Experimental section

Contents

General

Solvents were of analytical grade or distilled laboratory grade: ethyl acetate (EtOAc); dichloromethane (DCM); dimethyl formamide (DMF); methanol (MeOH); tetrahydrofuran (THF). Analytical TLC was performed on silica gel 60/F254 pre-coated aluminium sheets (0.25 mm, Merck). Flash column chromatography was carried out with silica gel 60, 0.63–0.20 mm (70–230 mesh, Merck). ^{1}H NMR spectra were recorded at 400, 500 MHz or 100 MHz (as specified). Chemical shifts (δ, ppm) are reported relative to the solvent peak ($CDCl_3$: 7.26 [^{1}H], DMSO-d_6: 2.50 [^{1}H], MeOD: 4.87 [^{1}H]). Proton resonances are annotated as: chemical shift (ppm), multiplicity (br.s broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J*, Hz), and number of protons.

Analytical HPLC was acquired on an Agilent 1260 Infinity analytical HPLC coupled with a G1322A degasser, G1312B binary pump, G1367E binary pump, G1367E high performance autosampler, G4212B diode array detector. Conditions: Zorbax Eclipse Plus C18 Rapid resolution column (4.6 × 100 mm) with UV detection at 254 nm and 214 nm, 30°C; sample was eluted using a gradient of 5 – 100% of solvent B in solvent A where solvent A: 0.1% aq. TFA, and solvent B: 0.1% TFA in CH_3CN (5 to 100% B [9 min], 100% B [1 min]; 0.5 mL/min). Low resolution mass spectrometry was performed on an Agilent 6100 Series Single Quad LCMS coupled with an Agilent 1200 Series HPLC, G1311A quaternary pump, G1329A thermostatted autosampler, and G1314B variable wavelength detector (214 and 254 nm). High resolution MS was performed on a Waters Autospec instrument (for compounds 3 - 20) or an Agilent 6224 TOF LCMS coupled to an Agilent 1290 Infinity LC. All data were acquired and reference mass corrected via a dual-spray electrospray ionization (ESI) source. LC conditions: Agilent Zorbax SB-C18 Rapid Resolution HT (2.1 × 50 mm, 1.8 μm column), 30°C; sample (5 μL) was eluted using a binary gradient (solvent A: 0.1% aq. HCO_2H; solvent B: 0.1% HCO_2H in CH_3CN; 5 to 100% B [3.5 min], 0.5 mL/min). Purity was determined by HPLC or ^{1}H NMR analysis and was found to be ≥95% for all compounds unless stated otherwise. Exchangeable protons for some compounds were not observed in the NMR spectra.

Biological assays

Trypanosoma cruzi intracellular imaging assay

Compounds were tested for antitrypanosomal activity against *T.cruzi* in H9c2 cells. Maintenance and methods were previously described.[1]

HepG2 cytotoxicity assay

HepG2 (human hepatoma) was provided by GSK-Biological Reagents and Assay Development Department (BRAD, Stevenage, UK). Cell viability was undertaken as previously described.[1]

T.b. brucei resazurin-based viability assay

The *T.b brucei* resazurin-based viability assay was undertaken as previously described. [2, 3]

HEK293 Alamar Blue viability assay

HEK293 was provided by the American Type Culture Collection [ATCC], Manassas, VA. The HEK293 assay was undertaken as previously described. [4]

Synthesis:

General procedure A: Alkylation 1*H*-benzo[*d*]imidazol-2-amine (3a, 3d-3e)

1*H*-benzo[*d*]imidazol-2-amine (1.0 equiv) was dissolved in THF and ethanol (2:1) in a sealed flask followed by the addition of finely ground KOH and the alkyl halide (1.0 equiv). The reaction mixture was heated to 65°C for 72 hours, then allowed to cool to room temperature. The reaction was filtered and the filtrate concentrated *in vacuo*. Purification by silica gel chromatography (eluent: 1% NH_4OH / 9% MeOH/ $CHCl_3$) afforded the desired product. Amine proton signal generally not observed in ^1H NMR due to proton exchange in $CDCl_3$.

General procedure B: Alkylation 1*H*-benzo[*d*]imidazol-2-amine (3b, 3c)

A mixture of 1*H*-benzo[*d*]imidazol-2-amine (1.0 equiv), the alkyl/aryl halide (1.0 equiv), finely ground KOH, K_2CO_3 and acetone was heated to reflux for 3 hours, with stirring. The reaction progression was monitored by TLC/LCMS. The mixture was cooled to room temperature, then the solvent was removed *in vacuo*. The residue was partitioned between water (100 mL) and CH_2Cl_2 (100 mL), the aqueous layer was further extracted twice with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was subsequently separated by column chromatography (eluent: 1% NH_4OH/9% MeOH/ $CHCl_3$) to afford the pure product. Amine proton signal generally not observed in ^1H NMR due to proton exchange in $CDCl_3$.

General procedure C: Amide Coupling (1), (4a-4x), (5a-5e), (6a-6d), (20a-20j)

The respective benzimidazol-2-amine (1.3 equiv) and phenyl acetic acid derivative (1.0 equiv) were added to HOBt.H_2O (1.0 equiv), EDCI (1.2 equiv) and DMF (3.0 mL). The mixture was left to stir at ambient temperature for 20 hours. Water was added to cause the solution to crash out. The solid product was filtered with water, collected and dried in oven vacuum. Amide proton signal generally not observed in ^1H NMR due to proton exchange in $CDCl_3$.

General procedure D: One pot amide coupling via triphosgene-intermediate (9)

The respective aryl starting material (3.0 equiv) was dissolved in DCM (10 mL). Under ice bath, saturated sodium bicarbonate solution (10 mL) was added. The mixture was stirred at 0°C and triphosgene (1.0 equiv) was added. The mixture is left to stir at room temperature for 5 hours, with the reaction progression monitored by thin layer chromatography. After confirmation of intermediate formation, 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (3.0 equiv) is added and the mixture is left to stir at room temperature for 72 hours. Solution is concentrated *in vacuo*, then dissolved in diethyl ether to cause the solution to crash out into a white solid. The white solid was filtered, collected and dried in oven vacuum. The crude material was purified via column chromatography is required (eluent: 1% NH_4OH/ 10% MeOH/ $CHCl_3$) to afford the pure product.

Genereal procedure E: Alkyl Amine Substitution (17a-17j)

Propylamine (7.8 mmol) and triethylamine (1.0 mL) was added to a solution of the respective fluoronitrobenzene in DMF (15 mL) and left to stir at room temperature over 72 hours. The mixture was washed and concentrated appropriately to afford the pure product. Amine proton signal generally not observed in ^1H NMR due to proton exchange in $CDCl_3$.

General procedure F: Hydrogenation (18a-18j, 25)

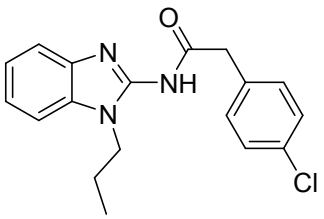
The respective nitro propylaniline was added to MeOH (5.0 mL). Platinum on carbon (10 %) was added to the solution under nitrogen gas. Nitrogen gas was then evacuated, the mixture stirred at room temperature under hydrogen gas for 18 hours. The solution was filtered through celite and MeOH and filtrate was concentrated to

the desired product. Excess solvent was removed under vacuum. Amine proton signal generally not observed in ^{1}H NMR due to proton exchange in $CDCl_3$.

General procedure G: Cyclization of benzimidazole derivatives (19a-19j)

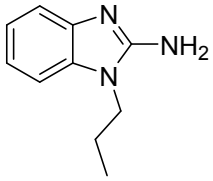
Cyanogen bromide (1.5 equiv) was added to a solution of the respective benzene diamine (1.0 equiv) and MeOH (5 mL). The reaction was left to stir at room temperature for 72hours. Excess cyanogen bromide (0.5 equiv) may be added when necessary. The solution was boiled to remove the methanol solution then basified with ammonia solution. The solution was filtered and concentrated then purified via recrystallization. Amine proton signal generally not observed in ^{1}H NMR due to proton exchange in $CDCl_3$.

2-(4-Chlorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(1)**



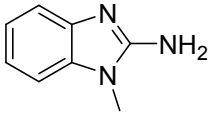
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (507 mg, 2.9 mmol) and 4-chlorophenyl acetic acid (400 mg, 2.4 mmol) according to General procedure C. The title product was afforded as an off-white solid. (150 mg, 20 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 – 7.23 (m, 2H), 7.22 – 7.13 (m, 6H), 3.99 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 2H), 1.82 – 1.65 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 327.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 328.1211 *m/z*, $C_{18}H_{18}ClN_3O^+$ $[M+H]^+$ found 328.1215 *m/z*.

1-Propyl-1H-benzo[d]imidazol-2-amine **(3a)**



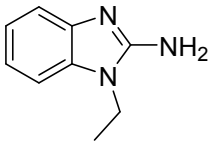
The title compound was prepared from 1*H*-benzo[*d*]imidazol-2-amine (3.9 g, 22.5 mmol), and 1-bromopropane (2.1 mL, 22.5 mmol) according to General procedure A. The title product was afforded as an orange solid (3.05 g, 77%). ^{1}H NMR (400 MHz, DMSO) δ_H 7.27 – 7.02 (m, 2H), 7.05 – 6.73 (m, 2H), 6.38 (s, 2H, NH2), 3.92 (t, *J* = 7.2 Hz, 2H), 1.70 – 1.59 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 176.1 *m/z*.

1-Methyl-1H-benzo[d]imidazol-2-amine**[5]** **(3b)**



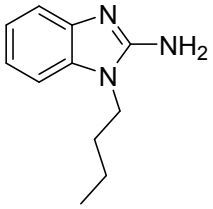
To a solution of 1*H*-benzo[*d*]imidazol-2-amine (500 mg, 4.1 mmol), KOH (4.9 mmol) and acetone (15 mL), methyl iodide (0.25 mL, 4.1 mmol), was added stirred at room temperature for 30 minutes. The reaction was diluted with ethyl acetate and the organic layer washed with water, brine and dried over anhydrous $MgSO_4$, to afford the title compound. (393 mg, 65%). LRMS $[M+H]^+$ 148.0 *m/z*.

1-Ethyl-1H-benzo[d]imidazol-2-amine**[5]** **(3c)**



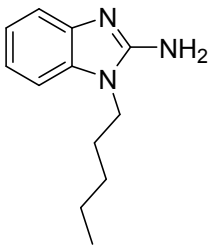
The title compound was prepared 1*H*-benzo[*d*]imidazol-2-amine (500 mg, 4.1 mmol) and 1-iodoethane (0.30 mL, 3.8 mmol) according to General procedure B. The title product was afforded as an orange solid. (301 mg, 49 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 – 7.39 (m, 1H), 7.16 – 7.05 (m, 3H), 4.48 (br.s, 2H, NH_2), 3.99 (q, *J* = 7.3 Hz, 2H), 1.40 (t, *J* = 7.3 Hz, 3H); LRMS $[M+H]^+$ 162.0 *m/z*.

1-Butyl-1H-benzo[d]imidazol-2-amine**[5]** **(3d)**



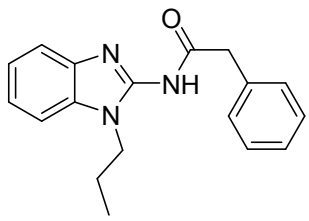
The title compound was prepared from 1*H*-benzo[*d*]imidazol-2-amine (300 mg, 2.3 mmol), and 1-bromopentane (0.24 mL, 2.26 mmol) according to General procedure A. The title product was afforded as an orange solid. (403 mg, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48 – 7.38 (m, 1H), 7.17 – 7.04 (m, 3H), 4.51 (br.s,2H), 3.92 (t, *J* = 7.2 Hz, 2H), 1.85 – 1.72 (m, 2H), 1.47 – 1.35 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); LRMS $[M+H]^+$ 190.1 *m/z*.

1-Pentyl-1H-benzo[d]imidazol-2-amine **(3e)**



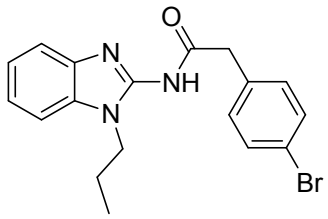
The title compound was prepared from 1*H*-benzo[*d*]imidazol-2-amine (300 mg, 2.3 mmol), and 1-bromopentane (0.24mL, 2.25 mmol) according to General procedure A. The title product was afforded as an orange solid. (233 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 – 7.40 (m, 1H), 7.18 – 7.07 (m, 3H), 5.17 (s, 2H, NH_2), 3.95 (t, J = 7.3 Hz, 2H), 1.86 – 1.67 (m, 2H), 1.40 – 1.31 (m, 4H), 0.93 – 0.85 (m, 3H); LRMS $[M+H]^+$ 204.1 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 204.1495 *m/z*, $C_{12}H_{17}N_3^+$ $[M+H]^+$ found 204.1501 *m/z*.

2-Phenyl-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4a)**



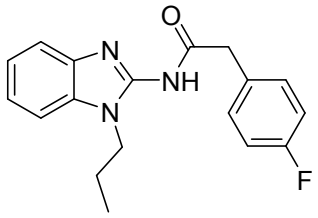
Palladium on carbon (10%) was added a mixture of 3-bromophenyl-*N*-(1-propyl-1*H*-benzo[*d*]imidazol-2-yl)acetamide **(**1.0 g, 2.6 mmol) and ammonium formate (1.7 g, 26.3 mmol) in ethanol (12 mL) under nitrogen gas. The solution was heated to 80°C and refluxed over 5 hours. Excess ammonium formate was added (5 eq). After reaction completion the solution was filtered with MeOH in celite. The solution was concentrated to a brown semi solid washed with $CHCl_3$ then 1% NH_4OH /10% MeOH/ 89% $CHCl_3$ in silica. The filtrate was then concentrated and required further purified via recrystalization in EtO to afford the title compound. (34 mg, 5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.34 – 7.29 (m, 2H), 7.26 – 7.18 (m, 5H), 4.12 (t, J = 7.2 Hz, 2H), 3.83 (s, 2H), 1.92 – 1.72 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 294.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 294.1601 *m/z*, $C_{18}H_{19}N_3O^+$ $[M+H]^+$ found 294.1607 *m/z*.

2-(4-Bromophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4b)**



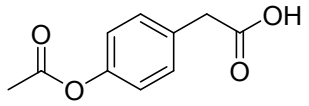
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (500 mg, 2.9 mmol) and 4-bromophenylacetic acid (500 mg, 2.3 mmol) according to General procedure C. The title product was afforded as a solid (714 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.38 (m, 2H), 7.30 – 7.17 (m, 6H), 4.09 – 4.01 (m, 2H), 3.73 (s, 2H), 1.86 – 1.75 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 371.9 *m/z* (^{79}Br), 372.8 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 372.0706 *m/z*, $C_{18}H_{18}BrN_3O^+$ $[M+H]^+$ found 372.0715 *m/z*.

2-(4-Fluorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4c)**



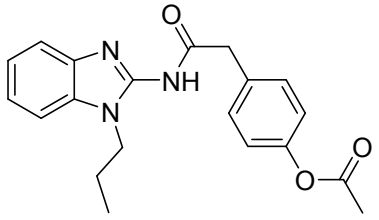
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.57 mmol) and 4-fluorophenylacetic acid (67 mg, 0.44 mmol) according to General procedure C. The title product was afforded as a solid. (109 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.31 (m, 2H), 7.26 – 7.17 (m, 4H), 7.04 – 6.94 (m, 2H), 4.09 (t, J = 7.1 Hz, 2H), 3.76 (s, 2H), 1.90 – 1.76 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 312.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 312.1507 *m/z*, $C_{18}H_{18}FN_3O^+$ $[M+H]^+$ found 312.1513 *m/z*.

2-(4-acetoxyphenyl)acetic acid **(4d.1)** [6] Used as protecting group for analogue **4d**



To a mixture of 4-hydroxyphenylacetic acid (1.4 g, 9.2 mmol) and acetic anhydride (3 mL), 3 drops of concentrated sulfuric acid was added drop wise. Reaction mixture was heated to reflux for 5 hours, monitored by TLC. On reaction completion, ice water was added to the reaction, forming an emulsion. The mixture was washed with DCM and H_2O and concentrated *in vacuo*. The title compound was collected as a white solid. (1.25 g, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32 – 7.28 (m, 2H), 7.08 – 7.03 (m, 2H), 3.64 (s, 2H), 2.29 (s, 3H); LRMS $[M+H]^+$ 194.9 *m/z*.

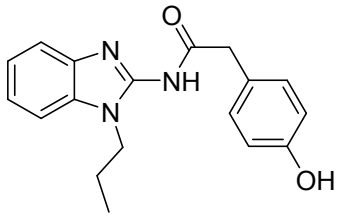
4-(2-Oxo-2-((1-propyl-1H-benzo[d]imidazol-2-yl)amino)ethyl)phenyl acetate **(4d)**



The title compound was prepared from 2-(4-acetoxyphenyl)acetic acid (500 mg, 2.6 mmol)and 1- propyl-1*H*-benzo[*d*]imidazol-2-amine (559 mg, 3.2

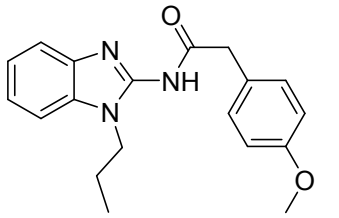
mmol) according to General procedure C. The title product was afforded as a white solid (515 mg, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.38 (m, 2H), 7.25 – 7.17 (m, 4H), 7.05 – 7.00 (m, 2H), 4.10 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 2H), 2.28 (s, 3H), 1.95 – 1.65 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 351.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 352.1656 *m/z*, $C_{20}H_{21}N_3O_3^+$ $[M+H]^+$ found 352.1663 *m/z*.

2-(4-Hydroxyphenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4e)**



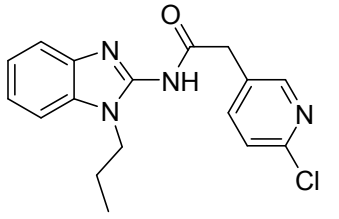
To a mixture of 4-(2-oxo-2-((1-propyl-1*H*-benzo[*d*]imidazol-2-yl)amino)ethyl)phenyl acetate (400 mg, 1.14 mmol) in a H_2O/ MeOH mixture (1:1; 20 mL) was added NaOH (91 mg, 2.3 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified with 6M HCl, filtered and dried. The desired product was collected as a white solid (302 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 – 7.26 (m, 1H), 7.25 – 7.17 (m, 5H), 6.80 – 6.75 (m, 2H), 4.13 – 4.02 (m, 2H), 3.71 (s, 2H), 1.89 – 1.76 (m, 2H), 1.01 – 0.91 (m, 3H); LRMS $[M+H]^+$ 310.2 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 310.155 *m/z*, $C_{18}H_{19}N_3O_2^+$ $[M+H]^+$ found 310.1556 *m/z*.

2-(4-Methoxyphenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4f)**



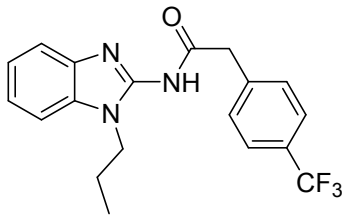
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (137 mg, 0.78 mmol) and 4-methoxyphenylacetic acid (100 mg, 0.60 mmol) according to General procedure C. The title product was afforded as an off-white solid. (124 mg, 64 %).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 – 7.29 (m, 2H), 7.26 – 7.16 (m, 4H), 6.90 – 6.83 (m, 2H), 4.13 – 4.07 (m, 2H), 3.79 (s, 3H), 3.75 (s, 2H), 1.93 – 1.75 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 323.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 324.1707 *m/z*, $C_{19}H_{21}N3O_2^+$ $[M+H]^+$ found 324.1712 *m/z*.

2-(6-Chloropyridin-3-yl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4g)**



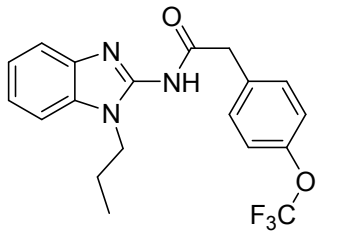
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (290 mg, 1.7 mmol) and 6-chloropyridin-3-ylacetic acid (218 mg, 1.3 mmol) according to General procedure C. The title product was afforded as a white solid. (409 mg, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.40 (d, *J* = 2.0 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.31 – 7.27 (m, 3H), 7.25 – 7.22 (m, 2H), 4.15 – 4.00 (m, 2H), 3.78 (s, 2H), 1.89 – 1.75 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); HPLC t_R=4.296 min >95% purity at 254nm; LRMS $[M+H]^+$ 328.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 329.1164 *m/z*, $C_{17}H_{17}ClN_4O^+$ $[M+H]^+$ found 329.1164 *m/z*.

N-(1-Propyl-1H-benzo[d]imidazol-2-yl)-2-(4-(trifluoromethyl)phenyl)acetamide **(4h)**



The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.57 mmol) and 4-trifluoromethylphenylacetic acid (89 mg, 0.44 mmol) according to General procedure C. The title product was afforded as a solid (107 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (dd, *J* = 23.8, 8.2 Hz, 4H), 7.25 – 7.17 (m, 4H), 4.14 – 3.98 (m, 2H), 3.83 (s, 2H), 1.87 – 1.73 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 361.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 362.1475 *m/z*, $C_{19}H_{18}F_3N_3O^+$ $[M+H]^+$ found 362.1477 *m/z*.

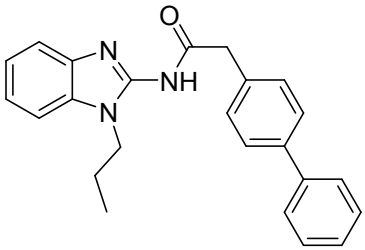
N-(1-Propyl-1H-benzo[d]imidazol-2-yl)-2-(4-(trifluoromethoxy)phenyl)acetamide **(4i)**



The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.57 mmol) and 4-trifluoromethoxyphenylacetic acid (97 mg, 0.44 mmol) according to General procedure C. The title product was afforded as a solid (160 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.37 (m, 2H), 7.26 – 7.12 (m, 6H), 4.13 – 4.01 (m, 2H), 3.79 (s, 2H), 1.90 – 1.73 (m, 2H), 0.99 – 0.87 (m,

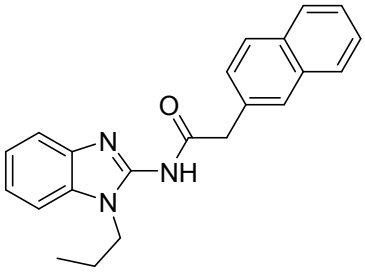
3H); LRMS [M+H] $^+$ 378.1 *m/z*; HRMS-ESI (*m/z*): [M+H]$^+$ 378.1424 *m/z*, $C_{19}H_{18}F_3N_3O_2$ $^+$ [M+H]$^+$ found 378.1432 *m/z*.

2-([1,1'-Biphenyl]-4-yl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4j)**



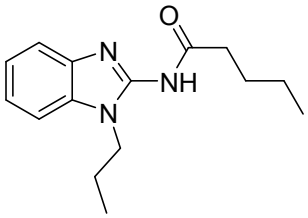
General procedure C was followed using 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (330 mg, 1.9 mmol) and 2-([1,1'-biphenyl]-4-yl)acetic acid (308 mg, 1.5 mmol) to afford the title compound. (688 mg, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 – 7.53 (m, 4H), 7.50 – 7.40 (m, 4H), 7.35 – 7.29 (m, 1H), 7.26 – 7.16 (m, 4H), 4.12 – 4.06 (m, 2H), 3.83 (s, 2H), 1.90 – 1.76 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); LRMS [M+H]$^+$ 370.0 *m/z;* HRMS-ESI (*m/z*): [M+H]$^+$ 370.1914 *m/z*, $C_{24}H_{23}N_3O^+$ found 370.192 *m/z*.

2-(Naphthalen-2-yl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4k)**



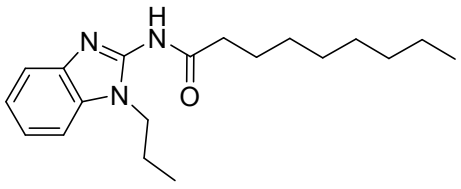
General procedure C was followed using using 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.1 mmol) and 2-(naphthalen-2-yl)acetic acid (163 mg, 0.88 mmol). The mixture was diluted with water and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated in *vacuo*. Further purification via silica gel chromatography was required (eluent 1 % NH_4OH/ 9 % MeOH/ 89 % $CHCl_3$) to afford the title compound. (153 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.92 – 7.77 (m, 4H), 7.61 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.24 – 7.08 (m, 4H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.99 (s, 2H), 1.97 – 1.68 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); LRMS [M+H]$^+$ 344.0 *m/z;* HRMS-ESI (*m/z*): [M+H]$^+$ 344.1757 *m/z*, $C_{22}H_{21}N_3O$ found 344.1766 *m/z*.

N-(1-Propyl-1H-benzo[d]imidazol-2-yl)pentanamide **(4l)**



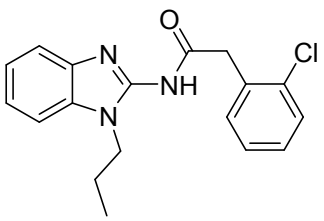
General procedure C was followed using using 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.1 mmol) and valeric acid (0.1 mL, 0.88 mmol). After aqueous filtration the concentrated crude mixture was purified via silica gel wash (100 mL 100 % $CHCl_3$, 100 mL 1 % NH_4OH/ 9 % MeOH/ $CHCl_3$, 100 mL 100 % MeOH). Product was concentrated *in vacuo* to yield the title product. (139 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.28 (m, 1H), 7.24 – 7.17 (m, 3H), 4.17 – 4.03 (m, 2H), 2.51 – 2.45 (m, 2H), 1.91 – 1.79 (m, 2H), 1.75 – 1.64 (m, 2H), 1.41 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.95 (q, *J* = 7.3 Hz, 6H); LRMS [M+H] $^+$ 260.0 *m/z;* HRMS-ESI (*m/z*): [M+H]$^+$ 260.1757 *m/z*, $C_{15}H_{21}N_3O^+$ found 260.1759 *m/z*.

N-(1-Propyl-1H-benzo[d]imidazol-2-yl)nonanamide **(4m)**



General procedure C was followed using 1-propyl-1H-benzo[d]imidazol-2-amine (200 mg, 1.1 mmol) and nonanoic acid (0.20 mL, 0.86 mmol) to afford the title compound as an orange solid. (265 mg, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.30 (m, 1H), 7.25 – 7.17 (m, 3H); 4.20 – 4.00 (m, 2H), 2.53 – 2.41 (m, 2H), 1.91 – 1.79 (m, 2H), 1.76 – 1.67 (m, 2H), 1.41 – 1.27 (m, 10H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.90 – 0.87 (m, 3H); LRMS [M+H]$^+$ 316.0 *m/z;* HRMS-ESI (*m/z*): [M+H]$^+$ 316.2383 *m/z*, $C_{19}H_{29}N_3O$ found 316.2368 *m/z*.

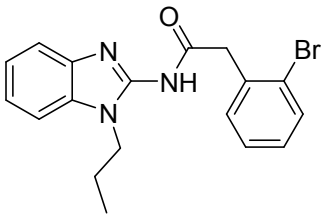
2-(2-Chlorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4n)**



The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (507 mg, 2.9 mmol) and 2-chlorophenyl acetic acid (400 mg, 2.4 mmol) according to General procedure C. The title product was afforded as a solid (388 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.35 (m, 2H), 7.24 – 7.19 (m, 6H), 4.04 – 3.99 (m, 2H), 3.97 (s, 2H), 1.83 – 1.71 (m, 2H), 0.90 (t, *J* = 7.4 Hz,

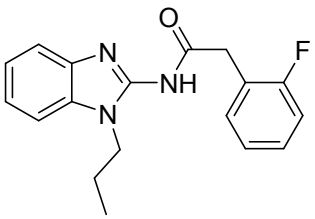
3H); LRMS [M+H] $^+$ 327.9 *m/z;* HRMS-ESI (*m/z*): [M+H]$^+$ 328.1211 *m/z*, $C_{18}H_{18}ClN_3O^+$ [M+H]$^+$ found 328.1218 *m/z*.

2-(2-Bromophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4o)**



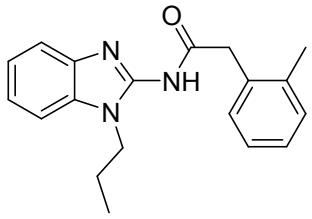
To a sealed tube was added 2-bromophenylacetic acid (200 mg, 0.9 mmol) CDI (1 eq) and $CHCl_3$ (1 mL) and stirred at room temperature for one hour. To this mixture 1-propyl-1H-benzo[d]imidazol-2-amine (195mg, 1.1mmol) was then added and left to stir for 20 hours. The mixture was suspended in ethanol, filtered, collected and dried via oven vacuum. The desired product was obtained as a white solid. (113 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 – 7.59 (m, 1H), 7.48 – 7.40 (m, 1H), 7.36 – 7.21 (m, 5H), 7.19 – 7.10 (m, 1H), 4.12 – 3.97 (m, 4H), 1.98 – 1.71 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 372.1 *m/z* (^{79}Br), 373.1 *m/z* (^{81}Br); HRMS-ESI (*m/z*): [M+H]$^+$ 372.0706 *m/z*, $C_{18}H_{18}BrN_3O^+$ [M+H]$^+$ found 372.0713 *m/z*.

2-(2-Fluorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4p)**



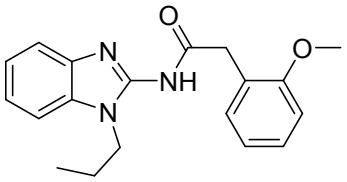
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.57 mmol) and 2-fluorophenylacetic acid (67 mg, 0.44 mmol) according to General procedure C. The title product was afforded as a solid. (94 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.32 (m, 1H), 7.25 – 7.19 (m, 5H), 7.13 – 7.02 (m, 2H), 4.10 – 3.99 (m, 2H), 3.87 (s, 2H), 1.87 – 1.66 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 312.0 *m/z*; HRMS-ESI (*m/z*): [M+H]$^+$ 312.1507 *m/z*, $C_{18}H_{18}FN_3O^+$ [M+H]$^+$ found 312.1513 *m/z*.

N-(1-Propyl-1H-benzo[d]imidazol-2-yl)-2-(o-tolyl)acetamide **(4q)**

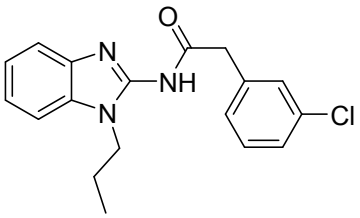


The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.1 mmol) and 2-(*o*-tolyl)acetic acid (134 mg, 0.89 mmol). according to General procedure C. The title product was afforded as a white solid. (160 mg, 59 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.27 (m, 2H), 7.25 – 7.12 (m, 6H), 4.13 (br.s, 2H), 3.90 (s, 2H), 2.41 (s, 3H), 1.90 – 1.72 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 308.0 *m/z*; HRMS-ESI (*m/z*): [M+H]$^+$ 308.1757 *m/z*, $C_{19}H_{21}N_3O^+$ [M+H]$^+$ found 308.1751 *m/z*.

2-(2-Methoxyphenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4r)**



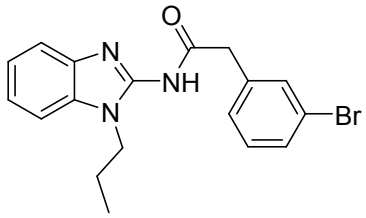
General procedure C was followed using 2-methoxyphenylacetic acid (363 mg, 2.2 mmol) and 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (500 mg, 2.8 mmol) to obtain the title compound as a solid. (51 mg, 7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32 – 7.27 (m, 1H), 7.25 – 7.16 (m, 5H), 6.96 – 6.87 (m, 2H), 4.06 – 4.00 (m, 2H), 3.85 (s, 2H), 3.83 (s, 3H), 1.84 – 1.70 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 324.0 *m/z*; HRMS-ESI (*m/z*): [M+H]$^+$ 324.1706 *m/z*, $C_{19}H_{21}N_3O_2^+$ [M+H]$^+$ found 324.1707 *m/z*.



The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.57 mmol) and 3-chlorophenylacetic acid (81 mg, 0.47 mmol) according to General procedure C. The title product was afforded as a solid. (111 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.41 (m, 1H), 7.26 – 7.18 (m, 7H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.76 (s, 2H), 1.91 – 1.76 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 327.9 *m/z*; HRMS-ESI (*m/z*): [M+H]$^+$ 328.1211 *m/z*, $C_{18}H_{18}ClN_3O^+$ [M+H]$^+$ found 328.122 *m/z*.

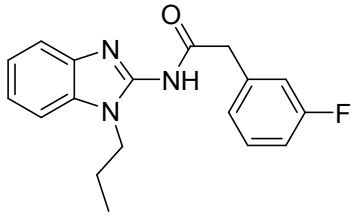
2-(3-Bromophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4t)**

The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.1 mmol) and 3-bromophenylacetic acid (200 mg, 0.93 mmol) according to General procedure C. The title product was afforded



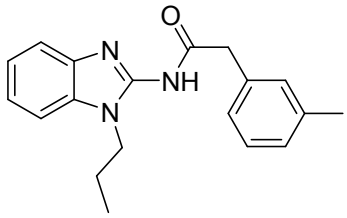
as a solid (212 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 1H), 7.37 – 7.26 (m, 3H), 7.25 – 7.14 (m, 4H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 2H), 1.91 – 1.77 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 372.1 *m/z* (^{79}Br), 373.1 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 372.0706 *m/z*, $C_{18}H_{18}BrN_3O^+$ $[M+H]^+$ found 372.0714 *m/z*.

2-(3-Fluorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4u)**



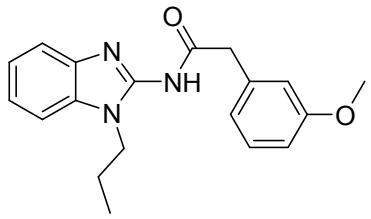
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.57 mmol) and 3-fluorophenylacetic acid (67 mg, 0.44 mmol) according to General procedure C. The title product was afforded as a solid. (84 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26 – 7.12 (m, 7H), 6.96 – 6.87 (m, 1H), 4.09 (t, *J* = 7.0 Hz, 2H), 3.79 (s, 2H), 1.88 – 1.74 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 312.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 312.1507 *m/z*, $C_{18}H_{18}FN_3O^+$ $[M+H]^+$ found 312.1511 *m/z*.

N-(1-Propyl-1H-benzo[d]imidazol-2-yl)-2-(m-tolyl)acetamide **(4v)**



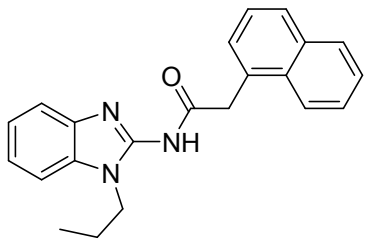
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.1 mmol) and 2-(*m*-tolyl)acetic acid (134 mg, 0.89 mmol) according to General procedure C. The title product was afforded as a white solid. (258 mg, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26 – 7.18 (m, 7H), 7.10 – 7.01 (m, 1H), 4.21 (br.s, 2H), 3.85 (s, 2H), 2.34 (s, 3H), 1.92 – 1.77 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 308.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 308.1757 *m/z*, $C_{19}H_{21}N_3O^+$ $[M+H]^+$ found 308.176 *m/z*.

2-(3-Methoxyphenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4w)**



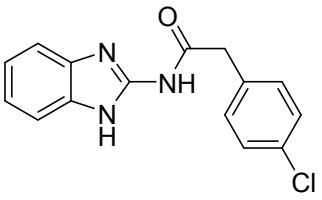
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (500 mg, 2.9 mmol) and 3-methoxyphenylacetic acid (358 mg, 2.2 mmol) according to General procedure C. The title product was afforded as a white solid. (209 mg, 30 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25 – 7.19 (m, 5H), 7.05 – 6.97 (m, 2H), 6.80 – 6.75 (m, 1H), 4.17 (t, *J* = 7.0 Hz, 2H), 3.83 (s, 2H), 3.81 (s, 3H), 1.96 – 1.75 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 324.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 324.1793 *m/z*, $C_{19}H_{21}N_3O_2^+$ $[M+H]^+$ found 324.1707 *m/z*.

2-(Naphthalen-1-yl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(4x)**



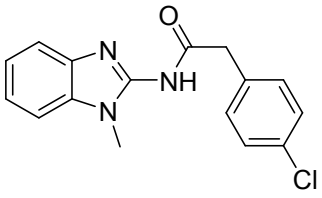
General procedure C was followed using using 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.1 mmol) and 2-(naphthalen-1-yl)acetic acid (163 mg, 0.88 mmol). The mixture was diluted with water and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated in *vacuo.* Further purification via silica gel chromatography was required (eluent 1 % NH_4OH/9 % MeOH/ 89 % $CHCl_3$) to afford the title compound. (263 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.32 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.82 (m, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.41 (m, 4H), 7.23 – 7.08 (m, 4H), 4.28 (s, 2H), 3.96 (t, *J* = 7.2 Hz, 2H), 1.83 – 1.55 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 344.0 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 344.1757 *m/z*, $C_{22}H_{21}N_3O$ found 344.1773 *m/z*.

N-(1H-Benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide **(5a)**



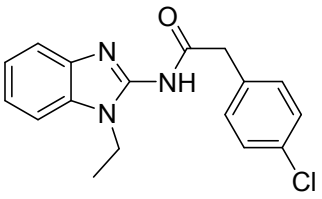
General procedure C was followed using 1*H*-benzo[*d*]imidazol-2-amine (509 mg, 3.8 mmol) and 4-chlorophenylacetic acid (500 mg, 2.9 mmol) to afford the title product. (673 mg, 80 %). ^{1}H NMR (400 MHz, MeOD) δ_H 7.54 – 7.48 (m, 2H), 7.46 – 7.38 (m, 4H), 7.24 – 7.19 (m, 2H), 3.87 (s, 2H); LRMS $[M+H]^+$ 285.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 286.0742 *m/z*, $C_{15}H_{12}ClN_3O^+$ found 286.0748$^+$ *m/z*.

