Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information:

Asymmetric α-arylation of alanine and the effect of the product α-methyl phenylglycine on the screw sense preference of helical Aib foldamers

Romain Costil,[a] Fernando Fernández Nieto,[b] Rachel C. Atkinson, [b] and Jonathan Clayden*[a]

[a] School of Chemistry, University of Bristol, Cantock's Close, BS8 1TS, Bristol, UK

[b] School of Chemistry, University of Manchester, Oxford Road, M13 9PL, Manchester, UK

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General Information

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

Capillary melting points were determined on a Stuart Scientific melting point SMP 10 apparatus.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram SIL G/UV_{254}). Visualisation was *via* UV light (at 254 nm) or by staining with phosphomolybdic acid then heating. Flash column chromatography used chromatography grade silica, 60 Å particle size, 40-63 microns from Aldrich and compounds were loaded as saturated solutions in the correct solvents.

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

All reactions were performed under an argon atmosphere in flame-dried apparatus. All reagents and chemicals were bought from chemical suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under nitrogen from sodium wire using benzophenone as an indicator. Diisopropylamine (DiPA) was obtained by distillation from calcium hydride under nitrogen. All solvents were removed under vacuum using a rotary evaporator. PE ether indicates fractions of PE boiling at 40-60 °C. Lithium chloride (LiCl) was dried in the oven and used directly. Acetone/dry ice cooling baths were used to obtain -78 °C.

Method for the synthesis of **$HAib_4Gly$-Ψ[CSNH]AibOMe and N_3Aib_4OH** have been reported previously.[1,2]

General Procedures

Procedure 1: Urea formation with carbamoyl chloride

To a solution of the DMB-protected amine (1.0 eq) in acetonitrile (0.3 M) was added triethylamine (1.2 eq). To the resulting mixture was added the corresponding carbamoyl chloride (1.0 eq). The reaction was heated to 65 °C and left overnight. The solution was then concentrated *in vacuo*. The resulting solid was dissolved in DCM, washed with 1.0 M HCl, saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography.

Procedure 2: Saponification of the ester

To a solution of the urea (1.0 eq) in a mixture of THF and water (2:1, 0.03 M) was added LiOH (20 eq.) portionwise. The reaction was heated to 45 °C and left overnight. The reaction mixture was quenched *via* a dropwise addition of 1.0 M HCl until pH 3 was reached. The resulting mixture was then extracted with ethyl acetate. Organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 3: Coupling with pseudoephedrine

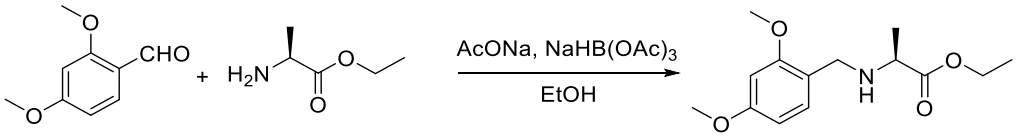
To a solution of the carboxylic acid (1.0 eq) in DCM (0.15 M) at 0°C was added EDC.HCl (1.2 eq), HOBt hydrate (1.0 eq) and diisopropylethylamine (1.2 eq). After 20 minutes (R,R)-pseudoephedrine (1.5 eq) was added and the reaction mixture was warmed to room temperature and stirred overnight. The solution was then concentrated *in vacuo*. The resulting solid was dissolved in ethyl acetate, washed with saturated aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Procedure 4: Rearrangement to hydantoin

In a separate flask, LDA was prepared: anhydrous THF (0.1 M (overall)) and diisopropylamine (6.5 eq) were cooled to 0°C, and *n*BuLi (6.5 eq) was added dropwise. The mixture was stirred for 20 minutes and added dropwise to a mixture of the urea (1.0 eq), and anhydrous LiCl (6.5 eq) in anhydrous THF (0.1 M (overall)), at -78°C. A colour change was observed. The reaction mixture was left to stir at -78°C for 15 minutes before it was allowed to warm to room temperature and stir for three hours. The reaction mixture was then quenched *via* dropwise addition of methanol at -78°C, followed by saturated aqueous NH_4Cl, and stirred for 15 minutes at room temperature. The reaction mixture was then extracted three times with ethyl acetate. Organics were combined, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography.

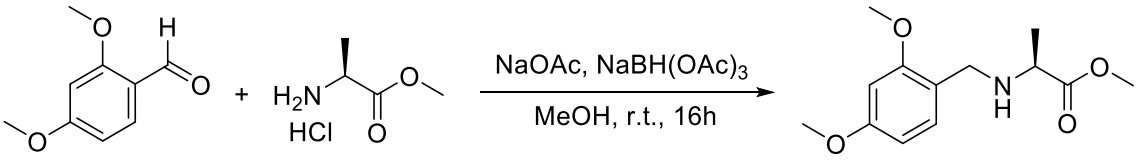
Characterisation Data

Synthesis of 2,4-dimethoxybenzyl alanine ethyl ester



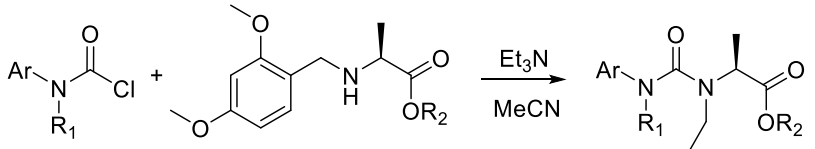
To a solution of L-alanine ethyl ester hydrochloride (5.0 g, 32.5 mmol) in ethanol (150 mL) was added anhydrous sodium acetate (13.8 g, 65.2 mmol) and 2,4-dimethoxybenzaldehyde (5.4 g, 32.5 mmol). After 10 minutes sodium triacetoxyborohydride (5.35 g, 65.1 mmol) was added and the reaction mixture was stirred 22 h. The solution was then concentrated in vacuo. The resulting solid was suspended in DCM, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated in vacuo. The title compound was yielded as light green oil without further purification. **Rf** (EA): 0.32. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.13 (1 H, d, *J* 7.8, C**H$_{Ar}$**), 6.43 (1 H, s, C**H$_{Ar}$**), 6.41 (1 H, d, *J* 2.3, C**H$_{Ar}$**), 4.13 (2 H, q, *J* 7.1, CO_2C**H$_2$**CH_3), 3.81 (3 H, s, OC**H$_3$**), 3.79 (3 H, s, OC**H$_3$**), 3.69 (2 H, q, *J* 13.0, C**H$_2$**N), 3.34 (1 H, q, *J* 7.0, C**H**CH_3), 1.93 (1 H, br. s, N**H**), 1.30 (3 H, d, *J* 7.0, , CHC**H$_3$**), 1.26 (3 H, t, *J* 7.1, CO_2CH_2C**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.6 (**C**=O), 160.1 (Ar**C**OMe), 158.6 (Ar**C**OMe), 130.3 (Ar**C**H), 120.2 (Ar**C**), 103.6 (Ar**C**H), 98.4 (Ar**C**H), 60.4 (O**C**H_2), 55.8 (N**C**H), 55.2 (O**C**H_3), 55.2 (O**C**H_3), 46.7 (N**C**H_2), 18.9 (**C**H_3), 14.1 (**C**H_3). **IR (film, cm^{-1}):** 3338, 2977, 2937, 2836, 1728. **HRMS (ESI+):** *m/z* calcd for $C_{14}H_{22}NO_4$ $[M+H]^+$ 268.1543, found 268.1545.

Synthesis of 2,4-dimethoxybenzyl alanine methyl ester



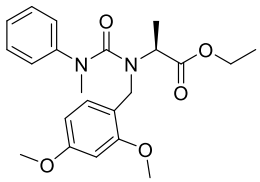
Alanine methyl ester hydrochloride (2 g, 14.33 mmol), 2,4-dimethoxybenzaldehyde (2.5 g, 15.05 mmol) and anhydrous sodium acetate (2.35 g, 28.66 mmol) were dissolved in MeOH (35 mL) and stirred for 5 minutes at room temperature. Then, sodium triacetoxyborohydride (6.07 g, 28.66 mmol) was added portionwise and the mixture was left stirring for another 16 h. The solvent was removed under reduced pressure and the resulting crude was partitioned between CH_2Cl_2 (60 mL) and saturated $NaHCO_3$ aqueous solution (60 mL). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash chromatography (SiO_2; CH_2Cl_2/MeOH 99:1 to 95:5) afforded the *N*-(2,4-dimethoxybenzyl)-alanine methyl ester (3.34 g, 13.18 mmol, 92%) as a yellowish oil. **Rf** 0.5 (SiO_2, CH_2Cl_2/MeOH 9:1). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ:7.13 (d, *J*=8.1 Hz, 1H, C**H$_{Ar}$**), 6.44-6.40 (m, 2H, 2* C**H$_{Ar}$**), 3.81 (s, 3H, ArOC**H$_3$**), 3.79 (s, 3H, ArOC**H$_3$**), 3.72 (d, *J*=13.0 Hz, 1H, C**H$_2$**N), 3.67 (s, 3H, CO_2C**H$_3$**), 3.66 (d, *J*=13.0 Hz, 1H, C**H$_2$**N), 3.37 (q, *J*=7.0 Hz, 1H, C**H**CH_3), 1.96 (bs, 1H, N**H**), 1.30 (d, *J*=7.0 Hz, 3H, CHC**H$_3$**). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 176.0 (**C**=O), 160.1 (Ar**C**OCH_3), 158.6 (Ar**C** OCH_3), 130.3 (Ar**C**H), 120.2 (Ar**C**), 103.7 (Ar**C**H), 98.4 (Ar**C**H), 55.7 (ArO**C**H_3), 55.2 (ArO**C**H_3+**C**HCH_3), 51.6 (CO_2**C**H_3), 46.7 (N**C**H_2Ar), 19.0 (CH**C**H_3). **IR** (film) ν_{max}: 2950 (N-H), 1730 (C=O). **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$ 254.3060, found 254.3063.

Synthesis of urea



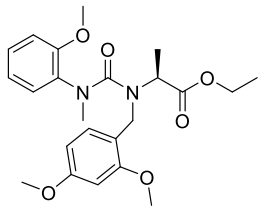
a R_1 = Me, R_2 = Et, Ar = Ph
b R_1 = Me, R_2 = Et, Ar = 2-MeOPh
c R_1 = Et, R_2 = Et, Ar = 1-naphthyl
d R_1 = Me, R_2 = Me, Ar = 2-pyridyl

ethyl N-(2,4-dimethoxyphenyl)-N'-(methyl(phenyl)carbamoyl)alaninate *(2a)*



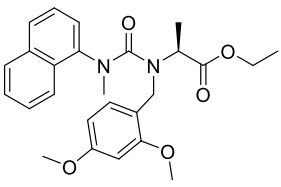
Following general procedure **1**, *N*-methyl-*N*-phenylcarbamoyl chloride (5.70 g, 32.8 mmol) was added to a solution of 2,4-dimethoxybenzyl alanine ethyl ester (8.6 g, 32.2 mmol) and Et_3N (5.40 mL, 38.6 mmol) in acetonitrile (110 mL) and heated to 85°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 4:1 PE/EA) yielded the title compound as a colourless oil (12.2 g, 30.5 mmol, 95%). **Rf** (EA/PE 1:1): 0.73; **$[\alpha]_D^{27}$ =** –6.5 (*c* = 1.2 in CHCl3); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.25 (2 H, m, 2* C**H$_{Ph}$**), 7.14 (2 H, dd, *J* 8.5, 1.1, 2* C**H$_{Ph}$**), 7.05 (1 H, tt, *J* 7.4, 1.1, para-C**H$_{Ph}$**), 6.98 (1 H, d, *J* 8.3, C**H$_{DMB}$**), 6.37 (1 H, dd, *J* 8.3, 2.4, C**H$_{DMB}$**), 6.33 (1 H, d, *J* 2.4, C**H$_{DMB}$**), 4.18 (3 H, m, OC**H$_2$**CH_3 + C**H**CH_3), 4.12 (1 H, d, *J* 16.3, NC**H$_A$**H_BDMB), 4.01 (1 H, d, *J* 16.3, NCH_A**H$_B$**DMB), 3.78 (3 H, s, *J* 5.6, OC**H$_3$**), 3.69 (3 H, s, OC**H$_3$**), 3.17 (3 H, s, NC**H$_3$**), 1.29 (3 H, t, *J* 7.2, OCH_2C**H$_3$**), 1.28 (3 H, d, *J* 7.0, CHC**H$_3$**). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 172.5 (C=O), 161.8, 160.1, 158.0, 146.3, 129.33 (**C$_{DMB}$**H), 129.29 (2* **C$_{Ph}$**H), 124.7 (**C$_{Ph}$**H), 124.3 (2* **C$_{Ph}$**H), 118.3 (**C$_{1\text{-}DMB}$**), 103.7 (**C$_{DMB}$**H), 98.2 (**C$_{DMB}$**H), 61.1 (O**C**H_2CH_3), 56.3 (**C**HCH_3), 55.5 (O**C**H_3), 55.2 (O**C**H_3), 46.0 (N**C**H_2DMB), 39.8 (N**C**H_3), 14.9 (CH**C**H_3 or CH**C**H_3), 14.4 (CH**C**H_3 or OCH_2**C**H_3). **IR (film, cm^{-1})**: 2980, 2939, 2906, 1735, 1646. **HRMS (ESI+):** *m/z* calcd for $C_{22}H_{29}N_2O_5$ $[M+H]^+$ 401.2071, found 401.2069.

ethyl N-(2,4-dimethoxyphenyl)-N'-(methyl(2-methoxyphenyl)carbamoyl)alaninate *(2b)*



Following general procedure **1**, N-methyl-2-methoxyphenylcarbamoyl chloride[3] (1.84 g, 9.23 mmol) was added to a solution of 2,4-dimethoxybenzyl alanine ethyl ester (2.35 g, 8.79 mmol) and Et_3N (1.47 mL, 10.55 mmol) in acetonitrile (3 mL) and heated to 85°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 3:2 PE/EA) yielded the title compound as pale yellow oil (3.2 g,ii 7.4 mmol, 92%). **Rf** (EA/PE 1:1): 0.57. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.09 (1 H, dd, *J* 7.7, 1.3, C**H$_{Ar}$**), 6.99 (1 H, m, C**H$_{Ar}$**), 6.87 (1 H, m, C**H$_{Ar}$**), 6.75 (1 H, t, *J* 7.2, C**H$_{Ar}$**), 6.71 (1 H, t, *J* 7.1, C**H$_{DMB}$**), 6.25 (2 H, dd, *J* 4.2, 2.1, C**H$_{DMB}$**), 4.27 (A of AB, 1 H, d, *J* 17.1, NC**H$_A$**H$_B$DMB), 4.18 (2 H, qd, *J* 7.0, 1.3, OC**H$_2$**CH$_3$), 4.05 (B of AB, 1 H, d, *J* 17.1, NCH$_A$**H$_B$**DMB), 3.86 (1 H, q, *J* 6.9, C**H**CH$_3$), 3.78 (3 H, s, *J* 7.6, OC**H$_3$**), 3.75 (3 H, s, OC**H$_3$**), 3.68 (3 H, s, OC**H$_3$**), 3.02 (3 H, s, NC**H$_3$**), 1.33 (3 H, d, *J* 7.0, CHC**H$_3$**), 1.28 (3 H, t, *J* 7.1, OCH$_2$C**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.7 (**C**=O ester), 162.9, 159.5, 157.5, 154.2, 134.1, 128.7 (**C$_{Ar}$**H), 128.5 (**C$_{Ar}$**H), 127.7 (**C$_{Ar}$**H), 121.0 (**C$_{Ar}$**H), 118.3 (**C$_{quat\ 1\text{-}DMB}$**), 111.4 (**C$_{DMB}$**H), 103.3 (**C$_{DMB}$**H), 97.7 (**C$_{DMB}$**H), 60.9 (O**C**H$_2$CH$_3$), 56.5 (N**C**HCH$_3$), 55.4 (O**C**H$_3$), 55.3 (O**C**H$_3$), 55.1 (O**C**H$_3$), 46.2 (N**C**H$_2$DMB), 38.6 (N**C**H$_3$), 14.8 (CH**C**H$_3$), 14.4 (OCH$_2$**C**H$_3$**). IR (film, cm^{-1}):** 2941, 2904, 2836, 1736, 1663. **HRMS (ESI$^+$):** *m/z* calcd for $C_{23}H_{31}N_2O_6Na$ $[M+Na]^+$ 454.2080, found 454.2071.

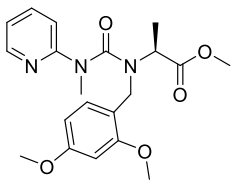
ethyl N-(2,4-dimethoxyphenyl)-N'-(ethyl(naphthalen-1-yl)carbamoyl)alaninate *(2c)*



Following general procedure **1**, N-ethyl-1-naphthylcarbamoyl chloride[3] (1.05 g, 4.5 mmol) was added to a solution of 2,4-dimethoxybenzyl alanine ethyl ester (1.10 g, 4.1 mmol) and Et_3N (0.69 mL, 4.9 mmol) in acetonitrile (140 mL) and heated to 85°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 4:1 PE/EA) yielded the title compound as a pale-yellow oil (1.40 g, 3.0 mmol, 73%). **Rf** (EA/PE 1:4): 0.50; **[α]$_D^{20}$**: -37.9 (c1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.82 (1 H, s, C**H$_{napht}$**), 7.75 (1 H, m, C**H$_{napht}$**), 7.55 (1 H, m, C**H$_{napht}$**), 7.43 (2 H, dd, *J* 6.2, 3.3, C**H$_{napht}$**), 7.25 (2 H, m, C**H$_{napht}$**), 6.75 (1 H, d, *J* 8.2, C**H$_{DMB}$**), 6.20 (1 H, d, *J* 8.0, C**H$_{DMB}$**), 6.10 (1 H, s, C**H$_{DMB}$**), 4.19 (2 H, q, *J* 7.1, OC**H2**CH3), 4.05 (1 H, m, C**H**CH3), 4.01 (1 H, m, NC**H$_A$**CH$_B$DMB), 3.82 (1 H, m, NCH$_A$C**H$_B$**DMB), 3.74 (3 H, s, OC**H$_3$**), 3.65 (1 H, m, NC**H$_A$**CH$_B$CH3), 3.58 (1 H, m, NCH$_A$C**H$_B$**CH3), 3.37 (4 H, s, OC**H$_3$**), 1.32 (3 H, d, *J* 6.9, CC**H$_3$**), 1.30 (3 H, t, *J* 7.1, OCH$_2$**CH$_3$**), 1.18 (3 H, t, *J* 7.0, NCH$_2$C**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.6 (**C**=O ester), 162.2 (**C**OCH$_3$), 159.6 (**C**OCH$_3$), 157.4 (**C$_{1\text{-}napht}$**), 140.2 (**C**=O urea), 134.8 (**C$_{quat\ napht}$**), 130.1 (**C$_{quat\ napht}$**), 128.4 (**C$_{napht}$**H), 128.1 (**C$_{DMB}$**H), 126.9 (**C$_{napht}$**H), 126.4 (**C$_{napht}$**H), 126.0 (**C$_{napht}$**H), 125.8 (**C$_{napht}$**H), 125.5 (**C$_{napht}$**H), 123.2 (**C$_{napht}$**H), 118.2 (**C$_{quat\ 1\text{-}DMB}$**), 103.4 (**C$_{DMB}$**H), 97.7 (**C$_{DMB}$**H), 60.9 (O**C**H$_2$CH$_3$), 56.7 (**C**HCH$_3$), 55.5 (O**C**H$_3$), 54.8 (O**C**H$_3$), 47.1 (N**C**H$_2$CH$_3$), 46.3

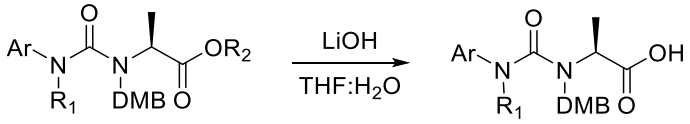
(N**C**H_2DMB), 14.8 (CH**C**H_3), 14.4 (OCH_2**C**H_3), 13.6 (NCH_2**C**H_3). **IR (film, cm^{-1}):** 2943, 2906, 2840, 1733, 1661. **HRMS (ESI$^+$):** *m/z* calcd for $C_{27}H_{32}N_2O_5Na$ $[M+Na]^+$ 487.2209, found 487.2212.

methyl N-(2,4-dimethoxyphenyl)-N'-(methyl(2-pyridyl)carbamoyl)alaninate *(2d)*



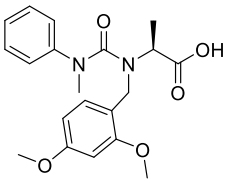
Following general procedure 1, 2-pyridyl carbamoyl chloride (2.14 g, 12.6 mmol) was added to a solution of 2,4-dimethoxybenzyl alanine methyl ester (3.03 g, 12.0 mmol) and Et_3N (2.00 mL, 14.3 mmol) in acetonitrile (40 mL) and heated to 85°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, EA) yielded the title compound as a yellow oil (4.6 g, 11.9 mmol, 99%). **Rf** (EA/PE 2:1): 0.55. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 8.29 (1 H, m, Ar**H**), 7.54 (1 H, m, Ar**H**), 7.25 (1 H, d, *J* 9.4, Ar**H**), 7.10 (1 H, d, *J* 8.2, Ar**H**), 6.83 (1 H, m, Ar**H**), 6.40 (2 H, m, 2* Ar**H**), 4.32 (A of AB, 1 H, d, *J* 15.5, C**H$_2$**DMB), 4.24 (B of AB, 1 H, d, *J* 15.5, C**H$_2$**DMB), 4.13 (1 H, q, *J* 7.0, C**H**CH_3), 3.78 (3 H, s, ArOC**H$_3$**), 3.73 (3 H, s, ArOC**H$_3$**), 3.71 (3 H, s, CO_2C**H$_3$**), 3.32 (3 H, s, NC**H$_3$**), 1.33 (3 H, d, *J* 7.0, CHC**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.5 (**C**=O), 161.1 (**C**=O), 160.6 (Ar**C**OCH_3), 158.5 (Ar**C**OCH_3), 157.0 (Ar**C**), 148.1 (Ar**C**H), 137.5 (Ar**C**H), 130.0 (Ar**C**H), 117.4 (Ar**C**), 117.1 (Ar**C**H), 114.4 (Ar**C**H), 103.9 (Ar**C**H), 98.4 (Ar**C**H), 56.1 (N**C**HCH_3), 55.4 (O**C**H_3), 55.3 (O**C**H_3), 52.4 (CO_2**C**H_3), 47.4 (N**C**H_2DMB), 35.5 (N**C**H_3), 15.0 (CH**C**H_3). **IR (film, cm^{-1}):** 3001, 2948, 2837, 1741, 1658. **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{25}N_3O_5Na$ $[M+Na]^+$ 410.1692, found 410.1687.

Synthesis of carboxylic acid



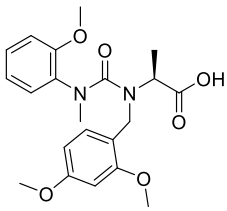
1. R_1 = Me, R_2 = Et, Ar = Ph, o-MeOPh
2. R_1 = Et, R_2 = Et, Ar = 1-naphthyl
3. R_1 = Me, R_2 = Me, Ar = 2-pyridyl

N-(2,4-dimethoxyphenyl)-N'-(methyl(phenyl)carbamoyl)alanine



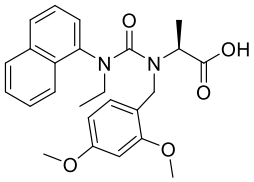
Following general procedure 2, LiOH (3.80 g, 160 mmol) was added portion-wise to a solution of urea 2a (2.90 g, 7.2 mmol) in 2:1 THF:H_2O (240 mL) and heated to 45°C. The reaction was complete overnight. The title compound was yielded as an off-white solid (2.60 g, 7.0 mmol, 97%). **Rf** (EA/PE 2:1): 0.38 (tailing). **mp**: 136-137 °C. **$[\alpha]_D^{21}$ =** +5.2 (*c* = 1.6 in $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 13.45 (1H, br. s, COO***H***), 7.42-7.37 (2H, m, Ph***H***), 7.23-7.17 (3H, m, Ph***H***), 6.84 (1H, d, *J* = 8.2, DMB***H***), 6.37 (1H, d, *J* = 2.3, DMB***H***), 6.34 (1H, dd, *J* = 8.2, 2.4, DMB***H***), 3.96-3.92 (2H, m, C***H***CH_3+ C***H***$_A$$H_B$N), 3.78 (3H, s, OC***H*****$_3$**), 3.75 (3H, s, OC***H*****$_3$**), 3.69 (1H, d, *J* = 13.9, CH_A***H***$_B$N), 3.42 (3H, s, NC***H*****$_3$**), 1.52 (3H, d, *J* = 7.4, CHC***H*****$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 173.5 (**C**=O), 164.5 (C=O), 161.5 (**C**OCH_3), 159.1 (**C**OCH_3), 145.1 (**$C_{1\text{-Ph}}$**), 131.2 (**C_{DMB}**H), 129.8 (2* **C_{Ph}**H), 125.8 (**C_{Ph}**H), 124.3 (2* **C_{Ph}**H), 115.6 (**$C_{1\text{-DMB}}$**), 103.9 (**C_{DMB}**H), 98.6 (**C_{DMB}**H), 57.8 (**C**CH_3), 55.5 (O***C***H_3), 55.4 (O***C***H_3), 49.5 (N**C**H_2DMB), 39.2 (N***C***H_3), 14.7 (C***C***H_3). **IR (film, cm–1)**: 2999, 2941, 2837, 1739, 1612. **HRMS (ESI+):** *m/z* calcd for $C_{20}H_{25}N_2O_5$ $[M+H]^+$ 373.1758, found 373.1757.

N-(2,4-dimethoxyphenyl)-N'-(methyl(naphthalen-1-yl)carbamoyl)alanine



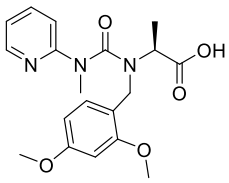
Following general procedure 2, LiOH (3.4 g, 144 mmol) was added portion-wise to a solution of urea 2c (3.1 g, 7.2 mmol) in 2:1 THF:H_2O (240 mL) and heated to 45°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 1:2 PE/EA) yielded the title compound as a white solid (2.8 g, 6.9 mmol, 96%). **Rf** (EA/PE 1:1): 0.10. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.21 (1 H, m, C**H_{Ar}**), 7.13 (1 H, d, *J* 7.6, C**H_{Ar}**), 6.93 (2 H, m, C**H_{Ar}**), 6.78 (1 H, d, *J* 8.2, C**H_{DMB}**), 6.34 (1 H, d, *J* 2.1, C**H_{DMB}**), 6.30 (1 H, dd, *J* 8.2, 2.3, C**H_{DMB}**), 3.94 (A of AB, 1 H, m, NC**H_A**H_BDMB), 3.83 (3 H, s, OC_{Ar}**H_3**), 3.82 (2 H, m, NCH_A**H_B**DMB + C**H**CH_3), 3.76 (3 H, s, OC_{DMB}**H_3**), 3.74 (3 H, s, OC_{DMB}**H_3**), 3.24 (3 H, s, NC**H_3**), 1.45 (3 H, d, *J* 7.3, CHC**H_3**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 174.0 (**C**=O_{acid}), 165.8, 161.2, 159.0, 154.0, 133.1, 130.7 (**C_{DMB}**H), 128.4 (**C_{Ar}**H), 128.1 (**C_{Ar}**H), 121.4 (**C_{Ar}**H), 115.9 (**$C_{1\text{-DMB}}$**), 112.2 (**C_{Ar}**H), 103.7 (**C_{DMB}**H), 98.4 (**C_{DMB}**H), 57.7 (**C**HCH_3), 55.6 (O**C_{Ar}**H_3), 55.4 (O**C_{DMB}**H_3), 55.3 (O**C_{DMB}**H_3), 48.9 (N**C**H_2DMB), 38.6 (N**C**H_3), 14.8 (CH**C**H_3). **HRMS (ESI$^+$):** *m/z* calcd for $C_{21}H_{27}N_2O_6$ $[M+H]^+$ 403.1864, found 403.1866

N-(2,4-dimethoxyphenyl)-N'-(ethyl(naphthalen-1-yl)carbamoyl)alanine



Following general procedure 2, LiOH (1.48 g, 62 mmol) was added portion-wise to a solution of urea 2b (1.44 g, 3.1 mmol) in 2:1 THF:H_2O (90 mL) and heated to 45°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 1:1 PE/EA) yielded the title compound as an off-white solid (1.18 g, 2.70 mmol, 87%). **Rf** (EA/PE 1:4): 0.20. **mp:** 156°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.89 (2 H, m, C**H$_{napht}$**), 7.78 (1 H, d, *J* 7.8, C**H$_{napht}$**), 7.53 (2 H, m, C**H$_{napht}$**), 7.45 (1 H, t, *J* 7.0, C**H$_{napht}$**), 7.29 (1 H, d, *J* 7.2, C**H$_{napht}$**), 6.65 (1 H, s, C**H$_{DMB}$**), 6.32 (1 H, s, C**H$_{DMB}$**), 6.24 (1 H, s, C**H$_{DMB}$**), 3.84 (4 H, m, 2* NCH_2CH_3, C**H**CH_3, NC**H$_A$**H$_B$**DMB), 3.77 (3 H, s, OC**H$_3$**), 3.73 (3 H, s, OC**H$_3$**), 3.43 (1 H, m, NC**H$_A$**H$_B$**DMB), 1.41 (1 H, d, *J* 7.2, CHC**H$_3$**), 1.25 (3 H, t, *J* 7.0, NCH_2C**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 173.7 (**C**=O acide), 165.4 (**C**OCH_3), 161.2 (**C**OCH_3), 158.9 (**C$_{1\text{-napht}}$**), 139.2 (**C**=O urea), 135.0 (**C$_{quat\ napht}$**), 130.8 (**C$_{DMB}$**H), 129.7 (**C$_{quat\ napht}$**), 128.9 (**C$_{napht}$**H), 127.9 (**C$_{napht}$**H), 127.3 (**C$_{napht}$**H), 126.6 (**C$_{napht}$**H), 125.7 (2* **C$_{napht}$**H), 122.7 (**C$_{napht}$**H), 115.7 (**C$_{1\text{-DMB}}$**), 103.7 (**C$_{DMB}$**H), 98.5 (**C$_{DMB}$**H), 58.4 (**C**HCH_3), 55.4 (2* O**C**H_3), 49,3 (N**C**H_2CH_3), 47.2 (N**C**H_2DMB), 14.8 (CH**C**H_3), 13.5 (NCH_2**C**H_3). **IR (film, cm^{-1}):** 2936, 1740, 1614. **HRMS (ESI$^+$):** *m/z* calcd for $C_{25}H_{28}N_2O_5$ $[M+H]^+$ 437.2071, found 437.2069.

N-(2,4-dimethoxyphenyl)-N'-(methyl(2-pyridyl)carbamoyl)alanine

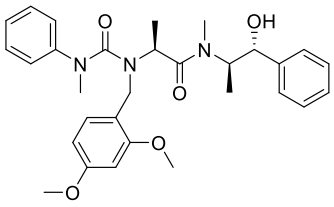


Following general procedure 2, LiOH (3.0 g, 124 mmol) was added portion-wise to a solution of urea 2d (2.4 g, 6.2 mmol) in 2:1 THF:H_2O (210 mL) and heated to 45°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 1:2 PE/EA) yielded the title compound as a sticky white foam (1.2 g, 3.2 mmol, 52%). The crude acid was used without further purification

Synthesis of pseudoephedrine coupled urea

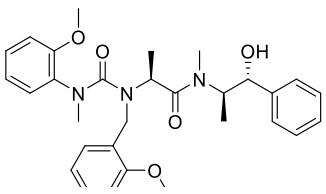
1. R = Me, Ar = Ph, o-MeOPh, 2-pyridyl
2. R = Et, Ar = 1-naphthyl

2-(1-(2,4-dimethoxyphenyl)-3-methyl-3-phenylureido)-N-methyl-N-((2R,3R)-3-phenylbutan-2-yl)propanamide *(3a)*



Following general procedure **3**, EDC.HCl (1.50 g, 8.1 mmol), HOBt hydrate (1.03 g, 6.7 mmol) and DIPEA (1.60 mL, 8.1 mmol) were added to a solution of N-(2,4-dimethoxyphenyl)-N'-(methyl(phenyl)carbamoyl)alanine (2.50 g, 6.7 mmol) in DCM (40.0 mL) at 0°C. After 20 minutes, (R,R)-pseudoephedrine (1.67 g, 10.1 mmol) was added and reaction mixture was warmed up to room temperature. The reaction was complete over week-end. Purification by flash column chromatography (SiO_2, 1:2 PE/EA) yielded the title compound as white solid (3.25 g, 6.3 mmol, 93%). **Rf** (EA/PE 2:1): 0.55. **mp:** 66°C. **$[\alpha]_D^{24}$**: -42.8° (*c* 1.0, $CHCl_3$). NMR data is a mixture of rotamers due to the pseudoephedrine and the DMB protecting group. Not all the rotamers for each carbon were observed. All visible signals are reported and only the major isomer is assigned. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.35 – 7.26 (2 H, m, Ar**H**), 7.26 – 7.20 (2 H, m, Ar**H**), 7.20 – 7.14 (4H H, m, Ar**H**), 7.09 (1 H, d, J 7.7, Ar**H**), 6.98 (1 H, t, J 7.3, Ar**H**), 6.87 (1 H, dd, J 16.0, 8.4, Ar**H**), 6.38 – 6.22 (2 H, m, Ar**H**), 4.86 – 4.31 (3 H, m, C**H$_2$**DMB + C**H**OH), 4.33 – 4.04 (1 H, m, C**H**CH_3), 3.89 (1 H, dd, J 24.7, 17.2, C**H**CH_3), 3.70 (3 H, d, J 7.7, OC**H$_3$**), 3.63 – 3.53 (3 H, m, OC**H$_3$**), 3.21 – 2.96 (3 H, m, NC**H$_3$**), 2.89 (3 H, s, NC**H$_3$**), 1.06 (3 H, dt, J 13.1, 6.6, CHC**H$_3$**), 0.95 – 0.78 (3 H, m, CHC**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 174.9 (**C**=O), 174.1, 163.7, 163.1 (**C**=O), 160.0, 159.9 (**C$_{Ar}$**), 157.9, 157.7 (**C$_{Ar}$**), 146.05, 146.01 (**C$_{Ar}$**), 142.5, 142.0 (**C$_{Ar}$**), 129.42 (**C$_{Ar}$**H), 129.37, 129.3, 128.9, 128.6 (**C$_{Ar}$**H), 128.4 (**C$_{Ar}$**H), 128.0, 127.8 (**C$_{Ar}$**H), 127.3, 127.2 (**C$_{Ar}$**H), 127.0, 125.1 (**C$_{Ar}$**H), 124.8, 124.7 (**C$_{Ar}$**H), 124.6, 124.5, 119.1 (**C$_{Ar}$**), 118.7, 103.9, 103.8 (**C$_{Ar}$**H), 98.4, 98.3 (**C$_{Ar}$**H), 76.1 (**C**HOH), 59.2 (**C**HCH_3), 55.5 (O**C**H_3), 55.3, 55.2 (O**C**H_3), 53.1, 52.3 (**C**HCH_3), 50.7, 44.6, 43.9 (**C**H_2DMB), 43.3, 40.0, 39.9 (N**C**H_3), 39.3, 27.3 (N**C**H_3), 16.3, 16.1, 15.0 (C**C**H_3), 14.6 (C**C**H_3). **IR (film, cm^{-1}):** 3406, 2934, 1633, 1593. **HRMS (ESI$^+$):** m/z calcd for $C_{30}H_{37}N_3O_5$ $[M+H]^+$ 520.2808, found 520.2806.

