Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

2,7-Diazabicyclo[2.2.1]heptanes: Novel Asymmetric Access and Controlled Bridge-Opening

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General Methods

All reactions were carried out under an atmosphere of nitrogen and using dry solvents unless otherwise stated. All reagents were used as received from commercial suppliers without further purification.

Microwave reactions were carried out in a CEM Discover-S microwave reactor using 150 Watts in dynamic mode.

The progress of reactions was monitored by thin layer chromatography using Merck silica gel 60 F_{254} plates, which were visualized with UV light and potassium permanganate. Flash column chromatography was carried out using Geduran 60 Å silica gel and the indicated solvent systems.

NMR data were recorded on a Bruker AVIII300, AVIII400, AVIII400neo or AVIII500neo spectrometer in deuterated chloroform (unless otherwise indicated) and spectra were calibrated using residual solvent peaks (^{1}H = 7.26 ppm; ^{13}C = 77.16 ppm). The multiplicities of ^{1}H NMR signals are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and combinations thereof.

Mass spectra were recorded on either a Waters Xevo G2-XS Tof or Synapt G2-S mass spectrometer using Zspray in ESI positive mode.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or a Varian 660-IR FT-IR spectrometer using Agilent Resolutions Pro for processing data. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected.

Optical rotations were measured using a Bellingham and Stanley ADP450 Series Peltier polarimeter at 20 °C using the sodium D line (589.3 nm) and the indicated concentration and solvent.

High performance liquid chromatography (HPLC) analysis was performed using an LC-20 prominence system from Shimazdu, Chromeleon client, version 6.80 SR15 Build 4656, Phenomenex Lux Cellulose-1 (250 x 4.6 mm), Phenomenex Lux Cellulose-3 (250 x 4.6 mm), Phenomenex Lux Amylose-2 (250 x 4.6 mm) and Shimazdu SPD-M20A diode Array Detector for the UV detection, monitored at 220 nm or 230 nm.

Some signals in the C-H aromatic region of the ^{13}C NMR spectra are not observed due to having equivalent resonances.

Preparation of Catalysts and Reagents

Catalysts **3**+**S2** were prepared according to literature procedure.[1]

Catalyst **S1** was prepared according to literature procedure.[2]

Catalyst **S3** was commercially available and purchased from Strem Chemicals, inc.

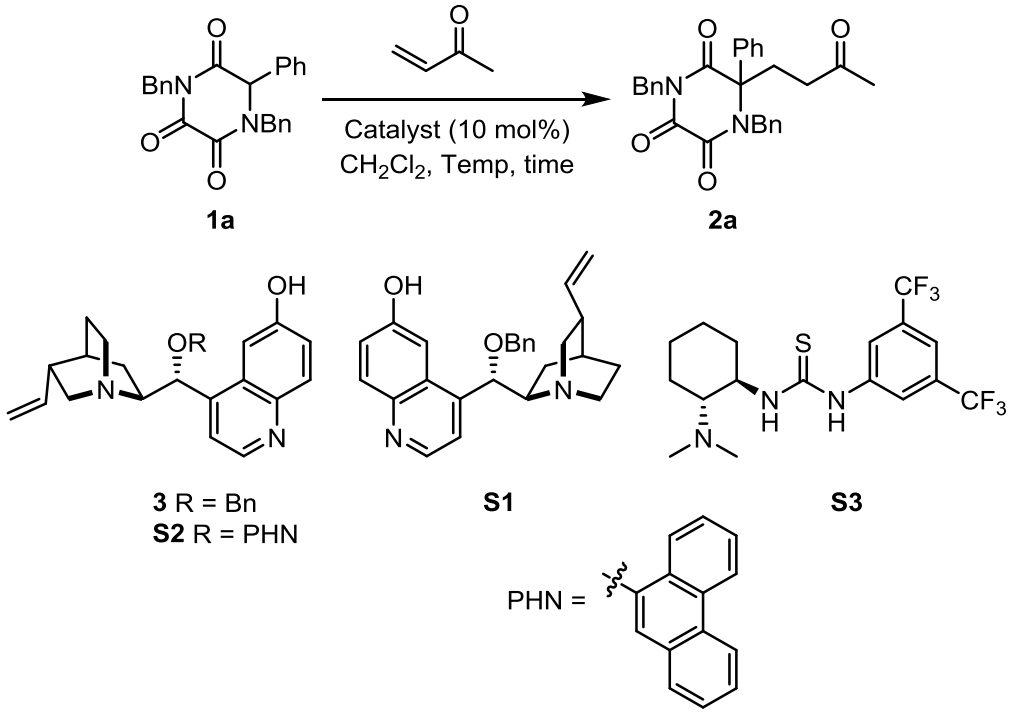
Triketopiperazine **S11** was prepared according to literature procedure.[3]

1,1'-(1,2-Dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (OxBzt) was prepared according to literature procedure.[4]

Phenyl vinyl ketone (PhVK) was prepared according to literature procedure.[5]

Optimisation Tables

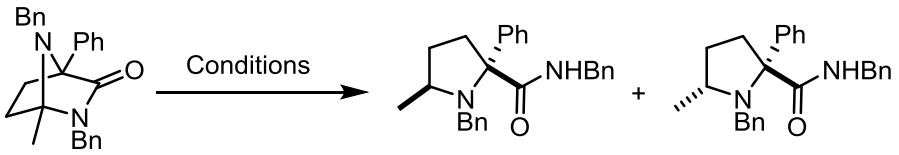
Asymmetric Michael Additions



Entry	Catalyst	Temp (°C)	Time	2a (%)	er
1	**3**	r.t.	16 h	98	90:10
2	**S2**	r.t.	2 days	22	77:23
3	**S3**	r.t.	4 days	37	82:18
4	**S1**	r.t.	16 h	82	14:86
5	**3**	3	16 h	90	92:8
6	**3**	−30	12 days	83	92:8

Figure 1. Optimisation of asymmetric Michael additions

Reductive Ring Opening



4a **5a** **5b**

Entry	Reducing agent	dr
1	$NaBH_4$	1.0:3.2
2	$NaBH_4/CeCl_3$	1.0:2.0
3	$NaCNBH_3$	1.0:1.8
4	$Na(OAc)_3BH$	2.7:1.0
5	DIBAL	4.5:1.0
6	DIBAL (-78 °C)	6.5:1.0
7	L-selectride	NR
8	$LiAlH_4$	NR
9	H-cube, H_2 Pd/C	NR
10	NH_4CO_2H, Pd/C	NR

General Procedures

General procedure A for the synthesis of amino amides (S6-S8)

To a 2-necked round bottomed flask containing phenylacetic acid derivative (1 eq.) was added thionyl chloride (0.5 M) under a nitrogen atmosphere. The reaction mixture was heated under reflux for 1 hour then allowed to cool to room temperature followed by the addition of NBS (1.5 eq.) and HBr (3 drops). The reaction mixture was then heated at 80 °C for 4 hours. Excess thionyl chloride was removed under reduced pressure and the resulting crude compound was heated with hexane (20 mL), filtered while hot and then washed with hot hexane (4 x 20 mL). The washings were concentrated under reduced pressure to give the crude α-bromo acid chloride as an oil. The acid chloride was then added dropwise to a solution of benzylamine (5 eq.) in MeCN (1 M) at 0 °C under a nitrogen atmosphere and stirred for 16 hours at room temperature. The reaction mixture was filtered, washed with MeCN and the filtrate was concentrated under reduced pressure. The reaction was purified by flash column chromatography using the indicated solvent system.

General procedure B for the synthesis of aryl triketopiperazines (1a-g)

To a microwave vial containing a suspension of 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (1.5 eq.) in THF (0.2 M) was added *N*-benzyl-2-(benzylamino)-2-phenylacetamide (1 eq.) in THF (0.2 M). The reaction mixture was stirred for 10 minutes then irradiated for 1 hour at 150 °C. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using the indicated solvent system.

General procedures Ci and Cii for the racemic and enantioselective Michael additions of α-aryl triketopiperazines (2a-q)

General procedure Ci for the racemic Michael additions of α-aryl triketopiperazines (2a-q)

To a solution of triketopiperazine **1a-j** (1 eq.) in CH_2Cl_2 (0.1 M) was added triethylamine (1 eq.) followed by the Michael acceptor (2.5 eq.) at room temperature. The mixture was left to react until the starting material was consumed. The reaction was directly purified by flash column chromatography using the indicated solvent system.

General procedure Cii for the enantioselective Michael additions of α-aryl triketopiperazines (2a-q)

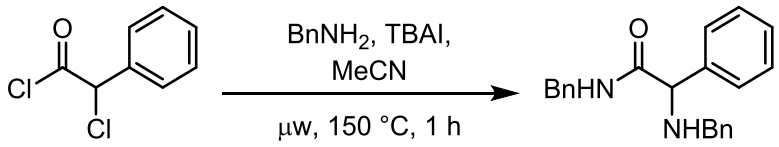
To a mixture of triketopiperazine **1a-j** (1 eq.) and catalyst **3** (10 mol%) in CH_2Cl_2 (0.1 M) at -78 °C, the Michael acceptor (2.5 eq.) was added neat. The reaction mixture was allowed to warm to 3 °C and left to react. After the starting material was consumed the reaction was directly purified by flash column chromatography using the indicated solvent system.

General procedure D for the synthesis of diazabicycles (4a-m)

To a solution of triketopiperazine **2a-k, 2n and 2q** (1 eq.) in THF (0.2 M) was added ethanolamine (0.2 M). The reaction mixture was heated under reflux for 1 hour. The reaction mixture was concentrated under reduced pressure and directly purified by flash column chromatography using the indicated solvent system.

Synthesis of Amino Amides (S4-S10)

N-benzyl-2-(benzylamino)-2-phenylacetamide **S4**

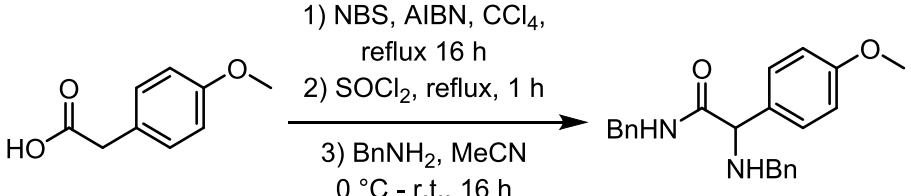


S4

To a microwave vial containing a solution of benzylamine (0.55 mL, 5 mmol) in MeCN (4 mL) was added α-chlorophenylacetyl chloride (0.16 mL, 1 mmol) dropwise at 0 °C. TBAI (185 mg, 0.5 mmol) dissolved in MeCN (1 mL) was added and the reaction mixture was irradiated for 1 hour in the microwave at 150 °C. The reaction mixture was filtered, washed with MeCN (5 mL) and the filtrate concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (1:0) to (2:1)) to afford **S4** (307 mg, 93%) as an orange oil.

IR ν_{max}/cm^{-1} 3302, 3061, 3028, 2845, 1657, 1515, 1453, 1028, 730, 694; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 – 7.19 (m, 16H), 4.46 (d, *J* = 5.9 Hz, 2H), 4.30 (s, 1H), 3.77 (s, 2H), 2.05 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.0, 139.3, 139.2, 138.5, 129.0, 128.8, 128.7, 128.3, 127.8, 127.6, 127.5, 127.5, 67.1, 52.7, 43.4; ***m/z*** (ES HRMS) $C_{22}H_{23}N_2O$ requires 331.1810, found $[MH]^+$ 331.1813.

N-benzyl-2-(benzylamino)-2-(4-methoxyphenyl)acetamide **S5**



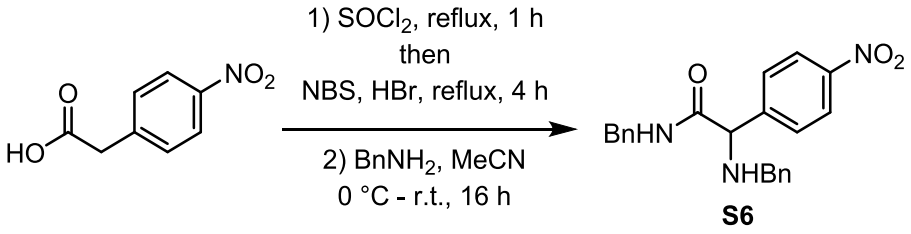
S5

To a 2-necked round bottomed flask containing 4-methoxyphenylacetic acid (1.81 g, 10 mmol), NBS (1.87 g, 10.5 mmol) and AIBN (330 mg, 2 mmol) was added CCl_4 (15 mL). The reaction mixture was heated under reflux for 16 hours then allowed to cool to room temperature, filtered, washed with CCl_4 and concentrated under reduced pressure. To the resulting oil was added thionyl chloride (15 mL) and the reaction mixture was heated under reflux for 1 hour. The solvent was removed under reduced pressure to give crude 2-bromo-2-(4-methoxyphenyl)acetyl chloride as an orange oil. The crude product was diluted with MeCN (5 mL) and added dropwise to a solution of benzylamine (5.4 mL, 50 mmol) in MeCN

(50 mL) at 0 °C and stirred for 16 hours at room temperature. The reaction mixture was filtered, washed with MeCN (10 mL) and the filtrate was concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford **S5** (1.79 g, 50%) as an orange oil.

IR ν_{max}/cm^{-1} 3289, 3030, 2931, 2838, 1511, 1453, 1251, 1177, 1026, 751, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.35 – 7.18 (m, 12H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.46 (d, *J* = 5.9 Hz, 2H), 4.25 (s, 1H), 3.80 (s, 3H), 3.75 (d, *J* = 3.5 Hz, 2H) 1.80 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 159.6, 139.4, 138.5, 131.5, 128.8, 128.7, 128.6, 128.3, 127.8, 127.6, 127.5, 114.4, 66.5, 55.5, 52.6, 43.4; ***m/z*** (ESI HRMS) $C_{23}H_{24}N_2O_2Na$ requires 383.1735, found $[MNa]^+$ 383.1732.

N-benzyl-2-(benzylamino)-2-(4-nitrophenyl)acetamide **S6**

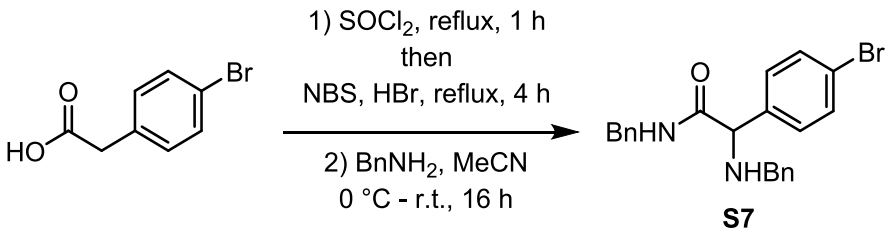


S6

Following procedure **A** using 4-nitrophenylacetic acid (1.81 g, 10 mmol), NBS (2.67 g, 15 mmol), HBr (3 drops) and benzylamine (5.4 mL, 50 mmol). The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (1:0) to (2:1)) to afford **S6** (1.85 g, 68%) as an orange oil.

IR ν_{max}/cm^{-1} 3347, 3258, 3033, 2933, 2846, 1668, 1519, 1452, 1343, 750, 734, 689; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.23 – 8.16 (m, 2H), 7.57 – 7.53 (m, 2H), 7.45 (br s, 1H), 7.37 – 7.19 (m, 10H), 4.45 (d, *J* = 5.9 Hz, 2H), 4.40 (s, 1H), 3.77 (s, 2H), 2.06 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.6, 147.8, 146.3, 138.6, 138.0, 128.9, 128.8, 128.4, 128.3, 127.8, 124.1, 66.3, 52.4, 43.5; ***m/z*** (ES HRMS) $C_{22}H_{22}N_3O_3$ requires 376.1661, found $[MH]^+$ 376.1665.

N-benzyl-2-(benzylamino)-2-(4-bromophenyl)acetamide **S7**

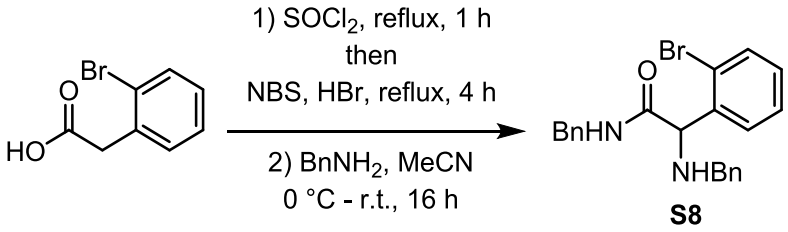


S7

Following general procedure **A** using 4-bromophenylacetic acid (860 mg, 4 mmol), NBS (1 g, 6 mmol), HBr (3 drops) and benzylamine (2.2 mL, 20 mmol). The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **S7** (708 mg, 45%) as an orange oil.

IR ν_{max}/cm^{-1} 3299, 3062, 3028, 2924, 2848, 1652, 1517, 1486, 1453, 1071, 1010, 907, 727, 696; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 3H), 7.38 – 7.22 (m, 12H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.27 (s, 1H), 3.77 (s, 2H), 2.06 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.5, 139.0, 138.3, 132.0, 129.1, 128.8, 128.7, 128.2, 127.7, 127.6, 127.5, 122.2, 66.3, 52.4, 43.3; ***m/z*** (ES HRMS) $C_{22}H_{22}N_2OBr$ requires 409.0916, found $[MH]^+$ 409.0924.

N-benzyl-2-(benzylamino)-2-(2-bromophenyl)acetamide **S8**

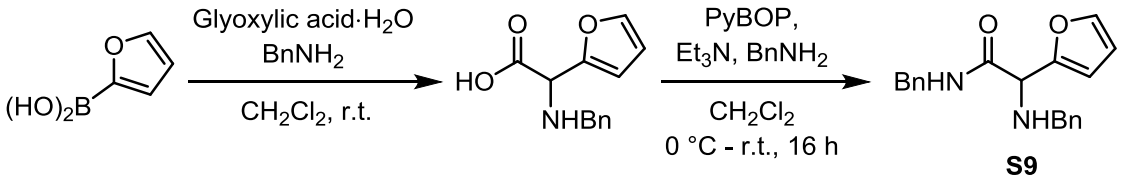


S8

Following general procedure **A** using 2-bromophenylacetic acid (430 mg, 2 mmol), NBS (530 mg, 3 mmol), HBr (3 drops) and benzylamine (1.1 mL, 10 mmol). The resulting oil was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **S8** (474 mg, 58%) as an orange oil.

IR ν_{max}/cm^{-1} 3315, 3061, 3027, 2922, 2844, 1658, 1514, 1453, 1080, 1025, 748, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 2H), 7.38 – 7.22 (m, 12H), 7.20 – 7.14 (m, 1H), 4.69 (s, 1H), 4.51 (dd, *J* = 6.0, 2.1 Hz, 2H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.71 (d, *J* = 12.7 Hz, 1H), 2.27 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 139.1, 138.5, 138.2, 133.4, 129.8, 129.6, 128.7, 128.6, 128.3, 127.9, 127.8, 127.5, 127.4, 124.3, 65.8, 52.6, 43.4; ***m/z*** (ES HRMS) $C_{22}H_{22}N_2OBr$ requires 409.0916, found $[MH]^+$ 409.0911.

N-benzyl-2-(benzylamino)-2-(furan-2-yl)acetamide **S9**



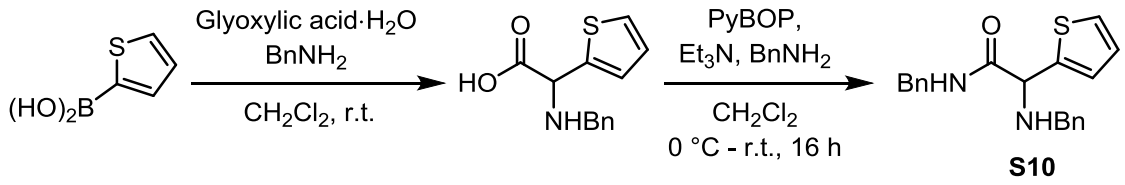
S9

To a solution of glyoxylic acid monohydrate (460 mg, 5 mmol) in CH_2Cl_2 (33 mL) was added benzylamine (0.55 mL, 5 mmol) and 2-furylboronic acid (560 mg, 5 mmol). The flask was

purged with argon and stirred at room temperature for 4 hours. The resulting precipitate was filtered, dried under reduced pressure and used without further purification. To a round bottomed flask containing the crude amino acid was added CH_2Cl_2 (25 mL) and the reaction mixture was cooled to 0 °C, followed by the addition of PyBOP (2.8 g, 5.5 mmol), triethylamine (1.1 mL, 7.5 mmol) and benzylamine (1.4 mL, 12.5 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **S9** (1.24 g, 78%) as an orange oil.

IR ν_{max}/cm^{-1} 3304, 3061, 3028, 2924, 2849, 1657, 1520, 1496, 1453, 1147, 1073, 1010, 734, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.38 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.36 – 7.23 (m, 10H), 6.38 – 6.29 (m, 2H), 4.50 (d, *J* = 5.9 Hz, 2H), 4.40 (s, 1H), 3.82 (d, *J* = 13.1 Hz, 1H), 3.74 (d, *J* = 13.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9, 151.6, 142.6, 139.0, 138.3, 128.8, 128.7, 128.4, 127.8, 127.6, 127.6, 110.7, 108.5, 60.4, 52.4, 43.5; ***m/z*** (ES HRMS) $C_{20}H_{21}N_2O_2$ requires 321.1603, found $[MH]^+$ 321.1604.

N-benzyl-2-(benzylamino)-2-(thiophen-2-yl)acetamide **S10**



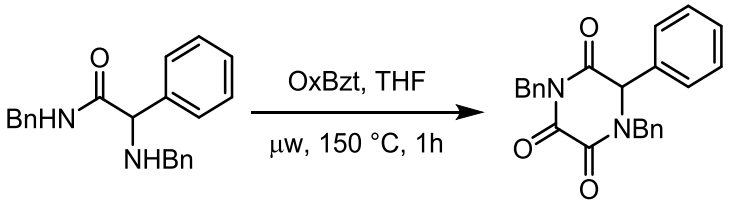
To a solution of glyoxylic acid monohydrate (368 mg, 4 mmol) in CH_2Cl_2 (26 mL) was added benzylamine (0.44 mL, 4 mmol) and 2-thiopheneboronic acid (512 mg, 4 mmol). The flask was purged with argon and stirred at room temperature for 72 hours. The resulting precipitate was filtered, dried under reduced pressure and used without further purification. To a round bottomed flask containing the crude amino acid was added CH_2Cl_2 (20 mL) and the reaction mixture was cooled to 0 °C, followed by the addition of PyBOP (2.3 g, 4.4 mmol), triethylamine (0.84 mL, 6 mmol) and benzylamine (1.1 mL, 10 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **S10** (749 mg, 56%) as an orange oil.

IR ν_{max}/cm^{-1} 3318, 3061, 2922, 2851, 1654, 1517, 1452, 1359, 1234, 1078, 1028, 847, 731, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 12H), 7.01 (d, *J* = 3.4 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.54 (s, 1H), 4.40 (d, *J* = 5.9 Hz, 2H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.72 (d, *J* = 13.3 Hz, 1H), 2.27 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 142.2, 139.0, 138.2, 128.7, 128.6,

128.3, 127.7, 127.5, 127.4, 126.9, 126.0, 125.5, 62.3, 52.3, 43.4; ***m/z*** (ES HRMS) $C_{20}H_{21}N_2OS$ requires 337.1375, found $[MH]^+$ 337.1372.

Synthesis of α-Aryl Triketopiperazines (1a-j)

1,4-dibenzyl-6-phenylpiperazine-2,3,5-trione **1a**

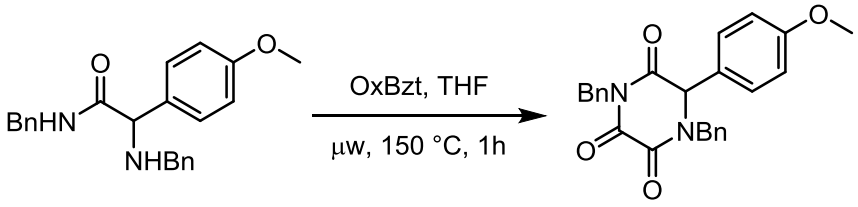


S4 **1a**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (394 mg, 1.35 mmol) in THF (2 mL), *N*-benzyl-2-(benzylamino)-2-phenylacetamide **S4** (307 mg, 0.9 mmol) in THF (3 mL). The residue was purified by flash column chromatography on silica gel (CH_2Cl_2) to afford **1a** (247.9 mg, 72%) as a white solid.

m.p. 159 – 161 °C; **IR** ν_{max}/cm^{-1} 3034, 1748, 1673, 1437, 1253, 1188, 720, 698; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.18 (m, 15H), 5.57 (d, *J* = 14.5 Hz, 1H), 5.15 (s, 1H), 5.07 (d, *J* = 13.7 Hz, 1H), 4.89 (d, *J* = 13.7 Hz, 1H), 3.63 (d, *J* = 14.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.8, 156.4, 153.0, 135.0, 134.1, 134.0, 130.0, 129.8, 129.3, 129.2, 128.9, 128.7, 128.2, 127.0, 63.8, 48.0, 44.7; ***m/z*** (ESI HRMS) $C_{24}H_{20}N_2O_3Na$ requires 407.1372, found $[MNa]^+$ 407.1370.

1,4-dibenzyl-6-(4-methoxyphenyl)piperazine-2,3,5-trione **1b**

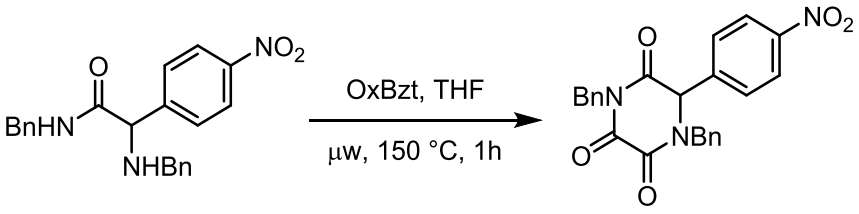


S5 **1b**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (438 mg, 1.5 mmol) in THF (2 mL), *N*-benzyl-2-(benzylamino)-2-(4-methoxyphenyl)acetamide **S5** (360 mg, 1.0 mmol) in THF (3 mL). The residue was purified by column chromatography on silica gel (gradient: CH_2Cl_2:acetone = (1:0) to (95:5)) to afford **1b** (117.8 mg, 28%) as a white solid.

m.p. 184 – 186 °C; **IR** ν_{max}/cm^{-1} 2966, 2842, 2358, 1749, 1674, 1515, 1352, 1251, 1176, 1022, 831, 728, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.31 – 7.14 (m, 8H), 7.14 – 7.09 (m, 2H), 6.93 – 6.88 (m, 2H), 5.52 (d, *J* = 14.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.85 (d, *J* = 13.7 Hz, 1H), 3.82 (s, 3H), 3.59 (d, *J* = 14.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1, 160.9, 156.5, 153.0, 135.1, 134.1, 129.3, 128.8, 128.7, 128.3, 128.2, 125.8, 115.2, 63.2, 55.6, 47.8, 44.7; ***m/z*** (ESI HRMS) $C_{25}H_{22}N_2O_4Na$ requires 437.1477, found $[MNa]^+$ 437.1482.

1,4-dibenzyl-6-(4-nitrophenyl)piperazine-2,3,5-trione **1c**

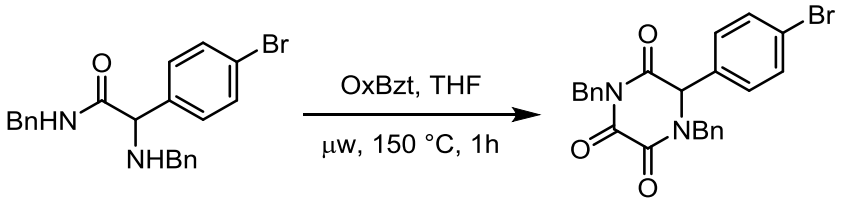


S6 **1c**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (438 mg, 1.5 mmol) in THF (2 mL), *N*-benzyl-2-(benzylamino)-2-(4-nitrophenyl)acetamide **S6** (375 mg, 1.0 mmol) in THF (3 mL). The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford **1c** (163 mg, 38%) as a white solid.

m.p. 167 – 169 °C; **IR** ν_{max}/cm^{-1} 3089, 3030, 1754, 1684, 1518, 1346, 1254, 976, 727, 702; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 – 8.20 (m, 2H), 7.43 – 7.10 (m, 12H), 5.51 (d, *J* = 14.5 Hz, 1H), 5.23 (s, 1H), 5.02 (d, *J* = 13.6 Hz, 1H), 4.87 (d, *J* = 13.6 Hz, 1H), 3.66 (d, *J* = 14.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.6, 155.8, 152.8, 148.9, 140.9, 134.7, 133.3, 129.5, 129.3, 129.2, 129.2, 128.8, 128.5, 128.2, 124.9, 63.3, 48.6, 45.0; ***m/z*** (ESI HRMS) $C_{24}H_{19}N_3O_5Na$ requires 452.1222, found $[MNa]^+$ 452.1219.

1,4-dibenzyl-6-(4-bromophenyl)piperazine-2,3,5-trione **1d**

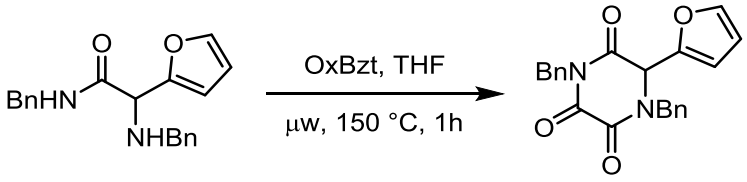


S7 **1d**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (86 mg, 0.30 mmol) in THF (1 mL), *N*-benzyl-2-(benzylamino)-2-(4-bromophenyl)acetamide **S7** (100 mg, 0.25 mmol) in THF (1 mL). The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford **1d** (23 mg, 21%) as an off white solid.

m.p. 159 – 162 °C; **IR** ν_{max}/cm^{-1} 3028, 2918, 1744, 1676, 1491, 1451, 1434, 1365, 1251, 1188, 1072, 1010, 823, 741, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.37 – 7.31 (m, 3H), 7.28 – 7.20 (m, 5H), 7.19 – 7.12 (m, 2H), 7.10 – 7.05 (m, 2H), 5.51 (d, *J* = 14.5 Hz, 1H), 5.07 (s, 1H), 5.02 (d, *J* = 13.7 Hz, 1H), 4.85 (d, *J* = 13.7 Hz, 1H), 3.60 (d, *J* = 14.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 156.2, 152.9, 134.9, 133.7, 133.1, 133.0, 129.3, 129.2, 129.0, 128.7, 128.6, 128.4, 124.3, 63.3, 48.1, 44.8; ***m/z*** (ES HRMS) $C_{24}H_{19}N_2O_3BrNa$ requires 485.0477, found $[MNa]^+$ 485.0476.

1,4-dibenzyl-6-(furan-2-yl)piperazine-2,3,5-trione **1e**

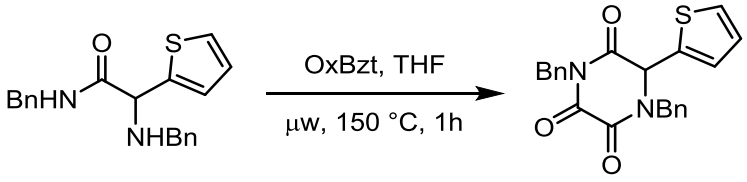


S9 **1e**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (225 mg, 0.77 mmol) in THF (2 mL), *N*-benzyl-2-(benzylamino)-2-(furan-2-yl)acetamide **S9** (204 mg, 0.64 mmol) in THF (2 mL). The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford **1e** (94.2 mg, 40%) as an off white solid.

m.p. 144 – 146 °C; **IR** ν_{max}/cm^{-1} 3062, 3033, 2925, 1748, 1688, 1496, 1430, 1361, 1255, 1208, 1013, 730, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.11 (m, 11H), 6.34 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.30 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.33 (d, *J* = 14.6 Hz, 1H), 5.10 (s, 1H), 4.99 (d, *J* = 13.9 Hz, 1H), 4.87 (d, *J* = 13.9 Hz, 1H), 3.72 (d, *J* = 14.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7, 156.4, 153.0, 145.8, 144.3, 135.0, 133.9, 129.2, 129.1, 129.1, 128.8, 128.7, 128.2, 111.6, 111.2, 57.8, 48.0, 44.9; ***m/z*** (ES HRMS) $C_{22}H_{18}N_2O_4Na$ requires 397.1164, found $[MNa]^+$ 397.1166.

1,4-dibenzyl-6-(thiophen-2-yl)piperazine-2,3,5-trione **1f**

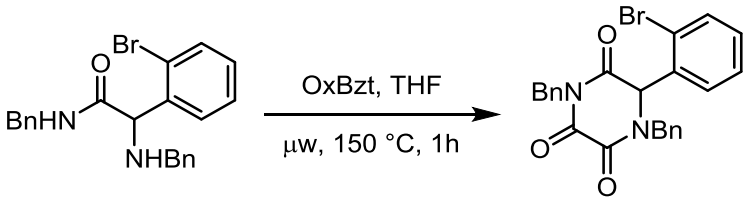


S10 **1f**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (105 mg, 0.36 mmol) in THF (1 mL), *N*-benzyl-2-(benzylamino)-2-(thiophen-2-yl)acetamide **S10** (100 mg, 0.30 mmol) in THF (1 mL). The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford **1f** (40 mg, 34%) as an off white solid.

m.p. 135 – 137 °C; **IR** ν_{max}/cm^{-1} 3033, 2923, 2853, 1747, 1688, 1495, 1431, 1361, 1253, 1207, 1087, 971, 729, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 11H), 7.06 – 7.02 (m, 2H), 5.56 (d, *J* = 14.6 Hz, 1H), 5.37 (s, 1H), 5.05 (d, *J* = 13.7 Hz, 1H), 4.91 (d, *J* = 13.7 Hz, 1H), 3.81 (d, *J* = 14.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9, 156.1, 152.5, 136.9, 134.9, 133.9, 129.3, 129.3, 129.2, 128.9, 128.7, 128.3, 127.9, 127.6, 59.4, 48.0, 44.9; ***m/z*** (ES HRMS) $C_{22}H_{18}N_2O_3SNa$ requires 413.0936, found $[MNa]^+$ 413.0926.

1,4-dibenzyl-6-(2-bromophenyl)piperazine-2,3,5-trione **1g**

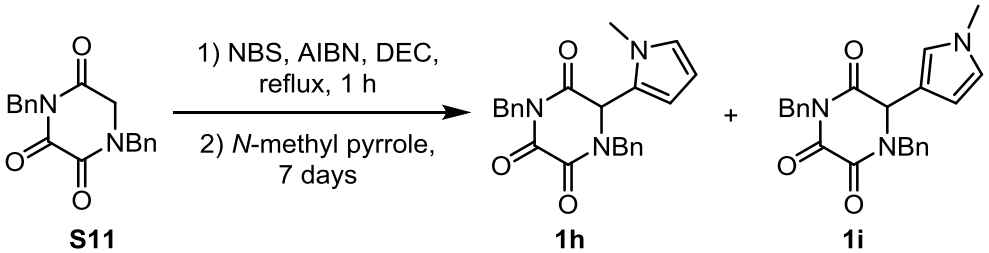


S8 **1g**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (85 mg, 0.30 mmol) in THF (1 mL), *N*-benzyl-2-(benzylamino)-2-(2-bromophenyl)acetamide **S8** (100 mg, 0.25 mmol) in THF (1 mL). The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford **1g** (43 mg, 38%) as an off white solid.

m.p. 153 – 155 °C; **IR** ν_{max}/cm^{-1} 3062, 3032, 2932, 1744, 1682, 1494, 1429, 1363, 1257, 1190, 1027, 908, 728, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.40 – 7.23 (m, 10H), 7.21 – 7.15 (m, 2H), 7.07 (dd, *J* = 7.4, 1.9 Hz, 1H), 5.64 (br s, 1H), 5.36 (d, *J* = 14.6 Hz, 1H), 5.07 (d, *J* = 13.6 Hz, 1H), 4.93 (d, *J* = 13.6 Hz, 1H), 3.59 (d, *J* = 14.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9, 156.3, 153.1, 134.9, 134.6, 134.0, 133.5, 131.4, 129.7, 129.3, 129.1, 128.7, 128.4, 128.3, 124.0, 63.8, 48.2, 44.8; ***m/z*** (ES HRMS) $C_{24}H_{19}N_2O_3BrNa$ requires 485.0477, found $[MNa]^+$ 485.0474.

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-2-yl)piperazine-2,3,5-trione **1h** and 1,4-dibenzyl-6-(1-methyl-1H-pyrrol-3-yl)piperazine-2,3,5-trione **1i**



S11 **1h** **1i**

To a round bottomed flask containing triketopiperazine **S11** (100 mg, 0.32 mmol), NBS (87 mg, 0.49 mmol) and AIBN (11 mg, 65 μmol, 20 mol%) was added diethylcarbonate (1.6 mL)

and the reaction mixture was heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, filtered, washed with diethylcarbonate (3 x 2 mL) and the filtrate concentrated under reduced pressure. The crude α-bromo triketopiperazine was then used without further purification. To the crude residue was added diethylcarbonate (2 mL) and *N*-methyl pyrrole (58 µL, 0.65 mmol) and the reaction mixture was stirred for 7 days at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **1h** (66.6 mg, 52%) as a colourless waxy solid and **1i** (10.4 mg, 8%) as a colourless waxy solid.

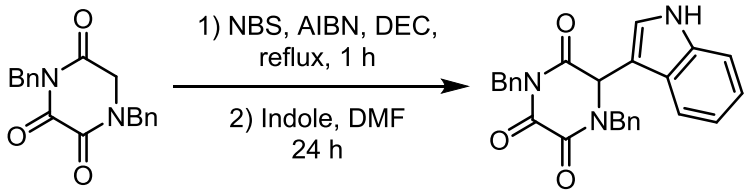
1,4-dibenzyl-6-(1-methyl-1H-pyrrol-2-yl)piperazine-2,3,5-trione **1h**

IR ν_{max}/cm^{-1} 3062, 3032, 2944, 1745, 1684, 1493, 1427, 1359, 1301, 1251, 1207, 1089, 908, 723, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 8H), 7.15 – 7.08 (m, 2H), 6.62 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.13 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.06 (dd, *J* = 3.9, 1.7 Hz, 1H), 5.47 (d, *J* = 14.4 Hz, 1H), 5.12 (s, 1H), 5.03 (d, *J* = 13.8 Hz, 1H), 4.86 (d, *J* = 13.9 Hz, 1H), 3.84 (d, *J* = 14.4 Hz, 1H), 3.39 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 156.2, 153.1, 135.1, 133.8, 129.4, 129.2, 129.1, 128.8, 128.7, 128.2, 125.3, 124.1, 109.0, 108.3, 56.5, 48.1, 44.6, 34.2; ***m/z*** (ES HRMS) $C_{23}H_{21}N_3O_3Na$ requires 410.1481, found $[MNa]^+$ 410.1489.

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-3-yl)piperazine-2,3,5-trione **1i**

IR ν_{max}/cm^{-1} 3062, 3031, 2942, 1745, 1683, 1495, 1429, 1357, 1253, 1207, 1155, 1088, 1029, 909, 726, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 5H), 7.28 – 7.21 (m, 5H), 6.55 (t, *J* = 2.5 Hz, 1H), 6.52 (t, *J* = 2.1 Hz, 1H), 5.92 (dd, *J* = 2.8, 1.9 Hz, 1H), 5.48 (d, *J* = 14.5 Hz, 1H), 5.06 – 5.01 (m, 2H), 4.87 (d, *J* = 13.8 Hz, 1H), 3.81 (d, *J* = 14.5 Hz, 1H), 3.60 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8, 156.9, 153.1, 135.3, 134.6, 129.5, 129.3, 129.2, 128.7, 128.6, 128.1, 123.5, 120.7, 117.5, 106.6, 58.2, 47.6, 44.6, 36.6; ***m/z*** (ES HRMS) $C_{23}H_{21}N_3O_3Na$ requires 410.1481, found $[MNa]^+$ 410.1484.

1,4-dibenzyl-6-(1H-indol-3-yl)piperazine-2,3,5-trione **1j**



S11 **1j**

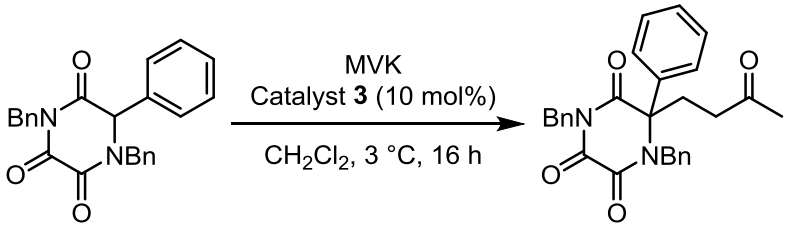
To a round bottomed flask containing triketopiperazine **S11** (308 mg, 1.0 mmol), NBS (267 mg, 1.5 mmol) and AIBN (30 mg, 0.20 mmol, 20 mol%) was added diethylcarbonate (5 mL) and the reaction mixture was heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, filtered, washed with diethylcarbonate (3 x 3 mL) and

the filtrate concentrated under reduced pressure. The crude α-bromo triketopiperazine was then used without further purification. To the crude residue was added DMF (5 mL) and indole (177 mg, 1.5 mmol) and the reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted with EtOAc (5 mL), washed with water (5 × 10 mL) and brine (10 mL) and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (1:0) to (1:1)) to afford **1j** (329 mg, 78%) as a white solid.

m.p. 178 – 180 °C; **IR** ν_{max}/cm^{-1} 3270, 3059, 1747, 1691, 1661, 1548, 1494, 1425, 1360, 1272, 1201, 1147, 1100, 1077, 970, 735, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.46 – 7.37 (m, 2H), 7.36 – 7.08 (m, 13H), 5.54 (d, *J* = 14.5 Hz, 1H), 5.45 (s, 1H), 5.08 (d, *J* = 13.7 Hz, 1H), 4.88 (d, *J* = 13.7 Hz, 1H), 3.79 (d, *J* = 14.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1, 156.8, 153.1, 136.7, 135.1, 134.5, 129.4, 129.2, 129.2, 128.7, 128.6, 128.2, 124.9, 124.0, 123.5, 121.2, 118.7, 112.0, 109.8, 57.6, 47.8, 44.8; ***m/z*** (ES HRMS) $C_{26}H_{21}N_3O_3Na$ requires 446.1481, found $[MNa]^+$ 446.1480.

Asymmetric Michael Additions (2a-q)

1,4-dibenzyl-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione **2a**

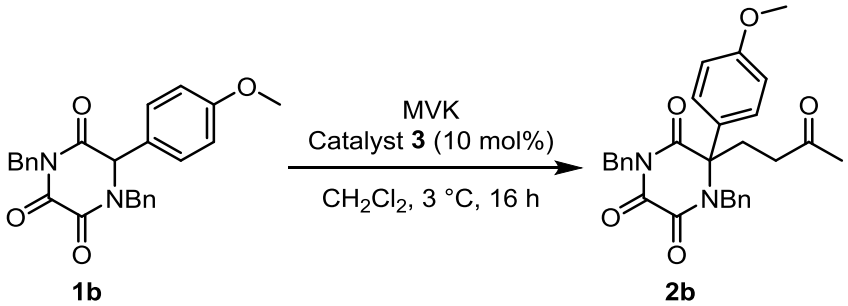


Following general procedure **Cii** using triketopiperazine **1a** (38 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2a** (44.6 mg, 98%) as a colourless oil in 8:92 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 220 nm, t(minor) = 20.5 min, t(major) = 22.4 min].

IR ν_{max}/cm^{-1} 3067, 3035, 1744, 1682, 1495, 1419, 1358, 1266, 1144, 1074, 1029, 707, 693; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.18 (m, 15H), 5.22 (d, *J* = 14.8 Hz, 1H), 5.09 (d, *J* = 13.6 Hz, 1H), 4.93 (d, *J* = 13.6 Hz, 1H), 3.64 (d, *J* = 14.8 Hz, 1H), 3.04 – 2.93 (m, 1H), 2.40 (ddd, *J* = 14.8, 9.2, 6.0 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.60 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.1, 169.1, 155.8, 155.1, 138.0, 136.6, 135.1, 129.7, 129.6, 129.2, 129.2, 128.9, 128.7, 128.3,

128.2, 126.3, 72.8, 48.9, 44.7, 37.1, 30.1, 29.4; ***m/z*** (ESI HRMS) $C_{28}H_{26}N_2O_4Na$ requires 477.1790, found $[MNa]^+$ 477.1792; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −23.4 (*c* 1.0, $CHCl_3$).

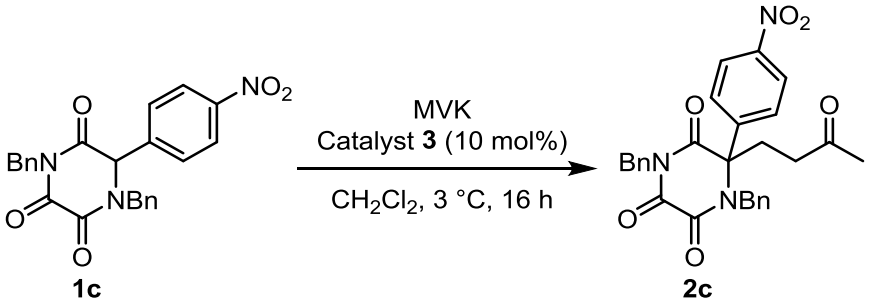
1,4-dibenzyl-6-(4-methoxyphenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2b**



Following general procedure **Cii** using triketopiperazine **1b** (41 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2b** (40.0 mg, 83%) as a colourless oil in 7:93 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 13.9 min, t(major) = 16.9 min].

IR ν_{max}/cm^{-1} 3036, 2959, 1739, 1683, 1512, 1420, 1358, 1260, 1229, 1184, 1077, 1031, 824, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 12H), 6.95 – 6.89 (m, 2H), 5.22 (d, *J* = 14.7 Hz, 1H), 5.11 (d, *J* = 13.6 Hz, 1H), 4.95 (d, *J* = 13.6 Hz, 1H), 3.84 (s, 3H), 3.70 (d, *J* = 14.8 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.38 (ddd, *J* = 14.8, 9.2, 6.1 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.62 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.2, 169.4, 160.4, 155.9, 155.1, 136.8, 135.2, 129.8, 129.3, 129.2, 128.9, 128.7, 128.3, 128.2, 127.6, 115.0, 72.4, 55.6, 48.8, 44.7, 37.2, 30.2, 29.4; ***m/z*** (ES HRMS) $C_{29}H_{28}N_2O_5Na$ requires 507.1896, found $[MNa]^+$ 507.1898; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −18.5 (*c* 1.0, $CHCl_3$).

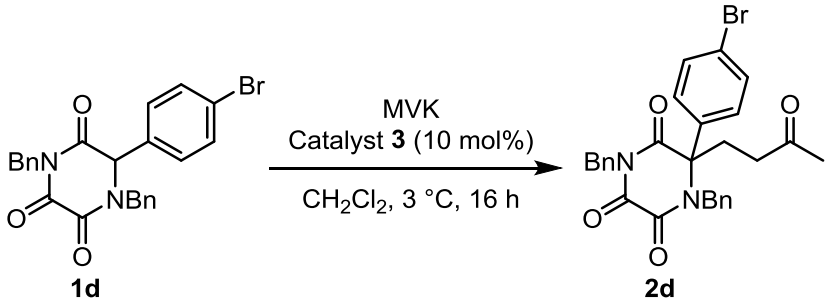
1,4-dibenzyl-6-(4-nitrophenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2c**



Following general procedure **Cii** using triketopiperazine **1c** (43 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2c** (34.6 mg, 70%) as a colourless oil in 5:95 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 45:55, 1.0 ml/min, λ 220 nm, t(minor) = 23.2 min, t(major) = 27.1 min].

IR ν_{max}/cm^{-1} 3080, 3003, 2939, 1751, 1680, 1517, 1417, 1345, 1229, 1109, 1079, 1030, 854, 730, 703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 – 8.23 (m, 2H), 7.63 – 7.57 (m, 2H), 7.40 – 7.22 (m, 10H), 5.20 – 5.11 (m, 2H), 5.02 (d, *J* = 13.6 Hz, 1H), 3.86 (d, *J* = 14.8 Hz, 1H), 3.03 (ddd, *J* = 14.4, 10.7, 5.8 Hz, 1H), 2.56 (ddd, *J* = 14.7, 10.8, 4.3 Hz, 1H), 1.99 – 1.82 (m, 2H), 1.73 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.7, 168.2, 155.4, 154.7, 148.4, 144.6, 136.1, 134.8, 129.4, 129.1, 129.0, 128.8, 128.6, 128.4, 127.9, 124.5, 72.3, 49.0, 45.0, 36.9, 30.5, 29.5; ***m/z*** (ES HRMS) $C_{28}H_{25}N_3O_6Na$ requires 522.1641, found $[MNa]^+$ 522.1638; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −7.5 (*c* 1.0, $CHCl_3$).

1,4-dibenzyl-6-(4-bromophenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2d**

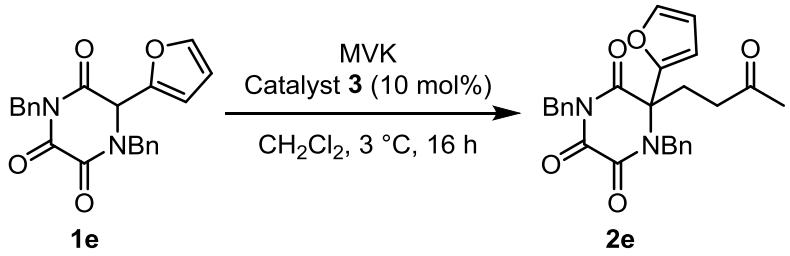


1d **2d**

Following general procedure **Cii** using triketopiperazine **1d** (46 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2d** (46.7 mg, 88%) as a colourless oil in 9:91 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 21.6 min, t(major) = 24.3 min].

IR ν_{max}/cm^{-1} 3063, 3032, 1743, 1716, 1680, 1491, 1360, 1228, 1077, 908, 727, 701; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.30 – 7.16 (m, 12H), 5.16 (d, *J* = 14.7 Hz, 1H), 5.08 (d, *J* = 13.6 Hz, 1H), 4.93 (d, *J* = 13.5 Hz, 1H), 3.69 (d, *J* = 14.8 Hz, 1H), 2.91 (ddd, *J* = 14.4, 10.0, 6.8 Hz, 1H), 2.38 (ddd, *J* = 14.8, 9.8, 5.4 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.61 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.9, 168.8, 155.6, 155.0, 137.1, 136.4, 135.0, 132.8, 129.3, 129.2, 128.9, 128.8, 128.5, 128.3, 128.1, 124.1, 72.4, 48.9, 44.9, 37.0, 30.2, 29.4; ***m/z*** (ES HRMS) $C_{28}H_{25}N_2O_4NaBr$ requires 555.0895, found $[MNa]^+$ 555.0900; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −4.7 (*c* 1.0, $CHCl_3$).

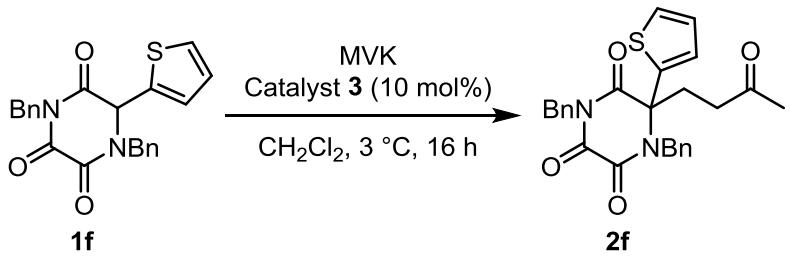
1,4-dibenzyl-6-(furan-2-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2e**



Following general procedure **Cii** using triketopiperazine **1e** (37 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2e** (44 mg, 99%) as a colourless oil in 94:6 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, MeCN:water, 35:65, 1.0 ml/min, λ 220 nm, t(major) = 24.4 min, t(minor) = 27.8 min].

IR ν_{max}/cm^{-1} 3036, 2935, 1746, 1684, 1495, 1415, 1365, 1342, 1231, 1147, 1015, 908, 731, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 11H), 6.57 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.36 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.12 (d, *J* = 13.7 Hz, 1H), 5.05 – 4.97 (m, 2H), 3.92 (d, *J* = 14.9 Hz, 1H), 2.74 (ddd, *J* = 14.7, 10.4, 6.5 Hz, 1H), 2.44 (ddd, *J* = 14.9, 10.0, 5.1 Hz, 1H), 1.89 – 1.81 (m, 2H), 1.67 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.0, 167.1, 155.8, 154.9, 149.8, 143.7, 136.3, 135.1, 129.2, 128.8, 128.8, 128.7, 128.3, 128.0, 111.1, 110.7, 68.5, 47.7, 44.9, 36.6, 29.5, 28.6; ***m/z*** (ES HRMS) $C_{26}H_{24}N_2O_5Na$ requires 467.1583, found $[MNa]^+$ 467.1590; $[\alpha]_D^{20}$ = −12.1 (*c* 1.0, $CHCl_3$).

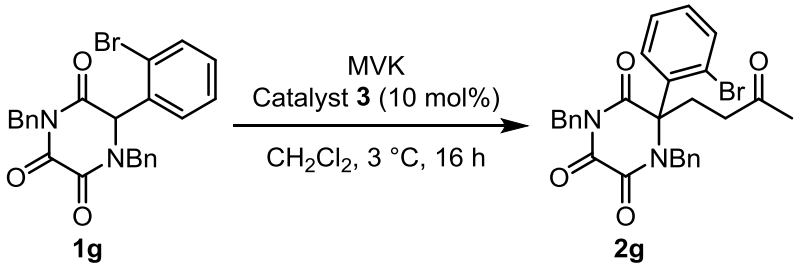
1,4-dibenzyl-6-(3-oxobutyl)-6-(thiophen-2-yl)piperazine-2,3,5-trione **2f**



Following general procedure **Cii** using triketopiperazine **1f** (39 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2f** (42.7 mg, 93%) as a colourless oil in 6:94 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 21.4 min, t(major) = 23.4 min].

IR ν_{max}/cm^{-1} 2924, 1742, 1687, 1495, 1416, 1363, 1227, 1079, 1028, 701; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.34 – 7.21 (m, 10H), 7.06 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.37 (d, *J* = 14.8 Hz, 1H), 5.08 (d, *J* = 13.7 Hz, 1H), 4.95 (d, *J* = 13.7 Hz, 1H), 3.84 (d, *J* = 14.9 Hz, 1H), 2.96 (ddd, *J* = 14.6, 11.6, 5.3 Hz, 1H), 2.48 (ddd, *J* = 14.8, 11.5, 3.5 Hz, 1H), 1.83 (ddd, *J* = 17.1, 11.5, 5.3 Hz, 1H), 1.72 (ddd, *J* = 17.8, 11.6, 3.5 Hz, 1H), 1.58 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.9, 167.9, 155.4, 154.8, 142.8, 136.7, 135.0, 129.1, 129.1, 129.0, 128.7, 128.3, 128.3, 127.8, 127.6, 126.9, 70.8, 48.8, 44.9, 37.3, 31.6, 29.3; ***m/z*** (ES HRMS) $C_{26}H_{24}N_2O_4NaS$ requires 483.1354, found $[MNa]^+$ 483.1353; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −33.5 (*c* 1.0, $CHCl_3$).

1,4-dibenzyl-6-(2-bromophenyl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2g**

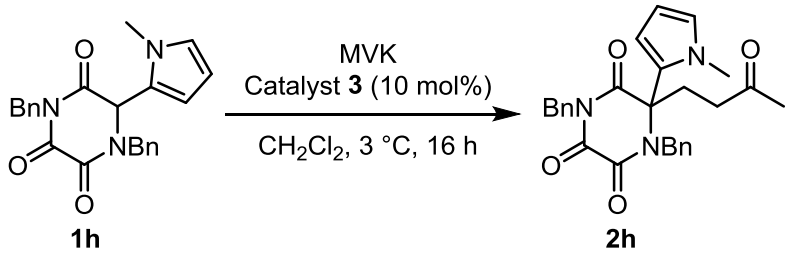


1g **2g**

Following general procedure **Cii** using triketopiperazine **1g** (46 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2g** (47.1 mg, 88%) as a colourless oil in 45:55 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 19.4 min, t(major) = 23.5 min].

IR ν_{max}/cm^{-1} 3064, 3033, 1741, 1717, 1680, 1494, 1419, 1361, 1262, 1227, 1075, 1027, 908, 727, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.32 – 7.23 (m, 4H), 7.18 – 7.07 (m, 3H), 7.04 – 6.98 (m, 2H), 5.18 (d, *J* = 13.3 Hz, 1H), 5.03 (d, *J* = 13.3 Hz, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 3.96 (d, *J* = 14.7 Hz, 1H), 2.55 (ddd, *J* = 14.0, 11.4, 4.2 Hz, 1H), 2.44 (ddd, *J* = 14.1, 11.0, 5.2 Hz, 1H), 1.90 (ddd, *J* = 17.6, 11.0, 4.2 Hz, 1H), 1.73 – 1.60 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.6, 169.3, 156.5, 155.0, 136.2, 135.9, 135.3, 134.9, 131.2, 130.4, 129.8, 129.0, 128.7, 128.6, 128.5, 128.1, 128.0, 124.5, 71.7, 47.7, 44.6, 36.4, 33.0, 29.7; ***m/z*** (ES HRMS) $C_{28}H_{25}N_2O_4BrNa$ requires 555.0895, found $[MNa]^+$ 555.0898; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 1.9 (*c* 1.0, $CHCl_3$).

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-2-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2h**

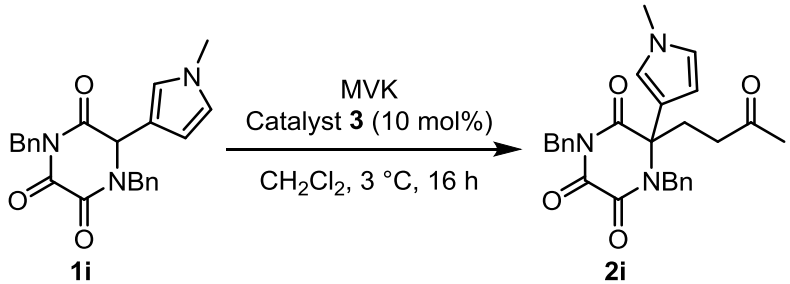


1h **2h**

Following general procedure **Cii** using triketopiperazine **1h** (39 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (20 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2h** (45.0 mg, 99%) as a colourless oil in 49:51 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, MeCN:water, 40:60, 1.0 ml/min, λ 220 nm, t(minor) = 15.9 min, t(major) = 18.3 min].

IR ν_{max}/cm^{-1} 3063, 3033, 2947, 1742, 1717, 1681, 1491, 1416, 1358, 1306, 1261, 1222, 1074, 908, 724, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.30 – 7.23 (m, 3H), 7.19 – 7.09 (m, 3H), 6.91 – 6.86 (m, 2H), 6.46 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.39 (dd, *J* = 2.8, 1.8 Hz, 1H), 6.14 (dd, *J* = 3.8, 2.8 Hz, 1H), 5.10 (d, *J* = 13.3 Hz, 1H), 5.05 (d, *J* = 13.3 Hz, 1H), 4.55 (d, *J* = 13.9 Hz, 1H), 4.32 (d, *J* = 13.9 Hz, 1H), 2.70 – 2.60 (m, 4H), 2.52 (ddd, *J* = 14.5, 9.9, 5.6 Hz, 1H), 2.15 – 1.93 (m, 2H), 1.86 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.9, 168.8, 156.1, 154.2, 135.8, 135.0, 130.1, 129.7, 128.7, 128.6, 128.3, 128.0, 126.9, 125.4, 112.2, 107.4, 67.6, 47.5, 44.9, 37.0, 34.0, 33.2, 29.9; ***m/z*** (ES HRMS) $C_{27}H_{27}N_3O_4Na$ requires 480.1899, found $[MNa]^+$ 480.1904; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 5.7 (*c* 1.0, $CHCl_3$).

1,4-dibenzyl-6-(1-methyl-1H-pyrrol-3-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2i**

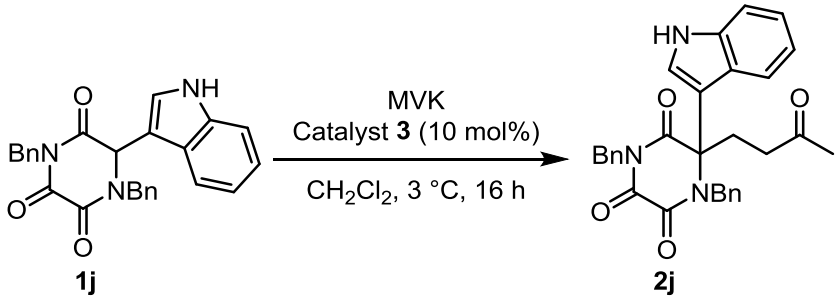


1i **2i**

Following general procedure **Cii** using triketopiperazine **1i** (34 mg, 90 µmol), chiral catalyst **3** (3.5 mg, 9 µmol 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (18 µL, 0.21 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2i** (25.1 mg, 63%) as a colourless oil in 77:23 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, MeCN:water, 35:65, 1.0 ml/min, λ 220 nm, t(major) = 19.5 min, t(minor) = 21.1 min].

IR ν_{max}/cm^{-1} 3062, 3031, 1741, 1714, 1682, 1495, 1419, 1362, 1227, 1166, 1080, 911, 729, 701; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 10H), 6.59 (t, *J* = 2.1 Hz, 1H), 6.55 (t, *J* = 2.5 Hz, 1H), 5.90 (dd, *J* = 2.9, 1.9 Hz, 1H), 5.29 (d, *J* = 14.9 Hz, 1H), 5.08 (d, *J* = 13.7 Hz, 1H), 4.95 (d, *J* = 13.7 Hz, 1H), 3.91 (d, *J* = 14.8 Hz, 1H), 3.61 (s, 3H), 2.81 (ddd, *J* = 14.8, 11.8, 5.3 Hz, 1H), 2.30 (ddd, *J* = 14.9, 11.6, 3.4 Hz, 1H), 1.82 (ddd, *J* = 17.1, 11.7, 5.3 Hz, 1H), 1.70 (ddd, *J* = 17.9, 11.8, 3.4 Hz, 1H), 1.57 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.7, 169.7, 156.1, 155.3, 137.4, 135.4, 129.2, 129.1, 128.8, 128.6, 128.1, 128.0, 123.3, 122.9, 120.4, 106.5, 69.5, 48.3, 44.7, 37.4, 36.7, 30.4, 29.4; ***m/z*** (ES HRMS) $C_{27}H_{28}N_3O_4$ requires 458.2080, found $[MH]^+$ 458.2082; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −21.2 (*c* 1.0, $CHCl_3$).

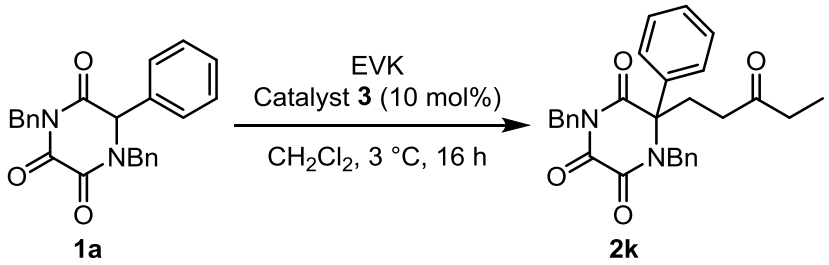
1,4-dibenzyl-6-(1H-indol-3-yl)-6-(3-oxobutyl)piperazine-2,3,5-trione **2j**



Following general procedure **Cii** using triketopiperazine **1j** (12 mg, 30 µmol), chiral catalyst **3** (1 mg, 3 µmol, 10 mol%), CH_2Cl_2 (1 mL) and methyl vinyl ketone (6 µL, 80 µmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2j** (12.5 mg, 91%) as a colourless oil in 27:73 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 60:40, 1.0 ml/min, λ 220 nm, t(minor) = 5.8 min, t(major) = 9.9 min].

IR ν_{max}/cm^{-1} 3343, 1739, 1715, 1676, 1496, 1416, 1362, 1225, 1166, 1017, 980, 909, 728, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 – 8.76 (m, 1H), 7.43 – 7.34 (m, 4H), 7.25 – 7.13 (m, 9H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.01 – 6.96 (m, 1H), 5.23 – 5.14 (m, 2H), 5.00 (d, *J* = 13.5 Hz, 1H), 3.94 (d, *J* = 14.7 Hz, 1H), 2.83 (ddd, *J* = 14.4, 11.5, 5.1 Hz, 1H), 2.50 – 2.41 (m, 1H), 1.90 (ddd, *J* = 17.6, 11.5, 3.7 Hz, 1H), 1.77 (ddd, *J* = 17.3, 11.7, 5.2 Hz, 1H), 1.66 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.3, 169.6, 156.4, 154.8, 136.9, 136.8, 135.2, 129.6, 129.1, 128.7, 128.4, 128.0, 124.8, 124.1, 123.3, 121.2, 118.4, 114.1, 112.2, 69.4, 48.0, 44.9, 36.7, 31.9, 29.6; ***m/z*** (ES HRMS) $C_{30}H_{27}N_3O_4Na$ requires 516.1899, found $[MNa]^+$ 516.1901; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −14.5 (*c* 1.0, $CHCl_3$).

1,4-dibenzyl-6-(3-oxopentyl)-6-phenylpiperazine-2,3,5-trione **2k**

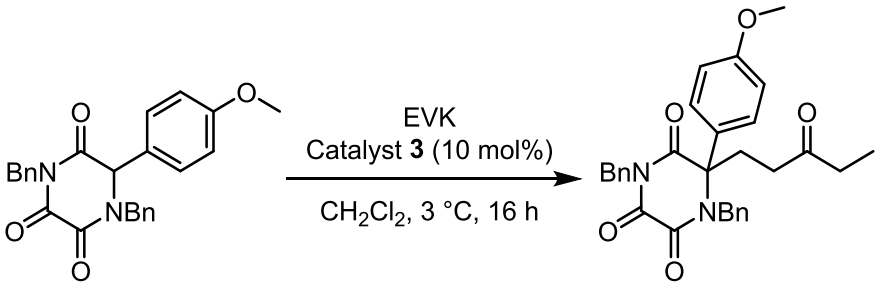


1a **2k**

Following general procedure **Cii** using triketopiperazine **1a** (38 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and ethyl vinyl ketone (25 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2k** (41.3 mg, 91%) as a colourless oil in 4:96 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 28.1 min, t(major) = 30.6 min].

IR ν_{max}/cm^{-1} 2938, 1743, 1680, 1495, 1416, 1362, 1261, 1222, 1144, 1077, 1030, 782, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.17 (m, 15H), 5.21 (d, *J* = 14.8 Hz, 1H), 5.09 (d, *J* = 13.6 Hz, 1H), 4.93 (d, *J* = 13.6 Hz, 1H), 3.64 (d, *J* = 14.8 Hz, 1H), 3.06 – 2.94 (m, 1H), 2.48 – 2.37 (m, 1H), 1.93 – 1.81 (m, 1H), 1.81 – 1.65 (m, 3H), 0.76 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.9, 169.2, 155.9, 155.2, 138.0, 136.7, 135.1, 129.7, 129.6, 129.2, 128.8, 128.7, 128.3, 128.1, 126.3, 72.8, 48.9, 44.7, 35.8, 35.4, 30.1, 7.7; ***m/z*** (ES HRMS) $C_{29}H_{28}N_2O_4Na$ requires 491.1947, found $[MNa]^+$ 491.1949; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −23.9 (*c* 1.0, $CHCl_3$).

1,4-dibenzyl-6-(4-methoxyphenyl)-6-(3-oxopentyl)piperazine-2,3,5-trione **2l**

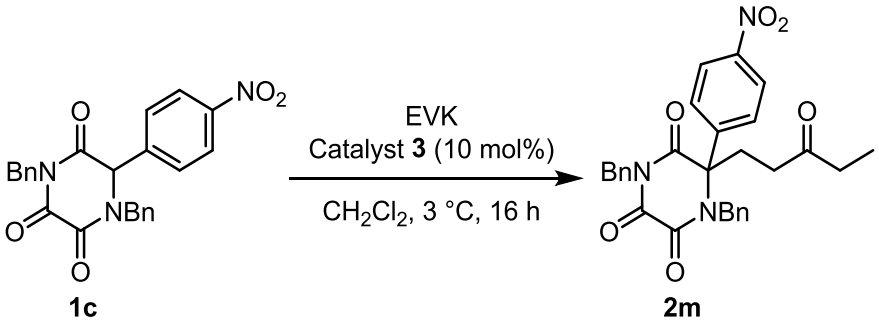


1b **2l**

Following general procedure **Cii** using triketopiperazine **1b** (41 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and ethyl vinyl ketone (25 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2l** (37 mg, 75%) as a colourless oil in 3:97 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 220 nm, t(minor) = 22.1 min, t(major) = 27.4 min].

IR ν_{max}/cm^{-1} 2970, 2936, 1742, 1681, 1605, 1511, 1416, 1362, 1256, 1222, 1183, 1078, 1031, 910, 832, 728, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 12H), 6.94 – 6.89 (m, 2H), 5.21 (d, *J* = 14.8 Hz, 1H), 5.11 (d, *J* = 13.6 Hz, 1H), 4.94 (d, *J* = 13.6 Hz, 1H), 3.84 (s, 3H), 3.69 (d, *J* = 14.7 Hz, 1H), 2.97 (ddd, *J* = 14.4, 9.2, 7.6 Hz, 1H), 2.46 – 2.33 (m, 1H), 1.88 (dq, *J* = 17.6, 7.4 Hz, 1H), 1.80 – 1.66 (m, 3H), 0.78 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.0, 169.4, 160.4, 156.0, 155.2, 136.8, 135.2, 129.8, 129.3, 129.3, 128.8, 128.7, 128.3, 128.1, 127.7, 115.0, 72.5, 55.6, 48.8, 44.7, 35.9, 35.5, 30.2, 7.7; ***m/z*** (ES HRMS) $C_{30}H_{30}N_2O_5Na$ requires 521.2052, found $[MNa]^+$ 521.2048; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −4.8 (*c* 1.0, $CHCl_3$).

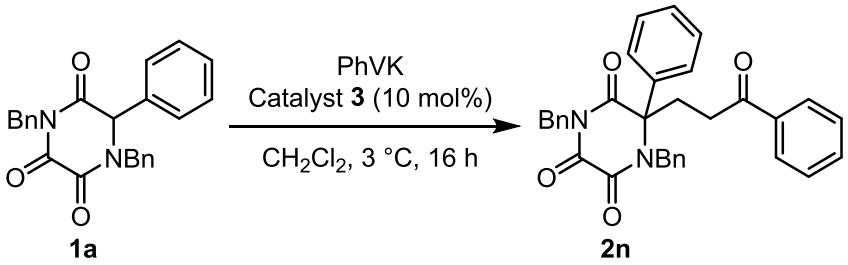
1,4-dibenzyl-6-(4-nitrophenyl)-6-(3-oxopentyl)piperazine-2,3,5-trione **2m**



Following general procedure **Cii** using triketopiperazine **1c** (43 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and ethyl vinyl ketone (25 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2m** (31.5 mg, 63%) as a colourless oil in 3:97 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 19.3 min, t(major) = 22.7 min].

IR ν_{max}/cm^{-1} 2980, 2933, 1744, 1682, 1608, 1525, 1495, 1415, 1349, 1221, 1113, 1078, 1030, 852, 729, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 2H), 7.56 – 7.49 (m, 2H), 7.32 – 7.14 (m, 10H), 5.13 – 5.04 (m, 2H), 4.94 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 14.8 Hz, 1H), 2.98 (ddd, *J* = 14.4, 10.2, 6.4 Hz, 1H), 2.51 (ddd, *J* = 14.7, 10.2, 5.1 Hz, 1H), 1.91 (dq, *J* = 17.6, 7.4 Hz, 1H), 1.84 – 1.72 (m, 3H), 0.79 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.5, 168.3, 155.4, 154.7, 148.4, 144.7, 136.1, 134.8, 129.4, 129.1, 128.9, 128.8, 128.6, 128.3, 127.9, 124.5, 72.4, 49.0, 45.0, 35.5, 30.6, 7.7; ***m/z*** (ES HRMS) $C_{29}H_{27}N_3O_6Na$ requires 536.1798, found $[MNa]^+$ 536.1800; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −7.2 (*c* 1.0, $CHCl_3$).

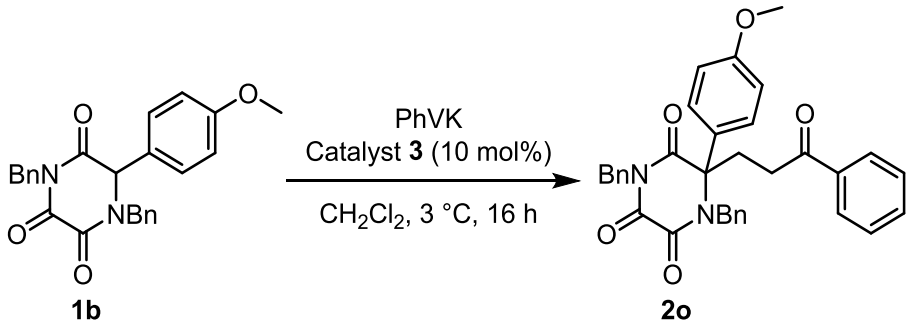
1,4-dibenzyl-6-(3-oxo-3-phenylpropyl)-6-phenylpiperazine-2,3,5-trione **2n**



Following general procedure **Cii** using triketopiperazine **1a** (38 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and phenyl vinyl ketone (33 mg, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2n** (46 mg, 90%) as a colourless oil in 85:15 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(major) = 61.3 min, t(minor) = 70.3 min].

IR ν_{max}/cm^{-1} 3064, 3029, 1742, 1678, 1597, 1494, 1415, 1361, 1262, 1228, 1138, 1073, 1002, 746, 690; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.29 (m, 12H), 7.25 – 7.17 (m, 5H), 7.06 – 6.99 (m, 2H), 6.96 – 6.89 (m, 1H), 5.23 (d, *J* = 14.8 Hz, 1H), 5.13 (d, *J* = 13.5 Hz, 1H), 4.98 (d, *J* = 13.6 Hz, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.18 (ddd, *J* = 14.4, 9.9, 6.6 Hz, 1H), 2.63 (ddd, *J* = 14.7, 9.4, 5.6 Hz, 1H), 2.41 – 2.25 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.8, 169.3, 155.9, 155.2, 138.1, 136.4, 136.1, 135.2, 133.2, 129.7, 129.6, 129.3, 128.9, 128.8, 128.4, 128.3, 128.0, 127.7, 126.4, 72.9, 49.0, 44.7, 32.5, 30.6; ***m/z*** (ES HRMS) $C_{23}H_{28}N_2O_4Na$ requires 539.1947, found $[MNa]^+$ 539.1957; $[\alpha]_D^{20}$ = −12.5 (*c* 1.0, $CHCl_3$).

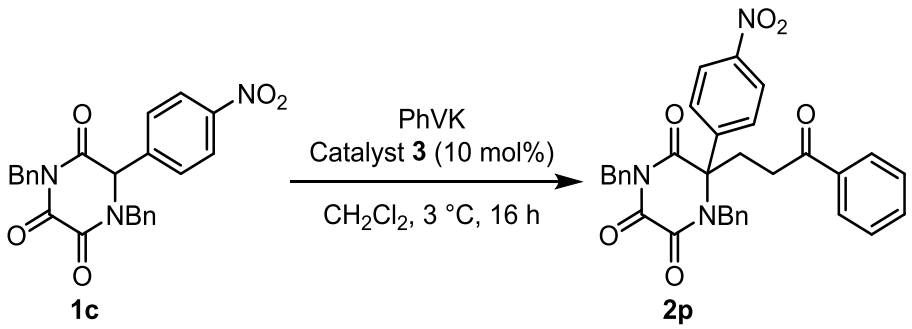
1,4-dibenzyl-6-(4-methoxyphenyl)-6-(3-oxo-3-phenylpropyl)piperazine-2,3,5-trione **2o**



Following general procedure **Cii** using triketopiperazine **1b** (41 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and phenyl vinyl ketone (33 mg, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2o** (52 mg, 95%) as a colourless oil in 87:13 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 60:40, 1.0 ml/min, λ 220 nm, t(major) = 22.1 min, t(minor) = 26.0 min].

IR ν_{max}/cm^{-1} 3061, 2958, 1741, 1678, 1603, 1511, 1447, 1415, 1362, 1256, 1227, 1182, 1077, 1030, 832, 733, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 1H), 7.38 – 7.27 (m, 8H), 7.25 – 7.18 (m, 5H), 7.07 – 6.98 (m, 2H), 6.96 – 6.89 (m, 3H), 5.21 (d, *J* = 14.8 Hz, 1H), 5.13 (d, *J* = 13.5 Hz, 1H), 4.97 (d, *J* = 13.6 Hz, 1H), 3.83 (s, 3H), 3.76 (d, *J* = 14.8 Hz, 1H), 3.14 (ddd, *J* = 14.4, 9.9, 6.5 Hz, 1H), 2.58 (ddd, *J* = 14.6, 9.4, 5.6 Hz, 1H), 2.39 – 2.23 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.9, 169.5, 160.4, 156.0, 155.2, 136.5, 136.1, 135.3, 133.2, 129.9, 129.4, 128.9, 128.8, 128.4, 128.3, 128.0, 127.7, 115.0, 72.6, 55.6, 48.8, 44.7, 32.5, 30.7; ***m/z*** (ES HRMS) $C_{34}H_{30}N_2O_5Na$ requires 569.2052, found $[MNa]^+$ 569.2048; $[\alpha]_D^{20}$ = −7.9 (*c* 1.0, $CHCl_3$).

