

Supporting Information

Reactive Deep Eutectic Solvents for EDC-mediated Amide Synthesis

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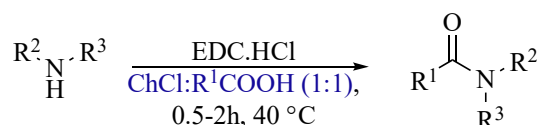
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1.	<i>General information</i>	2
2.	<i>General procedure: amide synthesis in RDES</i>	2
3.	<i>Characterization data of products</i>	3
4.	<i>References</i>	10
5.	<i>NMR spectra of the products</i>	12
6.	<i>E-Factor and PMI calculation</i>	41

1. General information

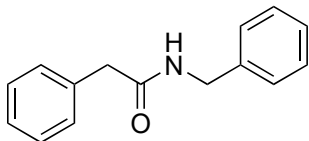
All starting materials were purchased from Aldrich (Merck) and used without further purification unless stated otherwise. Thin layer chromatography (TLC) was carried out on Schleicher&Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV254 light. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP- 5000 spectrometer, giving fragment ions in m/z with relative intensities (%) in parentheses. ^1H NMR (300 MHz) spectra were recorded on Bruker AC-300 NMR spectrometers respectively in proton coupled mode. ^{13}C NMR (75.5 MHz) spectra were recorded on Bruker AC-300 NMR spectrometer respectively in proton decoupled mode at 20 °C. Chemical shifts are given in δ (parts per million) and coupling constants (J) in Hertz. HPLC analysis were performed to determine the ee % value (DIACEL Chiralcel OD-H, n-hexane:2-propanol = 90:10 (1 mL/min), t_r = 13.4 min (R) and t_r = 18.1 min (S), 99 % ee, S-enantiomer).

2. General procedure: amide synthesis in RDES



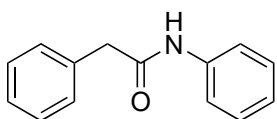
The different RDESs were prepared by mixing choline chloride and the carboxylic acid (benzoic, phenyl acetic or 4-hydroxyphenylacetic acid) in a round-bottom flask under inert atmosphere in a 1:1 molar ratio. The resulting mixture was magnetically stirred at 60-80 °C, until a clear liquid was observed. The obtained DESs were directly used without further purification. In a typical procedure, 1mmol of the coupling reagent was added to a ChCl: carboxylic acid (1:1)-based RDES. After stirring at 50°C for 10-15 minutes, the amine was added in equimolar ratio and the resulting mixture was vigorously stirred at the given temperature for an additional time (30-60 min). The progress of the reaction was monitored by TLC and GC/MS analysis. Upon completion, 2 mL of H_2O were added. The resulting aqueous suspension was then extracted with ethyl acetate (3×2 mL). The organic phases were dried over sodium sulphate, followed by evaporation under reduced pressure to give the corresponding amides. The reaction conversions were determined by GC/MS analysis. Spectral data were in accordance with the literature (See ESI).

3. Characterization data of products



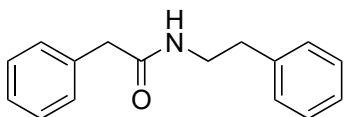
N-Benzyl-2-phenylacetamide (3a) White solid, yield 96%; ¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.18 (m, 10H), 5.86 (brs, 1H), 4.42 (d, J = 5.8 Hz, 2H), 3.64 (s, 2H) ppm; ¹³C NMR (75 MHz, CDCl₃) 171.0, 138.0, 134.6, 129.4, 129.0, 128.6, 127.4, 126.5, 43.7, 43.5 ppm. **EIMS m/z (%):** 225 (M⁺, 30), 91 (100), 77 (5), 65 (15)

The characterization data of the compound **3a** matched previous reports^{S1}.



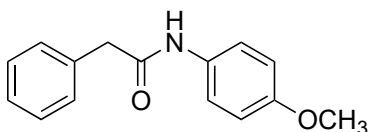
N,2-Diphenylacetamide (3b) White solid, yield 93%; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (s, 1H), 7.50 – 7.02 (m, 10H), 3.67 (d, J = 6.7 Hz, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) 169.6, 137.9, 134.7, 129.7, 129.3, 129.1, 128.9, 127.7, 127.3, 120.4, 44.6 ppm. **EIMS m/z (%):** 211 (M⁺, 80%), 119 (1), 93 (100), 77 (14), 65 (36)

The characterization data of the compound **3b** matched previous reports^{S2}.



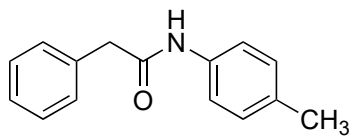
N-Phenethyl-2-phenylacetamide (3c) White solid, yield 97%; ¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.09 (m, 8H), 7.09 – 6.87 (m, 2H), 5.56 (s, 1H), 3.49 (s, 2H), 3.41 (q, J = 6.5 Hz, 2H), 2.70 (q, J = 6.9 Hz, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) 171.0, 138.7, 134.8, 130.3, 129.5, 128.7, 127.9, 127.1, 126.4, 43.9, 40.7, 35.5 ppm. **EIMS m/z (%):** 239 (M⁺, 54), 148 (13), 120 (9), 104 (69), 91 (100), 77 (11), 65 (23)

The characterization data of the compound **3c** matched previous reports^{S3}.



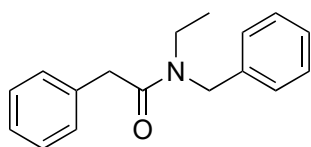
N-(4-Methoxyphenyl)-2-phenylacetamide (3d) White solid, yield 88%; ¹H NMR (300 MHz, CDCl₃) δ 7.48 – 7.21 (m, 7H), 7.04 (s, 1H), 6.90 – 6.71 (m, 2H), 3.79 (s, 3H), 3.75 (s, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) 168.9, 156.6, 134.6, 130.7, 129.2, 128.6, 127.6, 117.0, 114.9, 56.6, 44.7 ppm. **EIMS m/z (%):** 241 (M⁺, 82), 149 (10), 123 (100), 108 (57), 91 (50), 80 (7), 65 (16)

The characterization data of the compound **3d** matched previous reports^{S4}.



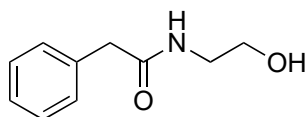
2-Phenyl-N-(p-tolyl)acetamide (3e) White solid, yield 91%; ¹H NMR (300 MHz, CDCl₃) δ 7.91 (s, 1H), 7.35 (td, J = 7.4, 3.8 Hz, 7H), 7.09 (d, J = 8.0 Hz, 2H), 3.67 (s, 2H), 2.32 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) 169.6, 135.2, 134.0, 129.7, 129.4, 128.8, 127.6, 127.2, 120.6, 44.8, 20.9 ppm. EIMS m/z (%): 225 (M⁺)

The characterization data of the compound **3e** matched previous reports^{S4}



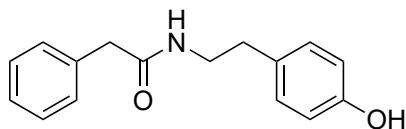
N-Benzyl-N-ethyl-2-phenylacetamide (3f) White solid, yield 78%; ¹H NMR (300 MHz, CDCl₃) δ 7.41 – 7.09 (m, 10H), 4.60 & 4.46 (2 singlets, rotamers, 2H), 3.77 & 3.67 (2 singlets, rotamers, 2H), 3.41 & 3.25 (2 quadruplets, rotamers, J = 7.2 Hz, 2H), 1.17 – 0.95 (m, rotamers, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃, mixture of two rotamers 1:1) δ 171.1, 170.9, 137.8, 136.9, 135.3, 129.0, 128.9, 128.7, 127.6, 127.9, 127.4, 127.1, 126.7, 50.9, 47.7, 43.4, 42.9, 42.2, 41.9, 13.6, 12.7 ppm. EIMS m/z (%): 253 (M⁺, 39), 162 (4), 106 (12), 91 (100), 65 (13)

The characterization data of the compound **3f** matched previous reports^{S2}



N-(2-Hydroxyethyl)-2-phenylacetamide (3g) White solid, yield 84%; ¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.11 (m, 5H), 5.54 (s, 1H), 4.25 – 4.01 (m, 1H), 3.55 – 3.40 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) 171.6, 135.3, 129.4, 129.0, 128.7, 127.4, 63.3, 43.7, 41.2 ppm. EIMS m/z (%): 162 (M⁺, 16%), 118 (28), 91 (100), 77 (5), 65 (13).

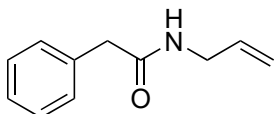
The characterization data of the compound **3g** matched previous reports^{S5}



N-(4-Hydroxyphenethyl)-2-phenylacetamide (3h): White solid, yield 89%; ¹H NMR (300 MHz, CDCl₃) δ 7.38 – 7.31 (m, 3H), 5.18 (d, J = 9 Hz, 2H), 6.91 (d, J = 6 Hz, 2H), 6.74 (d, 6 Hz, 2H), 5.40 (brs, 1H), 3.56 (s, 2H), 3.45 (q, 2H), 2.66 (t, J = 6 Hz, 2H) ppm. ¹³C NMR (75 MHz, DMSO-d₆) 170.4,

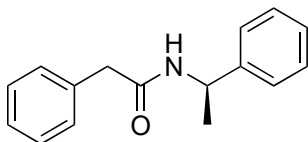
156.1, 136.9, 129.9, 129.5, 128.8, 128.5, 127.7, 116.5, 42.9, 40.5 ppm. **EIMS m/z (%)**: 255 (M^+ , 2%), 136 (13), 120 (100), 105 (20), 91 (48), 77 (12), 65 (10), 51 (4).

The characterization data of the compound **3h** matched previous reports^{S6}



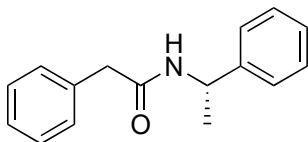
N-Allyl-2-phenylacetamide (3i): White solid, yield 83%; ¹H NMR (300 MHz, CDCl₃) δ 7.44 – 7.21 (m, 5H), 5.78 (ddt, J = 16.8, 10.8, 5.5 Hz, 1H), 5.54 (s, 1H), 5.10 – 4.99 (m, 2H), 3.86 (tt, J = 5.6, 1.6 Hz, 2H), 3.62 (s, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) 170.8, 138.6, 134.8, 134.0, 129.6, 127.5, 116.9, 43.8, 43.4 ppm. **EIMS m/z (%)**: 175 (M^+ , 18%), 118 (5), 91 (100), 84 (13), 77 (2), 65 (25), 57 (24), 51 (5), 41 (43).

The characterization data of the compound **3i** matched previous reports^{S7}



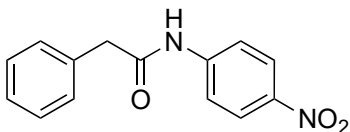
(R)-2-Phenyl-N-(1-phenylethyl)acetamide (3j) White solid, yield 91%; ¹H NMR (300 MHz, CDCl₃) δ 7.48 – 7.04 (m, 10H), 5.62 (s, 1H), 5.14 (p, J = 7.1 Hz, 1H), 3.61 (s, 2H), 1.42 (dd, J = 6.9, 0.6 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) 170.0, 143.0, 135.7, 129.4, 128.6, 127.4, 127.3, 125.9, 53.8, 46.1, 21.8 ppm. **EIMS m/z (%)**: 239 (M^+ , 34%), 224 (2), 120 (5), 105 (100), 91 (24), 77 (13), 65 (9), 51 (5).

The characterization data of the compound **3j** matched previous reports^{S8}



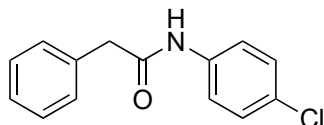
(S)-2-phenyl-N-(1-phenylethyl)acetamide (3k) White solid, yield 93%. ¹H NMR (300 MHz, CDCl₃) δ 7.48 – 7.18 (m, 10H), 5.67 (s, 1H), 5.15 (p, J = 7.1 Hz, 1H), 3.60 (s, 2H), 1.42 (d, J = 6.9 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) 170.0, 143.0, 134.9, 129.3, 129.0, 128.6, 127.4, 125.9, 48.7, 43.9, 21.7 ppm. **EIMS m/z (%)**: 239 (M^+ , 34%), 224 (3), 120 (7), 105 (100), 91 (21), 77 (13), 65 (10), 51 (5).

The characterization data of the compound **3k** matched previous reports^{S8}



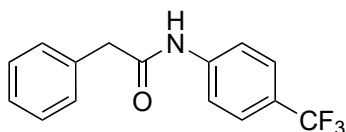
N-(4-nitrophenyl)-2-phenylacetamide (3l) Yellow solid, 69% yield. mixture of tautomers (85 % amidic tautomer + 15 % enamidic tautomer) $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 10.81 (brs, 1H), 8.20 (d, $J=9$ Hz, 2H, enamidic tautomer), 7.96 (d, $J=9$ Hz, 9H, amidic tautomer), 7.86 (d, $J=9$ Hz, 2H, enamidic tautomer), 7.20 (m, 10 H, amidic + enamidic tautomers), 6.71 (s, 1H), 6.63 (d, $J=9$ Hz, 10H, amidic tautomer), 3.75 (s, 2H, amidic tautomer), 3.65 (s, 1H, enamidic tautomer) ppm. $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) 170.7, 169.8, 156.2, 145.9, 142.7, 136.7, 136.2, 135.8, 129.5, 129.1, 126.6, 126.4, 119.7 ppm. **EIMS m/z (%)**: 256 (M^+ , 22%), 226 (10), 165 (6), 118 (60), 91 (100), 65 (17), 51 (4), 39 (7).

The characterization data of the compound **3l** matched previous reports^{S8}



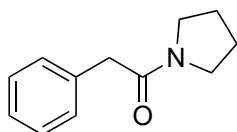
N-(4-chlorophenyl)-2-phenylacetamide (3m) White solid, 81% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.40-7.22 (m, 9H), 4.78 (brs, 1 H), 3.72 (s, 2 H) ppm. $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 169.3, 136.2, 134.2, 129.7, 129.4, 128.9, 127.9, 122.2, 121.3, 44.6 ppm. **EIMS m/z (%)**: 245 (M^+ , 60%), 247 (12), 153 (15), 127 (92), 118 (51), 91 (100), 65 (18), 51 (4), 39 (8).

The characterization data of the compound **3m** matched previous reports^{S8}



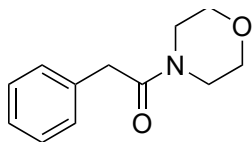
2-phenyl-N-(4-(trifluoromethyl)phenyl)acetamide (3n) White solid, 74% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.58-7.10 (m, 9H), 5.31 (brs, 1H), 3.77 (s, 2H) ppm. $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 181.0, 140.7, 133.9, 127.6, 126.7, 125.7, 124.9, 120.6, 119.8, 44.8 ppm. **EIMS m/z (%)**: 279 (M^+ , 18%), 260 (6), 161 (20), 118 (58), 91 (100), 75 (7), 65 (24), 51 (8), 39 (18).

The characterization data of the compound **3n** matched previous reports^{S8}



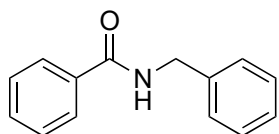
2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one (3o) White solid, 63% yield. mixture of conformers (18:83) at 25°C $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.17-7.09 (m, 5H), 3.51 (s, 2H), 3.36-3.25 (m, 4H), 1.78-1.76 (m, 4H), 1.01-0.92 (m, 1H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 170.0, 169.4, 135.3, 134.7, 130.0, 129.6, 128.9, 128.6, 127.9, 127.4, 126.6, 126.4, 45.7, 44.8, 43.1, 42.7, 25.9, 24.1 ppm

The characterization data of the compound **3o** matched previous reports^{S8}



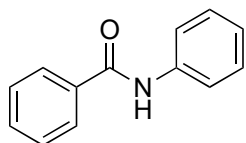
1-morpholino-2-phenylethan-1-one (3p) White solid, 68% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.76-7.07 (m, 5H), 3.57 (s, 2H), 3.47 (m, 4H), 3.30-3.26 (m, 4H) ppm. $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 169.4, 134.6, 129.4, 129.2, 128.4, 127.7, 127.4, 126.7, 66.5, 66.3, 46.3, 45.3, 42.1, 41.6 ppm. **EIMS m/z (%)**: 205 (M^+ , 40%), 190 (6), 114 (100), 91 (40), 86 (15), 70 (38), 65 (12), 56 (14), 42 (8), 29 (5).

The characterization data of the compound **3p** matched previous reports^{S8}



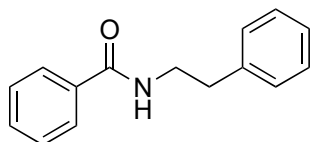
N-Benzylbenzamide (4a) White solid, yield 81%; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.84 – 7.68 (m, 2H), 7.52 – 7.18 (m, 8H), 6.68 (s, 1H), 4.59 (d, $J = 5.6$ Hz, 2H) ppm. $^{13}\text{C NMR}$ (300 MHz, CDCl_3): 167.5, 137.8, 134.3, 131.8, 128.8, 128.1, 127.5, 126.6 ppm. **EIMS m/z (%)**: 211 (M^+ , 69%), 105 (100), 91 (14), 77 (62), 65 (10), 51 (23).

The characterization data of the compound **4a** matched previous reports^{S1}



N-Phenylbenzamide (4b) White solid, yield 76%; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.91 – 7.80 (m, 2H), 7.53 (t, $J = 7.7$ Hz, 3H), 7.45 (t, $J = 7.2$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 2.35 (s, 3H) ppm. $^{13}\text{C NMR}$ (300 MHz, CDCl_3) δ 165.85, 137.94, 135.00, 131.85, 129.11, 128.79, 127.05, 124.60, 120.28 ppm. **EIMS m/z (%)**: 197 (M^+ , 39), 105 (100), 77 (63).

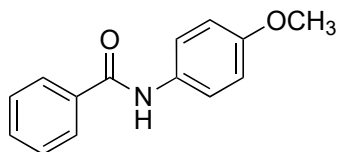
The characterization data of the compound **4b** matched previous reports^{S3}



N-Phenethylbenzamide (4c) White solid, yield 83%; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.69 (d, $J = 7.5$ Hz, 2H), 7.44 (t, $J = 7.3$ Hz, 1H), 7.37 (d, $J = 7.3$ Hz, 2H), 7.28 (d, $J = 7.1$ Hz, 2H), 7.21 (d, $J = 15.9$ Hz, 3H), 6.51 (t, $J = 6.2$ Hz, 1H), 3.66 (q, $J = 6.6$ Hz, 2H), 2.89 (t, $J = 7.0$ Hz, 2H) ppm. $^{13}\text{C NMR}$ (75 MHz,

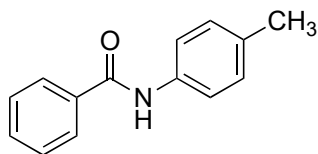
CDCl₃): δ 167.6, 138.9, 134.6, 131.2, 128.9, 128.8, 127.9, 127.7, 126.5 ppm. **EIMS m/z (%)**: 225 (M⁺, 41%), 134 (15), 105 (100), 91 (7), 77 (46), 65 (5), 51(12).

The characterization data of the compound **4c** matched previous reports^{S1}



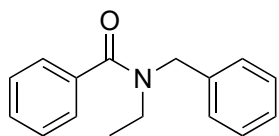
N-(4-Methoxyphenyl)benzamide (4d) White solid, yield 74%; **¹H NMR** (300 MHz, CDCl₃) δ 7.82 (d, J = 7.4 Hz, 2H), 7.73 (s, 1H), 7.47 (dd, J = 16.7, 8.0 Hz, 5H), 6.96 – 6.76 (m, 2H), 3.77 (d, J = 2.3 Hz, 3H) ppm. **¹³C NMR** (75 MHz, CDCl₃): δ 165.6, 158.6, 135.0, 131.5, 128.6, 127.4, 122.5, 121.9, 114.3, 55.9 ppm. **EIMS m/z (%)**: 227 (M⁺, 60%), 105 (100), 77 (53), 65 (1), 51 (10).

The characterization data of the compound **4d** matched previous reports^{S2}



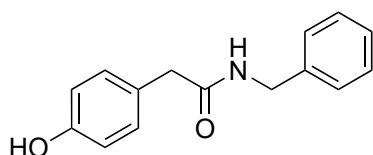
N-(p-Tolyl)benzamide (4e) White solid, yield 88%; **¹H NMR** (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.91 – 7.80 (m, 2H), 7.53 (t, J = 7.7 Hz, 3H), 7.45 (t, J = 7.2 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H) ppm. **¹³C NMR** (300 MHz, CDCl₃) δ 165.89, 135.41, 135.05, 134.47, 134.22, 131.70, 129.55, 129.04, 128.70, 128.16, 127.09, 120.48, 29.73, 20.95. **MS** (70 eV, EI): m/z (%): 211 (M⁺, 41), 105 (100), 77 (45) ppm. **EIMS m/z (%)**: 211 (M⁺, 44%), 105 (100), 77 (57), 65 (1), 51 (13).

The characterization data of the compound **4e** matched previous reports^{S1}



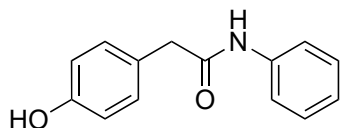
N-Benzyl-N-ethylbenzamide (4f) White solid, yield 56%; **¹H NMR** (300 MHz, CDCl₃) δ 7.32 (ddt, J = 26.3, 12.6, 5.9 Hz, 20H), 4.87 – 4.24 (2 singlets, rotamers 2H), 3.76 – 3.65 & 3.26 & 3.05 (2 multiplets, rotamers 2H), 1.21 – 1.00 (m, rotamers. 3H) ppm. **EIMS m/z (%)**: 329 (M⁺, 41%), 105 (100), 91 (16), 77 (40).

The characterization data of the compound **4f** matched previous reports^{S9}



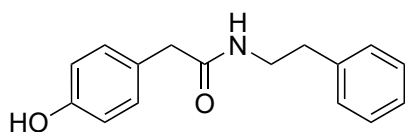
N-Benzyl-2-(4-hydroxyphenyl)acetamide (5a) White solid, yield 80%; $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 9.22 (s, 1H), 7.22 (d, $J = 7.9$ Hz, 4H), 7.10 – 7.02 (m, 3H), 6.71 – 6.65 (m, 2H), 4.26 (d, $J = 5.6$ Hz, 3H), 3.51 (d, $J = 8.9$ Hz, 2H) ppm. $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 171.0, 156.3, 140.2, 130.4, 129.6, 128.9, 128.5, 127.7, 121.8, 115.5, 42.6, 42.0 ppm. **EIMS m/z (%)**: 241 (M^+ , 33%), 147 (4), 107 (100), 91 (56), 77 (22), 65 (9), 51 (6).