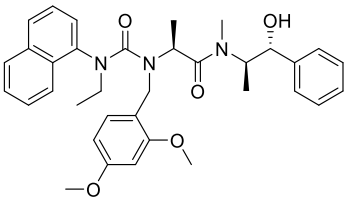
2-(1-(2,4-dimethoxyphenyl)-3-ethyl-3-(2-methoxyphenyl)ureido)-N-methyl-N-((2R,3R)-3-phenylbutan-2-yl)propanamide *(3b)*



Following general procedure **3**, EDC.HCl (1.46 g, 7.64 mmol), HOBt hydrate (0.98 g, 6.37 mmol) and DIPEA (1.49 mL, 7.64 mmol) were added

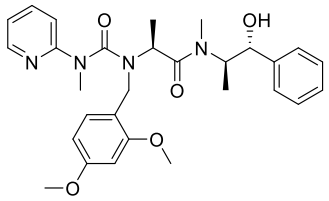
to a solution of N-(2,4-dimethoxyphenyl)-N'-(methyl(naphthalen-1-yl)carbamoyl)alanine (2.8 g, 6.37 mmol) in DCM (38.0 mL) at 0°C. After 20 minutes, (*R,R*)-pseudoephedrine (1.58 g, 9.56 mmol) was added and reaction mixture was warmed up to room temperature. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 99:1 MeOH/DCM) yielded the title compound as a white solid (3.09 g, 5.6 mmol, 88%). **Rf** (EA/PE 2:1): 0.50. **Mp:** 67°C. **$[\alpha]_D^{24}$**: -41.7° (*c* 1.0, $CHCl_3$). NMR data is a mixture of rotamers due to the pseudoephedrine and the DMB protecting group. Not all the rotamers for each carbon were observed, and only the major isomer is reported. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.61 – 7.22 (5 H, m, Ar**H**), 7.15 – 6.95 (2 H, m, Ar**H**), 6.90 (1 H, t, J 6.6, Ar**H**), 6.86 – 6.65 (2 H, m, Ar**H**), 6.41 – 6.17 (2 H, m, Ar**H**), 5.11 – 4.48 (3 H, m, C**H_2**DMB + C**H**OH), 4.45 – 4.13 (2 H, m, 2* C**H**CH_3), 3.76 (6 H, dt, J 8.9, 5.3, 2* O**C**H_3), 3.70 – 3.64 (3 H, m, O**C**H_3), 3.12 – 2.78 (6 H, m, 2* N**C**H_3), 1.23 – 0.57 (6 H, m, 2 * C**C**H_3). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.3 (**C**=O), 174.9, 174.2, 172.8, 164.3, 164.0 (**C**=O), 163.2, 162.8, 159.6, 159.5, 159.3 (**C_{Ar}**), 157.9, 157.5, 157.1 (**C_{Ar}**), 154.7, 154.4, 154.4 (**C_{Ar}**), 154.1, 142.4, 142.3, 141.9 (**C_{Ar}**), 141.3, 134.7, 133.9, 133.6 (**C_{Ar}**), 133.45, 130.40, 129.2, 128.94, 128.88 (**C**H_{Ar}), 128.8, 128.75, 128.68 (**C**H_{Ar}), 128.65, 128.58, 128.50, 128.48, 128.3 (**C**H_{Ar}), 128.2, 128.03, 127.99 (**C**H_{Ar}), 127.86, 127.76, 127.68 (**C**H_{Ar}), 127.4, 127.3, 127.1 (**C**H_{Ar}), 126.9, 121.1, 121.04, 121.01 (**C**H_{Ar}), 119.5 (**C_{Ar}**), 119.4, 119.3, 111.8, 111.6, 111.4 (**C**H_{Ar}), 111.2, 103.30, 103.26, 103.2 (**C**H_{Ar}), 97.8, 97.7, 97.6, 97.5 (**C**H_{Ar}), 76.1, 76.0 (**C**HOH), 75.9, 75.8, 58.9, 57.9, 55.5, 55.4 (O**C**H_3), 55.3 (O**C**H_3), 55.0 (O**C**H_3), 54.9 (**C**HCH_3), 54.1, 53.2 (**C**HCH_3), 51.5, 44.5, 44.3 (**C**H_2DMB), 43.2, 42.1, 39.1, 39.1 (N**C**H_3), 38.93, 38.88, 30.9 (N**C**H_3), 27.3, 27.1, 16.4, 16.1, 16.0, 14.9, 14.8, 14.7, 14.6 (CH**C**H_3), 14.5 (CH**C**H_3). **IR (film, cm^{-1}):** 3418, 2937, 2836, 1627, 1590. **HRMS (ESI$^+$):** *m/z* calcd for $C_{31}H_{39}N_3O_6Na$ $[M+Na]^+$ 572.2737, found 572.2718.

2-(1-(2,4-dimethoxyphenyl)-3-ethyl-3-(naphthalen-1-yl)ureido)-N-methyl-N-((2R,3R)-3-phenylbutan-2-yl)propanamide *(3c)*



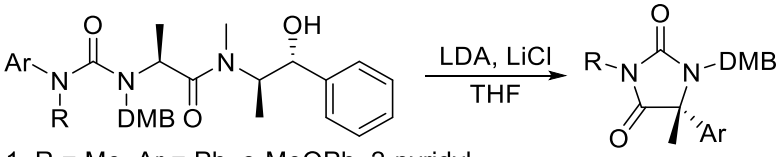
Following general procedure **3**, EDC.HCl (0.65 g, 3.4 mmol), HOBt hydrate (0.43 g, 2.8 mmol) and DIPEA (0.66 mL, 3.4 mmol) were added to a solution of N-(2,4-dimethoxyphenyl)-N'-(ethyl(naphthalen-1-yl)carbamoyl)alanine (1.25 g, 2.8 mmol) in DCM (20.0 mL) at 0°C. After 20 minutes, (*R,R*)-pseudoephedrine (0.71 g, 4.3 mmol) was added and reaction mixture was warmed up to room temperature. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 1:2 PE/EA) yielded the title compound as a foaming white solid (1.20 g, 2.06 mmol, 72%). **Rf** (EA/PE 1:2): 0.60. **Mp:** 99°C. **$[\alpha]_D^{24}$:** -32.9° (*c* 1.0, $CHCl_3$). NMR data is a mixture of rotamers due to the pseudoephedrine and the DMB protecting group. Not all the rotamers for each carbon were observed. All visible signals are reported and only the major isomer is assigned. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.82 – 7.50 (3 H, m, Ar**H**), 7.45 – 7.37 (4 H, m, Ar**H**), 7.37 – 7.28 (2 H, m, Ar**H**), 7.01 – 6.62 (1 H, m, Ar**H**), 6.41 – 5.86 (2 H, m, Ar**H**), 5.28 – 4.42 (3 H, m, C**H**OH + 2* C**H**CH_3), 4.34 – 3.86 (2 H, m, NC**H_2**DMB), 3.81 – 3.72 (3 H, m, OC**H_3**), 3.60 – 3.18 (5 H, m, NC**H_2**CH_3 + OC**H_3**), 3.16 – 2.83 (3 H, m, NC**H_3**), 1.34 – 1.01 (6 H, m, NCH_2C**H_3** + CHC**H_3**), 1.01 – 0.90 (3 H, m, CHC**H_3**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.4 (**C**=O), 174.7, 174.3, 164.2, 164.0 (**C**=O), 159.3 (**C_{Ar}**), 157.0 (**C_{Ar}**), 142.8, 142.4, 142.0 (**C_{Ar}**), 139.7 (**C_{Ar}**), 134.83, 134.78 (**C_{Ar}**), 134.7, 130.2 (**C_{Ar}**), 130.0, 128.9, 128.7 (**C**H_{Ar}), 128.5 (**C**H_{Ar}), 128.4 (**C**H_{Ar}), 128.0, 127.9, 127.84, 127.78 (**C**H_{Ar}), 127.34 (**C**H_{Ar}), 127.30, 127.24 (**C**H_{Ar}), 127.20, 127.0 (**C**H_{Ar}), 126.4 (**C**H_{Ar}), 126.2 (**C**H_{Ar}), 126.0, 125.9 (**C**H_{Ar}), 125.6, 123.1 (**C**H_{Ar}), 119.3, 119.1 (**C_{Ar}**), 103.2 (**C**H_{Ar}), 97.6 (**C**H_{Ar}), 76.8, 76.2, 76.1 (**C**HOH), 75.9, 58.9, 57.2 (br., **C**HCH_3), 55.5 (O**C**H_3), 54.8 (O**C**H_3), 52.8 (**C**HCH_3), 51.1, 47.6, 47.4 (N**C**H_2CH_3), 44.5 (br., N**C**H_2DMB), 30.9 (br., N**C**H_3), 27.6, 27.1, 16.5, 16.2, 14.9, 14.7 (**C**H_3), 14.6 (**C**H_3), 13.6, 13.5 (**C**H_3), 13.4. **IR (film, cm^{-1}):** 3419, 2935, 1617, 1590. **HRMS (ESI^+):** ***m/z*** calcd for $C_{35}H_{42}N_3O_5$ $[M+H]^+$ 584.3119, found 584.3108.

2-(1-(2,4-dimethoxybenzyl)-3-methyl-3-(pyridin-2-yl)ureido)-N-((1R,2R)-1-hydroxy-1-phenylpropan-2-yl)-N-methylpropanamide *(3d)*



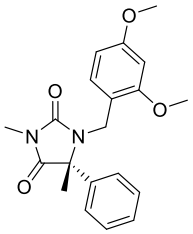
Following general procedure **3**, EDC.HCl (0.75 g, 3.9 mmol), HOBt hydrate (0.50 g, 3.2 mmol) and DIPEA (0.76 mL, 3.9 mmol) were added to a solution of N-(2,4-dimethoxyphenyl)-N'-(methyl(2-pyridyl)carbamoyl)alanine (1.2 g, 2.8 mmol) in DCM (20.0 mL) at 0°C. After 20 minutes, (R,R)-pseudoephedrine (0.80 g, 4.8 mmol) was added and reaction mixture was warmed up to room temperature. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, EA) yielded the title compound as a white solid (1.4 g, 2.7 mmol, 84%). **Rf** (EA): 0.40. **Mp:** 91-93°C. **$[\alpha]_D^{24}$**: -48.0° (*c* 1.0, $CHCl_3$). NMR data is a mixture of rotamers due to the pseudoephedrine and the DMB protecting group. Only the major isomer is reported. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 8.30 – 8.19 (1 H, m Ar**H**), 7.58 – 7.42 (1 H, m, Ar**H**), 7.41 – 7.34 (2 H, m, 2* Ar**H**), 7.34 – 7.21 (4 H, m, 4* Ar**H**), 7.04 – 6.94 (1 H, m, Ar**H**), 6.92 – 6.76 (1 H, m, Ar**H**), 6.49 – 6.28 (2 H, m, 2* Ar**H**), 5.15 – 4.76 (1 H, m, C**H**CH_3), 4.70 – 4.39 (2 H, m, C**H**CH_3 + C**H**OH), 4.35 – 4.15 (2 H, m, NC**H_2**DMB), 3.81 – 3.72 (3 H, m, OC**H_3**), 3.71 – 3.61 (3 H, m, OC**H_3**), 3.29 – 3.09 (3 H, m, NC**H_3**), 3.08 – 2.87 (3 H, m, NC**H_3**), 1.31 – 1.15 (3 H, m, C**C**H_3), 1.12 – 0.91 (3 H, m, C**C**H_3). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 174.25 (**C**=O), 162.12 (**C**=O), 160.06 (**C_{Ar}**), 157.79 (**C_{Ar}**), 157.10 (**C_{Ar}**), 147.99, 141.85 (**C_{Ar}**), 137.81 (**C_{Ar}**H), 128.65 (**C_{Ar}**H), 128.45 (**C_{Ar}**H), 128.37 (**C_{Ar}**H), 127.77 (**C_{Ar}**H), 127.05 (**C_{Ar}**H), 118.78 (**C_{Ar}**), 117.61 (**C_{Ar}**H), 114.88 (**C_{Ar}**H), 103.94 (**C_{Ar}**H), 98.32 (**C_{Ar}**H), 75.88 (**C**HOH), 57.60 (br., **C**HCH_3), 55.40 (O**C**H_3), 55.22 (O**C**H_3), 52.35 (**C**HCH_3), 44.21 (N**C**H_2DMB), 35.75 (N**C**H_3), 31.26 (br., NCH_3), 15.05 (CH**C**H_3), 14.47 (CH**C**H_3). **IR (film, cm^{-1}):** 3414, 2938, 1634, 1589. **HRMS** (ESI$^+$): *m/z* calcd for $C_{29}H_{36}N_4O_5Na$ $[M+Na]^+$ 543.2583, found 543.2587.

Synthesis of protected hydantoin



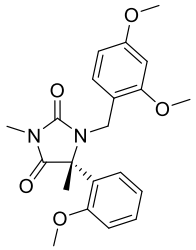
1. R = Me, Ar = Ph, o-MeOPh, 2-pyridyl
2. R = Et, Ar = 1-naphthyl

(R)-1-(2,4-dimethoxyphenyl)-3-methyl-5-methyl-5-phenylimidazolidine-2,4-dione *(4a)*



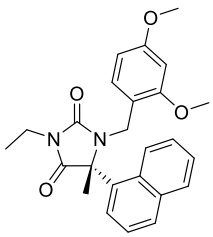
Following general procedure **4,** LDA was prepared by adding a solution of nBuLi (1.43 M, 1.55 mL, 2.2 mmol) dropwise to a solution of DiPA (0.31 mL, 2.2 mmol) in THF (1.5 mL) at 0°C. The reaction mixture was stirred for 20 minutes and added dropwise to a solution of coupled urea 3a (172 mg, 0.34 mmol) and LiCl (144 mg, 3.4 mmol) in THF (2.5 mL) at -78°C. The reaction was complete over 3h. Purification by flash column chromatography (SiO_2, 4:1 PE/EA) yielded the title compound as a yellow oil (83 mg, 0.23 mmol, 69%, ee 99:1). **Rf** (EA/PE 1:3): 0.35. **$[\alpha]_D^{23}$** : -54.4° (*c* 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.31 (3 H, m, 3* C_{Ph}**H**), 7.19 (3 H, m, 2* C_{Ph}**H** + C_{DMB}**H**)), 6.40 (1 H, dd, *J* 8.4, 2.4, C_{DMB}**H**), 6.27 (1 H, d, *J* 2.3, C_{DMB}**H**), 4.67 (1 H, d, *J* 15.4, NC**H_A**H_BDMB), 4.15 (1 H, d, *J* 15.4, NCH_A**H_B**DMB), 3.77 (3 H, s, OC**H_3**), 3.61 (3 H, s, OC**H_3**), 3.10 (3 H, s, NC**H_3**), 1.66 (3 H, s, CC**H_3**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.5 (**C**=O), 160.7 (**C**OCH_3), 157.9 (**C**OCH_3), 156.9 (**C**=O), 136.9 ($\mathbf{C}_{quat\ phenyl}$), 131.1 ($\mathbf{C}_{Ar}$H), 128.9 (2* $\mathbf{C}_{Ar}$H), 128.6 ($\mathbf{C}_{Ar}$H), 126.2 (2* $\mathbf{C}_{Ar}$H), 118.0 ($\mathbf{C}_{quat\ 1\text{-}DMB}$), 104.3 ($\mathbf{C}_{DMB}$H), 98.2 ($\mathbf{C}_{DMB}$H), 67.6 (**C**$CH_3$), 55.5 (O**C**$H_3$), 55.1 (O**C**$H_3$), 38.0 (N**C**$H_2$DMB), 25.4 (N**C**$H_3$), 20.5 (C**C**$H_3$). **IR (film, cm^{-1}):** 2924, 2852, 1769, 1707. **HRMS (ESI$^+$):** *m/z* calcd for $C_{11}H_{12}N_2O_2Na$ $[M+Na]^+$ 227.0791, found 229.0792.

(R)-1-(3,4-dimethylbenzyl)-5-(2-methoxyphenyl)-3,5-dimethylimidazolidine-2,4-dione *(4b)*



Following general procedure **4,** LDA was prepared by adding a solution of nBuLi (1.47 M, 3.6 mL, 5.30 mmol) dropwise to a solution of DiPA (0.75 mL, 5.30 mmol) in THF (4.0 mL) at 0°C. The reaction mixture was stirred for 20 minutes and added dropwise to a solution of coupled urea 3c (450 mg, 0.82 mmol) and LiCl (348 mg, 8.20 mmol) in THF (4.2 mL) at -78°C. The reaction was complete after 3 hours. Purification by flash column chromatography (SiO_2, 2:3 PE/EA) yielded the title compound as yellow oil (175 mg, 0.46 mmol, 56%, ee 55:45). **Rf** (EA/PE 2:1): 0.65. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.28 (2 H, m, Ar**H**), 7.11 (1 H, d, *J* 8.4, DMB**H**), 6.95 (1 H, td, *J* 7.6, 1.1, Ar**H**), 6.71 (1 H, d, *J* 8.2, Ar**H**), 6.34 (1 H, dd, *J* 8.4, 2.4, DMB**H**), 6.22 (1 H, d, *J* 2.4, DMB**H**), 4.49 (A of AB, 1 H, d, *J* 15.3, NC**H$_A$**H$_B$DMB), 3.96 (B of AB, 1 H, d, *J* 15.3, NCH$_A$**H$_B$**DMB), 3.76 (3 H, s, OC**H$_3$**), 3.67 (3 H, s, OC**H$_3$**), 3.66 (3 H, s, OC**H$_3$**), 3.15 (3 H, s, NC**H$_3$**), 1.61 (3 H, s, CC**H$_3$**). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 177.1 (**C**=O), 160.3 (**C**OCH$_3$), 157.7 (**C**OCH$_3$), 157.4 (**C**OCH$_3$), 157.1 (C=O), 131.09 (**C$_{DMB}$**H), 130.5 (**C$_{Ar}$**H), 129.1 (**C$_{Ar}$**H), 123.9 (**C**$_{quat\ 1\text{-}Ar}$), 120.2 (**C$_{Ar}$**H), 118.1 (**C**$_{quat\ 1\text{-}DMB}$), 110.9 (**C$_{Ar}$**H), 104.0 (**C$_{DMB}$**H), 97.8 (**C$_{DMB}$**H), 64.8 (**C**CH$_3$), 55.8 (O**C**H$_3$), 55.4 (O**C**H$_3$), 55.1 (O**C**H$_3$), 37.2 (N**C**H$_2$DMB), 25.1 (N**C**H$_3$), 21.7 (C**C**H$_3$). **IR (film, cm^{-1}):** 2939, 2837, 1766, 1703. **HRMS (ESI$^+$):** *m/z* calcd for $C_{21}H_{24}N_2O_5Na$ $[M+Na]^+$ 407.1583, found 407.1598.

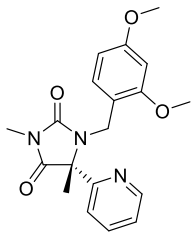
(R)-1-(2,4-dimethoxyphenyl)-3-ethyl-5-methyl-5-(naphthalen-1-yl)imidazolidine-2,4-dione *(4c)*



Following general procedure **4,** LDA was prepared by adding a solution of nBuLi (1.43 M, 0.78 mL, 1.12 mmol) dropwise to a solution of DiPA (0.16 mL, 1.12 mmol) in THF (1.0 mL) at 0°C. The reaction mixture was stirred for 20 minutes and added dropwise to a solution of coupled urea 3b (100 mg, 0.17 mmol) and LiCl (73 mg, 1.7 mmol) in THF (0.7 mL) at -78°C. The reaction was complete overnight. Purification by flash column chromatography (SiO_2, 2:1 PE/EA) yielded the title compound as pale yellow solid (40 mg, 0.099 mmol, 58%, ee 69:31). **Rf** (EA/PE 1:2): 0.70. **Mp:** 136-138°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.79 (2 H, d, *J* 7.9, C$_{napht}$**H**), 7.54 (1 H, d, *J* 7.2, C$_{napht}$**H**), 7.41 (4 H, m, C$_{napht}$**H**), 6.89 (1 H, d, *J* 8.3, C$_{DMB}$**H**), 6.09 (1 H, dd, *J* 8.3, 2.3, C$_{DMB}$**H**), 6.03 (1 H, d, *J* 2.3, C$_{DMB}$**H**), 4.47 (1 H, d, *J* 15.0, NC**H$_A$**H$_B$DMB), 4.07 (1 H, d, *J* 15.0, NCH$_A$**H$_B$**DMB), 3.81 (2 H, q, *J* 7.1, NC**H$_2$**CH$_3$), 3.67 (3 H, s, OC**H$_3$**), 3.50 (3 H, s, OC**H$_3$**), 1.82 (3 H, s, CC**H$_3$**), 1.40 (3 H, t, *J* 7.2, NCH$_2$C**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 176.1 (**C**=O), 160.3 (**C**OCH$_3$), 157.8 (**C**OCH$_3$), 155.9 (**C**$_{1\text{-}napht}$), 134.3 (**C**=O), 131.5 (**C$_{DMB}$**H), 131.4 (**C**$_{quat\ napht}$), 130.6 (**C**$_{napht}$H), 130.5 (**C**$_{quat\ napht}$), 129.4 (**C**$_{napht}$H), 128.1 (**C**$_{napht}$H), 126.8 (**C**$_{napht}$H), 125.6 (**C**$_{napht}$H), 124.5 (**C**$_{napht}$H), 122.9 (**C**$_{napht}$H), 117.0 (**C**$_{quat\ 1\text{-}DMB}$), 103.7 (**C$_{DMB}$**H), 97.6 (**C$_{DMB}$**H), 66.9 (**C**CH$_3$), 55.3 (O**C**H$_3$), 54.8 (O**C**H$_3$), 37.9 (N**C**H$_2$DMB), 34.4 (N**C**H$_2$CH$_3$), 24.7 (C**C**H$_3$), 13.4 (NCH$_2$**C**H$_3$). **IR (film, cm^{-1}):**

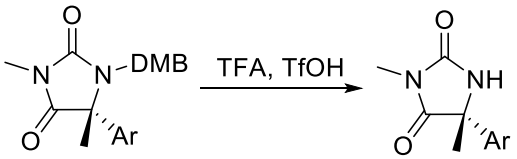
2936, 2837, 1764, 1703. **HRMS** (ESI^+): *m/z* calcd for $C_{25}H_{26}N_2O_4Na$ $[M+Na]^+$ 441.1790, found 441.1801.

(R)-1-(3,4-dimethylbenzyl)-3,5-dimethyl-5-(pyridin-2-yl)imidazolidine-2,4-dione *(4d)*

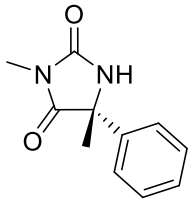


Following general procedure **4,** LDA was prepared by adding a solution of nBuLi (1.47 M, 1.3 mL, 1.90 mmol) dropwise to a solution of DiPA (0.27 mL, 1.90 mmol) in THF (1.4 mL) at 0°C. The reaction mixture was stirred for 20 minutes and added dropwise to a solution of coupled urea 3d (150 mg, 0.29 mmol) and LiCl (124 mg, 2.90 mmol) in THF (1.5 mL) at -78°C. The reaction was complete after 3 hours. Purification by flash column chromatography (SiO_2, 1:2 PE/EA) yielded the title compound as pale yellow oil (38 mg, 0.107 mmol, 37%, ee 78:22). **Rf** (EA/PE 2:1): 0.40. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 8.52 (1 H, d, *J* 4.0, Ar**H**), 7.57 (1 H, td, *J* 7.9, 1.5, Ar**H**), 7.15 (3 H, m, 2 * Ar**H +** DMB**H**), 6.35 (1 H, dd, *J* 8.3, 2.1, DMB**H**), 6.22 (1 H, d, *J* 2.0, DMB**H**), 4.58 (A of AB, 1 H, d, *J* 15.4, NC$\mathbf{H_A}H_B$DMB), 4.18 (B of AB, 1 H, d, *J* 15.4, $NCH_A\mathbf{H_B}$DMB), 3.74 (3 H, s, OC$\mathbf{H_3}$), 3.61 (3 H, s, OC$\mathbf{H_3}$), 3.11 (3 H, s, NC$\mathbf{H_3}$), 1.73 (3 H, s, CC$\mathbf{H_3}$). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.0 (**C**=O), 160.5 (**C**OCH_3), 157.8 (**C**OCH_3), 157.2 (C=O), 156.1 ($\mathbf{C_{quat}}$ $_{1\text{-pyr}}$), 149.6 ($\mathbf{C_{Ar}}H$), 136.5 ($\mathbf{C_{Ar}}H$), 131.2 ($\mathbf{C_{DMB}}H$), 123.2 ($\mathbf{C_{Ar}}H$), 121.1 ($\mathbf{C_{Ar}}H$), 117.7 ($\mathbf{C_{quat}}$ $_{1\text{-DMB}}$), 104.1 ($\mathbf{C_{DMB}}H$), 98.1 ($\mathbf{C_{DMB}}H$), 69.0 (**C**CH_3), 55.4 (O**C**H_3), 55.1 (O**C**H_3), 38.2 (N**C**H_2DMB), 25.4 (N**C**H_3), 19.4 (C**C**H_3). **IR (film, cm^{-1}):** 2939, 1770, 1706. **HRMS** (ESI^+): *m/z* calcd for $C_{19}H_{22}N_3O_4$ $[M+H]^+$ 356.1610, found 356.1597.

Removal of 2,4-dimethoxybenzyl protecting group

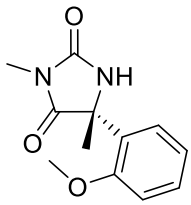


(R)-3-methyl-5-methyl-5-phenylimidazolidine-2,4-dione *(5a)*



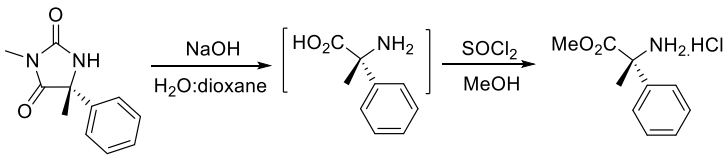
Hydantoin 4a (246 mg, 0.69 mmol) was dissolved in trifluoroacetic acid (2.5 mL) at 0°C. Trifluoromethanesulfonic acid (123 µL, 1.39 mmol) was then added dropwise. The deep purple solution was left stirring at room temperature for one hour and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 1:1 PE/EA) yielded the title compound as a white solid (122 mg, 0.60 mmol, 87%). **Rf** (EA/PE 1:1): 0.67. **Mp**: 99°C. **$[\alpha]_D^{20}$**: -96.5 (*c* 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.51 (2H, d, J = 8.0 Hz, o-Ar**H**), 7.36 (3H, m, 3* Ar**H**), 6.25 (1H, s, N**H**), 3.03 (3H, s, NC**H$_3$**), 1.84 (3H, s, CC**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.3 (**C**=O), 156.8 (**C**=O), 138.6 (Ar***C***), 128.9 (2* Ar***C***H), 128.5 (Ar***C***H), 125.2 (2* o-Ar***C***H), 63.8 (***C***CH_3(Ar)), 25.6 (N***C***H_3), 24.9 (C***C***H_3). **IR (film, cm^{-1}):** 3292, 1780, 1710. **HRMS (ESI$^+$):** *m/z* calcd for $C_{11}H_{12}N_2O_2Na$ $[M+Na]^+$ 227.0791, found 227.0792.

(R)-5-(2-methoxyphenyl)-3,5-dimethylimidazolidine-2,4-dione *(5b)*

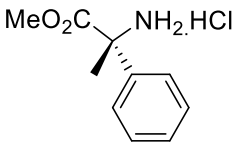


Hydantoin 4c (414 mg, 1.08 mmol) was dissolved in trifluoroacetic acid (4.0 mL) at 0°C. Trifluoromethanesulfonic acid (191 µL, 2.16 mmol) was then added dropwise. The deep purple solution was left stirring at room temperature for one hour and concentrated *in vacuo.* Purification by flash column chromatography (SiO2, 1:1 PE/EA) yielded the title compound as a white solid (188 mg, 0.80 mmol, 74%). **Rf** (EA): 0.80. **Mp:** 184-186°C. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ: 7.51 (1 H, dd, *J* 7.7, 1.5, Ar**H**), 7.32 (1 H, td, *J* 8.2, 1.6, Ar**H**), 6.93 (2 H, m, 2* Ar**H**), 6.28 (1 H, br. s, N**H**), 3.86 (3 H, s, OC**H$_3$**), 3.08 (3 H, s, *J* 6.0, NC**H$_3$**), 1.76 (3 H, s, CC**H$_3$**). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 175.9, 156.9, 156.6, 130.0 (**C$_{Ar}$**H), 126.4 (**C$_{Ar}$**H), 126.2 (**C$_{1\text{-}Ar}$**), 121.0 (**C$_{Ar}$**H), 111.7 (**C$_{Ar}$**H), 62.9 (**C**CH_3), 55.7 (O**C**H_3), 24.82 (N**C**H_3 or C**C**H_3), 24.80 (N**C**H_3 or C**C**H_3). **IR (film, cm^{-1}):** 3272, 2979, 1776, 1707. **HRMS (ESI$^+$):** *m/z* calcd for $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$ 257.0902, found 257.0908.

Deprotection of the alanine derivative

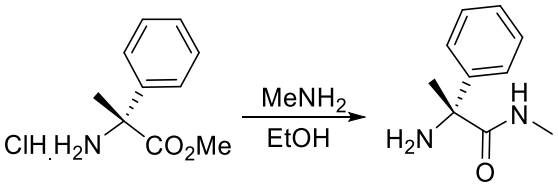


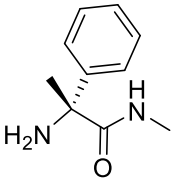
(R)-α-phenylalanine methyl ester hydrochloride salt *((R)-(aMe)PhgOMe)*



The deprotected hydantoin 5a (272 mg, 1.33 mmol) was suspended in water (5.0 mL) and NaOH 2M in water (5.5 mL, 11 mmol) and dioxane (1.1 mL) were added. The mixture was heated to reflux overnight, diluted in water, and concentrated HCl was added until the solution was acidic. The mixture was concentrated *in vacuo,* taken up in methanol (8.5 mL), cooled to 0°C and thionyl chloride (0.39 mL, 5.3 mmol) was added. The reaction was heated to reflux overnight. The reaction mixture was then cooled to room temperature, the solution was filtered and concentrated *in vacuo.* The solid was then suspended in chloroform, filtered and organic were evaporated to yield to title compound as a light green oil (278 mg, 1.29 mmol, 97%). **$[\alpha]_D^{20}$**: -61.1 (*c* 0.5, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 9.47 (3 H, br. S, N**H_3^+**), 7.57 (2 H, s, Ar**H**), 7.37 (3 H, s, Ar**H**), 3.76 (3 H, s, OC**H_3**), 2.07 (3 H, s, CC**H_3**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 169.7 (**C**=O), 135.1 (**C_{Ar}**), 129.0 (**$C_{Ar\ para}$**), 128.8 (2***C_{Ar}**), 125.4 (2***C_{Ar}**), 61.9 (**C**CH_3), 53.9 (O**C**H_3), 22.1 (C**C**H_3). **IR (film, cm^{-1}): ν_{max} =** 3376 (br.) 2851 (br.), 1746 (C=O). **HRMS (ESI^+):** *m/z* calcd for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1025, found 180.1028.

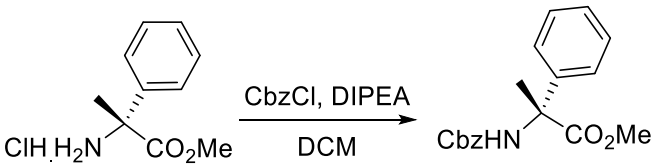
Conversion to amide derivative



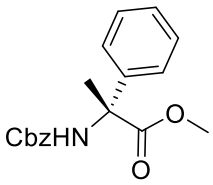


(R)-2-amino-N-methyl-2-phenylpropanamide *(6a)*

To (*R*)-(aMe)PhgOMe (95 mg, 0.44 mmol) was added methylamine 33% wt. in ethanol (33% wt, 0.38 mL, 3.1 mmol). The mixture was stirred at room temperature for 20 hours, evaporated and dissolved in chloroform. The solution was washed with a saturated solution of potassium carbonate and the aqueous layer was then extracted three times with chloroform. The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 97:3 DCM/MeOH) yielded the title compound as a yellow oil (37 mg, 0.21 mmol, 47%). **Rf** (DCM/MeOH 95:5): 0.58. **$[\alpha]_D^{24}$**: +25.0° (*c* 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.45 (2 H, m, C_{Ar}**H**), 7.40 (1 H, br s, CON**H**CH_3), 7.29 (2 H, m, C_{Ar}**H**), 7.21 (1 H, m, para-C_{Ar}**H**), 2.74 (3 H, d, *J* 5.0, NHC**H$_3$**), 1.84 (2 H, s, N**H$_2$**), 1.72 (3 H, s, CC**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 176.4 (**C**=O), 144.7 (**$C_{1\text{-}Ph}$**), 128.6 (2* **C_{Ph}**H), 127.4 (para **C_{Ph}**H), 125.4 (2* **C_{Ph}**H), 60.3 (**C**CH_3), 28.6 (C**C**H_3), 26.3 (CONH**C**H_3). **IR (film, cm^{-1}):** 3355, 2932, 1652. **HRMS (ESI$^+$):** *m/z* calcd for $C_{10}H_{15}N_2O$ $[M+H]^+$ 179.1184, found 179.1192.

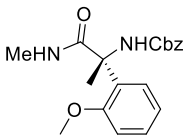


benzyl (R)-(1-fluoro-1-oxo-2-phenylpropan-2-yl)carbamate *(Cbz-(R)-(αMe)PhgOMe)*



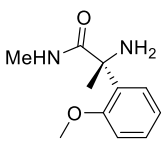
To a solution of (*R*)-(αMe)PhgOMe (59 mg, 0.27 mmol) in DCM (1.0 mL) at 0°C was added DIPEA (120 µL, 0.66 mmol). The mixture was stirred 25 minutes and benzylchloroformate (47 µL, 0.33 mmol) was added dropwise. The mixture was stirred at room temperature 3.5 hours, diluted in DCM and washed with a solution of HCl 0.5N in water, a saturated solution of sodium carbonate and brine. The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 5:1 PE/EA) yielded the title compound as a colorless oil (47 mg, 0.15 mmol, 55%). **Rf** (EA/PE 1:4): 0.45. **$[\alpha]_D^{20}$**: -37.9° (*c* 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.45 (2 H, m, C**H**$_{Ar}$), 7.33 (8 H, m, C**H**$_{Ar}$), 6.22 (1 H, s, N**H**), 5.05 (2 H, q, *J* 12.3, OC**H**$_2$Ar), 3.69 (3 H, s, OC**H**$_3$), 2.06 (3 H, s, CC**H**$_3$). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 173.6 (**C**$_{carbamate}$), 154.5 (**C**=O), 140.5 (**C**$_{Ar\ quat}$), 136.4 (**C**$_{Ar\ quat}$), 128.7 (2***C**$_{Ar}$), 128.6 (2***C**$_{Ar}$), 128.2 (2***C**$_{Ar}$), 128.1 (2***C**$_{Ar}$), 125.9 (2***C**$_{Ar}$), 66.7 (O**C**H$_2$Ar), 62.0 (**C**CH$_3$), 53.3 (O**C**H$_3$), 22.6 (C**C**H$_3$). **IR (film, cm^{-1}):** 3414, 2951, 1723. **HRMS (ESI$^+$):** *m/z* calcd for $C_{18}H_{19}N_2O_4Na$ $[M+Na]^+$ 336.1212, found 336.1218.

benzyl (R)-(2-(2-methoxyphenyl)-1-(methylamino)-1-oxopropan-2-yl)carbamate *(Cbz(o-MeOPh)AlaNHMe)*



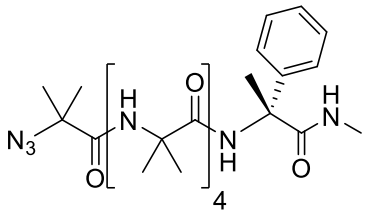
The deprotected hydantoin 5c (216 mg, 0.92 mmol) was suspended in water (3.5 mL) and NaOH 2M in water (3.9 mL, 7.8 mmol) and dioxane (0.9 mL) were added. The mixture was heated to reflux for 20h, diluted in water, and concentrated HCl was added until pH was acidic. The mixture was concentrated *in vacuo.* The solid was then suspended in ethanol, filtered and organic were evaporated. To the crude oil in DCM (5 mL) at 0°C was added DIPEA (0.40 mL, 2.3 mmol). The mixture was stirred 20 minutes and benzylchloroformate (0.16 mL, 1.10 mmol) was added dropwise. The mixture was stirred at room temperature 5 hours and washed with a solution of HCl 0.5N in water, a saturated solution of sodium carbonate and brine. The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 1:1 PE/EA) yielded the title compound as a colorless oil (229 mg, 0.64 mmol, 70%). **Rf** (EA/PE 1:1): 0.25. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.55 (1 H, d, *J* 6.3, C**H$_{Ar}$**), 7.32 (5 H, m, 5* C**H$_{Ar}$**), 7.01 (1 H, t, *J* 7.4, C**H$_{Ar}$**), 6.89 (1 H, d, *J* 8.1, C**H$_{Ar}$**), 6.74 (1 H, s, C**H$_{Ar}$**), 5.34 (1 H, s, N**H**Me), 5.00 (A of AB, 1 H, d, *J* 12.4, CbzC**H$_A$**H$_B$), 4.89 (B of AB, 1 H, d, *J* 12.4, CbzCH$_A$**H$_B$**), 3.75 (3 H, s, OC**H$_3$**), 2.73 (3 H, d, *J* 4.8, NHC**H$_3$**), 1.95 (3 H, s, CC**H$_3$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 175.0 (**C**=O), 157.1 (**C**=O or **C**OCH$_3$), 154.2 (**C**=O or **C**OCH$_3$), 136.9 (**C$_{1\text{-}Ar}$**), 129.9 (**C$_{Ar}$**H), 128.9 (**C$_{Ar}$**H), 128.7 (**C$_{1\text{-}Cbz}$**), 128.4 (2* **C$_{Cbz}$**H), 127.9 (2* **C$_{Cbz}$**H + **C$_{Ar}$**H), 120.5 (**C$_{Ar}$**H), 111.8 (**C$_{Ar}$**H), 66.0 (Cbz**C**H$_2$), 59.8 (**C**CH$_3$), 55.6 (O**C**H$_3$), 26.8 (NH**C**H$_3$), 23.9 (C**C**H$_3$). **IR (film, cm^{-1}):** 3388, 2944, 1721, 1670. **HRMS (ESI$^+$)**: *m/z* calcd for $C_{19}H_{22}N_2O_4$ $[M+H]^+$ 343.1658, found 343.1671.