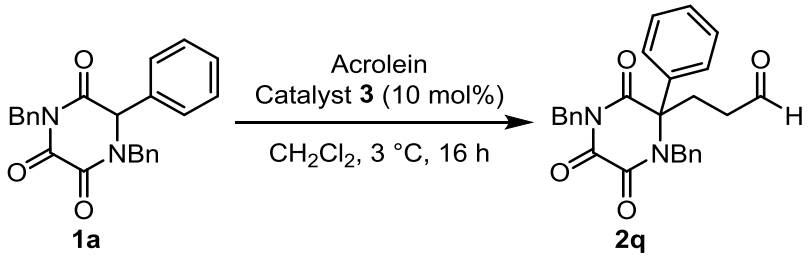
1,4-dibenzyl-6-(4-nitrophenyl)-6-(3-oxo-3-phenylpropyl)piperazine-2,3,5-trione **2p**



Following general procedure **Cii** using triketopiperazine **1c** (43 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and phenyl vinyl ketone (33 mg, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (2:1)) to afford **2p** (49.5 mg, 88%) as a colourless oil in 4:96 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 42.8 min, t(major) = 50.2 min].

IR ν_{max}/cm^{-1} 3064, 3034, 1744, 1679, 1597, 1521, 1495, 1417, 1348, 1263, 1227, 1140, 1077, 907, 851, 727, 702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 2H), 7.60 – 7.56 (m, 2H), 7.55 – 7.50 (m, 1H), 7.41 – 7.31 (m, 6H), 7.24 – 7.19 (m, 3H), 7.19 – 7.14 (m, 2H), 7.05 – 6.98 (m, 2H), 6.98 – 6.93 (m, 1H), 5.16 – 5.05 (m, 2H), 4.99 (d, *J* = 13.5 Hz, 1H), 3.90 (d, *J* = 14.8 Hz, 1H), 3.22 – 3.12 (m, 1H), 2.78 – 2.69 (m, 1H), 2.45 – 2.31 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.4, 168.4, 155.5, 154.8, 148.4, 144.8, 135.9, 134.9, 133.5, 129.5, 128.9, 128.8, 128.6, 128.6, 128.3, 127.9, 127.8, 124.5, 72.5, 49.0, 45.0, 32.2, 31.0; ***m/z*** (ES HRMS) $C_{33}H_{27}N_3O_6Na$ requires 584.1798, found $[MNa]^+$ 584.1803; $[\alpha]_D^{20}$ = −5.5 (*c* 1.0, $CHCl_3$).

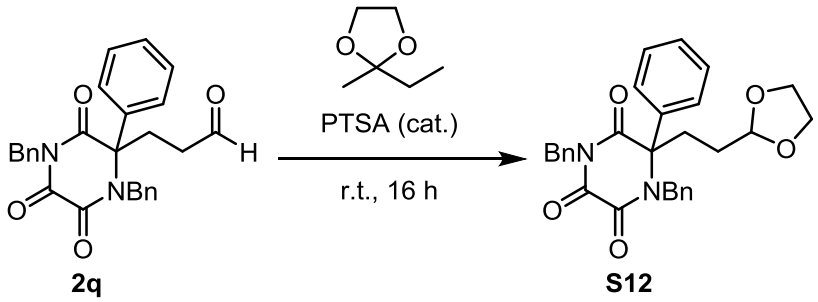
3-(1,4-dibenzyl-3,5,6-trioxo-2-phenylpiperazin-2-yl)propanal **2q**



Following general procedure **Cii** using triketopiperazine **1a** (38 mg, 0.10 mmol), chiral catalyst **3** (4 mg, 10 µmol, 10 mol%), CH_2Cl_2 (1 mL) and acrolein (17 µL, 0.25 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford **2q** (37.2 mg, 85%) as a colourless oil.

IR ν_{max}/cm^{-1} 3035, 2943, 1738, 1711, 1680, 1495, 1418, 1361, 1303, 1265, 1148, 1072, 911, 754, 692; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.47 – 7.17 (m, 15H), 5.29 (d, *J* = 14.8 Hz, 1H), 5.07 (d, *J* = 13.6 Hz, 1H), 4.93 (d, *J* = 13.6 Hz, 1H), 3.64 (d, *J* = 14.8 Hz, 1H), 3.05 (ddd, *J* = 14.4, 11.2, 5.3 Hz, 1H), 2.45 (ddd, *J* = 14.7, 11.1, 3.8 Hz, 1H), 1.97 – 1.75 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.2, 169.0, 155.7, 155.2, 137.8, 136.6, 135.0, 129.8, 129.7, 129.1, 129.1, 129.0, 128.7, 128.3, 126.2, 72.8, 49.0, 44.9, 38.1, 28.5; ***m/z*** (ES HRMS) $C_{27}H_{24}N_2O_4Na$ requires 463.1634, found $[MNa]^+$ 463.1631.

6-(2-(1,3-dioxolan-2-yl)ethyl)-1,4-dibenzyl-6-phenylpiperazine-2,3,5-trione **S12**



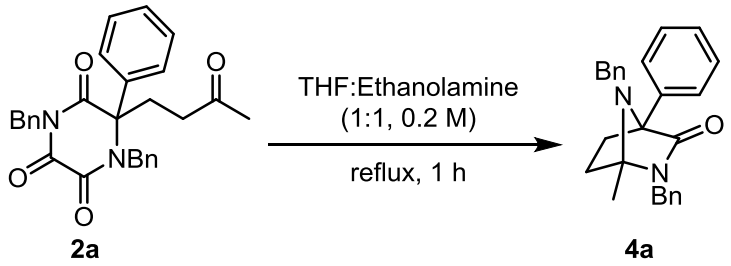
To a vial containing aldehyde **2q** (37 mg, 85 µmol) was added 2-ethyl-2-methyl-1,3-dioxolane (0.25 mL) and PTSA (5 mg) and the reaction mixture was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure and the reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford **S12** (40 mg, 98%) as a colourless oil in 42:58 er as determined by HPLC analysis [Phenomenex Lux Cellulose-1, MeCN:water, 50:50, 1.0 ml/min, λ 230 nm, t(minor) = 25.7 min, t(major) = 28.1 min].

IR ν_{max}/cm^{-1} 3062, 2951, 2885, 1742, 1683, 1494, 1418, 1363, 1263, 1234, 1128, 1076, 1029, 732, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.20 (m, 15H), 5.15 (d, *J* = 13.6 Hz, 1H), 5.07 –

4.98 (m, 2H), 4.35 (t, *J* = 4.9 Hz, 1H), 3.95 (d, *J* = 14.8 Hz, 1H), 3.81 – 3.67 (m, 4H), 2.93 (ddd, *J* = 13.8, 11.6, 5.1 Hz, 1H), 2.30 (ddd, *J* = 13.8, 11.7, 4.2 Hz, 1H), 1.35 – 1.13 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 156.0, 154.9, 138.5, 136.5, 135.1, 129.5, 129.4, 129.3, 128.6, 128.6, 128.2, 127.9, 126.4, 103.1, 73.1, 64.8, 64.8, 48.8, 44.7, 30.7, 28.6; ***m/z*** (ES HRMS) $C_{29}H_{28}N_2O_4Na$ requires 507.1896, found $[MNa]^+$ 507.1897.

2,7-Diazabicyclo[2.2.1]heptanes (4a-m)

2,7-dibenzyl-1-methyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4a**

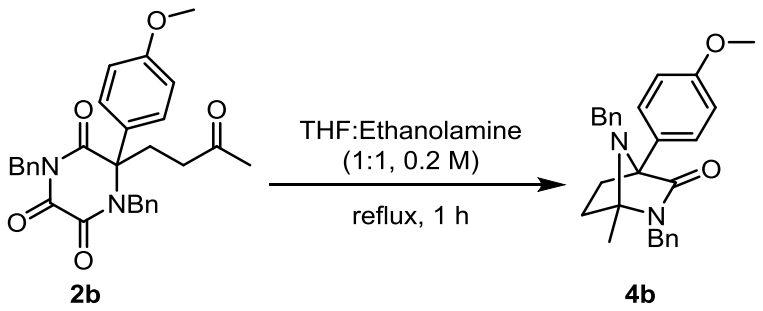


2a **4a**

Following general procedure **D** using triketopiperazine **2a** (19 mg, 40 µmol), THF (0.1 mL) and ethanolamine (0.1 mL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4a** (13.9 mg, 87%) as a colourless oil in 92:8 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 70:30, 1.0 ml/min, λ 220 nm, t(major) = 8.1 min, t(minor) = 9.8 min].

IR ν_{max}/cm^{-1} 3060, 3028, 2979, 2943, 1692, 1494, 1453, 1405, 1318, 1182, 955, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.41 – 7.24 (m, 8H), 7.24 – 7.09 (m, 5H), 4.58 (d, *J* = 15.2 Hz, 1H), 4.30 (d, *J* = 15.2 Hz, 1H), 3.46 (d, *J* = 15.6 Hz, 1H), 3.37 (d, *J* = 15.6 Hz, 1H), 2.29 – 2.16 (m, 1H), 1.98 – 1.86 (m, 2H), 1.60 – 1.49 (m, 1H), 1.12 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6, 140.8, 138.6, 136.5, 128.8, 128.5, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6, 126.5, 84.1, 75.3, 46.8, 43.7, 35.3, 35.2, 18.2 ; ***m/z*** (ES HRMS) $C_{26}H_{27}N_2O$ requires 383.2123, found $[MH]^+$ 383.2121; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 15.4 (*c* 1.0, $CHCl_3$).

2,7-dibenzyl-4-(4-methoxyphenyl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4b**

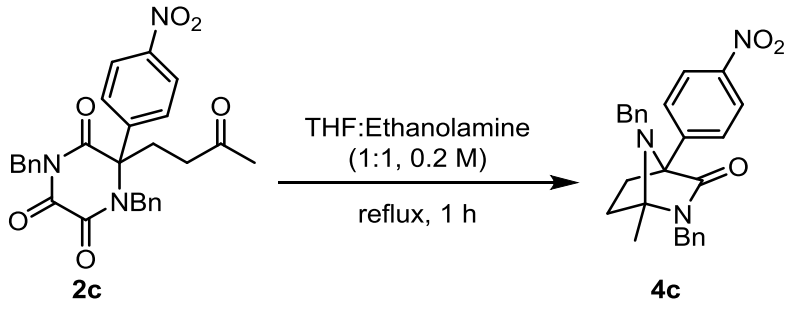


2b **4b**

Following general procedure **D** using triketopiperazine **2b** (26 mg, 53 µmol), THF (0.14 mL) and ethanolamine (0.14 mL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4b** (11.2 mg, 51%) as a colourless oil.

IR ν_{max}/cm^{-1} 2979, 2940, 2837, 1689, 1514, 1494, 1454, 1404, 1319, 1246, 1177, 1028, 831, 728, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.41 – 7.26 (m, 5H), 7.22 – 7.10 (m, 5H), 6.93 – 6.87 (m, 2H), 4.57 (d, *J* = 15.2 Hz, 1H), 4.29 (d, *J* = 15.2 Hz, 1H), 3.80 (s, 3H), 3.43 (d, *J* = 15.6 Hz, 1H), 3.35 (d, *J* = 15.5 Hz, 1H), 2.27 – 2.16 (m, 1H), 1.95 – 1.84 (m, 2H), 1.57 – 1.48 (m, 1H), 1.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8, 159.2, 140.8, 138.6, 129.3, 128.7, 128.3, 128.2, 128.1, 127.7, 127.6, 126.5, 113.9, 84.0, 75.0, 55.4, 46.7, 43.7, 35.2, 34.9, 18.2; ***m/z*** (ES HRMS) $C_{27}H_{29}N_2O_2$ requires 413.2229, found $[MH]^+$ 413.2231.

2,7-dibenzyl-1-methyl-4-(4-nitrophenyl)-2,7-diazabicyclo[2.2.1]heptan-3-one **4c**



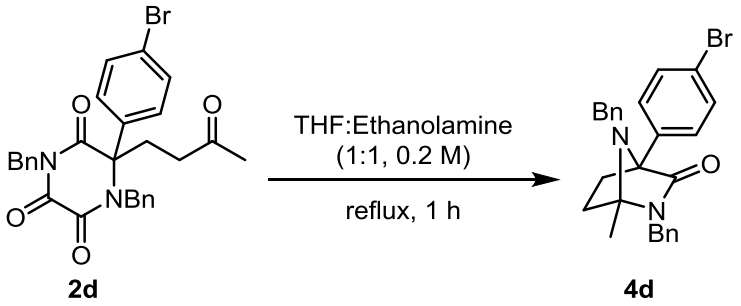
2c **4c**

Following general procedure **D** using triketopiperazine **2c** (25 mg, 50 µmol), THF (125 µL) and ethanolamine (125 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4c** (13.1 mg, 61%) as a colourless oil.

IR ν_{max}/cm^{-1} 2940, 2925, 2853, 1692, 1601, 1517, 1494, 1406, 1347, 1317, 1182, 1028, 956, 909, 852, 729, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 – 8.15 (m, 4H), 7.39 – 7.28 (m, 5H), 7.24 – 7.13 (m, 5H), 4.56 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H), 3.45 (d, *J* = 15.7 Hz, 1H), 3.36 (d, *J* = 15.7 Hz, 1H), 2.19 – 2.10 (m, 1H), 2.01 – 1.91 (m, 2H), 1.62 – 1.54 (m, 1H),

1.19 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.5, 147.4, 144.2, 139.8, 138.1, 128.9, 128.4, 128.2, 127.8, 127.5, 126.9, 123.6, 84.4, 74.9, 47.2, 43.9, 35.8, 35.5, 18.0; ***m/z*** (ES HRMS) $C_{26}H_{26}N_3O_3$ requires 428.1974, found $[MH]^+$ 428.1975.

2,7-dibenzyl-4-(4-bromophenyl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4d**

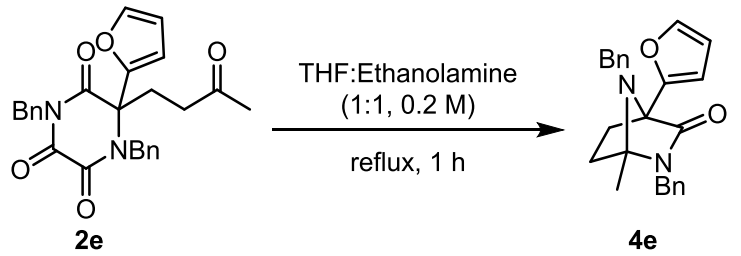


2d **4d**

Following general procedure **D** using triketopiperazine **2d** (45 mg, 85 µmol), THF (215 µL) and ethanolamine (215 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4d** (23.1 mg, 60%) as a colourless oil.

IR ν_{max}/cm^{-1} 3030, 2923, 2850, 1693, 1493, 1405, 1318, 1182, 1011, 955, 823, 703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 2H), 7.50 – 7.45 (m, 2H), 7.38 – 7.27 (m, 5H), 7.23 – 7.11 (m, 5H), 4.55 (d, *J* = 15.2 Hz, 1H), 4.30 (d, *J* = 15.2 Hz, 1H), 3.38 (s, 2H), 2.19 – 2.10 (m, 1H), 1.95 – 1.86 (m, 2H), 1.55 – 1.49 (m, 1H), 1.13 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2, 140.4, 138.4, 135.6, 131.6, 129.8, 128.8, 128.3, 128.2, 127.7, 127.6, 126.6, 122.0, 84.1, 74.9, 46.9, 43.8, 35.3, 18.1; ***m/z*** (ES HRMS) $C_{26}H_{26}N_2OBr$ requires 461.1229, found $[MH]^+$ 461.1226.

2,7-dibenzyl-4-(furan-2-yl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4e**

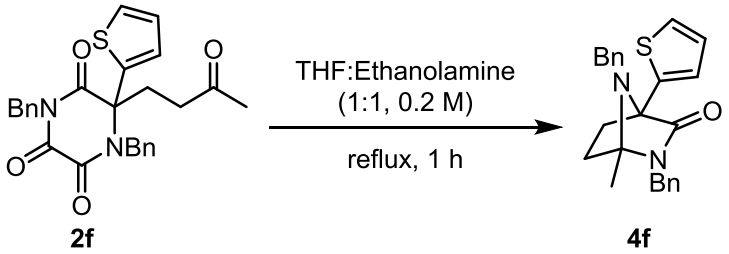


2e **4e**

Following general procedure **D** using triketopiperazine **2e** (59 mg, 0.13 mmol), THF (325 µL) and ethanolamine (325 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4e** (36.6 mg, 75%) as a colourless oil.

IR ν_{max}/cm^{-1} 3028, 2945, 1697, 1494, 1454, 1405, 1312, 1185, 1006, 910, 729, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 6H), 7.19 – 7.13 (m, 2H), 7.13 – 7.08 (m, 3H), 6.92 (dd, *J* = 3.3, 0.9 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.52 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H), 3.49 – 3.36 (m, 2H), 2.57 (ddd, *J* = 12.1, 10.4, 4.1 Hz, 1H), 1.88 (ddd, *J* = 11.5, 10.4, 4.2 Hz, 1H), 1.74 (ddd, *J* = 12.1, 9.2, 4.3 Hz, 1H), 1.49 (ddd, *J* = 11.4, 9.2, 4.2 Hz, 1H), 1.21 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2, 148.1, 142.9, 140.1, 138.3, 128.8, 128.2, 128.0, 127.7, 126.4, 111.8, 110.4, 84.3, 72.7, 47.1, 43.8, 35.1, 30.0, 17.9; ***m/z*** (ES HRMS) $C_{24}H_{25}N_2O_2$ requires 373.1916, found $[MH]^+$ 373.1919.

2,7-dibenzyl-1-methyl-4-(thiophen-2-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one **4f**

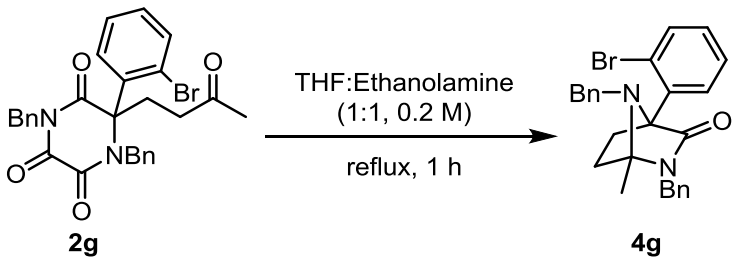


2f **4f**

Following general procedure **D** using triketopiperazine **2f** (12 mg, 26 µmol), THF (65 µL) and ethanolamine (65 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4f** (5 mg, 50%) as a colourless oil in 93:7 er as determined by HPLC analysis [Phenomenex Lux Amylose-2, MeCN:water, 70:30, 1.0 ml/min, λ 220 nm, t(major) = 7.8 min, t(minor) = 9.4 min].

IR ν_{max}/cm^{-1} 3062, 2928, 2851, 1699, 1484, 1454, 1405, 1296, 1182, 1028, 842, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.38 – 7.28 (m, 6H), 7.22 – 7.10 (m, 5H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.53 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H), 3.49 (d, *J* = 15.4 Hz, 1H), 3.34 (d, *J* = 15.3 Hz, 1H), 2.30 (ddd, *J* = 12.2, 10.3, 4.2 Hz, 1H), 1.98 (ddd, *J* = 12.2, 9.1, 4.3 Hz, 1H), 1.90 (ddd, *J* = 11.6, 10.3, 4.3 Hz, 1H), 1.49 (ddd, *J* = 11.6, 9.2, 4.3 Hz, 1H), 1.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.5, 140.6, 138.3, 128.8, 128.3, 128.1, 127.9, 127.7, 126.9, 126.5, 126.2, 84.5, 73.9, 46.7, 43.9, 36.0, 35.2, 18.2; ***m/z*** (ES HRMS) $C_{24}H_{25}N_2OS$ requires 389.1688, found $[MH]^+$ 389.1685; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −7.3 (*c* 1.0, $CHCl_3$).

2,7-dibenzyl-4-(2-bromophenyl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4g**

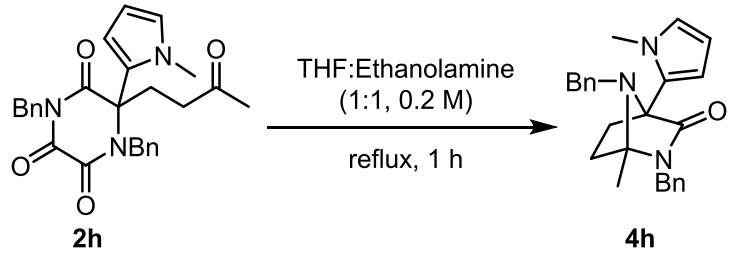


2g **4g**

Following general procedure **D** using triketopiperazine **2g** (36 mg, 68 µmol), THF (175 µL) and ethanolamine (175 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4g** (9 mg, 29%) as a colourless oil.

IR ν_{max}/cm^{-1} 2921, 2850, 1688, 1494, 1455, 1406, 1313, 1028, 755, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.08 (m, 13H), 4.65 (br s, 1H), 4.27 (d, *J* = 15.5 Hz, 1H), 3.32 (d, *J* = 15.1 Hz, 1H), 3.23 (d, *J* = 15.5 Hz, 1H), 1.99 (ddd, *J* = 11.8, 10.2, 4.5 Hz, 1H), 1.85 (br s, 1H), 1.62 (br s, 2H), 1.10 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 140.1, 138.5, 135.5, 133.9, 132.0, 129.9, 128.7, 128.4, 128.1, 128.0, 127.5, 127.2, 126.6, 84.0, 77.4, 48.0, 43.4, 34.8, 29.2, 18.2; ***m/z*** (ES HRMS) $C_{26}H_{26}N_2OBr$ requires 461.1229, found $[MH]^+$ 461.1233.

2,7-dibenzyl-1-methyl-4-(1-methyl-1H-pyrrol-2-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one **4h**



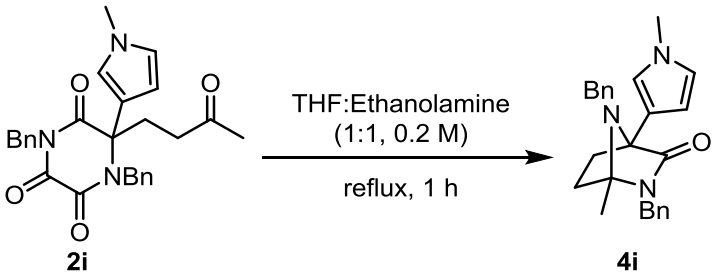
2h **4h**

Following general procedure **D** using triketopiperazine **2h** (34.7 mg, 76 µmol), THF (190 µL) and ethanolamine (190 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4h** (7.5 mg, 26%) as a colourless oil.

IR ν_{max}/cm^{-1} 3029, 2924, 2852, 1702, 1494, 1453, 1404, 1322, 1274, 1225, 1179, 1028, 950, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 7.21 – 7.10 (m, 3H), 7.06 – 7.01 (m, 2H), 6.66 (s, 1H), 6.53 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.09 (dd, *J* = 3.7, 2.7 Hz, 1H), 4.54 (d, *J* = 15.4 Hz, 1H), 4.39 (d, *J* = 15.4 Hz, 1H), 3.58 (s, 3H), 3.35 (d, *J* = 15.2 Hz, 1H), 3.23 (d, *J* = 15.2 Hz, 1H), 2.43 (ddd, *J* = 13.6, 10.4, 3.9 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.57 – 1.50 (m, 1H), 1.26 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0, 140.0, 138.4, 128.8, 128.1, 127.9, 127.5, 126.5,

124.7, 112.1, 107.0, 84.0, 72.6, 47.4, 43.3, 35.2, 33.5, 29.4, 17.7; ***m/z*** (ES HRMS) $C_{25}H_{28}N_3O$ requires 386.2232, found $[MH]^+$ 386.2230.

2,7-dibenzyl-1-methyl-4-(1-methyl-1H-pyrrol-3-yl)-2,7-diazabicyclo[2.2.1]heptan-3-one **4i**

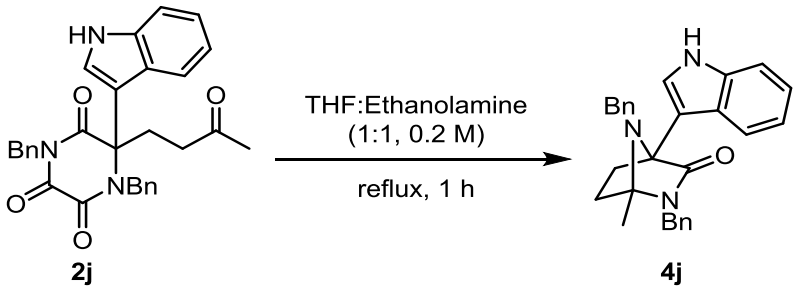


2i **4i**

Following general procedure **D** using triketopiperazine **2i** (16 mg, 35 µmol), THF (100 µL) and ethanolamine (100 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4i** (3.3 mg, 25%) as a colourless oil.

IR ν_{max}/cm^{-1} 2922, 2852, 1693, 1494, 1453, 1410, 1272, 1207, 1079, 1028, 793, 733, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 7H), 7.19 – 7.15 (m, 3H), 7.14 – 7.09 (m, 1H), 6.55 (t, *J* = 2.5 Hz, 1H), 6.27 (dd, *J* = 2.7, 1.7 Hz, 1H), 4.54 (d, *J* = 15.4 Hz, 1H), 4.27 (d, *J* = 15.2 Hz, 1H), 3.64 (s, 3H), 3.58 (d, *J* = 15.5 Hz, 1H), 3.27 (d, *J* = 15.3 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.86 – 1.74 (m, 2H), 1.48 – 1.41 (m, 1H), 1.08 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5, 141.6, 138.8, 128.7, 128.2, 128.0, 128.0, 127.5, 126.2, 122.4, 122.0, 117.8, 107.8, 84.2, 72.9, 46.4, 43.8, 36.3, 35.1, 34.1, 18.3; ***m/z*** (ES HRMS) $C_{25}H_{28}N_3O$ requires 386.2232, found $[MH]^+$ 386.2233.

2,7-dibenzyl-4-(1H-indol-3-yl)-1-methyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4j**

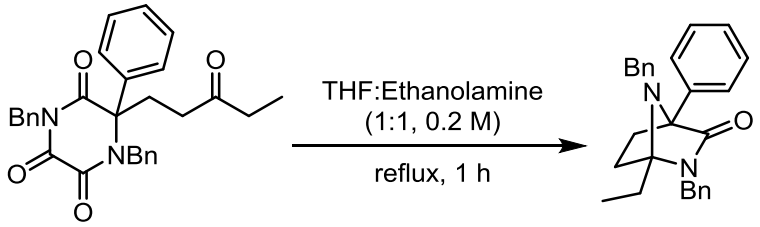


2j **4j**

Following general procedure **D** using triketopiperazine **2j** (9.5 mg, 19 µmol), THF (50 µL) and ethanolamine (50 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4j** (2 mg, 21%) as a colourless oil.

IR ν_{max}/cm^{-1} 3300, 2924, 2852, 1680, 1494, 1455, 1409, 1351, 1217, 1074, 942, 741, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 – 8.19 (m, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.31 – 7.26 (m, 1H), 7.19 – 7.09 (m, 6H), 7.07 – 7.03 (m, 1H), 4.56 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H), 3.46 (d, *J* = 15.2 Hz, 1H), 3.30 (d, *J* = 15.1 Hz, 1H), 2.72 (ddd, *J* = 12.4, 10.3, 4.0 Hz, 1H), 1.96 (ddd, *J* = 11.6, 10.3, 4.4 Hz, 1H), 1.73 (ddd, *J* = 12.4, 9.3, 4.4 Hz, 1H), 1.57 – 1.49 (m, 1H), 1.11 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.4, 140.9, 138.6, 136.4, 128.8, 128.2, 128.0, 128.0, 127.6, 126.3, 126.2, 125.4, 122.2, 120.9, 119.7, 111.3, 109.7, 84.2, 73.0, 47.2, 43.7, 35.5, 31.8, 18.6; ***m/z*** (ES HRMS) $C_{28}H_{28}N_3O$ requires 422.2232, found $[MH]^+$ 422.2235.

2,7-dibenzyl-1-ethyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4k**

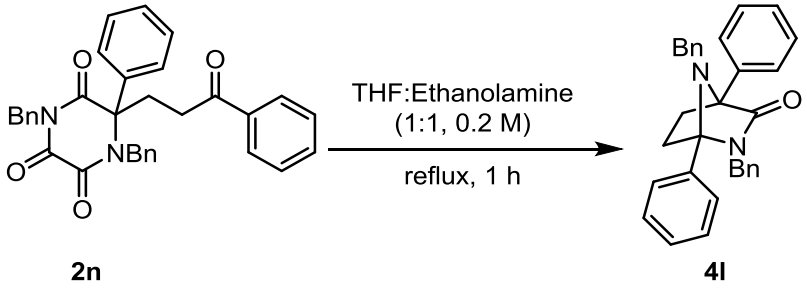


2k **4k**

Following general procedure **D** using triketopiperazine **2k** (24 mg, 50 µmol), THF (125 µL) and ethanolamine (125 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4k** (9.8 mg, 50%) as a colourless oil.

IR ν_{max}/cm^{-1} 3030, 2931, 2850, 1692, 1494, 1453, 1399, 1314, 1074, 1028, 760, 734, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.42 – 7.21 (m, 8H), 7.17 – 7.07 (m, 5H), 4.63 (d, *J* = 15.4 Hz, 1H), 4.27 (d, *J* = 15.3 Hz, 1H), 3.37 (s, 2H), 2.28 – 2.19 (m, 1H), 2.10 (ddd, *J* = 11.7, 10.4, 4.0 Hz, 1H), 1.90 (ddd, *J* = 12.1, 9.3, 3.9 Hz, 1H), 1.71 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.54 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.44 – 1.35 (m, 1H), 0.55 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 140.1, 138.8, 136.3, 128.7, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 126.5, 88.1, 75.7, 47.1, 43.7, 34.2, 30.8, 23.0, 7.8; ***m/z*** (ES HRMS) $C_{27}H_{29}N_2O$ requires 397.2280, found $[MH]^+$ 397.2281.

2,7-dibenzyl-1,4-diphenyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4l**

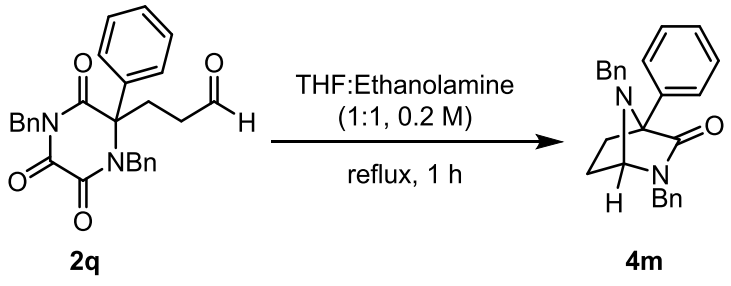


2n **4l**

Following general procedure **D** using triketopiperazine **2n** (18 mg, 35 µmol), THF (90 µL) and ethanolamine (90 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4l** (13 mg, 84%) as a colourless oil.

IR ν_{max}/cm^{-1} 3059, 3031, 2926, 1705, 1494, 1450, 1398, 1322, 1198, 1074, 1029, 951, 911, 752, 731, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.31 – 7.14 (m, 9H), 6.96 – 6.87 (m, 5H), 6.75 – 6.68 (m, 2H), 4.56 (d, *J* = 14.6 Hz, 1H), 3.82 (d, *J* = 14.7 Hz, 1H), 3.16 (d, *J* = 14.4 Hz, 1H), 3.07 (d, *J* = 14.4 Hz, 1H), 2.63 – 2.48 (m, 2H), 2.10 (ddd, *J* = 11.2, 8.7, 3.2 Hz, 1H), 1.87 (ddd, *J* = 11.9, 8.7, 2.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7, 139.4, 137.6, 134.6, 133.1, 130.3, 129.7, 129.5, 128.8, 128.7, 128.4, 128.2, 128.2, 127.5, 127.4, 126.1, 88.6, 77.5, 48.3, 44.2, 30.3, 26.5; ***m/z*** (ES HRMS) $C_{31}H_{29}N_2O$ requires 445.2280, found $[MH]^+$ 445.2281.

2,7-dibenzyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one **4m**



2q **4m**

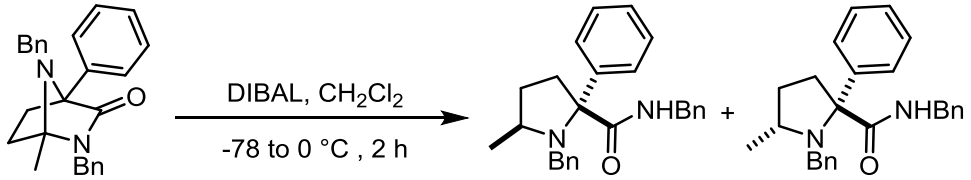
Following general procedure **D** using triketopiperazine **2q** (19 mg, 44 µmol), THF (110 µL) and ethanolamine (110 µL). After 1 hour the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (9:1) to (2:1)) to afford **4m** (4.4 mg, 28%) as a colourless oil.

IR ν_{max}/cm^{-1} 2916, 2854, 1694, 1494, 1451, 1411, 1330, 1249, 701; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 8.02 (m, 2H), 7.46 – 7.30 (m, 8H), 7.16 – 7.11 (m, 3H), 6.85 – 6.79 (m, 2H), 4.84 (d, *J* = 14.7 Hz, 1H), 4.26 (d, *J* = 2.4 Hz, 1H), 3.91 (d, *J* = 14.7 Hz, 1H), 3.33 (d, *J* = 13.0 Hz, 1H), 3.02 (d, *J* = 13.0 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.00 – 1.91 (m, 2H), 1.65 – 1.59 (m, 1H); **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 174.0, 138.7, 137.0, 135.4, 129.0, 129.0, 128.8, 128.6, 128.3, 128.0, 127.9, 127.9, 127.1, 84.1, 73.9, 48.6, 44.8, 29.9, 28.0; ***m/z*** (ES HRMS) $C_{25}H_{25}N_2O$ requires 369.1967, found $[MH]^+$ 369.1966.

Reduction of 4a

N,1-dibenzyl-5-methyl-2-phenylpyrrolidine-2-carboxamide **5a** and **5b**



4a **5a** **5b**

To a solution of diazabicycle **4a** (29 mg, 77 µmol) in CH_2Cl_2 (0.5 mL) was added DIBAL (65 µL, 77 µmol) at −78 °C. After 1 hour a further equivalent of DIBAL (65 µL, 77 µmol) was added and the reaction mixture was allowed to warm to 0 °C over 1 hour. The reaction mixture was then diluted with CH_2Cl_2 (2 mL) followed by the addition of aqueous Rochelle's salt (3 mL, 20% w/w) and stirred vigorously for 1 hour. The reaction mixture was extracted with CH_2Cl_2 (3 x 3 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane:EtOAc = 9:1) to afford **5a** (11.4 mg, 39%) and **5b** (5.4 mg, 18%) as colourless oils.

Major (2*R*, 5*S*) or (2*S*, 5*R*) *N*,1-dibenzyl-5-methyl-2-phenylpyrrolidine-2-carboxamide **5a**

IR ν_{max}/cm^{-1} 3351, 3060, 3028, 2958, 2924, 2864, 1666, 1495, 1452, 1374, 1317, 1111, 1077, 1027, 748, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.38 – 7.19 (m, 10H), 7.14 – 7.03 (m, 3H), 6.85 – 6.78 (m, 2H), 4.48 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.36 (dd, *J* = 14.6, 5.7 Hz, 1H), 3.41 (d, *J* = 14.3 Hz, 1H), 3.23 – 3.12 (m, 2H), 2.69 (ddd, *J* = 13.1, 7.4, 2.4 Hz, 1H), 2.52 (ddd, *J* = 13.1, 11.4, 7.2 Hz, 1H), 2.08 (dddd, *J* = 13.0, 7.1, 6.0, 2.4 Hz, 1H), 1.48 (dddd, *J* = 12.5, 11.3, 10.0, 7.4 Hz, 1H), 0.98 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8, 140.7, 139.4, 138.6, 129.3, 128.8, 128.7, 128.3, 128.2, 128.0, 127.7, 127.5, 126.9, 78.3, 63.3, 55.4, 43.8, 38.1, 33.1, 22.2; ***m/z*** (ES HRMS) $C_{26}H_{29}N_2O$ requires 385.2280, found $[MH]^+$ 385.2279.

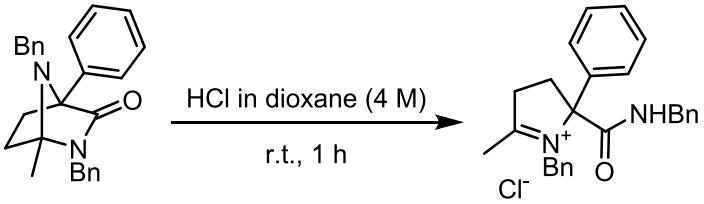
Minor (2*R*, 5*R*) or (2*S*, 5*S*) *N*,1-dibenzyl-5-methyl-2-phenylpyrrolidine-2-carboxamide **5b**

IR ν_{max}/cm^{-1} 3349, 3060, 3028, 2958, 2924, 2852, 1657, 1495, 1453, 1371, 1208, 1119, 1079, 1028, 751, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.37 – 7.24 (m, 8H), 7.21 – 7.12 (m, 5H), 4.54 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.45 (dd, *J* = 14.6, 5.5 Hz, 1H), 3.60 (d, *J* = 14.7 Hz, 1H), 3.46 (d, *J* = 14.7 Hz, 1H), 3.40 (pd, *J* = 6.5, 3.6 Hz, 1H), 2.70 (ddd, *J* = 12.9, 7.8, 3.6 Hz,

1H), 2.41 (ddd, *J* = 13.0, 10.0, 7.9 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.64 – 1.51 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 141.5, 140.6, 138.5, 128.9, 128.5, 128.4, 128.4, 128.2, 128.0, 127.6, 127.4, 126.8, 77.6, 57.5, 52.4, 43.9, 38.2, 31.7, 19.4, 1.2; ***m/z*** (ES HRMS) $C_{26}H_{29}N_2O$ requires 385.2280, found $[MH]^+$ 385.2282.

Formation of Iminium 6

1-benzyl-2-(benzylcarbamoyl)-5-methyl-2-phenyl-3,4-dihydro-2H-pyrrol-1-ium chloride **6**



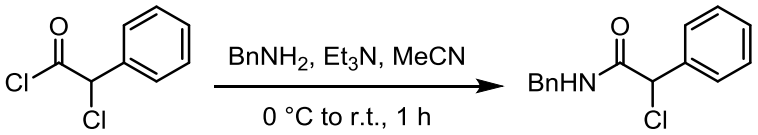
4a **6**

To a round bottomed flask containing diazabicycle **4a** (39 mg, 0.1 mmol) was added HCl in dioxane (0.2 mL, 4 M) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure to afford **6** (quant.) as a colourless residue.

IR ν_{max}/cm^{-1} 3169, 3030, 1666, 1530, 1496, 1452, 1359, 1271, 1127, 1079, 1028, 957, 729, 696; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.04 (t, *J* = 6.0 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.42 – 7.33 (m, 2H), 7.31 – 7.15 (m, 6H), 7.14 – 7.03 (m, 3H), 6.66 – 6.58 (m, 2H), 5.31 (d, *J* = 16.2 Hz, 1H), 4.72 (d, *J* = 16.2 Hz, 1H), 4.55 – 4.43 (m, 2H), 3.80 – 3.67 (m, 1H), 3.27 (d, *J* = 14.1 Hz, 3H), 2.53 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.5, 168.2, 138.6, 133.8, 131.2, 130.4, 129.2, 129.0, 128.7, 128.5, 127.3, 126.9, 89.0, 54.1, 44.1, 40.5, 33.4, 21.4; ***m/z*** (ES HRMS) $C_{26}H_{27}N_2O$ requires 383.2123, found $[M]^+$ 383.2124.

Synthesis of harmicine Amide 10

N-benzyl-2-chloro-2-phenylacetamide **S13**

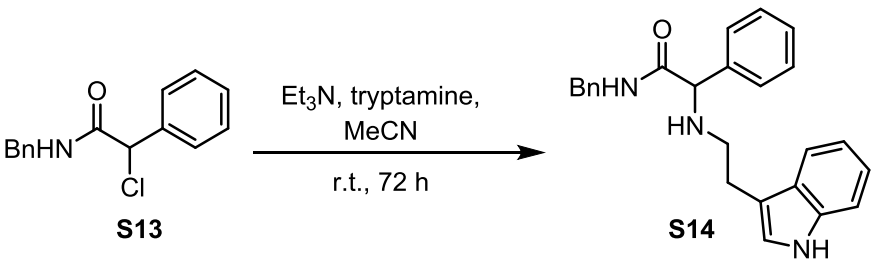


S13

To a solution of benzylamine (0.69 mL, 6.33 mmol) and triethylamine (1.06 mL, 7.60 mmol) in MeCN (30 mL) was added α-chlorophenylacetyl chloride (1.0 mL, 6.33 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 hour then filtered, washed with MeCN (3 x 5 mL) and the filtrate was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (20 mL) and washed with 1 M HCl (20 mL), the organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford **S13** as a pale yellow solid (1.55 g, 95%).

IR ν_{max}/cm^{-1} 3289, 3064, 3031, 1659, 1530, 1496, 1454, 1213, 1029, 730, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.05 (m, 10H), 6.91 (Br s, 1H), 5.33 (s, 1H), 4.42 (d, *J* = 5.7 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 137.5, 137.2, 129.3, 129.1, 129.0, 127.9, 61.9, 44.3; ***m/z*** (ES) $C_{15}H_{14}NOClNa$ requires 282.7, found $[MNa]^+$ 282.3. Data is in agreement with literature.[6]

2-((2-(1H-indol-3-yl)ethyl)amino)-*N*-benzyl-2-phenylacetamide **S14**



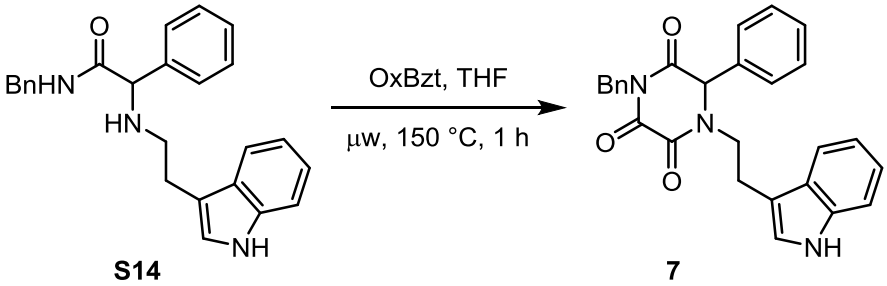
S13 **S14**

To a solution of **S13** (457 mg, 1.76 mmol) and triethylamine (0.98 mL, 7.04 mmol) in MeCN (9 mL) was added tryptamine (705 mg, 4.40 mmol) in one portion. The reaction mixture was stirred for 72 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 (15 mL), washed with 1 M HCl (15 mL), and the organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by flash column chromatography (CH_2Cl_2:Acetone = 9:1) to afford **S14** (215 mg, 32%) as a brown oil.

IR ν_{max}/cm^{-1} 3297, 3059, 2924, 2846, 1654, 1520, 1454, 1230, 908, 731; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.57 – 7.50 (m, 1H), 7.35 – 7.24 (m, 8H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz,

1H), 7.14 – 7.06 (m, 3H), 6.88 (d, *J* = 2.3 Hz, 1H), 4.36 (dd, *J* = 14.9, 6.2 Hz, 1H), 4.26 (s, 1H), 4.19 (dd, *J* = 14.9, 5.8 Hz, 1H), 3.05 – 2.87 (m, 4H), 1.99 (br s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 139.4, 138.5, 136.5, 128.9, 128.7, 128.2, 127.6, 127.4, 127.4, 122.2, 119.5, 118.9, 113.5, 111.4, 67.7, 48.8, 43.1, 25.9; ***m/z*** (ES HRMS) $C_{25}H_{26}N_3O$ requires 384.2076, found $[MH]^+$ 384.2084.

1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-phenylpiperazine-2,3,5-trione **7**

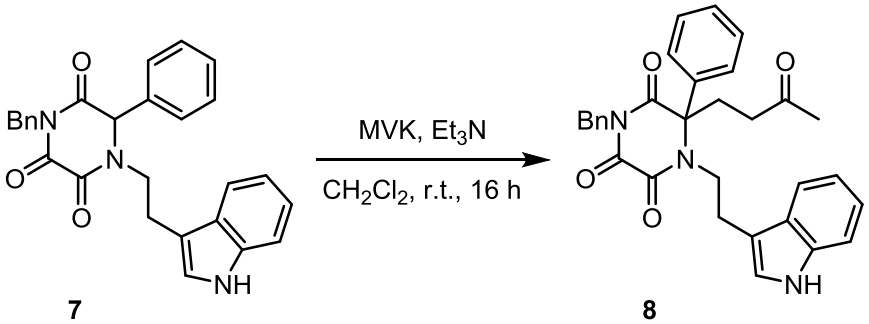


S14 **7**

Following general procedure **B** using 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (171 mg, 0.59 mmol) in THF (1.5 mL), **S14** (187 mg, 0.49 mmol) in THF (2 mL). The residue was purified by flash column chromatography on silica gel (gradient: CH_2Cl_2/MeOH = (1:0) to (99:1)) to afford **7** (67.5 mg, 32%) as a waxy yellow solid.

IR ν_{max}/cm^{-1} 3332, 3057, 3034, 2937, 1744, 1683, 1454, 1428, 1362, 1198, 908, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.44 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.40 – 7.27 (m, 4H), 7.25 (d, *J* = 8.9 Hz, 5H), 7.18 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.11 – 7.04 (m, 2H), 7.05 – 6.93 (m, 2H), 4.99 (d, *J* = 13.8 Hz, 1H), 4.85 – 4.77 (m, 2H), 4.20 (ddd, *J* = 13.1, 7.8, 4.4 Hz, 1H), 3.19 (dt, *J* = 13.8, 7.9 Hz, 1H), 3.08 (dt, *J* = 13.2, 7.4 Hz, 1H), 2.96 (dddd, *J* = 13.6, 7.1, 4.5, 0.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7, 156.6, 153.0, 136.4, 135.2, 134.5, 129.8, 129.6, 129.2, 128.7, 128.2, 127.1, 126.9, 122.6, 122.3, 119.9, 118.4, 112.0, 111.6, 66.3, 47.1, 44.6, 23.0; ***m/z*** (ES HRMS) $C_{27}H_{23}N_3O_3Na$ requires 460.1637, found $[MNa]^+$ 460.1635.

1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione **8**

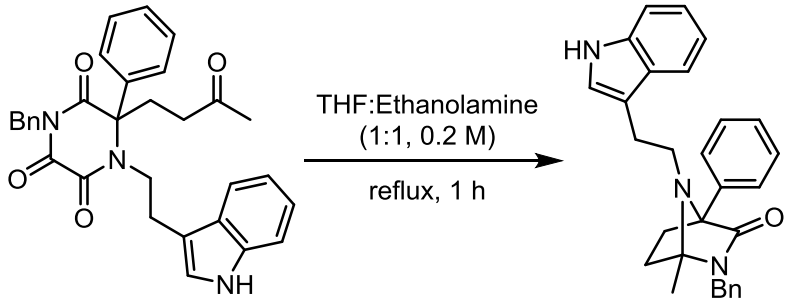


7 **8**

Following general procedure **Cii** using triketopiperazine **7** (66 mg, 0.15 mmol), triethylamine (20 µL, 0.15 mmol), CH_2Cl_2 (1.5 mL) and methyl vinyl ketone (30 µL, 0.375 mmol). The reaction mixture was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford **8** (75 mg, 99%) as a yellow oil.

IR ν_{max}/cm^{-1} 3339, 2950, 1741, 1712, 1677, 1419, 1362, 1227, 907, 726; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.36 (m, 5H), 7.35 – 7.28 (m, 6H), 7.15 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 5.20 (d, *J* = 13.5 Hz, 1H), 4.98 (d, *J* = 13.5 Hz, 1H), 3.49 (ddd, *J* = 13.5, 11.5, 4.7 Hz, 1H), 3.16 (ddd, *J* = 13.4, 11.4, 5.6 Hz, 1H), 3.01 – 2.75 (m, 3H), 2.61 (ddd, *J* = 14.3, 11.8, 3.6 Hz, 1H), 2.23 (ddd, *J* = 17.7, 11.5, 3.6 Hz, 1H), 2.04 (ddd, *J* = 17.3, 11.8, 5.1 Hz, 1H), 1.96 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.4, 169.7, 156.0, 153.8, 138.0, 136.2, 135.3, 129.5, 128.8, 128.5, 127.0, 126.6, 122.4, 122.3, 119.7, 118.9, 112.1, 111.3, 71.7, 47.4, 44.7, 37.3, 30.1, 30.0, 23.3; ***m/z*** (ES HRMS) $C_{31}H_{29}N_3O_4Na$ requires 530.2056, found $[MNa]^+$ 530.2057.

7-(2-(1H-indol-3-yl)ethyl)-2-benzyl-1-methyl-4-phenyl-2,7-diazabicyclo[2.2.1]heptan-3-one **9**

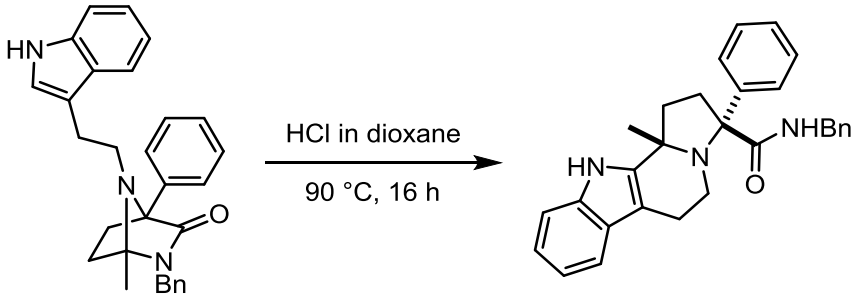


8 **9**

Following general procedure **D** using triketopiperazine **8** (54 mg, 0.11 mmol), THF (0.27 mL) and ethanolamine (0.27 mL). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford **9** (24 mg, 52%) as a colourless oil.

IR ν_{max}/cm^{-1} 3408, 3298, 3057, 2923, 2852, 1685, 1494, 1455, 1318, 1182, 961, 908, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 2H), 7.86 (br s, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.24 (m, 7H), 7.15 – 7.08 (m, 2H), 6.97 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 4.54 (d, *J* = 15.3 Hz, 1H), 4.29 (d, *J* = 15.3 Hz, 1H), 2.69 – 2.45 (m, 4H), 2.25 – 2.16 (m, 1H), 1.95 – 1.81 (m, 2H), 1.59 – 1.54 (m, 1H), 1.52 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.0, 138.5, 136.5, 136.2, 128.8, 128.5, 128.4, 128.2, 127.9, 127.5, 127.4, 122.0, 121.4, 119.3, 119.0, 114.4, 111.1, 83.9, 76.0, 44.0, 43.8, 35.1, 34.1, 27.1, 17.7; ***m/z*** (ES HRMS) $C_{29}H_{30}N_3O$ requires 436.2389, found $[MH]^+$ 436.2392.

N-benzyl-11b-methyl-3-phenyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-3-carboxamide **10**



9 **10**

To a round bottomed flask containing **9** (16 mg, 38 µmol) was added HCl in dioxane (0.5 ml) and the reaction mixture was heated at 90 °C for 16 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up in CH_2Cl_2 (3 mL), washed with sat. aq. $NaHCO_3$ (5 mL), the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL), the organic layers were combined and washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: hexane:EtOAc = (4:1) to (1:1)) to afford **10** (10.4 mg, 63%) as a pale yellow oil.

IR ν_{max}/cm^{-1} 3284, 2960, 2922, 2852, 1651, 1499, 1449, 1331, 1275, 1117, 908, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (t, *J* = 6.0 Hz, 1H), 7.81 (br s, 1H), 7.41 (d, *J* = 4.3 Hz, 4H), 7.36 – 7.23 (m, 7H), 7.14 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.05 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.70 (dd, *J* = 14.7, 6.6 Hz, 1H), 4.54 (dd, *J* = 14.7, 5.3 Hz, 1H), 3.17 (dd, *J* = 8.4, 2.8 Hz, 2H), 2.56 – 2.39 (m, 2H), 2.29 (ddd, *J* = 12.4, 6.1, 2.2 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.68 – 1.55 (m, 2H), 1.48 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0, 139.1, 139.0, 137.8, 135.7, 129.1, 128.9, 128.2, 128.1, 128.0, 127.7, 127.5, 121.9, 119.4, 118.3, 110.9, 109.9, 76.6, 62.5, 44.0, 39.9, 37.4, 33.6, 28.4, 19.4; ***m/z*** (ES HRMS) $C_{29}H_{30}N_3O$ requires 436.2389, found $[MH]^+$ 436.2388.

References

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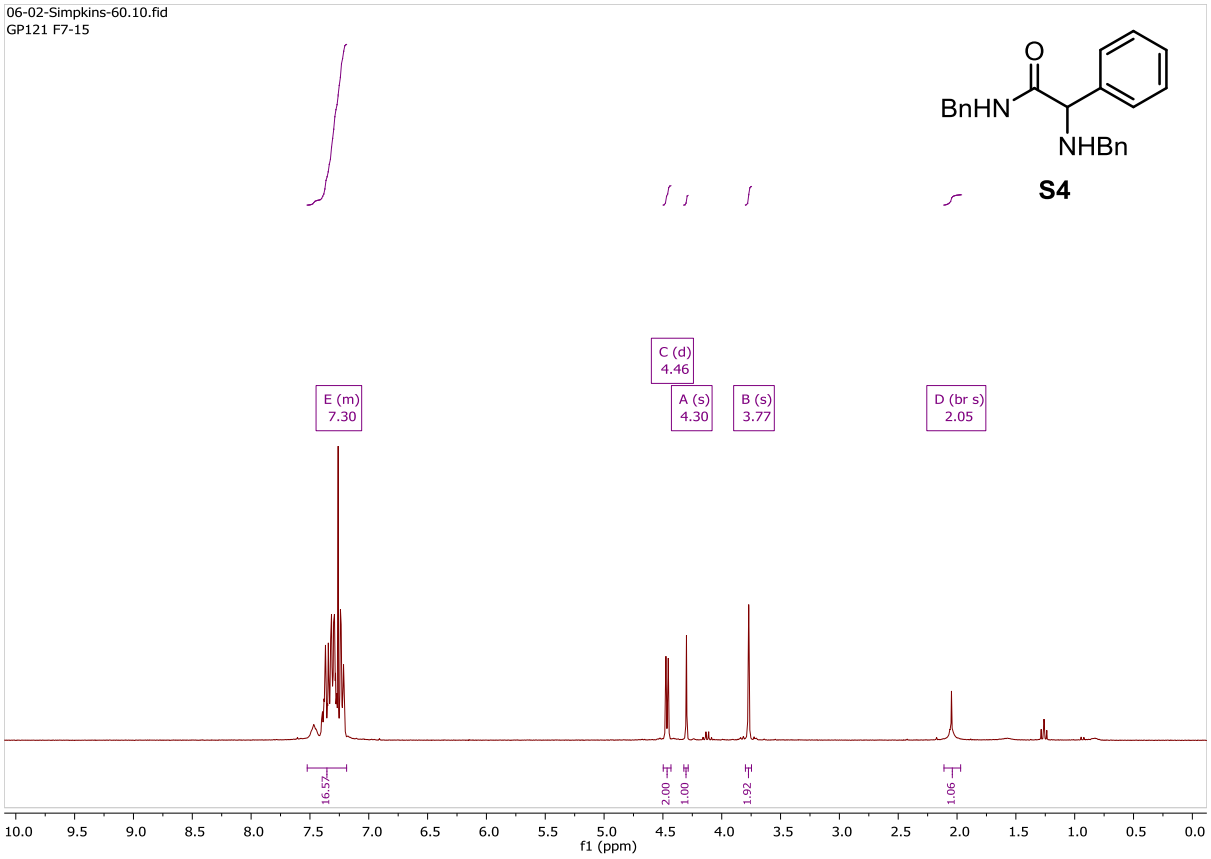
Appendix

