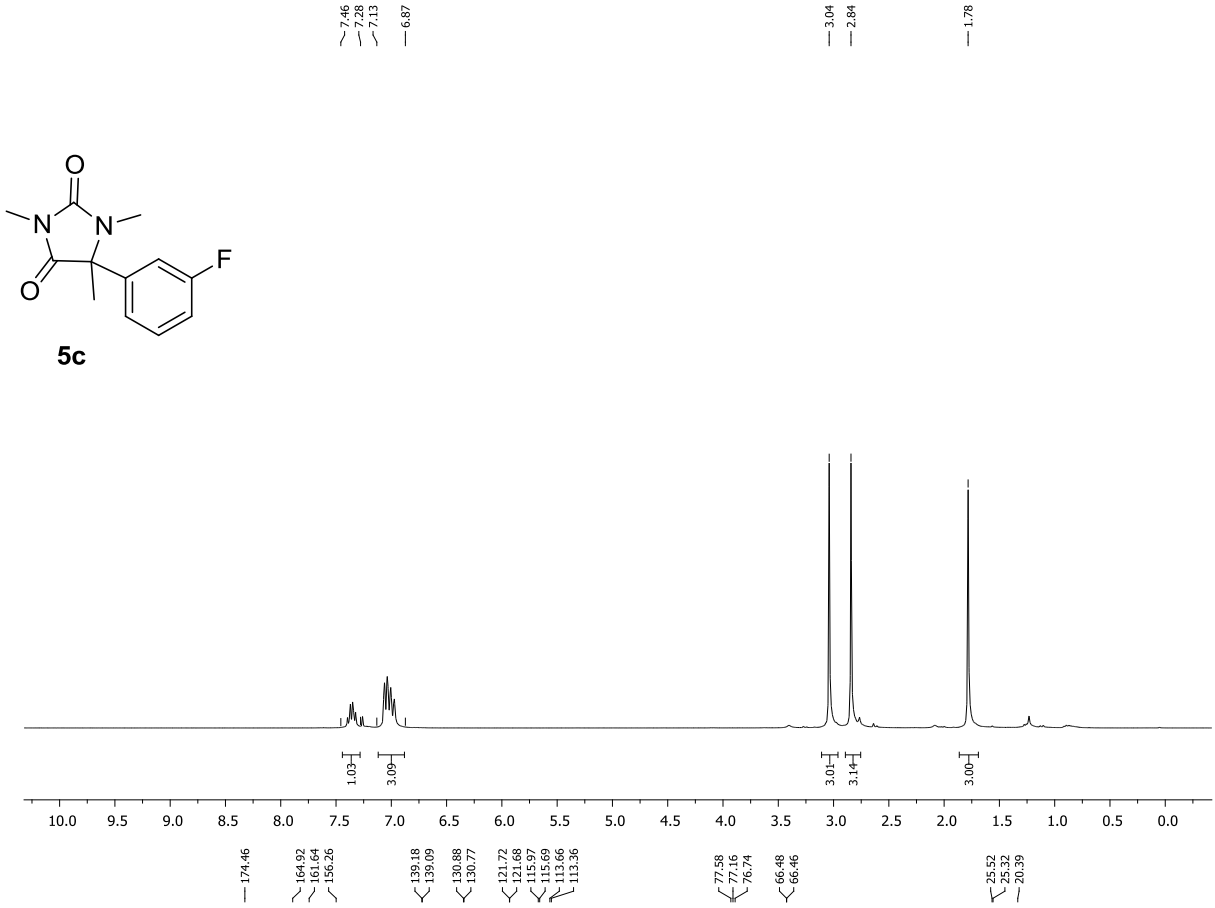
5a


174.976
156.285
136.270
129.101
128.671
125.873
66.668
25.355
25.144
20.207
200
150
100
50
0
ppm (t1)

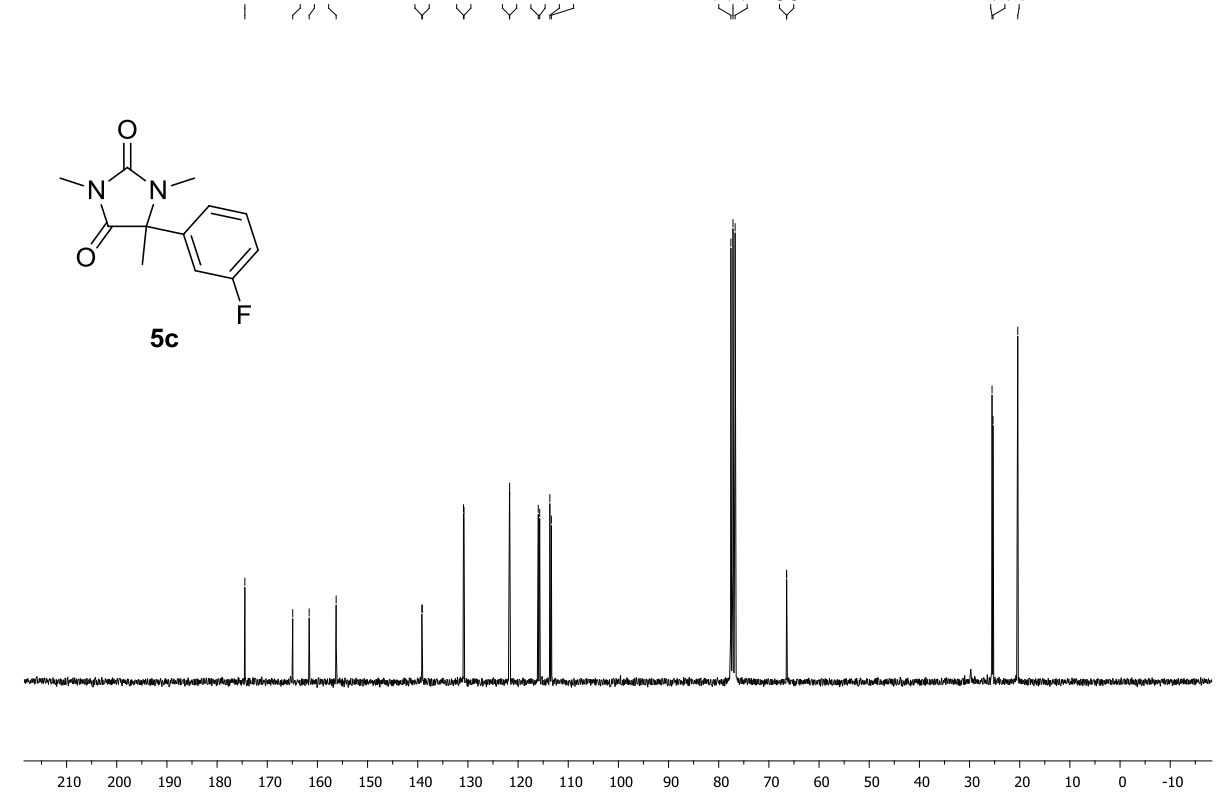
5a



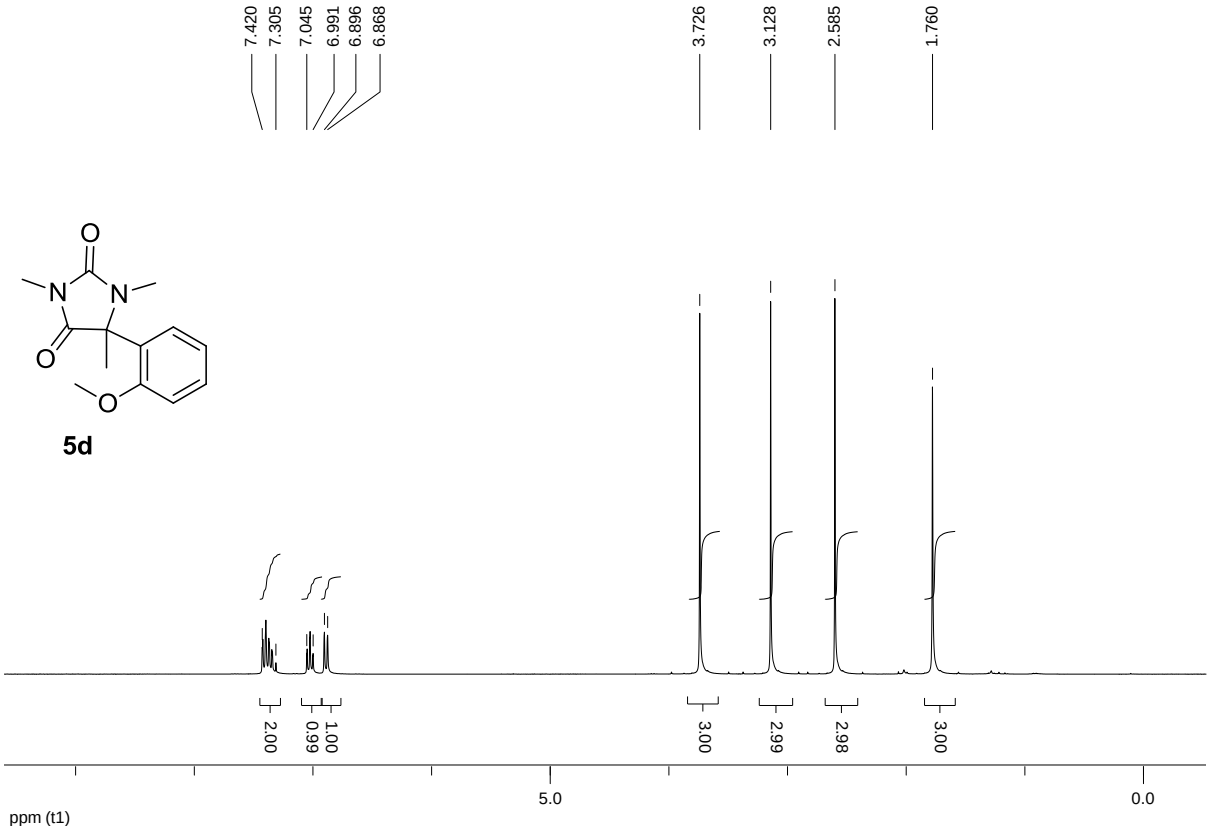


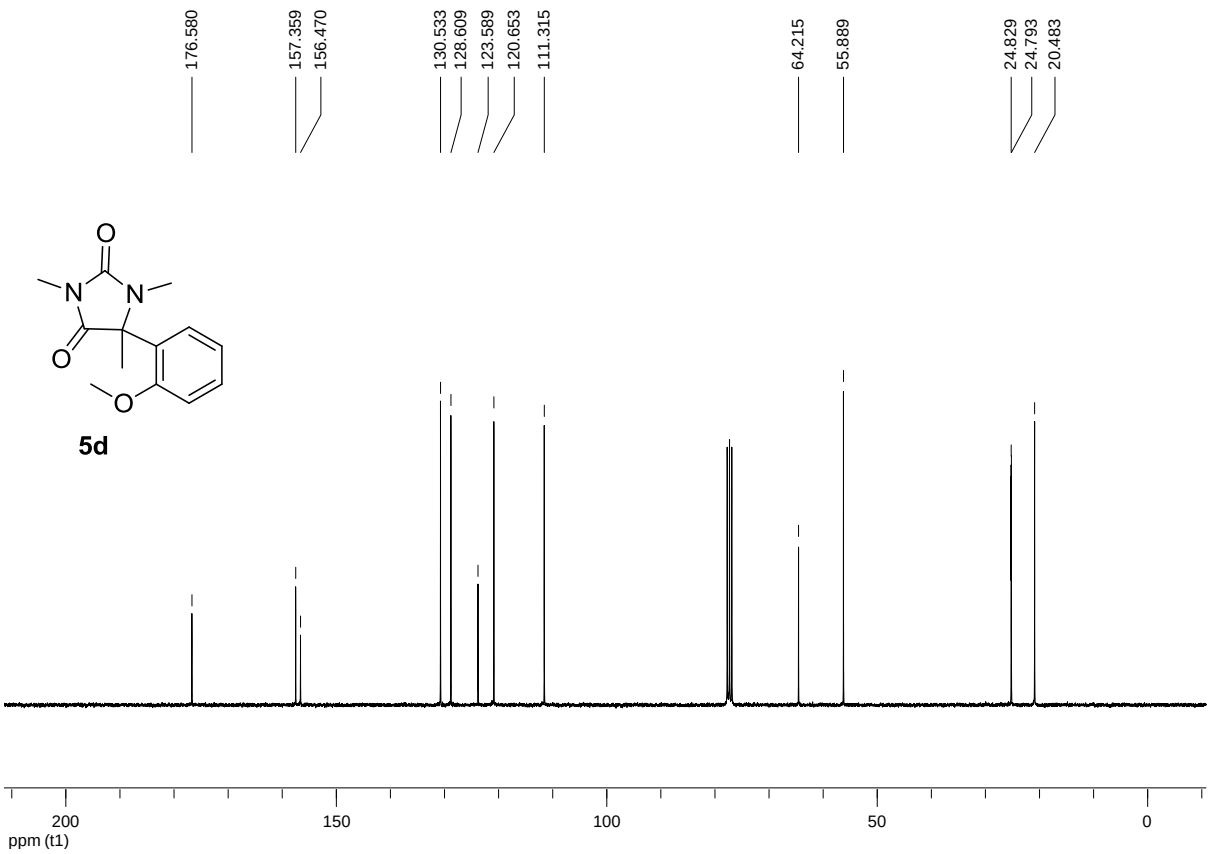

7.46
7.28
7.13
6.87
3.04
2.84
1.78
1.03
3.09
3.01
3.14
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

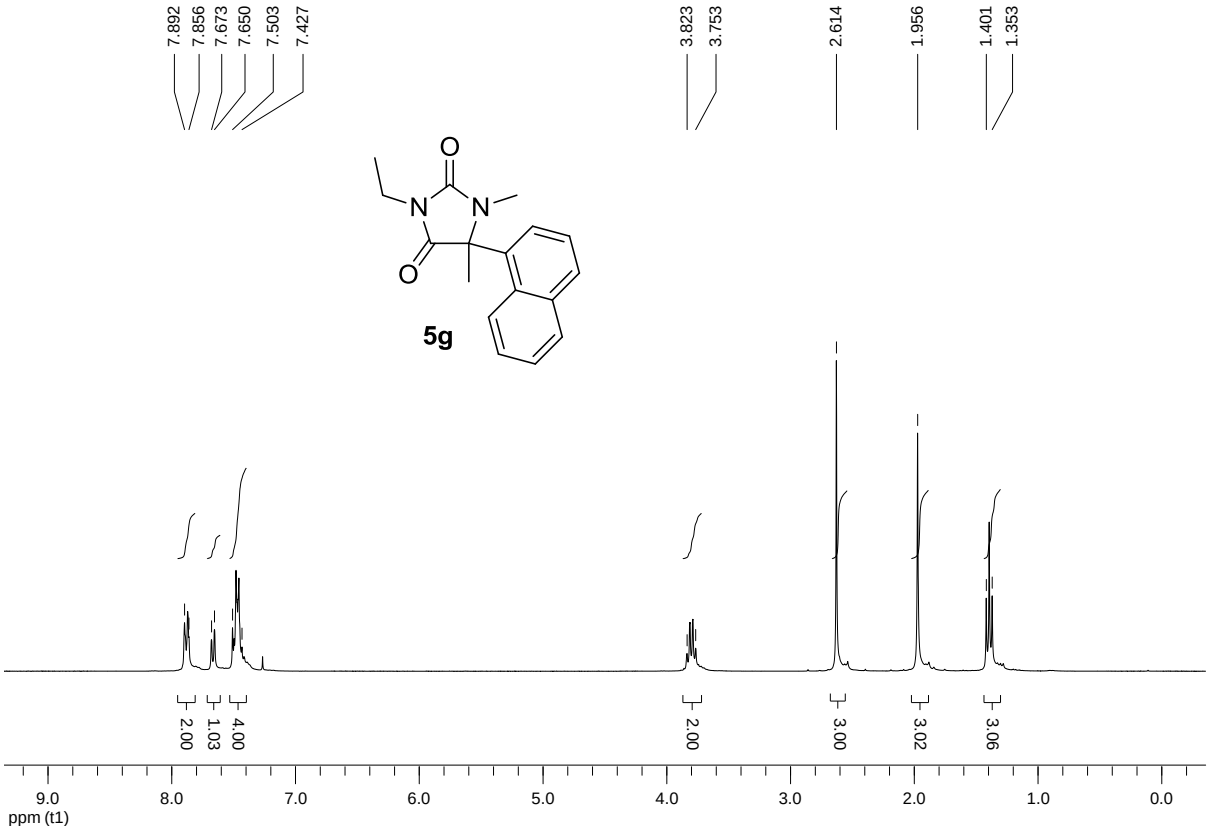
5c

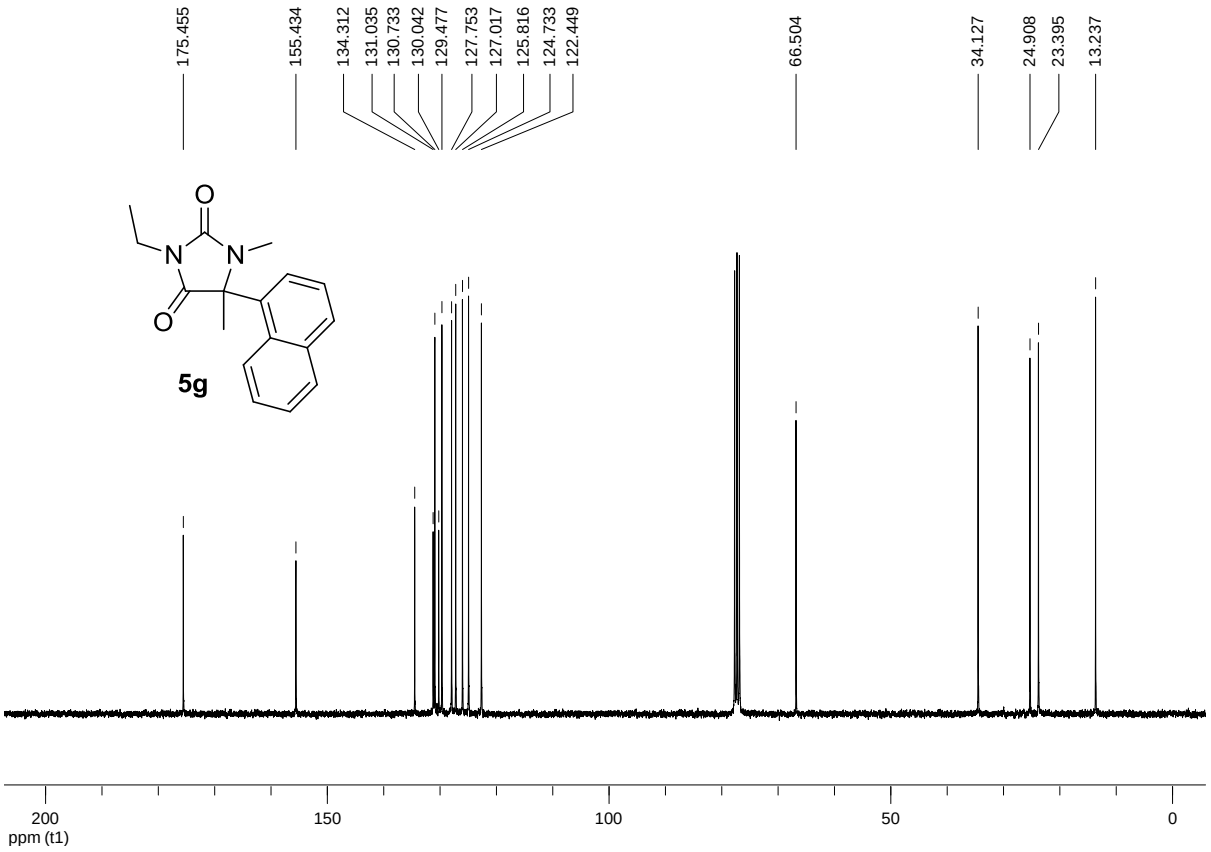

174.46
164.92
161.64
156.26
139.18
139.09
130.88
130.77
121.72
121.68
115.97
115.69
113.66
113.36
77.58
77.16
76.74
66.48
66.46
25.52
25.32
20.39
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

