

Supporting Information

Enantioselective Construction of Tetrasubstituted Stereocenter in Isoindolinones *via* Organocatalyzed Reaction Between Ketones and 3-Hydroxyisoindolinones

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§ 1. General Information

Unless otherwise indicated, solvents were used as supplied (analytical or HPLC grade) without further purification. Reagents were used directly as supplied by major chemical suppliers. Flash column chromatography was carried out using silica gel (Merck, 40–63 µm particle size). Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F254 0.25 mm precoated aluminium plates. Visualization was carried out under ultra-violet irradiation (254 nm) and by appropriate heating with ammonium molybdate solution and *p*-anisaldehyde solution. Ammonium molybdate solution was prepared by dissolving ammonium molybdate (5 g) and ceric sulfate (200 mg) in 5% aqueous sulfuric acid (100 mL). *p*-anisaldehyde solution was prepared by addition of concentrated sulfuric acid (5 mL), glacial acetic acid (1.5 mL) and *p*-anisaldehyde (3.7 mL) in absolute ethanol (135 mL).

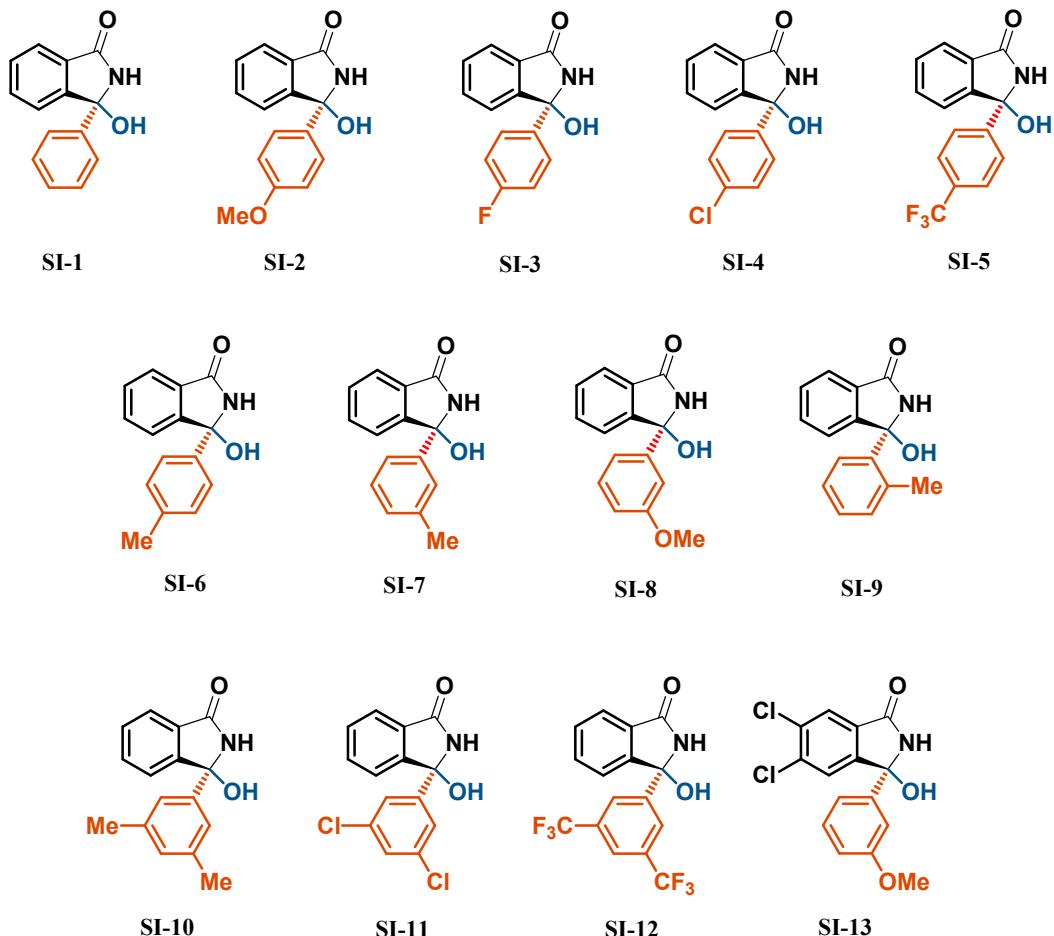
All NMR spectra were acquired on Bruker Avance 600 MHz and 300 MHz spectrometers. ¹H NMR chemical shifts were recorded relative to SiMe₄ (δ = 0.00 ppm) or residual protiated solvents (DMSO: δ = 2.50 ppm, (CD₃)₂CO: δ = 2.05 ppm, CDCl₃: δ = 7.26 ppm, CD₃CN: δ = 1.94). Multiplicities were given as: *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *td* (triplet of doublets), *qd* (quartet of doublets), *t* (triplet), *dt* (doublet of triplets), *q* (quartet) and *m* (multiplet). Coupling constants were reported as a *J* value in Hz. ¹³C NMR chemical shifts were recorded relative to solvent resonance (DMSO: δ = 39.52 ± 0.06 ppm, (CD₃)₂CO: δ = 29.84 ± 0.01 ppm, 206.26 ± 0.13 ppm, CDCl₃: δ = 77.16 ± 0.06 ppm, 206.26 ± 0.13 ppm, CD₃CN: δ = 1.32 ± 0.02 ppm, 118.26 ± 0.02 ppm).

Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorbtion maxima (ν_{max}) are reported in wavenumbers (cm⁻¹). High resolution mass spectrometry (HRMS) was performed on a 6530 LC/Q-TOF Agilent Technologies Analyzer. Melting points of enantioenriched products were determined using an Electrothermal 9100 apparatus in open capillaries and are uncorrected. Optical rotations were measured on an Autopol IV instrument (Rudolf Research Analytical, Flanders, USA).

Where given, systematic compound names are those generated by ChemBioDraw Ultra 12.0 following IUPAC conventions. The starting isoindolinone alcohols (**SI-1 – SI-13**) and chiral phosphoric acids (**BA1 – BA8**) have been synthesized according to the known procedures. Racemic standards were obtained by employing *p*-toluenesulfonic or phenylphosphonic acid

(20 mol%) instead of chiral catalyst. Enantiomeric ratios were determined using a normal phase chiral high performance liquid chromatography with PDA detector. Diasteromers **20/20'**, **21/21'** and **22/22'** are obtained as pure compounds, however, their respective *syn/anti* configuration cannot be assigned based on their NMR shifts.

§ 2. List of 3-aryl 3-hydroxyisoindolinones



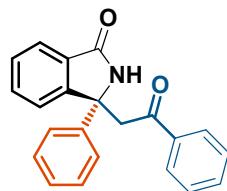
§ 3. Experimental Procedures and Analytical Data

3.1. General procedure for synthesis of 3-alkylaryl isoindolinone derivatives **1-15, 17-18 and 20-23**

In a 10 mL Schlenk tube equipped with a magnetic stir bar, 3-aryl 3-hydroxyisoindolinones (0.1 mmol) and chiral phosphoric acid **BA3** (7.5 mg, 0.01 mmol, 10 mol %) were dissolved or suspended in acetonitrile (1 mL) after stirring for 5 min at 80 °C under an argon atmosphere. Ketone (0.5 mmol) was added and resulting reaction mixture was stirred at 80 °C until full consumption of starting material (monitored by TLC), unless stated otherwise. The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by column chromatography on silica gel to afford the corresponding product(s).

3.1.1. Characterization data for 3-alkylaryl isoindolinone derivatives **1-15, 17-18 and 20-23**

(*R*)-3-(2-oxo-2-phenylethyl)-3-phenylisoindolin-1-one (**1**)



Isoindolinone alcohol **SI-1** (22.5 mg, 0.1 mmol) afforded product **1** (31.1 mg, 95% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 4/1. Reaction time: 48h. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 15.2 min (minor), t_{R2} = 19.2 min (major); 95:5 e.r.).

$[\alpha]_D^{20} = +139^\circ$ (c 0.56, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.92 (s, 1H), 7.95 (d, J = 7.4 Hz, 2H), 7.71 (d, J = 7.7 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 4.63 (d, J = 17.7 Hz, 1H), 3.84 (d, J = 17.7 Hz, 1H).

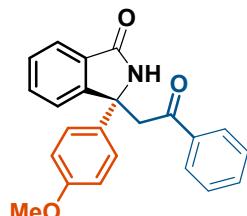
¹³C NMR (151 MHz, DMSO) δ 196.8, 169.1, 151.3, 142.9, 136.8, 133.4, 131.9, 130.70, 128.7, 128.6, 128.1, 128.1, 127.1, 125.0, 123.2, 123.0, 64.4, 46.0.

HRMS (ESI): m/z [M+H]⁺ for C₂₂H₁₇NO₂ (calcd 328.1293); found 328.1331

IR: ν = 3430, 1693, 1479, 1378, 1281, 1225, 1001, 830, 585 cm⁻¹

m.p. 114.5–116.2 °C

(R)-3-(4-methoxyphenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (2)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **2** (34.7 mg, 97% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 19h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 14.2 min (major), t_{R2} = 18.4 min (minor); 95:5 e.r.)

$[\alpha]_D^{20} = +324^\circ$ (c 0.96, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.80 (s, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.67 (d, J = 7.7 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.54 – 7.44 (m, 5H), 7.41 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 4.53 (d, J = 17.5 Hz, 1H), 3.80 (d, J = 17.5 Hz, 1H), 3.70 (s, 3H).

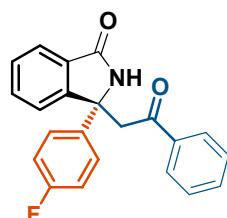
¹³C NMR (151 MHz, DMSO) δ 197.3, 169.6, 158.7, 151.9, 137.2, 134.9, 133.8, 132.4, 130.9, 129.1, 128.5, 128.4, 126.6, 123.5, 123.4, 114.3, 64.5, 55.5, 46.2.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₃ (calcd 358.1398); found 358.1429

IR: ν = 3433, 1692, 1523, 1379, 1266, 1227, 1000, 907, 863, 750, 570 cm⁻¹

m.p. 214.2–216.8 °C

(R)-3-(4-fluorophenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (3)



Isoindolinone alcohol **SI-3** (24.3 mg, 0.1 mmol) afforded product **3** (33.5 mg, 96% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 14.3 min (major), t_{R2} = 19.1 min (minor); 93:7 e.r.).

¹H NMR (600 MHz, Acetone) δ 8.04 (d, J = 7.6 Hz, 2H), 7.90 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.69 – 7.61 (m, 4H), 7.58 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.11 – 7.05 (m, 2H), 4.99 (d, J = 18.2 Hz, 1H), 3.60 (d, J = 18.2 Hz, 1H).

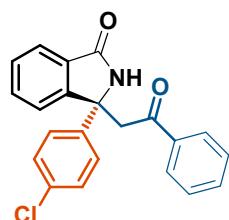
¹³C NMR (75 MHz, Acetone) δ 198.2, 169.6, 162.8 (d, $^1J_{C-F}$ = 242.5 Hz), 152.6, 139.6 (d, $^4J_{C-F}$ = 3.2 Hz), 137.9, 134.3, 133.1, 131.4, 129.5, 129.2, 129.0, 127.9 (d, $^3J_{C-F}$ = 8.1 Hz), 124.4, 123.8, 116.2 (d, $^2J_{C-F}$ = 21.4 Hz), 65.0, 47.4.

HRMS (ESI): m/z [M+H]⁺ for C₂₂H₁₆FNO₂ (calcd 346.1199); found 346.1231

IR: ν = 3232, 1682, 1523, 1355, 1281, 1215, 911, 857, 833, 749, 589, 438 cm⁻¹

m.p. 224.5–226.1 °C

(R)-3-(4-chlorophenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (**4**)



Isoindolinone alcohol **SI-4** (26.0 mg, 0.1 mmol) afforded product **4** (24.6 mg, 68% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 20/1. Reaction time: 19h.

Enantiomeric ratio determined by chiral (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 8.2 min (major), t_{R2} = 11.7 min (minor); 97:3 e.r.).

$[\alpha]_D^{20} = +291^\circ$ (c 0.80, CHCl₃)

¹H NMR (300 MHz, DMSO) δ 8.95 (s, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.75 – 7.58 (m, 5H), 7.58 – 7.32 (m, 6H), 4.64 (d, J = 18.0 Hz, 1H), 3.84 (d, J = 17.9 Hz, 1H).

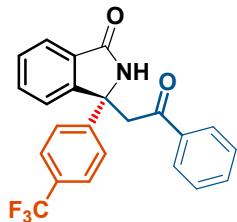
¹³C NMR (151 MHz, DMSO) δ 196.6, 169.0, 150.8, 142.0, 136.6, 133.4, 132.0, 131.7, 130.6, 128.6, 128.4, 128.2, 128.1, 127.0, 123.1, 123.0, 64.0, 46.1.

HRMS (ESI): m/z [M+H]⁺ for C₂₂H₁₆ClNO₂ (calcd 364.0874); found 362.0928

IR: ν = 3225, 1680, 1503, 1355, 1276, 1214, 859, 827, 739, 650, 589 cm⁻¹

m.p. 236.0–238.4 °C

(R)-3-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (5)



Isoindolinone alcohol **SI-5** (29.3 mg, 0.1 mmol) afforded product **5** (39.0 mg, 96% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 8/1; petroleum ether/ethyl acetate = 2/1. Reaction time: 8 days.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 10.4 min (major), t_{R2} = 15.4 min (minor); 93:7 e.r.).

¹H NMR (600 MHz, DMSO) δ 9.03 (s, 1H), 7.95 (dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 7.5 Hz, 1H), 7.65 – 7.61 (m, 1H), 7.56 (td, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.45 (td, J_1 = 7.5 Hz, J_2 = 0.8 Hz, 1H), 4.75 (d, J = 18.1 Hz, 1H), 3.88 (d, J = 18.1 Hz, 1H).

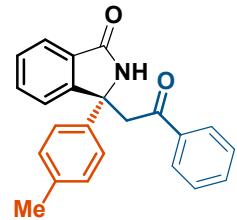
¹³C NMR (151 MHz, DMSO) δ 196.6, 169.0, 150.5, 147.7 (2C), 136.5, 133.4, 132.1, 130.6, 128.6, 128.3, 128.1, 127.6 (q, $^2J_{C-CF_3}$ = 31.9 Hz), 125.8, 125.5 (q, $^3J_{C-CF_3}$ = 3.6 Hz), 124.2 (q, $^1J_{C-CF_3}$ = 272.1 Hz), 123.1, 64.2, 46.3.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₆F₃NO₂ (calcd 396.1167); found 396.1207

IR: ν = 3064, 1677, 1483, 1325, 1239, 1115, 904, 783, 686, 618 cm⁻¹

m.p. 175.4–177.1 °C

(R)-3-(2-oxo-2-phenylethyl)-3-(p-tolyl)isoindolin-1-one (6)



Isoindolinone alcohol **SI-6** (23.9 mg, 0.1 mmol) afforded product **6** (31.1 mg, 97% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 7/1. Reaction time: 48h. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 9.9 min (major), t_{R2} = 13.1 min (minor); 95:5 e.r.).

$[\alpha]_D^{20} = +355^\circ$ (c 1.02, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.82 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.7 Hz, 1H), 7.62 (dt, J_1 = 7.4 Hz, J_2 = 3.6 Hz, 2H), 7.54 – 7.47 (m, 3H), 7.45 (d, J = 8.3 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 4.58 (d, J = 17.6 Hz, 1H), 3.79 (d, J = 17.6 Hz, 1H), 2.23 (s, 3H).

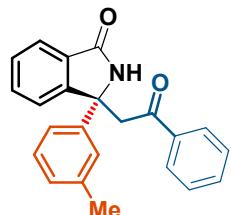
¹³C NMR (75 MHz, DMSO) δ 196.8, 169.0, 151.4, 139.8, 136.8, 136.2, 133.3, 131.8, 130.6, 129.0, 128.6, 128.0, 127.9, 124.9, 123.1, 122.9, 64.2, 46.0, 20.4.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₂ (calcd 342.1449); found 342.1482

IR: ν = 3235, 1682, 1525, 1351, 1211, 1112, 990, 910, 859, 752, 590 cm⁻¹

m.p. 162.7–164.5 °C

(R)-3-(2-oxo-2-phenylethyl)-3-(m-tolyl)isoindolin-1-one (7)



Isoindolinone alcohol **SI-7** (23.9 mg, 0.1 mmol) afforded product **7** (31.7 mg, 93% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 9.7 min (major), t_{R2} = 12.6 min (minor); 95:5 e.r.).

$[\alpha]_D^{20} = +377^\circ$ (c 1.01, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.82 (s, 1H), 7.94 (d, J = 7.3 Hz, 2H), 7.67 (d, J = 7.7 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.54 – 7.47 (m, 3H), 7.45 (d, J = 8.3 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 4.58 (d, J = 17.6 Hz, 1H), 3.79 (d, J = 17.6 Hz, 1H), 2.23 (s, 3H).

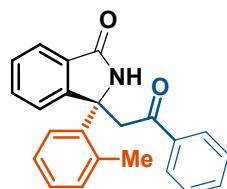
¹³C NMR (151 MHz, DMSO) δ 196.8, 169.0, 151.4, 139.8, 136.8, 136.2, 133.3, 131.8, 130.6, 129.0, 128.6, 128.0, 127.9, 124.9, 123.1, 122.8, 64.2, 45.9, 20.4.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₂ (calcd 342.1449); found 342.1480

IR: ν = 3430, 3162, 3061, 1693, 1530, 1378, 1279, 1225, 900, 857, 823, 685, 580 cm⁻¹

m.p. 160.2–162.2 °C

(R)-3-(2-oxo-2-phenylethyl)-3-(o-tolyl)isoindolin-1-one (8)



Isoindolinone alcohol **SI-9** (23.9 mg, 0.1 mmol) afforded product **8** (25.3 mg, 74% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 6 days. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 11.5 min (minor), t_{R2} = 14.5 min (major); 94:6 e.r.).

¹H NMR (600 MHz, DMSO) δ 8.72 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.55 – 7.47 (m, 4H), 7.45 (t, J = 7.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.03 (d, J = 7.1 Hz, 1H), 4.73 (d, J = 17.6 Hz, 1H), 3.55 (d, J = 17.6 Hz, 1H), 1.83 (s, 3H).

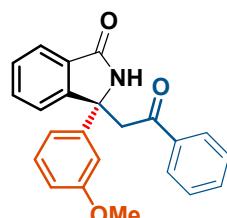
¹³C NMR (151 MHz, DMSO) δ 197.2, 168.9, 150.0, 138.0, 136.8, 136.1, 133.3, 132.8, 132.2, 132.0, 128.6, 128.5, 128.1, 128.1, 127.5, 127.4, 126.0, 124.9, 123.2, 122.6, 65.0, 48.2, 20.6.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₂ (calcd 342.1449); found 342.1468

IR: ν = 3446, 2967, 1693, 1512, 1371, 1257, 1218, 984, 833, 578 cm⁻¹

m.p. 178.1–180.0 °C

(R)-3-(3-methoxyphenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (9)



Isoindolinone alcohol **SI-8** (25.5 mg, 0.1 mmol) afforded product **9** (35.2 mg, 98% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 8/1. Reaction time: 48h. Enantiomeric ratio determined by chiral (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 13.5 min (major), t_{R2} = 19.0 min (minor); 94:6 e.r.).

¹H NMR (600 MHz, Acetone) δ 8.05 (dd, J_1 = 8.3 Hz, J_2 = 1.1 Hz, 2H), 7.88 (s, 1H), 7.72 (t, J = 13.3, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.56 (td, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.47 (td, J_1 = 7.5 Hz, J_2 = 0.6 Hz, 1H), 7.27 – 7.14 (m, 3H), 6.82 – 6.71 (m, 1H), 5.01 (d, J = 18.1 Hz, 1H), 3.72 (s, 3H), 3.52 (d, J = 18.1 Hz, 1H).

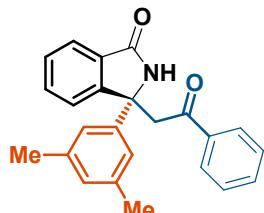
¹³C NMR (151 MHz, Acetone) δ 198.3, 169.8, 161.0, 152.6, 145.0, 137.9, 134.3, 132.9, 131.4, 130.6, 129.5, 129.1, 129.0, 124.3, 123.9, 118.0, 112.9, 112.1, 65.4, 55.5, 47.3.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₃ (calcd 358.1398); found 358.1434

IR: ν = 3439, 1667, 1510, 1375, 219, 1000, 914, 817, 687, 566 cm⁻¹

m.p. 144.0–145.7 °C

(R)-3-(3,5-dimethylphenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (**10**)



Isoindolinone alcohol **SI-10** (25.3mg, 0.1 mmol) afforded product **10** (29.9 mg, 84% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 27h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 70/30, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 7.7 min (minor), t_{R2} = 15.3 min (major); 94:6 e.r.).

¹H NMR (600 MHz, DMSO) δ 8.78 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 7.7 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.56 – 7.46 (m, 3H), 7.41 (t, J = 7.4 Hz, 1H), 7.21 (s, 2H), 6.84 (s, 1H), 4.55 (d, J = 17.6 Hz, 1H), 3.79 (d, J = 17.6 Hz, 1H), 2.22 (s, 6H).

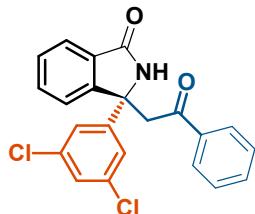
¹³C NMR (151 MHz, DMSO) δ 196.8, 169.0, 151.3, 142.8, 137.5, 136.8, 133.3, 131.8, 130.6, 128.6, 128.4, 128.0, 127.9, 123.1, 122.8, 122.6, 64.2, 46.0, 21.1.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₂₁NO₂ (calcd 356.1606); found 356.1638

IR: ν = 3433, 2917, 1694, 1508, 1373, 1244, 1225, 1001, 918, 782, 580, 558 cm⁻¹

m.p. 180.5-182.3 °C

(R)-3-(3,5-dichlorophenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (11)



Isoindolinone alcohol **SI-11** (29.4 mg, 0.1 mmol) afforded product **11** (31.7 mg, 80% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 13 days. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 15.9 min (major), t_{R2} = 20.9 min (minor); 96:4 e.r.).

$[\alpha]_D^{20} = +376^\circ$ (c 1.06, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 9.05 (s, 1H), 7.95 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 7.7 Hz, 1H), 7.70 (s, 2H), 7.68 – 7.57 (m, 3H), 7.57 – 7.40 (m, 4H), 4.74 (d, J = 18.2 Hz, 1H), 3.85 (d, J = 18.2 Hz, 1H).

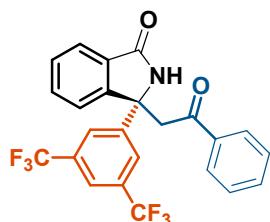
¹³C NMR (151 MHz, DMSO) δ 196.5, 150.0, 147.5, 136.4, 134.3, 133.5, 132.3, 130.4, 128.6, 128.5, 128.1, 126.8, 123.9, 123.2, 123.0, 63.9, 46.4.

HRMS (ESI): m/z [M+H]⁺ for C₂₂H₁₅Cl₂NO₂ (calcd 396.0513); found 396.0555

IR: ν = 3430, 3128, 3074, 1696, 1479, 1372, 1264, 1227, 918, 869, 817, 680, 622, 569 cm⁻¹

m.p. 201.9-203.6 °C

(R)-3-(3,5-bis(trifluoromethyl)phenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (12)



Isoindolinone alcohol **SI-12** (36.1 mg, 0.1 mmol) afforded product **12** (16.2 mg, 35% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 20/1. Reaction was stopped after 14 days.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 7.9 min (major), t_{R2} = 11.6 min (minor); 96.5:4.5 e.r.).

¹H NMR (300 MHz, DMSO) δ 9.31 (s, 1H), 8.33 (s, 2H), 8.03 – 7.91 (m, 3H), 7.84 (d, J = 7.7 Hz, 1H), 7.72 – 7.58 (m, 3H), 7.55 – 7.41 (m, 3H), 4.95 (d, J = 18.4 Hz, 1H), 3.95 (d, J = 18.4 Hz, 1H).

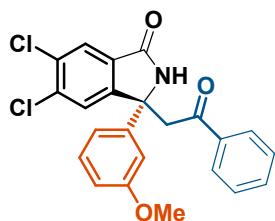
¹³C NMR (151 MHz, DMSO) δ 197.0, 169.5, 150.3, 147.4, 136.8, 134.0, 133.0, 131.0 (q, $^{2}J_{C-CF_3}$ = 32.6 Hz), 130.9, 129.2, 129.1, 128.6, 126.3, 123.8, 123.8 (q, $^{1}J_{C-CF_3}$ = 273.2 Hz) 123.5, 121.5, 64.6, 47.3.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₁₅F₆NO₂ (calcd 464.1041); found 464.1080

IR: ν = 3370, 1694, 1519, 1278, 1127, 960, 780, 749, 683 cm⁻¹

m.p. 147.7–149.5 °C

(R)-5,6-dichloro-3-(3-methoxyphenyl)-3-(2-oxo-2-phenylethyl)isoindolin-1-one (**13**)



Isoindolinone alcohol **SI-13** (32.4 mg, 0.1 mmol) afforded product **13** (41.8 mg, 98% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 50/1. Reaction time: 4 days. Enantiomeric ratio determined by chiral (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 14.4 min (major), t_{R2} = 22.0 min (minor); 93:7 e.r.).

¹H NMR (600 MHz, DMSO) δ 9.21 (s, 1H), 8.09 (s, 1H), 7.95 (dd, J_1 = 8.3, J_2 = 1.1 Hz, 2H), 7.83 (s, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 8.3 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.84 (dd, J_1 = 8.2, J_2 = 1.7 Hz, 1H), 4.56 (d, J = 17.8 Hz, 1H), 3.99 (d, J = 17.8 Hz, 1H), 3.73 (s, 3H).

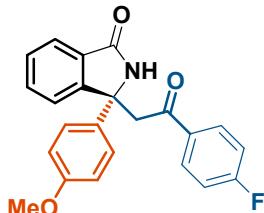
¹³C NMR (151 MHz, DMSO) δ 196.5, 166.9, 159.5, 150.9, 143.5, 136.6, 134.5, 133.4, 131.5, 131.3, 129.9, 128.7, 128.0, 125.5, 124.7, 117.1, 112.4, 111.4, 64.1, 55.1, 45.3.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₇Cl₂NO₃ (calcd 426.0619); found 426.0656

IR: ν = 3432, 3163, 3012, 1697, 1506, 1395, 1274, 1228, 1004, 830, 727, 692, 469 cm⁻¹

m.p. 226.9–228.4 °C

(R)-3-(2-(4-fluorophenyl)-2-oxoethyl)-3-(4-methoxyphenyl)isoindolin-1-one (14)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **14** (35.3 mg, 94% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 7/1. Reaction time: 69h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 90/10, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 12.9 min (major), t_{R2} = 20.9 min (minor); 92:8 e.r.).

¹H NMR (300 MHz, DMSO) δ 8.82 (s, 1H), 8.09 – 7.94 (m, 2H), 7.68 – 7.58 (m, 2H), 7.56 – 7.37 (m, 4H), 7.31 (t, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 4.52 (d, J = 17.5 Hz, 1H), 3.81 (d, J = 17.4 Hz, 1H), 3.70 (s, 3H).

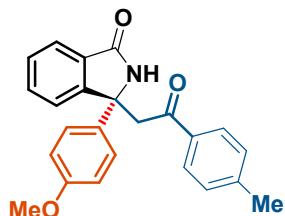
¹³C NMR (151 MHz, DMSO) δ 195.5, 168.9, 165.0 (d, $^1J_{C-F}$ = 252.0 Hz), 158.3, 151.4, 134.6, 133.6 (d, $^4J_{C-F}$ = 2.7 Hz), 131.7, 131.1 (d, $^3J_{C-F}$ = 9.5 Hz), 130.6, 127.9, 126.2, 123.1, 122.8, 115.6 (d, $^2J_{C-F}$ = 21.9 Hz), 113.8, 64.0, 55.1, 45.8.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₈FNO₃ (calcd 376.1304); found 376.1346

IR: ν = 3377, 1690, 1480, 1221, 1185, 1054, 869, 697, 579 cm⁻¹

m.p. 191.9–193.5 °C

(R)-3-(4-methoxyphenyl)-3-(2-oxo-2-(p-tolyl)ethyl)isoindolin-1-one (15)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **15** (34.1 mg, 92% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 7/1. Reaction time: 67h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 12.9 min (major), t_{R2} = 17.6 min (minor); 91:9 e.r.).

¹H NMR (300 MHz, CD₃CN) δ 7.87 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 7.4 Hz, 1H), 7.67 – 7.20 (m, 8H), 6.83 (d, J = 8.9 Hz, 2H), 4.73 (d, J = 18.1 Hz, 1H), 3.72 (s, 3H), 3.38 (d, J = 18.1 Hz, 1H), 2.40 (s, 3H).

¹H NMR (300 MHz, DMSO) δ 8.78 (s, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.70 – 7.58 (m, 2H), 7.57 – 7.36 (m, 4H), 7.30 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 4.52 (d, J = 17.5 Hz, 1H), 3.90 – 3.54 (m, 4H), 2.36 (s, 3H).

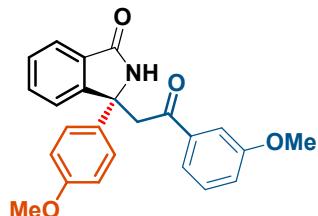
¹³C NMR (151 MHz, DMSO) δ 196.3, 168.9, 158.2, 151.6, 143.7, 134.7, 134.4, 131.7, 130.6, 129.1, 128.2, 127.8, 126.2, 123.1, 122.8, 113.8, 64.0, 55.0, 45.7, 21.1.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₂₁NO₃ (calcd 372.1555); found 372.1596

IR: ν = 3439, 1689, 1480, 1238, 1185, 1061, 857, 770, 740, 569 cm⁻¹

m.p. 190.5–192.0 °C

(R)-3-(4-methoxyphenyl)-3-(2-(3-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (17)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **17** (32.9 mg, 85% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 7/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 80/20, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 19.0 min (major), t_{R2} = 24.7 min (minor); 92:8 e.r.).

¹H NMR (300 MHz, DMSO) δ 8.81 (s, 1H), 7.71 – 7.59 (m, 2H), 7.59 – 7.33 (m, 7H), 7.19 (dd, J_1 = 7.8 Hz, J_2 = 2.2 Hz, 1H), 6.86 (d, J = 8.9 Hz, 2H), 4.53 (d, J = 17.6 Hz, 1H), 3.91 – 3.75 (m, 4H), 3.70 (s, 3H).

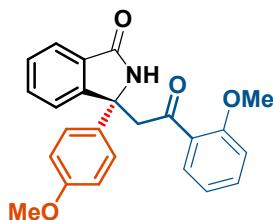
¹³C NMR (75 MHz, DMSO) δ 196.6, 168.9, 159.3, 158.2, 151.5, 138.2, 134.6, 131.7, 130.6, 129.8, 127.8, 126.2, 123.1, 122.8, 120.6, 119.3, 113.8, 112.5, 64.0, 55.3, 55.1, 46.0.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₂₁NO₄ (calcd 388.1504); found 388.1546

IR: ν = 3266, 1690, 1498, 1288, 1258, 1064, 1018, 846, 764, 655, 583 cm⁻¹

m.p. 171.3–173.0 °C

(R)-3-(4-methoxyphenyl)-3-(2-(2-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (**18**)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **18** (36.8 mg, 95% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IB (25 cm × 0.46 cm ID), hexane/iso-propanol = 60/40, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 9.1 min (major), t_{R2} = 11.1 min (minor); 92:8 e.r.).

¹H NMR (600 MHz, DMSO) δ 8.84 (s, 1H), 7.58 (t, J = 7.1 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.35 (m, 3H), 7.26 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.88 – 6.83 (m, 2H), 4.23 (d, J = 17.1 Hz, 1H), 3.85 (s, 3H), 3.82 (d, J = 17.1 Hz, 1H).

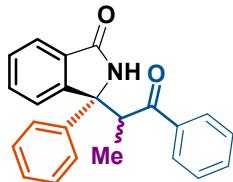
¹³C NMR (151 MHz, DMSO) δ 198.6, 168.8, 158.2, 157.8, 151.2, 134.6, 133.5, 131.7, 130.8, 129.1, 128.3, 127.8, 126.2, 123.0, 122.8, 120.3, 113.8, 112.2, 64.2, 55.7, 55.1, 50.9.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₂₁NO₄ (calcd 388.1504); found 388.1548

IR: ν = 3233, 1684, 1529, 1345, 1252, 1008, 923, 869, 727, 589 cm⁻¹

m.p. 173.6–174.9 °C

(R)-3-((S)-1-oxo-1-phenylpropan-2-yl)-3-phenylisoindolin-1-one (20/20')



Isoindolinone alcohol **SI-1** (22.5 mg, 0.1 mmol) afforded products **20** (9.5 mg, 28% yield) and **20'** (23.5 mg, 69% yield) as white solids.

Compound 20

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IC (25 cm × 0.46 cm ID), hexane/iso-propanol = 70/30, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 16.1 min (minor), t_{R2} = 35.8 min (major); 66:34 e.r.).

¹H NMR (300 MHz, DMSO) δ 8.55 (s, 1H), 8.10 (d, J = 7.4 Hz, 2H), 7.94 (d, J = 7.7 Hz, 1H), 7.79 – 7.36 (m, 8H), 7.21 (t, J = 7.5 Hz, 2H), 7.12 (d, J = 7.2 Hz, 1H), 5.29 (d, J = 7.1 Hz, 1H), 0.79 (d, J = 7.0 Hz, 3H).

¹³C NMR (75 MHz, DMSO) δ 202.4, 169.3, 150.1, 142.9, 135.7, 133.7, 132.2, 130.7, 128.9, 128.5, 128.4, 128.4, 127.1, 124.8, 123.1, 122.9, 68.1, 45.9, 12.9.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₂ (calcd 342.1449); found 342.1494

IR: ν = 3417, 3190, 3058, 1694, 1513, 1375, 1219, 1111, 971, 831, 702, 580 cm⁻¹

m.p. 238.4–240.3 °C (decomposition)

Compound 20'

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IC (25 cm × 0.46 cm ID), hexane/iso-propanol = 60/40, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 12.3 min (major), t_{R2} = 23.5 min (minor); 87:13 e.r.).

¹H NMR (300 MHz, DMSO) δ 9.40 (s, 1H), 7.87 – 7.59 (m, 5H), 7.58 – 7.11 (m, 9H), 5.02 (q, J = 6.9 Hz, 1H), 1.08 (d, J = 6.9 Hz, 3H).

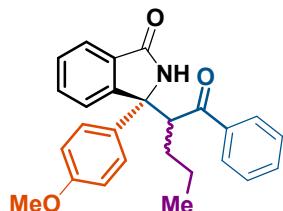
¹³C NMR (151 MHz, DMSO) δ 200.6, 169.0, 148.4, 141.7, 137.7, 132.6, 131.4, 131.1, 128.6, 128.2, 128.0, 127.7, 127.4, 125.7, 124.1, 122.4, 68.5, 45.6, 13.9.

MS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₂ (calcd 342.1449); found 342.2

IR: ν = 2932, 1689, 1509, 1262, 1235, 973, 887, 747, 576 cm⁻¹

m.p. 207.3–208.8 °C

(R)-3-(4-methoxyphenyl)-3-((S)-1-oxo-1-phenylpentan-2-yl)isoindolin-1-one (21/21')



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded products **21** (20.4 mg, 54% yield) and **21'** (14.4 mg, 39% yield) as white solids.

Compound 21

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 120h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IC (25 cm × 0.46 cm ID), hexane/iso-propanol = 70/30, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 16.2 min (minor), t_{R2} = 19.5 min (major); 80:20 e.r.).

¹H NMR (600 MHz, DMSO) δ 8.55 (s, 1H), 8.17 – 7.98 (m, 3H), 7.70 – 7.55 (m, 5H), 7.55 – 7.42 (m, 3H), 6.69 (d, J = 8.9 Hz, 2H), 5.09 (dd, J_1 = 9.4 Hz, J_2 = 2.6 Hz, 1H), 3.59 (s, 3H), 1.51 – 1.40 (m, 1H), 1.05 – 0.87 (m, 3H), 0.58 (t, J = 6.9 Hz, 3H).

¹³C NMR (75 MHz, DMSO) δ 203.4, 168.9, 158.2, 150.2, 137.8, 134.1, 133.5, 132.0, 130.8, 128.7, 128.4, 128.3, 126.5, 123.3, 122.8, 113.5, 68.2, 54.9, 50.6, 31.1, 20.6, 14.1.

HRMS (ESI): m/z [M+H]⁺ for C₂₆H₂₅NO₃ (calcd 400.1868); found 400.1914

IR: ν = 2958, 1692, 1529, 1326, 1298, 1252, 863, 776, 695, 593 cm⁻¹

m.p. 103.4–104.8 °C

Compound 21'

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 120h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IG (25 cm × 0.46 cm ID), hexane/iso-propanol = 50/50, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 22.3 min (major), t_{R2} = 37.0 min (minor); 56:44 e.r.).

¹H NMR (600 MHz, DMSO) δ 9.32 (s, 1H), 7.79 – 7.61 (m, 4H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.89 (dd, *J₁* = 11.3 Hz, *J₂* = 1.7 Hz, 1H), 3.72 (s, 3H), 1.97 – 1.86 (m, 1H), 1.25 – 1.22 (m, 1H), 1.21 – 1.13 (m, 1H), 1.11 – 1.00 (m, 1H), 0.75 (t, *J* = 7.3 Hz, 3H).

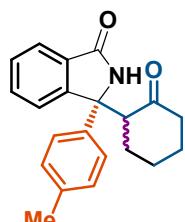
¹³C NMR (151 MHz, DMSO) δ 200.7, 168.8, 158.4, 148.4, 139.0, 133.5, 132.5, 130.9, 130.8, 128.1, 127.8, 127.5, 126.9, 124.1, 122.3, 113.9, 68.1, 55.1, 51.2, 31.1, 20.8, 14.1.

MS (ESI): m/z [M+H]⁺ for C₂₆H₂₅NO₃ (calcd 400.1868); found 400.3

IR: ν = 3058, 2961, 1679, 1530, 1351, 1331, 1254, 1031, 873, 687, 655, 573 cm⁻¹

m.p. 103.4–104.8 °C

(R)-3-((S)-2-oxocyclohexyl)-3-(p-tolyl)isoindolin-1-one (22/22')



Isoindolinone alcohol **SI-6** (23.9 mg, 0.1 mmol) afforded products **22** (26.2 mg, 82% yield) and **22'** (4.5 mg, 15% yield) as white solids.

Compound 22

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 70/30, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 12.0 min (major), t_{R2} = 15.3 min (minor); 63:37 e.r.).

¹H NMR (300 MHz, Acetone) δ 7.68 (d, *J* = 7.4 Hz, 1H), 7.62 – 7.37 (m, 5H), 7.30 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.30 (dd, *J₁* = 10.8 Hz, *J₂* = 6.7 Hz, 1H), 2.68 – 2.55 (m, 1H), 2.30 – 2.06 (m, 5H), 2.17 – 2.07 (m, 1H), 1.87 – 1.53 (m, 3H), 1.50 – 1.30 (m, 2H).

¹H NMR (300 MHz, DMSO) δ 8.26 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.44 – 7.35 (m, 3H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.25 (dd, *J₁* = 11.9 Hz, *J₂* = 5.3 Hz, 1H), 2.61 – 2.53 (m, 1H), 2.21 (s, 3H), 2.13 (d, *J* = 12.3 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.76 – 1.60 (m, 2H), 1.59 – 1.41 (m, 1H), 1.39 – 1.12 (m, 2H).

¹³C NMR (151 MHz, DMSO) δ 210.1, 169.5, 150.6, 140.6, 135.6, 132.2, 130.5, 128.9, 127.9, 124.3, 122.9, 122.4, 66.6, 55.2, 42.7, 28.6, 28.1, 24.3, 20.4.

HRMS (ESI): m/z [M+H]⁺ for C₂₁H₂₁NO₂ (calcd 320.1606); found 320.1645

IR: ν = 3306, 3109, 2935, 1689, 1480, 1306, 1164, 1130, 914, 739, 548 cm⁻¹

m.p. 243.5–245.1 °C

Compound 22'

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 5.8 min (minor), t_{R2} = 8.8 min (major); 78:22 e.r.).

¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.58 – 7.41 (m, 2H), 7.24 – 7.00 (m, 5H), 3.36 (dd, *J*₁ = 12.6 Hz, *J*₂ = 5.0 Hz, 1H), 2.46 – 2.14 (m, 6H), 2.13 – 1.98 (m, 1H), 1.97 – 1.79 (m, 1H), 1.74 – 1.63 (m, 2H), 1.54 – 1.32 (m, 1H).

¹H NMR (600 MHz, CD₃CN) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.50 (td, *J*₁ = 7.6 Hz, *J*₂ = 1.1 Hz, 1H), 7.40 (td, *J*₁ = 7.4 Hz, *J*₂ = 0.7 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.27 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 3.80 (dd, *J*₁ = 12.9 Hz, *J*₂ = 4.7 Hz, 1H), 2.41 (m, 1H), 2.28 (s, 3H), 2.15 – 2.11 (m, 2H), 2.06 – 1.99 (m, 1H), 1.99 – 1.95 (m, 1H), 1.85 – 1.78 (m, 1H), 1.77 – 1.66 (m, 1H), 1.63 – 1.52 (m, 1H), 1.35 (qd, *J*₁ = 12.9 Hz, *J*₂ = 3.7 Hz, 1H).

¹³C NMR (151 MHz, CD₃CN) δ 209.9, 170.9, 156.0, 155.4, 151.6, 140.4, 138.2, 133.1, 132.8, 130.3, 128.7, 126.2, 124.4, 123.8, 68.2, 56.3, 44.0, 30.8, 28.7, 26.0, 20.9.

MS (ESI): m/z [M+H]⁺ for C₂₁H₂₁NO₂ (calcd 320.1606); found 320.2

IR: ν = 3195, 2937, 1687, 1529, 1314, 1281, 1125, 867, 740, 613, 546 cm⁻¹

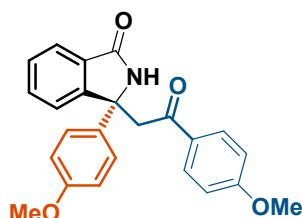
m.p. 144.8–146.3 °C

3.2. General procedure for synthesis of 3-alkylaryl isoindolinone derivatives **16**, **19** and **24-34**

3-aryl 3-hydroxyisoindolinones (0.1 mmol), chiral phosphoric acid **BA3** (7.5 mg, 0.01 mmol, 10 mol %) and ketone (0.5 mmol) were placed in a 10 mL Schlenk tube equipped with a magnetic stir bar under an argon atmosphere. Acetonitrile (1 mL) was added and reaction mixture was stirred at 80 °C until full consumption of starting material (monitored by TLC). The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by column chromatography on silica gel to afford the corresponding products.

3.2.1. Characterization data for 3-alkylaryl isoindolinone derivatives **16**, **19** and **24-34**

(*R*)-3-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (**16**)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **16** (34.4 mg, 89% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 72h. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 13.9 min (major), t_{R2} = 22.7 min (minor); 92:8 e.r.).

¹H NMR (600 MHz, CD₃CN) δ 8.01 – 7.89 (m, 2H), 7.76 – 7.68 (m, 1H), 7.62 (s, 1H), 7.55 (td, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.44 (td, J_1 = 7.4 Hz, J_2 = 0.9 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.02 – 6.96 (m, 2H), 6.86 – 6.78 (m, 2H), 4.71 (d, J = 18.0 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.33 (d, J = 18.0 Hz, 1H).

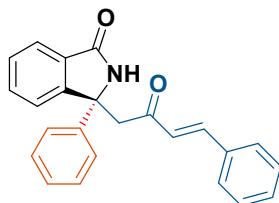
¹³C NMR (151 MHz, CD₃CN) δ 197.2, 170.0, 165.0, 159.9, 153.2, 134.9, 133.3, 131.5, 131.1, 130.8, 129.2, 127.1, 124.4, 123.7, 115.0, 114.8, 65.2, 56.4, 55.9, 46.7.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₂₁NO₄ (calcd 388.1504); found 388.1544

IR: ν = 3394, 2949, 1697, 1532, 1371, 1284, 1177, 1023, 867, 789, 697, 580 cm⁻¹

m.p. 160.4–161.7 °C

(*R,E*)-3-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylisoindolin-1-one (19)



Isoindolinone alcohol **SI-1** (22.5 mg, 0.2 mmol) afforded product **19** (48.4 mg, 69% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 4/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IB (25 cm × 0.46 cm ID), hexane/iso-propanol = 50/50, λ 310 nm, 1.0 mL/min flow rate; t_{R1} = 23.7 min (major), t_{R2} = 37.6 min (minor); 96:4 e.r.).

$[\alpha]_D^{20} = +395^\circ$ (c 1.04, CHCl₃)

¹H NMR (300 MHz, DMSO) δ 8.97 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.66 – 7.50 (m, 7H), 7.47 – 7.38 (m, 4H), 7.37 – 7.30 (m, 2H), 7.28 – 7.21 (m, 1H), 6.77 (d, J = 16.3 Hz, 1H), 4.05 (d, J = 16.0 Hz, 1H), 3.62 (d, J = 16.0 Hz, 1H).

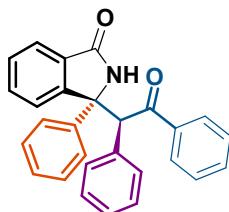
¹³C NMR (151 MHz, DMSO) δ 196.3, 168.8, 150.7, 142.7, 142.4, 134.3, 131.8, 130.8, 130.6, 129.0, 128.5, 128.4, 128.1, 127.2, 126.8, 125.1, 123.3, 122.9, 64.5, 48.0.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₁₉NO₂ (calcd 354.1449); found 354.1492

IR: ν = 3309, 3113, 2922, 1674, 1509, 1237, 1201, 1004, 817, 700 cm⁻¹

m.p. 221.2–222.5 °C

(*R*)-3-((*S*)-2-oxo-1,2-diphenylethyl)-3-phenylisoindolin-1-one (23)



Isoindolinone alcohol **SI-1** (22.5 mg, 0.1 mmol) afforded product **23** (27.9 mg, 69% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 12.3 min (major), t_{R2} = 22.7 min (minor); 95:5 e.r.).

$[\alpha]_D^{20} = -272^\circ$ (c 0.56, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.90 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.59 – 7.50 (m, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.34 – 7.21 (m, 4H), 7.21 – 7.11 (m, 3H), 7.05 – 6.96 (m, 3H), 6.61 (s, 1H).

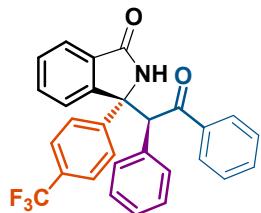
¹³C NMR (75 MHz, DMSO) δ 198.1, 169.4, 149.8, 143.1, 136.0, 133.7, 133.2, 131.7, 130.3, 130.2, 128.9, 128.8, 128.8, 128.0, 127.8, 127.5, 127.3, 124.9, 123.8, 122.6, 68.8, 58.1.

HRMS (ESI): m/z [M+H]⁺ for C₂₈H₂₁NO₂ (calcd 404.1606); found 404.1650

IR: ν = 3433, 1699, 1512, 1365, 1215, 980, 789, 700, 570 cm⁻¹

m.p. 272.8–274.7 °C (decomposition)

(R)-3-((S)-2-oxo-1,2-diphenylethyl)-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (24)



Isoindolinone alcohol **SI-5** (29.3 mg, 0.1 mmol) afforded product **24** (43.4 mg, 92% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 20/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 8.5 min (major), t_{R2} = 14.6 min (minor); >99:1 e.r.).

$[\alpha]_D^{20} = -490^\circ$ (c 1.02, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 9.11 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 7.3 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.60 – 7.51 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.15 – 7.10 (m, 2H), 7.05 – 6.98 (m, 3H), 6.69 (s, 1H).

¹³C NMR (151 MHz, DMSO) δ 197.8, 169.1, 148.8, 148.2, 135.7, 133.6, 133.0, 131.7, 130.4, 130.1, 128.8, 128.7, 128.2 (q, ²*J*_{C-CF₃} = 31.2 Hz), 128.2, 127.7, 127.4, 126.1 (q, ³*J*_{C-CF₃} = 3.6 Hz), 125.7, 124.6 (q, ¹*J*_{C-CF₃} = 272.1 Hz), 123.7, 122.6, 68.5, 58.4.

HRMS (ESI): m/z [M+H]⁺ for C₂₉H₂₀F₃NO₂ (calcd 472.1480); found 472.1513

IR: ν = 3449, 1693, 1526, 1319, 1265, 120, 897, 843, 787, 696, 568 cm⁻¹

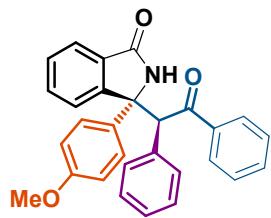
m.p. 278.3–279.9 °C (decomposition)

Scale-up procedure

3-hydroxyisoindolinone **SI-5** (600.0 mg, 2.0 mmol), chiral phosphoric acid **BA3** (154.4 mg, 0.2 mmol) and ketone (2.94 g, 10.2 mmol) were placed in a 50 mL Schlenk tube equipped with a magnetic stir bar under an argon atmosphere. Acetonitrile (20 mL) was added and reaction mixture was stirred at 80 °C until full consumption of **SI-5** (monitored by TLC) (70 hours). The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 20/1) to afford the corresponding product **24** as a white solid (888 mg, 92% yield, 99:1 e.r.).