^{1}H and ^{13}C NMR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NHBn
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4.46
E (m)
7.30
A (s)
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B (s)
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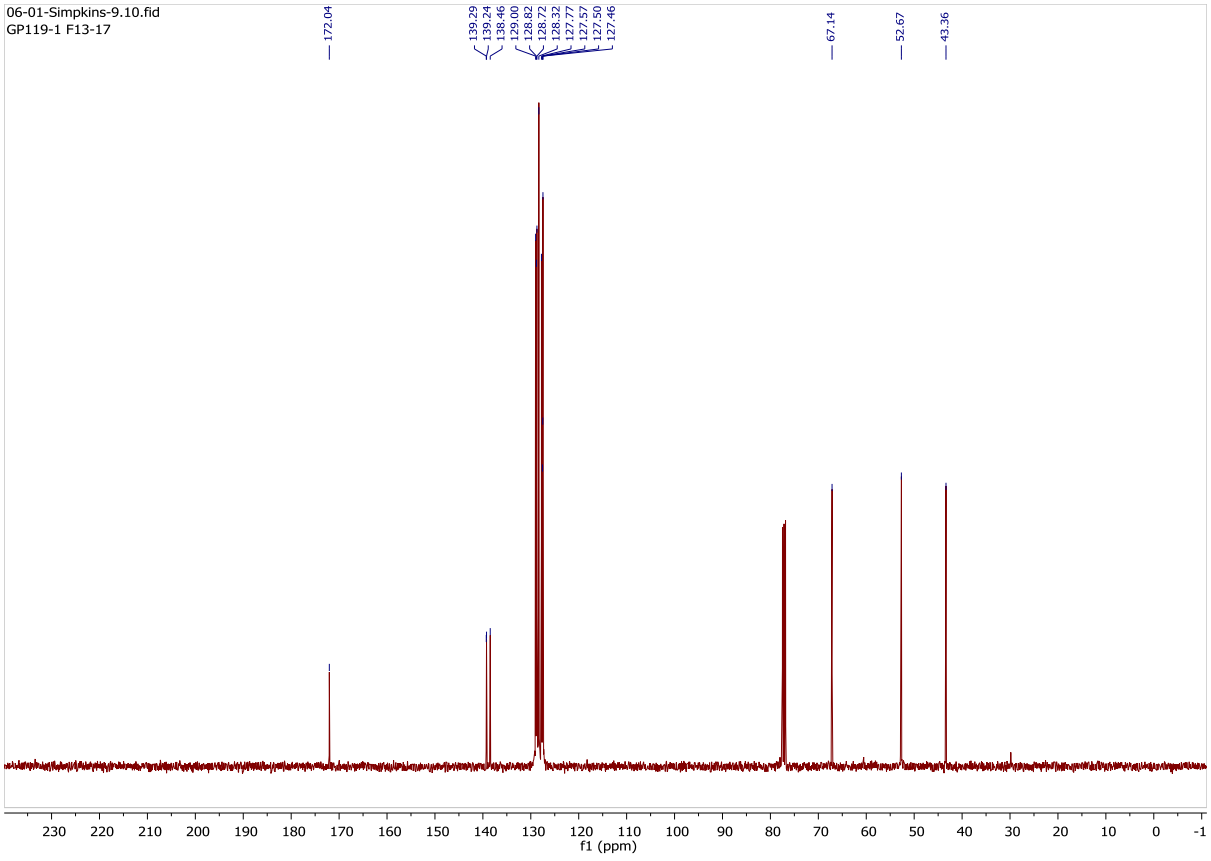
D (br s)
2.05
16.57
2.00
1.00
1.92
1.06
f1 (ppm)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127.46
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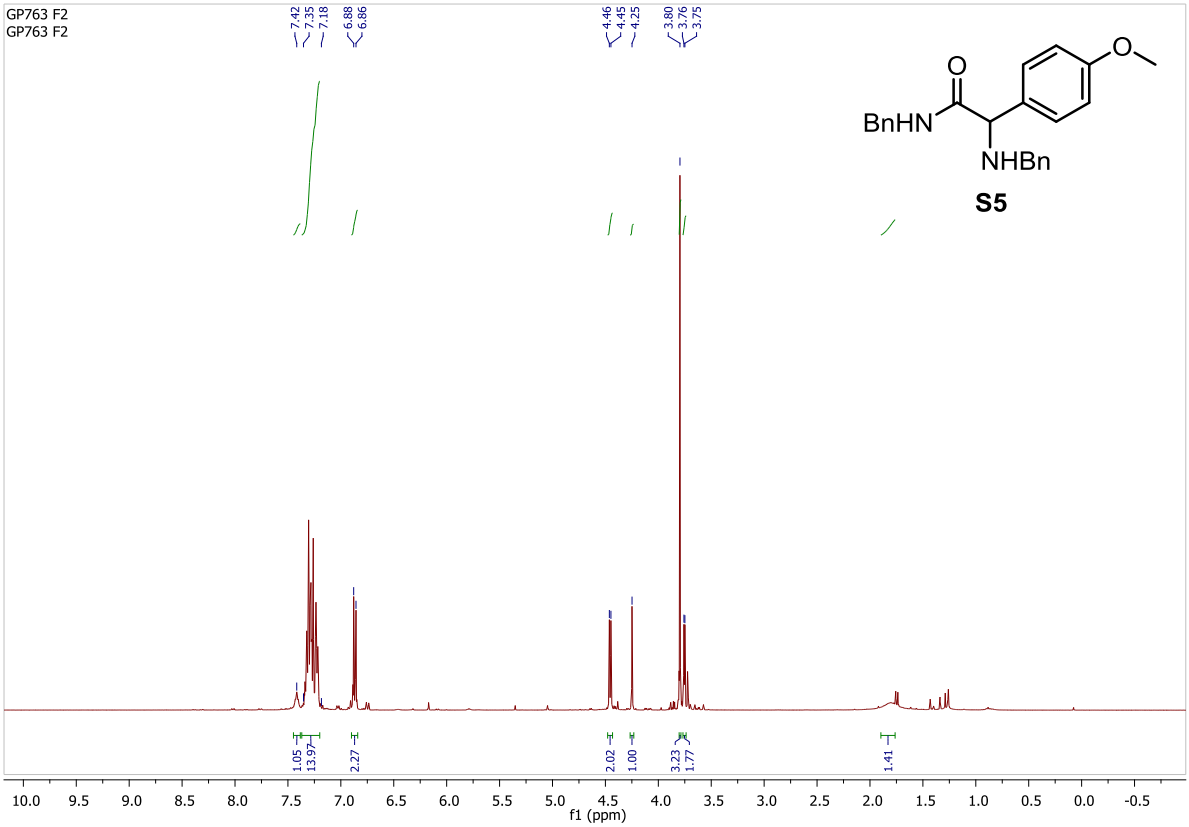
52.67
43.36
f1 (ppm)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GP763 F2
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7.35
7.18
6.88
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4.25
3.80
3.76
3.75
BnHN
NHBn
O
O
S5
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13.97
2.27
2.02
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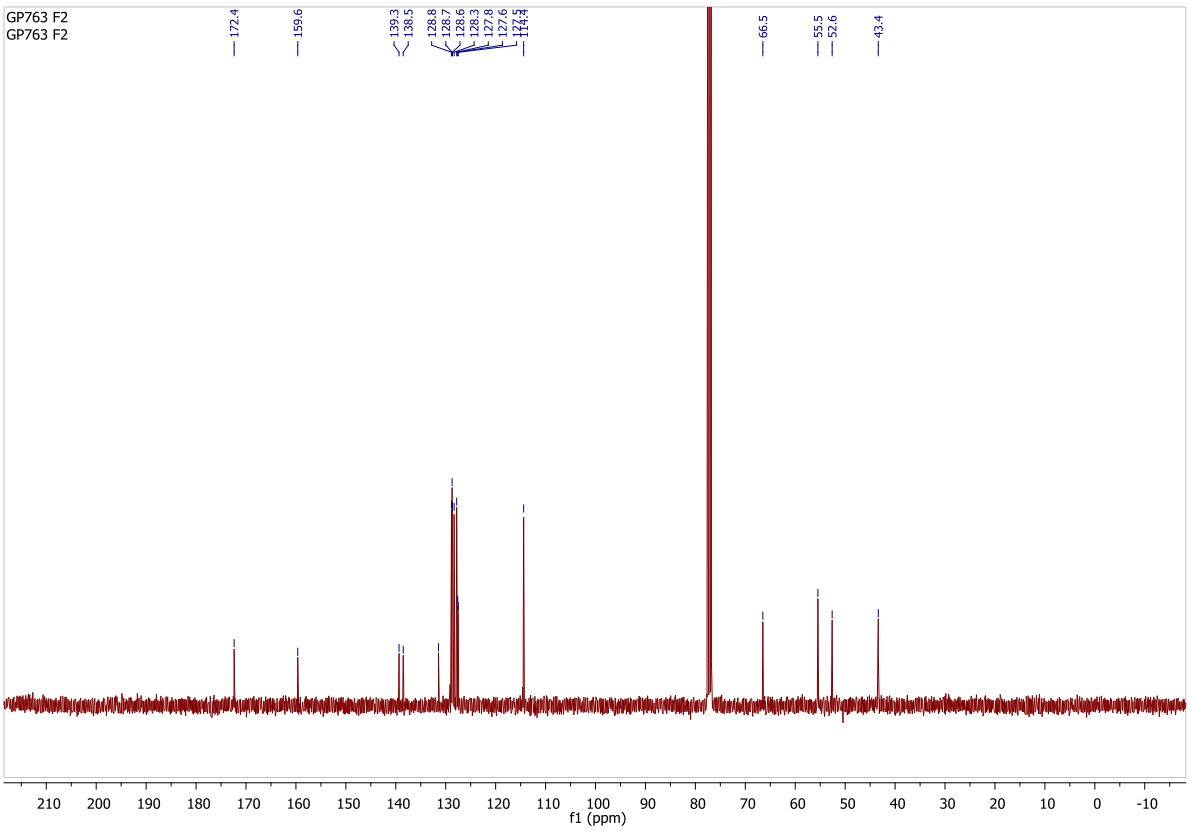
3.23
1.77
1.41
f1 (ppm)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GP763 F2
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66.5
55.5
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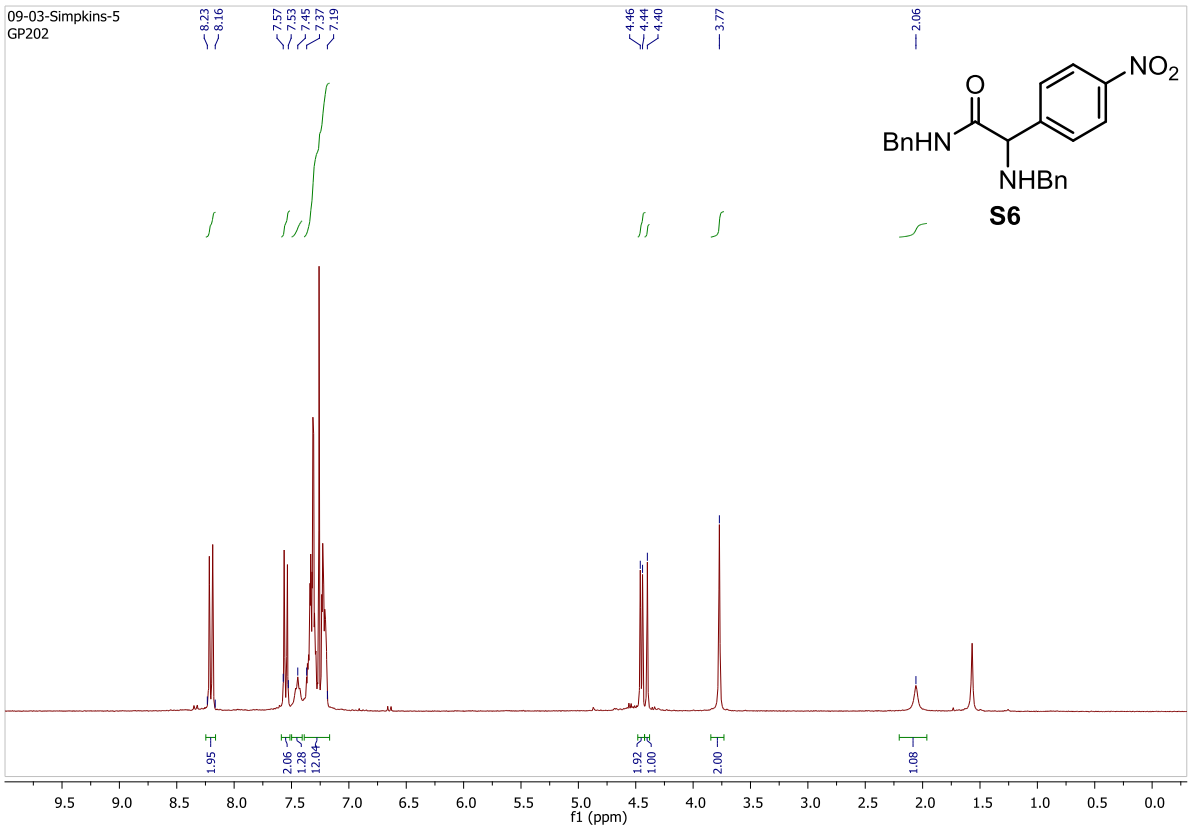
43.4
f1 (ppm)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7.57
7.53
7.45
7.37
7.19
4.46
4.44
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2.06
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2.06
1.28
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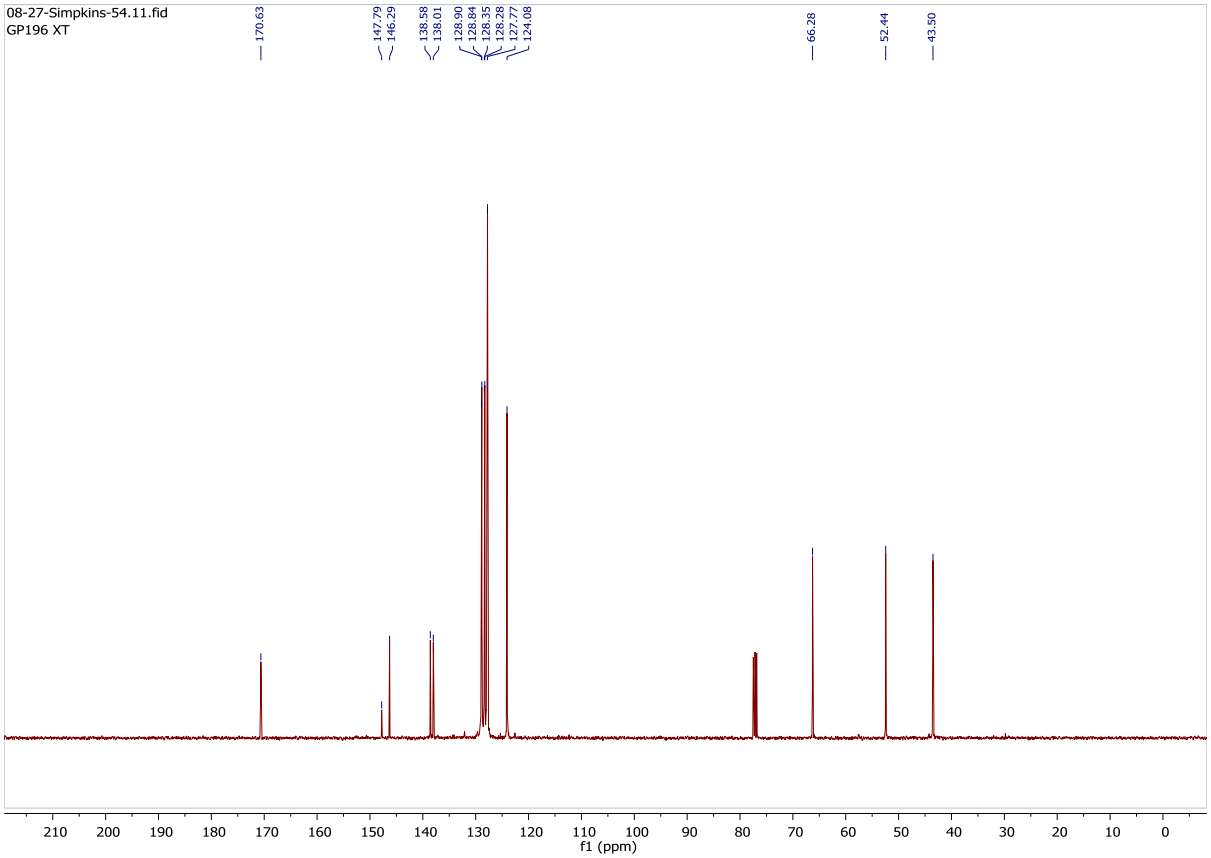
f1 (ppm)
NO2
O
BnHN
NHBn
S6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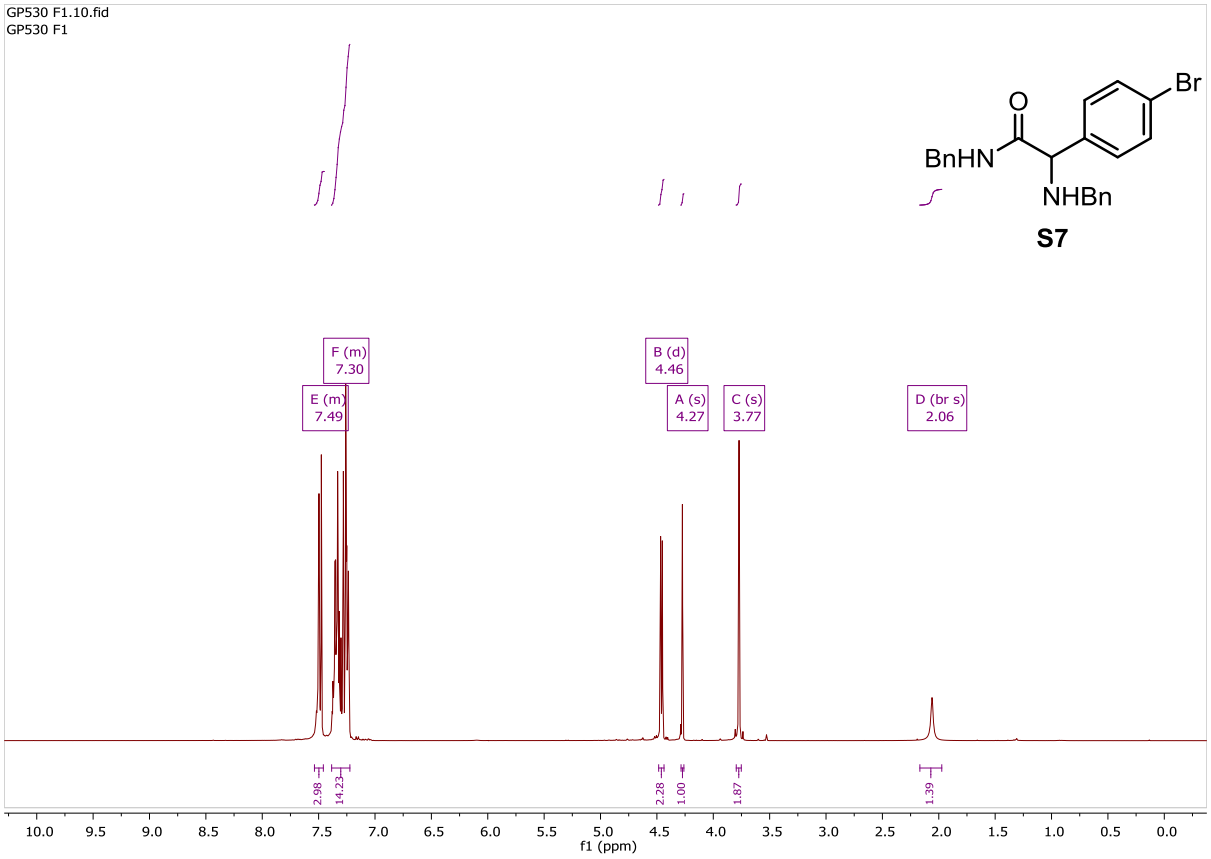
43.50
f1 (ppm)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NHBn
S7
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7.30
E (m)
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B (d)
4.46
A (s)
4.27
C (s)
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D (br s)
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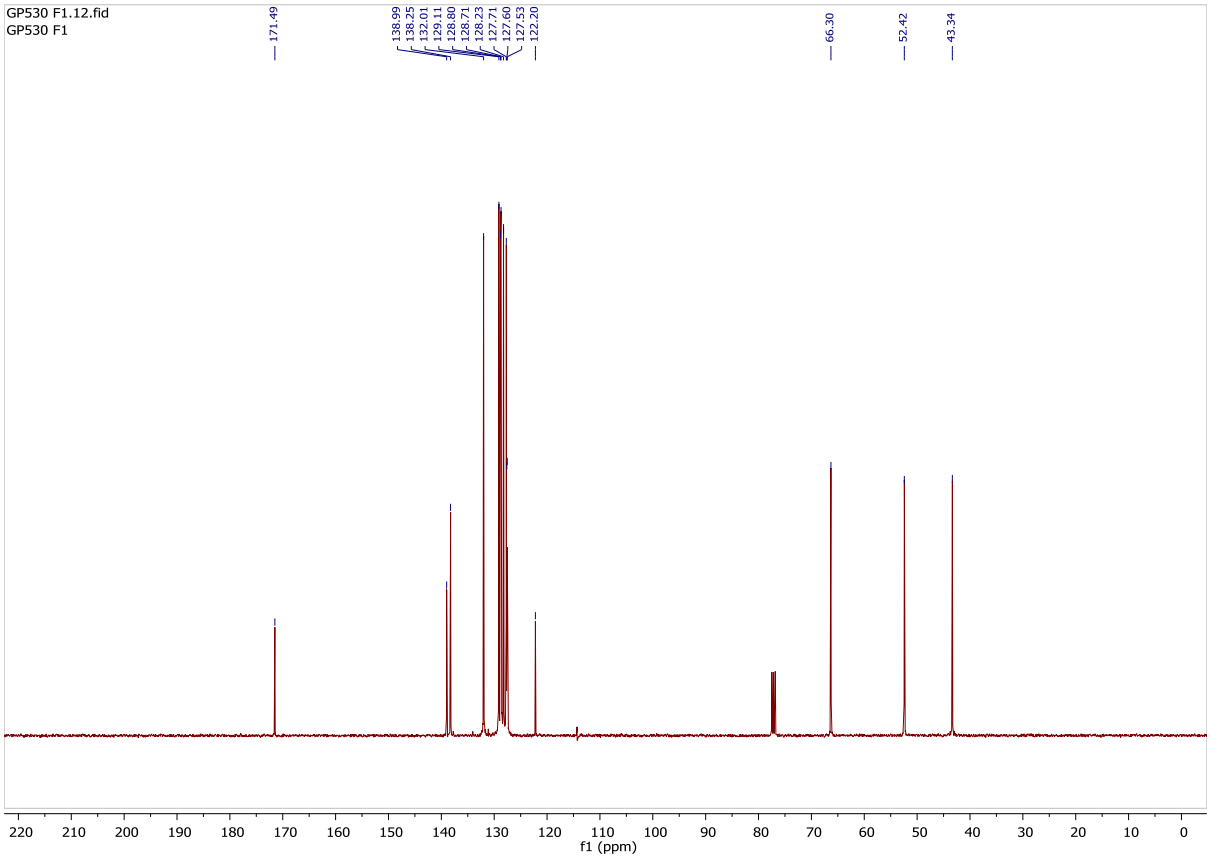
2.98
14.23
2.28
1.00
1.87
1.39
f1 (ppm)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GP530 F1
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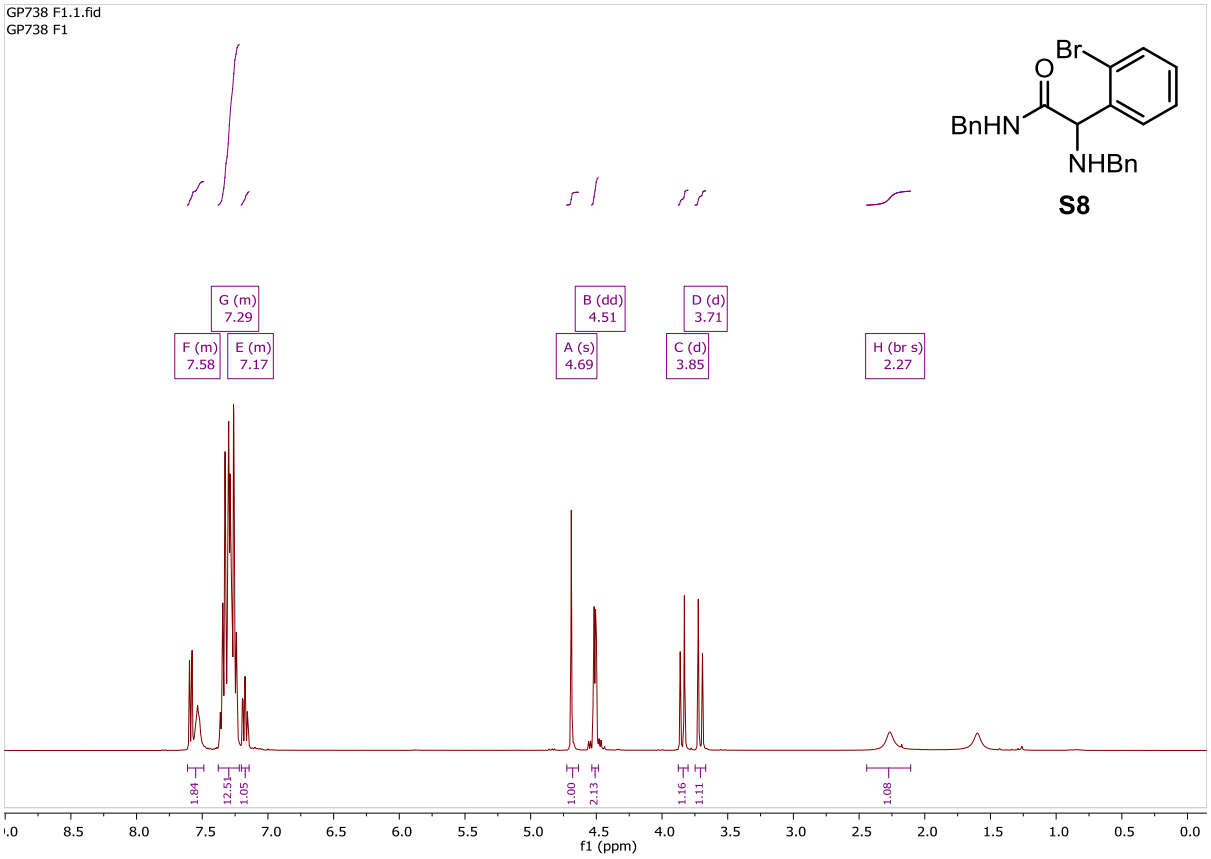
127.53
122.20
66.30
52.42
43.34
f1 (ppm)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O
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NHBn
S8
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A (s) 4.69
D (d) 3.71
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1.05
1.00
2.13
1.16
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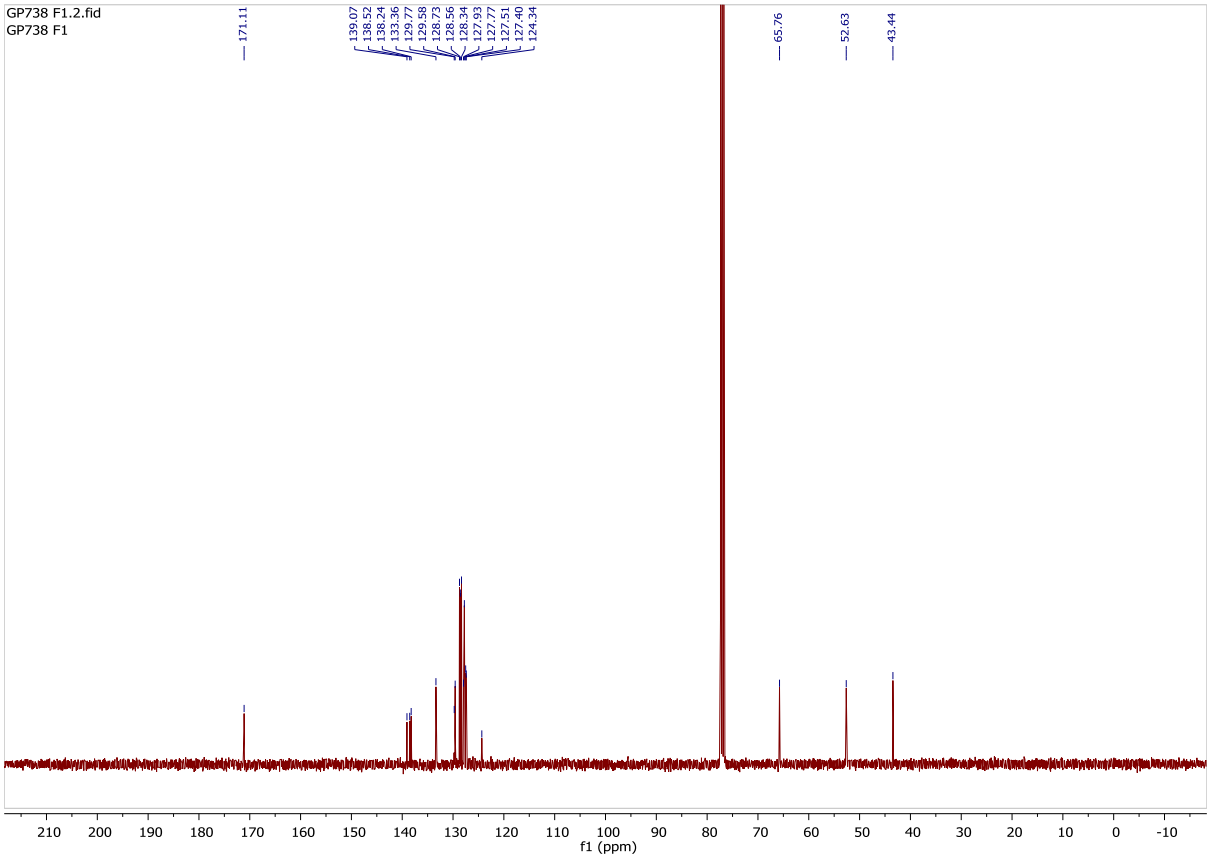
1.08
f1 (ppm)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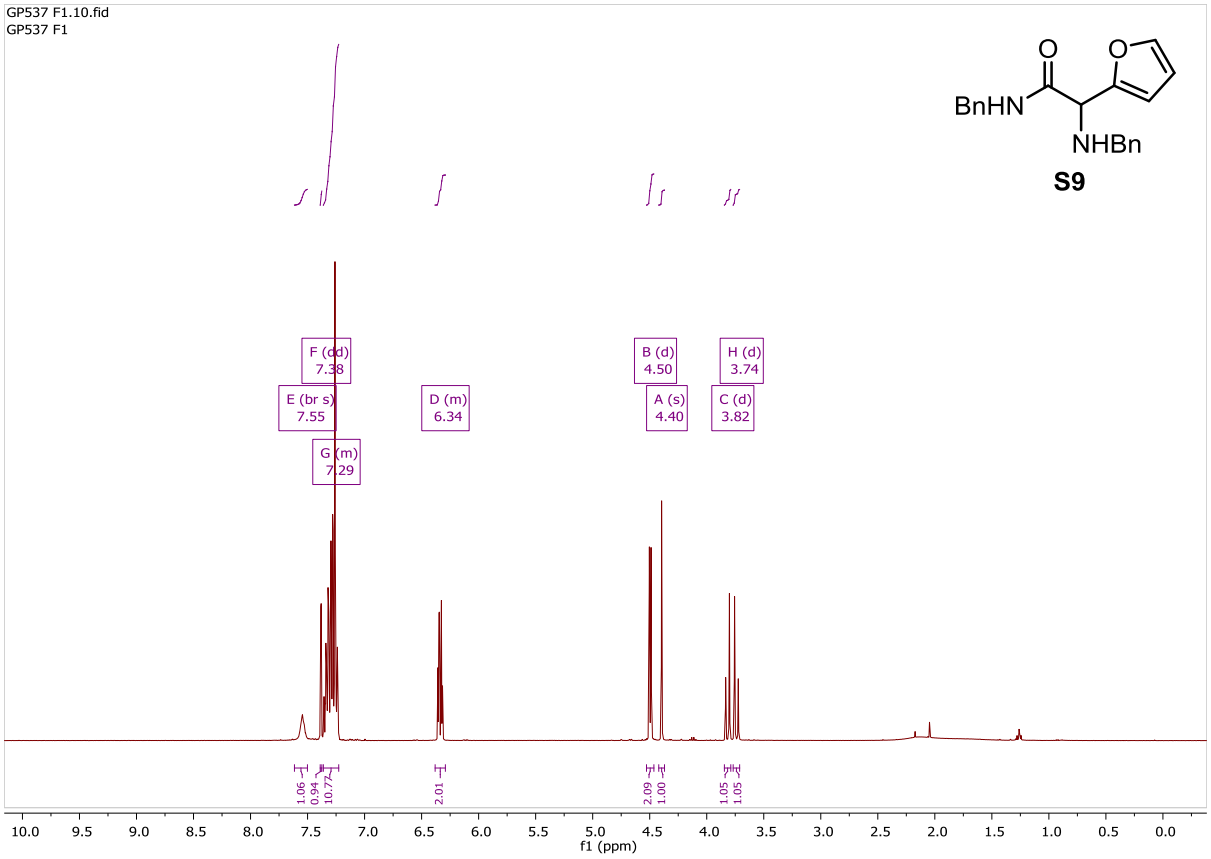
124.34
65.76
52.63
43.44
f1 (ppm)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NHBn
S9
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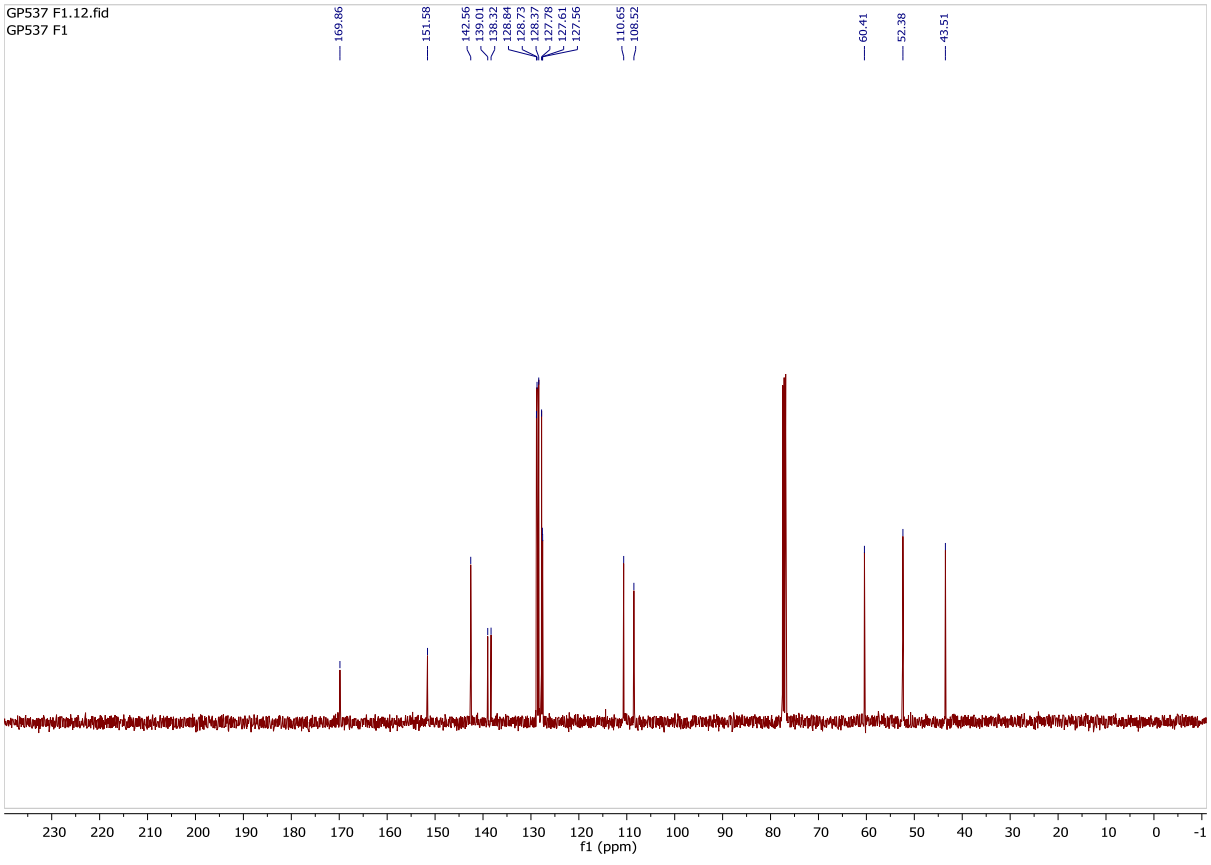
f1 (ppm)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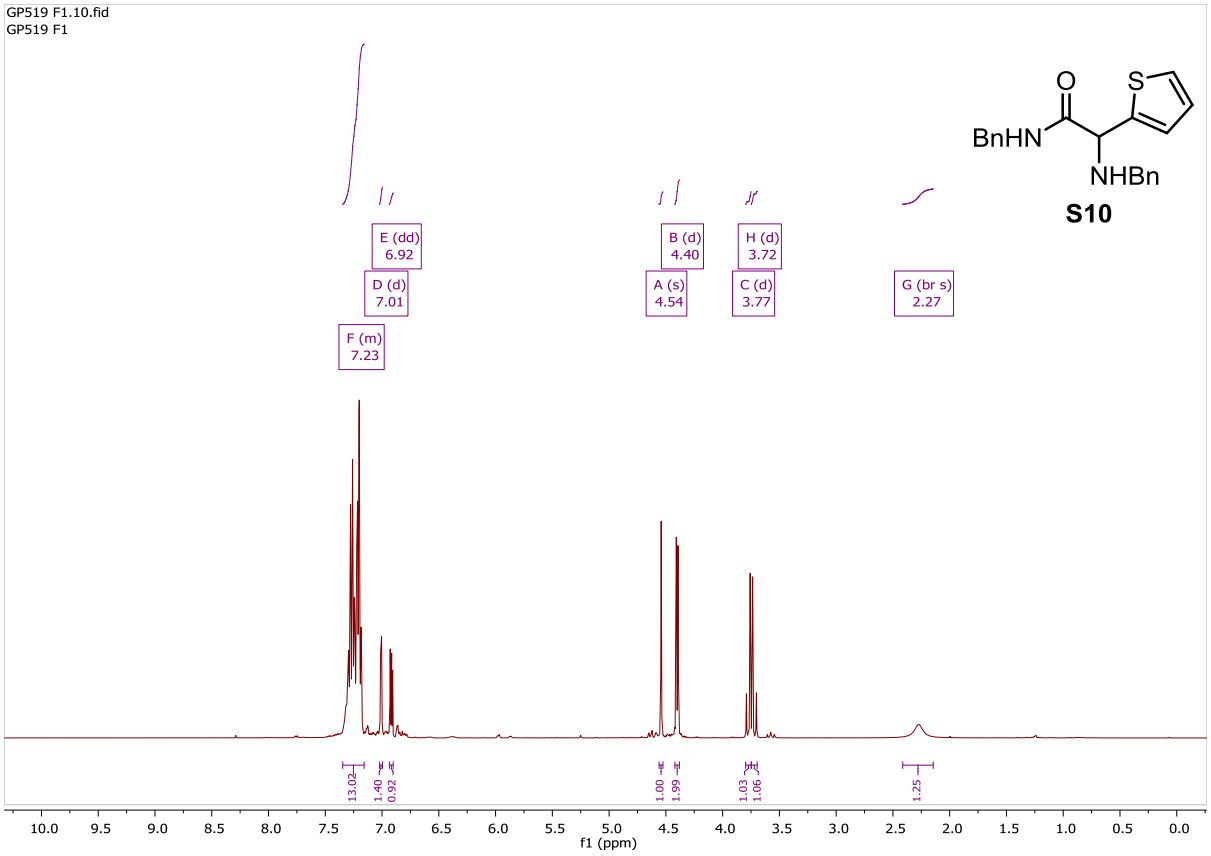
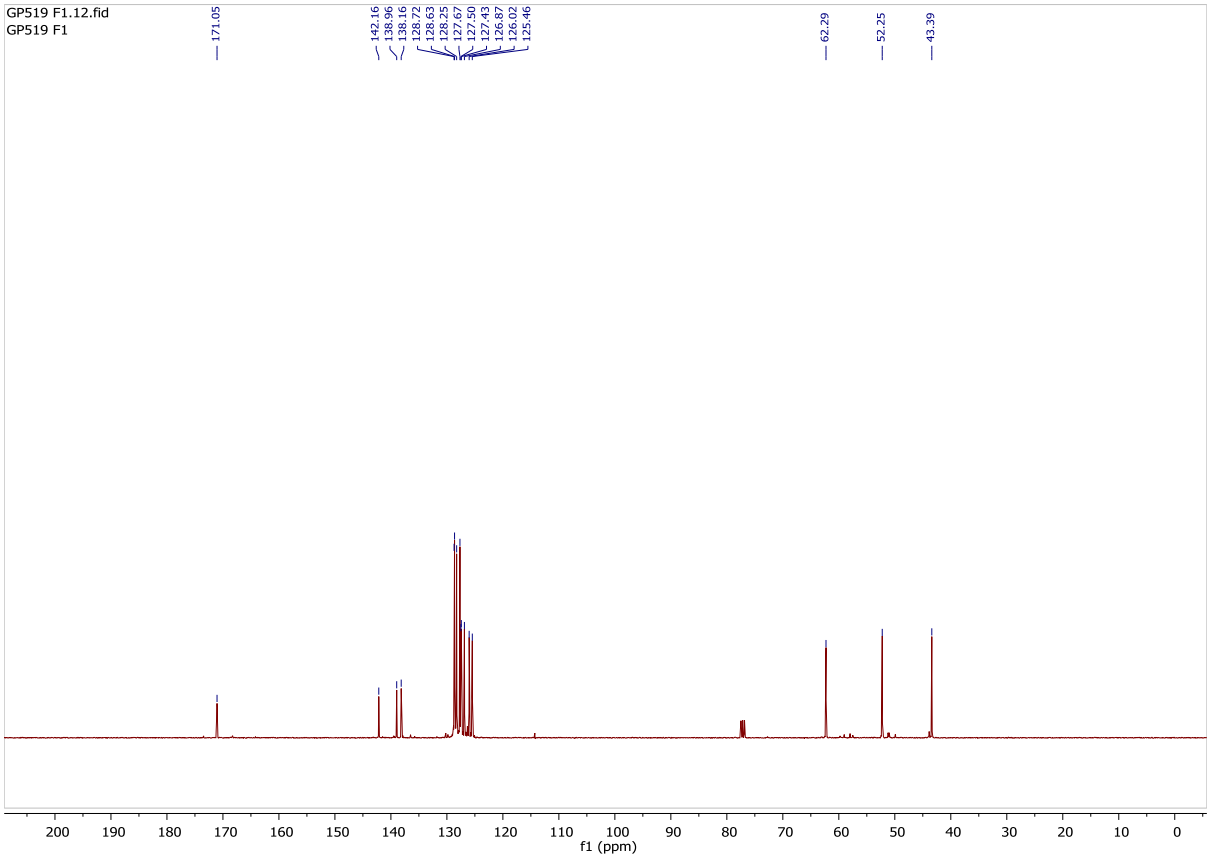
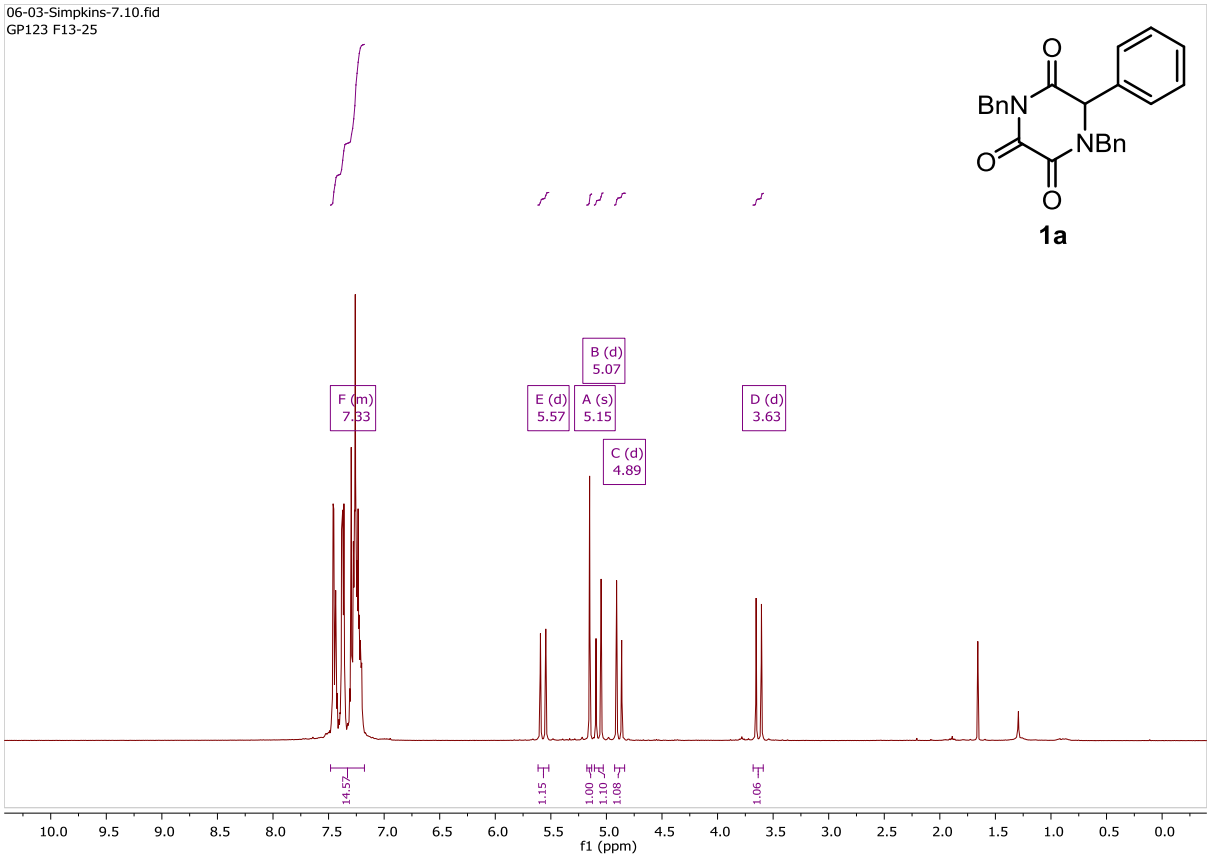
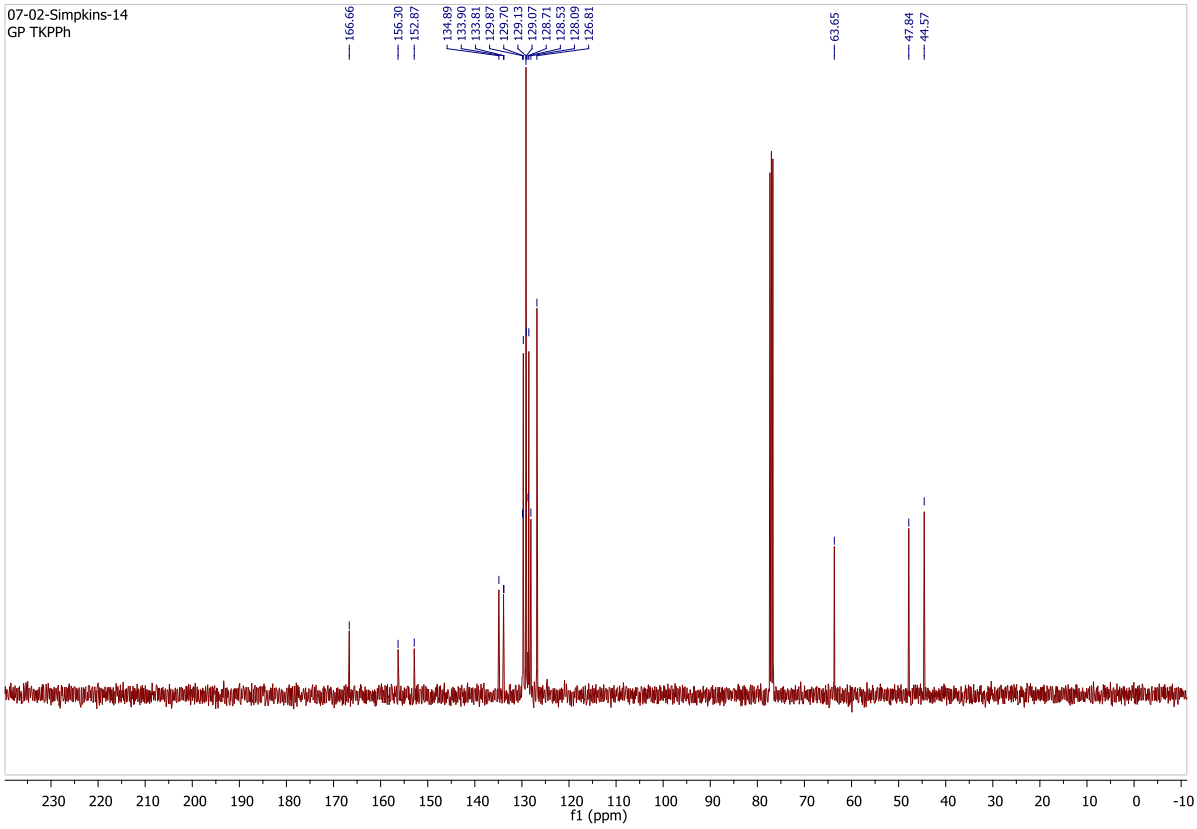
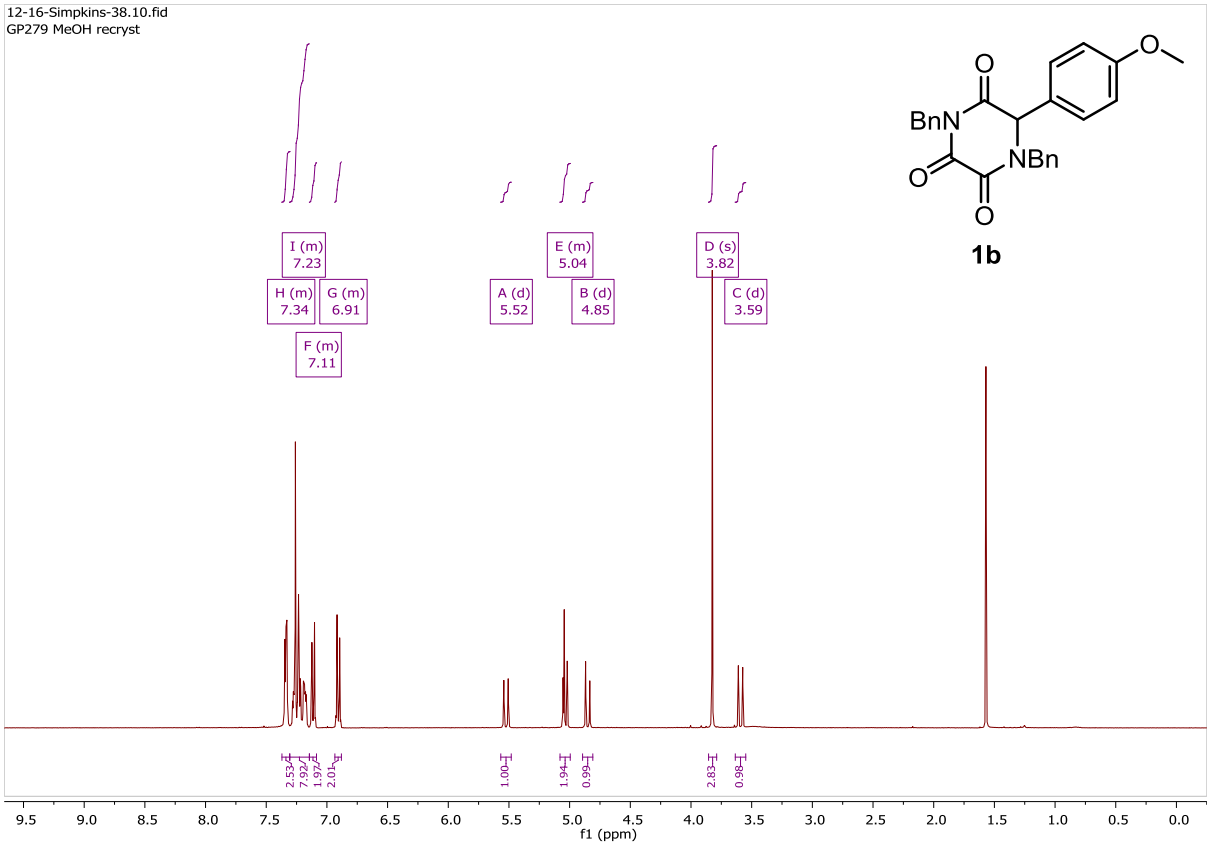
142.56
139.01
138.32
128.84
128.73
128.37
127.78
127.61
127.56
110.65
108.52
60.41
52.38
43.51
f1 (ppm)

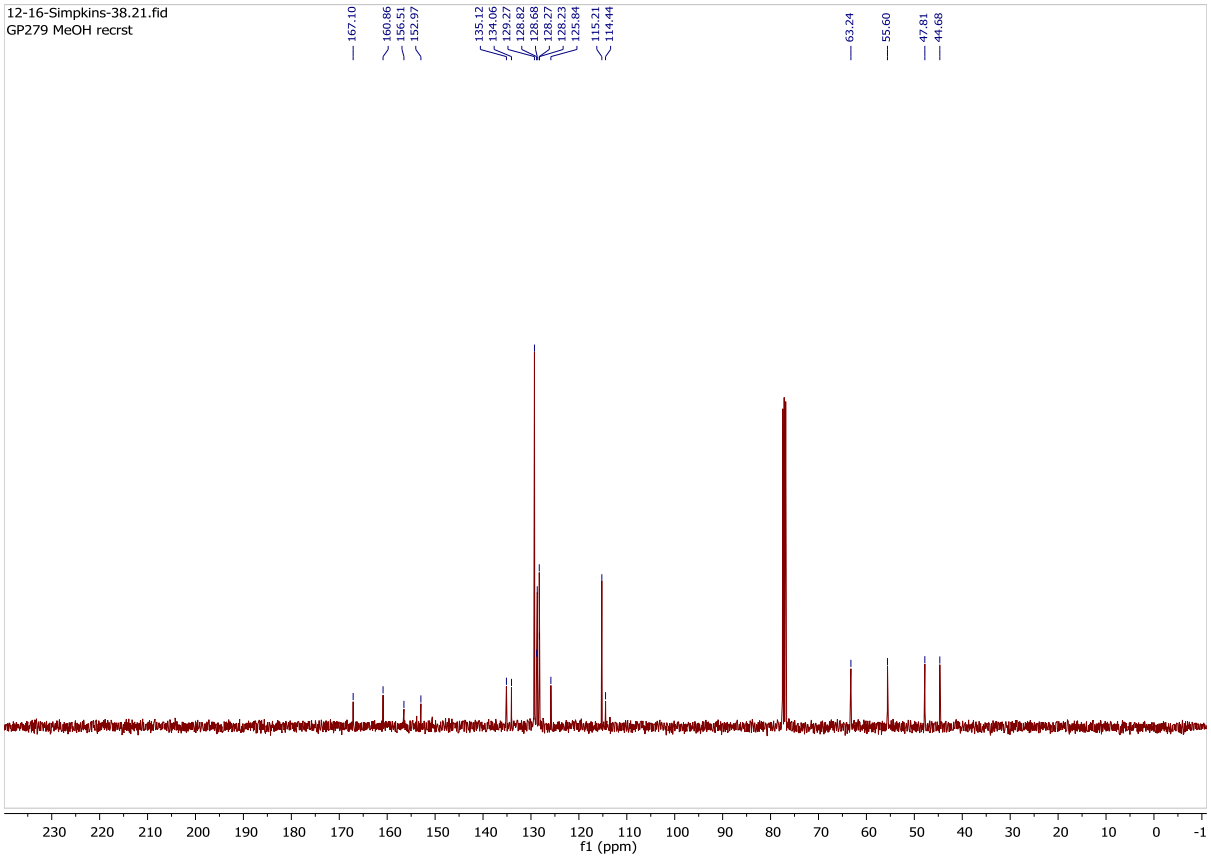

GP519 F1.10.fid
GP519 F1
O
S
BnHN
NHBn
S10
E (dd)
6.92
D (d)
7.01
F (m)
7.23
B (d)
4.40
A (s)
4.54
H (d)
3.72
C (d)
3.77
G (br s)
2.27
13.02
1.40
0.92
1.00
1.99
1.03
1.06
1.25
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

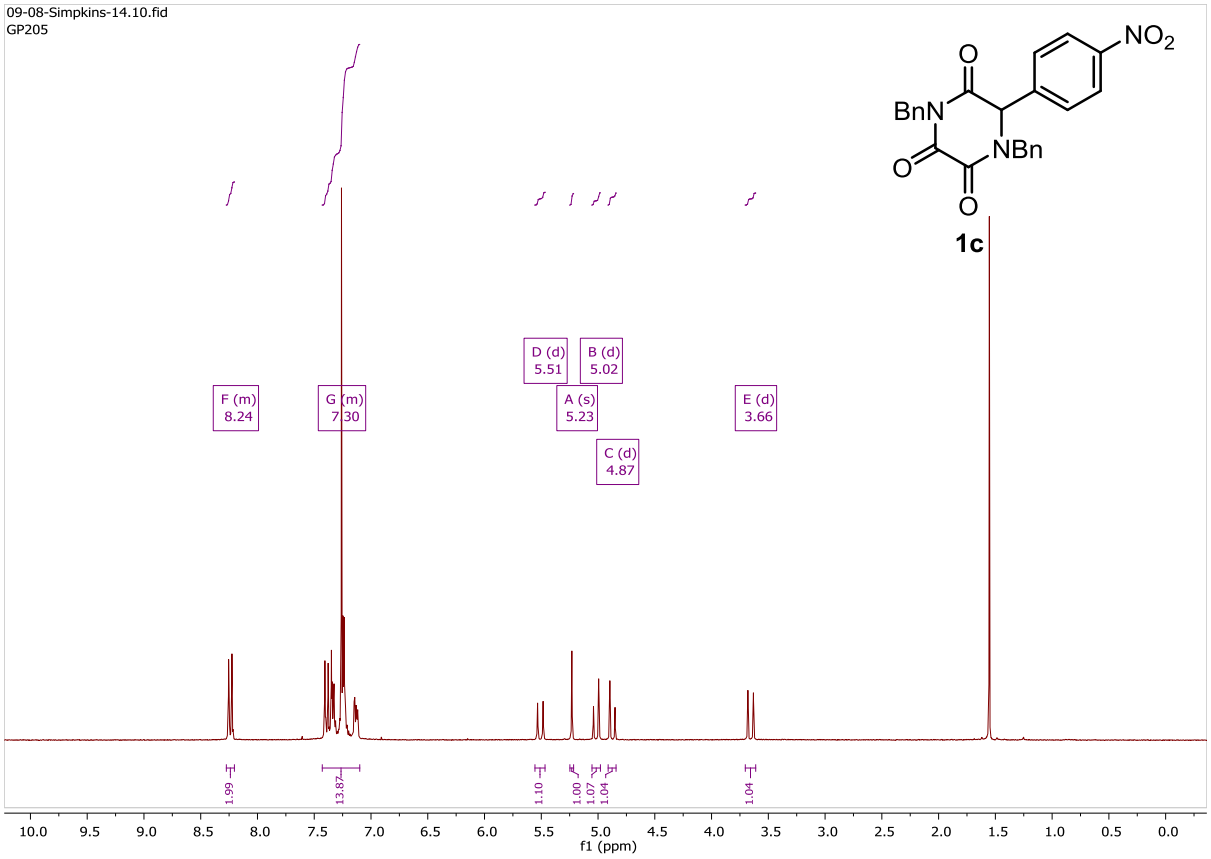

GP519 F1.12.fid
GP519 F1
171.05
142.16
138.96
138.16
128.72
128.63
128.25
127.67
127.50
127.43
126.87
126.02
125.46
62.29
52.25
43.39
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

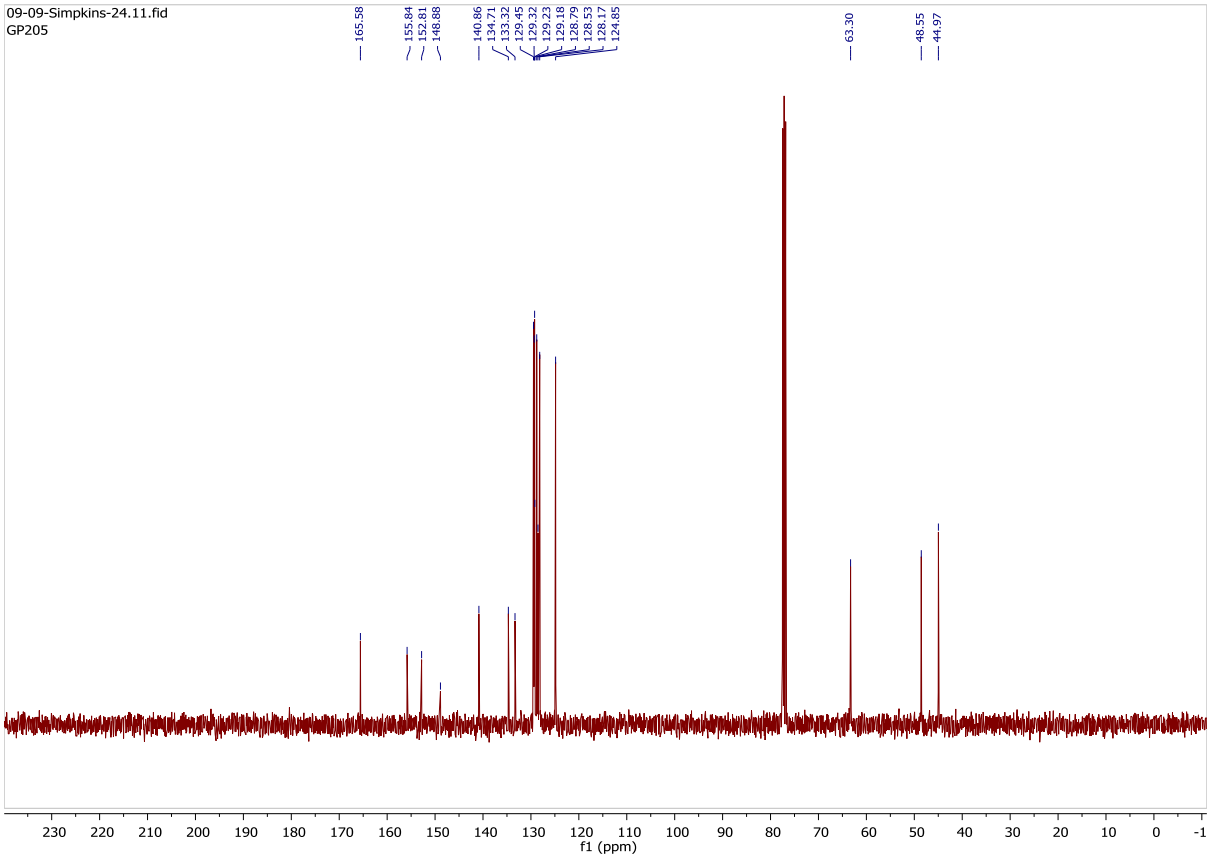

06-03-Simpkins-7.10.fid
GP123 F13-25
BnN
NBn
O
O
O
1a
F (m)
7.33
E (d)
5.57
A (s)
5.15
B (d)
5.07
C (d)
4.89
D (d)
3.63
14.57
1.15
1.00
1.10
1.08
1.06
f1 (ppm)

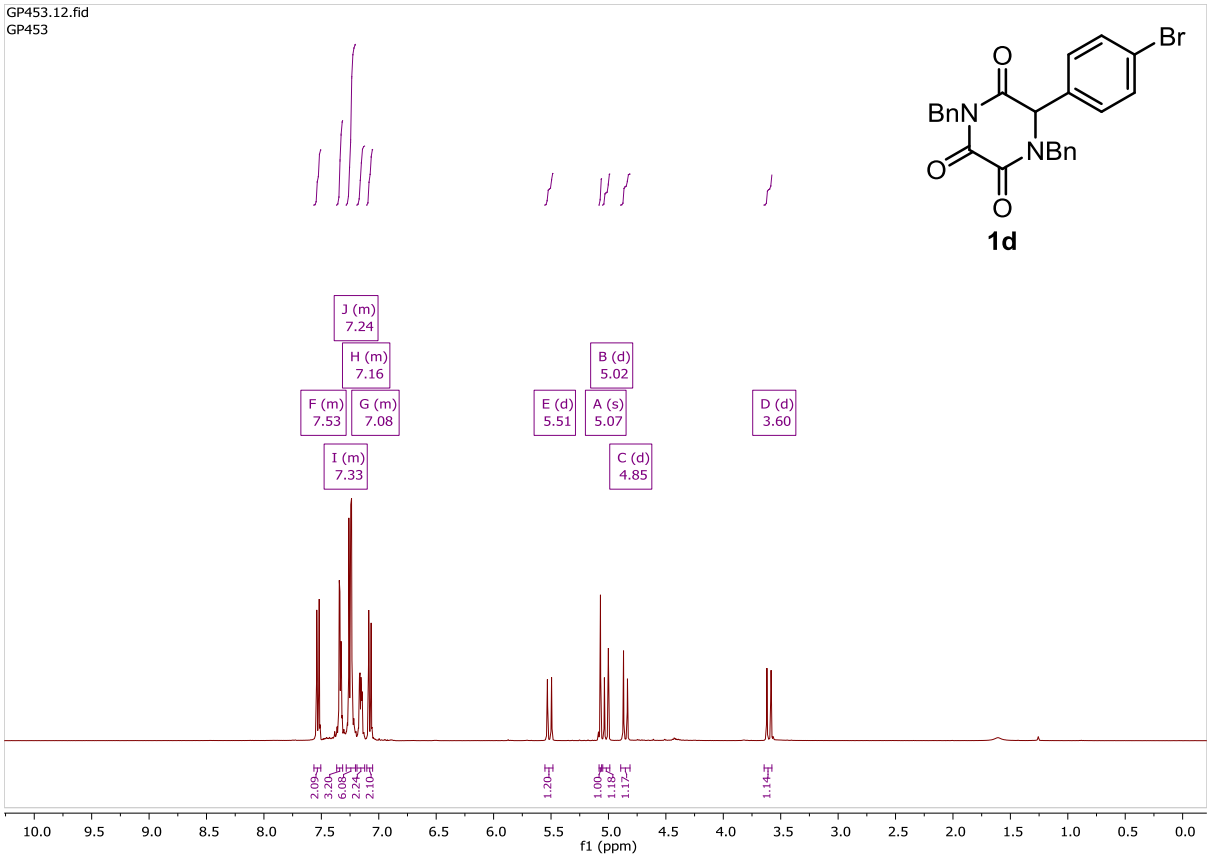

07-02-Simpkins-14
GP TKPPh
166.66
156.30
152.87
134.89
133.90
133.81
129.87
129.70
129.13
129.07
128.71
128.53
128.09
126.81
63.65
47.84
44.57
f1 (ppm)

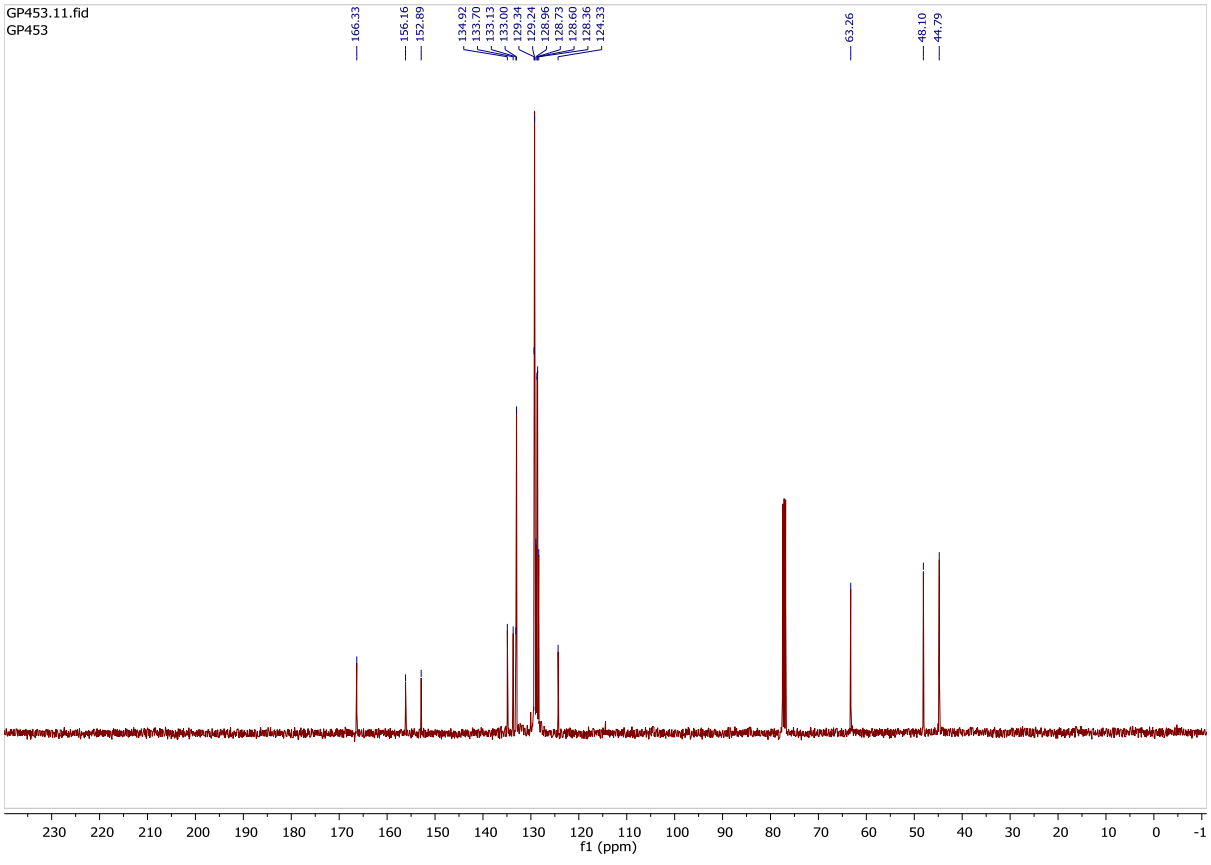

12-16-Simpkins-38.10.fid
GP279 MeOH recryst
I (m) 7.23
H (m) 7.34
G (m) 6.91
F (m) 7.11
A (d) 5.52
E (m) 5.04
B (d) 4.85
D (s) 3.82
C (d) 3.59
BnN
NBn
O
O
O
O
1b
f1 (ppm)

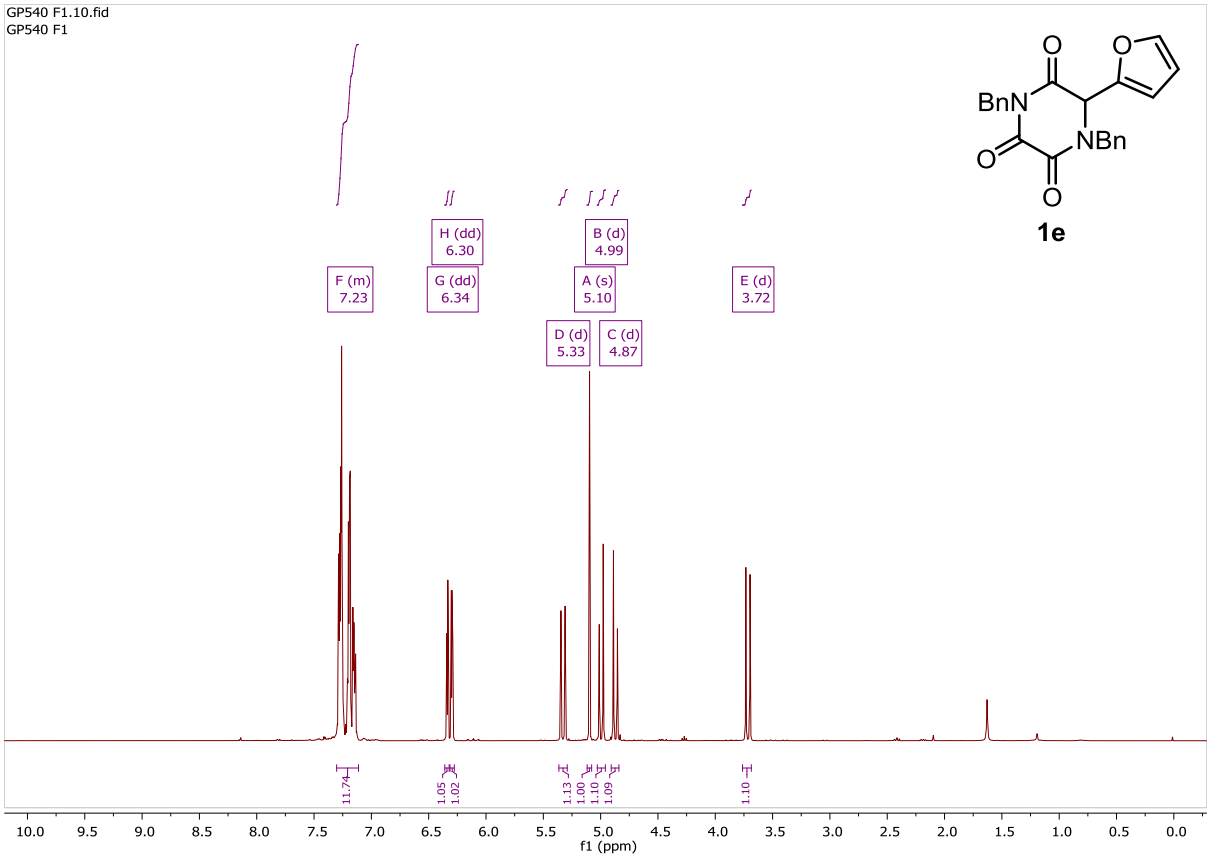

12-16-Simpkins-38.21.fid
GP279 MeOH recrst
167.10
160.86
156.51
152.97
135.12
134.06
129.27
128.82
128.68
128.27
128.23
125.84
115.21
114.44
63.24
55.60
47.81
44.68
f1 (ppm)

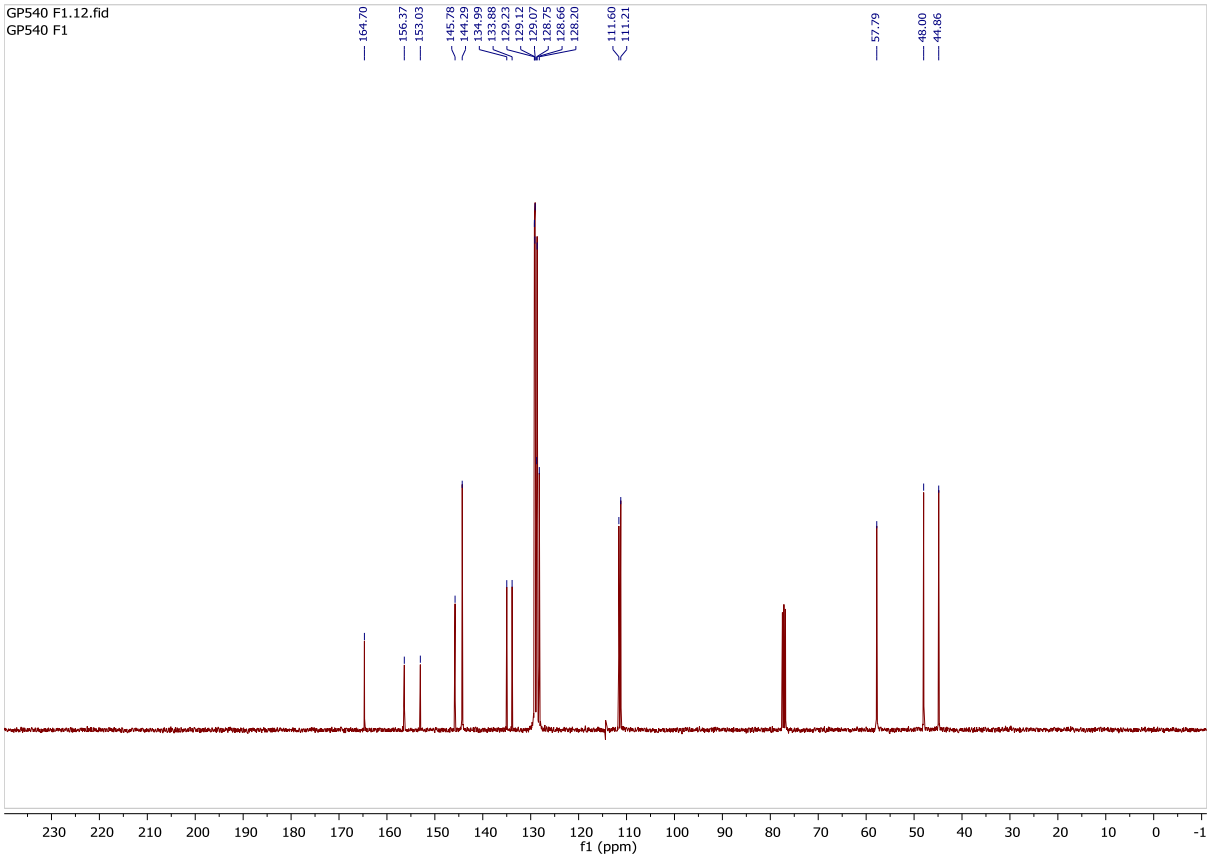

09-08-Simpkins-14.10.fid
GP205
NO2
BnN
NBn
O
O
O
1c
F (m)
8.24
G (m)
7.30
D (d)
5.51
B (d)
5.02
A (s)
5.23
C (d)
4.87
E (d)
3.66
1.99
13.87
1.10
1.00
1.07
1.04
1.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

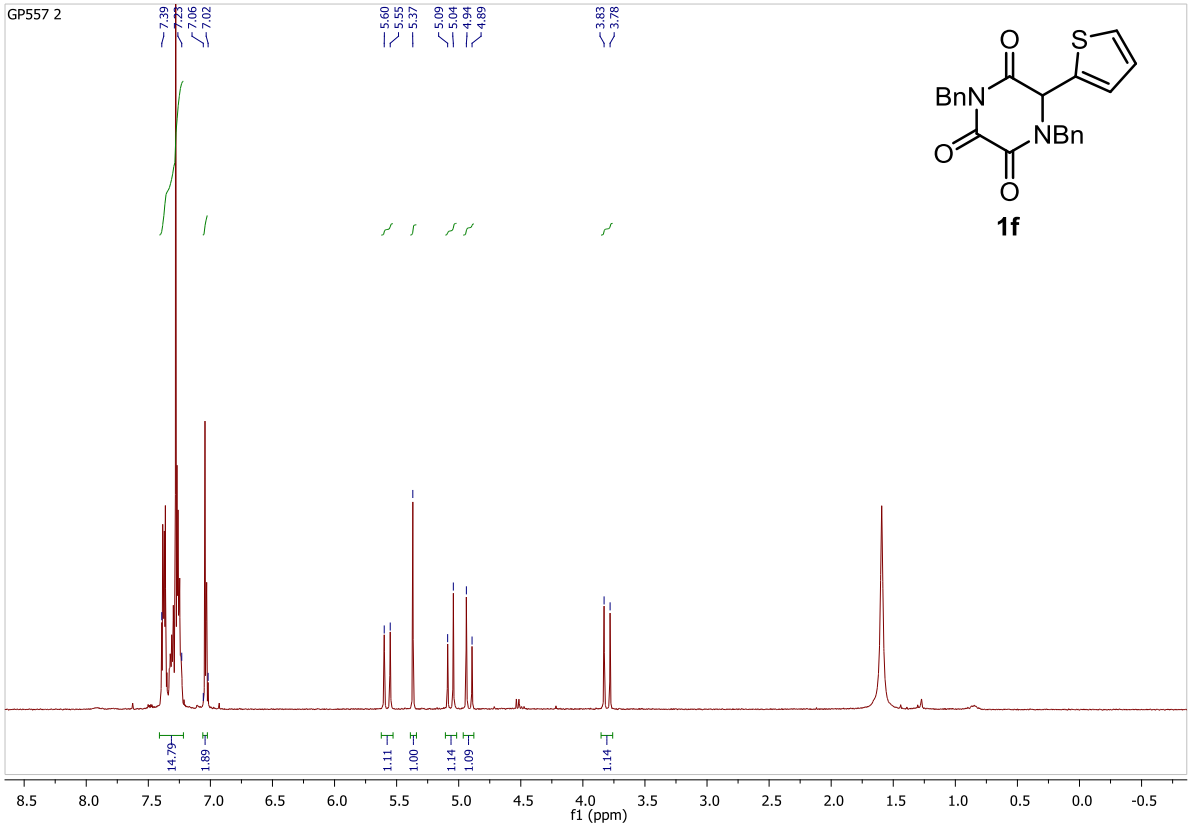

09-09-Simpkins-24.11.fid
GP205
165.58
155.84
152.81
148.88
140.86
134.71
133.32
129.45
129.32
129.23
129.18
128.79
128.53
128.17
124.85
63.30
48.55
44.97
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

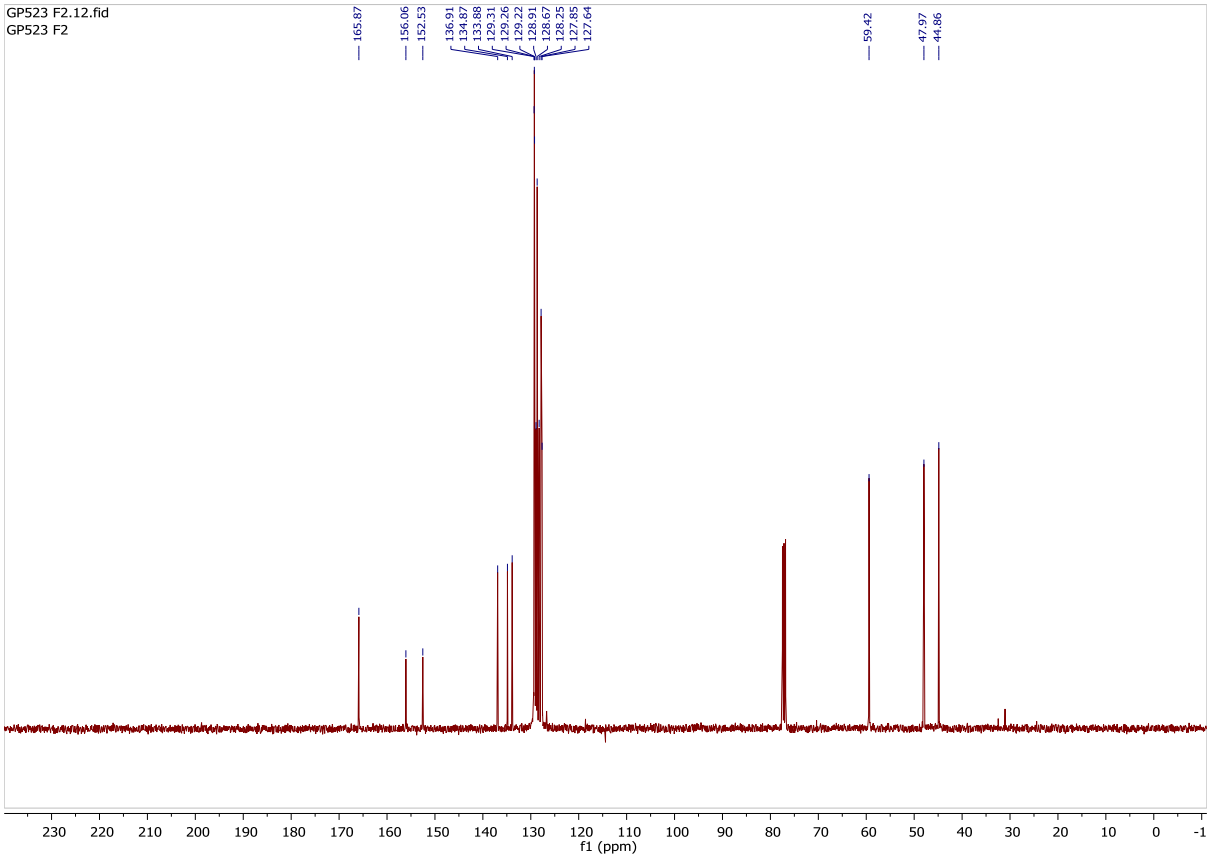

GP453.12.fid
GP453
Br
BnN
NBn
O
O
O
O
1d
J (m) 7.24
H (m) 7.16
F (m) 7.53
G (m) 7.08
I (m) 7.33
E (d) 5.51
B (d) 5.02
A (s) 5.07
C (d) 4.85
D (d) 3.60
2.09
3.20
6.08
2.24
2.10
1.20
1.00
1.18
1.17
1.14
f1 (ppm)

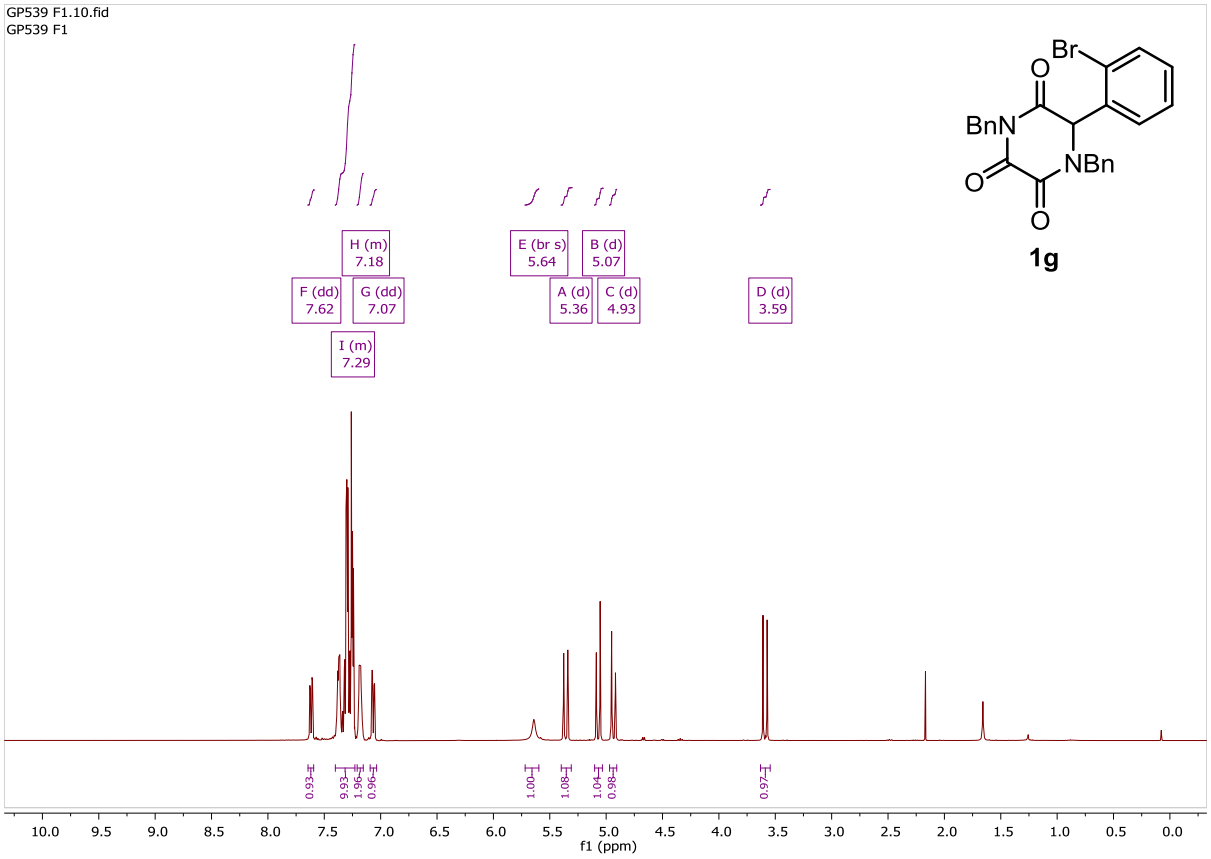

GP453.11.fid
GP453
166.33
156.16
152.89
134.92
133.70
133.13
133.00
129.34
129.24
128.96
128.73
128.60
128.36
124.33
63.26
48.10
44.79
f1 (ppm)

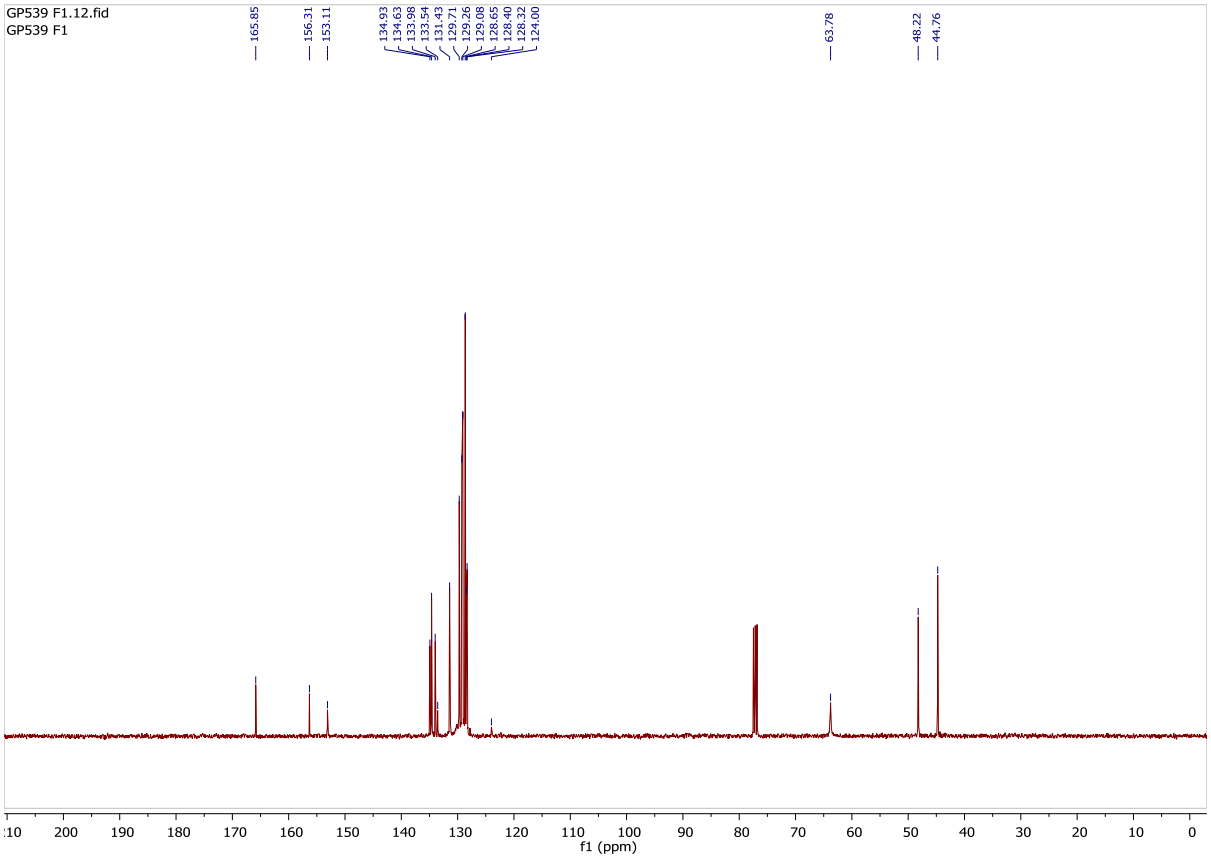

GP540 F1.10.fid
GP540 F1
BnN
NBn
O
O
O
O
O
1e
F (m)
7.23
G (dd)
6.34
H (dd)
6.30
D (d)
5.33
A (s)
5.10
C (d)
4.87
B (d)
4.99
E (d)
3.72
11.74
1.05
1.02
1.13
1.00
1.10
1.09
1.10
f1 (ppm)

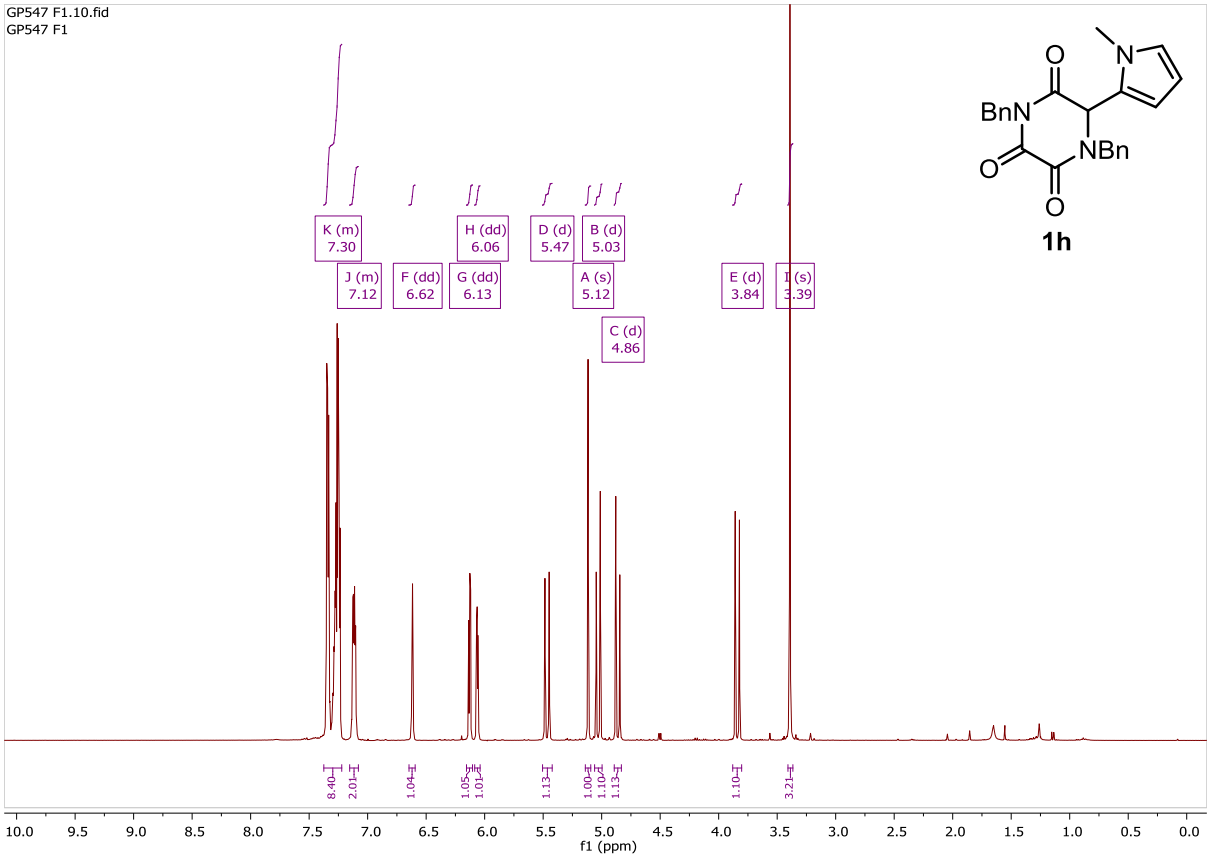

GP540 F1.12.fid
GP540 F1
164.70
156.37
153.03
145.78
144.29
134.99
133.88
129.23
129.12
129.07
128.75
128.66
128.20
111.60
111.21
57.79
48.00
44.86
f1 (ppm)

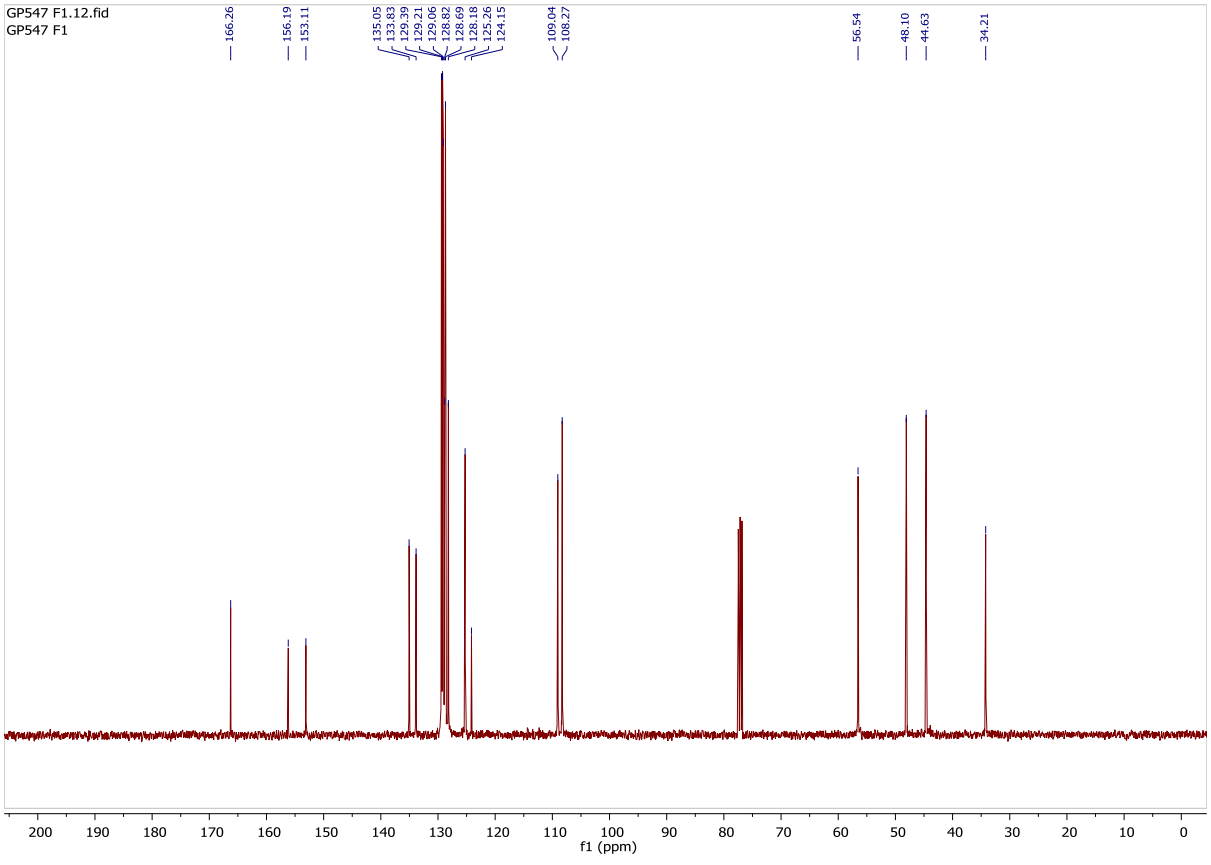

GP557 2
7.39
7.23
7.06
7.02
5.60
5.55
5.37
5.09
5.04
4.94
4.89
3.83
3.78
14.79
1.89
1.11
1.00
1.14
1.09
1.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
BnN
NBn
O
S
1f

