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The kinetic resolution of oxazinones by alcoholysis: access to orthogonally protected -amino acids

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General

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Advance II 600MHz spectrometers, using as solvent CDCl3, DMSO-d_6 or D_2O and referenced relative to residual CHCl3 (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical Ionization (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F254 slides, and visualized by UV irradiation and KMnO4 staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1} . CHCl3 was pre-treated with K_2CO_3, distilled over P_2O_5 and was stored under argon. Toluene was dried over activated 3Å molecular sieves. Anhydrous acetonitrile (CH_3CN), dichloromethane (CH2Cl2), tetrahydrofuran (THF) and diethyl ether (Et2O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Commercially available anhydrous t-butyl methyl ether (MTBE), MeOH, EtOH and allyl alcohol was used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm x 25 cm) columns or ACQUITY UPC2 on chiral Trefoil AMY1, CEL1, CEL2 (2,5 µm, 3.0 x 150mm) columns.

1.1 Gradient tables for HPLC conditions

1.1.1 Table 1.2.1

A: CO_2 B: EtOH/ACN (1:1)

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	40.0	60.0	6
12.00	1.200	40.0	60.0	6
12.10	1.200	97.0	3.0	6

1.1.2 Table 1.2.2

A: CO_2 B: EtOH/IPA

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
6.00	1.200	40.0	60.0	6
8.00	1.200	40.0	60.0	6
8.10	1.200	97.0	3.0	6

1.1.3 Table 1.2.3

A: CO_2 B: EtOH/ACN

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	90.0	60.0	6
13.00	1.200	40.0	60.0	6
18.00	1.200	40.0	3.0	6

1.1.4 Table 1.2.4

A: CO_2 B: EtOH/ACN

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	90.0	60.0	6
13.00	1.200	40.0	60.0	6
18.00	1.200	40.0	3.0	6

1.1.5 Table 1.2.5

A: CO_2 B: EtOH/ACN

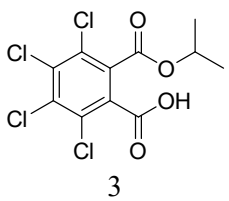
Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
5.00	1.200	8.00	60.0	6
12.00	1.200	40.0	60.0	6
13.00	1.200	40.0	3.0	6

1.1.6 Table 1.2.6

A: CO_2 B: EtOH/ACN

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	90.0	60.0	6
15.00	1.200	40.0	60.0	6
20.00	1.200	40.0	3.0	6

1.1.7 2,3,4,5-Tetrachloro-6-(*iso*propoxycarbonyl)benzoic acid (S1)



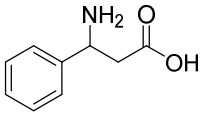
A suspension of 3,4,5,6-tetrachlorophthalic anhydride (10.0 g, 35.0 mmol), IPA (60.0 mL) and NEt_3 (4.9 mL, 35.0 mmol) were stirred under argon for 16 h. Aqueous HCl (2N, 30 mL) was added and the reaction mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to furnish **S1** as a white solid (9.5 g, 94%). M.p. 141-143 °C (lit.[1] 143-145 °C). The isolated product exhibited identical spectroscopic data to those in the literature.[1]

δ_H (400 MHz, $CDCl_3$): 10.34 (1H, s), 5.31 (1H, sept., *J* 6.3), 1.39 (6H, d, *J* 6.3).

1.1.8 General procedure A: *β*-amino acid synthesis

A suspension of malonic acid (1.0 equiv.), the appropriate aldehyde (1.1 equiv.) and ammonium acetate (1.3 equiv.), in EtOH (1.0 M) was heated under at 87 °C for 16 h. The resulting precipitate was cooled, filtered and washed with ice cold EtOH to yield the corresponding *β*-amino acid.

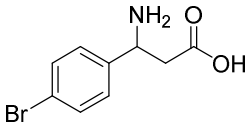
1.1.8.1 3-Amino-3-phenylpropanic acid (S2)



Prepared according to **General Procedure A** using malonic acid (10.0 g, 96.0 mmol), benzaldehyde (10.9 mL, 105.7 mmol) and ammonium acetate (9.6 g, 124.9 mmol) in EtOH (100.0 mL) to yield compound **S2** (9.7 g, 61%) as a white solid. M.p. 218-220 °C (lit.[2] 222-223 °C). The isolated product exhibited identical spectroscopic data to those in the literature.[3]

δ_H (400 MHz, D_2O): 7.31-7.35 (5H, m), 4.51 (1H, dd, *J* 7.9, 6.6), 2.65-2.80 (2H, m).

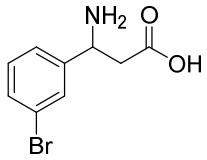
1.1.8.2 3-Amino-3-(4-bromophenyl)propanoic acid (S2)



Prepared according to **General Procedure A** using malonic acid (4.5 g, 43.2 mmol), 4-bromobenzaldehyde (8.0 g, 43.2 mmol) and ammonium acetate (4.3 g, 56.1 mmol) in EtOH (50.0 mL) to yield compound **S2** (5.6 g, 54%) as a white solid. M.p. 227-228 °C, (lit.[4] 228-229 °C). The isolated product exhibited identical spectroscopic data to those in the literature.[4]

δ_H (400 MHz, D_2O): 7.44-7.39 (2H, m), 7.19-7.15 (2H, m), 4.09 (1H, m), 2.50-2.36 (2H, m).

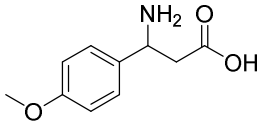
1.1.8.3 3-Amino-3-(3-bromophenyl)propanoic acid (S3)



Prepared according to **General Procedure A** using malonic acid (3.6 g, 34.1 mmol), 4-bromobenzaldehyde (6.3 g, 34.1 mmol) and ammonium acetate (3.4 g, 44.3 mmol) in EtOH (40.0 mL) to yield compound **S3** (4.7 g, 52%) as a white solid. M.p. 225-227 °C, (lit.[4] 225-226 °C). The isolated product exhibited identical spectroscopic data to those in the literature.[4]

δ_H (400 MHz, D_2O): 7.45 (1H, s), 7.35 (1H, d, *J* 7.5), 7.26-7.14 (2H, m), 4.09 (1H, m), 2.48-2.38 (2H, m).

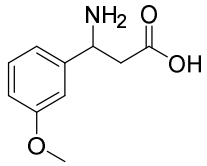
1.1.8.4 3-Amino-3-(4-methoxyphenyl)propanoic acid (S4)



Prepared according to **General Procedure A** using malonic acid (3.6 g, 34.6 mmol), 4-anisaldehyde (4.2 mL, 34.6 mmol) and ammonium acetate (3.5 g, 45.0 mmol) in EtOH (40.0 mL) to yield compound **S4** (2.7 g, 38%) as a white solid. M.p. 233-234 °C (lit.[5] 238-239 °C). The isolated product exhibited identical spectroscopic data to those in the literature.[5]

δ_H (400 MHz, D_2O): 7.31-7.26 (2H, m), 6.95-6.91 (2H, m) 4.49 (1H, m), 3.73 (3H, s), 2.82-2.64 (2H, m).

1.1.8.5 3-Amino-3-(3-methoxyphenyl)propanoic acid (S5)



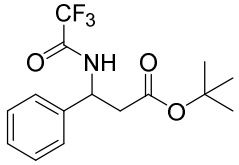
Prepared according to **General Procedure A** using malonic acid (7.6 g, 73.4 mmol), 3-anisaldehyde (9.0 mL, 73.4 mmol) and ammonium acetate (3.5 g, 45.0 mmol) in EtOH (40.0 mL) to yield compound **S5** (9.3 g, 65%) as a white solid. M.p. 209-210 °C (lit.[3] 213-214 °C). The isolated product exhibited identical spectroscopic data to those in the literature.[3]

δ_H (400 MHz, D_2O): 7.25 (1H, m), 7.00-6.82 (3H, m) 4.19 (1H, m), 3.73 (3H, s), 2.35-2.28 (2H, m).

1.1.9 General procedure B: Two-step protection as the trifluoroacetamide *t*-butyl ester

Triflouroacetic anhydride (1.3 equiv.) was added to a suspension of the appropriate *β*-amino acid (1.0 equiv.) at 0 °C under argon. The resulting solution was heated under reflux for 16 h. The mixture was concentrated *in vacuo* to give the trifluoroacetamide. To this was added DMAP (0.4 equiv.) and DCC (1.0 equiv.) and the flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (0.5 M) was added and the mixture was cooled to 0 °C. *tert*-Butanol (4.0 equiv.) was added *via* syringe and the mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered and washed with CH_2Cl_2. The filtrate was purified *via* silica chromatography to yield the di-protected product.

1.1.9.1 *tert*-Butyl 3-phenyl-3-(2,2,2-trifluoroacetamido)propanoate (S7)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **S2** (14.2 g, 44.7 mmol) and TFAA (18.9 mL, 134.1 mmol) and was brought forward to the next step. To this was added DMAP (545.0 mg, 4.5 mmol), DCC (10.1 g, 49.1 mmol), CH_2Cl_2 (88.0 mL) and *tert*-Butanol (13.2 mL, 178.6 mmol). The product was purified *via* silica chromatography, eluting with 10 % EtOAc in hexane to yield **S7** as a white solid (13.0 g, 91%). M.p. 57-60 °C.

δ_H (400 MHz, $CDCl_3$): 7.85 (1H, br-s), 7.86-7.29 (5H, m), 5.43-5.39 (1H, m), 2.93-2.82 (2H, m), 1.38 (9H, s).

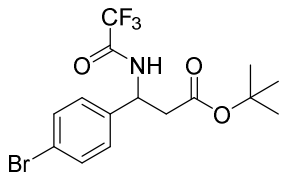
δ_C (100 MHz, $CDCl_3$): 170.2, 156.4 (C=O, $J_{C\text{-}F}$ = 37.1) 138.6, 128.9, 128.1, 126.1, 111.6-120.2 (q, $J_{C\text{-}F}$ = 289.4), 82.3, 50.1, 40.3, 27.9.

δ_F (376 MHz, $CDCl_3$) -76.41.

ν_{max} (neat)/cm^{-1}: 3277, 1728, 1696.

HRMS (*m/z* - ESI): Found: 316.1166 $(M\text{-}H)^-$ $C_{15}H_{17}F_3NO_3$ Requires: 316.1611.

1.1.9.2 *tert*-Butyl 3-(4-bromophenyl)-3-(2,2,2-trifluoroacetamido)propanoate (S8)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **S3** (5.1, g, 17.3 mmol) and TFAA (7.3 mL, 51.8 mmol) and was brought forward to the next step. To this was added DMAP (0.8 g, 6.9 mmol), DCC (4.1 g, 19.7 mmol), CH_2Cl_2 (34.0 mL) and *tert*-Butanol (6.5 mL,

69.0 mmol).The product was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to yield **S8** as a white solid (5.0 g, 73%). M.p. 83-85 °C.

δ_H (400 MHz, $CDCl_3$): 7.97 (1H, d, *J* 7.5), 7.47 (2H, d, *J* 8.3), 7.16 (2H, d, *J* 8.3), 5.33-5.27 (1H, m) 2.81 (2H, m), 1.37 (9H, s).

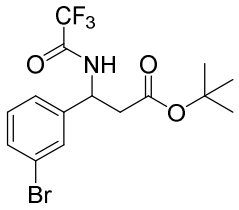
δ_C (100 MHz, $CDCl_3$): 170.1, 156.5 (C=O, J_{C-F} = 37.5) 137.9, 132.0, 127.9, 115.8 (q, J_{C-F} = 287.8), 82.6, 49.7, 40.0, 27.9.

δ_F (376 MHz, $CDCl_3$) -75.9.

ν_{max} (neat)/cm^{-1}: 3276, 1727, 1698.

HRMS (*m/z* - ESI): Found: 418.0237 $(M+Na)^+$ $C_{15}H_{17}BrF_3NNaO_3$ Requires: 418.0236.

1.1.9.3 *tert*-Butyl 3-(3-bromophenyl)-3-(2,2,2-trifluoroacetamido)propanoate (S9)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **S4** (4.0 g, 13.7 mmol) and TFAA (5.8 mL, 41.0 mmol) and was brought forward to the next step. To this DMAP was added (0.7 g, 5.5 mmol), DCC (3.1 g, 15.0 mmol), CH_2Cl_2 (28.0 mL) and *tert*-Butanol (5.2 mL, 54.7 mmol). The product was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to yield **S9** as a white solid (4.2 g, 78%). M.p. 99-101°C.

δ_H (400 MHz, $CDCl_3$): 8.01-7.90 (1H, br-s,), 7.47-7.40 (2H, m,), 7.25-7.29 (2H, m), 5.36-5.29 (1H, m), 2.81 (2H, app. d), 1.38 (9H, s).

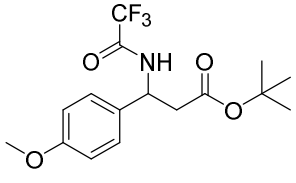
δ_C (100 MHz, $CDCl_3$): 170.1, 156.4 (C=O, J_{C-F} = 37.0) 141.1, 131.3, 130.4, 129.3, 124.9, 122.9, 115.7 (q, J_{C-F} = 290.5), 82.7, 49.7, 40.1, 27.9.

δ_F (376 MHz, $CDCl_3$) -75.90.

ν_{max} (neat)/cm^{-1}: 3277, 1727, 1697.

HRMS (*m/z* - ESI): Found: 394.0264 $(M-H)^-$ $C_{15}H_{16}BrF_3NO_3$ Requires: 394.0271.

1.1.9.4 *tert*-Butyl 3-(4-methoxyphenyl)-3-(2,2,2-trifluoroacetamido)propanoate (S10)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **S5** (9.8 g, 49.9 mmol) and TFAA (21.2 mL, 149.8 mmol) and was brought forward to the next step. To this was added DMAP (2.4 g, 19.9 mmol), DCC (11.4 g, 59.9 mmol) CH_2Cl_2 (100.0 mL) and *tert*-Butanol (19.0 mL, 199.7 mmol) were added. The product was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to yield **S10** as a white solid (7.9 g, 45%). M.p. 61-64 °C.

δ_H (400 MHz, $CDCl_3$): 7.76-7.66 (1H, m), 7.20 (2H, d *J* 8.6), 6.89 (2H, d, *J* 8.9), 5.36-5.30 (1H, m), 3.80 (3H, s), 2.89-2.76 (2H, m), 1.37 (9H, s).

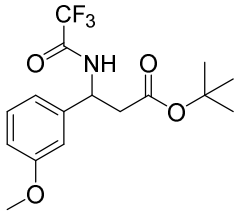
δ_c (400 MHz, $CDCl_3$): 170.2, 159.3, 156.3 (C=O, J_{C-F} = 37.3) 130.8, 127.4, 115.6 (q, J_{C-F} = 288.1), 114.2, 81.2, 55.3, 49.8 40.4, 27.9.

δ_F (376 MHz, $CDCl_3$) -75.96.

ν_{max} (neat)/cm^{-1}: 3256, 1721, 1698.

HRMS (*m/z* - ESI): Found: 370.1236 $(M+Na)^+$ $C_{16}H_{20}F_3NNaO_3$ Requires: 370.1236.

1.1.9.5 *tert*-Butyl 3-(3-methoxyphenyl)-3-(2,2,2-trifluoroacetamido)propanoate (S11)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **S6** (5. 3 g, 27.4 mmol) and TFAA (11.6 mL, 81.8 mmol) and was brought forward to the next step. To this was added DMAP (1.3 g, 10.9 mmol), DCC (6.2 g, 30.0 mmol,), CH_2Cl_2 (55.0 mL) and *tert*-Butanol (10.4 mL, 109.1 mmol). The product was purified *via* silica chromatography eluting with 10% EtOAc in hexane to yield **S11** as a white solid (2.6 g, 27%). M.p. 66-68 °C.

δ_H (400 MHz, $CDCl_3$): 7.85-7.79 (1H, m), 7.29-7.24 (1H, m), 6.89-76.79 (3H, m), 5.39-5.31 (1H, m), 3.80 (3H, s), 2.89-2.76 (2H, m), 1.37 (9H, s).

δ_c (400 MHz, $CDCl_3$): 165.5, 155.2, 151.6 (C=O, J_{C-F} = 38.1) 135.5, 125.2, 113.5, 111.4 (q, J_{C-F} = 286.2), 108.6, 107.4, 77.6, 50.5, 45.4 35.5, 23.1.

δ_F (376 MHz, $CDCl_3$) -80.7.

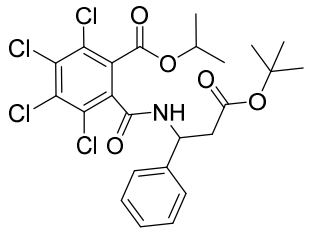
ν_{max} (neat)/cm^{-1}: 3277, 1724, 1700.

HRMS (*m/z* - ESI): Found: 370.1226 $(M+Na)^+$ $C_{16}H_{20}F_3NNaO_3$ Requires: 370.1237.

1.1.10 General procedure C: Trifluroacetamide removal and subsequent amide coupling

A solution of LiOH (1M, aq., 2 mL/mmol) was added to an RBF containing a magnetic stirring bar and the appropriate protected amino acid (1.0 equiv.) in 1,4-dioxane (2.5 mL/mmol) at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The solution was concentrated *in vacuo* and the resulting residue was re-dissolved in H_2O and extracted with EtOAc (x3). The combined organic layers were dried oved $MgSO_4$, filtered and concentrated *in vacuo* to give the free amine. To this **S1** (1.1 equiv.) and DCC (1.1 equiv.) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (0.5M) was added *via* syringe at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered *via* suction filtration and the filtrate was purified *via* silica chromatography.

1.1.10.1 *iso*Propyl-2-((3-(*tert*-butoxy)-3-oxo-1-phenylpropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S12)



Prepared according to **General Procedure C** using compound **S7** (5.4 g, 17.0 mmol), LiOH (1M, aq. 34.0 mL), and 1,4- dioxane (50.0 mL) to yield the free amine (4.0 g, 12.6 mmol). To this was added **S1** (4.3 g, 12.7 mmol) and DCC (2.6 g, 12.7 mmol) and anhydrous CH_2Cl_2 (25.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **S12** as a white solid (4.0 g, 54%), M.p. 67-70 °C.

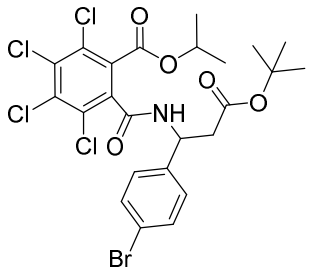
δ_H (400 MHz, $CDCl_3$): 7.35-7.15 (5H, m), 5.52-5.47 (1H, m), 5.08 (1H, sept., *J* 6.3), 2.94 (1H, dd, *J* 4.8, 15.8), 2.80 (1H, dd, *J* 6.2, 15.8), 1.28 (9H, s), 1.22-1.18 (6H, m).

δ_C (100 MHz, $CDCl_3$): 170.3 (C=O), 163.4 (C=O), 162.3 (C=O), 139.4 (q), 135.0 (q), 134.8 (q), 134.4 (q), 132.9 (q), 130.0 (q), 129.8 (q), 128.5, 127.7, 126.6, 81.6 (q), 71.2, 50.4, 40.3, 27.9, 21.3, 21.3.

ν_{max} (neat)/cm^{-1}: 3275, 1729, 1645, 1541.

HRMS (*m/z* - ESI): Found: 570.0366 $(M+Na)^+$ $C_{24}H_{25}Cl_4NO_5Na$ Requires: 570.0385.

1.1.10.2 *iso*Propyl 2-((1-(4-bromophenyl)-3-(*tert*-butoxy)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S13)



Prepared according to **General Procedure C** using **S8** (4.7 g, 12.5 mmol), LiOH (1M, aq., 25.0 mL), and 1,4- dioxane (32.0 mL) to yield the free amine (2.1 g, 6.9 mmol, 53%). To this was added **S1** (2.4 g, 6.9 mmol) and DCC (1.4 g, 6.9 mmol) and anhydrous CH_2Cl_2 (14.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **S13** as a white solid (2.1 g, 48%), M.p. 153-155 °C.

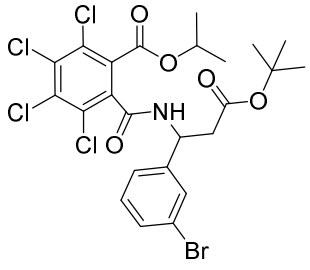
δ_H (400 MHz, $CDCl_3$): 7.51-7.45 (2H, m), 7.28-7.23 (2H, m), 5.50-5.42 (1H, m), 5.12 (1H, sept., *J* 6.3), 2.90 (1H, dd, *J* 4.8, 16.1), 2.80 (1H, dd, *J* 5.8, 16.2), 1.33 (9H, s), 1.28-1.20 (6H, m).

δ_C (100 MHz, $CDCl_3$): 165.4, 158.7, 157.7, 133.9, 130.30, 130.2, 129.5, 128.1, 126.8, 125.3, 125.0, 123.7, 116.9, 77.2, 66.5, 45.1, 35.2, 23.2, 23.2, 23.1, 16.7, 16.6.

ν_{max} (neat)/cm^{-1}: 3247, 1727, 1655, 1545.

HRMS (*m/z* - ESI): Found: 647.9475 $(M+Na)^+$ $C_{24}H_{24}BrCl_4NNaO_5Na$ Requires: 647.9484.

1.1.10.3 *iso*Propyl-2-((1-(3-bromophenyl)-3-(*tert*-butoxy)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S14)



Prepared according to **General Procedure C** using **S9** (4.2 g, 10.6 mmol), LiOH (1M, aq., 22.0 mL), and 1,4-dioxane (27.0 mL) to yield the free amine (1.7 g, 5.7 mmol, 53%). To this was added **S1** (2.0 g, 5.7 mmol) and DCC (1.2 g, 5.7 mmol) and anhydrous CH_2Cl_2 (12.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **S14** as a white solid (2.1 g, 60%). M.p. 157-159 °C.

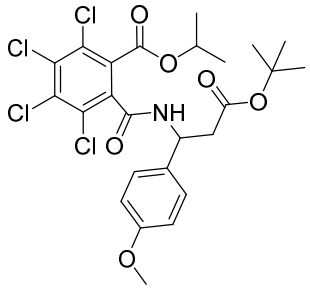
δ_H (400 MHz, $CDCl_3$): 7.51-7.45 (2H, m), 7.28-7.23 (2H, m), 5.50-5.42 (1H, m), 5.12 (1H, sept., *J* 6.3), 2.90 (1H, dd, *J* 4.9, 15.9), 2.80 (1H, dd, *J* 5.9, 15.9), 1.33 (9H, s), 1.28-1.20 (6H, m).

δ_C (100 MHz, $CDCl_3$): 170.1, 163.4, 162.5, 142.0, 135.0, 135.0, 134.3, 132.9, 130.8, 130.1, 130.1, 129.8, 129.7, 125.4, 122.6, 82.1, 71.3, 71.2, 49.9, 49.9, 40.1, 27.9, 21.3.

ν_{max} (neat)/cm^{-1}: 3274, 1728, 1648, 1538.

HRMS (*m/z* - ESI): Found: 647.9471 $(M+Na)^+$ $C_{24}H_{24}BrCl_4NNaO_5Na$ Requires: 647.9484.

1.1.10.4 *iso*Propyl-2-((3-(*tert*-butoxy)-1-(4-methoxyphenyl)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S15)



Prepared according to **General Procedure C** using **S10** (7.8 g, 22.7 mmol), LiOH (1M, aq., 44.0 mL), and 1,4-dioxane (56.0 mL) to yield the free amine (5.2 g, 20.6 mmol, 90%). To this was added **S1** (7.2 g, 20.6 mmol) and DCC (4.3 g, 20.6 mmol) and anhydrous CH_2Cl_2 (40.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **S15** as a colourless oil (7.7 g, 65%).

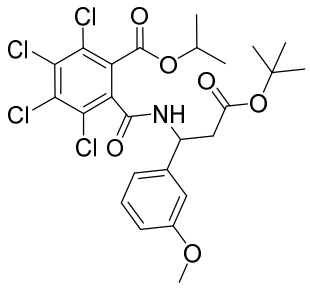
δ_H (400 MHz, $CDCl_3$): 7.34-7.27 (2H, m), 7.13 (1H, d, *J* 8.3), 6.91-6.86 (2H, m), 5.50-5.42 (1H, m), 5.12 (1H, sept., *J* 6.3), 3.81 (3H, s), 2.97 (1H, dd, *J* 4.8, 15.8), 2.80 (IH, dd, *J* 6.5, 15.8), 1.34 (9H, s), 1.29-1.23 (6H, m).

δ_C (100 MHz, $CDCl_3$): 170.4, 163.5, 162.2, 159.1, 135.0, 134.8, 134.5, 132.9, 131.6, 130.0, 129.8, 127.9, 113.9, 81.6, 71.2, 55.3, 50.0, 40.4, 27.9, 21.4.

ν_{max} (neat)/cm^{-1}: 2981, 1775, 1735, 1717.

HRMS (*m/z* - ESI): Found: 600.0496 $(M+Na)^+$ $C_{25}H_{27}Cl_4NNaO_6$ Requires: 600.0485.

1.1.10.5 *iso*Propyl-2-((3-(*tert*-butoxy)-1-(3-methoxyphenyl)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S16)



Prepared according to **General Procedure C** using compound **S11** (2.6 g, 7.4 mmol), LiOH (1M, aq., 14.0 mL), and 1,4-dioxane (21.0 mL) to yield the free amine (2.2 g, 5.6 mmol, 76%). To this was added **S1** (1.9 g, 5.6 mmol) and DCC (1.2 g, 5.6 mmol) and dry CH_2Cl_2 (12.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **S16** as a colourless oil (2.2 g, 69%).

δ_H (400 MHz, $CDCl_3$): 7.29-7.17 (2H, m), 6.96-6.78 (3H, m), 5.53-5.45 (1H, m), 5.11 (1H, sept., *J* 6.3), 3.81 (3H, s), 2.94 (1H, dd, *J* 4.8, 15.9), 2.82 (1H, dd, *J* 6.1, 15.9), 1.32 (9H, s), 1.26-1.19 (6H, m).

δ_C (100 MHz, $CDCl_3$): 170.4, 170.2, 163.4, 159.8, 141.1, 140.3, 134.9, 134.5, 132.9, 130.1, 129.9, 129.6, 1187, 118.3, 113.5, 113.3, 112.2, 81.7, 71.2, 55.3, 50.3, 50.1, 40.2, 27.9, 27.8, 21.35.

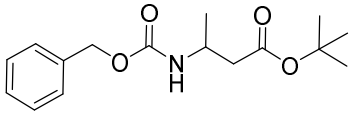
ν_{max} (neat)/cm^{-1}: 3279, 1728, 1649, 1538.

HRMS (*m/z* - ESI): Found: 600.0482 $(M+Na)^+$ $C_{25}H_{27}Cl_4NNaO_6$ Requires: 600.0485.

1.1.11 General procedure D: Two step protection as the Cbz-amino-*t*-Butyl ester

The appropriate *β*-amino acid (1.0 equiv.) was dissolved in 2M $NaOH_{aq}$ solution (1 mL /mmol) and was cooled to 0 °C. Benzyl chloroformate (1.2 equiv.) was added and the mixture was stirred at 0 °C for 30 min, followed by rt for another 2 h. The mixture was acidified to pH 2 using conc. HCl and was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the Cbz-protected amine. To this was added DMAP (0.4 equiv.) and DCC (1.0 equiv.) and the flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (0.5 M) was added and the mixture was cooled to 0 °C. *tert*-Butanol (4.0 equiv.) was added *via* syringe and the mixture was allowed to warm to rt and was stirred for 16 h. The resulting suspension was filtered and washed with CH_2Cl_2. The filtrate was purified *via* silica chromatography to yield the di-protected product.

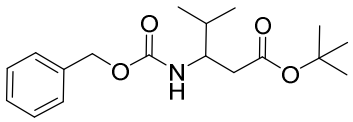
1.1.11.1 *tert*-Butyl 3-(((benzyloxy)carbonyl)amino)butanoate (S17)



Prepared according to **General Procedure D**. The amine was protected as the Cbz-amide using DL-3-aminobutanoic acid (2.0 g, 19.4 mmol), NaOH (2M, aq., 20.0 mL), and benzyl chloroformate (3.3 mL, 23.3 mmol). To this DMAP (0.9 g, 7.8 mmol), DCC (4.4 g, 21.3 mmol), CH_2Cl_2 (40.0 mL) and *tert*-Butanol (7.3 mL, 77.6 mmol) were added. The product was purified *via* silica chromatography eluting with a gradient of 0-10% EtOAc in hexane to yield the **S17** as a colourless oil (4.70 g, 82%). The isolated product exhibited identical spectroscopic data to those in the literature.[6]

δ_H (400 MHz, $CDCl_3$): 7.36-7.27 (5H, m), 5.30-5.00 (3H, m), 4.14-4.0 (1H, m), 2.44-2.36 (2H, m), 1.42 (9H, s), 1.21 (3H, d, *J* 6.7).

1.1.11.2 *tert*-Butyl 3-(((benzyloxy)carbonyl)amino)-4-methylpentanoate (S18)

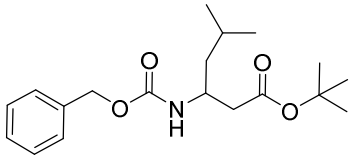


Prepared according to **General Procedure D**. The amine was protected as the Cbz-amide using DL-*β*-leucine (2.0 g, 15.5 mmol), NaOH (2M, aq., 16.0 mL), and benzyl chloroformate (2.7 mL, 18.5 mmol). To this DMAP (0.8 g, 6.2 mmol), DCC (3.5 g, 17.0 mmol), CH_2Cl_2 (25.0 mL) and *tert*-Butanol (5.8 mL, 62.0 mmol) were added. The product was purified *via* silica chromatography eluting with a gradient of 0-10% EtOAc in hexane to yield the **S18** as a colourless oil (3.5 g, 76%). The isolated product exhibited identical spectroscopic data to those in the literature.[7]

δ_H (400 MHz, $CDCl_3$): 7.33-7.28 (5H, m), 5.17-5.04 (3H, m, NH), 3.84-3.72 (1H, m), 2.47-2.30 (2H, m), 1.88-1.73 (1H, m),1.40 (9H, s), 1.26-1.19 (6H, m).

HRMS (*m/z* - ESI): Found: 322.1936 $(M+H)^+$ $C_{19}H_{29}NO_5$ Requires: 322.1940.

1.1.11.3 *tert*-Butyl 3-(((benzyloxy)carbonyl)amino)-5-methylhexanoate (S19)



Synthesised according to **General Procedure D**. The amine was protected as the Cbz-amide using DL-*β*-homoleucine (1.7 g, 12.0 mmol), NaOH (2M, aq., 12.0 mL), and benzyl chloroformate (2.1 mL, 14.4 mmol). To this DMAP (0.6 g, 4.8 mmol), DCC (2.7 g, 13.2 mmol), CH_2Cl_2 (10.0 mL) and *tert*-Butanol (4.5 mL, 47.9 mmol) were added. The product was purified *via* silica chromatography eluting with a

gradient of 0-10% EtOAc in hexane to yield the **S19** as an oil (3.0 g, 71%). The isolated product exhibited identical spectroscopic data to those in the literature.[8]

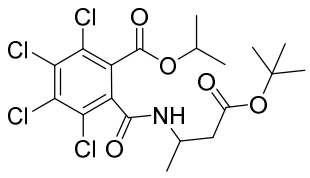
δ_H (400 MHz, $CDCl_3$): 7.39-7.26 (5H, m), 5.19-5.02 (3H, m), 4.07-3.95 (1H, m), 2.50-2.31 (2H, m), 1.72-1.57 (1H, m), 1.51-1.36 (10H, m), 1.35-1.24 (1H, m), 0.98-0.79 (6H, m).

HRMS (*m/z* - APCI): Found: 336.2169 $(M+H)^+$ $C_{19}H_{30}NO_4$ Requires: 336.2169.

1.1.12 General procedure E: Removal of Cbz protecting group and subsequent amide coupling

MeOH (0.5 M) was added to an RBF containing a magnetic stirring bar and the appropriate protected amino acid (1.0 equiv.) and the flask was flushed with argon. $Pd(OH)_2/C$ (20 wt. %, 0.1 equiv.) was added, the flask was evacuated and purged with argon (x 3). On the final evacuation of the flask a septum and hydrogen balloon were fitted. The reaction mixture was stirred vigorously for 16 h. This mixture was filtered *via* suction filtration and the filtrate was concentrated *in vacuo* to yield the free amine. To this **S1** (1.1 equiv.) and DCC (1.1 equiv.) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (0.5M) was added *via* syringe at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered *via* suction filtration and the filtrate was purified *via* silica chromatography.

1.1.12.1 *iso*Propyl 2-((4-(*tert*-butoxy)-4-oxobutan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S20)



The Cbz deprotection of **S17** (1.7 g, 7.1 mmol) was achieved using $Pd(OH)_2/C$ (20 wt. %, 0.4 g, 0.7 mmol) and MeOH (14.0 mL). **S1** (2.7 g, 7.8 mmol), DCC (1.6 g, 7.8 mmol) and anhydrous CH_2Cl_2 (14.0 mL) were added to the resulting amine (1.3 g, 7.1 mmol). The product of the reaction was purified by silica chromatography eluting with a 0-20% EtOAc in hexane gradient to yield **S20** colourless oil (1.6 g, 46%).

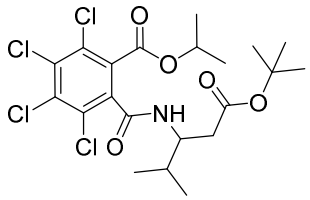
δ_H (400 MHz, $CDCl_3$): 6.68 (1H, d, *J* 8.3), 5.24 (1H, sept., *J* 6.3), 4.44 (1H, m), 2.52 (2H, m,), 1.45 (9H, s), 1.40-1.29 (9H, m).

δ_C (100 MHz, $CDCl_3$): 170.9, 163.5, 162.2, 135.0, 134.7, 134.7, 132.7, 130.0, 129.7, 81.5, 71.1, 43.0, 40.2, 28.1, 21.5, 19.3.

ν_{max} (neat)/cm^{-1}: 2955, 1777, 1735, 1713.

HRMS (*m/z* - ESI): Found: 508.0222 $(M+Na)^+$ $C_{19}H_{23}Cl_4NNaO_5$ Requires: 508.0222.

1.1.12.2 *iso*Propyl-2-((1-(*tert*-butoxy)-4-methyl-1-oxopentan-3-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S21)



The Cbz deprotection of **S18** (3.5 g, 9.1 mmol) was achieved using $Pd(OH)_2/C$ (20 wt. %, 0.9 g, 0.9 mmol), and MeOH (18.0 mL). **S1** (3.2 g, 9.2 mmol), DCC (1.9 g, 9.2 mmol) and anhydrous CH_2Cl_2 (18.0 mL) were added to the resulting amine (1.7 g, 9.1 mmol). The product of the reaction was purified by silica chromatography, eluting with a 0-20% EtOAc in hexane gradient to yield **S21** as a colourless oil (3.12 g, 67%).

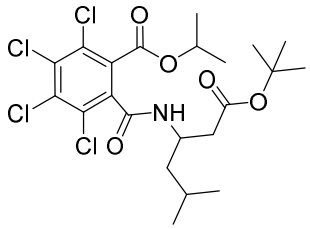
δ_H (400 MHz, $CDCl_3$): 6.72 (1H, d, *J* 9.3), 5.27-5.26 (1H, m), 4.13-4.02 (1H, m), 2.63-2.46 (2H, m), 2.02-1.89 (1-H, m) 1.43 (9H, s), 1.37-1.32 (6H, m), 1.02-0.90 (6H, m).

δ_C (100 MHz, $CDCl_3$): 169.3, 161.7, 160.7, 133.0, 132.9, 132.7, 131.1, 128.0, 127.7, 79.4, 69.2, 50.9, 34.7, 29.0, 26.1, 19.6, 19.6, 17.5, 17.4.

ν_{max} (neat)/cm^{-1}: 3282, 1728, 1646, 1551.

HRMS (*m/z* - ESI): Found: 536.0547 $(M+Na)^+$ $C_{21}H_{27}Cl_4NO_5$ Requires: 536.0536.

1.1.12.3 *iso*Propyl 2-((1-(*tert*-butoxy)-5-methyl-1-oxohexan-3-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S22)



The Cbz deprotection of **S19** (2.6 g, 7.8 mmol) was achieved using $Pd(OH)_2/C$ (20 wt. %, 0.5 g, 0.8 mmol) and MeOH (16.0 mL). **S1** (2.7 g, 7.9 mmol), DCC (1.6 g, 7.9 mmol) and dry CH_2Cl_2 (16.0 mL) were added to the resulting amine (1.6 g, 7.8 mmol). The product of the reaction was purified by silica chromatography, eluting with a 0-20% EtOAc in hexane gradient to yield **S22** as a colourless oil (2.7, 64%).

δ_H (400 MHz, $CDCl_3$): 6.58 (1H, d *J* 9.1), 5.30-5.16 (1H, m), 4.45-4.33 (1H, m), 2.54-2.50 (2H, m), 1.79-1.52 (3H, m) 1.43 (9H, s), 1.37-1.32 (6H, m), 0.98-0.89 (6H, m).

δ_C (100 MHz, $CDCl_3$): 170.1, 163.6, 162.4, 134.9, 134.8, 134.7, 133.0, 130.0, 129.7, 81.4, 71.2, 45.3, 42.5, 39.0, 28.1, 24.9, 22.9, 22.1, 21.6, 21.5.

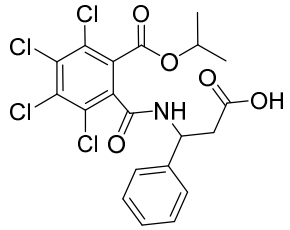
ν_{max} (neat)/cm^{-1}: 3281, 1728, 1654, 1551.

HRMS (*m/z* - ESI): Found: 550.0695 $(M+Na)^+$ $C_{22}H_{29}Cl_4NNaO_5$ Requires: 550.0692.

1.1.13 General procedure F: *t*-Butyl ester deprotection

An RBF containing a magnetic stirring bar was charged with the appropriate *tert*-butyl ester (1.0 equiv.). The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (2.0 mL/mmol) and trifluoroacetic acid (TFA) (2.0 mL/mmol) were added *via* syringe and the mixture was stirred for 16 h. The resulting solution was concentrated *in vacuo* to yield the free acid.

1.1.13.1 3-Phenyl-3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)propanoic acid (S23)



Prepared according to **General Procedure D** using **S12** (4.0 g, 7.7 mmol), TFA (20.0 mL) and anhydrous CH_2Cl_2 (20.0 mL) to yield **S23** (3.8 g, 99 %) as a white solid. M.p 195-197 °C.

