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SUPPORTING INFORMATION

Stereospecific Intramolecular Arylation of 2- and 3-Pyridyl Substituted Alkylamines via Configurationally Stable α -Pyridyl Organolithiums

Julien Maury[‡], Wojciech Zawodny[‡] and Jonathan Clayden

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General Information

All reactions were performed under a nitrogen or argon atmosphere in flame-dried apparatus. All reagents and chemicals were bought from chemical suppliers and used without further purification (unless otherwise stated). Tetrahydrofuran (THF) was distilled under nitrogen from sodium wire using benzophenone as an indicator. Triethylamine was stored over KOH. All solvents were removed under vacuum using a rotary evaporator. Pet.Ether indicates fractions of petroleum ether boiling at 40-60 °C. LDA was used as a solution in THF/heptane/ethylbenzene (2.0 M from sigma Aldrich) or prepared by General procedure 6. -78 °C, -40 °C and other low temperatures were reached using a Thermo Scientific Haake Immersion Cooler EK90.

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. H₂SO₄, 90.50 mL H₂O) 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.

Capillary melting points were determined on a Stuart Scientific melting point SMP 10 apparatus and are uncorrected. Optical rotations $[\alpha]_{\lambda}^T$ were recorded on an AA-100 polarimeter using a cell with a pathlength of 0.25 dm at 18-22 °C with the solvent and concentration (c) quoted in g/100 mL.

Nuclear Magnetic Resonance (NMR) spectra (1H NMR and 13C NMR) were recorded on either Bruker Ultrashield 300 (Avance), 400 (Avance III or Avance III HD fitted with nitrogen cooled prodigy cold probe) or 500 MHz (Avance II) spectrometers. The residual solvent peak for CDCl₃ (δ_H : 7.26 ppm; δ_C : 77.16 ppm), CD₃OD (δ_H : 3.31 ppm; δ_C : 49.00 ppm) were used as internal standards when assigning NMR spectra.¹

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.

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 cm⁻¹ and the samples were run as solids or evaporated films.

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; high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP mass spectrometer or Waters.

¹ Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512

General Experimental Procedure

General procedure 1: Urea formation from carbamoyl chloride (**9**, **10**, **17** and **18**)

The pyridine-derived amine **5** or **6** (1.0 equiv), anhydrous acetonitrile (0.4 M) and triethylamine (1.1 equiv) were combined and stirred for 10 minutes under nitrogen at room temperature. The carbamoyl chloride (1.0 equiv) was added. The reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and quenched with saturated aqueous NaHCO₃ solution. The organic layer was removed and the aqueous layer was extracted twice with CH₂Cl₂. The combined organic layers were washed with NH₄Cl and brine and dried over MgSO₄, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

General procedure 2: Methylation of ureas (**7** and **8**)

A – in THF as a solvent

The urea derivative **17** (1.0 equiv) was dissolved in anhydrous THF (0.4 M) and methyl iodide (1.2 eq) was added. The solution was cooled to 0 °C before sodium hydride (1.3 equiv, (60% suspension in oil)) was added. The reaction was allowed to warm to room temperature, monitored by TLC and worked up when complete (between 2 hours and overnight). The reaction mixture was quenched with MeOH and saturated aqueous NH₄Cl solution was added before being extracted three times with ethyl acetate. The combined organic extracts were washed twice with water and once with brine then dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

B – in DMF as a solvent

To a solution of the urea derivative **18** (1.0 equiv) in anhydrous DMF (0.1 M) at 0 °C was added sodium hydride (1.5 equiv, (60% suspension in oil)). The reaction mixture was stirred at 0 °C for 15 min, then methyl iodide was added dropwise. The reaction was allowed to warm to room temperature, monitored by TLC and worked up when complete (1 h - overnight). The reaction mixture was quenched with H₂O. The solvent was evaporated *in vacuo*. The residue was dissolved in CH₂Cl₂ and extracted from H₂O three times. The combined organic phase was washed three times with 5% aqueous LiCl solution and once with brine, then dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General procedure 3: LDA-mediated rearrangement of ureas (**11**, **13**, **14** and **15**)

A solution of a pyridine derivative (1.0 equiv) in anhydrous THF (0.1 M) was cooled to -78 °C and LDA (2.5 equiv) was added dropwise. After stirring at -78 °C for 3-18 h the reaction mixture was quenched with NH₄Cl or MeOH. The mixture was extracted three times with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

General procedure 4: Hydrolysis of ureas (12 and 16)

A solution of a pyridine derivative (1.0 equiv), aqueous NaOH (2.0 M) and EtOH (1.2 M) was microwaved at 130 °C for 3 h. The reaction mixture was concentrated and extracted with ethyl acetate, dried over MgSO₄, and concentrated under reduced pressure.

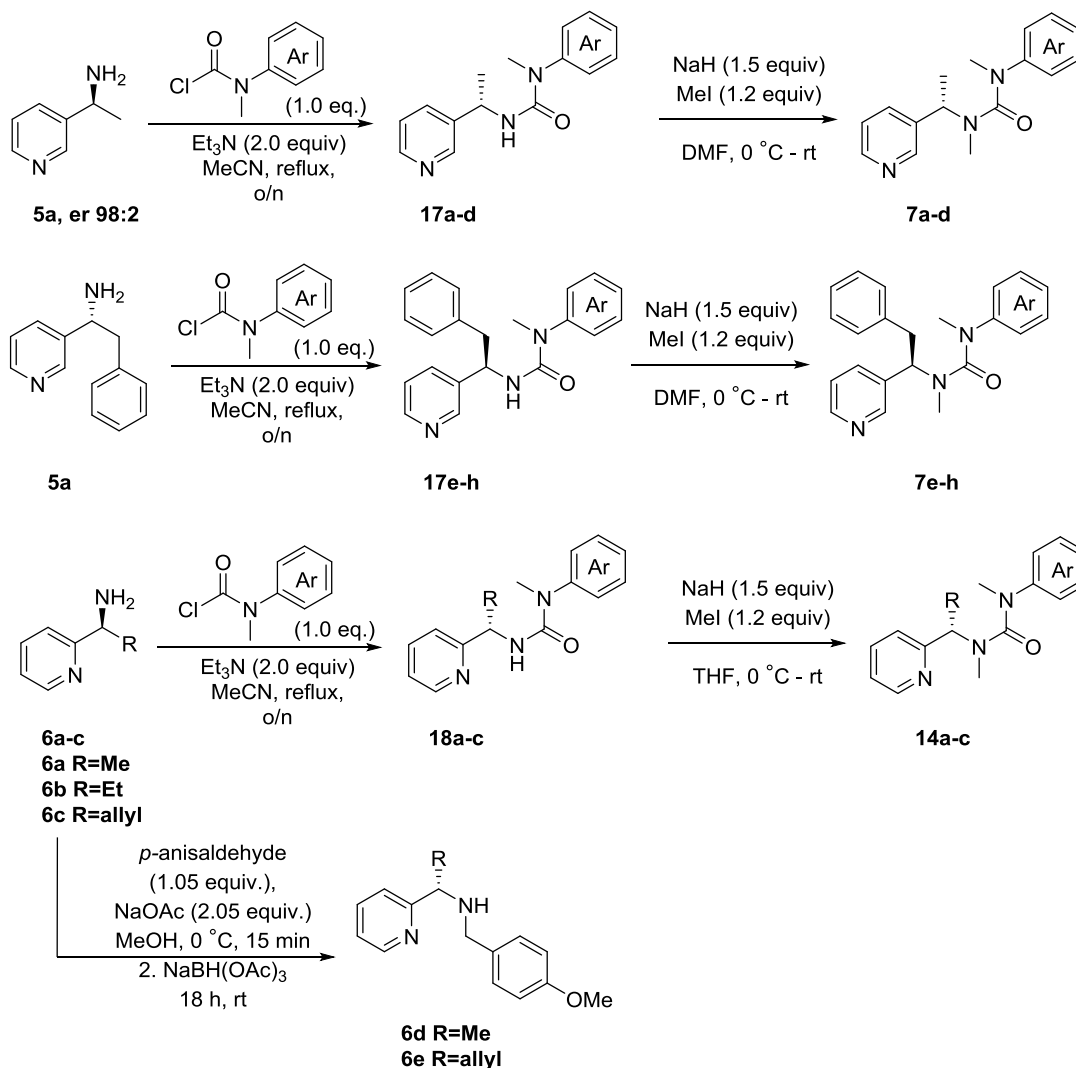
General procedure 5: Amine protection

To a solution of aminopyridine (1.0 equiv) in methanol (0.2 M) were added *p*-anisaldehyde (1.05 equiv) and NaOAc (2.05 equiv) and stirred at room temperature for 15 minutes. The reaction mixture was cooled to 0 °C and NaBH(OAc)₃ (2.05 equiv) was added portionwise. After stirring for 18 h at room temperature, the solvent was evaporated. The crude mixture was dissolved in EtOAc, washed (with NaHCO₃ and brine), dried over MgSO₄, and concentrated under reduced pressure.

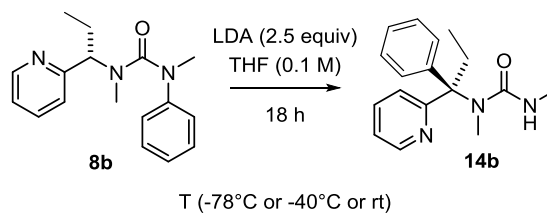
General procedure 6: Preparation of LDA

To a cooled solution of distilled diisopropylamine (1.0 equiv.) in THF (0.75 M) at 0 °C was added *n*-BuLi (1.0 equiv.) The reaction mixture was stirred at 0 °C for 20 min before immediate use.

For clarity, compounds **6d**, **6e**, **17a-h** and **18a-c** were not included in the main text, but were isolated and purified before **7a-h** were made.



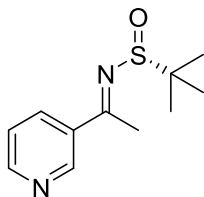
Effect of the temperature reaction on the er (HPLC traces of **14b** in HPLC part)



- **Conditions A** : LDA (2.5 equiv) in THF at **-78 °C** for 18 hours => **er > 99:1**
- **Conditions B** : LDA (2.5 equiv) in THF at **-40 °C** for 18 hours => **er = 98:2**
- **Conditions C** : LDA (2.5 equiv) in THF at **room temperature** for 18 hours => **er = 86:4**

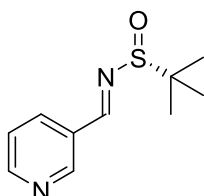
Synthetic procedures

(*R,E*)-2-methyl-*N*-(1-(pyridin-3-yl)ethylidene)propane-2-sulfinamide ((*R*)-1)²



Procedure by Chellucci *et al.* was followed.² A solution of 1-(pyridin-3-yl)ethan-1-one (4.54 mL, 41.27 mmol), (*R*)-(+)-2-methylpropane-2-sulfinamide (5.0 g, 41.27 mmol) and Ti(OEt)₄ (18.8 g, 82.6 mmol) in CH₂Cl₂ (165 mL) was refluxed for 72 h. The reaction mixture was allowed to cool down to room temperature, then it was concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL). The solution was stirred vigorously and brine was added (150 mL) slowly. After 15 min, the mixture was filtered over a pad of Celite, and the filter cake was washed with copious amounts of EtOAc. The filtrate was dried over MgSO₄. The solvent was evaporated *in vacuo* and the crude was purified by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH) to give (*R*)-1 as yellow oil (5.73 g, 61%). ¹H NMR (400 MHz, CDCl₃) δ = 9.14-9.03 (1H, m, =CH), 8.71 (1H, dd, *J* = 4.8, 1.7, =CH), 8.16 (1H, ddd, *J* = 8.1, 2.4, 1.6, =CH), 7.38 (1H, ddd, *J* = 8.0, 4.8, 0.9, =CH), 2.80 (3H, s, N=C-CH₃), 1.33 (9H, s, C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ = 174.4 (C=N), 152.4 (=CH), 148.8 (=CH), 134.6 (=CH), 134.4 (=C), 123.5 (=CH), 58.0 (C(CH₃)₃), 22.7 (C(CH₃)₃), 19.8 (N=C-CH₃).

(*R,E*)-2-methyl-*N*-(pyridin-3-ylmethylene)propane-2-sulfinamide ((*R*)-2)³



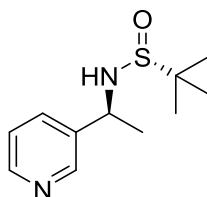
Literature procedure was followed.³ To a solution of 3-pyridinecarboxaldehyde (6.00 mL, 63.58 mmol) and (*R*)-(+)-2-methylpropane-2-sulfinamide (7.72 g, 63.58 mmol) in anhydrous THF was added Ti(OEt)₄ (29.00 g, 127.2 mmol). The reaction mixture turned instantly orange and was stirred at room temperature overnight. Brine (100 mL) was added to the vigorously stirred reaction mixture. The suspension was filtered through a pad of Celite. The filter cake was washed with copious amount of EtOAc. The organic phase was washed with brine, dried over MgSO₄ and evaporated *in vacuo*. The crude was purified by flash column chromatography (SiO₂, 60:40 to 100:0 EtOAc:Petrol) to give (*R*)-2 as yellow oil (5.73 g, 61%). ¹H NMR (400 MHz, CDCl₃) δ = 9.03 (1H, dd, *J* = 2.1, 0.9, =CH), 8.74 (1H, dd, *J* = 4.8, 1.7, =CH), 8.65 (1H, s, =CH), 8.17 (1H,

² Data in agreement with the literature (Reference: Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F.; *Tetrahedron: Asymmetry*, **2006**, *17*, 3163)

³ Data in accordance with the literature (Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.*, **1999**, *64*, 1278)

dt, $J = 8.0, 1.9, =CH$), 7.46 – 7.40 (1H, m, =CH), 1.28 (9H, s, $C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 160.5$ (N=CH), 153.0 (=CH), 151.1 (=CH), 135.9 (=CH), 129.9 (=C), 124.1 (=CH), 58.3 ($C(CH_3)_3$), 22.8 ($C(CH_3)_3$).

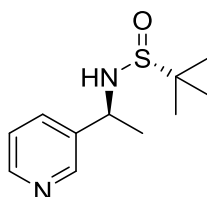
(R)-2-methyl-N-((S)-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide (3a, dr 98:2)²



Procedure by Chellucci *et al.* was followed.² To a solution of **1** (2.01 g, 8.96 mmol) in anhydrous THF (90 mL) at -78 °C was added dropwise tri-*sec*-butylborohydride (L-Selectride) (1.0 M solution in THF, 8.96 mL, 8.96 mmol). The reaction mixture was stirred at -78 °C overnight, then allowed to warm up to room temperature, quenched with saturated aqueous solution of NH_4Cl . The organic and aqueous phases were separated, the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield a crude brown oil, which was purified by flash column chromatography (SiO_2 , 95:5 CH_2Cl_2 :MeOH) to yield **3a** as a yellow oil (1.46 g, 72%, >95:5 d.r. (R_S,S):(R,R)). The exact diastereomeric ratio (d.r. 98:2) was later confirmed by er of **7b** and **7c**, which were determined by chiral HPLC.

1H NMR (500 MHz, $CDCl_3$) $\delta = 8.58$ (1H, d, $J = 2.3, =CH$), 8.50 (1H, dd, $J = 4.8, 1.6, =CH$), 7.62 (1H, dt, $J = 7.9, 2.0, =CH$), 7.25 (1H, dd, $J = 7.9, 4.8, =CH$), 4.59 (1H, qd, $J = 6.7, 3.4, CH-CH_3$), 3.40 (1H, d, $J = 2.7, NH$), 1.55 (3H, d, $J = 6.7, CH-CH_3$), 1.18 (9H, s, $C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 149.0$ (=CH), 148.8 (=CH), 138.80 (=C), 134.6 (=CH), 123.5 (=CH), 55.8 ($C(CH_3)_3$), 52.5 ($CH-CH_3$), 24.9 ($CH-CH_3$), 22.5 ($C(CH_3)_3$). HRMS (ESI⁺): m/z calcd for $C_{11}H_{19}N_2OS$ [M+H]⁺ 227.1213, found 227.1213.

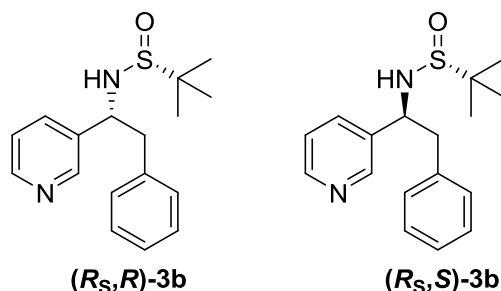
(R)-2-methyl-N-((S)-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide (3a, dr 73:27)²



To a solution of **2** (6.00 g, 28.54 mmol) in CH_2Cl_2 (140 mL) at -40 °C was added dropwise methylmagnesium bromide (3.0 M solution in Et_2O , 19.1 mL, 57.12 mmol). The reaction mixture was stirred overnight at -40 °C, then warmed up to room temperature, quenched with saturated aqueous solution of NH_4Cl . The organic and aqueous phases were separated, the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give a crude mixture of diastereoisomers **3a** (d.r. 73:27) that was used without further purification. 1H NMR (500 MHz, $CDCl_3$) $\delta = 8.62-8.59$ (1H, m, =CH, major and minor isomer), 8.55 (0.27H, dd, $J = 4.9, 1.8, =CH$, minor

isomer), 8.53 (0.73H, dd, $J = 4.8, 1.7$, =CH, major isomer), 7.68 (0.27H, dt, $J = 7.9, 2.0$, =CH, minor isomer), 7.64 (0.73H, dt, $J = 7.9, 2.0$ Hz, =CH, major isomer), 7.31 – 7.24 (1H, m, =CH, major and minor isomer), 4.66 – 4.54 (1H, m, CH-CH₃, major and minor isomer), 3.42 (0.27H, d, $J = 2.9$, NH, minor isomer), 3.34 (0.73H, d, $J = 3.4$, major isomer), 1.57 (2.19H, d, $J = 6.7$, CH-CH₃, major isomer), 1.55 (0.81H, d, $J = 6.7$, CH-CH₃, minor isomer), 1.24 (2.43H, s, C(CH₃)₃, minor isomer), 1.20 (6.57H, s, C(CH₃)₃, major isomer).

(*R*)-2-methyl-*N*-((*R*)-2-phenyl-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide (*R_S,R*-3b)⁴ and (*R*)-2-methyl-*N*-((*S*)-2-phenyl-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide (*R_S,S*-3b))

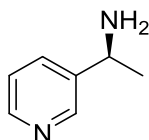


To a solution of **2** (3.46 g, 16.45 mmol) in CH₂Cl₂ (97 mL) at -40 °C was added dropwise benzylmagnesium chloride (2.0 M solution in THF, 16.5 mL, 32.90 mmol). The reaction mixture was stirred overnight at -40 °C, then warmed up to room temperature, quenched with saturated aqueous solution of NH₄Cl. The organic and aqueous phases were separated, the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄ and evaporated *in vacuo* to give a crude mixture of diastereoisomers (72:28 ratio of (*R_S,R*)-**3b** to (*R_S,S*)-**3b** determined by ¹H NMR) that was separated by flash column chromatography (SiO₂, EtOAc, then 90:10 CH₂Cl₂:MeOH) to yield (*R_S,R*)-**3b** as a yellow oil (3.21 g, 64%) and (*R_S,S*)-**3b** as a white solid (0.92 g, 19%). (*R_S,R*)-**3b**: *R_f* 0.1 (EtOAc). ¹H NMR (500 MHz, CDCl₃) $\delta = 8.45$ (1H, d, $J = 2.3$, =CH), 8.41 (1H, dd, $J = 4.8, 1.6$, =CH), 7.51 (1H, dt, $J = 8.0, 2.0$, =CH), 7.22 – 7.04 (4H, m, 4 x =CH), 6.98 – 6.92 (2H, m, 2 x =CH), 4.55 (1H, td, $J = 7.2, 4.9$, CHNH), 3.80 (1H, d, $J = 5.1$, CHNH), 3.26 (1H, dd, $J = 13.5, 6.9$, CH_AH_BBn), 2.95 (1H, dd, $J = 13.5, 7.5$, CH_AH_BBn), 1.07 (9H, s, C(CH₃)₃). ¹³C NMR (126 MHz, CDCl₃) $\delta = 148.9$ (=CH), 148.7 (=CH), 137.6 (=C), 136.7 (=C), 135.5 (=CH), 129.7 (=CH), 128.5 (=CH), 126.9 (=CH), 123.6 (=CH), 59.1 (CH-Bn), 56.4 (C(CH₃)₃), 43.5 (CH₂Ph), 22.6 (C(CH₃)₃).

(*R_S,S*)-**3b**: *R_f* 0.3 (EtOAc). ¹H NMR (500 MHz, CDCl₃) $\delta = 8.52 - 8.42$ (2H, m, 2 x =CH), 7.49 (1H, dt, $J = 7.9, 2.0$, =CH), 7.26 – 7.12 (4H, m, 4 x =CH), 7.05 – 6.99 (2H, m, 2 x =CH), 4.62 (1H, ddd, $J = 8.4, 6.5, 2.3$, CHNH), 3.55 (1H, d, $J = 2.3$, CHNH), 3.10 – 2.92 (2H, m, CH₂Ph), 1.08 (9H, s, C(CH₃)₃). ¹³C NMR (126 MHz, CDCl₃) $\delta = 149.5$ (=CH), 149.2 (=CH), 136.9 (=C), 136.0 (=C), 135.7 (=CH), 129.6 (=CH), 129.0 (=CH), 127.4 (=CH), 123.4 (=CH), 57.3 (CH-Bn), 55.9 (C(CH₃)₃), 45.3 (CH₂Ph), 22.6 (C(CH₃)₃). **Mp** = 112-114 °C. **IR** (film, cm⁻¹): $\nu_{\max} = 3194, 3028, 1578, 1454, 1428, 1363, 1057$. $[\alpha]_{\text{D}}^{25} = -20$ ($c = 1.00$; CH₂Cl₂). **HRMS** (ESI⁺): m/z calcd for C₁₇H₂₃N₂OS [M+H]⁺ 303.1526, found 303.1525.

⁴ Data for (*R_S,R*)-**3b** in accordance with the literature (Reference: Buesking, A. W.; Baguley, T. D.; Ellman, J. A.; *Org. Lett.*, 2011, 13, 964)

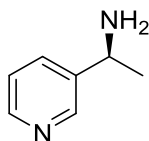
(S)-1-(pyridin-3-yl)ethan-1-amine (5a, er 98:2)⁵



To a solution of **3aa** (4.50 g, 19.88 mmol) in anhydrous MeOH (100 mL) was added HCl in dioxane (4.0 M, 24.9 mL, 99.4 mmol). Reaction mixture was stirred for 2 h, evaporated *in vacuo* and the solid residue was washed with Et₂O and then dissolved in 1 M aqueous KOH solution until pH was higher than 10. The aqueous phase was extracted three times with EtOAc. The combined organic extract was dried over MgSO₄ and evaporated *in vacuo* to give **5a (er 98:2)** as brown oil (1.60 g, 66%) that was used without further purification.

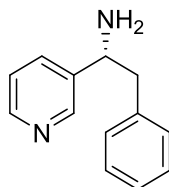
¹H NMR (400 MHz, CDCl₃) δ = 8.53 (1H, t, J = 1.9, =CH), 8.48 – 8.37 (1H, m, =CH), 7.70 – 7.60 (1H, m, =CH), 7.27 – 7.13 (1H, m, =CH), 4.12 (1H, q, J = 6.7, CH-CH₃), 1.50 (2H, s, NH₂), 1.34 (3H, d, J = 6.6, CH-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 148.6 (=CH), 148.2 (=CH), 142.7 (=C), 133.4 (=CH), 123.6 (=CH), 49.2 (CH-CH₃), 25.8 (CH-CH₃). HRMS (ESI⁺): m/z calcd for C₇H₁₁N₂ [M+H]⁺ 123.0917, found 123.0920.

(S)-1-(pyridin-3-yl)ethan-1-amine (5a, er 73:27)



Same procedure and data as for **5a (er 98:2)**, (**3a, dr 73:27**) used as the starting material instead.

(R)-2-phenyl-1-(pyridin-3-yl)ethan-1-amine (5b)⁵



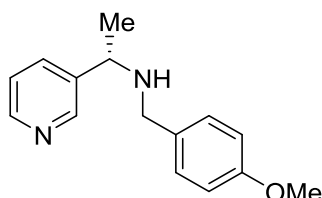
To a solution of (*R*,*R*)-**3b** (5.20 g, 17.19 mmol) in anhydrous MeOH (85 mL) was added HCl in dioxane (4.0 M, 21.5 mL, 86.0 mmol). Reaction mixture was stirred for 2 h, evaporated *in vacuo* and the solid residue was washed with Et₂O and then dissolved in 1 M aqueous KOH solution until pH was higher than 10. The aqueous phase was extracted three times with EtOAc. The combined organic extract was dried over MgSO₄ and evaporated *in vacuo* to give **5b** as brown oil (2.90 g, 85%) that was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ = 8.50 (1H, d, J = 2.2, =CH), 8.44 (1H, dd, J = 4.8, 1.7, =CH), 7.63 (1H, ddd, J = 7.9, 2.3, 1.6, =CH), 7.29 – 7.12 (4H, m, 4 x =CH), 7.10 – 7.06 (2H, m, 2 x =CH), 4.18 (1H, dd, J = 8.7, 5.2, CH-CH₂), 2.92 (1H, dd, J = 13.4, 5.2, CH-CH_AH_B), 2.78 (1H, dd, J = 13.3, 8.7, CH-CH_AH_B), 1.50 (2H, s, NH₂). ¹³C NMR

⁵ The data are in agreement with the literature (Reference: Baucom, K. D.; Guram, A. S.; Borths, C. J. *Synlett*, 2015, 26, 201).

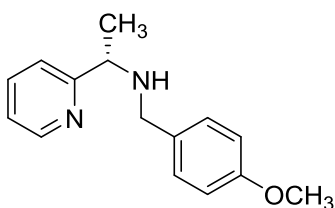
(101 MHz, CDCl₃) δ = 148.8 (2 x =CH), 140.8 (=C), 138.3 (=C), 134.2 (=CH), 129.5 (=CH), 128.7 (=CH), 126.8 (=CH), 123.5 (=CH), 55.4 (N-CH-CH₂), 46.4 (N-CH-CH₂). **HRMS** (ESI⁺): m/z calcd for C₁₃H₁₅N₂ [M+H]⁺ 199.1230, found 199.1230.

(S)-N-(4-methoxybenzyl)-1-phenyl-1-(pyridin-3-yl)ethan-1-amine (5c)



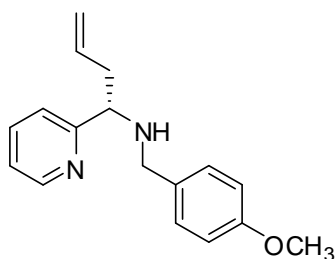
Following General procedure 5, aminopyridine **5a**, **er 73:27** (2.075 g, 16.99 mmol), *p*-anisaldehyde (2.17 mL, 17.83 mmol), NaOAc (2.86 g, 34.82 mmol) and NaBH(OAc)₃ (7.38 g, 34.82 mmol) in MeOH (77 ml) gave after purification by flash column chromatography (SiO₂, 95:5 CH₂Cl₂:MeOH) **5c** as an oil (2.27 g, 55%). **¹H NMR** (500 MHz, CDCl₃) δ = 8.57 (1H, d, J = 2.2, =CH), 8.51 (1H, dd, J = 4.8, 1.7, =CH), 7.73 (1H, dt, J = 8.0, 2.0, =CH), 7.30 – 7.24 (1H, m, =CH), 7.20 – 7.16 (2H, m, 2 x =CH), 6.87 – 6.81 (2H, m, 2 x =CH), 3.84 (1H, q, J = 6.6, CH-CH₃), 3.79 (3H, s, OCH₃), 3.58 (1H, d, J = 13.0, NHCH_AH_B), 3.53 (1H, d, J = 13.0, NHCH_AH_B), 1.68 (1H, br s, NH), 1.37 (3H, d, J = 6.6, CH-CH₃). **¹³C NMR** (126 MHz, CDCl₃) δ = 158.8 (=C), 149.2 (=CH), 148.7 (=CH), 140.8 (=C), 134.4 (=CH), 132.4 (=C), 129.4 (=CH), 123.7 (=CH), 114.0 (=CH), 55.4 (OCH₃), 55.2 (CH-CH₃), 51.2 (NH-CH₂), 24.5 (CH-CH₃). $[\alpha]_D^{23}$ = -31.7 (c = 1.00; CH₂Cl₂). **IR** (film, cm⁻¹): ν_{\max} = 3357, 2930, 1365, 1168. **HRMS** (ESI⁺): m/z calcd for C₁₅H₁₉N₂O [M+H]⁺ 243.1492, found 243.1497.

[(4-Methoxyphenyl)methyl][(1S)-1-(pyridin-2-yl)ethyl]amine (6d)



Following General procedure 5, aminopyridine **6a** (440 mg, 3.60 mmol), *p*-anisaldehyde (0.46 ml), NaOAc (605 mg) and NaBH(OAc)₃ (1.56 g) in MeOH (16.4 ml) gave **6d** as an oil (477 mg, 55%). **¹H NMR** (400 MHz, CDCl₃) δ = 8.63-8.54 (1H, m, =CH), 7.65 (1H, td, J = 7.7 and 1.8, =CH), 7.34 (1H, d, J = 7.8, =CH), 7.24-7.20 (2H, m, 2 x =CH), 7.16 (1H, ddd, J = 14.3, 4.9 and 1.1, =CH), 6.90-6.77 (2H, m, 2 x =CH), 3.90 (1H, q, J = 6.7, NCHCH₃), 3.79 (3H, s, OCH₃), 3.57 (2H, AB pattern, J = 12.9, $\Delta\nu$ = 9.0, NHCH₂), 1.88 (1H, brs, NH), 1.39 (3H, d, J = 6.7, CHCH₃). **¹³C NMR** (100 MHz, CDCl₃) δ = 164.8 (=C), 158.6 (=C), 149.5 (=CH), 136.7 (=CH), 132.7 (=C), 129.5 (=CH), 122.0 (=CH), 121.4 (=CH), 113.8 (2 x =CH), 58.7 (NCH), 55.4 (OCH₃), 51.3 (CH₂), 23.1 (CH₃). $[\alpha]_D^{20}$ = -159 (c = 1.00; CHCl₃). **IR** (film, cm⁻¹): ν_{\max} = 2975, 1214, 1041, 748. **HRMS** (ESI⁺): m/z calcd for C₁₅H₁₉N₂O [M+H]⁺ 243.1419, found 243.1495.

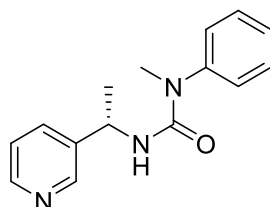
[(4-Methoxyphenyl)methyl][(1S)-1-(pyridin-2-yl)but-3-en-1-yl]amine (6e)



Following General procedure 5, aminopyridine **6c** (200 mg, 1.35 mmol), *p*-anisaldehyde (0.17 ml), NaOAc (227 mg) and NaBH(OAc)₃ (0.59 mg) in MeOH (6.13 ml) gave **6e** as an oil (90 mg, 25%). ¹H NMR (400 MHz, CDCl₃) δ = 8.63-8.51 (1H, m, =CH), 7.66 (1H, td, *J* = 7.6 and 1.8, =CH), 7.37 (1H, d, *J* = 7.8, =CH), 7.23-7.13 (3H, m, 3 x =CH), 6.88-6.79 (2H, m, 2 x =CH), 5.79-5.65 (1H, m, CH₂=CHCH₂), 5.10-4.97 (1H, m, CH₂=CH), 3.82 (1H, dd, *J* = 7.7 and 5.9, NHCHCH₂), 3.79 (3H, s, OCH₃), 3.61 (1H, d, *J* = 12.9, NHCH_AH_B), 3.51 (1H, d, *J* = 13.0, NHCH_AH_B), 2.63-2.35 (2H, m, CHCH₂CH=), 1.92 (1H, brs, NH). ¹³C NMR (100 MHz, CDCl₃) δ = 163.4 (=C), 158.7 (=C), 149.5 (=CH), 136.4 (=CH), 135.4 (=CH), 132.7 (=C), 129.4 (=CH), 122.1 (=CH), 122.0 (=CH), 117.6 (=CH₂), 113.8 (=CH), 63.0 (NCH), 55.4 (OCH₃), 51.3 (CH₂), 41.7 (CH₂). [α]_D²⁰ = -64 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3010, 2957, 1639, 1245, 1037, 750. HRMS (ESI⁺): *m/z* calcd for C₁₇H₂₁N₂O [M+H]⁺ 269.1648, found 269.1650.

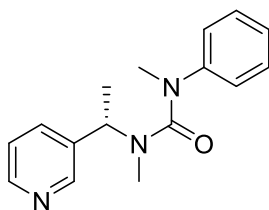
- Urea formation

(S)-1-methyl-1-phenyl-3-(1-(pyridin-3-yl)ethyl)urea (17a)



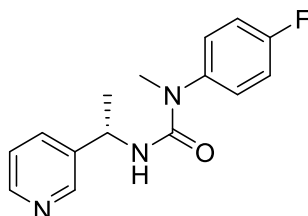
Following General procedure 1, *N*-methyl-*N*-phenyl carbamoyl chloride (416 mg, 2.456 mmol, 1.2 eq.), 3-pyridine **5a (er 98:2)** (250 mg, 2.036 mmol, 1.0 eq.) and Et₃N (570 μl, 4.072 mmol, 2.0 eq.) in acetonitrile (20.0 ml) gave after 20 h heating at reflux a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH) to obtain **17a** as a brown oil (239 mg, 46%). R_f 0.21 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.50 (1H, d, *J* = 2.3, =CH), 8.47 (1H, dd, *J* = 4.8, 1.6, =CH), 7.54 (1H, dt, *J* = 7.9, 1.8, =CH), 7.47 – 7.42 (2H, m, 2 x =CH), 7.36 – 7.30 (1H, m, =CH), 7.28 – 7.24 (2H, m, 2 x =CH), 7.22 (ddd, *J* = 7.9, 4.8, 0.7 Hz, 1H, =CH), 5.03 (quin, *J* = 7.1 Hz, 1H, NHCHCH₃), 4.54 (d, *J* = 7.2 Hz, 1H, NHCHCH₃), 3.25 (s, 3H, NCH₃), 1.36 (d, *J* = 7.0 Hz, 3H, NHCHCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 156.4 (C=O), 148.5 (=CH), 147.9 (=CH), 143.3 (=C), 140.0 (=C), 133.9 (=CH), 130.4 (=CH), 127.7 (=CH), 127.5 (=CH), 123.5 (=CH), 48.3 (NHCHCH₃), 37.4 (NCH₃), 22.5 (NHCHCH₃). [α]_D²⁵ = +90 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3327, 2979, 1650, 1495, 1346. HRMS (ESI⁺): *m/z* calcd for C₁₅H₁₈N₃O [M+H]⁺ 256.1444, found 256.1447.

(S)-1,3-dimethyl-3-phenyl-1-(1-(pyridin-3-yl)ethyl)urea (7a)



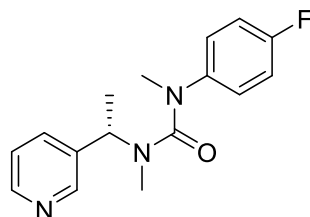
Following general procedure 2B, urea **17a** (193 mg, 0.715 mmol), NaH (43 mg, 1.073 mmol), MeI (53 μ L, 0.858 mmol) in DMF (10.0 ml) gave after 2.5 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), to obtain **7a** as a yellow oil (173 mg, 85%). *R*_f 0.25 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.52 (1H, d, *J* = 2.3, =CH), 8.49 (1H, dd, *J* = 4.8, 1.4, =CH), 7.66 – 7.58 (1H, m, =CH), 7.37 – 7.29 (2H, m, 2 x =CH), 7.24 (1H, ddd, *J* = 7.9, 4.9, 0.7, =CH), 7.15 – 7.07 (3H, m, 3 x =CH), 5.57 (1H, q, *J* = 7.1, NCHCH₃), 3.25 (3H, s, CH₃N-C=CH), 2.21 (3H, s, CH₃NCHCH₃), 1.45 (3H, d, *J* = 7.1, NCHCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 162.3 (C=O), 149.0 (=CH), 148.6 (=CH), 147.0 (=C), 136.7 (=C), 135.2 (=CH), 129.7 (=CH), 125.1 (=CH), 124.6 (=CH), 123.4 (=CH), 52.3 (NCHCH₃), 40.4 (CH₃NCHCH₃), 31.1 (CH₃NC=CH), 15.6 (NCHCH₃). [α]_D²⁵ = -10 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν _{max} = 2973, 1637, 1439, 1338, 1119, 760, 698.

(S)-1-(4-fluorophenyl)-1-methyl-3-(1-(pyridin-3-yl)ethyl)urea (17b)



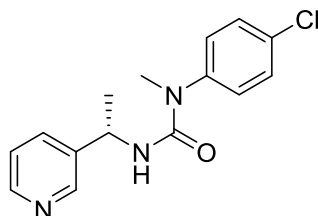
Following General procedure 1, *N*-methyl-*N*-(4-fluorophenyl) carbamoyl chloride (461 mg, 2.456 mmol, 1.2 eq.), 3-pyridine **5a** (er **98:2**) (250 mg, 2.036 mmol, 1.0 eq.) and Et₃N (570 μ L, 4.072 mmol, 2.0 eq.) in acetonitrile (20.0 ml) gave after 20 h heating at reflux a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH) to yield **17b** as a yellow oil (261 mg, 47%). *R*_f 0.28 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.58 – 8.41 (2H, m, 2 x =CH), 7.50 – 7.44 (1H, m, =CH), 7.35 – 7.03 (5H, m, 5 x =CH), 5.01 (1H, quint, *J* = 7.1, NHCHCH₃), 4.44 (1H, d, *J* = 6.8, NHCHCH₃), 3.21 (3H, s, NCH₃), 1.37 (3H, d, *J* = 7.0, NHCHCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 161.7 (d, ¹*J*_{CF} = 248.3 Hz, =CF), 156.4 (C=O), 148.6 (=CH), 147.9 (=CH), 139.9 (=C-CHCH₃), 139.2 (d, ⁴*J*_{CF} = 3.4 Hz, N-C=CH), 133.8 (=CH), 129.4 (d, ³*J*_{CF} = 8.7 Hz, =CH), 123.5 (=CH), 117.3 (d, ²*J*_{CF} = 22.6 Hz, =CH), 48.4 (NHCHCH₃), 37.6 (NCH₃), 22.5 (NHCHCH₃). [α]_D²⁵ = +90 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν _{max} = 3326, 2976, 1649, 1507, 1220, 843. HRMS (ESI⁺): *m/z* calcd for C₁₅H₁₆N₃OFNa [M+Na]⁺ 296.1170, found 296.1156.

((S)-1-(4-fluorophenyl)-1,3-dimethyl-3-(1-(pyridin-3-yl)ethyl)urea (7b)



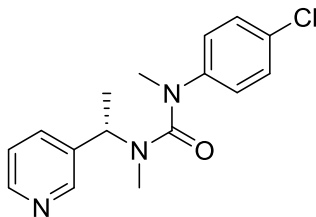
Following general procedure 2B, urea **17b** (223 mg, 0.817 mmol), NaH (49 mg, 1.226 mmol), MeI (61 μ L, 0.981 mmol) in DMF (12.0 ml) gave after 3 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), to yield **7b** as a yellow oil (186 mg, 79%). *R_f* 0.29 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.59 – 8.42 (1H, m, 2 x =CH), 7.66 – 7.54 (1H, m, =CH), 7.27 – 7.21 (2H, m, 2 x =CH), 7.11 – 6.98 (3H, m, 3 x =CH), 5.55 (1H, q, *J* = 7.1, NCHCH₃), 3.20 (3H, s, CH₃NC=CH), 2.22 (3H, s, CH₃NCHCH₃), 1.45 (3H, d, *J* = 7.1, NCHCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 162.3 (C=O), 160.0 (d, ¹*J*_{CF} = 245.3 Hz, =CF), 149.0 (=CH), 148.7 (=CH), 143.1 (d, ⁴*J*_{CF} = 3.4 Hz = 3.0 Hz, N-C=CH), 136.6 (=C-CHCH₃), 135.1 (=CH), 126.4 (d, ³*J*_{CF} = 8.1 Hz, =CH), 123.4 (=CH), 116.5 (d, ²*J*_{CF} = 22.6 Hz, =CH), 52.4 (NCHCH₃), 40.8 (CH₃NCHCH₃), 31.1 (CH₃NC=CH), 15.7 (NCHCH₃). [α]_D²⁵ = -10 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{\max} = 2923, 1639, 1507, 1331, 1218, 1120, 716. HRMS (ESI⁺): *m/z* calcd for C₁₆H₁₉N₃OF [M+H]⁺ 288.1507, found 288.1494.

(S)-1-(4-chlorophenyl)-1-methyl-3-(1-(pyridin-3-yl)ethyl)urea (17c)



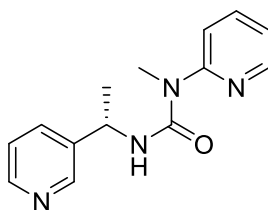
Following general procedure 1, *N*-methyl-*N*-(4-chlorophenyl) carbamoyl chloride (501 mg, 2.456 mmol, 1.2 eq.), 3-pyridine **5a (er 98:2)** (250 mg, 2.036 mmol, 1.0 eq.) and Et₃N (570 μ L, 4.072 mmol, 2.0 eq.) in acetonitrile (20.0 ml) gave after 20 h heating at reflux a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH) to yield **17c** as a brown solid (248 mg, 42%). *R_f* 0.31 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.51 (1H, d, *J* = 2.2, =CH), 8.48 (1H, dd, *J* = 4.8, 1.5, =CH), 7.55 (1H, dt, *J* = 7.9, 1.8, =CH), 7.43 – 7.38 (2H, m, 2 x =CH), 7.25 – 7.17 (3H, m, 3 x =CH), 5.02 (1H, quint, *J* = 7.1, NHCHCH₃), 4.49 (1H, d, *J* = 7.3, NHCHCH₃), 3.22 (3H, s, NCH₃), 1.38 (3H, d, *J* = 7.0, NHCHCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 156.1 (C=O), 148.6 (=CH), 147.9 (=CH), 141.9 (=C), 139.8 (=C), 133.9 (=CH), 133.4 (=C), 130.5 (=CH), 128.8 (=CH), 123.5 (=CH), 48.4 (NHCHCH₃), 37.4 (NCH₃), 22.4 (NHCHCH₃). *Mp* = 110-112 °C. [α]_D²⁵ = +60 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{\max} = 3319, 2975, 1647, 1516, 1492, 1341, 1091, 714. HRMS (ESI⁺): *m/z* calcd for C₁₅H₁₇N₃OCl [M+H]⁺ 290.1055, found 290.1058.

(S)-1-(4-chlorophenyl)-1,3-dimethyl-3-(1-(pyridin-3-yl)ethyl)urea (7c)



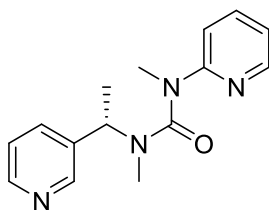
Following general procedure 2B, urea **17c** (248 mg, 0.856 mmol), NaH (51 mg, 1.283 mmol), MeI (64 μ L, 1.027 mmol) in DMF (15.0 ml) gave after 3 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO_2 , 99:1 to 97:3 CH_2Cl_2 :MeOH), to yield **7c** as a yellow oil (215 mg, 83%). R_f 0.22 (95:5 CH_2Cl_2 :MeOH). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.54 (1H, d, J = 1.5 Hz, =CH), 8.50 (1H, d, J = 3.8 Hz, =CH), 7.61 (1H, d, J = 7.9 Hz, =CH), 7.31 – 7.22 (4H, m, 4 x =CH), 7.04 – 6.99 (2H, m, 2 x =CH), 5.56 (1H, q, J = 7.1, NCHCH₃), 3.21 (3H, s, CH₃NC=CH), 2.24 (3H, s, CH₃NCHCH₃), 1.46 (3H, d, J = 7.1, NCHCH₃). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 161.9 (C=O), 149.0 (=CH), 148.8 (=CH), 145.4 (=C), 136.5 (=C), 135.1 (=CH), 130.3 (=C), 129.8 (=CH), 125.6 (=CH), 123.4 (=CH), 52.3 (NCHCH₃), 40.2 (CH₃NCHCH₃), 31.2 (CH₃NC=CH), 15.6 (NCHCH₃). Mp = 77-78 °C. $[\alpha]_D^{25}$ = -10 (c = 1.00; CH_2Cl_2). IR (film, cm^{-1}): ν_{max} = 2974, 1642, 1492, 1330, 1120, 834, 715. HRMS (ESI⁺): m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{OCl}$ [M+H]⁺ 304.1211, found 304.1214.

(S)-1-methyl-1-(pyridin-2-yl)-3-(1-(pyridin-3-yl)ethyl)urea (17d)



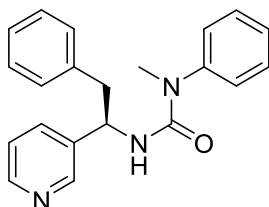
Following general procedure 1, *N*-methyl-*N*-(3-pyridyl) carbamoyl chloride (419 mg, 2.456 mmol, 1.2 eq.), 3-pyridine **5a (er 98:2)** (250 mg, 2.036 mmol, 1.0 eq.) and Et₃N (570 μ L, 4.072 mmol, 2.0 eq.) in acetonitrile (20.0 ml) gave after 2 h heating at reflux a crude product that was purified by flash column chromatography (SiO_2 , 99:1 to 97:3 CH_2Cl_2 :MeOH) to yield **17d** as a brown oil (203 mg, 39%). R_f 0.24 (95:5 CH_2Cl_2 :MeOH). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 10.89 (1H, d, J = 6.7, NHCHCH₃), 8.65 (1H, d, J = 2.2, =CH), 8.48 (1H, dd, J = 4.8, 1.5, =CH), 8.31 – 8.24 (1H, m, =CH), 7.75 – 7.65 (2H, m, 2 x =CH), 7.26 – 7.22 (1H, m, =CH), 7.01 – 6.95 (2H, m, 2 x =CH), 5.13 (1H, quint, J = 7.0, NCHCH₃), 3.38 (3H, s, J = 8.4, NCH₃), 1.57 (3H, d, J = 7.0, NHCHCH₃). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 156.2 (C=O), 155.9 (=C), 148.4 (=CH), 148.2 (=CH), 140.4 (=C), 138.9 (=CH), 133.9 (=CH), 123.5 (=CH), 117.1 (=CH), 111.6 (=CH), 48.6 (NHCHCH₃), 32.9 (NCH₃), 23.2 (NHCHCH₃). $[\alpha]_D^{25}$ = +110 (c = 1.00; CH_2Cl_2). IR (film, cm^{-1}): ν_{max} = 3172, 2972, 1666, 1529, 1435, 1317, 777. HRMS (ESI⁺): m/z calcd for $\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}$ [M+H]⁺ 257.1397, found 257.1400.

(S)-1,3-dimethyl-3-(pyridin-2-yl)-1-(1-(pyridin-3-yl)ethyl)urea (7d)



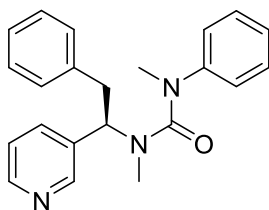
Following general procedure 2B, urea **17d** (248 mg, 0.856 mmol), NaH (51 mg, 1.283 mmol), MeI (64 μ L, 1.027 mmol) in DMF (15.0 ml) gave after 3 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO_2 , 99:1 to 97:3 CH_2Cl_2 :MeOH), to yield **7d** as a yellow oil (215 mg, 74%). R_f 0.28 (95:5 CH_2Cl_2 :MeOH). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.64 (1H, s, =CH), 8.52 (1H, d, J = 4.2, =CH), 8.32 (1H, dd, J = 4.8, 1.3, =CH), 7.74 (1H, d, J = 7.9, =CH), 7.61 – 7.53 (1H, m, =CH), 7.33 – 7.22 (1H, m, =CH), 6.94 – 6.84 (2H, m, =CH), 5.69 (1H, q, J = 7.1, NCHCH₃), 3.33 (3H, s, CH₃NC=CH), 2.42 (3H, s, CH₃NCHCH₃), 1.59 (3H, d, J = 7.1, NCHCH₃). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 161.3 (C=O), 157.5 (=C), 149.1 (=CH), 148.8 (=CH), 148.6 (=CH), 137.9 (=CH), 136.2 (=C), 135.3 (=CH), 123.5 (=CH), 117.8 (=CH), 114.3 (=CH), 52.3 (NCHCH₃), 36.5 (CH₃NCHCH₃), 30.7 (CH₃NC=CH), 15.7 (NCHCH₃). $[\alpha]_D^{25}$ = +10 (c = 1.00; CH_2Cl_2). IR (film, cm^{-1}): ν_{max} = 2978, 1651, 1589, 1477, 1428, 1332, 1104, 775. HRMS (ESI⁺): m/z calcd for C₁₅H₁₈N₄ONa [M+Na]⁺ 293.1373, found 293.1365.

(R)-1-methyl-1-phenyl-3-(2-phenyl-1-(pyridin-3-yl)ethyl)urea (17e)



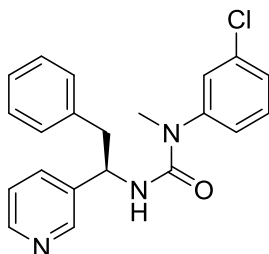
Following general procedure 1, *N*-methyl-*N*-phenyl carbamoyl chloride (0.308 g, 1.816 mmol, 1.2 eq.), 3-pyridine **5b** (300 mg, 1.513 mmol, 1.0 eq.) and Et₃N (422 μ L, 3.026 mmol, 2.0 eq.) in acetonitrile (15.0 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2 , 99:1 to 97:3 CH_2Cl_2 :MeOH) to yield **17e** as a brown oil (261 mg, 52%). R_f 0.18 (95:5 CH_2Cl_2 :MeOH). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.46 (1H, dd, J = 4.8, 1.6, =CH), 8.41 (1H, d, J = 2.2, =CH), 7.47 – 7.29 (4H, m, 4 x =CH), 7.23 – 7.14 (4H, m, 4 x =CH), 7.09 – 7.03 (2H, m, 2 x =CH), 6.88 – 6.80 (2H, m, 2 x =CH), 5.12 (1H, dd, J = 14.6, 6.5, NHCHCH₂), 4.65 (1H, d, J = 6.8, NHCHCH₂), 3.17 (3H, s, N-CH₃), 3.00 (1H, dd, J = 13.8, 6.0, NHCHCH_AH_B), 2.80 (1H, dd, J = 13.8, 8.2, NHCHCH_AH_B); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 156.4 (C=O), 148.4 (=CH), 148.1 (=CH), 143.0 (=C), 138.6 (=C), 136.6 (=C), 134.3 (=CH), 130.3 (=CH), 129.3 (=CH), 128.7 (=CH), 127.7 (=CH), 127.5 (=CH), 126.9 (=CH), 123.3 (=CH), 53.8 (NHCHCH₂), 43.0 (NHCHCH₂), 37.1 (NCH₃). $[\alpha]_D^{25}$ = -10 (c = 1.00; CH_2Cl_2). IR (film, cm^{-1}): ν_{max} = 3337, 3028, 2926, 1656, 1495. HRMS (ESI⁺): m/z calcd for C₂₁H₂₁N₃ONa [M+Na]⁺ 354.1577, found 354.1561.

(R)-1,3-dimethyl-3-phenyl-1-(2-phenyl-1-(pyridin-3-yl)ethyl)urea (7e)



Following general procedure 2B, urea **17e** (224 mg, 0.677 mmol), NaH (41 mg, 1.016 mmol), MeI (51 μ L, 0.813 mmol) in DMF (6.8 ml) gave after 2 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO_2 , 99:1 to 97:3 CH_2Cl_2 :MeOH), to obtain **7e** as an orange oil (211 mg, 90%). R_f 0.18 (95:5 CH_2Cl_2 :MeOH). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.66 (1H, d, J = 2.2, =CH), 8.51 (1H, dt, J = 18.8, 9.4, =CH), 7.80 (1H, dt, J = 7.9, 1.7, =CH), 7.44 – 7.23 (6H, m, 6 x =CH), 7.10 – 6.95 (3H, m, 3 x =CH), 6.48 – 6.40 (2H, m, 2 x =CH), 6.02 (1H, dd, J = 11.4, 5.5, NCHCH₂), 3.34 (1H, dd, J = 14.4, 5.5 Hz, NCHCH_AH_B), 3.12 (3H, s, =CH-NCH₃), 3.09 (1H, dd, J = 14.4, 11.4, NCHCH_AH_B), 2.23 (3H, s, CH₂CHNCH₃). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 162.1 (C=O), 149.2 (=CH), 148.9 (=CH), 146.5 (=C), 137.9 (=C), 135.9 (2 peaks, =CH, =C), 129.6 (=CH), 129.1 (=CH), 129.0 (=CH), 126.9 (=CH), 124.5 (=CH), 124.3 (=CH), 123.5 (=CH), 57.1 (NCHCH₂), 40.5 (=CH-NCH₃), 36.6 (NCHCH₂), 31.6 (CH₂CHNCH₃). $[\alpha]_D^{25}$ = +95 (c = 1.00; CH_2Cl_2). IR (film, cm^{-1}): ν_{max} = 3029, 2931, 1634, 1494, 1342, 1118. HRMS (ESI⁺): m/z calcd for $\text{C}_{22}\text{H}_{24}\text{N}_3\text{O}$ [M+H]⁺ 346.1914, found 346.1900.

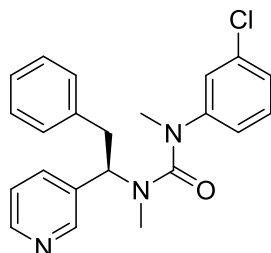
(R)-1-(3-chlorophenyl)-1-methyl-3-(2-phenyl-1-(pyridin-3-yl)ethyl)urea (17f)



Following general procedure 1, *N*-methyl-*N*-(3-chlorophenyl) carbamoyl chloride (0.371 g, 1.816 mmol, 1.2 eq.), 3-pyridine **5b** (300 mg, 1.513 mmol, 1.0 eq.) and Et₃N (420 μ L, 3.026 mmol, 2.0 eq.) in acetonitrile (11.0 ml) gave, after 2 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2 , 97:3 to 95:5 CH_2Cl_2 :MeOH) to yield **17f** as a brown oil (474 mg, 86%). R_f 0.23 (95:5 CH_2Cl_2 :MeOH). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.41 (1H, dd, J = 4.8, 1.6, =CH), 8.37 (1H, d, J = 2.3, =CH), 7.41 – 7.35 (1H, m, =CH), 7.26 – 7.22 (2H, m, 2 x =CH), 7.18 – 7.10 (4H, m, 4 x =CH), 7.05 (1H, dt, J = 2.0, 0.9, =CH), 6.89 – 6.85 (1H, m, =CH), 6.85 – 6.78 (2H, m, 2 x =CH), 5.06 (1H, dt, J = 8.2, 6.4, NHCHCH₂), 4.56 (1H, d, J = 6.7, NHCHCH₂), 3.09 (3H, s, NCH₃), 2.99 (1H, dd, J = 13.9, 5.9, NHCHCH_AH_B), 2.76 (1H, dd, J = 13.9, 8.4, NHCHCH_AH_B). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 155.9 (C=O), 148.6 (=CH), 148.1 (=CH), 144.3 (=C), 138.4 (=C), 136.5 (=C), 135.6 (=C), 134.3 (=CH), 131.2 (=CH), 129.3 (=CH), 128.8 (=CH), 127.9 (=CH), 127.8 (=CH), 127.1 (=CH), 125.6 (=CH), 123.4 (=CH), 53.9 (NHCHCH₂), 42.9 (NHCHCH₂), 37.2 (NCH₃). $[\alpha]_D^{25}$ = -10 (c = 1.00;

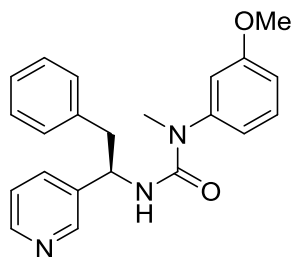
CH₂Cl₂). IR (film, cm⁻¹): ν_{\max} = 3310, 3028, 1656, 1591, 1509, 1337. HRMS (ESI⁺): m/z calcd for C₂₁H₂₁N₃OCl [M+H]⁺ 366.1368, found 366.1354.

(R)-1-(3-chlorophenyl)-1,3-dimethyl-3-(2-phenyl-1-(pyridin-3-yl)ethyl)urea (7f)



Following general procedure 2B, urea **17f** (282 mg, 0.772 mmol), NaH (51 mg, 1.278 mmol), MeI (64 μ L, 1.02 mmol) in DMF (8.5 ml) gave after 2 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), to obtain **7f** as a yellow oil (282 mg, 96%). R_f 0.18 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.61 (1H, d, J = 1.5, =CH), 8.47 (1H, d, J = 3.6 Hz, =CH), 7.75 – 7.69 (1H, m, =CH), 7.35 – 7.17 (6H, m, =CH), 6.93 – 6.75 (3H, m, =CH), 5.96 – 5.88 (2H, m, =CH and NCHCH₂), 3.28 (1H, dd, J = 14.5, 5.7, NCHCH_AH_B), 3.12 – 3.04 (1H, m, NCHCH_AH_B), 3.02 (3H, s, =CH-NCH₃), 2.23 (3H, s, CH₂CHNCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 161.6 (C=O), 149.2 (=CH), 149.1 (=CH), 147.6 (s), 137.7 (=C), 135.9 (=CH), 135.5 (=C), 134.8 (=C), 130.6 (=CH), 129.0 (2 x =CH), 127.0 (=CH), 124.5 (=CH), 123.8 (=CH), 123.6 (=CH), 121.8 (=CH), 57.4 (NCHCH₂), 40.0 (=CH-NCH₃), 36.5 (NCHCH₂), 31.8 (CH₂CHNCH₃). $[\alpha]_D^{25}$ = +110 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{\max} = 3028, 2925, 1640, 1591, 1478, 1330, 1099. HRMS (ESI⁺): m/z calcd for C₂₂H₂₃N₃OCl [M+H]⁺ 380.1524, found 380.1511.

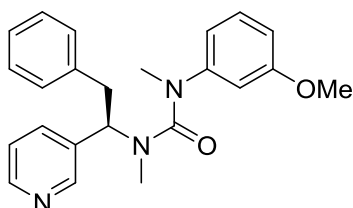
(R)-1-(3-methoxyphenyl)-1-methyl-3-(2-phenyl-1-(pyridin-3-yl)ethyl)urea (17g)



Following general procedure 1, *N*-methyl-*N*-(3-methoxyphenyl) carbamoyl chloride (0.302 g, 1.513 mmol, 1.2 eq.), 3-pyridine **5b** (250 mg, 1.261 mmol, 1.0 eq.) and Et₃N (350 μ L, 2.522 mmol, 2.0 eq.) in acetonitrile (13.0 ml) gave, after 2 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH) to yield **17g** as a brown oil (313 mg, 69%). R_f 0.17 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.46 (1H, dd, J = 4.8, 1.5, =CH), 8.41 (1H, d, J = 2.1, =CH), 7.42 (1H, dt, J = 7.8, 1.8, =CH), 7.33 – 7.24 (2H, m, 2 x =CH), 7.22 – 7.13 (3H, m, 3 x =CH), 6.91 – 6.81 (3H, m, 3 x =CH), 6.67 – 6.60 (2H, m, 2 x =CH), 5.11 (1H, dd, J = 6.8, 6.6, NHCHCH₂), 4.75 (1H, d, J = 6.8, NHCHCH₂), 3.79 (3H, s, OCH₃), 3.16 (3H, s, N-CH₃), 3.00 (1H, dd, J = 13.8, 6.1, NHCHCH_AH_B), 2.82 (1H, dd, J = 13.8, 8.1,

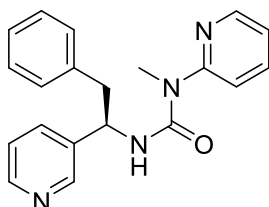
NHCHCH_AH_B). ¹³C NMR (100 MHz, CDCl₃) δ = 161.0 (C=O), 156.3 (=C-OCH₃), 148.5 (=CH), 148.2 (=CH), 144.2 (=C), 138.6 (=C), 136.6 (=C), 134.3 (=CH), 131.0 (=CH), 129.3 (=CH), 128.7 (=CH), 126.9 (=CH), 123.4 (=CH), 119.5 (=CH), 113.5 (=CH), 113.0 (=CH), 55.5 (OCH₃), 53.8 (NHCHCH₂), 43.0 (NHCHCH₂), 37.1 (NCH₃). IR (film, cm⁻¹): ν_{max} = 3322, 3028, 2935, 1659, 1598, 1489. HRMS (ESI⁺): *m/z* calcd for C₂₂H₂₄N₃O₂ [M+H]⁺ 362.1863, found 362.1848.

(R)-1-(3-methoxyphenyl)-1,3-dimethyl-3-(2-phenyl-1-(pyridin-3-yl)ethyl)urea (7g)



Following general procedure 2B, urea **17g** (236 mg, 0.653 mmol), NaH (39 mg, 0.979 mmol), MeI (49 μL, 0.784 mmol) in DMF (7.0 ml) gave after 2 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), to obtain **7g** as a yellow oil (86mg, 35%). R_f 0.27 (95:5 CH₂Cl₂:MeOH). ¹H NMR (500 MHz, CDCl₃) δ = 8.63 (1H, br s, =CH), 8.50 (1H, d, *J* = 4.1, =CH), 7.75 (1H, d, *J* = 7.9, =CH), 7.34 (2H, t, *J* = 7.4, 2 x =CH), 7.30 – 7.22 (3H, m, 3 x =CH), 6.91 (1H, t, *J* = 8.1, =CH), 6.60 – 6.53 (1H, m, =CH), 6.45 (1H, t, *J* = 2.2, =CH), 5.94 (1H, dd, *J* = 10.3, 6.2, =CH), 5.86 (1H, d, *J* = 7.9, =CH), 3.70 (3H, s, OCH₃), 3.32 (1H, dd, *J* = 14.4, 6.2, NCHCH_AH_B), 3.17 – 3.12 (1H, m, NCHCH_AH_B), 3.10 (3H, s, CH₂CHNCH₃), 2.32 (3H, s, =CH-NCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 161.9 (C=O), 160.5 (=C), 149.3 (=CH), 148.9 (=CH), 147.7 (=C), 137.8 (=C), 135.9 (=CH), 135.6 (=C), 130.3 (=CH), 129.0 (=CH), 128.9 (=CH), 126.8 (=CH), 123.5 (=CH), 116.6 (=CH), 110.3 (=CH), 109.8 (=CH), 57.5 (NCHCH₂), 55.3 (OCH₃), 40.3 (=CH-NCH₃), 36.6 (NCHCH₂), 31.6 (CH₂CHNCH₃). [α]_D²⁵ = +65 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 2938, 1637, 1594, 1487, 1328, 1111, 1042, 699. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₆N₃O₂ [M+H]⁺ 376.2020, found 376.2025.

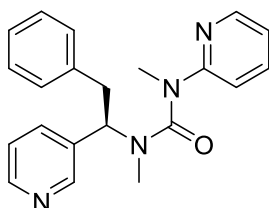
(R)-1-methyl-3-(2-phenyl-1-(pyridin-3-yl)ethyl)-1-(pyridin-2-yl)urea (17h)



Following general procedure 1, *N*-methyl-*N*-(3-pyridyl) carbamoyl chloride (310 mg, 1.816 mmol, 1.2 eq.), 3-pyridine **5b** (300 mg, 1.513 mmol, 1.0 eq.) and Et₃N (420 μl, 3.026 mmol, 2.0 eq.) in acetonitrile (15.0 ml) gave after 2 h heating at reflux a crude product that was purified by flash column chromatography (SiO₂, 97:3 CH₂Cl₂:MeOH) to yield **17h** as a brown oil (450 mg, 90%). R_f 0.15 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 11.10 (1H, d, *J* = 7.0 Hz, NHCHCH₂), 8.51 (1H, d, *J* = 2.2 Hz, =CH), 8.46 (1H, dd, *J* = 4.8, 1.6 Hz,

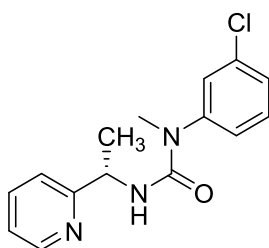
=CH), 8.19 (1H, ddd, $J = 5.0, 2.0, 0.8$ Hz, =CH), 7.70 (1H, ddd, $J = 8.6, 7.4, 2.0$ Hz, =CH), 7.48 (1H, dt, $J = 7.9, 1.8$ Hz, =CH), 7.28 – 7.15 (4H, m, 4 x =CH), 7.08 – 7.03 (2H, m, 2 x =CH), 6.99 – 6.93 (2H, m, 2 x =CH), 5.32 (1H, q, $J = 6.8$ Hz, NHCHCH₂), 3.33 (3H, s, N-CH₃), 3.18 – 3.13 (2H, m, NHCHCH₂). ¹³C NMR (101 MHz, CDCl₃) $\delta = 156.0$ (C=O and N=C-N), 148.6 (=CH), 148.4 (=CH), 145.7 (=CH), 138.9 (=CH), 138.5 (=C), 137.1 (=C), 134.5 (=CH), 129.9 (=CH), 128.4 (=CH), 126.8 (=CH), 123.2 (=CH), 117.1 (=CH), 111.5 (=CH), 54.7 (NHCHCH₂), 43.6 (NHCHCH₂), 32.7 (NCH₃). $[\alpha]_{\text{D}}^{25} = -5$ (c = 1.00; CH₂Cl₂). **Mp** = 85–86 °C. **IR** (film, cm⁻¹): $\nu_{\text{max}} = 3028, 1665, 1521, 1434, 1316$. **HRMS** (ESI⁺): m/z calcd for C₂₀H₂₁N₄O [M+H]⁺ 333.1710, found 333.1705.

(R)-1,3-dimethyl-1-(2-phenyl-1-(pyridin-3-yl)ethyl)-3-(pyridin-2-yl)urea (7h)



Following general procedure 2B, urea **17h** (330 mg, 0.993 mmol), NaH (60 mg, 1.490 mmol), MeI (74 μ L, 1.192 mmol) in DMF (10.0 ml) gave after 2.5 h of stirring at room temperature a crude product that was purified by flash column chromatography (SiO₂, 97:3 CH₂Cl₂:MeOH), to obtain **7h** as a yellow oil (286 mg, 83%). **R_f** 0.21 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.75$ (1H, d, $J = 2.0$, =CH), 8.56 (1H, dd, $J = 4.7, 1.3$, =CH), 8.24 (1H, ddd, $J = 5.0, 2.0, 0.8$ Hz, =CH), 7.87 (1H, dt, $J = 7.9, 1.7$ Hz, =CH), 7.45 – 7.28 (6H, m, 6 x =CH), 7.21 (1H, ddd, $J = 8.3, 7.3, 2.0$, =CH), 6.78 (1H, ddd, $J = 7.3, 4.9, 0.9$, =CH), 6.06 (1H, dd, $J = 11.4, 5.6$, NCHCH₂), 5.89 (1H, d, $J = 8.3$, =CH), 3.43 (1H, dd, $J = 14.5, 5.6$, NCHCH_AH_B), 3.23 (1H, dd, $J = 14.5, 11.5$, NCHCH_AH_B), 3.14 (3H, s, CH₂CHNCH₃), 2.45 (3H, s, =CH-NCH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 161.5$ (C=O), 157.1 (=C), 149.2 (2 x =CH), 148.4 (=CH), 137.9 (=CH), 137.7 (=C), 135.9 (=CH), 135.3 (=C), 129.1 (2 x =CH), 123.6 (=CH), 117.5 (=CH), 114.8 (=CH), 57.2 (NCHCH₂), 36.6 (NCHCH₂), 36.1 (=CH-NCH₃), 31.4 (CH₂CHNCH₃). $[\alpha]_{\text{D}}^{25} = +90$ (c = 1.00; CH₂Cl₂). **HRMS** (ESI⁺): m/z calcd for C₂₁H₂₃N₄O [M+H]⁺ 347.1866, found 347.1851.

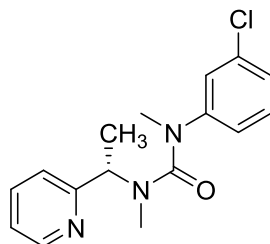
1-(3-Chlorophenyl)-1-methyl-3-[(1S)-1-phenylethyl]urea (18a)



Following general procedure 1, *N*-methyl-*N*-(3-chlorophenyl) carbamoyl chloride (1.40 g), 2-pyridine **6a** (835 mg, 6.87 mmol), synthesized from **4**, Et₃N (1.05 ml) and DMAP (cat) in dichloroethane (17.20 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH) to yield the title compound as an oil (1.28 g, 64%). ¹H NMR (400 MHz, CDCl₃) $\delta =$

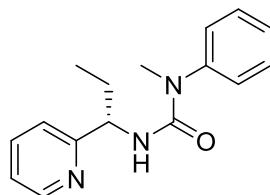
8.50-8.38 (1H, m, =CH), 7.64 (1H, td, $J = 7.7$ and 1.4 , =CH), 7.35 (1H, t, $J = 7.9$, =CH), 7.30-7.21 (3H, m, 3 x =CH), 7.20-7.09 (2H, m, 2 x =CH), 5.97-5.79 (1H, brd, CHNH), 5.05 (1H, q, $J = 6.9$, NHCHCH₃), 3.27 (3H, s, NCH₃), 1.41 (3H, d, $J = 6.8$, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 161.8$ (C=O), 156.3 (=C), 148.9 (=CH), 144.9 (=C), 137.0 (=CH), 135.2 (=C), 130.8 (=CH), 127.3 (=CH), 127.1 (=CH), 125.2 (=CH), 122.3 (=CH), 121.5 (=CH), 51.2 (NCH), 37.2 (NCH₃), 23.1 (CH₃). [α]_D²⁰ = -137 ($c = 1.00$; CHCl₃). IR (film, cm⁻¹): $\nu_{\max} = 3320, 2971, 2928, 1642$. HRMS (ESI⁺): m/z calcd for C₁₅H₁₆ClN₃ONa [M+Na]⁺ 312.0880, found 312.0871.

1-(3-Chlorophenyl)-1,3-dimethyl-3-[(1S)-1-phenylethyl]urea (**8a**)



Following general procedure 2A, urea **18a** (689 mg, 2.38 mmol), MeI (0.18 ml), NaH (124 mg) in THF (5.95 ml) gave, after purification by flash column chromatography (SiO₂, 80:20 to 0:100 Pet.Ether:EtOAc), **8a** as an oil (720 mg, 99%). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.61$ -8.52 (1H, m, =CH), 7.65 (1H, td, $J = 7.7$ and 1.7 , =CH), 7.32 (1H, d, $J = 7.9$, =CH), 7.21 (1H, t, $J = 8.1$, =CH), 7.18-7.10 (2H, m, 2 x =CH), 7.06-7.01 (1H, m, =CH), 7.00-6.95 (1H, m, =CH), 5.25 (1H, q, $J = 7.1$, NCHCH₃), 3.23 (3H, s, NCH₃), 2.38 (3H, s, NCH₃), 1.52 (3H, d, $J = 7.1$, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 161.6$ (C=O), 160.2 (=C), 149.0 (=CH), 147.9 (=C), 136.7 (=CH), 134.9 (=C), 130.4 (=CH), 124.3 (=CH), 123.8 (=CH), 122.5 (=CH), 122.3 (=CH), 121.6 (=CH), 56.0 (NCH), 39.7 (NCH₃), 31.6 (NCH₃), 15.5 (CH₃). [α]_D²⁰ = -237 ($c = 1.00$; CHCl₃). IR (film, cm⁻¹): $\nu_{\max} = 2992, 2945, 1639$. HRMS (ESI⁺): m/z calcd for C₁₆H₁₈ClN₃ONa [M+H]⁺ 326.1036, found 326.1048.