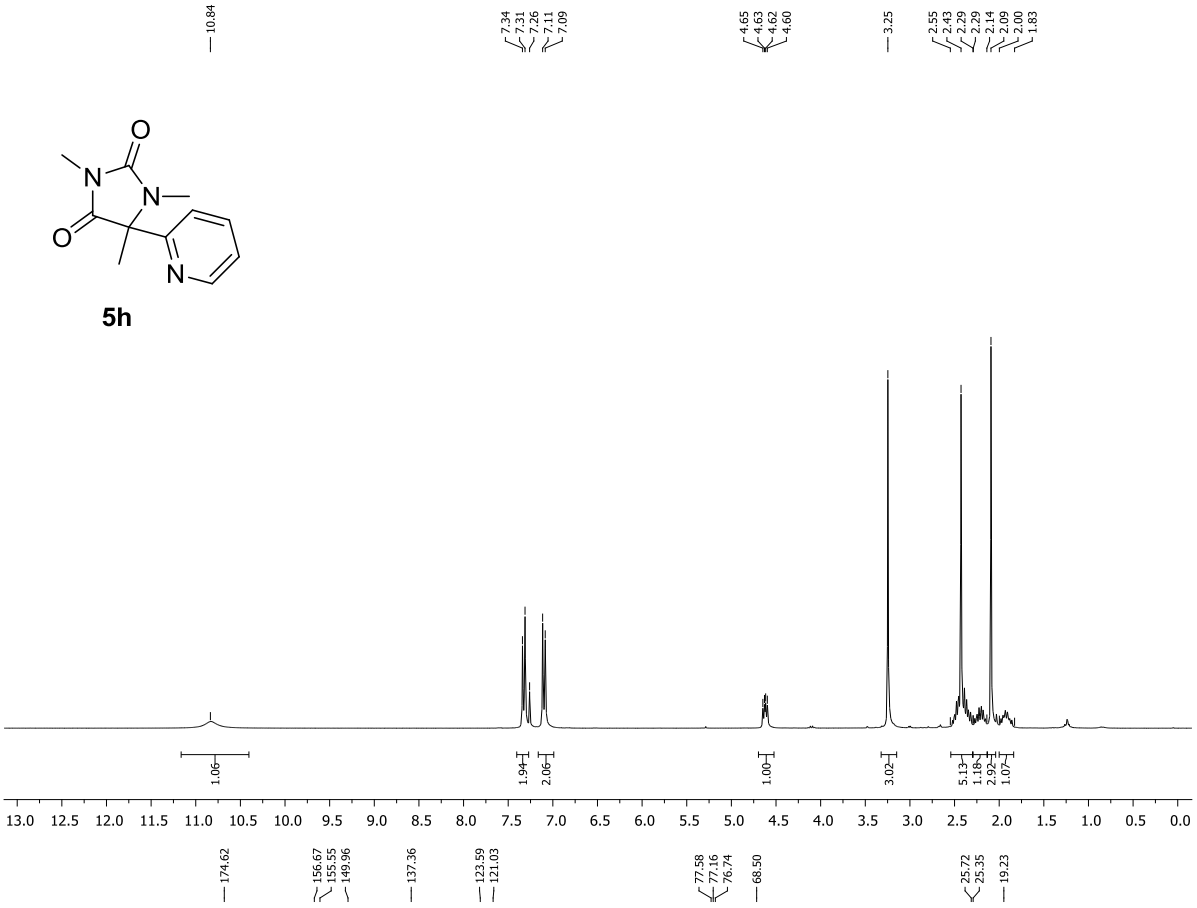
5c



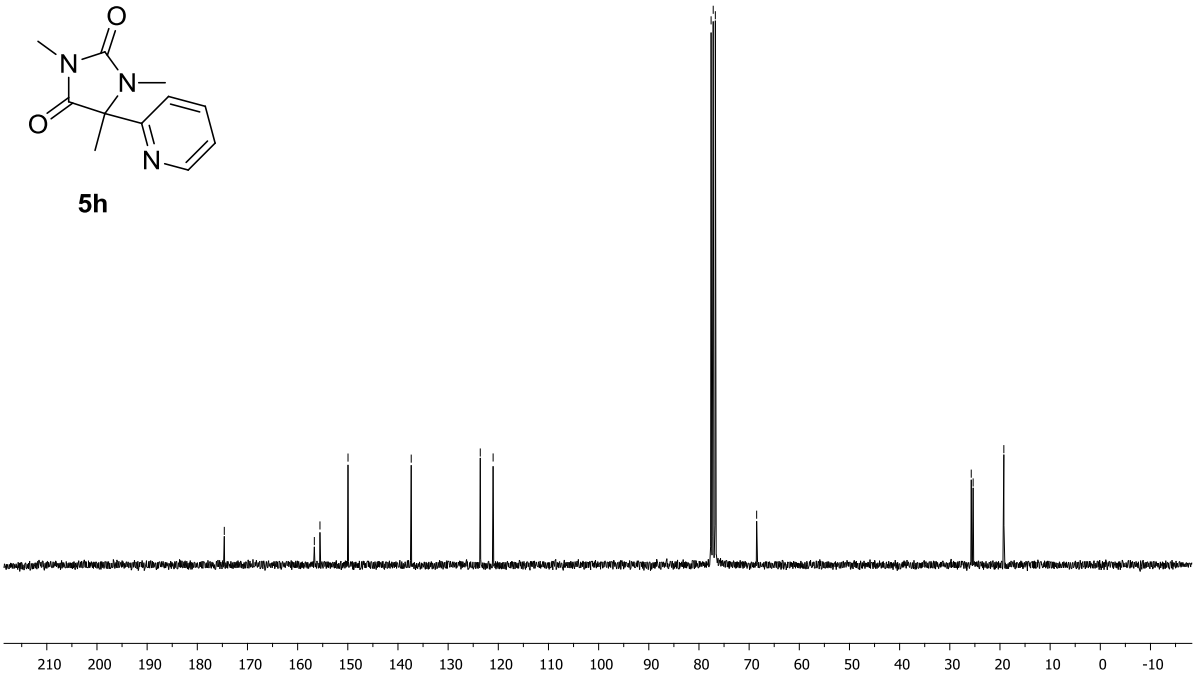



7.892
7.856
7.673
7.650
7.503
7.427
3.823
3.753
2.614
1.956
1.401
1.353
5g
2.00
1.03
4.00
2.00
3.00
3.02
3.06
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

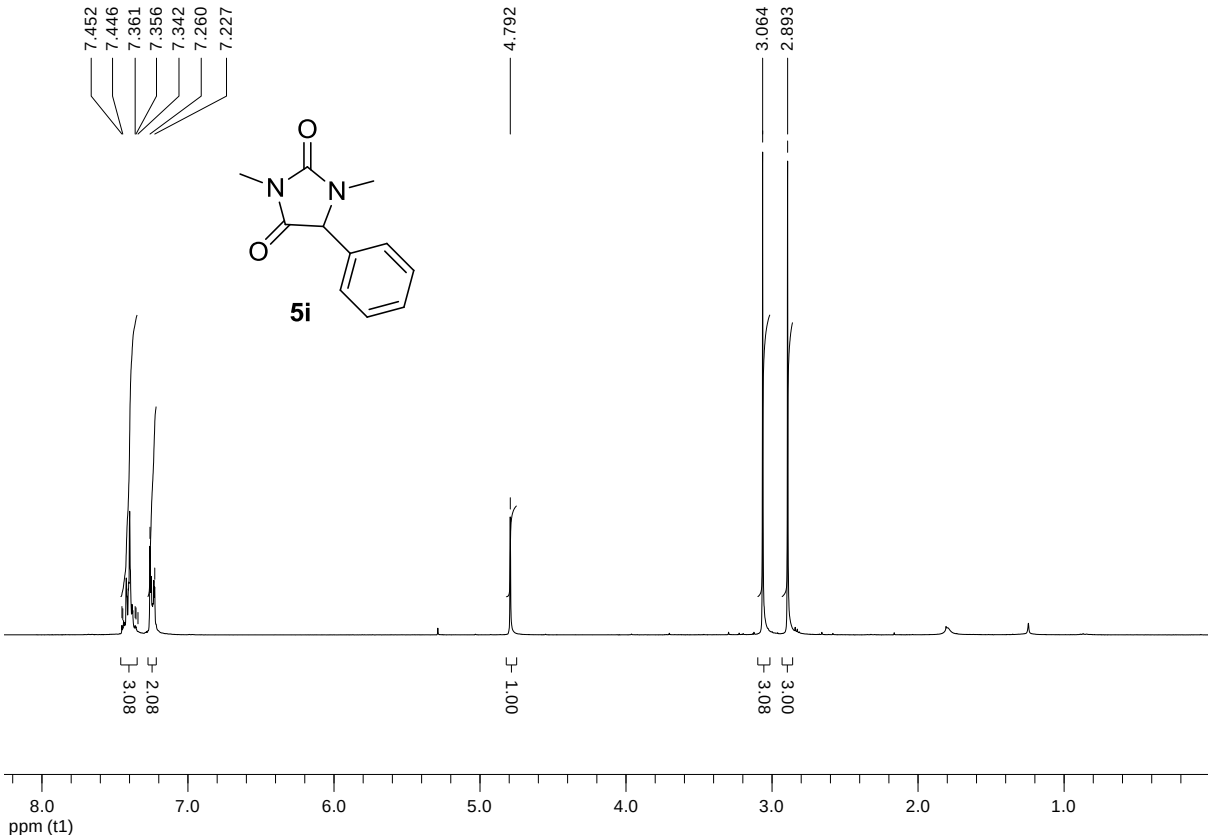

175.455
155.434
134.312
131.035
130.733
130.042
129.477
127.753
127.017
125.816
124.733
122.449
66.504
34.127
24.908
23.395
13.237
5g
200
150
100
50
0
ppm (t1)

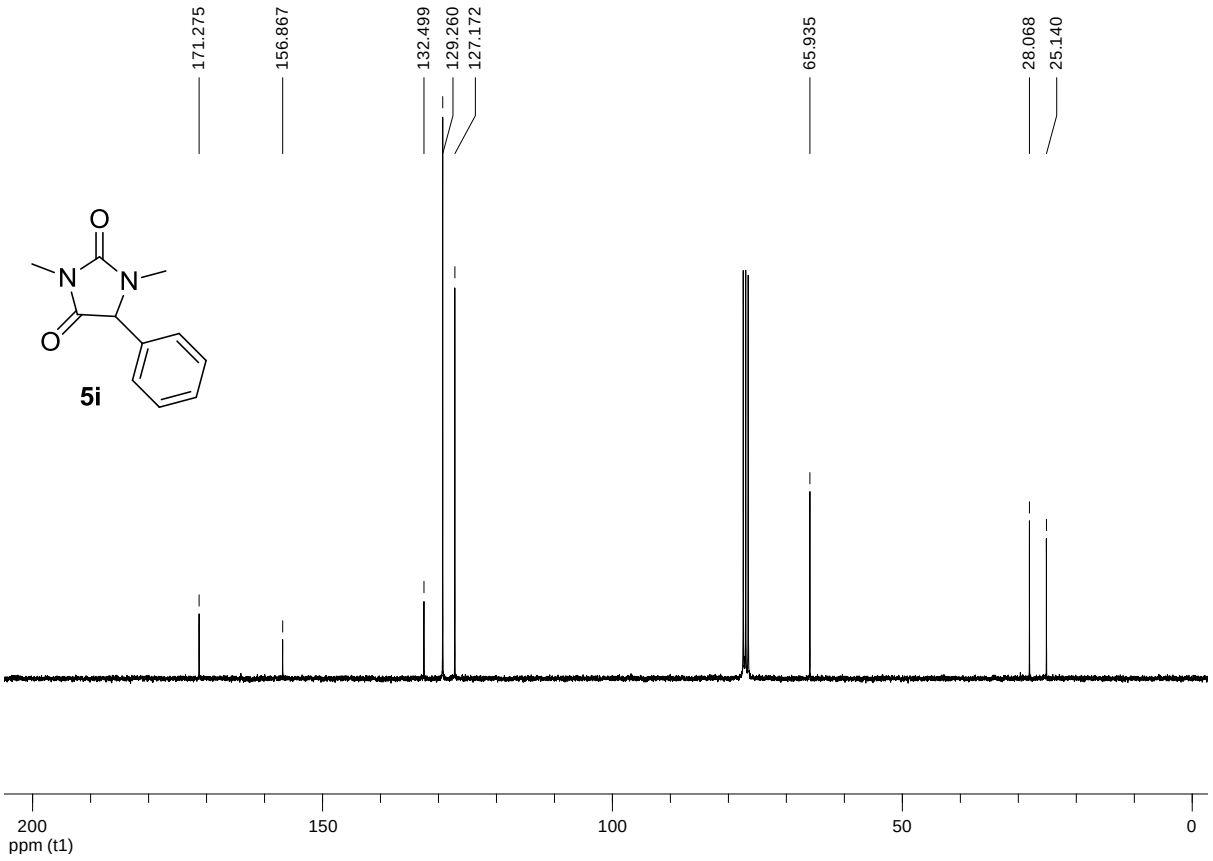

10.84
7.34
7.31
7.26
7.11
7.09
4.65
4.63
4.62
4.60
3.25
2.55
2.43
2.29
2.29
2.14
2.09
2.00
1.83
1.06
1.94
2.06
1.00
3.02
5.13
1.18
2.92
1.07
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

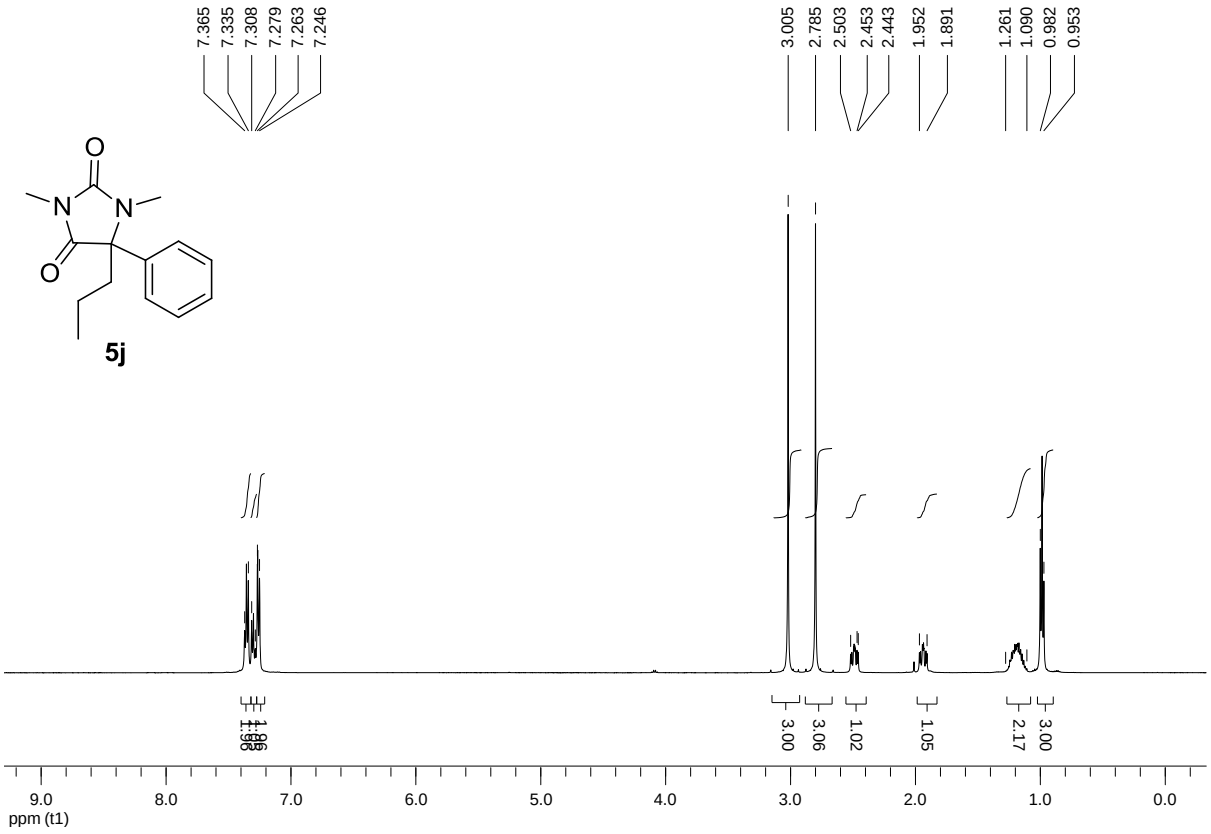
5h

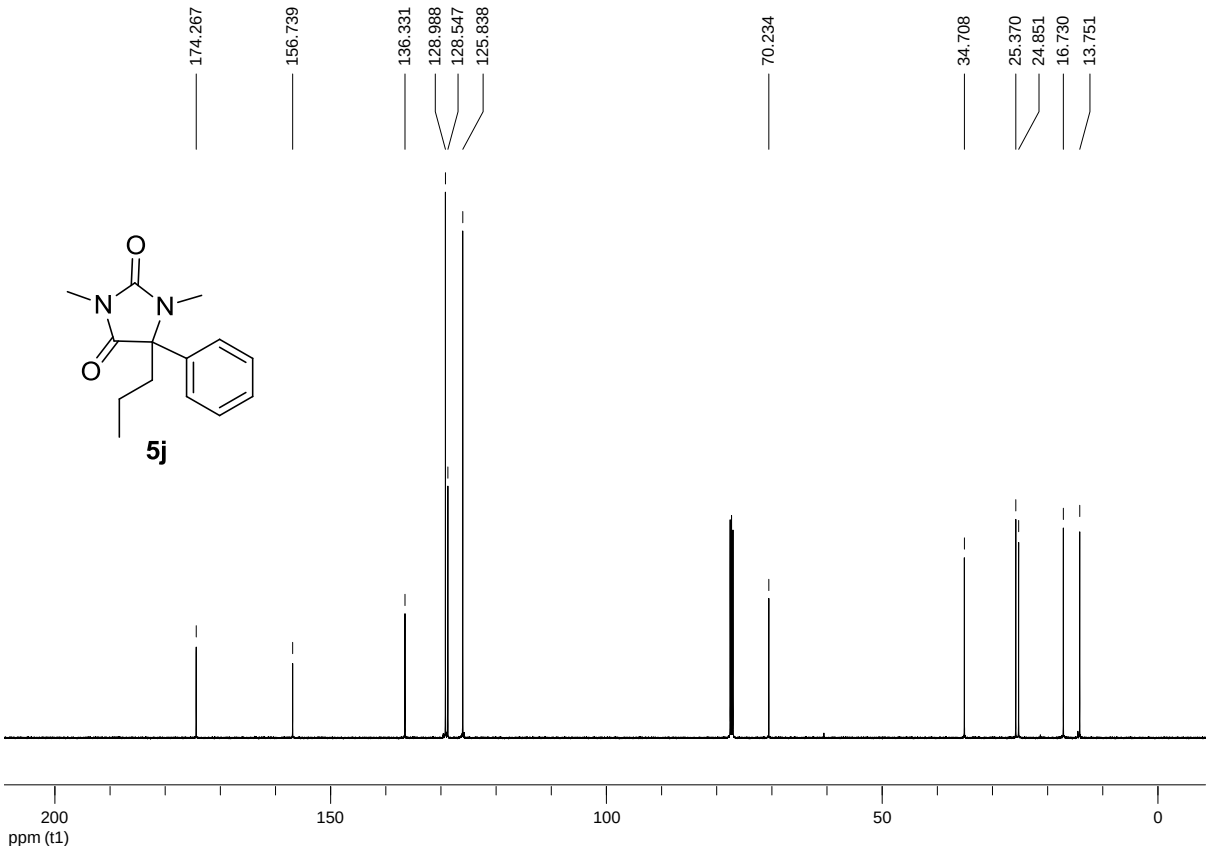

174.62
156.67
155.55
149.96
137.36
123.59
121.03
77.58
77.16
76.74
68.50
25.72
25.35
19.23
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