Enantiomeric ratio determined by chiral HPLC (Dr. Maisch ReproSil Chiral-AM (15 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 6.1 min (major), t_{R2} = 10.6 min (minor)).

(*R*)-3-(4-methoxyphenyl)-3-((*S*)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (**25**)



Isoindolinone alcohol **SI-2** (25.5 mg, 0.1 mmol) afforded product **25** (38.6 mg, 89% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 60h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 17.0 min (major), t_{R2} = 28.0 min (minor); 99:1 e.r.).

$[\alpha]_D^{20} = -463^\circ$ (c 1.02, CHCl₃).

¹H NMR (600 MHz, DMSO) δ 8.83 (s, 1H), 8.13 – 8.01 (m, 3H), 7.72 (d, J = 8.5 Hz, 2H), 7.54 (dd, J_1 = 16.0, J_2 = 7.9 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.30 – 7.19 (m, 2H), 7.18 – 7.10 (m, 2H), 7.06 – 6.94 (m, 3H), 6.84 (d, J = 8.5 Hz, 2H), 6.56 (s, 1H), 3.67 (s, 3H).

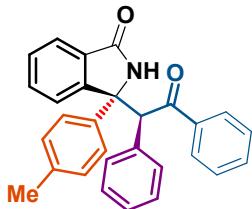
¹³C NMR (75 MHz, DMSO) δ 198.0, 169.1, 158.2, 150.1, 136.0, 134.8, 133.5, 133.2, 131.4, 130.2, 130.1, 128.7, 128.7, 127.7, 127.7, 127.3, 126.1, 123.7, 122.4, 113.9, 68.2, 57.8, 55.0.

HRMS (ESI): m/z [M+H]⁺ for C₂₉H₂₃NO₃ (calcd 434.1711); found 434.1760

IR: ν = 3336, 1694, 1527, 1299, 1282, 1245, 891, 784, 699, 630 cm⁻¹

m.p. 262.4–264.0 °C (decomposition)

(R)-3-(4-methylphenyl)-3-((S)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (26)



Isoindolinone alcohol **SI-6** (23.9 mg, 0.1 mmol) afforded product **26** (32.6 mg, 78% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 40h. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 13.1 min (major), t_{R2} = 21.4 min (minor); 96:4 e.r.).

$[\alpha]_D^{20} = -480^\circ$ (c 1.03, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.83 (s, 1H), 8.10 – 8.03 (m, 3H), 7.69 (d, J = 8.4 Hz, 2H), 7.56 – 7.51 (m, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.28 – 7.21 (m, 2H), 7.17 – 7.12 (m, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.03 – 6.97 (m, 3H), 6.58 (s, 1H), 2.19 (s, 3H).

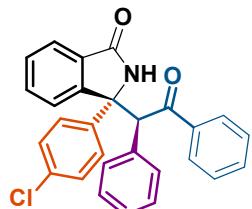
¹³C NMR (75 MHz, DMSO) δ 198.0, 169.0, 149.8, 140.1, 136.2, 135.9, 133.5, 133.1, 131.4, 130.2, 130.1, 129.2, 128.7, 128.6, 127.7, 127.7, 127.3, 124.7, 123.7, 122.4, 68.4, 57.8, 20.3.

HRMS (ESI): m/z [M+H]⁺ for C₂₉H₂₃NO₂ (calcd 418.1762); found 418.1810

IR: ν = 3357, 2922, 1693, 1526, 1215, 1140, 1020, 890, 695 cm⁻¹

m.p. 260.2–262.0 °C (decomposition)

(R)-3-(4-chlorophenyl)-3-((S)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (27)



Isoindolinone alcohol **SI-4** (26.0 mg, 0.1 mmol) afforded product **27** (38.1 mg, 87% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 11.5 min (major), t_{R2} = 21.8 min (minor); 97.5:2.5 e.r.).

$[\alpha]_D^{20} = -465^\circ$ (c 1.02, CHCl₃)

¹H NMR (300 MHz, DMSO) δ 9.00 (s, 1H), 8.15 – 7.99 (m, 3H), 7.86 (d, J = 8.7 Hz, 2H), 7.61 – 7.51 (m, 2H), 7.48 – 7.34 (m, 4H), 7.31 – 7.22 (m, 2H), 7.17 – 6.95 (m, 5H), 6.60 (s, 1H).

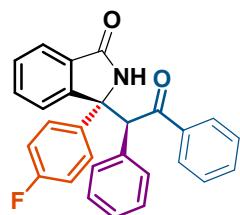
¹³C NMR (151 MHz, DMSO) δ 197.8, 169.1, 149.2, 142.3, 135.8, 133.5, 133.0, 131.8, 131.6, 130.3, 130.1, 128.7, 128.7, 128.6, 128.0, 127.7, 127.4, 126.8, 123.6, 122.5, 68.3, 58.2.

HRMS (ESI): m/z [M+H]⁺ for C₂₈H₂₀ClNO₂ (calcd 438.1216); found 438.1262

IR: ν = 3356, 1696, 1508, 1302, 1218, 1130, 886, 829, 780, 690 cm⁻¹

m.p. 272.6–273.8 °C (decomposition)

(R)-3-(4-fluorophenyl)-3-((S)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (**28**)



Isoindolinone alcohol **SI-3** (24.3 mg, 0.1 mmol) afforded product **28** (37.1 mg, 88% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 11.6 min (major), t_{R2} = 20.1 min (minor); 97:3 e.r.).

$[\alpha]_D^{20} = -551^\circ$ (c 1.16, CHCl₃).

¹H NMR (600 MHz, DMSO) δ 8.98 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.91 – 7.82 (m, 2H), 7.60 – 7.50 (m, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.32 – 7.22 (m, 2H), 7.19 – 7.08 (m, 4H), 7.05 – 6.96 (m, 3H), 6.59 (s, 1H).

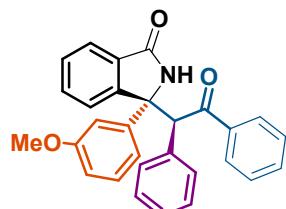
¹³C NMR (151 MHz, DMSO) δ 197.9, 169.0, 161.2 (d, $^1J_{C-F}$ = 243.9 Hz), 149.5, 139.3 (d, $^4J_{C-F}$ = 2.9 Hz), 135.9, 133.5, 133.1, 131.6, 130.3, 130.1, 128.7, 128.7, 127.9, 127.7, 127.3, 127.0 (d, $^3J_{C-F}$ = 7.9 Hz), 123.7, 122.5, 115.3 (d, $^2J_{C-F}$ = 21.3 Hz), 68.2, 58.2.

HRMS (ESI): m/z [M+H]⁺ for C₂₈H₂₀FNO₂ (calcd 422.1512); found 422.1558

IR: ν = 3430, 1694, 1525, 1214, 1165, 1045, 891, 689, 569 cm⁻¹

m.p. 271.7–273.2 °C (decomposition)

(R)-3-(3-methoxyphenyl)-3-((S)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (29)



Isoindolinone alcohol **SI-8** (25.5 mg, 0.1 mmol) afforded product **29** (33.9 mg, 78% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 48h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 13.6 min (major), t_{R2} = 25.2 min (minor); 94:6 e.r.).

¹H NMR (600 MHz, DMSO) δ 8.89 (s, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.10 – 8.05 (m, 2H), 7.59 – 7.50 (m, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.30 – 7.23 (m, 2H), 7.21 (t, J = 8.2 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.04 – 6.97 (m, 3H), 6.78 – 6.72 (m, 1H), 6.60 (s, 1H), 3.68 (s, 3H).

¹³C NMR (75 MHz, DMSO) δ 197.9, 169.1, 159.5, 149.5, 144.8, 136.0, 133.5, 133.1, 131.4, 130.3, 130.1, 129.7, 128.7 (2C), 127.9, 127.7, 127.3, 123.7, 122.4, 117.1, 112.0, 111.3, 68.6, 57.8, 55.0.

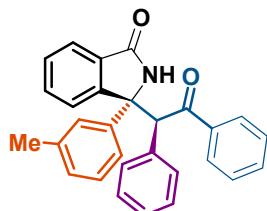
¹³C NMR (75 MHz, Acetone) δ 198.5, 169.0, 160.1, 149.8, 144.6, 136.4, 133.4, 132.9, 131.3, 130.8, 130.2, 129.8, 128.7, 128.6, 127.8, 127.7, 127.3, 123.4, 122.7, 117.0, 112.2, 111.1, 68.8, 58.4, 54.5.

HRMS (ESI): m/z [M+H]⁺ for C₂₉H₂₃NO₃ (calcd 434.1711); found 434.1761

IR: ν = 3417, 1673, 1513, 1366, 1217, 1047, 903, 823, 700, 549 cm⁻¹

m.p. 270.6–272.0 °C (decomposition)

(R)-3-((S)-2-oxo-1,2-diphenylethyl)-3-(m-tolyl)isoindolin-1-one (30)



Isoindolinone alcohol **SI-7** (23.9 mg, 0.1 mmol) afforded product **30** (31.9 mg, 77% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Dr. Maisch ReproSil Chiral-AM (15 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 8.7 min (major), t_{R2} = 13.6 min (minor); 97.5:2.5 e.r.).

$[\alpha]_D^{20} = -385^\circ$ (c 0.95, CHCl₃)

¹H NMR (600 MHz, DMSO) δ 8.83 (s, 1H), 8.07 (dd, J_1 = 11.1 Hz, J_2 = 7.9 Hz, 3H), 7.69 (d, J = 8.2 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.31 – 7.20 (m, 2H), 7.18 – 7.13 (m, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 6.6 Hz, 3H), 6.58 (s, 1H), 2.19 (s, 3H).

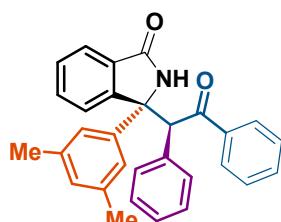
¹³C NMR (151 MHz, DMSO) δ 197.9, 169.2, 149.8, 140.1, 136.2, 135.9, 134.3, 133.5, 133.1, 132.6, 131.4, 130.2, 130.1, 129.1, 128.7, 127.7, 127.6, 127.2, 124.7, 123.6, 122.9, 122.3, 68.4, 57.8, 20.3.

HRMS (ESI): m/z [M+H]⁺ for C₂₉H₂₃NO₂ (calcd 418.1762); found 418.1811

IR: ν = 3357, 1693, 1525, 1214, 1155, 1131, 887, 780, 693 cm⁻¹

m.p. 246.9–248.7 °C (decomposition)

(R)-3-(3,5-dimethylphenyl)-3-((S)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (31)



Isoindolinone alcohol **SI-10** (25.3 mg, 0.1 mmol) afforded product **31** (32.0 mg, 74% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 40h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 5.7 min (major), t_{R2} = 8.4 min (minor); 90:10 e.r.).

¹H NMR (600 MHz, DMSO) δ 8.77 (s, 1H), 8.11 – 8.02 (m, 3H), 7.58 – 7.50 (m, 2H), 7.48 – 7.41 (m, 4H), 7.29 – 7.21 (m, 2H), 7.17 – 7.12 (m, 2H), 7.04 – 6.96 (m, 3H), 6.80 (s, 1H), 6.57 (s, 1H), 2.19 (s, 6H).

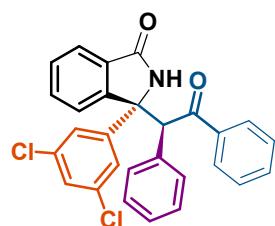
¹³C NMR (75 MHz, DMSO) δ 198.1, 169.1, 149.7, 143.0, 137.6, 136.1, 133.4, 133.1, 131.4, 130.3, 130.1, 128.7, 128.7, 128.5, 127.8, 127.6, 127.2, 123.7, 122.6, 122.4, 68.5, 57.9, 21.1.

HRMS (ESI): m/z [M+H]⁺ for C₃₀H₂₅NO₂ (calcd 432.1919); found 432.1968

IR: ν = 3441, 1696, 1510, 1365, 1232, 1214, 891, 849, 780, 586 cm⁻¹

m.p. 284.4–286.1 °C (decomposition)

(*R*)-3-(3,5-dichlorophenyl)-3-((*S*)-2-oxo-1,2-diphenylethyl)isoindolin-1-one (**32**)



Isoindolinone alcohol **SI-11** (29.4 mg, 0.1 mmol) afforded product **32** (45.2 mg, 96% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 10/1. Reaction time: 60h.

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 5.7 min (major), t_{R2} = 7.3 min (minor); 91:9 e.r.).

¹H NMR (300 MHz, DMSO) δ 9.20 (s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.11 – 7.88 (m, 4H), 7.69 – 7.38 (m, 5H), 7.36 – 7.23 (m, 2H), 7.21 – 6.89 (m, 5H), 6.62 (s, 1H).

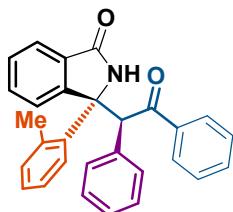
¹³C NMR (151 MHz, DMSO) δ 197.7, 169.0, 148.3, 147.8, 135.8, 134.5, 133.6, 132.9, 131.9, 130.3, 130.1, 128.8, 128.7, 128.4, 127.8, 127.4, 126.9, 123.9, 123.6, 122.6, 68.1, 58.5.

HRMS (ESI): m/z [M+H]⁺ for C₂₈H₁₉Cl₂NO₂ (calcd 472.0826); found 472.0882

IR: ν = 3417, 1693, 1480, 1215, 1181, 976, 906, 819, 706 cm⁻¹

m.p. 295.3–297.1 °C (decomposition)

(R)-3-((S)-2-oxo-1,2-diphenylethyl)-3-(*o*-tolyl)isoindolin-1-one (33)



Isoindolinone alcohol **SI-9** (23.9 mg, 0.1 mmol) afforded product **33** (16.3 mg, 39% yield) as a white solid.

Column chromatography eluent: dichloromethane/ethyl acetate = 15/1. Reaction time: 5 days. Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack AD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 10.7 min (major), t_{R2} = 17.4 min (minor); 60:40 e.r.).

¹H NMR (600 MHz, Acetone) δ 8.14 (d, J = 7.6 Hz, 2H), 7.92 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.47 (t, J = 7.7 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.16 – 7.04 (m, 5H), 7.04 – 6.96 (m, 3H), 6.61 (s, 1H), 2.00 (s, 3H).

¹³C NMR (151 MHz, DMSO) δ 198.1, 169.2, 148.1, 139.1, 136.3, 135.9, 133.5, 133.2, 132.7, 132.2, 131.5, 130.5, 128.8, 128.7, 127.9, 127.5, 127.2, 127.1, 126.8, 126.1, 123.6, 121.7, 69.0, 58.6, 21.4.

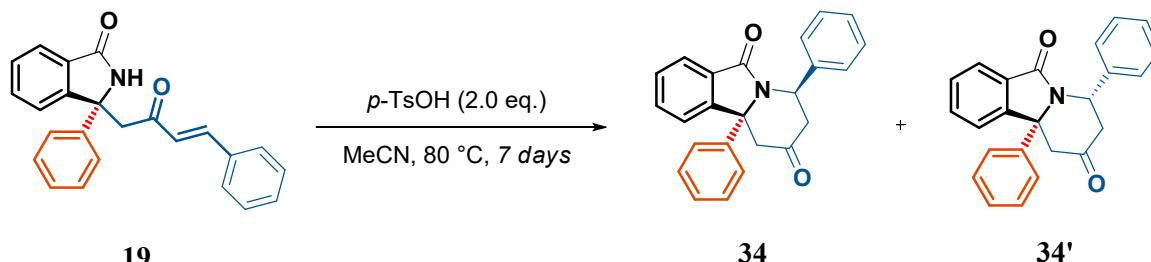
HRMS (ESI): m/z [M+H]⁺ for C₂₉H₂₃NO₂ (calcd 418.1762); found 418.1812

IR: ν = 3437, 1670, 1513, 1361, 1264, 1217, 980, 826, 703, 553 cm⁻¹

m.p. 243.3–245.0 °C (decomposition)

3.3. Transformations of products

3.3.1. Transformation 1:



To a solution of **19** (30 mg, 0.085 mmol) in acetonitrile (1.0 mL) *p*-toluenesulfonic acid monohydrate (32.3 mg, 0.17 mmol) was added, and the resulting mixture was stirred in an oil bath at 80 °C. After 7 days, the solvent was evaporated and the residue was purified by column chromatography (dichloromethane/ethyl acetate = 50/1) to afford products **34** (2.9 mg, 10% yield) and **34'** (13.2 mg, 44% yield) as white solids.

Compound 34

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IB (25 cm × 0.46 cm ID), hexane/iso-propanol = 85/15, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 21.9 min (minor), t_{R2} = 24.0 min (major); 93:7 e.r.).

¹H NMR (300 MHz, DMSO) (600 MHz, DMSO) δ 7.65 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 6.8 Hz, 3H), 7.58 (td, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.34 – 7.28 (m, 3H), 7.25 – 7.20 (m, 3H), 5.48 (dd, J_1 = 7.3 Hz, J_2 = 2.4 Hz, 1H), 4.27 (d, J = 18.5 Hz, 1H), 3.20 (d, J = 18.5 Hz, 1H), 2.70 (dd, J_1 = 16.4 Hz, J_2 = 7.4 Hz, 1H), 2.38 (dd, J_1 = 16.3 Hz, J_2 = 2.5 Hz, 1H).

¹³C NMR (75 MHz, DMSO) δ 205.0, 166.6, 150.4, 142.5, 141.3, 132.5, 129.7, 128.5, 127.9, 127.0, 125.9, 124.5, 123.3, 122.3, 67.6, 53.3, 47.3, 46.0.

MS (ESI): m/z [M+H]⁺ for C₂₄H₁₉NO₂ (calcd 354.1449); found 354.2

IR: ν = 2898, 1682, 1510, 1372, 1043, 994, 803, 703, 573, 424 cm⁻¹

m.p. 232.6–234.0 °C (decomposition)

Compound 34'

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack IB (25 cm × 0.46 cm ID), hexane/iso-propanol = 85/15, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 18.2 min (major), t_{R2} = 37.9 min (minor); 93:7 e.r.).

$^1\text{H NMR}$ (300 MHz, DMSO) (600 MHz, DMSO) δ 7.84 – 7.77 (m, 1H), 7.57 – 7.48 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 7.15 – 7.04 (m, 9H), 5.78 (t, J = 7.1 Hz, 1H), 3.96 (d, J = 16.0 Hz, 1H), 2.99 – 2.87 (m, 2H), 2.58 – 2.52 (m, 1H).

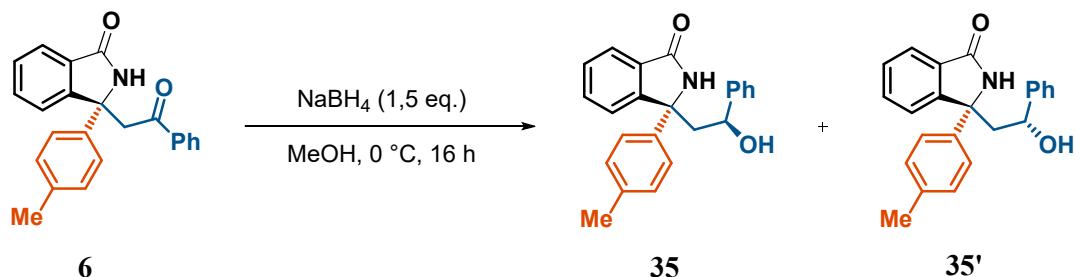
$^{13}\text{C NMR}$ (75 MHz, DMSO) δ 206.1, 168.5, 151.9, 140.9, 139.3, 132.7, 129.0, 128.6, 128.3, 127.8, 127.5, 126.8, 126.3, 123.3, 122.2, 67.6, 52.3, 47.5, 42.8.

HRMS (ESI): m/z [M+H]⁺ for C₂₄H₁₉NO₂ (calcd 354.1449); found 354.1501

IR: ν = 3029, 1679, 1512, 1373, 1227, 1128, 1025, 859, 692, 483, 446 cm⁻¹

m.p. 168.2–169.9 °C (decomposition)

3.3.2. Transformation 2:



To a stirred solution of **6** (75.0 mg, 0.22 mmol) in methanol (2.2 mL), NaBH₄ (12.5 mg, 0.33 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature until full consumption of **6** (monitored by TLC), and then quenched by saturated NH₄Cl (aq.). The mixture was extracted with EtOAc (3×10 mL), the organic extracts were combined, dried over Na₂SO₄, filtered and concentrated in vacuo. The obtained crude residue was purified by column chromatography (dichloromethane/ethyl acetate = 4/1) to give the corresponding alcohols **35** (39.0 mg, 52% yield) and **35'** (31.3 mg, 41% yield) as white solids.

Compound 35

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 90/10, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 8.0 min (major), t_{R2} = 10.9 min (minor); 95:5 e.r.).

$[\alpha]_D^{20} = +135^\circ$ (c 1.00, CHCl₃)

¹H NMR (300 MHz, CD₃CN) δ 7.82 – 7.61 (m, 2H), 7.61 – 7.45 (m, 4H), 7.45 – 7.11 (m, 8H), 4.78 – 4.58 (m, 1H), 3.53 (dd, *J*₁ = 3.9 Hz, *J*₂ = 1.5 Hz, 1H), 3.00 – 2.88 (m, 1H), 2.32 (s, 3H).

¹H NMR (600 MHz, CDCl₃) δ 8.03 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.29 (m, 5H), 7.28 – 7.24 (m, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.87 (dt, *J*₁ = 11.0 Hz, *J*₂ = 2.2 Hz, 1H), 3.43 (d, *J* = 1.9 Hz, 1H), 2.89 (dt, *J*₁ = 14.7 Hz, *J*₂ = 1.9 Hz, 1H), 2.35 (s, 3H), 2.18 (dd, *J*₁ = 14.9 Hz, *J*₂ = 11.0 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 170.6, 152.4, 144.6, 138.0, 137.5, 132.3, 130.1, 129.9, 128.8, 128.2, 128.0, 125.7, 125.3, 124.2, 122.1, 72.1, 66.9, 48.2, 21.1.

MS (ESI): m/z [M+H]⁺ for C₂₃H₂₁NO₂ (calcd 344.1606); found 344.3

IR: ν = 3383, 1682, 1479, 1381, 1125, 1102, 851, 693, 578 cm⁻¹

m.p. 223.9–225.0 °C

Compound 35'

Enantiomeric ratio determined by chiral HPLC (Daicel Chiralpack OD-H (25 cm × 0.46 cm ID), hexane/iso-propanol = 75/25, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 7.0 min (major), t_{R2} = 15.2 min (minor); 95:5 e.r.)

[α]_D²⁰ = +130 ° (c 1.00, CHCl₃)

¹H NMR (300 MHz, CD₃CN) δ 7.73 – 7.59 (m, 1H), 7.49 – 7.31 (m, 5H), 7.31 – 7.03 (m, 8H), 4.41 – 4.27 (m, 1H), 3.33 (d, *J* = 4.1 Hz, 1H), 2.92 – 2.66 (m, 2H), 2.27 (s, 3H).

¹³C NMR (151 MHz, CD₃CN) δ 170.5, 152.3, 146.5, 141.2, 138.3, 133.1, 131.9, 130.3, 129.2, 129.1, 128.1, 126.8, 126.2, 124.1, 123.8, 71.5, 66.6, 48.0, 20.9.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₂₁NO₂ (calcd 344.1606); found 344.1647

IR: ν = 3236, 2030, 1683, 1527, 1316, 1135, 1018, 859, 697, 541 cm⁻¹

m.p. 87.0–88.2 °C

3.3.3. Transformation 3:



To a 25 mL Schlenk flask, **15** (25.5 mg, 0.069 mmol) was added, followed by freshly distilled dichloromethane (1.4 mL) under an argon atmosphere, and the mixture was cooled to 0 °C. Then BBr₃ (280 µL, 1.0 M solution in dichloromethane, 0.28 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 48 hours, and then quenched by H₂O. The resulting mixture was extracted with DCM (3×6 mL), the organic extracts were combined, dried over Na₂SO₄, filtered and concentrated in vacuo. The obtained crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford product **36** (24.8 mg, 97% yield) as a white solid.

Enantiomeric ratio determined by chiral HPLC (Dr. Maisch ReproSil Chiral-AM (15 cm × 0.46 cm ID), hexane/iso-propanol = 65/35, λ 254 nm, 1.0 mL/min flow rate; t_{R1} = 19.7 min (major), t_{R2} = 26.9 min (minor); 90:10 e.r.).

¹H NMR (300 MHz, DMSO) δ 9.36 (s, 1H), 8.73 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.68 – 7.57 (m, 2H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.45 – 7.23 (m, 5H), 6.67 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 17.3 Hz, 1H), 3.71 (d, *J* = 17.3 Hz, 1H), 2.36 (s, 3H).

¹³C NMR (75 MHz, DMSO) δ 196.3, 168.8, 156.3, 151.7, 143.6, 134.4, 132.8, 131.6, 130.6, 129.1, 128.1, 127.7, 126.2, 123.0, 122.7, 115.1, 64.0, 45.5, 21.1.

HRMS (ESI): m/z [M+H]⁺ for C₂₃H₁₉NO₃ (calcd 358.1398); found 358.1427

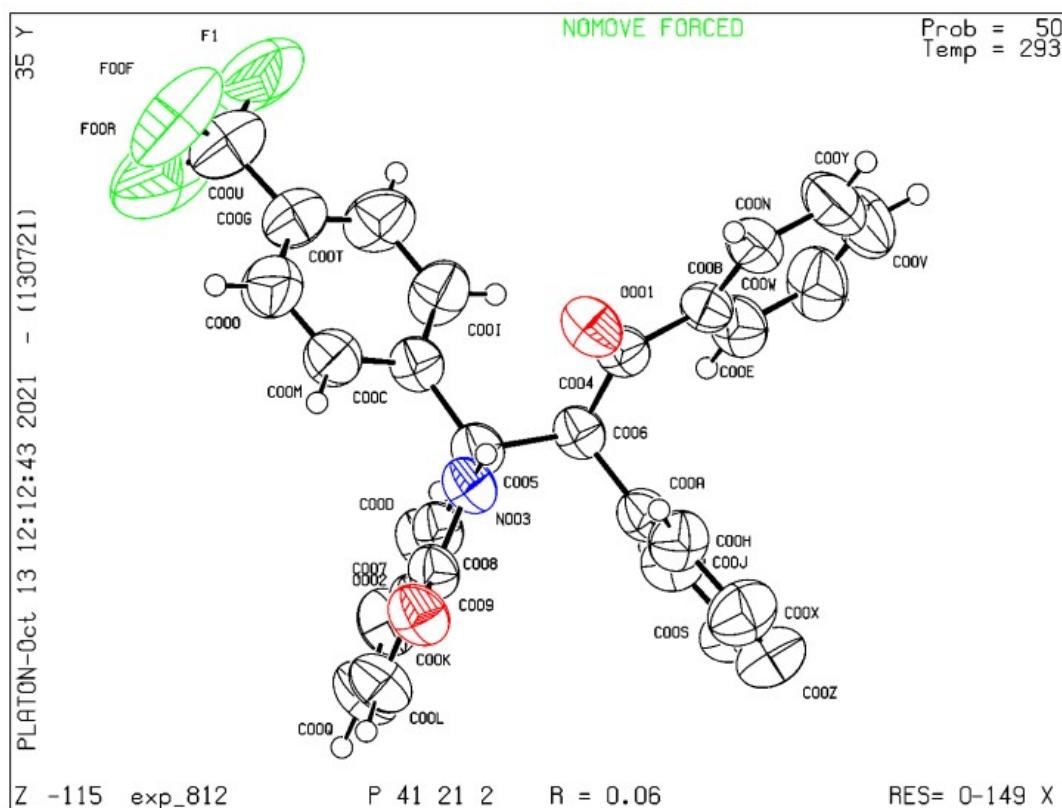
IR: $\nu = 3252, 1667, 1533, 1227, 1179, 918, 696, 580, 481 \text{ cm}^{-1}$

m.p.

146.3-148.2°

§ 4. X-ray Crystallography

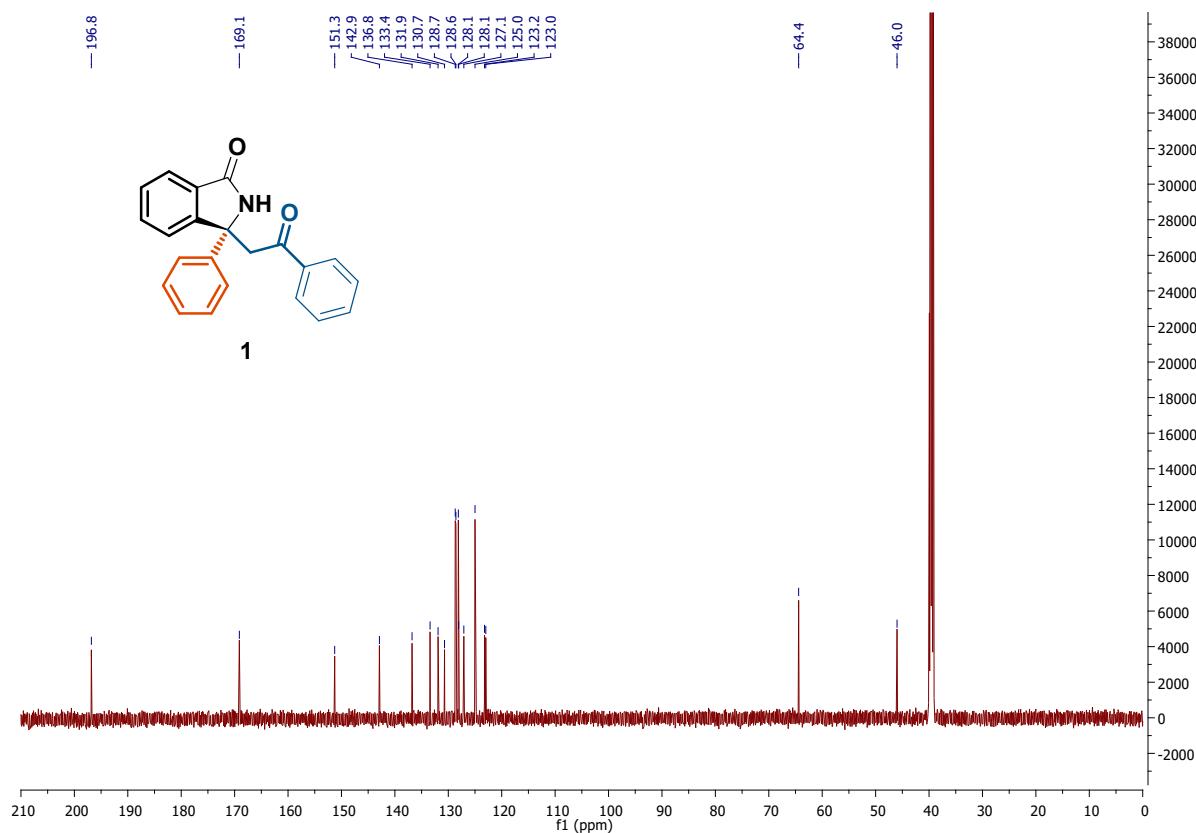
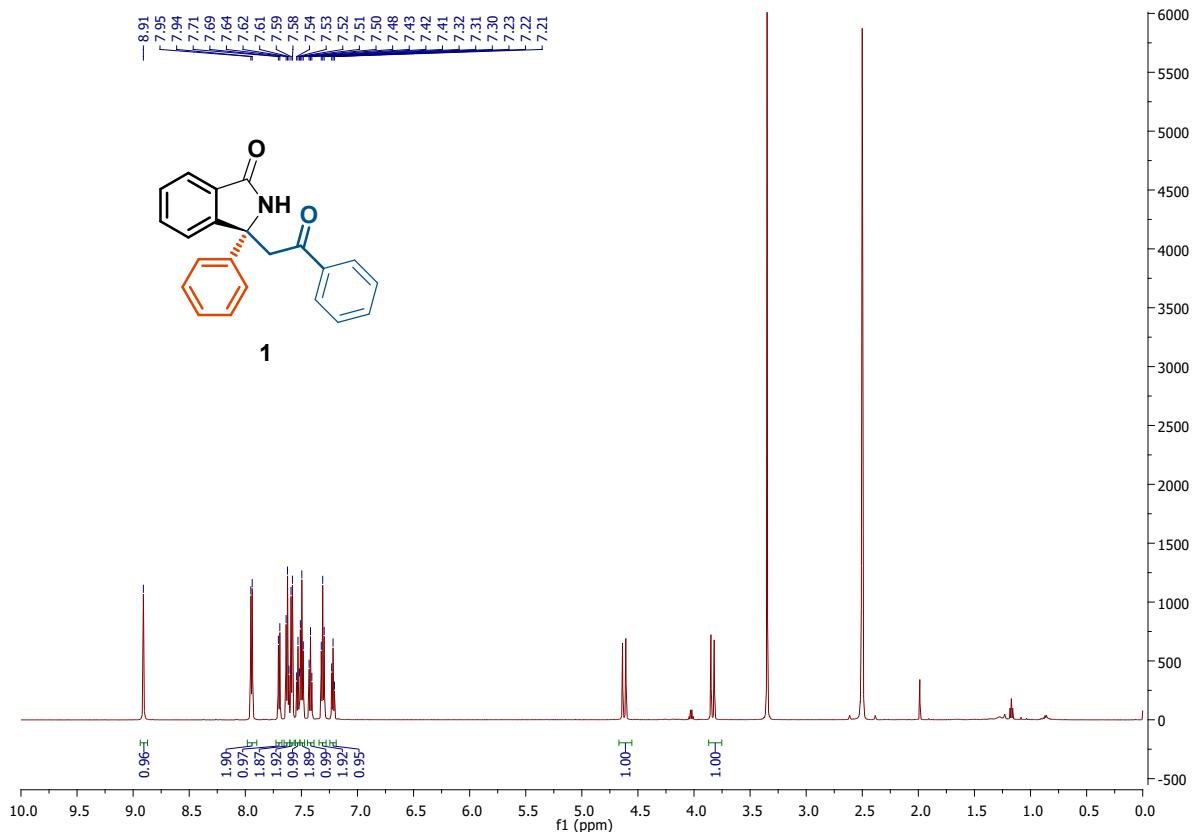
Single crystal measurement was performed on an Oxford Diffraction Xcalibur Nova R (microfocus Cu tube) at room temperature [293(2) K]. Friedel pairs were measured to unambiguously establish absolute configuration of the stereogenic centre. Program package CrysAlis PRO [CrysAlis] was used for data reduction and multi-scan absorption correction. The crystal structure was solved by direct methods using Olex2.¹ Non-hydrogen atoms were refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F_2 . Hydrogen atoms were first located in the Fourier difference map, then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication materials were generated using ORTEP3,² PLATON³ and Mercury[®]. Absolute configuration of the product **24** was determined by solving its crystal structure. Absolute configuration of other products was assigned by analogy. The crystal structure has been deposited at the Cambridge Crystallographic Centre (deposition number: CCDC 2102771). The data can be obtained free of charge at www.ccdc.cam.ac.uk/getstructures

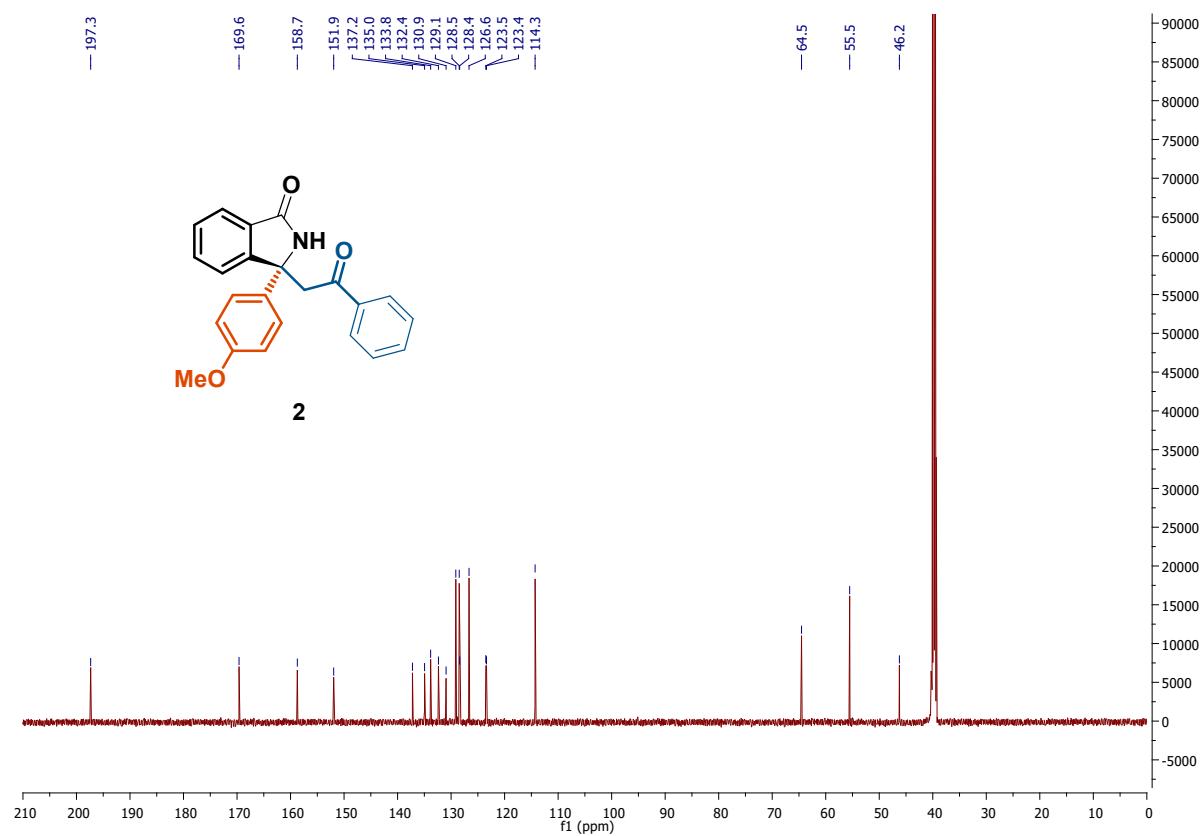
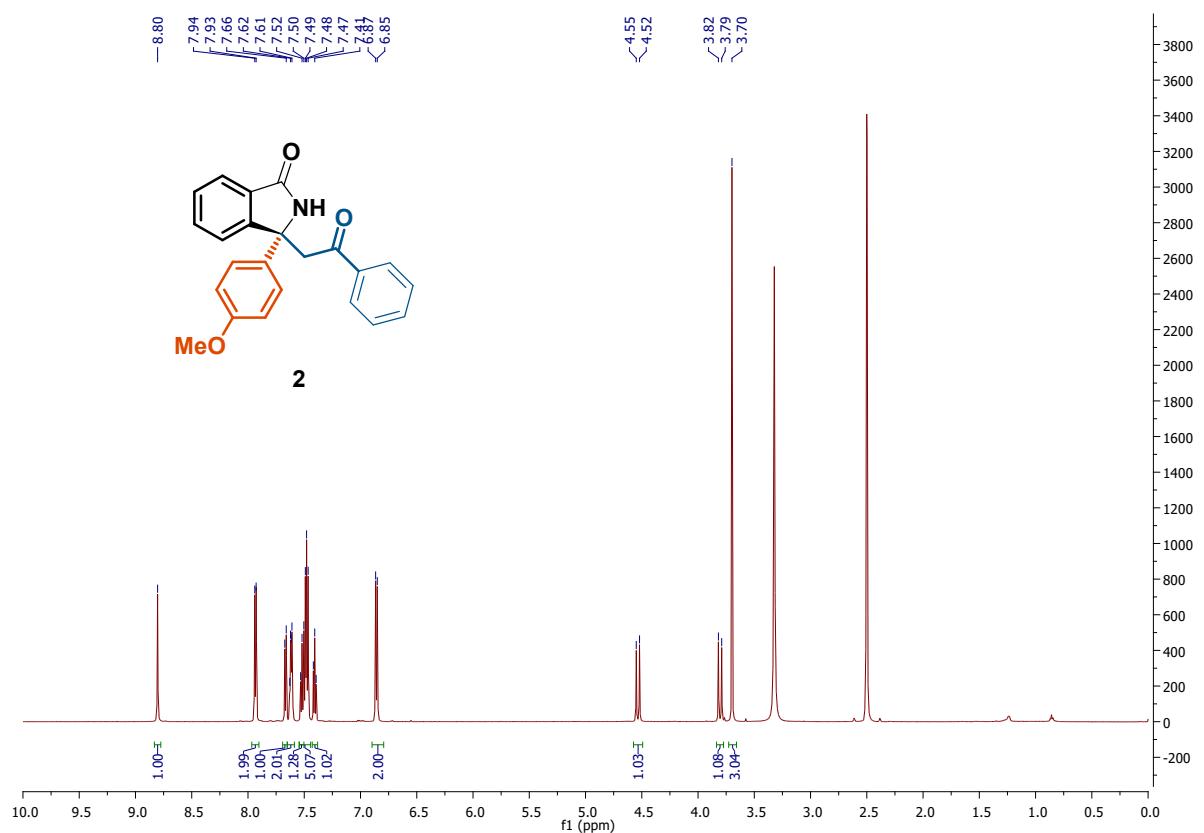


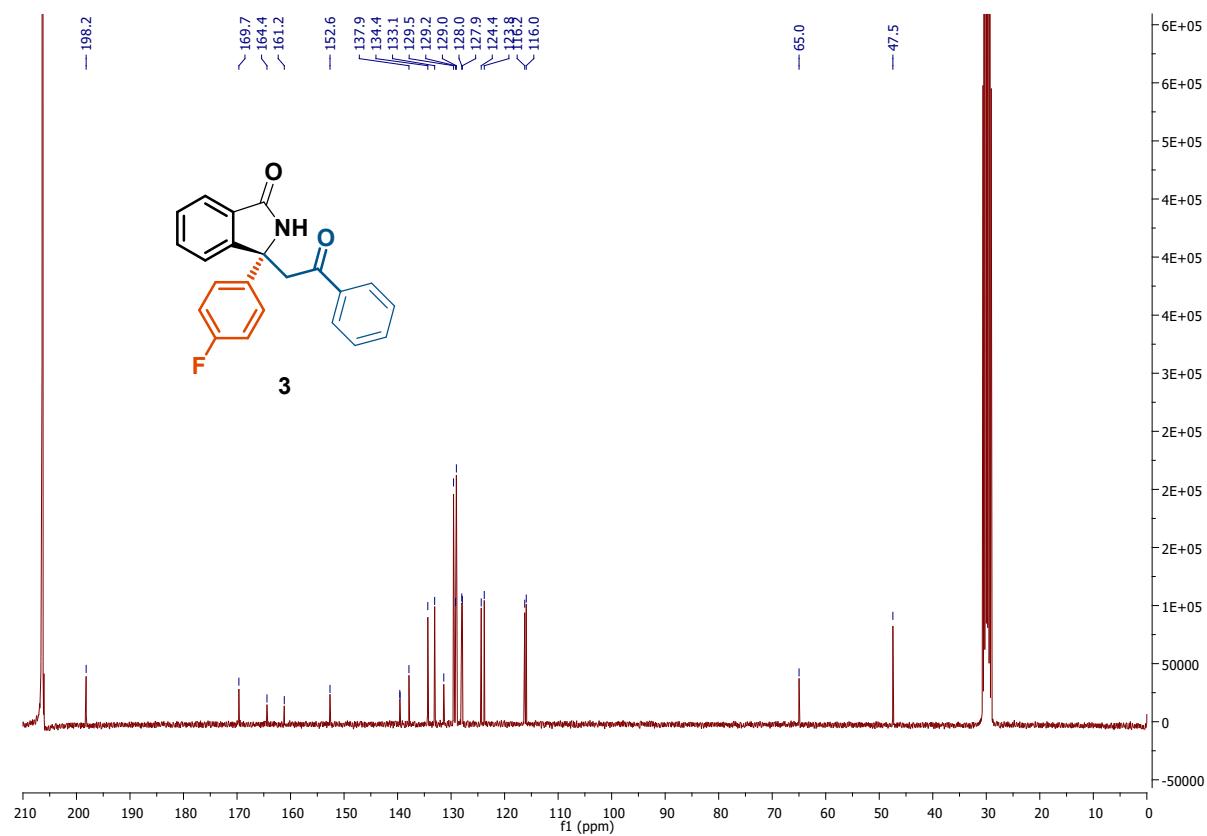
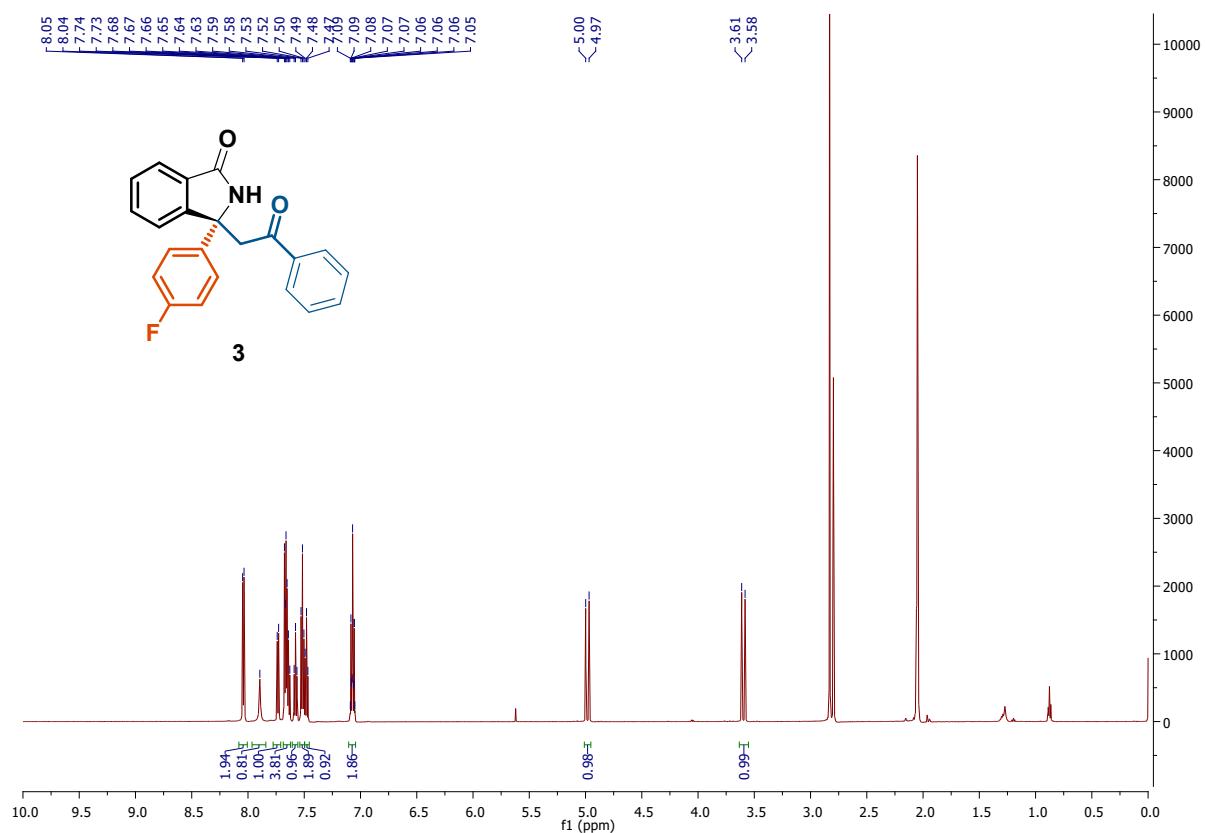
§ 5. References

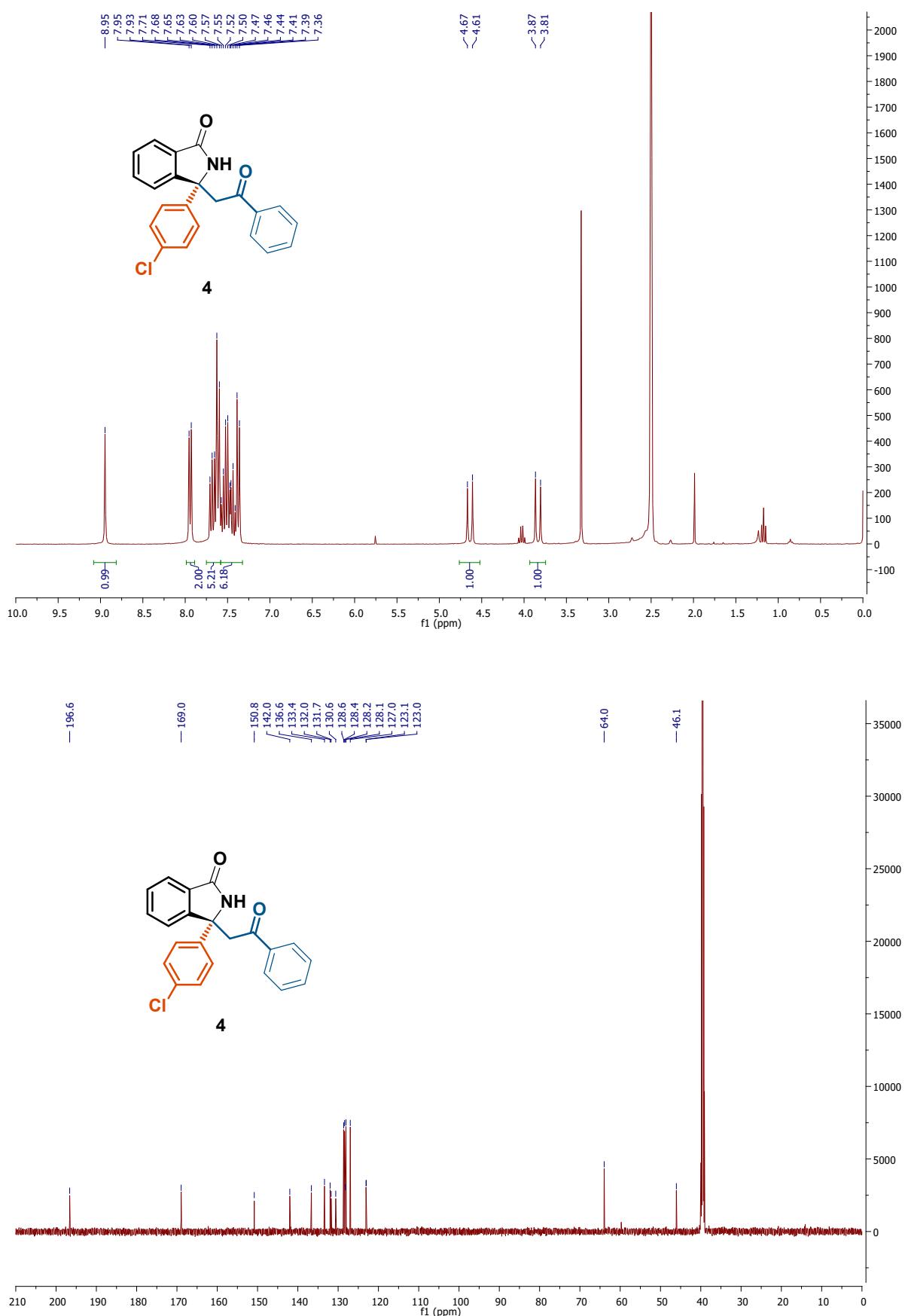
- [1] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K., Puschmann, H. *J. Appl. Cryst.* **2009**, 42, 339.
- [2] Farrugia, L. J. *J. Appl. Crystallogr.* **2012**, 45, 849.
- [3] Spek, A. L. *J. Appl. Crystallogr.* **2003**, 36, 7.