The characterization data of the compound **5a** matched previous reports^{S10}



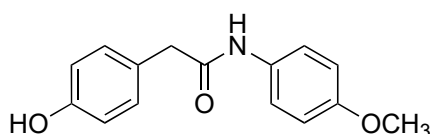
2-(4-Hydroxyphenyl)-N-phenylacetamide (5b) White solid, yield 74%; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.38 (d, $J = 8.2$ Hz, 2H), 7.33 – 7.18 (m, 4H), 7.19 – 7.08 (m, 2H), 6.78 (dd, $J = 8.3, 3.8$ Hz, 2H), 3.60 (d, $J = 11.4$ Hz, 2H) ppm. $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.0, 155.7, 138.7, 130.8, 129.8, 128.8, 124.6, 122.2, 120.1, 116.2, 43.9 ppm. **EIMS m/z (%)**: 227 (M^+ , 52), 134 (43), 107 (100), 93 (67), 77 (44), 51 (13).

The characterization data of the compound **5b** matched previous reports^{S11}



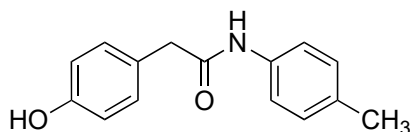
2-(4-Hydroxyphenyl)-N-phenethylacetamide (5c) White solid, yield 61%; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.31 – 7.17 (m, 4H), 7.10 – 7.02 (m, 2H), 6.98 (d, $J = 8.3$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.76 (d, $J = 6.0$ Hz, 1H), 3.47 (d, $J = 6.0$ Hz, 4H), 2.73 (t, $J = 6.9$ Hz, 2H) ppm. $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 172.6, 156.2, 138.3, 131.3, 129.7, 128.6, 127.8, 126.5, 116.6, 42.6, 41.8, 35.3 ppm. **EIMS m/z (%)**: 255 (M^+ , 29), 207 (3), 151 (16), 136 (14), 107 (100), 91 (15), 77 (19), 51 (5).

The characterization data of the compound **5c** matched previous reports^{S11}



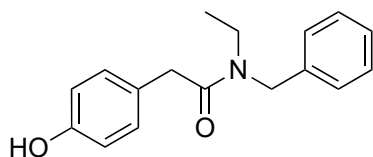
2-(4-Hydroxyphenyl)-N-(4-methoxyphenyl)acetamide (5d) White solid, yield 74%; $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 10.04 (s, 1H), 9.93 (s, 2H), 9.29 (s, 3H), 7.51 (d, $J = 8.5$ Hz, 7H), 7.17 – 6.98 (m, 13H), 6.87 (d, $J = 8.5$ Hz, 6H), 6.74 (dd, $J = 12.7, 8.1$ Hz, 9H), 3.98 (s, 2H), 3.81 (s, 5H), 3.71 (s, 12H), 3.60 (d, $J = 12.4$ Hz, 5H), 3.47 (s, 7H) ppm. $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 170.9, 159.1, 155.6, 132.0, 130.9, 129.6, 121.8, 116.2, 114.1, 55.7, 43.7 ppm. **EIMS m/z (%)**: 257 (M^+ , 66%), 207 (3), 149 (13), 123 (100), 107 (72), 92 (7), 77 (25), 52 (10).

The characterization data of the compound **5d** matched previous reports^{S11}



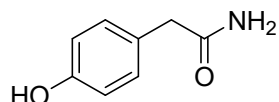
2-(4-Hydroxyphenyl)-N-(p-tolyl)acetamide (5e) White solid, yield 58%; $^1\text{H NMR}$ (300 MHz, DMSO-d₆) δ 9.95 (s, 1H), 9.24 (s, 1H), 7.48 (d, $J = 8.0$ Hz, 3H), 7.21 – 6.98 (m, 6H), 6.74 (t, $J = 10.4$ Hz, 3H), 3.49 (s, 3H), 2.24 (s, 4H) ppm. $^{13}\text{C NMR}$ (75 MHz, DMSO-d₆) δ 169.8, 156.5, 137.3, 132.4, 130.4, 129.5, 126.7, 120.7, 116.1, 42.9, 20.9 ppm. **EIMS m/z (%)**: 241 (M^+ , 66%), 242 (100), 108 (54), 104 (65).

The characterization data of the compound **5e** matched previous reports^{S11}



N-Benzyl-N-ethyl-2-(4-hydroxyphenyl)acetamide (5f) White solid; yield 54%; $^1\text{H NMR}$ (300 MHz, DMSO) δ 9.24 (s, 1H), 7.36 – 6.59 (m, 9H), 4.54 & 4.52 (2 singlets, rotamers, 2H) 3.59 & 3.49 (2 singlets, rotamers, 2H) 3.41 (m., 2H), 0.99 (m, rotamers, 3H) ppm. $^{13}\text{C NMR}$ (75 MHz, DMSO-d₆) δ 171.1, 156.3, 138.1, 137.8, 131.1, 130.3, 128.9, 128.0, 127.8, 127.2, 126.4, 115.6, 47.5, 42.2, 40.8, 13.4, 11.2 ppm. **EIMS m/z (%)**: 269 (M^+ , 33%), 162 (3), 107 (49), 91 (100), 77 (12), 51 (3).

The characterization data of the compound **5f** matched previous reports^{S11}



2-(4-Hydroxyphenyl)acetamide (5g) White solid, yield 94% ; $^1\text{H NMR}$ (300 MHz, DMSO-d₆) δ 9.22 (brs, 1H), 7.36 (brs, 1H), 7.04 (d, $J = 6$ Hz, 2H), 6.80 (brs, 1H), 6.08 (d, $J = 6$ Hz, 2H), 3.24 (s, 2H). $^{13}\text{C NMR}$ (75 MHz, DMSO-d₆) δ 173.9, 156.8, 130.9, 130.1, 127.6, 115.9, 43.2 ppm. **EIMS m/z (%)**: 151 (M^+ , 30%), 107 (100), 77 (24), 51 (10), 44 (8), 39 (6)

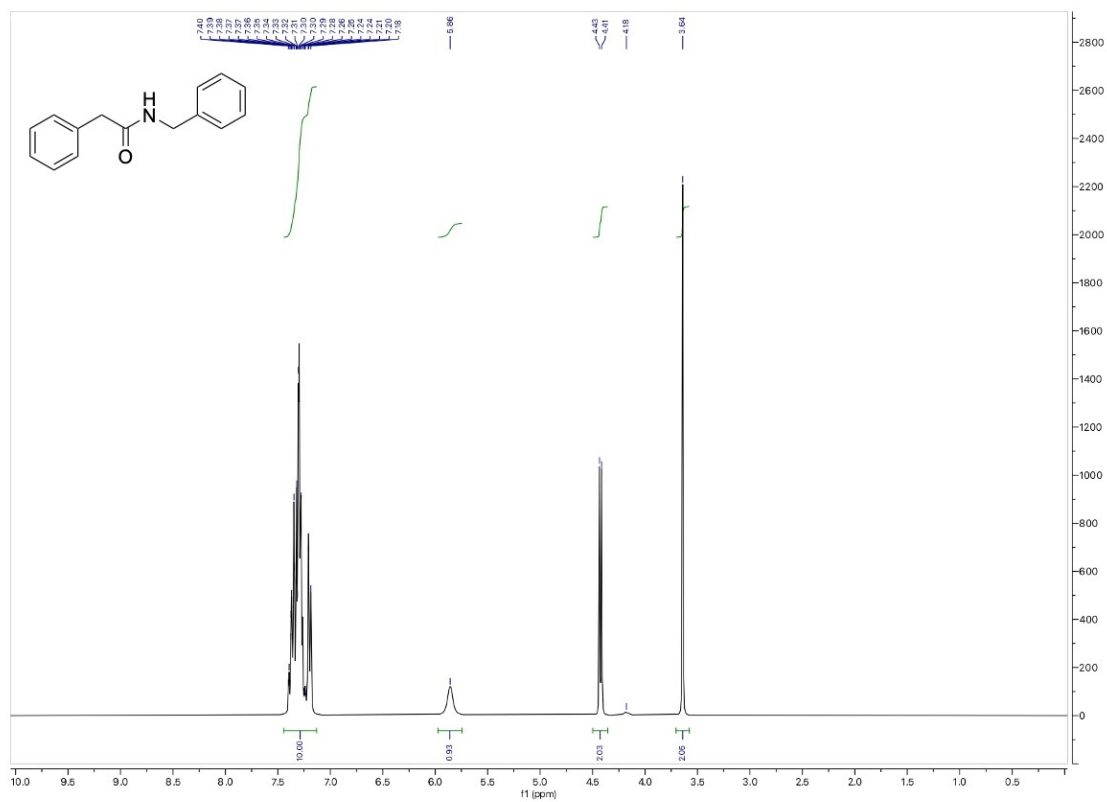
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 S3. A. Álvarez-Pérez, M. A. Esteruelas, S. Izquierdo, J. A. Varela, C. Saá. *Org. Lett.*, **2019**, *21*, 5346-5350;
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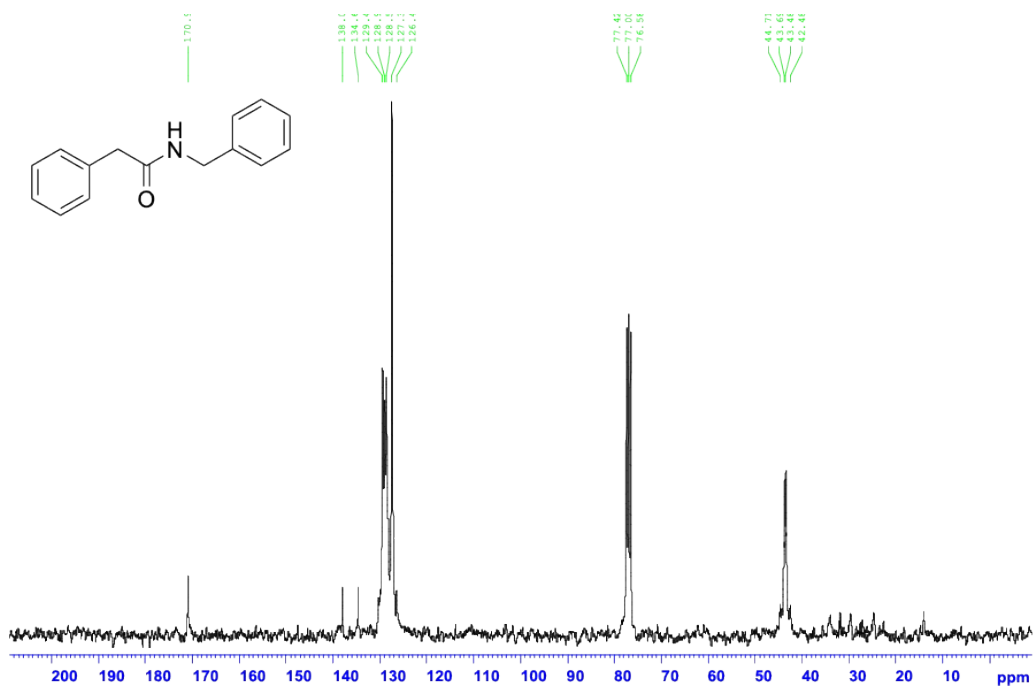
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5. NMR spectra of the products

