Easy access to Ugi-derived Isatin-peptoids and their potential as small-molecule anticancer agents

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1. Experimental Section

1.1. General Remarks

All reagents were obtained from Sigma–Aldrich, Acros, Alfa Aesar and TCI and were used as received. Solvents were used as received. Reactions were conducted in round-bottom flasks, or in a Radley's® 12-position carousel reactor, or in vials or beakers. Microwave reactions were conducted with a Biotage Initator+ Microwave System with an automated position system. Column chromatography was carried out on silica gel (Carlo Erba, 40-63 μm, 60Å). Thin-layer chromatography (TLC) was carried out on aluminium-backed Kieselgel 60 F254 plates (Merck and Macherey–Nagel). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. NMR spectra were recorded with a Bruker Avance III instrument (400 MHz). Chemical shifts (δ) are given in parts per million (ppm) with respect to the solvent ($CDCl_3$, ^1H: δ = 7.26 ppm, ^{13}C: δ = 77.2 ppm). Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. Splitting patterns are reported as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad). Mass spectra (MS) were recorded with a quadrupole mass spectrometer Waters ZQ4000 (Chemistry department, University of Salamanca). The ionization was performed by ESI and the samples were infused in methanol.

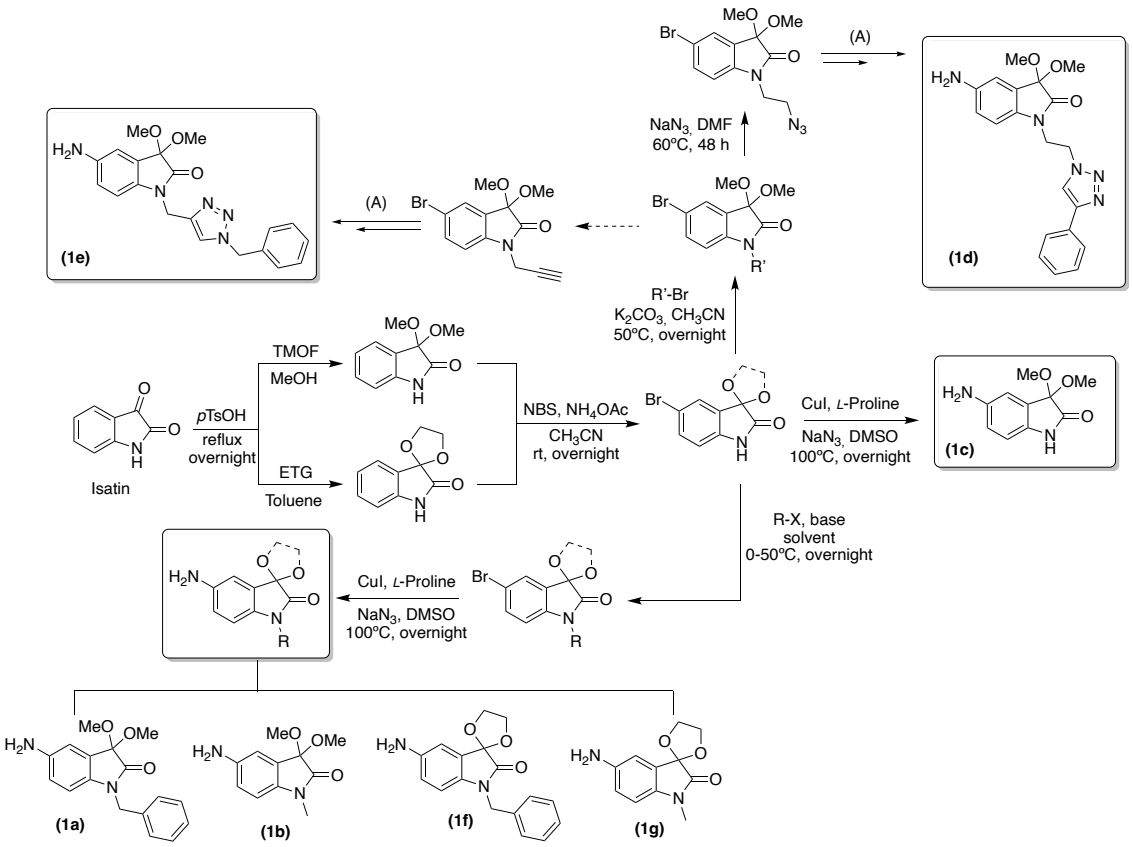
ETG: ethylene glycol; NBS: N-bromosuccinimide; TMOF: trimethyl orthoformate; DMF: dimethylformamide; DMSO: dimethyl sulfoxide. TFA: trifluoroacetic acid.

1.2. Synthesis of 5-Amino-3,3-protected-oxindole Derivatives (1)

The synthesis and characterization of nearly all the 5-amino-3,3-protected-oxindole derivatives **(1)** was already reported in the literature by our group[1,2]. Similar procedures were implemented to achieve compounds **(1a-f)**. A general scheme is given in Scheme S1.

5-Amino-1-methylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **(1g)**: In a Radley's® 12-position carousel reactor under a nitrogen atmosphere was added 5-bromo-1-methylspiro[indoline-3,2'-[1,3]dioxolan]-2-one[2] (716 mg, 2.5 mmol), CuI (476 mg, 2.5 mmol, 1 equiv.), *L*-proline (374 mg, 3.3 mmol, 1.3 equiv.), NaN_3 (325 mg, 5.0 mmol, 2 equiv.) and DMSO (5 mL) and the reaction mixture stirred at 100ºC, overnight and monitored by TLC. The reaction was cool down and quenched by the addition of NH_4Cl aq. sat. solution (10 mL) and AcOEt (10 mL). This biphasic mixture was left stirring 1 hour vigorously, at room temperature. The resulting reaction mixture was filtered through a porous plate glass funnel packed with a celite layer and washed with AcOEt and water. The filtrate was extracted with AcOEt, and the combined organic phases washed with *brine* solution. After being dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure the crude product was purified by silica gel flash chromatography using AcOEt as eluent. The corresponding 5-amino-1-methylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **(1g)** (276.3 mg, 50% yield) was obtained as a pale yellow oily solid. ^1H

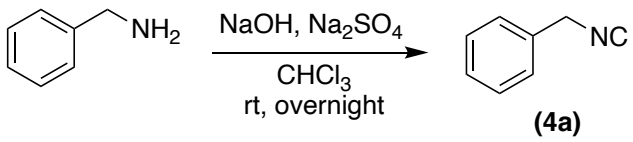
NMR ($CDCl_3$, 400 MHz) δ: 6.75-6.74 (m, 1H, Ar), 6.67-6.64 (m, 1H, Ar), 6.58-6.56 (m, 1H, Ar), 4.57-4.54 (m, 2H, CH_2), 4.28-4.25 (m, 2H, CH_2), 3.47 (s br, 2H, NH_2), 3.05 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.0, 143.0, 136.4, 125.0, 117.3, 112.8, 109.4, 102.6, 65.9, 25.9.



Scheme S1. General synthetic path to access the 5-amino-3,3-protected-oxindole derivatives **(1)**.[1,2] (A): 1. $Cu(OAc)_2$, ascorbic acid, DMF, MW, 120ºC, 15 min.; 2. CuI, *L*-proline, NaN_3, DMSO, 100ºC, overnight.

1.3. Synthesis of Benzyl Isocyanide (4a)

Due to the high cost and difficulty in acquiring commercially available benzyl isocyanide, we decided to synthesize it using literature protocols.[3]
Important observation: Due to the unpleasant and strong odour of this reagent, it is important to manage everything in a fume hood and isolate the waste (organic solvents and inorganic solids, pipets, gloves, etc), retaining them in closed containers.



Benzyl isocyanide **(4a)**: In a round-bottom flask was added benzylamine (0.55 mL, 5 mmol), NaOH (2.4 g, 60 mmol, 12 equivalents), Na_2SO_4 (1.0 g, 7 mmol,

1.4 equivalents) and $CHCl_3$ (20 mL). The reaction was left stirring overnight. A porous plate glass funnel was packed with a layer of celite and a layer of SiO_2 gel. The reaction mixture was filtered through the glass funnel and washed with hexane:AcOEt (9:1) mixture. The solvent was evaporated under reduced pressure and the benzyl isocyanide **(4a)** (258.2 mg, 44% yield) was obtained as a pale stinky yellow low viscous liquid. It was stored in a closed glass vial in the freezer (-20ºC) and used in all the Ugi4CRs described in this work. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.32 (m, 5H, Ar), 4.65 (s, 2H, CH_2). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 157.7, 132.7, 129.1, 128.5, 126.7, 45.7.

1.4. The Ugi4CR: General Procedure

In a glass vial with a magnetic stirrer was added the corresponding 5-amino-3,3-protected-oxindole derivative **(1)** (1 equivalent), the carboxylic acid **(2)** (1.5 equivalents), the aldehyde **(3)** (1.5 equivalents), the isocyanide **(4)** (1.5 equivalents), ZnF_2 (10 mol%) and MeOH (2-3 mL). The vial was closed with a plastic cap (Figure S1) and the reaction mixture was left stirring for 2 hours at room temperature. The solvent was evaporated under reduced pressure and the crude reaction mixture purified in a short chromatographic glass column with SiO_2 flash using CH_2Cl_2:AcOEt (5:1), (1:1) as eluents.

The reagent scope for the Ugi4CR can be seen in Figure S2.

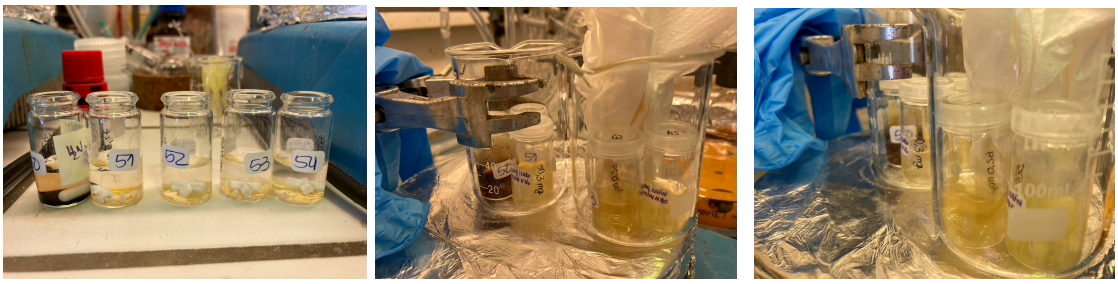


Figure S1. The Ugi4CRs in glass vials with plastic caps.

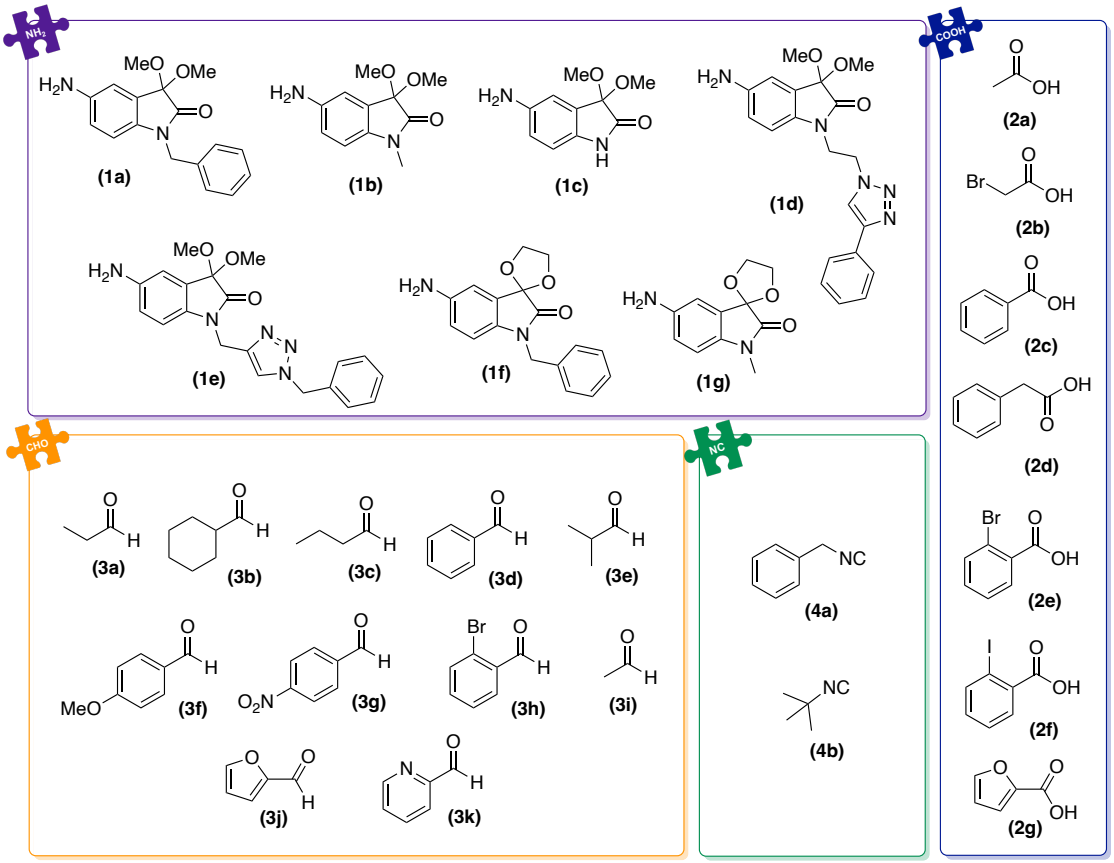


Figure S2. Reagent scope for the Ugi4CR.

N-Benzyl-2-(*N*-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)butanamide **(5aaaa)**: **(1a)** (73.7 mg, 0.25 mmol), **(2a)** (22 µL, 0.38 mmol, 1.5 equivalents), **(3a)** (27 µL, 0.38 mmol, 1.5 equivalents), **(4a)** (46 µL, 0.38 mmol, 1.5 equivalents), ZnF_2 (2.6 mg, 0.025 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5aaaa)** as a pale yellow foam type solid (116.2 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.28 (m, 10H, Ar), 7.13 (s, 1H, Ar), 7.03 (s br, 1H, NH), 6.95-6.93 (d, *J*= 8 Hz, 1H, Ar), 6.67-6.65 (d, *J*= 8 Hz, 1H, Ar), 4.94-4.90 (m, 1H, CH), 4.84 (s, 2H, CH_2), 4.45-4.42 (m, 2H, CH_2), 3.59 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 1.81 (s, 3H, CH_3), 1.62-1.55 (m, 1H, CH_2), 1.35-1.27 (m, 1H, CH_2), 0.89-0.86 (t, *J*= *6* Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 170.6, 171.0, 172.2, 142.5, 138.5, 135.0, 134.1, 131.8, 129.1, 128.8, 128.1, 127.7, 127.5, 126.2, 96.6, 60.0, 51.0, 50.9, 43.8, 43.5, 23.4, 22.1, 11.0. HRMS (ESI) m/z: calculated for $C_{30}H_{34}O_5N_3$ $[M]^+$ 516.2493, found 516.2487.

N-Benzyl-2-(N-(3,3-dimethoxy-1-methyl-2-oxoindolin-5-yl)acetamido)butanamide **(5baaa)**: **(1b)** (82.3 mg, 0.37 mmol), **(2a)** (32 µL, 0.56 mmol, 1.5 equivalents), **(3a)** (40 µL, 0.56 mmol, 1.5 equivalents), **(4a)** (68 µL, 0.56 mmol, 1.5 equivalents), ZnF_2 (4.0 mg, 0.037 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5baaa)** as a pale yellow foam type solid (104.9 mg, 65% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.27 (m, 5H, Ar),

7.14 (s, 1H, Ar), 7.06-7.05 (m, 2H, NH+Ar), 6.78-6.76 (d, *J*= 8 Hz, 1H, Ar), 4.96-4.92 (m, 1H, CH), 4.46-4.44 (m, 2H, CH_2), 3.55 (s br, 3H, OCH_3), 3.50 (s br, 3H, OCH_3), 3.16 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.63-1.57 (m, 1H, CH_2), 1.37-1.31 (m, 1H, CH_2), 0.91-0.88 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.2, 170.7, 170.7, 143.4, 138.5, 134.0, 132.0, 128.8, 127.8, 127.5, 126.2, 96.9, 60.0, 51.0, 50.8, 43.6, 26.1, 23.4, 22.2, 11.0. HRMS (ESI) m/z: calculated for $C_{24}H_{30}O_5N_3$ $[M]^+$ 440.218, found 440.2178.

N-Benzyl-2-(N-(3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)butanamide **(5caaa)**: **(1c)** (97.9 mg, 0.47 mmol), **(2a)** (40 µL, 0.71 mmol, 1.5 equivalents), **(3a)** (51 µL, 0.71 mmol, 1.5 equivalents), **(4a)** (86 µL, 0.71 mmol, 1.5 equivalents), ZnF_2 (4.9 mg, 0.047 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5caaa)** as a pale yellow foam type solid (102.6 mg, 58% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 9.06 (s br, 1H, NH), 7.33-7.20 (m, 8H, Ar), 7.11 (s, 1H, Ar), 6.96 (s br, 1H, NH), 6.74 (s br, 1H, Ar), 4.97-4.93 (m, 1H, CH), 4.50-4.40 (m, 2H, CH_2), 3.50 (s, 3H, OCH_3), 3.46 (s br, 3H, OCH_3), 1.84 (s, 3H, CH_3), 1.65-1.58 (m, 1H, CH_2), 1.38-1.33 (m, 1H, CH_2), 0.92-0.88 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.4, 170.8, 141.0, 138.4, 134.4, 133.7, 131.9, 130.6, 128.8, 128.7, 127.8, 127.6, 127.5, 126.5, 96.9, 60.1, 50.9, 50.8, 43.6, 23.4, 22.3, 11.0. HRMS (ESI) m/z: calculated for $C_{23}H_{26}O_5N_3$ $[M]^-$ 424.18779, found 424.1881.

N-Benzyl-2-(N-(3,3-dimethoxy-2-oxo-1-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)indolin-5-yl)acetamido)butanamide **(5daaa)**: **(1d)** (39.1 mg, 0.1 mmol), **(2a)** (10 µL, 0.15 mmol, 1.5 equivalents), **(3a)** (11 µL, 0.15 mmol, 1.5 equivalents), **(4a)** (19 µL, 0.15 mmol, 1.5 equivalents), ZnF_2 (1.1 mg, 0.015 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5daaa)** as a pale yellow foam type solid (37 mg, 60% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.64-7.62 (d, *J*= 8 Hz, 1H, Ar), 7.59 (s, 1H, CH), 7.35-7.23 (m, 8H, Ar), 7.05 (s, 1H, Ar), 7.00 (s br, 1H, NH), 6.84-6.82 (d, *J*= 8 Hz, 1H, Ar), 6.41-6.39 (d, *J*= 8 Hz, 1H, Ar), 4.83-4.79 (m, 1H, CH), 4.71-4.68 (m, 2H, CH_2), 4.45-4.35 (m, 2H, CH_2), 4.16-4.15 (m, 2H, CH_2), 3.54 (s, 3H, OCH_3), 3.47 (s br, 3H, OCH_3), 1.50 (s, 3H, CH_3), 1.39 (s br, 1H, CH_2), 1.12 (s br, 1H, CH_2), 0.74 (s br, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.0, 171.1, 170.6, 148.1, 141.6, 138.4, 134.2, 132.0, 130.0, 128.9, 128.7, 128.4, 127.7, 127.4, 126.3, 125.5, 125.3, 121.0, 96.2, 59.8, 50.9, 50.8, 47.5, 43.4, 40.3, 22.9, 22.0, 10.8. HRMS (ESI) m/z: calculated for $C_{33}H_{37}O_5N_6$ $[M]^+$ 597.28199, found 597.2814.

N-Benzyl-2-(N-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)butanamide **(5eaaa)**: **(1e)** (84.7 mg, 0.22 mmol), **(2a)** (19 µL, 0.33 mmol, 1.5 equivalents), **(3a)** (24 µL, 0.33 mmol, 1.5 equivalents), **(4a)** (40 µL, 0.33 mmol, 1.5 equivalents), ZnF_2 (2.3 mg, 0.022 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5eaaa)** as a white foam type solid (55.8 mg, 43% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (s, 1H, CH), 7.33-7.22 (m, 11H, Ar), 7.10-7.08 (d, *J*= 8 Hz, 2H, Ar), 7.02 (s br, 1H, NH), 5.44 (s, 2H, CH_2), 4.93-4.88 (m, 2H, CH_2), 4.73 (s, 1H, CH), 4.47-4.36 (m, 2H, CH_2), 3.50 (s br, 3H, OCH_3), 3.42 (s br, 3H, OCH_3), 1.78 (s, 3H, CH_3), 1.56-1.54 (m, 1H, CH_2), 1.32-1.28 (m, 1H, CH_2), 0.88-0.84 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 176.6, 172.1, 170.5, 142.5, 141.9, 138.4, 134.4, 134.2, 134.1, 132.0, 129.2, 129.1, 128.9, 128.7, 128.3, 128.2, 127.7, 127.4, 126.1,

122.8, 110.5, 96.4, 59.8, 54.4, 50.9, 50.7, 43.4, 35.2, 23.3, 22.1, 10.9. HRMS (ESI) m/z: calculated for $C_{33}H_{37}O_5N_6$ $[M]^+$ 597.28199, found 597.2822.

N-Benzyl-2-(N-(1-benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)butanamide **(5faaa)**: **(1f)** (103 mg, 0.35 mmol), **(2a)** (30 µL, 0.52 mmol, 1.5 equivalents), **(3a)** (38 µL, 0.52 mmol, 1.5 equivalents), **(4a)** (64 µL, 0.52 mmol, 1.5 equivalents), ZnF_2 (3.6 mg, 0.035 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5faaa)** as a pale yellow foam type solid (126.4 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.25 (m, 9H, Ar), 7.19 (s br, 1H, NH), 6.96-6.94 (d, *J*= 8 Hz, 1H, Ar), 6.62-6.60 (d, *J*= 8 Hz, 1H, Ar), 4.85-4.83 (m, 1H, CH), 4.80 (s, 2H, CH_2), 4.63-4.57 (m, 2H, CH_2), 4.45-4.44 (d, *J*= 4 Hz, 2H, CH_2), 4.37-4.28 (m, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.62-1.56 (m, 1H, CH_2), 1.38-1.31 (m, 1H, CH_2), 0.89-0.86 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.4, 172.0, 170.8, 143.8, 138.4, 134.9, 134.8, 132.8, 129.0, 128.6, 127.9, 127.6, 127.3, 127.3, 126.2, 110.1, 101.8, 65.9, 65.9, 60.3, 43.6, 43.4, 23.3, 22.4, 10.9. HRMS (ESI) m/z: calculated for $C_{30}H_{32}O_5N_3$ $[M]^+$ 514.23365, found 514.2336.

N-Benzyl-2-(N-(1-methyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)butanamide **(5gaaa)**: **(1g)** (72.5 mg, 0.33 mmol), **(2a)** (29 µL, 0.5 mmol, 1.5 equivalents), **(3a)** (36 µL, 0.5 mmol, 1.5 equivalents), **(4a)** (60 µL, 0.5 mmol, 1.5 equivalents), ZnF_2 (3.4 mg, 0.033 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5gaaa)** as a pale yellow foam type solid (79.4 mg, 55% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.24 (m, 5H, Ar), 7.17 (s br, 1H, NH), 7.08-7.06 (m, 2H, Ar), 6.72-6.70 (d, *J*= 8 Hz, 1H, Ar), 4.86-4.82 (m, 1H, CH), 4.54-4.51 (m, 2H, CH_2), 4.45-4.43 (m, 2H, CH_2), 4.28-4.25 (m, 2H, CH_2), 3.09 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.62-1.54 (m, 1H, CH_2), 1.38-1.32 (m, 1H, CH_2), 0.88-0.85 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.3, 172.1, 170.8, 144.7, 138.4, 134.9, 133.0, 128.6, 127.7, 127.3, 126.1, 125.0, 109.1, 101.8, 65.9, 65.8, 43.5, 26.0, 23.3, 22.4, 10.9. HRMS (ESI) m/z: calculated for $C_{24}H_{28}O_5N_3$ $[M]^+$ 438.20235, found 438.2021.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-2-bromoacetamido)butanamide **(5abaa)**: **(1a)** (76.7 mg, 0.26 mmol), **(2b)** (54.2 mg, 0.39 mmol, 1.5 equivalents), **(3a)** (28 µL, 0.39 mmol, 1.5 equivalents), **(4a)** (48 µL, 0.39 mmol, 1.5 equivalents), ZnF_2 (2.7 mg, 0.026 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5abaa)** as a white foam type solid (86.9 mg, 56% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.28 (m, 11H, Ar), 7.10-7.03 (m, 1H, Ar), 6.91 (s br, 1H, NH), 6.69 (s br, 1H, Ar), 4.87-4.84 (m, 3H, CH+CH_2), 4.47-4.38 (m, 2H, CH_2), 3.61-3.48 (m, 8H, OCH_3+CH_2), 1.58 (s br, 1H, CH_2), 1.34 (s br, 1H, CH_2), 0.89 (s br, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 170.8, 169.8, 168.2, 143.2, 138.2, 134.9, 132.4, 129.1, 128.8, 128.1, 127.9, 127.8, 127.6, 127.5, 97.0, 61.0, 51.1, 50.9, 43.7, 27.3, 22.2, 10.9. HRMS (ESI) m/z: calculated for $C_{30}H_{33}O_5N_3{}^{79}Br$ $[M]^+$ 594.15981, found 594.1595.

N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(1-(benzylamino)-1-oxobutan-2-yl)benzamide **(5acaa)**: **(1a)** (68.8 mg, 0.23 mmol), **(2c)** (44 mg, 0.36 mmol, 1.5 equivalents), **(3a)** (26 µL, 0.36 mmol, 1.5 equivalents), **(4a)** (44 µL, 0.36 mmol, 1.5 equivalents), ZnF_2 (2.4 mg, 0.023 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5acaa)** as a pale yellow foam type solid (131.6

mg, 99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.11-8.09 (d, *J*= 8 Hz, 1H, Ar), 7.62-7.58 (t, *J*= 8 Hz, 1H, Ar), 7.49-7.45 (t, *J*= 8 Hz, 2H, Ar), 7.33-7.29 (m, 5H, Ar), 7.27-7.22 (m, 3H, Ar), 7.19-7.11 (m, 4H, Ar), 7.01-7.00 (m, 1H, Ar), 6.96 (s br, 1H, NH), 6.51-6.49 (d, *J*= 8 Hz, 1H, Ar), 5.17-5.13 (m, 1H, CH), 4.77 (s, 2H, CH_2), 4.58-4.53 (dd, *J*= 14 Hz, 1H, CH_2), 4.45-4.40 (dd, *J*= 14 Hz, 1H, CH_2), 3.45 (s, 3H, OCH_3), 3.15-3.12 (s br, 3H, OCH_3), 1.84-1.77 (m, 1H, CH_2), 1.53-1.46 (m, 1H, CH_2), 0.96-0.92 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.1, 171.0, 170.7, 141.7, 138.5, 136.0, 135.0, 134.7, 133.7, 130.3, 120.8, 129.0, 128.8, 128.6, 128.3, 128.1, 128.0, 127.8, 127.5, 127.4, 126.9, 109.8, 96.8, 61.4, 50.9, 50.8, 43.7, 43.6, 22.2, 11.1. HRMS (ESI) m/z: calculated for $C_{35}H_{36}O_5N_3$ $[M]^+$ 578.26495, found 578.2646.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-2-phenylacetamido)butanamide **(5adaa)**: **(1a)** (65.6 mg, 0.22 mmol), **(2d)** (45 mg, 0.33 mmol, 1.5 equivalents), **(3a)** (24 µL, 0.33 mmol, 1.5 equivalents), **(4a)** (40 µL, 0.33 mmol, 1.5 equivalents), ZnF_2 (2.3 mg, 0.022 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5adaa)** as a white foam type solid (65.1 mg, 50% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.08 (m, 15H, Ar), 6.93 (s br, 2H, Ar), 6.79-6.77 (s br, 1H, NH), 6.66-6.55 (m, 1H, Ar), 4.96-4.92 (m, 1H, Ar), 4.86 (s, 2H, CH_2), 4.45 (s br, 1H, CH_2), 4.34-4.29 (m, 1H, CH_2), 3.57-3.54 (m, 4H, OCH_3+CH_2), 3.40-3.37 (m, 4H, OCH_3+CH_2), 1.59 (s br, 1H, CH_2), 1.31 (s br, 1H, CH_2), 0.87 (s br, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.7, 171.0, 170.4, 142.5, 138.3, 135.0, 134.6, 133.2, 132.2, 129.0, 128.7, 128.5, 128.0, 127.8, 127.5, 127.3, 126.9, 126.7, 126.5, 126.2, 110.4, 109.5, 96.7, 60.3, 50.9, 50.7, 43.6, 43.4, 41.8, 22.1, 10.9. HRMS (ESI) m/z: calculated for $C_{36}H_{36}O_5N_3$ $[M]^-$ 590.26604, found 590.2665.

N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(1-(benzylamino)-1-oxobutan-2-yl)-2-bromobenzamide **(5aeaa)**: **(1a)** (49.8 mg, 0.17 mmol), **(2e)** (50 mg, 0.25 mmol, 1.5 equivalents), **(3a)** (18 µL, 0.25 mmol, 1.5 equivalents), **(4a)** (30 µL, 0.25 mmol, 1.5 equivalents), ZnF_2 (1.8 mg, 0.017 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5aeaa)** as a white foam type solid (63 mg, 56% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36-7.23 (m, 9H, Ar), 7.19-7.17 (m, 4H, Ar), 7.08-6.98 (m, 4H, Ar+NH), 6.46-6.44 (d, *J*= 8 Hz, 1H, Ar), 5.11-5.08 (m, 1H, CH), 4.72 (s br, 2H, CH_2), 4.62-4.56 (dd, *J*= 16 Hz, 1H, CH_2), 4.42-4.37 (dd, *J*= 14 Hz, 1H, CH_2), 3.48 (s, 3H, OCH_3), 3.28 (s br, 3H, OCH_3), 1.77-1.72 (m, 1H, CH_2), 1.50-1.44 (m, 1H, CH_2), 0.97-0.93 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 170.0, 170.2. 170.2, 142.2, 138.3, 138.2, 134.9, 132.7, 130.1, 128.9, 128.8, 128.4, 128.2, 127.9, 127.6, 127.3, 126.9, 124.9, 119.3, 109.5, 96.8, 60.8, 50.9, 50.9, 43.7, 43.6, 22.0, 11.0. HRMS (ESI) m/z: calculated for $C_{35}H_{33}O_5N_3{}^{79}Br$ $[M]^-$ 654.16091, found 654.1622.

N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(1-(benzylamino)-1-oxobutan-2-yl)-2-iodobenzamide **(5afaa)**: **(1a)** (52.4 mg, 0.18 mmol), **(2f)** (64.4 mg, 0.26 mmol, 1.5 equivalents), **(3a)** (19 µL, 0.26 mmol, 1.5 equivalents), **(4a)** (32 µL, 0.26 mmol, 1.5 equivalents), ZnF_2 (2.0 mg, 0.018 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5afaa)** as a pale yellow foam type solid (77.3 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60-7.58 (d, *J*= 8 Hz, 1H, Ar), 7.39-7.25 (m, 12H, Ar), 7.21-7.18 (m, 2H, Ar), 7.08 (s br, 1H, NH), 6.85-6.81 (t, *J*= 8 Hz, 1H, Ar), 6.49-6.46 (d, *J*= 12 Hz, 1H, Ar), 5.12-5.08 (t, *J*= 8 Hz,

1H, CH), 4.72 (s, 1H, CH_2), 4.64 (s, 1H, CH_2), 4.62-4.41 (m, 2H, CH_2), 3.50 (s br, 3H, OCH_3), 3.29 (s br, 3H, OCH_3), 2.67 (s, 3H, CH_3), 1.79-1.72 (m, 1H, CH_2), 1.51-1.45 (m, 1H, CH_2), 0.98-0.94 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 177.0, 171.5, 170.9, 142.2, 142.0, 141.6, 139.1, 138.3, 135.8, 134.9, 132.9, 131.5, 130.0, 128.9, 128.9, 128.8, 128.7, 128.2, 128.0, 127.9, 127.6, 127.3, 109.5, 96.8, 93.1, 60.9, 51.0, 51.0, 43.6, 42.4, 22.0, 11.0. HRMS (ESI) m/z: calculated for $C_{35}H_{35}O_5N_3{}^{127}I$ $[M]^+$ 704.16159, found 704.1616.

N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(1-(benzylamino)-1-oxobutan-2-yl)furan-2-carboxamide **(5agaa)**: **(1a)** (102.8 mg, 0.34 mmol), **(2g)** (58 mg, 0.52 mmol, 1.5 equivalents), **(3a)** (38 µL, 0.52 mmol, 1.5 equivalents), **(4a)** (63 µL, 0.52 mmol, 1.5 equivalents), ZnF_2 (3.5 mg, 0.034 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5agaa)** as a pale yellow foam type solid (95.9 mg, 50% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.17 (m, 12H, Ar), 7.07 (s br, 1H, NH), 7.00-6.97 (dd, *J*= 4 Hz, 1H, CH), 6.63-6.61 (d, *J*= 8 Hz, 1H, Ar), 5.65-5.64 (m, 1H, CH), 5.06-5.02 (m, 1H, CH), 4.83 (s br, 2H, CH_2), 4.46-4.35 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 1.73-1.66 (m, 1H, CH_2), 1.49-1.42 (m, 1H, CH_2), 0.92-0-88 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.1, 170.3, 160.4, 146.5, 145.1, 142.9, 138.4, 135.0, 133.5, 132.3, 129.1, 128.7, 128.1, 127.8, 127.5, 127.0, 125.9, 117.5, 111.4, 110.1, 96.8, 61.2, 51.0, 50.9, 43.8, 43.6, 22.1, 11.0. HRMS (ESI) m/z: calculated for $C_{33}H_{32}O_6N_3$ $[M]^-$ 566.22966, found 566.2300.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-cyclohexylacetamide **(5aaba)**: **(1a)** (74.8 mg, 0.25 mmol), **(2a)** (22 µL, 0.38 mmol, 1.5 equivalents), **(3b)** (46 µL, 0.38 mmol, 1.5 equivalents), **(4a)** (46 µL, 0.38 mmol, 1.5 equivalents), ZnF_2 (2.6 mg, 0.025 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaba)** as a pale yellow foam type solid (99.7 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.25 (m, 11H, Ar), 7.17 (s br, 1H, NH), 6.99-6.97 (d, *J*= 8 Hz, 1H, Ar), 6.67-6.65 (d, *J*= 8 Hz, Ar, 1H), 4.85 (s, 2H, CH_2), 4.47-4.36 (m, 3H, CH_2+CH), 3.56 (s br, 6H, OCH_3), 1.89-1.86 (m, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.75-1.64 (m, 5H, CH_2+CH), 1.18-1.10 (m, 2H, CH_2), 0.99-0.90 (m, 2H, CH_2). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.6, 171.0, 170.1, 142.4, 138.5, 135.0, 131.2, 129.1, 128.7, 128.0, 127.7, 127.5, 127.4, 125.7, 110.2, 96.7, 51.0, 50.9, 43.8, 43.4, 35.9, 30.5, 29.9, 26.4, 25.7, 25.6, 23.9. HRMS (ESI) m/z: calculated for $C_{34}H_{40}O_5N_3$ $[M]^+$ 570.29625, found 570.2960.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)pentanamide **(5aaca)**: **(1a)** (100.0 mg, 0.34 mmol), **(2a)** (29 µL, 0.5 mmol, 1.5 equivalents), **(3c)** (45 µL, 0.5 mmol, 1.5 equivalents), **(4a)** (61 µL, 0.5 mmol, 1.5 equivalents), ZnF_2 (3.5 mg, 0.034 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaca)** as a pale yellow foam type solid (43.7 mg, 24% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.28 (m, 10H, Ar), 7.11 (s, 1H, Ar), 7.03 (s br, 1H, NH), 6.93-6.91 (m, 1H, Ar), 6.67-6.65 (d, *J*= 8 Hz, 1H, Ar), 5.05-5.01 (m, 1H, CH), 4.84 (s, 2H, CH_2), 4.48-4.37 (m, 2H, CH_2), 3.58 (s, 3H, OCH_3), 3.53 (s br, 3H, OCH_3), 1.81 (s, 3H, CH_3), 1.58-1.55 (m, 1H, CH_2), 1.30-1.25 (m, 3H, CH_2), 0.86-0.83 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.3, 171.0, 170.8, 142.6, 138.5, 135.1, 134.1, 131.8, 129.1, 128.8, 128.1, 127.8, 127.5, 127.5, 126.2, 84.6, 58.2, 51.0, 50.9, 43.8, 43.5, 30.8, 23.5,

19.6, 14.0. HRMS (ESI) m/z: calculated for $C_{31}H_{36}O_5N_3$ $[M]^+$ 530.26495, found 530.2646.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-phenylacetamide **(5aada)**: **(1a)** (74.1 mg, 0.25 mmol), **(2a)** (22 µL, 0.38 mmol, 1.5 equivalents), **(3d)** (39 µL, 0.38 mmol, 1.5 equivalents), **(4a)** (46 µL, 0.38 mmol, 1.5 equivalents), ZnF_2 (2.6 mg, 0.025 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aada)** as a pale yellow foam type solid (81.6 mg, 58% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.08 (m, 17H, Ar), 6.54 (s br, 1H, NH), 6.14-6.12 (m, 2H, Ar+CH), 4.85-4.73 (m, 2H, CH_2), 4.50-4.40 (m, 2H, CH_2), 3.53 (s, 3H, OCH_3), 3.10 (s br, 3H, OCH_3), 1.84 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.5, 171.0, 169.8, 142.1, 138.0, 135.2, 135.0, 134.5, 130.5, 129.0, 128.9, 128.7, 128.6, 128.5, 127.9, 127.6, 127.5, 127.4, 125.4, 109.8, 96.8, 64.7, 50.9, 50.9, 43.8, 43.6, 23.4. HRMS (ESI) m/z: calculated for $C_{34}H_{34}O_5N_3$ $[M]^+$ 564.2493, found 564.2490.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-3-methylbutanamide **(5aaea)**: **(1a)** (50.7 mg, 0.17 mmol), **(2a)** (15 µL, 0.26 mmol, 1.5 equivalents), **(3e)** (24 µL, 0.26 mmol, 1.5 equivalents), **(4a)** (31 µL, 0.26 mmol, 1.5 equivalents), ZnF_2 (1.8 mg, 0.017 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5aaea)** as a pale yellow foam type solid (65.8 mg, 73% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.22 (m, 11H, Ar), 7.20 (s br, 1H, NH), 7.04-7.01 (m, 1H, Ar), 6.66-6.64 (d, *J*= 8 Hz, 1H, Ar), 4.87-4.79 (m, 2H, CH_2), 4.48-4.40 (m, 3H, CH_2+CH), 3.56 (s, 3H, OCH_3), 3.54 (s br, 3H, OCH_3), 2.11-2.08 (m, 1H, CH), 1.80 (s, 3H, CH_3), 0.96-0.91 (m, 6H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.6, 170.9, 170.2, 142.3, 138.4, 135.4, 135.0, 131.3, 129.0, 128.7, 128.0, 127.7, 127.4, 127.4, 125.9, 125.8, 110.0, 96.6, 51.0, 50.8, 43.7, 43.3, 26.6, 23.7, 20.0, 19.7. HRMS (ESI) m/z: calculated for $C_{31}H_{36}O_5N_3$ $[M]^+$ 530.25495, found 530.2648.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-(4-methoxyphenyl)acetamide **(5aafa)**: **(1a)** (72.7 mg, 0.24 mmol), **(2a)** (21 µL, 0.37 mmol, 1.5 equivalents), **(3f)** (45 µL, 0.37 mmol, 1.5 equivalents), **(4a)** (45 µL, 0.37 mmol, 1.5 equivalents), ZnF_2 (2.5 mg, 0.024 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aafa)** as a pale yellow foam type solid (92.0 mg, 65% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.19 (m, 12H, Ar), 7.01-6.98 (d, *J*= 8 Hz, 2H, Ar), 6.67-6.65 (d, *J*= 8 Hz, 2H, Ar), 6.53 (s br, 1H, NH), 6.07-6.06 (m, 2H, Ar+CH), 4.86-4.78 (m, 2H, CH_2), 4.50-4.40 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.13 (s br, 3H, OCH_3), 1.84 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.4, 170.9, 170.0, 159.7, 142.0, 138.0, 135.2, 135.0, 131.7, 130.5, 128.9, 128.6, 128.6, 127.9, 127.5, 127.4, 127.3, 126.3, 113.9, 109.7, 96.7, 63.9, 55.2, 50.9, 50.7, 43.7, 43.5, 23.3. HRMS (ESI) m/z: calculated for $C_{35}H_{36}O_6N_3$ $[M]^+$ 594.25986, found 594.2596.

N-Nenzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-(4-nitrophenyl)acetamide **(5aaga)**: **(1a)** (71.2 mg, 0.24 mmol), **(2a)** (21 µL, 0.36 mmol, 1.5 equivalents), **(3g)** (54 mg, 0.36 mmol, 1.5 equivalents), **(4a)** (44 µL, 0.36 mmol, 1.5 equivalents), ZnF_2 (2.5 mg, 0.024 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaga)** as a pale yellow foam type solid (67.0 mg, 46% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.00-7.98 (d, *J*= 8 Hz,

2H, Ar), 7.34-7.20 (m, 14H, Ar), 6.51 (s br, 1H, NH), 6.43-6.40 (m, 1H, Ar), 6.17 (s, 1H, CH), 4.85-4.74 (m, 2H, CH_2), 4.53-4.41 (m, 2H, CH_2), 3.53 (s, 3H, OCH_3), 3.38-3.34 (s br, 3H, OCH_3), 1.86 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.8, 170.8, 168.8, 147.9, 142.6, 141.5, 137.7, 134.9, 134.5, 132.8, 131.5, 130.6, 129.1, 129.0, 128.9, 128.8, 128.7, 128.1, 127.8, 127.3, 127.0, 126.2, 123.5, 110.1, 96.7, 63.6, 51.0, 50.8, 44.0, 43.7, 23.3. HRMS (ESI) m/z: calculated for $C_{34}H_{31}O_7N_4$ $[M]^-$ 607.21982, found 607.2202.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-(2-bromophenyl)acetamide **(5aaha)**: **(1a)** (57.6 mg, 0.19 mmol), **(2a)** (17 µL, 0.29 mmol, 1.5 equivalents), **(3h)** (34 µL, 0.29 mmol, 1.5 equivalents), **(4a)** (35 µL, 0.29 mmol, 1.5 equivalents), ZnF_2 (1.9 mg, 0.019 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaha)** as a pale yellow foam type solid (76.4 mg, 63% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.47-7.45 (d, *J*= 8 Hz, 1H, Ar), 7.31-7.14 (m, 12H, Ar), 7.04-6.93 (m, 3H, Ar), 6.46 (s, 1H, Ar), 6.28-6.25 (m, 1H, CH), 4.81-4.78 (m, 2H, CH_2), 4.48-4.47 (d, *J*= 4 Hz, 2H, CH_2), 3.54 (s, 3H, OCH_3), 3.10 (s br, 3H, OCH_3), 1.85 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.4, 171.0, 169.7, 142.1, 137.9, 135.0, 134.9, 134.1, 132.9, 132.0, 130.2, 128.9, 128.7, 127.9, 127.7, 127.5, 127.3, 126.3, 125.3, 109.7, 96.8, 63.7, 50.9, 50.9, 43.9, 43.6, 23.2. HRMS (ESI) m/z: calculated for $C_{34}H_{33}O_5N_3{}^{79}Br$ $[M]^+$ 642.15981, found 642.1598.

N-Benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)propanamide **(5aaia)**: **(1a)** (65.6 mg, 0.22 mmol), **(2a)** (19 µL, 0.33 mmol, 1.5 equivalents), **(3i)** (19 µL, 0.33 mmol, 1.5 equivalents), **(4a)** (40 µL, 0.33 mmol, 1.5 equivalents), ZnF_2 (2.3 mg, 0.022 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaia)** as a pale yellow foam type solid (79.7 mg, 72% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.23 (m, 10H, Ar), 7.15-7.14 (m, 1H, Ar), 7.08 (s br, 1H, NH), 6.96-6.93 (m, 1H, Ar), 6.67-6.65 (d, *J*= 8 Hz, 1H, Ar), 5.20-5.14 (m, 1H, CH), 4.83 (s, 2H, CH_2), 4.47-4.34 (m, 2H, CH_2), 3.57 (s, 3H, OCH_3), 3.51 (s br, 3H, OCH_3), 1.79 (s, 3H, CH_3), 1.05-1.04 (d, *J*= 4 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.0, 171.4, 170.9, 142.5, 138.4, 134.9, 133.7, 132.0, 129.0, 128.8, 128.7, 128.0, 127.7, 127.4, 126.4, 126.0, 125.8, 110.1, 96.5, 53.5, 50.9, 50.8, 43.6, 43.4, 23.3, 15.0. HRMS (ESI) m/z: calculated for $C_{29}H_{32}O_5N_3$ $[M]^+$ 502.23365, found 502.2336.

N-benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-(furan-2-yl)acetamide **(5aaja)**: **(1a)** (123.2 mg, 0.41 mmol), **(2a)** (35 µL, 0.62 mmol, 1.5 equivalents), **(3j)** (52 µL, 0.62 mmol, 1.5 equivalents), **(4a)** (76 µL, 0.62 mmol, 1.5 equivalents), ZnF_2 (4.2 mg, 0.041 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaja)** as a pale orange foam type solid (48.8 mg, 22% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.22 (m, 13H, Ar+CH), 6.60-6.57 (m, 1H, Ar), 6.45-6.42 (s br, 1H, NH), 6.29 (m, 1H, CH), 6.24 (s, 1H, CH), 6.19-6.18 (m, 1H, CH), 4.87-4.75 (m, 2H, CH_2), 4.51-4.42 (m, 2H, CH_2), 3.55 (s, 3H, OCH_3), 3.44 (s br, 3H, OCH_3), 1.84 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.4, 171.1, 167.5, 147.8, 143.0, 142.4, 138.0, 135.2, 135.1, 129.0, 128.8, 128.0, 127.7, 127.6, 127.4, 126.6, 127.5, 112.5, 110.9, 109.9, 96.8, 58.2, 51.0, 43.9, 43.7, 23.1. HRMS (ESI) m/z: calculated for $C_{32}H_{30}O_6N_3$ $[M]^-$ 552.21401, found 552.2141.