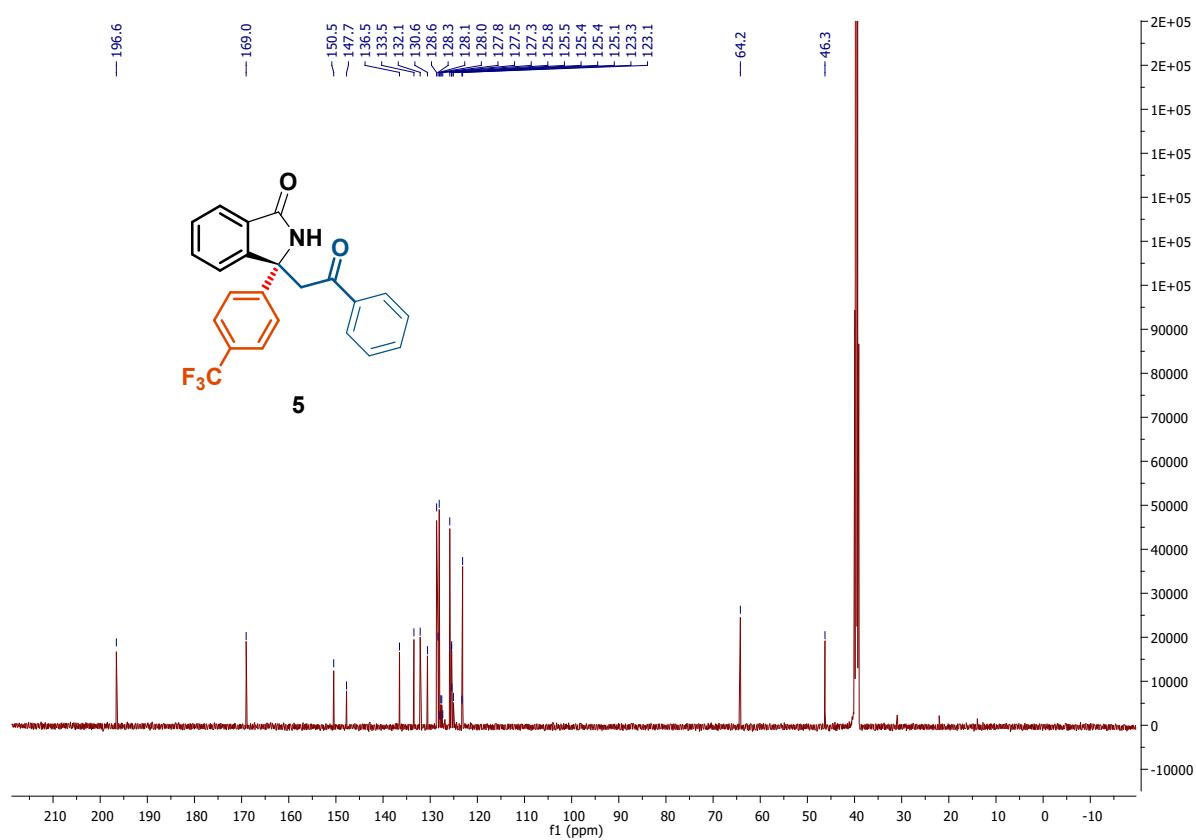
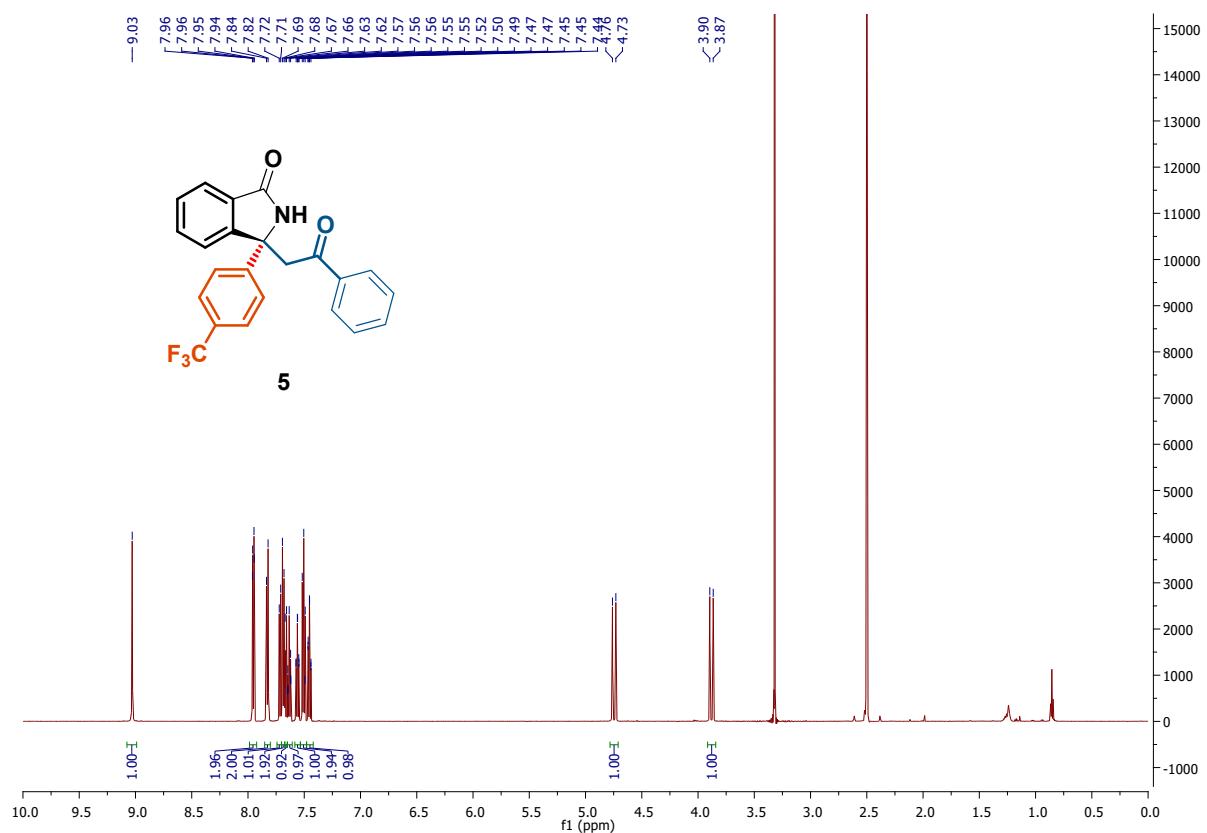
§ 6. NMR Spectra

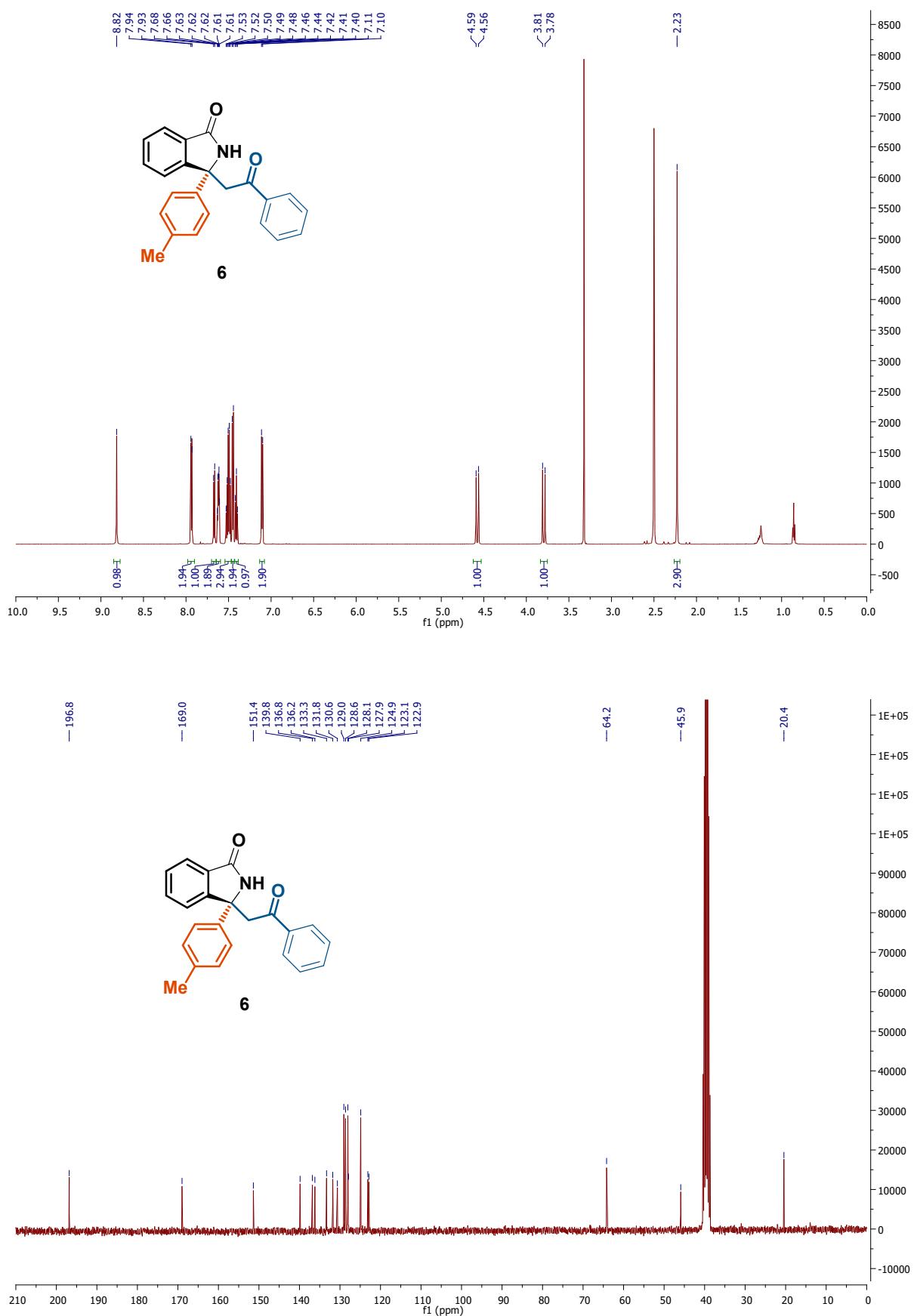


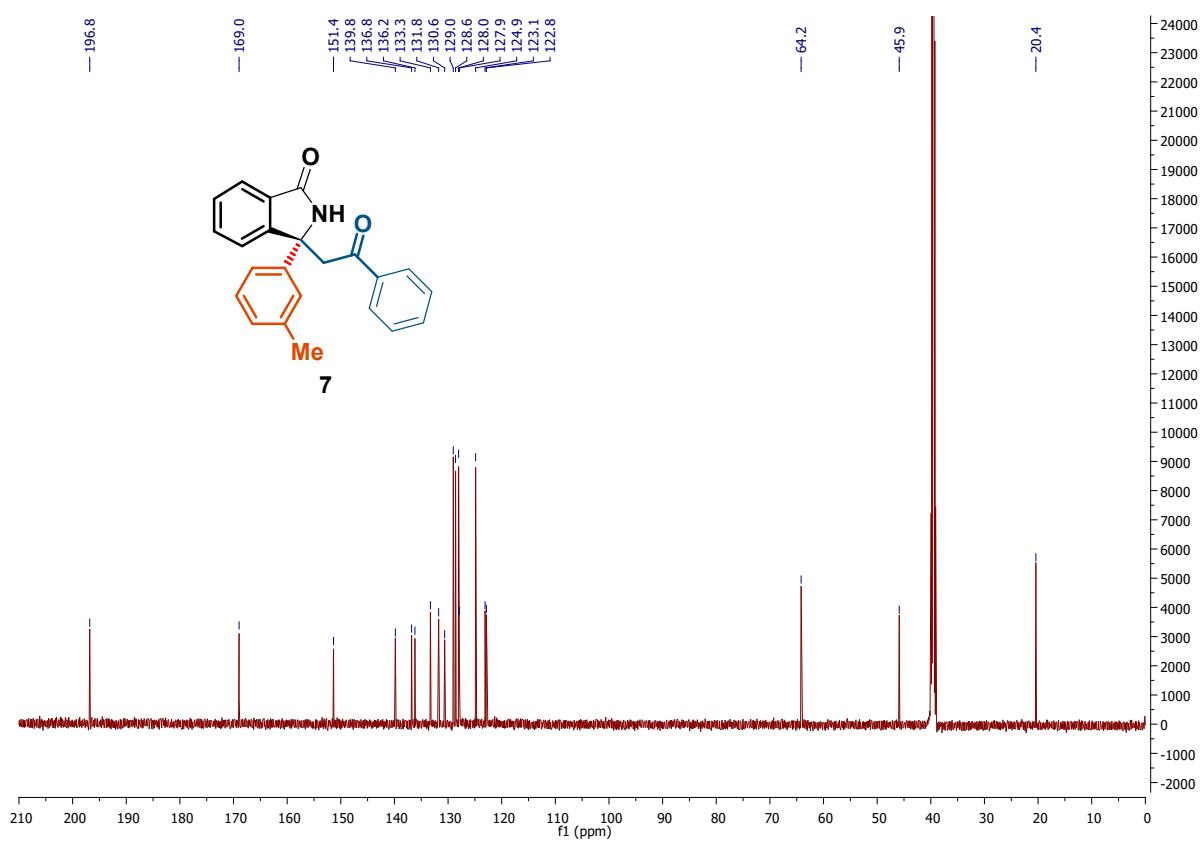
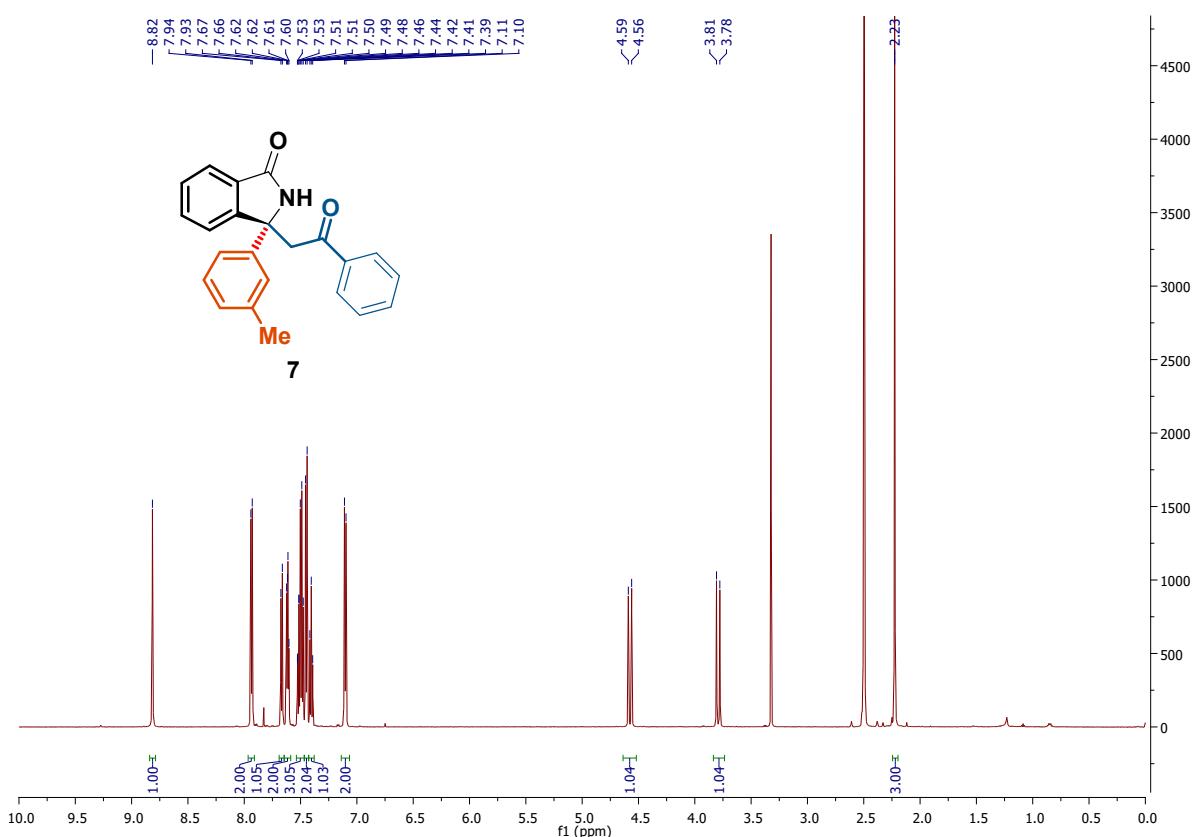


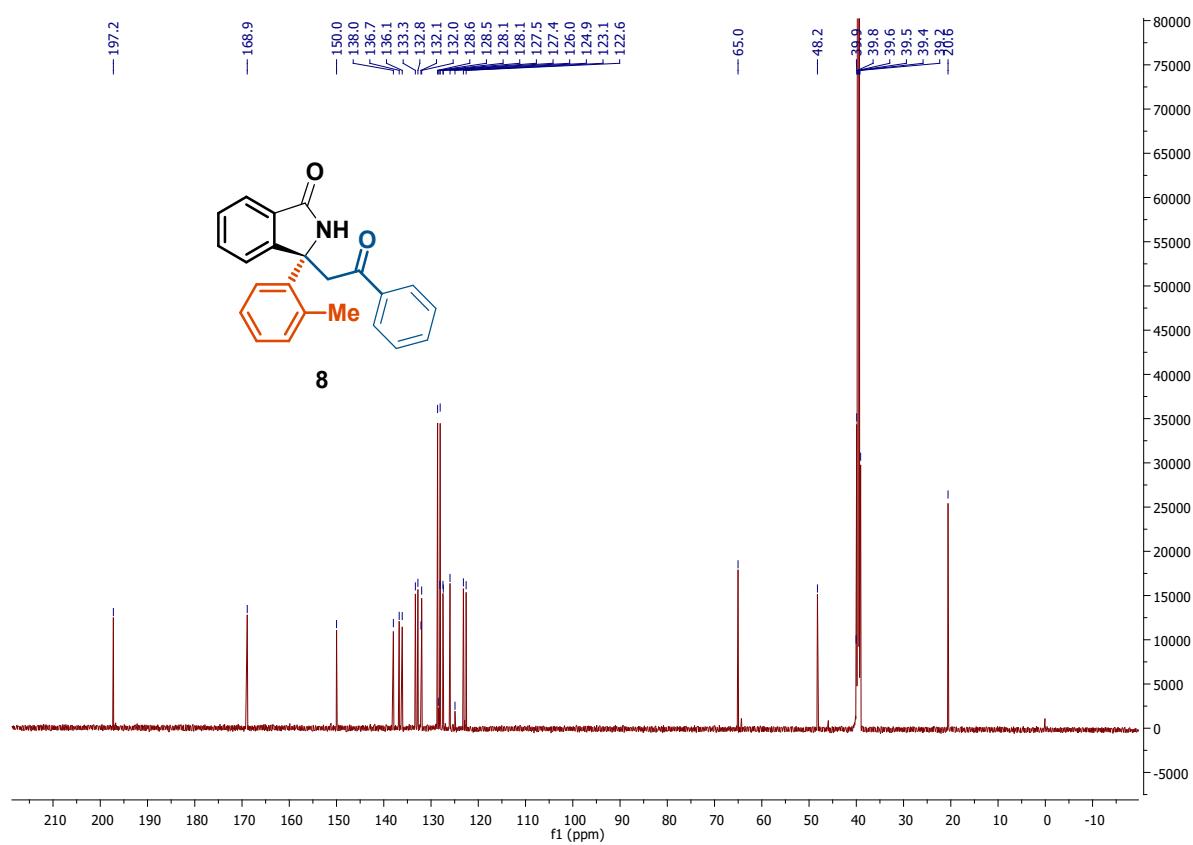
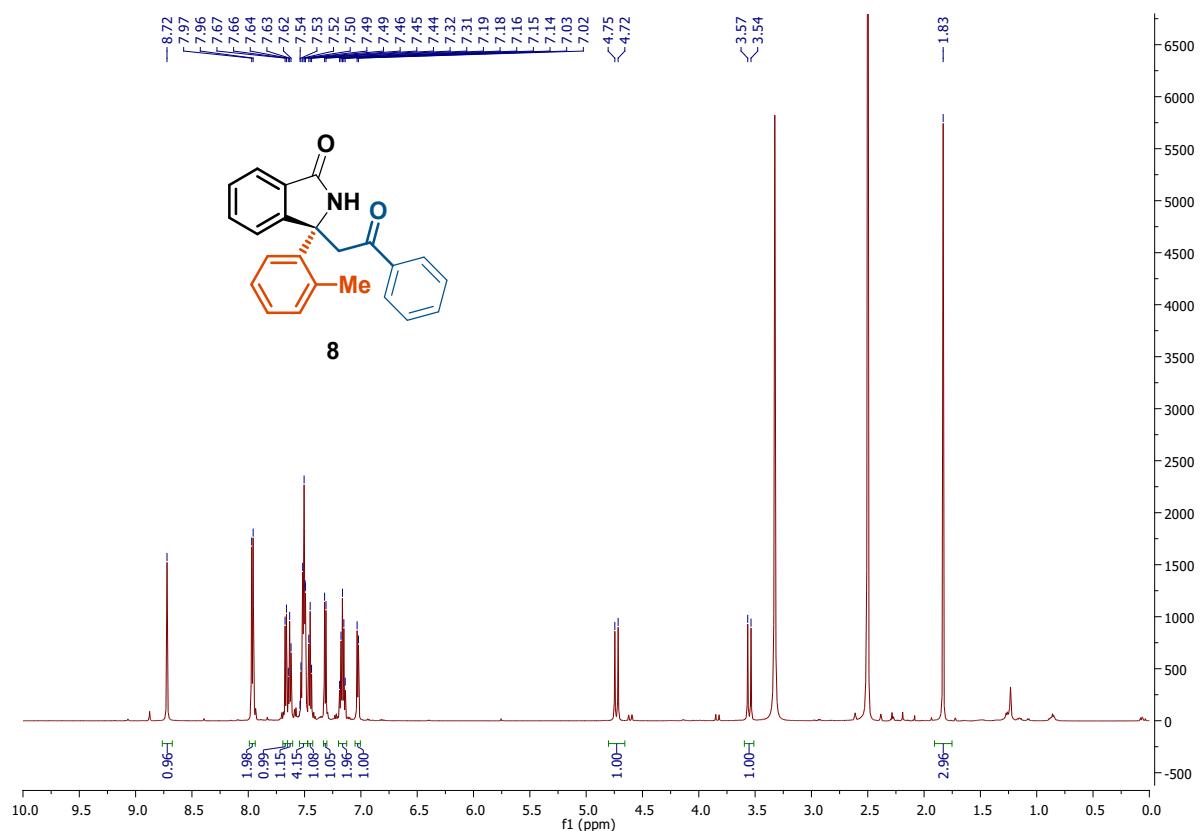


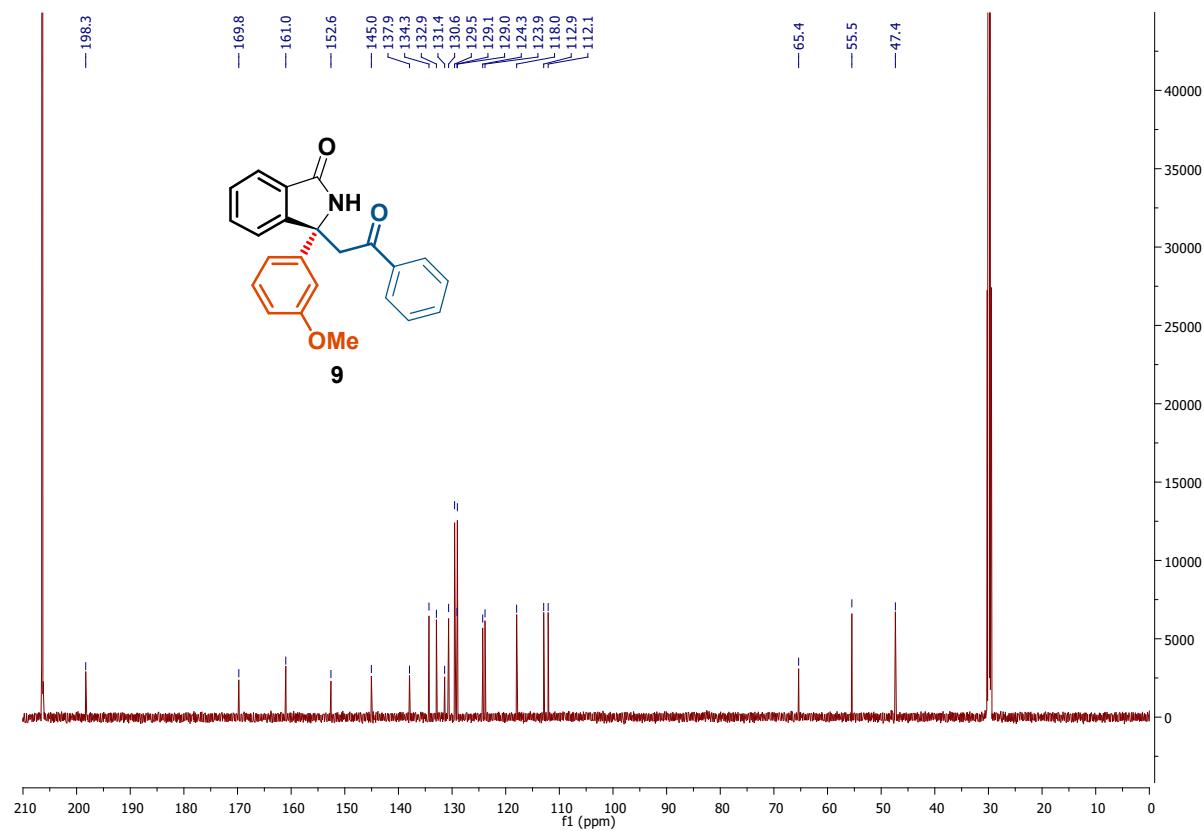
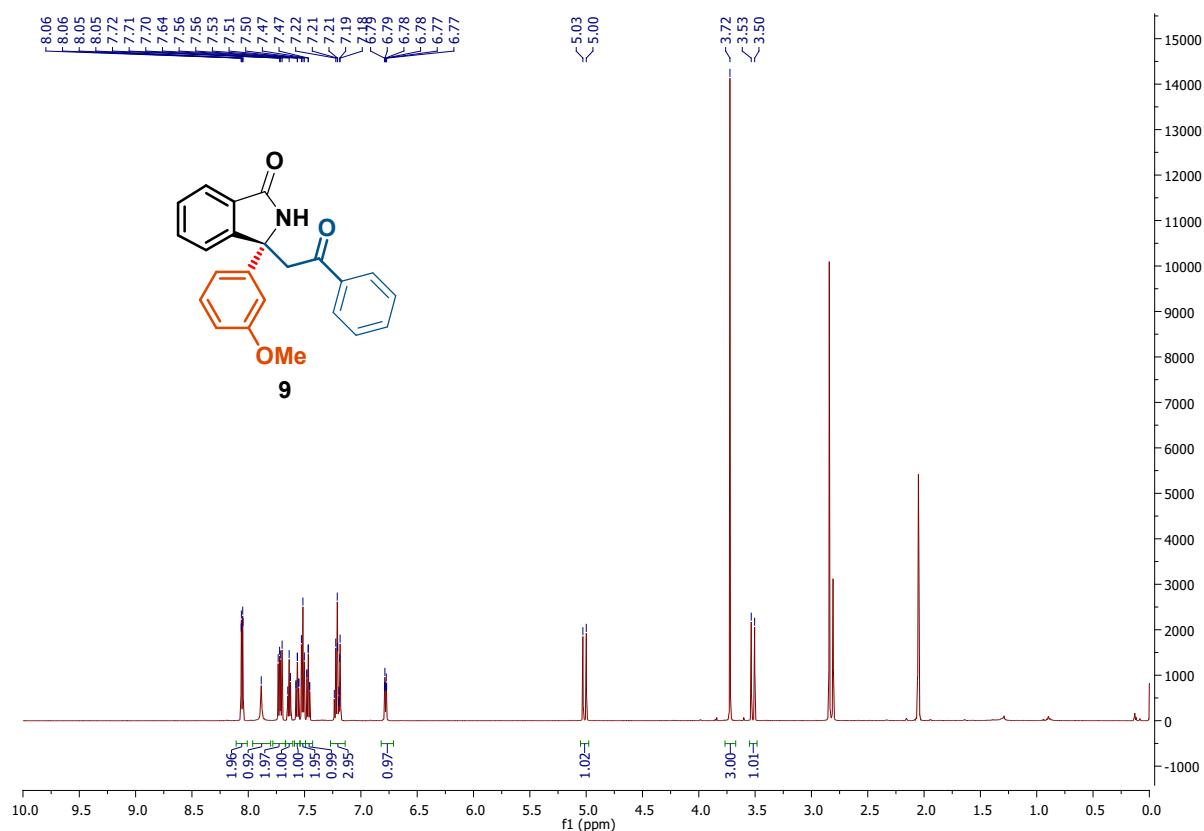


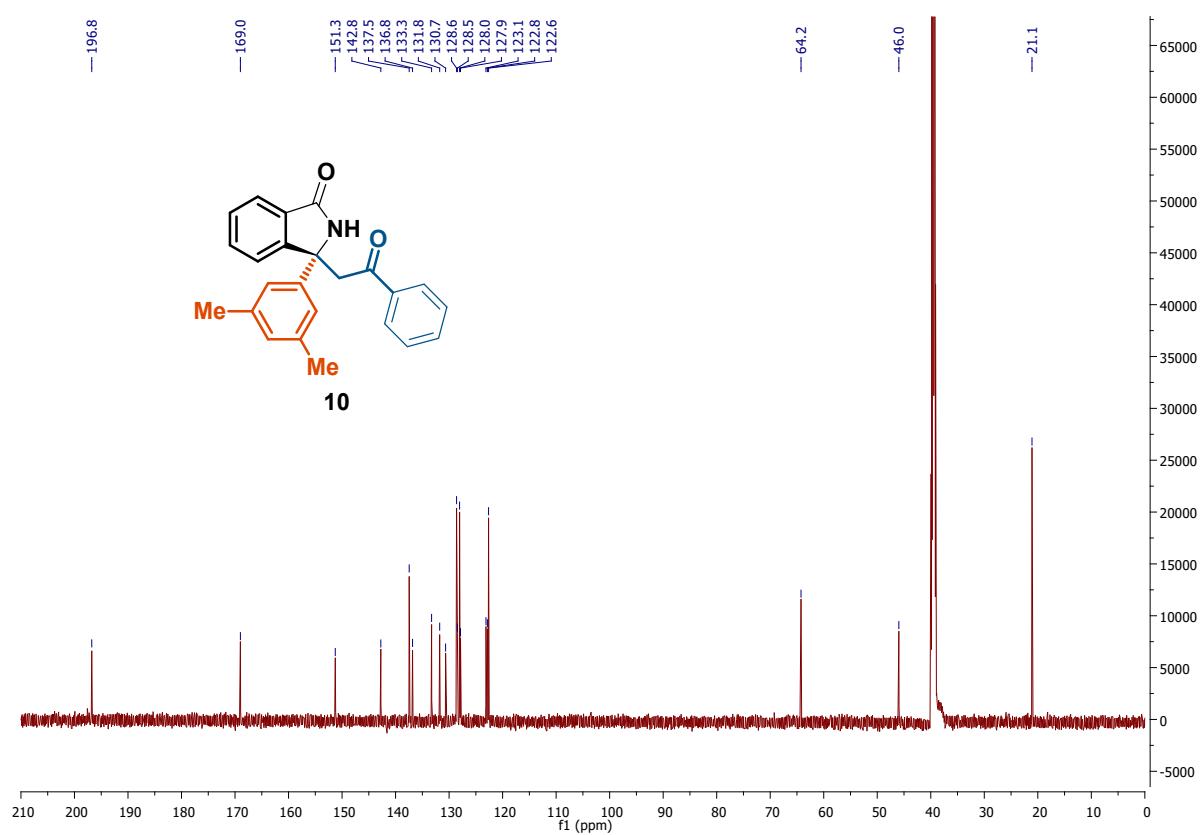
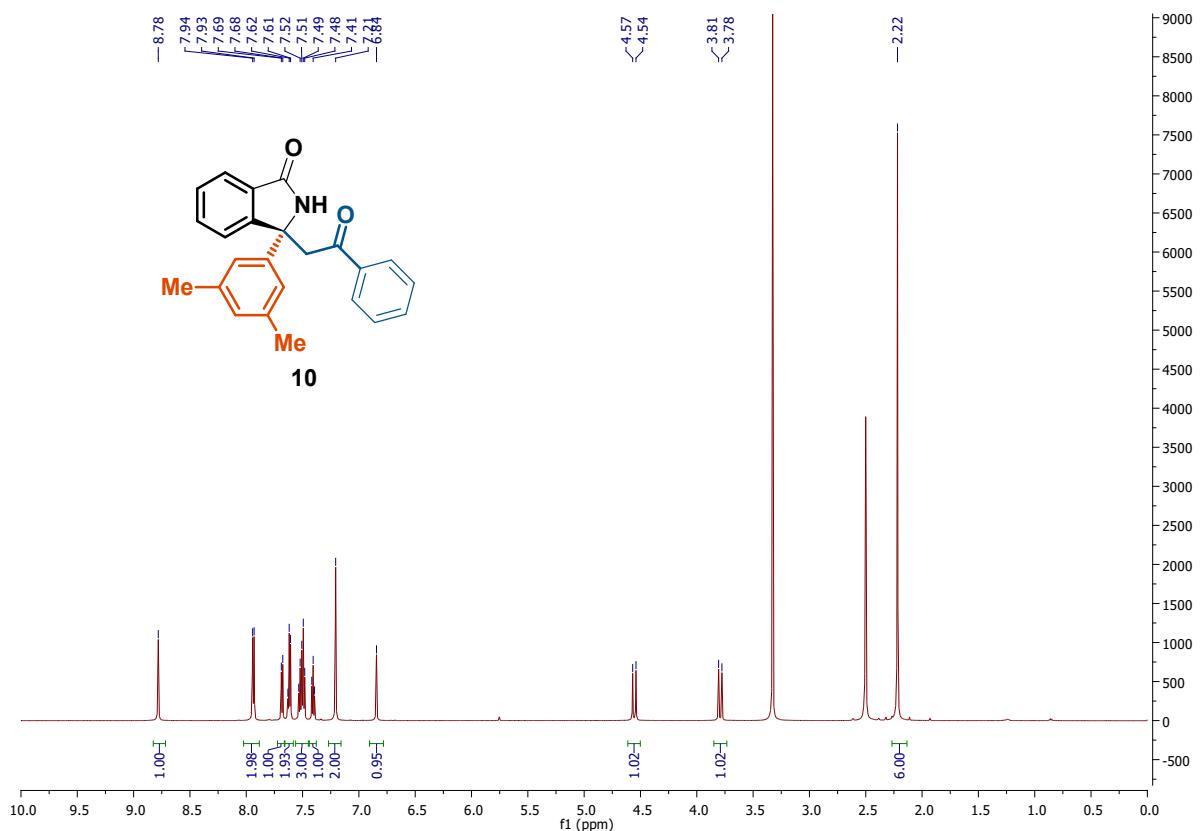