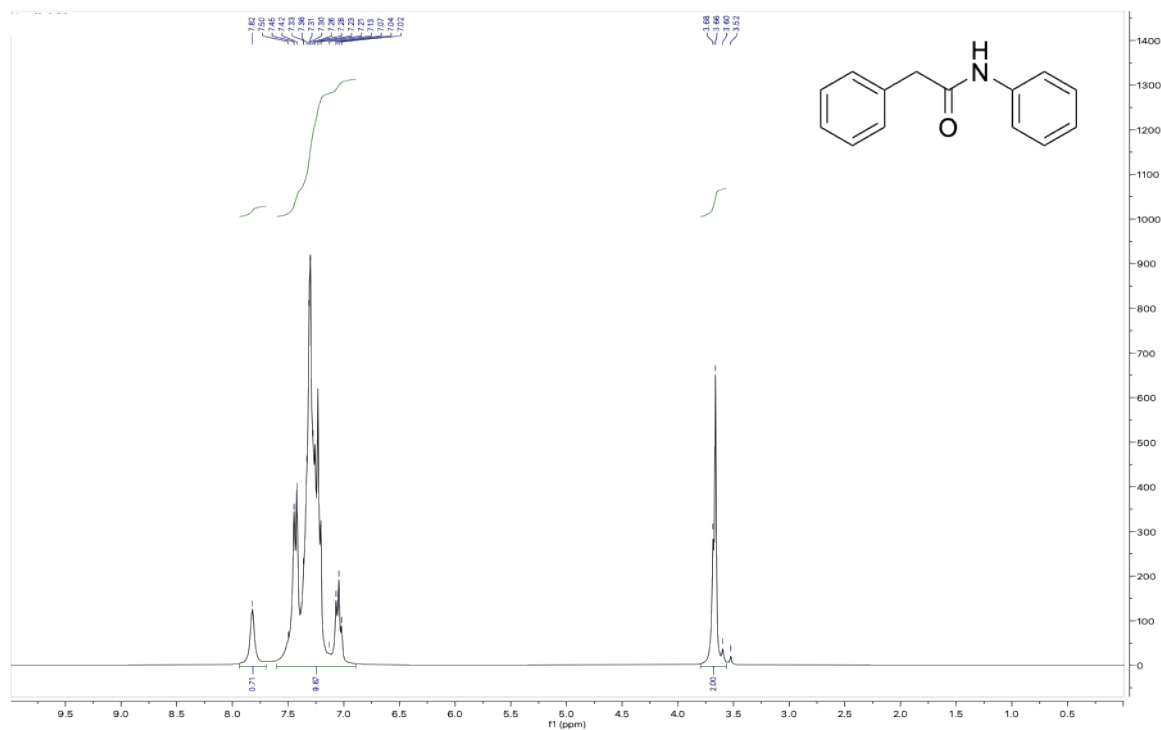
^1H NMR: (300 MHz, CDCl_3) of **3a**



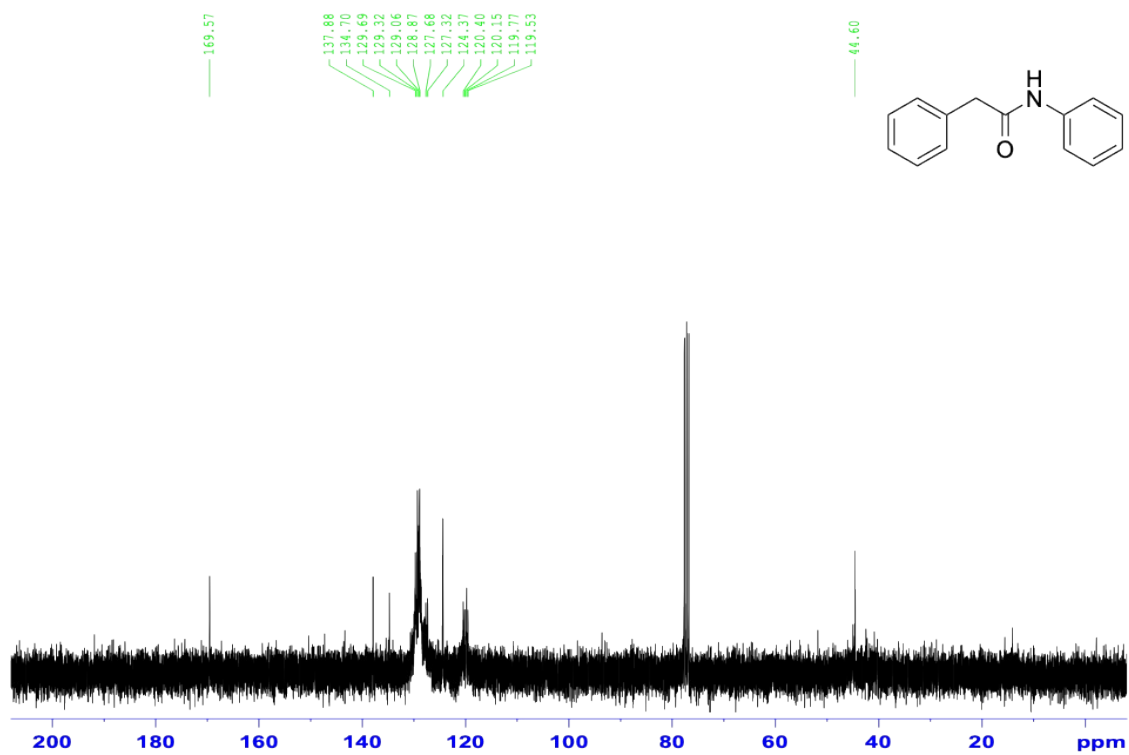
^{13}C NMR: (75 MHz, CDCl_3) of **3a**



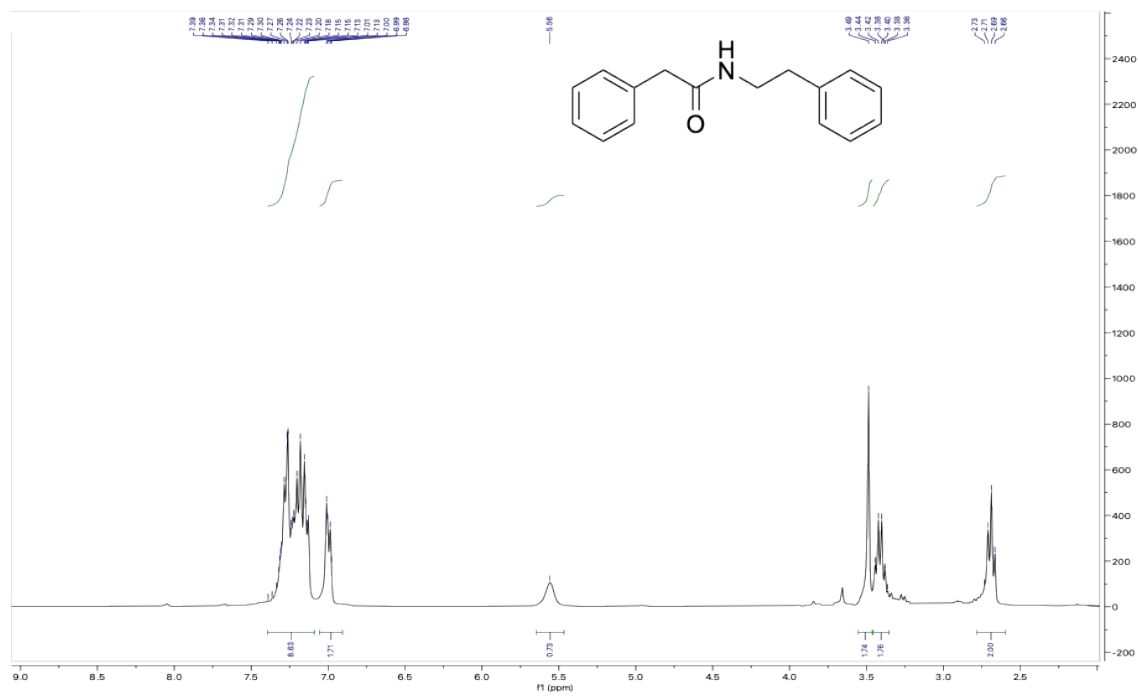
^1H NMR: (300 MHz, CDCl_3) of **3b**



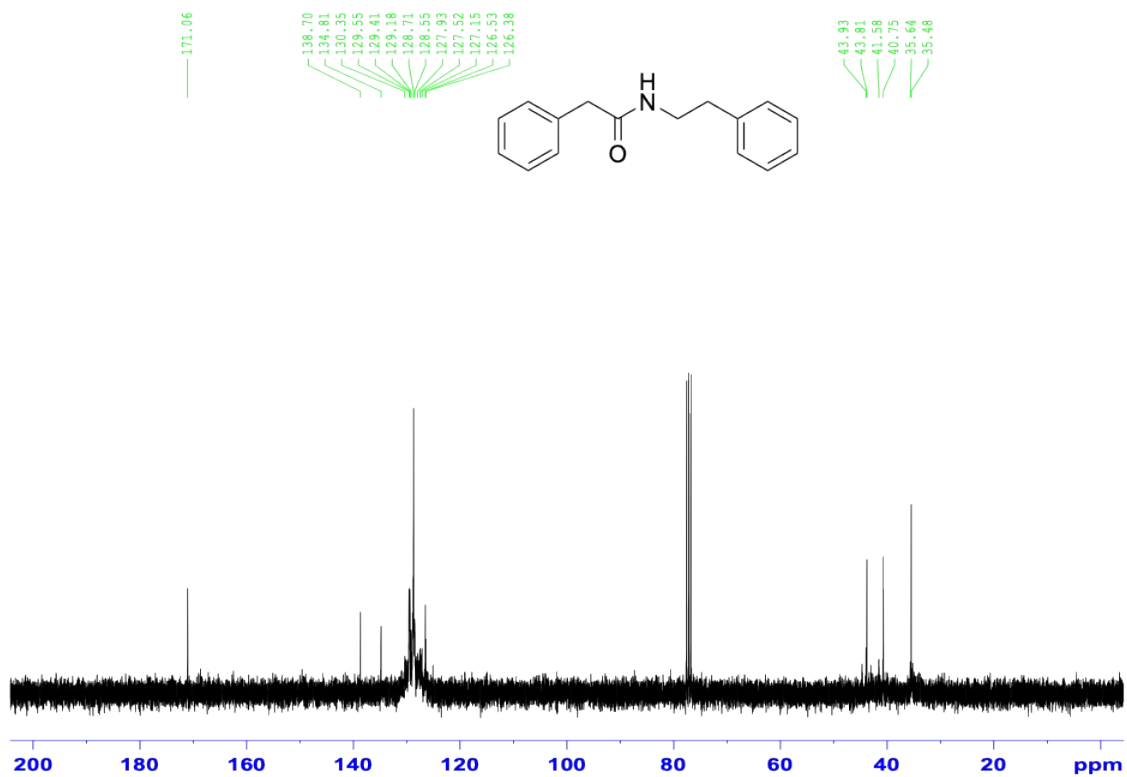
^{13}C NMR: (75 MHz, CDCl_3) of **3b**



^1H NMR: (300 MHz, CDCl_3) of **3c**



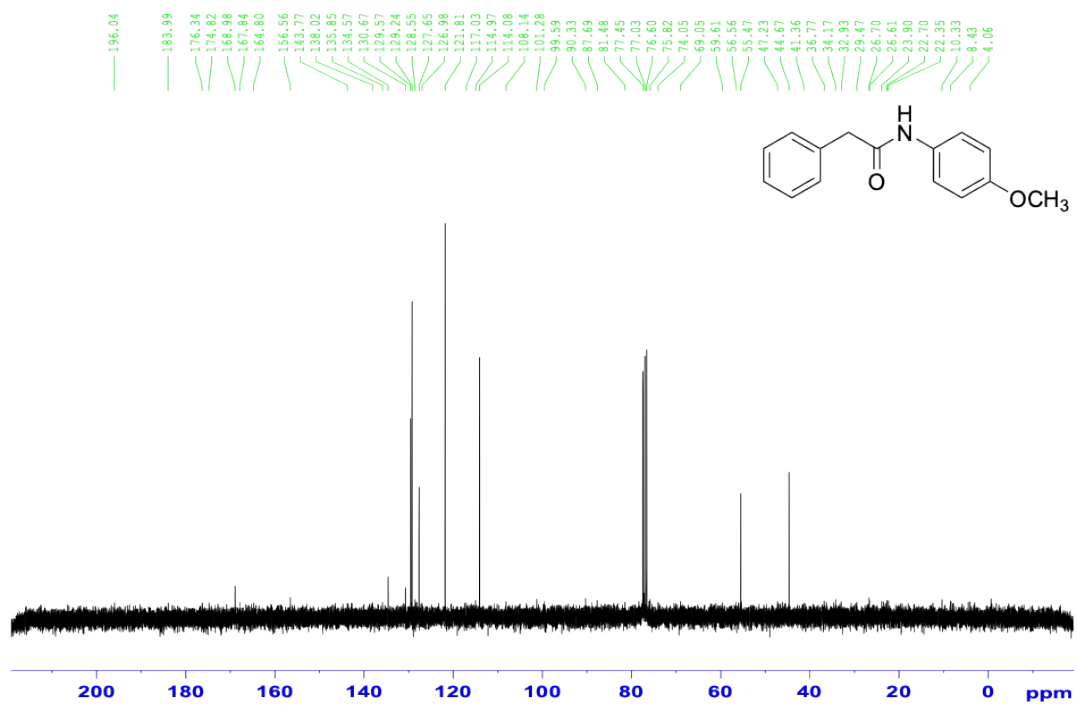
^{13}C NMR: (75 MHz, CDCl_3) of **3c**



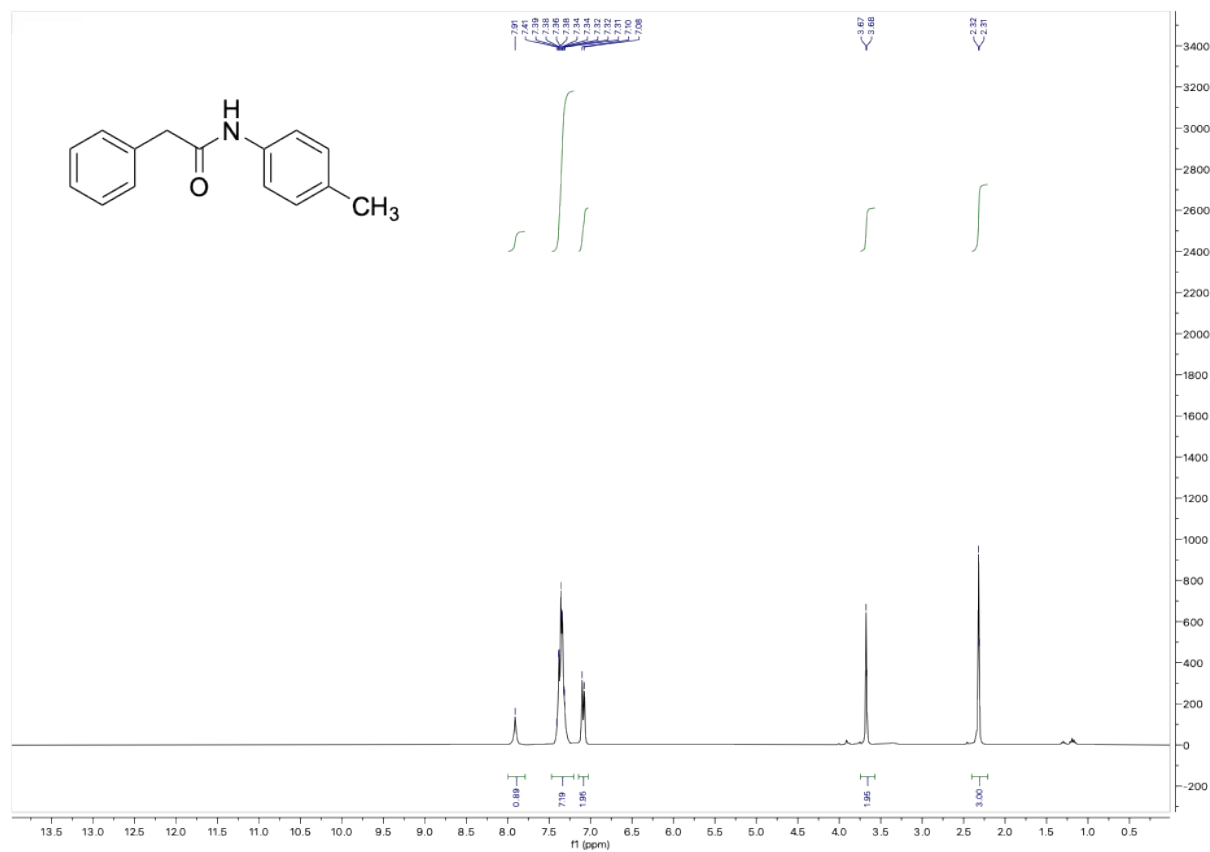
^1H NMR: (300 MHz, CDCl_3) of **3d**



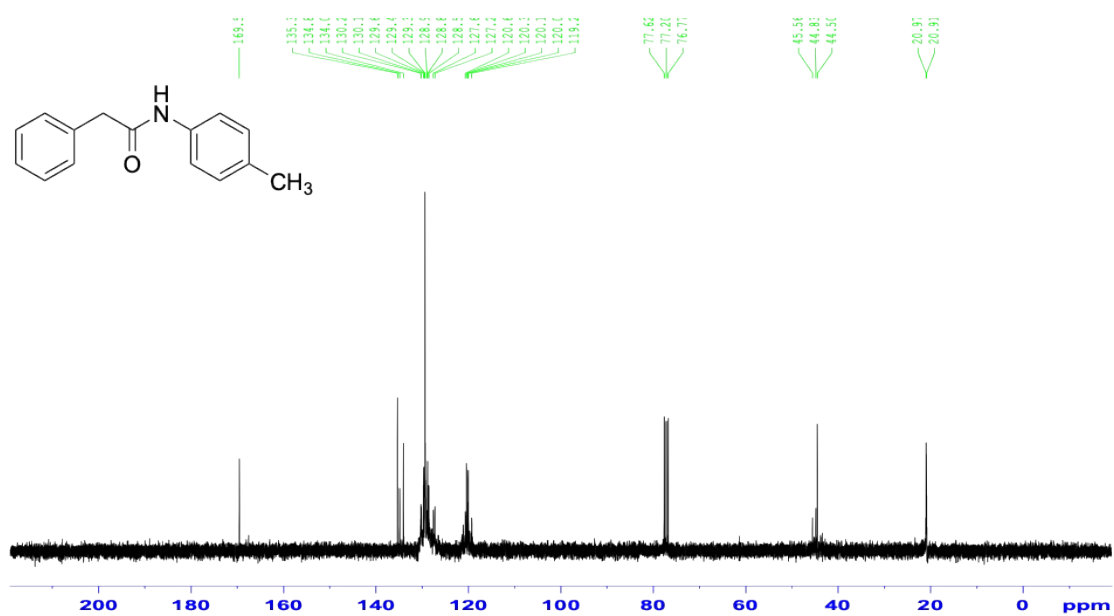
^{13}C NMR: (75 MHz, CDCl_3) of **3d**



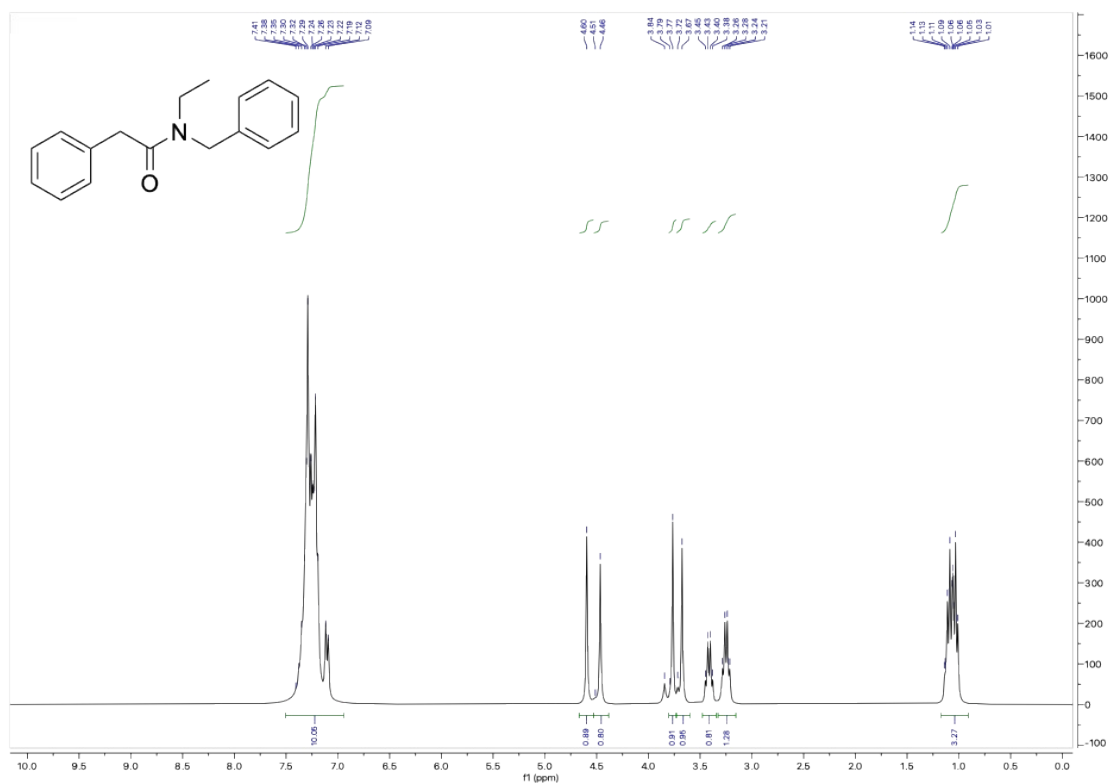
^1H NMR: (300 MHz, CDCl_3) of **3e**



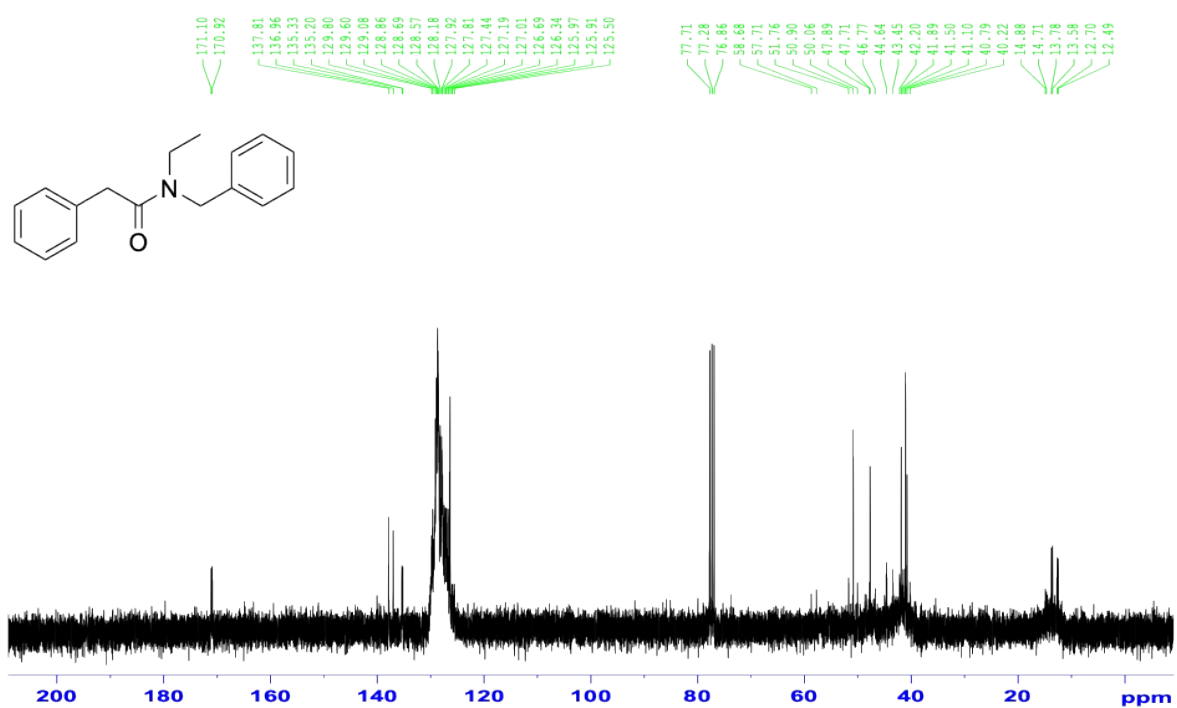
^{13}C NMR: (75 MHz, CDCl_3) of **3e**



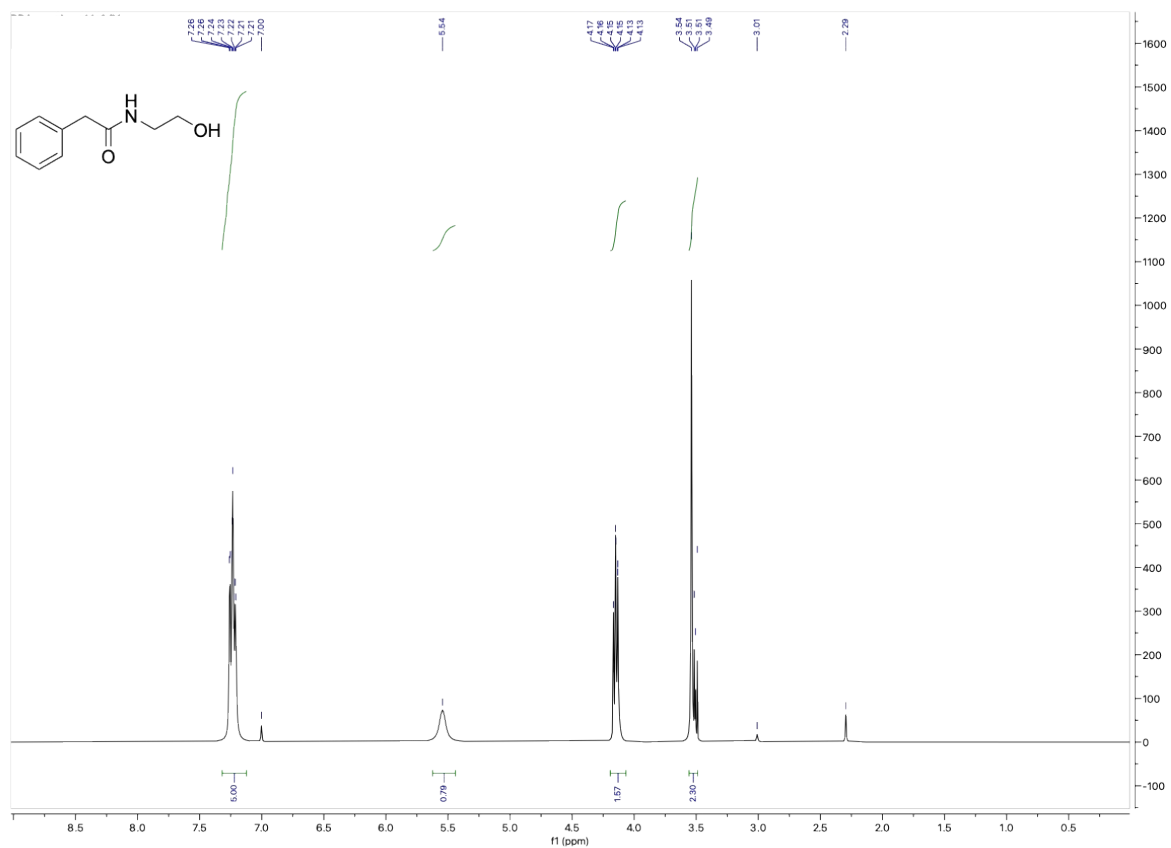
^1H NMR: (300 MHz, CDCl_3) of **3f** – mixture of two rotamers



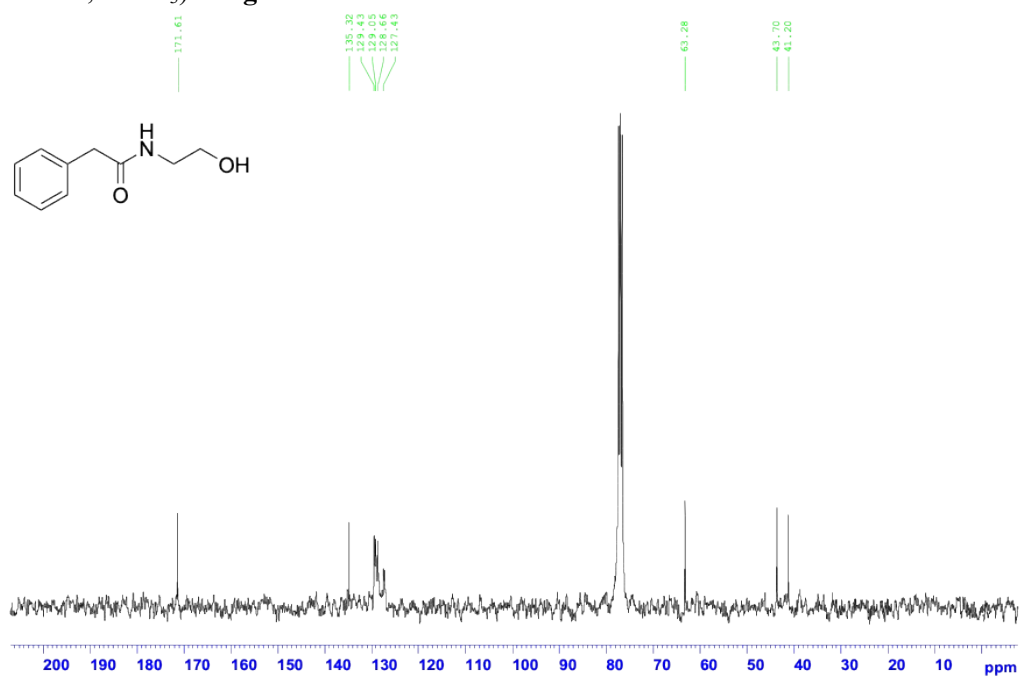
^{13}C NMR: (75 MHz, CDCl_3) of **3f** - mixture of two rotamers