N-benzyl-2-(N-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-(pyridin-2-yl)acetamide **(5aaka)**: **(1a)** (67.8 mg, 0.23 mmol), **(2a)** (20 µL, 0.34 mmol, 1.5 equivalents), **(3k)** (33 µL, 0.34 mmol, 1.5 equivalents), **(4a)** (42 µL, 0.34 mmol, 1.5 equivalents), ZnF_2 (2.3 mg, 0.023 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaka)** as a pale orange foam type solid (17.4 mg, 13% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.43-8.41 (d, *J*= 8 Hz, 1H, Ar), 8.14-8.11 (m, 1H, Ar), 7.65-7.61 (t, *J*= 8 Hz, 1H, Ar), 7.48-7.46 (d, *J*= 8 Hz, 1H, Ar), 7.31-7.15 (m, 12H, Ar), 6.60-6.58 (d, *J*= 8 Hz, 1H, Ar), 7.12 (s br, 1H, NH), 6.06 (s, 1H, CH), 4.87-4.77 (m, 2H, CH_2), 4.50-4.38 (m, 2H, CH_2), 3.55 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 1.88 (s, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.4, 171.0, 168.0, 155.9, 148.6, 142.3, 138.1, 137.3, 136.5, 135.1, 132.3, 129.1, 128.7, 128.0, 127.5, 127.5, 127.4, 126.6, 125.9, 124.8, 123.0, 110.1, 96.8, 66.1, 51.0, 50.9, 43.7, 23.2. HRMS (ESI) m/z: calculated for $C_{33}H_{31}O_5N_4$ $[M]^-$ 563.22999, found 563.2302.

2-(N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-N-(tert-butyl)butanamide **(5aaab)**: **(1a)** (164.5 mg, 0.55 mmol), **(2a)** (48 µL, 0.83 mmol, 1.5 equivalents), **(3a)** (60 µL, 0.83 mmol, 1.5 equivalents), **(4b)** (94 µL, 0.83 mmol, 1.5 equivalents), ZnF_2 (6.0 mg, 0.055 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5aaab)** as a pale yellow foam type solid (198.0 mg, 75% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.28 (m, 5H, Ar), 7.19 (s, 1H, Ar), 7.08 (s br, 1H, NH), 6.71-6.69 (d, *J*= 8 Hz, 1H, Ar), 6.47 (s, 1H, Ar), 4.90-4.76 (m, 3H, CH_2+CH), 3.60 (s br, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3), 1.34 (s, 9H, CH_3), 1.26-1.23 (m, 2H, CH_2), 0.86-0.83 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.0, 170.9, 169.8, 142.5, 135.0, 134.2, 131.8, 129.1, 128.1, 127.5, 126.3, 96.7, 60.5, 51.2, 51.1, 50.9, 43.8, 28.8, 23.5, 22.1, 10.9. HRMS (ESI) m/z: calculated for $C_{27}H_{36}O_5N_3$ $[M]^+$ 482.26495, found 482.2646.

N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(1-(tert-butylamino)-1-oxobutan-2-yl)benzamide **(5acab)**: **(1a)** (64.1 mg, 0.22 mmol), **(2c)** (39 mg, 0.32 mmol, 1.5 equivalents), **(3a)** (23 µL, 0.32 mmol, 1.5 equivalents), **(4b)** (36 µL, 0.32 mmol, 1.5 equivalents), ZnF_2 (2.2 mg, 0.022 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5acab)** as a pale yellow foam type solid (98.1 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12-8.10 (d, *J*= 8 Hz, 1H, Ar), 7.49-7.45 (t, *J*= 8 Hz, 1H, Ar), 7.33-7.27 (m, 3H, Ar), 7.22-7.15 (m, 7H, Ar), 6.96 (s br, 1H, NH), 6.57 (s, 1H, Ar), 5.04-5.01 (m, 1H, CH), 4.82-4.73 (m, 2H, CH_2), 3.46 (s, 3H, OCH_3), 3.11 (s br, 3H, OCH_3), 1.78-1.71 (m, 1H, CH_2), 1.43-1.36 (m, 10H, CH_3+CH_2), 0.93-0.89 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.9, 171.0, 169.0, 141.6, 136.4, 135.0, 134.8, 133.8, 131.4, 130.3, 129.7, 129.0, 128.6, 128.2, 128.1, 128.0, 127.4, 127.0, 125.0, 109.8, 96.9, 61.7, 51.4, 50.9, 50.9, 43.7, 28.8, 22.1, 11.0. HRMS (ESI) m/z: calculated for $C_{32}H_{38}O_5N_3$ $[M]^+$ 544.2806, found 544.2804.

N-(1-Benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(2-(tert-butylamino)-1-cyclohexyl-2-oxoethyl)benzamide **(5acbb)**: **)**: **(1a)** (67.3 mg, 0.23 mmol), **(2c)** (42 mg, 0.34 mmol, 1.5 equivalents), **(3b)** (41 µL, 0.34 mmol, 1.5 equivalents), **(4b)** (38 µL, 0.34 mmol, 1.5 equivalents), ZnF_2 (2.4 mg, 0.023 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5acbb)** as a white foam type solid (105.9 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.09-8.07 (d, *J*=

8 Hz, 1H, Ar), 7.32-7.28 (m, 3H, Ar), 7.24-7.12 (m, 8H, Ar), 6.94 (s br, 1H, NH), 6.56-6.54 (d, *J*= 8 Hz, 1H, Ar), 4.82-4.73 (m, 2H, CH_2), 4.46 (s br, 1H, CH), 3.30 (s, 3H, OCH_3), 3.21 (s br, 3H, OCH_3), 1.92-1.80 (m, 2H, CH_2+CH), 1.70-1.64 (m, 4H, CH_2), 1.34 (s, 9H, CH_3), 1.06-0.98 (m, 5H, CH_2). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.3, 171.1, 169.4, 141.4, 136.5, 135.0, 133.5, 130.6, 130.2, 129.8, 129.0, 128.5, 128.4, 128.1, 127.9, 127.3, 126.5, 124.8, 109.9, 97.2, 51.3, 51.0, 50.9, 43.7, 36.2, 30.3, 30.1, 28.8, 26.4, 25.8, 25.7. HRMS (ESI) m/z: calculated for $C_{36}H_{44}O_5N_3$ $[M]^+$ 598.32755, found 598.3273.

N-(tert-Butyl)-2-(N-(3,3-dimethoxy-2-oxo-1-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)indolin-5-yl)acetamido)butanamide **(5daab)**: **(1d)** (46.4 mg, 0.12 mmol), **(2a)** (10 µL, 0.18 mmol, 1.5 equivalents), **(3a)** (13 µL, 0.18 mmol, 1.5 equivalents), **(4b)** (21 µL, 0.18 mmol, 1.5 equivalents), ZnF_2 (1.9 mg, 0.012 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5daab)** as a pale yellow foam type solid (52.1 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65-7.63 (d, *J*= 8 Hz, 2H, Ar), 7.60 (s, 1H, CH), 7.36-7.32 (m, 2H, Ar), 7.29-7.27 (m, 2H, Ar), 7.13 (s br, 1H, Ar), 6.96 (s br, 1H, NH), 6.48-6.46 (m, 1H, Ar), 6.37 (s br, 1H, Ar), 4.73-4.68 (m, 3H, CH_2+CH), 4.19-4.18 (m, 2H, CH_2), 3.57-3.54 (s br, 6H, OCH_3), 1.52 (s, 3H, CH_3), 1.33 (s, 9H, CH_3), 1.27-1.25 (m, 1H, CH_2), 1.10 (m, 1H, CH_2), 0.76-0.73 (m, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.8, 171.0, 169.7, 148.0, 141.6, 134.3, 132.0, 130.0, 128.9, 128.3, 126.3, 125.5, 125.2, 121.0, 96.0, 70.7, 60.2, 51.1, 51.0, 50.8, 40.3, 28.7, 22.9, 21.9, 10.8. HRMS (ESI) m/z: calculated for $C_{30}H_{39}O_5N_6$ $[M]^+$ 563.29764, found 563.2972.

N-(1-(Benzylamino)-1-oxobutan-2-yl)-N-(3,3-dimethoxy-2-oxo-1-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)indolin-5-yl)benzamide **(5dcaa)**: **(1d)** (43.7 mg, 0.12 mmol), **(2c)** (21 mg, 0.17 mmol, 1.5 equivalents), **(3a)** (12 µL, 0.17 mmol, 1.5 equivalents), **(4a)** (15 µL, 0.17 mmol, 1.5 equivalents), ZnF_2 (1.2 mg, 0.012 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5dcaa)** as a pale yellow foam type solid (30.0 mg, 38% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70-7.68 (d, *J*= 8 Hz, 2H, Ar), 7.60 (s, 1H, CH), 7.43-7.24 (m, 8H, Ar), 7.17-7.15 (m, 1H, Ar), 7.06-6.96 (m, 6H, Ar), 6.89 (s br, 1H, NH), 6.41-6.39 (d, *J*= 8 Hz, 1H, Ar), 5.08-5.04 (t, *J*= 8 Hz, 1H, CH), 4.66-4.63 (m, 2H, CH_2), 4.55-4.50 (m, 1H, CH_2), 4.43-4.37 (m, 1H, CH_2), 4.15-4.04 (m, 2H, CH_2), 3.55 (s, 3H, OCH_3), 3.07 (s br, 3H, OCH_3), 1.68-1.60 (m, 1H, CH_2), 1.34-1.29 (m, 1H, CH_2), 0.83-0.79 (m, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 171.9, 171.2, 170.2, 148.0, 140.7, 135.8, 129.8, 129.0, 128.8, 128.4, 128.1, 128.0, 127.7, 127.5, 125.7, 120.9, 108.3, 96.4, 61.2, 50.8, 47.3, 43.6, 40.2, 22.1, 11.0. HRMS (ESI) m/z: calculated for $C_{38}H_{39}O_5N_6$ $[M]^+$ 659.29764, found 659.2974.

N-Benzyl-2-cyclohexyl-2-(N-(3,3-dimethoxy-2-oxo-1-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)indolin-5-yl)acetamido)acetamide **(5daba)**: **(1d)** (53.8 mg, 0.14 mmol), **(2a)** (12 µL, 0.21 mmol, 1.5 equivalents), **(3b)** (25 µL, 0.21 mmol, 1.5 equivalents), **(4a)** (26 µL, 0.21 mmol, 1.5 equivalents), ZnF_2 (1.4 mg, 0.014 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5daba)** as a pale yellow foam type solid (52.8 mg, 58% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65-7.63 (d, *J*= 8 Hz, 2H, Ar), 7.62 (s, 1H, CH), 7.35-7.22 (m, 9H, Ar), 7.09 (s br, 1H, NH), 6.90-6.88 (d, *J*= 8 Hz, 1H, Ar), 6.45-6.43 (d, *J*= 8 Hz, 1H, Ar), 4.69 (s br, 2H, CH_2), 4.43-4.36 (m, 3H, CH_2+CH), 4.15-4.09 (s br, 2H, CH_2), 3.50 (s

br, 6H, OCH_3), 1.81-1.57 (m, 6H, CH_2), 1.47 (s, 3H, CH_3), 1.25-1.22 (m, 1H, CH), 1.11-0.99 (m, 2H, CH_2), 0.92-0.85 (m, 2H, CH_2). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.4, 171.1, 169.0, 148.0, 141.4, 138.4, 130.1, 128.9, 128.7, 128.4, 127.6, 127.4, 125.5, 121.0, 108.6, 96.4, 51.0, 50.8, 47.5, 43.3, 40.3, 35.8, 30.3, 29.7, 26.3, 25.6, 25.4, 23.3. HRMS (ESI) m/z: calculated for $C_{37}H_{43}O_5N_6$ $[M]^+$ 651.32894, found 651.3281.

2-(N-(1-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-N-(tert-butyl)butanamide **(5eaab)**: **(1e)** (87.9 mg, 0.23 mmol), **(2a)** (20 µL, 0.35 mmol, 1.5 equivalents), **(3a)** (25 µL, 0.35 mmol, 1.5 equivalents), **(4b)** (40 µL, 0.35 mmol, 1.5 equivalents), ZnF_2 (2.4 mg, 0.023 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5eaab)** as a white foam type solid (54.6 mg, 42% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (s, 1H, CH), 7.36-7.33 (m, 3H, Ar), 7.25-7.20 (m, 3H, Ar), 7.15 (m, 2H, Ar+NH), 6.46 (s br, 1H, Ar), 5.50-5.42 (m, 2H, CH_2), 4.95-4.85 (m, 2H, CH_2), 4.82-4.75 (m, 1H, CH), 3.52 (s br, 3H, OCH_3), 3.49 (s br, 3H, OCH_3), 1.81 (s, 3H, CH_3), 1.53-1.50 (m, 1H, CH_2), 1.34 (s, 9H, CH_3), 1.26-1.24 (m, 1H, CH_2), 0.87-0.83 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.9, 170.4, 169.7, 142.5, 141.9, 134.2, 132.0, 129.2, 128.9, 128.3, 126.1, 122.8, 110.6, 96.5, 60.4, 54.4, 51.1, 50.9, 50.7, 35.2, 28.7, 23.4, 22.0, 10.8. HRMS (ESI) m/z: calculated for $C_{30}H_{39}O_5N_6$ $[M]^+$ 563.29764, found 563.2975.

N-(1-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-3,3-dimethoxy-2-oxoindolin-5-yl)-N-(1-(benzylamino)-1-oxobutan-2-yl)benzamide **(5ecaa)**: **(1e)** (94.2 mg, 0.25 mmol), **(2c)** (46.4 mg, 0.38 mmol, 1.5 equivalents), **(3a)** (27 µL, 0.38 mmol, 1.5 equivalents), **(4a)** (46 µL, 0.38 mmol, 1.5 equivalents), ZnF_2 (2.6 mg, 0.025 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5ecaa)** as a white foam type solid (95.7 mg, 58% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.42 (s, 1H, CH), 7.36-7.12 (m, 15H, Ar), 7.04-6.98 (m, 2H, Ar), 6.92 (s, 1H, Ar), 5.46 (s, 2H, CH_2), 5.16-5.12 (m, 1H, CH), 4.83 (s, 2H, CH_2), 4.59-4.39 (m, 2H, CH_2), 3.36 (s br, 3H, OCH_3), 3.10 (s br, 3H, OCH_3), 1.83-1.76 (m, 1H, CH_2), 1.54-1.47 (m, 1H, CH_2), 0.97-0.93 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 172.1, 170.6, 170.6, 142.5, 141.2, 138.5, 136.0, 134.8, 130.2, 129.8, 129.3, 129.0, 128.8, 128.5, 128.3, 128.2, 128.1, 127.8, 127.5, 126.8, 122.9, 110.2, 96.7, 61.4, 54.4, 50.8, 43.6, 35.3, 22.2, 11.1. HRMS (ESI) m/z: calculated for $C_{38}H_{39}O_5N_6$ $[M]^+$ 659.29764, found 659.2974.

N-Benzyl-2-(N-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)-2-cyclohexylacetamide **(5eaba)**: **(1e)** (98.6 mg, 0.26 mmol), **(2a)** (22 µL, 0.39 mmol, 1.5 equivalents), **(3b)** (47 µL, 0.39 mmol, 1.5 equivalents), **(4a)** (47 µL, 0.39 mmol, 1.5 equivalents), ZnF_2 (2.7 mg, 0.026 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5eaba)** as a white foam type solid (70.4 mg, 42% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (s, 1H, CH), 7.37-7.23 (m, 11H, Ar), 7.18-7.16 (d, *J*= 8 Hz, 1H, Ar), 7.11 (s, 1H, Ar), 7.05-7.03 (m, 1H, Ar), 5.46 (s, 2H, CH_2), 4.90 (s br, 2H, CH_2), 4.52 (s br, 1H, CH), 4.45-4.34 (m, 2H, CH_2), 3.48 (s br, 6H, OCH_3), 1.90-1.87 (m, 2H, CH_2), 1.76 (s, 3H, CH_3), 1.71-1.64 (m, 4H, CH_2), 1.14-1.10 (m, 3H, CH_2), 1.00-0.90 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.4, 170.5, 169.8, 142.5, 141.7, 138.5, 134.2, 131.4, 129.2, 128.9, 128.6, 128.2, 127.6, 127.3, 125.6, 122.8, 110.7, 96.5,

60.4, 54.3, 50.8, 50.7, 43.2, 35.8, 35.2, 30.4, 29.7, 26.3, 25.6, 25.5, 23.7. HRMS (ESI) m/z: calculated for $C_{37}H_{43}O_5N_6$ $[M]^+$ 651.32894, found 651.3286.

2-(N-(1-Benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)-N-(tert-butyl)butanamide **(5faab)**: **(1f)** (97.5 mg, 0.33 mmol), **(2a)** (28 µL, 0.49 mmol, 1.5 equivalents), **(3a)** (36 µL, 0.49 mmol, 1.5 equivalents), **(4b)** (55 µL, 0.49 mmol, 1.5 equivalents), ZnF_2 (3.4 mg, 0.033 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5faab)** as a pale orange foam type solid (94.8 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.27 (m, 5H, Ar), 7.19 (s, 1H, Ar), 7.09 (s, 1H, Ar), 6.67-6.65 (d, *J*= 8 Hz, 1H, Ar), 6.39 (s br, 1H, NH), 4.80-4.79 (m, 2H, CH_2), 4.73-4.69 (m, 1H, CH), 4.61-4.58 (m, 2H, CH_2), 4.33-4.29 (m, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.53-1.49 (m, 1H, CH_2), 1.34 (s, 9H, CH_3), 1.26-1.22 (m, 1H, CH_2), 0.85-0.82 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.5, 172.0, 169.9, 143.9, 135.0, 134.9, 132.8, 129.1, 128.0, 127.4, 126.2, 110.2, 101.9, 66.1, 66.0, 60.8, 51.2, 43.8, 28.7, 23.5, 22.3, 10.9. HRMS (ESI) m/z: calculated for $C_{27}H_{34}O_5N_3$ $[M]^+$ 480.2493, found 480.2490.

N-(1-Benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)-N-(1-(benzylamino)-1-oxobutan-2-yl)benzamide **(5fcaa)**: **(1f)** (86.4 mg, 0.29 mmol), **(2c)** (54 mg, 0.44 mmol, 1.5 equivalents), **(3a)** (32 µL, 0.44 mmol, 1.5 equivalents), **(4a)** (53 µL, 0.44 mmol, 1.5 equivalents), ZnF_2 (3.0 mg, 0.029 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5fcaa)** as a pale yellow foam type solid (109.9 mg, 66% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.08-8.07 (d, *J*= 4 Hz, 1H, Ar), 7.57-7.55 (m, 1H, Ar), 7.46-7.42 (m, 1H, Ar), 7.40-7.37 (m, 1H, NH), 7.30-7.13 (m, 13H, Ar), 6.79-6.77 (d, *J*= 8 Hz, 1H, Ar), 6.36-6.34 (d, *J*= 8 Hz, 1H, Ar), 5.02-5.08 (t, *J*= 8 Hz, 1H, CH), 4.69-4.68 (m, 2H, CH_2), 4.57-4.42 (m, 4H, CH_2), 4.30-4.24 (m, 2H, CH_2), 1.85-1.77 (m, 1H, CH_2), 1.56-1.49 (m, 1H, CH_2), 0.95-0.92 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.4, 172.0, 170.8, 142.9, 138.4, 135.6, 134.8, 133.4, 133.0, 130.1, 129.7, 128.9, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.3, 127.2, 126.1, 109.5, 101.8, 65.9, 65.8, 61.8, 43.5, 22.4, 11.0. HRMS (ESI) m/z: calculated for $C_{35}H_{34}O_5N_3$ $[M]^+$ 576.2493, found 576.2493.

N-Benzyl-2-(N-(1-benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)-2-cyclohexylacetamide **(5faba)**: **(1f)** (80.7 mg, 0.27 mmol), **(2a)** (23 µL, 0.41 mmol, 1.5 equivalents), **(3b)** (50 µL, 0.41 mmol, 1.5 equivalents), **(4a)** (50 µL, 0.41 mmol, 1.5 equivalents), ZnF_2 (2.8 mg, 0.027 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5faba)** as a pale yellow foam type solid (113.9 mg, 74% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36-7.24 (m, 1H, Ar), 7.20 (s br, 1H, NH), 6.98-6.95 (dd, *J*= 4 Hz, 1H, Ar), 6.62-6.60 (d, *J*= 8 Hz, 1H, Ar), 4.85-4.77 (m, 2H, CH_2), 4.64-4.59 (m, 2H, CH_2), 4.44-4.42 (m, 2H, CH_2), 4.35-4.31 (m, 2H, CH_2), 4.22 (s br, 1H, CH), 1.87-1.84 (m, 1H, CH), 1.80 (s, 3H, CH_3), 1.70-1.65 (m, 4H, CH_2), 1.29-1.14 (m, 4H, CH_2), 0.98-0.91 (m, 2H, CH_2). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.4, 172.5, 170.2, 143.7, 138.5, 134.8, 132.2, 129.0, 128.6, 127.9, 127.6, 127.3, 127.2, 125.3, 110.2, 101.8, 65.9, 60.4, 43.6, 43.2, 35.9, 30.5, 29.8, 26.2, 25.5, 25.4, 23.8. HRMS (ESI) m/z: calculated for $C_{34}H_{38}O_5N_3$ $[M]^+$ 568.2806, found 568.2803.

N-(tert-Butyl)-2-(N-(1-methyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)butanamide **(5gaab)**: **(1g)** (50.3 mg, 0.23 mmol), **(2a)** (19 µL, 0.34

mmol, 1.5 equivalents), **(3a)** (25 µL, 0.34 mmol, 1.5 equivalents), **(4b)** (39 µL, 0.34 mmol, 1.5 equivalents), ZnF_2 (2.4 mg, 0.023 mmol, 10 mol%) and MeOH (2 mL) were used to obtain the corresponding **(5gaab)** as a pale yellow foam type solid (51.2 mg, 55% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.16 (m, 2H, Ar), 6.78-6.75 (d, *J*= 12 Hz, 1H, Ar), 6.37 (s br, 1H, NH), 4.72-4.69 (m, 1H, CH), 4.53-4.50 (m, 2H, CH_2), 4.27-4.23 (m, 2H, CH_2), 3.10 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.54-1.48 (m, 1H, CH_2), 1.33 (s, 9H, CH_3), 1.27-1.21 (m, 1H, CH_2), 0.85-0.81 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.3, 171.9, 169.8, 144.7, 134.9, 132.9, 126.1, 109.1, 101.8, 65.9, 65.8, 60.8, 51.2, 28.7, 26.0, 23.4, 22.3, 10.9. HRMS (ESI) m/z: calculated for $C_{21}H_{30}O_5N_3$ $[M]^+$ 404.218, found 404.2178.

N-(1-(Benzylamino)-1-oxobutan-2-yl)-N-(1-methyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)benzamide **(5gcaa)**: **(1g)** (62.0 mg, 0.28 mmol), **(2c)** (51.3 mg, 0.42 mmol, 1.5 equivalents), **(3a)** (30 µL, 0.42 mmol, 1.5 equivalents), **(4a)** (51 µL, 0.42 mmol, 1.5 equivalents), ZnF_2 (2.9 mg, 0.028 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5gcaa)** as a pale yellow foam type solid (67.2 mg, 48% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.14 (m, 11H, Ar), 6.86-6.84 (d, *J*= 8 Hz, 1H, Ar), 6.47-6.45 (d, *J*= 8 Hz, 1H, Ar), 5.12-5.08 (t, *J*= 8 Hz, 1H, CH), 4.56-4.40 (m, 4H, CH_2), 4.26-4.18 (m, 2H, CH_2), 2.99 (s, 3H, CH_3), 1.85-1.77 (m, 1H, CH_2), 1.57-1.50 (m, 1H, CH_2), 0.96-0.92 (t, *J*= 8 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.2, 172.0, 170.7, 143.7, 138.4, 135.8, 135.3, 133.2, 129.7, 128.7, 128.2, 128.0, 127.7, 127.4, 126.0, 124.6, 108.5, 101.7, 65.8, 65.7, 61.6, 43.5, 25.8, 22.3, 11.1. HRMS (ESI) m/z: calculated for $C_{29}H_{30}O_5N_3$ $[M]^+$ 500.218, found 500.2177.

N-Benzyl-2-cyclohexyl-2-(N-(1-methyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)acetamide **(5gaba)**: **(1g)** (55.8 mg, 0.25 mmol), **(2a)** (22 µL, 0.38 mmol, 1.5 equivalents), **(3b)** (46 µL, 0.38 mmol, 1.5 equivalents), **(4a)** (46 µL, 0.38 mmol, 1.5 equivalents), ZnF_2 (2.6 mg, 0.025 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(5gaba)** as a pale yellow foam type solid (90.0 mg, 73% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.27 (m, 6H, Ar), 7.21 (s br, 1H, NH), 7.10-7.07 (m, 1H, Ar), 6.74-6.72 (d, *J*= 8 Hz, 1H, Ar), 4.58-4.54 (m, 2H, CH_2), 4.45-4.42 (m, 2H, CH_2), 4.32-4.26 (m, 3H, CH_2+CH), 3.12 (s, 3H, CH_3), 2.05-2.02 (m, 1H, CH), 1.89-1.86 (m, 2H, CH_2), 1.82 (s, 3H, CH_3), 1.75-1.65 (m, 4H, CH_2), 1.19-1.14 (m, 2H, CH_2), 1.00-0.91 (m, 2H, CH_2). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.3, 172.6, 170.3, 144.6, 138.5, 132.5, 128.7, 127.8, 127.4, 125.3, 109.2, 101.9, 65.9, 43.4, 36.0, 30.6, 30.0, 26.3, 26.0, 25.7, 25.5, 23.9. HRMS (ESI) m/z: calculated for $C_{28}H_{34}O_5N_3$ $[M]^+$ 492.2493, found 492.2491.

1.5. The Ugi4CR with Ketones as Carbonyl Input

General procedure: In a glass vial with a magnetic stirrer was added the corresponding 5-amino-1-benzylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **(1f)** (1 equivalent), acetic acid **(2a)** (1.5 equivalents), the ketone **(6)** (1.5 equivalents), *tert*-butyl isocyanide **(4b)** (1.5 equivalents), ZnF_2 (10 mol%) and MeOH (2-3 mL). The vial was closed with a plastic cap (Figure S1) and the reaction mixture was left stirring for 3 days at room temperature. The solvent was evaporated under reduced pressure and the crude reaction mixture purified in a short

chromatographic glass column with SiO_2 flash using CH_2Cl_2:AcOEt (5:1), (1:1) as eluents.

The ketone scope for the Ugi4CR can be seen in Figure S3.

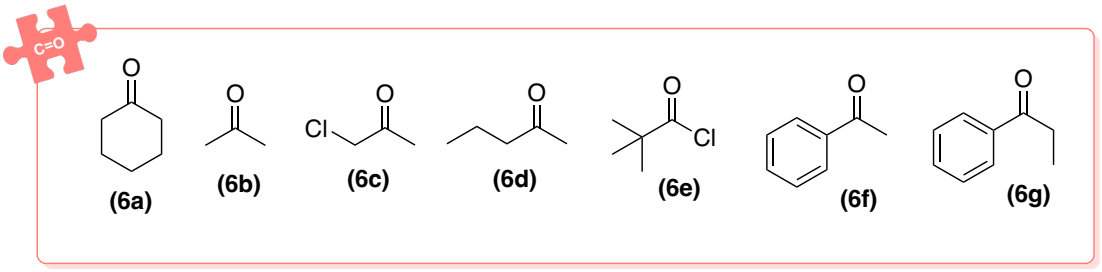


Figure S3. Ketone **(6)** scope for the Ugi4CR.

1-(N-(1-Benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)-N-(tert-butyl)cyclohexane-1-carboxamide **(7faab)**: **(1f)** (87.1 mg, 0.4 mmol), **(2a)** (34 µL, 0.59 mmol, 1.5 equivalents), **(6a)** (61 µL, 0.59 mmol, 1.5 equivalents), **(4b)** (67 µL, 0.59 mmol, 1.5 equivalents), ZnF_2 (4.1 mg, 0.04 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(7faab)** as a pale yellow foam type solid (116.8 mg, 56% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.32 (m, 1H, Ar), 7.28-7.22 (m, 5H, Ar), 7.18-7.15 (m, 1H, Ar), 6.64-6.62 (d, *J*= 8 Hz, 1H, Ar), 6.13 (s br, 1H, NH), 4.80-4.72 (m, 2H, CH_2), 4.58-4.53 (m, 2H, CH_2), 4.33-4.25 (m, 2H, CH_2), 2.29-2.27 (m, 1H, CH_2), 2.19-2.16 (m, 1H, CH_2), 1.61 (s, 3H, CH_3), 1.49-1.41 (m, 4H, CH_2), 1.34-1.30 (m, 10H, CH_2+CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.5, 172.4, 171.5, 143.6, 136.4, 134.9, 133.7, 128.9, 127.9, 127.3, 127.2, 124.8, 109.7, 101.9, 66.4, 65.9, 65.9, 51.2, 43.6, 34.6, 34.2, 28.6, 25.4, 25.4, 22.9, 22.8. HRMS (ESI) m/z: calculated for $C_{30}H_{38}O_5N_3$ $[M]^+$ 520.2806, found 520.2802.

2-(N-(1-Benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)-N-(tert-butyl)-2-methylpropanamide **(7fabb)**: **(1f)** (97.6 mg, 0.44 mmol), **(2a)** (38 µL, 0.66 mmol, 1.5 equivalents), **(6b)** (48 µL, 0.66 mmol, 1.5 equivalents), **(4b)** (75 µL, 0.66 mmol, 1.5 equivalents), ZnF_2 (4.5 mg, 0.044 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(7fabb)** as a pale yellow foam type solid (109.9 mg, 52% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.31 (m, 1H, Ar), 7.28-7.22 (m, 5H, Ar), 7.17-7.15 (d, *J*= 8 Hz, 1H, Ar), 6.65-6.63 (d, *J*= 8 Hz, 1H, Ar), 5.58 (s br, 1H, NH), 4.81-4.72 (m, 2H, CH_2), 4.59-4.53 (m, 2H, CH_2), 4.32-4.26 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 1.32 (s, 9H, CH_3), 1.25 (s, 6H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 173.9, 173.4, 170.5, 143.7, 136.2, 134.8, 133.3, 128.9, 127.9, 127.3, 126.8, 125.2, 109.9, 101.8, 65.9, 62.7, 51.0, 43.6, 28.6, 25.8, 25.5, 24.5. HRMS (ESI) m/z: calculated for $C_{27}H_{34}O_5N_3$ $[M]^+$ 480.2493, found 480.2489.

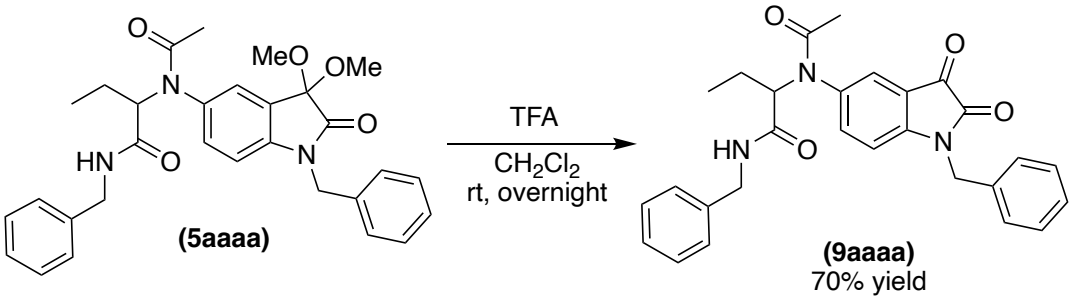
2-(N-(1-Benzyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-5-yl)acetamido)-N-(tert-butyl)-3-hydroxy-2-methylpropanamide **(7facb)**: **(1f)** (93.3 mg, 0.42 mmol), **(2a)** (37 µL, 0.64 mmol, 1.5 equivalents), **(6c)** (51 µL, 0.64 mmol, 1.5 equivalents), **(4b)** (72 µL, 0.64 mmol, 1.5 equivalents), ZnF_2 (4.3 mg, 0.042 mmol, 10 mol%) and MeOH (3 mL) were used to obtain the corresponding **(7facb)** as a pale yellow

foam type solid (68.4 mg, 33% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29-7.23 (m, 5H, Ar), 6.87 (s, 1H, Ar), 6.71 (s br, 1H, Ar), 6.46-6.45 (m, 2H, Ar), 4.78-4.70 (m, 2H, CH_2), 4.59-4.56 (m, 2H, CH_2), 4.34-4.23 (m, 4H, CH_2), 2.02 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.29 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.2, 171.5, 170.9, 140.5, 136.6, 135.4, 128.9, 127.7, 127.3, 125.1, 118.8, 114.2, 110.2, 102.5, 67.5, 66.0, 61.6, 51.0, 43.6, 28.4, 20.8, 20.0. HRMS (ESI) m/z: calculated for $C_{27}H_{34}O_6N_3$ $[M]^+$ 496.24421, found 496.2438.

1.6. The Ugi-Smiles4CR

General procedure: In a glass vial with a magnetic stirrer was added the corresponding 5-amino-3,3-dimethoxy-1-methylindolin-2-one **(1b)** (55.1 mg, 0.25 mmol), **2,4-dinitrophenol** (68 mg, 0.37 mmol, 1.5 equivalents), **(3a)** (27 µL, 0.37 mmol, 1.5 equivalents), **(4a)** (45 µL, 0.37 mmol, 1.5 equivalents), ZnF_2 (2.6 mg, 0.025 mmol, 10 mol%) and MeOH (2 mL). The vial was closed with a plastic cap (Figure S1) and the reaction mixture was left stirring for 3 days at room temperature. The solvent was evaporated under reduced pressure and the crude reaction mixture purified in a short chromatographic glass column with SiO_2 flash using hexane:AcOEt (1:1) and AcOEt as eluents. The corresponding *N-benzyl-2-((3,3-dimethoxy-1-methyl-2-oxoindolin-5-yl)(2,4-dinitrophenyl)amino)butanamide* **(8)** was obtained as an orange foam type solid (33.3 mg, 24% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.38 (s, 1H, Ar), 8.30-8.27 (m, 1H, Ar), 7.57-7.54 (m, 1H, Ar), 7.31-7.30 (s br, 1H, NH), 7.23-7.21 (m, 3H, Ar), 7.16-7.14 (m, 2H, Ar), 6.99 (s, 1H, Ar), 6.93-6.90 (m, 1H, Ar), 6.65-6.63 (d, *J*= 8 Hz, 1H, Ar), 4.62-4.52 (m, 3H, CH+CH_2), 4.33-4.28 (m, 1H, CH_2), 3.43 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.12 (s, 3H, CH_3), 2.37-2.30 (m, 1H, CH_2), 1.79-1.73 (m, 1H, CH_2), 1.01-0.98 (m, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 170.6, 169.9, 146.3, 142.3, 141.4, 140.9, 138.4, 137.6, 128.8, 128.4, 128.1, 127.7, 127.3, 126.6, 123.4, 122.6, 121.8, 109.5, 96.8, 68.5, 51.0, 44.1, 26.0, 22.2, 11.7. HRMS (ESI) m/z: calculated for $C_{28}H_{29}O_8N_5{}^{23}Na$ $[M]^{+Na}$ 586.19083, found 586.1914.

1.7. Post-Ugi Reaction Transformations



N-Benzyl-2-(N-(1-benzyl-2,3-dioxoindolin-5-yl)acetamido)butanamide **(9aaaa)**: In a round-bottom flask was added *N*-benzyl-2-(*N*-(1-benzyl-3,3-dimethoxy-2-oxoindolin-5-yl)acetamido)butanamide **(5aaaa)** (116.2 mg, 0.23 mmol), CH_2Cl_2 (5 mL) and trifluoroacetic acid (1 mL, 0.012 mmol, 0.05 equivalents). The mixture

was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, carefully, to neutralize the acid. The resulting crude mixture was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified in a short chromatographic glass column with SiO_2 flash and CH_2Cl_2:AcOEt (5:1) and (1:1) as eluents. The corresponding *N-benzyl-2-(N-(1-benzyl-2,3-dioxoindolin-5-yl)acetamido)butanamide* **(9aaaa)** was obtained as an orange foam type solid (75.8 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.22 (m, 11H, Ar), 7.09-7.06 (m, 1H, Ar), 6.76-6.74 (d, *J*= 8 Hz, 1H, Ar), 4.90-4.86 (m, 3H, CH_2+CH), 4.41-4.40 (d, *J*= 4 Hz, 2H, CH_2), 1.74 (s, 3H, CH_3), 1.58-1.51 (m, 1H, CH_2), 1.35-1.28 (m, 1H, CH_2), 0.87-0.84 (t, *J*= 6 Hz, 3H, CH_3). ^{13}C APT NMR ($CDCl_3$, 100 MHz) δ: 182.4, 171.5, 170.3, 158.1, 150.3, 138.2, 134.2, 129.2, 128.7, 128.4, 127.8, 127.6, 127.4, 126.3, 117.9, 111.7, 59.9, 44.3, 43.5, 23.2, 22.5, 10.8. HRMS (ESI) m/z: calculated for $C_{28}H_{28}O_4N_3$ $[M]^+$ 470.20743, found 470.2071.

2. Biological Assays

2.1. Cell lines, culture and maintenance

The following human solid tumor cell lines were used in this study: HBL-100 (breast), HeLa (cervix), T-47D (breast), A549 (lung), and WiDr (colon). These cell lines were a kind gift from Prof. G. J. Peters (VU Medical Center, Amsterdam, The Netherlands). Cells were maintained in 25 cm^2 culture flasks in RPMI 1640 supplemented with 5% heat-inactivated fetal calf serum and 2 mM L-glutamine in a 37 °C, 5% CO_2, 95% humidified air incubator. Exponentially growing cells were trypsinized and resuspended in antibiotic containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single cell suspensions were counted with Moxi Z automated cell counter (Orflo, Technologies, Ketchum, ID 83340, USA). After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 µL per well at densities of 5,000 (WiDr and T-47D), and 2,500 (A549, HBL-100, and HeLa) cells per well, based on their doubling times.

2.2. Antiproliferative activity

Chemosensitivity tests were performed using the SRB assay of the NCI with slight modifications. Briefly, pure compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (0.25% v/v, negative control). Each agent was tested in triplicates at different dilutions in the range 0.001–100 µM. Drug treatment started on day 1 after plating. Drug incubation periods were 48 h, after which cells were precipitated with 25 µL of ice-cold 50% (w/v) trichloroacetic acid and fixed for 60 min at 4 °C. Then, the SRB assay was performed. The optical density (OD) of each well was measured at 530 nm, using BioTek's

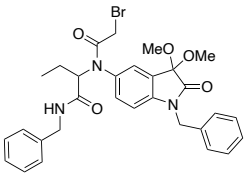
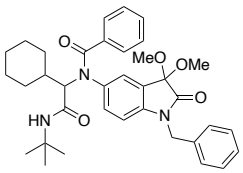
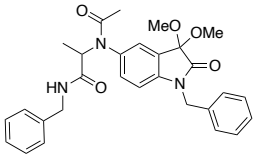
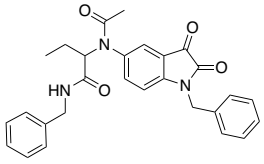
PowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells containing only culture medium. The percentage growth (PG) was calculated with respect to untreated control cells (C) at each level of drug concentrations based on the difference in OD at the start time (T_0) and at the end of drug exposure (T), according to NCI formulas. Therefore, if T is greater than or equal to T0, the calculation is $100 \times [(T - T_0)/(C - T_0)]$. If T is lower than T_0, denoting cell death, the calculation is $100 \times [(T - T_0)/(T_0)]$. The effect is defined as the growth percentage, where 50% growth inhibition (GI_{50}) represents the concentration at which PG is +50. Based on these calculations, a PG value of 0 corresponds to the number of cells present at the beginning of drug exposure, while negative PG values denote net cell death.

Table S1. Antiproliferative activity (GI_{50}, μM) of Ugi-derived Isatin-peptoids against human solid tumour cells

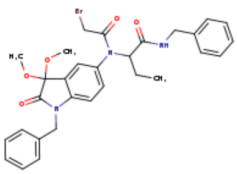
Compound	Cell line				
	A549	**HBL-100**	**HeLa**	**T-47D**	**WiDr**
5aaaa	43±17	69±17	30±10	79±36	70±6.1
5baaa	>100	>100	>100	>100	>100
5caaa	41±4.8	>100	36±1.2	>100	>100
5daaa	>100	>100	>100	>100	>100
5gaaa	>100	>100	>100	>100	>100
5abaa	0.10±0.02	0.060±0.006	0.16±0.03	2.3±0.2	0.31±0.04
5acaa	54±19	80±34	26±8.6	93±12	>100
5adaa	86±20	>100	>100	>100	>100
5aeaa	>100	>100	>100	>100	>100
5aaba	31±9.5	47±15	28±14	91±16	83±24
5aaca	31±1.1	34±5.0	24±3.3	49±3.4	39±7.7
5aada	41±3.6	54±15	38±8.7	>100	60±17
5aaea	31±3.2	43±4.9	30±10	41±1.5	41±12
5aafa	25±5.5	36±6.1	49±16	>100	>100
5aaga	30±0.8	64±26	34±6.4	>100	82±22
5aaia	7.6±2.2	>100	78±30	95±9.5	42±3.0
5aaab	>100	>100	>100	>100	>100
5acab	40±2.7	45±14	40±10	93±13	76±13
5acbb	5.8±0.7	82±26	10±1.1	>100	>100
5daab	>100	>100	93±12	>100	97±4.7
5dcaa	>100	>100	>100	>100	>100
5daba	49±5.4	65±6.1	43±8.8	65±18	82±31
5gaab	>100	>100	>100	>100	>100
5gaba	>100	>100	>100	>100	>100
9aaaa	26±4.3	21±3.4	8.1±1.8	19±1.1	25±6.6
CDDP	4.9±0.2	1.9±0.2	1.8±0.5	17±3.3	23±4.3

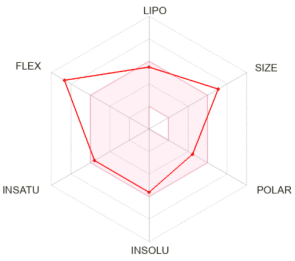
GI_{50} values are given in μM. Standard deviation was calculated from two to four independent experiments. Cisplatin (CDDP) was used as a reference cytotoxic drug. Highlighted values represent the best antiproliferative data against tumor cell lines with GI_{50} values < 10 μM.