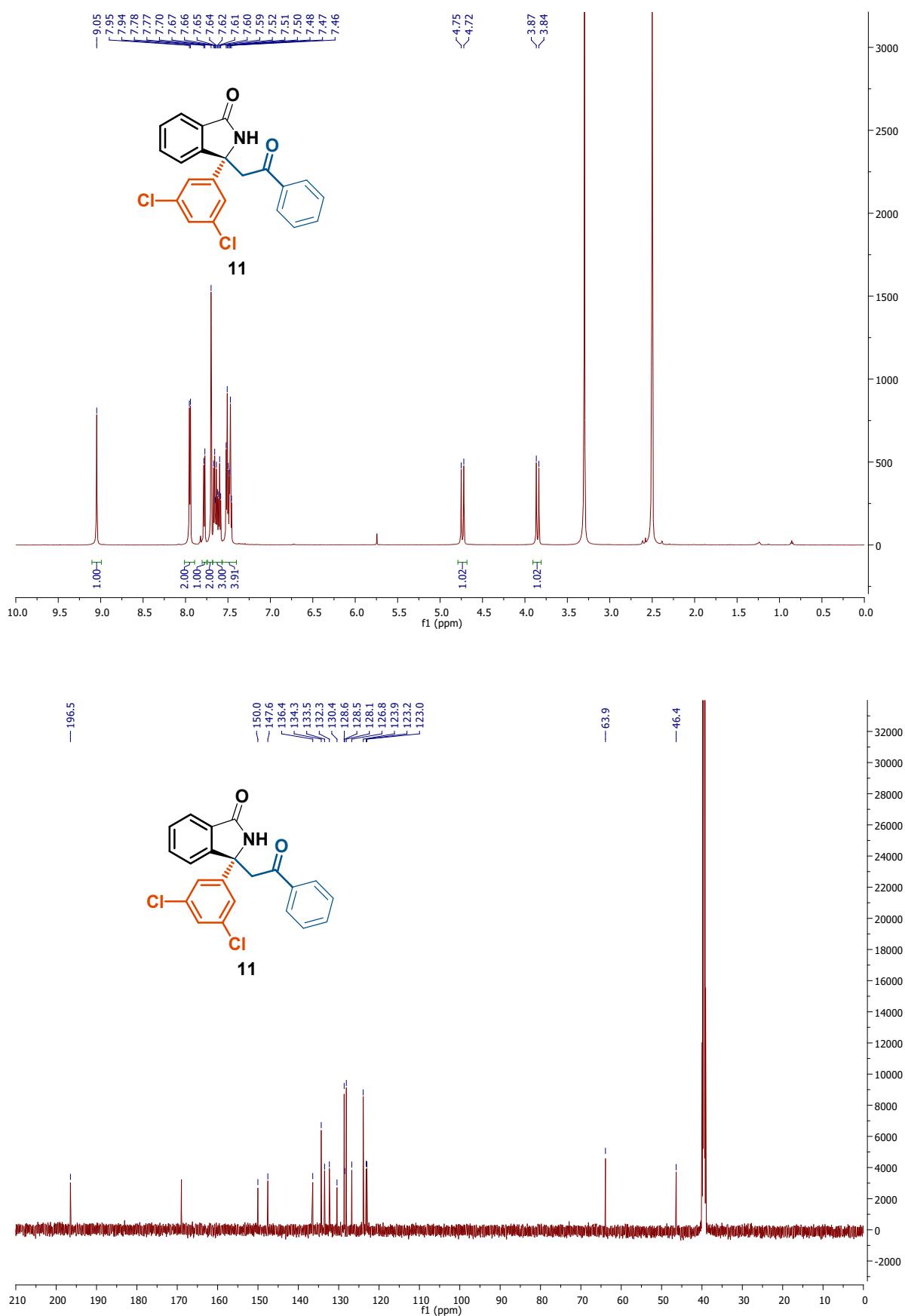


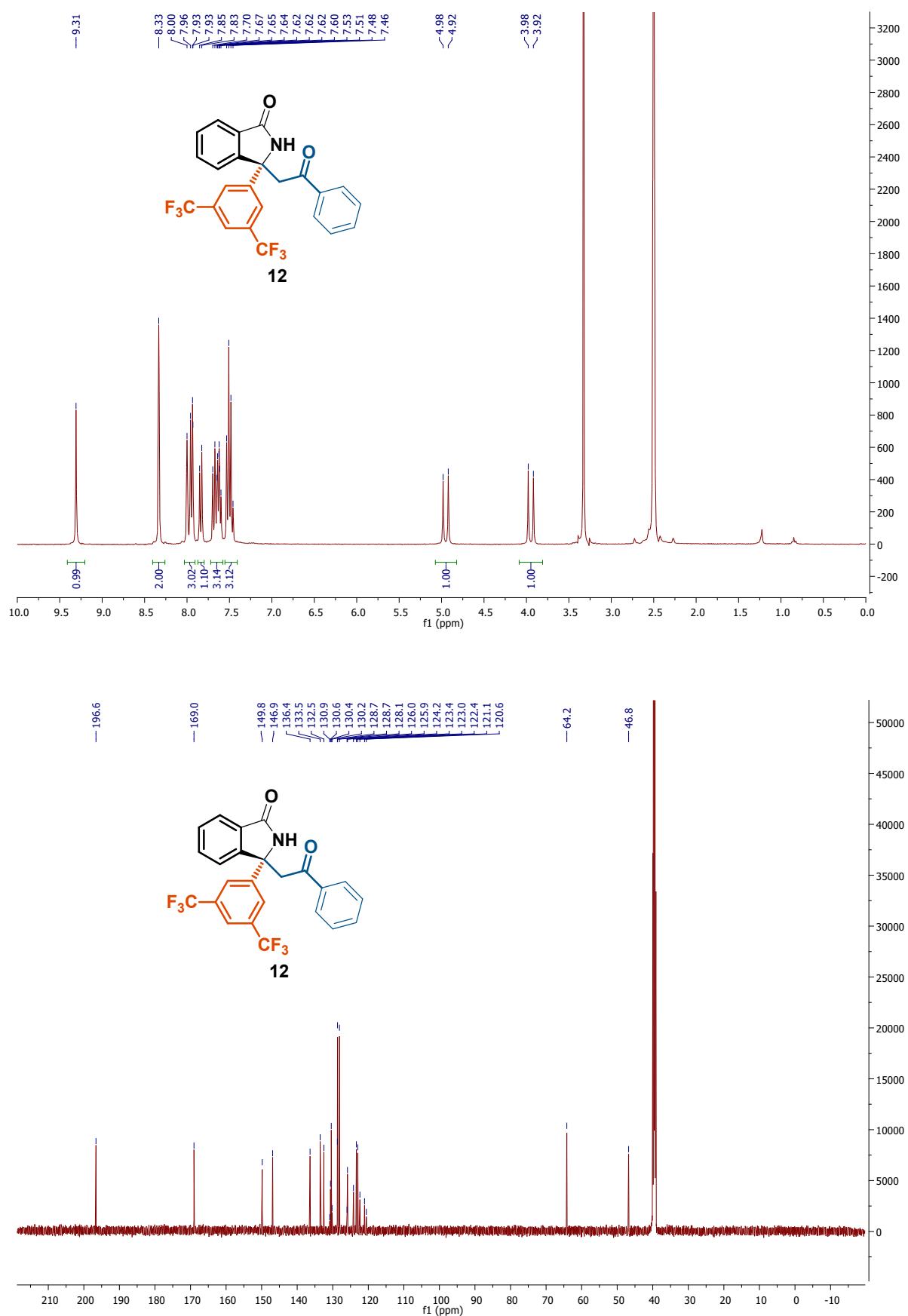


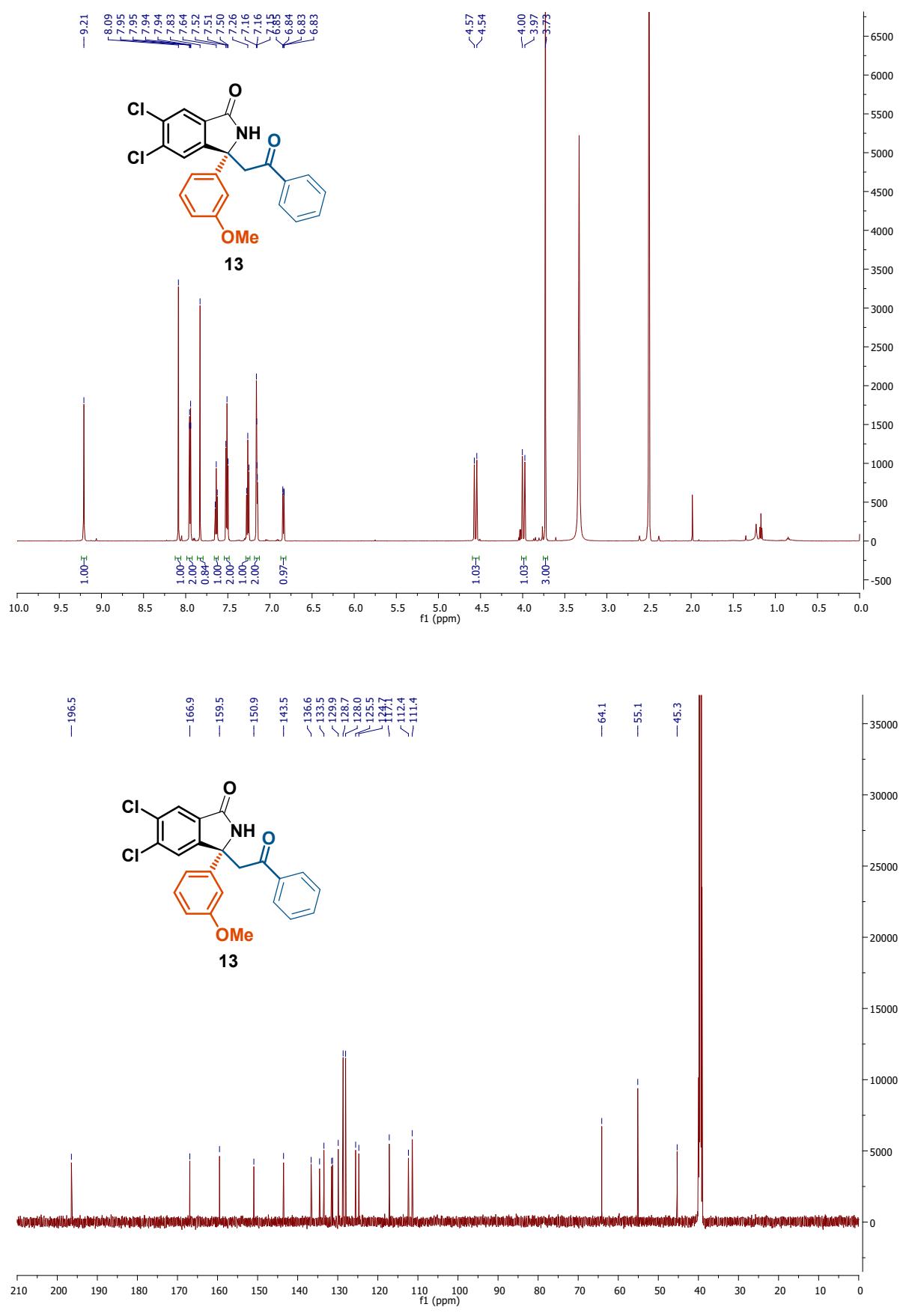


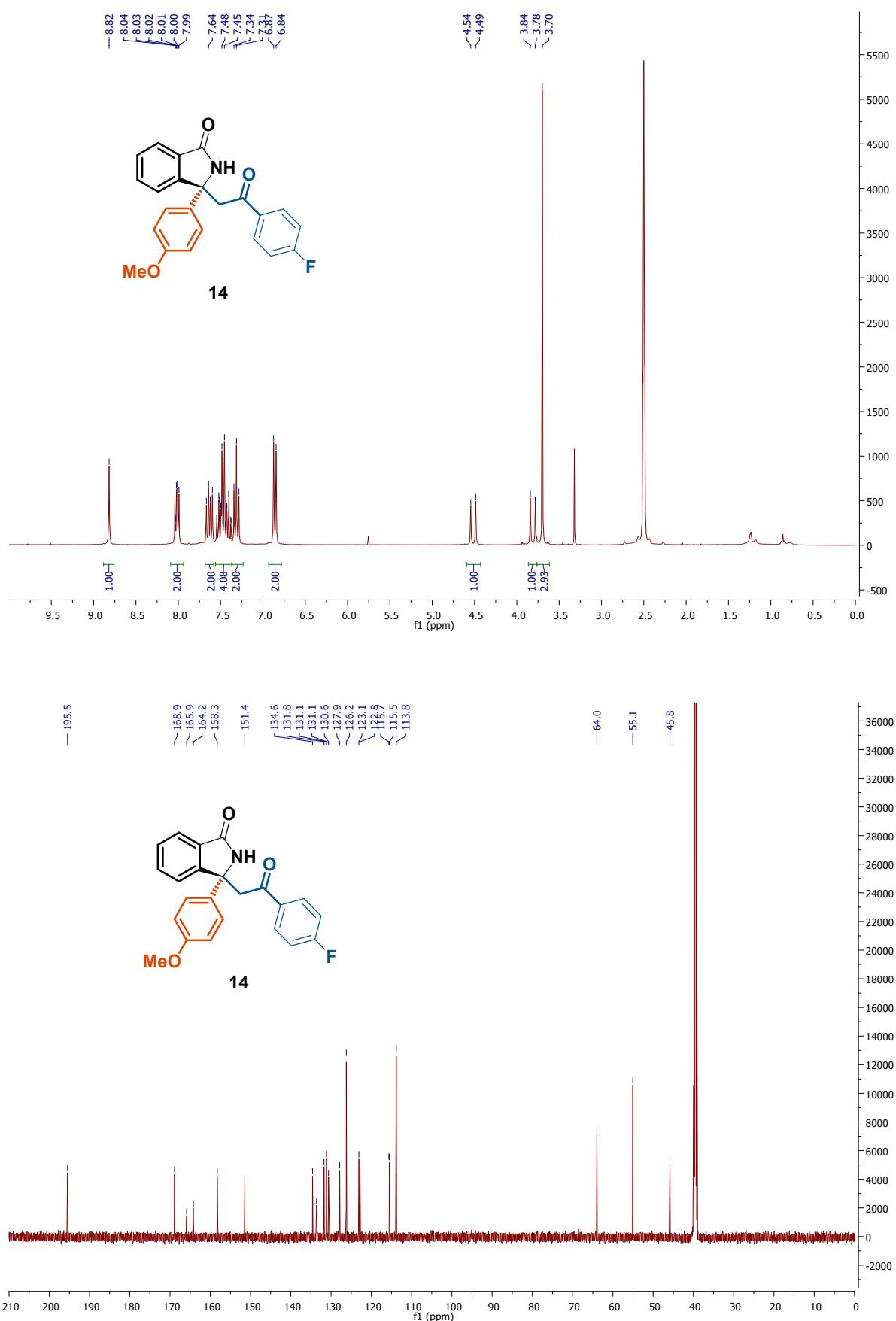


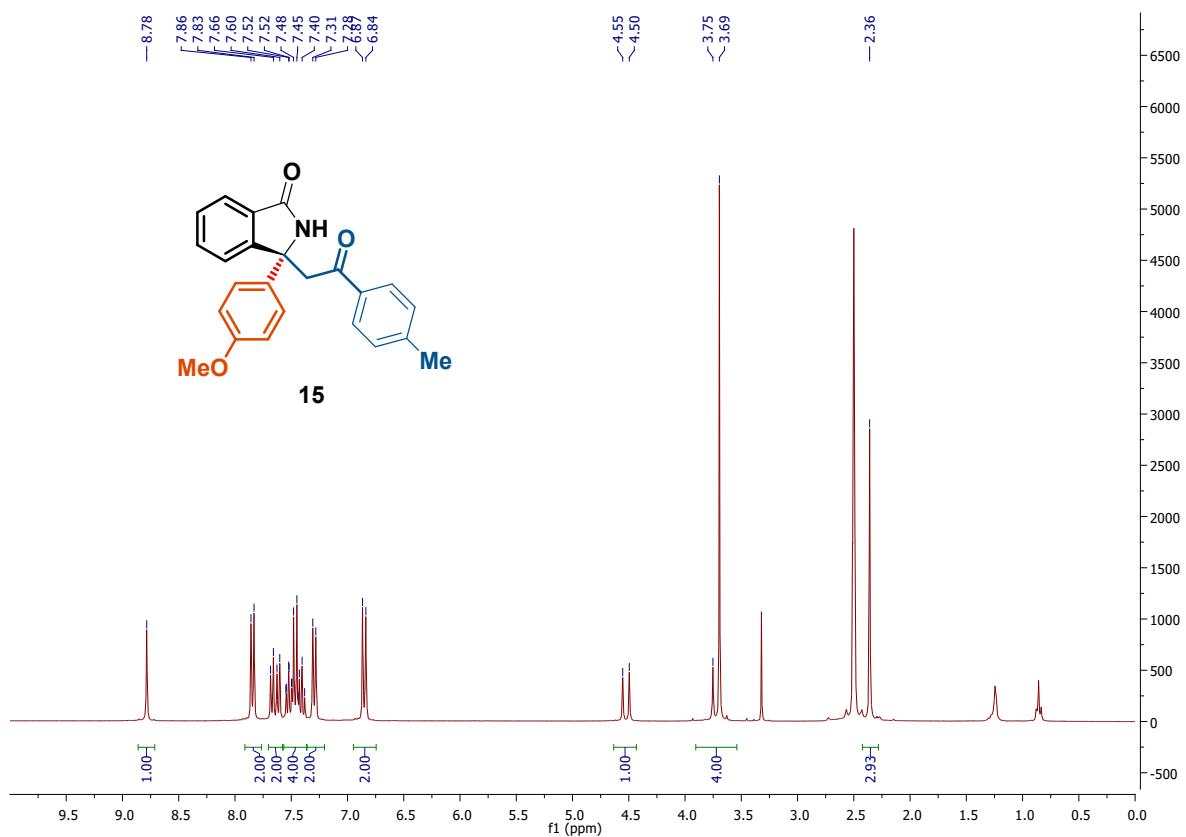
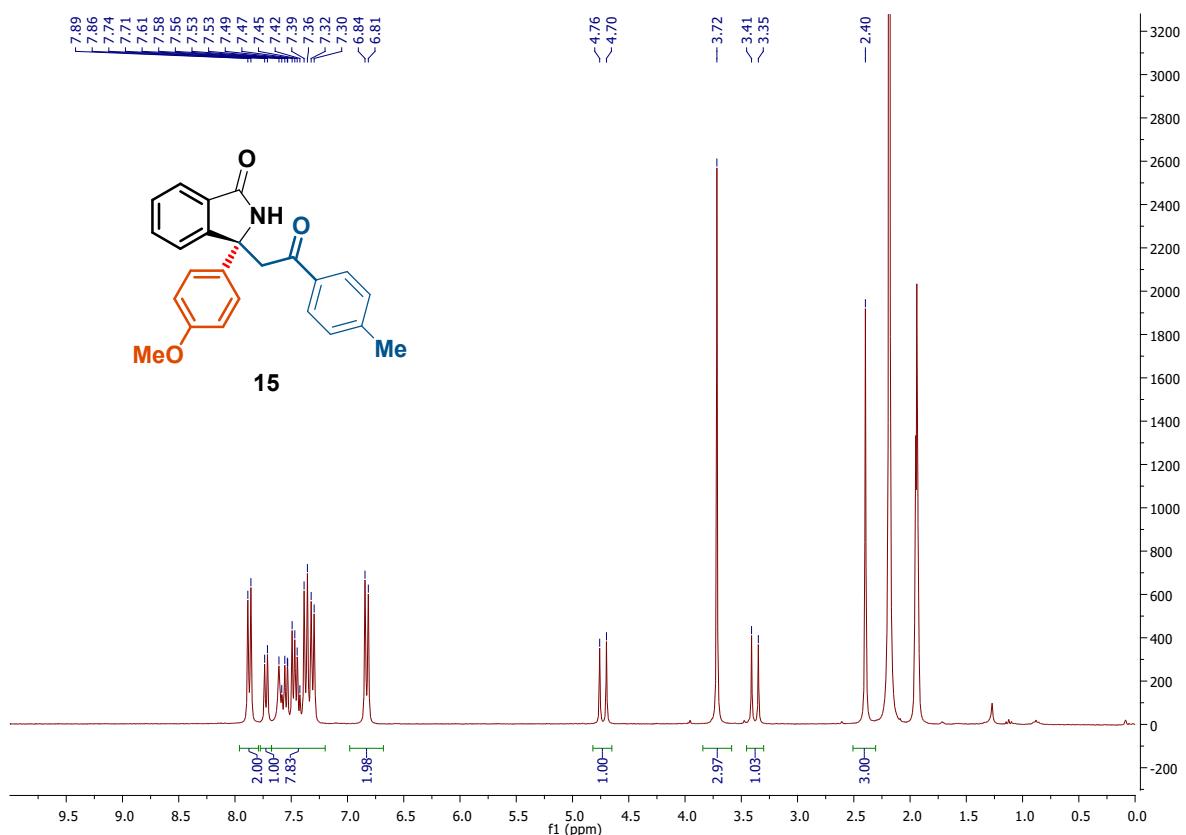


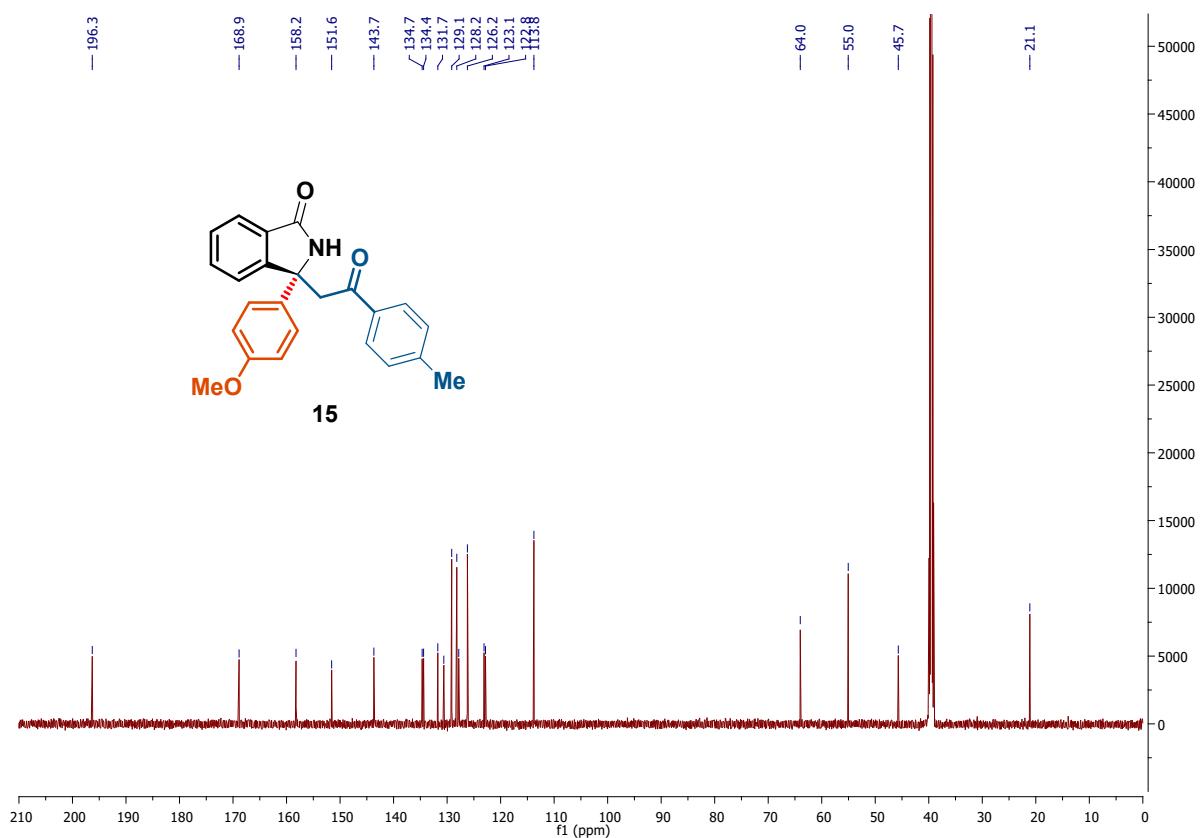


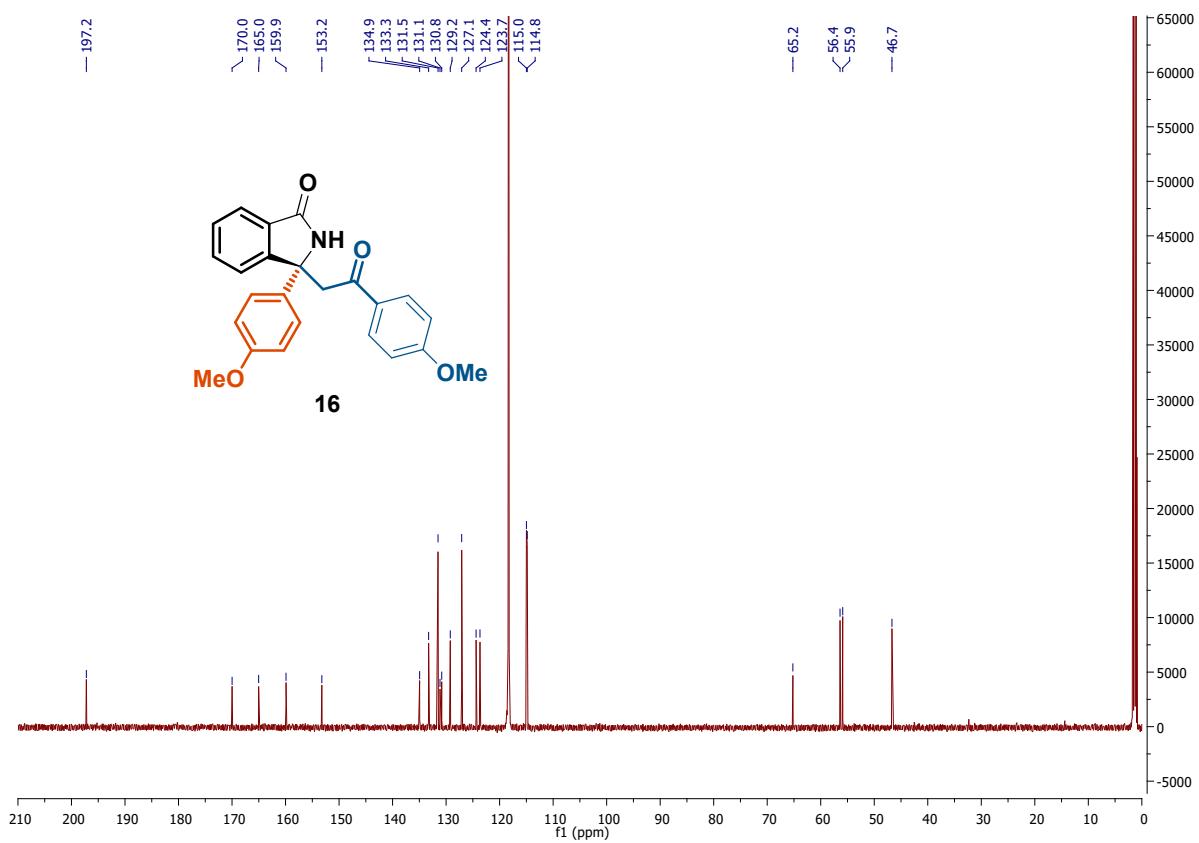
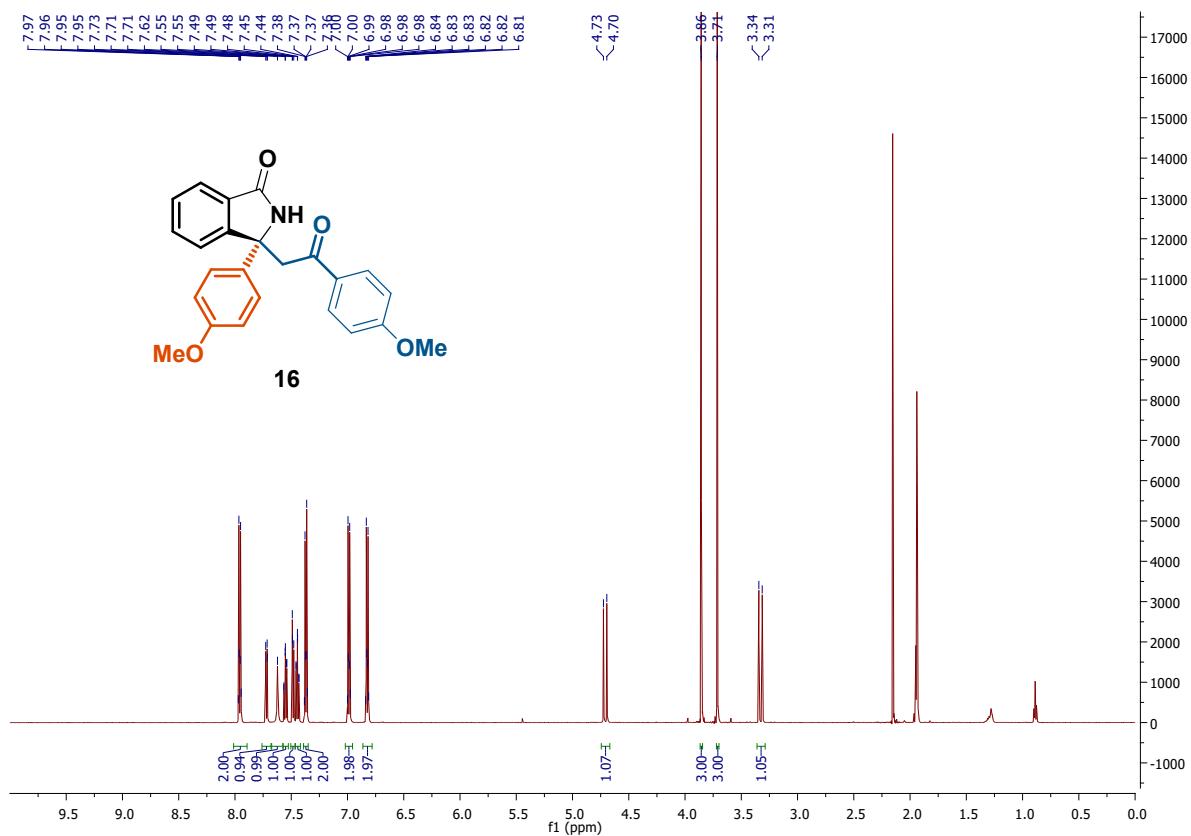


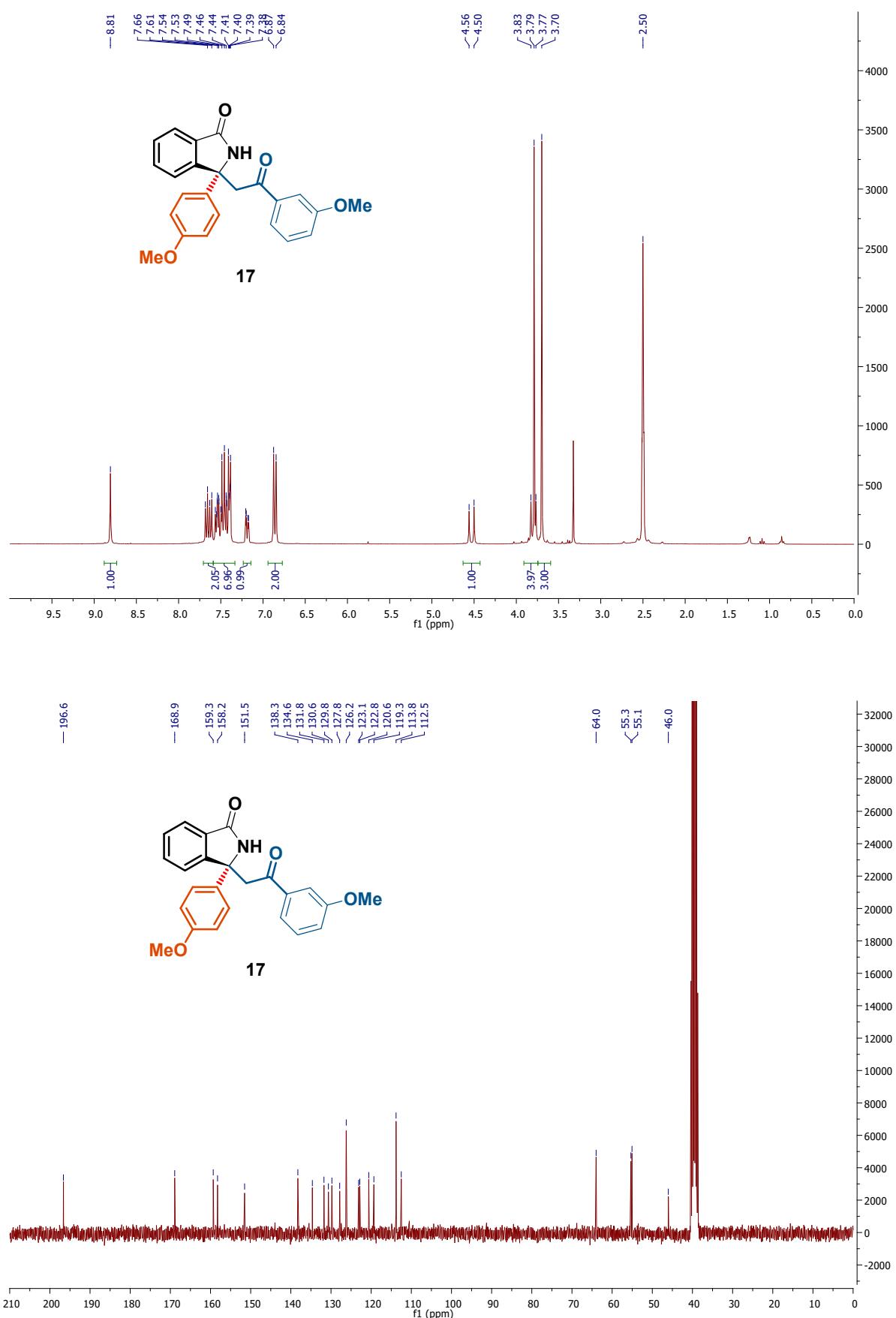


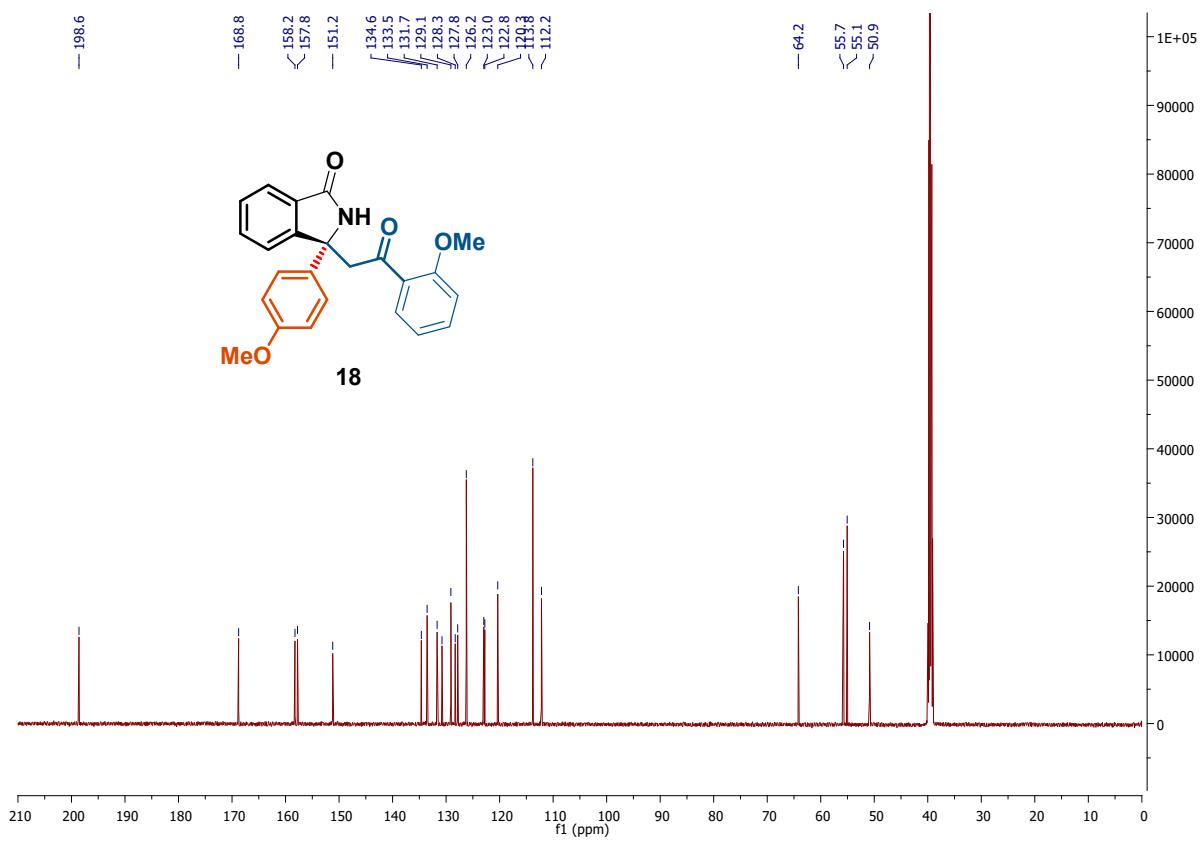
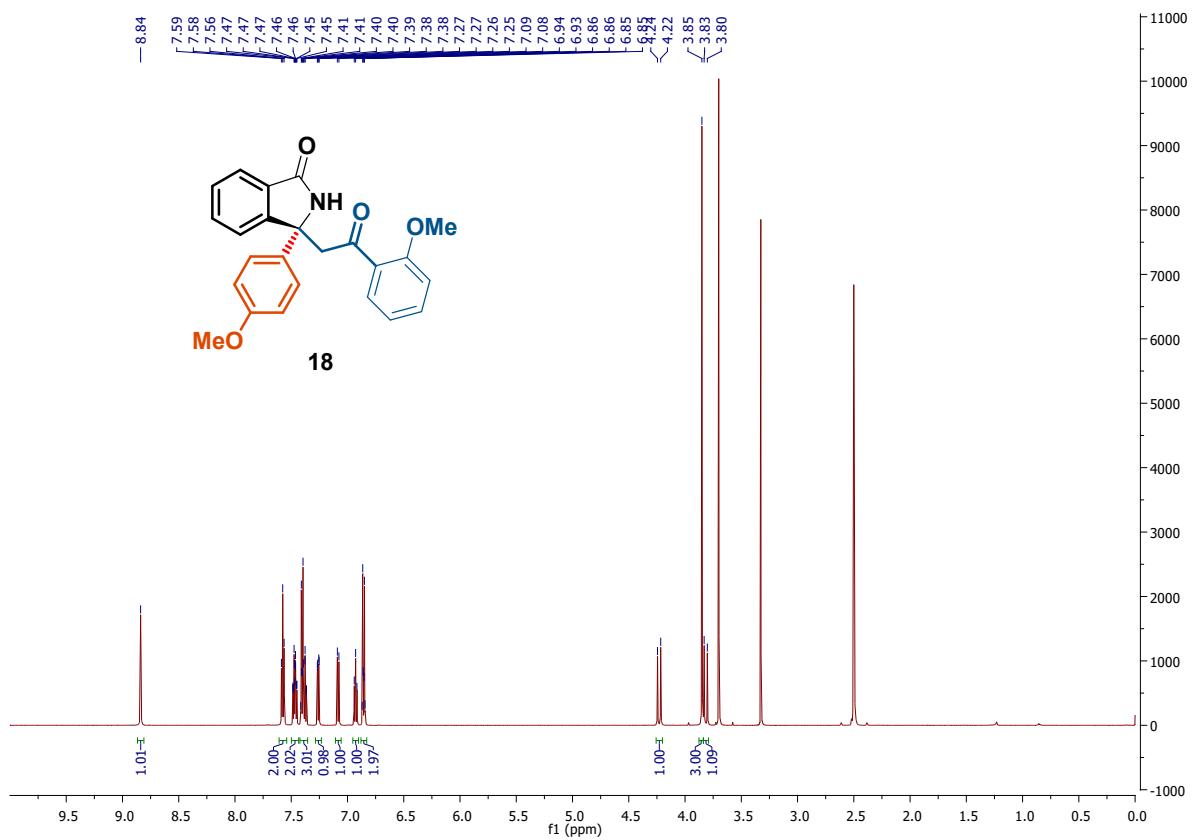


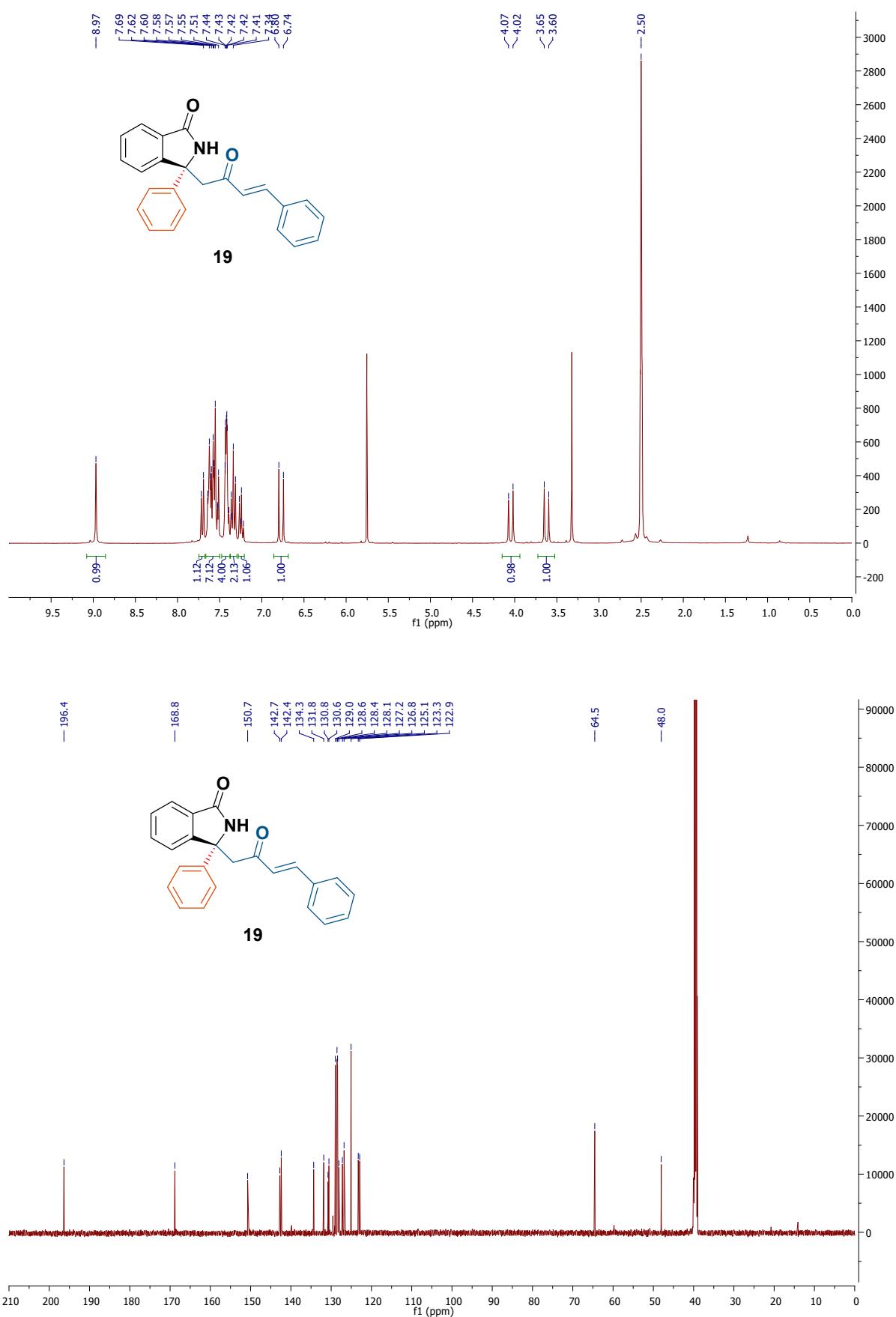


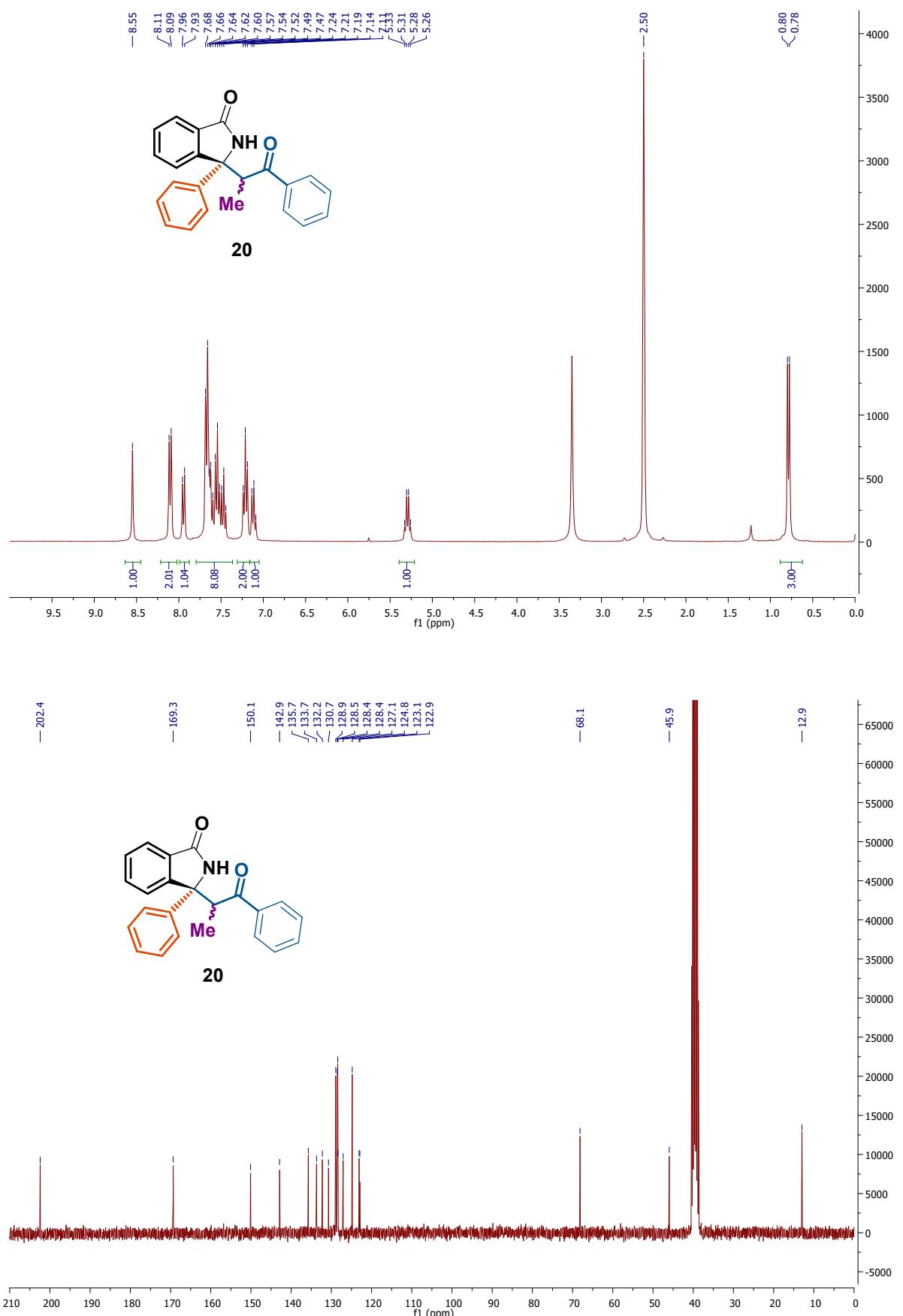


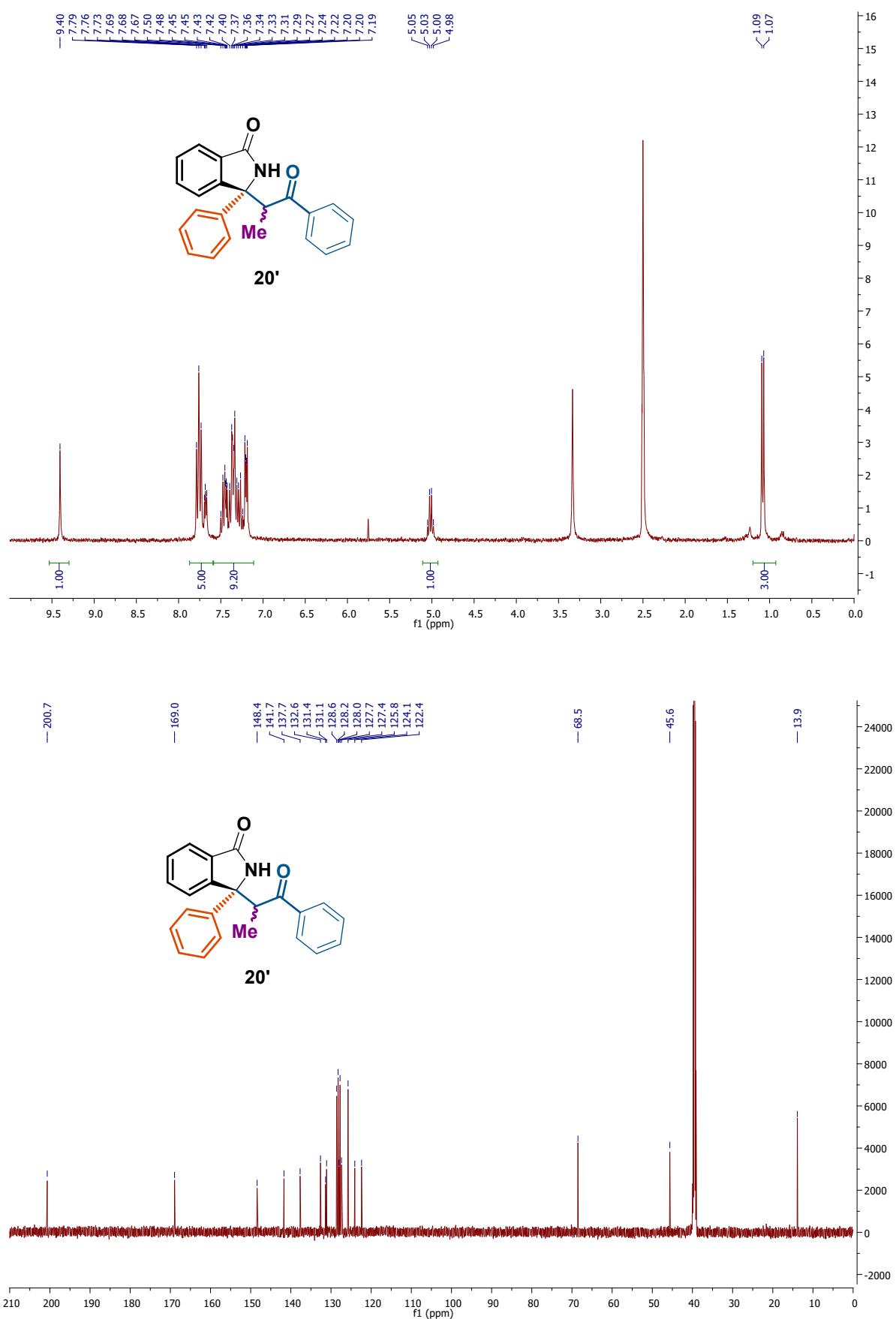


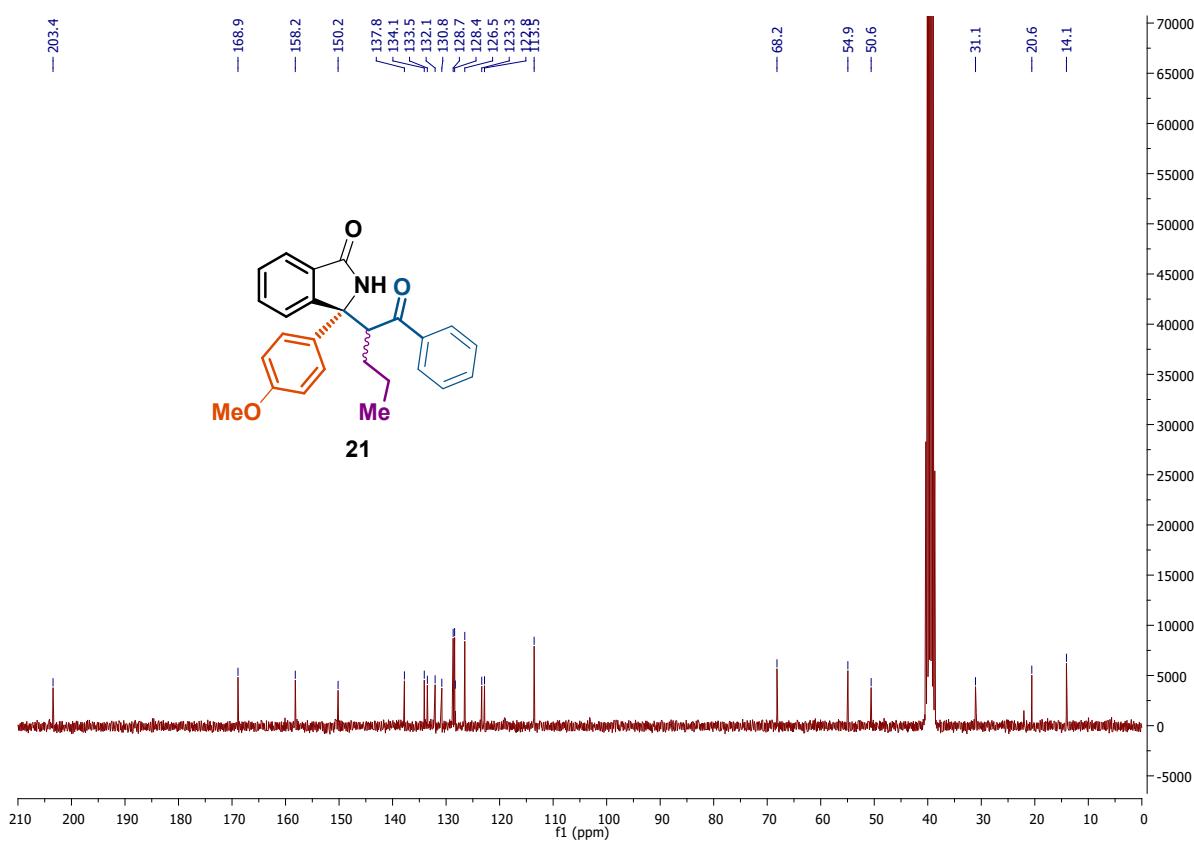
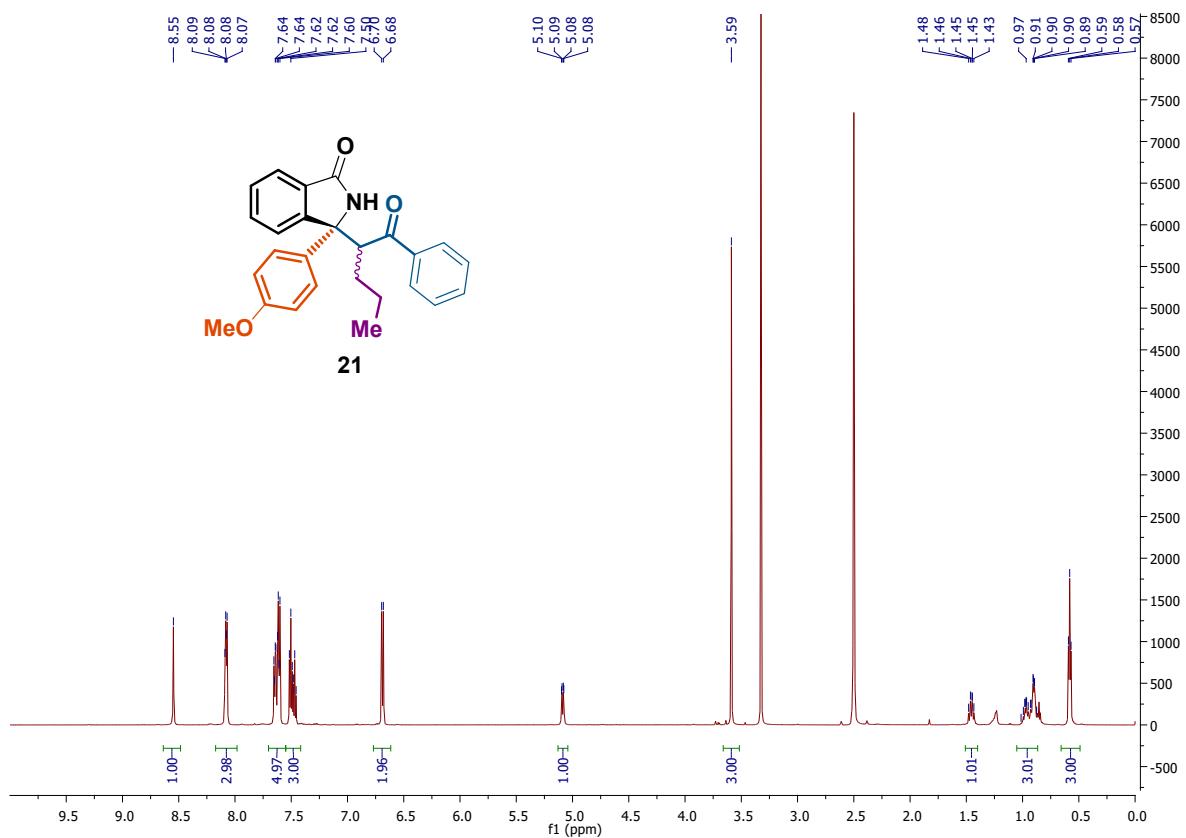


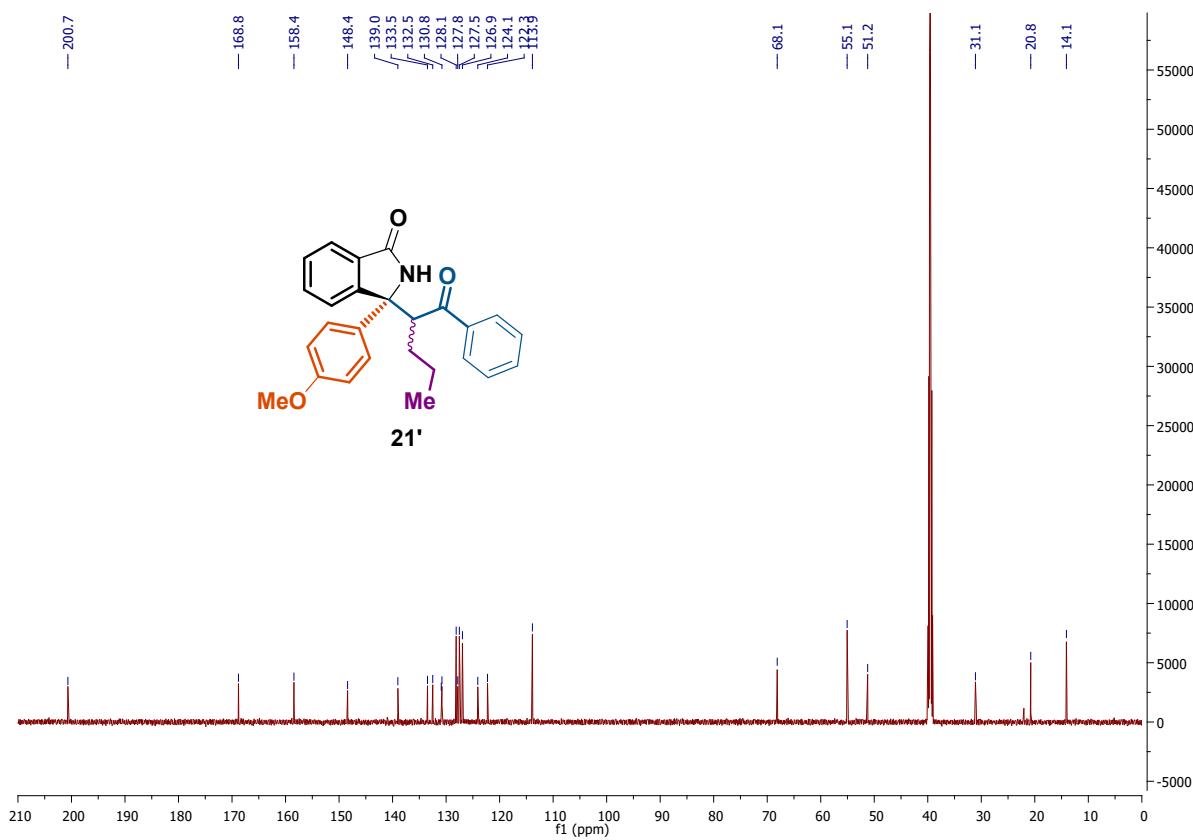
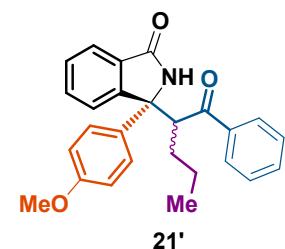
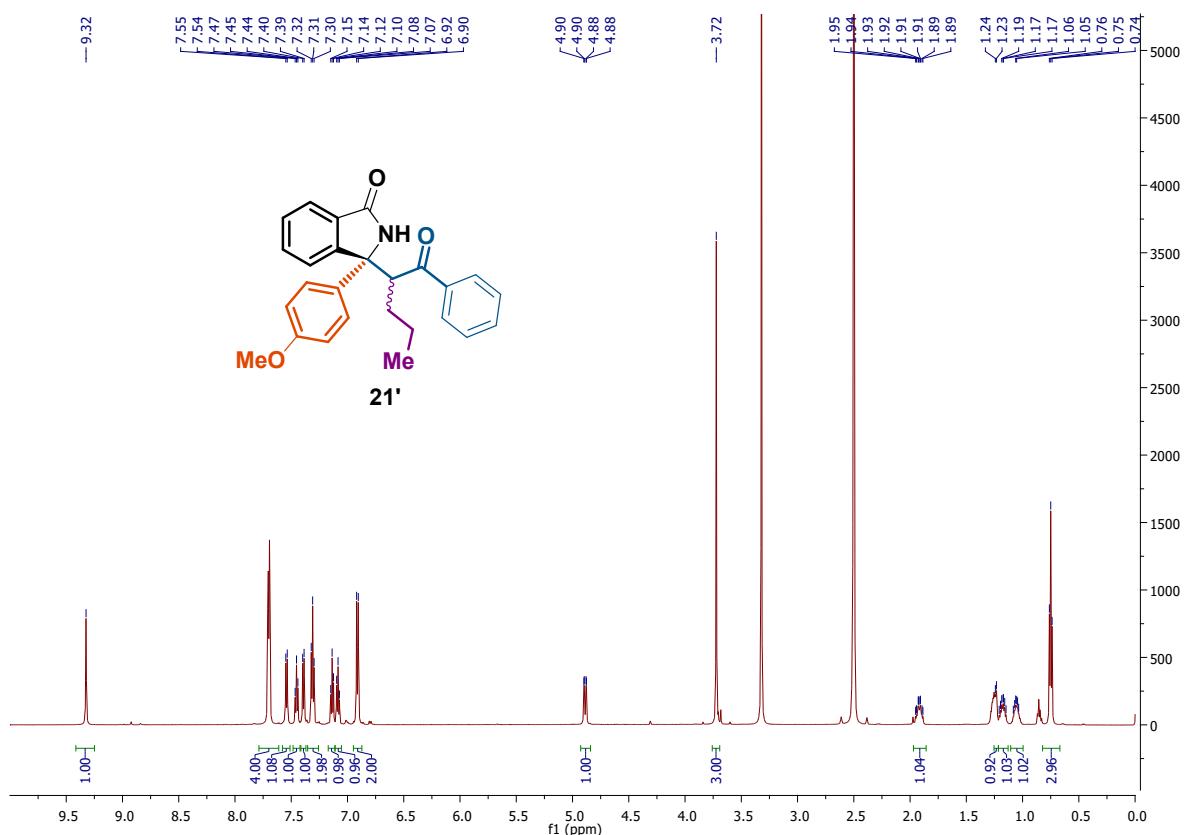