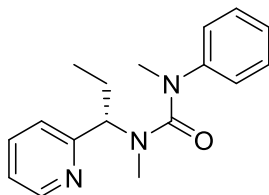
1,3-dimethyl-1-phenyl-3-[(1S)-1-(pyridin-2-yl)propyl]urea (**18b**)



Following general procedure 1, *N*-methyl-*N*-phenyl carbamoyl chloride (477 mg), 2-pyridine **6b** (383 mg, 2.81 mmol), synthesized from **4**, and Et₃N (431 μ l) in acetonitrile (7.00 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH) to yield **18b** as an oil (280 mg, 37%). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.45$ -8.37 (1H, m, =CH), 7.60 (1H, td, $J = 7.6$ and 1.8 , =CH), 7.47-7.38 (2H, m, 2 x =CH), 7.34-7.23 (3H, m, 3 x =CH), 7.22-7.18 (1H, m, =CH), 7.11 (1H, ddd, $J = 7.5, 4.9$ and 1.1 , =CH), 5.50 (1H, d, $J = 8.0$, CHNH), 4.87 (1H, dt, $J = 7.8$ and 6.9 , NHCHCH₂), 3.26 (3H, s, NCH₃), 1.85-1.63 (2H, m, CHCH₂CH₃), 0.78 (3H, t, $J = 7.4$, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 161.3$ (C=O), 157.0 (=C), 149.2 (=CH), 143.5 (=C), 136.5 (=CH), 130.0 (=CH), 127.3 (=CH), 127.2 (=CH), 122.2 (=CH),

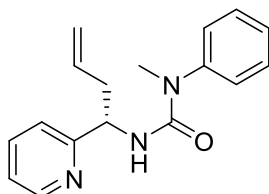
122.1 (=CH), 56.8 (NCH), 37.3 (NCH₃), 29.5 (CH₂), 10.3 (CH₃). $[\alpha]_D^{20} = -151$ (c = 1.00; CHCl₃). IR (film, cm⁻¹): $\nu_{\max} = 3421, 2965, 2931, 1658, 750$. HRMS (ESI⁺): m/z calcd for C₁₆H₂₀N₃O [M+H]⁺ 270.1601, found 270.1607.

1,3-dimethyl-1-phenyl-3-[(1S)-1-(pyridin-2-yl)propyl]urea (**8b**)



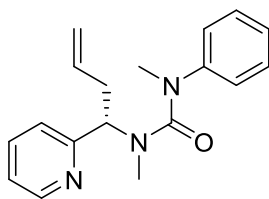
Following General procedure 2A, urea **18b** (230 mg, 0.85 mmol), MeI (0.06 ml), NaH (45 mg) in THF (2.13 ml) gave, after purification by flash column chromatography (SiO₂, 80:20 to 0:100 Pet.Ether:EtOAc), **8b** as an oil (230 mg, 95%). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.57$ -8.47 (1H, m, =CH), 7.62 (1H, td, $J = 10.7$ and 1.8, =CH), 7.34 (1H, d, $J =$, =CH), 7.31-7.25 (2H, m, 2 x =CH), 7.14 (1H, ddd, $J = 7.5, 4.9$ and 1.1, =CH), 7.11-7.05 (3H, m, 3 x =CH), 5.25 (1H, dd, $J = 8.9$ and 6.7, NCHCH₂), 3.21 (3H, s, NCH₃), 2.43 (3H, s, NCH₃), 2.13 (1H, dq, $J = 14.4$ and 7.3, CHCH_AH_BCH₃), 1.83 (1H, ddq, $J = 14.0, 8.9$ and 7.5, CHCH_AH_BCH₃), 0.91 (3H, t, $J = 7.4$, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 162.7$ (C=O), 160.0 (=C), 148.8 (=CH), 147.1 (=C), 136.5 (=CH), 129.5 (=CH), 124.7 (=CH), 124.6 (=CH), 123.6 (=CH), 122.2 (=CH), 61.9 (NCH), 40.4 (NCH₃), 31.5 (NCH₃), 23.3 (CH₂), 11.5 (CH₃). $[\alpha]_D^{20} = -88$ (c = 1.00; CHCl₃). IR (film, cm⁻¹): $\nu_{\max} = 2968, 2931, 1641$. HRMS (ESI⁺): m/z calcd for C₁₇H₂₂N₃O [M+H]⁺ 284.1757, found 284.1760.

1,3-dimethyl-1-phenyl-3-[(1S)-1-(pyridin-2-yl)but-3-en-1-yl]urea (**18c**)



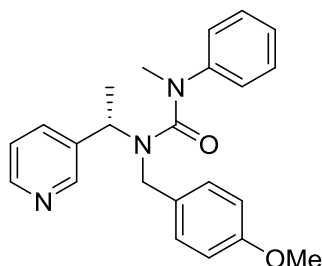
Following general procedure 1, *N*-methyl-*N*-phenyl carbamoyl chloride (230 mg), 2-pyridine **6c** (200 mg, 1.35 mmol), synthesized from **4**, and Et₃N (207 μ l) in acetonitrile (3.40 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH) to yield **18c** as an oil (270 mg, 71%). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.48$ -8.37 (1H, m, =CH), 7.60 (1H, td, $J = 7.7$ and 1.8, =CH), 7.47-7.37 (2H, m, 2 x =CH), 7.35-7.23 (3H, m, 3 x =CH), 7.20 (1H, d, $J = 7.8$, =CH), 7.11 (1H, ddd, $J = 7.5, 4.8$ and 1.0, =CH), 5.61 (1H, ddt, $J = 17.1, 10.4$ and 7.2, CH₂CH=CH₂), 5.43 (1H, d, $J = 7.7$, CHNH), 5.01 (1H, dt, $J = 7.1$ and 6.8, NHCHCH₂), 4.97-4.83 (2H, m, =CH₂), 3.26 (3H, s, NCH₃), 2.61-2.39 (2H, m, CHCH₂CH=). ¹³C NMR (100 MHz, CDCl₃) $\delta = 160.9$ (C=O), 156.8 (=C), 149.2 (=CH), 143.5 (=C), 136.5 (=CH), 134.4 (=CH), 130.0 (=CH), 127.4 (=CH), 127.3 (=CH), 122.1 (=CH), 121.9 (=CH), 117.9 (=CH₂), 55.1 (NCH), 40.7 (CH₂), 37.3 (NCH₃). $[\alpha]_D^{20} = +40$ (c = 1.00; CHCl₃). IR (film, cm⁻¹): $\nu_{\max} = 3080, 2946, 1656, 1493$. HRMS (ESI⁺): m/z calcd for C₁₇H₂₀N₃O [M+H]⁺ 282.1601, found 282.1602.

1,3-dimethyl-1-phenyl-3-[(1S)-1-(pyridin-2-yl)but-3-en-1-yl]urea (**8c**)



Following General procedure 2A, urea **18c** (260 mg, 0.92 mmol), MeI (0.07 mL), NaH (48 mg) in THF (2.30 mL) gave, after purification by flash column chromatography (SiO₂, 80:20 to 0:100 Pet.Ether:EtOAc), **8c** as an oil (230 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ = 8.58-8.45 (1H, m, =CH), 7.62 (1H, td, J = 7.8 and 1.8, =CH), 7.37 (1H, d, J = 7.9, =CH), 7.30-7.21 (2H, m, 2 x =CH), 7.13 (1H, ddd, J = 7.5, 4.9 and 0.8, =CH), 7.12-7.03 (3H, m, 3 x =CH), 5.82 (1H, dddd, J = 17.2, 10.2, 8.2 and 5.6, CH₂=CHCH₂), 5.53 (1H, dd, J = 9.7 and 5.9, NCHCH₂), 5.17-4.99 (2H, m, =CH₂), 3.22 (3H, s, NCH₃), 2.95-2.82 (1H, m, CHCH_AH_BCH=), 2.70-2.54 (1H, m, CHCH_AH_BCH=), 2.41 (3H, s, NCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.5 (C=O), 159.6 (=C), 148.8 (=CH), 146.9 (=C), 136.6 (=CH), 135.8 (=CH), 129.4 (=CH), 124.7 (2 x =CH), 123.6 (=CH), 122.4 (=CH), 117.3 (=CH₂), 60.0 (NCH), 40.4 (NCH₃), 34.6 (CH₂), 31.8 (NCH₃). [α]_D²⁰ = -96 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3064, 3005, 2925, 1640. HRMS (ESI⁺): m/z calcd for C₁₈H₂₂N₃O [M+H]⁺ 296.1757, found 296.1761.

(S)-1-(4-methoxybenzyl)-3-methyl-3-phenyl-1-(1-(pyridin-3-yl)ethyl)urea (**9**), er 73:27

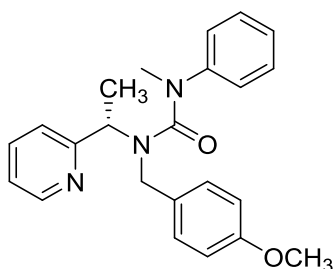


To a solution of **5c** (1.299 g, 5.36 mmol) in CH₂Cl₂ (54 mL) at room temperature was added phenyl isocyanate (0.58 mL, 5.36 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in anhydrous DMF (54 mL), and the solution was cooled down to 0 °C. To the solution was added in portions NaH (60% suspension in oil, 0.43 g, 10.72 mmol). The reaction mixture was stirred at 0 °C for 15 min, then MeI (0.500 mL, 8.04 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and was stirred overnight. Then it was quenched at room temperature with water and evaporated *in vacuo*. The residue was dissolved in ethyl acetate and extracted from water three times. The combined organic layer was washed with brine, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash column chromatography (50:50 Petrol-EtOAc, then 0:100) to give **9** as a brown oil (1.48 g, 74%, er 73:27).

R_f 0.37 (100% EtOAc). ¹H NMR (400 MHz, CDCl₃) δ = 8.48 (1H, dd, J = 4.7, 1.6, =CH), 8.41 (1H, d, J = 2.3, =CH), 7.52 (1H, dt, J = 8.0, 1.9, =CH), 7.35 – 7.29 (2H, m, 2 x =CH), 7.25 – 7.13 (2H, m, 2 x =CH), 6.99 – 6.93 (2H, m, 2 x =CH), 6.92 – 6.86 (2H, m, 2 x =CH), 6.80 – 6.74 (2H, m, 2 x =CH), 5.26 (1H, q, J = 7.0, CH-CH₃), 3.87 (1H, d, J = 15.5, NHCH_AH_B), 3.77 (3H, s, OCH₃), 3.71 (1H, d, J = 15.5, NHCH_AH_B), 3.10 (3H, s, NCH₃), 1.37

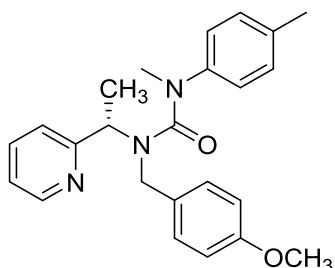
(3H, d, $J = 7.0$, CH-CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 162.5$ (C=O), 158.6 (=C), 149.2 (=CH), 148.7 (=CH), 146.4 (=C), 136.9 (=C), 135.2 (=CH), 130.8 (=C), 129.6 (=CH), 128.7 (=CH), 125.5 (=CH), 125.0 (=CH), 123.3 (=CH), 113.6 (=CH), 55.3 (OCH₃), 54.4 (CH-CH₃), 47.3 (NHCH₂), 39.9 (NCH₃), 16.5 (CH-CH₃). IR (film, cm⁻¹): $\nu_{\max} = 2996, 2928, 2835, 1644, 1495, 1243$. $[\alpha]_D^{23} = +11.9$ (c = 1.00; CH₂Cl₂); HRMS (ESI⁺): m/z calcd for C₂₃H₂₆N₃O₂ [M+H]⁺ 376.2020, found 376.2007.

1-[(4-[Methoxyphenyl)methyl]-3,3-dimethyl-1-[(1S)-1-(pyridin-2-yl)ethyl]urea (10a)



Following General procedure 1, *N*-methyl-*N*-phenyl carbamoyl chloride (77 mg), 2-pyridine **6d** (100 mg, 0.41 mmol) and Et₃N (63 μ l) in acetonitrile (1.03 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10a** as an oil (155 mg, quant.). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.55$ -8.44 (1H, m, =CH), 7.66-7.53 (1H, m, =CH), 7.33-7.06 (5H, m, 5 x =CH), 6.99-6.82 (4H, m, 4 x =CH), 6.81-6.66 (2H, m, 2 x =CH), 5.39-5.19 (1H, m, NCHCH₃), 4.06 (1H, d, $J = 15.7$, NCH_AH_B), 3.85-3.64 (1H, superimposed d, NCH_AH_B), 3.78 (3H, s, OCH₃), 3.08 (3H, s, NCH₃), 1.39 (3H, d, $J = 7.0$, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 162.5$ (C=O), 160.6 (=C), 158.4 (=C), 149.0 (=CH), 146.4 (=C), 136.5 (=CH), 131.5 (=C), 129.4 (=CH), 128.7 (=CH), 125.0 (=CH), 124.6 (=CH), 123.0 (=CH), 122.4 (=CH), 113.5 (=CH), 57.9 (NCH), 55.4 (OCH₃), 47.0 (CH₂), 39.6 (NCH₃), 16.2 (CH₃). $[\alpha]_D^{20} = +90$ (c = 1.00; CHCl₃). IR (film, cm⁻¹): $\nu_{\max} = 2941, 2928, 1644, 1247$. HRMS (ESI⁺): m/z calcd for C₂₃H₂₆N₃O₂ [M+H]⁺ 376.2025, found 376.2026.

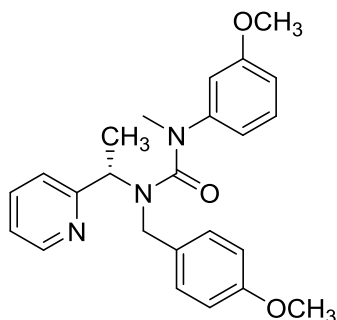
3-[(4-[Methoxyphenyl)methyl]-1-methyl-1-(4-methylphenyl)-3-[(1S)-1-(pyridin-2-yl)ethyl]urea (10b)



Following General procedure 1, *N*-methyl-*N*-(4-methylphenyl) carbamoyl chloride (39 mg), 2-pyridine **6d** (50 mg, 0.21 mmol) and Et₃N (32 μ l) in acetonitrile (0.52 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10b** as an oil (52 mg, 64%). ¹H NMR (400 MHz, CDCl₃) $\delta = 8.57$ -8.44 (1H, m, =CH), 7.66-7.54 (1H, m, =CH), 7.24-7.05 (4H, m, 4 x =CH), 6.96-6.81 (4H, m, 4 x =CH), 6.80-6.70 (2H, m, 2 x =CH), 5.34 (1H, q, $J = 7.0$,

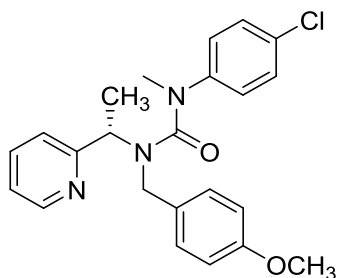
NCHCH₃), 4.07 (1H, d, *J* = 15.5, NCH_AH_B), 3.77 (1H, d, *J* = 15.4, NCH_AH_B), 3.77 (3H, s, OCH₃), 3.06 (3H, s, NCH₃), 2.32 (3H, s, CH₃), 1.60 (3H, d, *J* = 7.0, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.6 (C=O), 160.8 (=C), 158.4 (=C), 149.0 (=CH), 143.9 (=C), 136.4 (=CH), 134.8 (=C), 131.6 (=C), 130.0 (=CH), 128.7 (=CH), 124.7 (=CH), 123.0 (=CH), 122.3 (=CH), 113.5 (=CH), 57.9 (NCH), 55.3 (OCH₃), 47.0 (CH₂), 39.9 (NCH₃), 21.0 (CH₃), 16.2 (CH₃). [α]_D²⁰ = +20 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2976, 1646, 1245, 1038. HRMS (ESI⁺): *m/z* calcd for C₂₄H₂₈N₃O₂ [M+H]⁺ 390.2176, found 390.2181.

1-(3-Methoxyphenyl)-3-[(4-[methoxyphenyl)methyl]-1-methyl-3-[(1S)-1-(pyridin-2-yl)ethyl]urea (10c)



Following General procedure 1, *N*-methyl-*N*-(3-methoxyphenyl) carbamoyl chloride (82 mg), 2-pyridine **6d** (100 mg, 0.41 mmol) and Et₃N (63 μl) in acetonitrile (1.03 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10c** as an oil (64 mg, 38%). ¹H NMR (400 MHz, CDCl₃) δ = 8.56-8.45 (1H, m, =CH), 7.60 (1H, td, *J* = 7.7 and 1.8, =CH), 7.23-7.10 (3H, m, 3 x =CH), 6.97-6.89 (2H, m, 2 x =CH), 6.78-6.71 (2H, m, 2 x =CH), 6.66 (1H, dd, *J* = 8.3 and 1.9, =CH), 6.61-6.54 (1H, m, =CH), 6.53-6.47 (1H, m, =CH), 5.35 (1H, q, *J* = 7.0, NCHCH₃), 4.14 (1H, d, *J* = 15.5, NCH_AH_B), 3.84 (1H, d, *J* = 15.5, NCH_AH_B), 3.75 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 3.08 (3H, s, NCH₃), 1.43 (3H, d, *J* = 7.0, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.3 (C=O), 160.6 (=C), 160.4 (=C), 158.4 (=C), 149.0 (=CH), 147.6 (=C), 136.5 (=CH), 131.6 (=C), 130.0 (=CH), 128.7 (=CH), 122.9 (=CH), 122.3 (=CH), 116.6 (=CH), 113.5 (=CH), 110.7 (=CH), 109.8 (=CH), 57.9 (NCH), 55.3 (2 x OCH₃), 47.0 (CH₂), 39.5 (NCH₃), 16.4 (CH₃). [α]_D²⁰ = -34 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2973, 2918, 1652, 1250, 1034. HRMS (ESI⁺): *m/z* calcd for C₂₄H₂₈N₃O₃ [M+ H]⁺ 406.2125, found 406.2130.

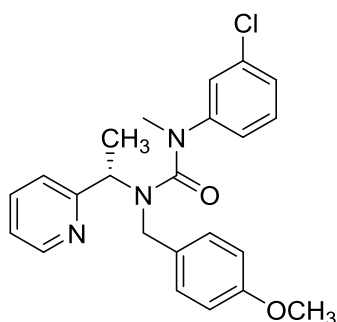
1-(4-Chlorophenyl)-3-[(4-[methoxyphenyl)methyl]-1-methyl-3-[(1S)-1-(pyridin-2-yl)ethyl]urea (10d)



Following general procedure 1, *N*-methyl-*N*-(4-chlorophenyl) carbamoyl chloride (43 mg), 2-pyridine **6d** (50 mg, 0.21 mmol) and Et₃N (32 μl) in acetonitrile (0.52 ml) gave, after 20 h heating at reflux, a crude product

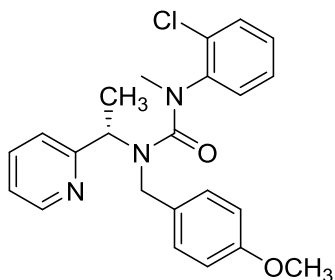
that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10d** as an oil (48 mg, 56%). ¹H NMR (400 MHz, CDCl₃) δ = 8.89-8.48 (1H, m, =CH), 7.64 (1H, td, *J* = 7.6 and 1.8, =CH), 7.29-7.20 (3H, m, 3 x =CH), 7.18-7.10 (1H, m, =CH), 6.95-6.82 (4H, m, 4 x =CH), 6.79-6.69 (2H, m, 2 x =CH), 5.35 (1H, q, *J* = 6.9, NCHCH₃), 4.05 (1H, d, *J* = 15.7, NCH_AH_B), 3.80 (1H, d, *J* = 15.7, NCH_AH_B), 3.77 (3H, s, OCH₃), 3.02 (3H, s, NCH₃), 1.45 (3H, d, *J* = 7.0, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.1 (C=O), 160.4 (=C), 158.5 (=C), 149.2 (=CH), 144.8 (=C), 136.6 (=CH), 131.3 (=C), 129.9 (=C), 129.4 (=CH), 128.5 (=CH), 125.2 (=CH), 122.7 (=CH), 122.5 (=CH), 113.6 (=CH), 57.9 (NCH), 55.4 (OCH₃), 47.2 (CH₂), 39.2 (NCH₃), 16.5 (CH₃). [α]_D²⁰ = +16 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2978, 1648, 1245, 1040. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₄ClN₃O₂Na [M+Na]⁺ 432.1449, found 432.1448.

1-(3-Chlorophenyl)-3-[(4-[methoxyphenyl)methyl]-1-methyl-3-[(1S)-1-(pyridin-2-yl)ethyl]urea (10e)



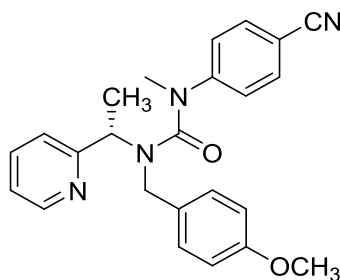
Following General procedure 1, *N*-methyl-*N*-(3-chlorophenyl) carbamoyl chloride (84 mg), 2-pyridine **6d** (100 mg, 0.41 mmol), Et₃N (63 μl) and DMAP (cat.) in dichloroethane (1.03 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10e** as an oil (78 mg, 46%). ¹H NMR (400 MHz, CDCl₃) δ = 8.61-8.52 (1H, m, =CH), 7.65 (1H, td, *J* = 7.7 and 1.8, =CH), 7.28-7.14 (3H, m, 3 x =CH), 7.06 (1H, ddd, *J* = 8.0, 1.9 and 0.9, =CH), 7.00-6.96 (1H, m, =CH), 6.92-6.86 (2H, m, 2 x =CH), 6.82 (1H, ddd, *J* = 8.1, 2.2 and 0.9, =CH), 6.80-6.73 (2H, m, 2 x =CH), 5.36 (1H, q, *J* = 7.0, NCHCH₃), 4.03 (1H, d, *J* = 15.6, NCH_AH_B), 3.81 (1H, d, *J* = 15.7, NCH_AH_B), 3.78 (3H, s, OCH₃), 3.02 (3H, s, NCH₃), 1.48 (3H, d, *J* = 7.0, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 161.8 (C=O), 160.3 (=C), 158.5 (=C), 149.3 (=CH), 147.3 (=C), 136.7 (=CH), 134.7 (=C), 131.1 (=C), 130.2 (=CH), 128.5 (=CH), 124.4 (=CH), 123.9 (=CH), 122.7 (=CH), 122.5 (=CH), 121.5 (=CH), 113.6 (=CH), 57.8 (NCH), 55.4 (OCH₃), 47.3 (CH₂), 38.9 (NCH₃), 16.4 (CH₃). [α]_D²⁰ = +36.6 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2985, 1642, 1239, 1043. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₅ClN₃O₂ [M+H]⁺ 410.1635, found 410.1638.

1-(2-Chlorophenyl)-3-[(4-[methoxyphenyl)methyl]-1-methyl-3-[(1S)-1-(pyridin-2-yl)ethyl]urea (10f)



Following General procedure 1, *N*-methyl-*N*-(2-chlorophenyl) carbamoyl chloride (43 mg), 2-pyridine **6d** (50 mg, 0.21 mmol), Et₃N (32 μ l) and DMAP (cat.) in dichloroethane (0.52 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10f** as an oil (83 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ = 8.53-8.42 (1H, m, =CH), 7.57 (1H, td, *J* = 7.7 and 1.8, =CH), 7.48-7.38 (1H, m, =CH), 7.22-7.15 (2H, m, 2 x =CH), 7.14-7.07 (2H, m, 2 x =CH), 7.05-6.97 (2H, m, 2 x =CH), 6.93-6.85 (1H, m, =CH), 6.82-6.69 (2H, m, 2 x =CH), 4.95 (1H, q, *J* = 7.0, NCHCH₃), 4.12 (1H, d, *J* = 15.0, NCH_AH_B), 3.85 (1H, d, *J* = 15.0, NCH_AH_B), 3.77 (3H, s, OCH₃), 3.08 (3H, s, NCH₃), 1.22 (3H, d, *J* = 7.0, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.9 (C=O), 160.4 (=C), 158.4 (=C), 148.8 (=CH), 143.7 (=C), 136.5 (=CH), 131.8 (=C), 131.1 (=C), 130.8 (=CH), 129.4 (=CH), 129.3 (=CH), 128.0 (=CH), 127.9 (=CH), 122.9 (=CH), 122.3 (=CH), 113.4 (=CH), 58.3 (NCH), 55.3 (OCH₃), 47.1 (CH₂), 38.4 (NCH₃), 15.9 (CH₃). [α]_D²⁰ = -16 (*c* = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{\max} = 2993, 1640, 1235, 1039. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₄ClN₃O₂Na [M+Na]⁺ 432.1449, found 432.1443.

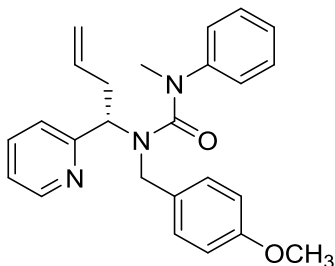
1-(4-Cyanophenyl)-3-[(4-[methoxyphenyl)methyl]-1-methyl-3-[(1S)-1-(pyridin-2-yl)ethyl]urea (10g)



Following general procedure 1, *N*-methyl-*N*-(4-cyanophenyl) carbamoyl chloride (41 mg), 2-pyridine **6d** (50 mg, 0.21 mmol) and Et₃N (32 μ l) in acetonitrile (0.52 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10g** as an oil (84 mg, quant. yield). ¹H NMR (400 MHz, CDCl₃) δ = 8.60-8.50 (1H, m, =CH), 7.68 (1H, td, *J* = 7.7 and 1.8, =CH), 7.55-7.45 (2H, m, 2 x =CH), 7.36-7.29 (1H, m, =CH), 7.21 (1H, ddd, *J* = 7.5, 4.8 and 1.0, =CH), 7.01-6.91 (2H, m, 2 x =CH), 6.85-6.68 (4H, m, 4 x =CH), 5.46 (1H, q, *J* = 7.1, NCHCH₃), 4.10 (1H, d, *J* = 15.8, NCH_AH_B), 3.91 (1H, d, *J* = 15.8, NCH_AH_B), 3.76 (3H, s, OCH₃), 2.95 (3H, s, NCH₃), 1.60 (3H, d, *J* = 7.1, CHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 160.9 (C=O), 159.8 (=C), 158.8 (=C), 149.4 (=CH), 149.2 (=C), 136.8 (=CH), 133.2 (=CH), 130.7 (=C), 128.1 (=CH), 122.7 (=CH), 122.5 (=CH), 120.1 (=CH), 119.2 (=C), 113.8 (=CH), 105.1 (CN), 57.7

(NCH), 55.4 (OCH₃), 47.7 (CH₂), 37.2 (NCH₃), 16.8 (CH₃). [α]_D²⁰ = +12 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{\max} = 2935, 2221, 1657, 1245, 1034. HRMS (ESI⁺): m/z calcd for C₂₄H₂₄N₄O₂Na [M+Na]⁺ 423.1791, found 423.1791.

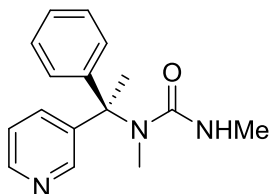
1-[(4-[Methoxyphenyl)methyl]-3-methyl-3-phenyl-1-[(1S)-1-(pyridin-2-yl)but-3-en-1-yl]urea (10h)



Following general procedure 1, *N*-methyl-*N*-phenyl carbamoyl chloride (58 mg), 2-pyridine **6e** (90 mg, 0.34 mmol) and Et₃N (52 μ l) in acetonitrile (0.84 ml) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO₂, 80:20 to 20:80 Pet.Ether:EtOAc) to yield **10h** as an oil (80 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ = 8.50-8.41 (1H, m, =CH), 7.57 (1H, td, J = 7.7 and 1.8, =CH), 7.32-7.22 (2H, m, 2 x =CH), 7.16-7.02 (3H, m, 3 x =CH), 6.95-6.88 (2H, m, =CH), 6.68 (4H, s, 4 x =CH), 5.67 (1H, dddd, J = 17.1, 10.0, 7.6 and 6.4, CH₂=CHCH₂), 5.30 (1H, t, J = 7.6, CHCH₂), 5.09-4.90 (2H, m, =CH₂), 4.23 (1H, d, J = 15.5, NCH_AH_B), 3.94 (1H, d, J = 15.5, NCH_AH_B), 3.75 (3H, s, OCH₃), 3.04 (3H, s, NCH₃), 2.94-2.79 (1H, m, CH_ACH_BCH=), 2.68-2.52 (1H, m, CH_ACH_BCH=). ¹³C NMR (100 MHz, CDCl₃) δ = 162.4 (C=O), 158.9 (=C), 158.3 (=C) 149.0 (=CH), 143.4 (=C), 136.5 (=CH), 135.3 (=CH), 131.5 (=C), 129.4 (=CH), 128.5 (=CH), 124.9 (=CH), 124.7 (=CH), 124.5 (=CH), 122.6 (=CH), 117.5 (=CH₂), 113.4 (=CH), 61.9 (NCH), 55.3 (OCH₃), 46.6 (CH₂), 39.6 (NCH₃), 35.5 (CH₂). [α]_D²⁰ = -40 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{\max} = 3064, 2930, 1642, 1244, 1036. HRMS (ESI⁺): m/z calcd for C₂₅H₂₈N₃O₂ [M+H]⁺ 402.2176, found 402.2178.

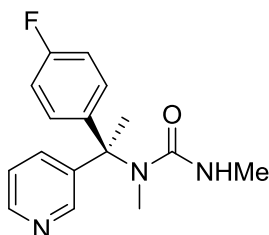
- LDA-mediated rearrangement of ureas and their hydrolysis

(*R*)-1,3-dimethyl-1-(1-phenyl-1-(pyridin-3-yl)ethyl)urea (**11a**)⁶



Following General procedure 3, urea **7a** (72 mg, 0.266 mmol), freshly prepared LDA (0.75 M in THF, 0.89 ml, 0.666 mmol) and THF (2.7 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), **11a** as a yellow solid (47 mg, 65%). *R_f* 0.14 (95:5 CH₂Cl₂:MeOH); ¹H NMR (400 MHz, CDCl₃) δ = 8.52 (1H, br s, =CH), 8.42 (1H, br s, =CH), 7.56 – 7.48 (m, 1H, =CH), 7.32 – 7.14 (6H, m, 6 x =CH), 4.13 (1H, br s, NHCH₃), 2.83 (3H, s, CH₃CNCH₃), 2.55 (3H, d, *J* = 4.6 Hz, NHCH₃), 2.08 (3H, s, CH₃CNCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 159.7 (C=O), 148.6 (=CH), 147.9 (=CH), 144.7, 141.3, 134.6 (=CH), 128.9 (=CH), 127.6 (=CH), 127.1 (=CH), 123.2 (=CH), 66.2 (CH₃CNCH₃), 34.6 (CH₃CNCH₃), 29.8 (CH₃CNCH₃), 27.7 (NHCH₃). **Mp** = 145-146 °C. HRMS (ESI⁺): *m/z* calcd for C₁₆H₂₀N₃O [M+H]⁺ 270.1601, found 270.1625.

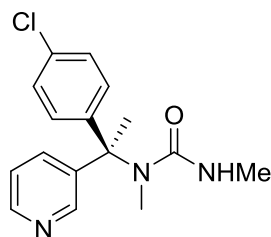
(*R*)-1-(1-(4-fluorophenyl)-1-(pyridin-3-yl)ethyl)-1,3-dimethylurea (**11b**)



Following general procedure 3, urea **7b** (94 mg, 0.328 mmol), freshly prepared LDA (0.75 M in THF, 1.09 ml, 0.819 mmol) and THF (3.3 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH), **11b** as a white solid (70 mg, 74%). *R_f* 0.14 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.59 – 8.35 (2H, m, 2 x =CH), 7.52 – 7.47 (1H, m, =CH), 7.23 – 7.15 (3H, m, 3 x =CH), 7.00 – 6.92 (2H, m, 2 x =CH), 4.24 (1H, dd, *J* = 8.7, 4.4, NHCH₃), 2.79 (3H, s, CH₃C-N-CH₃), 2.59 (3H, d, *J* = 4.6, NHCH₃), 2.06 (3H, s, CH₃-C-N-CH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 161.8 (d, ¹*J*_{CF} = 247.2 Hz, =C-F), 159.6 (C=O), 148.3 (=CH), 147.8 (=CH), 141.5 (=C), 140.5 (d, ⁴*J*_{CF} = 3.4 Hz, =C), 134.5 (=CH), 128.8 (d, ³*J*_{CF} = 8.0 Hz, =CH), 123.3 (=CH), 115.6 (d, ²*J*_{CF} = 21.3 Hz, =CH), 65.8 (CH₃C-N-CH₃), 34.7 (CH₃C-N-CH₃), 29.7 (CH₃C-N-CH₃), 27.7 (NHCH₃). **Mp** = 126-127 °C. [α]_D²⁵ = +10 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3345, 2946, 1635, 1507, 1323, 1226, 1163, 1081, 814, 728. HRMS (ESI⁺): *m/z* calcd for C₁₆H₁₉N₃OF [M+H]⁺ 288.1507, found 288.1492.

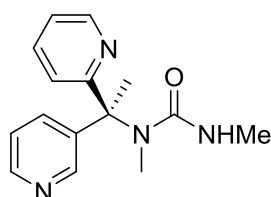
⁶ Data in agreement with the literature (reference: Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567).

(R)-1-(1-(4-chlorophenyl)-1-(pyridin-3-yl)ethyl)-1,3-dimethylurea (11c)



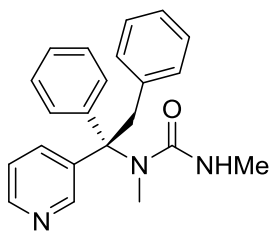
Following general procedure 3, urea **7c** (91 mg, 0.298 mmol), freshly prepared LDA (0.75 M in THF, 0.99 ml, 0.750 mmol) and THF (3.0 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH), **11c** as a white solid (57 mg, 63%). *R_f* 0.12 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.64 – 8.43 (2H, m, 2 x =CH), 7.56 (1H, ddd, *J* = 8.1, 2.3, 1.5, =CH), 7.33 – 7.19 (5H, m, 6 x =CH), 4.28 (1H, dd, *J* = 8.4, 4.1, NHCH₃), 2.86 (3H, s, CH₃C-NCH₃), 2.67 (3H, d, *J* = 4.7 Hz, NHCH₃), 2.12 (3H, s, CH₃C-NCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 159.6 (C=O), 148.4 (=CH), 148.0 (=CH), 143.5 (=C), 141.2 (=C), 134.5 (=C), 133.3 (=CH), 128.9 (=CH), 128.5 (=CH), 123.3 (=CH), 65.9 (CH₃C-NCH₃), 34.8 (CH₃C-NCH₃), 29.4 (CH₃C-NCH₃), 27.7 (NHCH₃). *Mp* = 58-59 °C. [α]_D²⁵ = +20 (c = 2.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3345, 2948, 1639, 1532, 1491, 1415, 1326, 1095, 729. HRMS (ESI⁺): *m/z* calcd for C₁₆H₁₈N₃OCl [M+H]⁺ 304.1211, found 304.1207.

(S)-1,3-dimethyl-1-(1-(pyridin-2-yl)-1-(pyridin-3-yl)ethyl)urea (11d)



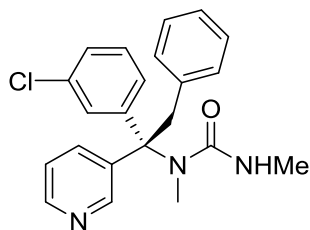
Following General procedure 3, urea **7d** (92 mg, 0.302 mmol), freshly prepared LDA (0.75 M in THF, 1.01 ml, 0.756 mmol) and THF (3.0 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH), **11d** as a yellow oil (61 mg, 76%). *R_f* 0.10 (95:5 CH₂Cl₂:MeOH); ¹H NMR (400 MHz, CDCl₃) δ = 8.56 (1H, d, *J* = 2.4, =CH), 8.55 – 8.52 (1H, m, =CH), 8.47 (1H, dd, *J* = 4.7, 0.9, =CH), 7.72 – 7.64 (2H, m, 2 x =CH), 7.39 (1H, d, *J* = 8.1, =CH), 7.27 – 7.22 (1H, m, =CH), 7.17 (1H, dd, *J* = 7.4, 4.8, =CH), 5.00 (1H, br s, NHCH₃), 3.01 (3H, s, CH₃C-NCH₃), 2.55 (3H, d, *J* = 4.6, NHCH₃), 2.08 (3H, s, CH₃C-NCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 163.4 (=C), 159.7 (C=O), 149.0 (=CH), 148.5 (=CH), 148.0 (=CH), 140.4 (=C), 137.0 (=CH), 135.0 (=CH), 123.0 (=CH), 122.1 (=CH), 121.5 (=CH), 66.9 (CH₃C-NCH₃), 33.5 (CH₃C-NCH₃), 28.9 (CH₃C-NCH₃), 27.5 (NHCH₃). *Mp* = 111-113 °C. IR (film, cm⁻¹): ν_{max} = 3350, 2924, 1640, 1533, 1329, 1082, 714. HRMS (ESI⁺): *m/z* calcd for C₁₅H₁₉N₄O [M+H]⁺ 271.1553, found 271.1541.

(S)-1-(1,2-diphenyl-1-(pyridin-3-yl)ethyl)-1,3-dimethylurea (11e)



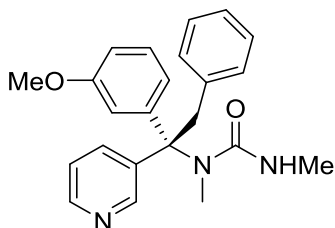
Following General procedure 3, urea **7e** (85 mg, 0.246 mmol), freshly prepared LDA (0.75 M in THF, 0.82 ml, 0.615 mmol) and THF (2.5 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH), **11e** as a yellow solid (62 mg, 87%). *R*_f 0.19 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.62 – 8.31 (2H, m, 2 x =CH), 7.60 (1H, d, *J* = 8.1 Hz, =CH), 7.38 – 7.08 (9H, m, 9 x =CH), 6.88 (2H, dd, *J* = 7.9, 1.4, 2 x =CH), 4.36 (1H, dd, *J* = 9.0, 4.7, NHCH₃), 4.19 – 4.11 (2H, m, CH₂Ph), 2.72 (3H, d, *J* = 4.6, NHCH₃), 2.63 (3H, s, CH₂C-NCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 160.3 (C=O), 148.8 (=CH), 147.4 (=CH), 143.1 (=C), 140.7 (=C), 137.1 (=C), 135.0 (=CH), 131.2 (=CH), 128.3 (=CH), 128.0 (2 x =CH), 127.2 (=CH), 126.8 (=CH), 71.3 (NC-CH₂), 43.4 (NC-CH₂), 37.0 (CH₂C-NCH₃), 27.7 (NHCH₃). *Mp* = 150-151 °C. [α]_D²⁵ = +37 (c = 2.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3362, 2924, 1636, 1527, 1414, 1319. HRMS (ESI⁺): *m/z* calcd for C₂₂H₂₄N₃O [M+H]⁺ 346.1914, found 346.1899.

(S)-1-(1-(3-chlorophenyl)-2-phenyl-1-(pyridin-3-yl)ethyl)-1,3-dimethylurea (11f)



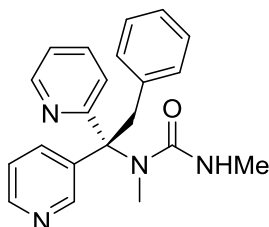
Following General procedure 3, urea **7f** (87 mg, 0.230 mmol), freshly prepared LDA (0.75 M in THF, 0.76 ml, 0.573 mmol) and THF (2.3 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), **11f** as a yellow solid (19 mg, 22%). *R*_f 0.19 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.51 (1H, d, *J* = 1.0, =CH), 8.43 (1H, d, *J* = 4.1 Hz, =CH), 7.59 (1H, ddd, *J* = 8.1, 2.3, 1.5, =CH), 7.27 – 7.10 (8H, m, 8 x =CH), 6.89 – 6.84 (2H, m, 2 x =CH), 4.51 (1H, dd, *J* = 9.3, 5.3, NHCH₃), 4.13 (2H, s, CH₂Ph), 2.75 (3H, d, *J* = 4.6, NHCH₃), 2.59 (3H, s, CH₂C-NCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 160.1 (C=O), 148.8 (=CH), 147.7 (=CH), 145.8 (=C), 139.9 (=C), 136.7 (=C), 135.1 (=CH), 134.1 (=CH), 131.1 (=CH), 129.5 (=CH), 128.1 (=CH), 127.9 (=CH), 127.2 (=CH), 126.9 (=CH), 125.8 (=CH), 122.9 (=CH), 71.0 (NCCH₂), 43.0 (NCCH₂), 37.2 (CH₂C-NCH₃), 27.7 (NHCH₃). *Mp* = 88-90 °C. [α]_D²⁵ = +20 (c = 2.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3349, 2953, 1639, 1529, 1413, 1309, 907, 725, 700. HRMS (ESI⁺): *m/z* calcd for C₂₂H₂₃N₃OCl [M+H]⁺ 380.1524, found 380.1520.

(S)-1-(1-(3-methoxyphenyl)-2-phenyl-1-(pyridin-3-yl)ethyl)-1,3-dimethylurea (11g)



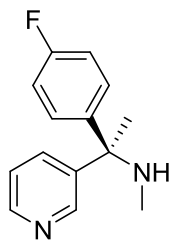
Following General procedure 3, urea **7g** (68 mg, 0.181 mmol), freshly prepared LDA (0.75 M in THF, 0.61 ml, 0.453 mmol) and THF (1.8 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 97:3 CH₂Cl₂:MeOH), **11g** as a yellow solid (18 mg, 26%). *R_f* 0.15 (95:5 CH₂Cl₂:MeOH). ¹H NMR (500 MHz, CDCl₃) δ = 8.52 (1H, br s, =CH), 8.40 (1H, br d, *J* = 4.1, =CH), 7.58 (1H, ddd, *J* = 8.0, 2.2, 1.5, =CH), 7.24 – 7.10 (5H, m, 5 x =CH), 6.95 – 6.89 (3H, m, 3 x =CH), 6.85 (1H, t, *J* = 2.1, =CH), 6.76 (1H, dd, *J* = 8.2, 2.3, =CH), 4.37 (1H, dd, *J* = 8.5, 4.2, NHCH₃), 4.15 (1H, d, *J* = 13.6, CH_AH_BPh), 4.11 (1H, d, *J* = 13.6, CH_AH_BPh), 3.70 (3H, s, OCH₃), 2.72 (3H, d, *J* = 4.6, NHCH₃), 2.64 (3H, s, CH₂C-NCH₃). ¹³C NMR (126 MHz, CDCl₃) δ = 160.2 (C=O), 159.4 (=C-OCH₃), 148.9 (=CH), 147.5 (=CH), 144.9 (=C), 140.6 (=C), 137.2 (=C), 134.9 (=CH), 131.3 (=CH), 129.3 (=CH), 128.1 (=CH), 126.8 (=CH), 122.7 (=CH), 120.3 (=CH), 114.6 (=CH), 112.1 (=CH), 71.2 (NC-CH₂), 55.3 (OCH₃), 43.3 (NC-CH₂), 37.2 (CH₂C-NCH₃), 27.7 (NHCH₃). *Mp* = 71-73 °C. [α]_D²⁵ = +10 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3349, 2953, 1640, 1530, 1315, 724. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₅N₃O₂Na [M+Na]⁺ 398.1839, found 398.1842.

(R)-1,3-dimethyl-1-(2-phenyl-1-(pyridin-2-yl)-1-(pyridin-3-yl)ethyl)urea (11h)



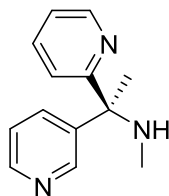
Following General procedure 3, urea **7h** (96 mg, 0.276 mmol), freshly prepared LDA (0.75 M in THF, 0.92 ml, 0.691 mmol) and THF (2.8 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH), **11h** as a yellow solid (84 mg, 88%). *R_f* 0.21 (95:5 CH₂Cl₂:MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 8.54 (1H, ddd, *J* = 4.8, 1.8, 0.9, =CH), 8.47 (1H, d, *J* = 2.2, =CH), 8.37 (1H, dd, *J* = 4.7, 1.4, =CH), 7.66 (1H, ddd, *J* = 8.1, 7.5, 1.9, =CH), 7.60 – 7.53 (2H, m, 2 x =CH), 7.20 – 7.06 (5H, m, 5 x =CH), 6.90 (2H, dd, *J* = 7.9, 1.5, 2 x =CH), 4.71 (1H, dd, *J* = 8.5, 4.0, NHCH₃), 4.28 (1H, d, *J* = 13.1, CH_AH_BPh), 4.04 (1H, d, *J* = 13.1, CH_AH_BPh), 2.73 (3H, d, *J* = 5.3, NHCH₃), 2.64 (3H, d, *J* = 4.6, CH₂C-NCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 162.1 (=C), 159.8 (C=O), 149.1 (=CH), 148.1 (=CH), 147.4 (=CH), 139.4 (=C), 137.0 (=C), 136.7 (=CH), 135.2 (=CH), 131.2 (=CH), 128.1 (=CH), 126.8 (=CH), 123.0 (=CH), 122.5 (=CH), 122.1 (=CH), 71.9 (NCCH₂), 42.5 (NCCH₂), 35.8 (CH₂C-NCH₃), 27.6 (NHCH₃). *Mp* = 166-168 °C. [α]_D²⁵ = +5 (c = 2.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3349, 2923, 1640, 1533, 1319, 730. HRMS (ESI⁺): *m/z* calcd for C₂₁H₂₃N₄O [M+H]⁺ 347.1866, found 347.1851.

1-(4-fluorophenyl)-N-methyl-1-(pyridin-3-yl)ethan-1-amine (12b)



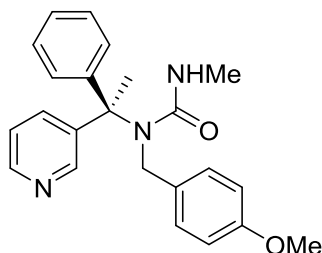
Following General procedure 4, urea **11b** (32 mg, 0.111 mmol), 10% aqueous NaOH solution (0.45 mL, 1.11 mmol), EtOH (0.89 mL) gave **12b** as a yellow oil (23 mg, 88%) without further purification. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.61 (1H, d, J = 2.0, =CH), 8.47 (1H, dd, J = 4.7, 1.3, =CH), 7.63 (1H, ddd, J = 8.0, 2.3, 1.7, =CH), 7.33 – 7.27 (2H, m, 2 x =CH), 7.22 (1H, ddd, J = 8.1, 4.7, 0.5, =CH), 7.03 – 6.95 (2H, m, 2 x =CH), 2.20 (3H, s, N-C- CH_3), 1.79 (3H, s, NHCH_3). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 161.7 (d, $^1J_{\text{CF}}$ = 245.2 Hz, =CF), 149.0 (=CH), 148.0 (=CH), 143.1 (=C), 142.5 (d, $^4J_{\text{CF}}$ = 3.1 Hz, =C), 134.8 (=CH), 128.8 (d, $^3J_{\text{CF}}$ = 7.7 Hz, =CH), 123.1 (=CH), 115.1 (d, $^2J_{\text{CF}}$ = 20.4 Hz, =CH), 61.5 ($\text{CH}_3\text{NH-C-CH}_3$), 29.8 ($\text{CH}_3\text{NH-C-CH}_3$), 26.9 ($\text{CH}_3\text{NH-C-CH}_3$). IR (film, cm^{-1}): ν_{max} = 3289, 2981, 1506, 1414. $[\alpha]_{\text{D}}^{23}$ = -5.0 (c = 1.00; CH_2Cl_2). HRMS (ESI $^+$): m/z calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{F}$ $[\text{M}+\text{H}]^+$ 231.1292, found 231.1289.

(R)-1-(4-fluorophenyl)-N-methyl-1-(pyridin-3-yl)ethan-1-amine (12d)



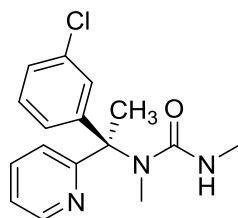
Following general procedure 4, urea **11d** (27 mg, 0.098 mmol), 10% aqueous NaOH solution (0.39 mL, 0.98 mmol), EtOH (0.78 mL) gave **12d** as a yellow oil (14 mg, 64%) without further purification. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.58 – 8.47 (2H, m, 2 x =CH), 8.42 – 8.35 (1H, m, =CH), 7.66 (1H, dq, J = 8.1, 1.8, =CH), 7.55 (1H, tt, J = 7.8, 1.7, =CH), 7.22 – 7.13 (2H, m, 2 x =CH), 7.10 – 7.06 (1H, m, =CH), 2.16 (3H, s, N-C- CH_3), 1.79 (3H, s, NHCH_3). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ = 165.1 (=C), 149.2 (=CH), 149.1 (=CH), 148.0 (=CH), 142.4 (=C), 136.5 (=CH), 134.9 (=CH), 123.2 (=CH), 121.9 (=CH), 121.6 (=CH), 63.1 ($\text{CH}_3\text{NH-C-CH}_3$), 29.7 ($\text{CH}_3\text{NH-C-CH}_3$), 25.1 ($\text{CH}_3\text{NH-C-CH}_3$). IR (film, cm^{-1}): ν_{max} = 3304, 2983, 2923, 1587, 1430, 1414. $[\alpha]_{\text{D}}^{23}$ = +8.7 (c = 1.00; CH_2Cl_2). HRMS (ESI $^+$): m/z calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3$ $[\text{M}+\text{H}]^+$ 214.1339, found 214.1324.

(R)-1-(4-methoxybenzyl)-3-methyl-1-(1-phenyl-1-(pyridin-3-yl)ethyl)urea (13)



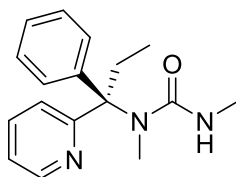
Following General procedure 3, urea **9** (0.995 g, 2.65 mmol), freshly prepared LDA (0.75 M in THF, 8.84 ml, 6.627 mmol) and THF (26.5 ml) gave after purification by flash column chromatography (SiO₂, 99:1 to 95:5 CH₂Cl₂:MeOH), **13** as a yellow solid (0.845 g, 85%). *R*_f 0.26 (95:5 CH₂Cl₂:MeOH); ¹H NMR (500 MHz, CDCl₃) δ = 8.54 (1H, d, *J* = 2.5, =CH), 8.39 (1H, dd, *J* = 4.7, 1.5, =CH), 7.48 (1H, ddd, *J* = 8.1, 2.5, 1.5, =CH), 7.27 – 7.10 (8H, m, 8 x =CH), 6.86 – 6.80 (2H, m, 2 x =CH), 4.44 (1H, d, *J* = 17.5, NHCH_AH_B), 4.35 (1H, d, *J* = 17.5 Hz, NHCH_AH_B), 4.24 (1H, q, *J* = 4.7 Hz, CH-CH₃), 3.75 (3H, s, OCH₃), 2.51 (3H, d, *J* = 4.5, CH-CH₃), 2.02 (3H, s, NCH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 160.3 (=C), 158.8 (=C), 148.8 (=CH), 147.8 (=CH), 144.2 (=C), 141.6 (=C), 134.9 (=CH), 131.5 (=CH), 128.6 (=CH), 127.5 (3x =CH), 123.0 (=CH), 114.4 (=CH), 67.2 (NH-C-CH₃), 55.4 (OCH₃), 50.5 (NHCH₂), 31.0 (NH-C-CH₃), 27.7 (NHCH₃). *Mp* = 56-58 °C. [α]_D²⁵ = +0.25 (c = 1.00; CH₂Cl₂). IR (film, cm⁻¹): ν_{max} = 3440, 2951, 1645, 1510, 1243. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₆N₃O₂ [M+H]⁺ 376.2020, found 376.2003.

1-[(1*R*)-1-(3-Chlorophenyl)-1-(pyridine-2-yl)ethyl]-1,3-dimethylurea (**14a**)



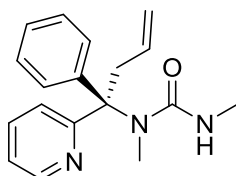
Following general procedure 3, LDA (0.21 ml), urea **8a** (50 mg, 0.17 mmol) and THF (1.56 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **14a** as an oil (48 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ = 8.58-8.49 (1H, m, =CH), 7.69-7.58 (1H, m, =CH), 7.37-7.09 (6H, m, 6 x =CH), 5.08-4.85 (1H, brs, NHCH₃), 2.95 (3H, s, NCH₃), 2.55 (3H, d, *J* = 4.6, NHCH₃), 2.06 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 163.5 (C=O), 159.9 (=C), 148.4 (=CH), 147.2 (=C), 136.8 (=CH), 134.1 (=C), 129.5 (=CH), 127.5 (=CH), 127.1 (=CH), 125.5 (=CH), 121.9 (=CH), 121.5 (=CH), 68.1 (NC), 33.7 (NCH₃), 28.6 (NCH₃), 27.4 (CH₃). [α]_D²⁰ = -53 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3337, 2980, 2935, 1630. HRMS (ESI⁺): *m/z* calcd for C₁₆H₁₈ClN₃ONa [M+Na]⁺ 326.1036, found 326.1043.

1,3-Dimethyl-1-[(1R)-1-phenyl-1(pyridin-2-yl)propyl]urea (**14b**)



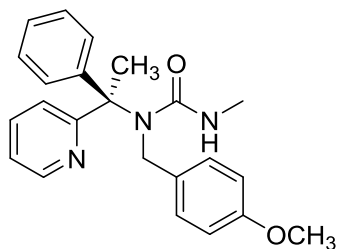
Following general procedure 3, LDA (0.44 ml), urea **8b** (100 mg, 0.35 mmol) and THF (3.53 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **14b** as an oil (88 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ = 8.58-8.53 (1H, m, =CH), 7.69 (1H, td, *J* = 7.9 and 1.8, =CH), 7.52-7.44 (1H, m, =CH), 7.35-7.27 (4H, m, 4 x =CH), 7.24-7.14 (2H, m, 2 x =CH), 5.82-5.63 (1H, m, NHCH₃), 3.03 (3H, m, NCH₃), 2.65-2.52 (2H, m, CH₂CH₃), 2.51 (3H, d, *J* = 4.6, NHCH₃), 0.76 (3H, t, *J* = 7.3, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.6 (C=O), 160.3 (=C), 148.3 (=CH), 142.8 (=C), 136.6 (=CH), 128.3 (2 x =CH), 127.7 (=CH), 126.8 (=CH), 122.0 (=CH), 70.9 (NC), 33.5 (NCH₃), 33.1 (CH₂), 27.3 (NCH₃), 10.1 (CH₃). [α]_D²⁰ = -80 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3341, 2970, 2937, 1635. HRMS (ESI⁺): *m/z* calcd for C₁₇H₂₁N₃ONa [M+Na]⁺ 306.1577, found 306.1581.

1,3-Dimethyl-1-[(1R)-1-phenyl-1(pyridin-2-yl)but-3-en-1-yl]urea (**14c**)



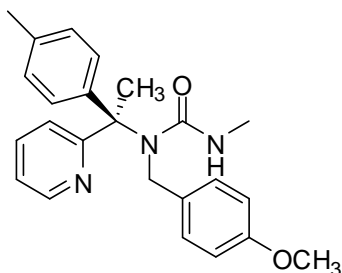
Following general procedure 3, LDA (0.42 ml), urea **8c** (100 mg, 0.34 mmol) and THF (3.39 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **14c** as an oil (67 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ = 8.59-8.46 (1H, m, =CH), 7.63 (1H, td, *J* = 8.0 and 1.8, =CH), 7.44 (1H, d, *J* = 8.1, =CH), 7.38-7.31 (2H, m, 2 x =CH), 7.30-7.23 (2H, m, 2 x =CH), 7.22-7.16 (1H, m, =CH), 7.12 (1H, ddd, *J* = 7.4, 4.8 and 0.8, =CH), 5.71 (1H, ddt, *J* = 17.1, 10.2 and 6.9, CH₂=CHCH₂), 5.23-5.08 (1H, m, NHCH₃), 5.08-4.91 (2H, m, =CH₂) 3.51 (1H, dd, *J* = 14.6 and 6.8, CH_ACH_BCH=), 3.41 (1H, dd, *J* = 14.6 and 7.0, CH_ACH_BCH=), 2.97 (3H, s, NCH₃), 2.56 (3H, d, *J* = 4.6, NHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 163.2 (C=O), 160.1 (=C), 148.3 (=CH), 143.0 (=C), 136.3 (=CH), 134.7 (=CH), 128.1 (=CH), 128.0 (=CH), 127.0 (=CH), 122.1 (=CH), 121.7 (=CH), 118.3 (=CH₂), 71.0 (NC), 44.0 (CH₂), 34.9 (CH₃), 27.4 (NCH₃). [α]_D²⁰ = -36 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3345, 3060, 2925, 1635, 1218, 1081. HRMS (ESI⁺): *m/z* calcd for C₁₈H₂₁N₃ONa [M+Na]⁺ 318.1577, found 318.1577.

1-[(4-Methoxyphenyl)methyl]-3-methyl-1-[(1R)-1-phenyl-1-(pyridin-2-yl)ethyl]urea (**15a**)



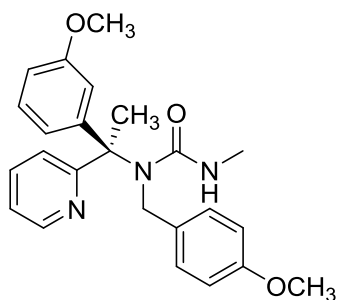
Following General procedure 3, LDA (0.48 ml), urea **10a** (145 mg, 0.39 mmol) and THF (3.86 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15a** as an oil (138 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ = 8.62-8.50 (1H, m, =CH), 7.59 (1H, td, *J* = 7.9 and 1.8, =CH), 7.35-7.18 (8H, m, 8 x =CH), 7.15 (1H, ddd, *J* = 7.4, 4.9 and 0.7, =CH), 6.89-6.79 (2H, m, 2 x =CH), 5.42-5.26 (1H, m, NHCH₃), 4.77 (1H, d, *J* = 17.0, NCH_AH_B), 4.49 (1H, d, *J* = 17.1, NCH_AH_B), 3.81 (3H, s, OCH₃), 2.51 (3H, d, *J* = 4.6, NHCH₃), 2.04 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 164.4 (C=O), 160.7 (=C), 158.5 (=C), 148.2 (=CH), 145.1 (=C), 136.5 (=CH), 132.7 (=C), 128.2 (=CH), 128.1 (=CH), 127.4 (2 x =CH), 127.0 (=CH), 122.2 (=CH), 121.8 (=CH), 114.0 (=CH), 69.2 (NC), 55.4 (OCH₃), 49.7 (CH₂), 30.8 (NCH₃), 27.5 (CH₃). [α]_D²⁰ = -44 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2990, 2937, 1641. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₆N₃O₂ [M+H]⁺ 376.2025, found 376.2025.

1-[(4-Methoxyphenyl)methyl]-3-methyl-1-[(1R)-1-(4-methylphenyl)-1-(pyridin-2-yl)ethyl]urea (**15b**)



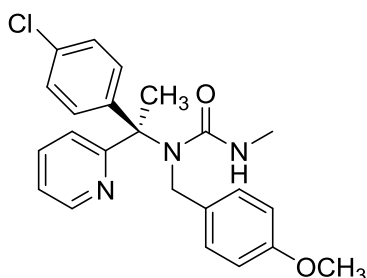
Following general procedure 3, LDA (0.14 ml), urea **10b** (45 mg, 0.12 mmol) and THF (1.16 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15b** as an oil (44 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ = 8.55 (1H, ddd, *J* = 4.8, 1.9 and 0.7, =CH), 7.58 (1H, td, *J* = 7.7 and 1.8, =CH), 7.33-7.27 (3H, m, 3 x =CH), 7.16-7.11 (3H, m, 3 x =CH), 7.10-7.04 (2H, m, 2 x =CH), 6.89-6.81 (2H, m, 2 x =CH), 5.18 (1H, q, *J* = 4.6, NHCH₃), 4.76 (1H, d, *J* = 17.0, NCH_AH_B), 4.47 (1H, d, *J* = 17.0, NCH_AH_B), 3.80 (3H, s, OCH₃), 2.51 (3H, d, *J* = 4.6, NHCH₃), 2.31 (3H, s, CH₃), 2.03 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 164.6 (C=O), 160.7 (=C), 158.5 (=C), 148.2 (=CH), 141.9 (=C), 136.7 (=CH), 136.4 (=C), 132.8 (=C), 128.9 (=CH), 128.2 (=CH), 127.4 (CH), 122.2 (=CH), 121.7 (=CH), 114.0 (=CH), 69.1 (NC), 55.4 (OCH₃), 49.8 (CH₂), 30.7 (NCH₃), 27.5 (CH₃), 21.1 (CH₃). [α]_D²⁰ = -48 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2924, 1641, 1243, 1034, 748. HRMS (ESI⁺): *m/z* calcd for C₂₄H₂₇N₃O₂Na [M+Na]⁺ 412.1995, found 412.1994.

1-[(1R)-1-(3-Methoxyphenyl)-1-(pyridin-2-yl)ethyl]-1-[(4-[methoxyphenyl]methyl)-3-methylurea (15c)



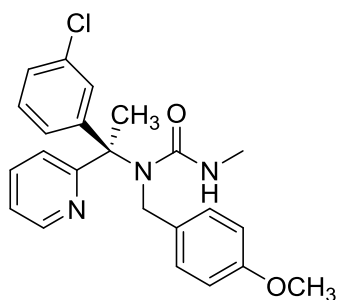
Following general procedure 3, LDA (0.19 ml), urea **10c** (63 mg, 0.16 mmol) and THF (1.55 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15c** as an oil (64 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ = 8.57 (1H, dd, *J* = 4.7 and 0.9, =CH), 7.59 (1H, td, *J* = 7.9 and 1.8, =CH), 7.36-7.24 (3H, m, 3 x =CH), 7.18 (1H, t, *J* = 8.0, =CH), 7.14 (1H, dd, *J* = 7.4 and 5.5, =CH), 6.90-6.70 (5H, m, 5 x =CH), 5.37-5.22 (1H, brq, NHCH₃), 4.69 (1H, d, *J* = 17.0, NCH_AH_B), 4.51 (1H, d, *J* = 17.1, NCH_AH_B), 3.80 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 2.53 (3H, d, *J* = 4.6, NHCH₃), 2.06 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 164.2 (C=O), 160.6 (=C), 159.4 (=C), 159.5 (=C), 148.3 (=CH), 147.0 (=C), 136.4 (=CH), 132.6 (=C), 129.1 (=CH), 128.1 (2 x =CH), 122.1 (=CH), 121.8 (=CH), 119.8 (=CH), 114.0 (2 x =CH), 113.7 (=CH), 112.1 (=CH), 69.3 (NC), 55.4 (OCH₃), 55.2 (OCH₃), 49.9 (CH₂), 30.4 (NCH₃), 27.5 (CH₃). [α]_D²⁰ = -28 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2957, 2924, 1670, 1250, 1034. HRMS (ESI⁺): *m/z* calcd for C₂₄H₂₈N₃O₃ [M+ H]⁺ 406.2125, found 406.2111.

1-[(1R)-1-(4-Chlorophenyl)-1-(pyridin-2-yl)ethyl]-1-[(4-[methoxyphenyl]methyl)-3-methylurea (15d)



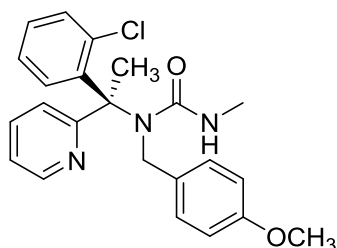
Following general procedure 3, LDA (0.13 ml), urea **10d** (41 mg, 0.10 mmol) and THF (1.00 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15d** as an oil (35 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ = 8.55 (1H, ddd, *J* = 4.8, 1.9 and 0.9, =CH), 7.59 (1H, td, *J* = 7.6 and 1.9, =CH), 7.32-7.17 (7H, m, 7 x =CH), 7.15 (1H, ddd, *J* = 7.5, 4.8 and 0.8, =CH), 6.92-6.76 (2H, m, 2 x =CH), 5.34 (1H, q, *J* = 4.5, NHCH₃), 4.76 (1H, d, *J* = 17.1, NCH_AH_B), 4.44 (1H, d, *J* = 17.1, NCH_AH_B), 3.80 (3H, s, OCH₃), 2.53 (3H, d, *J* = 4.6, NHCH₃), 2.01 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 164.0 (C=O), 160.5 (=C), 158.7 (=C), 148.4 (=CH), 143.8 (=C), 136.6 (=CH), 132.7 (=C), 132.3 (=C), 128.9 (2 x =CH), 128.2 (2 x =CH), 128.1 (2 x =CH), 122.1 (=CH), 122.0 (=CH), 114.1 (2 x =CH), 68.8 (NC), 55.4 (OCH₃), 49.7 (CH₂), 30.5 (NCH₃), 27.5 (CH₃). [α]_D²⁰ = +16 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2980, 1642, 1215, 1038, 747. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₄ClN₃O₂Na [M+Na]⁺ 432.1449, found 432.1437.

1-[(1R)-1-(3-Chlorophenyl)-1-(pyridin-2-yl)ethyl]-1-[(4-[methoxyphenyl)methyl]-3-methylurea (15e)



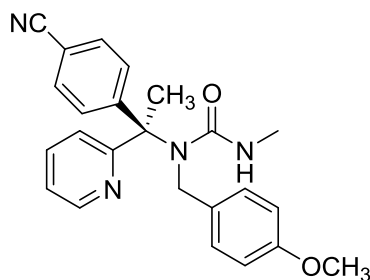
Following general procedure 3, LDA (0.21 ml), urea **10e** (70 mg, 0.17 mmol) and THF (1.71 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15e** as an oil (67 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ = 8.62-8.51 (1H, m, =CH), 7.60 (1H, td, *J* = 7.9 and 1.7, =CH), 7.35-7.23 (8H, m, 8 x =CH), 6.90-6.80 (2H, m, 2 x =CH), 5.47-5.34 (1H, m, NHCH₃), 4.76 (1H, d, *J* = 17.1, NCH_AH_B), 4.45 (1H, d, *J* = 17.1, NCH_AH_B), 3.80 (3H, s, OCH₃), 2.53 (3H, d, *J* = 4.6, NHCH₃), 2.01 (3H, m, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 163.4 (C=O), 160.4 (=C), 158.6 (=C), 148.3 (=CH), 147.4 (=C), 136.7 (=CH), 134.0 (=C), 132.2 (=C), 129.4 (=CH), 128.1 (2 x =CH), 127.6 (=CH), 127.1 (=CH), 125.6 (=CH), 122.2 (=CH), 122.1 (=CH), 114.1 (2 x =CH), 68.9 (NC), 55.4 (OCH₃), 49.7 (CH₂), 30.5 (NCH₃), 27.5 (CH₃). [α]_D²⁰ = -53 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2985, 1653, 1207, 1036, 751. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₅ClN₃O₂ [M+H]⁺ 410.1635, found 410.1637.

1-[(1R)-1-(2-Chlorophenyl)-1-(pyridin-2-yl)ethyl]-1-[(4-[methoxyphenyl)methyl]-3-methylurea (15f)



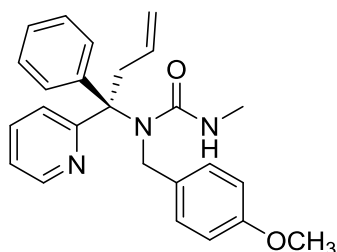
Following general procedure 3, LDA (0.23 ml), urea **10f** (74 mg, 0.18 mmol) and THF (1.81 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15f** as an oil (49 mg, 66%). ¹H NMR (400 MHz, CDCl₃) δ = 8.56-8.38 (1H, m, =CH), 7.61-7.51 (1H, m, =CH), 7.38-7.31 (1H, m, =CH), 7.27-7.17 (6H, m, 6 x =CH), 7.16-7.10 (1H, m, =CH), 6.87-6.71 (2H, m, 2 x =CH), 6.23-6.02 (1H, m, NHCH₃), 5.11 (1H, d, *J* = 16.9, NCH_AH_B), 4.45 (1H, d, *J* = 16.9, NCH_AH_B), 3.80-3.75 (3H, m, OCH₃), 2.59-2.46 (3H, m, NHCH₃), 2.21-2.07 (3H, m, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.5 (C=O), 160.4 (=C), 158.4 (=C), 147.2 (=CH), 141.9 (=C), 136.7 (=CH), 132.9 (=C), 132.8 (=C), 132.0 (=CH), 129.0 (=CH), 128.3 (=CH), 128.2 (2 x =CH), 126.7 (=CH), 122.9 (=CH), 122.2 (=CH), 113.9 (2 x =CH), 69.4 (NC), 55.4 (OCH₃), 49.3 (CH₂), 27.4 (NCH₃), 27.3 (CH₃). [α]_D²⁰ = -28 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3017, 1628, 1215, 1035, 745. HRMS (ESI⁺): *m/z* calcd for C₂₃H₂₄ClN₃O₂Na [M+Na]⁺ 432.1449, found 432.1447.

1-[(1R)-1-(4-Cyanophenyl)-1-(pyridin-2-yl)ethyl]-1-[(4-methoxyphenyl)methyl]-3-methylurea (**15g**)



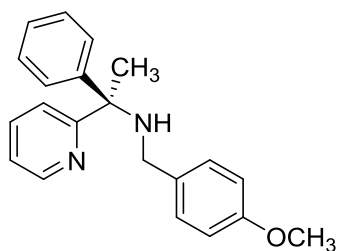
Following general procedure 3, LDA (0.24 ml), urea **10g** (78 mg, 0.20 mmol) and THF (1.95 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15g** as an oil (66 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ = 8.57 (1H, ddd, *J* = 4.8, 1.9 and 0.9, =CH), 7.55 (1H, ddd, *J* = 9.4, 7.5 and 1.9, =CH), 7.58-7.53 (2H, m, 2 x =CH), 7.41-7.35 (2H, m, 2 x =CH), 7.32-7.26 (3H, m, 3 x =CH), 7.18 (1H, ddd, *J* = 7.5, 4.8 and 1.0, =CH), 6.89-6.83 (2H, m, 2 x =CH), 5.46 (1H, q, *J* = 4.3, NHCH₃), 4.73 (1H, d, *J* = 17.3, NCH_AH_B), 4.42 (1H, d, *J* = 17.3, NCH_AH_B), 3.81 (3H, s, OCH₃), 2.53 (3H, d, *J* = 4.6, NHCH₃), 2.01 (3H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 162.9 (C=O), 160.3 (=C), 158.8 (=C), 151.4 (=C), 148.4 (=CH), 136.8 (=CH), 131.9 (2 x =CH), 131.7 (=C), 128.0 (2 x =CH), 127.9 (2 x =CH), 122.4 (=CH), 122.3 (=CH), 119.1 (=C), 114.3 (2 x =CH), 110.4 (CN), 69.1 (NC), 55.5 (OCH₃), 49.7 (CH₂), 30.1 (NCH₃), 27.4 (CH₃). [α]_D²⁰ = -56 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 2999, 2227, 1647, 1244, 1033, 749. HRMS (ESI⁺): *m/z* calcd for C₂₄H₂₄N₄O₂Na [M+Na]⁺ 423.1791, found 423.1793.