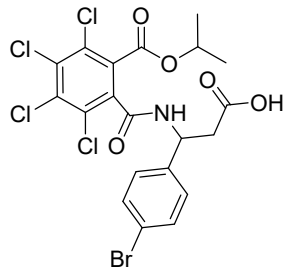
δ_H (400 MHz, DMSO-D_6): 9.65 (1H, d, *J* 8.0), 7.52-7.38 (5H m), 5.30 (1H, m), 5.92 (1H, sept. *J* 6.3), 2.66-2.79 (2H, m), 1.09-1.06 (6H, m).

δ_C (100 MHz, DMSO-D_6): 176.4, 167.5, 166.4, 146.2, 140.6, 138.9, 138.1, 137.3, 134.9, 133.8, 133.4, 132.5, 132.1, 75.9, 55.6, 45.9, 26.1, 26.0.

ν_{max} (neat)/cm^{-1}: 3273, 2981, 1735, 1697, 1647.

HRMS (*m/z* - ESI): Found: 591.8857 $(M+Na)^+$ $C_{20}H_{16}BrCl_4NNaO_5$ Requires: 591.8858.

1.1.13.2 3-(4-Bromophenyl)-3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)propanoic acid (S24)



Prepared according to **General Procedure D** using **S13** (2.1 g, 3.3 mmol), TFA (7.0 mL) and anhydrous CH_2Cl_2 (7.0 mL) to yield **S24** (1.7 g, 99%) as a white solid. M.p. 208-209 °C.

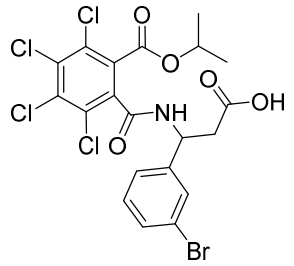
δ_H (400 MHz, $CDCl_3$): 7.54 (1H, s), 7.44 (1H, m), 7.32-7.20 (2H, m), 7.0 (1H, d *J* 8.9), 5.59-5.51 (1H, m), 5.14 (1H, sept. *J* 6.3), 3.11-2.94 (2H, m), 1.85 (1H, bs), 1.27-1.21 (6H, m).

δ_C (100 MHz, MeOD): 170.4, 161.6, 161.4, 138.3, 133.3, 132.6, 132.4, 131.1, 129.8, 127.3, 119.6, 69.6, 50.0, 38.2 18.7.

ν_{max} (neat)/cm^{-1}: 3297, 2981, 1733, 1698, 1640.

HRMS (*m/z* - ESI): Found: 591.8857 $(M+Na)^+$ $C_{20}H_{16}BrCl_4NNaO_5$ Requires: 591.8858.

1.1.13.3 3-(3-Bromophenyl)-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (S25)



Prepared according to **General Procedure D** using **S14** (2.1 g, 3.4 mmol), TFA (7.0 mL) and anhydrous CH_2Cl_2 (7.0 mL) to yield **S25** (1.9 g, 99%) as a white solid. M.p. 172-174 °C.

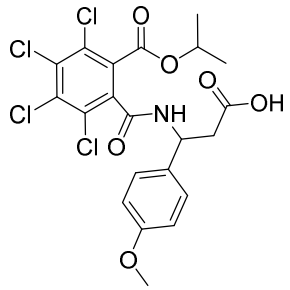
δ_H (400 MHz, $CDCl_3$): 7.54 (1H, s), 7.44 (1H, m), 7.32-7.20 (2H, m), 7.0 (1H, d *J* 8.9), 5.59-5.51 (1H, m), 5.14 (1H, sept. *J* 6.3), 3.11-2.94 (2H, m), 1.85 (1H, bs), 1.27-1.21 (6H, m).

δ_C (100 MHz, MeOD): 172.3, 163.6, 163.2, 143.6, 135.2, 134.7, 134.4, 133.0, 131.0, 130.9, 130.6, 130.4, 130.3, 126.0, 71.5, 51.0, 40.3, 39.4, 20.6, 20.6.

ν_{max} (neat)/cm^{-1}: 3292, 2925, 1738, 1720, 1636.

HRMS (*m/z* - ESI): Found: 591.8859 $(M+Na)^+$ $C_{20}H_{16}BrCl_4NNaO_5$ Requires: 591.8858.

1.1.13.4 3-(4-Methoxyphenyl)-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (S26)



Prepared according to **General Procedure D** using compound **S15** (7.7 g, 13.2 mmol), TFA (26.0 mL) and anhydrous CH_2Cl_2 (26.0 mL) to yield **S26** (6.9 g, 99%) as a white solid. M.p. 149-151 °C.

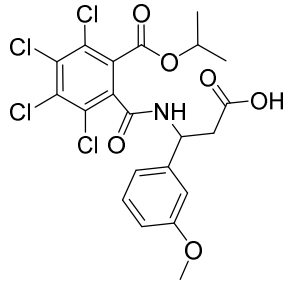
δ_H (400 MHz, $CDCl_3$): 7.32-7.21 (2H, m), 6.93-6.80 (2H, m), 5.58-5.44 (1H, m), 5.18-5.03 (1H, m), 3.79 (3H, s), 3.16-2.85 (2H, m), 1.34-1.15 (6H, m).

δ_C (100 MHz, $CDCl_3$): 174.6, 163.8, 162.4, 159.3, 135.1, 135.0, 134.3, 132.7, 131.1, 130.0, 129.8, 127.8, 114.2, 71.5, 55.3, 49.6, 38.9, 21.4, 21.4.

ν_{max} (neat)/cm^{-1}: 3275, 2971, 1735, 1720, 1636.

HRMS (*m/z* - ESI): Found: 543.9842 $(M+Na)^+$ $C_{21}H_{19}Cl_4NNaO_6$ Requires: 543.9859.

1.1.13.5 3-(4-Methoxyphenyl)-3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)propanoic acid (S27)



Prepared according to **General Procedure D** using compound **S16** (2.2 g, 3.8 mmol), TFA (8.0 mL) and anhydrous CH_2Cl_2 (8.0 mL) to yield **S27** (1.9 g, 97%) as a white solid. M.p. 170-172 °C.

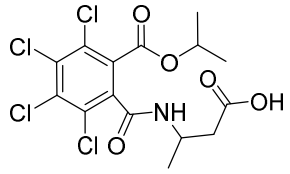
δ_H (400 MHz, $CHCl_3$) 7.32-7.27 (1H, m), 6.95-6.83 (3H, m), 5.16 (1H, sept., *J* 6.2), 5.00-4.94 (1H, m), 3.82 (3H, s), 3.06 (1H, dd, *J* 5.14, 16.3), 2.75 (1H, dd, *J* 11.5, 16.3), 1.32-1.23 (6H, m).

δ_C (100 MHz, $CHCl_3$): 172.7, 163.7, 162.6, 160.0, 140.6, 135.1, 135.1, 134.3, 132.8, 130.1, 129.9, 120.0, 118.5, 113.6, 113.6, 112.3, 71.5, 55.3, 50.0, 38.5, 21.4, 21.4.

ν_{max} (neat)/cm^{-1}: 3306, 2977, 1736, 1691, 1640.

HRMS (*m/z* - ESI): Found: 543.9835 $(M+Na)^+$ $C_{21}H_{19}Cl_4NNaO_6$ Requires: 543.9859.

1.1.13.6 3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)butanoic acid (S28)



Prepared according to **General Procedure D** using **S20** (1.6 g, 3.2 mmol), TFA (6.0 mL) and anhydrous CH_2Cl_2 (6.0 mL) to yield **S28** (1.3 g, 97%) as a white solid. M.p 162-164 °C.

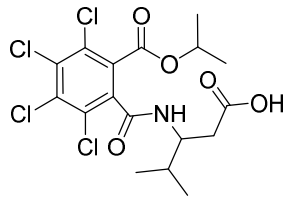
δ_H (400 MHz, $CHCl_3$): 6.49 (1H, d *J* 8.4), 5.22 (1H, sept., *J* 6.3), 4.55-4.42 (1H, m) 2.70-2.64 (2H, m), 1.37-1.30 (9H, m).

δ_C (100 MHz, $CHCl_3$): 175.3, 163.8, 162.5, 135.1, 134.9, 134.4, 132.6, 130.0, 129.7, 71.4, 42.7, 38.9, 21.5, 19.4.

ν_{max} (neat)/cm^{-1}: 3278, 2981, 1736, 1697, 1642.

HRMS (*m/z* - ESI): Found: 451.9594 $(M+Na)^+$ $C_{15}H_{15}Cl_4NNaO_5$ Requires: 451.9597.

1.1.13.7 4-Methyl-3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)pentanoic acid (S29)



Prepared according to **General Procedure D** using **S21** (3.1 g, 6.1 mmol), TFA (12.0 mL) and anhydrous CH_2Cl_2 (12.0 mL) to yield **S29** (2.8 g, 99%) as a white solid. M.p 109-111 °C.

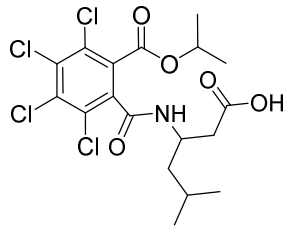
δ_H (400 MHz, $CHCl_3$): 6.68 (1H, d *J* 9.2), 5.24 (1H, sept., *J* 6.3), 4.22-4.13 (1H, m), 2.77-2.63 (2H, m), 2.02-1.89 (1H, m), 1.40-1.35 (6H, m), 1.05-0.96 (6H, m).

δ_C (100 MHz, $CHCl_3$): 175.7, 164.2, 163.2, 135.1, 134.9, 134.5, 132.6, 130.0, 129.7, 71.8, 52.7, 35.4, 30.8, 21.5, 21.5, 19.3, 19.1.

ν_{max} (neat)/cm^{-1}: 3336, 2980, 1718, 1699, 1620.

HRMS (*m/z* - ESI): Found: 479.990 $(M+Na)^+$ $C_{17}H_{19}Cl_4NNaO_5$ Requires: 479.9910.

1.1.13.8 5-Methyl-3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)hexanoic acid (S30)



Prepared according to **General Procedure D** using **S22** (2.7 g, 5.0 mmol), TFA (10.0 mL) and dry CH_2Cl_2 (10.0 mL) to yield **S30** (2.4 g, 99%) as a white solid. M.p 116-118 °C.

δ_H (400 MHz, $CHCl_3$): 6.46 (1H, d *J* 9.1), 5.25 (1H, sept., *J* 6.3), 4.54-4.43 (1H, m) 2.78 (1H, dd, *J* 5.6, 17.0) 2.68 (1H, dd, *J* 4.3, 17.0), 1.82-1.62 (2H, m), 1.46-1.35 (7H, m), 1.02-0.94 (6H, m).

δ_C (100 MHz, $CHCl_3$): 175.2, 163.9, 162.7, 135.0, 134.8, 134.6, 132.8, 130.0, 129.7, 71.5, 45.0, 42.5, 37.8, 24.9, 23.0, 21.9, 21.6, 21.5.

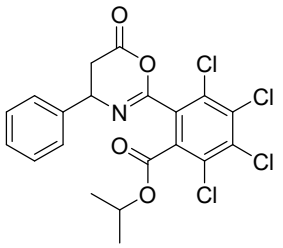
ν_{max} (neat)/cm^{-1}: 3263, 2980, 1719, 1644, 1554.

HRMS (*m/z* - APCI): Found: 472.0242 $(M+H)^+$ $C_{18}H_{22}Cl_4NO_5$ Requires: 472.0247.

1.1.14 General procedure G: Preparation of TCIC-oxazinones

An RBF containing a magnetic stirrer bar was charged with the appropriate carboxylic acid (1.0 equiv.). The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (2M) and freshly distilled NEt_3 (1.1 equiv.) were added *via* syringe and the solution was cooled to -30 °C. Freshly distilled $SOCl_2$ (1.1 equiv.) was added *via* syringe and the mixture was stirred for 5 min followed by a further dropwise addition of freshly distilled NEt_3 (2.2 equiv.) *via* syringe. The mixture was stirred for 1 h at -30 °C followed by evaporation of the solvent *in vacuo* at -30 °C. The remaining solid was re-dissolved in dry toluene and was filtered under argon to remove the insoluble solid (Et_3NHCl). The filtrate was concentrated *in vacuo* and was purified as instructed to yield the appropriate TCIC-oxazinone.

1.1.14.1 *iso*Propyl-2,3,4,5-tetrachloro-6-(6-oxo-4-phenyl-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (9)



Prepared according to **General Procedure G** using **S23** (5.5 g, 11.1 mmol), CH_2Cl_2 (5.0 mL), NEt_3 (1.7 mL, 12.3 mmol), $SOCl_2$ (0.9 mL, 12.3 mmol) and a second aliquot of NEt_3 (3.4 mL, 24.6 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAC in hexane followed by recrystallisation from a mixture of diisopropyl ether (iPr$_2$O) and EtOAc to furnish **9** as pale yellow crystals (3.4 g, 65%). M.p 103-106 °C.

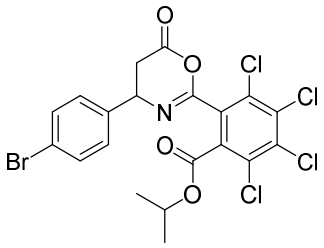
δ_H (400 MHz, $CDCl_3$): 7.42-7.38 (5H, m), 5.18 (1H, app. sept.), 5.02 (1H, dd, *J* 5.1, 11.7), 3.09 (1H, dd, *J* 5.1, 16.3), 2.77 (1H, dd, *J* 11.7, 16.3), 1.32-1.30 (6H, m).

δ_C (100 MHz, $CDCl_3$): 164.1, 163.6, 151.0, 139.3, 136.0, 135.5, 134.0, 131.9, 130.4, 129.0, 128.1, 126.2, 71.4, 57.4, 35.4, 21.6, 21.5.

ν_{max} (neat)/cm^{-1}: 1793, 1722, 1708.

HRMS (*m/z* - ESI): Found: 469.9886 (M-H) $C_{21}H_{16}Cl_4NO_3$ Requires: 469.9884.

1.1.14.2 *iso*Propyl-2-(4-(4-bromophenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (31a)



Prepared according to **General Procedure G** using **S24** (1.6 g, 2.7 mmol), CH_2Cl_2 (3.0 mL), NEt_3 (0.4 mL, 3.0 mmol), $SOCl_2$ (0.2 mL, 3.0 mmol) and a second aliquot of NEt_3 (0.8 mL, 6.0 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAC in hexane followed by recrystallisation using a mixture of iPr$_2$O and EtOAc to furnish **31a** as pale yellow crystals (1.0 g, 68%). M.p. 100-103 °C.

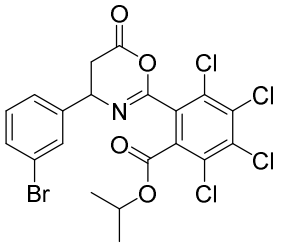
δ_H (400 MHz, $CHCl_3$): 7.55-7.48 (2H, m), 7.30-7.21 (2H, m), 7.24-7.22 (1H, m), 5.02-4.92 (1H, m), 3.06 (1H, dd, *J* 4.1, 16.0), 2.69 (1H, dd, *J* 12.3, 16.0), 1.34-1.24 (6H, m).

δ_C (100 MHz, $CHCl_3$): 163.7, 163.7, 151. 3, 138.4, 136.1, 135.6, 133.9, 132.1, 131.8, 130.4, 130.2, 127.9, 122.1, 71.4, 56.8, 35.3, 21.6, 21.5.

ν_{max} (neat)/cm^{-1}: 1783, 1717, 1693.

HRMS (*m/z* - APCI): Found: 551.8941 $(M+H)^+$ $C_{20}H_{15}BrCl_4NO_4$ Requires: 551.8933.

1.1.14.3 *iso*Propyl-2-(4-(3-bromophenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (31b)



Prepared according to **General Procedure G** using **S25** (1.8 g, 3.1 mmol), CH_2Cl_2 (3.5 mL), NEt_3 (0.5 mL, 3.5 mmol), $SOCl_2$ (0.3 mL, 3.5 mmol) and a second aliquot of NEt_3 (1.0 mL, 6.9 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAc in hexane followed by recrystallisation using a mixture of iPr$_2$O and EtOAc to furnish **31b** as pale yellow crystals (1.0 g, 62%). M.p. 109-110 °C.

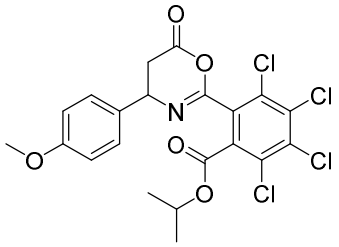
δ_H (400 MHz, $CHCl_3$): 7.57-7.53 (1H, m), 7.49-7.44 (1H, m), 7.31-7.22 (2H, m), 5.18 (1H, sept., *J* 6.2), 5.00-4.93 (1H, m), 3.07 (1H, dd, *J* 4.9, 16.3), 2.71 (1H, dd, *J* 12.3, 16.3), 1.34-1.27 (6H, m).

δ_C (100 MHz, $CHCl_3$): 163.7, 151.5, 141.6, 136.1, 135.6, 133.8, 131.9, 131.3, 130.5, 130.5, 130.2, 129.4, 124.9, 123.0, 71.5, 56.7, 35.2, 21.6, 21.5

ν_{max} (neat)/cm^{-1}: 1799, 1720, 1696.

HRMS (*m/z* - APCI): Found: 551.8938 $(M+H)^+$ $C_{20}H_{15}BrCl_4NO_4$ Requires: 551.8933.

1.1.14.4 *iso*Propyl-2,3,4,5-tetrachloro-6-(4-(4-methoxyphenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31c)



Prepared according to **General Procedure G** using **S26** (4.9 g, 9.3 mmol), CH_2Cl_2 (9.5 mL), NEt_3 (1.4 mL, 10.3 mmol), $SOCl_2$ (0.7 mL, 10.3 mmol) and a second aliquot of NEt_3 (2.9 mL, 20.5 mmol). The product was purified *via* silica chromatography, eluting with a gradient of 5-20% EtOAc in hexane to furnish **31c** as pale yellow solid (2.6 g, 54%). M.p. 50-52 °C.

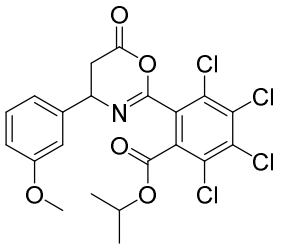
δ_H (400 MHz, $CHCl_3$): 7.27 (2H, d, *J* 8.7), 6.89 (2H, d, *J* 8.7), 5.16 (1H, sept., *J* 6.2), 5.02-4.91 (1H, m), 3.79 (3H, s), 3.05 (1H, dd, *J* 5.1, 16.2), 2.73 (1H, dd, *J*, 11.5, 16.2), 1.35-1.24 (6H, m).

δ_C (100 MHz, $CHCl_3$): 164.3, 163.6, 159.4, 150.7, 135.9, 135.4, 134.0, 131.9, 131.4, 130.3, 127.8, 127.4, 114.3, 71.4, 56.9, 55.3, 35.5, 21.6, 21.5.

ν_{max} (neat)/cm^{-1}: 1799, 1719, 1696.

HRMS (*m/z* - APCI): Found: 503.9945 $(M+H)^+$ $C_{21}H_{18}Cl_4NO_5$ Requires: 503.9934.

1.1.14.5 *iso*-Propyl-2,3,4,5-tetrachloro-6-(4-(3-methoxyphenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31d)



Prepared according to **General Procedure G** using **S27** (3.4 g, 6.6 mmol), CH_2Cl_2 (6.5 mL), NEt_3 (1.0 mL, 7.2 mmol), $SOCl_2$ (0.5 mL, 7.2 mmol) and a second aliquot of NEt_3 (2.0 mL, 14.9 mmol). The product was purified *via* silica chromatography, eluting with a gradient of 5-20% EtOAc in hexane to furnish **31d** as pale yellow solid (1.3 g, 38%). M.p. 48-50 °C.

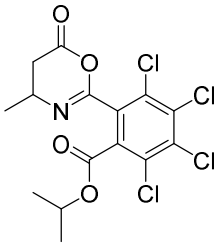
δ_H (400 MHz, $CHCl_3$): 7.30 (1H, t, *J* 8.1), 6.96-6.81 (3H, m), 5.17 (1H, sept., *J* 6.2), 5.02-4.95 (1H, m), 3.80 (3H, s), 3.07 (1H, dd, *J* 5.1, 16.5), 2.74 (1H, dd, *J*, 11.8, 16.5), 1.33-1.25 (6H, m).

δ_C (100 MHz, $CHCl_3$): 164.1 (C=O), 163.6 (C=O), 160.1 (q) 150.9 (C=N), 140.8, 135.9, 135.4, 134.0, 131.9, 130.3, 130.3, 130.0, 118.4, 113.5, 112.1, 71.4, 57.3, 55.3, 35.4, 21.6, 21.4.

ν_{max} (neat)/cm^{-1}: 1800, 1720, 1695.

HRMS (*m/z* - APCI): Found: 503.9943 $(M+H)^+$ $C_{21}H_{18}Cl_4NO_5$ Requires: 503.9934.

1.1.14.6 *iso*Propyl-2,3,4,5-tetrachloro-6-(4-methyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31e)



Prepared according to **General Procedure G** using **S28** (1.2 g, 2.7 mmol), CH_2Cl_2 (3.0 mL), NEt_3 (0.4 mL, 3.0 mmol), $SOCl_2$ (0.2 mL, 3.0 mmol) and a second aliquot of NEt_3 (0.8 mL, 6.0 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAc in hexane and the resulting product was triturated in hexane to furnish **31e** as white solid (845 mg, 75%). M.p. 64-66 °C.

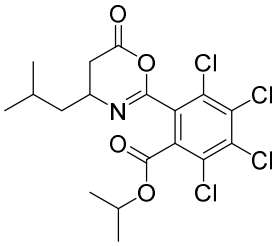
δ_H (400 MHz, $CHCl_3$): 5.23 (1H, sept., *J* 6.3), 4.04-3.91 (1H, m), 2.80 (1H, dd, *J* 5.2, 16.1), 2.50 (1H, dd, *J* 9.3, 16.1), 1.40-1.34 (9H, m).

δ_C (100 MHz, $CHCl_3$): 164.5, 163.5, 149.9, 135.7, 135.3, 133.9, 131.8, 130.2, 130.2, 71.2, 49.9, 34.8, 21.6, 21.6, 20.7.

ν_{max} (neat)/cm^{-1}: 1804, 1728, 1708.

HRMS (*m/z* - APCI): Found: 411.9683 $(M+H)^+$ $C_{15}H_{14}Cl_4NO_4$ Requires: 411.9671.

1.1.14.7 *iso*Propyl-2,3,4,5-tetrachloro-6-(4-*iso*butyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31f)



Prepared according to **General Procedure G** using **S30** (1.3 g, 2.7 mmol), CH_2Cl_2 (3.0 mL), NEt_3 (0.4 mL, 2.9 mmol), $SOCl_2$ (0.2 mL, 2.9 mmol) and a second aliquot of NEt_3 (0.6 mL, 5.9 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAc in hexane followed by trituration in Et_2O to furnish **31f** as pale yellow solid (630 mg, 52%). M.p. 90-92 °C.

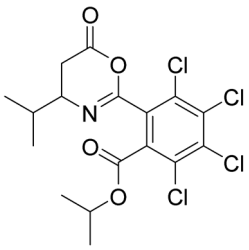
δ_H (400 MHz, $CHCl_3$): 5.29-5.18 (1H, m), 3.96-3.85 (1H, m), 2.80 (1H, dd, *J* 4.8, 16.1), 2.56-2.40 (1H, dd, *J* 9.7, 16.1), 1.93-1.83 (1H, m), 1.70-1.55 (2H, m), 1.46-1.32 (6H, m), 1.04-0.91 (6H, m).

δ_C (100 MHz, $CHCl_3$): 164.9, 163.6, 149.7, 135.7, 135.4, 133.8, 131.9, 130.4, 130.3, 71.3, 52.3, 44.3, 33.7, 24.4, 22.7, 22.1, 21.7, 21.6.

ν_{max} (neat)/cm^{-1}: 1804, 1728, 1687.

HRMS (*m/z* - APCI): Found: 454.0151 $(M+H)^+$ $C_{18}H_{20}Cl_4NO_4$ Requires: 454.0141.

1.1.14.8 *iso*Propyl-2,3,4,5-tetrachloro-6-(4-*iso*propyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31g)



Prepared according to **General Procedure G** using **S29** (2.8 g, 6.1 mmol), CH_2Cl_2 (6.0 mL), NEt_3 (0.9 mL, 6.7 mmol), $SOCl_2$ (0.5 mL, 6.7 mmol) and a second aliquot of NEt_3 (1.9 mL, 13.4 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAc in hexane followed by trituration in Et_2O to furnish **31g** a white solid (1.69 g, 63%). M.p. 55-57 °C.

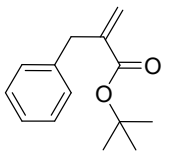
δ_H (400 MHz, $CHCl_3$): 5.22 (1H, sept., *J* 6.5), 3.63-3.58 (1H, m), 2.76 (1H, dd, *J* 4.8, 16.1), 2.51 (1H, dd, *J* 11.9, 16.1), 1.96-1.88 (1H, m), 1.40-1.36 (6H, m), 1.06-1.02 (6H, m).

δ_C (100 MHz, $CHCl_3$): 165.5, 163.6, 149.8, 135.7, 135.4, 133.8, 131.9, 130.5, 130.3, 71.3, 59.6, 32.5, 30.6, 21.7, 18.5, 18.3.

ν_{max} (neat)/cm^{-1}: 1799, 1728, 1693.

HRMS (*m/z* - APCI): Found: 439.9972 $(M+H)^+$ $C_{17}H_{18}Cl_4NO_4$ Requires: 439.9984.

1.1.15 *tert*-Butyl 2-benzylacrylate (S31)

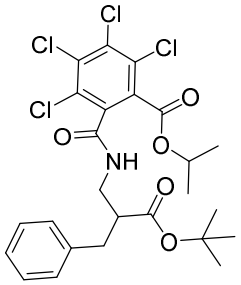


Benzyl acrylic acid (12.1 g, 74.9 mmol).), $(Boc)_2O$ (24.5 g, 112.3 mmol) and DMAP (3.7 mg, 29.9 mmol) were dissolved in anhydrous CH_2Cl_2 (150.0 mL) at 0 °C. The reaction mixture was warmed to rt and was stirred for 16 h. The crude material was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to furnish **S31** as a colourless oil (15.3 g, 93%). The spectroscopic data obtained for **S31** was identical to those found in the literature.[10]

δ_H (400 MHz, $CHCl_3$): 7.29-7.18 (5H, m), 6.13-6.11 (1H, m), 5.36-5.33 (1H, m), 3.57 (2H, s), 1.41 (9H, s).

HRMS (*m/z* - ESI): Found: 219.13307 $(M+H)^+$ $C_{14}H_{19}O_2$ Requires: 219.1307.

1.1.16 *iso*Propyl-2-((2-benzyl-3-(tert-butoxy)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (S32)



S31 (4.3 g, 19.5 mmol) and $BnNH_2$ (6.4 mL, 58.5 mmol) were dissolved in MeOH (20.0 mL) and I_2 (247 mg, 2.0 mmol) was added. The mixture was refluxed for 48 h and was concentrated *in vacuo*. The crude material was purified *via* silica chromatography eluting with a mixture of 9:1:0.5 hexane:EtOAc:NEt_3 to yield the hydroaminated product (5.5 g, 16.8 mmol). To this, $Pd(OH)_2/C$ (20 wt. %, 1.2 g, 1.7 mmol) and MeOH (17 mL) were added under an atmosphere of argon. The flask was subsequently evacuated and purged with argon (x 3). On the final evacuation of the flask a septum and hydrogen balloon were fitted. The reaction mixture was stirred vigorously for 16 h. This mixture was filtered *via* suction filtration and the filtrate was evaporated to yield the free amine (4.0 g, 99%). To this **S1** (7.3 g, 18.5 mmol) and HBTU (7.0 g, 18.5 mmol) NEt_3 (2.6 mL, 18.5 mmol) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (34.0 mL) was added *via* syringe and the mixture was stirred for 16 h. HCl (1.5M, aq., 20 mL) and the product was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* silica chromatography eluting with a gradient of 5-10% EtOAC in hexane to yield **S32** as a white solid (3.4 g, 36%). M.p 105-107 °C.

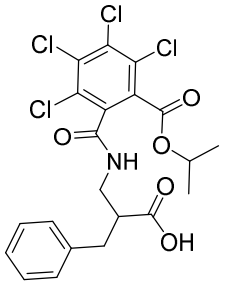
δ_H (400 MHz, $CHCl_3$): 7.33-7.17 (5H, m), 6.52 (1H, t, *J* 5.5), 5.23 (1H, sept., *J* 6.3), 3.69-3.58 (1H, m), 3.54-3.42 (1H, m), 3.01-2.86 (2H, m), 1.34 (9H, s).

δ_C (100 MHz, $CHCl_3$): 173.5, 163.4, 163.2, 138.0, 135.0, 134.8, 132.8, 134.7, 132.8, 130.1, 129.6, 129.1, 128.4, 126.6, 81.6, 71.1, 71.1, 46.8, 40.6, 36.2, 27.9, 21.5, 21.5.

ν_{max} (neat)/cm^{-1}: 1721, 1641, 1572.

HRMS (*m/z* - APCI): Found: 584.0537 $(M+Na)^+$ $C_{25}H_{27}Cl_4NNaO_5$ Requires: 584.0536.

1.1.17 2-Benzyl-3-(2,3,4,5-tetrachloro-6-(*iso*propoxycarbonyl)benzamido)propanoic acid (S33)



Prepared according to **General Procedure F** using **S32** (3.1 g, 5.5 mmol), TFA (11.0 mL) and CH_2Cl_2 (11.0 mL) to yield **S33** as a product (3.1 g, 99%) as a white solid. M.p 57-60 °C.

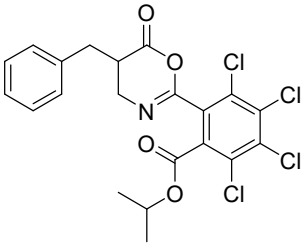
δ_H (400 MHz, $CHCl_3$): 7.37-7.17 (5H, m, H-8, H-9, H-10), 6.81-6.68 (1H, m, NH), 5.30-5.21 (1H, m, H-5), 3.78-3.67 (1H, m, H-1a), 3.53-3.41 (1H, m, H-1b), 3.12-2.87 (2H, m, H-7a, H-7b), 1.39-1.33 (6H, m, H-4, H-6).

δ_C (100 MHz, $CHCl_3$): 164.2 (C=O), 164.1 (C=O), 163.4 (C=O), 137.5 (q), 135 (q), 134.8 (q), 134.5 (q), 129.0, 128.8, 128.7 (q), 128.3 (q), 126.9, 71.7, 46.2, 40.4, 35.8, 21.5.

ν_{max} (neat)/cm^{-1}: 1778, 1725, 1715.

HRMS (*m/z* - ESI): Found: 527.9901 $(M+Na)^+$ $C_{21}H_{19}Cl_4NNaO_5$ Requires: 527.9909.

1.1.18 *iso*Propyl-2-(5-benzyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (35)



S33 (2.6 g, 4.5 mmol) and NEt_3 (758 µL, 5.5 mmol) were dissolved in anhydrous CH_2Cl_2 (20.0 mL) under an atmosphere of argon. The mixture was cooled to -15 °C and *iso*-propylchloroformate (1M in toluene, 5.5 mmol, 5.5 mL) was added dropwise. The mixture was stirred for 20 mins and a second aliquot of NEt_3 (758 µL, 5.5 mmol) was added. The mixture was warmed to 0 °C and was stirred for 1 h followed by evaporation of the solvent *in vacuo* at 0 °C. The remaining solid was re-dissolved in dry toluene and was filtered under argon to remove the insoluble solid (Et_3NHCl). The filtrate was concentrated *in vacuo* and was purified *via* silica chromatography using a gradient of 0-10% EtOAc in hexane to yield the product **35** as a colourless oil (1.3 g, 58%).

δ_H (400 MHz, $CHCl_3$): 7.40-7.23 (5H, m), 5.24 (1H, sept., *J* 6.3), 3.78 (1H, dd, *J* 6.2, 16.2), 3.51 (1H, dd, *J* 10.5, 16.2), 3.30-3.34 (1H, m), 3.01-2.85 (2H, m), 1.38-1.32 (6H, m).

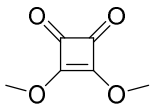
δ_C (100 MHz, $CHCl_3$): 166.9, 163.6, 151.0, 136.8, 135.9, 135.3, 134.1, 131.8, 130.2, 130.0, 129.1, 128.8, 127.2, 71.2, 47.1, 39.4, 33.4, 21.6, 21.6.

ν_{max} (neat)/cm^{-1}: 1729, 1721, 1709.

HRMS (*m/z* - APCI): Found: 487.9982 $(M+H)^+$ $C_{21}H_{18}Cl_4NO_5$ Requires: 487.9984.

1.2 Catalyst Synthesis

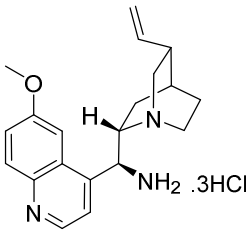
1.2.1 3,4-Dimethoxycyclobut-3-ene-1,2-dione (S34)



Squaric acid (2.0 g, 17.5 mmol) was dissolved in anhydrous MeOH (20 mL) under argon followed by the addition of trimethyl orthoformate (5.8 mL, 52.6 mmol) and TFA (0.3 mL, 3.5 mmol). The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 48 h and then cooled to rt. The reaction mixture was concentrated *in vacuo* and was purified by silica column chromatography, eluting with 30% EtOAc in hexane to furnish **S34** as a white solid (2.9 g, 88%). M.p. 51-53 °C (lit.[11] m.p. 52-54 °C). Spectral data for this compound were consistent with those in the literature.[11]

δ_H (400 MHz, $CDCl_3$): 4.38 (6 H, s).

1.2.2 (*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl (S35)

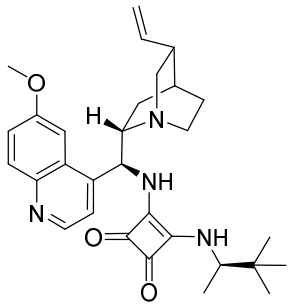


Quinine (10.0 g, 30.8 mmol) and triphenylphosphine (9.7 g, 37.0 mmol) were dissolved in anhydrous THF (140 mL) at 0 °C under argon atmosphere. Diisopropyl azodicarboxylate (DIAD) (7.3 mL, 37.0 mmol) was added and the mixture was stirred for 30 min followed by the dropwise addition of a solution of diphenylphosphoryl azide (DPPA, 8.0 mL, 37.0 mmol) in anhydrous THF (64 mL). The reaction

mixture warmed to rt and stirred followed by heating at 50 °C for 2 h. The reaction was cooled to rt and triphenylphosphine (10.5 g, 40.1 mmol) was added portion-wise followed by further heating at 50 °C until the gas evolution had ceased (2 h). After cooling to rt, water (10 mL) was added and the mixture was stirred for an additional 4 h. The THF was removed *in vacuo* and the residue was dissolved in aqueous HCl (2N, 80 mL). The aqueous layer washed with $CHCl_2$ (3 x 40 mL) and concentrated under reduced pressure to yield **S35** as a yellow solid (11.5 g, 84%). M.p. 218 °C (decomp.) (lit.[12] m.p. 220-222 °C); $[\alpha]_D^{20}$ = +22.1 (*c* = 0.75, MeOH). Spectral data for this compound were consistent with those in the literature.[12]

δ_H (400 MHz, D_2O): 9.04 (1 H, d, *J* 5.8), 8.29 (1 H, d, *J* 9.4), 8.15 (1 H, d, *J* 5.8), 7.94 (1H, dd, *J* 2.4, 9.4), 7.84 (1 H, bs), 5.90 (1 H, ddd, *J* 6.8, 10.5, 17.2), 5.56 (1 H, d, *J* 10.6), 5.32-5.18 (2 H, m), 4.35-4.23 (1 H, m), 4.13 (3 H, s), 4.04-3.92 (1 H, m), 3.85 (1 H, dd, *J* 10.6, 13.3), 3.59-3.45 (2 H, m), 3.00-2.90 (1 H, m), 2.17-2.00 (3 H, m), 1.96-1.84 (1 H, m), 1.18 (1 H, dd, *J* 7.2).

1.2.3 methyl-(2*S*)-2-((2-(((1*S*)-(6-methoxyquinolin-4-yl)((2*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanoate (30)



(*S*)-3,3-dimethylbutan-2-amine (0.3 mL, 1.9 mmol) and squaric ester **S34** (295 mg, 2.1 mmol) were dissolved in MeOH (4.0 mL) under an atmosphere of argon at rt and were stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 30% EtOAc in hexane to furnish the mono-amine product (327 mg, 1.6 mmol, 82%) which was redissolved in MeOH under argon. To this the free amine of **S35** (552 mg, 1.7 mmol) was added and the reaction was stirred at rt for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 0-5% MeOH in CH_2Cl_2 to furnish **30** (382 mg, 49%) as a white solid. M.p. 180 °C (decomp.). $[\alpha]_D^{20}$ = -94.1 (*c* 0.12, $CHCl_3$).

δ_H (400 MHz, MeOD): 8.75 (1H, d, *J* 4.7), 8.00 (1H, d, *J* 9.3), 7.91-7.88 (1H, bs), 7.58 (1H, d, *J* 4.7), 7.48 (1H, dd, *J* 2.6, 9.3) 6.29-6.20 (1H, m), 6.00-5.93 (1H, m), 5.15-5.05 (2H, m), 4.05-3.98 (4H, m), 3.67-3.47 (2H, m), 3.40-3.30 (1H, m), 2.90-2.76 (2H, m), 2.50-2.39 (1H, m), 1.76-1.63 (4H, m), 1.22 (3H, d, *J* 6.8), 0.88 (9H, s), 0.78-0.68 (1H, m).

δ_C (151 MHz, MeOD): 181.8, 181.7, 167.9, 166.6, 159.1, 147.0, 144.5, 144.1, 130.2, 128.2, 123.1, 118.6, 113.8, 100.7, 78.1, 77.9, 77.7, 59.7, 58.7, 55.8, 55.4, 40.3, 39.3, 34.1, 27.5, 27.0, 26.2, 24.7, 15.8.

ν_{max} (neat)/cm^{-1}: 3536, 3258, 2985, 1646, 1566, 1528, 1428, 1268.

HRMS (*m/z* - ESI): Found: 503.3021 $(M+H)^+$ $C_{30}H_{39}N_4O_3$ Requires: 503.3017.

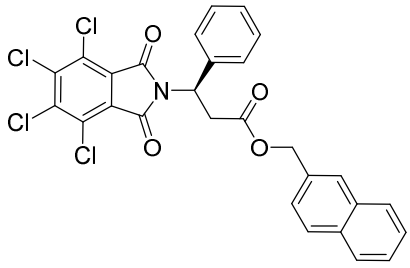
1.3 General procedure H: Synthesis of the amino acid allyl ester racemates

The appropriate oxazinone (1.0 equiv.) was dissolved in anhydrous $CHCl_3$ under argon at rt and allyl alcohol (1.2 equiv.) was added *via* syringe. To this TBAF (1M in THF, 0.2 equiv.) was added and the reaction was stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 15% EtOAc in hexane to furnish the racemic product.