***2-(4-Chlorophenyl)-N-(1-methyl-1H-benzo[d]imidazol-2-yl)acetamide*[7] (5b)**



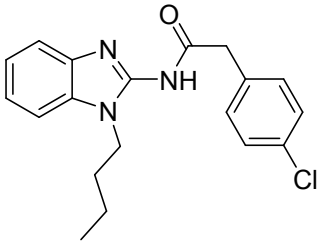
The title compound was prepared from 1-methyl-1*H*-benzo[*d*]imidazol-2-amine (300 mg, 2.0 mmol) and 4-chlorophenylacetic acid (244 mg, 1.4 mmol) according to General procedure C. The title product was afforded as a white solid (294 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.27 (m, 4H), 7.26 – 7.20 (m, 4H), 3.77 (s, 2H), 3.63 (s, 3H); LRMS $[M+H]^+$ 300.1 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 300.0898 *m/z*, $C_{16}H_{14}ClN_3O^+$ $[M+H]^+$ found 300.0903 *m/z*.

***2-(4-Chlorophenyl)-N-(1-ethyl-1H-benzo[d]imidazol-2-yl)acetamide* (5c)**



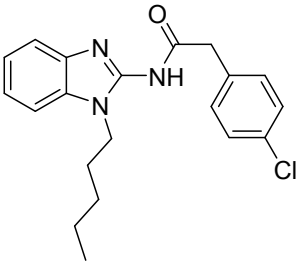
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.62 mmol) and 4-chlorophenylacetic acid (81 mg, 0.47 mmol) according to General procedure C. The title product was afforded as a white solid. (130 mg, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.26 (m, 8H), 4.38 (br.s, 2H), 3.89 (br.s, 2H), 1.43 (t, J = 7.3 Hz, 3H); LRMS $[M+H]^+$ 313.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 314.1055 *m/z*, $C_{17}H_{16}ClN_3O^+$ $[M+H]^+$ found 314.1059 *m/z*.

***N-(1-Butyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide* (5d)**



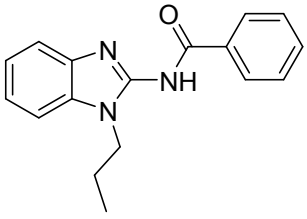
The title compound was prepared from 1-butyl-1*H*-benzo[*d*]imidazol-2-amine (395 mg, 2.1 mmol) and 4-chlorophenylacetic acid (273 mg, 1.6 mmol according to General procedure C. The title product was afforded as a solid (291 mg, 53 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 – 7.26 (m, 4H), 7.25 – 7.18 (m, 4H), 4.09 (t, J = 7.2 Hz, 2H), 3.74 (s, 2H), 1.83 – 1.67 (m, 2H), 1.43 – 1.27 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 341.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 342.1368 *m/z*, $C_{19}H_{20}ClN_3O^+$ $[M+H]^+$ found 342.1373 *m/z*.

***2-(4-Chlorophenyl)-N-(1-pentyl-1H-benzo[d]imidazol-2-yl)acetamide* (5e)**



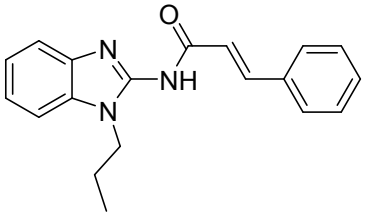
The title compound was prepared from 1-pentyl-1*H*-benzo[*d*]imidazol-2-amine (230 mg, 1.13 mmol) and 4-chlorophenylacetic acid (148 mg, 0.87 mmol) according to General procedure C. The title product was afforded as a white solid (294 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 – 7.30 (m, 2H), 7.29 – 7.26 (m, 2H), 7.26 – 7.18 (m, 4H), 4.10 (t, J = 7.3 Hz, 2H), 3.76 (s, 2H), 1.84 – 1.69 (m, 2H), 1.41 – 1.23 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); LRMS $[M+H]^+$ 356.2 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 356.1524 *m/z*, $C_{20}H_{22}ClN_3O^+$ $[M+H]^+$ found 356.1544 *m/z*.

***N-(1-Propyl-1H-benzo[d]imidazol-2-yl)benzamide* (6a)**



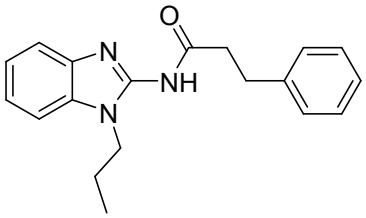
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (354 mg, 2.0 mmol) and benzoic acid (200 mg, 1.6 mmol) according to General procedure C. The title product was afforded as a white solid (342 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.37 – 8.32 (m, 2H), 7.50 – 7.42 (m, 3H), 7.37 – 7.32 (m, 1H), 7.29 – 7.26 (m, 2H), 7.26 – 7.22 (m, 1H), 4.30 – 4.21 (m, 2H), 2.00 – 1.90 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 280.2 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 280.1444 *m/z*, $C_{17}H_{17}N_3O^+$ $[M+H]^+$ found 280.1447 *m/z*.

***N-(1-Propyl-1H-benzo[d]imidazol-2-yl)cinnamamide* (6b)**



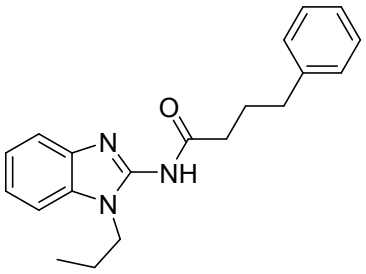
The title compound was prepared from trans-cinnamic acid (458 mg, 2.6 mmol) and 1- propyl-1*H*-benzo[*d*]imidazol-2-amine (302 mg, 2.0 mmol) according to General procedure C. The title compound was afforded as a white solid. (426 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (d, J = 15.9 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.42 – 7.30 (m, 6H), 7.26 – 7.23 (m, 1H), 6.82 (d, J = 15.9 Hz, 1H), 4.22 – 4.15 (m, 2H), 2.05 – 1.78 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); HPLC tR= 6.01 min >94 % purity at 254nm; LRMS $[M+H]^+$ 306.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 305.1523 *m/z*, $C_{19}H_{19}N_3O^+$ $[M+H]^+$ found 305.1513 *m/z*.

3-Phenyl-N-(1-propyl-1H-benzo[d]imidazol-2-yl)propanamide **(6c)**



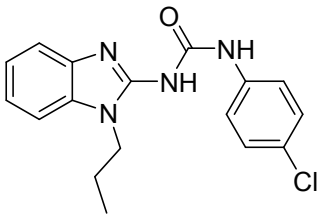
The title compound was prepared from 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (300 mg, 1.7 mmol) and 3-phenylpropanoic acid (198 mg, 1.3 mmol) according to General procedure C. The desired product was obtained as a white solid (300 mg, 75 %).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26 – 7.12 (m, 9H), 4.21 – 3.98 (m, 2H), 3.11 – 2.94 (m, 2H), 2.90 – 2.70 (m, 2H), 1.95 – 1.68 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 308.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 308.1757 *m/z*, $C_{19}H_{21}N_3O^+$ $[M+H]^+$ found 308.1762 *m/z*.

4-Phenyl-N-(1-propyl-1H-benzo[d]imidazol-2-yl)butanamide **(6d)**



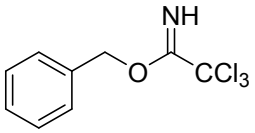
General procedure C was followed using using 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (100 mg, 0.58 mmol) and 4-phenylbutyric acid (74 mg, 0.45 mmol). The mixture was diluted with water and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo.* Further purification via silica gel chromatography was required (eluent 1 % NH_4OH/ 9 % MeOH/ 89 % $CHCl_3$) to afford the title compound. (81 mg, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.15 (m, 9H), 4.13 – 4.03 (m, 2H), 2.75 – 2.70 (m, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.12 – 2.02 (m, 2H), 1.90 – 1.80 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 322.0 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 322.1914 *m/z*, $C_{20}H_{23}N_3O$ found 322.1923 *m/z*.

1-(4-chlorophenyl)-3-(1-propyl-1H-benzo[d]imidazol-2-yl)urea **(9)**



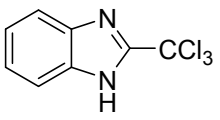
The title compound was prepared from 4-chloroaniline (400 mg, 3.2 mmol) and 1-propyl-1*H*-benzo[*d*]imidazol-2-amine (554 mg, 3.2 mmol) according to General procedure D. The crude mixture was concentrated then diluted with diethyl ether to cause partial precipitation. The mixture was filtered via suction filtration and the solid precipitate was collected and dried to afford the title product. (151 mg, 14 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 – 7.45 (m, 2H), 7.30 – 7.27 (m, 1H), 7.25 – 7.09 (m, 5H), 4.04 (br.s, 2H), 1.95 – 1.73 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 328.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 329.1164 *m/z*, $C_{17}H_{17}Cl\,N_4O^+$ $[M+H]^+$ found 329.1172 *m/z*.

Benzyl 2,2,2-trichloroacetimidate **[8]** **(11)**



To a solution of KOH (50% aq) and tetrabutylammonium hydrogensulfate (60 mg) was added to benzyl alcohol (4.0 g, 37.0 mmol) in DCM (40 mL) at -15-to -10°C. The mixture was stirred for 30 minutes. Solution was warmed to room temperature and left to stir for 1 hour. The organic layer was extracted, filtered and concentrated to 1/3 of the original volume. The solution was filtered through celite and washed with DCM. The filtrate was concentrated *in vacuo* to obtain title compound as a yellow liquid. (6.8 mL, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.38 – 7.27 (m, 5H), 5.25 (s, 2H).

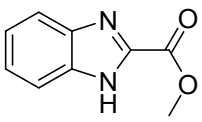
2-(Trichloromethyl)-1H-benzo[d]imidazole **[9]** **(12)**



Benzyl 2,2,2-trichloroacetimidate (1.7 mL, 9.2 mmol) was added to a solution of benzene-1,2-diamine (1.0 g, 9.2 mmol) in acetic acid (30 mL) and stirred at room temperature for 1

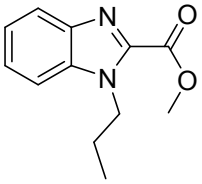
hour. The solution was filtered with water, collected and dried under oven vacuum to afford the title compound as a white solid.(2.1 g, 99 %). ^{1}H NMR (400 MHz, DMSO) δ 7.13 – 6.94 (m, 2H), 6.84 – 6.63 (m, 2H).

***Methyl 1H-benzo[d]imidazole-2-carboxylate*[9] (13)**



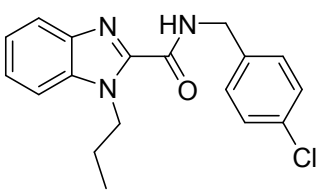
Bromopropane (0.3 mL, 2.8 mmol) was added to a solution of methyl 1*H*-benzo[*d*]imidazole-2-carboxylate (250 mg, 1.4 mmol), DMF (3 mL) and K_2CO_3 (392 mg, 2.8 mmol). The reaction mixture was heated to 65°C and stirred for 18 hours. Reaction mixture was then cooled to room temperature and concentrated. The mixture was extracted with EtOAc and brine concentrated to afford the title compound. (237 mg, 76 %). The crude mixture was taken to the next step without further purification. LRMS $[M+H]^+$ 177.0 *m/z*.

***Methyl 1-propyl-1H-benzo[d]imidazole-2-carboxylate* (14)**



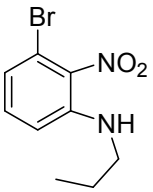
Bromopropane (0.27 mL, 2.8 mmol) was added to a solution of methyl 1*H*-benzo[*d*]imidazole-2-carboxylate (250 mg, 1.4 mmol), DMF (3 mL) and K_2CO_3 (392 mg, 2.8 mmol). The reaction mixture was heated to 65°C and stirred for 18 hours. Reaction mixture was then cooled to room temperature and concentrated. The mixture was extracted with EtOAc and brine concentrated to afford the title. The crude mixture was taken to the next step without further purification (237 mg, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 1H), 7.48 – 7.31 (m, 3H), 4.68 – 4.55 (m, 2H), 4.04 (s, 3H), 1.98 – 1.80 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 219.0 *m/z*.

***N-(4-chlorobenzyl)-1-propyl-1H-benzo[d]imidazole-2-carboxamide* (15)**



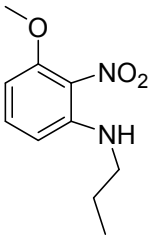
Methyl 1-propyl-1*H*-benzo[*d*]imidazole-2-carboxylate (237 mg, 1.1 mmol) was added to 4-chlorobenzylamine (2.6 mL, 21.7 mmol) and the mixture was boiled to 120°C. The mixture was cooled to room temperature, dissolved in DCM and filtered. The filtrate was further purified by silica gel chromatography (eluent:30% EtOAc/70% Petroleum spirits) to afford the title compound. (15 mg, 4%).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (br.s, 1H, NH), 7.81 – 7.75 (m, 1H), 7.51 – 7.47 (m, 1H), 7.44 – 7.30 (m, 6H), 4.79 – 4.69 (m, 2H), 4.64 (d, *J* = 6.2 Hz, 2H), 2.07 – 1.87 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 327.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 328.1211 *m/z*, $C_{18}H_{18}ClN_3O^+$ $[M+H]^+$ found 328.1222 *m/z*.

***3-bromo-2-nitro-N-propylaniline*[10] (17a)**



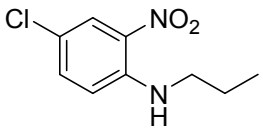
General procedure E was followed using 1-bromo-3-fluoro-2-nitrobenzene (1.6 g, 7.1 mmol). Upon reaction completion the mixture was filtered via suction filtration causing the product to solidify on the frit of the funnel. The crystal product was collected, and the remaining filtrate was extracted with EtOAc and brine. The organic layer was dried, filtered and concentrated to an orange solid. (1.8 g, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.06 (t, *J* = 7.9 Hz, 1H), 6.84 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.68 (dd, *J* = 8.6, 0.8 Hz, 1H), 5.68 (s, 1H, NH), 3.08 (td, *J* = 7.1, 5.3 Hz, 2H), 1.71 – 1.46 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 260.8 *m/z* (^{79}Br), 261.8 *m/z* (^{81}Br).

***3-methoxy-2-nitro-N-propylaniline* (17b)**



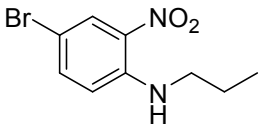
General procedure E was followed using 1-fluoro-3-methoxy-2-nitrobenzene (1.2 g, 7.1 mmol). Upon reaction completion the mixture was filtered with water and extracted with EtOAc and brine. The organic layer was dried and concentrated to afford the title compound as an orange semi solid. The crude mixture was taken to the next step without further purification. (1.4 g, 94 %). LRMS $[M+H]^+$ 211.0 *m/z.*

***4-chloro-2-nitro-N-propylaniline*[11] (17c)**



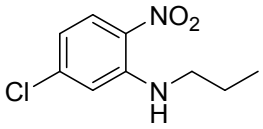
General procedure E was followed using 5-chloro-2-fluoronitrobenzene (1.3 g 7.1 mmol). On reaction completion the reaction mixture was diluted with EtOAc and washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound as orange crystals. (1.2 g, 79 %).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (d, *J* = 2.5 Hz, 1H), 7.36 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 3.26 (td, *J* = 7.0, 4.0 Hz, 2H), 1.80 – 1.69 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 215.0 *m/z*.

***4-bromo-2-nitro-N-propylaniline*[12] (17d)**



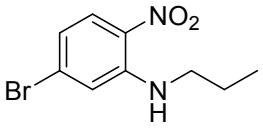
General procedure E was followed using 4-bromo-1-fluoro-2-nitrobenzene (0.87 mL, 7.1 mmol). After reaction completion, the mixture was diluted with EtOAc and washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound as orange crystals. (1.7 g, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.4 Hz, 1H), 8.05 (br.s, 1H, NH), 7.48 (ddd, *J* = 9.2, 2.4, 0.6 Hz, 1H), 6.76 (d, *J* = 9.2 Hz, 1H), 3.26 (td, *J* = 7.1, 5.3 Hz, 2H), 1.87 – 1.62 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); HRMS-ESI (*m/z*): $[M+H]^+$ 257.9998 *m/z*, $C_9H_{11}BrN_2O_2^+$ $[M+H]^+$ found 258.003 *m/z* (^{79}Br), 259.0077 *m/z*, found 259.0078 *m/z* (^{81}Br)

***5-chloro-2-nitro-N-propylaniline*[13] (17e)**



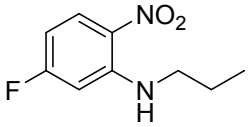
General procedure E was followed using 4-chloro-2-fluoronitrobenzene (1.3 g 7.1 mmol). After completion the reaction mixture was diluted with DCM and washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound as orange crystals. (889 mg, 59 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.10 (d, *J* = 9.1 Hz, 1H), 6.82 (d, *J* = 2.1 Hz, 1H), 6.58 (dd, *J* = 9.1, 2.1 Hz, 1H), 3.23 (td, *J* = 7.1, 5.2 Hz, 2H), 1.77 – 1.71 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 214.9 *m/z*.

5-Bromo-2-nitro-*N*-propylaniline[14] (17f)



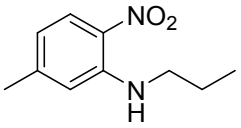
General procedure E was followed using 4-bromo-2-fluoro-1-nitrobenzene (1.6 g, 7.1 mmol). After reaction completion the mixture was diluted with water and filtered via suction filtration and product was collected as orange crystals. (812 mg, 45 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.1 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.74 (dd, *J* = 9.1, 2.0 Hz, 1H), 3.24 (td, *J* = 7.1, 5.2 Hz, 2H), 1.88 – 1.65 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); HRMS-ESI (*m/z*): $[M+H]^+$ 259.0077 *m/z*, $C_9H_{11}BrN_2O_2^+$ $[M+H]^+$ found 259.0072 *m/z*.

***5-fluoro-2-nitro-N-propylaniline*[15] (17g)**



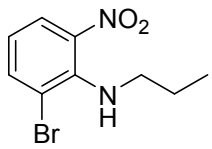
General procedure E was followed using 2,4-difluoro-1-nitrobenzene (0.78 mL, 7.1 mmol). Upon reaction completion, mixture was diluted with EtOAc and extracted with brine. The organic layer was dried under vacuum and concentrated to afford the title compound. (1.36 g, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.25 – 8.16 (m, 1H), 6.47 (dd, *J* = 11.5, 2.6 Hz, 1H), 6.38 – 6.27 (m, 1H), 3.22 (td, *J* = 7.0, 5.4 Hz, 2H), 1.82 – 1.71 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 199.0 *m/z*.

***5-methyl-2-nitro-N-propylaniline*[11] (17h)**



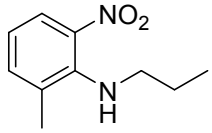
General procedure E was followed using 2-fluoro-4-methyl-1-nitrobenzene (1.1 g, 7.1 mmol). After reaction completion the solution was concentrated, to remove excess solvent. The mixture was then diluted with EtOAc, washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound. (937 mg, 68 %).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.10 (br.s, 1H, NH), 8.05 (d, *J* = 8.8 Hz, 1H), 6.61 (s, 1H), 6.44 (dd, *J* = 8.8, 1.5 Hz, 1H), 3.26 (td, *J* = 7.1, 5.2 Hz, 2H), 1.83 – 1.69 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 195.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 195.1128 *m/z*, $C_{10}H_{14}N_2O_2^+$ $[M+H]^+$ found 195.1119 *m/z*.

***2-bromo-6-nitro-N-propylaniline* (17i)**



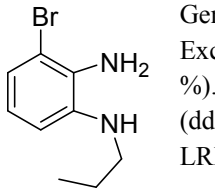
General procedure E was followed using 1-bromo-2-fluoro-3-nitrobenzene (1.0 g, 4.6 mmol). The mixture was filtered with water on reaction completion and extracted with EtOAc. The organic layer was dried and concentrated to afford the title compound. (958 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.80 – 6.60 (m, 1H), 6.08 (br.s, 1H, NH), 3.24 (td, *J* = 7.0, 5.5 Hz, 2H), 1.79 – 1.56 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 259.9 *m/z* (^{79}Br), 260.9 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 259.0077 *m/z*, $C_9H_{11}BrN_2O_2^+$ $[M+H]^+$ found 259.008 *m/z* (^{79}Br), 261.0057 *m/z*, found 261.006 *m/z* (^{81}Br)

***2-methyl-6-nitro-N-propylaniline*[11] (17j)**



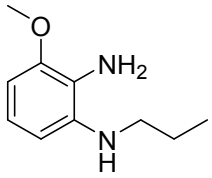
General procedure E was followed using 2-fluoro-1-methyl-3-nitrobenzene (1.1 g, 7.1 mmol). After reaction completion the solution was concentrated. The mixture was then diluted with EtOAc, washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound. (796 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97 – 7.87 (m, 1H), 7.31 – 7.27 (m, 1H), 6.82 – 6.70 (m, 1H), 3.22 (t, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.66 – 1.52 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); LRMS [M+H] $^+$ 195.0 *m/z*.

***3-bromo-N^1-propylbenzene-1,2-diamine*[10] (18a)**



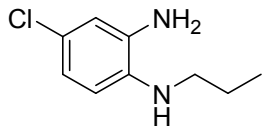
General procedure F was followed using 3-bromo-2-nitro-*N*-propylaniline (1.5 g, 5.8 mmol). Excess solvent was removed *in vacuo* to afford the title compound as a brown solid. (1.2 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.91 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.66 (t, *J* = 8.0 Hz, 1H), 6.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 3.06 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.63 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 230.9 *m/z* (^{79}Br), 231.9 *m/z* (^{81}Br);

***3-methoxy-N^1-propylbenzene-1,2-diamine* (18b)**



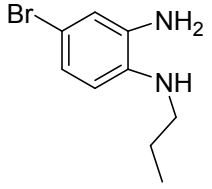
General procedure F was followed using 3-methoxy-2-nitro-*N*-propylaniline (1.3 g, 6.1 mmol). Excess solvent was removed *in* vacuo. The title compound was obtained as a dark purple solid. The crude mixture was taken to the next step without further purification. (901 mg, 82 %). LRMS $[M+H]^+$ 181.0 *m/z*.

***4-chloro-N^1-propylbenzene-1,2-diamine* (18c)**



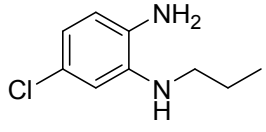
General procedure F was followed using 4-chloro-2-nitro-*N*-propylaniline (1.0 g, 4.7 mmol). The crude mixture was taken to the next step without further purification. The desired product was obtained as a dark purple solid. (850 mg, 98%). LRMS [M+H] $^+$ 185.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 184.0762 *m/z*, $C_9H_{13}ClN_2^+$ $[M+H]^+$ found 184.0753 *m/z*.

***4-bromo-N^1-propylbenzene-1,2-diamine* (18d)**



General procedure F was followed using 4-bromo-2-nitro-*N*-propylaniline (800 mg, 3.1 mmol). Excess solvent was removed *in vacuo* to afford the title product as a brown solid. (570 mg, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 3.04 (t, *J* = 7.1 Hz, 2H), 1.75 – 1.60 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); HRMS-ESI (*m/z*): $[M+H]^+$ 228.0257 *m/z*, $C_9H_{13}BrN_2^+$ $[M+H]^+$ found 228.0231 *m/z* (^{79}Br), 229.0335 *m/z*, found 229.0326 *m/z* (^{81}Br).

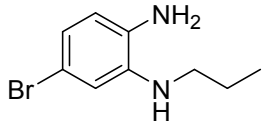
***5-chloro-N^1-propylbenzene-1,2-diamine*[13] (18e)**



General procedure F was followed using 5-chloro-2-nitro-*N*-propylaniline (710 mg, 3.3 mmol). The desired product was obtained as a dark purple solid. (496 mg, 81 %).

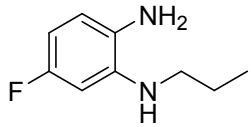
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.63 – 6.58 (m, 3H), 3.05 (t, *J* = 7.1 Hz, 2H), 1.74 – 1.64 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 185.0 *m/z*.

5-bromo-N^1-propylbenzene-1,2-diamine **(18f)**



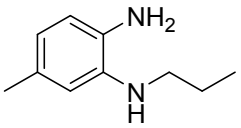
General procedure F was followed using 5-bromo-2-nitro-*N*-propylaniline (500 mg, 1.9 mmol). Excess solvent was removed *in* vacuo. Purification by silica gel chromatography was required. (eluent: 5% MeOH/ 95% DCM) to afford the title product was obtained as a dark purple solid. (395 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.68 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 3.04 (t, *J* = 7.0 Hz, 2H), 1.78 – 1.62 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 228.9 *m/z* (^{79}Br), 229.9 *m/z* (^{81}Br).

***5-fluoro-N^1-propylbenzene-1,2-diamine*$^{(15)}$** **(18g)**



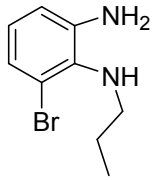
General procedure F was followed using 5-fluoro-2-nitro-N-propylaniline (1.2 g, 6.1 mmol). Excess solvent was removed *in vacuo* to afford the title product as a purple solid. (978 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.62 (dd, *J* = 8.3, 5.6 Hz, 1H), 6.35 (dd, *J* = 11.0, 2.7 Hz, 1H), 6.29 (ddd, *J* = 7.3, 6.5, 2.3 Hz, 1H), 3.04 (t, *J* = 7.1 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 169.0 *m/z*.

***5-methyl-N^1-propylbenzene-1,2-diamine*$^{(15)}$** **(18h)**



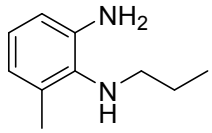
General procedure F was followed using 5-methyl-2-nitro-*N*-propylaniline (800 mg, 4.1 mmol) to obtain the title compound as a dark green solid. (668 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.63 – 6.60 (m, 1H), 6.51 – 6.43 (m, 2H), 3.11 – 3.03 (m, 2H), 2.27 (s, 3H), 1.74 – 1.64 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 165.1 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 164.1308 *m/z*, $C_{10}H_{16}N_2$ found 164.1299 *m/z*.

6-bromo-N^1-propylbenzene-1,2-diamine **(18i)**



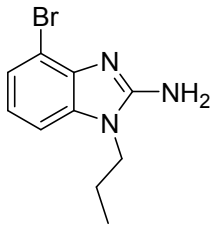
General procedure F was followed using 2-bromo-6-nitro-*N*-propylaniline (600 mg, 2.3 mmol). The crude mixture was taken to the next step without further purification. The title compound was obtained as a brown solid. (427 mg, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.73 (t, *J* = 7.9 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.4 Hz, 1H), 2.92 – 2.84 (m, 2H), 1.67 – 1.55 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 230.9 *m/z* (^{79}Br), 231.9 *m/z* (^{81}Br).

***6-methyl-N^1-propylbenzene-1,2-diamine*$^{(15)}$** **(18j)**



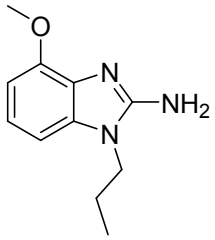
General procedure F was followed using 2-methyl-6-nitro-N-propylaniline (569 mg, 2.9 mmol) to afford the title product as a brown solid without further purification. (235 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.78 (m, 1H), 6.62 – 6.55 (m, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.67 – 1.55 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 165.1 *m/z*.

4-bromo-1-propyl-1H-benzo[d]imidazol-2-amine **(19a)**



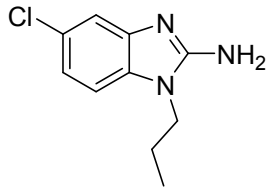
General procedure G was followed using 3-bromo-*N*^{1}-propylbenzene-1,2-diamine (1.0 g, 230 mg). Product was further purified via silica gel chromatography (eluent:10 % MeOH/ 89 % Chloroform/ 1 % Ammonia solution) and the appropriate fractions were concentrated to afford the title compound as orange crystals. (136 mg, 12 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.07 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 3.98 (t, *J* = 7.2 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 255.9 *m/z* (^{79}Br), 256.9 *m/z* (^{81}Br).

4-methoxy-1-propyl-1H-benzo[d]imidazol-2-amine **(19b)**



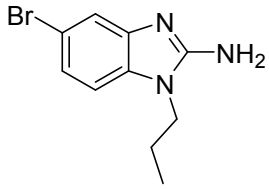
General procedure G was followed using 3-methoxy-*N*[1]-propylbenzene-1,2-diamine (713 mg, 3.9 mmol) to afford the title product as a dark purple solid. The crude mixture was taken to the next step without further purification (723 mg, 87 %). LRMS $[M+H]^+$ 206.0 *m/z*.

5-chloro-1-propyl-1H-benzo[d]imidazol-2-amine **(19c)**



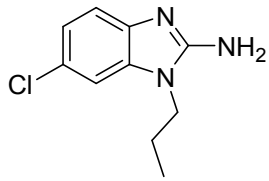
General procedure G was followed using 4-chloro-*N*[1]-propylbenzene-1,2-diamine (830 mg, 4.5 mmol). After reaction completion, MeOH was boiled off and basified with ammonia. The solution was filtered, and the crude brown solid was recrystalized with EtOH to give the title compound. (396 mg, 42 %).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 (d, *J* = 1.6 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 3.97 (t, *J* = 7.2 Hz, 2H), 1.82 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 209.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 210.0793 *m/z*, $C_{10}H_{12}ClN_3^+$ $[M+H]^+$ found 210.0798 *m/z*.

5-bromo-1-propyl-1H-benzo[d]imidazol-2-amine **(19d)**



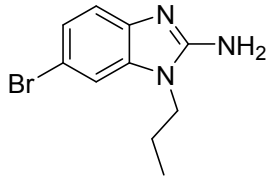
General procedure G was followed using 4-bromo-*N*[1]-propylbenzene-1,2-diamine (537 mg, 2.3 mmol) to afford the title product without further purification. (399 mg, 67 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.5 Hz, 1H), 7.40 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 4.23 (t, *J* = 7.3 Hz, 2H), 2.04 – 1.79 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 255.9 *m/z* (^{79}Br), 256.9 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 254.0287 *m/z*, $C_{10}H_{12}BrN_3^+$ $[M+H]^+$ found 254.0289 *m/ z* (^{79}Br), 255.0316 *m/z*, found 255.0314*m/ z* (^{81}Br),

6-chloro-1-propyl-1H-benzo[d]imidazol-2-amine **(19e)**



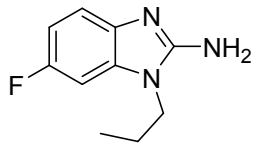
General procedure G was followed using 5-chloro-*N*[1]-propylbenzene-1,2-diamine (320 mg, 1.7 mmol). The crude product was purified by silica gel chromatography (eluent: 5% MeOH/ 95% DCM). (360 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 1H), 7.25 – 7.17 (m, 2H), 4.12 (t, *J* = 7.4 Hz, 2H), 1.95 – 1.75 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 210.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 210.0793 *m/z*, $C_{10}H_{12}ClN_3^+$ $[M+H]^+$ found 210.0798 *m/z*.

6-bromo-1-propyl-1H-benzo[d]imidazol-2-amine **(19f)**



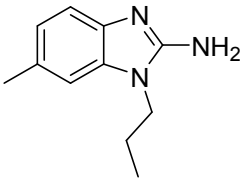
General procedure G was followed using 5-bromo-*N*[1]-propylbenzene-1,2-diamine (288 mg, 1.3 mmol). Crude product required purification via silica gel chromatography (eluent: 1% NH_4OH/9% MeOH/ $CHCl_3$) to afford the title product as a cream coloured powder. (319 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.27 (m, 1H), 7.24 – 7.20 (m, 2H), 4.49 (br.s, 2H, NH_2), 3.85 (t, *J* = 7.2 Hz, 2H), 1.94 – 1.72 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 255.9 *m/z* (^{79}Br), 256.9 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 254.0287 *m/z*, $C_{10}H_{12}BrN_3^+$ $[M+H]^+$ found 254.0294 *m/z*.

6-fluoro-1-propyl-1H-benzo[d]imidazol-2-amine **(19g)**



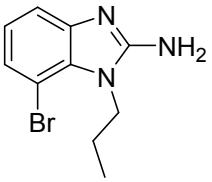
General procedure G was followed using 5-fluoro-*N*[1]-propylbenzene-1,2-diamine (600 mg, 3.6 mmol). Product was further purified via silica gel chromatography (eluent: 30 % EtOAc/ 70 % Petroleum spirits) and the appropriate fractions were concentrated to afford the title compound as brown crystals. (245 mg, 36 %).^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.31 (m, 1H), 7.03 – 6.90 (m, 2H), 4.22 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 194.0 *m/z*.

6-methyl-1-propyl-1H-benzo[d]imidazol-2-amine **(19h)**



General procedure G was followed using 5-methyl-N^1-propylbenzene-1,2-diamine (623 mg, 3.8 mmol) to afford the title product as a dark green solid. The crude mixture was taken to the next step without further purification (710 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.23 (m, 1H), 7.05 (d, J = 8.2 Hz, 1H), 7.00 (s, 1H), 4.20 (t, J = 7.4 Hz, 2H), 2.44 (s, 3H), 2.01 – 1.78 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 190.1 *m/z.*

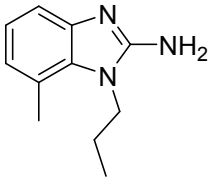
7-bromo-1-propyl-1H-benzo[d]imidazol-2-amine **(19i)**



General procedure G was followed using 6-bromo-N^1-propylbenzene-1,2-diamine (280 mg, 0.74 mmol) to afford the title product without further purification. (301 mg, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (s, 2H, NH_2), 7.47 – 7.36 (m, 2H), 7.14 (t, J = 8.1 Hz, 1H), 4.64 – 4.49 (m, 2H), 2.01 – 1.86 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 253.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 254.0287 *m/z* $C_{10}H_{12}BrN_3^+$, found 254.0292 *m/z*.

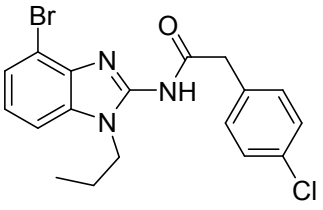
7-methyl-1-propyl-1H-benzo[d]imidazol-2-amine **(19j)**

General procedure G was followed using 6-methyl-N^1-propylbenzene-1,2-diamine (180 mg, 1.1 mmol) to afford the title compound as an orange solid. . The crude mixture was taken to the next step without further purification



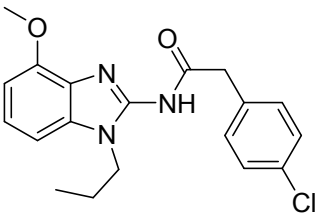
(200 mg, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.23 (d, J = 7.9 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 5.67 (br.s, 2H), 4.25 – 4.16 (m, 2H), 2.59 (s, 3H), 1.91 – 1.74 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 190.1 *m/z.*

N-(4-bromo-1-propyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide **(20a)**



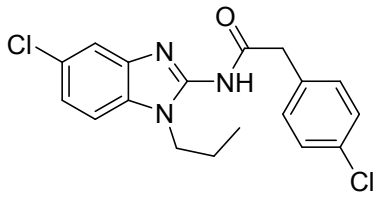
General procedure C was followed using 4-bromo-1-propyl-1H-benzo[d]imidazol-2-amine (96 mg, 0.38 mmol) and 4-chlorophenylacetic acid (50 mg, 0.29 mmol). After aqueous filtration, the mixture was extracted with EtOAc and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Further purification via silica gel chromatography was required (eluent: 0-50% MeOH/ Petroleum Spirits) and the appropriate fractions were collected and concentrated to afford the title compound as a yellow solid. (5 mg, 3 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 (dd, J = 7.8, 1.0 Hz, 1H), 7.29 – 7.27 (m, 2H), 7.22 – 7.18 (m, 3H), 7.10 (t, J = 7.9 Hz, 1H), 4.05 – 3.99 (m, 2H), 3.73 (s, 2H), 1.88 – 1.63 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); HPLC tR= 6.84 min >94 % purity at 254nm; LRMS $[M+H]^+$ 405.8 *m/z* (^{79}Br), 406.8 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 406.0316 *m/z*, $C_{18}H_{17}BrClN_3O$ found 406.0316 *m/z*.

2-(4-chlorophenyl)-N-(4-methoxy-1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(20b)**



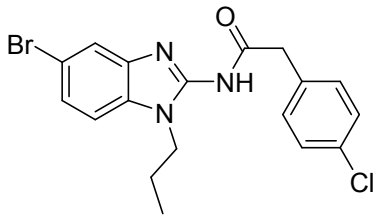
General procedure C was followed using 4-methoxy-1-propyl-1H-benzo[d]imidazol-2-amine (300 mg, 1.5 mmol) and 4-chlorophenylacetic acid (190 mg, 1.1 mmol). After aqueous filtration, the mixture was extracted with EtOAc and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Further purification via silica gel chromatography was required (eluent: 50% MeOH/ Petroleum Spirits) to afford the title compound as a yellow solid. (31 mg, 6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.17 – 7.12 (m, 1H), 6.85 – 6.81 (m, 1H), 6.72 – 6.68 (m, 1H); 4.06 – 4.00 (m, 2H), 3.90 (s, 3H), 3.74 (s, 2H), 1.84 – 1.75 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 357.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 358.1317 *m/z*, $C_{19}H_{20}ClN_3O_2$ found 358.1316 *m/z*.

N-(5-chloro-1-propyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide **(20c)**



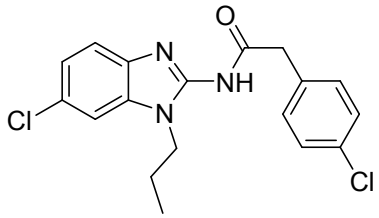
General procedure C was followed using 5-chloro-1-propyl-1*H*-benzo[*d*]imidazol-2-amine (319 mg, 1.5 mmol) and 4-chlorophenylacetic acid (199 mg, 1.2 mmol). The title product was obtained as a brown solid. (293 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.27 (m, 4H), 7.25 – 7.18 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 4.07 – 3.94 (m, 2H), 3.74 (s, 2H), 1.85 – 1.71 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 361.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 362.0821 *m/z*, $C_{18}H_{17}Cl_2N_3O^+$ $[M+H]^+$ found 362.0832 *m/z*.

