SUPPORTING INFORMATION

Rhodium-catalyzed addition of organozinc iodides to carbon-11 isocyanates

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Section 1: General Information

All chemicals and solvents used were bought commercially and were not further purified unless indicated otherwise. All reactions were routinely carried out under inert (argon or nitrogen) atmosphere. All solvents used were anhydrous. 1,4-dioxane was distilled in the lab. All reaction products were confirmed using TLC, mass spectrometry, and ^{1}H-NMR. Purification of reaction products was carried out by flash column chromatography using silica gel. Analytical thin layer chromatography (TLC) was performed on aluminum or glass backing. Visualization was accomplished with UV light. ^{1}H-NMR spectra obtained using Magritek Spinsolve 80 Carbon, Bruker AVANCE 300 or Bruker AVANCE 400. Spectral data are reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm for ^{1}H NMR). ^{1}H NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant(s) in Hz. Mass spectrometry was performed using Waters Xevo TQD with an Acquity UPLC H-Class Plus system. Radiolabeled amides were synthesized using Synthra MeIplus Research module. All products generated were characterized in accordance to the literature.

Phenyl Isocyanate (≥ 98%), phenethyl isocyanate (96%), 4-(trifluoromethyl) phenyl isocyanate (98%), o-tolyl isocyanate (98%), m-tolyl Isocyanate (98%), and isopropyl isocyanate (98%+) were purchased from Alfa Aesar. 4-fluorophenyl isocyanate (99%), 2-methoxyphenyl isocyanate (99%), and phenethyl isocyanate (98%) were purchased from Oakwood Chemicals. 2,6-dimethylphenyl isocyanate (99%) and benzyl isocyanate (99%) were purchased from Thermo Fischer Scientific. Iodobenzene (98%), 4-methoxy iodobenzene (98%), ethyl 3-iodobenzoate (98%), 4'-iodoacetophenone (98%), 1-chloro-4-iodobenzene (99%) were purchased from sigma Aldrich. Anhydrous tetrahydrofuran (THF, ≥ 99%, distilled before use), ethyl acetate (EtOAc, ≥ 99.9%), anhydrous diethylene glycol dimethyl ether (diglyme ≥ 99.5%), acetonitrile (99.8%+), trichloromethylsilane (TMSCl, 99%), and 1,2-dibromoethane (98%+) were purchased from Sigma-Aldrich. Hydroxy(1,5-cyclooctadiene) rhodium(I) dimer (min. 97%), chloro(1,5-cyclooctadiene)rhodium(I) dimer (min. 97%), and palladium(II) acetate (min. 98%) and zinc powder (99.9%) were purchased from Strem Chemicals.

Section 2: Synthetic Procedures

P1 - Synthesis of alkylzinc iodides.

Following literature methods,[1] a flame dried flask (equipped with magnetic stir bar and reflux condenser) was charged with zinc dust (26.00 mmol) in THF (2.00 mL). 1,2-Dibromoethane (0.10 mL) was added and the mixture was heated to reflux with a heat gun. This was repeated a further two times, after which the reaction mixture was cooled to room temperature and TMSCl (0.10 mL) was added slowly followed by 10 minutes of vigorous stirring. Primary alkyl iodide (26.00 mmol) was added as a solution of THF (10.0 mmol) then stirred and heated at 50 °C for 18 hours. The concentration of alkylzinc iodide was determined using iodometric titration.[2]

P2 - Synthesis of phenyl zinc iodide.

Following literature methods,[3] 10 mmol (654 mg) of zinc dust was added to a 10 mL oven-dried round bottom flask. The flask was heated by a heat gun for 10 minutes under vacuum. To the solid, 2.5 mL of diglyme, followed by 0.16 mmol (0.02 mL) of TMSCl, followed by 5 mmol (0.56 mL) of iodobenzene were added under inert atmosphere (argon). The reaction mixture was then stirred for 24 hours at 130 °C. The final mixture was centrifuged, and the supernatant was extracted. Concentration of the phenylzinc iodide solution was determined using an iodometric titration procedure.[2] The final concentration of the phenylzinc iodide used for the reactions in Tables 1 and 2 was 1.03 M.

P3 - Synthesis of functional arylzinc iodide-lithium chloride compounds.

Following literature methods[4] and applying modifications, a dry and argon-flushed Schlenk-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with LiCl (0.90 mmol) and heated to 250 °C for 5 min under high vacuum. After cooling to room temperature under vigorous stirring, $InCl_3$ (0.09 mmol) was added and the Schlenk-tube was again heated to 250 °C for 5 min under high vacuum. After cooling to room temperature, zinc powder (9.0 mmol, 3.0 equiv) and dry THF (4.5 mL) were added. The resulting suspension was treated with a few drops of trimethylsilyl chloride and heated briefly to reflux. Subsequently, the corresponding aryl iodide (3.0 mmol, 1.0 equiv) was added and the reaction mixture was heated under given conditions.[5] The reaction mixture was then centrifuged. The supernatant liquid was transferred via a syringe into an oven-dried test tube. The final concentration of the resulting arylzinc iodides were determined by iodometric titration.[2]

P4 - Synthesis of amides using organozinc iodides and isocyanates.

To a 10 mL oven-dried round bottom flask, 0.005 mmol (2.3 mg) of $[Rh(OH)(cod)]_2$ is added. Then, 2 mL of THF and 0.2 mmol of isocyanate are added. The reaction mixture is stirred for 5 minutes before the addition of 0.4 mmol of arylzinc iodide or 0.6 mmol of alkylzinc iodide. The reaction is stirred for 30 minutes (24 hours for alkylzinc iodides) under inert atmosphere at room temperature. The reaction is then quenched with 2.0 mL saturated aqueous ammonium chloride ($NH_4^+Cl^-$) The mixture was extracted with EtOAc (3 x 10 mL); the organic phase was washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (using silica gel, 0–25% ethyl acetate/hexane gradient).

*This procedure is better completed when scaled out rather than scaled up. In testing on a 1 mmol scale, the reactivity was not consistent from batch to batch; comparatively, multiple reaction set ups in parallel could reliably reproduce similar results.

P5 - Synthesis of radiolabeled amides.

Using Synthra MeIplus Research module, 22.90 μmol of the amine with 35.50 μmol of DBU in 500 μL ACN are added in Reactor 1. 45.80 μmol of DBAD with 45.80 μmol of PBu_3 in 200uL ACN are added in Vial 1. Carbon-11 CO_2 ($[^{11}C]CO_2$) — generated from bombardment of a gas target filled with a pressurized N_2/O_2 mixture using a Siemens 11 MeV cyclotron, typically 40–55 μA for 1–2 minutes — was trapped at -180 °C in a steel coil. $[^{11}C]CO_2$ is then bubbled into a 2 mL glass reactor vessel, after which the contents in vial 1 are immediately added into the reactor to convert the carbamate to the radiolabeled isocyanate. After reacting for 1 minute, the solution is transferred to a vial charged with 1.0 mg of $[Rh(OH)(cod)]_2$. 0.3 mL of organozinc iodide is then added and allowed to react for 15* minutes. The mixture is subsequently quenched with 1.0 mL of deionized water, followed by addition of ethyl acetate. The mixture is centrifuged to rapidly separate the layers. The organic phase is sampled and analyzed using radioHPLC. Trapping efficiency is calculated as the decay-corrected activity yield in the reactor relative to the steel coil using calibrated proximal radiation detectors. Product yield is determined according to relative peak integrations on radioHPLC, with decay-correction to time of injection. When needed, a sand bath was used to heat the reaction.

*Products $[^{11}C]$**6d** and $[^{11}C]$**6g** were reacted for 10 minutes.

P6 – Automated synthesis of radiolabeled amides.

Using Synthra MeIplus Research module, 22.90 μmol of the amine with 35.50 μmol of DBU in 500 μL ACN are added in Reactor 1. 45.80 μmol of DBAD with 45.80 μmol of PBu_3 in 200uL ACN are added in Vial A3. 1.0 mg of $[Rh(OH)(cod)]_2$ in 0.4 mL ACN was added in Vial A2. 0.3 mL of organozinc iodide was placed in Reactor 2 while 1.0 mL of 1 M HCl (aq) was added to Vial B1. Carbon-11 CO_2 ($[^{11}C]CO_2$) — generated from bombardment of a gas target filled with a pressurized N_2/O_2 mixture using a Siemens 11 MeV cyclotron, 55 μA for 20 minutes — was trapped at -180 °C in a steel coil. $[^{11}C]CO_2$ is then bubbled into a 2 mL glass reactor vessel, after which the contents in Vial A3 are immediately added into the reactor to convert the carbamate to the radiolabeled isocyanate, stirring for 1 minute. Vial A2 was added to the reaction mixture, then directed towards reactor 2. The solution was allowed to react for 10 minutes with the organozinc iodide. The mixture is subsequently quenched with the contents of B1. This solution was added to the HPLC injection loop and injected onto a Macherey-Nagel Nucleodur C18 HTec column (5 μm, 250x10 mm). It was purified using 45:55 acetonitrile to 0.1 M ammonium formate mobile phase at a flow rate of 5 mL/min. The isolated product was verified by analytical radioHPLC and molar activity was determined via a calibration curve. Trapping efficiency is calculated as the decay-corrected activity yield in the reactor relative to the steel coil using calibrated proximal radiation detectors.

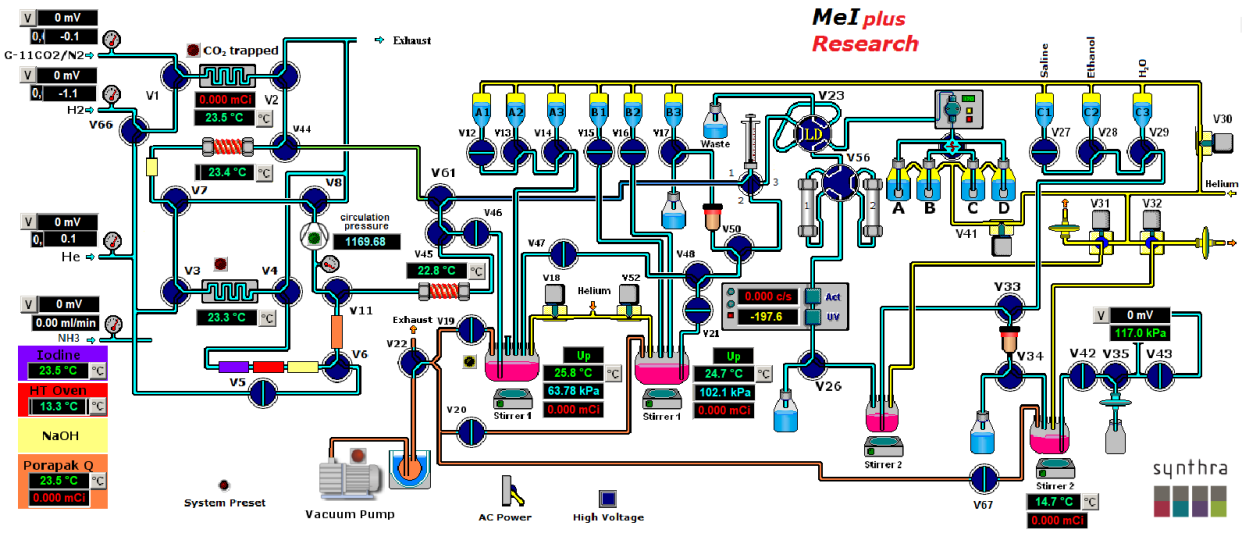
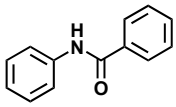


Figure S1. Synthra MeIplus Research apparatus scheme.

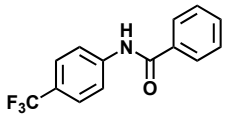
Section 3: Experimental Data

3a. *N*-phenyl benzamide



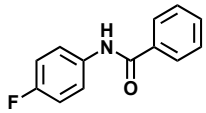
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (31 mg, yield 78%). ^{1}H-NMR (80 MHz, $CDCl_3$): d 7.87 (d, 2H), 7.83 (s, 1H), 7.63 (d, 2H), 7.57 (t, 1H), 7.50 (t, 2H), 7.39 (t, 2H), 7.17 (t, 1H). MS (ESI+): Calculated $C_{11}H_{13}NO$ as 197.08, [M+H] found as 198.22 m/z. Characterized in accordance to the literature.[6]

3b. *N*-4-trifluoromethylphenyl benzamide



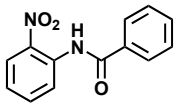
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (45 mg, yield 87%), ^{1}H-NMR (80 MHz, $CDCl_3$): d 7.91 (s, 1H), 7.89 (d, 2H), 7.79 (d, 2H), 7.65 (d, 2H), 7.60 (m, 1H), 7.53 (t, 2H). MS (ESI+): Calculated $C_{14}H_{10}F_3NO$ as 265.07, [M+H] found as 266.08 m/z. Characterized in accordance to the literature.[6]

3c. *N*-4-fluorophenyl benzamide



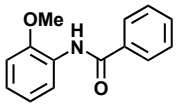
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (35 mg, yield 81%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.89 (m, 2H), 7.77 (s, 1H), 7.62 (d, 2H), 7.38 (t, 2H), 7.23 (m, 3H). MS (ESI+): Calculated $C_{13}H_{10}FNO$ as 215.07, [M+H] found 216.03 m/z. Characterized in accordance to the literature.[7]

3d. *N*-2-nitrophenyl benzamide



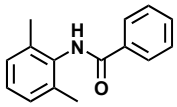
Followed the general procedure of amide synthesis (P4), product obtained as a yellow solid (38 mg, yield 79%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.24 (t, 1H), 7.55 (m, 2H), 7.63 (t, 1H), 7.74 (t, 1H), 8.01 (m, 2H), 8.30 (dd, 1H), 9.03 (dd, 1H), 11.38 (s, 1H). MS (ESI+): Calculated $C_{13}H_{10}N_2O_3$ as 242.07 [M+H] found 243.07 m/z. Characterized in accordance to the literature.[8]

3e. *N*-2-methoxyphenyl benzamide



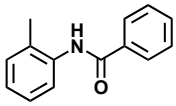
Followed the general procedure of amide synthesis (P4), product obtained as a white solid. (14 mg, yield 31%), ^{1}H-NMR (80 MHz, $CDCl_3$): 8.55 (m, 2H), 7.91 (m, 2H), 7.50 (m, 3H), 6.94 (m, 3H) 3.96 (s, 3H). MS (ESI+): Calculated $C_{14}H_{13}NO_2$ as 227.09, [M+H] found 228.09 m/z. Characterized in accordance to the literature.[9]

3f. *N*-2,6-dimethylphenyl benzamide



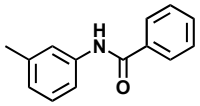
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (28 mg, yield 62%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.94 (m, 2H), 7.59 (m, 1H), 7.51 (m, 3H), 7.15 (m, 3H), 2.41 (s, 6H). MS (ESI+): Calculated $C_{15}H_{15}NO$ as 225.12, [M+H] found 226.13 m/z. Characterized in accordance to the literature.[10]

3g. *N*-2-methylphenyl benzamide



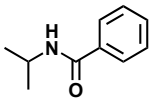
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (17 mg, yield 68%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.98 (d, 1H), 7.90 (d, 2H), 7.65 (s, 1H), 7.58 (m, 1H), 7.52 (m, 2H), 7.29 (m, 1H), 7.24 (m, 1H), 7.14 (m, 1H), 2.35 (s, 3H). MS (ESI+): Calculated $C_{14}H_{13}NO$ as 211.10, [M+H] found 212.13 m/z. Characterized in accordance to the literature.[6]

3h. *N*-3-methylphenyl benzamide



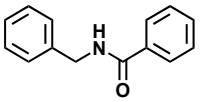
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (18 mg, yield 71%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.87 (d, 2H), 7.75 (s, 1H), 7.56 (m, 4H), 7.42 (d, 1H), 7.26 (m, 1H), 6.98 (m, 1H), 2.21 (s, 3H). MS (ESI+): Calculated $C_{14}H_{13}NO$ as 211.10, [M+H] found 212.10 m/z. Characterized in accordance to the literature.[6]

3i. *N*-isopropyl benzamide



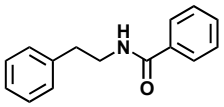
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (8 mg, yield 25%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.60 (dd, 2H), 7.25 (tt, 1H), 7.20 (dt, 2H), 5.75 (bs, 1H), 4.15 (sept, 1H), 1.15 (d, 6H). MS (ESI+): Calculated $C_{10}H_{13}NO$ as 163.10, [M+H] found 164.15 m/z. Characterized in accordance to the literature.[11]

3j. *N*-benzyl benzamide



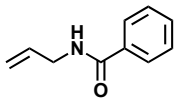
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (24 mg, yield 57%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.82 (d, 2H), 7.51 (t, 1H), 7.43 (t, 2H), 7.36 (m, 4H), 7.29 (m, 1H), 6.69 (s, 1H), 4.64 (d, 2H). MS (ESI+): Calculated $C_{14}H_{13}NO$ as 211.10, [M+H] found 212.04 m/z. Characterized in accordance to the literature.[12]

3k. *N*-phenethyl benzamide



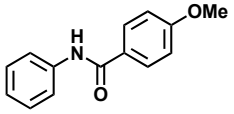
Followed the general procedure of amide synthesis (P4), product obtained as a white solid. (26mg, yield 63%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.69 (d, 2H), 7.46 (t, 1H), 7.38 (t, 2H), 7.31 (t, 2H), 7.23 (t, 3H), 6.40 (s, 1H), 3.69 (q, 2H), 2.91 (t, 2H). MS (ESI+): Calculated $C_{15}H_{15}NO$ as 225.12, [M+H] found 226.21 m/z. Characterized in accordance to the literature.[13]

3l. *N*-allyl benzamide



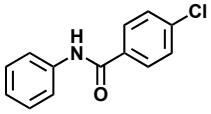
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (9 mg, yield 27%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.78 (dd, 2H), 7.45-7.50 (m, 1H), 7.25 (dt, 2H), 6.75 (bs, 1H), 5.85-5.95 (m, 1H), 5.20 (dd, 1H), 5.13 (ddd, 1H), 4.00-4.05 (m, 2H). MS (ESI+): Calculated $C_{10}H_{11}NO$ as 161.08, [M+H] found 162.08 m/z. Characterized in accordance to the literature.[11]

3m. *N*-phenyl 4-methoxybenzamide



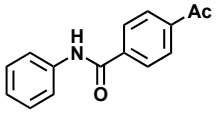
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (34 mg, yield 74%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.82 (m, 1H), 7.62 (m, 2H), 7.37 (m, 2H), 7.14 (m, 1H), 6.96 (m, 2H), 3.87 (s, 3H). MS (ESI+): Calculated $C_{14}H_{13}NO_2$ as 227.09, [M+H] found 228.27 m/z. Characterized in accordance to the literature.[14]