3. SwissADME® Reports

Molecule 1	(5abaa)		Molecule 3	(5acbb)	
Molecule 2	(5aaia)		Molecule 4	(9aaaa)	

Molecule 1





SMILES BrCC(=O)N(C(C(=O)NCc1ccccc1)CC)c1ccc2c(c1)C(OC)(OC)C(=O)N2Cc1ccccc1

Physicochemical Properties	
Formula	C30H32BrN3O5
Molecular weight	594.50 g/mol
Num. heavy atoms	39
Num. arom. heavy atoms	18
Fraction Csp3	0.30
Num. rotatable bonds	13
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	156.59
TPSA	88.18 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.13
Log $P_{o/w}$ (XLOGP3)	4.12
Log $P_{o/w}$ (WLOGP)	3.71
Log $P_{o/w}$ (MLOGP)	2.84
Log $P_{o/w}$ (SILICOS-IT)	4.70
Consensus Log $P_{o/w}$	3.90

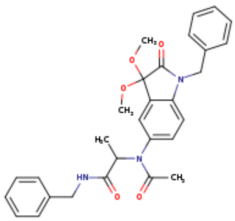
Water Solubility	
Log *S* (ESOL)	-5.61
Solubility	1.48e-03 mg/ml ; 2.48e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.68
Solubility	1.25e-03 mg/ml ; 2.10e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-9.35
Solubility	2.66e-07 mg/ml ; 4.48e-10 mol/l
Class	Poorly soluble

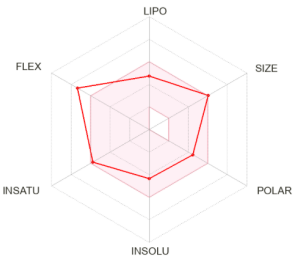
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.00 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: alkyl_halide, het-C-het_not_in_ring
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	4.40

Molecule 2



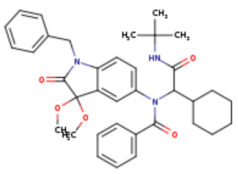


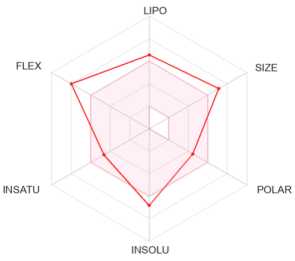
SMILES COC1(OC)c2cc(ccc2N(C1=O)Cc1ccccc1)N(C(C(=O)NCc1ccccc1)C)C(=O)C

Physicochemical Properties	
Formula	C29H31N3O5
Molecular weight	501.57 g/mol
Num. heavy atoms	37
Num. arom. heavy atoms	18
Fraction Csp3	0.28
Num. rotatable bonds	11
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	143.91
TPSA	88.18 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.68
Log $P_{o/w}$ (XLOGP3)	2.80
Log $P_{o/w}$ (WLOGP)	2.94
Log $P_{o/w}$ (MLOGP)	2.36
Log $P_{o/w}$ (SILICOS-IT)	3.73
Consensus Log $P_{o/w}$	3.10

Water Solubility	
Log *S* (ESOL)	-4.35
Solubility	2.25e-02 mg/ml ; 4.49e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.31
Solubility	2.46e-02 mg/ml ; 4.91e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-8.19
Solubility	3.25e-06 mg/ml ; 6.47e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.37 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: het-C-het_not_in_ring
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	4.10

Molecule 3



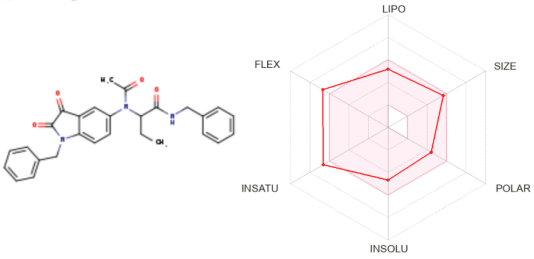


SMILES COC1(OC)C(=O)N(c2c1cc(cc2)N(C(=O)c1ccccc1)C(C(=O)NC(C)(C)C)C1CCCCC1)Cc1ccccc1

Physicochemical Properties	
Formula	C36H43N3O5
Molecular weight	597.74 g/mol
Num. heavy atoms	44
Num. arom. heavy atoms	18
Fraction Csp3	0.42
Num. rotatable bonds	12
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	175.71
TPSA	88.18 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.79
Log $P_{o/w}$ (XLOGP3)	5.96
Log $P_{o/w}$ (WLOGP)	5.55
Log $P_{o/w}$ (MLOGP)	3.93
Log $P_{o/w}$ (SILICOS-IT)	5.39
Consensus Log $P_{o/w}$	5.12

Water Solubility	
Log *S* (ESOL)	-6.81
Solubility	9.23e-05 mg/ml ; 1.54e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.59
Solubility	1.54e-05 mg/ml ; 2.58e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.54
Solubility	1.73e-07 mg/ml ; 2.90e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.71 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: het-C-het_not_in_ring
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	4.86

Molecule 4



SMILES CCC(N(c1ccc2c(c1)C(=O)C(=O)N2Cc1ccccc1)C(=O)C)C(=O)NCc1ccccc1

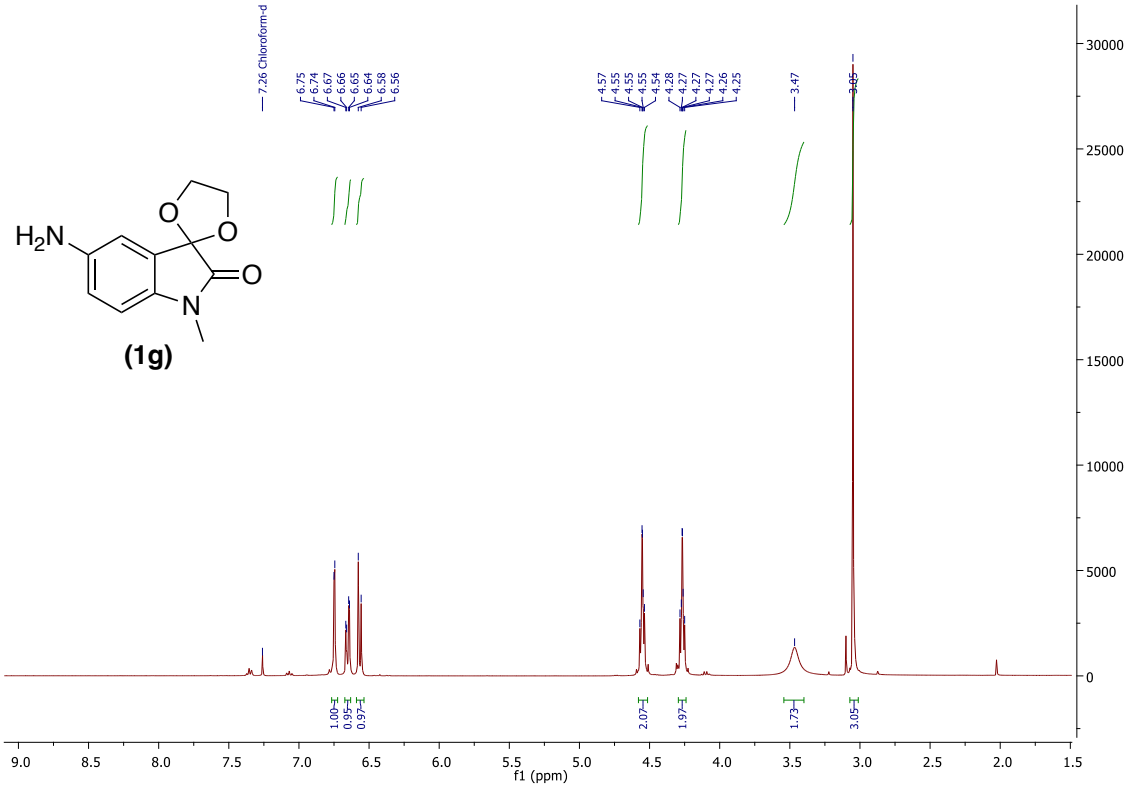
Physicochemical Properties	
Formula	C28H27N3O4
Molecular weight	469.53 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	18
Fraction Csp3	0.21
Num. rotatable bonds	10
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	137.48
TPSA	86.79 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.18
Log $P_{o/w}$ (XLOGP3)	3.52
Log $P_{o/w}$ (WLOGP)	3.18
Log $P_{o/w}$ (MLOGP)	2.21
Log $P_{o/w}$ (SILICOS-IT)	4.10
Consensus Log $P_{o/w}$	3.24

Water Solubility	
Log *S* (ESOL)	-4.69
Solubility	9.60e-03 mg/ml ; 2.05e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.03
Solubility	4.42e-03 mg/ml ; 9.41e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-8.27
Solubility	2.50e-06 mg/ml ; 5.32e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.66 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: diketo_group
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.72

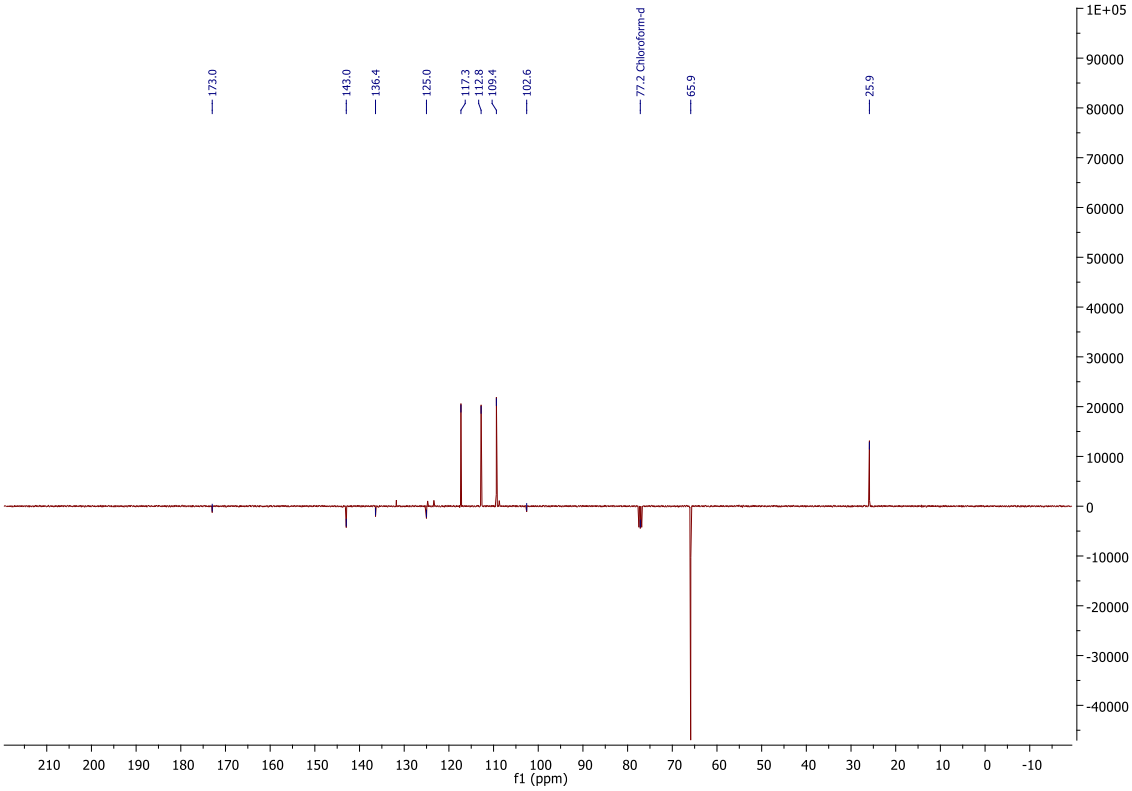
4. References

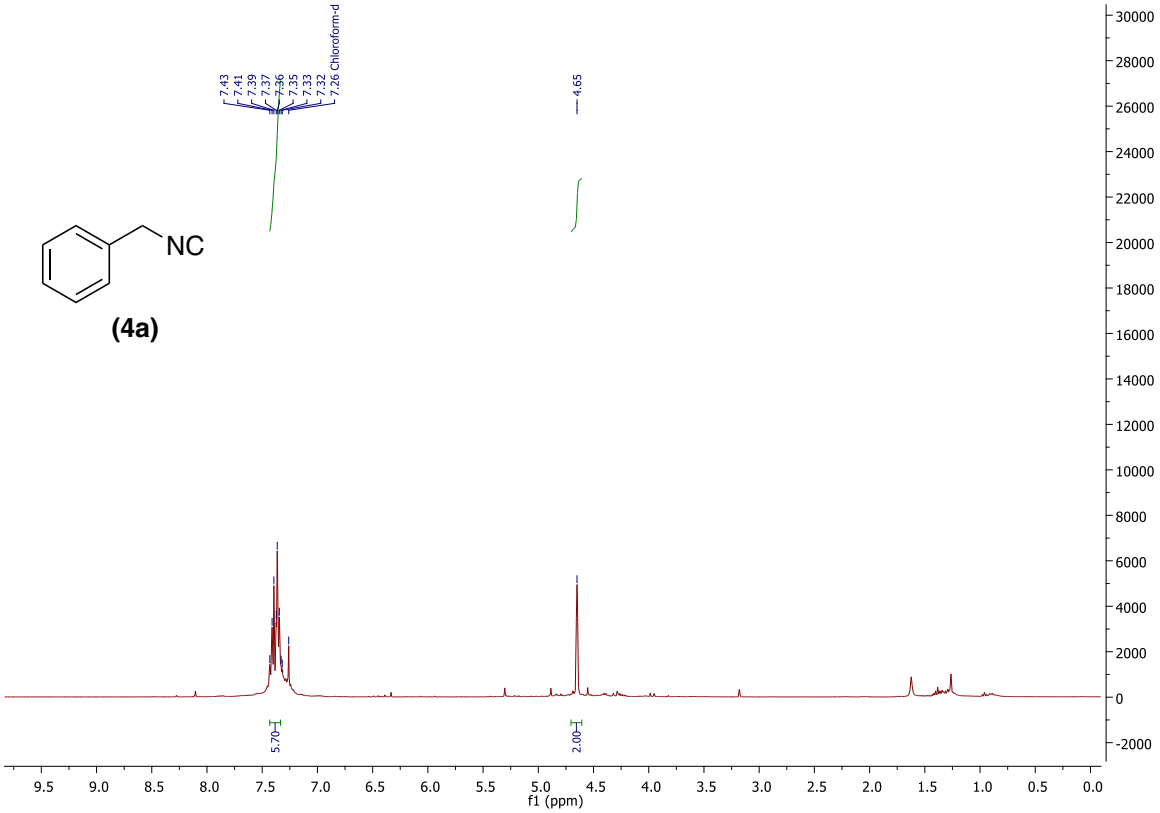
[1]. C. S. Marques, Ó. López, L. Leitzbach, J. G. Fernández-Bolaños, H. Stark, A. J. Burke, *Synthesis*, **2022**. doi: 10.1055/s-0041-1737343.
[2]. C. S. Marques, P. McArdle, A. Erxleben, A. J. Burke, *Eur. J. Org. Chem.*, **2020**, 3622. doi: 10.1002/ejoc.202000334.
[3] (a) A. W. Hofmann, *Grundlagen der organischem Chemie; Verlag Sauerlander Aarau, Diesterweg*, **1970**. (b) R. Mocci, S. Murgia, L. De Luca, E. Colacino, F. Delogu, A. Porcheddu, *Org. Chem. Front.*, **2018**, 5, 531.

5. ^{1}H and ^{13}C NMR spectra



(1g)

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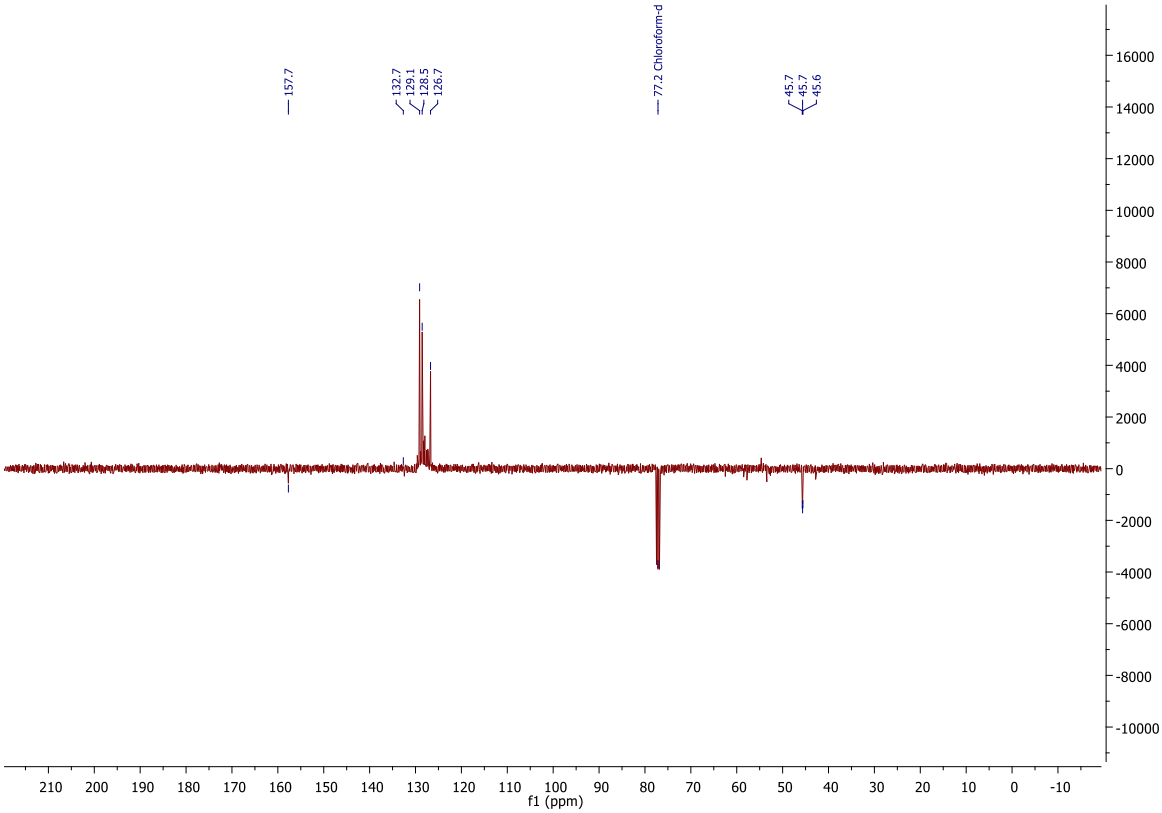
7.41
7.39
7.37
7.36
7.35
7.33
7.32
7.26 Chloroform-d
4.65
NC
(4a)
5.70
2.00
f1 (ppm)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132.7
129.1
128.5
126.7
77.2 Chloroform-d
45.7
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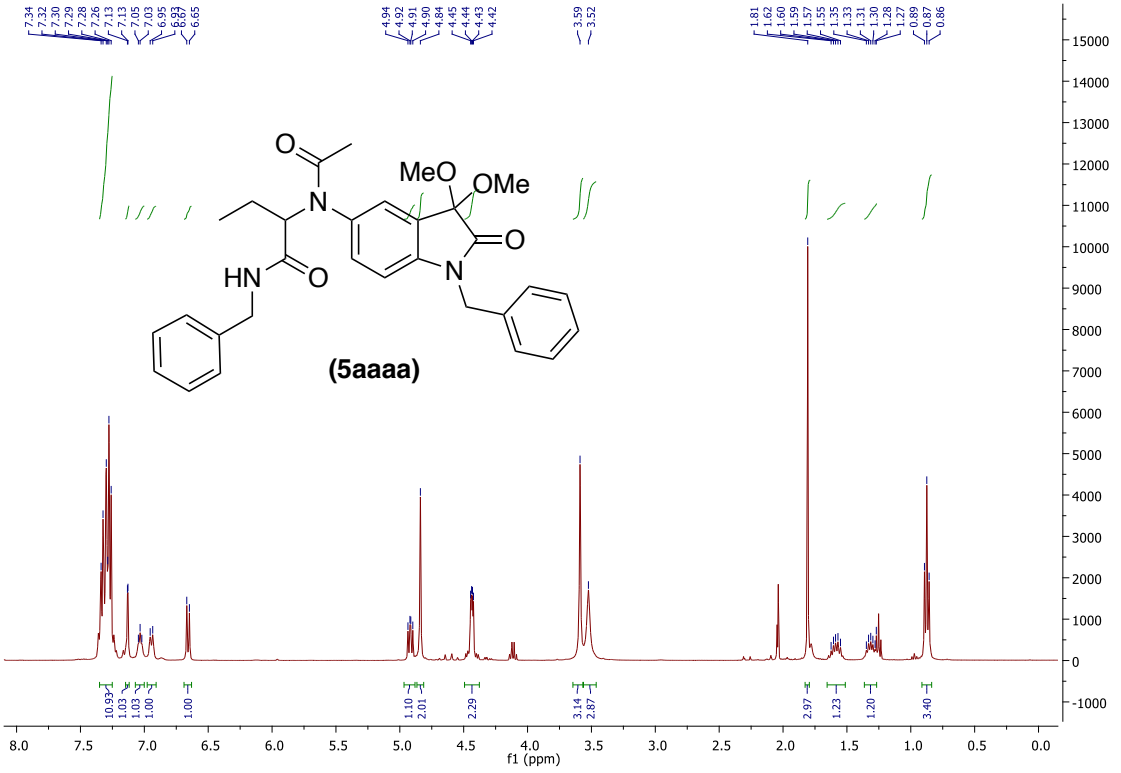
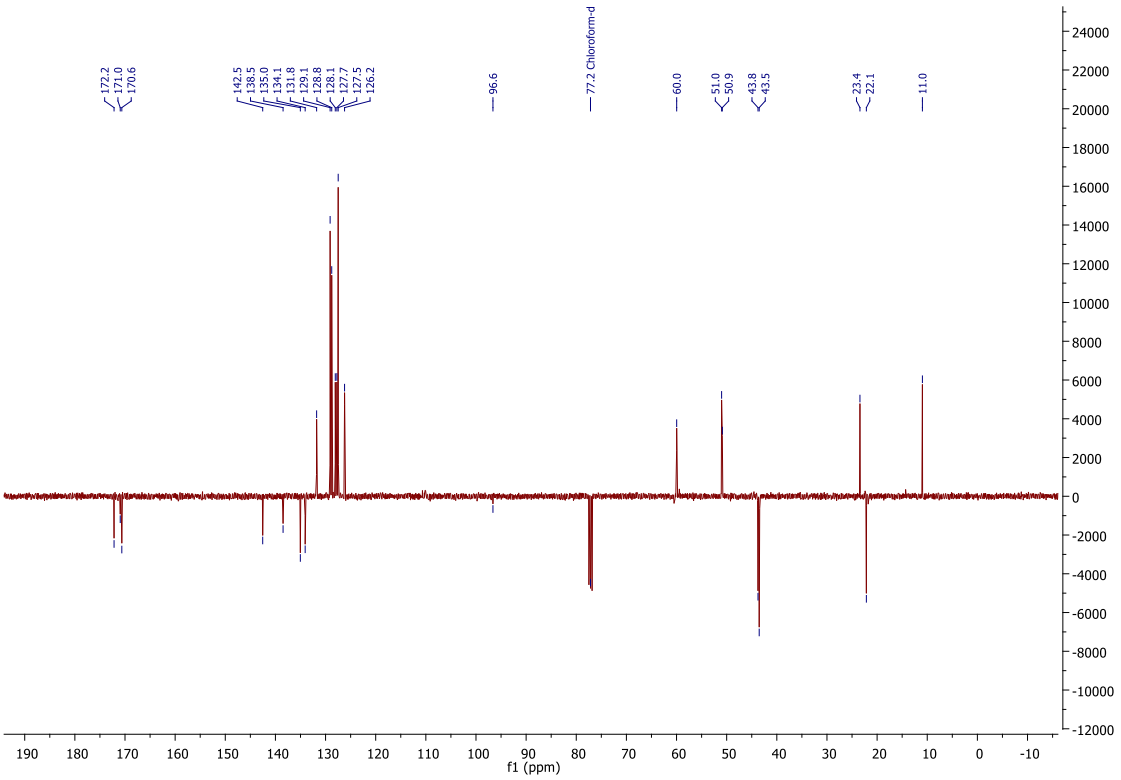
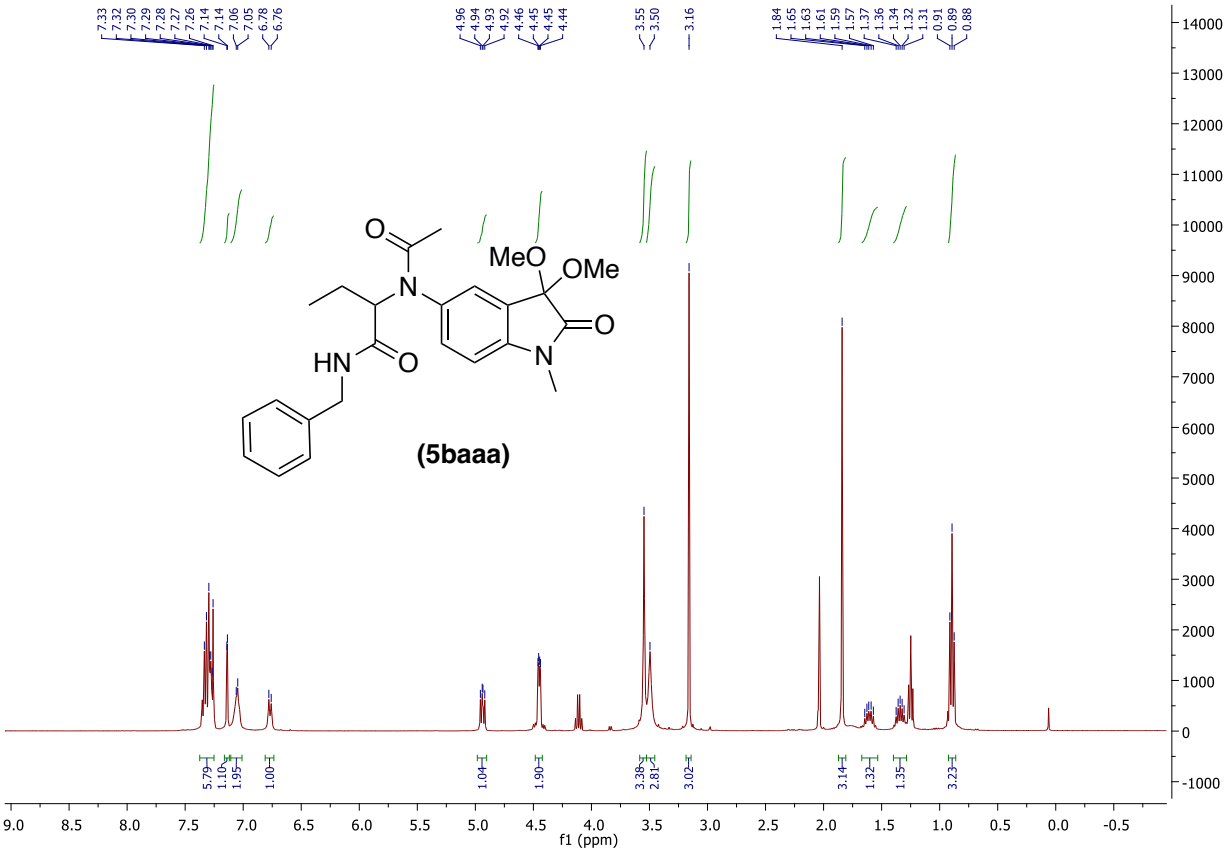
45.6
f1 (ppm)


MeO
OMe
O
N
HN
O
(5aaaa)
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)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7.27
7.26
7.14
7.06
7.05
6.78
6.76
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4.94
4.93
4.92
4.46
4.45
4.45
4.44
3.55
3.50
3.16
1.84
1.65
1.63
1.61
1.59
1.57
1.37
1.36
1.34
1.32
1.31
0.91
0.89
0.88
O
N
MeO
OMe
O
HN
O
N
(5baaa)
5.79
1.10
1.95
1.00
1.04
1.90
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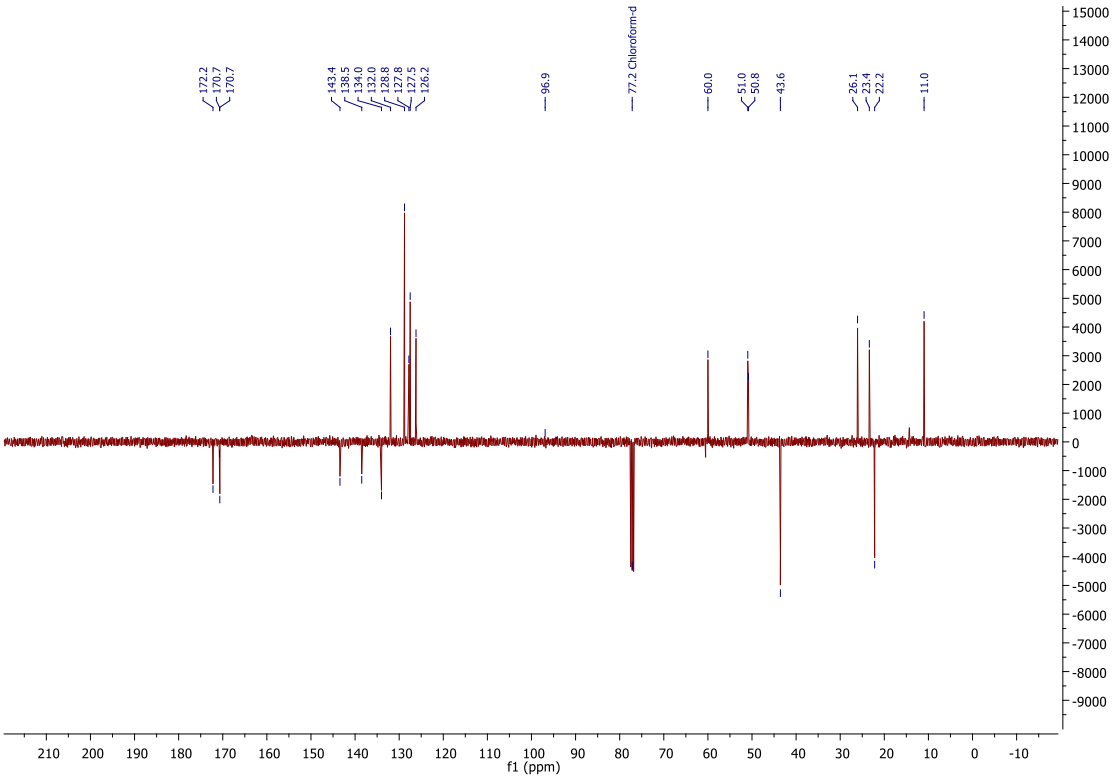
2.81
3.02
3.14
1.32
1.35
3.23
f1 (ppm)


172.2
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170.7
143.4
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127.5
126.2
96.9
77.2 Chloroform-d
60.0
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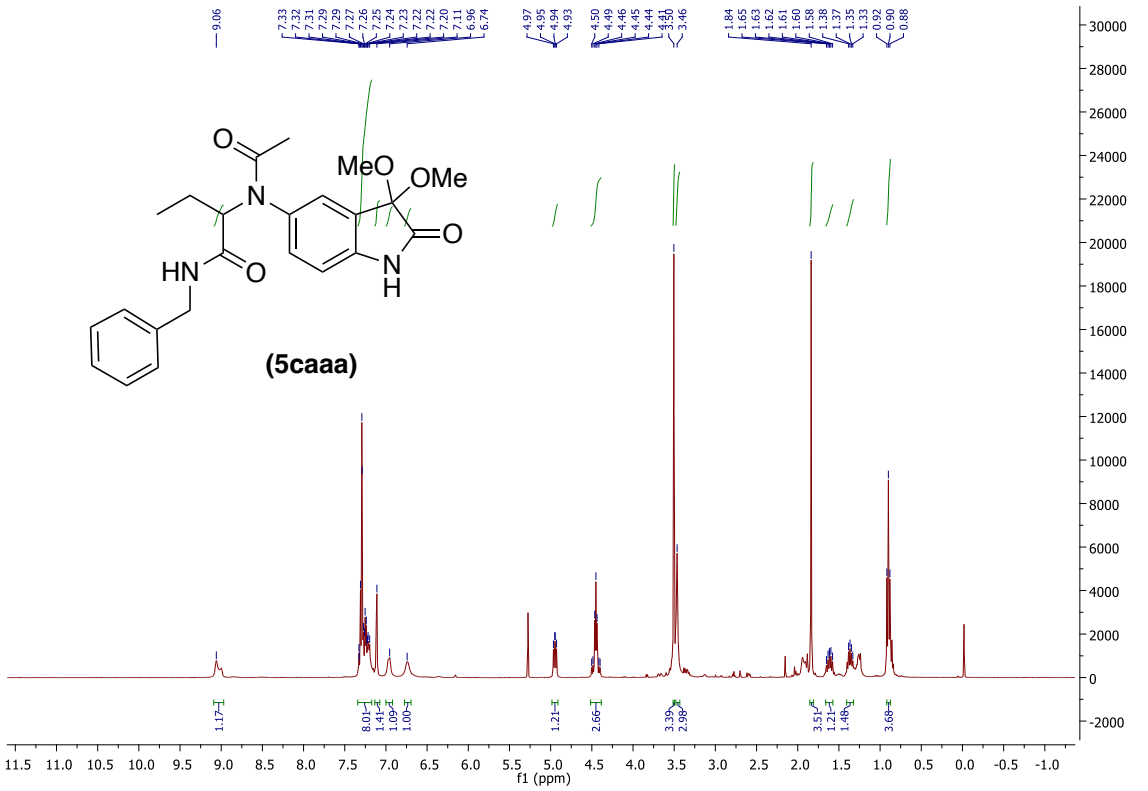
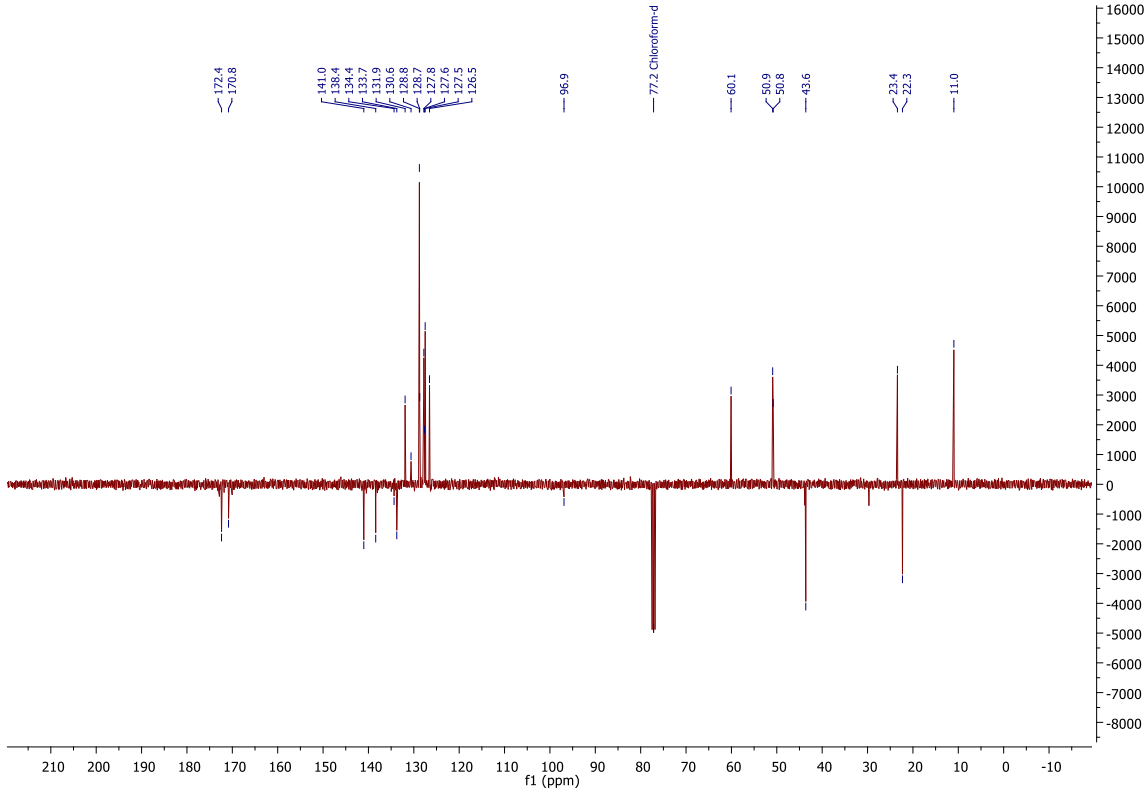
50.8
43.6
26.1
23.4
22.2
11.0
f1 (ppm)


(5caaa)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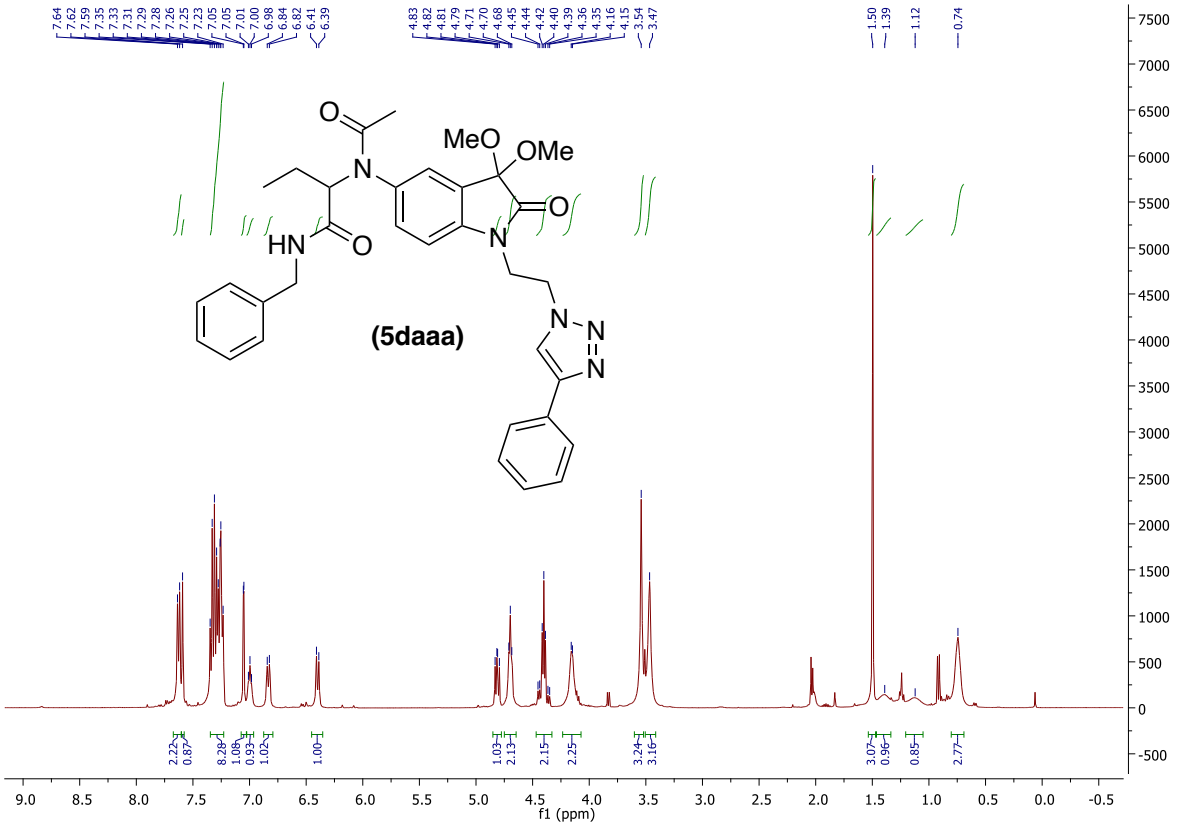
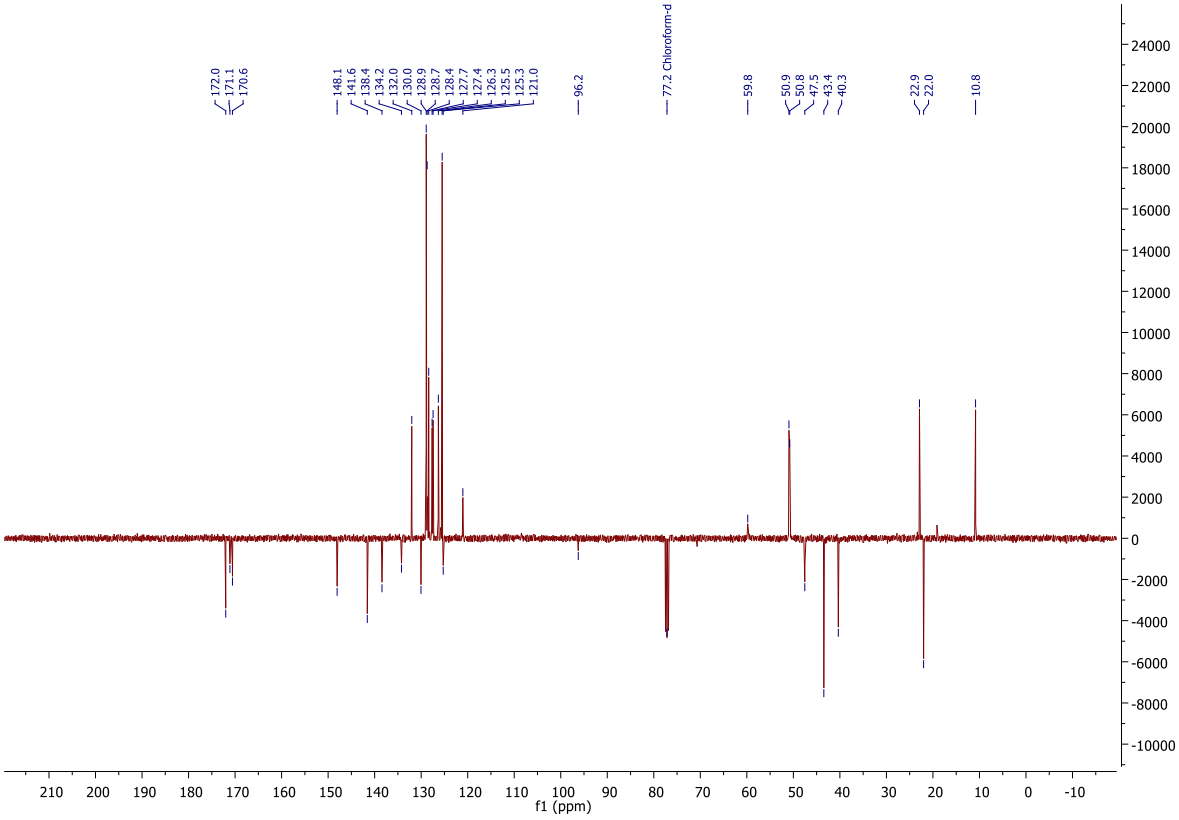
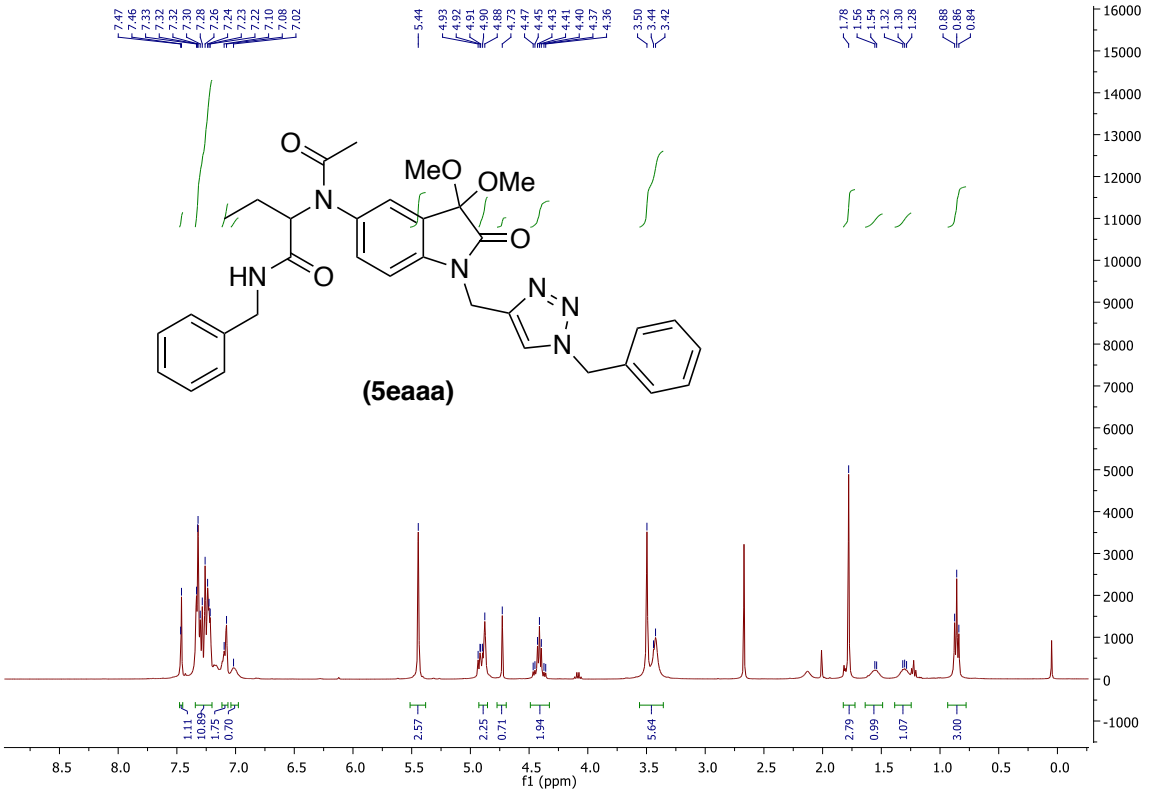