***N-(5-bromo-1-propyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide* (20d)**



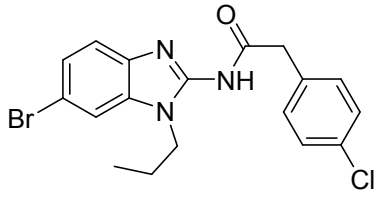
General procedure C was followed using 5-bromo-1-propyl-1*H*-benzo[*d*]imidazol-2-amine (369 mg, 1.5 mmol) and 4-chlorophenylacetic acid (191 mg, 1.1 mmol) to afford the title compound as a red-brown solid. (145 mg, 32 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 (d, *J* = 1.6 Hz, 1H), 7.37 – 7.27 (m, 6H), 7.08 (d, *J* = 8.5 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.73 (s, 2H), 1.87 – 1.66 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 405.8 *m/z* (^{79}Br), 406.8 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 406.0316 *m/z,* $C_{18}H_{17}BrClN_3O^+$ found 406.0327 *m/z*.

***N-(6-chloro-1-propyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide* (20e)**



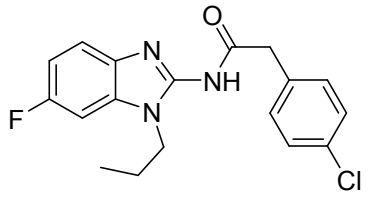
General procedure C was followed using 6-chloro-1-propyl-1*H*-benzo[*d*]imidazol-2-amine (309 mg, 1.5 mmol) and 4-chlorophenylacetic acid (192 mg, 1.1 mmol). The title compound was obtained as a dark grey solid. (403 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.27 (m, 4H), 7.21 – 7.13 (m, 3H); 4.03 – 3.94 (m, 2H), 3.73 (s, 2H), 1.89 – 1.71 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 361.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 362.0821 *m/z*, $C_{18}H_{17}Cl_2N_3O^+$ $[M+H]^+$ found 362.0828 *m/z*.

***N-(6-bromo-1-propyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide* (20f)**



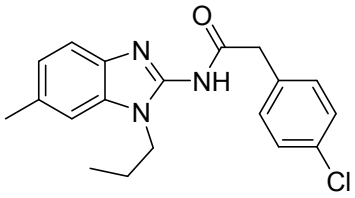
General procedure C was followed using 6-bromo-1-propyl-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 0.78 mmol) and 4-chlorophenylacetic acid (103 mg, 0.60 mmol). The crude product required purification by silica gel chromatography (eluent 5% MeOH/ 95% DCM) to afford the title product as a purple solid. (160 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 6H), 7.10 (d, *J* = 8.4 Hz, 1H), 4.04 – 3.95 (m, 2H), 3.73 (s, 2H), 1.88 – 1.71 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); LRMS $[M+H]^+$ 405.8 *m/z* (^{79}Br), 406.8 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 406.0316 *m/z*, $C_{18}H_{17}BrClN_3O^+$ $[M+H]^+$ found 406.0329 *m/z*.

***2-(4-chlorophenyl)-N-(6-fluoro-1-propyl-1H-benzo[d]imidazol-2-yl)acetamide* (20g)**



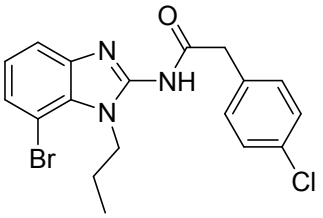
General procedure C was followed using 6-fluoro-1-propyl-1*H*-benzo[*d*]imidazol-2-amine (176 mg, 0.91 mmol) and 4-chlorophenylacetic acid (119 mg, 0.70 mmol). After aqueous filtration, the mixture was extracted with EtOAc and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Further purification via silica gel chromatography was required (eluent: 0-50% MeOH/ Petroleum Spirits) and the appropriate fractions were collected and concentrated to afford the title compound as a light pink solid. (10 mg, 4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 6.98 – 6.87 (m, 2H); 4.02 – 3.97 (m, 2H), 3.71 (s, 2H), 1.82 – 1.71 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); HPLC tR= 5.03 min >94 % purity at 254nm; LRMS $[M+H]^+$ 345.0 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 346.1115 *m/z*, $C_{18}H_{17}ClFN_3O$ found 346.1117 *m/z*.

***2-(4-chlorophenyl)-N-(6-methyl-1-propyl-1H-benzo[d]imidazol-2-yl)acetamide* (20h)**



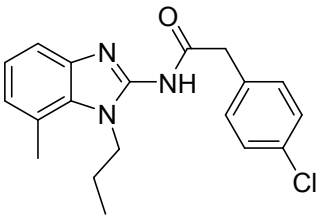
General procedure C was followed using 6-methyl-1-propyl-1*H*-benzo[*d*]imidazol-2-amine (664 mg, 3.5 mmol) and 4-chlorophenylacetic acid to afford the title compound (86 mg, 9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.30 (m, 2H), 7.30 – 7.27 (m, 2H), 7.11 (d, J = 8.4 Hz, 1H), 7.01 (dd, J = 5.0, 2.4 Hz, 2H), 4.07 – 3.95 (m, 2H), 3.73 (s, 2H), 2.45 (s, 3H), 1.90 – 1.70 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 341.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 342.1369 *m/z*, $C_{19}H_{20}ClN_3O$ found 342.1368 *m/z*.

N-(7-bromo-1-propyl-1H-benzo[d]imidazol-2-yl)-2-(4-chlorophenyl)acetamide **(20i)**



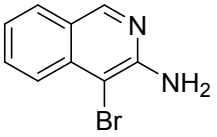
General procedure C was followed using 7-bromo-1-propyl-1*H*-benzo[d]imidazol-2-amine (230 mg, 0.91 mmol) and 4-chlorophenylacetic acid (118 mg, 0.70 mmol). Further purification via silica gel chromatography was required (eluent 1 % NH_4OH /9 % MeOH/ 89 % $CHCl_3$) to afford the title compound. (28.9 mg, 10 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.26 (m, 5H), 7.20 – 7.12 (m, 1H), 7.04 (t, J = 8.0 Hz, 1H), 4.44 – 4.37 (m, 2H) , 3.75 (s, 2H), 1.86 – 1.72 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 405.8 *m/z* (^{79}Br), 406.8 *m/z* (^{81}Br); HRMS-ESI (*m/z*): $[M+H]^+$ 406.0316 *m/z*, $C_{18}H_{17}BrClN_3O$ found 406.0318 *m/z*.

2-(4-chlorophenyl)-N-(7-methyl-1-propyl-1H-benzo[d]imidazol-2-yl)acetamide **(20j)**



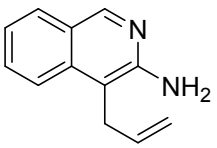
General procedure C was followed using 7-methyl-1-propyl-1H-benzo[d]imidazol-2-amine (164 mg, 0.86 mmol) and 4-chlorophenylacetic acid (113 mg, 0.66 mmol) to afford the title compound. (78 mg, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 – 7.18 (m, 4H), 7.05 – 6.97 (m, 2H), 6.94 – 6.82 (m, 1H), 4.18 – 4.12 (m, 2H), 3.66 (s, 2H), 2.56 (s, 3H), 1.77 – 1.54 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H); LRMS $[M+H]^+$ 341.9 *m/z;* HRMS-ESI (*m/z*): $[M+H]^+$ 342.1368 *m/z*, $C_{19}H_{20}ClN_3O$ found 342.1369 *m/z*.

4-Bromoisoquinolin-3-amine **[16]** **(22)**



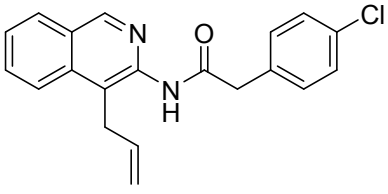
To a mixture of isoquinolin-3-amine (865 mg, 6.0 mmol) and ammonium acetate (46 mg, 0.6 mmol) in acetonitrile (12 mL), *N*-bromosuccinimide (1.2 g, 6.3 mmol) dissolved in acetonitrile (8 mL) was added dropwise. The reaction mixture stirred at room temperature for 5 minutes. Excess solvent was reduced *in vacuo* and the reaction product was recrystalized using water to afford the title compound as yellow crystals.(1.3g, 80%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.90 (dd, J = 8.6, 0.8 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.32 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 4.97 (s, 2H, NH_2); LRMS $[M+H]^+$ 224.9 *m/z*.

4-allylisoquinolin-3-amine **[17]** **(23)**



Allyltributyltin (1.6 mL, 5.2 mmol), $Pd(PPh_3)_4$ (159 mg, 0.14 mmol) in DMF was added to 4-bromoisoquinolin-3-amine (970 mg, 4.3 mmol) under nitrogen. Mixture was heated to 80°C and refluxed over 72 hours. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The organic layer was washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated. Further purification by silica gel wash (30% EtOAc/ 70% Petroleum spirits) was used to afford the title compound[18] (505 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.81 (s, 1H), 8.01 (s, 1H), 7.83 – 7.74 (m, 2H), 7.50 – 7.43 (m, 1H), 7.30 – 7.26 (m, 1H), 6.07 – 5.86 (m, 1H), 5.03 (ddd, J = 17.1, 3.5, 1.8 Hz, 1H), 4.45 (s, 2H, NH_2), 3.63 (dt, J = 5.6, 1.8 Hz, 2H); LRMS $[M+H]^+$ 185.0 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 185.1073 *m/z*, $C_{12}H_{12}N_2$ $^+$ $[M+H]^+$ found 185.1074 *m/z*.

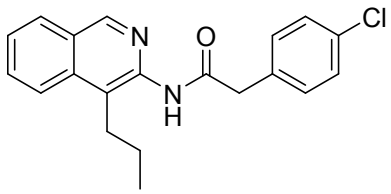
N-(4-allylisoquinolin-3-yl)-2-(4-chlorophenyl)acetamide **(24)**



The title compound was formed following General procedure C using 4-allylisoquinolin-3-amine (441 mg, 2.4 mmol) and 4-chlorophenylacetic acid (314 mg, 1.9 mmol). The title compound was formed as a solid. (110

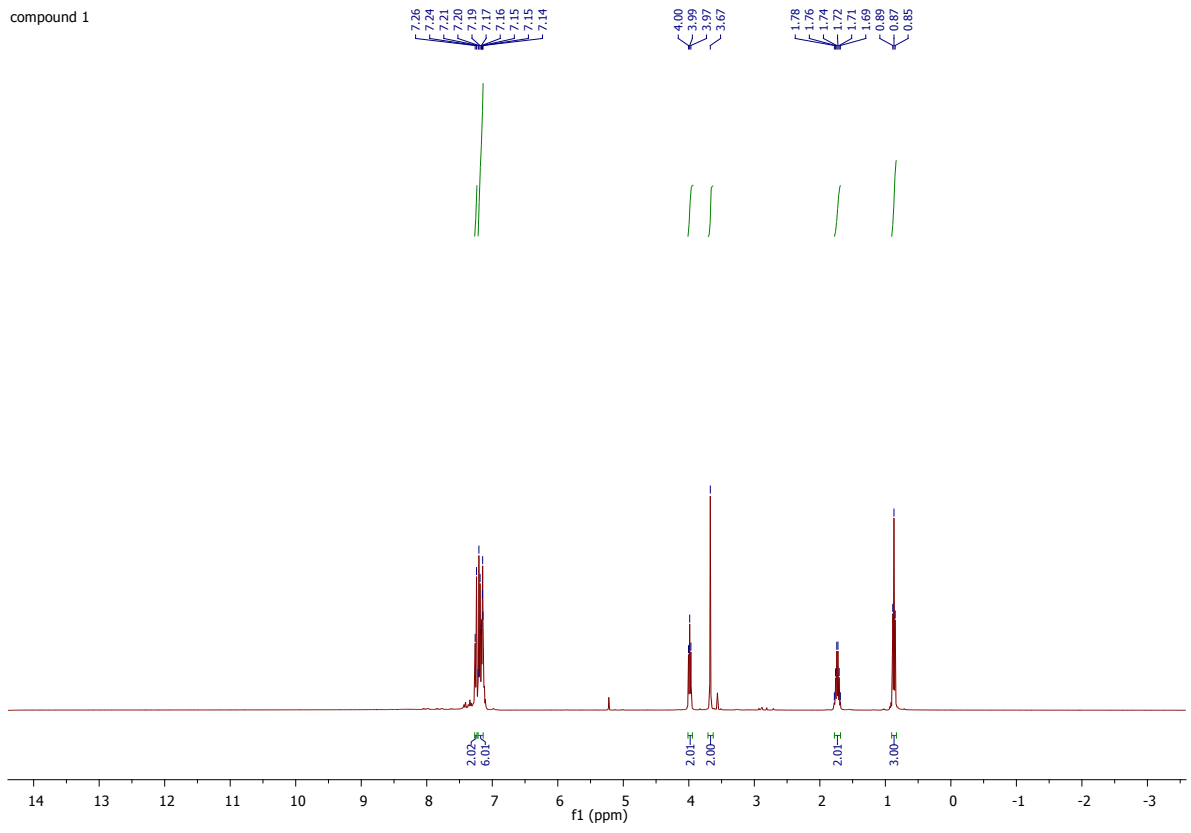
mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.05 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 2H), 7.76 – 7.71 (m, 1H), 7.62 – 7.57 (m, 1H), 7.35 – 7.27 (m,4H), 5.00 (d, *J* = 9.3 Hz, 1H), 4.79 (dd, *J* = 17.2, 1.4 Hz, 1H), 3.84 (s, 2H), 3.66 (dt, *J* = 5.7, 1.7 Hz, 2H); HPLC tR= 6.07 min >95 % LRMS $[M+H]^+$ 336.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 337.1102 *m/z*, $C_{20}H_{17}ClN_2O^+$ $[M+H]^+$ found 337.1107 *m/z*.

***2-(4-chlorophenyl)-N-(4-propylisoquinolin-3-yl)acetamide* (25)**

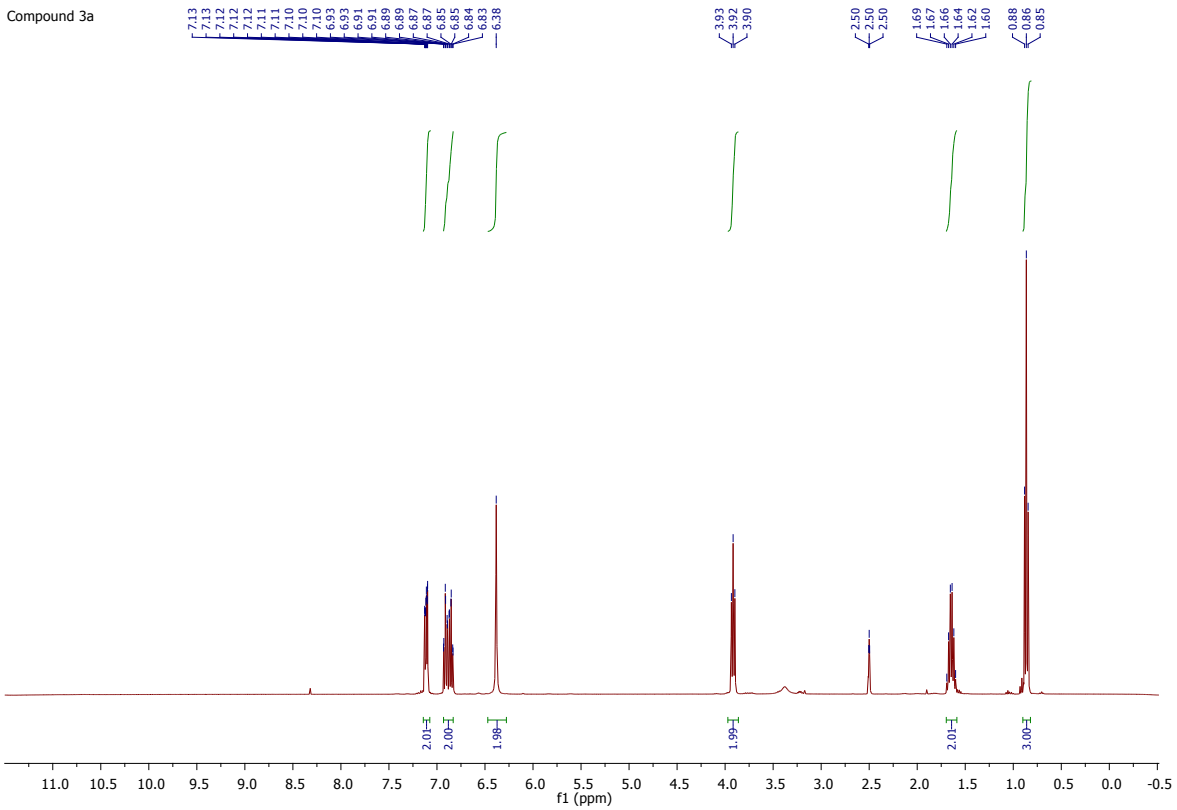


General procedure F was followed using *N*-(4-allylisoquinolin-3-yl)-2-(4-chlorophenyl)acetamide (60 mg, 0.18 mmol) to afford the title compound. (60 mg, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.00 (s, 1H), 7.96 (t, *J* = 9.3 Hz, 2H), 7.74 – 7.66 (m, 1H), 7.49 – 7.43 (m, 2H), 7.40 – 7.30 (m, 3H), 3.83 (s, 2H), 2.92 – 2.76 (m, 2H), 1.59 – 1.46 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); HPLC tR= 5.14 min >93 %; LRMS $[M+H]^+$ 338.9 *m/z*; HRMS-ESI (*m/z*): $[M+H]^+$ 339.1259 *m/z*, $C_{20}H_{19}ClN_2O^+$ $[M+H]^+$ found 339.1252 *m/z*.