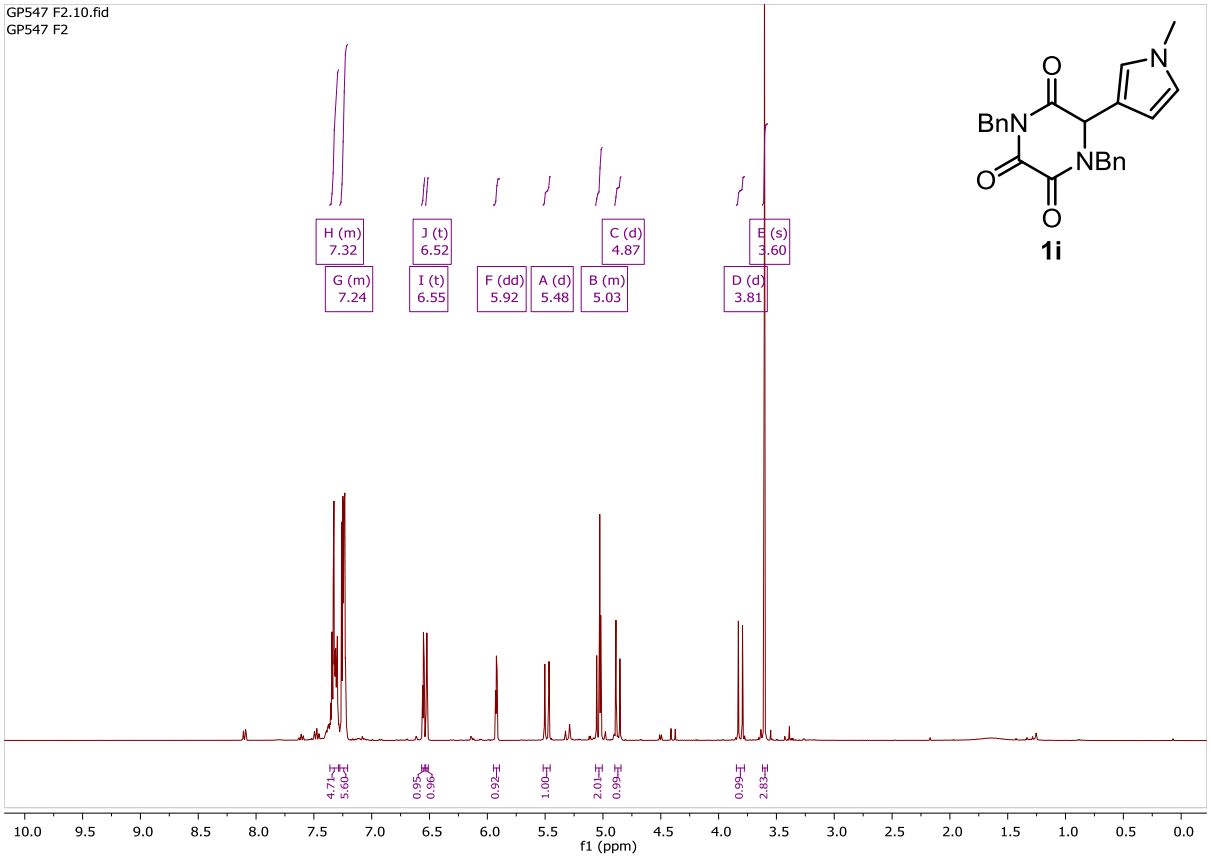

GP523 F2.12.fid
GP523 F2
165.87
156.06
152.53
136.91
134.87
133.88
129.31
129.26
129.22
128.91
128.67
128.25
127.85
127.64
59.42
47.97
44.86
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


GP539 F1.10.fid
GP539 F1
Br
O
BnN
NBn
O
O
1g
H (m)
7.18
E (br s)
5.64
B (d)
5.07
F (dd)
7.62
G (dd)
7.07
A (d)
5.36
C (d)
4.93
D (d)
3.59
I (m)
7.29
0.93
9.93
1.96
0.96
1.00
1.08
1.04
0.98
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


GP539 F1.12.fid
GP539 F1
165.85
156.31
153.11
134.93
134.63
133.98
133.54
131.43
129.71
129.26
129.08
128.65
128.40
128.32
124.00
63.78
48.22
44.76
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

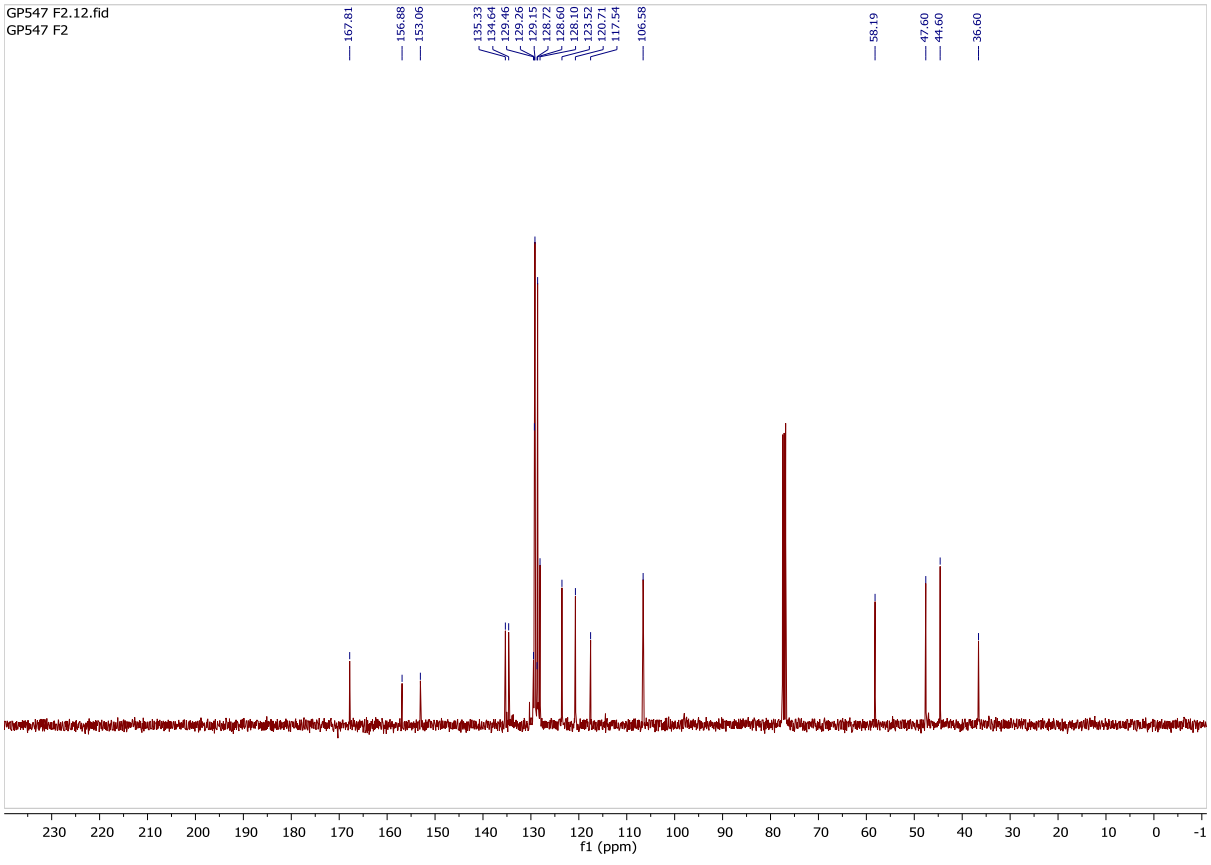

GP547 F1.10.fid
GP547 F1
K (m) 7.30
J (m) 7.12
F (dd) 6.62
G (dd) 6.13
H (dd) 6.06
D (d) 5.47
B (d) 5.03
A (s) 5.12
C (d) 4.86
E (d) 3.84
I (s) 3.39
8.40
2.01
1.04
1.05
1.01
1.13
1.00
1.10
1.13
1.10
3.21
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

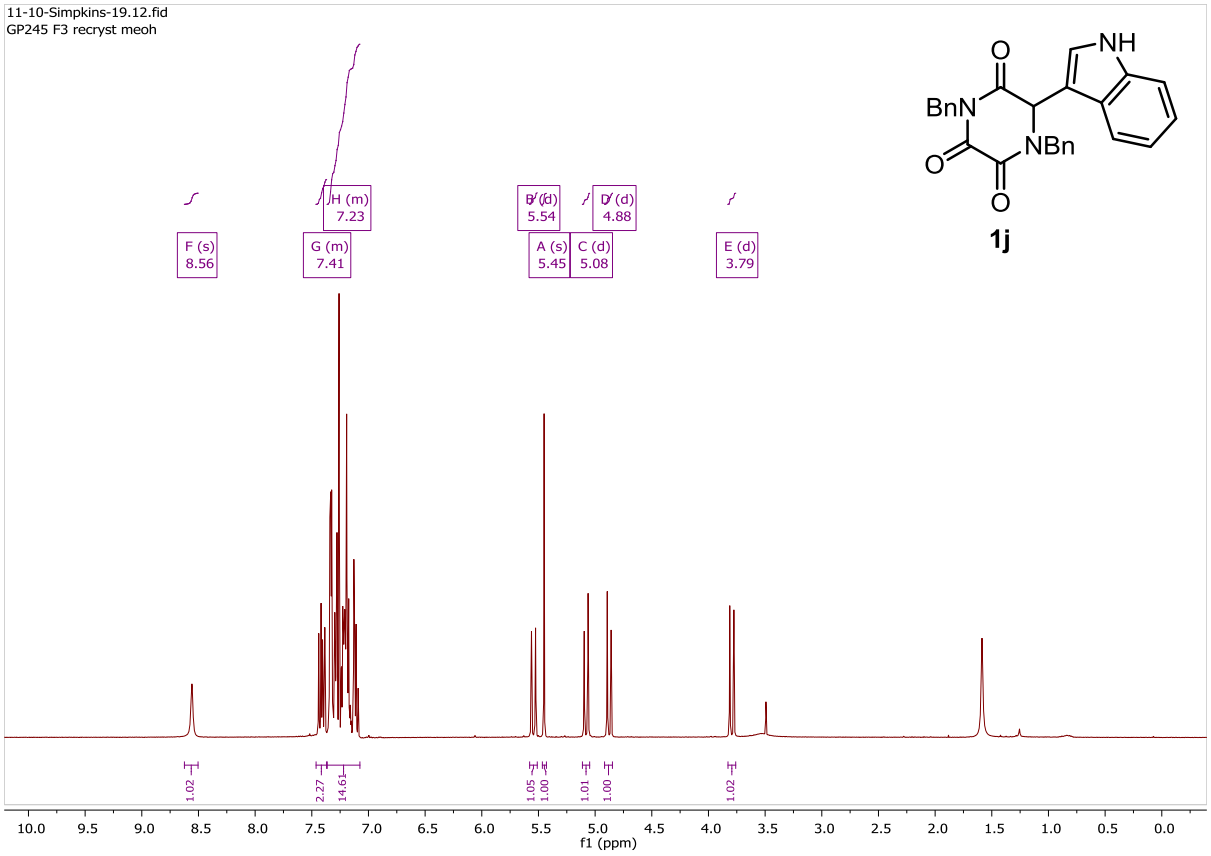

GP547 F1.12.fid
GP547 F1
166.26
156.19
153.11
135.05
133.83
129.39
129.21
129.06
128.82
128.69
128.18
125.26
124.15
109.04
108.27
56.54
48.10
44.63
34.21
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


GP547 F2.10.fid
GP547 F2
H (m) 7.32
G (m) 7.24
J (t) 6.52
I (t) 6.55
F (dd) 5.92
A (d) 5.48
C (d) 4.87
B (m) 5.03
E (s) 3.60
D (d) 3.81
4.71
5.60
0.95
0.96
0.92
1.00
2.01
0.99
0.99
2.83
f1 (ppm)

O
N
BnN
NBn
O
O

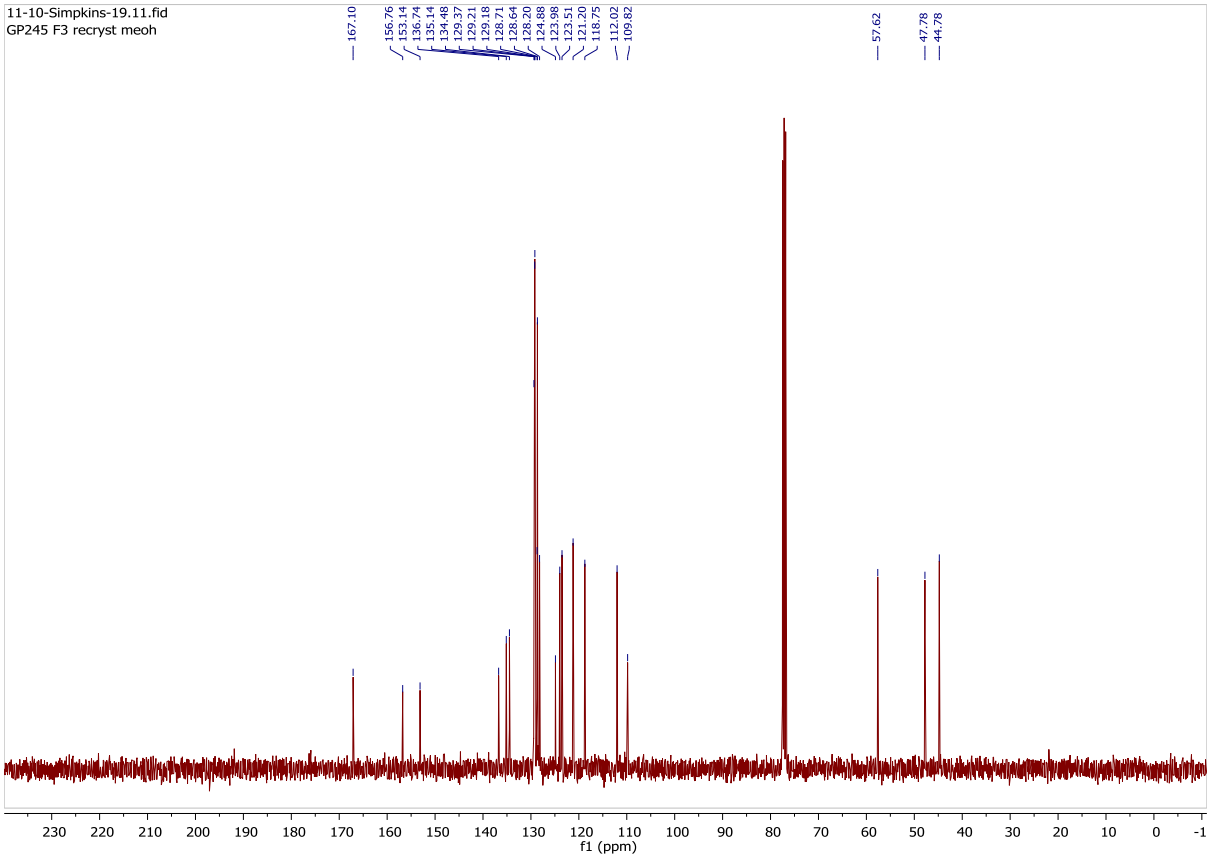
1i

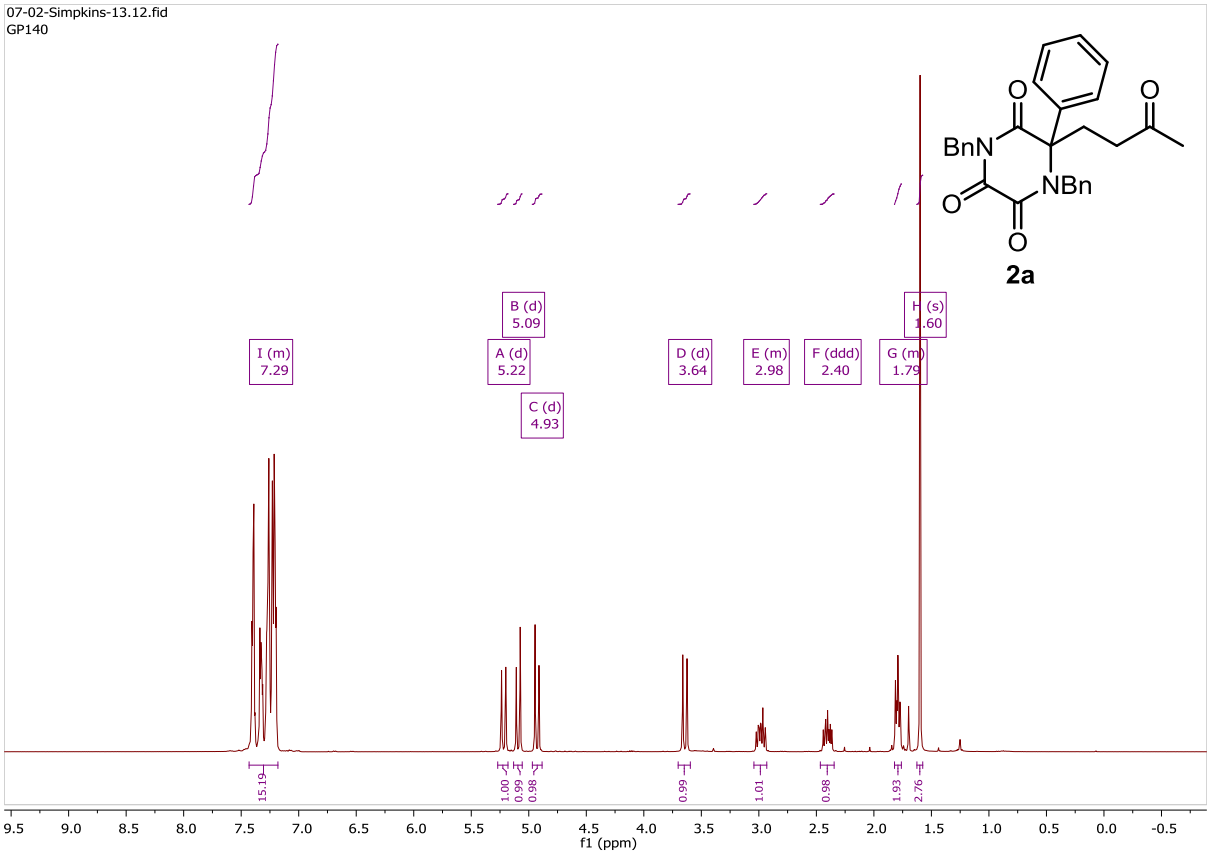

GP547 F2.12.fid
GP547 F2
167.81
156.88
153.06
135.33
134.64
129.46
129.26
129.15
128.72
128.60
128.10
123.52
120.71
117.54
106.58
58.19
47.60
44.60
36.60
f1 (ppm)

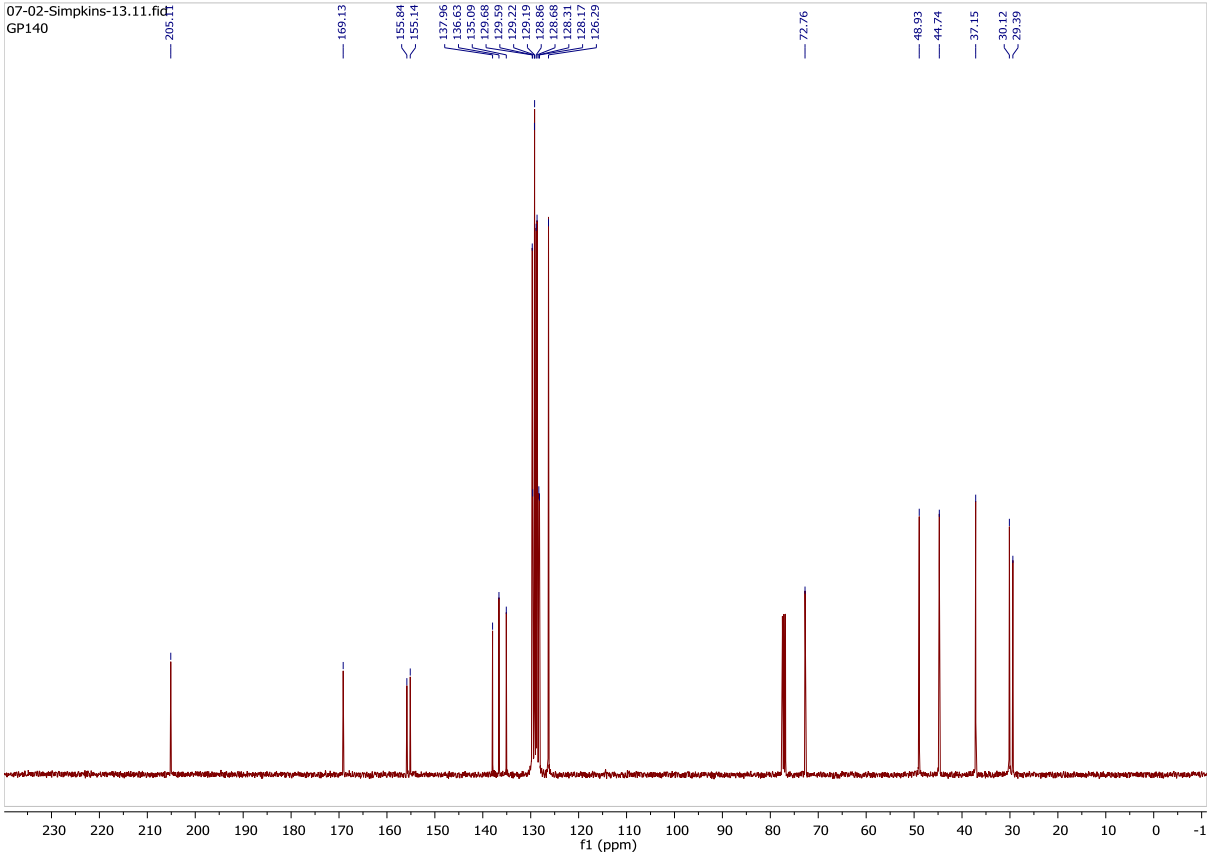

11-10-Simpkins-19.12.fid
GP245 F3 recryst meoh
F (s) 8.56
H (m) 7.23
G (m) 7.41
B (d) 5.54
D (d) 4.88
A (s) 5.45
C (d) 5.08
E (d) 3.79
1.02
2.27
14.61
1.05
1.00
1.01
1.00
1.02
f1 (ppm)

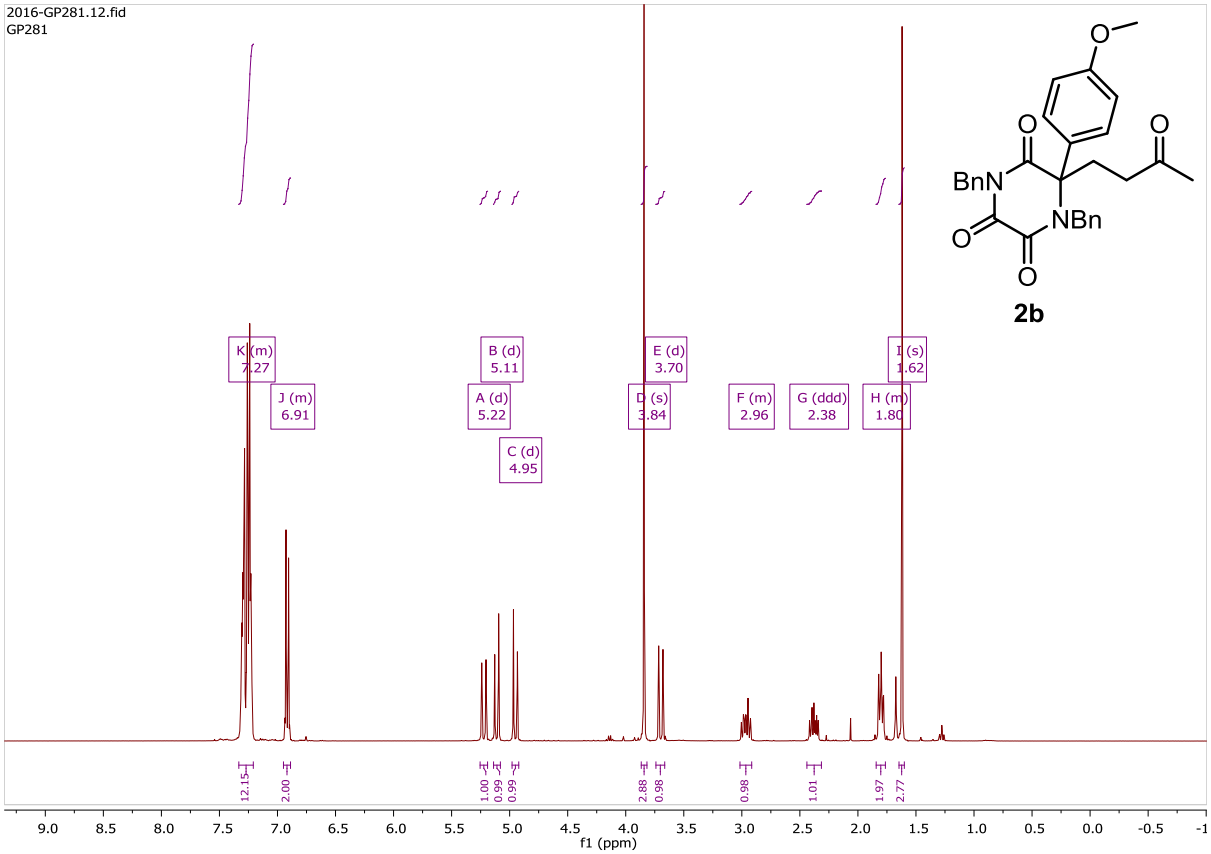
O
NH
BnN
NBn
O
O

1j


11-10-Simpkins-19.11.fid
GP245 F3 recryst meoh
167.10
156.76
153.14
136.74
135.14
134.48
129.37
129.21
129.18
128.71
128.64
128.20
124.88
123.98
123.51
121.20
118.75
112.02
109.82
57.62
47.78
44.78
f1 (ppm)

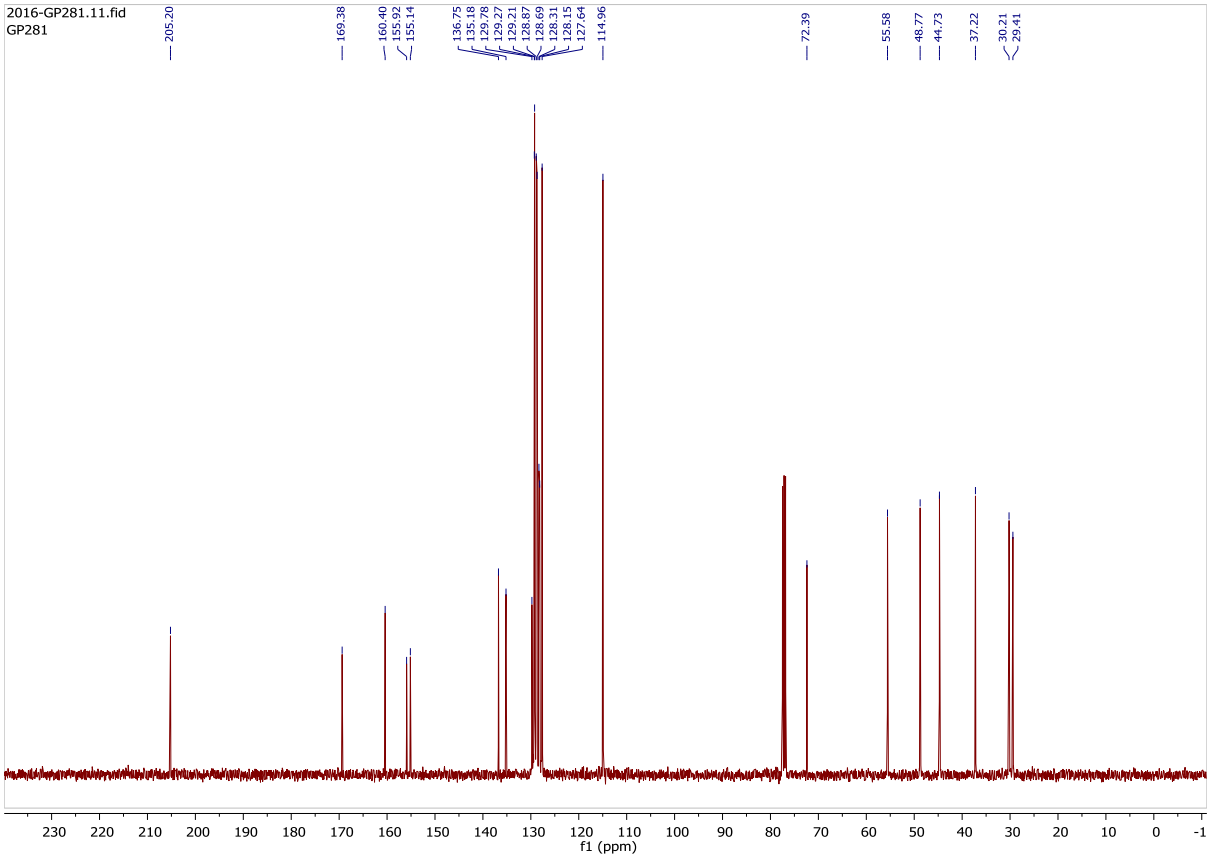

07-02-Simpkins-13.12.fid
GP140
BnN
NBn
O
O
O
O
2a
I (m) 7.29
B (d) 5.09
A (d) 5.22
C (d) 4.93
D (d) 3.64
E (m) 2.98
F (ddd) 2.40
G (m) 1.79
H (s) 1.60
15.19
1.00
0.99
0.98
0.99
1.01
0.98
1.93
2.76
f1 (ppm)

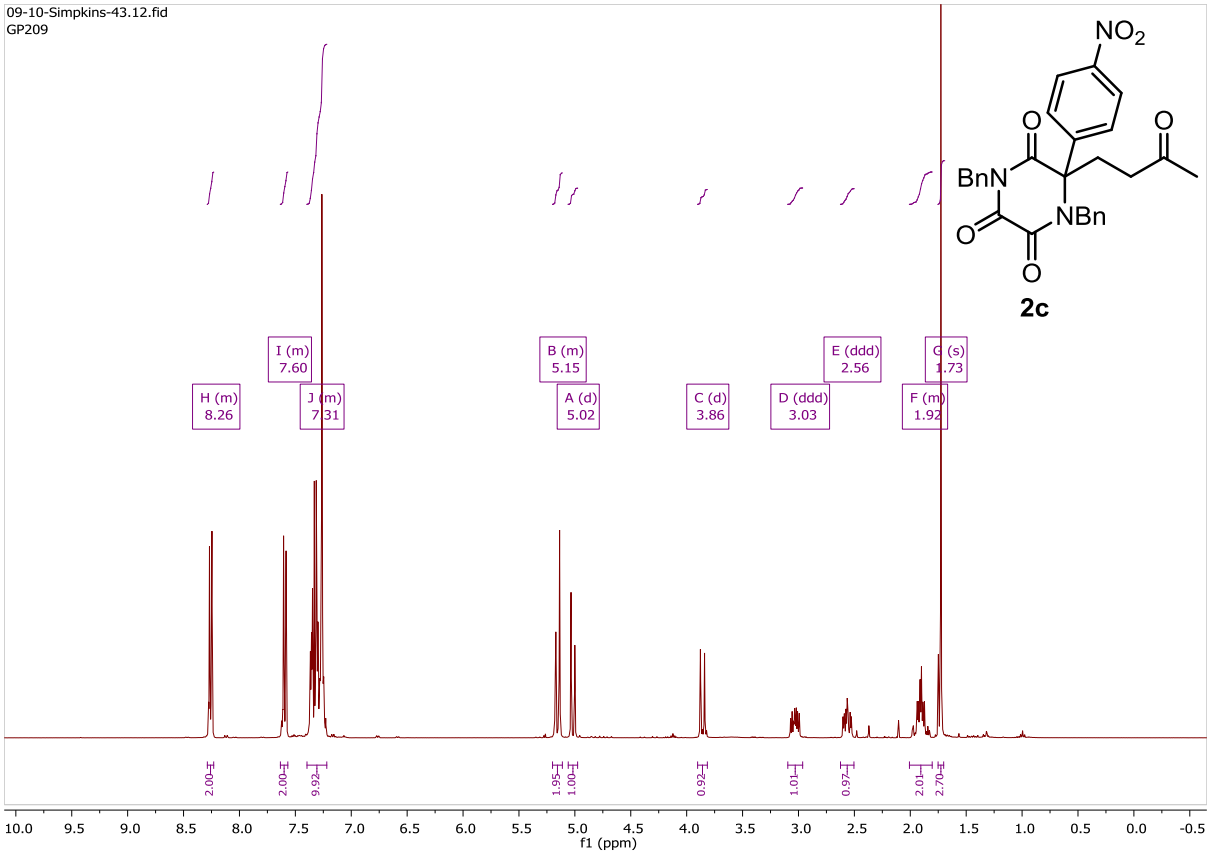

07-02-Simpkins-13.11.fid
GP140
205.11
169.13
155.84
155.14
137.96
136.63
135.09
129.68
129.59
129.22
129.19
128.86
128.68
128.31
128.17
126.29
72.76
48.93
44.74
37.15
30.12
29.39
f1 (ppm)

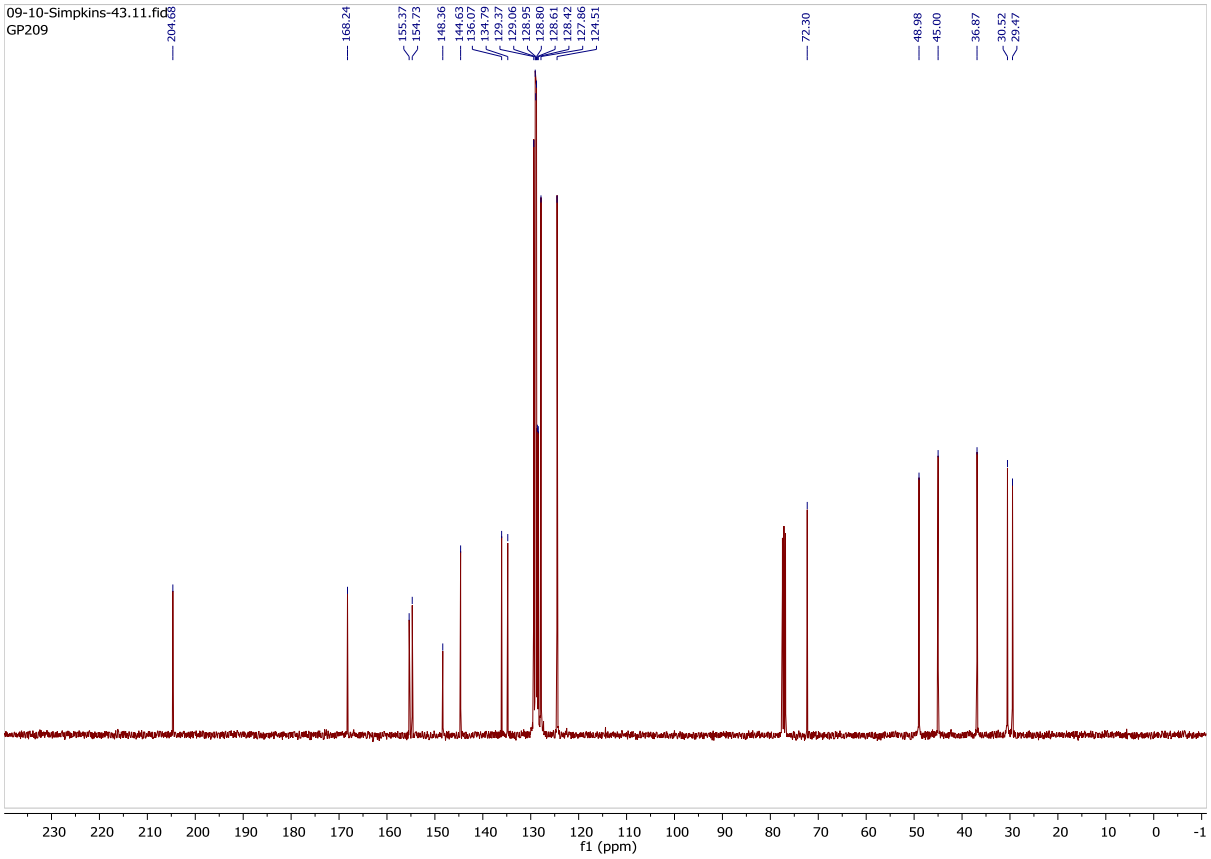

2016-GP281.12.fid
GP281
K (m) 7.27
J (m) 6.91
B (d) 5.11
A (d) 5.22
C (d) 4.95
E (d) 3.70
D (s) 3.84
F (m) 2.96
G (ddd) 2.38
I (s) 1.62
H (m) 1.80
12.15
2.00
1.00
0.99
0.99
2.88
0.98
0.98
1.01
1.97
2.77
f1 (ppm)

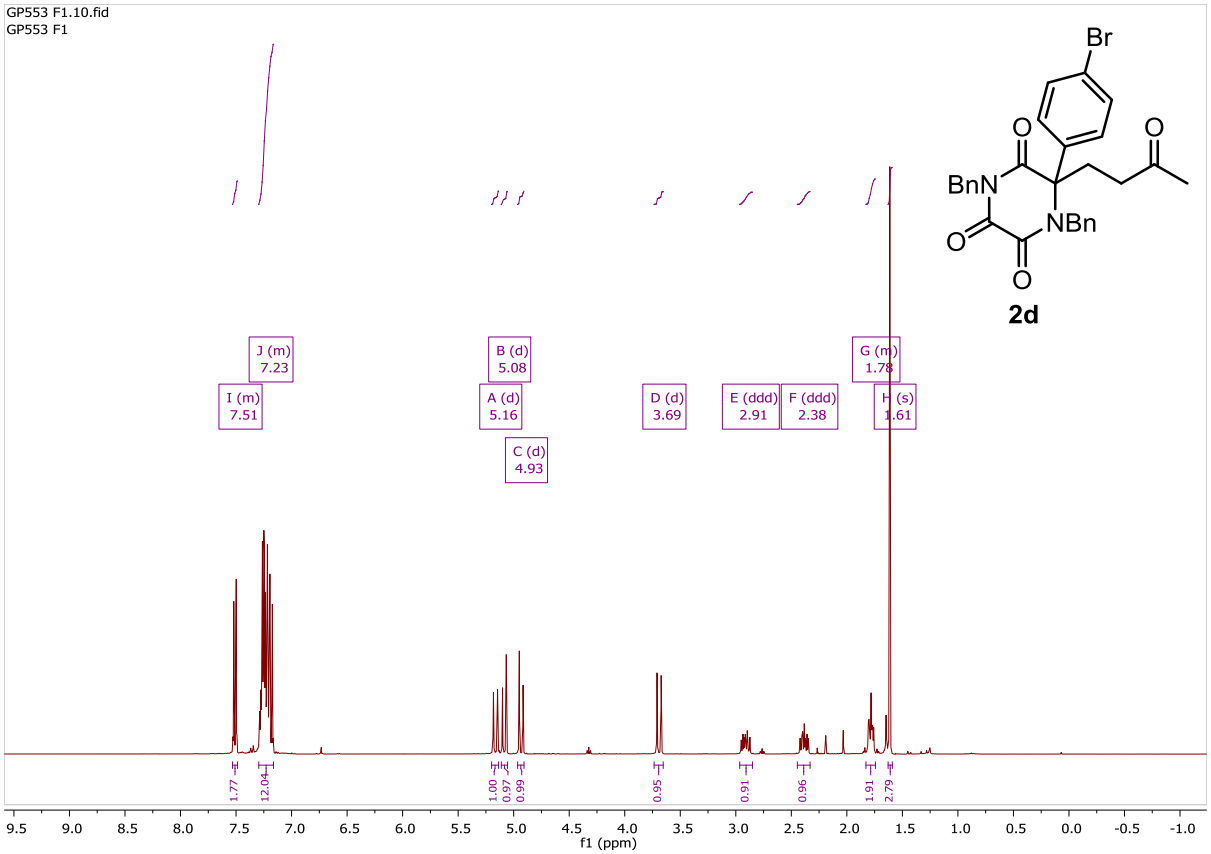
O
BnN
NBn
O
O
O
O

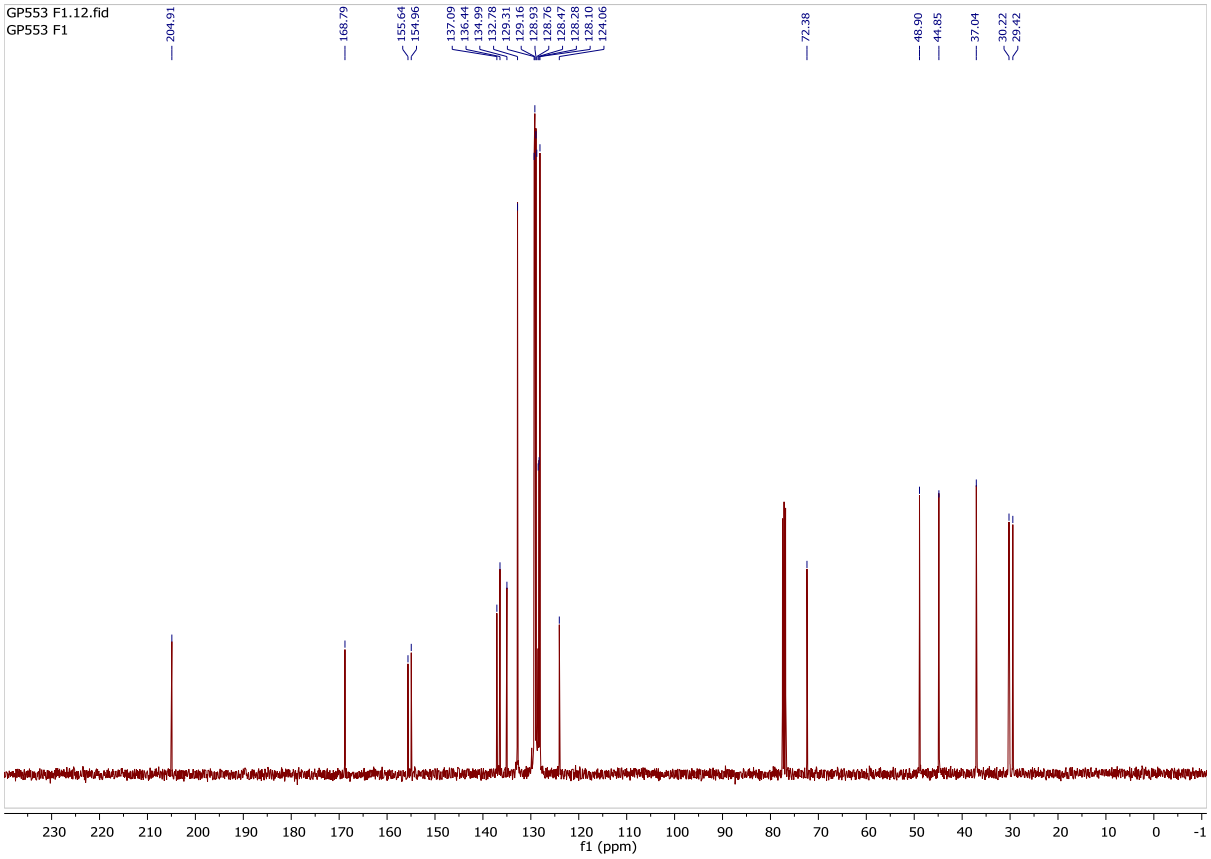
2b

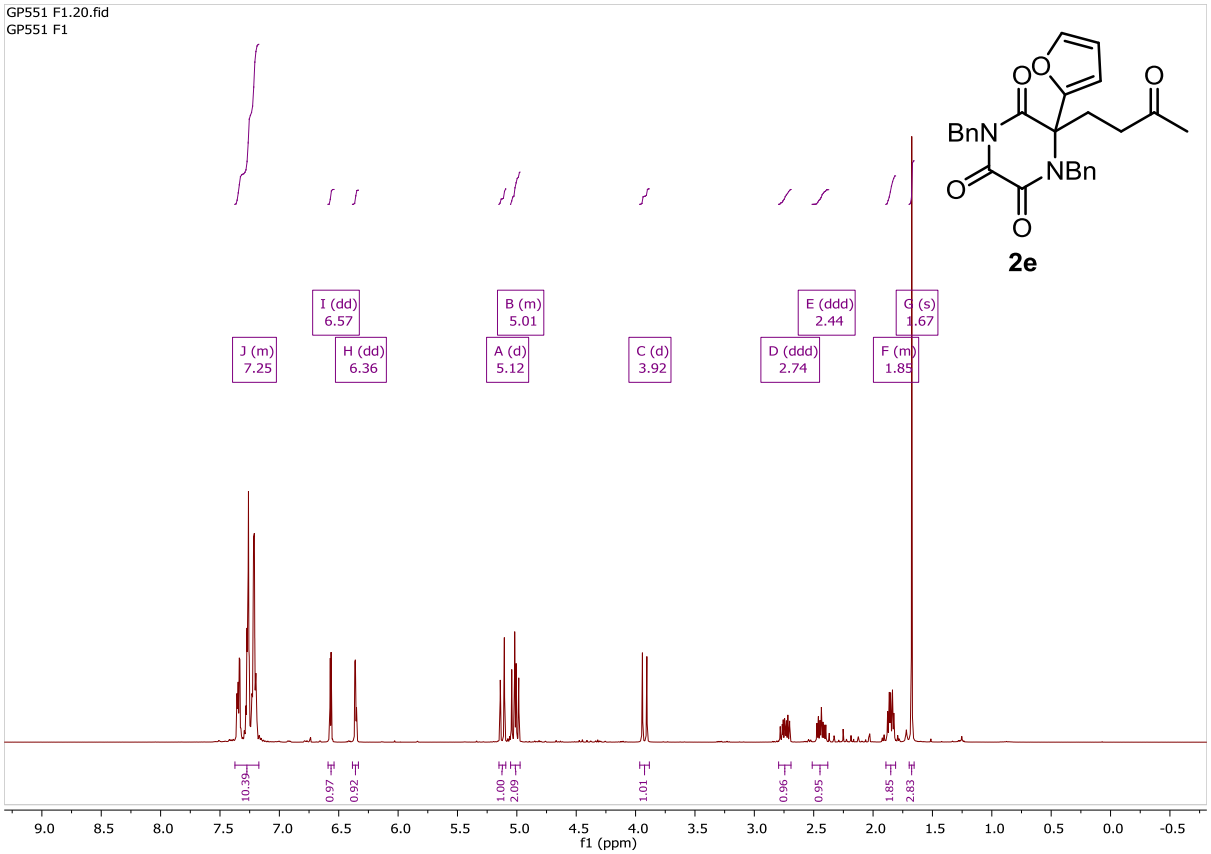

2016-GP281.11.fid
GP281
205.20
169.38
160.40
155.92
155.14
136.75
135.18
129.78
129.27
129.21
128.87
128.69
128.31
128.15
127.64
114.96
72.39
55.58
48.77
44.73
37.22
30.21
29.41
f1 (ppm)


09-10-Simpkins-43.12.fid
GP209
NO2
O
O
BnN
NBn
O
O
2c
H (m) 8.26
I (m) 7.60
J (m) 7.31
A (d) 5.02
B (m) 5.15
C (d) 3.86
D (ddd) 3.03
E (ddd) 2.56
F (m) 1.92
G (s) 1.73
2.00
2.00
9.92
1.95
1.00
0.92
1.01
0.97
2.01
2.70
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


09-10-Simpkins-43.11.fid
GP209
204.68
168.24
155.37
154.73
148.36
144.63
136.07
134.79
129.37
129.06
128.95
128.80
128.61
128.42
127.86
124.51
72.30
48.98
45.00
36.87
30.52
29.47
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

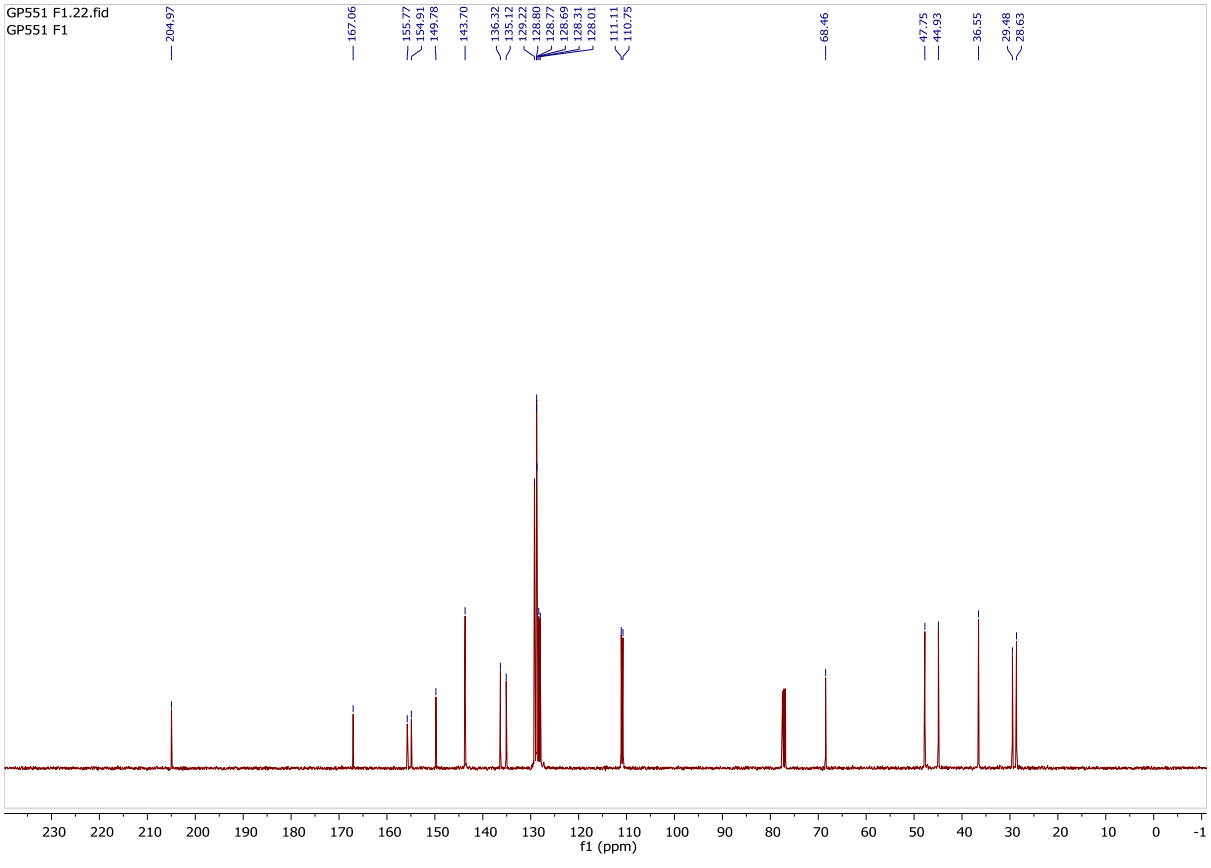

GP553 F1.10.fid
GP553 F1
Br
O
O
BnN
NBn
O
O
2d
J (m) 7.23
I (m) 7.51
B (d) 5.08
A (d) 5.16
C (d) 4.93
D (d) 3.69
E (ddd) 2.91
F (ddd) 2.38
G (m) 1.78
H (s) 1.61
1.77
12.04
1.00
0.97
0.99
0.95
0.91
0.96
1.91
2.79
f1 (ppm)

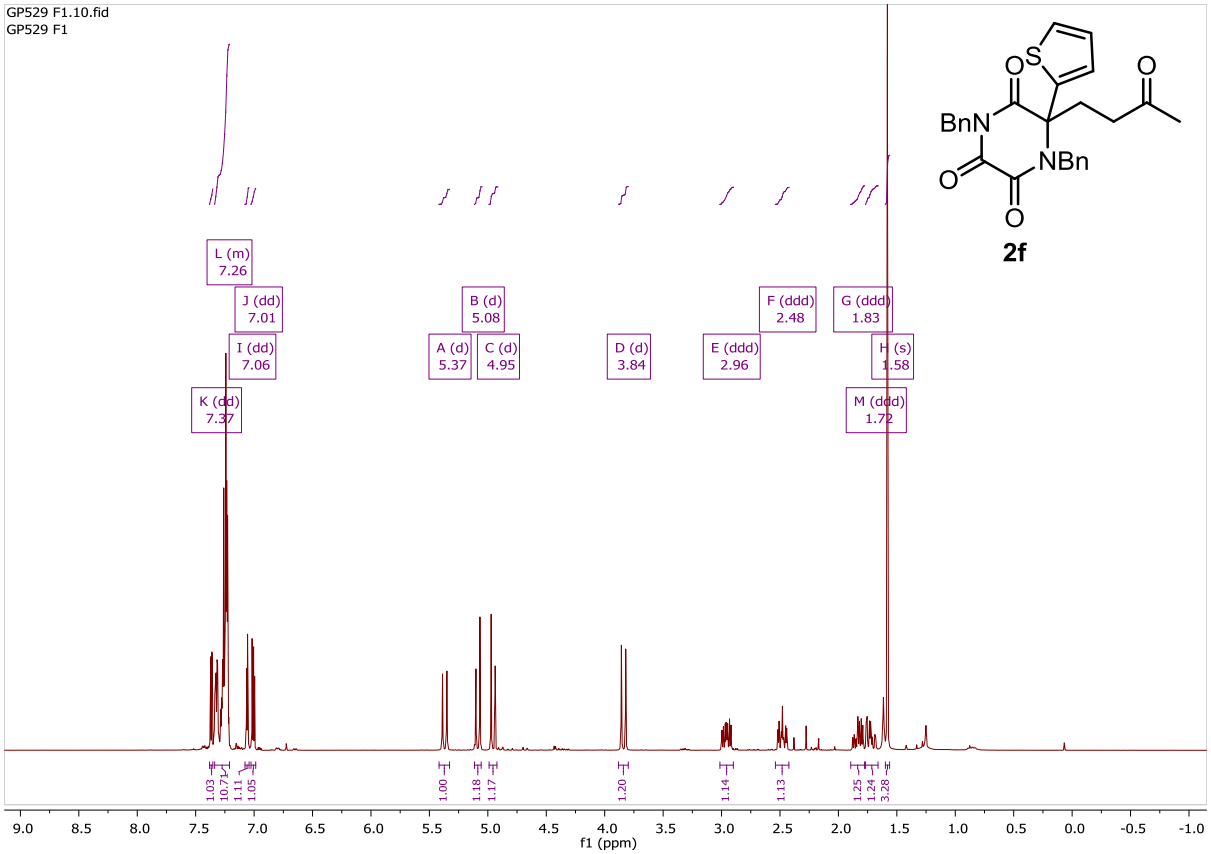

GP553 F1.12.fid
GP553 F1
204.91
168.79
155.64
154.96
137.09
136.44
134.99
132.78
129.31
129.16
128.93
128.76
128.47
128.28
128.10
124.06
72.38
48.90
44.85
37.04
30.22
29.42
f1 (ppm)

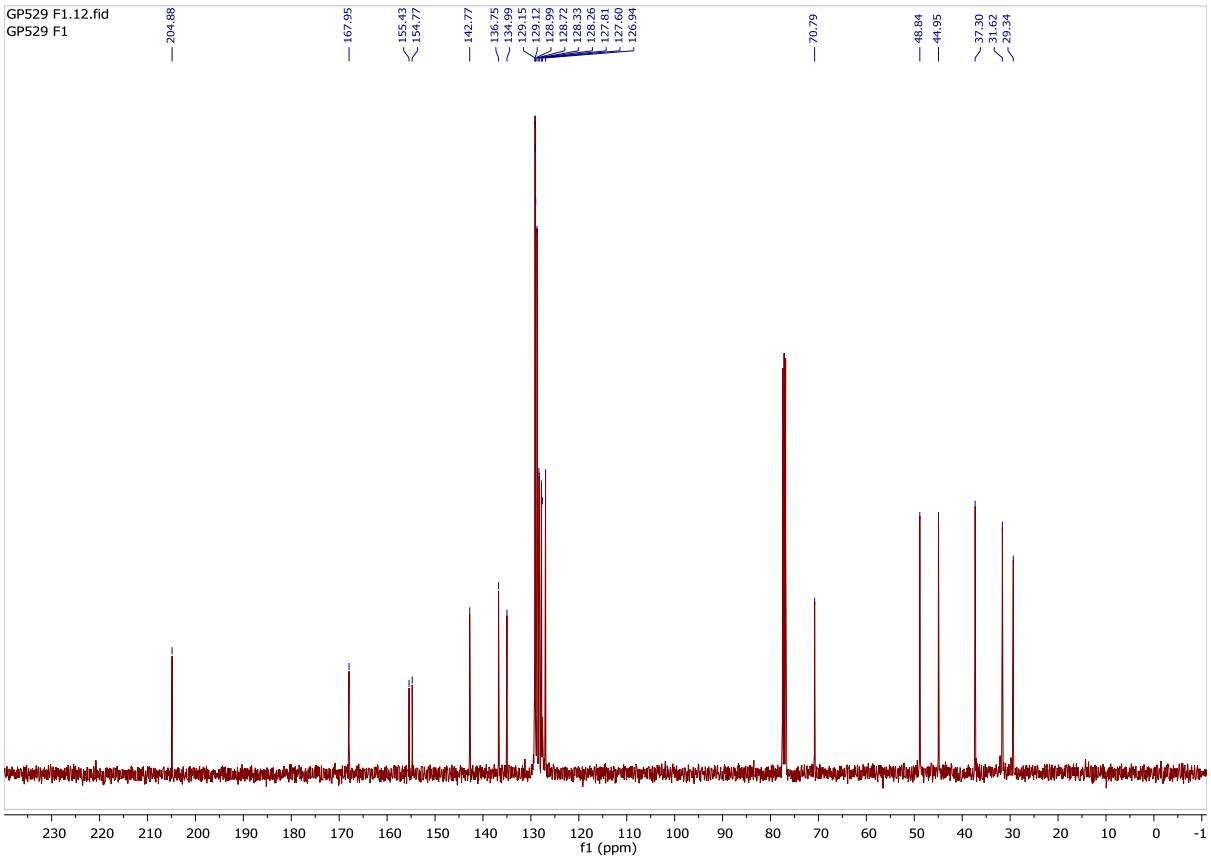

GP551 F1.20.fid
GP551 F1
J (m) 7.25
I (dd) 6.57
H (dd) 6.36
B (m) 5.01
A (d) 5.12
C (d) 3.92
E (dddd) 2.44
D (ddd) 2.74
G (s) 1.67
F (m) 1.85
10.39
0.97
0.92
1.00
2.09
1.01
0.96
0.95
1.85
2.83
f1 (ppm)

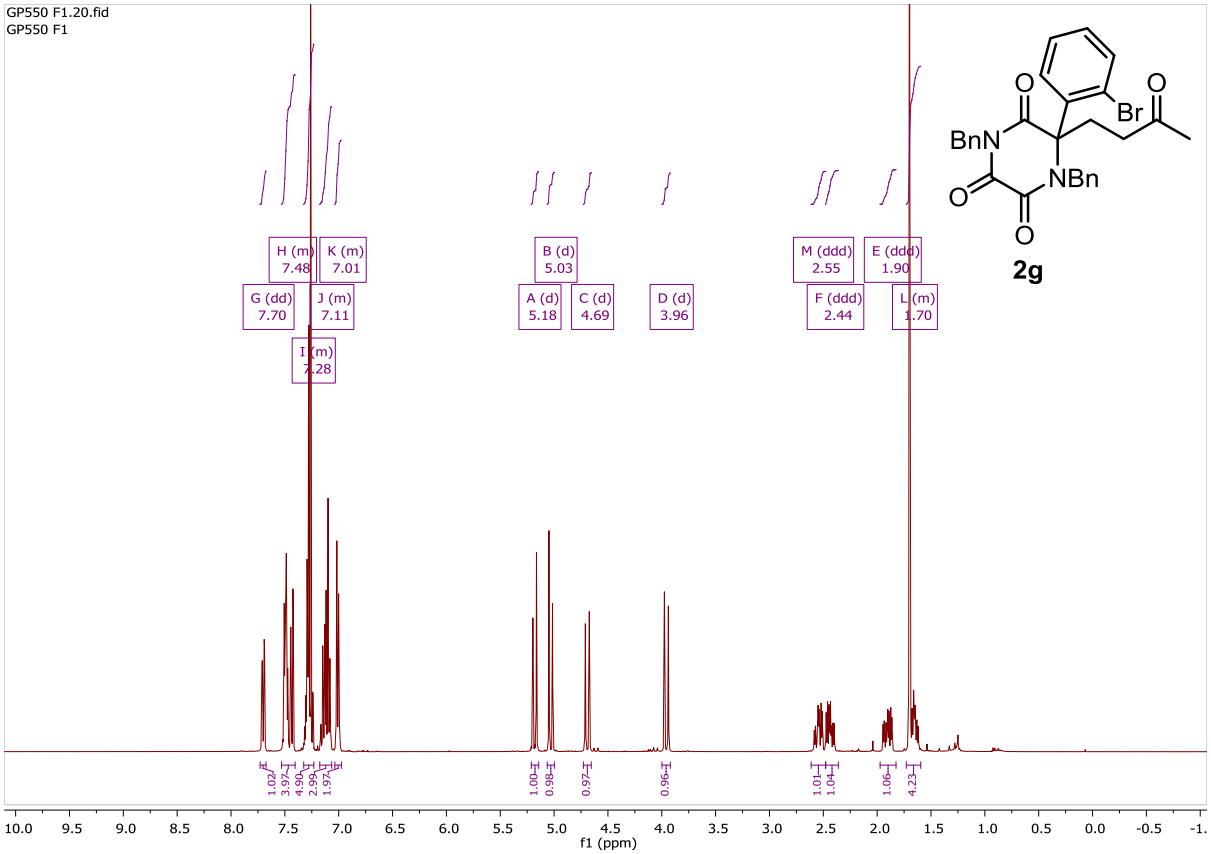
BnN
NBn
O
O
O
O
O

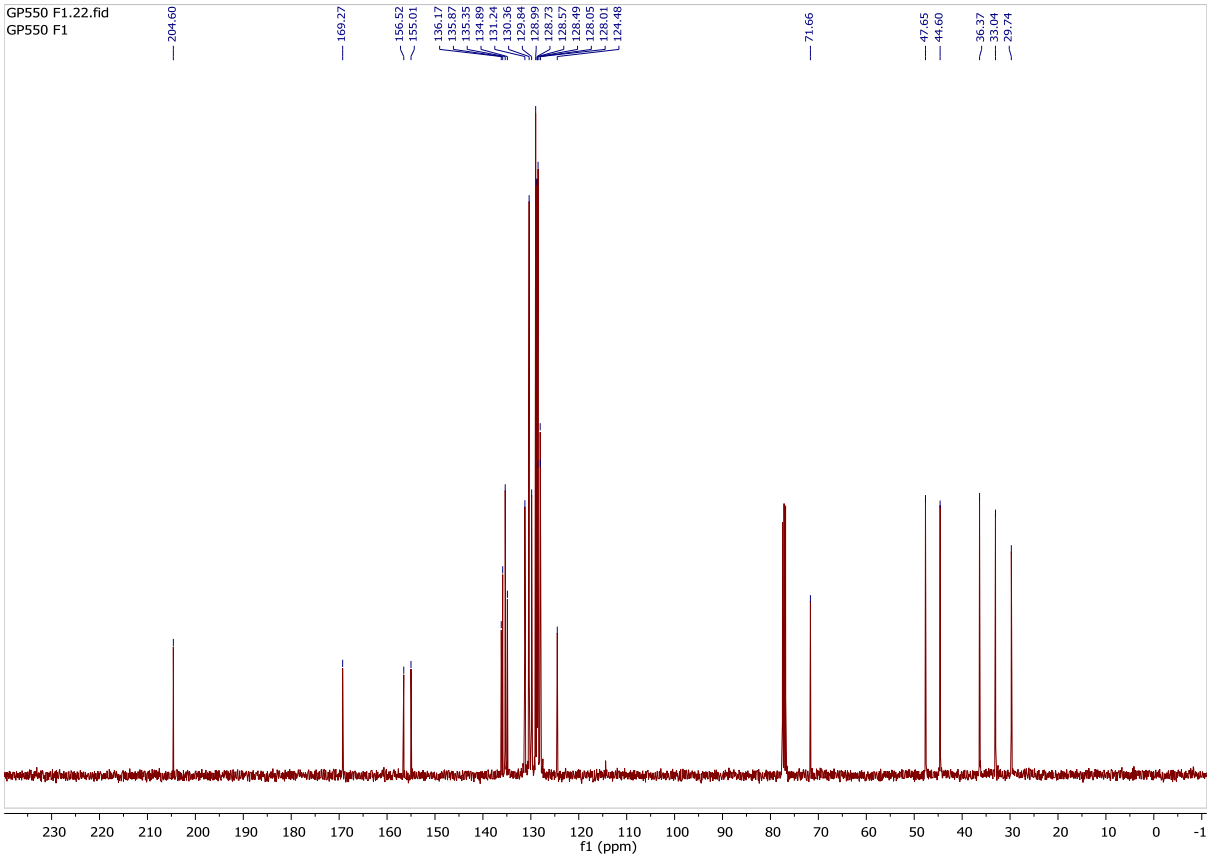
2e

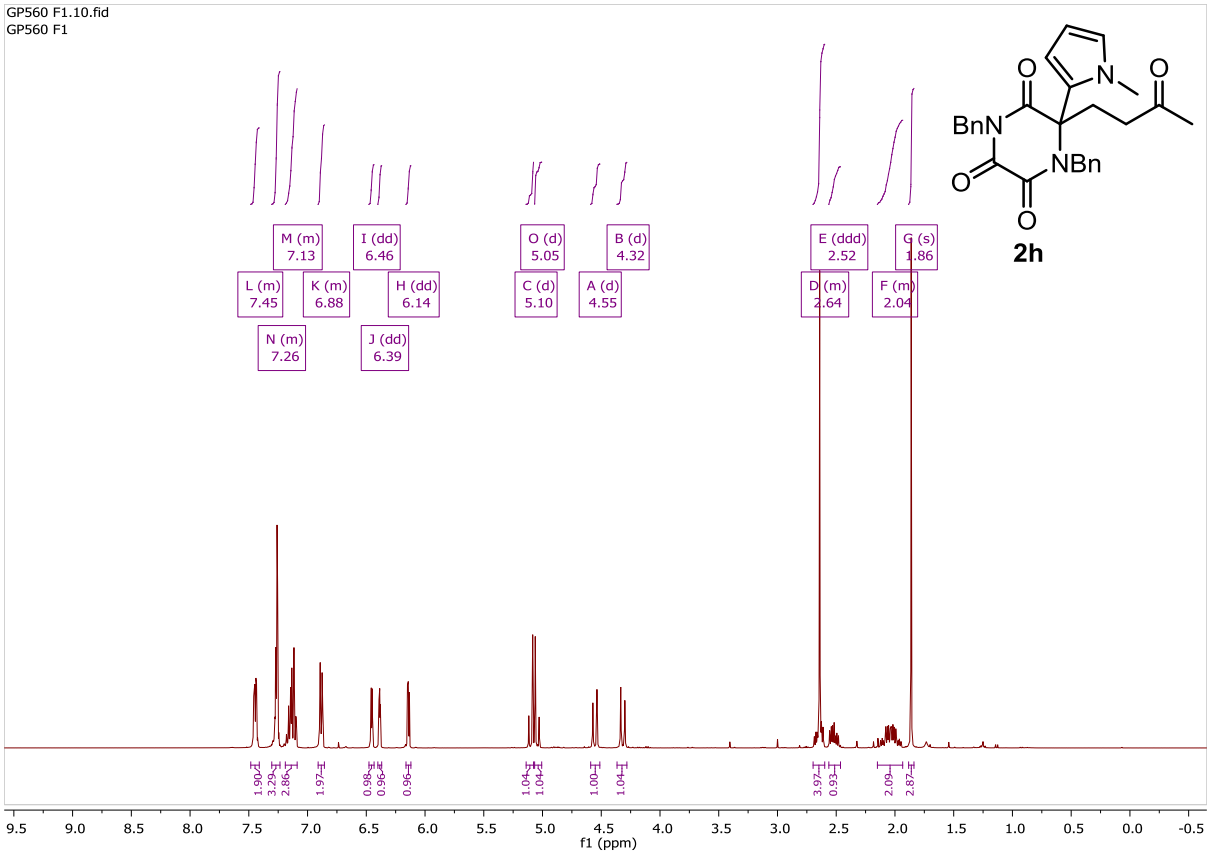

GP551 F1.22.fid
GP551 F1
204.97
167.06
155.77
154.91
149.78
143.70
136.32
135.12
129.22
128.80
128.77
128.69
128.31
128.01
111.11
110.75
68.46
47.75
44.93
36.55
29.48
28.63
f1 (ppm)

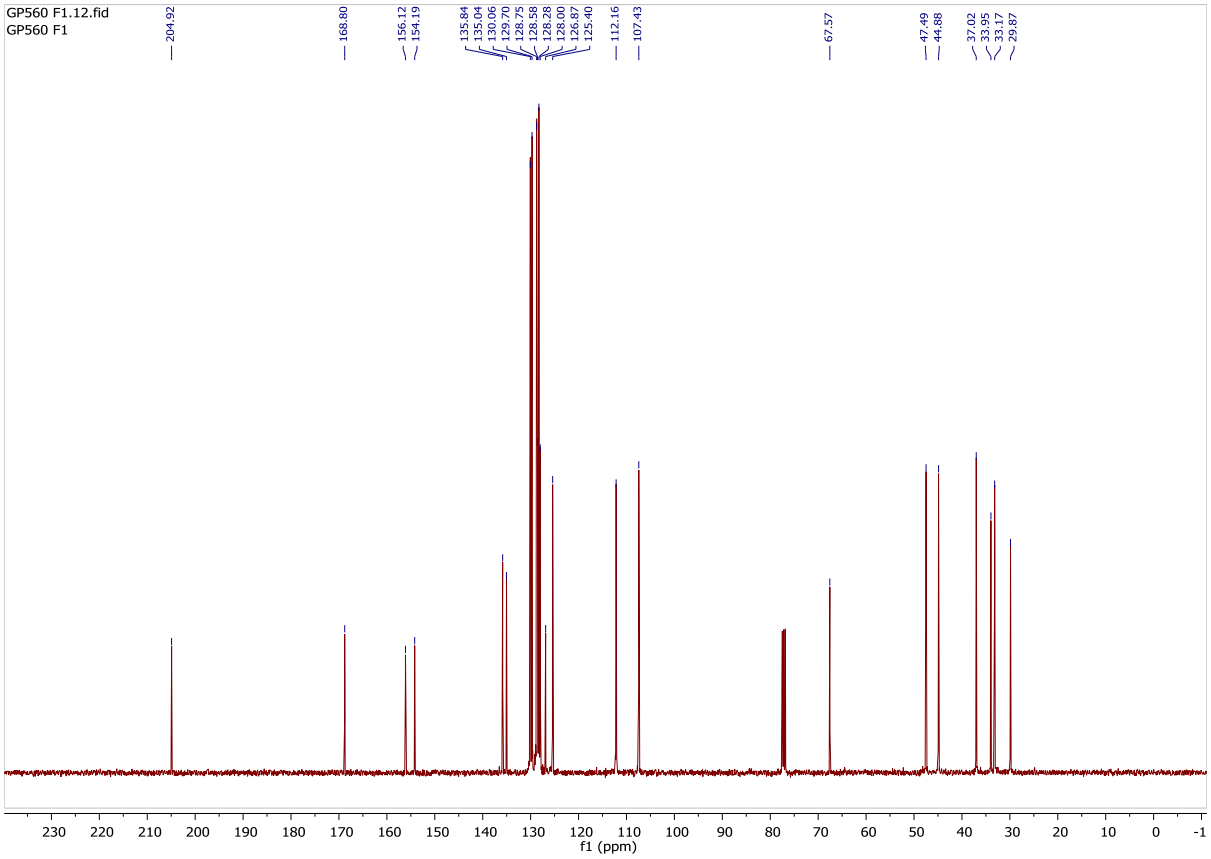

GP529 F1.10.fid
GP529 F1
L (m) 7.26
J (dd) 7.01
I (dd) 7.06
K (dd) 7.37
B (d) 5.08
A (d) 5.37
C (d) 4.95
D (d) 3.84
E (ddd) 2.96
F (ddd) 2.48
G (ddd) 1.83
H (s) 1.58
M (ddd) 1.72
1.03
10.71
1.11
1.05
1.00
1.18
1.17
1.20
1.14
1.13
1.25
1.24
3.28
f1 (ppm)

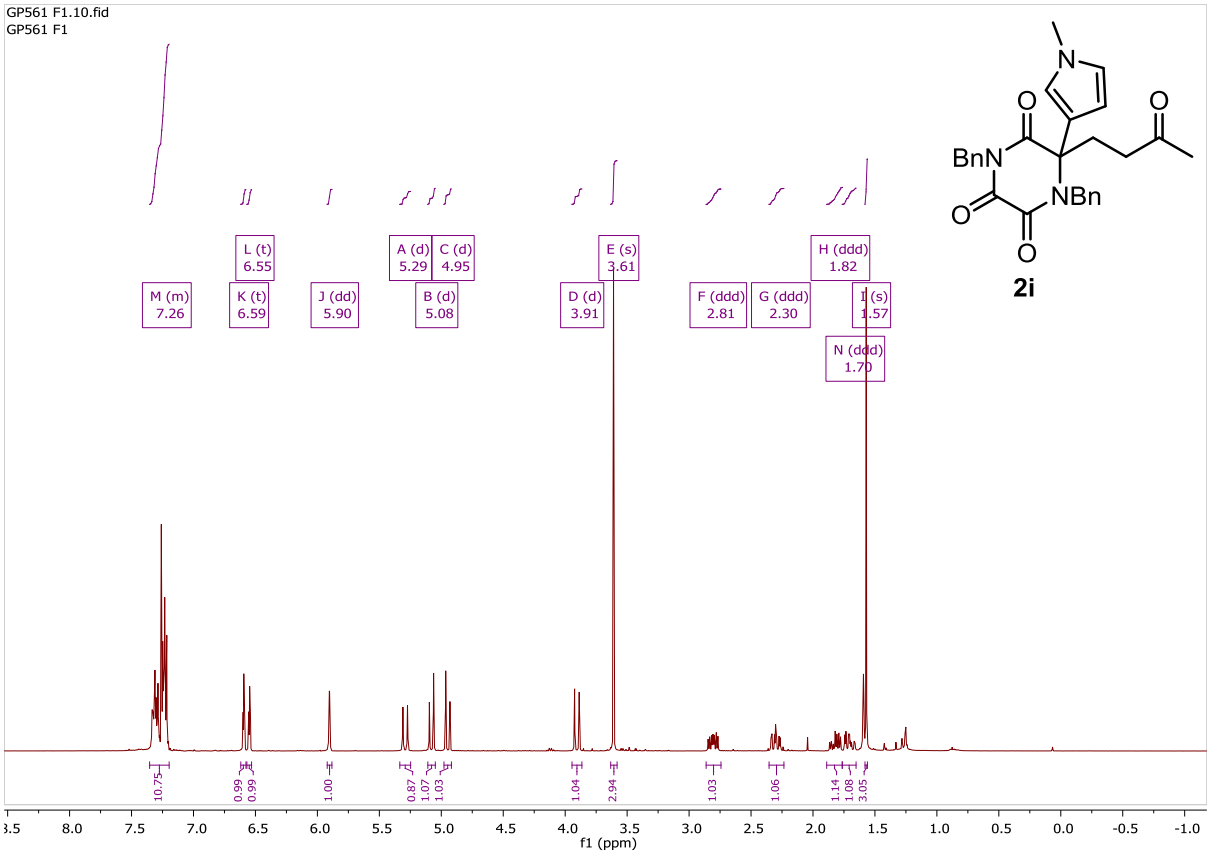

GP529 F1.12.fid
GP529 F1
204.88
167.95
155.43
154.77
142.77
136.75
134.99
129.15
129.12
128.99
128.72
128.33
128.26
127.81
127.60
126.94
70.79
48.84
44.95
37.30
31.62
29.34
f1 (ppm)

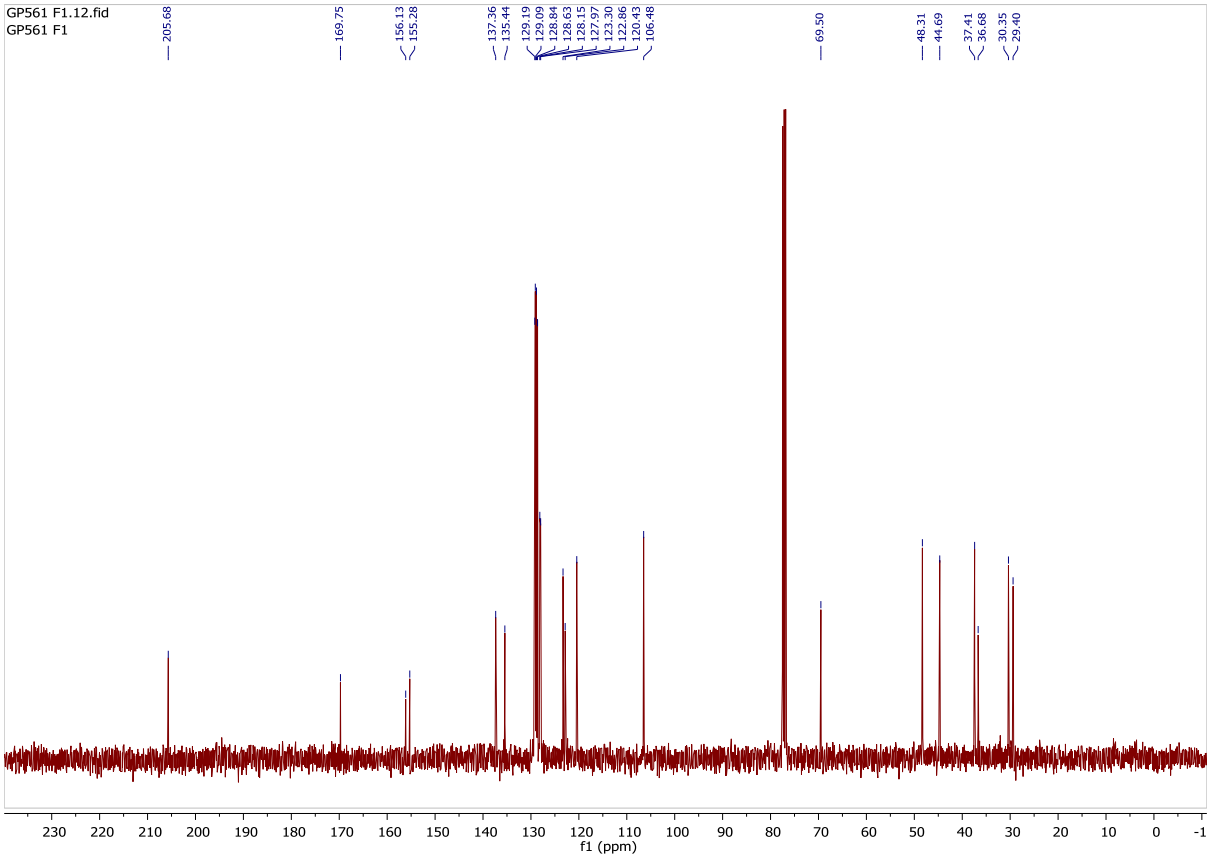

GP550 F1.20.fid
GP550 F1
H (m) 7.48
K (m) 7.01
G (dd) 7.70
J (m) 7.11
I (m) 7.28
B (d) 5.03
A (d) 5.18
C (d) 4.69
D (d) 3.96
M (ddd) 2.55
E (ddd) 1.90
F (ddd) 2.44
L (m) 1.70
1.02
3.97
4.90
2.99
1.97
1.00
0.98
0.97
0.96
1.01
1.04
1.06
4.23
f1 (ppm)
BnN
NBn
Br
O
2g