1-[(4-Methoxyphenyl)methyl]-3-methyl-1-[(1R)-1-phenyl-1-(pyridin-2-yl)but-3-en-1-yl]urea (**15h**)



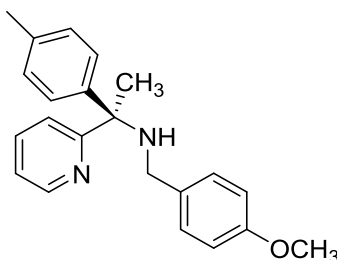
Following general procedure 3, LDA (0.24 ml), urea **10h** (77 mg, 0.19 mmol) and THF (1.92 ml) gave, after purification by flash column chromatography (SiO₂, 99:1 to 90:10 DCM:MeOH), **15h** as an oil (70 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ = 8.58-8.50 (1H, m, =CH), 7.54 (1H, td, *J* = 8.0 and 1.9, =CH), 7.34-7.29 (1H, m, =CH), 7.28-7.15 (7H, m, 7 x =CH), 6.85-6.76 (2H, m, 2 x =CH), 7.22-7.16 (1H, m, =CH), 7.12 (1H, ddd, *J* = 7.4, 4.8 and 0.9, =CH), 5.76-5.67 (1H, m, NHCH₃), 5.59 (1H, ddt, *J* = 17.1, 10.2 and 6.8, CH₂=CHCH₂), 5.03-4.87 (2H, m, =CH₂) 3.80 (3H, s, OCH₃), 3.49 (1H, dd, *J* = 14.5 and 6.8, CH_ACH_BCH=), 3.40 (1H, dd, *J* = 14.5 and 7.5, CH_ACH_BCH=), 2.52 (3H, d, *J* = 4.6, NHCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 163.3 (C=O), 160.6 (=C), 158.5 (=C), 148.1 (=CH), 143.1 (=C), 136.1 (=CH), 134.8 (=CH), 132.4 (=C), 128.1 (2 x =CH), 128.0 (2 x =CH), 127.8 (2 x =CH), 126.9 (=CH), 122.7 (=CH), 121.7 (=CH), 118.3 (=CH₂), 114.0 (2 x =CH), 71.8 (NC), 55.4 (OCH₃), 50.3 (CH₂), 44.8 (CH₂), 27.4 (NCH₃). [α]_D²⁰ = -36 (c = 1.00; CHCl₃). IR (film, cm⁻¹): ν_{max} = 3441, 3064, 2930, 1645, 1244, 1036. HRMS (ESI⁺): *m/z* calcd for C₂₅H₂₈N₃O₂ [M+H]⁺ 402.2182, found 402.2174.

[(4-[Methoxyphenyl)methyl][(1R)-1-phenyl-1-(pyridin-2-yl)ethyl]amine (16a)



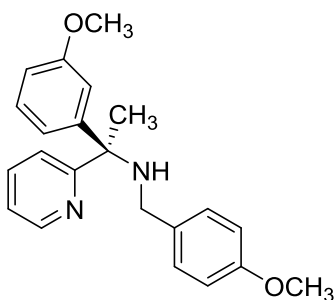
Following general procedure 4, urea **15a** (130 mg, 0.35 mmol) gave **16a** as an oil (100 mg, 91%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.61-8.53 (1H, m, =CH), 7.58 (1H, td, J = 7.8 and 1.9, =CH), 7.53-7.46 (2H, m, 2 x =CH), 7.35-7.29 (2H, m, 2 x =CH), 7.28-7.25 (3H, m, 3 x =CH), 7.25-7.19 (1H, m, =CH), 7.11 (1H, ddd, J = 7.5, 4.8 and 1.1, =CH), 6.92-6.78 (2H, m, 2 x =CH), 3.79 (3H, s, OCH_3), 3.50 (2H, AB pattern, J = 12.2, $\Delta\nu$ = 18.8, NHCH_2), 2.95-2.21 (1H, brs, NHCH_2), 1.95 (3H, s, CH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 166.4 (=C), 158.6 (=C), 148.8 (=CH), 147.1 (=C), 136.3 (=CH), 133.6 (=C), 129.5 (2 x =CH), 128.3 (2 x =CH), 127.3 (2 x =CH), 126.7 (=CH), 121.7 (=CH), 121.5 (=CH), 113.9 (2 x =CH), 64.3 (NC), 55.4 (OCH_3), 46.9 (CH_2), 26.2 (CH_3). $[\alpha]_{\text{D}}^{20}$ = -49 (c = 1.00; CHCl_3). IR (film, cm^{-1}): ν_{max} = 2.954, 2931, 1241. HRMS (ESI $^+$): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_1$ $[\text{M}+\text{H}]^+$ 319.1805, found 319.1809.

[(4-[Methoxyphenyl)methyl][(1R)-1-(4-methylphenyl)-1-(pyridin-2-yl)ethyl]amine (16b)



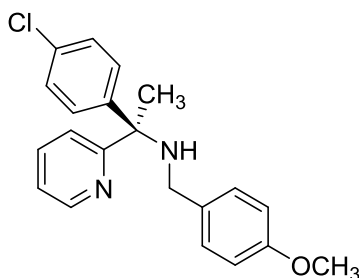
Following general procedure 4, urea **15b** (37 mg, 0.09 mmol) gave **16b** as an oil (28 mg, 90%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.63-8.50 (1H, m, =CH), 7.63-7.50 (1H, m, =CH), 7.42-7.32 (2H, m, 2 x =CH), 7.30-7.21 (3H, m, 3 x =CH), 7.17-7.03 (3H, m, 3 x =CH), 6.89-6.77 (2H, m, 2 x =CH), 3.79 (3H, s, OCH_3), 3.50 (2H, AB pattern, J = 12.1, $\Delta\nu$ = 12.6, NHCH_2), 2.73-2.37 (1H, brs, NH), 2.32 (3H, s, CH_3), 1.93 (3H, s, CH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 166.4 (=C), 158.6 (=C), 148.7 (=CH), 143.9 (=C), 136.3 (=CH), 136.2 (=C), 133.5 (=C), 129.5 (2 x =CH), 129.0 (2 x =CH), 127.2 (2 x =CH), 121.6 (=CH), 121.5 (=CH), 113.8 (2 x =CH), 64.1 (NC), 55.4 (OCH_3), 46.9 (CH_2), 26.2 (CH_3), 21.1 (CH_3). $[\alpha]_{\text{D}}^{20}$ = -24 (c = 1.00; CHCl_3). IR (film, cm^{-1}): ν_{max} = 2926, 1246, 1036. HRMS (ESI $^+$): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 333.1961, found 333.1961.

[(1R)-1-(3-Methoxyphenyl)-1-(pyridin-2-yl)ethyl][(4-[methoxyphenyl)methyl]amine (16c)



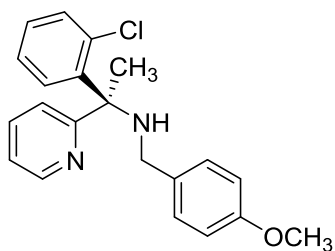
Following general procedure 4, urea **15c** (57 mg, 0.14 mmol) gave **16c** as an oil (28 mg, 90%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.61-8.54 (1H, m, =CH), 7.58 (1H, td, J = 7.9 and 1.8, =CH), 7.32-7.20 (4H, m, 4 x =CH), 7.15-7.10 (2H, m, 2 x =CH), 7.09-7.02 (1H, m, =CH), 6.89-6.82 (2H, m, 2 x =CH), 6.78 (1H, ddd, J = 7.1, 1.5 and 0.6, =CH), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.51 (2H, AB pattern, J = 15.5, $\Delta\nu$ = 18.4, NHCH_2), 2.58-2.31 (1H, brs, NH), 1.94 (3H, s, CH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 166.1 (=C), 159.6 (=C), 158.6 (=C), 148.8 (=C), 148.7 (=CH), 136.3 (=CH), 133.5 (=C), 129.5 (2 x =CH), 129.2 (=CH), 121.6 (=CH), 121.5 (=CH), 119.9 (=CH), 113.8 (2 x =CH), 113.5 (=CH), 111.8 (=CH), 64.2 (NC), 55.4 (OCH_3), 55.3 (OCH_3), 46.9 (CH_2), 26.2 (CH_3). $[\alpha]_{\text{D}}^{20}$ = -9.4 (c = 1.00; CHCl_3). IR (film, cm^{-1}): ν_{max} = 3011, 2960, 1246, 1037. HRMS (ESI $^+$): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 349.1911, found 349.1914.

[(1R)-1-(4-Chlorophenyl)-1-(pyridin-2-yl)ethyl][(4-[methoxyphenyl)methyl]amine (16d)



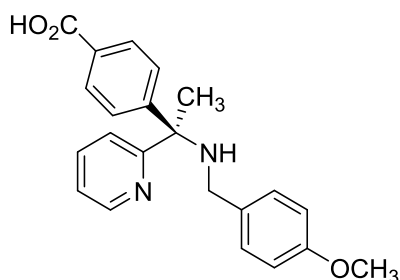
Following general procedure 4, urea **15d** (30 mg, 0.07 mmol) gave **16d** as an oil (25 mg, 97%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.65-8.50 (1H, m, =CH), 7.60 (1H, td, J = 7.6 and 1.4, =CH), 7.49-7.39 (2H, m, 2 x =CH), 7.30-7.22 (5H, m, 5 x =CH), 7.13 (1H, dd, J = 7.1 and 4.9, =CH), 6.92-6.76 (2H, m, 2 x =CH), 3.79 (3H, s, OCH_3), 3.48 (2H, AB pattern, J = 12.1, $\Delta\nu$ = 15.9, NHCH_2), 2.71-2.40 (1H, brs, NH), 1.92 (3H, s, CH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 165.8 (=C), 158.7 (=C), 149.0 (=CH), 145.7 (=C), 136.4 (=CH), 133.2 (=C), 132.5 (=C), 129.4 (2 x =CH), 128.8 (2 x =CH), 128.4 (2 x =CH), 121.7 (=CH), 121.4 (=CH), 113.9 (2 x =CH), 64.0 (NC), 55.4 (OCH_3), 46.9 (CH_2), 26.2 (CH_3). $[\alpha]_{\text{D}}^{20}$ = -48 (c = 1.00; CHCl_3). IR (film, cm^{-1}): ν_{max} = 3002, 2934, 1238, 1042, 767. HRMS (ESI $^+$): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 353.1415, found 353.1421.

[(1R)-1-(2-Chlorophenyl)-1-(pyridin-2-yl)ethyl][(4-[methoxyphenyl)methyl]amine (16e)



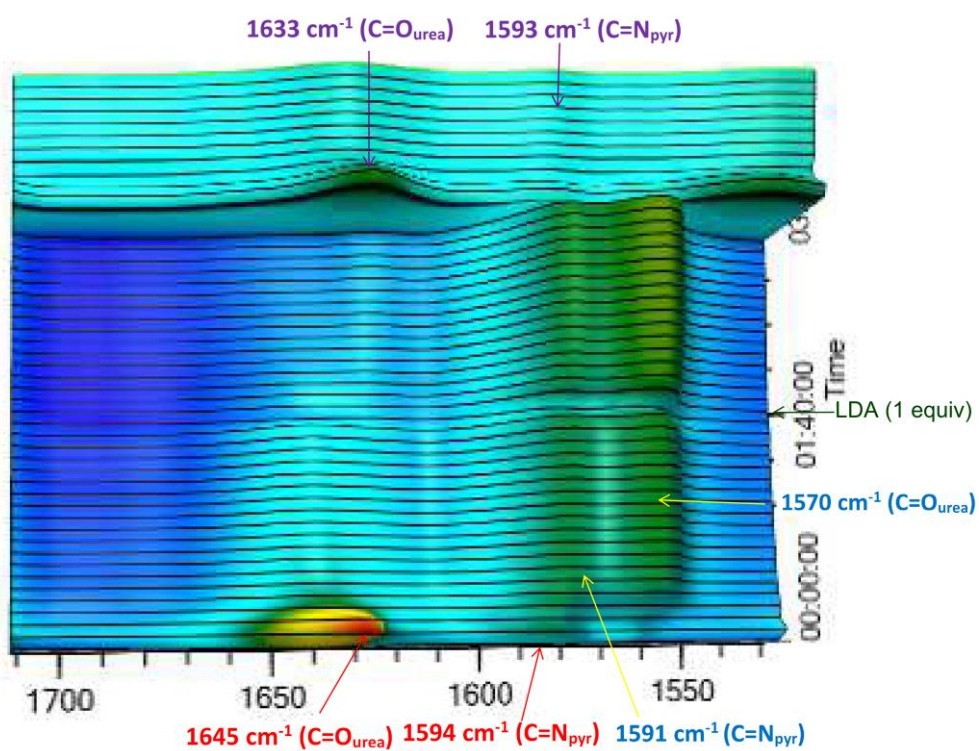
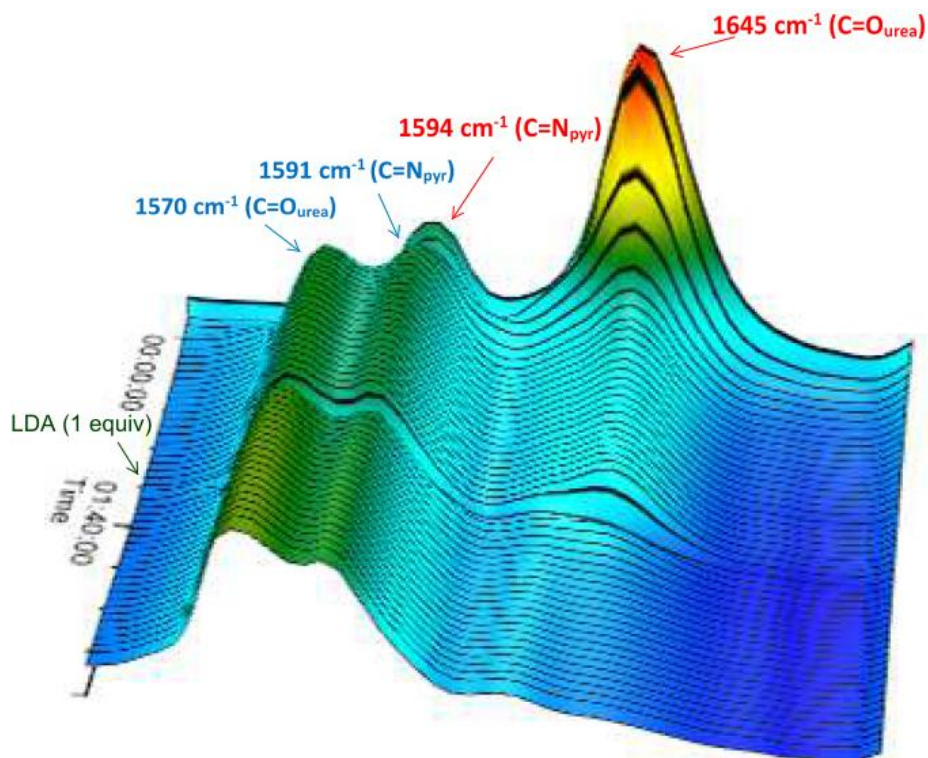
Following general procedure 4, urea **15f** (41 mg, 0.10 mmol) gave **16e** as an oil (32 mg, 91%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.56-8.46 (1H, m, =CH), 7.87 (1H, d, J = 7.9, =CH), 7.60 (1H, td, J = 8.0 and 1.7, =CH), 7.46 (1H, d, J = 8.0, =CH), 7.39-7.33 (1H, m, =CH), 7.32-7.28 (1H, m, =CH), 7.27-7.23 (1H, m, =CH), 7.22-7.16 (2H, m, 2 x =CH), 7.15-7.06 (1H, m, =CH), 6.89-6.75 (2H, m, 2 x =CH), 3.78 (3H, s, OCH_3), 3.54 (1H, d, J = 12.0, NHCH_AH_B), 3.28 (1H, d, J = 12.0, NHCH_AH_B), 2.98-2.59 (1H, brs, NH), 1.91 (3H, s, CH_3). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ = 166.4 (=C), 158.7 (=C), 157.5 (=C), 148.7 (=CH), 146.2 (=C), 136.2 (=CH), 133.3 (=C), 131.5 (=CH), 129.6 (3 x =CH), 128.5 (=CH), 126.8 (=CH), 121.4 (=CH), 121.1 (=CH), 113.9 (2 x =CH), 65.3 (NC), 55.4 (OCH_3), 47.1 (CH_2), 26.7 (CH_3). $[\alpha]_D^{20}$ = -36 (c = 1.00; CHCl_3). IR (film, cm^{-1}): ν_{max} = 2929, 1245, 1034, 750. HRMS (ESI $^+$): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_2\text{O}_1$ $[\text{M}+\text{H}]^+$ 353.1415, found 353.1416.

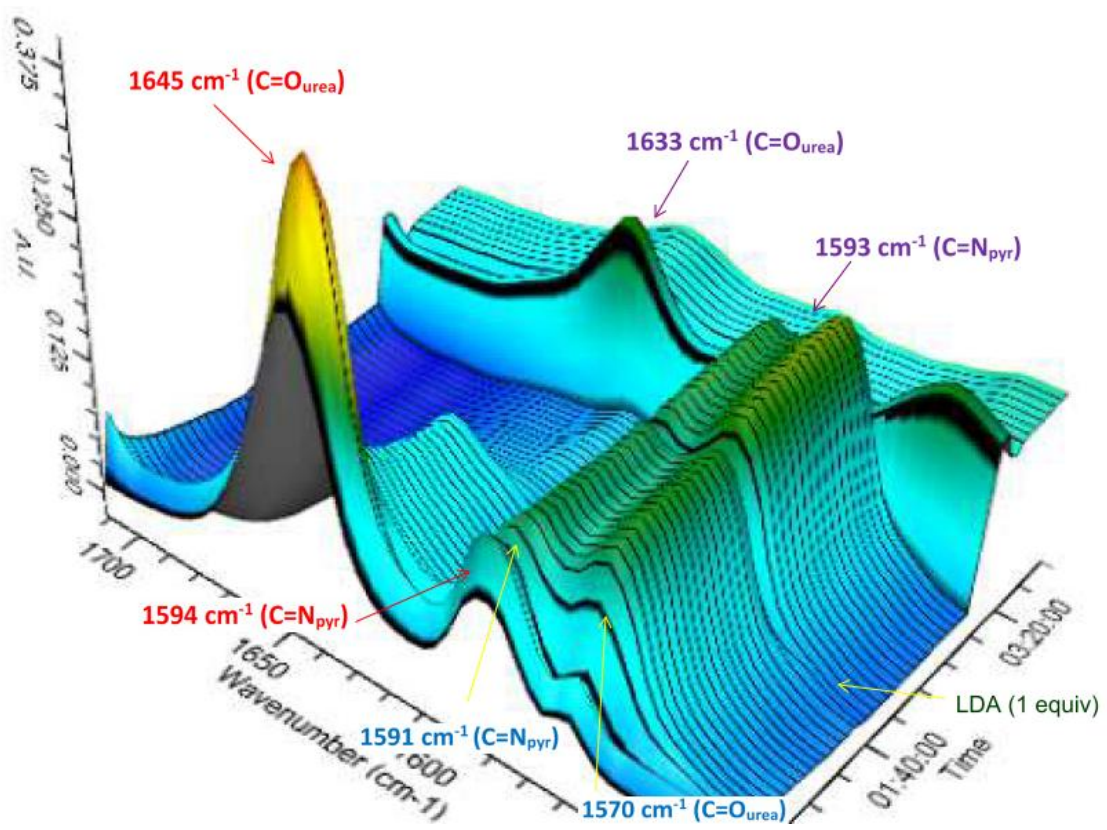
4-[(1R)-1-[(4-Methoxyphenyl)methyl]amino]-1-(pyridin-2-yl)ethyl]benzoic acid (16f)



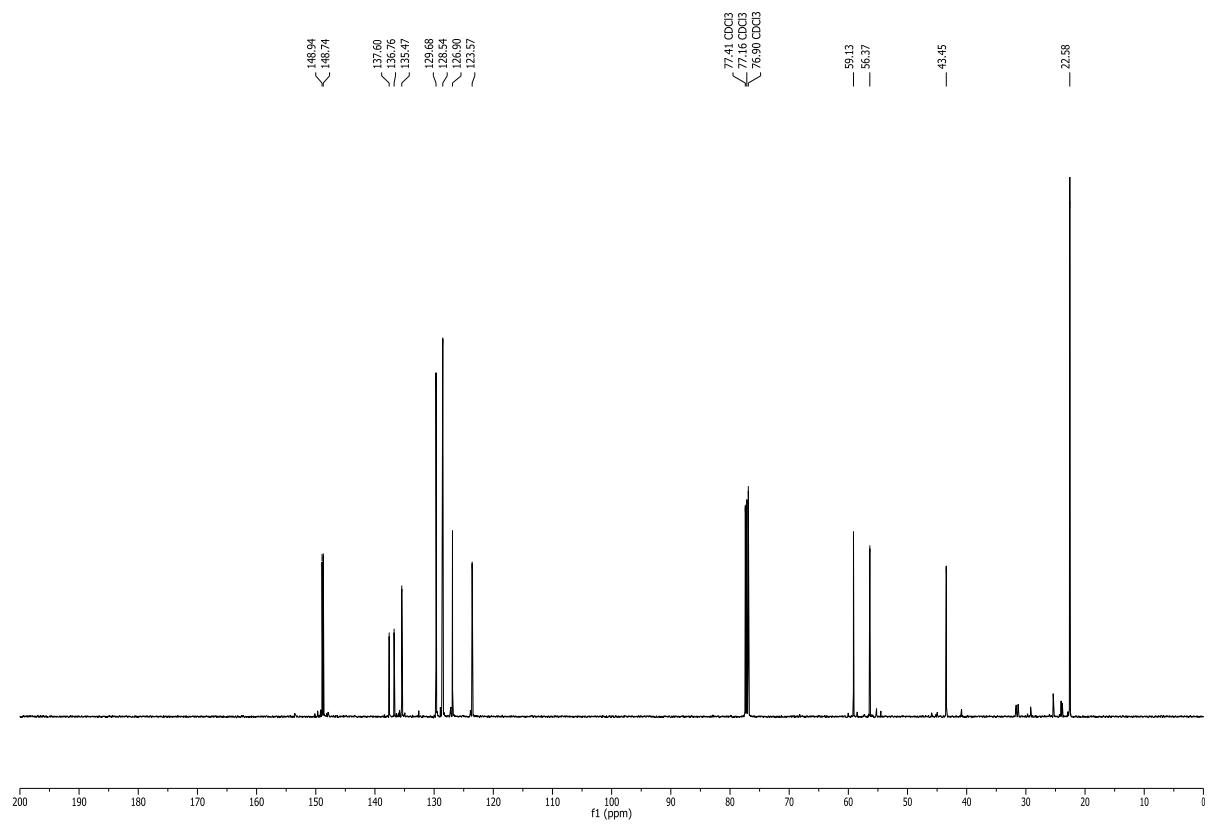
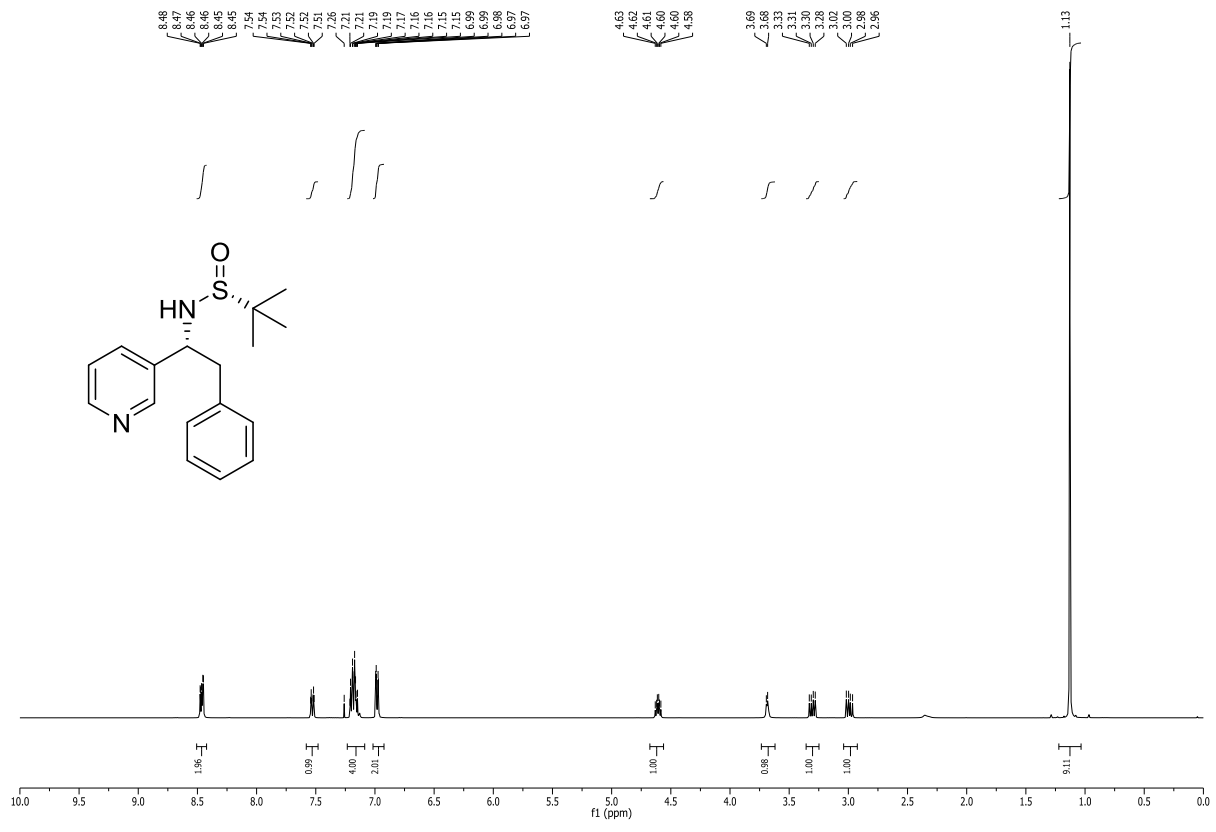
A solution of urea **15g** (62 mg, 0.16 mmol), aqueous NaOH (2.0 M) and EtOH (1.2 M) was microwaved at 130 °C for 3 h. The reaction mixture was concentrated and extracted with ethyl acetate. The aqueous phase was acidified with conc. HCl (pH = 1) and concentrated under reduced pressure. The amine **16f** was obtained by filtration on acidic Dowx ion exchange column (32 mg, 57%). $^1\text{H NMR}$ (400 MHz, MeOD) δ = 8.78-8.66 (1H, m, =CH), 8.10-7.95 (2H, m, 2 x =CH), 7.84 (1H, td, J = 7.8 and 1.6, =CH), 7.58-7.48 (2H, m, 2 x =CH), 7.46-7.38 (1H, m, =CH), 7.36-7.29 (2H, m, 2 x =CH), 7.27 (1H, d, J = 8.1, =CH), 6.98-6.87 (2H, m, 2 x =CH), 3.83 (2H, s, NHCH_2), 3.79 (3H, s, OCH_3), 2.18 (3H, s, CH_3). $^{13}\text{C NMR}$ (100 MHz, MeOD) δ = 164.3 (=C), 164.1 (=C), 159.1 (=C), 151.9 (=CH), 145.5 (=C), 141.5 (=CH), 140.3 (=C), 134.9 (2 x =CH), 133.5 (2 x =CH), 131.3 (2 x =CH), 128.7 (=C), 127.1 (=CH), 126.0 (=CH), 117.8 (2 x =CH), 70.9 (NC), 58.3 (OCH_3), 50.7 (CH_2), 26.8 (CH_3). $[\alpha]_D^{20}$ = -68 (c = 1.00; MeOH). IR (film, cm^{-1}): ν_{max} = 3317, 2947, 2834, 1652, 1253. HRMS (ESI $^+$): m/z calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 363.1703, found 363.1699.

React-IR experiments pictures

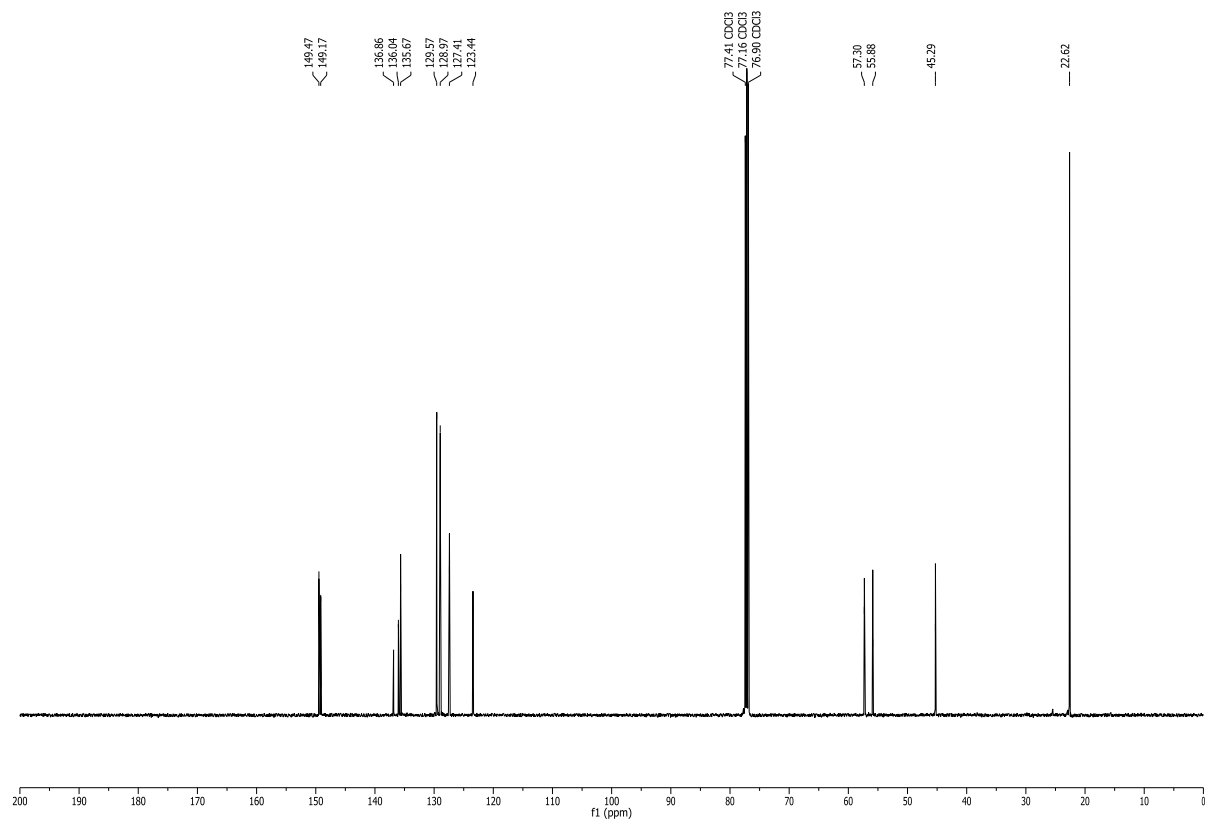
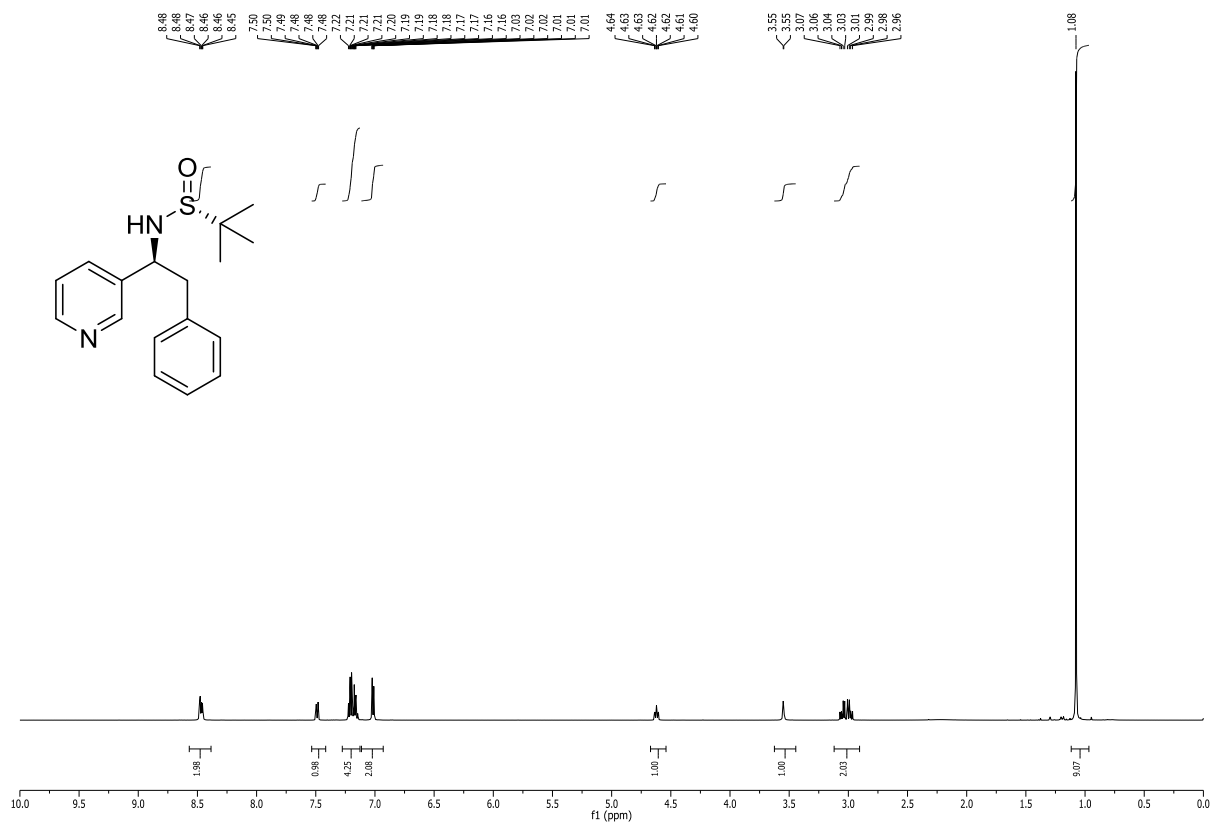




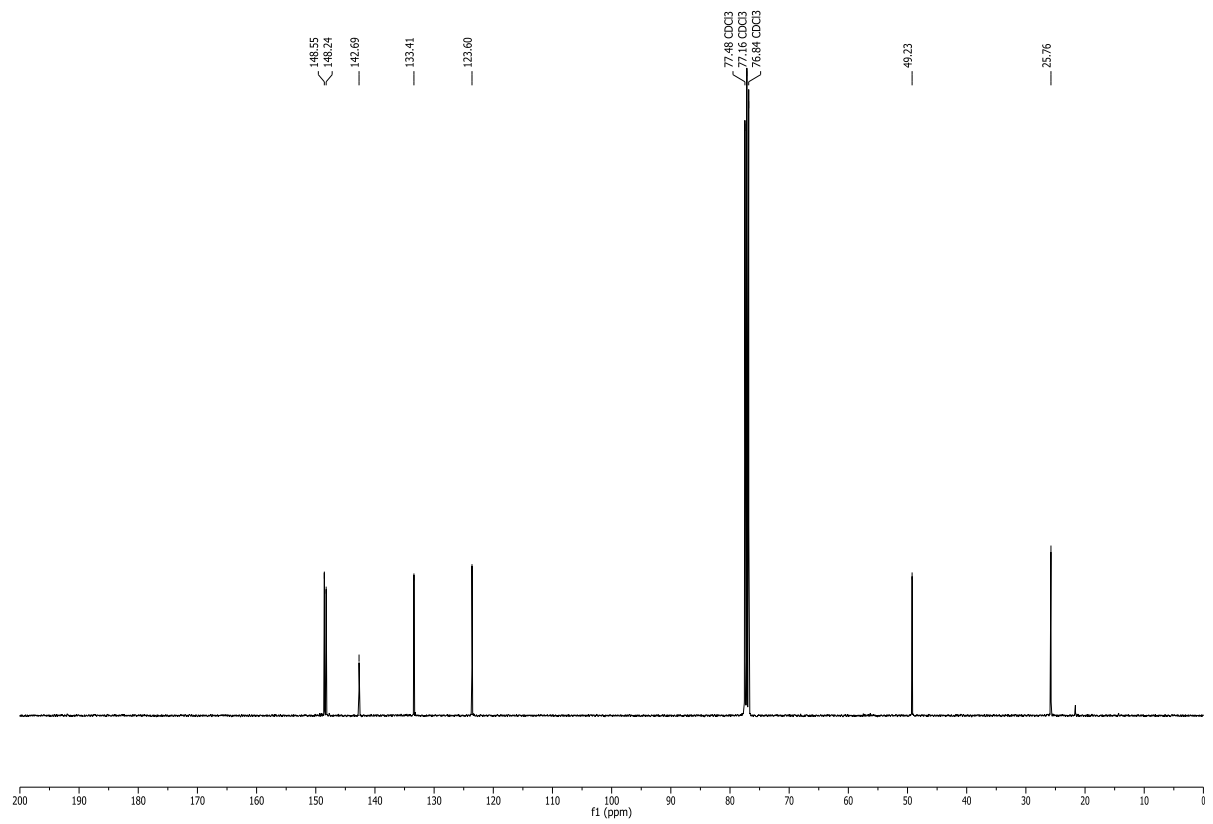
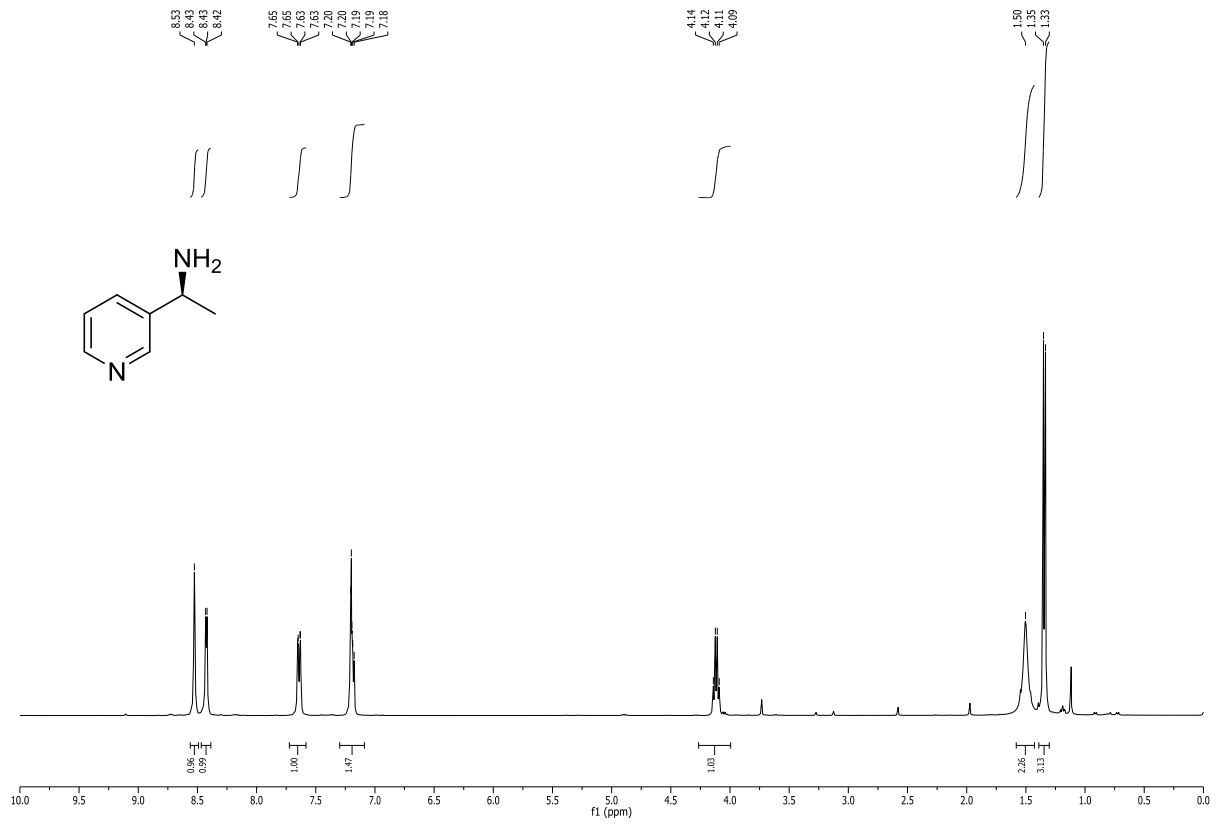
NMR
(*R_S*,*R*)-3b



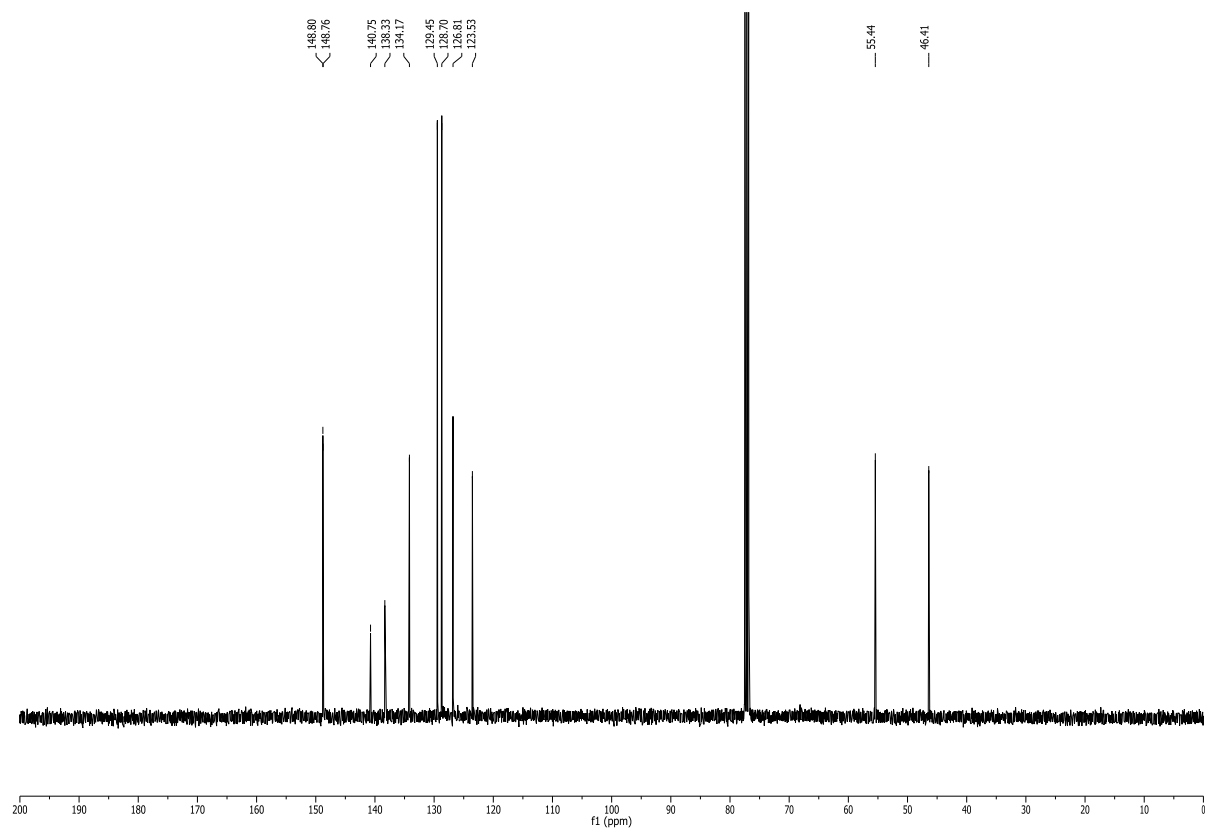
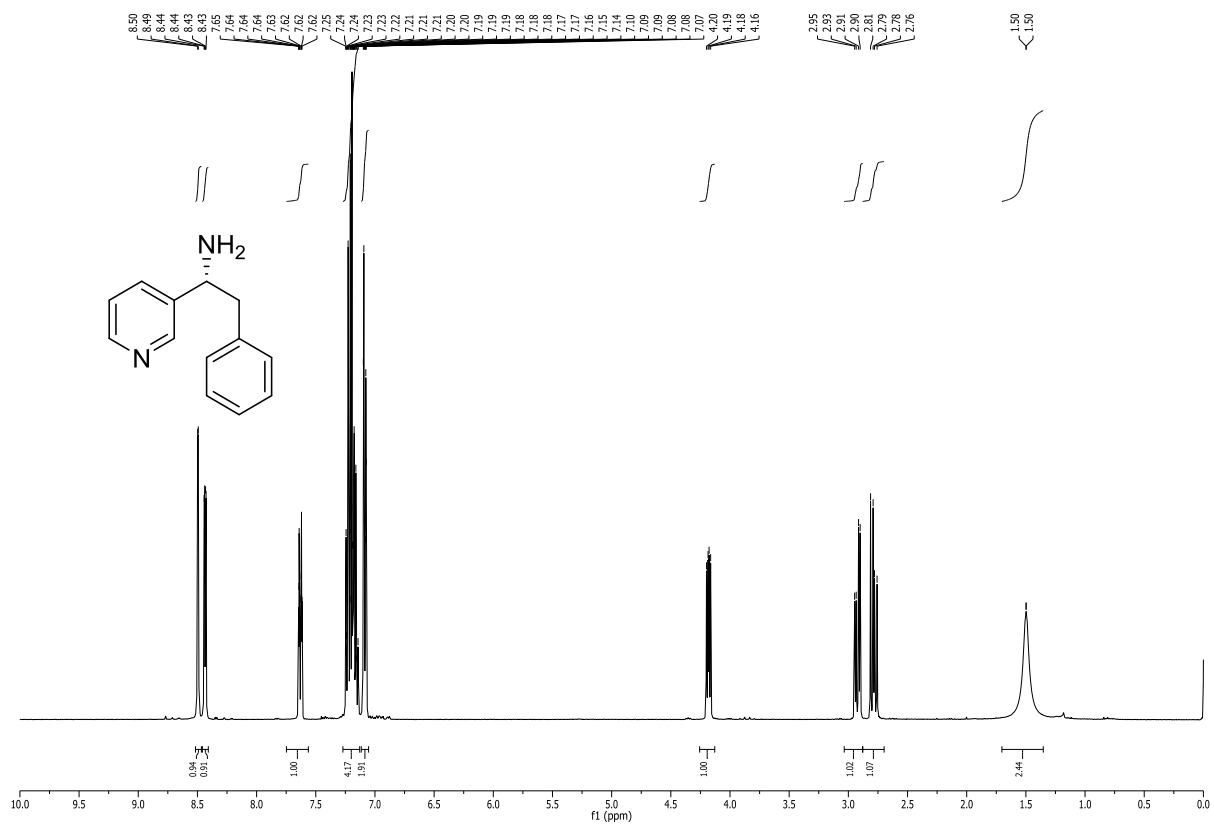
(*R,S*)-3b



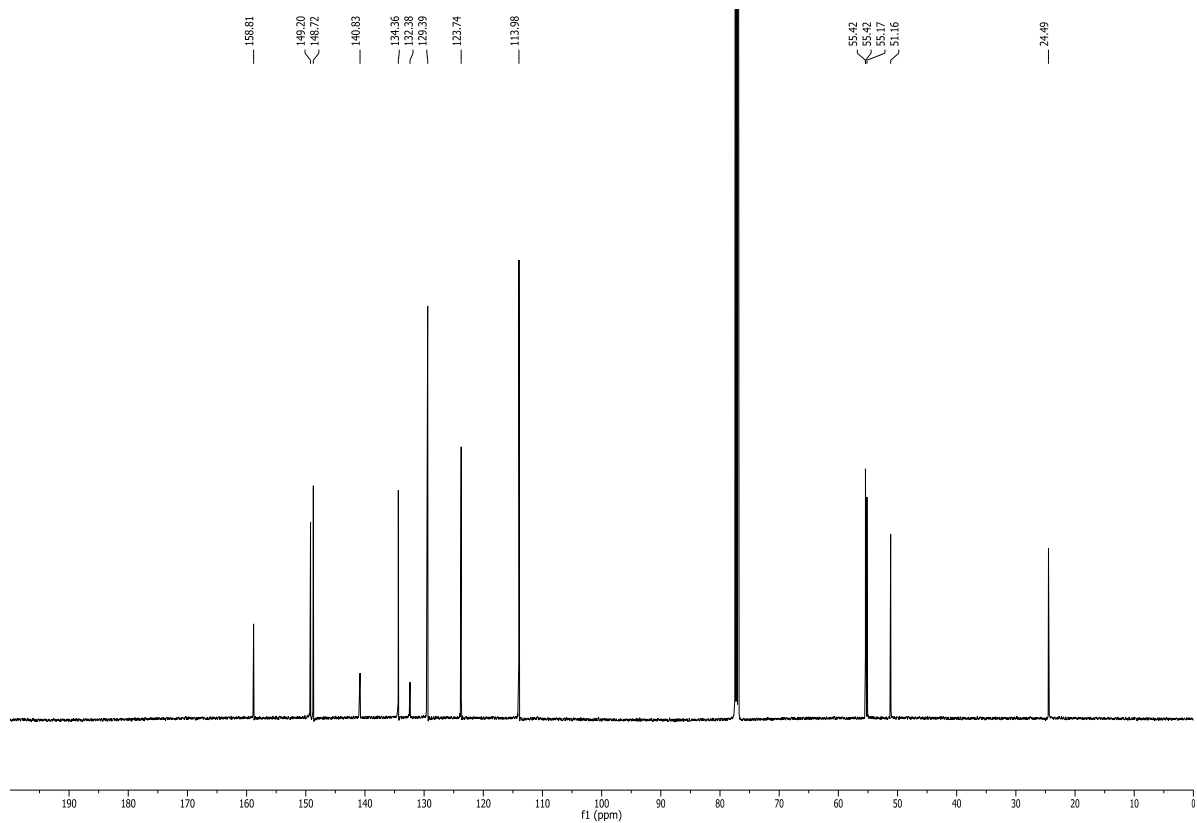
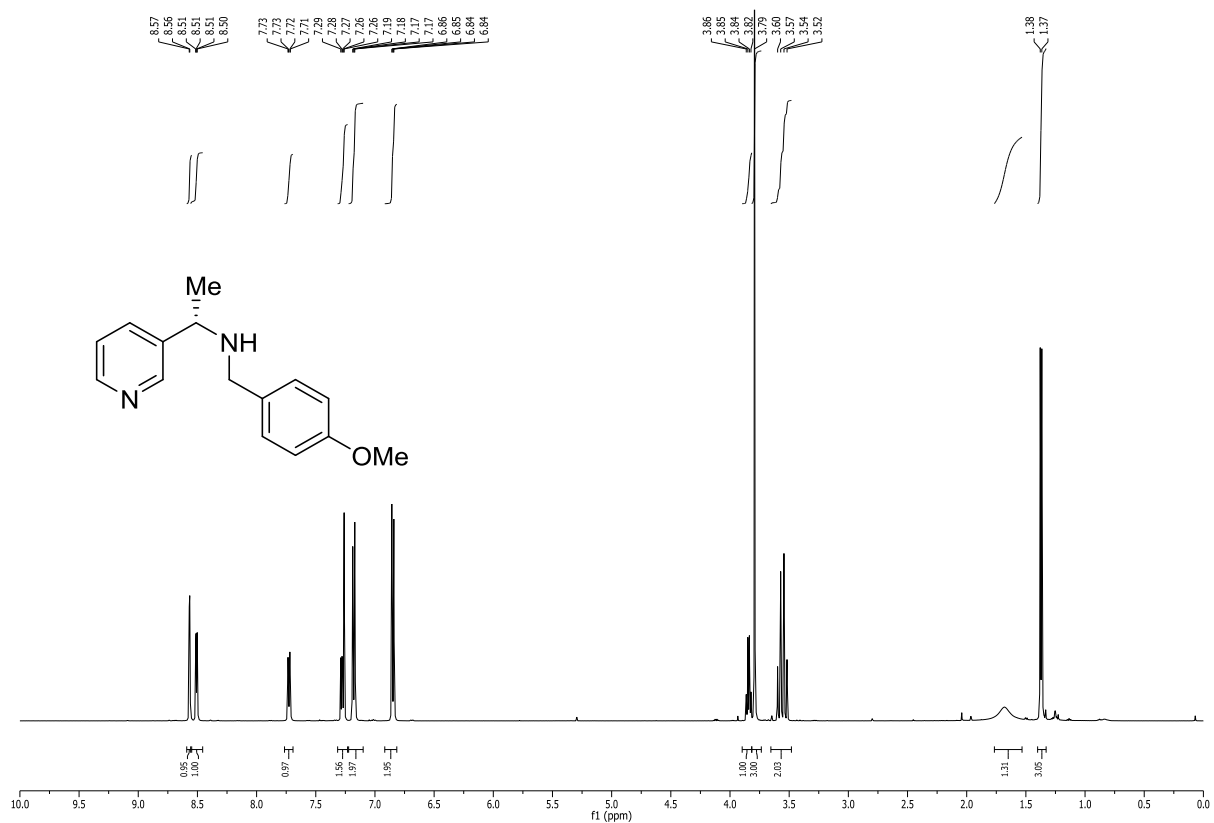
5a



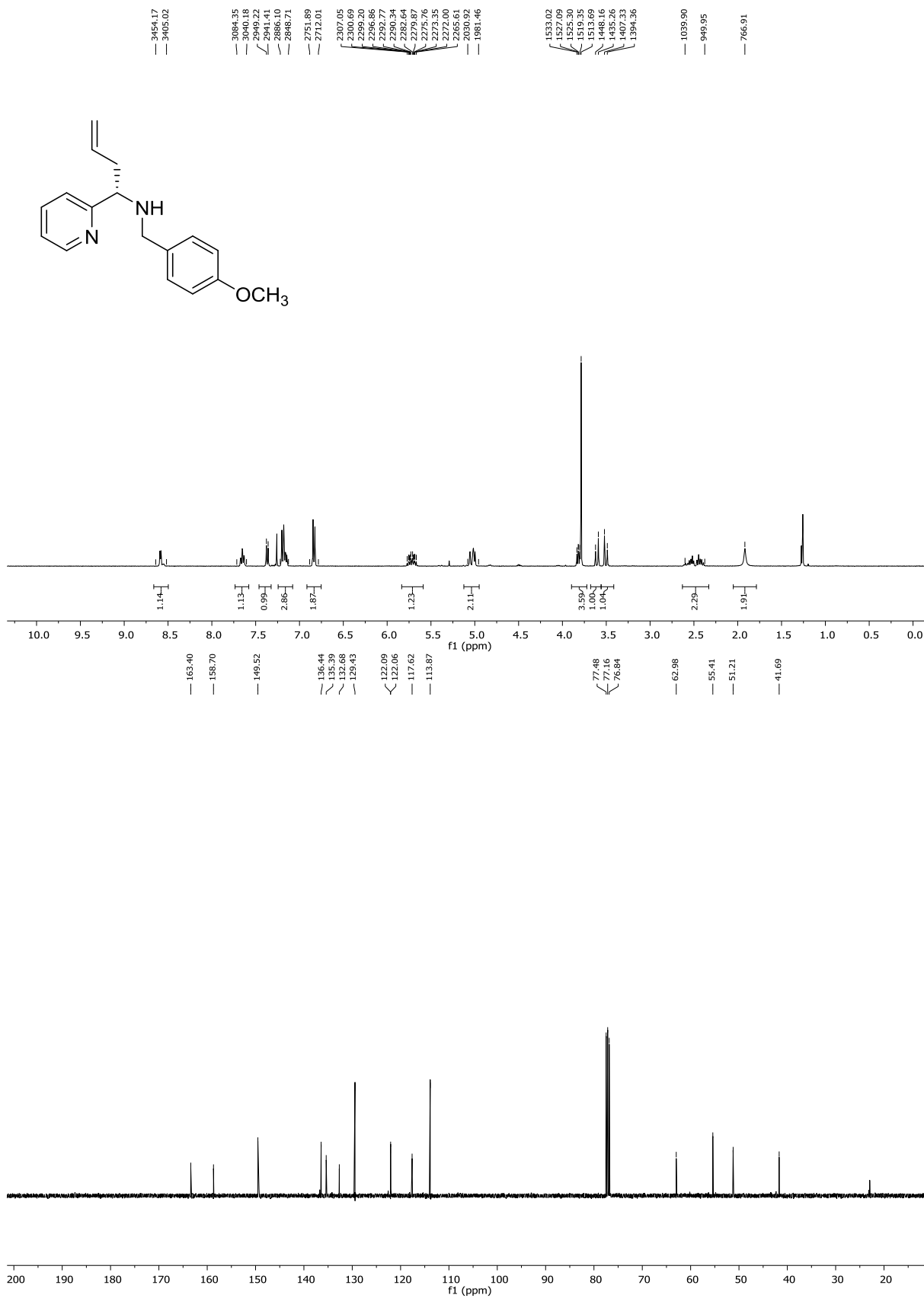
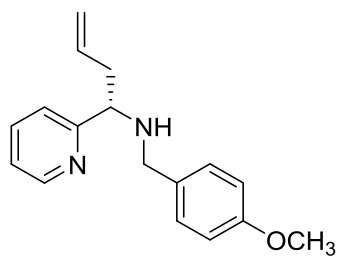
5b



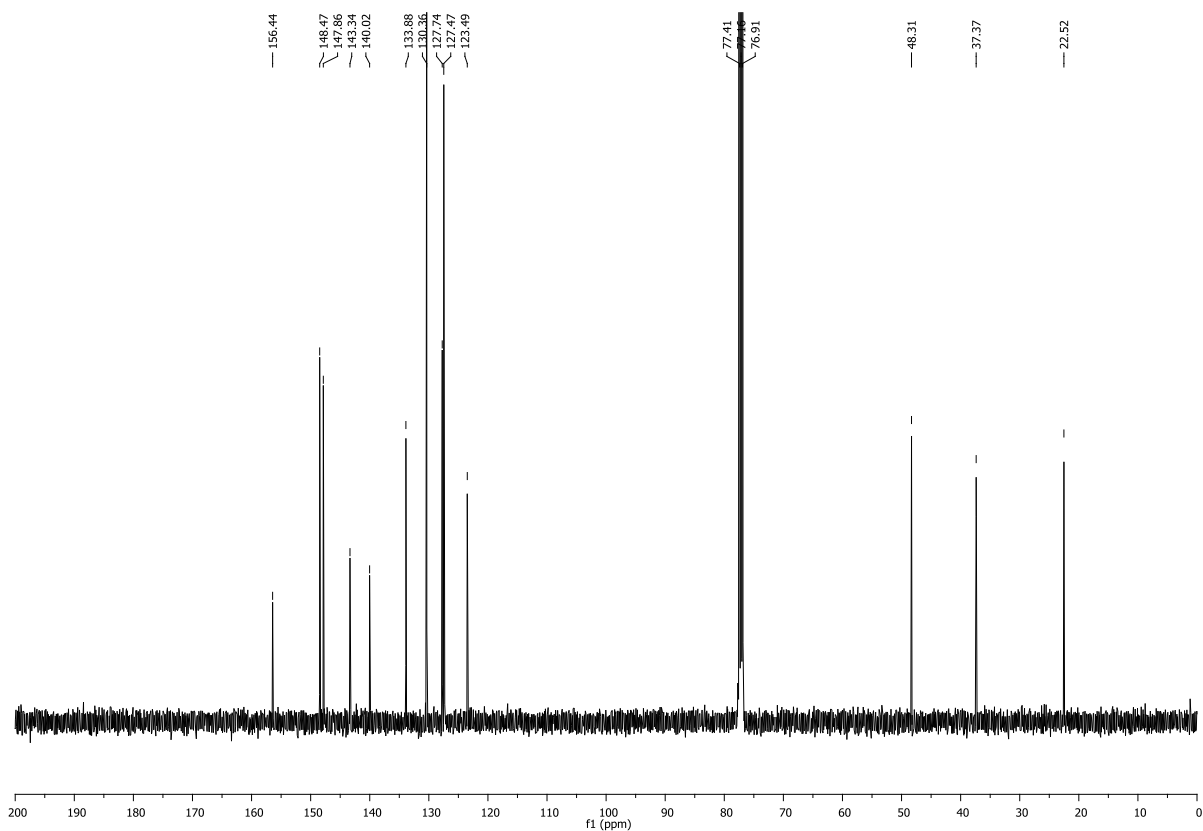
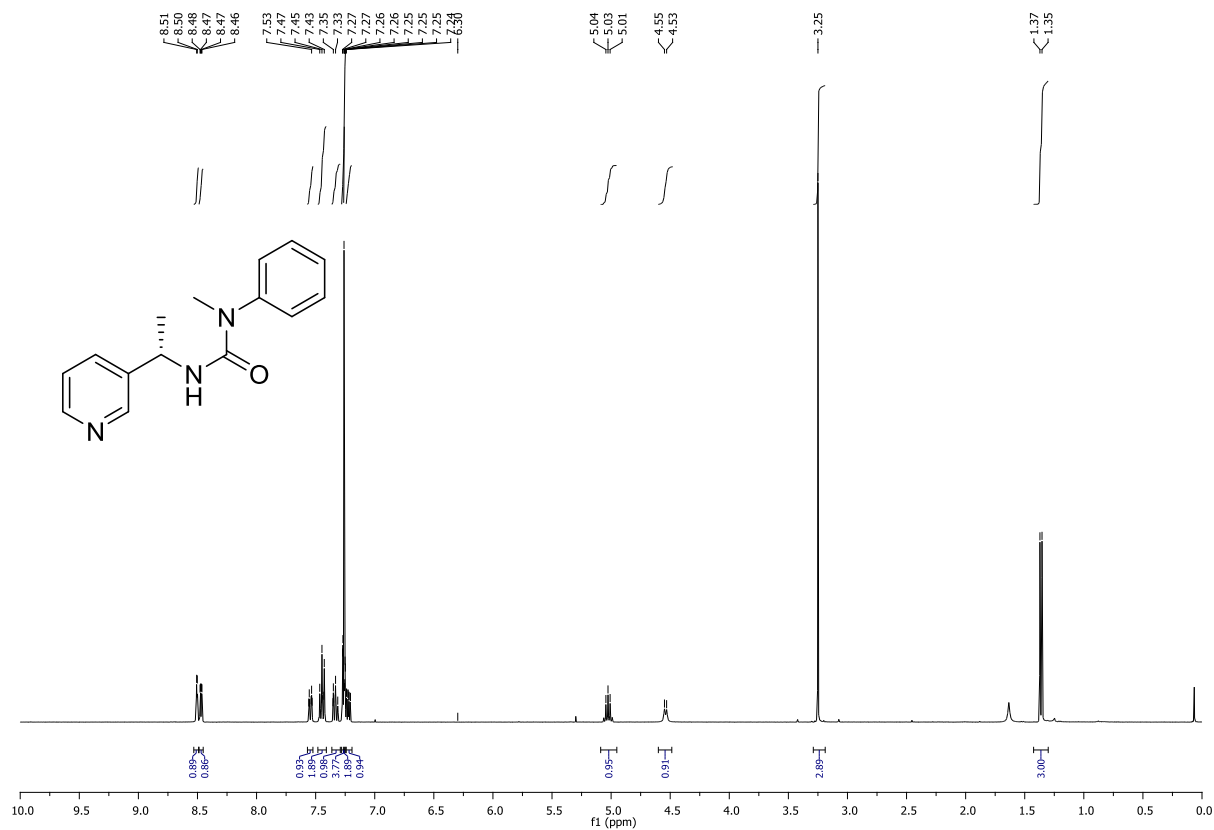
5c