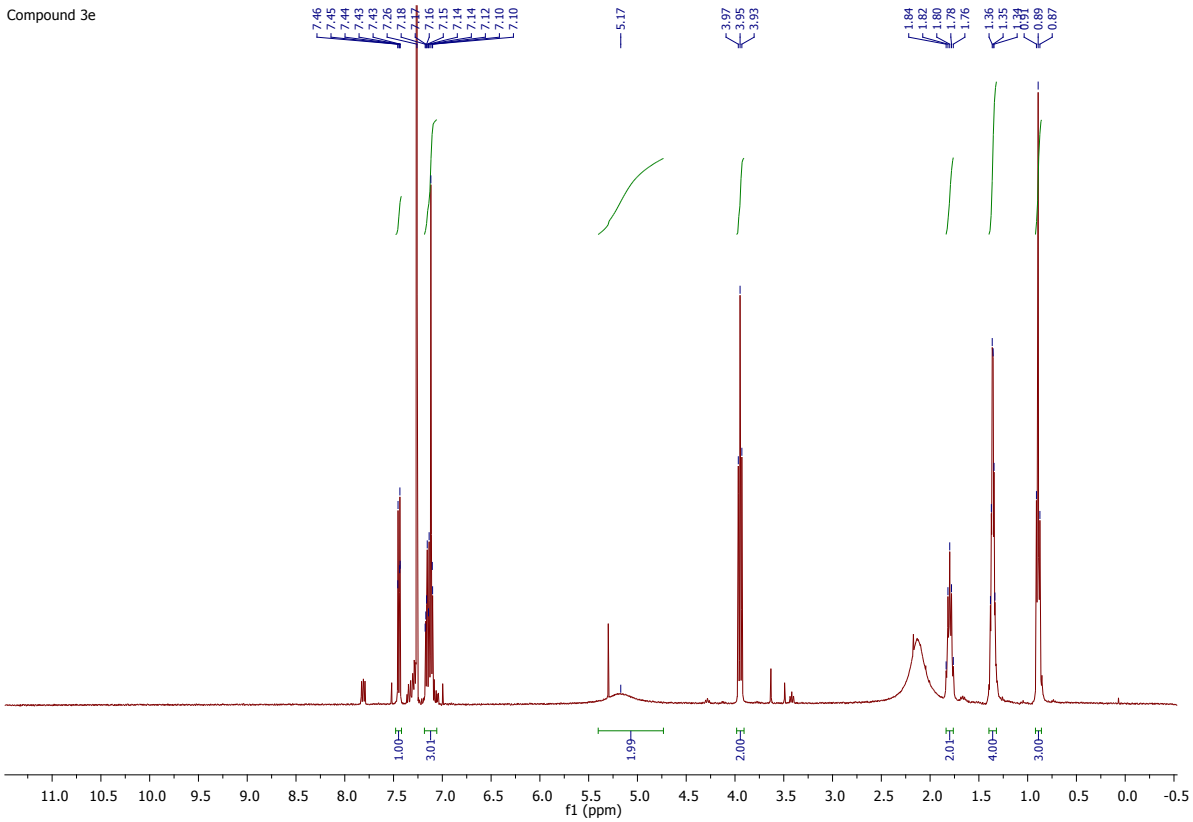
NMR Spectra



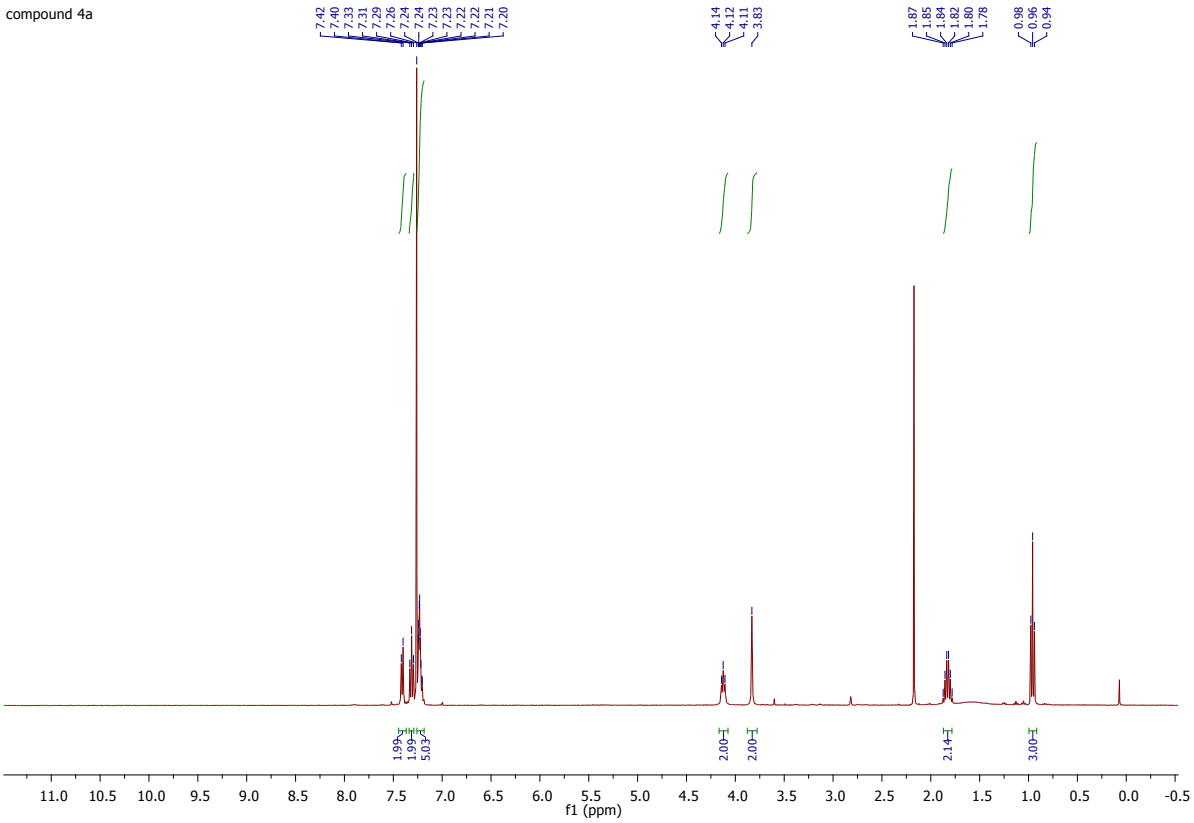
Compound 3a



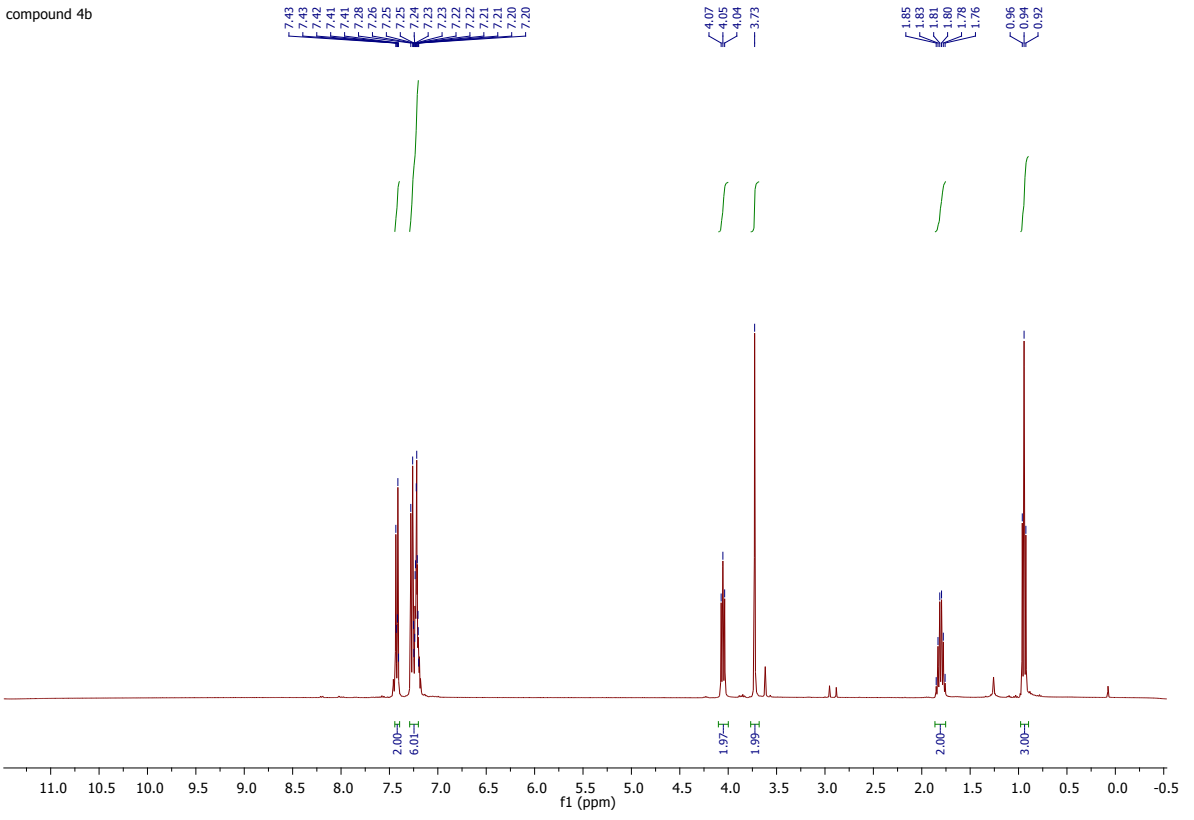
Compound 3e



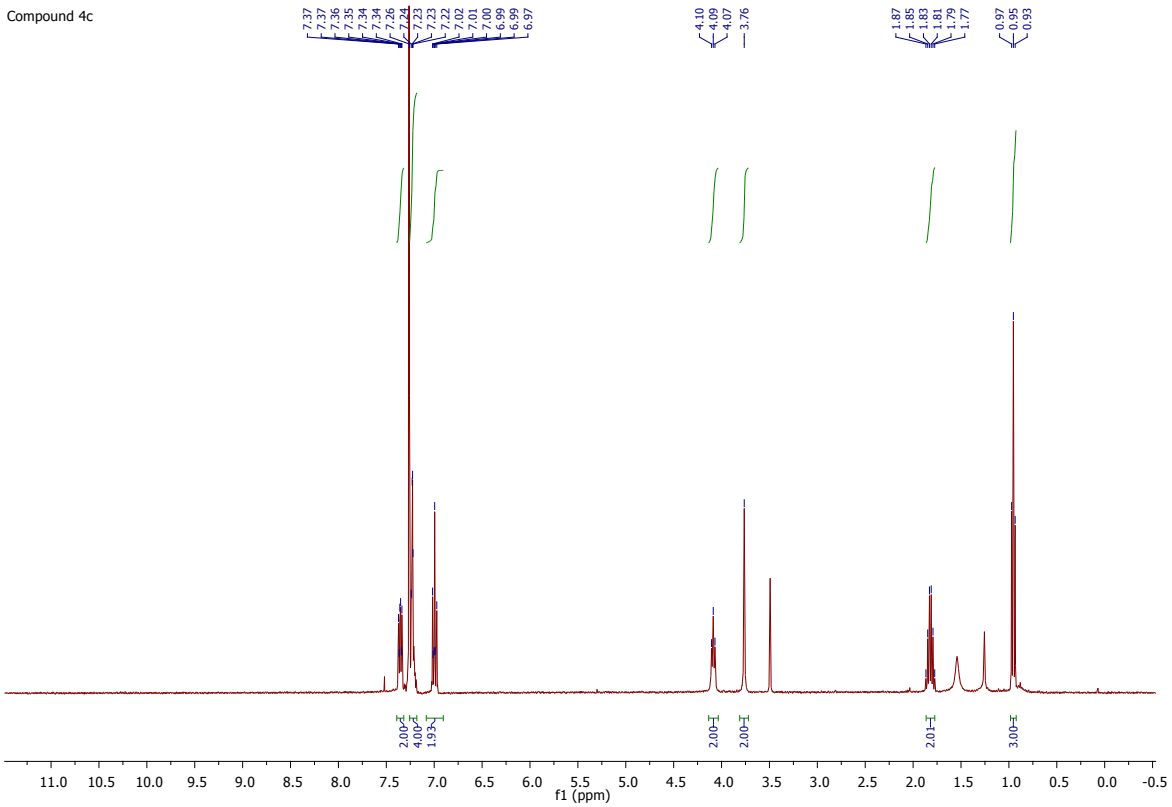
compound 4a



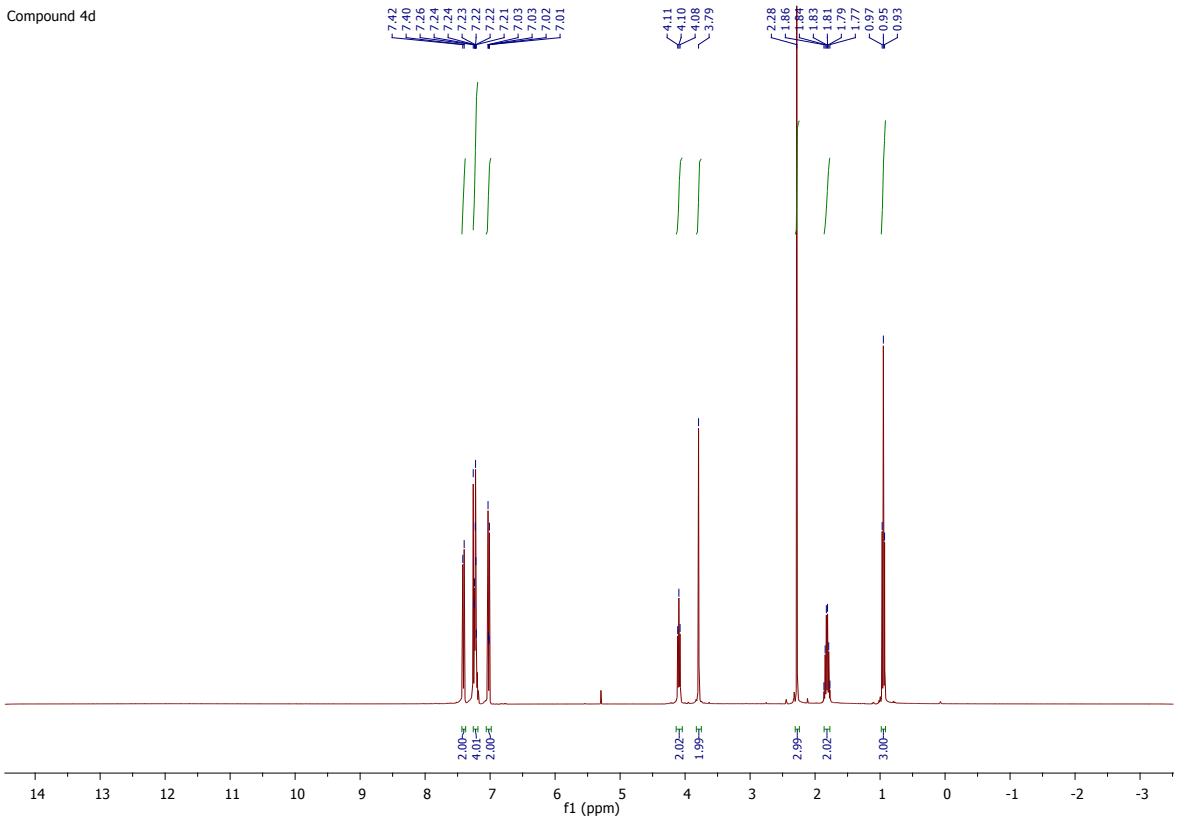
compound 4b



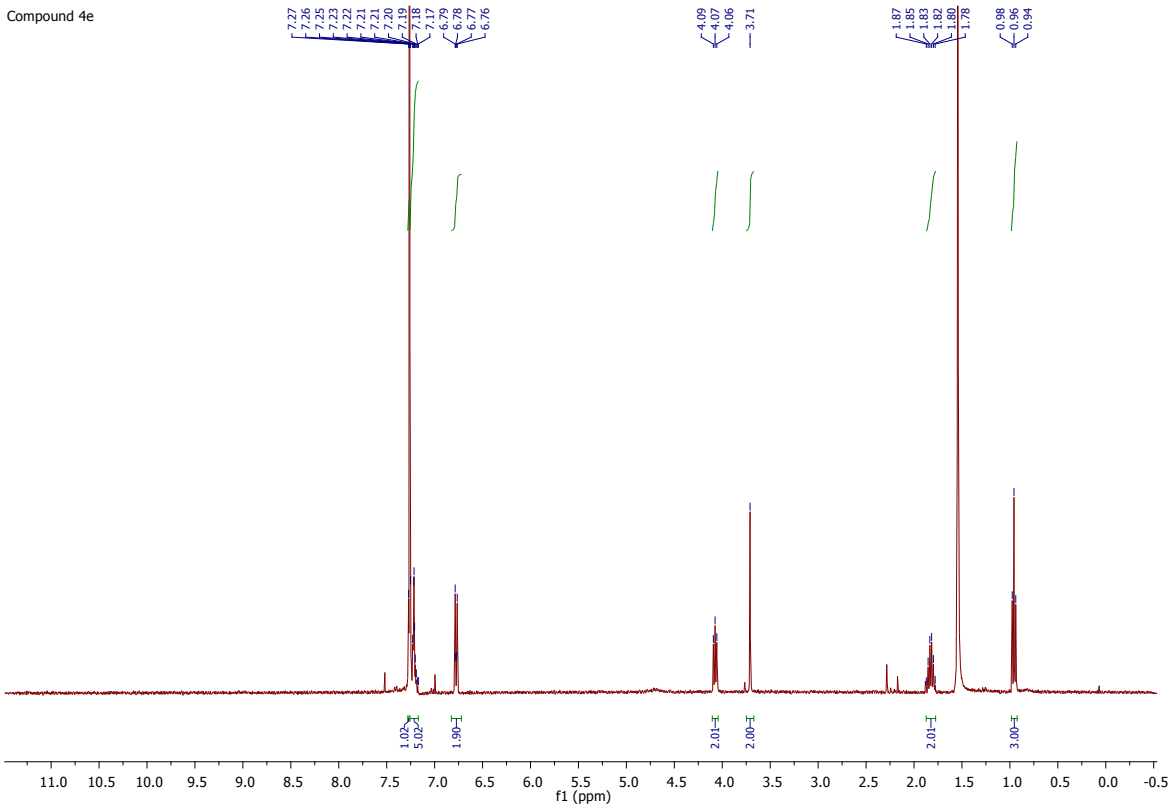
Compound 4c



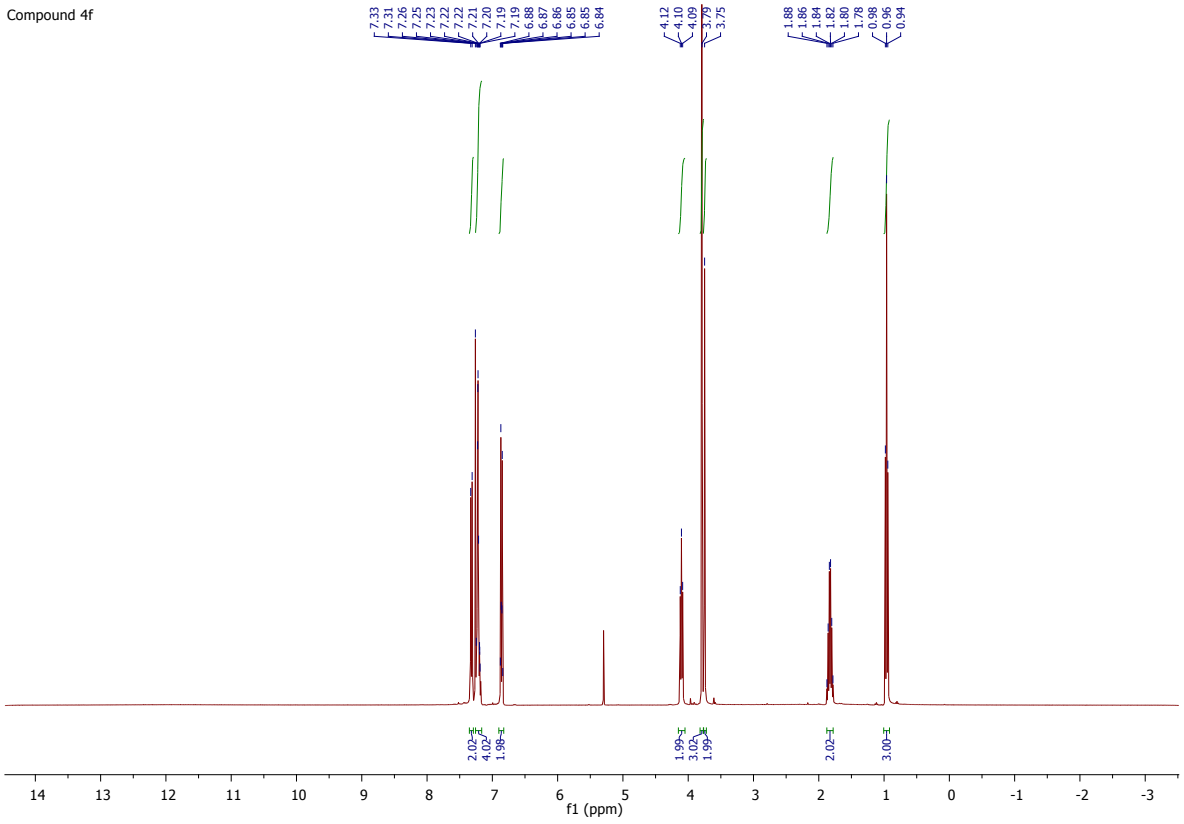
Compound 4d



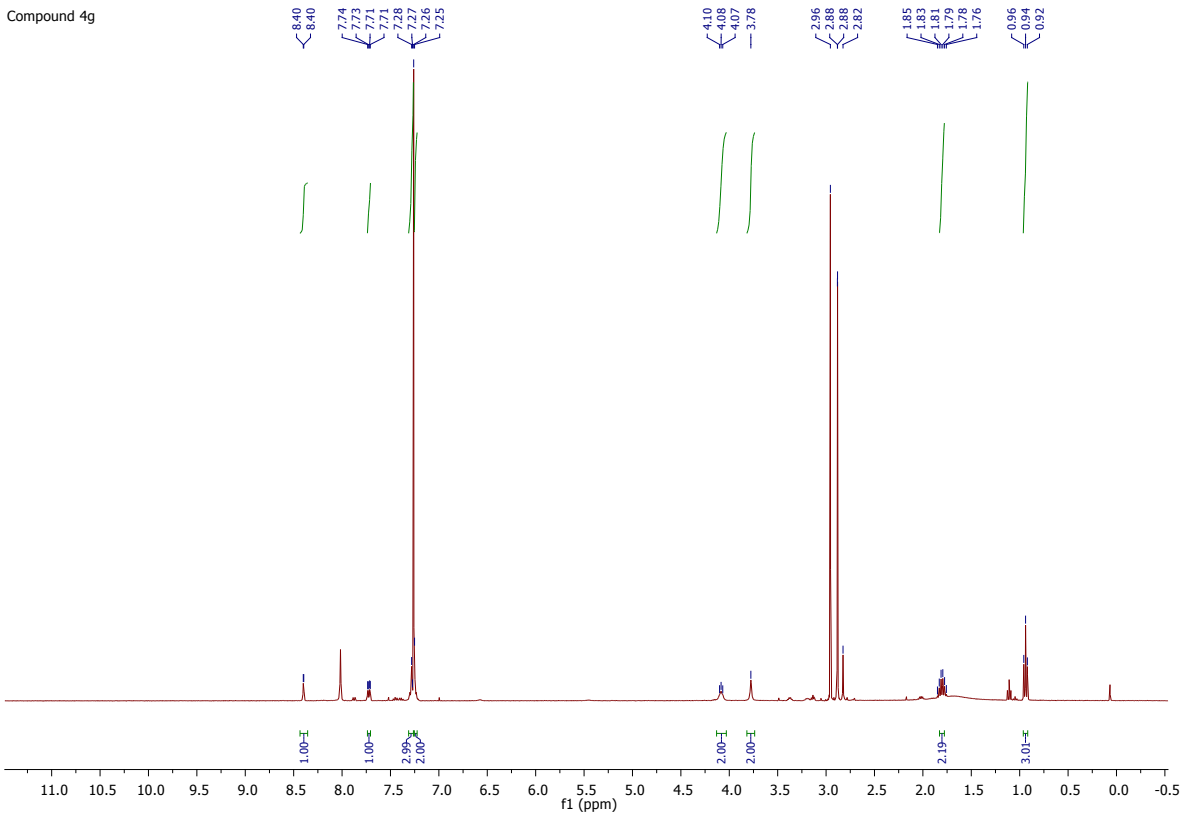
Compound 4e



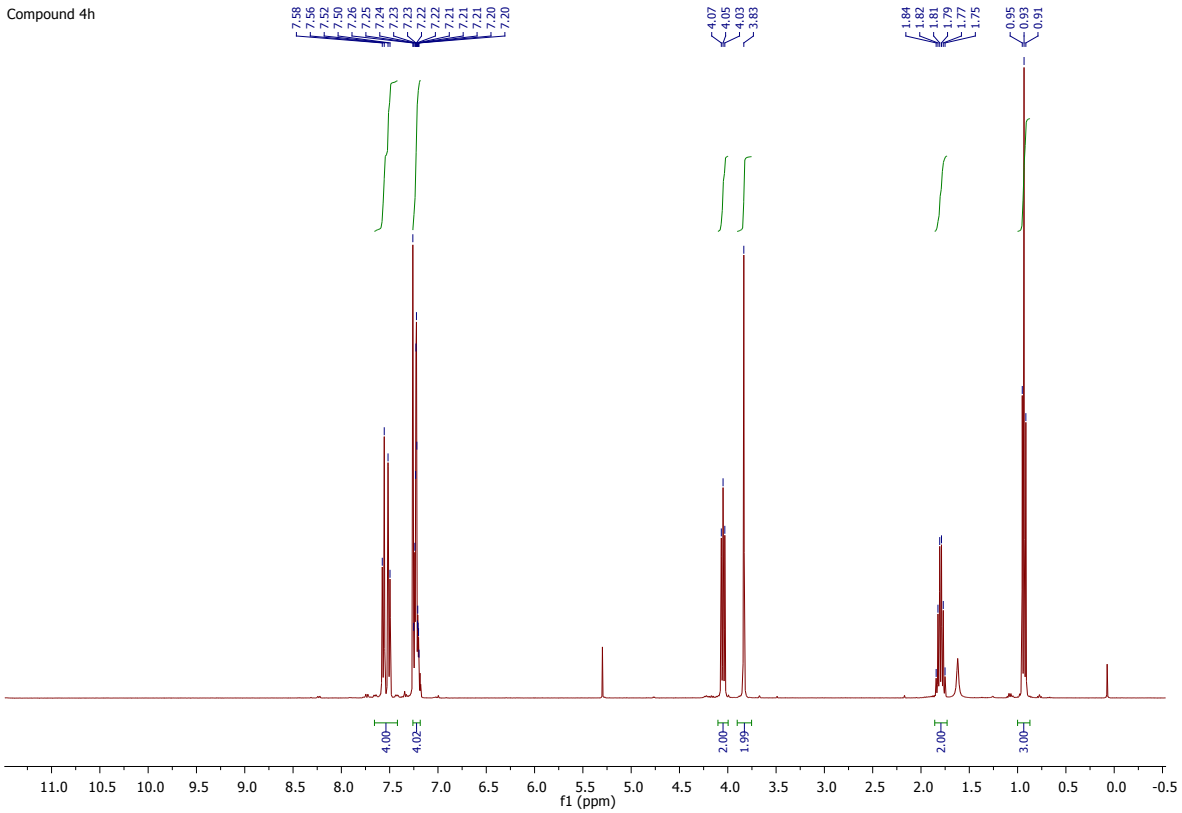
Compound 4f



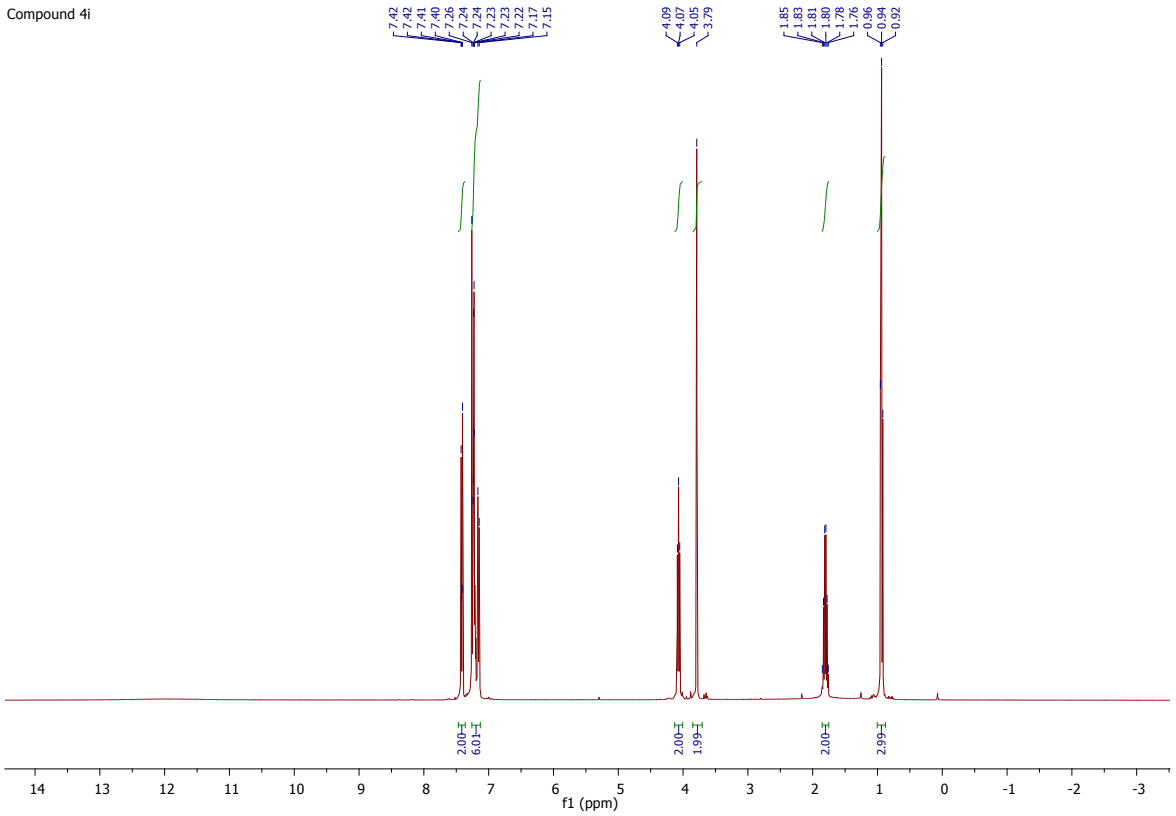
Compound 4g



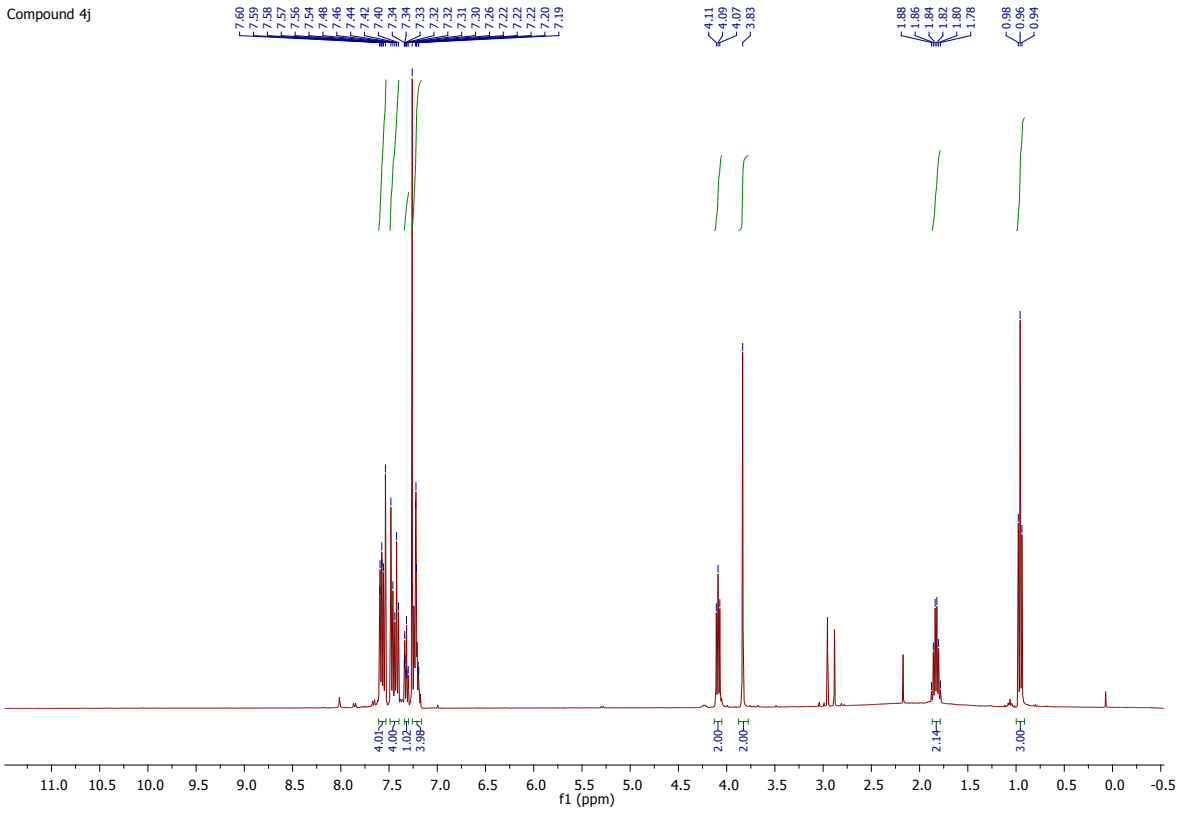
Compound 4h



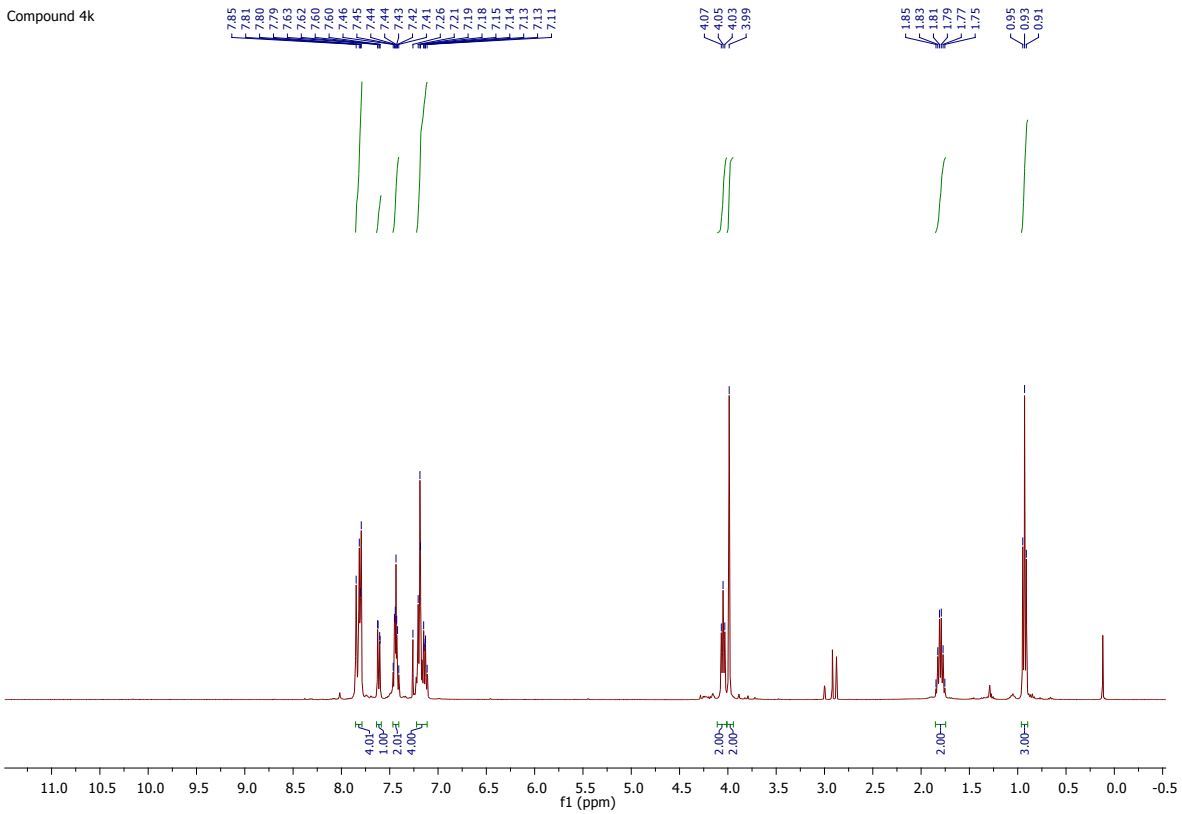
Compound 4i



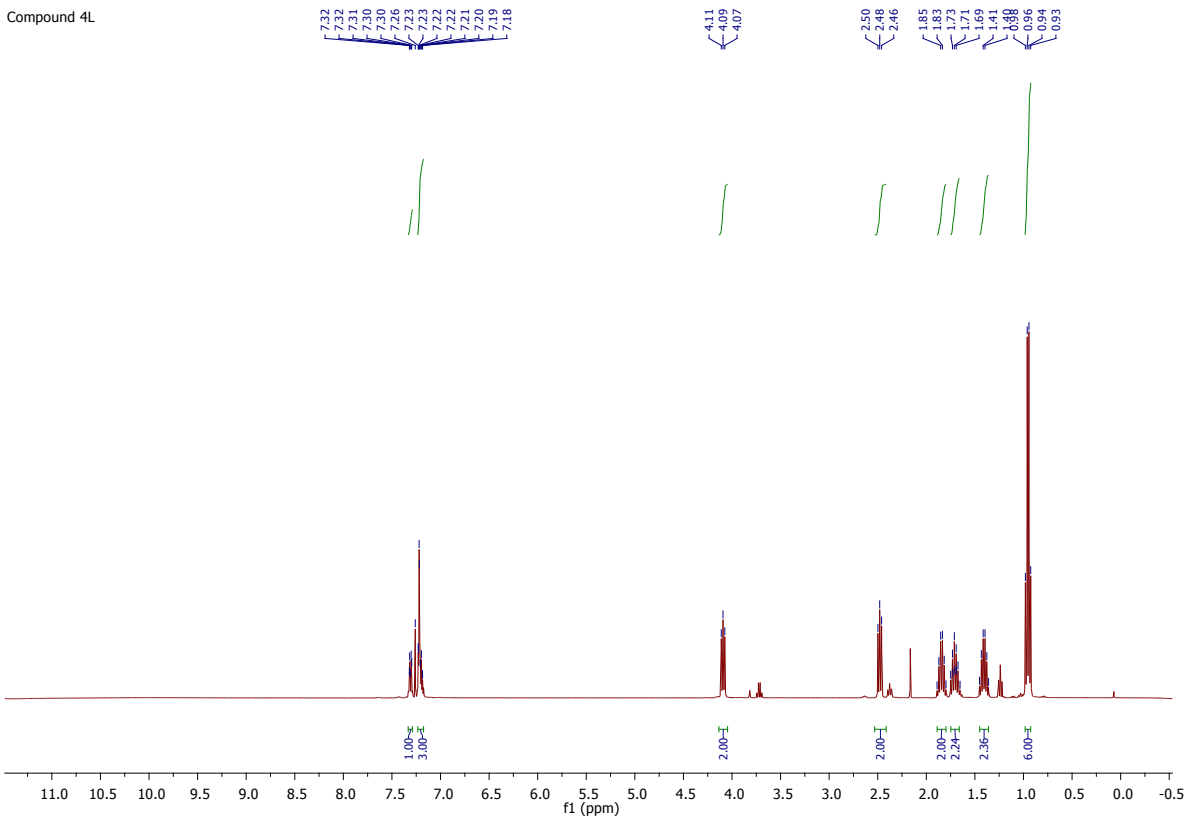
Compound 4j



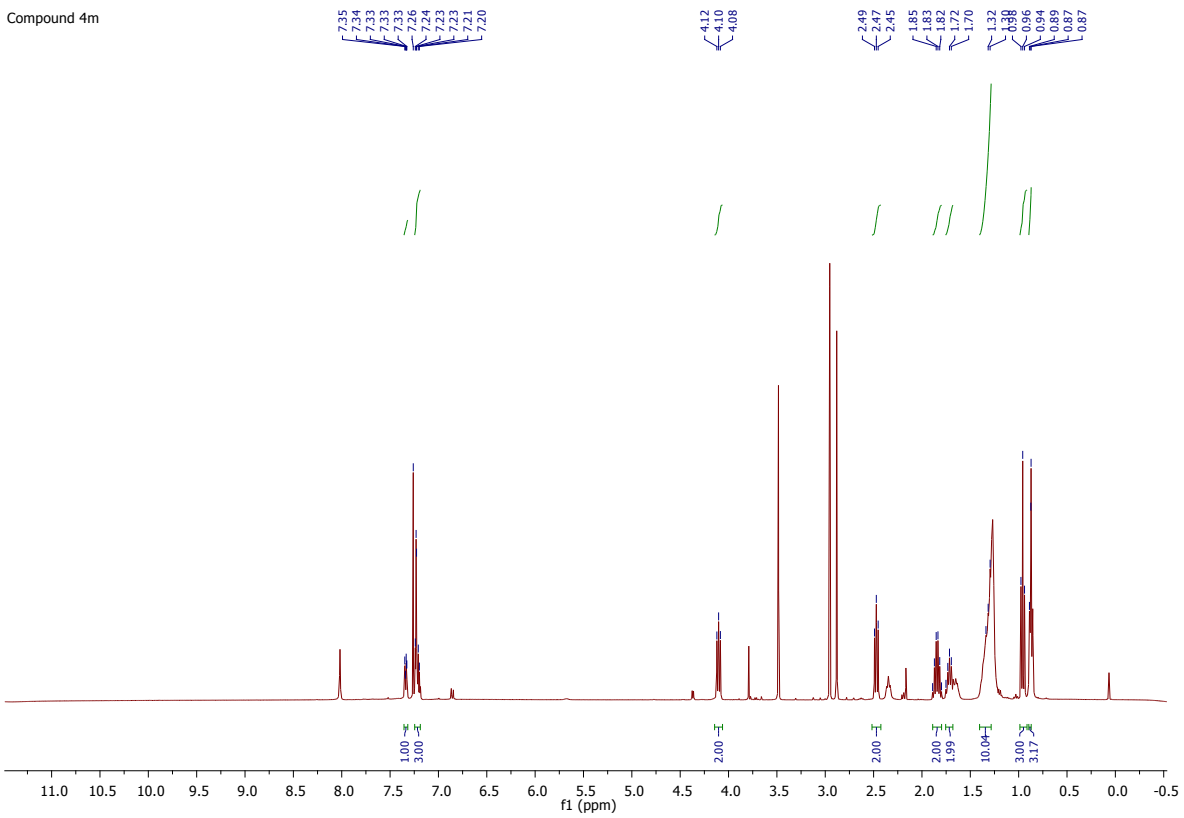
Compound 4k



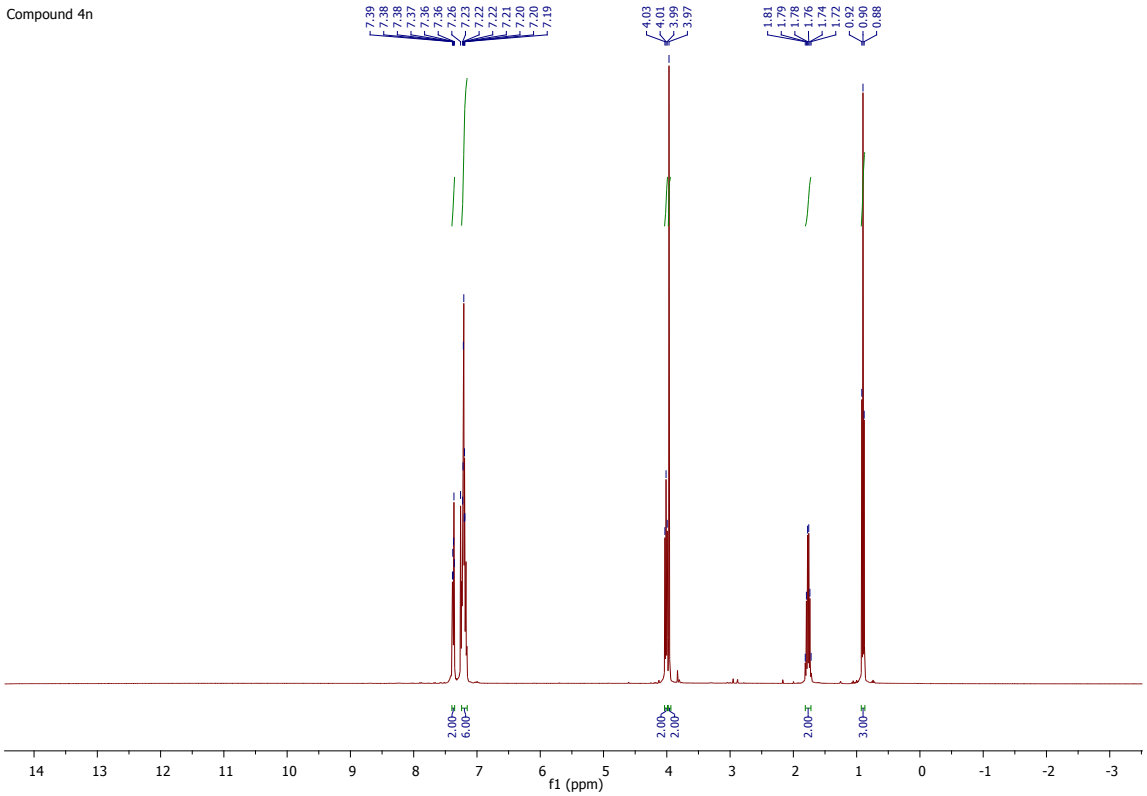
Compound 4L



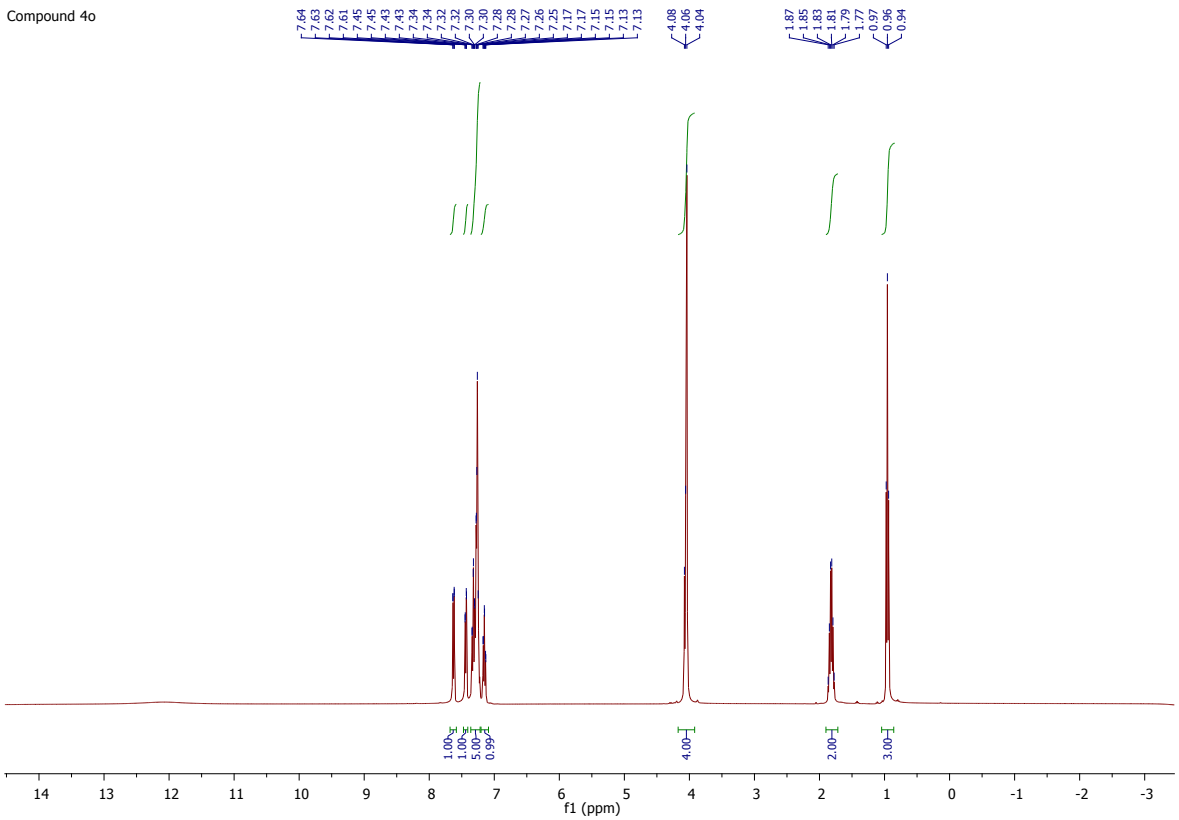
Compound 4m



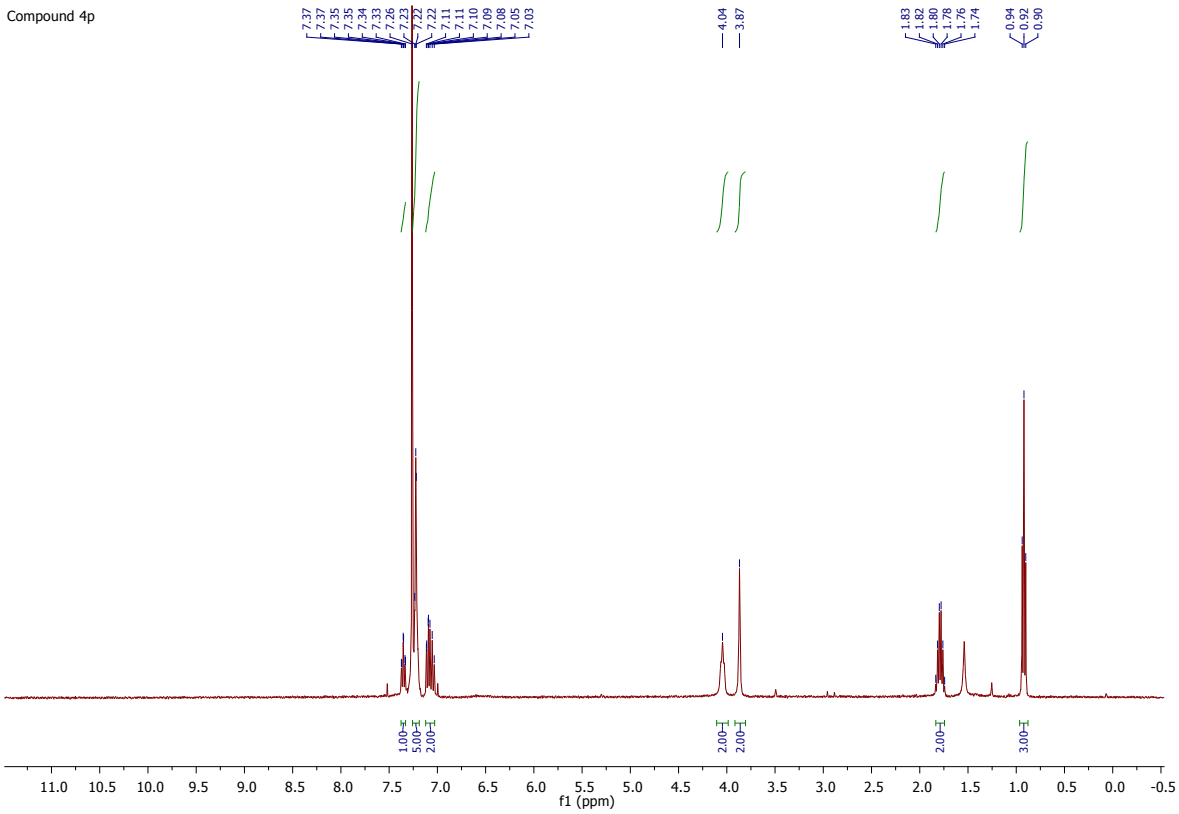
Compound 4n



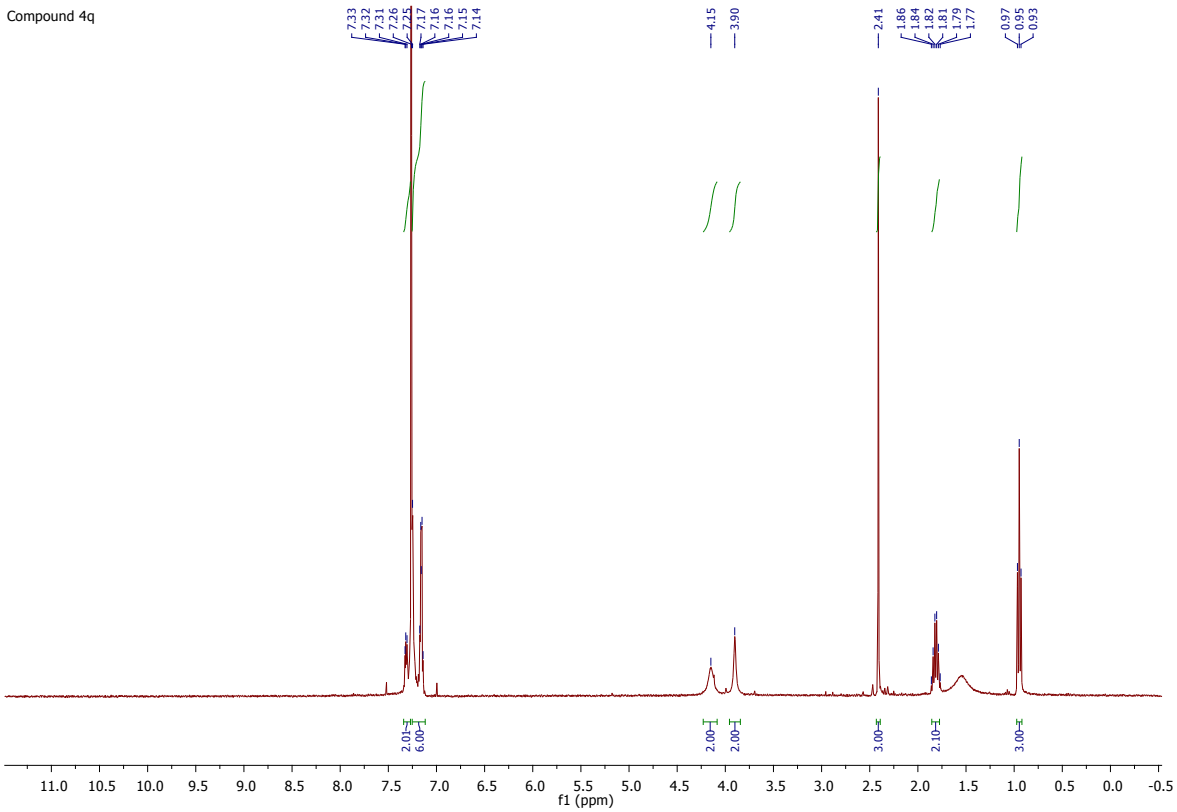
Compound 4o



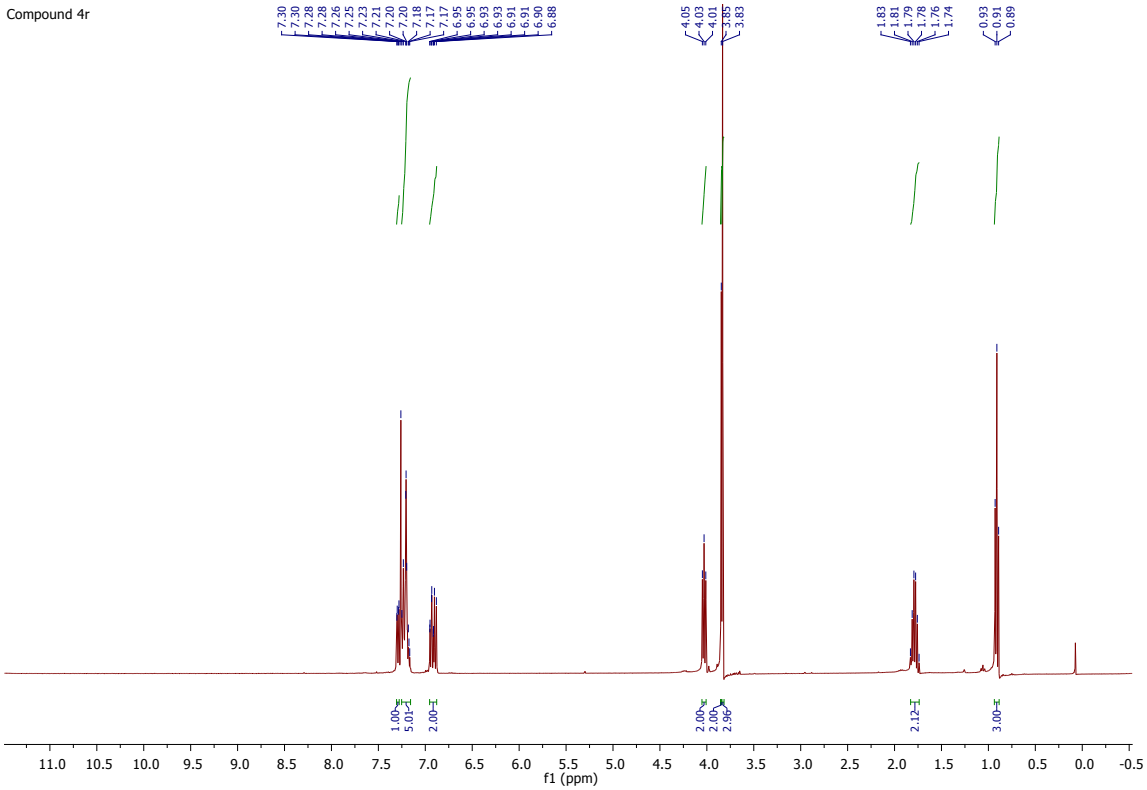
Compound 4p



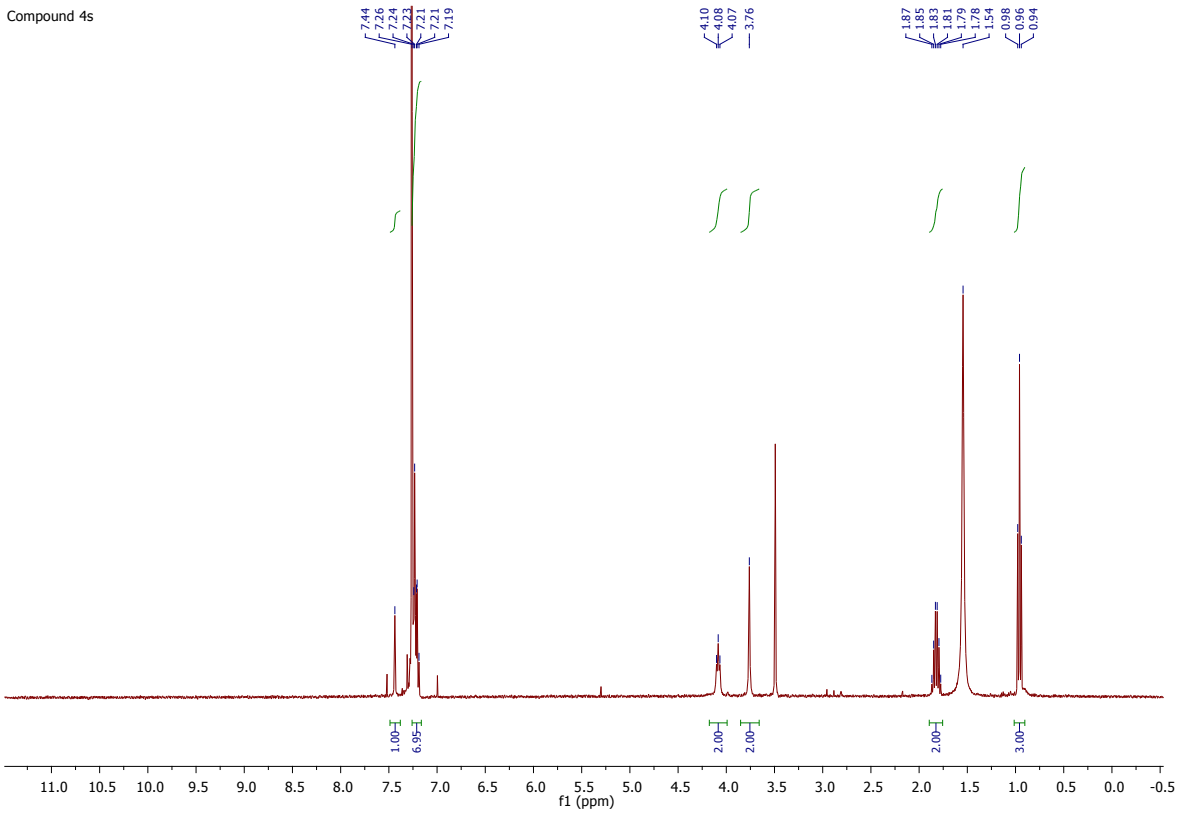
Compound 4q



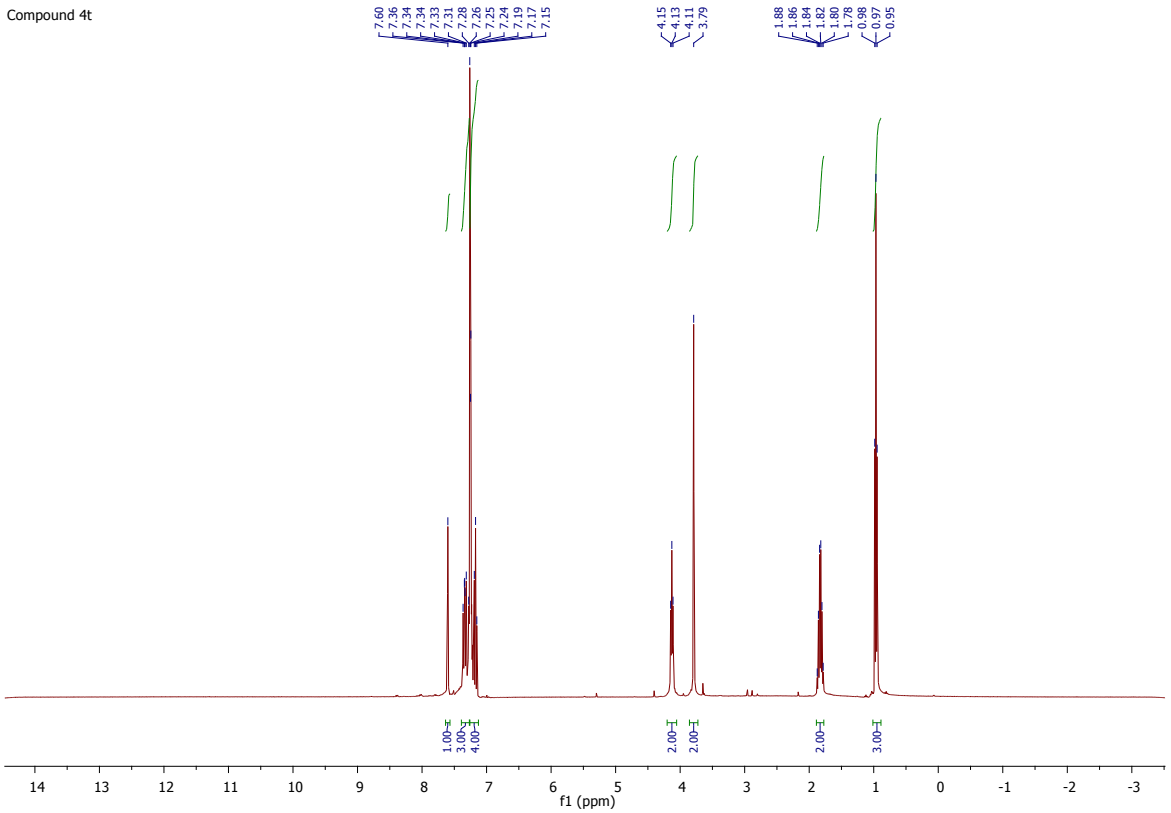
Compound 4r



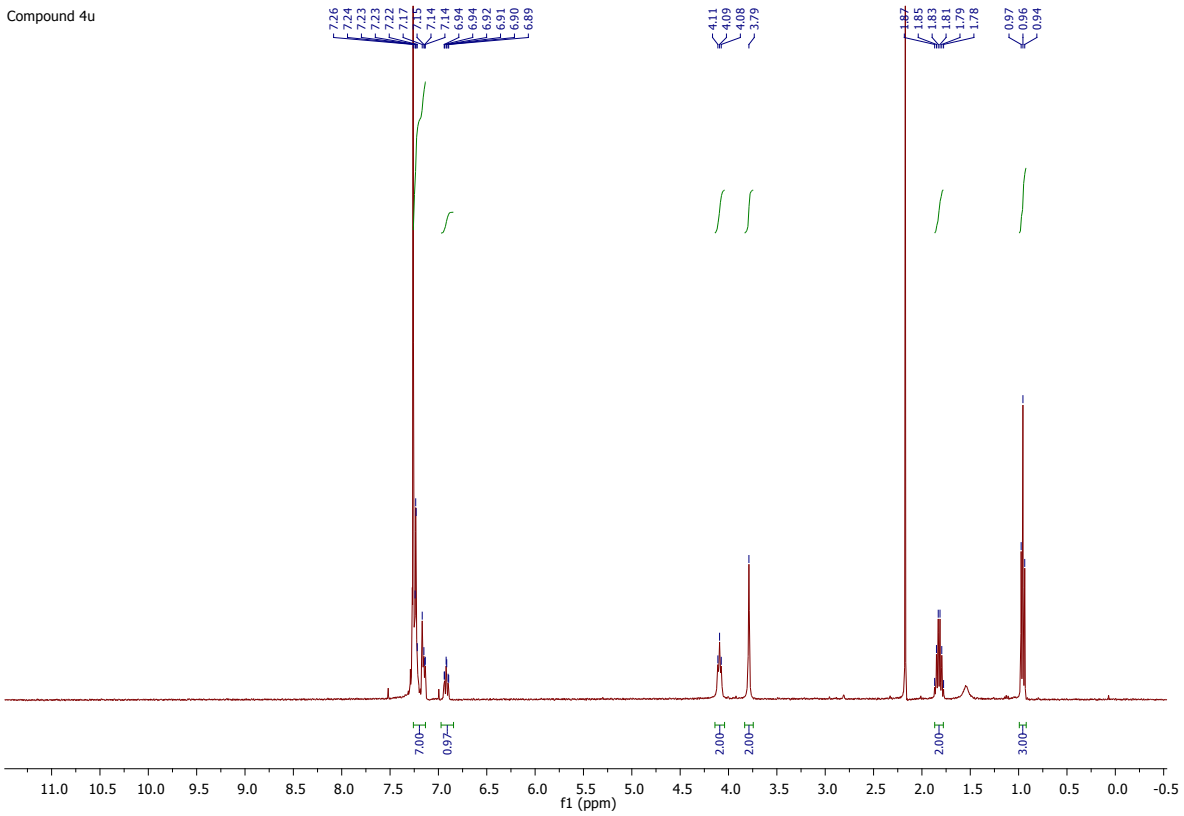
Compound 4s



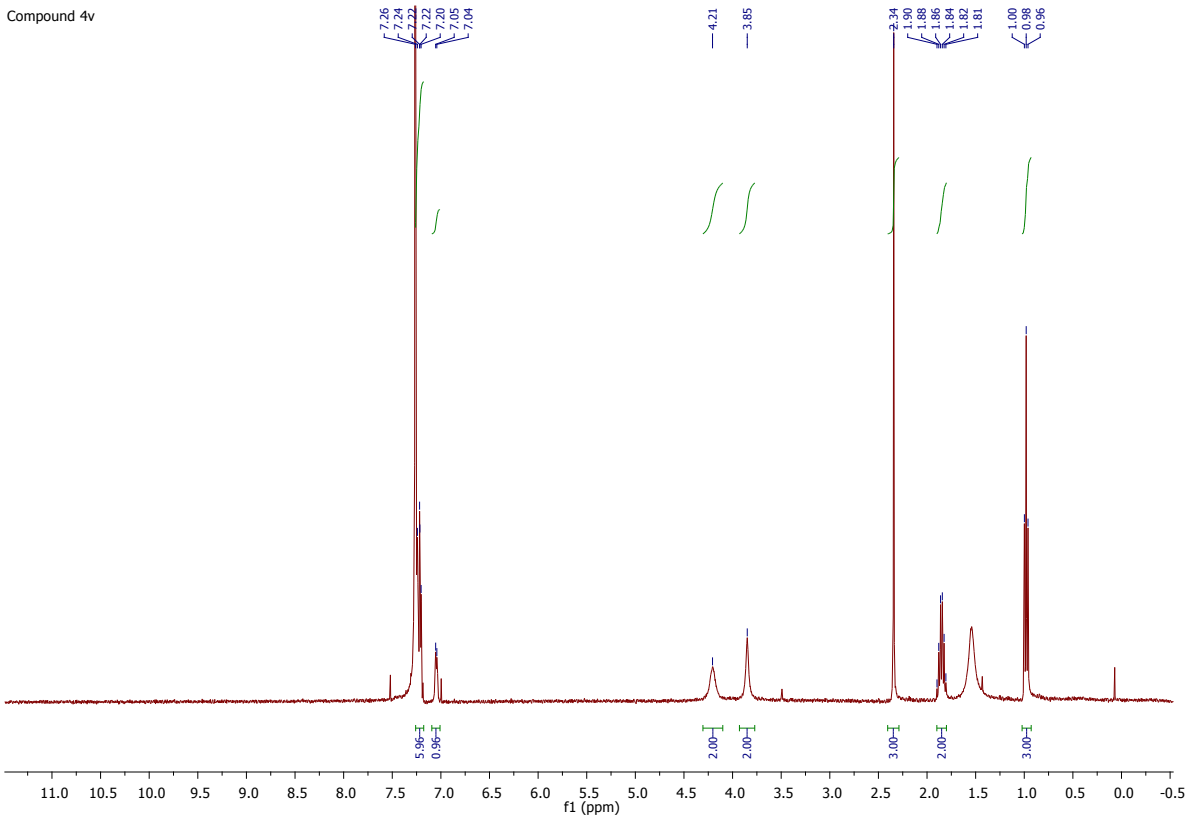
Compound 4t



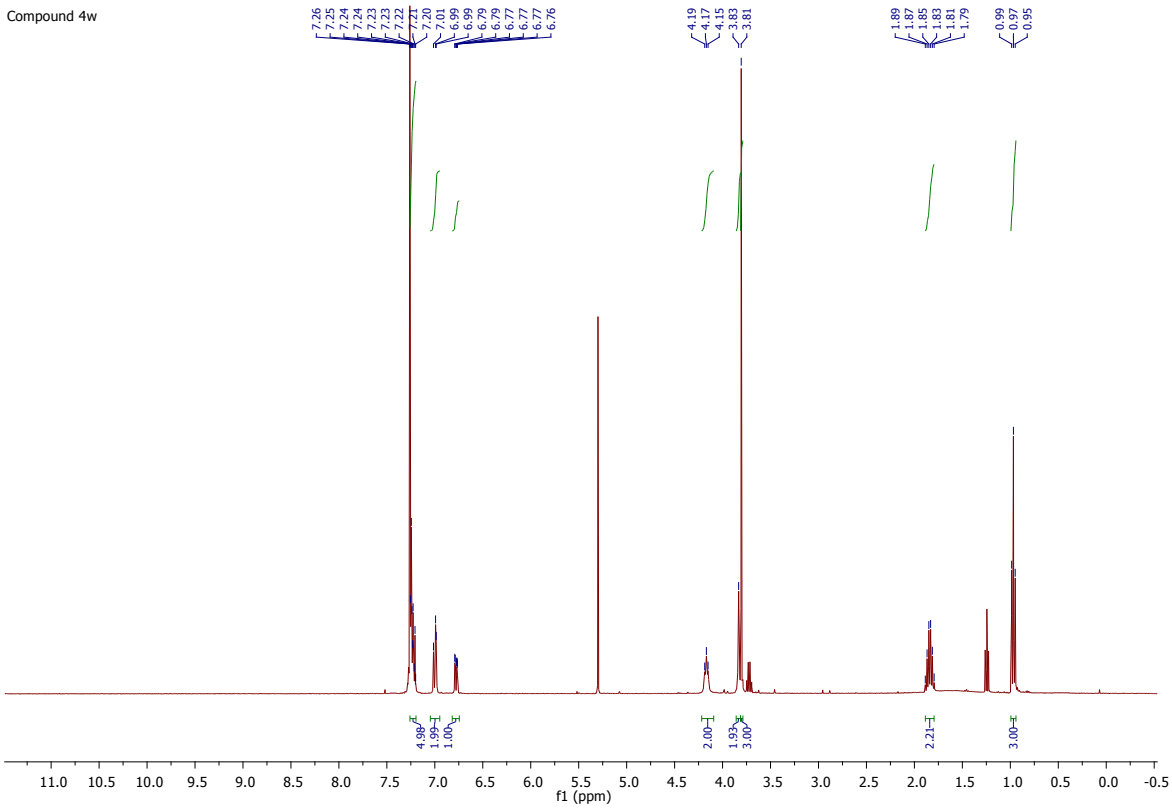
Compound 4u



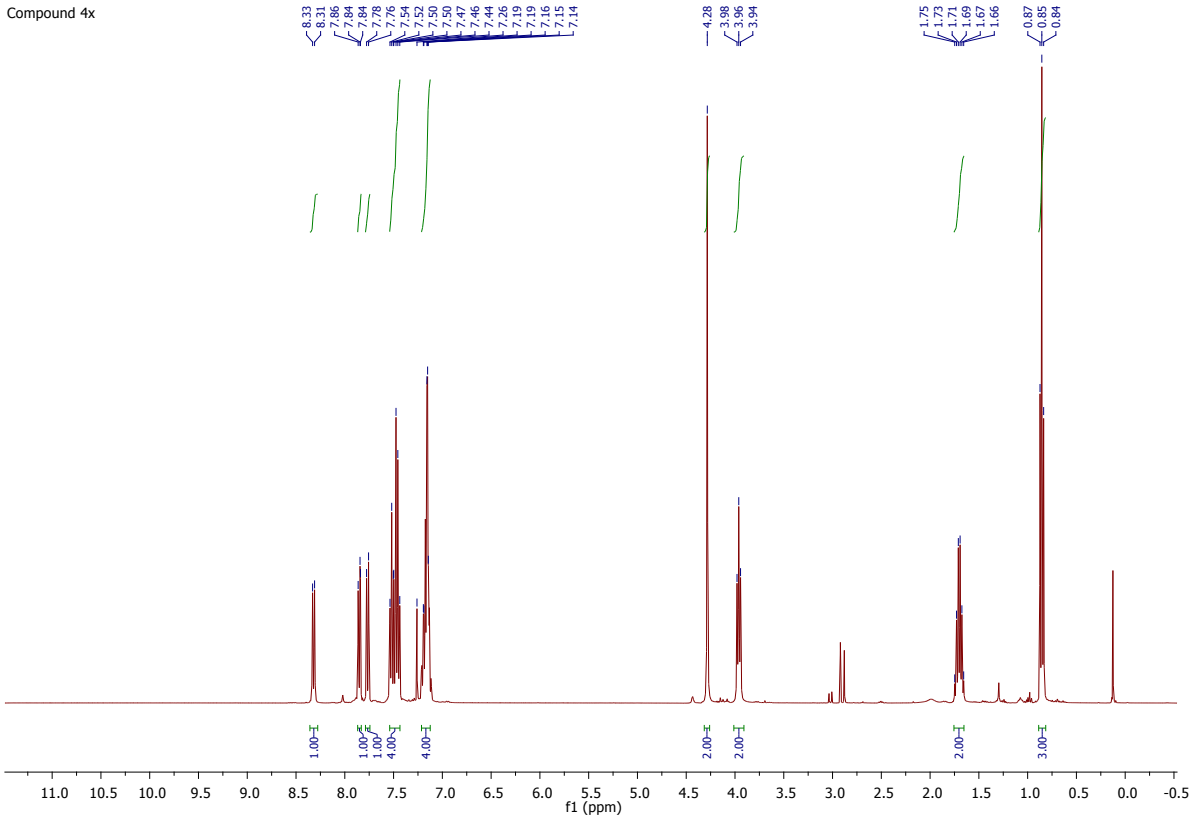
Compound 4v



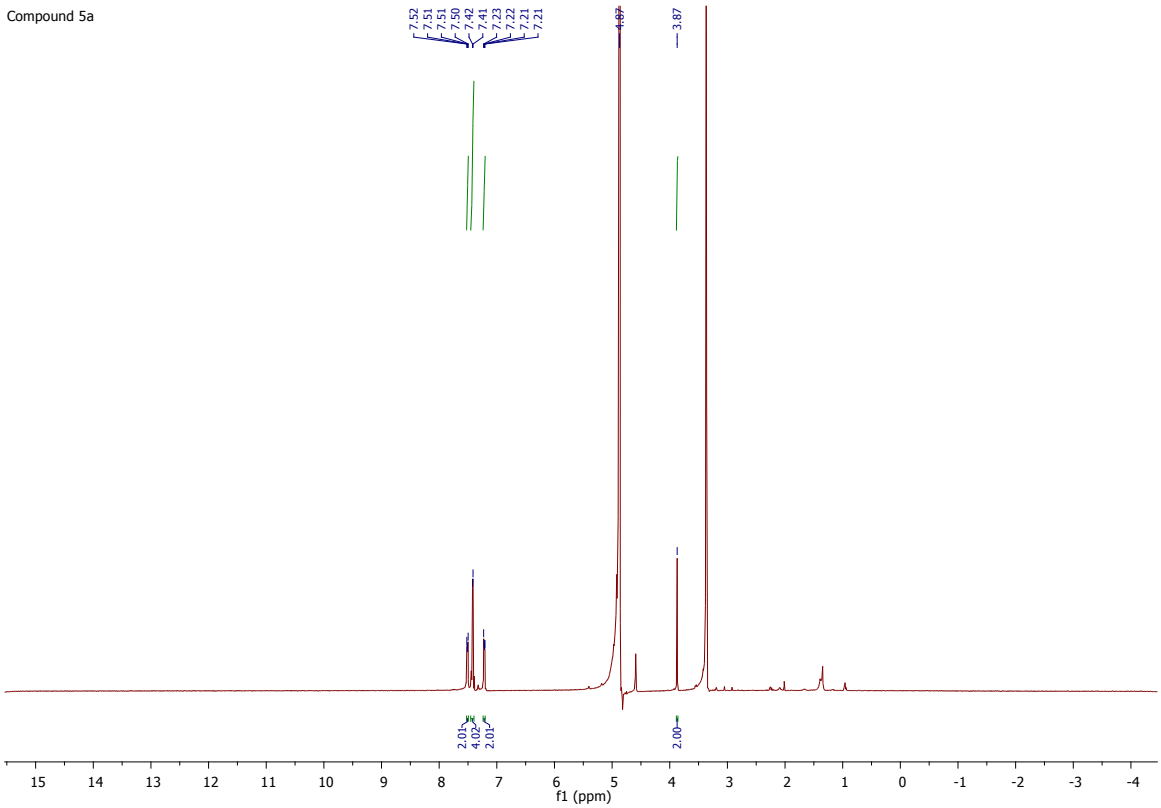
Compound 4w



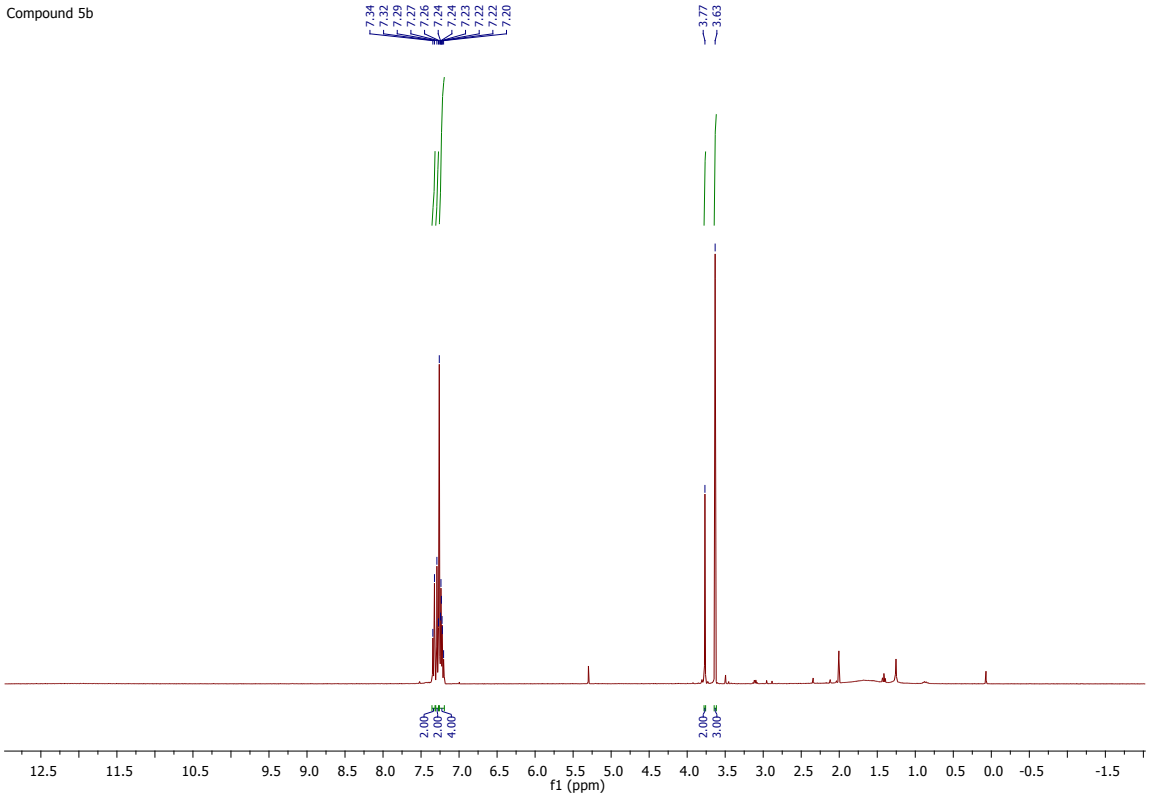