(5daaa)
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)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7.28
7.26
7.24
7.23
7.22
7.10
7.08
7.02
5.44
4.93
4.92
4.91
4.90
4.88
4.73
4.47
4.45
4.43
4.41
4.40
4.37
4.36
3.50
3.44
3.42
1.78
1.56
1.54
1.32
1.30
1.28
0.88
0.86
0.84
O
N
MeO
OMe
O
HN
O
N
N
N
N
(5eaaa)
1.11
10.89
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2.25
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1.94
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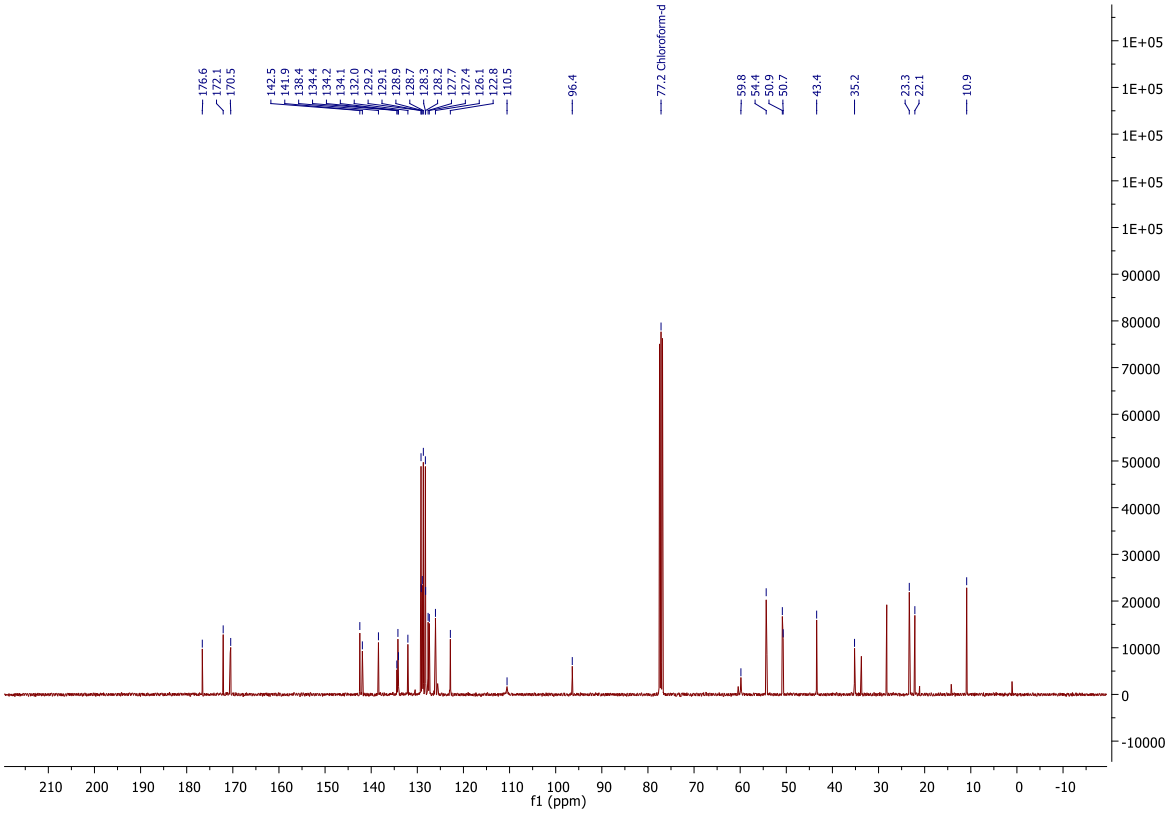
3.00
f1 (ppm)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132.0
129.2
129.1
128.9
128.7
128.3
128.2
127.7
127.4
126.1
122.8
110.5
96.4
77.2 Chloroform-d
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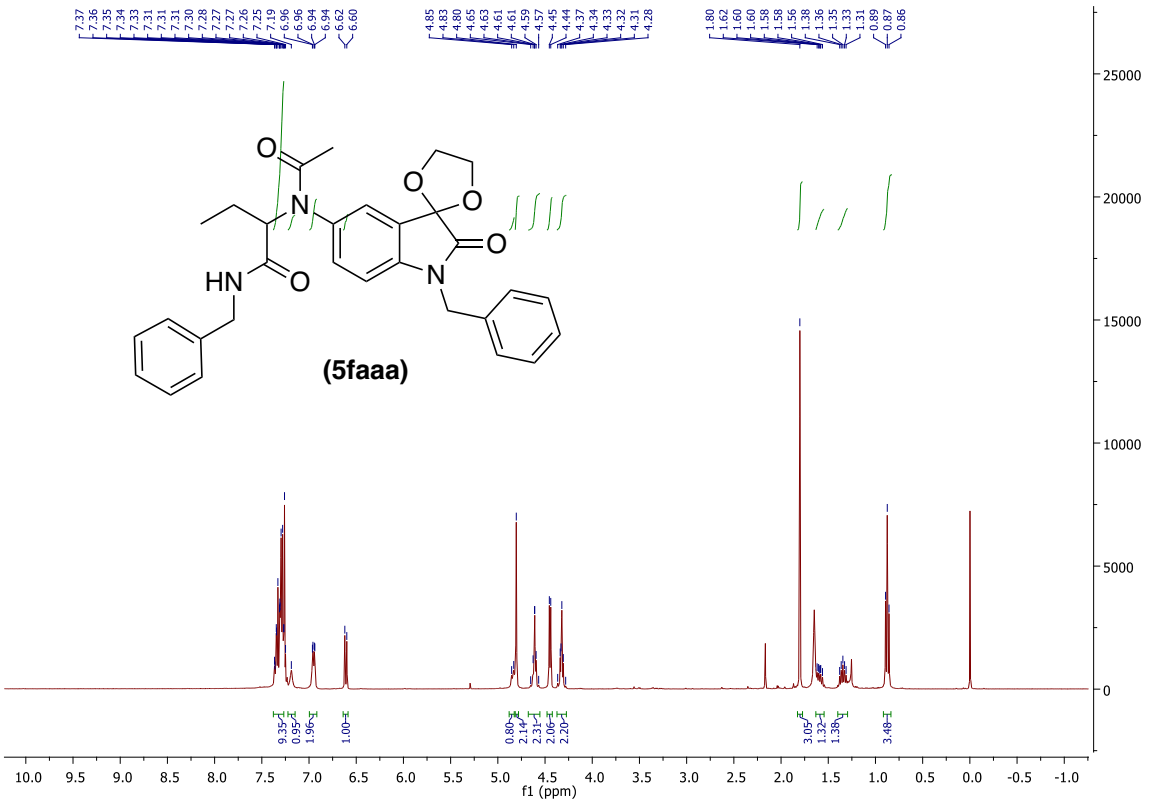
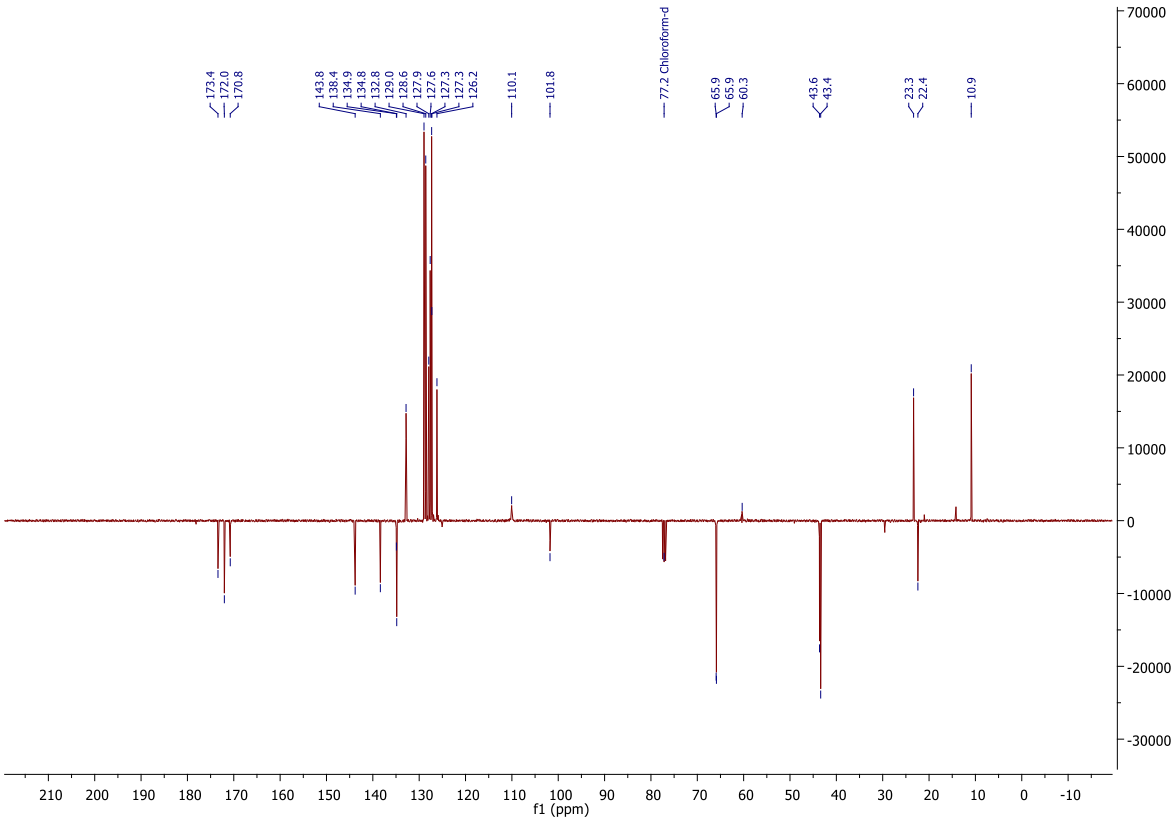
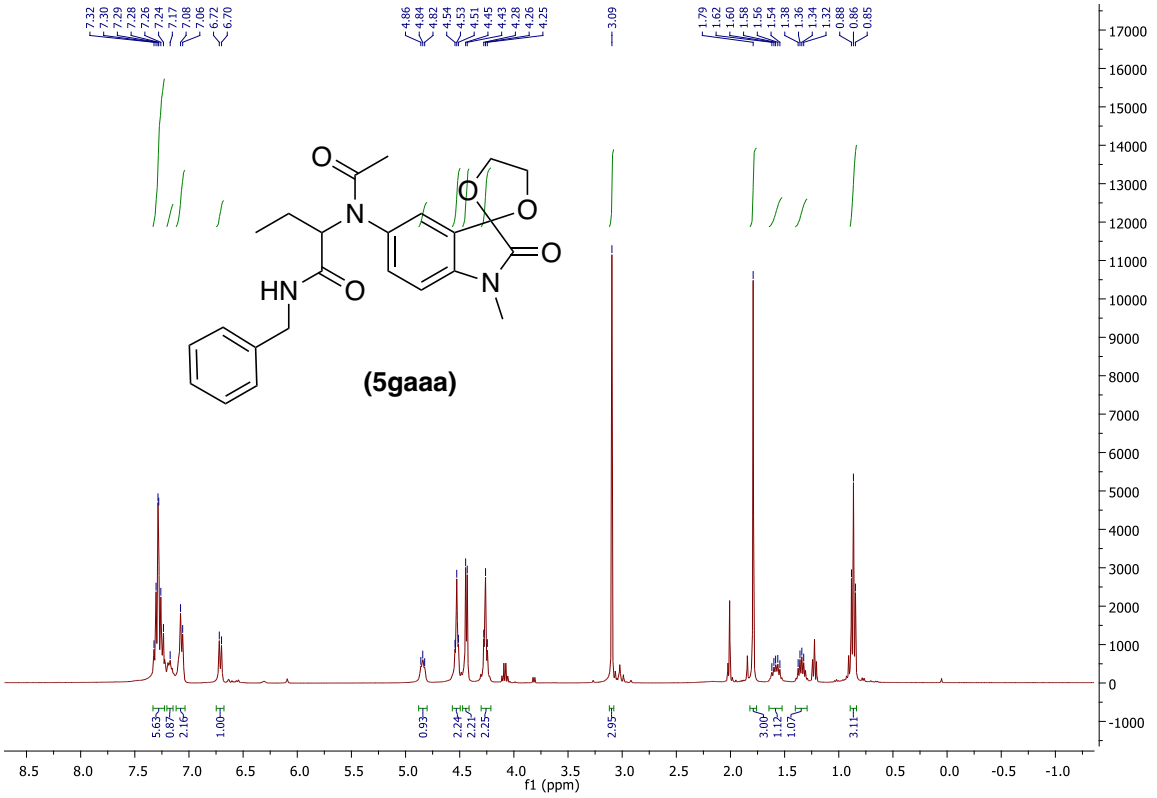
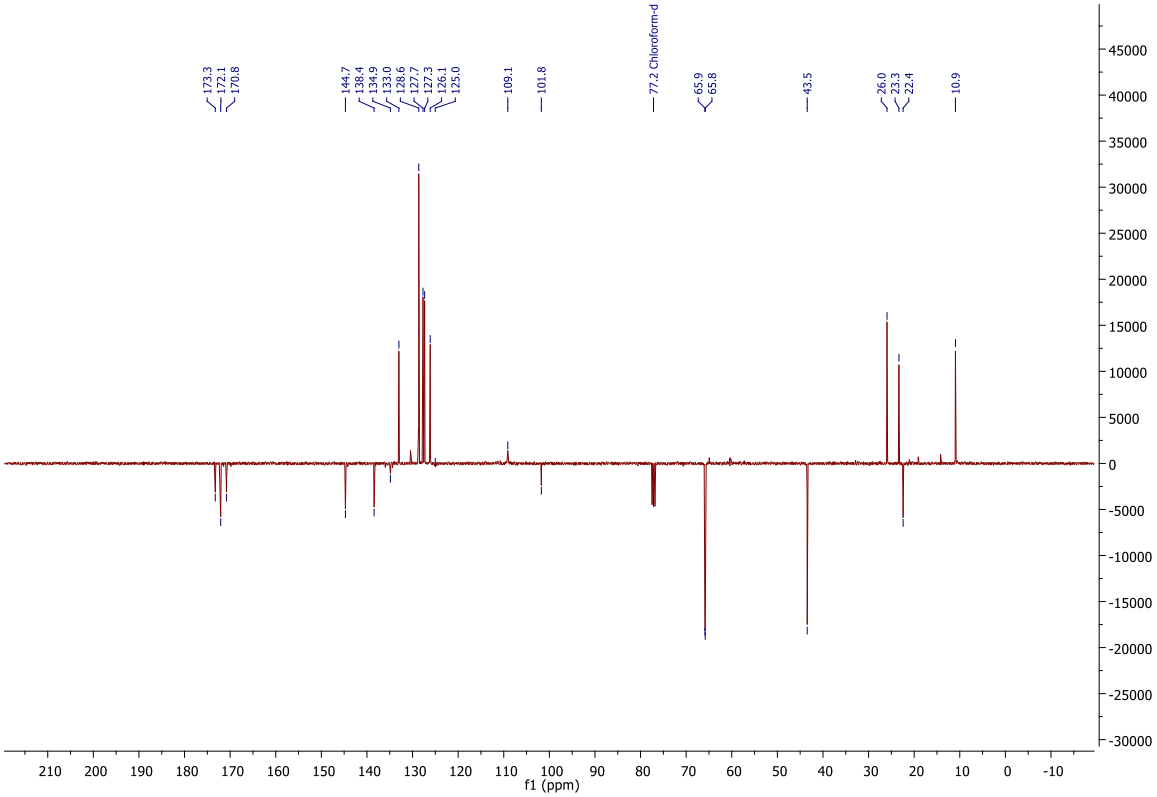
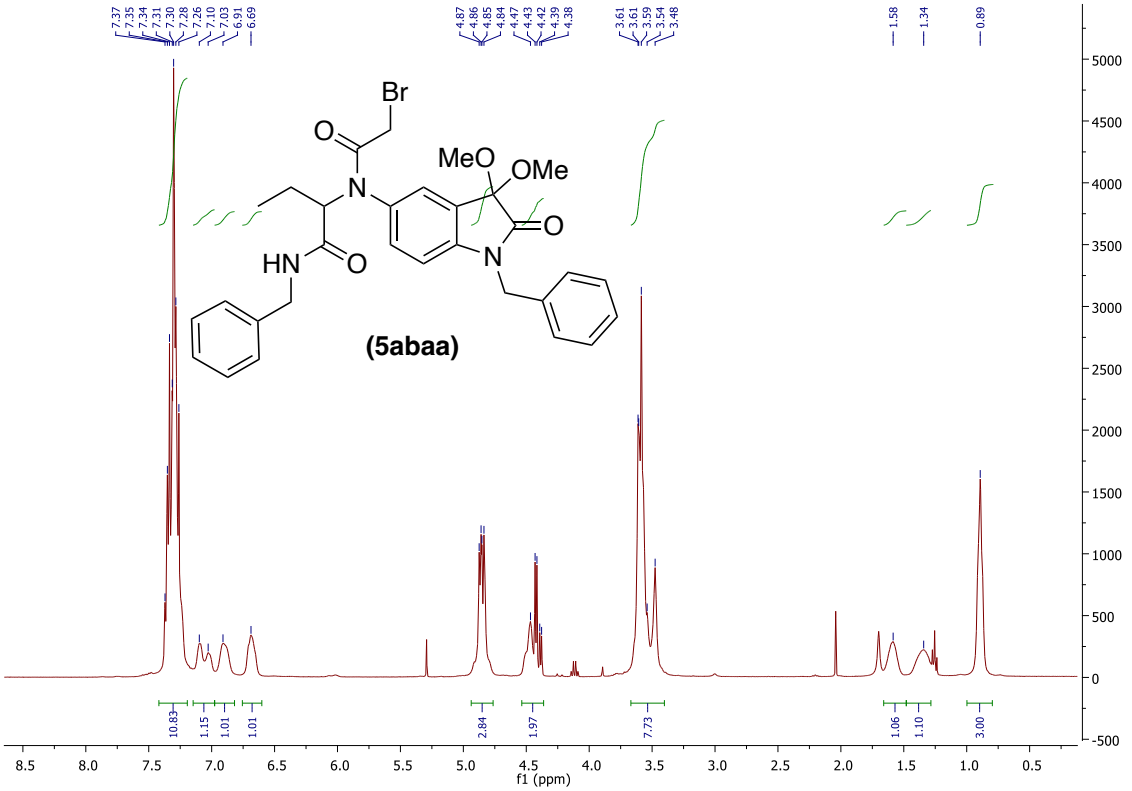
54.4
50.9
50.7
43.4
35.2
23.3
22.1
10.9
f1 (ppm)


(5faaa)
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)


(5gaaa)
f1 (ppm)


f1 (ppm)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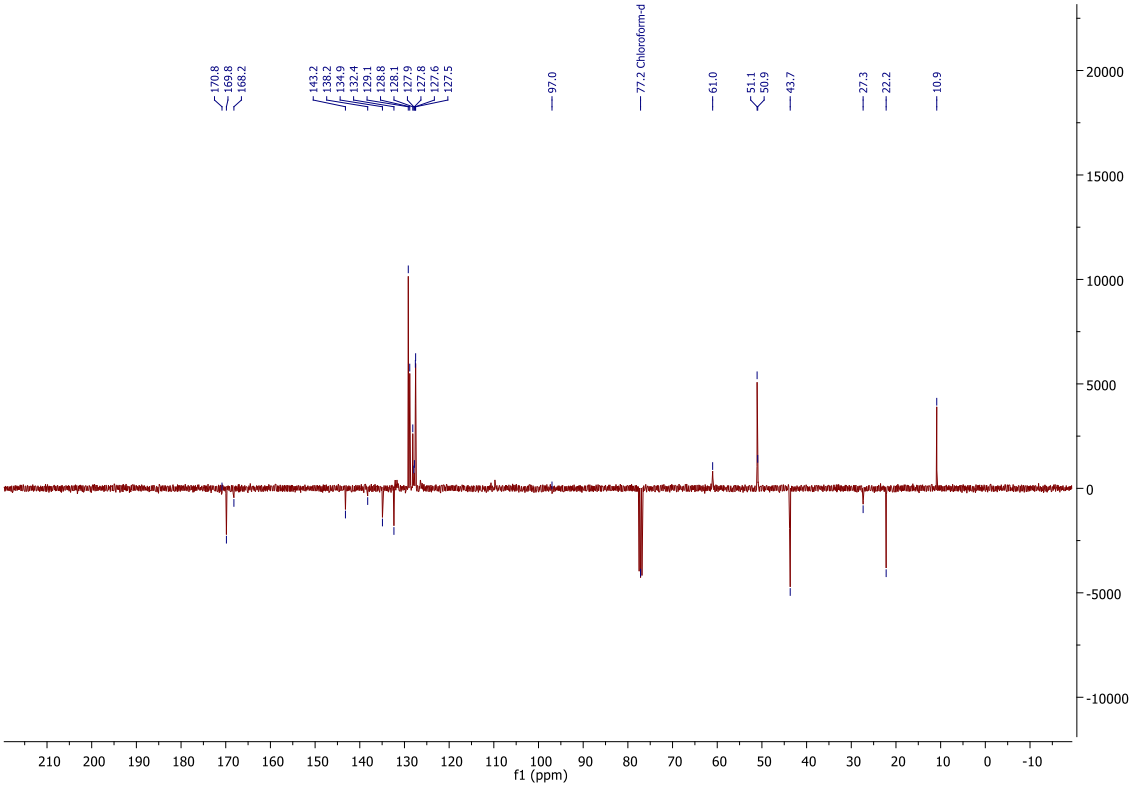
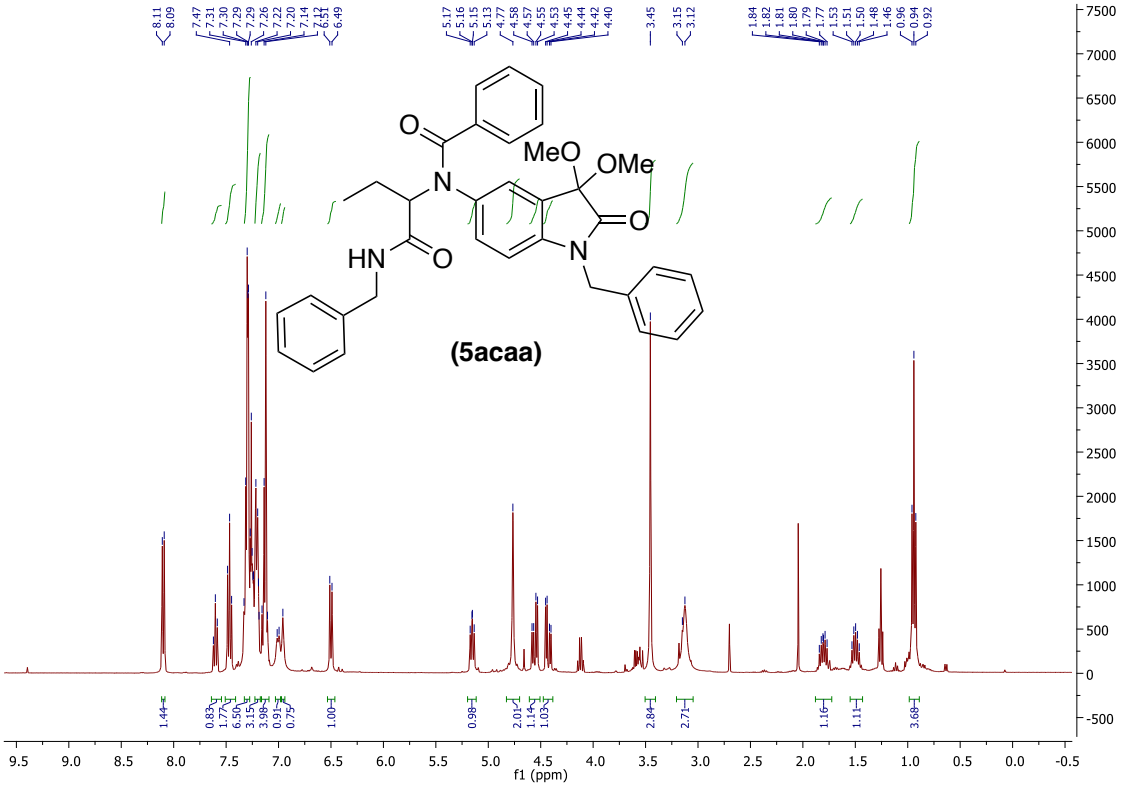
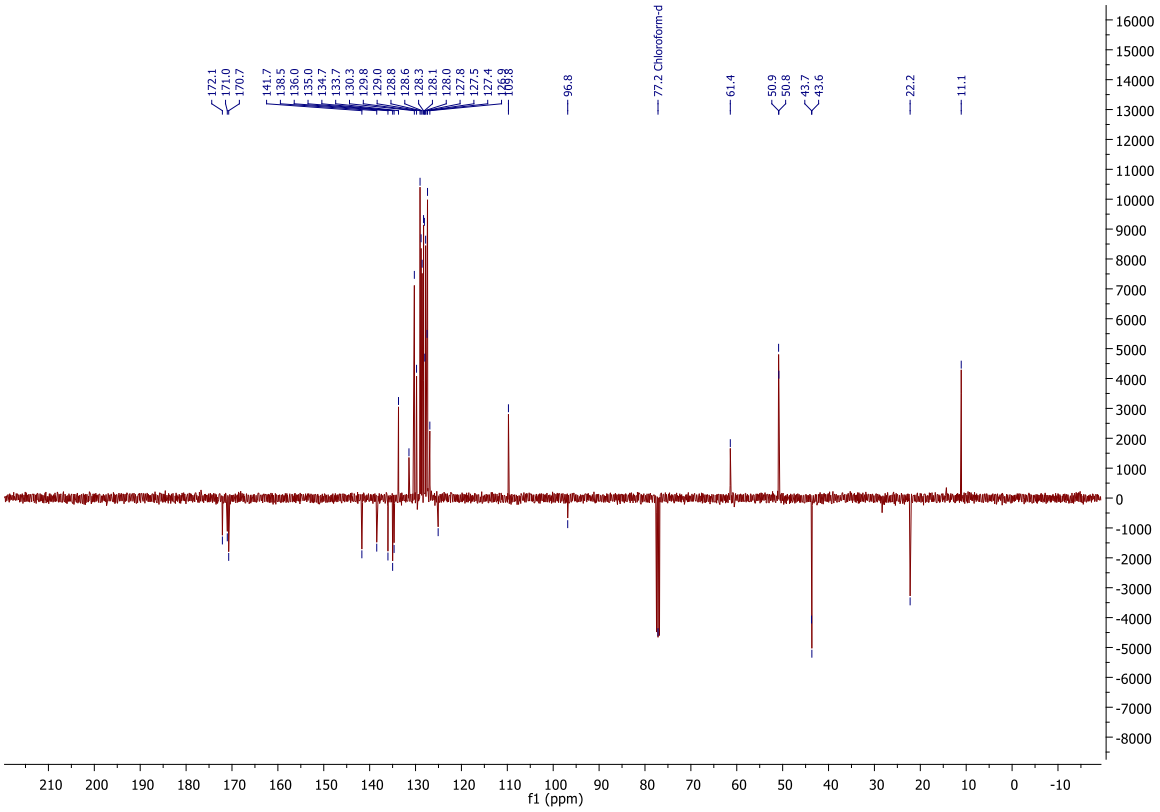
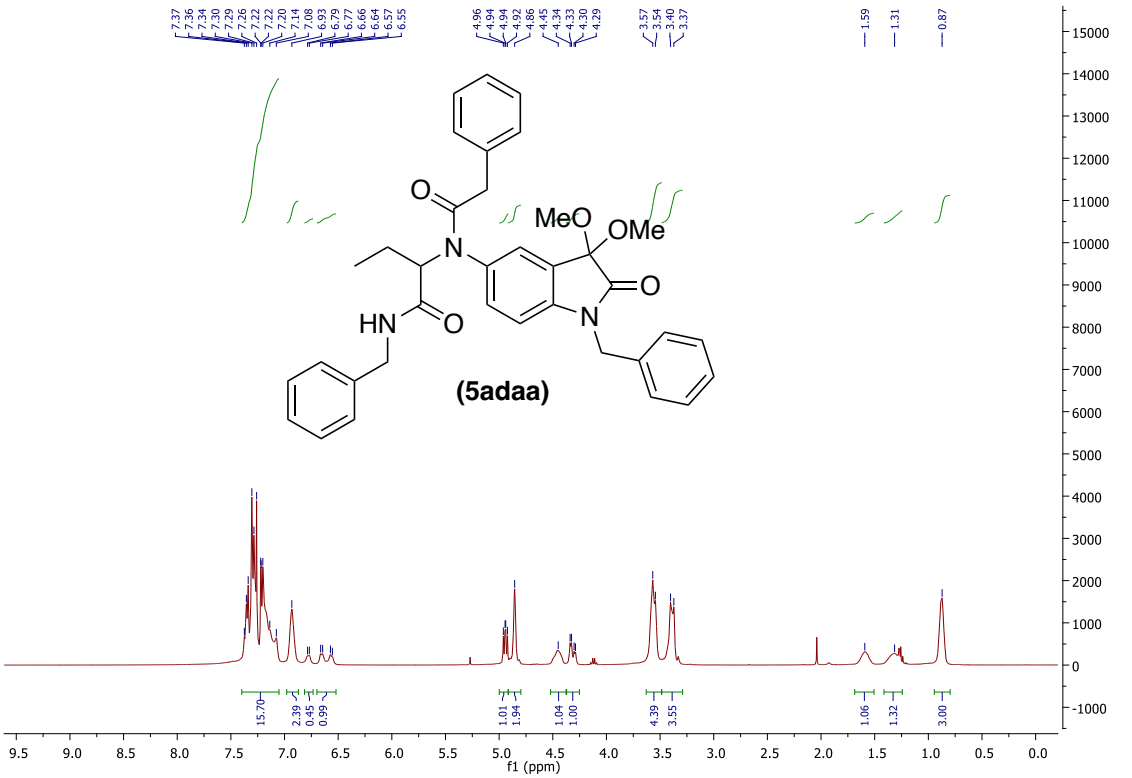
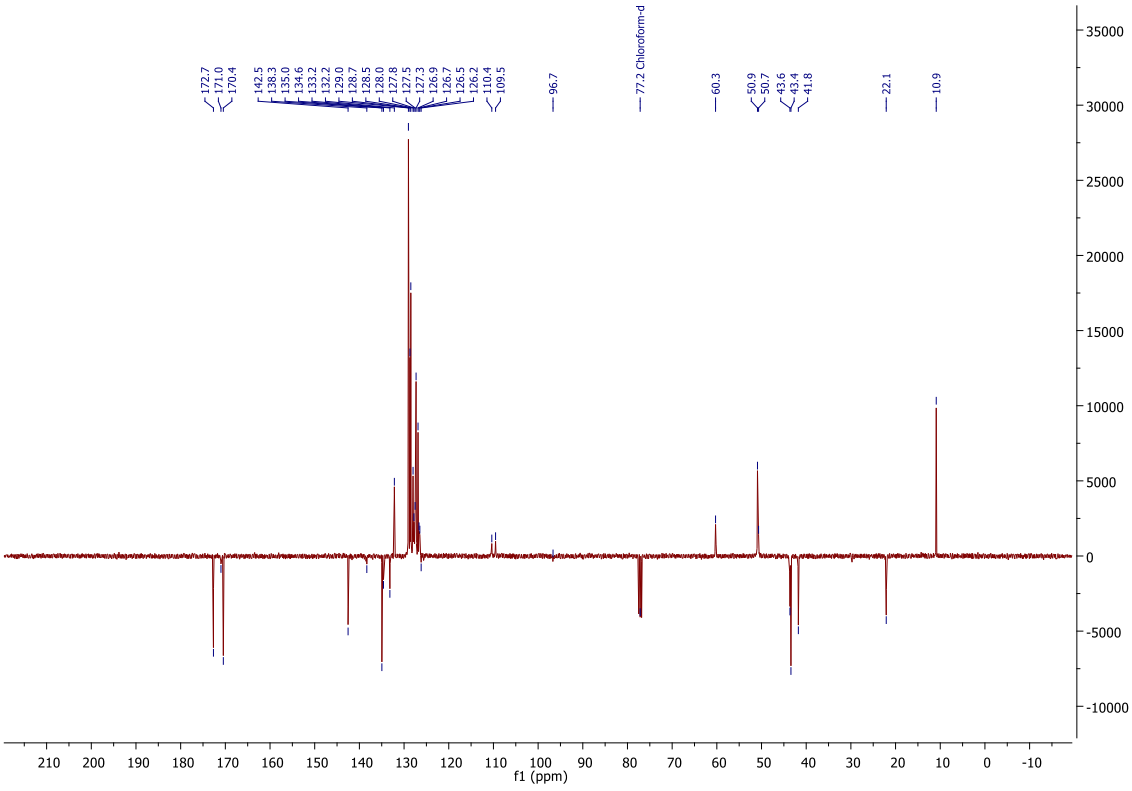
7.28
7.26
7.10
7.03
6.91
6.69
4.87
4.86
4.85
4.84
4.47
4.43
4.42
4.39
4.38
3.61
3.61
3.59
3.54
3.48
1.58
1.34
0.89
Br
O
N
MeO
OMe
O
HN
O
N
(5abaa)
10.83
1.15
1.01
1.01
2.84
1.97
7.73
1.06
1.10
3.00
f1 (ppm)

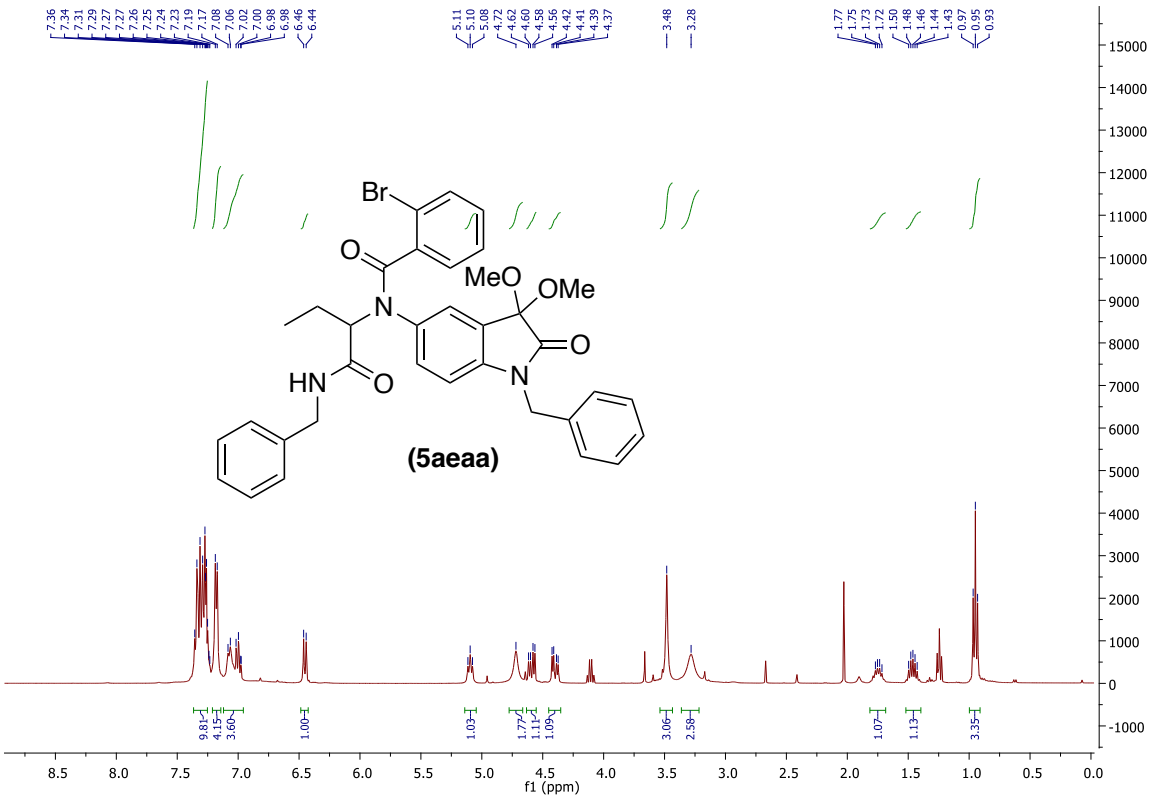

170.8
169.8
168.2
143.2
138.2
134.9
132.4
129.1
128.8
128.1
127.9
127.8
127.6
127.5
97.0
77.2 Chloroform-d
61.0
51.1
50.9
43.7
27.3
22.2
10.9
f1 (ppm)

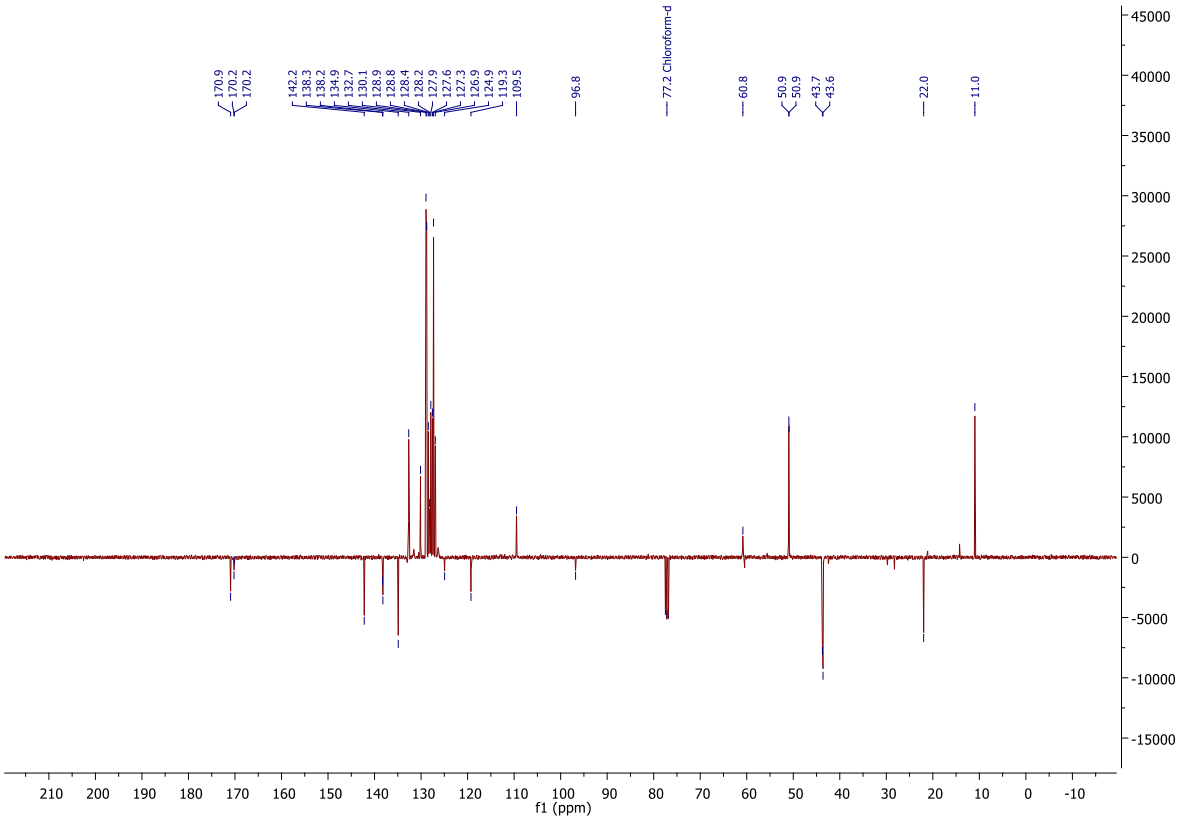

(5acaa)
f1 (ppm)

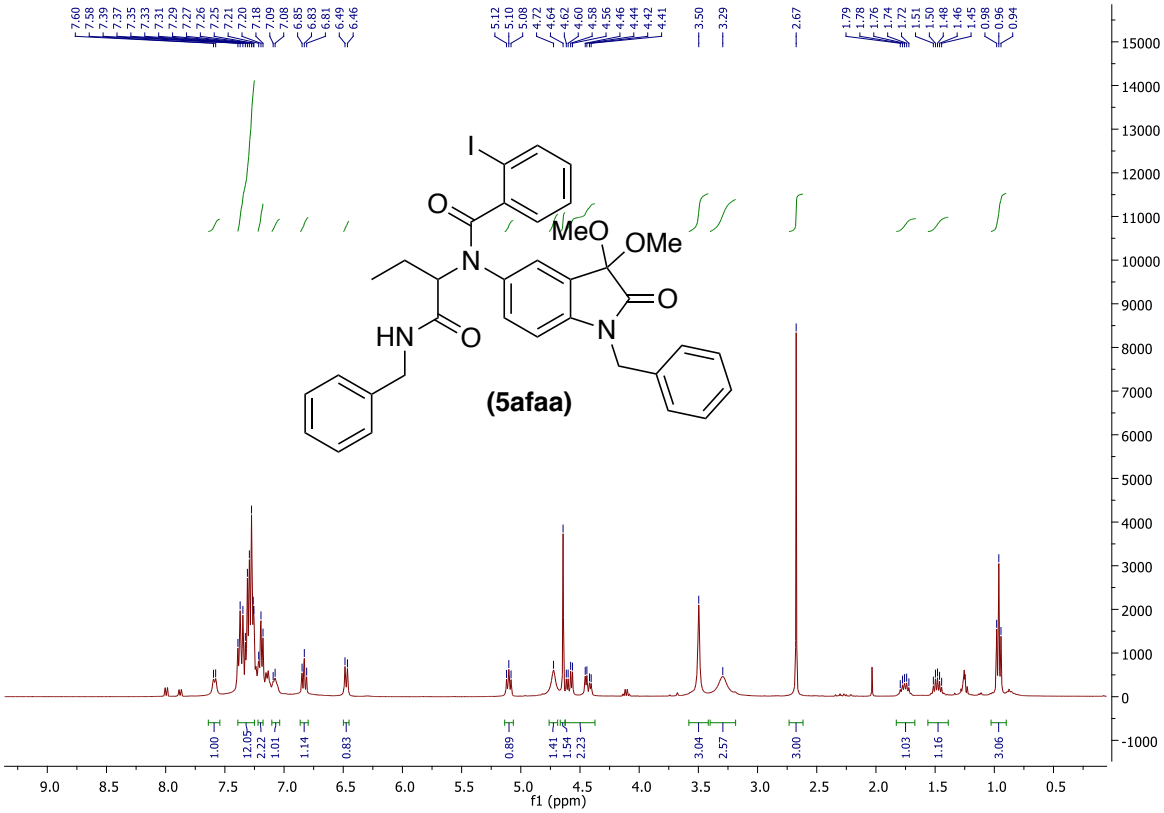

77.2 Chloroform-d
f1 (ppm)

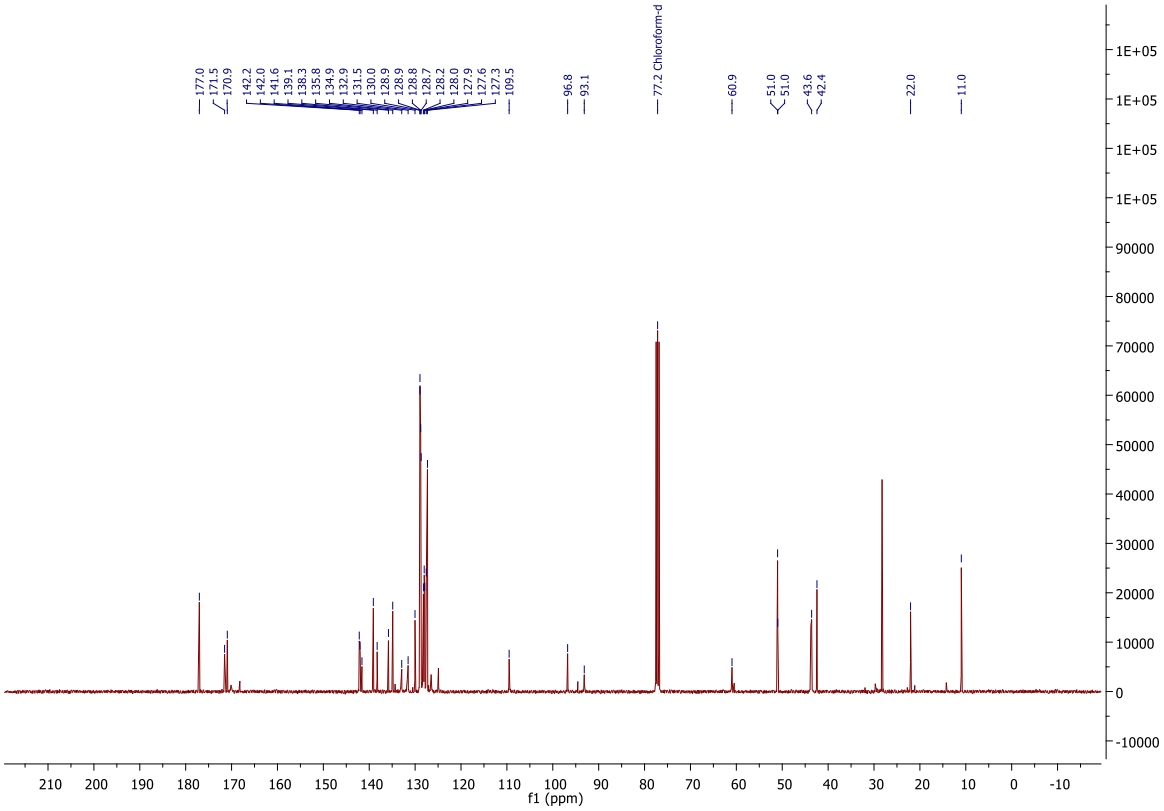

MeO
OMe
O
N
HN
O
O
N
(5adaa)
f1 (ppm)

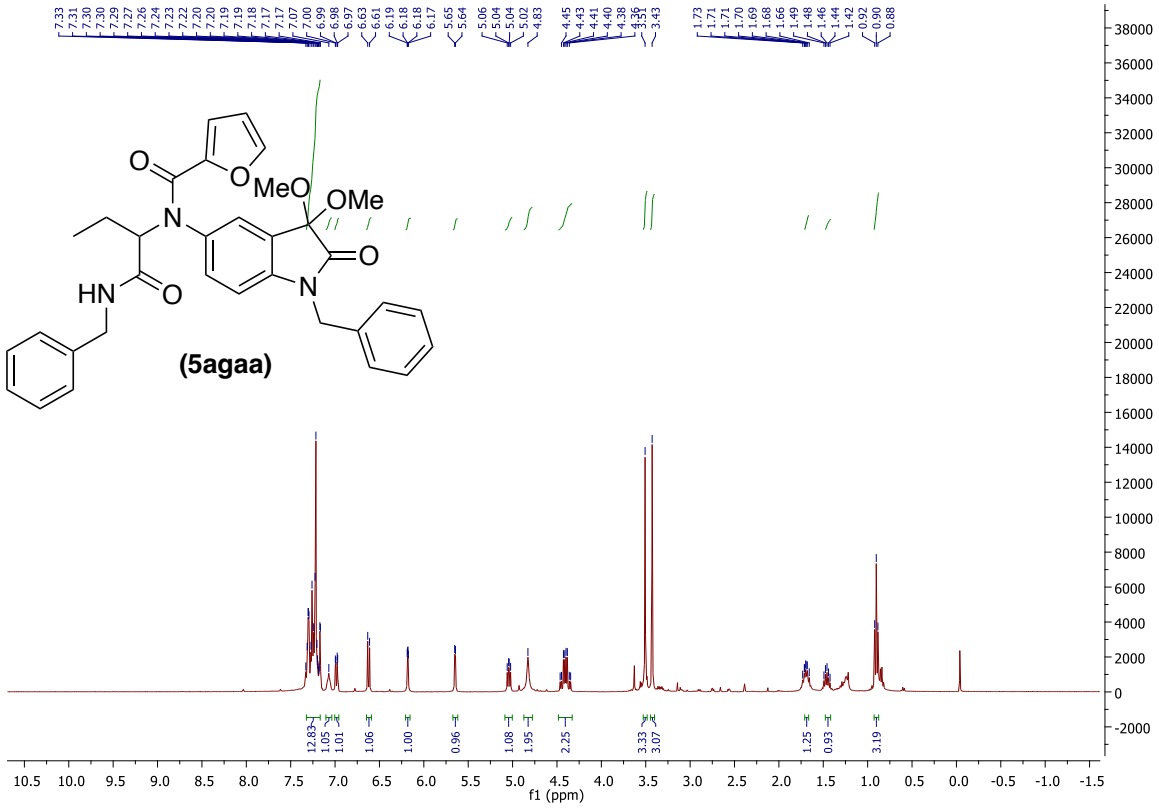

77.2 Chloroform-d
f1 (ppm)

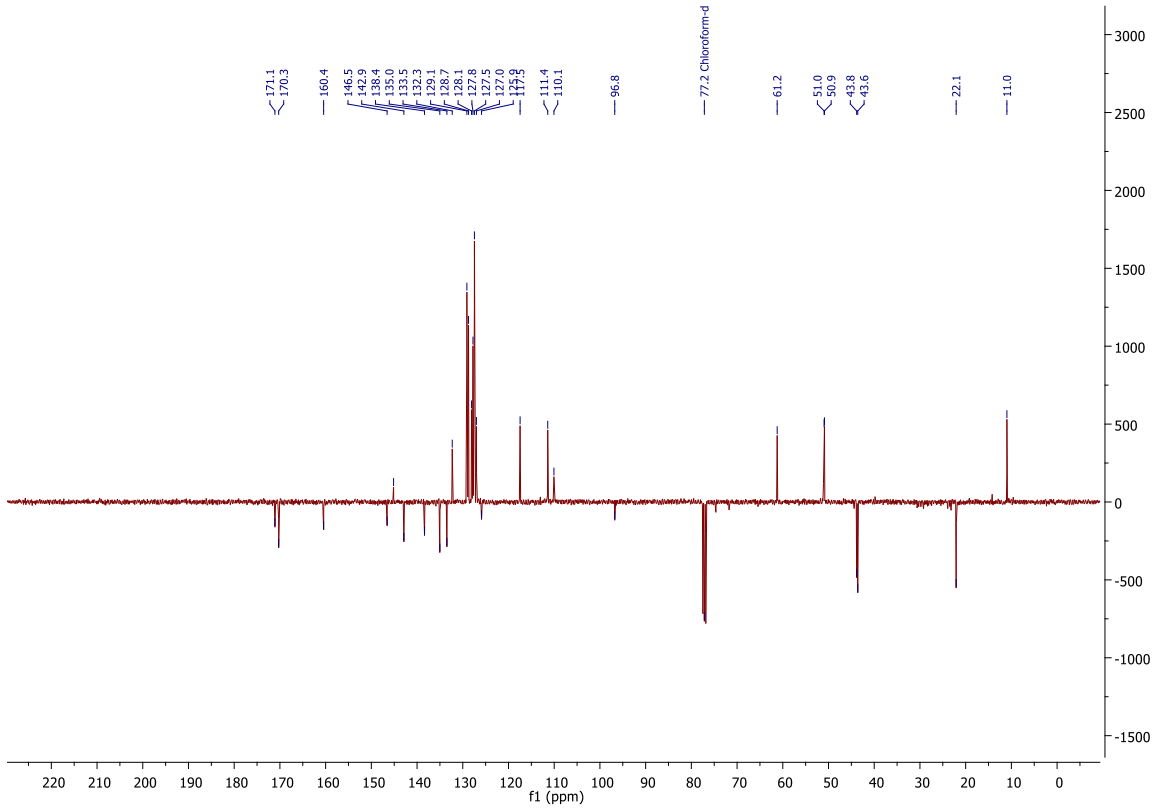

Br
O
N
MeO
OMe
O
HN
O
N
(5aeaa)
f1 (ppm)