1.4 General procedure I: Optimised protocol for the KR of oxazinones

The appropriate oxazinone (1.0 equiv.), 2-napthylmethanol (0.5 equiv.) and catalyst **30** (0.1 equiv.) were cooled to the required temperature under argon and anhydrous $CHCl_3$ (0.1 M) was added. The reaction was stirred until full consumption of 2-napthylmethanol was observed (using ^1H NMR spectroscopy). Allyl alcohol (5.0 equiv.) was added and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo* and redissolved in anhydrous $CHCl_3$. Freshly distilled NEt_3 (1.0 equiv.) was added and the mixture was heated to 55 °C for 24 h. The resulting mixture was purified *via* chromatography, eluting with a gradient of 3-15% EtOAc in hexane to furnish the naphthalen-2-ylmethyl ester and allyl ester products.

1.4.1 Naphthalen-2-ylmethyl-3-(*R*)-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (11)



Prepared according to **General Procedure I** using **9** (50.00 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.0 mL) at -50 °C. After 60 h allyl alcohol (35.0 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **11** (29.0 mg, 46%) as a white solid. M.p. 135-138 °C. $[\alpha]_D^{20} = -27.3$ (*c* 0.11, $CHCl_3$).

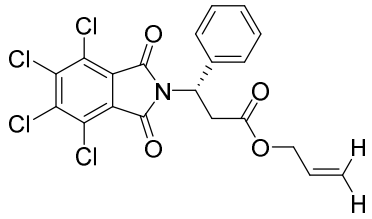
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in **Table 1.2.1**, column temperature : 30 °C, UV detection at 254 nm, retention times: 5.47 min and 6.03 min.

δ_H (400 MHz, $CHCl_3$): 7.71-7.23 (12H, m), 5.77 (1H, dd, *J* 4.5, 12.1), 5.26 (1H, d, *J* 11.7), 5.20 (1H, d, *J* 11.7), 4.04 (1H, dd, *J* 12.3, 15.9), 3.08 (1H, dd, *J* 4.5, 15.9).

δ_C (100 MHz, $CHCl_3$): 169.9, 163.0, 139.6, 137.5, 132.8, 132.7, 132.6, 129.2, 128.9, 128.6, 128.2, 128.1, 127.7, 127.7, 127.4, 126.7, 126.6, 126.5, 126.3, 66.7, 52.0, 35.8.

ν_{max} (neat)/cm^{-1}: 1776, 1738, 1716.

1.4.2 Allyl 3-(*S*)-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (33)



Prepared according to **General Procedure I** using **9** (50.00 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.0 mL) at -50 °C. After 60 h allyl alcohol (35.0 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.6 µL, 0.11 mmol) in $CHCl_3$ (0.5 mL). The crude material was purified as instructed to furnish **33** (27.0 mg, 51%) as a white solid. M.p. 60-63 °C. $[\alpha]_D^{20}$ = -10.5 (*c* 0.19, $CHCl_3$).

CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1}, rt, UV detection at 220 nm, retention times 18.70 min and 20.97 min.

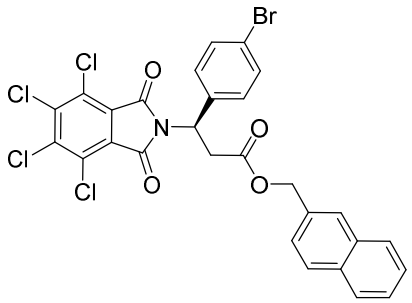
δ_H (400 MHz, $CHCl_3$): 7.54-7.28 (5H, m), 5.88-5.76 (2H, m), 5.28-5.14 (2H, m), 4.56-4.50 (2H, m), 3.87 (1H, dd, *J* 10.7, 16.8), 3.21 (1H, dd, *J* 5.1, 16.8).

δ_C (100 MHz, $CHCl_3$): 170.1, 163.3, 140.2, 137.5, 131.6, 129.8, 128.9, 128.6, 127.9,127.3, 118.7, 65.6, 51.6, 35.1.

ν_{max} (neat)/cm^{-1}: 1776, 1738, 1711.

HRMS (*m/z* - APCI): Found: 471.9678 $(M+H)^+$ $C_{20}H_{14}Cl_4NO_4$ Requires: 471.9671.

1.4.3 Naphthalen-2-ylmethyl-3-(*R*)-(4-bromophenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32a)



Prepared according to **General Procedure I** using **31a** (58.20 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 63 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32a** (33.70 mg, 47%) as a white solid. M.p. 168-170 °C. $[\alpha]_D^{20} = 19.4$ (*c* 0.16, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in **Table 1.2.1**, column temperature : 30 °C, UV detection at 254 nm, retention times: 5.11 min and 5.32 min.

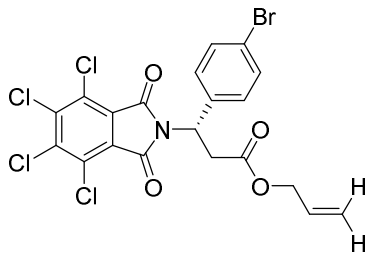
δ_H (400 MHz, $CHCl_3$): 7.72-7.28 (11H, m), 5.71 (1H, dd, *J* 4.9, 11.8), 5.25 (1H, d, *J* 11.7), 5.19 (1H, d, *J* 11.7), 3.95 (1H, dd, *J* 4.0, 15.9), 3.07 (1H, dd, *J* 4.9, 15.9).

δ_C (100 MHz, $CHCl_3$): 169.6, 162.9, 139.8, 136.4, 132.7, 132.6, 132.6, 132.1, 129.5, 129.3, 128.2, 128.1, 127.7, 127.4, 126.7, 126.5, 126.5, 126.3, 122.7, 66.8, 51.3, 35.7.

ν_{max} (neat)/cm^{-1}: 1744, 1741, 1713.

HRMS (*m/z* - DIP): Found: 648.8817 $(M+H)^+$ $C_{28}H_{16}BrCl_4NO_4$ Requires: 648.9011.

1.4.4 Allyl 3-(4-bromophenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34a)



Prepared according to **General Procedure I** using **31a** (58.20 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 63 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL,

0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34a** (30.40 mg, 50%) as a white solid. M.p. 106-108 °C. $[\alpha]_D^{20}$ = -8.7 (*c* 0.16, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:IPA (1:1, *v:v*) gradient as shown in **Table 1.2.2**, column temperature : 30 °C, UV detection at 254 nm, retention times: 6.71 min and 8.05 min.

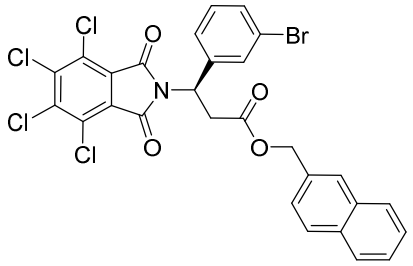
δ_H (400 MHz, $CHCl_3$): 7.55-7.45 (2H, m) 7.42-7.37 (2H, m), 5.88-5.71 (2H, m), 5.31-5.13 (2H, m), 4.55-4.51 (2H, m), 3.77 (1H, dd, *J* 10.4, 16.8), 3.21 (1H, dd, *J* 5.6, 16.8).

δ_C (100 MHz, $CHCl_3$): 169.7, 163.2, 140.4, 136.3, 132.0, 131.5, 129.9, 129.7, 129.5, 127.2, 122.8, 118.8, 65.7, 50.9, 35.0.

ν_{max} (neat)/cm^{-1}: 1777, 1734, 1708.

HRMS (*m/z* - DIP): Found: 549.8661 $(M-C_2H_3)^+$ $C_{20}H_{13}BrCl_4NO_4$ Requires: 549.8777.

1.4.5 Naphthalen-2-ylmethyl-3-(*R*)-(3-bromophenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (371c)



Prepared according to **General Procedure I** using **31b** (58.20 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 60 h and allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32b** as a white solid (33.70 mg, 47%). M.p. 230 °C (decomp.). $[\alpha]_D^{20}$ = 17.7 (*c* 0.13, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in **Table 1.2.1**, column temperature : 30 °C, UV detection at 230 nm, retention times: 5.14 min and 5.58 min.

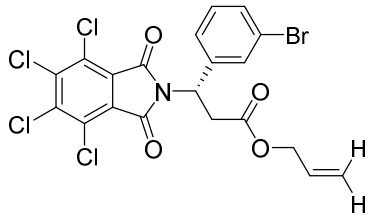
δ_H (400 MHz, $CHCl_3$): 7.75-7.16 (11H, m), 5.73 (1H, dd, *J* 4.7, 11.9), 5.30 (1H, d, *J* 11.7) 5.22 (1H, d, *J* 11.7), 4.00 (1H, dd, *J* 11.9, 16.0), 3.10 (1H, dd, *J* 4.7, 16.0).

δ_C (100 MHz, $CHCl_3$): 169.6, 162.9, 139.8, 139.5, 132.7, 132.7, 132.6, 131.8, 130.8, 130.5, 129.3, 128.2, 128.1, 127.7, 127.4, 126.7, 126.5, 126.5, 126.3, 126.3, 122.9, 66.8, 51.3, 35.6.

ν_{max} (neat)/cm^{-1}: 1774, 1734, 1713.

HRMS (*m/z* - DIP): Found: 648.8773 $(M+H)^+$ $C_{28}H_{16}BrCl_4NO_4$ Requires: 648.9011.

1.4.6 Allyl 3-(3-bromophenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34b)



Prepared according to **General Procedure I** using **31b** (58.20 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 60 h and allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34b** (29.10 mg, 28%) as a white solid. M.p. 70-72 °C. $[\alpha]_D^{20}$ = -17.5 (*c* 0.12, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in **Table 1.2.3**, column temperature : 30 °C, UV detection at 254 nm, retention times: 5.03 min and 6.53 min.

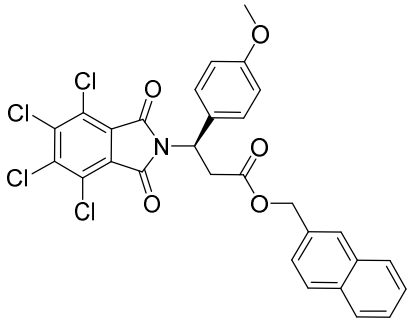
δ_H (400 MHz, $CHCl_3$): 6.69-7.64 (1H, m) 7.51-7.44 (2H, m), 7.28-7.22 (1H, m), 5.92-5.74 (2H, m), 5.28-5.18 (2H, m), 4.56-4.51 (2H, m), 3.86 (1H, dd, *J* 10.7, 16.8), 3.21 (1H, dd, *J* 5.2, 16.8).

δ_C (100 MHz, $CHCl_3$): 169.7, 163.1, 140.3, 139.5, 131.8, 131.5, 131.0, 130.5, 129.9, 127.2, 126.5, 118.8, 65.7, 50.6, 35.0.

ν_{max} (neat)/cm^{-1}: 1776, 1735, 1715.

HRMS (*m/z* – DIP-APCI): Found: 549.8652 $(M-C_2H_3)^+$ $C_{20}H_{13}BrCl_4NO_4$ Requires: 549.8777.

1.4.7 Naphthalen-2-ylmethyl-3-(*R*)-(4-methoxyphenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32c)



Prepared according to **General Procedure I** using **31c** (53.0 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 60 h allyl alcohol (0.35 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32c** (32.50 mg, 49%) as a white solid. M.p. 182-184 °C. $[\alpha]_D^{20} = 15.0$ (*c* 0.12, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1, *v:v*) gradient as shown in **Table 1.2.4**, column temperature : 30 °C, UV detection at 254 nm, retention times: 14.87 min and 16.10 min.

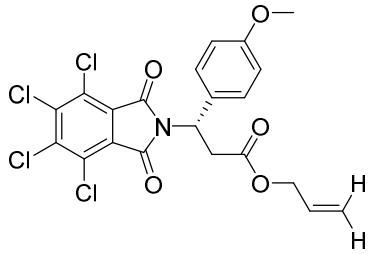
δ_H (400 MHz, $CHCl_3$): 7.56-7.31 (4H, m), 7.46-7.20 (5H, m), 6.87-6.81 (2H, m), 5.73 (1H, dd, *J* 4.7, 11.3), 5.27 (1H, d, *J* 11.8), 5.22 (1H, d, *J* 11.8), 4.02 (1H, dd, *J* 12.0, 15.8), 3.77 (3H, s), 3.09 (1H, dd, *J* 4.7, 15.8).

δ_C (100 MHz, $CHCl_3$): 170.0, 163.0, 159.7, 139.6, 132.8, 132.6, 132.6, 129.6, 129.1, 129.1, 128.1, 128.0, 127.7, 127.4, 126.6, 126.6 (q), 126.5, 126.3, 114.1, 66.6, 55.2, 51.5, 36.0.

ν_{max} (neat)/cm^{-1}: 1774, 1734, 1714.

HRMS (*m/z* - ESI): Found: 623.9915 $(M+Na)^+$ $C_{29}H_{19}Cl4NNaO_5$ Requires: 623.9905.

1.4.8 Allyl-3-(4-methoxyphenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34c)



Prepared according to **General Procedure I** using **31c** (53.00 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 60 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34c** (26.0 mg, 47%) as a white solid. M.p. 102-104 °C. $[\alpha]_D^{20} = -26.3$ (*c* 0.11, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in **Table 1.2.3**, column temperature : 30 °C, UV detection at 212 nm, retention times: 4.64 min and 4.93 min.

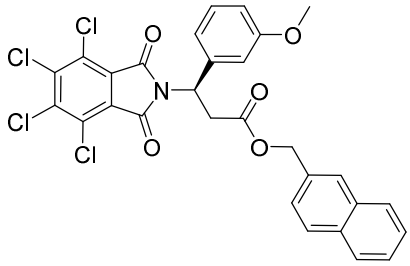
δ_H (400 MHz, $CHCl_3$): 7.48 (2H, d, *J* 8.6), 6.88 (2H, d, *J* 8.6) 5.90-5.76 (2H, m, H-1), 5.31-5.18 (2H, m), 4.58-4.53 (2H, m), 3.90-3.78 (4H, m), 3.22 (1H, dd, *J* 5.4, 16.8).

δ_C (100 MHz, $CHCl_3$): 170.1, 163.3, 159.6, 140.1, 131.6, 129.7, 129.6, 129.3, 127.3, 118.7, 114.1, 65.5, 55.3, 51.0, 35.3.

ν_{max} (neat)/cm^{-1}: 1780, 1734, 1710.

HRMS (*m/z* - ESI): Found: 501.9766 $(M+Na)^+$ $C_{21}H_{15}Cl_4NO_5$ Requires: 501.978.

1.4.9 Naphthalen-2-ylmethyl-3-(*R*)-(3-methoxyphenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32d)



Prepared according to **General Procedure I** using **31d** (53.00 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 60 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32d** (32.40 mg, 49%) as a white solid. M.p. 102-104 °C. $[\alpha]_D^{20} = 23.3$ (*c* 0.15, $CHCl_3$).

CSP-HPLC analysis: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1}, r.t, UV detection at 220 nm, retention times 25.50 min and 31.05 min

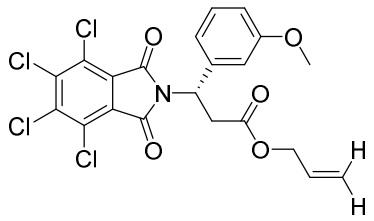
δ_H (400 MHz, $CHCl_3$): 7.73-6.75 (11H, m), 5.71 (1H, dd, *J* 4.6, 12.0), 5.25 (1H, d, *J* 11.7), 5.20 (1H, d, *J* 11.7), 4.01(1H, dd, *J* 12.0, 16.8) 3.76 (3H, s), 3.07 (1H, dd, *J* 3.1, 16.8).

δ_C (100 MHz, $CHCl_3$): 169.9, 163.0, 159.8, 136.0, 138.9, 132.8, 132.6, 132.6, 130.0, 129.1, 128.2, 128.0, 127.7, 127.4, 126.7, 126.6, 126.5, 126.3, 119.1, 114.0, 113.4, 66.7, 55.2, 51.9, 35.8.

ν_{max} (neat)/cm^{-1}: 1774, 1734, 1714.

HRMS (*m/z* – DIP-APCI): Found: 601.9925 $(M-H)^-$ $C_{29}H_{20}BrCl_4NO_5$ Requires: 602.0090.

1.4.10 Allyl-3-(3-methoxyphenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34d)



Prepared according to **General Procedure I** using **31d** (53.00 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -50 °C. After 60 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34d** as a white solid (26.60 mg, 48%). M.p. 139-141 °C. $[\alpha]_D^{20} = -20.0$ (*c* 0.01, $CHCl_3$).

CSP-HPLC analysis: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1}, r.t, UV detection at 220 nm, retention times 18.70 min and 20.97 min

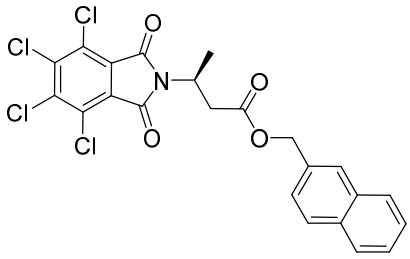
δ_H (400 MHz, $CHCl_3$): 7.28-6.79 (4H, m), 5.91-5.69 (2H, m), 5.32-5.11 (2H, m), 4.58-4.47 (2H, m), 3.91-3.73 (4H, m), 3.19 (1H, dd, *J* 5.1, 16.8).

δ_C (100 MHz, $CHCl_3$): 170.0, 163.2, 159.8, 140.1, 138.9, 131.6, 129.9, 129.7, 127.3, 120.0, 118.7, 65.5, 55.3, 51.5, 35.1.

ν_{max} (neat)/cm^{-1}: 1777, 1709, 1599.

HRMS (*m/z* –APCI): Found: 501.9704 $(M+H)^+$ $C_{21}H_{26}Cl_4NO_5$ Requires: 501.9704.

1.4.11 Naphthalen-2-ylmethyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)butanoate (32e)



Prepared according to **General Procedure I** using **31e** (45.60 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -30 °C. After 63 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32e** (26.40 mg, 47%) as a white solid. M.p. 170-173 °C. $[\alpha]_D^{20} = 2.5$ (*c* 0.12, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in **Table 1.2.1**, column temperature : 30 °C, UV detection at 254 nm, retention times: 4.58 min and 4.79 min.

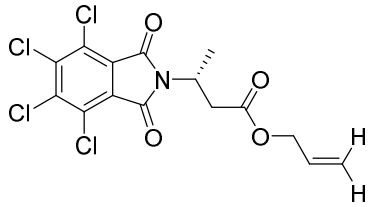
δ_H (400 MHz, $CHCl_3$): 7.75-7.26 (7H, m), 5.17 (2H, s), 4.82-4.71 (1H, m), 3.39 (1H, dd, *J* 11.1, 15.4), 2.71 (1H, dd, *J* 4.7, 15.4), 1.44 (3H, d, *J* 6.7).

δ_C (100 MHz, $CHCl_3$): 170.2, 163.1, 139.6, 132.8, 132.7, 132.7, 129.1, 128.1, 127.8, 127.7, 127.5, 126.8, 126.6, 126.5, 126.2, 66.7, 44.7, 37.8, 18.8.

ν_{max} (neat)/cm^{-1}: 1772, 1716, 1702.

HRMS (*m/z* – DIP-APCI): Found: 508.9608 $(M+H)^+$ $C_{23}H_{15}Cl_4NO_4$ Requires: 508.9750.

1.4.12 Allyl 3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)butanoate (34e)



Prepared according to **General Procedure I** using **31e** (45.60 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -30 °C. After 63 h allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34e** (21.30 mg, 47%) as a white solid. M.p. 147-150 °C. $[\alpha]_D^{20}$ = -10.0 (*c* 0.12, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in **Table 1.2.5**, column temperature : 30 °C, UV detection at 254 nm, retention times: 6.48 min and 6.79 min.

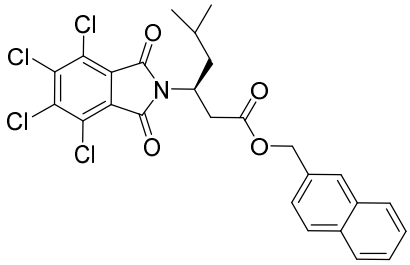
δ_H (400 MHz, $CHCl_3$): 5.90-5.76 (1H, m), 5.29-5.13 (2H, m), 4.86-4.75 (1H, m), 4.53-4.49 (2H, m), 3.22 (1H, dd, *J* 9.8, 16.6), 2.78 (1H, dd, *J* 5.4, 16.6), 1.51 (3H, d, *J* 6.9).

δ_C (100 MHz, $CHCl_3$): 170.2, 163.3, 140.1, 131.7, 129.7, 127.4, 118.7, 65.4, 44.4, 37.3, 18.6.

ν_{max} (neat)/cm^{-1}: 1733, 1713, 1702.

HRMS (*m/z* - APCI): Found: 409.9520 $(M+H)^+$ $C_{21}H_{15}Cl_4NNaO_5$ Requires: 409.9515.

1.4.13 Naphthalen-2-ylmethyl-5-methyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)hexanoate (32f)



Prepared according to **General Procedure I** using **31f** (47.80 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -30 °C. After 63 h, allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32f** (24.30 mg, 40%) as a white solid. M.p. 110-112 °C. $[\alpha]_D^{20} = 12.0$ (*c* 0.05, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, *v:v*) gradient as shown in **Table 1.2.4**, column temperature : 30 °C, UV detection at 254 nm, retention times: 8.36 min and 8.80 min.

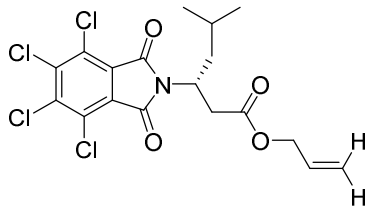
δ_H (400 MHz, $CHCl_3$): 7.75-7.26 (7H, m), 5.18-5.10 (2H, m), 4.75-4.65 (1H, m), 3.35 (1H, dd, *J* 11.6, 15.4), 2.68 (1H, dd, *J* 4.3, 15.4), 2.04-1.93 (1H, m), 1.49-1.30 (2H, m), 0.92-0.84 (6H, m).

δ_C (100 MHz, $CHCl_3$): 170.3, 163.3, 139.6, 132.7, 132.7, 132.7, 129.1, 128.1, 127.8, 127.7, 127.5, 126.7, 126.6, 126.6, 126.5, 126.1, 66.6, 47.4, 41.3, 36.9, 25.0, 22.8, 21.7.

ν_{max} (neat)/cm^{-1}: 1773, 1731, 1712.

HRMS (*m/z* - ESI): Found: 574.0105 $(M+Na)^+$ $C_{26}H_{21}Cl_4NNaO_4$ Requires: 574.0117.

1.4.14 Allyl 5-methyl-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxo*iso*indolin-2-yl)hexanoate (34f)



Prepared according to **General Procedure I** using **31f** (47.80 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at -30 °C. After 63 h, allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11

mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34f** (27.90 mg, 56%) as a white solid. M.p. 85-87 °C. $[\alpha]_D^{20} = -40.0$ (*c* 0.01, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in **Table 1.2.1**, column temperature : 30 °C, UV detection at 230 nm, retention times: 2.52 min and 2.86 min.

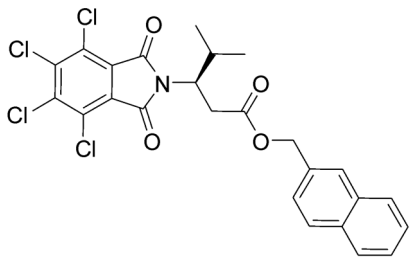
δ_H (400 MHz, $CHCl_3$): 5.89-5.78 (1H, m), 5.32-5.16 (2H, m), 4.80-4.72 (1H, m), 4.51 (2H, app. d, *J* 5.9), 3.21 (1H, dd, *J* 10.3, 16.4, H-), 2.74 (1H, dd, *J* 4.9, 16.4), 2.16-2.08 (1H, m), 1.53-1.42 (2H, m), 1.01-0.91 (6H, m).

δ_C (100 MHz, $CHCl_3$): 170.3, 163.6, 140.1, 131.7, 129.7, 127.3, 118.7, 65.5, 47.2, 41.1, 36.5, 25.1, 23.0, 21.7.

ν_{max} (neat)/cm^{-1}: 1731, 1720, 1715.

HRMS (*m/z* - ESI): Found: 451.9980. $(M+H)^+$ $C_{18}H_{18}Cl_4NO_4$ Requires: 451.9984.

1.4.15 Naphthalen-2-ylmethyl-4-methyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentanoate (32g)



Prepared according to **General Procedure I** using **31g** (46.30 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at rt. After 60 h, allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **32g** (25.50 mg, 43%) as a white solid. M.p. 102-104 °C. $[\alpha]_D^{20} = 5.0$ (*c* 0.04, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in **Table 1.2.3**, column temperature : 30 °C, UV detection at 230 nm, retention times: 4.08 min and 4.43 min.

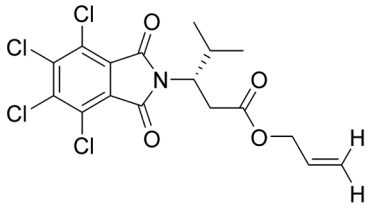
δ_H (400 MHz, $CHCl_3$): 7.73-7.26 (7H, m), 5.16 (1H, d, *J* 11.7), 5.11 (1H, d, *J* 11.7), 4.92-4.20 (1H, m), 3.36 (1H, dd, *J* 12.2, 15.2), 2.83 (1H, dd, *J* 4.0, 15.2), 2.30-2.19 (1H, m), 1.01 (3H, d, *J* 6.5), 0.78 (3H, d, *J* 6.8).

δ_C (100 MHz, $CHCl_3$): 170.7, 163.4, 139.6, 132.8, 132.6, 132.6, 129.1, 128.1, 128.0, 127.7, 127.5, 126.7, 126.5, 126.5, 126.3, 66.5, 55.3, 34.5, 30.6, 20.0, 19.7.

ν_{max} (neat)/cm^{-1}: 1774, 1731, 1715.

HRMS (*m/z* - APCI): Found: 538.0126 $(M+H)^+$ $C_{25}H_{20}Cl_4NO_4$ Requires: 538.0141.

1.4.16 Allyl 4-methyl-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentanoate (34f)



Prepared according to **General Procedure I** using **31g** (46.30 mg, 0.11 mmol), 2-napthylmethanol (8.30 mg, 0.05 mmol), **30** (7.91 mg, 0.01 mmol), $CHCl_3$ (1.00 mL) at rt. After 60 h, allyl alcohol (35.00 µL, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 µL, 0.11 mmol) in $CHCl_3$ (0.50 mL). The crude material was purified as instructed to furnish **34f** as a white solid (21.70 mg, 45%). M.p. 55-57 °C. $[\alpha]_D^{20}$ = -16.7 (*c* 0.03, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in **Table 1.2.3**, column temperature : 30 °C, UV detection at 230 nm, retention times: 2.76 min and 3.73 min.

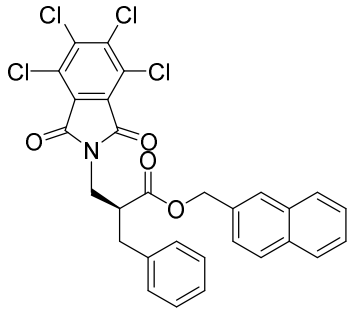
δ_H (400 MHz, $CHCl_3$): 5.88-5.74 (1H, m), 5.28-5.13 (2H, m), 4.78-4.69 (1H, m), 4.51-4.47 (2H, m), 3.19 (1H, dd, *J* 10.1, 16.1), 2.71 (1H, dd, *J* 4.8, 16.1), 2.15-2.02 (1H, m), 0.75-0.88 (6H, m).

δ_C (100 MHz, $CHCl_3$): 170.7, 163.7, 140.1, 131.6, 129.7, 127.2, 118.8, 65.4, 55.0, 33.8, 30.4, 20.0, 19.7.

ν_{max} (neat)/cm^{-1}: 1732, 1728, 1717.

HRMS (*m/z* - ESI): Found: 437.9755 $(M+H)^+$ $C_{17}H_{15}Cl_4NO_4$ Requires: 437.9755.

1.4.17 Naphthalen-2-ylmethyl-(*R*)-2-benzyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (36)



35 (35.70 mg, 0.07 mmol), 2 napthylmethanol (5.80 mg, 0.04 mmol) and catalyst **30** (3.70 mg, 0.01 mmol) were dissolved in anhydrous $CHCl_3$ under argon at -50 °C and the mixture was stirred for 14 days until the alcohol was completely consumed by the reaction (monitored by ^1H NMR spectroscopy). Allyl alcohol (24.80 µL, 0.37 mmol) was added and the mixture was warmed to rt and was stirred for a further 3 h. DABCO (3.30 mg, 0.29 mmol) was added and the mixture was stirred for 24 h. The resulting mixture was purified *via* silica chromatography to afford **36** (20.14 mg, 49%) as a white solid. M.p. 128-130 °C. $[\alpha]_D^{20} = 23.3$ (*c* 0.12, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, *v:v*) gradient as shown in **Table 1.2.6**, column temperature : 30 °C, UV detection at 254 nm, retention times: 14.07 min and 16.87 min.

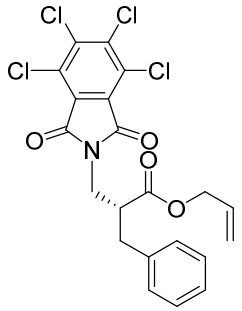
δ_H (400 MHz, $CHCl_3$): 7.75-7.40 (7H, m), 7.26-7.20 (5H, m), 5.20 (1H, d, *J* 12.0), 5.02 (1H, d, *J* 12.0), 3.99 (1H, dd, *J* 9.7, 13.9), 3.70 (1H, dd, *J* 5.8, 13.9), 3.47 (1H, m), 3.18 (1H, dd, *J* 7.7, 14.3), 2.83 (1H, dd, *J* 7.5, 14.3).

δ_C (100 MHz, $CHCl_3$): 172.3, 163.1, 139.7, 137.7, 132.7, 132.7, 132.6, 129.2, 128.7 128.6, 128.0, 127.7, 127.6, 127.1, 126.9, 126.6, 126.5, 126.4, 125.7, 66.8, 44.3, 40.2, 35.7, 29.7.

ν_{max} (neat)/cm^{-1}: 2981, 2929, 1791, 1721.

HRMS (*m/z* – DIP-APCI): Found: 584.9875 $(M-H)^+$ $C_{29}H_{19}Cl_4NO_4$ Requires: 585.0063.

1.4.18 Allyl (*S*)-2-benzyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (37)



35 (35.7 mg, 0.07 mmol), 2 napthylmethanol (5.8 mg, 0.04 mmol) and catalyst **30** (3.70 mg, 0.01 mmol) were dissolved in anhydrous $CHCl_3$ under argon at -50 °C and the mixture was stirred for 14 days until the alcohol was completely consumed by the reaction (monitored by ^1H NMR spectroscopy). Allyl alcohol (24.80 μL, 0.37 mmol) was added and the mixture was warmed to rt and was stirred for a further 3 h. DABCO (3.30 mg, 0.29 mmol) was added and the mixture was stirred for 24 h. The resulting mixture was purified *via* silica chromatography to afford **27** as a colourless oil (14.42 mg, 40%). $[\alpha]_D^{20}$ = -26.7 (*c* 0.15, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, *v:v*) gradient as shown in **Table 1.2.3**, column temperature : 30 °C, UV detection at 254 nm, retention times: 4.46 min and 4.84 min.

δ_H (400 MHz, $CHCl_3$): 7.24-7.07 (5H, m), 5.84-5.69 (1H, m), 5.22-5.10 (2H, m), 4.49 (2H, app. d, *J* 5.8), 3.98 (1H, dd, *J* 8.1, 13.9), 3.86 (1H, dd, *J* 6.6, 13.8), 3.39-2.86 (1H, m), 3.13 (1H, dd, *J* 7.2, 14.5), 2.80 (1H, dd, *J* 8.3, 14.7).

δ_C (100 MHz, $CHCl_3$): 172.2, 163.2, 140.0, 137.7, 131.7, 129.6, 128.6 128.5, 127.3, 126.4, 118.8, 65.9, 44.6, 40.0, 36.0.

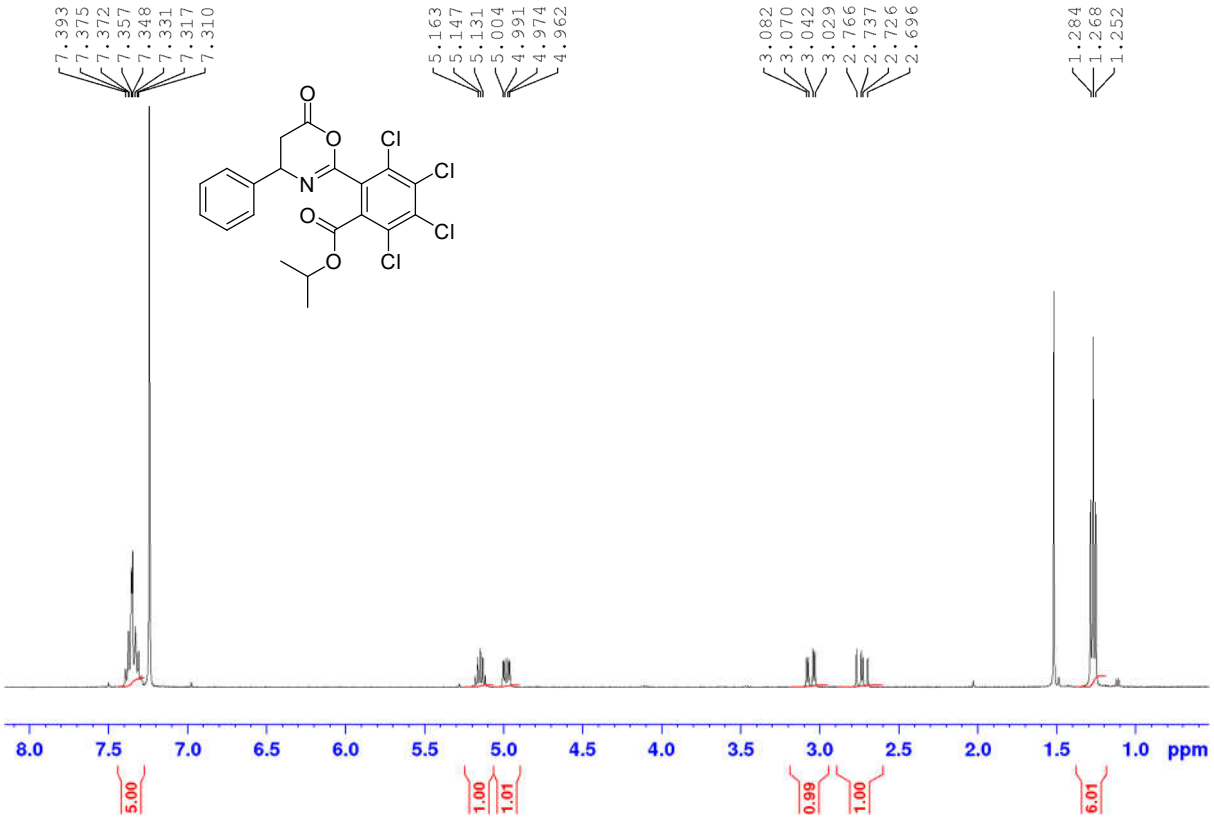
ν_{max} (neat)/cm^{-1}: 2922, 1723, 1673.

HRMS (*m/z* - DIP): Found: 485.9972 $(M\text{-}C_2H_3)^+$ $C_{21}H_{16}Cl_4NO_4$ Requires: 485.9828.