Compound 4x



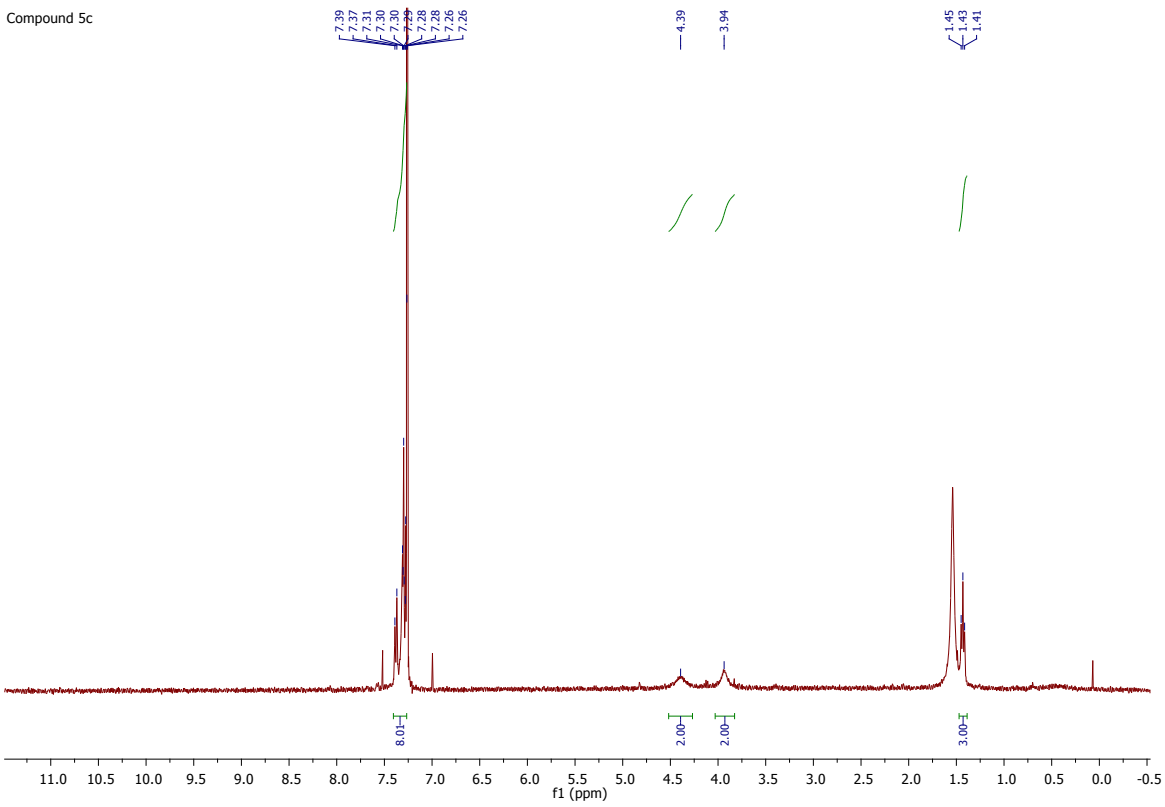
Compound 5a



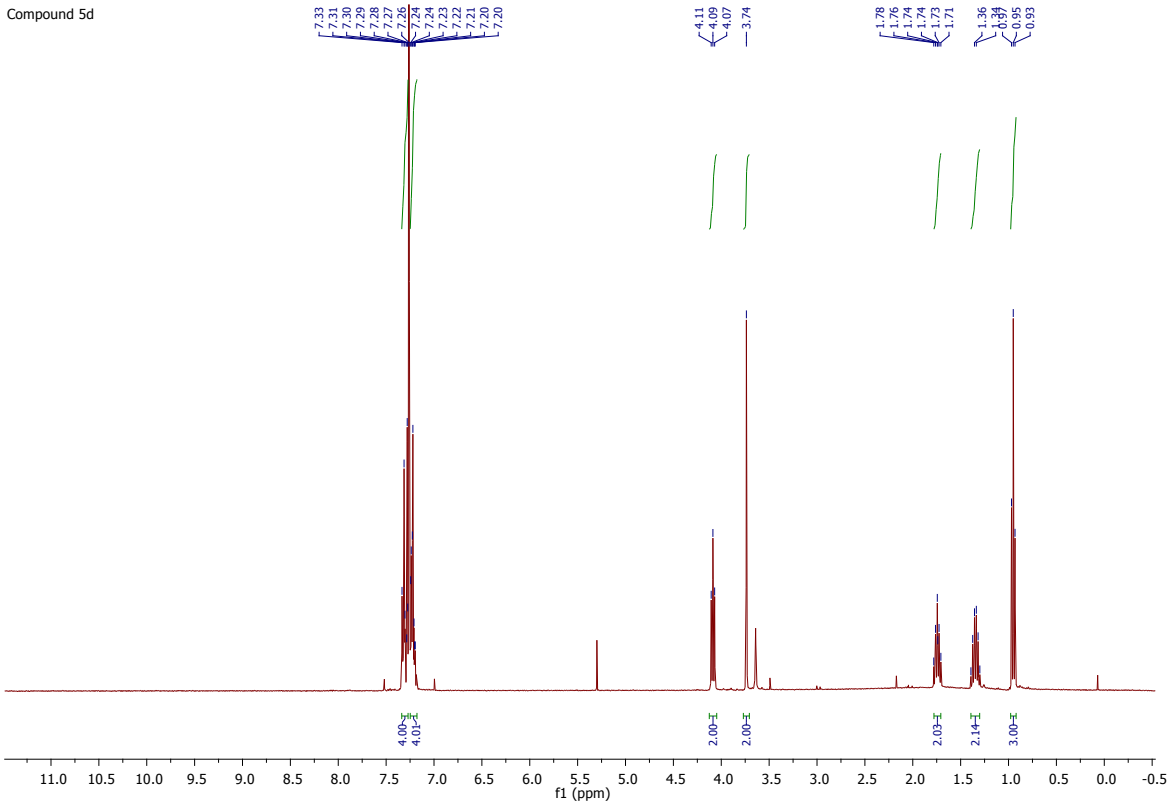
Compound 5b



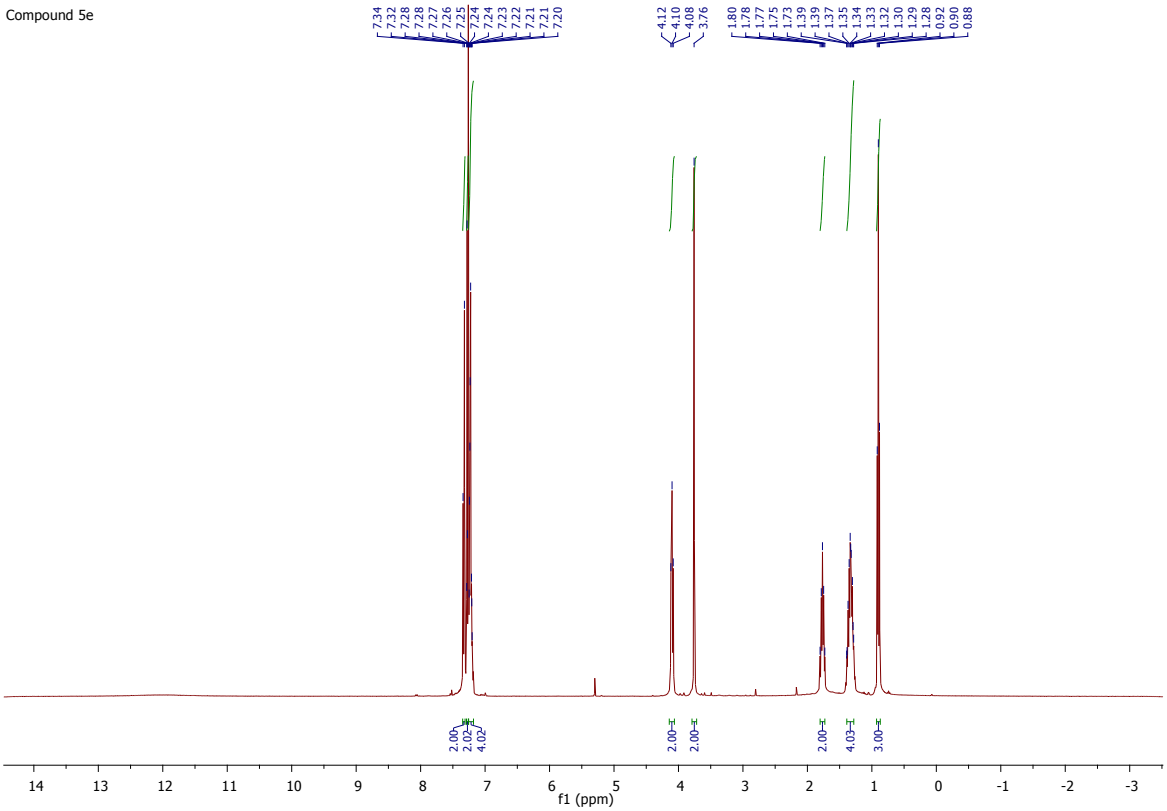
Compound 5c



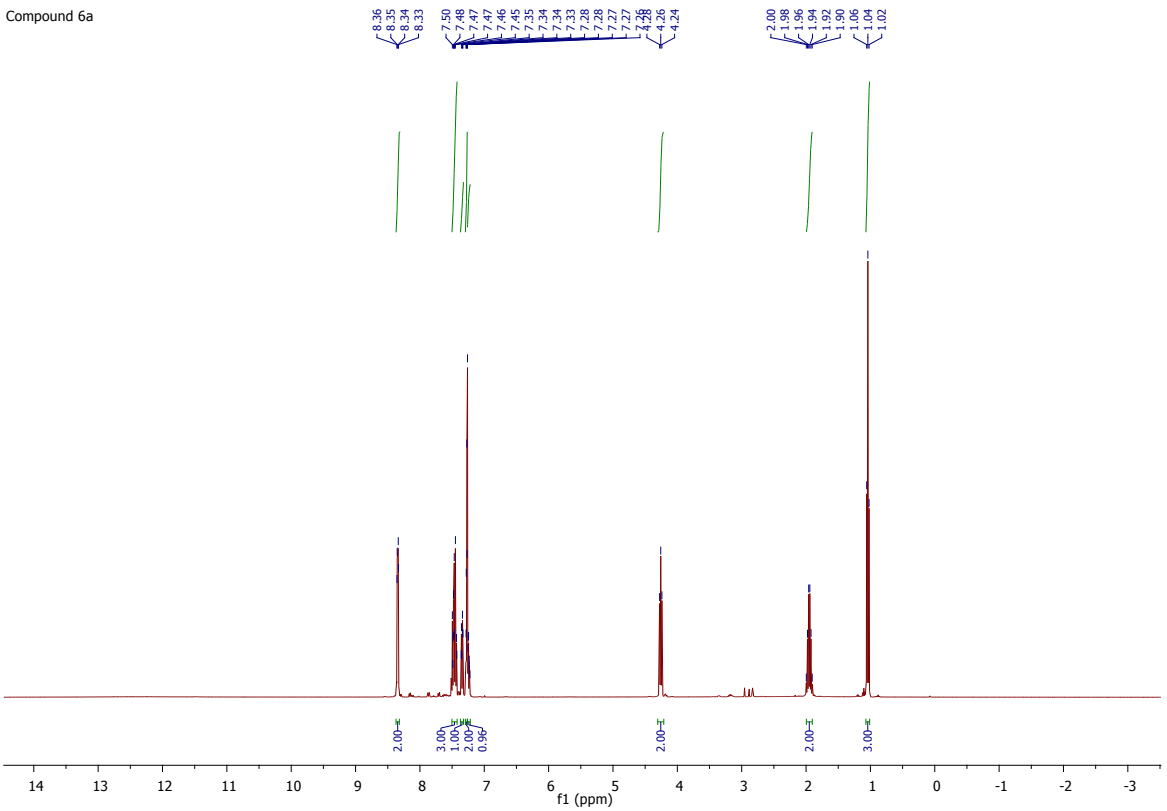
Compound 5d



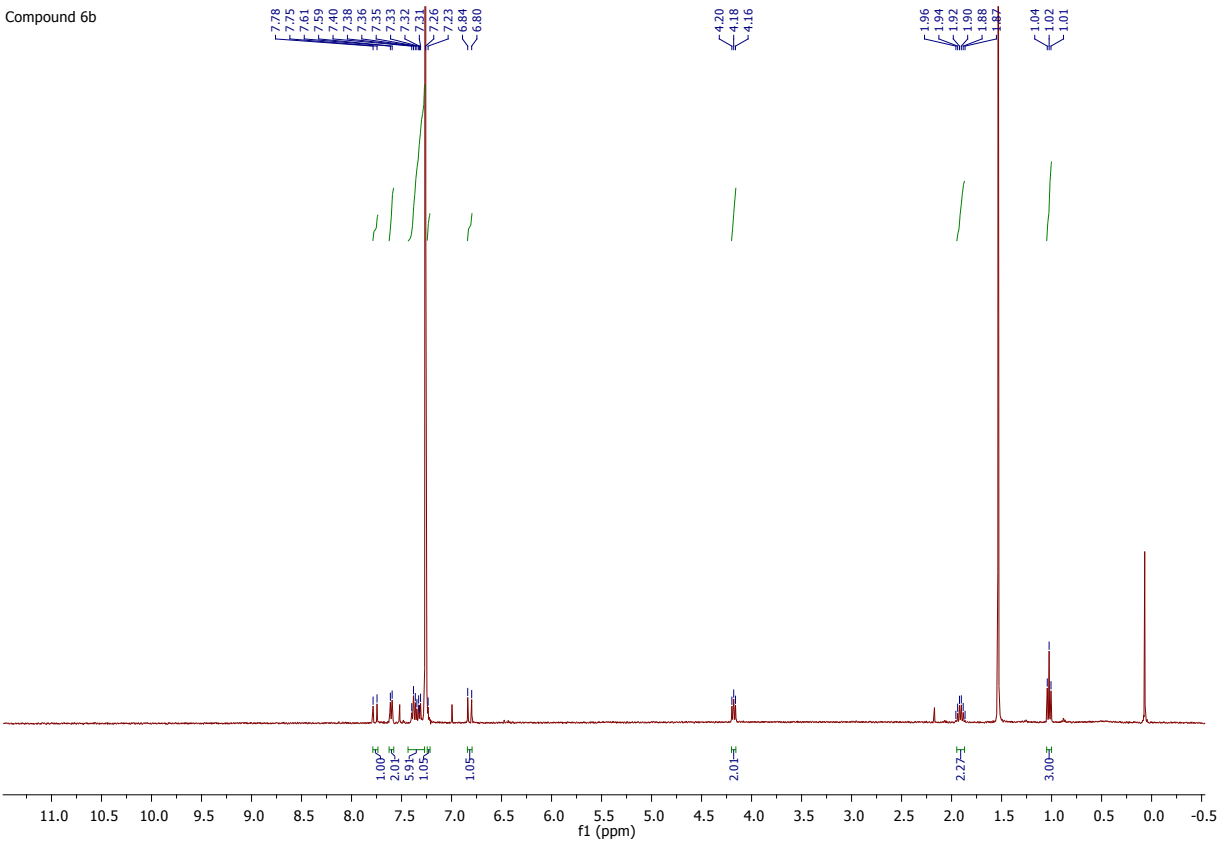
Compound 5e



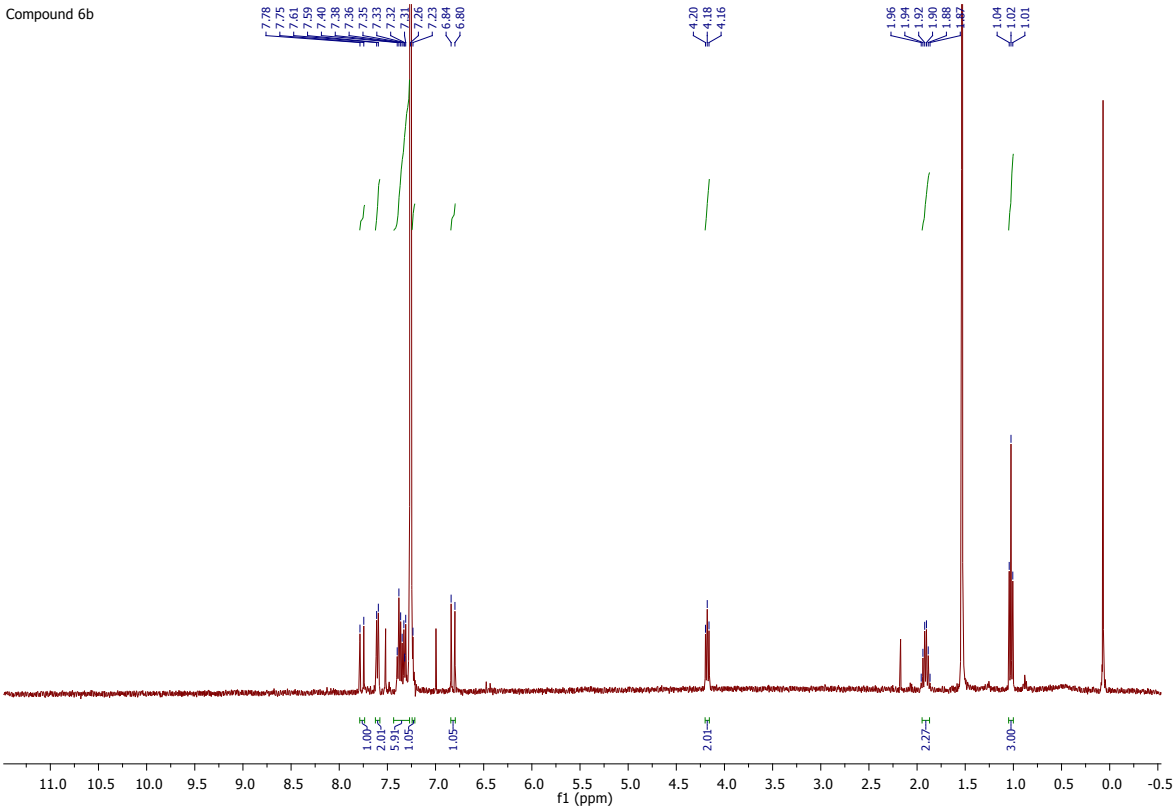
Compound 6a



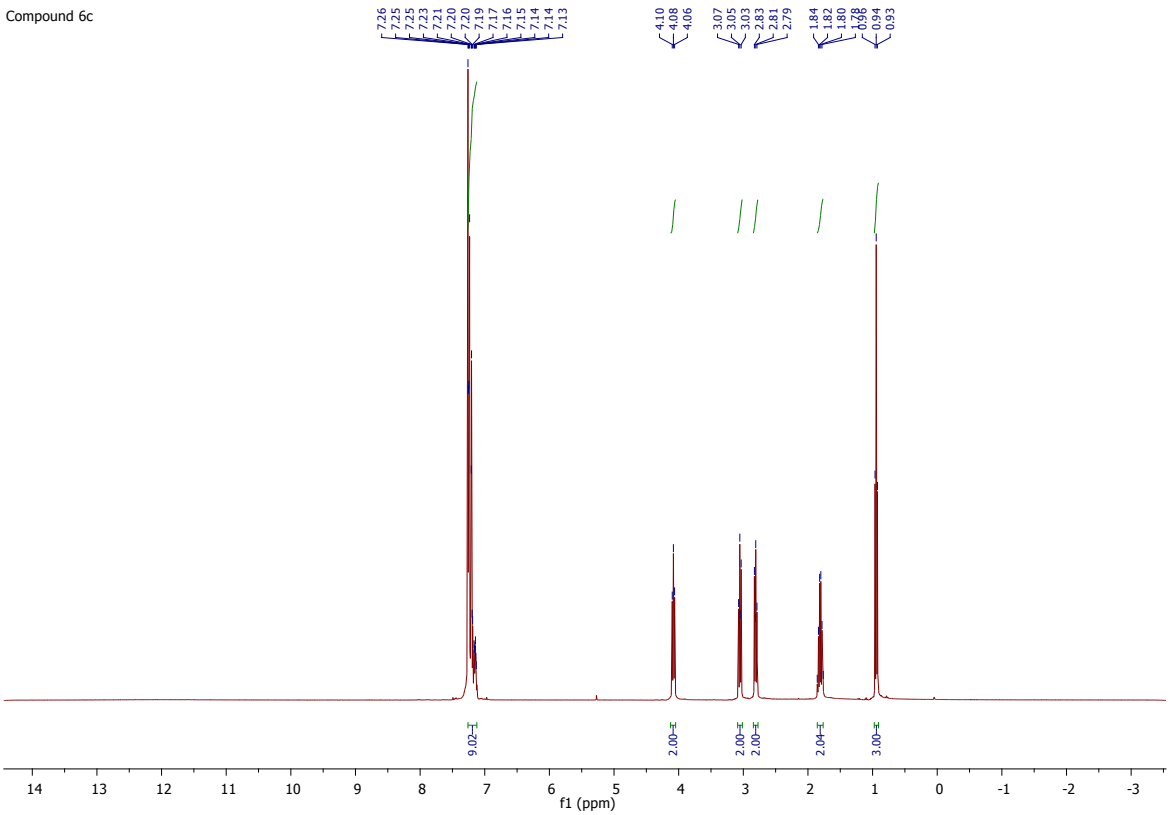
Compound 6b



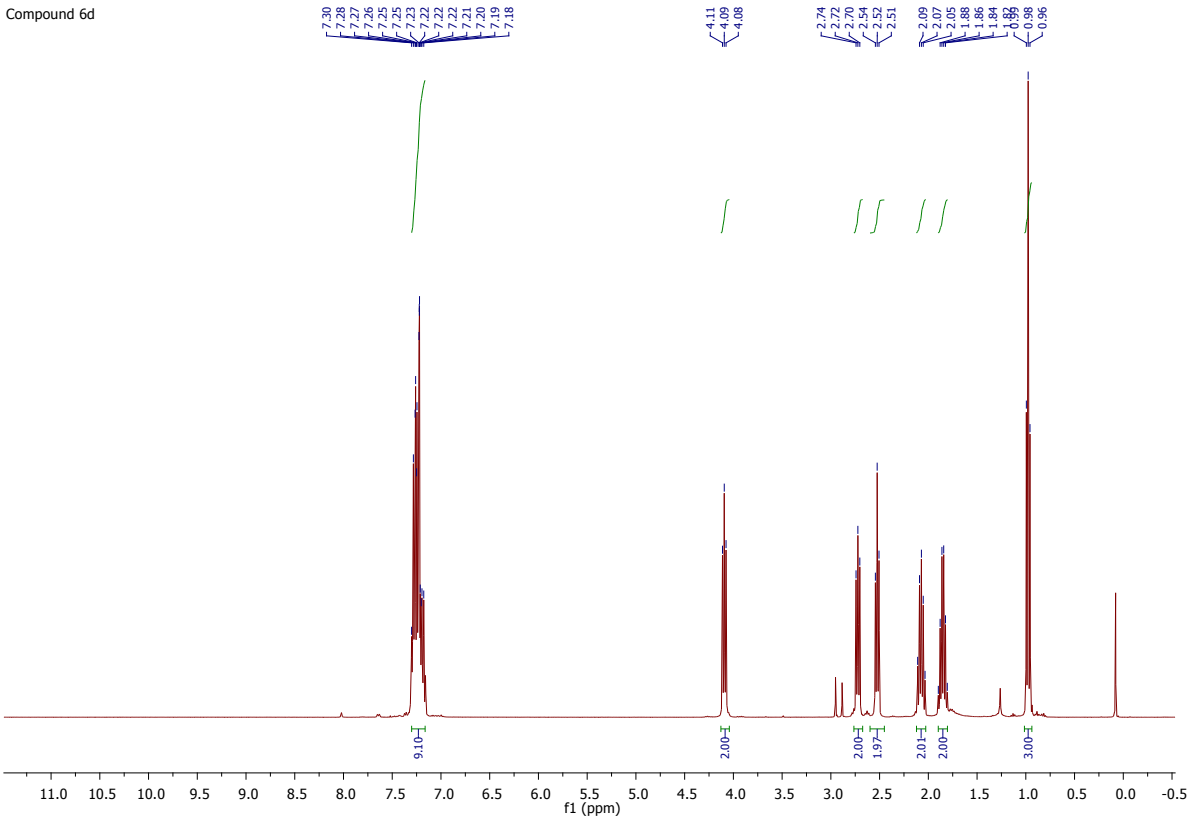
Compound 6b



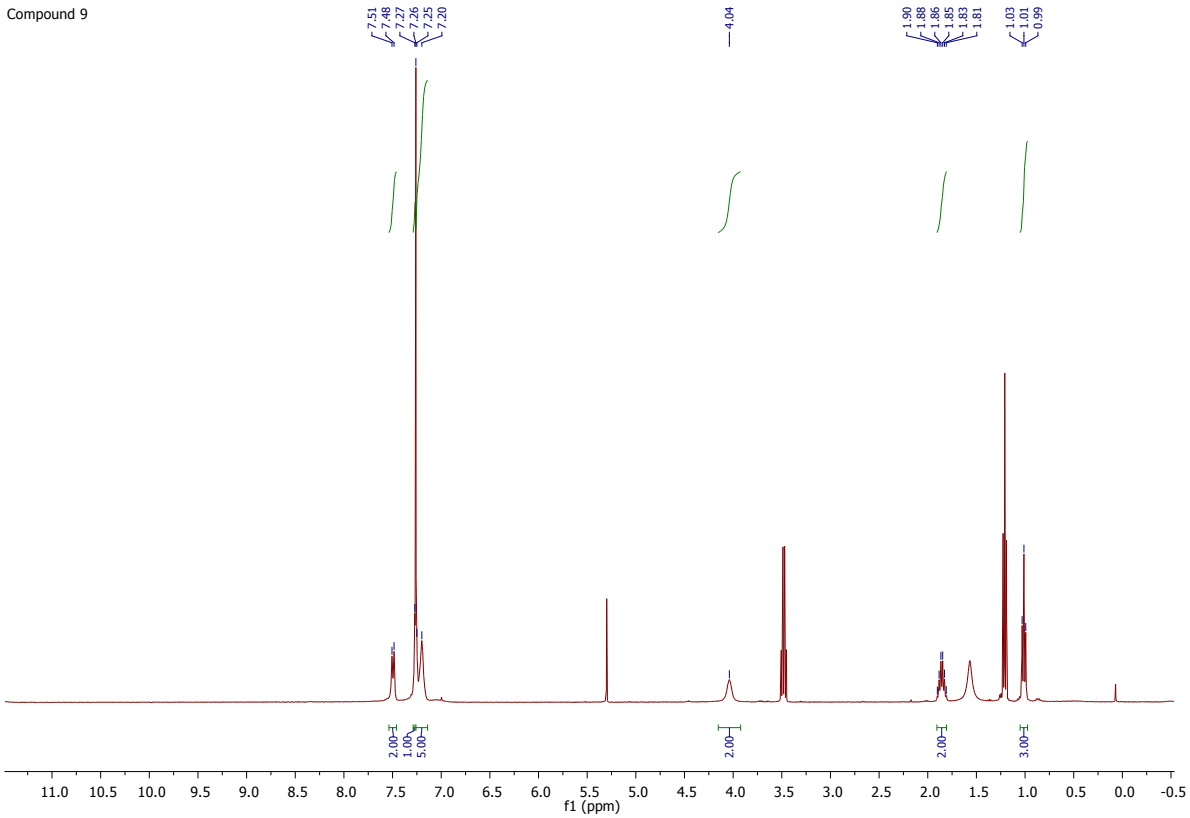
Compound 6c



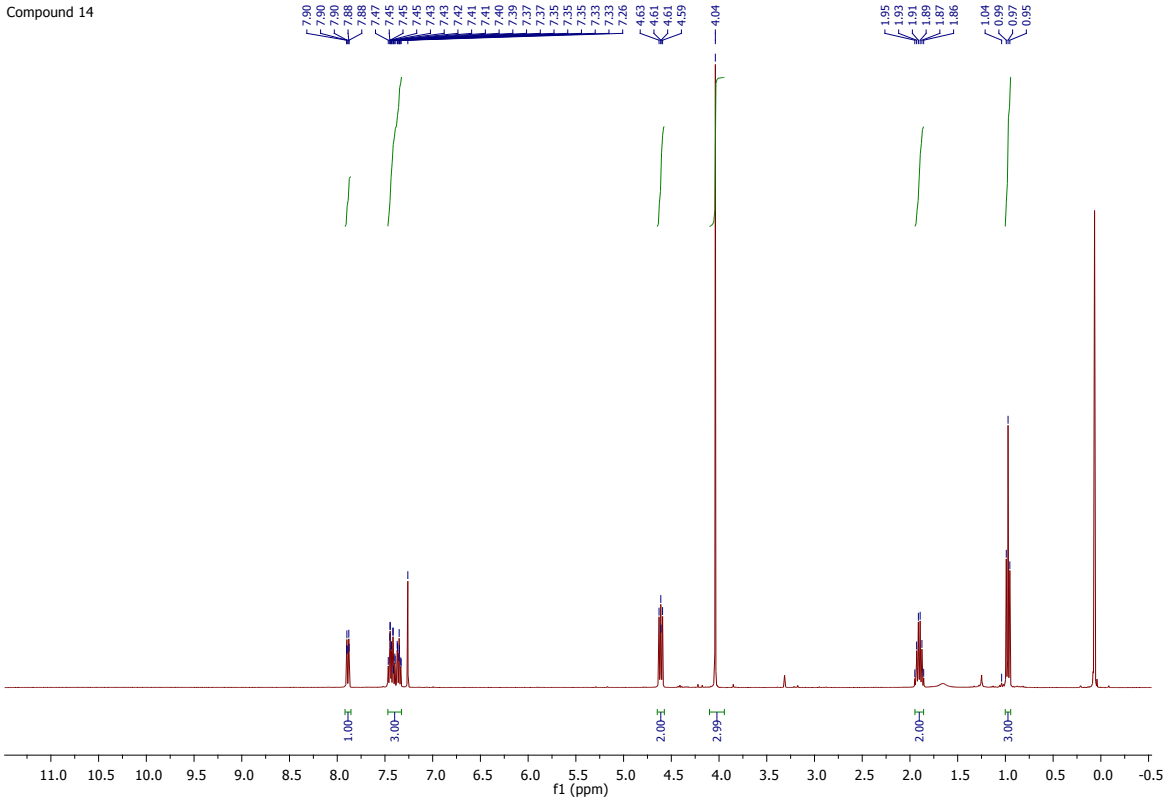
Compound 6d



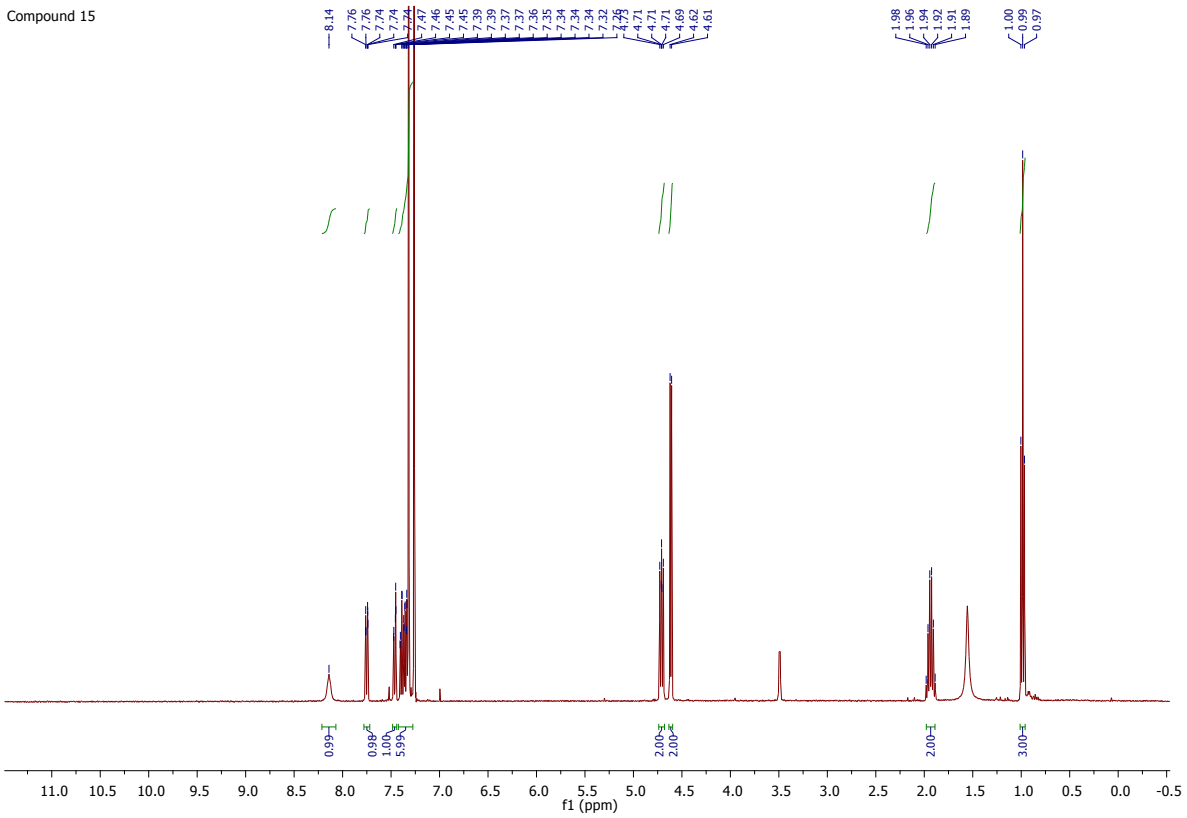
Compound 9



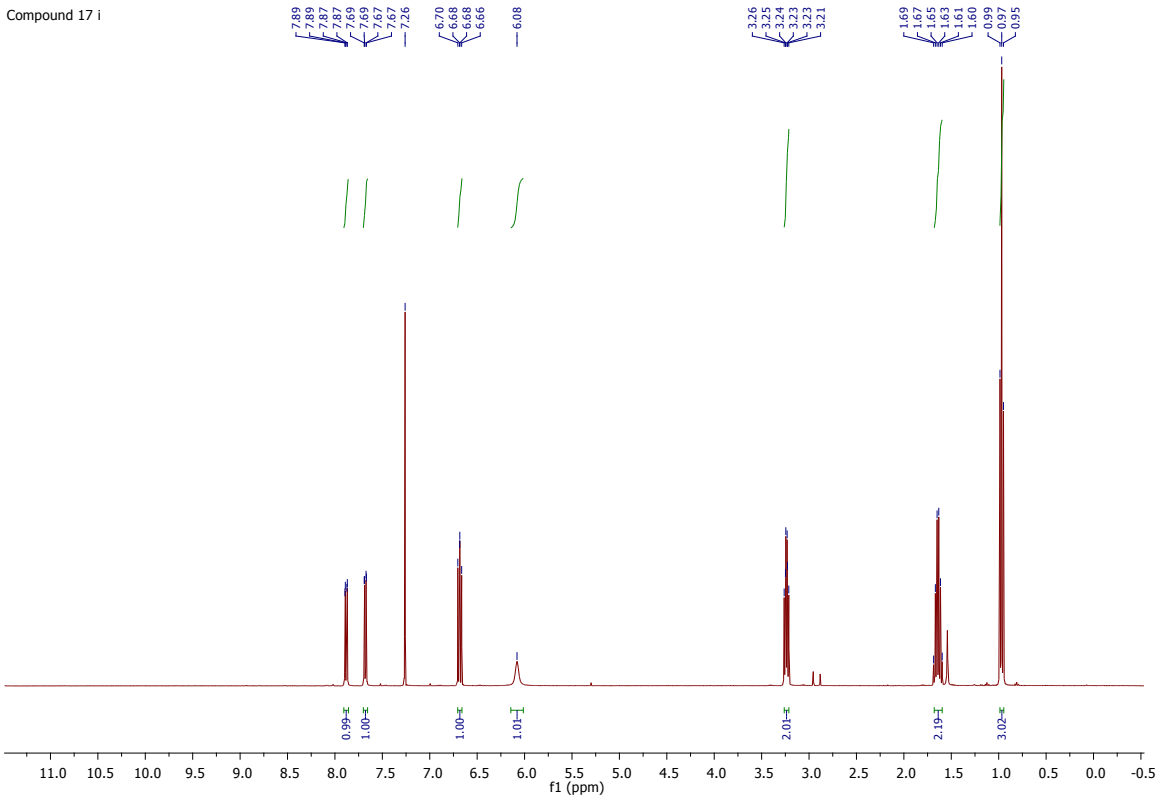
Compound 14



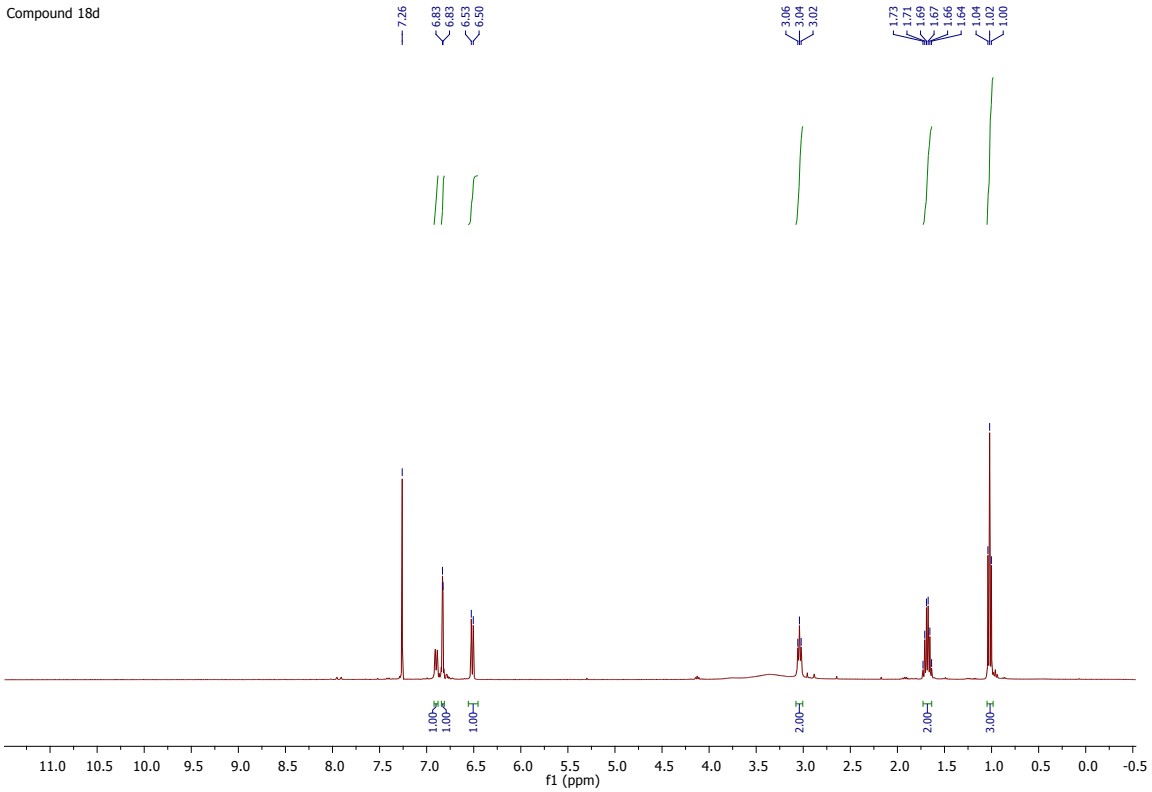
Compound 15



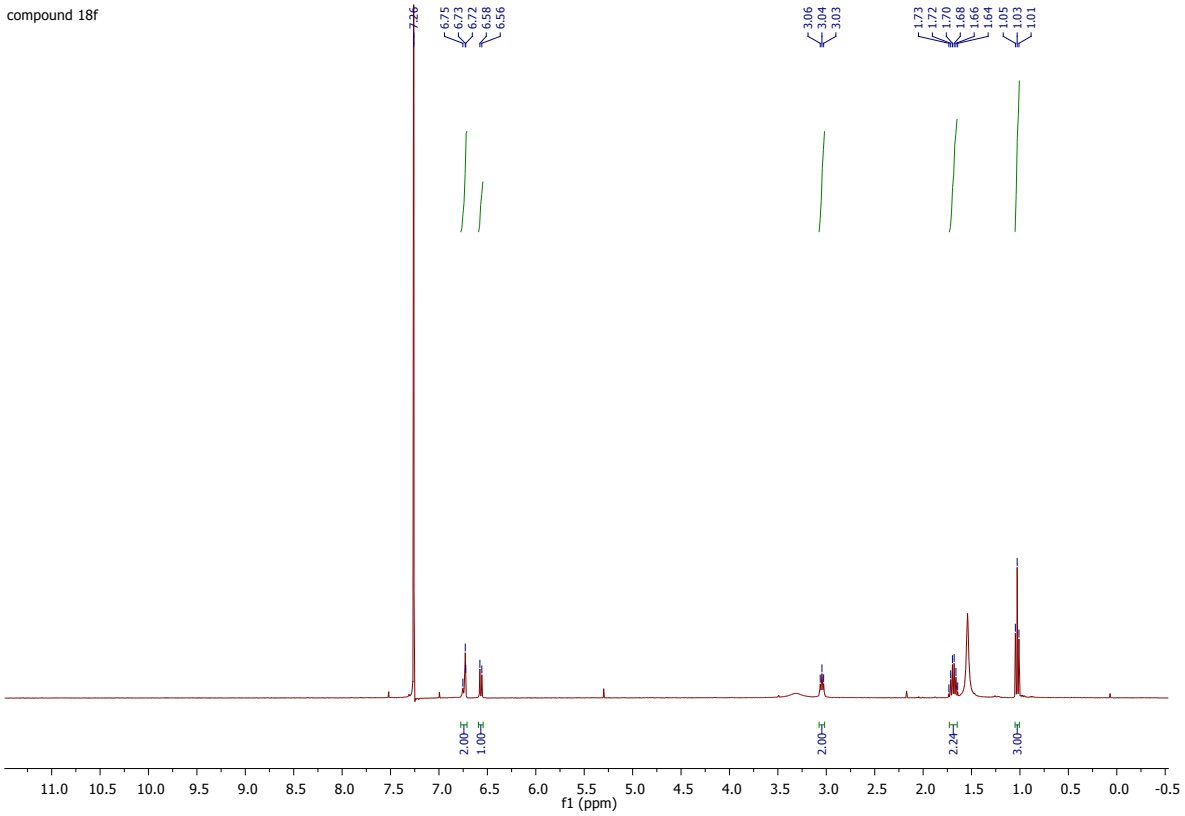
Compound 17 i



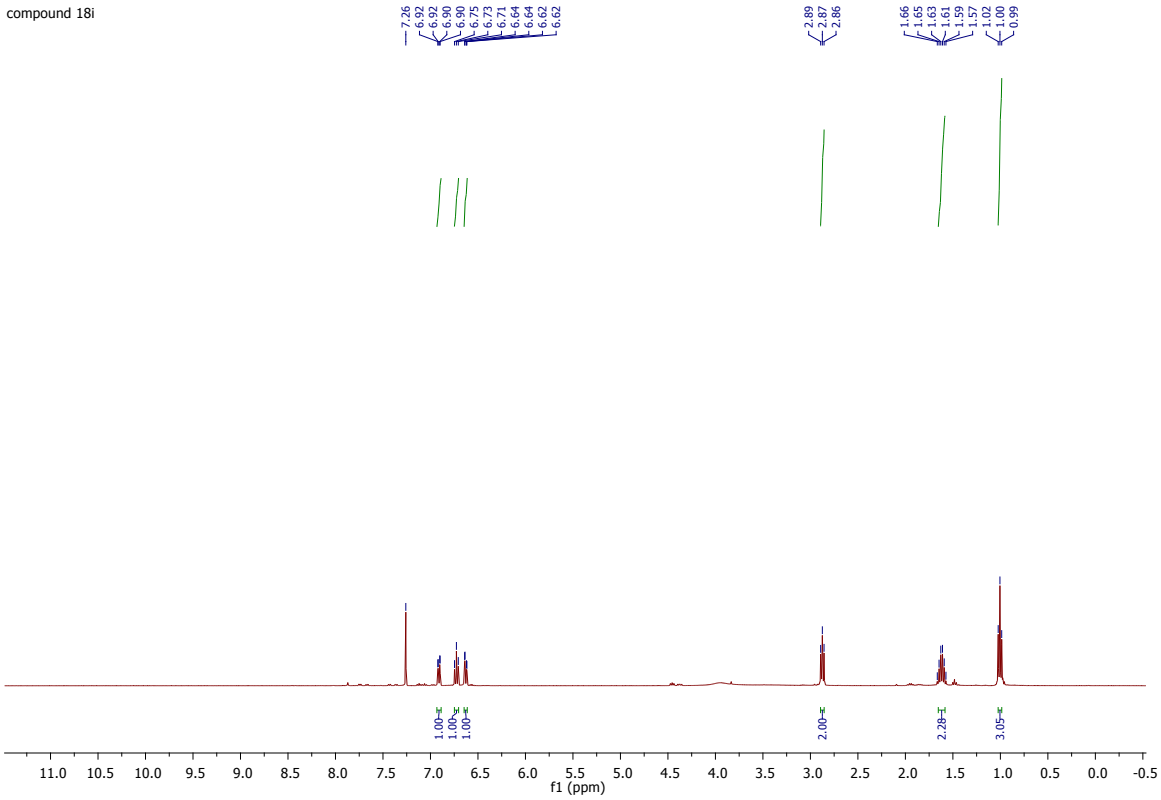
Compound 18d



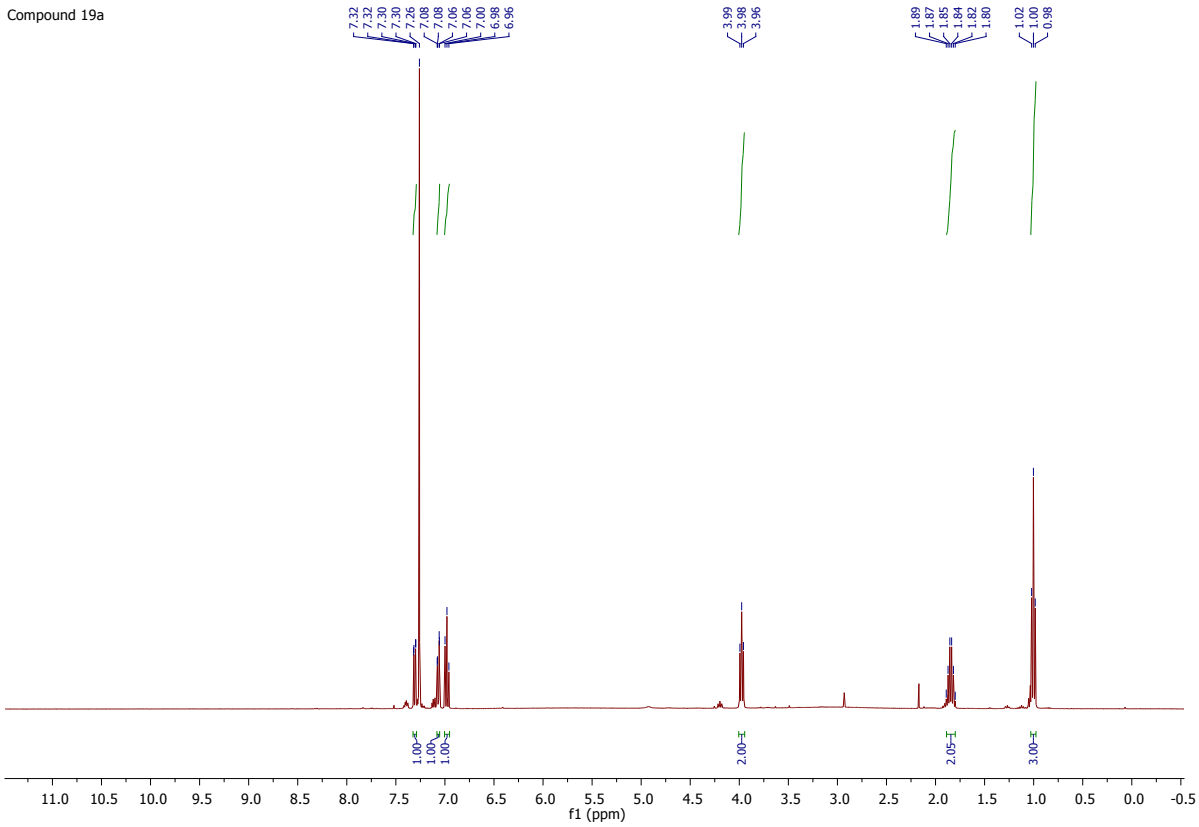
compound 18f



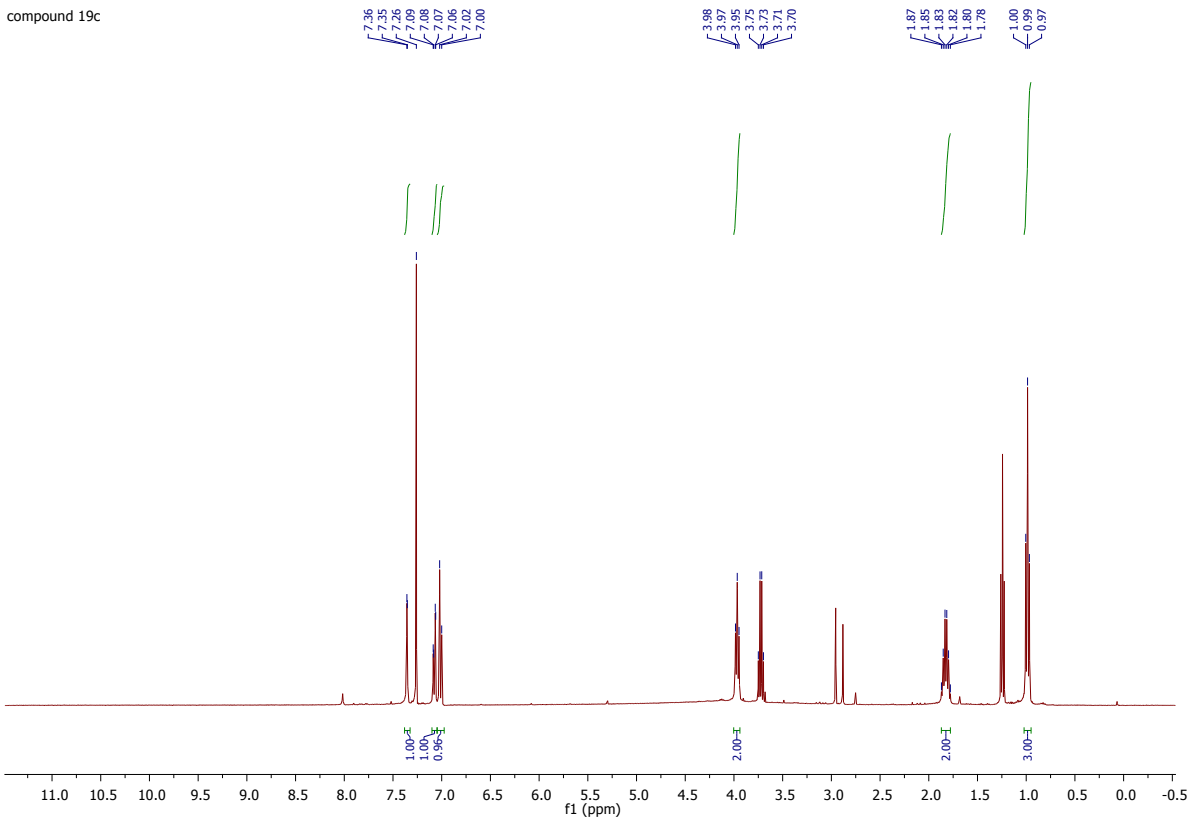
compound 18i



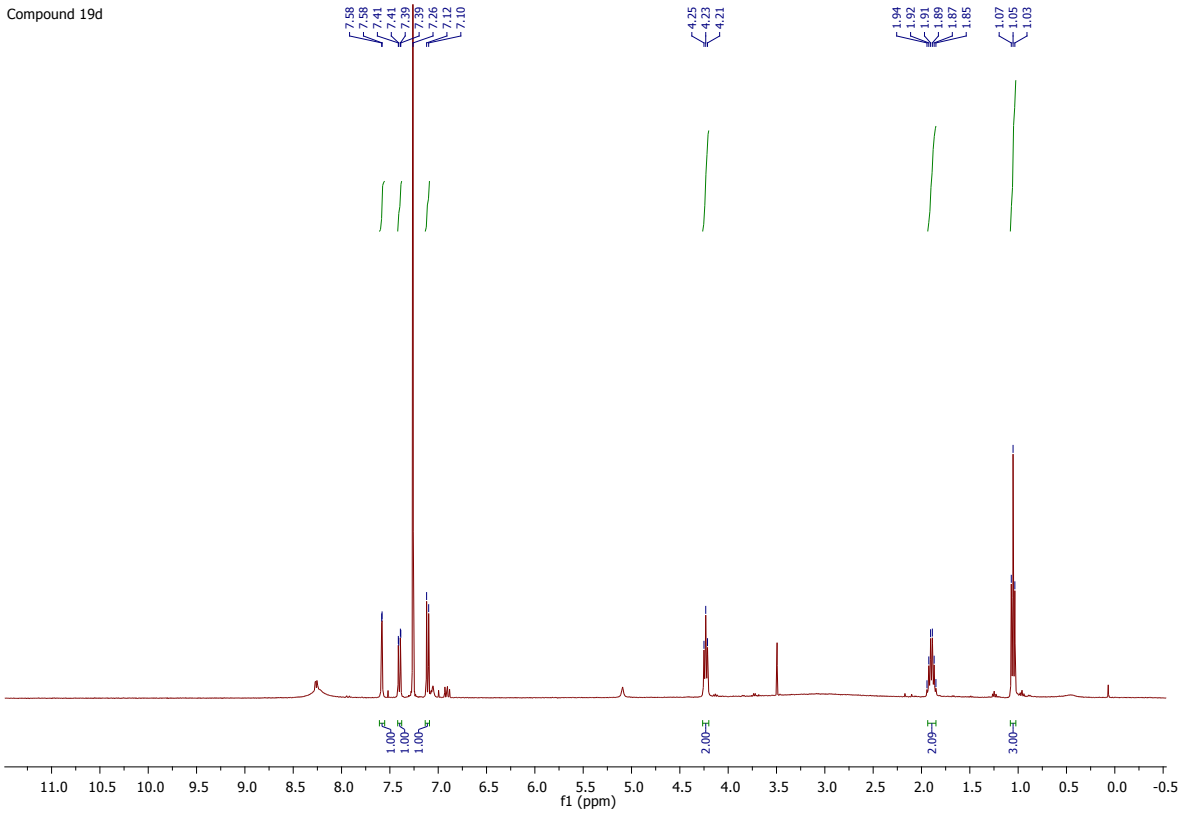
Compound 19a



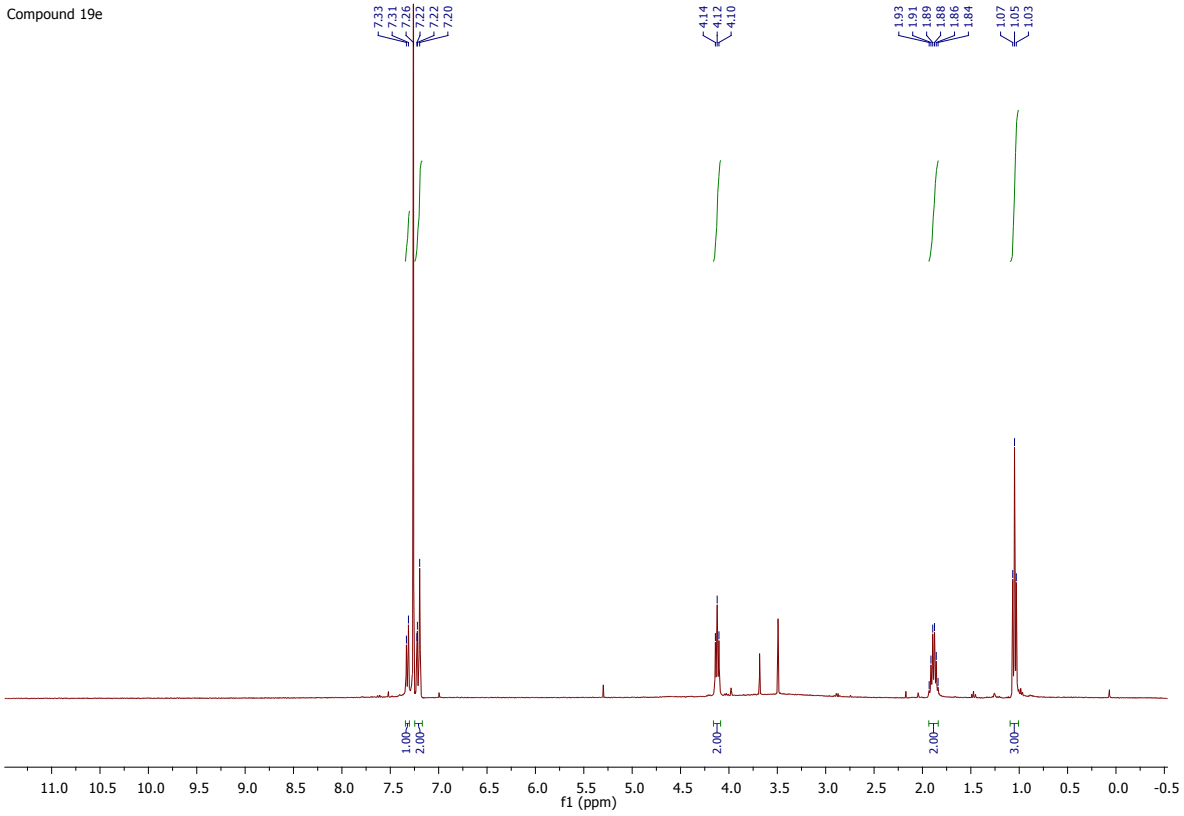
compound 19c



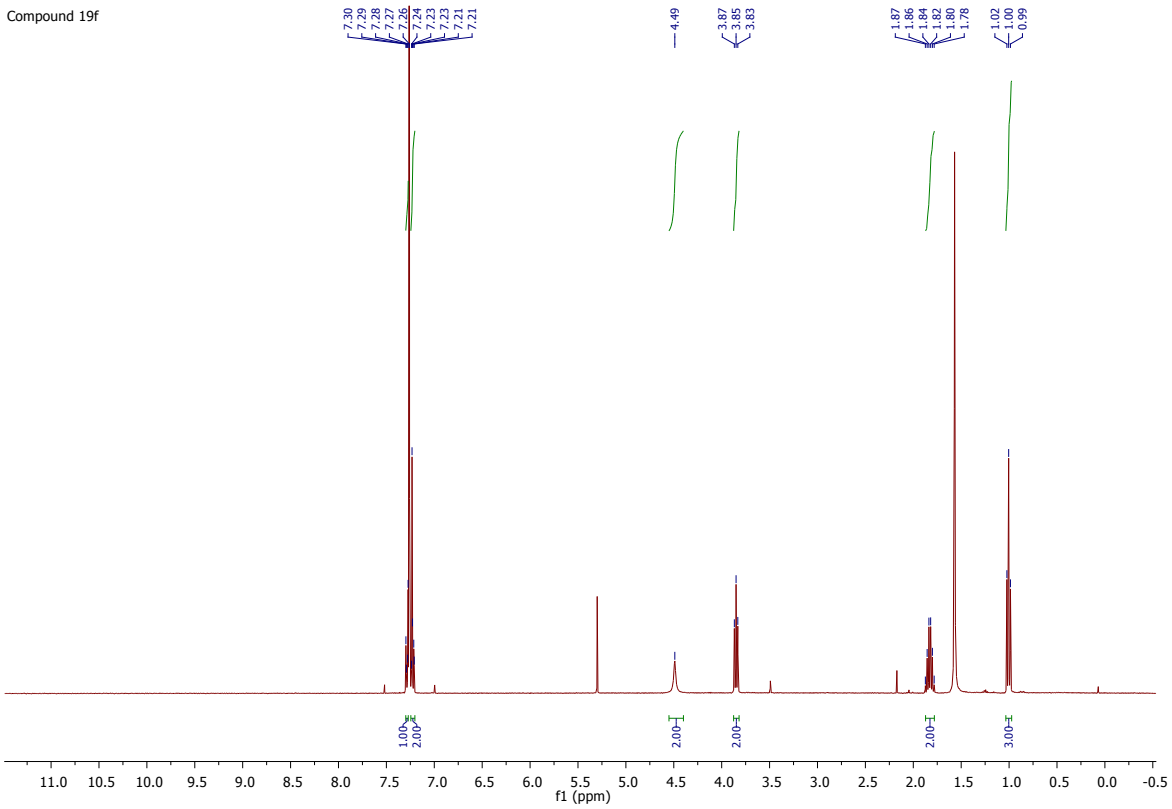
Compound 19d



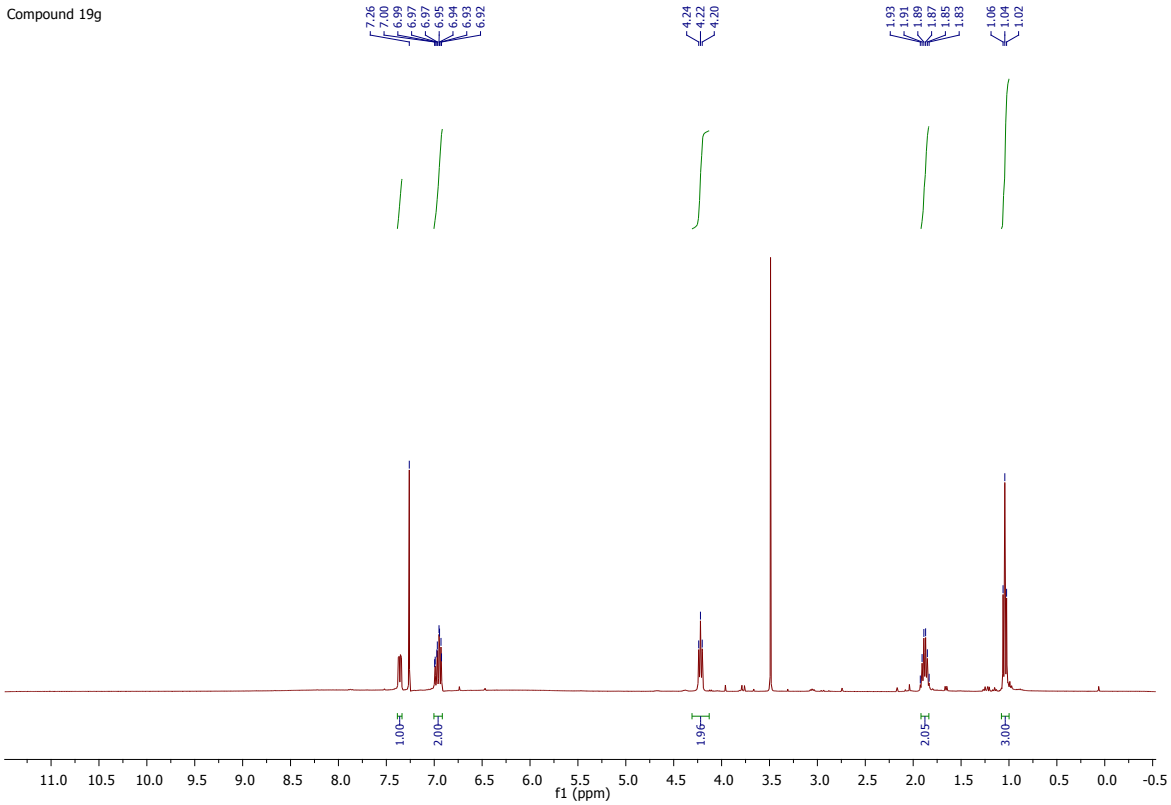
Compound 19e



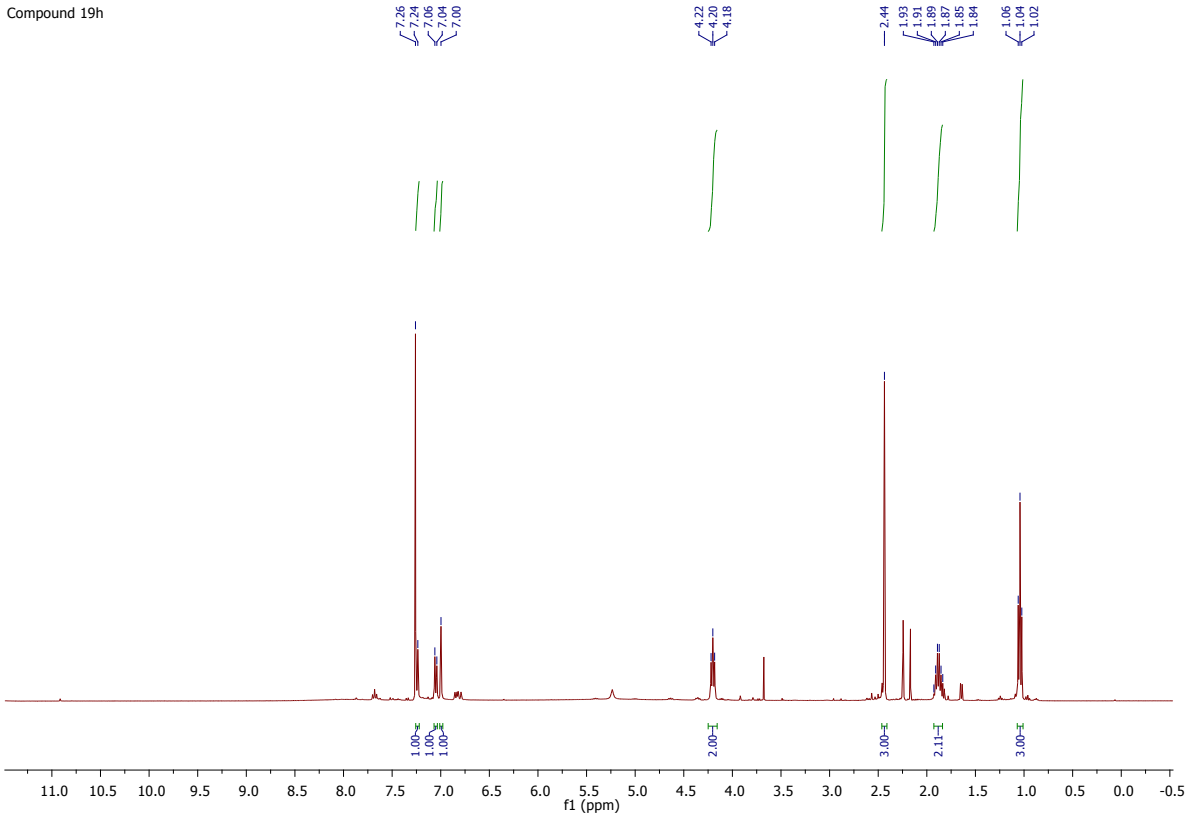
Compound 19f



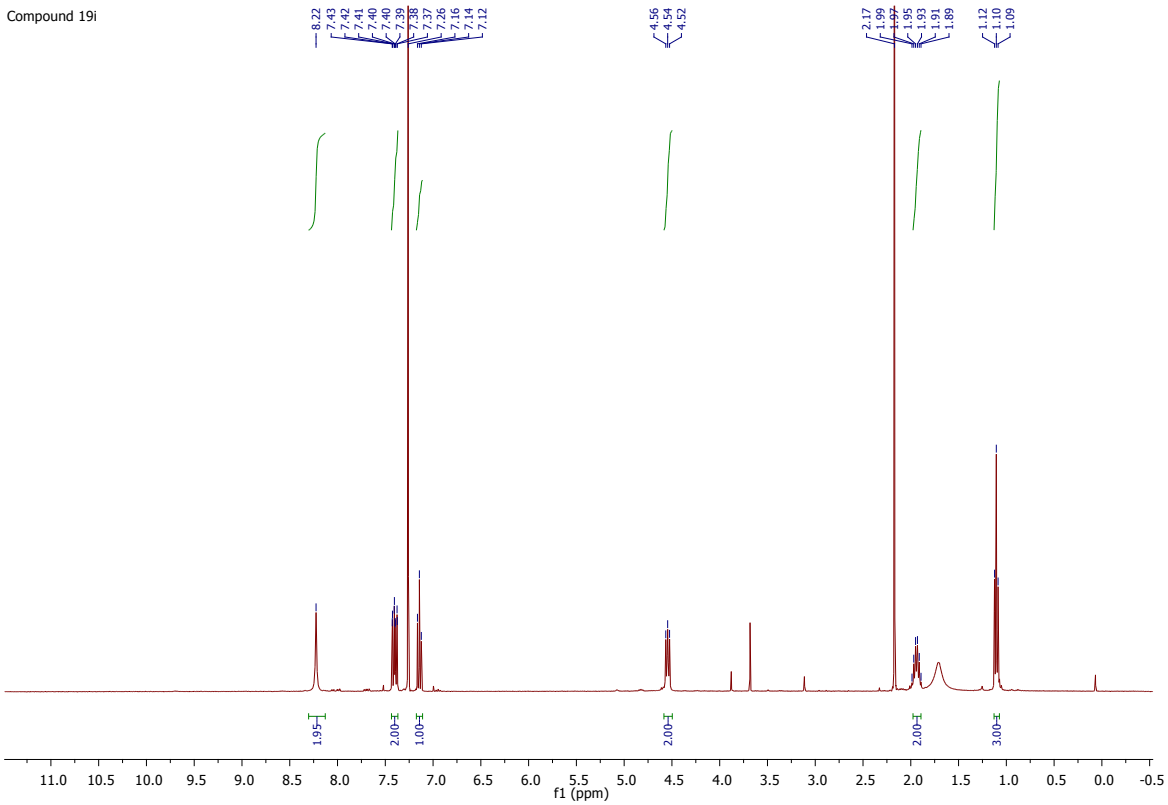
Compound 19g



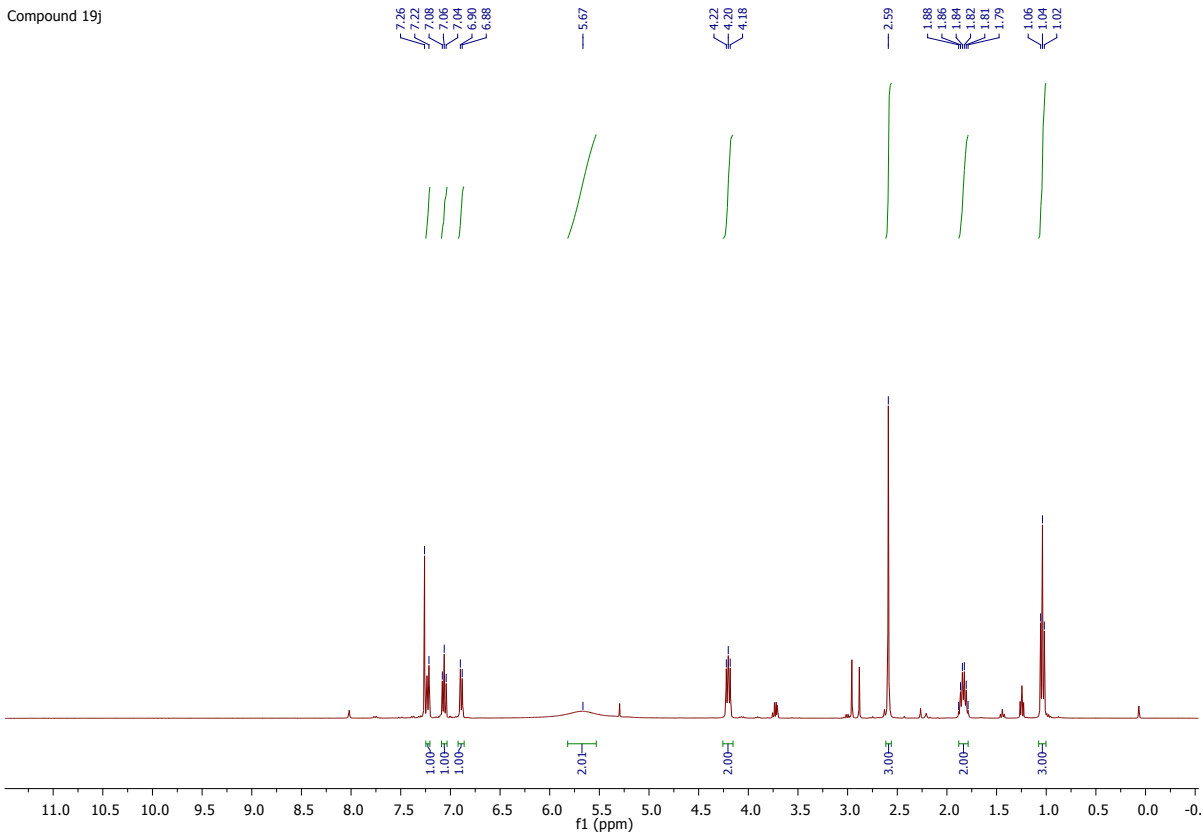
Compound 19h



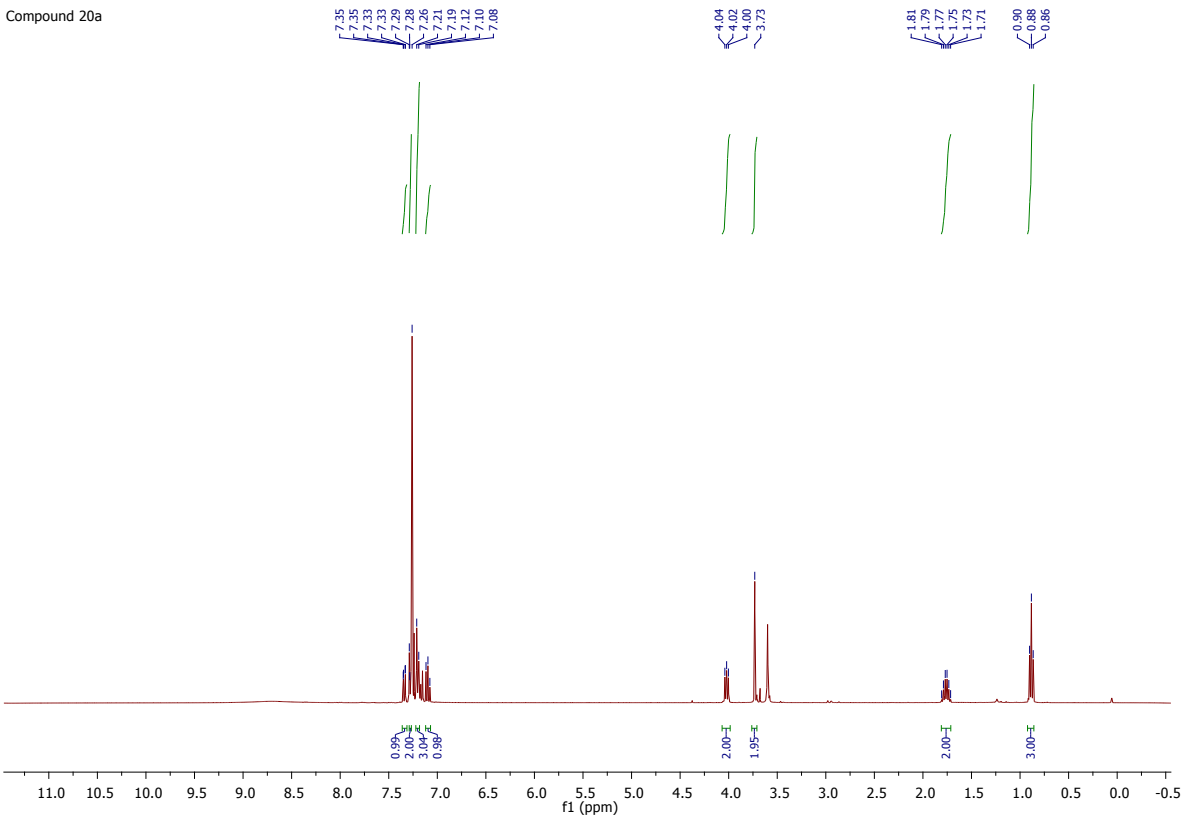
Compound 19i



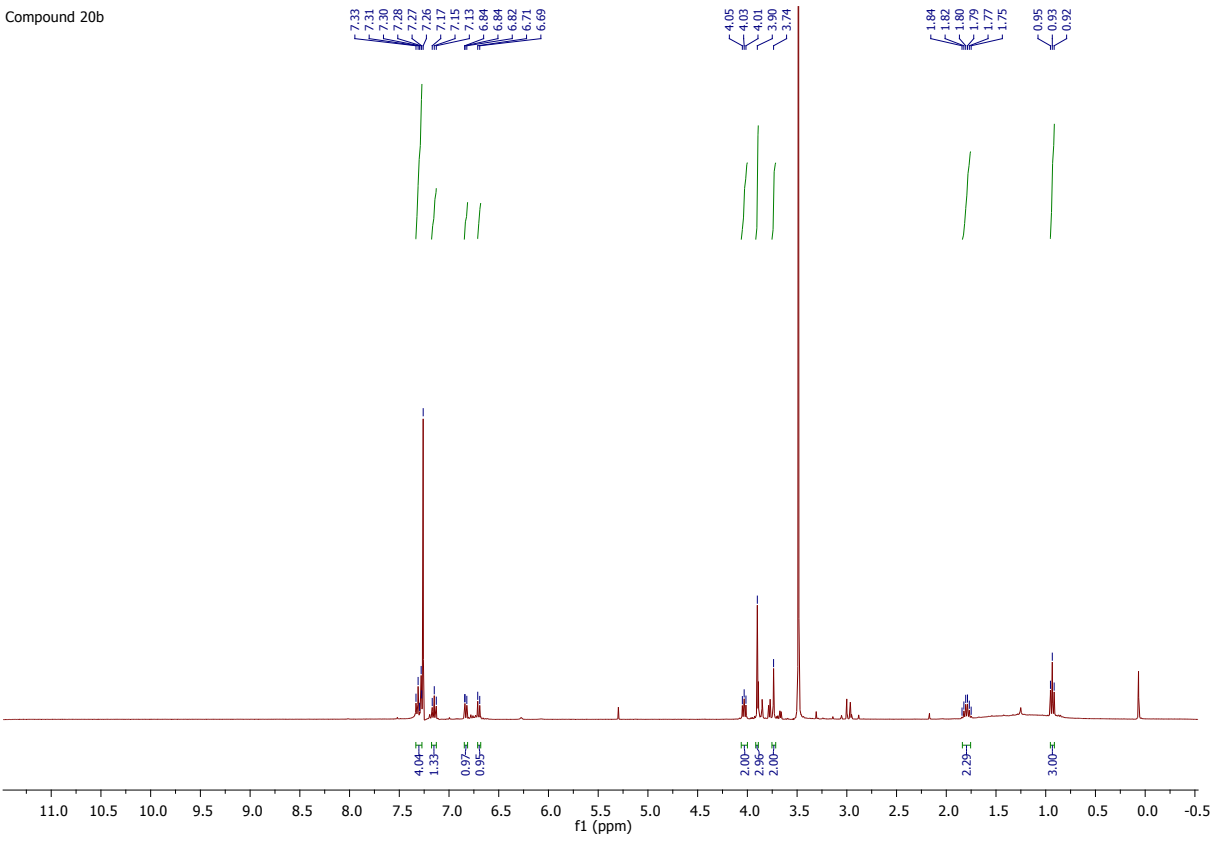
Compound 19j