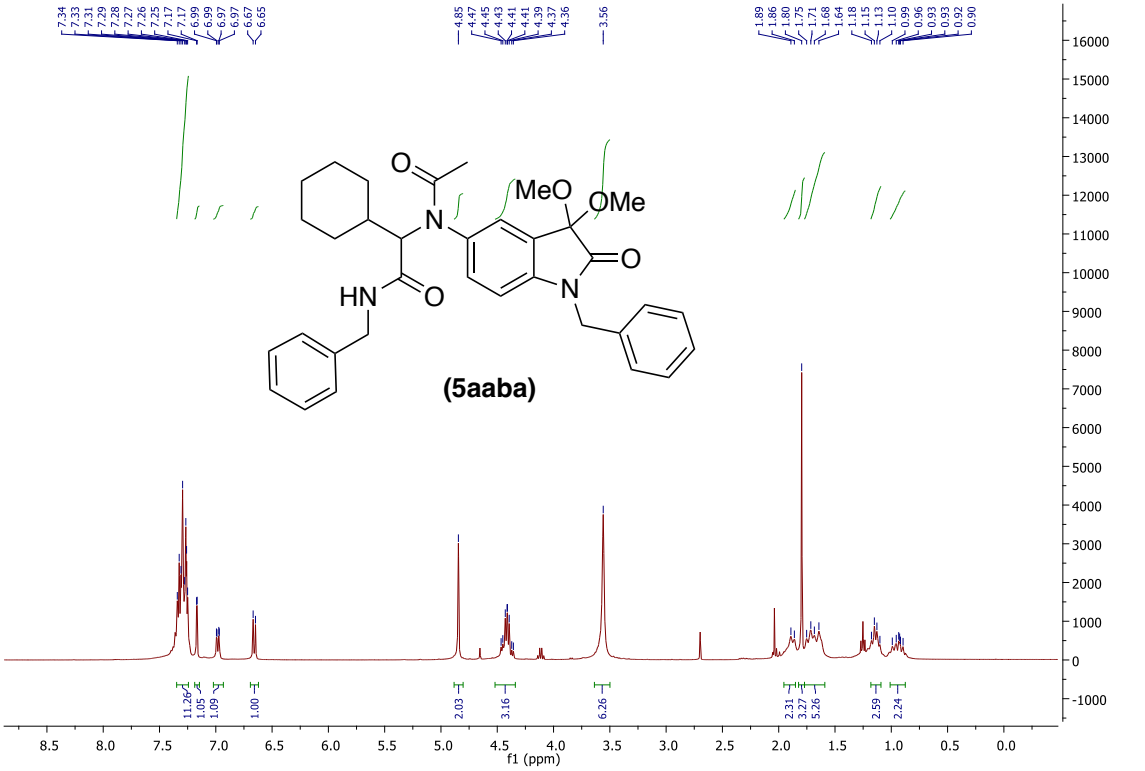

77.2 Chloroform-d
f1 (ppm)

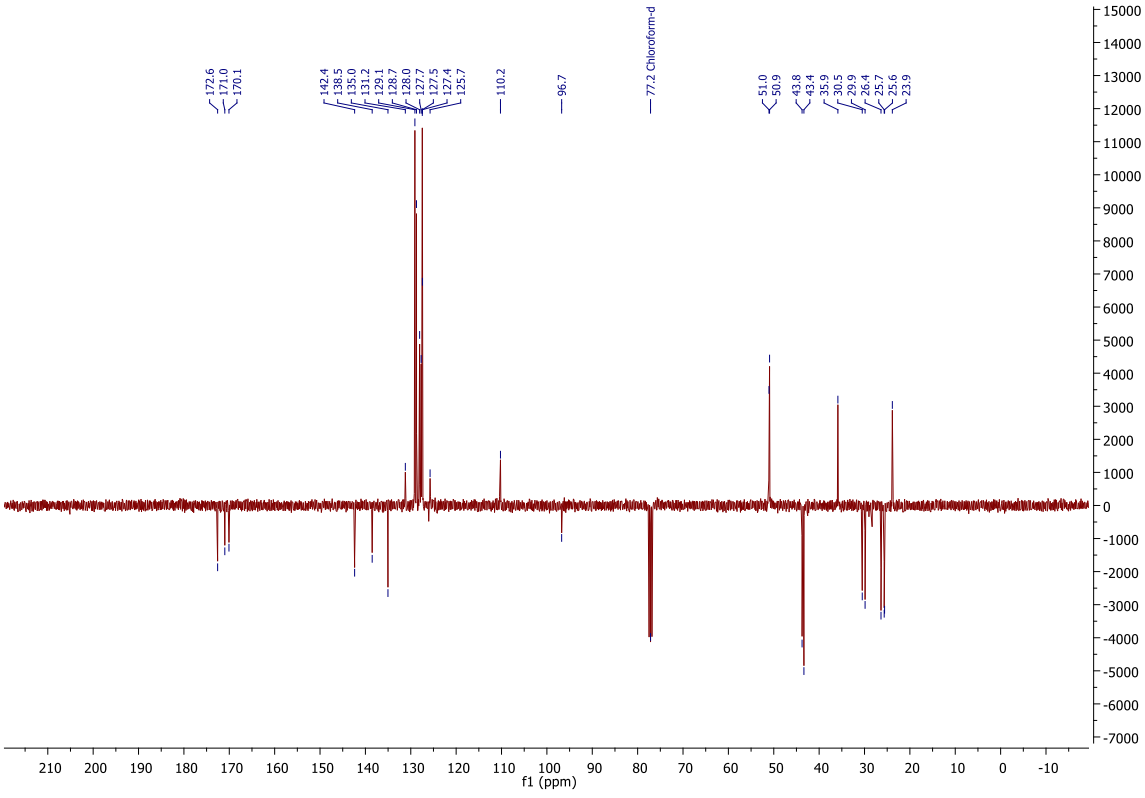

I
O
N
MeO
OMe
O
HN
O
N
(5afaa)
f1 (ppm)

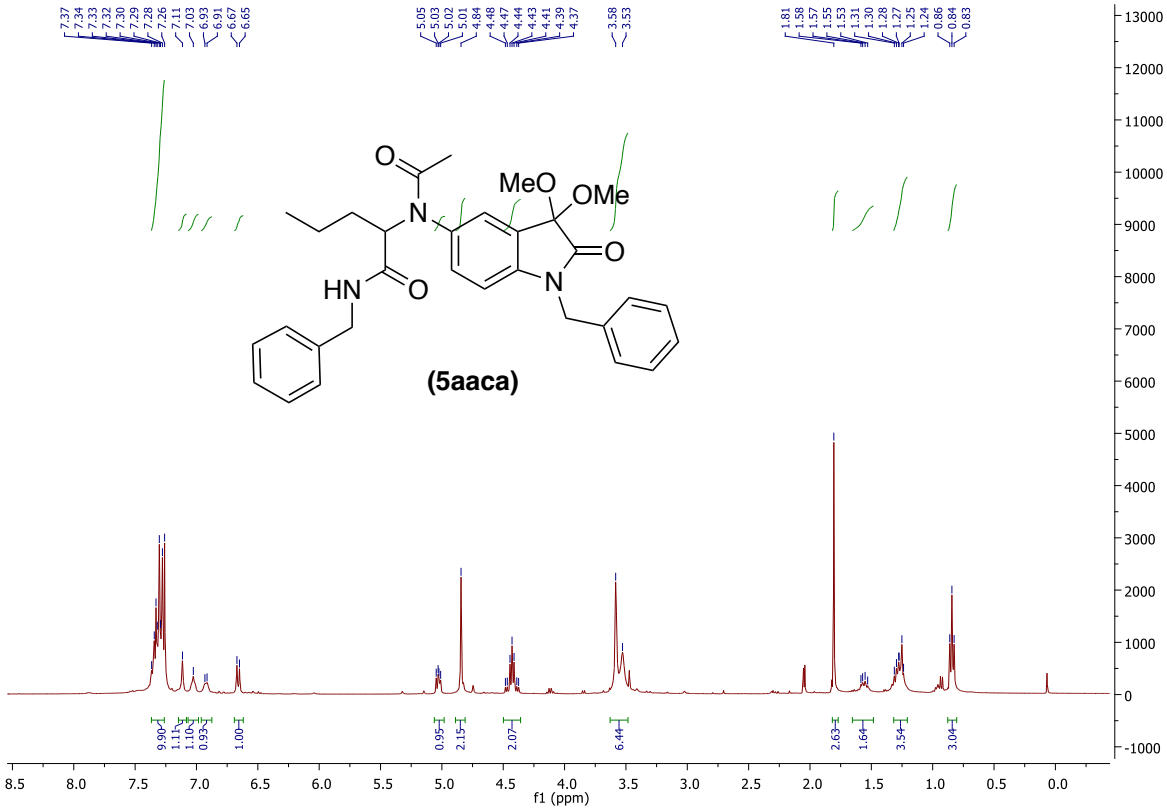

77.2 Chloroform-d
f1 (ppm)


(5agaa)


77.2 Chloroform-d


(5aaba)
f1 (ppm)


f1 (ppm)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7.32
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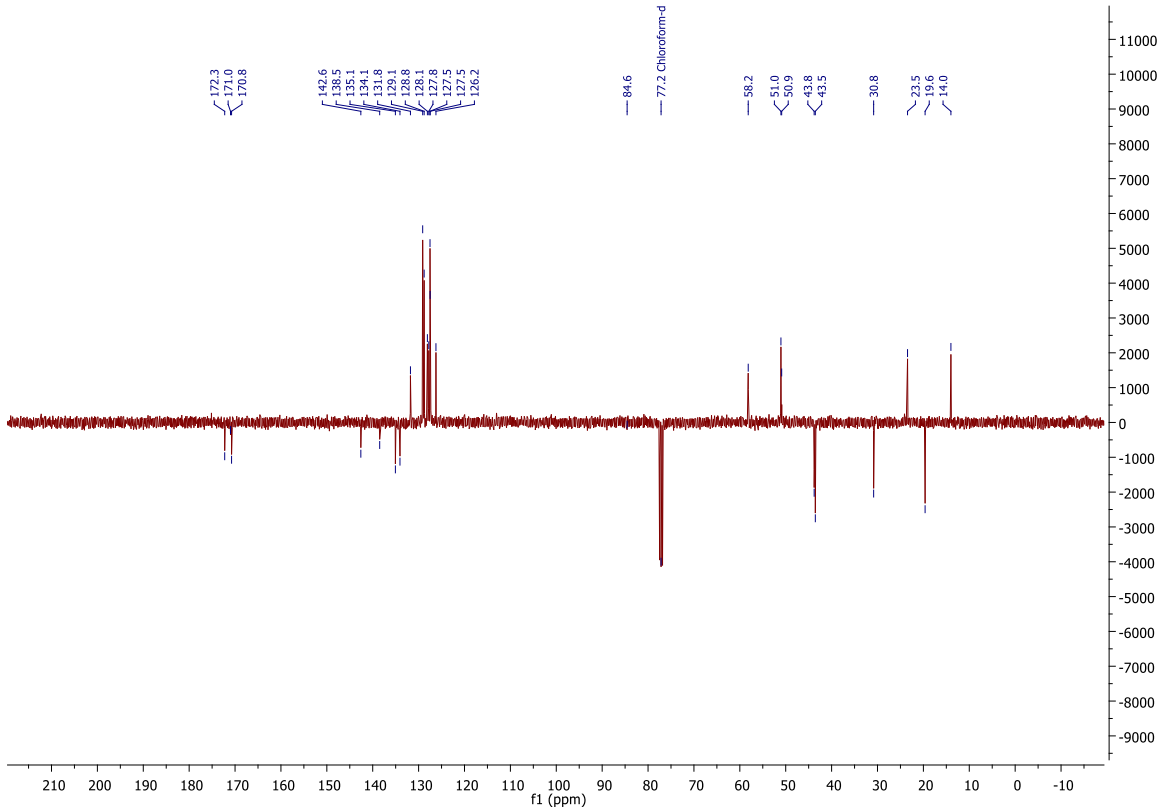
7.29
7.28
7.26
7.11
7.03
6.93
6.91
6.67
6.65
5.05
5.03
5.02
5.01
4.84
4.48
4.47
4.44
4.43
4.41
4.39
4.37
3.58
3.53
1.81
1.58
1.57
1.55
1.53
1.31
1.30
1.28
1.27
1.25
1.24
0.86
0.84
0.83
O
N
MeO
OMe
O
HN
O
N
(5aaca)
9.90
1.11
1.16
0.93
1.00
0.95
2.15
2.07
6.44
2.63
1.64
3.54
3.04
f1 (ppm)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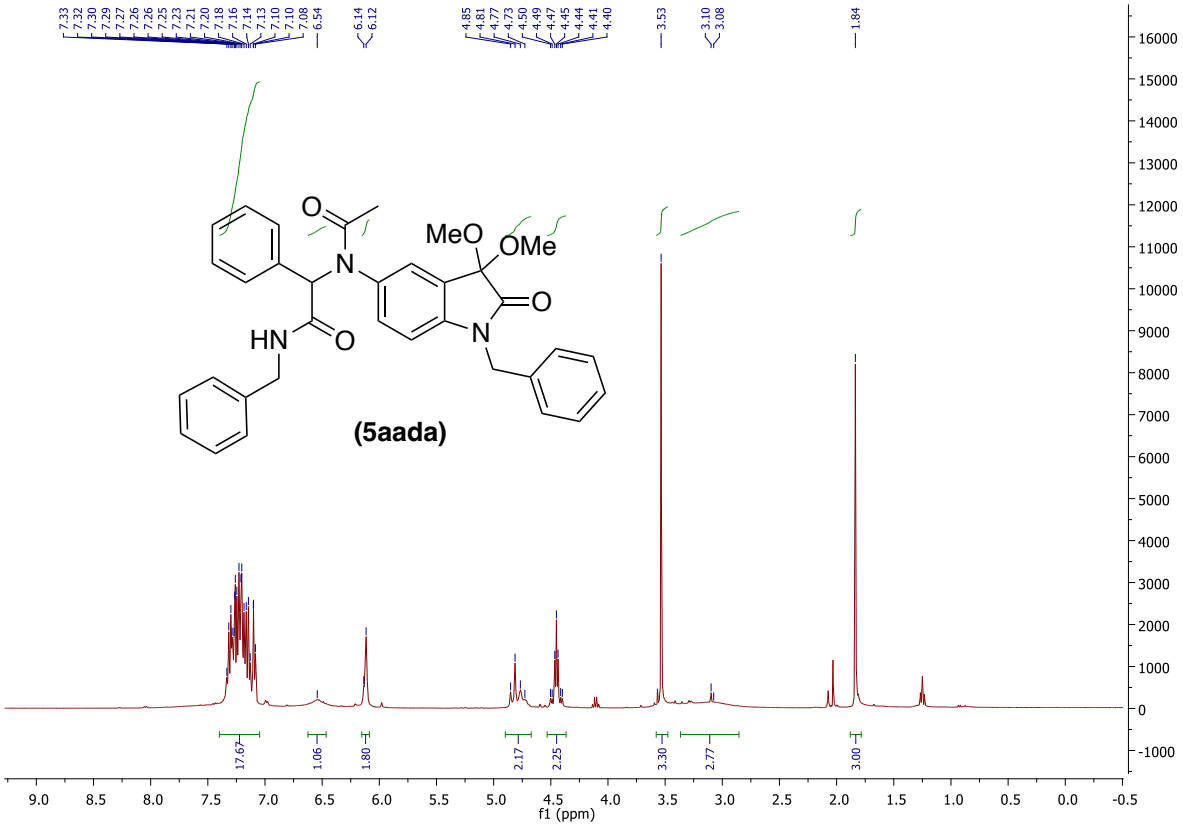
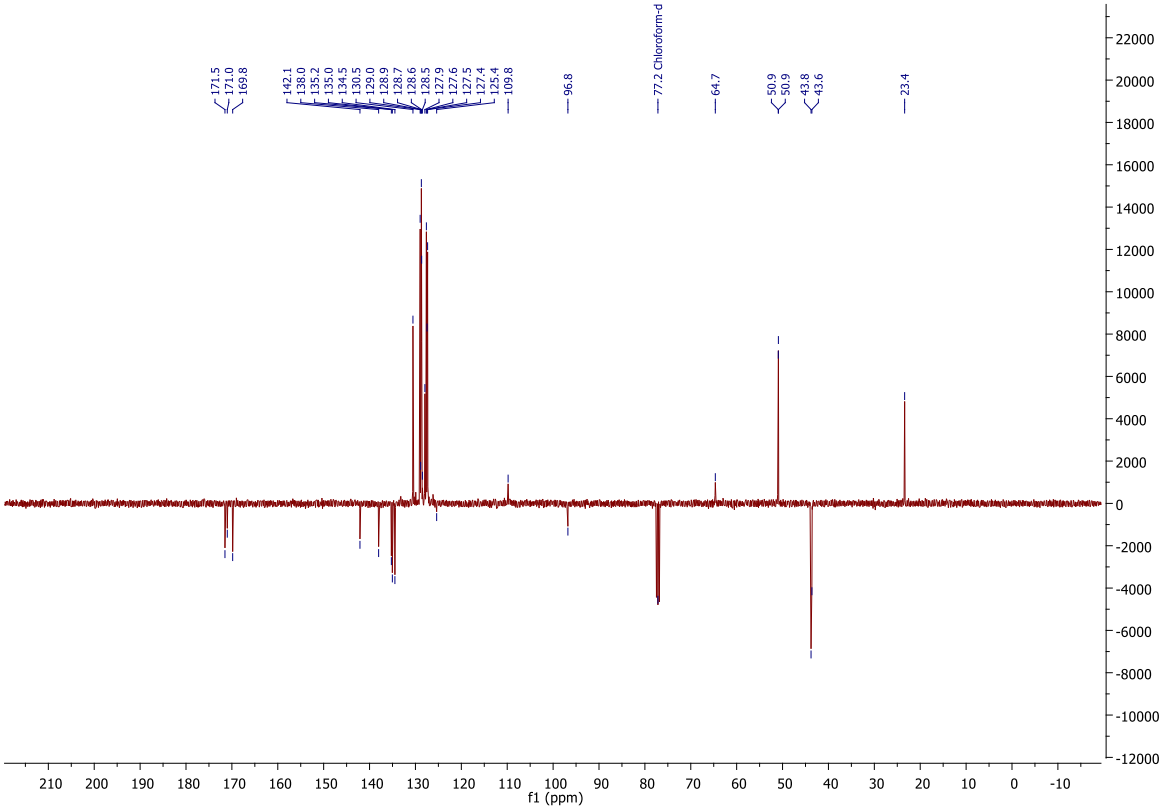
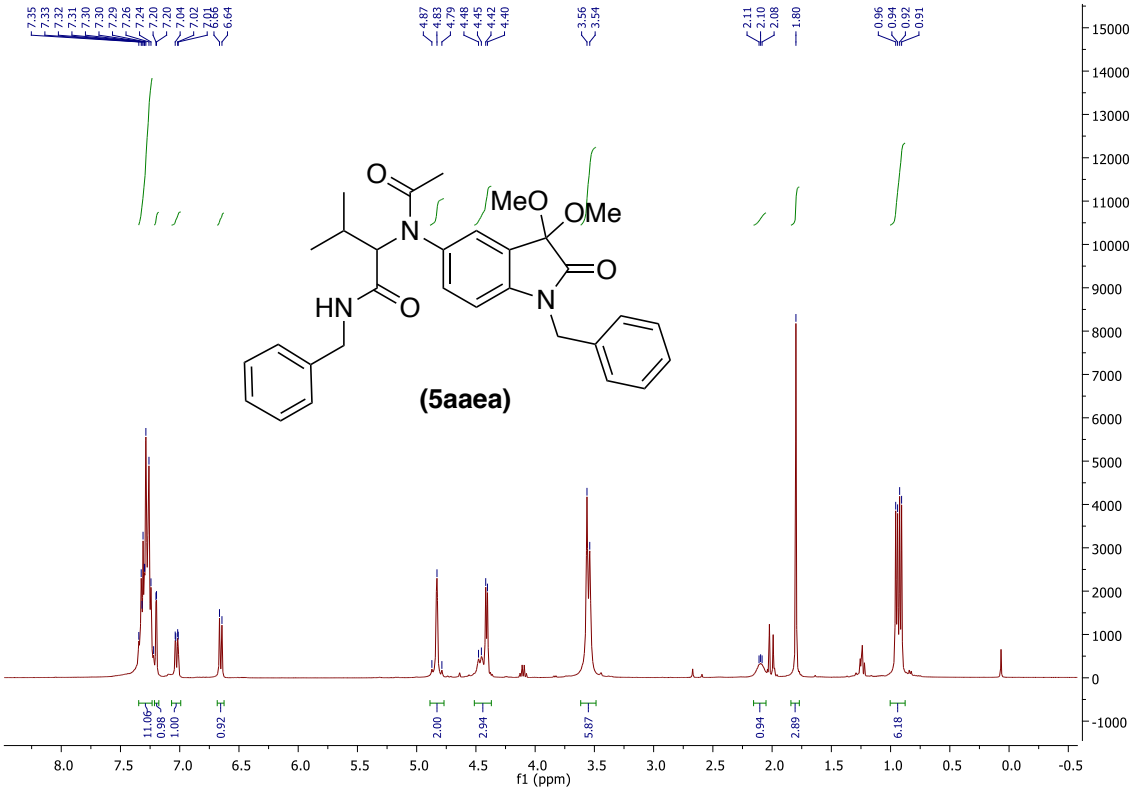
171.0
170.8
142.6
138.5
135.1
134.1
131.8
129.1
128.8
128.1
127.8
127.5
127.5
126.2
84.6
77.2 Chloroform-d
58.2
51.0
50.9
43.8
43.5
30.8
23.5
19.6
14.0
f1 (ppm)


MeO
OMe
O
N
HN
O
(5aada)
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)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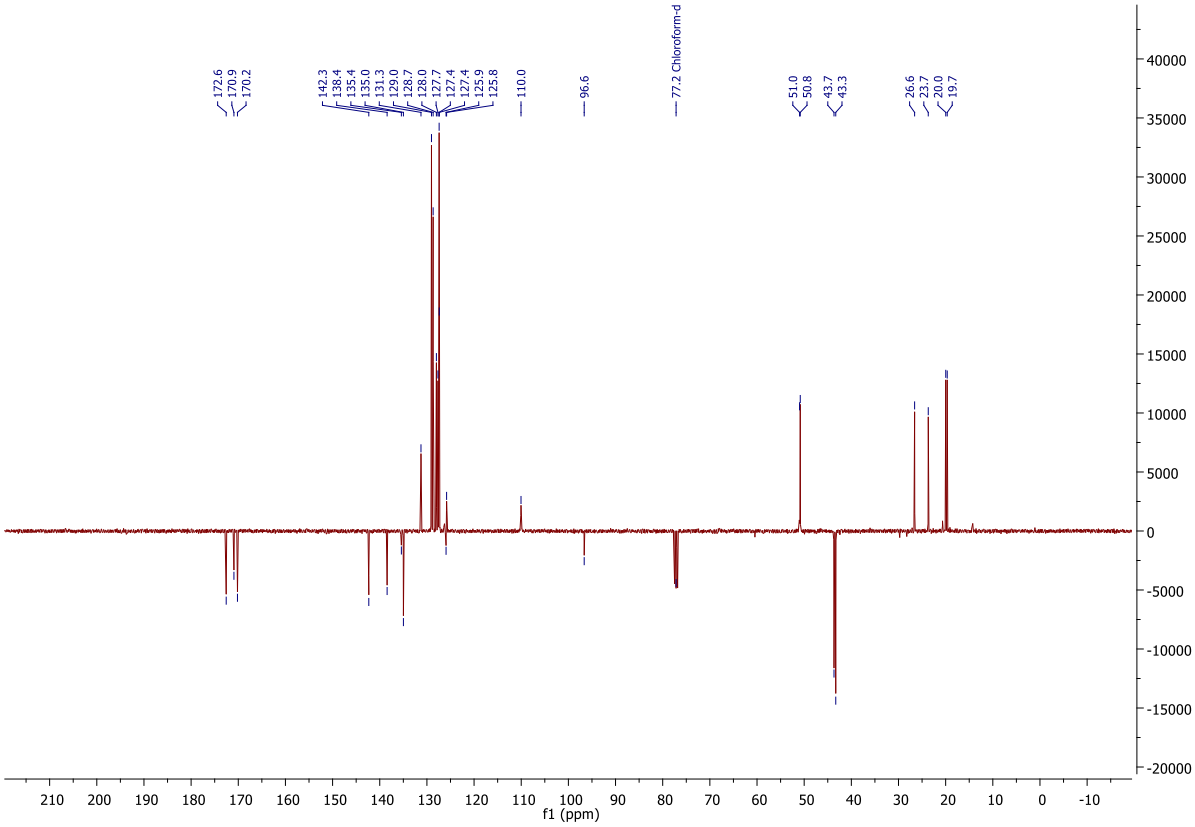
7.32
7.31
7.30
7.30
7.29
7.26
7.24
7.20
7.20
7.04
7.02
7.01
6.65
6.64
4.87
4.83
4.79
4.48
4.45
4.42
4.40
3.56
3.54
2.11
2.10
2.08
1.80
0.96
0.94
0.92
0.91
O
N
MeO
OMe
O
N
HN
O
(5aaea)
11.06
0.98
1.00
0.92
2.00
2.94
5.87
0.94
2.89
6.18
f1 (ppm)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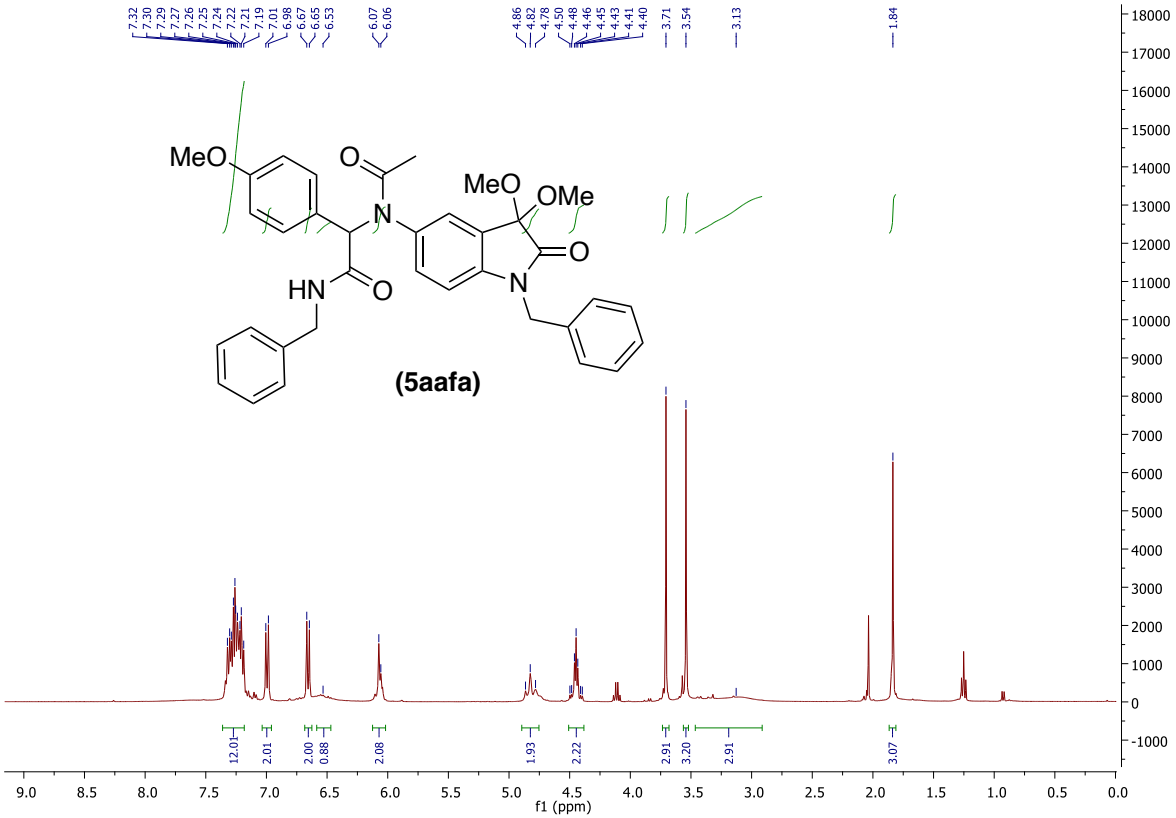
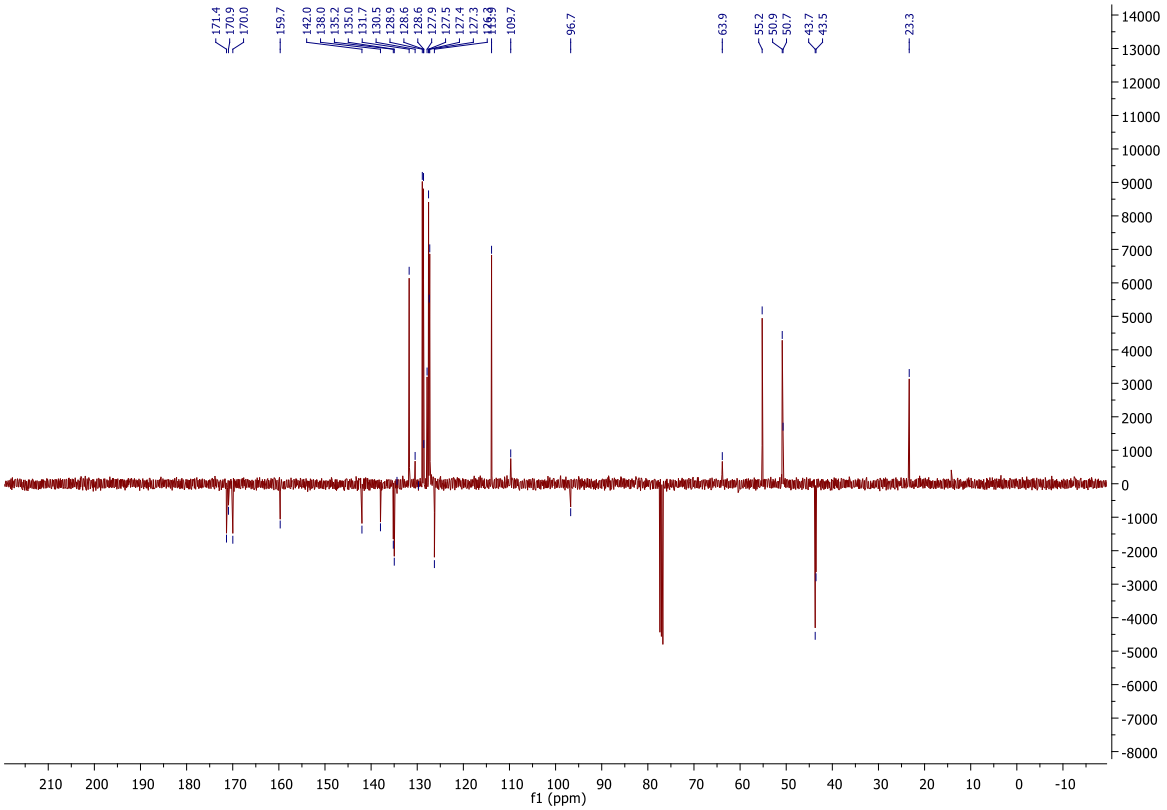
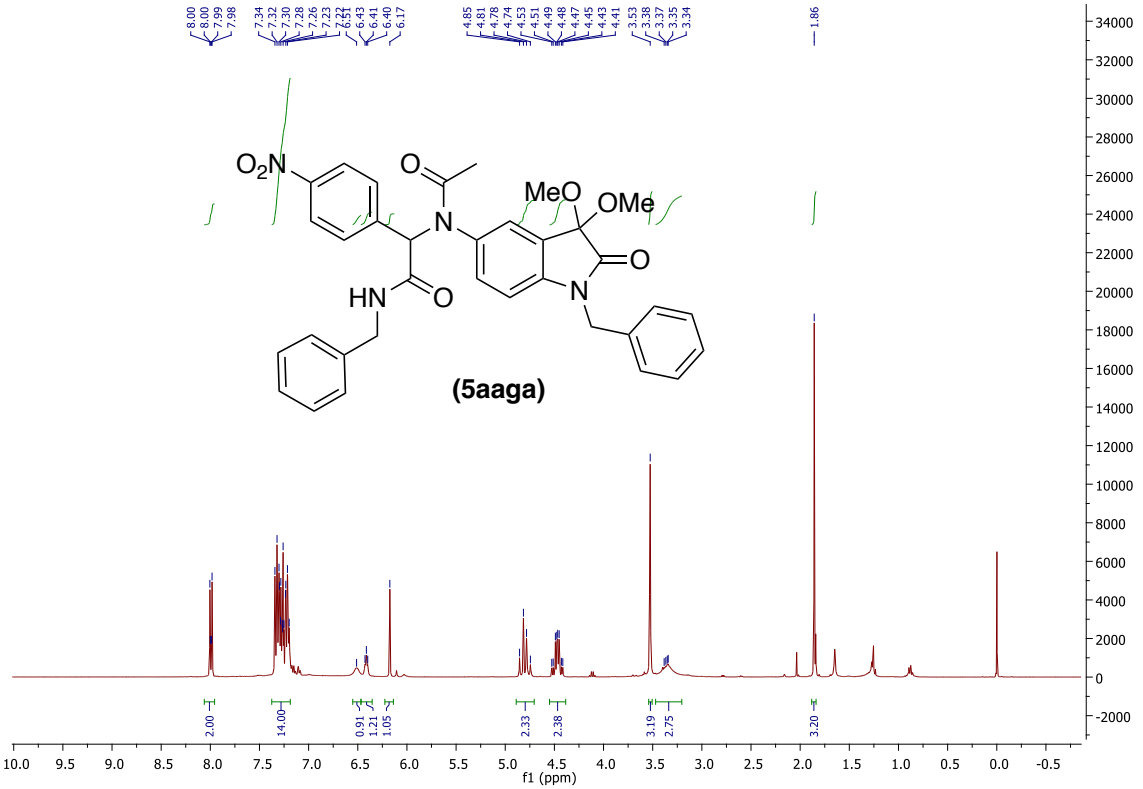
170.2
142.3
138.4
135.4
135.0
131.3
129.0
128.7
128.0
127.7
127.4
127.4
125.9
125.8
110.0
96.6
77.2 Chloroform-d
51.0
50.8
43.7
43.3
26.6
23.7
20.0
19.7
f1 (ppm)


MeO
O
N
MeO
OMe
O
HN
O
N
(5aafa)
f1 (ppm)


f1 (ppm)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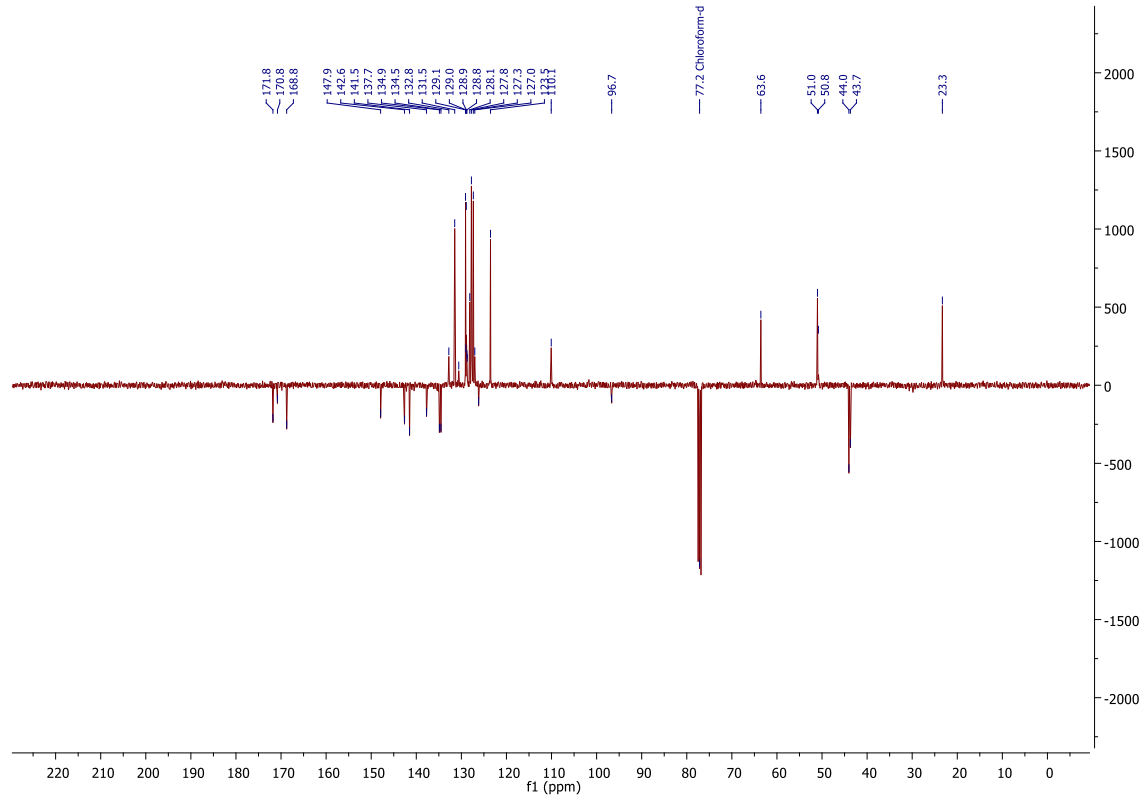
7.32
7.30
7.28
7.26
7.23
6.43
6.41
6.40
6.17
4.85
4.81
4.78
4.74
4.53
4.51
4.49
4.48
4.47
4.45
4.43
4.41
3.53
3.38
3.37
3.35
3.34
1.86
O2N
O
N
MeO
OMe
O
HN
O
N
(5aaga)
2.00
14.00
0.91
1.21
1.05
2.33
2.38
3.19
2.75
3.20
f1 (ppm)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170.8
168.8
147.9
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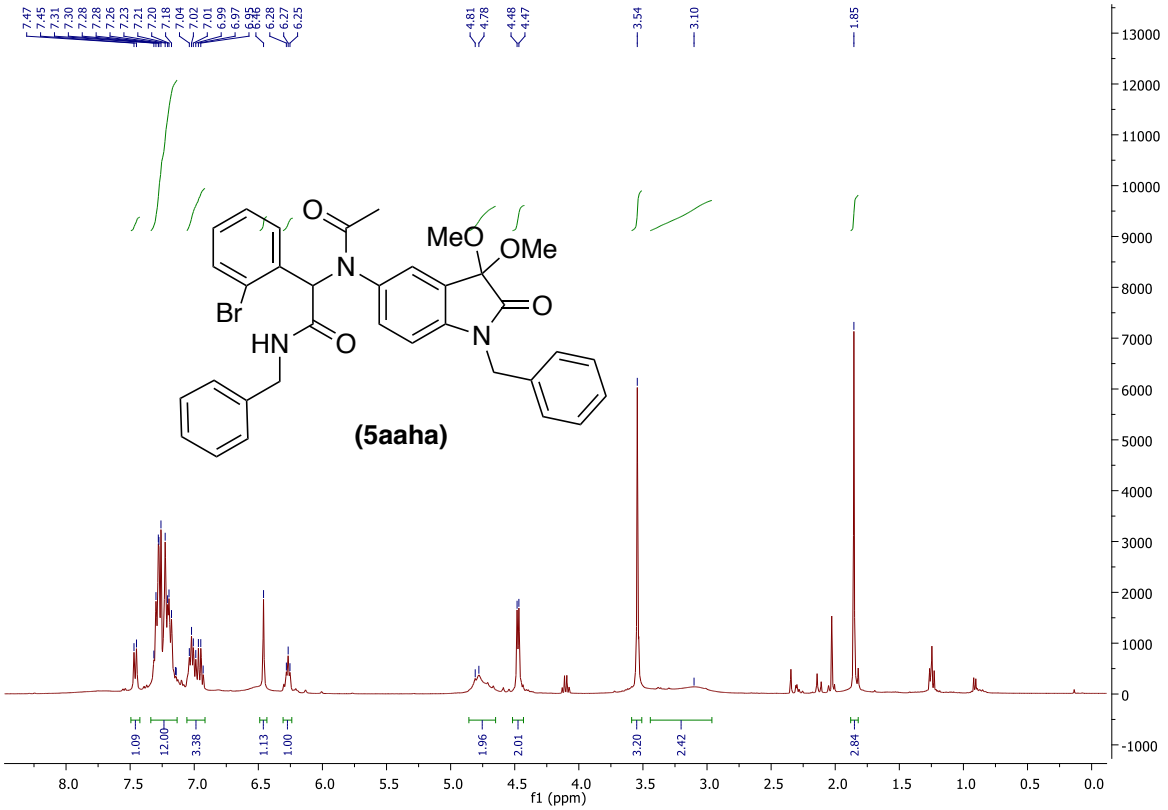
141.5
137.7
134.9
134.5
132.8
131.5
129.1
129.0
128.9
128.8
128.1
127.8
127.3
127.0
123.5
110.1
96.7
77.2 Chloroform-d
63.6
51.0
50.8
44.0
43.7
23.3
f1 (ppm)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7.45
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7.30
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7.28
7.26
7.23
7.21
7.20
7.18
7.04
7.02
7.01
6.99
6.97
6.95
6.28
6.27
6.25
4.81
4.78
4.48
4.47
3.54
3.10
1.85
O
N
MeO
OMe
Br
HN
O
O
N
(5aaha)
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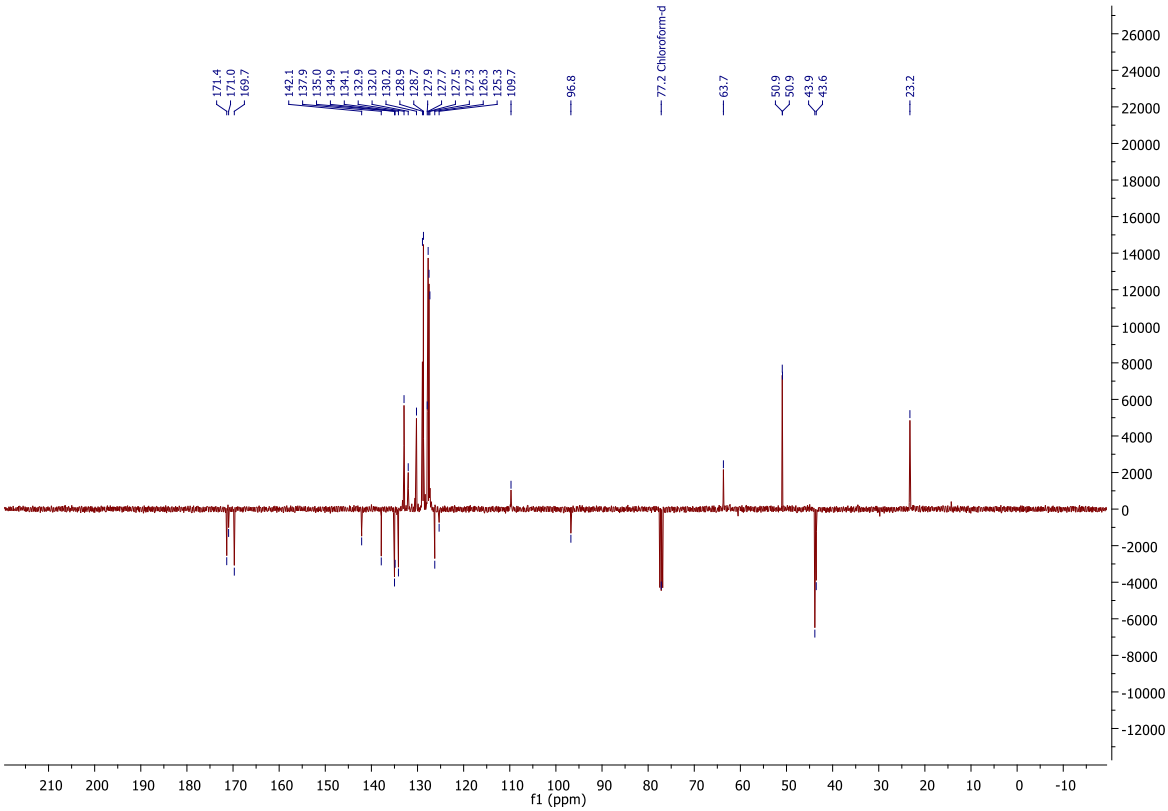
3.38
1.13
1.00
1.96
2.01
3.20
2.42
2.84
f1 (ppm)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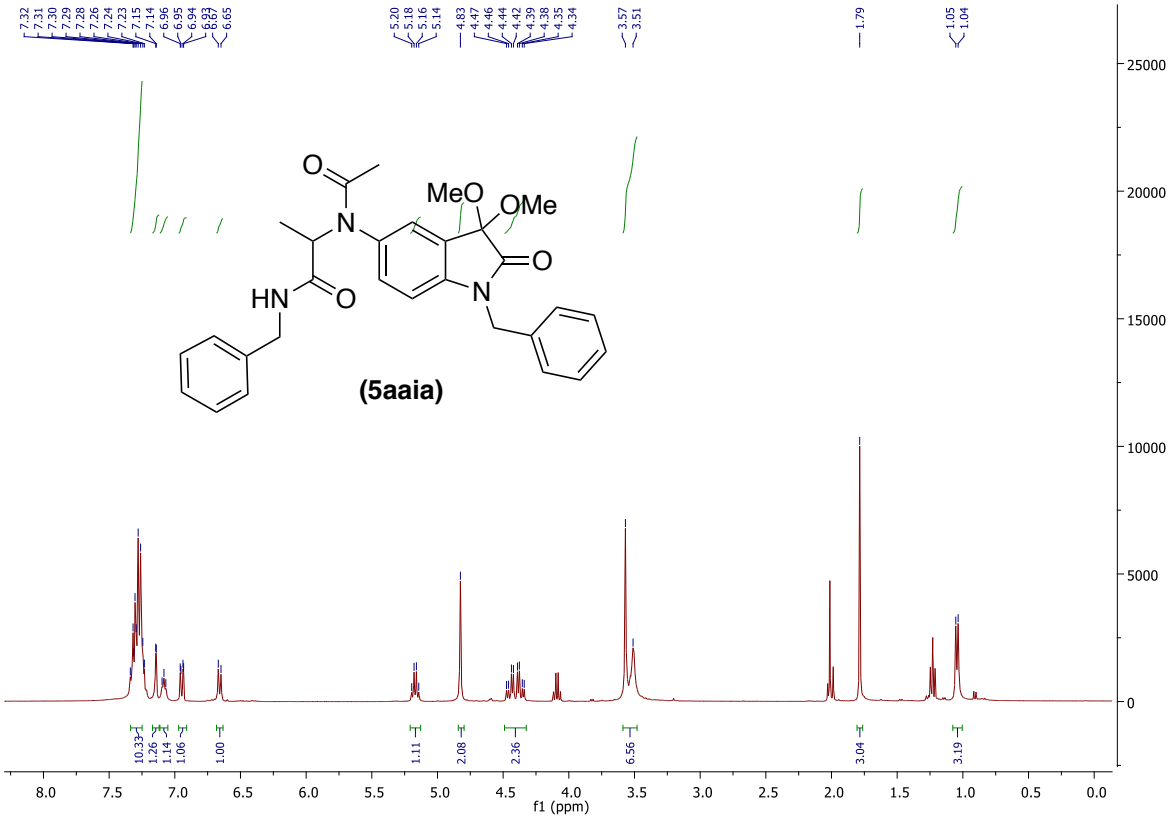
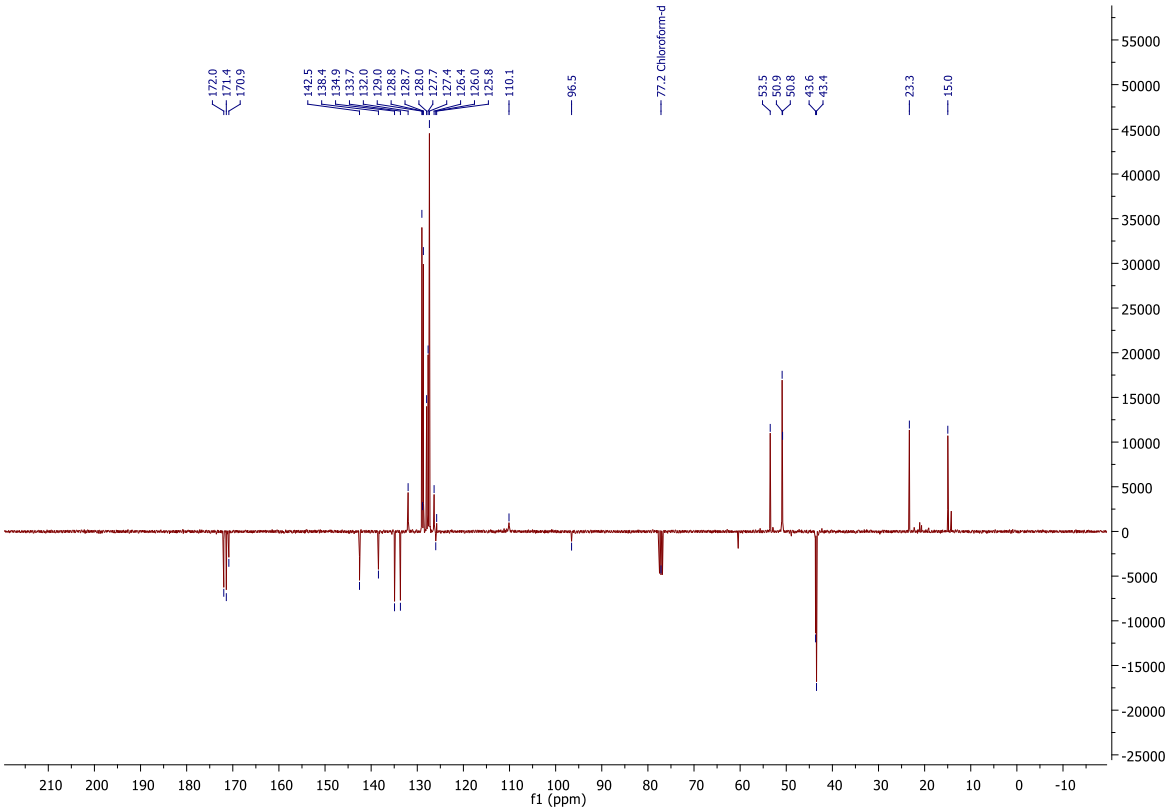
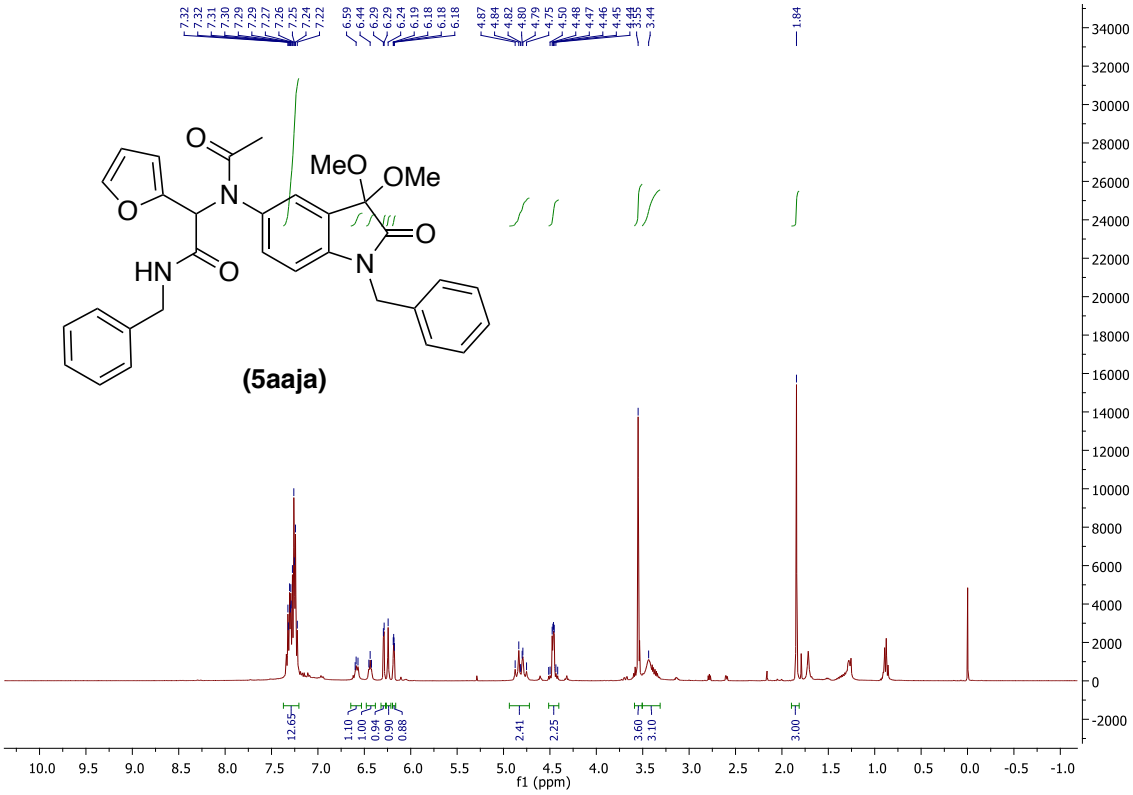
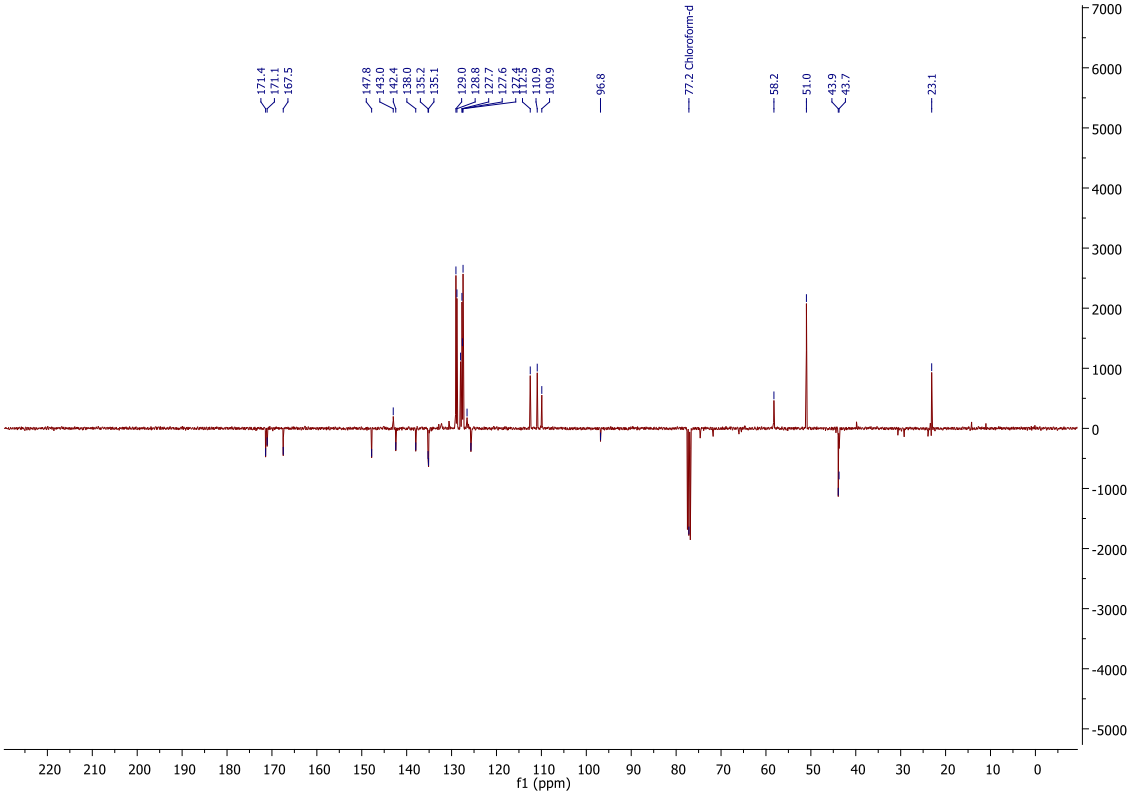
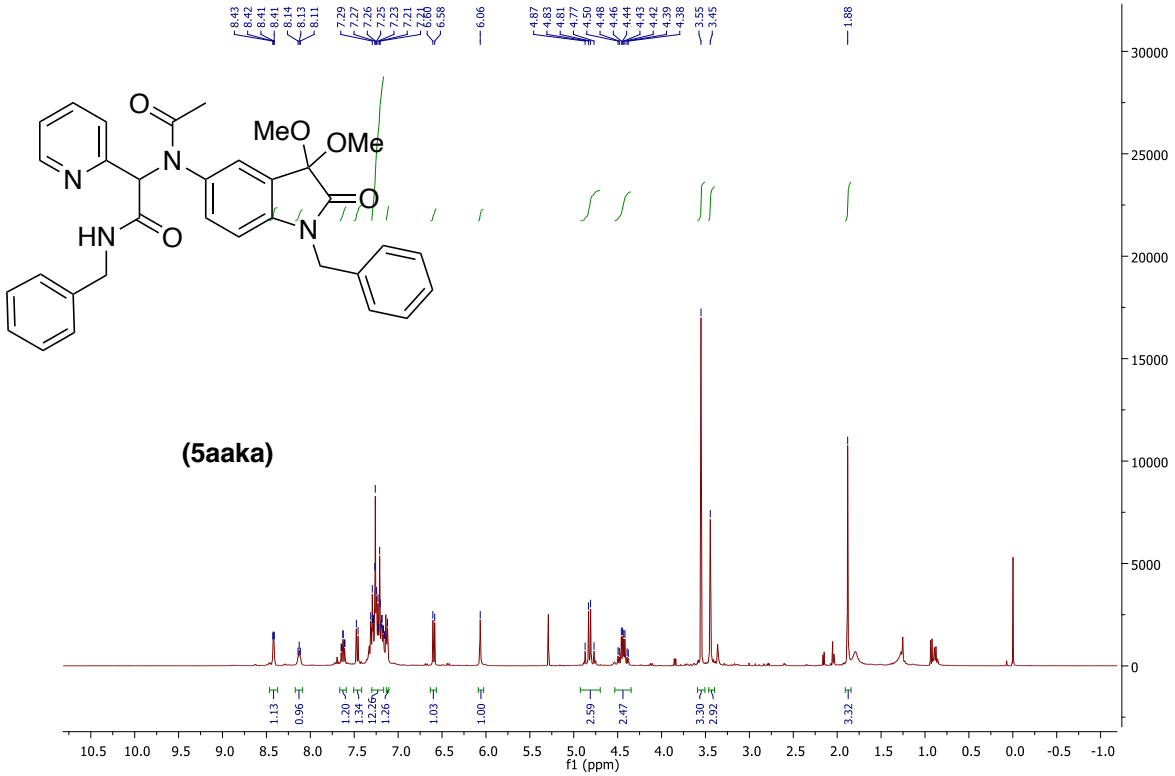
137.9
135.0
134.9
134.1
132.9
132.0
130.2
128.9
128.7
127.9
127.7
127.5
127.3
126.3
125.3
109.7
96.8
77.2 Chloroform-d
63.7
50.9
50.9
43.9
43.6
23.2
f1 (ppm)