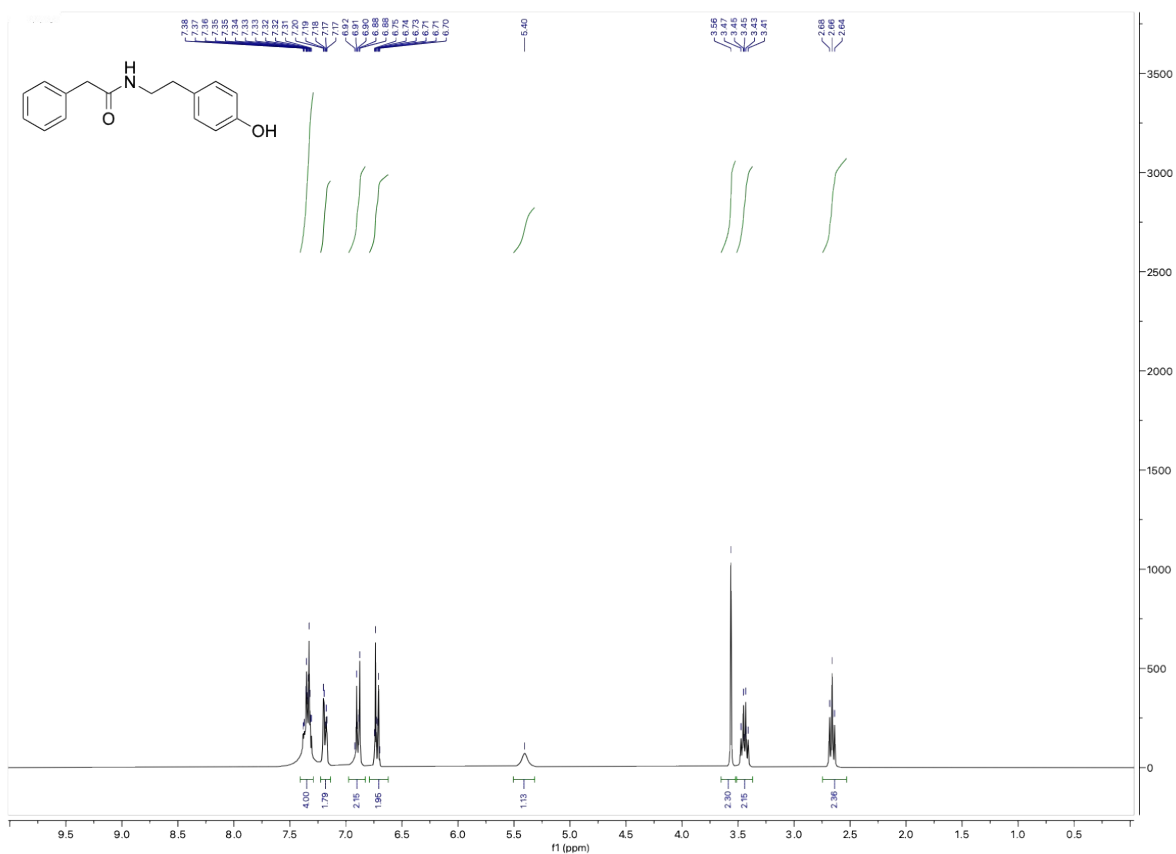
^1H NMR: (300 MHz, CDCl_3) of **3g**



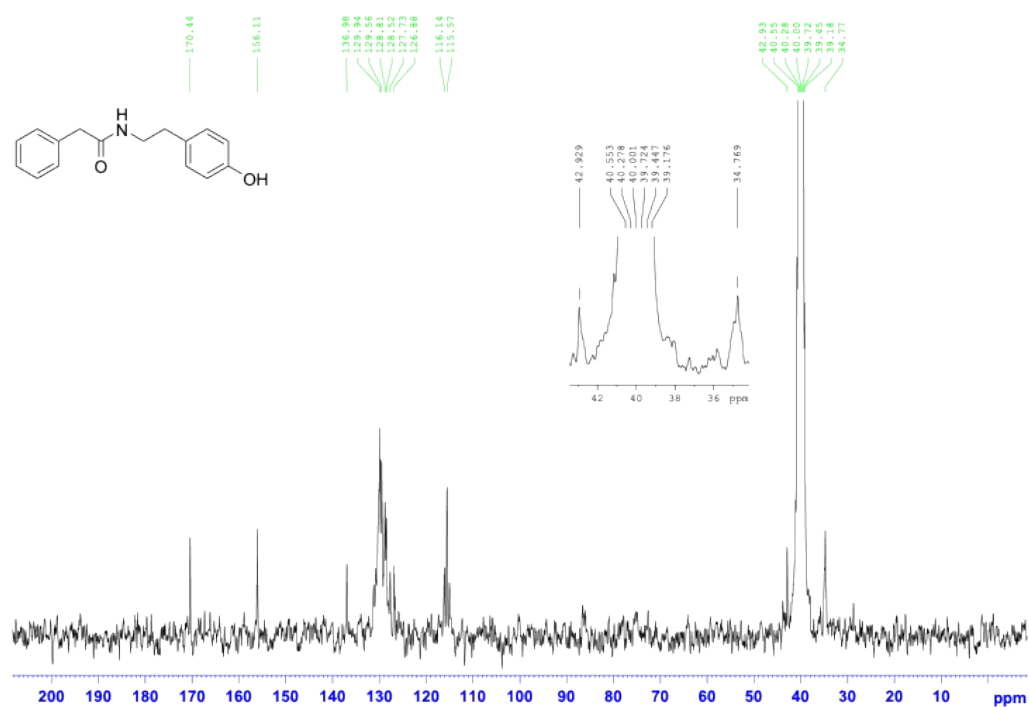
^{13}C NMR: (75 MHz, CDCl_3) of **3g**



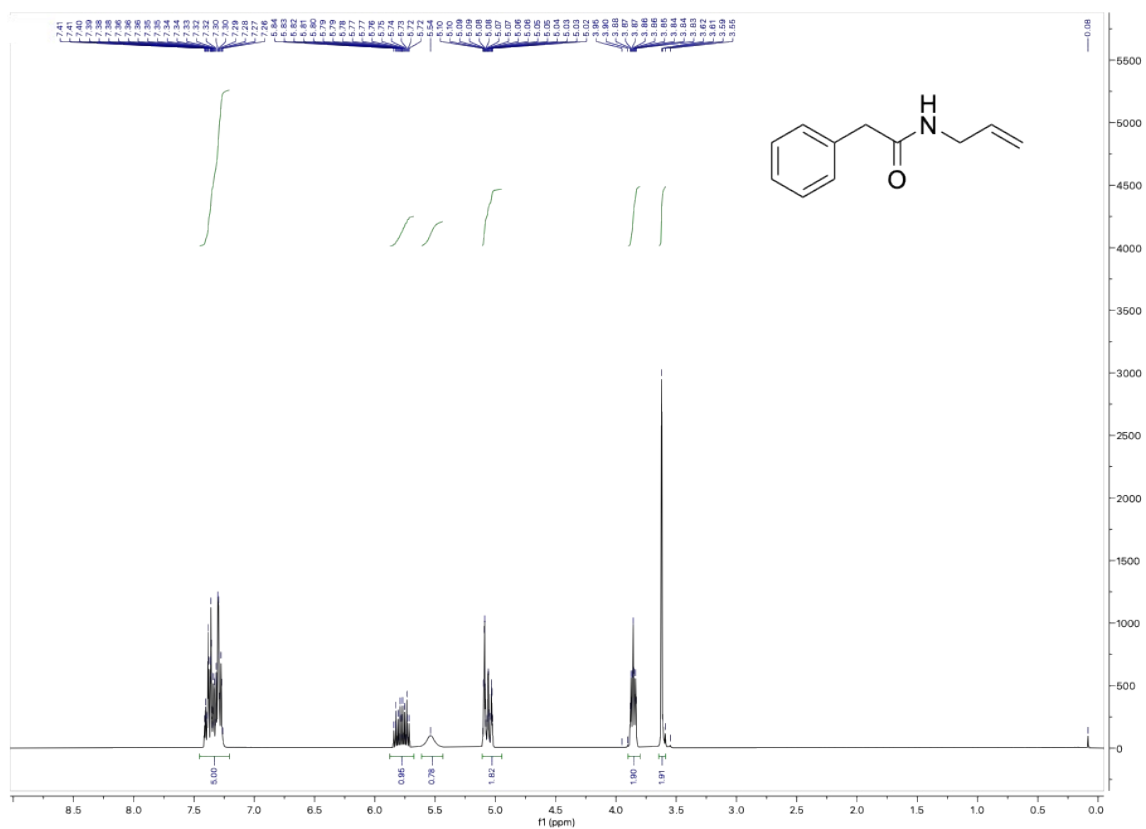
^1H NMR: (300 MHz, CDCl_3) of **3h**



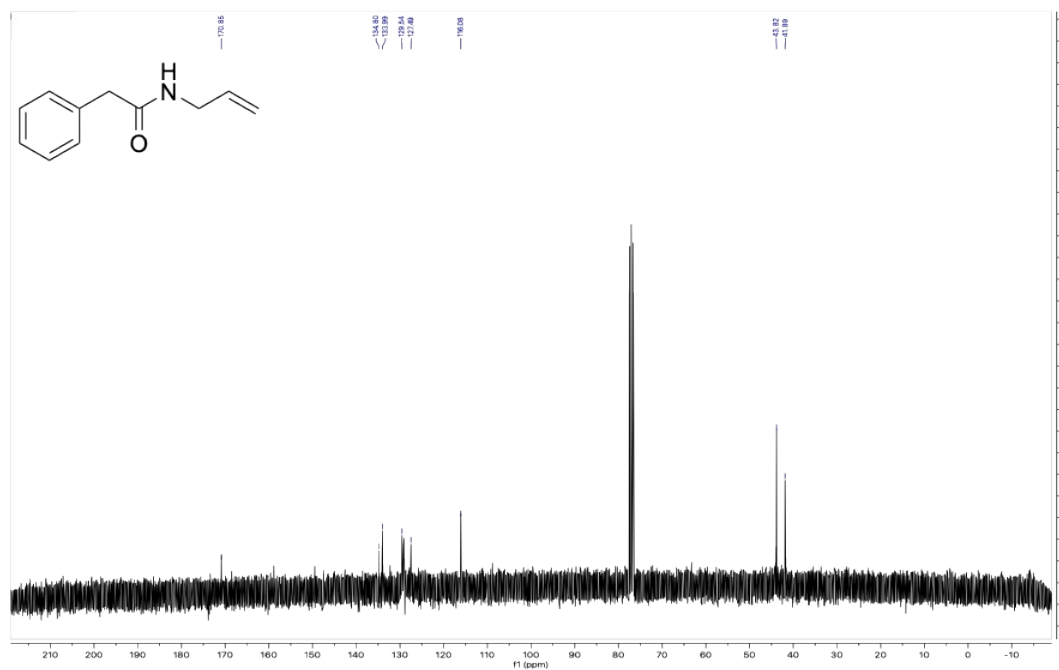
^{13}C NMR: (75 MHz, DMSO-d_6) of **3h**



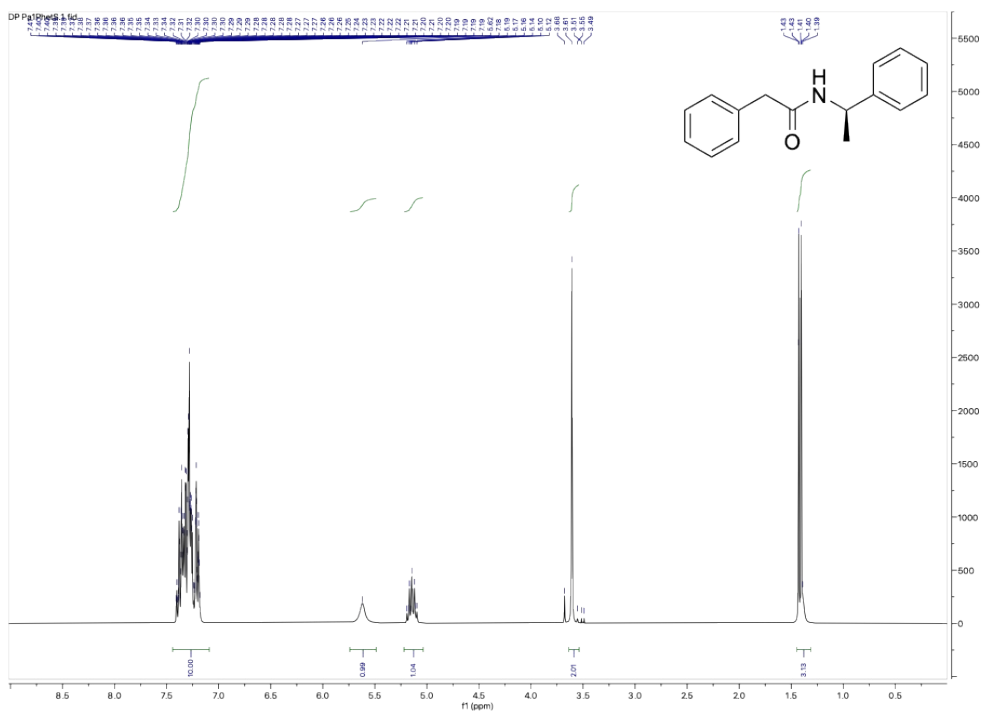
^1H NMR: (300 MHz, CDCl_3) of **3i**



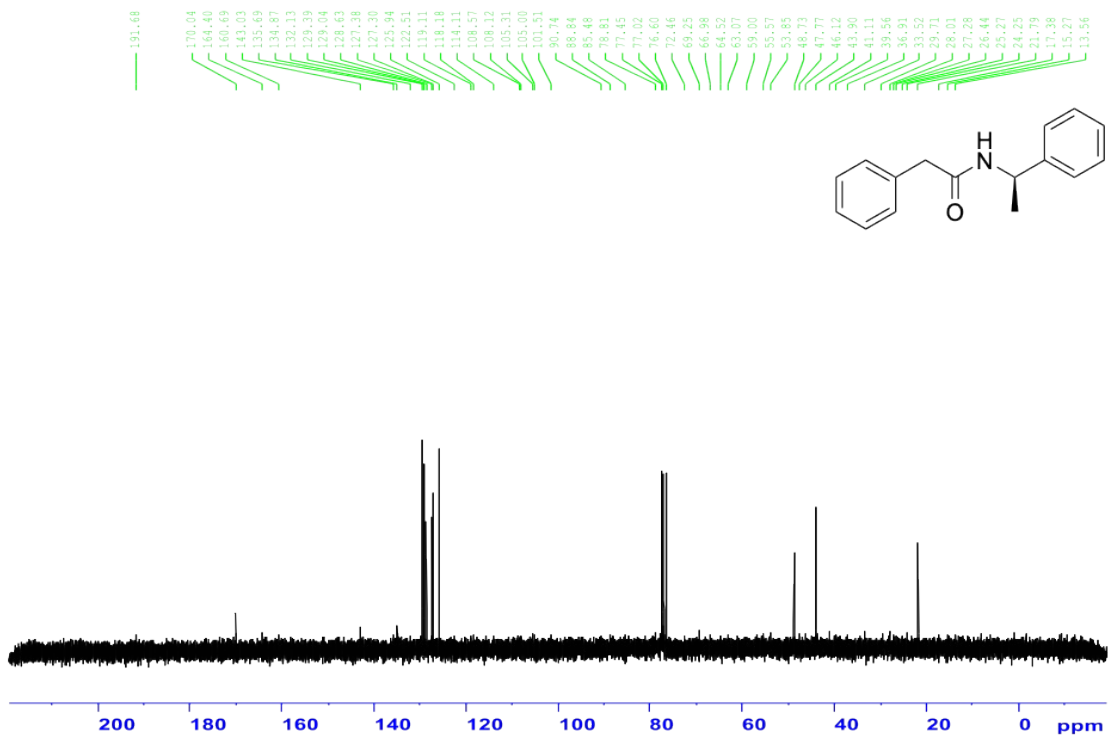
^{13}C NMR: (75 MHz, CDCl_3) of **3i**



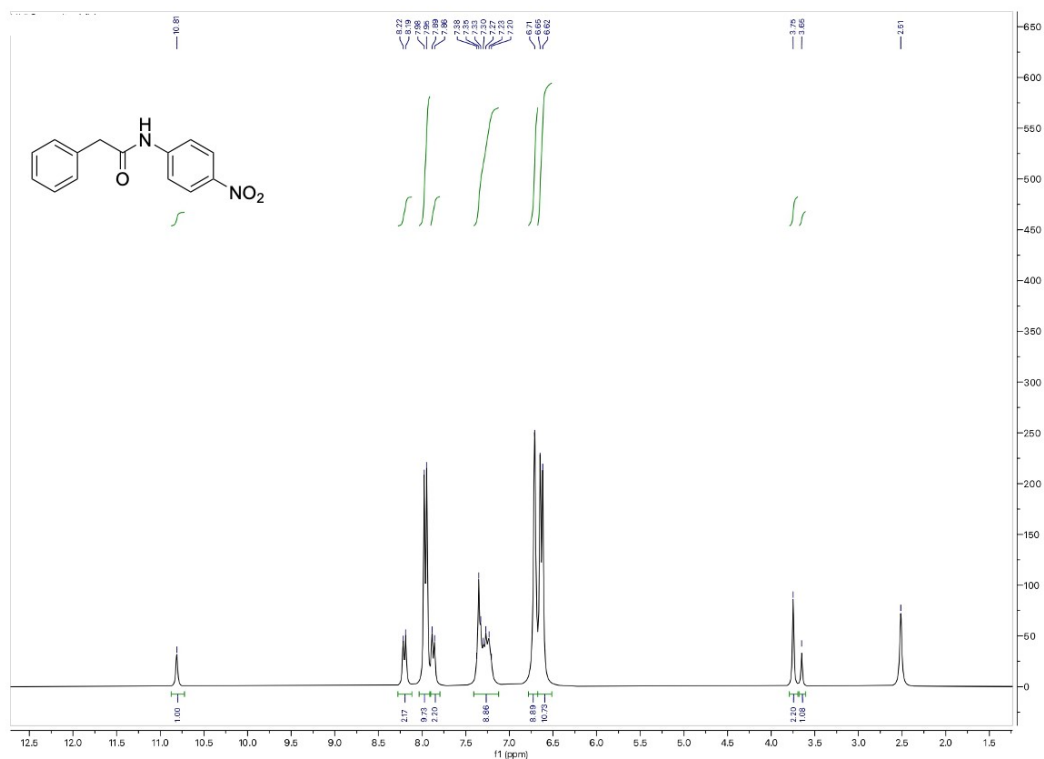
^1H NMR: (300 MHz, CDCl_3) of **3j**



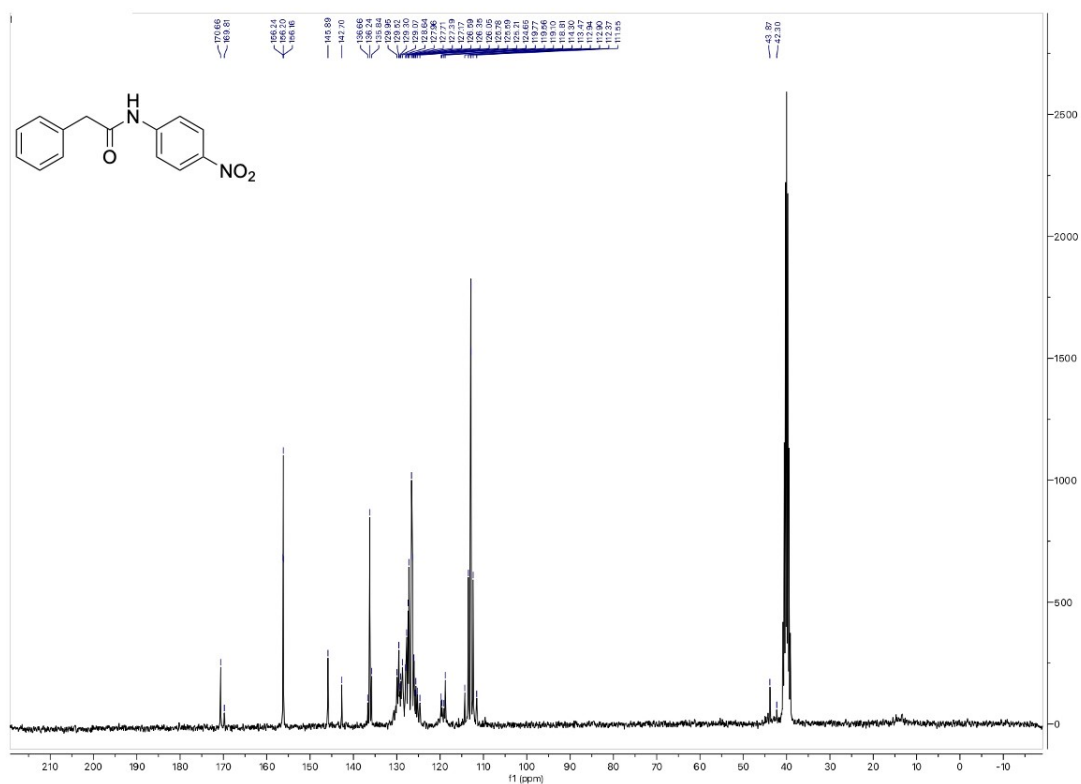
^{13}C NMR: (75 MHz, CDCl_3) of **3j**



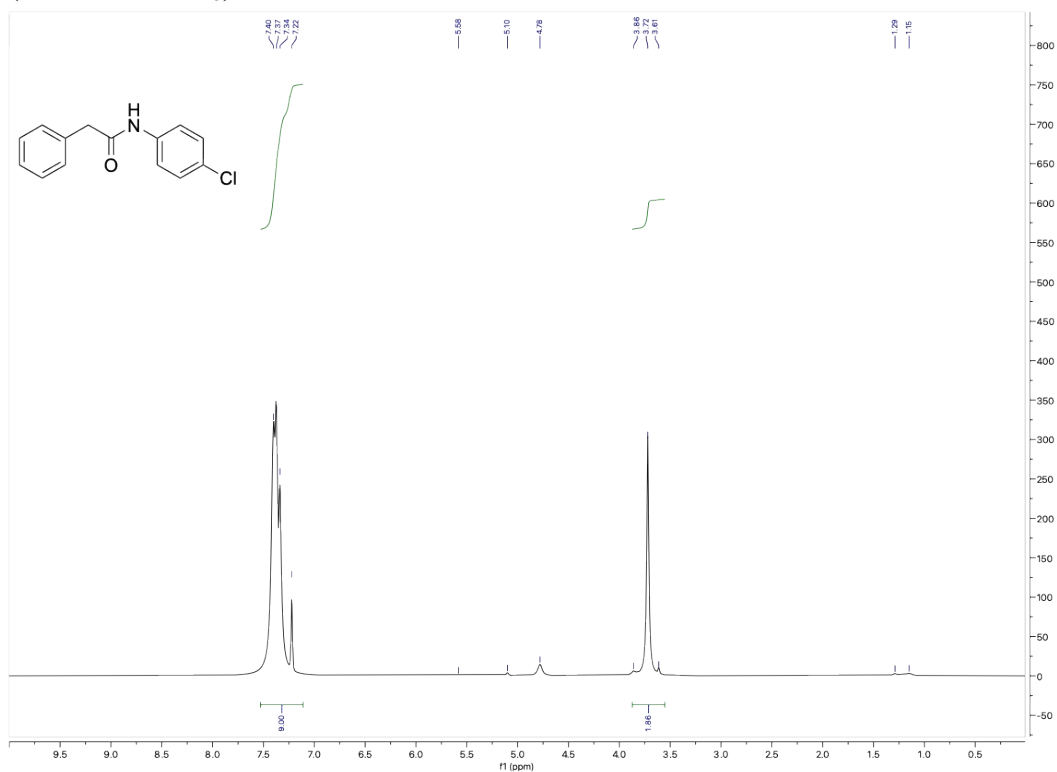
^1H NMR: (300 MHz, DMSO- d_6) of **31** mixture of tautomers (85 % amidic tautomer + 15 % enamidic tautomer)