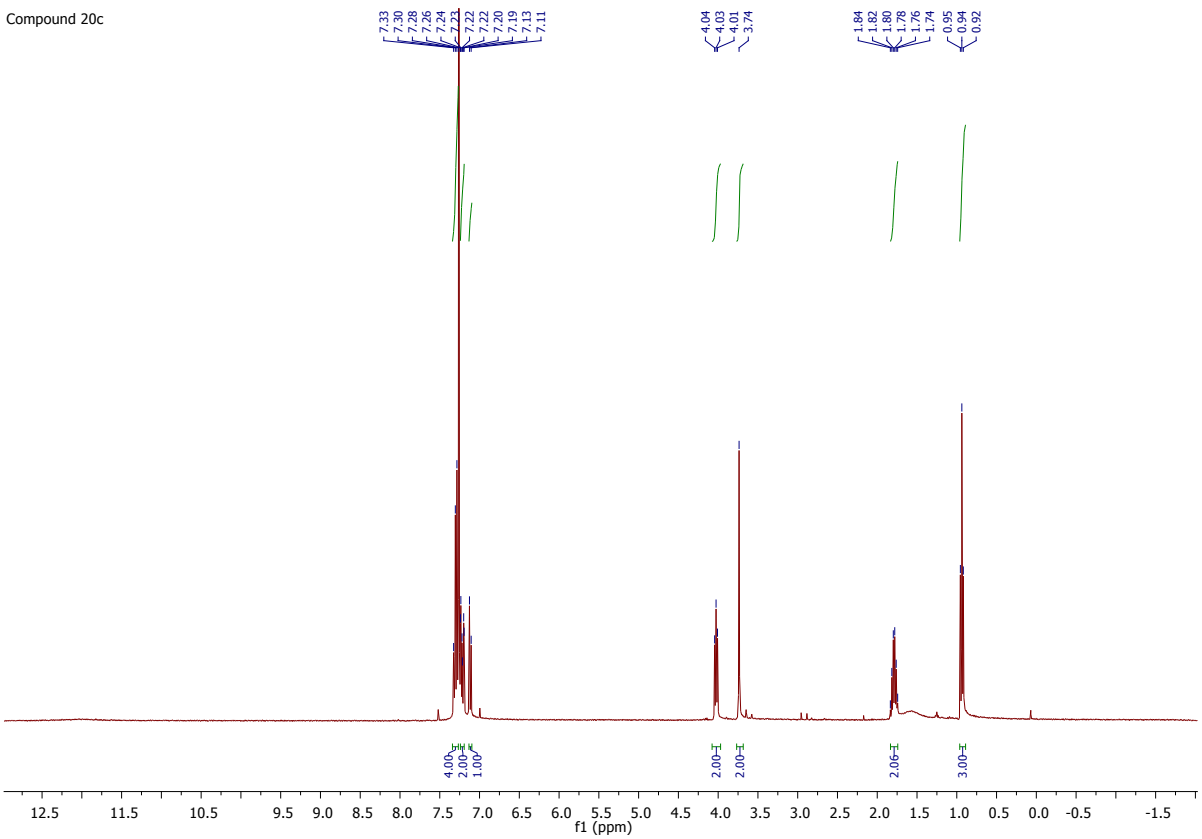
Compound 20a



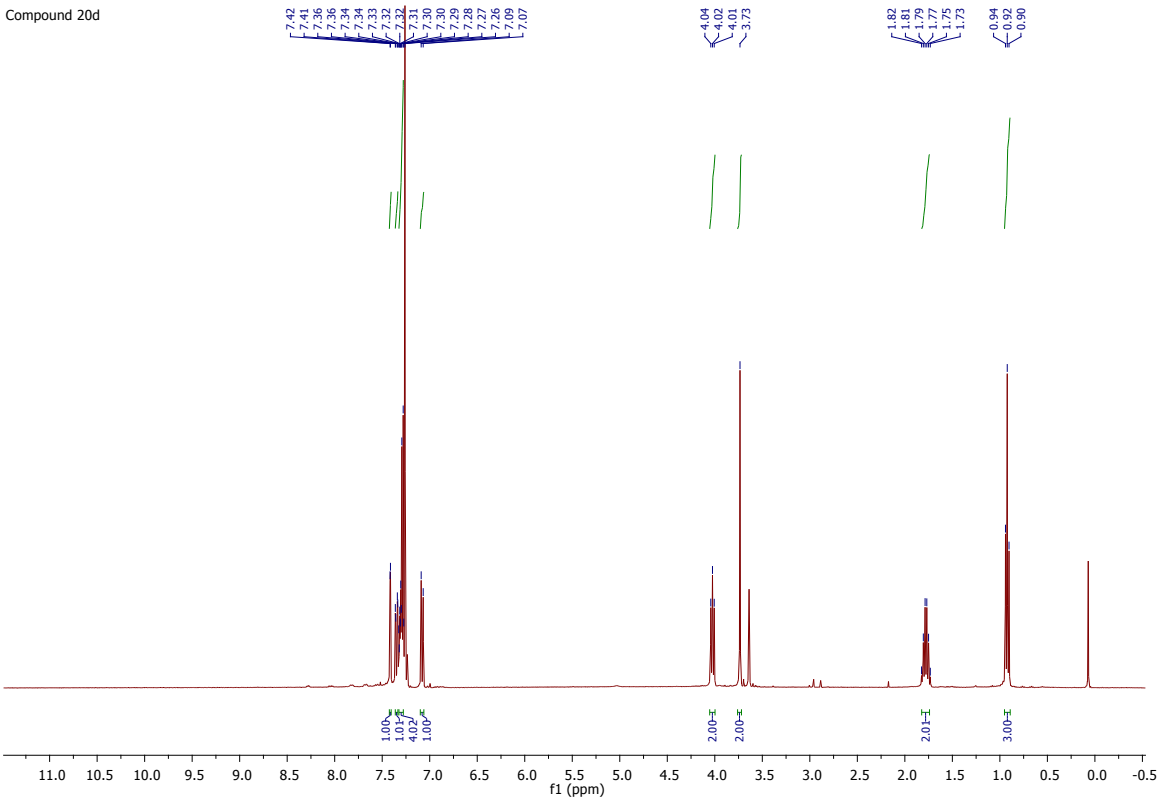
Compound 20b



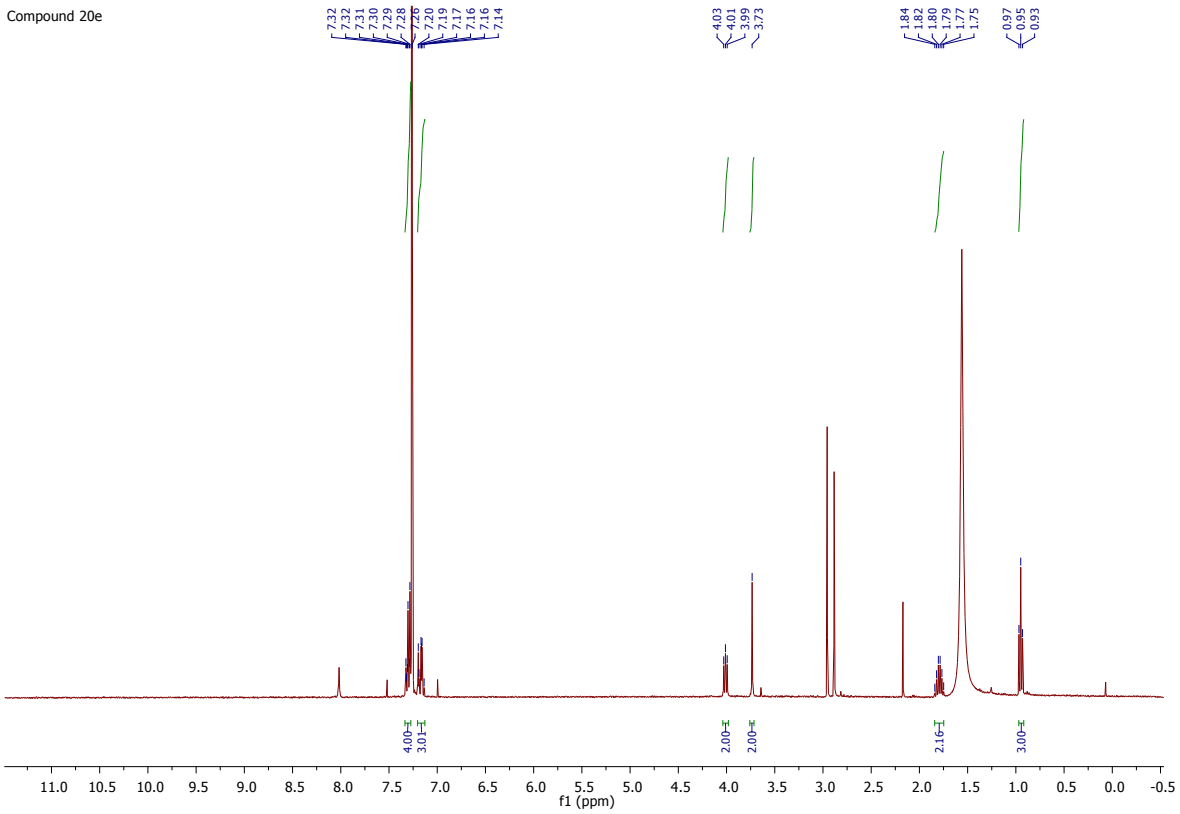
Compound 20c



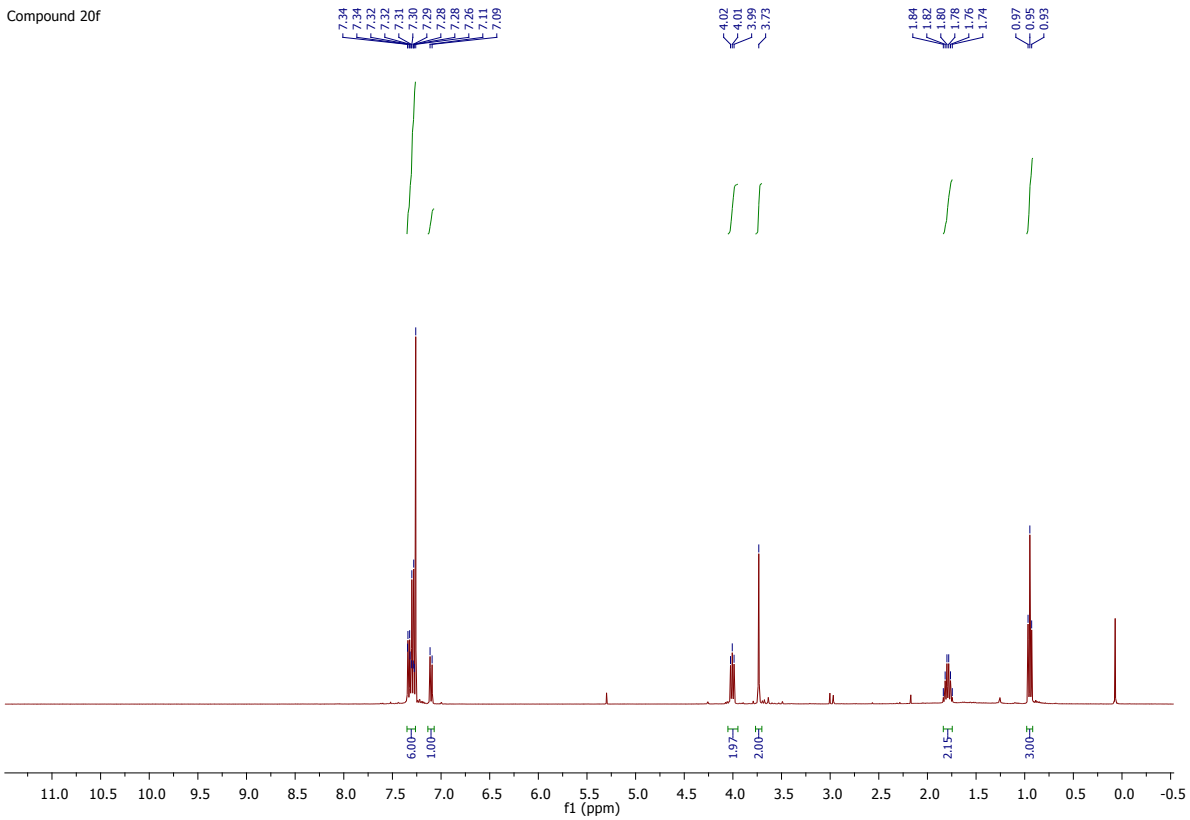
Compound 20d



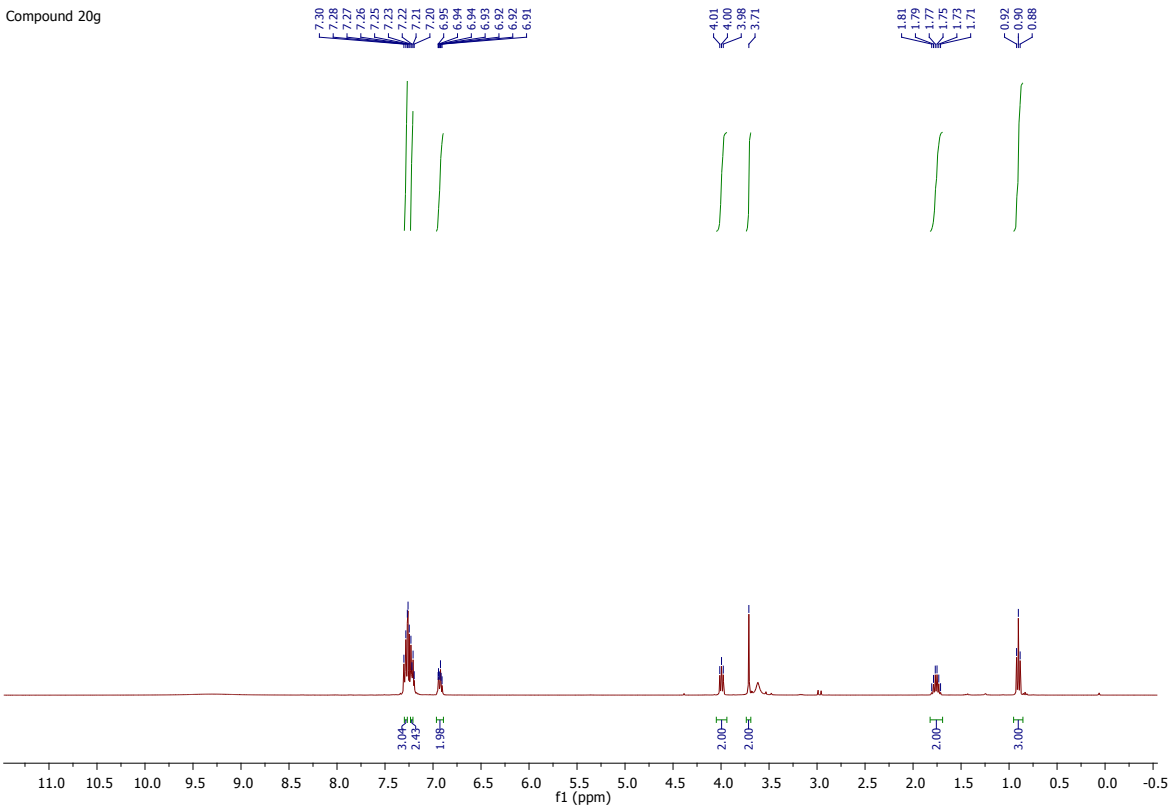
Compound 20e



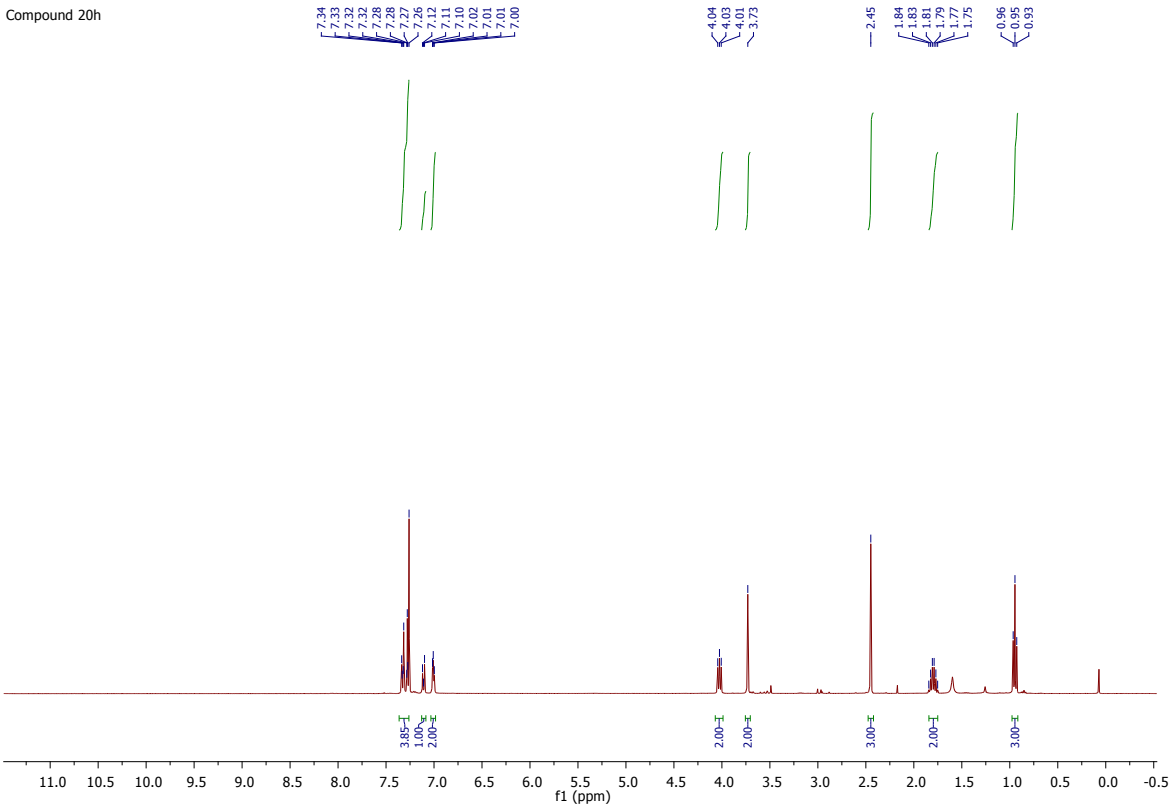
Compound 20f



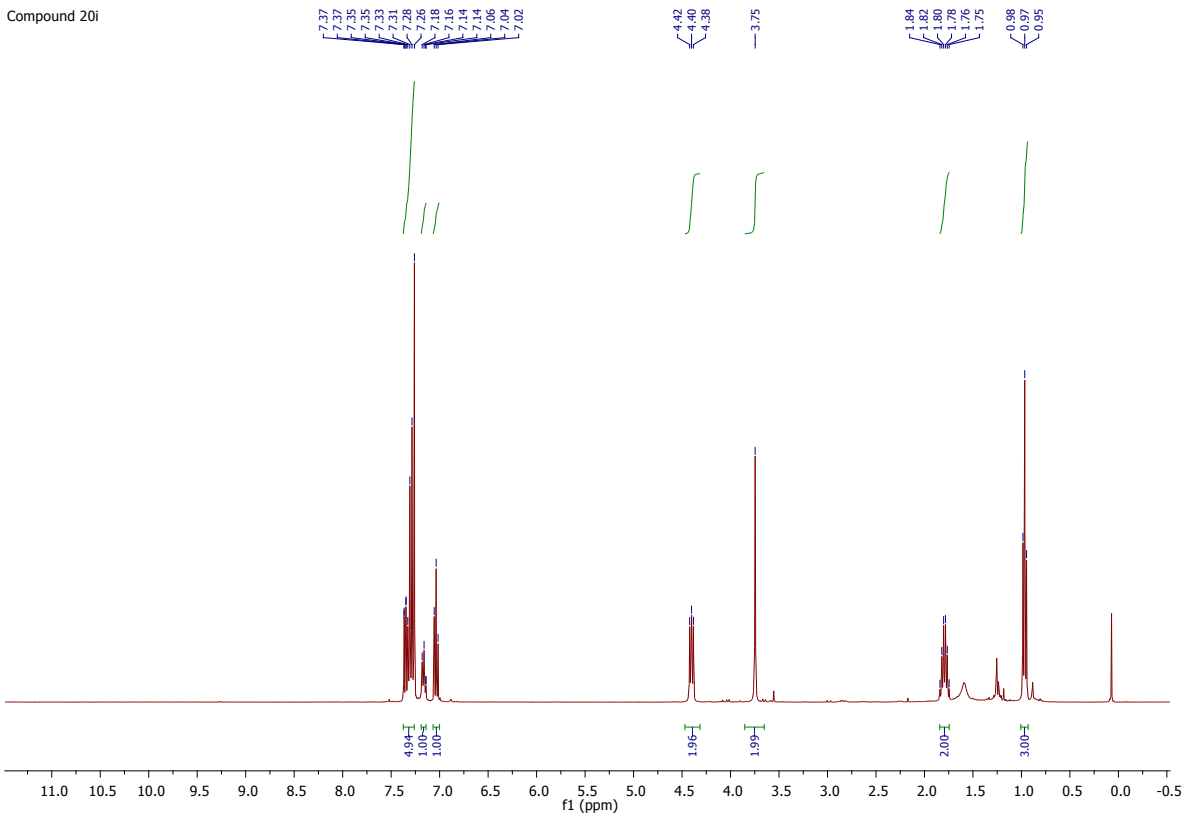
Compound 20g



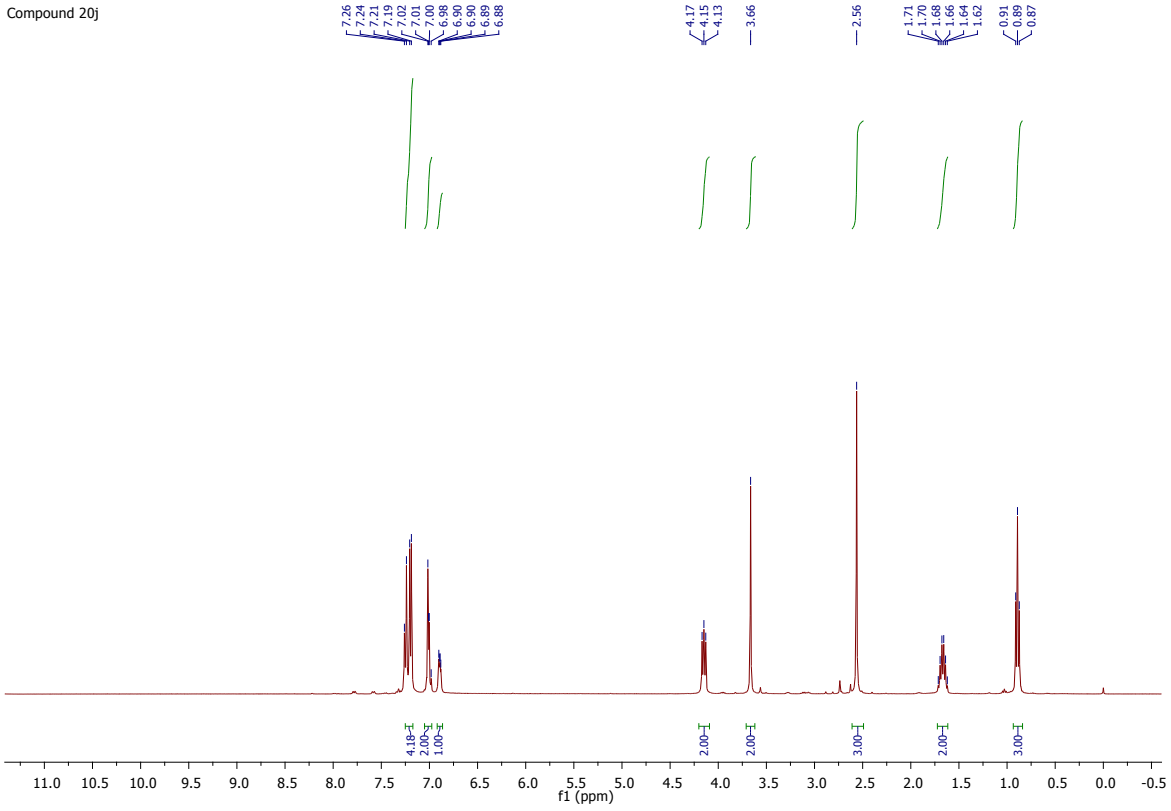
Compound 20h



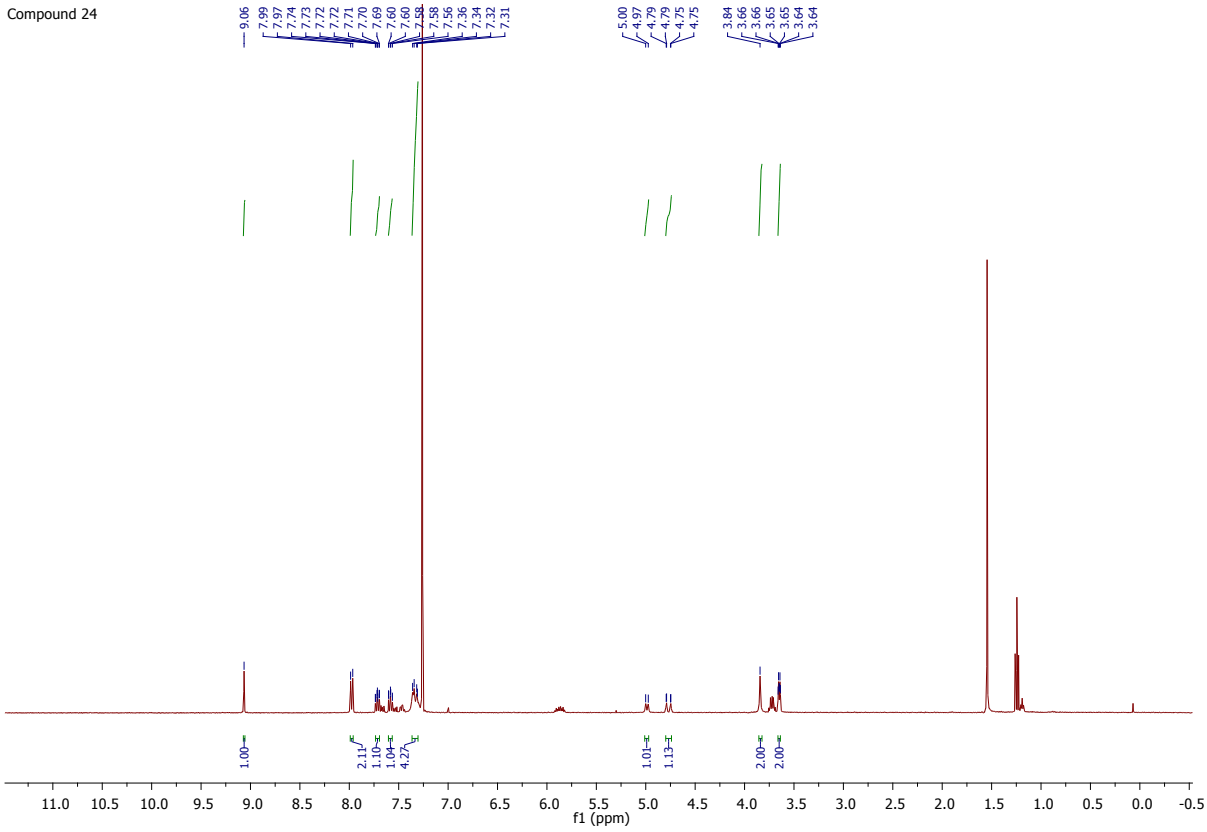
Compound 20i



Compound 20j



Compound 24


9.06
7.99
7.97
7.74
7.73
7.72
7.72
7.71
7.70
7.69
7.60
7.60
7.58
7.58
7.56
7.36
7.34
7.32
7.31
5.00
4.97
4.79
4.79
4.75
4.75
3.84
3.66
3.66
3.65
3.65
3.64
3.64
1.00
2.11
1.10
1.04
4.22
1.01
1.13
2.00
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

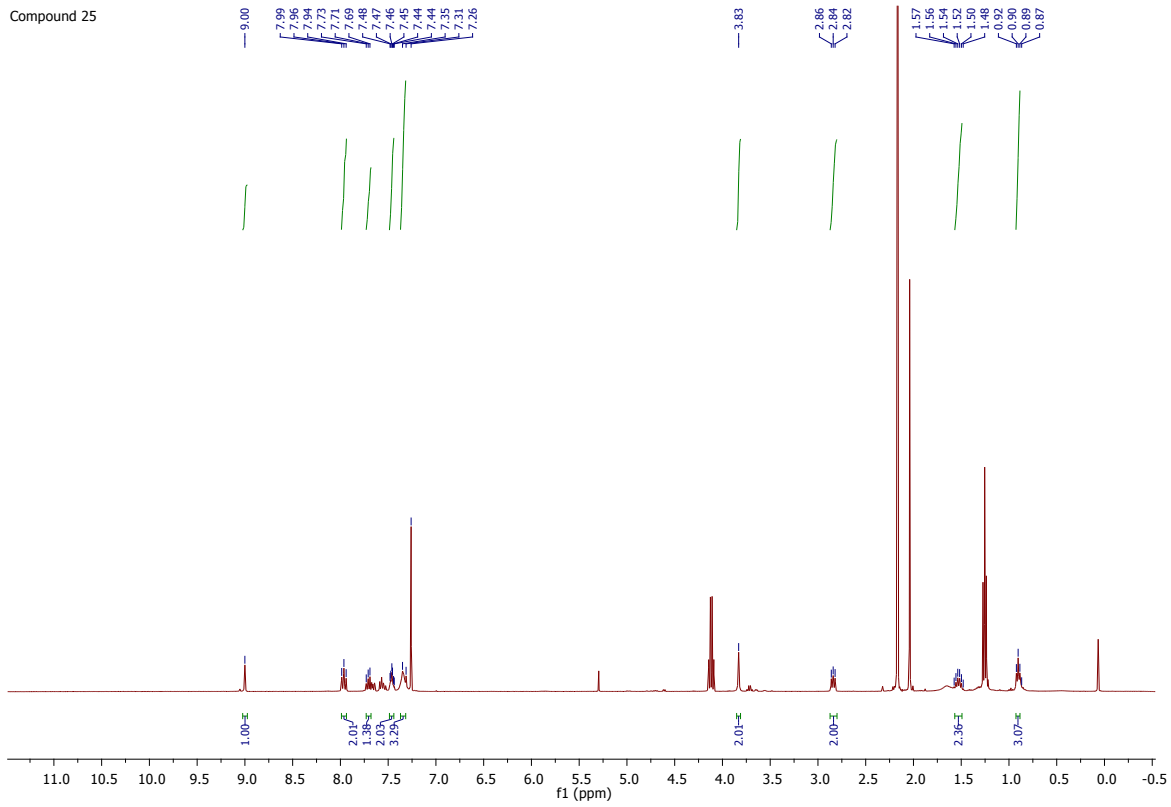
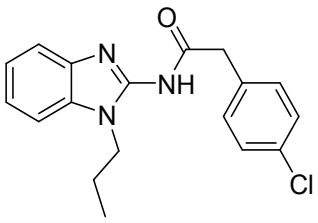
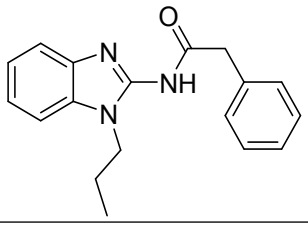
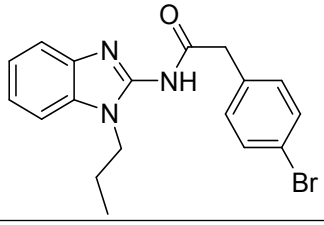
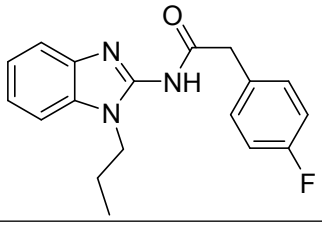
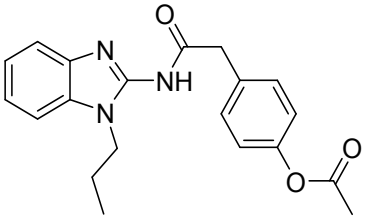
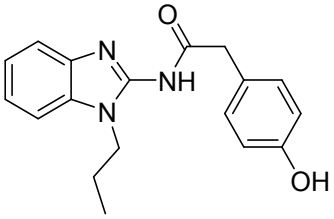
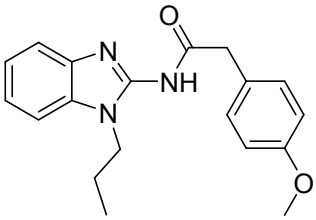
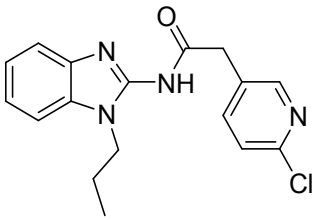
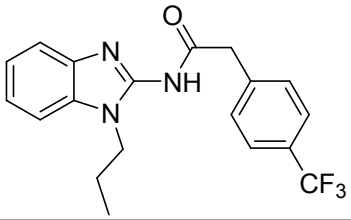
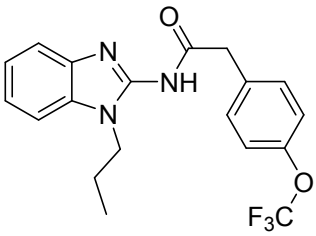
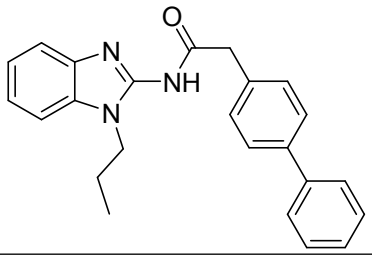
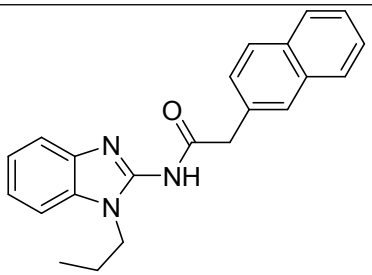
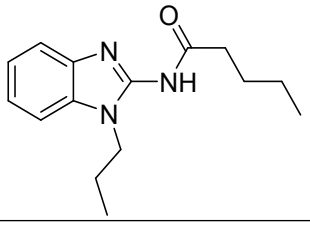
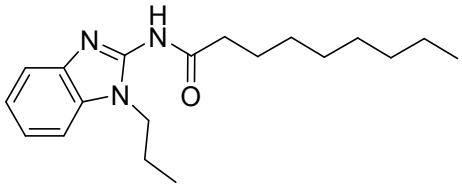
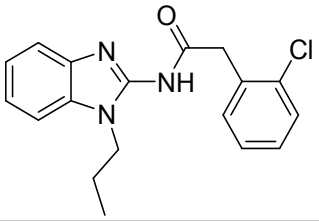
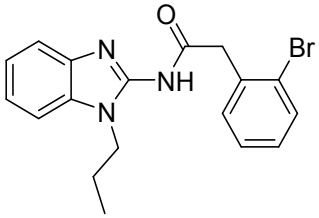