3n. *N*-phenyl 4-chlorobenzamide



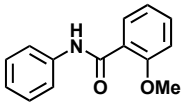
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (14 mg, yield 44%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.96 (d, 2H), 7.84 (d, 2H), 7.61 (t, 1H), 7.55 (t, 2H), 7.42 (d, 2H). MS (ESI+): Calculated $C_{13}H_{10}ClNO$ as 231.05, [M+H] found 232.07 m/z. Characterized in accordance to the literature.[14]

3o. *N*-phenyl 4-acetylbenzamide



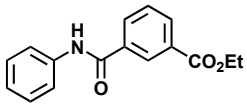
Followed the general procedure of amide synthesis (P4), product obtained as a light yellow solid (9mg, yield 34%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.89 (m, 2H), 7.67 (s, 1H), 7.54 (m, 4H), 2.61 (s, 3H). MS (ESI+): Calculated $C_{15}H_{13}NO_2$ as 239.09, [M+H] found 240.12 m/z. Characterized in accordance to the literature.[15]

3p. *N*-phenyl 2-methoxybenzamide



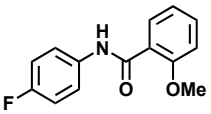
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (20 mg, yield 43%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.28 (m, 1H), 7.69 (m, 2H), 7.37 (m, 1H), 7.34 (m, 2H), 7.13 (m, 2H), 7.02 (m, 1H), 4.03 (s, 3H). MS (ESI+): Calculated $C_{14}H_{13}NO_2$ as 227.09, [M+H] found 228.23 m/z. Characterized in accordance to the literature.[14]

3q. *N*-phenyl 3-ethylester benzamide



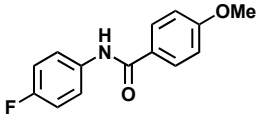
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (16 mg, yield 47%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.92 (d, 2H), 7.65 (dd, 1H), 7.39 (t, 2H), 7.30 (t, 2H), 7.21 (dd, 1H), 4.51 (q, 2H), 1.52 (t, 3H). MS (ESI+): Calculated $C_{16}H_{15}NO_3$ as 269.11, [M+H] found 270.08 m/z. Characterized in accordance to the literature.[16]

3r. *N*-4-fluorophenyl-2-methoxybenzamide



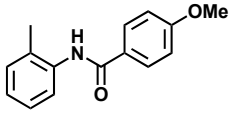
Followed the general procedure of amide synthesis (P4), product obtained as a yellow solid (13 mg, yield 27%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.29-8.27 (m, 1H), 7.65-7.62 (m, 3H), 7.52-7.48 (m, 1H), 7.13 (t, H), 7.07-7.02 (m, 3H), 4.05 (s, 3H). MS (ESI+): Calculated $C_{14}H_{12}FNO_2$ as 245.09, [M+H] found 246.24 m/z. Characterized in accordance to the literature.[17]

3s. *N*-4-fluorophenyl 4-methoxybenzamide



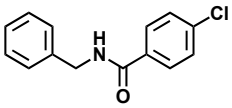
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (27mg, yield 83%),[1]H-NMR (80 MHz, $CDCl_3$): δ 7.95 (d, 2H), 7.80 (m, 2H), 7.19 (m, 2H), 7.06 (d, 2H), 3.83 (s, 3H). MS (ESI+): Calculated $C_{14}H_{12}FNO_2$ as 245.09, [M+H] found 260.21 m/z. Characterized in accordance to the literature.[18]

3t. *N*-2-methylphenyl 4-methoxybenzamide



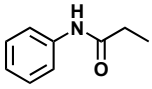
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (24mg, yield 76%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.87 (m, 1H), 7.83 (dd, 1H), 7.17 (dd, 2H), 6.68 (d, 2H), 3.87 (s, 3H), 2.33 (s, 3H). MS (ESI+): Calculated $C_{15}H_{15}NO_2$ as 241.11, [M+H] found 242.13 m/z. Characterized in accordance to the literature.[19]

3u. *N*-benzyl 4-chlorobenzamide



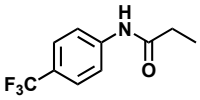
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (14mg, yield 44%), 1H-NMR (80 MHz, CDCl3): δ 7.76 (d, 2H), 7.64 (d, 2H), 7.55 (t, 1H), 7.41 (t, 2H), 7.17 (d, 2H), 4.54 (d, 2H) . MS (ESI+): Calculated $C_{14}H_{12}ClNO$ as 245.06, [M+H] found 246.07 m/z. Characterized in accordance to the literature.[20]

4a. *N*-phenyl propanamide



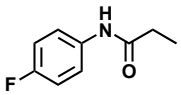
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (19.6mg, yield 64%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 7.52 (m, 2H), 7.33 (t, 2H), 7.11 (m, 2H), 2.39 (q, 2H), 1.25 (t, 3H, CH3).). MS (ESI+): Calculated $C_9H_{11}NO$ as 149.08, [M+H] found 150.11 m/z. Characterized in accordance to the literature.[21]

4b. *N*-4-trifluoromethylphenyl propanamide



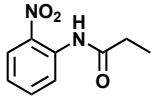
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (26 mg, yield 60%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, 4H), 7.37 (bs, 1H), 2.41 (dd, 2H), 1.24 (t, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.52, 141.12, 126.45, 124.24, 119.50, 118.82, 30.97, 9.66. MS (ESI+): Calculated $C_{10}H_{10}F_3NO$ as 217.07, [M+H] found 218.23 m/z, calculated 218.20. Spectra given, page S22.

4c. *N*-4-fluorophenyl propanamide



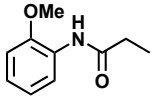
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (13.7mg, yield 41%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 4.43 (dd, 2H), 6.94 (t, 2H), 2.33 (q, 2H), 1.27 (t, 3H). MS (ESI+): Calculated $C_9H_{10}FNO$ as 167.07, [M+H] found 168.08 m/z. Characterized in accordance to the literature.[21]

4d. *N*-2-nitrophenyl propanamide



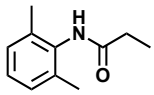
Followed the general procedure of amide synthesis (P4), product obtained as a yellow solid (22.8mg, yield 59%), ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 10.34 (s, 1H), 8.83 (dd, 1H), 8.22 (dd, 1H), 7.71 (m, 1H), 7.16 (m, 1H), 2.57 (q, 2H), 1.28 (t, 3H). MS (ESI+): Calculated $C_9H_{10}N_2O_3$ as 194.07, [M+H] found 195.13 m/z. Characterized in accordance to the literature.[22]

4e. *N*-2-methoxyphenyl propanamide



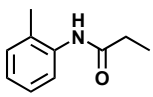
Followed the general procedure of amide synthesis (P4), product obtained as a brown oil (3.6 mg, yield 10%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 10.34 (s, 1H), 8.83 (dd, 1H), 8.22 (dd, 1H), 7.71 (m, 1H), 7.16 (m, 1H), 2.57 (q, 2H), 1.28 (t, 3H). MS (ESI+): Calculated $C_{10}H_{13}NO_2$ as 179.09, [M+H] found 180.06 m/z. Characterized in accordance to the literature.[22]

4f. *N*-2,6-dimethylphenyl propanamide



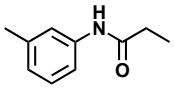
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (3.5mg, yield 10%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.94 (m, 2H), 7.59 (m, 1H), 2.41 (s, 6H), 2.54 (q, 2H), 1.23 (t, 3H). MS (ESI+): Calculated $C_{11}H_{15}NO$ as 177.12, [M+H] found 178.22 m/z. Characterized in accordance to the literature.[23]

4g. *N*-2-methylphenyl propanamide



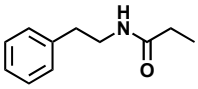
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (10.4 mg, yield 32%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 7.68 (m, 1H), 7.37 (m, 1H), 7.31 (d, 1H), 7.17 (t, 1H), 2.38 (s, 2H), 2.30 (q, 2H), 1.22 (t, 3H). MS (ESI+): Calculated $C_{10}H_{13}NO$ as 163.10, [M+H] found 164.18 m/z. Characterised in accordance to the literature.[24]

4h. *N*-3-methylphenyl propanamide



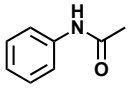
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (10.2 mg, yield 31%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 7.72 (m, 1H), 7.37 (d, 1H), 7.31 (d, 1H), 7.15 (t, 1H), 6.90 (d, 1H), 2.37 (q, 2H), 2.31 (s, 3H), 1.21 (t, 3H). MS (ESI+): Calculated $C_{10}H_{13}NO$ as 163.10, [M+H] found 164.13 m/z. Characterised in accordance to the literature.[25]

4j. *N*-phenethyl propanamide



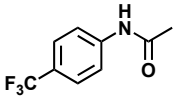
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (7.8mg, yield 22%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 7.15 (m, 4H), 6.02 (s, 1H), 3.55 (q, 2H), 2.86 (t, 2H), 2.17 (q, 2H), 1.13 (t, 3H). MS (ESI+): Calculated $C_{11}H_{15}NO$ as 177.12, [M+H] found 178.02 m/z. Characterised in accordance to the literature.[24]

4k. *N*-phenyl acetamide



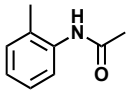
Followed the general procedure of amide synthesis (P4), product obtained as a white solid (11.6mg, yield 43%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 9.02 (s, 1H), 7.53 (d, 2H), 7.29 (t, 2H), 7.11 (t, 1H), 2.13 (s, 3H). MS (ESI+): Calculated C_8H_9NO as 135.07, [M+H] found 136.05 m/z. Characterised in accordance to the literature.[24]

4l. *N*-4-trifluoromethyl acetamide



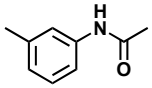
Followed the general procedure of amide synthesis (P4), product was obtained as a white solid (19.1mg, yield 47%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 10.28 (s, 1 H), 7.74 (m, 4H), 2.12 (s, 3H). MS (ESI+): Calculated $C_9H_8F_3NO$ as 203.06, [M+H] found 204.16 m/z. Characterised in accordance to the literature.[26]

4m. *N*-2-methylphenyl acetamide



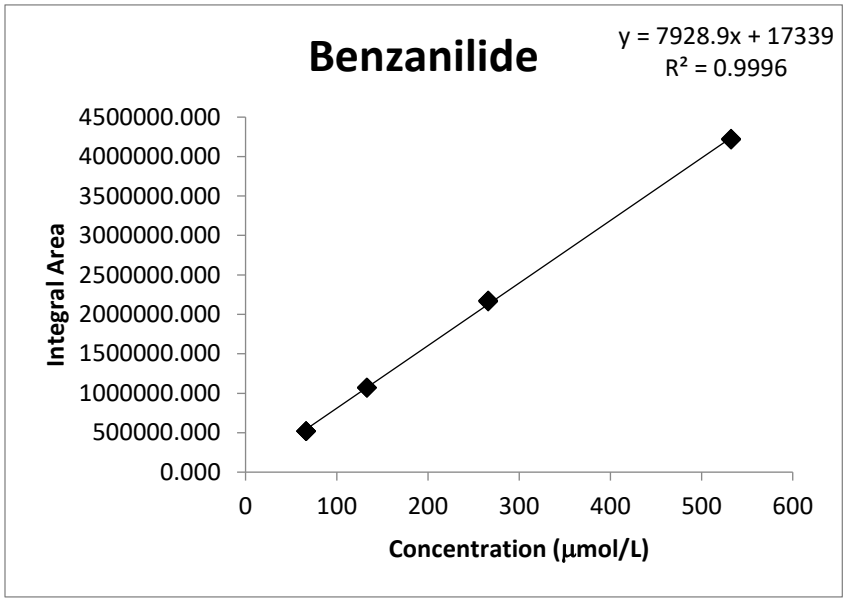
Followed the general procedure of amide synthesis (P4), product was obtained as a white solid (3.1 mg, yield 10%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 8.52 (s, 1H), 7.39 (s, 1H), 7.25 (m, 1H), 7.21 (t, 1H), 6.88 (t, J= 7.6 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H). MS (ESI+): Calculated $C_9H_{11}NO$ as 149.08, [M+H] found 150.02 m/z. Characterised in accordance to the literature.[27]

4n. *N*-3-methylphenyl acetamide

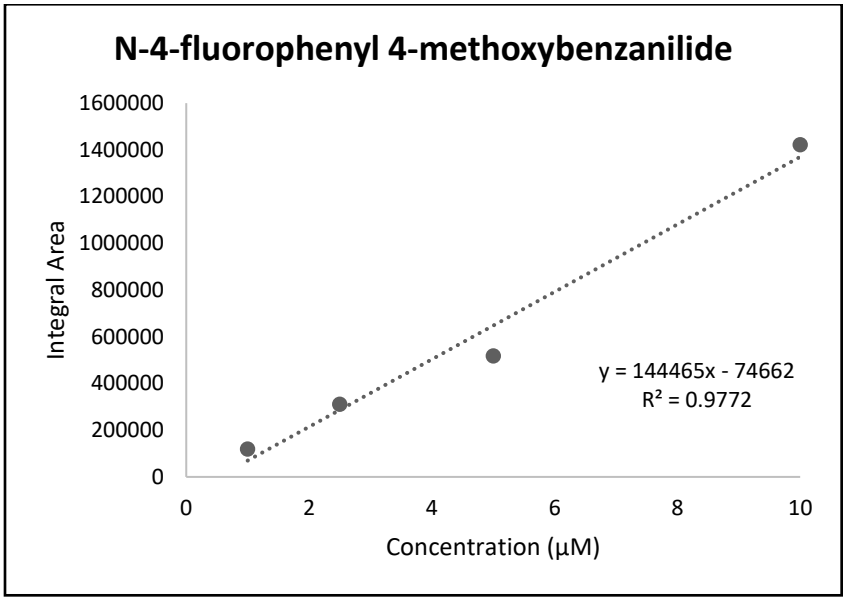


Followed the general procedure of amide synthesis (P4), product was obtained as a white solid (3.2 mg, yield 13%). ^{1}H-NMR (80 MHz, $CDCl_3$): δ = 8.57 (s, 1H), 7.42 (m, 1H), 7.31 (m, 1H), 7.08 (t, 1H), 7.02 (t, 1H), 2.30 (s, 3H), 2.22 (s, 3H). MS (ESI+): Calculated $C_9H_{11}NO$ as 149.08, [M+H] found 150.08 m/z. Characterised in accordance to the literature.[28]

Section 4: Calibration Curves

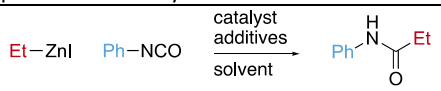


*Used with HPLC to determine benzanilide conversion.



Section 5: Optimization

Table S1 Optimization of alkyl zinc iodide reaction conditions[a]



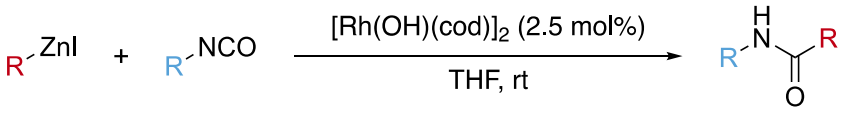
1i **2a** **4a**

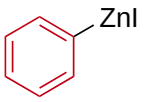
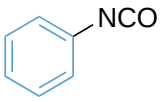
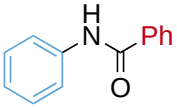
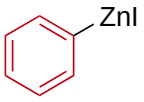
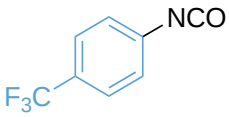
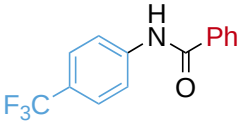
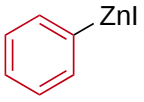
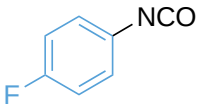
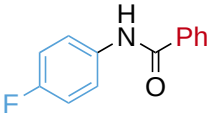
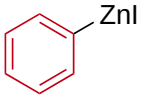
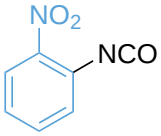
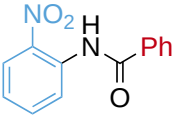
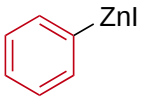
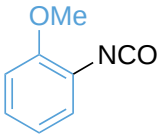
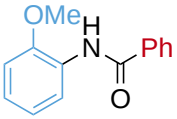
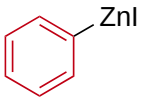
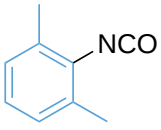
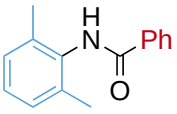
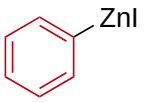
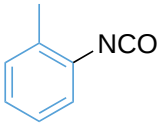
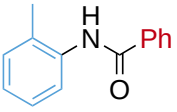
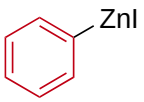
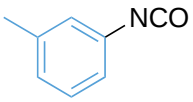
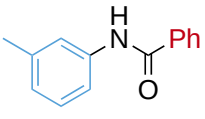
Entry	Temperature (°C)	Additives [b]	Catalyst [c]	Conversion [d]
1	rt	-	-	0%
2	rt	-	$[Rh(OH)(cod)]_2$	60%
3	50	-	$[Rh(OH)(cod)]_2$	60%
4	0	-	$[Rh(OH)(cod)]_2$	50%
5	rt	NEt_3	$[Rh(OH)(cod)]_2$	10%
6	rt	PhOH	$[Rh(OH)(cod)]_2$	60%
7	rt	DBU	$[Rh(OH)(cod)]_2$	40%
8	rt	DBAD	$[Rh(OH)(cod)]_2$	50%
9	rt	-	$[Pd(PPh_3)_4]$	0%
10	rt	-	$Pd(OAc)_2$	0%
11	rt	-	$[RhCl(PPh_3)_3]$	0%
12	rt	-	$[Rh(Cl)(cod)]_2$	60%

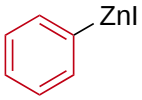
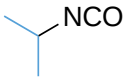
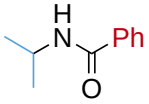
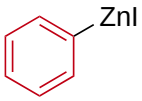
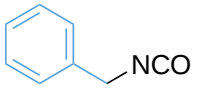
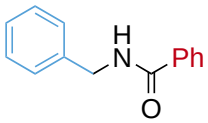
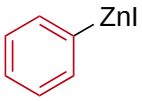
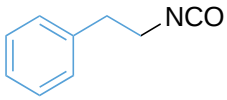
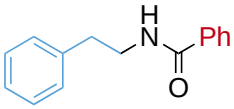
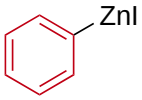
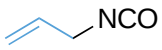
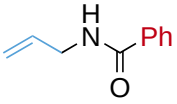
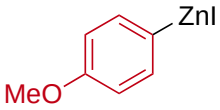
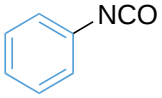
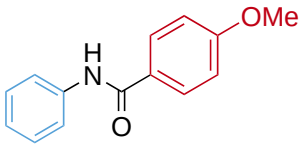
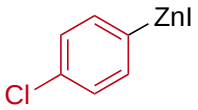
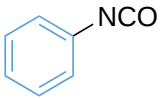
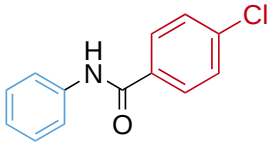
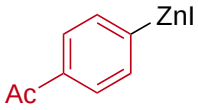
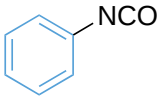
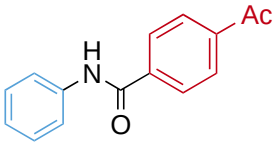
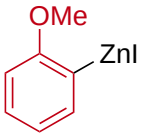
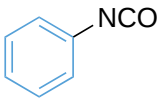
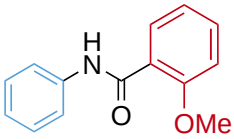
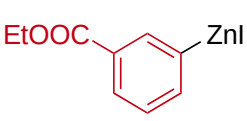
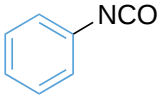
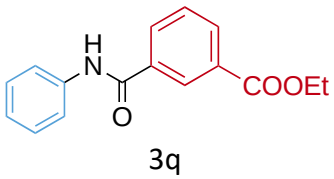
[a] Reaction conditions: **1a** (3 equiv., 0.6 mmol), phenyl isocyanate (1 equiv., 0.2 mmol), THF (2 mL), 18 h, under Ar. [b] Additive (1 equiv., 0.2 mmol). [c] 2.5 mol% catalyst charge was employed. [d] Conversions determined based on relative UPLC peak intensities compared to undesired side products.