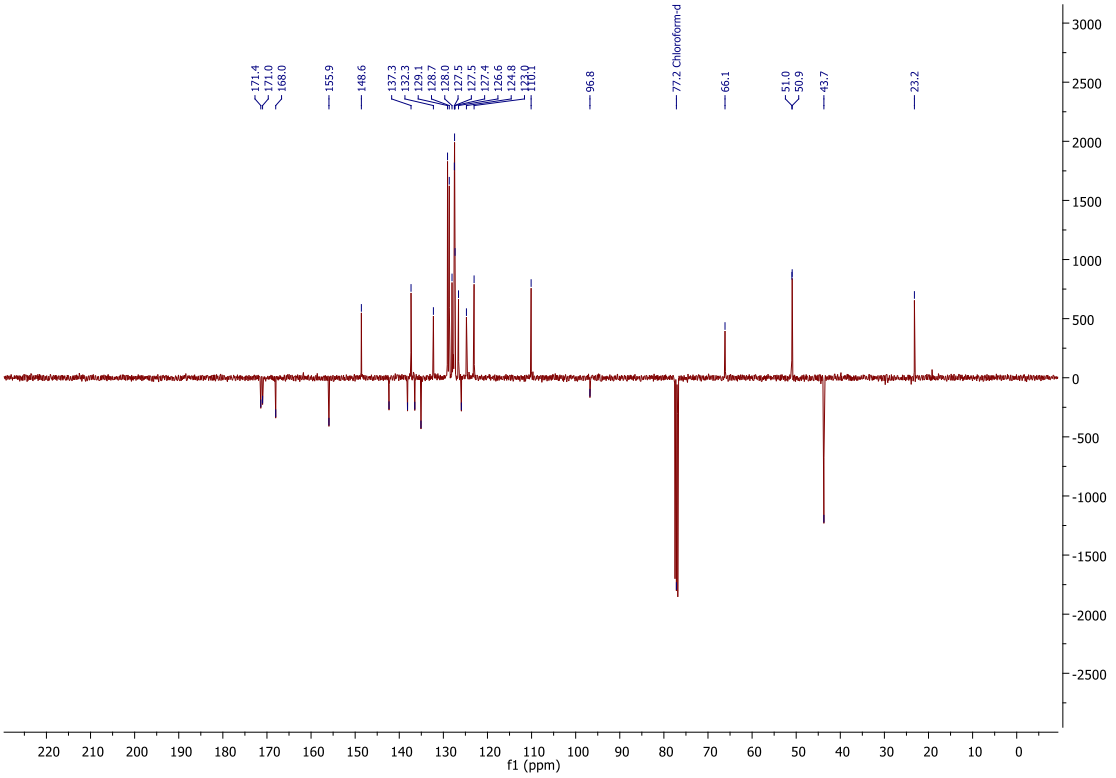

MeO
OMe
HN
(5aaia)
f1 (ppm)

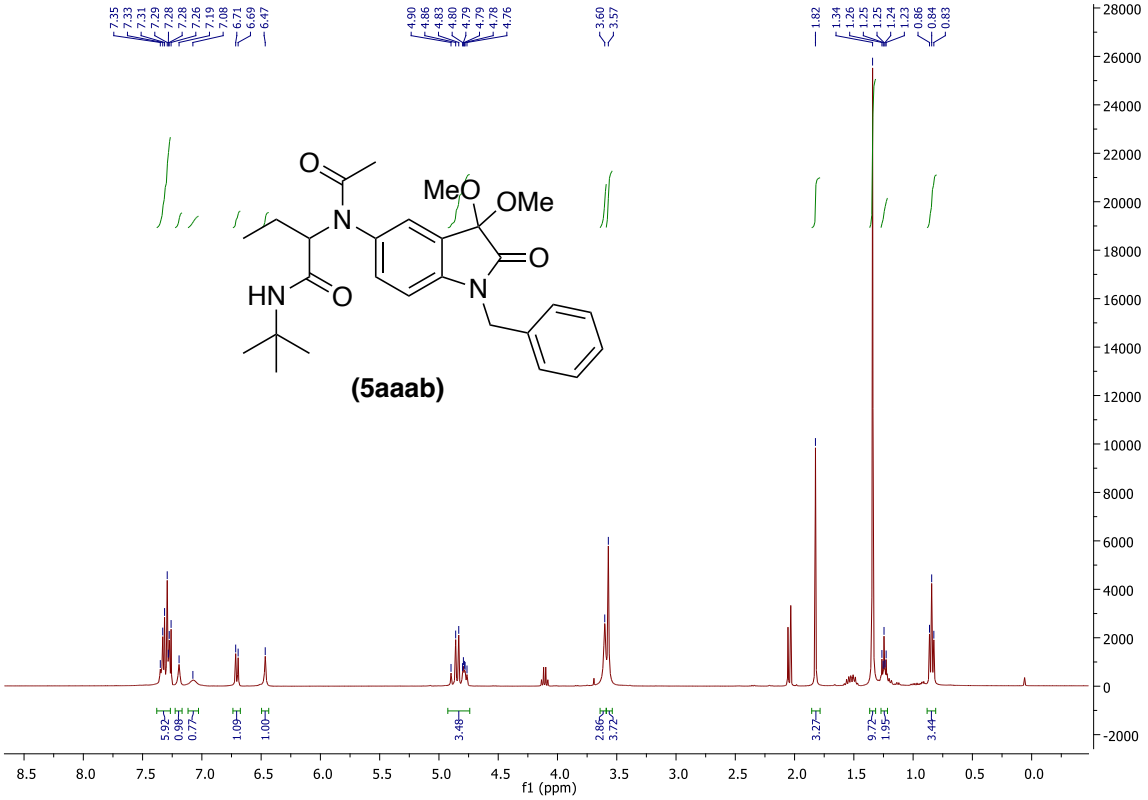

77.2 Chloroform-d
f1 (ppm)


(5aaja)




MeO
OMe
O
N
HN
O
(5aaka)
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)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6.71
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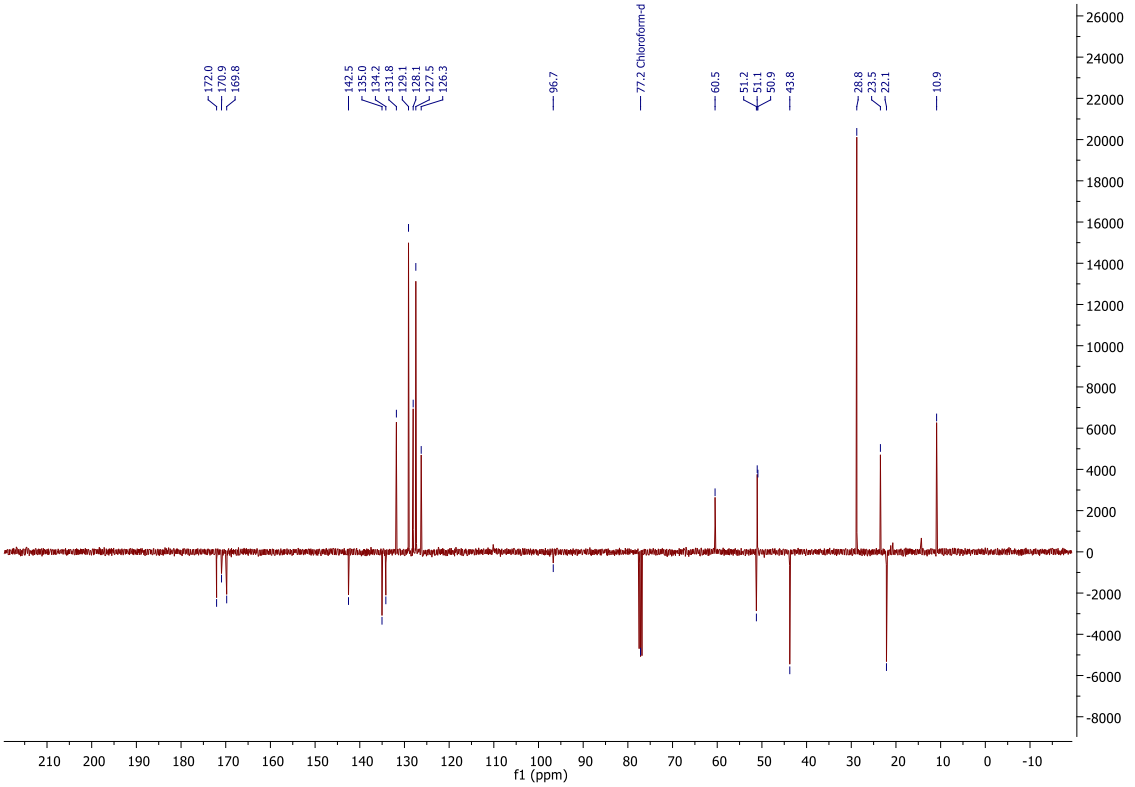
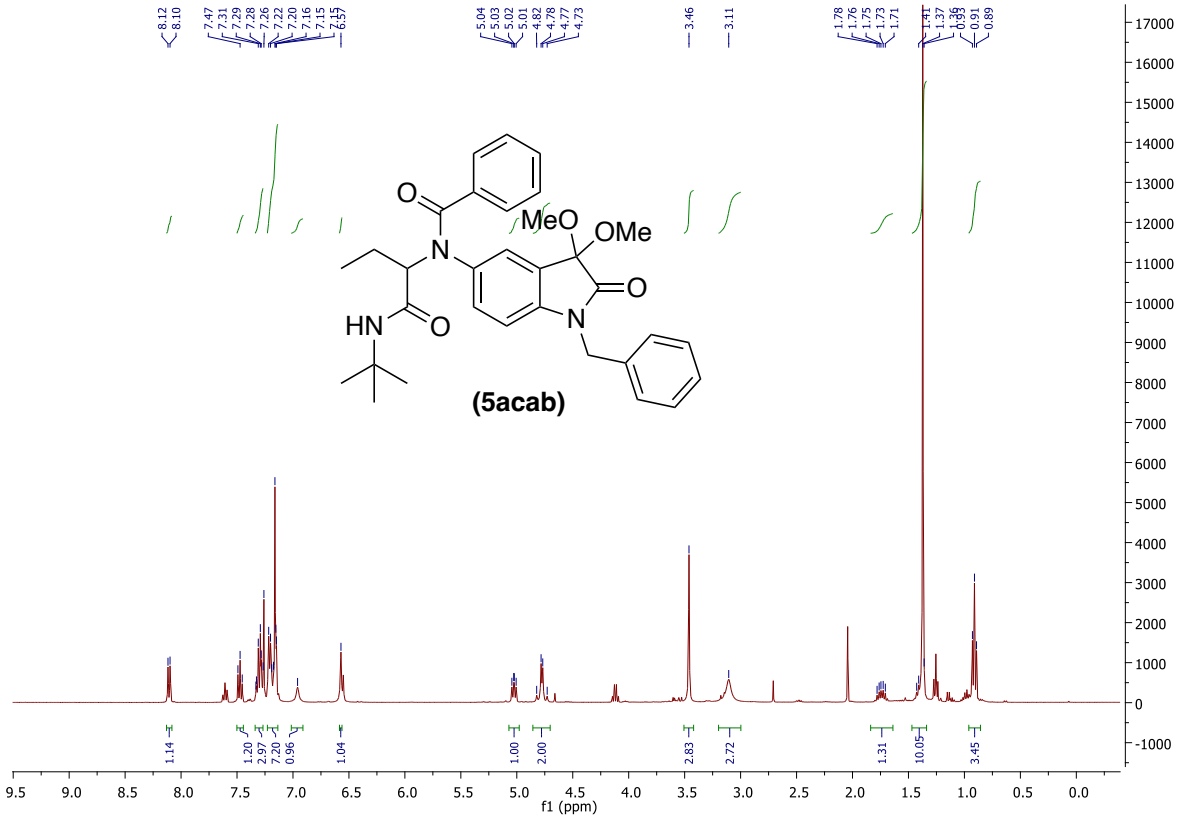
6.47
4.90
4.86
4.83
4.80
4.79
4.79
4.78
4.76
3.60
3.57
1.82
1.34
1.26
1.25
1.25
1.24
1.23
0.86
0.84
0.83
O
N
MeO
OMe
O
HN
O
N
(5aaab)
5.92
0.98
0.77
1.09
1.00
3.48
2.86
3.72
3.27
9.72
1.95
3.44
f1 (ppm)


172.0
170.9
169.8
142.5
135.0
134.2
131.8
129.1
128.1
127.5
126.3
96.7
77.2 Chloroform-d
60.5
51.2
51.1
50.9
43.8
28.8
23.5
22.1
10.9
f1 (ppm)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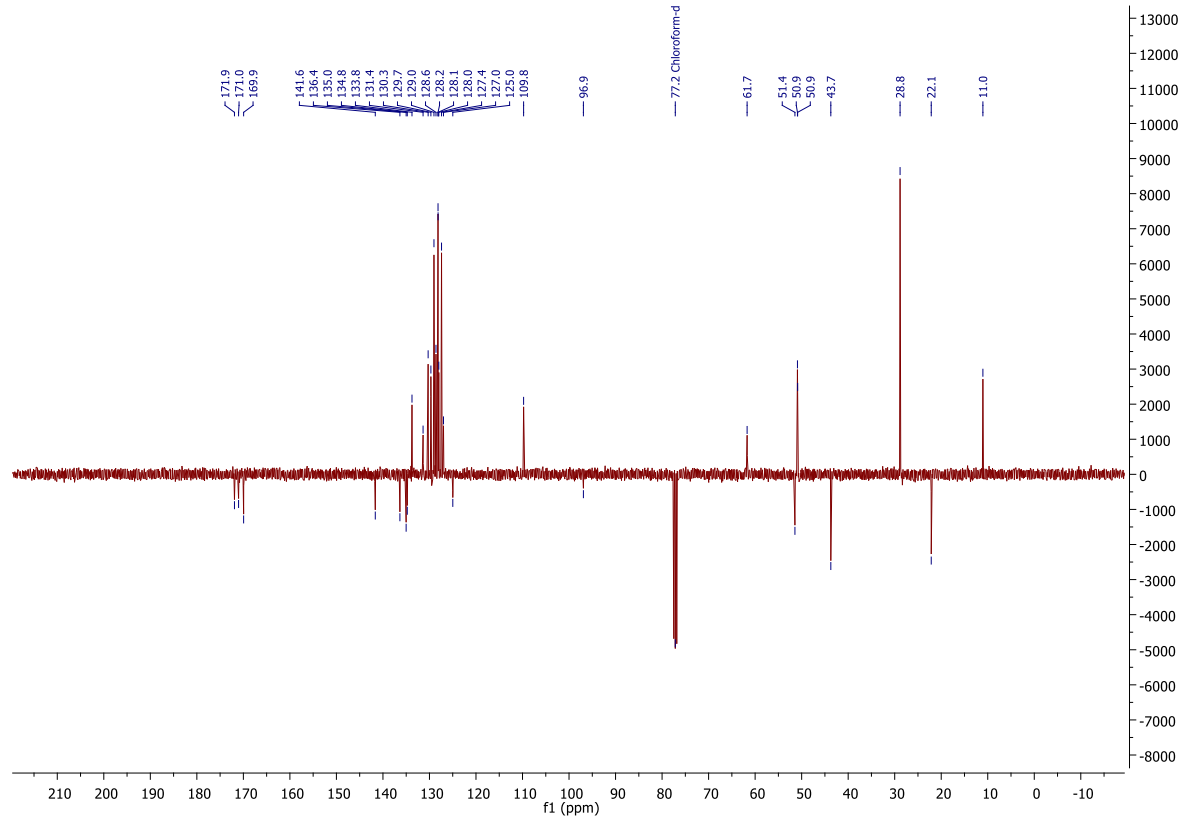
8.10
7.47
7.31
7.29
7.28
7.26
7.22
7.20
7.16
7.15
7.15
6.57
5.04
5.03
5.02
5.01
4.82
4.78
4.77
4.73
3.46
3.11
1.78
1.76
1.75
1.73
1.71
1.41
1.37
1.35
0.93
0.91
0.89
O
N
MeO
OMe
O
HN
O
N
(5acab)
1.14
1.20
2.97
7.20
0.96
1.04
1.00
2.00
2.83
2.72
1.31
10.05
3.45
f1 (ppm)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134.8
133.8
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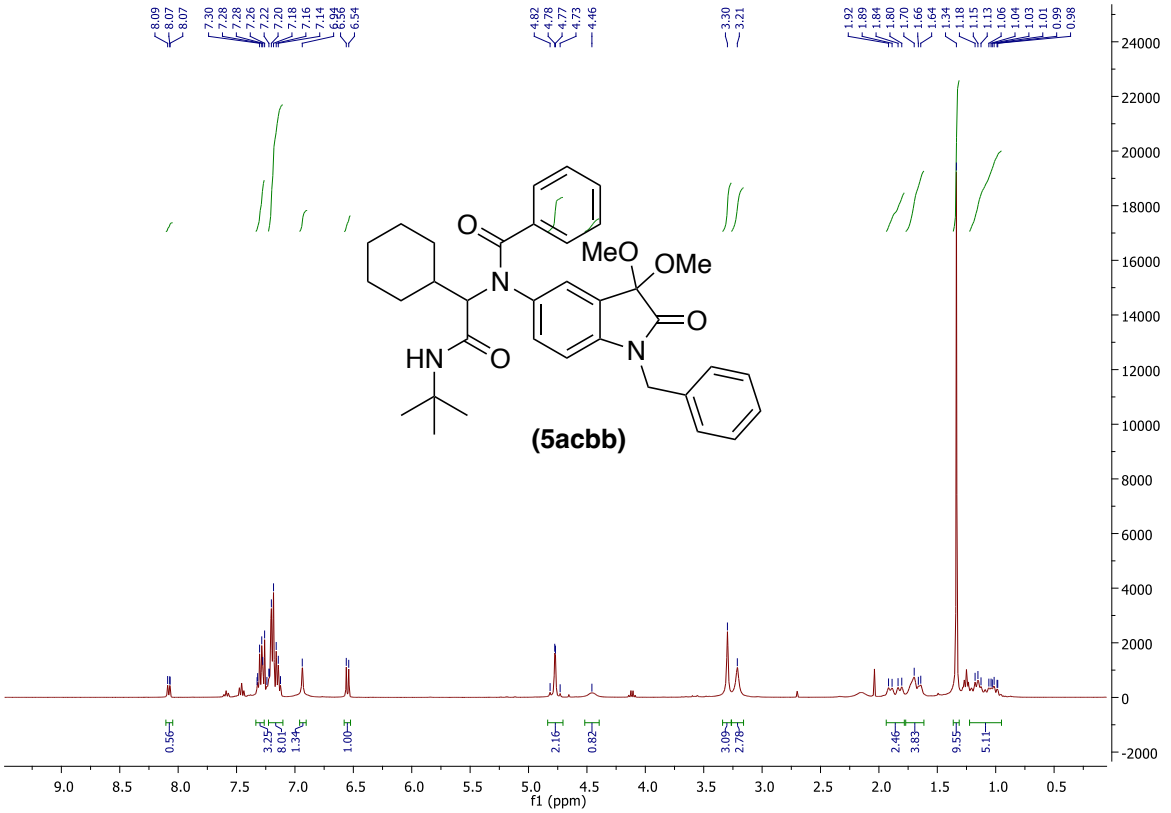
130.3
129.7
129.0
128.6
128.2
128.1
128.0
127.4
127.0
125.0
109.8
96.9
77.2 Chloroform-d
61.7
51.4
50.9
50.9
43.7
28.8
22.1
11.0
f1 (ppm)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8.07
8.07
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7.28
7.26
7.22
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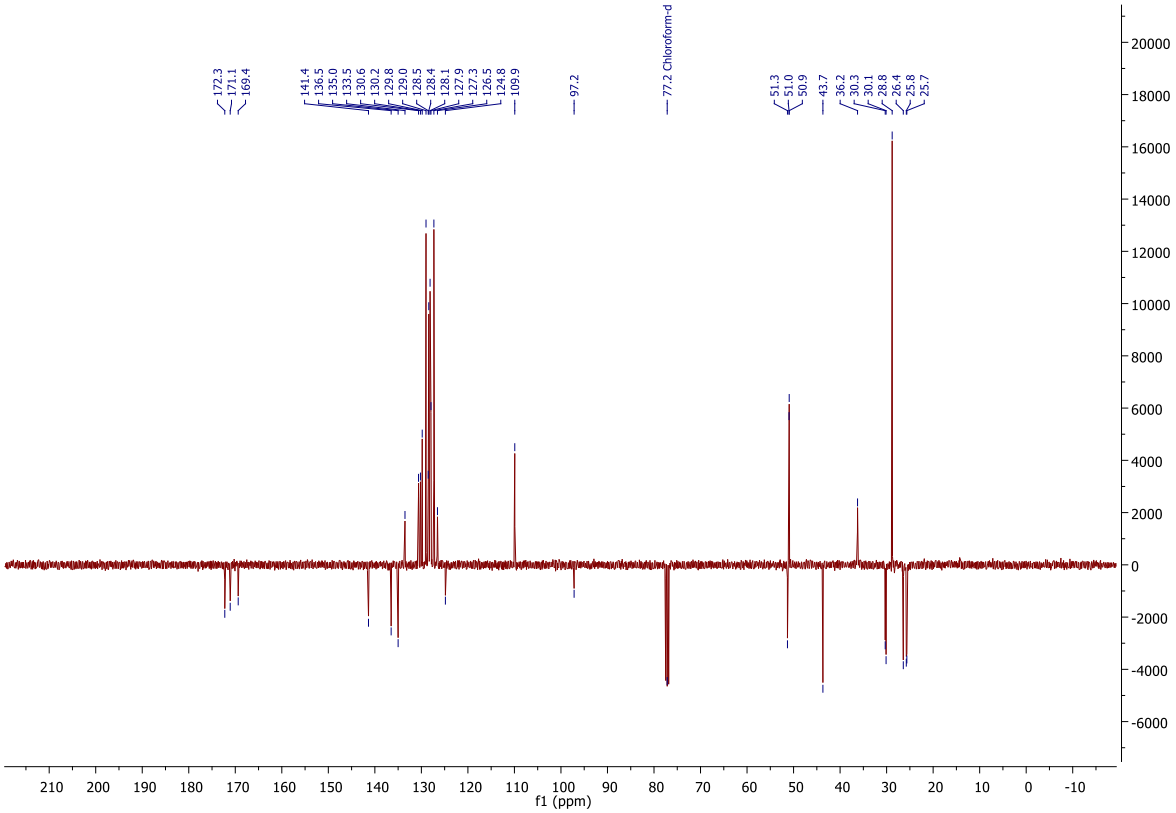
7.18
7.16
7.14
6.94
6.56
6.54
4.82
4.78
4.77
4.73
4.46
3.30
3.21
1.92
1.89
1.84
1.80
1.70
1.66
1.64
1.34
1.18
1.15
1.13
1.06
1.04
1.03
1.01
0.99
0.98
O
N
MeO
OMe
O
HN
O
N
(5acbb)
0.56
3.25
8.01
1.34
1.00
2.16
0.82
3.09
2.78
2.46
3.83
9.55
5.11
f1 (ppm)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129.0
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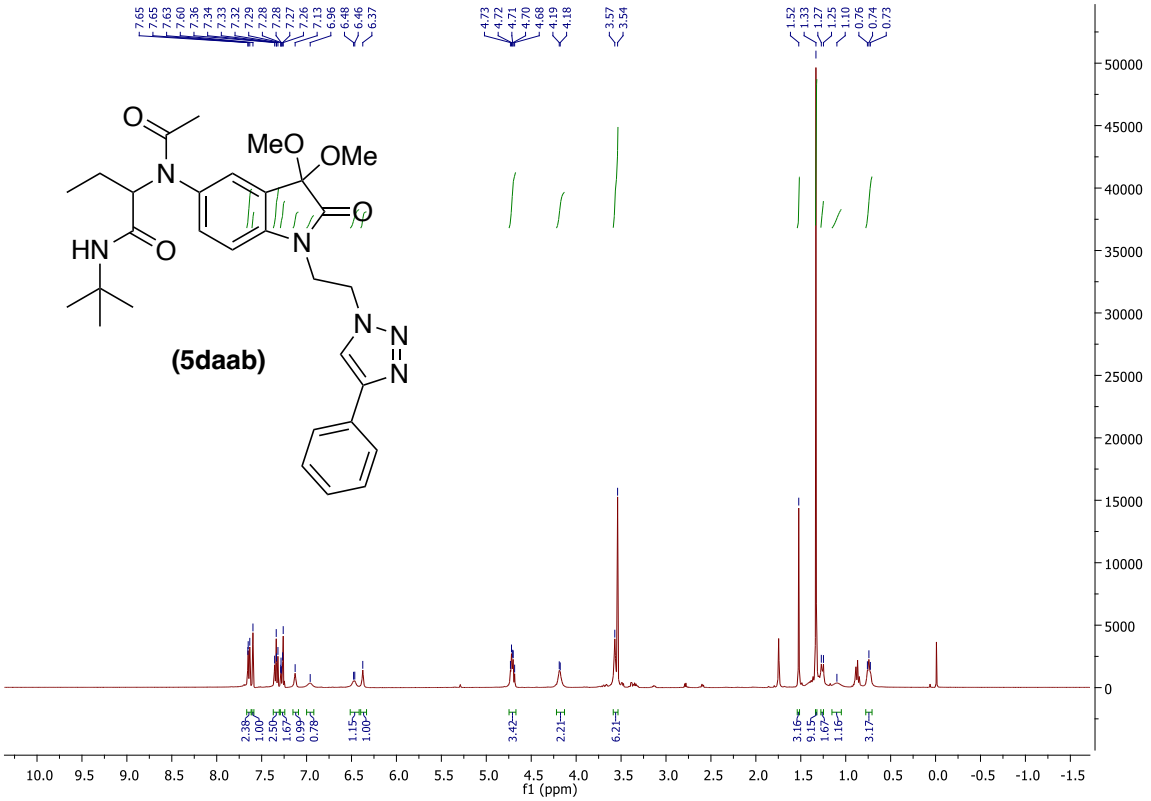
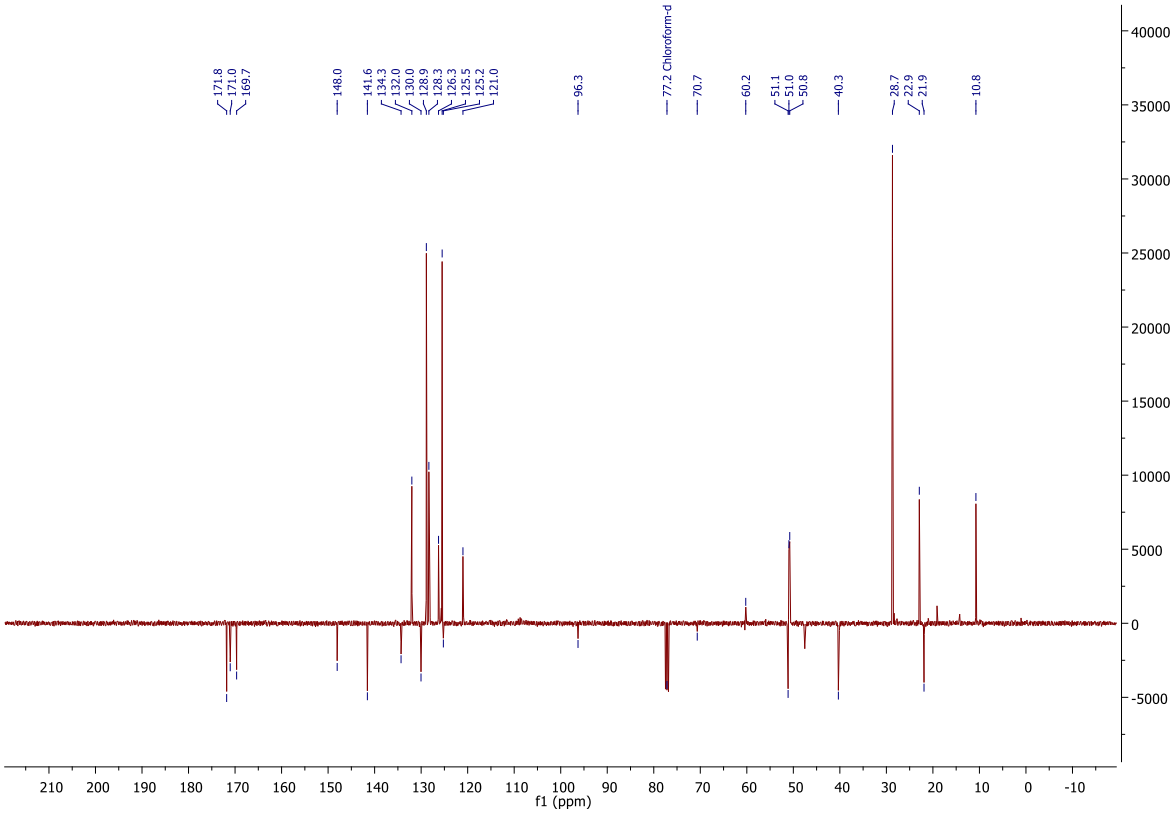
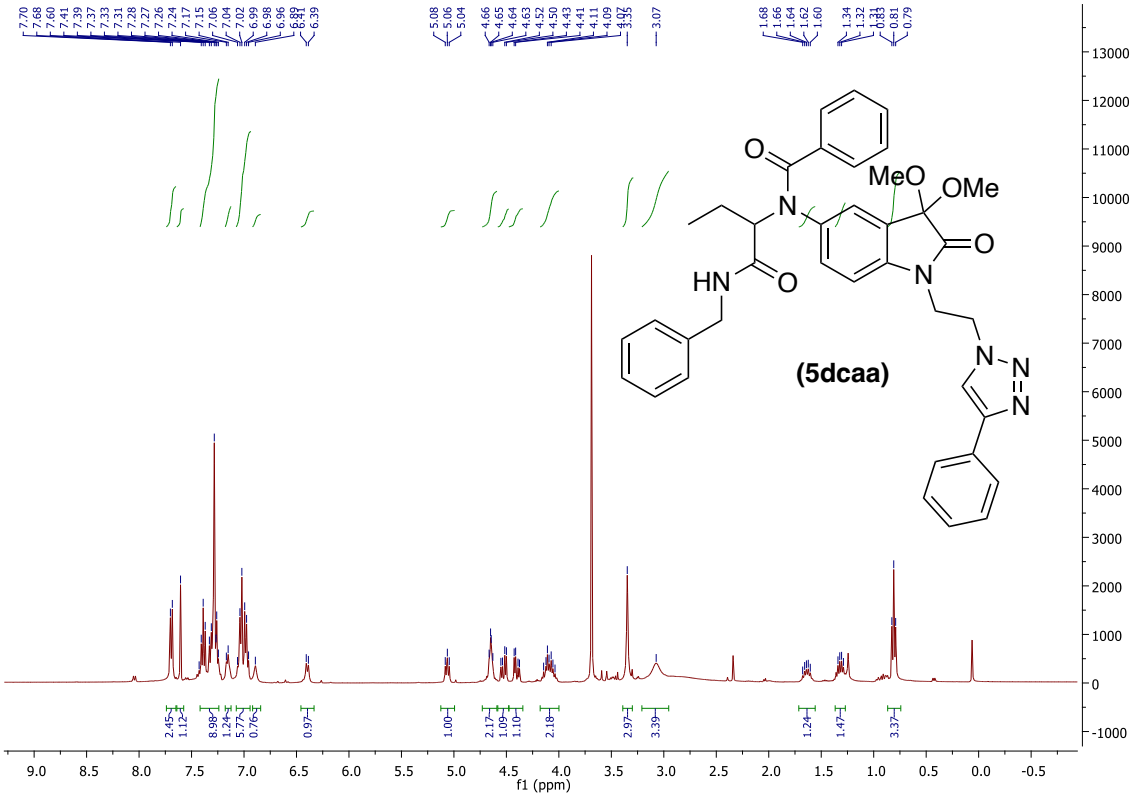
128.4
128.1
127.9
127.3
126.5
124.8
109.9
97.2
77.2 Chloroform-d
51.3
51.0
50.9
43.7
36.2
30.3
30.1
28.8
26.4
25.8
25.7
f1 (ppm)


(5daab)
f1 (ppm)


Chloroform-d
f1 (ppm)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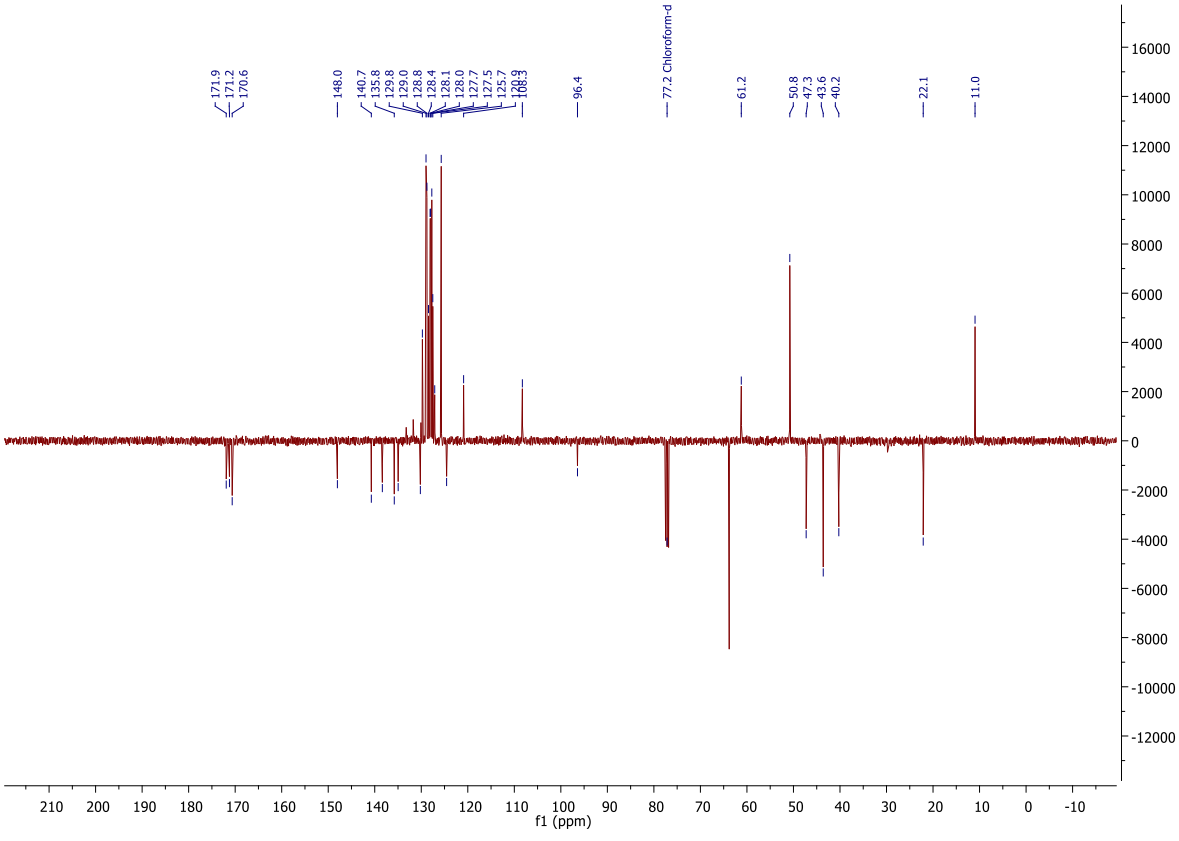
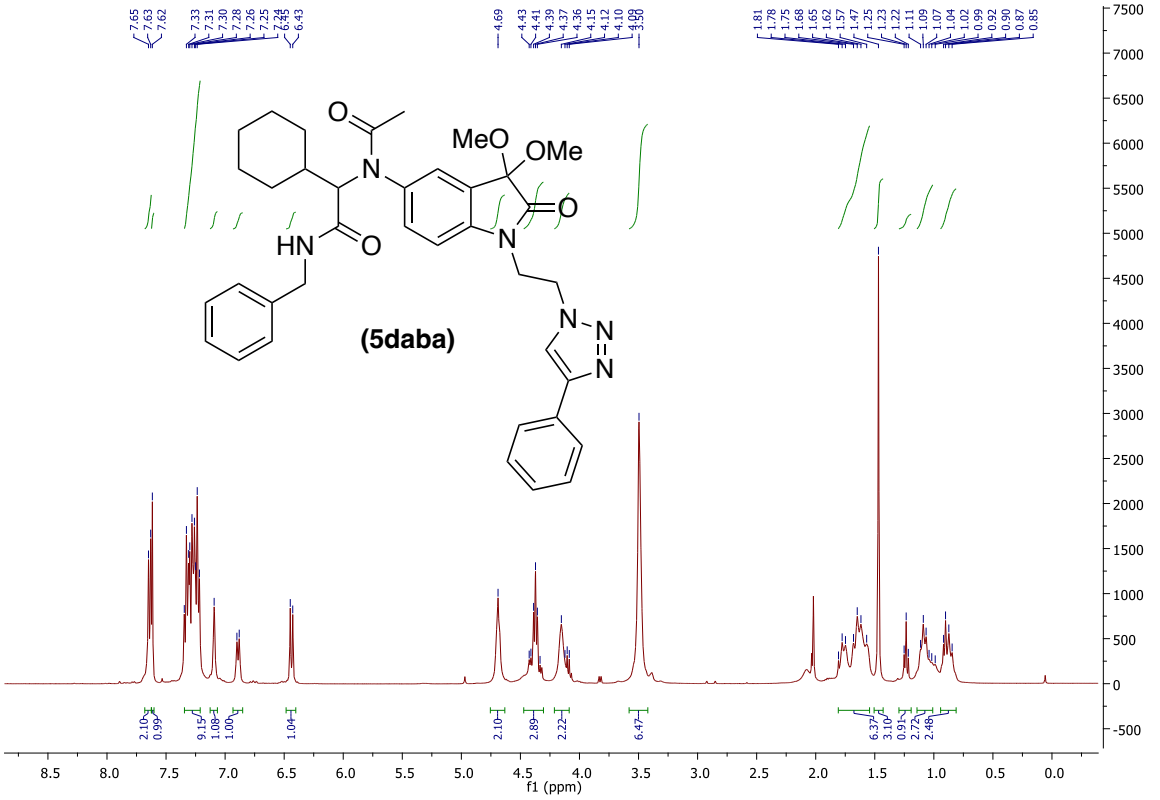