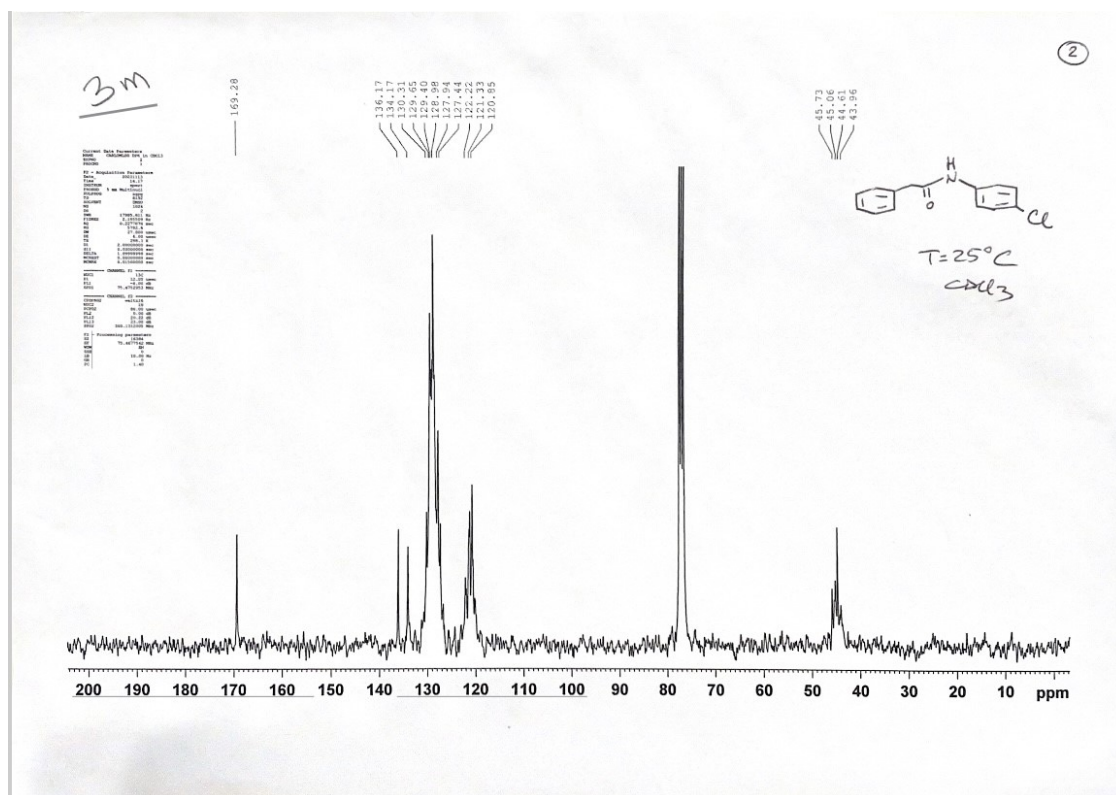
^{13}C NMR: (75 MHz, DMSO- d_6) of **31** mixture of tautomers (85 % amidic tautomer + 15 % enamidic tautomer)



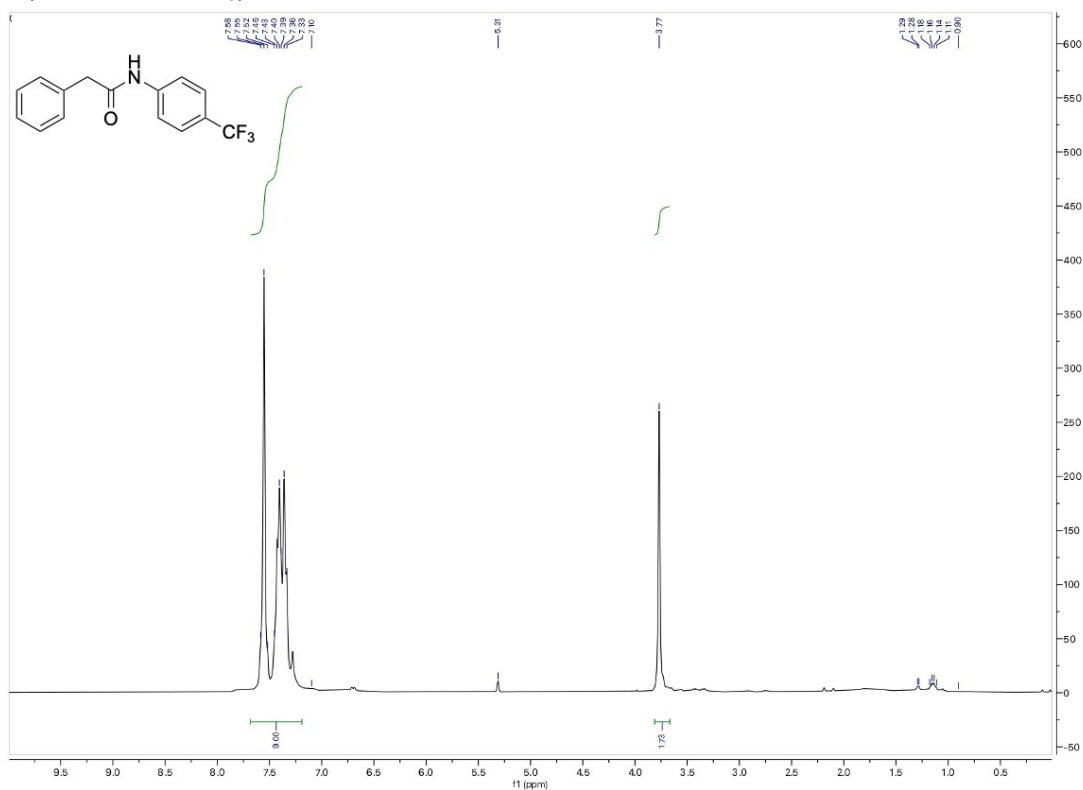
^1H NMR: (300 MHz, CDCl_3) of **3m**



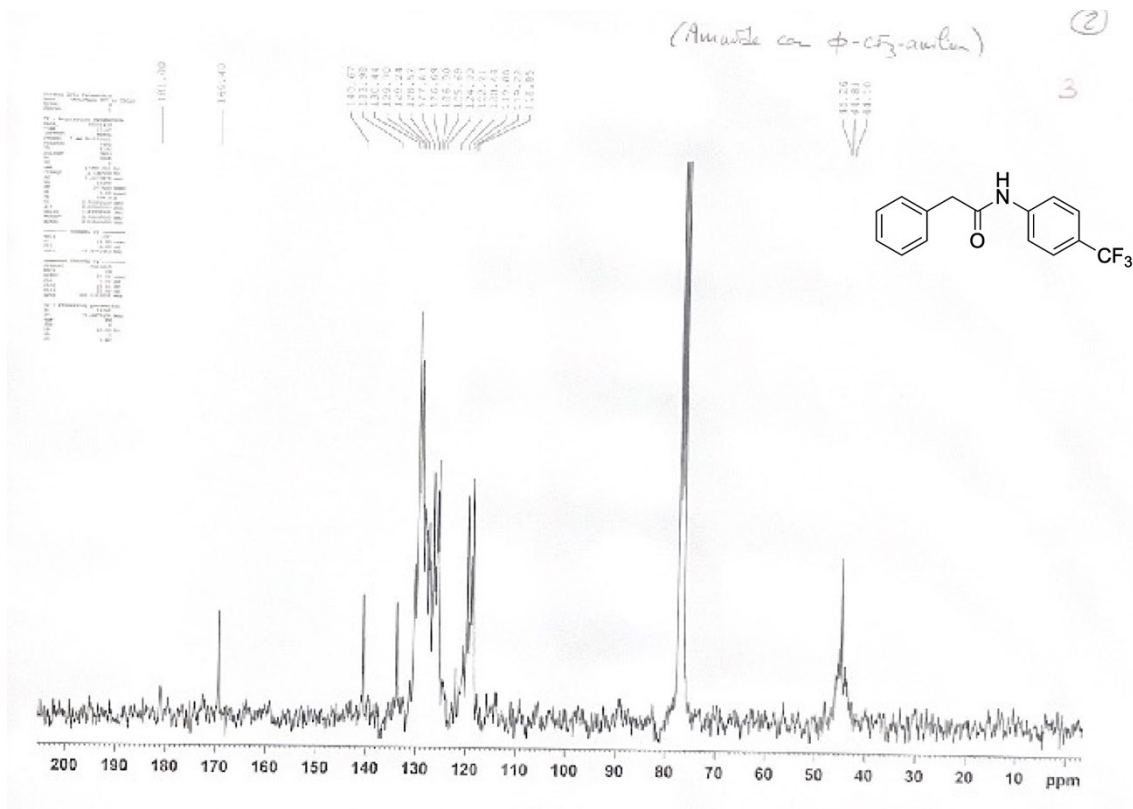
^{13}C NMR: (75 MHz, CDCl_3) of **3m**



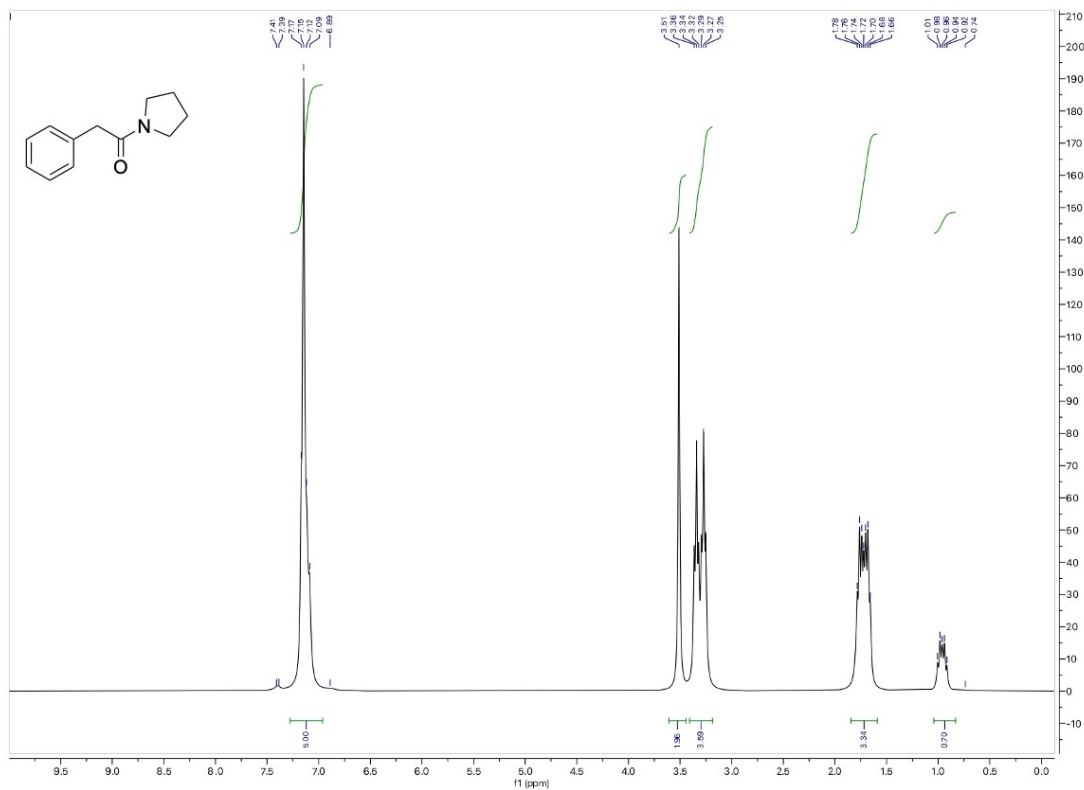
^1H NMR: (300 MHz, CDCl_3) of **3n**



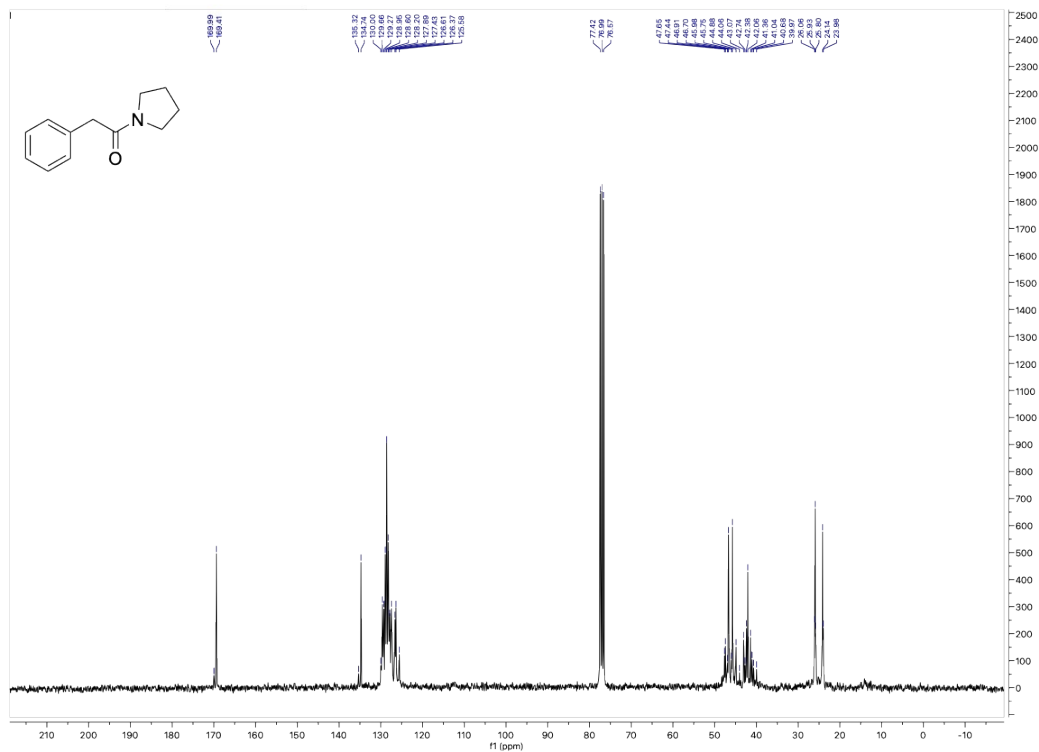
^{13}C NMR: (75 MHz, CDCl_3) of **3n**



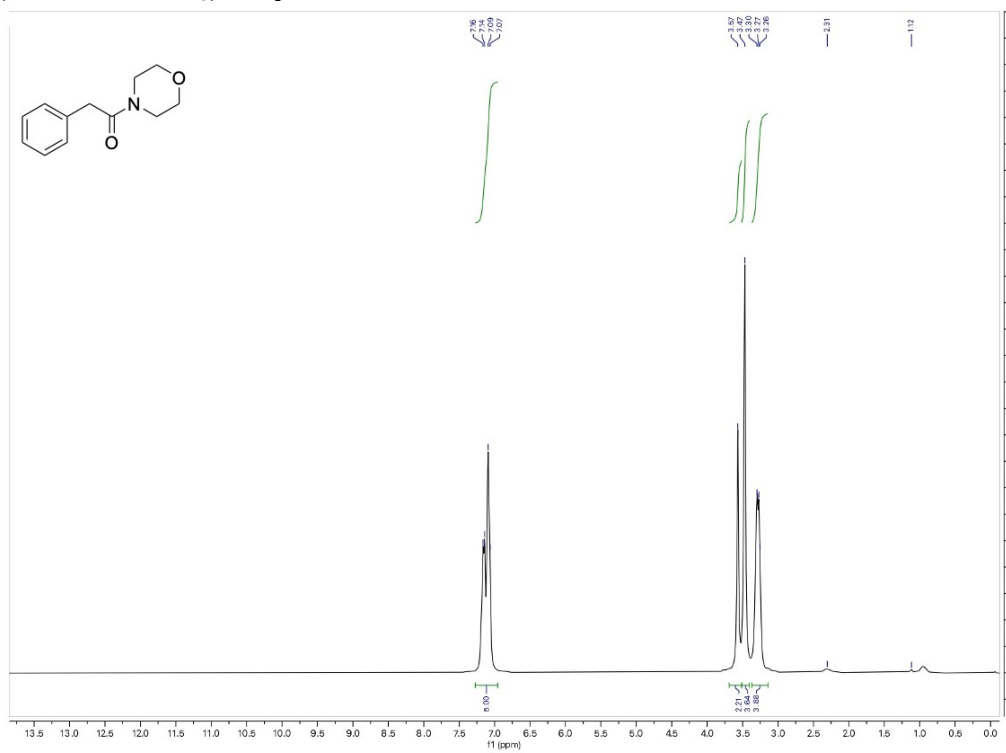
^1H NMR: (300 MHz, CDCl_3) of **3o** mixture of conformers (18:83) at 25°C



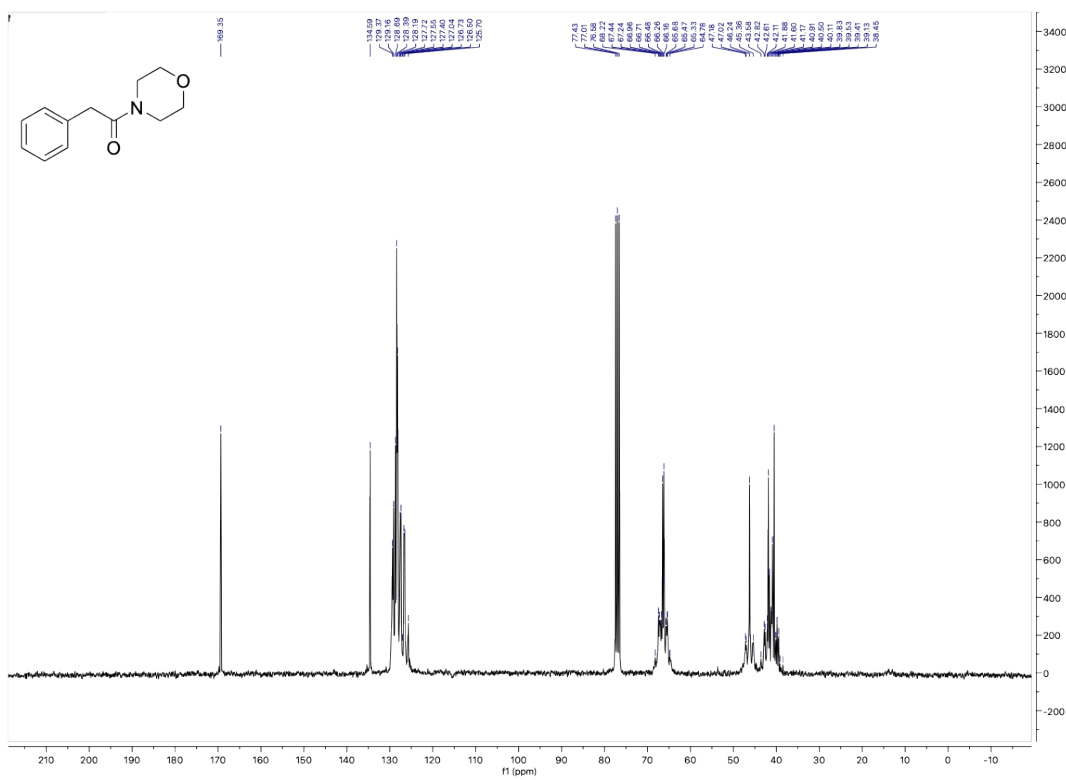
^{13}C NMR: (75 MHz, CDCl_3) of **3o** mixture of conformers at 25°C