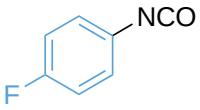
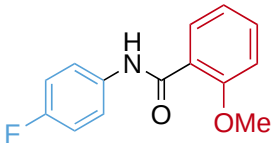
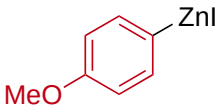
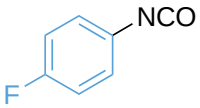
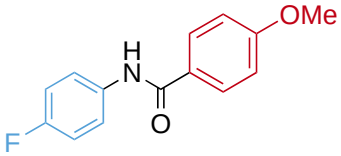
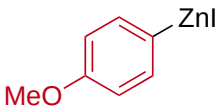
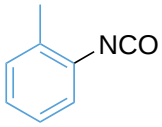
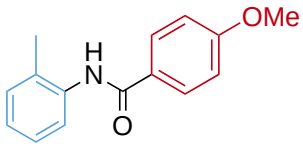
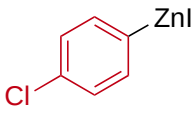
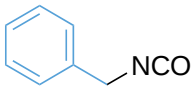
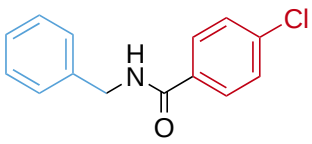
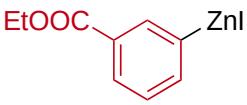
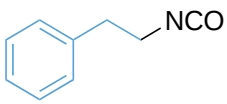
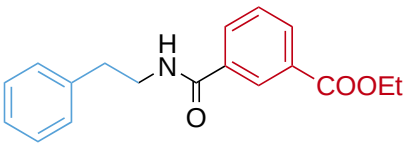
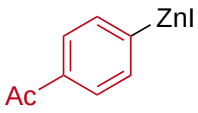
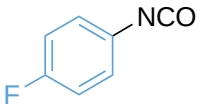
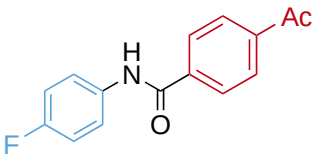
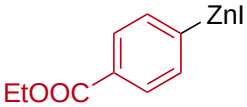
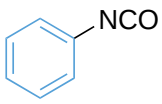
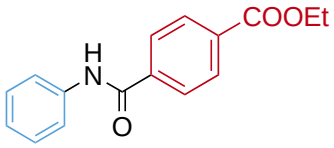
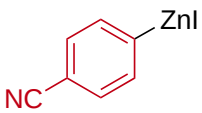
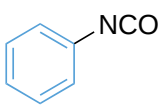
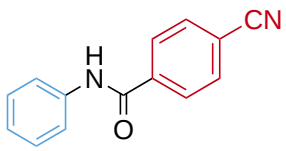
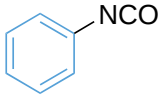
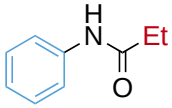
Section 6: Substrate Scope

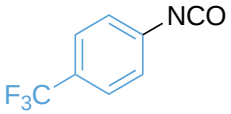
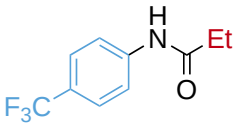
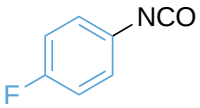
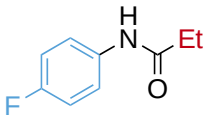
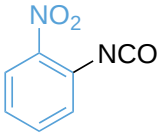
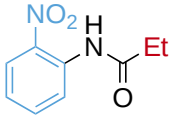
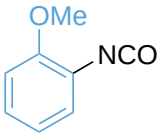
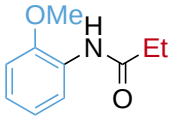
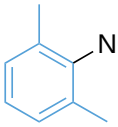
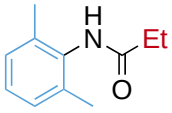
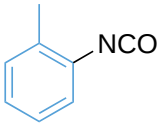
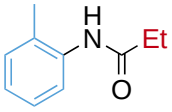
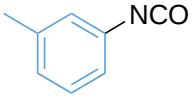
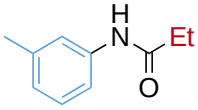
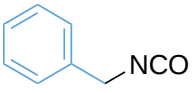
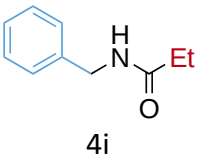
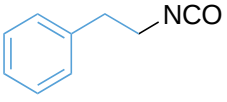
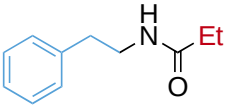
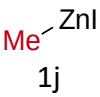
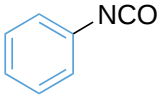
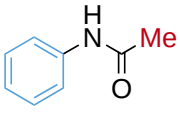
Table S2. Amide synthesis using organozinc iodides and isocyanates.

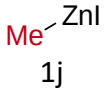
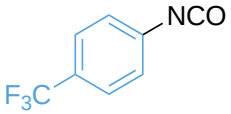
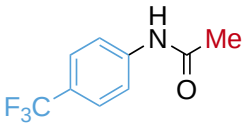
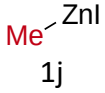
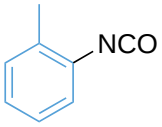
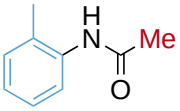
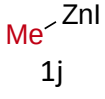
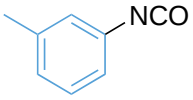
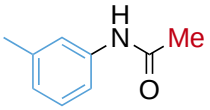
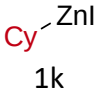
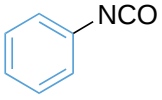
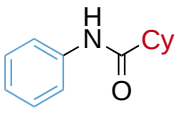
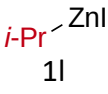
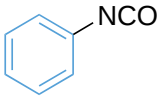
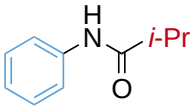
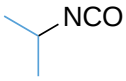
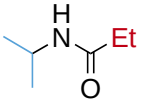
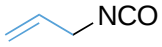
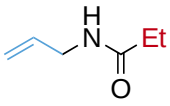
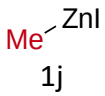
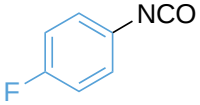
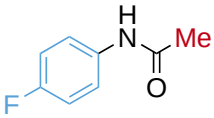
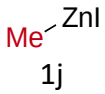
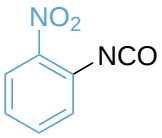
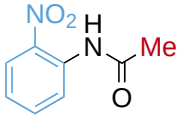


Entry	Organozinc Reagent **1(a – m)**	Isocyanate **2(a – l)**	Amide Product **3(a – x) or 4(a – t)**	Yield [%]
1	 1a	 2a	 3a	78
2	 1a	 2b	 3b	87
3	 1a	 2c	 3c	81
4	 1a	 2d	 3d	79
5	 1a	 2e	 3e	31
6	 1a	 2f	 3f	62
7	 1a	 2g	 3g	68
8	 1a	 2h	 3h	71

Entry	Organozinc Reagent	Isocyanate	Amide Product	Yield [%]
9	 1a	 2i	 3i	25
10	 1a	 2j	 3j	57
11	 1a	 2k	 3k	63
12	 1a	 2l	 3l	27
13	 1b	 2a	 3m	74
14	 1c	 2a	 3n	44
15	 1d	 2a	 3o	34
16	 1e	 2a	 3p	43
17	 1f	 2a	 3q	47

Entry	Organozinc Reagent	Isocyanate	Amide Product	Yield [%]
18	 1e	 2c	 3r	27
19	 1b	 2c	 3s	83
20	 1b	 2g	 3t	76
21	 1c	 2j	 3u	32
22	 1f	 2k	 3v	Trace
23	 1d	 2c	 3w	Trace
24	 1g	 2a	 3x	Trace
25	 1h	 2a	 3y	0
26	 1i	 2a	 4a	64

Entry	Organozinc Reagent	Isocyanate	Amide Product	Yield [%]
27	 1i	 2b	 4b	60
28	 1i	 2c	 4c	41
29	 1i	 2d	 4d	59
30	 1i	 2e	 4e	10
31	 1i	 2f	 4f	13
32	 1i	 2g	 4g	32
33	 1i	 2h	 4h	31
34	 1i	 2j	 4i	Trace
35	 1i	 2k	 4j	22
36	 1j	 2a	 4k	43

Entry	Organozinc Reagent	Isocyanate	Amide Product	Yield [%]
37	 1j	 2b	 4l	47
38	 1j	 2g	 4m	10
39	 1j	 2h	 4n	13
40	 1k	 2a	 4o	Trace
41	 1l	 2a	 4p	0
42	 1i	 2i	 4q	0
43	 1i	 2l	 4r	0
44	 1j	 2c	 4s	14
45	 1j	 2d	 4t	Trace

Section 7: References

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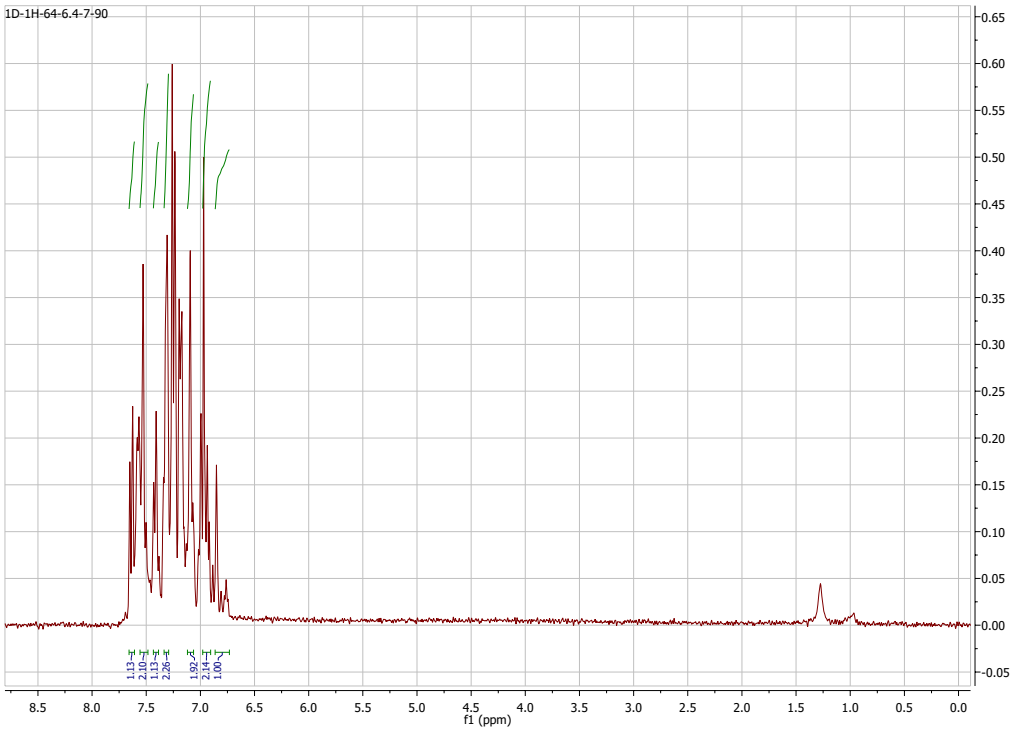
Section 8: Characterization

3a. *N*-phenyl benzamide (80 MHz, $CDCl_3$)



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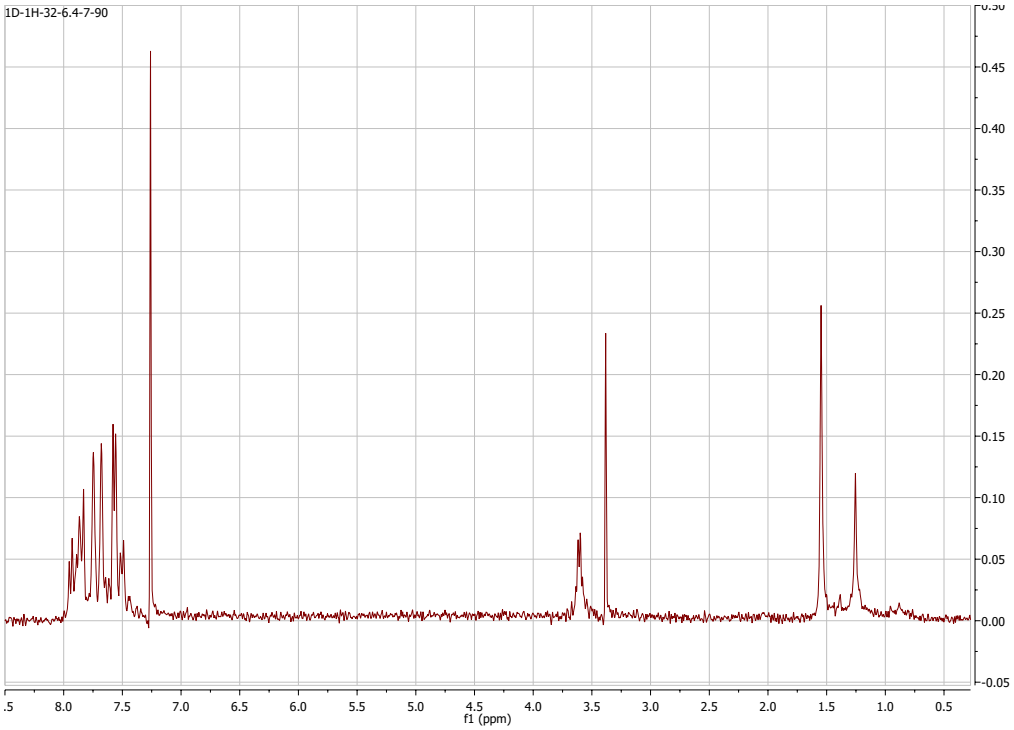

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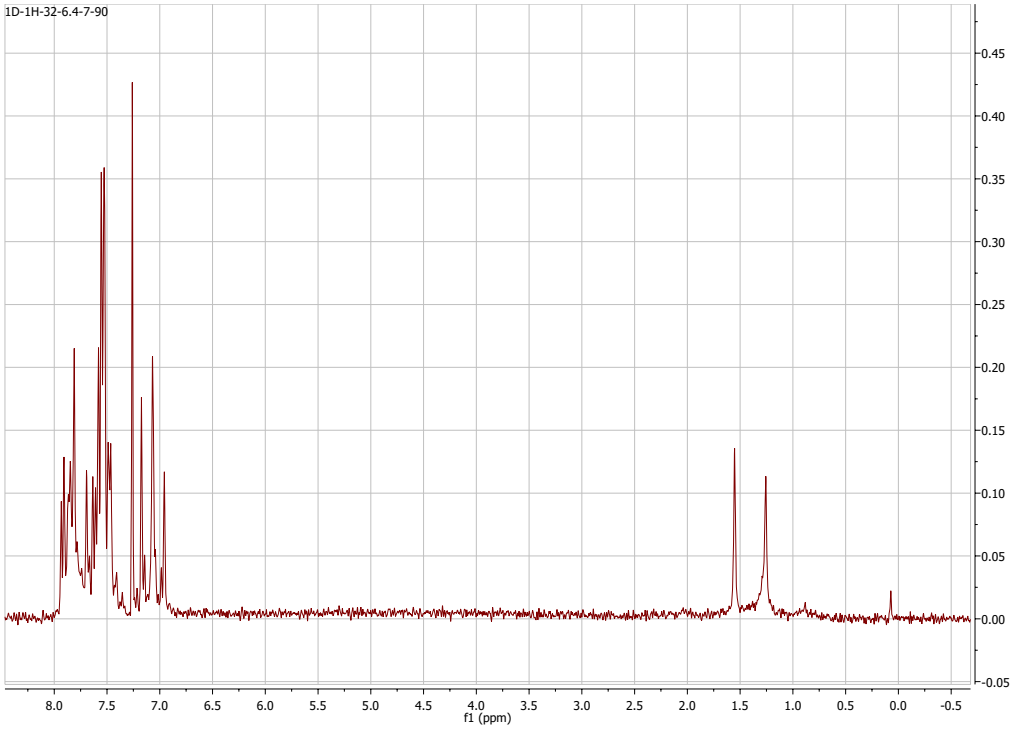
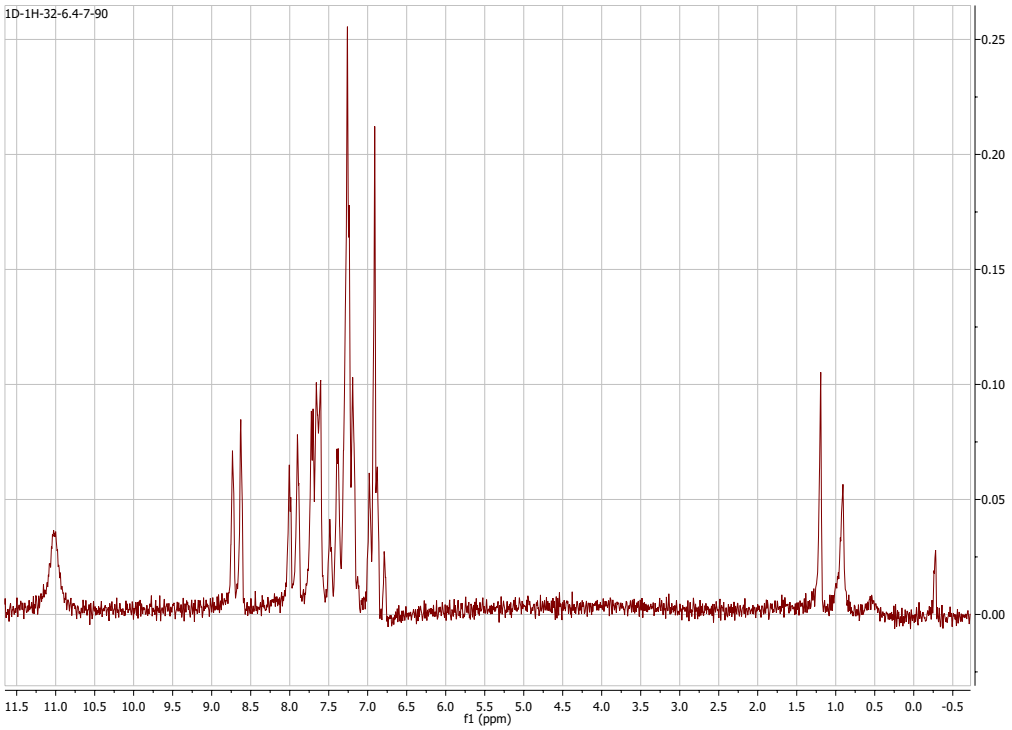