Chloroform-d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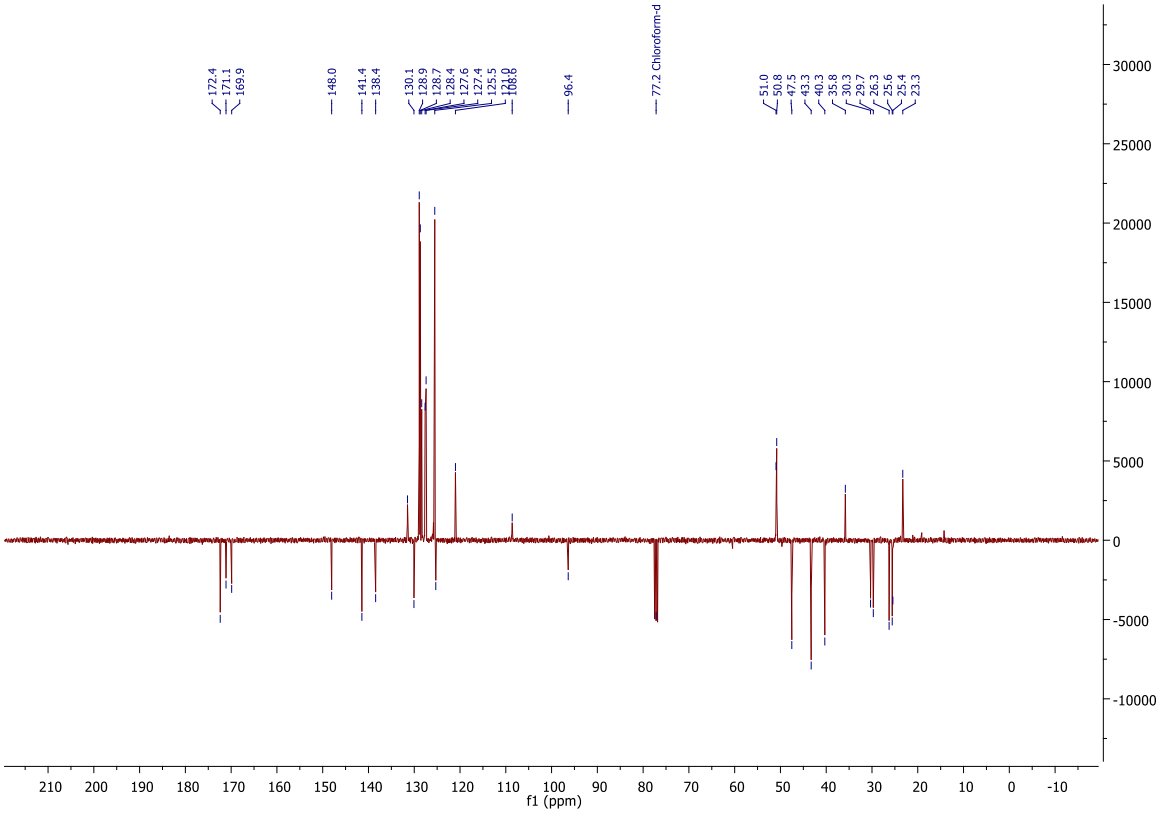
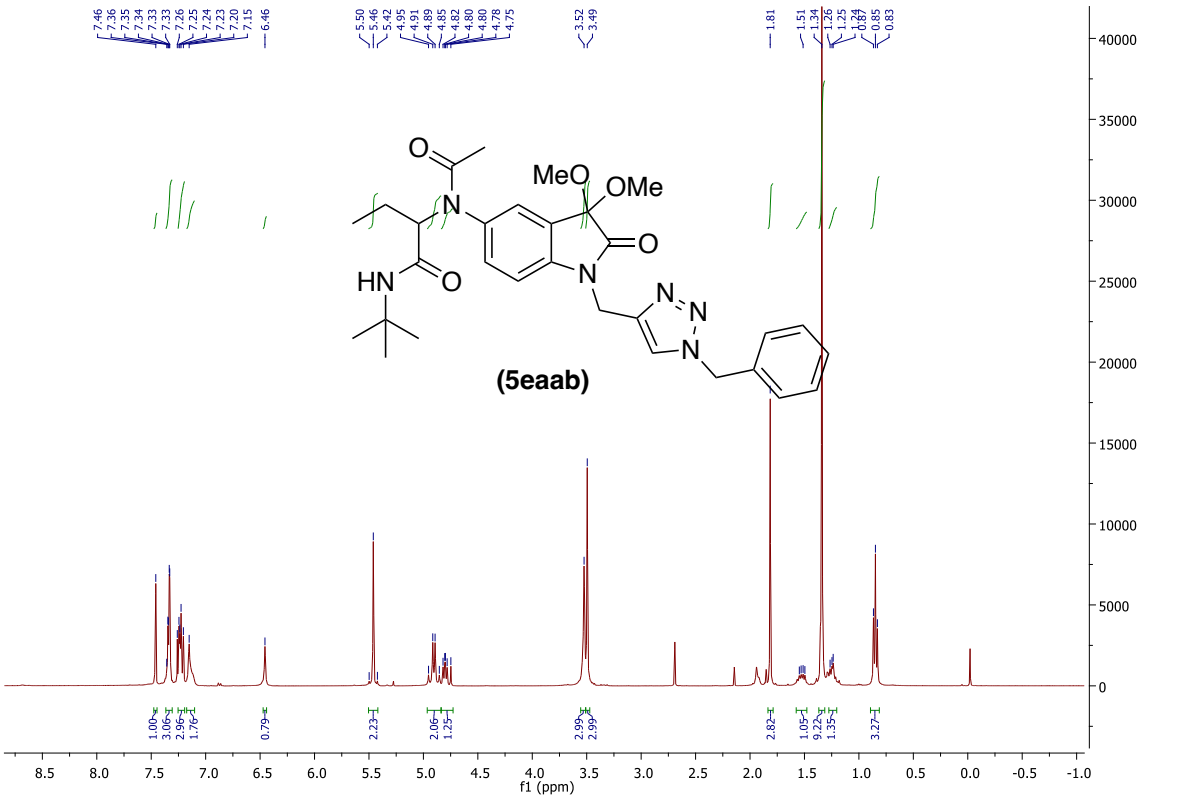
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)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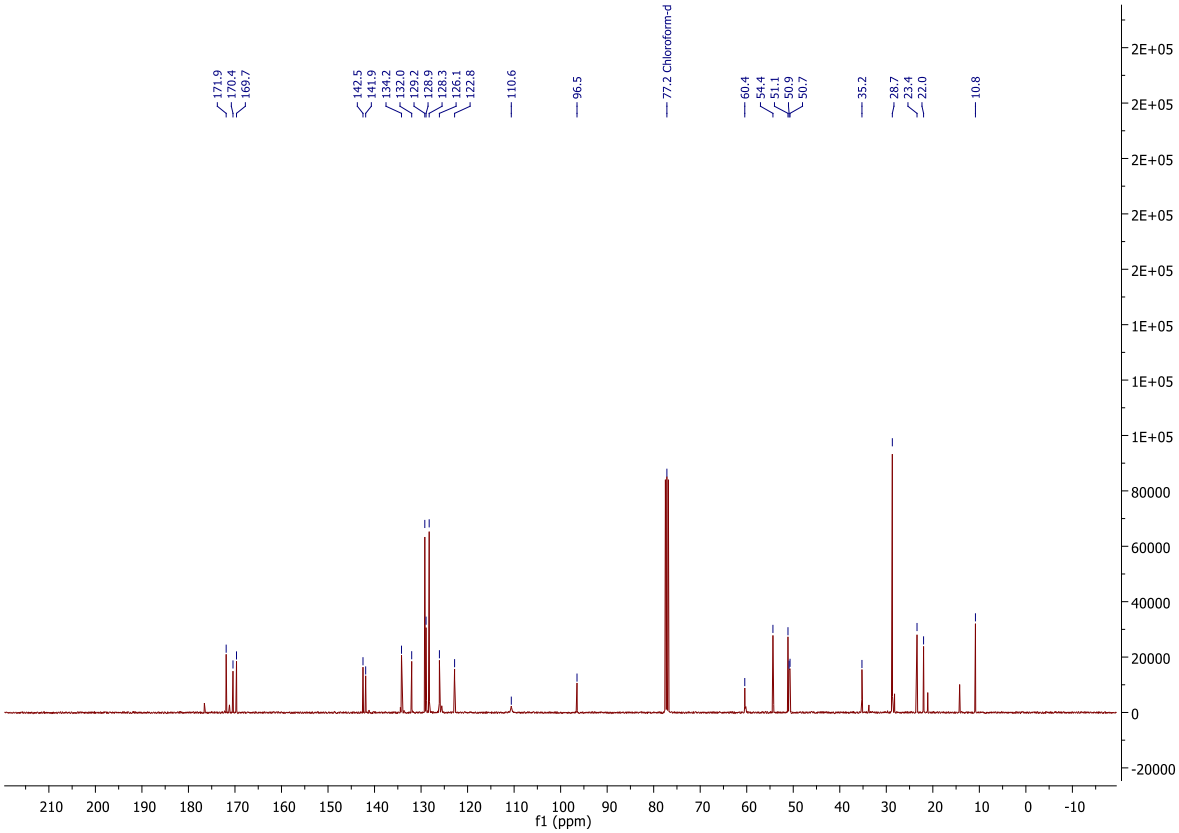
6.46
5.50
5.46
5.42
4.95
4.91
4.89
4.85
4.82
4.80
4.80
4.78
4.75
3.52
3.49
1.81
1.51
1.34
1.26
1.25
1.24
0.87
0.85
0.83
O
N
MeO
OMe
O
HN
O
N
N
N
N
(5eaab)
40000
35000
30000
25000
20000
15000
10000
5000
0
1.00
3.06
2.96
1.76
0.79
2.23
2.06
1.25
2.99
2.99
2.82
1.05
9.22
1.35
3.27
8.5
8.0
7.5
7.0
6.5
6.0
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
-1.0
f1 (ppm)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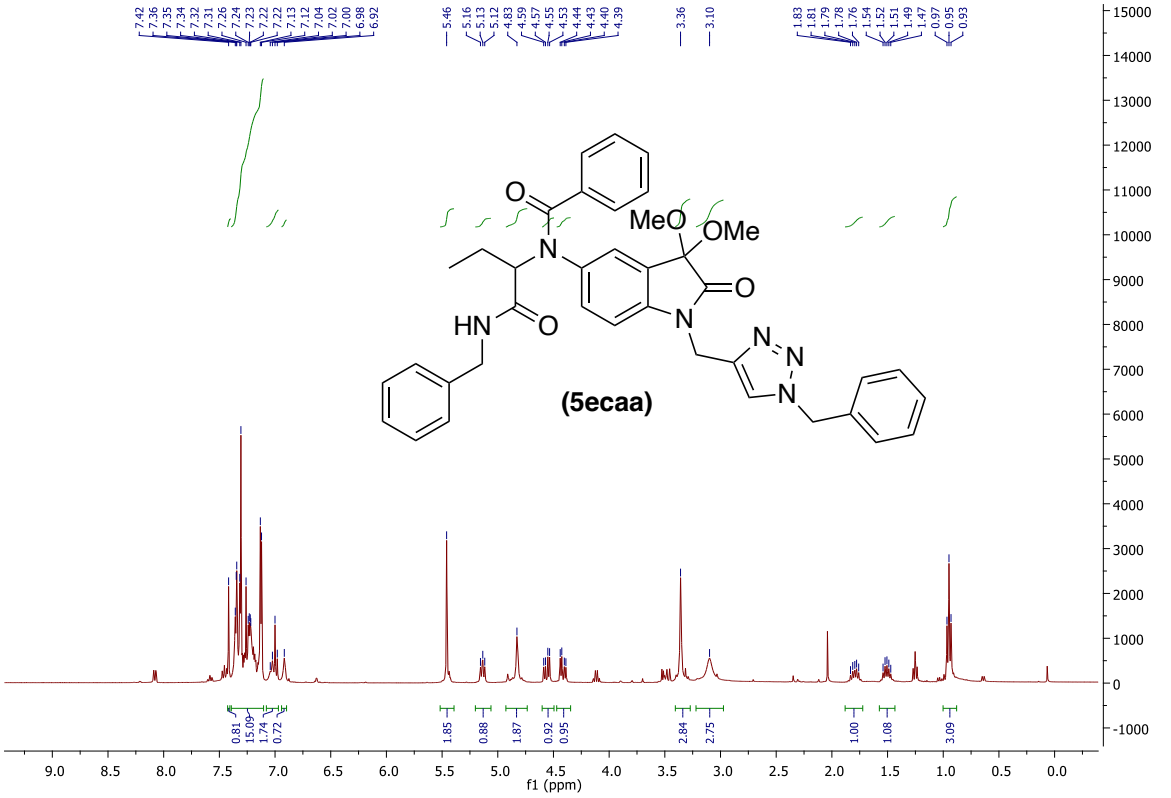
170.4
169.7
142.5
141.9
134.2
132.0
129.2
128.9
128.3
126.1
122.8
110.6
96.5
77.2 Chloroform-d
60.4
54.4
51.1
50.9
50.7
35.2
28.7
23.4
22.0
10.8
2E+05
2E+05
2E+05
2E+05
2E+05
1E+05
1E+05
1E+05
80000
60000
40000
20000
0
-20000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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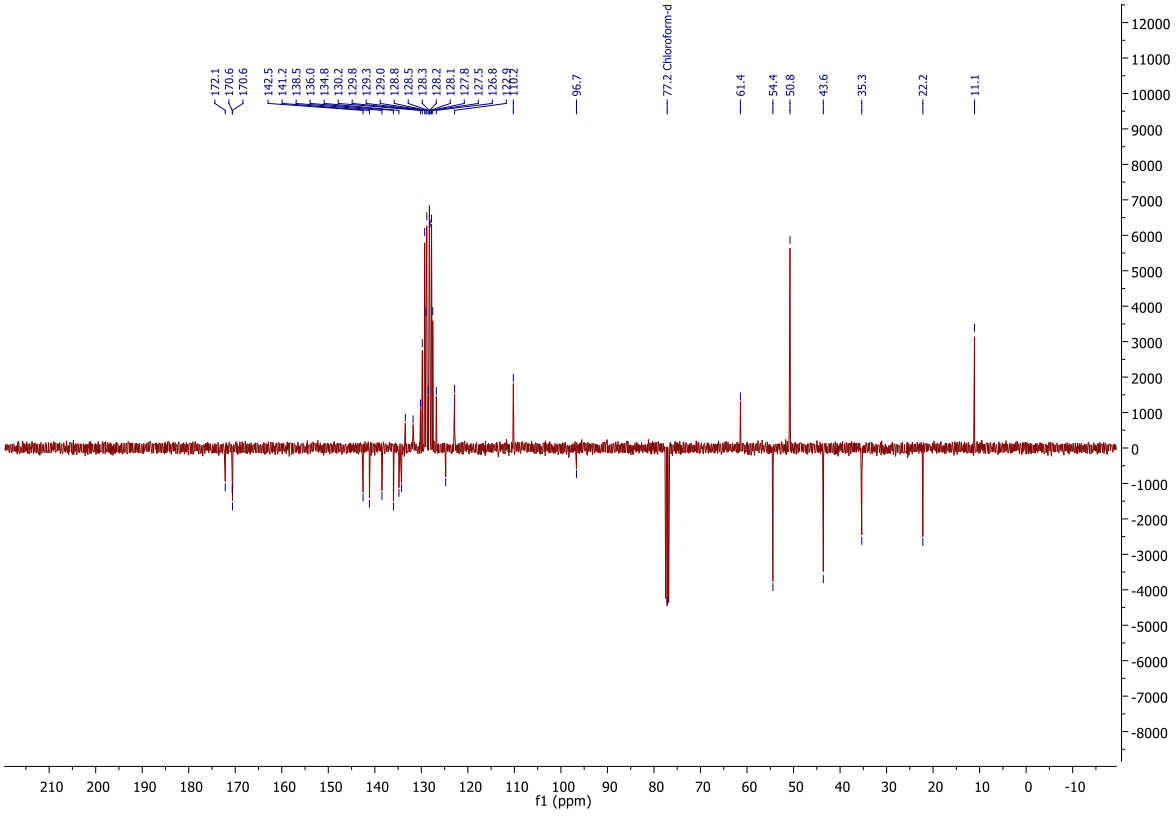
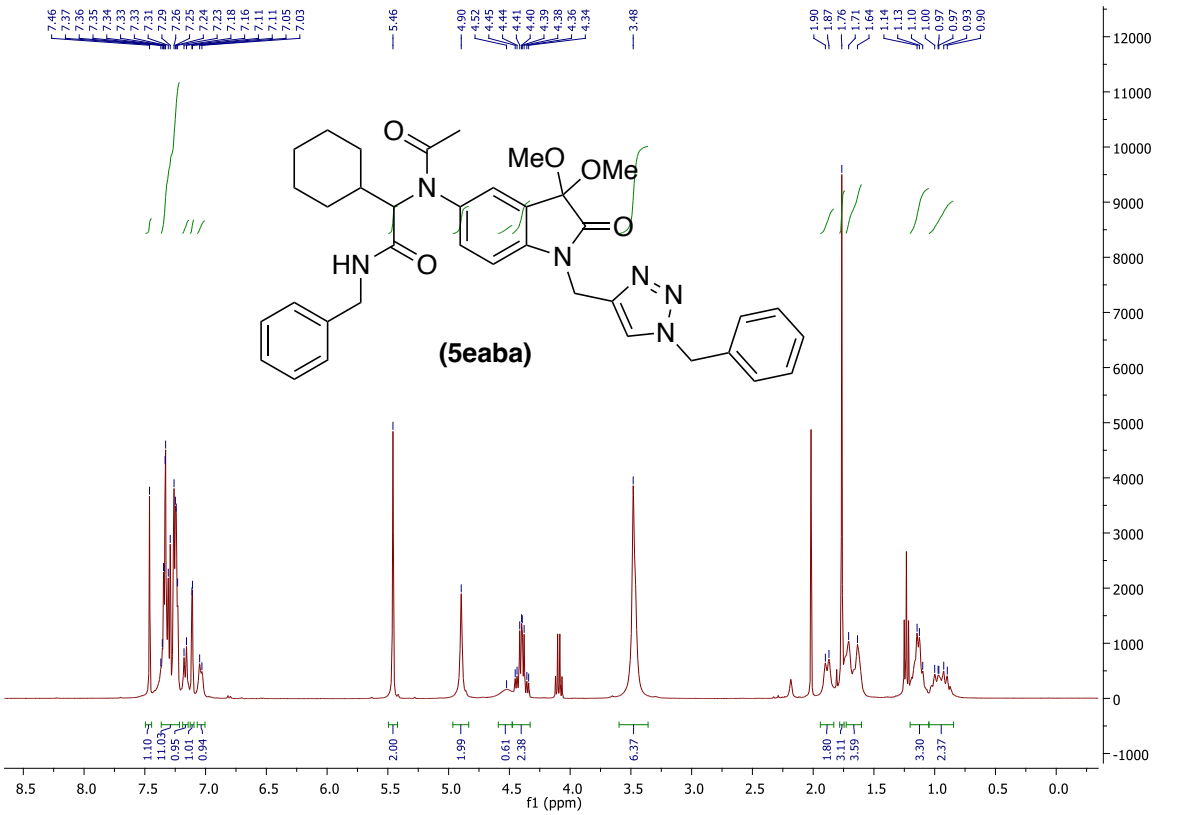

77.2 Chloroform-d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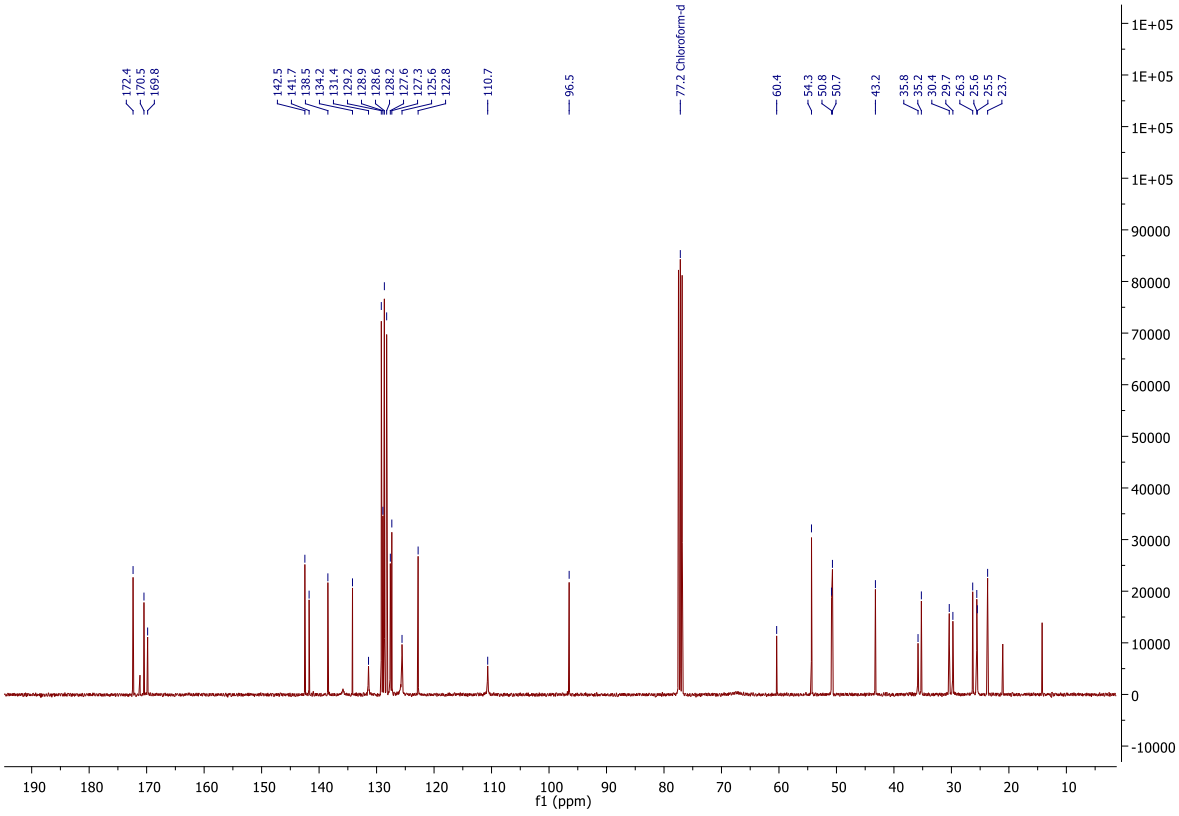

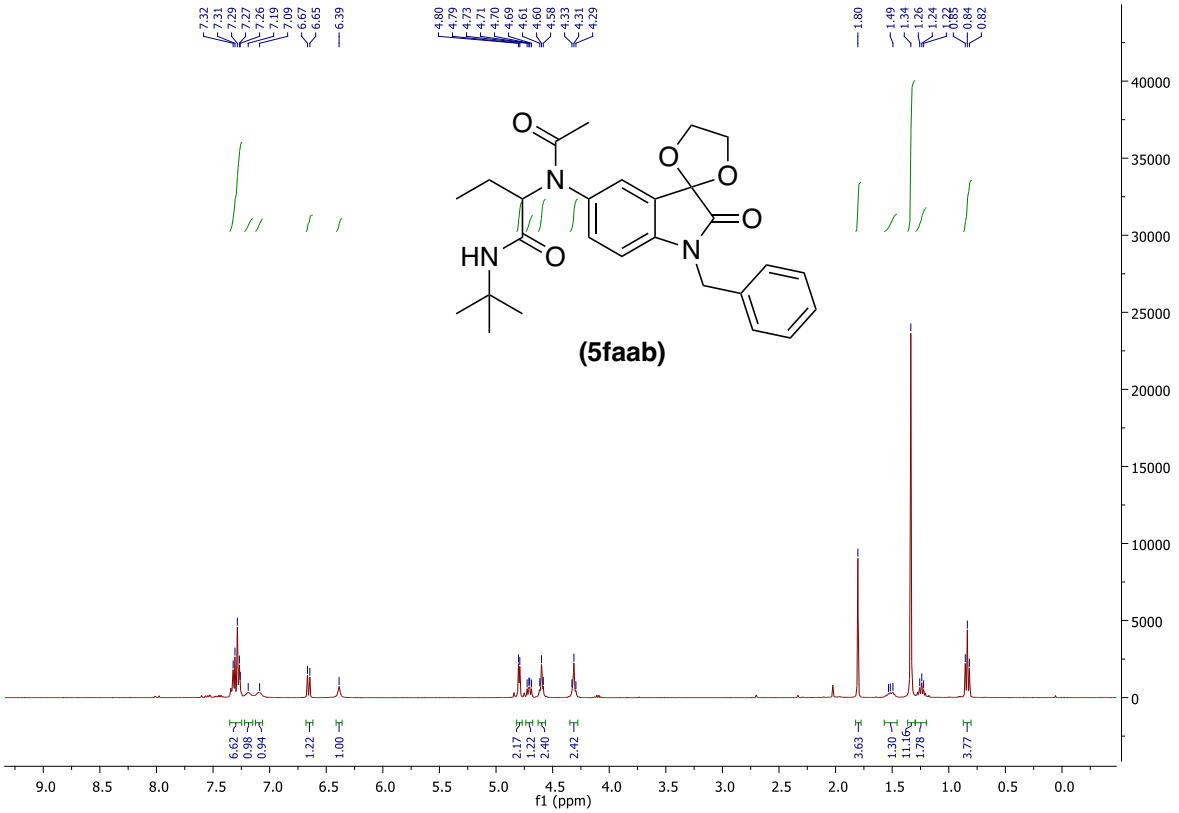
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7.26
7.19
7.09
6.67
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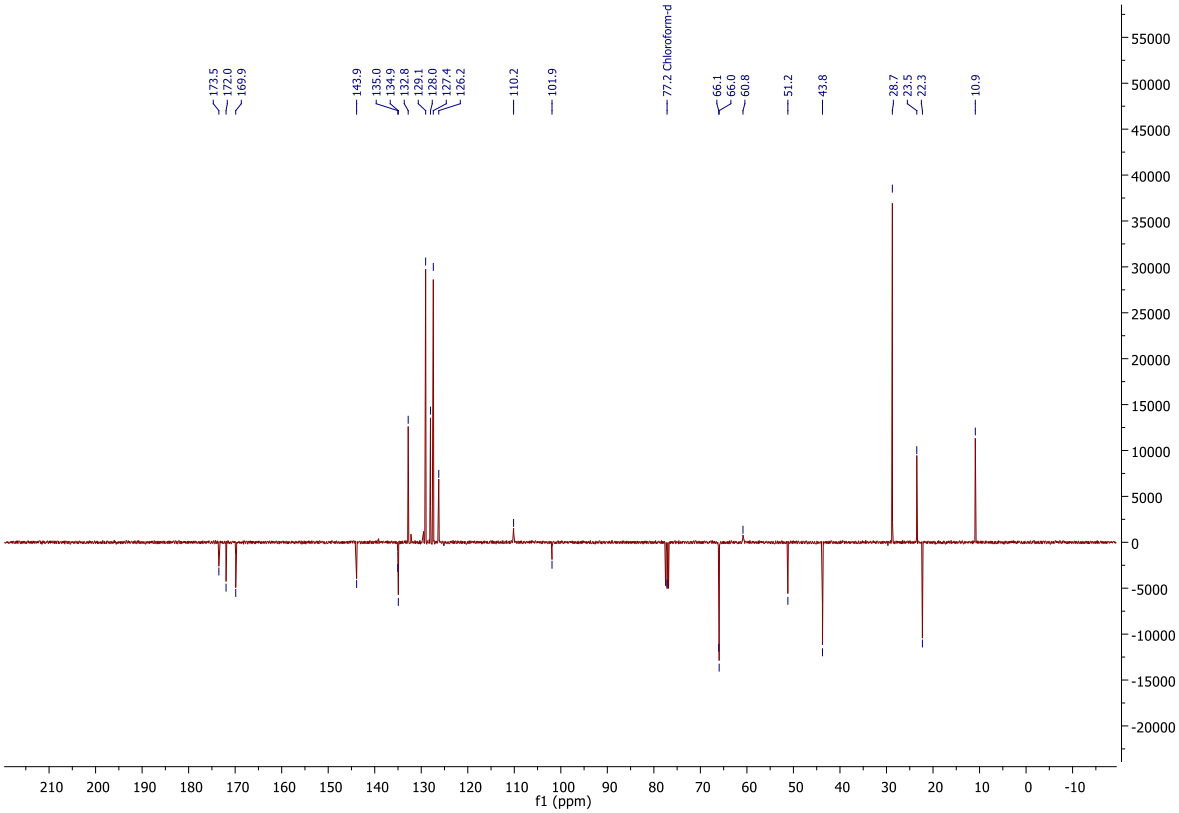
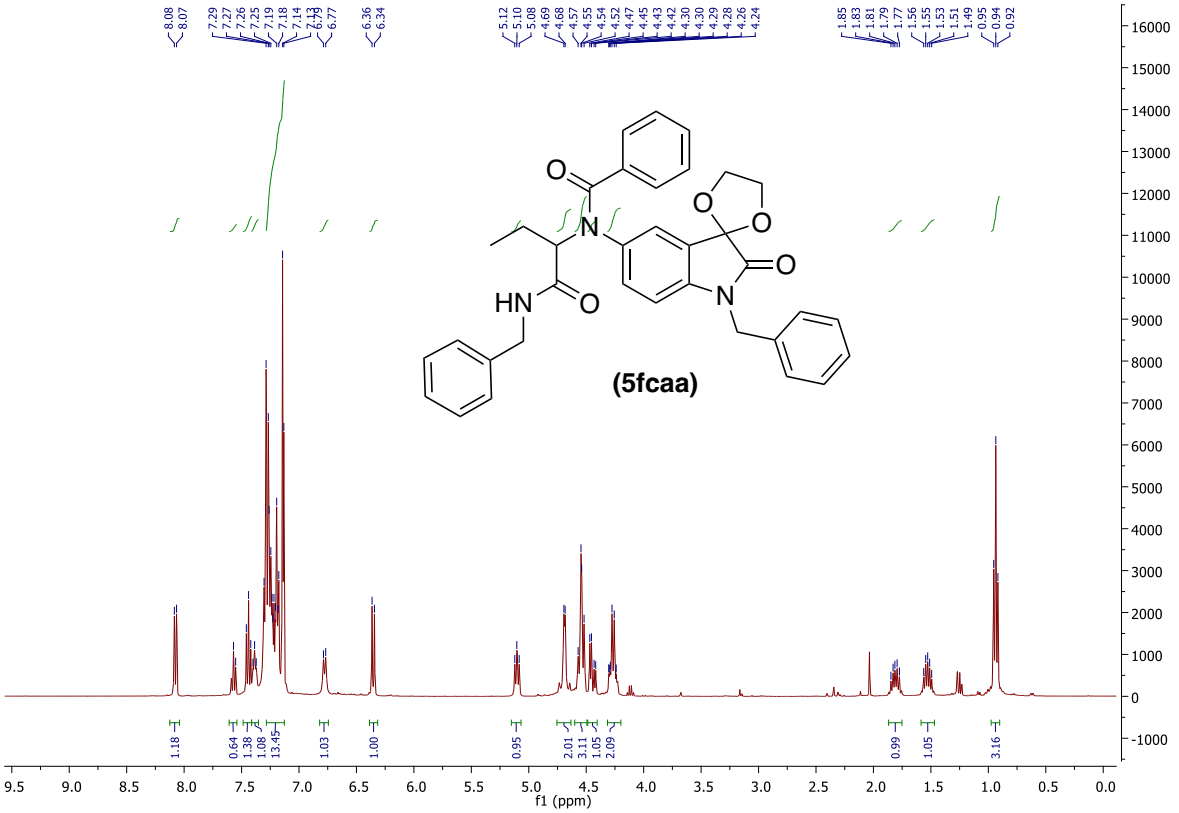
6.39
4.80
4.79
4.73
4.71
4.70
4.69
4.61
4.60
4.58
4.33
4.31
4.29
1.80
1.49
1.34
1.26
1.24
0.85
0.84
0.82
O
N
O
O
O
N
HN
O
(5faab)
6.62
0.98
0.94
1.22
1.00
2.17
1.22
2.40
2.42
3.63
1.30
11.16
1.78
3.77
f1 (ppm)


173.5
172.0
169.9
143.9
135.0
134.9
132.8
129.1
128.0
127.4
126.2
110.2
101.9
77.2 Chloroform-d
66.1
66.0
60.8
51.2
43.8
28.7
23.5
22.3
10.9
f1 (ppm)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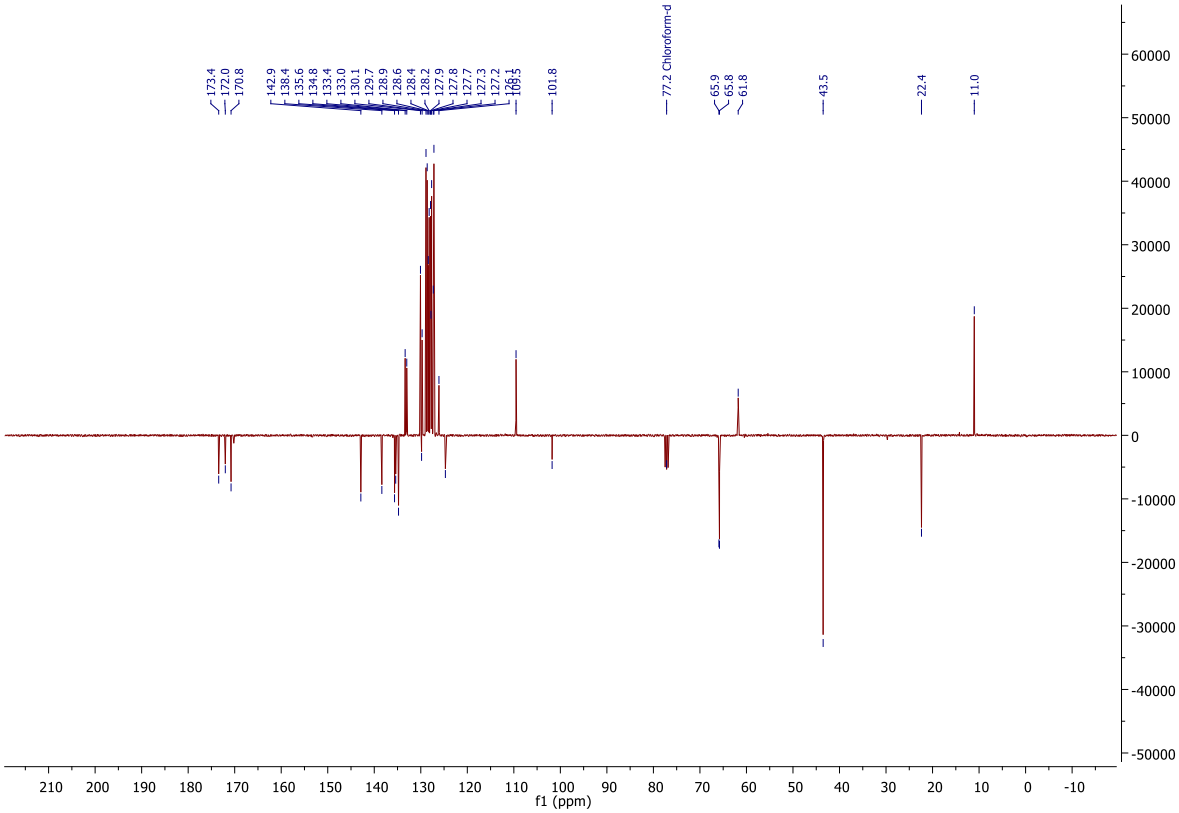
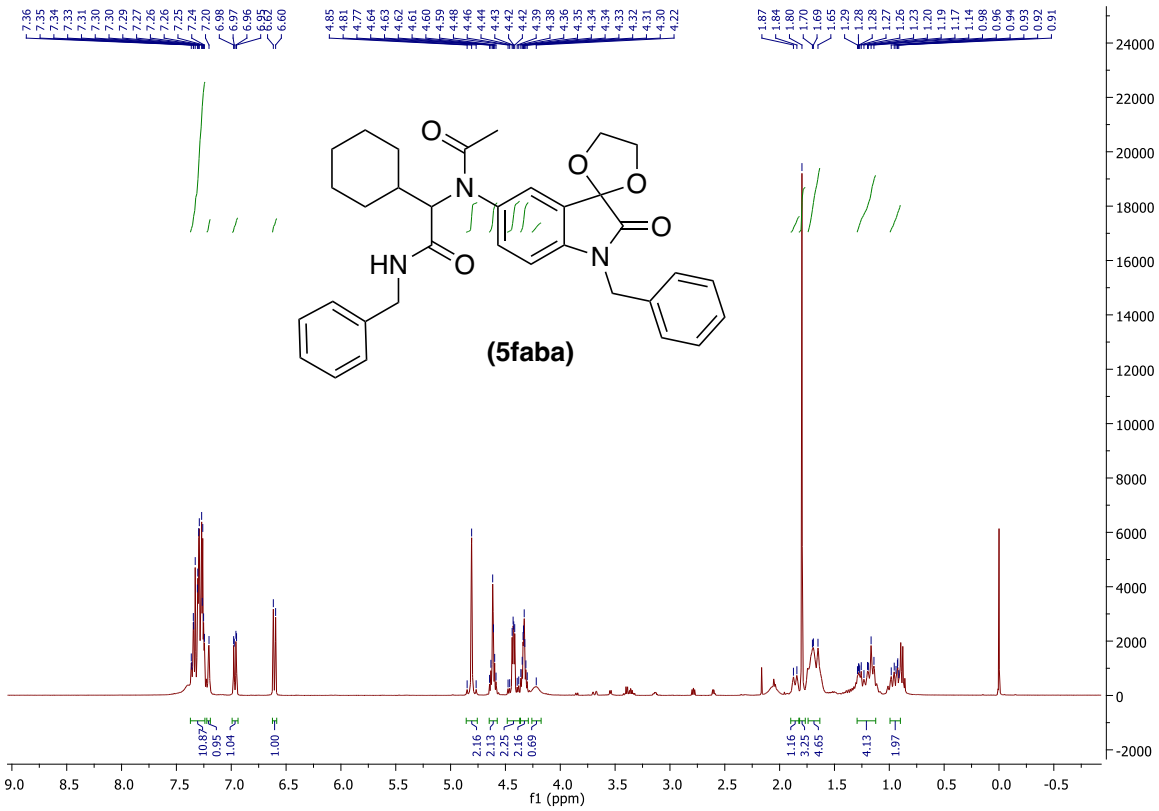
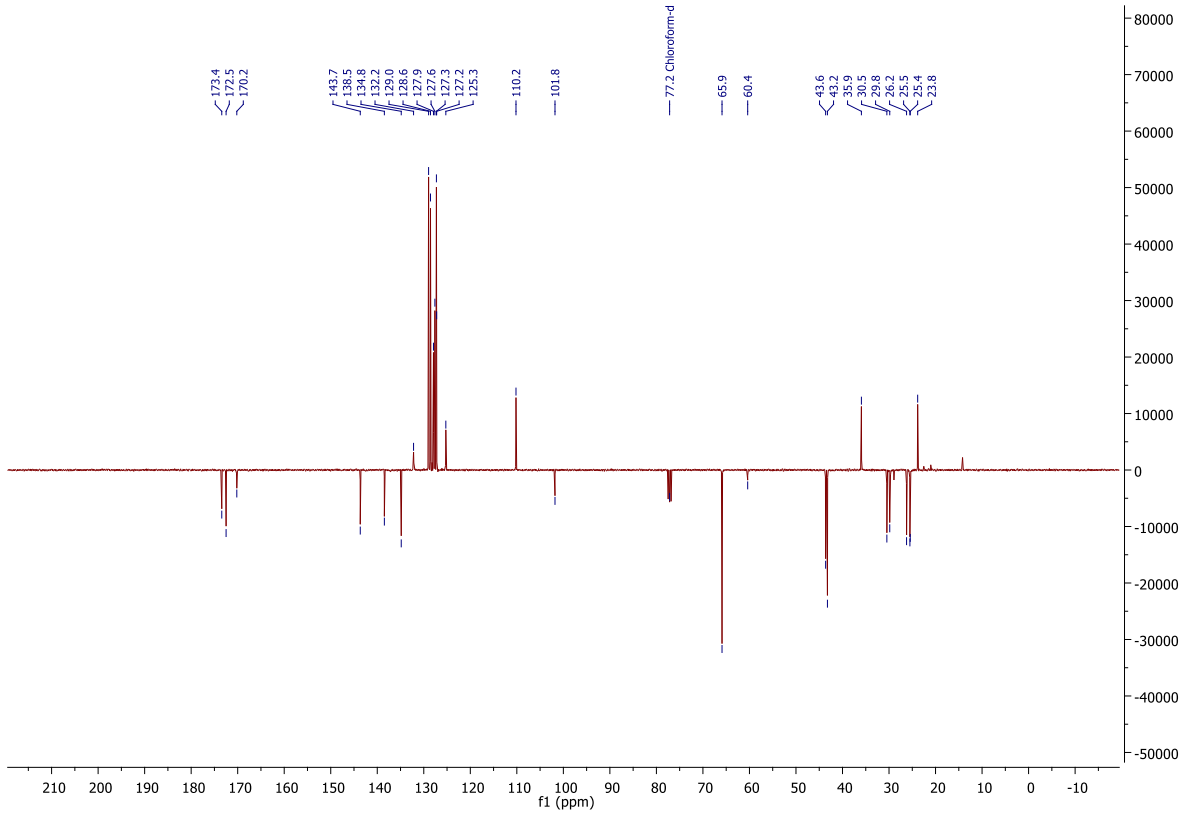
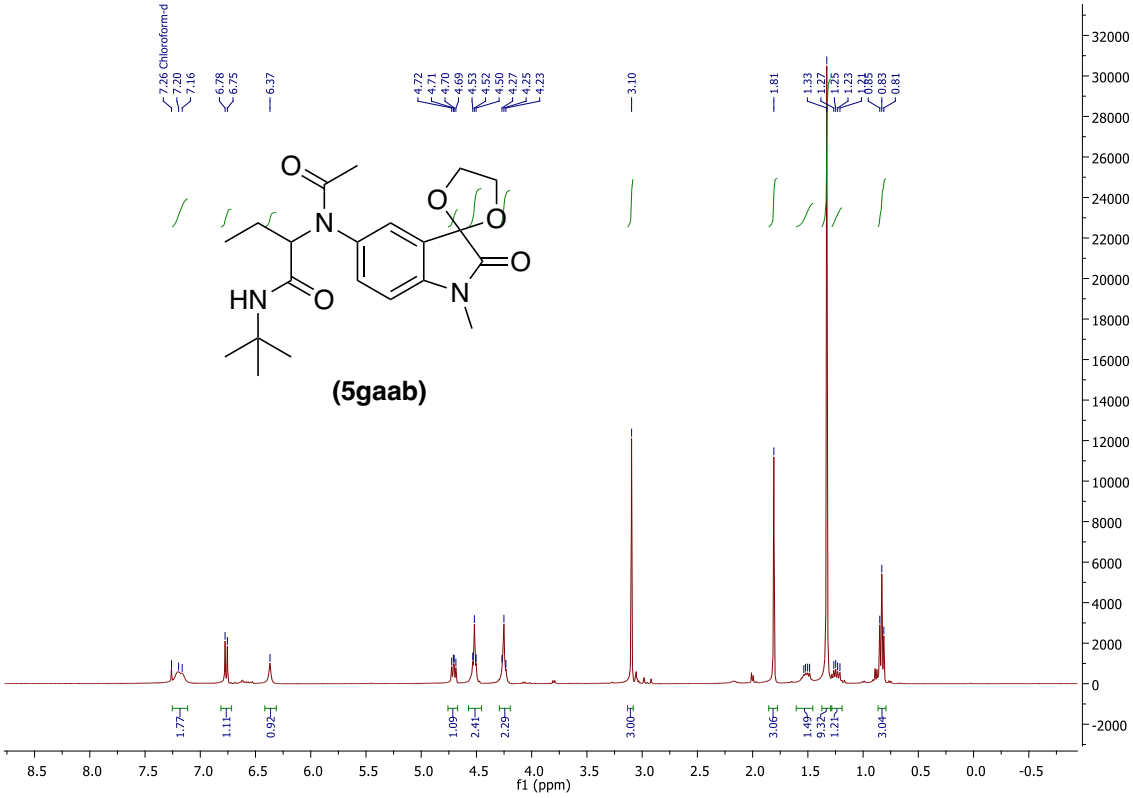
f1 (ppm)