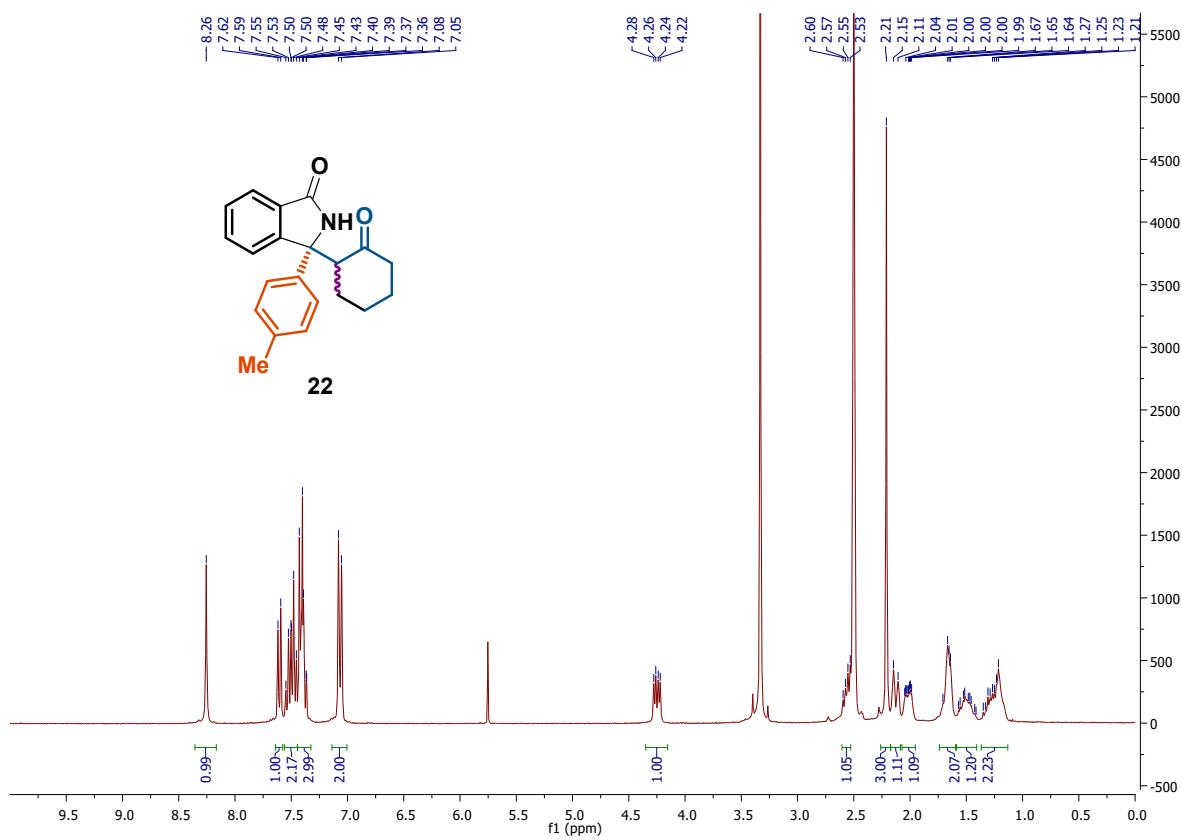
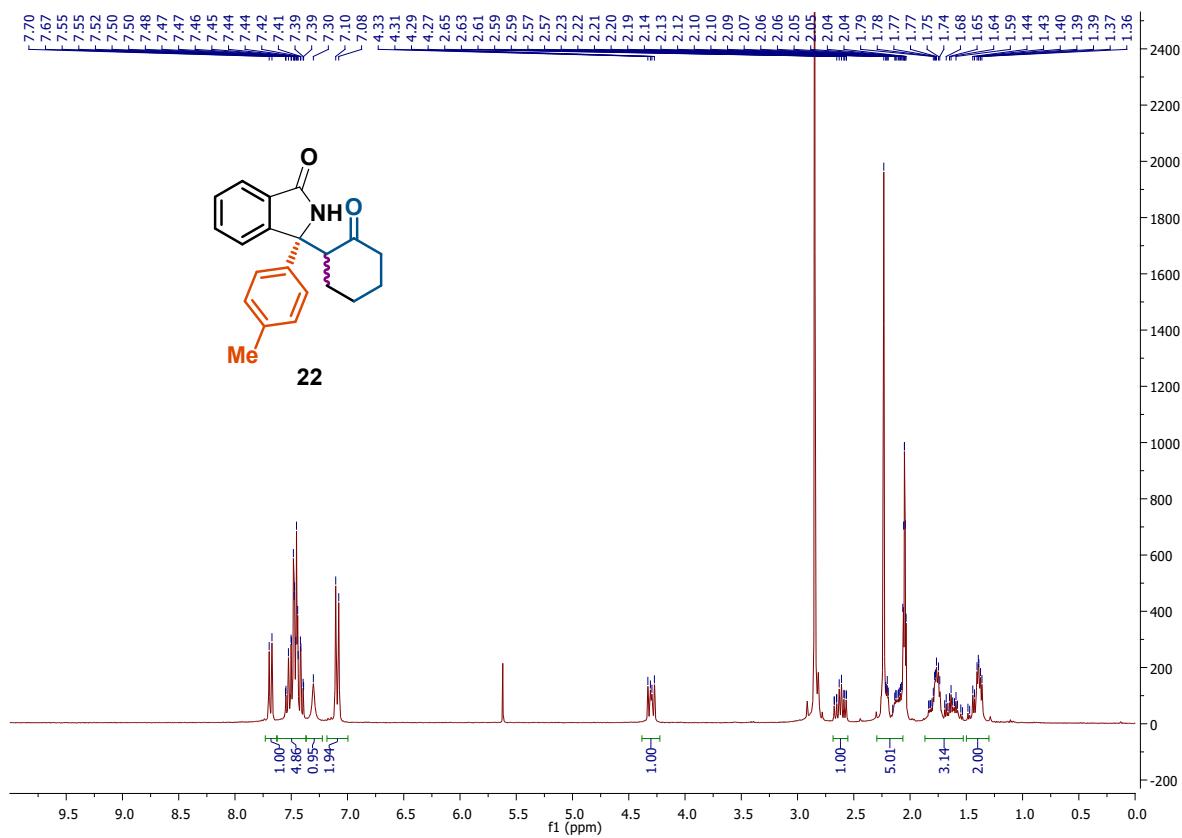


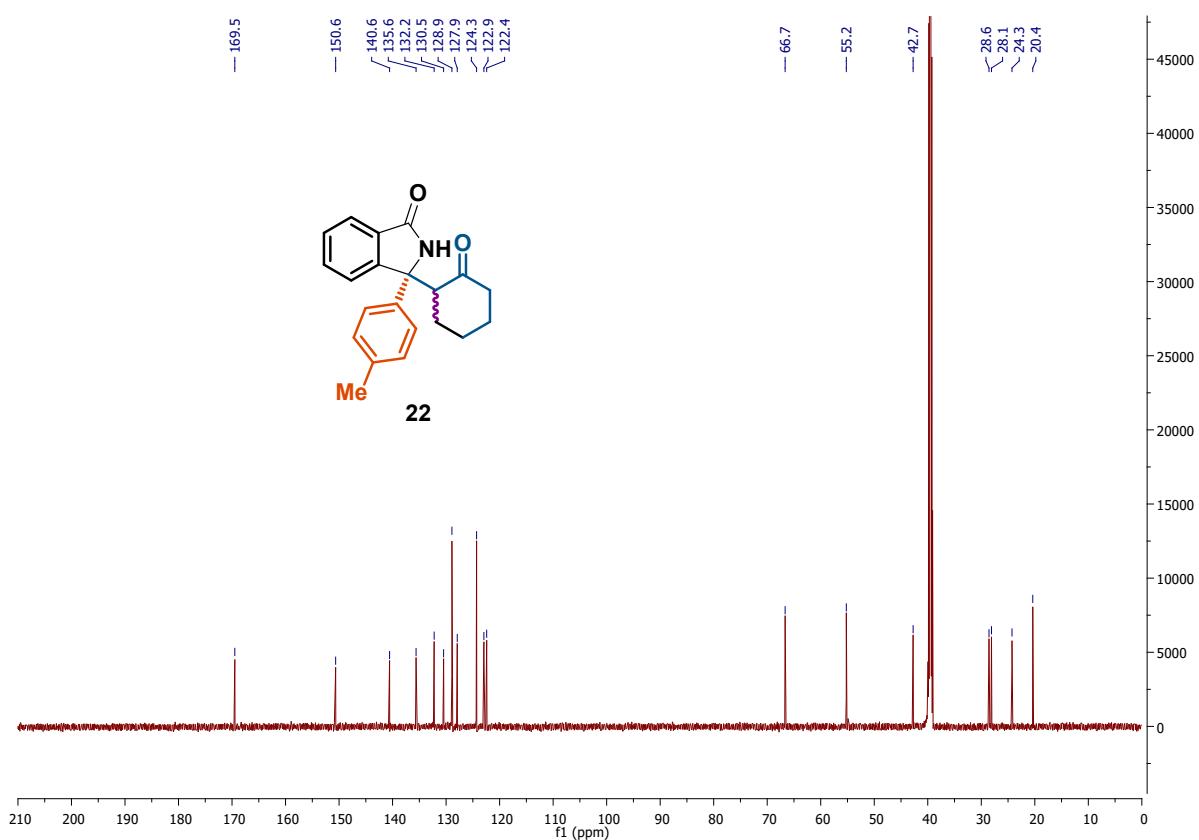


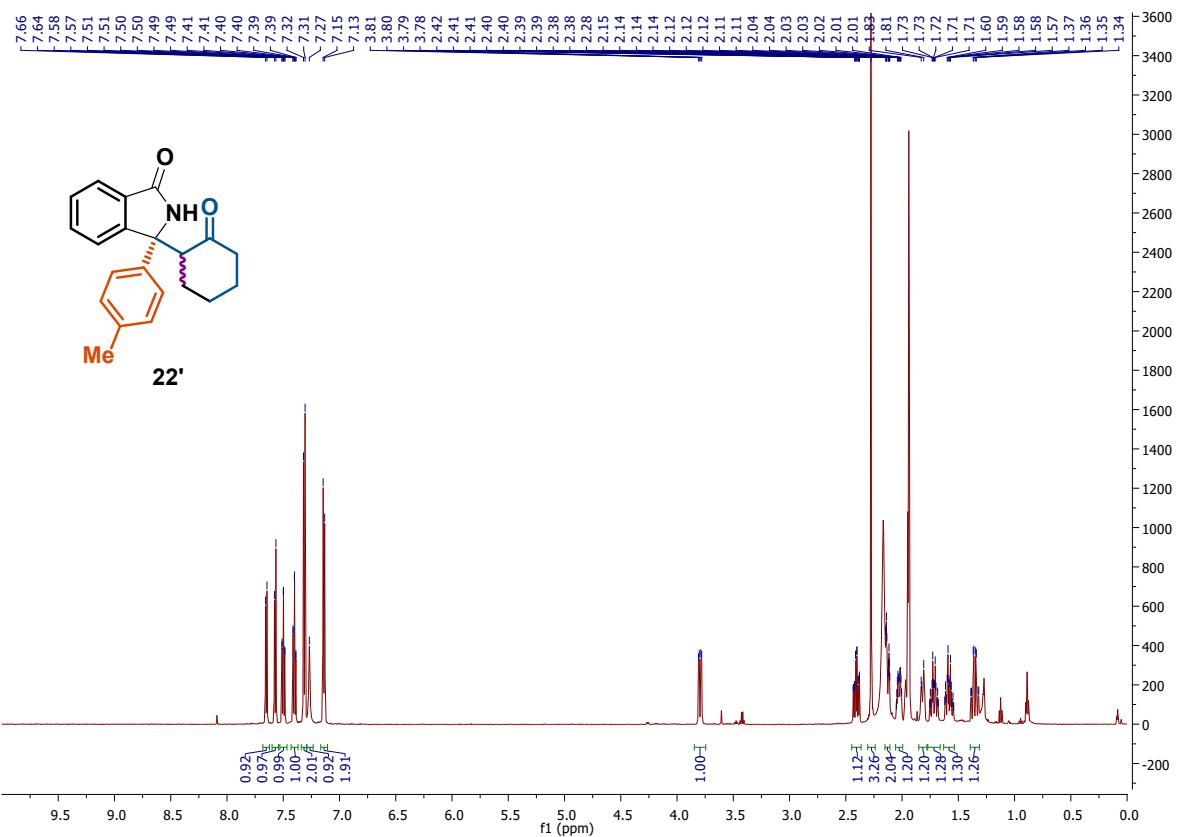
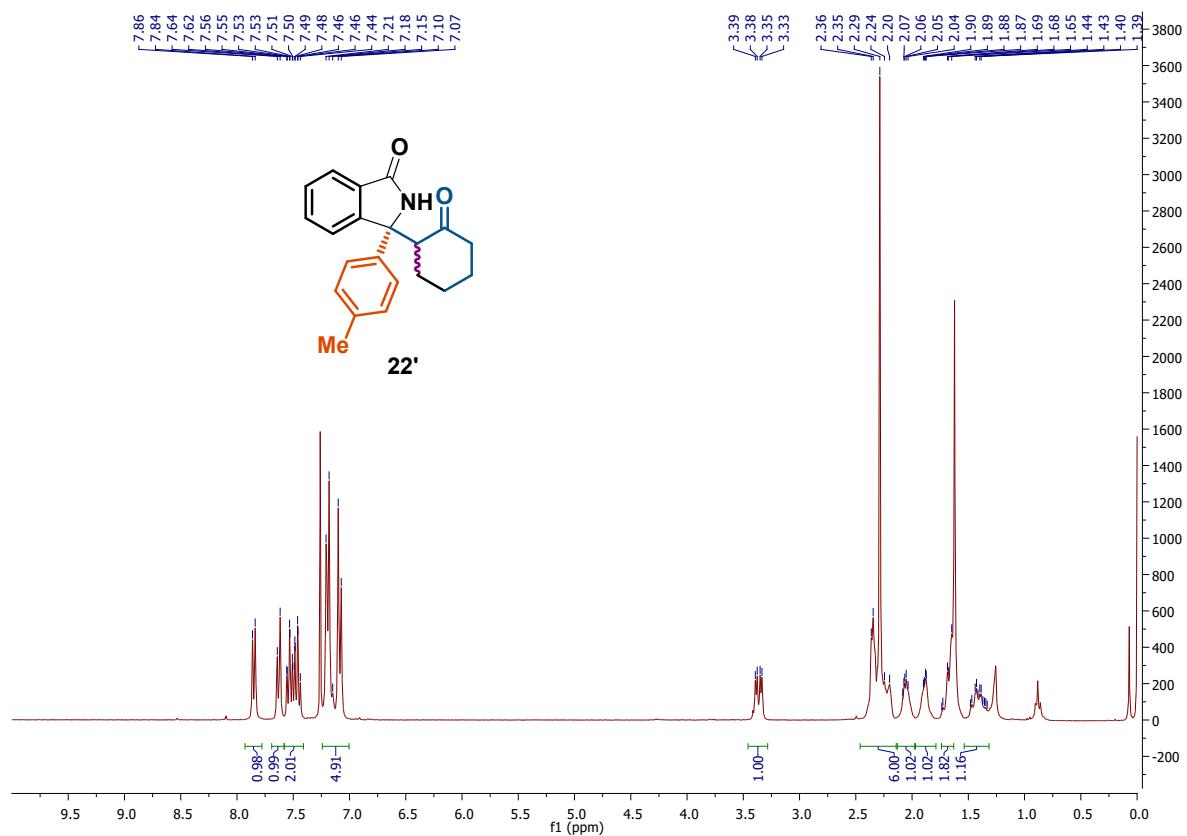


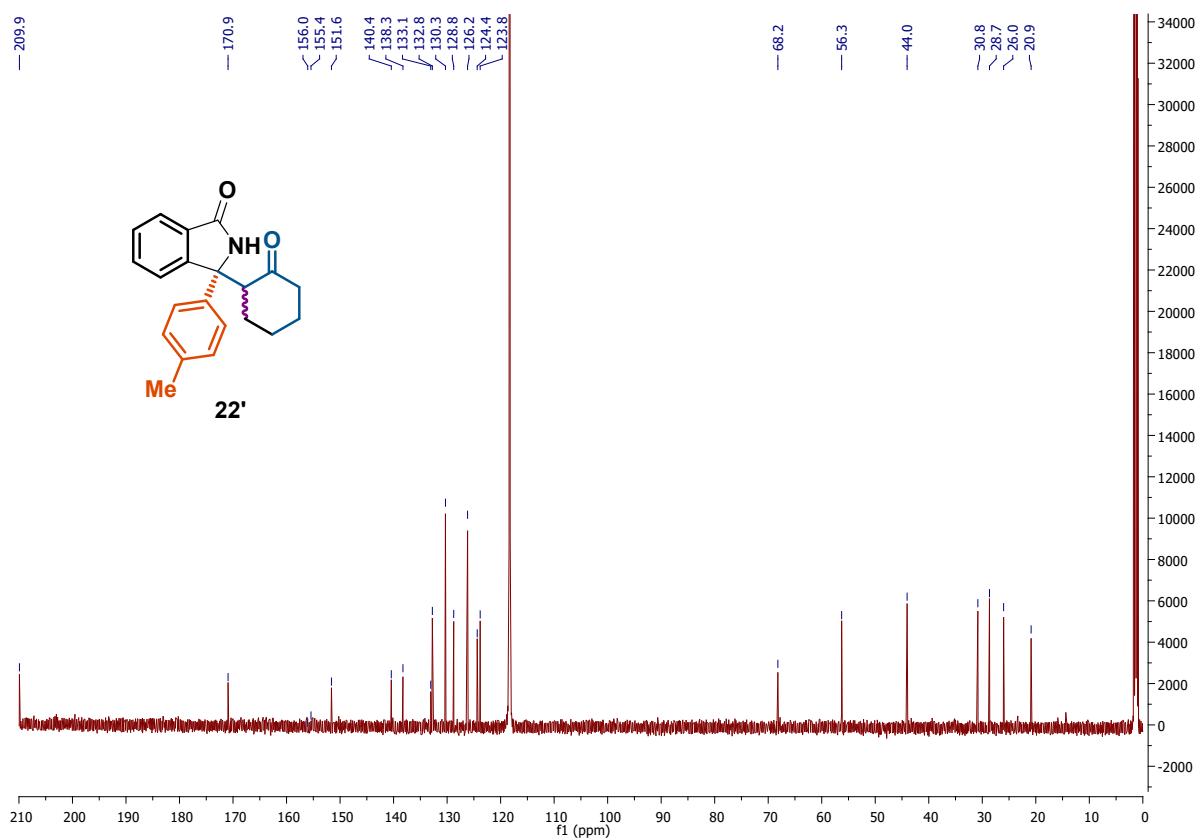


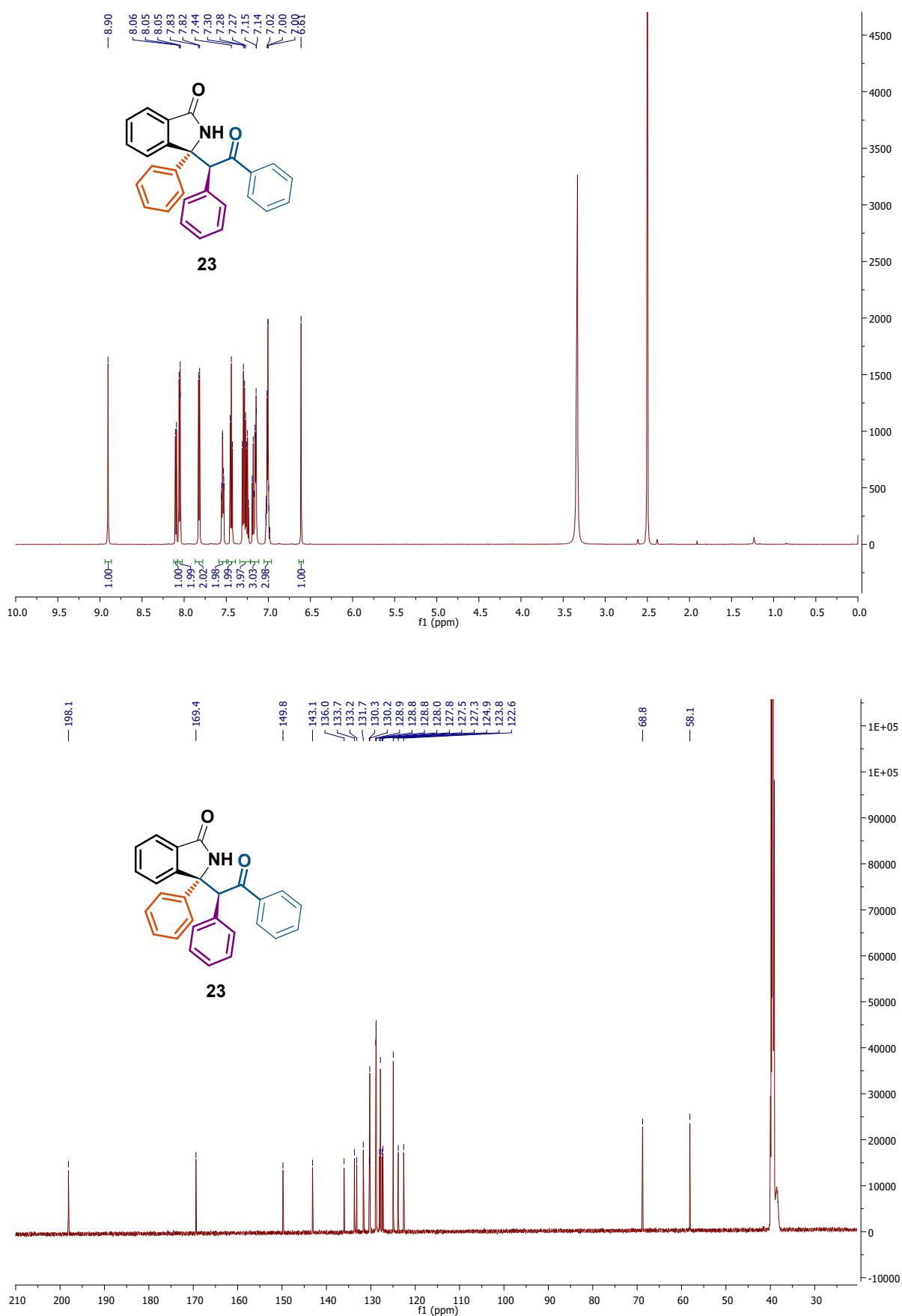


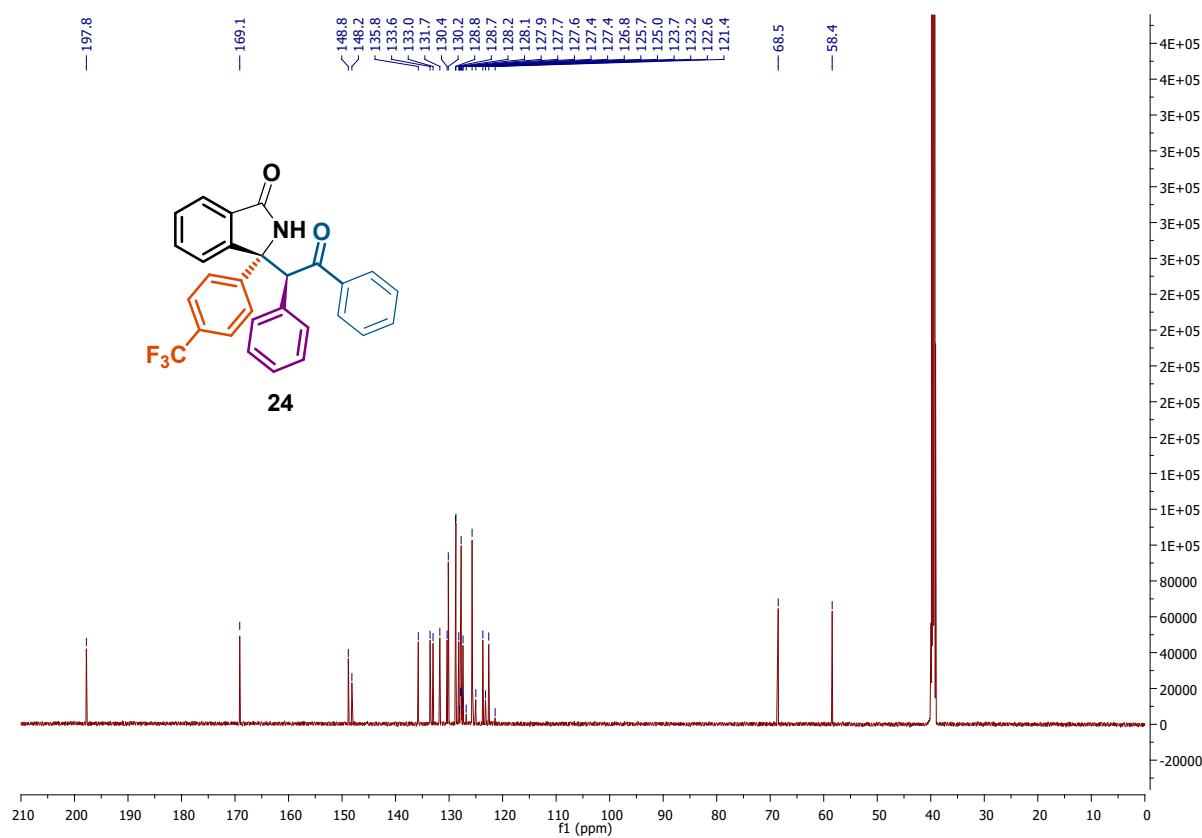
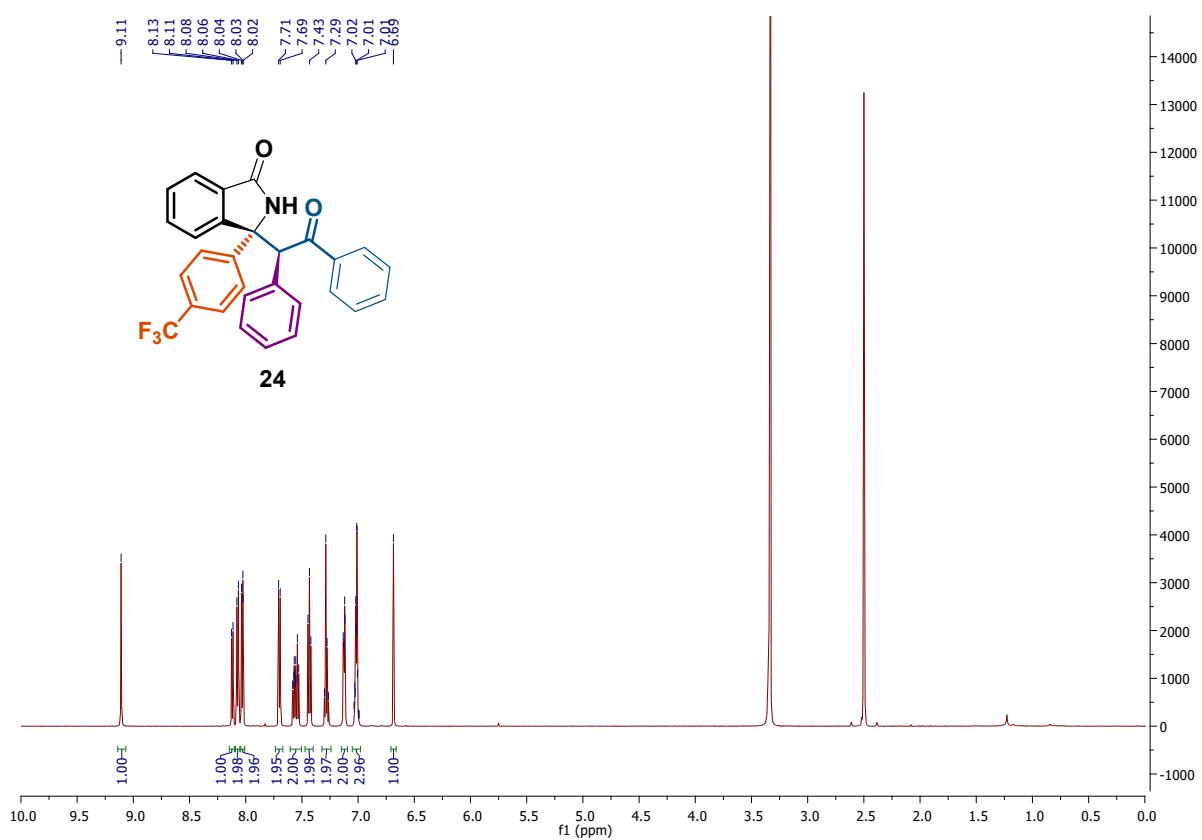


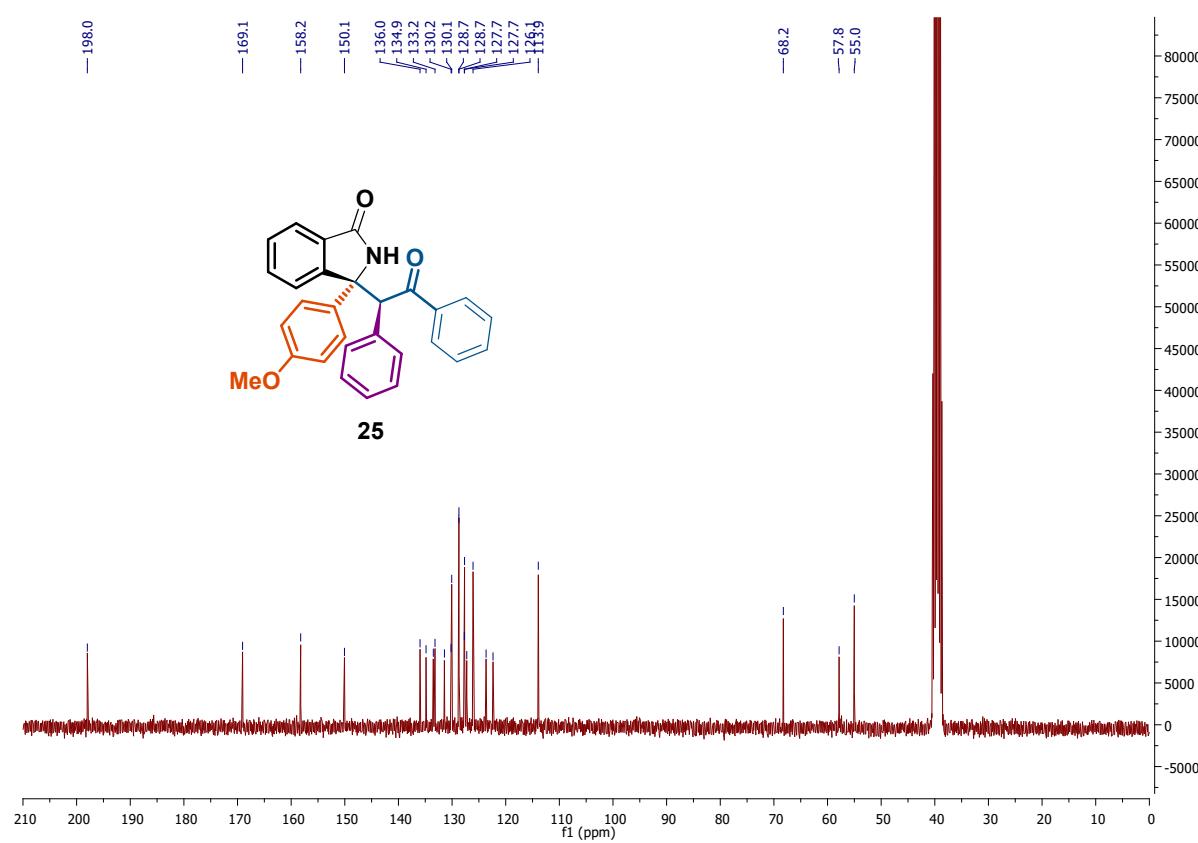
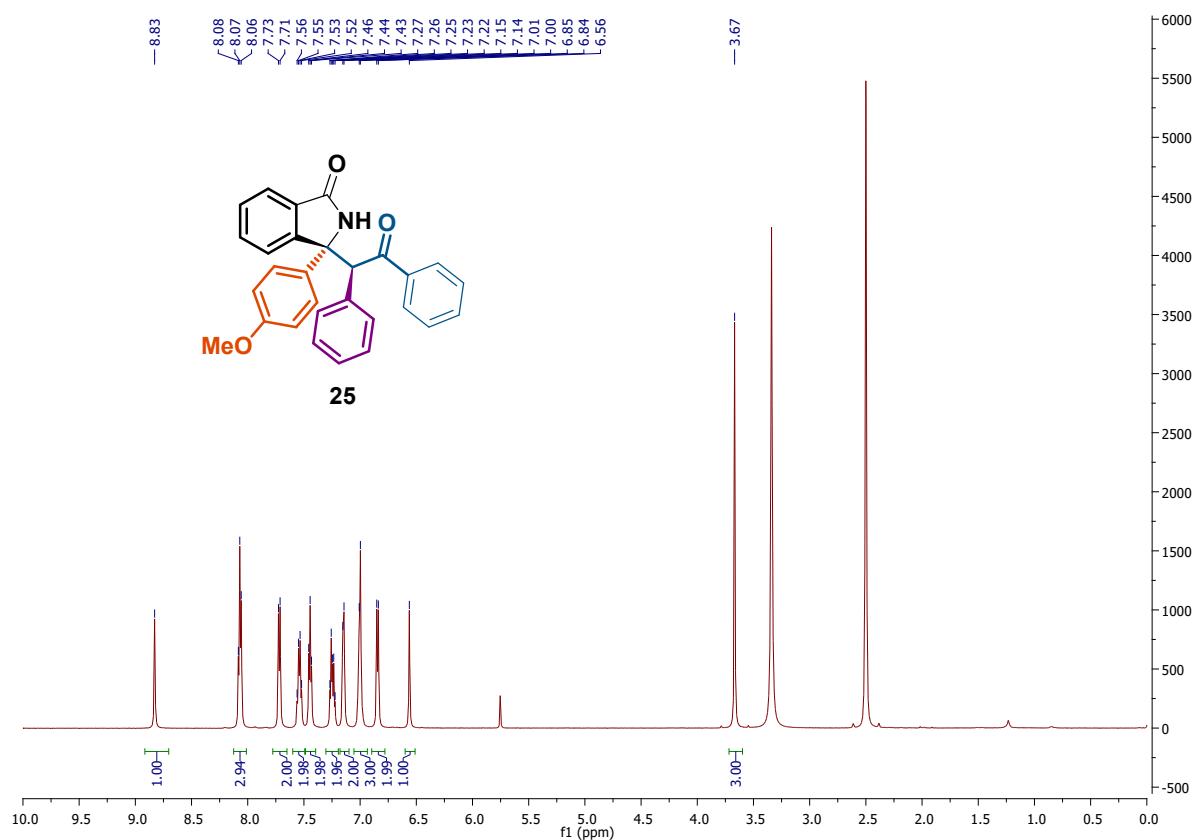


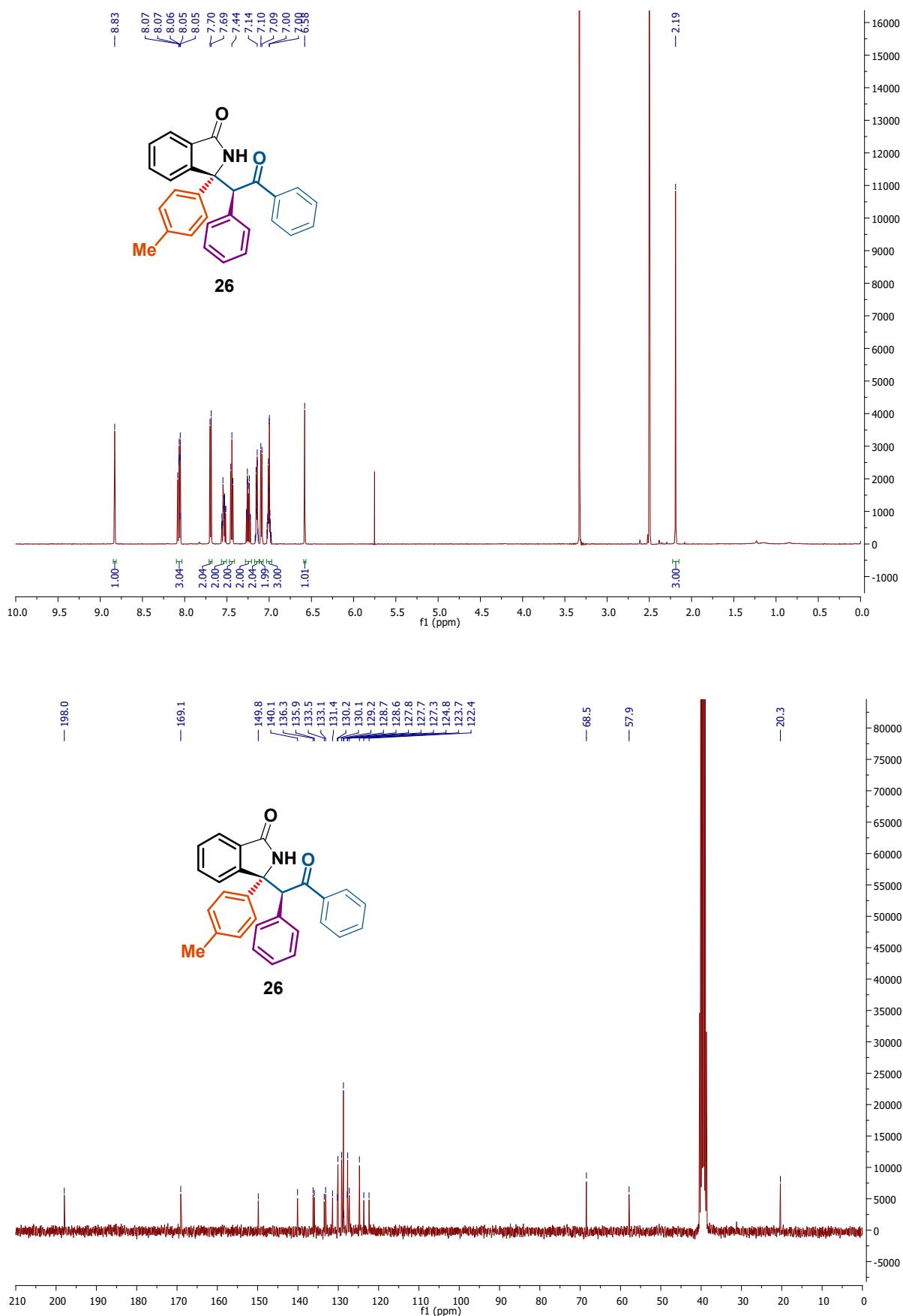


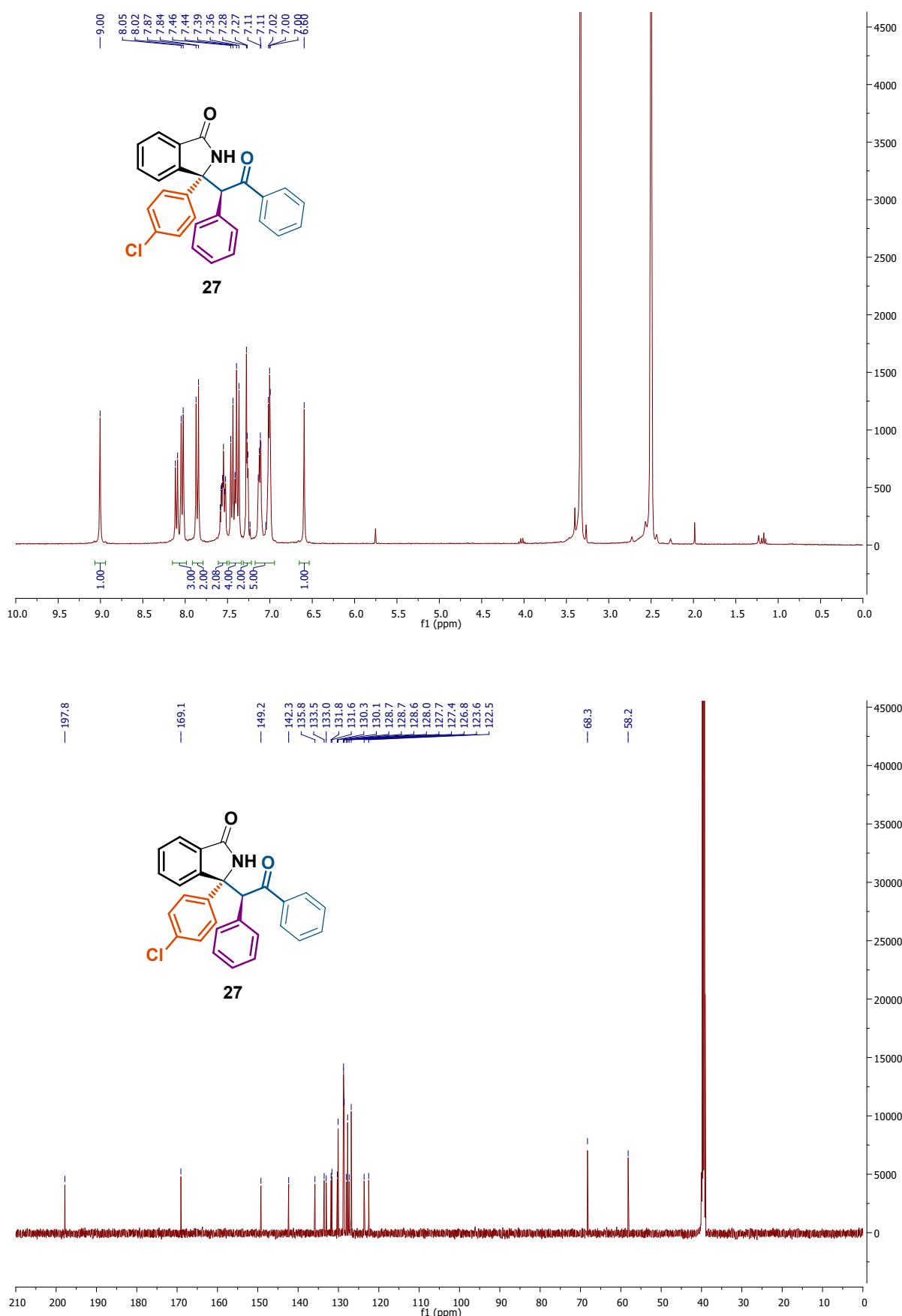


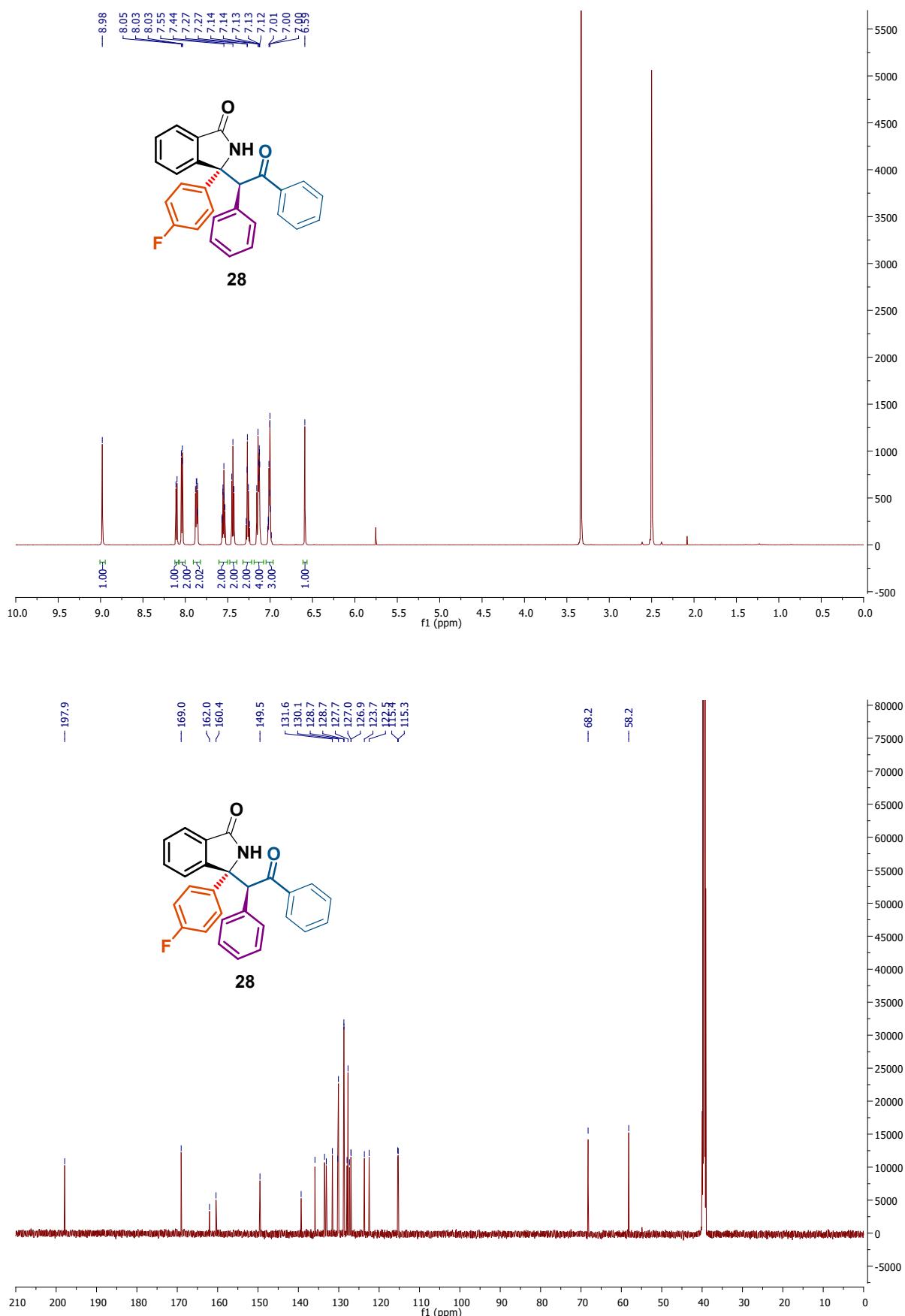


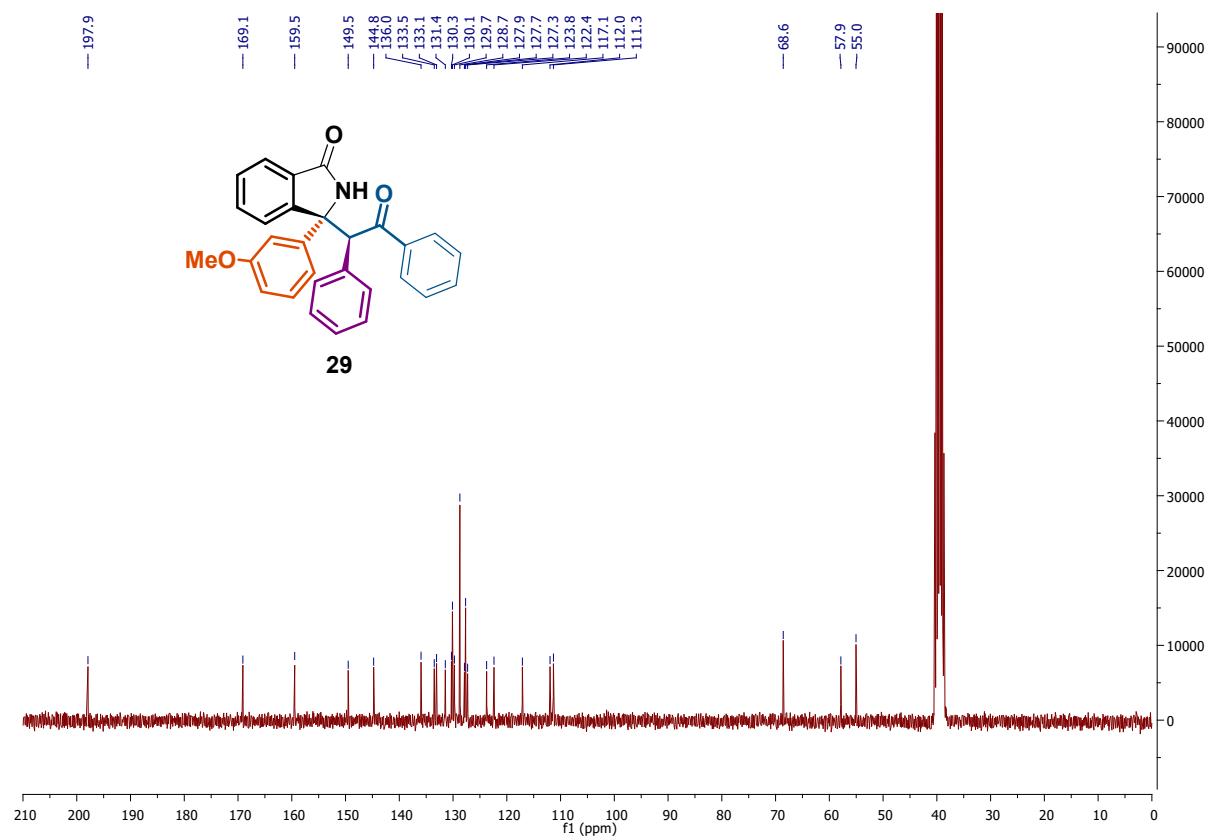
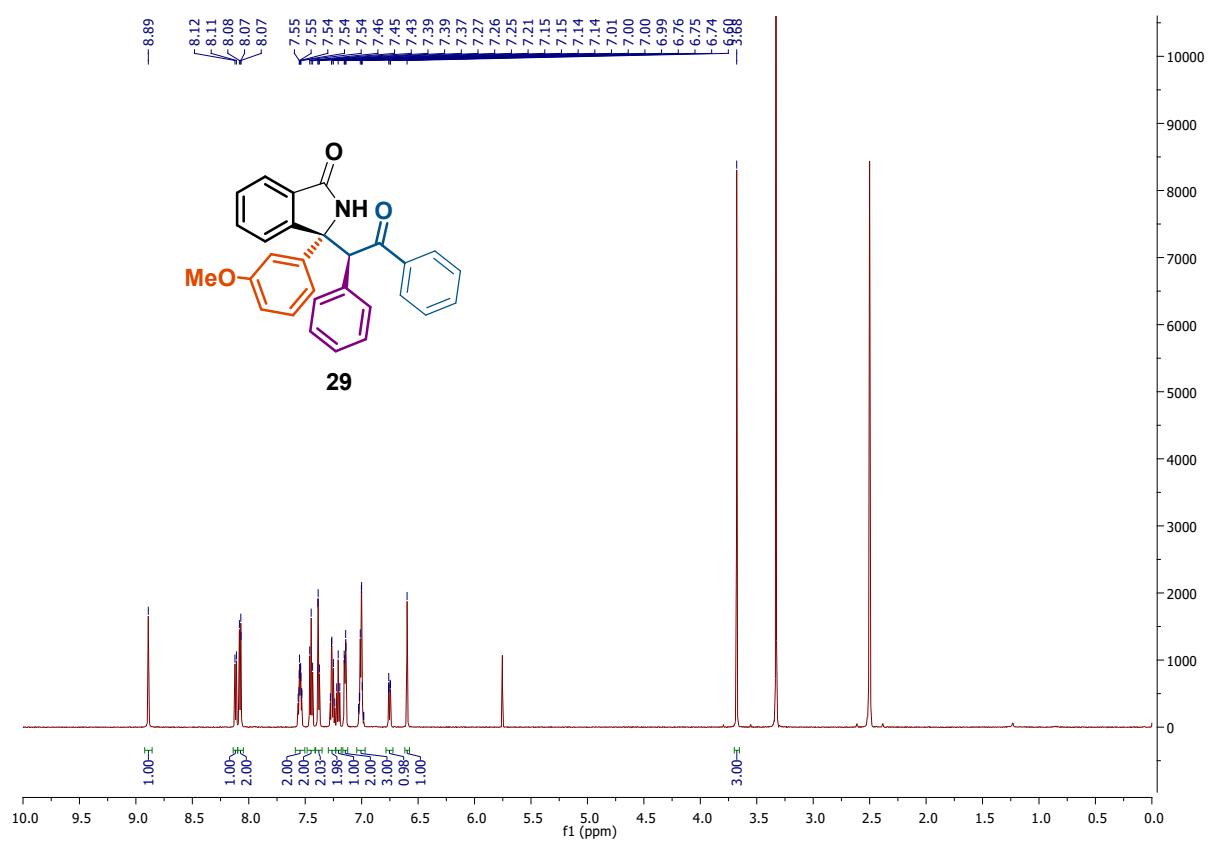