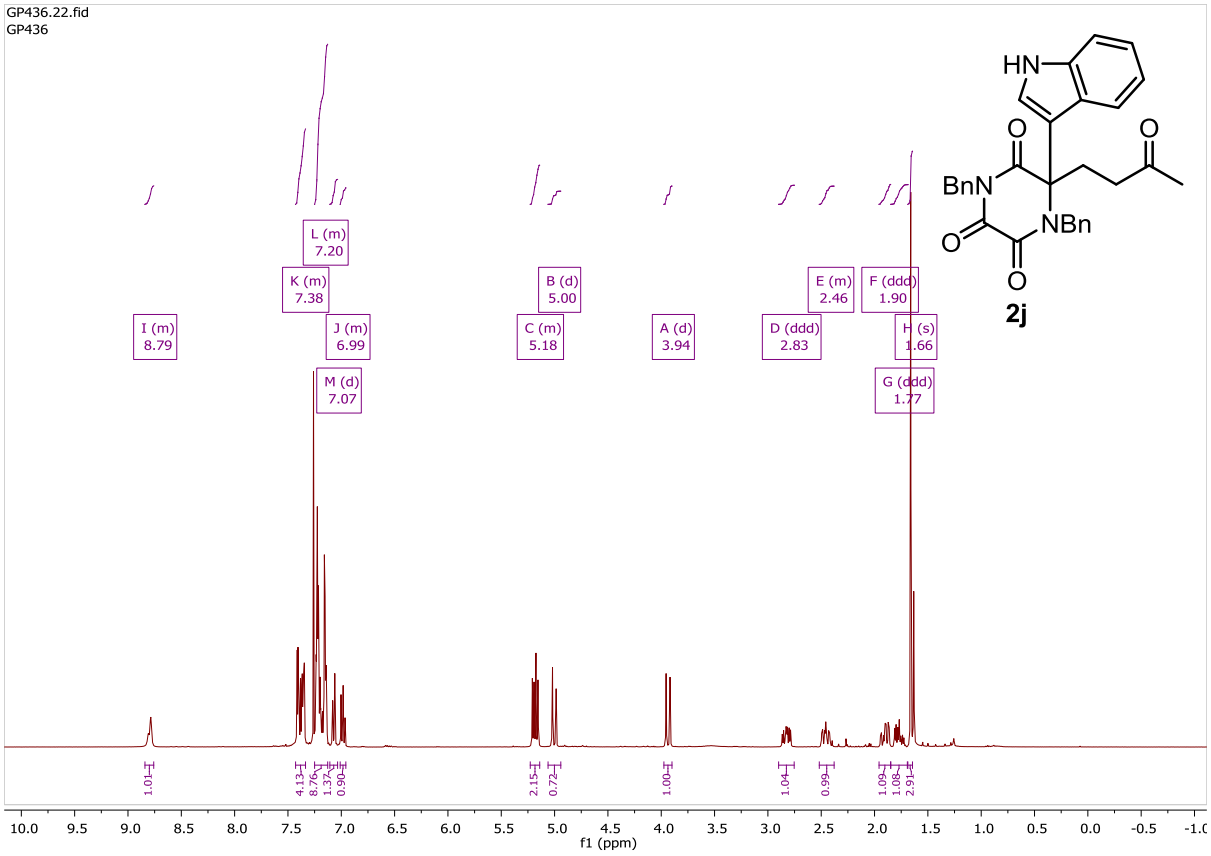

GP550 F1.22.fid
GP550 F1
204.60
169.27
156.52
155.01
136.17
135.87
135.35
134.89
131.24
130.36
129.84
128.99
128.73
128.57
128.49
128.05
128.01
124.48
71.66
47.65
44.60
36.37
33.04
29.74
f1 (ppm)

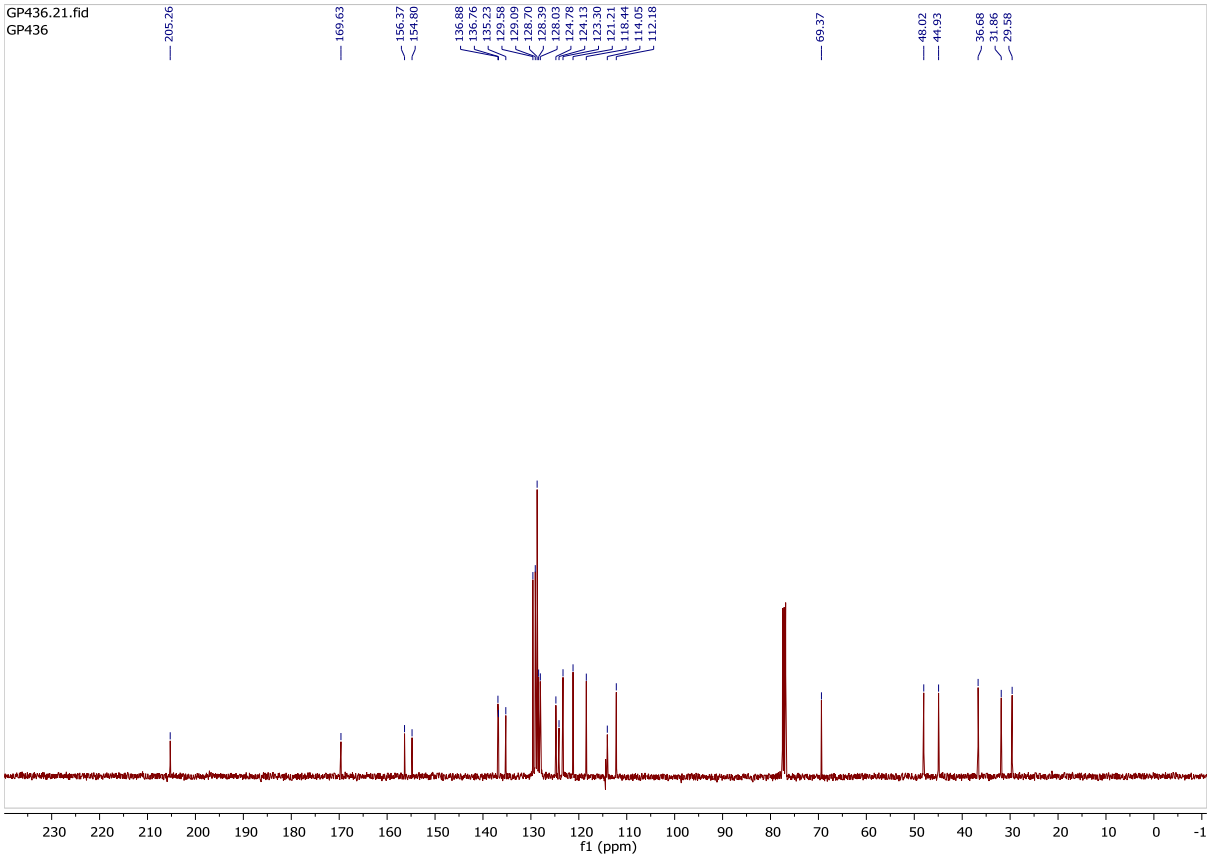

GP560 F1.10.fid
GP560 F1
M (m) 7.13
I (dd) 6.46
O (d) 5.05
B (d) 4.32
E (ddd) 2.52
G (s) 1.86
L (m) 7.45
K (m) 6.88
H (dd) 6.14
C (d) 5.10
A (d) 4.55
D (m) 2.64
F (m) 2.04
N (m) 7.26
J (dd) 6.39
1.90
3.29
2.86
1.97
0.98
0.96
0.96
1.04
1.04
1.00
1.04
3.97
0.93
2.09
2.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
BnN
NBn
O
N
O
O
O
2h

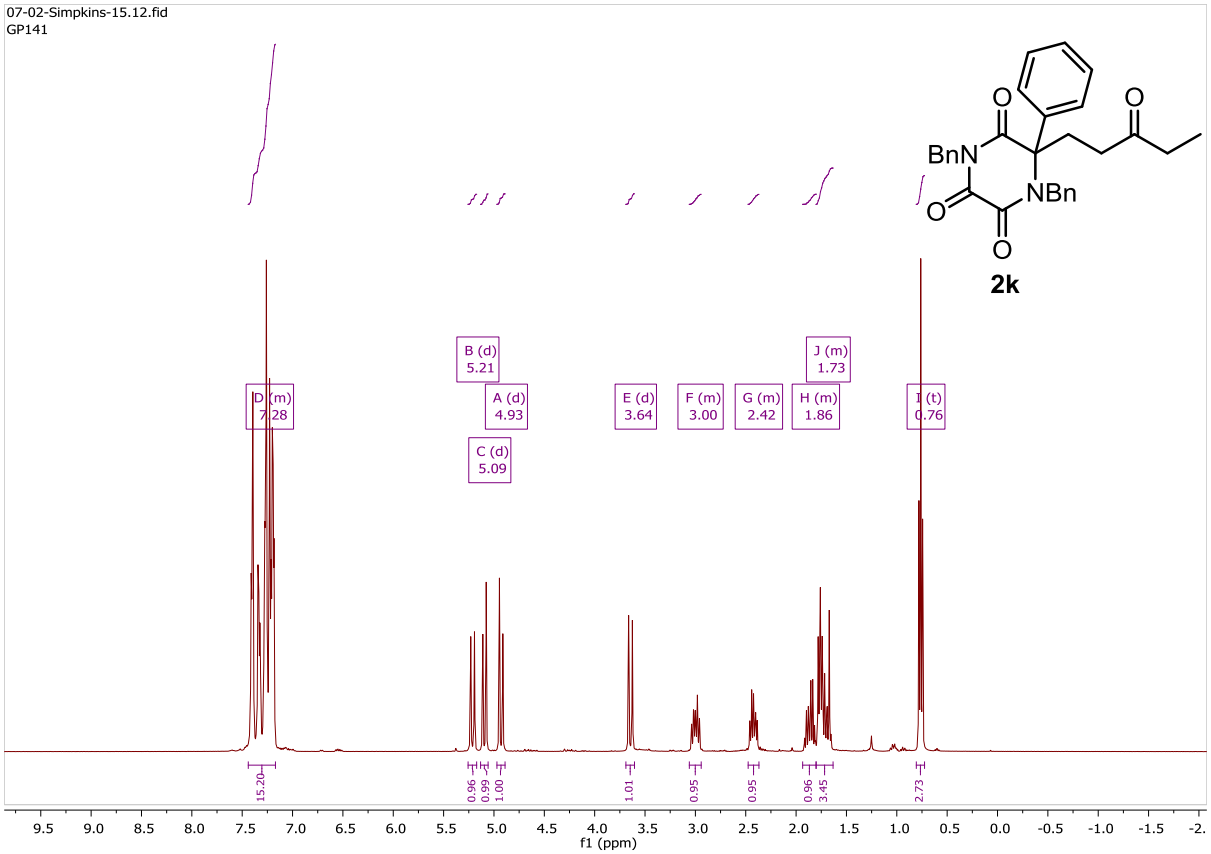

GP560 F1.12.fid
GP560 F1
204.92
168.80
156.12
154.19
135.84
135.04
130.06
129.70
128.75
128.58
128.28
128.00
126.87
125.40
112.16
107.43
67.57
47.49
44.88
37.02
33.95
33.17
29.87
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

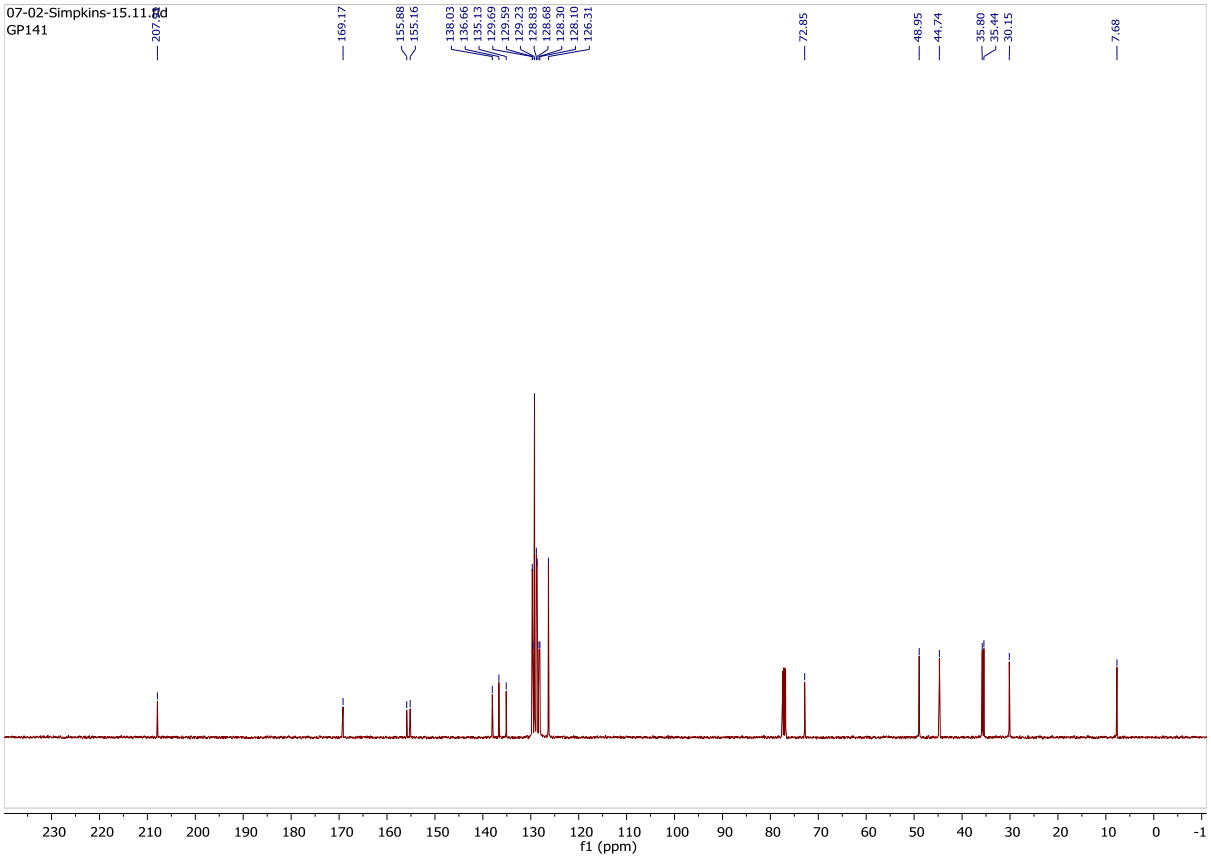

GP561 F1.10.fid
GP561 F1
L (t) 6.55
A (d) 5.29
C (d) 4.95
E (s) 3.61
H (ddd) 1.82
M (m) 7.26
K (t) 6.59
J (dd) 5.90
B (d) 5.08
D (d) 3.91
F (ddd) 2.81
G (ddd) 2.30
I (s) 1.57
N (ddd) 1.70
10.75
0.99
0.99
1.00
0.87
1.07
1.03
1.04
2.94
1.03
1.06
1.14
1.08
3.05
f1 (ppm)

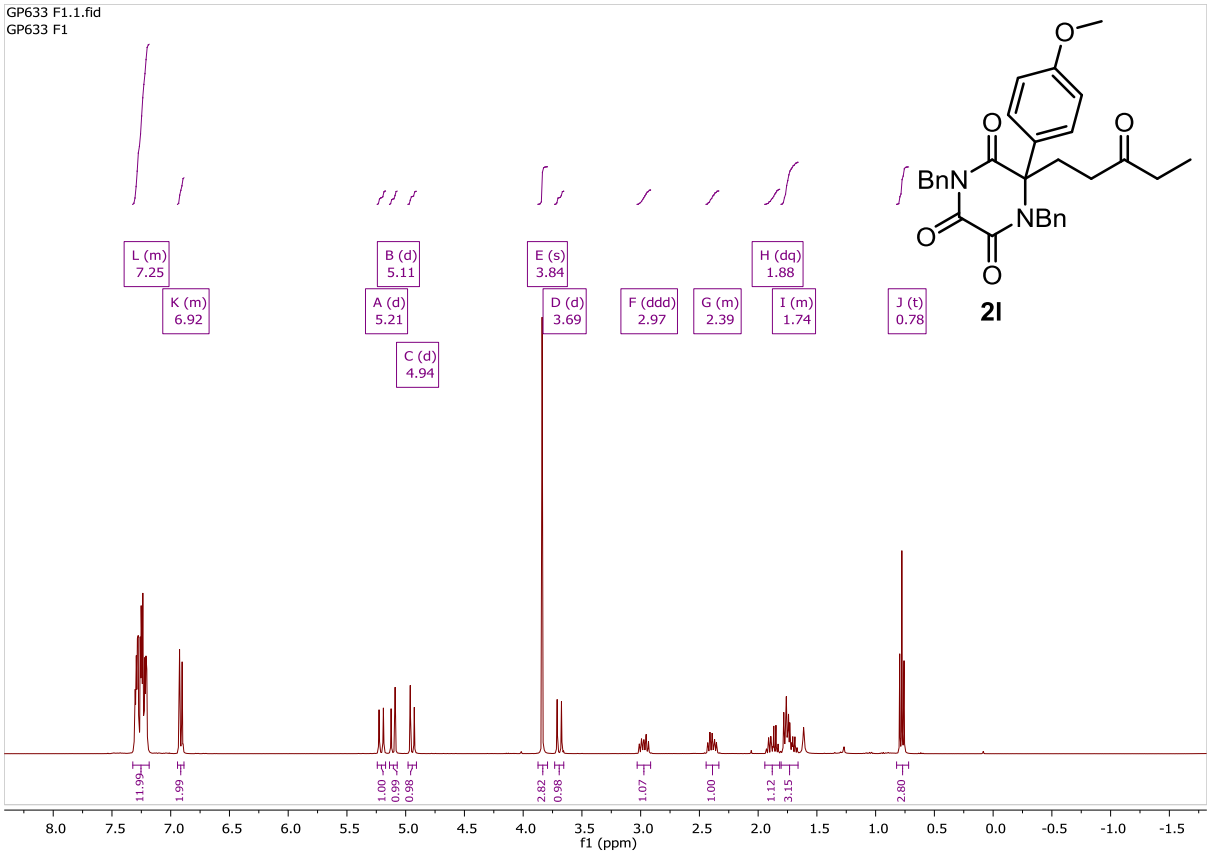

GP561 F1.12.fid
GP561 F1
205.68
169.75
156.13
155.28
137.36
135.44
129.19
129.09
128.84
128.63
128.15
127.97
123.30
122.86
120.43
106.48
69.50
48.31
44.69
37.41
36.68
30.35
29.40
f1 (ppm)

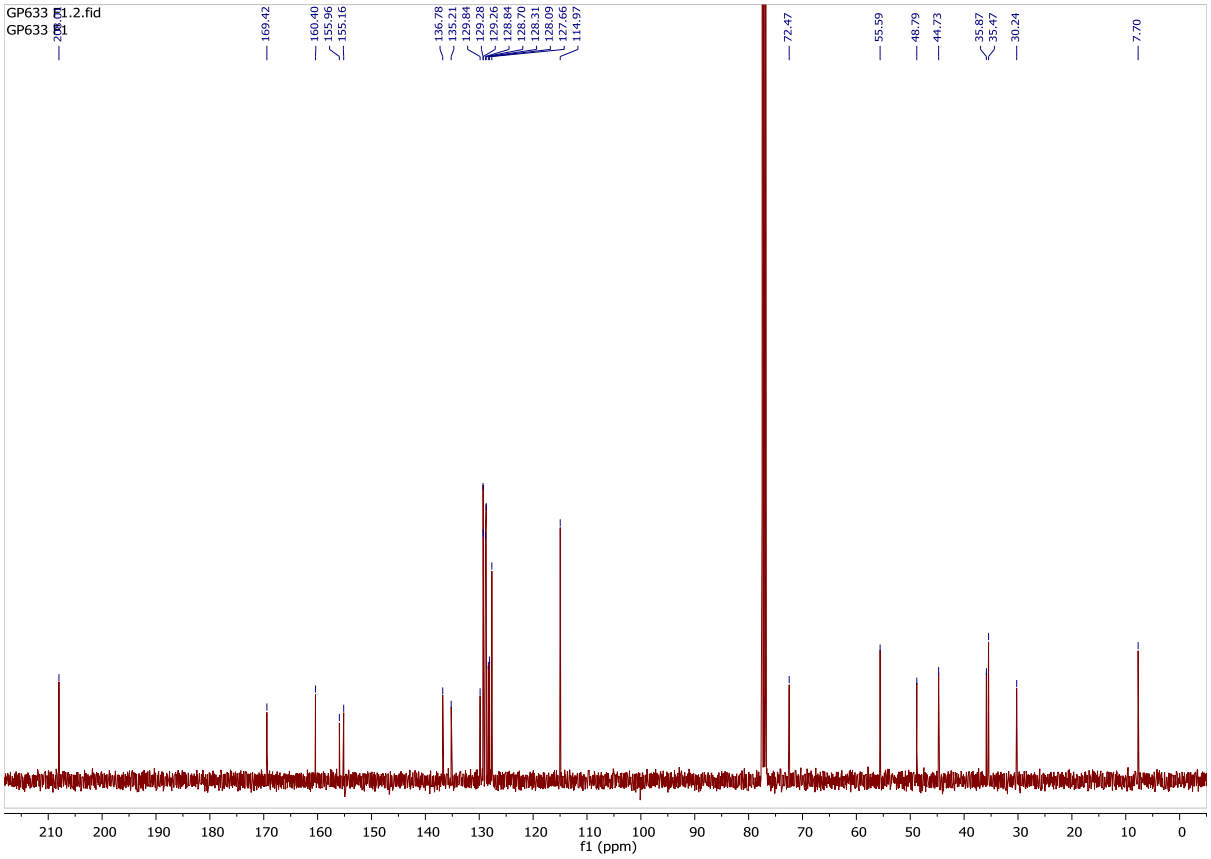

GP436.22.fid
GP436
HN
O
O
BnN
NBn
O
O
2j
L (m) 7.20
K (m) 7.38
B (d) 5.00
E (m) 2.46
F (ddd) 1.90
I (m) 8.79
J (m) 6.99
C (m) 5.18
A (d) 3.94
D (ddd) 2.83
H (s) 1.66
M (d) 7.07
G (ddd) 1.77
1.01
4.13
8.76
1.37
0.90
2.15
0.72
1.00
1.04
0.99
1.09
1.08
2.91
f1 (ppm)

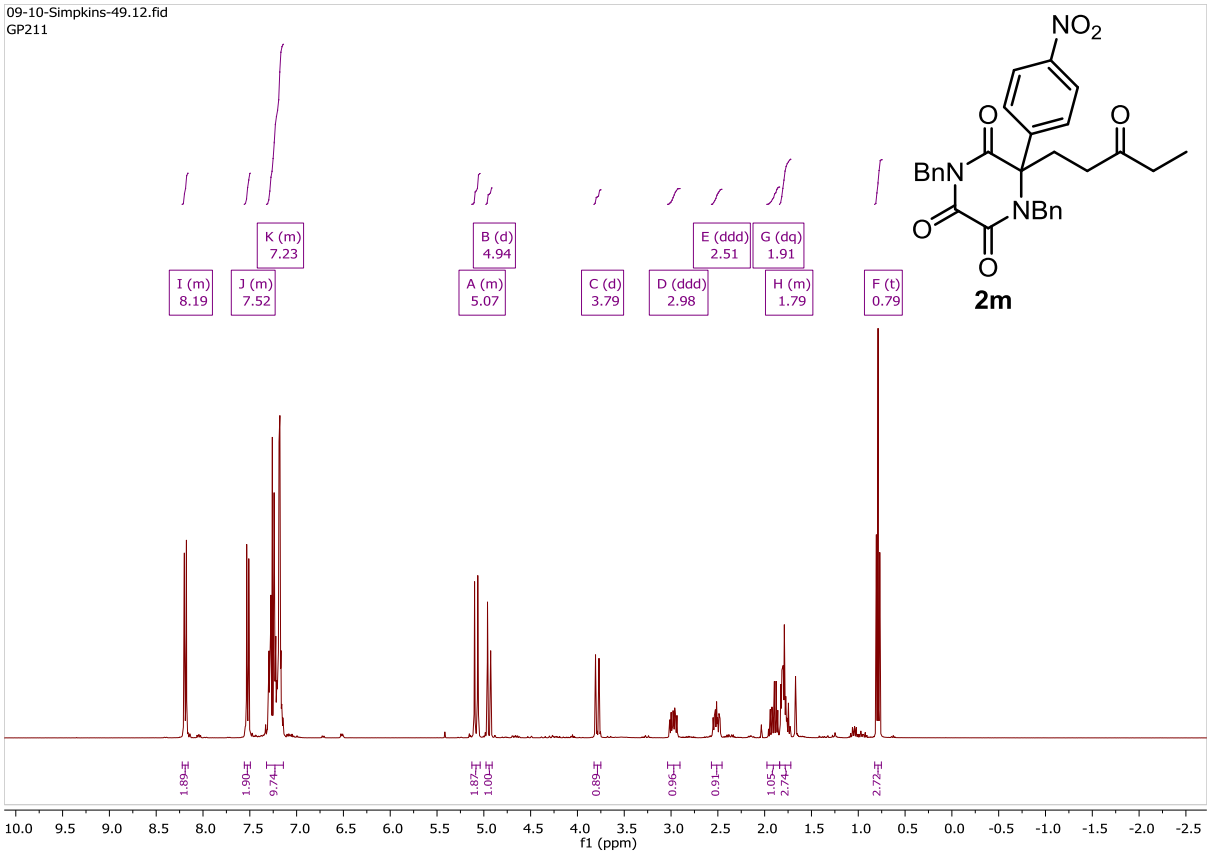

GP436.21.fid
GP436
205.26
169.63
156.37
154.80
136.88
136.76
135.23
129.58
129.09
128.70
128.39
128.03
124.78
124.13
123.30
121.21
118.44
114.05
112.18
69.37
48.02
44.93
36.68
31.86
29.58
f1 (ppm)

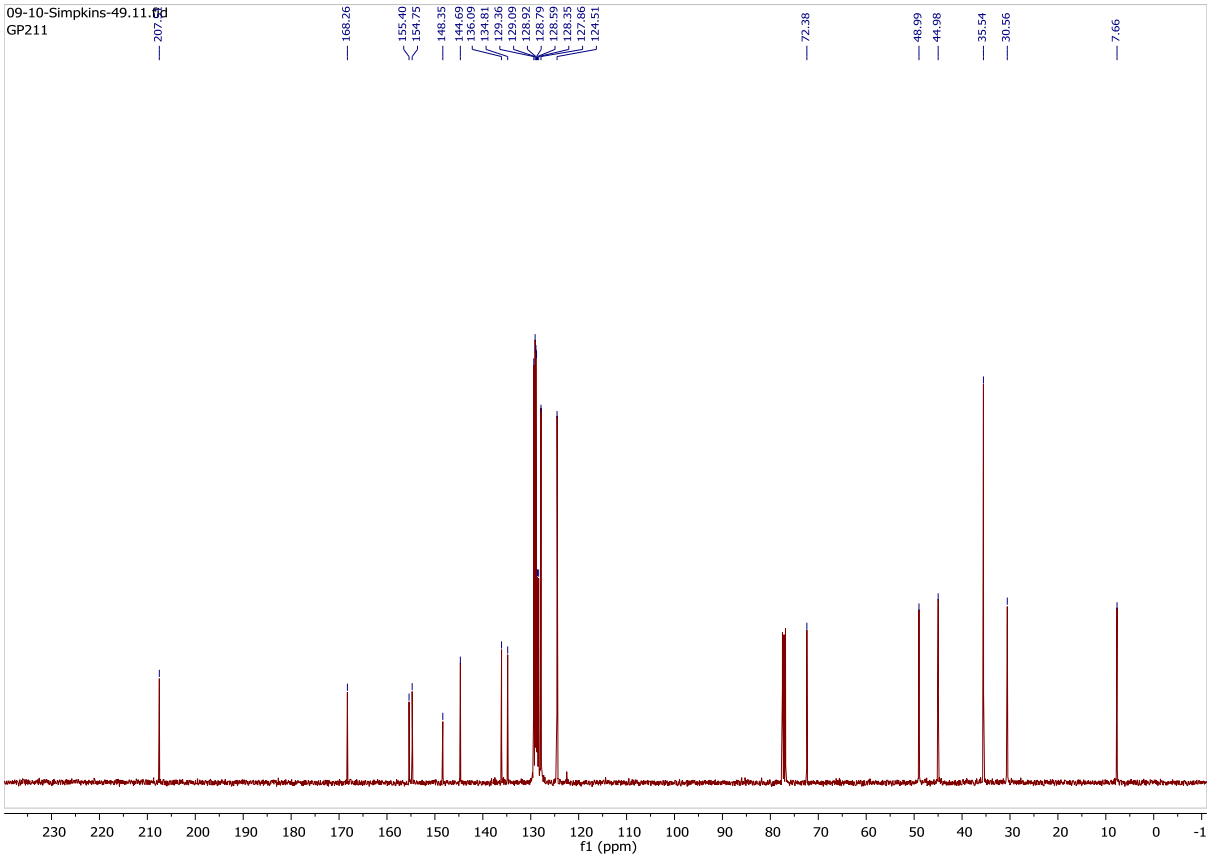

07-02-Simpkins-15.12.fid
GP141
BnN
NBn
O
O
O
O
O
2k
B (d) 5.21
A (d) 4.93
C (d) 5.09
D (m) 7.28
E (d) 3.64
F (m) 3.00
G (m) 2.42
H (m) 1.86
J (m) 1.73
I (t) 0.76
15.20
0.96
0.99
1.00
1.01
0.95
0.95
0.96
3.45
2.73
f1 (ppm)

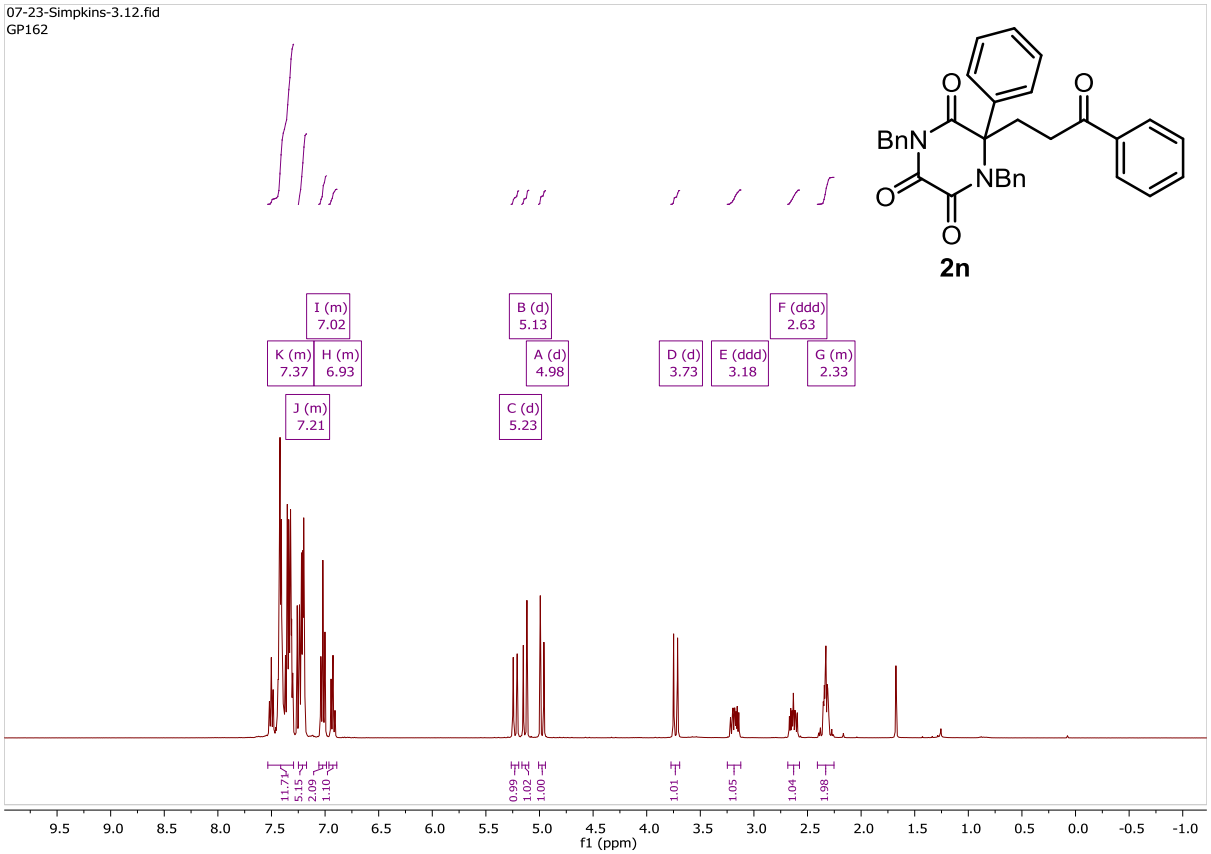

07-02-Simpkins-15.11.fid
GP141
207.78
169.17
155.88
155.16
138.03
136.66
135.13
129.69
129.59
129.23
128.83
128.68
128.30
128.10
126.31
72.85
48.95
44.74
35.80
35.44
30.15
7.68
f1 (ppm)

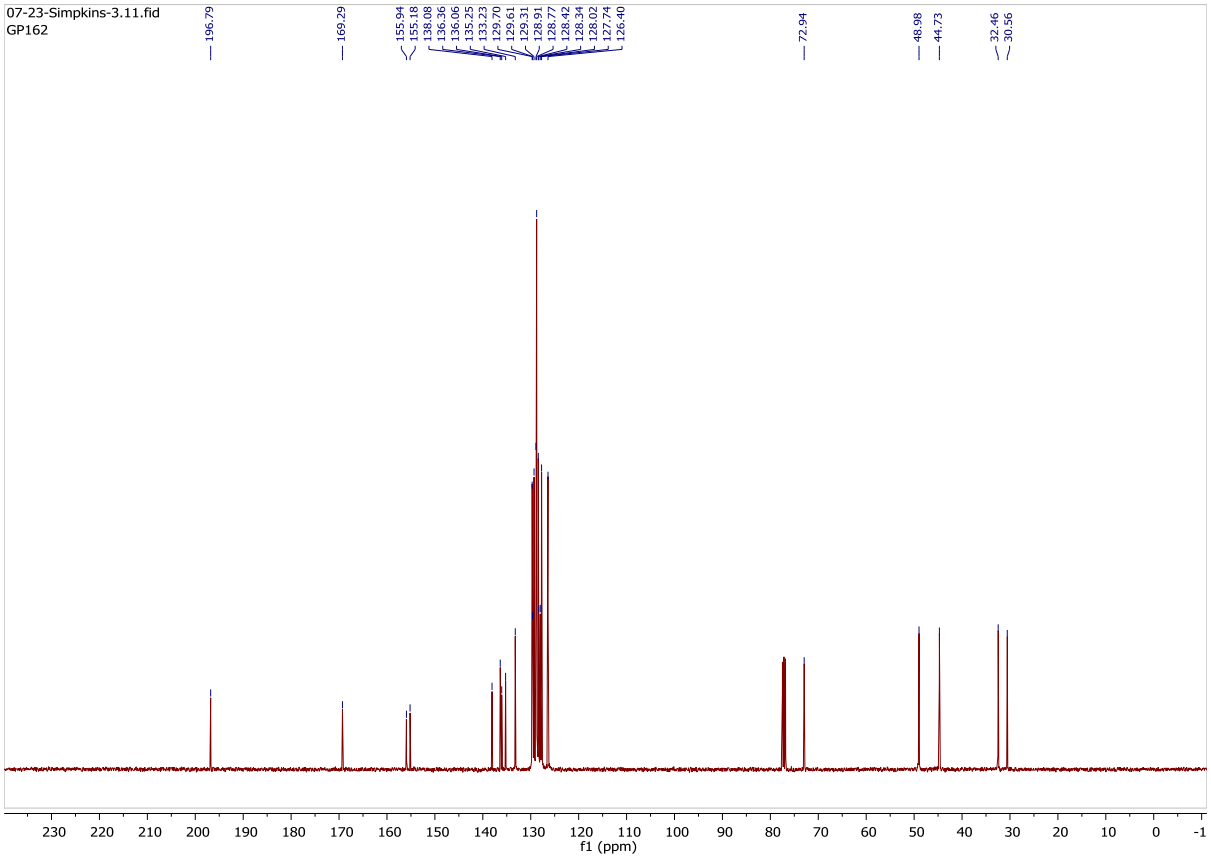

GP633 F1.1.fid
GP633 F1
L (m) 7.25
K (m) 6.92
B (d) 5.11
A (d) 5.21
C (d) 4.94
E (s) 3.84
D (d) 3.69
F (ddd) 2.97
G (m) 2.39
H (dq) 1.88
I (m) 1.74
J (t) 0.78
11.99
1.99
1.00
0.99
0.98
2.82
0.98
1.07
1.00
1.12
3.15
2.80
f1 (ppm)
BnN
NBn
O
2l

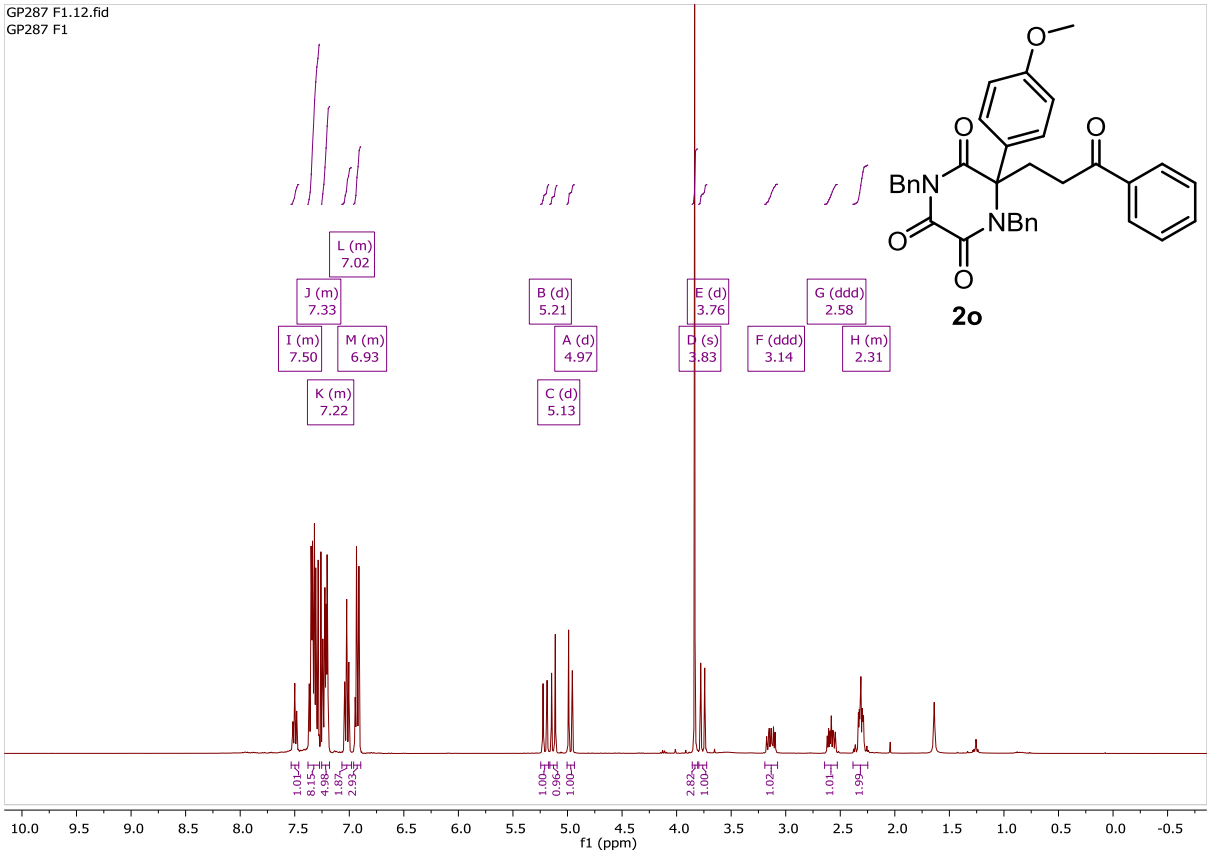

GP633 F1.2.fid
GP633 F1
169.42
160.40
155.96
155.16
136.78
135.21
129.84
129.28
129.26
128.84
128.70
128.31
128.09
127.66
114.97
72.47
55.59
48.79
44.73
35.87
35.47
30.24
7.70
f1 (ppm)

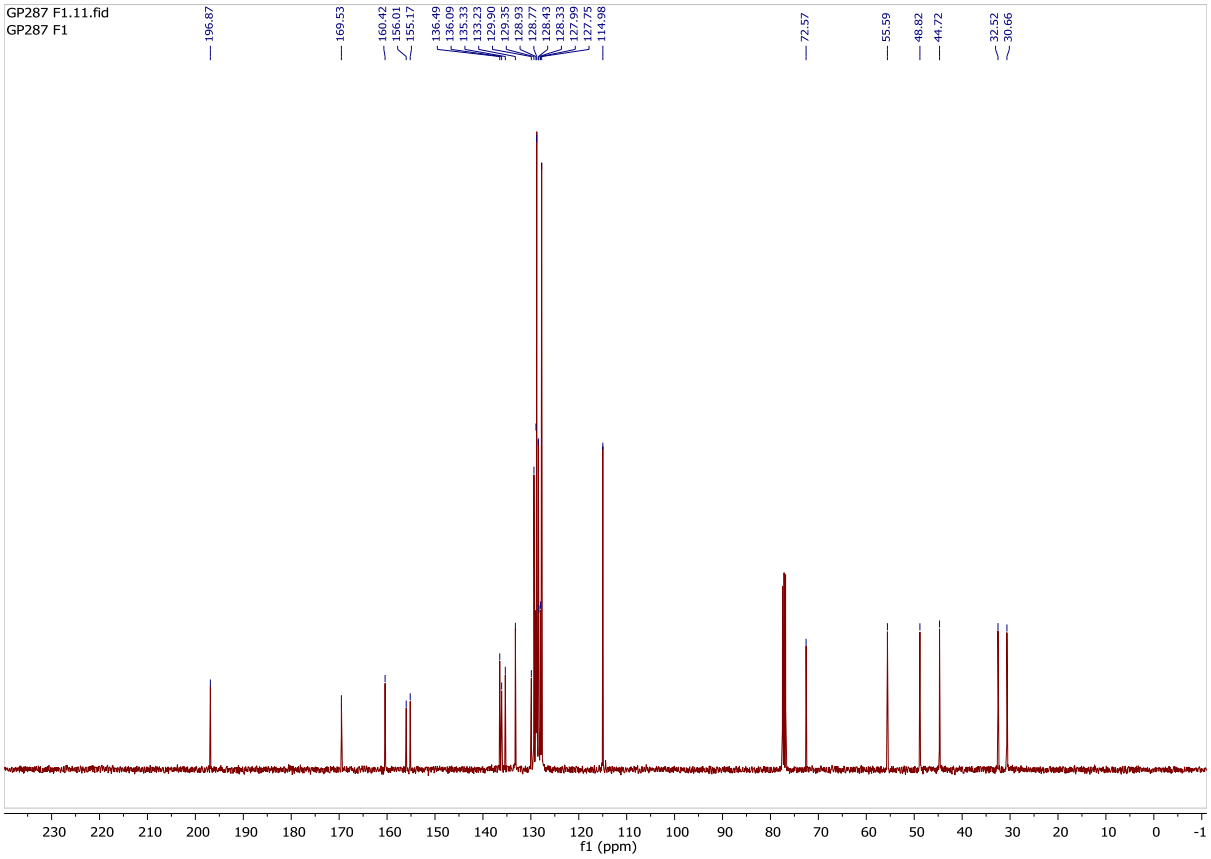

09-10-Simpkins-49.12.fid
GP211
I (m) 8.19
J (m) 7.52
K (m) 7.23
A (m) 5.07
B (d) 4.94
C (d) 3.79
D (ddd) 2.98
E (ddd) 2.51
G (dq) 1.91
H (m) 1.79
F (t) 0.79
1.89
1.90
9.74
1.87
1.00
0.89
0.96
0.91
1.05
2.74
2.72
f1 (ppm)

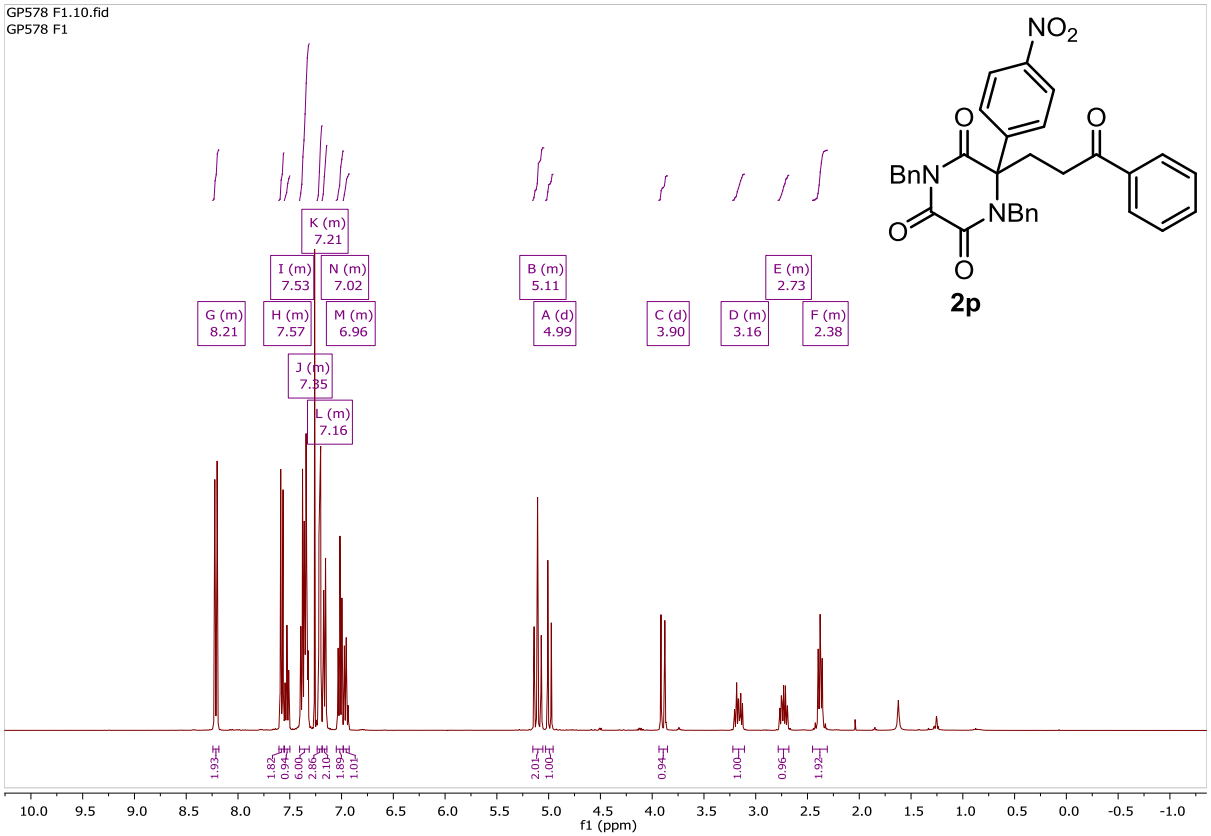

09-10-Simpkins-49.11.fid
GP211
207.76
168.26
155.40
154.75
148.35
144.69
136.09
134.81
129.36
129.09
128.92
128.79
128.59
128.35
127.86
124.51
72.38
48.99
44.98
35.54
30.56
7.66
f1 (ppm)

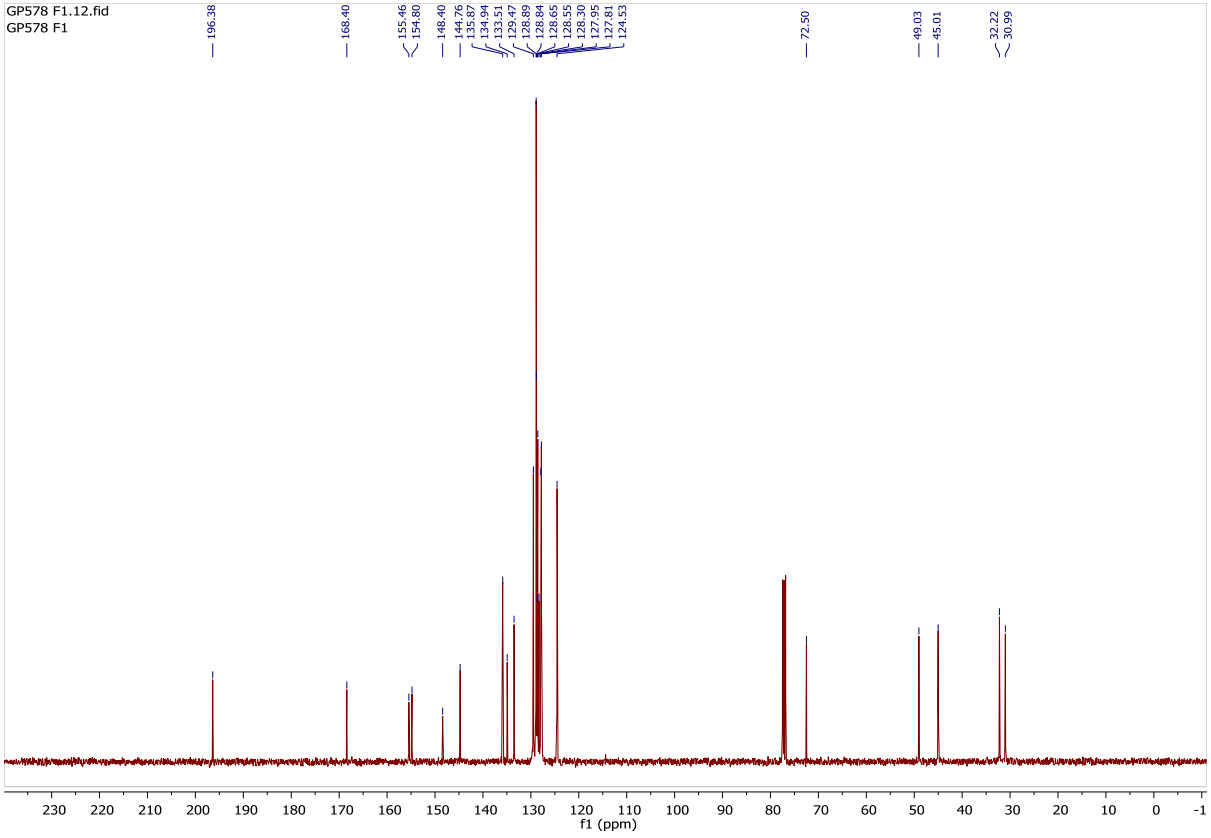

07-23-Simpkins-3.12.fid
GP162
BnN
NBn
O
O
O
O
2n
I (m) 7.02
K (m) 7.37
H (m) 6.93
J (m) 7.21
B (d) 5.13
A (d) 4.98
C (d) 5.23
D (d) 3.73
E (ddd) 3.18
F (ddd) 2.63
G (m) 2.33
11.71
5.15
2.09
1.10
0.99
1.02
1.00
1.01
1.05
1.04
1.98
f1 (ppm)

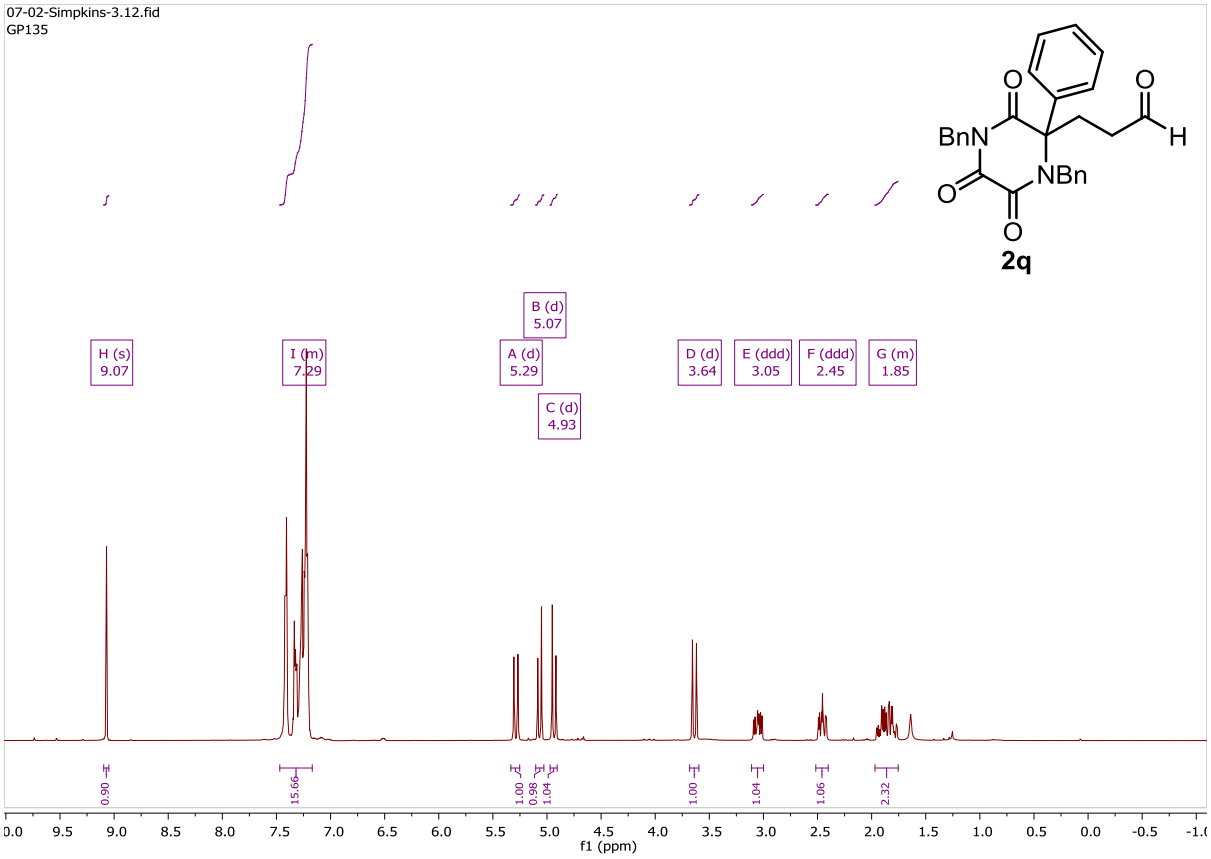

07-23-Simpkins-3.11.fid
GP162
196.79
169.29
155.94
155.18
138.08
136.36
136.06
135.25
133.23
129.70
129.61
129.31
128.91
128.77
128.42
128.34
128.02
127.74
126.40
72.94
48.98
44.73
32.46
30.56
f1 (ppm)

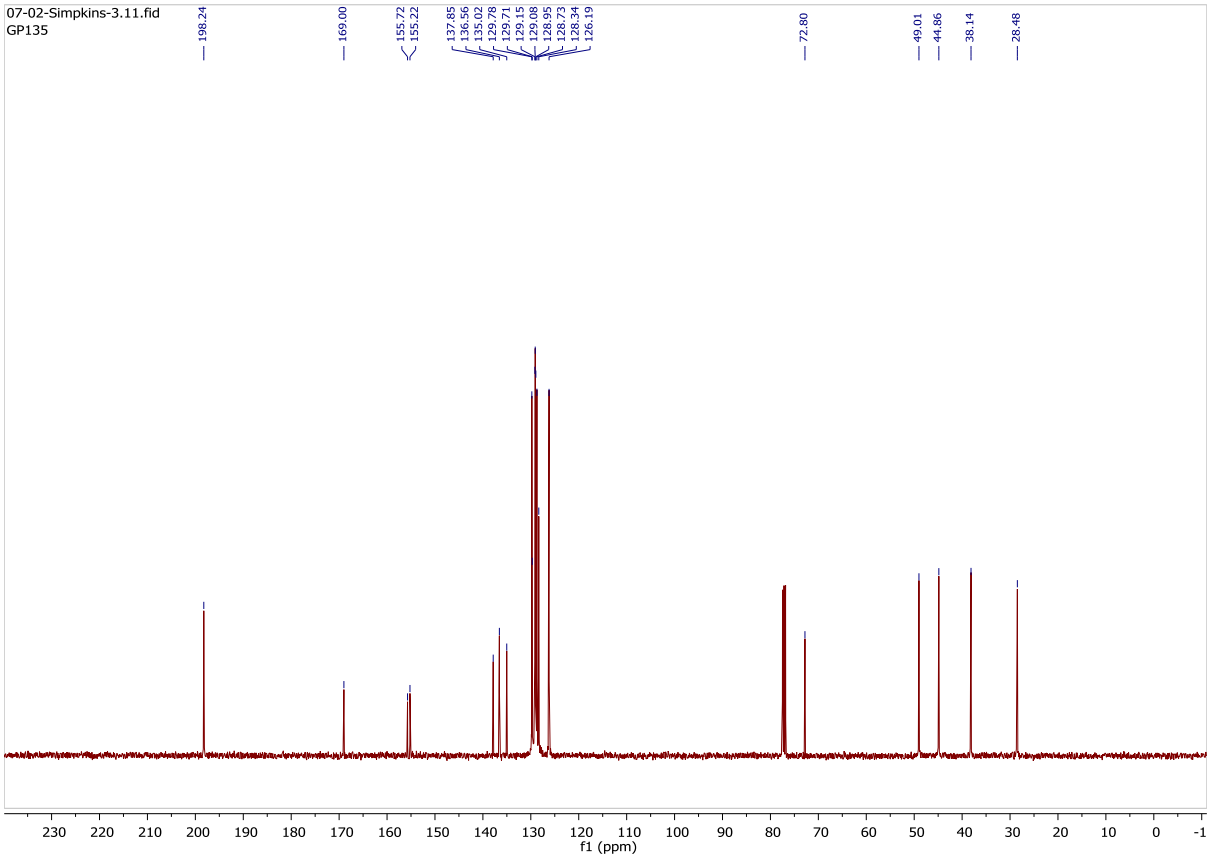

GP287 F1.12.fid
GP287 F1
L (m) 7.02
J (m) 7.33
I (m) 7.50
M (m) 6.93
K (m) 7.22
B (d) 5.21
A (d) 4.97
C (d) 5.13
E (d) 3.76
D (s) 3.83
G (ddd) 2.58
F (ddd) 3.14
H (m) 2.31
BnN
NBn
O
2o
f1 (ppm)

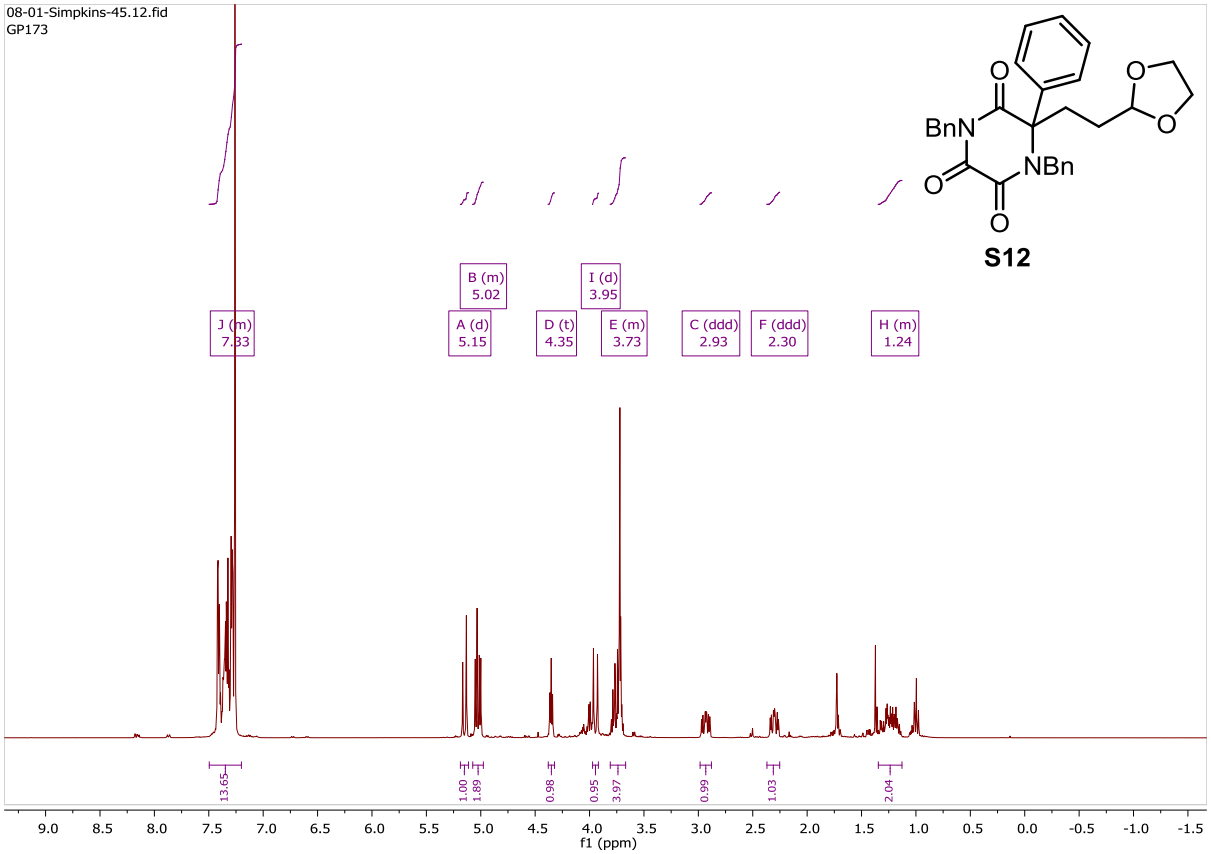

GP287 F1.11.fid
GP287 F1
196.87
169.53
160.42
156.01
155.17
136.49
136.09
135.33
133.23
129.90
129.35
128.93
128.77
128.43
128.33
127.99
127.75
114.98
72.57
55.59
48.82
44.72
32.52
30.66
f1 (ppm)

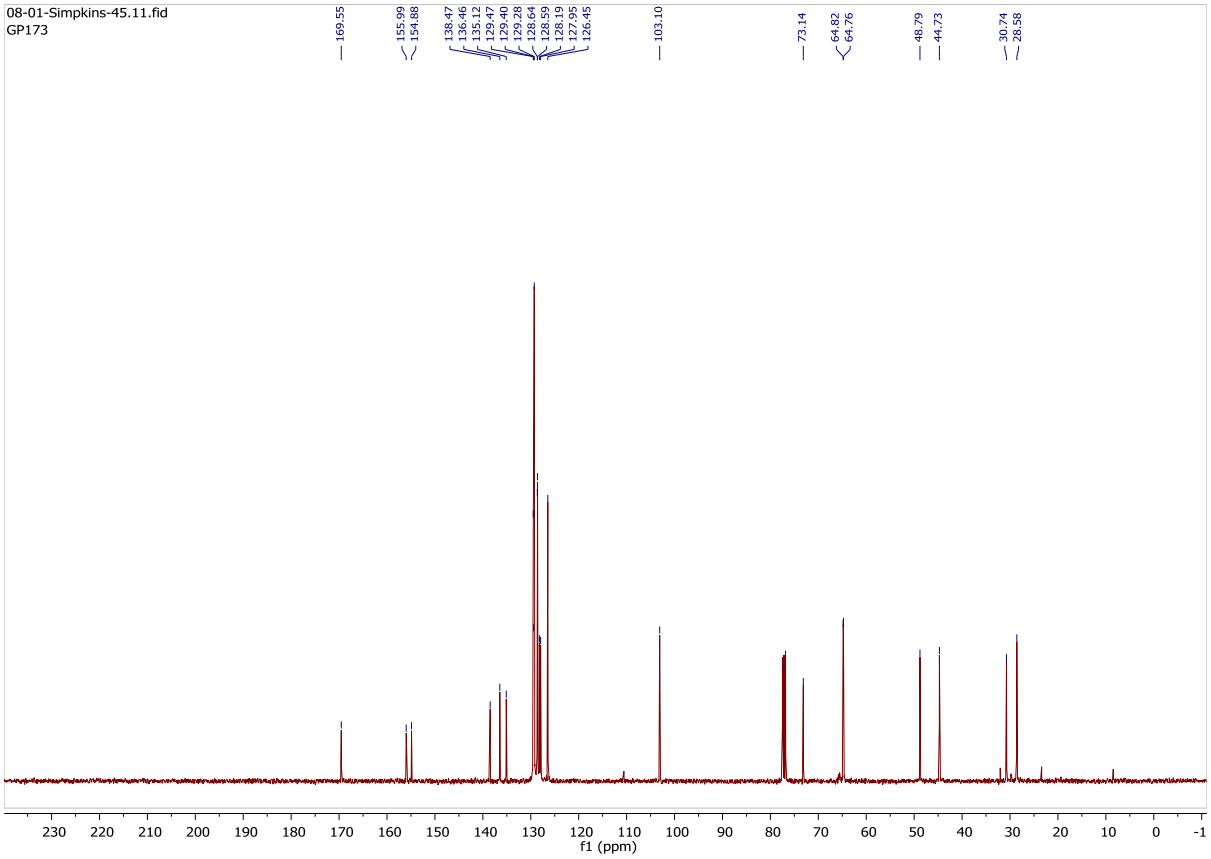

GP578 F1.10.fid
GP578 F1
K (m) 7.21
I (m) 7.53
N (m) 7.02
B (m) 5.11
E (m) 2.73
G (m) 8.21
H (m) 7.57
M (m) 6.96
A (d) 4.99
C (d) 3.90
D (m) 3.16
F (m) 2.38
J (m) 7.35
L (m) 7.16
1.93
1.82
0.94
6.00
2.86
2.10
1.89
1.01
2.01
1.00
0.94
1.00
0.96
1.92
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
NO2
O
O
BnN
NBn
O
O
2p

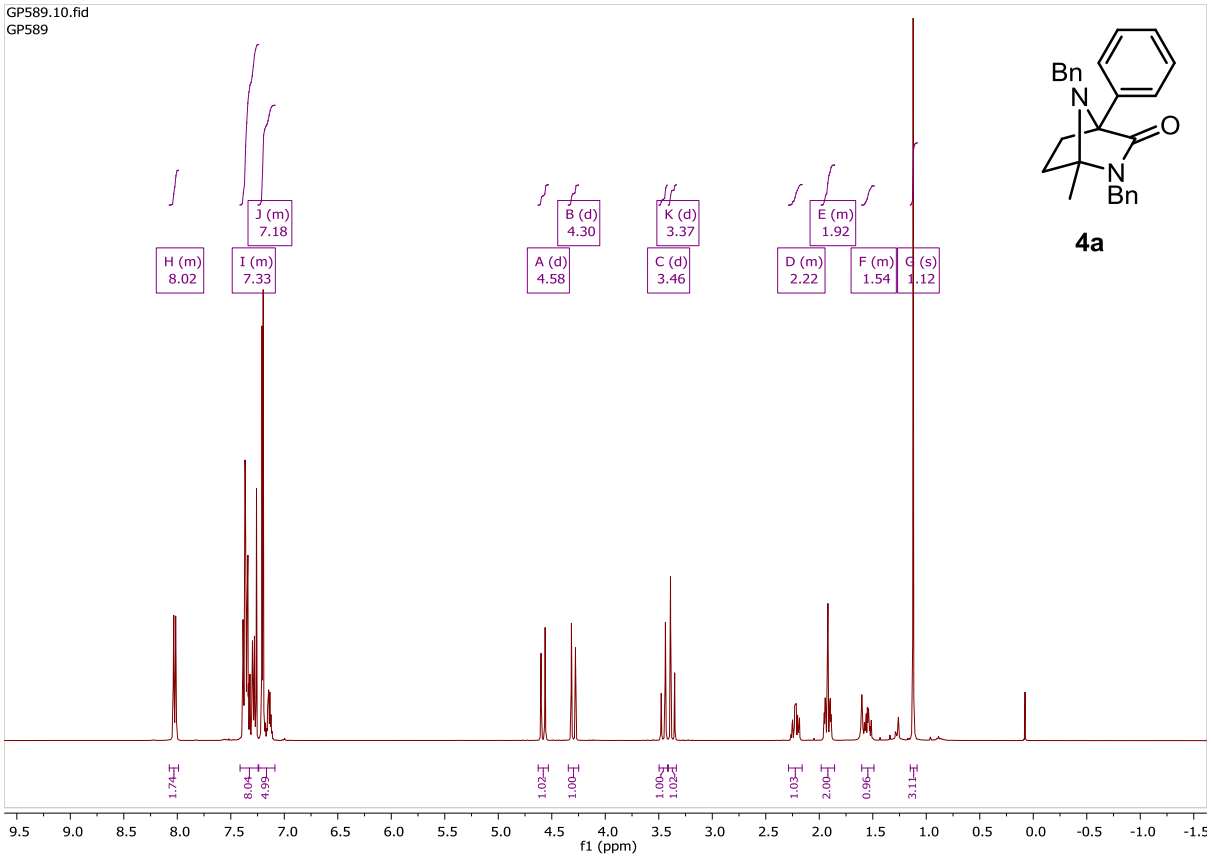

GP578 F1.12.fid
GP578 F1
196.38
168.40
155.46
154.80
148.40
144.76
135.87
134.94
133.51
129.47
128.89
128.84
128.65
128.55
128.30
127.95
127.81
124.53
72.50
49.03
45.01
32.22
30.99
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

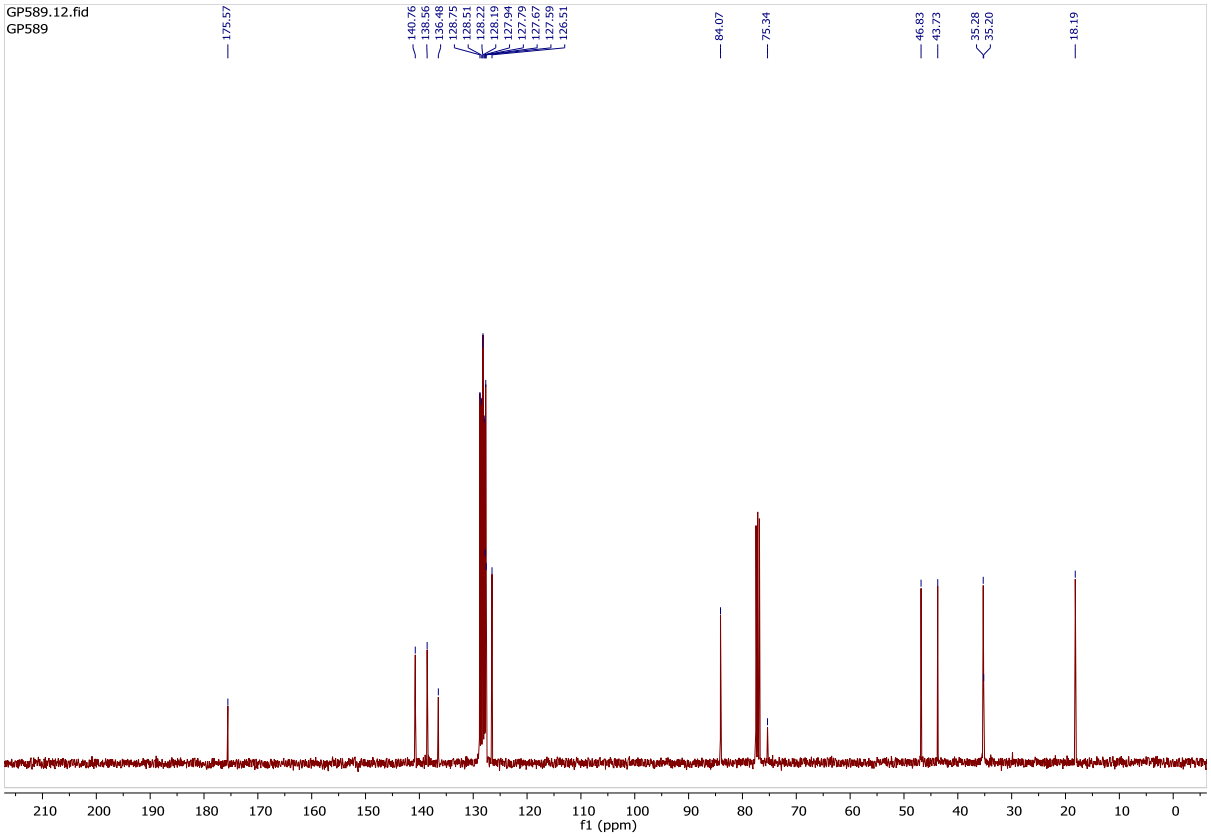

07-02-Simpkins-3.12.fid
GP135
BnN
NBn
O
O
O
O
H
2q
H (s) 9.07
I (m) 7.29
A (d) 5.29
B (d) 5.07
C (d) 4.93
D (d) 3.64
E (ddd) 3.05
F (ddd) 2.45
G (m) 1.85
0.90
15.66
1.00
0.98
1.04
1.00
1.04
1.06
2.32
f1 (ppm)

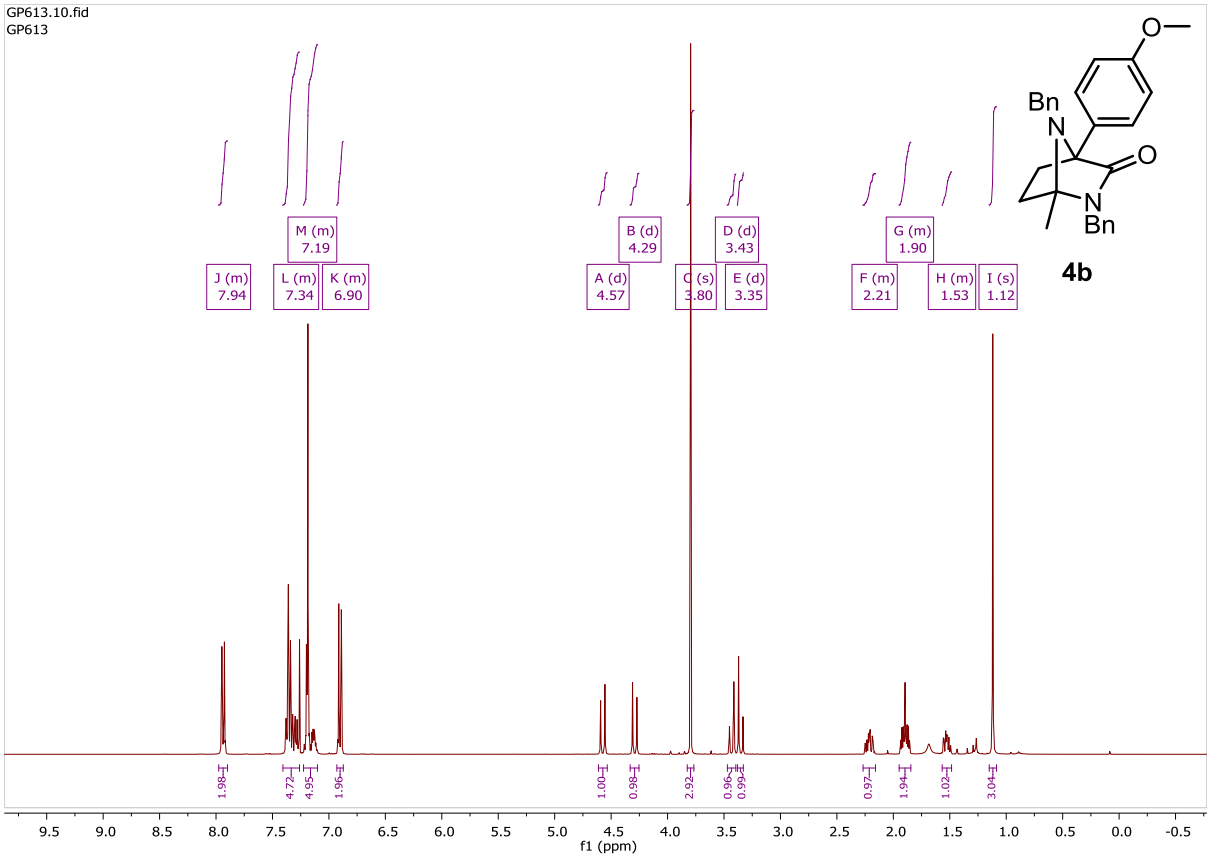

07-02-Simpkins-3.11.fid
GP135
198.24
169.00
155.72
155.22
137.85
136.56
135.02
129.78
129.71
129.15
129.08
128.95
128.73
128.34
126.19
72.80
49.01
44.86
38.14
28.48
f1 (ppm)