(R)-2-amino-2-(2-methoxyphenyl)-N-methylpropanamide (*6b)*



Pd/C (10% Pd, 16 mg) was added to a solution of Cbz(o-MeOPh)AlaNHMe (160 mg, 0.47 mmol) in methanol (9 mL) and set under an atmosphere of H_2. The mixture was stirred 15h then filtered over diatomaceous earth. Volatiles were removed *in vacuo* to yield the title compound as a colorless oil (95 mg, 0.46 mmol, 98%). **Rf** (DCM/MeOH 97:3): 0.22. **^{1}H-NMR** (400 MHz, CD_3OD) δ: 7.46 (1 H, d, *J* 6.7, Ar**H**), 7.33 (1 H, td, *J* 8.0, 1.4, Ar**H**), 7.01 (2 H, m, 2* Ar**H**), 3.81 (3 H, s, OC**H$_3$**), 2.72 (3 H, s, NHC**H$_3$**), 1.65 (3 H, s, CC**H$_3$**). **^{13}C-NMR** (100 MHz, CD_3OD) δ: 180.1 (**C**=O), 158.5 (**C**OCH$_3$), 133.0 (**C$_{1\text{-}Ar}$**), 130.4 (**C$_{Ar}$**H), 128.0 (**C$_{Ar}$**H), 121.9 (**C$_{Ar}$**H), 112.6 (**C$_{Ar}$**H), 59.9 (**C**CH$_3$), 56.0 (O**C**H$_3$), 26.7 (NH**C**H$_3$), 25.5 (C**C**H$_3$). **IR (film, cm^{-1}):** 3369, 2939, 2838, 1665. **HRMS (ESI$^+$)**: *m/z* calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ 209.1290, found 209.1280.

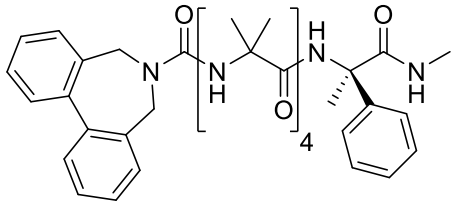
N_3Aib_4(αMe)PhgNHMe



(1) Azlactone formation. N_3Aib_4OH (80 mg, 0.21 mmol) was dissolved in dry DCM (12 mL) and EDC.HCl (60 mg, 0.31 mmol) was added. The resulting solution was left stirring for 3 h at room temperature. The solvent was evaporated in vacuo and the residue was taken up in EA and washed with $KHSO_4$ 5%. The organic phase was dried ($MgSO_4$) and concentrated to give the crude azlactone product, which was used directly in the next step.

(2) Azlactone coupling. The crude azlactone was dissolved in dry acetonitrile (12 mL) and 6a (37 mg, 0.21 mmol) was added. The mixture was left stirring at room temperature for 5 days, after which the solvent was evaporated under reduced pressure. The residue was taken up in EA and washed with $KHSO_4$ 5%. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH, 95:5) to yield pure N_3Aib_4(αMe)PhgNHMe (40 mg, 0.073mmol, 35%) as a colourless oil while (αMe)PhgNHMe (20 mg, 0.11 mmol) was recovered by extraction of the basified aqueous solution. **Rf** (DCM/MeOH, 95:5) = 0.30. **$[\alpha]_D^{24}$**: +3.6° (*c* 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.63 (1 H, d, *J* 4.1, N**H**CH_3), 7.47 (4 H, t, *J* 6.1, 2* C**H**$_{Ph}$ + 2* N**H**), 7.26 (2 H, m, 2* C**H**$_{Ph}$), 7.18 (1 H, t, *J* 7.1 C**H**$_{Ph}$), 6.95 (1 H, s, N**H**), 6.26 (1 H, s, N**H**), 2.85 (3 H, d, *J* 4.4, NHC**H**$_3$), 1.87 (3 H, s, C(Ar)C**H**$_3$), 1.51 (3 H, s, C**H**$_3$), 1.51 (3 H, s, C**H**$_3$), 1.47 (3 H, s, C**H**$_3$), 1.44 (3 H, s, C**H**$_3$), 1.40 (6 H, s, 2*C**H**$_3$), 1.38 (3 H, s, C**H**$_3$), 1.32 (3 H, s, C**H**$_3$). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 174.4 (**C**=O), 174.1 (**C**=O), 173.7 (**C**=O), 173.1 (**C**=O), 172.9 (**C**=O), 142.8 (**C**$_{1\text{-}Ph}$), 128.0 (2* **C**$_{Ph}$H), 126.9 (**C**$_{Ph}$H), 126.4 (2* **C**$_{Ph}$H), 64.0 (**C**$_{quat\ Aib}$), 63.5 (**C**$_{quat\ Aib}$), 57.3 (**C**$_{quat\ Aib}$), 56.9 (**C**$_{quat\ Aib}$), 56.8 (**C**$_{quat\ Aib}$), 27.3 (C(Ar)**C**H_3), 26.7 (NH**C**H_3), 25.3 (2* **C**$_{Aib}H_3$), 25.1 (**C**$_{Aib}H_3$), 25.0 (**C**$_{Aib}H_3$), 24.9 (**C**$_{Aib}H_3$), 24.7 (**C**$_{Aib}H_3$), 24.4 (2* **C**$_{Aib}H_3$). **IR (film, cm^{-1}):** 3313, 2985, 2937, 2112 (azide), 1658, 1526, 1223. **HRMS (ESI$^+$)**: *m/z* calcd for $C_{26}H_{40}N_8O_5Na$ $[M+Na]^+$ 567.3019, found 567.2992.

AzeAib$_4$(αMe)PhgNHMe (9a)

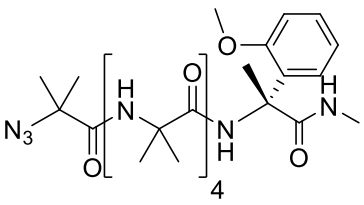


(1) Reduction of the azide: Pd/C (4 mg) was added to a solution of N_3Aib_4(αMe)PhgNHMe (38.0 mg, 0.069 mmol) in methanol (1 mL) and set under an atmosphere of H_2. The mixture was stirred 15h then filtered over diatomaceous earth. Volatiles were removed *in vacuo* to yield H_2NAib_4(αMe)PhgNHMe a colorless oil (33 mg, 0.64 mmol, 93%).

(2) Activation of the amine: To a suspension of *N,N'*-Disuccinimidyl carbonate (18 mg, 0.072 mmol) in DCM (0.5 mL) was added a solution of H_2NAib_4(αMe)PhgNHMe (25 mg, 0.048 mmol) in DCM (0.75 mL) at 0°C. The mixture was then warmed up to room temperature and stirred 20 h, washed with 5% $KHSO_4$ aq., dried with $MgSO_4$ and volatiles were removed *in vacuo*.

(3) Coupling with the probe: A solution of the carbamate in acetonitrile (0.5 mL) was then added to a solution of 6,7-dihydro-5H-dibenzo[c,e]azepine hydrochloride (11.1 mg, 0.048 mmol) and DIPEA (33 µL, 0.192 mmol) in acetonitrile (0.75 mL) at 0°C. The mixture was then warmed up to room temperature and stirred 20 h, washed with 5% $KHSO_4$ aq., sat. $NaHCO_3$ aq., brine, dried with $MgSO_4$ and volatiles were removed *in vacuo*. The crude product was purified by column chromatography to yield pure 9a (10.4 mg, 0.014 mmol, 30%) as a white solid. **Rf** (EA/DCM, 3:2) = 0.25. **$[\alpha]_D^{23}$**: +14.7° (*c* 1.0, MeOH). **^{1}H-NMR** (400 MHz, CD_3OD) δ: 7.57 (2 H, d, *J* 7.5, C**H$_{Ar}$**), 7.50 (4 H, m, C**H$_{Ar}$**), 7.41 (4 H, m, C**H$_{Ar}$**), 7.29 (2 H, m, C**H$_{Ar}$**), 7.22 (1 H, m, C**H$_{Ar}$**), 4.32 (A of AB, 2 H, d, *J* 12.8, NC**H$_A$**H$_B$), 4.26 (B of AB, 2 H, d, *J* 12.8, NCH$_A$**H$_B$**), 2.83 (3 H, s, NDC**H$_3$**), 1.88 (3 H, s, C(Ph)C**H$_3$**), 1.57 (3 H, s, C**H$_3$**), 1.56 (3 H, s, C**H$_3$**), 1.48 (3 H, s, C**H$_3$**), 1.47 (9 H, s, C**H$_3$**), 1.32 (3 H, s, C**H$_3$**), 1.24 (3 H, s, C**H$_3$**). **^{13}C-NMR** (100 MHz, CD_3OD) δ: 178.1 (**C**=O), 177.7 (**C**=O), 176.8 (**C**=O), 176.5 (**C**=O), 175.6 (**C**=O), 158.2 (**C**=O), 143.2 (**C$_{1\text{-}Ph}$**), 141.8 (2* **C$_{quat\ Ar}$**), 135.4 (2* **C$_{quat\ Ar}$**), 130.3 (2* **C$_{Ar}$**H), 129.8 (2* **C$_{Ar}$**H), 129.4 (2* **C$_{Ar}$**H), 129.2 (2* **C$_{Ar}$**H), 129.0 (2* **C$_{Ar}$**H), 128.1 (**C$_{Ar}$**H), 127.4 (2* **C$_{Ar}$**H), 64.2 (**C$_{quat\ aMePhg}$**), 58.0 (**C$_{quat\ Aib}$**), 57.9 (**C$_{quat\ Aib}$**), 57.7 (**C$_{quat\ Aib}$**), 57.3 (**C$_{quat\ Aib}$**), 48.5 (Overlaps with solvent signal, deduced from the DEPT experiment, 2* N**C**H$_2$), 26.8 (ND**C**H$_3$), 26.7 (**C$_{Aib}$**H$_3$), 26.0 (**C$_{Aib}$**H$_3$), 25.8 (**C$_{Aib}$**H$_3$), 25.6 (**C$_{Aib}$**H$_3$), 25.5 (**C$_{Aib}$**H$_3$), 25.3 (**C$_{Aib}$**H$_3$), 25.2 (**C$_{Aib}$**H$_3$), 25.0 (**C$_{Aib}$**H$_3$). **IR (film, cm^{-1}):** 3292, 2982, 2926, 2854, 1658, 1630, 1533 1232. **HRMS** (ESI$^+$): *m/z* calcd for $C_{41}H_{54}N_7O_6$ $[M+H]^+$ 740.4130, found 740.4132.

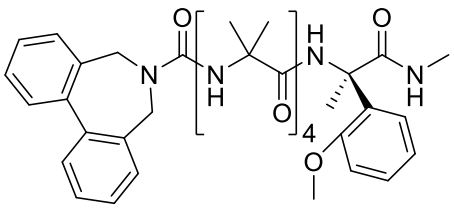
N_3Aib_4(o-MeOPh)AlaNHMe



1) Azlactone formation. N_3Aib_4OH (200 mg, 0.52 mmol) was dissolved in dry DCM (30 mL) and EDC.HCl (150 mg, 0.78 mmol) was added. The resulting solution was left stirring for 3 h at room temperature. The solvent was evaporated in vacuo and the residue was taken up in EA and washed with $KHSO_4$ 5%. The organic phase was dried ($MgSO_4$) and concentrated to give the crude azlactone product, which was used directly in the next step.

(2) Azlactone coupling. The crude azlactone was dissolved in dry acetonitrile (30 mL) and 6b (90 mg, 0.43 mmol)[3] was added. The mixture was left stirring at room temperature for 5 days, after which the solvent was evaporated under reduced pressure. The residue was taken up in EA and washed with KHSO4 5%. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography to yield pure N_3Aib_4(αMe)PhgNHMe as a colourless oil (16 mg, 0.028 mmol, 6.5%). **Rf** (DCM/MeOH, 90:10) = 0.50. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.52 (2 H, m, C**H**$_{Ar}$ + N**H**), 7.31 (1 H, s, N**H**), 7.23 (1 H, m, C**H**$_{Ar}$), 6.97 (1 H, d, *J* 7.6, C**H**$_{Ar}$), 6.93 (1 H, s, N**H**), 6.84 (1 H, t, *J* 8.0, C**H**$_{Ar}$), 6.69 (1 H, d, *J* 4.0, N**H**CH_3), 6.31 (1 H, s, N**H**), 3.76 (3 H, s, OC**H$_3$**), 2.79 (3 H, d, *J* 4.7, NHC**H$_3$**), 1.93 (3 H, s, CC**H$_3$**), 1.53 (6 H, s, 2 * C**H$_{3\ Aib}$**), 1.46 (6 H, s, 2 * C**H$_{3\ Aib}$**), 1.45 (6 H, s, 2 * C**H$_{3\ Aib}$**), 1.44 (6 H, s, 2 * C**H$_{3\ Aib}$**). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 174.4 (**C**=O), 173.8 (**C**=O), 173.2 (**C**=O), 172.7 (**C**=O), 172.5 (**C**=O), 156.9 (**C$_{2\text{-}Ar}$**), 129.3 (**C$_{1\text{-}Ar}$**), 129.2 (2* **C$_{Ph}$**H), 129.0 (2* **C$_{Ph}$**H), 120.7, 111.4, 64.2 (**C$_{quat\ Aib}$**), 62.0 (**C$_{quat\ Aib}$**), 57.2 (**C$_{quat\ Aib}$**), 57.1 (**C$_{quat\ Aib}$**), 56.9 (**C$_{quat\ Aib}$**), 55.3 (O**C**H_3), 26.8 (NH**C**H_3), 25.39 (**C$_{Aib}$**H_3), 25.29 (**C$_{Aib}$**H_3), 25.28 (**C$_{Aib}$**H_3), 25.0 (**C$_{Aib}$**H_3), 24.9 (**C$_{Aib}$**H_3), 24.5 (**C$_{Aib}$**H_3), 24.4 (**C$_{Aib}$**H_3), 24.3 (**C$_{Aib}$**H_3), 23.7 (C(Ar)**C**H_3). **IR (film, cm^{-1}):** 3324, 2984, 2937, 2113, 1660, 1526, 1247. **HRMS (ESI$^+$)**: *m/z* calcd for $C_{27}H_{43}N_8O_6$ $[M+H]^+$ 575.3306, found 575.3314.

AzeAib$_4$(o-MeOPh)AlaNHMe (9b)

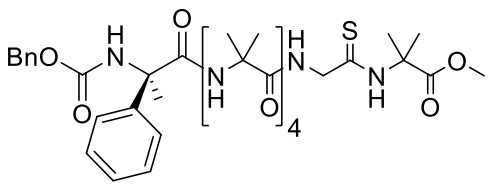


(1) Reduction of the azide: Pd/C (3 mg) was added to a solution of N_3Aib$_4$(o-MeOPh)AlaNHMe (13.0 mg, 0.023 mmol) in methanol (0.5 mL) and set under an atmosphere of H_2. The mixture was stirred 20h then filtered over diatomaceous earth. Volatiles were removed *in vacuo* to yield H_2NAib$_4$(o-MeOPh)AlaNHMe a colorless oil (13 mg, 0.023 mmol, quant.).

(2) Activation of the amine: To a suspension of *N,N'*-Disuccinimidyl carbonate (9.0 mg, 0.035 mmol) in DCM (0.25 mL) was added a solution of H_2NAib$_4$(αMe)PhgNHMe (13 mg, 0.023 mmol) in DCM (0.50 mL) at 0°C. The mixture was then warmed up to room temperature and stirred 20 h, washed with 5% $KHSO_4$ aq., dried with $MgSO_4$ and volatiles were removed *in vacuo*.

(3) Coupling with the probe: A solution of the carbamate in acetonitrile (0.50 mL) was then added to a solution of 6,7-dihydro-5H-dibenzo[c,e]azepine hydrochloride (8.0 mg, 0.035 mmol) and DIPEA (16 µL, 0.092 mmol) in acetonitrile (0.25 mL) at 0°C. The mixture was then warmed up to room temperature and stirred 20 h, washed with 5% $KHSO_4$ aq., sat. $NaHCO_3$ aq., brine, dried with $MgSO_4$ and volatiles were removed *in vacuo*. The crude product was purified by column chromatography to yield pure 9b (8.5 mg, 0.011 mmol, 48%) as a white solid. **Rf** (DCM/MeOH, 98:2) = 0.25. **^{1}H-NMR** (400 MHz, CD_3OD) δ: 8.38 (1 H, s), 7.97 (1 H, s), 7.81 (1 H, s), 7.58 (2 H, d, *J* 7.5, C**H$_{Ar}$**), 7.51 (2 H, t, *J* 7.3, C**H$_{Ar}$**), 7.42 (5 H, m, C**H$_{Ar}$**), 7.24 (1 H, t, *J* 7.1, C**H$_{Ar}$**), 6.94 (1 H, d, *J* 8.2, C**H$_{Ar}$**), 6.91 (1 H, t, *J* 7.7, C**H$_{Ar}$**), 4.36 (A of AB, 2 H, d, *J* 12.9, NC**H$_A$**H$_B$), 4.26 (B of AB, 2 H, d, *J* 12.8, NC**H$_A$**H$_B$), 3.78 (3 H, s, OC**H$_3$**), 2.78 (3 H, s, *J* 3.5, NDC**H$_3$**), 1.91 (3 H, s, CC**H$_3$**), 1.54 (6 H, s, 2 * C**H$_{3\ Aib}$**), 1.49 (3 H, s, C**H$_{3\ Aib}$**), 1.46 (3 H, s, C**H$_{3\ Aib}$**), 1.44 (3 H, s, C**H$_{3\ Aib}$**), 1.42 (3 H, s, C**H$_{3\ Aib}$**), 1.33 (3 H, s, C**H$_{3\ Aib}$**), 1.24 (3 H, s, C**H$_{3\ Aib}$**). **^{13}C-NMR** (100 MHz, CD_3OD) δ: 177.8 (**C**=O), 176.9 (**C**=O), 176.8 (**C**=O), 176.4 (**C**=O), 175.8 (**C**=O), 158.4 (**C$_{2\text{-}Ar}$**), 142.0 (2 * **C$_{Ar\ quat}$**H), 135.7 (2 * **C$_{Ar\ quat}$**H), 130.5 (2 * **C$_{Ar}$**H), 130.3 (**C$_{1\text{-}Ar}$**), 130.1 (**C$_{Ar}$**H), 130.0 (2 * **C$_{Ar}$**H), 129.9 (**C$_{Ar}$**H), 129.5 (2 * **C$_{Ar}$**H), 129.3 (2 * **C$_{Ar}$**H), 121.2 (**C$_{Ar}$**H), 112.6 (**C$_{Ar}$**H), 63.5 (**C$_{quat\ Aib}$**), 58.3 (**C$_{quat\ Aib}$**), 58.2 (**C$_{quat\ Aib}$**), 58.1 (**C$_{quat\ Aib}$**), 57.4 (**C$_{quat\ Aib}$**), 55.8 (O**C**H$_3$), 48.6 (Overlaps with solvent signal, deduced from the DEPT experiment, 2 * N**C**H$_2$), 26.9 (ND**C**H$_3$), 26.8 (**C$_{Aib}$**H$_3$), 26.2 (**C$_{Aib}$**H$_3$), 26.0 (**C$_{Aib}$**H$_3$), 25.8 (**C$_{Aib}$**H$_3$), 25.4, 25.2 (**C$_{Aib}$**H$_3$), 24.9 (**C$_{Aib}$**H$_3$), 24.26 (**C$_{Aib}$**H$_3$), 24.24 (**C$_{Aib}$**H$_3$), 23.5 (C(Ar)**C**H$_3$). **IR (film, cm^{-1}):** 3439, 2984, 2936, 2471, 1656, 1624, 1419, 1245. **HRMS (ESI$^+$)**: *m/z* calcd for $C_{41}H_{53}N_7O_6Na$ $[M+Na]^+$ 762.3955, found 762.3964.

Cbz(αMe)PhgAib$_4$Gly-*Ψ*[CSNH]AibOMe (10)



(1) Acyl fluoride formation: To a solution of TFFH (33 mg, 0.125 mmol) and Cbz-(*R*)-(αMe)PhgOH[4] (23 mg, 0.077 mmol)

in DCM (1mL) was added pyridine (7 µL, 0.084 mmol). The mixture was stirred for 3 h and diluted in DCM, washed with ice-cold water, dried over $MgSO_4$ and volatiles were removed *in vacuo*.

(2) The crude acyl fluoride was added to a solution of $HAib_4Gly$-*Ψ*[CSNH]AibOMe[2] (53 mg, 0.101 mmol) in DCM (4 mL), and DIPEA was added (18 µL, 0.101 mmol). The mixture was stirred 20h and diluted in ethyl acetate, washed with 5% $KHSO_4$ aq., sat. $NaHCO_3$ aq., and brine. Organics were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The crude product was purified by column chromatography to yield pure 10 (40 mg, 0.049 mmol, 64%) as a white solid. **Rf** (DCM/MeOH 9 :1) = 0.50. **Mp** : 96-98°C. **$[\alpha]_D^{23}$**: -5.2° (*c* 1.0, MeOH). **^{1}H-NMR** (400 MHz, CD_3OD) δ: 7.50 (2 H, m, Ar**H**), 7.42 (2 H, m, Ar**H**), 7.36 (4 H, m, Ar**H**), 7.31 (2 H, m, Ar**H**), 5.24 (, A of AB, 1 H, d, *J* 12.7, $ArC\mathbf{H_A}H_B$), 5.14 (B of AB, 1 H, d, *J* 12.7, $ArCH_A\mathbf{H_B}$), 4.30 (A of AB, 1 H, d, *J* 17.7, $NC\mathbf{H_A}H_BCS$), 4.09 (B of AB, 1 H, d, *J* 17.7, $NCH_A\mathbf{H_B}CS$), 3.62 (3 H, s, $OC\mathbf{H_3}$), 1.81 (3 H, s, $CC\mathbf{H_3}$), 1.66 (6 H, s, $C(C\mathbf{H_3})_2CO_2CH_3$), 1.49 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 1.46 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 1.26 (3 H, s, CH_3). **^{13}C-NMR** (100 MHz, CD_3OD) δ: 199.7 (**C**=S), 178.0 (**C**=O), 177.7 (**C**=O), 177.6 (**C**=O), 176.8 (**C**=O), 175.3 (**C**=O), 175.0 (**C**=O), 158.4 ($N\mathbf{C}O_2Bn$), 142.1 ($\mathbf{C_{Ar}}$), 138.5 ($\mathbf{C_{Ar}}$), 129.6 ($\mathbf{C_{Ar}}H$), 129.6 ($\mathbf{C_{Ar}}H$), 129.1 ($\mathbf{C_{Ar}}H$), 129.0 ($\mathbf{C_{Ar}}H$), 128.7 ($\mathbf{C_{Ar}}H$), 126.8 ($\mathbf{C_{Ar}}H$), 68.0 ($Ar\mathbf{C}H_2O$), 64.1 ($\mathbf{C_{aib}}(CH_3)_2$), 61.3 ($\mathbf{C}(CH_3)Ph$), 58.0 ($\mathbf{C_{aib}}(CH_3)_2$), 57.95 ($\mathbf{C_{aib}}(CH_3)_2$), 57.87 ($\mathbf{C_{aib}}(CH_3)_2$), 57.7 ($\mathbf{C_{aib}}(CH_3)_2$), 52.7 ($O\mathbf{C}H_3$), 52.2 ($\mathbf{C}H_2CS$), 26.5 ($\mathbf{C_{Aib}}H_3$), 26.4 ($\mathbf{C_{Aib}}H_3$), 26.3 ($\mathbf{C_{Aib}}H_3$), 26.1 ($\mathbf{C_{Aib}}H_3$), 25.4 ($C(Ph)\mathbf{C}H_3$), 24.9 ($\mathbf{C_{Aib}}H_3$), 24.7 ($\mathbf{C_{Aib}}H_3$), 24.6 ($\mathbf{C_{Aib}}H_3$), 24.5 ($\mathbf{C_{Aib}}H_3$), 24.1 ($\mathbf{C_{Aib}}H_3$), 23.7 ($\mathbf{C_{Aib}}H_3$). **IR (film, cm^{-1}):** 3304, 2986, 2930, 1707, 1659, 1531. **HRMS** (ESI^+): *m/z* calcd for $C_{40}H_{61}N_8O_9Na$ $[M+Na]^+$ 829.4277, found 829.4280.

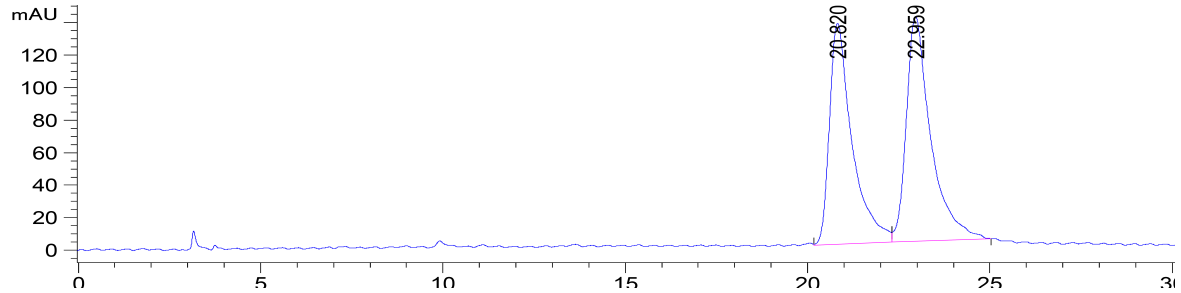
HPLC Data for enantiomeric ratio determination

The following traces were run at 20 °C.

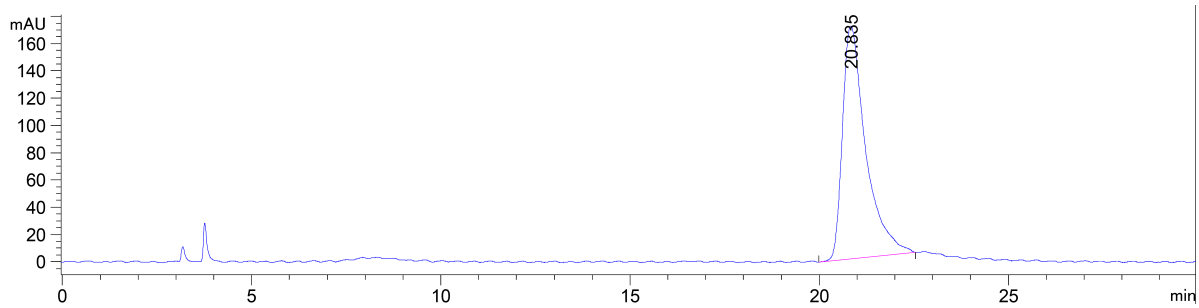
Compound **4a**

Conditions: Daicel Chiralpak OD-H, hexane/2-propanol (90 :10), flow: 1.0 mL/min. t_R = 20.8, 23.0 min.

Rearrangement of the carboxylic acid



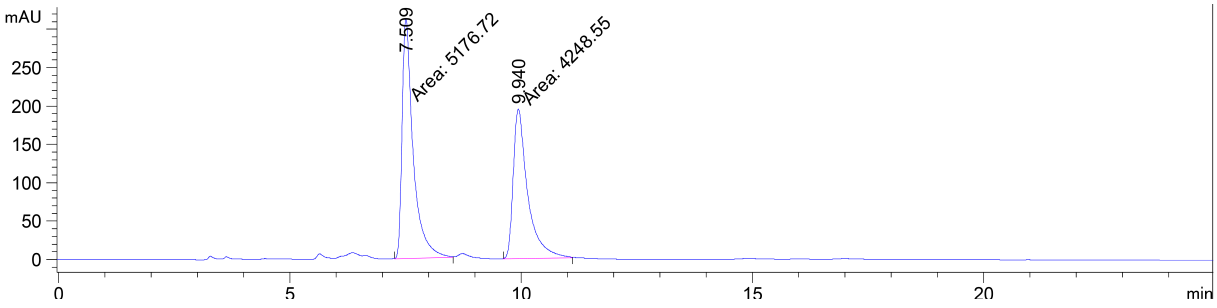
Rearrangement of 4a



Compound **4b**

Conditions: Daicel Chiralpak AD-H, hexane/2-propanol (80 :20), flow: 1.0 mL/min. t_R = 7.5, 9.9 min.

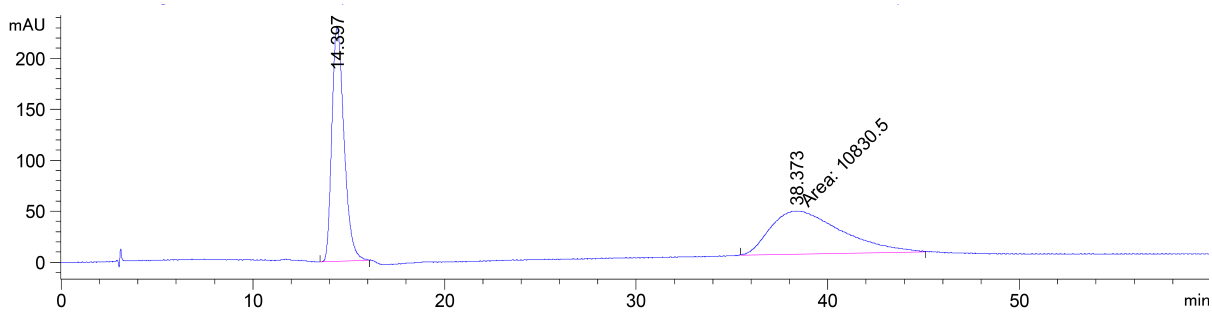
Rearrangement of 4b



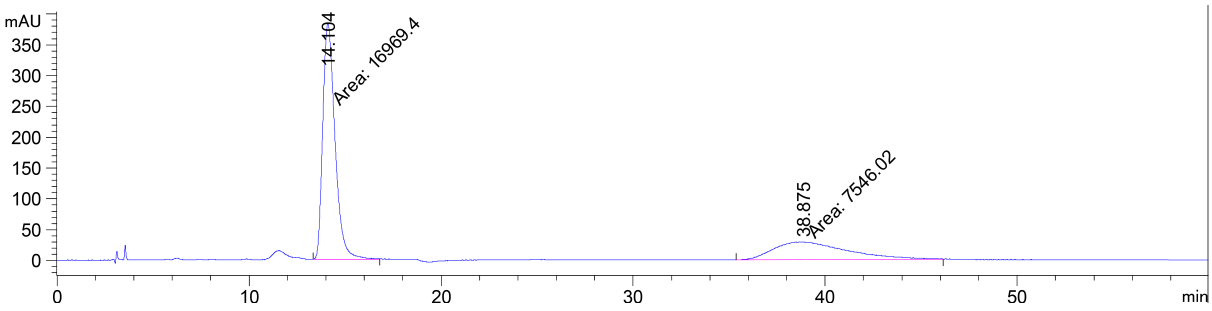
Compound **4c**

Conditions: Daicel Chiralpak OD-H, hexane/2-propanol (90 :10), flow: 1.0 mL/min. t_R = 14.1, 38.9 min.

Rearrangement of the carboxylic acid



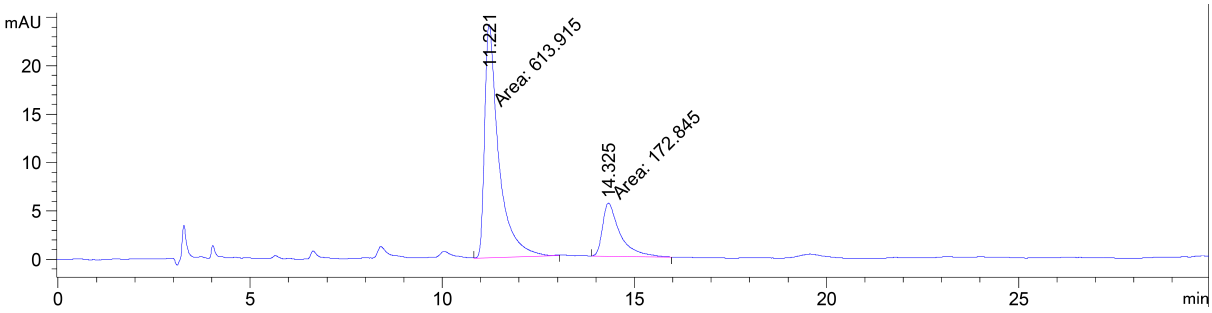
Rearrangement of 4c



Compound **4d**

Conditions: Daicel Chiralpak AD-H, hexane/2-propanol (85:15), flow: 1.0 mL/min. t_R = 11.2, 14.3 min.

Rearrangement of 4d



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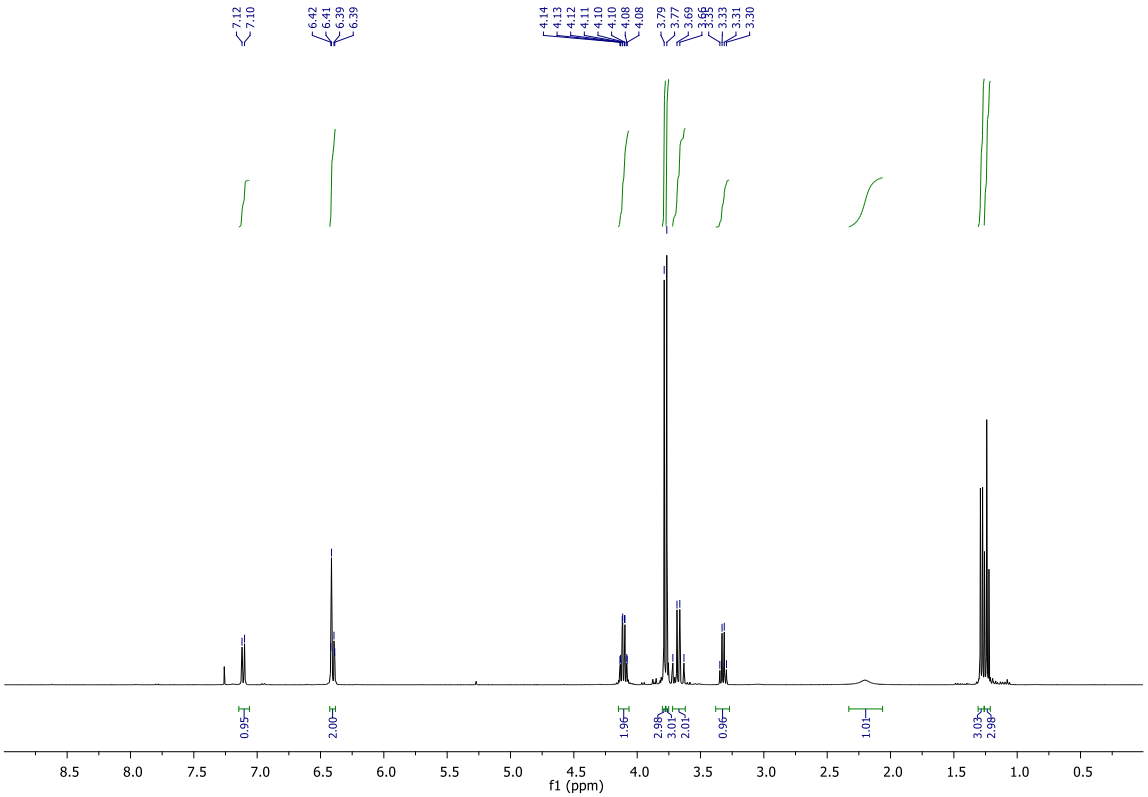
[2] J. Clayden, A. Castellanos, J. Solà, G. A. Morris, *Angew. Chem. Int. Ed*., **2009**, *48*, 5962.