3d. *N*-2-nitrophenyl benzamide (80 MHz, $CDCl_3$)



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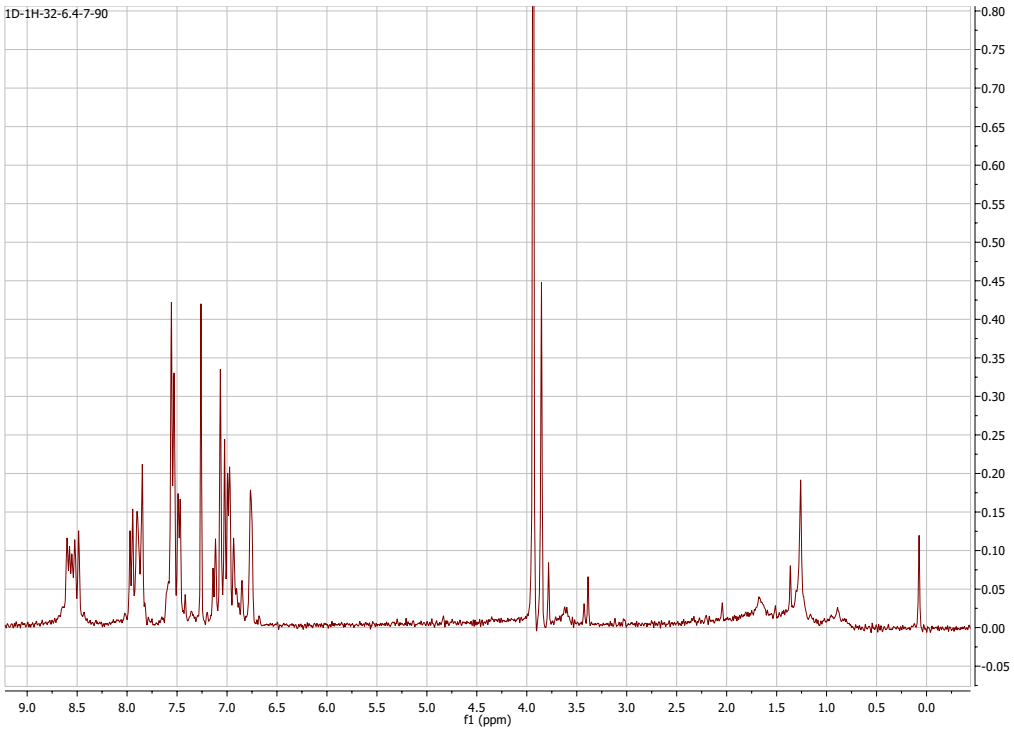
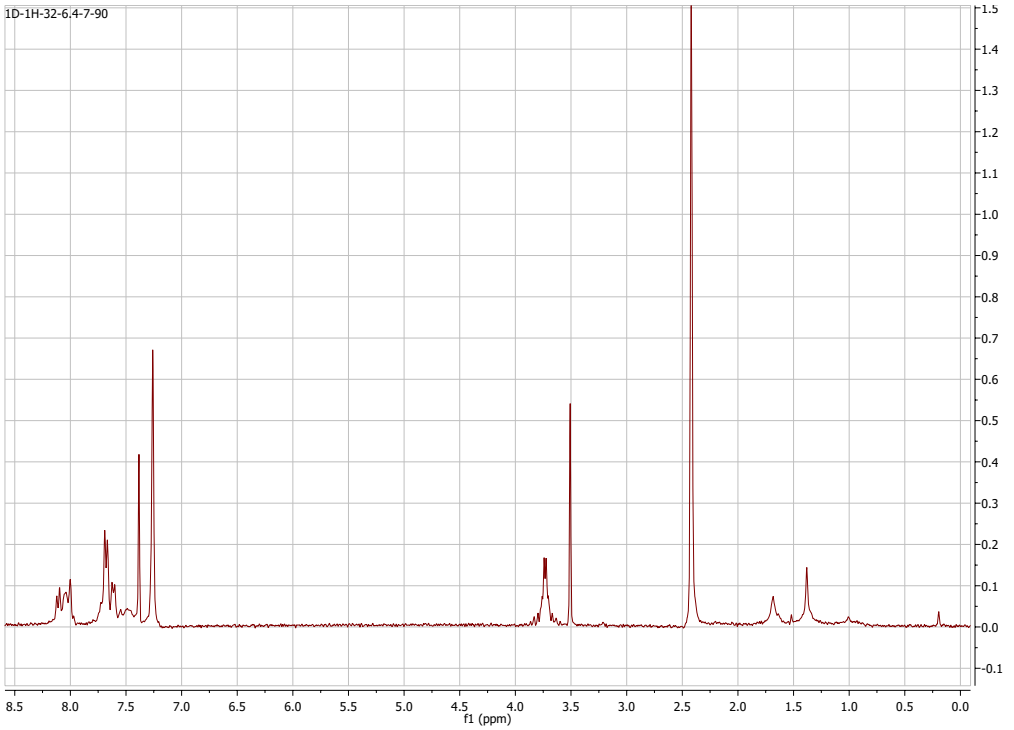
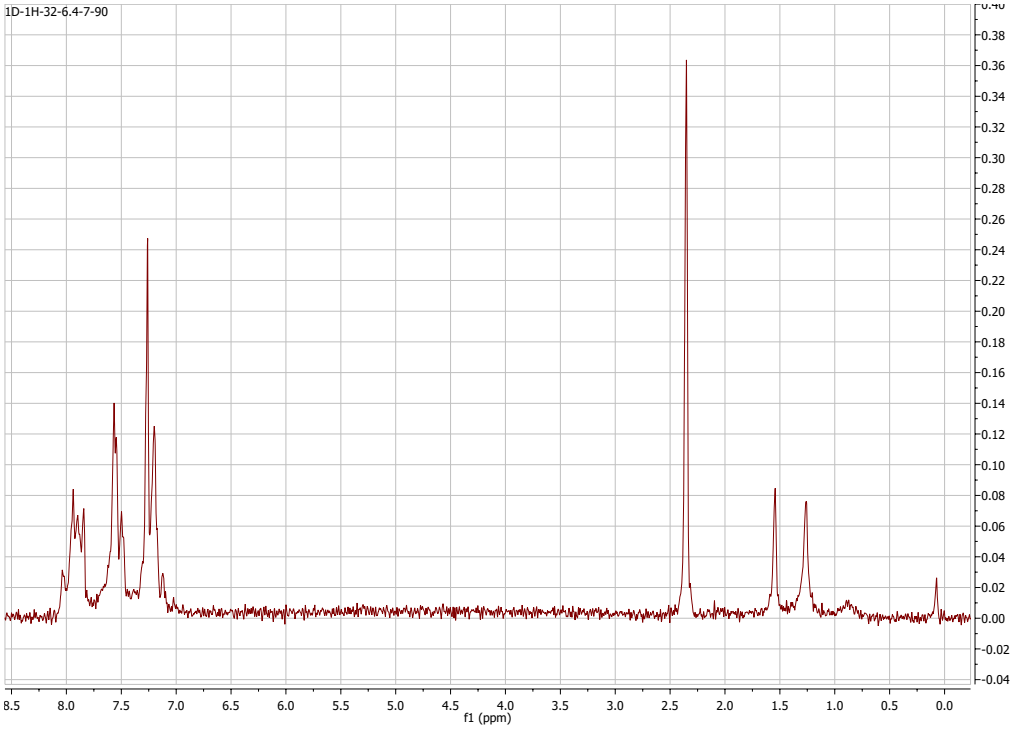


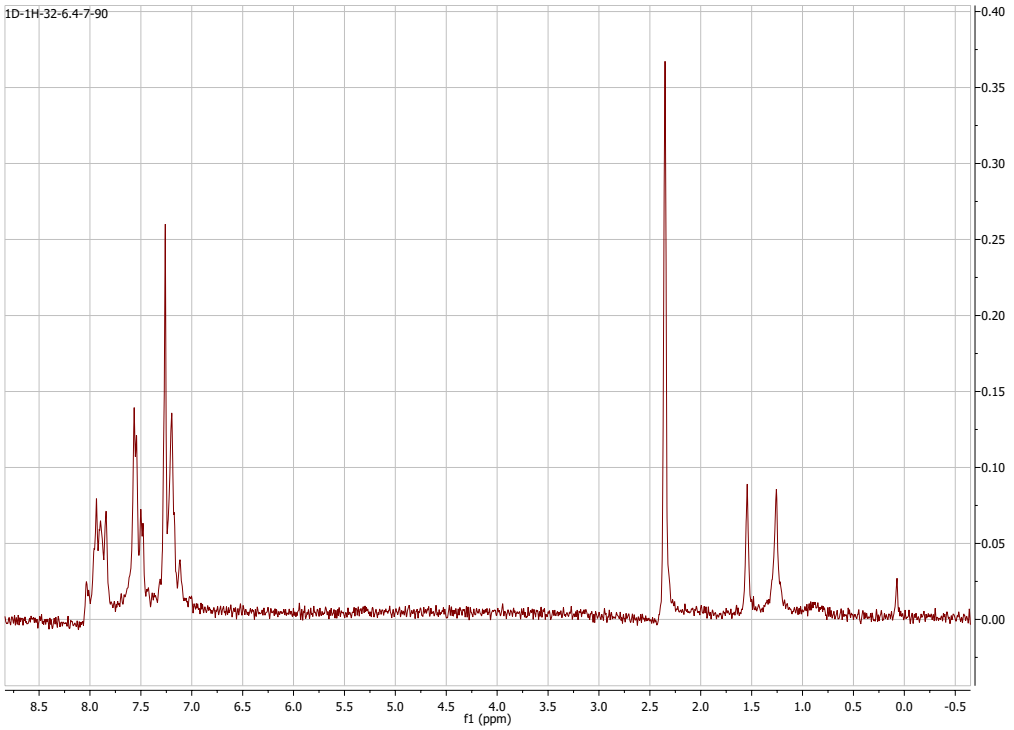
3f. *N*-2,6-dimethylphenyl benzamide (80 MHz, $CDCl_3$)



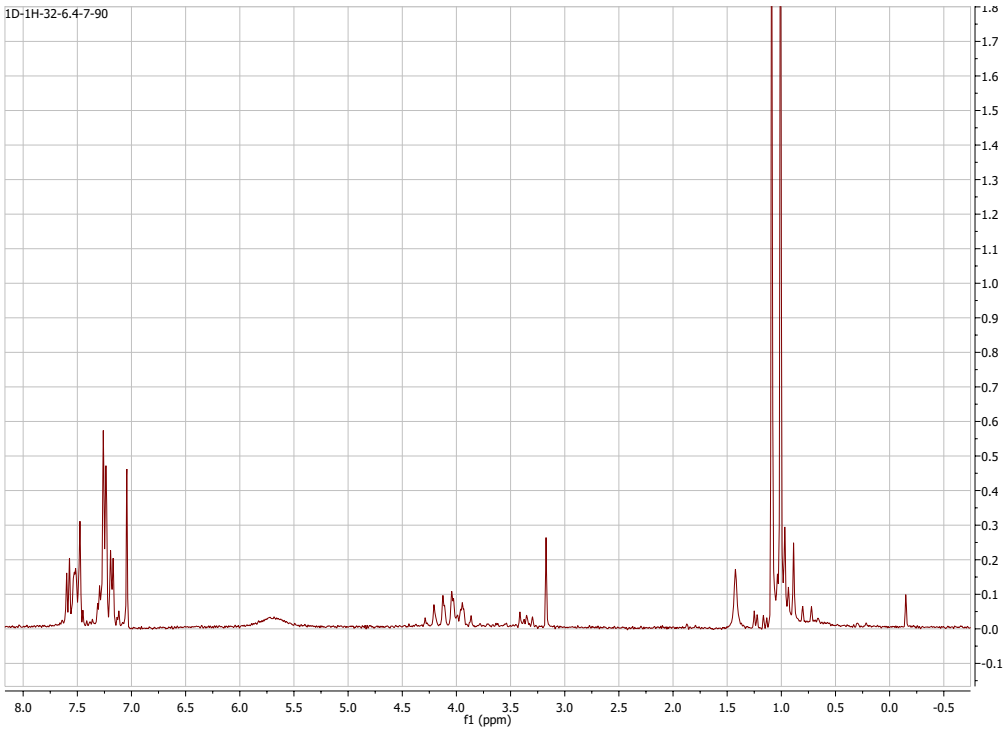
3g. *N*-2-methylphenyl benzamide (80 MHz, $CDCl_3$)



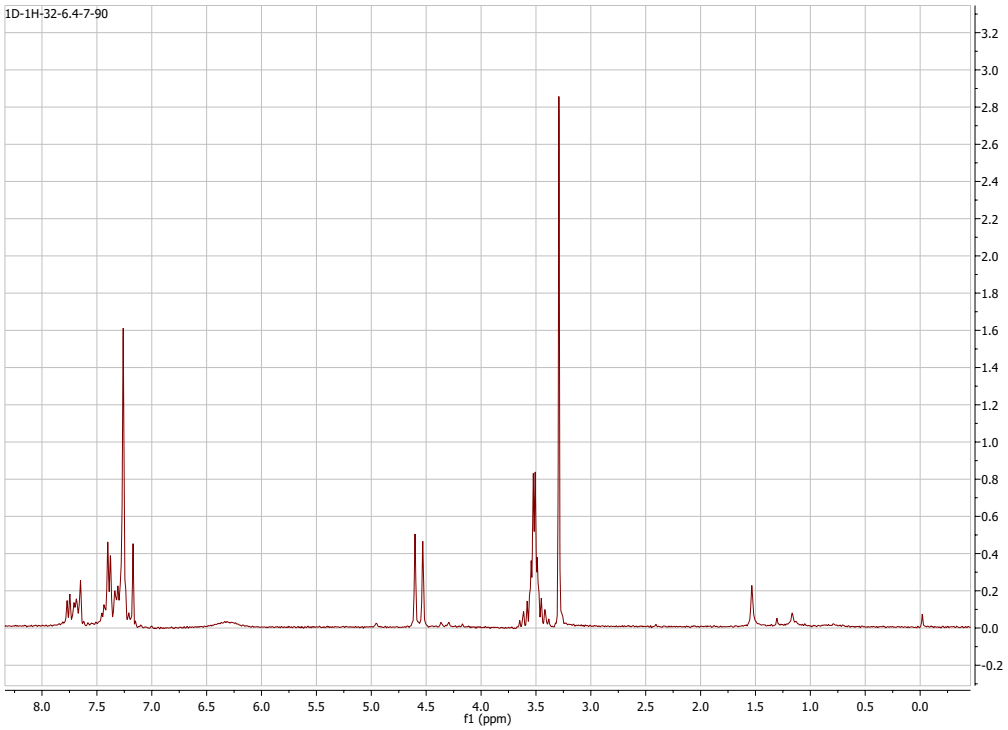
3h. *N*-3-methylphenyl benzamide (80 MHz, $CDCl_3$)



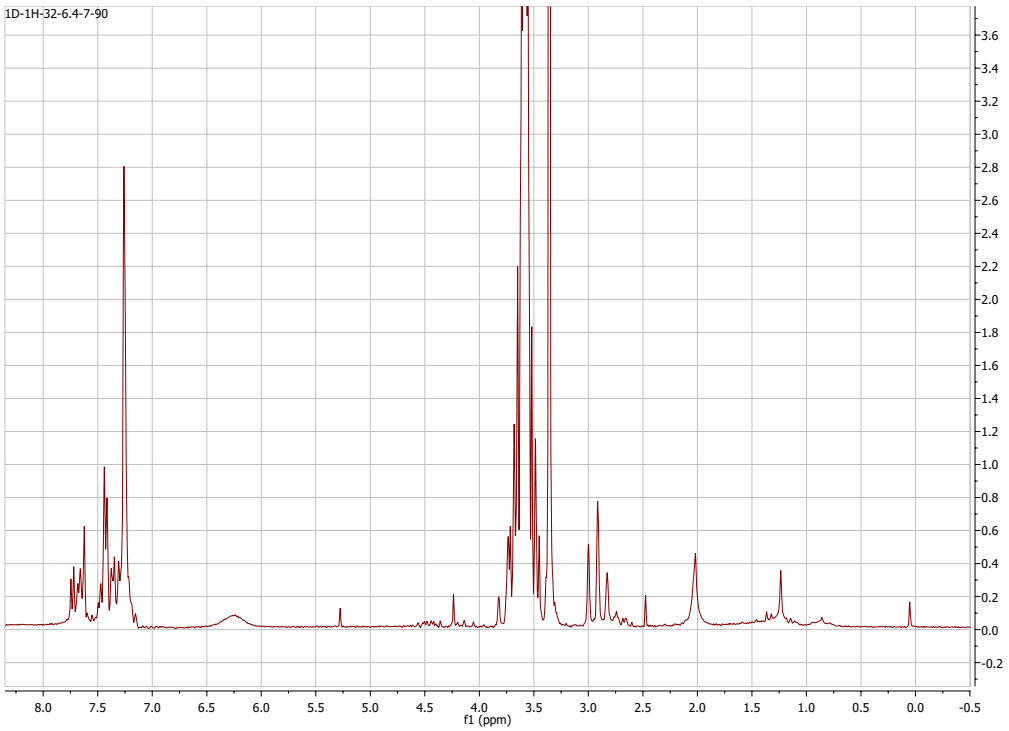
3i. *N*-isopropyl benzamide (80 MHz, $CDCl_3$)