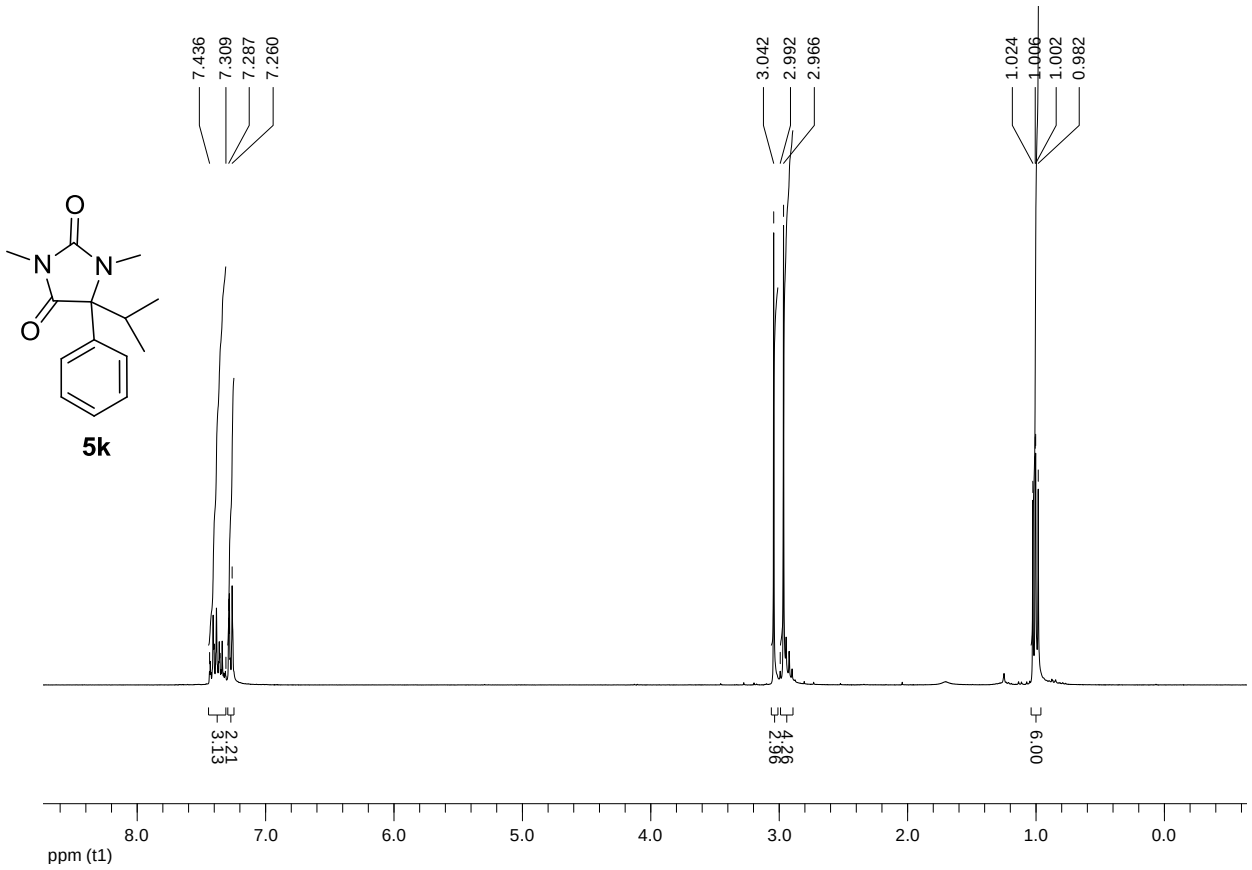
5h

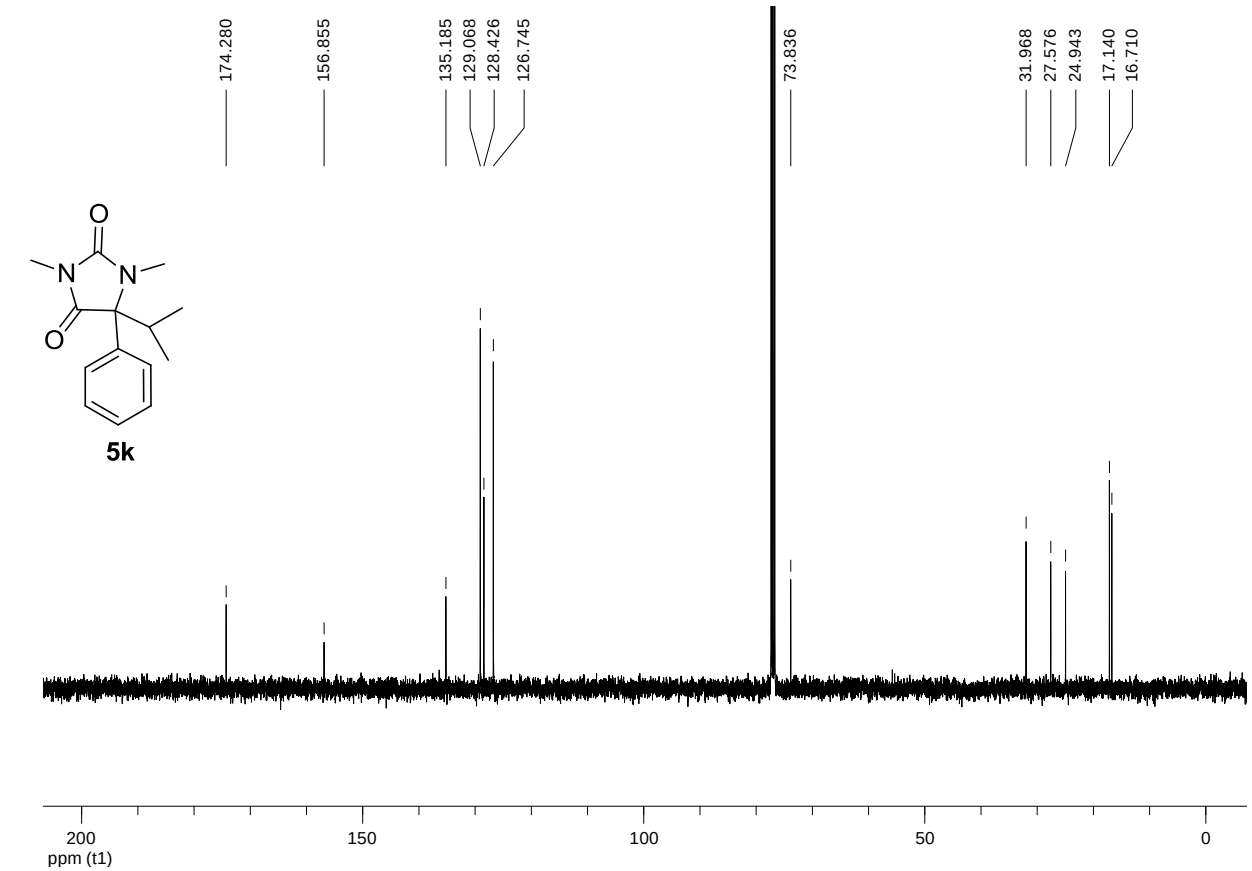

7.452
7.446
7.361
7.356
7.342
7.260
7.227
4.792
3.064
2.893
5i
3.08
2.08
1.00
3.08
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

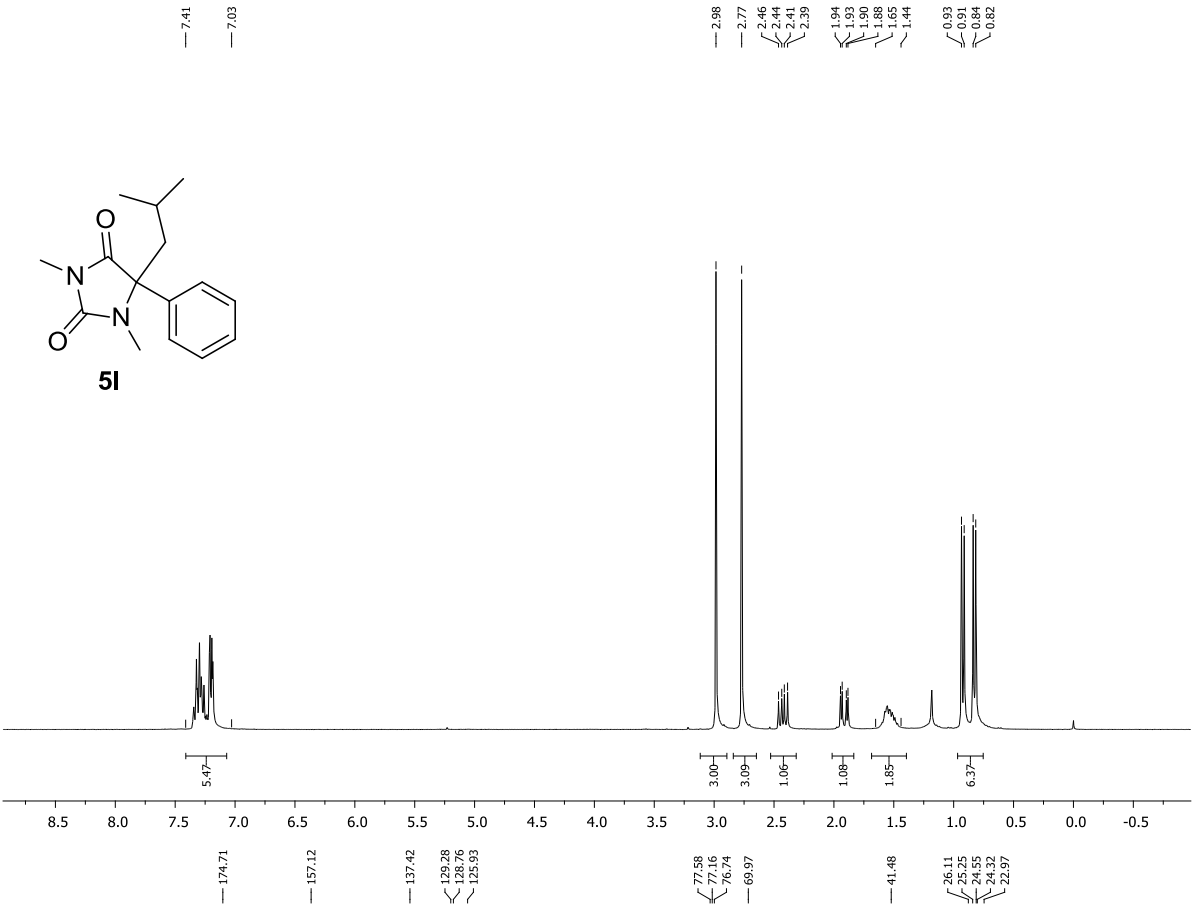

171.275
156.867
132.499
129.260
127.172
65.935
28.068
25.140
5i
200
150
100
50
0
ppm (t1)



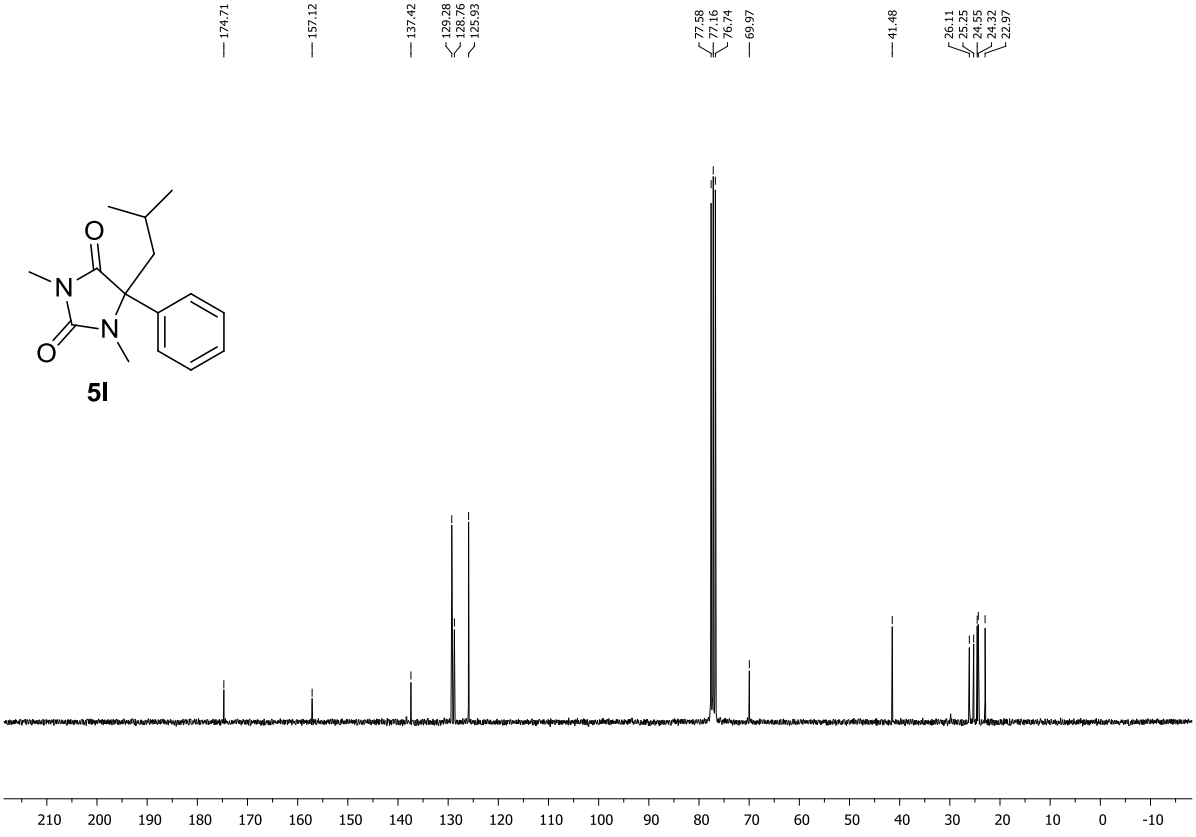



7.436
7.309
7.287
7.260
3.042
2.992
2.966
1.024
1.006
1.002
0.982
5k
2.21
3.13
4.26
6.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

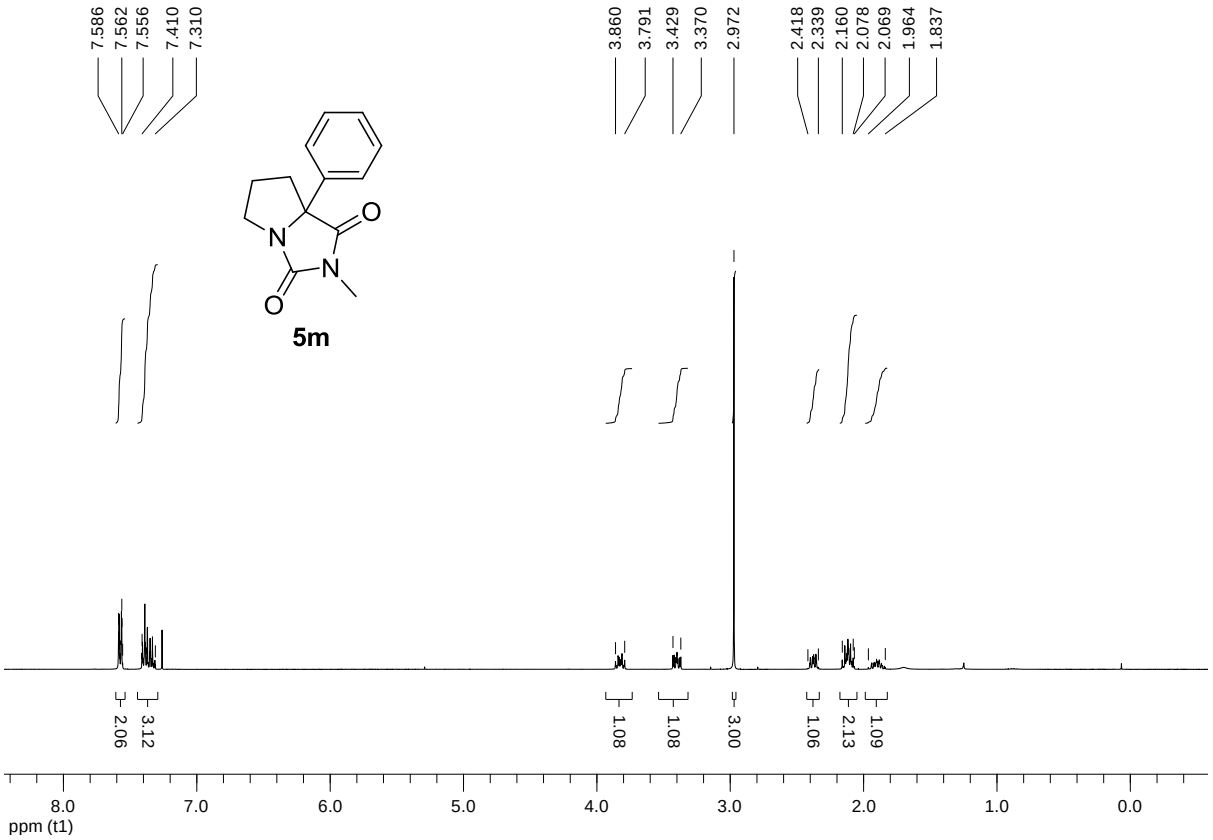

174.280
156.855
135.185
129.068
128.426
126.745
73.836
31.968
27.576
24.943
17.140
16.710
5k
200
150
100
50
0
ppm (t1)

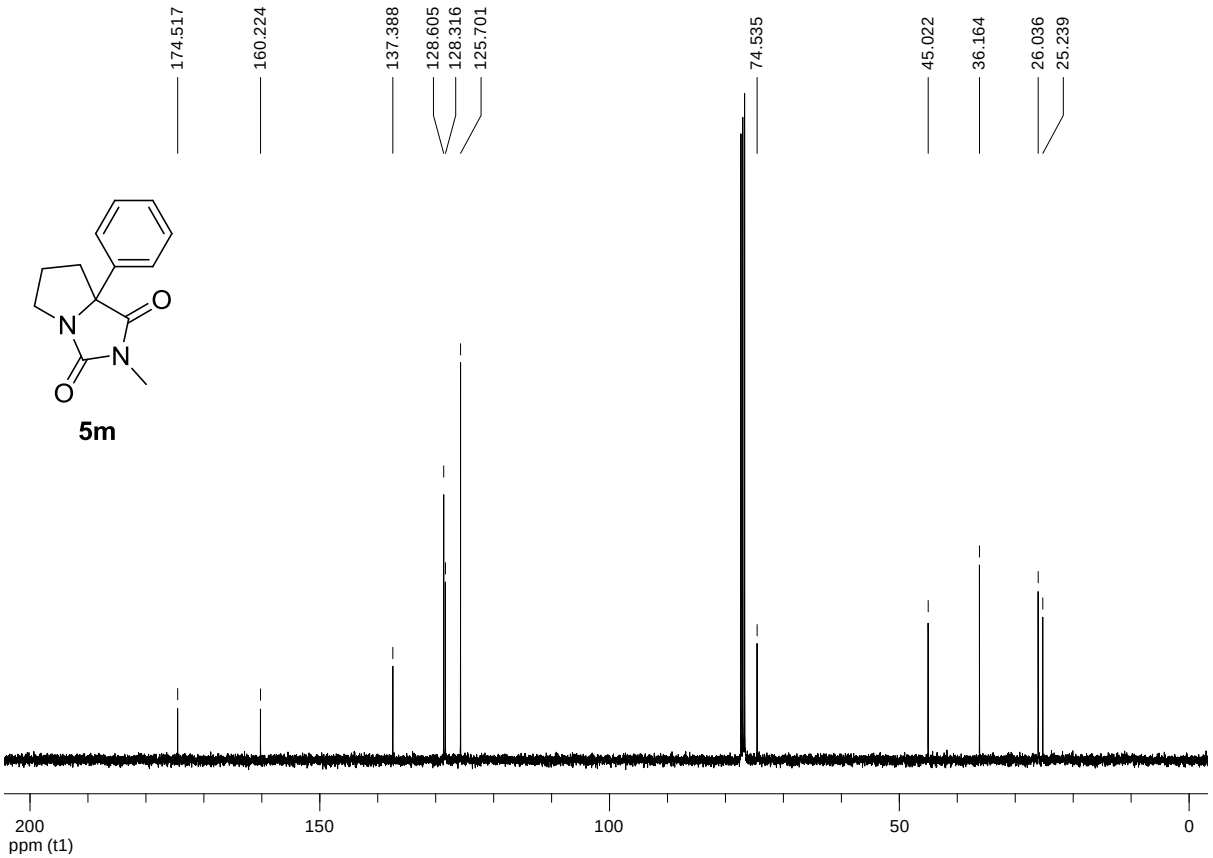

7.41
7.03
2.98
2.77
2.46
2.44
2.41
2.39
1.94
1.93
1.90
1.88
1.65
1.44
0.93
0.91
0.84
0.82
5.47
3.00
3.09
1.06
1.08
1.85
6.37
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

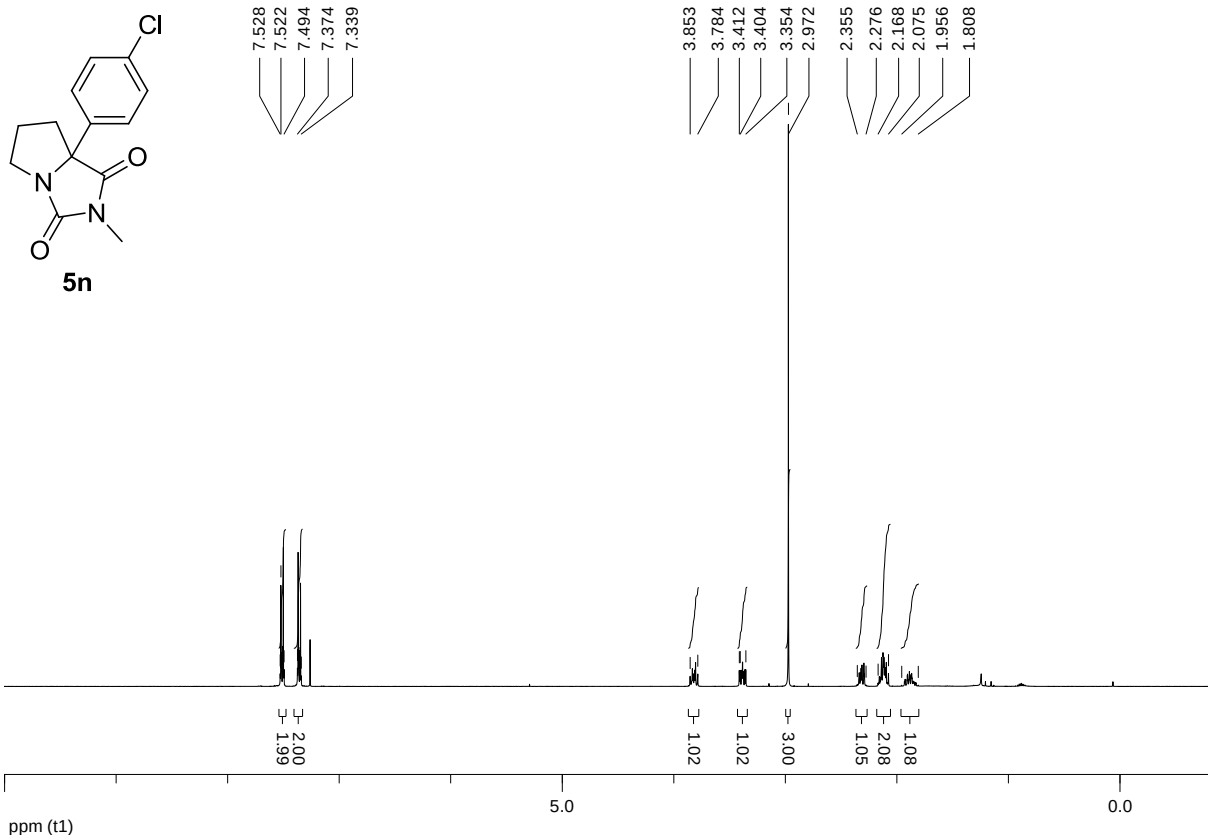
5l

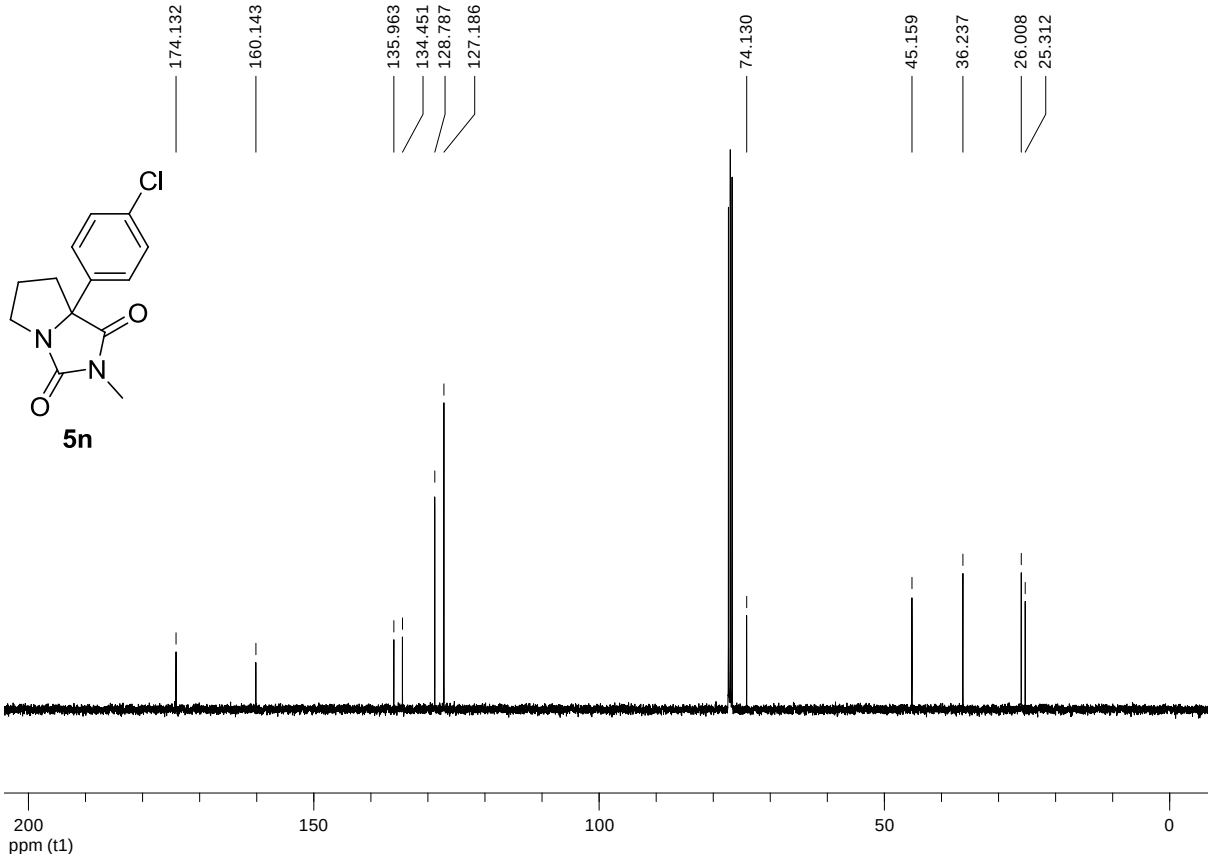

174.71
157.12
137.42
129.28
128.76
125.93
77.58
77.16
76.74
69.97
41.48
26.11
25.25
24.55
24.32
22.97
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