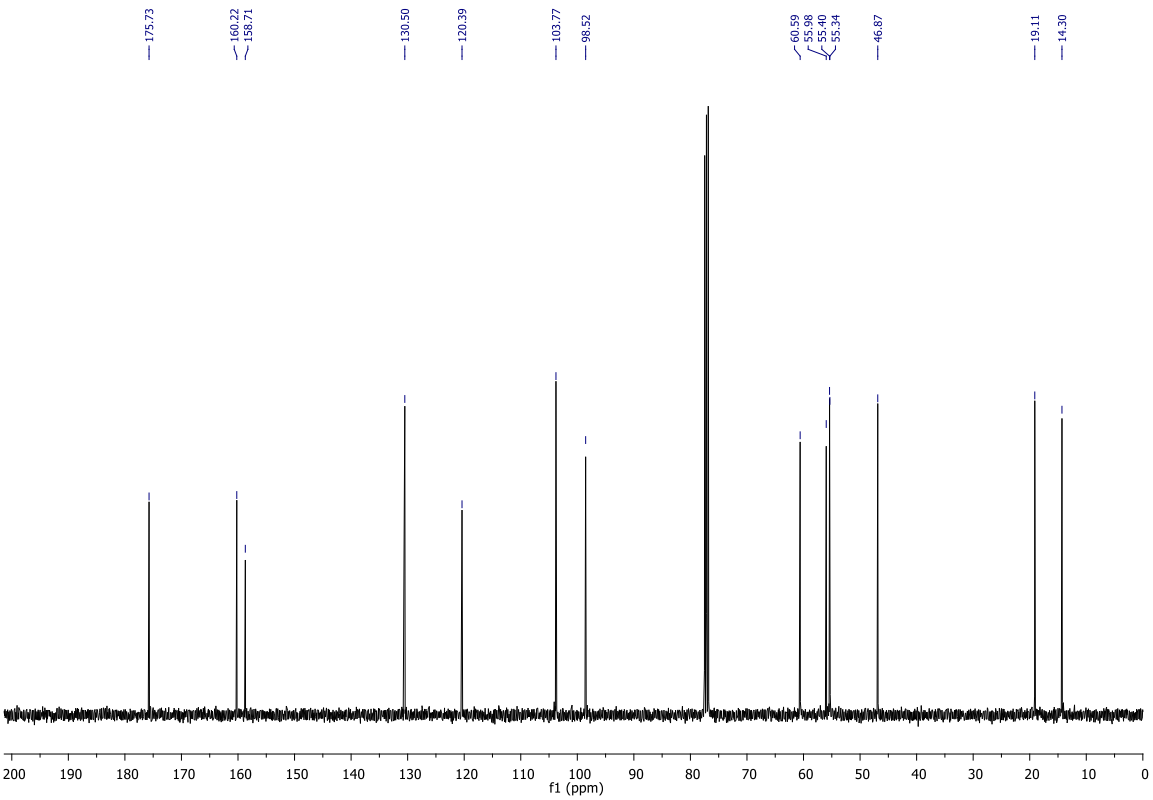
[3] R. C. Atkinson, D. J. Leonard, J. Maury, D. Castagnolo, N. Volz, J. Clayden, *Chem. Commun.*, **2013**, *49*, 9734-9736.

[4] V. Iosub, A. R. Haberl, J. Leung, M. Tang, K. Vembaiyan, M. Parvez, T. G. Back, *J. Org. Chem.*, **2010**, *75*, 1612–1619.

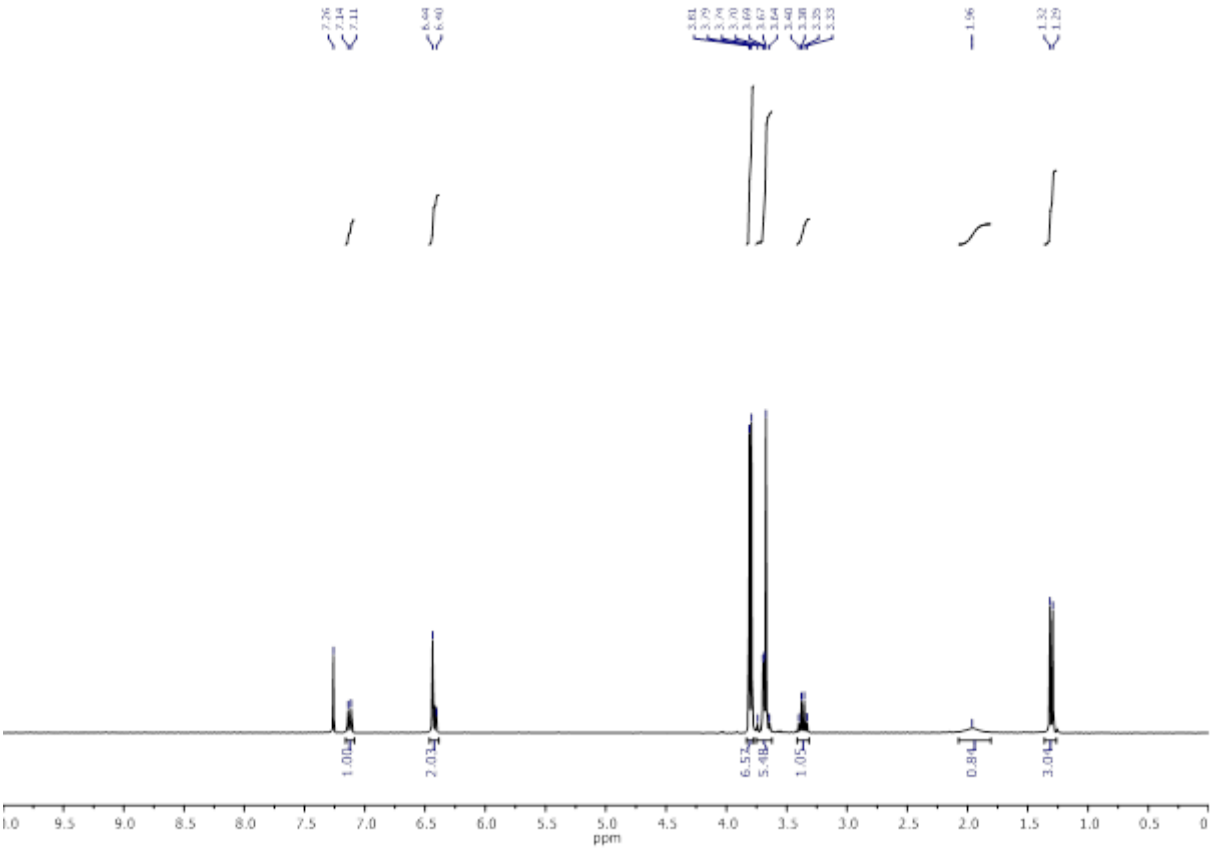
NMR Spectrum



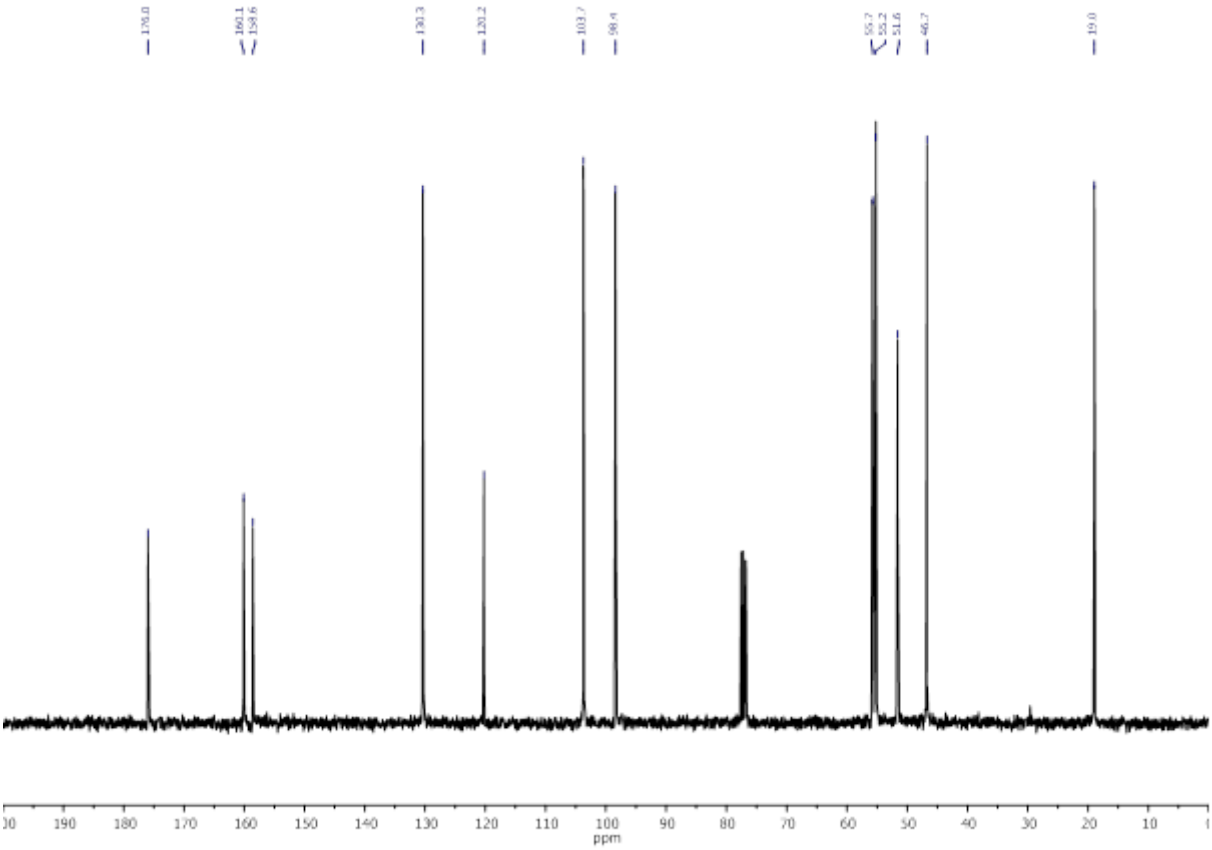
^{1}H NMR of 2,4-dimethoxybenzyl alanine ethyl ester



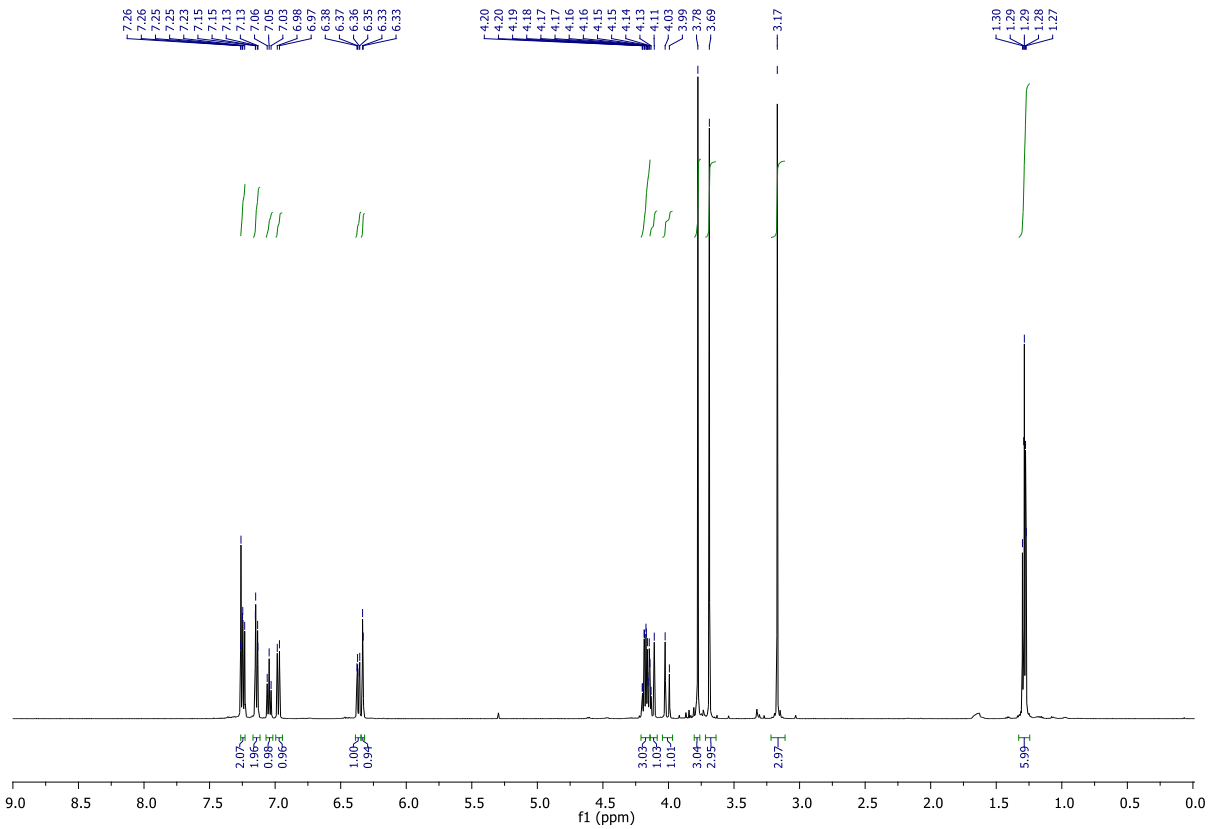
^{13}C NMR of 2,4-dimethoxybenzyl alanine ethyl ester



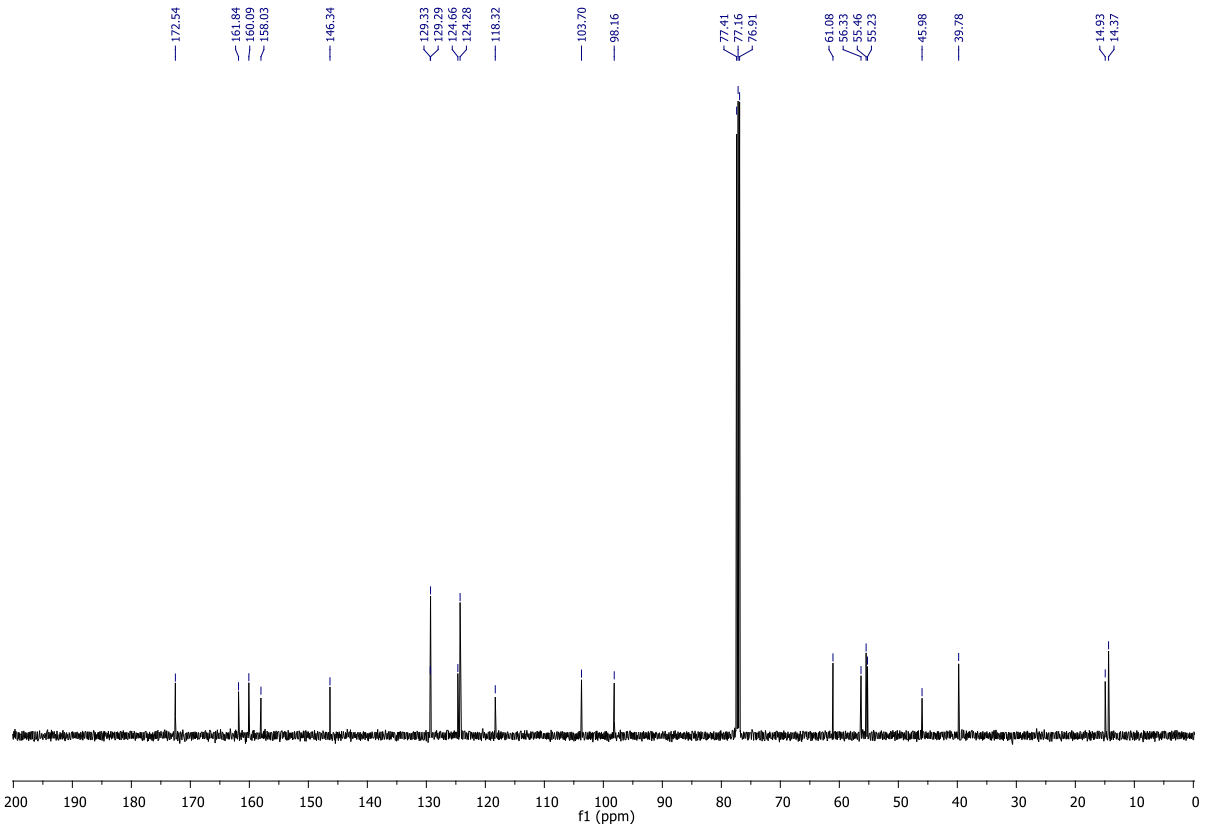
^{1}H NMR of 2,4-dimethoxybenzyl alanine methyl ester



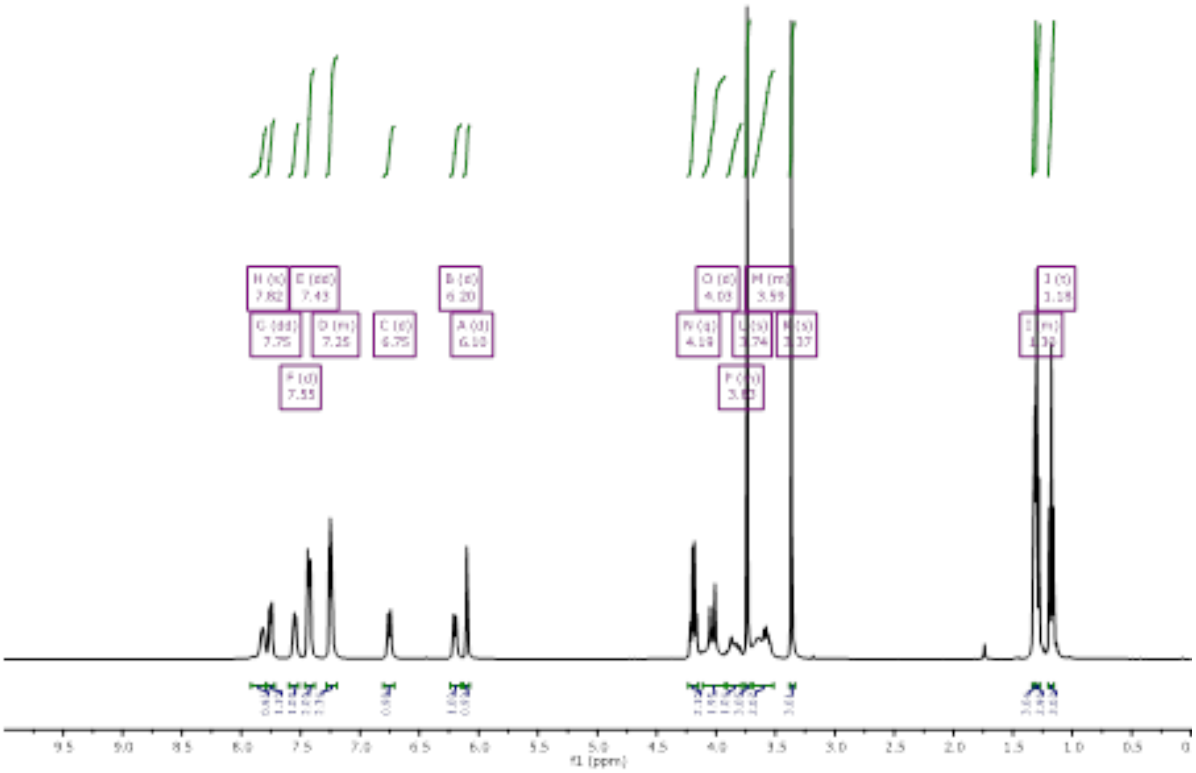
^{13}C NMR of 2,4-dimethoxybenzyl alanine methyl ester



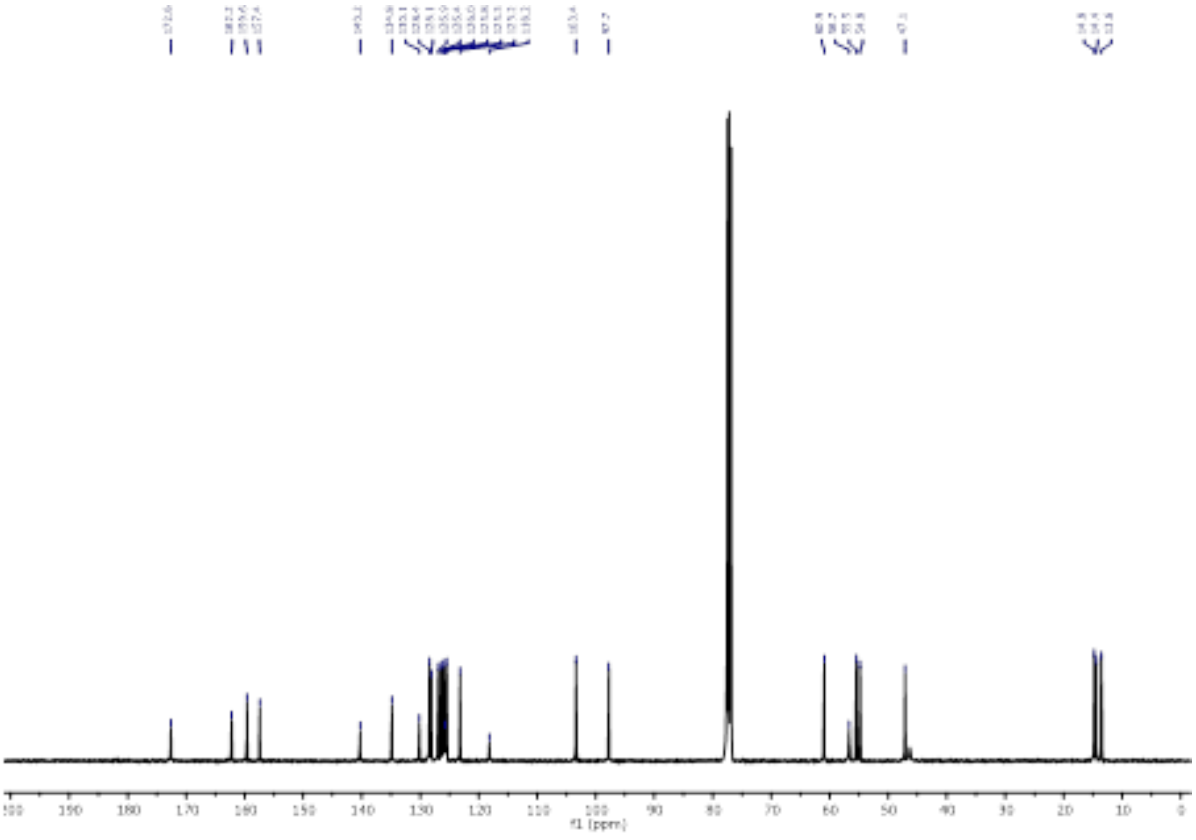
^{1}H NMR of 2a



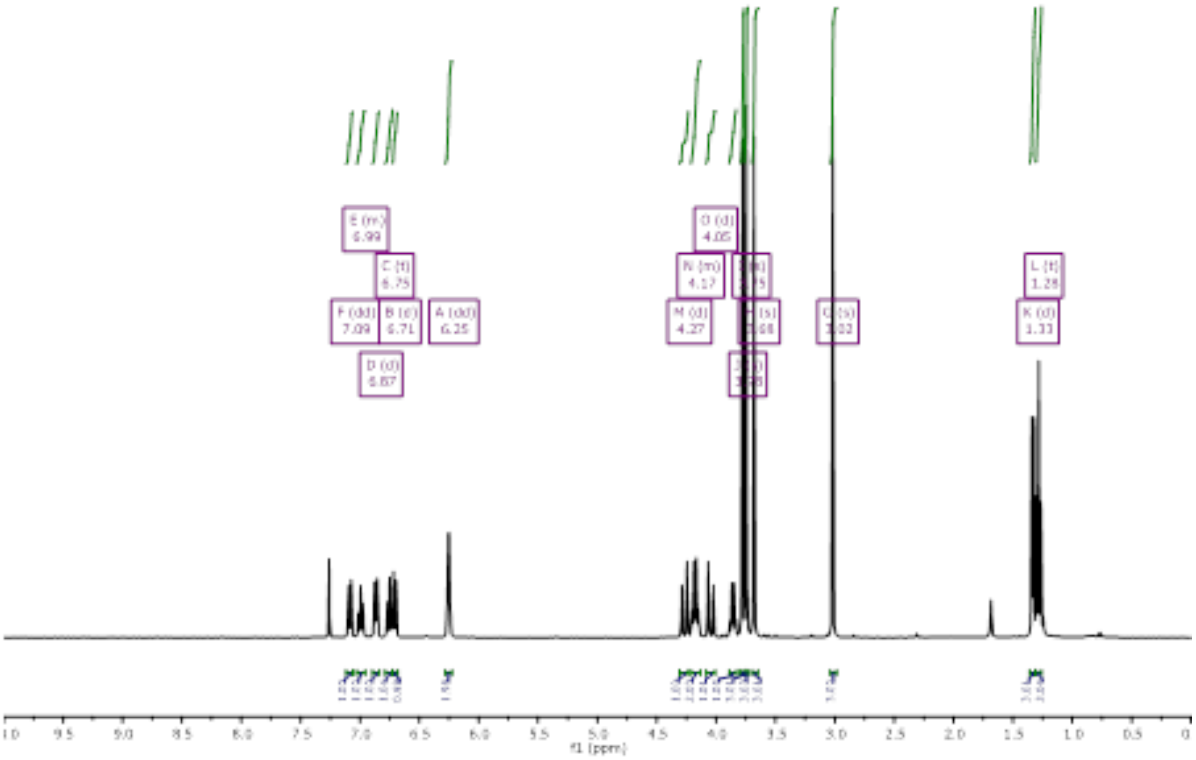
^{13}C NMR of 2a



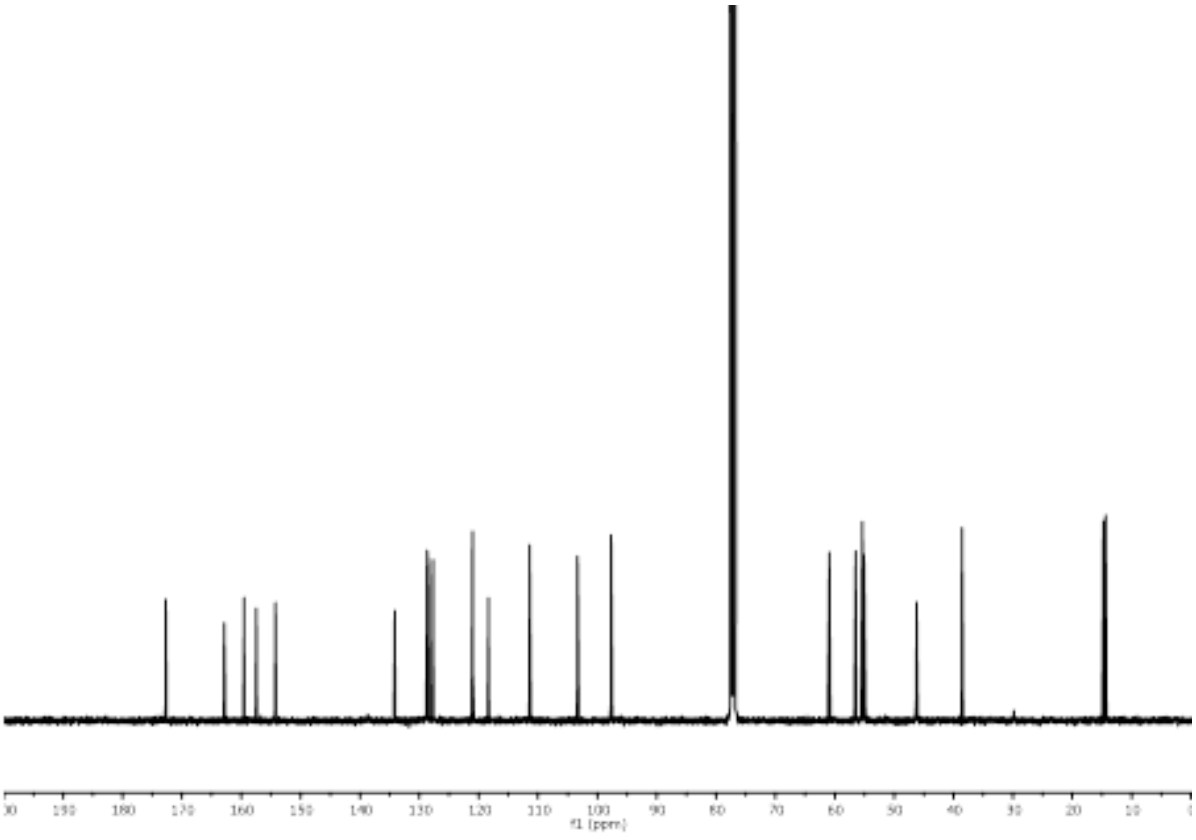
^{1}H NMR of 2b



^{13}C NMR of 2b



^{1}H NMR of 2c



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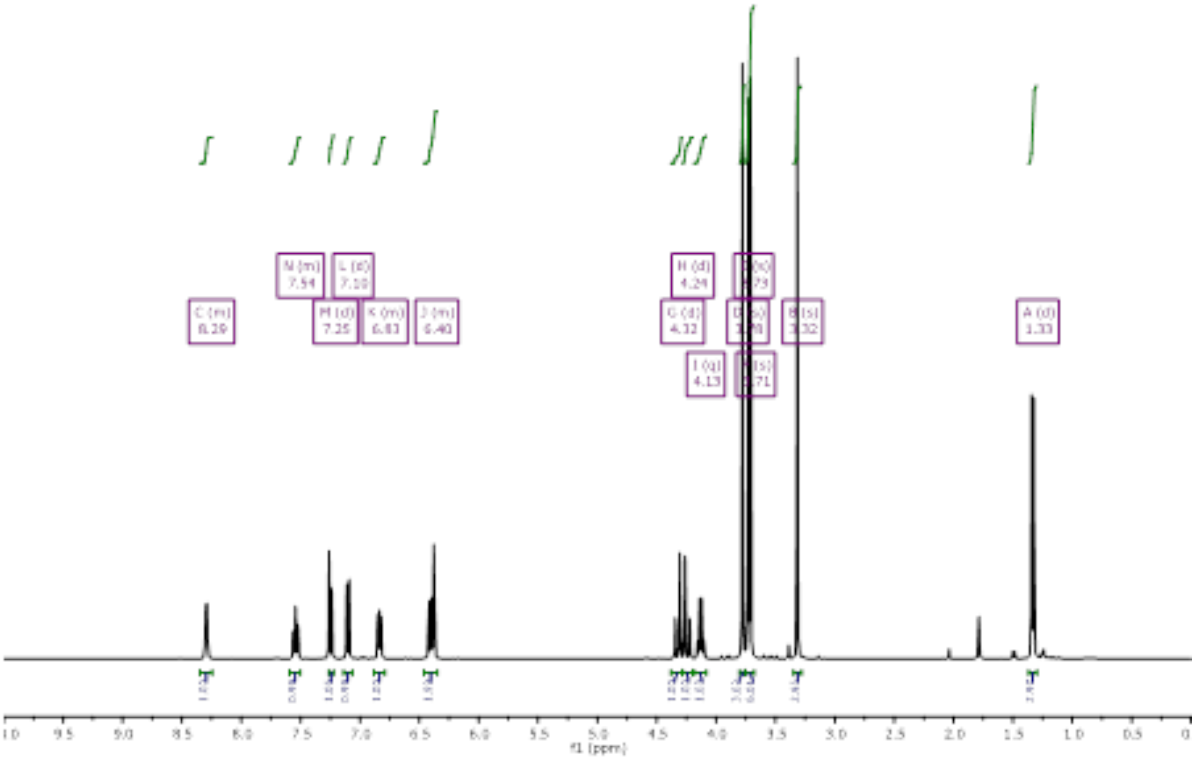
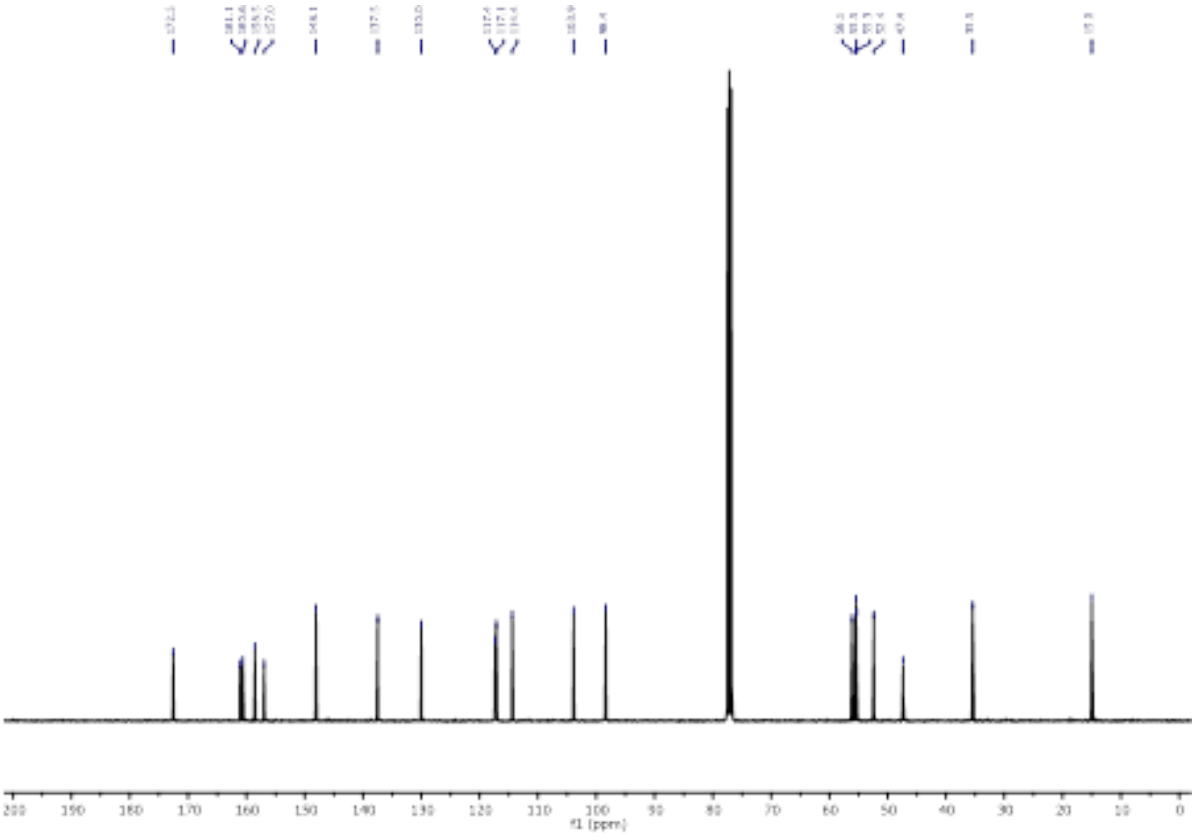
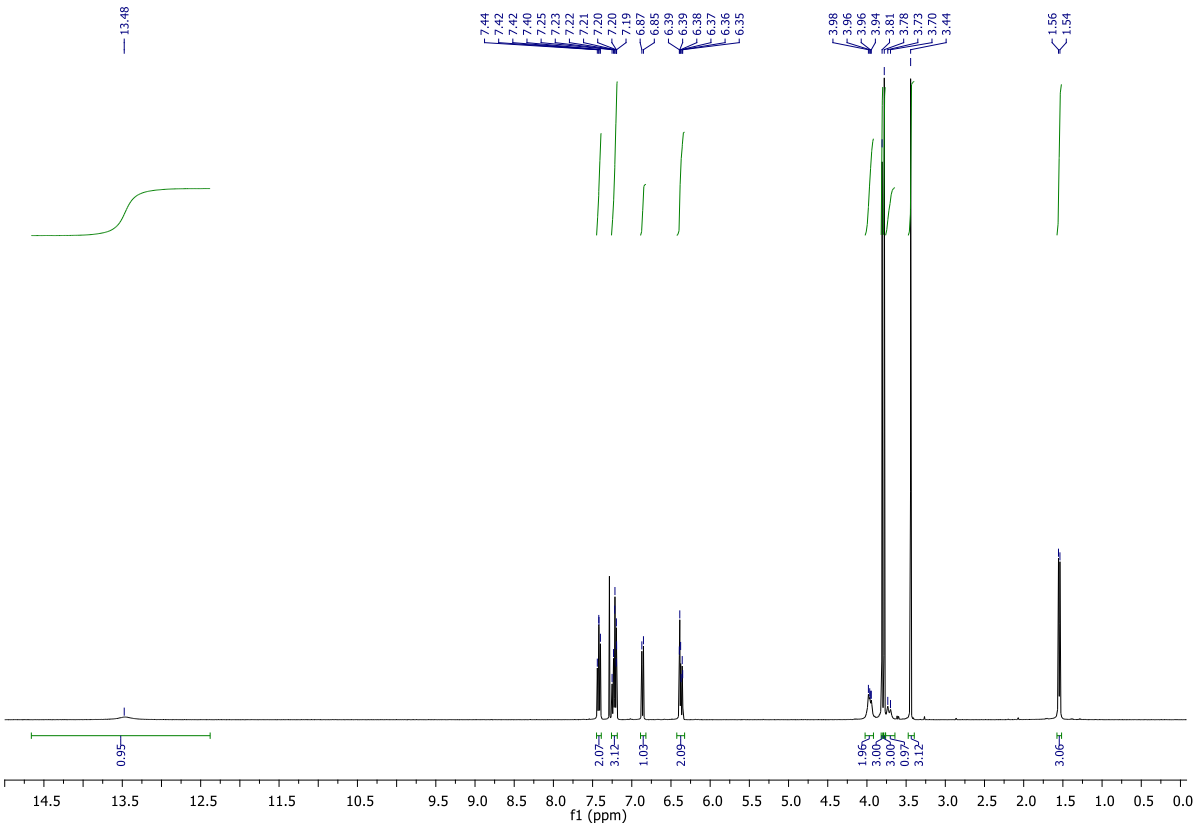