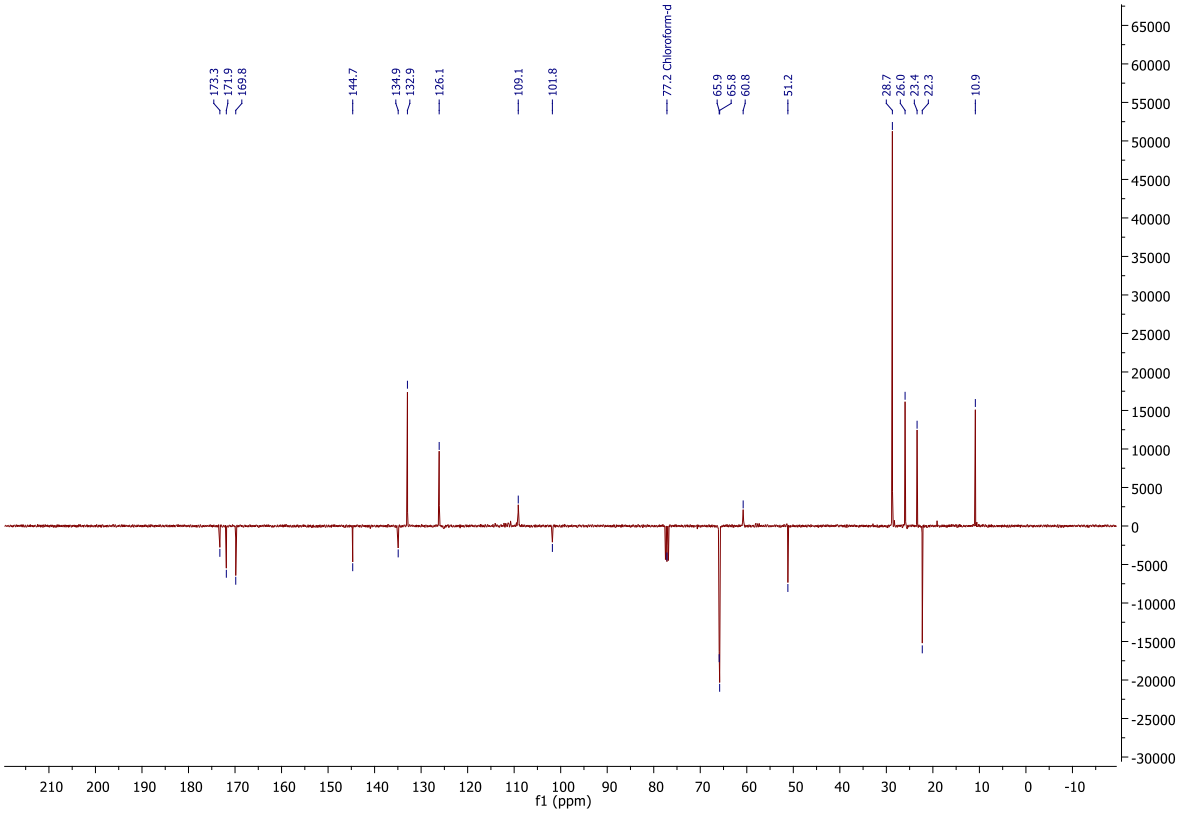

77.2 Chloroform-d
f1 (ppm)

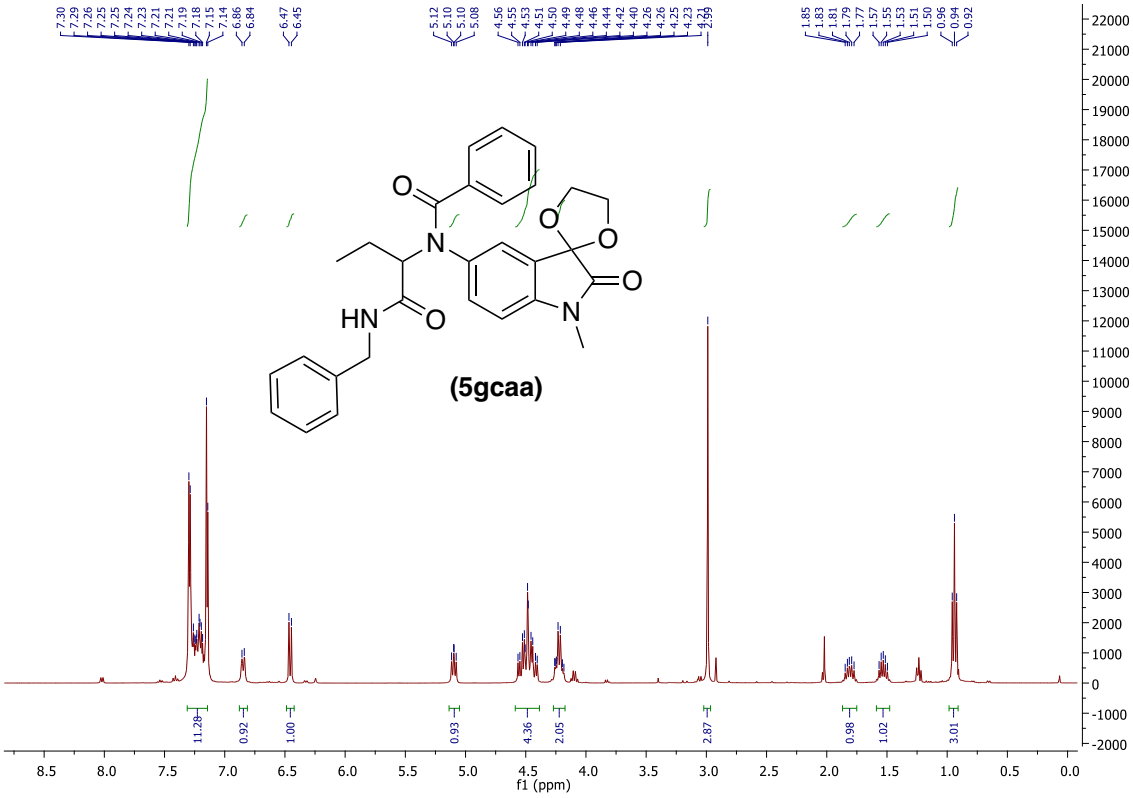

(5faba)
f1 (ppm)

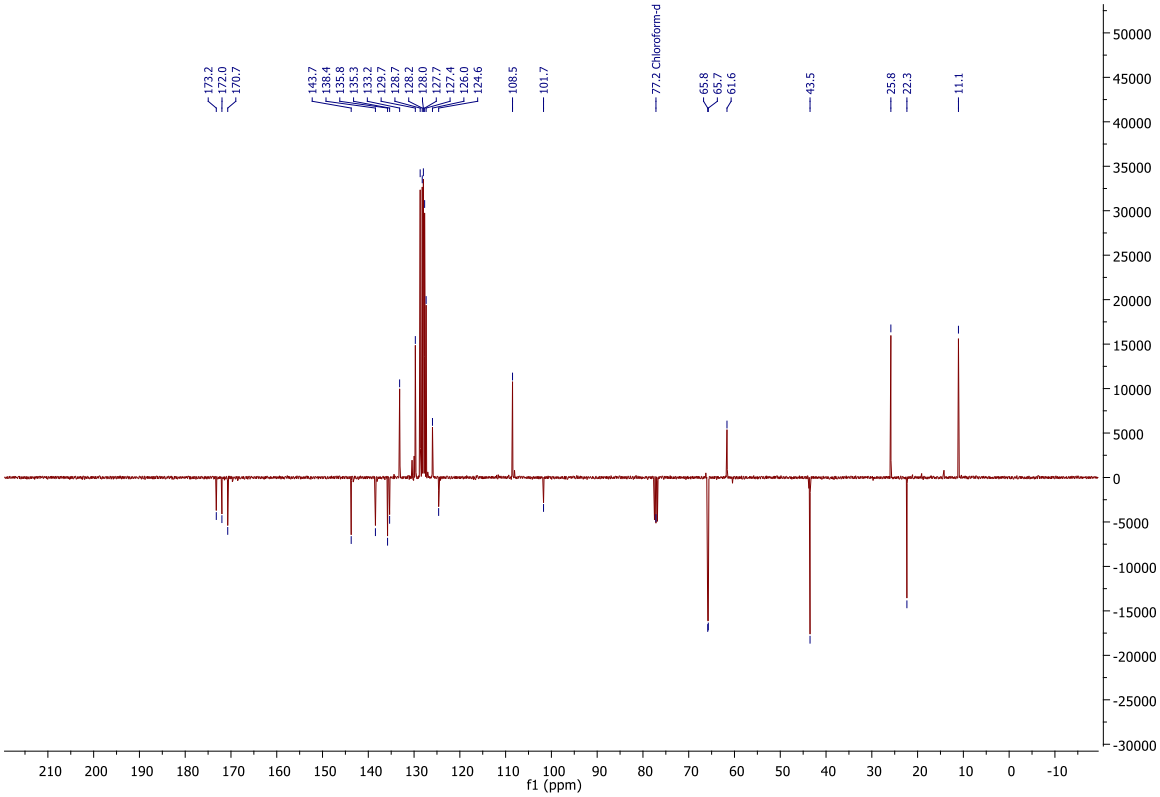

77.2 Chloroform-d
f1 (ppm)

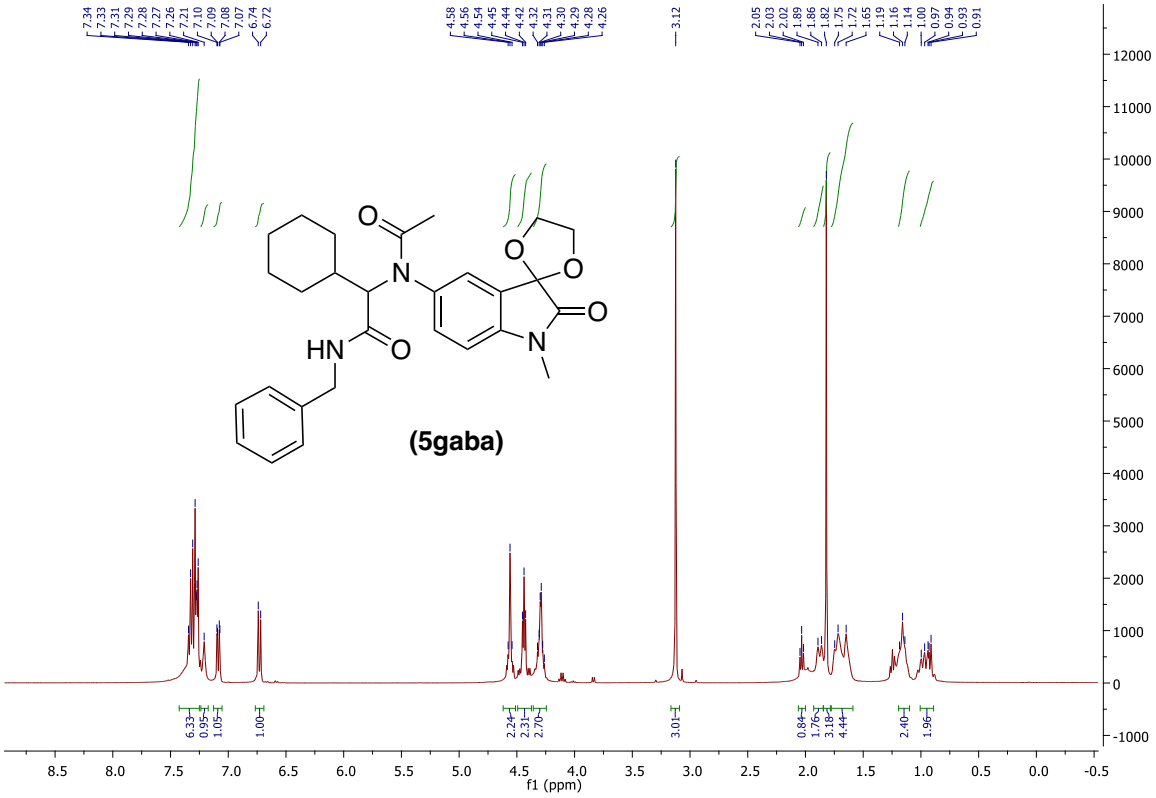

7.26 Chloroform-d
7.20
7.16
6.78
6.75
6.37
4.72
4.71
4.70
4.69
4.53
4.52
4.50
4.27
4.25
4.23
3.10
1.81
1.33
1.27
1.25
1.23
0.85
0.83
0.81
1.77
1.11
0.92
1.09
2.41
2.29
3.00
3.06
1.49
9.32
1.21
3.04
f1 (ppm)

(5gaab)


173.3
171.9
169.8
144.7
134.9
132.9
126.1
109.1
101.8
77.2 Chloroform-d
65.9
65.8
60.8
51.2
28.7
26.0
23.4
22.3
10.9
f1 (ppm)


(5gcaa)
f1 (ppm)


77.2 Chloroform-d
f1 (ppm)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7.07
6.74
6.72
4.58
4.56
4.54
4.45
4.44
4.42
4.32
4.31
4.30
4.29
4.28
4.26
3.12
2.05
2.03
2.02
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1.86
1.82
1.75
1.72
1.65
1.19
1.16
1.14
1.00
0.97
0.94
0.93
0.91
O
N
O
O
O
HN
O
N
(5gaba)
6.33
0.95
1.05
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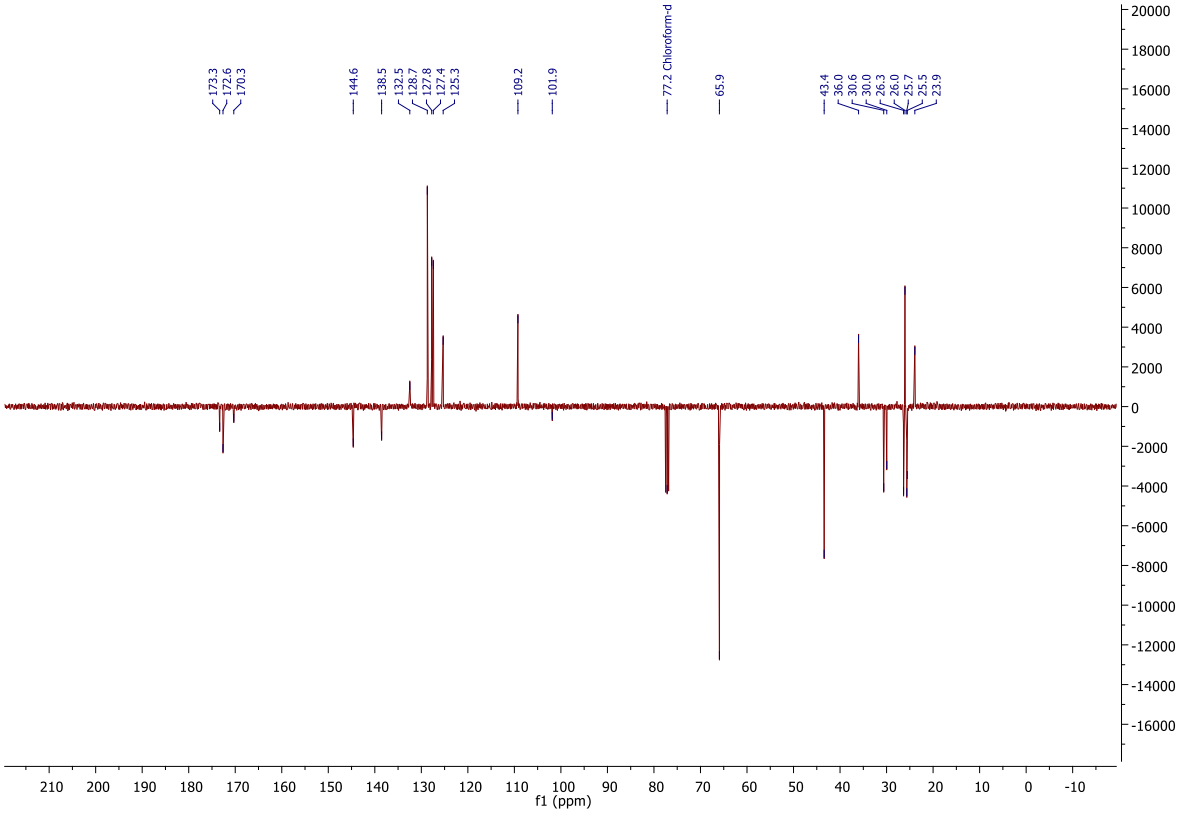
f1 (ppm)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170.3
144.6
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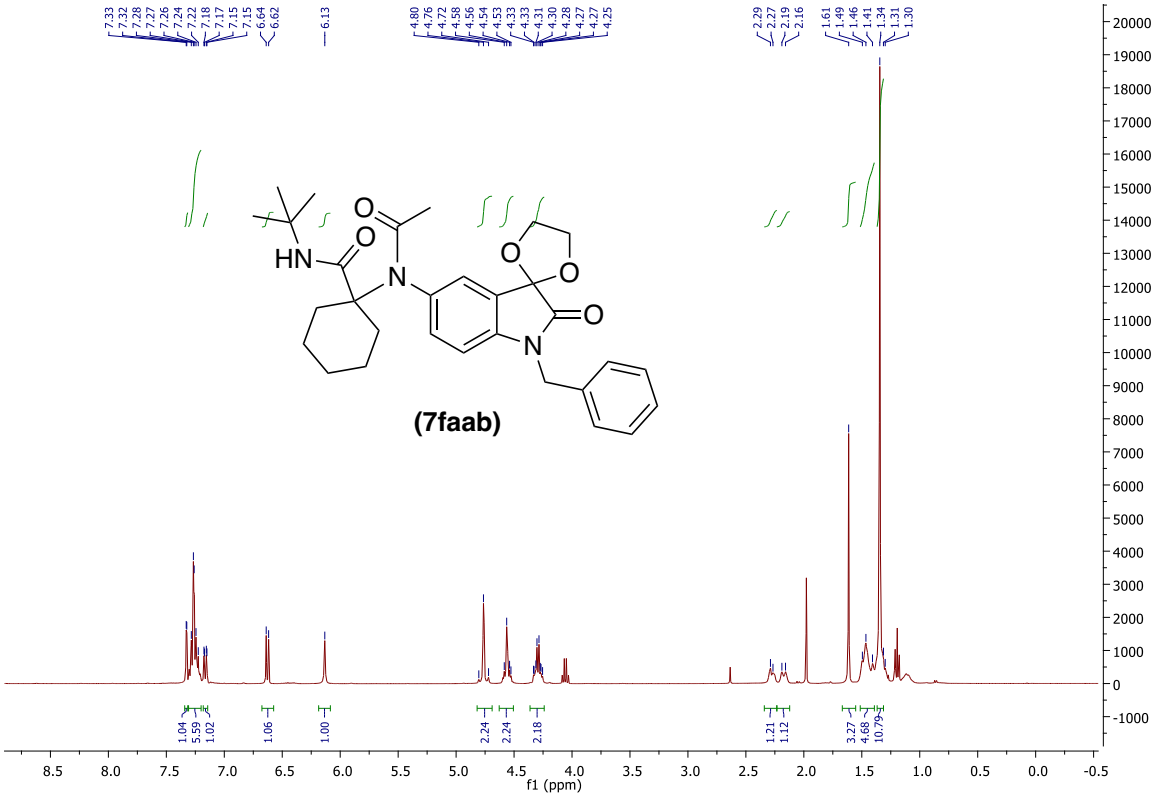
132.5
128.7
127.8
127.4
125.3
109.2
101.9
77.2 Chloroform-d
65.9
43.4
36.0
30.6
30.0
26.3
26.0
25.7
25.5
23.9
f1 (ppm)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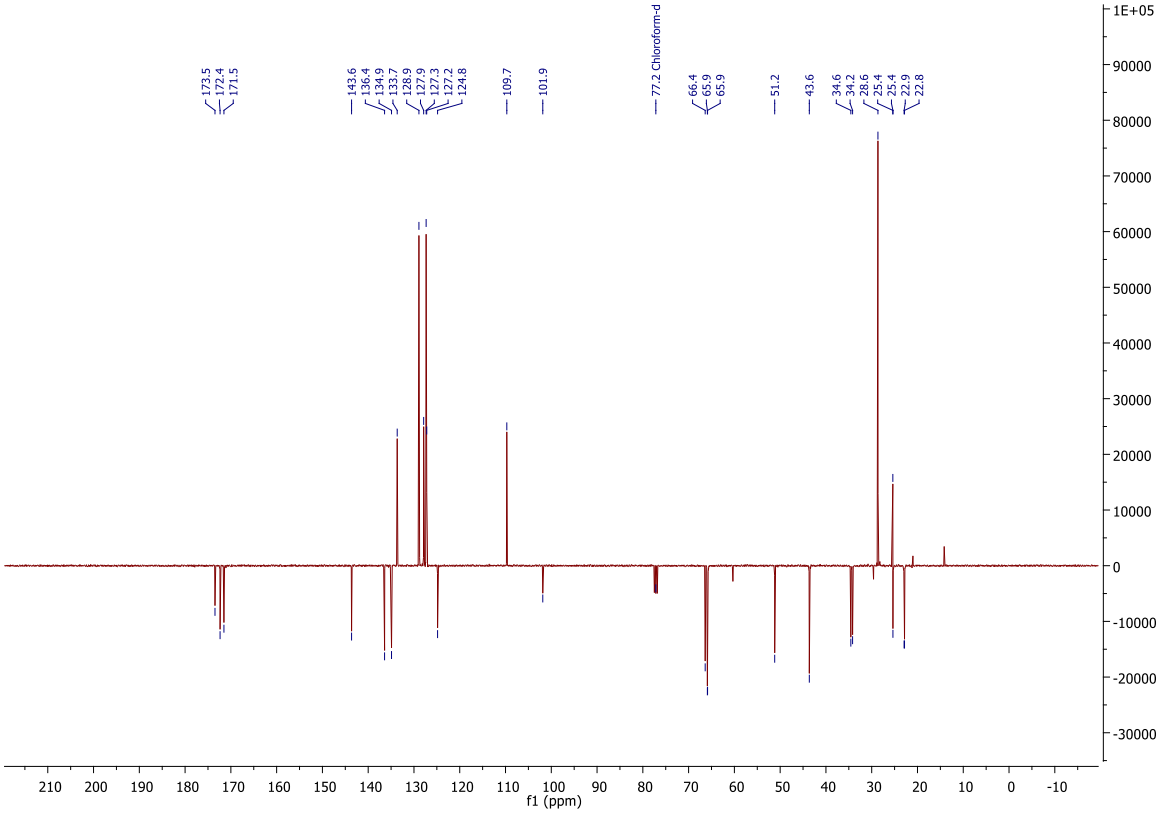
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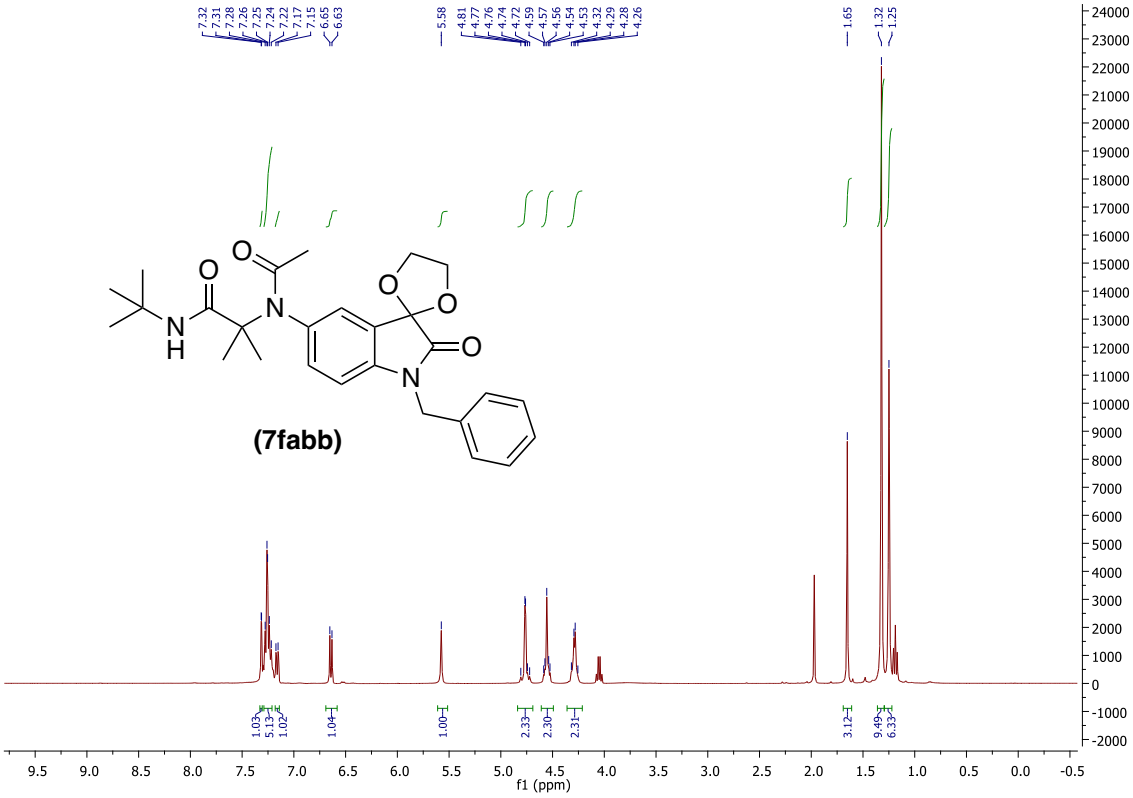
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4.77
4.76
4.74
4.72
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4.57
4.56
4.54
4.53
4.32
4.29
4.28
4.26
1.65
1.32
1.25
(7fabb)
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1.04
1.00
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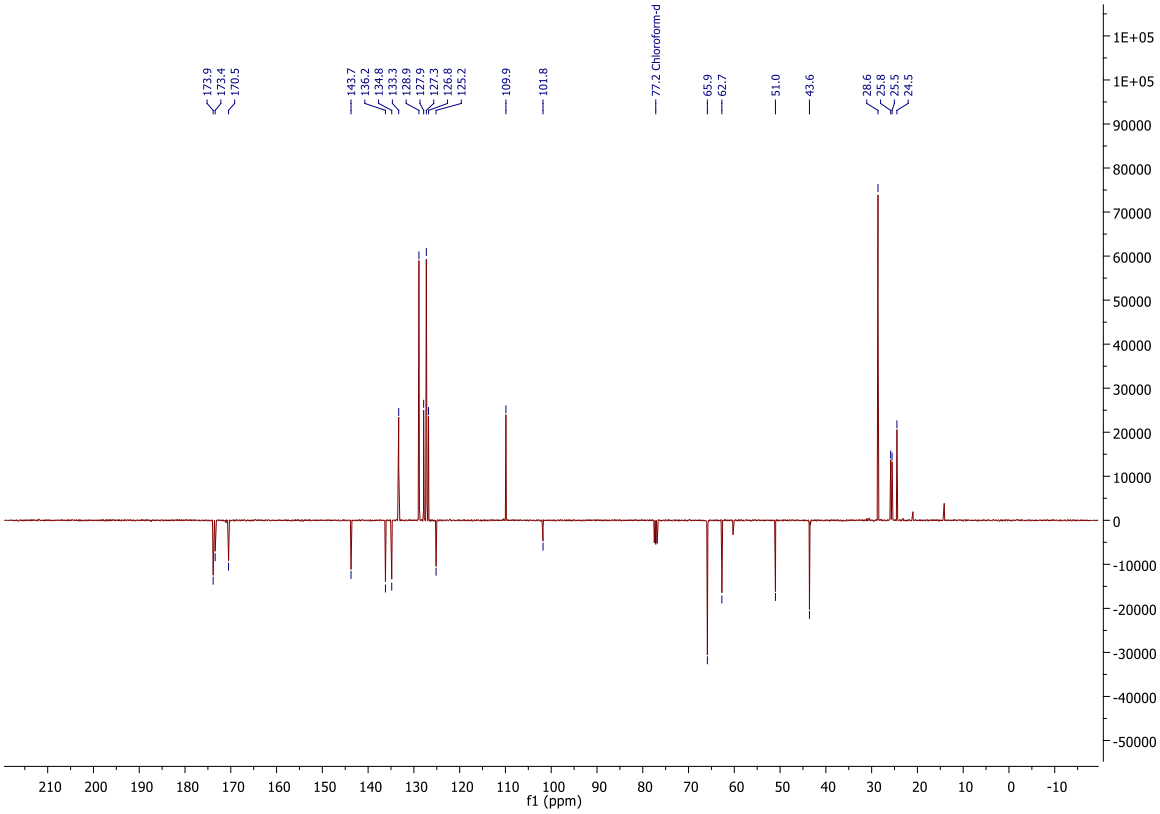
2.30
2.31
3.12
9.49
6.33
f1 (ppm)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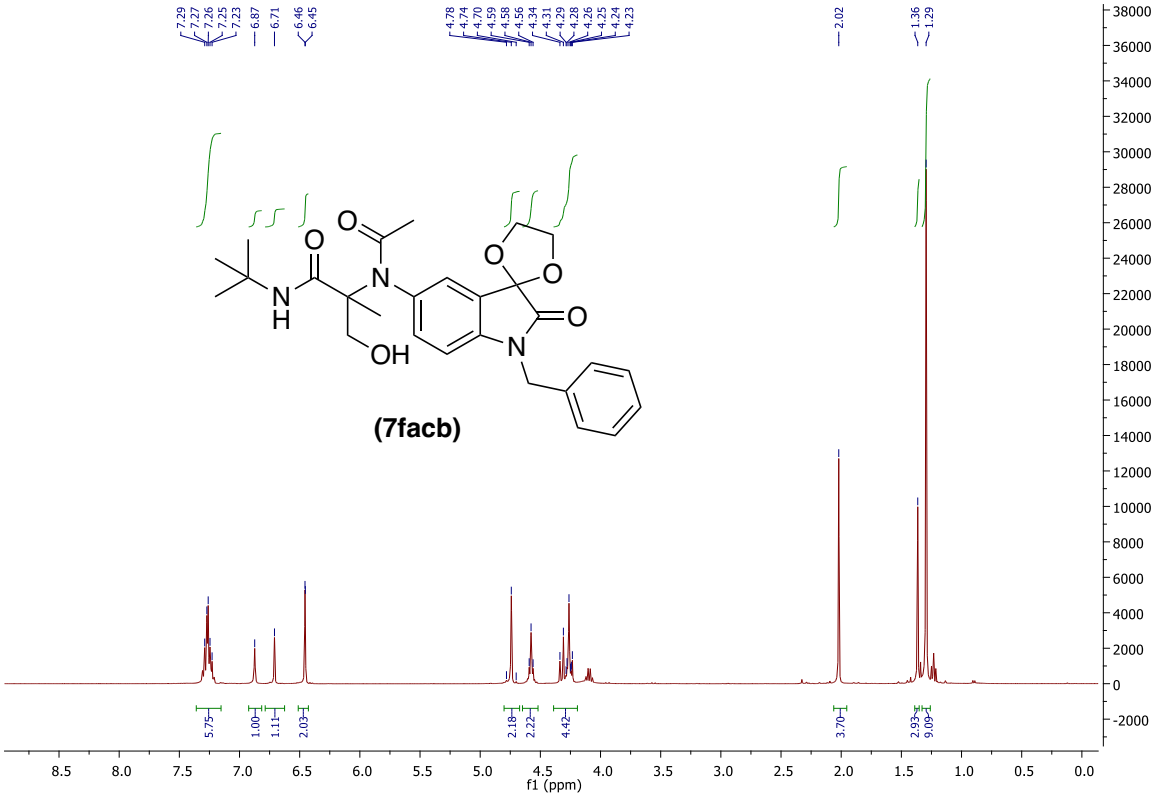
173.4
170.5
143.7
136.2
134.8
133.3
128.9
127.9
127.3
126.8
125.2
109.9
101.8
77.2 Chloroform-d
65.9
62.7
51.0
43.6
28.6
25.8
25.5
24.5
f1 (ppm)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4.74
4.70
4.59
4.58
4.56
4.34
4.31
4.29
4.28
4.26
4.25
4.24
4.23
2.02
1.36
1.29
O
O
N
H
O
N
O
O
O
OH
N
(7facb)
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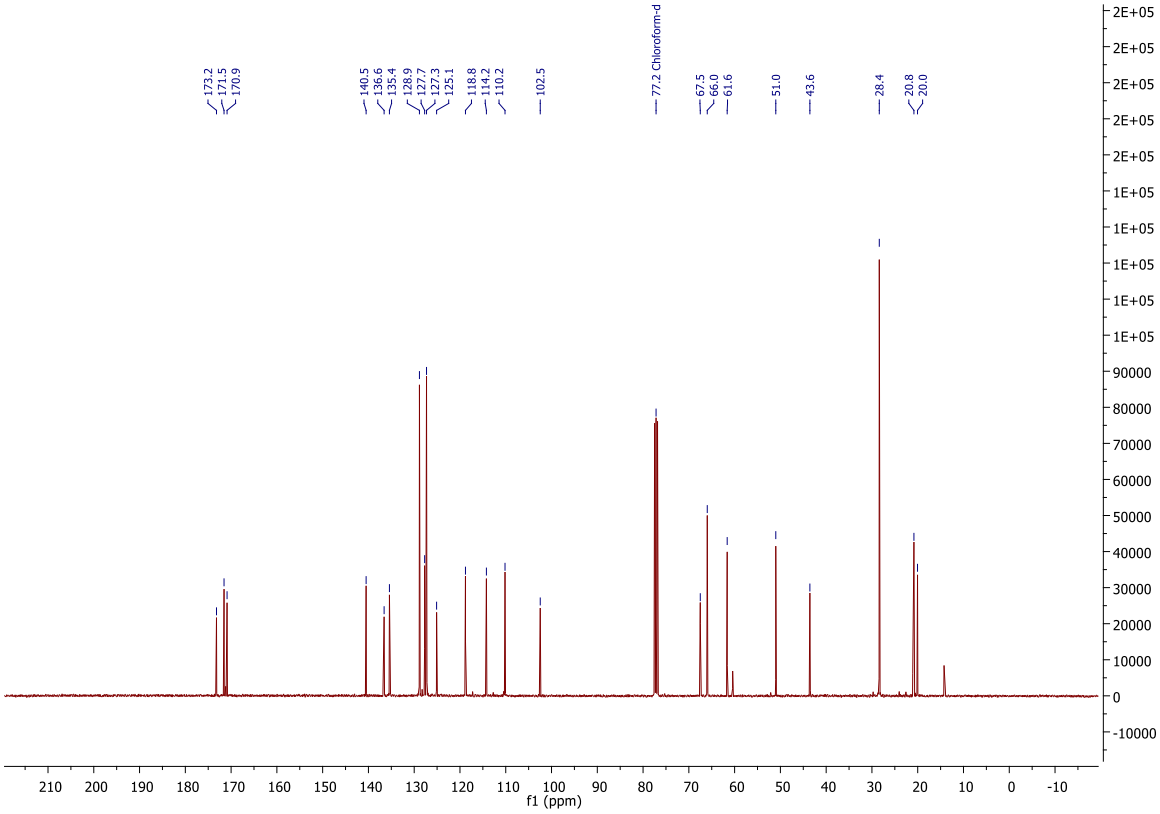
1.11
2.03
2.18
2.22
4.42
3.70
2.93
9.09
f1 (ppm)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171.5
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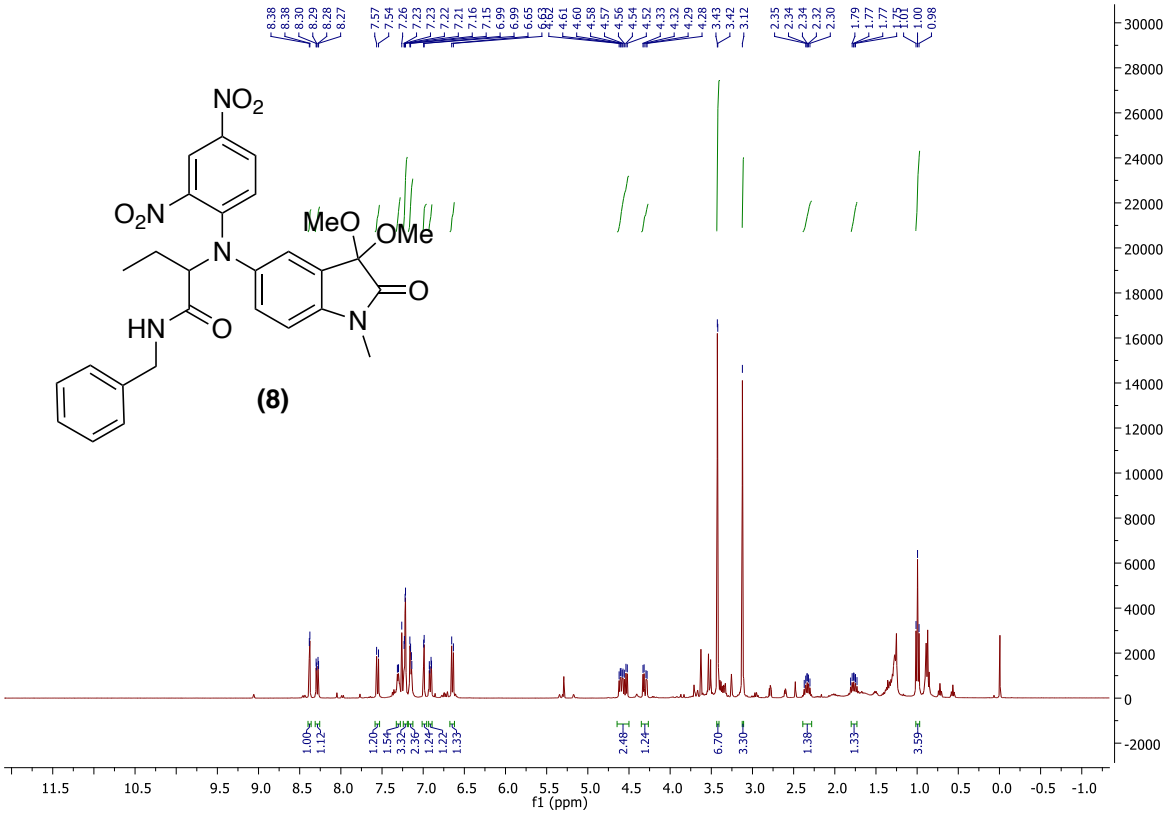
140.5
136.6
135.4
128.9
127.7
127.3
125.1
118.8
114.2
110.2
102.5
77.2 Chloroform-d
67.5
66.0
61.6
51.0
43.6
28.4
20.8
20.0
f1 (ppm)


NO2
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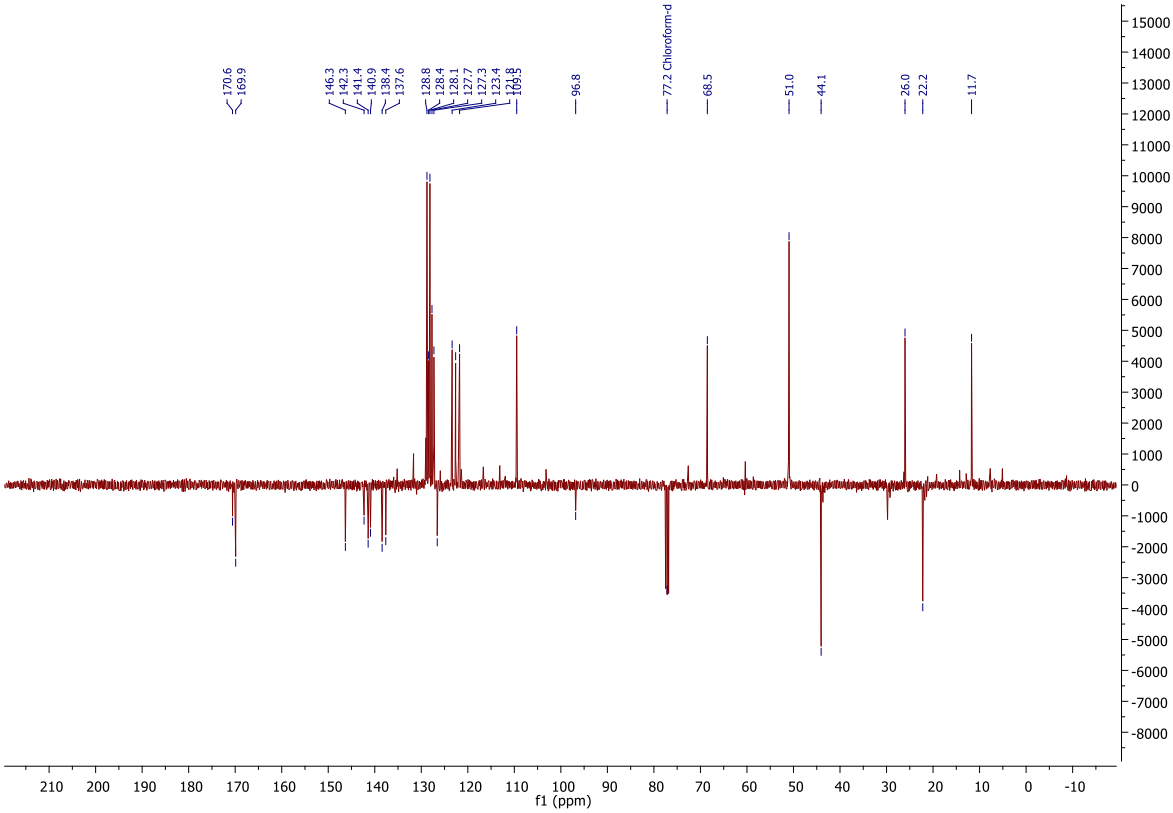
MeO
OMe
N
O
HN
O
N
O
(8)
f1 (ppm)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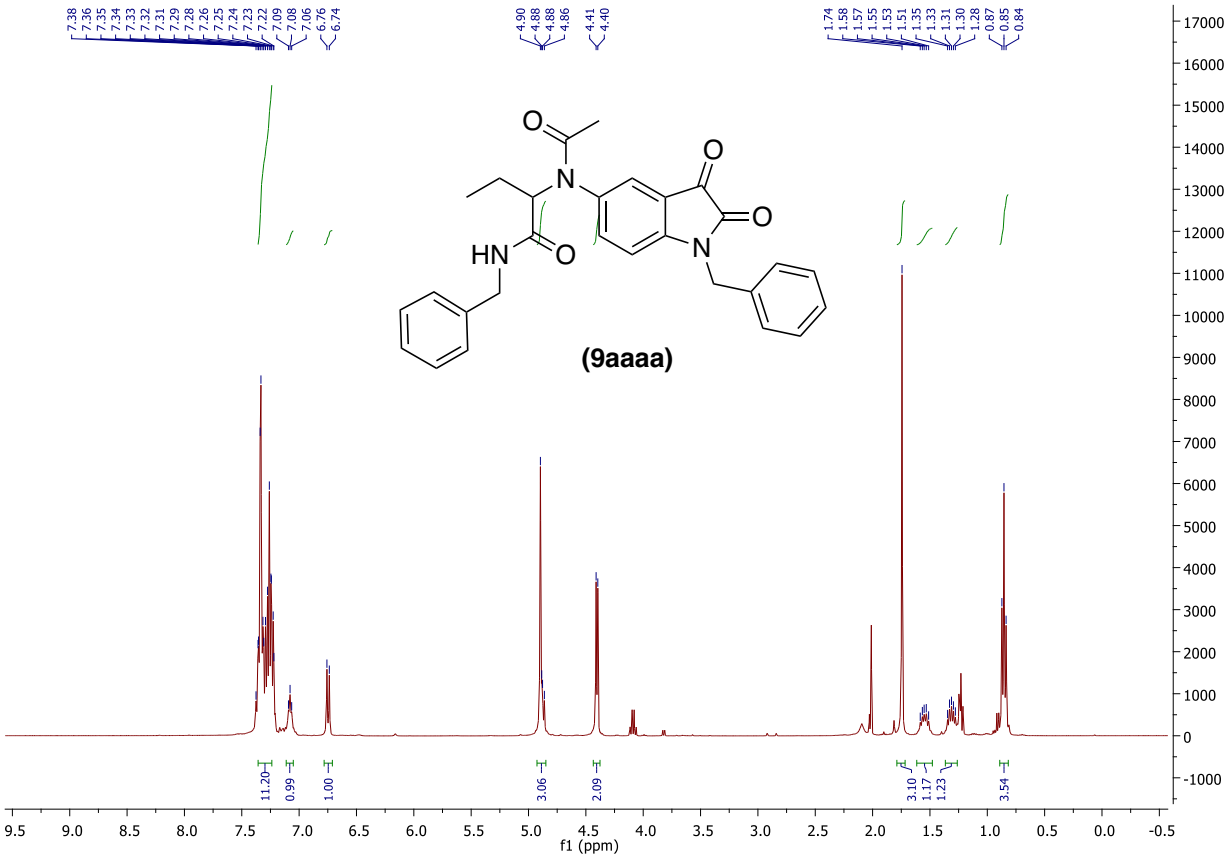
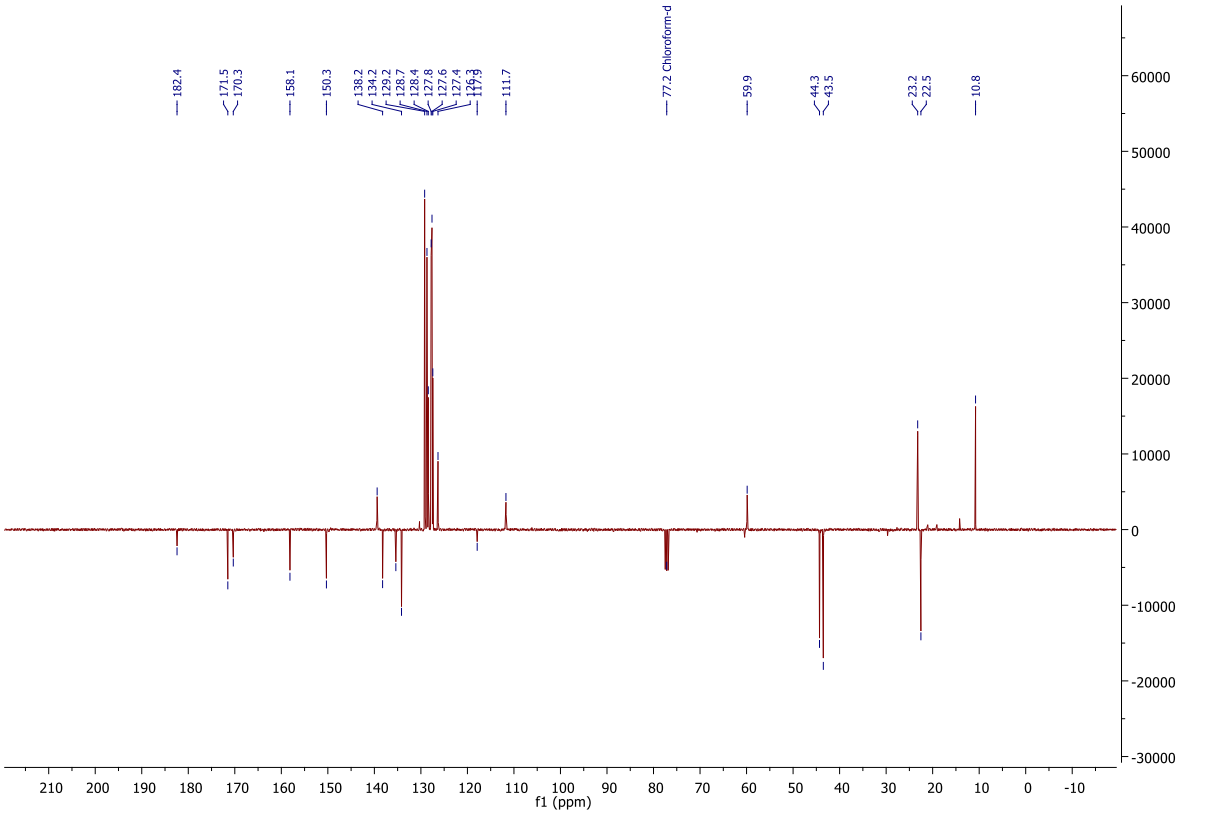
169.9
146.3
142.3
141.4
140.9
138.4
137.6
128.8
128.4
128.1
127.7
127.3
123.4
96.8
77.2 Chloroform-d
68.5
51.0
44.1
26.0
22.2
11.7
f1 (ppm)


7.38
7.36
7.35
7.34
7.33
7.32
7.31
7.29
7.28
7.26
7.25
7.24
7.23
7.22
7.09
7.08
7.06
6.76
6.74
4.90
4.88
4.88
4.86
4.41
4.40
1.74
1.58
1.57
1.55
1.53
1.51
1.35
1.33
1.31
1.30
1.28
0.87
0.85
0.84
O
N
O
HN
O
O
N
(9aaaa)
11.20
0.99
1.00
3.06
2.09
3.10
1.17
1.23
3.54
f1 (ppm)


182.4
171.5
170.3
158.1
150.3
138.2
134.2
129.2
128.7
128.4
127.8
127.6
127.4
119.3
111.7
77.2 Chloroform-d
59.9
44.3
43.5
23.2
22.5
10.8
f1 (ppm)