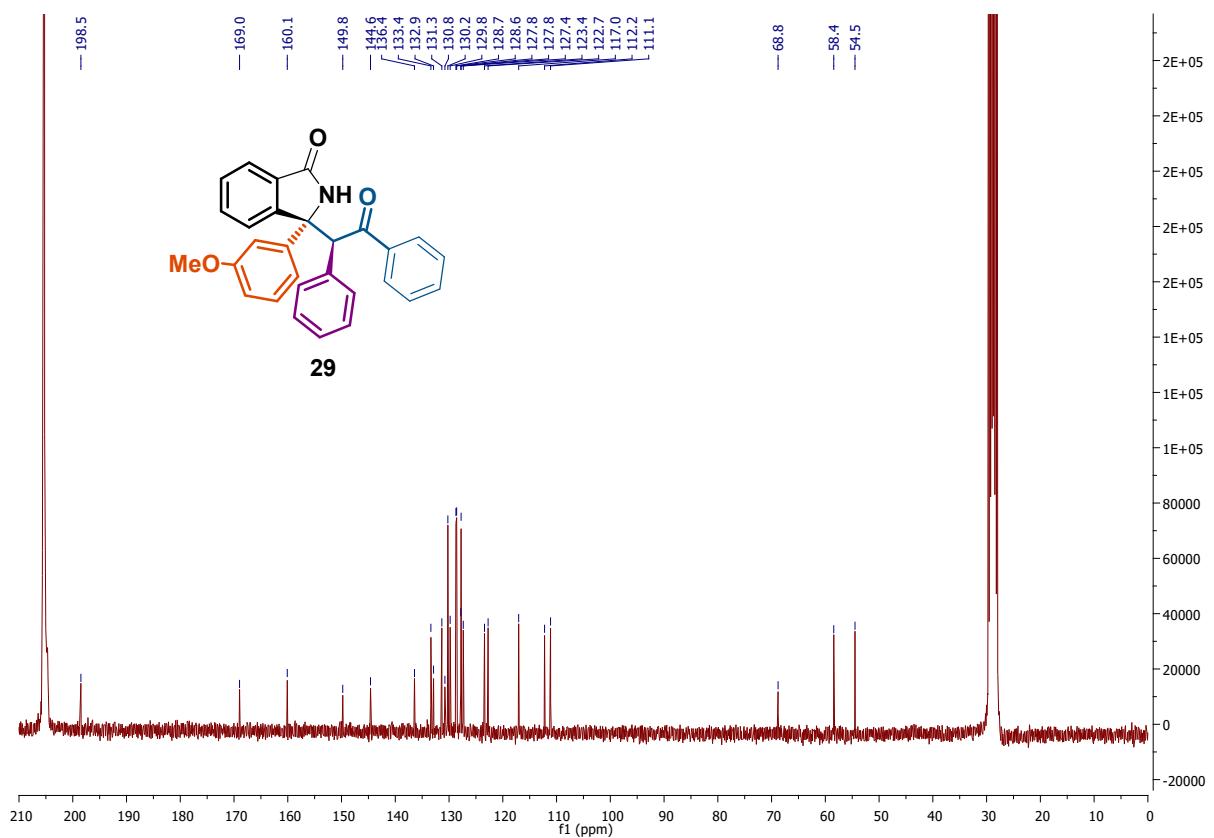


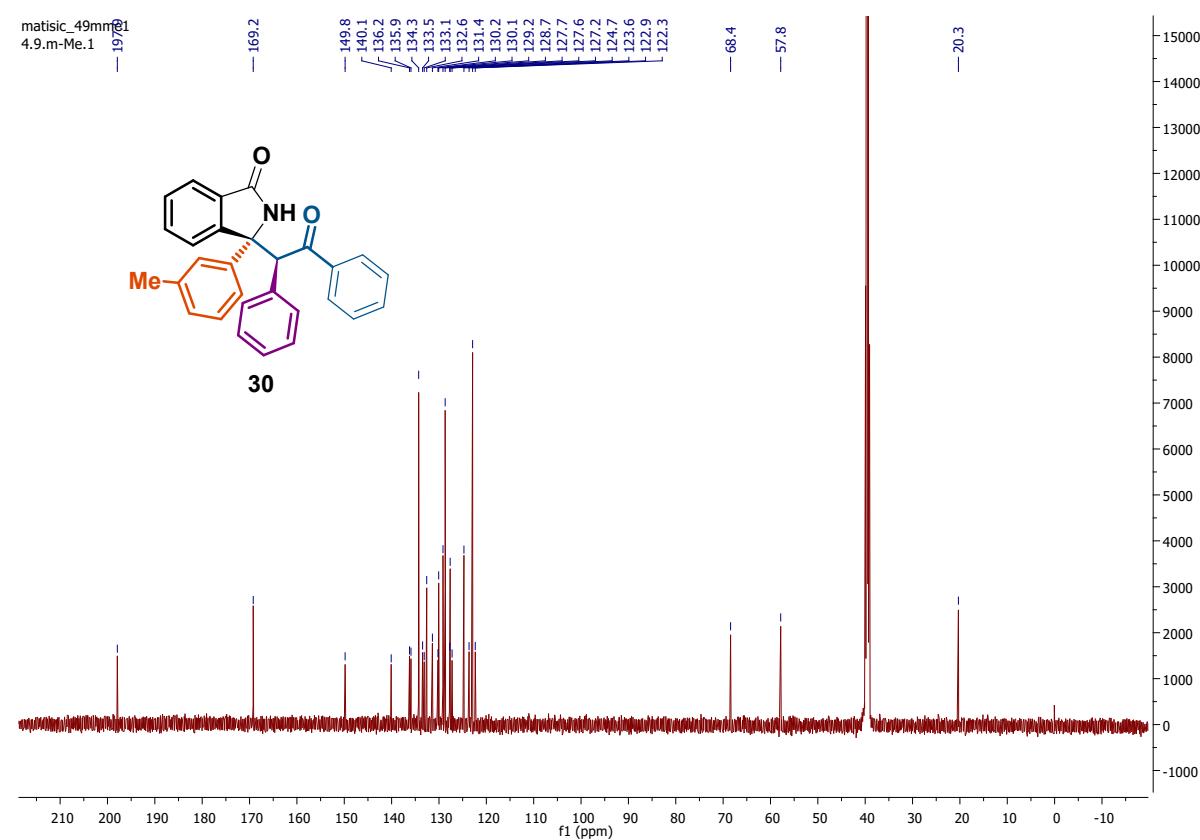
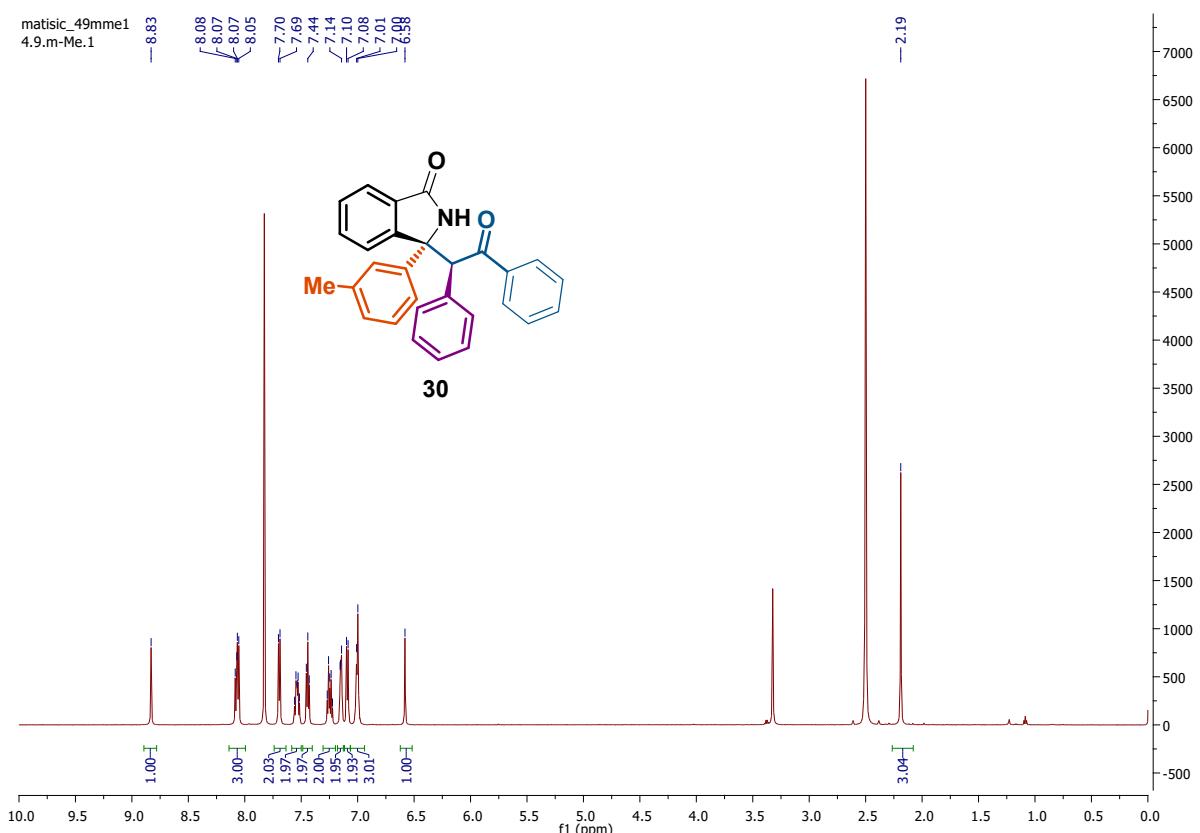


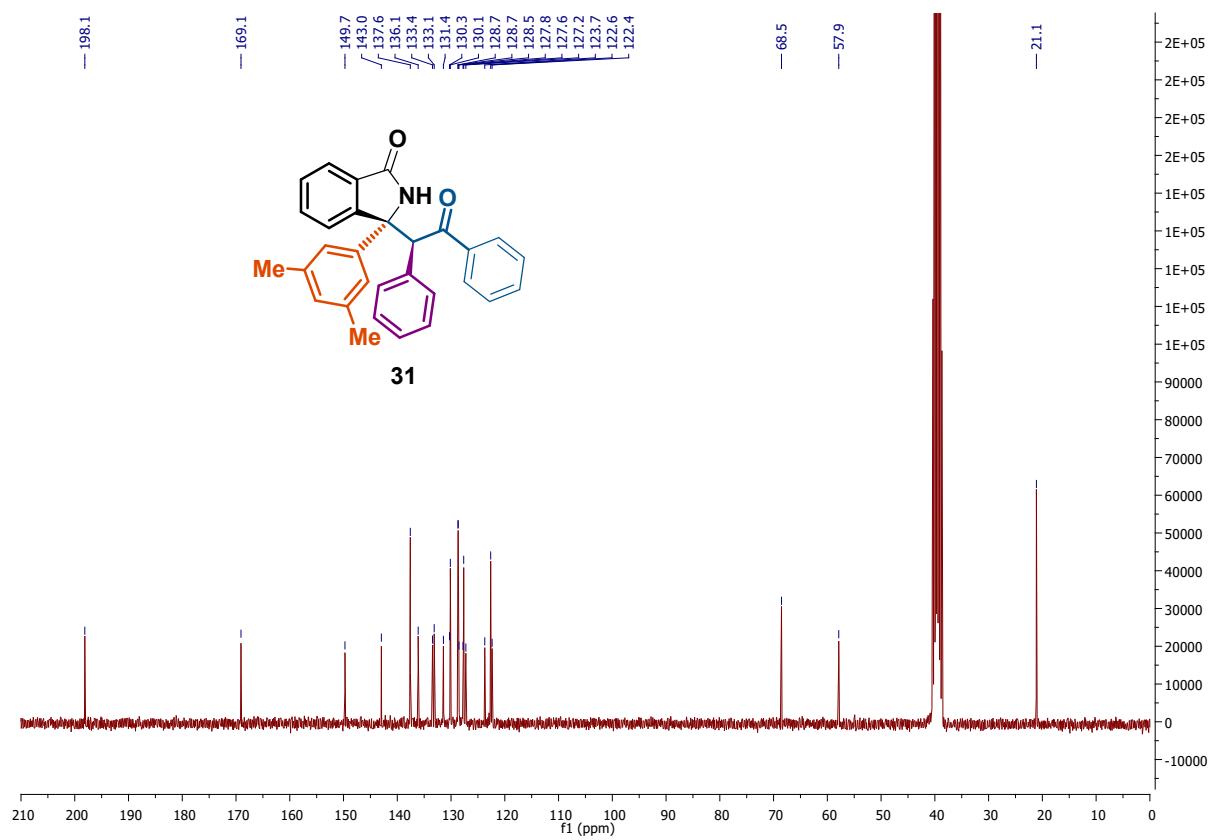
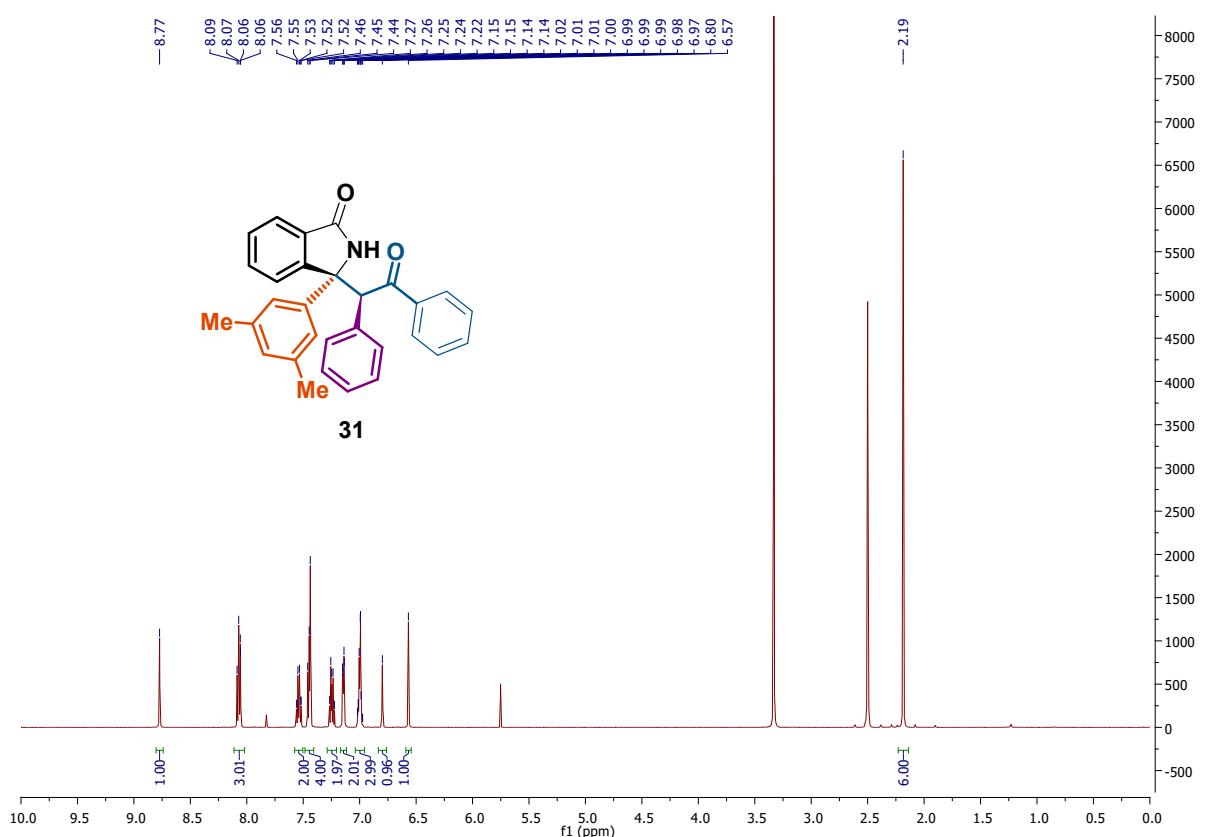


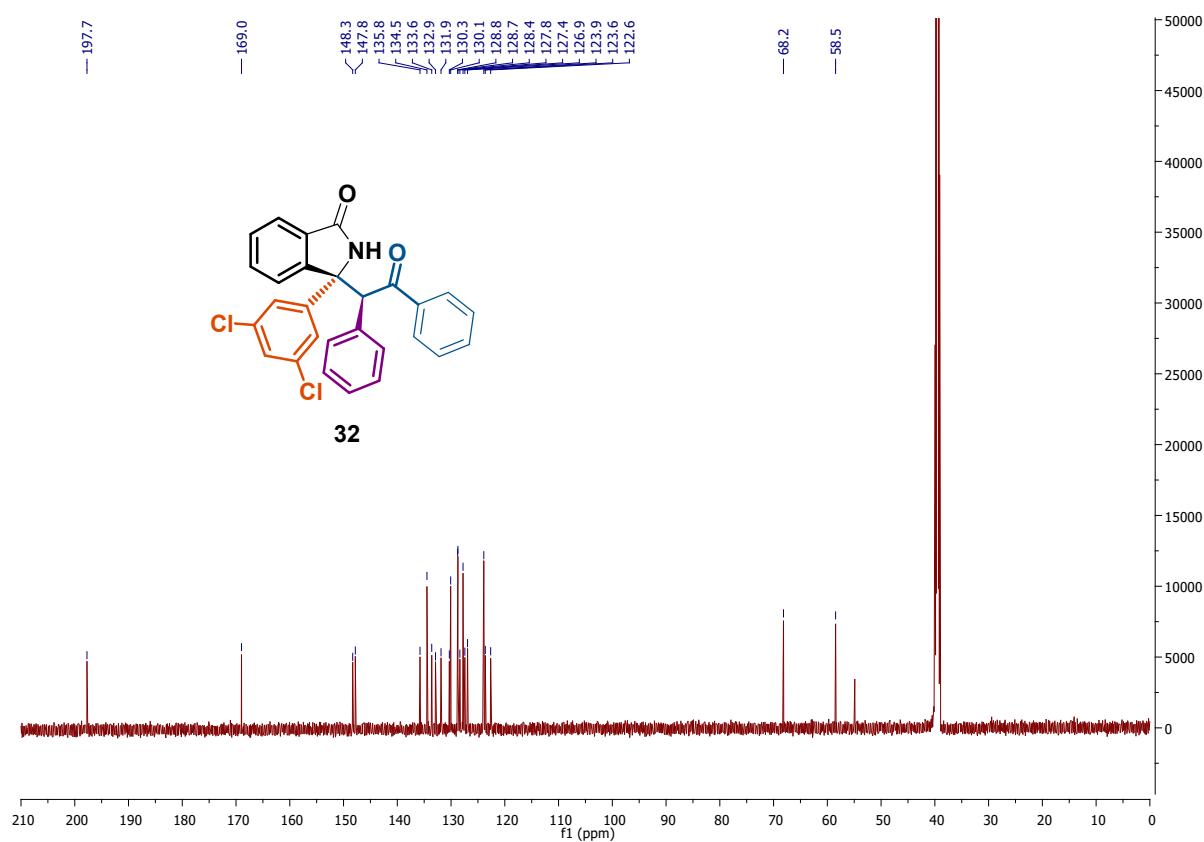
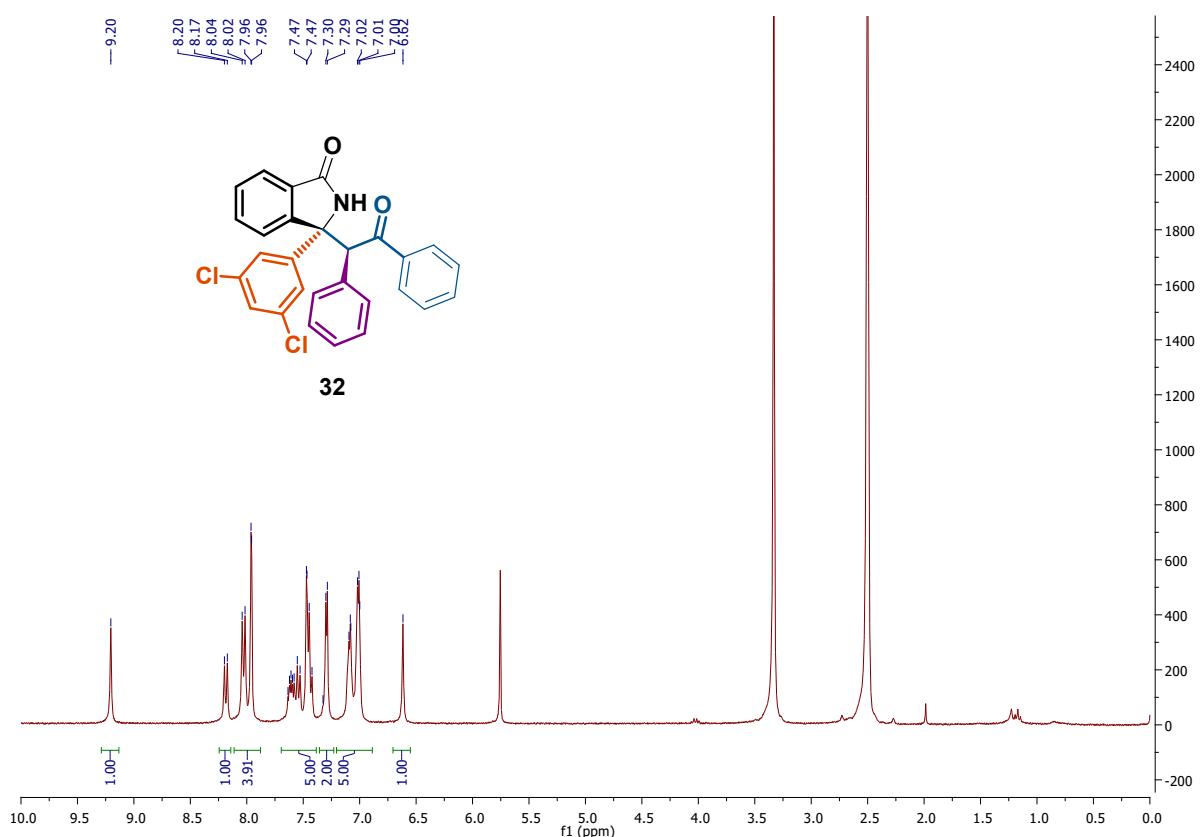


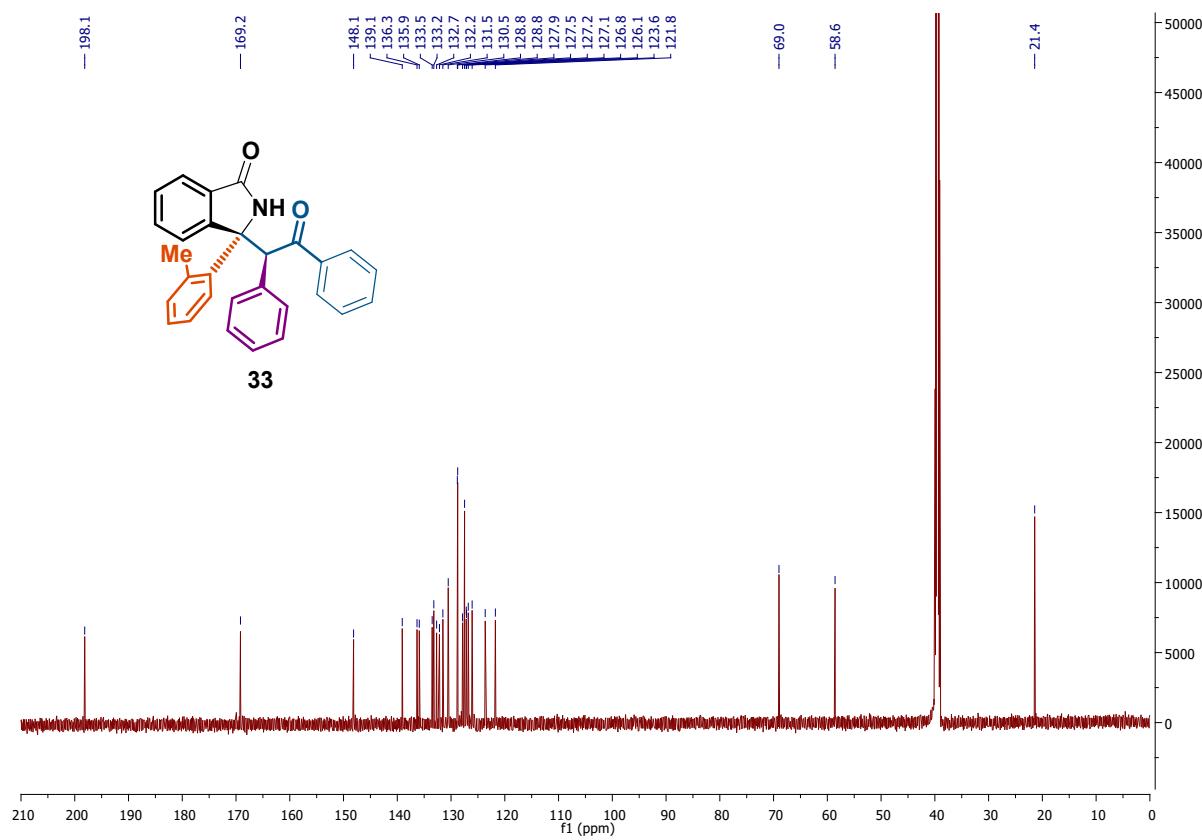
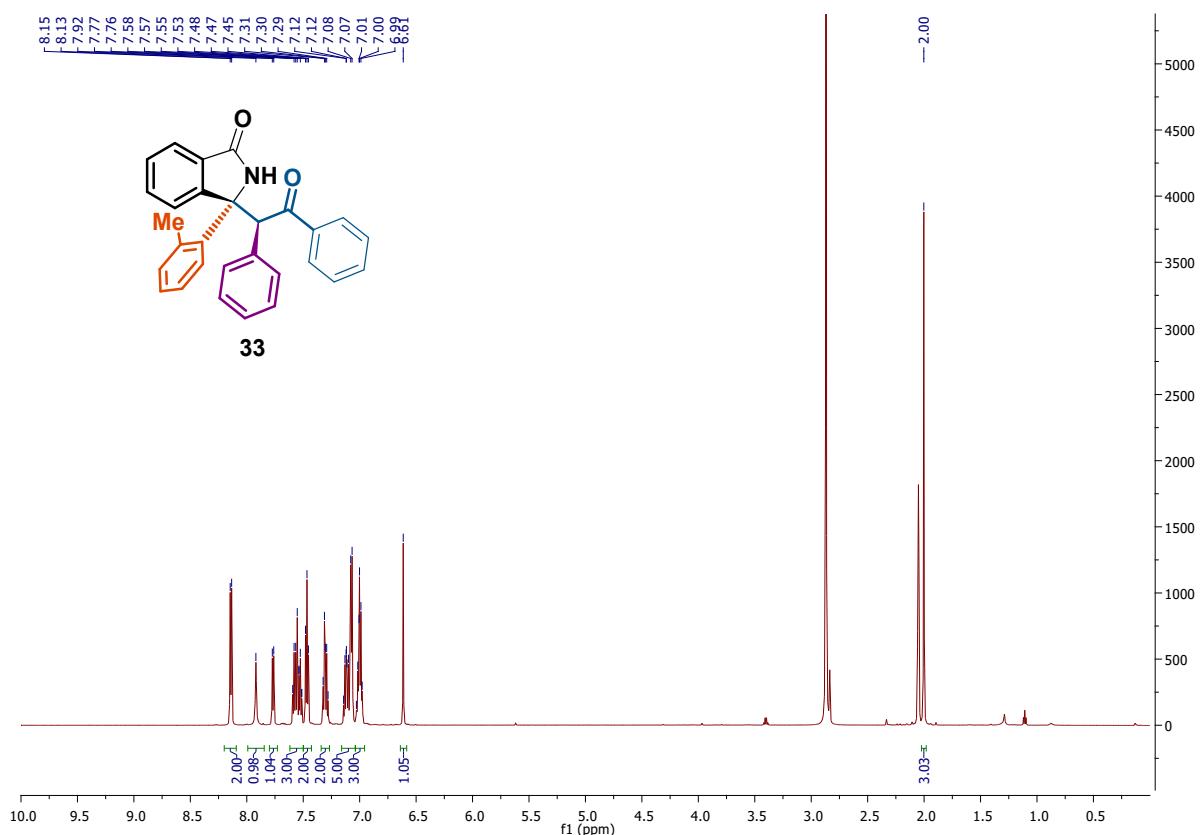


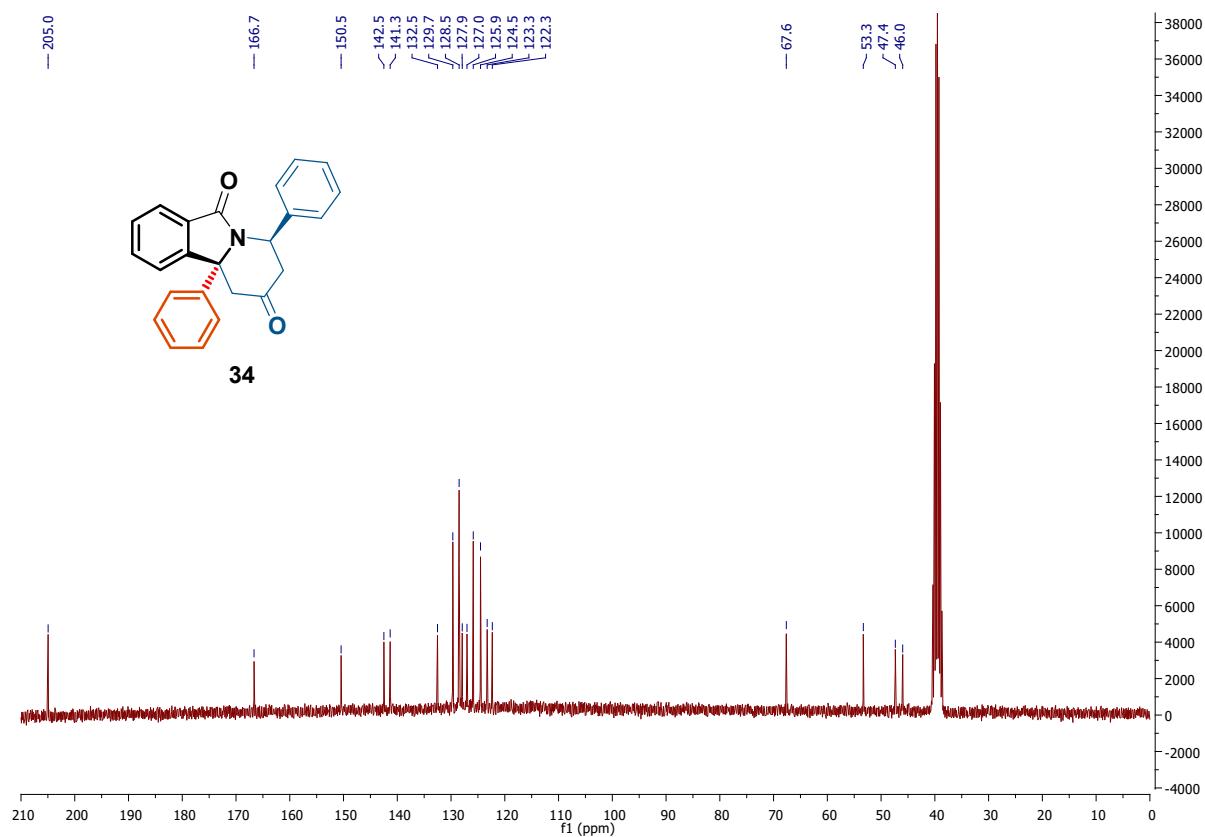
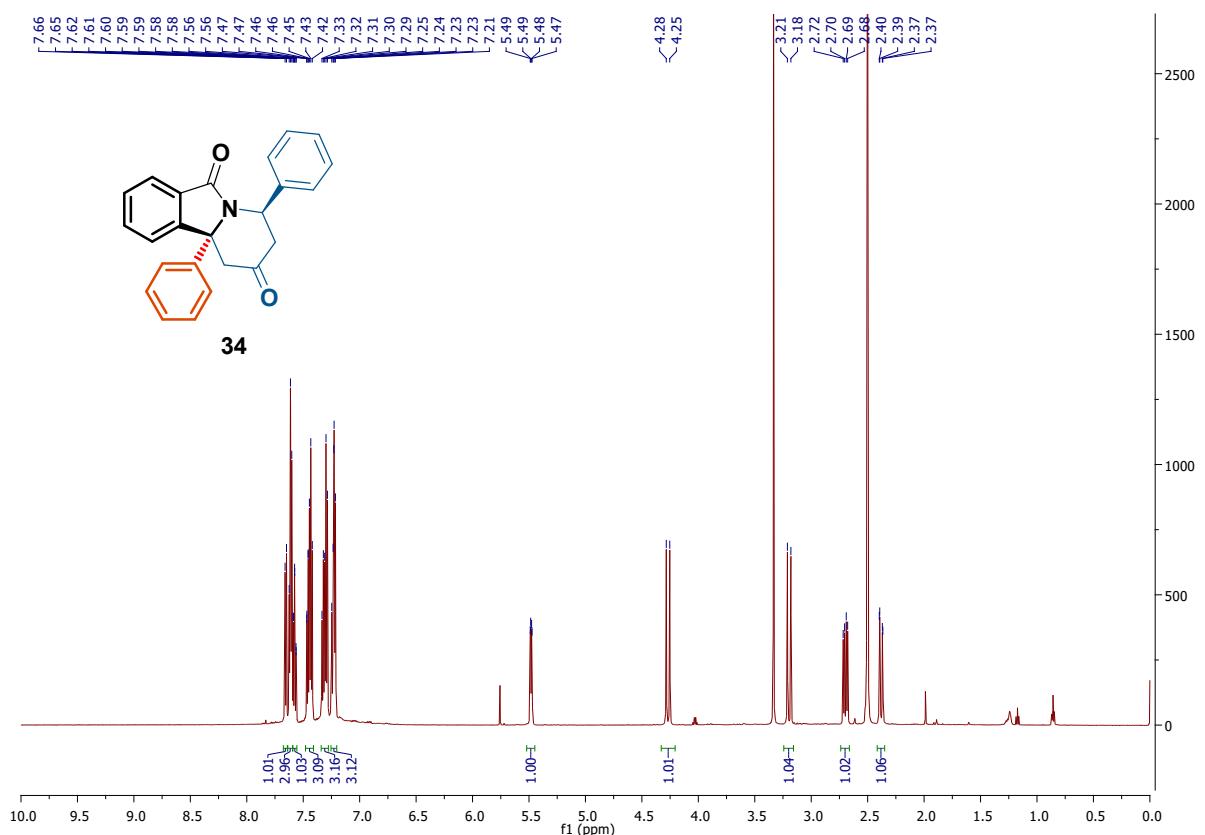


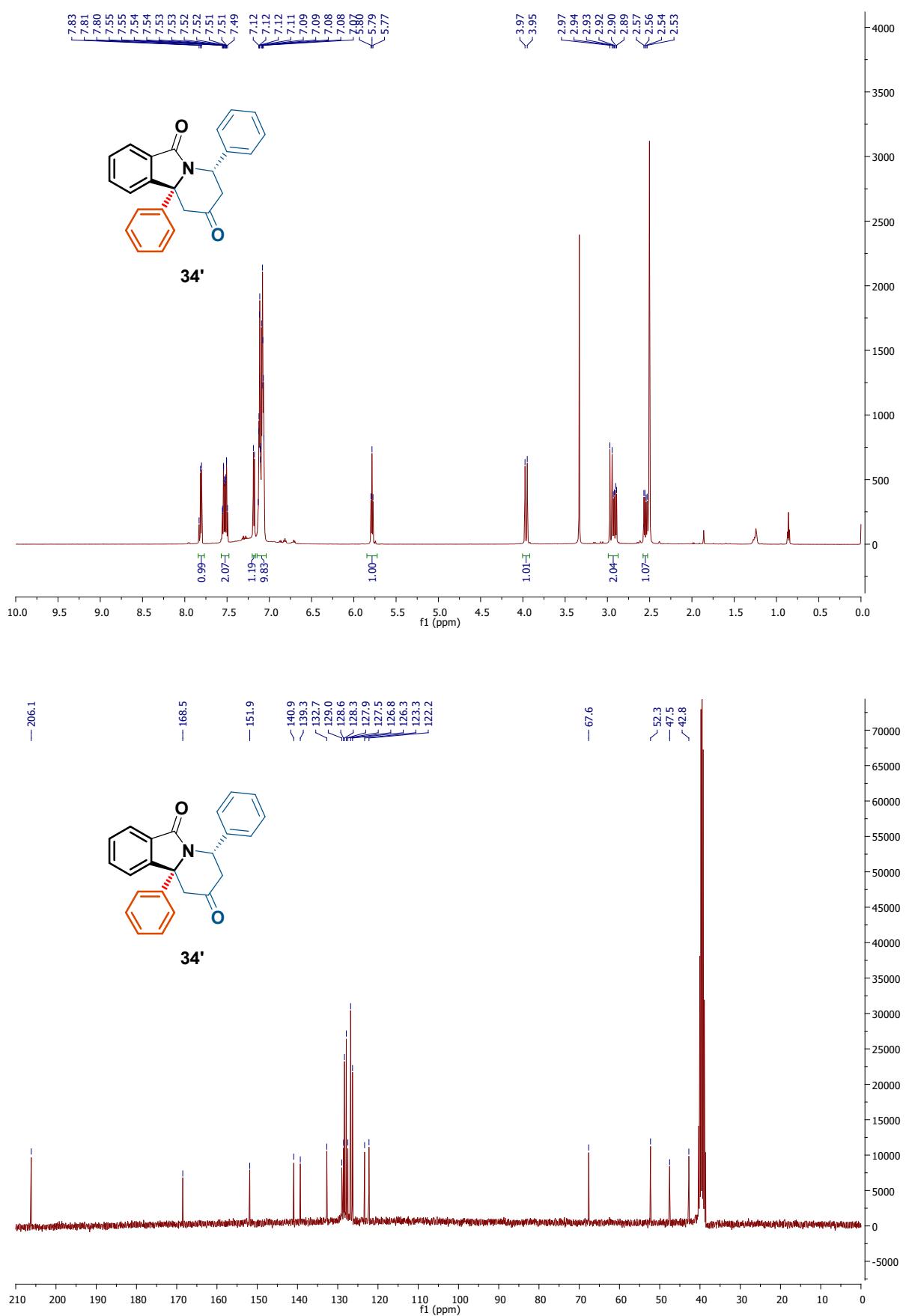


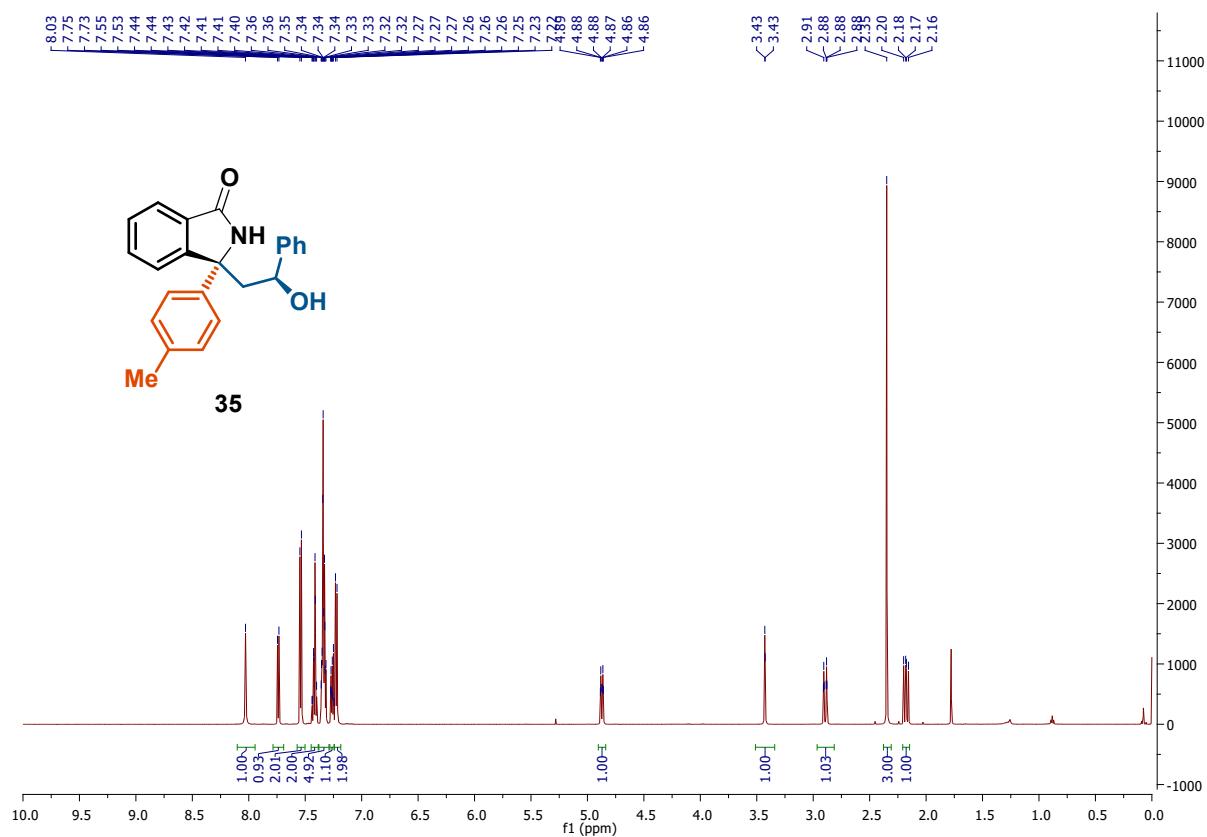
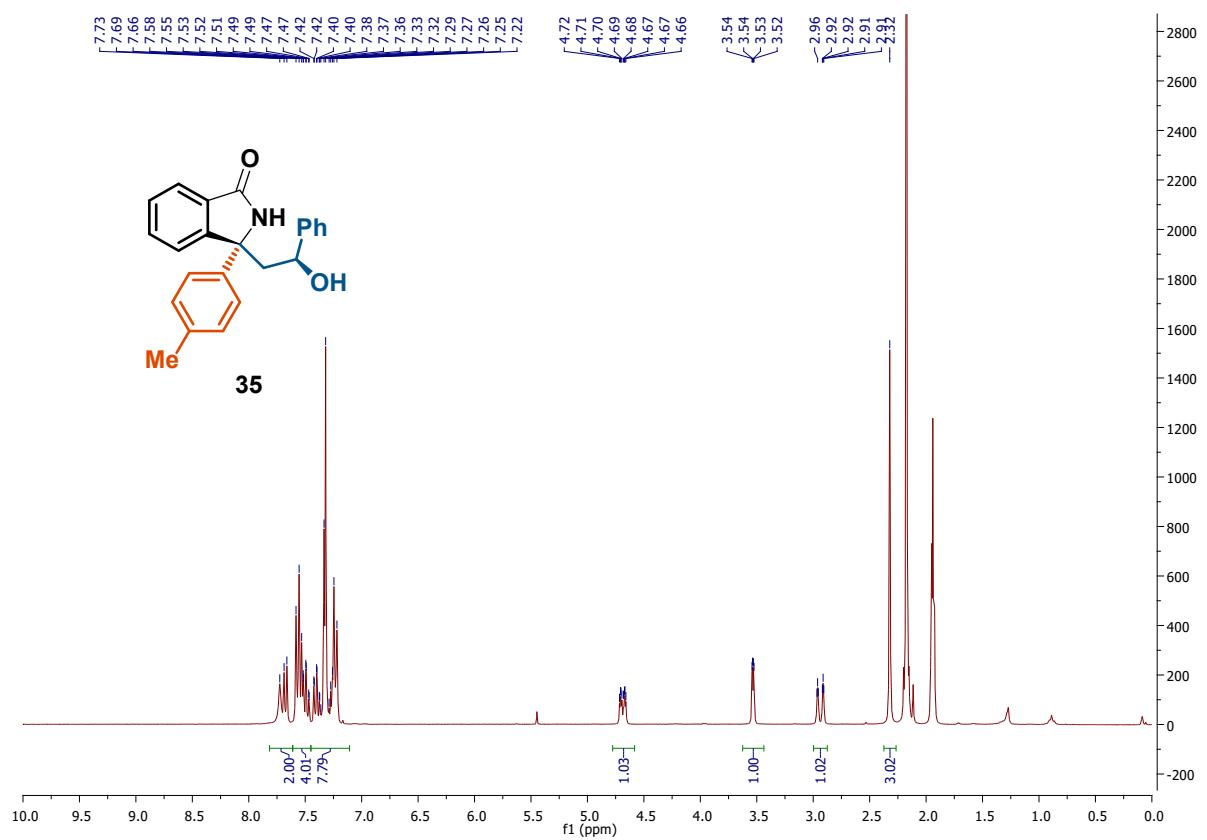