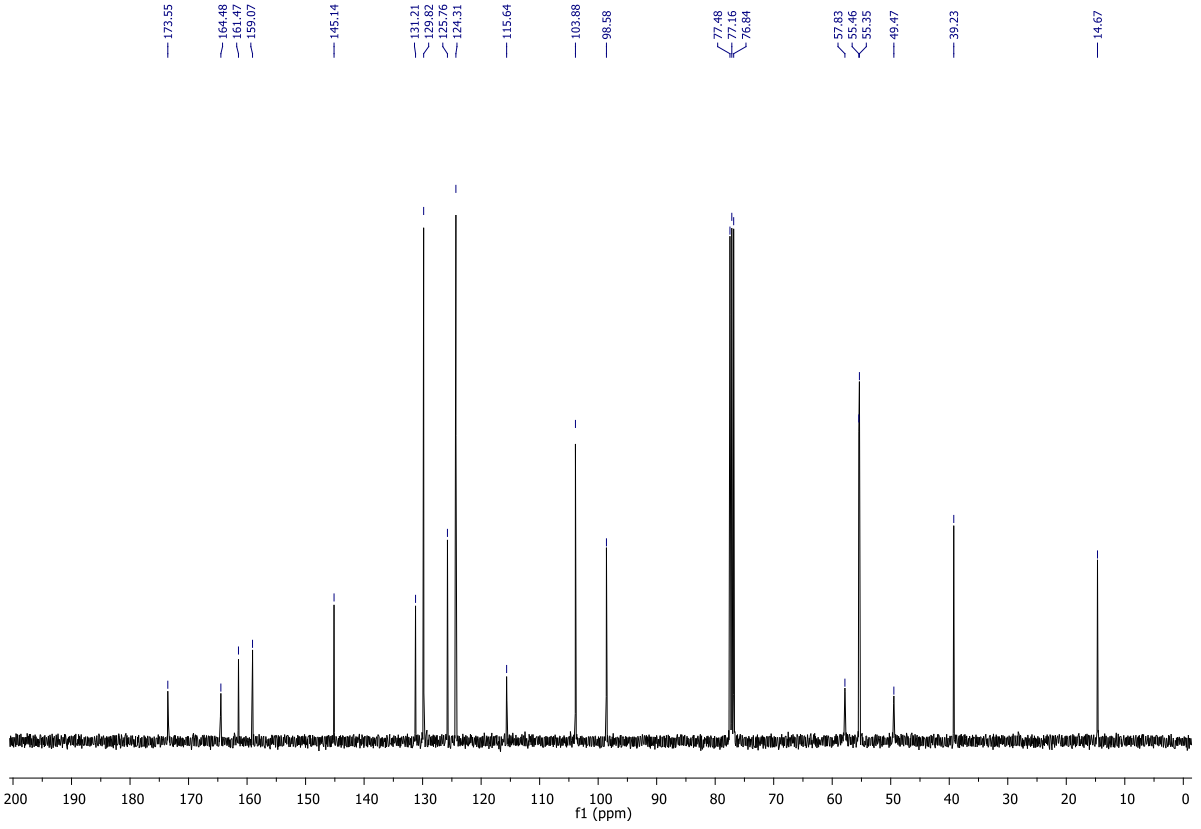
^{1}H NMR of 2d



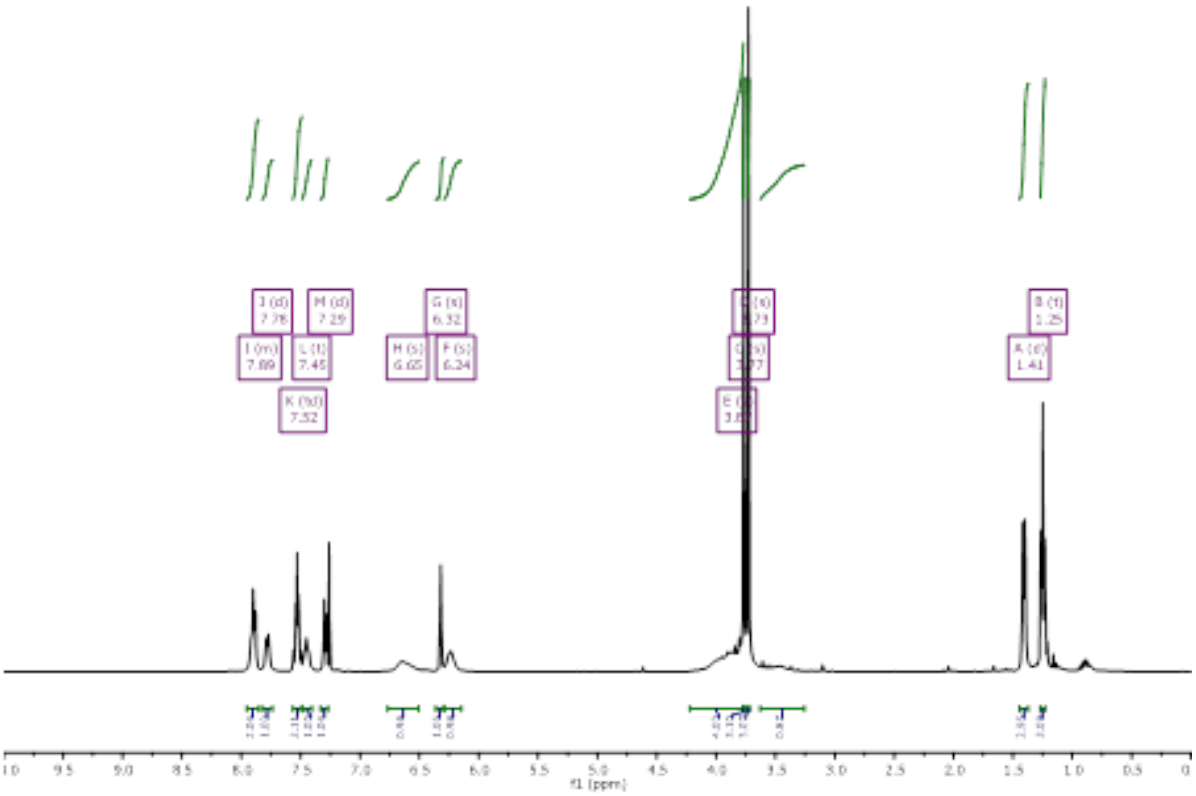
^{13}C NMR of 2d



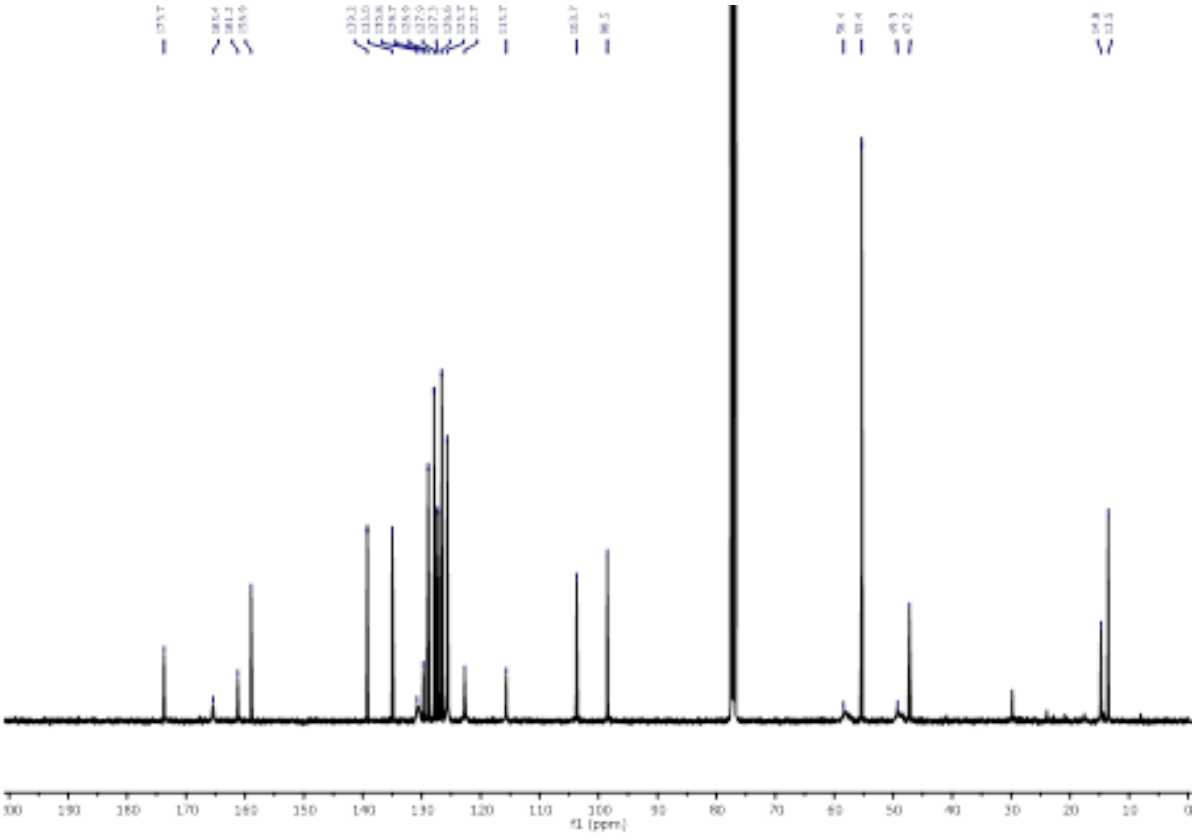
^{1}H NMR of N-(2,4-dimethoxyphenyl)-N’-(methyl(phenyl)carbamoyl)alanine



^{13}C NMR of N-(2,4-dimethoxyphenyl)-N’-(methyl(phenyl)carbamoyl)alanine



^{1}H NMR of N-(2,4-dimethoxyphenyl)-N’-(ethyl(naphthalen-1-yl)carbamoyl)alanine



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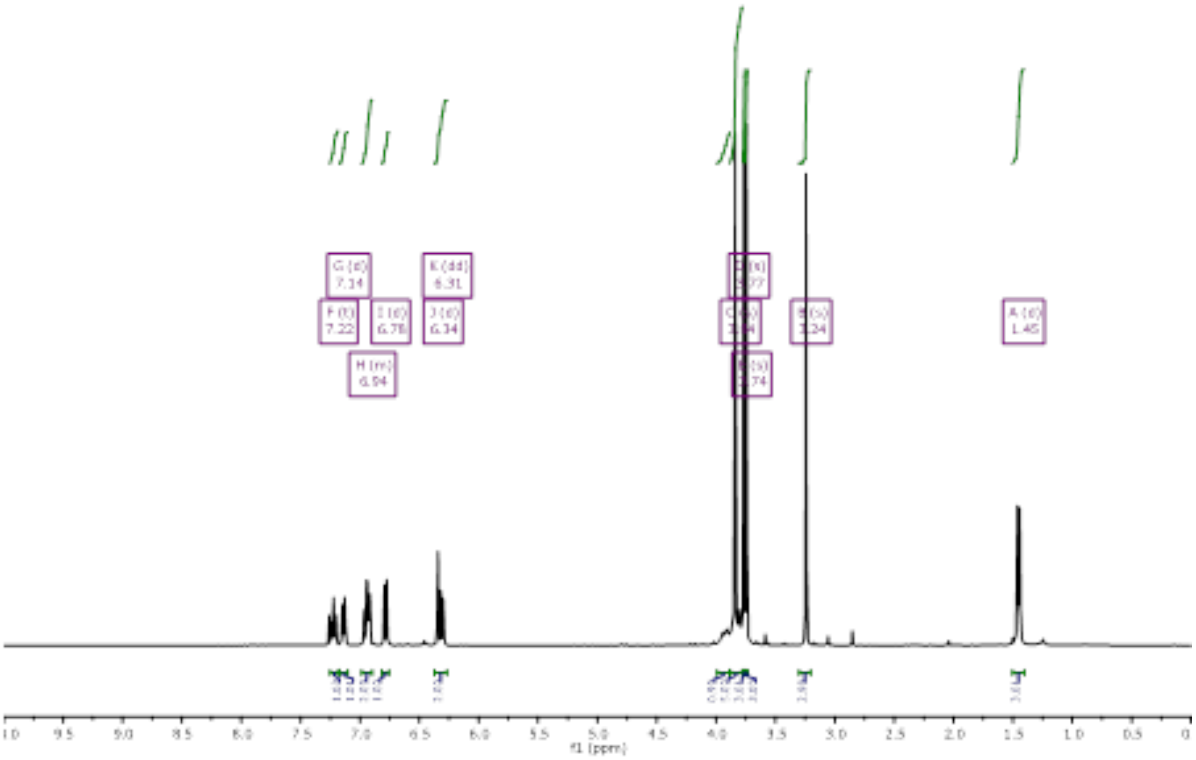
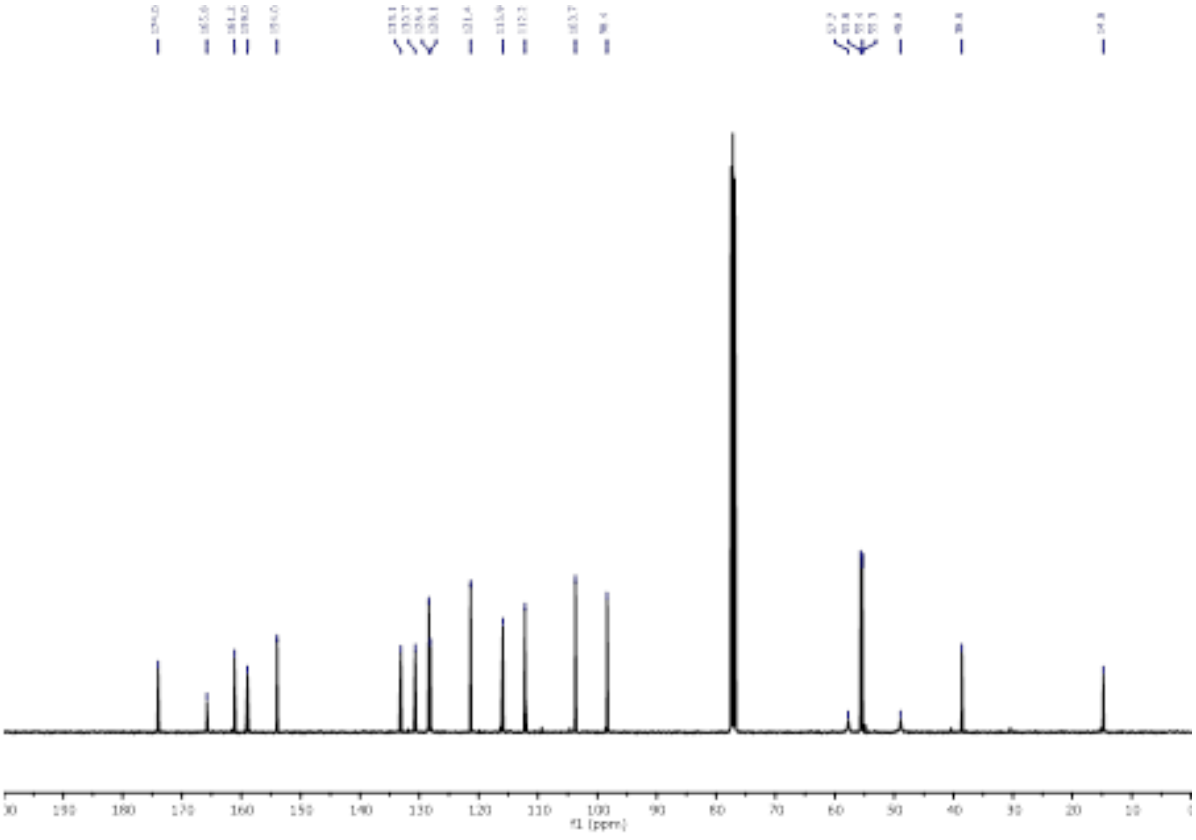
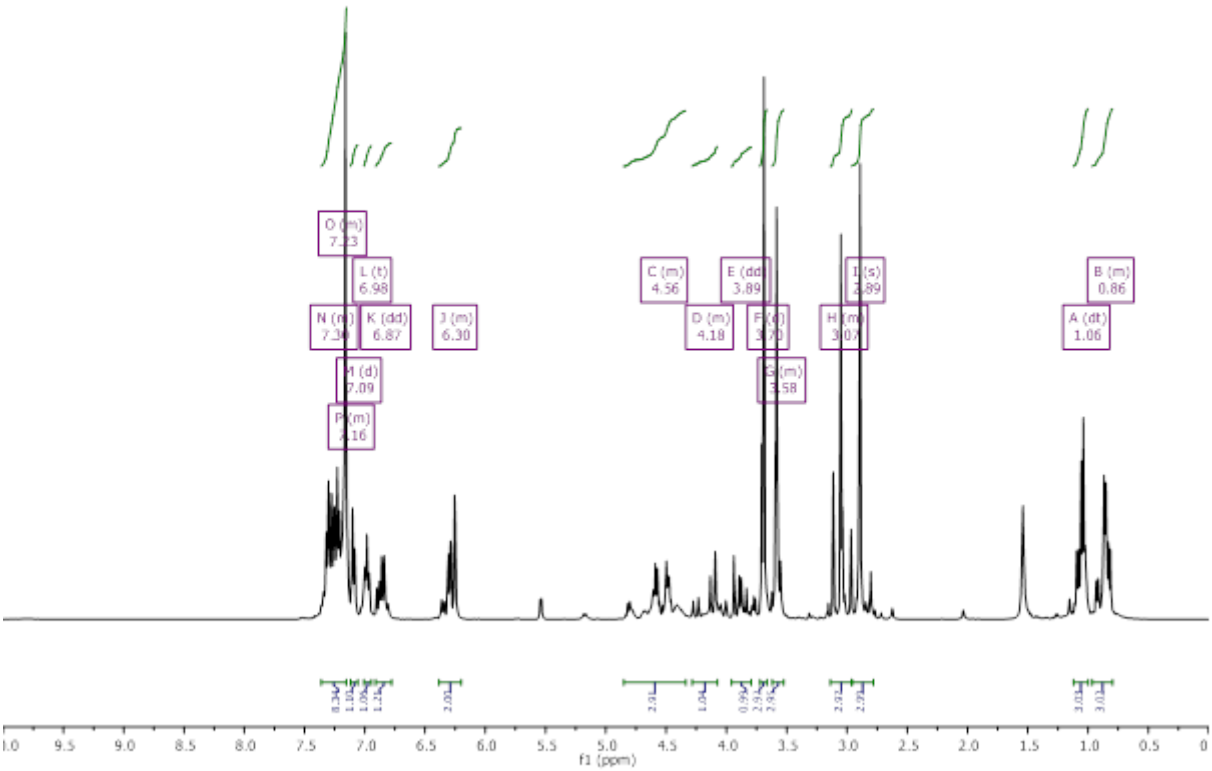


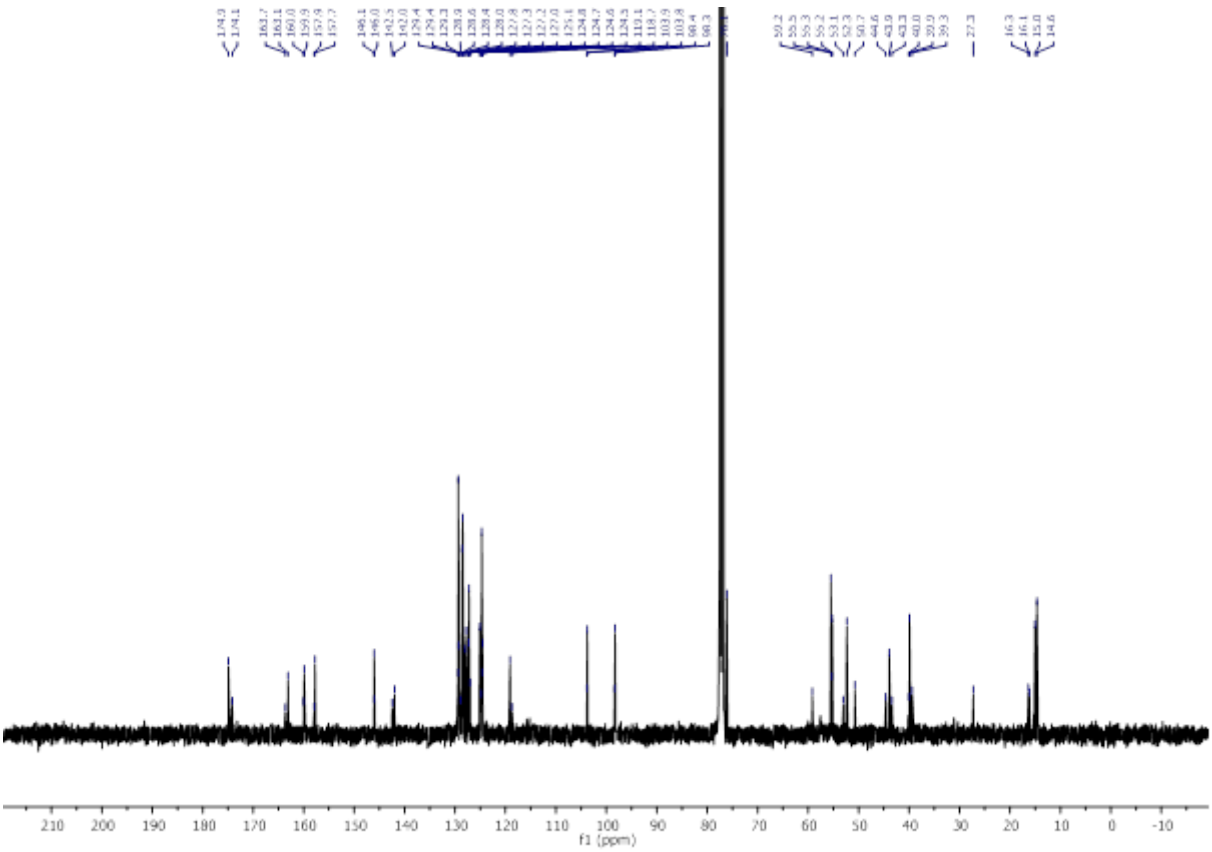
^{1}H NMR of N-(2,4-dimethoxyphenyl)-N’-(methyl(naphthalen-1-yl)carbamoyl)alanine



^{13}C NMR of N-(2,4-dimethoxyphenyl)-N’-(methyl(naphthalen-1-yl)carbamoyl)alanine



^{1}H NMR of 3a



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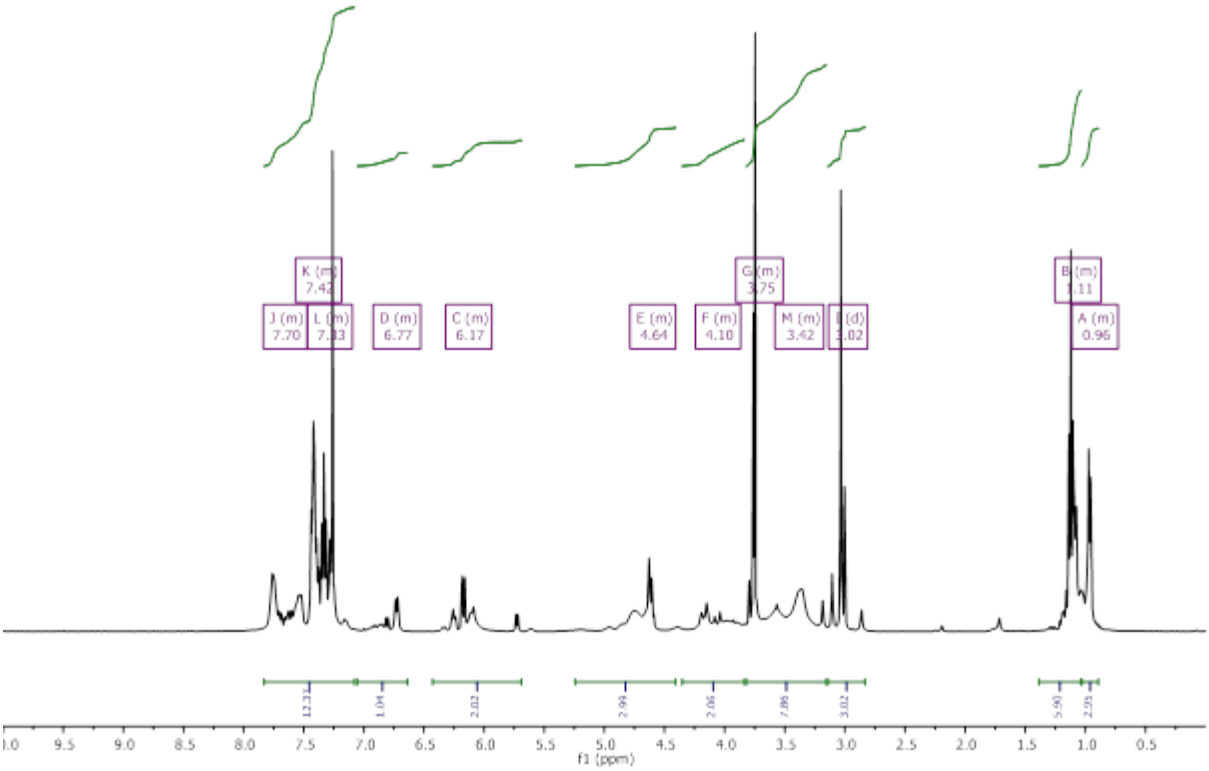

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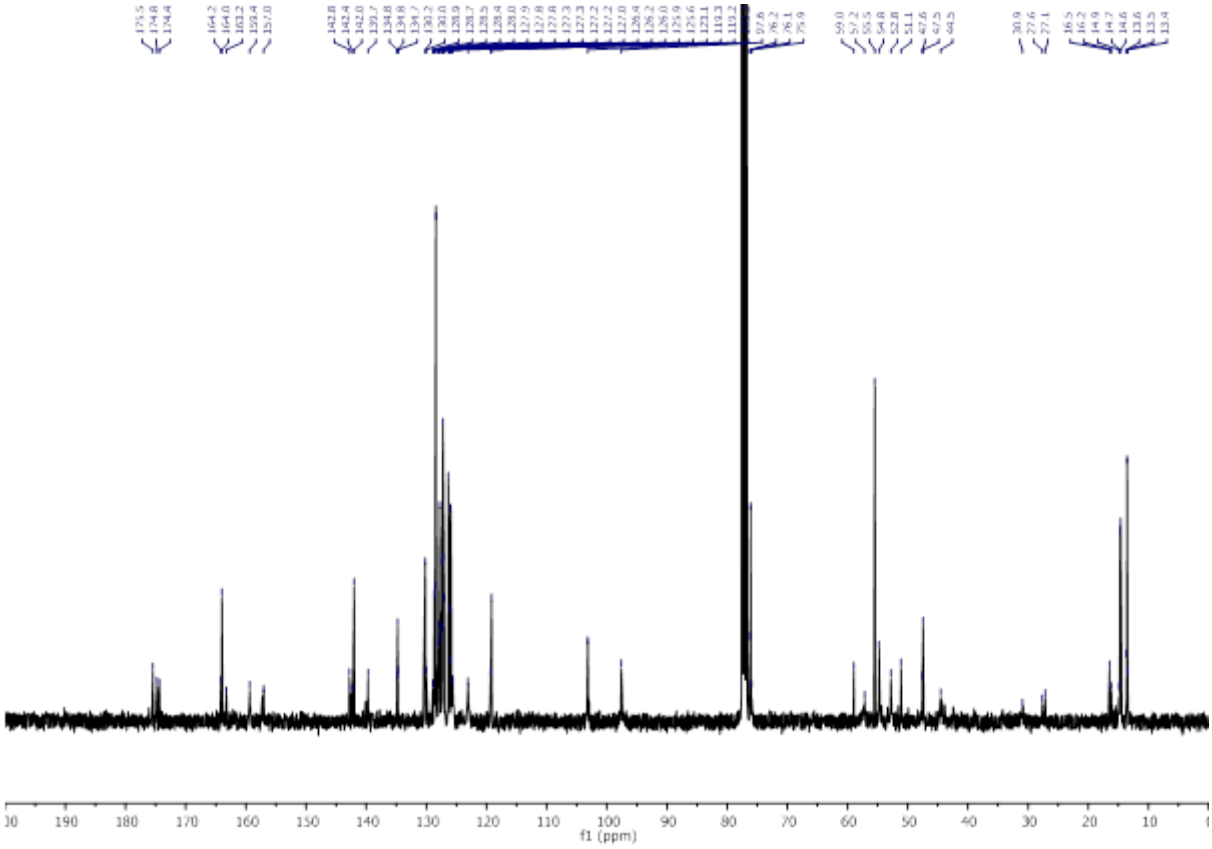

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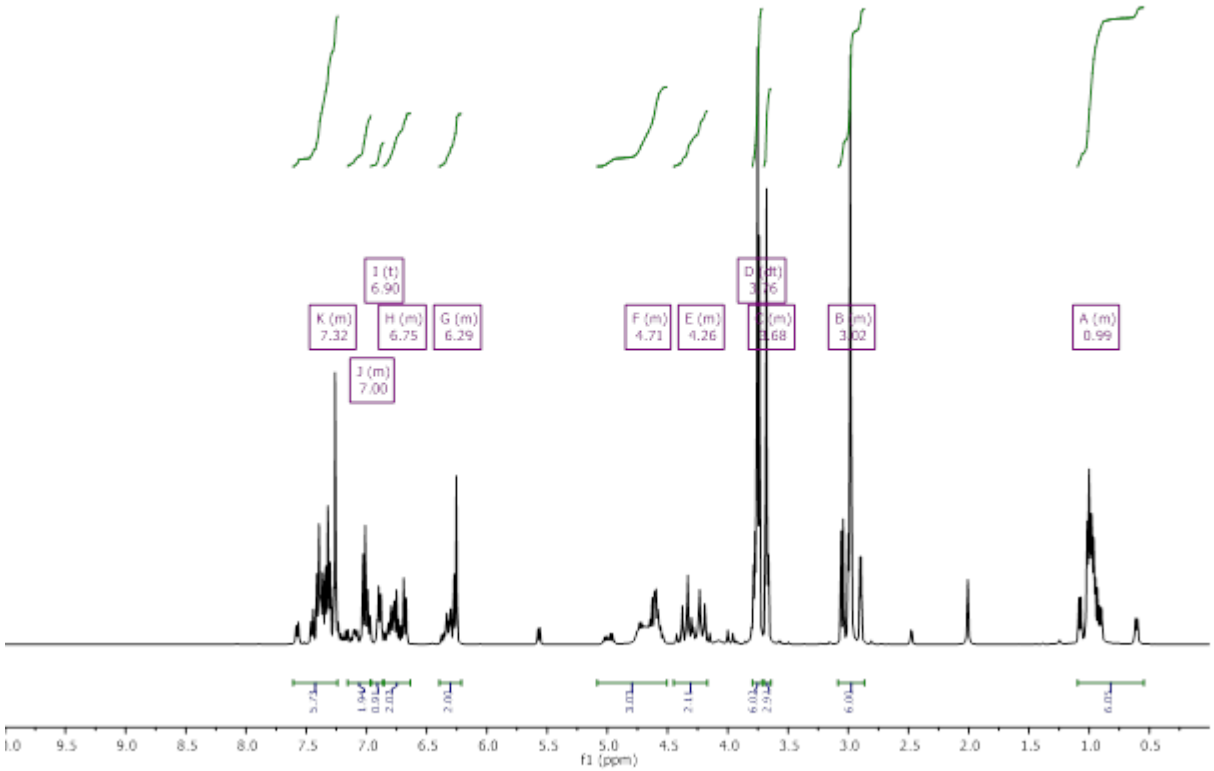

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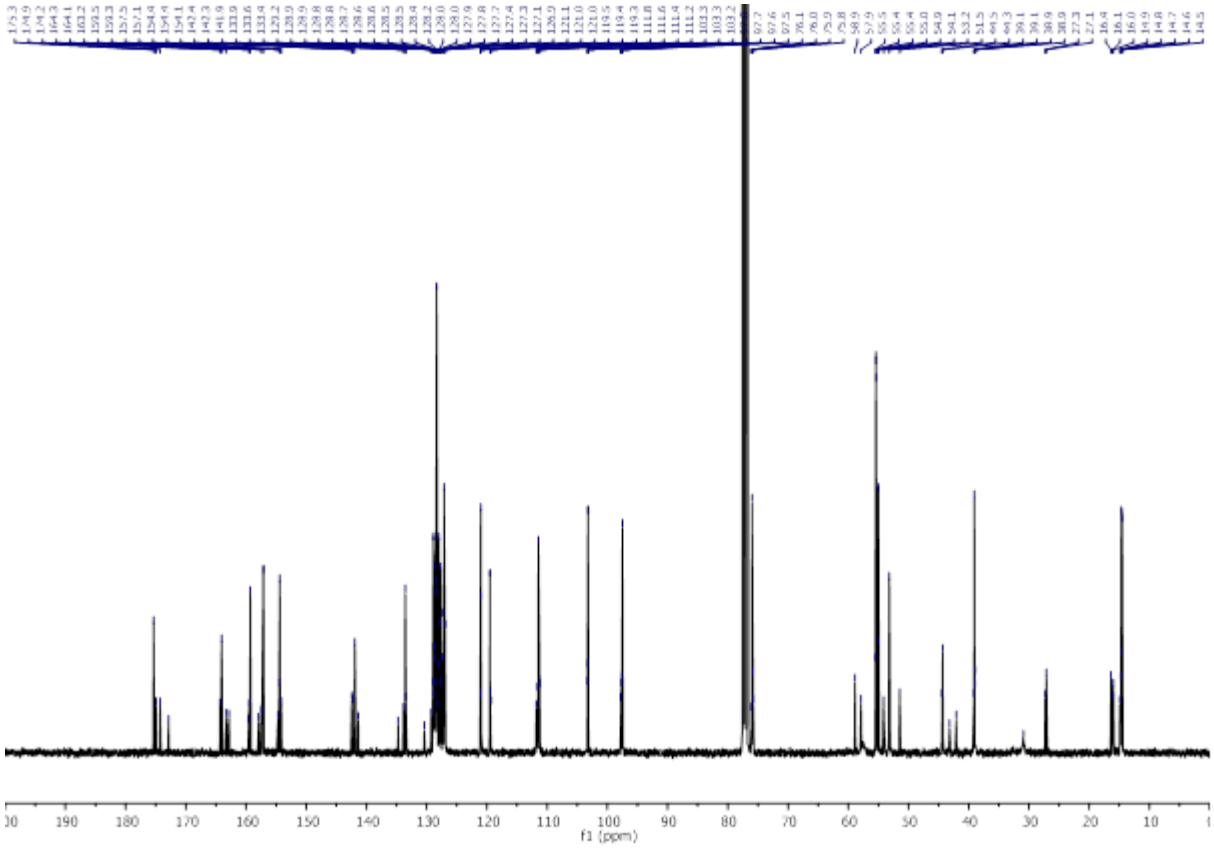

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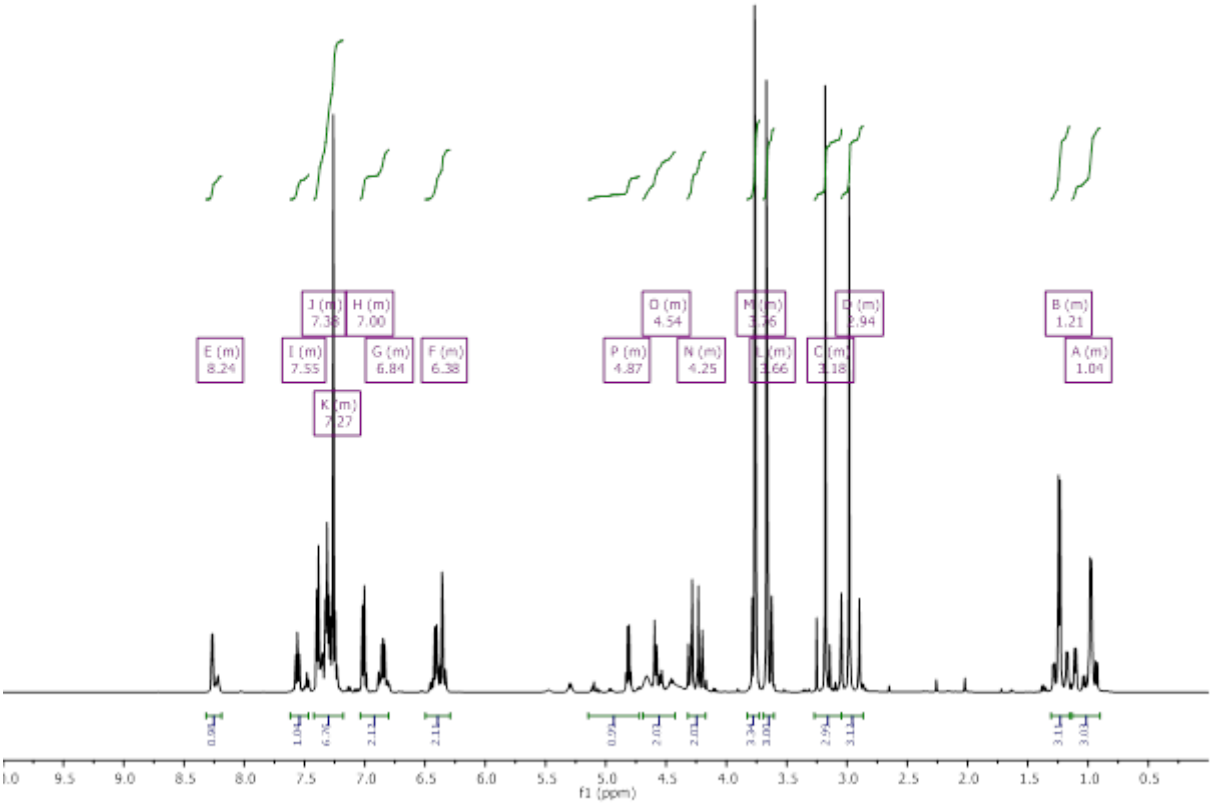