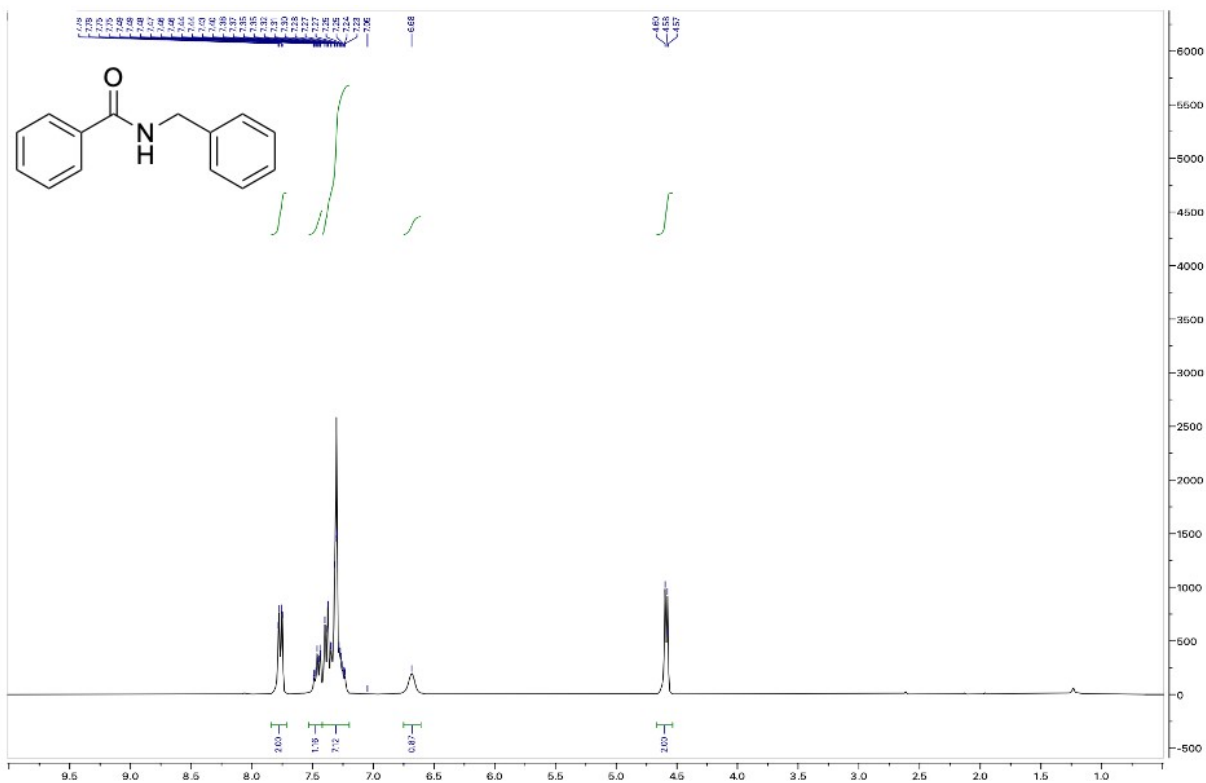
¹H NMR: (300 MHz, CDCl₃) of **3p**



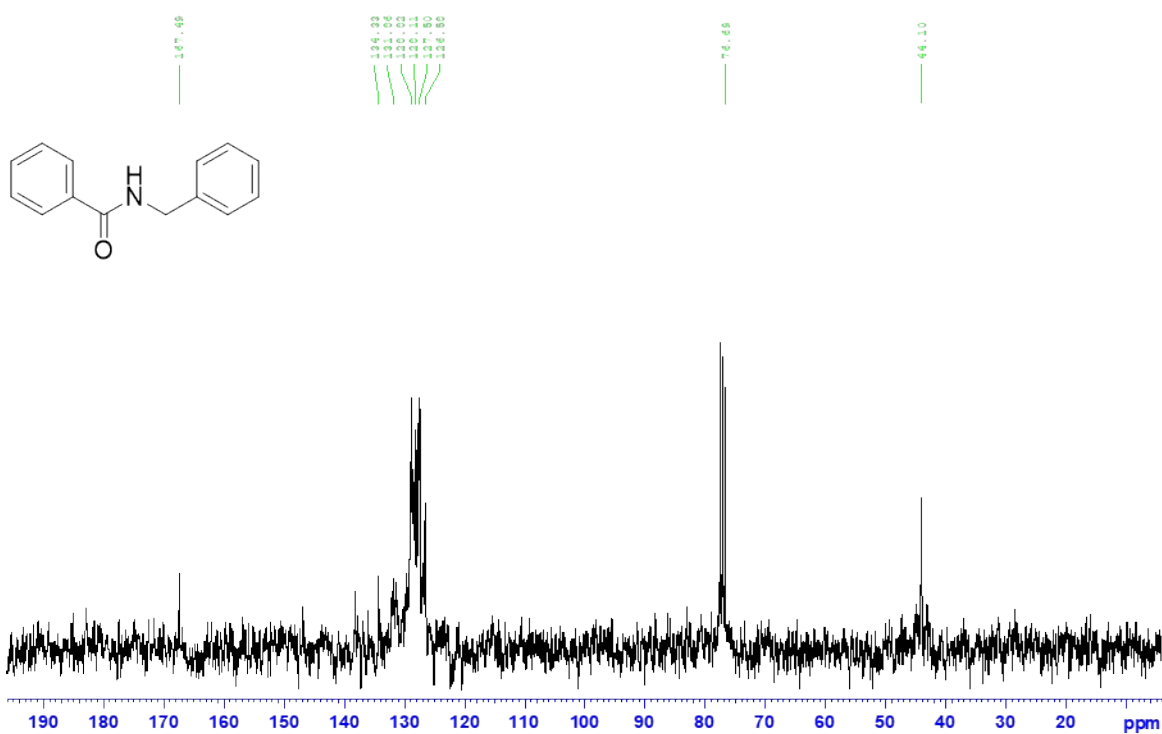
¹³C NMR: (75 MHz, CDCl₃) of **3p**



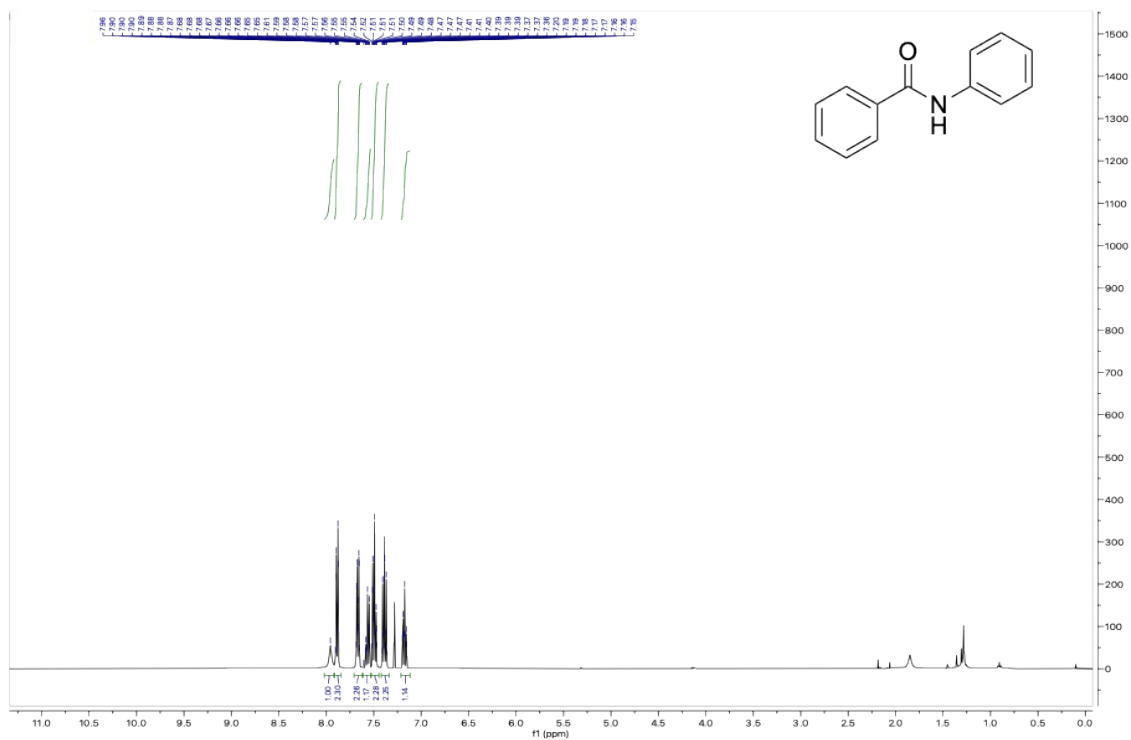
^1H NMR: (300 MHz, CDCl_3) of **4a**



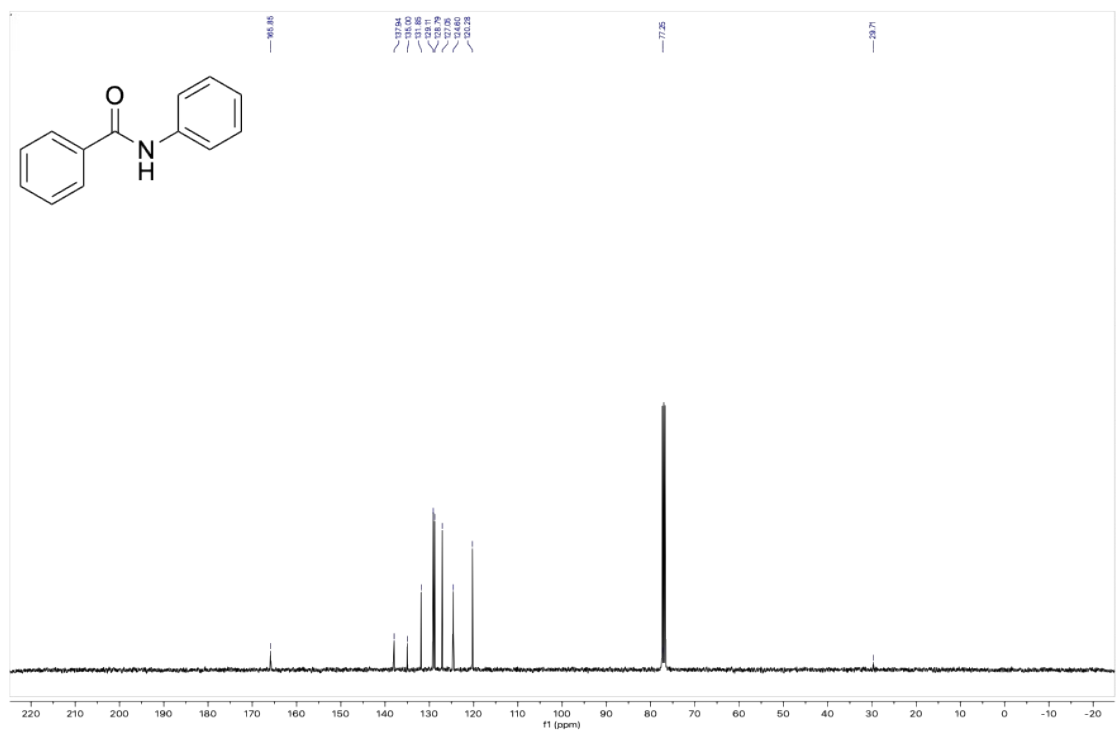
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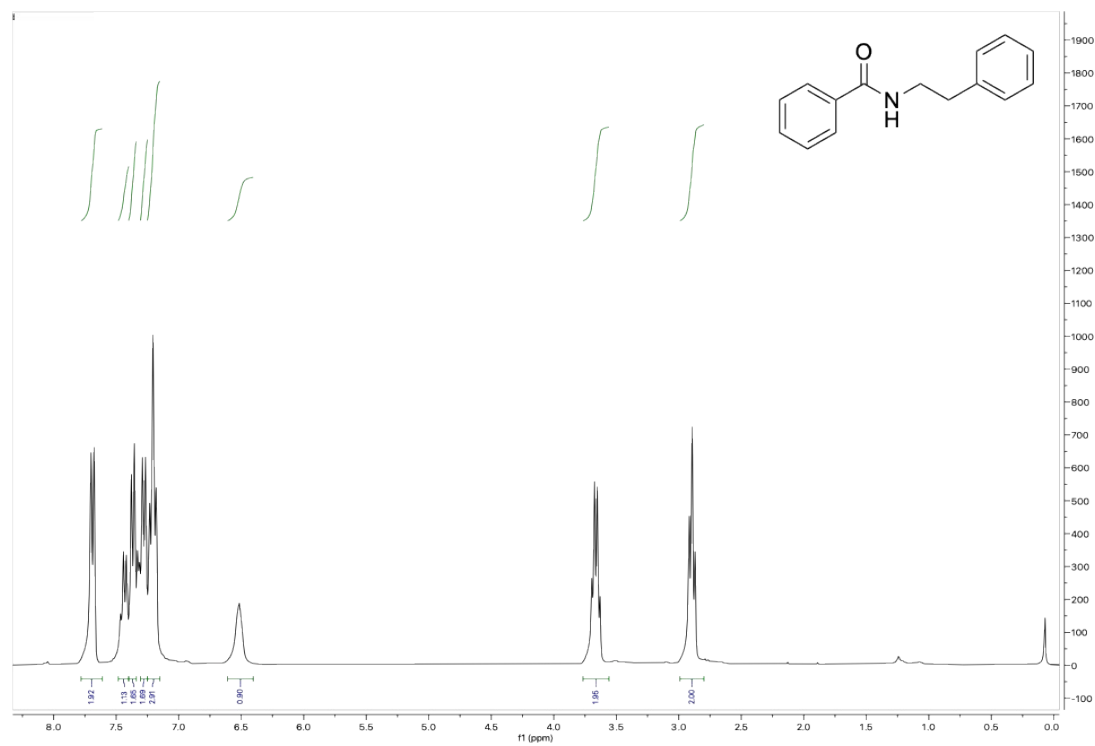
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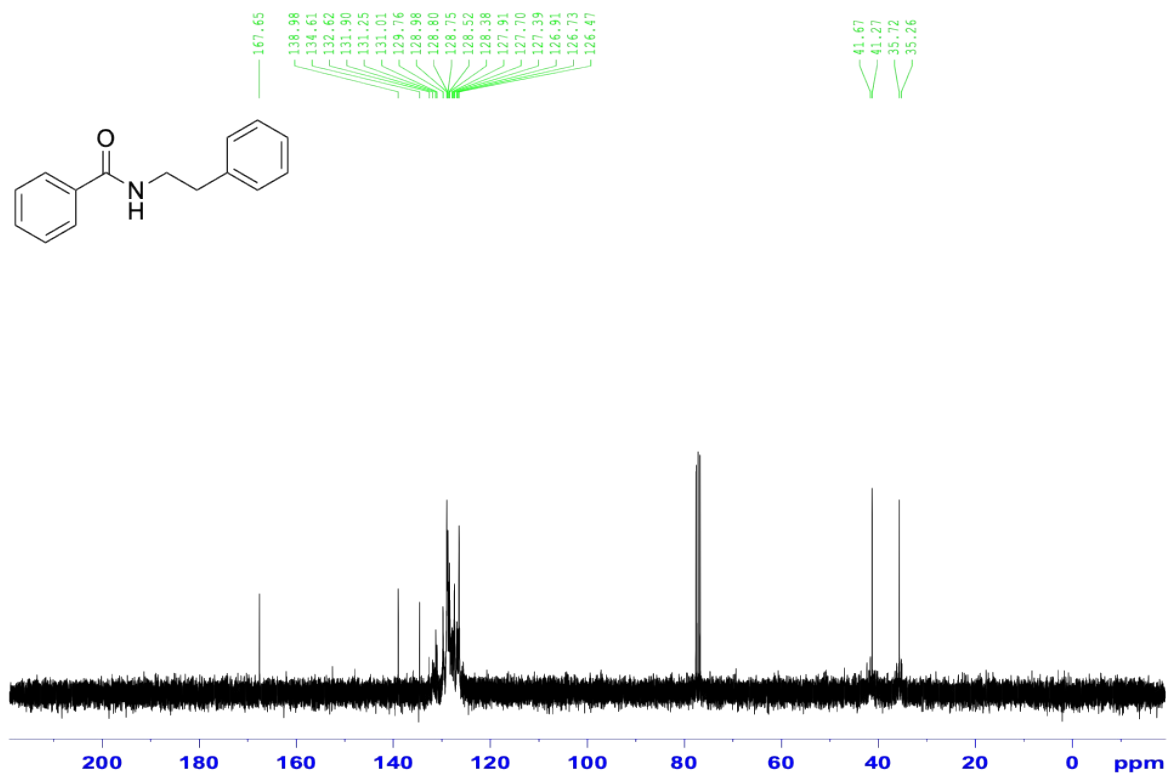
^{13}C NMR: (75 MHz, CDCl_3) of **4b**