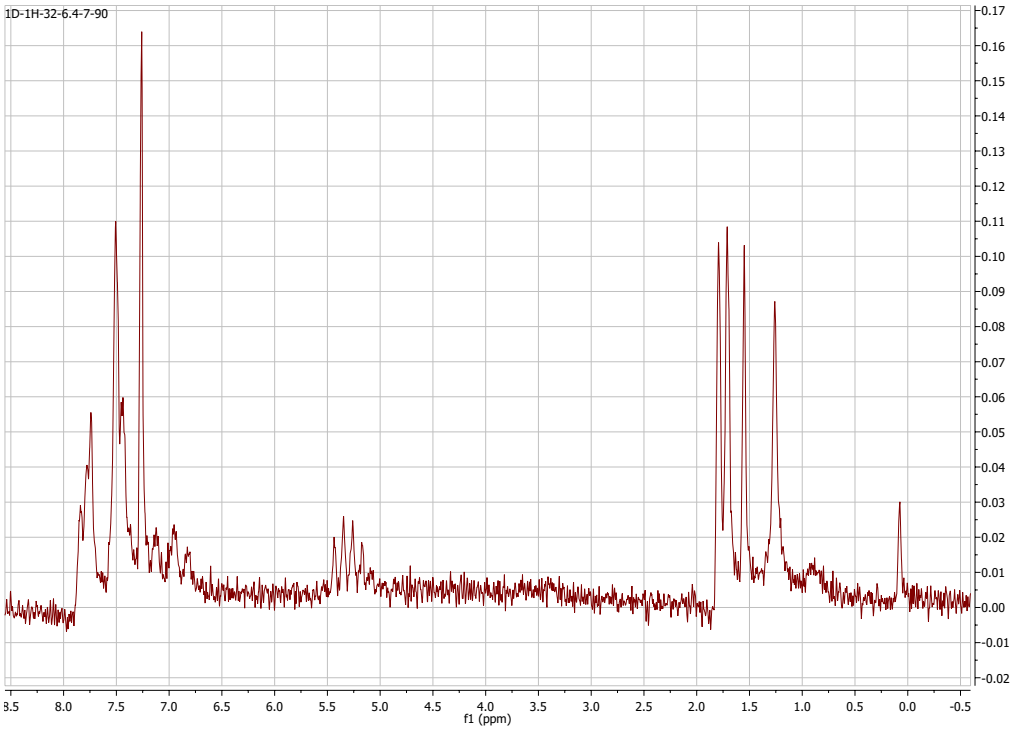
3j. *N*-benzyl benzamide (80 MHz, $CDCl_3$)



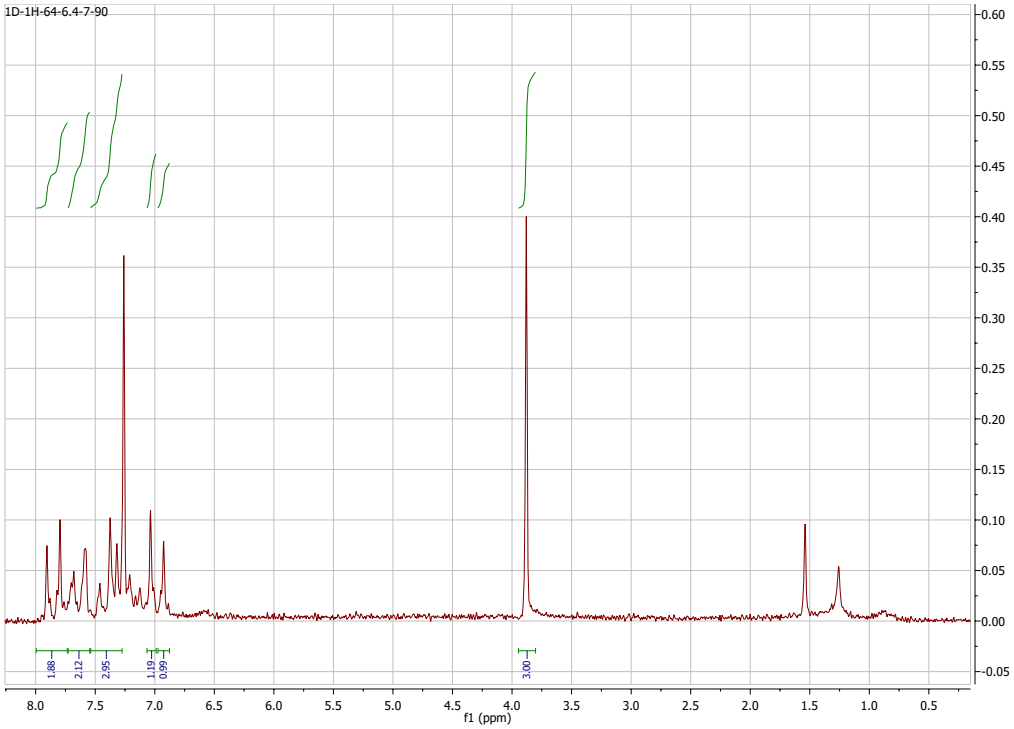
3k. *N*-phenethyl benzamide (80 MHz, $CDCl_3$)



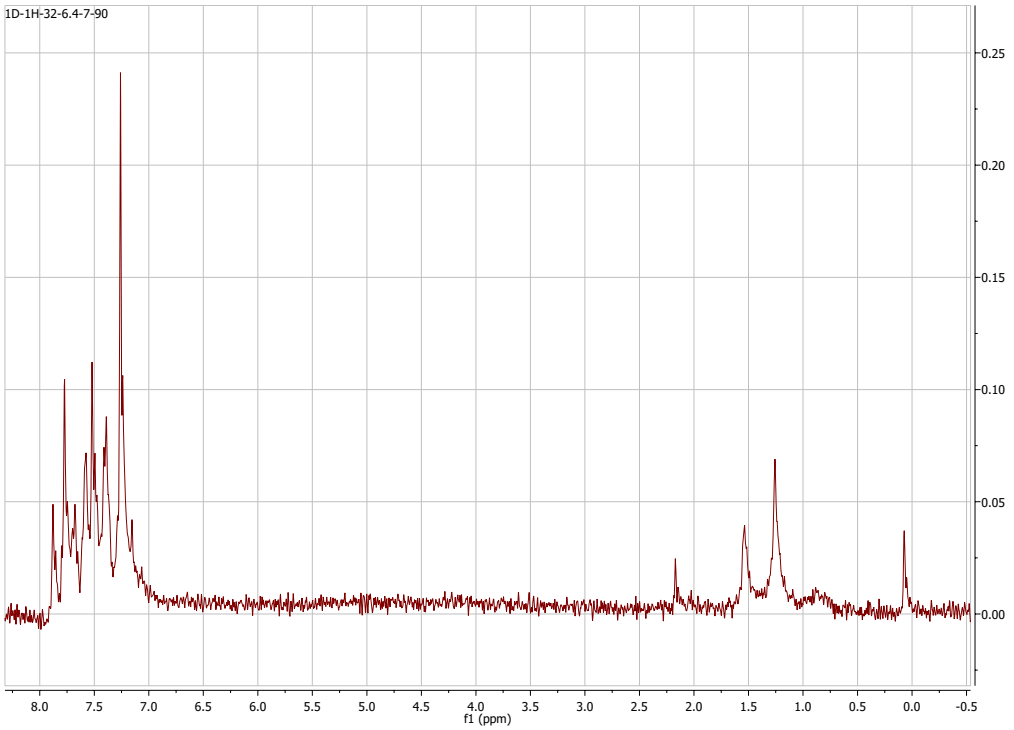
3l. *N*-allyl benzamide (80 MHz, $CDCl_3$)



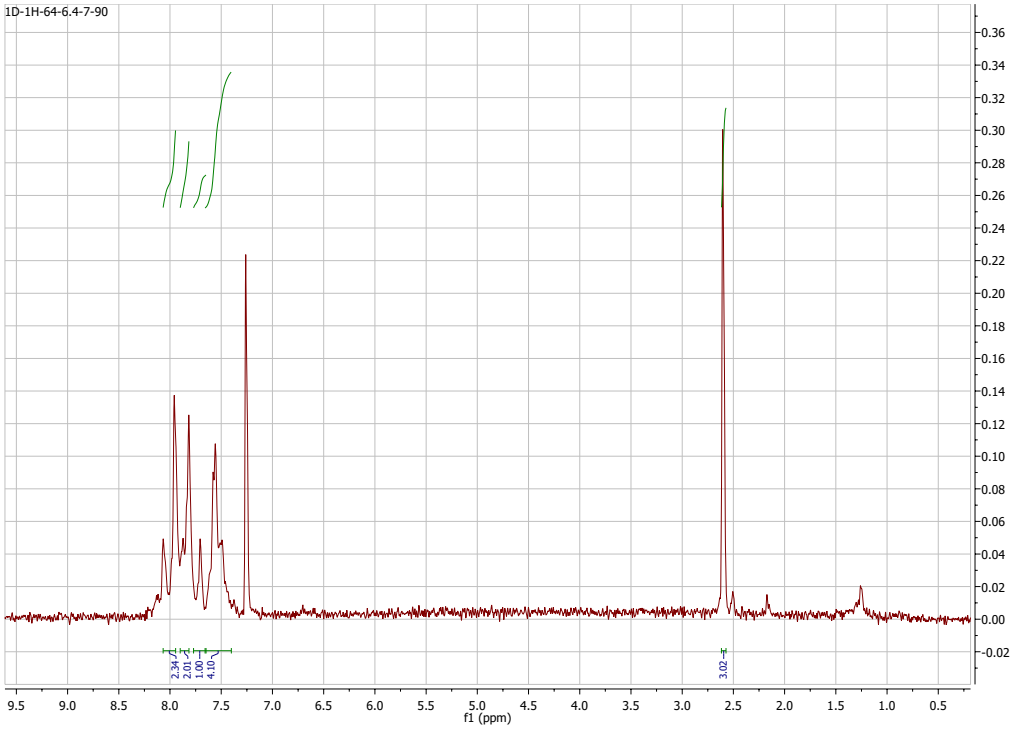
3m. *N*-phenyl 4-methoxybenzamide (80 MHz, $CDCl_3$)



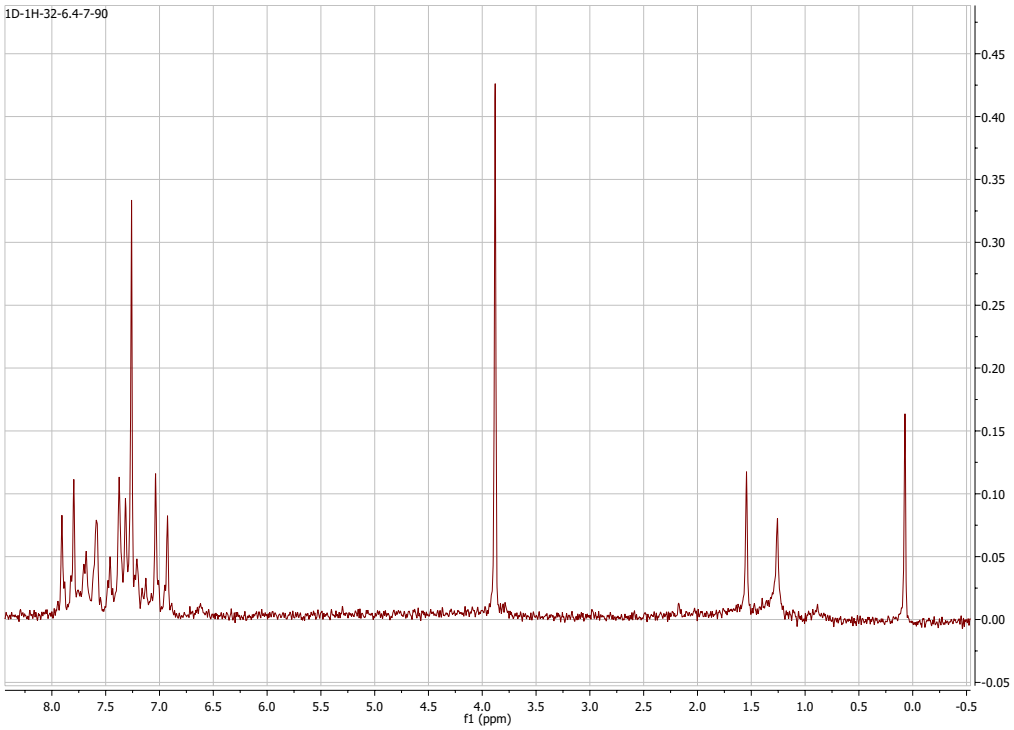
3n. *N*-phenyl 4-chlorobenzamide (80 MHz, $CDCl_3$)



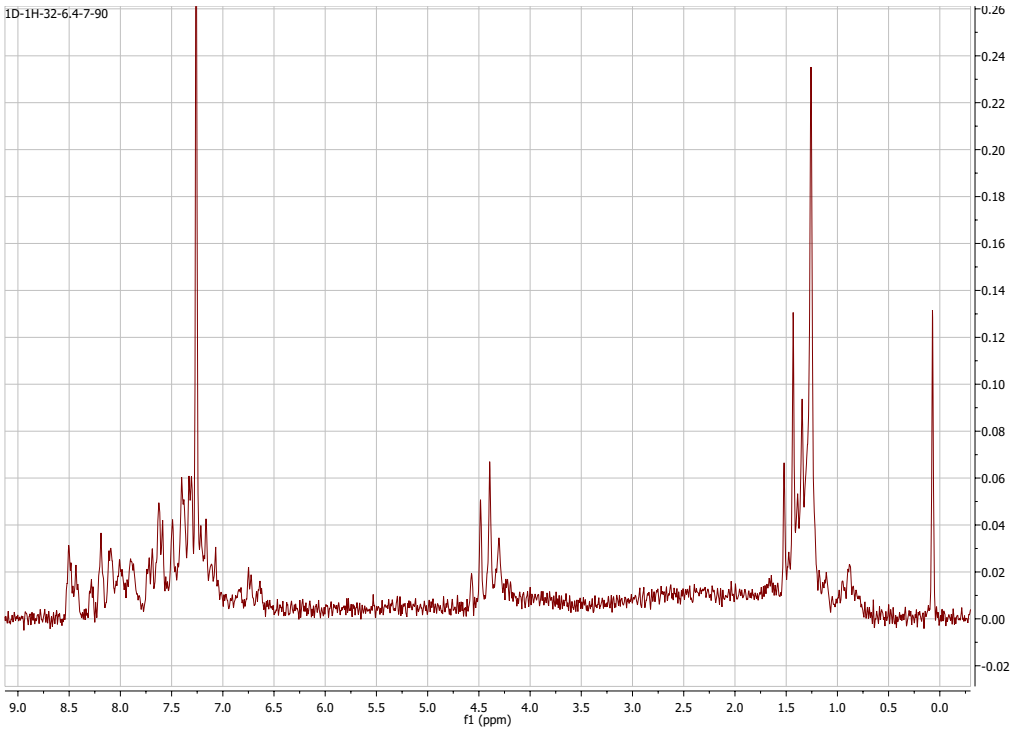
3o. *N*-phenyl 4-acetylbenzamide (80 MHz, $CDCl_3$)



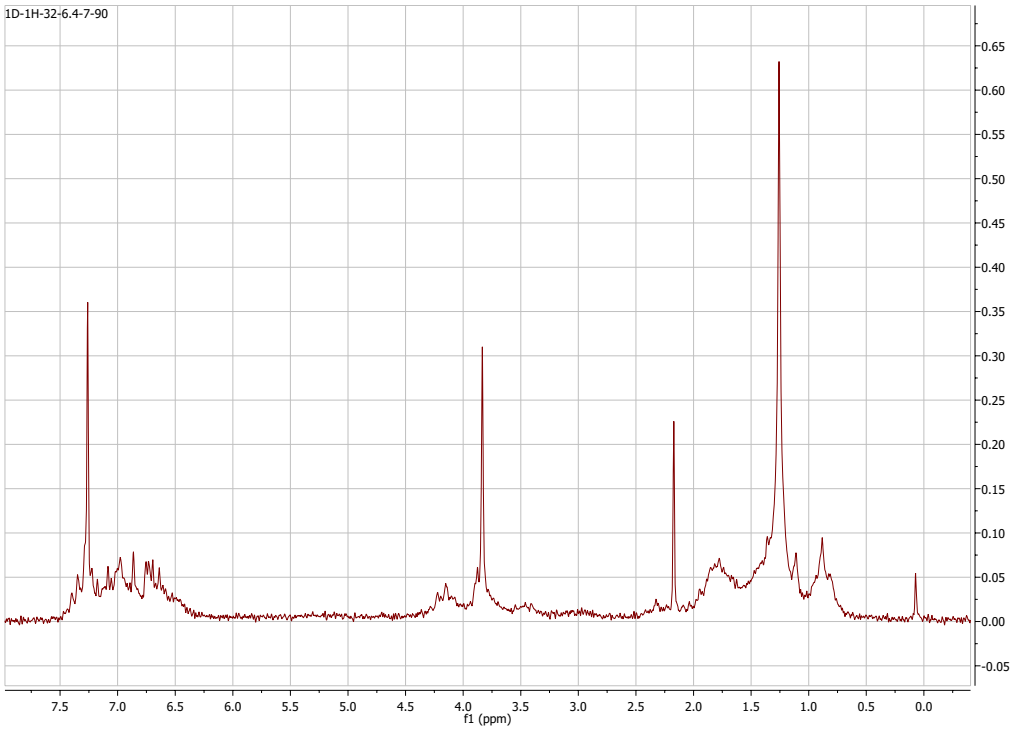
3p. *N*-phenyl 2-methoxybenzamide (80 MHz, $CDCl_3$)



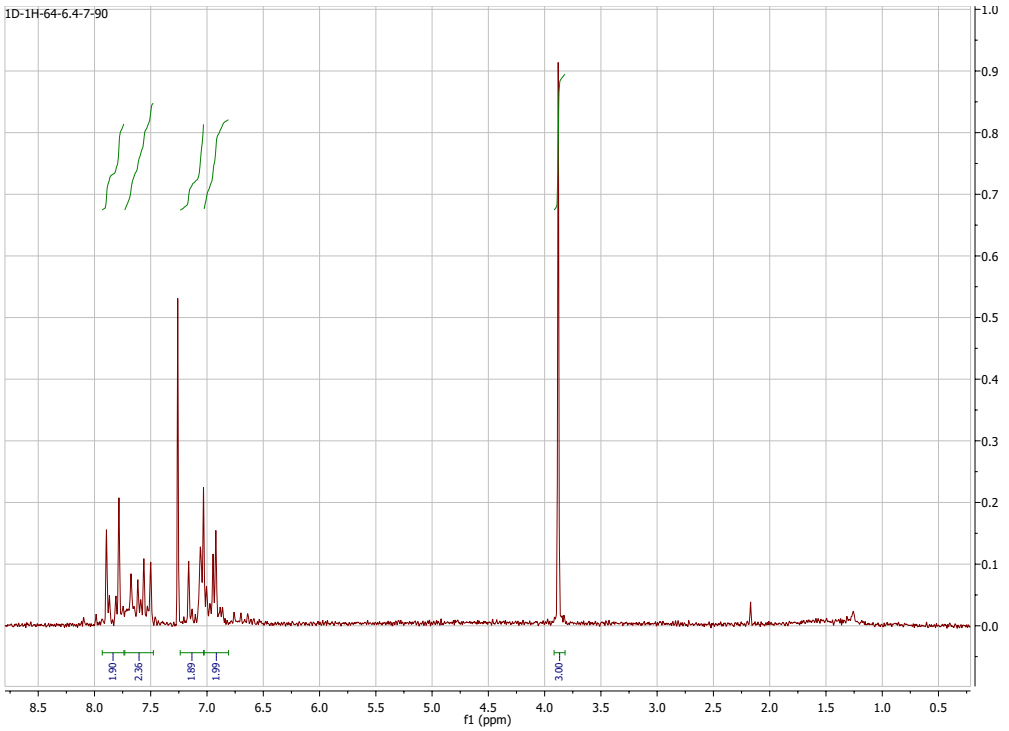
3q. ethyl 3-(phenylcarbamoyl)benzoate (80 MHz, $CDCl_3$)