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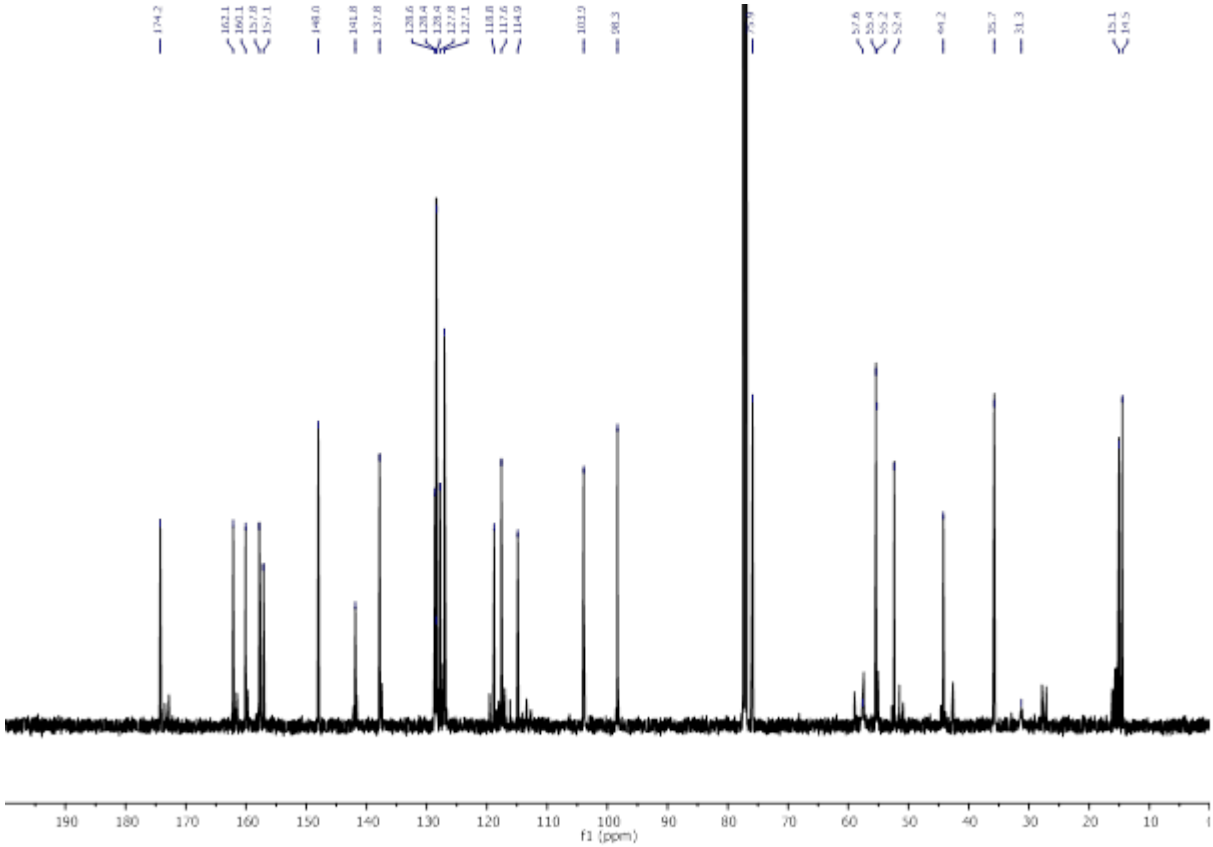
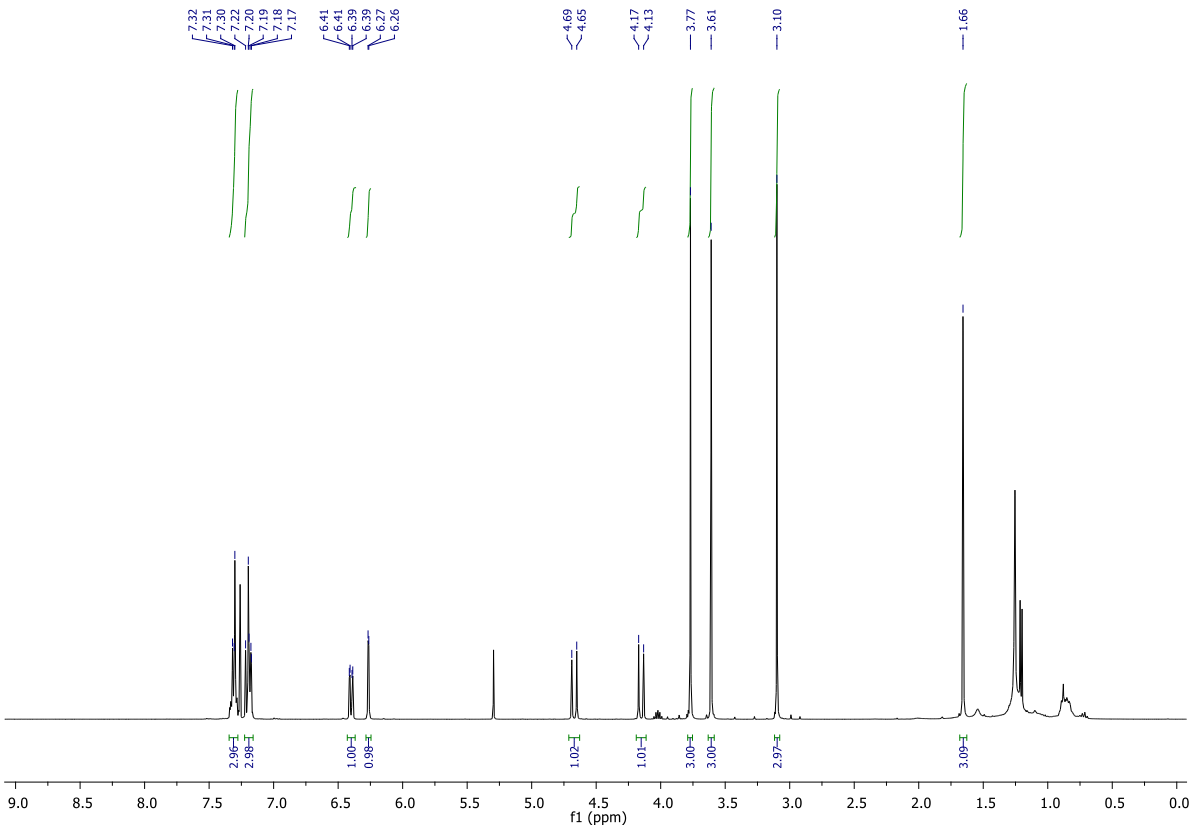
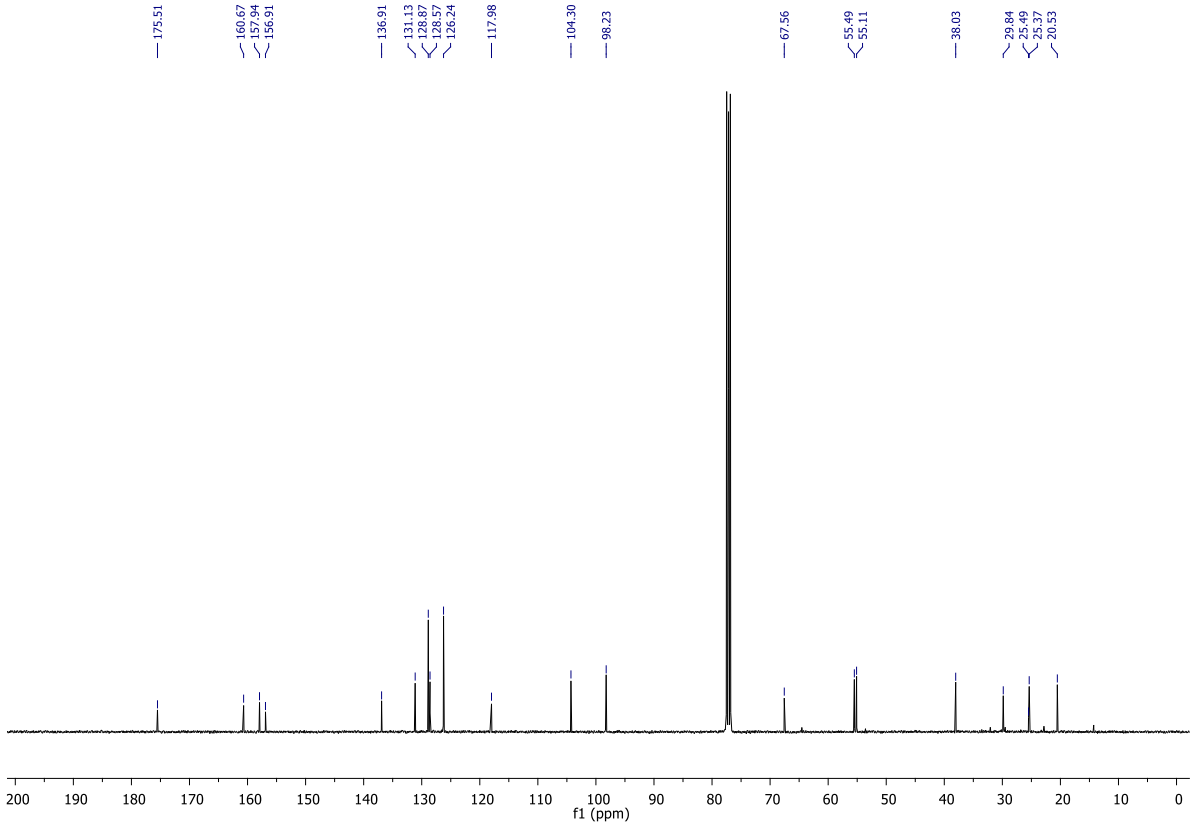