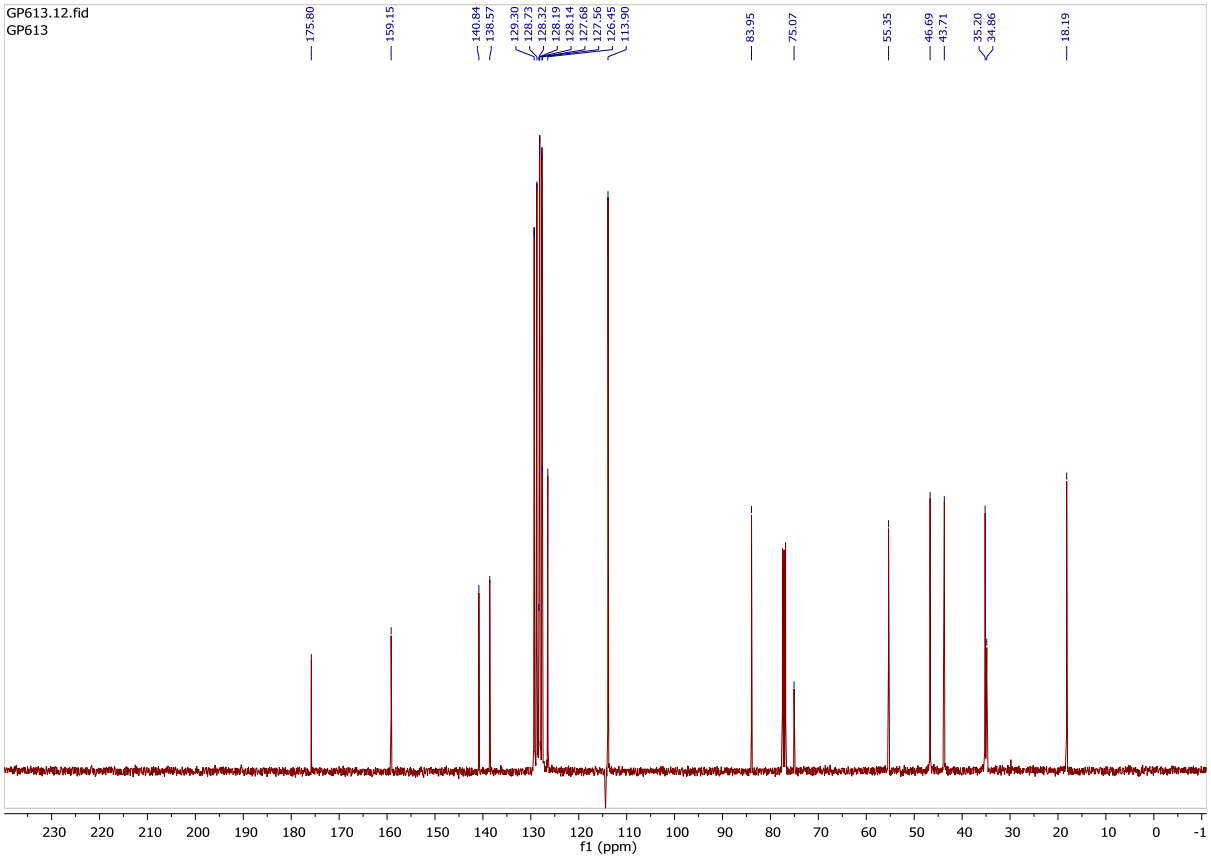

08-01-Simpkins-45.12.fid
GP173
BnN
NBn
O
O
O
O
O
S12
J (m) 7.33
B (m) 5.02
A (d) 5.15
D (t) 4.35
I (d) 3.95
E (m) 3.73
C (ddd) 2.93
F (ddd) 2.30
H (m) 1.24
13.65
1.00
1.89
0.98
0.95
3.97
0.99
1.03
2.04
f1 (ppm)

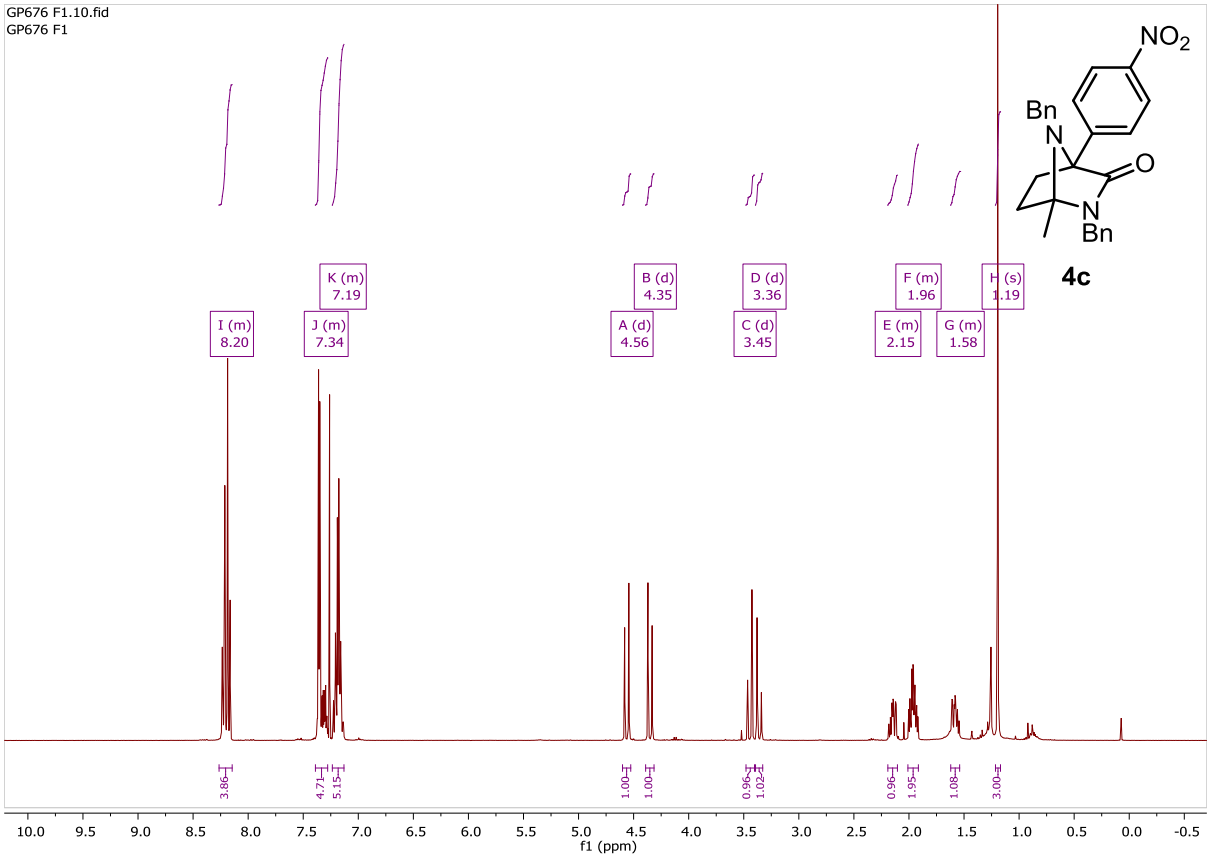

08-01-Simpkins-45.11.fid
GP173
169.55
155.99
154.88
138.47
136.46
135.12
129.47
129.40
129.28
128.64
128.59
128.19
127.95
126.45
103.10
73.14
64.82
64.76
48.79
44.73
30.74
28.58
f1 (ppm)

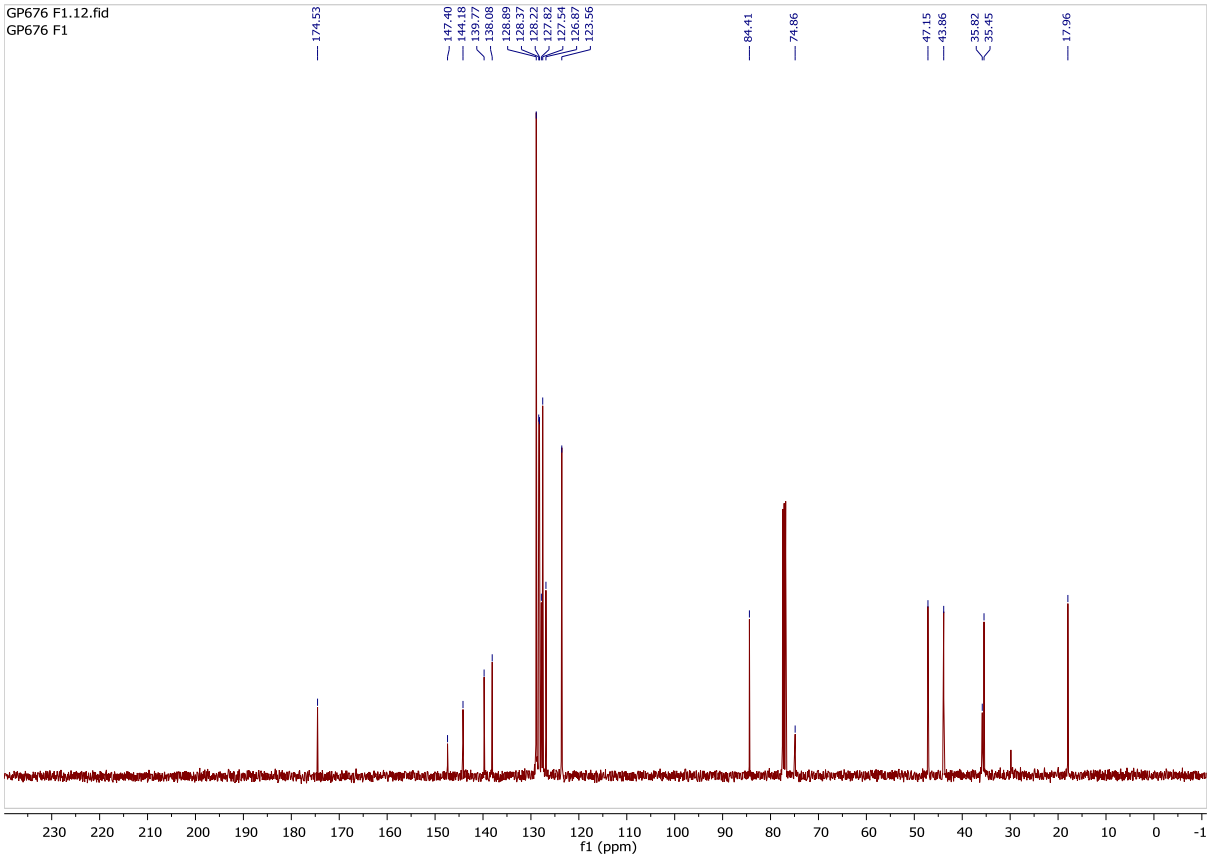

GP589.10.fid
GP589
Bn
N
O
N
Bn
4a
H (m) 8.02
I (m) 7.33
J (m) 7.18
A (d) 4.58
B (d) 4.30
C (d) 3.46
K (d) 3.37
D (m) 2.22
E (m) 1.92
F (m) 1.54
G (s) 1.12
1.74
8.04
4.99
1.02
1.00
1.00
1.02
1.03
2.00
0.96
3.11
f1 (ppm)

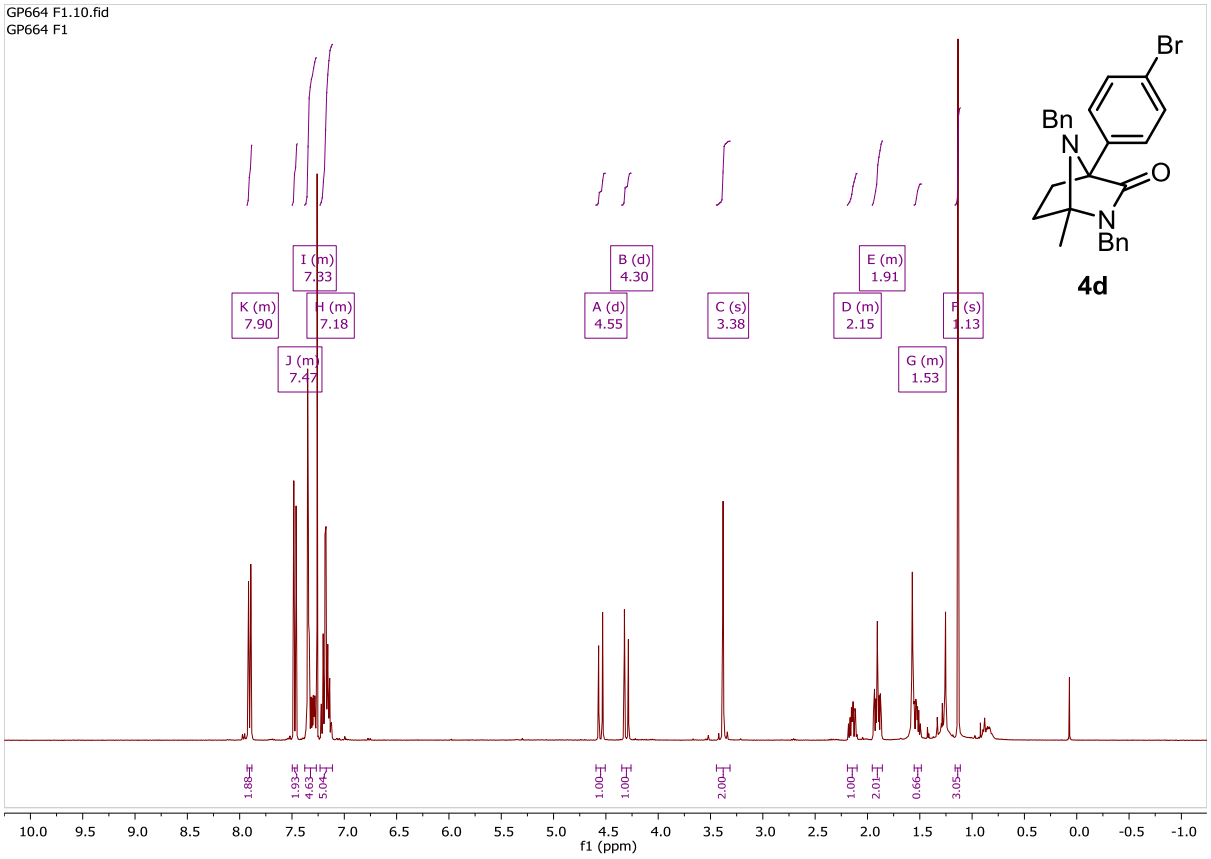

GP589.12.fid
GP589
175.57
140.76
138.56
136.48
128.75
128.51
128.22
128.19
127.94
127.79
127.67
127.59
126.51
84.07
75.34
46.83
43.73
35.28
35.20
18.19
f1 (ppm)

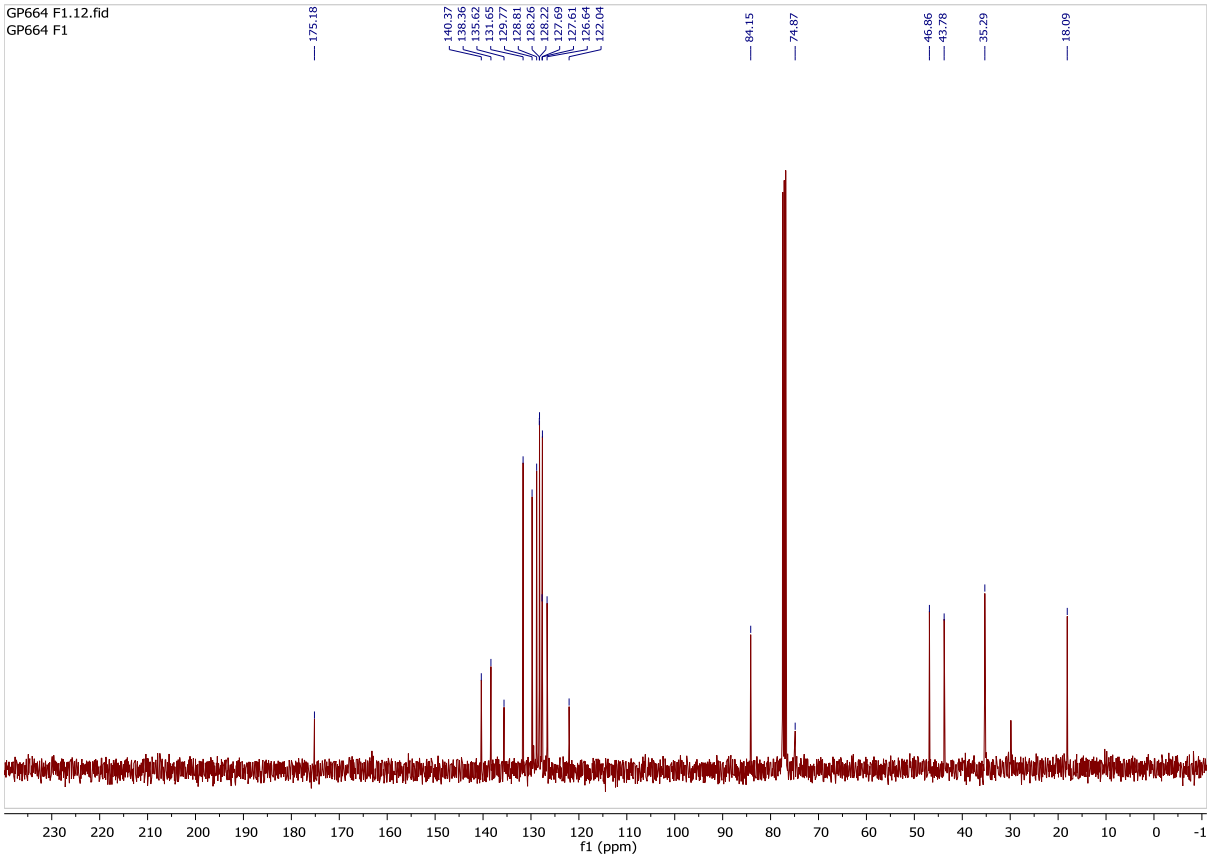

GP613.10.fid
GP613
M (m) 7.19
B (d) 4.29
D (d) 3.43
G (m) 1.90
J (m) 7.94
L (m) 7.34
K (m) 6.90
A (d) 4.57
C (s) 3.80
E (d) 3.35
F (m) 2.21
H (m) 1.53
I (s) 1.12
Bn
N
O
O
N
Bn
4b
f1 (ppm)

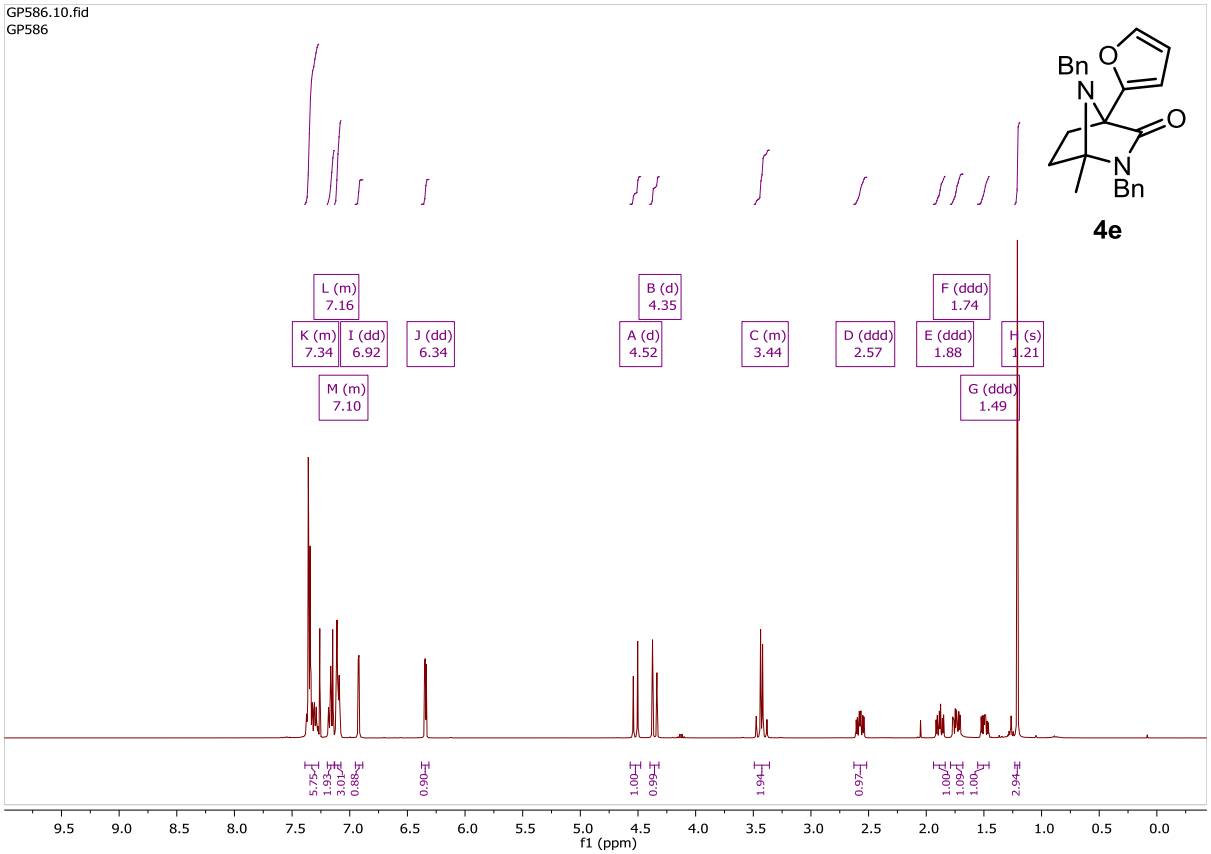

GP613.12.fid
GP613
175.80
159.15
140.84
138.57
129.30
128.73
128.32
128.19
128.14
127.68
127.56
126.45
113.90
83.95
75.07
55.35
46.69
43.71
35.20
34.86
18.19
f1 (ppm)

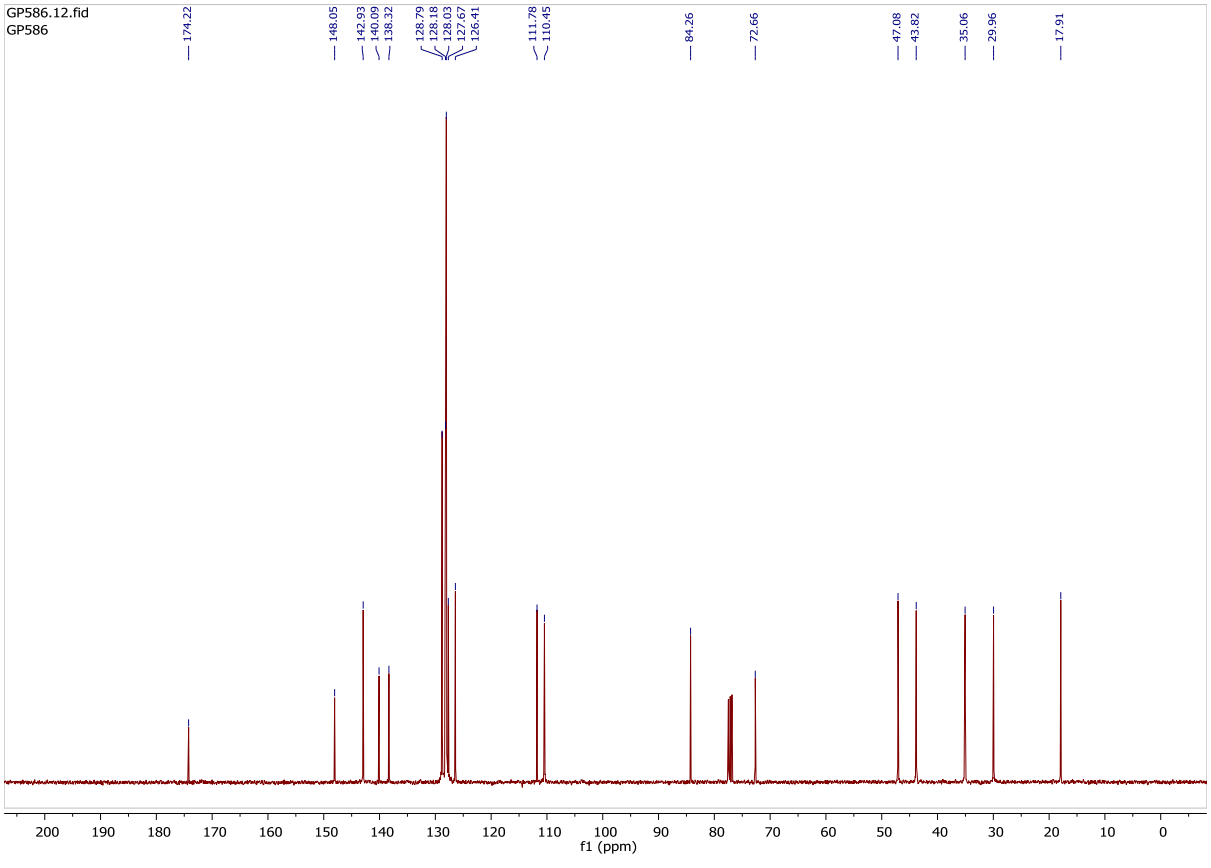

GP676 F1.10.fid
GP676 F1
NO2
Bn
N
O
N
Bn
4c
I (m) 8.20
J (m) 7.34
K (m) 7.19
A (d) 4.56
B (d) 4.35
C (d) 3.45
D (d) 3.36
E (m) 2.15
F (m) 1.96
G (m) 1.58
H (s) 1.19
3.86
4.71
5.15
1.00
1.00
0.96
1.02
0.96
1.95
1.08
3.00
f1 (ppm)

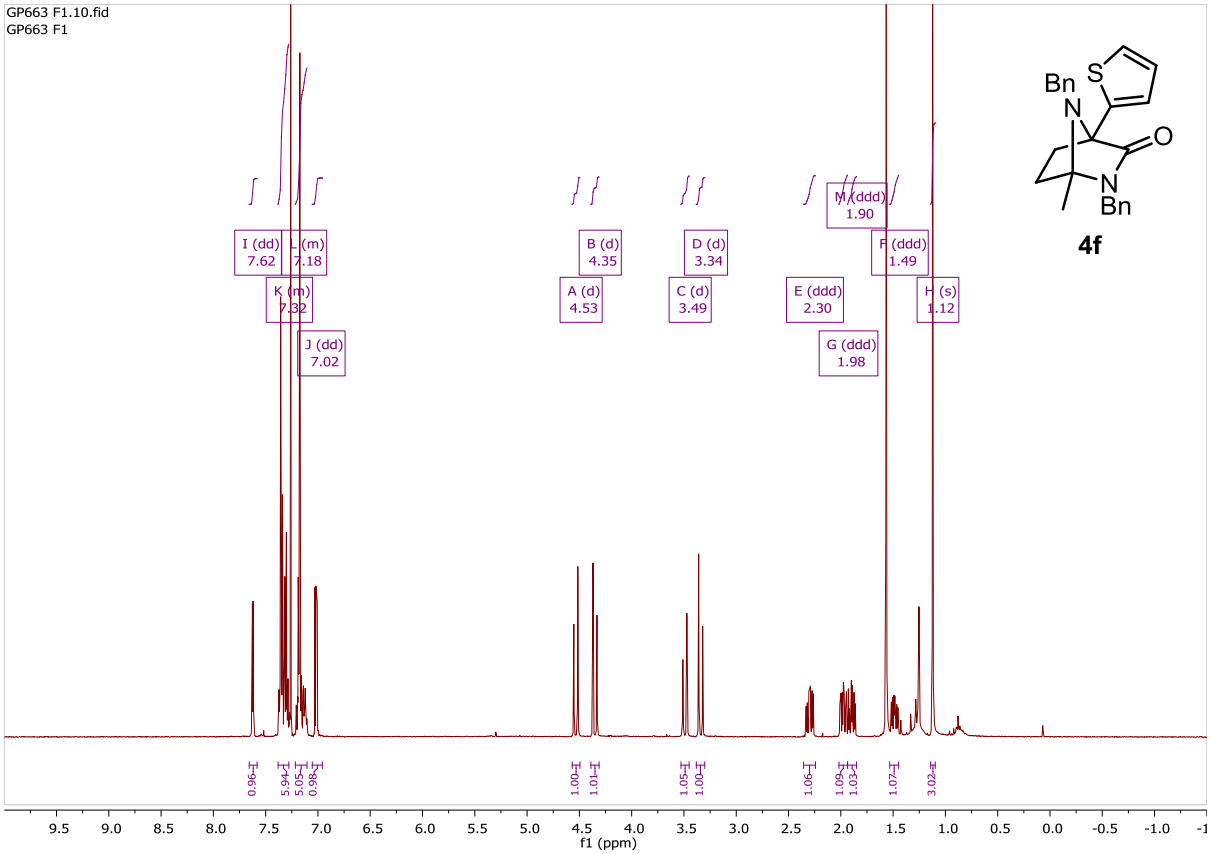

GP676 F1.12.fid
GP676 F1
174.53
147.40
144.18
139.77
138.08
128.89
128.37
128.22
127.82
127.54
126.87
123.56
84.41
74.86
47.15
43.86
35.82
35.45
17.96
f1 (ppm)


GP664 F1.10.fid
GP664 F1
Br
Bn
N
O
N
Bn
4d
I (m)
7.33
K (m)
7.90
H (m)
7.18
J (m)
7.47
B (d)
4.30
A (d)
4.55
C (s)
3.38
E (m)
1.91
D (m)
2.15
F (s)
1.13
G (m)
1.53
1.88
1.93
4.63
5.04
1.00
1.00
2.00
1.00
2.01
0.66
3.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


GP664 F1.12.fid
GP664 F1
175.18
140.37
138.36
135.62
131.65
129.77
128.81
128.26
128.22
127.69
127.61
126.64
122.04
84.15
74.87
46.86
43.78
35.29
18.09
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

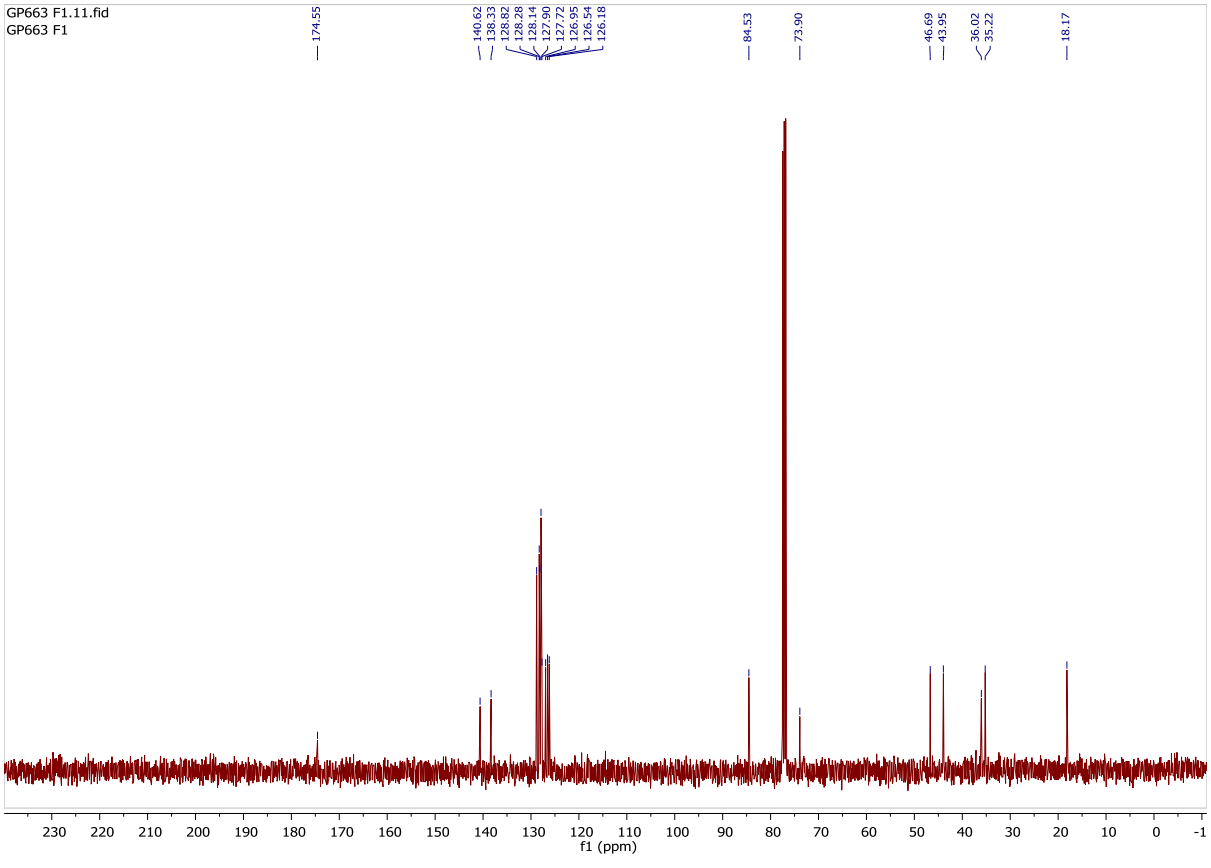

GP586.10.fid
GP586
Bn
N
O
O
N
Bn
4e
L (m) 7.16
K (m) 7.34
I (dd) 6.92
J (dd) 6.34
M (m) 7.10
B (d) 4.35
A (d) 4.52
C (m) 3.44
D (ddd) 2.57
F (ddd) 1.74
E (ddd) 1.88
H (s) 1.21
G (ddd) 1.49
5.75
1.93
3.01
0.88
0.90
1.00
0.99
1.94
0.97
1.00
1.09
1.00
2.94
f1 (ppm)

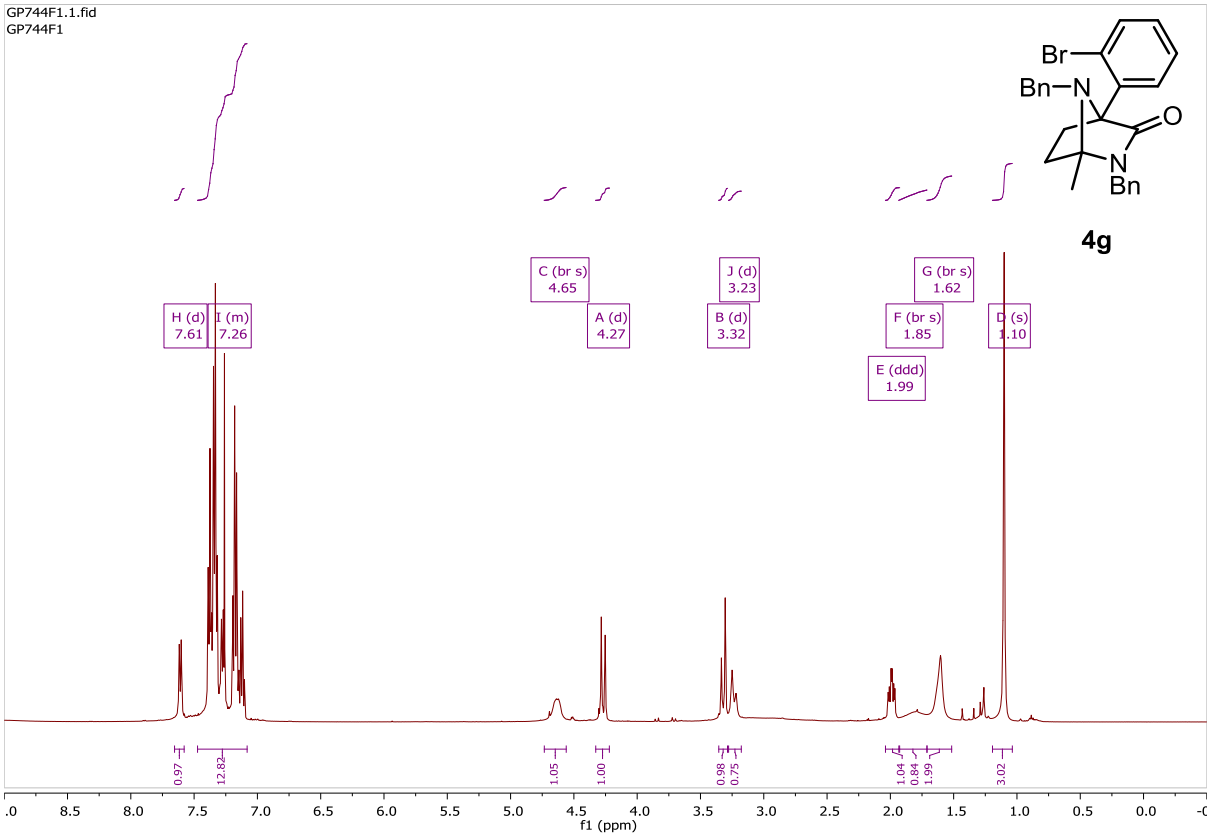

GP586.12.fid
GP586
174.22
148.05
142.93
140.09
138.32
128.79
128.18
128.03
127.67
126.41
111.78
110.45
84.26
72.66
47.08
43.82
35.06
29.96
17.91
f1 (ppm)

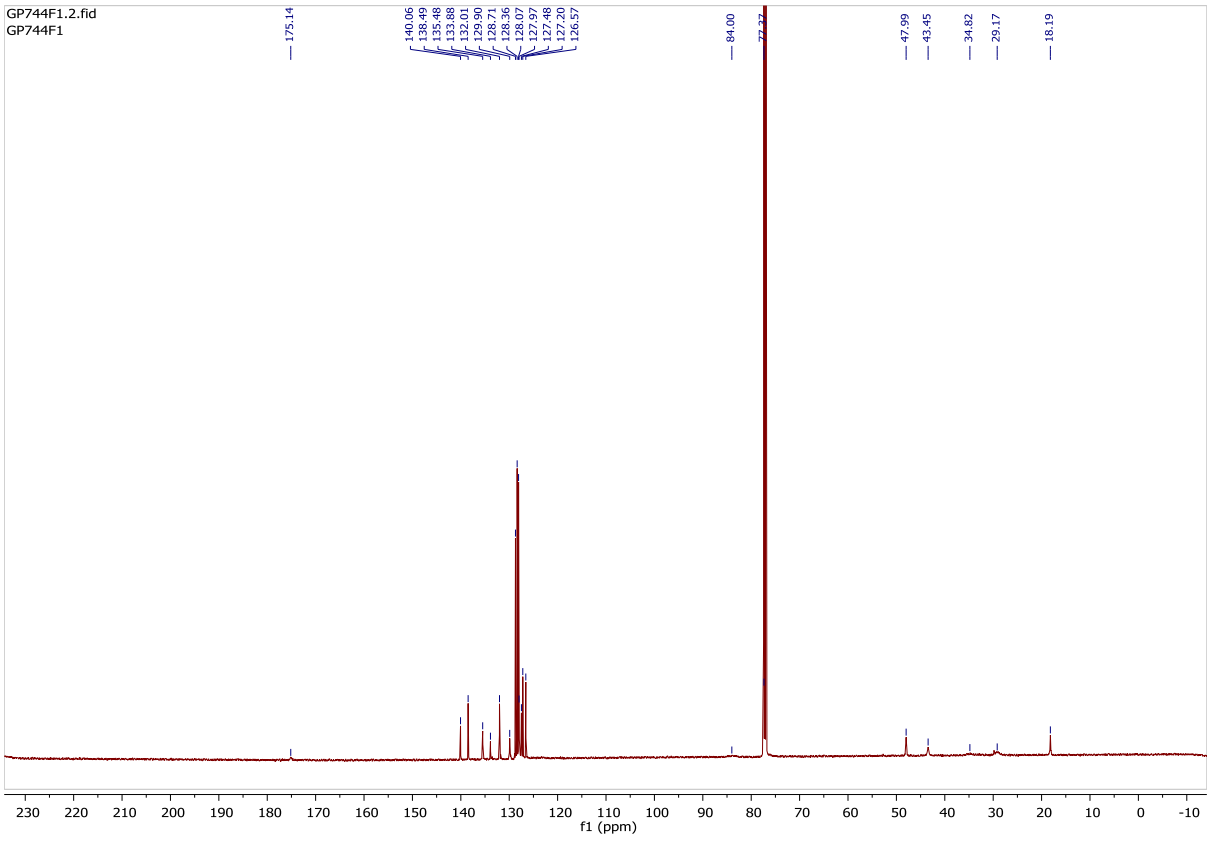

GP663 F1.10.fid
GP663 F1
I (dd) 7.62
L (m) 7.18
K (m) 7.32
J (dd) 7.02
B (d) 4.35
A (d) 4.53
D (d) 3.34
C (d) 3.49
M (ddd) 1.90
F (ddd) 1.49
E (ddd) 2.30
G (ddd) 1.98
H (s) 1.12
0.96
5.94
5.05
0.98
1.00
1.01
1.05
1.00
1.06
1.09
1.03
1.07
3.02
f1 (ppm)

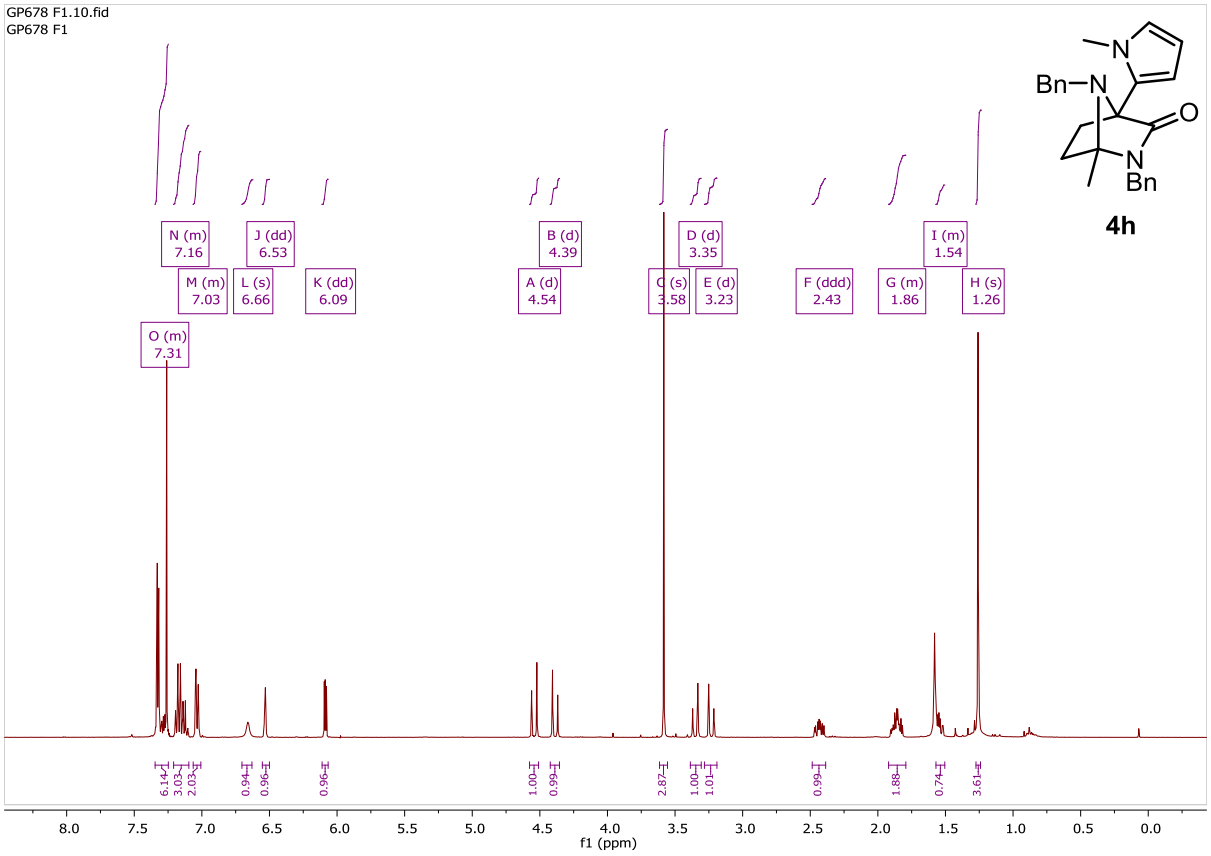
Bn
N
S
O
N
Bn

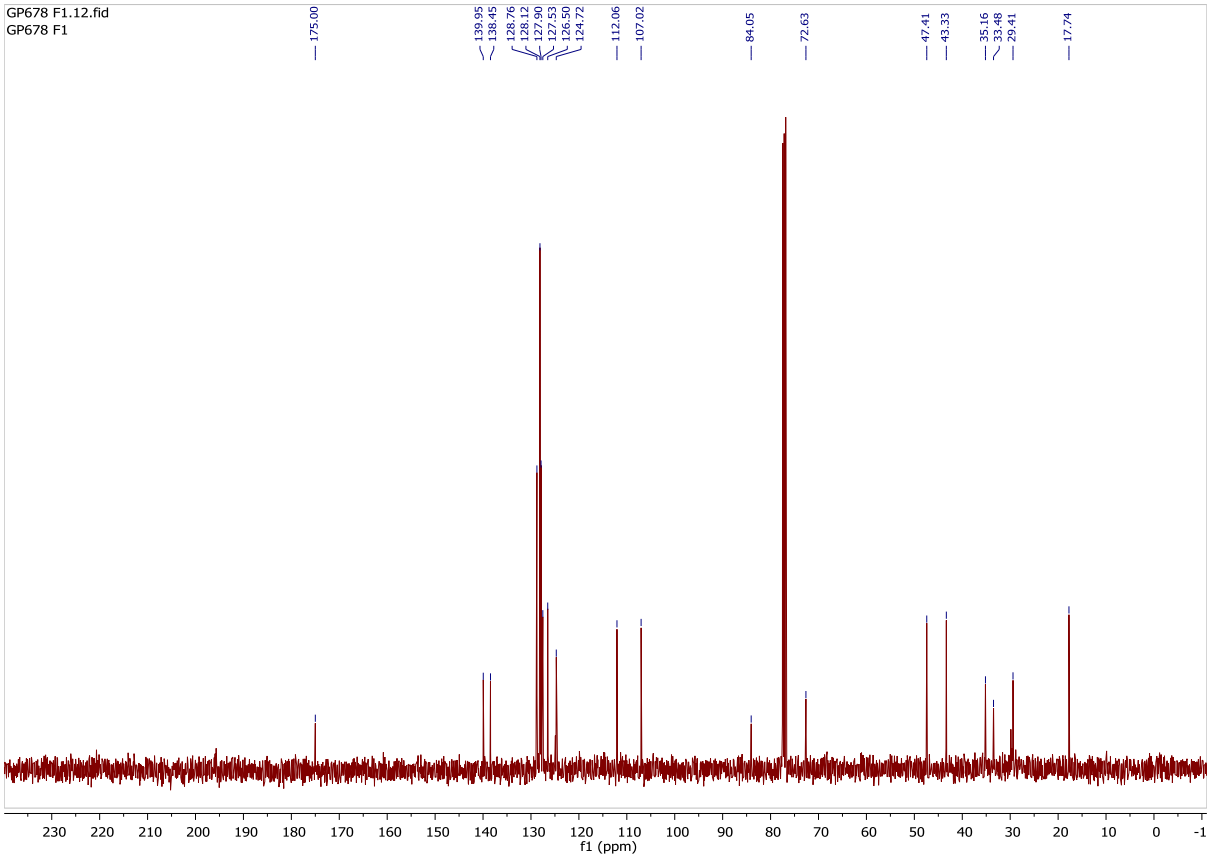
4f

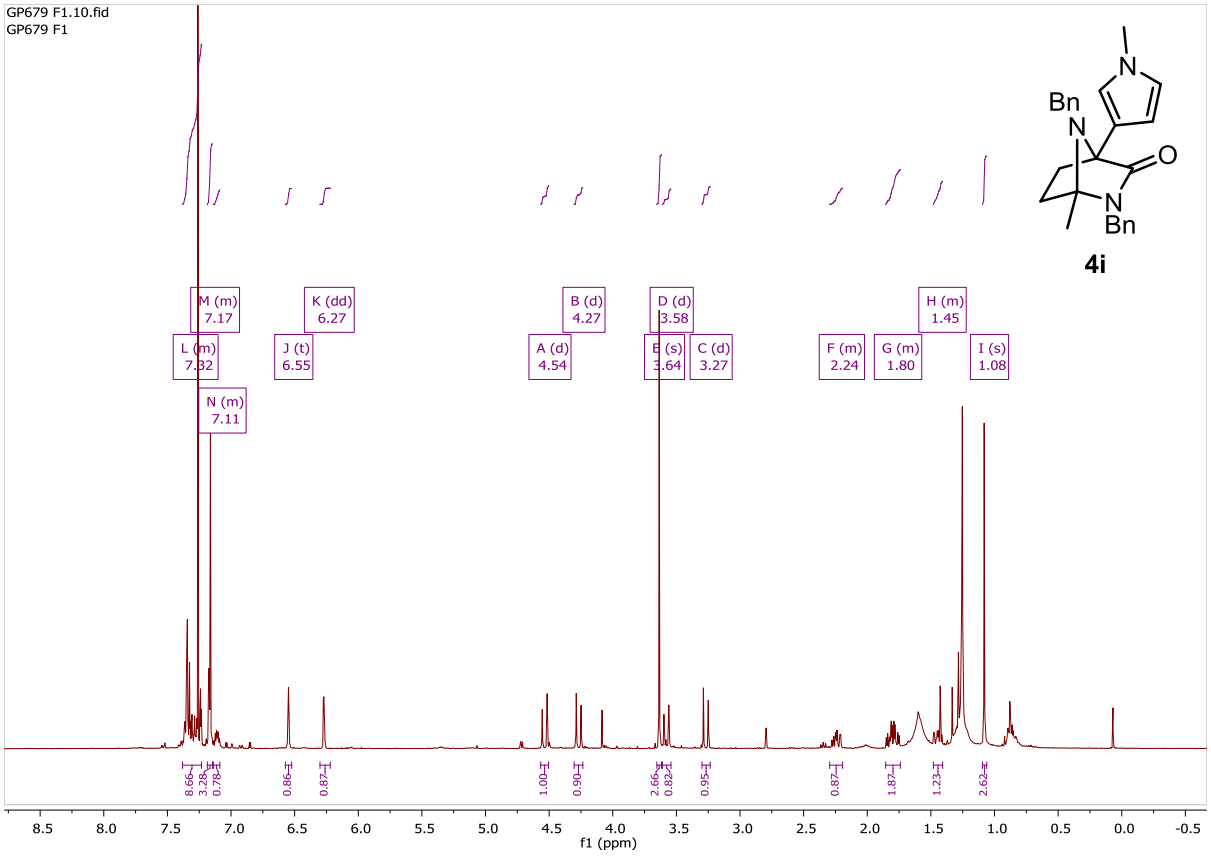

GP663 F1.11.fid
GP663 F1
174.55
140.62
138.33
128.82
128.28
128.14
127.90
127.72
126.95
126.54
126.18
84.53
73.90
46.69
43.95
36.02
35.22
18.17
f1 (ppm)

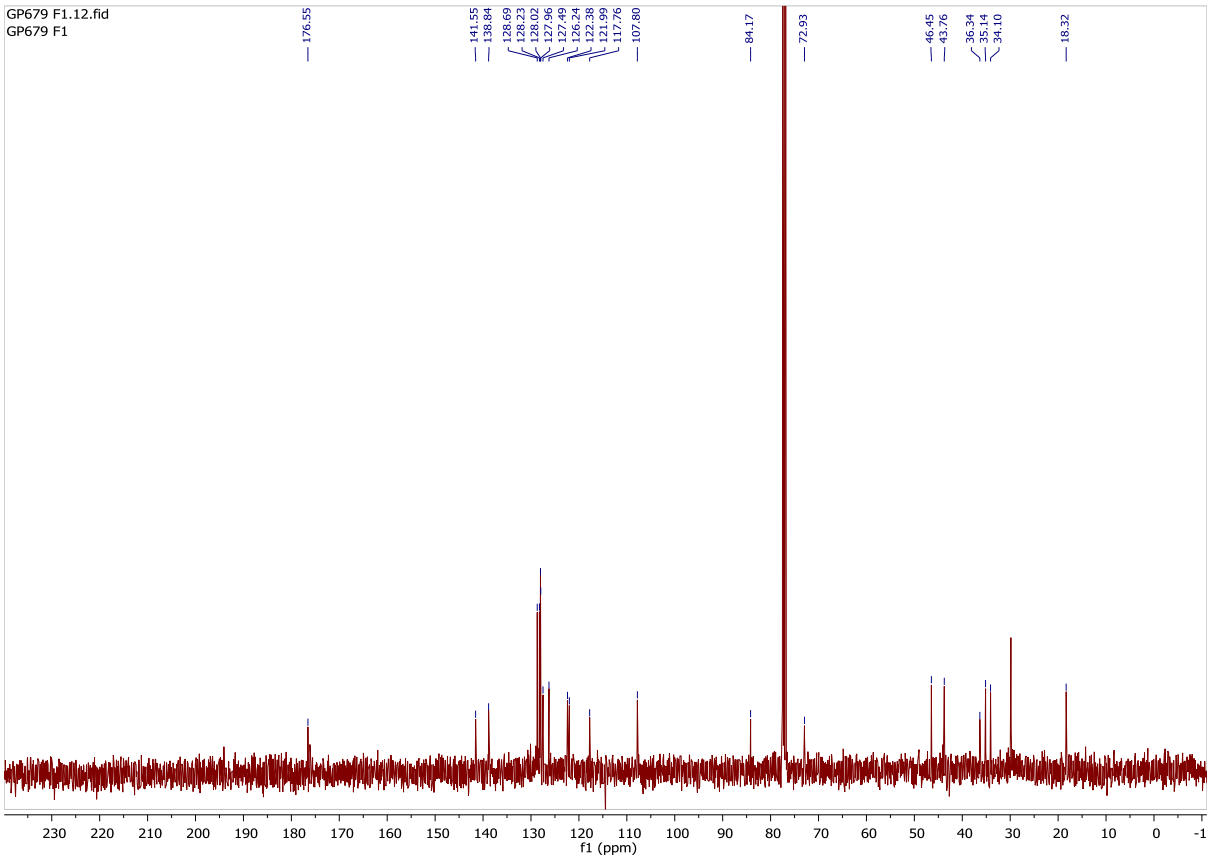

GP744F1.1.fid
GP744F1
Br
Bn–N
O
N
Bn
4g
H (d) 7.61
I (m) 7.26
C (br s) 4.65
A (d) 4.27
J (d) 3.23
B (d) 3.32
G (br s) 1.62
F (br s) 1.85
E (ddd) 1.99
D (s) 1.10
0.97
12.82
1.05
1.00
0.98
0.75
1.04
0.84
1.99
3.02
f1 (ppm)

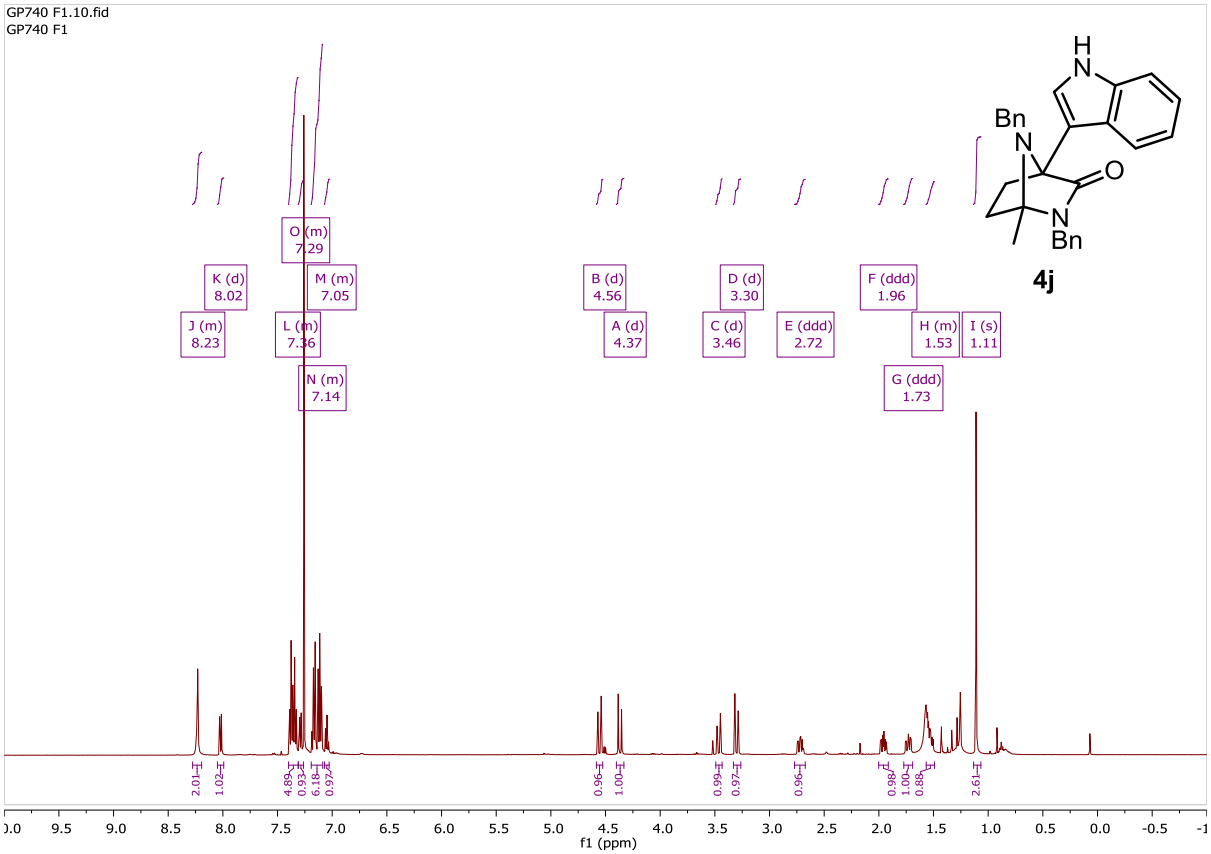

GP744F1.2.fid
GP744F1
175.14
140.06
138.49
135.48
133.88
132.01
129.90
128.71
128.36
128.07
127.97
127.48
127.20
126.57
84.00
77.32
47.99
43.45
34.82
29.17
18.19
f1 (ppm)

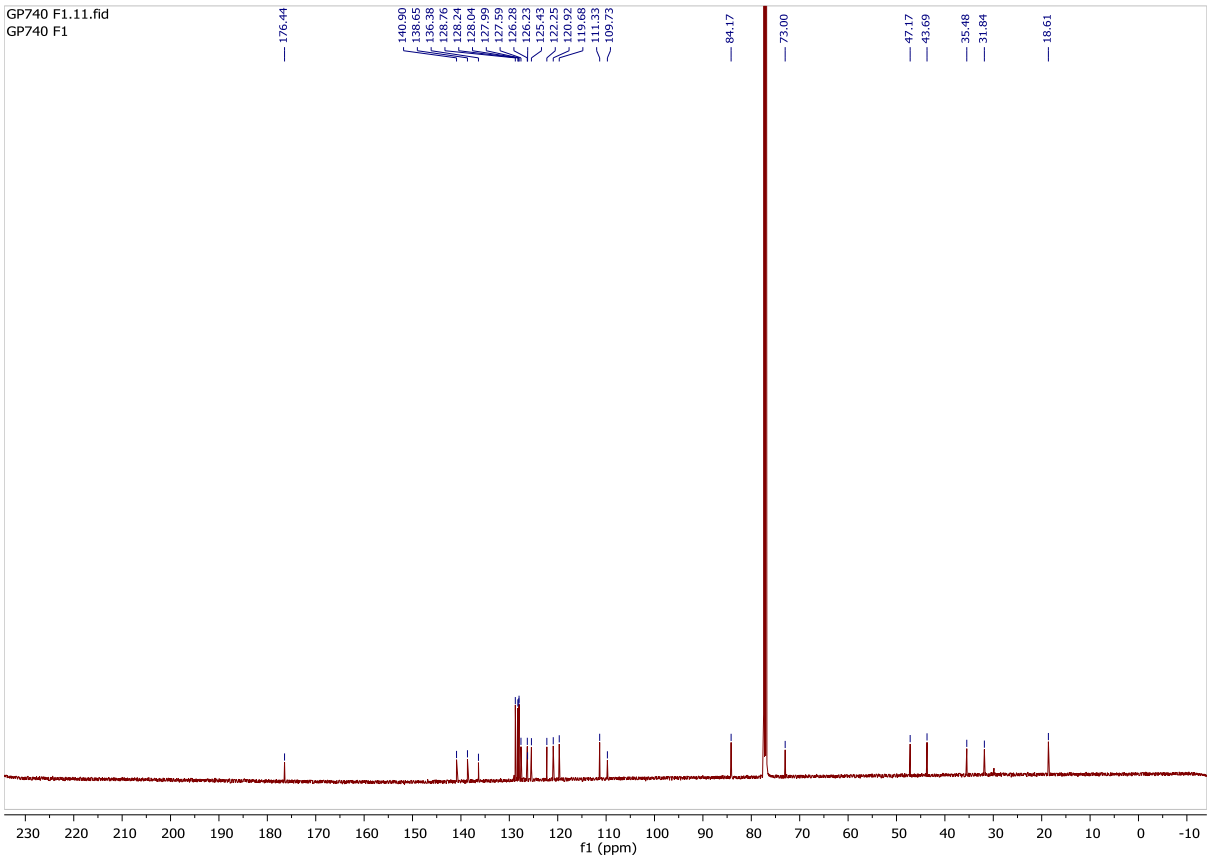

GP678 F1.10.fid
GP678 F1
N (m) 7.16
J (dd) 6.53
B (d) 4.39
D (d) 3.35
I (m) 1.54
M (m) 7.03
L (s) 6.66
K (dd) 6.09
A (d) 4.54
C (s) 3.58
E (d) 3.23
F (ddd) 2.43
G (m) 1.86
H (s) 1.26
O (m) 7.31
6.14
3.03
2.03
0.94
0.96
0.96
1.00
0.99
2.87
1.00
1.01
0.99
1.88
0.74
3.61
f1 (ppm)
Bn
N
O
4h

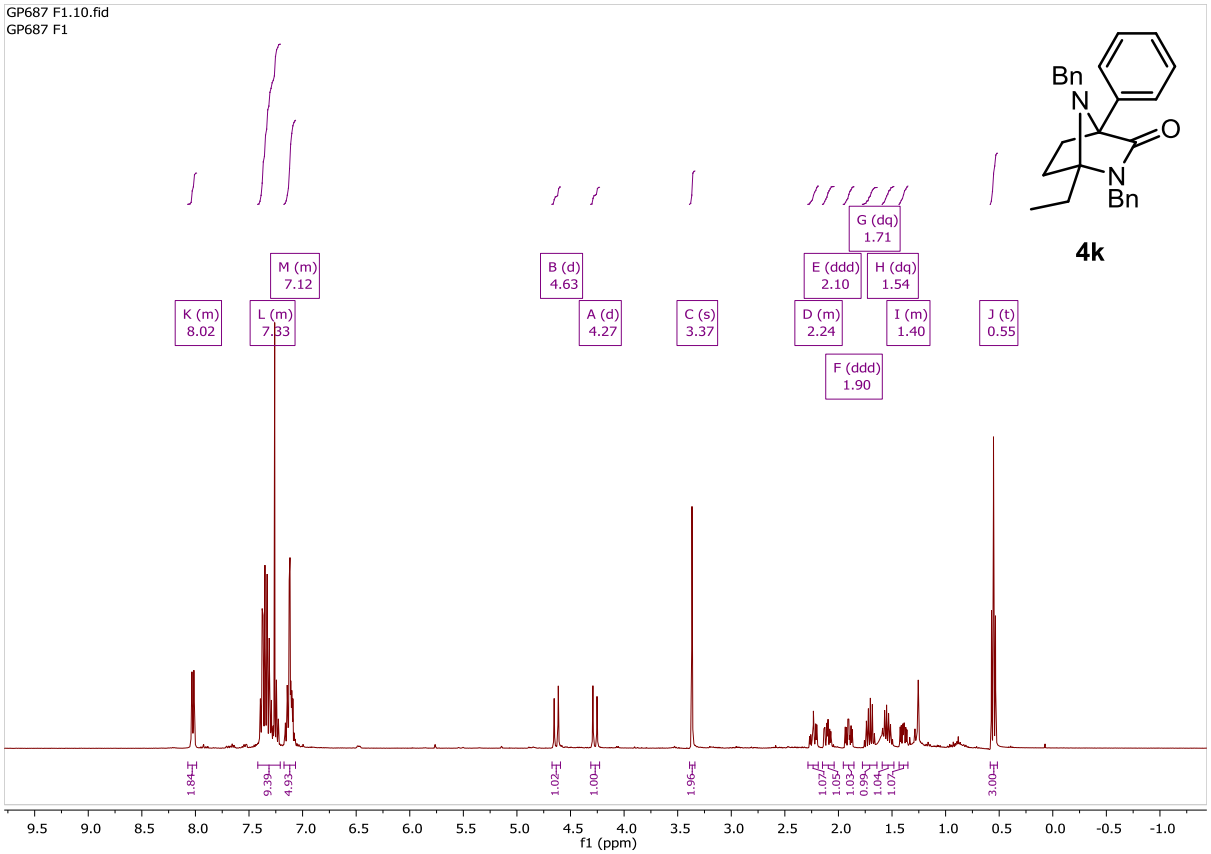

GP678 F1.12.fid
GP678 F1
175.00
139.95
138.45
128.76
128.12
127.90
127.53
126.50
124.72
112.06
107.02
84.05
72.63
47.41
43.33
35.16
33.48
29.41
17.74
f1 (ppm)

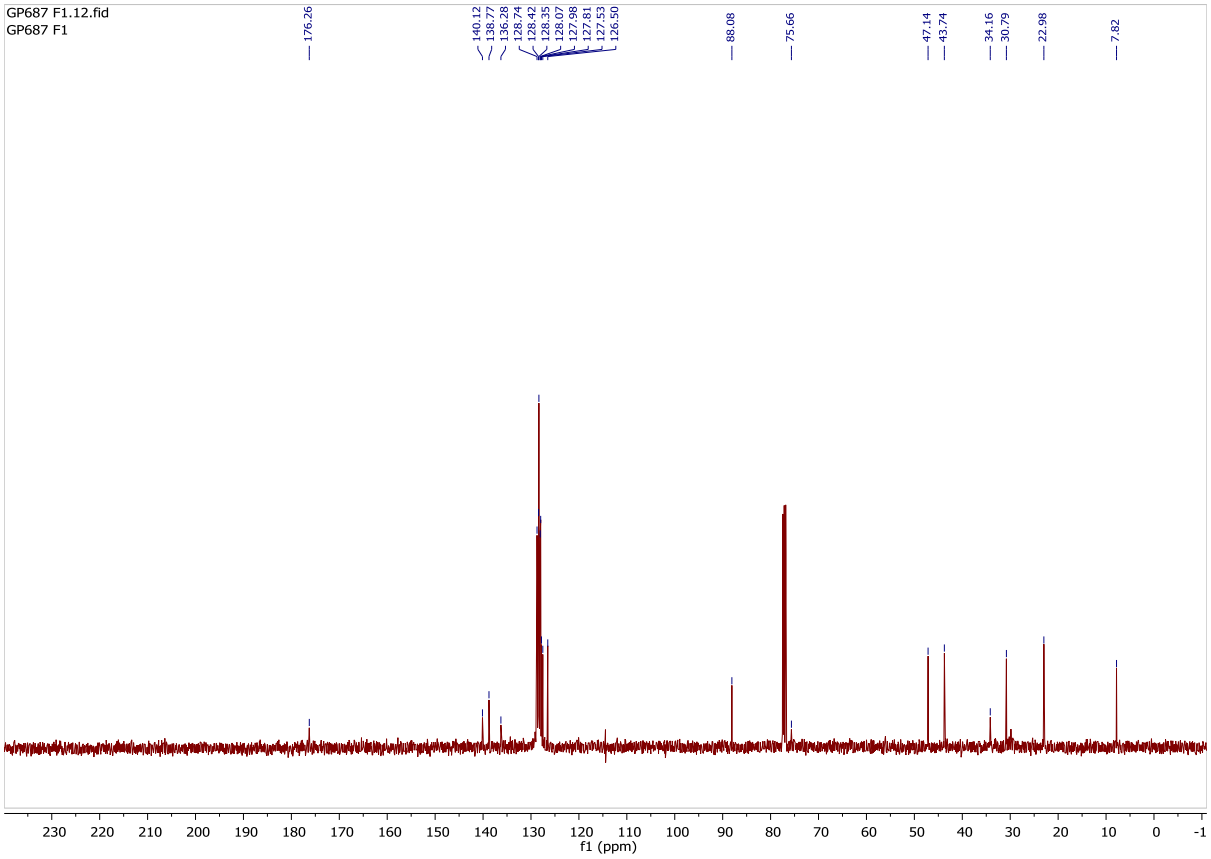

GP679 F1.10.fid
GP679 F1
Bn
N
O
N
Bn
4i
M (m) 7.17
K (dd) 6.27
B (d) 4.27
D (d) 3.58
H (m) 1.45
L (m) 7.32
J (t) 6.55
A (d) 4.54
E (s) 3.64
C (d) 3.27
F (m) 2.24
G (m) 1.80
I (s) 1.08
N (m) 7.11
8.66
3.28
0.78
0.86
0.87
1.00
0.90
2.66
0.82
0.95
0.87
1.87
1.23
2.62
f1 (ppm)

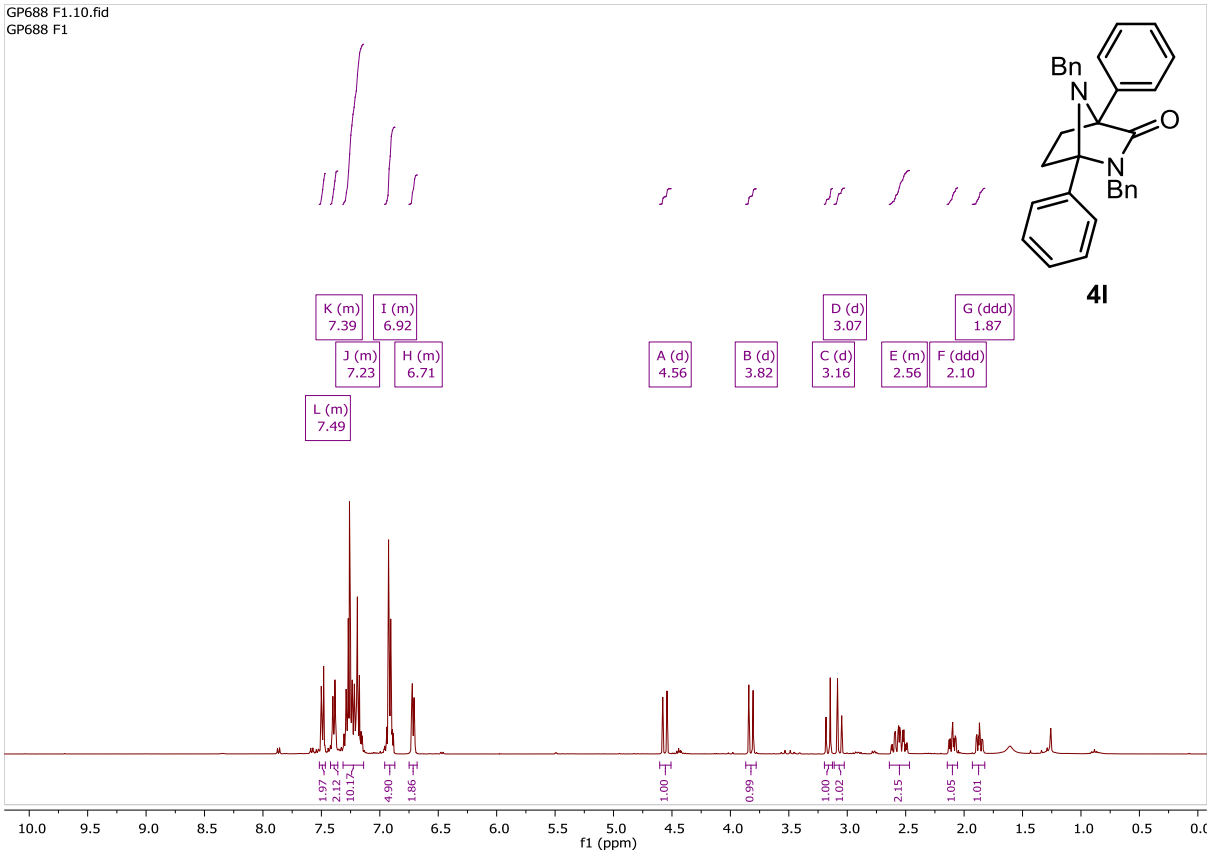

GP679 F1.12.fid
GP679 F1
176.55
141.55
138.84
128.69
128.23
128.02
127.96
127.49
126.24
122.38
121.99
117.76
107.80
84.17
72.93
46.45
43.76
36.34
35.14
34.10
18.32
f1 (ppm)

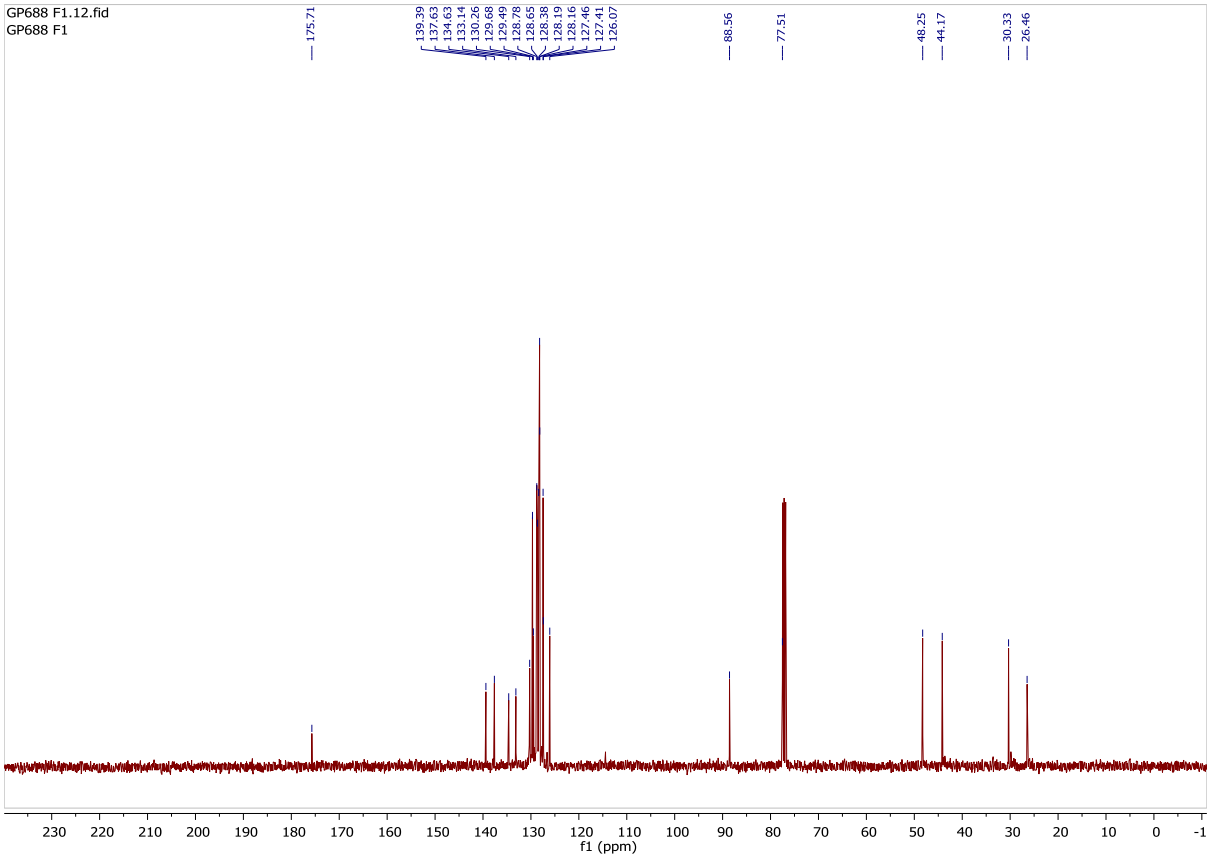

GP740 F1.10.fid
GP740 F1
O (m) 7.29
K (d) 8.02
M (m) 7.05
J (m) 8.23
L (m) 7.36
N (m) 7.14
B (d) 4.56
A (d) 4.37
D (d) 3.30
C (d) 3.46
E (ddd) 2.72
F (ddd) 1.96
H (m) 1.53
I (s) 1.11
G (ddd) 1.73
f1 (ppm)

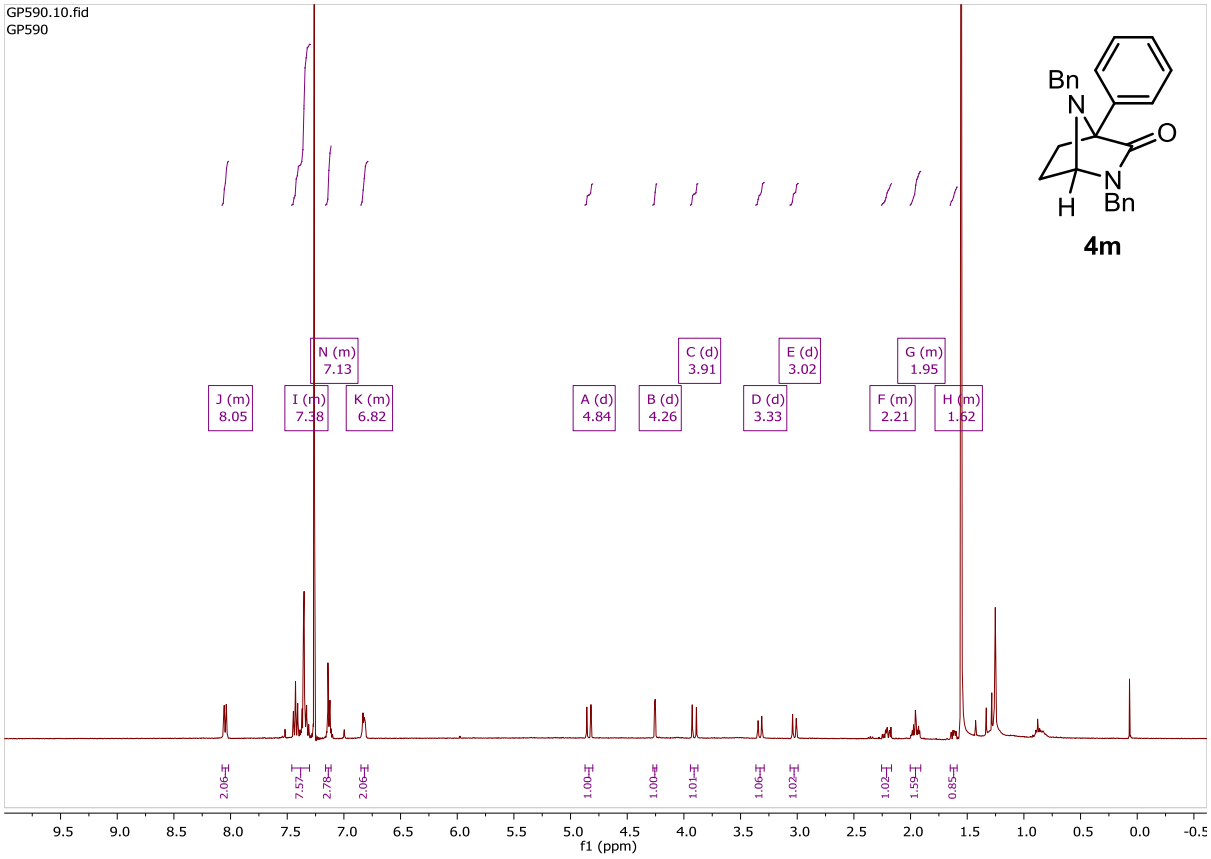

GP740 F1.11.fid
GP740 F1
176.44
140.90
138.65
136.38
128.76
128.24
128.04
127.99
127.59
126.28
126.23
125.43
122.25
120.92
119.68
111.33
109.73
84.17
73.00
47.17
43.69
35.48
31.84
18.61
f1 (ppm)