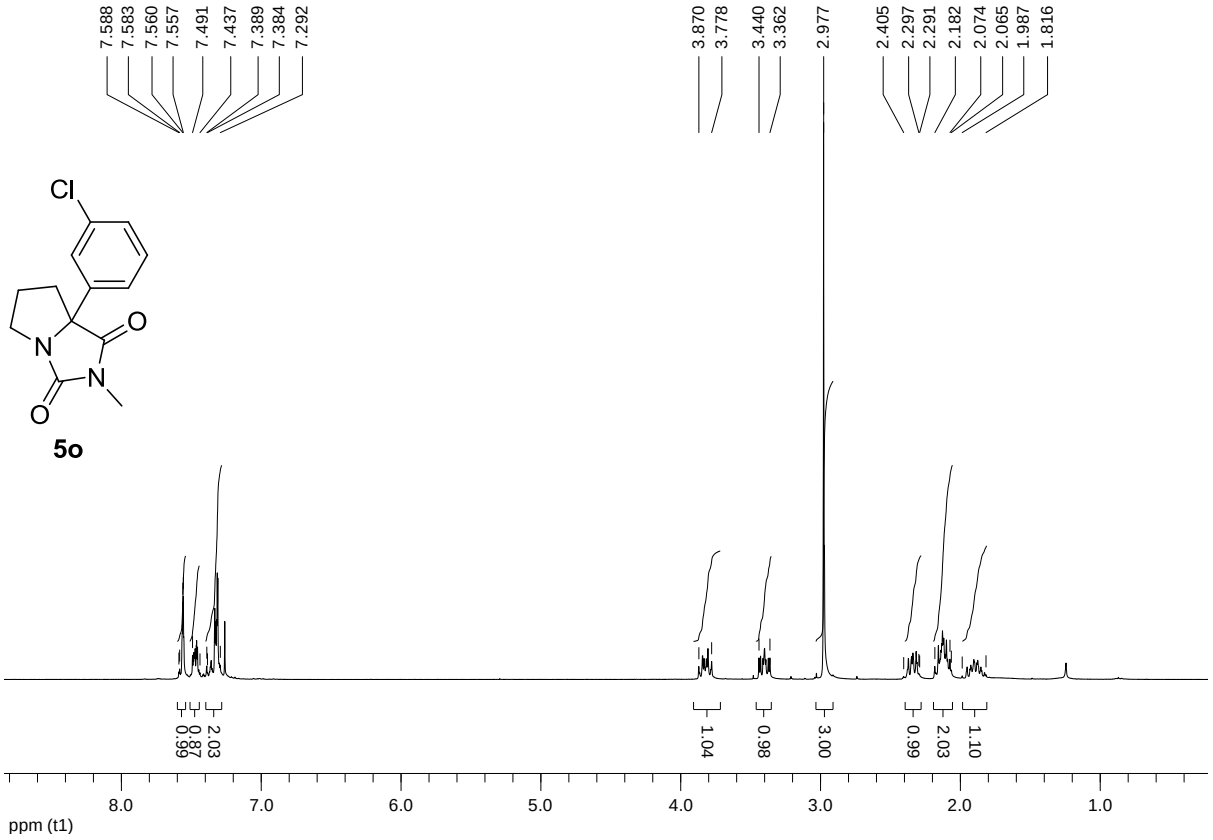
5l

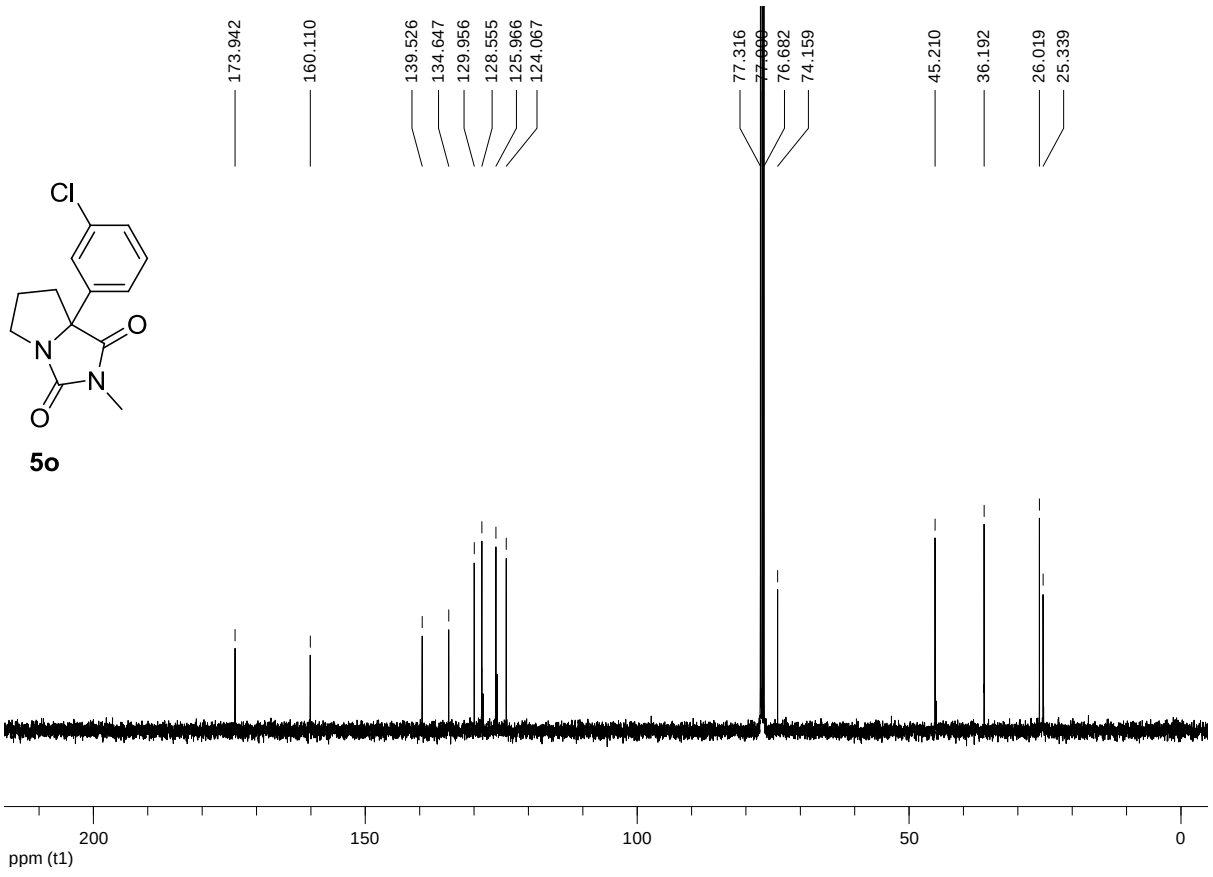

7.586
7.562
7.556
7.410
7.310
3.860
3.791
3.429
3.370
2.972
2.418
2.339
2.160
2.078
2.069
1.964
1.837
5m
2.06
3.12
1.08
1.08
3.00
1.06
2.13
1.09
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

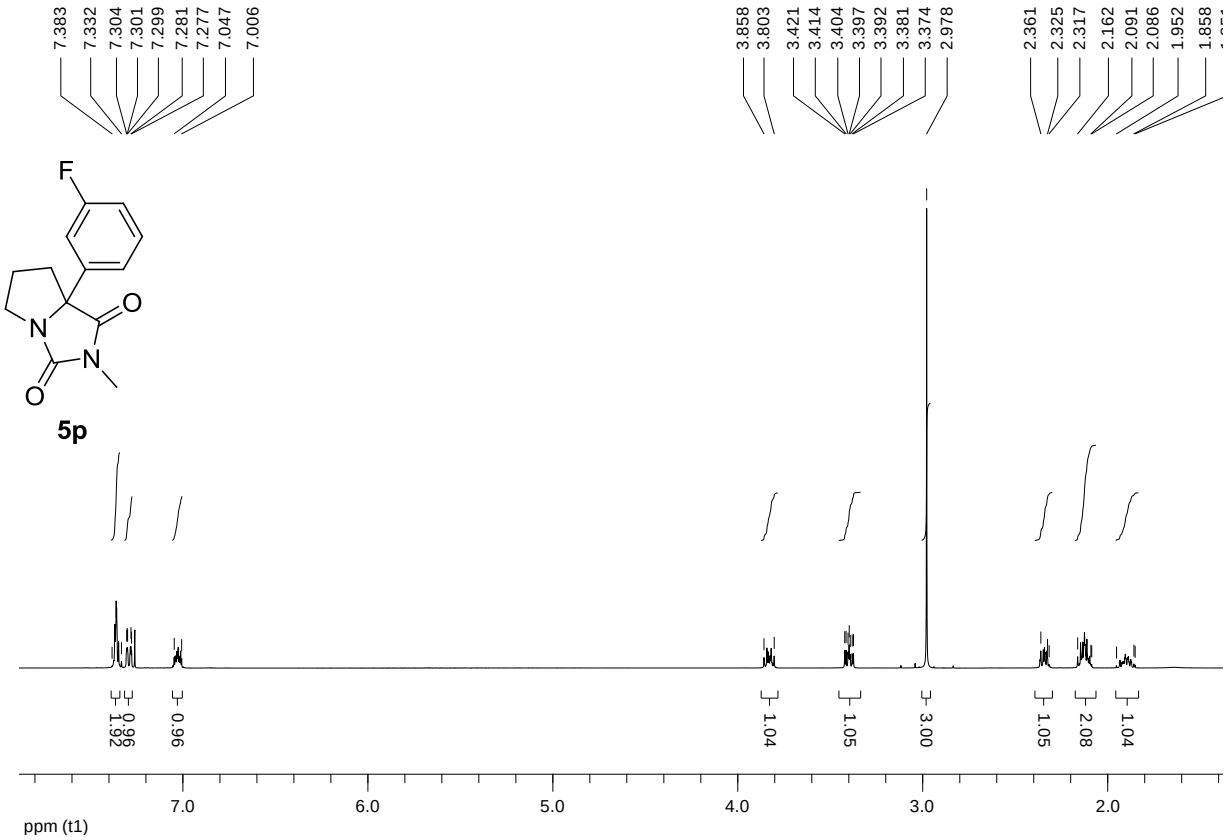

174.517
160.224
137.388
128.605
128.316
125.701
74.535
45.022
36.164
26.036
25.239
5m
200
150
100
50
0
ppm (t1)

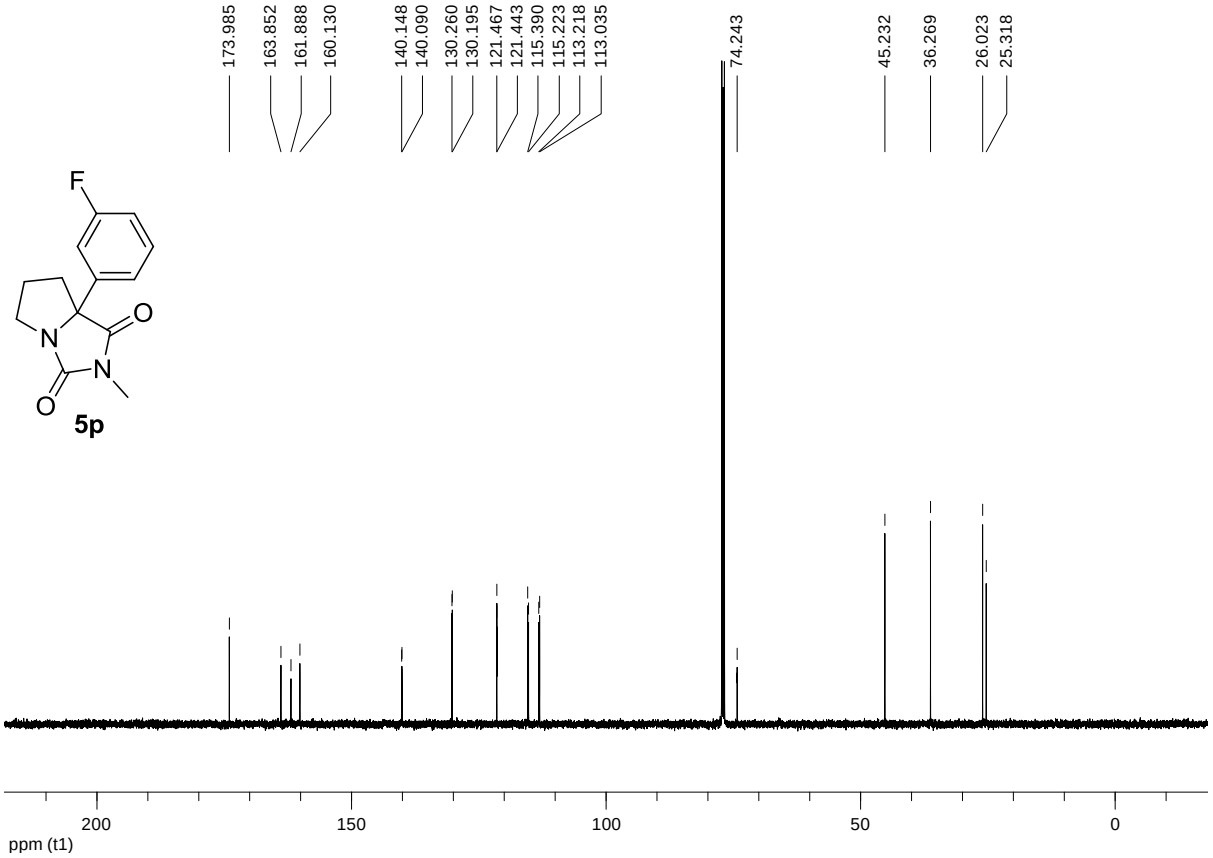

Cl
O
N
N
O
O
5n
7.528
7.522
7.494
7.374
7.339
3.853
3.784
3.412
3.404
3.354
2.972
2.355
2.276
2.168
2.075
1.956
1.808
1.99
2.00
1.02
1.02
3.00
1.05
2.08
1.08
5.0
0.0
ppm (t1)

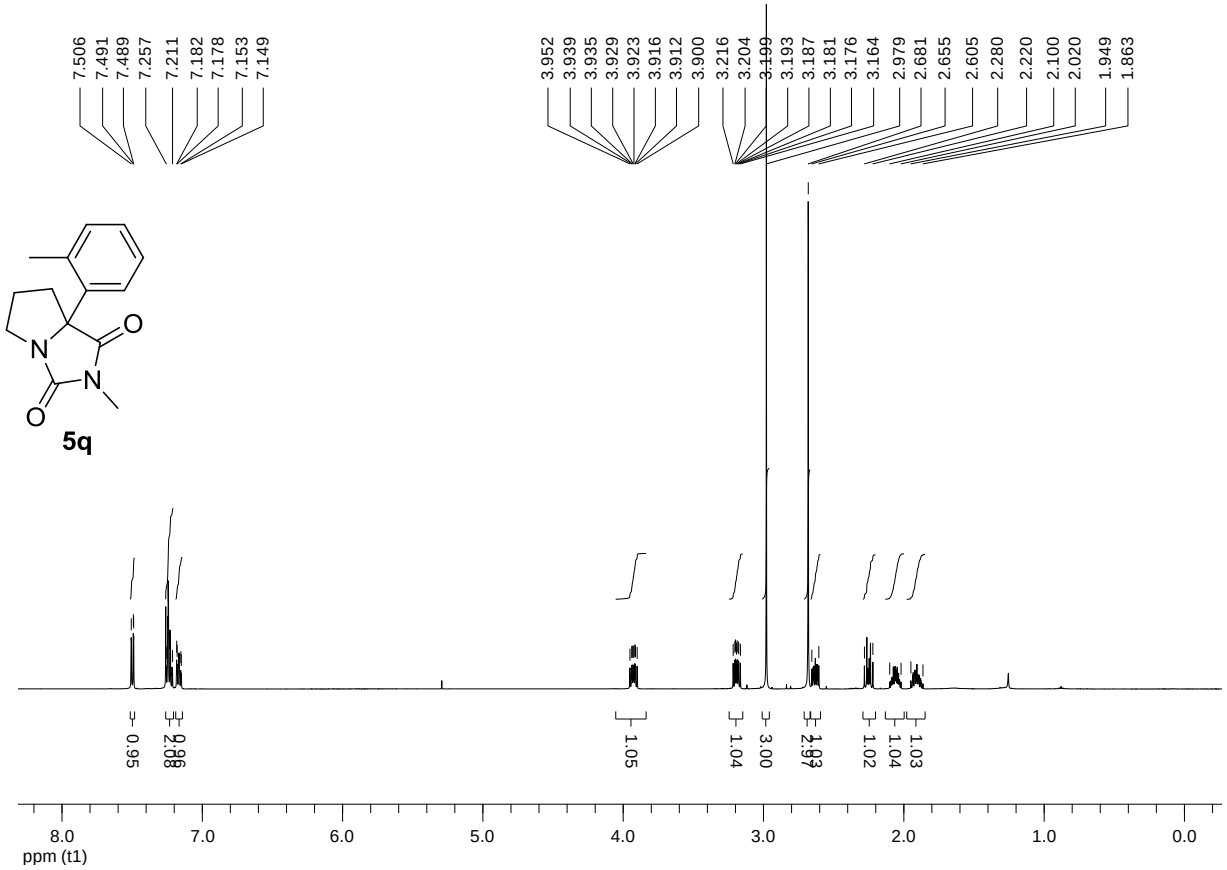

Cl
O
N
N
O
O
5n
174.132
160.143
135.963
134.451
128.787
127.186
74.130
45.159
36.237
26.008
25.312
200
150
100
50
0
ppm (t1)