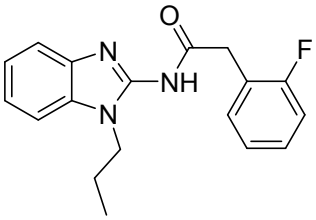
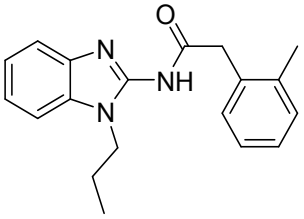
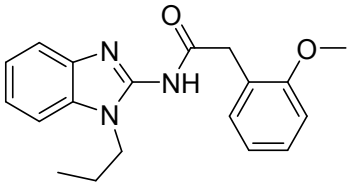
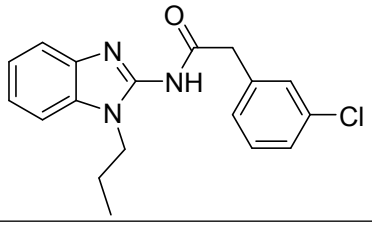
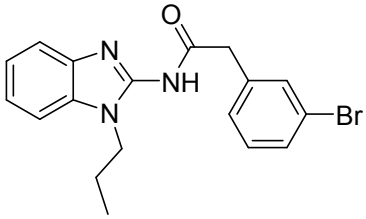
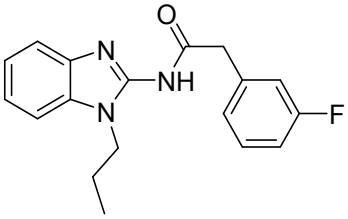
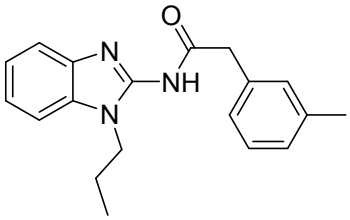
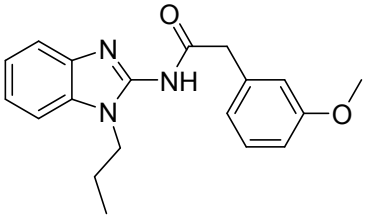
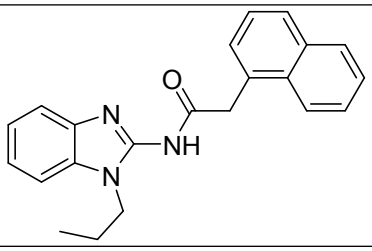
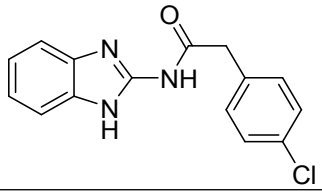
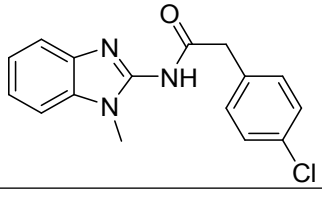


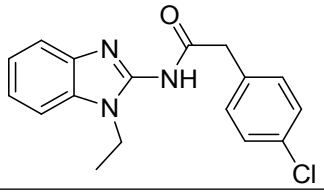
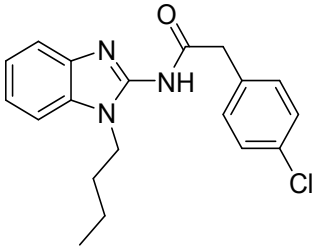
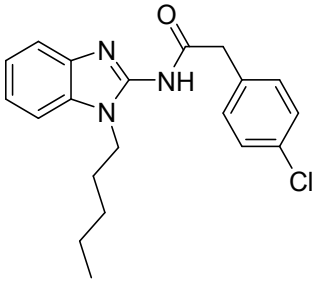
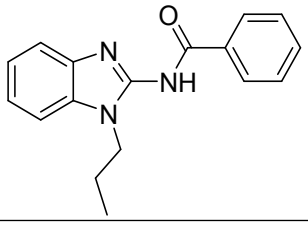
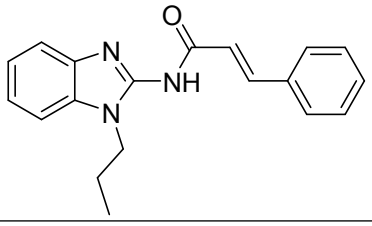
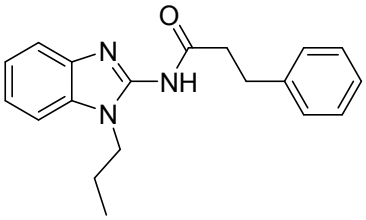
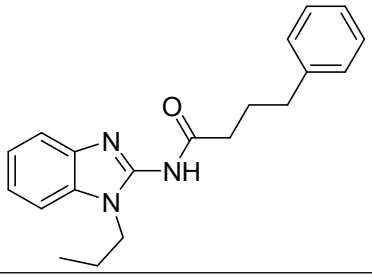
Table 1: LiPE calculations

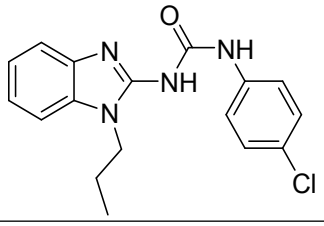
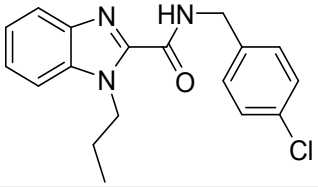
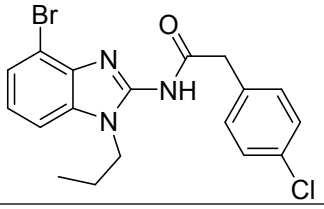
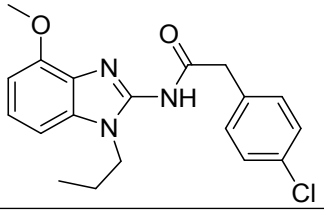
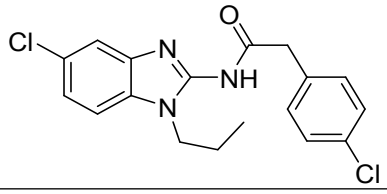
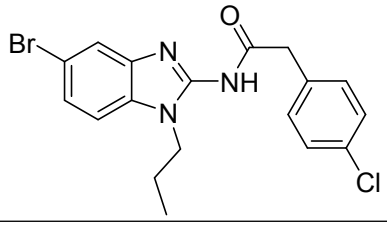
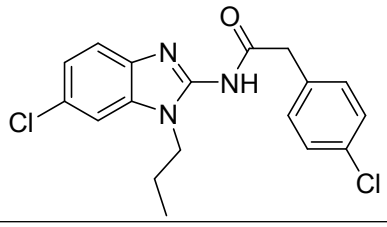
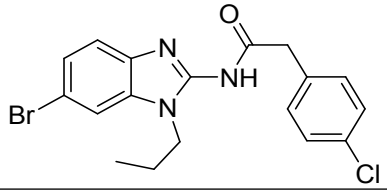
#	Structure	Activity (*T. cruzi* pIC_{50})	Log P*	LipE= pIC50- log P
1		5.7	4.7	1
4a		5.4	4.1	1.3
4b		5.7	4.9	0.8

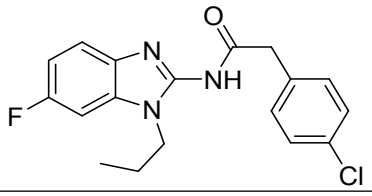
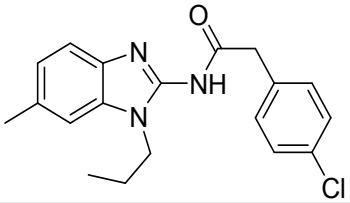
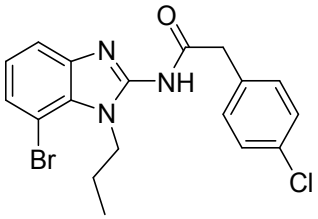
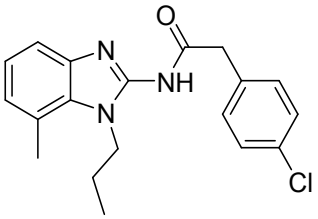
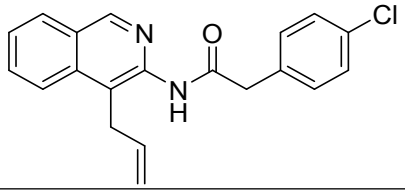
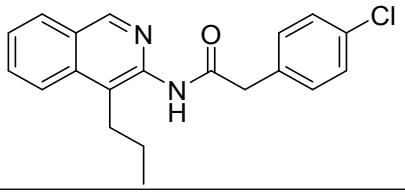
4c		5.6	4.3	1.3
4d		4.5	3.7	0.8
4e		4.4	3.8	0.6