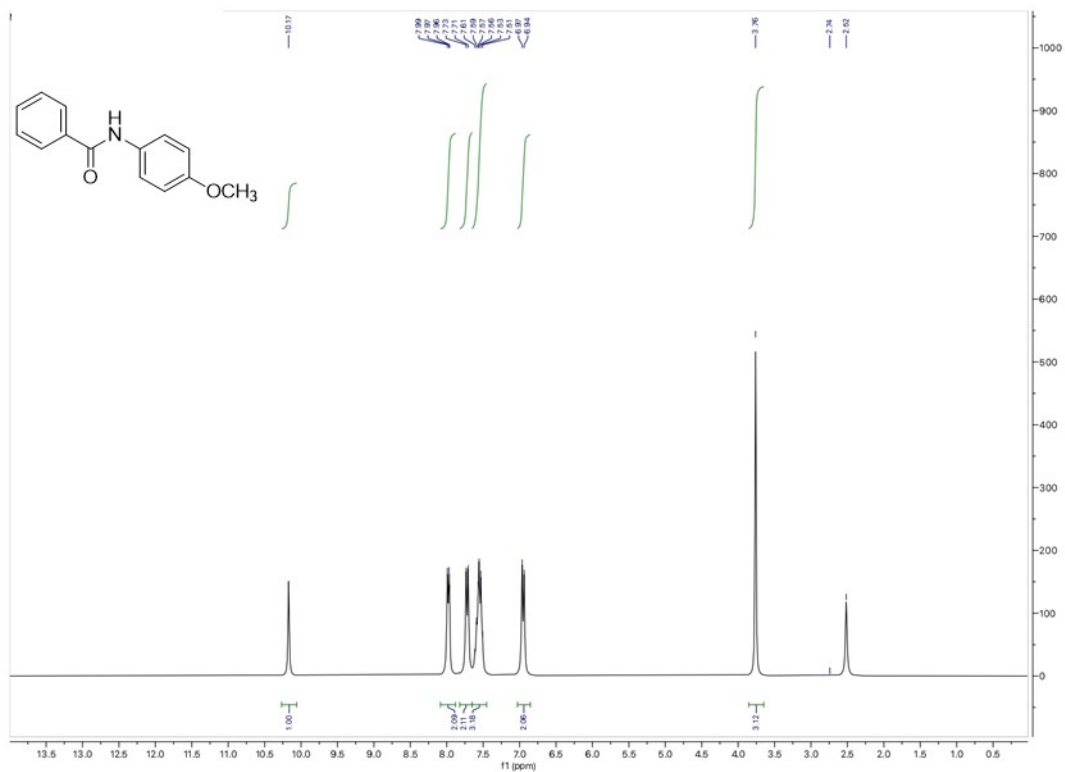
^1H NMR: (300 MHz, CDCl_3) of **4c**



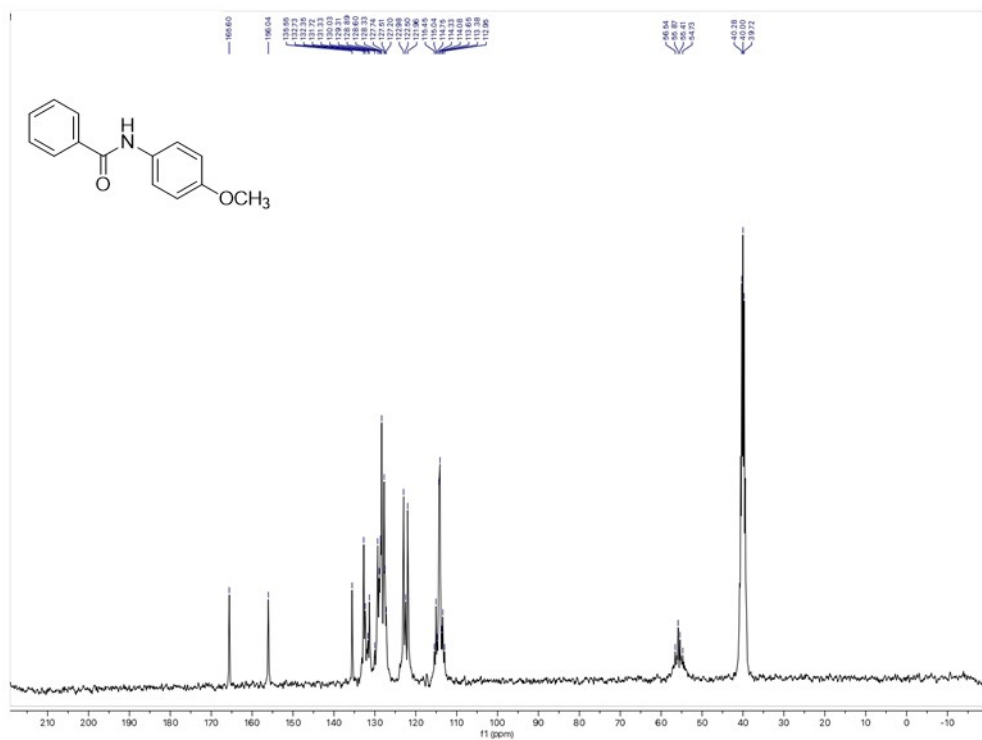
^{13}C NMR: (75 MHz, CDCl_3) of **4c**



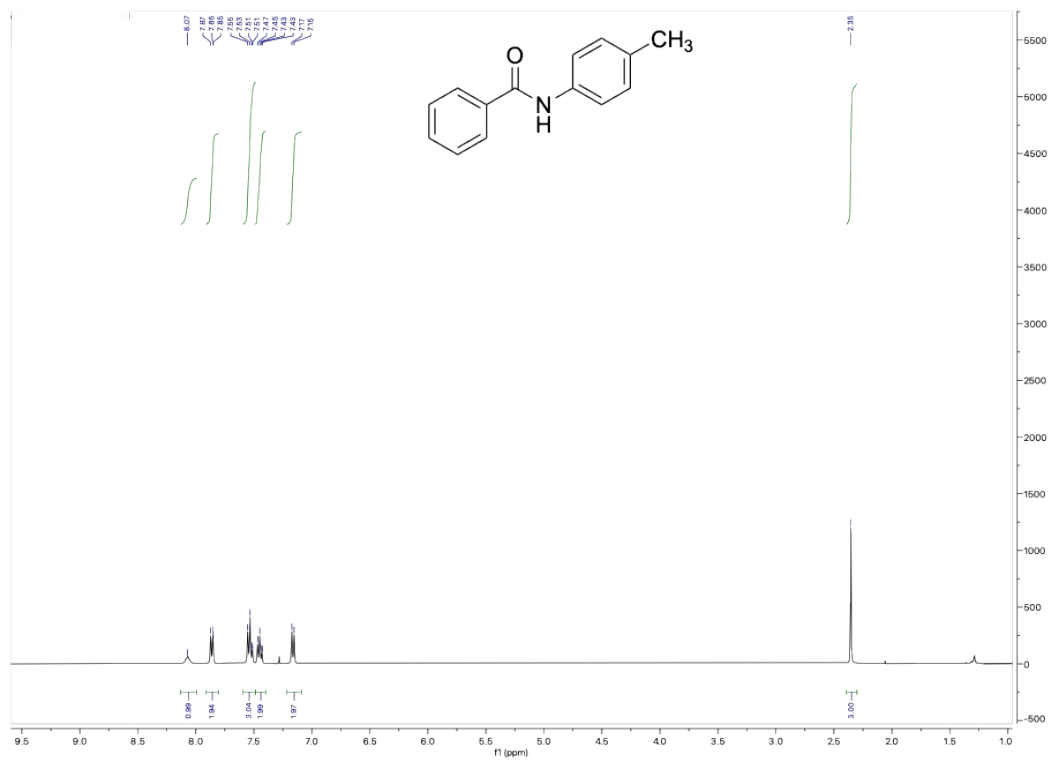
^1H NMR: (300 MHz, DMSO-d₆) of **4d**



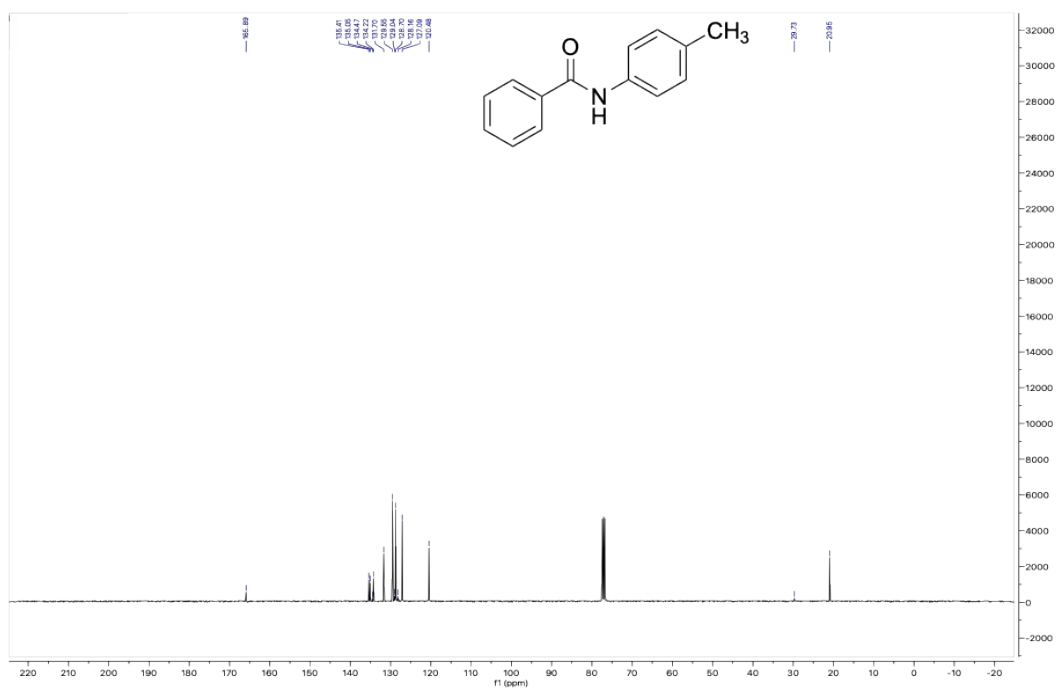
^{13}C NMR: (75 MHz, DMSO-d₆) of **4d**



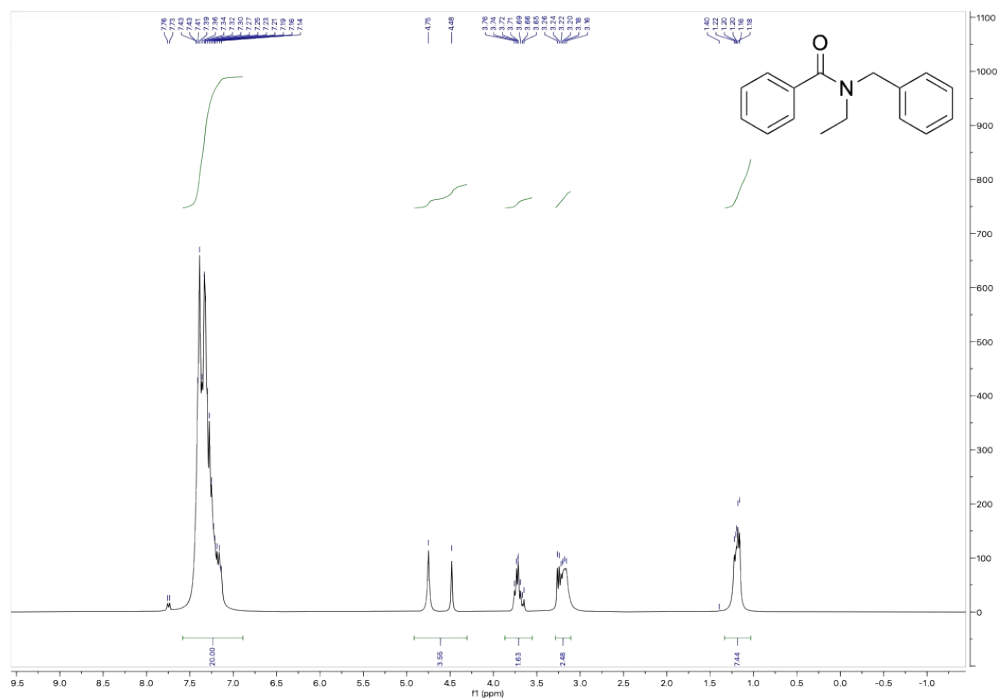
^1H NMR: (300 MHz, CDCl_3) of **4e**



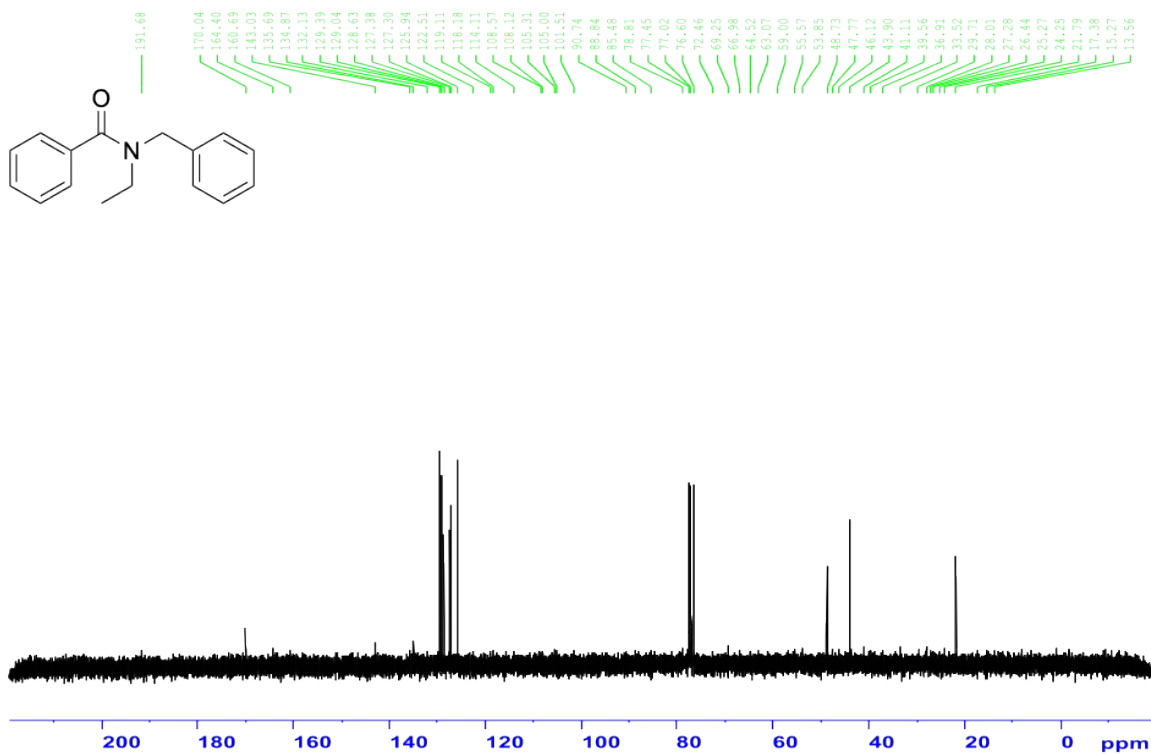
^{13}C NMR: (75 MHz, CDCl_3) of **4e**



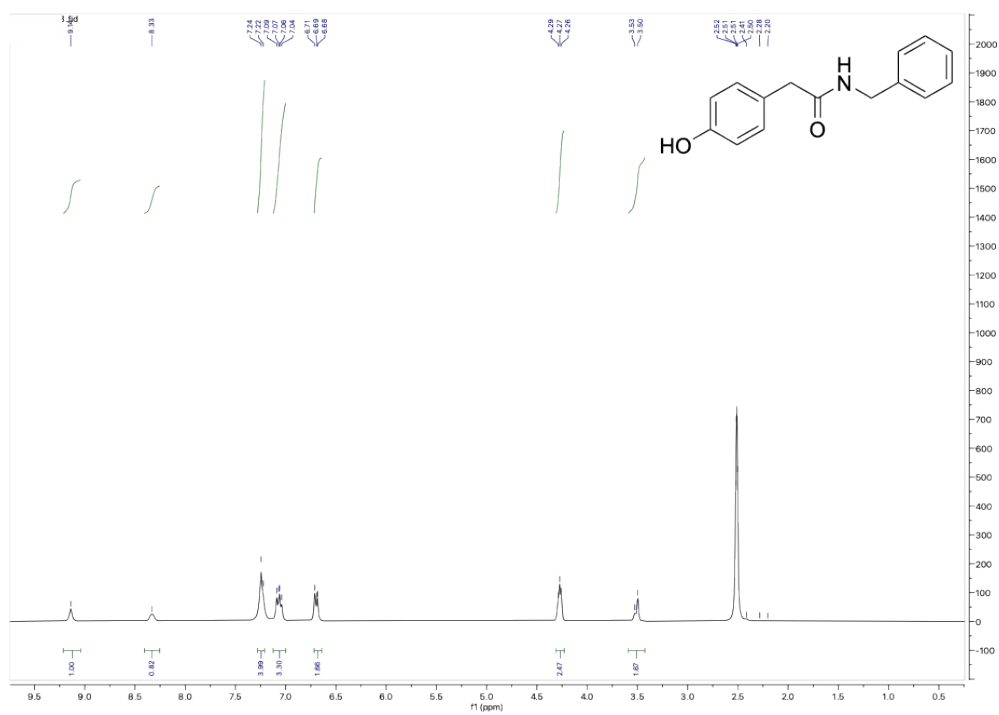
^1H NMR: (300 MHz, CDCl_3) of **4f**



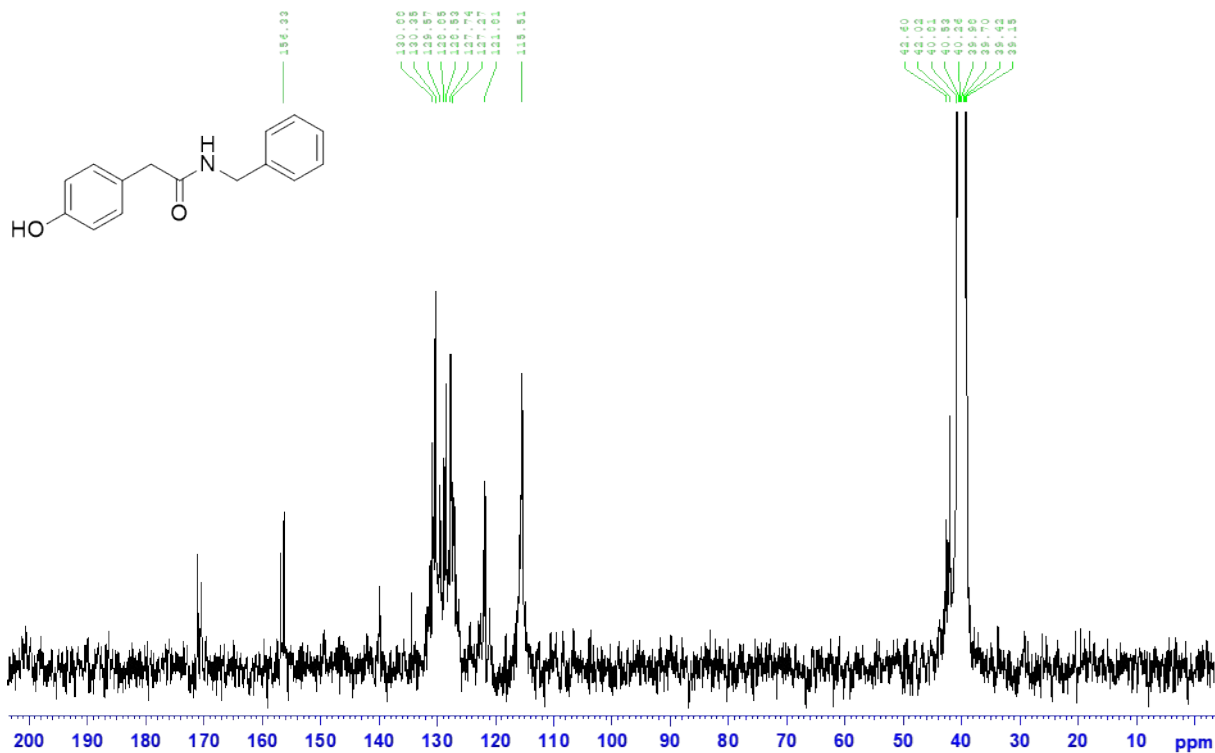
^{13}C NMR: (75 MHz, CDCl_3) of **4f**



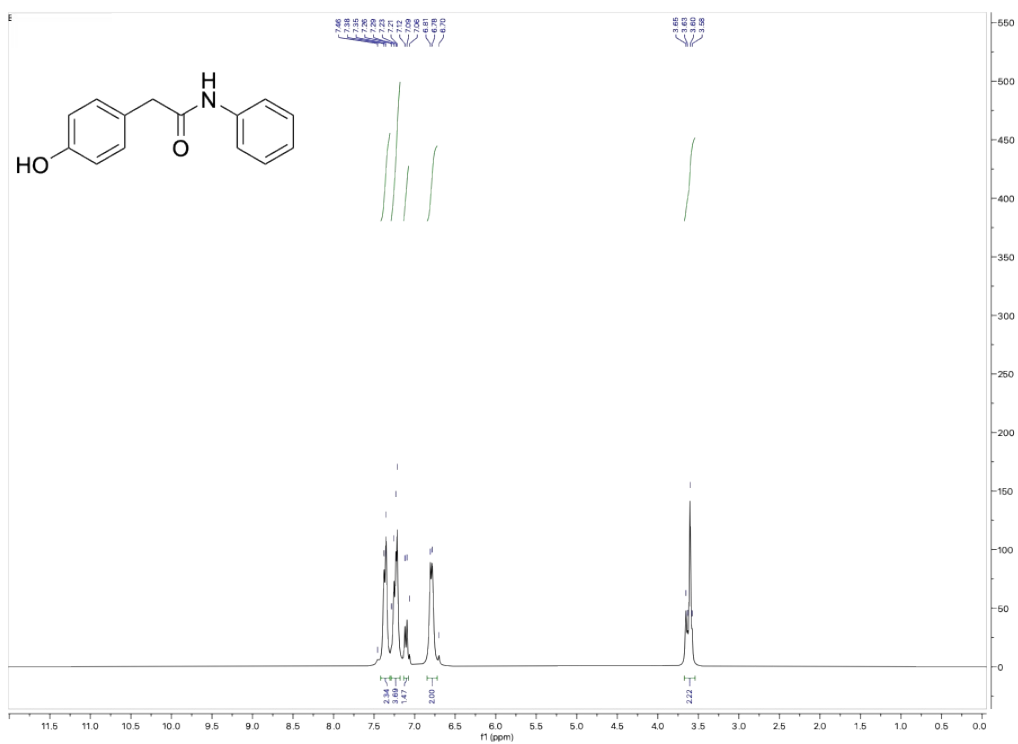
^1H NMR: (300 MHz, DMSO- d_6) of **5a**



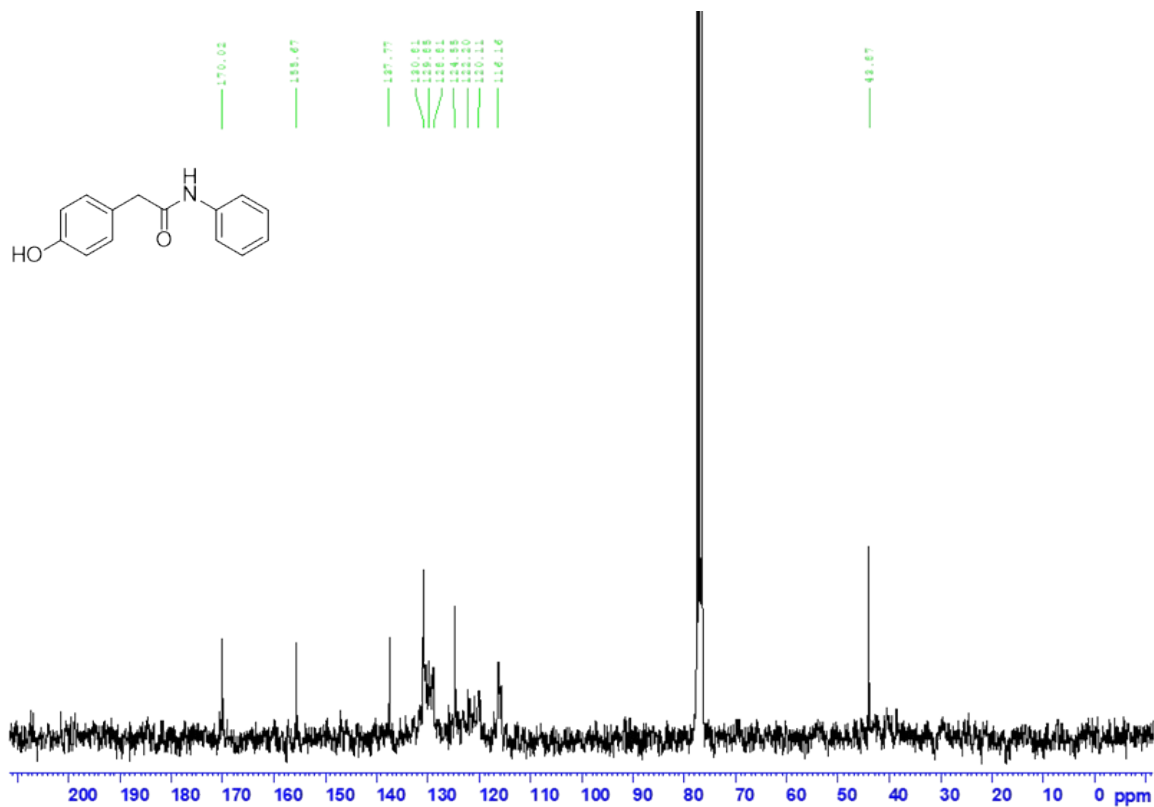
^{13}C NMR: (75 MHz, DMSO- D_6) of **5a**



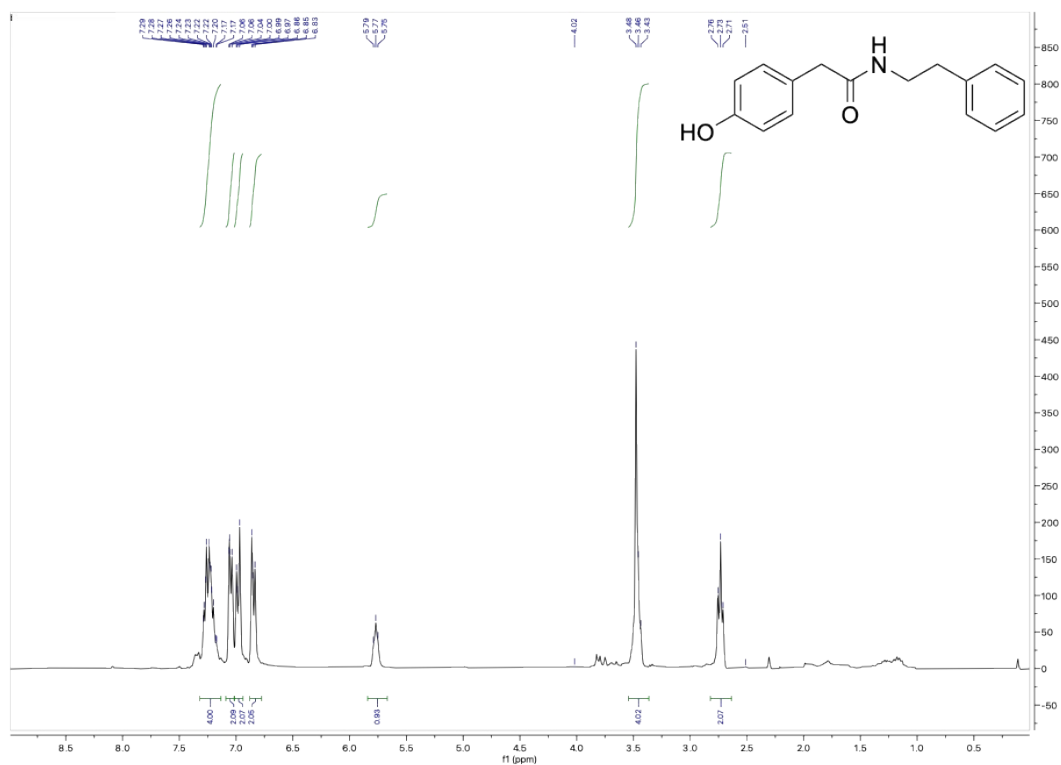
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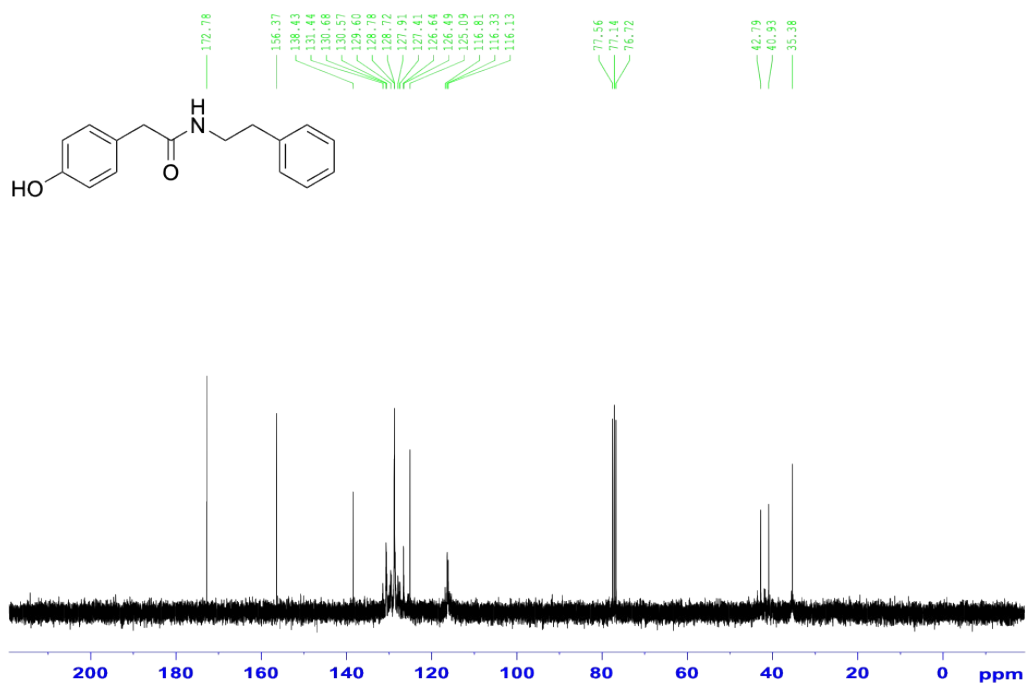
^{13}C NMR: (75 MHz, CDCl_3) of **5b**