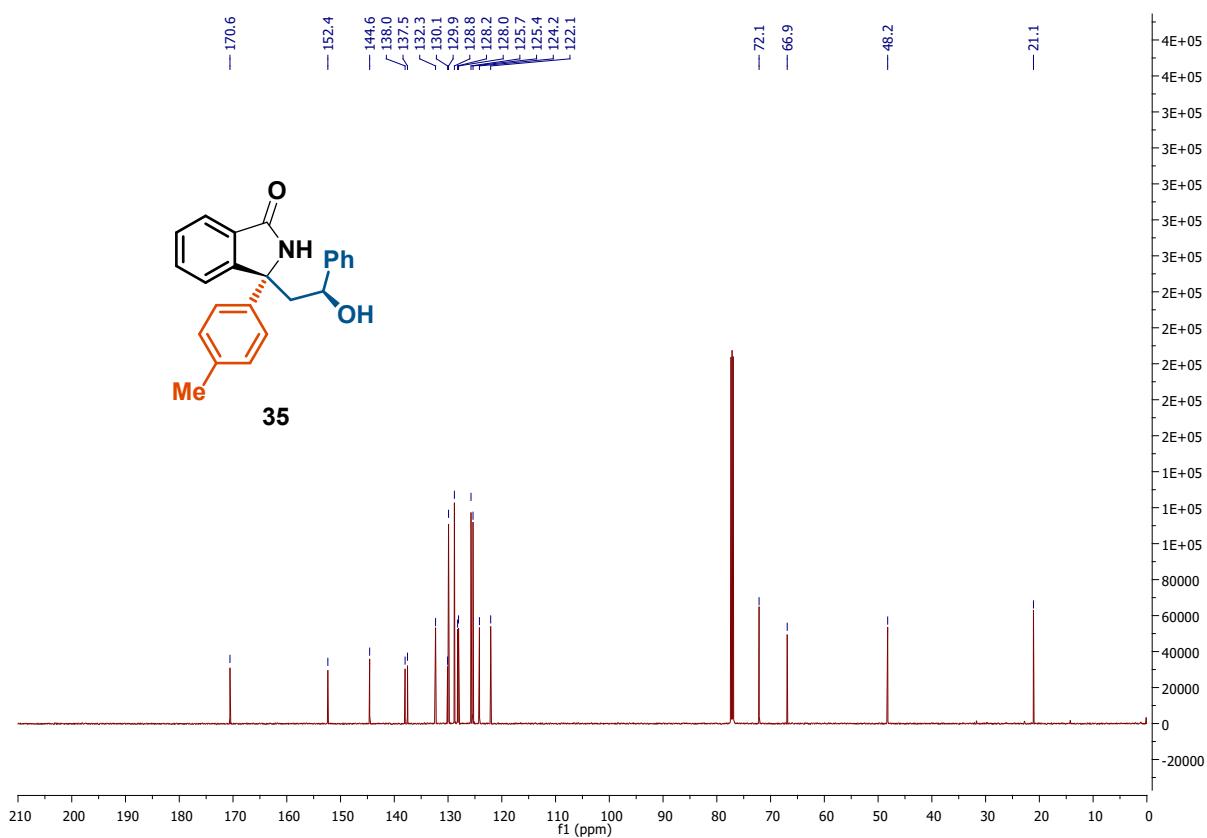


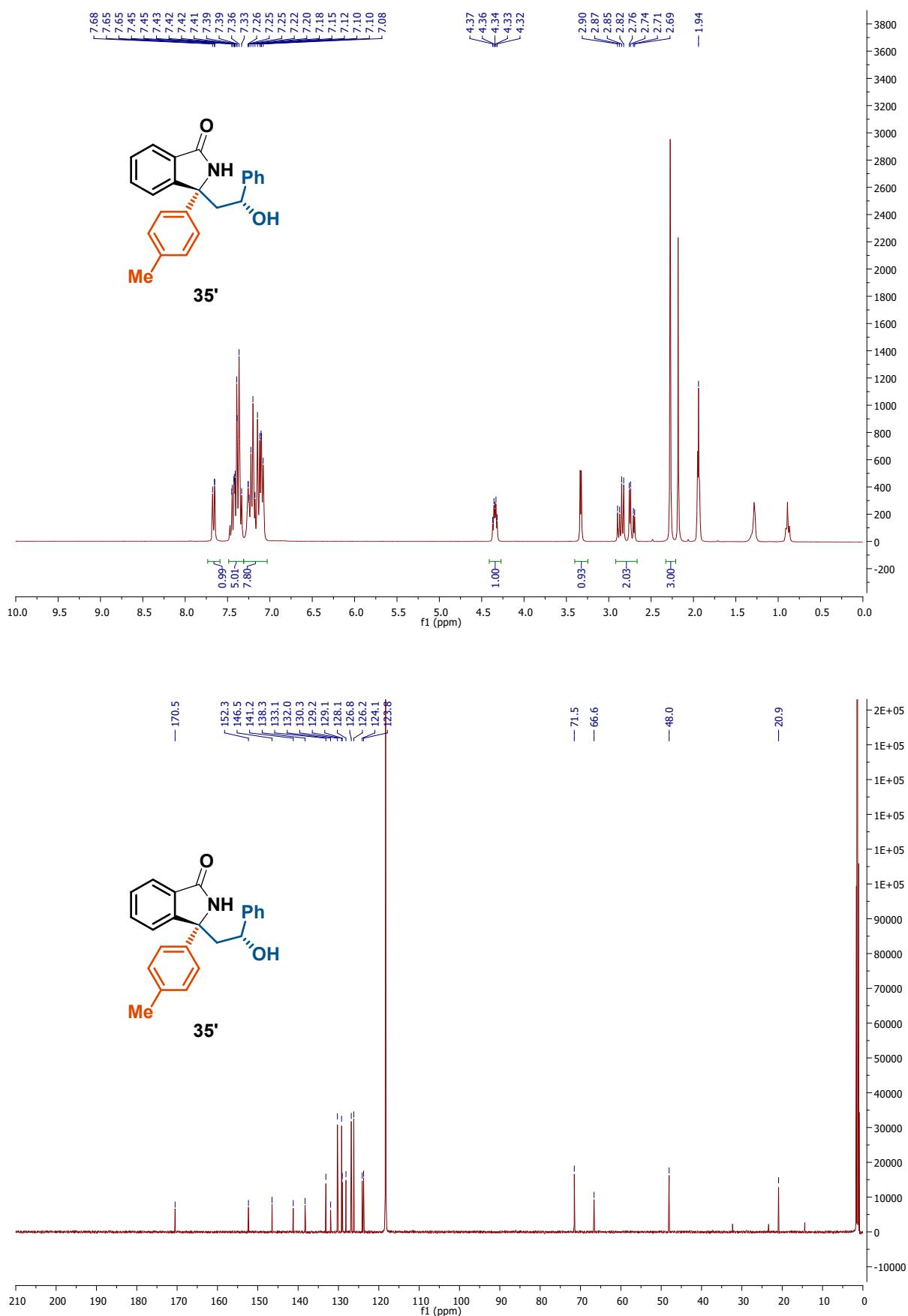


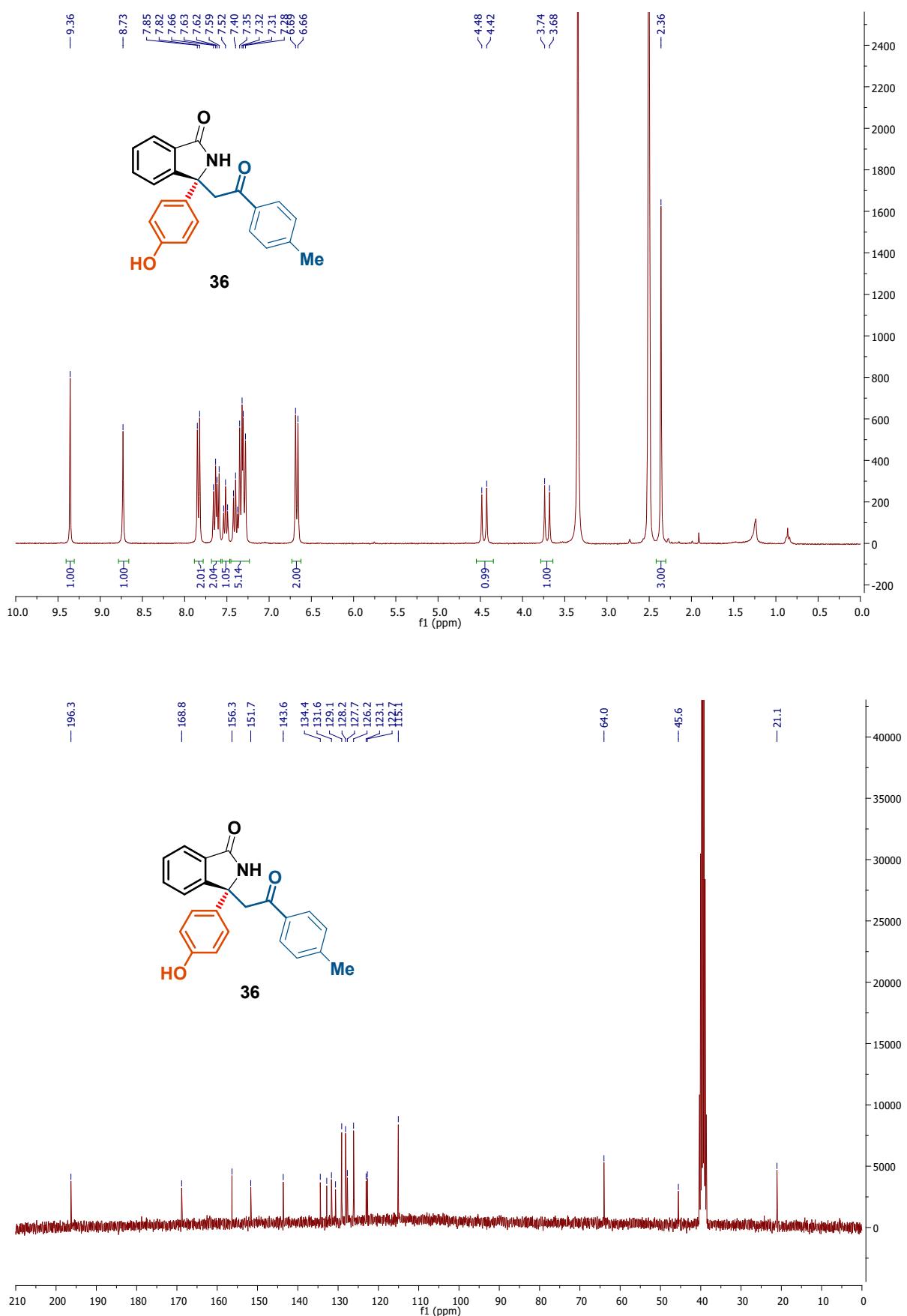




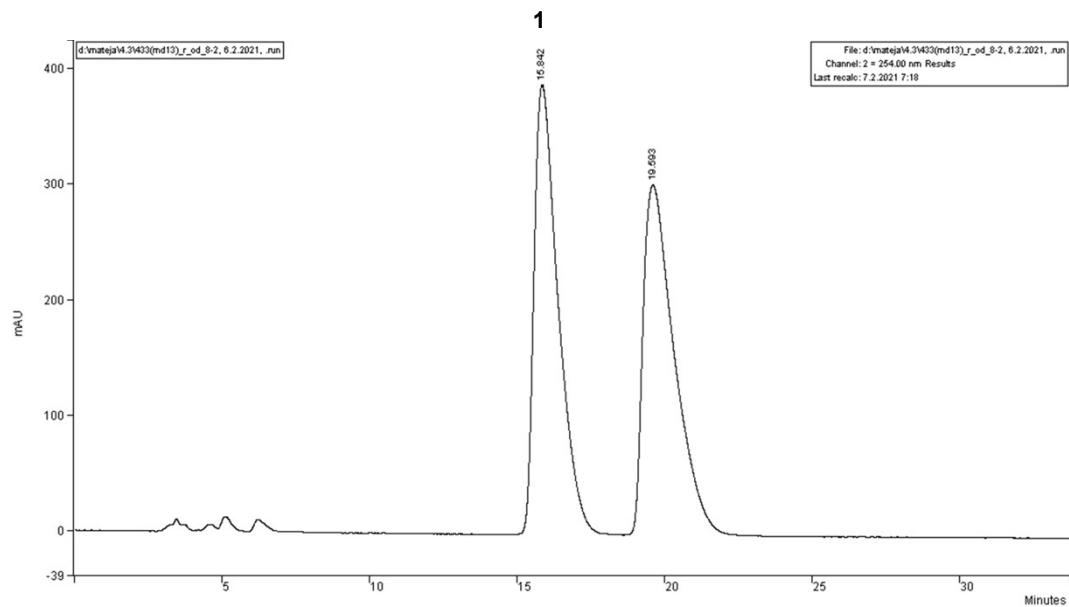
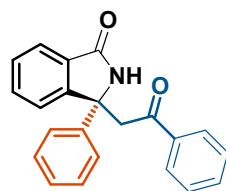




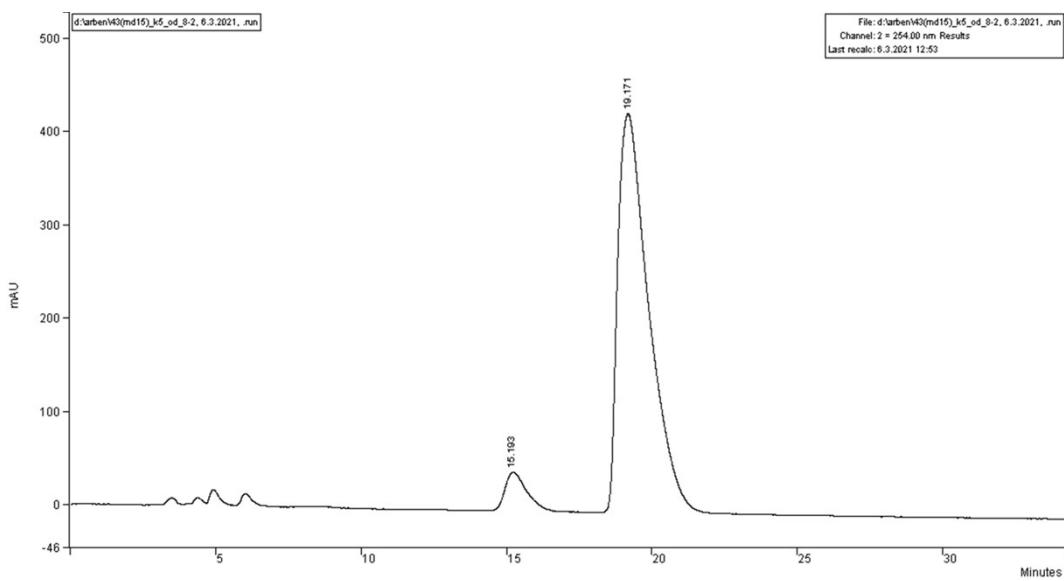




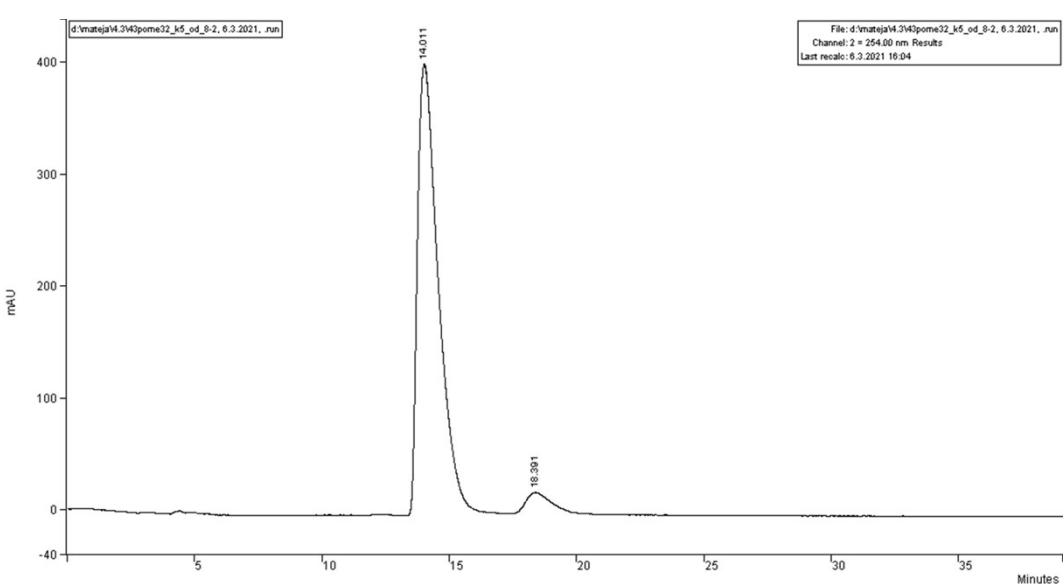
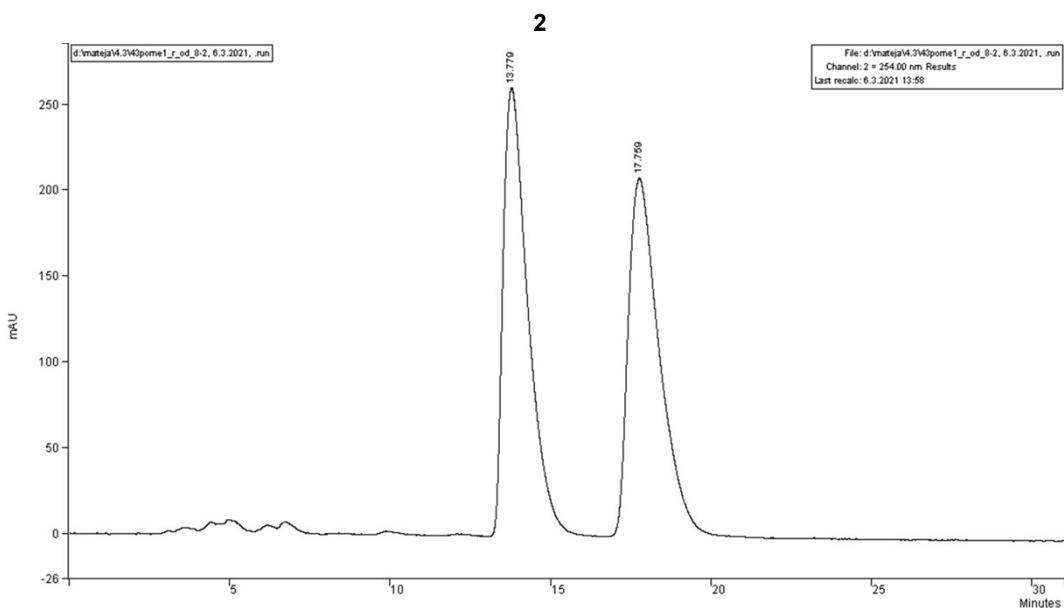
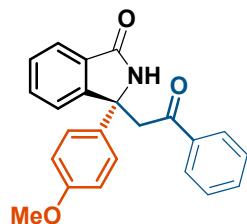
§ 7. HPLC Traces

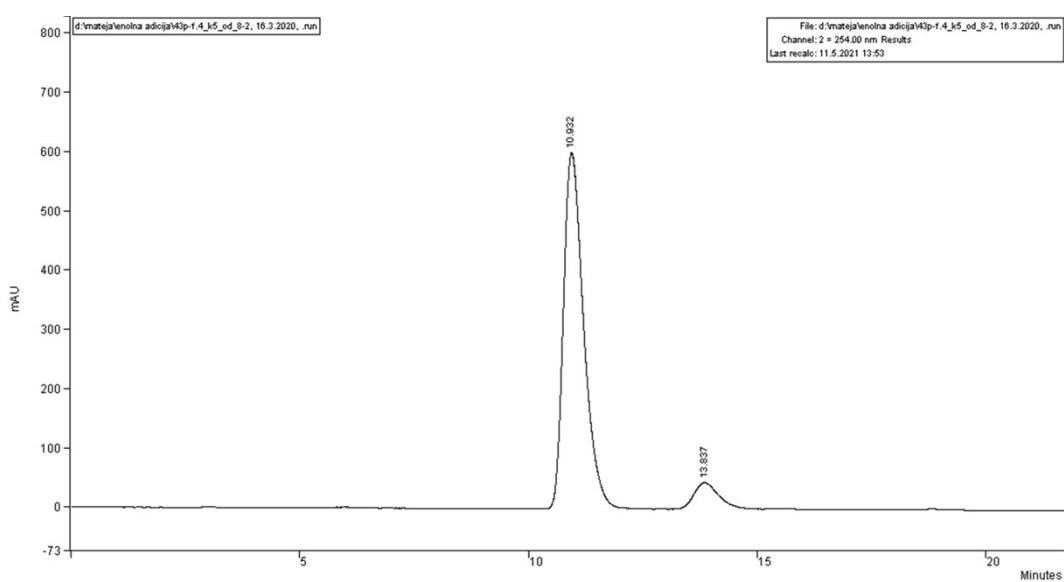
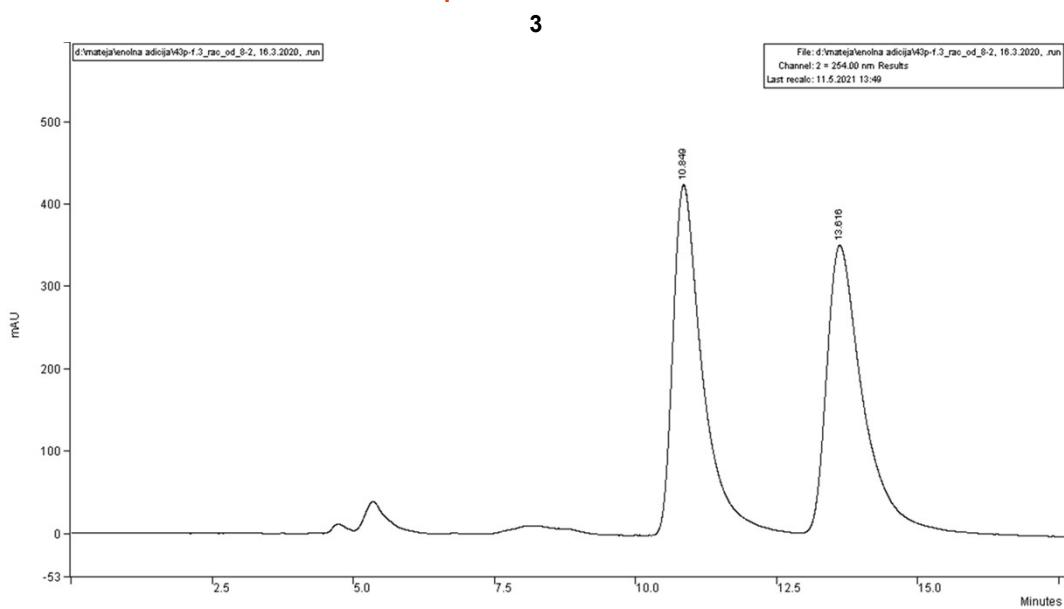
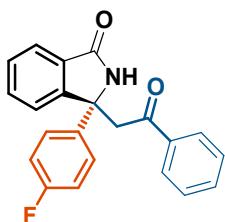


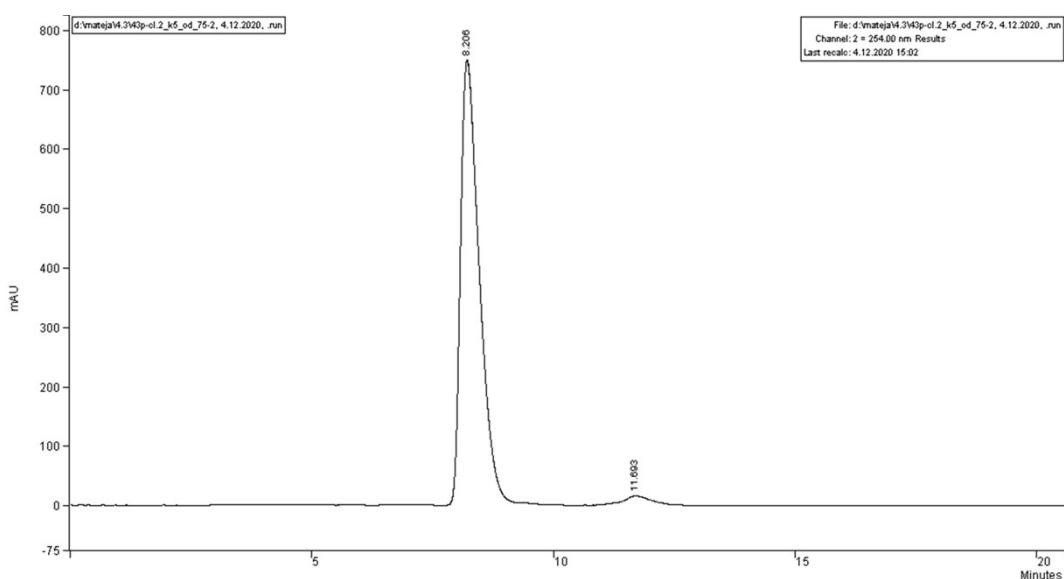
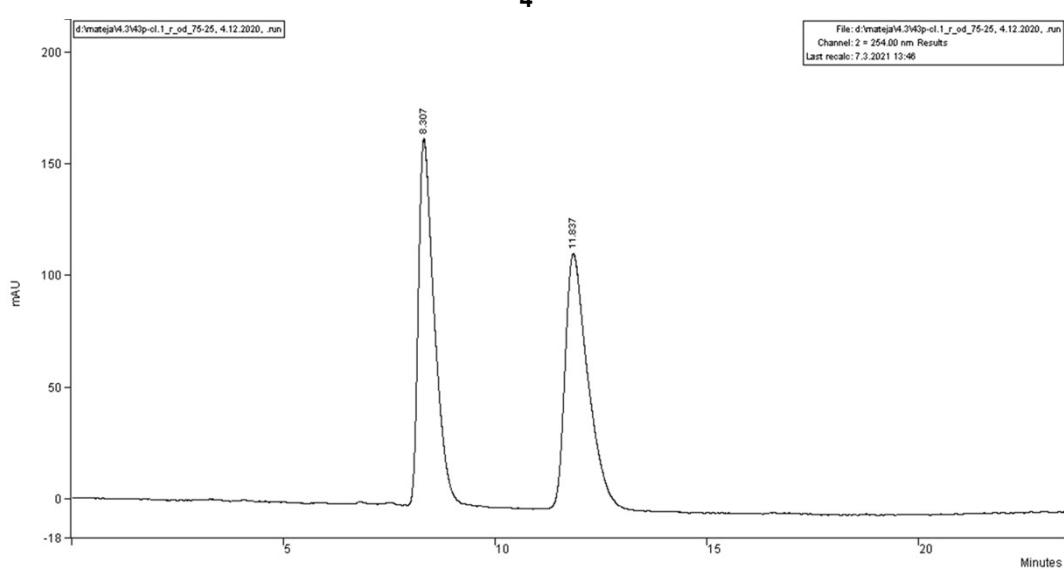
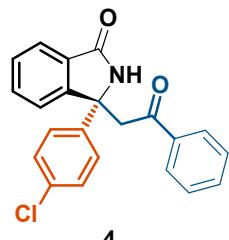
Peak No.	Peak Name	Result (l)	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code (sec)	Width 1/2 (sec)	Status Codes
1		49.9115	15.842	0.000	220341696	BB	51.7	
2		50.0885	19.593	0.000	221122688	BB	67.4	
Totals:			100.0000		441464384			

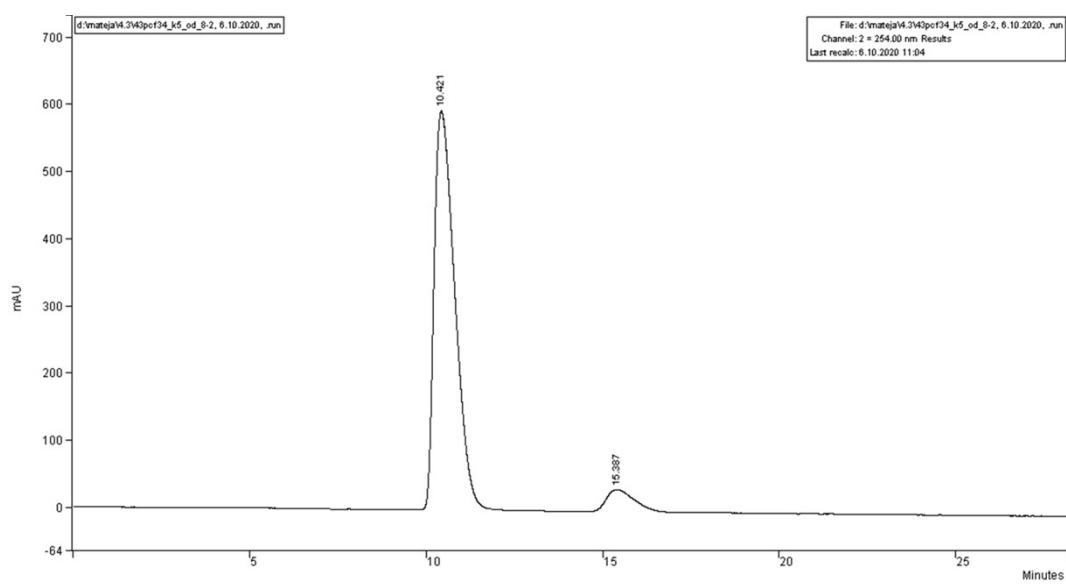
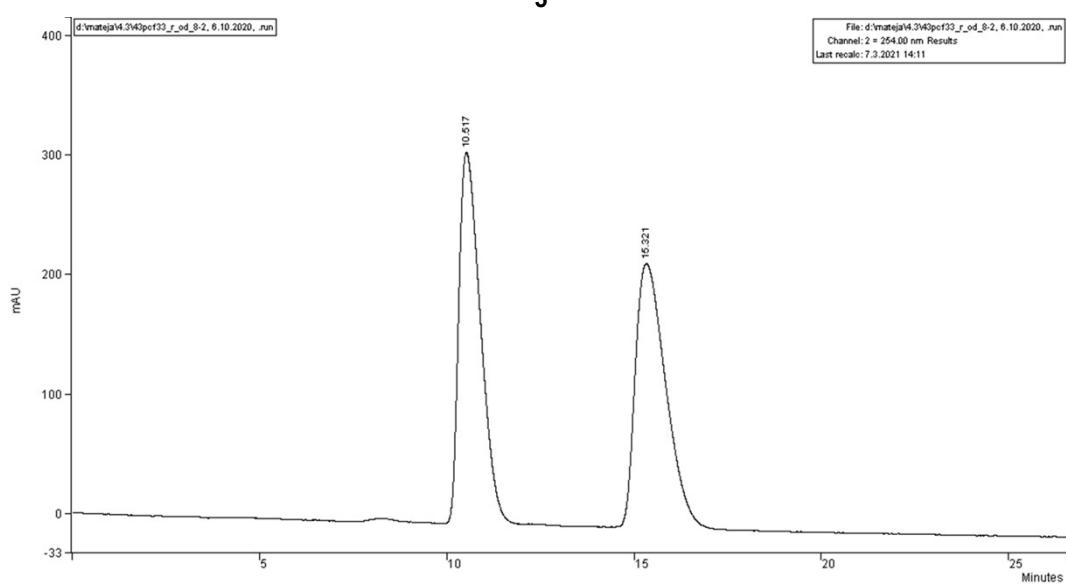
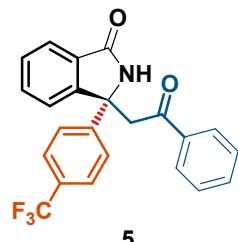


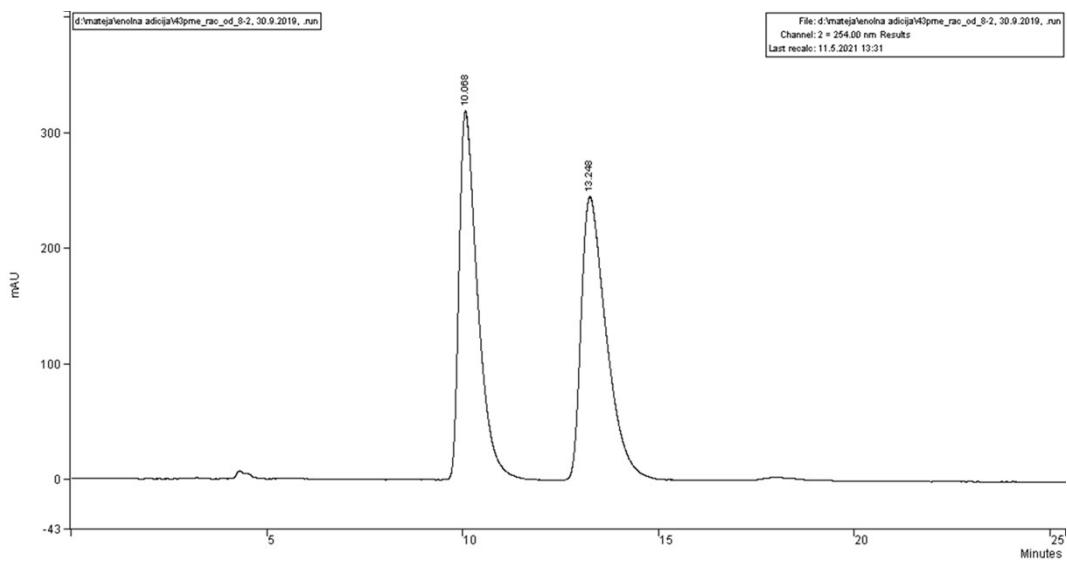
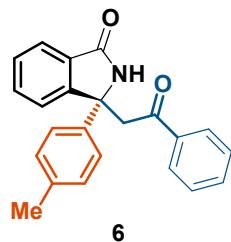
Peak No.	Peak Name	Result (l)	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code (sec)	Width 1/2 (sec)	Status Codes
1		6.1498	15.193	0.000	20703530	BB	45.9	
2		93.8502	19.171	0.000	315949536	BB	67.9	
Totals:			100.0000		336653066			



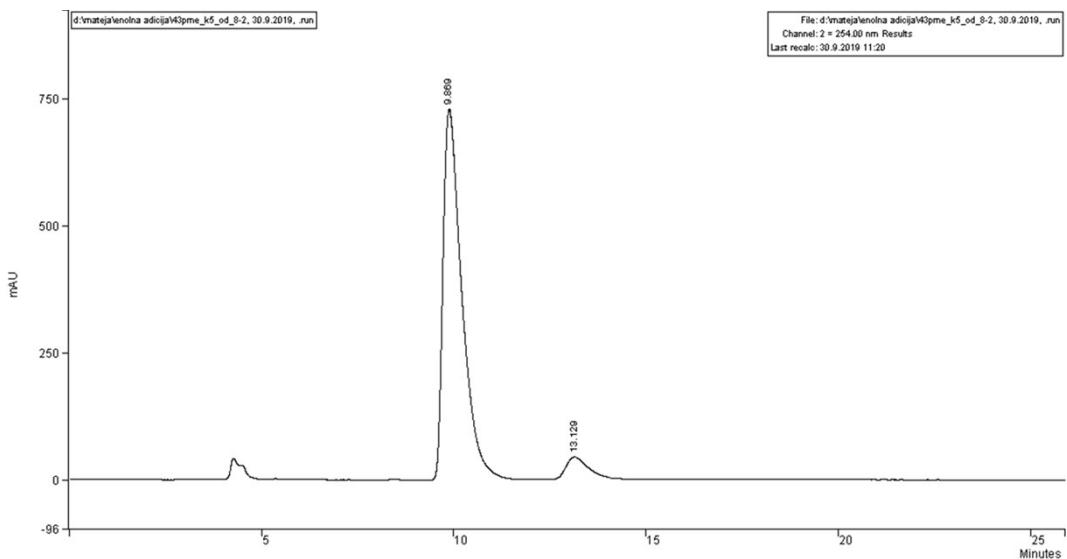




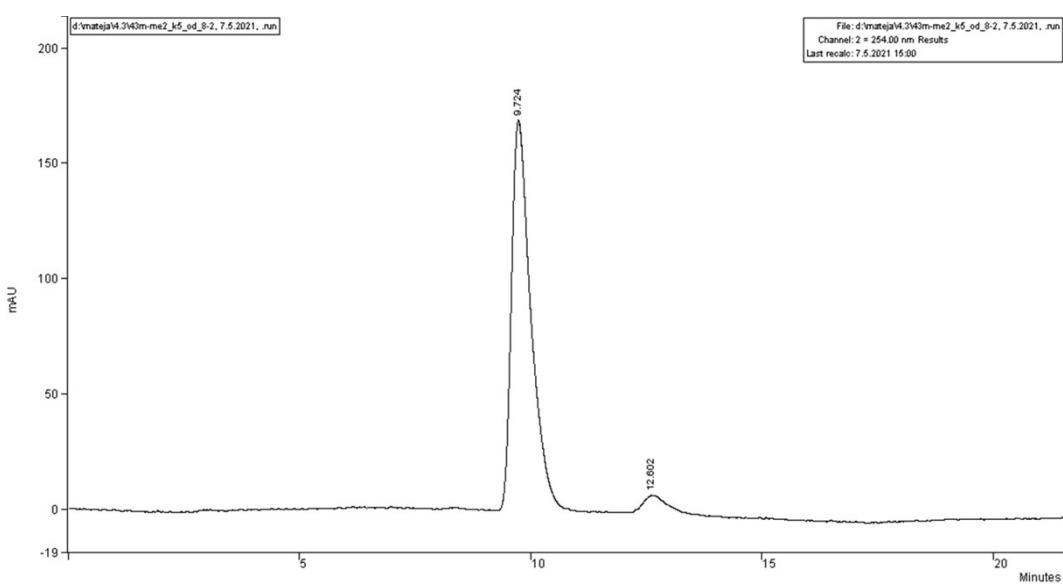
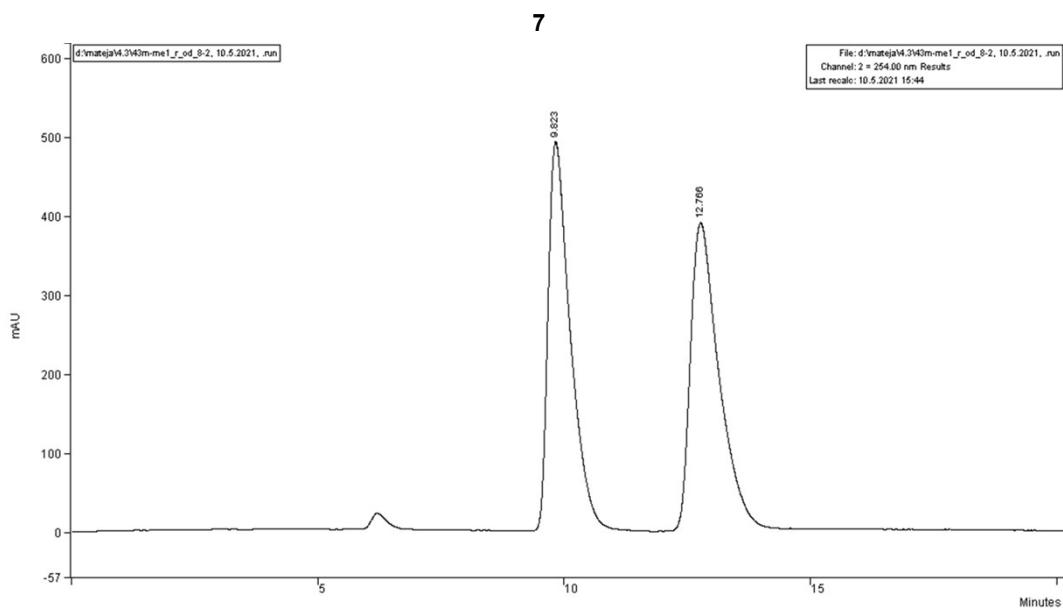
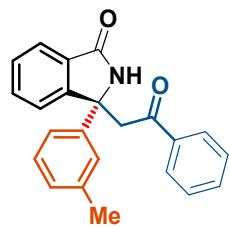


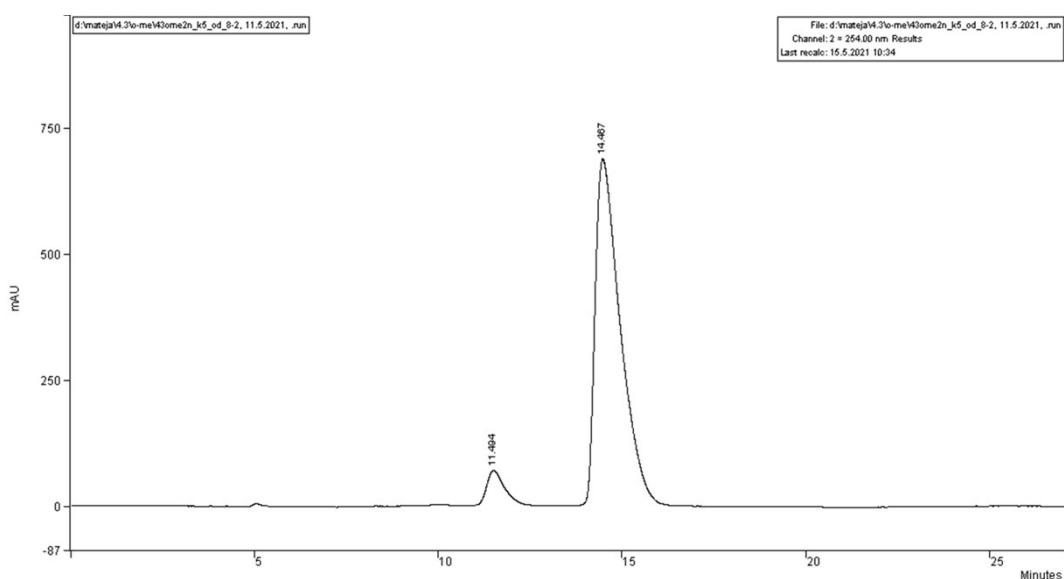
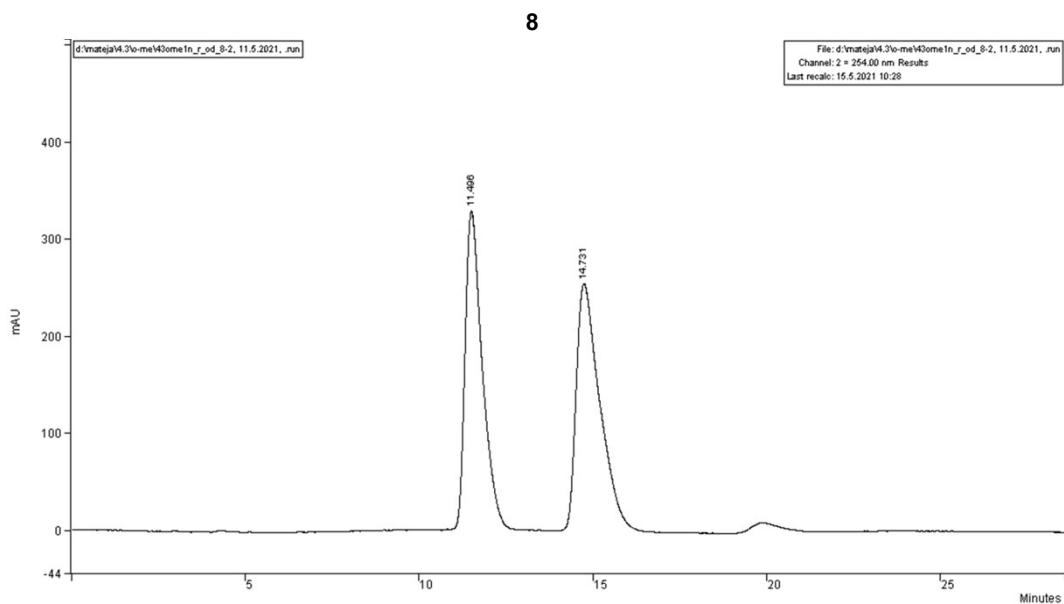
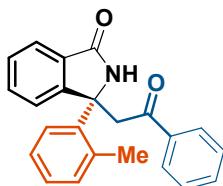


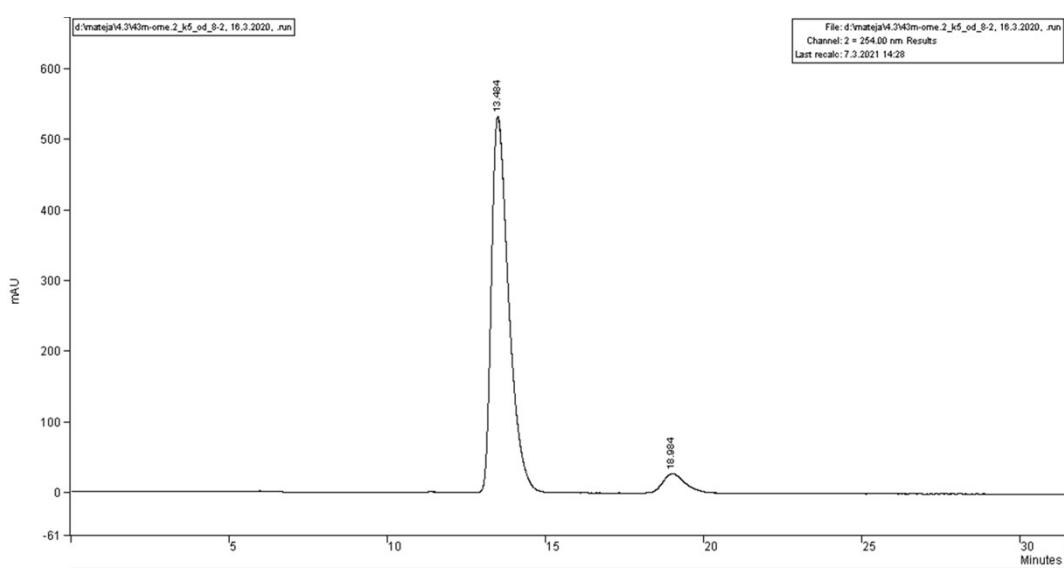
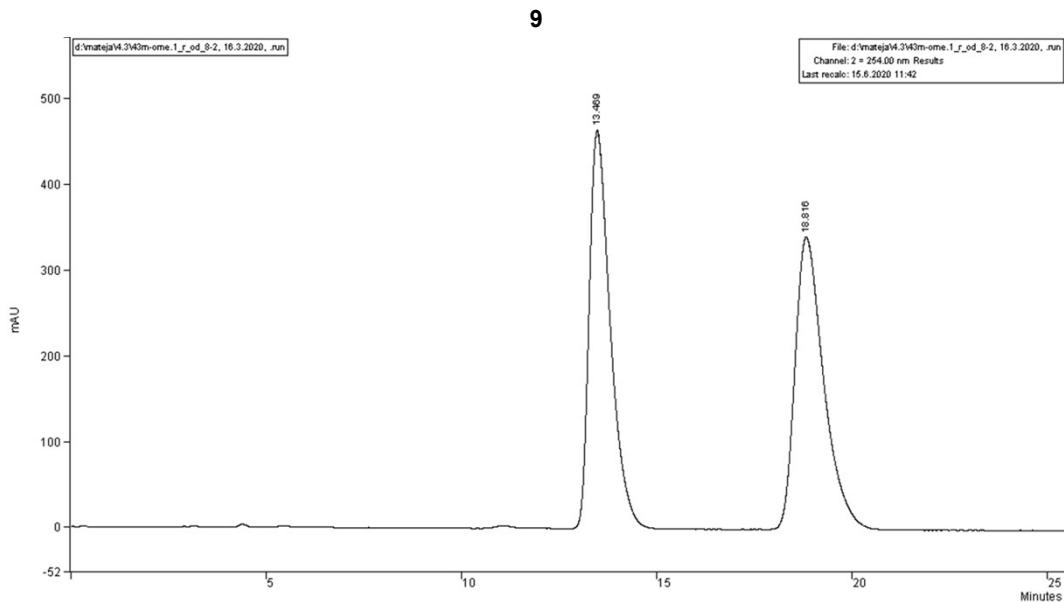
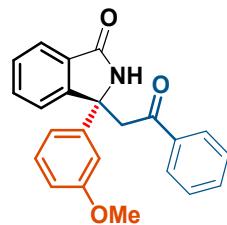
Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	1/2 sec	Status Codes
1		49.4188	10.068	0.000	104665448	BB	29.3	
2		50.5812	13.248	0.000	107127120	BB	40.4	
Totals:		100.0000			0.000			