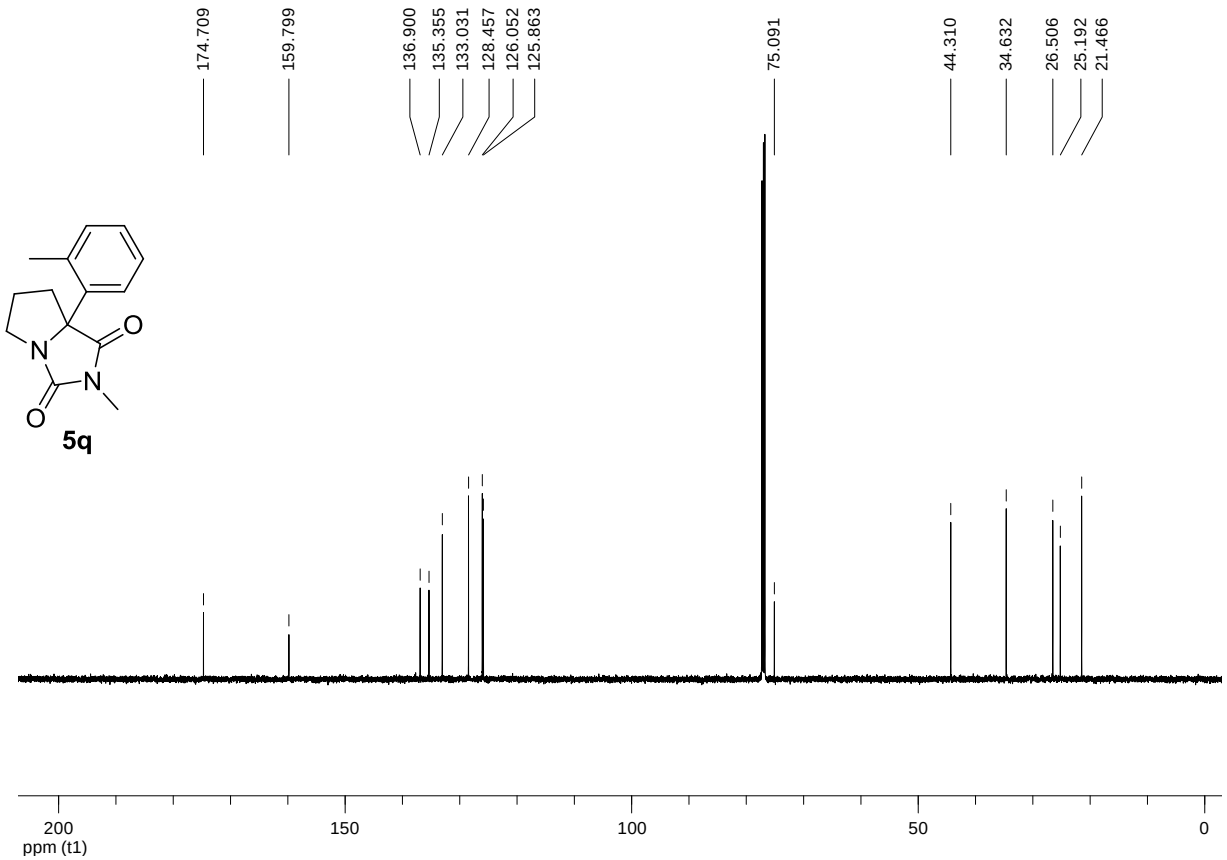

7.588
7.583
7.560
7.557
7.491
7.437
7.389
7.384
7.292
3.870
3.778
3.440
3.362
2.977
2.405
2.297
2.291
2.182
2.074
2.065
1.987
1.816
Cl
O
N
N
O
5o
0.99
0.87
2.03
1.04
0.98
3.00
0.99
2.03
1.10
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


173.942
160.110
139.526
134.647
129.956
128.555
125.966
124.067
77.316
77.000
76.682
74.159
45.210
36.192
26.019
25.339
Cl
O
N
N
O
5o
200
150
100
50
0
ppm (t1)


7.383
7.332
7.304
7.301
7.299
7.281
7.277
7.047
7.006
3.858
3.803
3.421
3.414
3.404
3.397
3.392
3.381
3.374
2.978
2.361
2.325
2.317
2.162
2.091
2.086
1.952
1.858
F
O
N
N
O
5p
0.96
0.96
1.92
1.04
1.05
3.00
1.05
2.08
1.04
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)


173.985
163.852
161.888
160.130
140.148
140.090
130.260
130.195
121.467
121.443
115.390
115.223
113.218
113.035
74.243
45.232
36.269
26.023
25.318
F
O
N
N
O
5p
200
150
100
50
0
ppm (t1)


7.506
7.491
7.489
7.257
7.211
7.182
7.178
7.153
7.149
3.952
3.939
3.935
3.929
3.923
3.916
3.912
3.900
3.216
3.204
3.199
3.193
3.187
3.181
3.176
3.164
2.979
2.681
2.655
2.605
2.280
2.220
2.100
2.020
1.949
1.863
5q
0.95
2.08
2.00
1.05
1.04
3.00
2.97
1.02
1.04
1.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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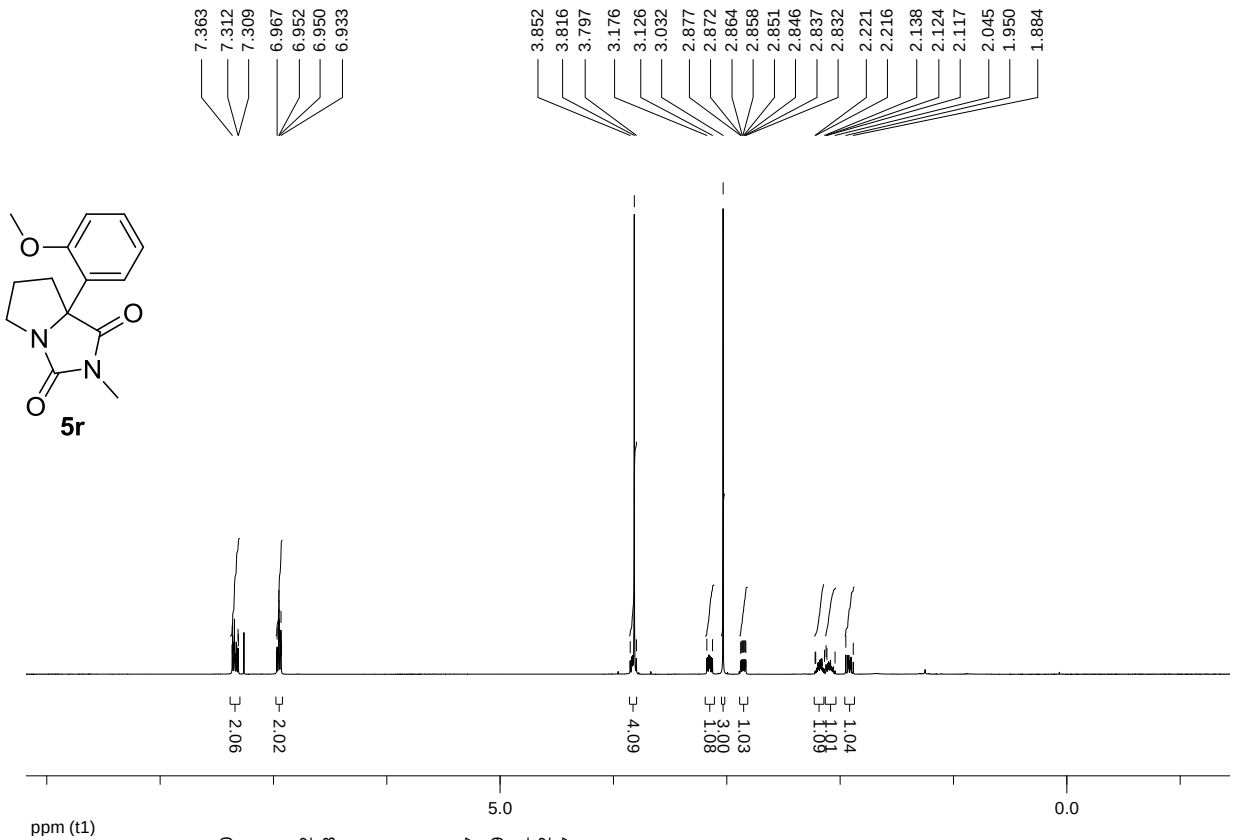
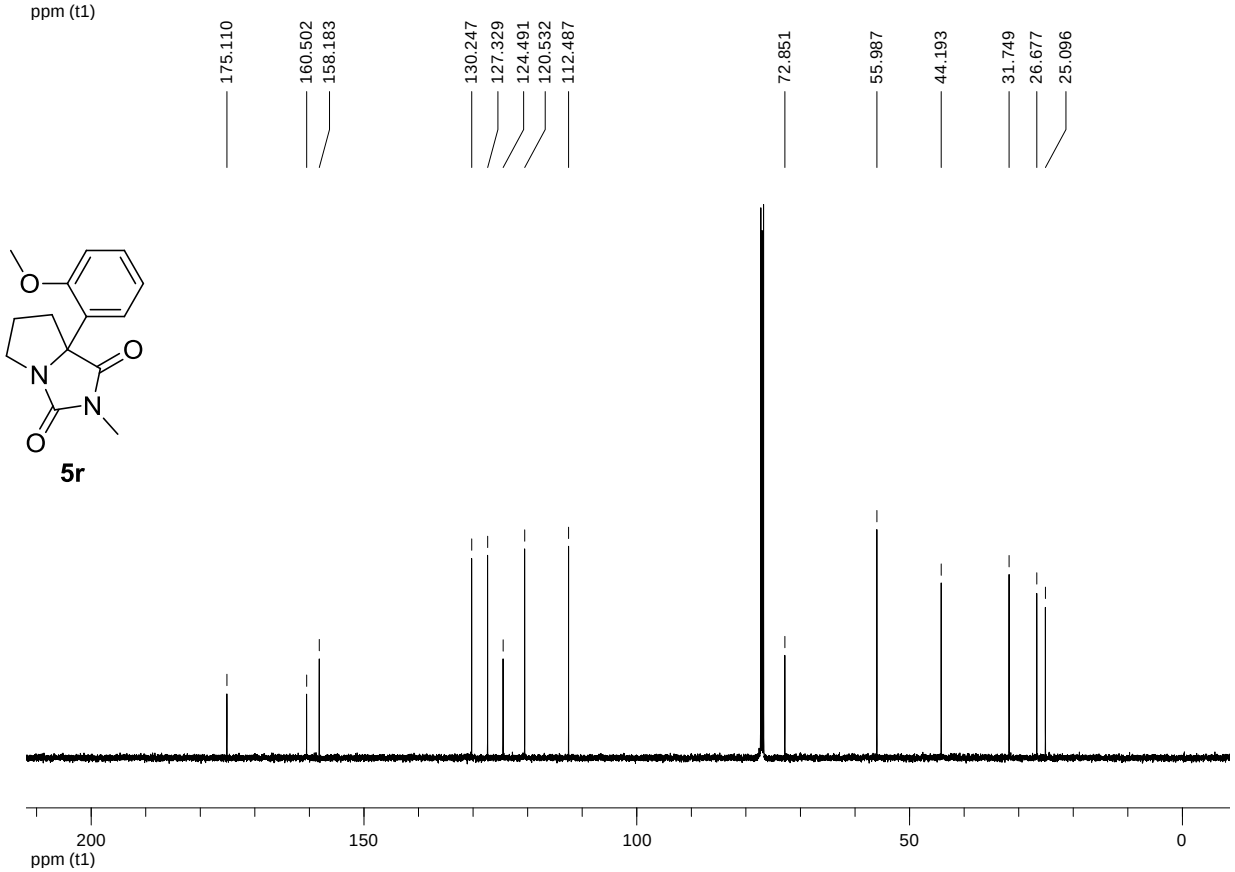
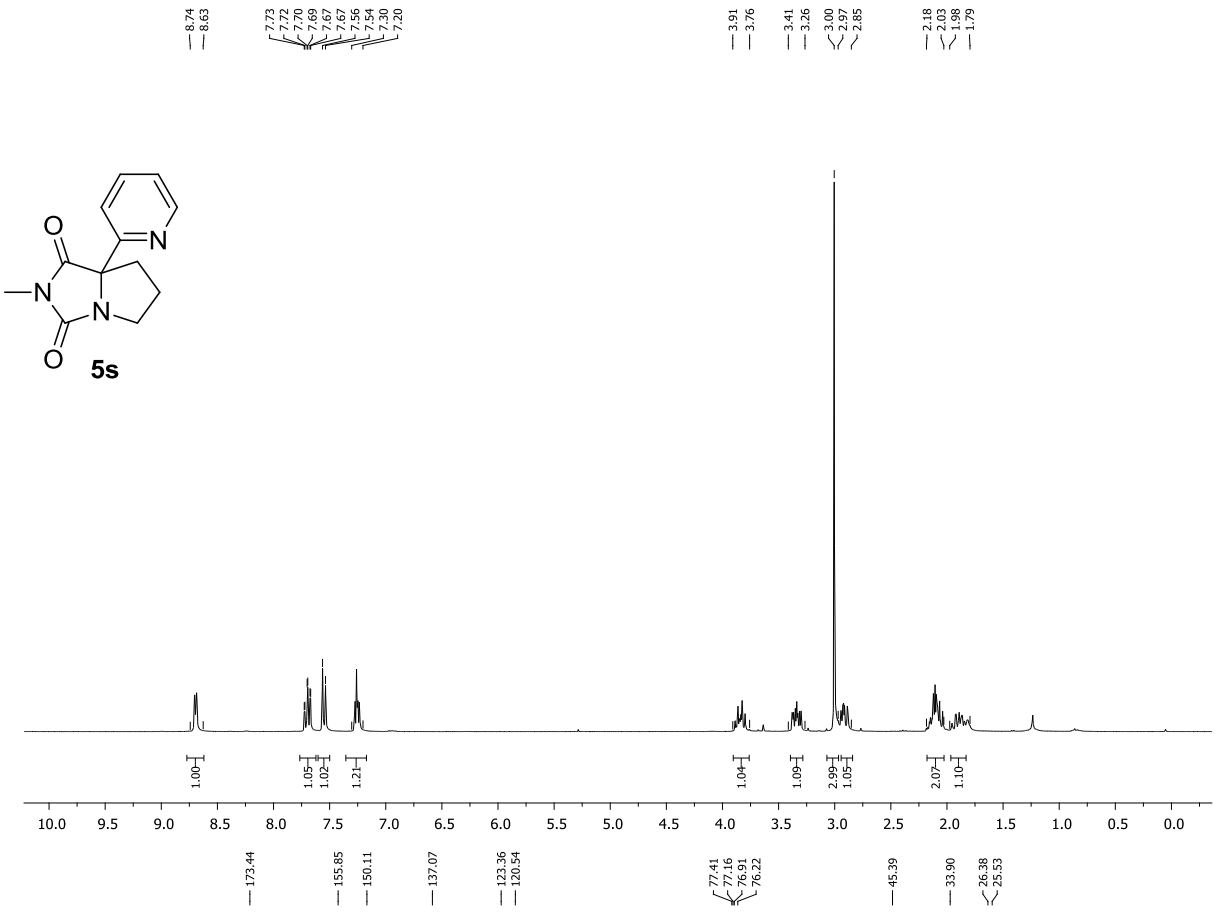
159.799
136.900
135.355
133.031
128.457
126.052
125.863
75.091
44.310
34.632
26.506
25.192
21.466
5q
200
150
100
50
0
ppm (t1)


7.363
7.312
7.309
6.967
6.952
6.950
6.933
3.852
3.816
3.797
3.176
3.126
3.032
2.877
2.872
2.864
2.858
2.851
2.846
2.837
2.832
2.221
2.216
2.138
2.124
2.117
2.045
1.950
1.884
O
N
O
N
O
5r
2.06
2.02
4.09
3.00
1.08
1.03
1.01
1.09
1.04
5.0
0.0
ppm (t1)


175.110
160.502
158.183
130.247
127.329
124.491
120.532
112.487
72.851
55.987
44.193
31.749
26.677
25.096
O
N
O
N
O
5r
200
150
100
50
0
ppm (t1)


8.74
8.63
7.73
7.72
7.70
7.69
7.67
7.67
7.56
7.54
7.30
7.20
3.91
3.76
3.41
3.26
3.00
2.97
2.85
2.18
2.03
1.98
1.79
5s
1.00
1.05
1.02
1.21
1.04
1.09
2.99
1.05
2.07
1.10
10.0
9.5
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
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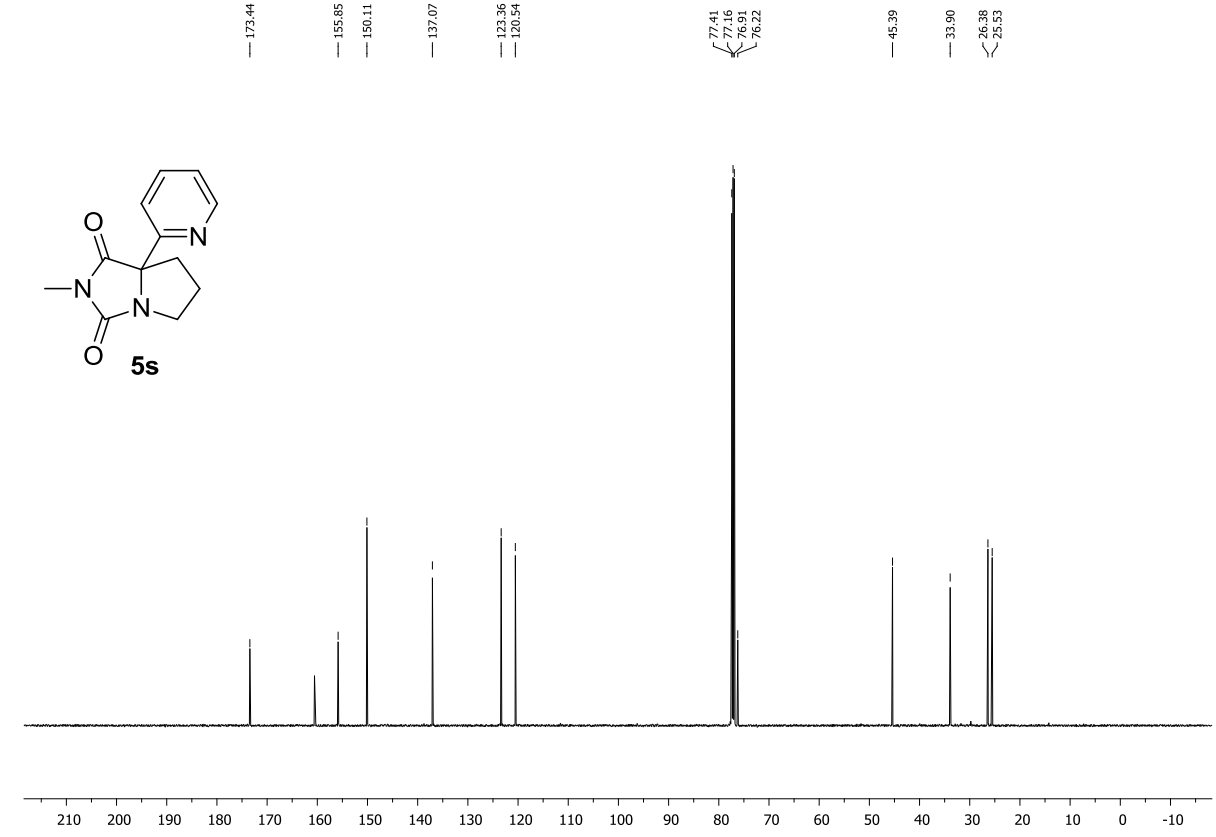
0.0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150.11
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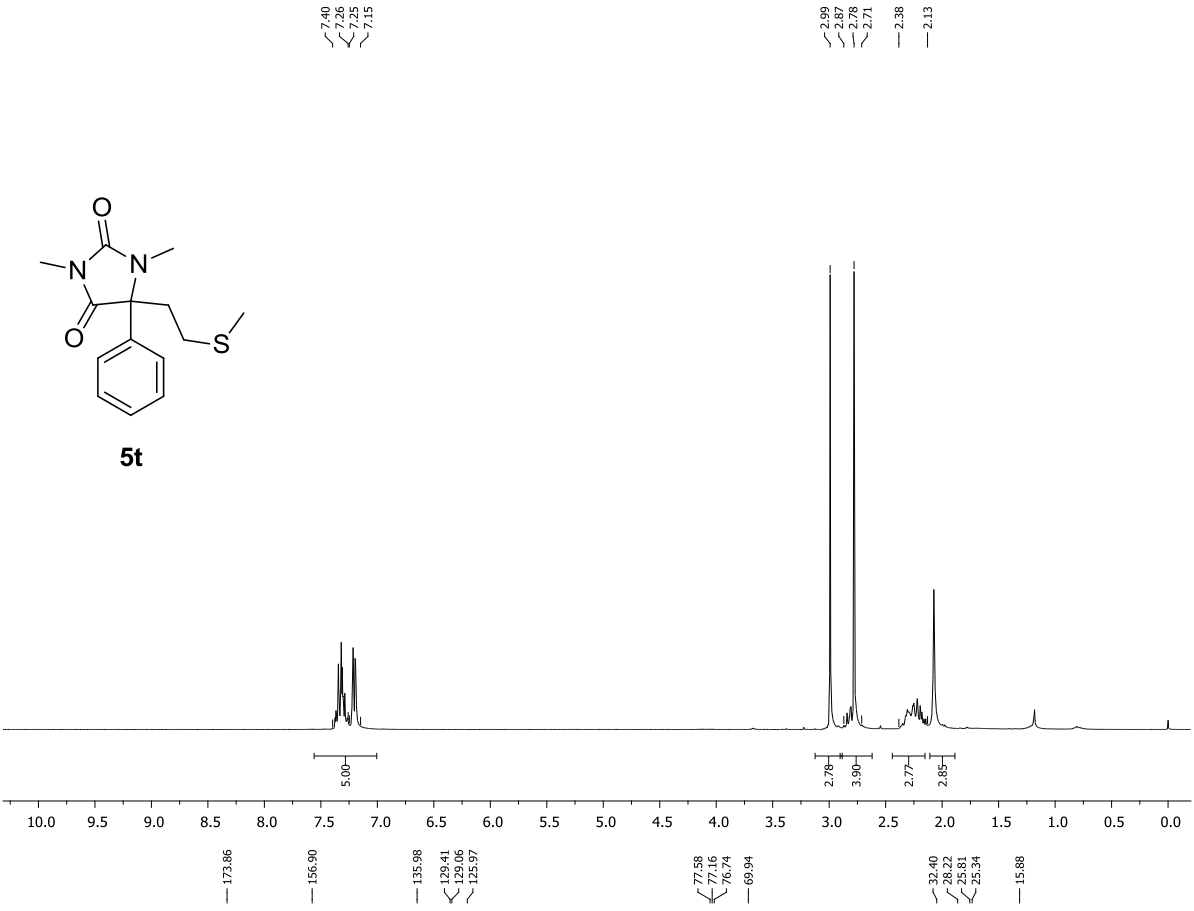
123.36
120.54
77.41
77.16
76.91
76.22
45.39
33.90
26.38
25.53
5s
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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7.26
7.25
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2.87
2.78
2.71
2.38
2.13
5.00
2.78
3.90
2.77
2.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
2.5
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1.5
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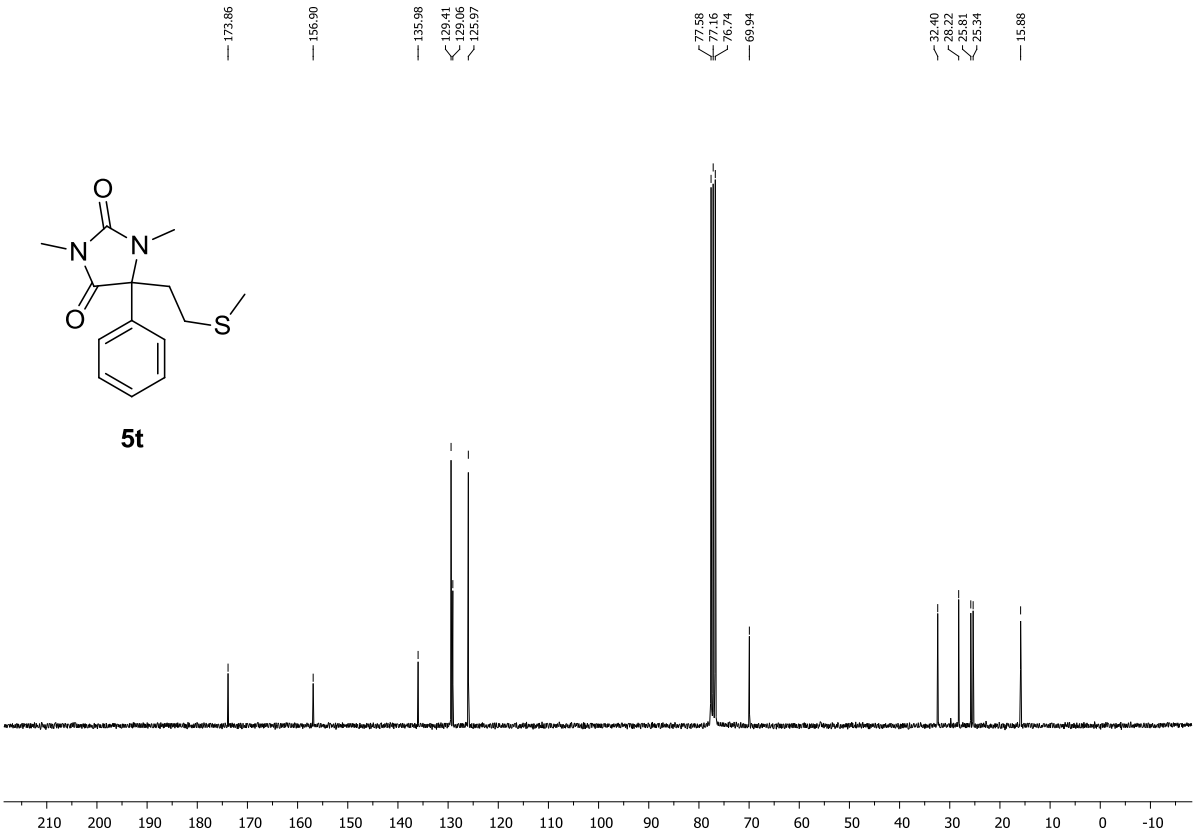
0.5
0.0