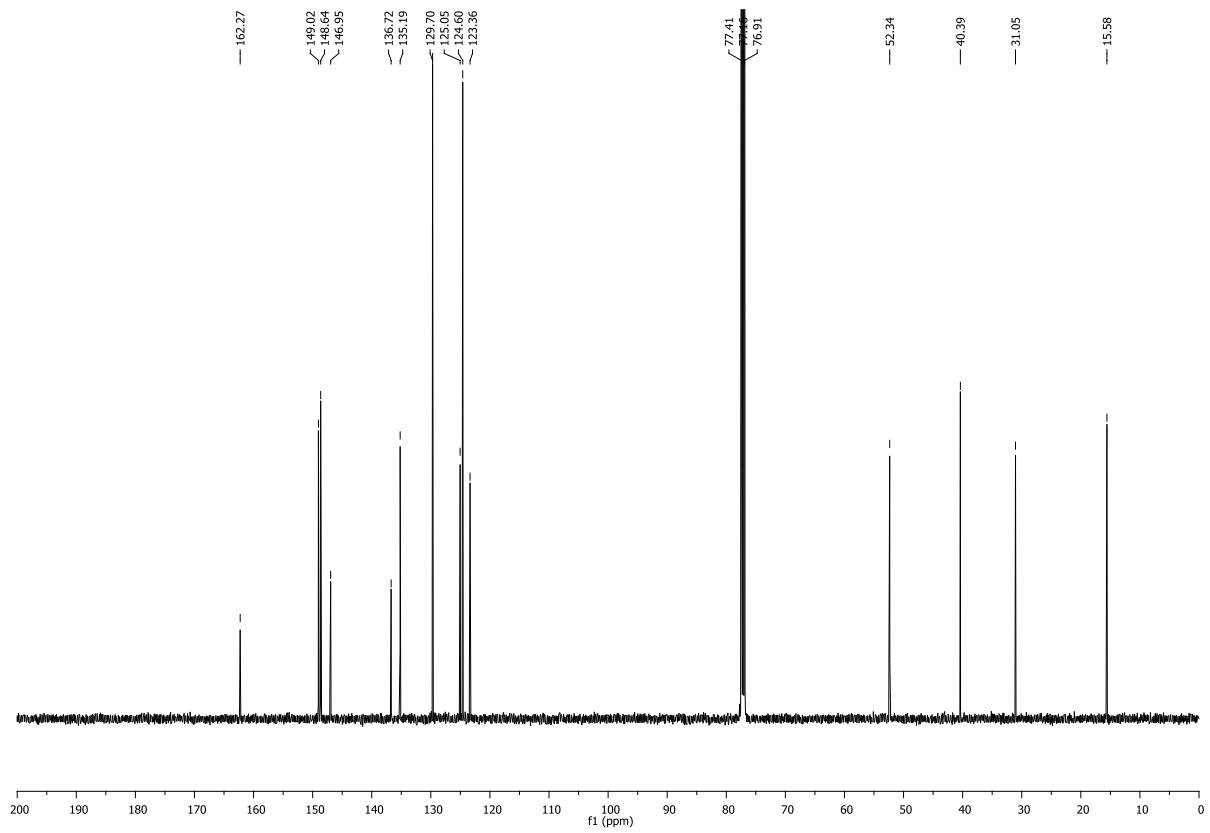
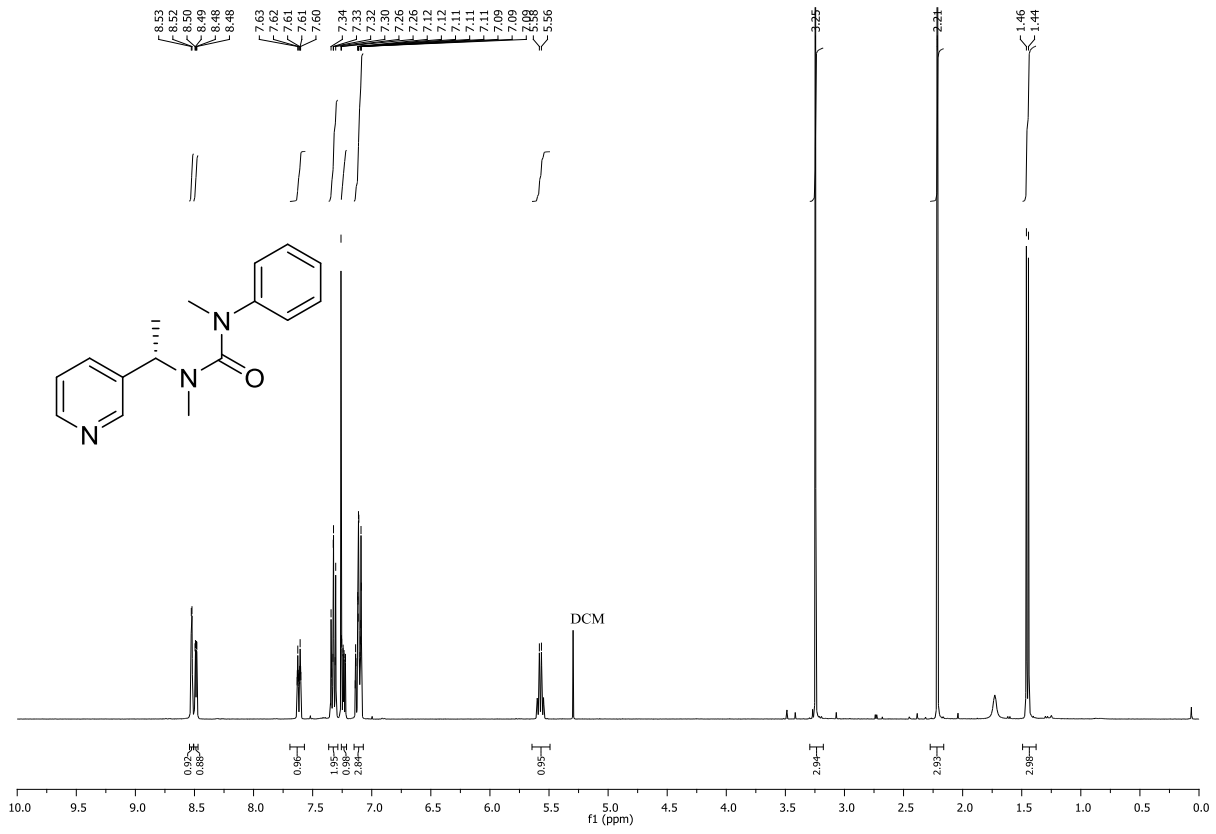
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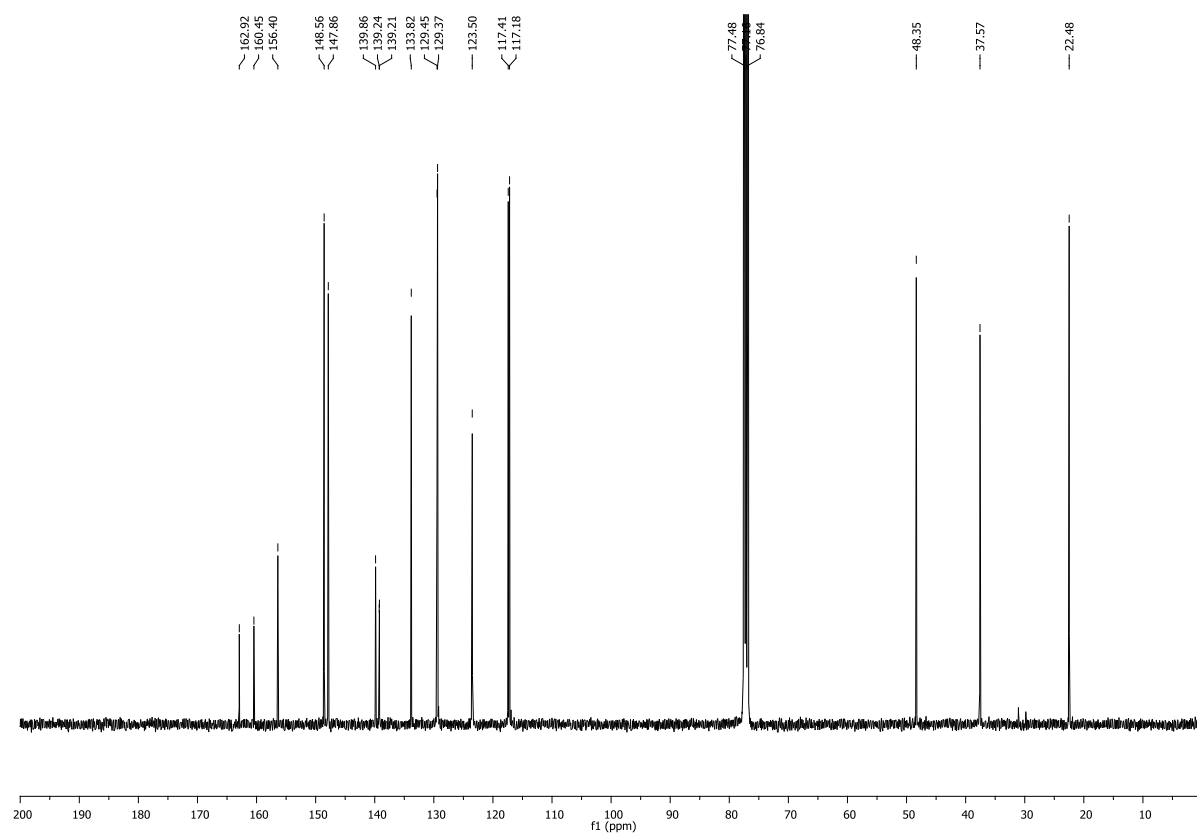
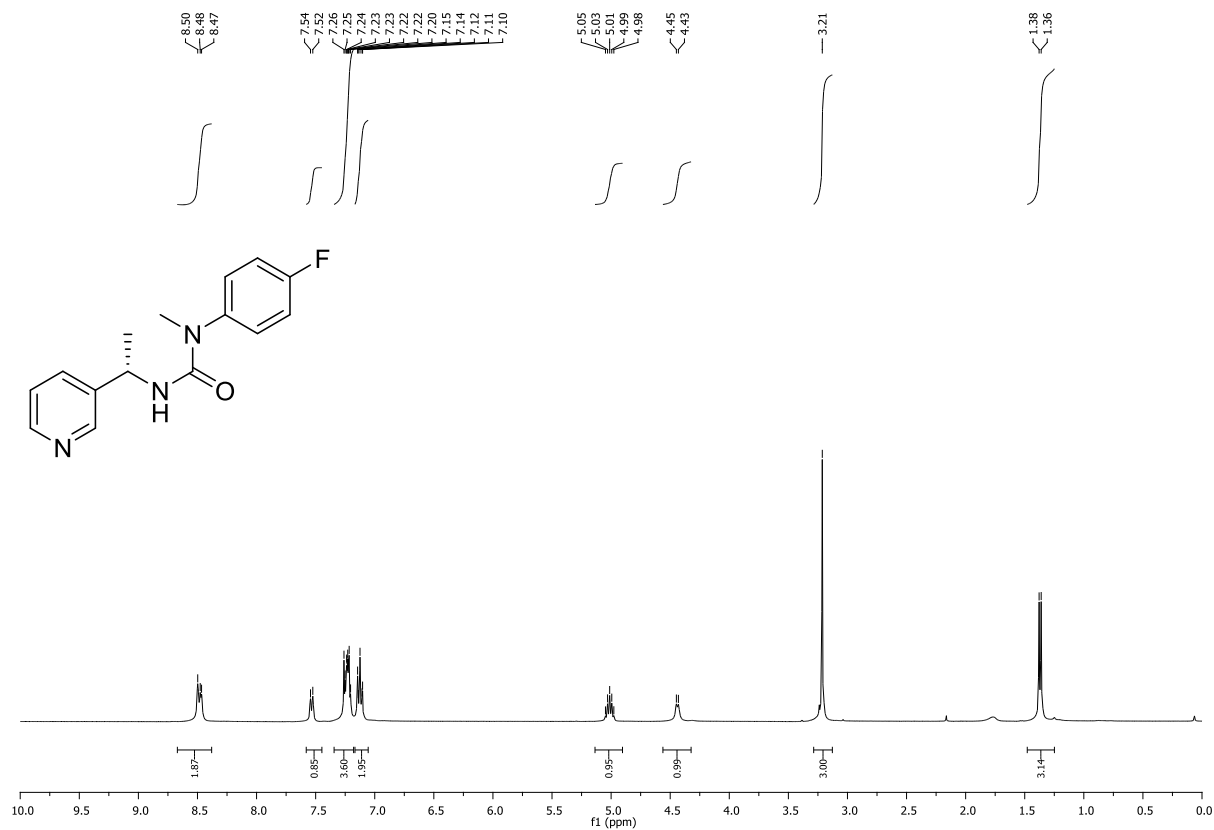
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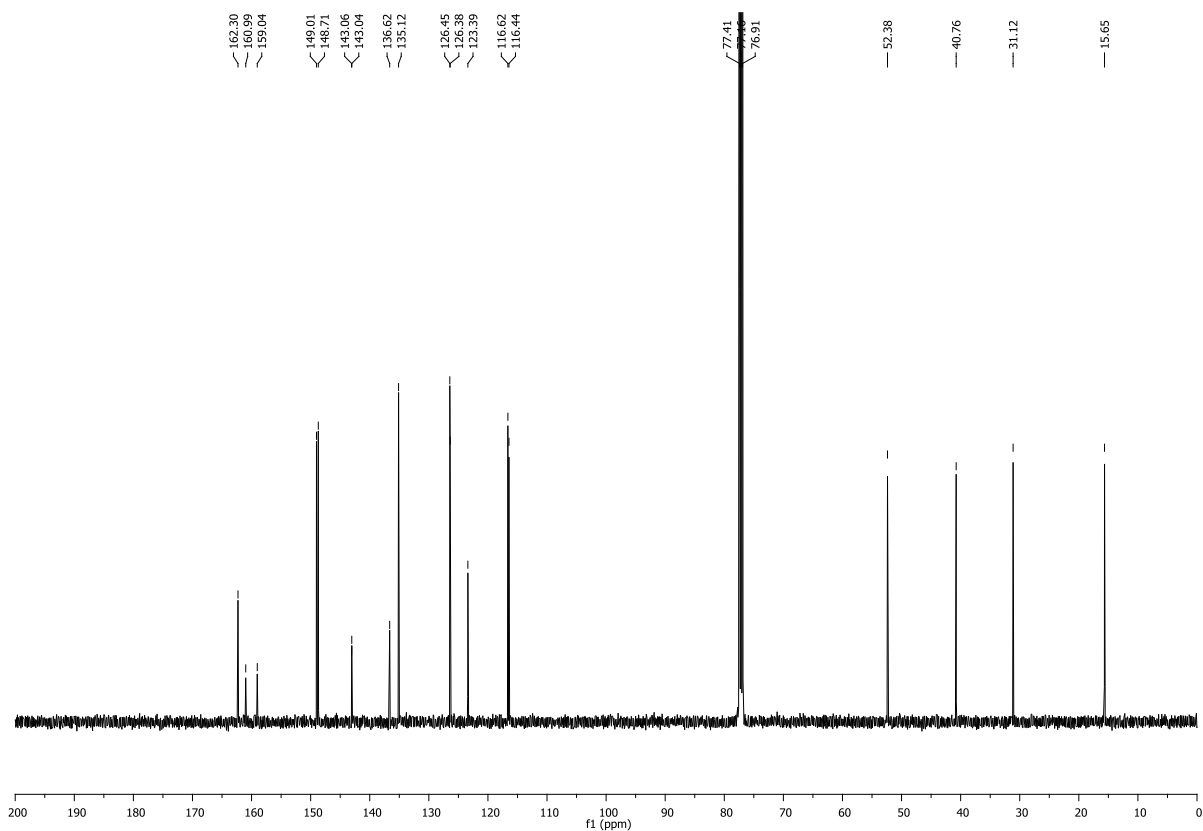
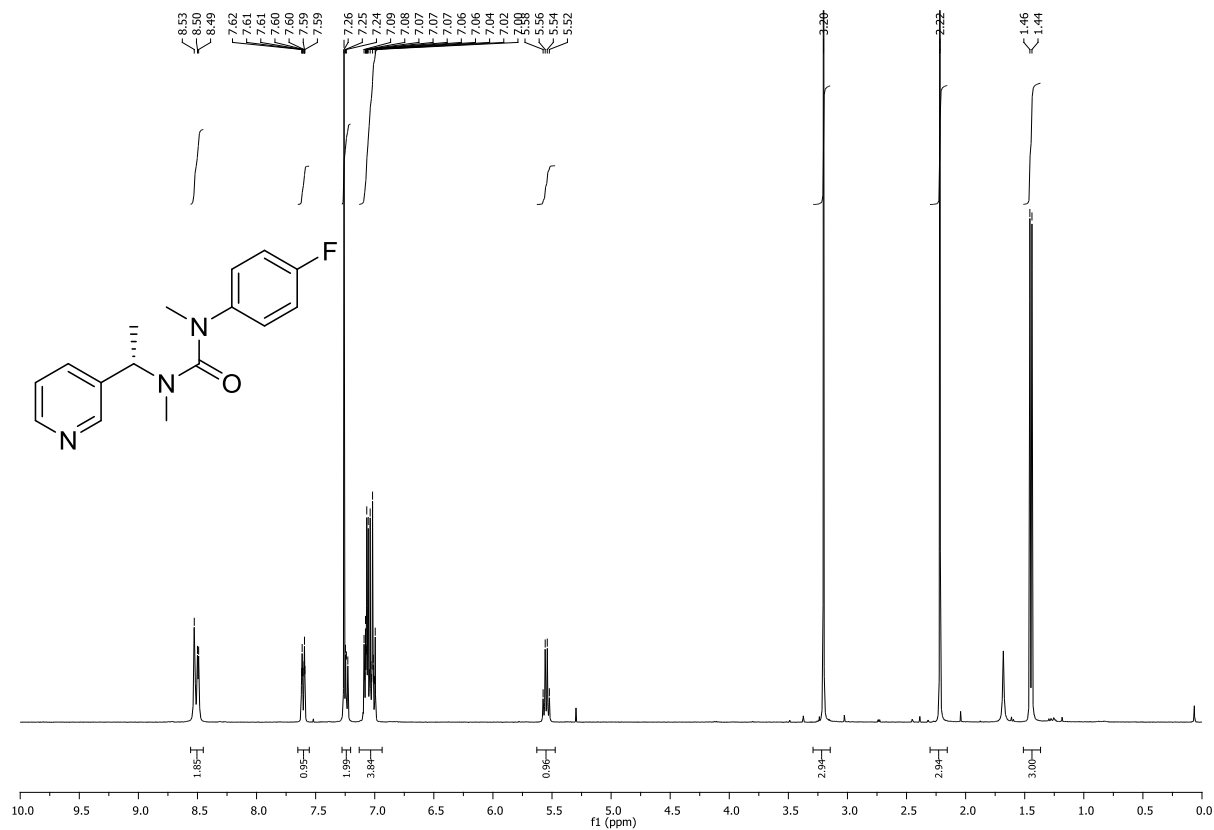
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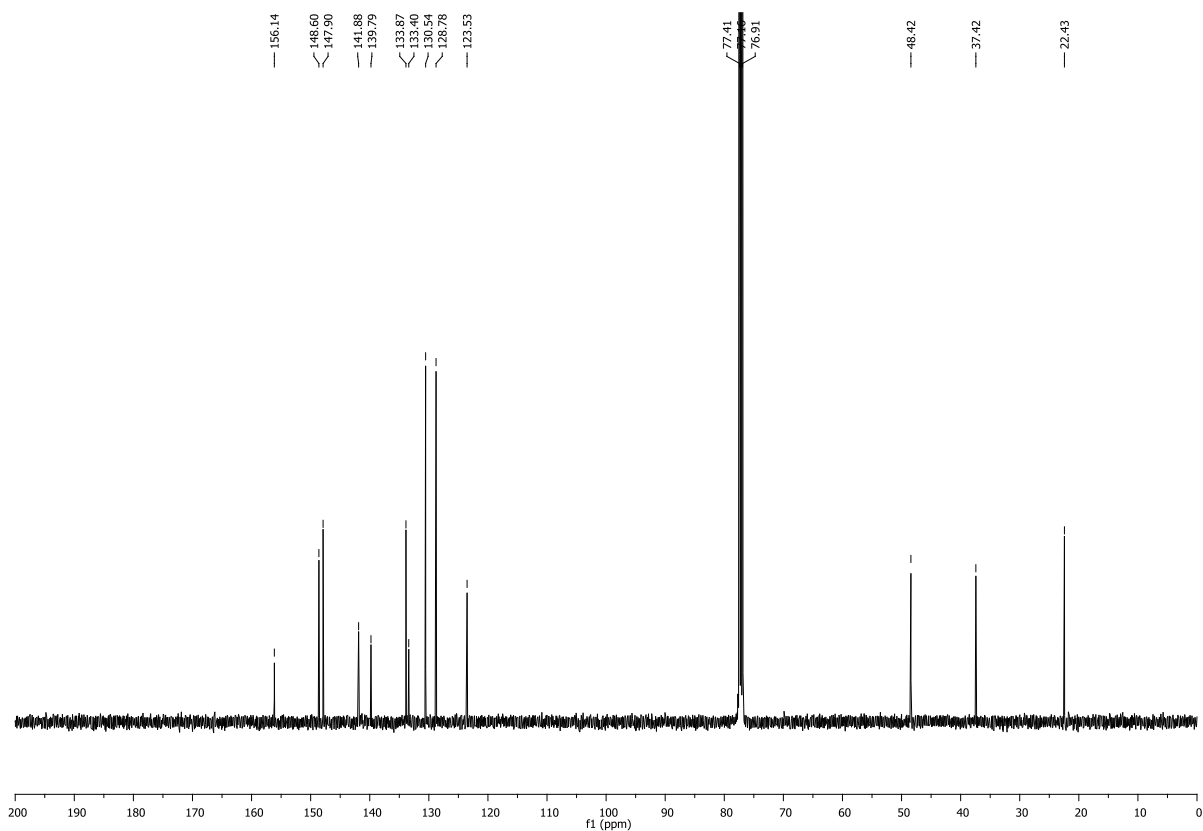
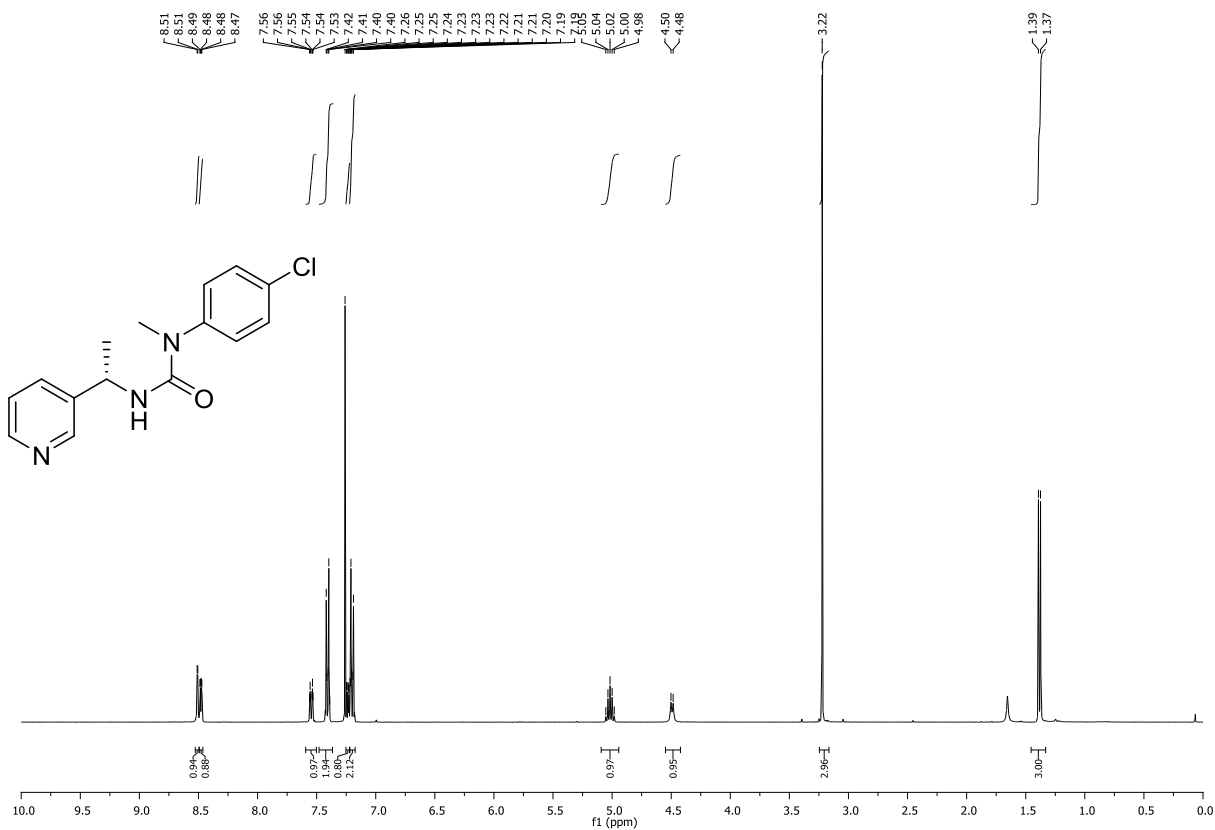
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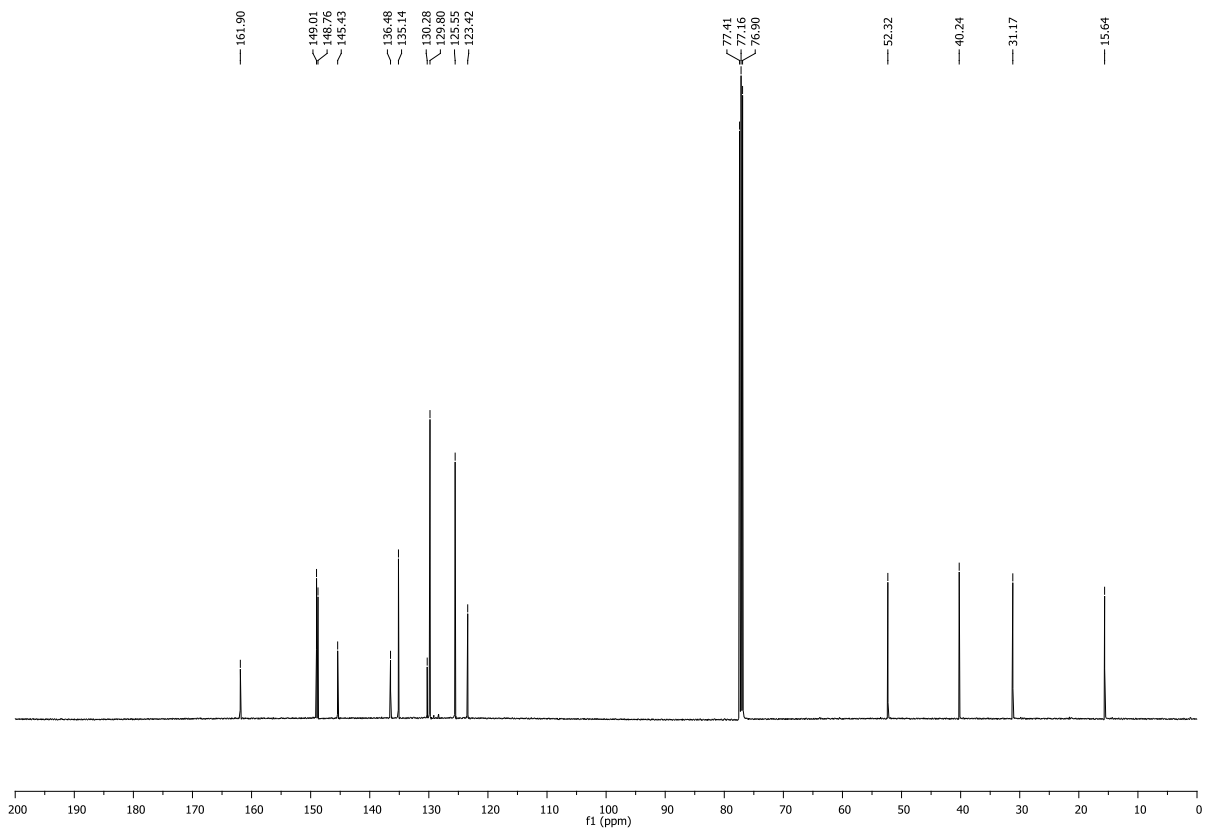
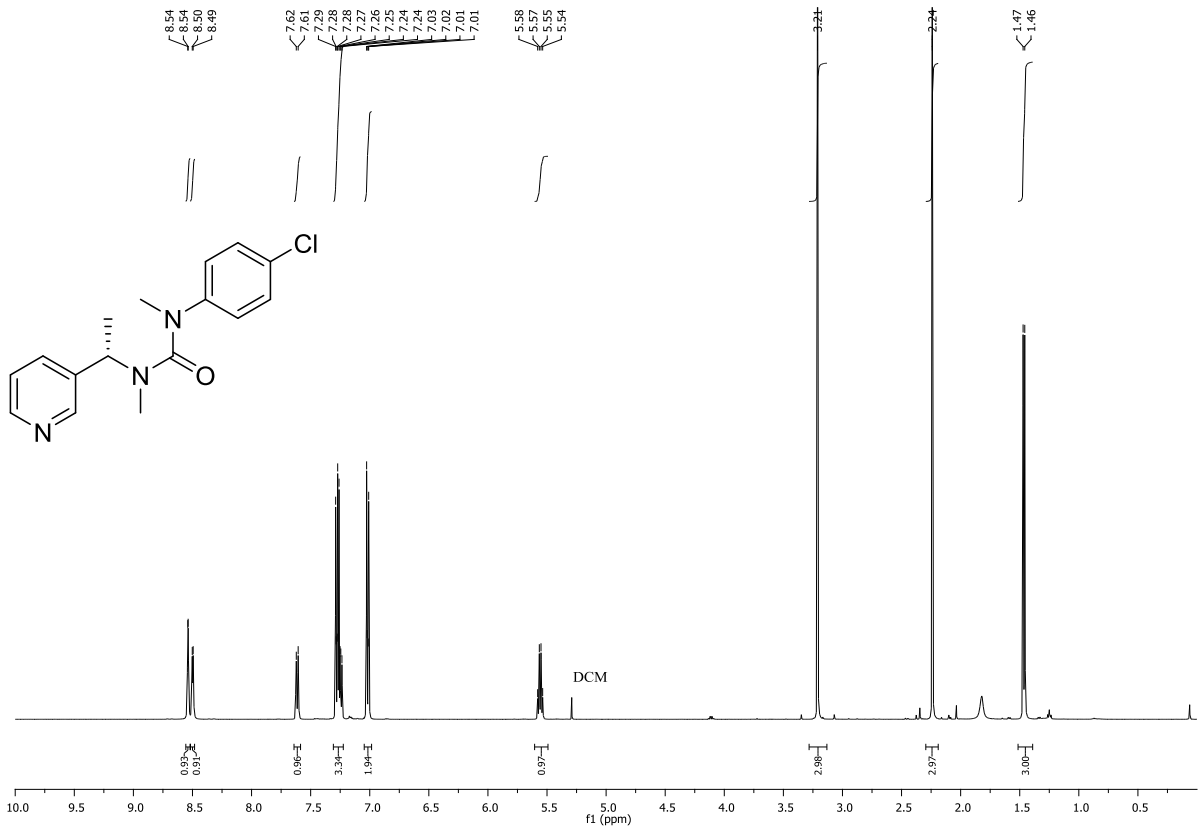
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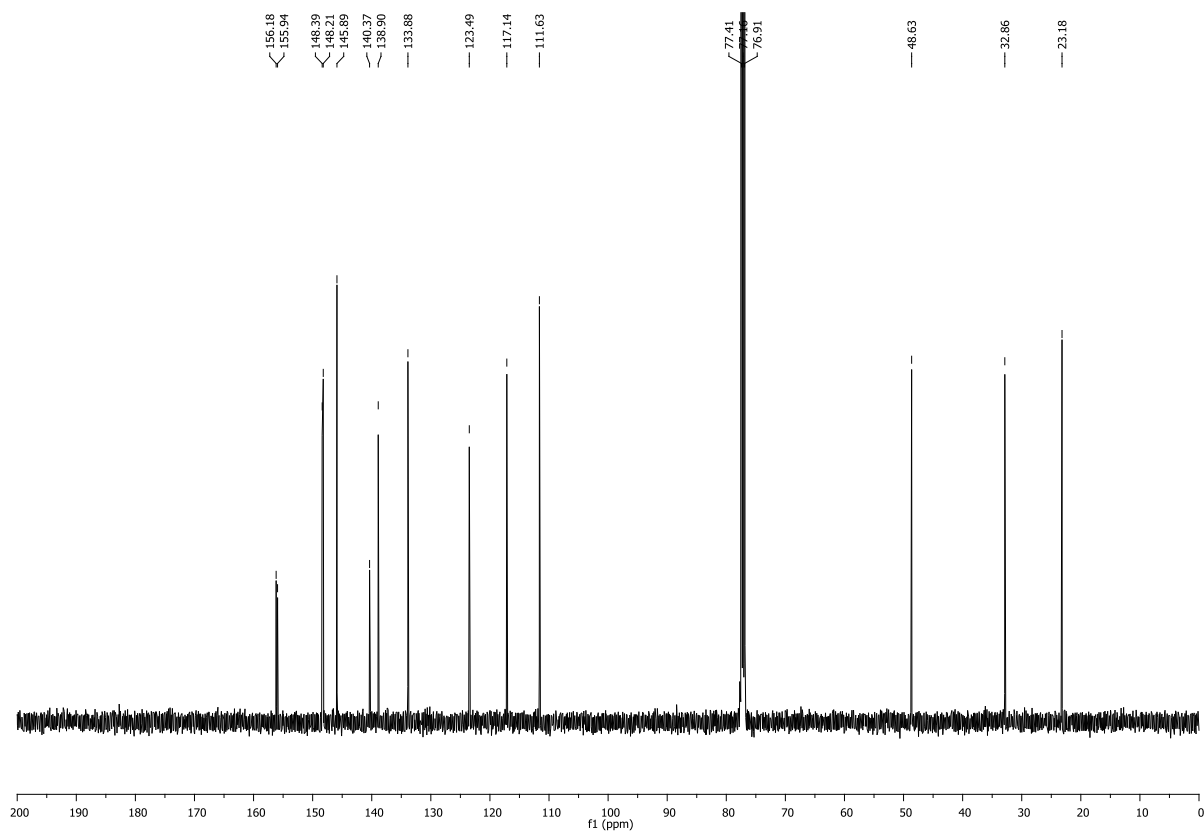
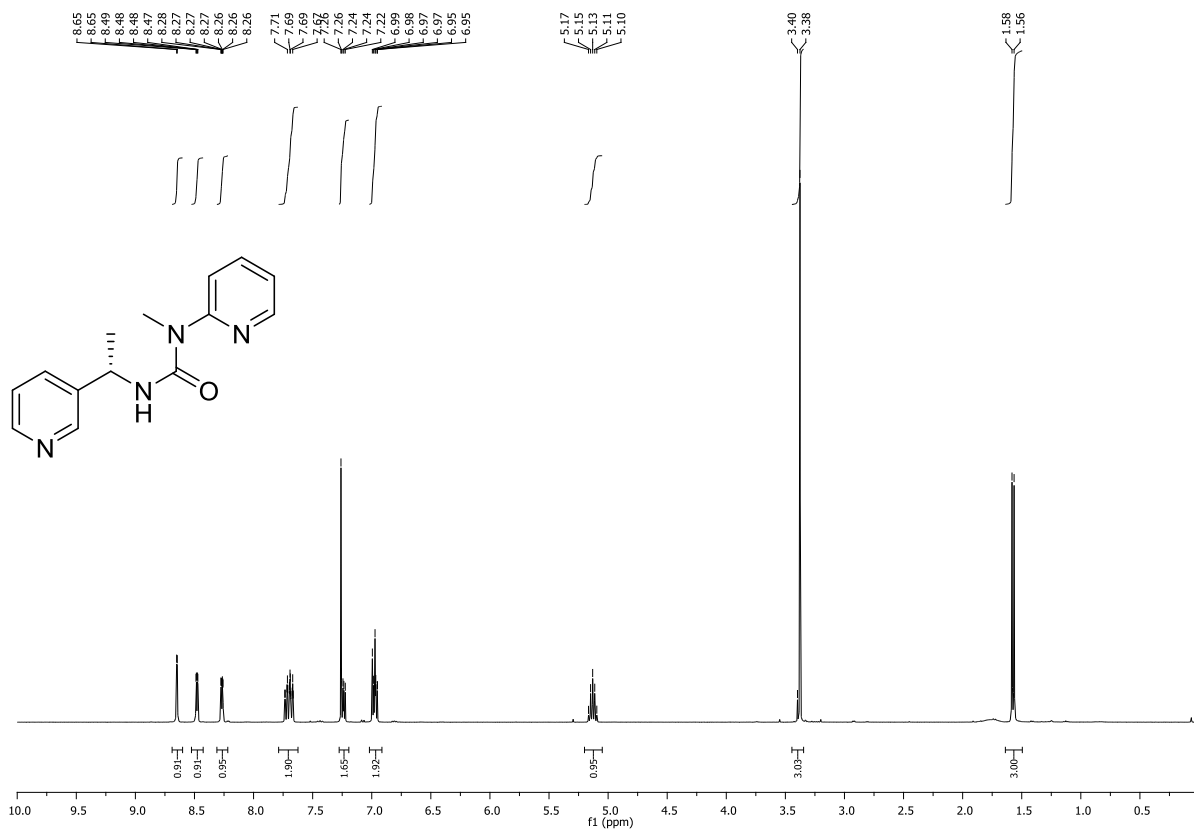
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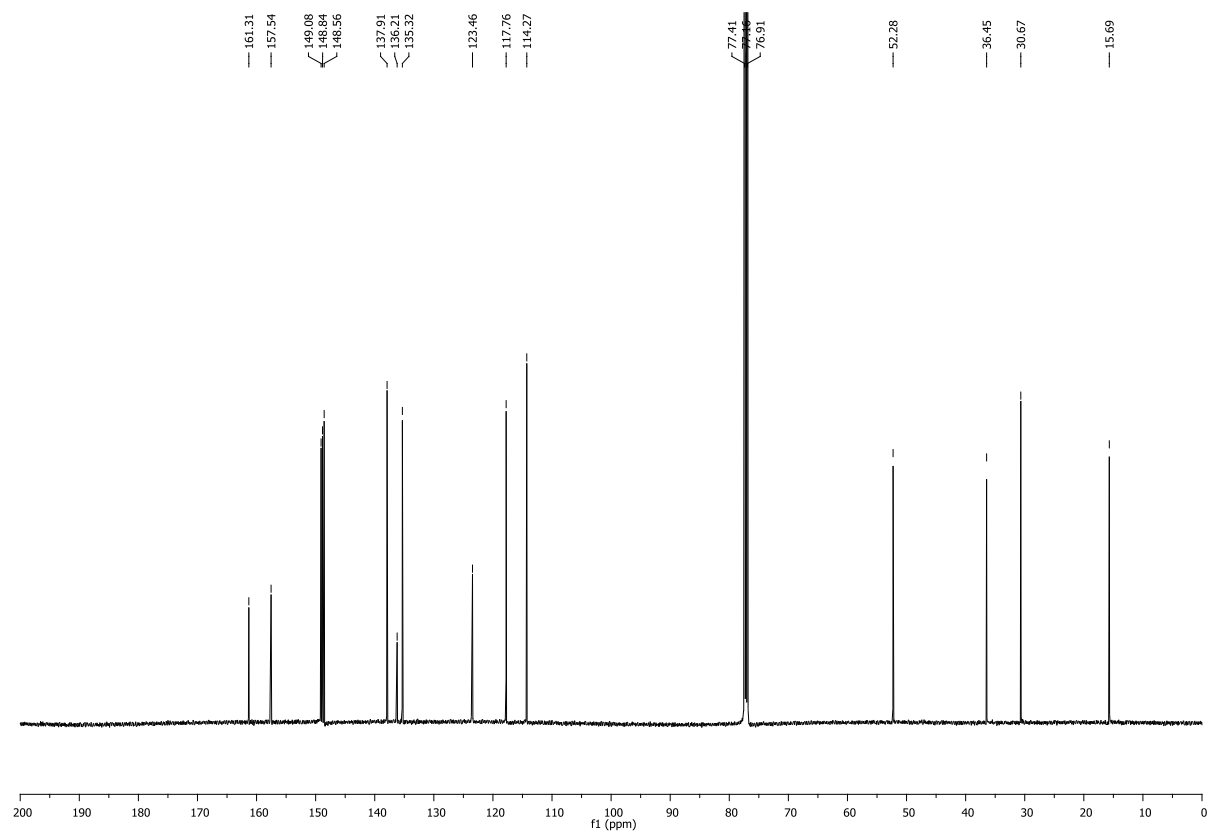
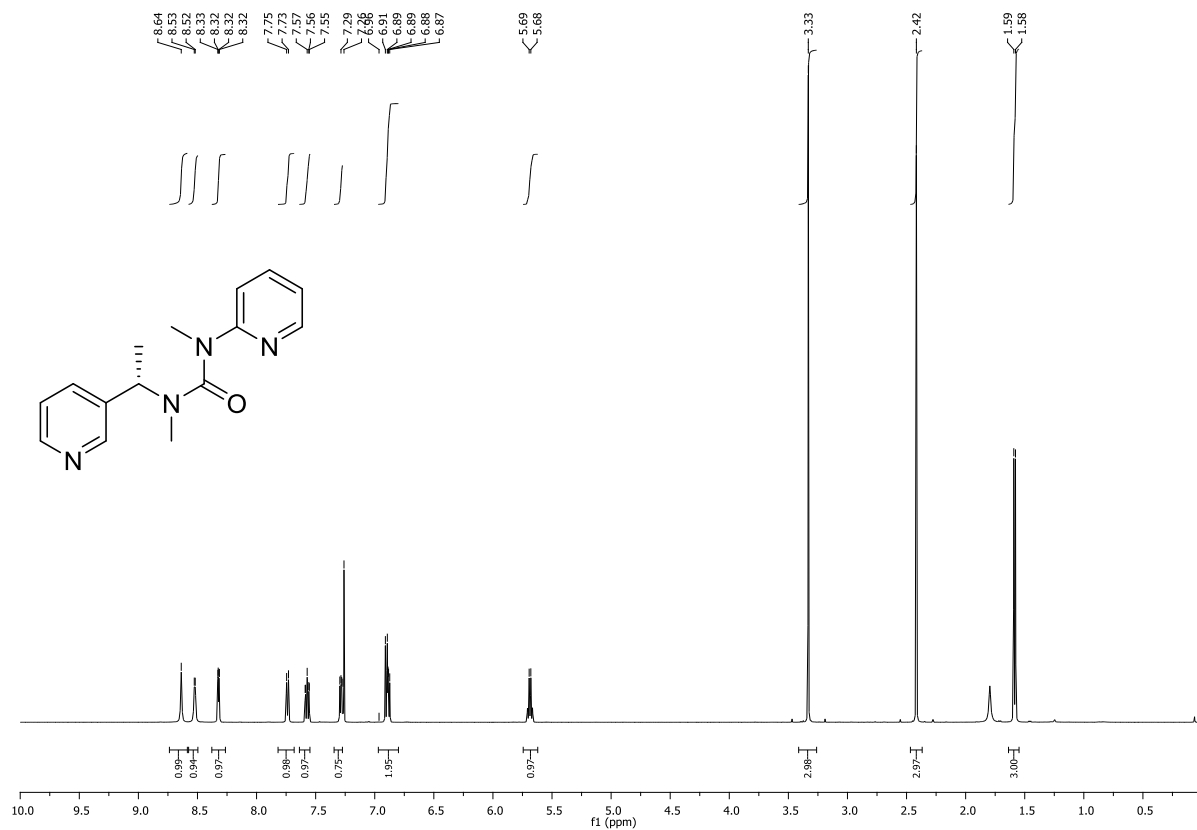
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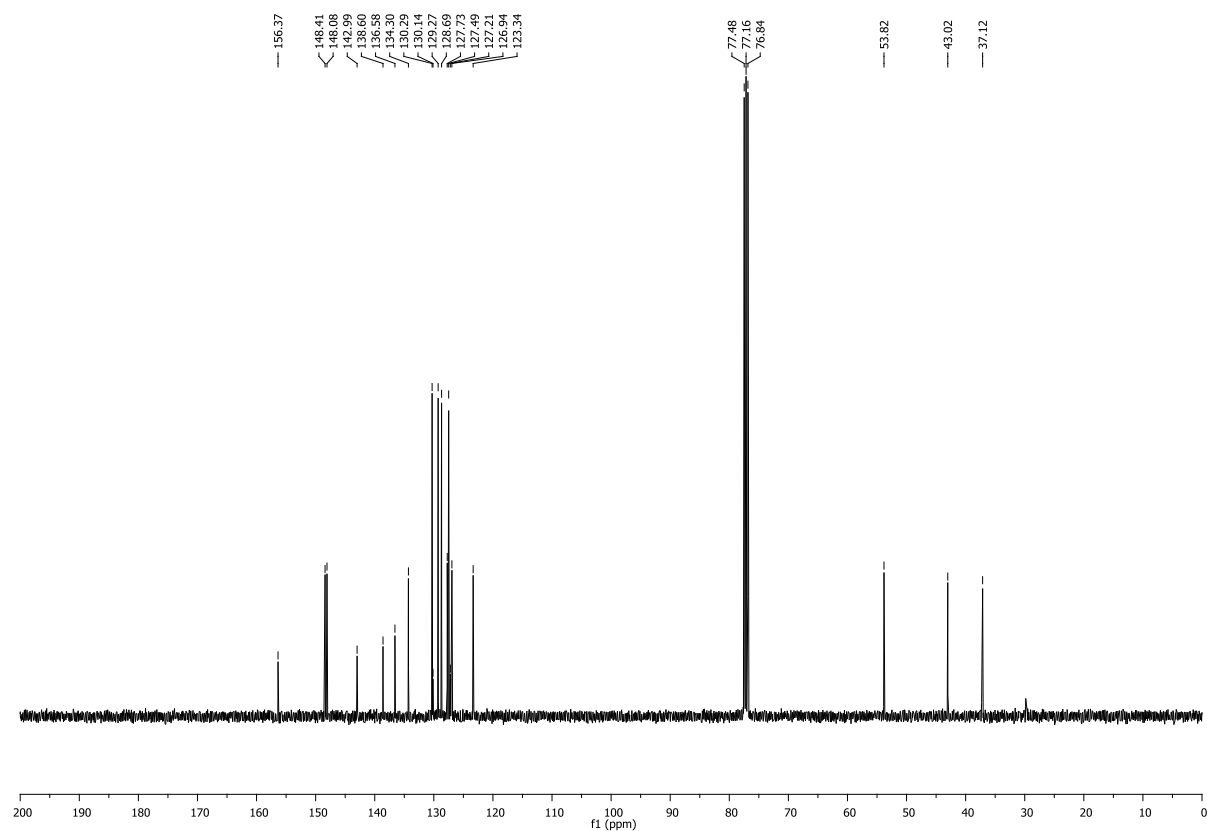
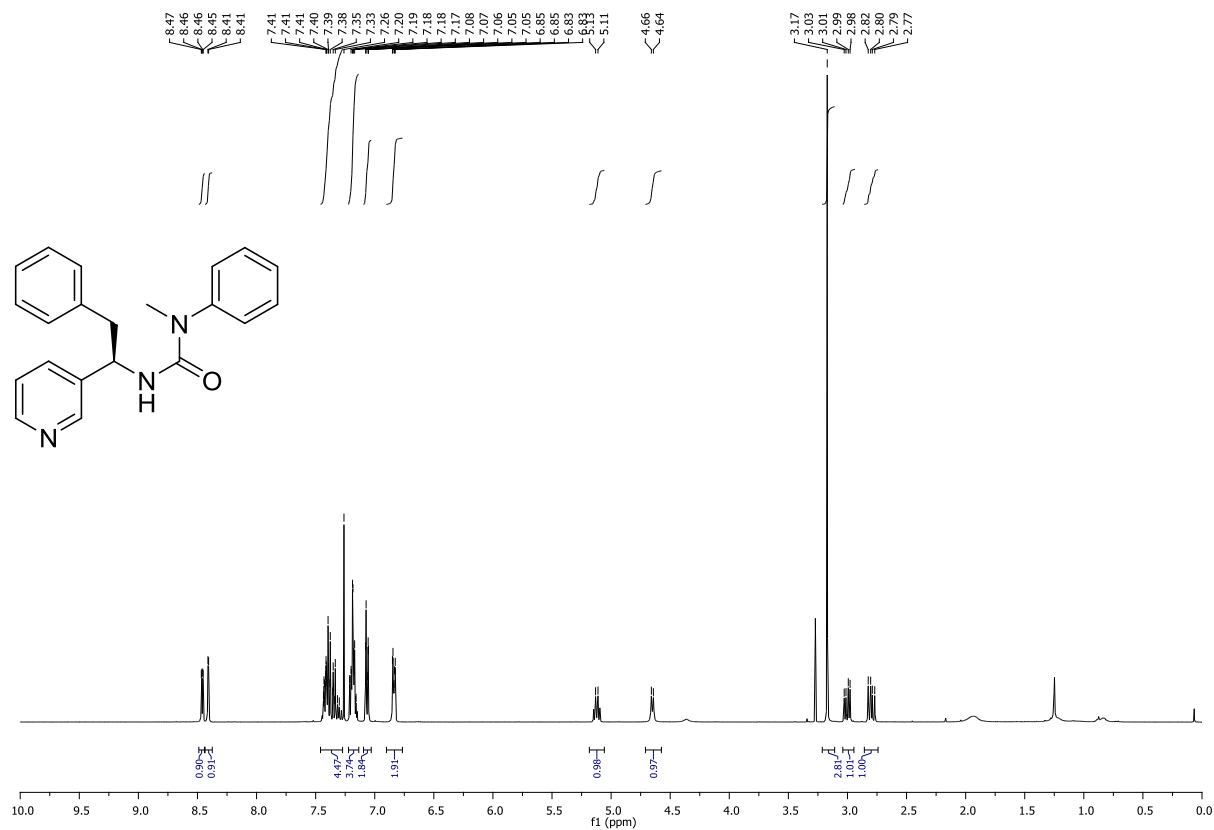
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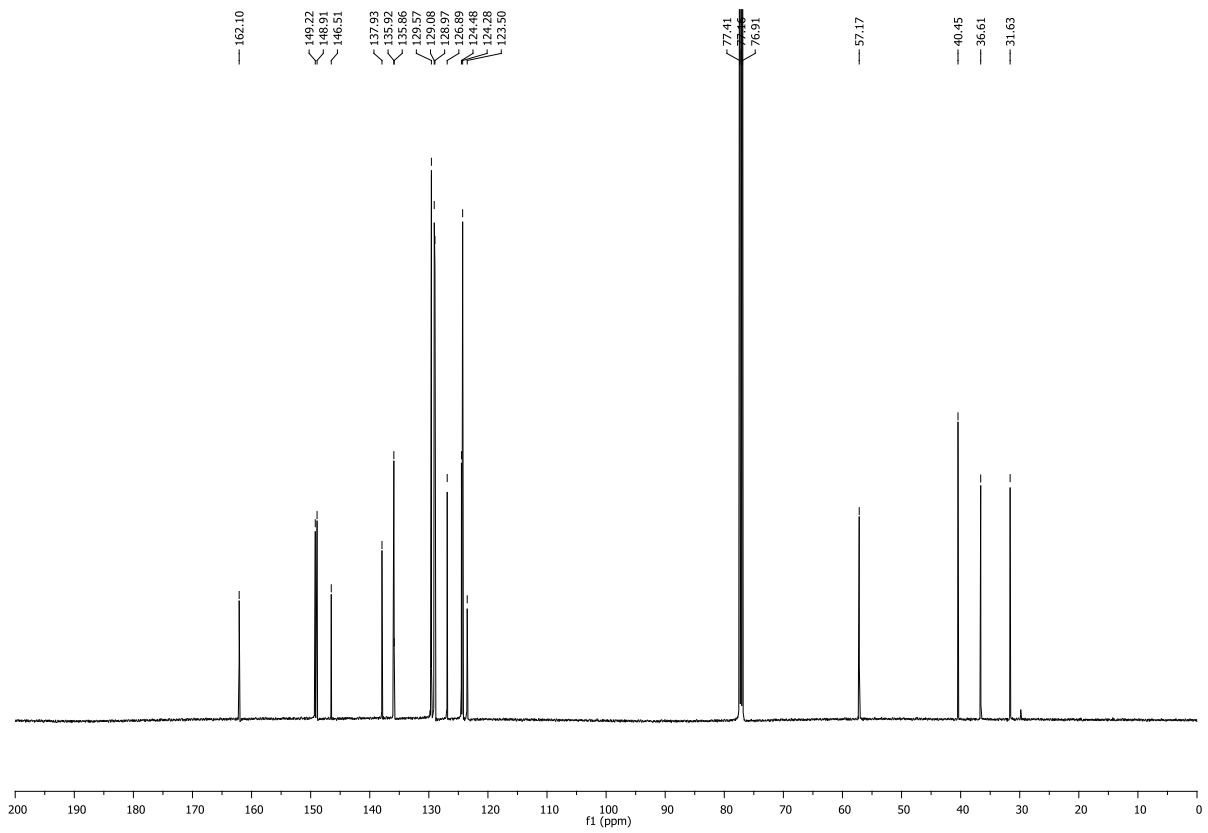
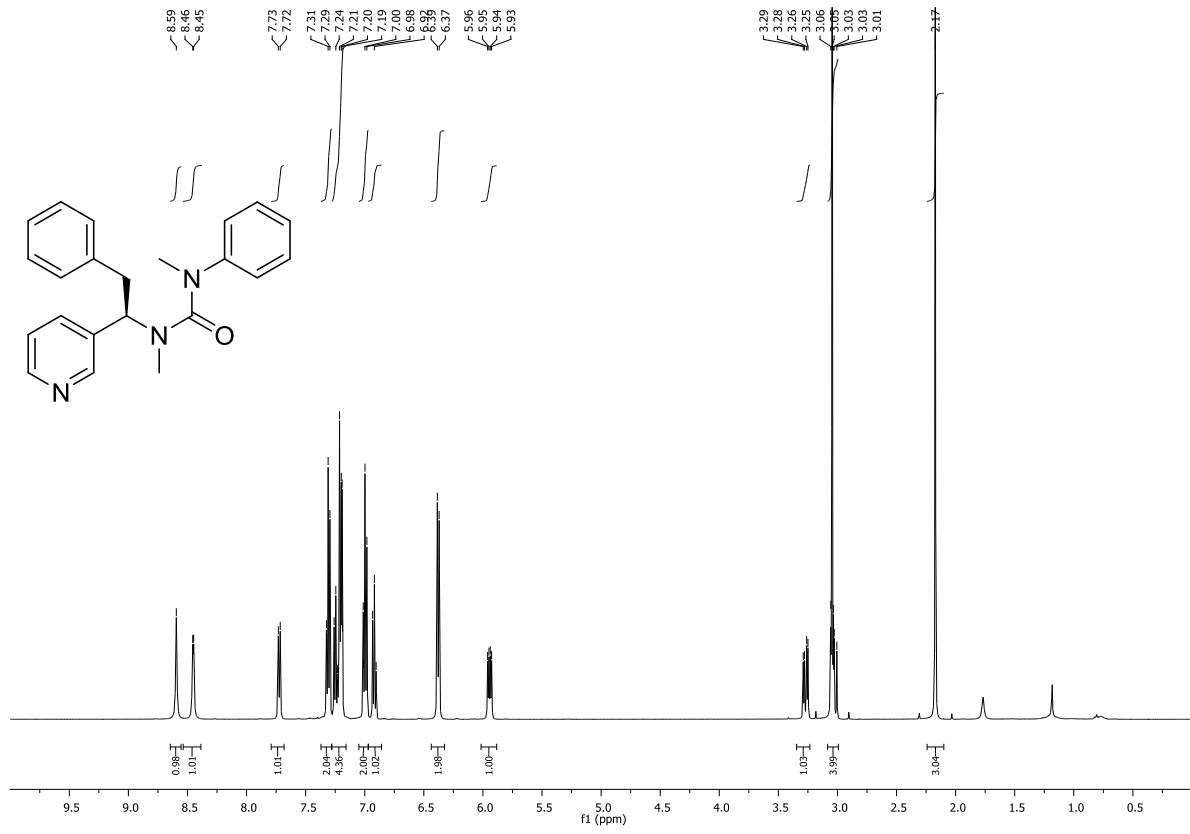
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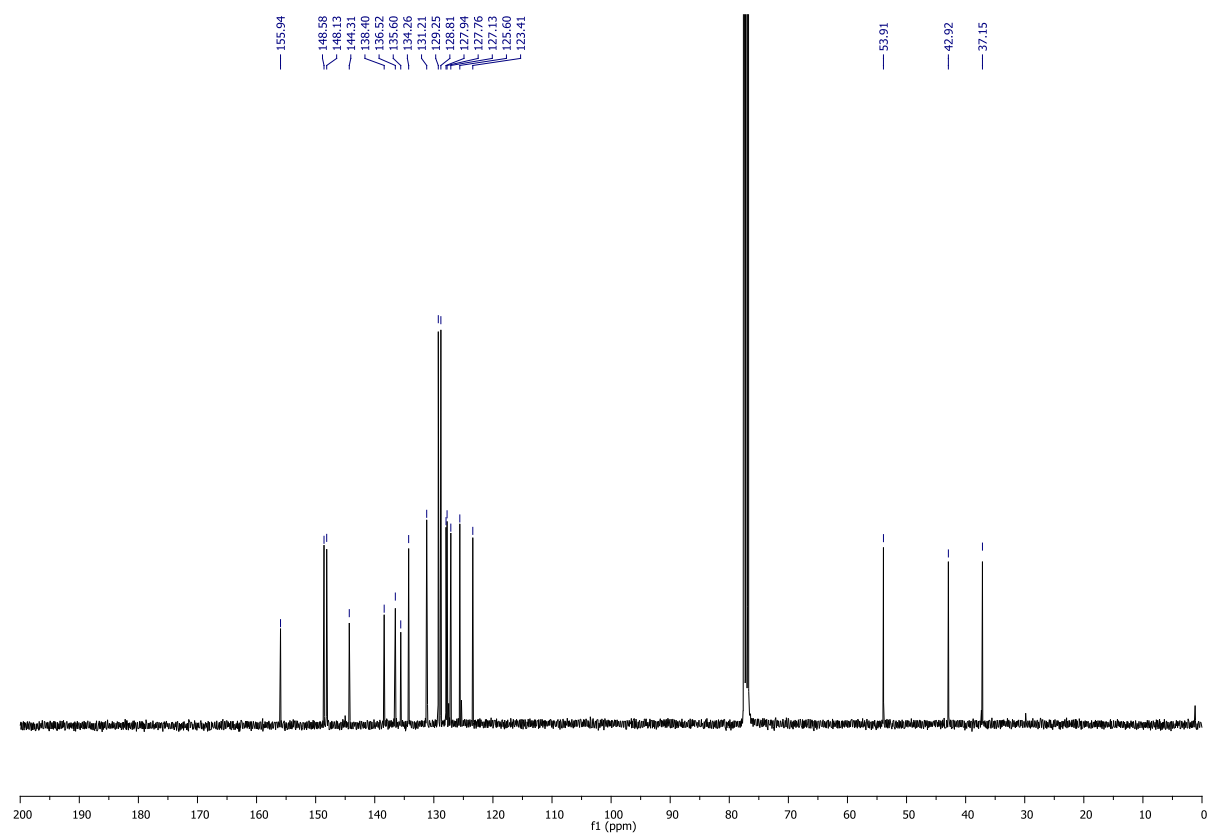
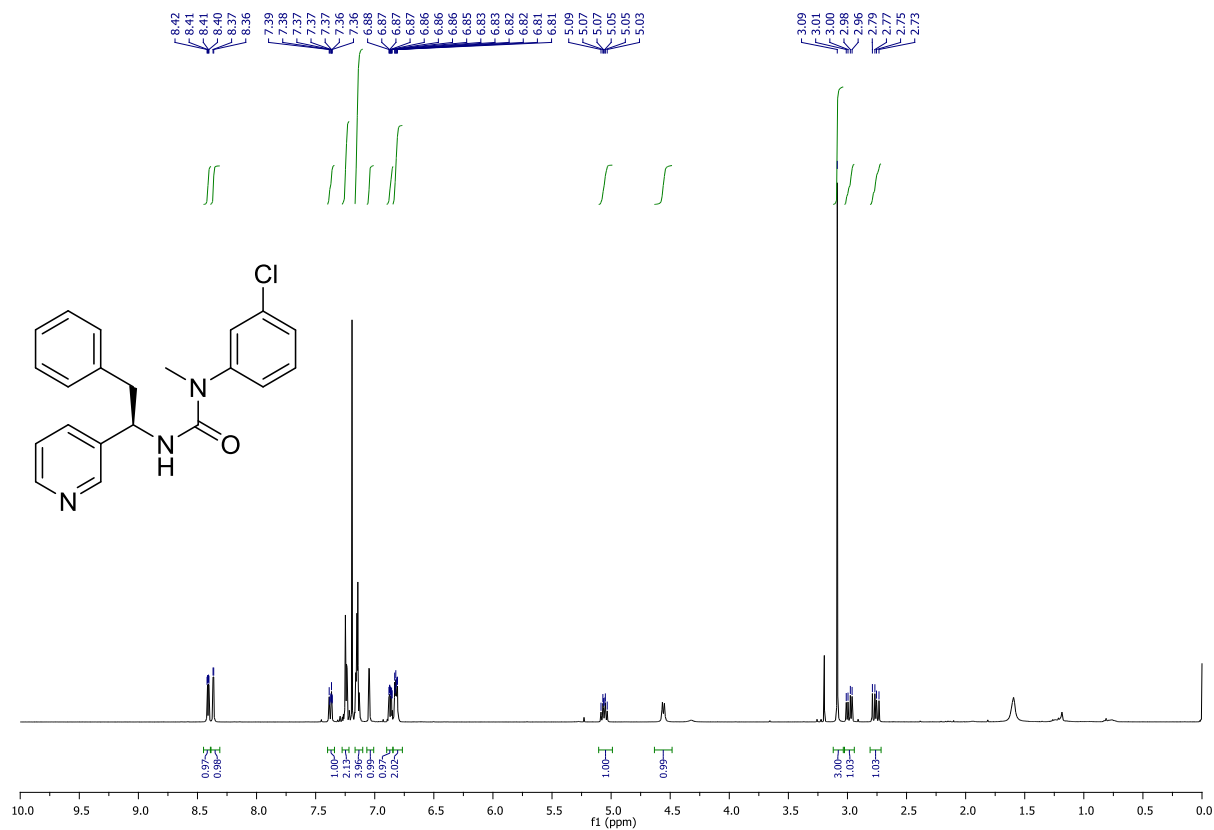
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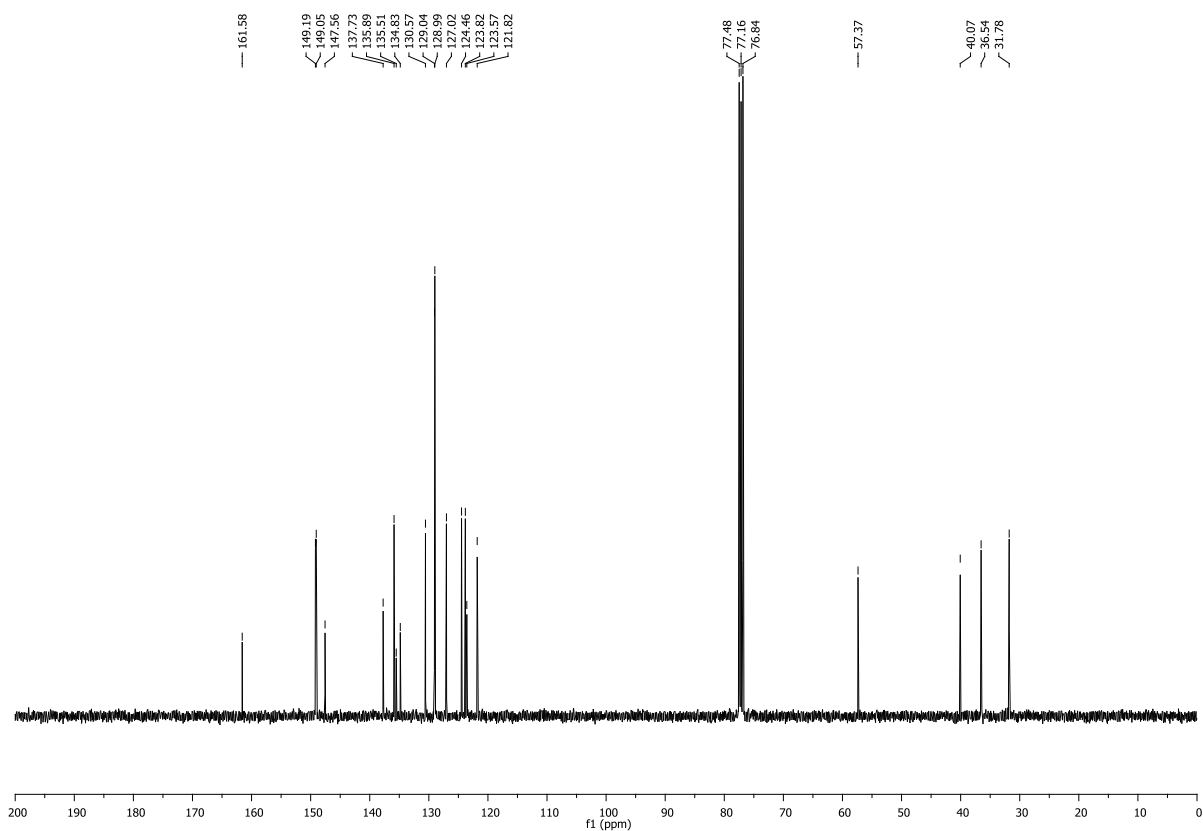
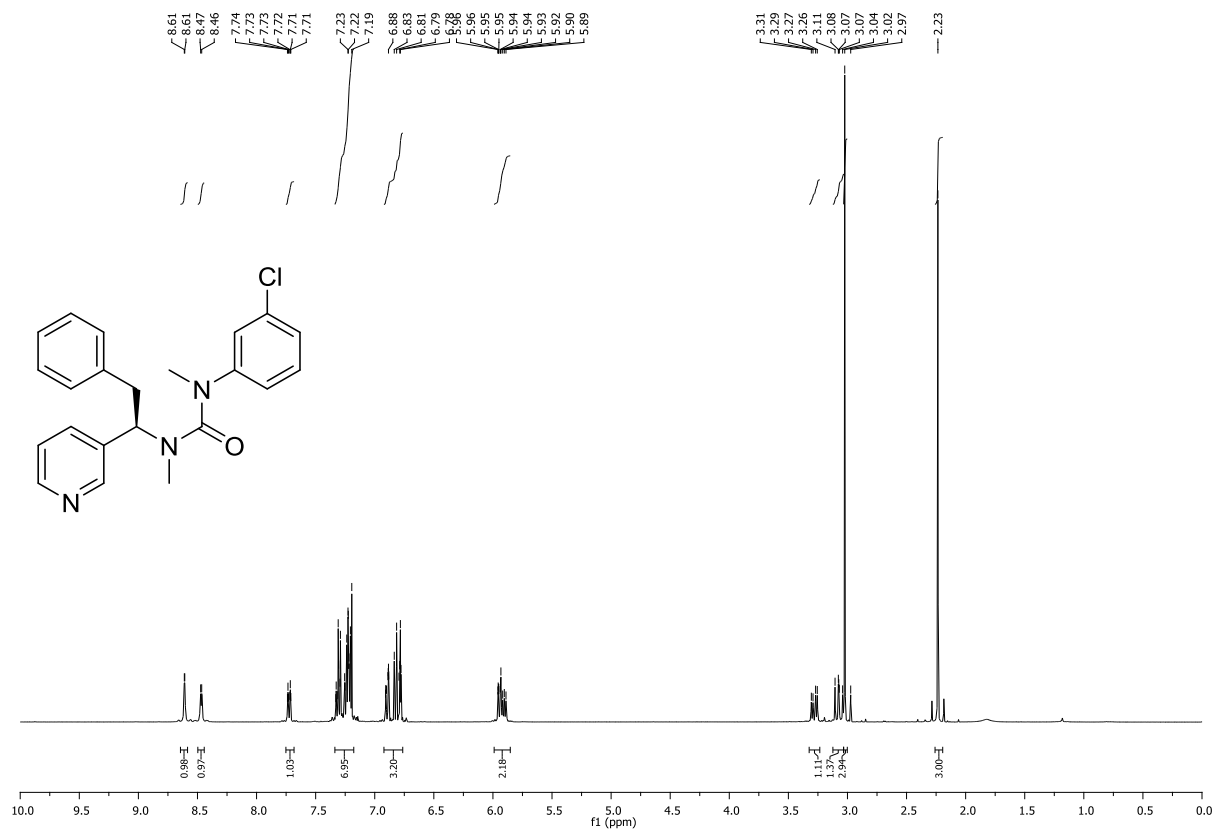
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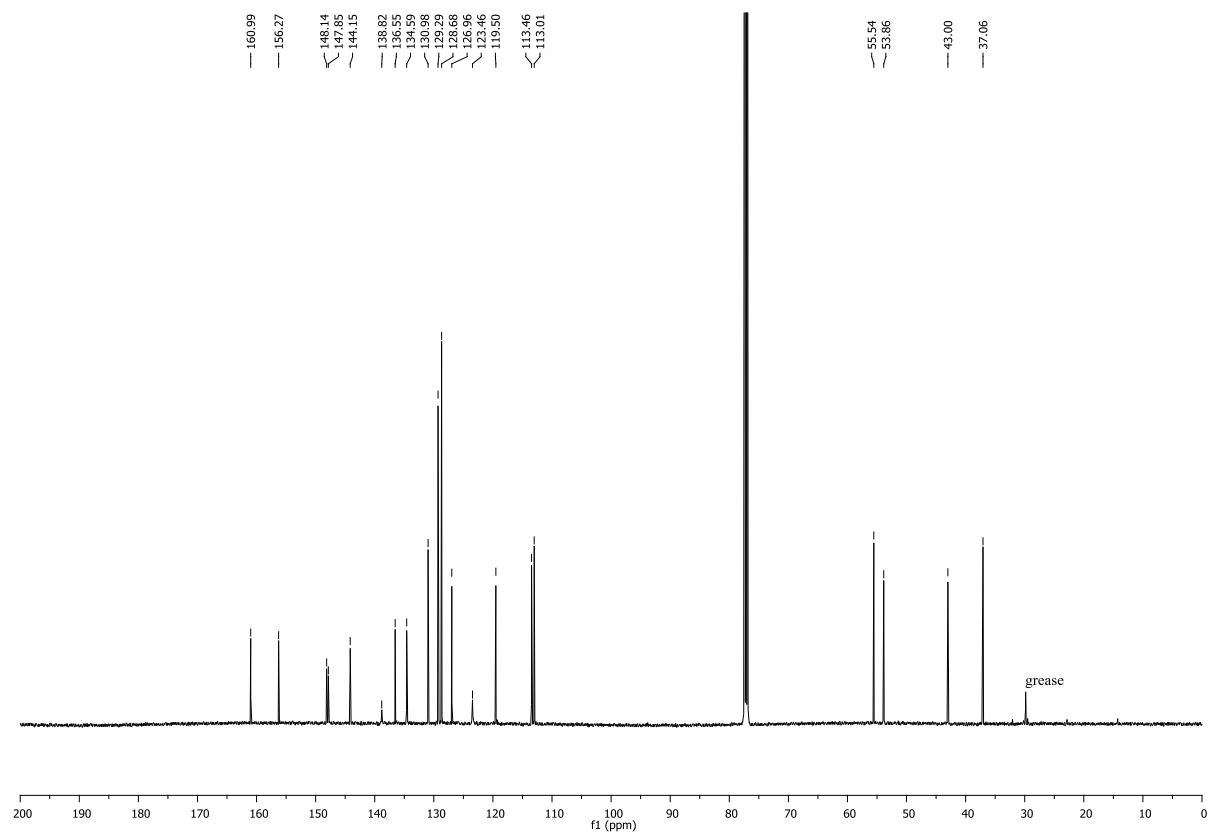
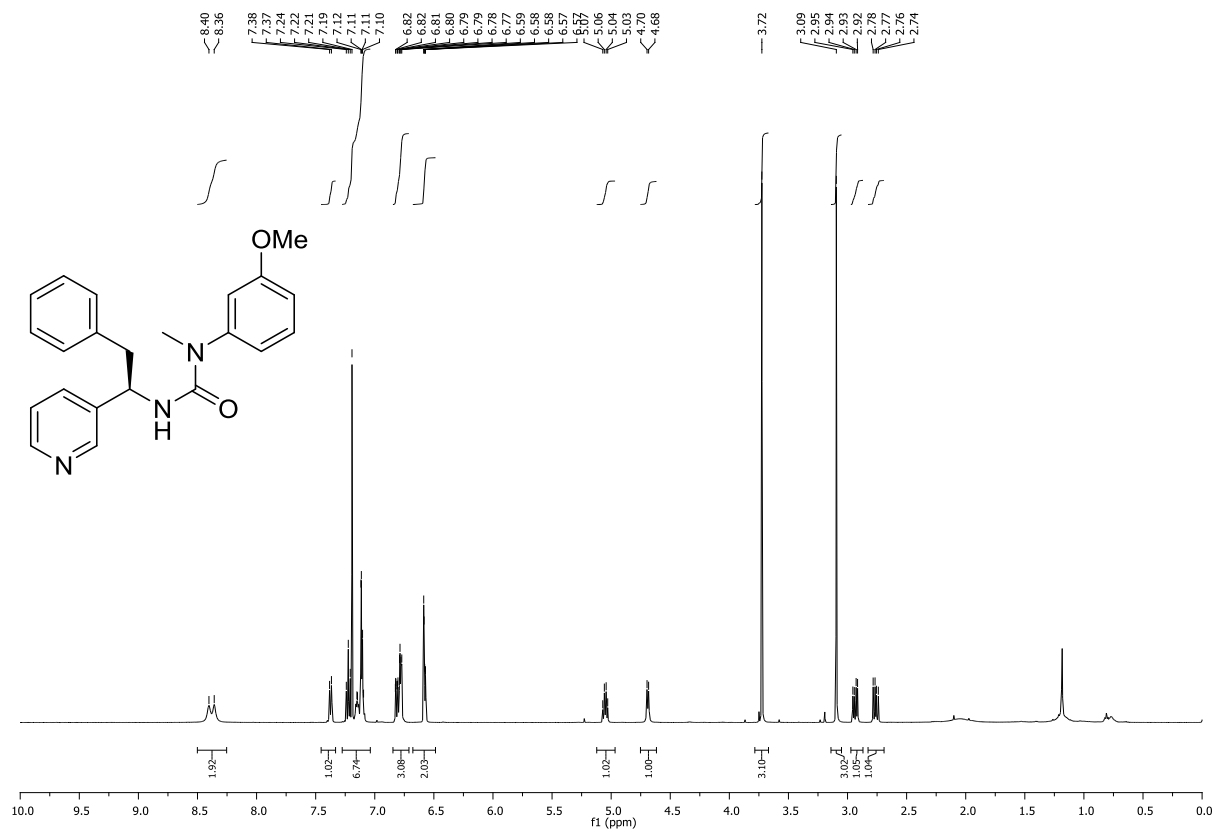
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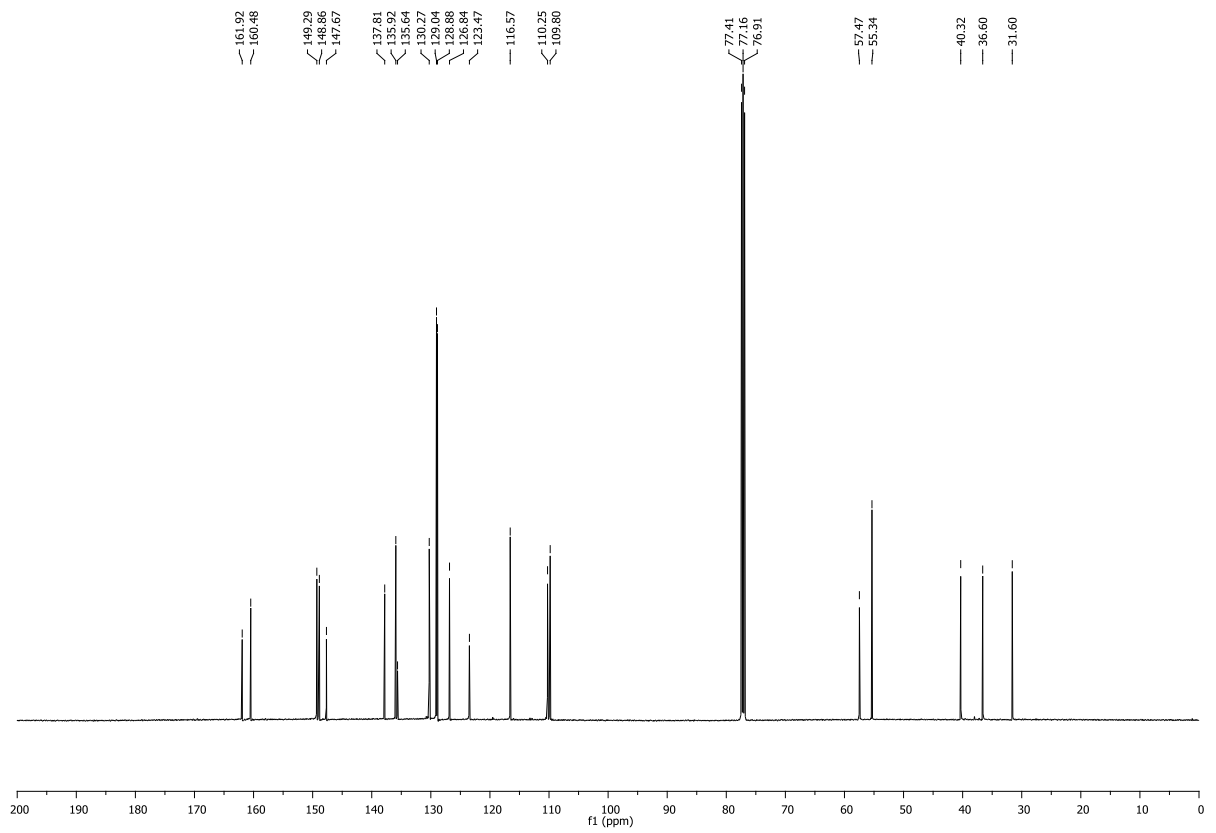
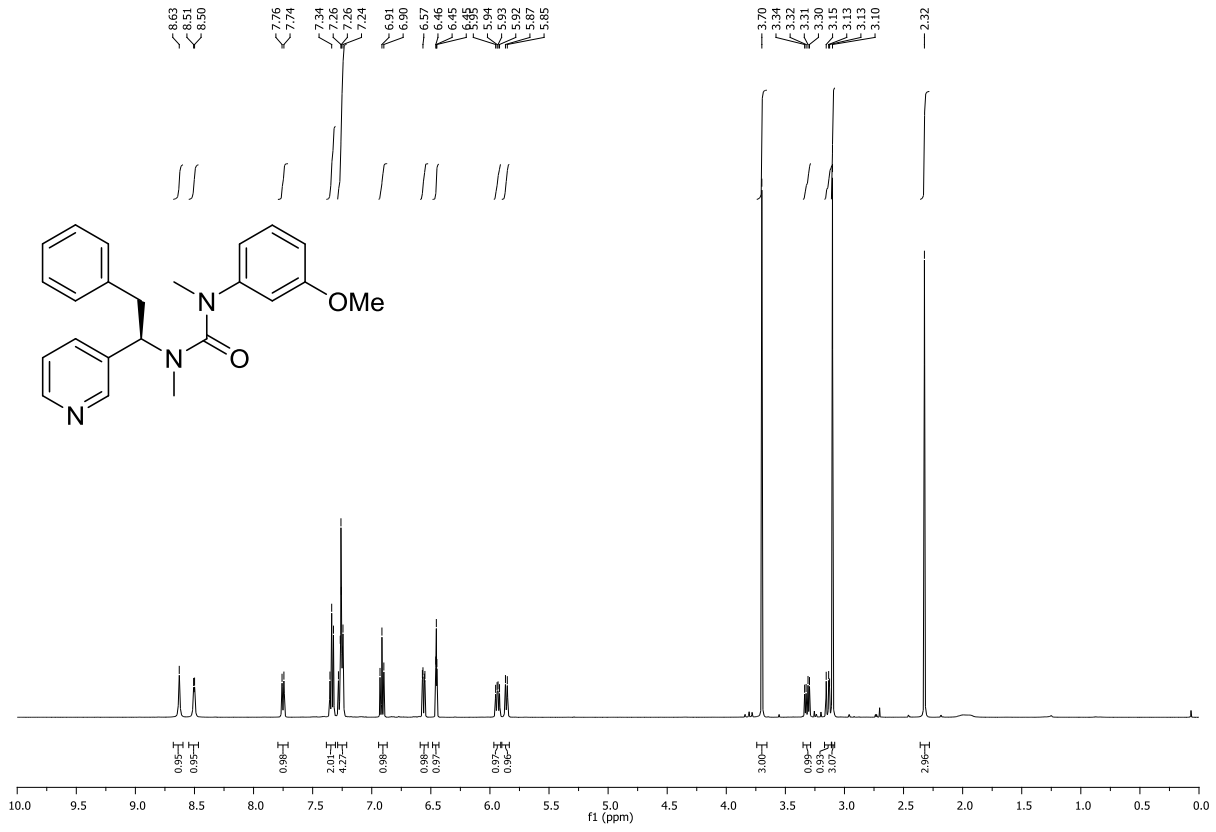
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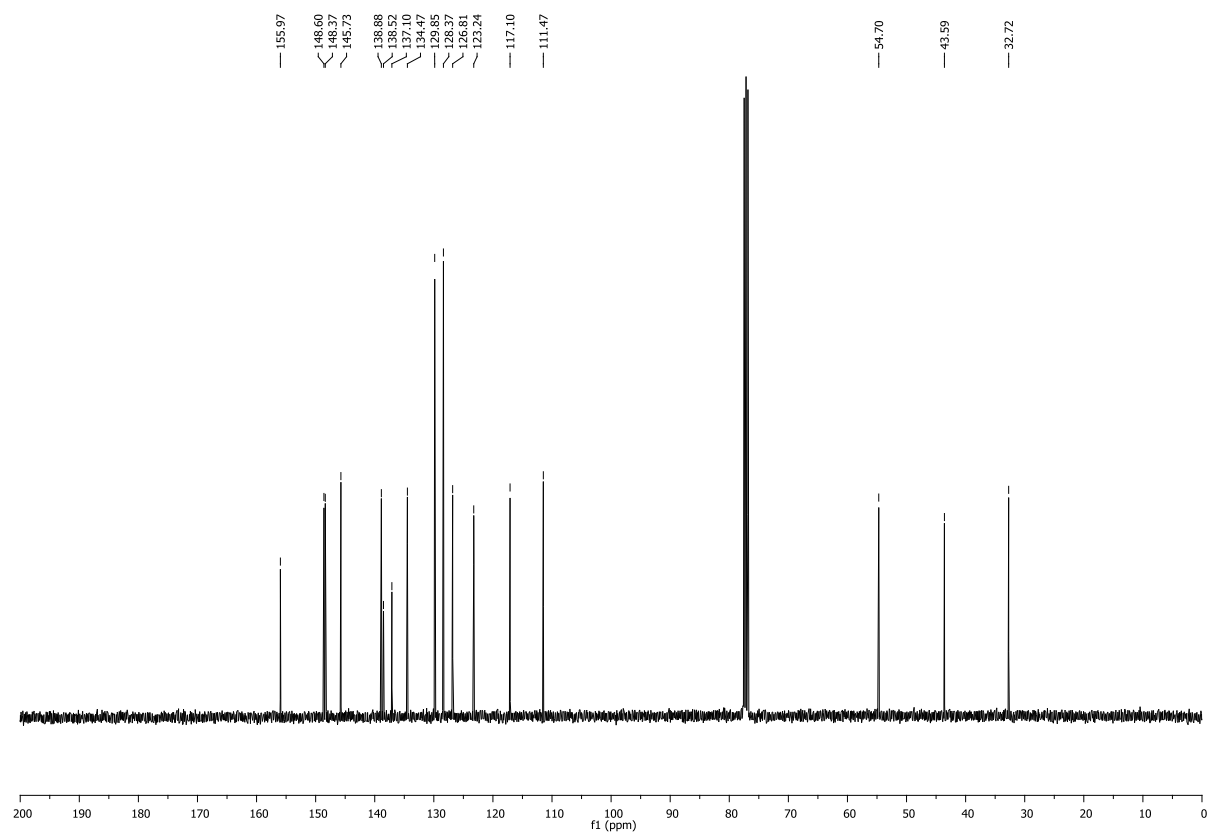
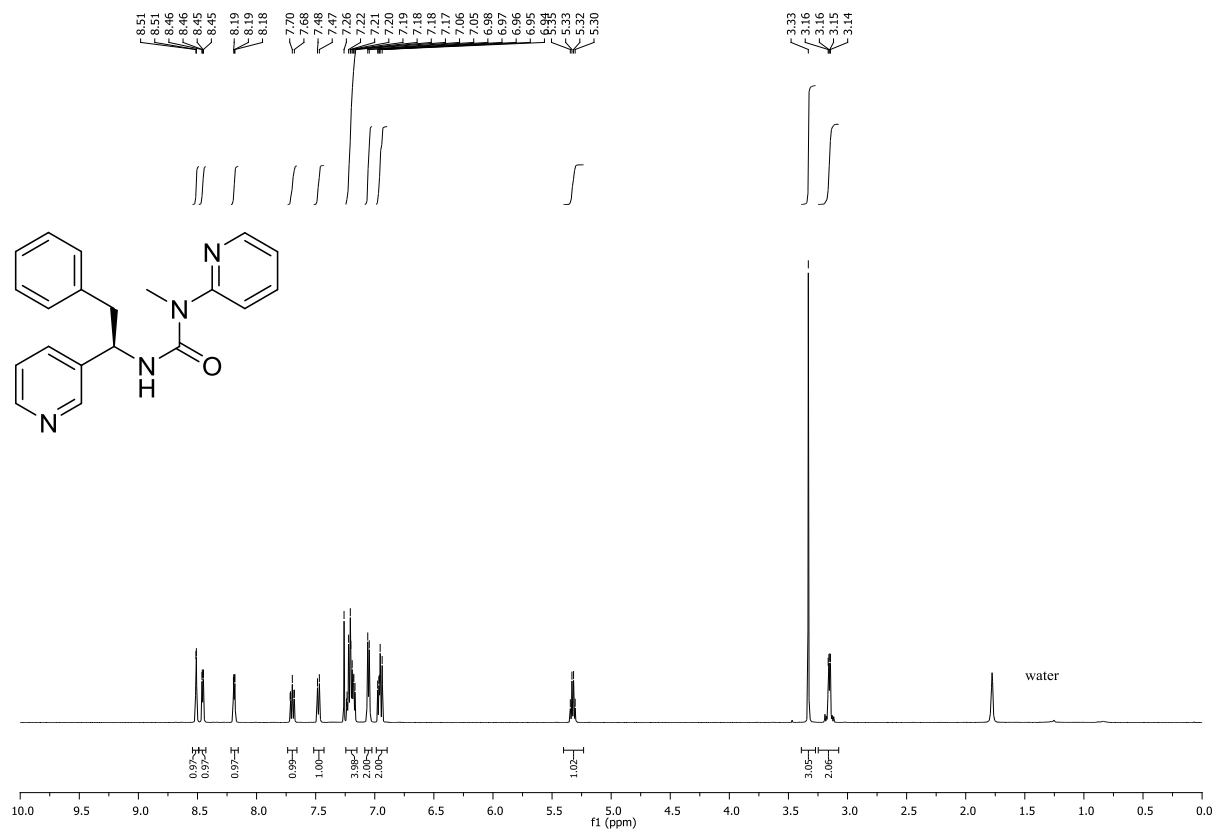
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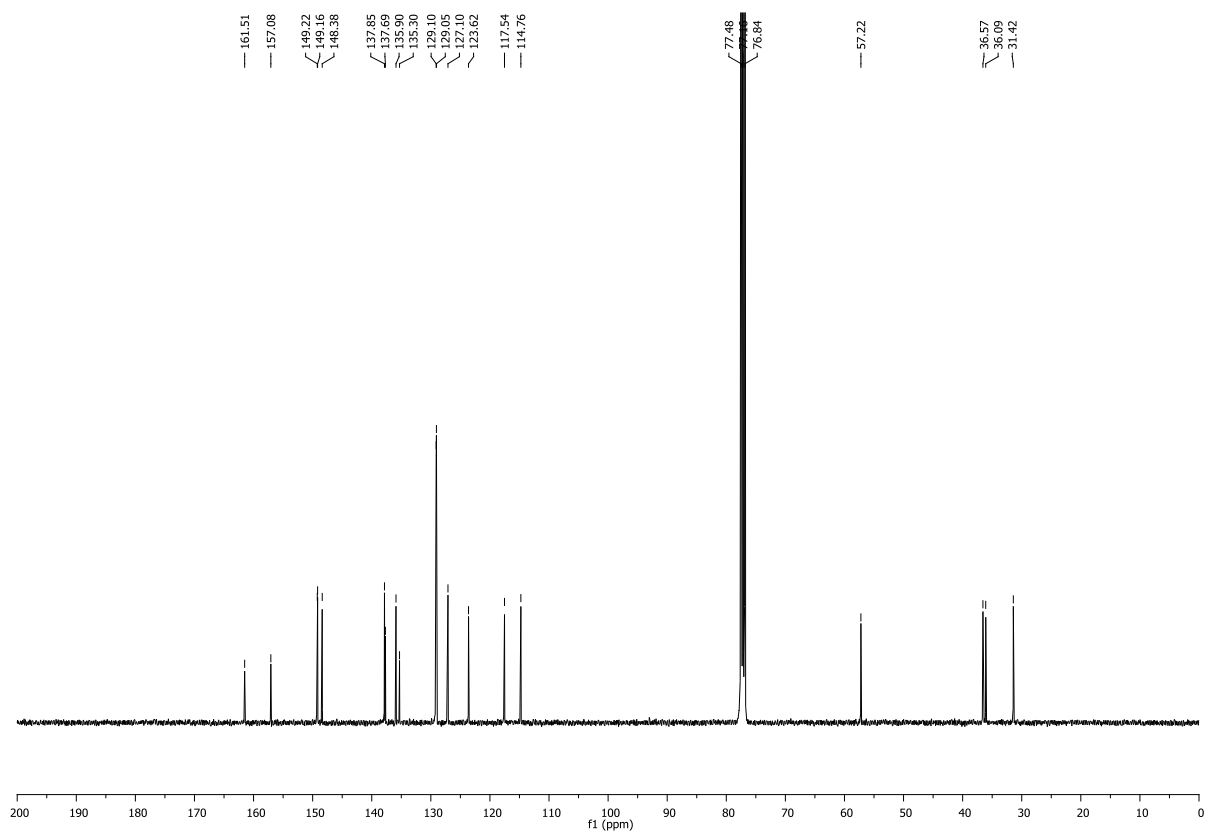
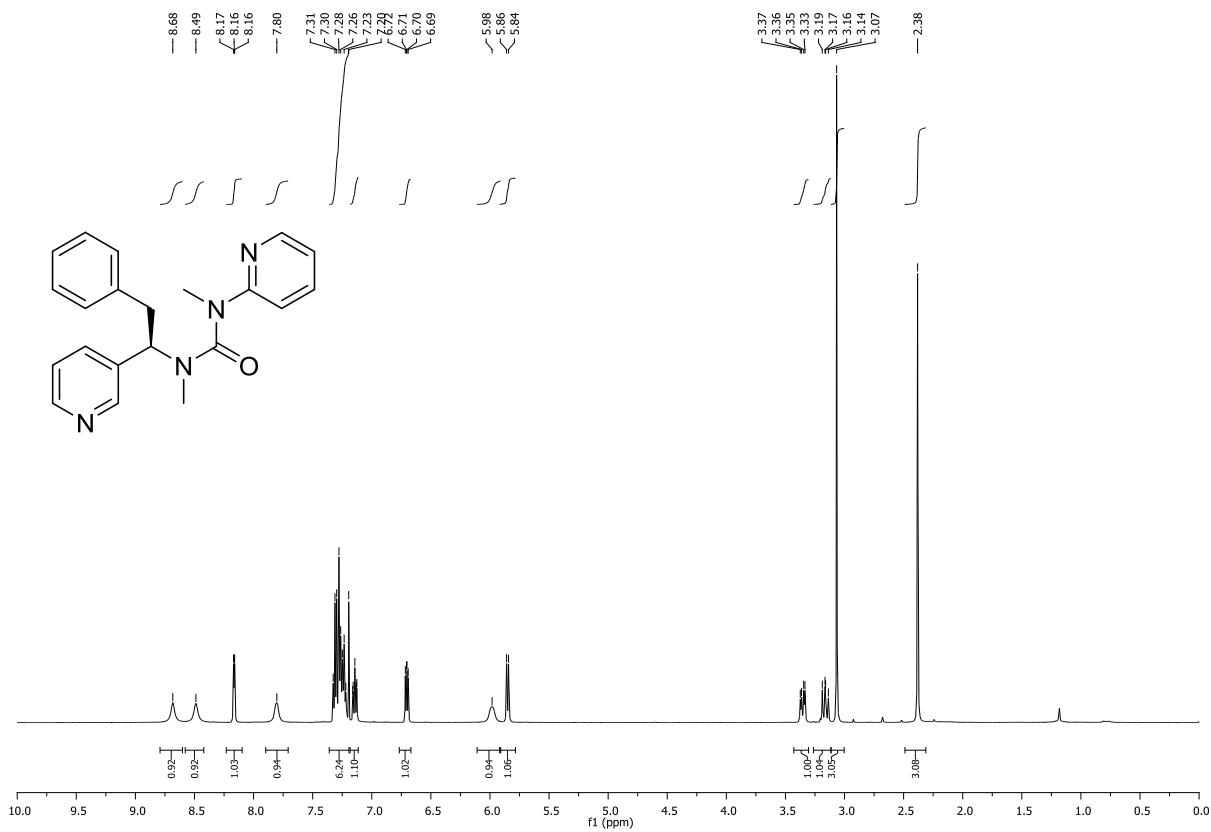
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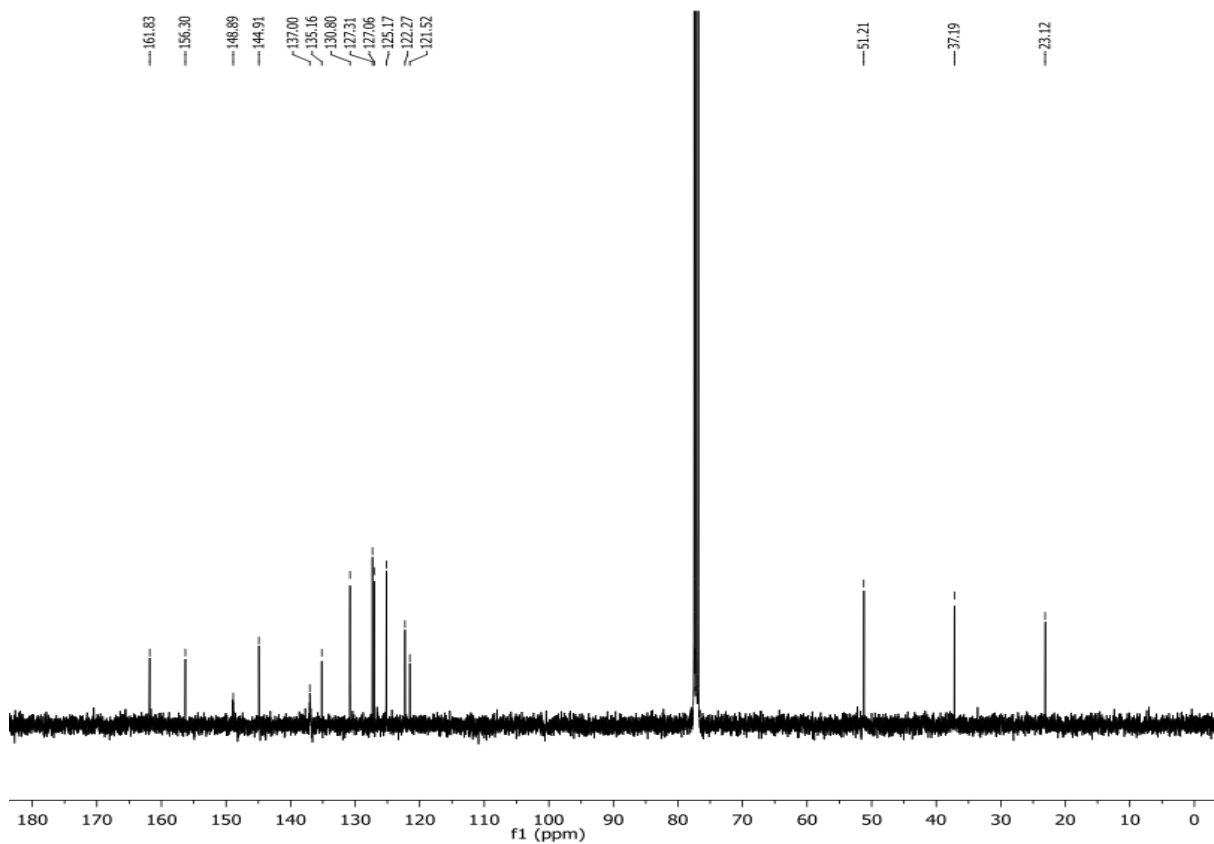
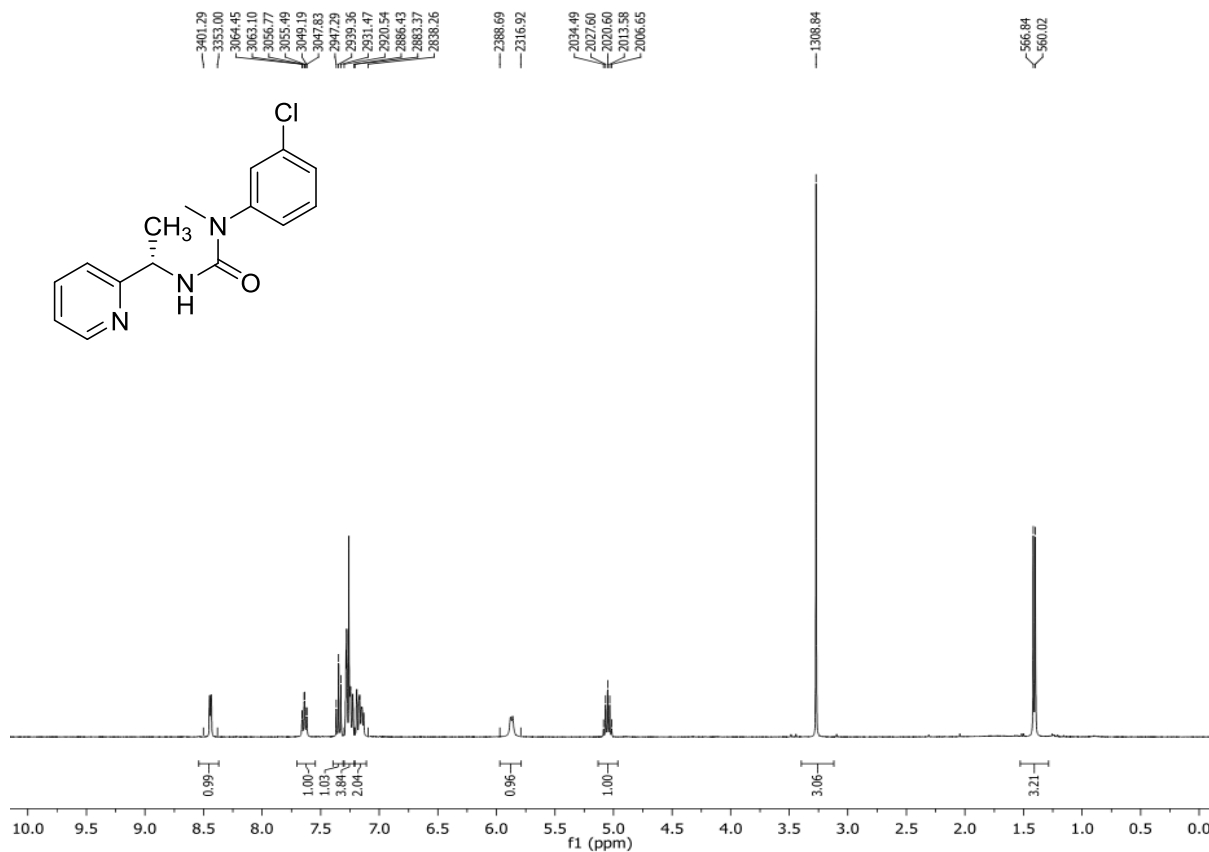
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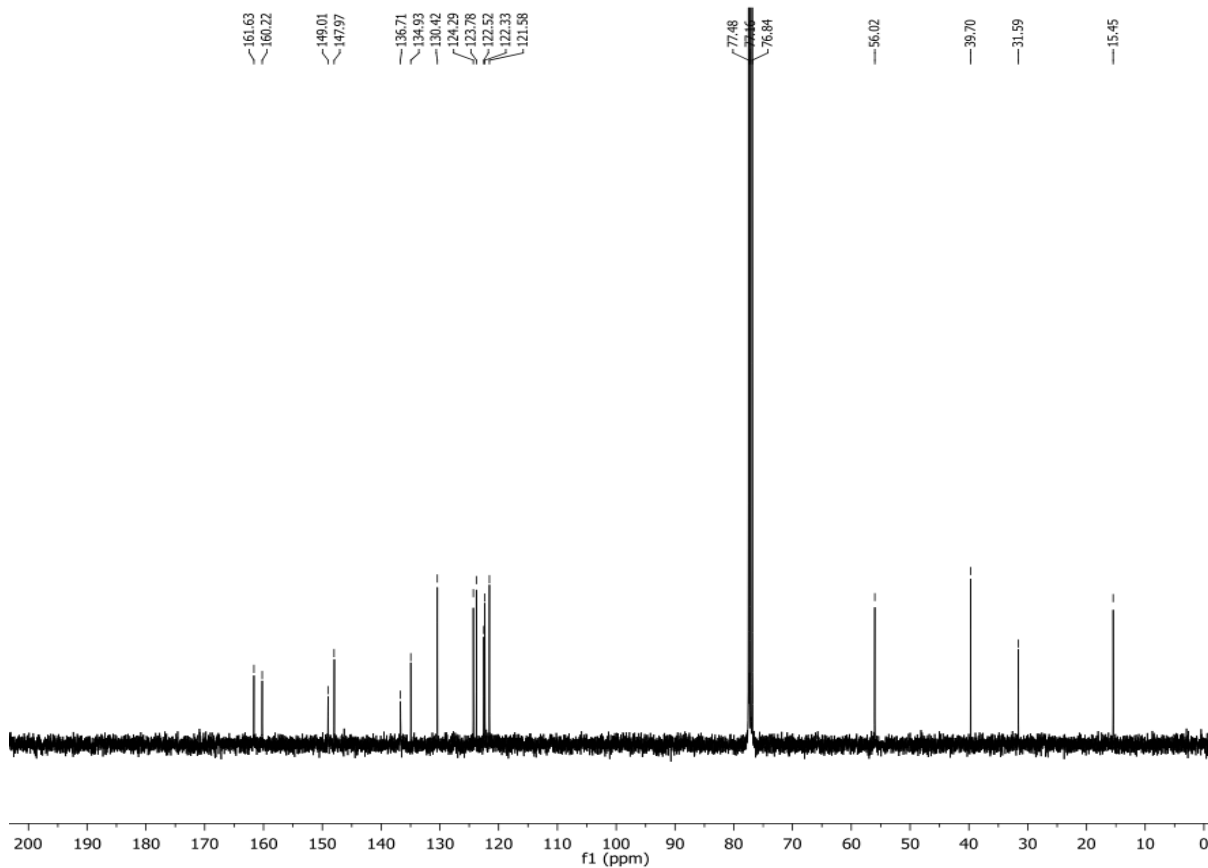
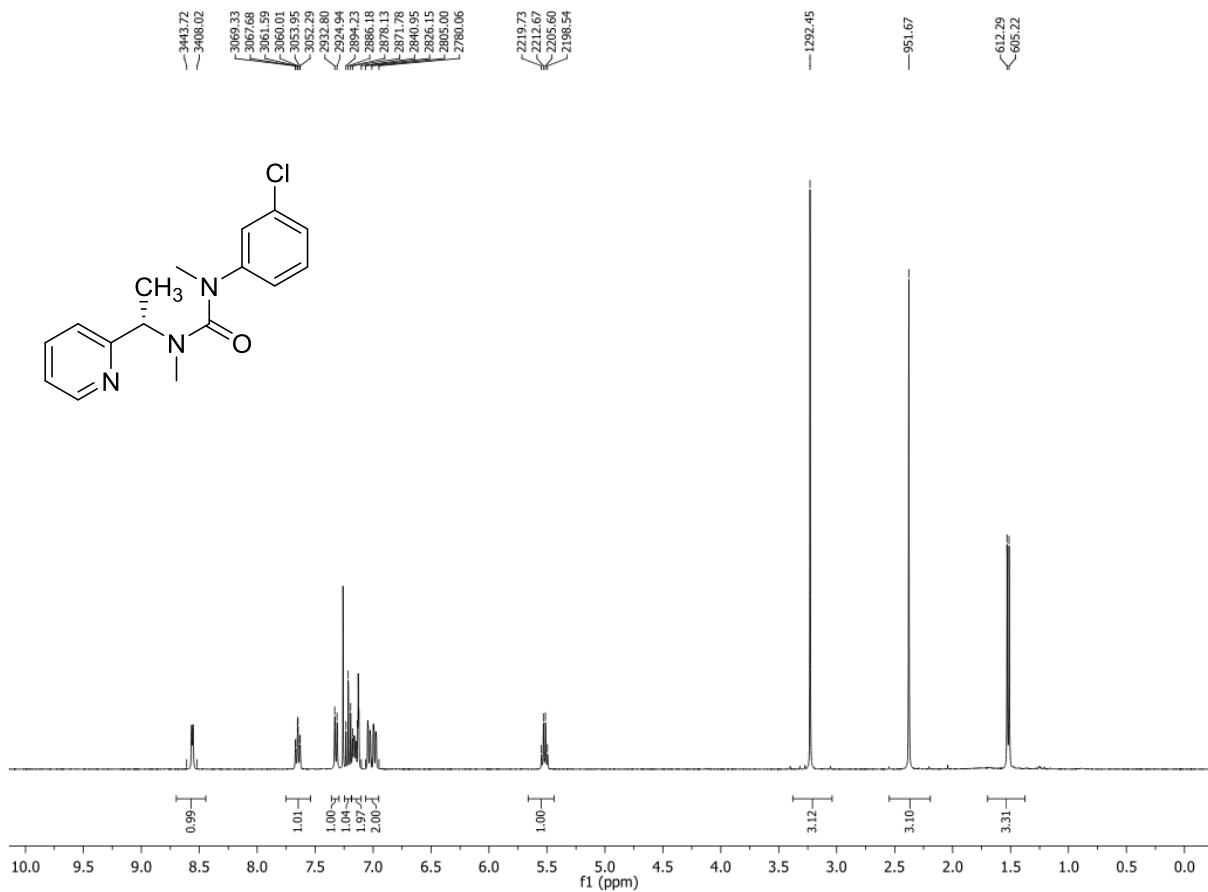
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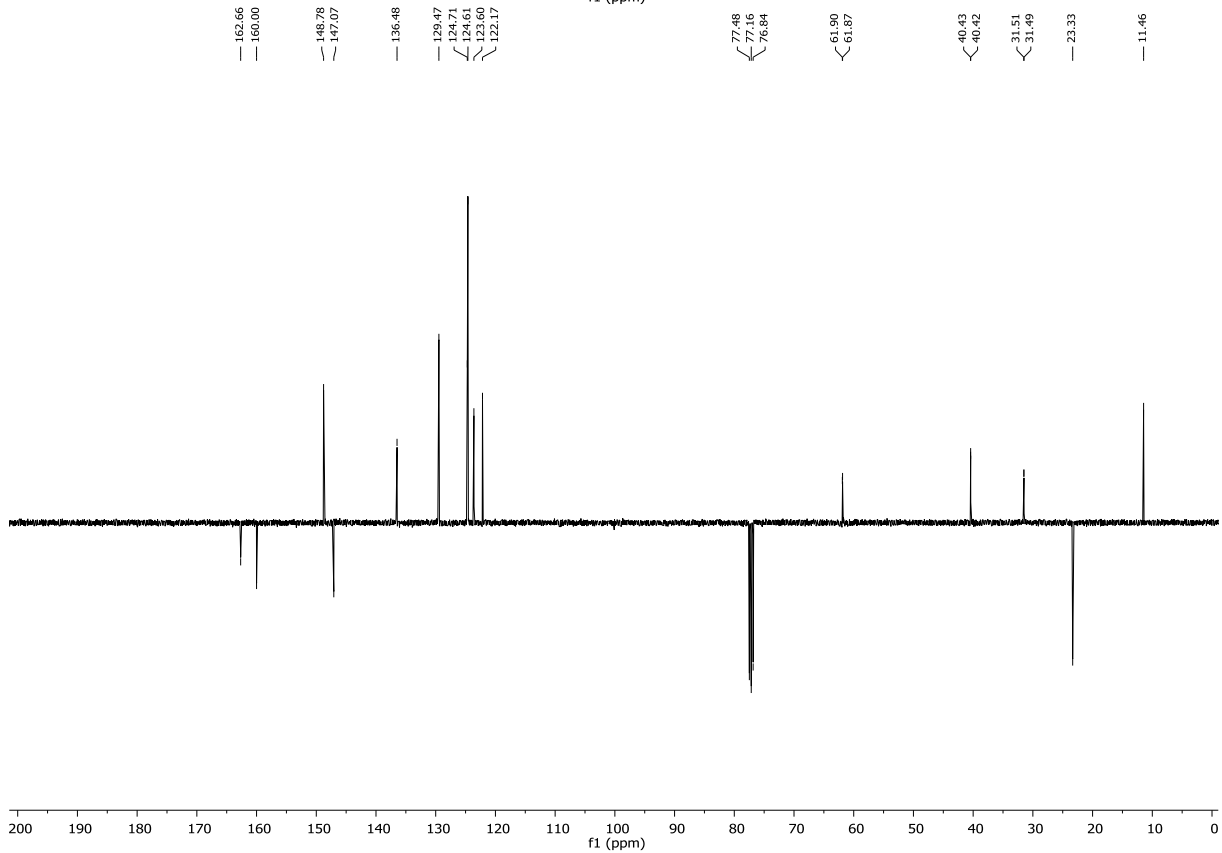
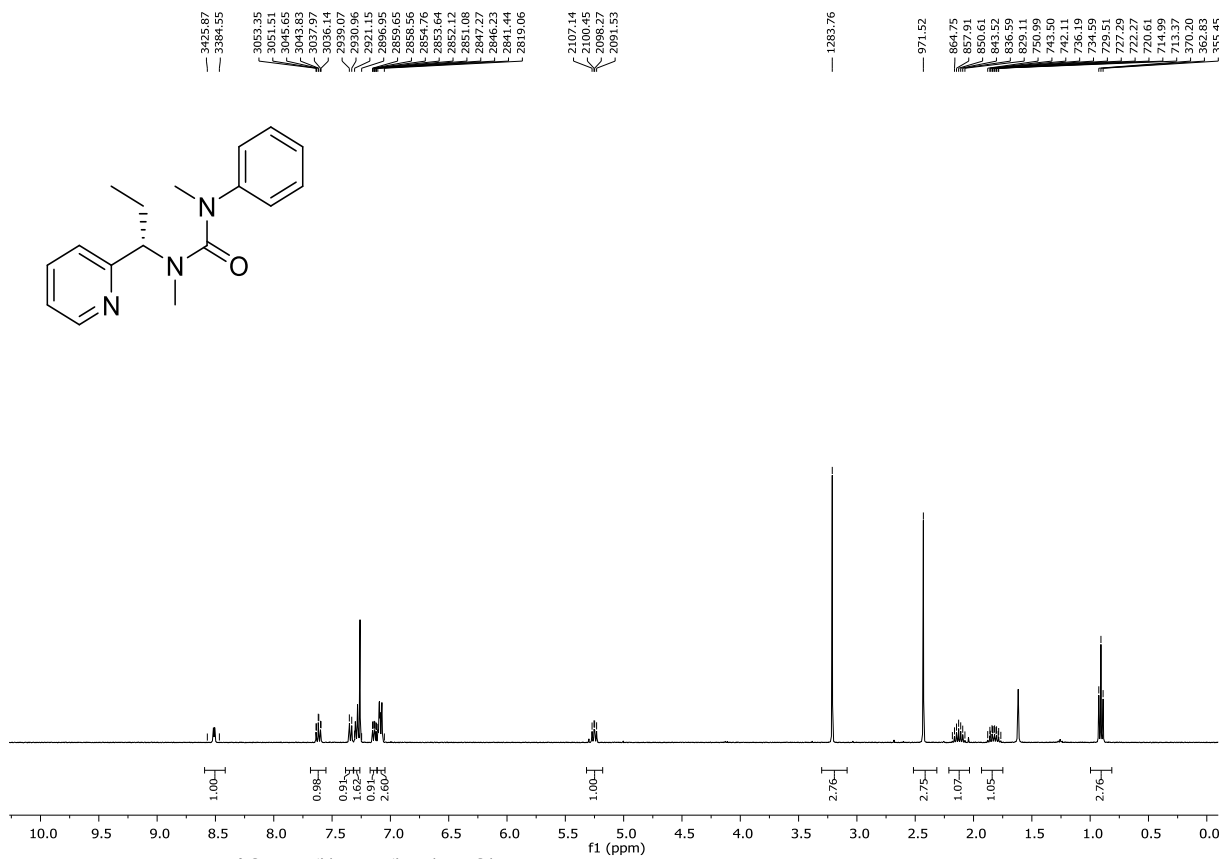
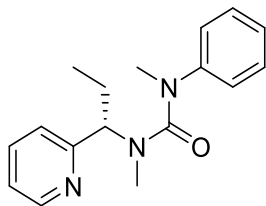
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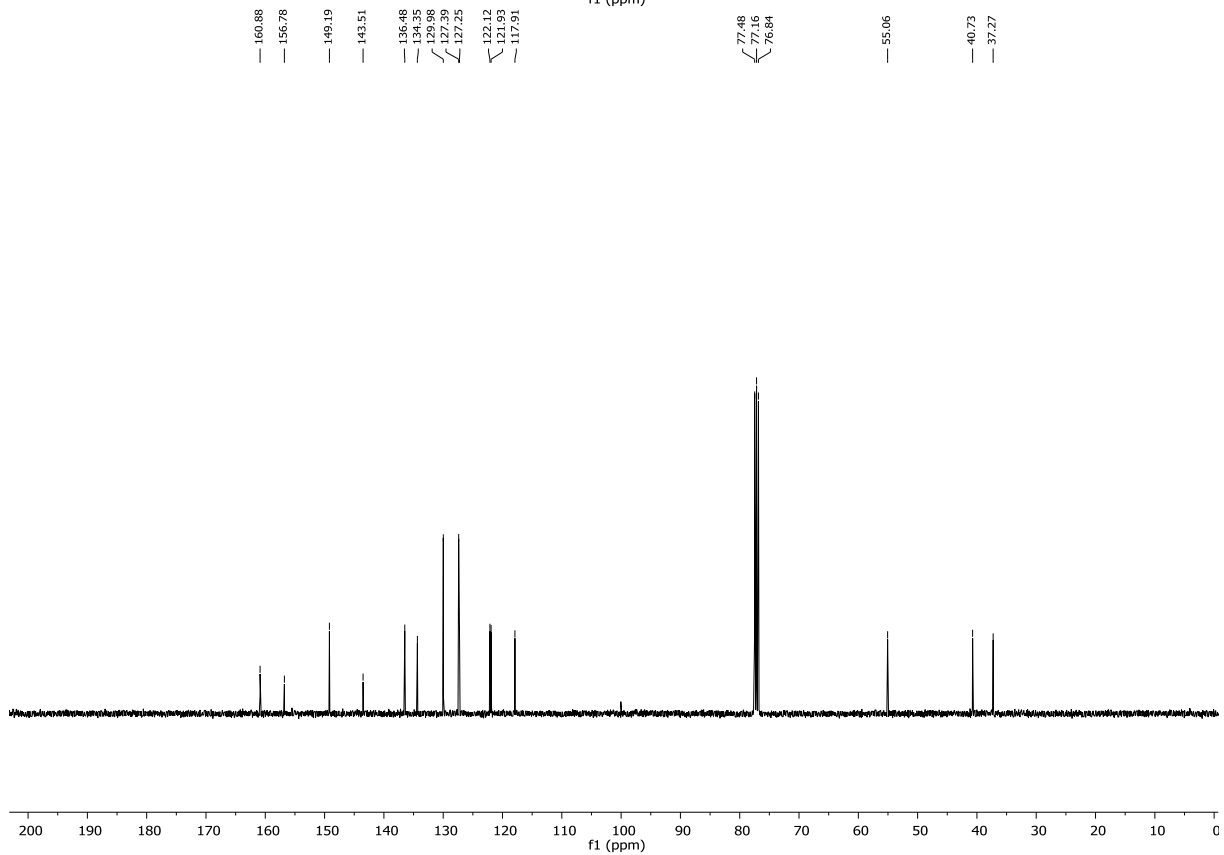
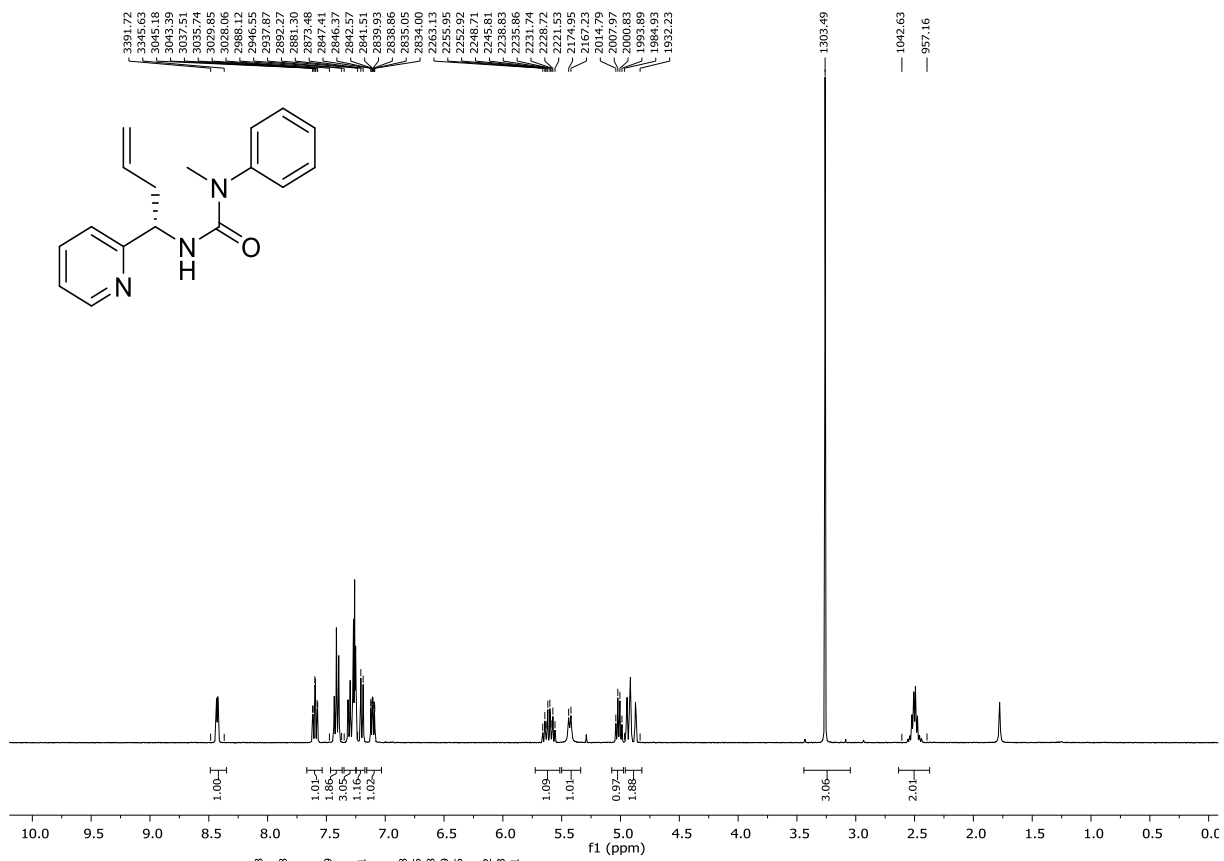
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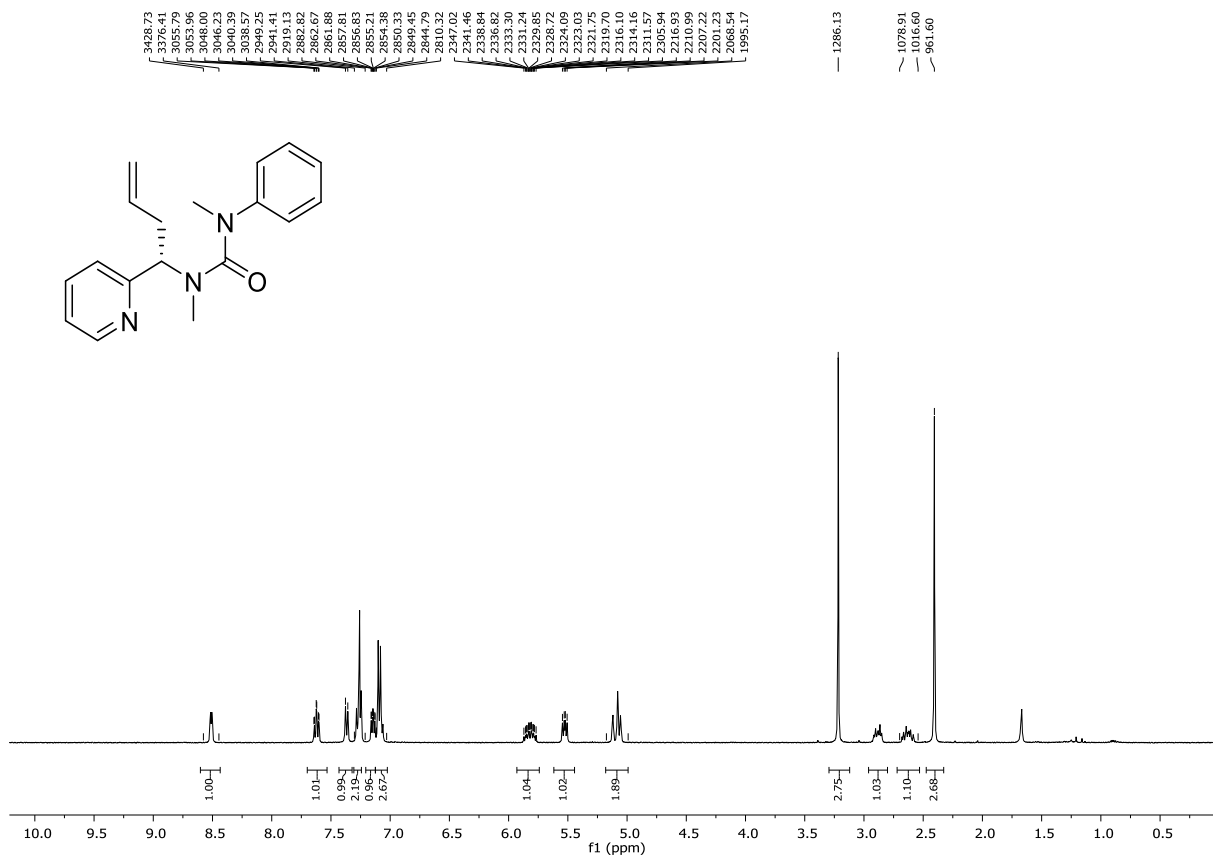
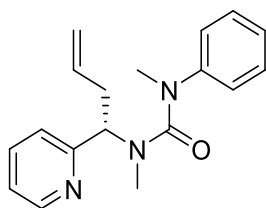
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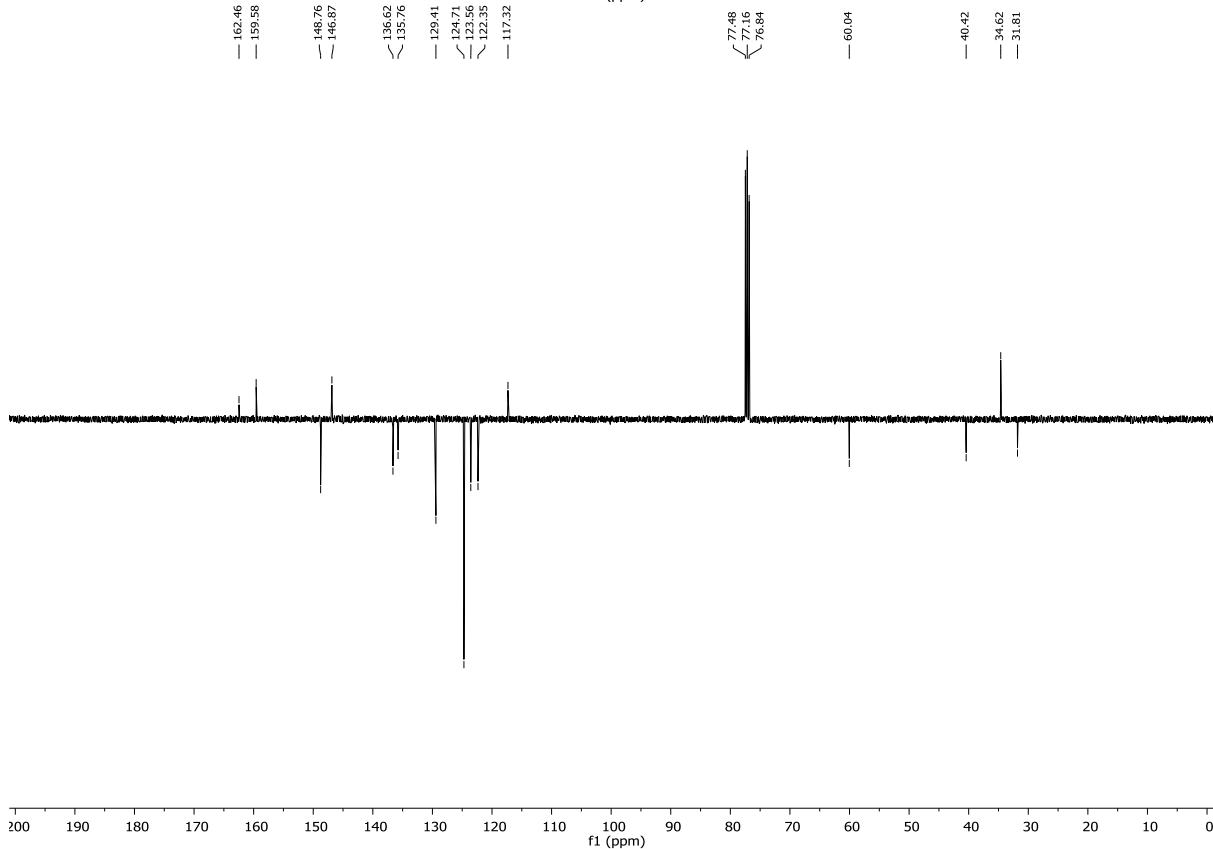