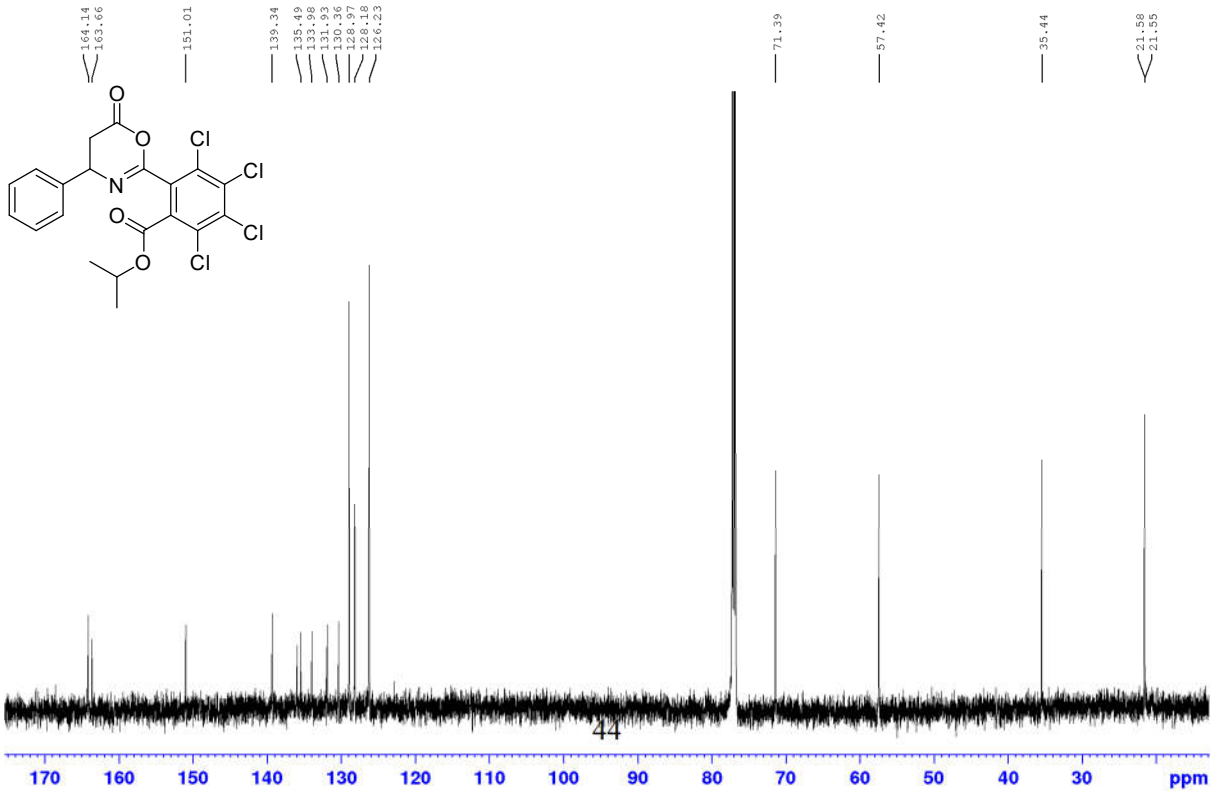
Note: KR product ^{1}H NMR spectra are racemates