5t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125.97
77.58
77.16
76.74
69.94
32.40
28.22
25.81
25.34
15.88
210
200
190
180
170
160
150
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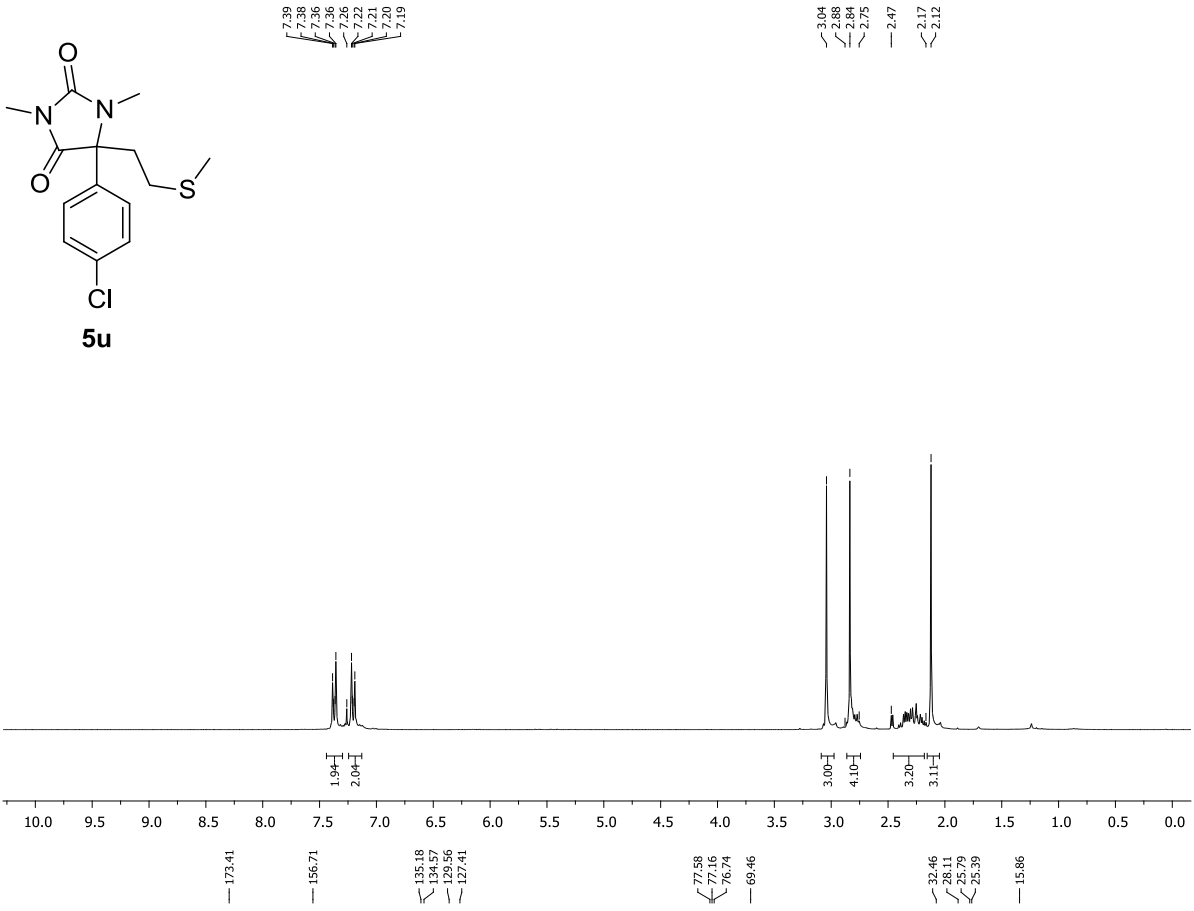
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

5t


7.39
7.38
7.36
7.36
7.26
7.22
7.21
7.20
7.19
3.04
2.88
2.84
2.75
2.47
2.17
2.12
1.94
2.04
3.00
4.10
3.20
3.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
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1.5
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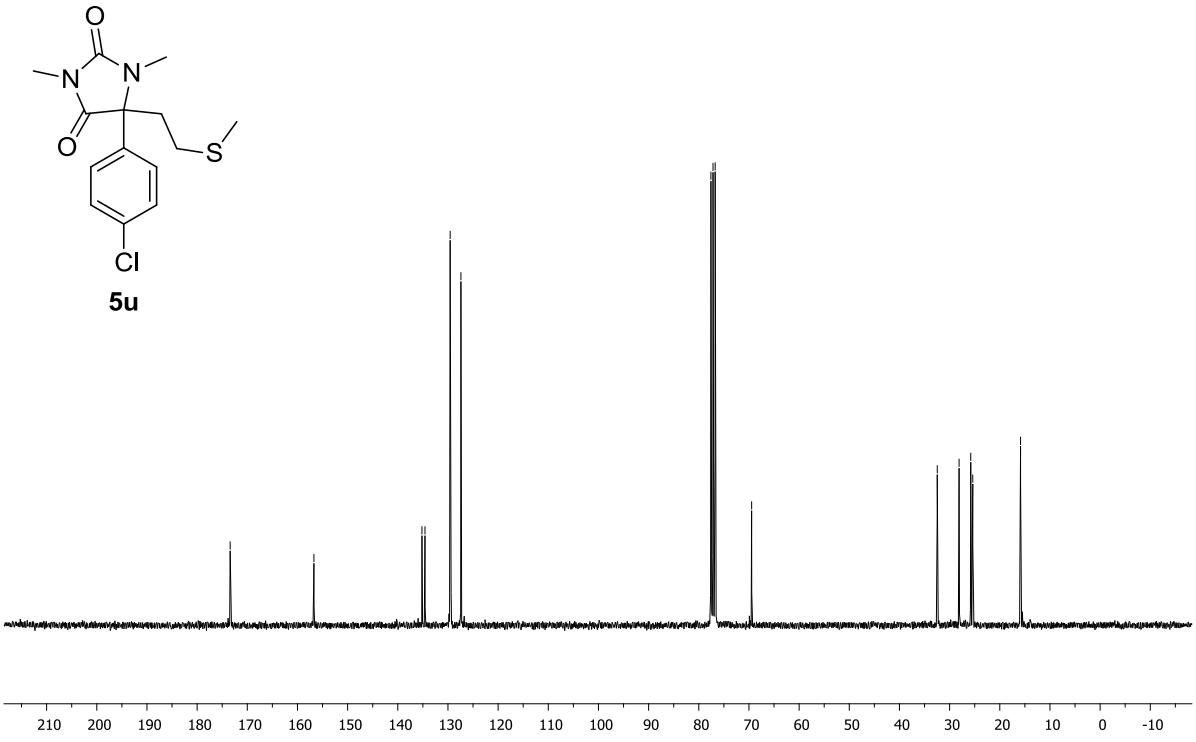
5u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129.56
127.41
77.58
77.16
76.74
69.46
32.46
28.11
25.79
25.39
15.86
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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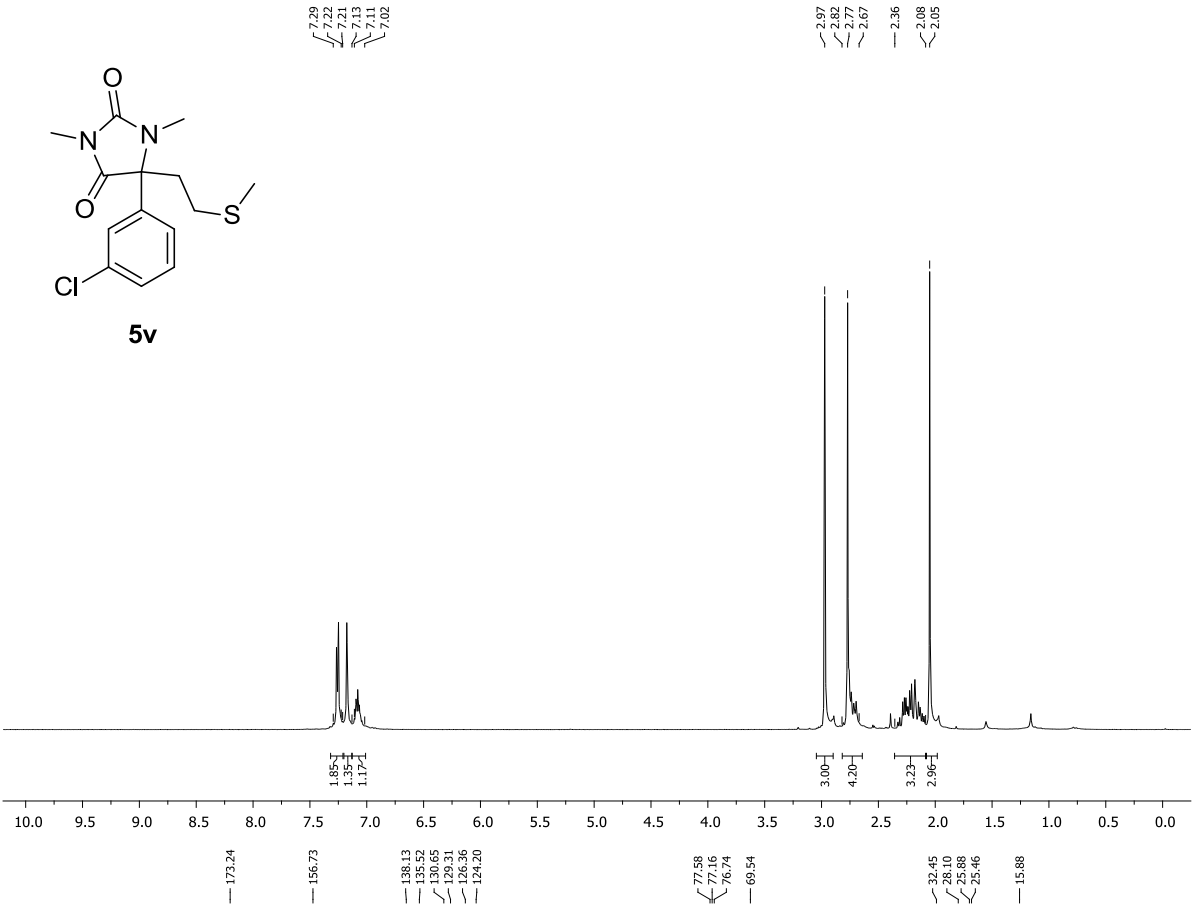
0
-10

5u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7.22
7.21
7.13
7.11
7.02
2.97
2.82
2.77
2.67
2.36
2.08
2.05
O
N
N
O
S
Cl
5v
1.85
1.35
1.17
3.00
4.20
3.23
2.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
3.5
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2.0
1.5
1.0
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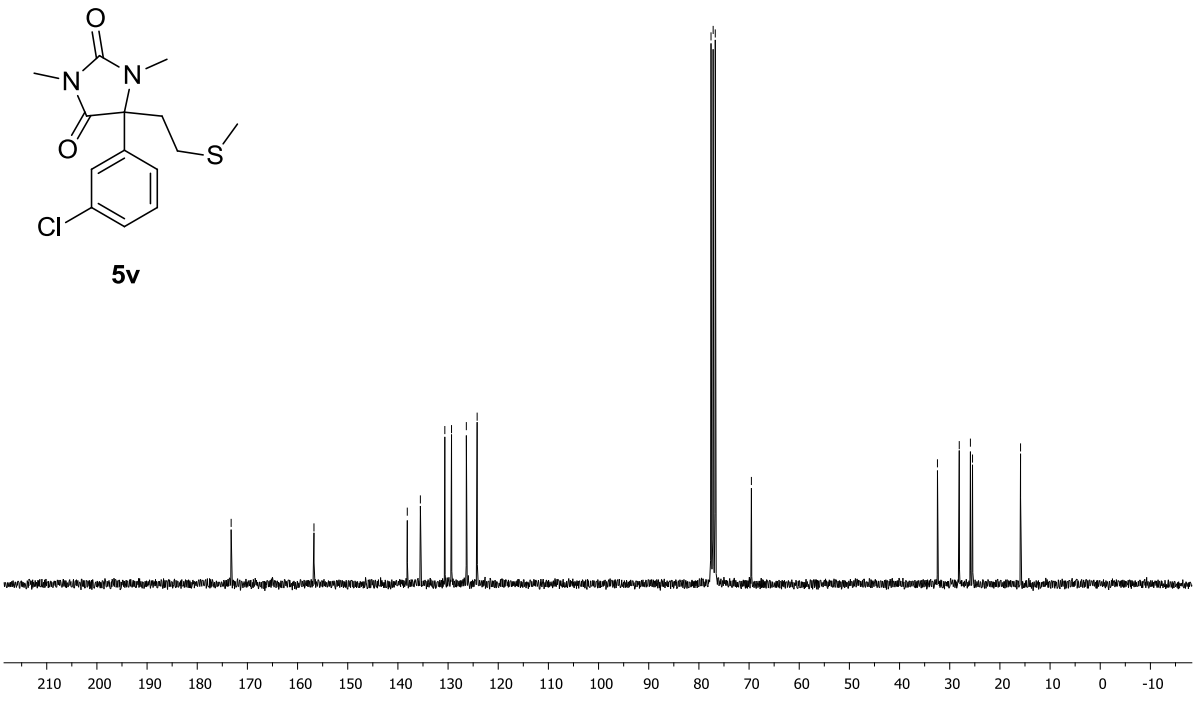
0.0


173.24
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129.31
126.36
124.20
77.58
77.16
76.74
69.54
32.45
28.10
25.88
25.46
15.88
O
N
N
O
S
Cl
5v
210
200
190
180
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140
130
120
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100
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60
50
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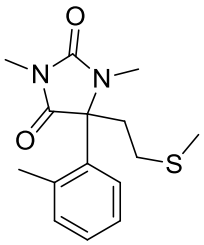
10
0
-10



5w

7.52
7.38
7.29
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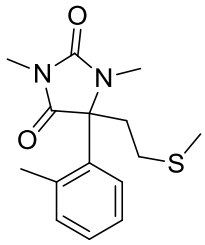
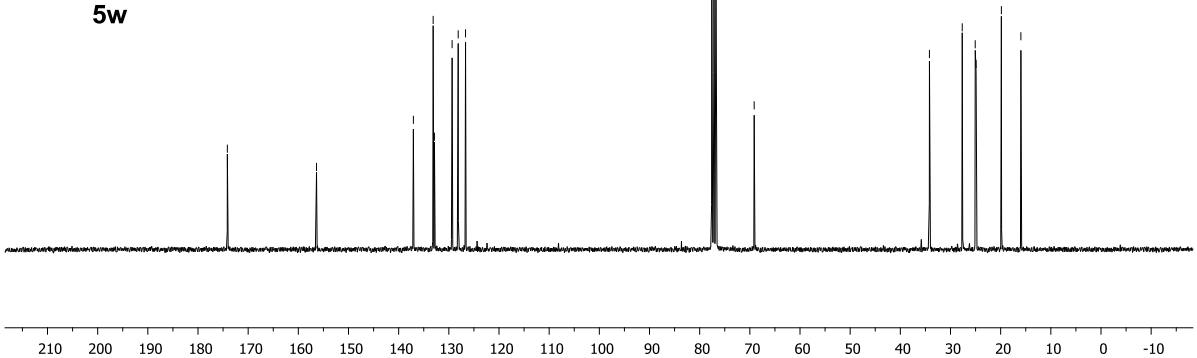
7.20
7.08
3.10
2.81
2.66
2.62
2.57
2.21
2.14
2.05
1.00
2.05
1.08
2.87
1.04
2.80
3.33
6.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

174.15
156.37
137.07
133.12
132.87
129.35
128.13
126.67
77.58
77.16
76.74
69.13
34.20
27.66
25.07
24.90
19.86
15.97



5w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200
190
180
170
160
150
140
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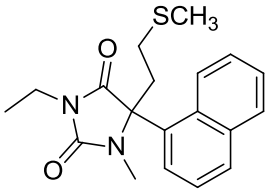
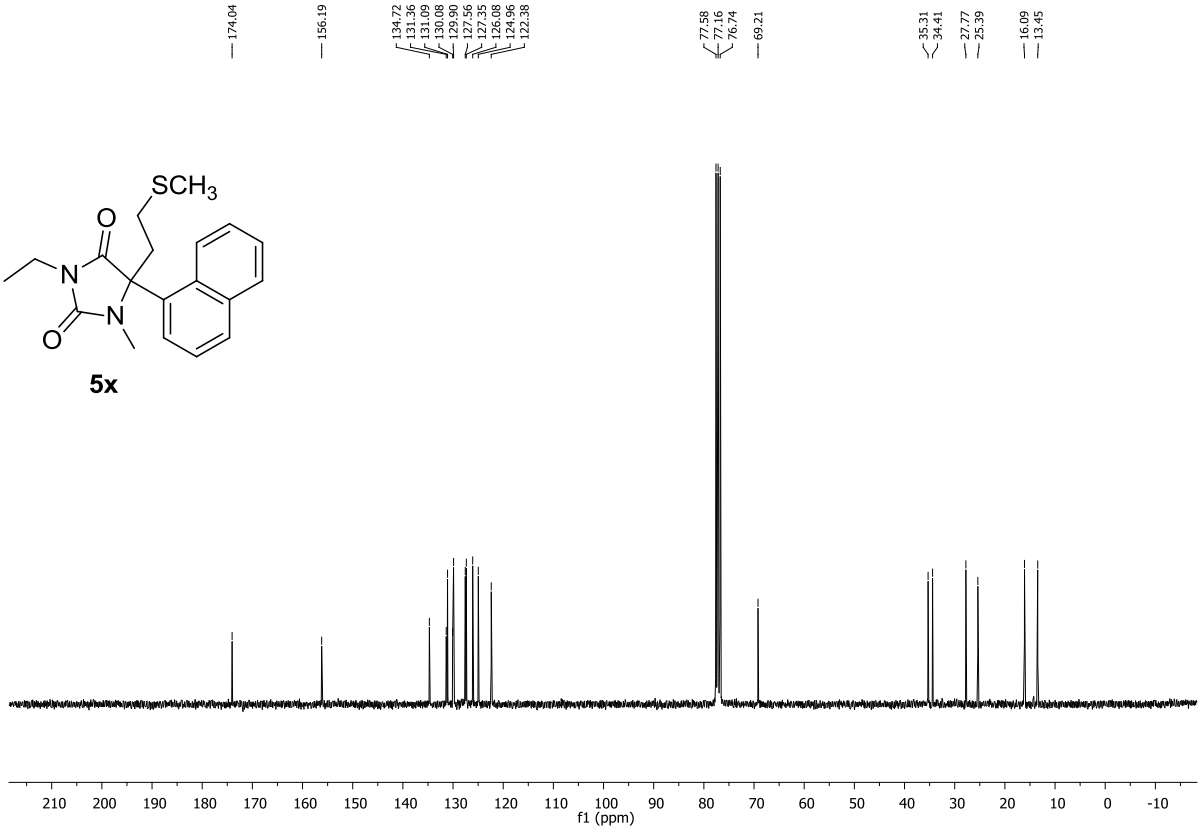
110
100
90
80
70
60
50
40
30
20
10
0
-10