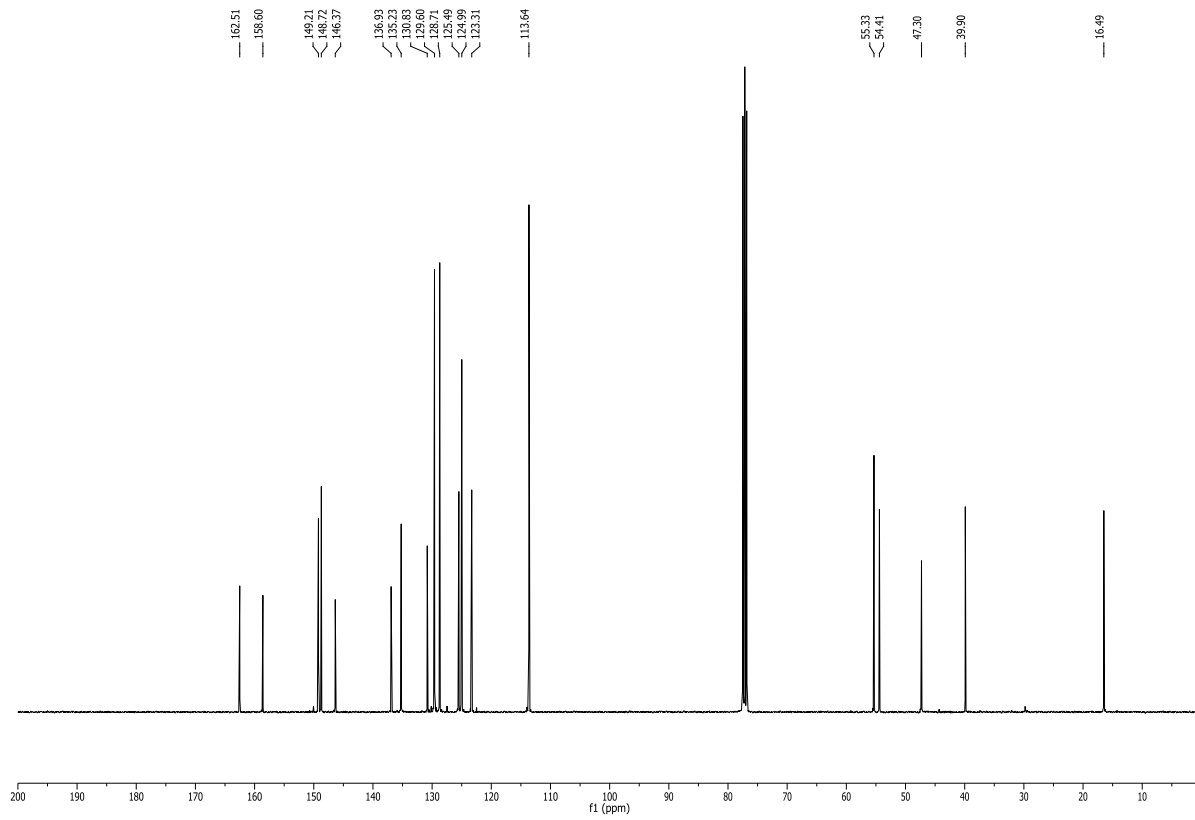
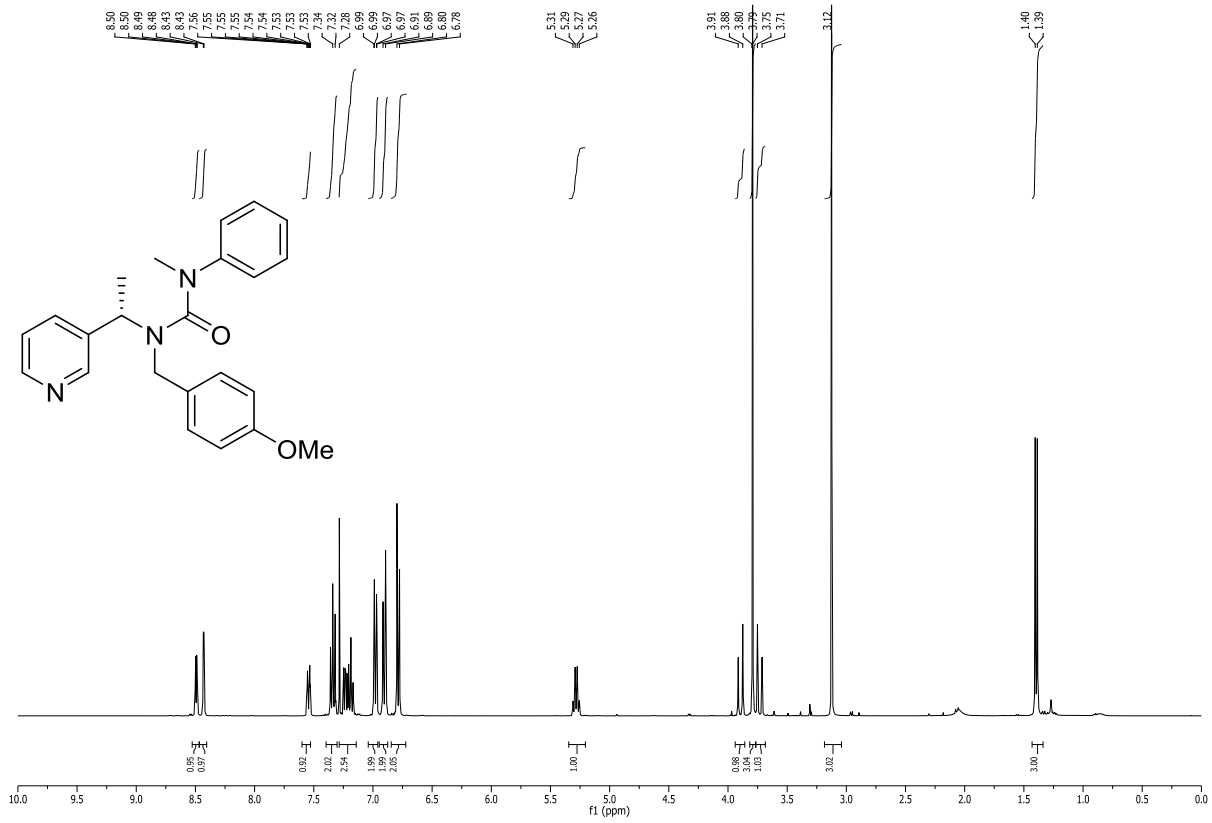
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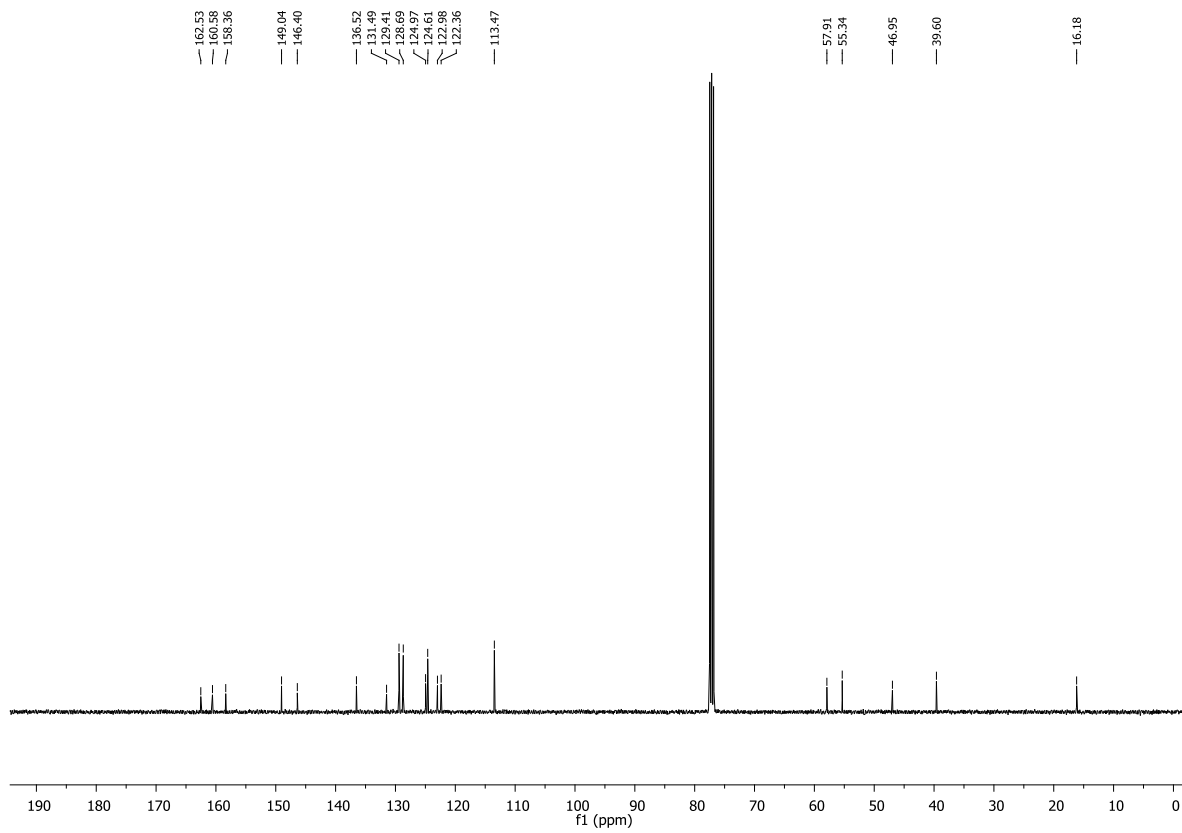
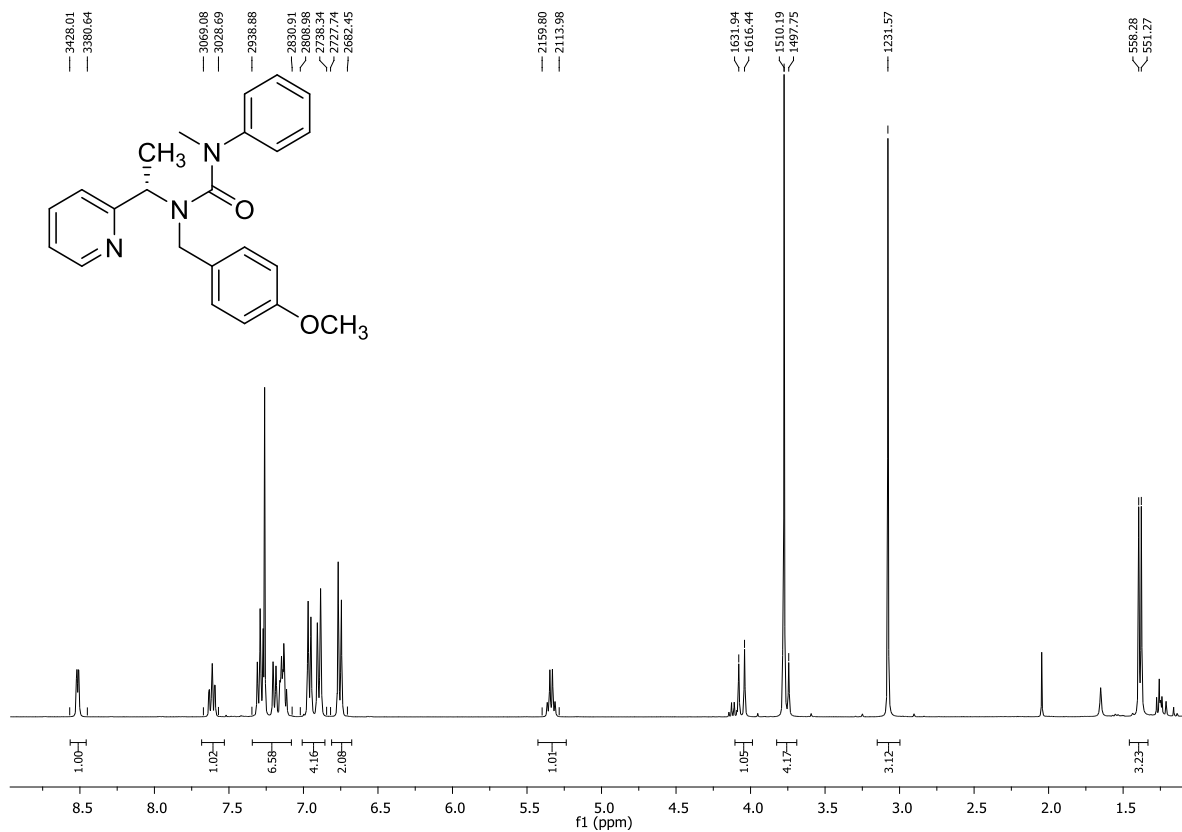
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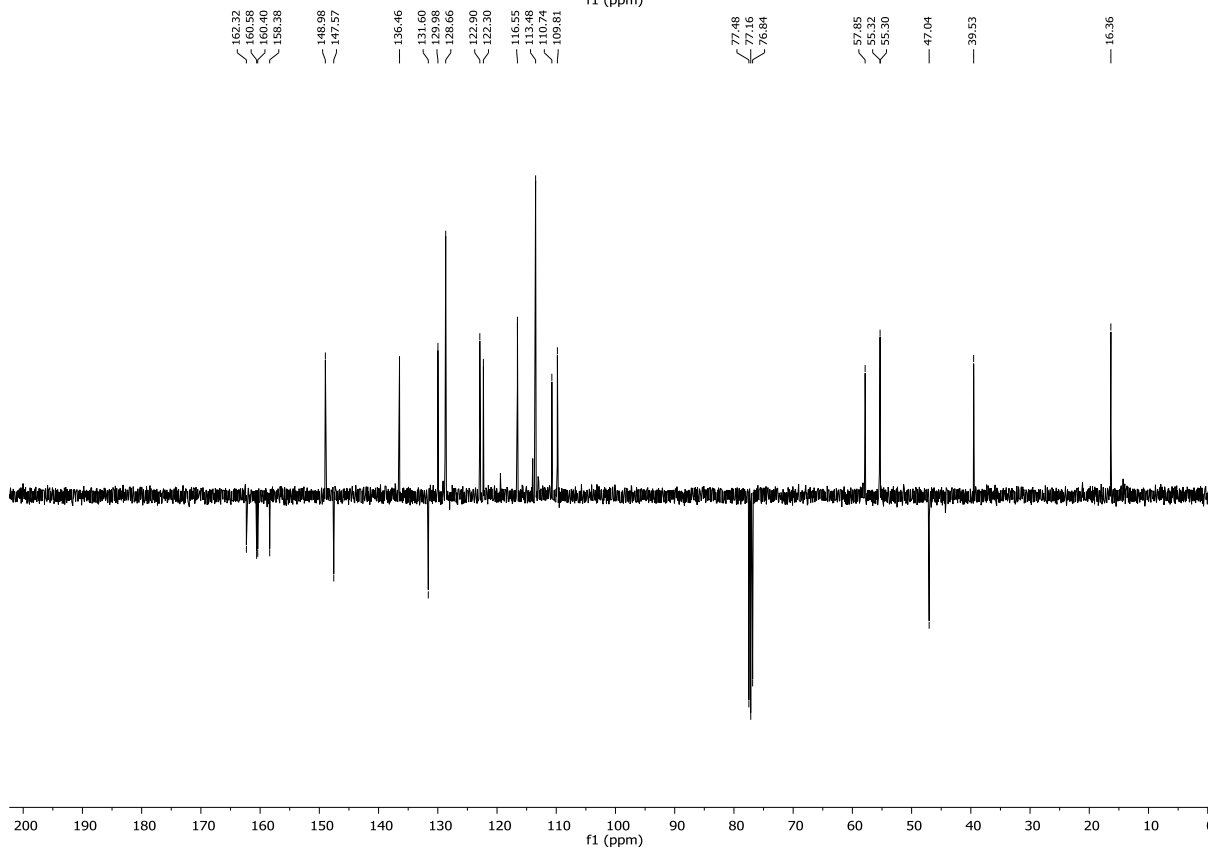
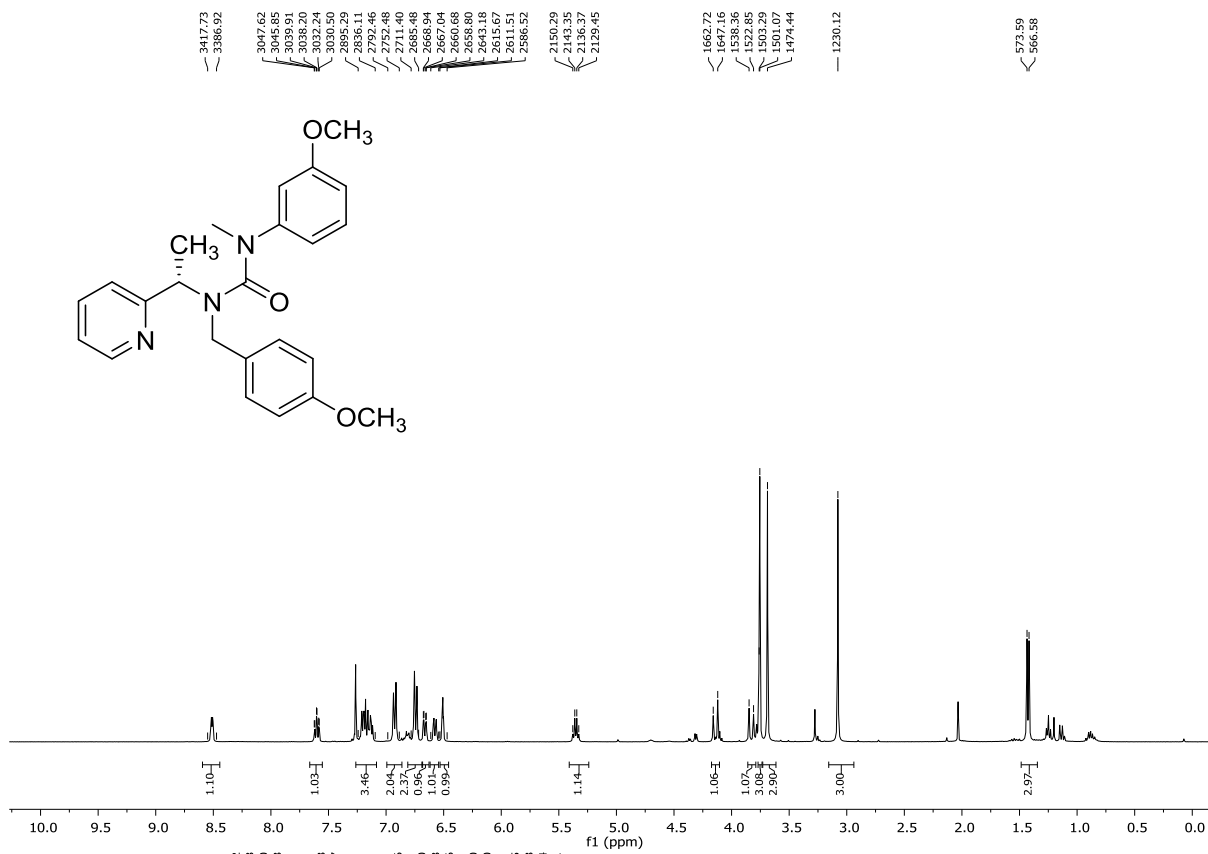
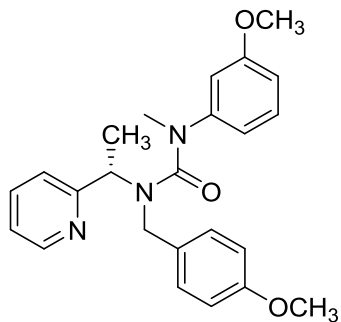