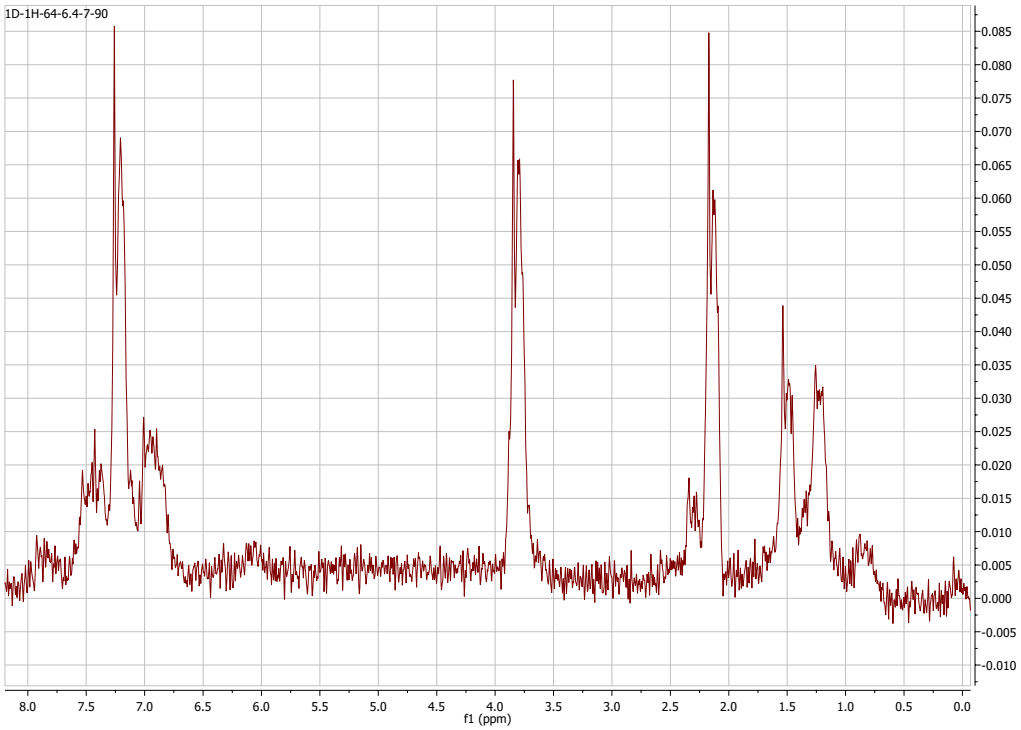
3r. *N*-4-fluorophenyl 2-methoxybenzamide (80 MHz, $CDCl_3$)



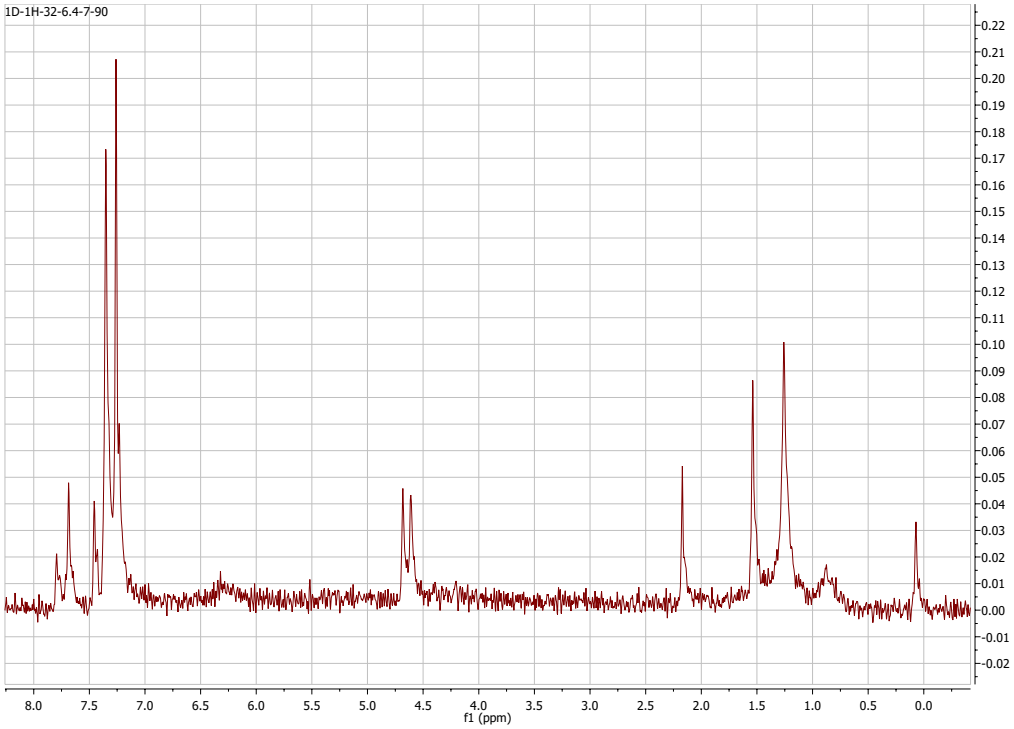
3s. *N*-4-fluorophenyl 4-methoxybenzamide (80 MHz, $CDCl_3$)



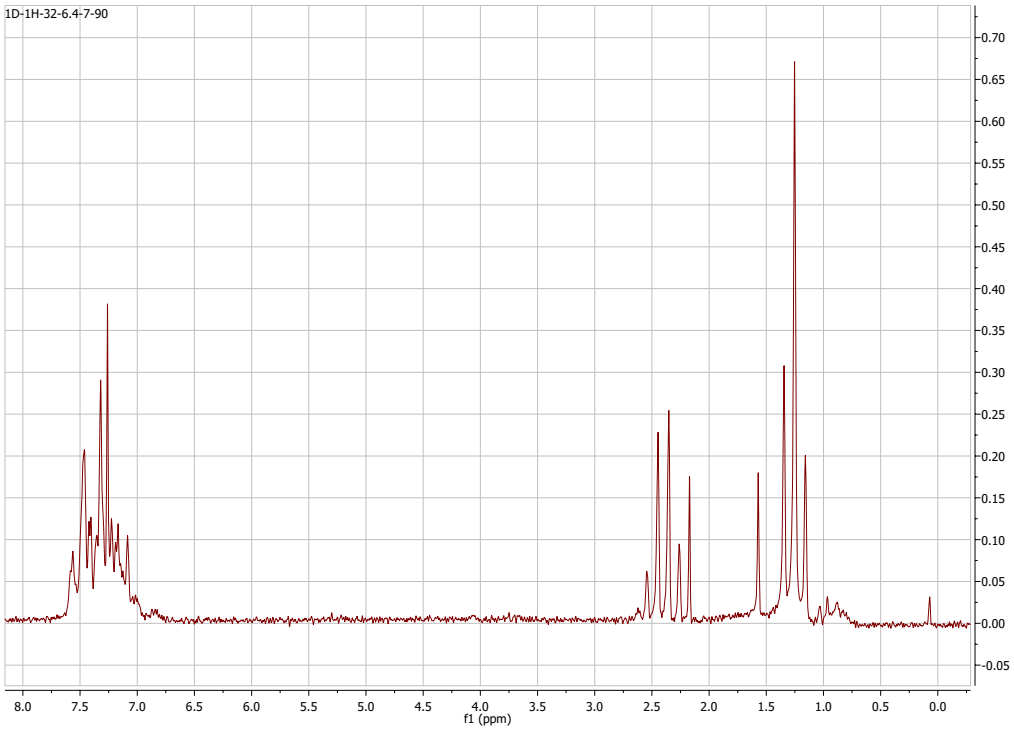
3t. *N*-2-methylphenyl 4-methoxybenzamide (80 MHz, $CDCl_3$)



3u. *N*-benzyl 4-chlorobenzamide (80 MHz, $CDCl_3$)



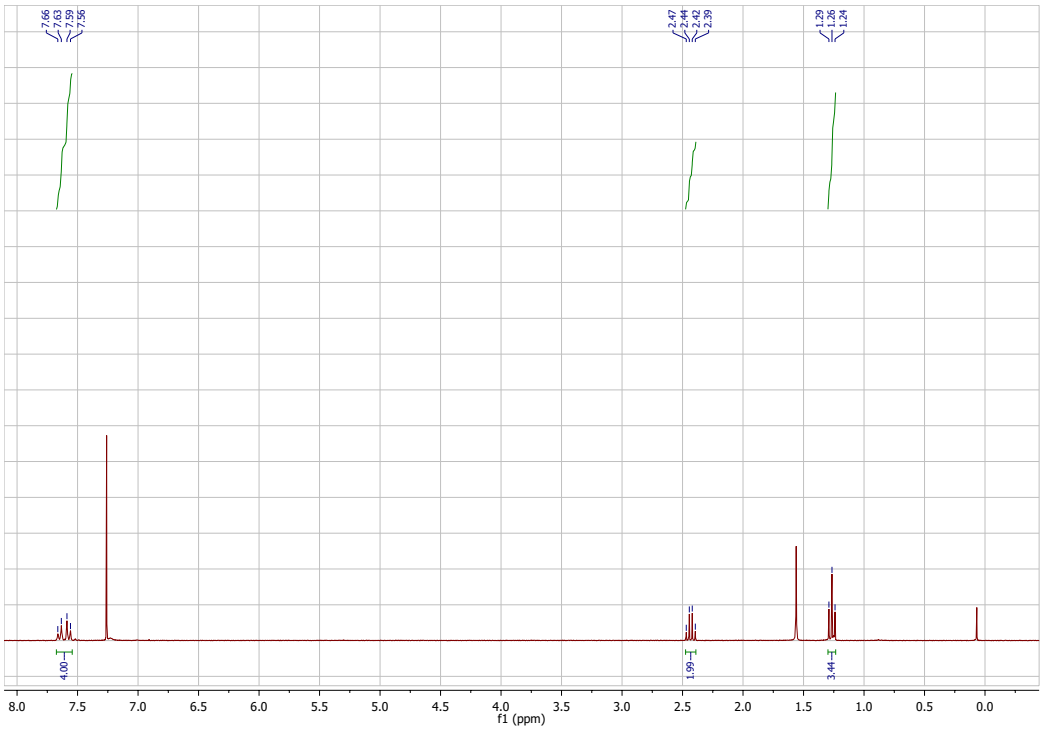
4a. *N*-phenyl propanamide (80 MHz, $CDCl_3$)

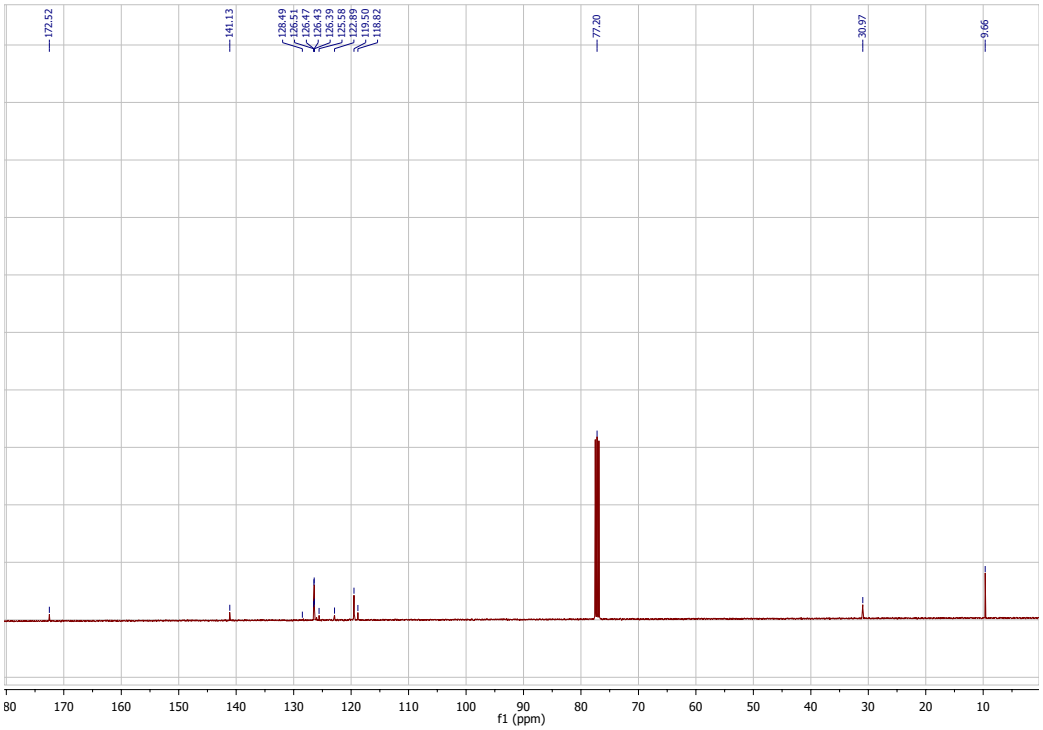


4b. *N*-4-trifluoromethylphenyl propanamide

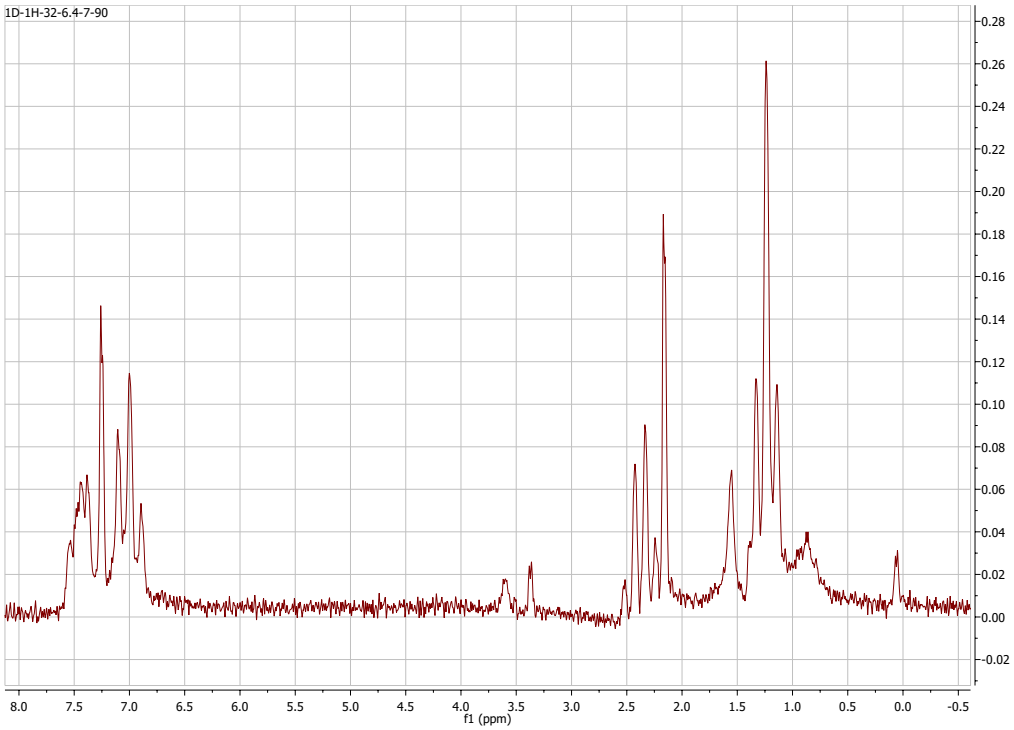
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, 4H), 7.37 (bs, 1H), 2.41 (dd, 2H), 1.24 (t, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 172.52, 141.12, 126.45, 124.24, 119.50, 118.82, 30.97, 9.66.

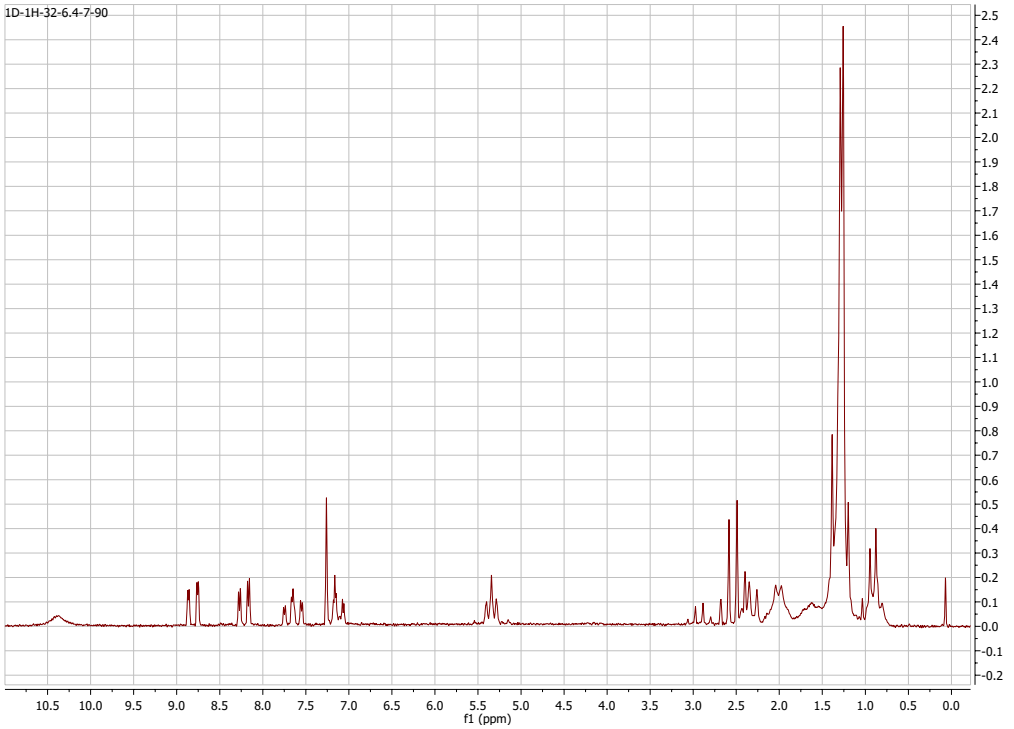




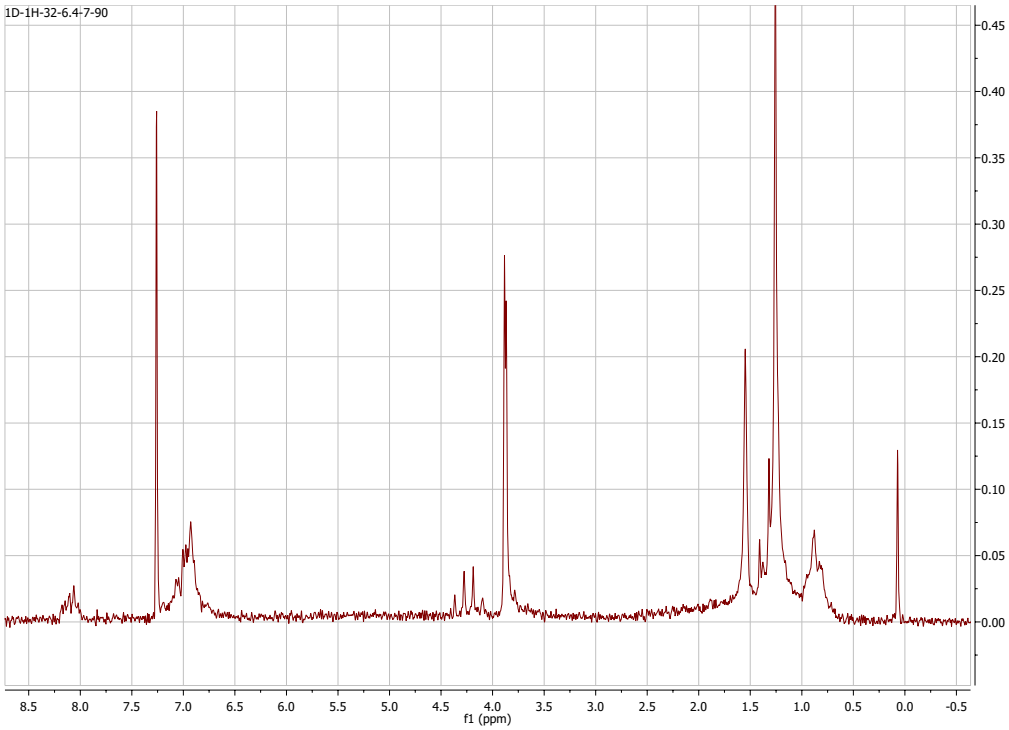
4c. *N*-4-fluorophenyl propanamide (80 MHz, $CDCl_3$)