SCH3
O
N
N
O

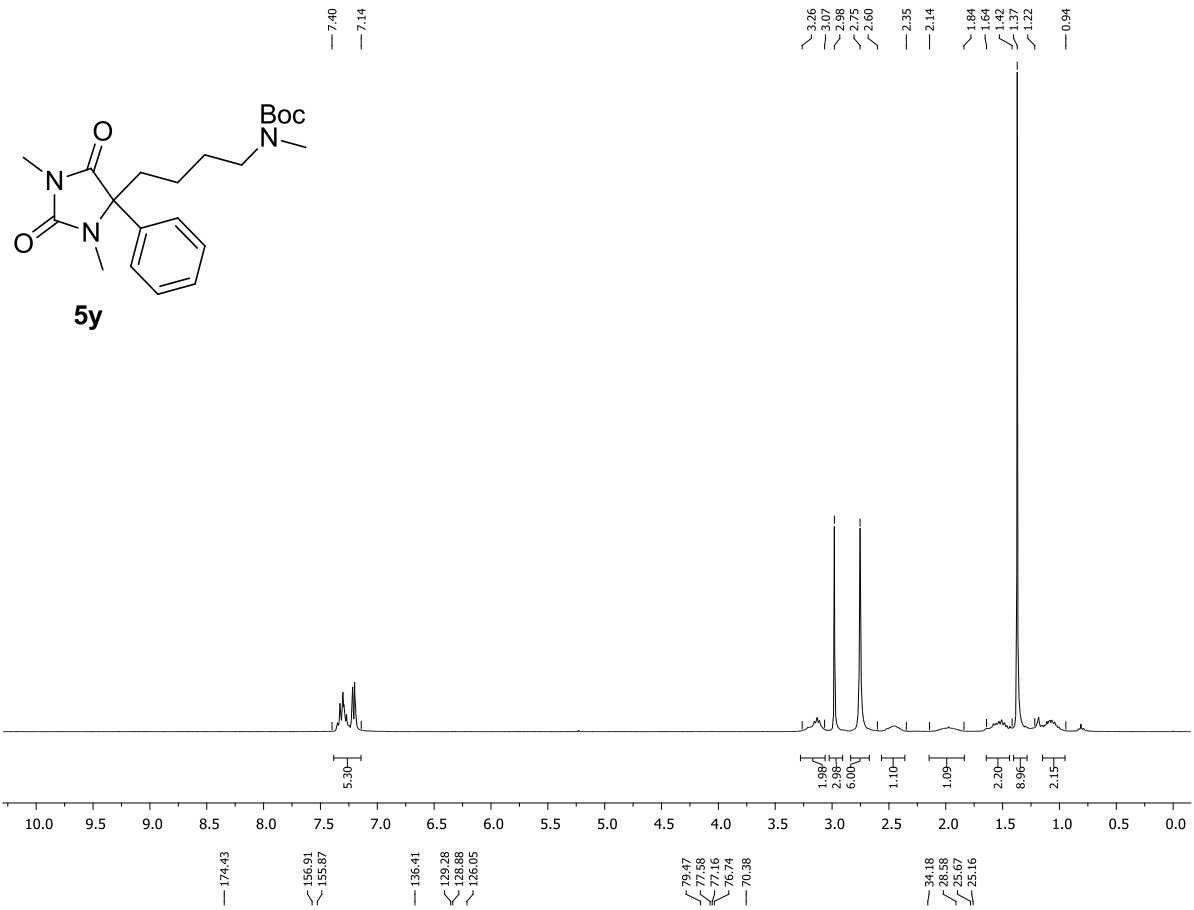
5x

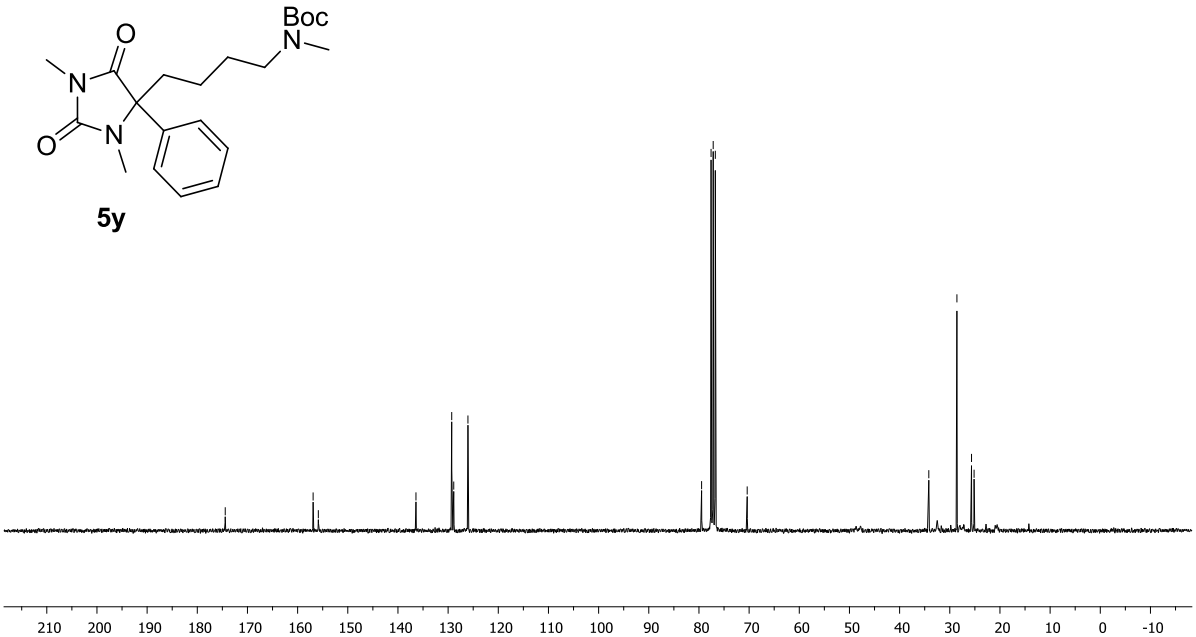
7.95
7.79
7.77
7.66
7.59
7.35
7.26
3.82
3.80
3.77
3.75
2.94
2.92
2.91
2.90
2.88
2.88
2.86
2.84
2.63
2.54
2.48
1.40
1.37
1.35
2.05
0.97
4.18
2.00
1.00
4.12
2.12
2.98
3.00
f1 (ppm)


174.04
156.19
134.72
131.36
131.09
130.08
129.90
127.56
127.35
126.08
124.96
122.38
77.58
77.16
76.74
69.21
35.31
34.41
27.77
25.39
16.09
13.45
f1 (ppm)

SCH3
O
N
N
O

5x


7.40
7.14
3.26
3.07
2.98
2.75
2.60
2.35
2.14
1.84
1.64
1.42
1.37
1.22
0.94
Boc
N
O
N
O
N
5y
5.30
1.98
2.98
6.00
1.10
1.09
2.20
8.96
2.15
10.0
9.5
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


174.43
156.91
155.87
136.41
129.28
128.88
126.05
79.47
77.58
77.16
76.74
70.38
34.18
28.58
25.67
25.16
Boc
N
O
N
O
N
5y
210
200
190
180
170
160
150
140
130
120
110
100
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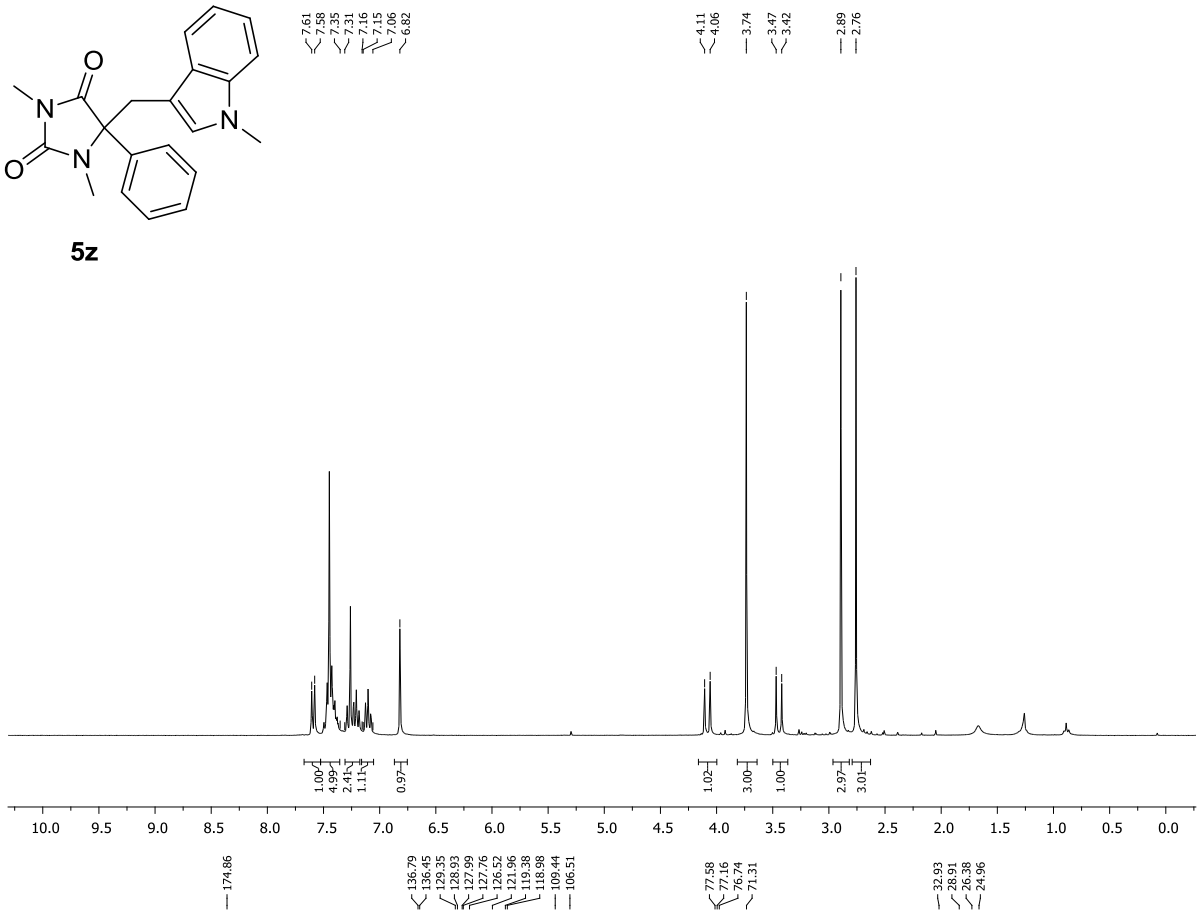
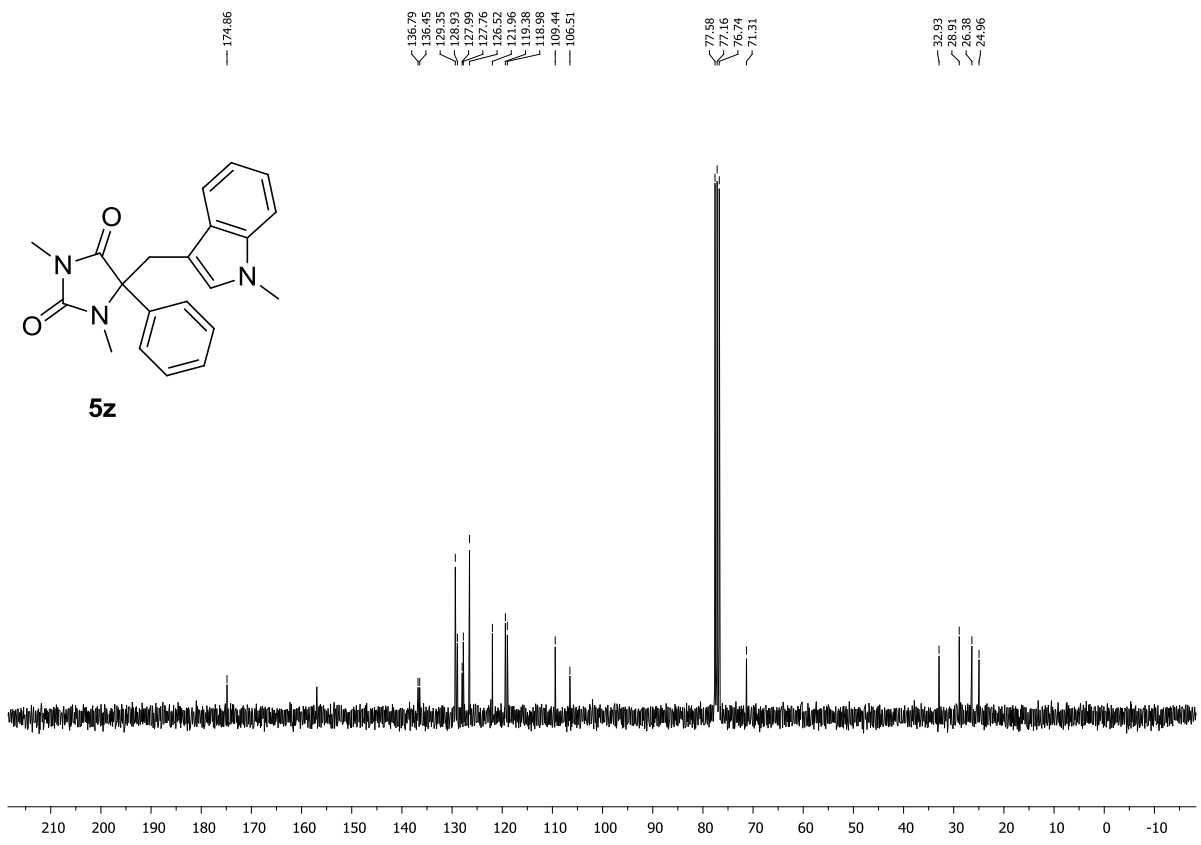
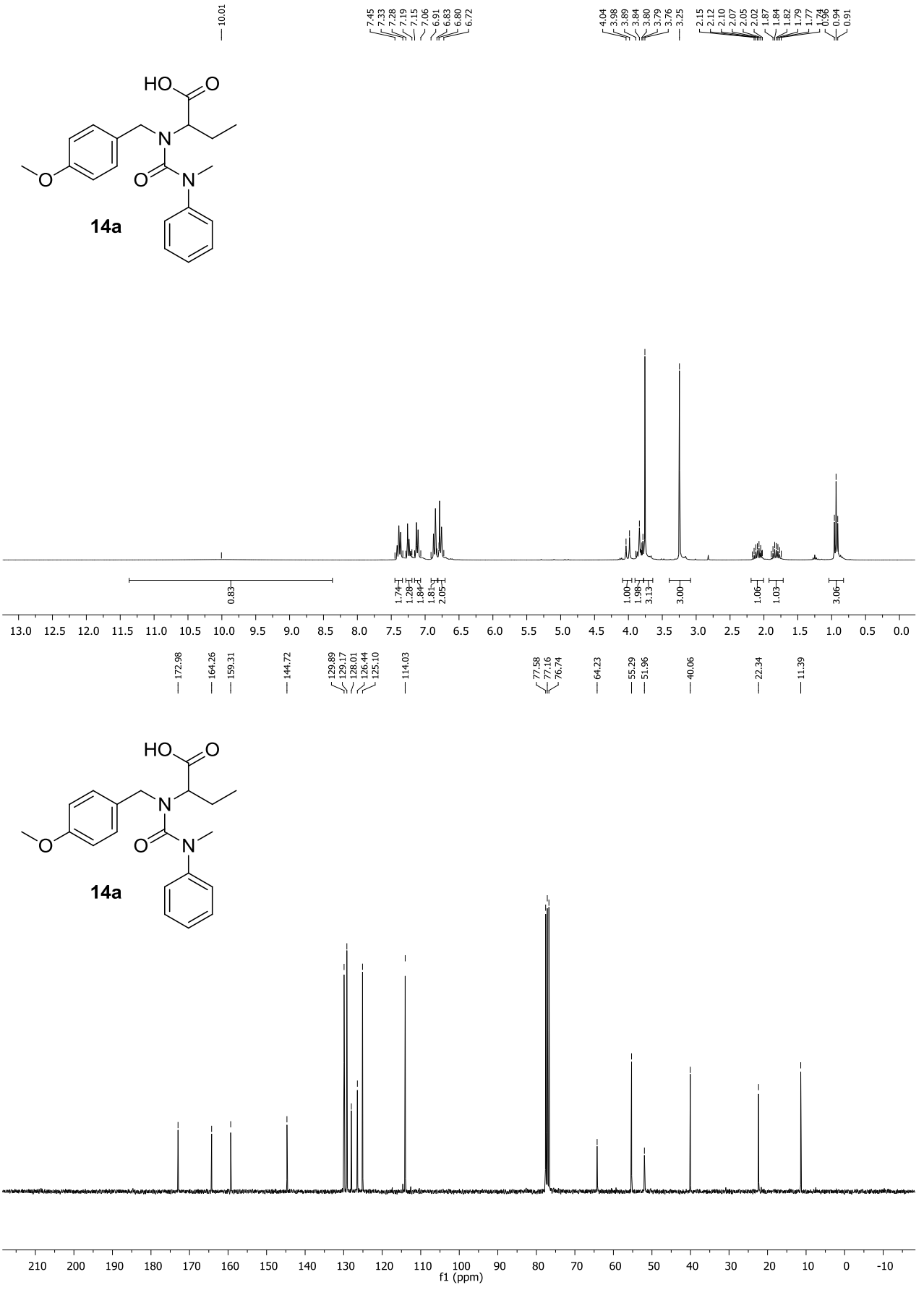
80
70
60
50
40
30
20
10
0
-10

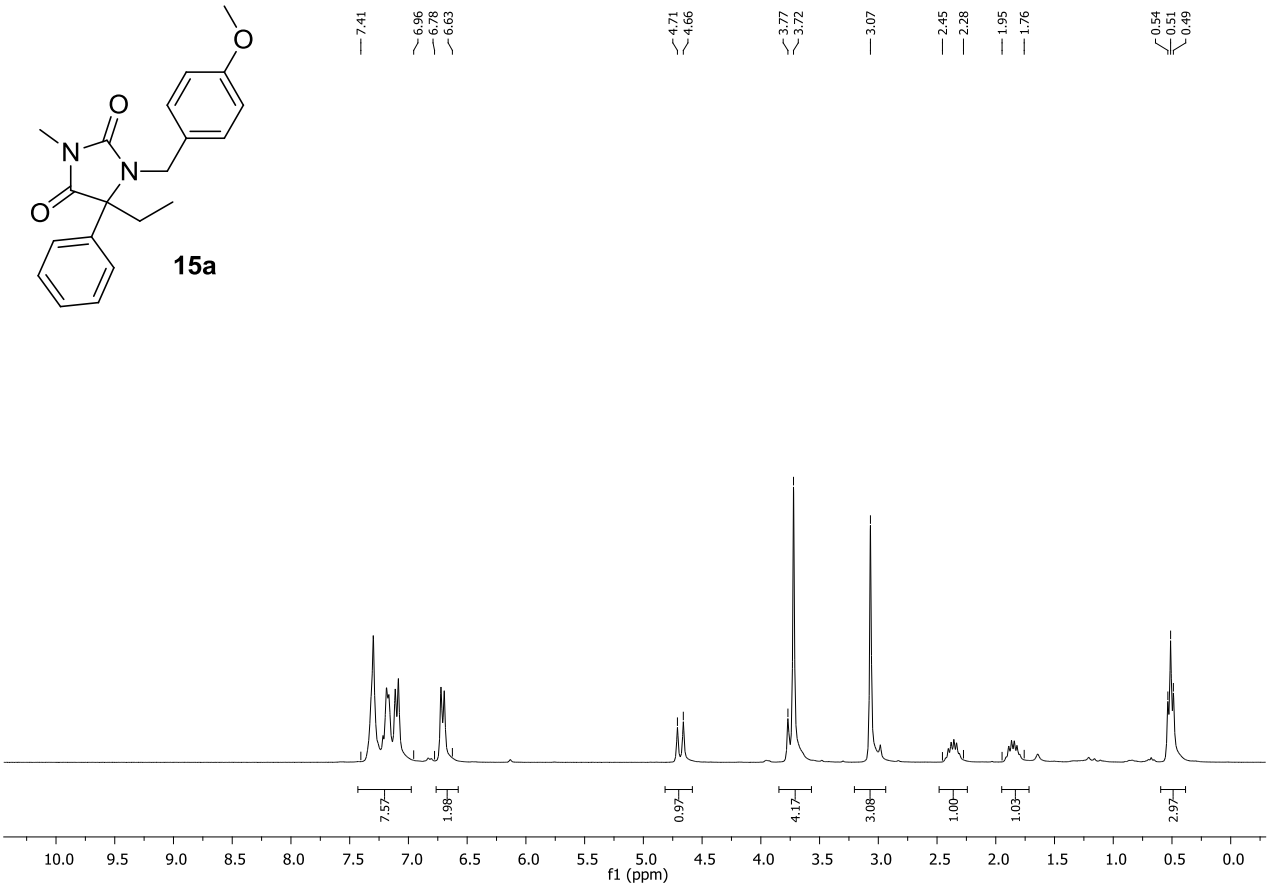

7.61
7.58
7.35
7.31
7.16
7.15
7.06
6.82
4.11
4.06
3.74
3.47
3.42
2.89
2.76
1.00
4.99
2.41
1.11
0.97
1.02
3.00
1.00
2.97
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