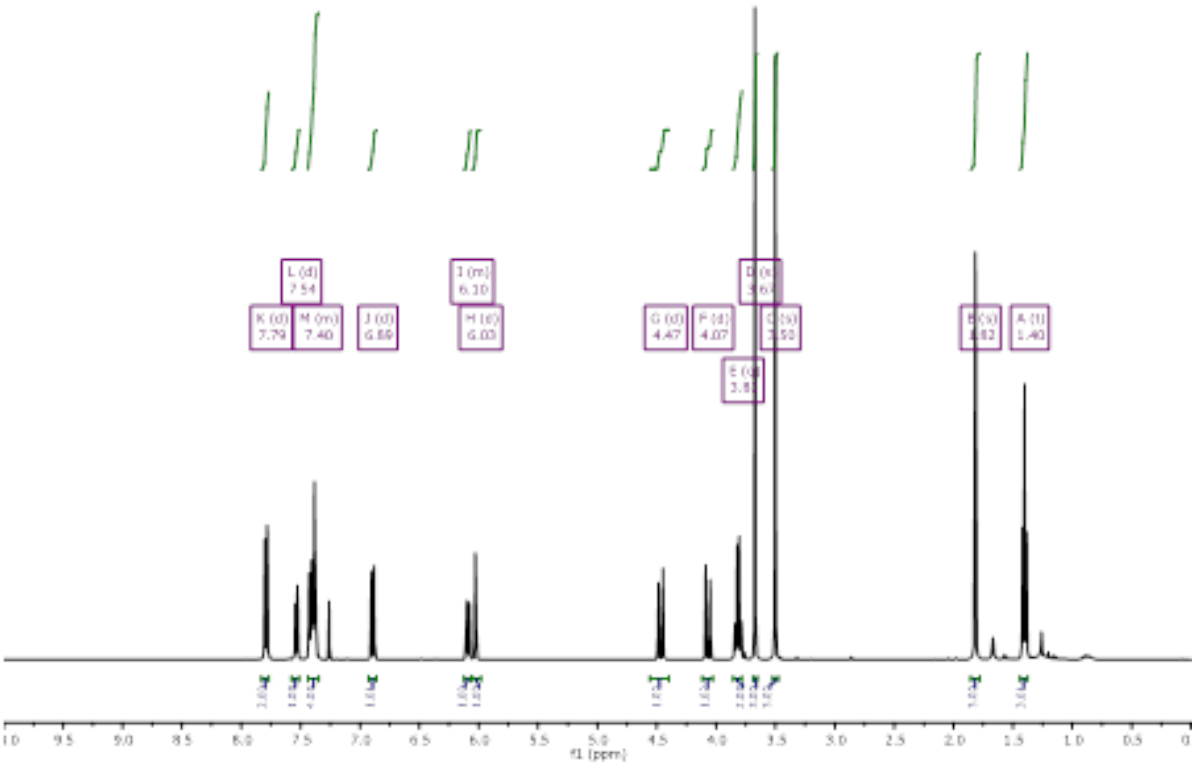
^{13}C NMR of 3d



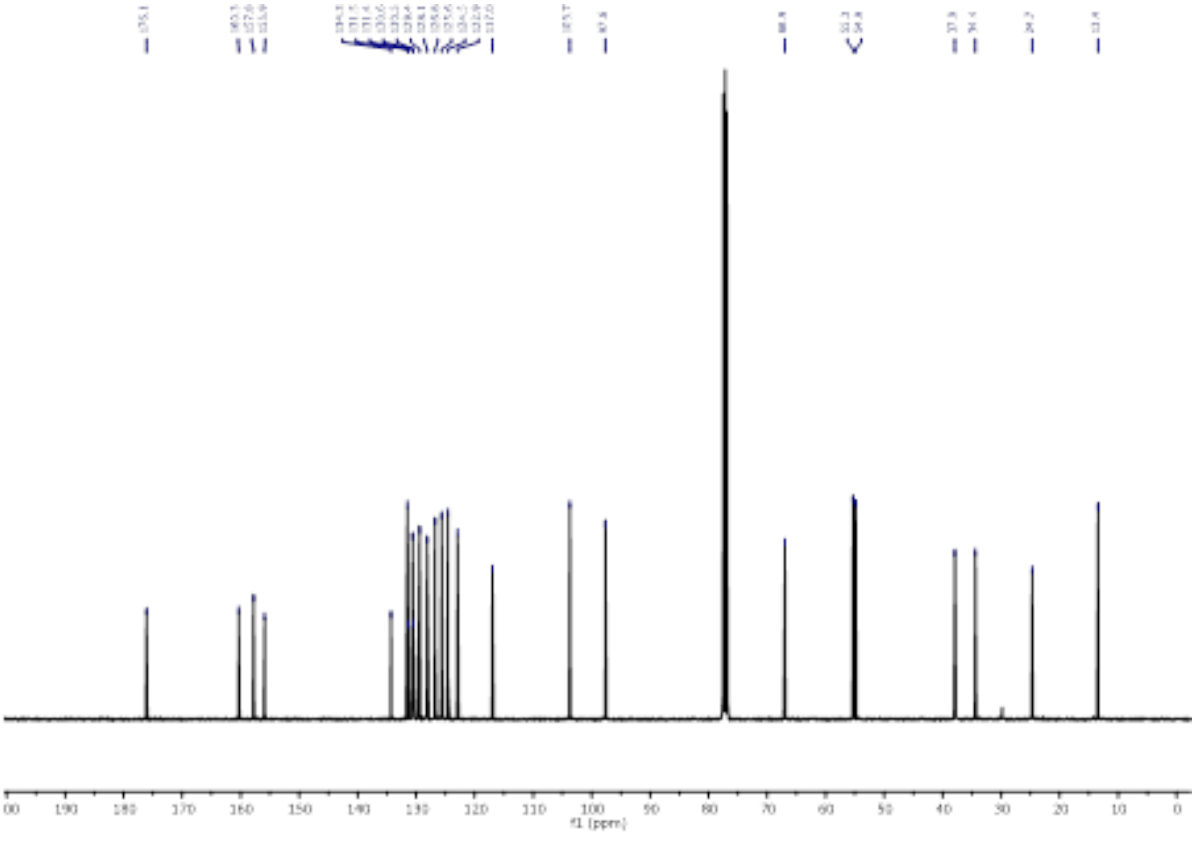
^{1}H NMR of 4a



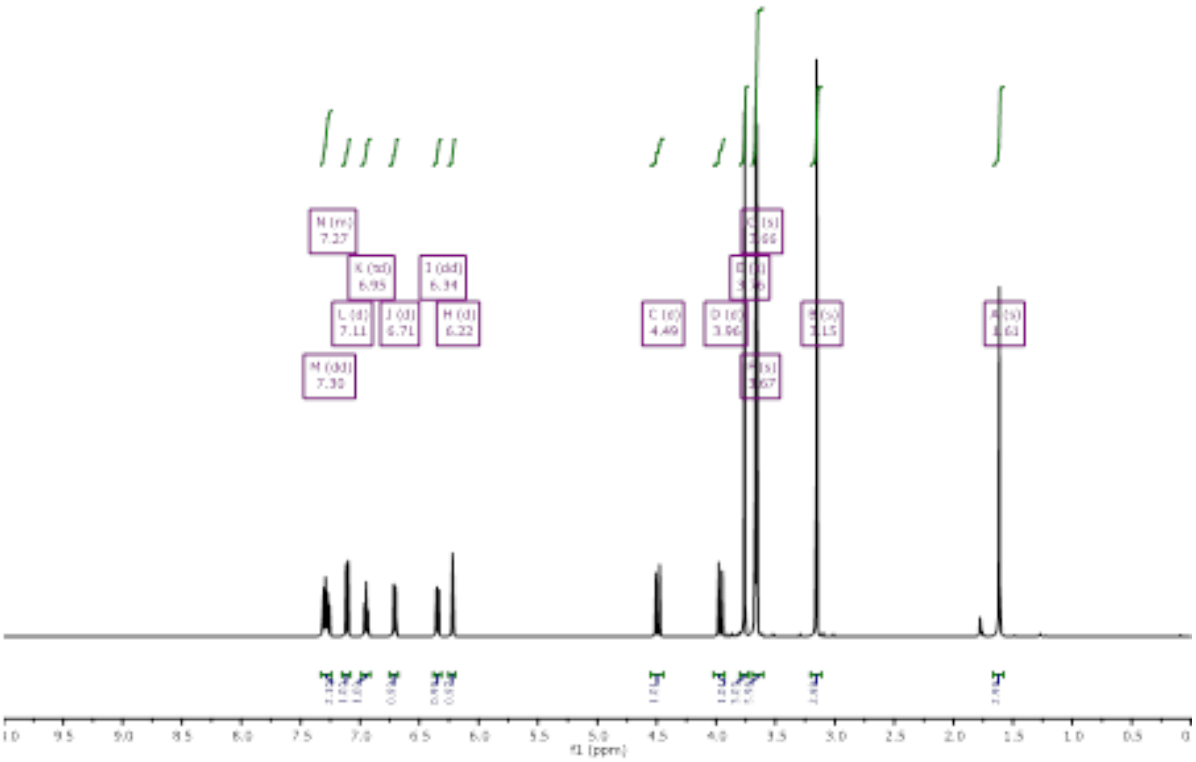
^{13}C NMR of 4a



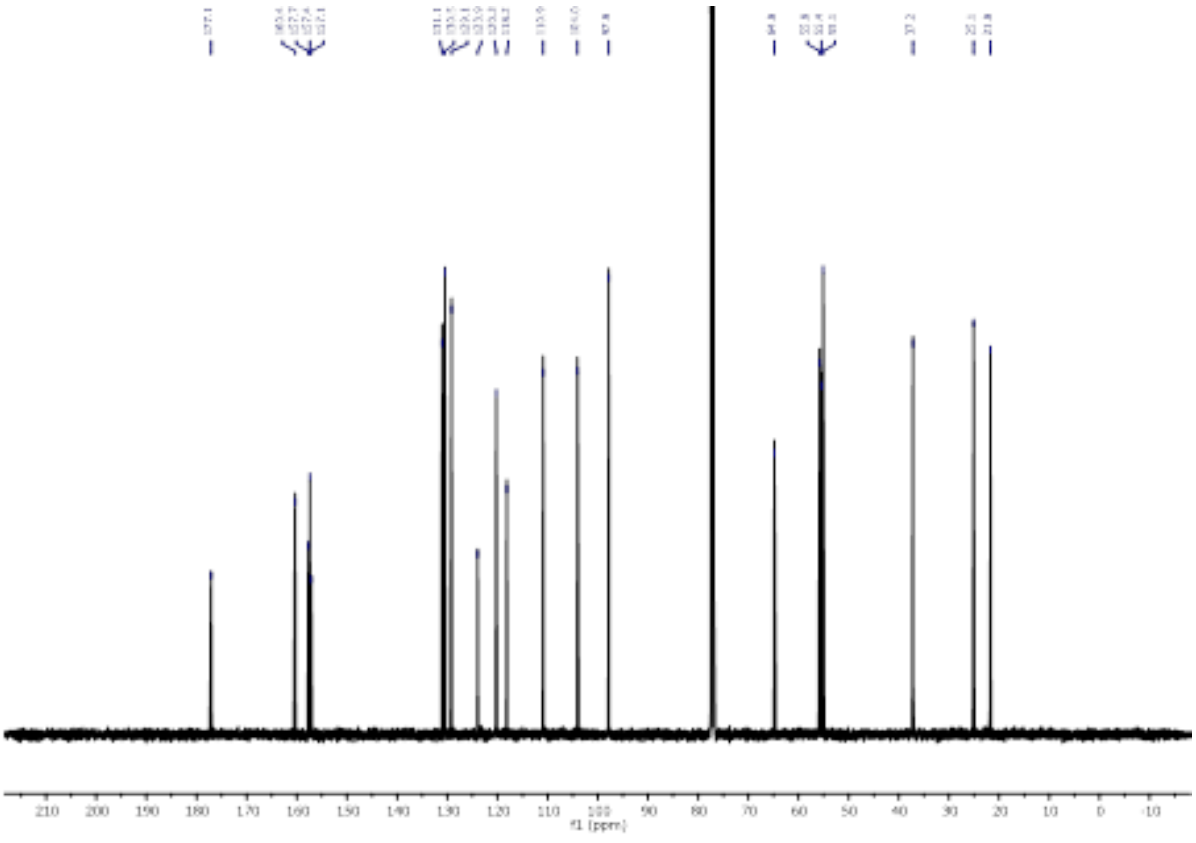
^{1}H NMR of 4b



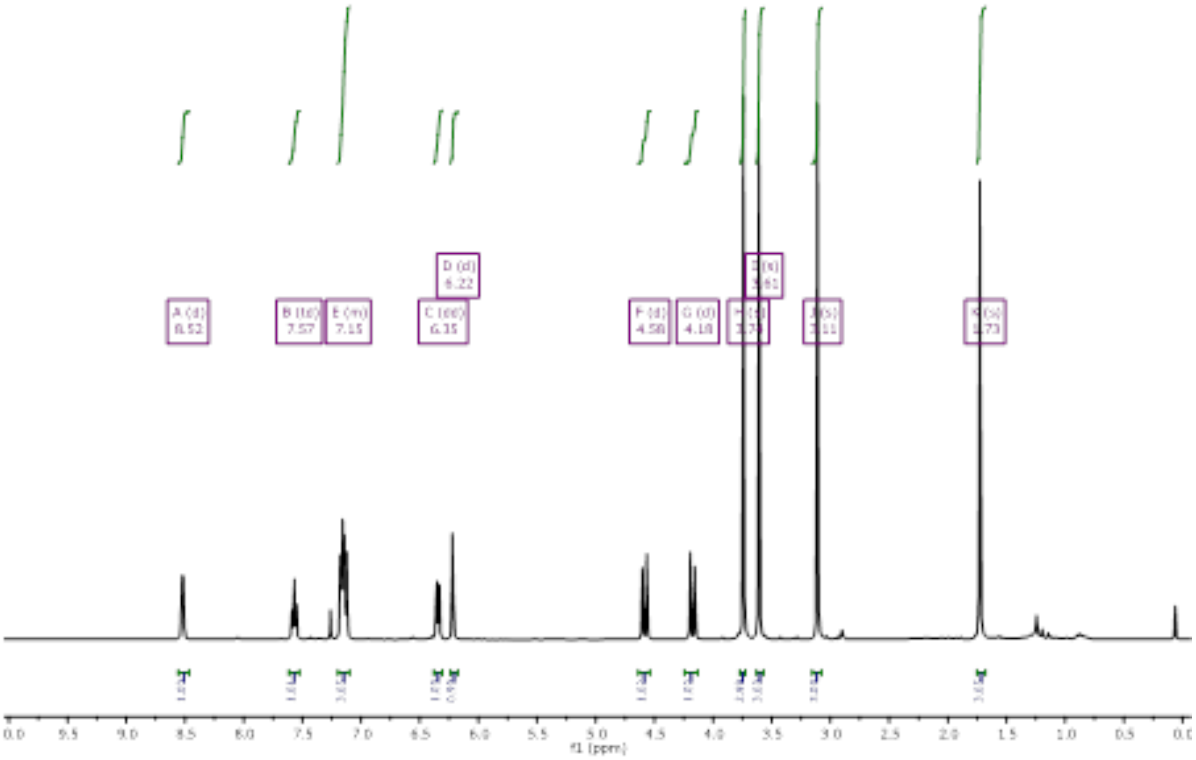
^{13}C NMR of 4b



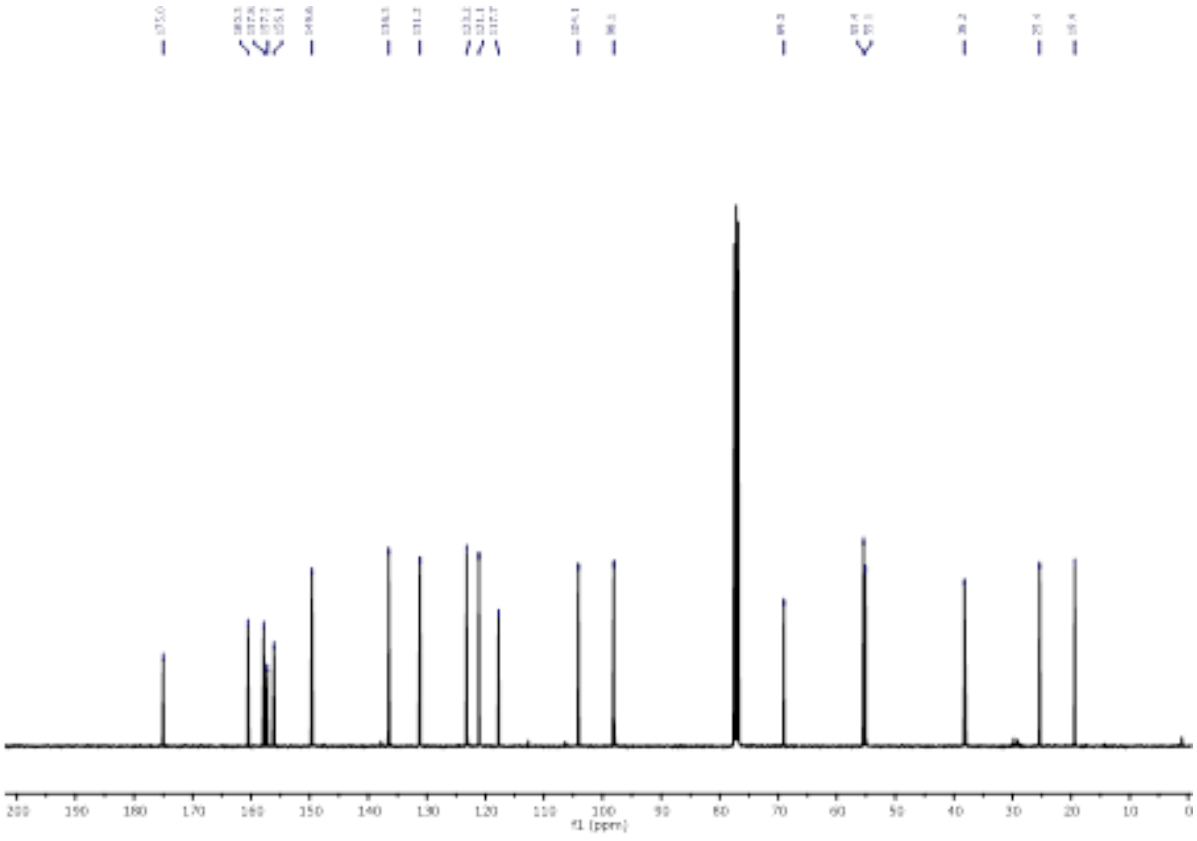
^{1}H NMR of 4c



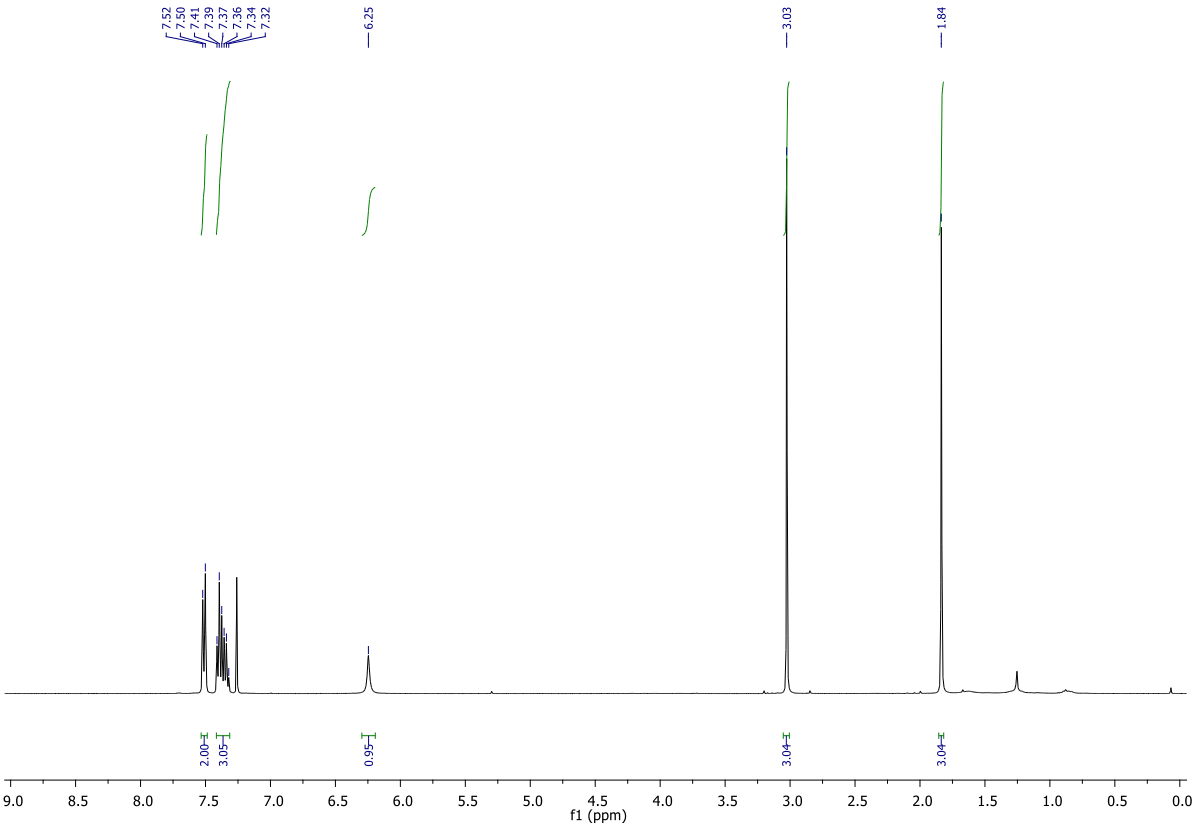
^{13}C NMR of 4c



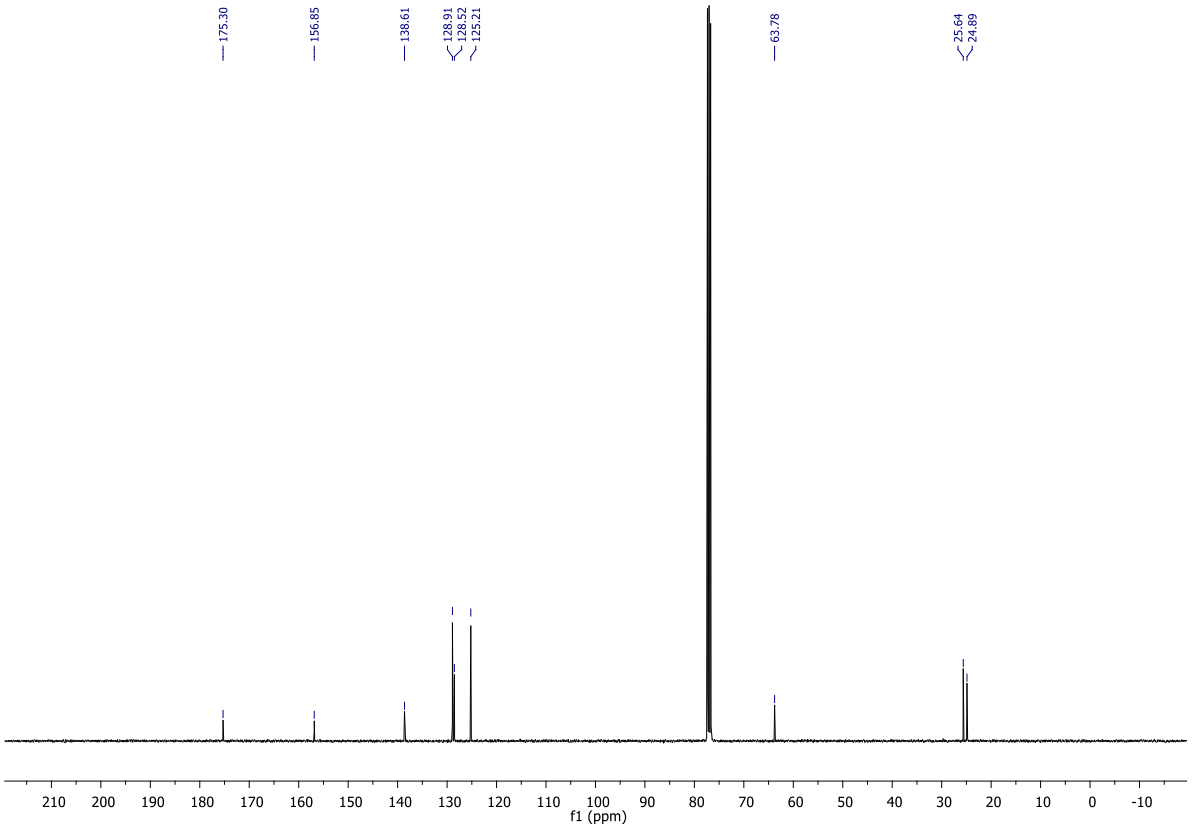
^{1}H NMR of 4d



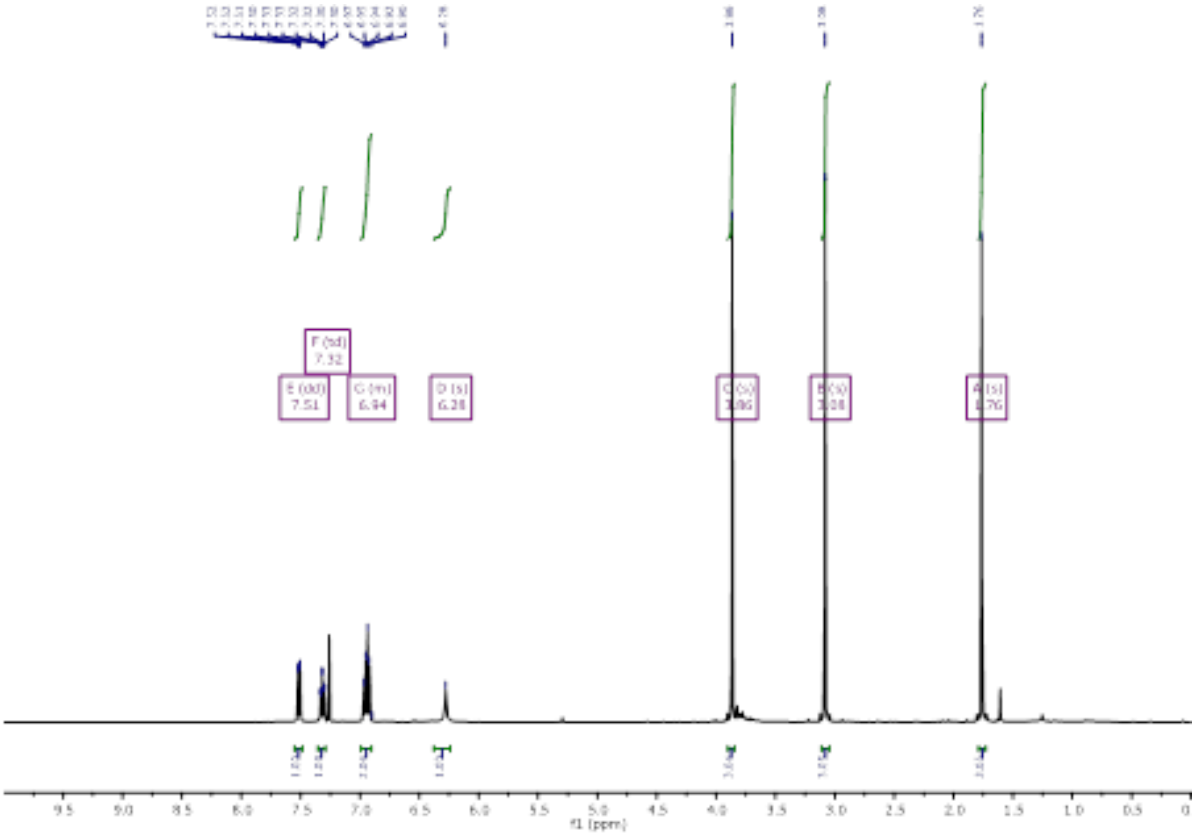
^{13}C NMR of 4d



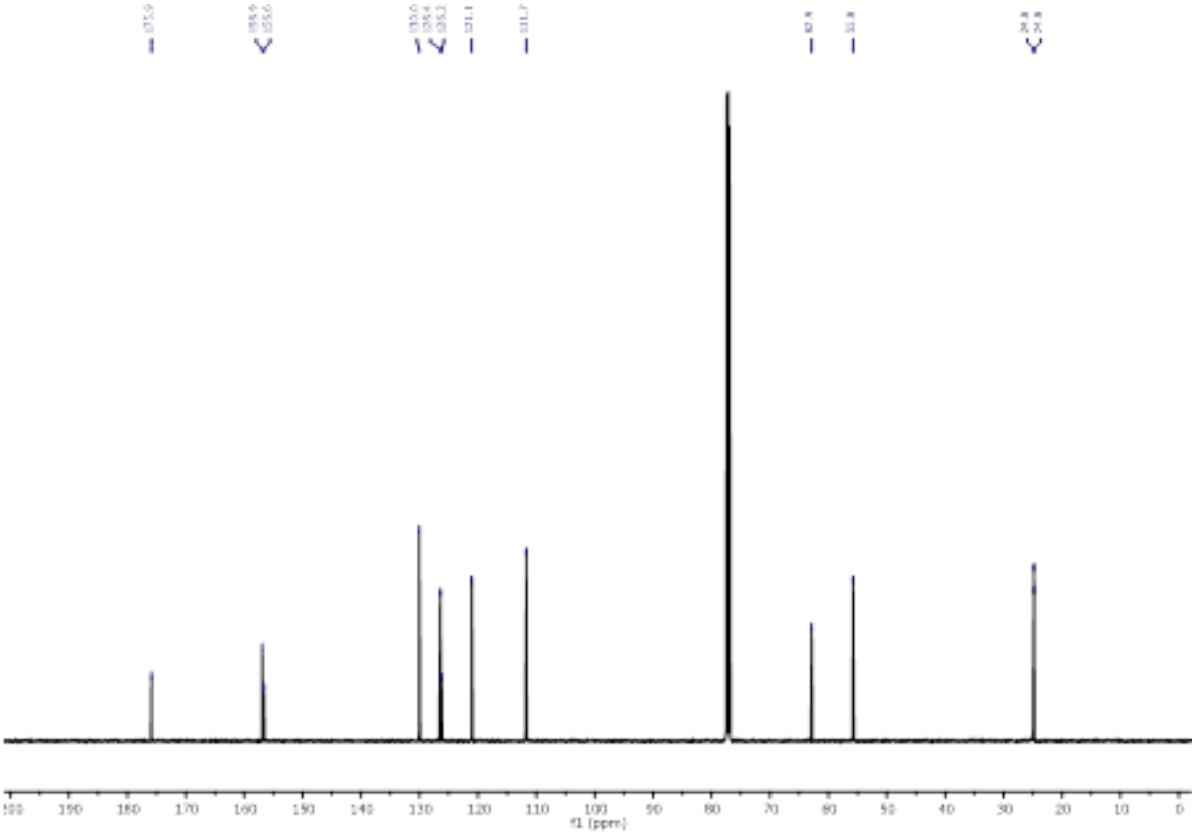
^{1}H NMR of 5a



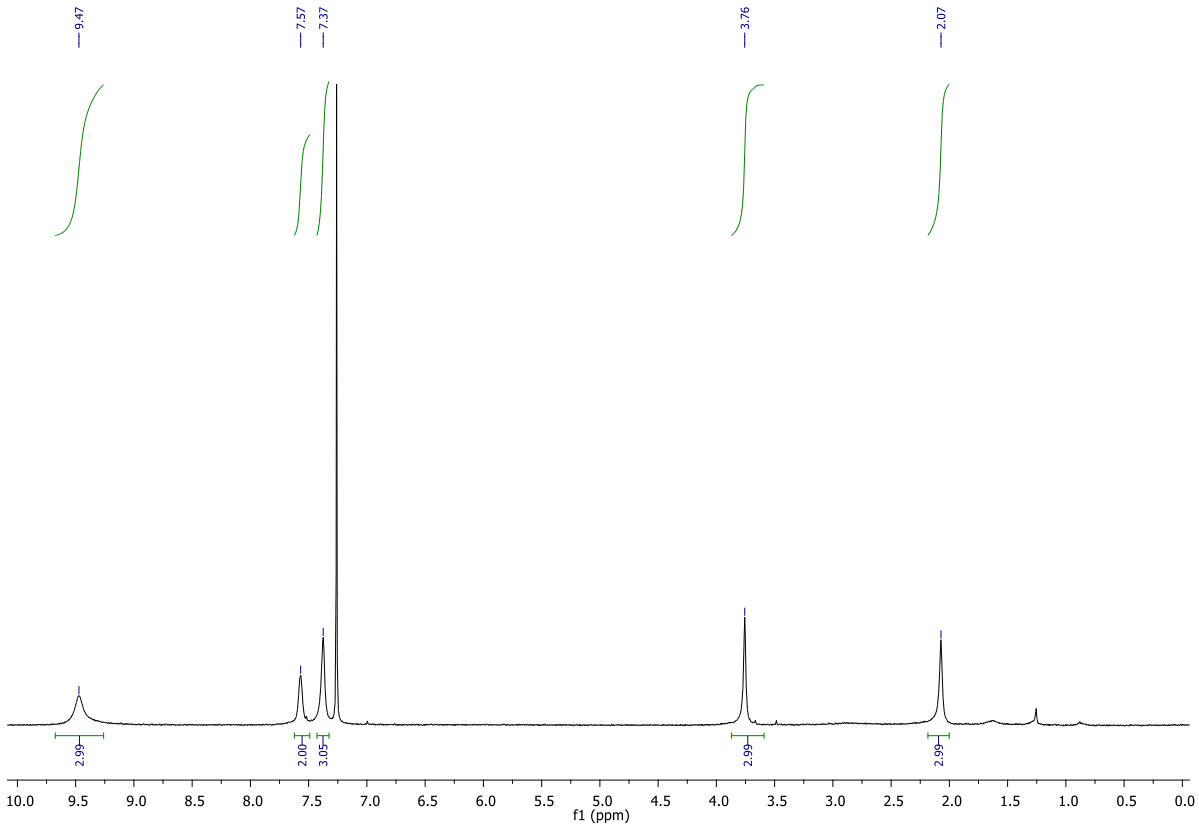
^{13}C NMR of 5a



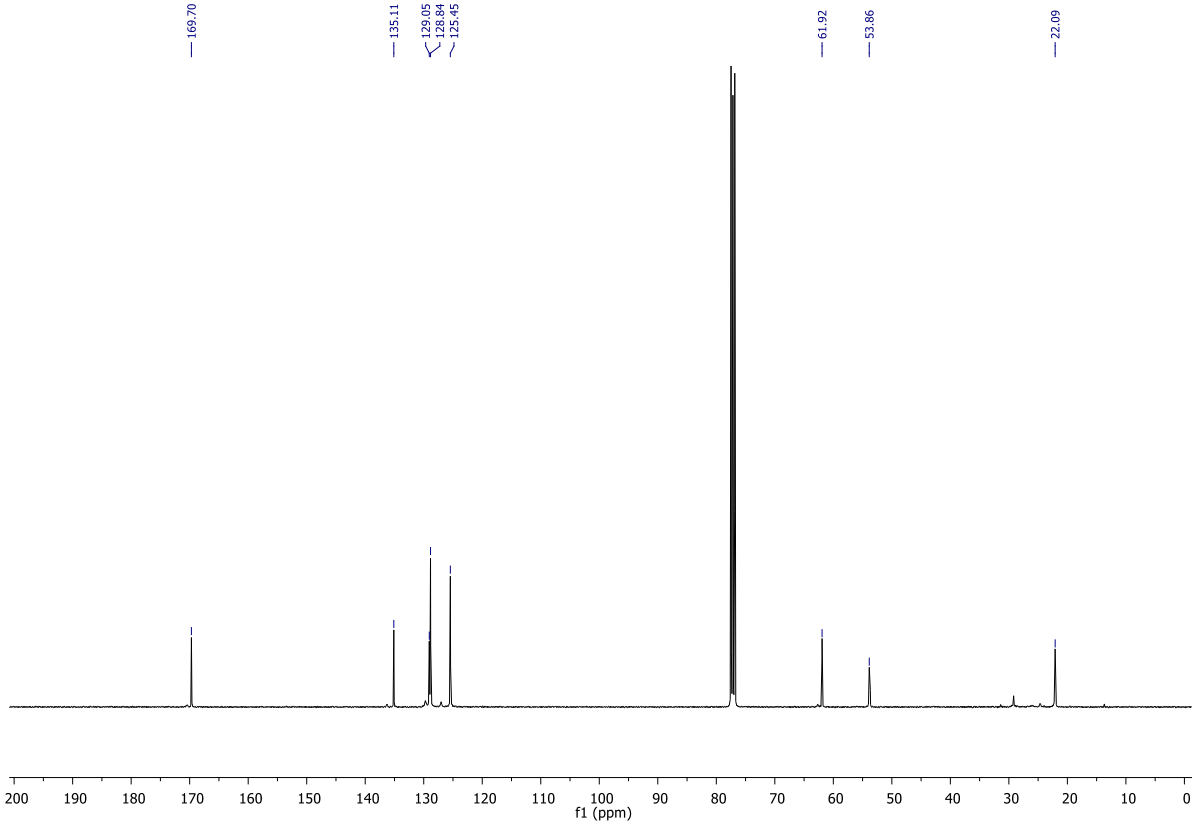
^{1}H NMR of 5c



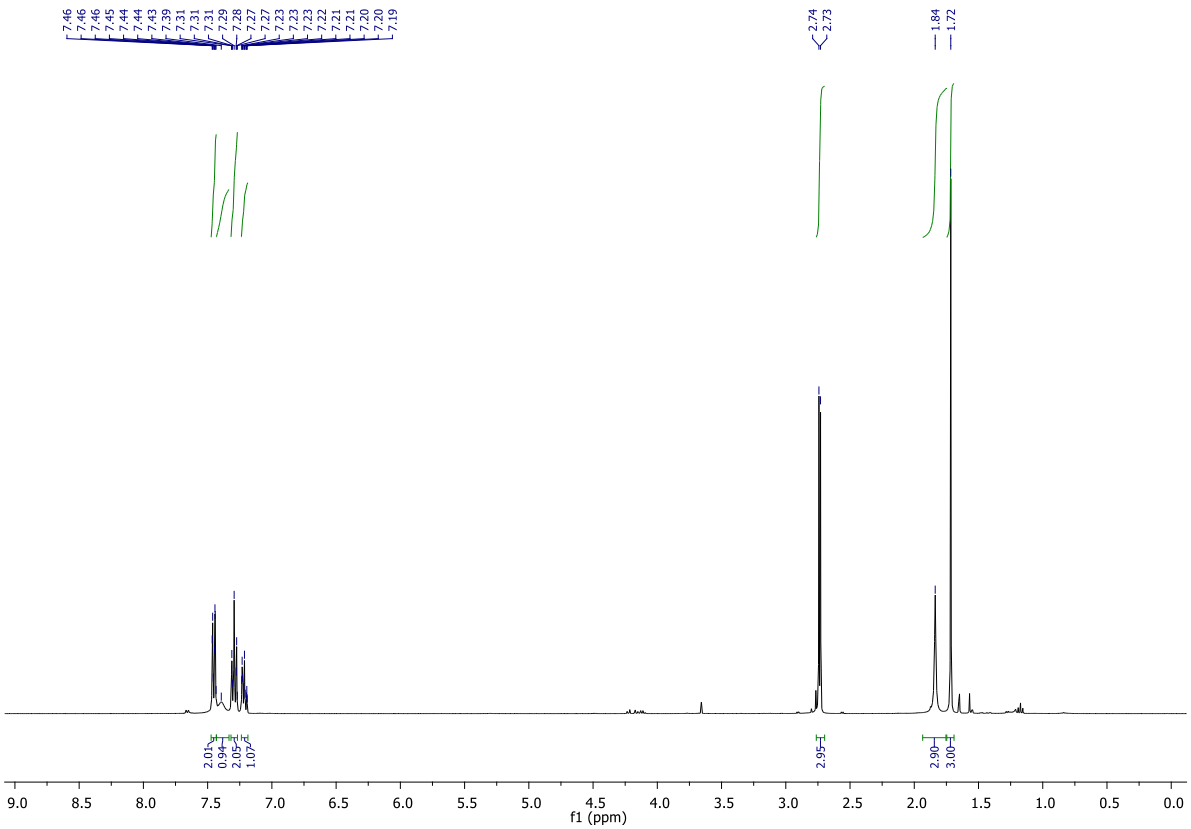
^{13}C NMR of 5c



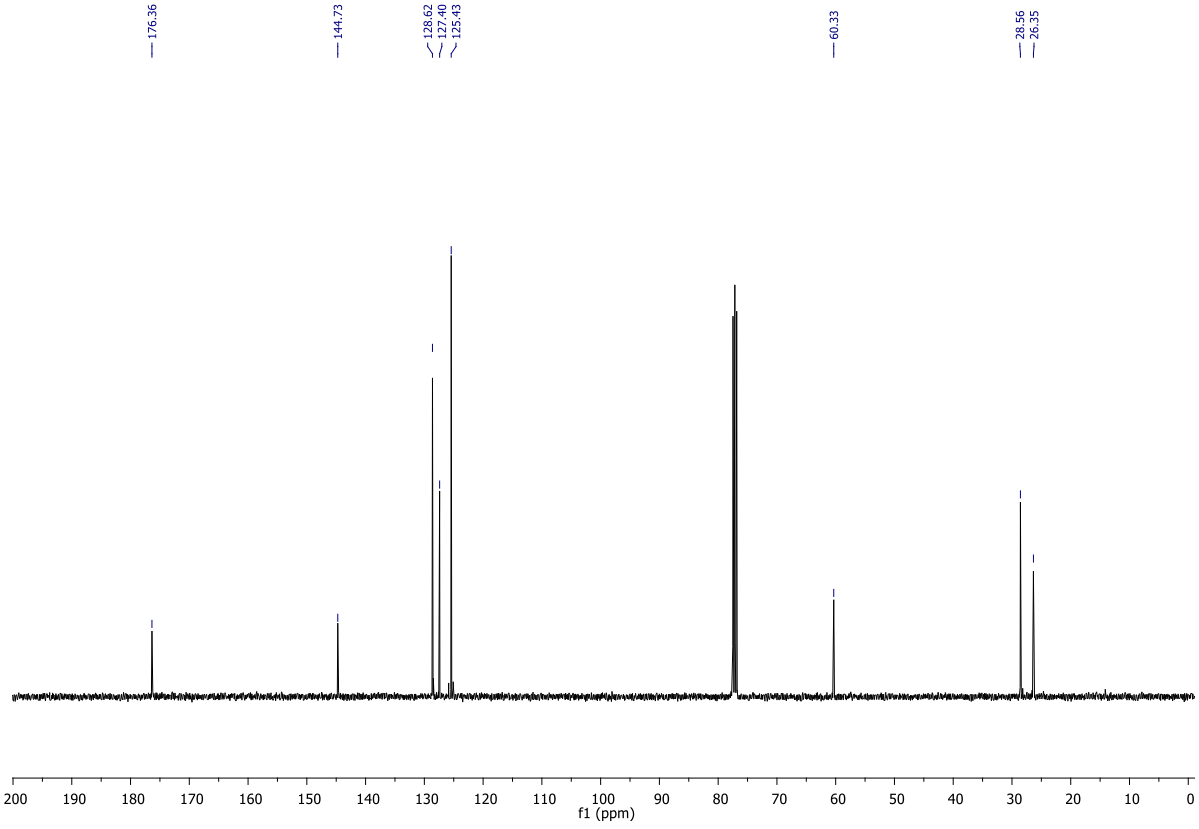
^{1}H NMR of (aMe)PhgOMe



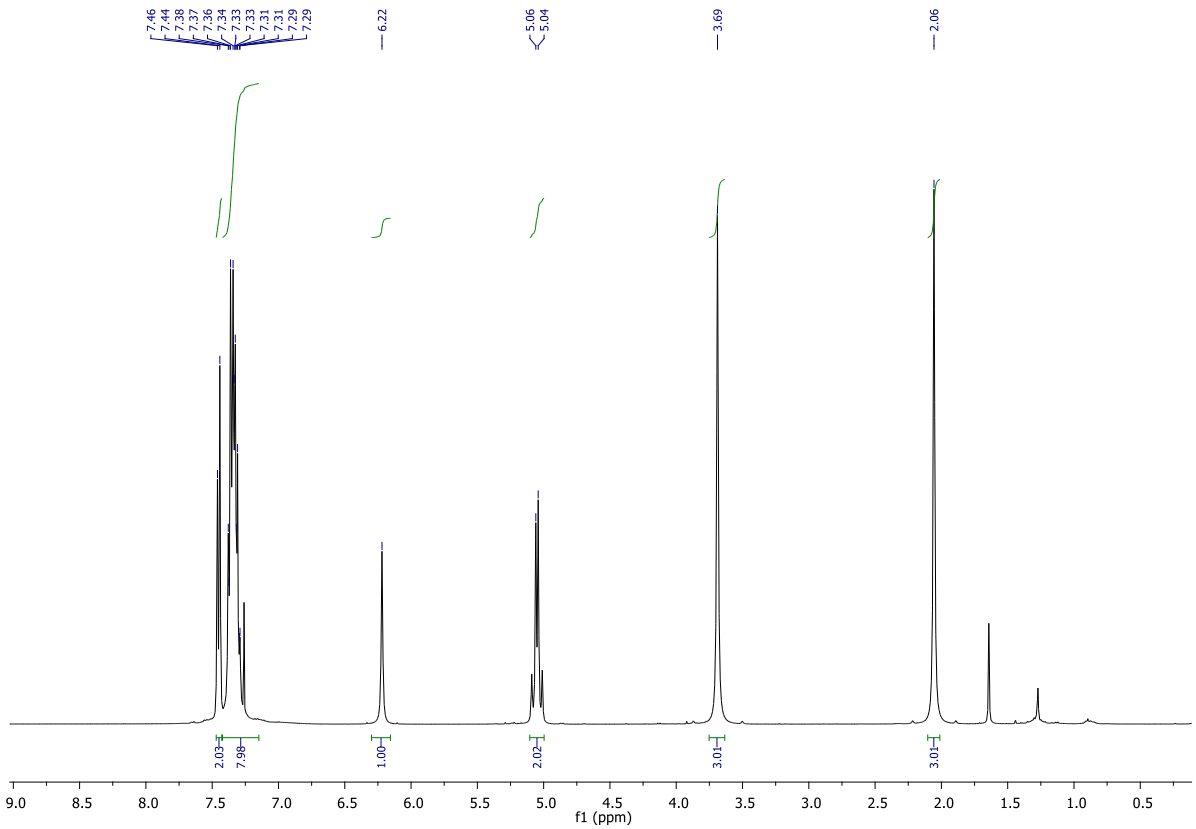
^{13}C NMR of (aMe)PhgOMe



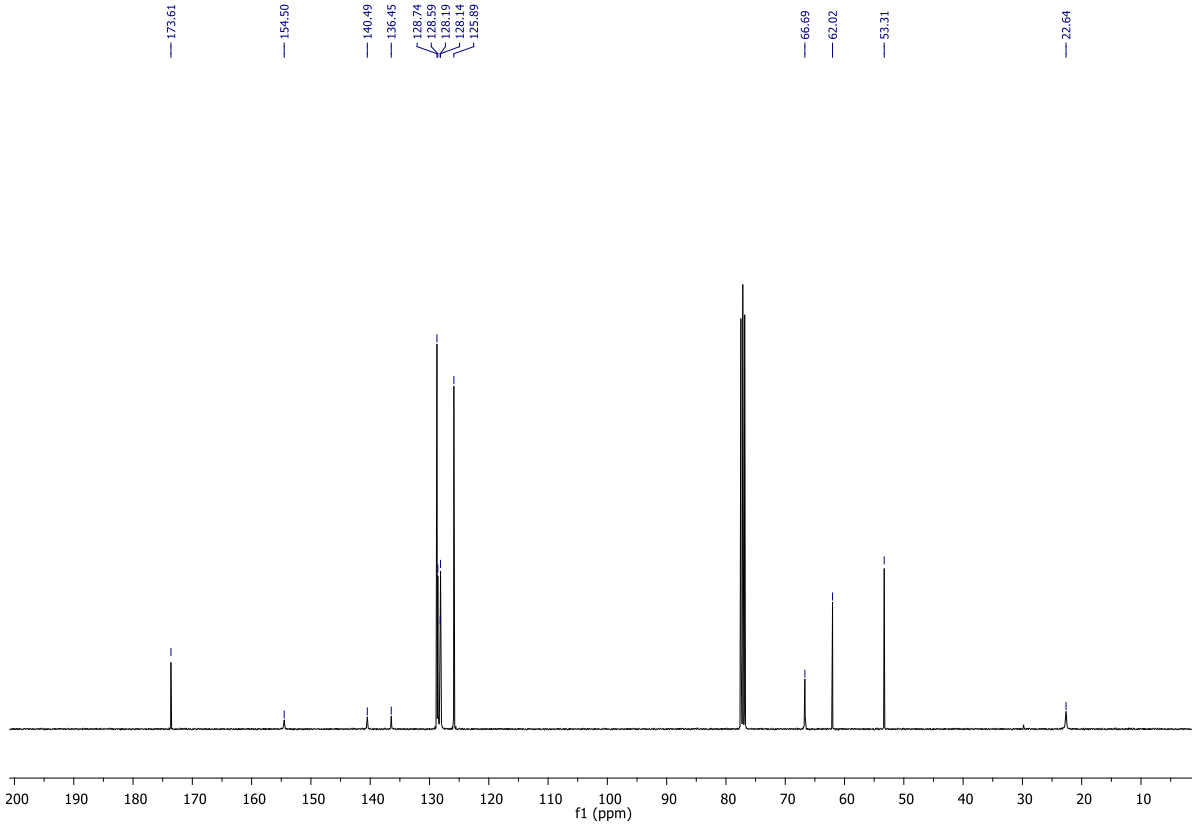
^{1}H NMR of 6a



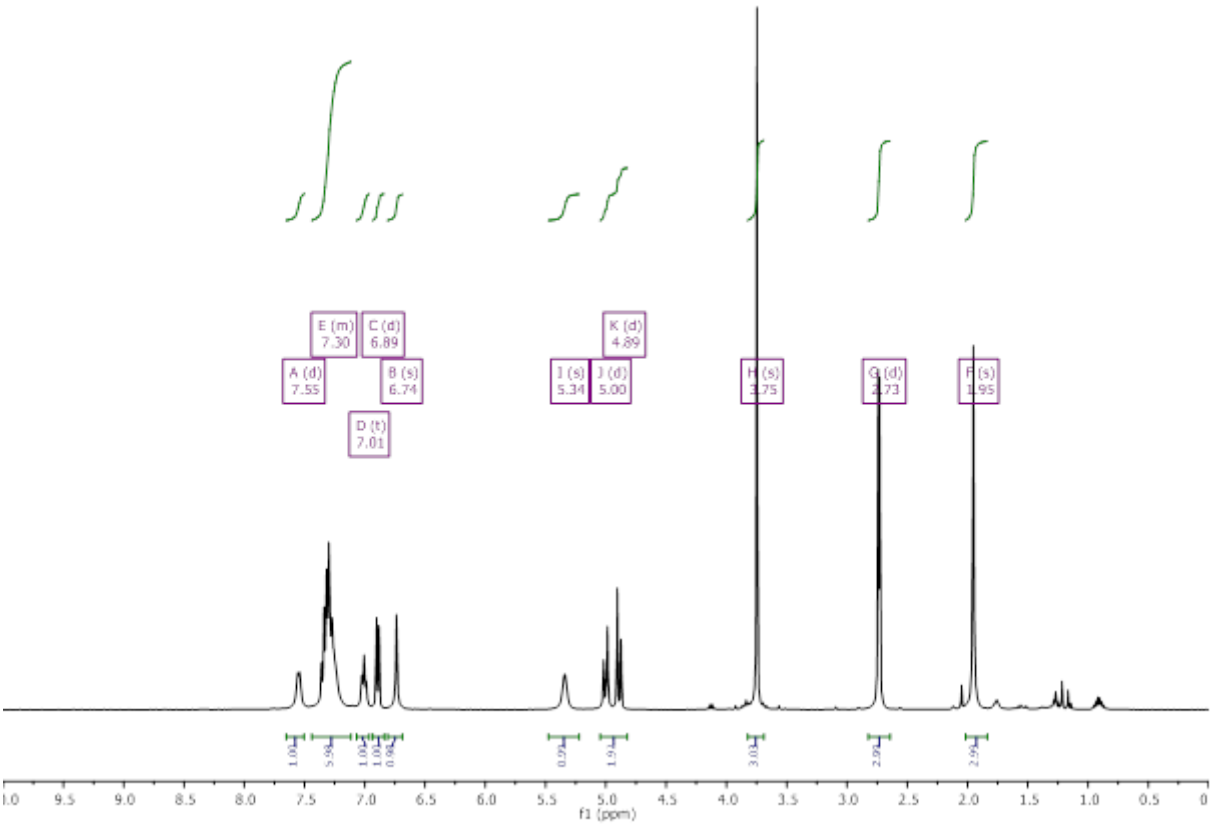
^{13}C NMR of 6a



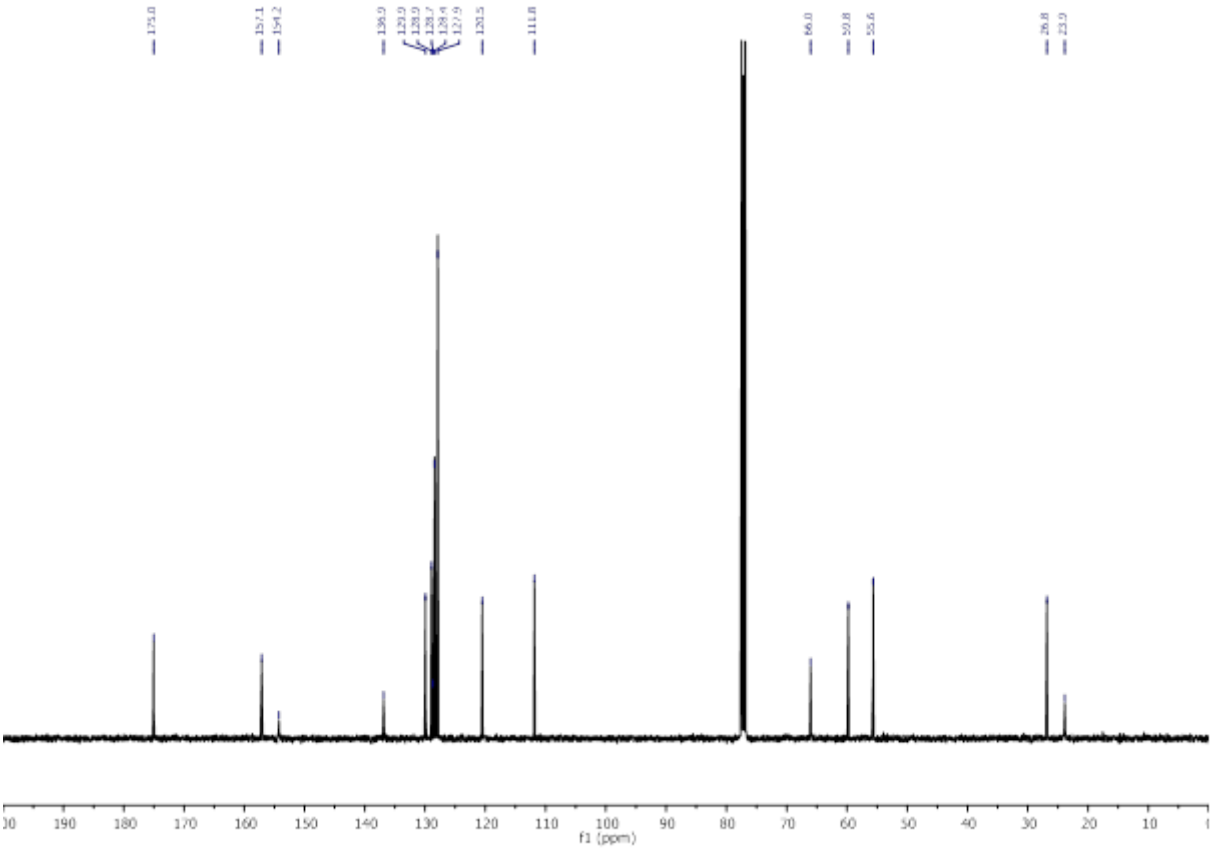