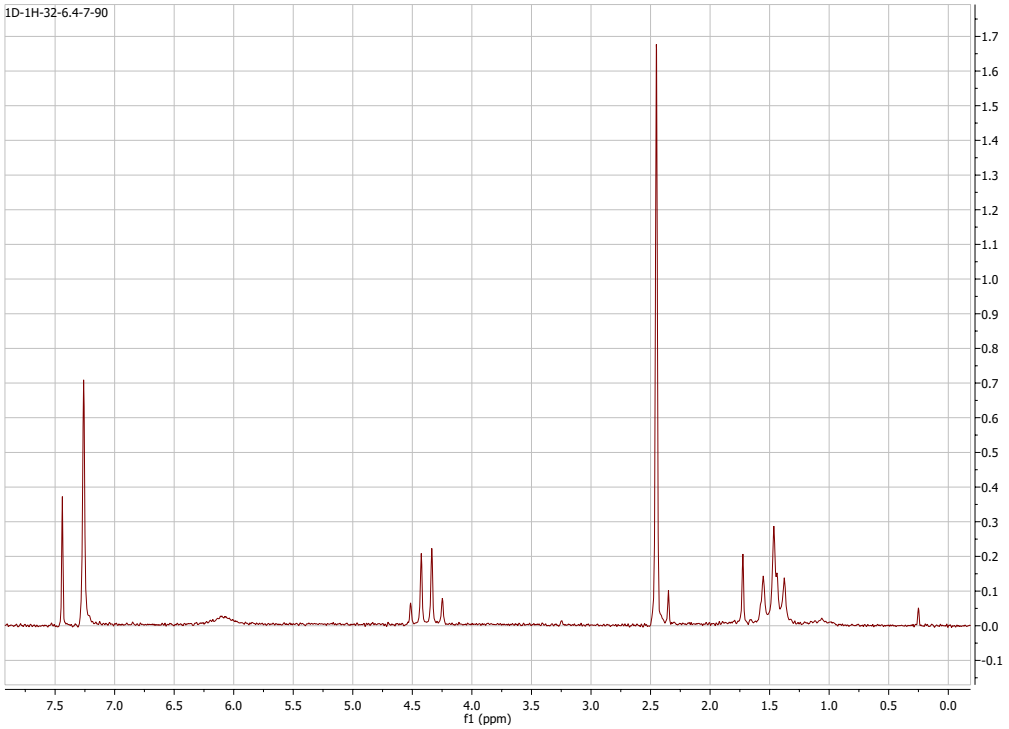
4d. *N*-2-nitrophenyl propanamide (80 MHz, $CDCl_3$)



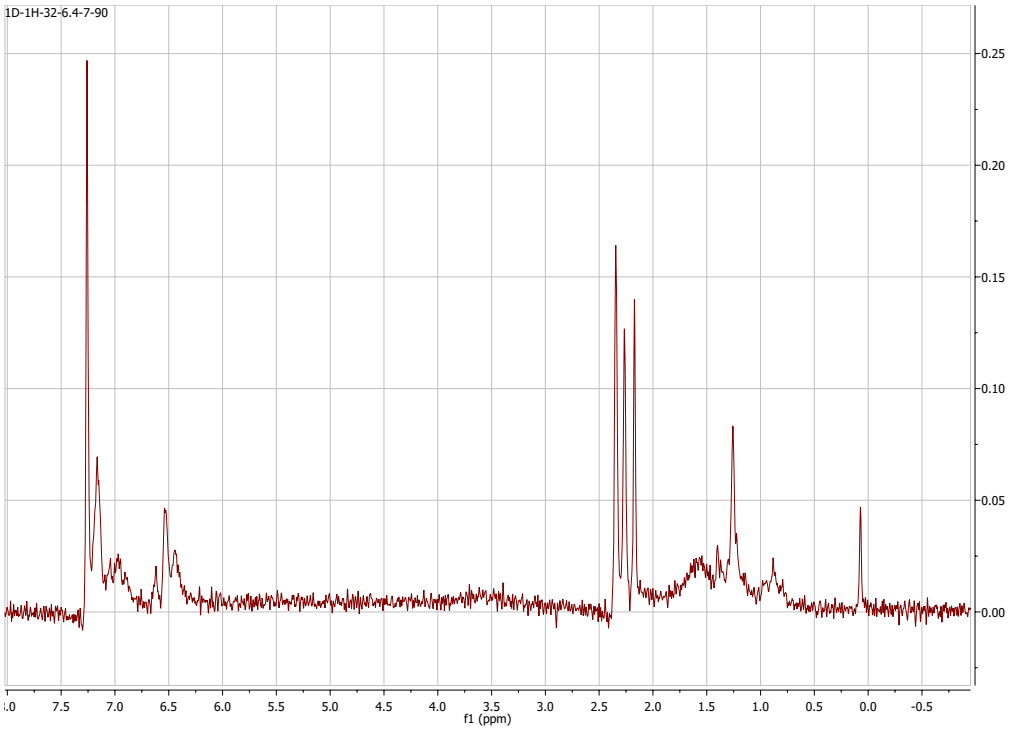
4e. *N*-2-methoxyphenyl propanamide (80 MHz, $CDCl_3$)



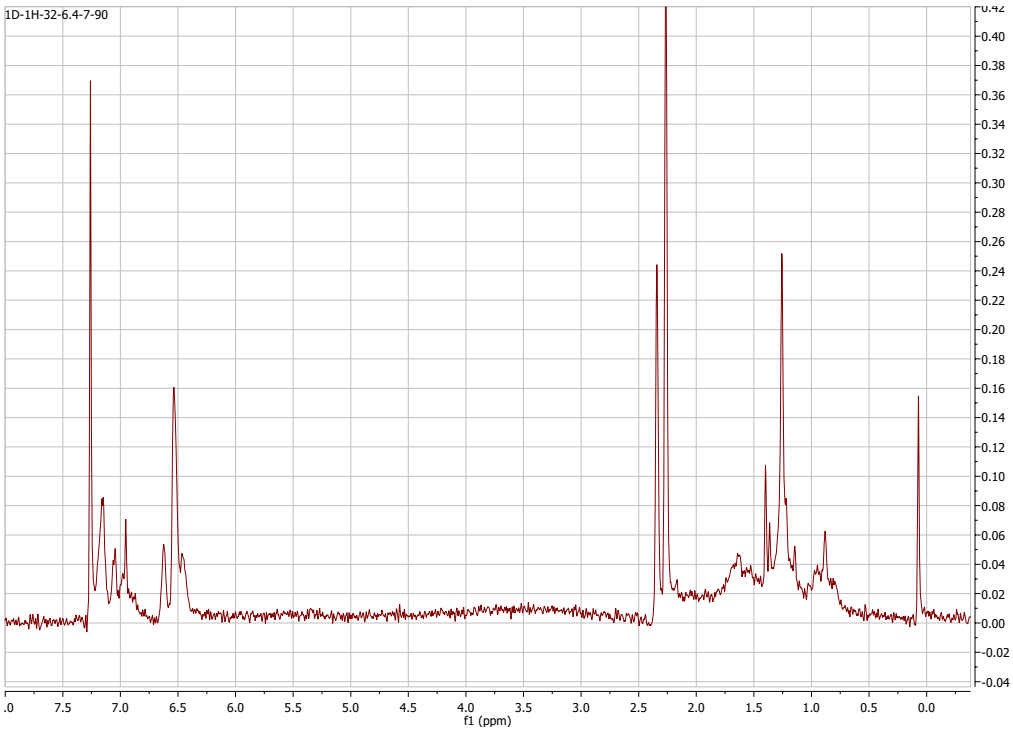
4f. *N*-2,6-dimethylphenyl propanamide (80 MHz, $CDCl_3$)



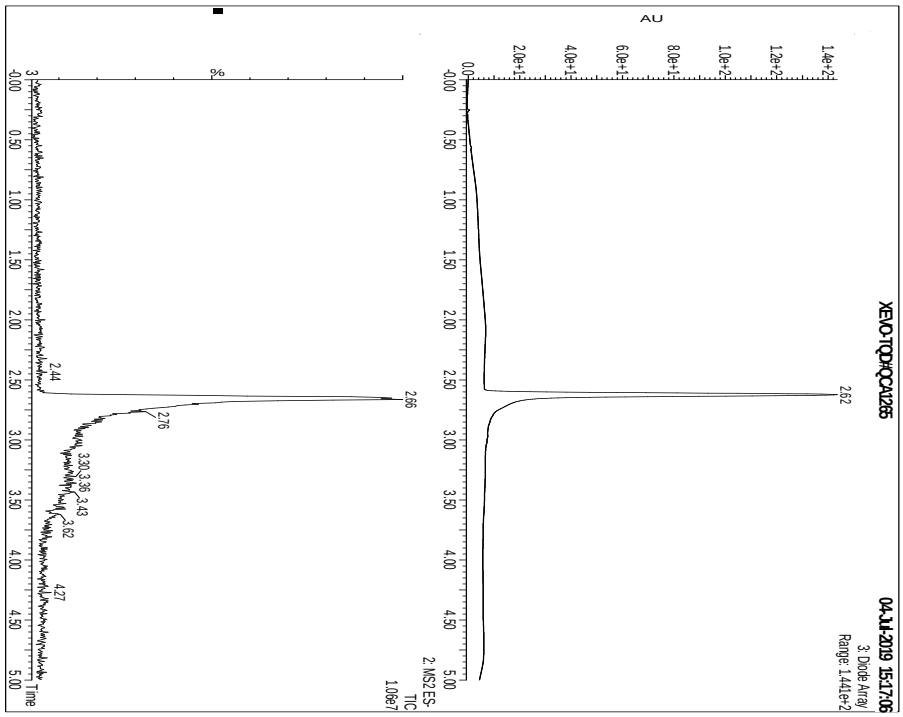
4g. *N*-2-methylphenyl propanamide (80 MHz, $CDCl_3$)



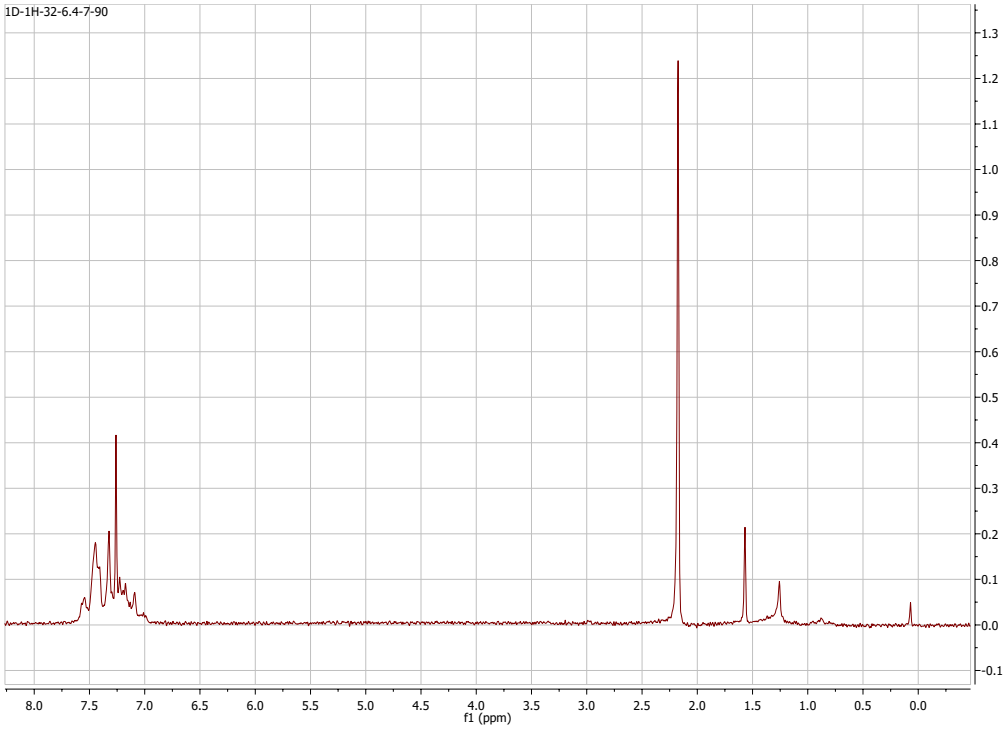
4h. *N*-3-methylphenyl propanamide (80 MHz, $CDCl_3$)



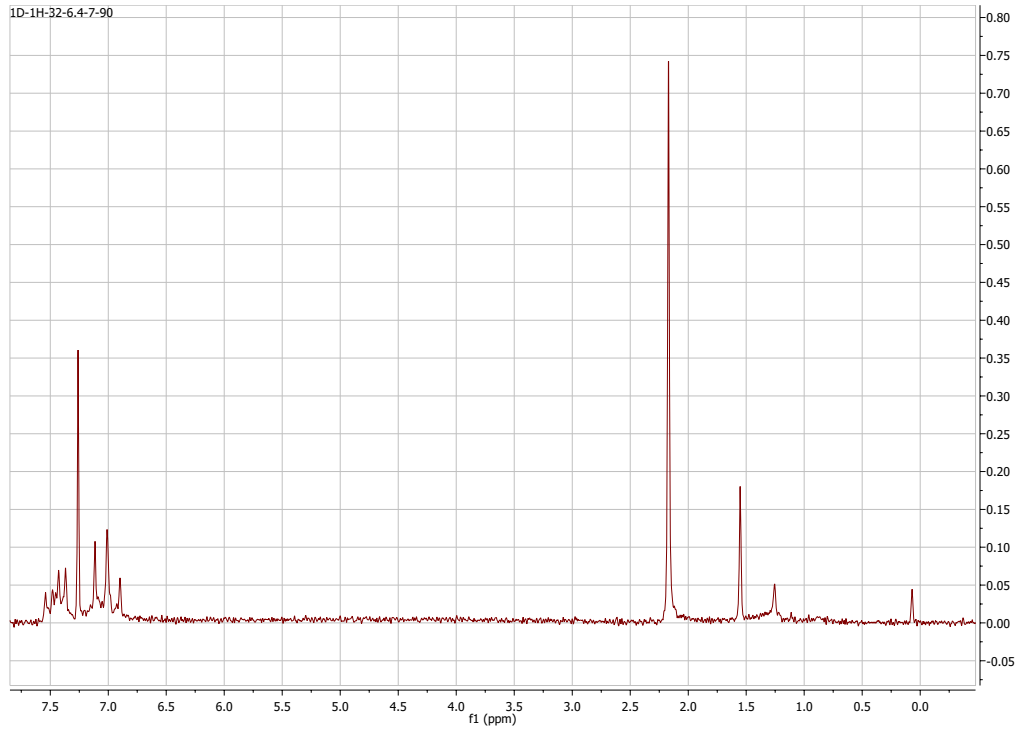
4j. *N*-phenethyl propanamide (80 MHz, $CDCl_3$)



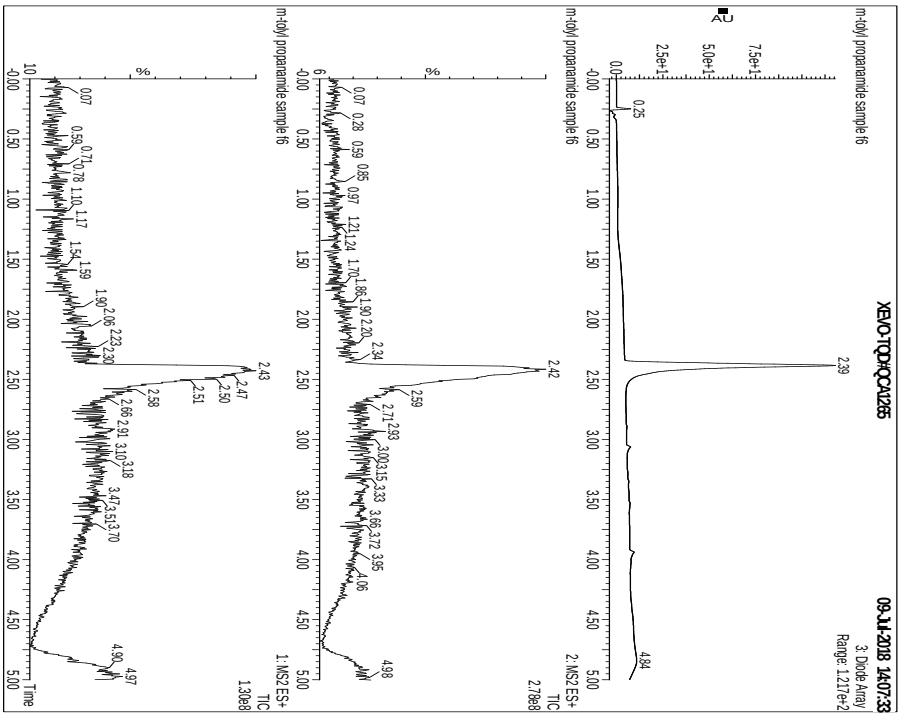
4k. *N*-phenyl acetamide (80 MHz, $CDCl_3$)