***iso*Propyl-2,3,4,5-tetrachloro-6-(6-oxo-4-phenyl-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (9)**

^{1}H NMR in $CDCl_3$

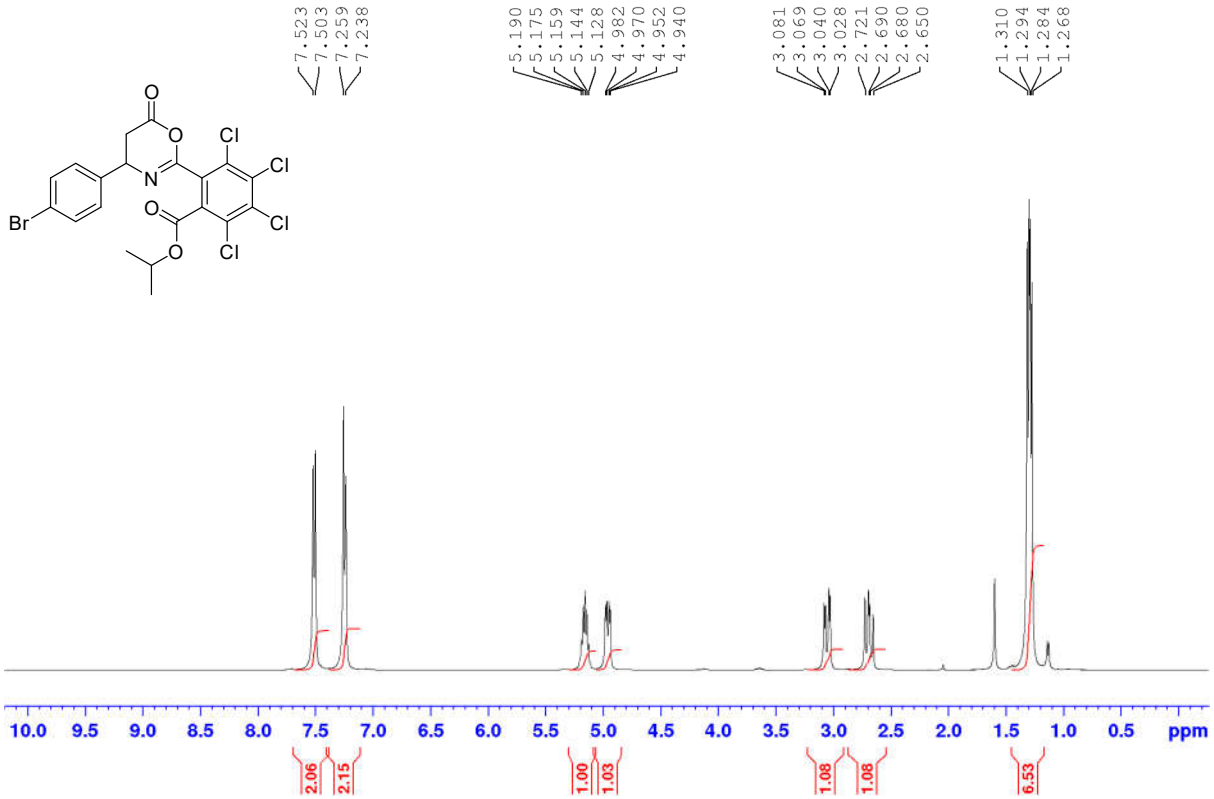


^{13}C NMR in $CDCl_3$

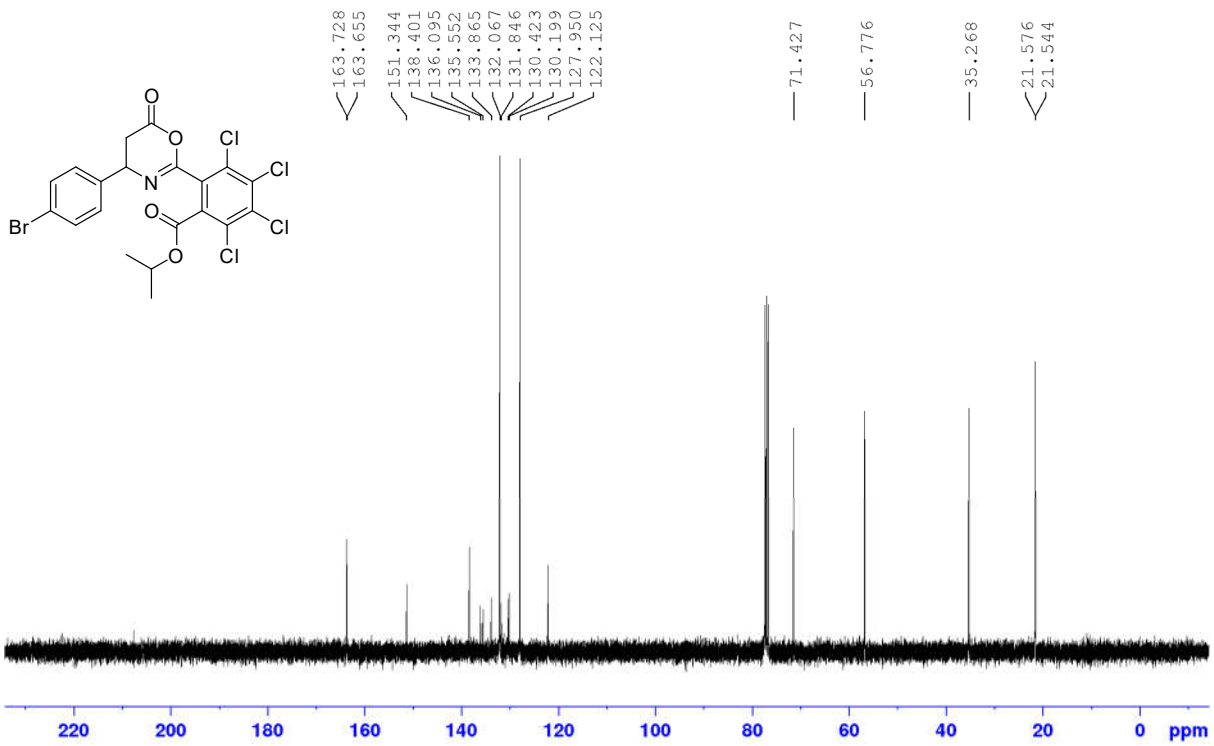


***iso*Propyl-2-(4-(4-bromophenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (31a)**

^{1}H NMR in $CDCl_3$

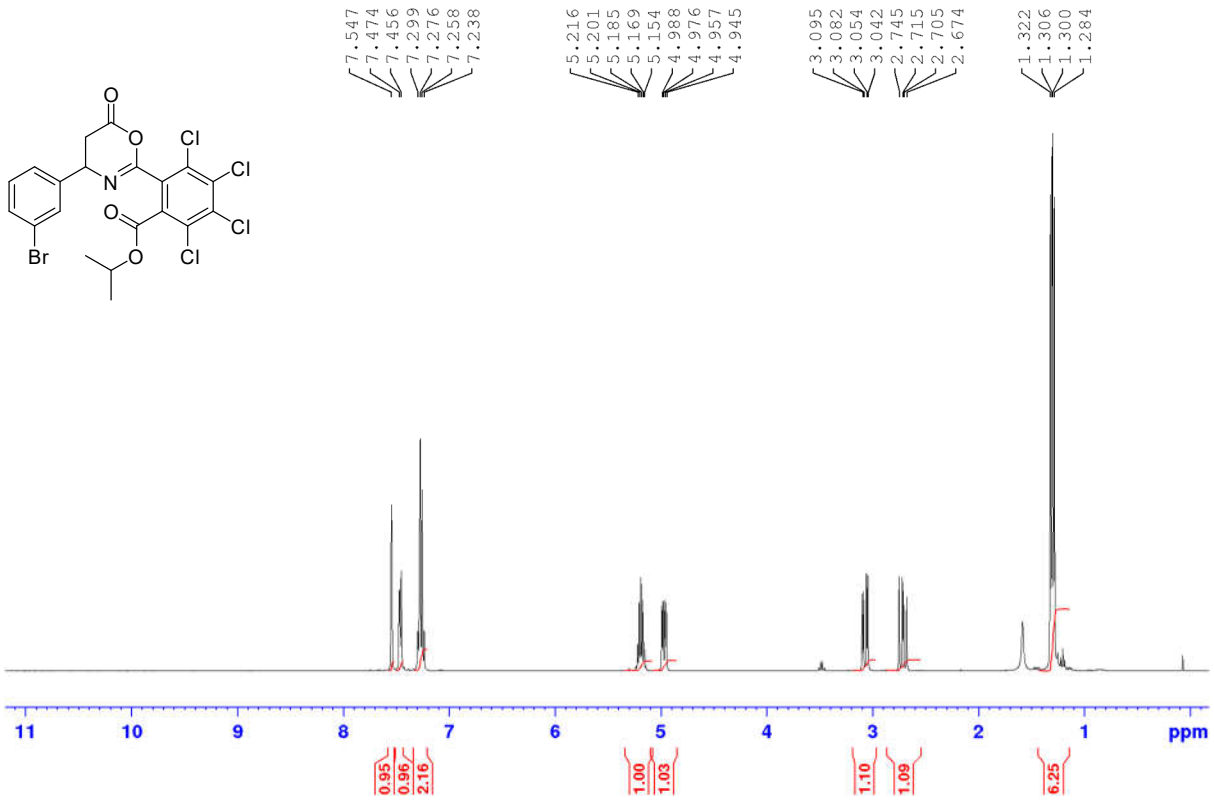


^{13}C NMR in $CDCl_3$

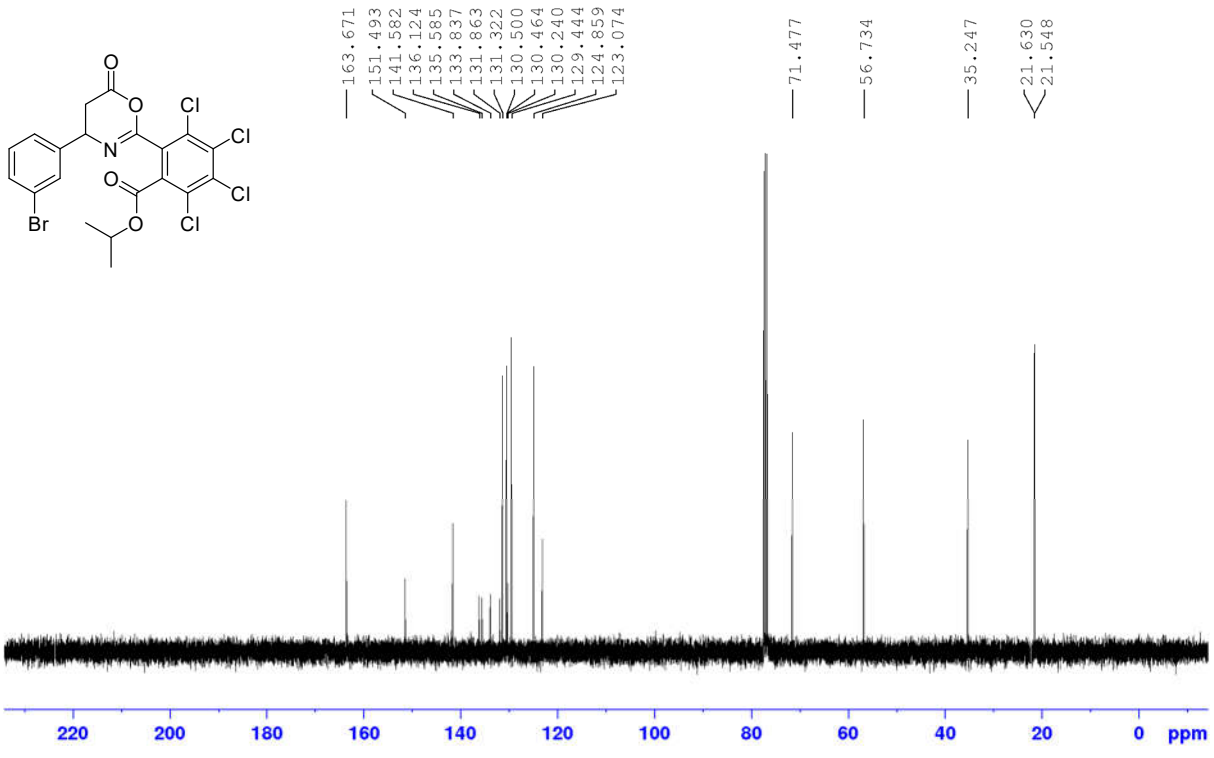


***iso*Propyl-2-(4-(3-bromophenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (31b)**

^{1}H NMR in $CDCl_3$

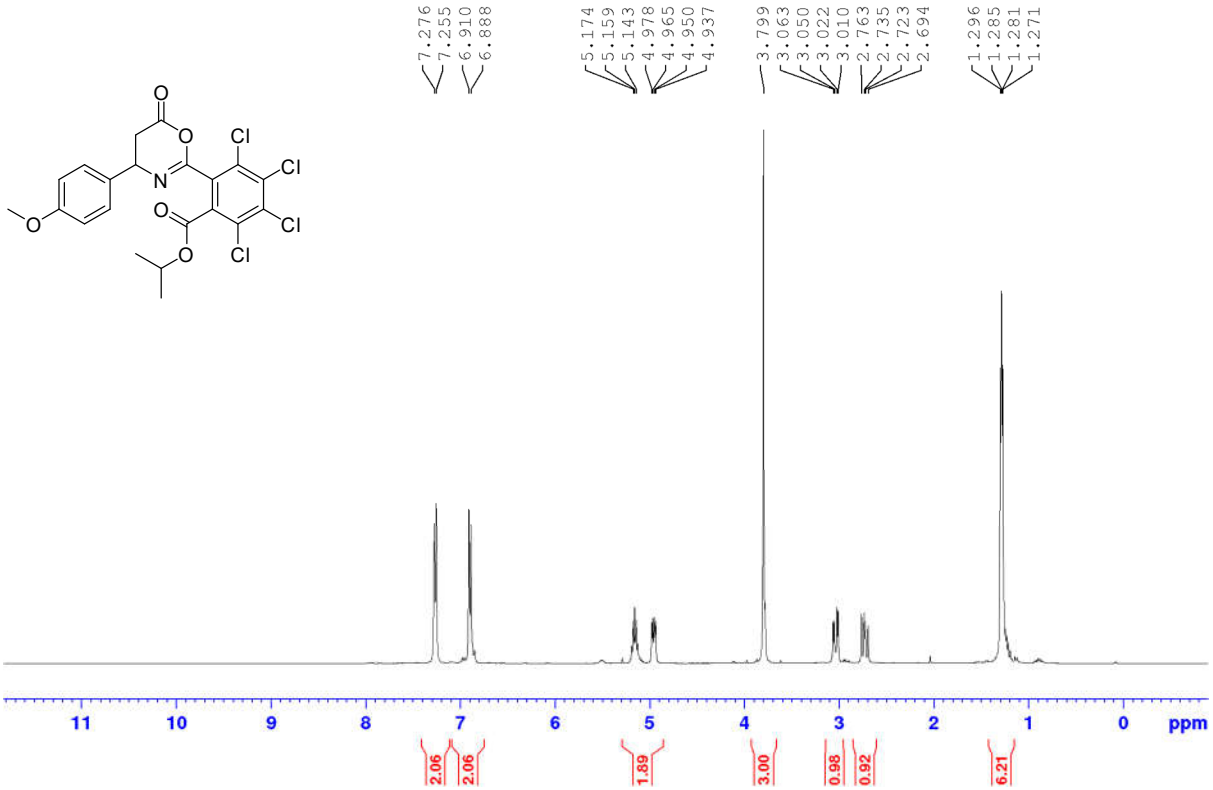


^{13}C NMR in $CDCl_3$

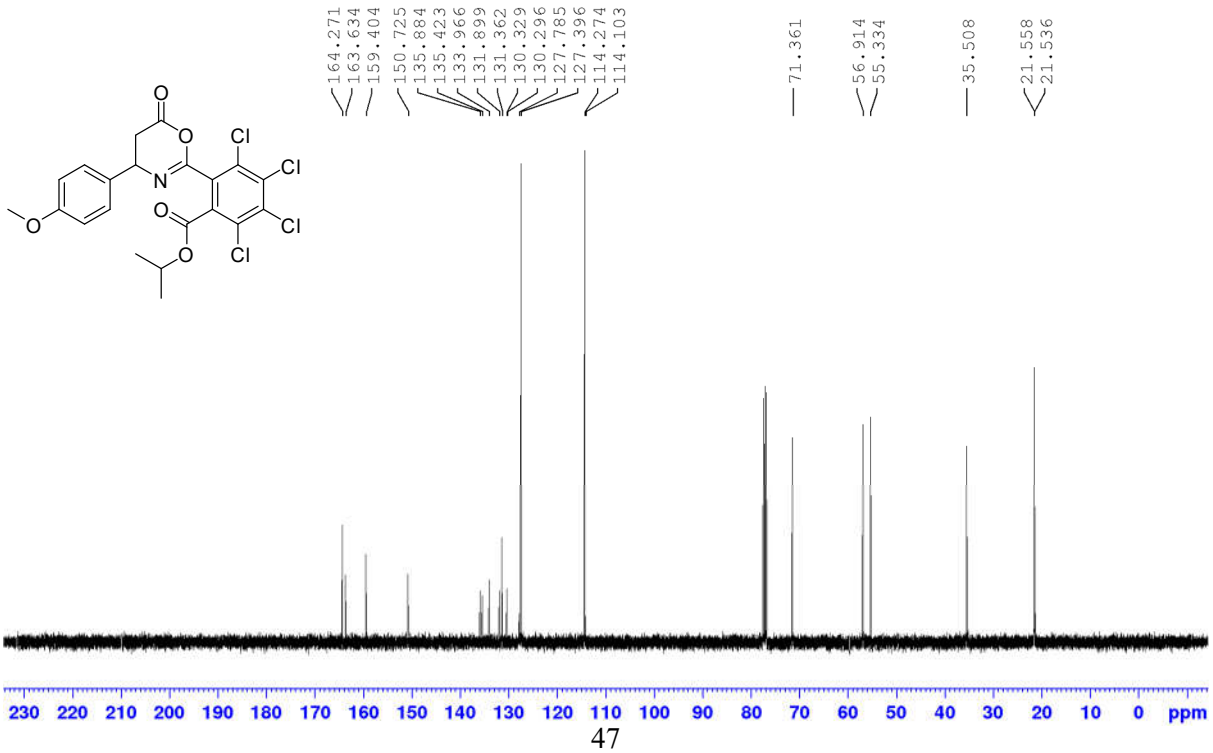


***iso*Propyl 2,3,4,5-tetrachloro-6-(4-(4-methoxyphenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31c)**

^{1}H NMR in $CDCl_3$

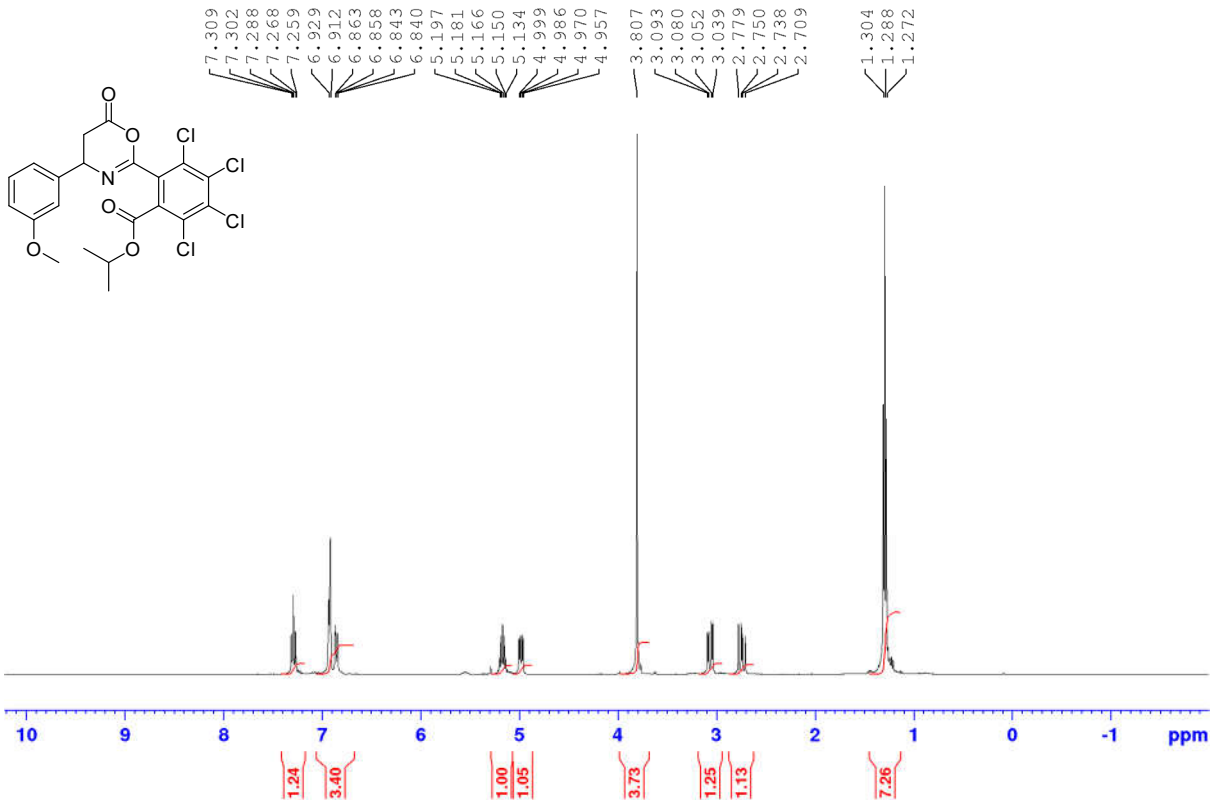


^{13}C NMR in $CDCl_3$

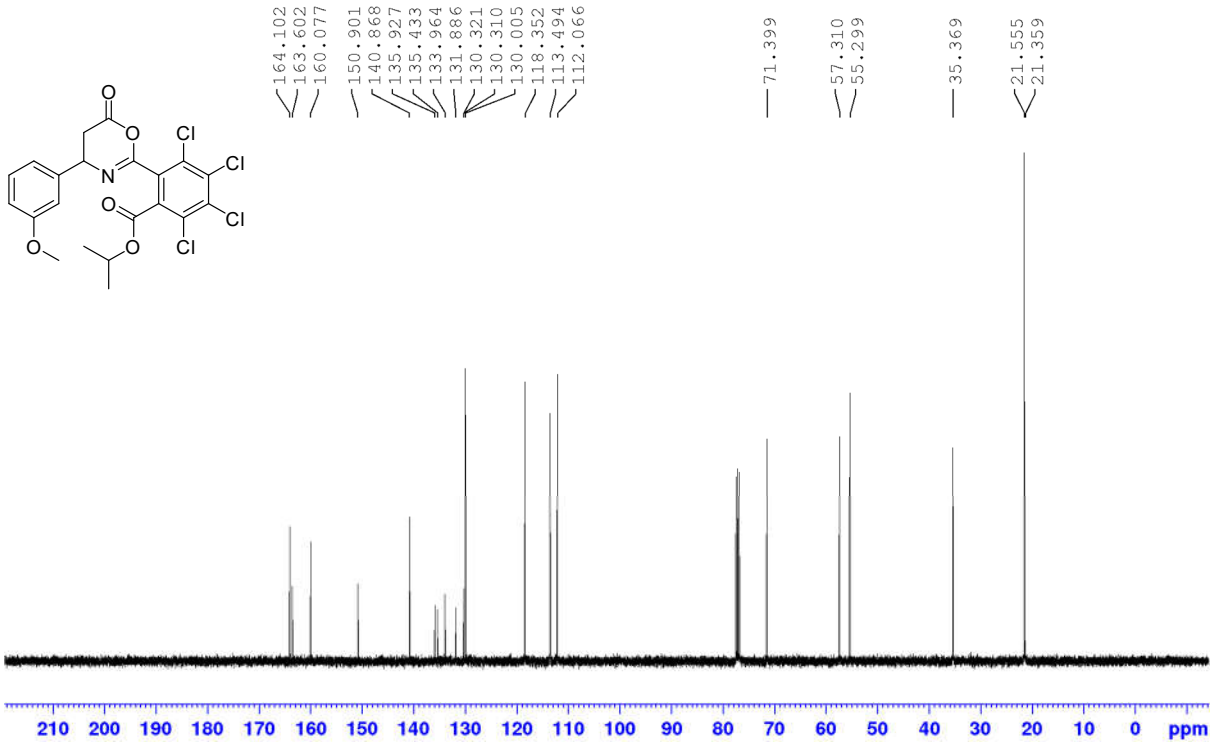


***isopropyl*-2,3,4,5-tetrachloro-6-(4-(3-methoxyphenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31d)**

^{1}H NMR in $CDCl_3$

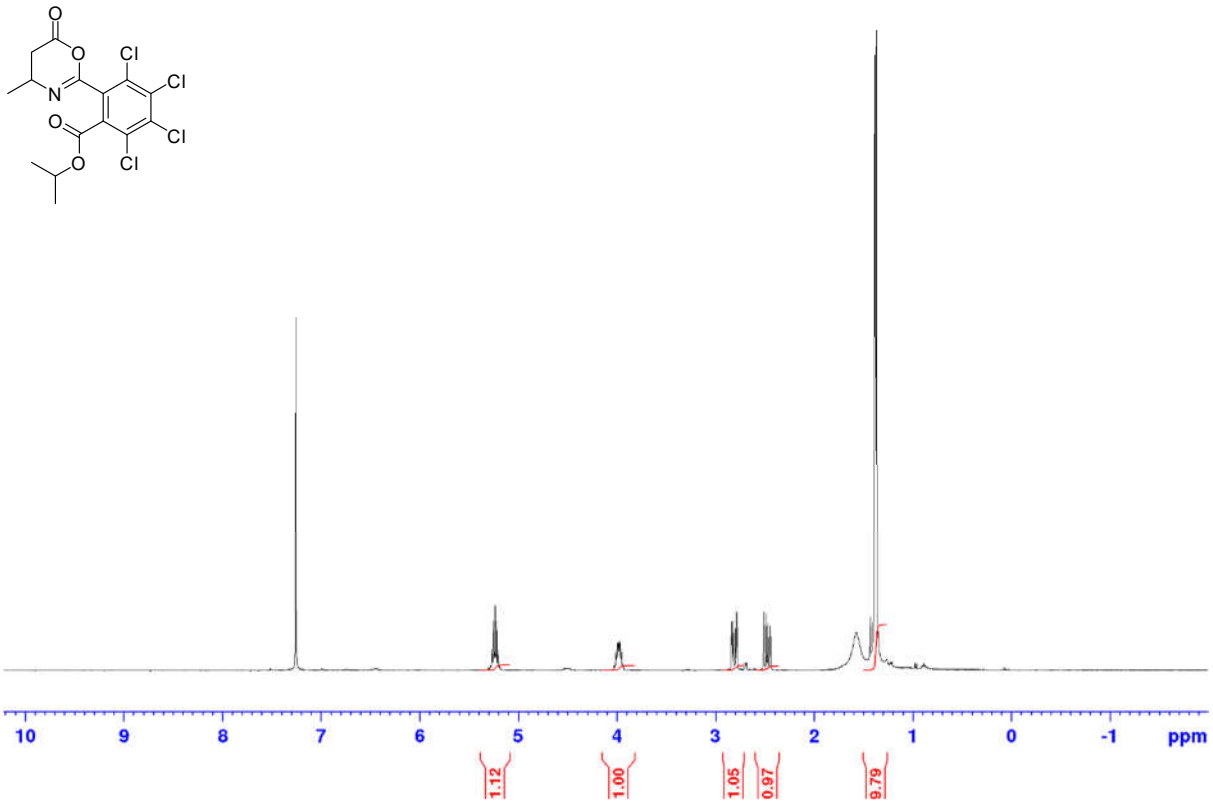


^{13}C NMR in $CDCl_3$

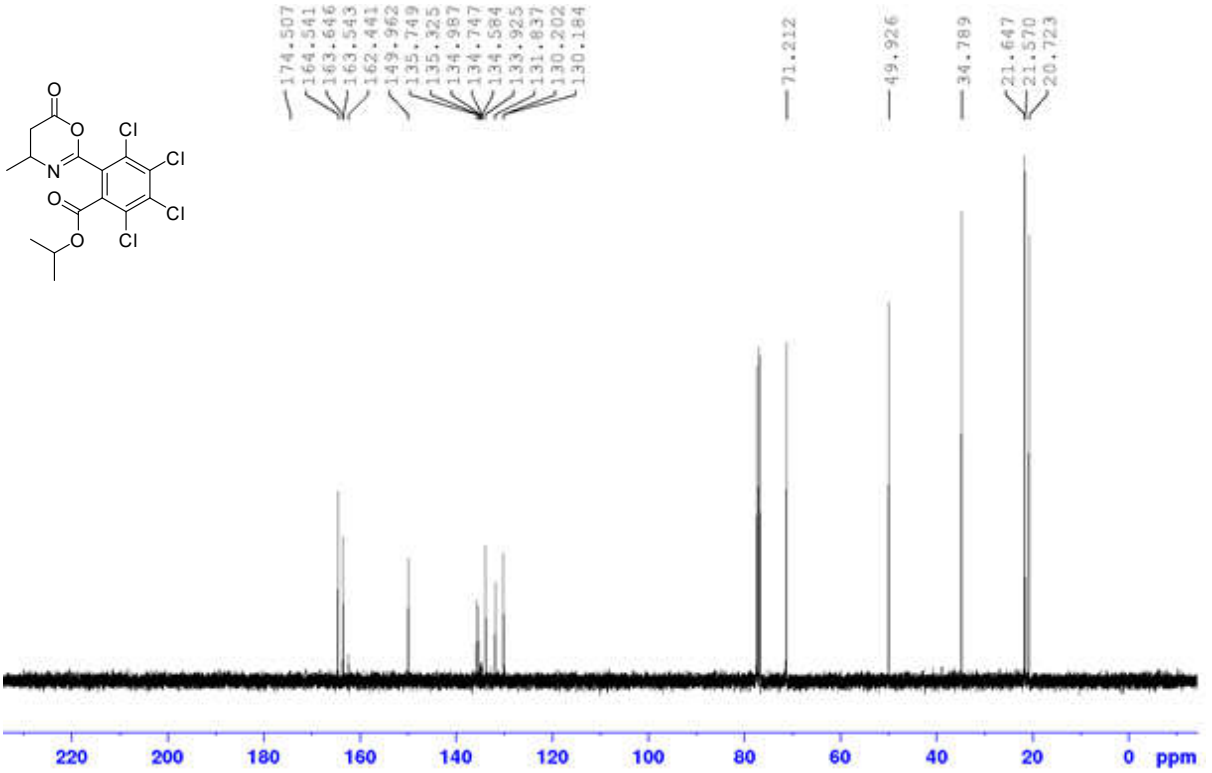


***iso*Propyl-2,3,4,5-tetrachloro-6-(4-methyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31e)**

^{1}H NMR in $CDCl_3$

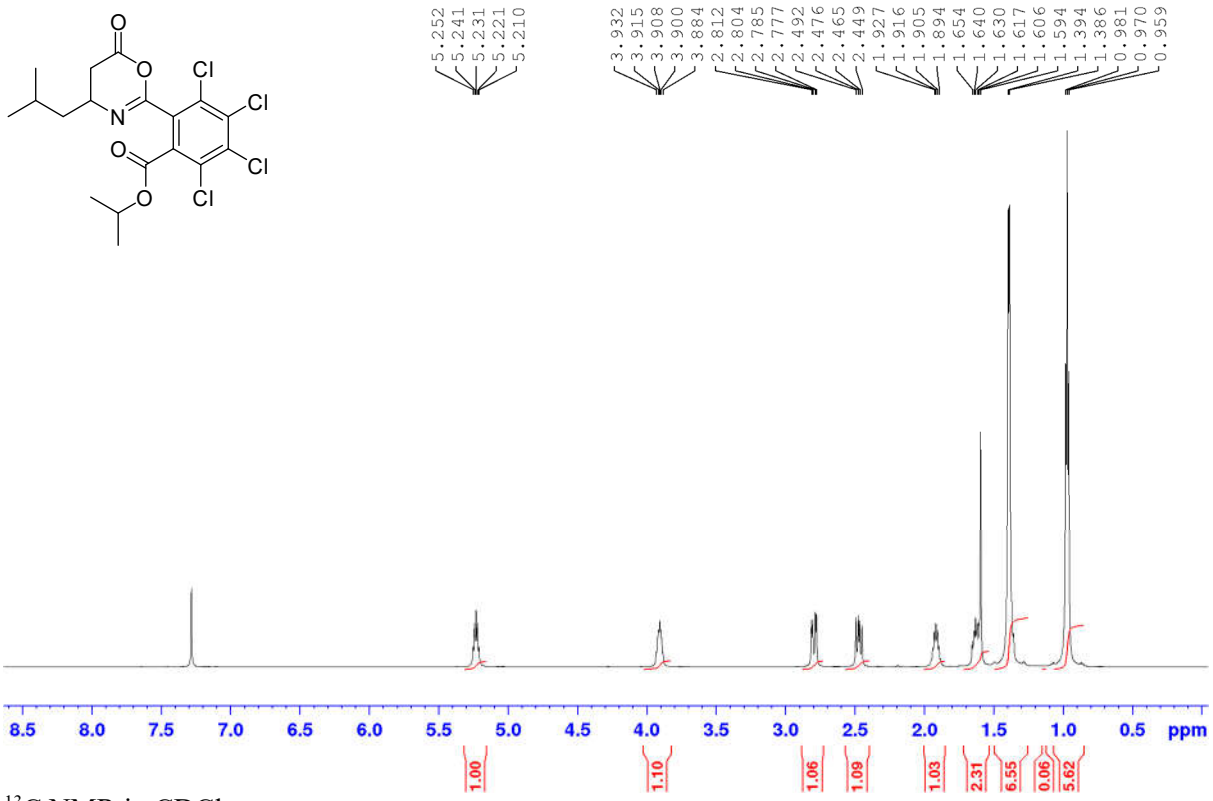


^{13}C NMR in $CDCl_3$

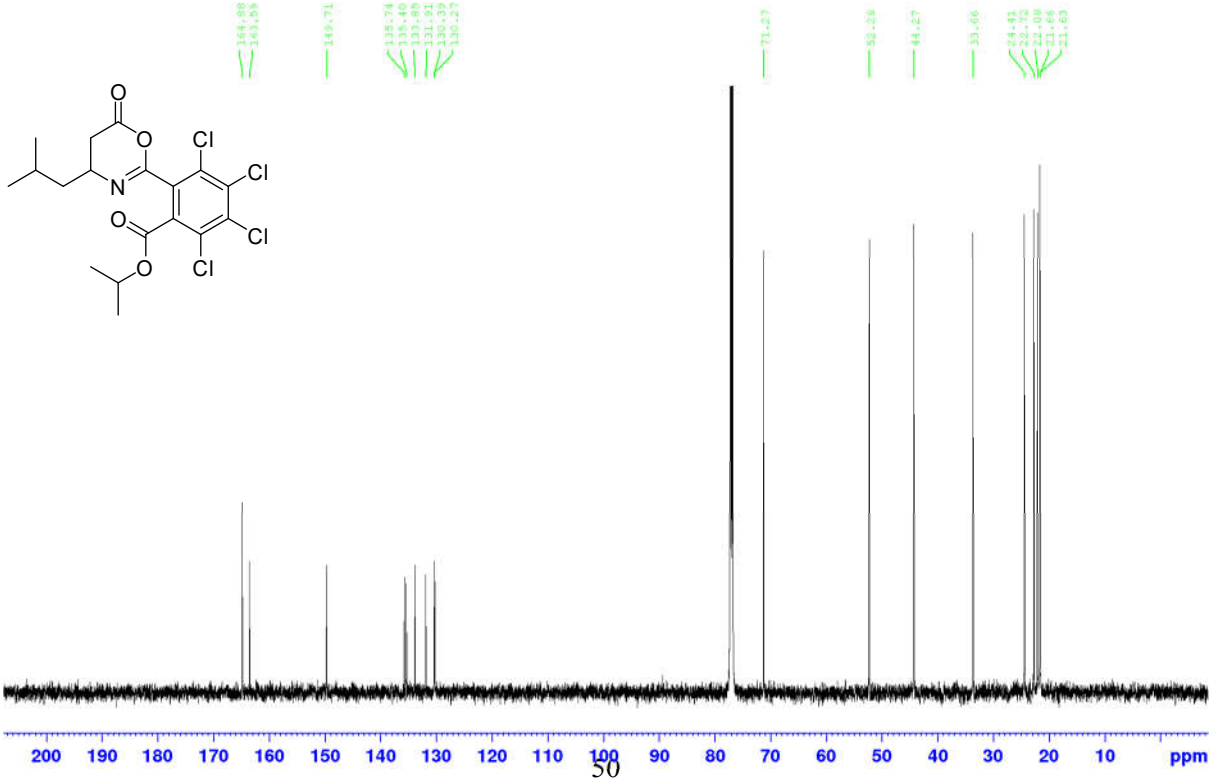


***iso*Propyl-2,3,4,5-tetrachloro-6-(4-*iso*butyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31f)**

^{1}H NMR in $CDCl_3$

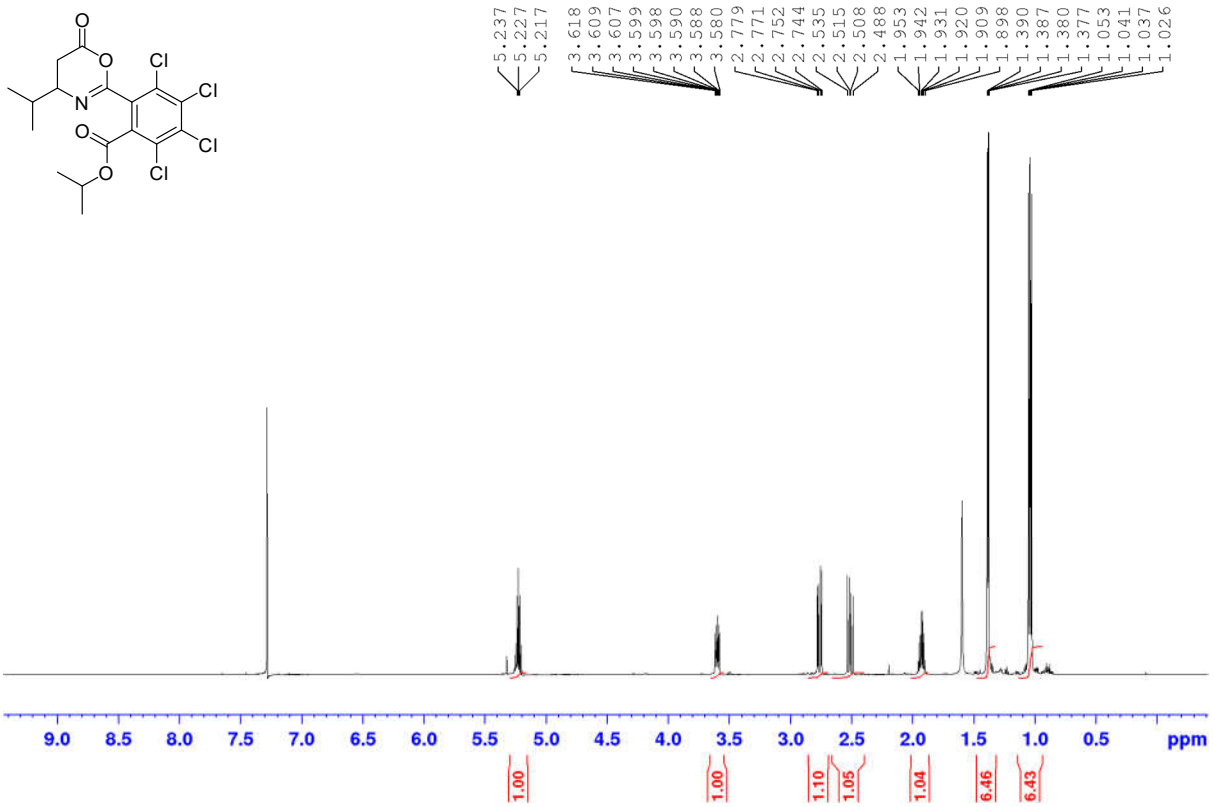


^{13}C NMR in $CDCl_3$

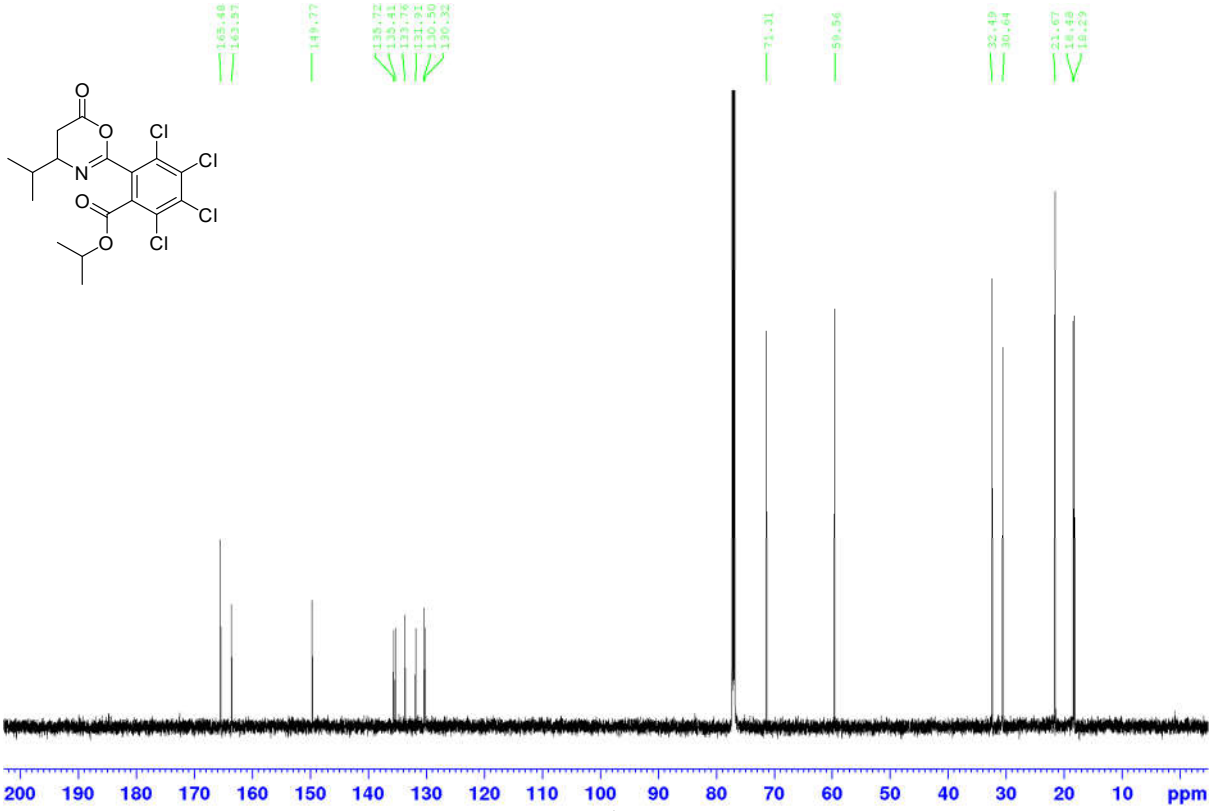


***iso*Propyl 2,3,4,5-tetrachloro-6-(4-*iso*propyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (31g)**

^{1}H NMR in $CDCl_3$

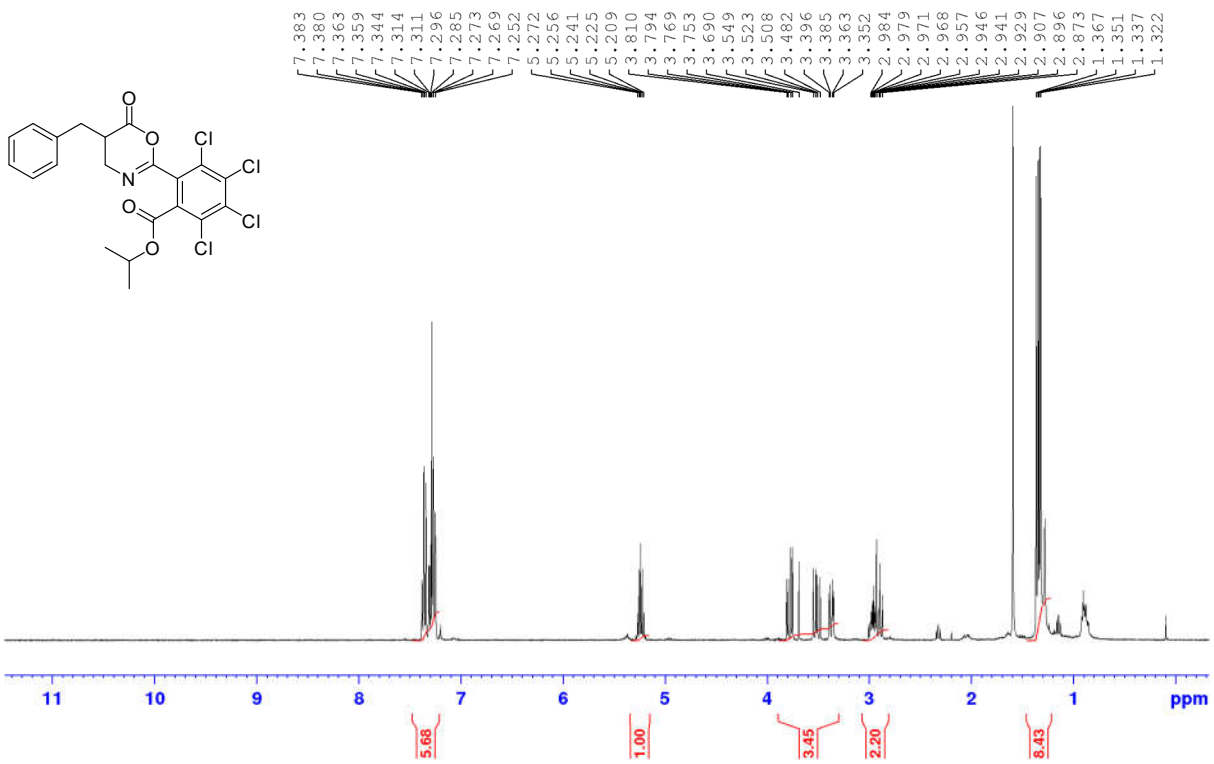


^{13}C NMR in $CDCl_3$

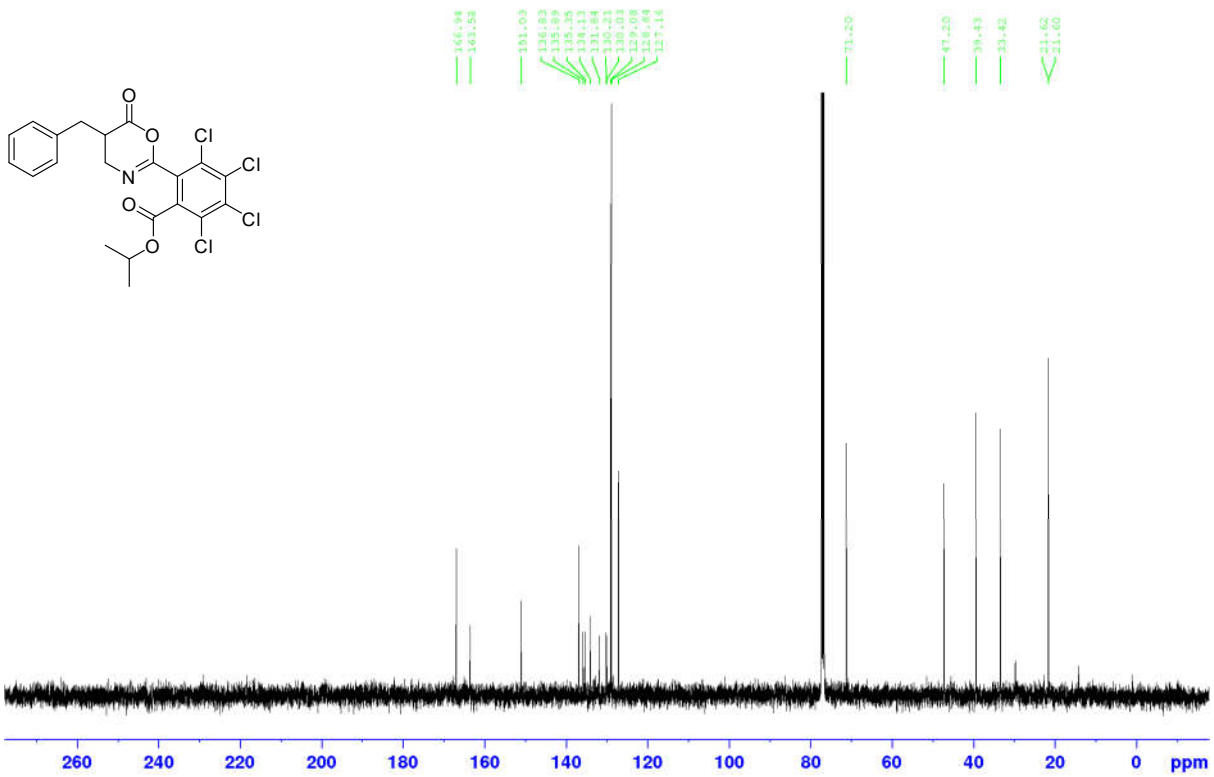


***iso*Propyl 2-(5-benzyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (35)**

^{1}H NMR in $CDCl_3$

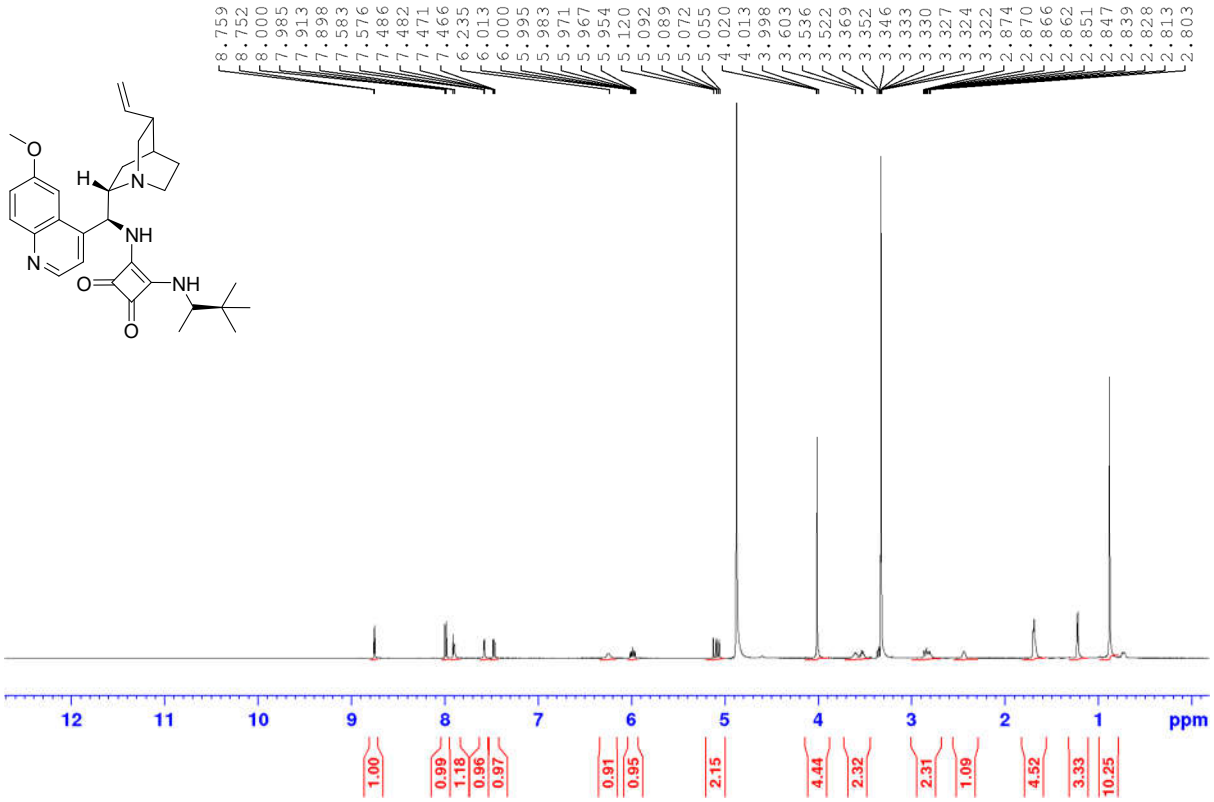


^{13}C NMR in $CDCl_3$

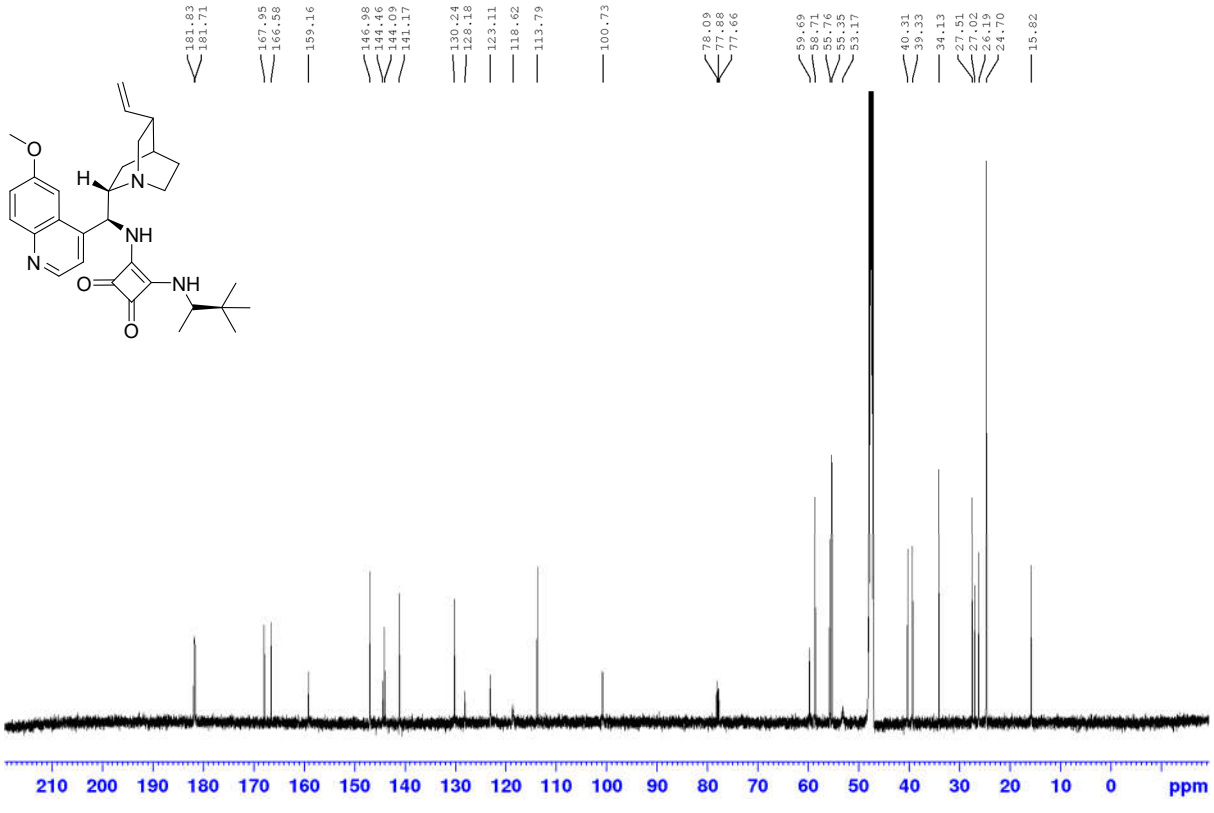


methyl-(2*S*)-2-((2-(((1*S*)-(6-methoxyquinolin-4-yl)((2*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanoate (30)

^{1}H NMR in $CDCl_3$

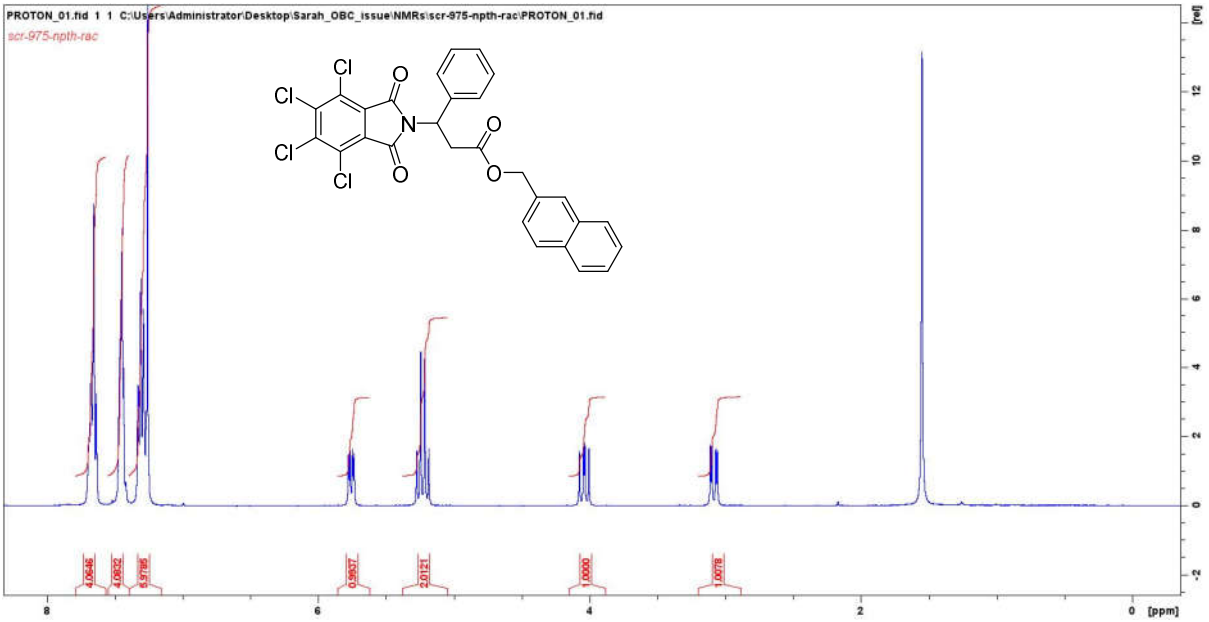


^{13}C NMR in $CDCl_3$

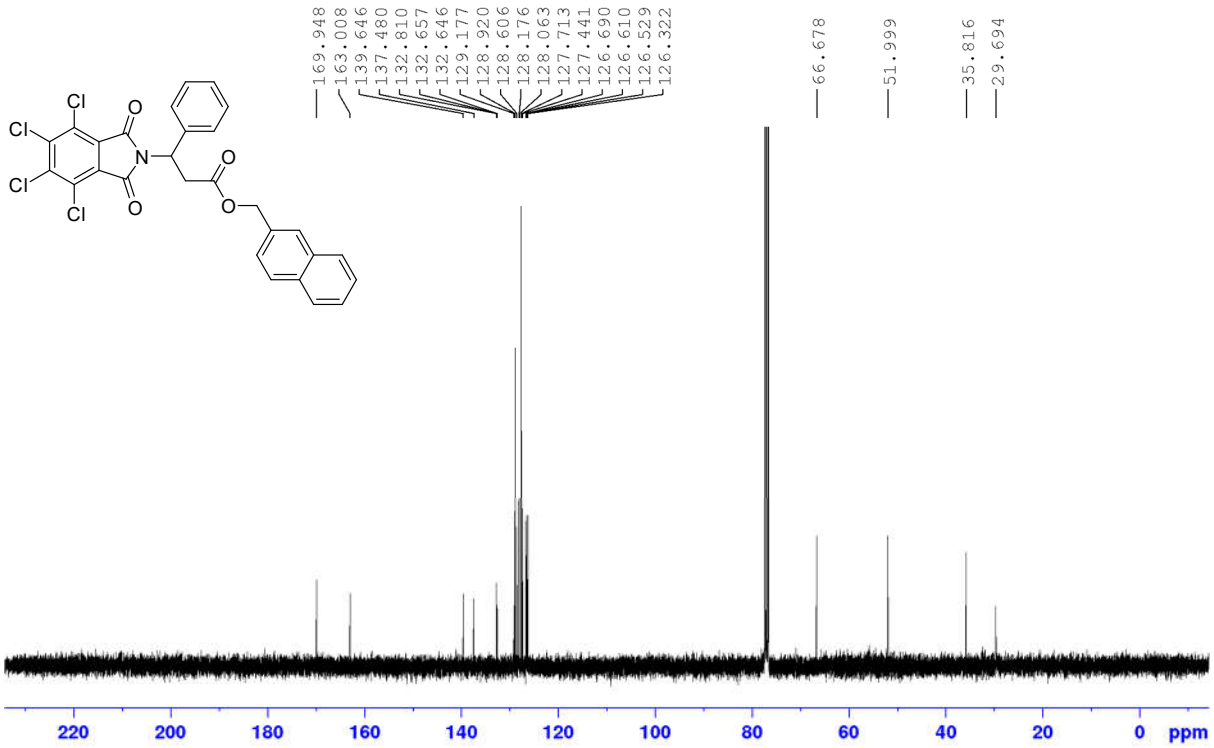


Naphthalen-2-ylmethyl-3-(*R*)-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (11)

^{1}H NMR in $CDCl_3$

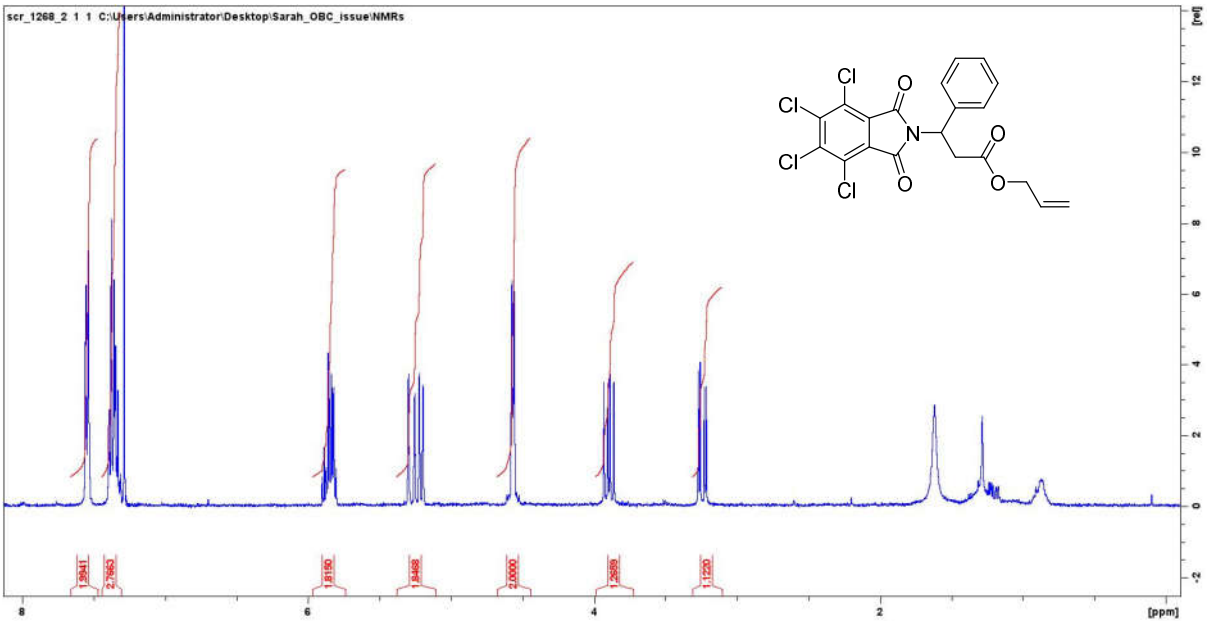


^{13}C NMR in $CDCl_3$

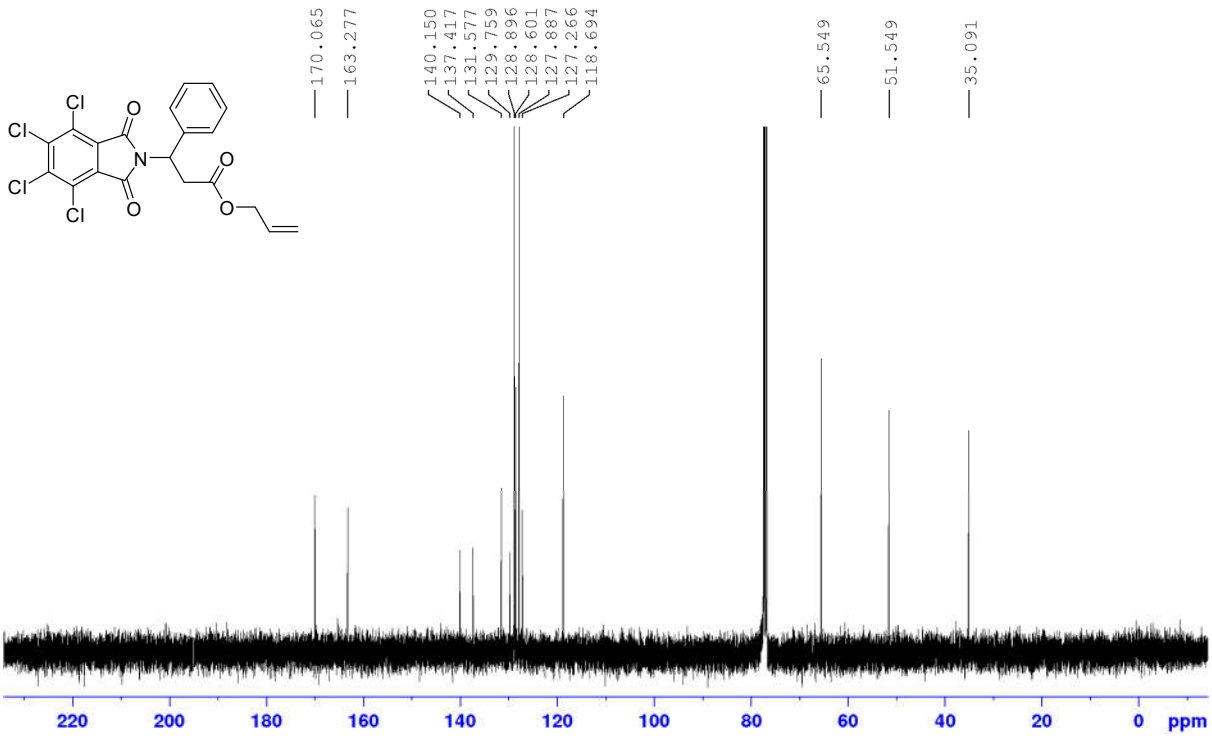


Allyl 3-(*S*)-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (33)

^{1}H NMR in $CDCl_3$

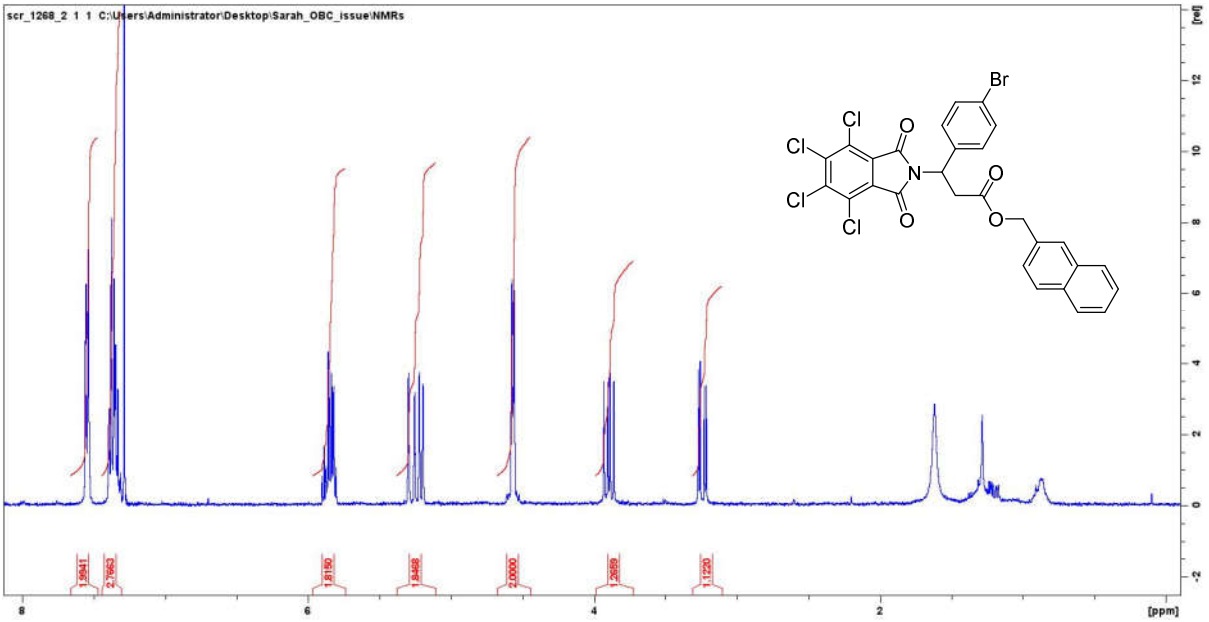


^{13}C NMR in $CDCl_3$

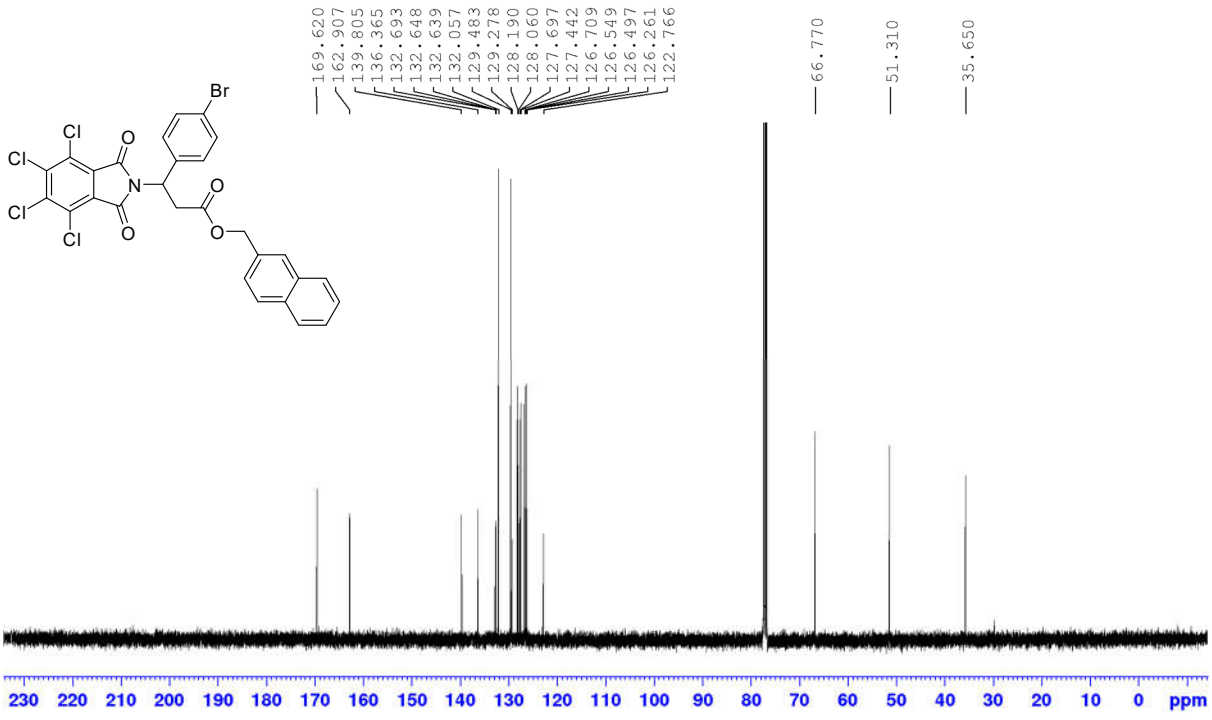


Naphthalen-2-ylmethyl 3-(*R*)-(4-bromophenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32a)

^{1}H NMR in $CDCl_3$

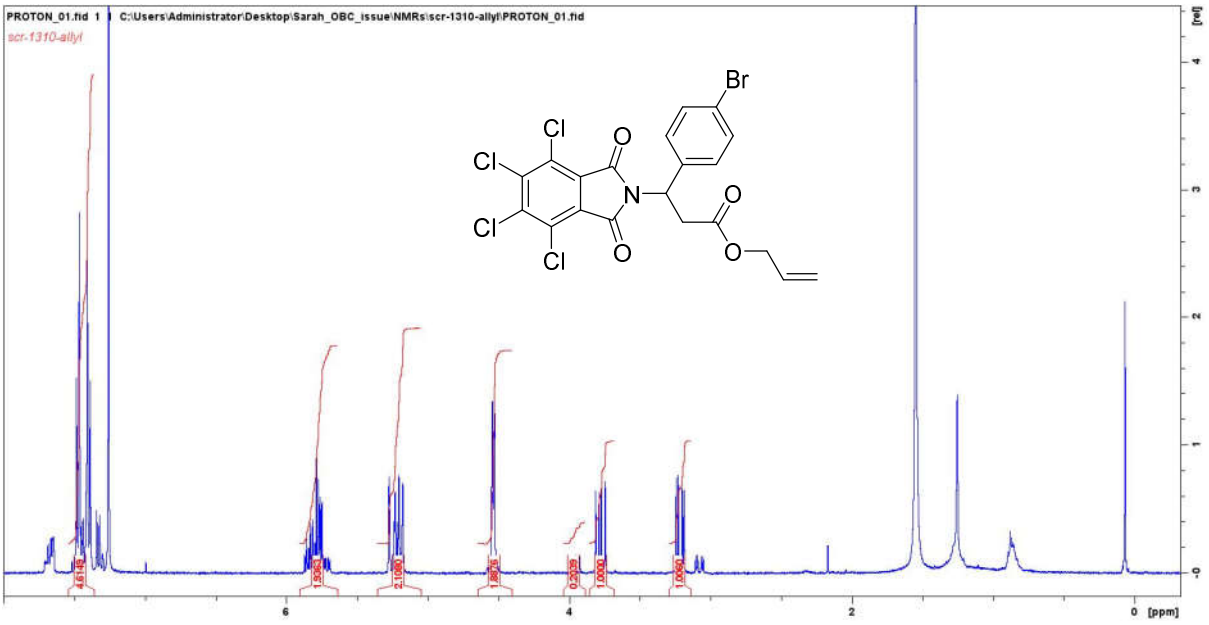


^{13}C NMR in $CDCl_3$

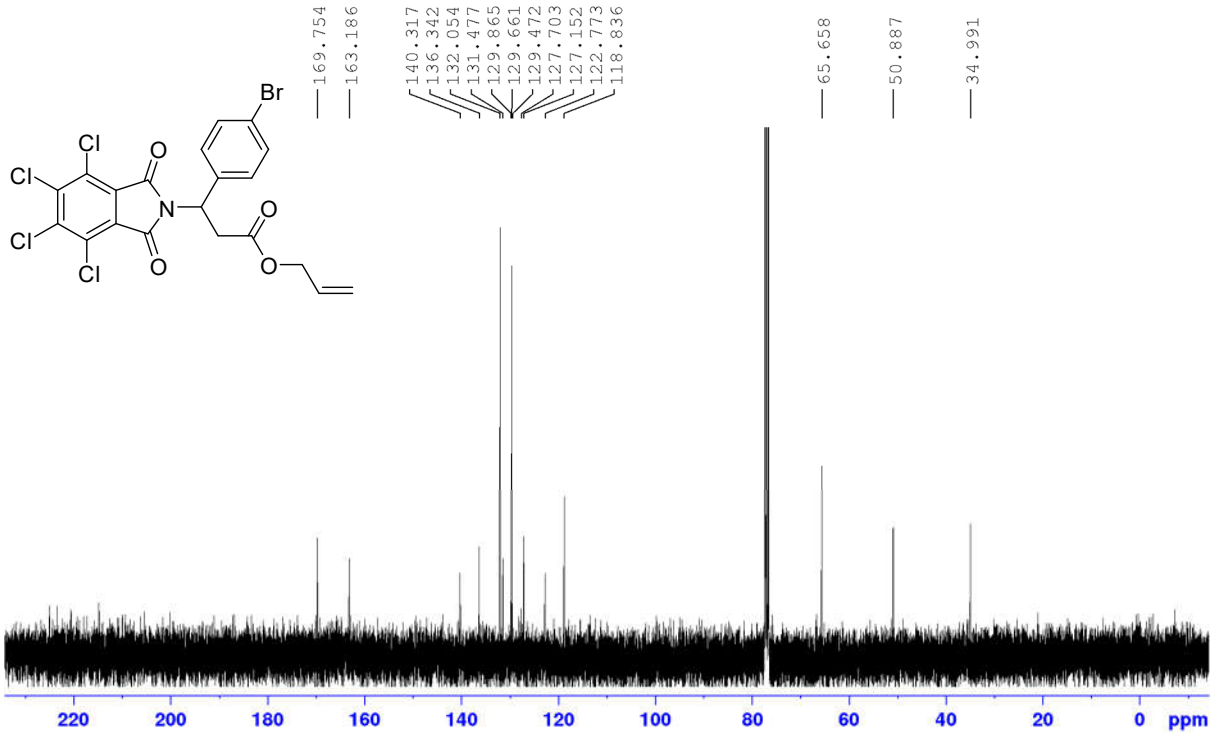


Allyl 3-(4-bromophenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34a)