4f		5.5	4	1.5
4g		5.1	3.7	1.4
4h		6	5	1
4i		6	5.6	0.4
4j		6	5.8	0.2

4k		5.9	5.1	0.8
4l		4.9	3.9	1
4m		5.6	5.7	-0.1
4n		5.7	4.7	1
4o		5.8	4.9	0.9
4p		5.5	4.3	1.2
4q		5.6	4.6	1
4r		5.2	4	1.2

4s		5.8	4.7	1.1
4t		6	4.9	1.1
4u		5.7	4.3	1.4
4v		5.7	4.6	1.1
4w		5.4	4	1.4
4x		6	5.1	0.9
5a		4.3	3.6	0.7
5b		5.5	3.8	1.7

5c		5.6	4.2	1.4
5d		5.8	5.2	0.6
5e		6	5.6	0.4
6a		5.3	4.1	1.2
6b		5.9	4.6	1.3
6c		5.3	4.6	0.7
6d		5.8	5	0.8

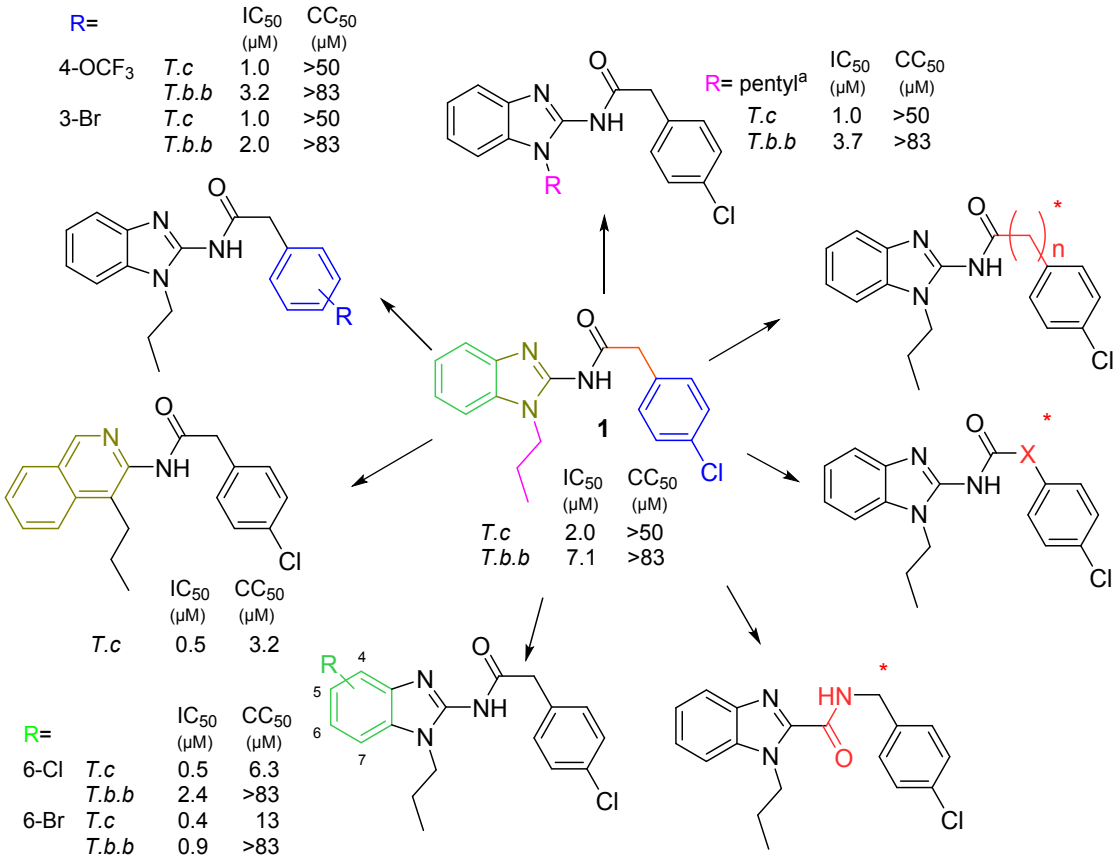
9		5.6	4.8	0.8
15		5	4.1	0.9
20a		5	5.5	-0.5
20b		5.5	4.6	0.9
20c		6.3	5.3	1
20d		6.1	5.5	0.6
20e		6.3	5.3	1
20f		6.4	5.5	0.9

20g		5.9	4.9	1
20h		-	5.2	-
20i		-	5.5	-
20j		5.9	5.2	0.7
24		4.7	5.1	-0.4
25		6.3	5.4	0.9

Summary of chemical space investigated

Figure 1 depicts a summary of the exploration surrounding our initial hit discussed in the main paper. The most improved analogues active against both *T.cruzi* and *T.b. brucei* have been listed below. A summary of SAR indicating the required features for the scaffold are shown in Figure 2. This further suggests which chemical space that cannot be altered and which should be explored further.

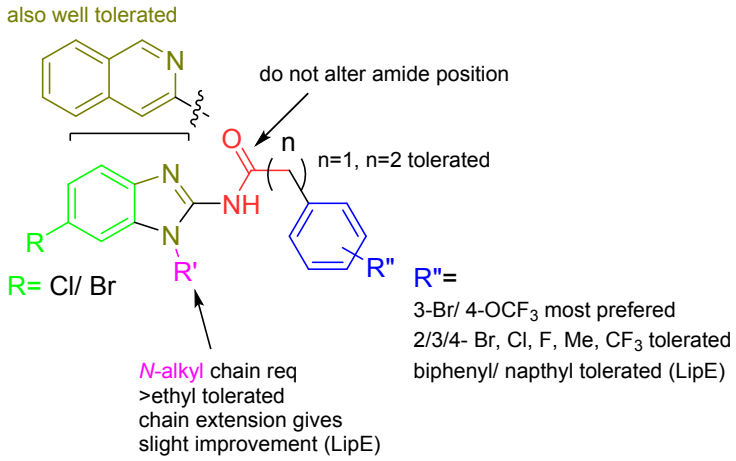
Figure 1: Summary of investigation with most improved analogues listed



*.No significant improvement in potency was made in this chemical space

a. Improvement most likely due to the LipE effect as discussed in main paper

Figure 2: Summary of SAR observed around Compound 1



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