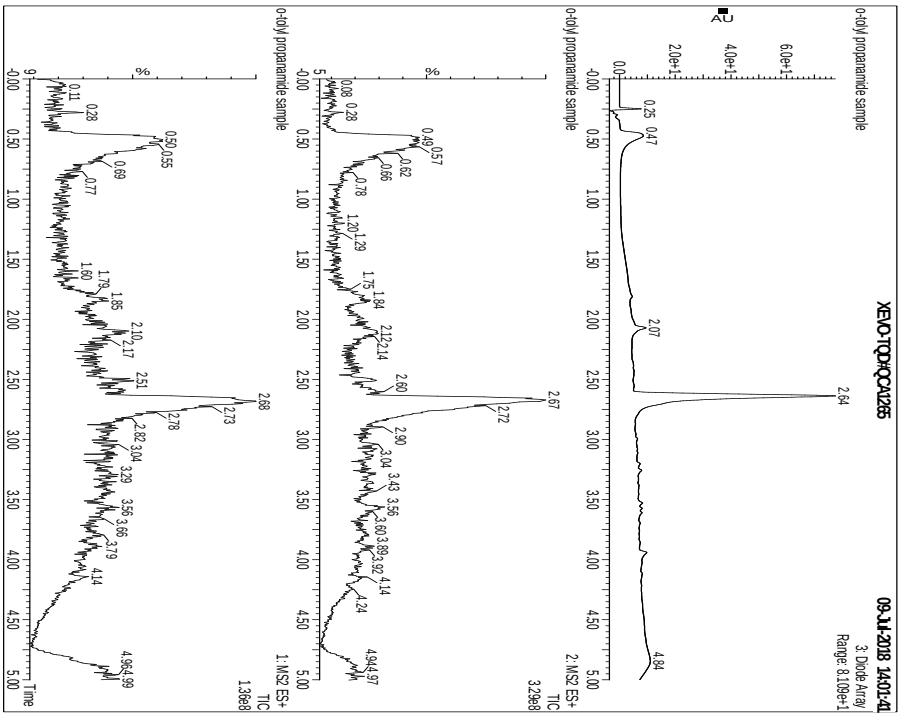
4l. *N*-trifluoromethyl acetamide (80 MHz, $CDCl_3$)



4m. *N*-2-methylphenyl acetamide (UPLC trace)



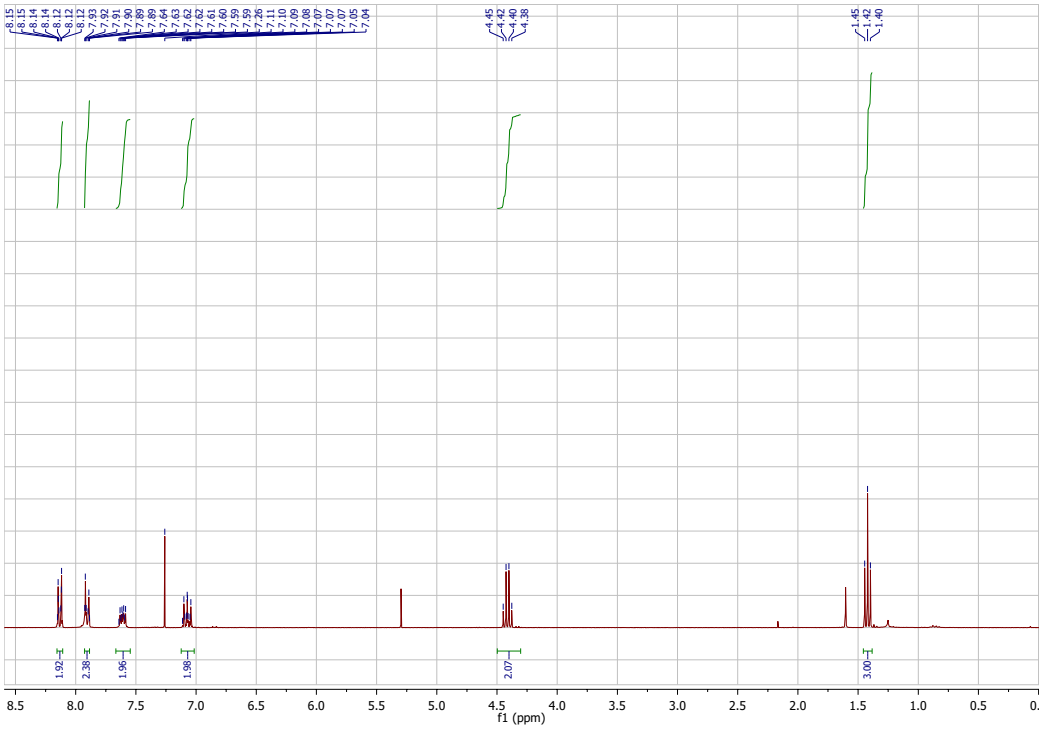
4n. *N*-3-methylphenyl acetamide (UPLC trace)

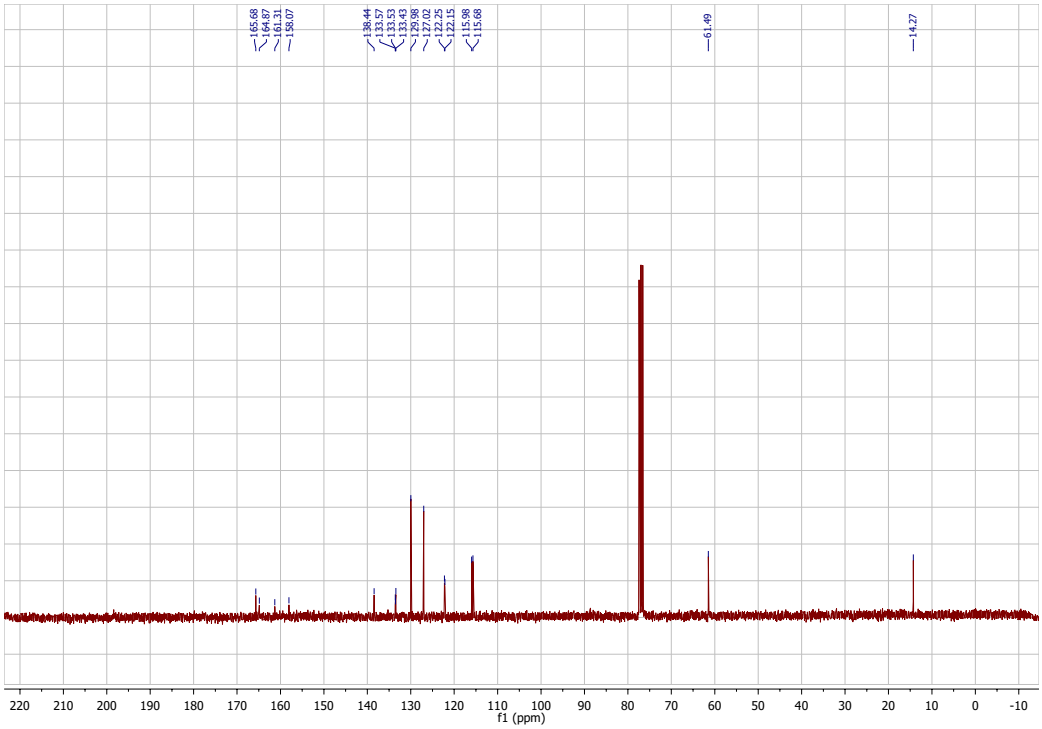


6c. Ethyl 4-[(4-fluorophenyl)carbamoyl]benzoate

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.13 (dd, 2H), 7.91 (dd, 2H), 7.61 (m, 2H), 7.07 (m, 2H), 4.41 (q, 2H), 1.42 (t, 3H)

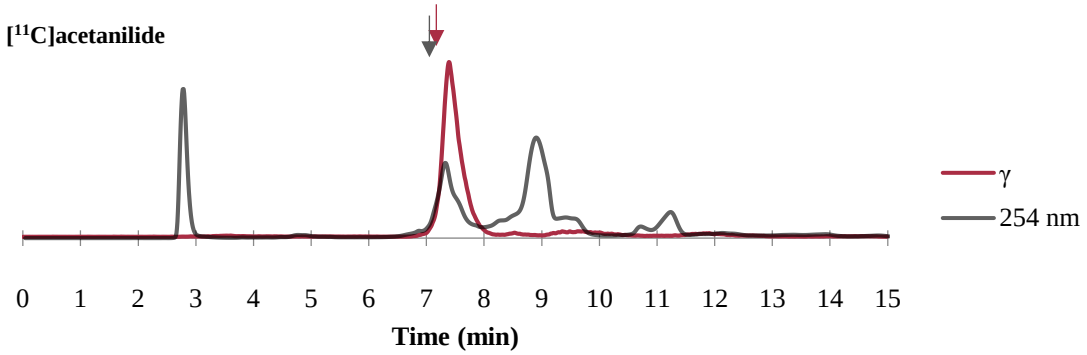
^{13}C-NMR (75 MHz, $CDCl_3$): 165.7, 164.9, 159.7 (d, J = 243), 138.4, 133.6 (d, J = 3), 130.0, 127.0, 122.2 (d, J = 7.5), 115.8 (d, J = 22.5), 61.5, 14.3

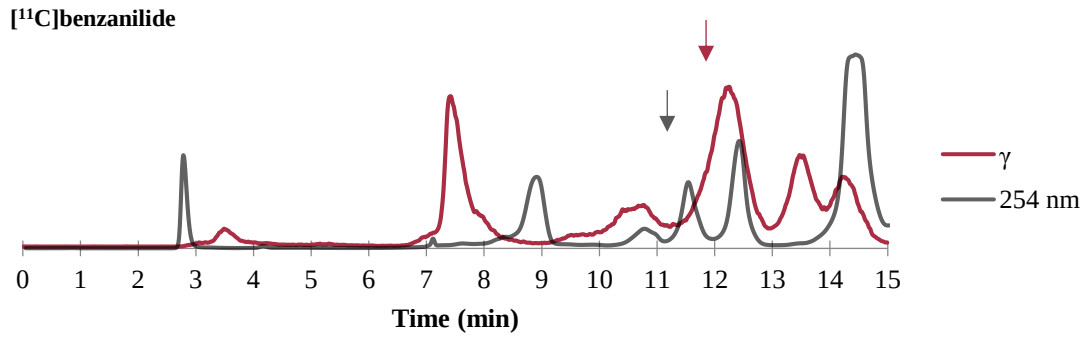


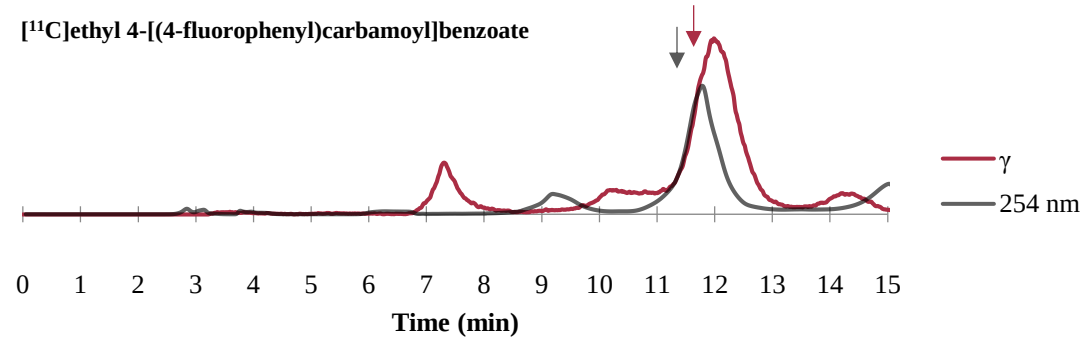


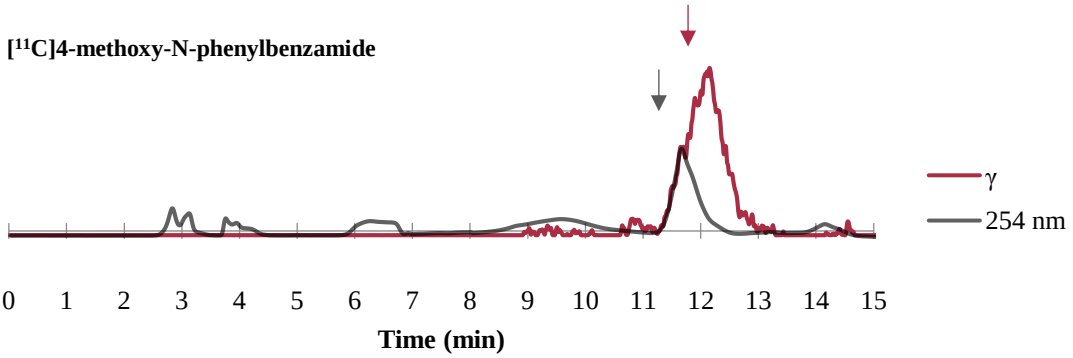
Section 9: Representative HPLC Data

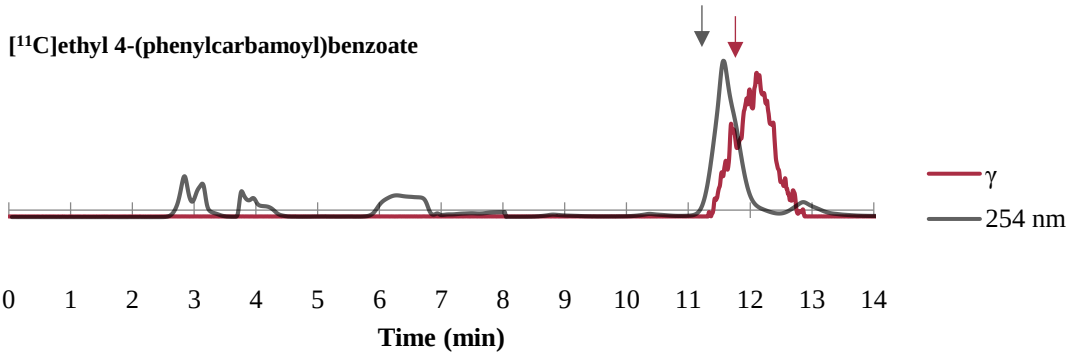
The peaks indicated by solid arrows are present in the chromatograms following coinjection of products with additional nonradioactive standard. The differences in elution times are due to UV-Vis and radiation detectors placed in series, and in all cases were consistent with delays observed at the time of acquisition. Due to modifications of the radioHPLC system, these delays have varied over the course of this project.

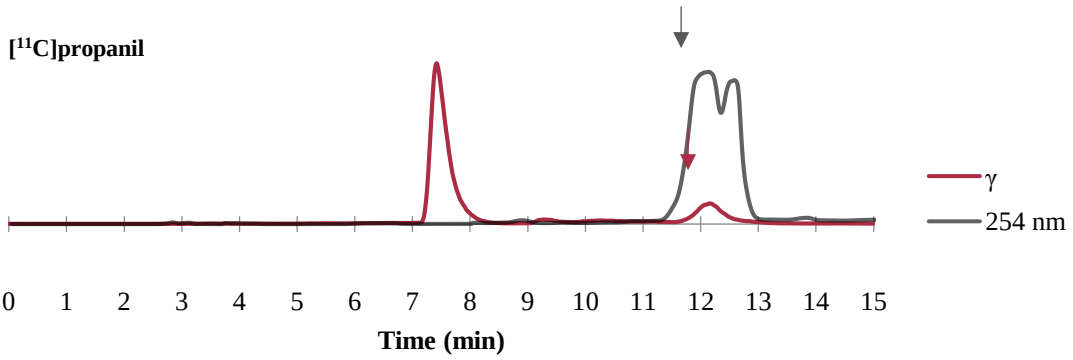


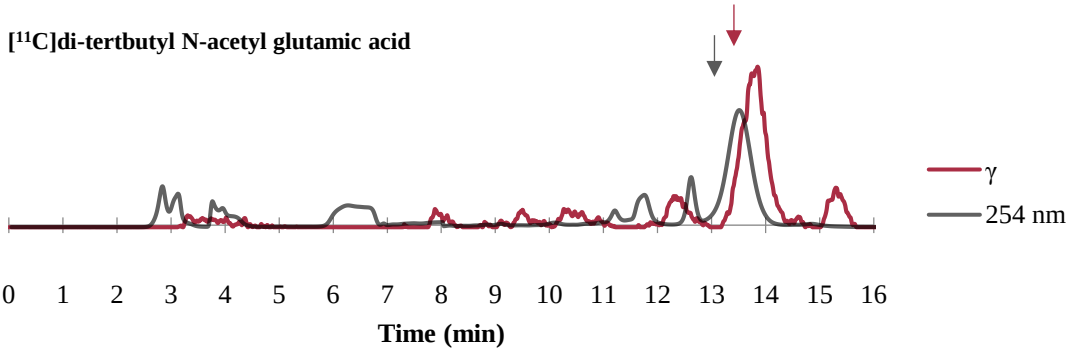


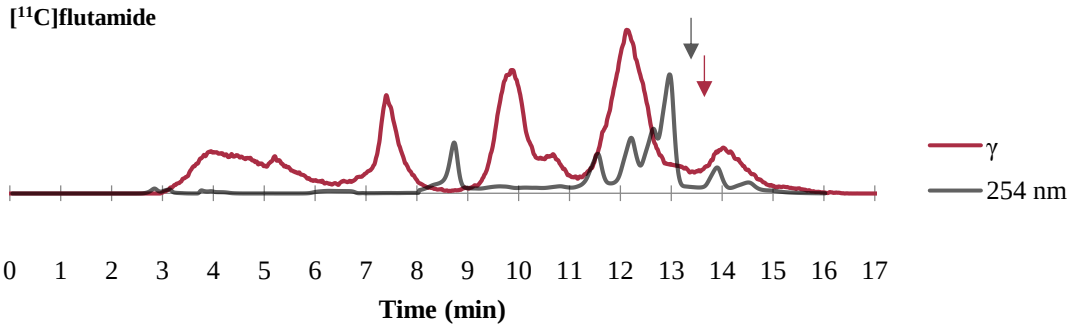


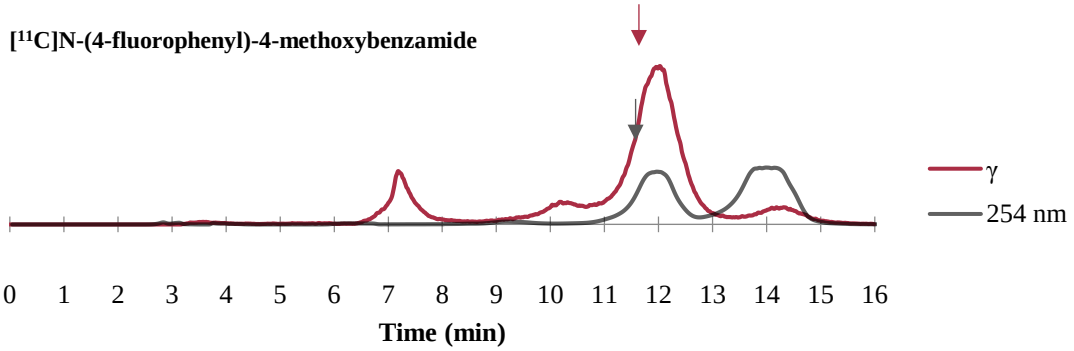

[11C]4-methoxy-N-phenylbenzamide
γ
254 nm
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (min)


[11C]ethyl 4-(phenylcarbamoyl)benzoate
γ
254 nm
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (min)


[11C]propanil
γ
254 nm
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (min)


[11C]di-tertbutyl N-acetyl glutamic acid
γ
254 nm
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time (min)





ISOLATION OF [^{11}C]N-(4-fluorophenyl)-4-methoxybenzamide