^{1}H NMR in $CDCl_3$

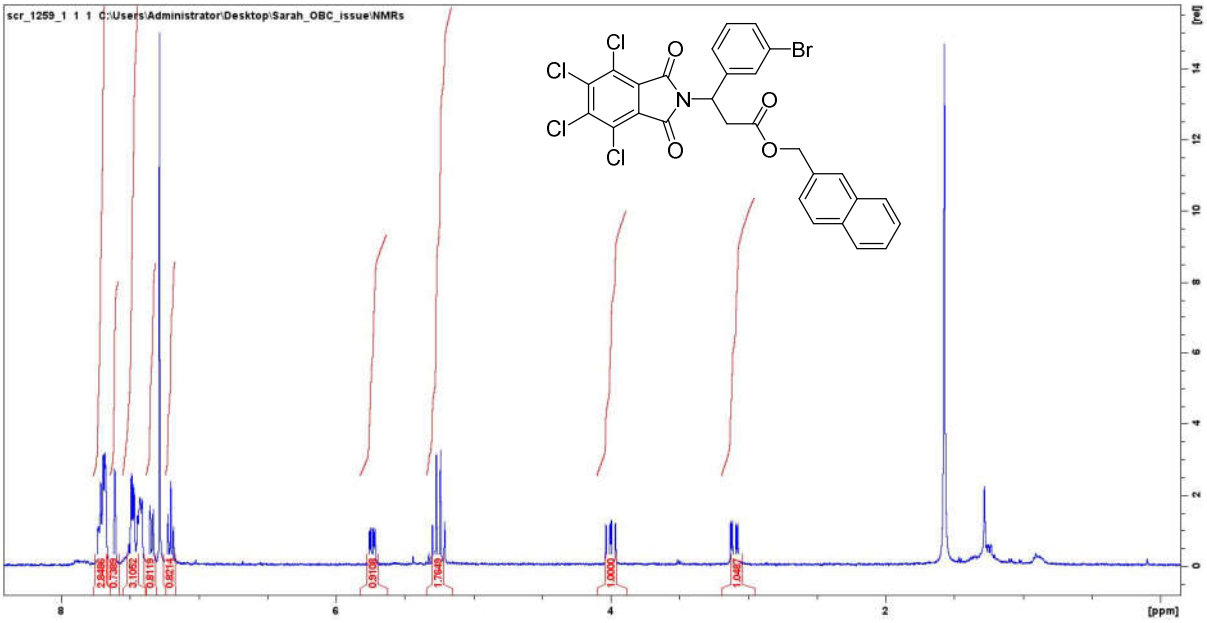


^{13}C NMR in $CDCl_3$

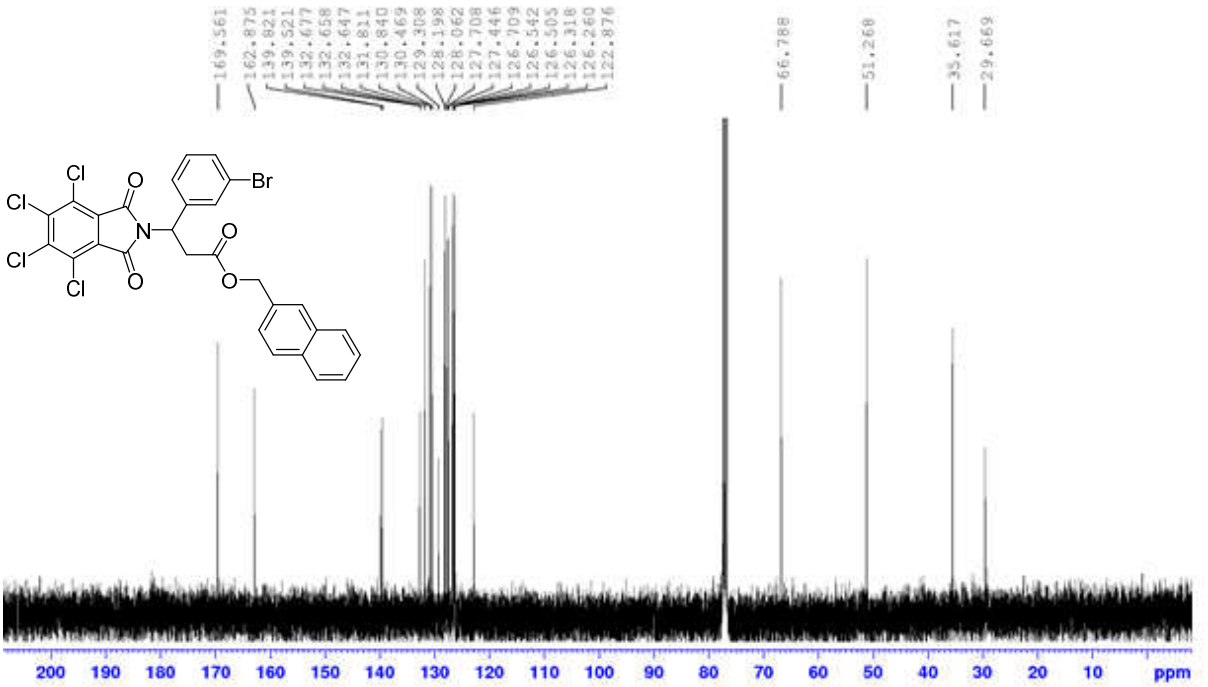


Naphthalen-2-ylmethyl-3-(*R*)-(3-bromophenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32b)

^{1}H NMR in $CDCl_3$

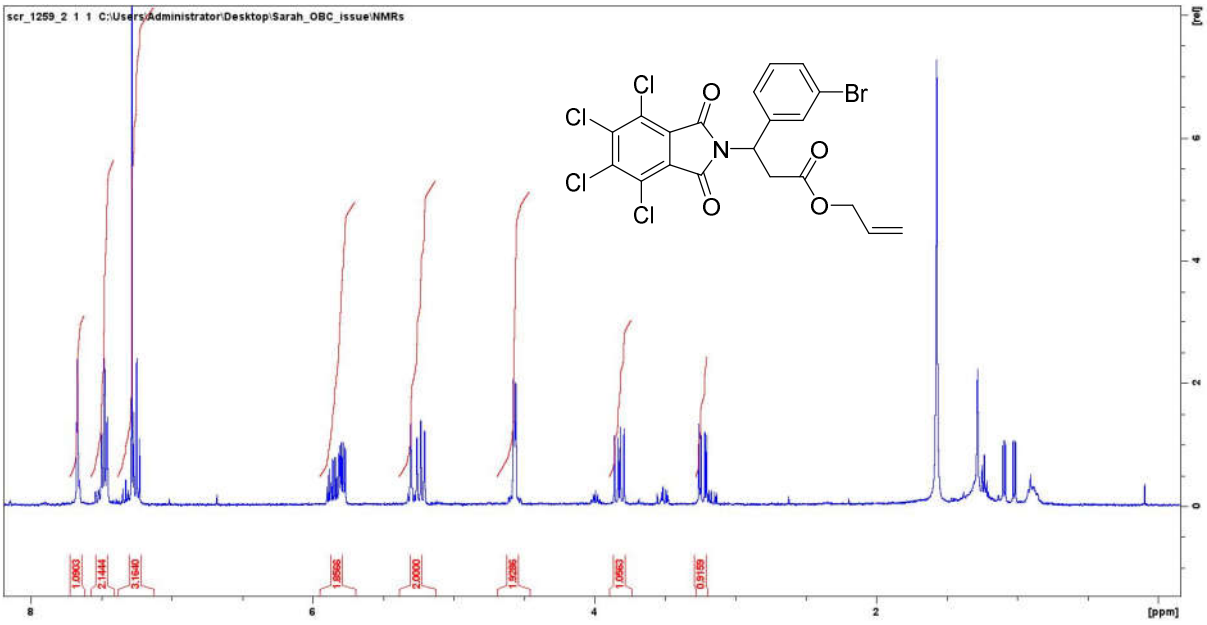


^{13}C NMR in $CDCl_3$



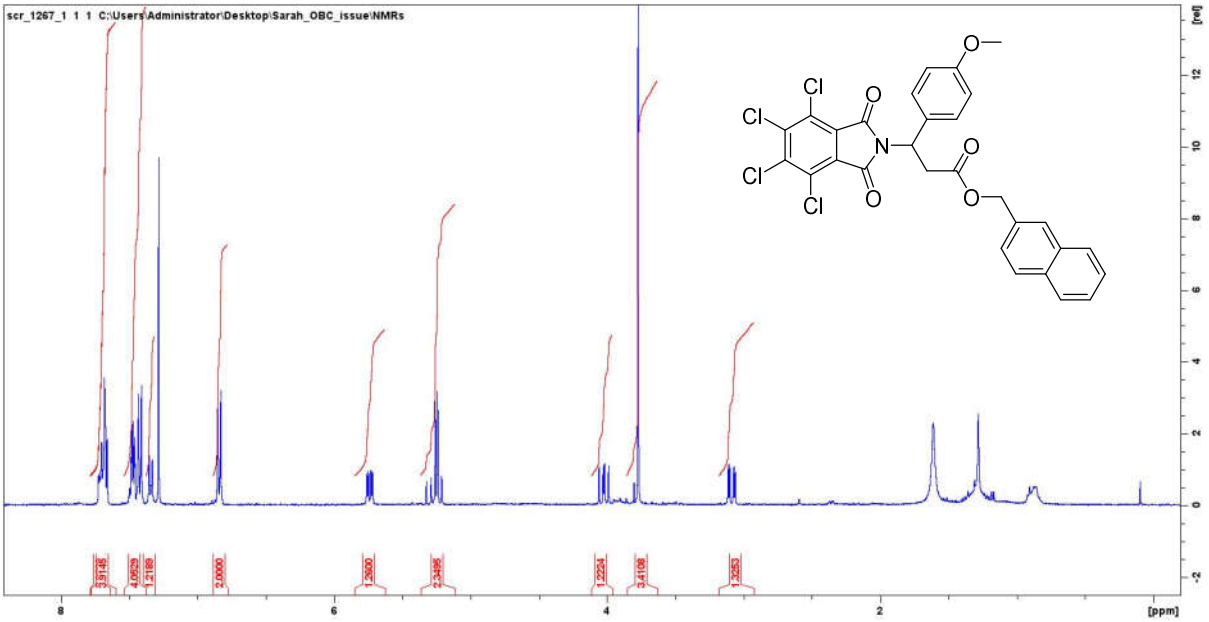
Allyl 3-(3-bromophenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34b)

^{1}H NMR in $CDCl_3$

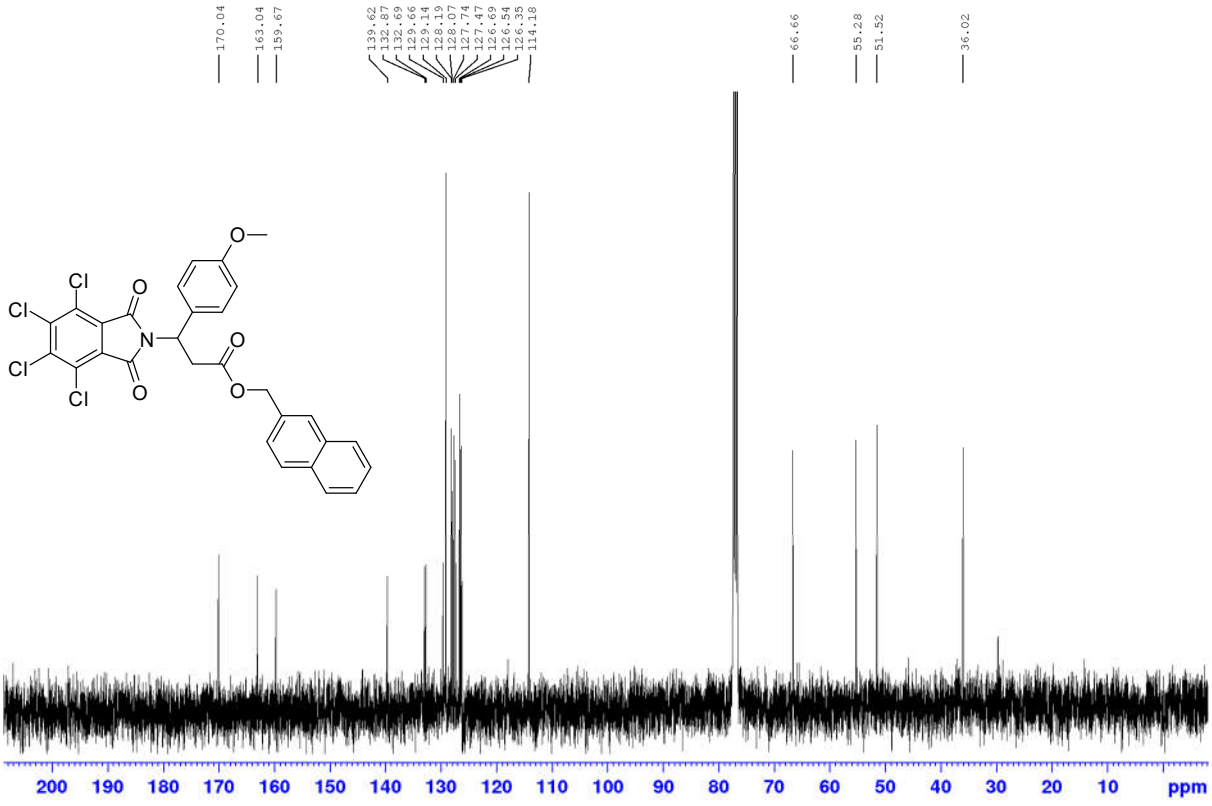


Naphthalen-2-ylmethyl-3-(*R*)-(4-methoxyphenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32c)

^{1}H NMR in $CDCl_3$

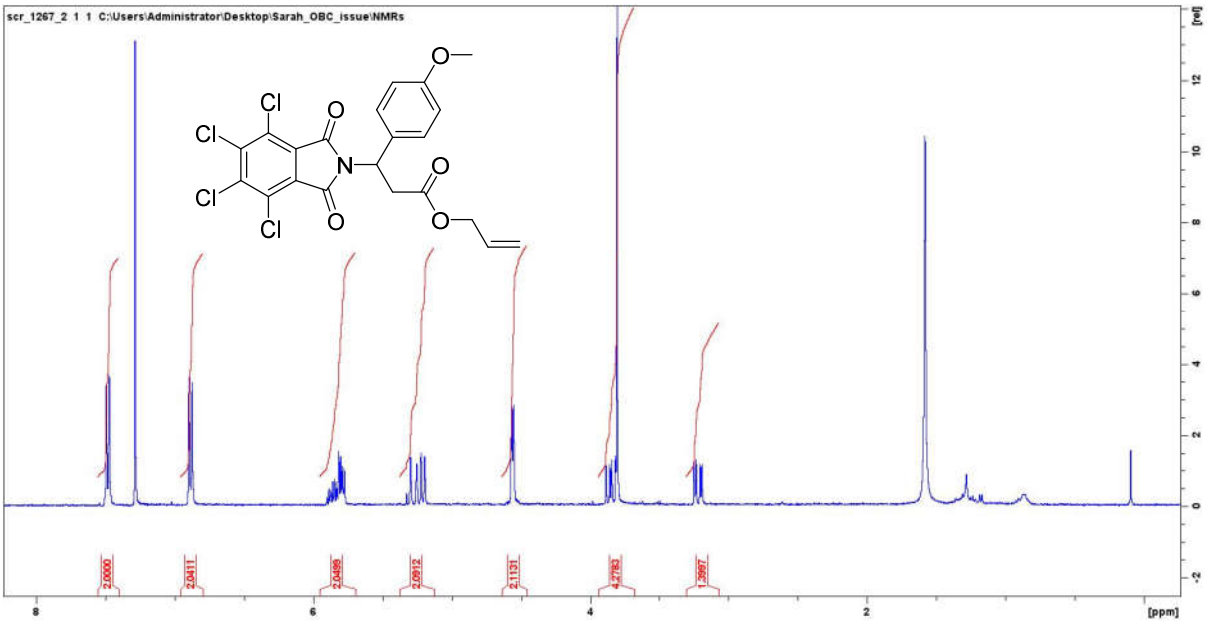


^{13}C NMR in $CDCl_3$

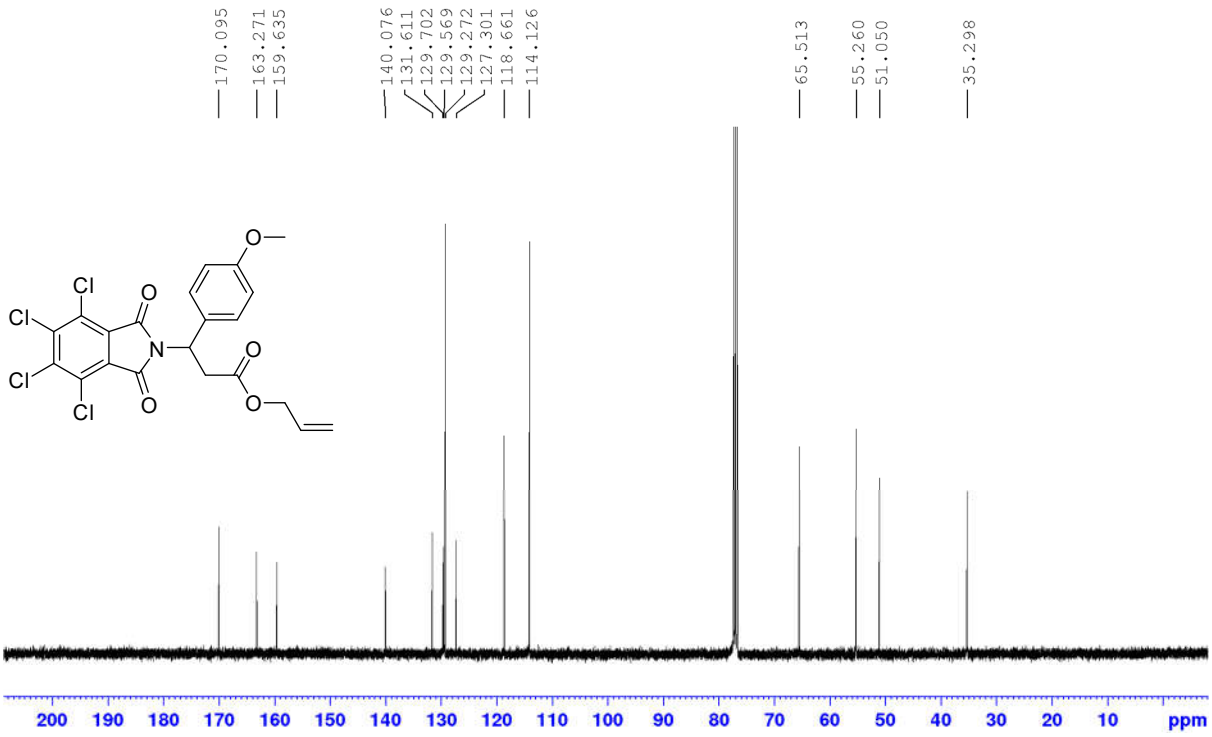


Allyl-3-(4-methoxyphenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34c)

^{1}H NMR in $CDCl_3$

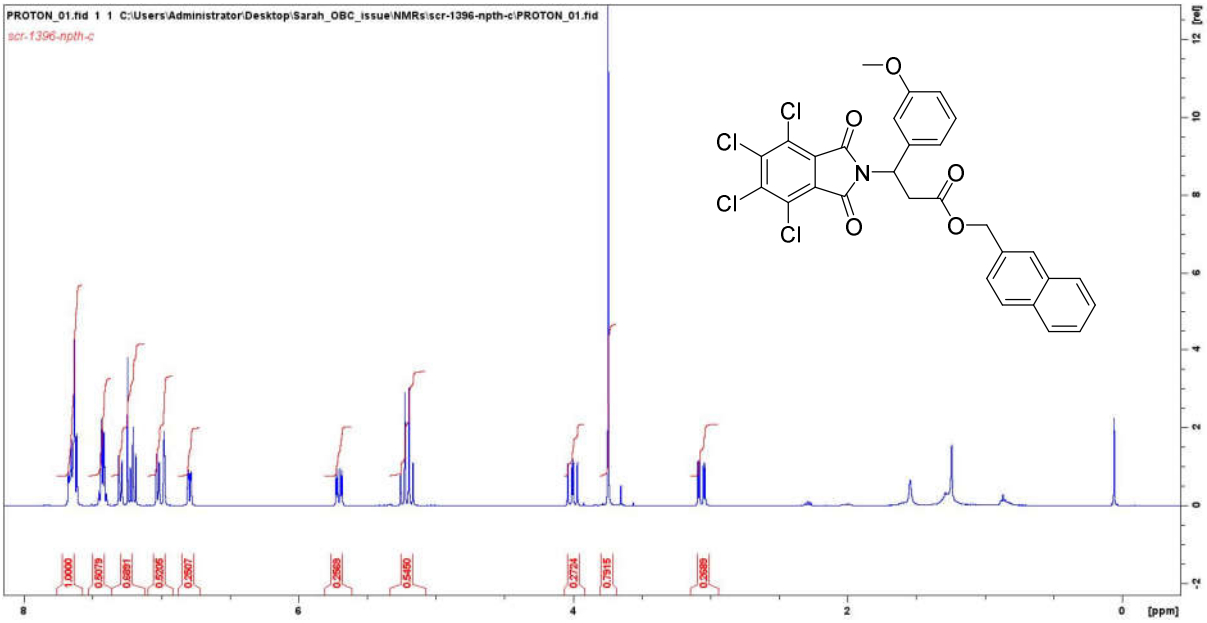


^{13}C NMR in $CDCl_3$

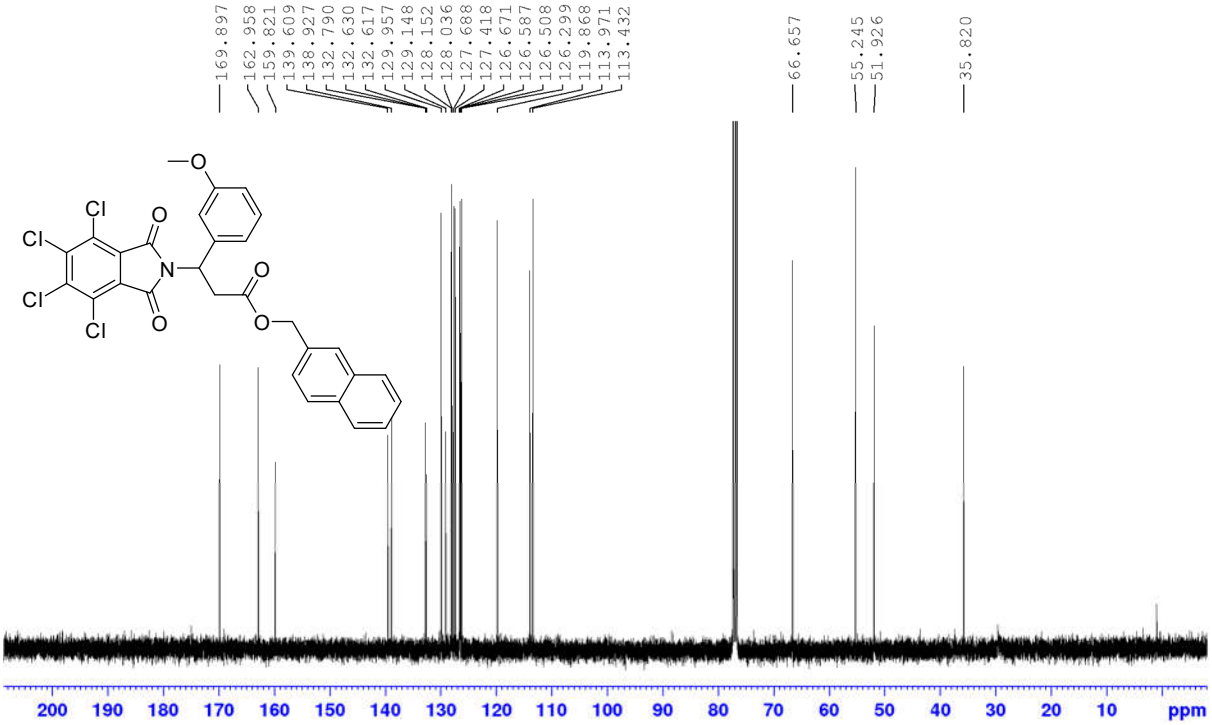


Naphthalen-2-ylmethyl-3-(*R*)-(3-methoxyphenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (32d)

^{1}H NMR in $CDCl_3$

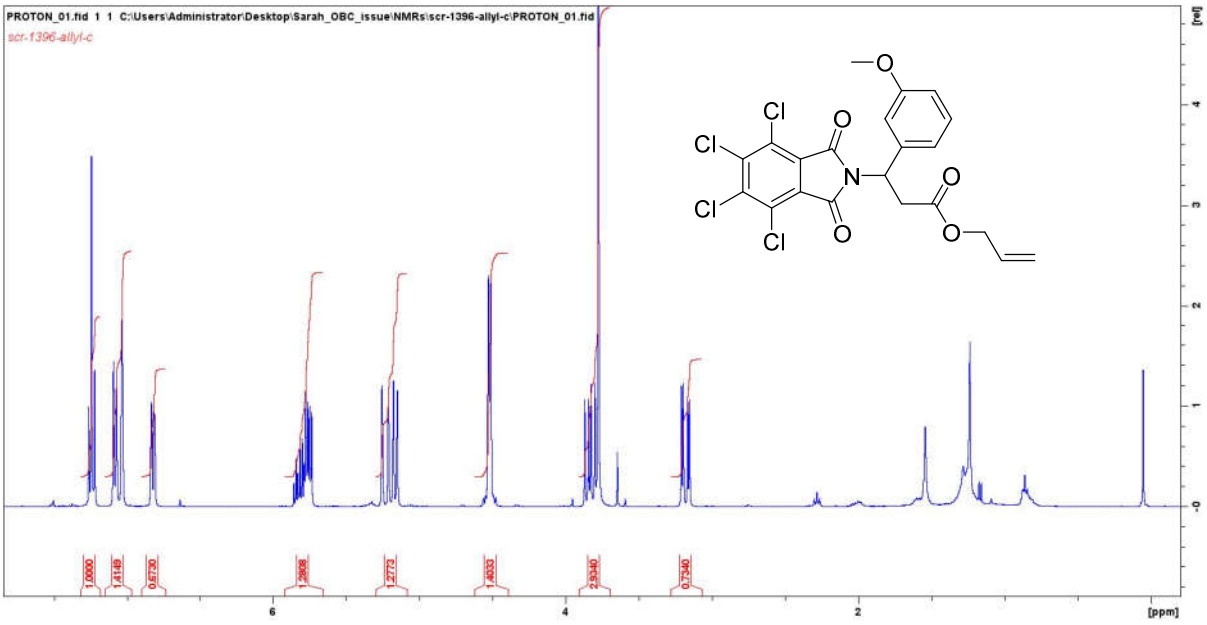


^{13}C NMR in $CDCl_3$

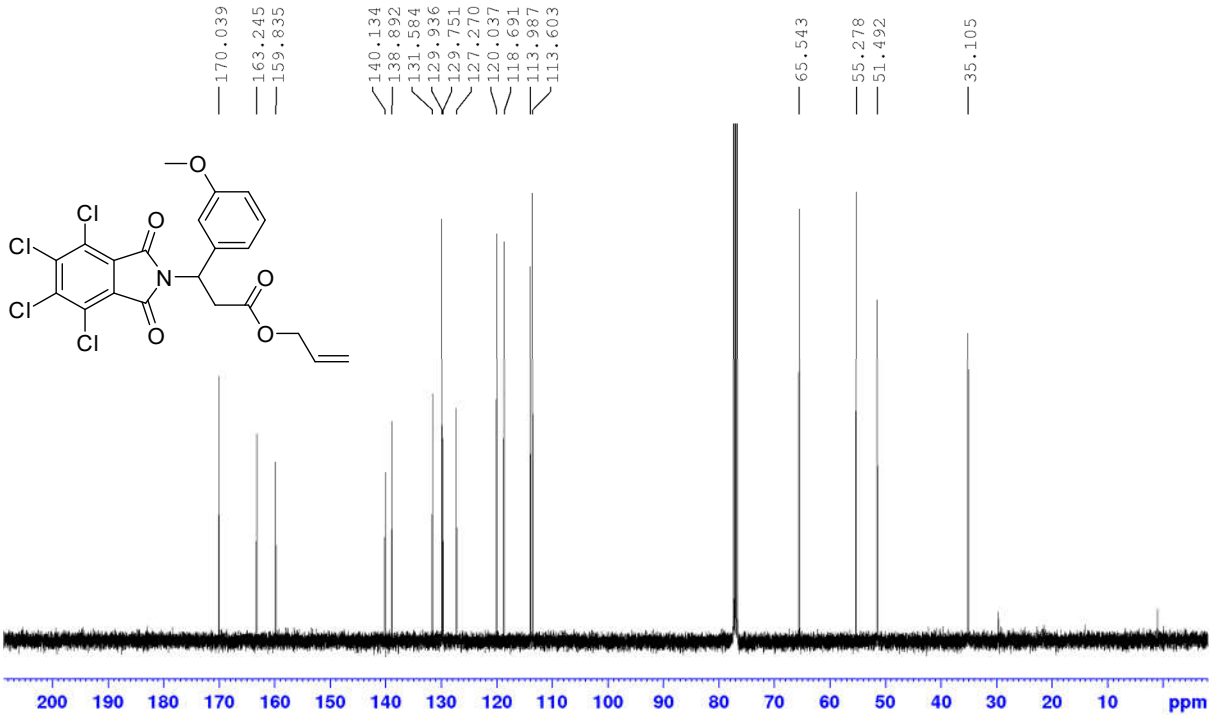


Allyl-3-(3-methoxyphenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (34d)

^{1}H NMR in $CDCl_3$

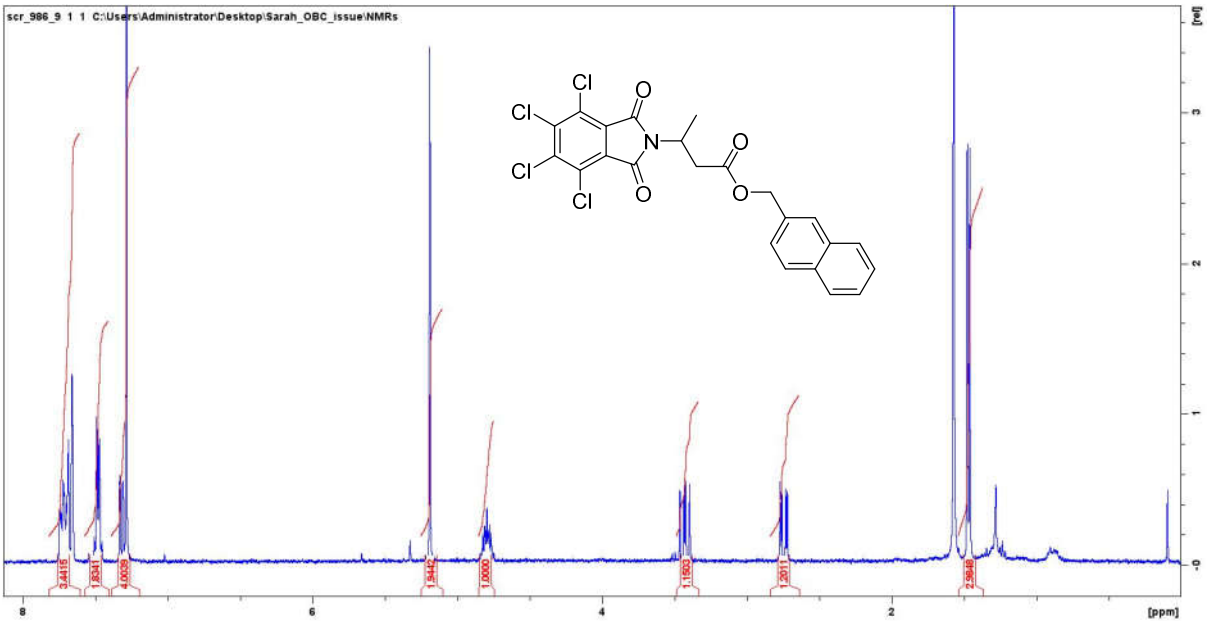


^{13}C NMR in $CDCl_3$

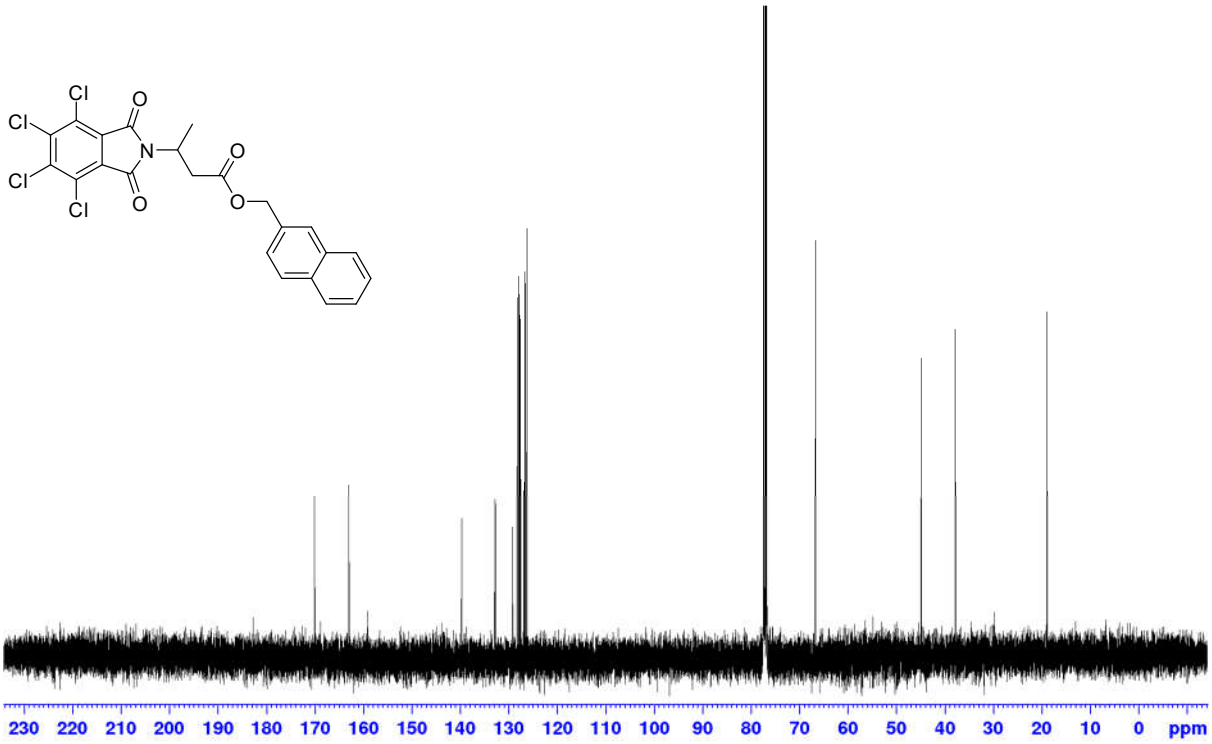


Naphthalen-2-ylmethyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)butanoate (32e)

^{1}H NMR in $CDCl_3$

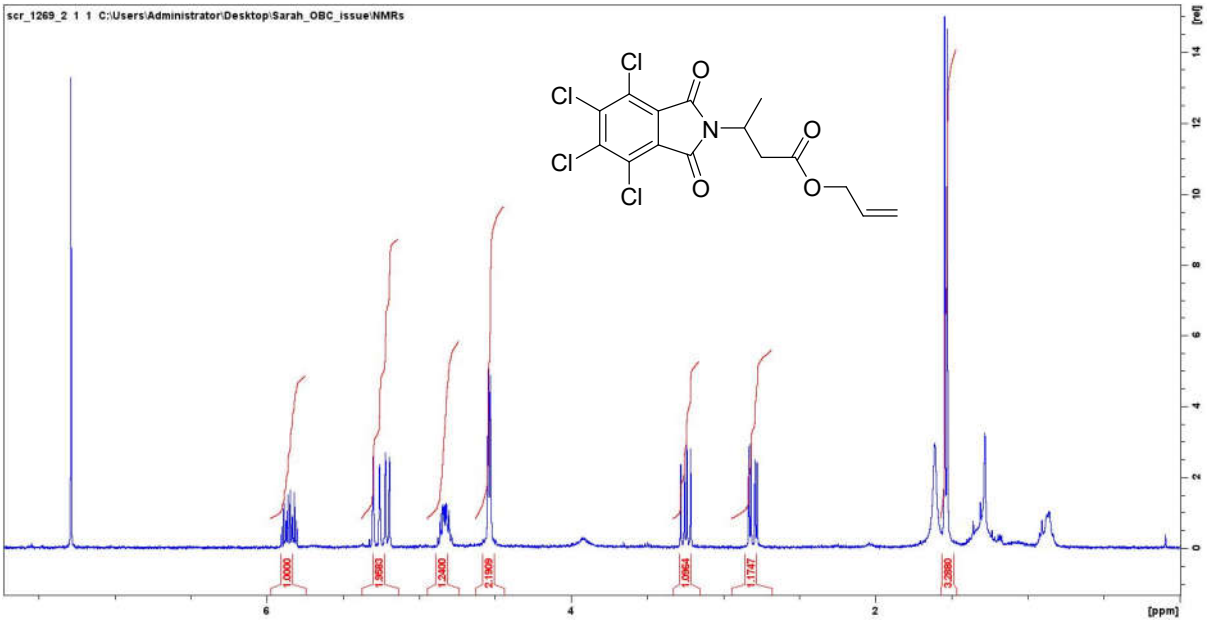


^{13}C NMR in $CDCl_3$

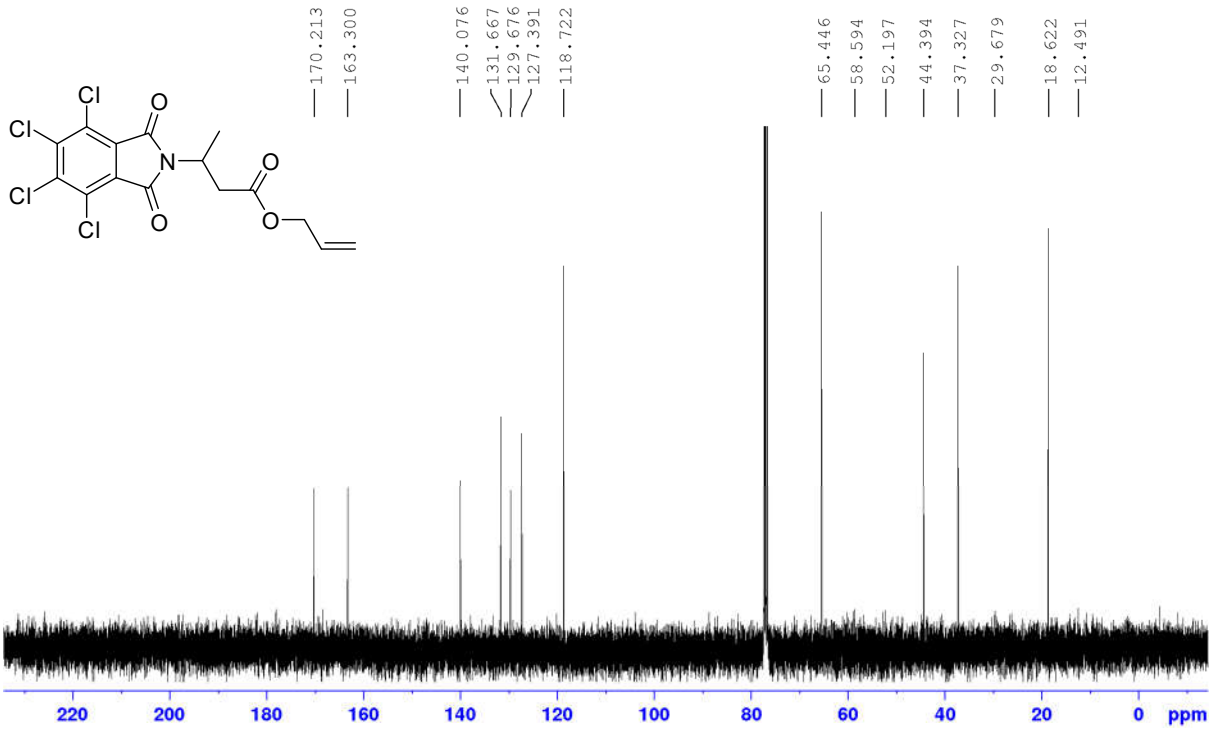


Allyl 3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)butanoate (34e)