^{1}H NMR of Cbz-(aMe)PhgOMe



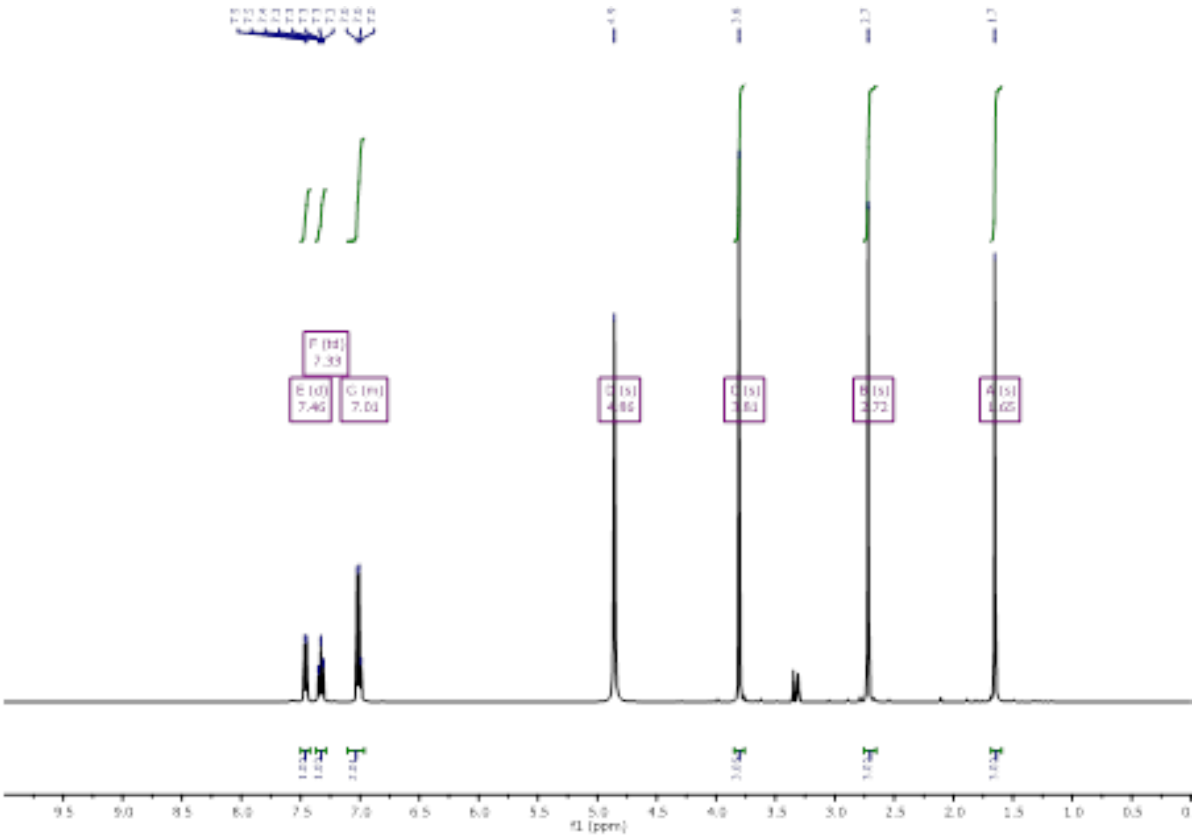
^{13}C NMR of Cbz-(aMe)PhgOMe



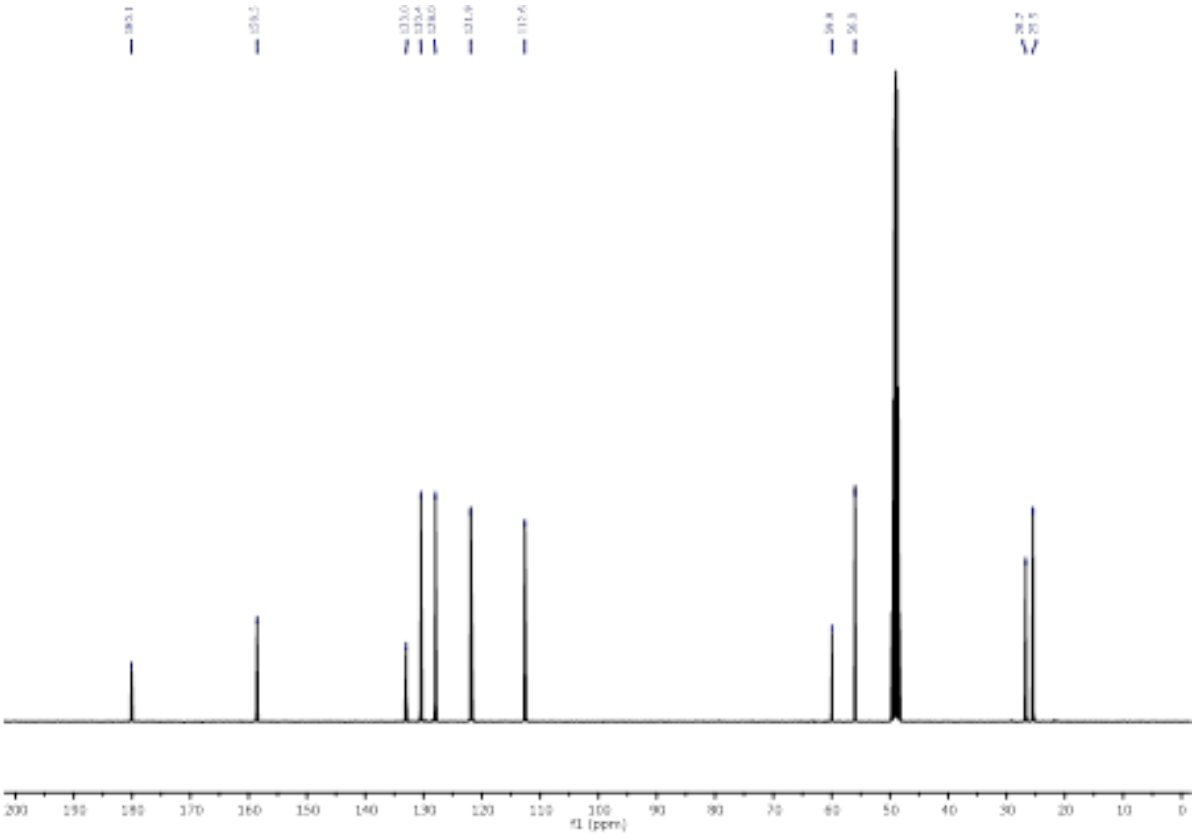
^{1}H NMR of Cbz*(o*-MeOPh)AlaNHMe



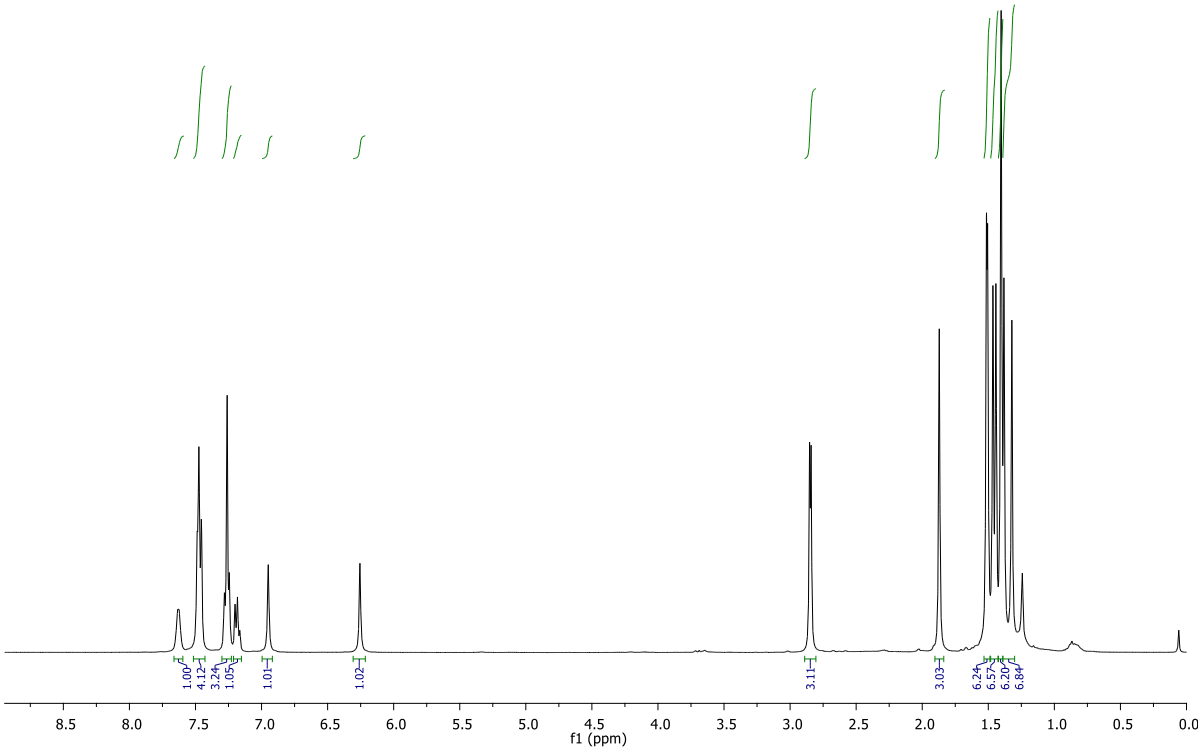
^{13}C NMR of Cbz*(o*-MeOPh)AlaNHMe



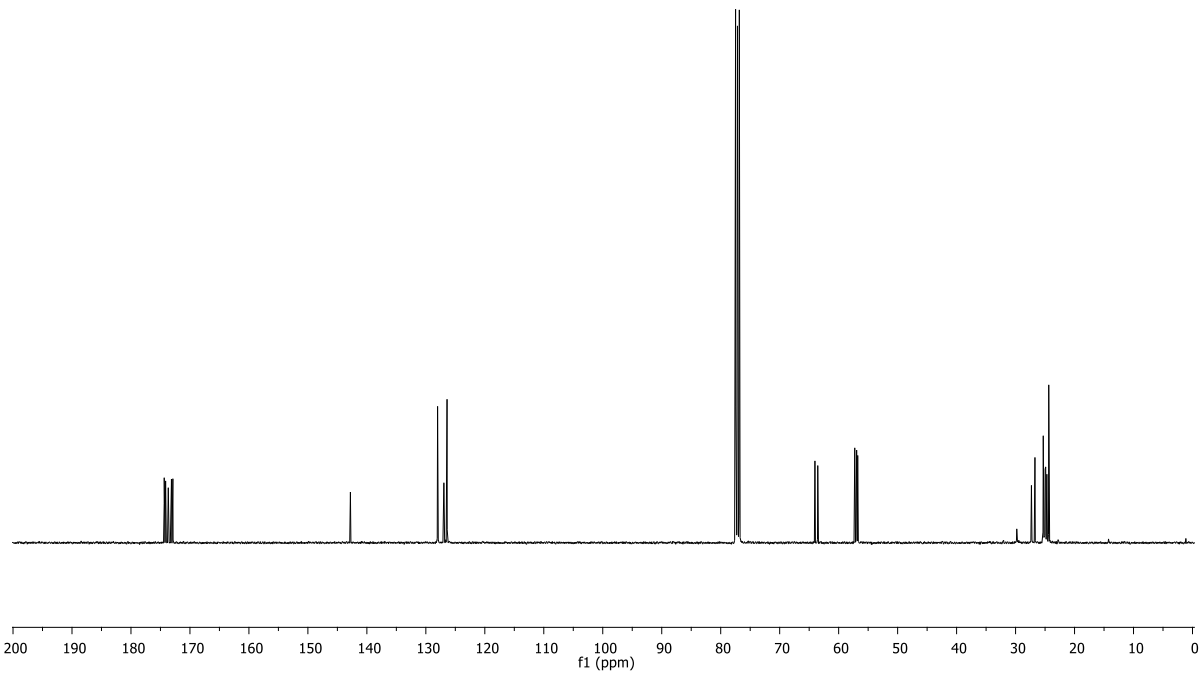
^{1}H NMR of 6b



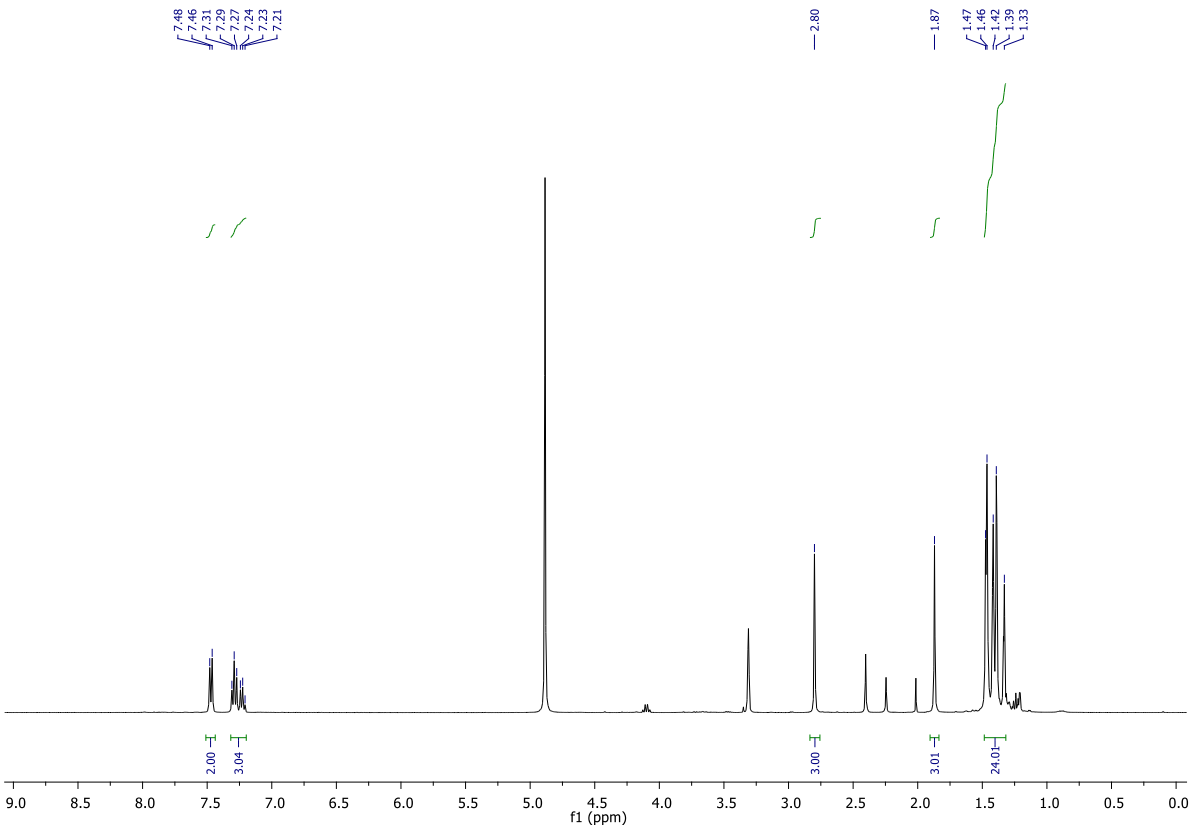
^{13}C NMR of 6b



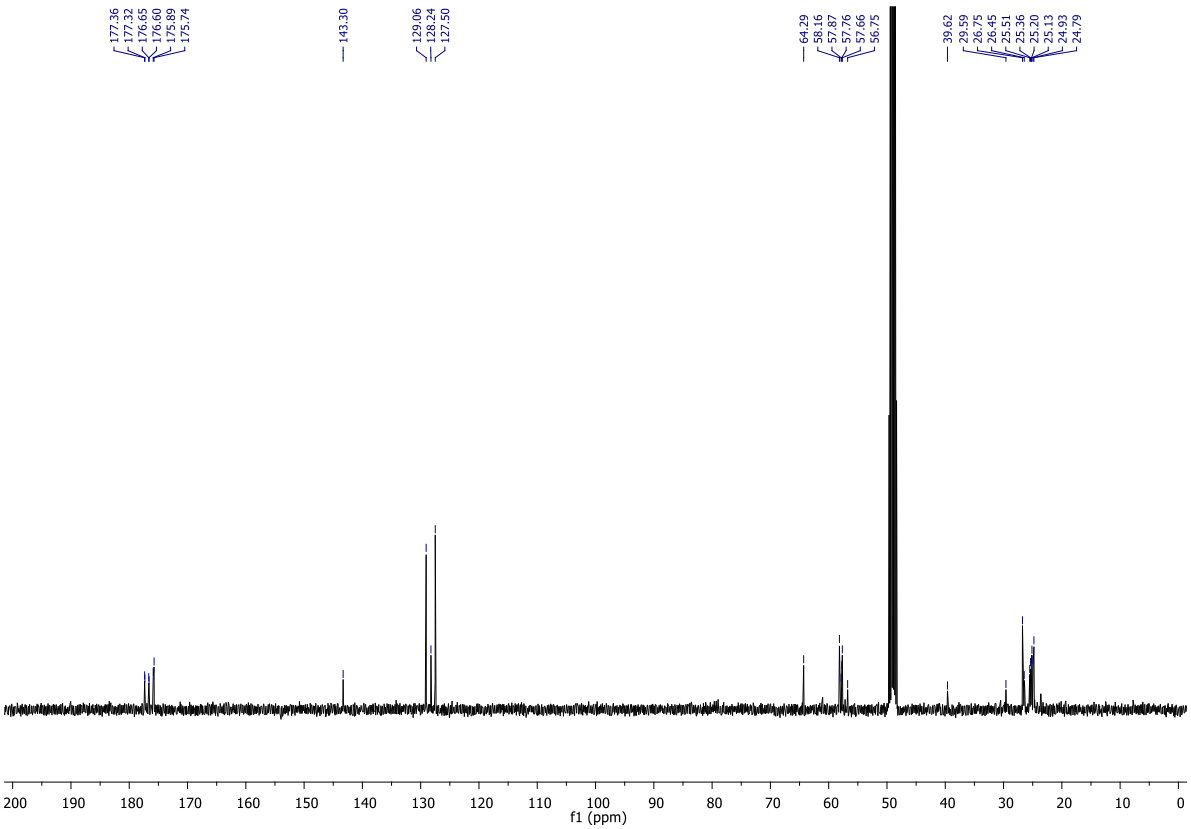
^{1}H NMR of $N_3Aib_4(\alpha Me)PhgNHMe$



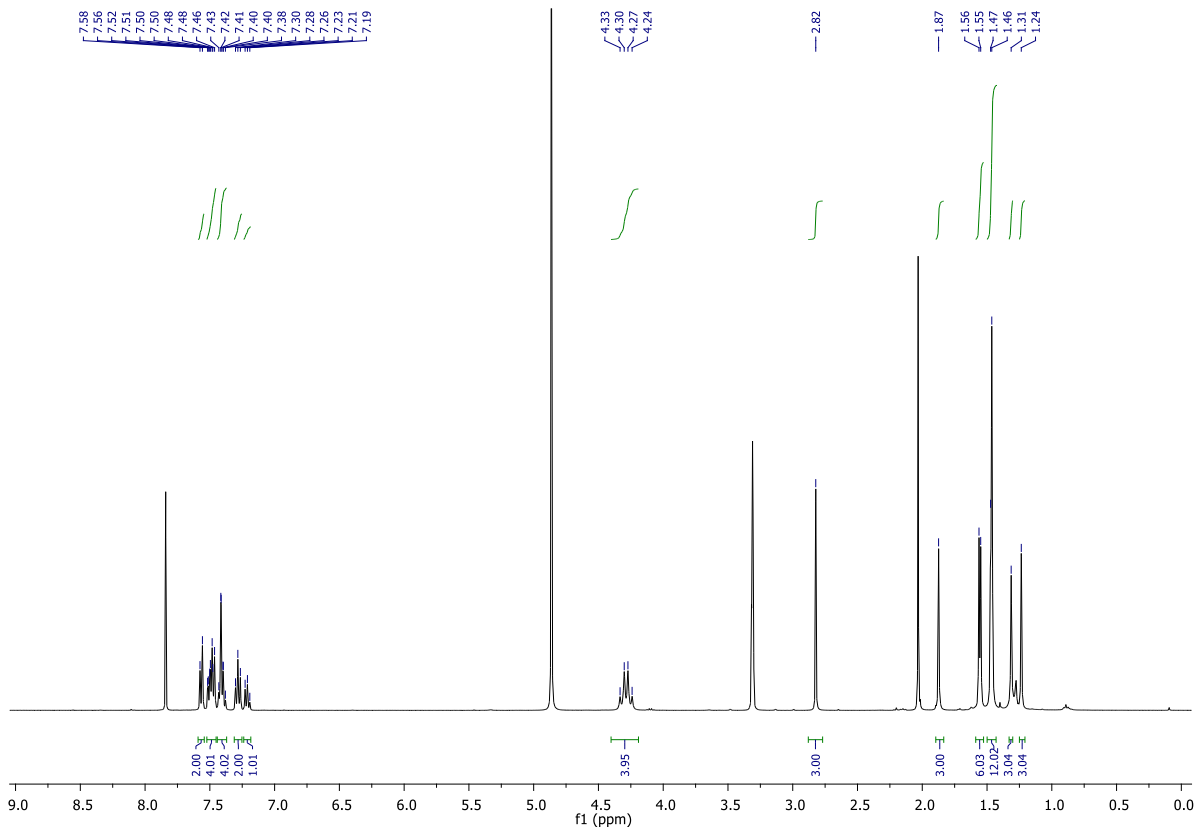
^{13}C NMR of $N_3Aib_4(\alpha Me)PhgNHMe$



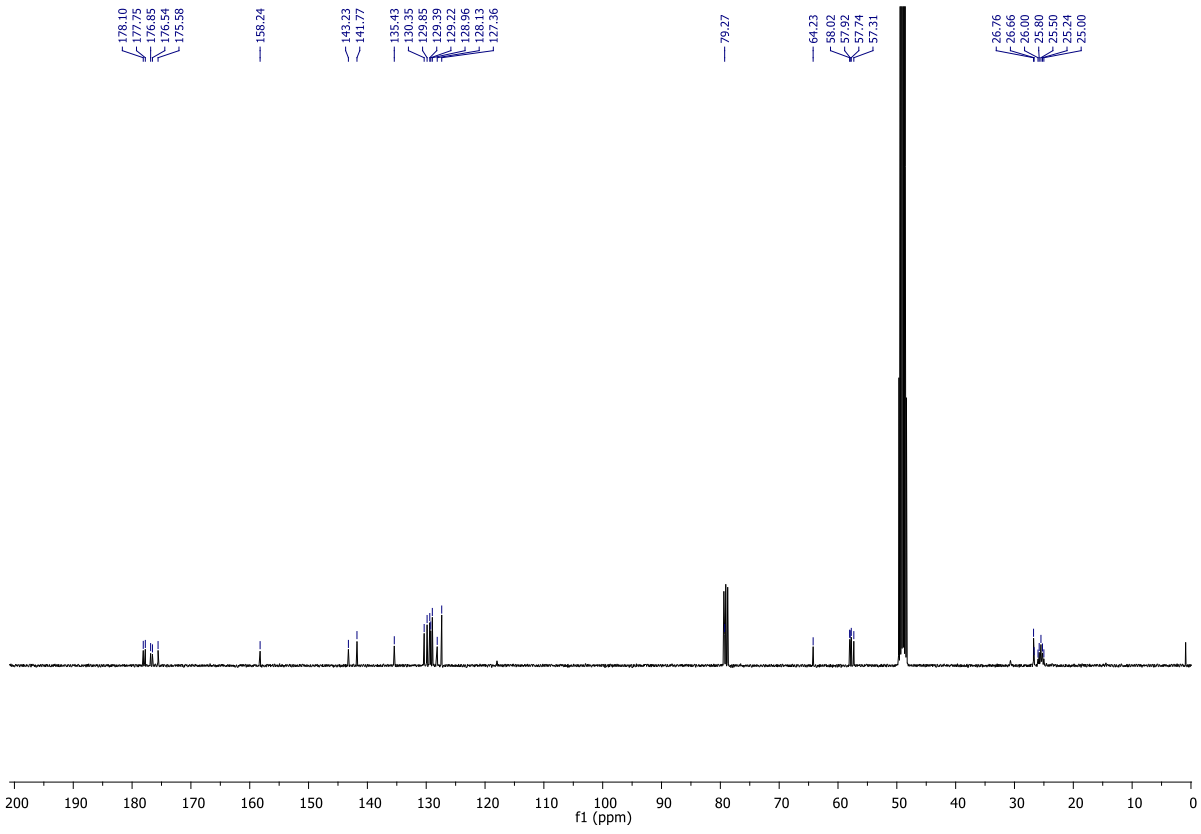
^{1}H NMR of 8a



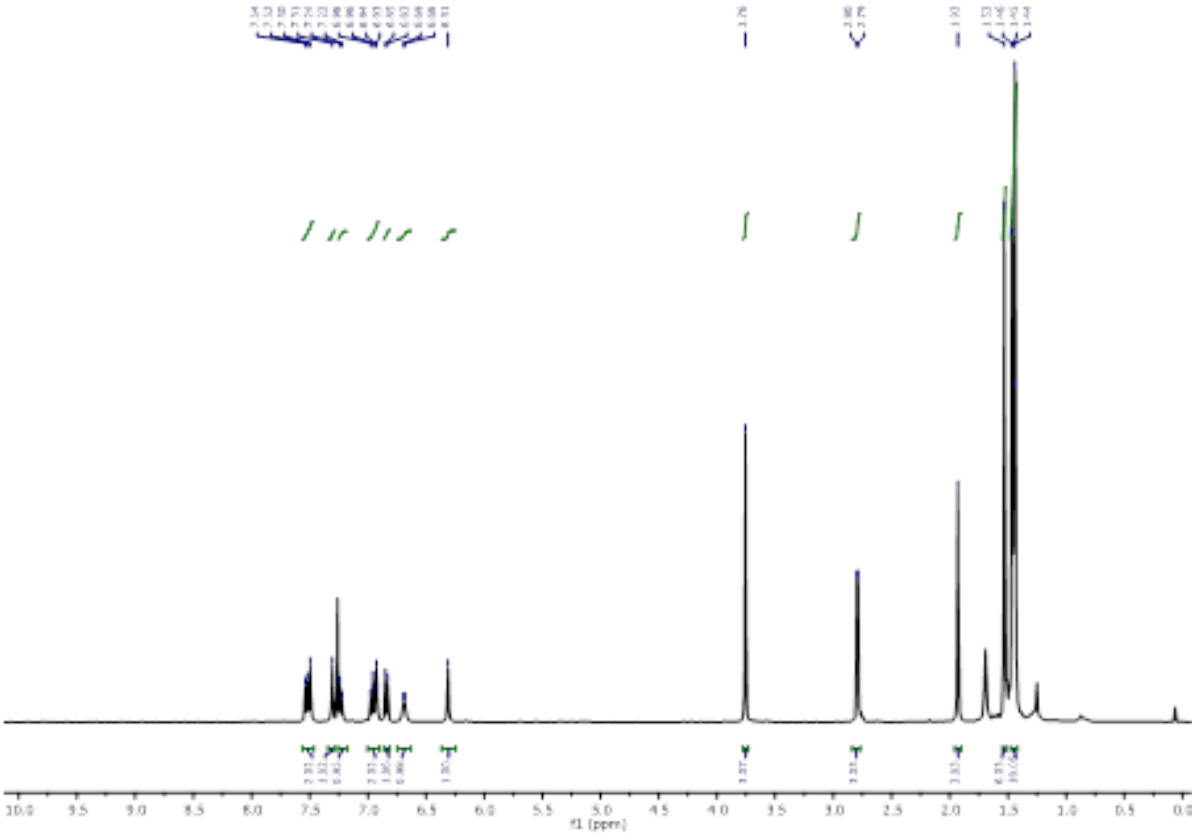
^{13}C NMR of 8a



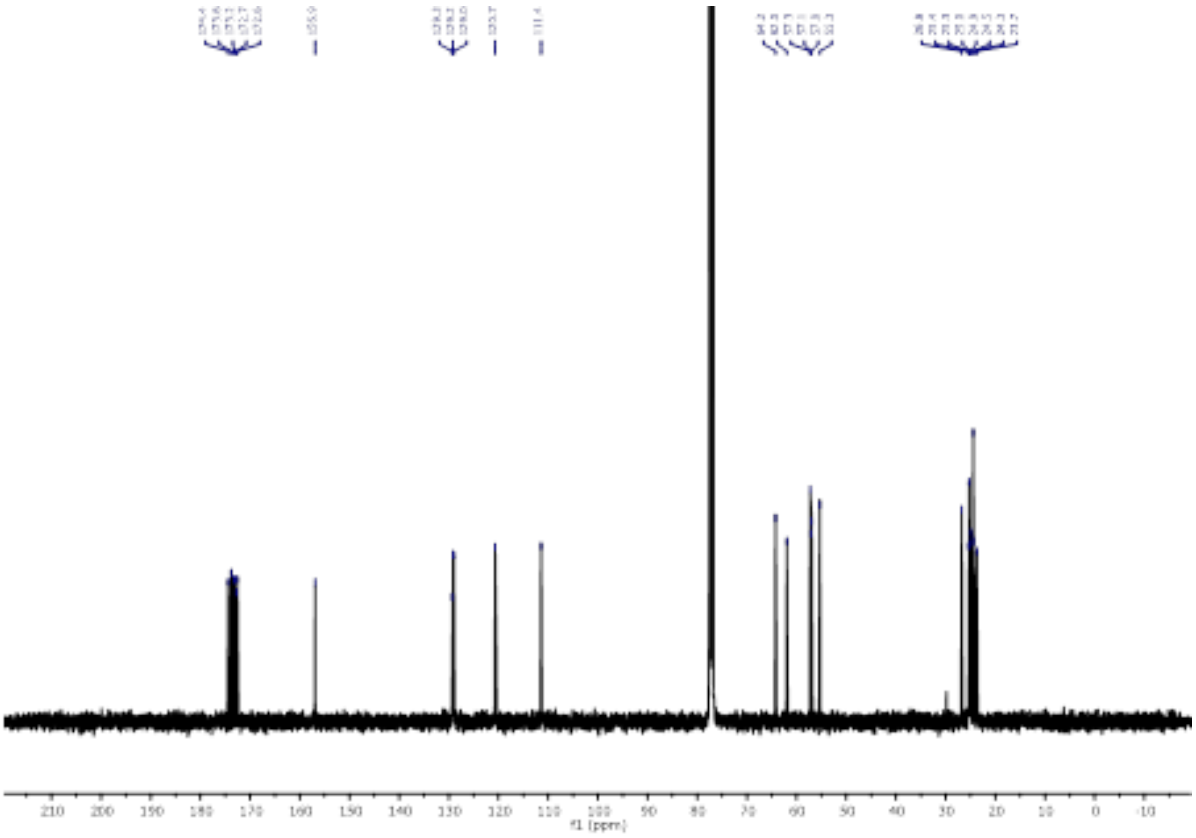
^{1}H NMR of 9a



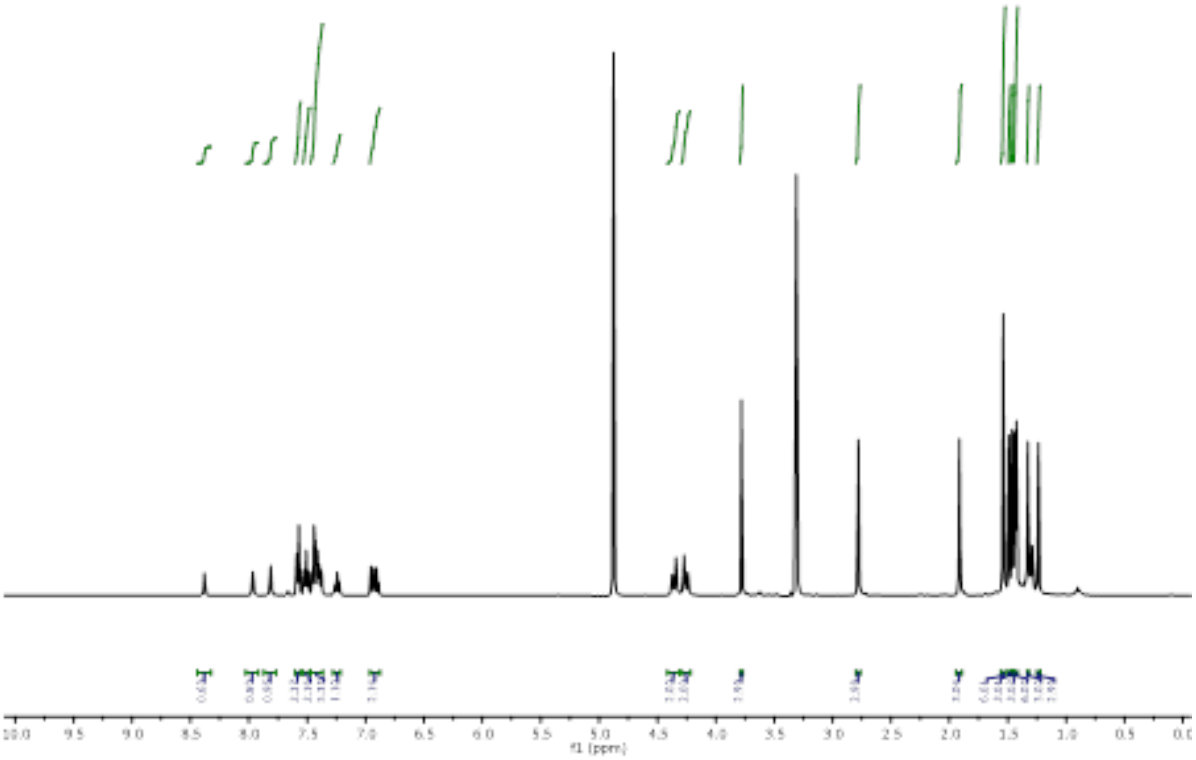
^{13}C NMR of 9a



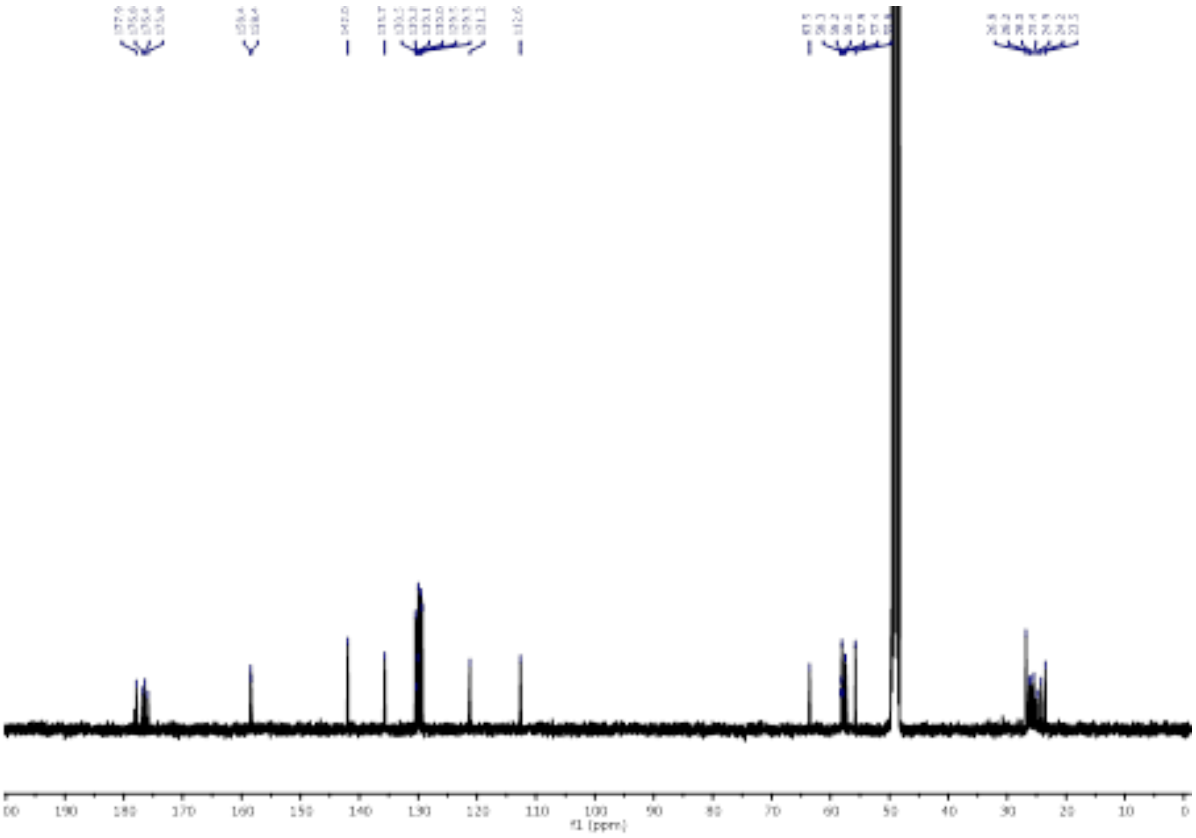
^{1}H NMR of N_3Aib_4(o-MeOPh)AlaNHMe



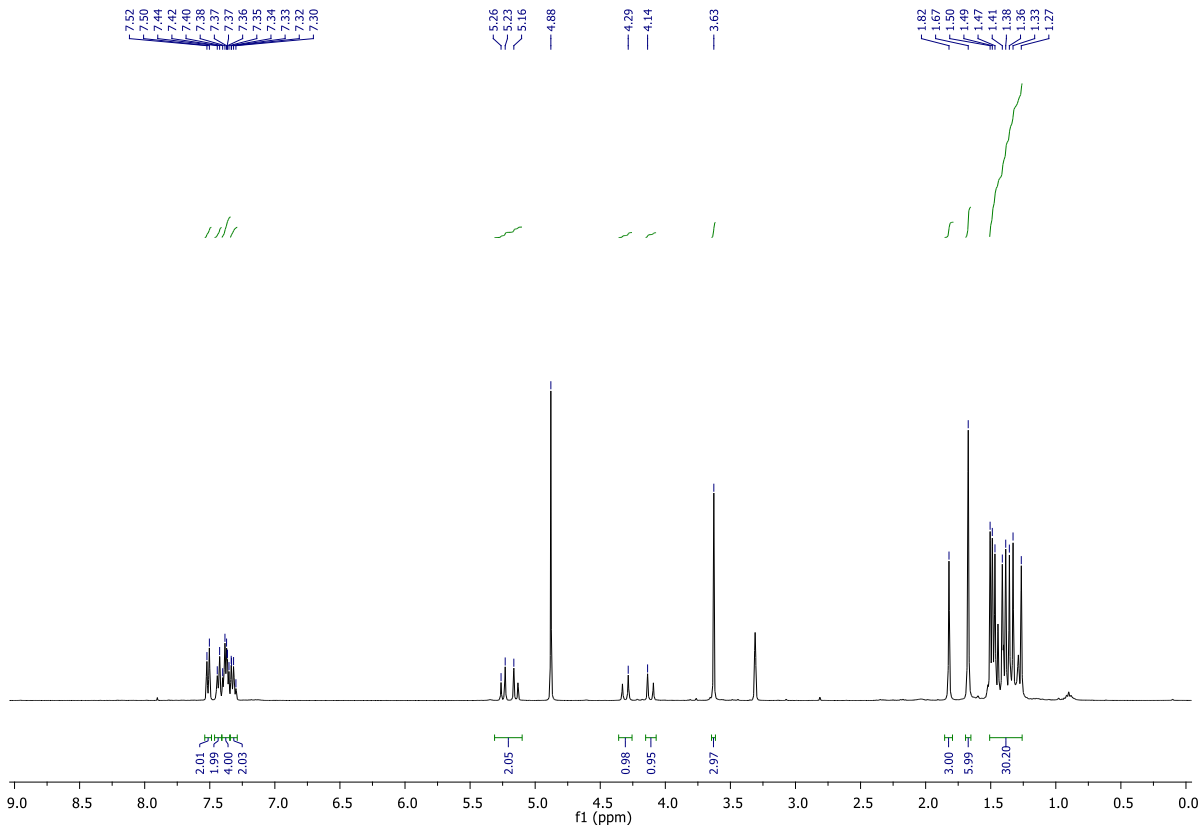
^{13}C NMR of N_3Aib_4(o-MeOPh)AlaNHMe



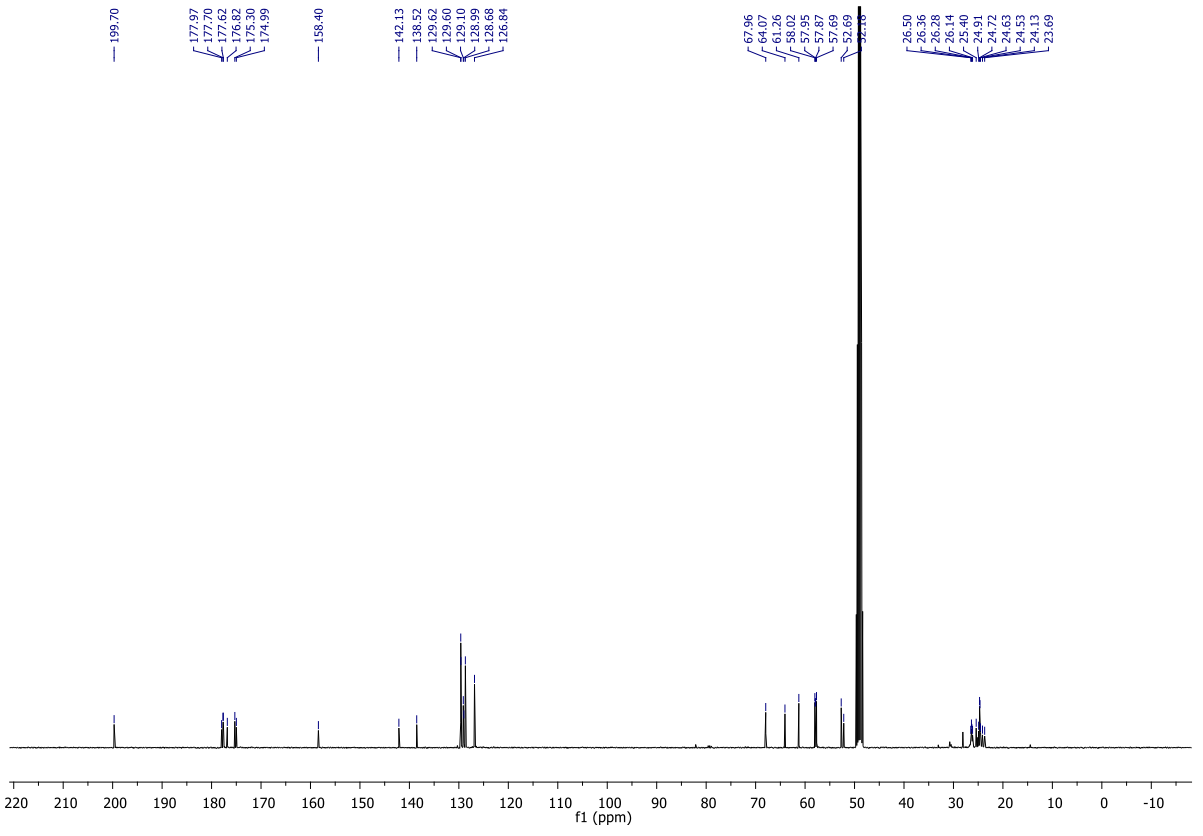
^{1}H NMR of 9b



^{13}C NMR of 9a



^{1}H NMR of 10



^{13}C NMR of 10