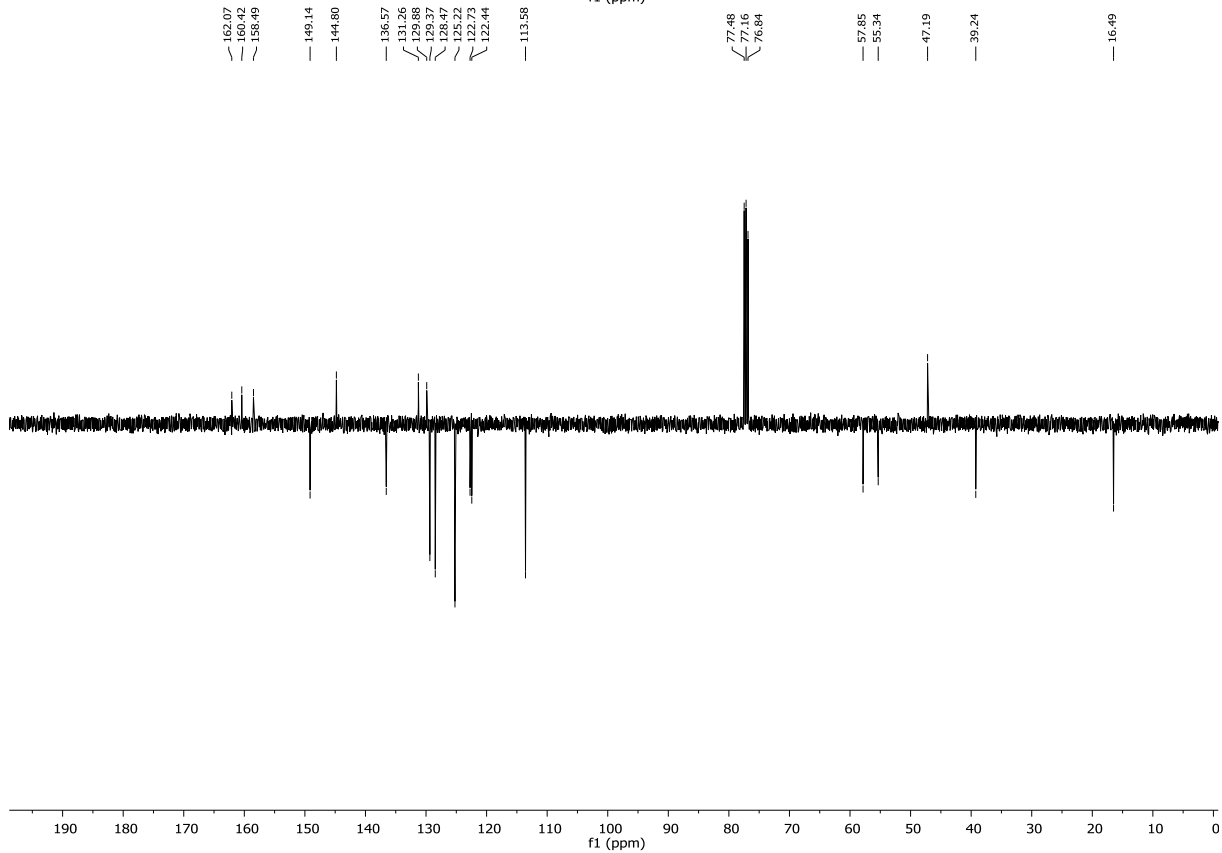
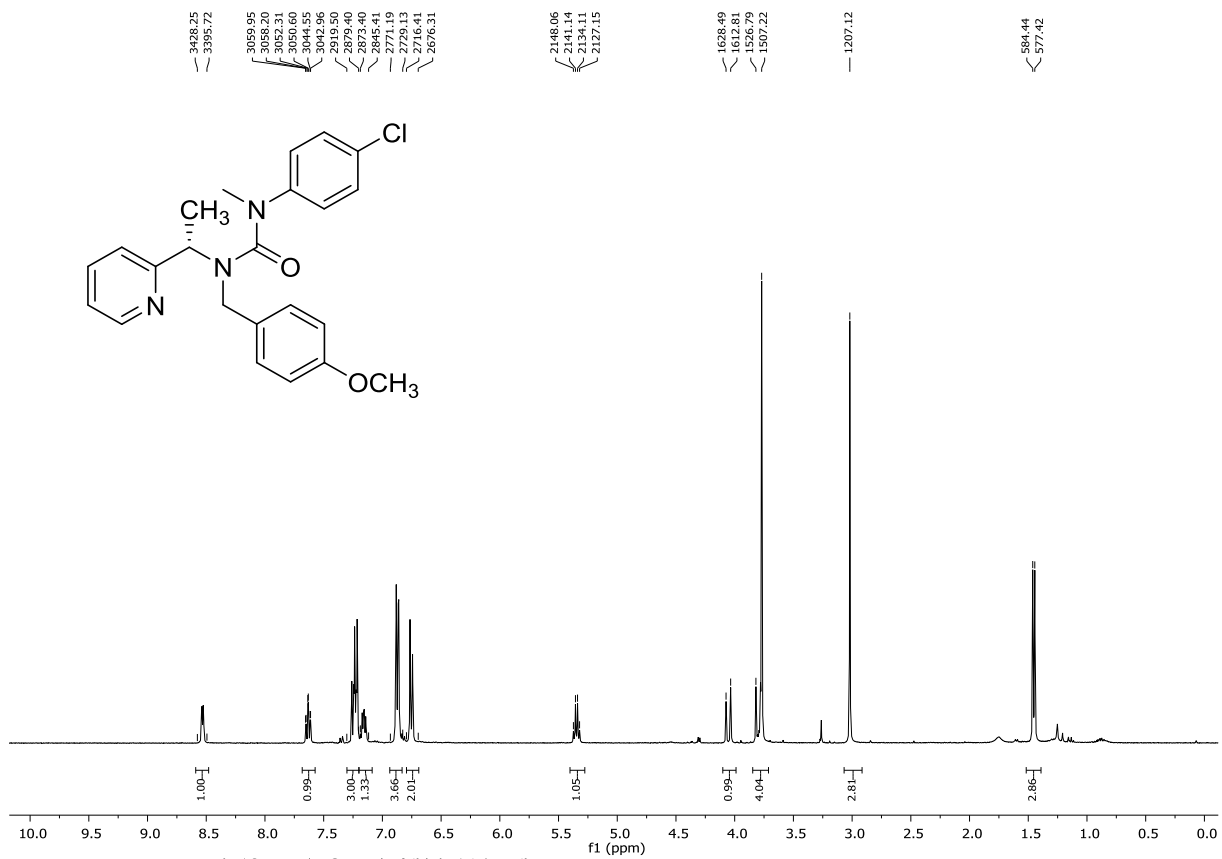
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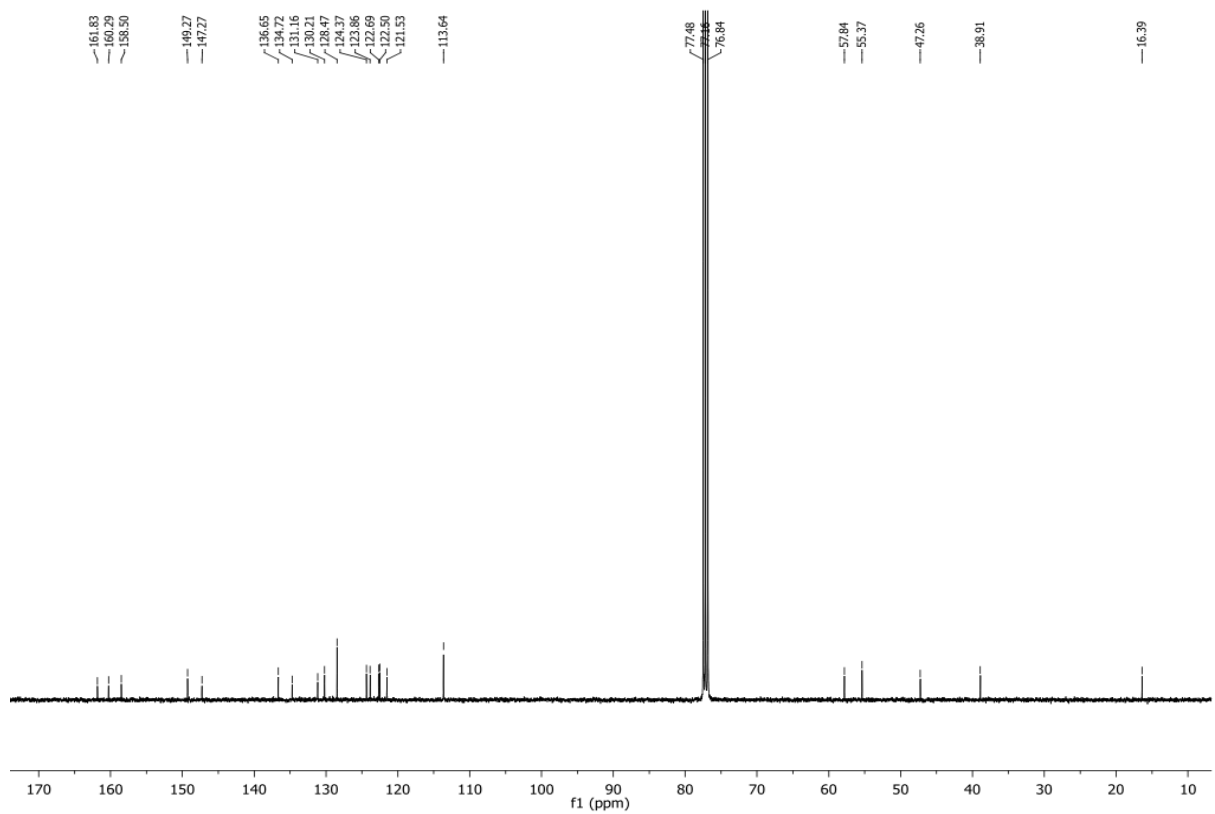
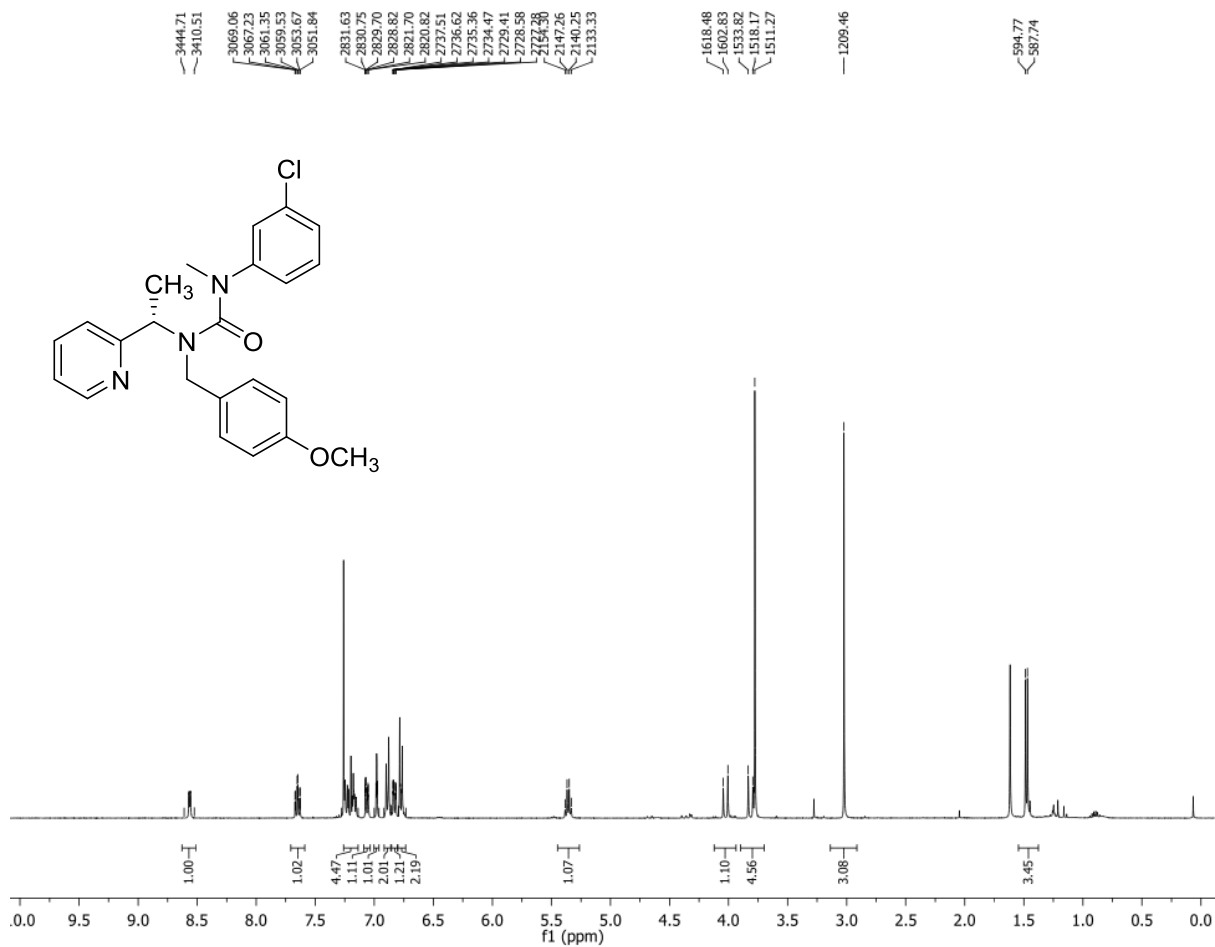
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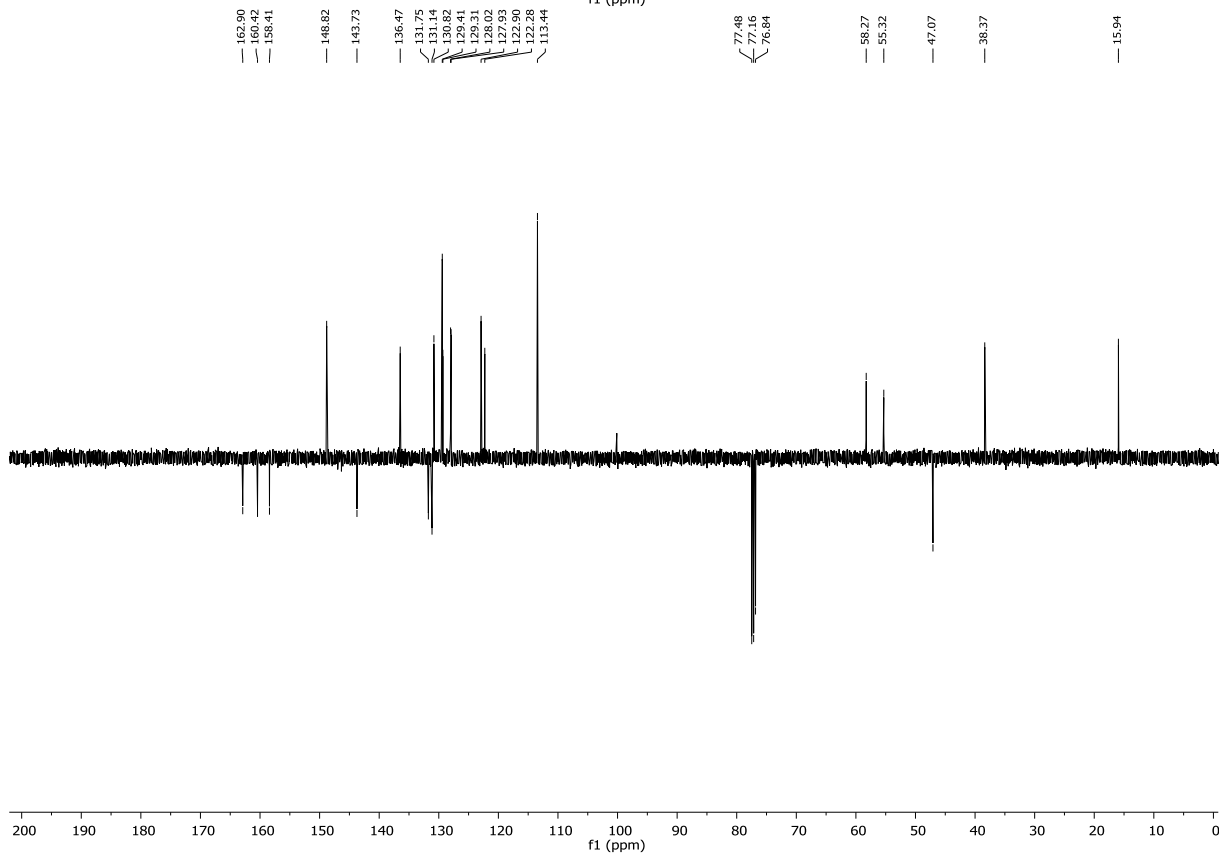
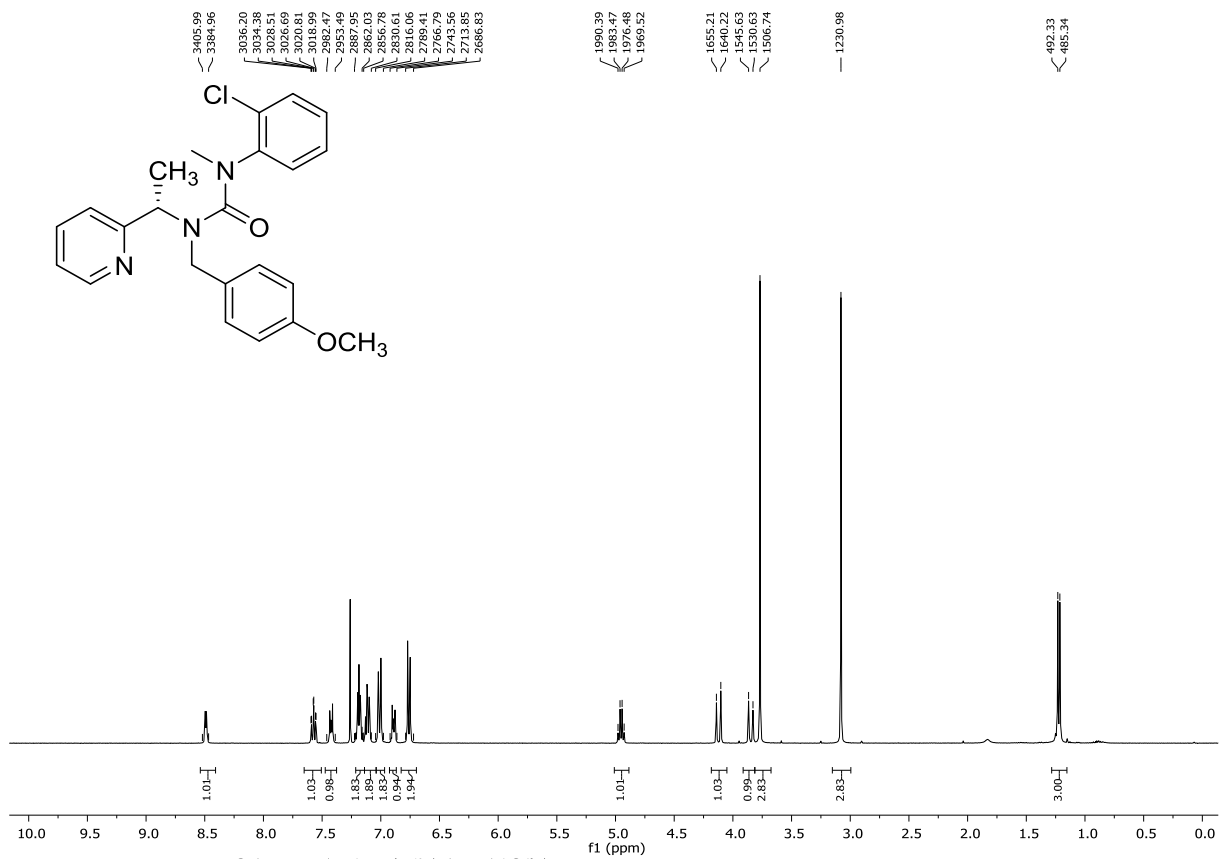
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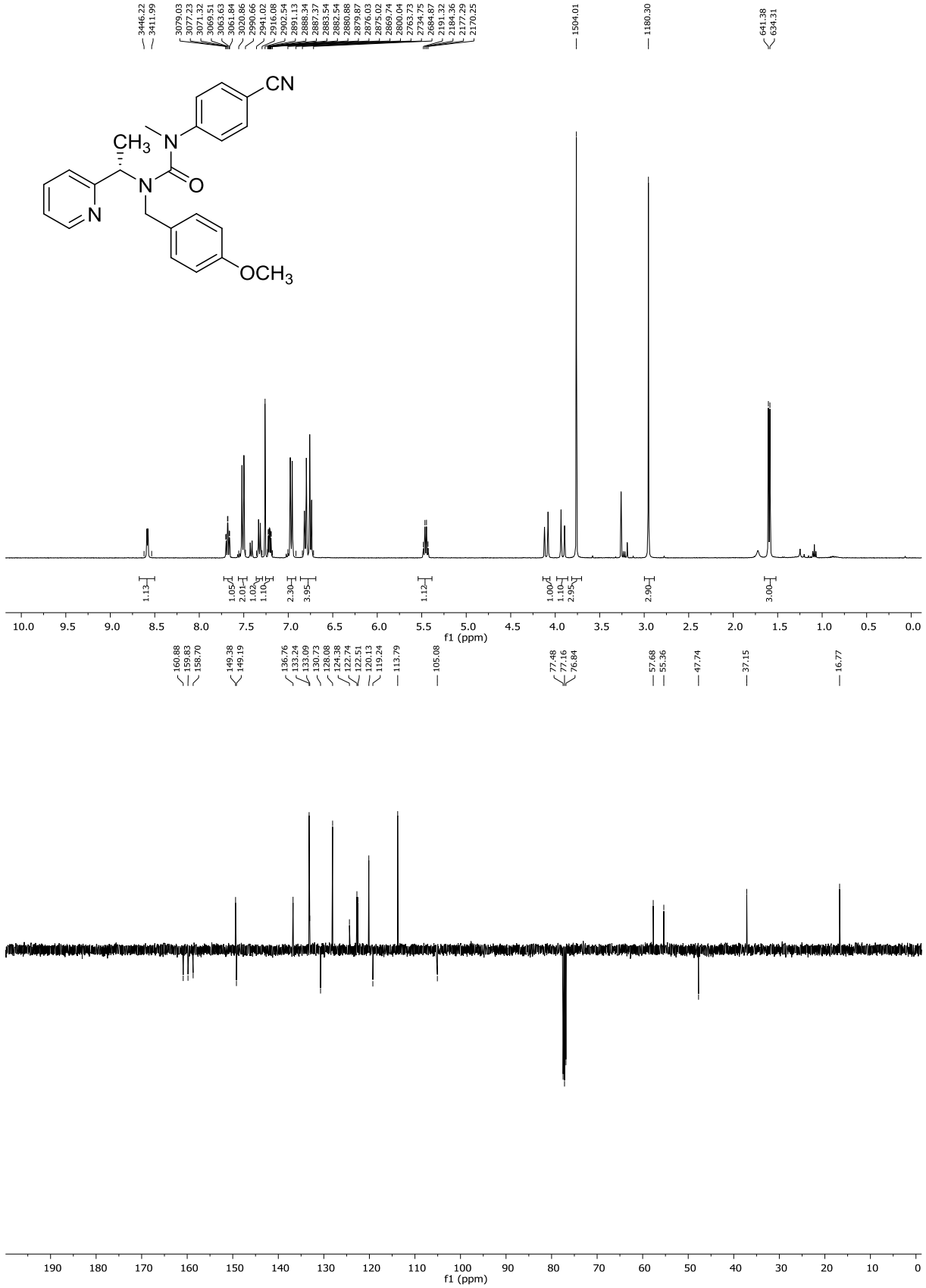
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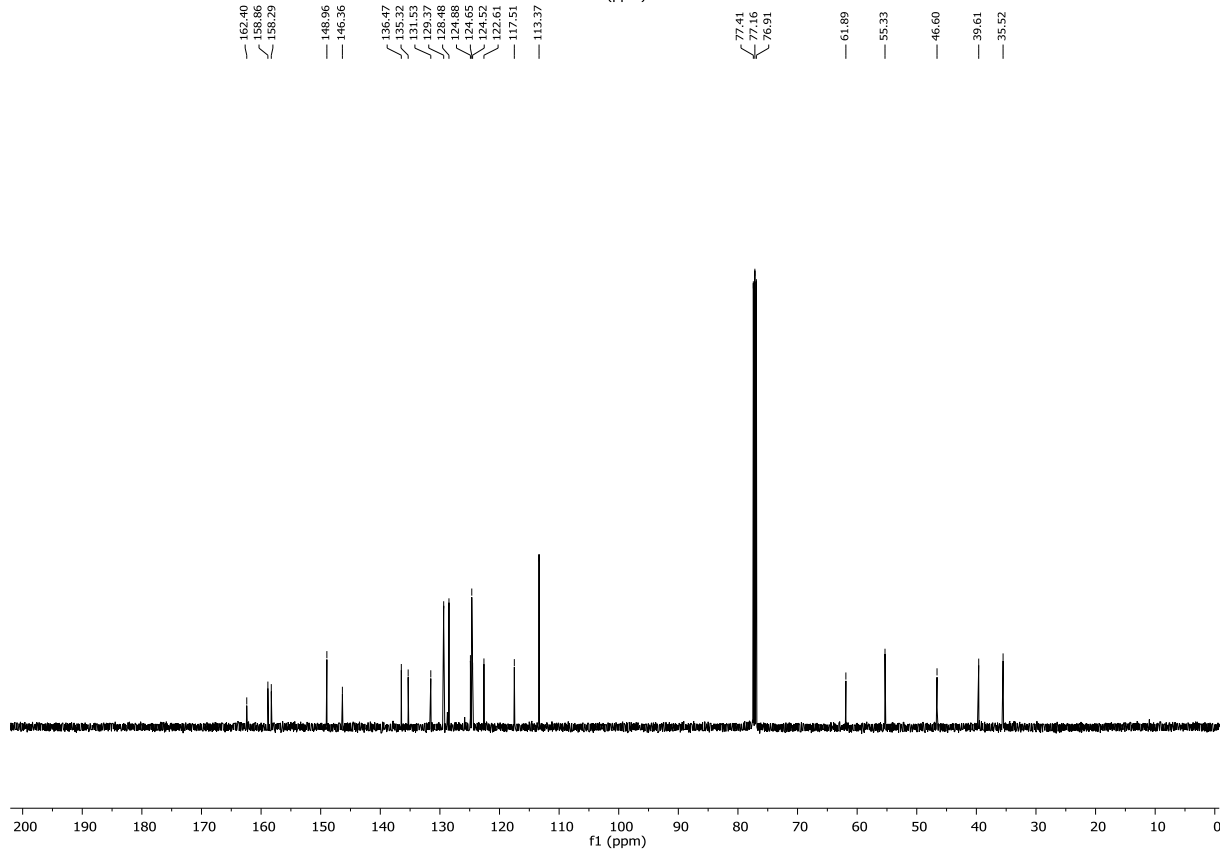
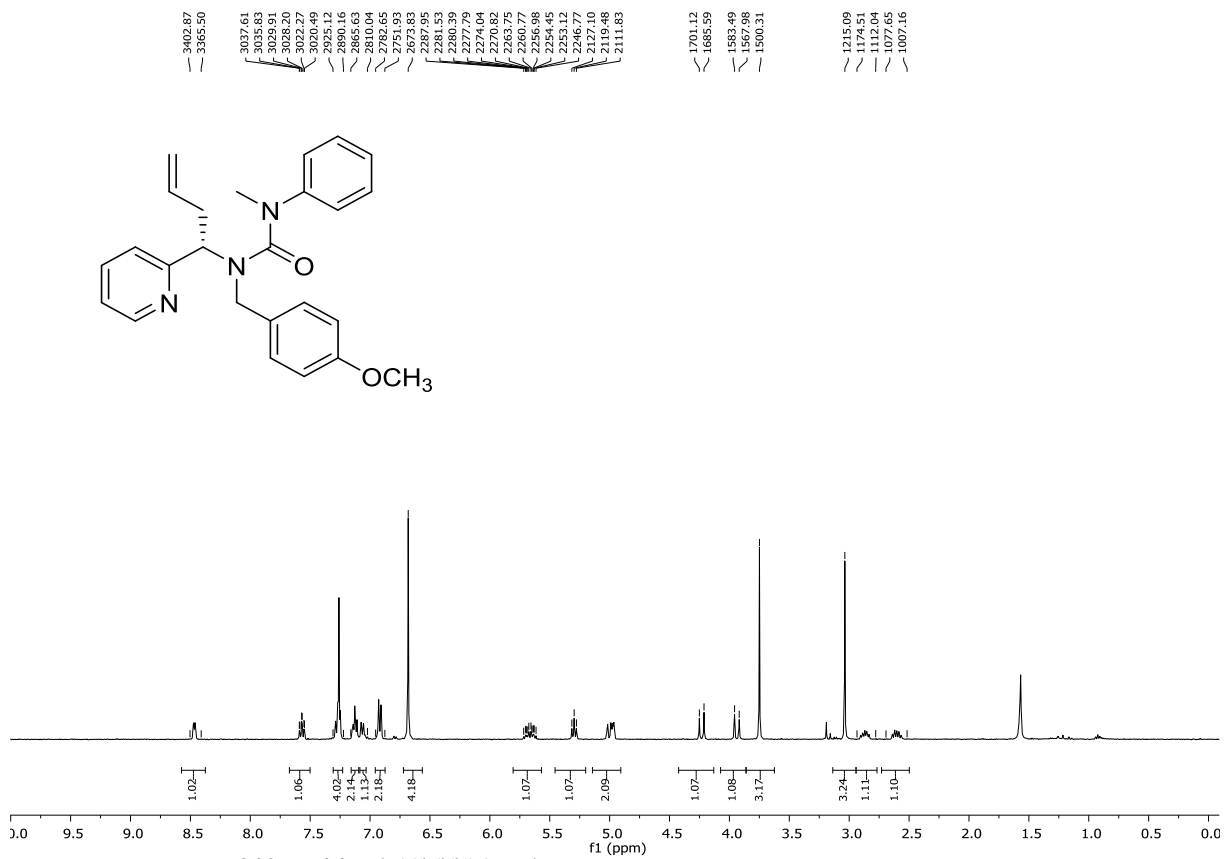
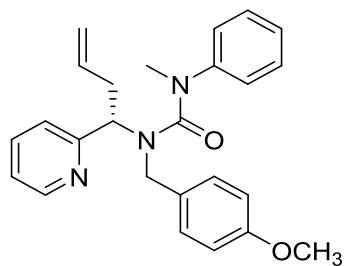
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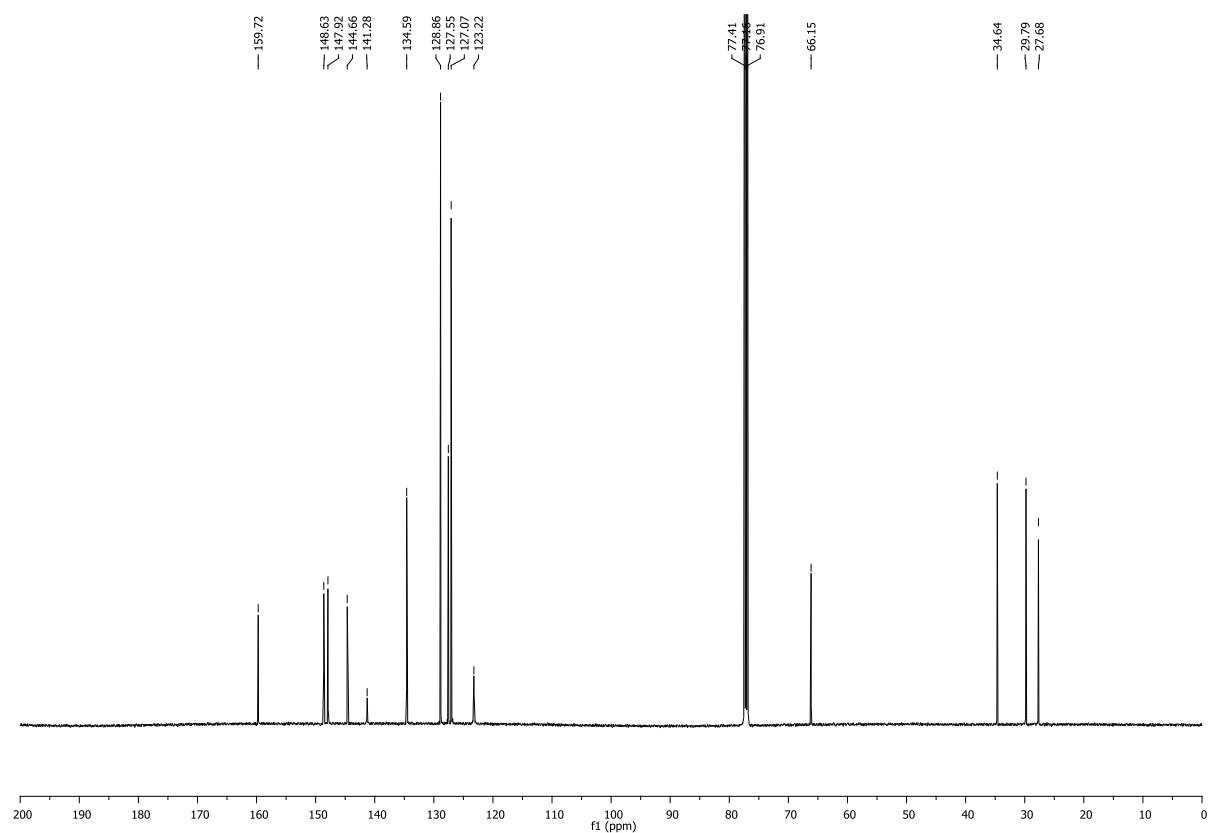
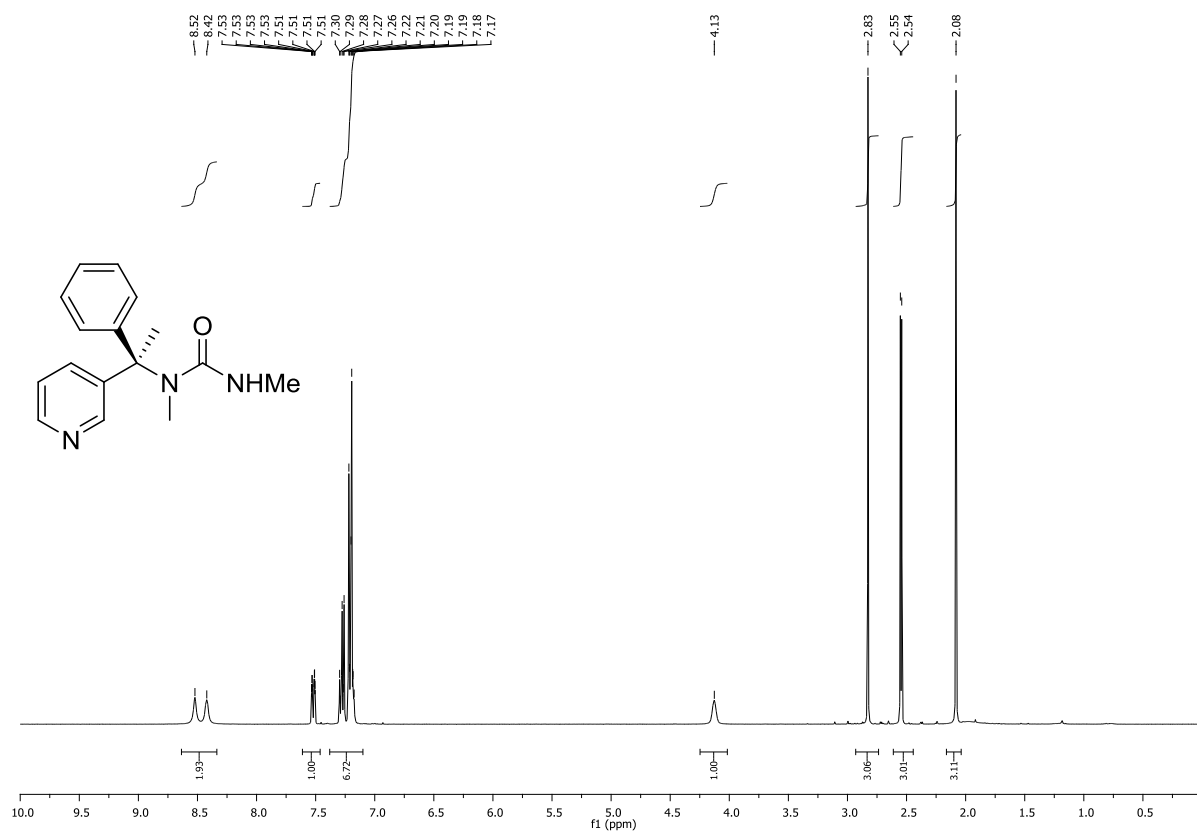
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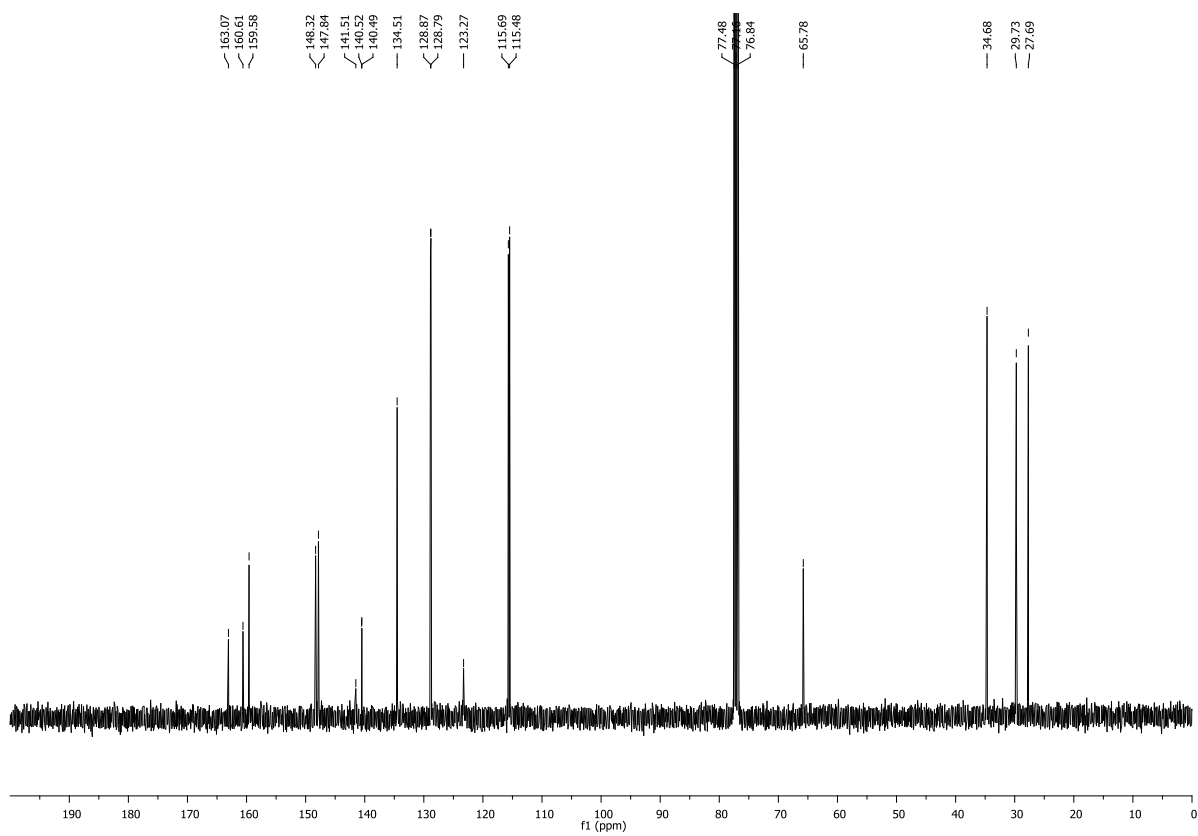
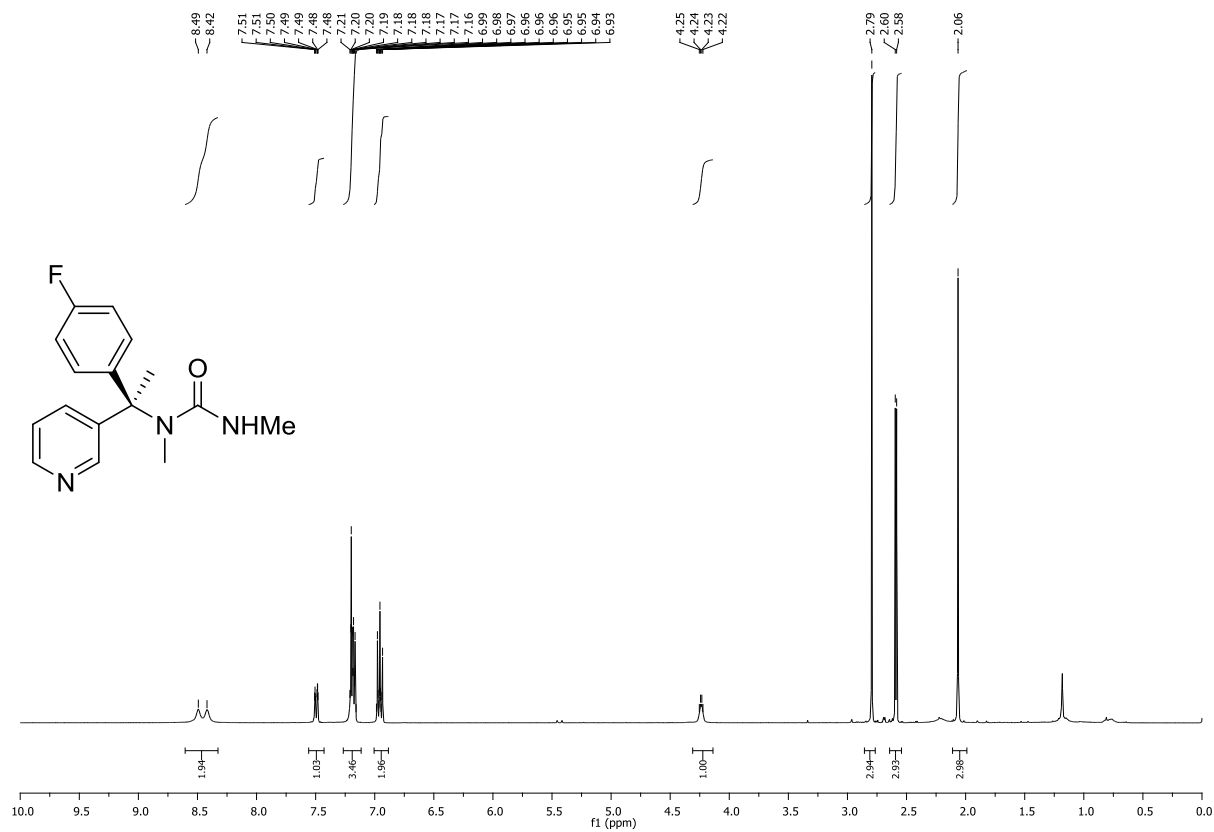
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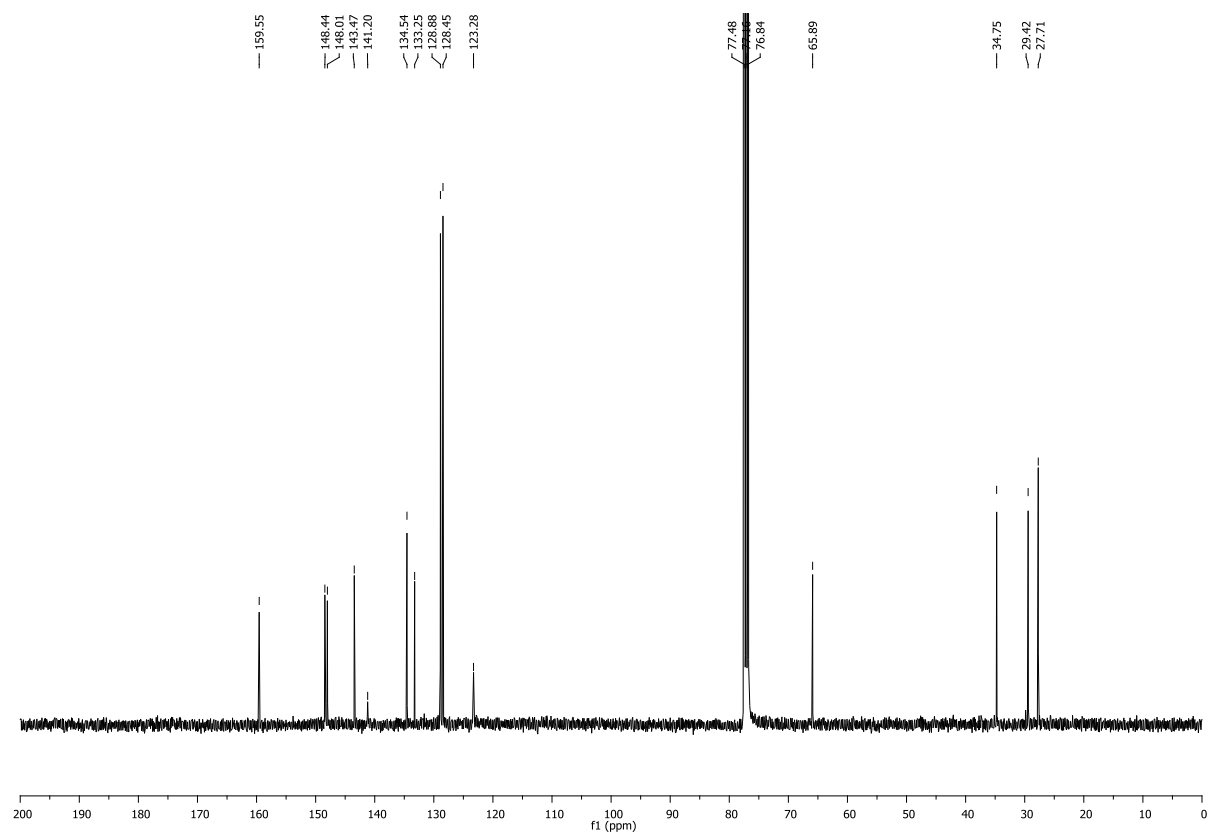
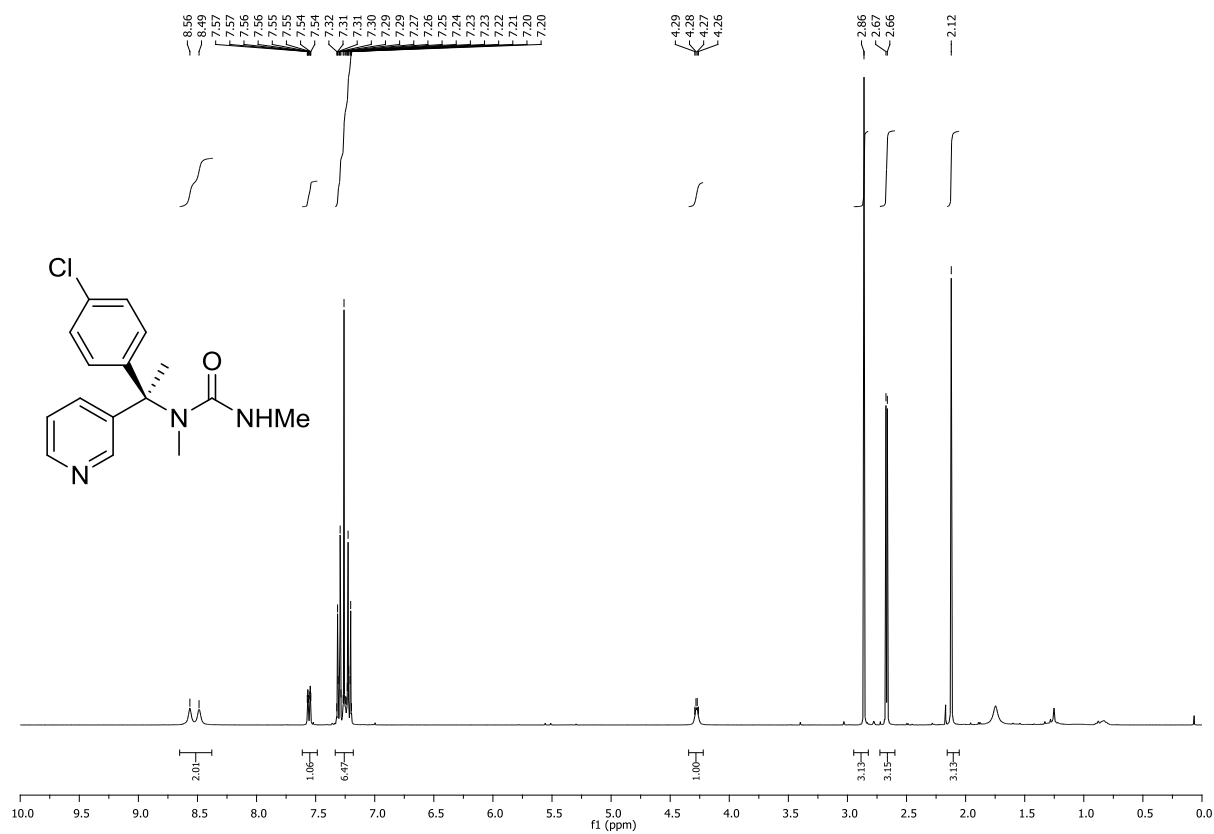
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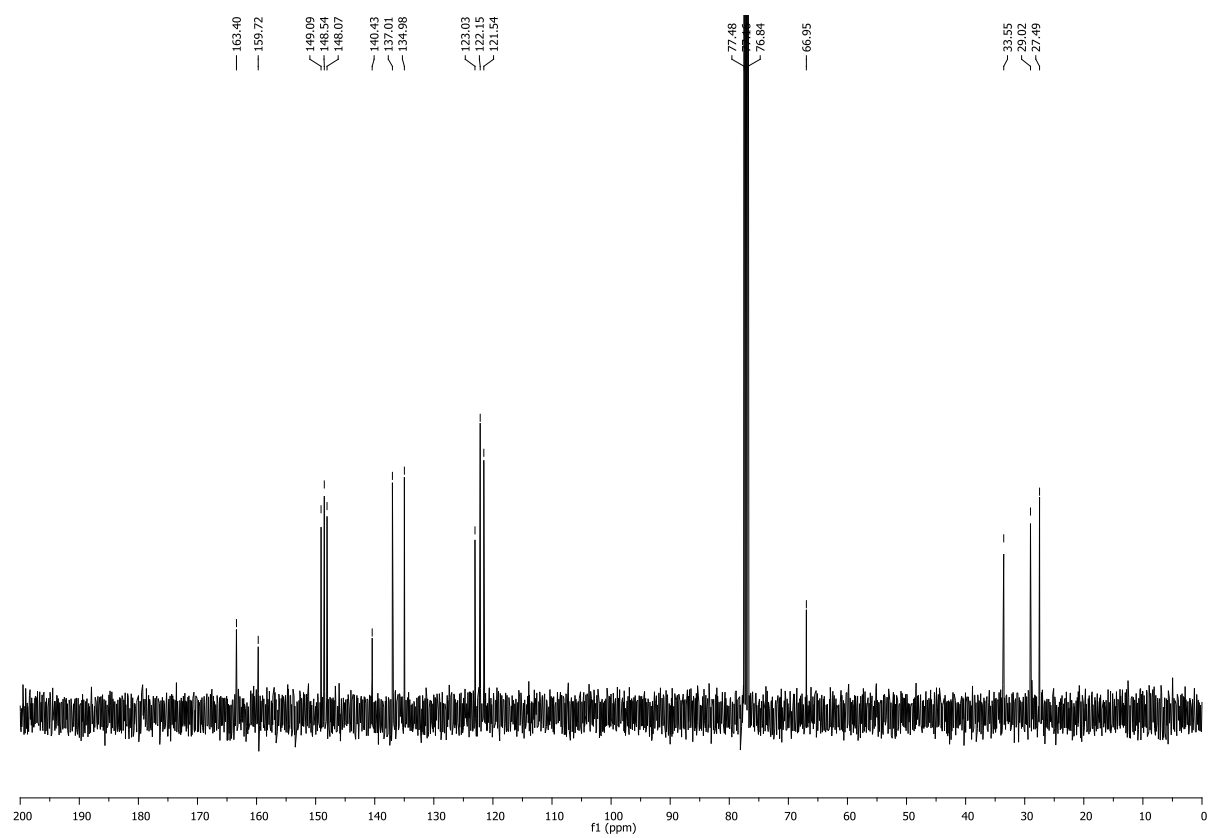
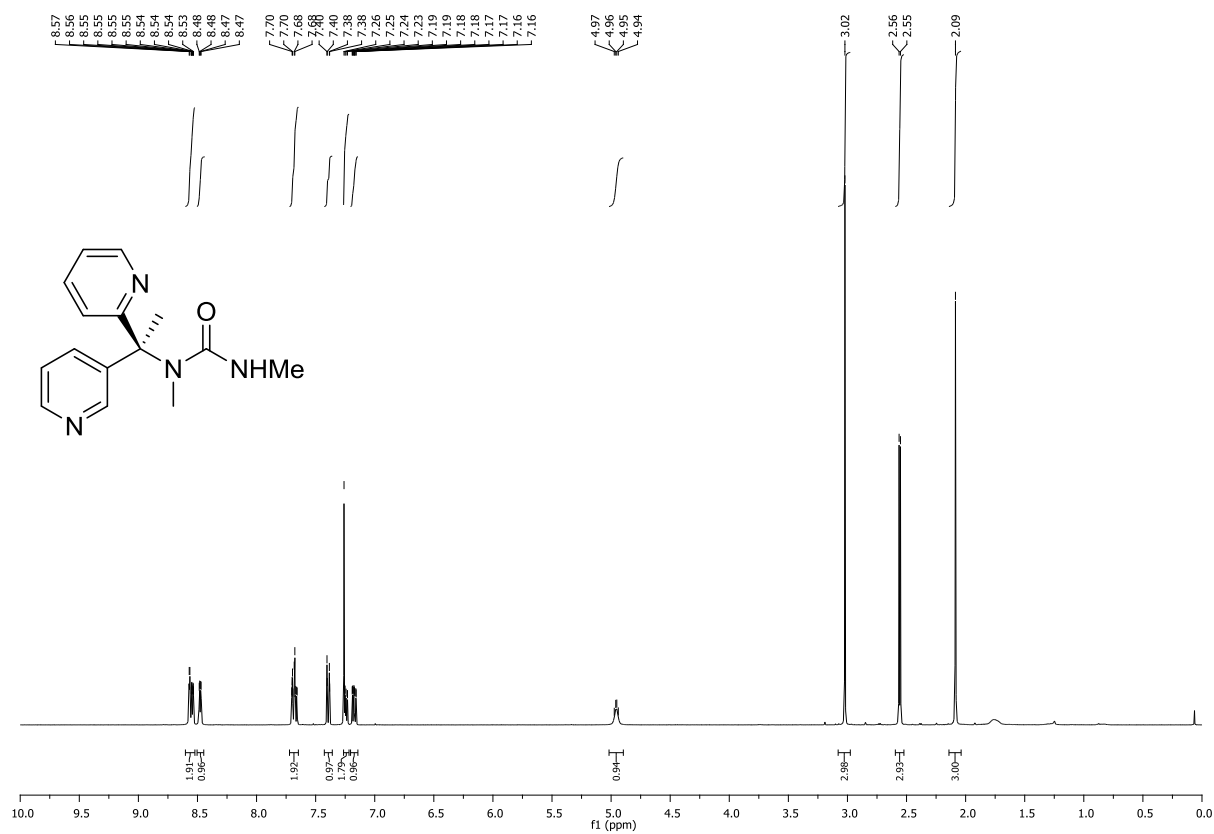
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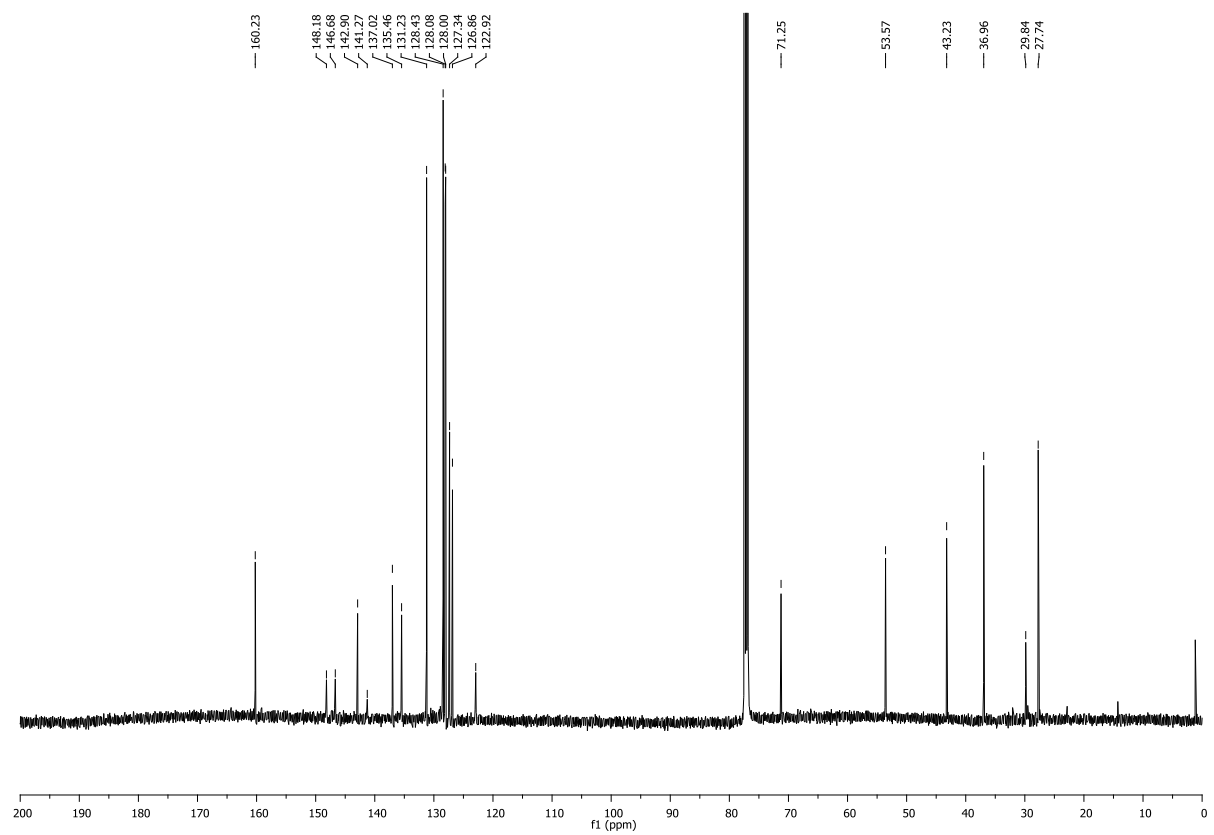
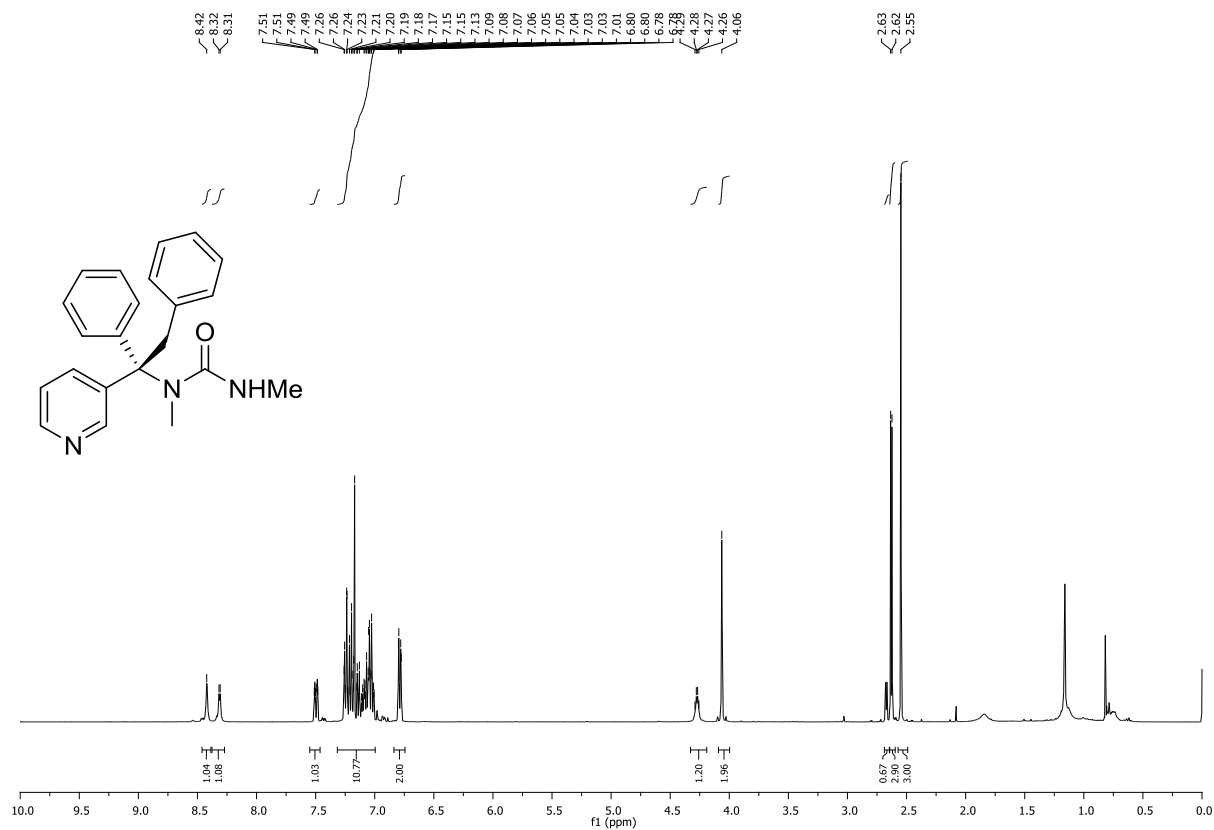
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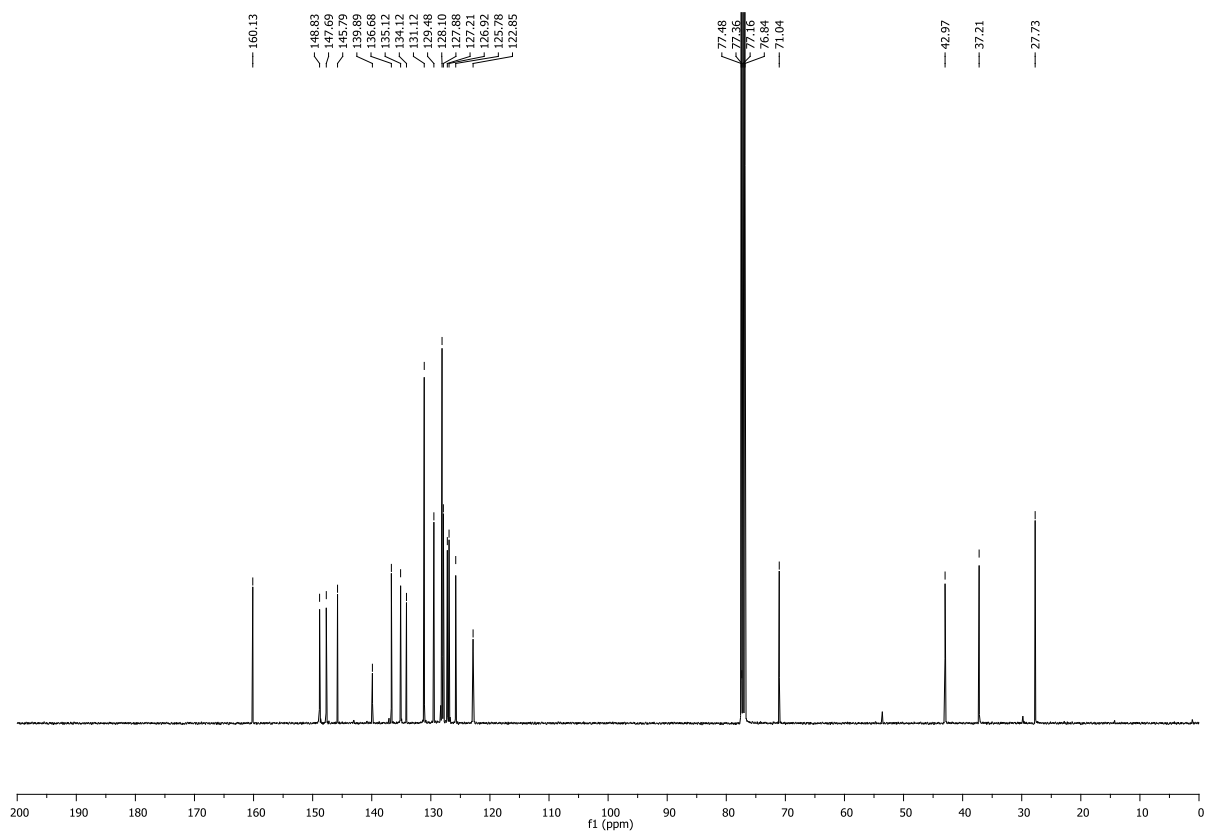
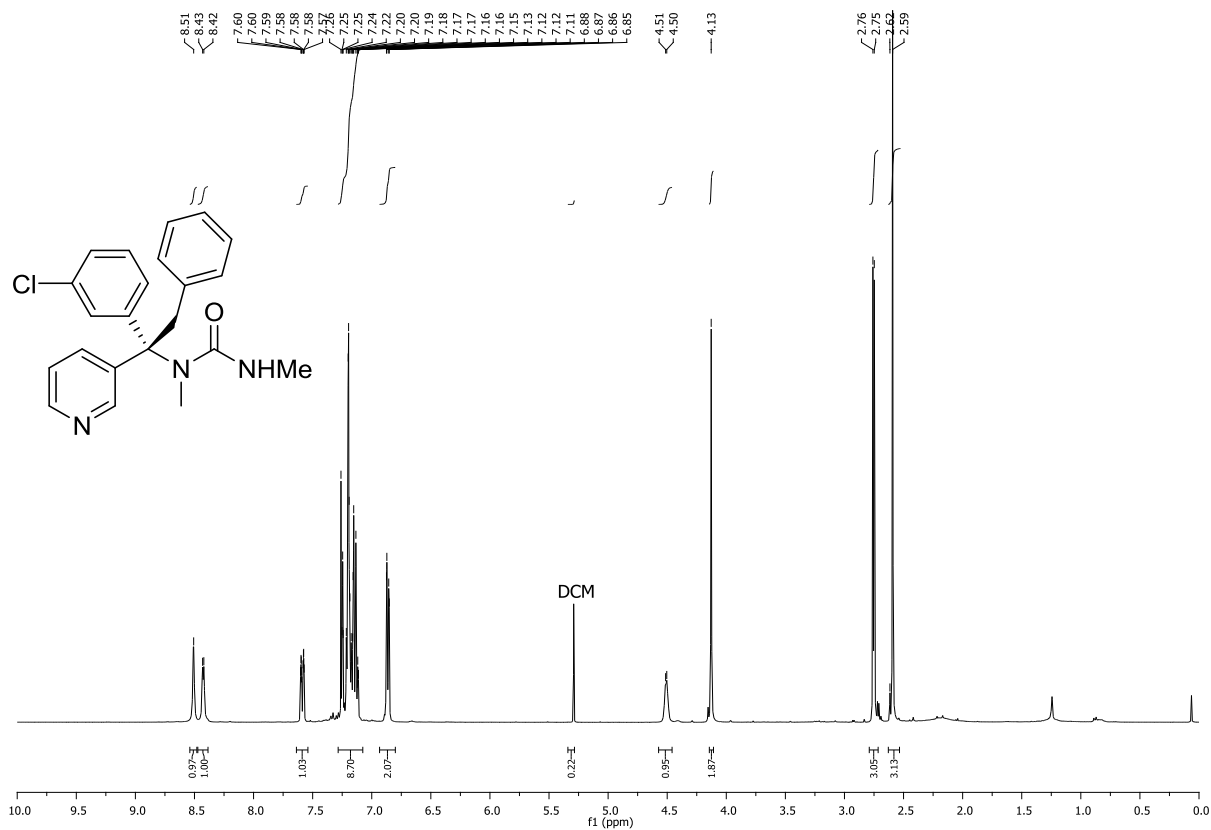
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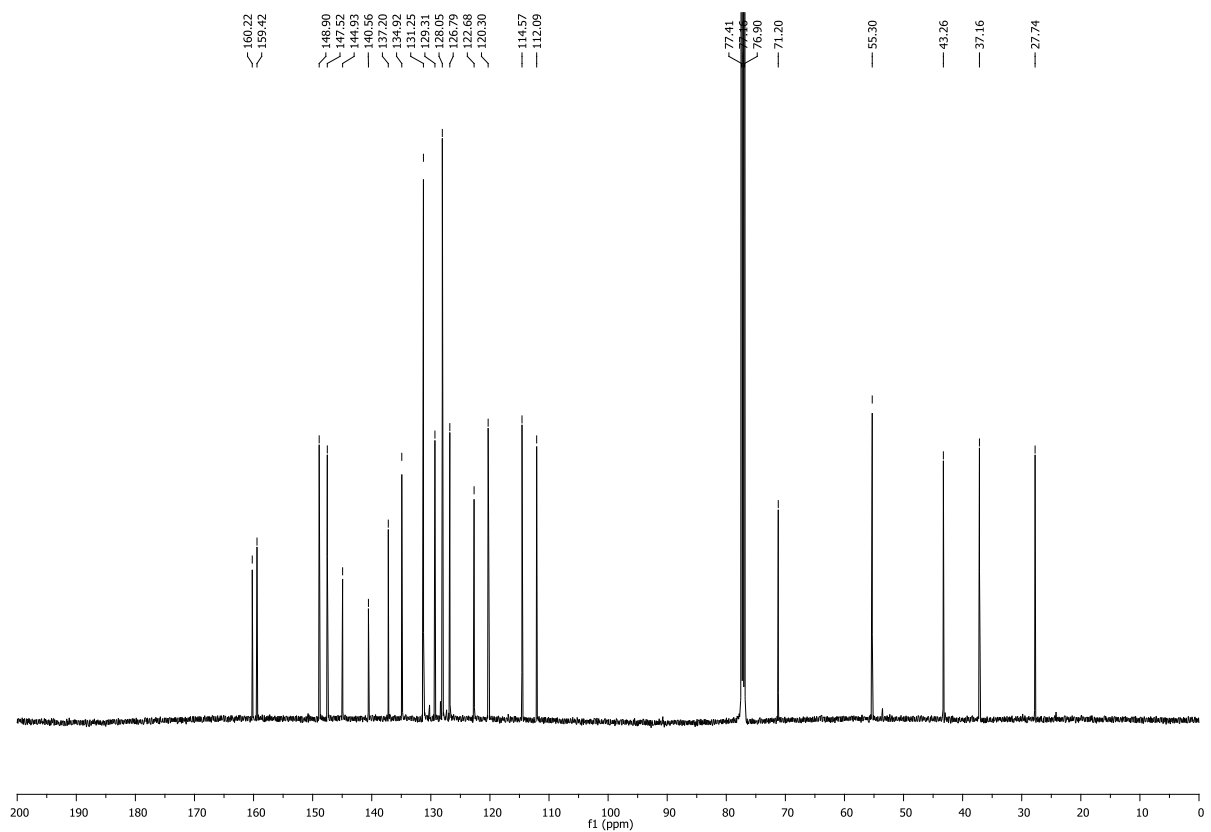
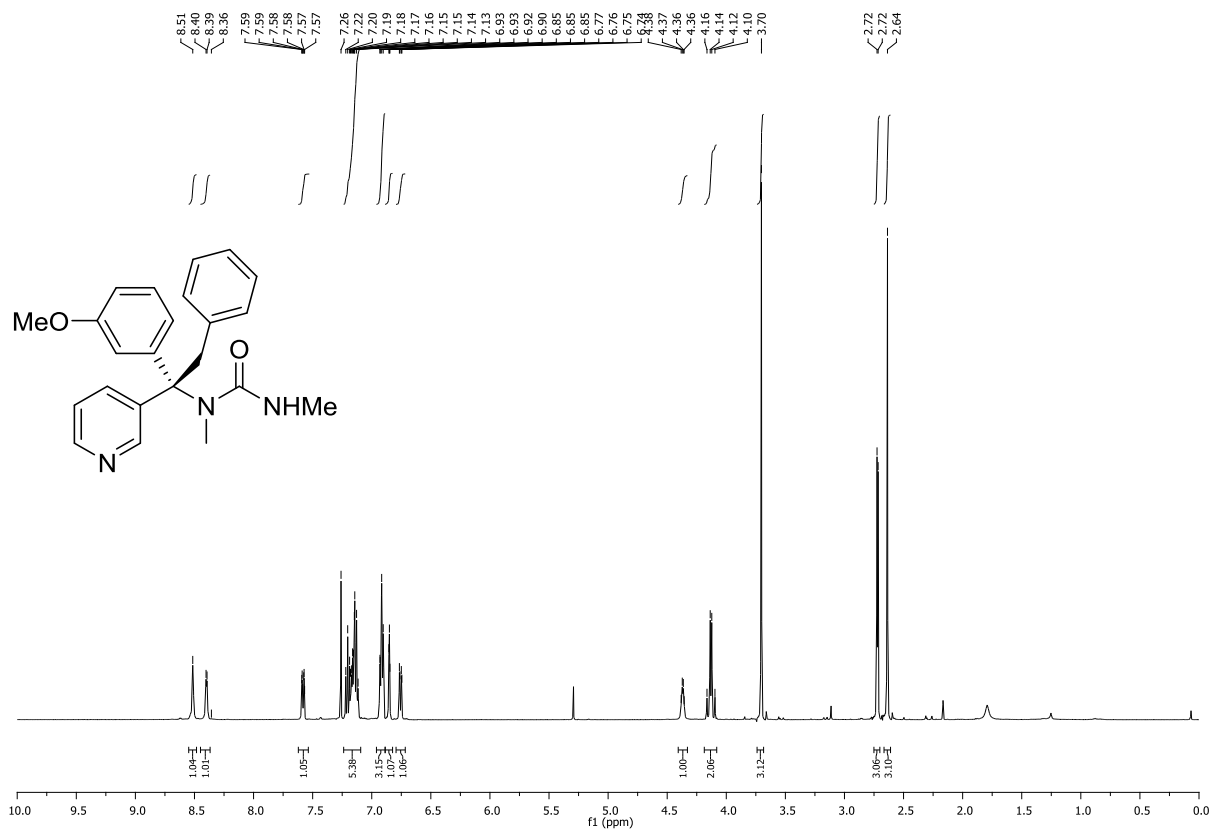
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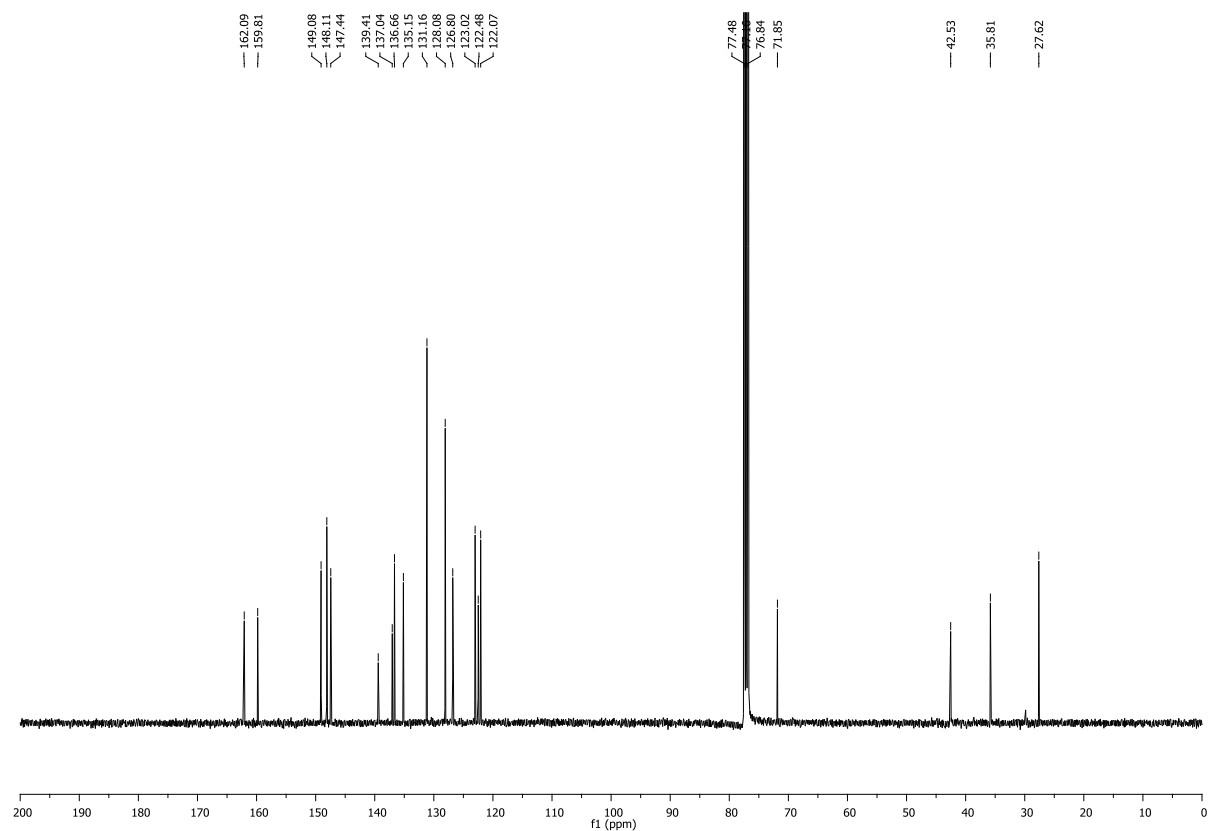
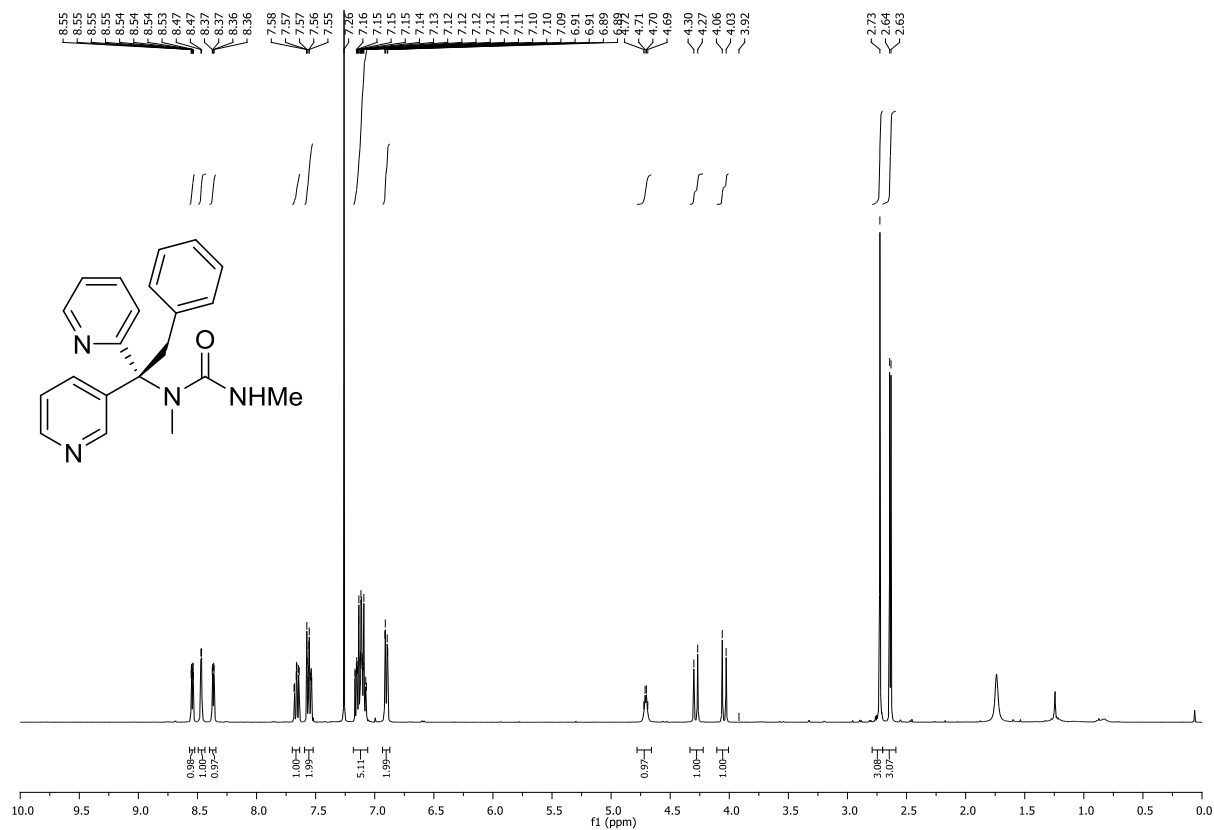
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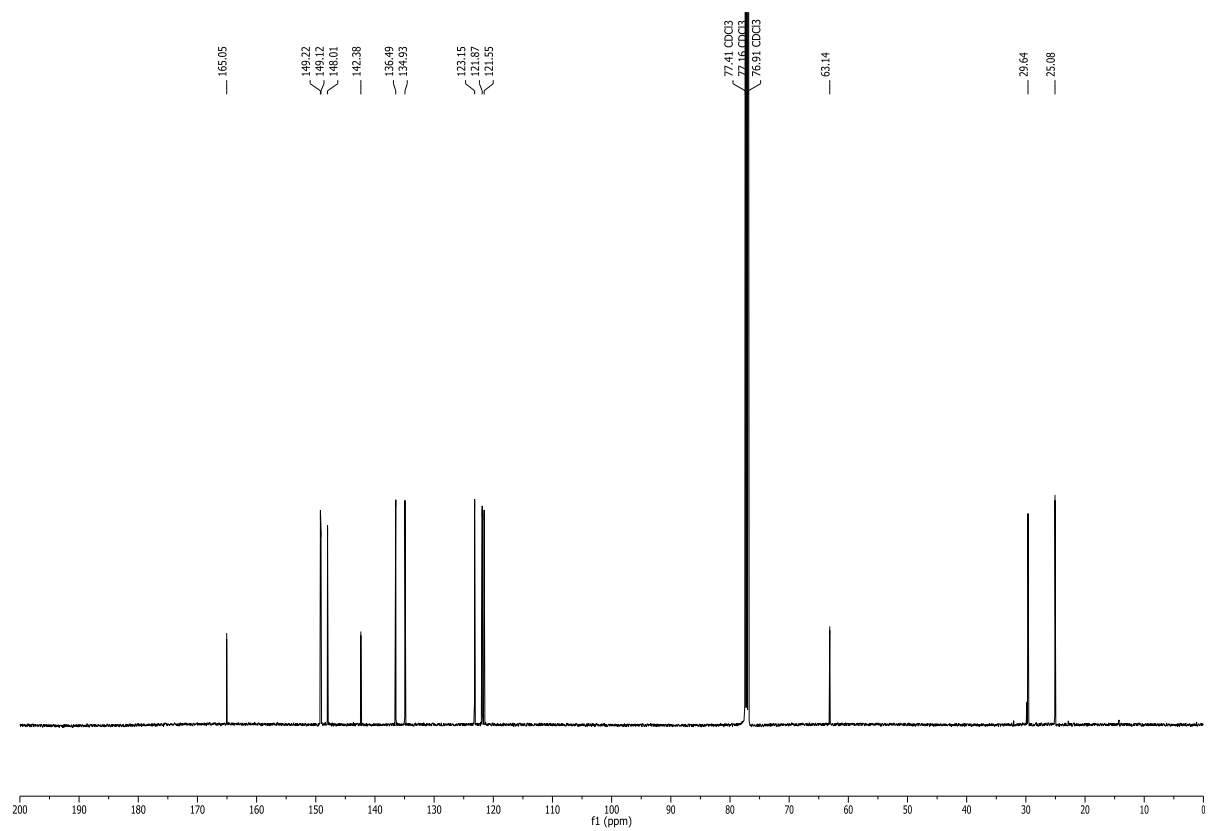
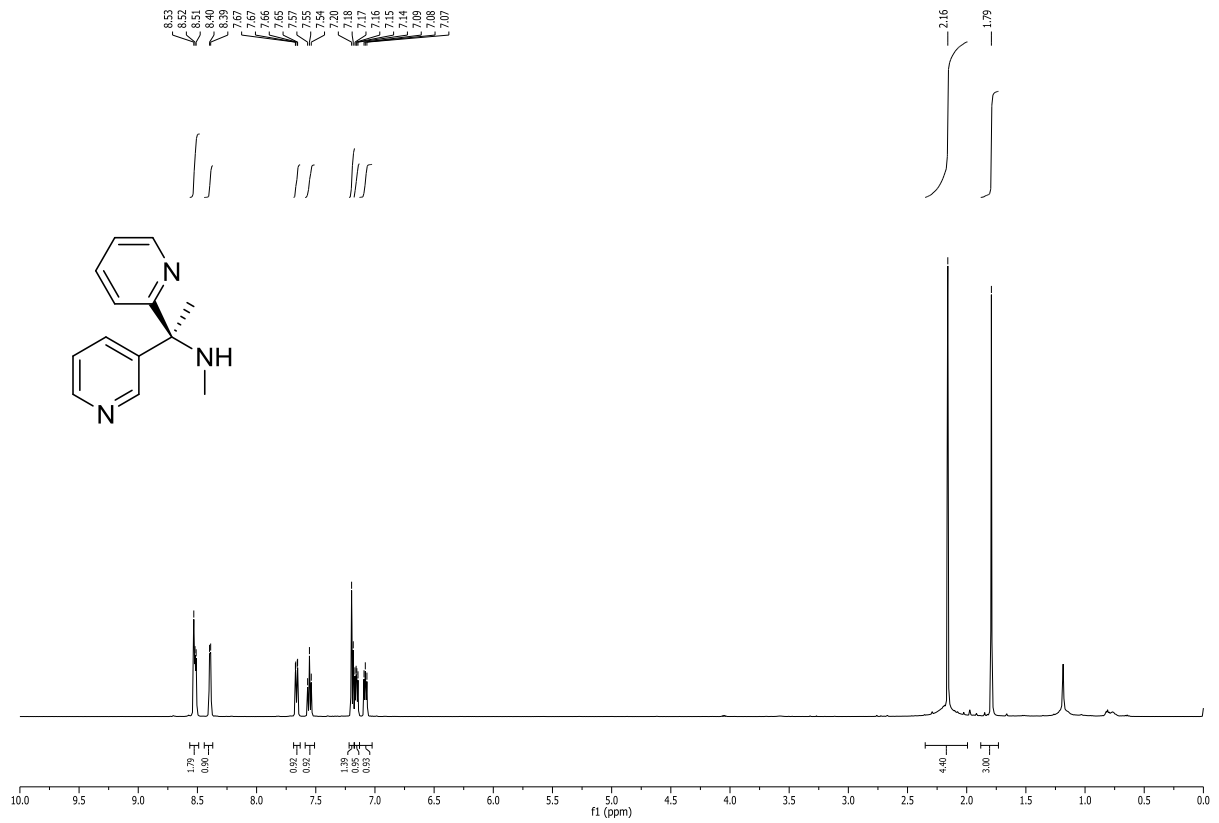
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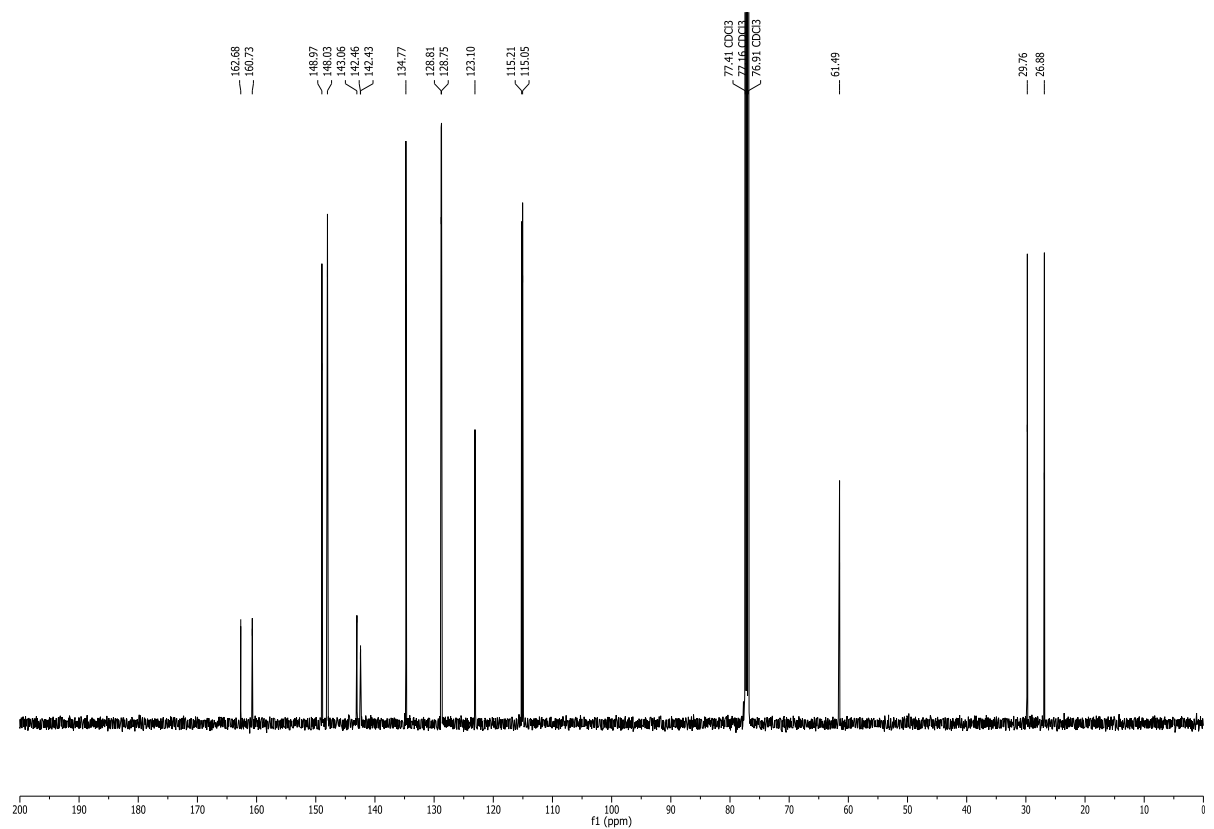
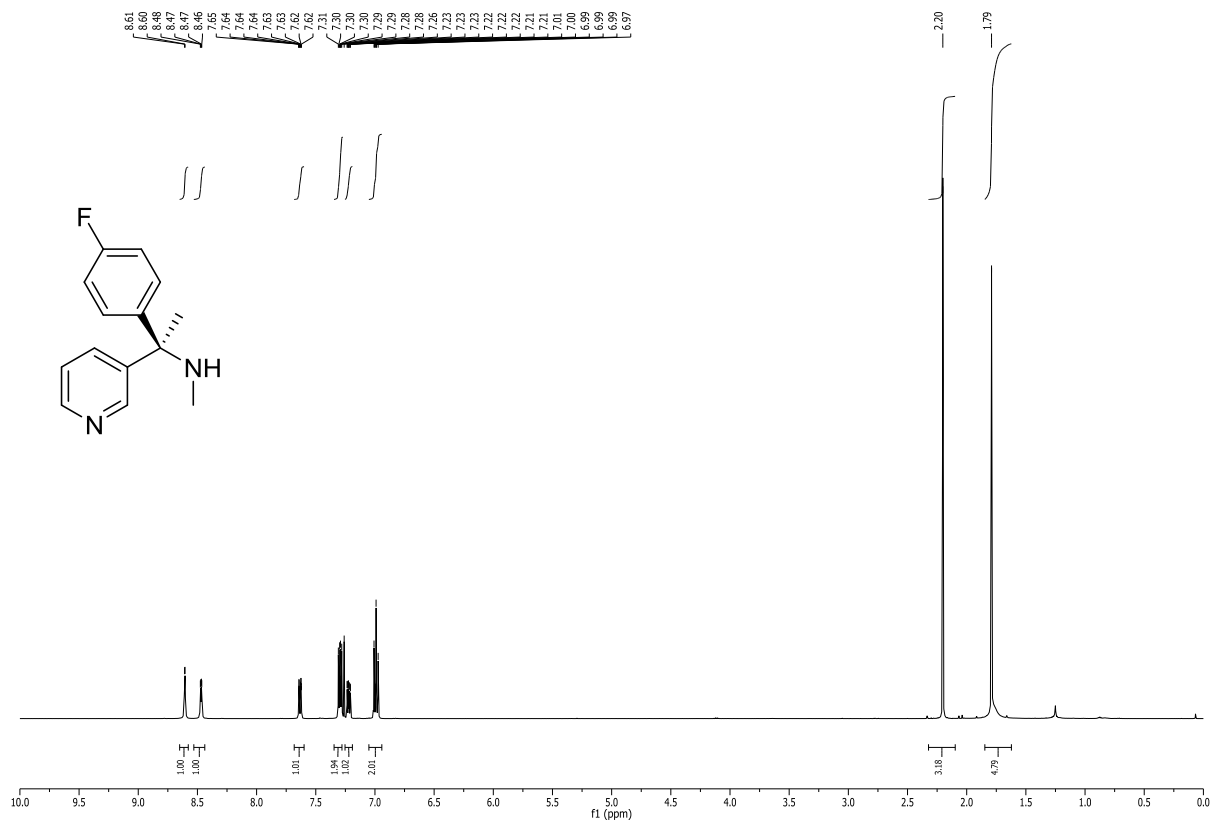
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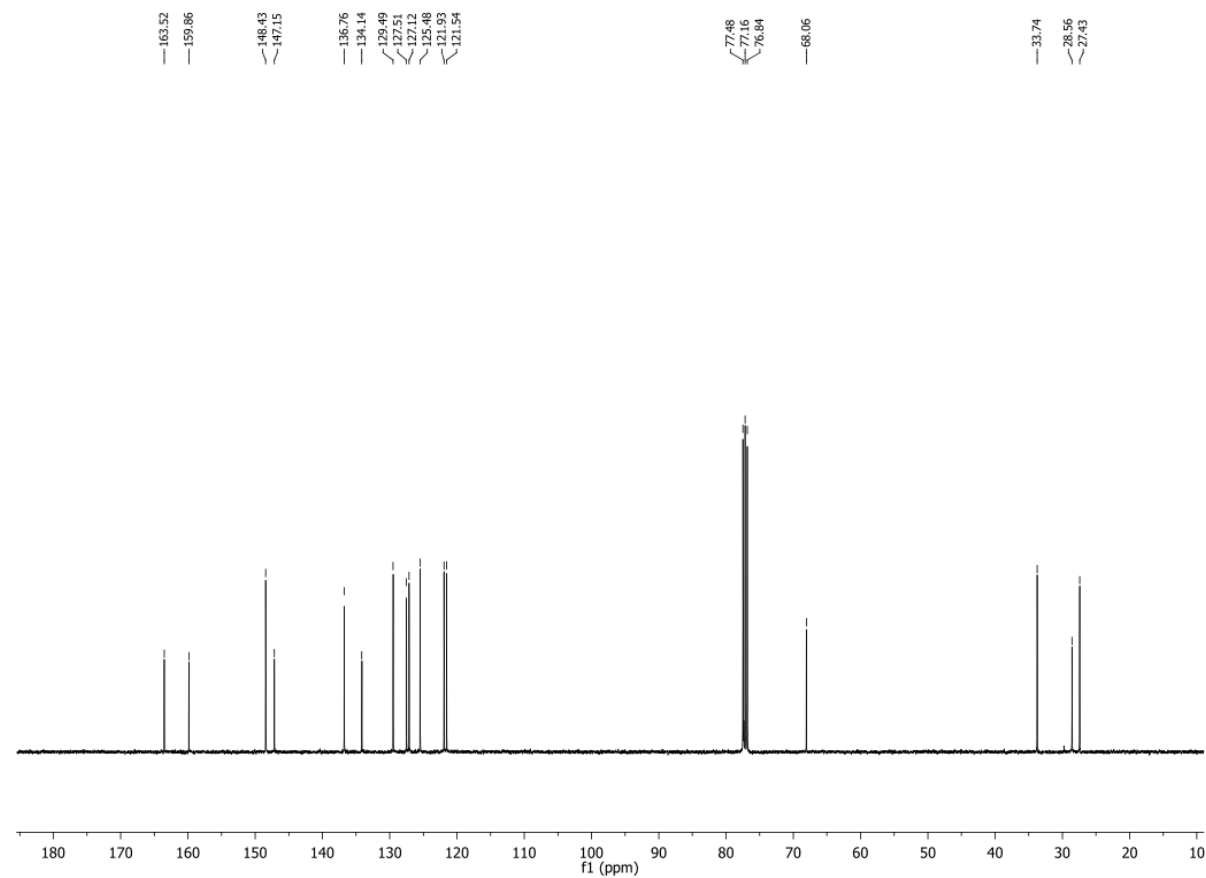
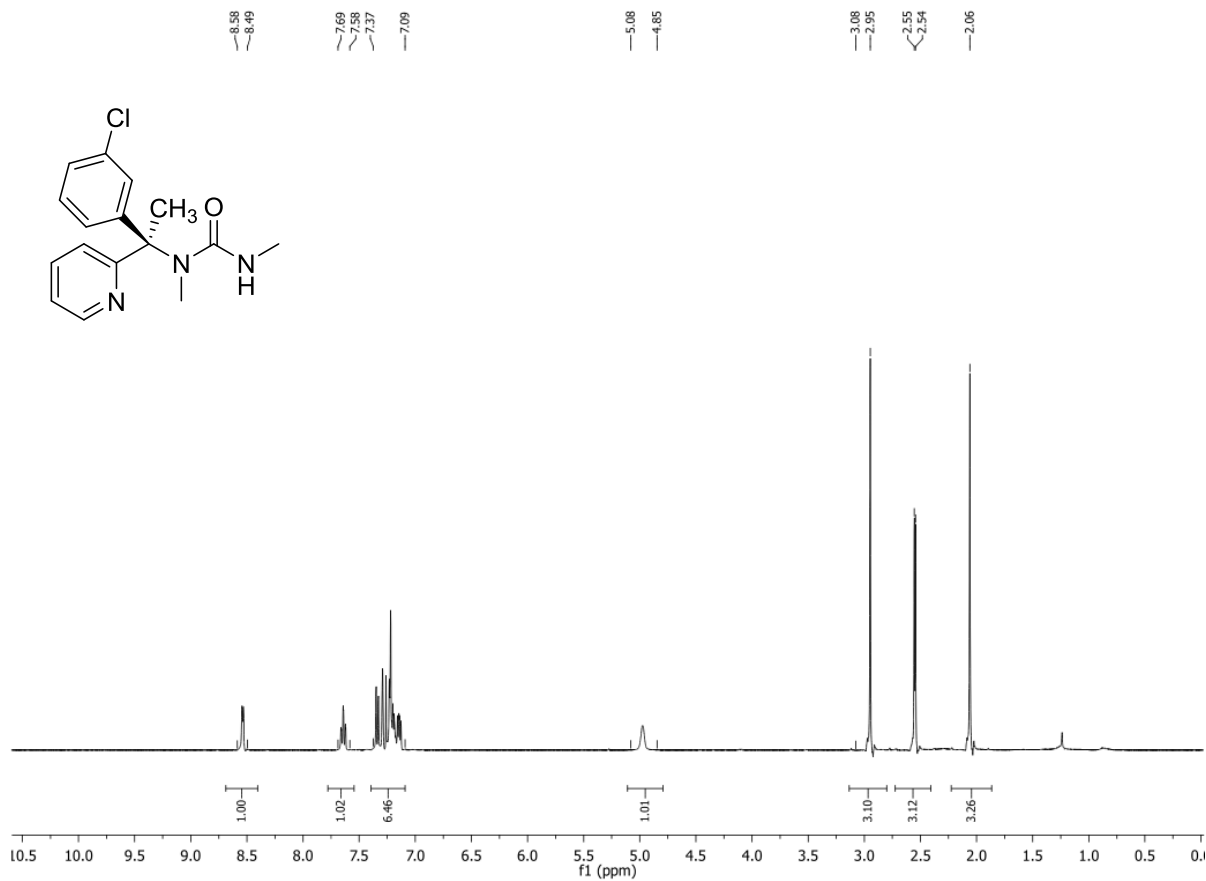
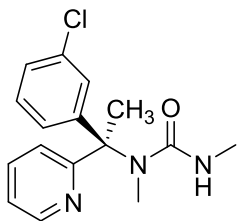
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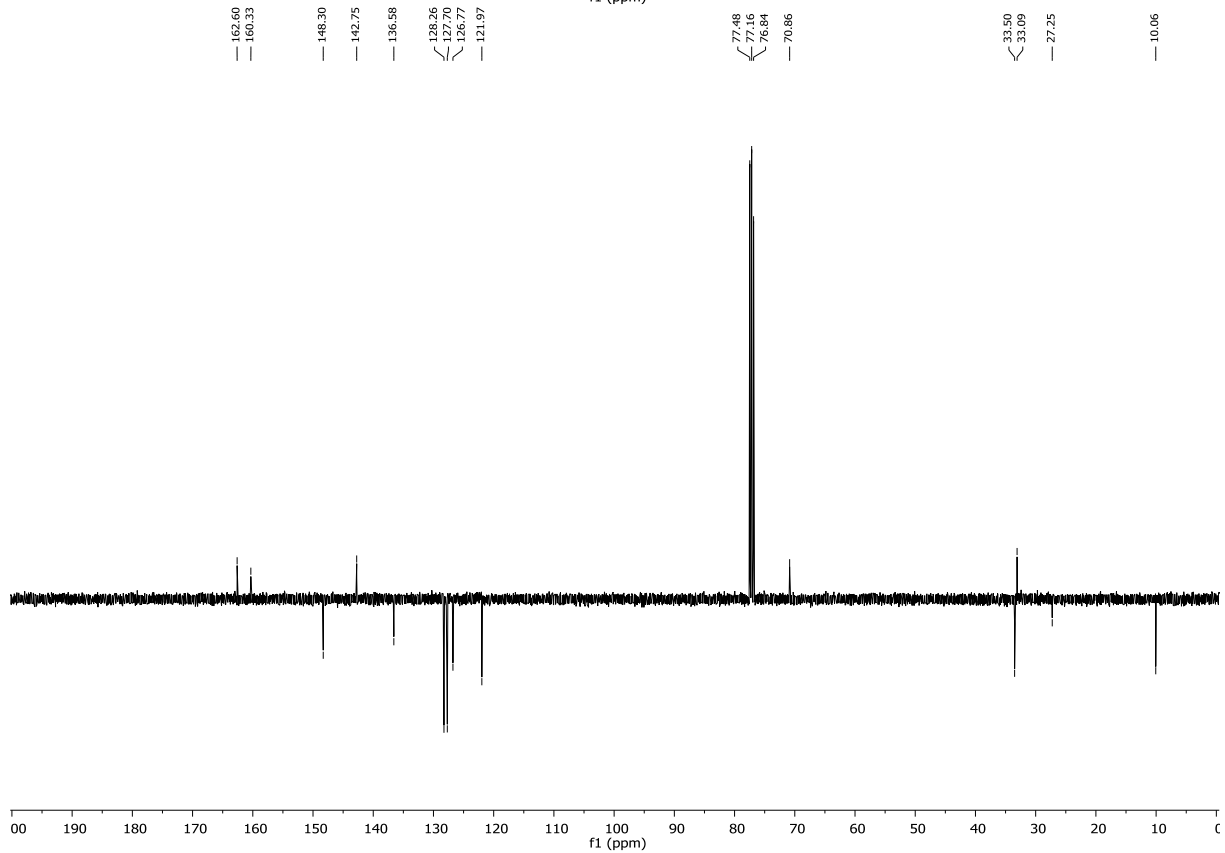
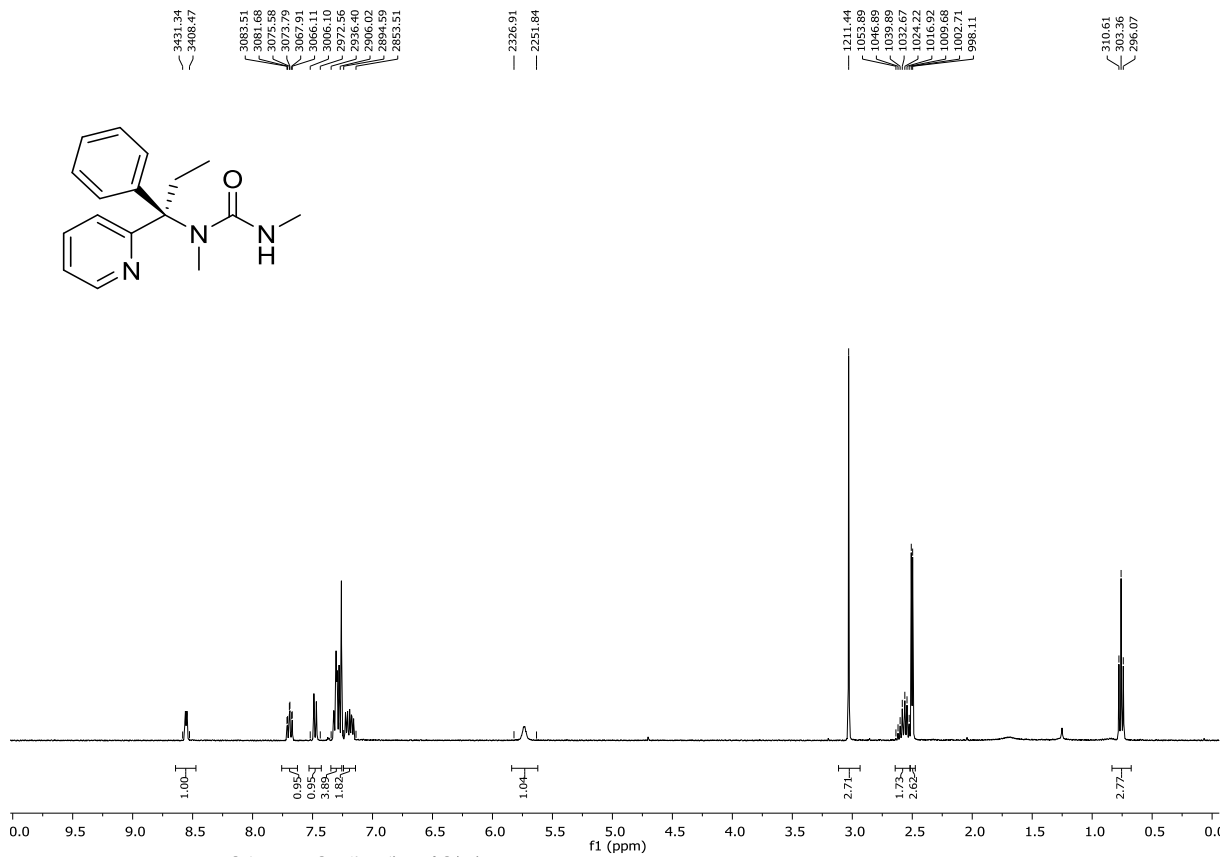
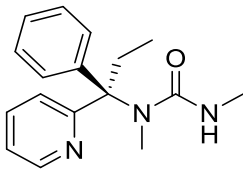
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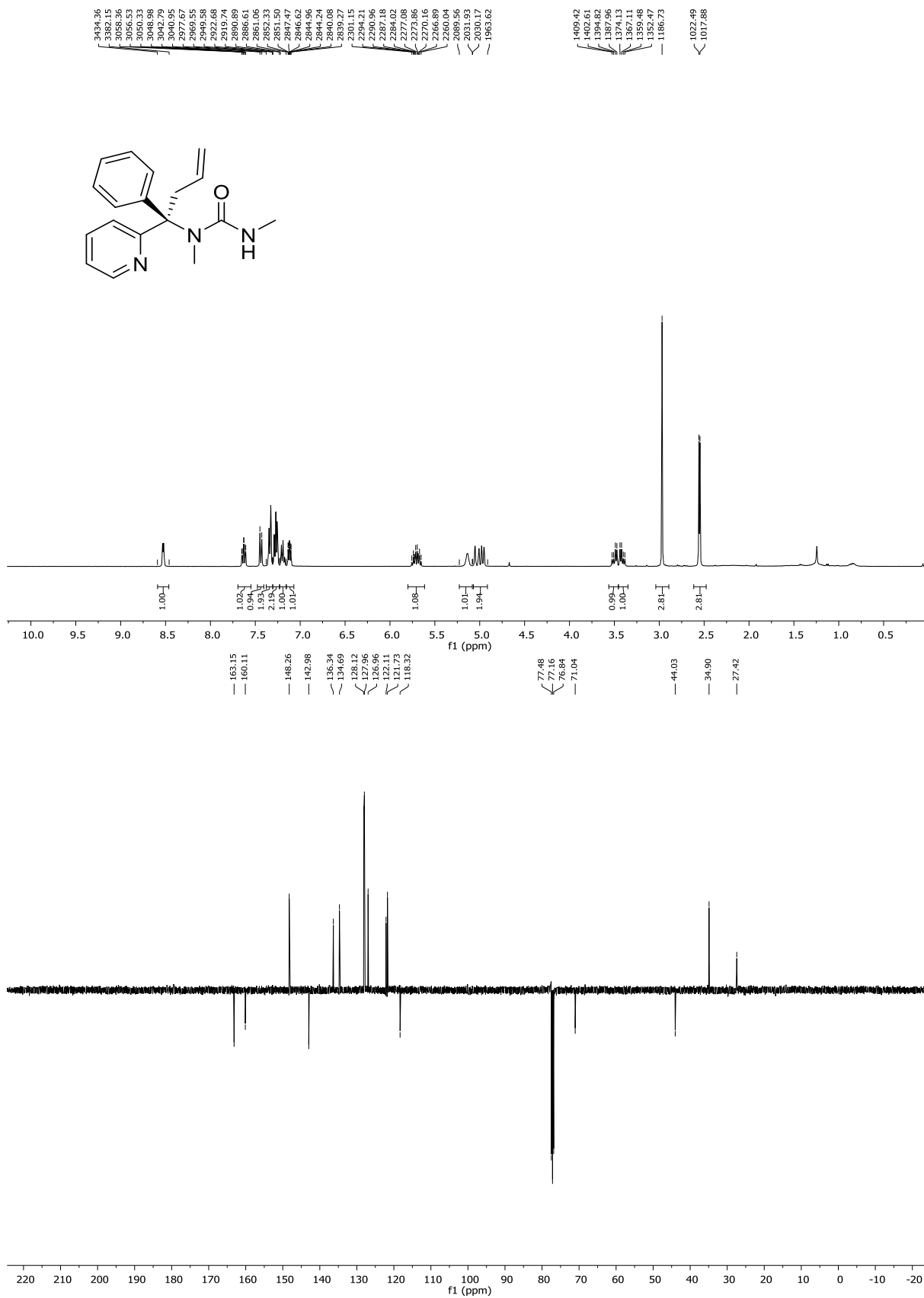
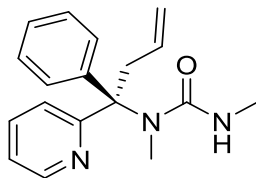
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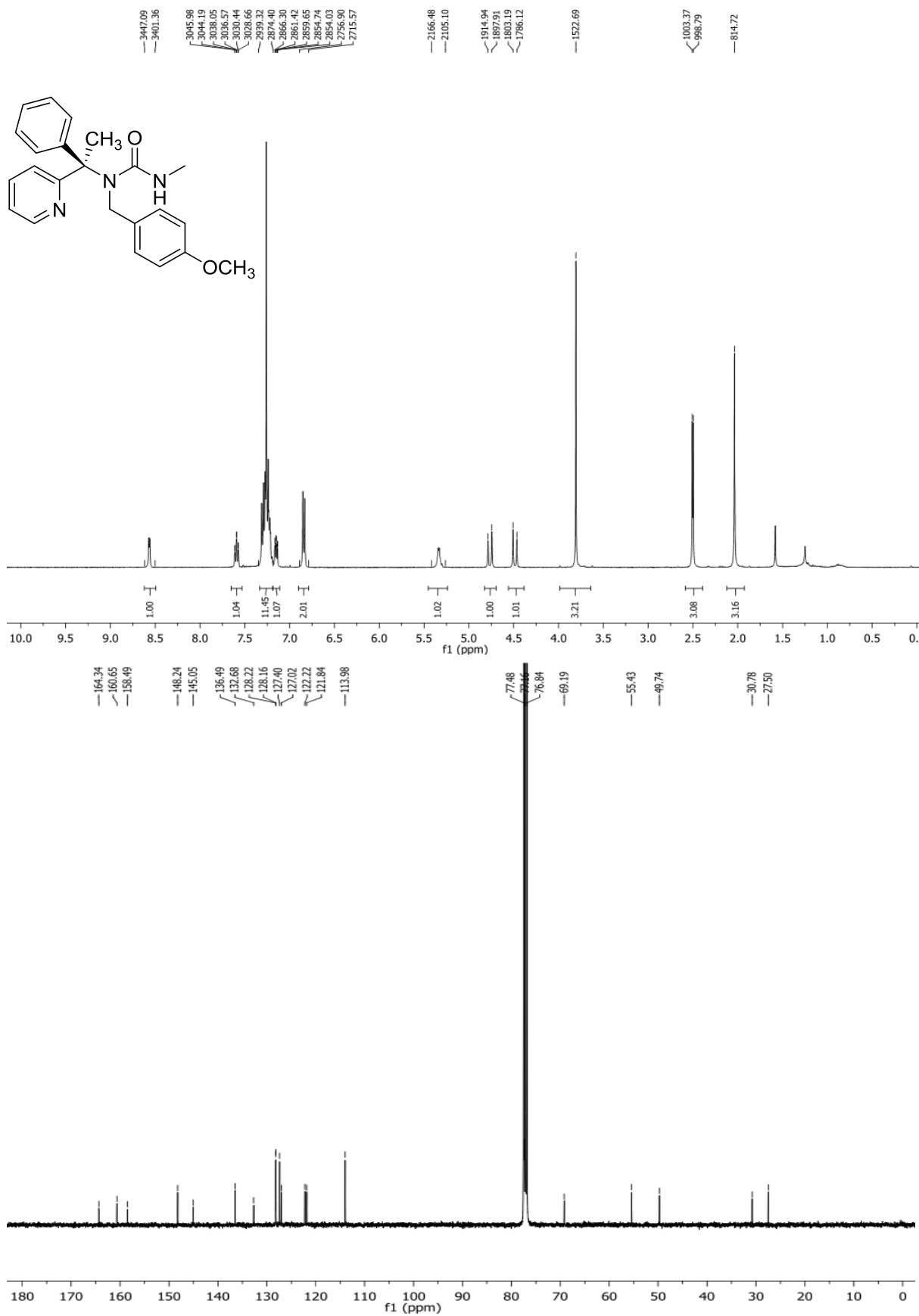
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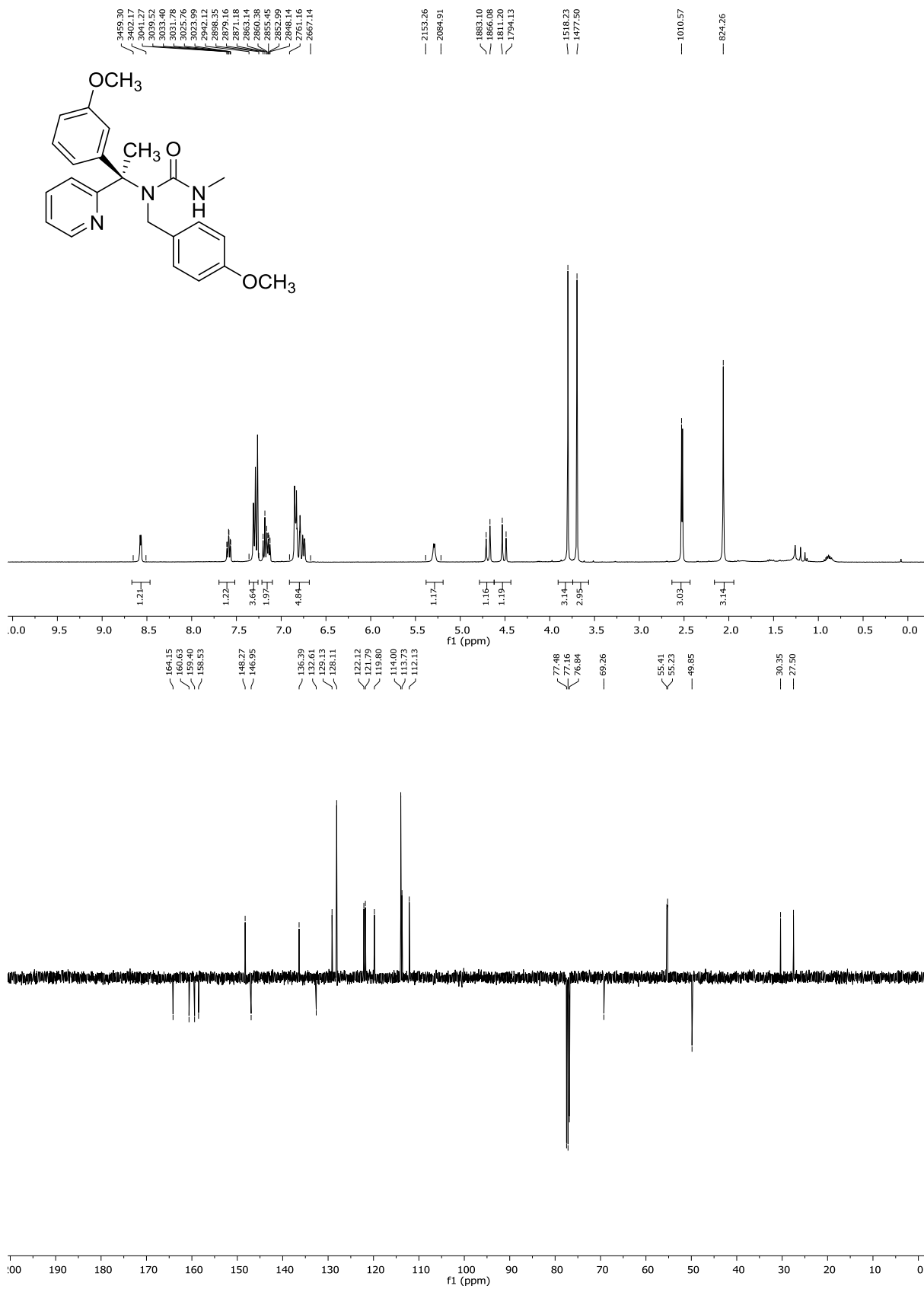
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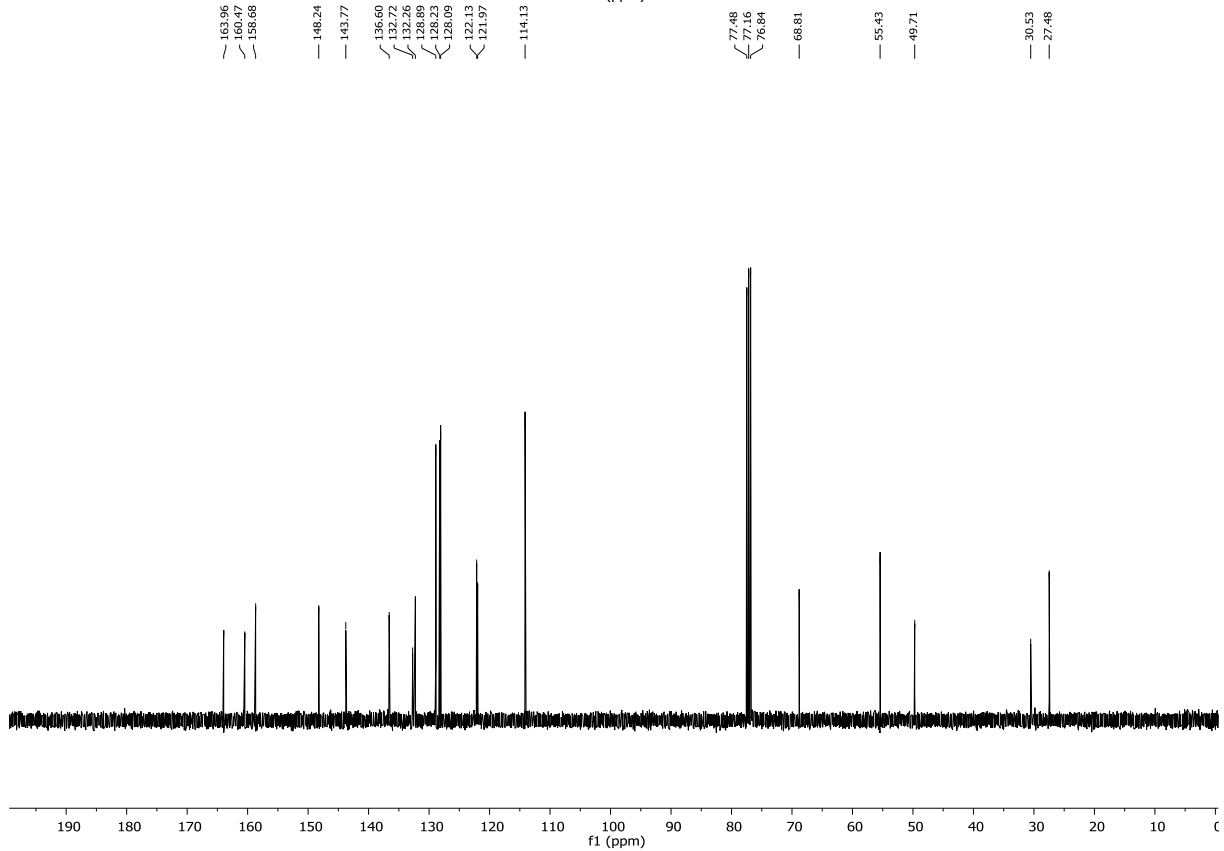
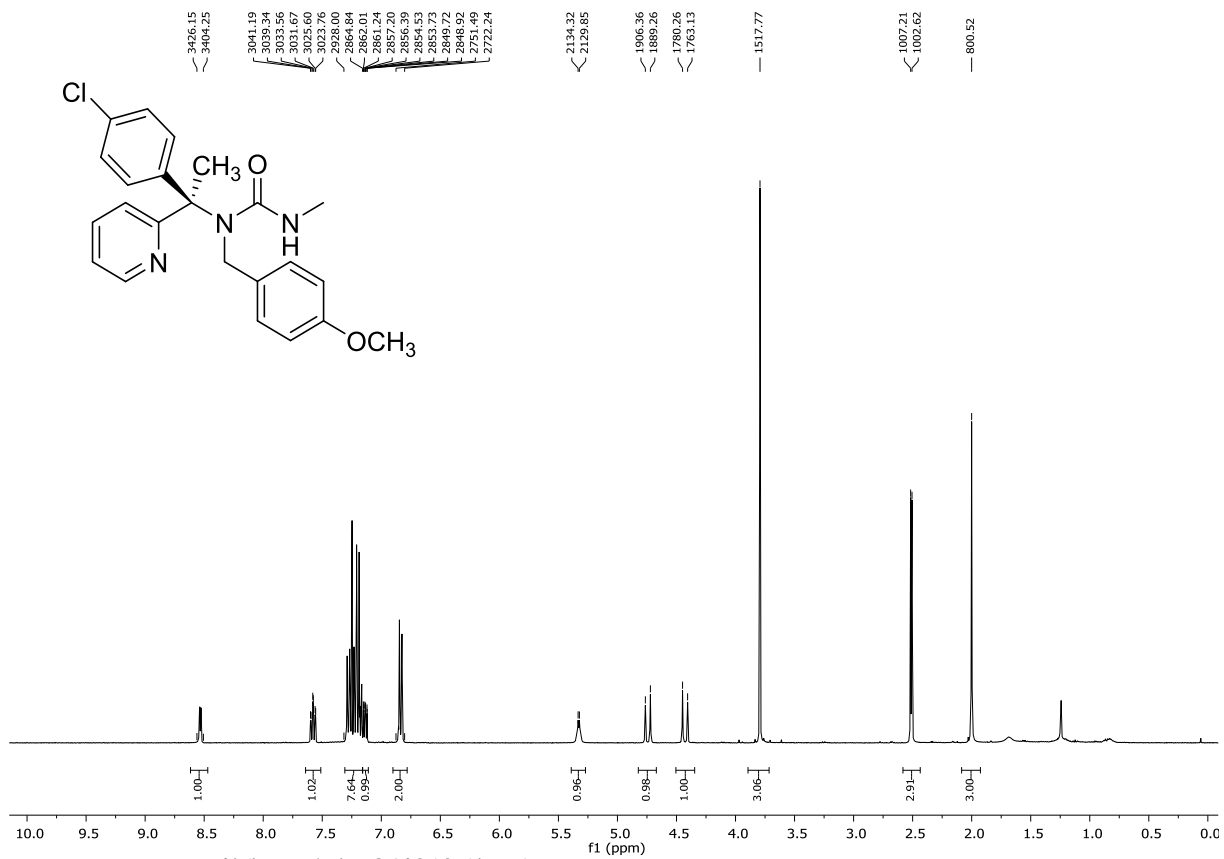
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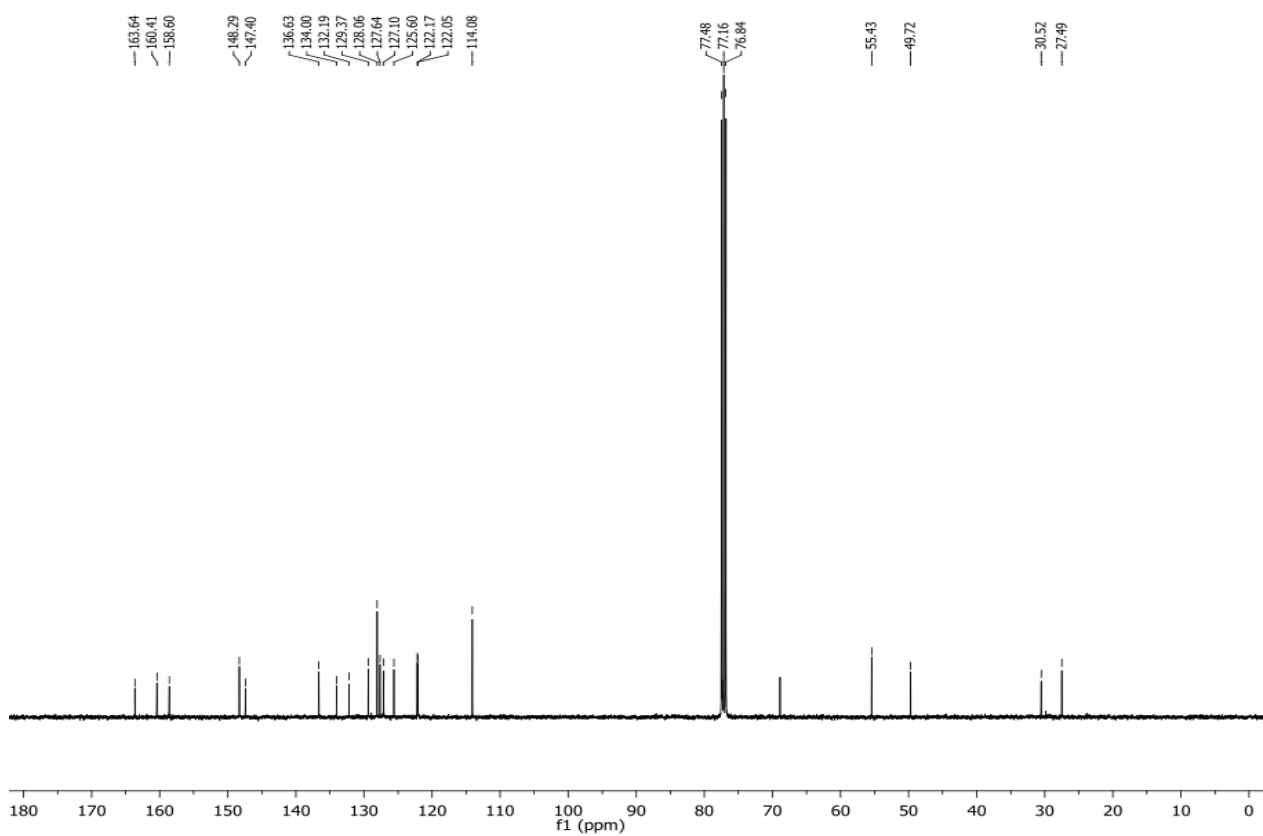
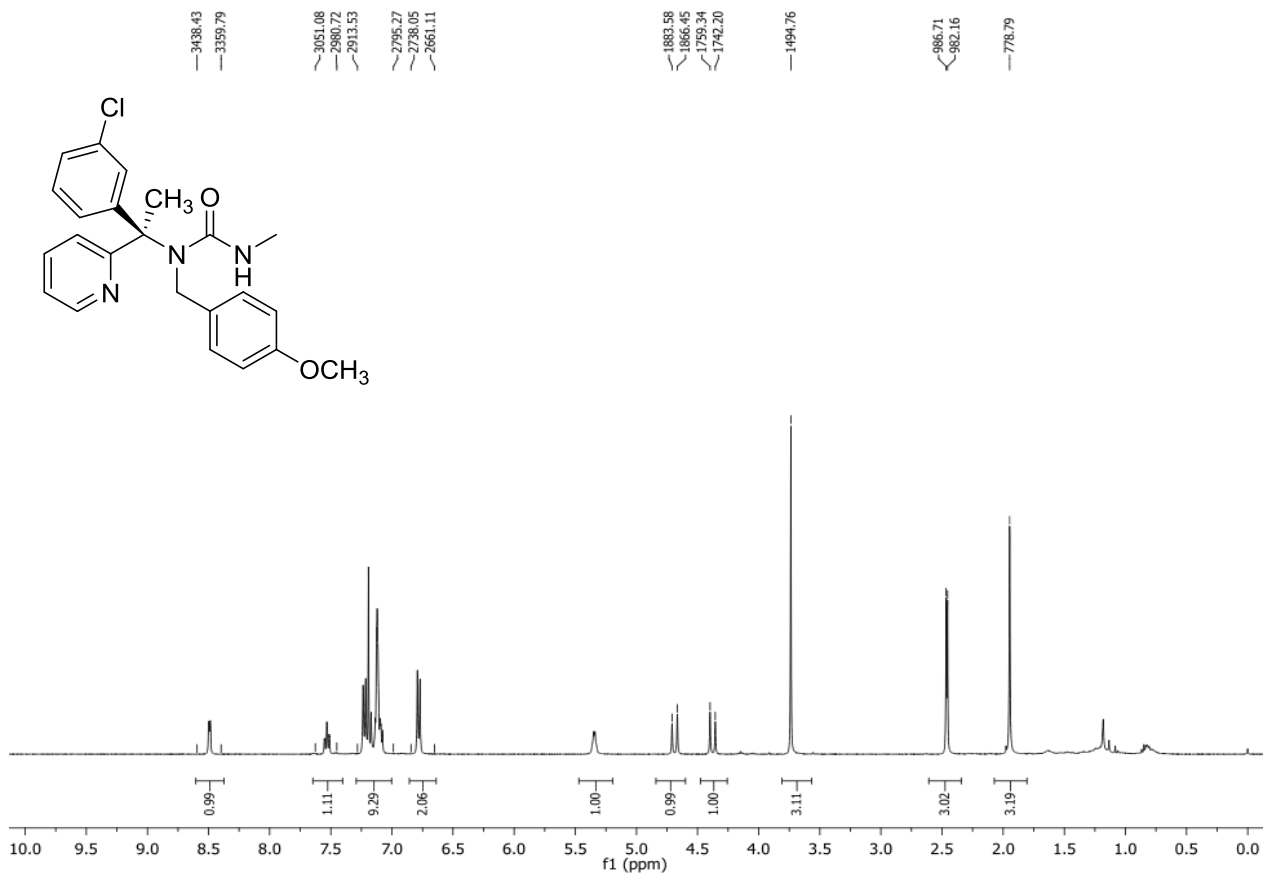
15c