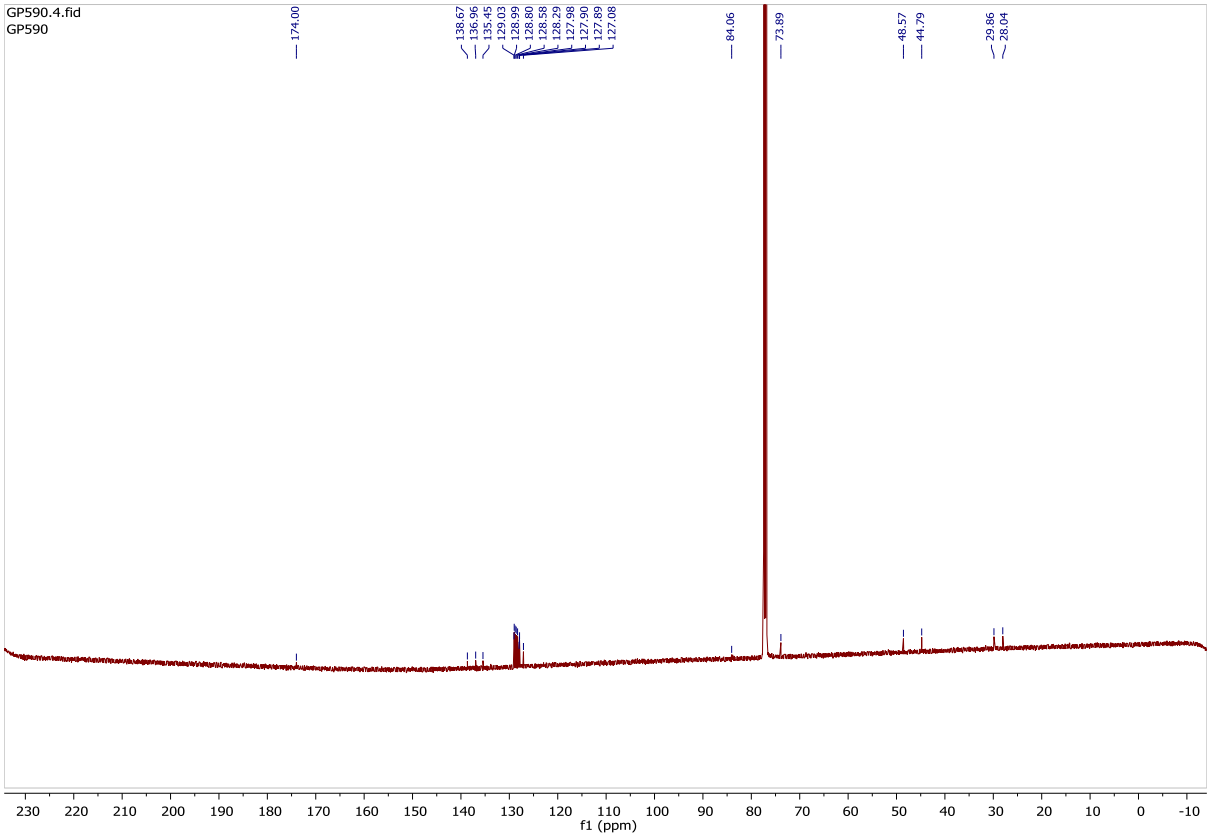

GP687 F1.10.fid
GP687 F1
Bn
N
O
N
Bn
4k
K (m) 8.02
L (m) 7.33
M (m) 7.12
B (d) 4.63
A (d) 4.27
C (s) 3.37
D (m) 2.24
F (ddd) 1.90
E (ddd) 2.10
G (dq) 1.71
H (dq) 1.54
I (m) 1.40
J (t) 0.55
f1 (ppm)

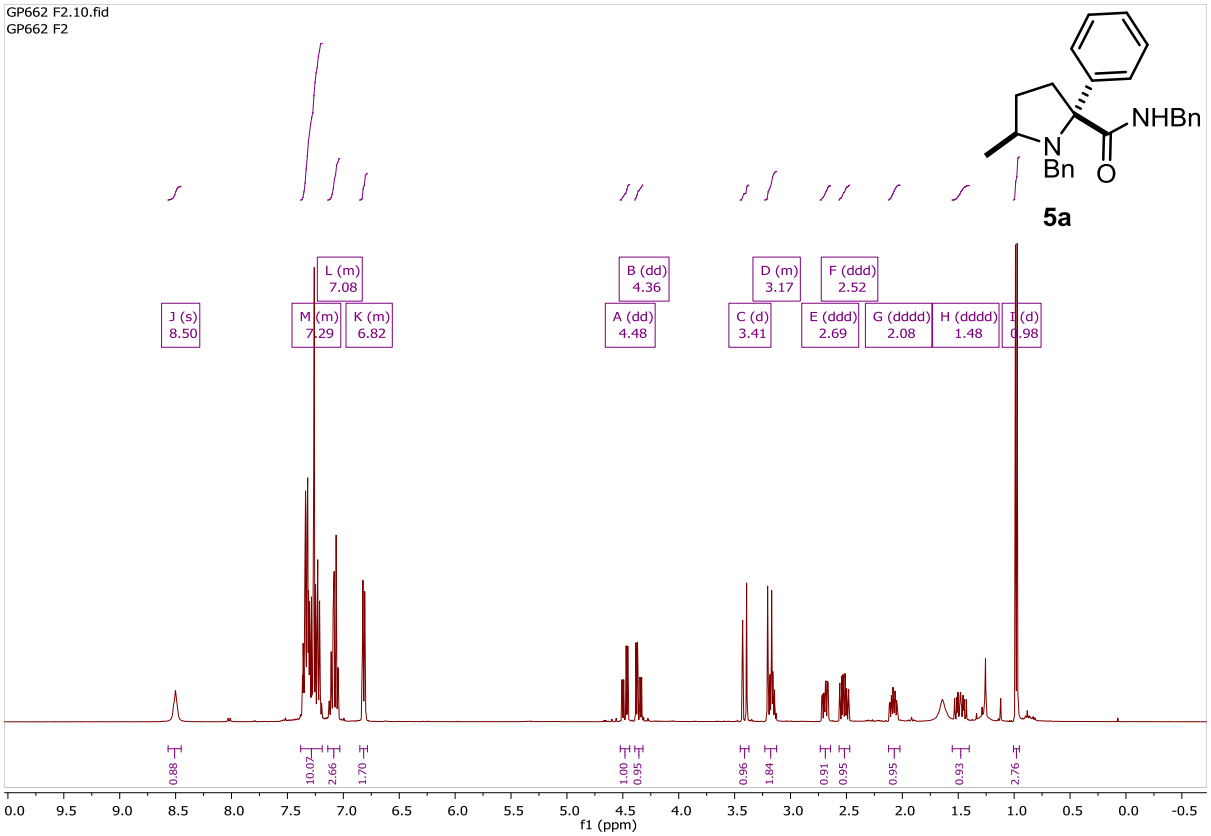

GP687 F1.12.fid
GP687 F1
176.26
140.12
138.77
136.28
128.74
128.42
128.35
128.07
127.98
127.81
127.53
126.50
88.08
75.66
47.14
43.74
34.16
30.79
22.98
7.82
f1 (ppm)

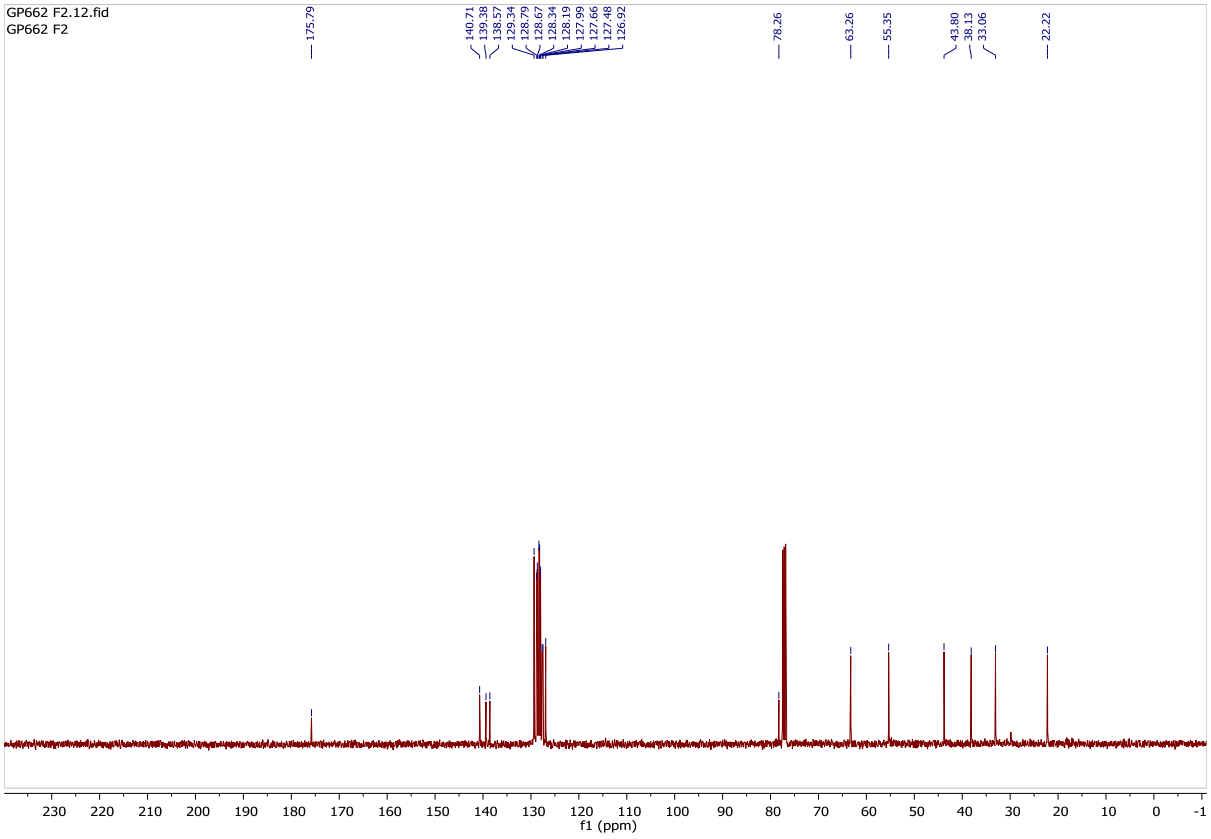

GP688 F1.10.fid
GP688 F1
Bn
N
O
N
Bn
4l
K (m) 7.39
I (m) 6.92
J (m) 7.23
H (m) 6.71
L (m) 7.49
A (d) 4.56
B (d) 3.82
D (d) 3.07
C (d) 3.16
E (m) 2.56
G (ddd) 1.87
F (ddd) 2.10
1.97
2.12
10.17
4.90
1.86
1.00
0.99
1.00
1.02
2.15
1.05
1.01
f1 (ppm)

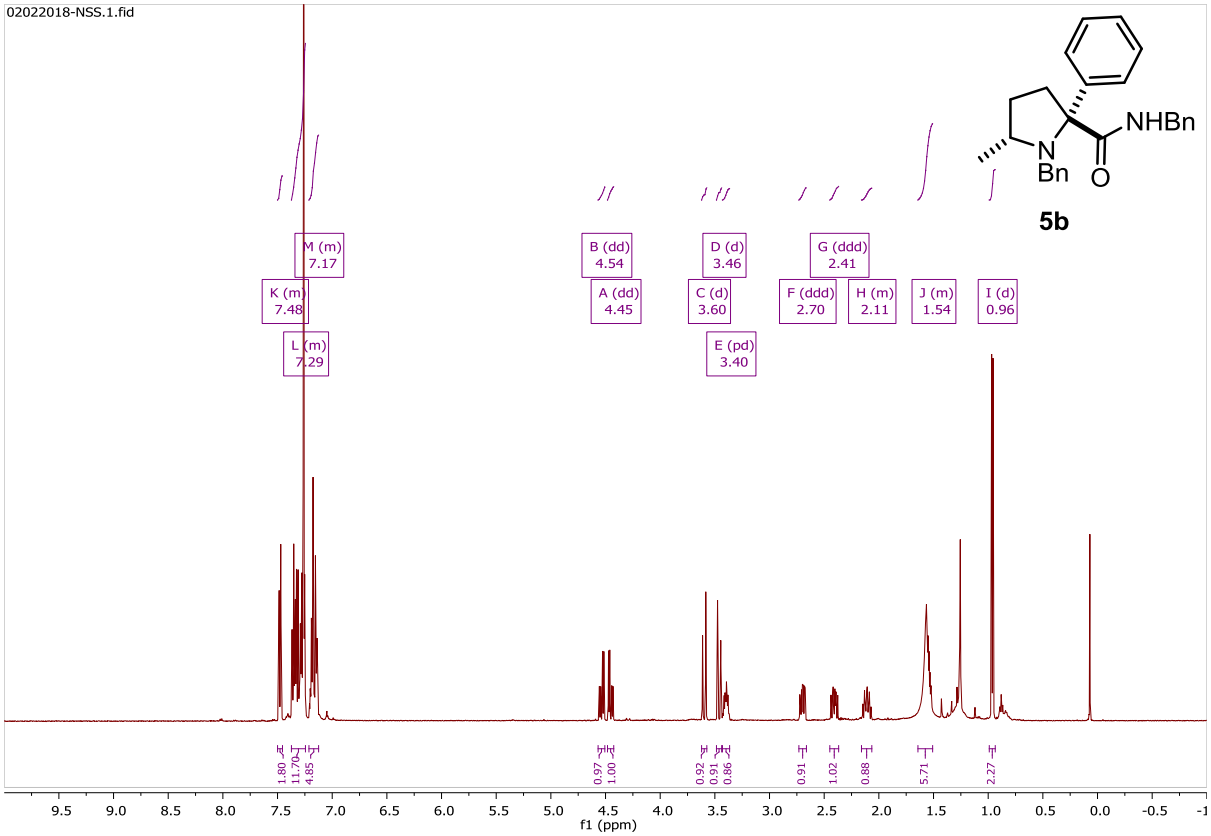

GP688 F1.12.fid
GP688 F1
175.71
139.39
137.63
134.63
133.14
130.26
129.68
129.49
128.78
128.65
128.38
128.19
128.16
127.46
127.41
126.07
88.56
77.51
48.25
44.17
30.33
26.46
f1 (ppm)

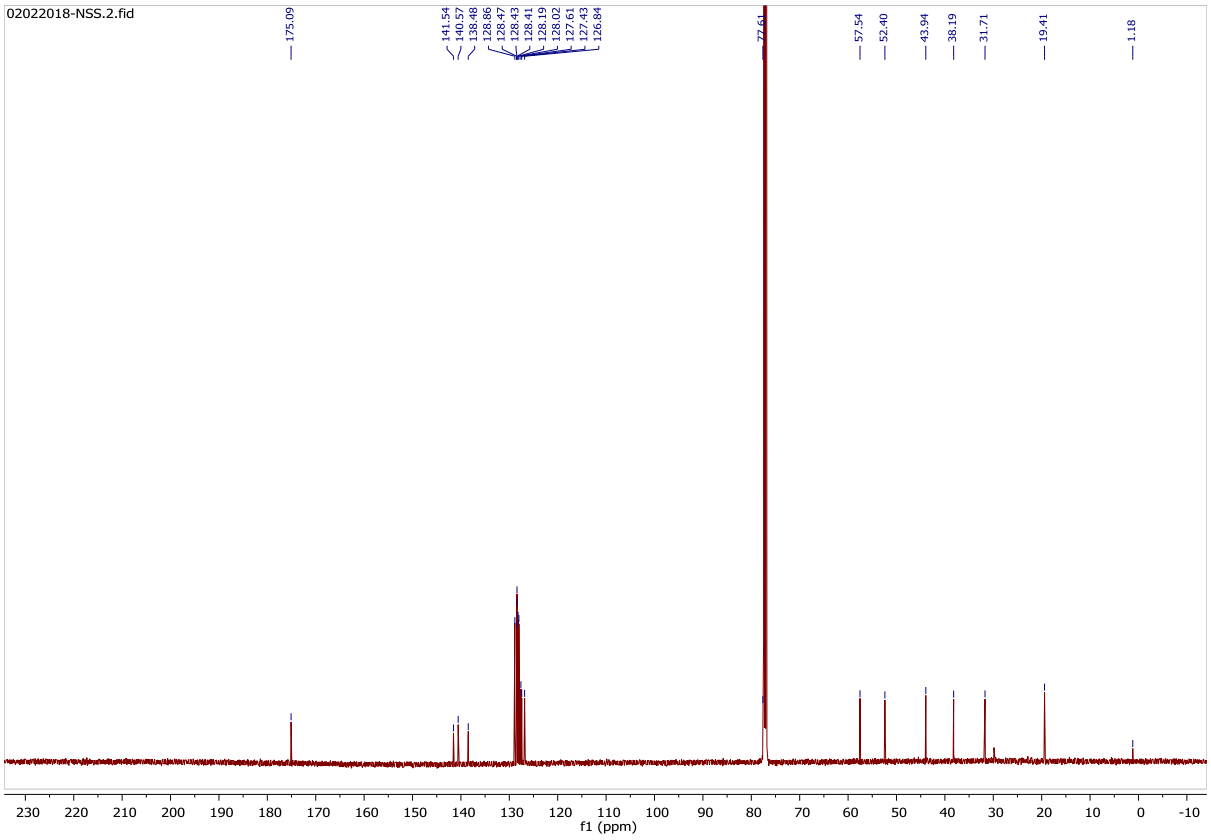

GP590.10.fid
GP590
Bn
N
O
N
Bn
H
4m
N (m) 7.13
C (d) 3.91
E (d) 3.02
G (m) 1.95
J (m) 8.05
I (m) 7.38
K (m) 6.82
A (d) 4.84
B (d) 4.26
D (d) 3.33
F (m) 2.21
H (m) 1.52
2.06
7.57
2.78
2.06
1.00
1.00
1.01
1.06
1.02
1.02
1.59
0.85
f1 (ppm)

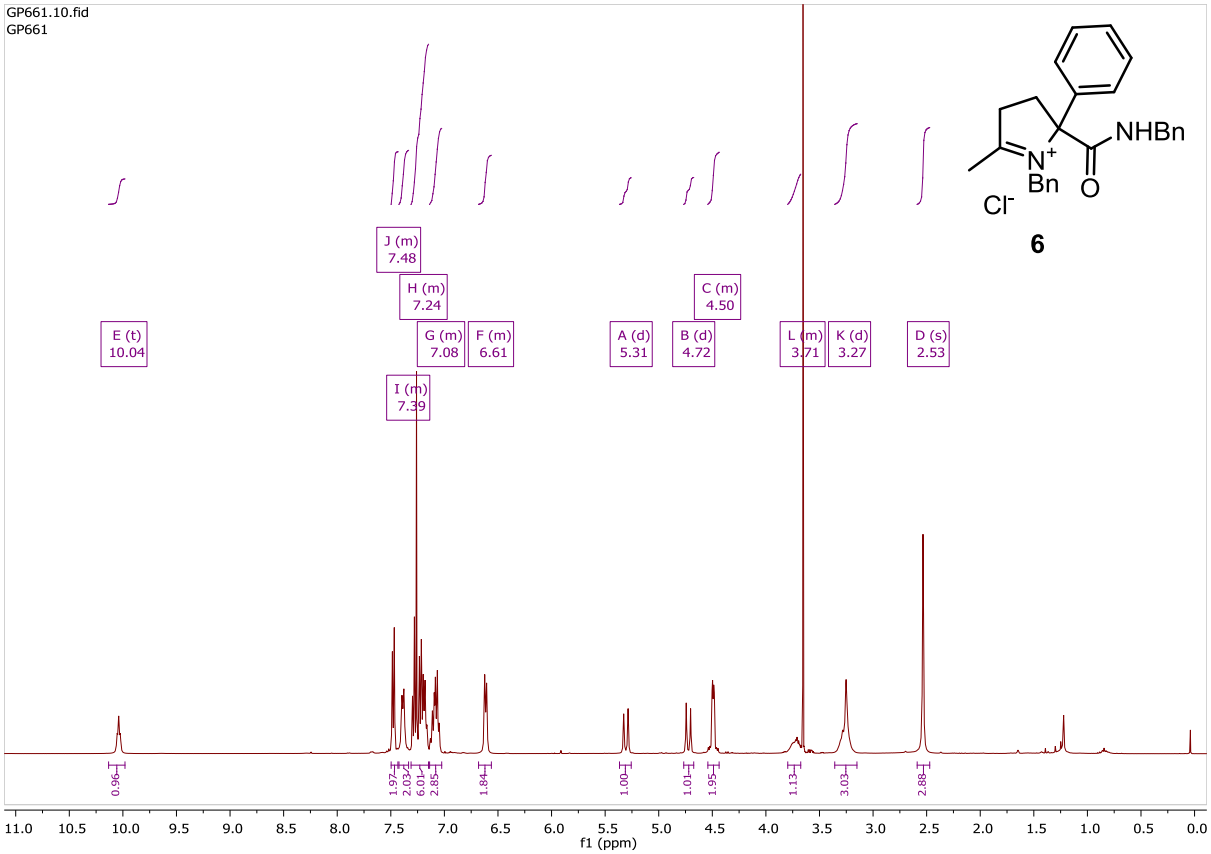

GP590.4.fid
GP590
174.00
138.67
136.96
135.45
129.03
128.99
128.80
128.58
128.29
127.98
127.90
127.89
127.08
84.06
73.89
48.57
44.79
29.86
28.04
f1 (ppm)

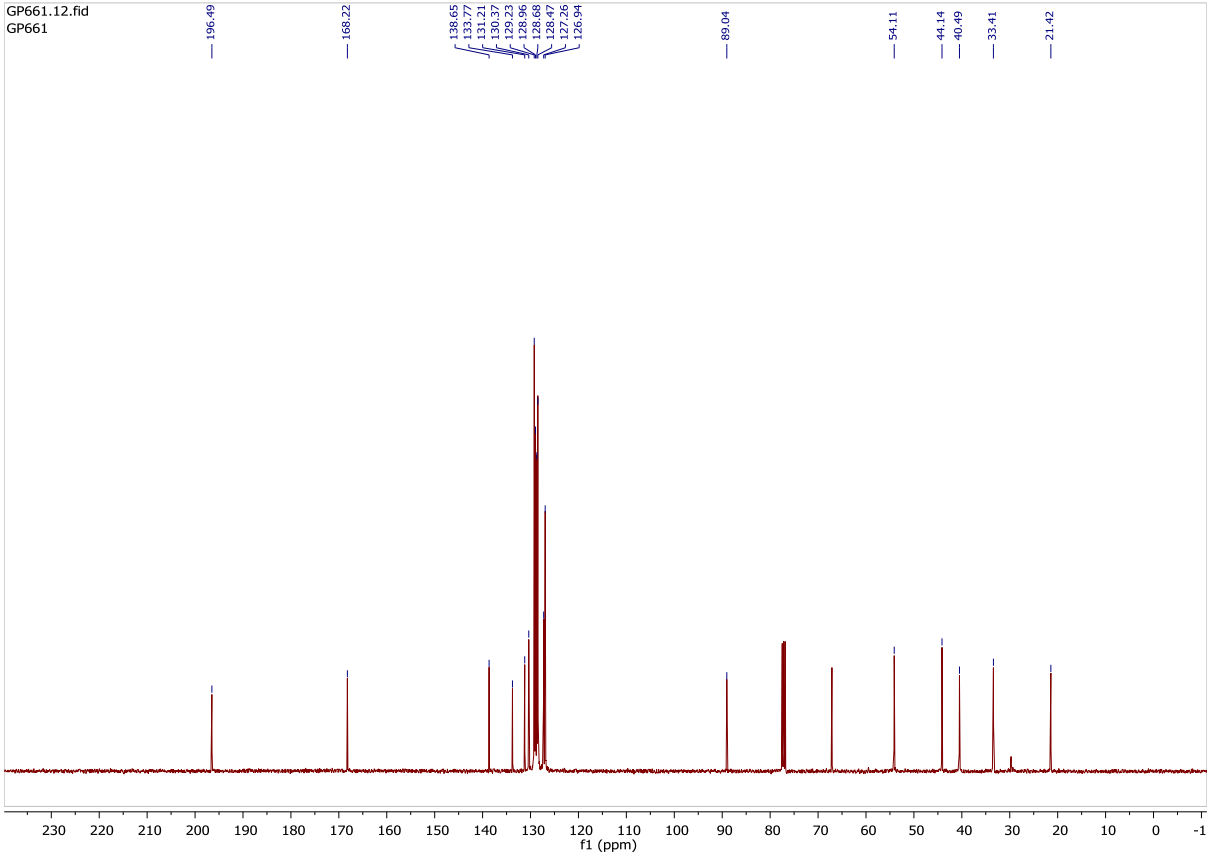

GP662 F2.10.fid
GP662 F2
NHBn
N
Bn
O
5a
J (s) 8.50
L (m) 7.08
M (m) 7.29
K (m) 6.82
B (dd) 4.36
A (dd) 4.48
D (m) 3.17
C (d) 3.41
F (ddd) 2.52
E (ddd) 2.69
G (dddd) 2.08
H (dddd) 1.48
I (d) 0.98
0.88
10.07
2.66
1.70
1.00
0.95
0.96
1.84
0.91
0.95
0.95
0.93
2.76
f1 (ppm)

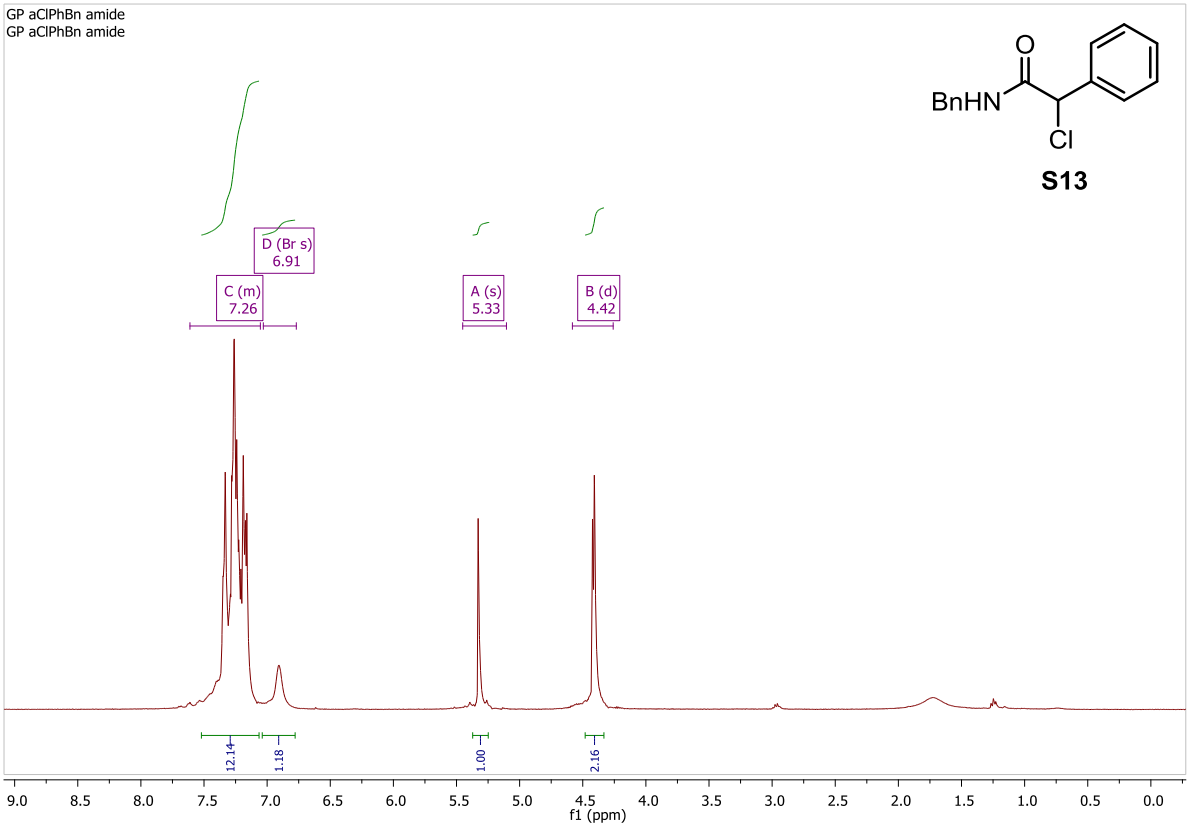

GP662 F2.12.fid
GP662 F2
175.79
140.71
139.38
138.57
129.34
128.79
128.67
128.34
128.19
127.99
127.66
127.48
126.92
78.26
63.26
55.35
43.80
38.13
33.06
22.22
f1 (ppm)

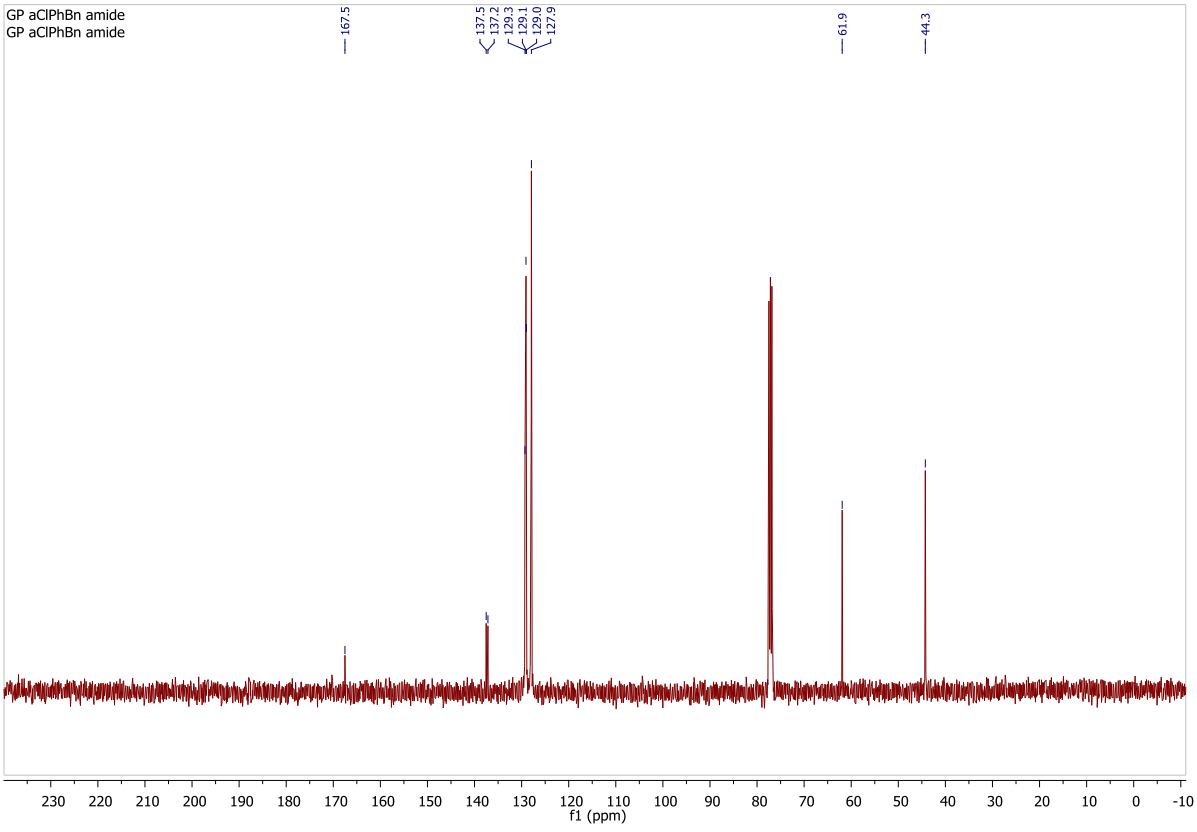

02022018-NSS.1.fid
NHBn
N
Bn
O
5b
M (m) 7.17
K (m) 7.48
L (m) 7.29
B (dd) 4.54
A (dd) 4.45
D (d) 3.46
C (d) 3.60
E (pd) 3.40
G (ddd) 2.41
F (ddd) 2.70
H (m) 2.11
J (m) 1.54
I (d) 0.96
1.80
11.70
4.85
0.97
1.00
0.92
0.91
0.86
0.91
1.02
0.88
5.71
2.27
f1 (ppm)

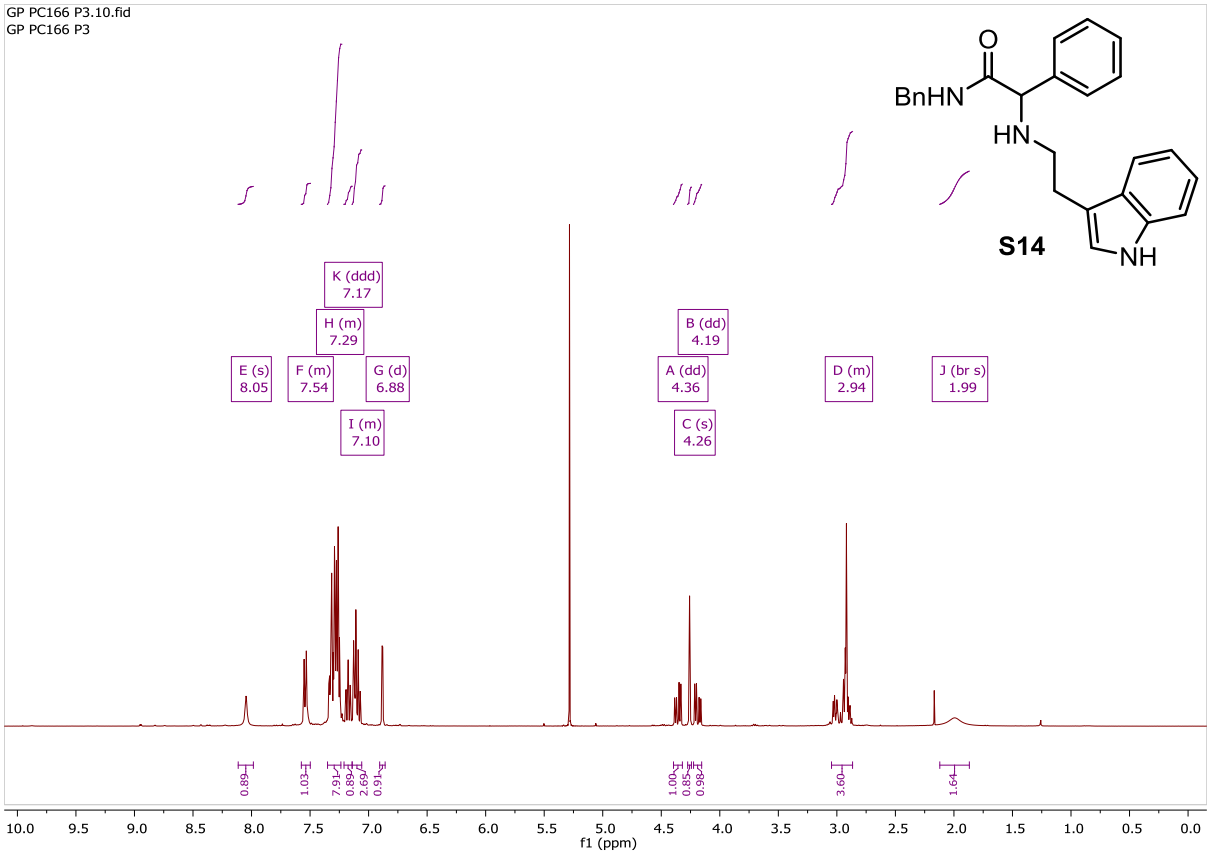

02022018-NSS.2.fid
175.09
141.54
140.57
138.48
128.86
128.47
128.43
128.41
128.19
128.02
127.61
127.43
126.84
77.61
57.54
52.40
43.94
38.19
31.71
19.41
1.18
f1 (ppm)

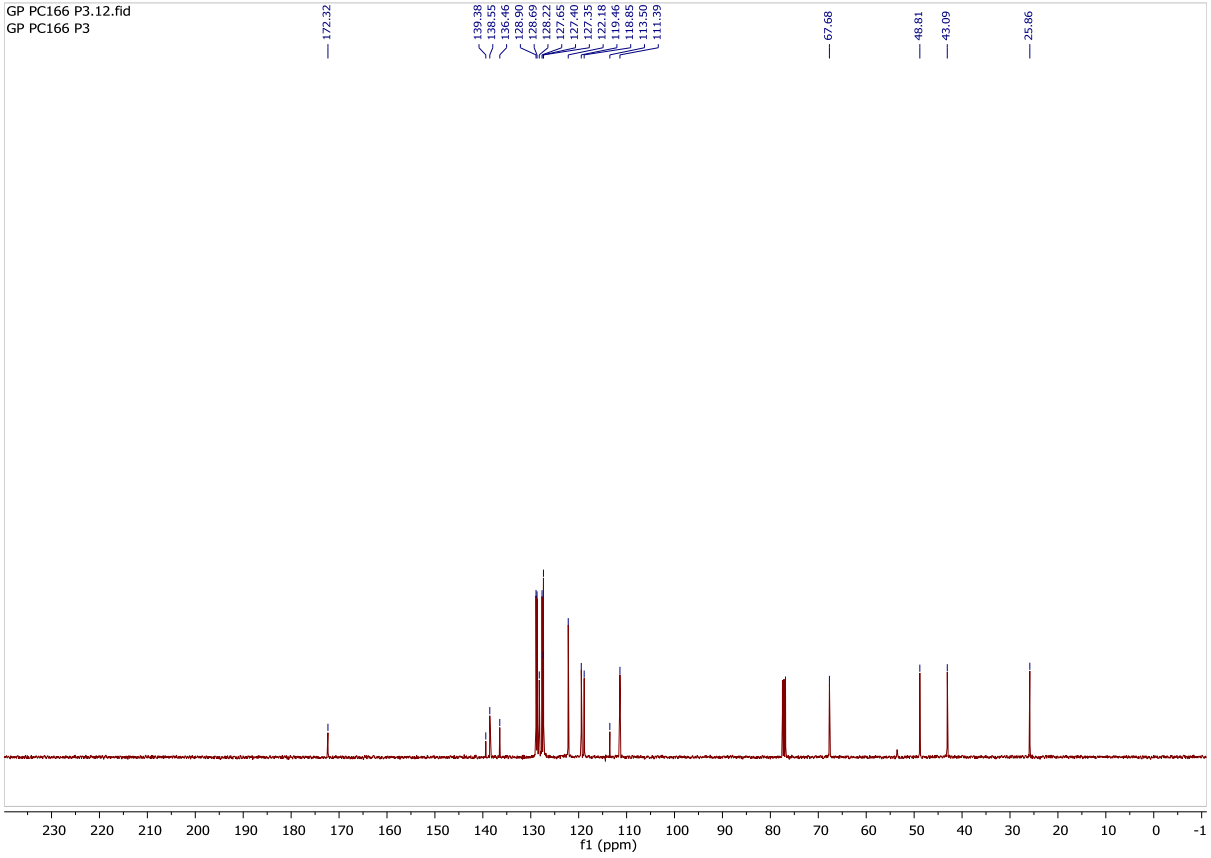

GP661.10.fid
GP661
NHBn
N+
Bn
O
Cl-
6
J (m) 7.48
H (m) 7.24
C (m) 4.50
E (t) 10.04
G (m) 7.08
F (m) 6.61
A (d) 5.31
B (d) 4.72
L (m) 3.71
K (d) 3.27
D (s) 2.53
I (m) 7.39
0.96
1.97
2.03
6.01
2.85
1.84
1.00
1.01
1.95
1.13
3.03
2.88
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

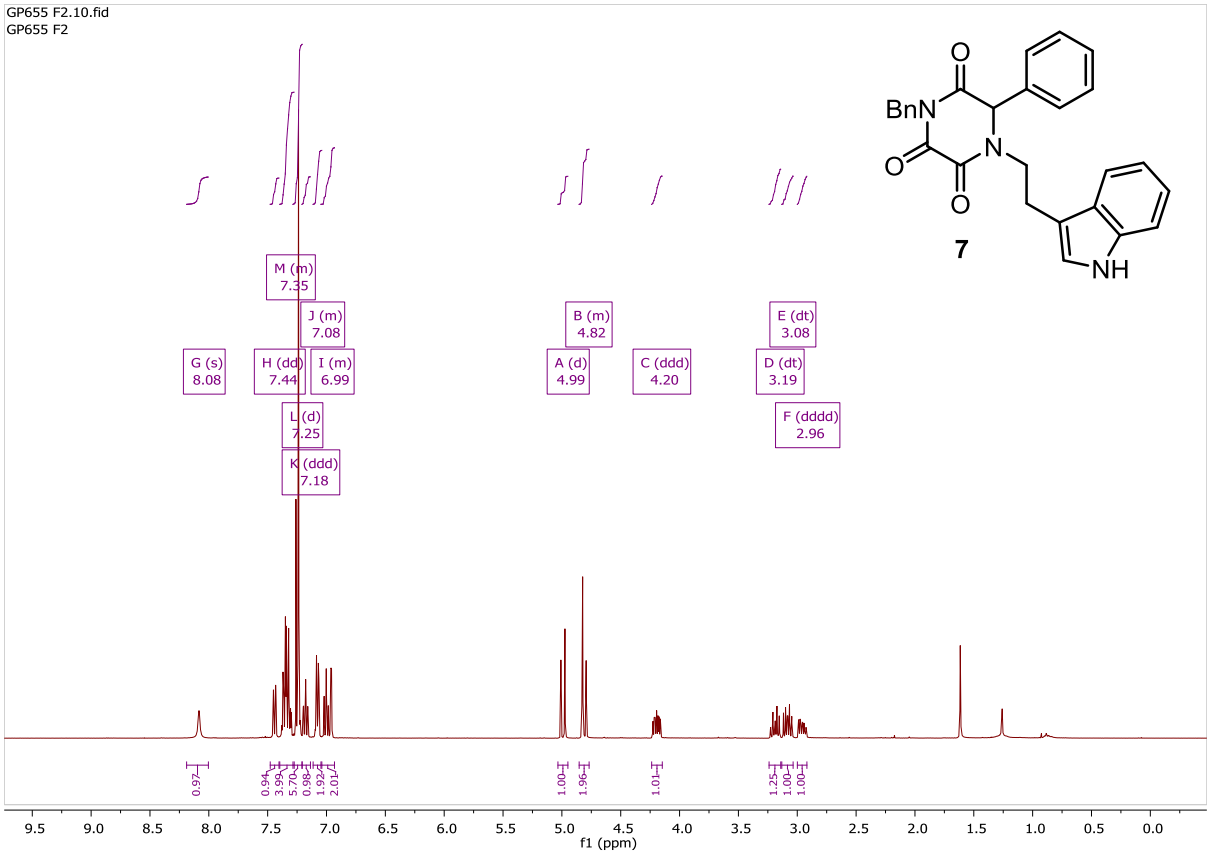

GP661.12.fid
GP661
196.49
168.22
138.65
133.77
131.21
130.37
129.23
128.96
128.68
128.47
127.26
126.94
89.04
54.11
44.14
40.49
33.41
21.42
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

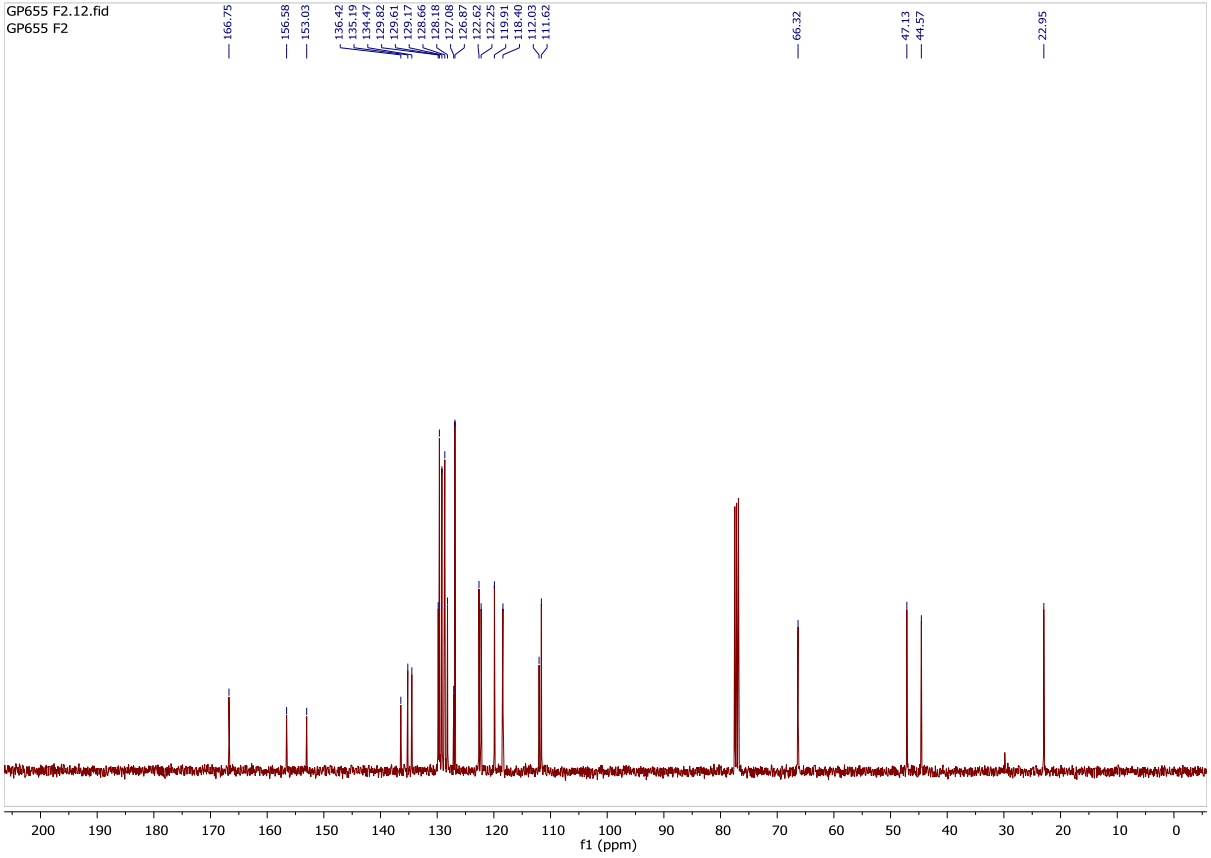

GP aClPhBn amide
GP aClPhBn amide
O
BnHN
Cl
S13
D (Br s)
6.91
C (m)
7.26
A (s)
5.33
B (d)
4.42
12.14
1.18
1.00
2.16
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

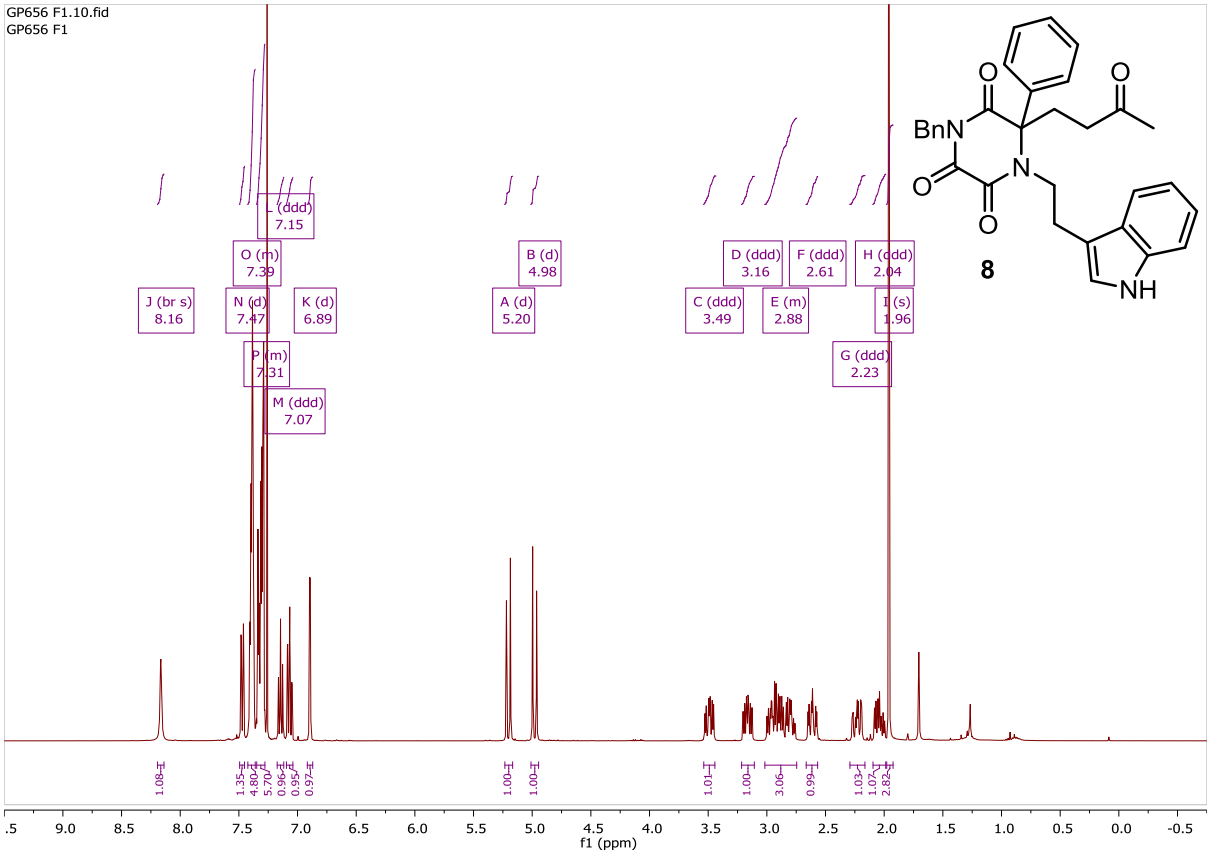

GP aClPhBn amide
GP aClPhBn amide
167.5
137.5
137.2
129.3
129.1
129.0
127.9
61.9
44.3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

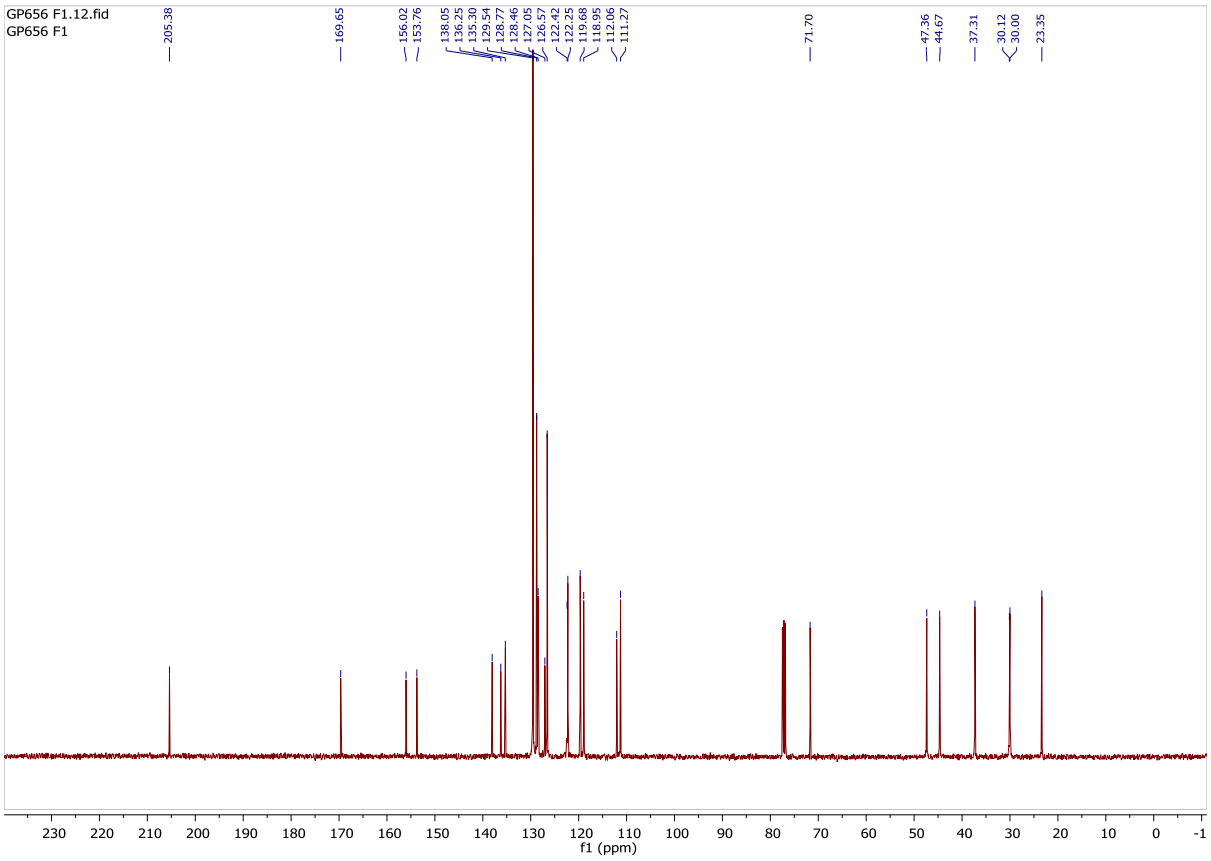

GP PC166 P3.10.fid
GP PC166 P3
BnHN
O
HN
NH
S14
K (ddd) 7.17
H (m) 7.29
E (s) 8.05
F (m) 7.54
G (d) 6.88
I (m) 7.10
B (dd) 4.19
A (dd) 4.36
C (s) 4.26
D (m) 2.94
J (br s) 1.99
0.89
1.03
7.91
0.89
2.69
0.91
1.00
0.85
0.98
3.60
1.64
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

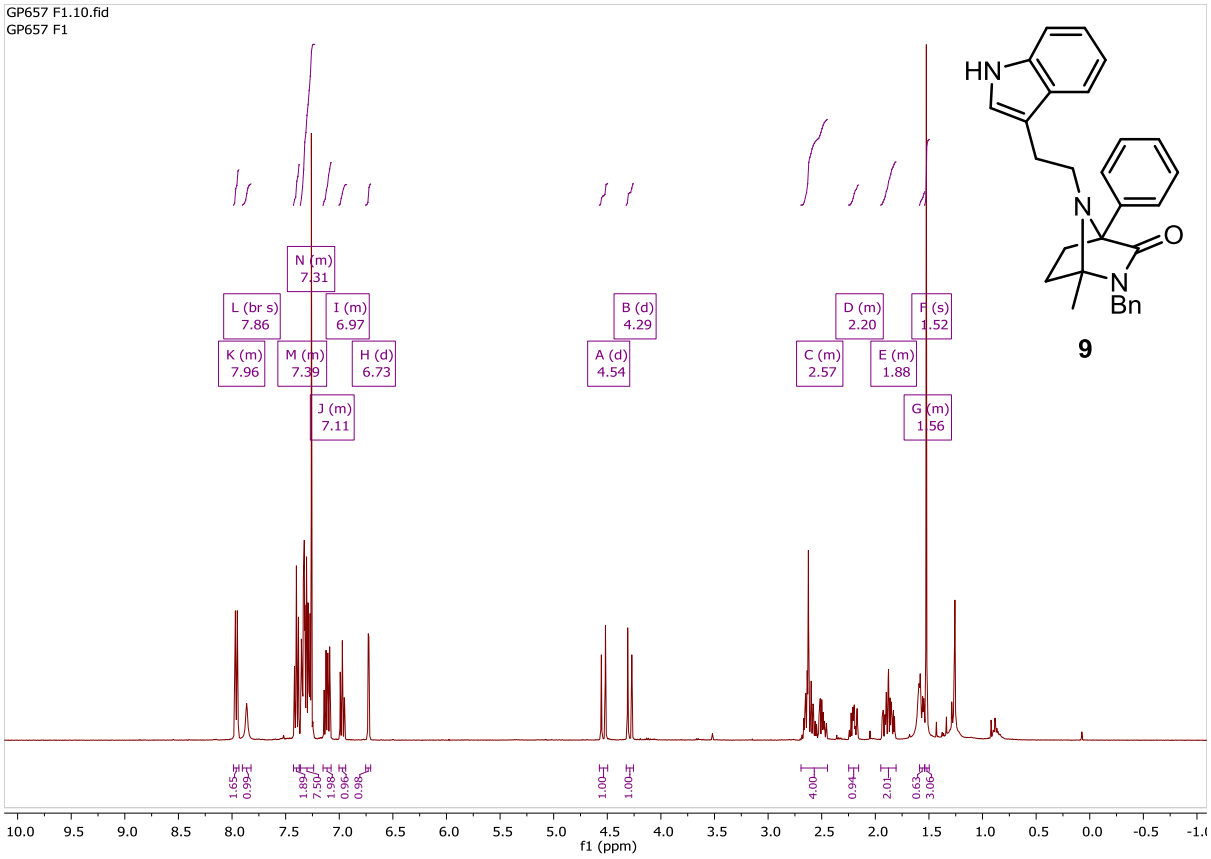

GP PC166 P3.12.fid
GP PC166 P3
172.32
139.38
138.55
136.46
128.90
128.69
128.22
127.65
127.40
127.35
122.18
119.46
118.85
113.50
111.39
67.68
48.81
43.09
25.86
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

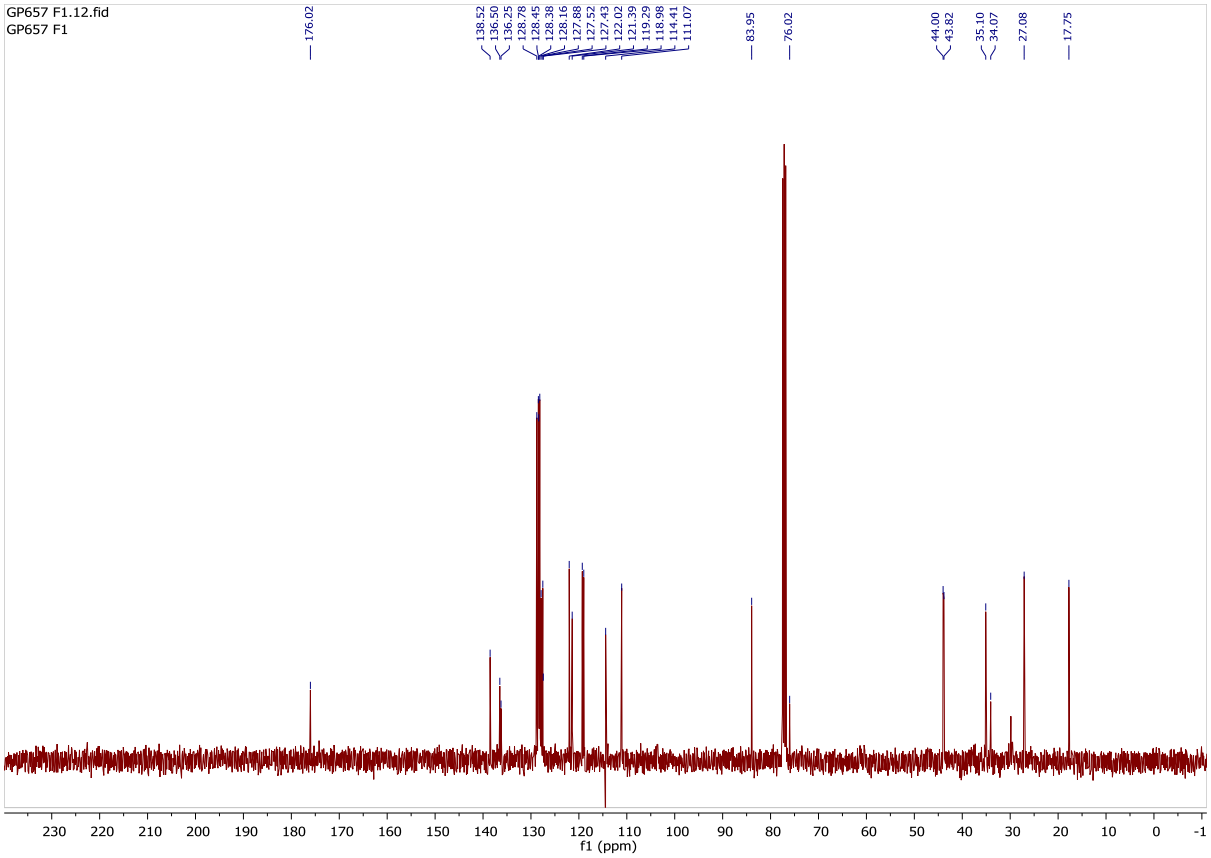

GP655 F2.10.fid
GP655 F2
BnN
O
N
O
O
NH
7
M (m)
7.35
J (m)
7.08
B (m)
4.82
E (dt)
3.08
G (s)
8.08
H (dd)
7.44
I (m)
6.99
A (d)
4.99
C (ddd)
4.20
D (dt)
3.19
L (d)
7.25
F (dddd)
2.96
K (ddd)
7.18
0.97
0.94
3.95
5.70
0.98
1.92
2.01
1.00
1.96
1.01
1.25
1.00
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

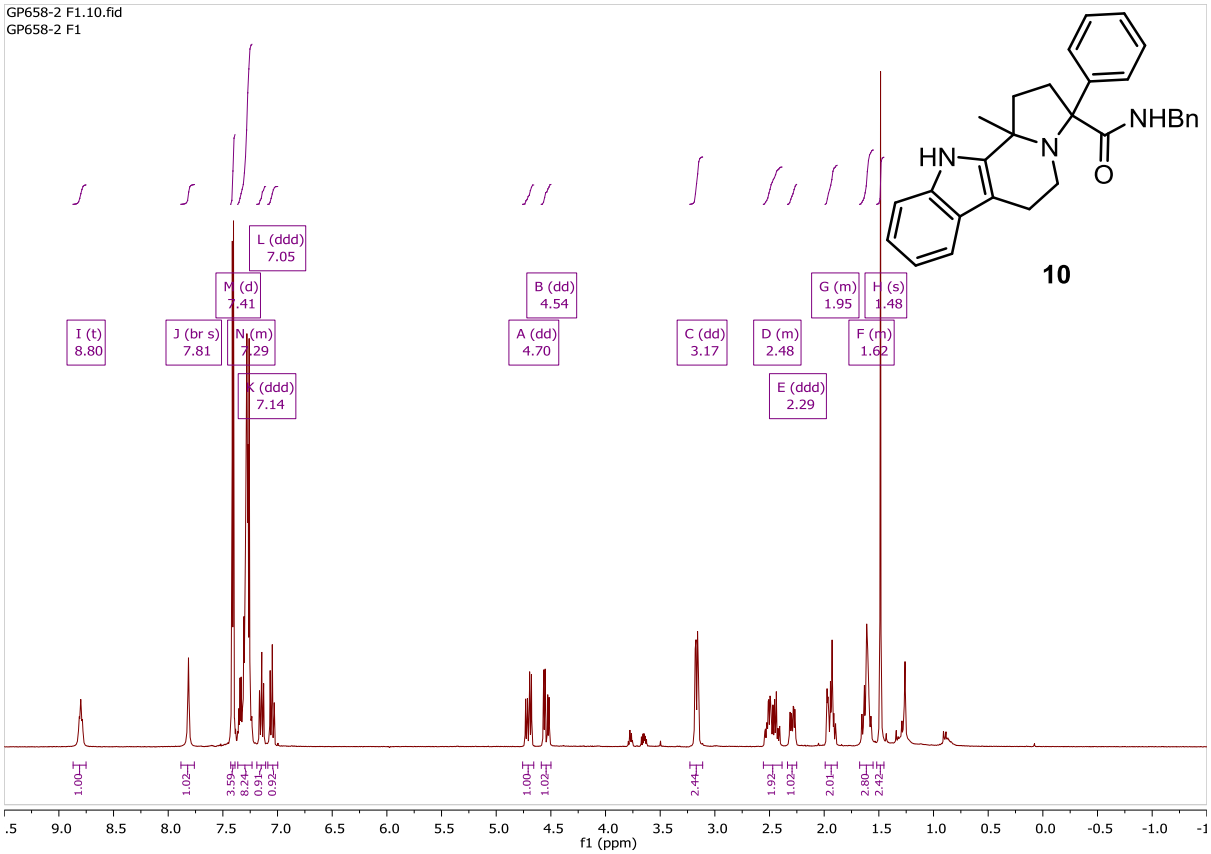

GP655 F2.12.fid
GP655 F2
166.75
156.58
153.03
136.42
135.19
134.47
129.82
129.61
129.17
128.66
128.18
127.08
126.87
122.62
122.25
119.91
118.40
112.03
111.62
66.32
47.13
44.57
22.95
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

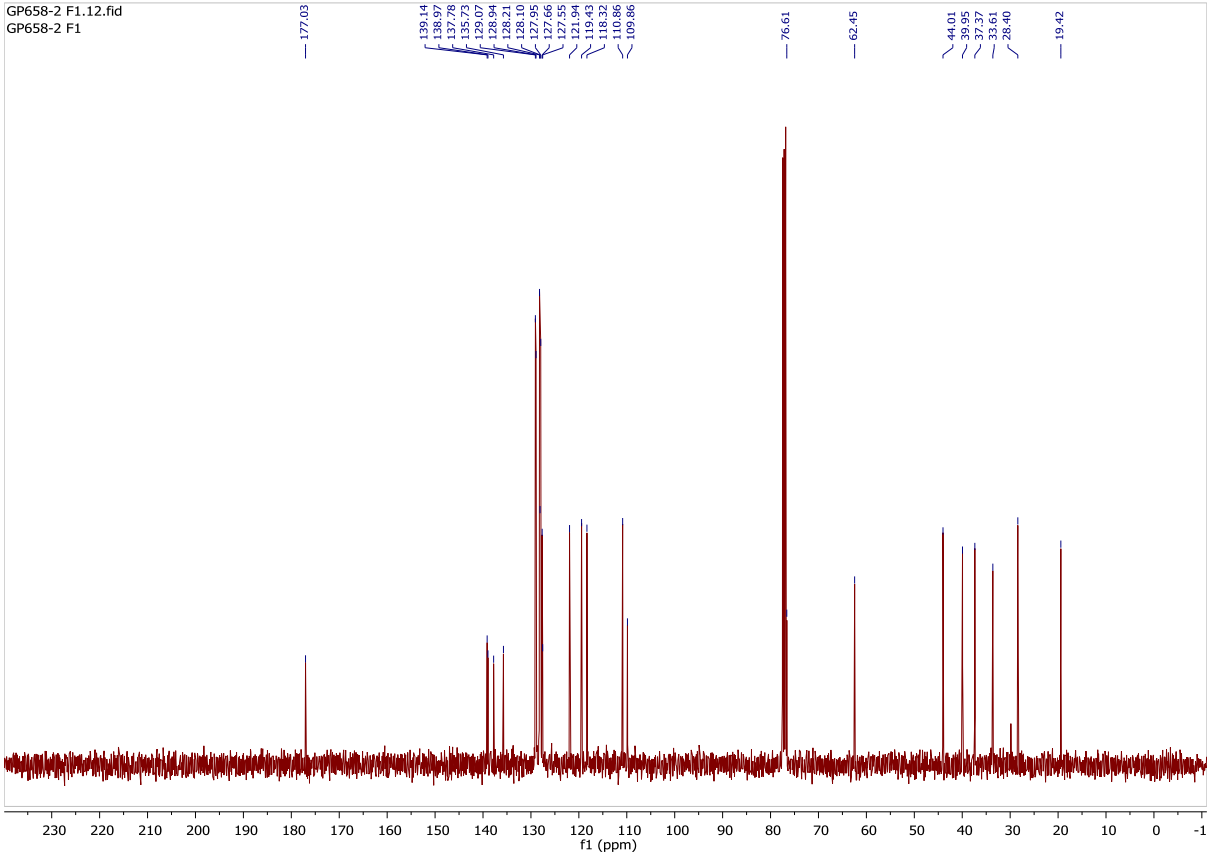

GP656 F1.10.fid
GP656 F1
L (ddd) 7.15
O (m) 7.39
J (br s) 8.16
N (d) 7.47
K (d) 6.89
P (m) 7.31
M (ddd) 7.07
B (d) 4.98
A (d) 5.20
D (ddd) 3.16
F (ddd) 2.61
H (ddd) 2.04
C (ddd) 3.49
E (m) 2.88
I (s) 1.96
G (ddd) 2.23
BnN
O
N
NH
8
f1 (ppm)


GP656 F1.12.fid
GP656 F1
205.38
169.65
156.02
153.76
138.05
136.25
135.30
129.54
128.77
128.46
127.05
126.57
122.42
122.25
119.68
118.95
112.06
111.27
71.70
47.36
44.67
37.31
30.12
30.00
23.35
f1 (ppm)


GP657 F1.10.fid
GP657 F1
N (m) 7.31
L (br s) 7.86
I (m) 6.97
K (m) 7.96
M (m) 7.39
H (d) 6.73
J (m) 7.11
B (d) 4.29
A (d) 4.54
D (m) 2.20
F (s) 1.52
C (m) 2.57
E (m) 1.88
G (m) 1.56
HN
N
O
N
Bn
9
f1 (ppm)

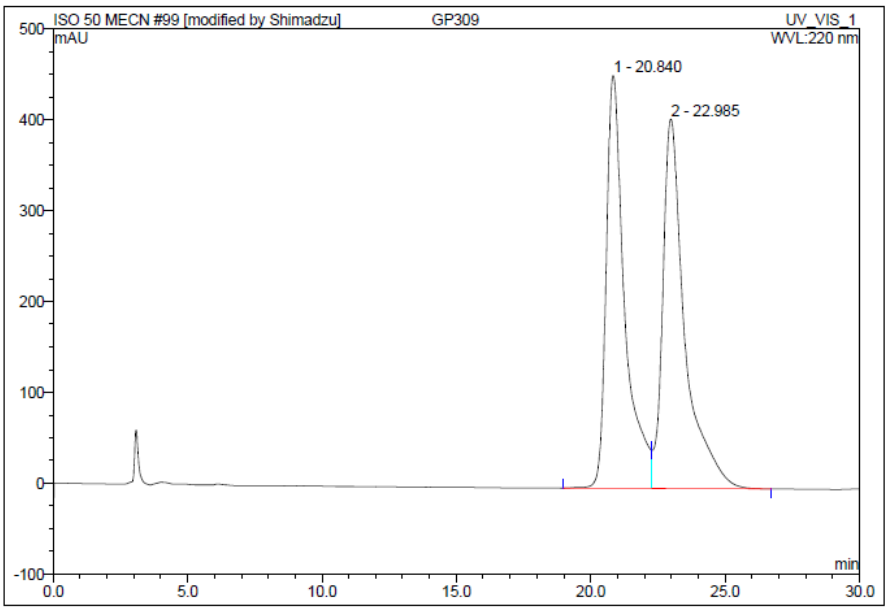

GP657 F1.12.fid
GP657 F1
176.02
138.52
136.50
136.25
128.78
128.45
128.38
128.16
127.88
127.52
127.43
122.02
121.39
119.29
118.98
114.41
111.07
83.95
76.02
44.00
43.82
35.10
34.07
27.08
17.75
f1 (ppm)

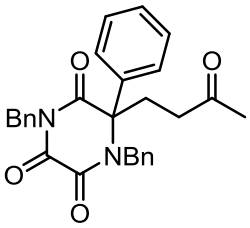

GP658-2 F1.10.fid
GP658-2 F1
NHBn
HN
N
O
10
L (ddd) 7.05
M (d) 7.41
B (dd) 4.54
G (m) 1.95
H (s) 1.48
I (t) 8.80
J (br s) 7.81
N (m) 7.29
A (dd) 4.70
C (dd) 3.17
D (m) 2.48
F (m) 1.62
K (ddd) 7.14
E (ddd) 2.29
f1 (ppm)


GP658-2 F1.12.fid
GP658-2 F1
177.03
139.14
138.97
137.78
135.73
129.07
128.94
128.21
128.10
127.95
127.66
127.55
121.94
119.43
118.32
110.86
109.86
76.61
62.45
44.01
39.95
37.37
33.61
28.40
19.42
f1 (ppm)

HPLC Traces

Racemic **2a**

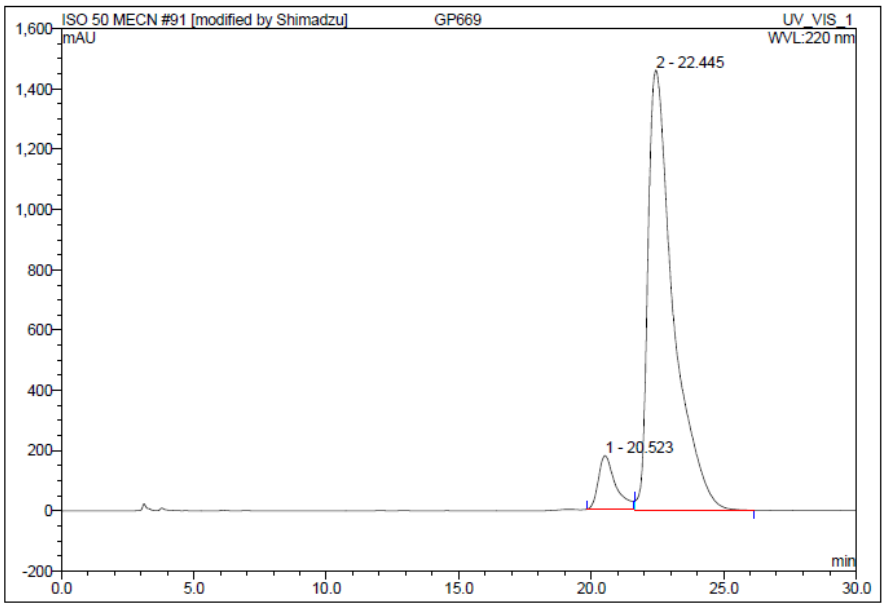




2a

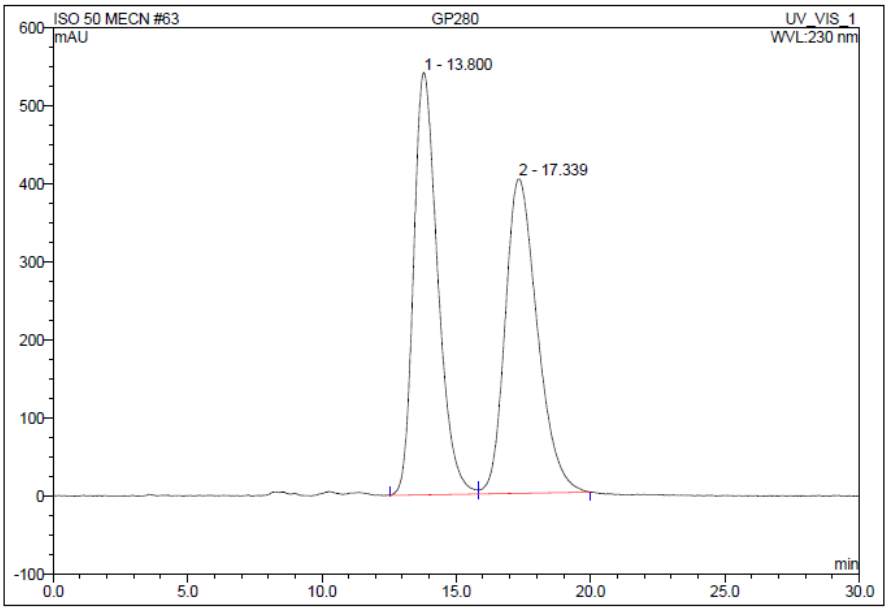
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.84	n.a.	454.144	364.908	48.52	n.a.	BM
2	22.98	n.a.	406.479	387.150	51.48	n.a.	MB
Total:			860.623	752.058	100.00	0.000	

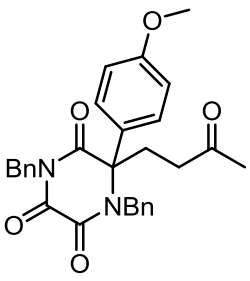
Enantioenriched **2a**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.52	n.a.	177.646	132.404	7.58	n.a.	BM *
2	22.45	n.a.	1460.047	1613.796	92.42	n.a.	MB*
Total:			1637.693	1746.200	100.00	0.000	

Racemic **2b**

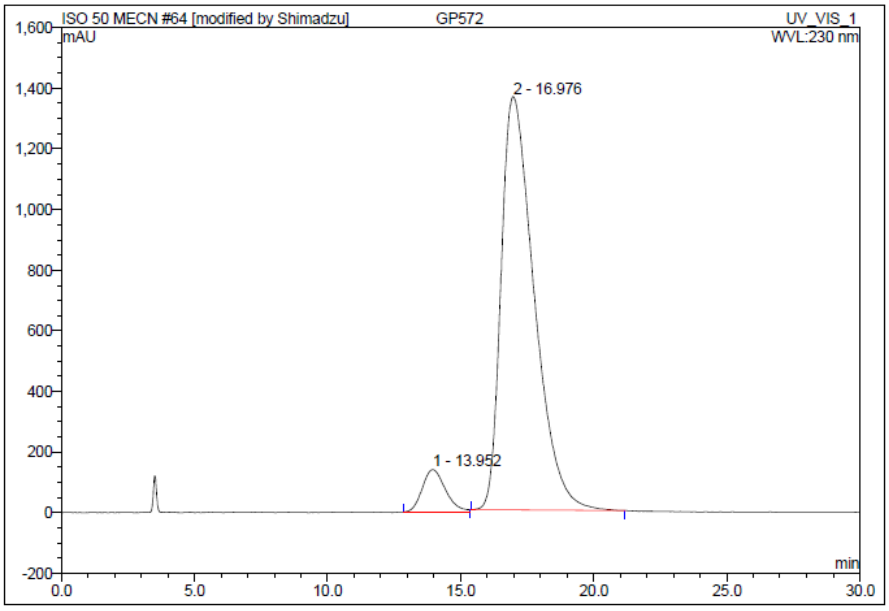




2b

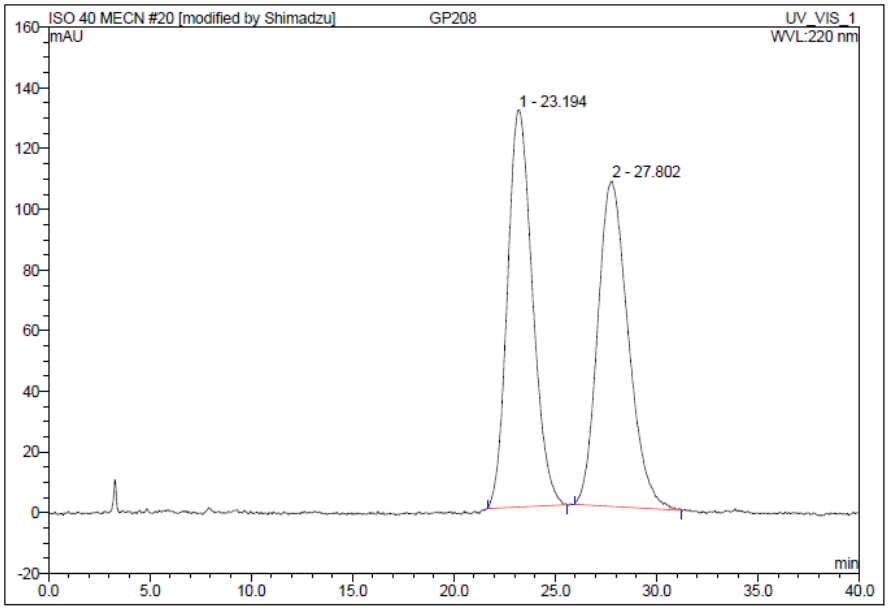
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.80	n.a.	541.362	562.858	50.17	n.a.	BM
2	17.34	n.a.	403.063	559.055	49.83	n.a.	MB
Total:			944.425	1121.913	100.00	0.000	