^{1}H NMR in $CDCl_3$

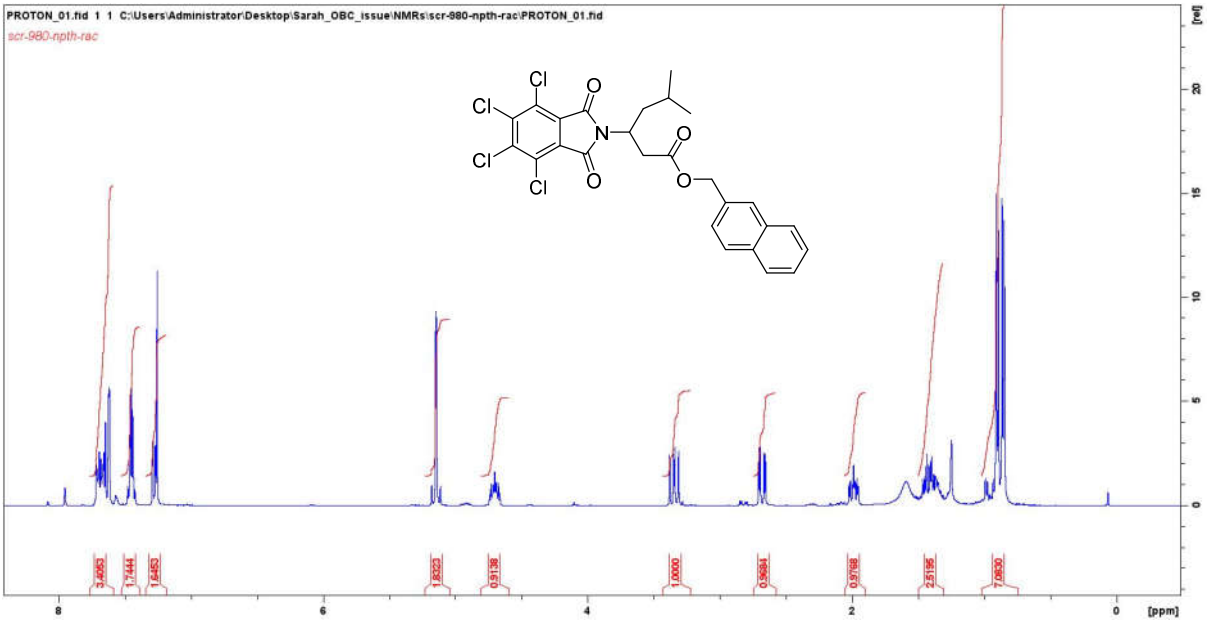


^{13}C NMR in $CDCl_3$

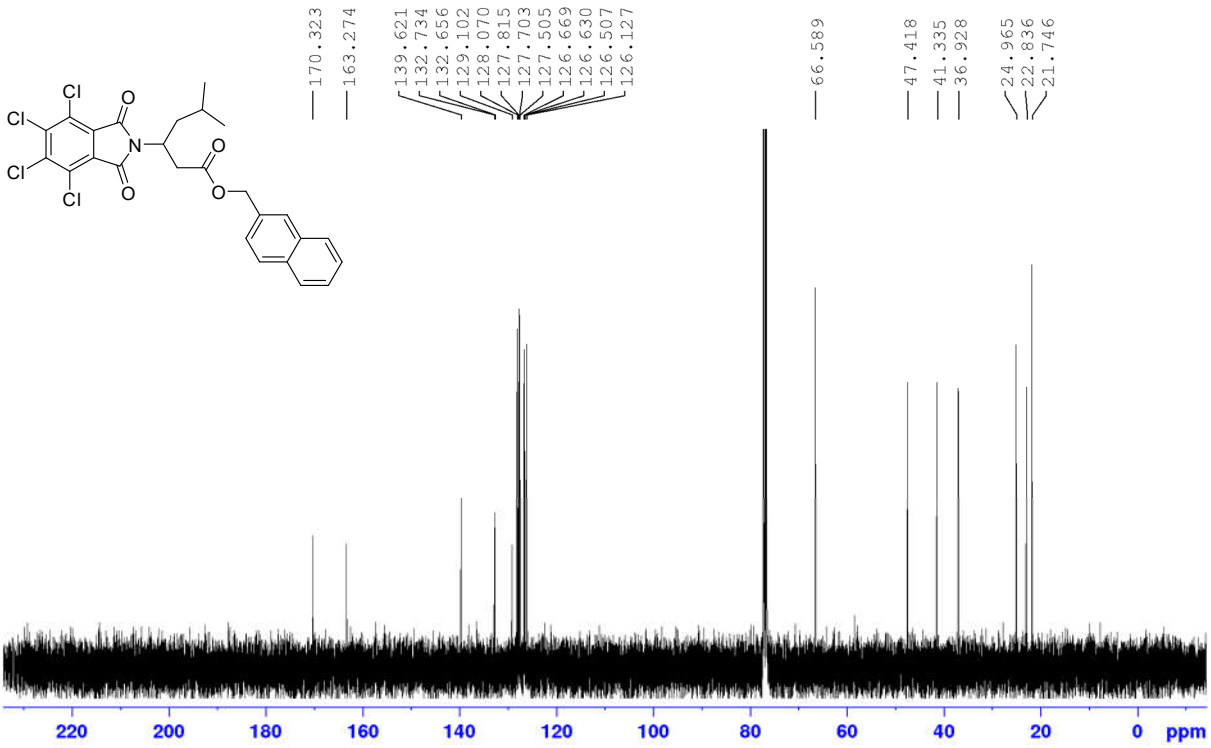


Naphthalen-2-ylmethyl-5-methyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)hexanoate (32f)

^{1}H NMR in $CDCl_3$

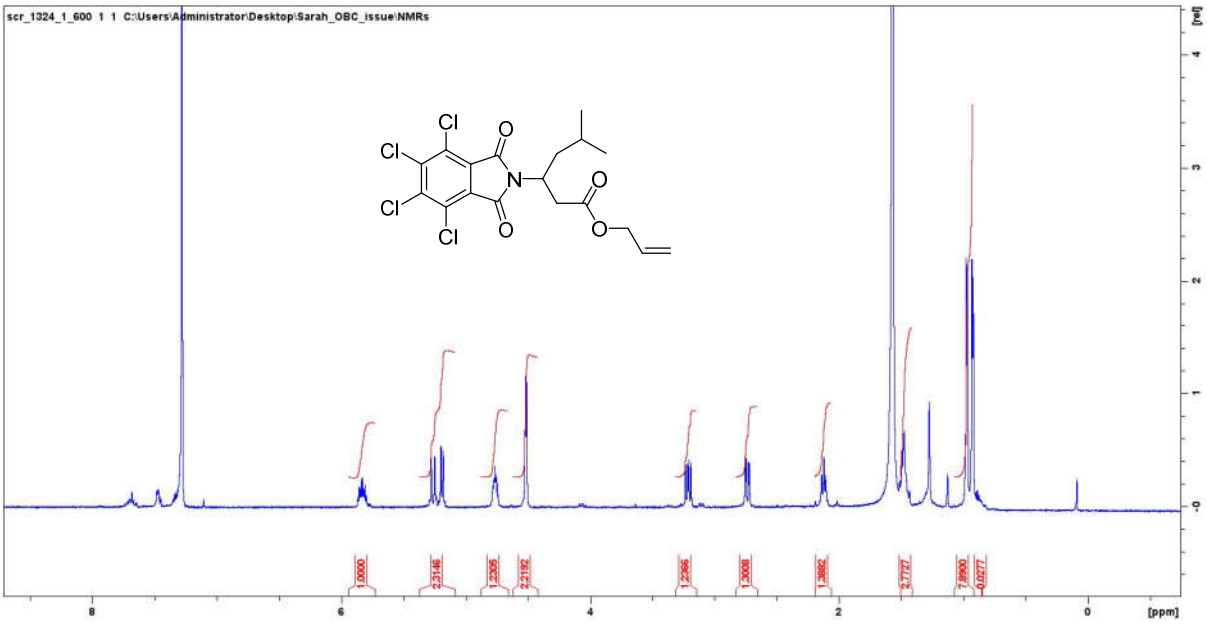


^{13}C NMR in $CDCl_3$

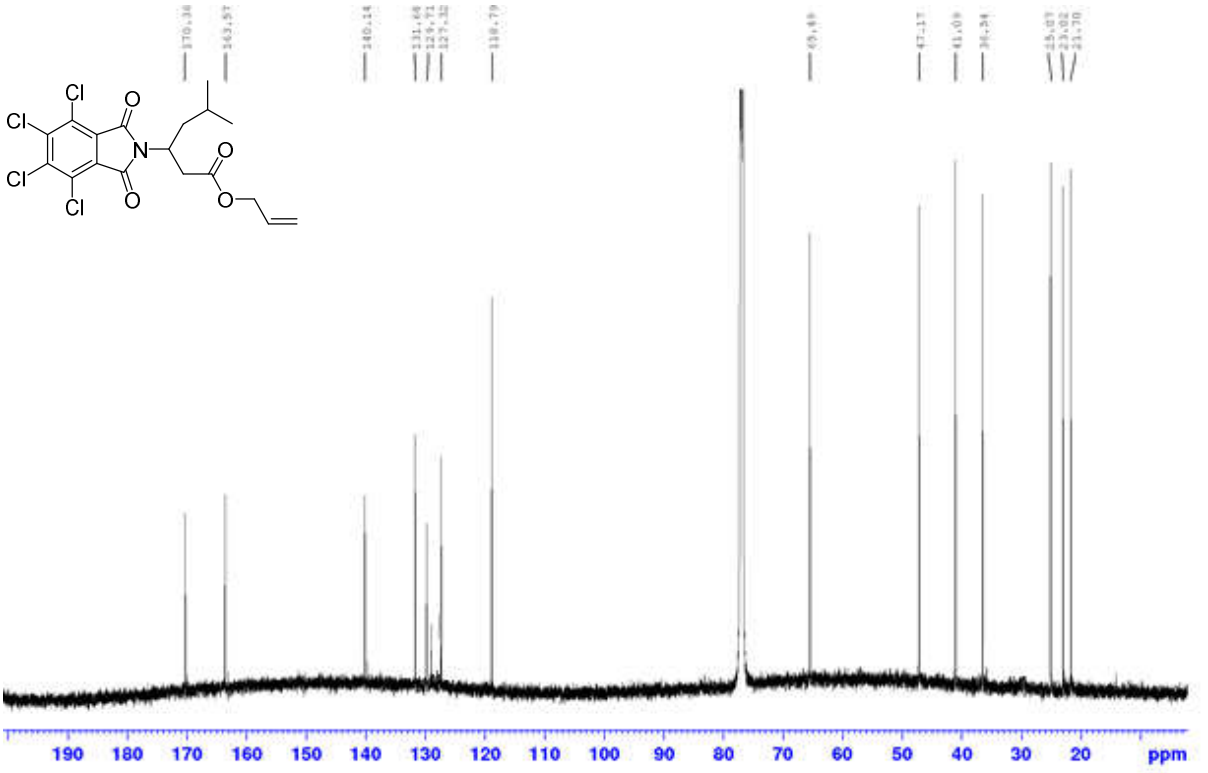


Allyl 5-methyl-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxo*iso*indolin-2-yl)hexanoate (34f)

^{1}H NMR in $CDCl_3$

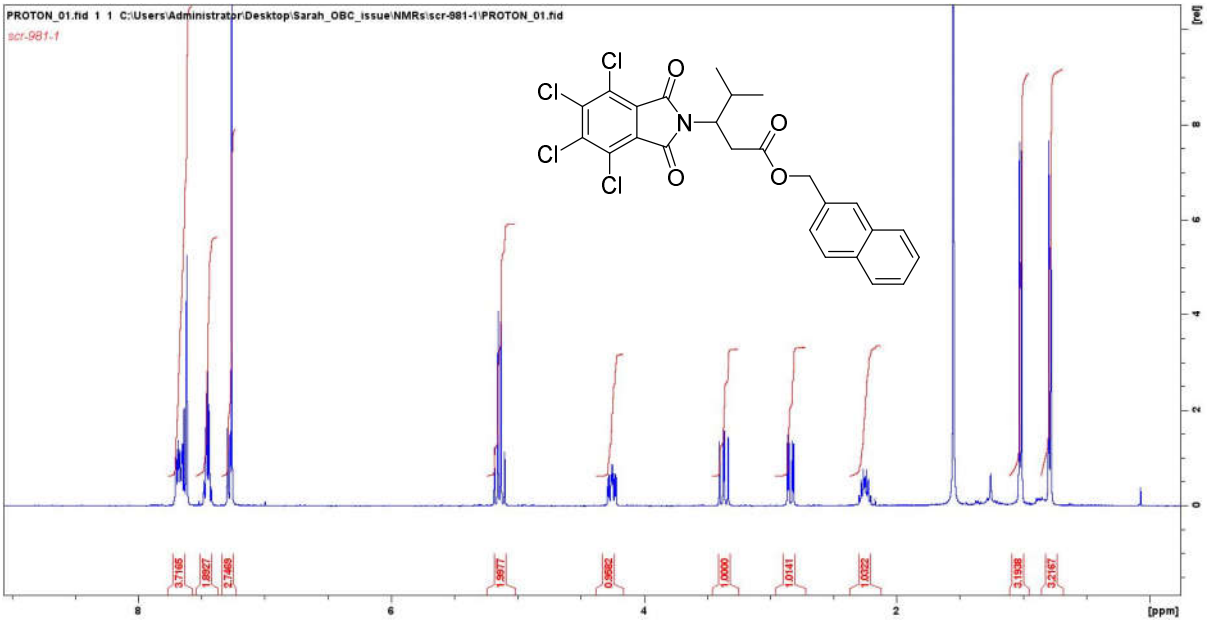


^{13}C NMR in $CDCl_3$

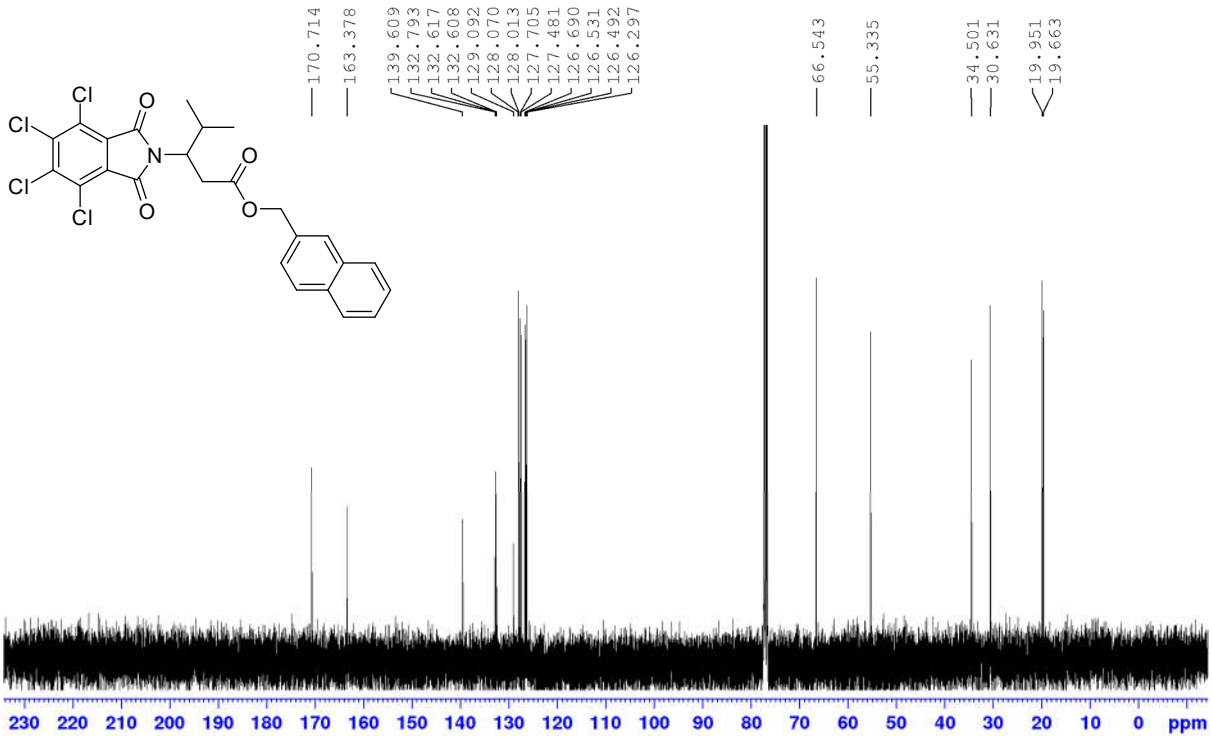


Naphthalen-2-ylmethyl-4-methyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentanoate (32g)

^{1}H NMR in $CDCl_3$

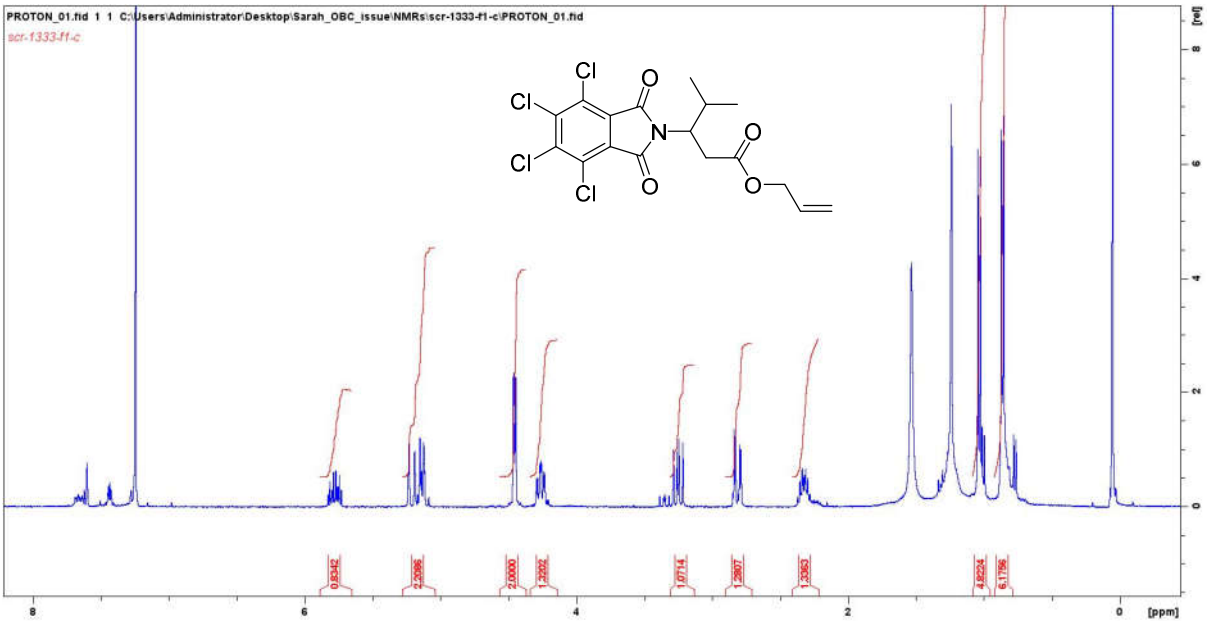


^{13}C NMR in $CDCl_3$

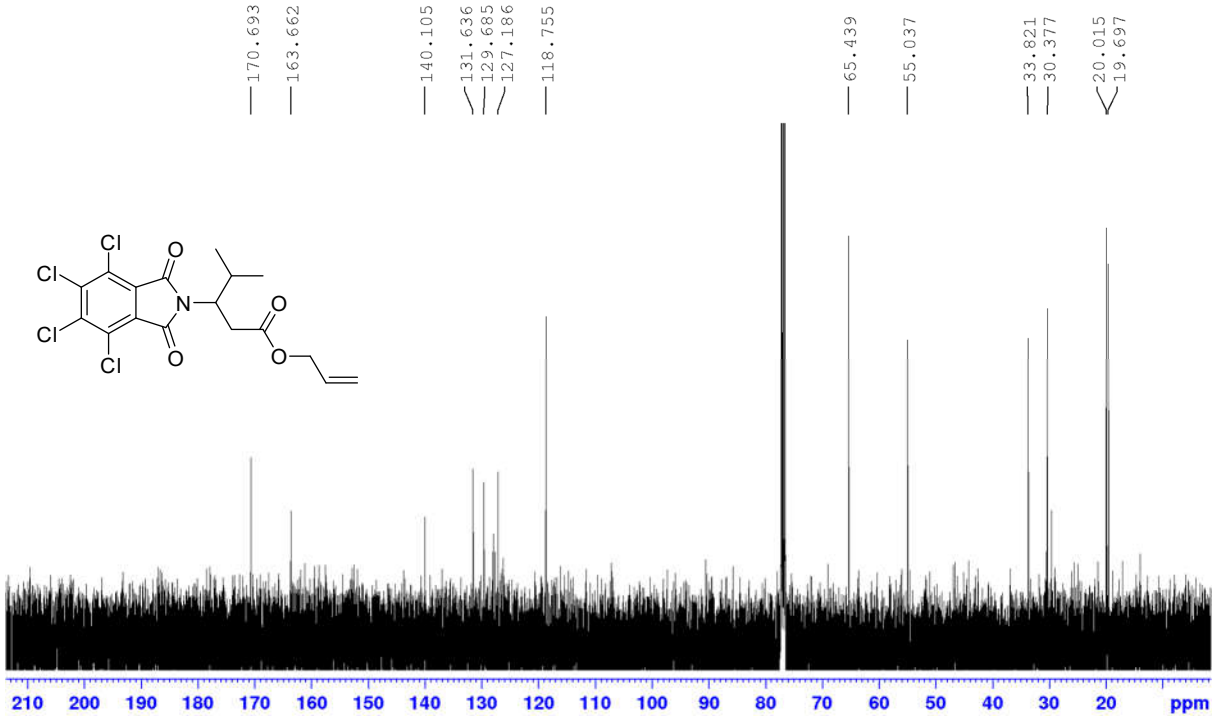


Allyl 4-methyl-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)pentanoate (34g)

^{1}H NMR in $CDCl_3$

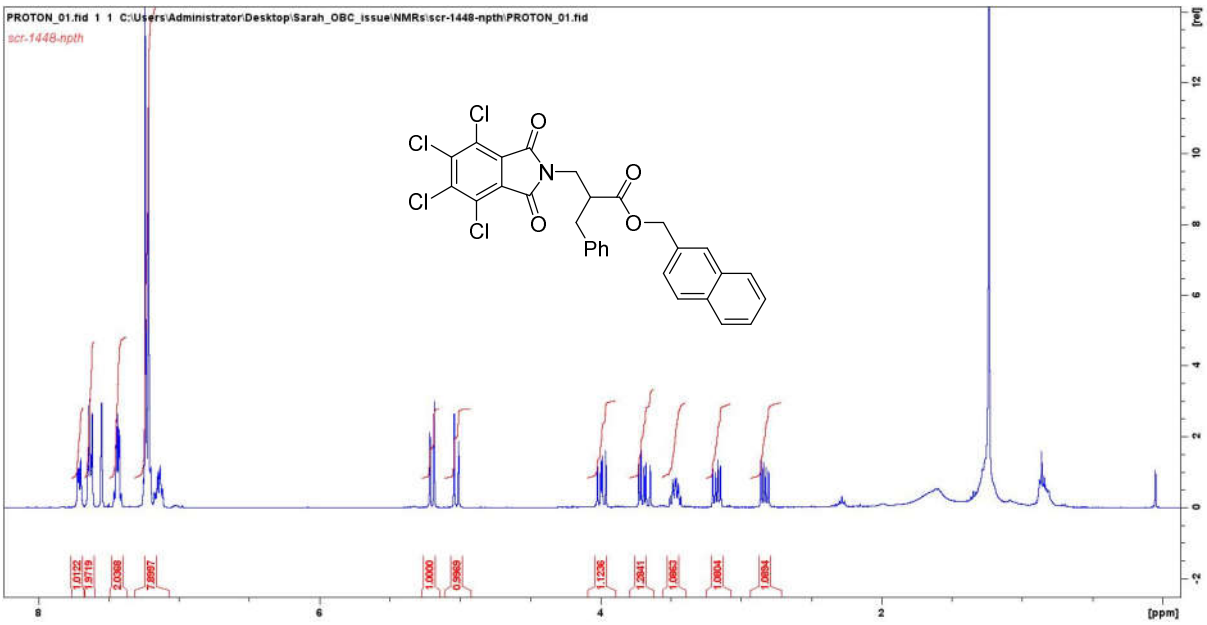


^{13}C NMR in $CDCl_3$

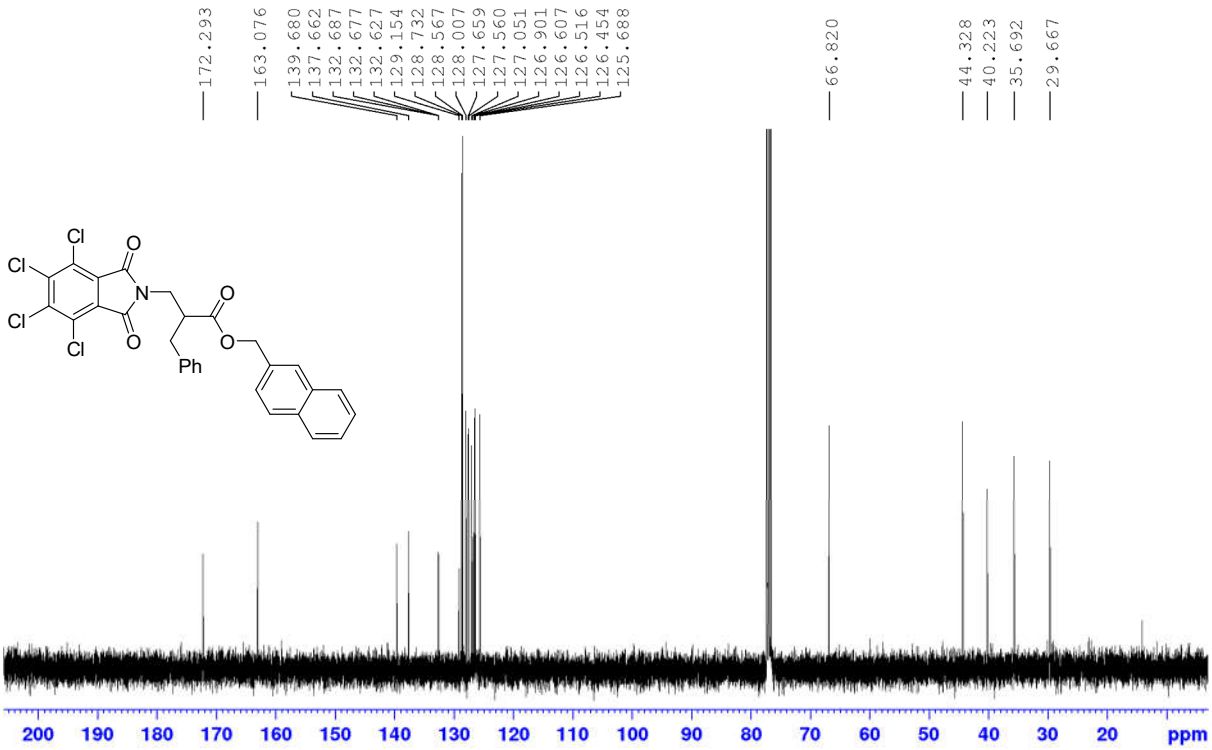


Naphthalen-2-ylmethyl-(*R*)-2-benzyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (36)

^{1}H NMR in $CDCl_3$

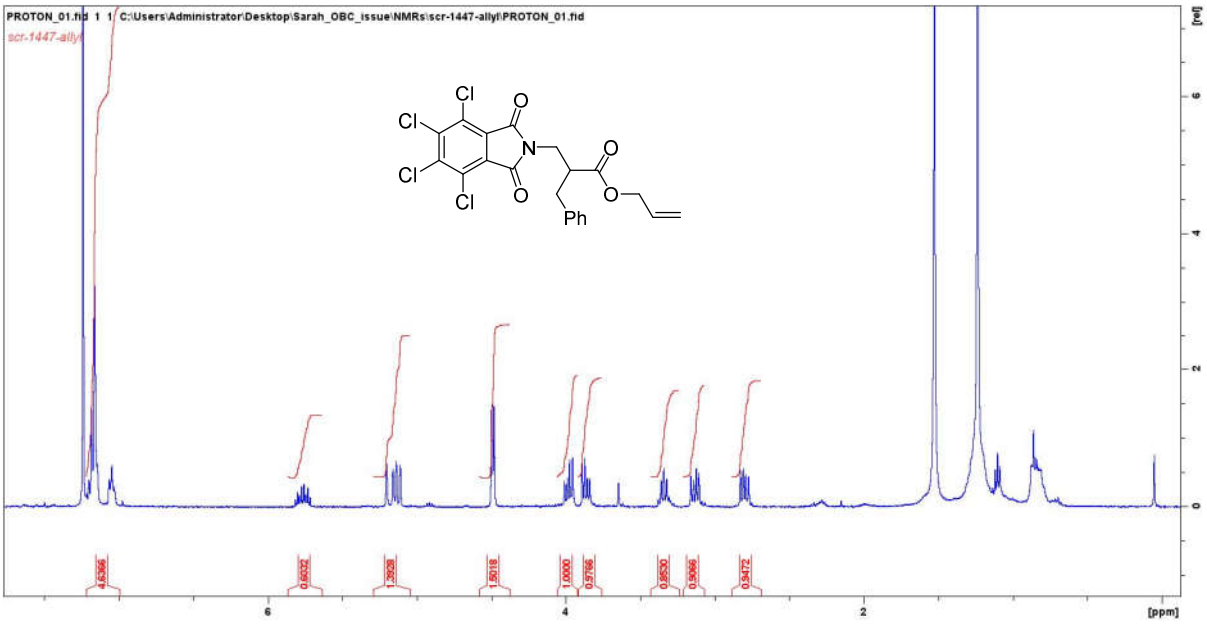


^{13}C NMR in $CDCl_3$

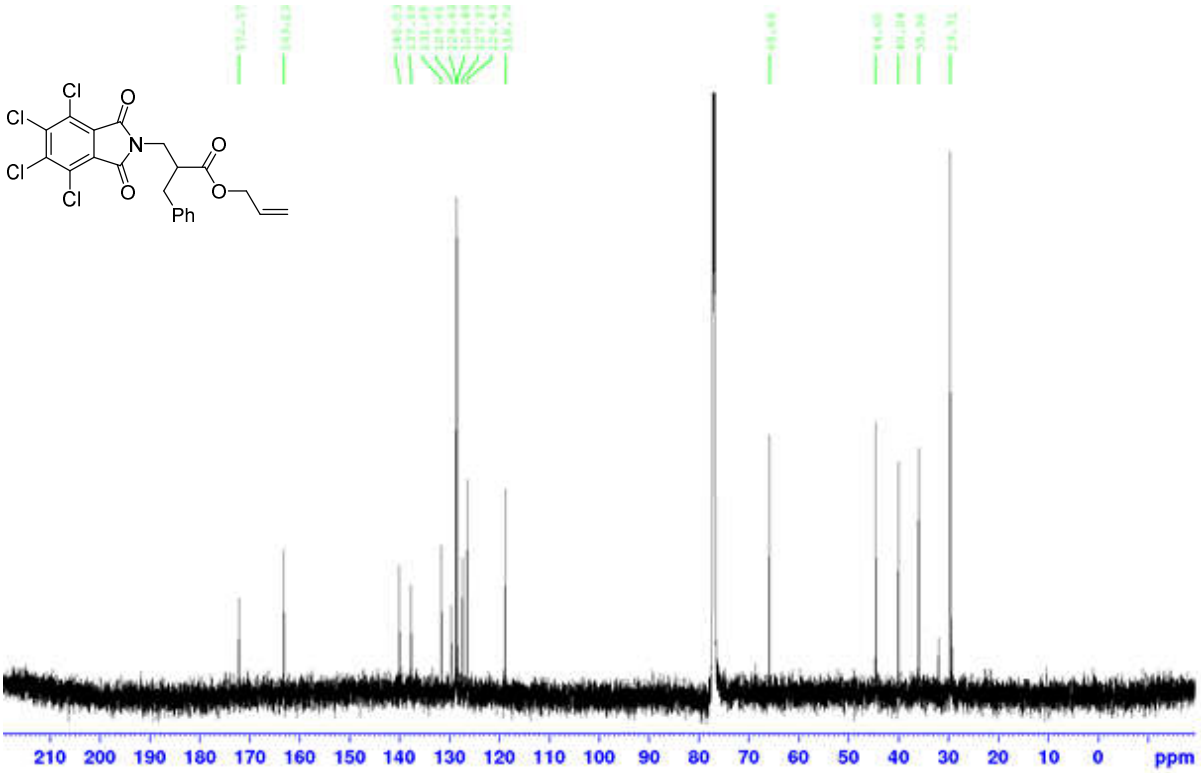


Allyl (*S*)-2-benzyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)propanoate (37)

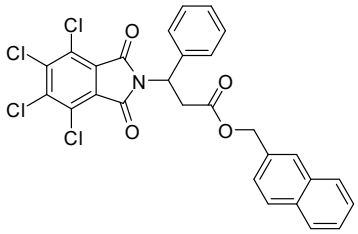
^{1}H NMR in $CDCl_3$



^{13}C NMR in $CDCl_3$

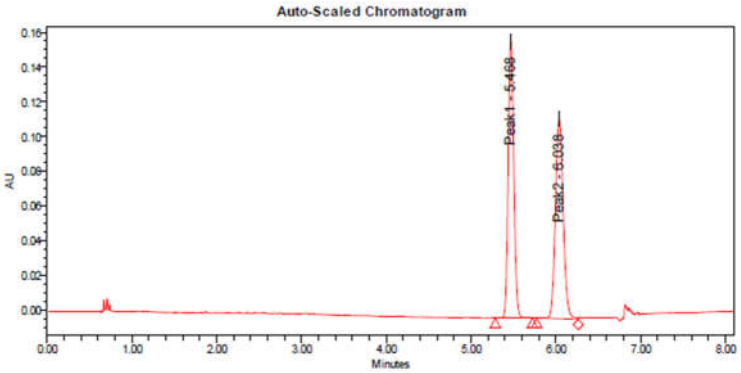


Compound **11**



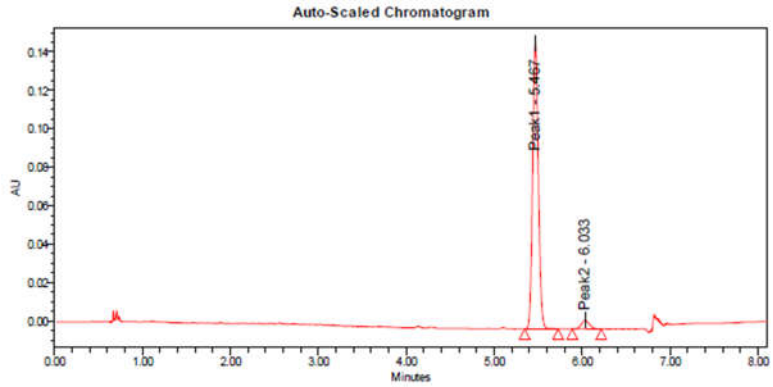
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in Table 1.2.1, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



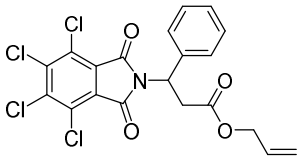
No.	Ret. Time	Rel. Area
	min	%
1	5.47	50.0
2	6.04	50.0
Total:		100

Chiral: 94% *ee*



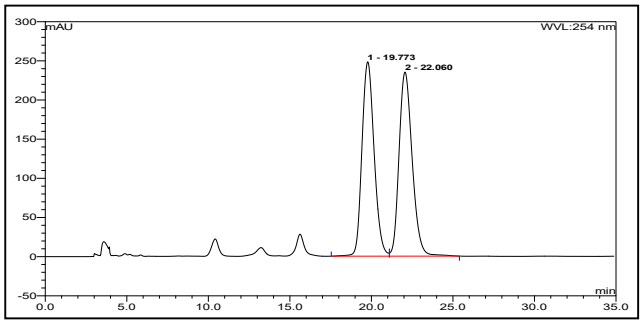
No.	Ret. Time	Rel. Area
	min	%
1	5.47	97.0
2	6.03	3.0
Total:		100

Compound **33:**



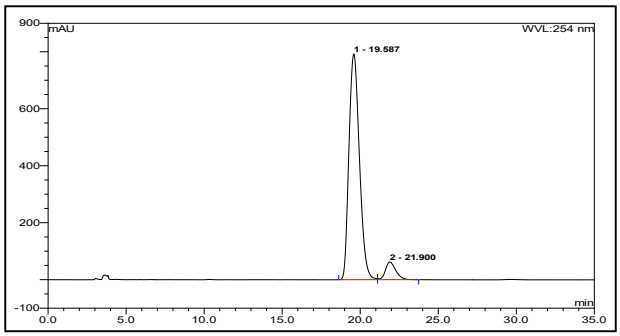
CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1}, rt, UV detection at 220 nm.