5z

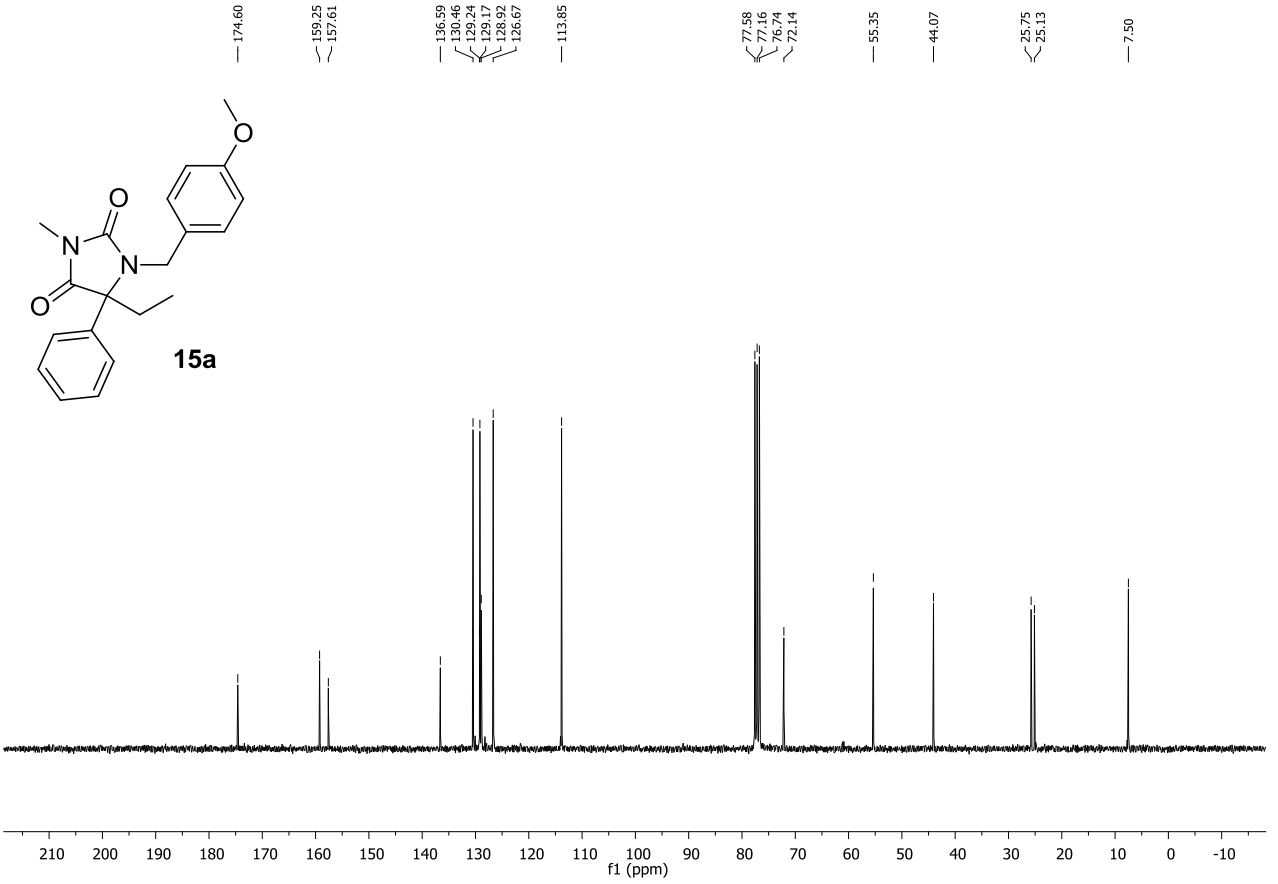

174.86
136.79
136.45
129.35
128.93
127.99
127.76
126.52
121.96
119.38
118.98
109.44
106.51
77.58
77.16
76.74
71.31
32.93
28.91
26.38
24.96
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

5z


14a
14a
f1 (ppm)


7.41
6.96
6.78
6.63
4.71
4.66
3.77
3.72
3.07
2.45
2.28
1.95
1.76
0.54
0.51
0.49
7.57
1.98
0.97
4.17
3.08
1.00
1.03
2.97
f1 (ppm)

15a


174.60
159.25
157.61
136.59
130.46
129.24
129.17
128.92
126.67
113.85
77.58
77.16
76.74
72.14
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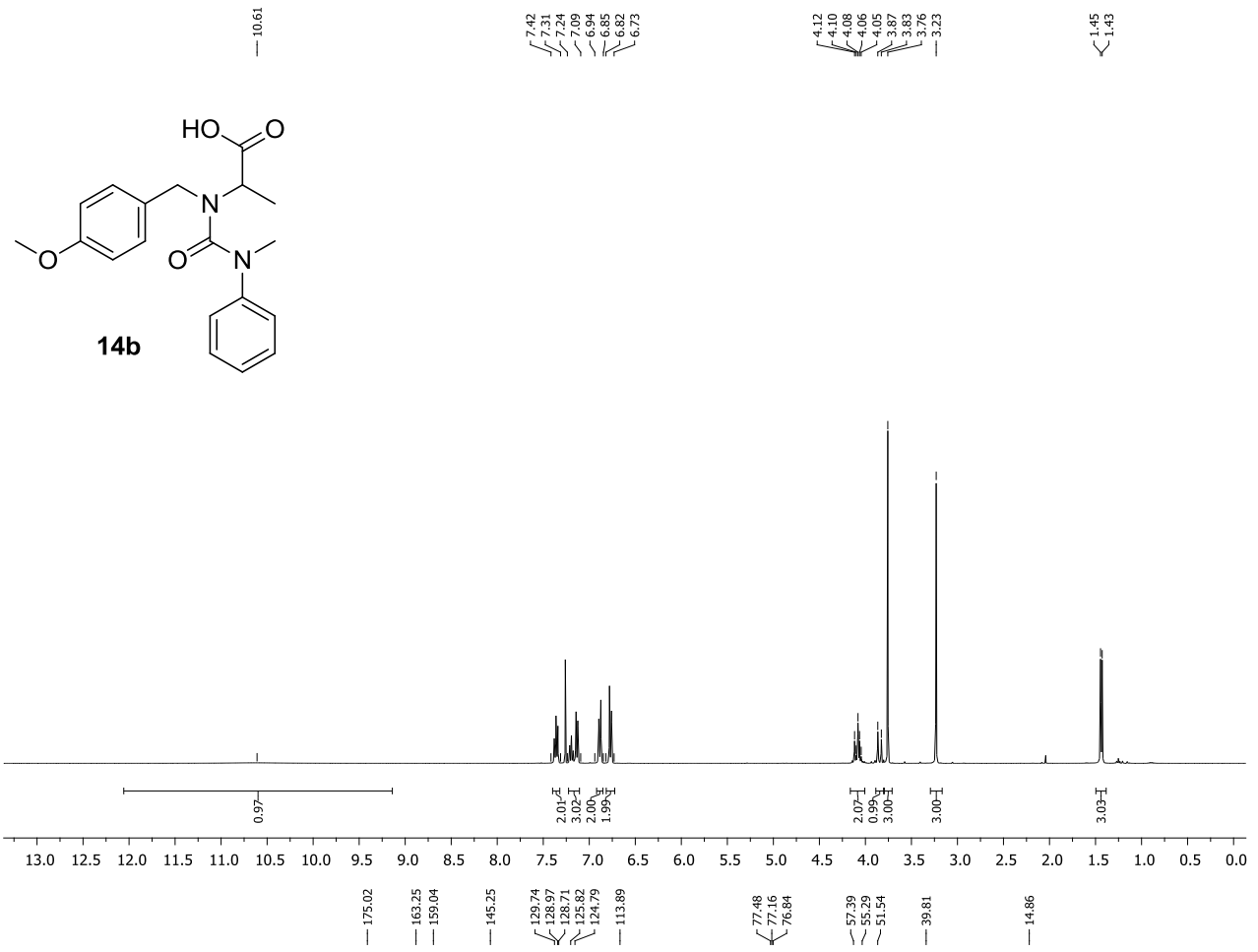
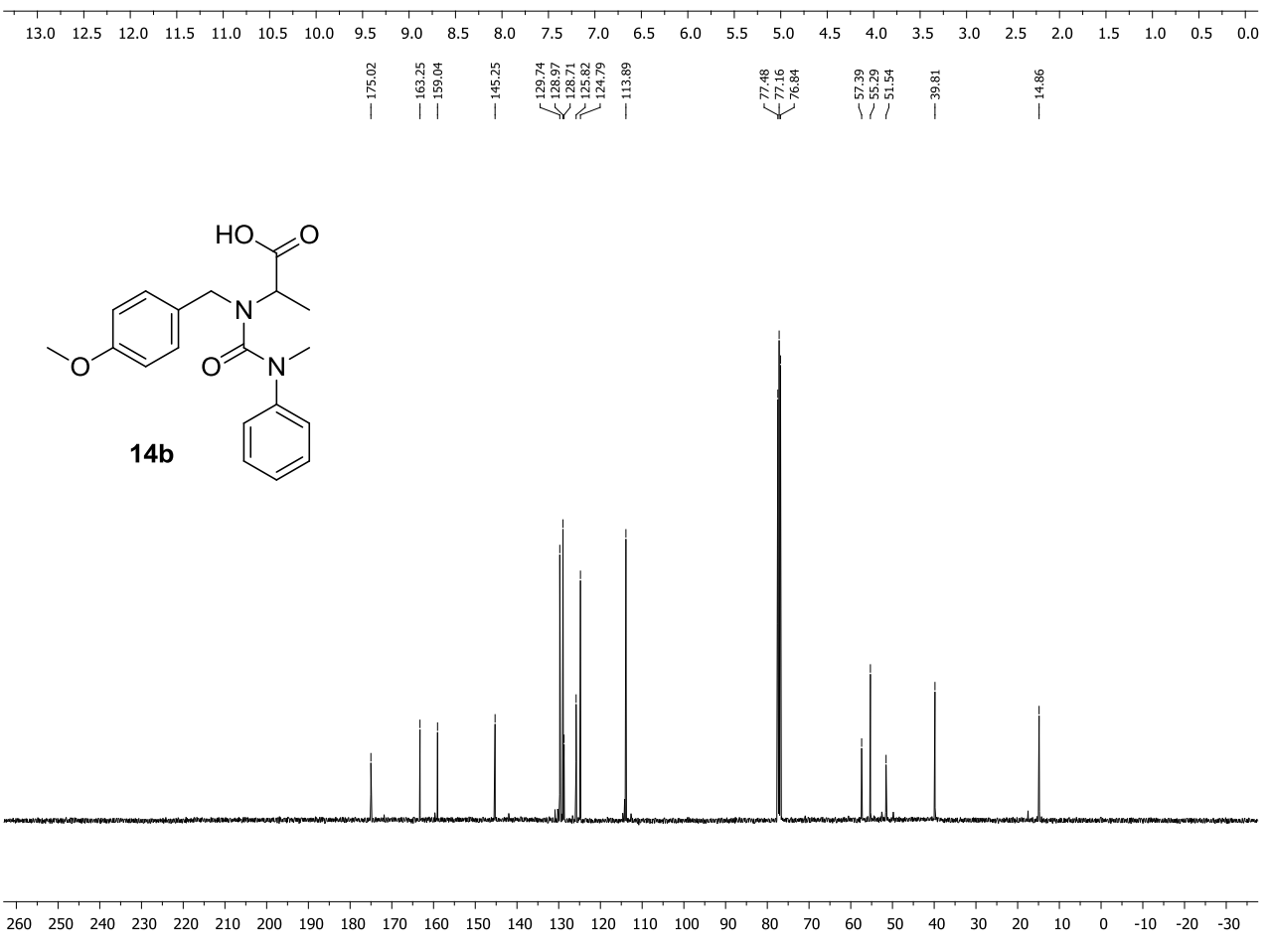
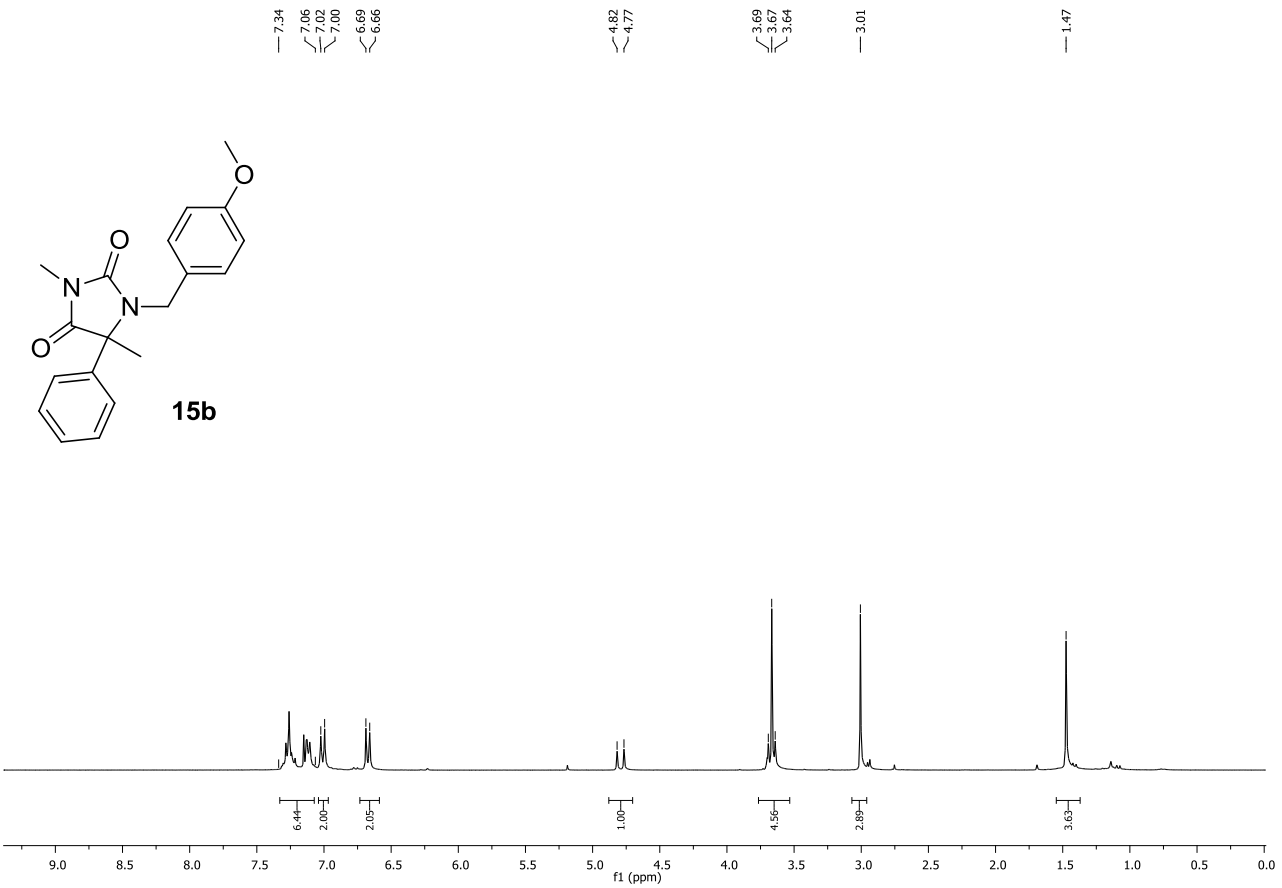
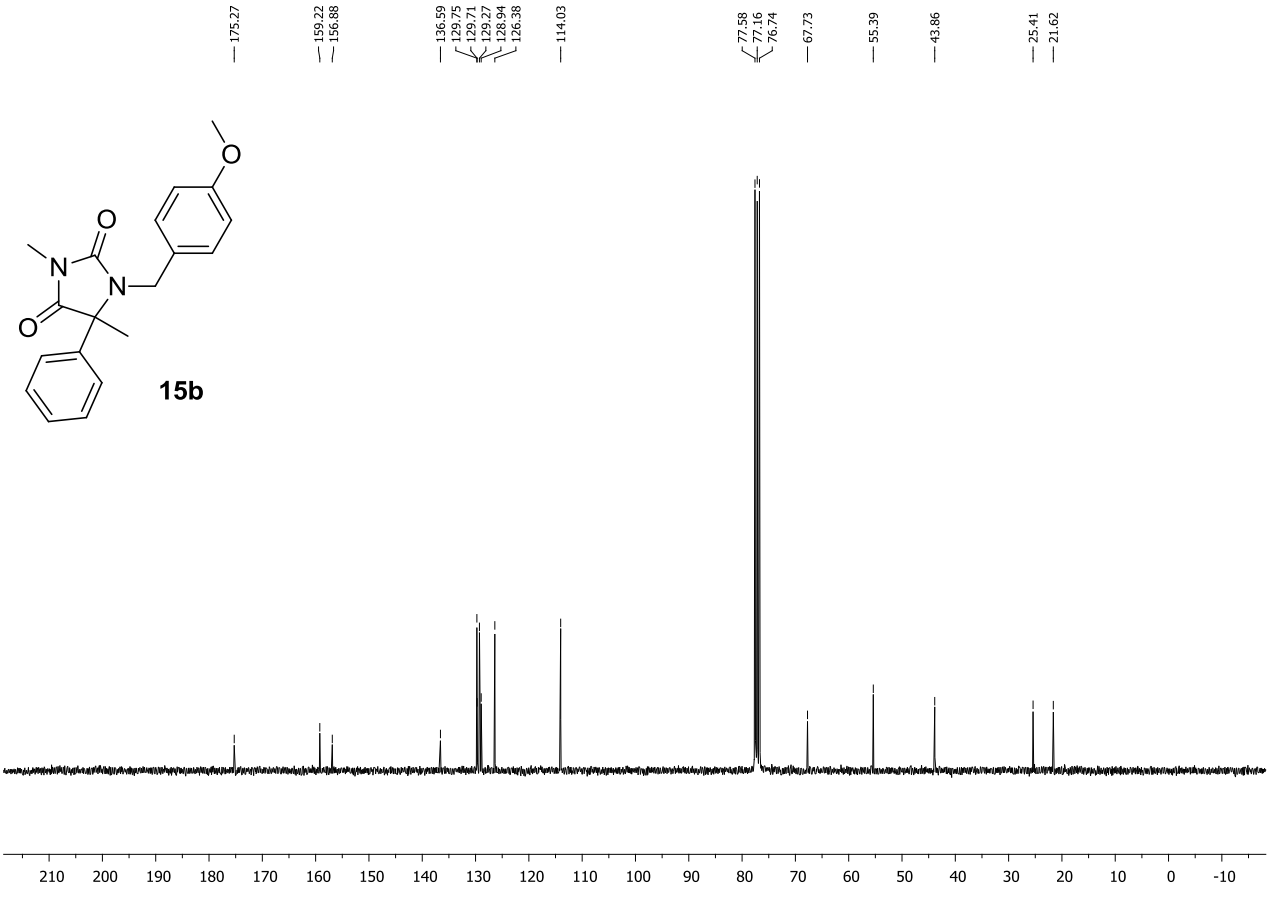
44.07
25.75
25.13
7.50
f1 (ppm)

15a


10.61
7.42
7.31
7.24
7.09
6.94
6.85
6.82
6.73
4.12
4.10
4.08
4.06
4.05
3.87
3.83
3.76
3.23
1.45
1.43
HO
O
N
O
O
N
14b
0.97
2.01
3.02
2.00
1.99
2.07
0.99
3.00
3.00
3.03
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 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


175.02
163.25
159.04
145.25
129.74
128.97
128.71
125.82
124.79
113.89
77.48
77.16
76.84
57.39
55.29
51.54
39.81
14.86
HO
O
N
O
O
N
14b
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30


7.34
7.06
7.02
7.00
6.69
6.66
4.82
4.77
3.69
3.67
3.64
3.01
1.47
15b
6.44
2.00
2.05
1.00
4.56
2.89
3.63
f1 (ppm)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156.88
136.59
129.75
129.71
129.27
128.94
126.38
114.03
77.58
77.16
76.74
67.73
55.39
43.86
25.41
21.62
15b