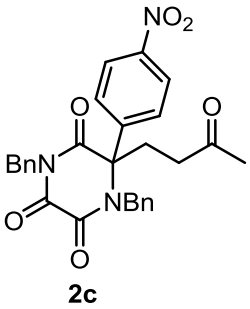
Enantioenriched **2b**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.95	n.a.	140.291	142.204	6.75	n.a.	BM *
2	16.98	n.a.	1363.126	1964.114	93.25	n.a.	BMB*
Total:			1503.417	2106.317	100.00	0.000	

Racemic **2c**

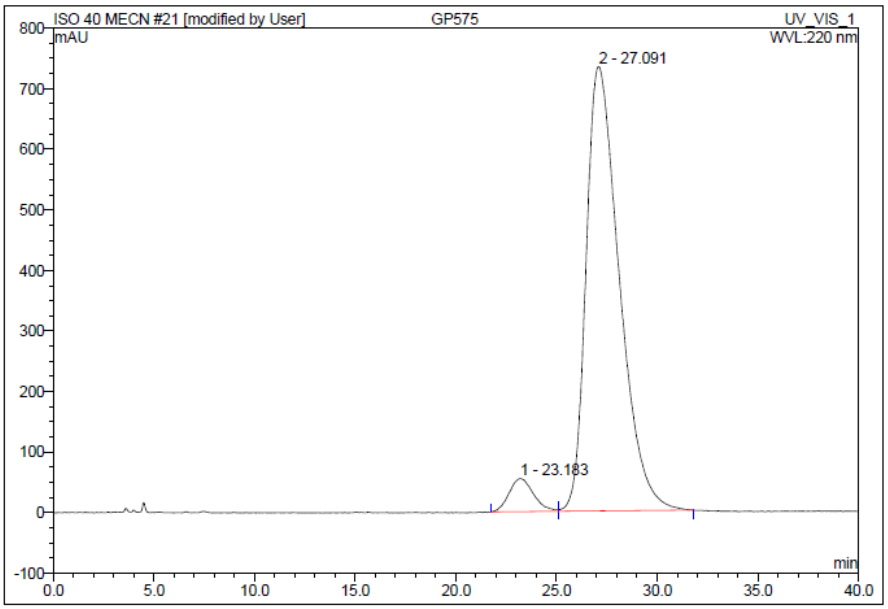




2c

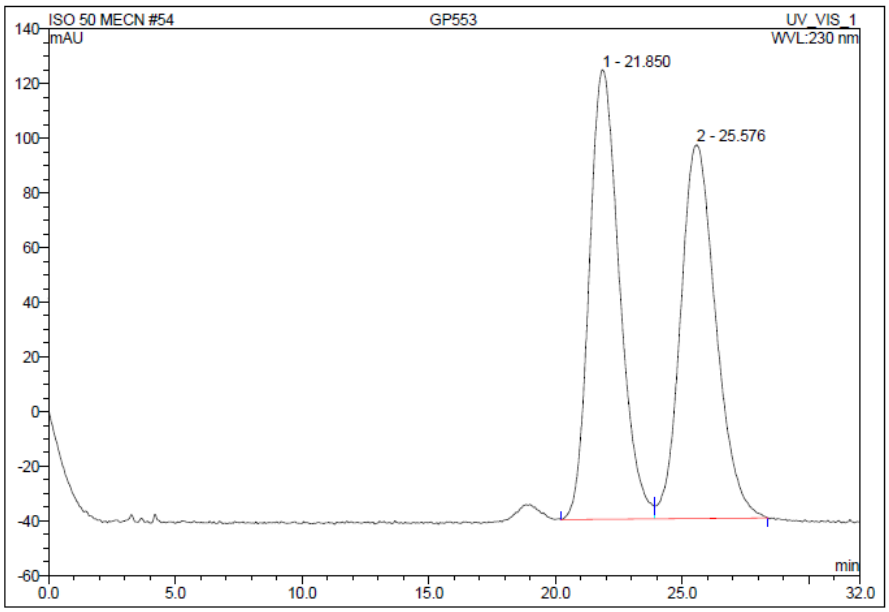
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.19	n.a.	130.978	187.560	50.09	n.a.	BMB*
2	27.80	n.a.	107.295	186.869	49.91	n.a.	BMB*
Total:			238.272	374.428	100.00	0.000	

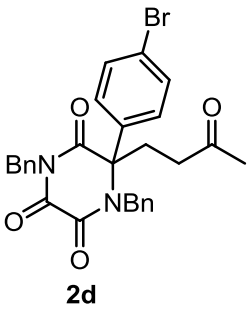
Enantioenriched **2c**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.18	n.a.	54.700	76.651	5.18	n.a.	BM *
2	27.09	n.a.	733.882	1402.155	94.82	n.a.	MB*
Total:			788.582	1478.805	100.00	0.000	

Racemic **2d**

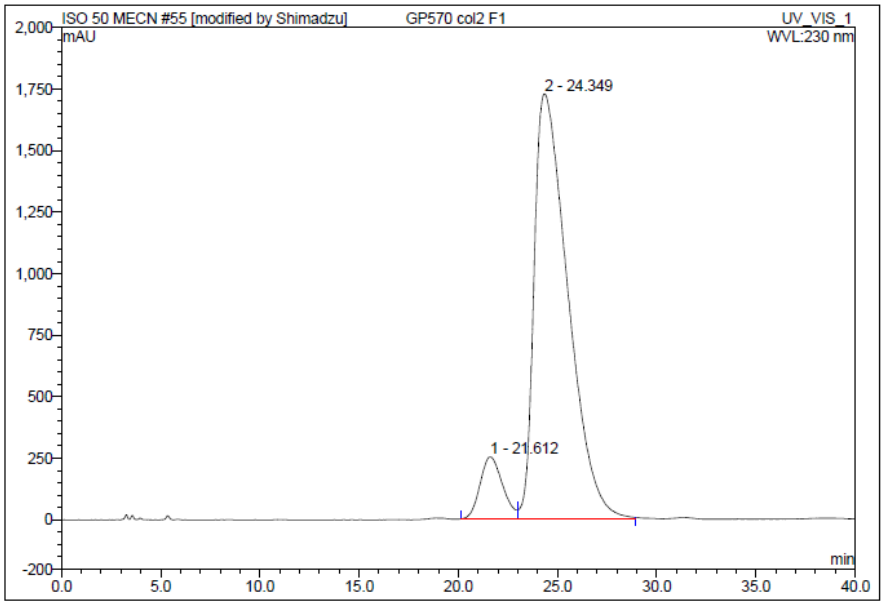




2d

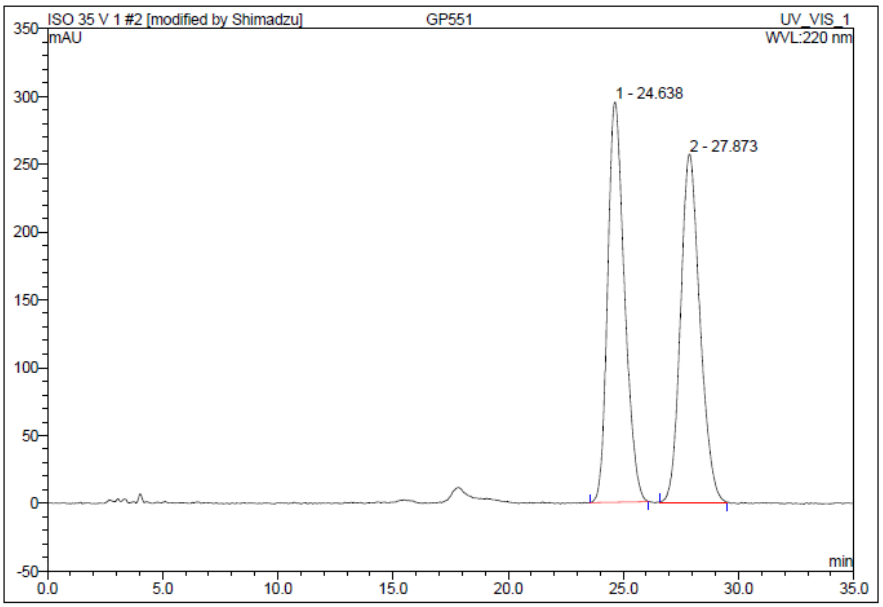
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.85	n.a.	164.480	226.832	50.69	n.a.	BM
2	25.58	n.a.	136.763	220.650	49.31	n.a.	MB
Total:			301.243	447.481	100.00	0.000	

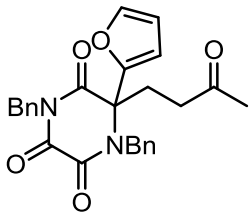
Enantioenriched **2d**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.61	n.a.	251.463	330.308	8.85	n.a.	BM *
2	24.35	n.a.	1726.188	3401.101	91.15	n.a.	M *
Total:			1977.651	3731.409	100.00	0.000	

Racemic **2e**

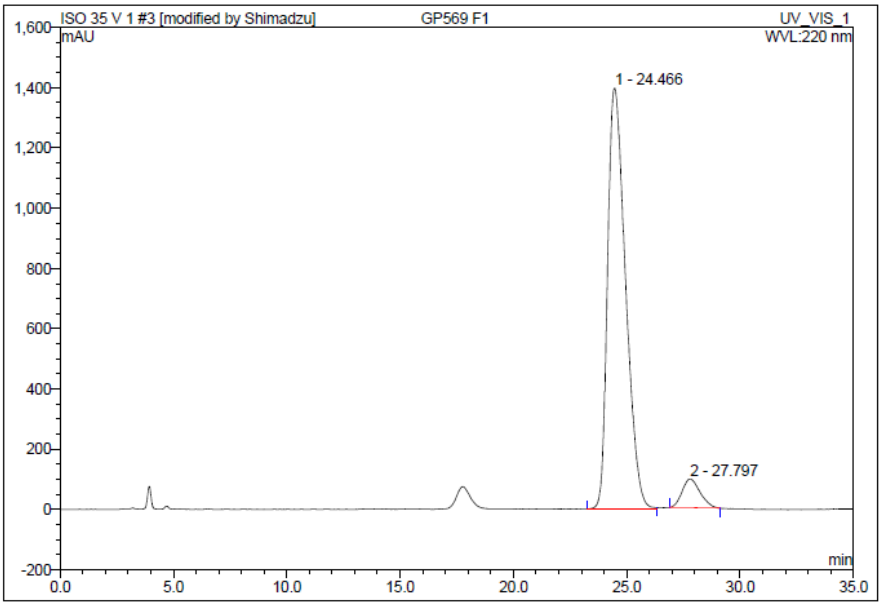




2e

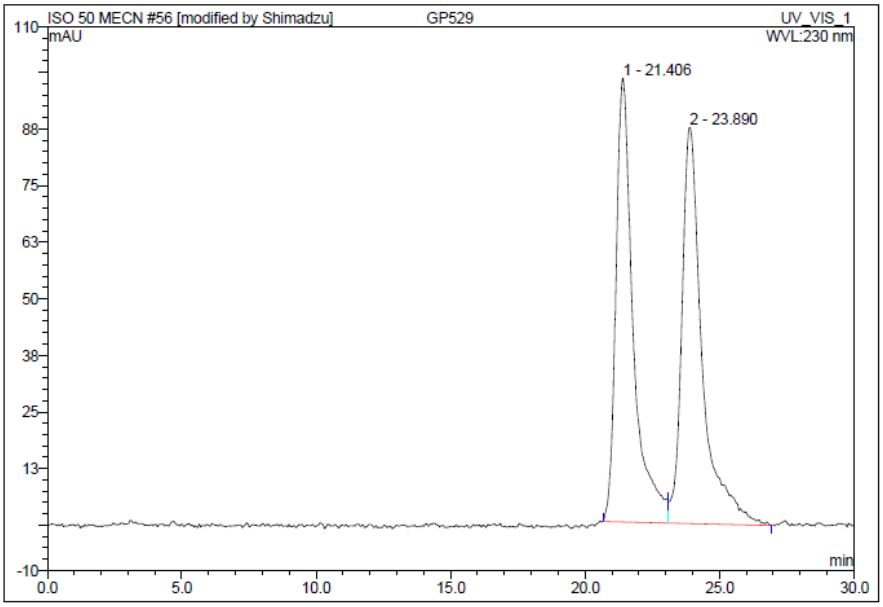
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.64	n.a.	294.928	249.797	49.97	n.a.	BMB
2	27.87	n.a.	256.581	250.075	50.03	n.a.	BMB
Total:			551.509	499.872	100.00	0.000	

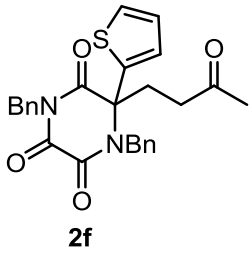
Enantioenriched **2e**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.47	n.a.	1397.277	1282.471	93.61	n.a.	BM *
2	27.80	n.a.	95.256	87.511	6.39	n.a.	BMB*
Total:			1492.533	1369.982	100.00	0.000	

Racemic **2f**

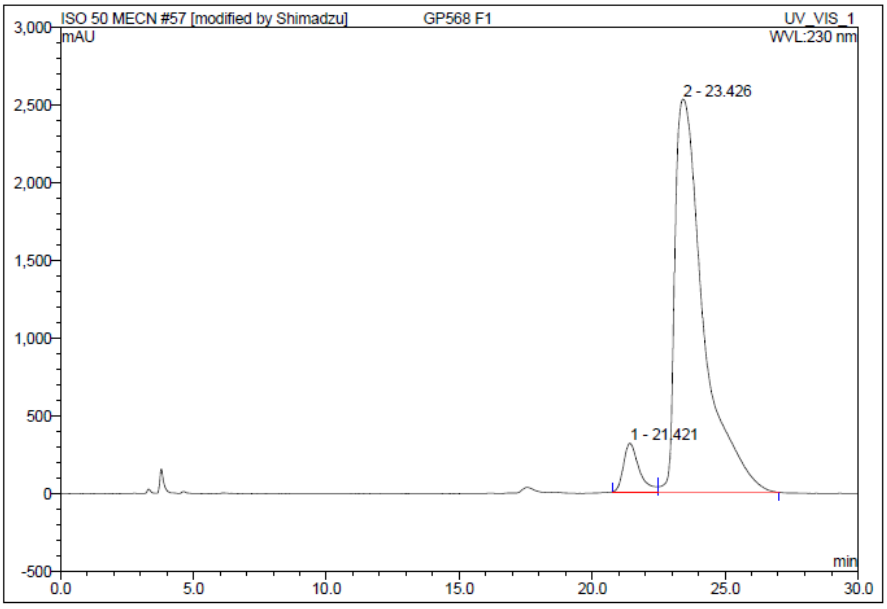




2f

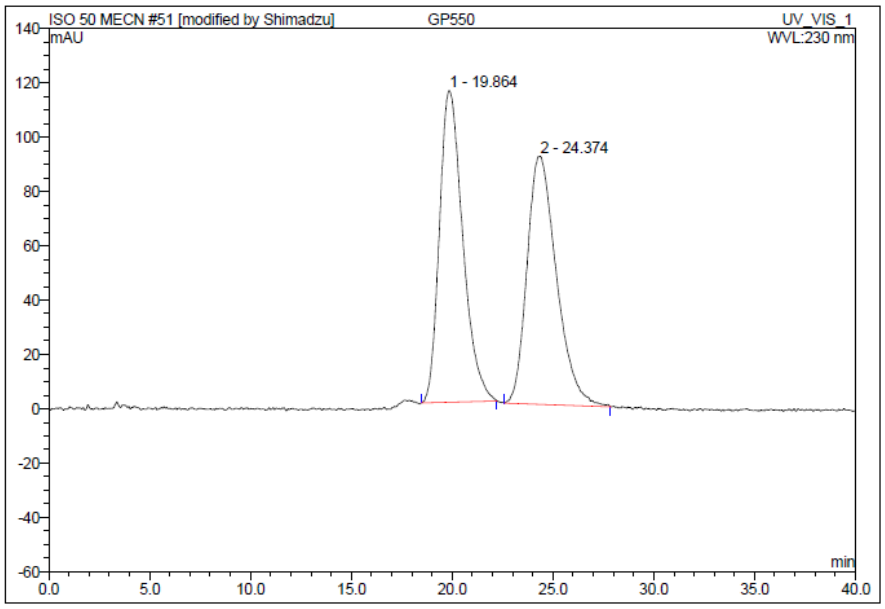
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.41	n.a.	98.037	73.320	48.81	n.a.	BM *
2	23.89	n.a.	87.496	76.908	51.19	n.a.	MB*
Total:			185.533	150.228	100.00	0.000	

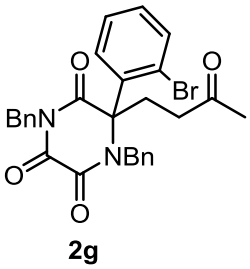
Enantioenriched **2f**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.42	n.a.	311.979	212.461	6.33	n.a.	BM *
2	23.43	n.a.	2529.509	3144.680	93.67	n.a.	MB*
Total:			2841.488	3357.141	100.00	0.000	

Racemic **2g**

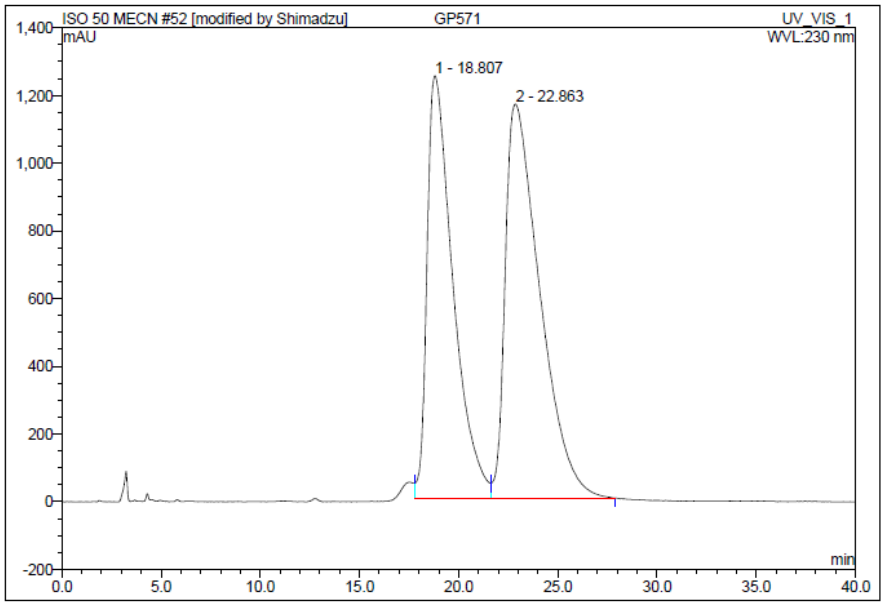




2g

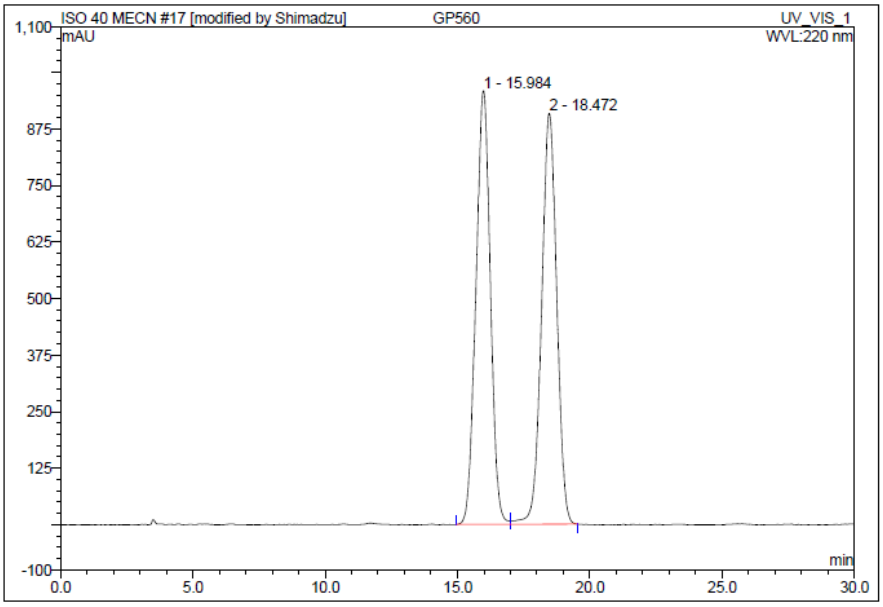
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.86	n.a.	114.742	154.150	49.95	n.a.	BMB
2	24.37	n.a.	91.413	154.475	50.05	n.a.	BMB*
Total:			206.155	308.625	100.00	0.000	

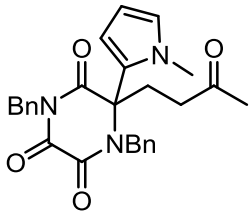
Enantioenriched **2g**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.81	n.a.	1246.977	1888.738	44.52	n.a.	M *
2	22.86	n.a.	1163.774	2354.138	55.48	n.a.	MB*
Total:			2410.751	4242.876	100.00	0.000	

Racemic **2h**

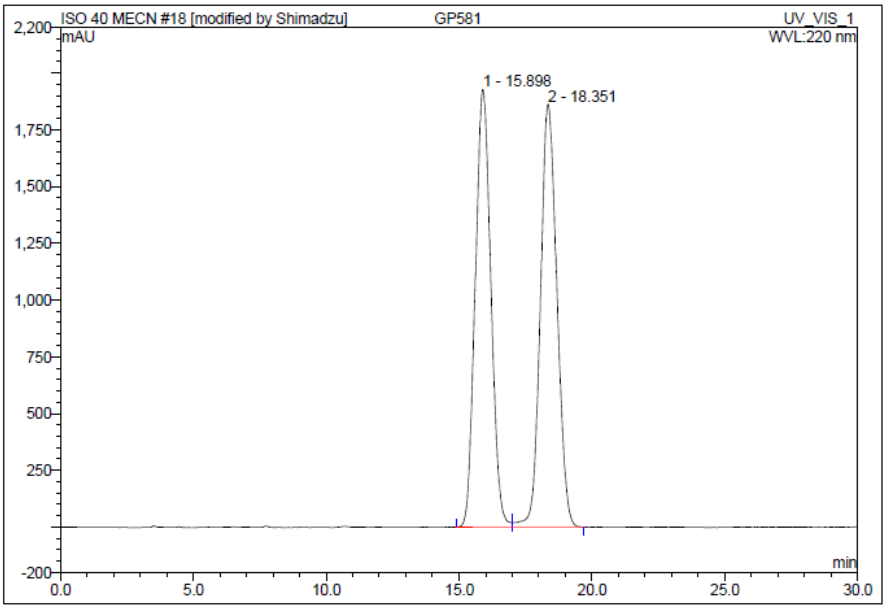




2h

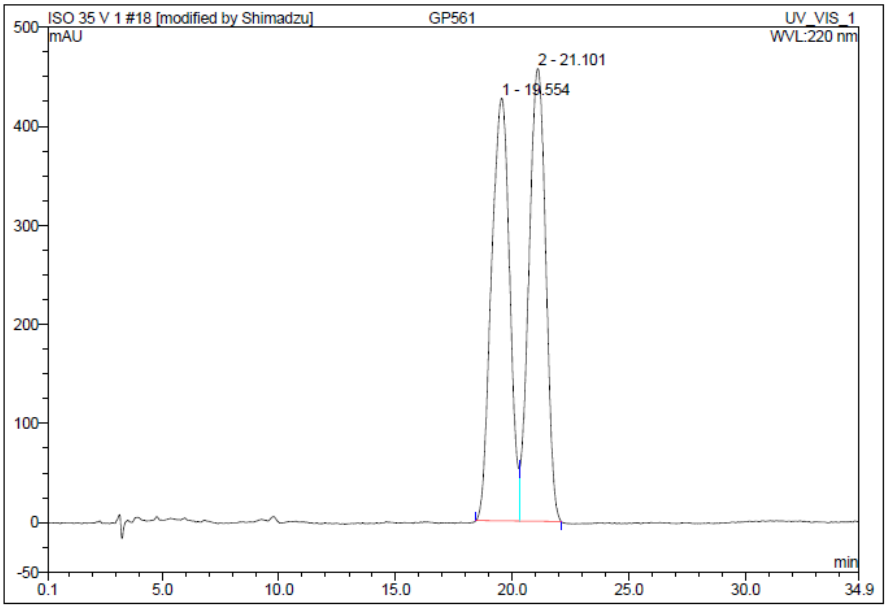
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.98	n.a.	958.754	607.956	50.14	n.a.	BM
2	18.47	n.a.	908.054	604.457	49.86	n.a.	MB
Total:			1866.807	1212.413	100.00	0.000	

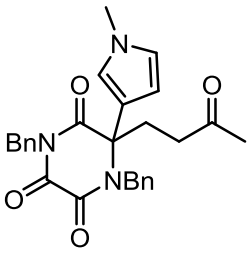
Enantioenriched **2h**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.90	n.a.	1927.872	1316.173	49.44	n.a.	BM
2	18.35	n.a.	1862.252	1346.180	50.56	n.a.	MB
Total:			3790.124	2662.353	100.00	0.000	

Racemic **2i**

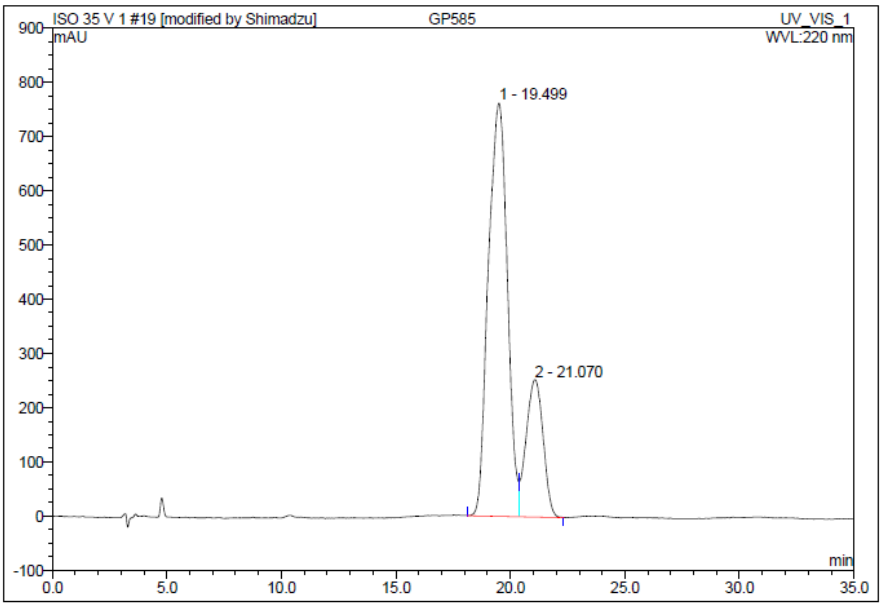




2i

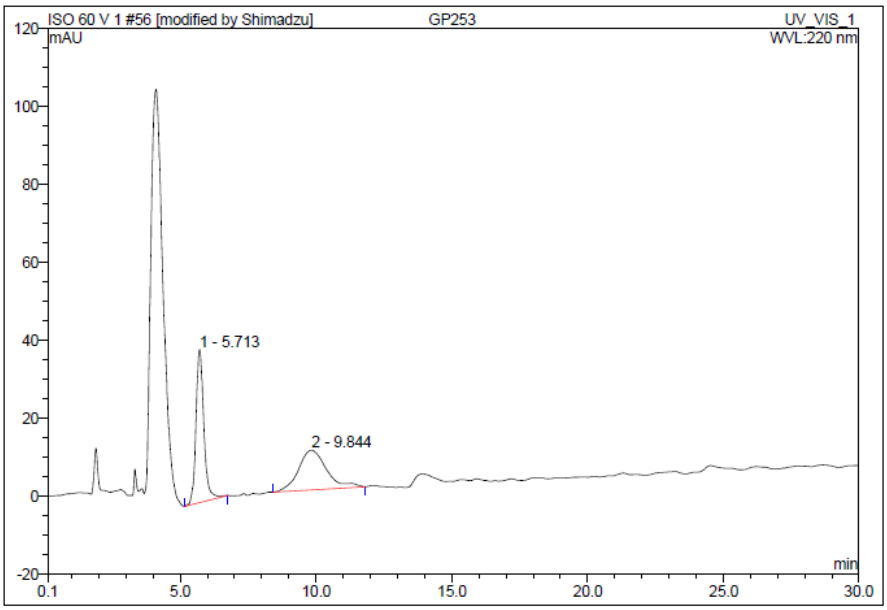
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.55	n.a.	426.460	384.961	50.07	n.a.	BM *
2	21.10	n.a.	456.759	383.860	49.93	n.a.	MB*
Total:			883.219	768.822	100.00	0.000	

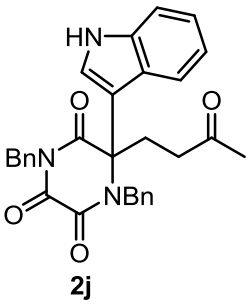
Enantioenriched **2i**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.50	n.a.	761.853	730.578	76.98	n.a.	BM
2	21.07	n.a.	253.055	218.440	23.02	n.a.	MB
Total:			1014.909	949.018	100.00	0.000	

Racemic **2j**

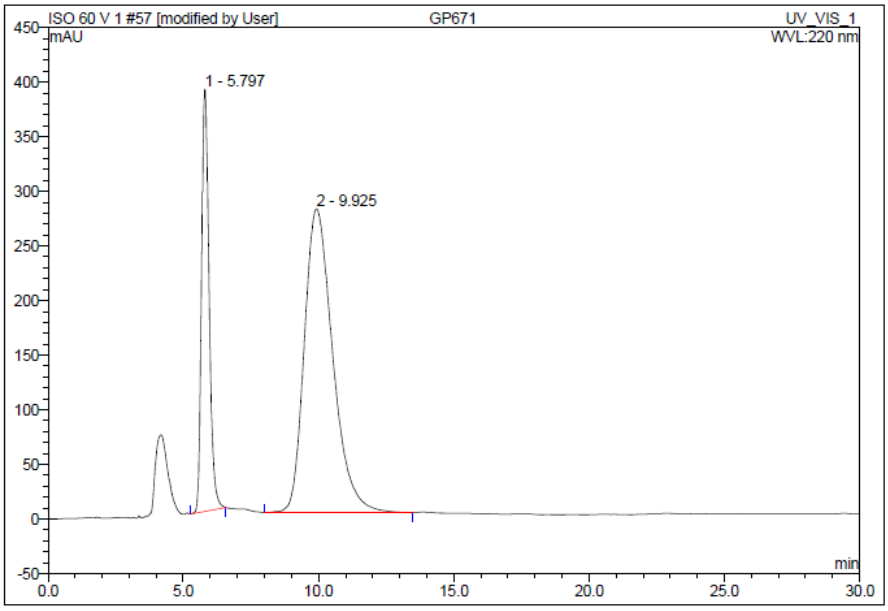




2j

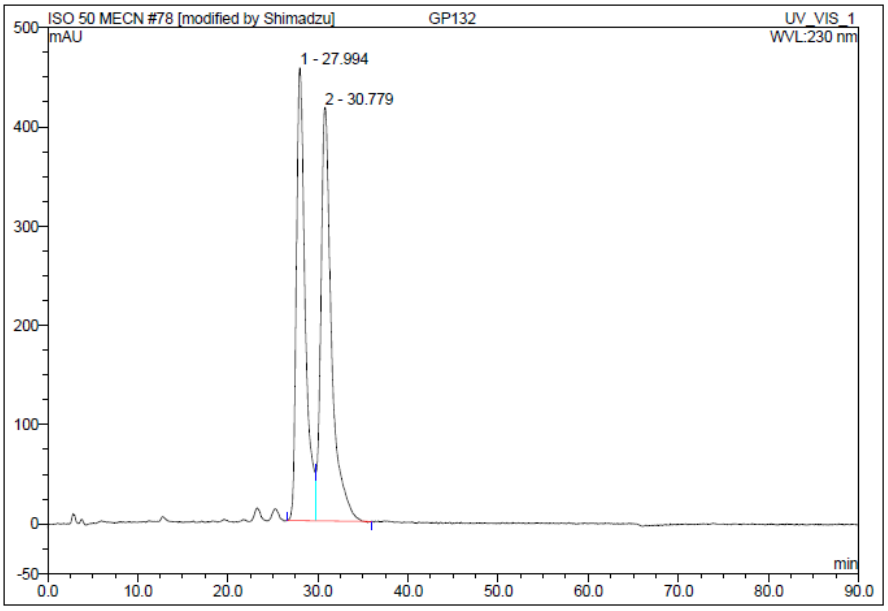
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.71	n.a.	39.245	13.113	51.85	n.a.	BMB*
2	9.84	n.a.	10.163	12.176	48.15	n.a.	BMB
Total:			49.409	25.289	100.00	0.000	

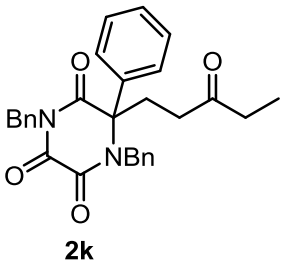
Enantioenriched **2j**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.80	n.a.	386.569	125.565	26.97	n.a.	BMB*
2	9.92	n.a.	278.305	339.956	73.03	n.a.	BMB*
Total:			664.874	465.521	100.00	0.000	

Racemic **2k**

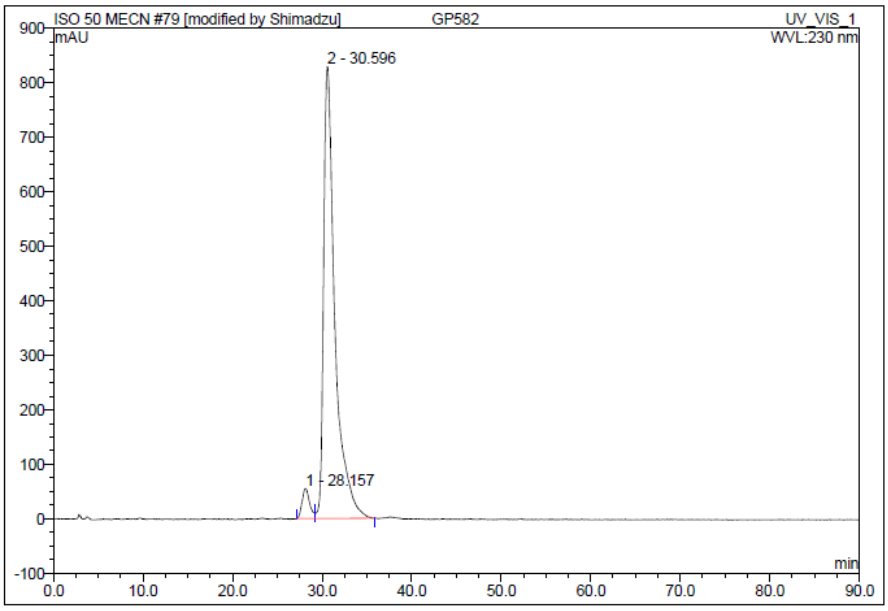




2k

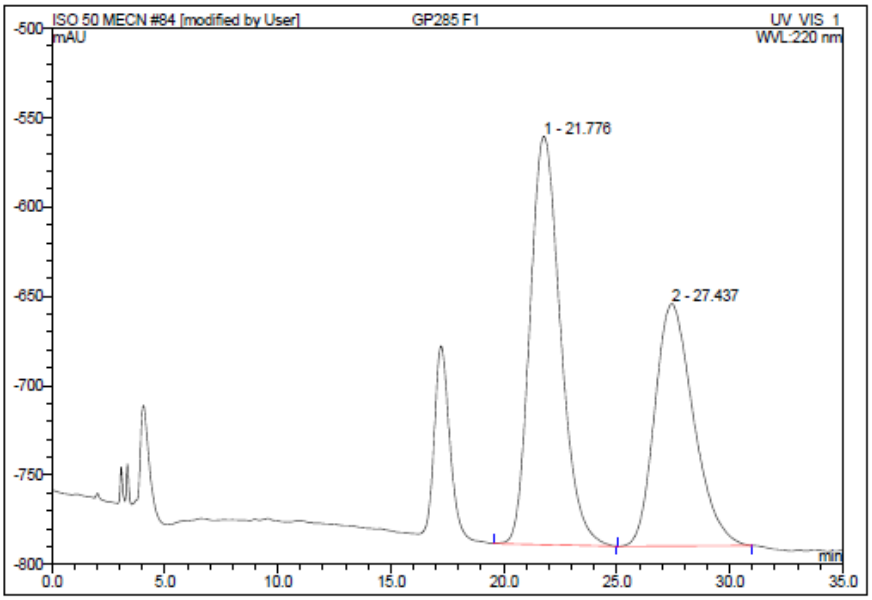
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	27.99	n.a.	456.057	518.128	47.41	n.a.	BM *
2	30.78	n.a.	416.599	574.848	52.59	n.a.	MB*
Total:			872.656	1092.976	100.00	0.000	

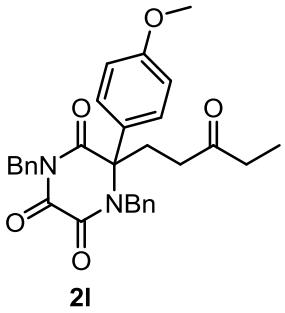
Enantioenriched **2k**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.16	n.a.	54.747	53.896	4.28	n.a.	BM *
2	30.60	n.a.	828.738	1205.445	95.72	n.a.	MB*
Total:			883.485	1259.341	100.00	0.000	

Racemic **2l**

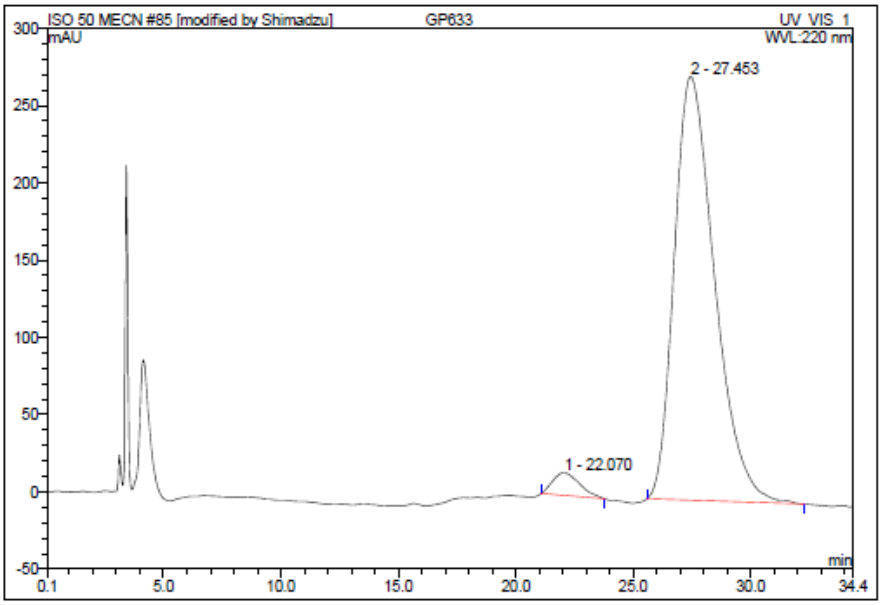




2l

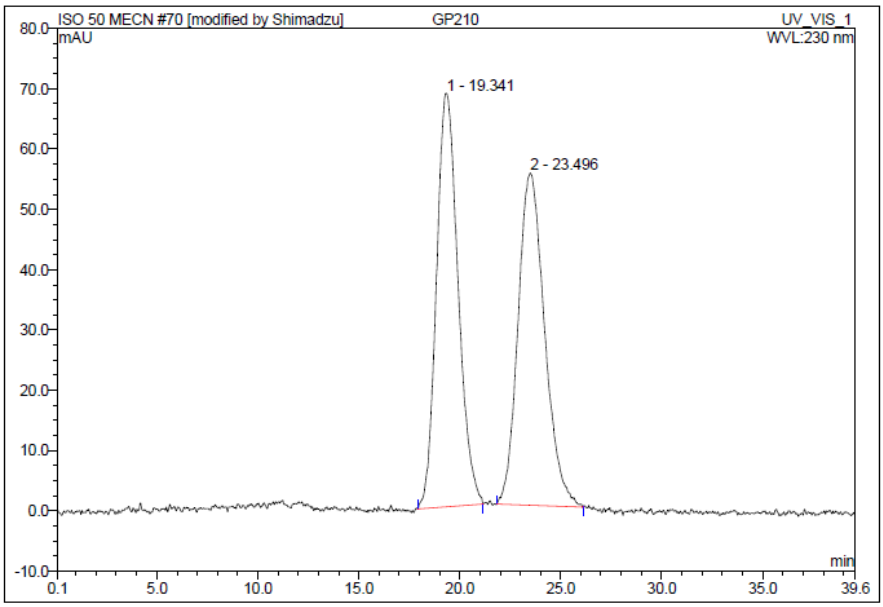
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.78	n.a.	228.350	356.991	56.96	n.a.	BMB
2	27.44	n.a.	135.520	269.763	43.04	n.a.	BMB
Total:			363.870	626.754	100.00	0.000	

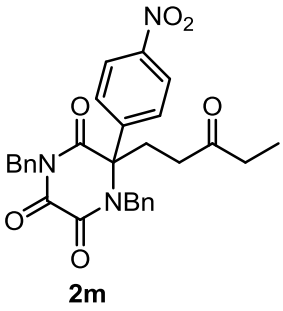
Enantioenriched **2l**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.07	n.a.	14.675	19.493	3.45	n.a.	BMB*
2	27.45	n.a.	274.201	546.040	96.55	n.a.	BMB*
Total:			288.876	565.534	100.00	0.000	

Racemic **2m**

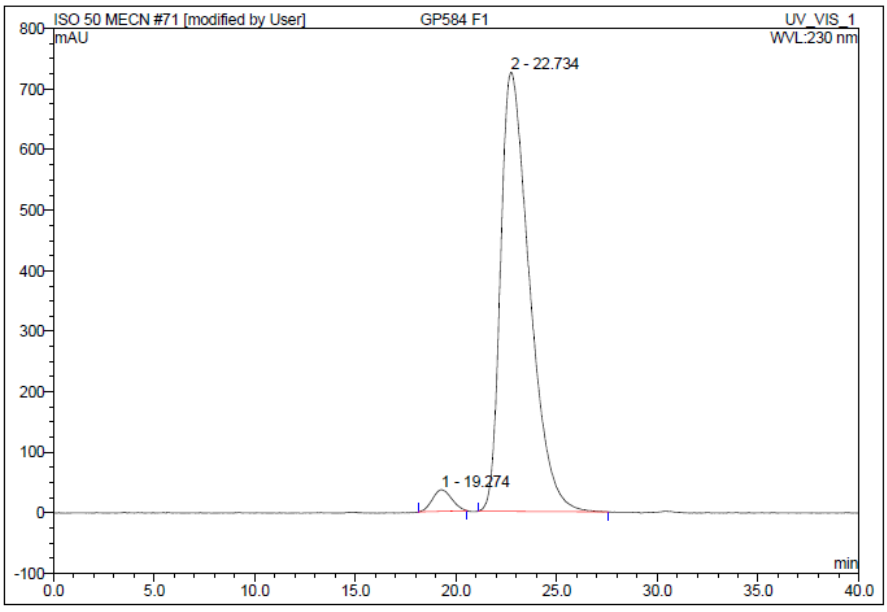




2m

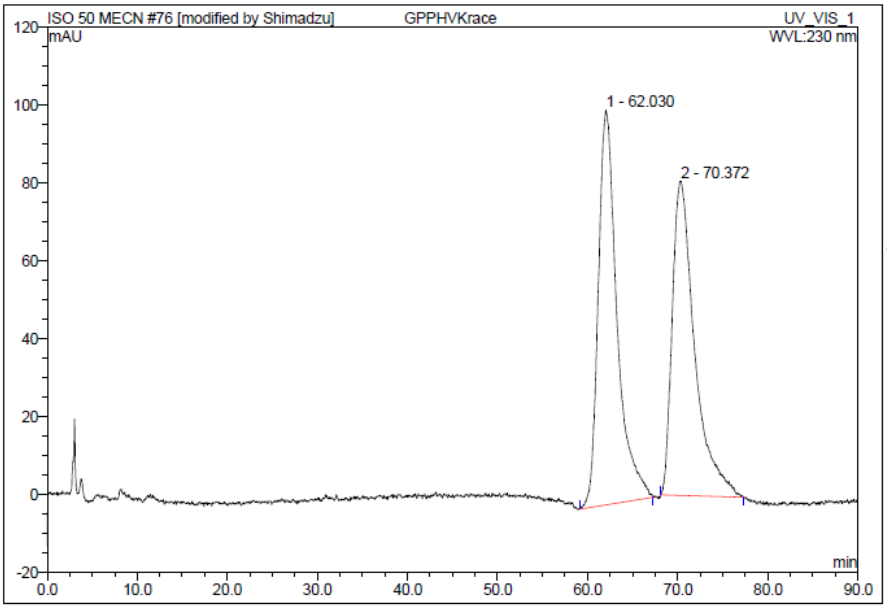
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.34	n.a.	68.582	85.180	50.35	n.a.	BMB
2	23.50	n.a.	55.127	83.995	49.65	n.a.	BMB*
Total:			123.708	169.175	100.00	0.000	

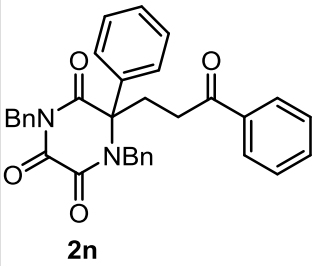
Enantioenriched **2m**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.27	n.a.	35.861	39.429	3.16	n.a.	BMB*
2	22.73	n.a.	725.399	1207.175	96.84	n.a.	BMB*
Total:			761.260	1246.603	100.00	0.000	

Racemic **2n**

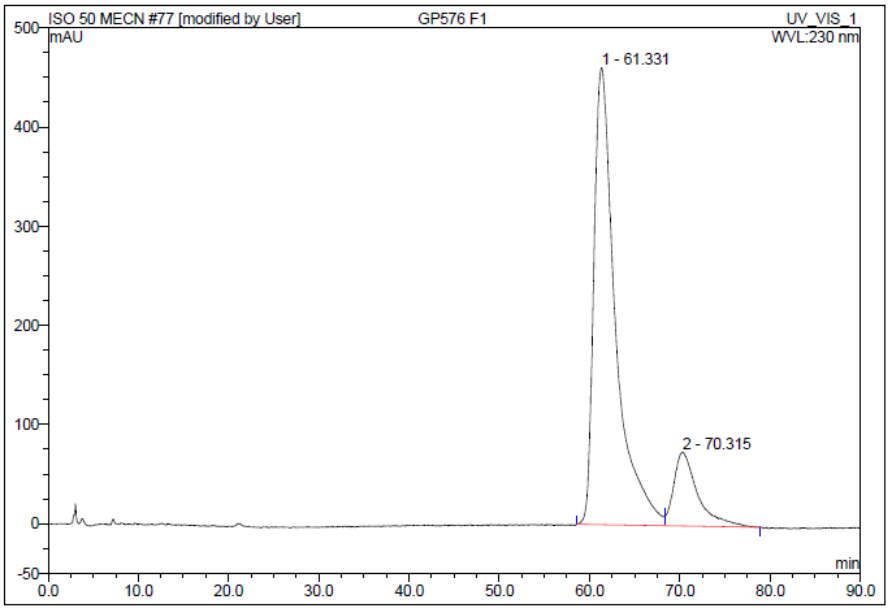




2n

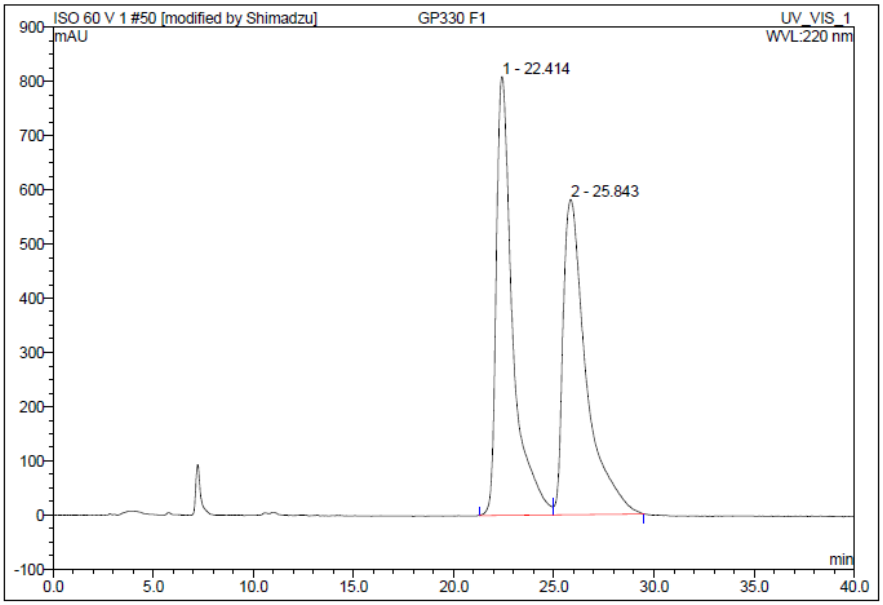
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	62.03	n.a.	101.474	244.752	51.33	n.a.	BMB*
2	70.37	n.a.	80.817	232.108	48.67	n.a.	BMB*
Total:			182.291	476.860	100.00	0.000	

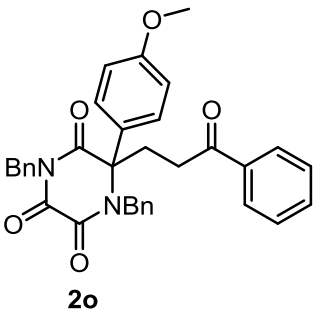
Enantioenriched **2n**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	61.33	n.a.	460.948	1277.125	84.82	n.a.	BM *
2	70.31	n.a.	74.566	228.631	15.18	n.a.	MB*
Total:			535.514	1505.755	100.00	0.000	

Racemic **2o**

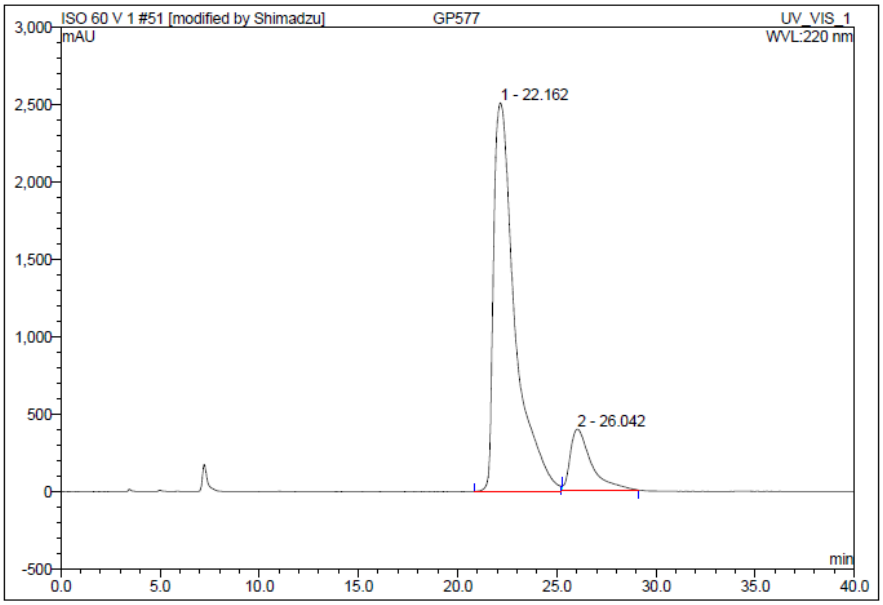




2o

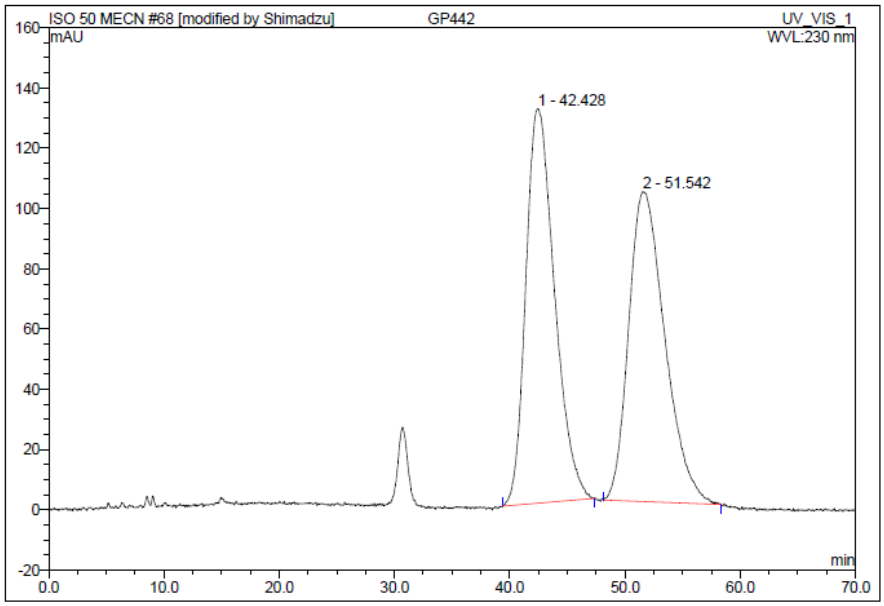
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.41	n.a.	809.199	773.125	49.87	n.a.	BM
2	25.84	n.a.	581.731	777.194	50.13	n.a.	MB
Total:			1390.930	1550.319	100.00	0.000	

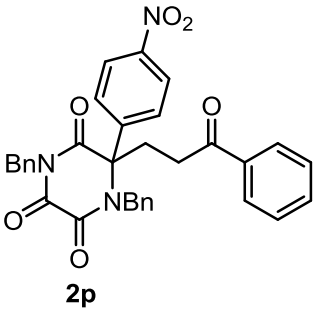
Enantioenriched **2o**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.16	n.a.	2511.561	3130.746	86.65	n.a.	BM *
2	26.04	n.a.	392.916	482.445	13.35	n.a.	MB*
Total:			2904.477	3613.191	100.00	0.000	

Racemic **2p**

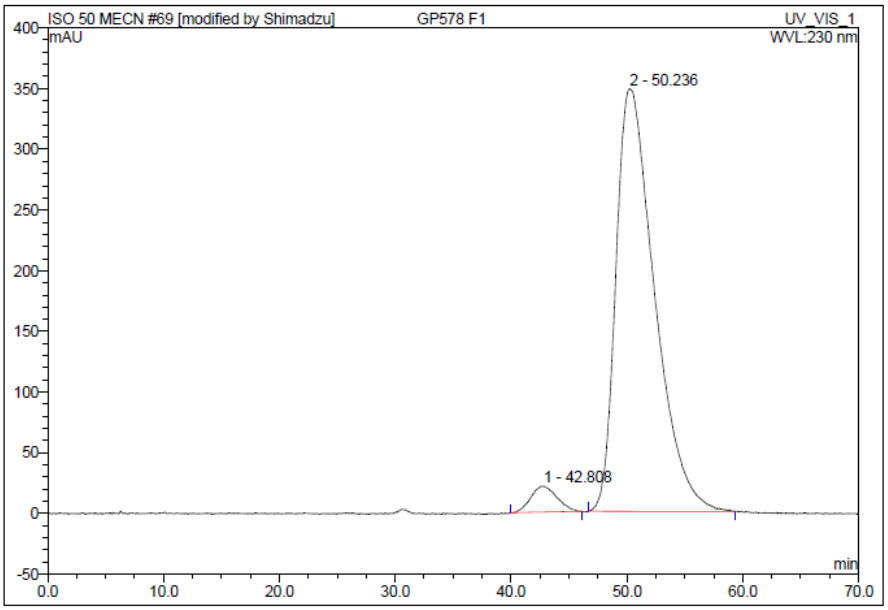




2p

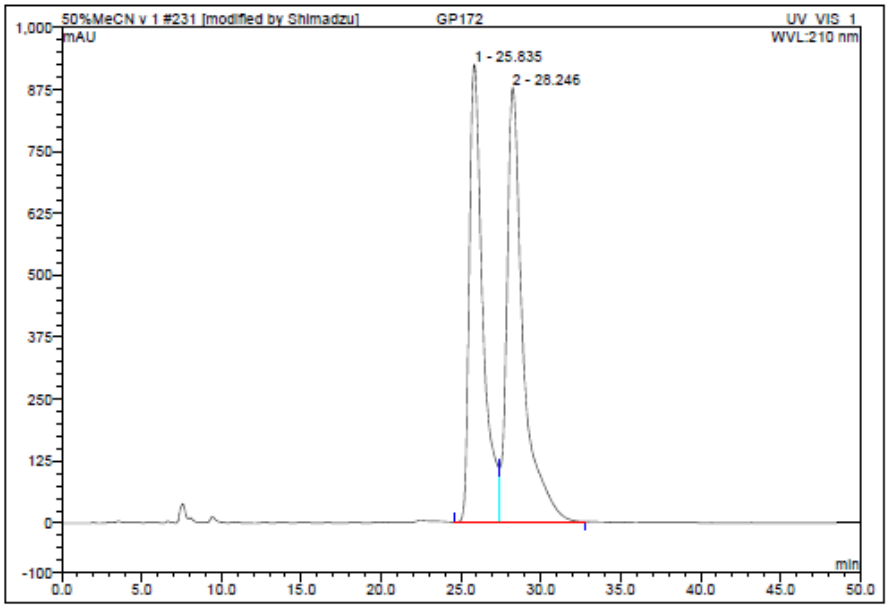
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	42.43	n.a.	130.933	378.436	50.31	n.a.	BMB*
2	51.54	n.a.	102.868	373.771	49.69	n.a.	BMB*
Total:			233.802	752.207	100.00	0.000	

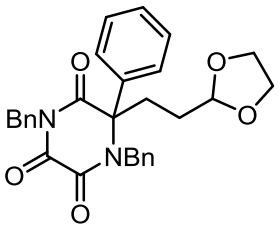
Enantioenriched **2p**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	42.81	n.a.	21.362	54.970	3.93	n.a.	BMB*
2	50.24	n.a.	348.274	1343.057	96.07	n.a.	BMB*
Total:			369.636	1398.027	100.00	0.000	

Racemic **S12**

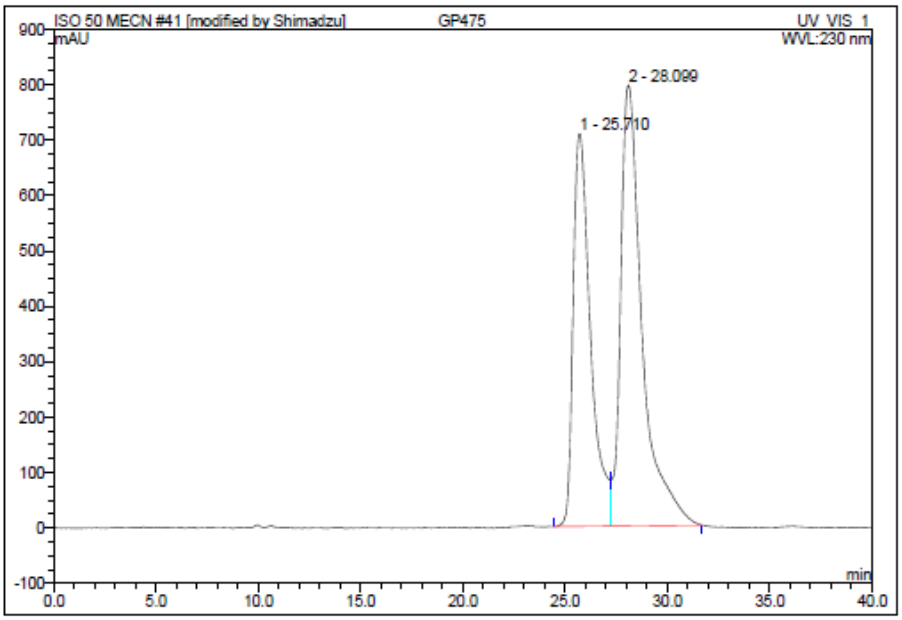




S12

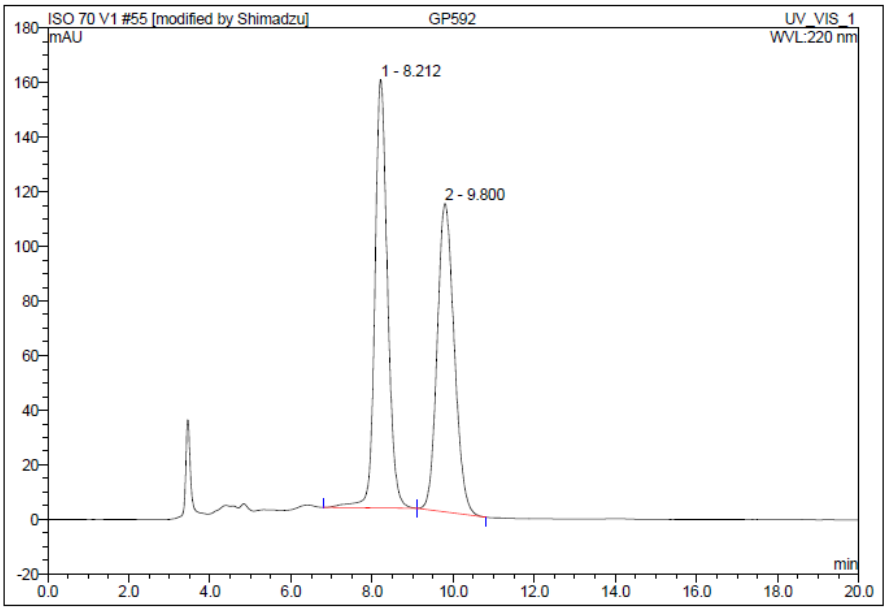
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.84	n.a.	923.568	905.571	46.59	n.a.	BM *
2	28.25	n.a.	876.679	1038.263	53.41	n.a.	M *
Total:			1800.247	1943.834	100.00	0.000	

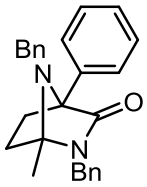
Enantioenriched **S12**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.71	n.a.	708.926	700.257	41.99	n.a.	BM
2	28.10	n.a.	795.741	967.366	58.01	n.a.	MB
Total:			1504.667	1667.623	100.00	0.000	

Racemic **4a**

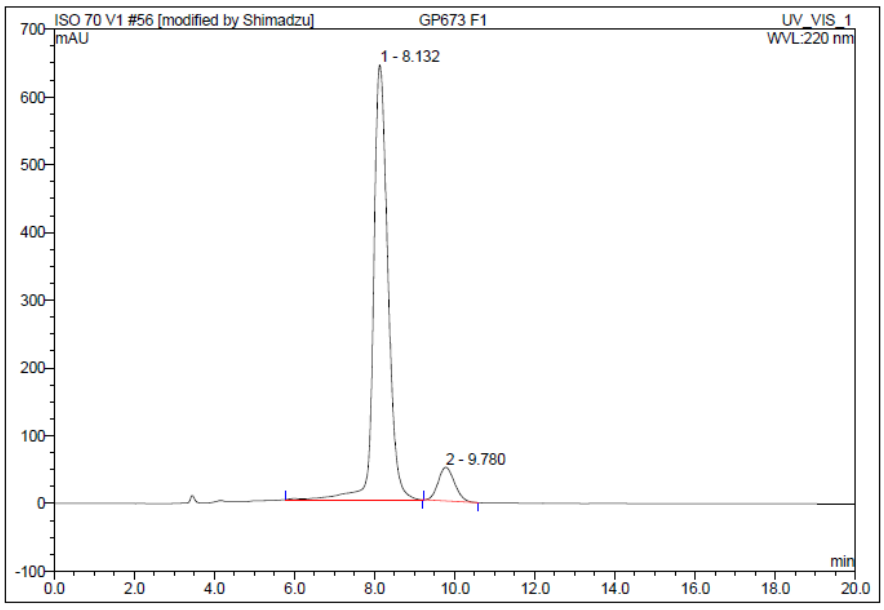




4a

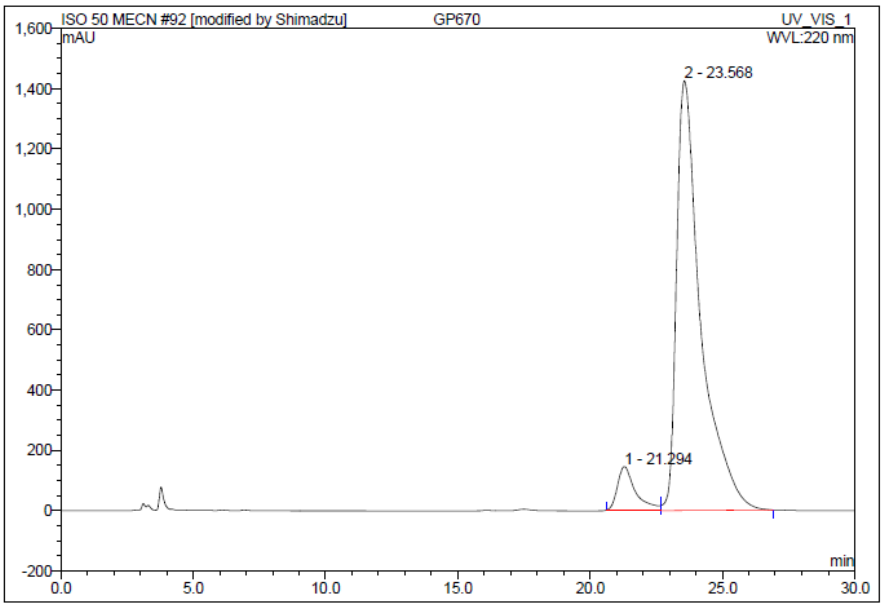
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.21	n.a.	156.872	56.766	50.82	n.a.	BMB
2	9.80	n.a.	112.994	54.941	49.18	n.a.	BMB
Total:			269.866	111.707	100.00	0.000	

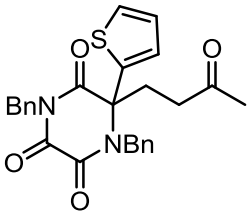
Enantioenriched **4a**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.13	n.a.	641.599	267.022	91.89	n.a.	MB*
2	9.78	n.a.	49.709	23.556	8.11	n.a.	BMB
Total:			691.308	290.578	100.00	0.000	

Enantioenriched sample of **2f** used to generate diazabicycle **4f**

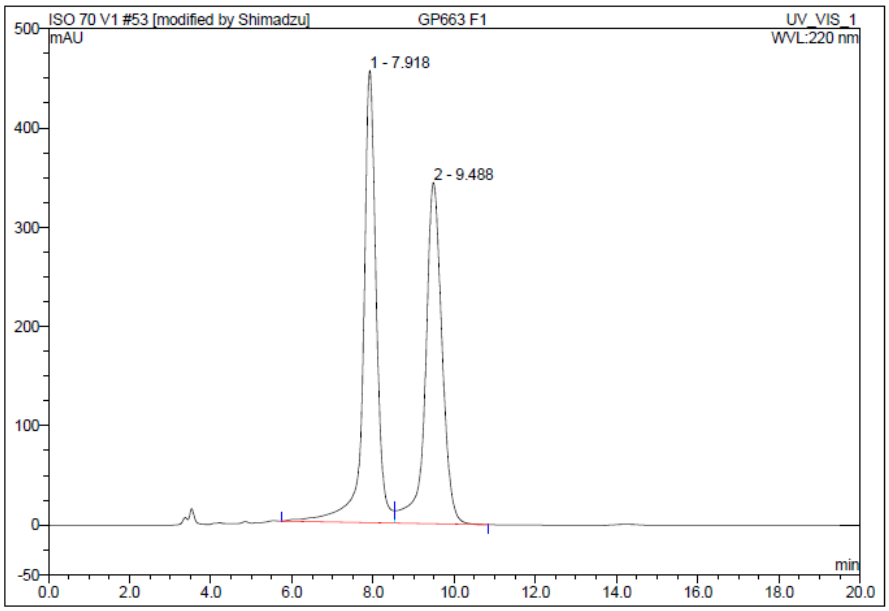


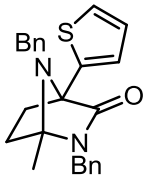


2f

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.29	n.a.	144.430	113.348	6.95	n.a.	BM *
2	23.57	n.a.	1426.436	1516.427	93.05	n.a.	MB*
Total:			1570.867	1629.776	100.00	0.000	

Racemic **4f**

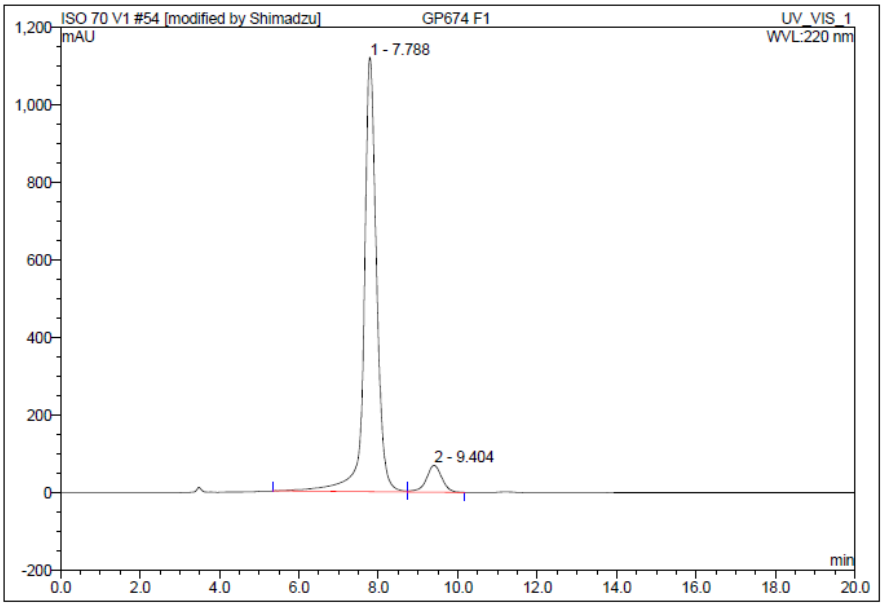




4f

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.92	n.a.	455.326	168.503	50.97	n.a.	BM
2	9.49	n.a.	343.722	162.098	49.03	n.a.	MB
Total:			799.047	330.601	100.00	0.000	

Enantioenriched **4f**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.79	n.a.	1120.559	406.547	92.86	n.a.	BM *
2	9.40	n.a.	69.116	31.260	7.14	n.a.	MB*
Total:			1189.675	437.807	100.00	0.000	

X-ray Crystal Structures

The datasets were measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collections were driven and processed and absorption corrections were applied using CrysAlisPro.[S1] The structure of **2f** was solved using ShelXT[S2] and that of **4a** was solved using ShelXS[S3] and both structures were refined by a full-matrix least-squares procedure on F^2 in ShelXL.[S4] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. Figures and reports were produced using OLEX2.[S5]

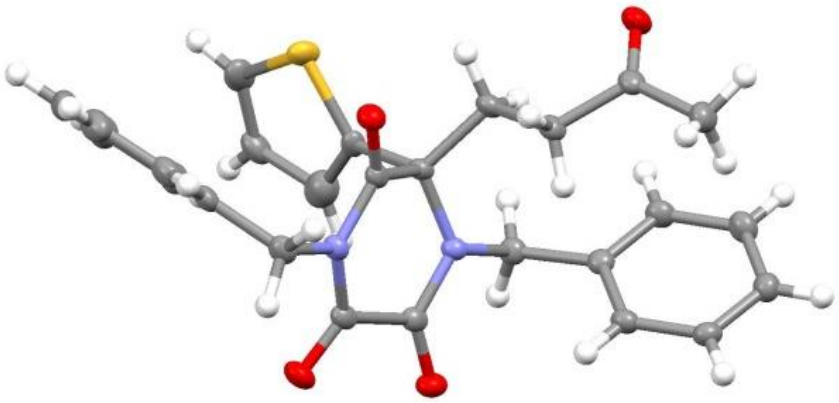
The structure of **2f** occupies a chiral space group and the absolute structure has been determined from the diffraction data, with the Flack parameter being -0.004 (6).

In **2f** the thiophene ring, C(7)-S(8)-C(9)-C(10)-C(11), (C(7')-S(8')-C(9')-C(10')-C(11')) is disordered over two positions at a refined percentage occupancy ratio of 63. 9(3) : 36.1 (3).

The structure of **4a** occupies a centrosymmetric space group. Thus in one molecule in the unit cell C(6) is *R* and C(9) is *S* while in the other molecule C(6) is *S* and C(9) is *R*. The relative stereochemistry is the same in all molecules.

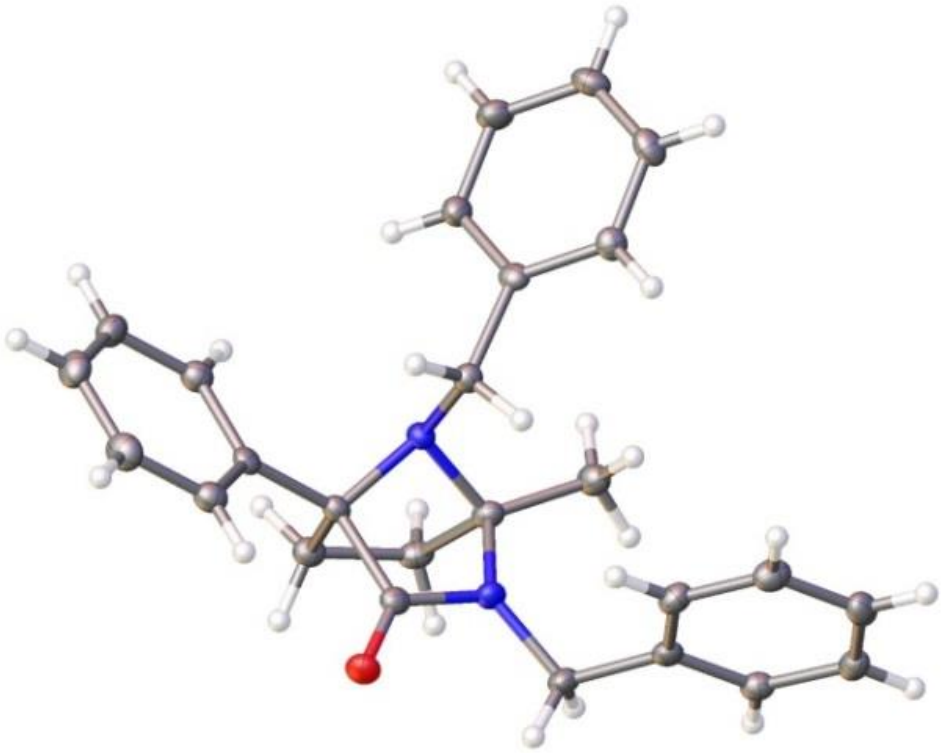
The CIFs for the crystal structures of **2f** and **4a** have been deposited with the CCDC and have been given the deposition numbers: CCDC 1880502 and CCDC 1880503 respectively.

Crystal structure determination of **2f**:



Crystal Data for $C_{26}H_{24}N_2O_4S$ (*M* =460.53 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 7.27000(10) Å, *b* = 11.16340(10) Å, *c* = 14.17310(10) Å, *β* = 96.9580(10)°, *V* = 1141.79(2) $Å^3$, *Z* = 2, *T* = 100.01(10) K, μ(CuKα) = 1.556 mm^{-1}, *Dcalc* = 1.340 g/cm^3, 21276 reflections measured (12.264° ≤ 2Θ ≤ 144.218°), 4388 unique (R_{int} = 0.0209, R_{sigma} = 0.0147) which were used in all calculations. The final R_1 was 0.0227 (I > 2σ(I)) and wR_2 was 0.0582 (all data). Flack = -0.004(6).

Crystal structure determination of **4a**:



Crystal Data for $C_{26}H_{26}N_2O$ (*M* =382.49 g/mol): triclinic, space group P-1 (no. 2), *a* = 9.9803(5) Å, *b* = 10.7055(5) Å, *c* = 11.0770(7) Å, *α* = 76.953(5)°, *β* = 64.440(6)°, *γ* = 72.474(4)°, *V* = 1011.80(11) Å^3, *Z* = 2, *T* = 100.01(10) K, μ(MoKα) = 0.076 mm^{-1}, *Dcalc* = 1.255 g/cm^3, 8126 reflections measured (7.212° ≤ 2Θ ≤ 53.462°), 4266 unique (R_{int} = 0.0201, R_{sigma} = 0.0362) which were used in all calculations. The final R_1 was 0.0451 (I > 2σ(I)) and wR_2 was 0.1063 (all data).

[S1] CrysAlisPro, Agilent Technologies, Version 1.171.36.28, **2013**.

[S2] G. M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3-8.

[S3] G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112-122.

[S4] G. M. Sheldrick, *Acta Cryst.* **2015**, *C71*, 3-8.

[S5] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339-341.