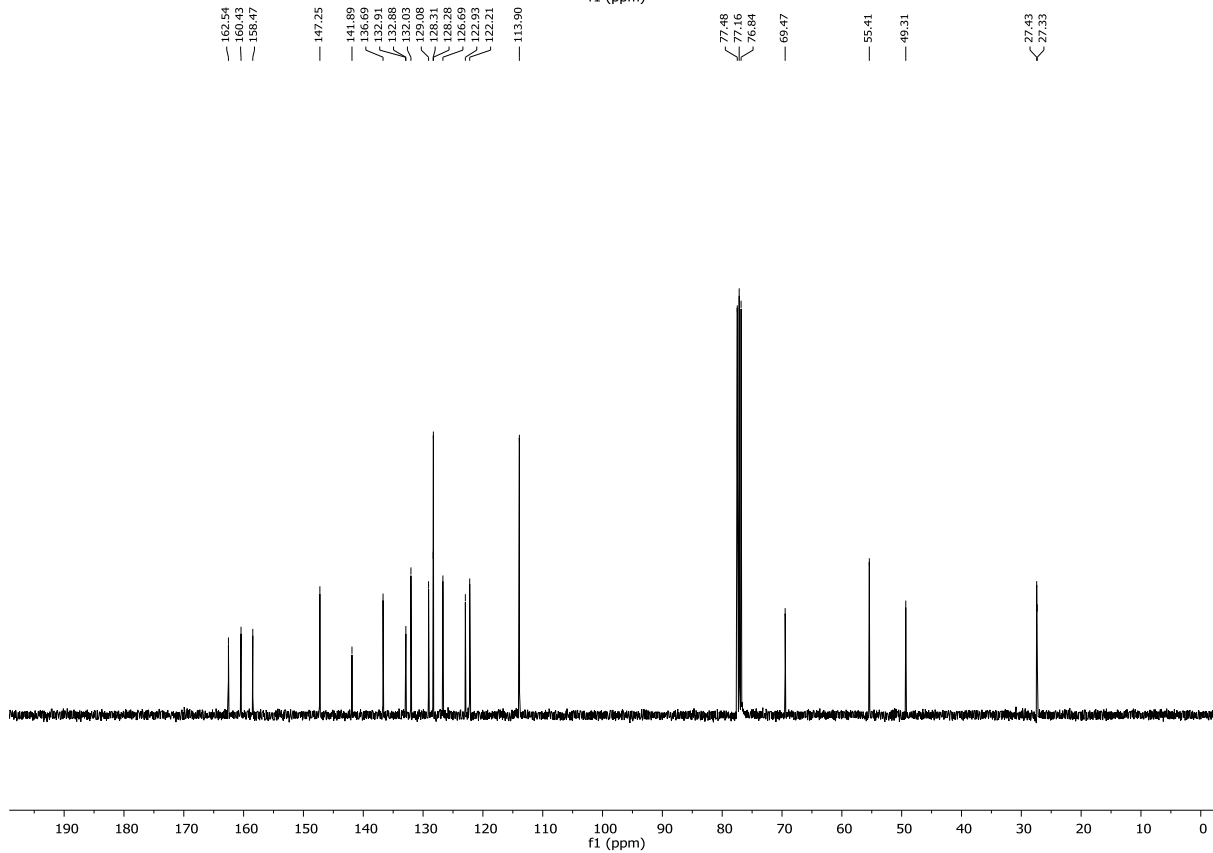
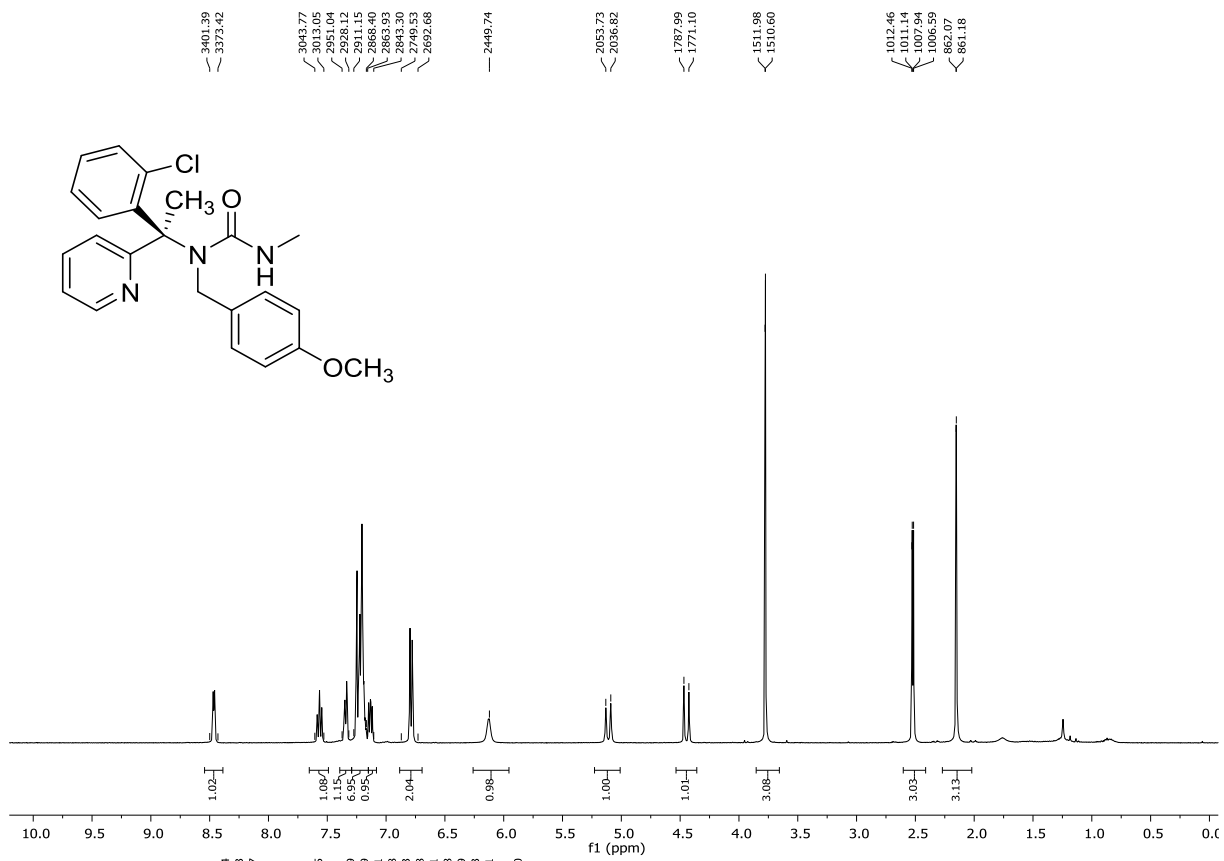
15d



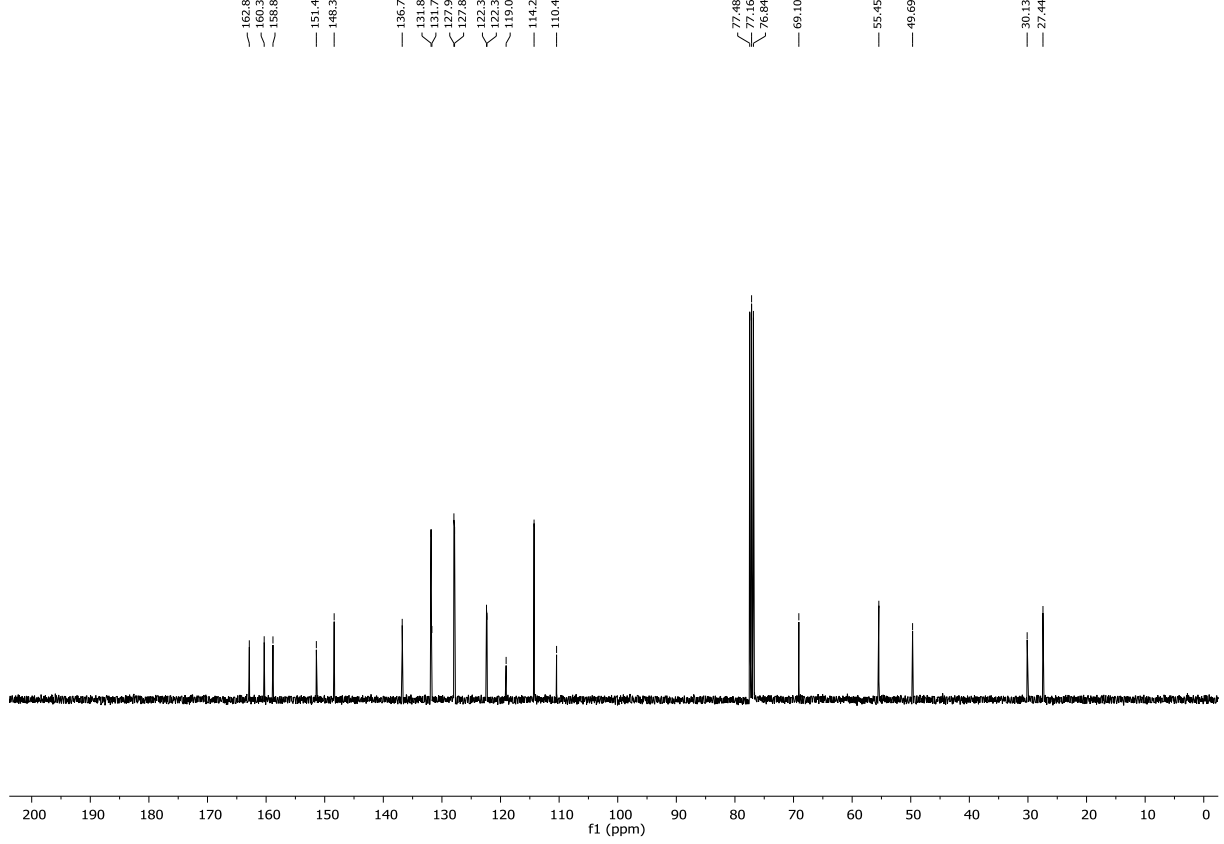
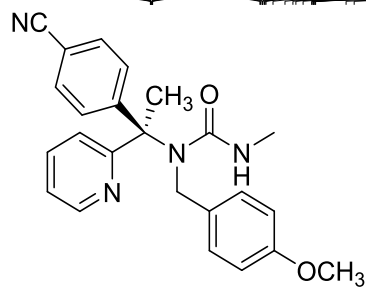
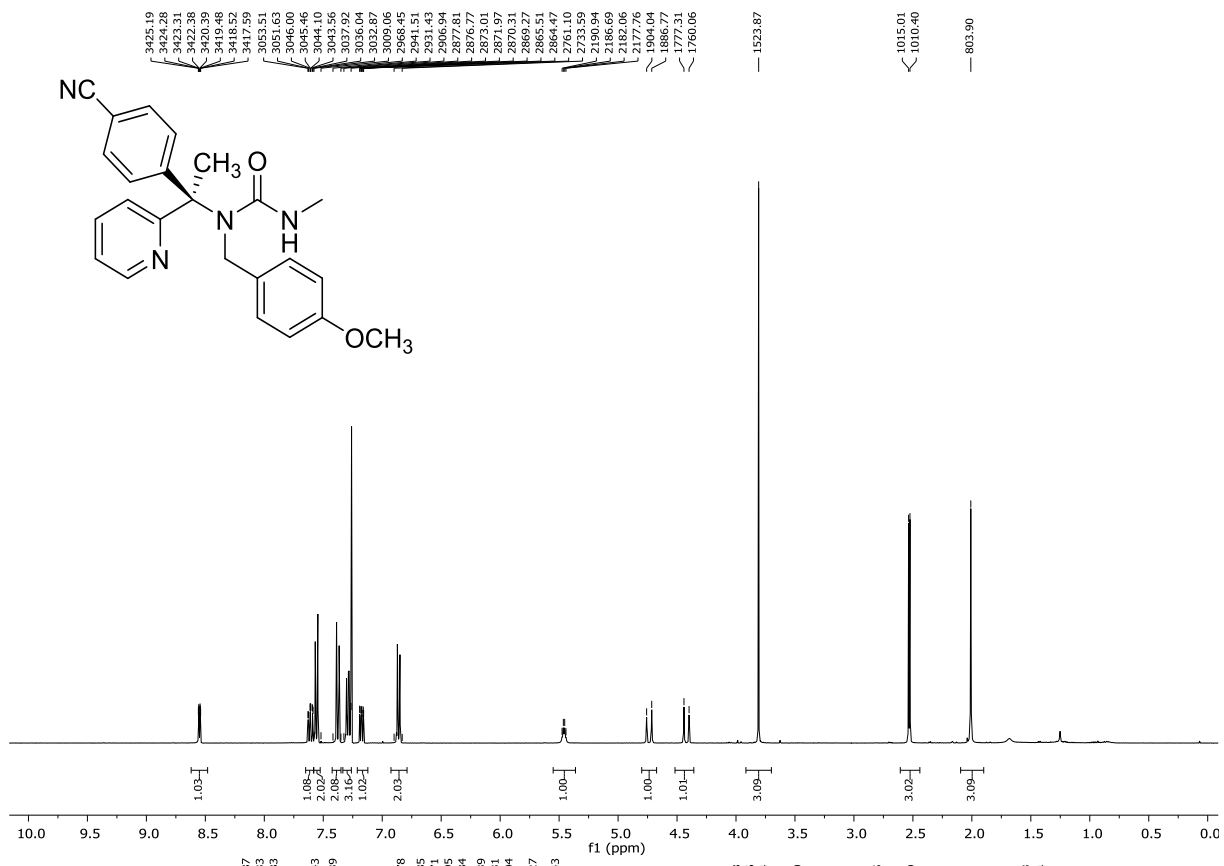
15e