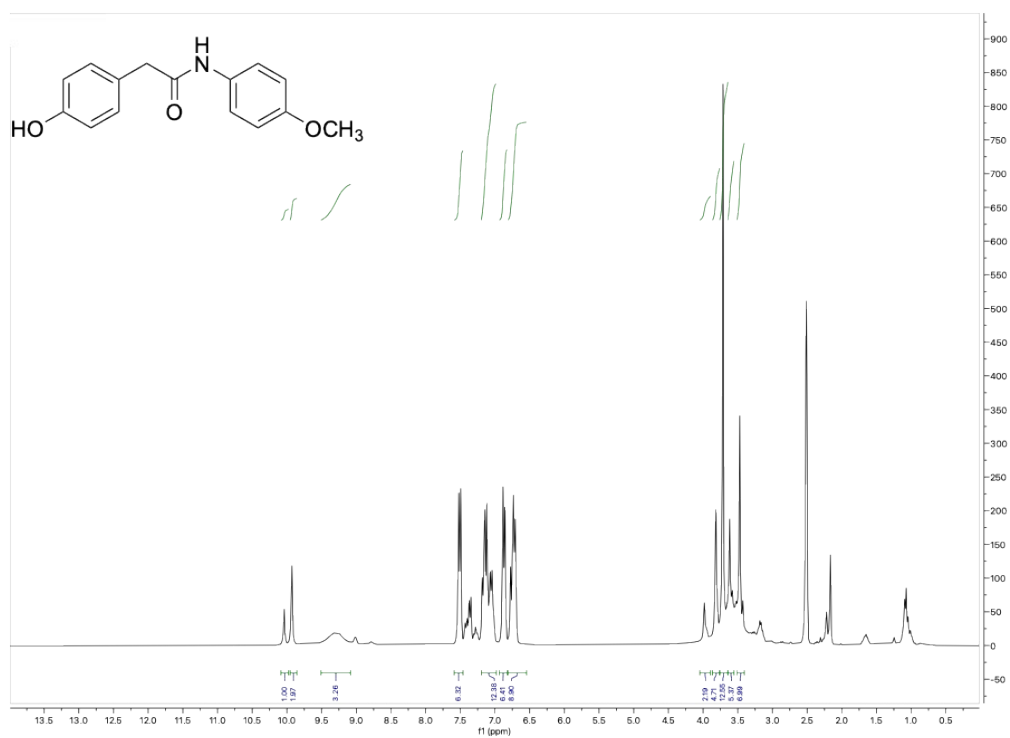
^1H NMR: (300 MHz, CDCl_3) of **5c**



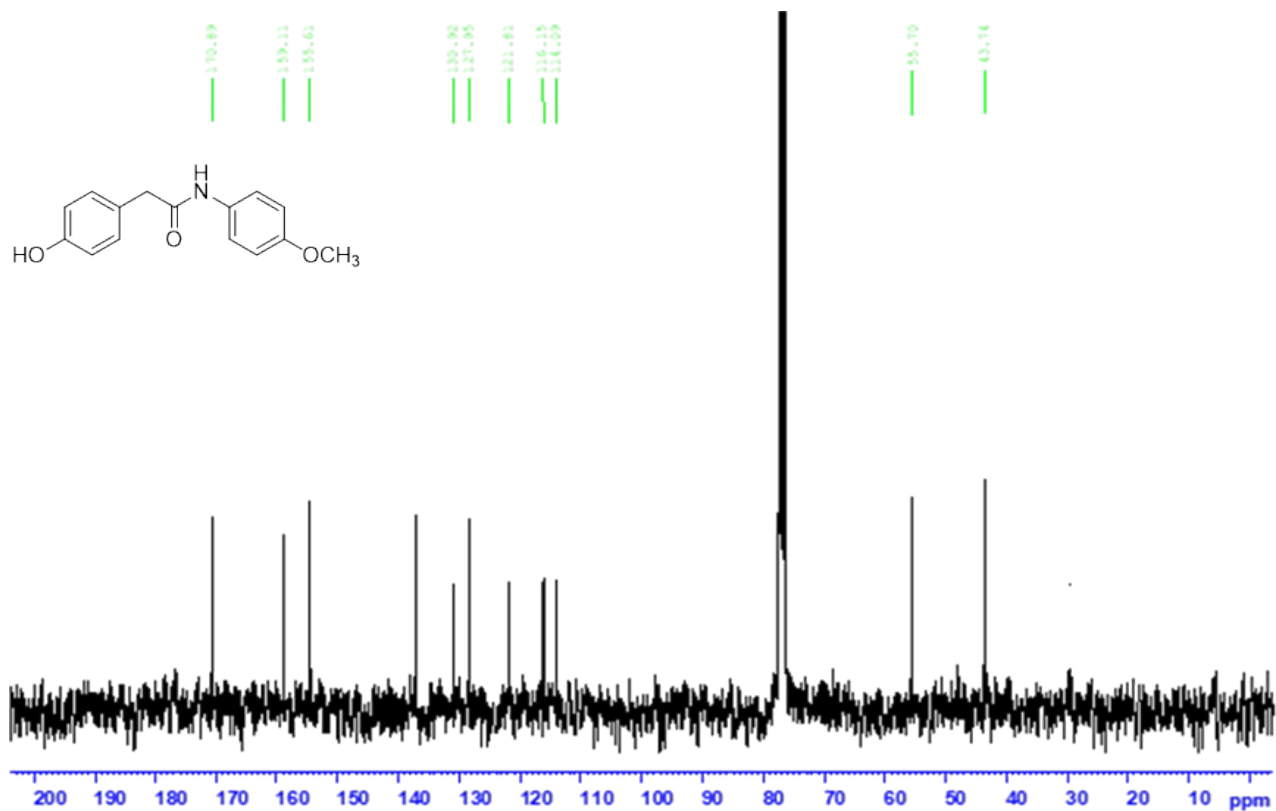
^{13}C NMR: (75 MHz, CDCl_3) of **5c**



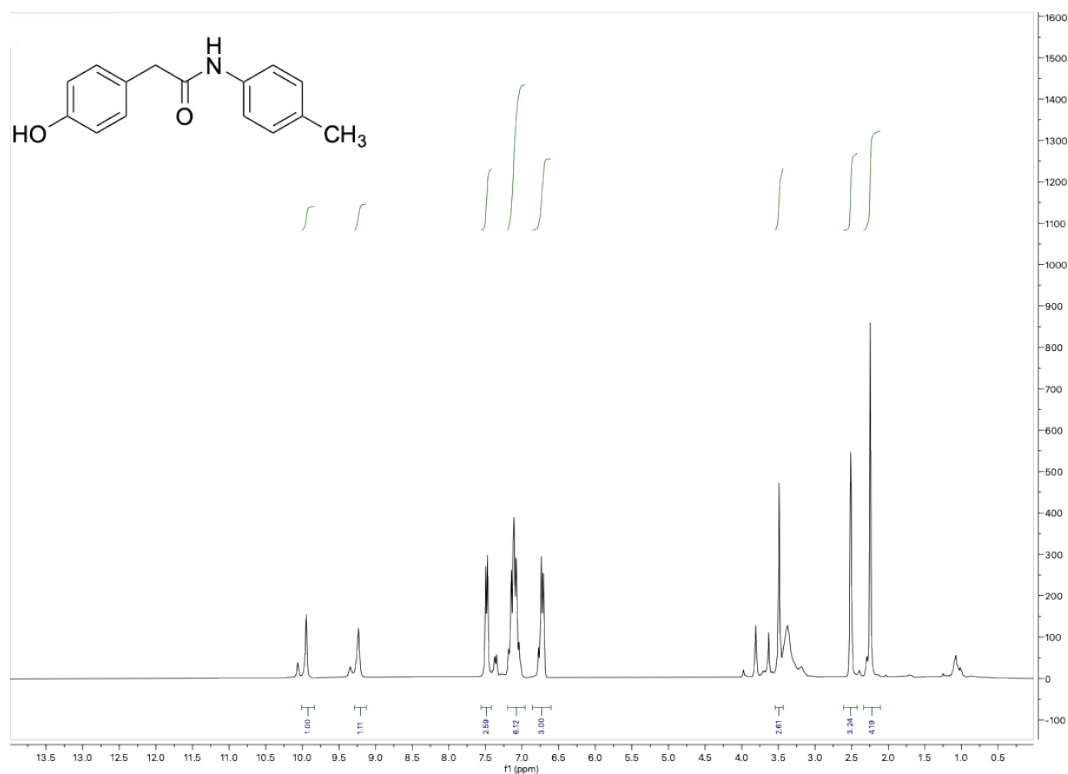
^1H NMR: (300 MHz, DMSO- d_6) of **5d**



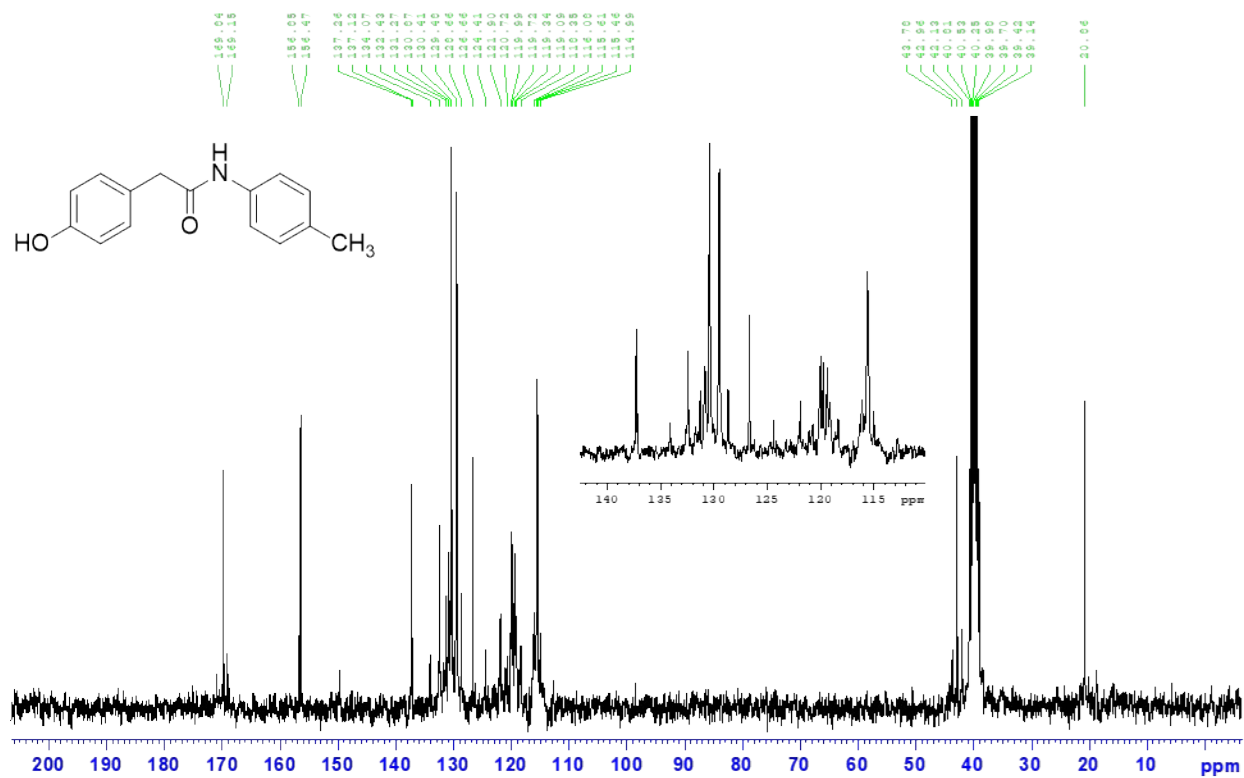
^{13}C NMR: (75 MHz, CDCl_3) of **5d**



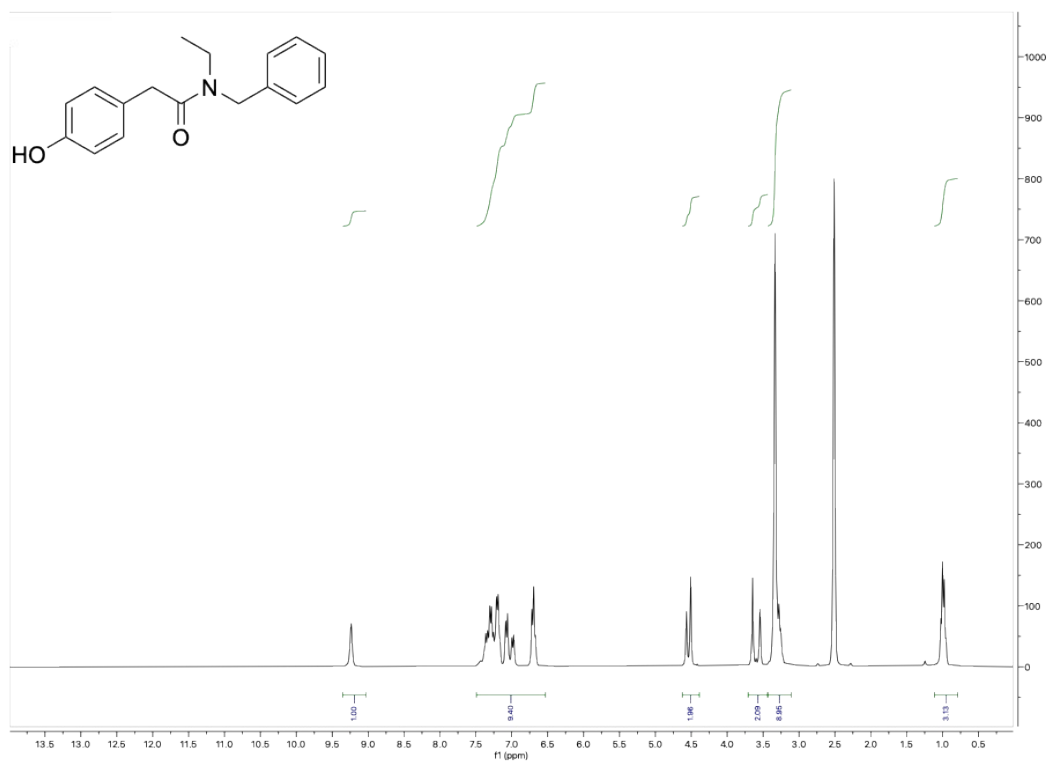
^1H NMR: (300 MHz, DMSO- d_6) of **5e**



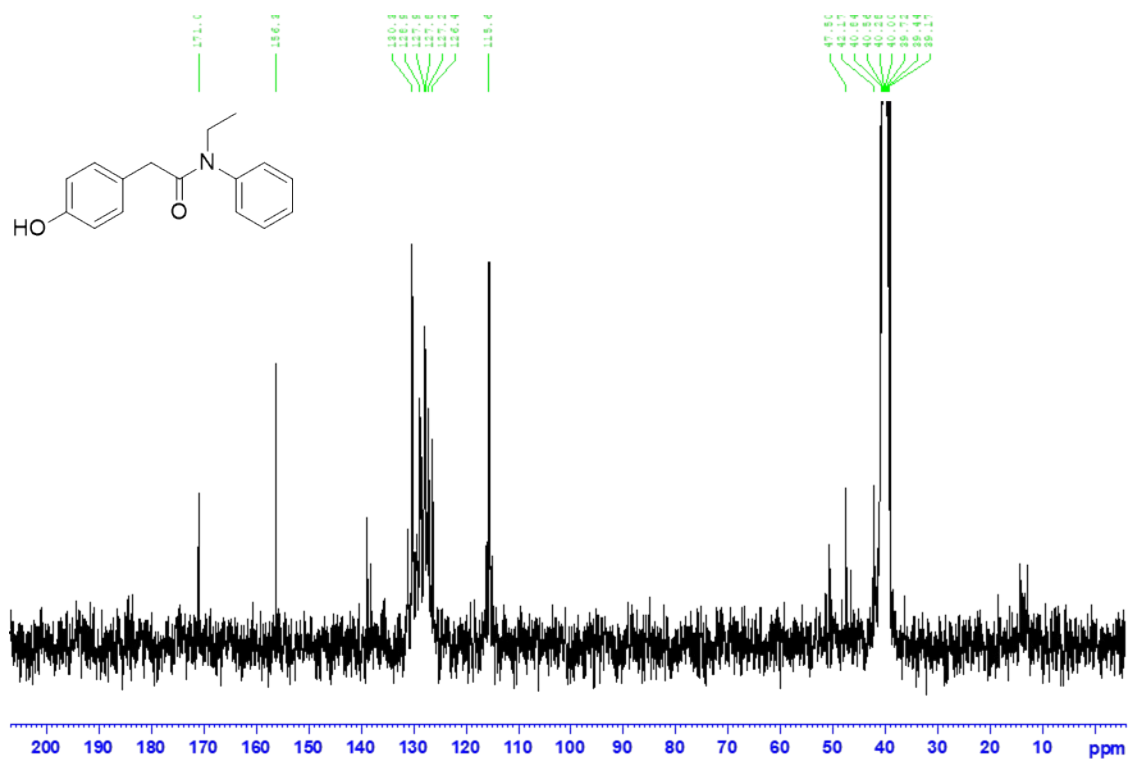
^{13}C NMR: (75 MHz, DMSO- d_6) of **5e**



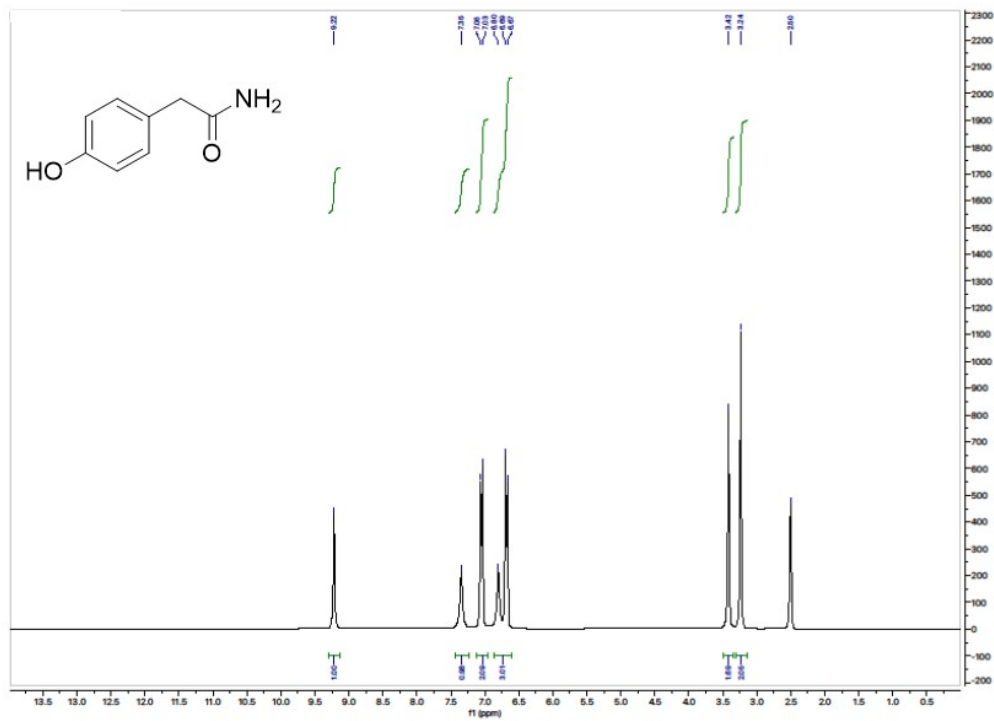
^1H NMR: (300 MHz, DMSO- d_6) of **5f** – mixture of two rotamers



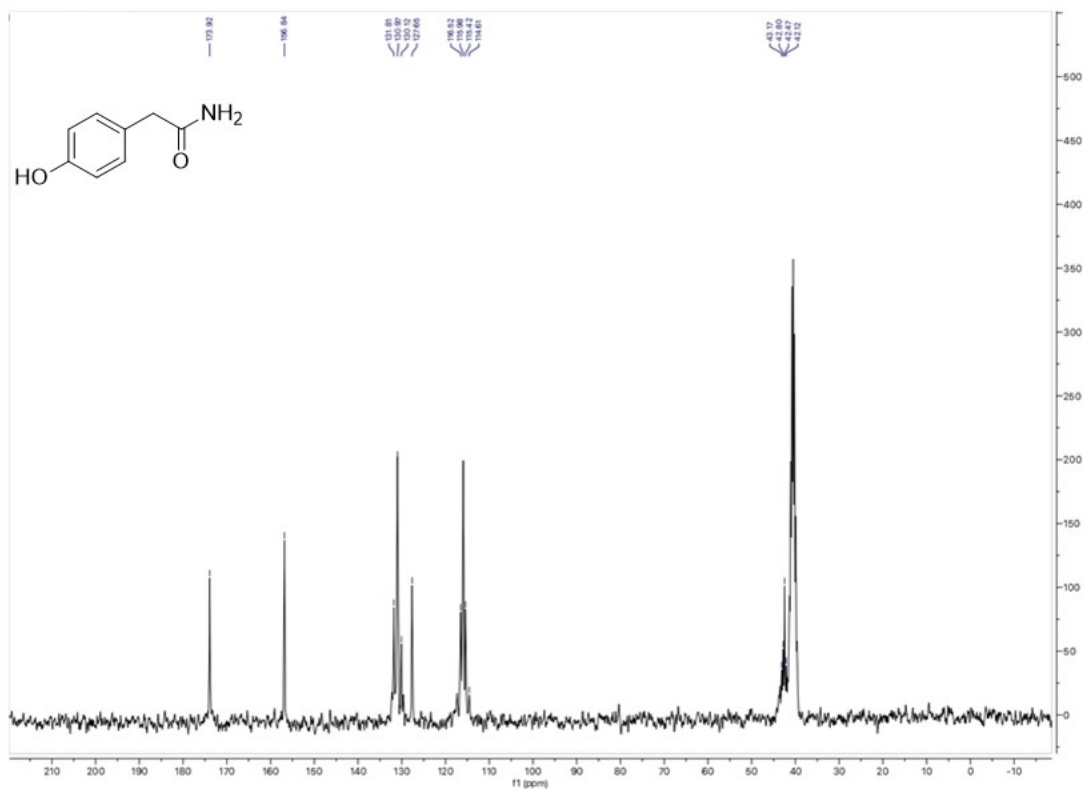
^{13}C NMR: (75 MHz, DMSO- d_6) of **5f** mixture of two rotamers



^1H NMR: (300 MHz, DMSO- d_6) of **5g**



^{13}C NMR: (75 MHz, DMSO- d_6) of **5g**



6. E-Factor and PMI calculation

PMI and E-factor of pilot reaction	
Substrate	mass (g)
<i>N-Phenethyl-2-phenylacetamide</i>	1,00
Reagents	mass (g)
<i>Phenylacetic acid</i>	1,11
<i>ChCl</i>	1,17
<i>EDC</i>	1,28
Organic Solvents	mass (g)
<i>Ethyl acetate</i>	30,00
Water or Aqueous Solutions	mass (g)
<i>water</i>	11,00
Desired Product	mass (g)
<i>AMIDE</i>	1,89

Material Inputs	mass (g)
Substrate	1,00
Reagents	3,56
Solvents	30,00

Aqueous	11,00
Total	45,56
Material Outputs	mass (g)
Product	1,89
Waste	43,67

PMI	24
E-factor	23