Racemic:



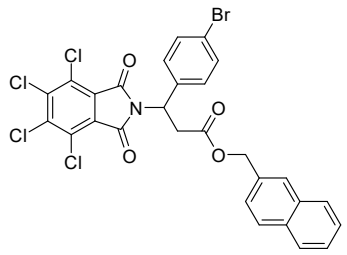
No.	Ret. Time	Rel. Area
	min	%
1	19.77	50.0
2	22.06	50.0
Total:		100

Chiral: 86% *ee*



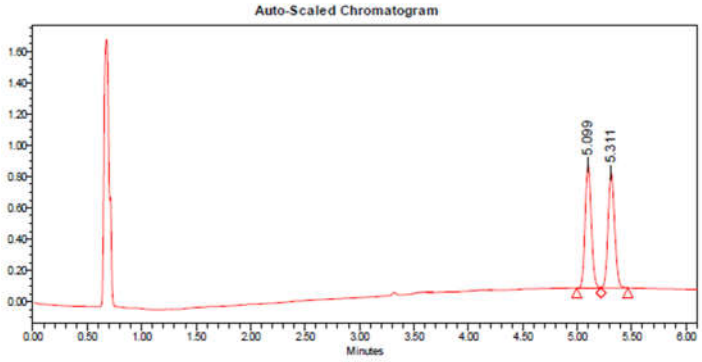
No.	Ret. Time	Rel. Area
	min	%
1	19.59	92.8
2	21.9	7.2
Total:		100

Compound **32a:**



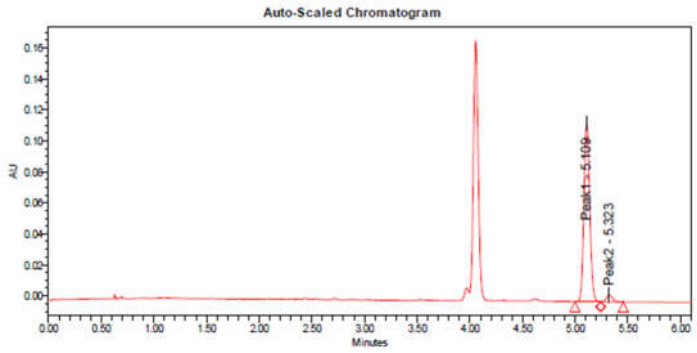
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in Table 1.2.1, column temperature : 30 °C, UV detection at 254 nm.

Racemic



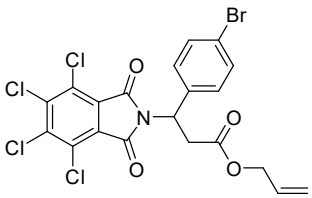
No.	Ret. Time	Rel. Area
	min	%
1	5.10	51.2
2	5.31	48.8
Total:		100

Chiral: 94% *ee*



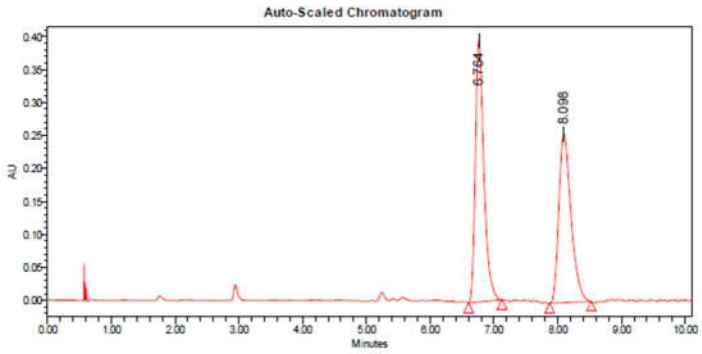
No.	Ret. Time	Rel. Area
	min	%
1	5.10	96.9
2	5.32	3.1
Total:		100

Compound **34a**:



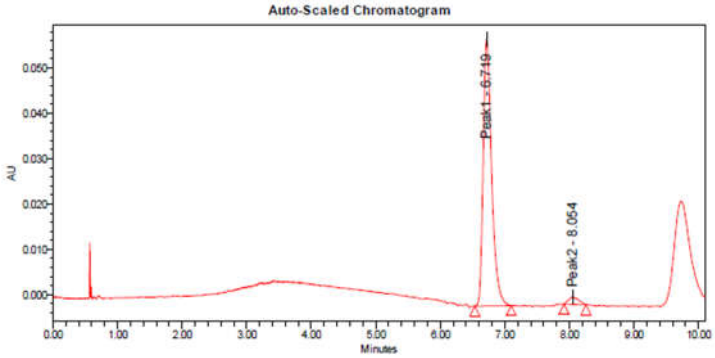
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:IPA (1:1, *v:v*) gradient as shown in Table 1.2.1, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



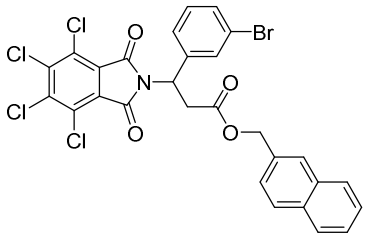
No.	Ret. Time	Rel. Area
	min	%
1	6.76	51.2
2	8.10	48.8
Total:		100

Chiral: 91% *ee*



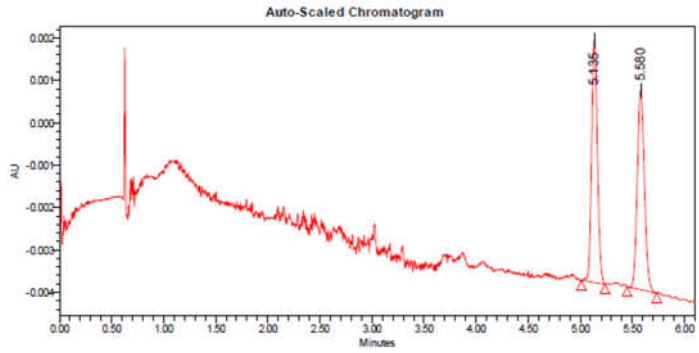
No.	Ret. Time	Rel. Area
	min	%
1	6.72	95.7
2	8.10	4.3
Total:		100

Compound **32b**:



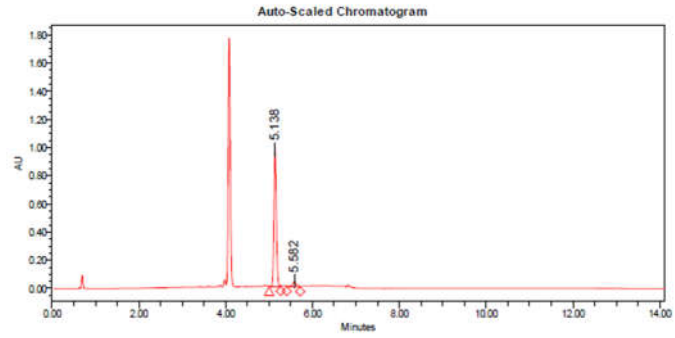
HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in Table 1.2.1, column temperature : 30 °C, UV detection at 230 nm.

Racemic:



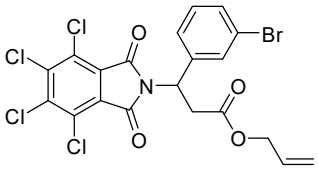
No.	Ret. Time	Rel. Area
	min	%
1	5.14	50.1
2	5.58	49.9
Total:		100

Chiral: 92% *ee*



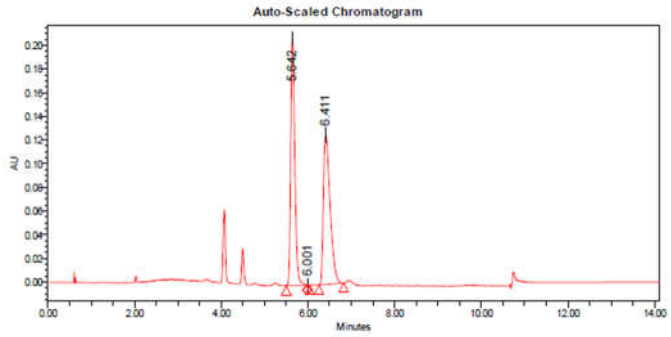
No.	Ret. Time	Rel. Area
	min	%
1	5.14	95.9
2	5.58	4.1
Total:		100

Compound **34b**:



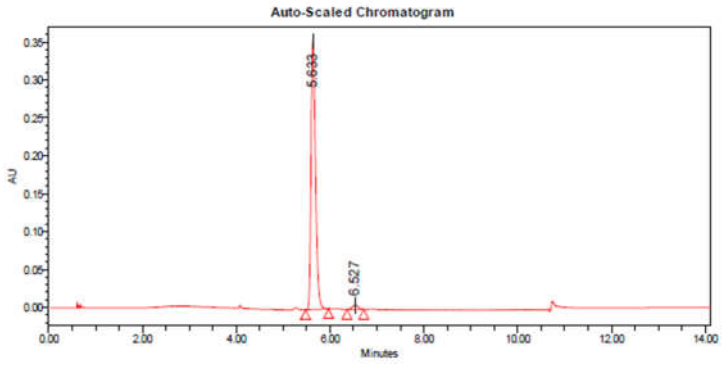
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in Table 1.2.3, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



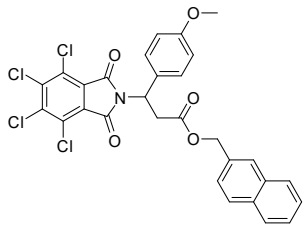
No.	Ret. Time	Rel. Area
	min	%
1	5.64	50
2	6.41	50
Total:		100

Chiral: 97% *ee*



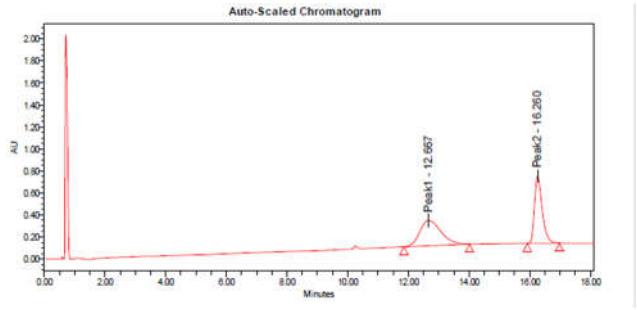
No.	Ret. Time	Rel. Area
	min	%
1	5.64	98.3
2	6.43	1.7
Total:		100

Compound **32c**:



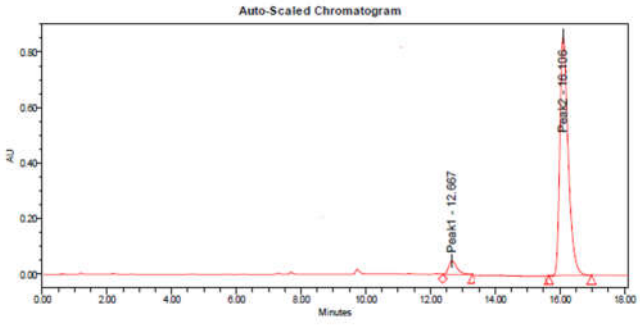
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1, *v*:*v*) gradient as shown in Table 1.2.4, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



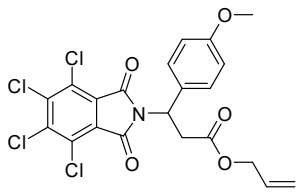
No.	Ret. Time	Rel. Area
	min	%
1	12.67	50.0
2	16.26	50.0
Total:		100

Chiral: 90% *ee*



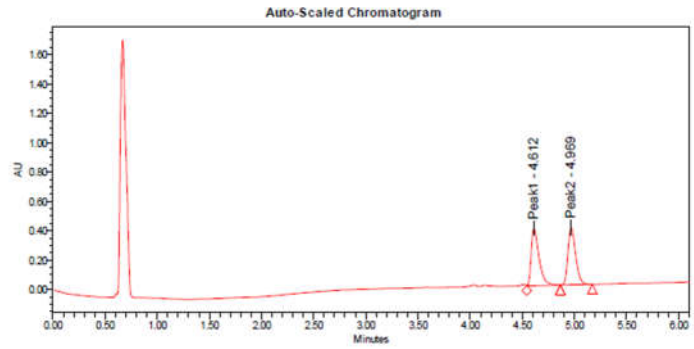
No.	Ret. Time	Rel. Area
	min	%
1	12.67	95.1
2	16.10	4.9
Total:		100

Compound **34c**:



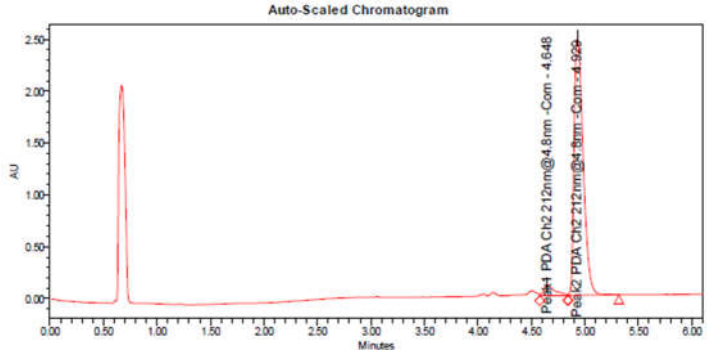
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in Table 1.2.3, column temperature : 30 °C, UV detection at 212 nm.

Racemic:



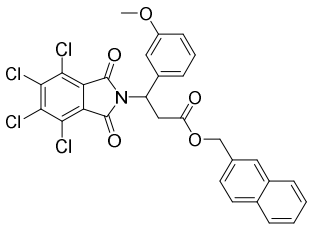
No.	Ret. Time	Rel. Area
	min	%
1	4.61	50.0
2	4.97	50.0
Total:		100

Chiral: 94% *ee*



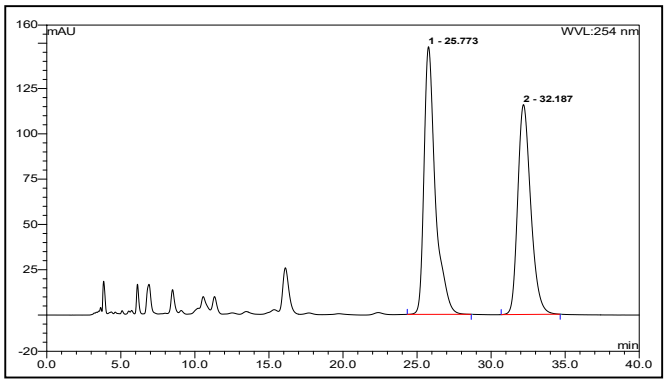
No.	Ret. Time	Rel. Area
	min	%
1	4.65	96.8
2	4.93	3.2
Total:		100

Compound **32d**:



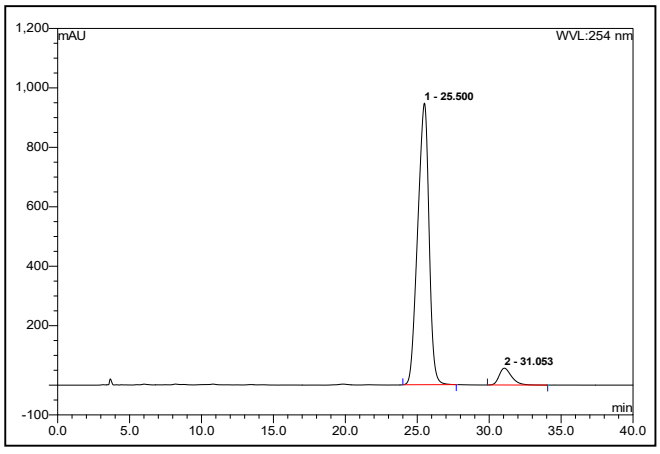
CSP-HPLC analysis: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1}, r.t, UV detection at 220 nm.

Racemic:



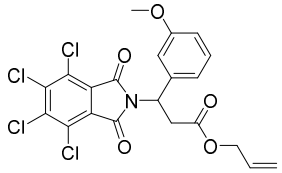
No.	Ret. Time	Rel. Area
	min	%
1	25.77	52.5
2	32.19	47.5
Total:		100

Chiral: 88% *ee*



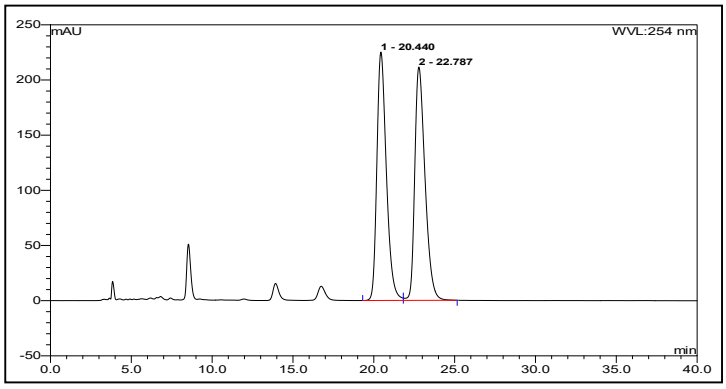
No.	Ret. Time	Rel. Area
	min	%
1	25.5	93.9
2	31.1	6.1
Total:		100

Compound **34d**:



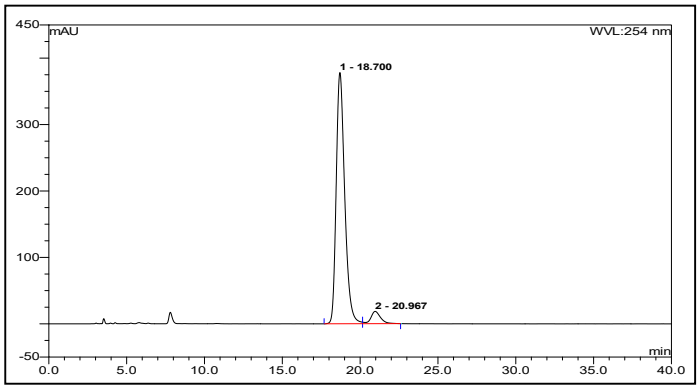
CSP-HPLC analysis: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1}, r.t, UV detection at 220 nm.

Racemic:



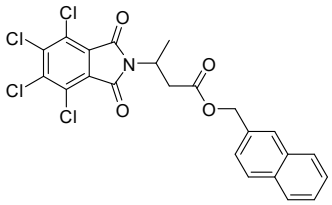
No.	Ret. Time	Rel. Area
	min	%
1	20.4	49.6
2	22.8	50.4
Total:		100

Chiral: 89%



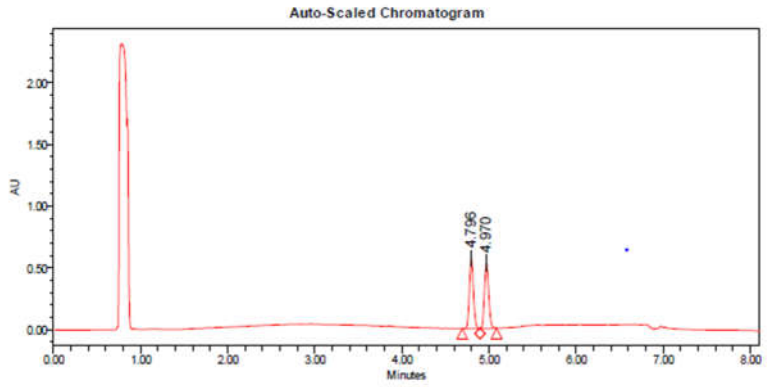
No.	Ret. Time	Rel. Area
	min	%
1	18.7	94.7
2	21.0	5.3
Total:		100

Compound **32e**:



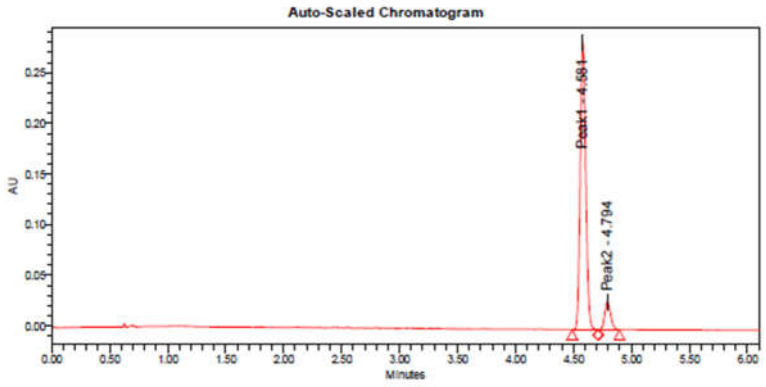
HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in Table 1.2.1, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



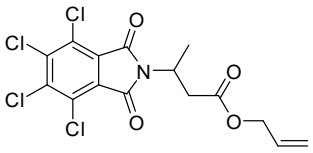
No.	Ret. Time	Rel. Area
	min	%
1	4.79	49.1
2	4.97	50.9
Total:		100

Chiral: 82% *ee*



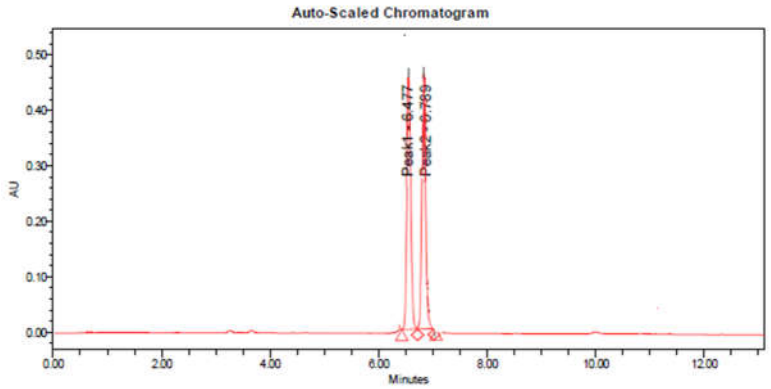
No.	Ret. Time	Rel. Area
	min	%
1	4.58	90.8
2	4.79	9.2
Total:		100

Compound **34e:**



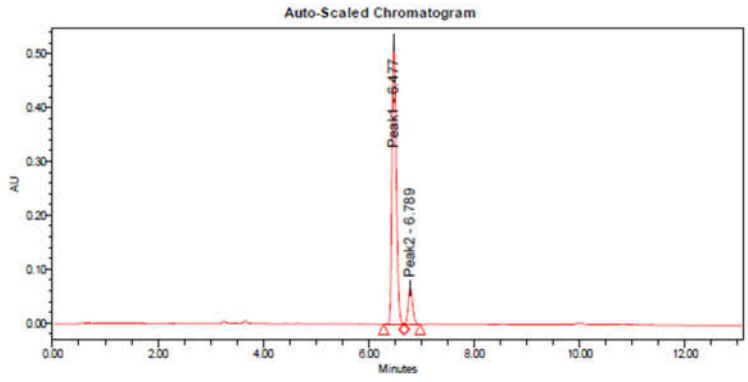
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in Table 1.2.5, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



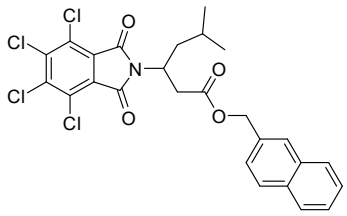
No.	Ret. Time	Rel. Area
	min	%
1	6.48	50.0
2	6.79	50.0
Total:		100

Chiral: 77% *ee*



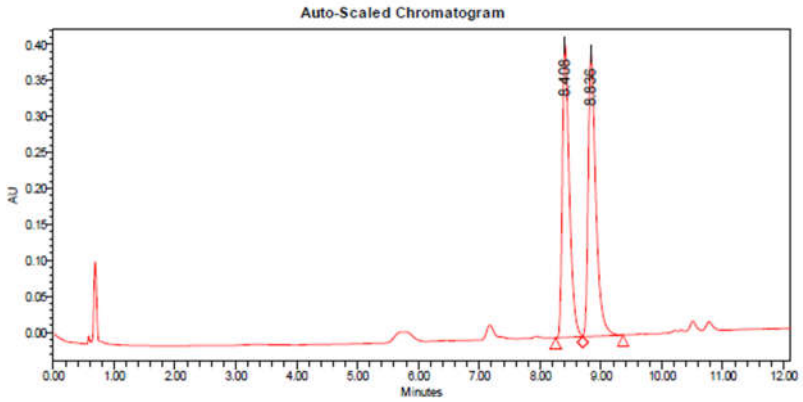
No.	Ret. Time	Rel. Area
	min	%
1	6.48	88.7
2	6.79	11.3
Total:		100

Compound **32f**:



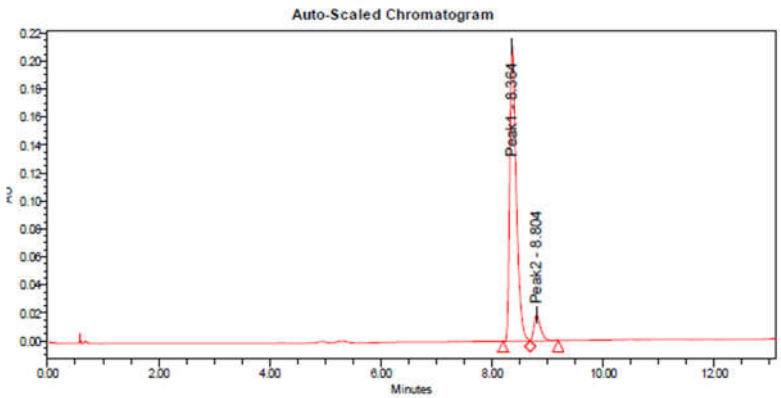
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, *v:v*) gradient as shown in Table 1.2.4, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



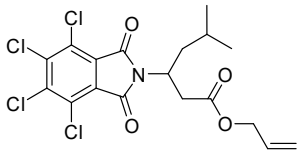
No.	Ret. Time	Rel. Area
	min	%
1	8.41	48.8
2	8.83	51.2
Total:		100

Chiral: 85% *ee*



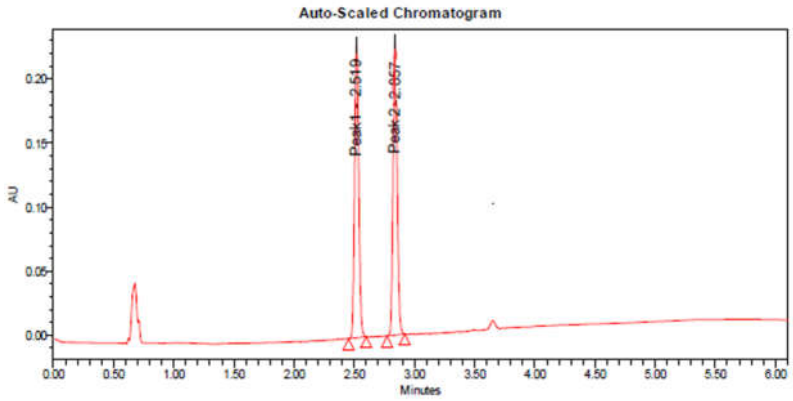
No.	Ret. Time	Rel. Area
	min	%
1	8.36	92.3
2	8.80	7.7
Total:		100

Compound **34f:**



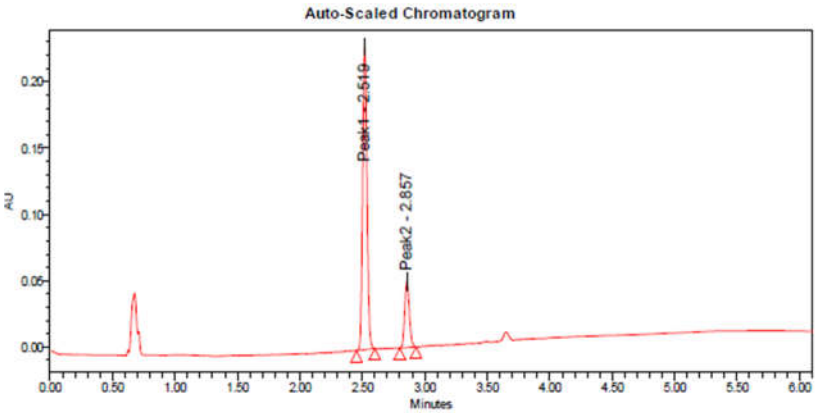
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:MeCN (1:1, *v:v*) gradient as shown in Table 1.2.1, column temperature : 30 °C, UV detection at 230 nm.

Racemic:



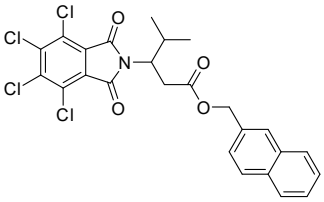
No.	Ret. Time	Rel. Area
	min	%
1	2.52	50.2
2	2.86	49.8
Total:		100

Chiral: 63% *ee*



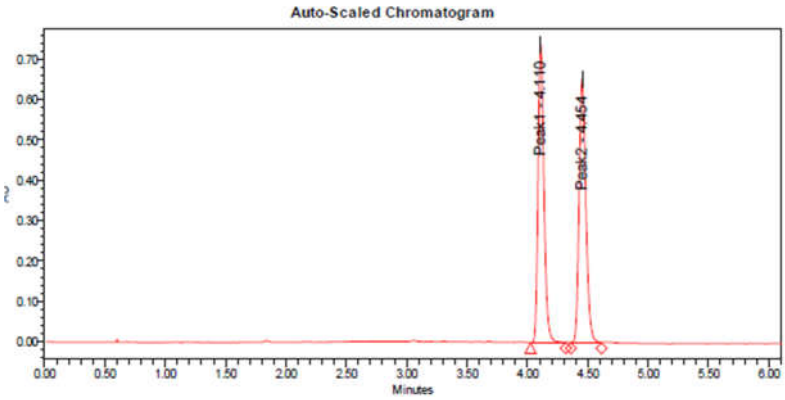
No.	Ret. Time	Rel. Area
	min	%
1	2.52	81.5
2	2.86	18.5
Total:		100

Compound **32g**:



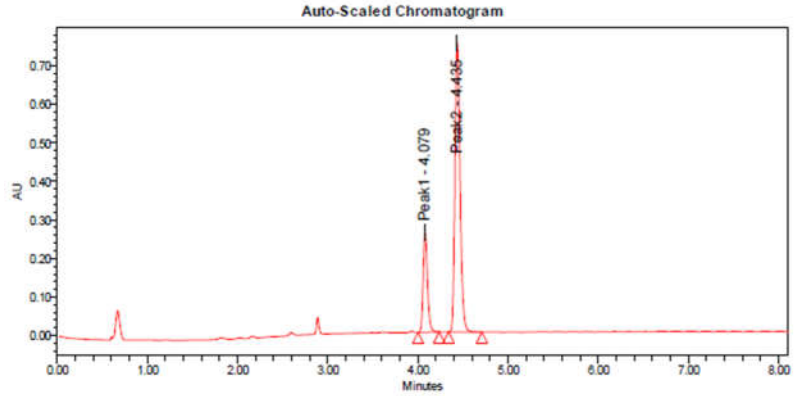
HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in Table 1.2.3, column temperature : 30 °C, UV detection at 230 nm.

Racemic:



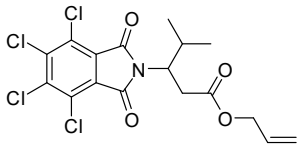
No.	Ret. Time	Rel. Area
	min	%
1	4.11	50.0
2	4.45	50.0
Total:		100

Chiral: 54% *ee*



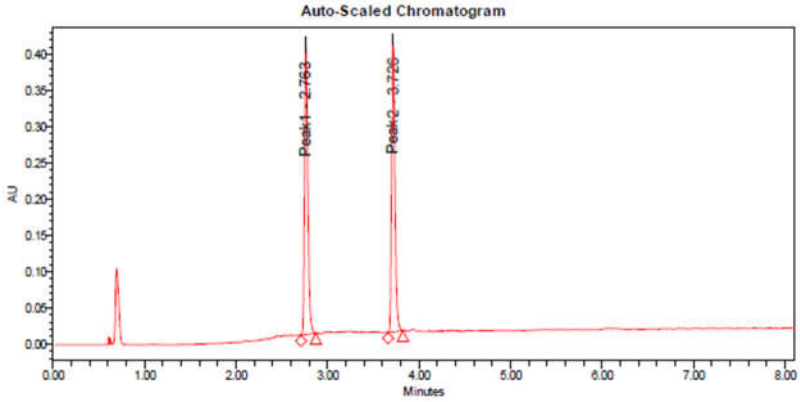
No.	Ret. Time	Rel. Area
	min	%
1	4.08	22.6
2	4.44	77.4
Total:		100

Compound **34g**:



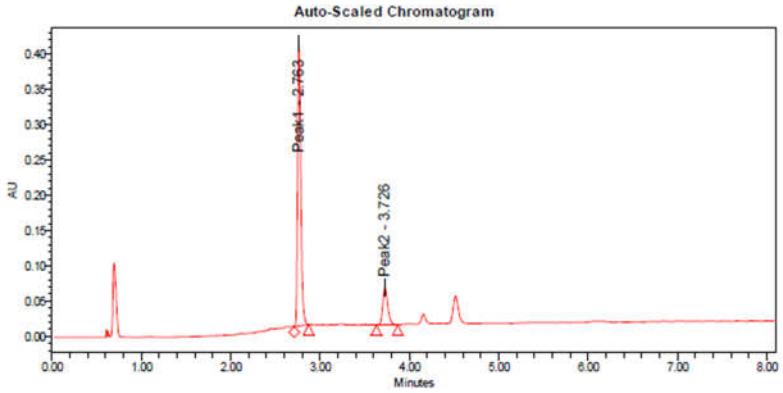
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, *v:v*) gradient as shown in Table 1.2.3, column temperature : 30 °C, UV detection at 230 nm.

Racemic:



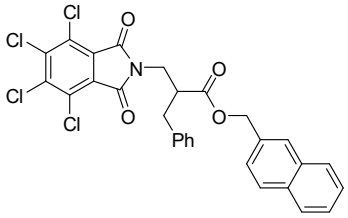
No.	Ret. Time	Rel. Area
	min	%
1	2.76	51.3
2	3.73	48.7
Total:		100

Chiral: 68% *ee*



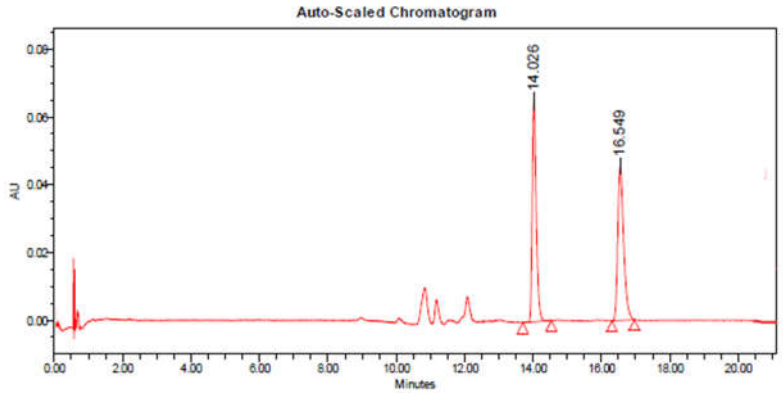
No.	Ret. Time	Rel. Area
	min	%
1	2.76	84
2	3.73	16
Total:		100

Compound **36:**



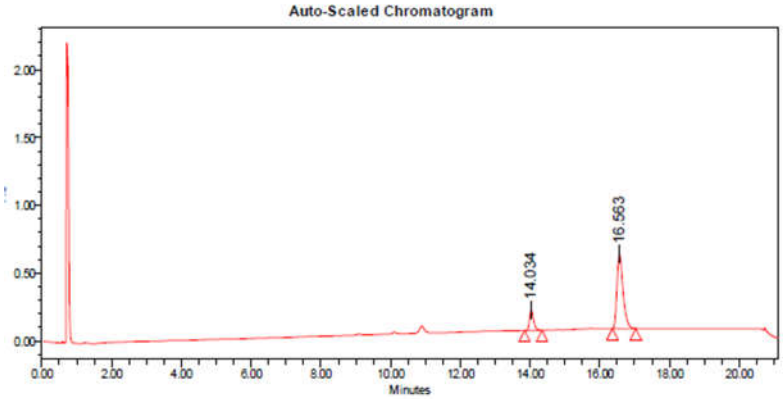
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, *v:v*) gradient as shown in **Error! Reference source not found.**, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



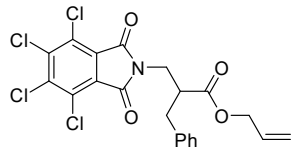
No.	Ret. Time	Rel. Area
	min	%
1	14.03	48.5
2	16.55	51.5
Total:		100

Chiral: 79% *ee*



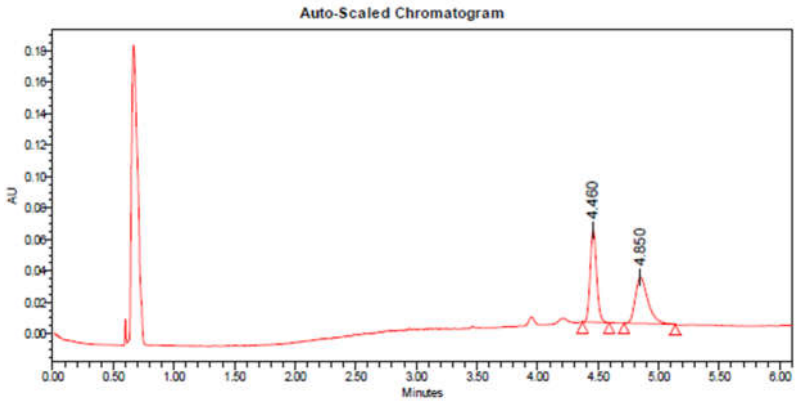
No.	Ret. Time	Rel. Area
	min	%
1	14.03	89.6
2	16.56	10.4
Total:		100

Compound **37**



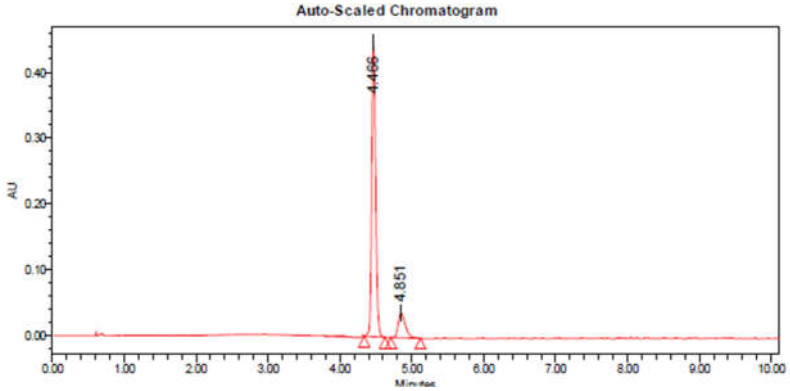
HPLC analysis. ACQUITY UPC^2 Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, *v:v*) gradient as shown in Table 1.2.3, column temperature : 30 °C, UV detection at 254 nm.

Racemic:



No.	Ret. Time	Rel. Area
	min	%
1	4.46	51.48
2	4.85	48.52
Total:		100

Chiral: 87% *ee*



No.	Ret. Time	Rel. Area
	min	%
1	4.47	93.3
2	4.85	6.7
Total:		100

References

1. S. Tallon, F. Manoni and S. J. Connon, *Angew. Chem. Int. Ed.*, 2014, **54**, 813-817.
2. H. Mäenpää, L. T. Kanerva and A. Liljeblad, *ChemCatChem*, 2016, **8**, 1226-1232.
3. A. Berkessel, F. Cleemann and S. Mukherjee, *Angew. Chem. Int. Ed.*, 2005, **44**, 7466-7469.
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