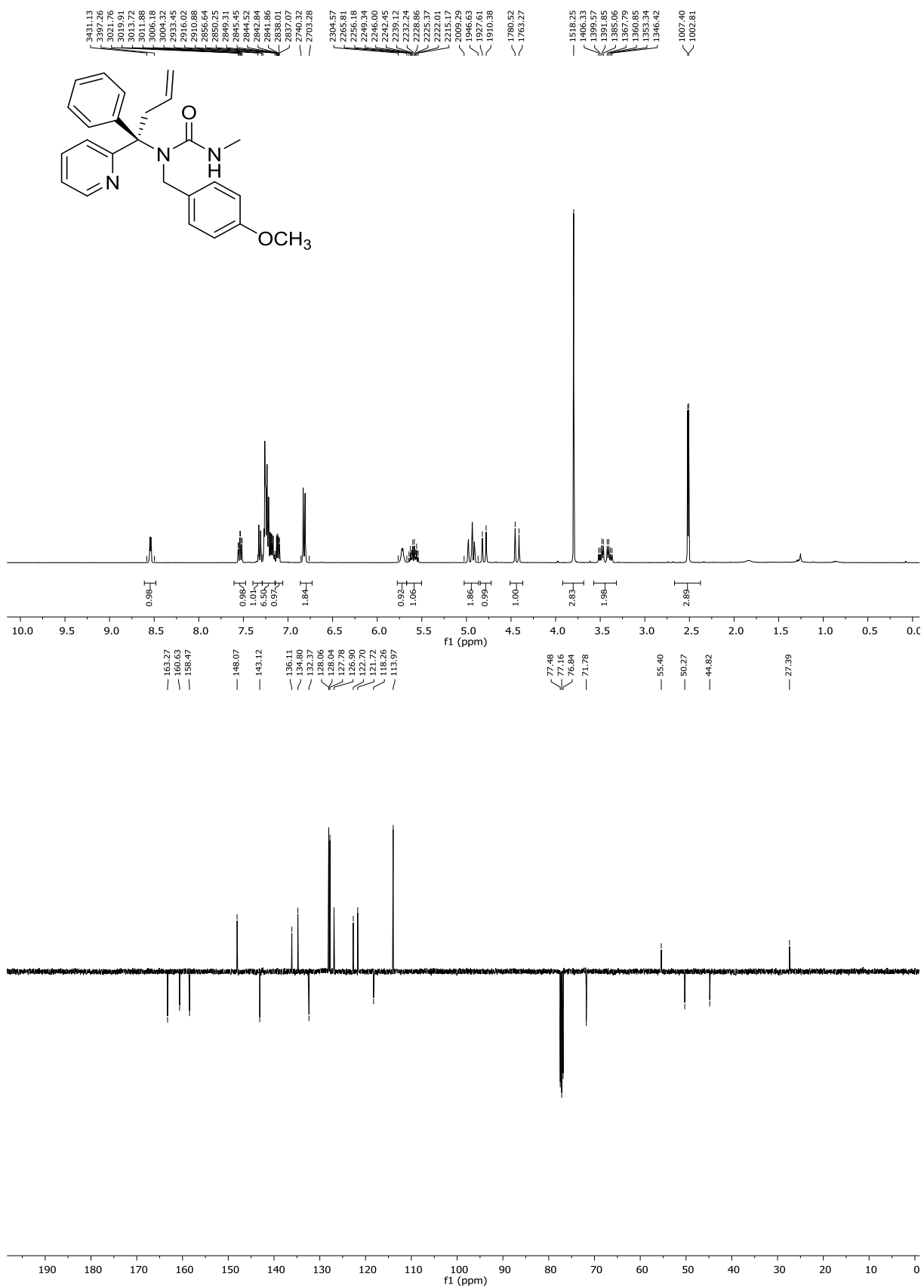
15f



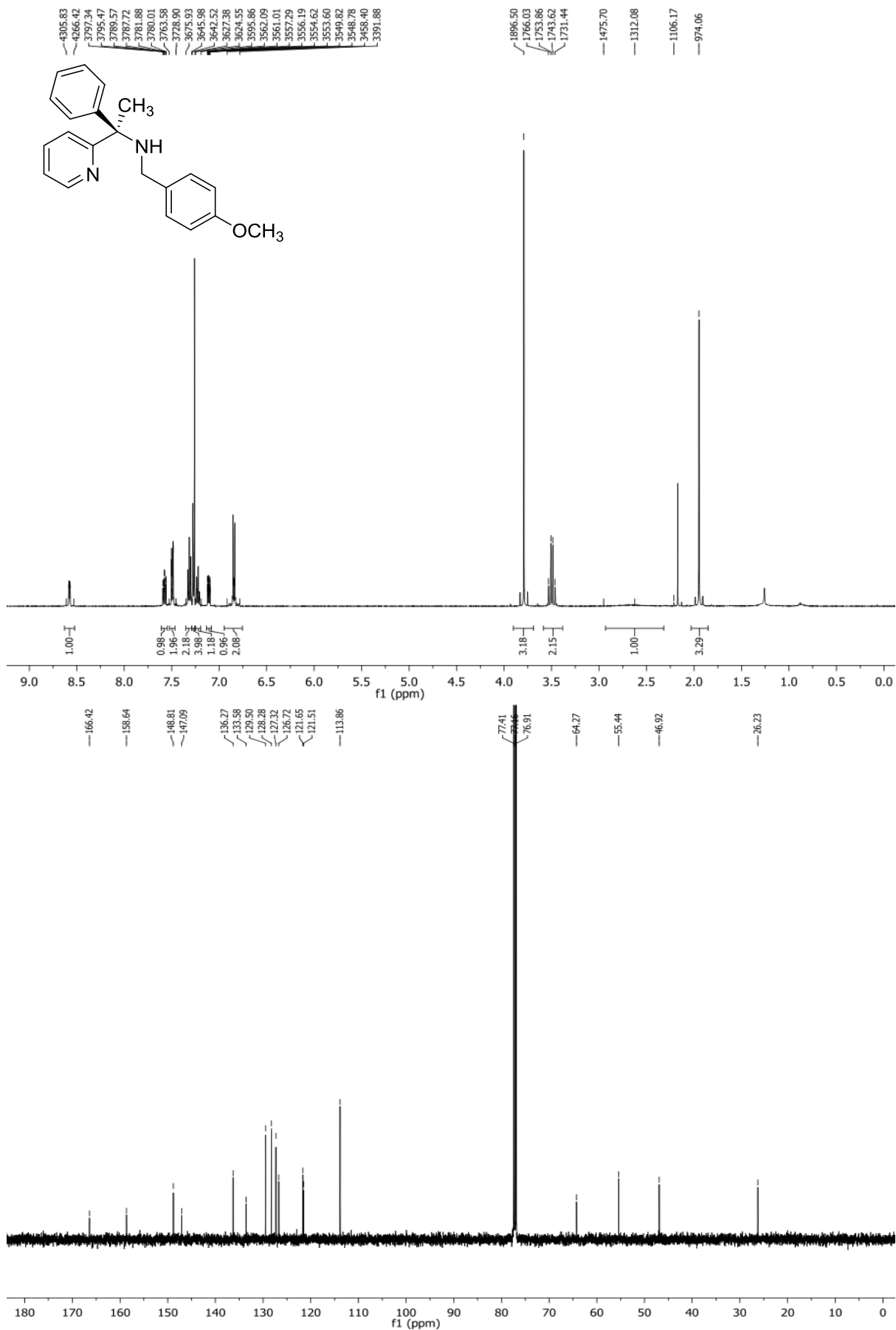
15g



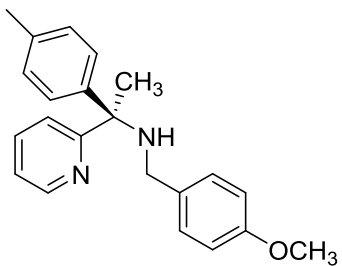
15h



16a



16b



3451.11
3397.31

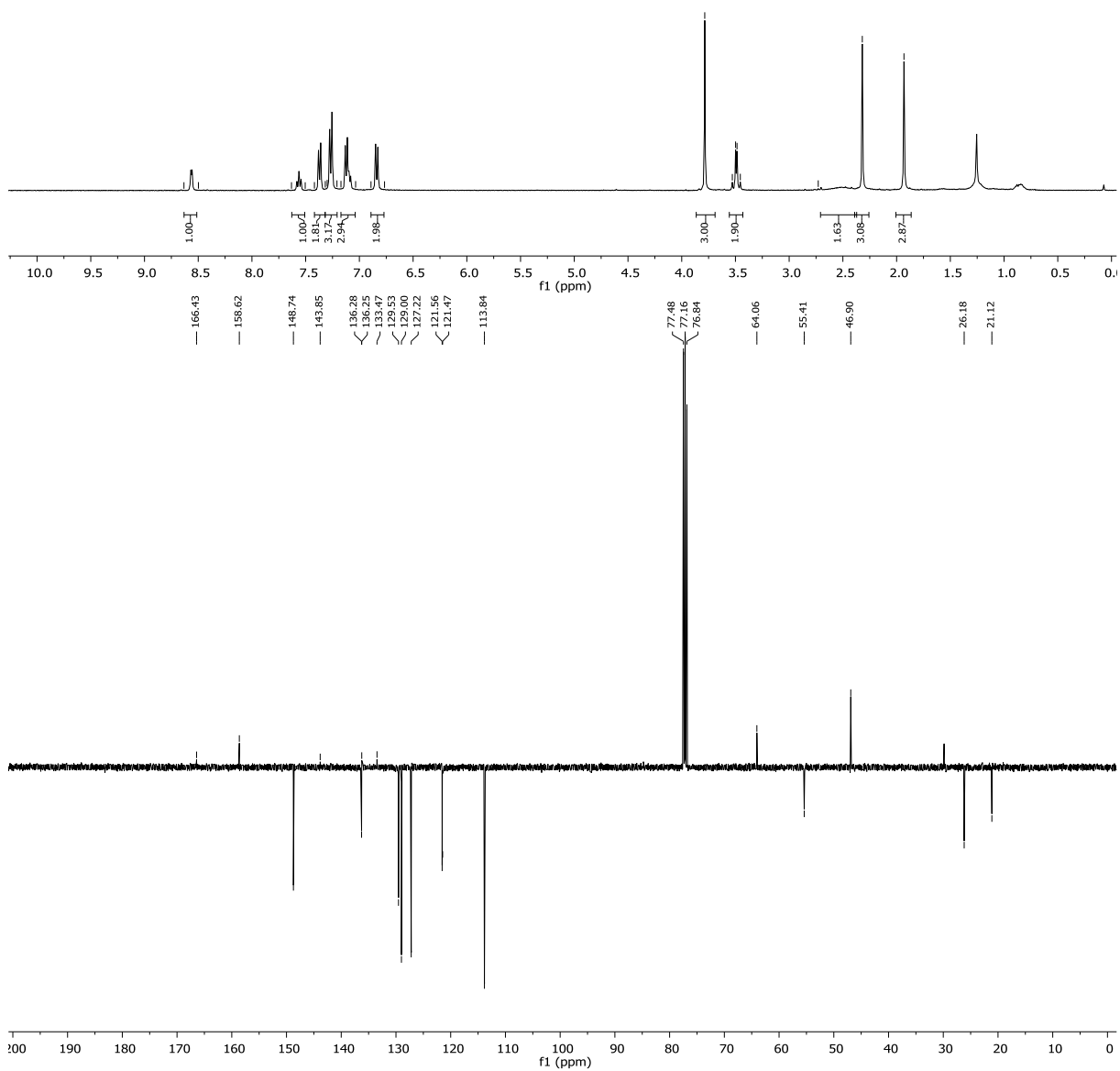
3051.06
2965.72
2925.25
2918.15
2881.84
2866.92
2812.38
2795.17
2704.81

1513.37
1410.80
1383.32
1381.01

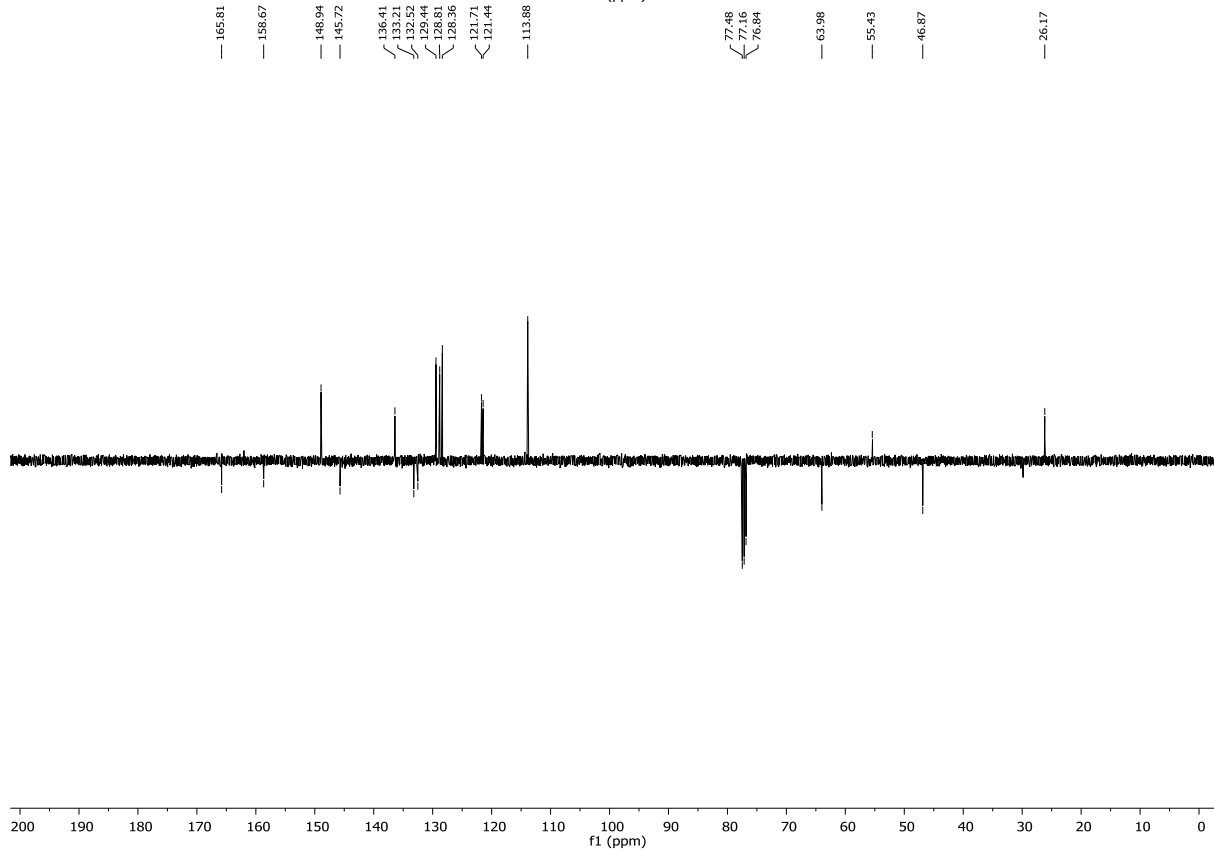
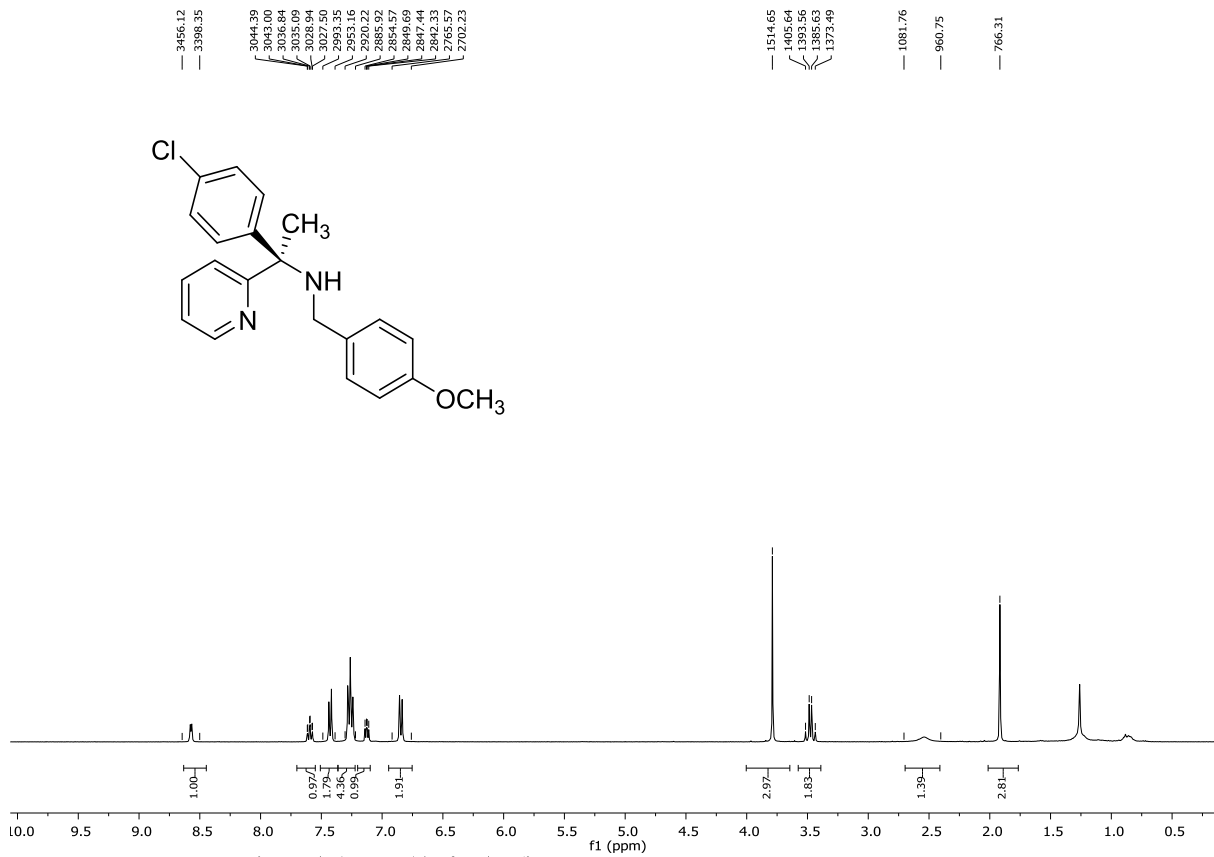
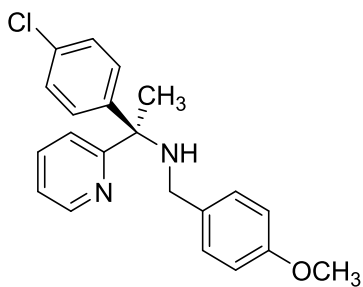
1091.13

927.17

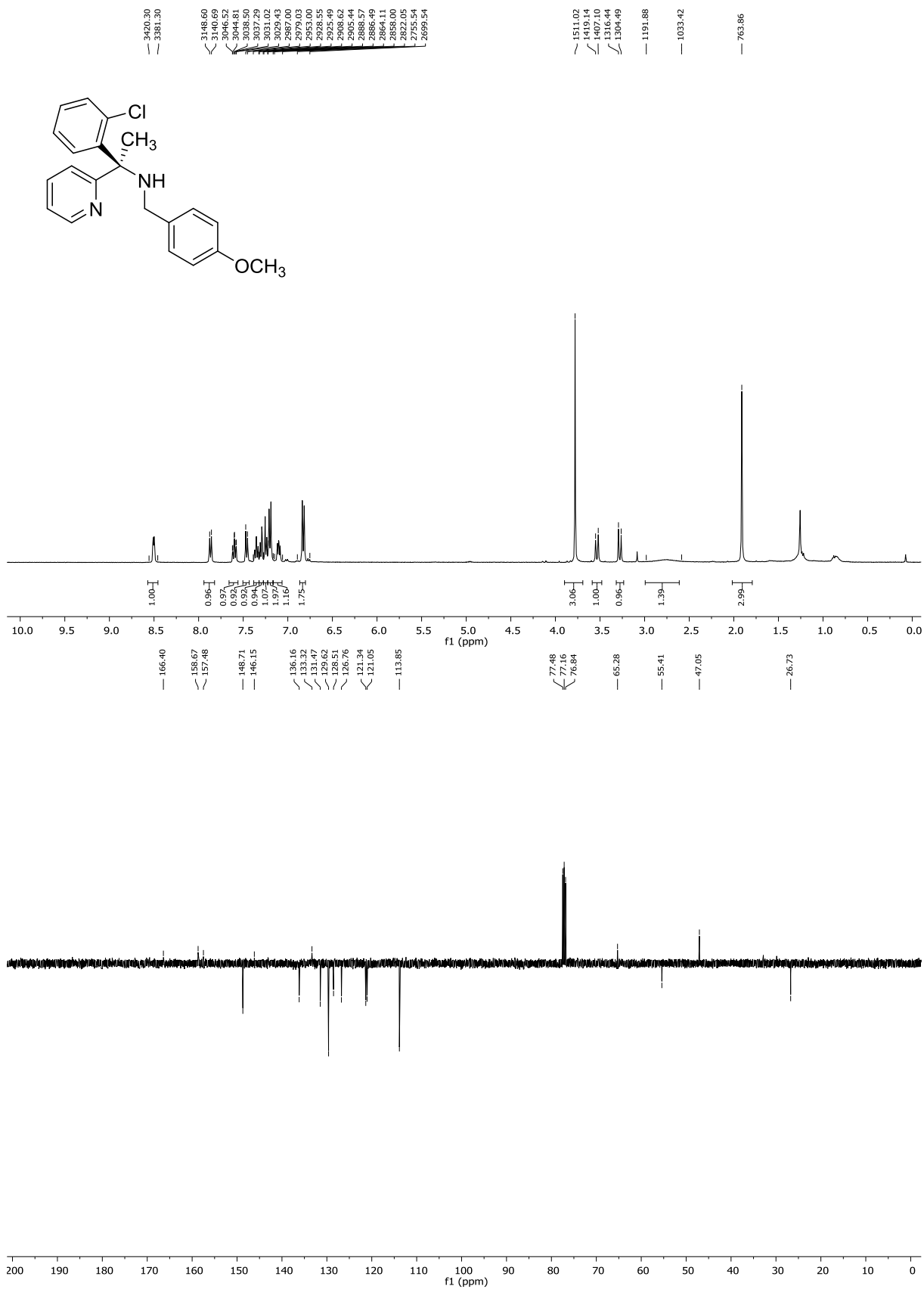
772.17



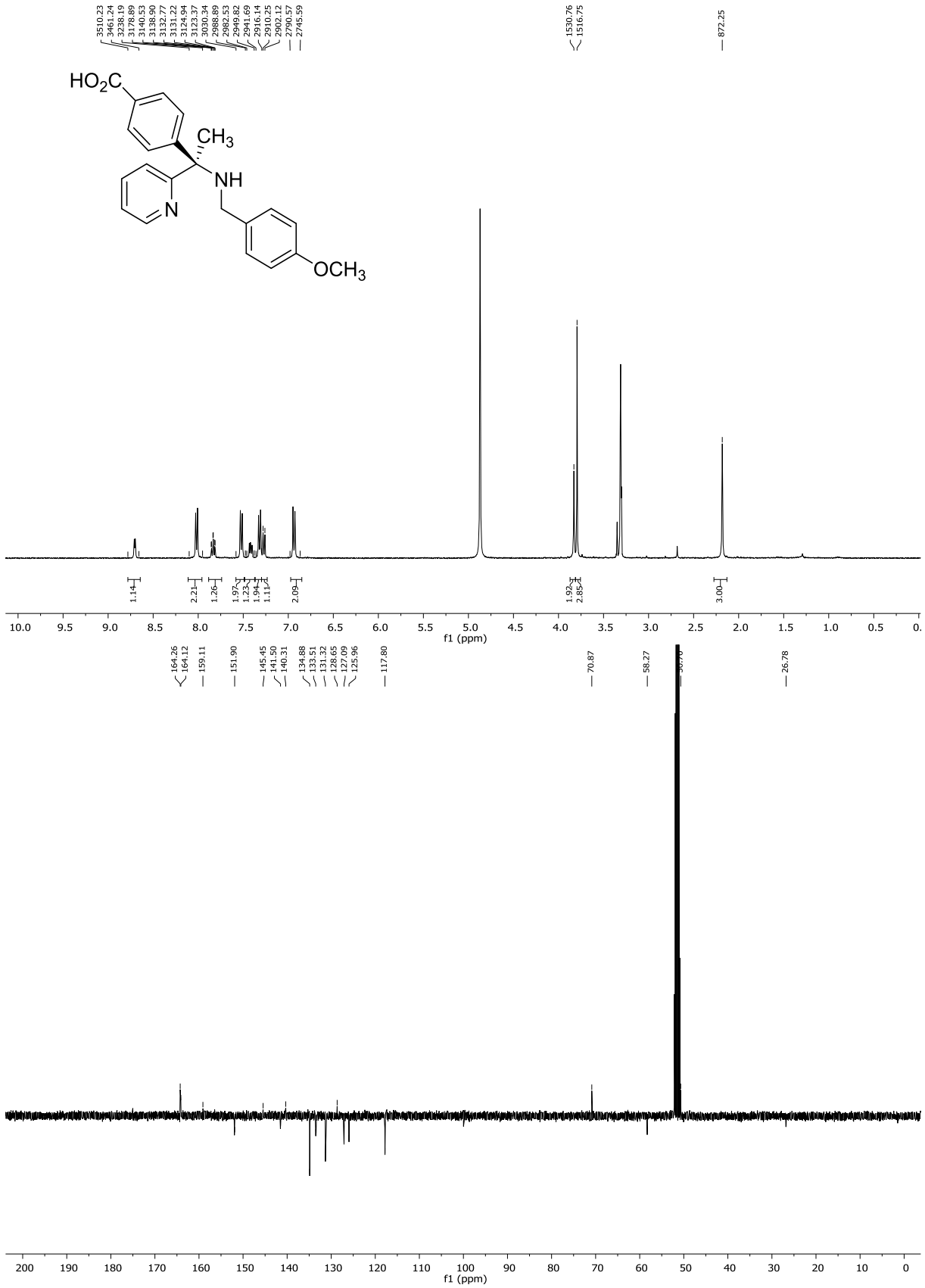
16d



16e

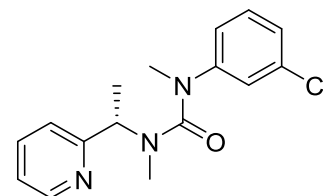
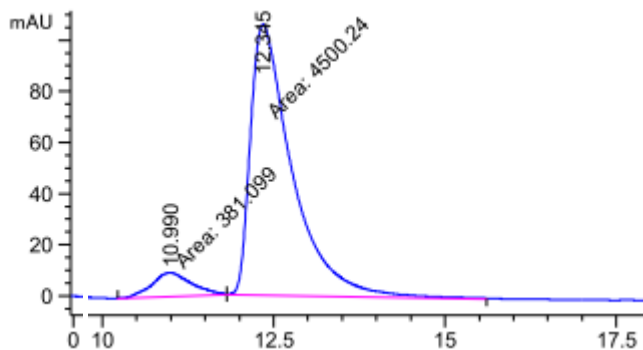


16f



HPLC data

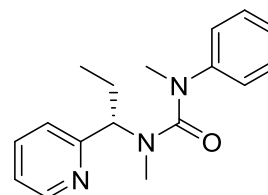
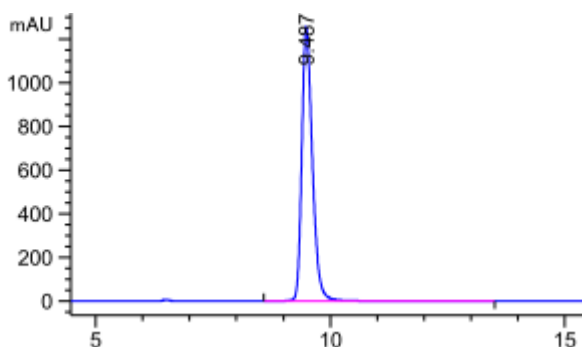
8a : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.990	MM	0.6792	381.09869	9.35218	7.8073
2	12.345	MM	0.7080	4500.23926	105.93288	92.1927

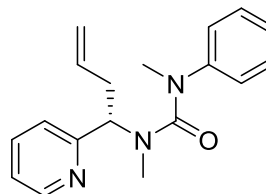
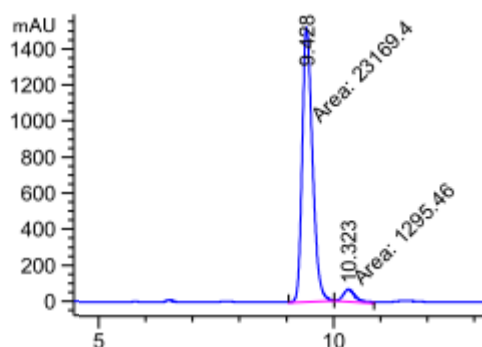
8b : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.487	BB	0.2424	1.98642e4	1256.81714	100.0000

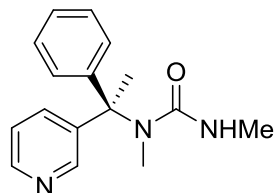
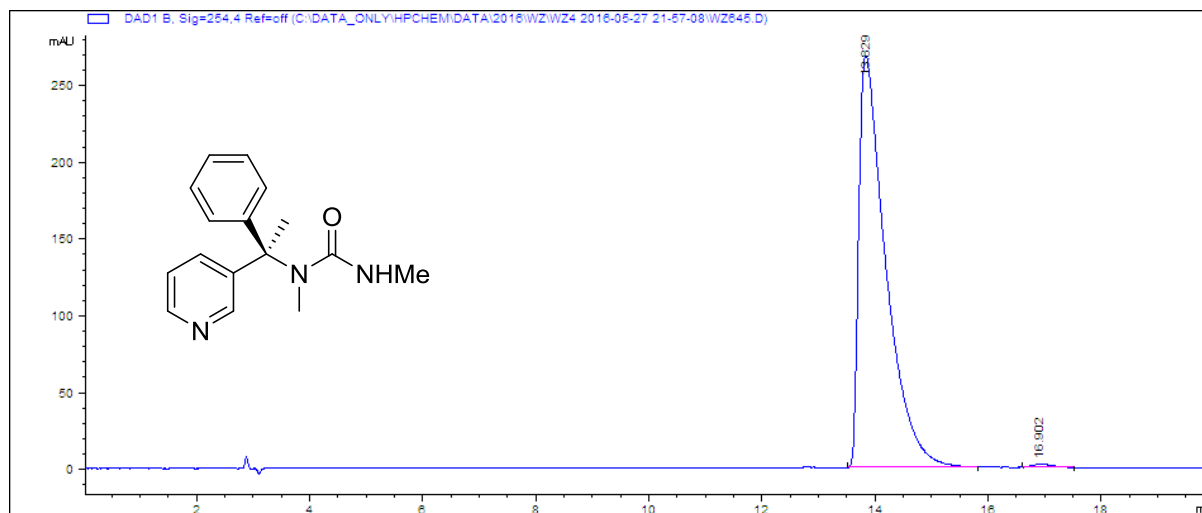
8c : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

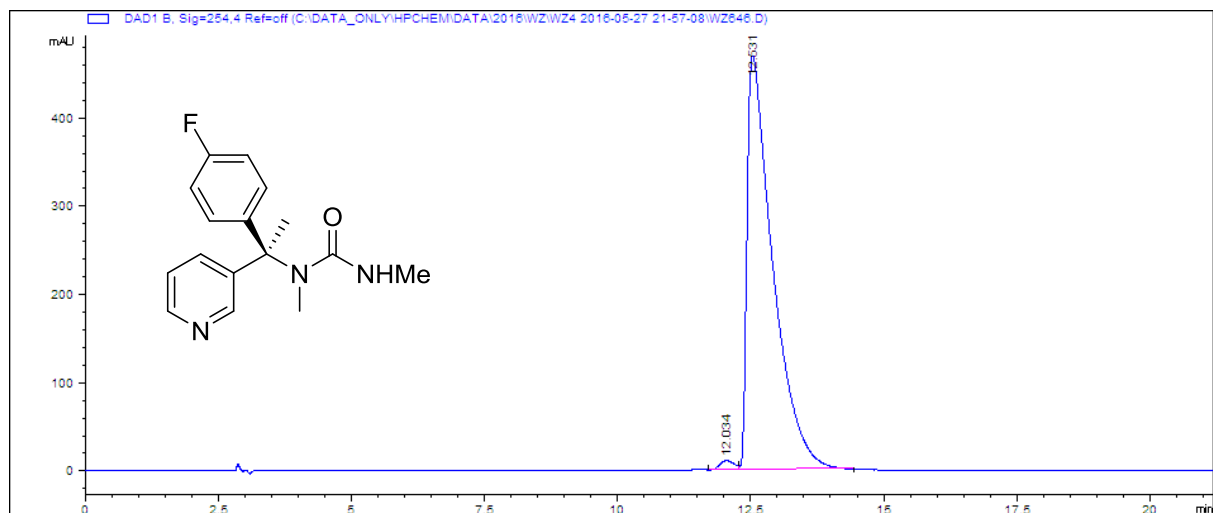
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.428	MM	0.2546	2.31694e4	1516.86768	94.7048
2	10.323	MM	0.3179	1295.46326	67.91454	5.2952

11a : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



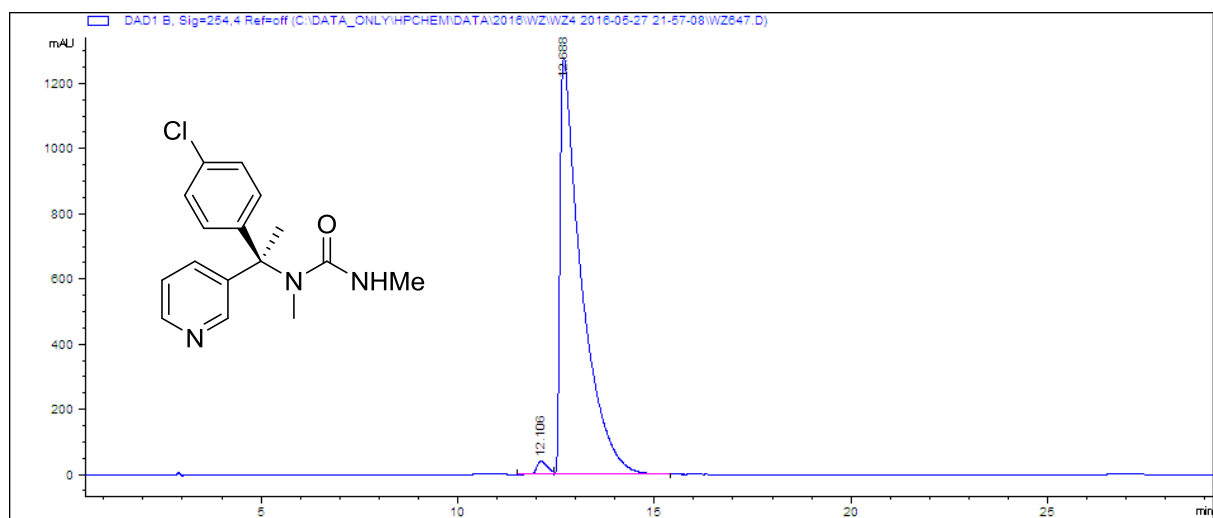
#	Time	Area	Height	Width	Area%	Symmetry
1	13.829	8886.2	268.3	0.4644	99.399	0.32
2	16.902	53.7	2.2	0.3035	0.601	0.588

11b : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



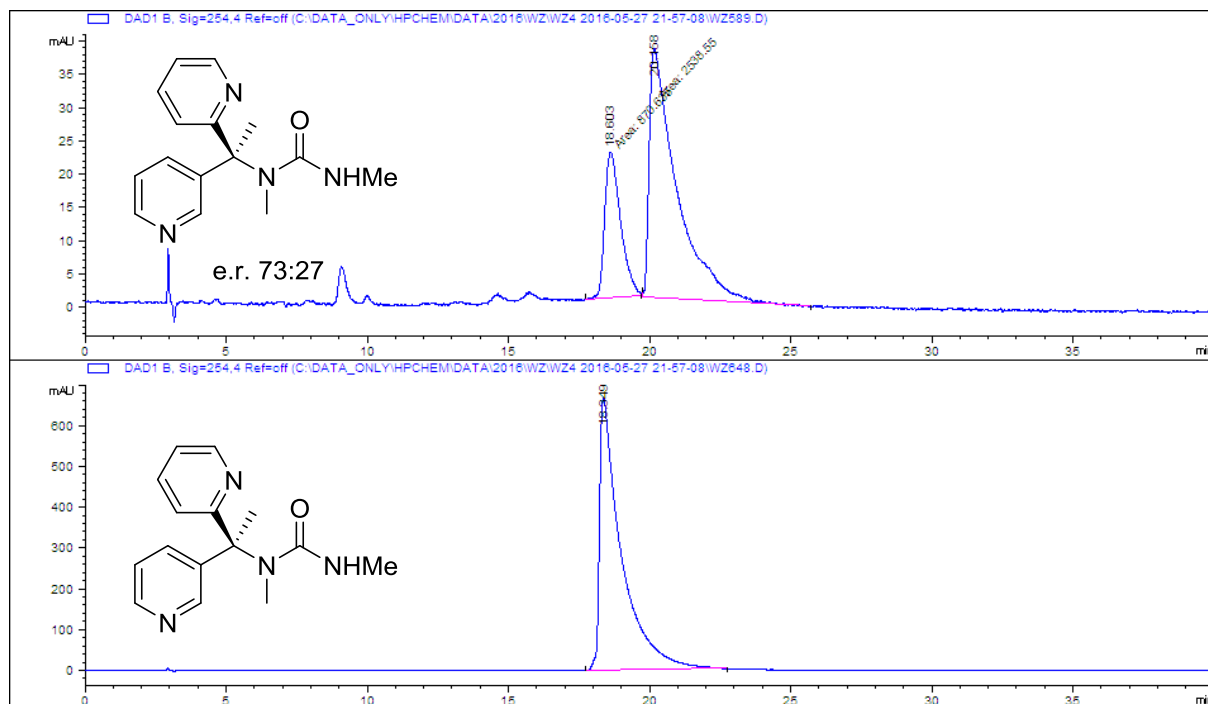
#	Time	Area	Height	Width	Area%	Symmetry
1	12.034	196.5	10.4	0.2675	1.234	0.829
2	12.531	15732.6	469.1	0.4692	98.766	0.26

11c : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



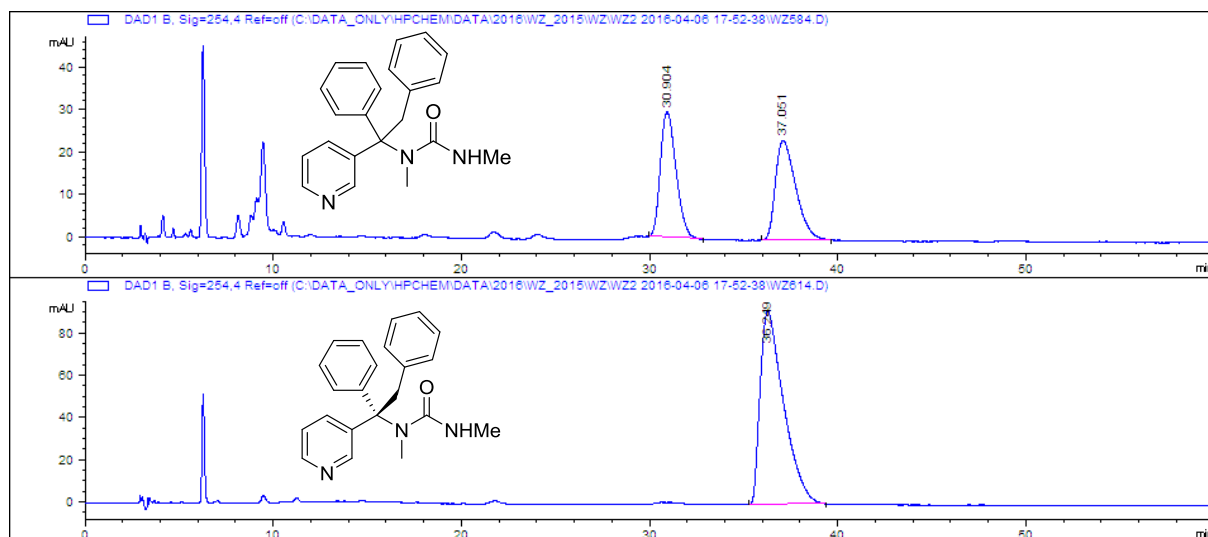
#	Time	Area	Height	Width	Area%	Symmetry
1	12.106	796.7	40.1	0.2915	1.634	0.646
2	12.688	47945.1	1279.3	0.4972	98.366	0.199

11d : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



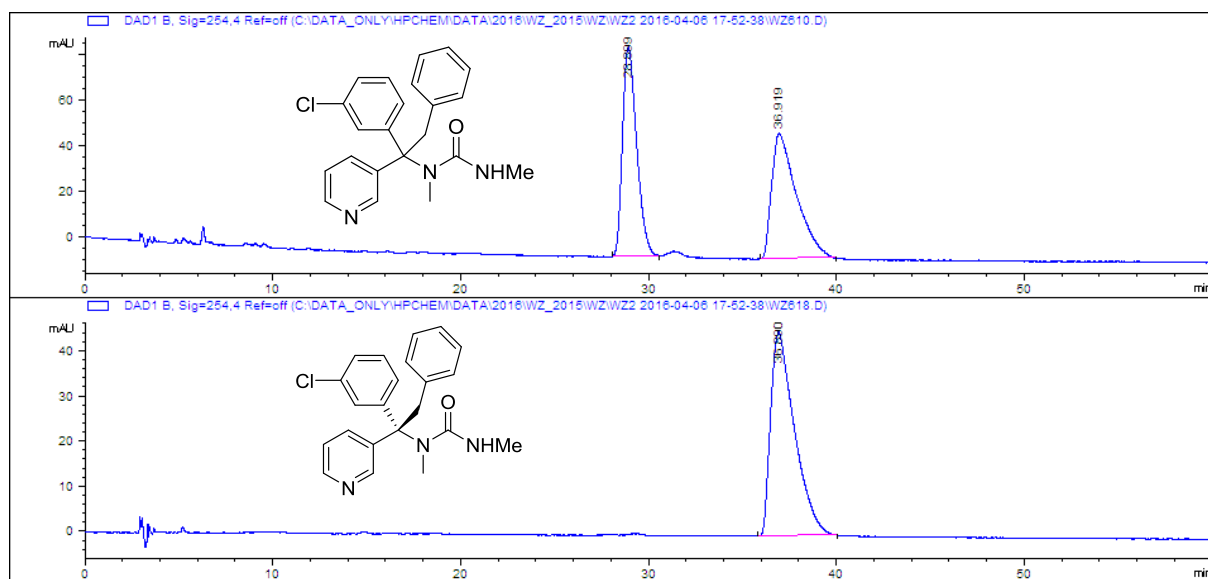
#	Time	Area	Height	Width	Area%	Symmetry
1	18.603	870.6	22	0.6583	25.538	0.584
2	20.158	2538.6	37.5	1.1268	74.462	0.227

11e : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm

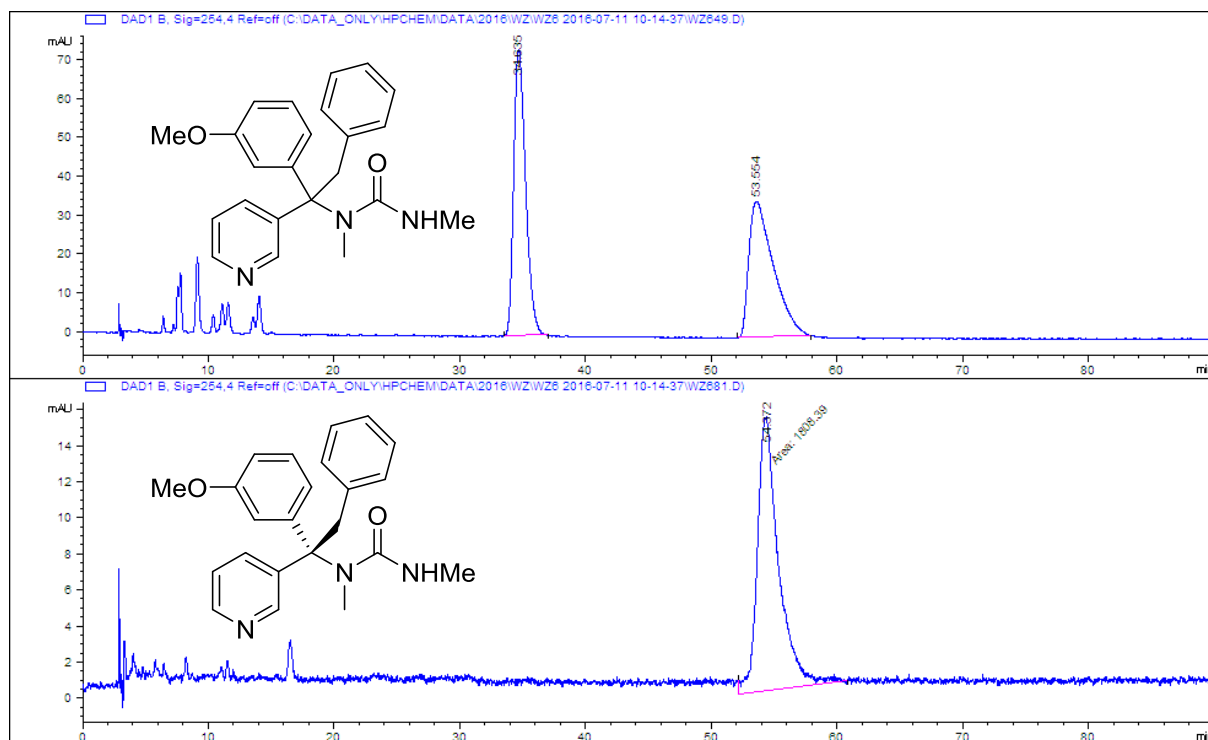


#	Time	Area	Height	Width	Area%	Symmetry
1	30.904	1715	29.5	0.7738	49.206	0.717
2	37.051	1770.3	23.5	0.9315	50.794	0.527

11f : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm

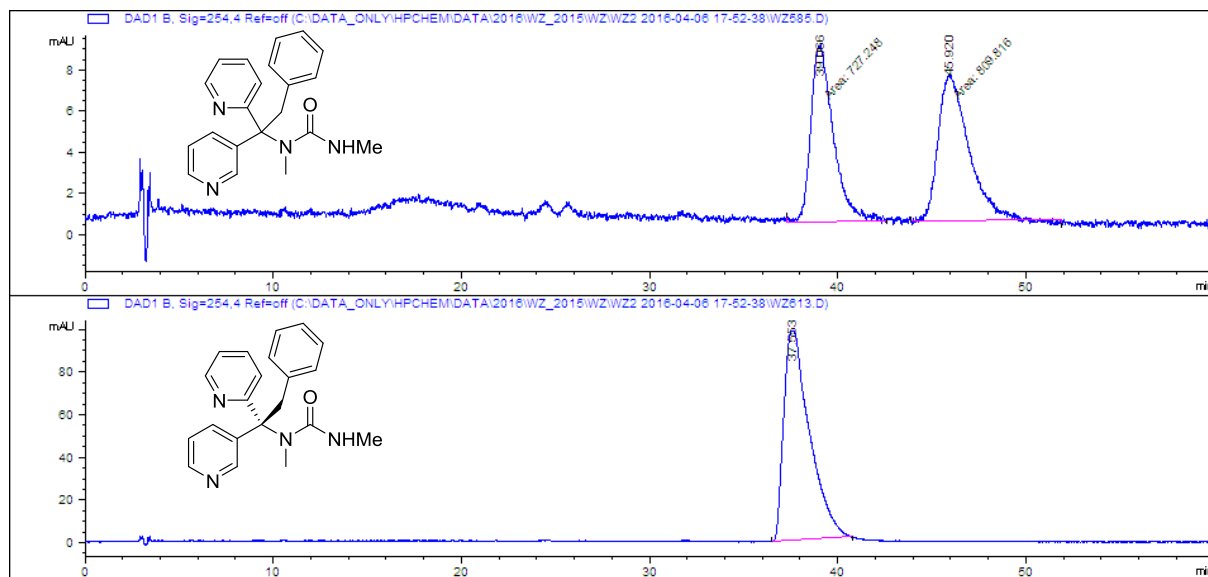


11g : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



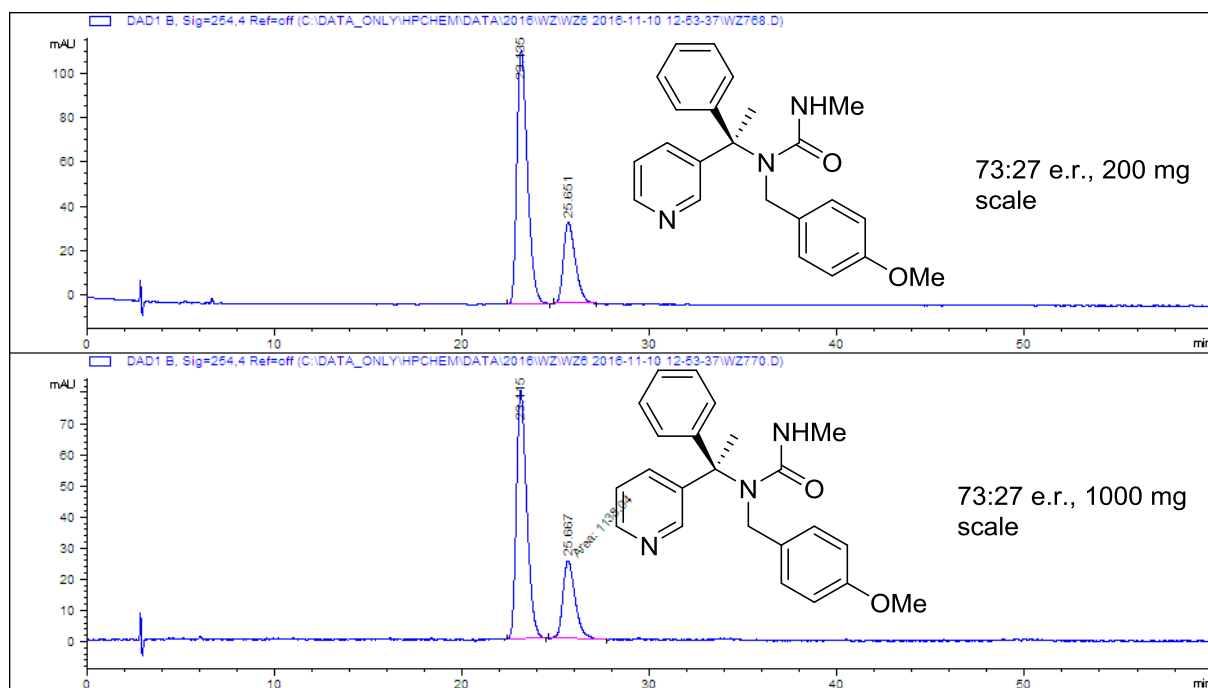
#	Time	Area	Height	Width	Area%	Symmetry
1	37.163	4098.4	55.3	0.873	54.364	0.617
2	58.026	3440.4	25	1.6159	45.636	0.517

11h : Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



#	Time	Area	Height	Width	Area%	Symmetry
1	39.066	727.2	8.6	1.4106	47.314	0.739
2	45.92	809.8	7.1	1.896	52.686	0.589

13: Phenomenex LUX® 5 µm Amylose-1 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



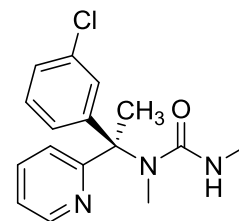
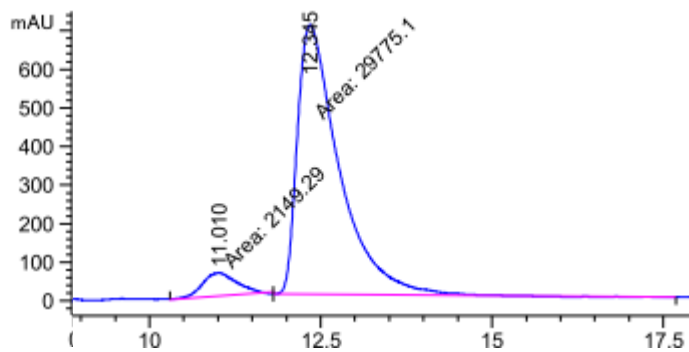
200 mg scale

#	Time	Area	Height	Width	Area%	Symmetry
1	23.135	4458.8	114.2	0.5996	73.306	0.636
2	25.651	1623.6	36.6	0.6299	26.694	0.653

1.00 g scale

#	Time	Area	Height	Width	Area%	Symmetry
1	23.115	3072.9	79.8	0.5615	72.974	0.681
2	25.667	1138	24.9	0.7607	27.026	0.645

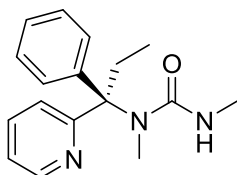
14a : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 85:15 hexane-IPA, 1 mL/min, 210 nm



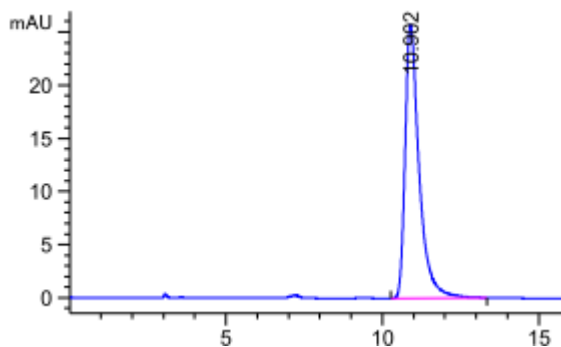
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.010	MM	0.5926	2149.28882	60.44871	6.7324
2	12.345	MM	0.7126	2.97751e4	696.35681	93.2676

14b : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



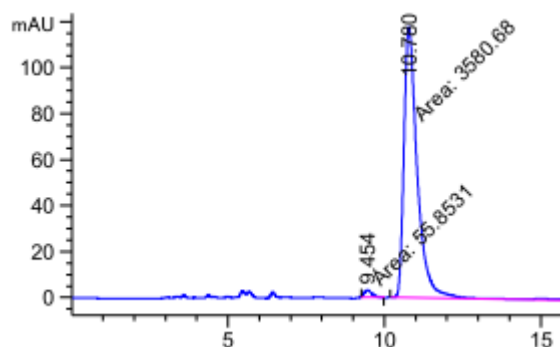
At -78 °C :



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.902	BB	0.4629	3812.61108	122.56915	100.0000

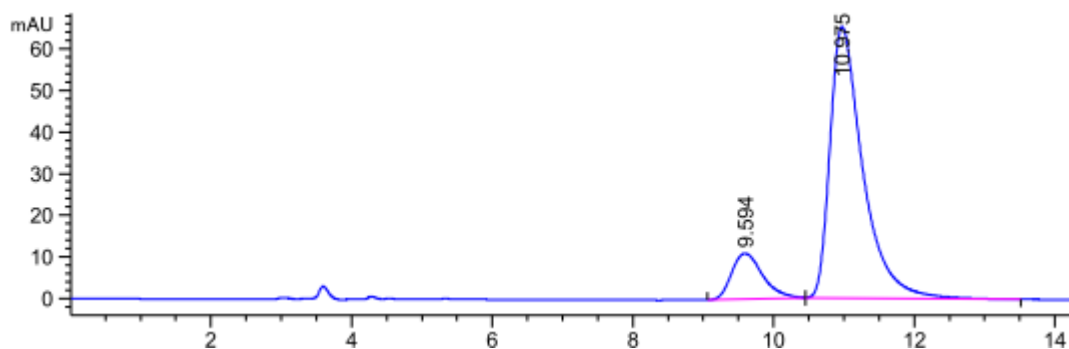
At -40 °C :



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.452	MM	0.4783	325.75943	11.35186	1.9338
2	10.780	MM	0.4935	1.65200e4	557.91547	98.0662

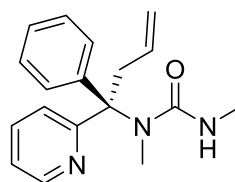
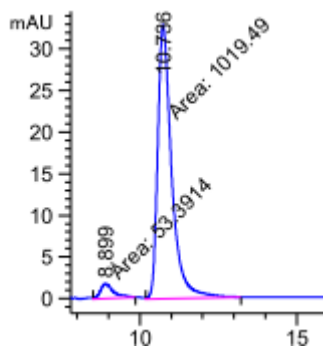
At-RT:



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.594	BV	0.4888	1686.06079	53.04249	14.1670
2	10.975	VB	0.4911	1.02153e4	309.43759	85.8330

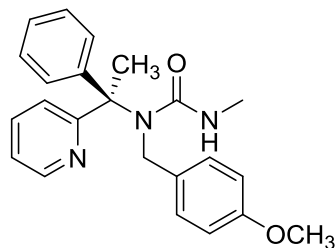
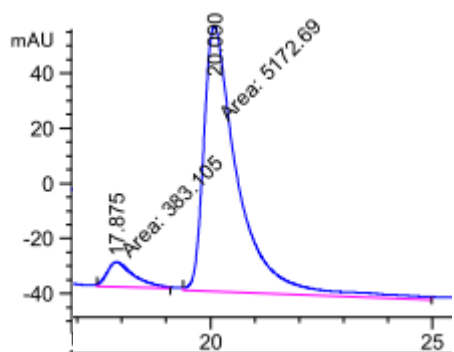
14c : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.899	MM	0.4987	53.39144	1.78439	4.9764
2	10.736	MM	0.5158	1019.49408	32.94215	95.0236

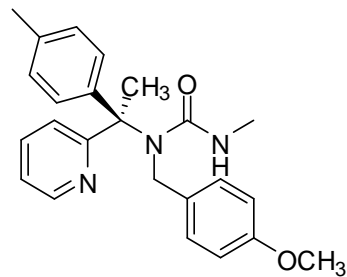
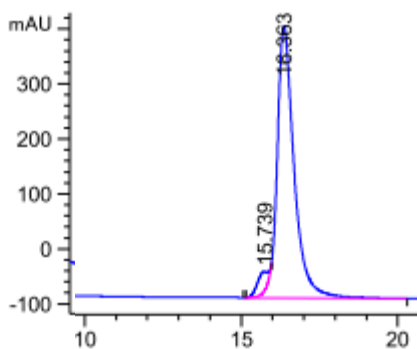
15a : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.875	MM	0.7054	383.10529	9.05111	6.8956
2	20.090	MM	0.8961	5172.68652	96.20653	93.1044

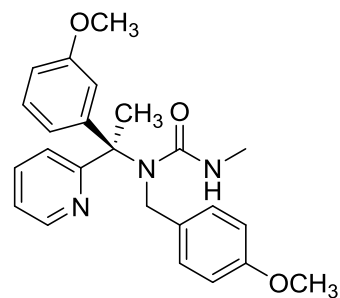
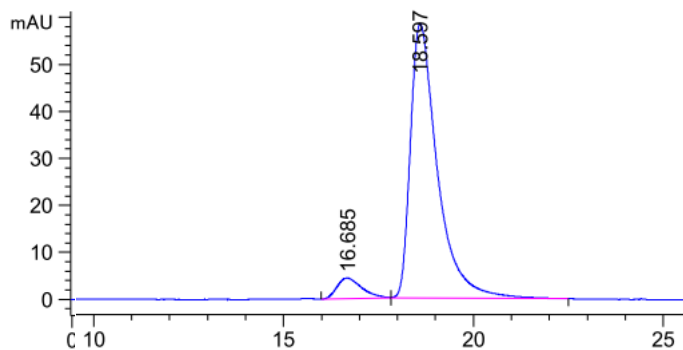
15b : CHIRALPAK® AD-H 5 µm Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 210.4 nm



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.739	BV E	0.3682	846.94214	34.76965	4.3293
2	16.363	VB R	0.5629	1.87161e4	492.98035	95.6707

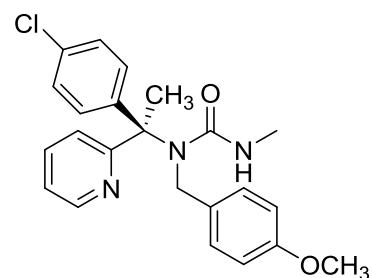
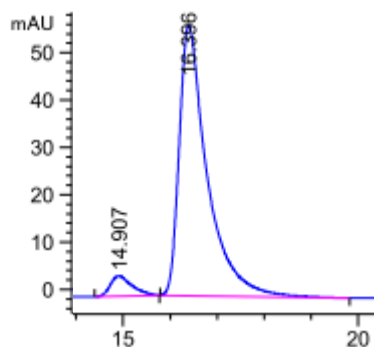
15c : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.685	BB	0.5405	195.72812	4.35365	6.3669
2	18.597	BB	0.7201	2878.44189	58.28962	93.6331

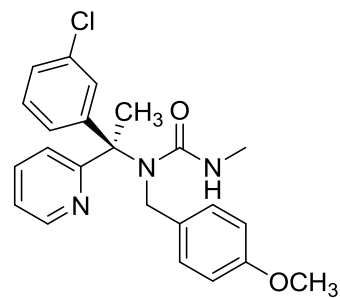
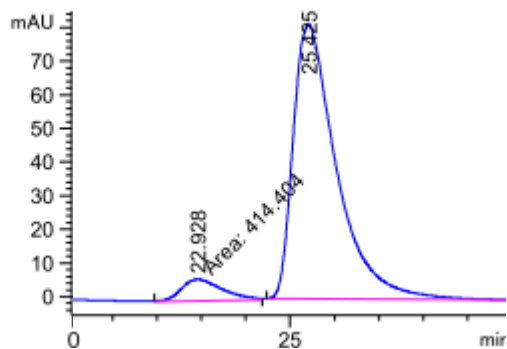
15d : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

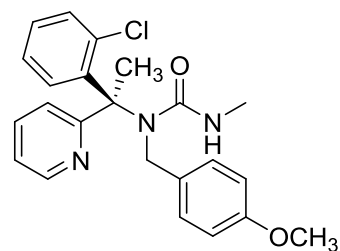
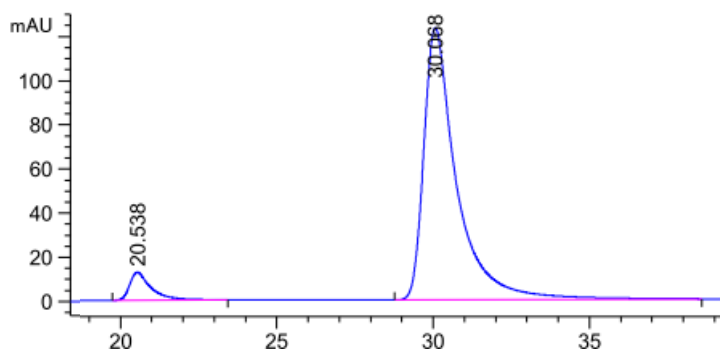
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.907	BB	0.4735	135.96097	4.24698	5.4596
2	16.396	BB	0.5971	2354.35156	56.85265	94.5404

15e : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 85:15 hexane-IPA, 1 mL/min, 254 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.928	MM	1.0764	414.40408	6.41670	6.9338
2	25.425	BBA	1.0069	5562.18359	81.64005	93.0662

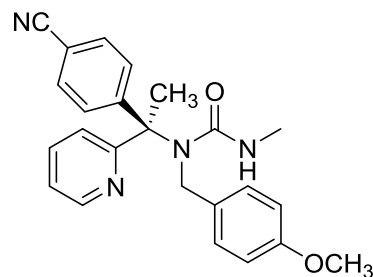
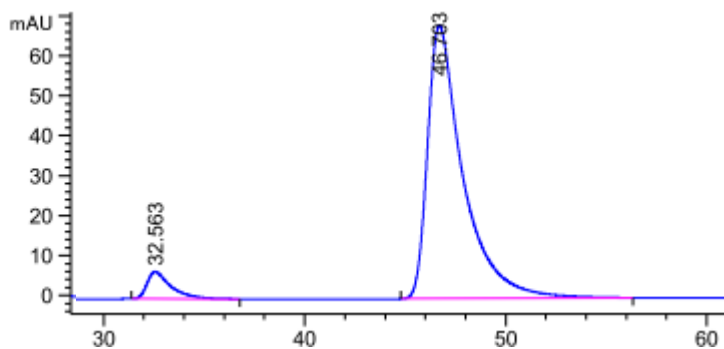
15f : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 230.4 nm



Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.538	BB	0.6862	601.03552	12.56179	6.2515
2	30.068	BB	1.0576	9013.16895	122.89481	93.7485

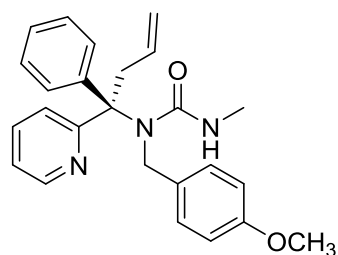
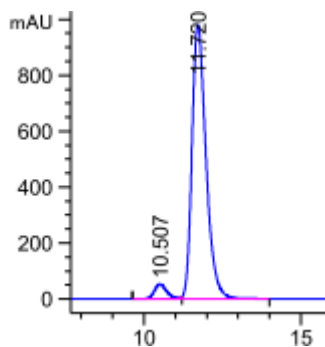
15g : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.563	BB	1.1684	561.90320	6.78379	6.2634
2	46.793	BB	1.7692	8409.32227	68.36113	93.7366

15h : CHIRALPAK® AD-H 5 µm LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 210.4 nm



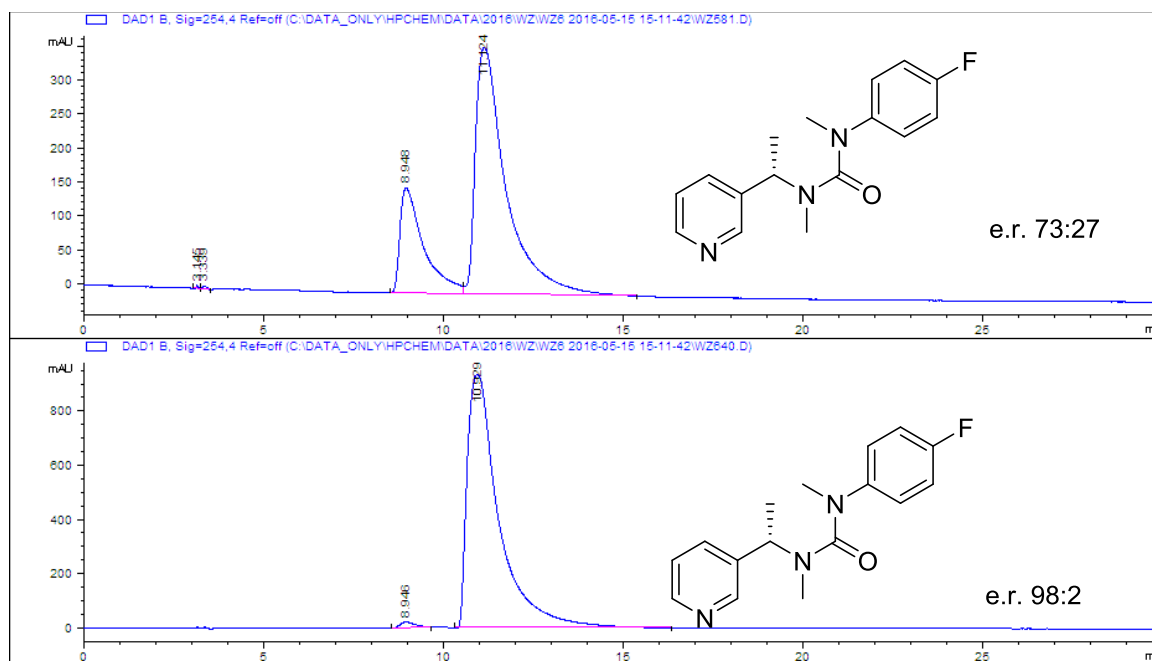
Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.507	BV E	0.4170	1762.75281	64.86910	4.5262
2	11.720	VB R	0.4768	3.71832e4	1195.57593	95.4738

Determination of d.r. in 3aa, and e.r. in the corresponding compounds 17a-d and 7a-d

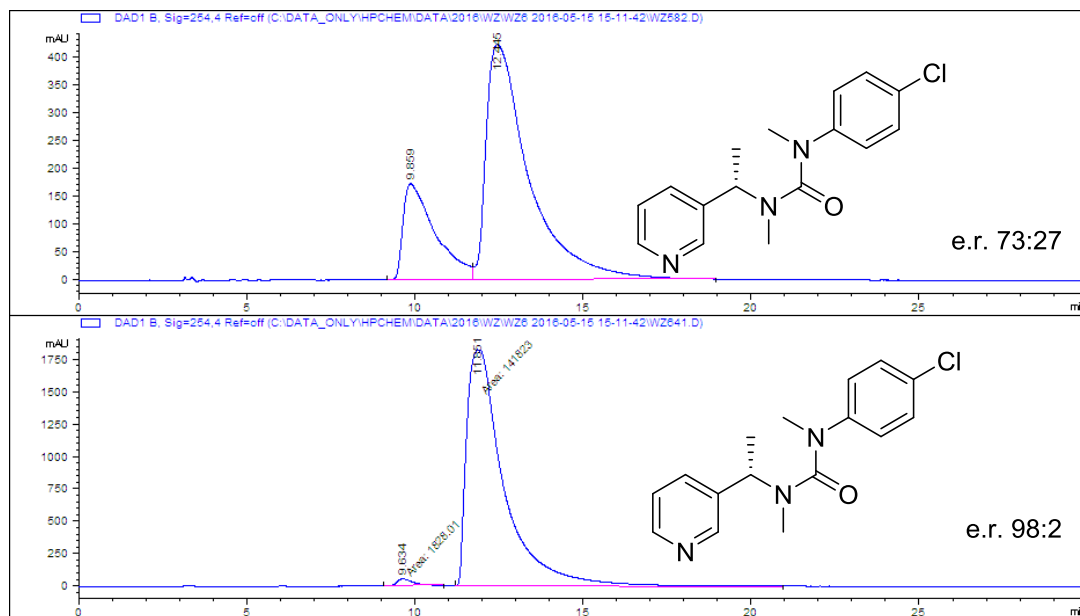
To determine the exact diastereomeric ratio in **3a**, at a later stage of the synthesis **5a** was converted to **7b** and **7c** and the e.r. of the compounds was measured by chiral HPLC.

Phenomenex LUX® 5 µm Cellulose-3 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



#	Time	Area	Height	Width	Area%	Symmetry
1	8.946	1024	23.7	0.7215	1.728	0.364
2	10.929	58247.6	936.4	1.0367	98.272	0.425

Phenomenex LUX® 5 µm Cellulose-3 LC Column 250 x 4.6 mm, 90:10 hexane-IPA, 1 mL/min, 254 nm



#	Time	Area	Height	Width	Area%	Symmetry
1	9.634	1860	52.9	0.586	1.368	0.516
2	11.851	134068.5	1823.2	1.2256	98.632	0.414

X-RAY

Table 1. Crystallographic data and structure refinement for compound (*R*)-**11c**; the Cambridge Crystallographic Data Centre (CCDC) code is 1519696

Identification code	1519696	
Empirical formula	C ₁₆ H ₁₈ Cl N ₃ O	
Formula weight	303.78	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 8.54450(10) Å	α = 90°.
	b = 9.1514(2) Å	β = 90°.
	c = 19.7296(4) Å	γ = 90°.
Volume	1542.74(5) Å ³	
Z	4	
Density (calculated)	1.308 Mg/m ³	
Absorption coefficient	2.207 mm ⁻¹	
F(000)	640	
Crystal size	0.250 x 0.150 x 0.080 mm ³	
Theta range for data collection	4.482 to 72.143°.	
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -23 ≤ l ≤ 17	
Reflections collected	18119	
Independent reflections	3026 [R(int) = 0.0404]	
Completeness to theta = 67.679°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.843 and 0.767605	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3026 / 0 / 197	
Goodness-of-fit on F ²	1.040	
Final R indices [I > 2σ(I)]	R1 = 0.0247, wR2 = 0.0617	
R indices (all data)	R1 = 0.0261, wR2 = 0.0623	
Absolute structure parameter	0.031(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.184 and -0.257 e.Å ⁻³	