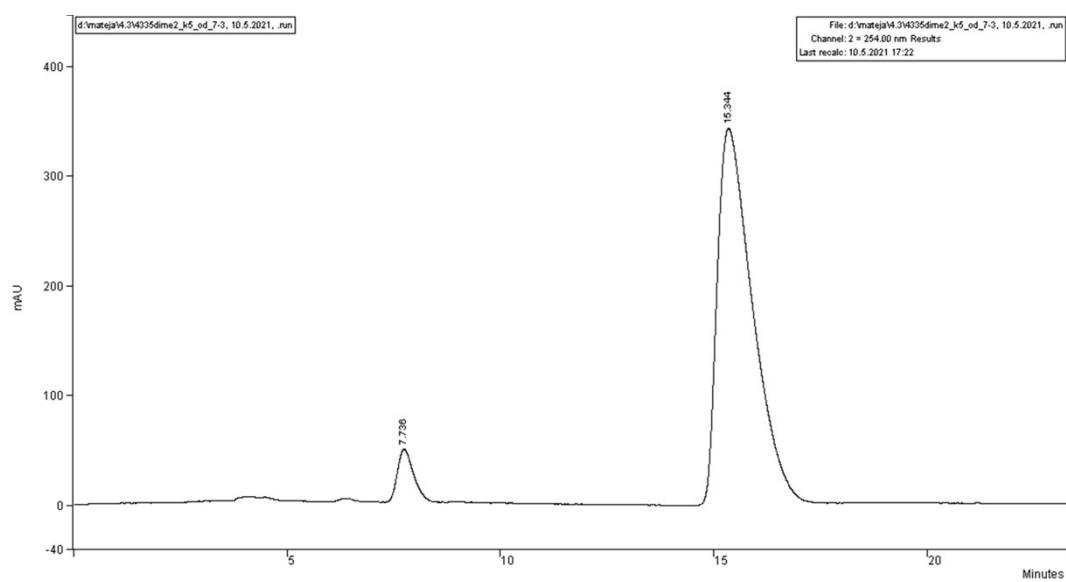
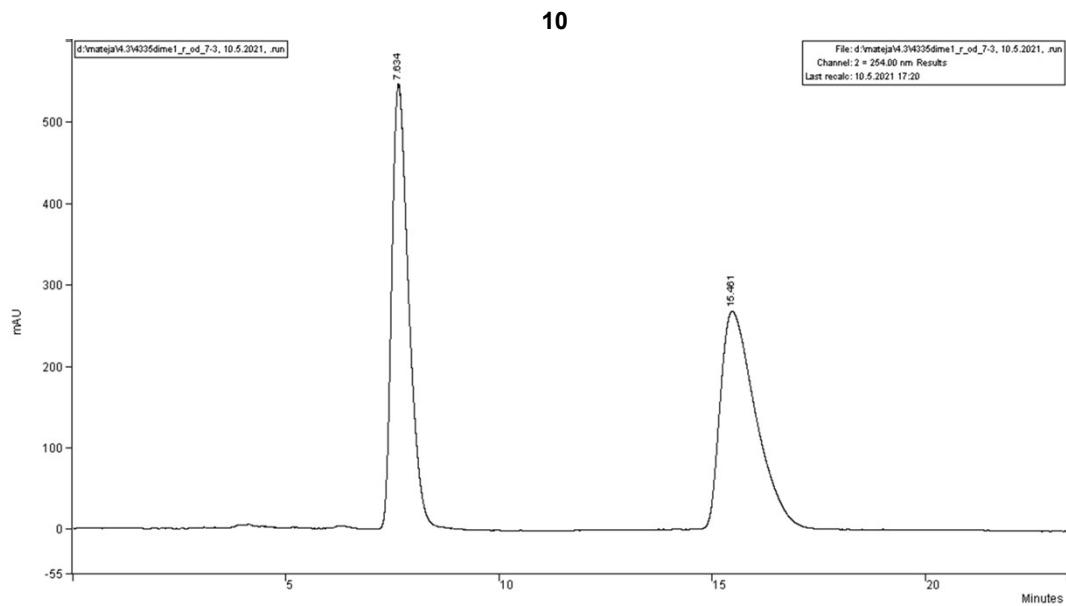
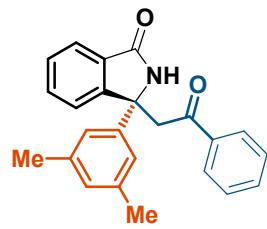


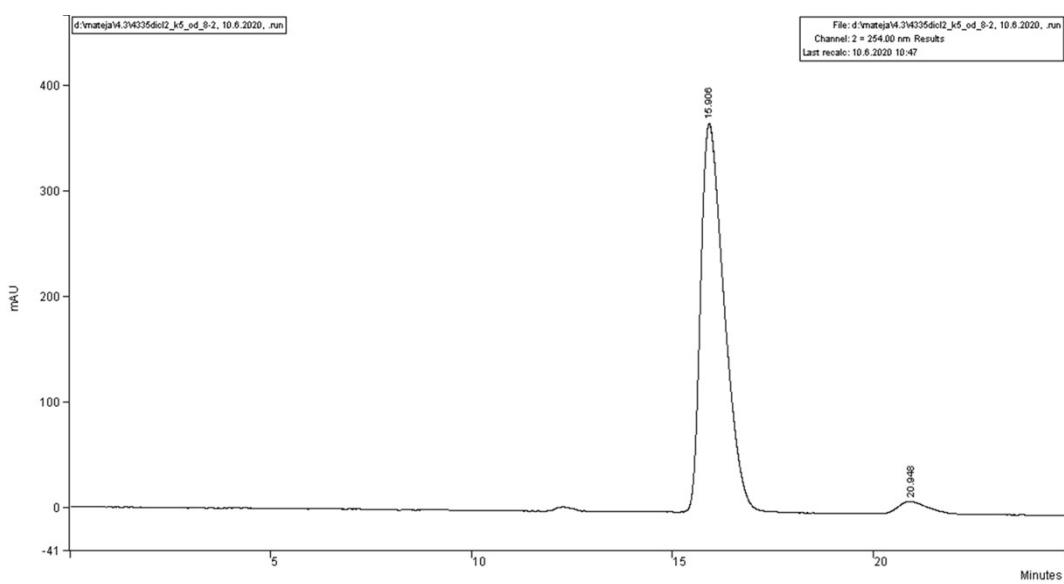
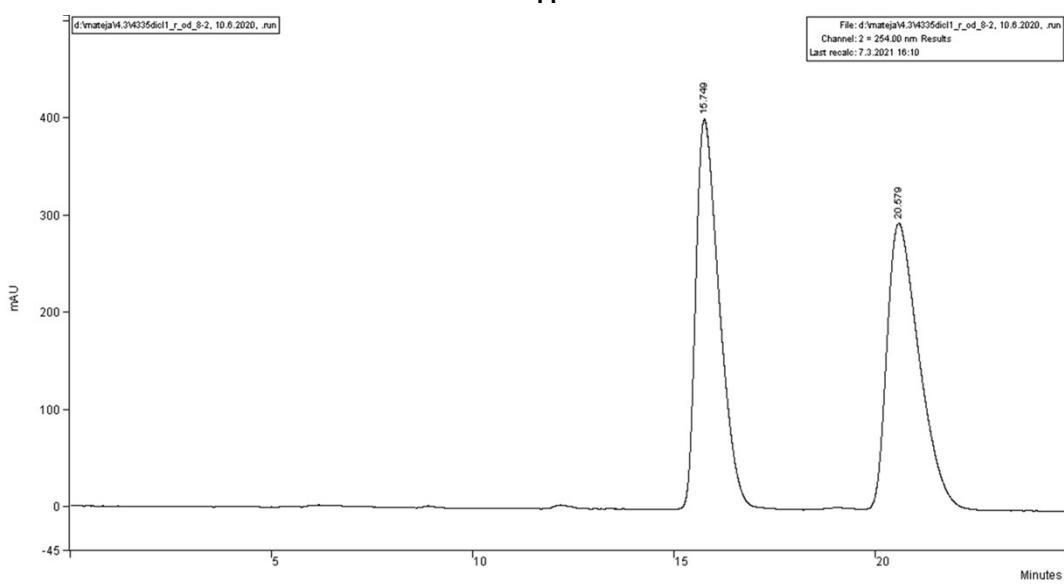
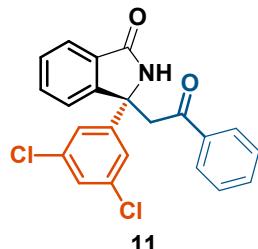
Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	1/2 sec	Status Codes
1		94.6315	9.869	0.000	248307568	BB	30.5	
2		5.3685	13.129	0.000	14086662	BB	32.6	
Totals:		100.0000			0.000			

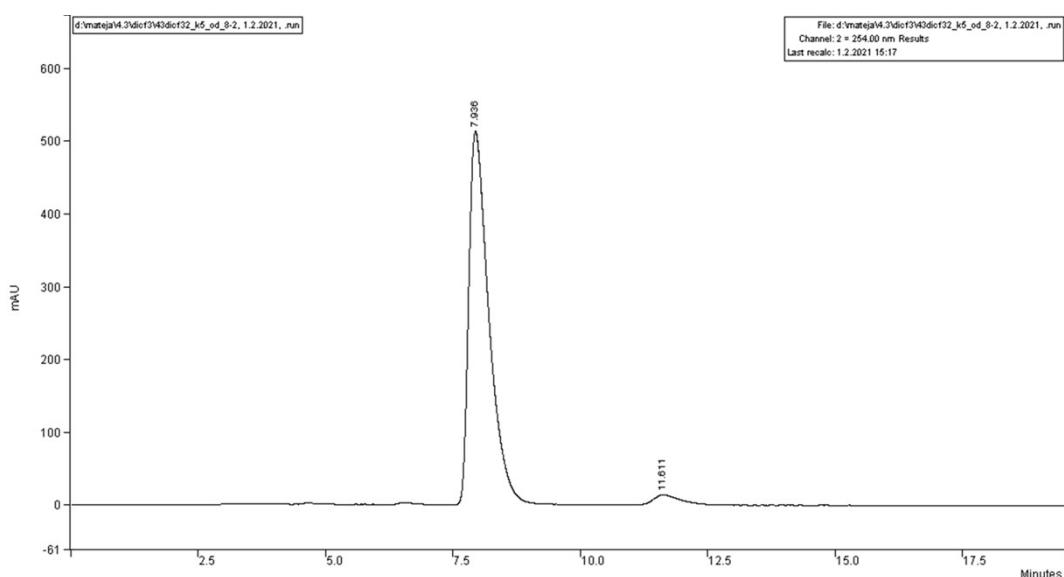
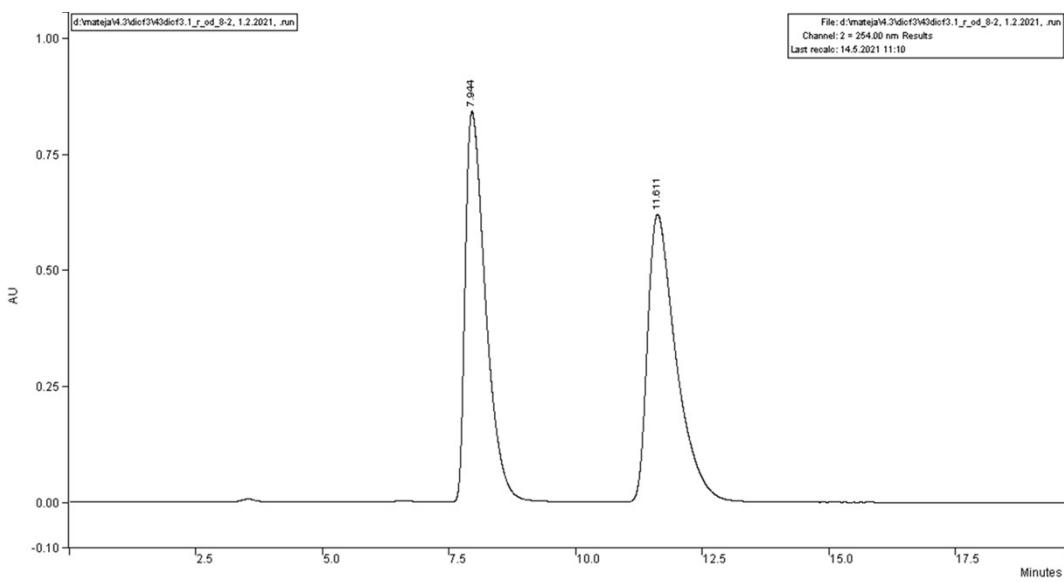
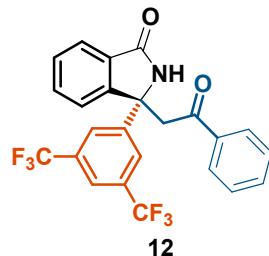


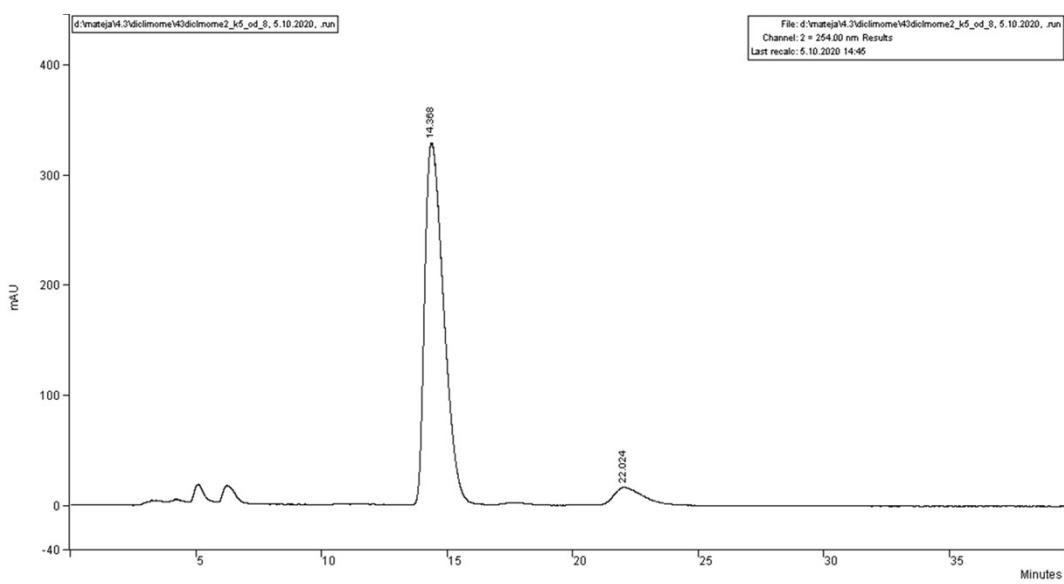
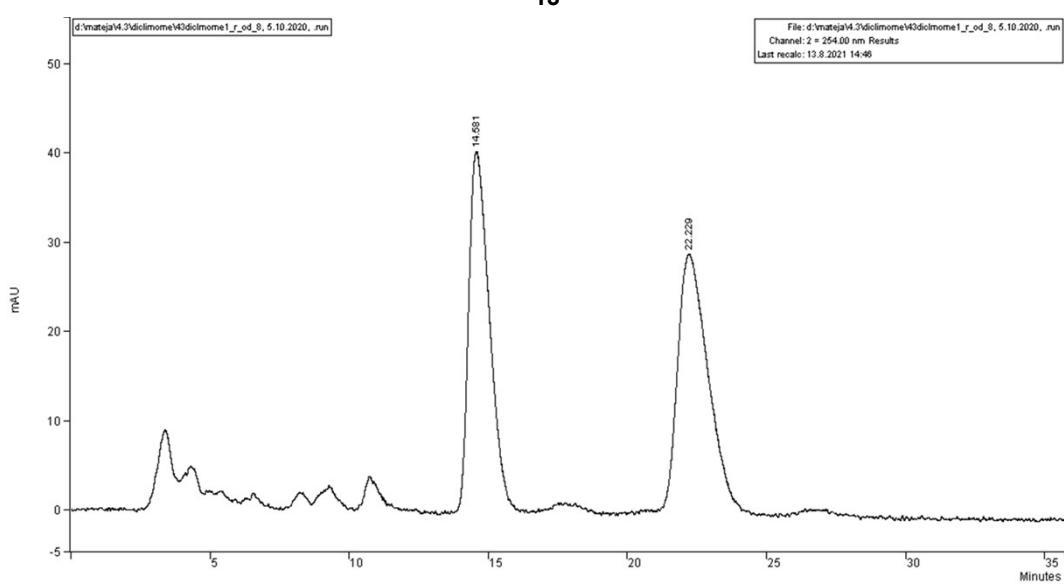
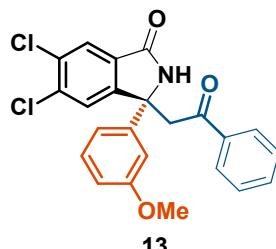


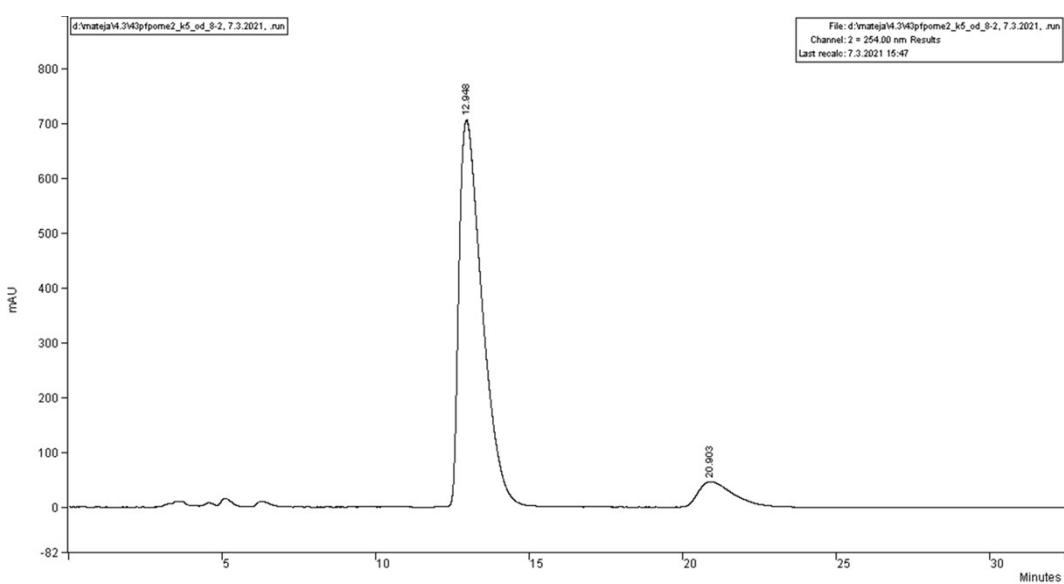
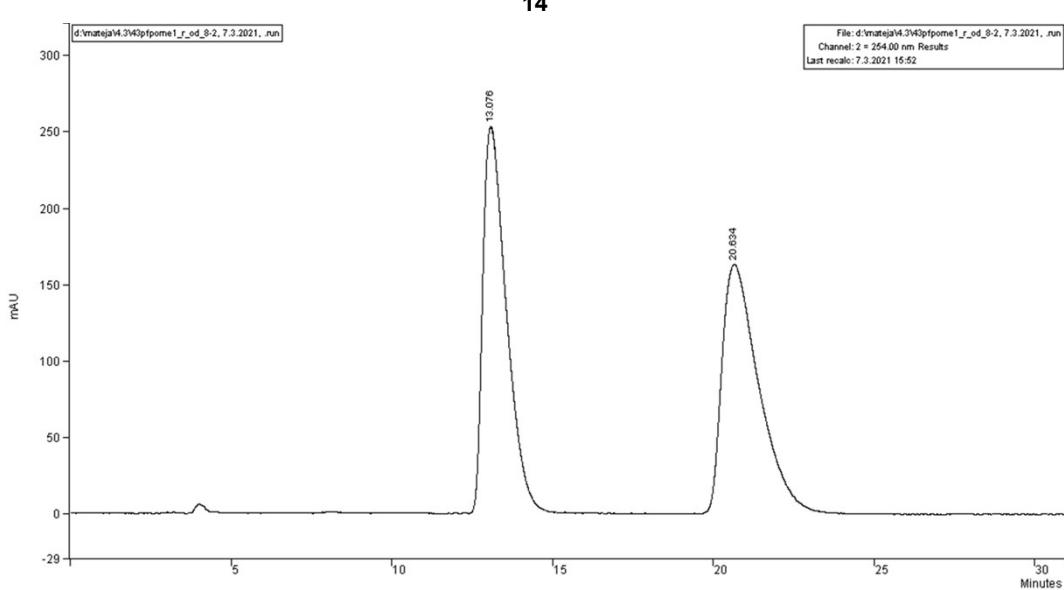
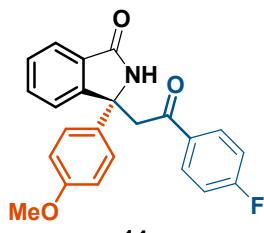


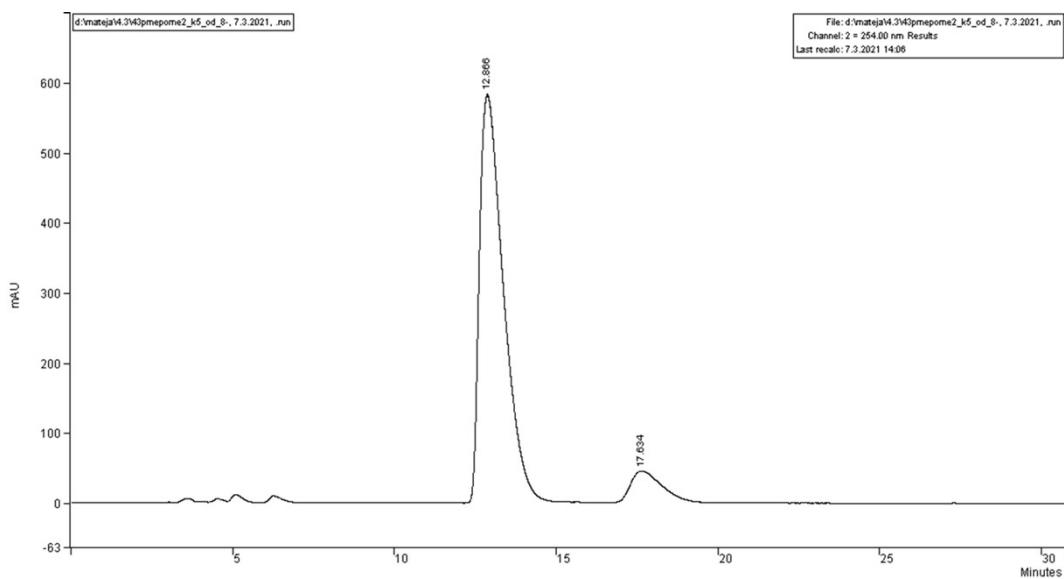
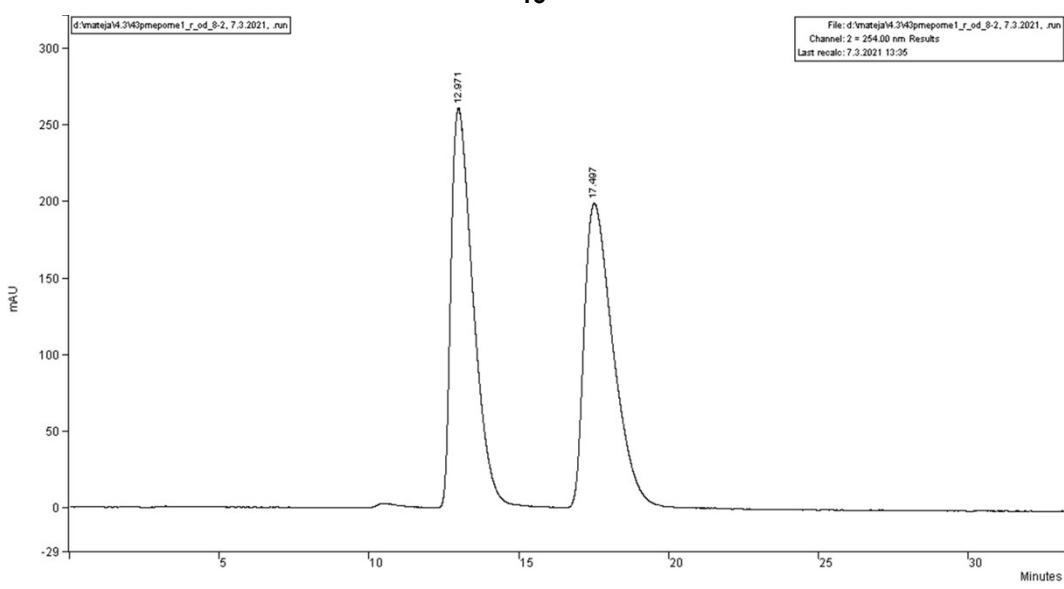
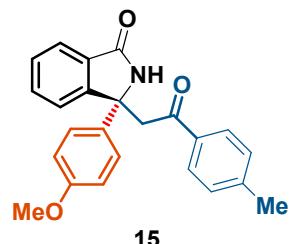


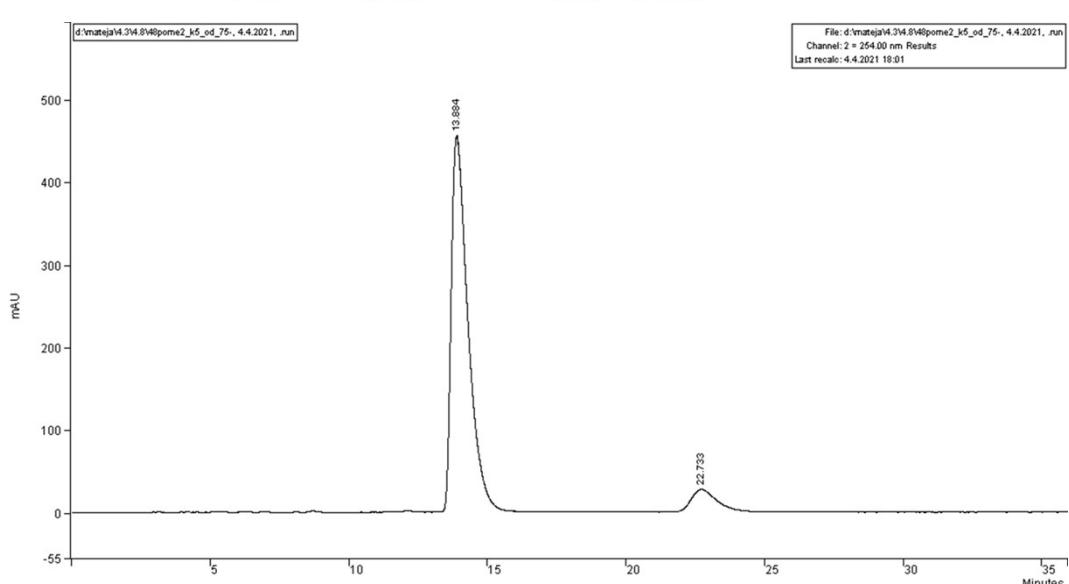
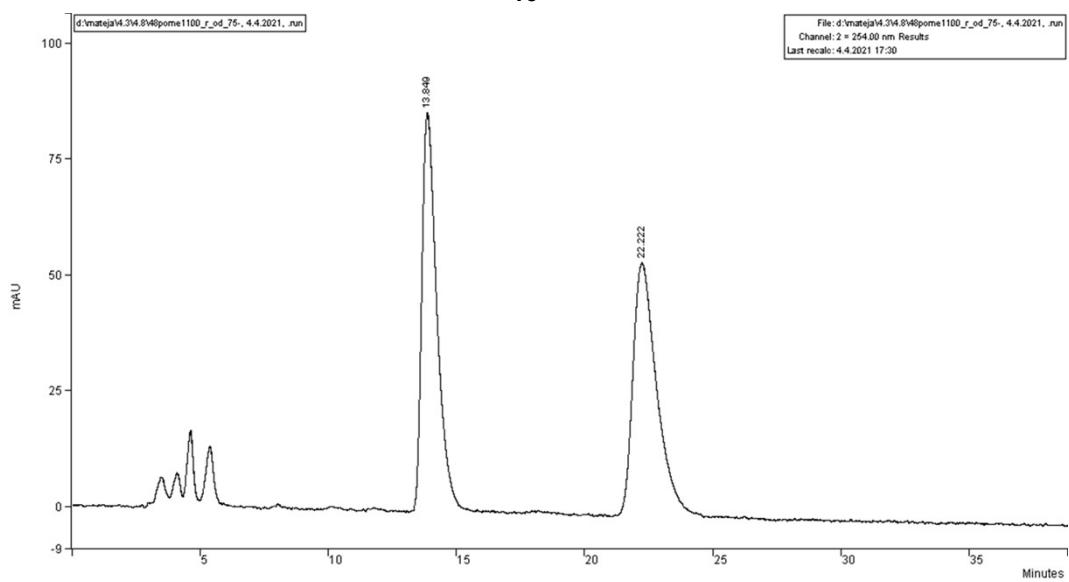
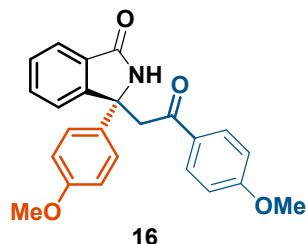


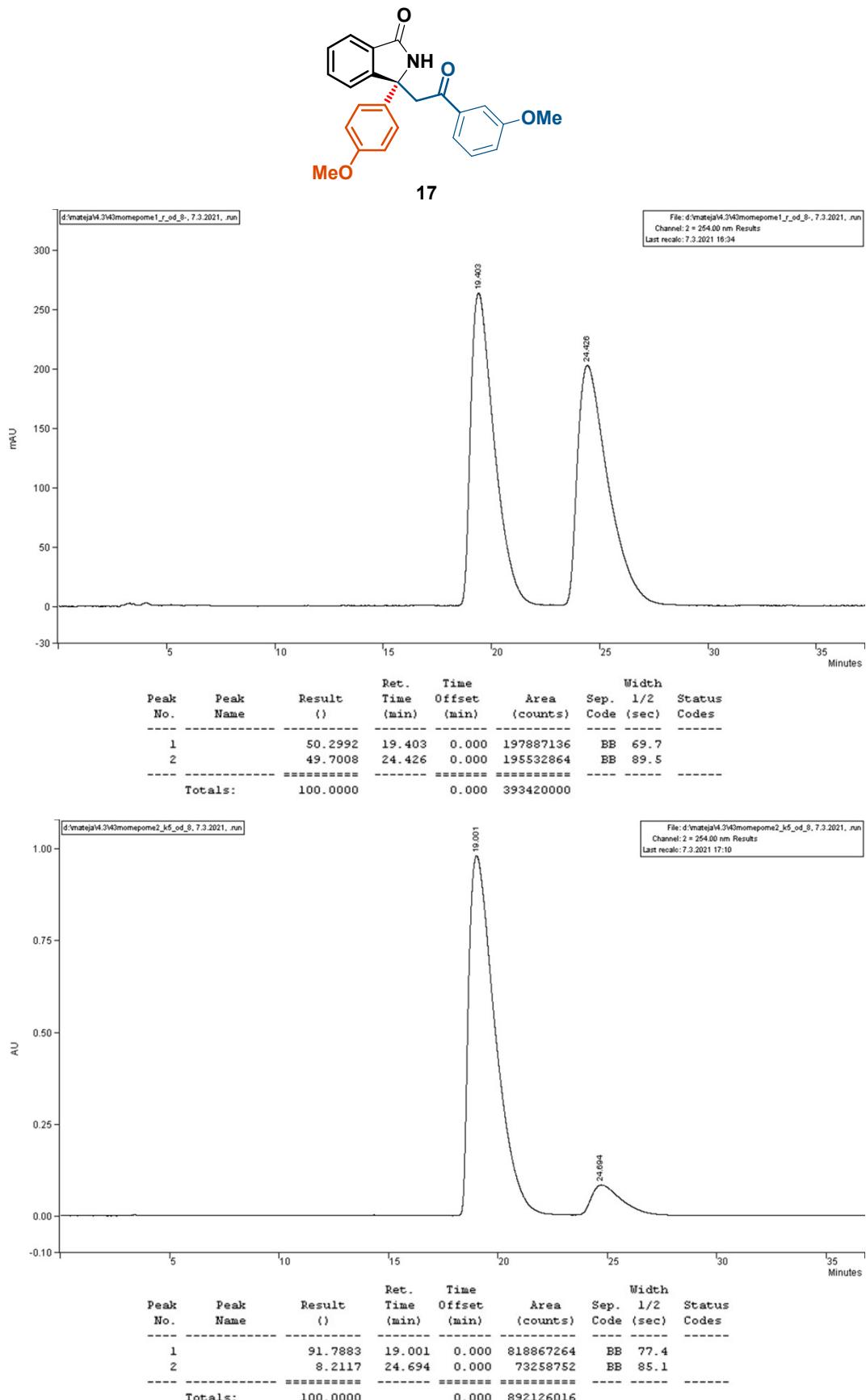


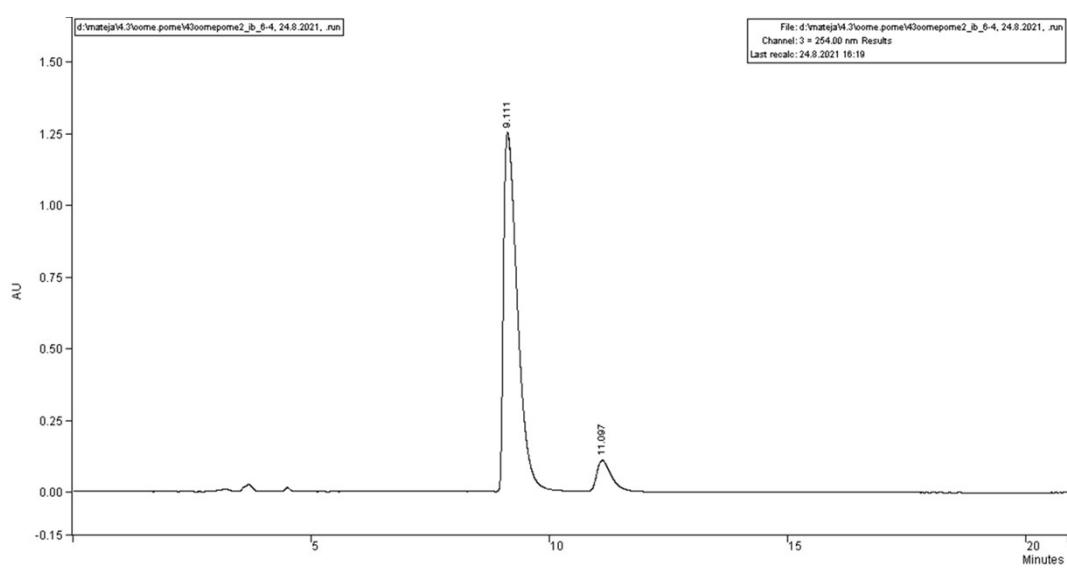
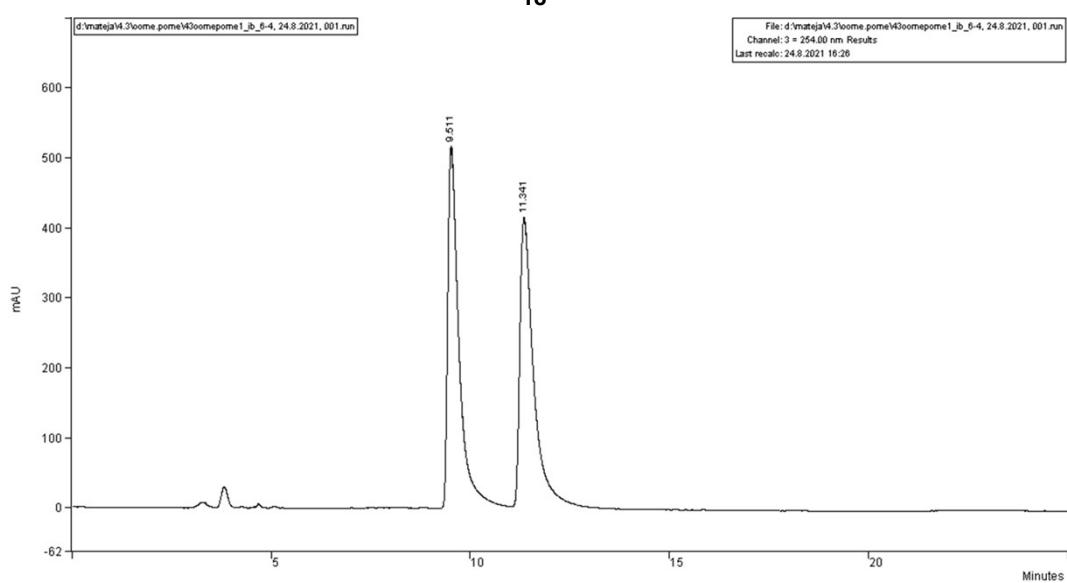
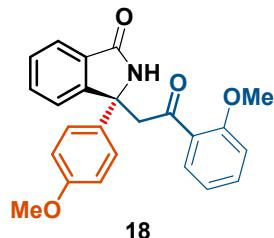


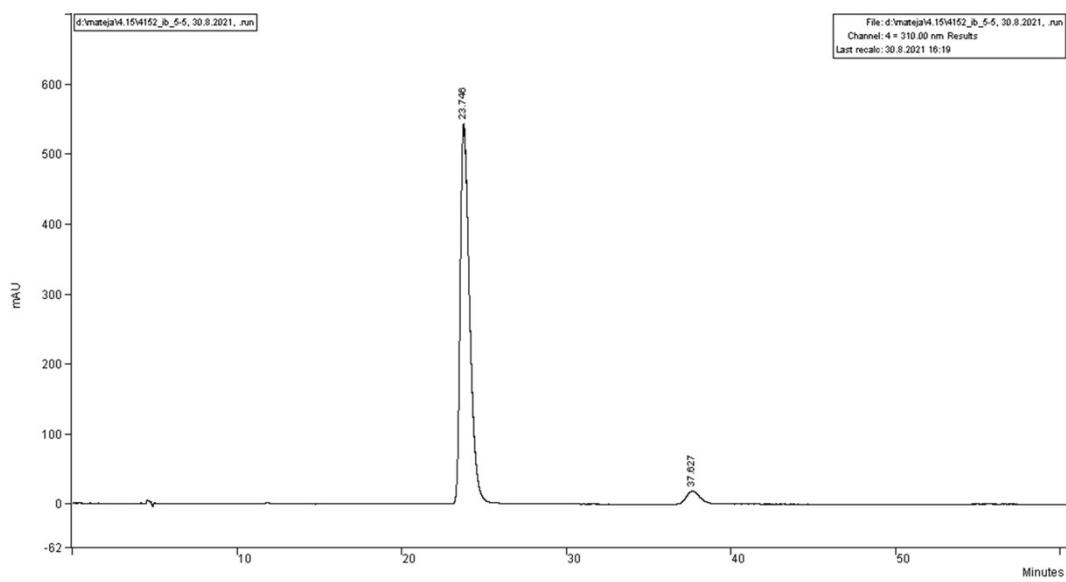
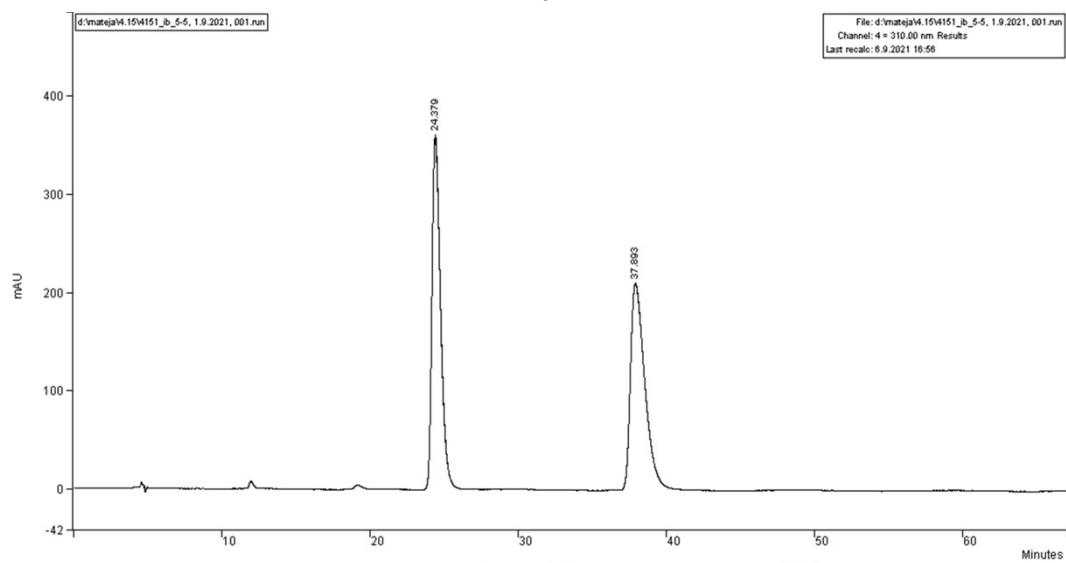
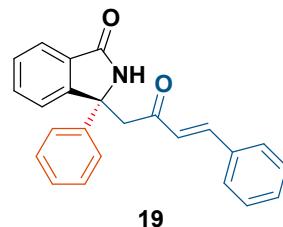


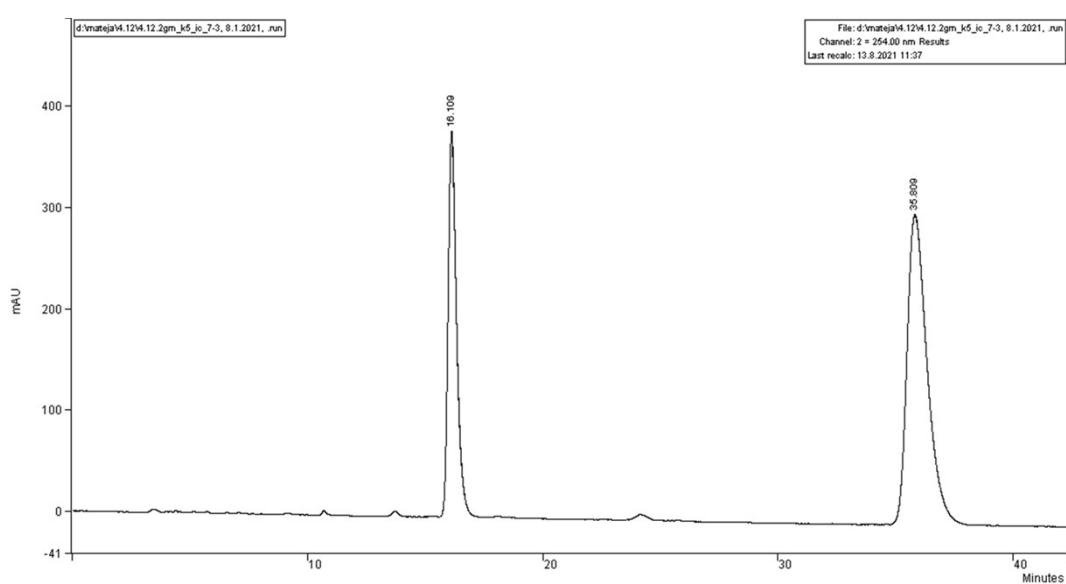
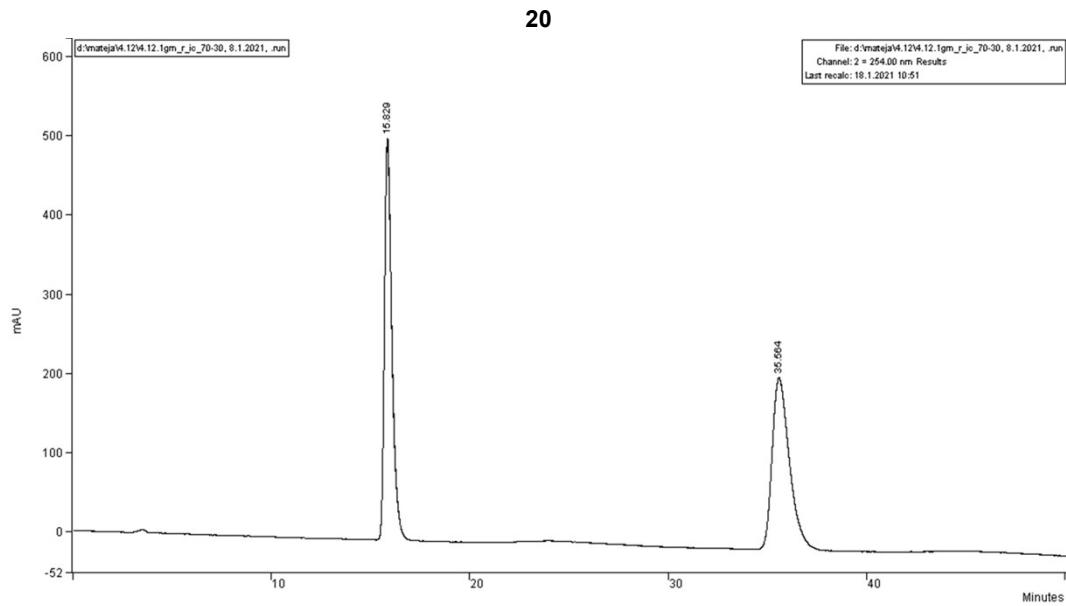
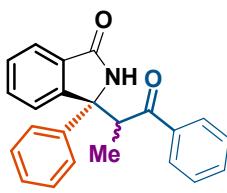


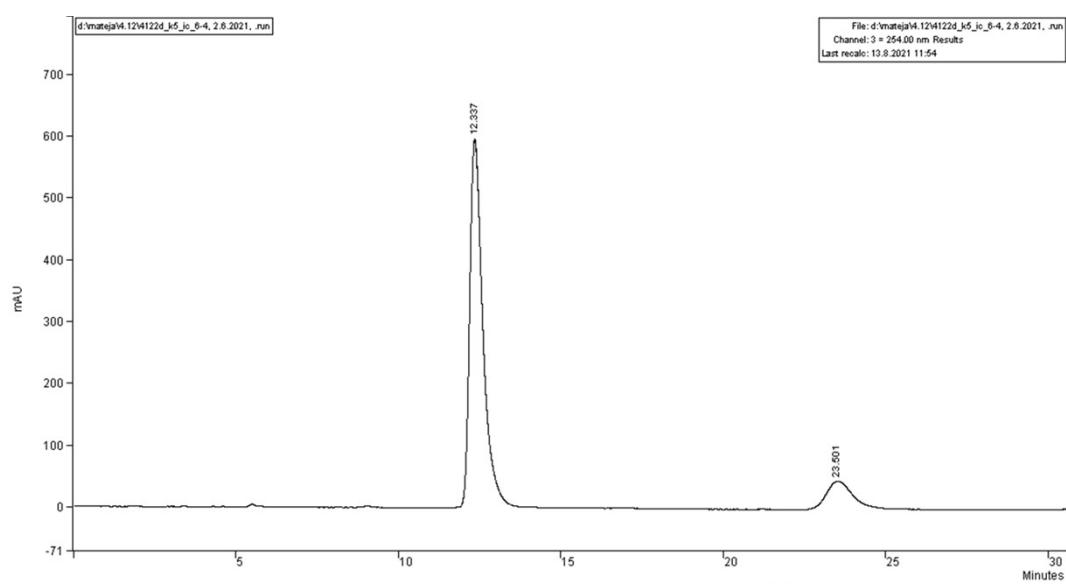
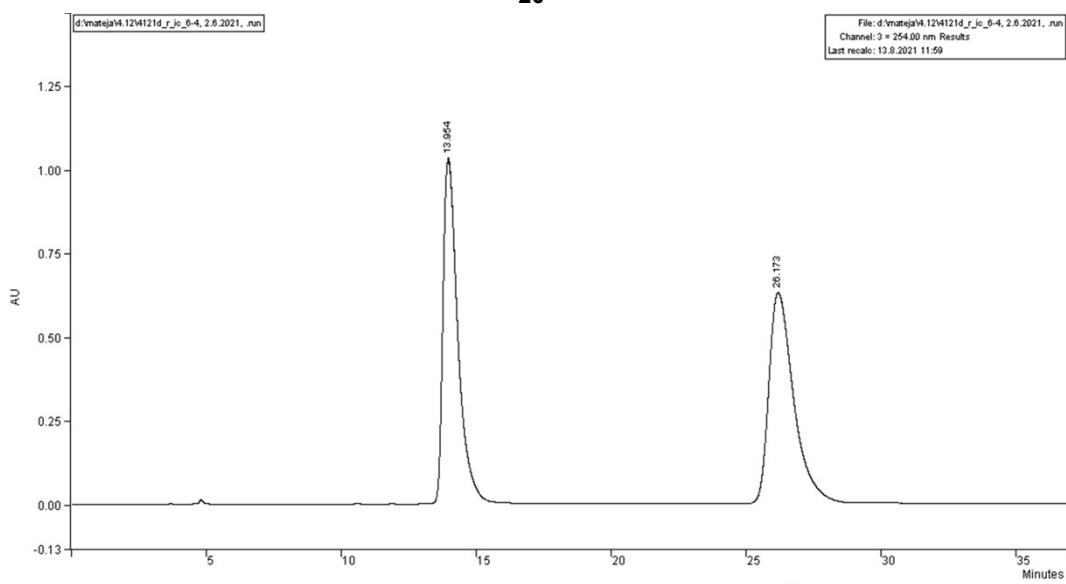
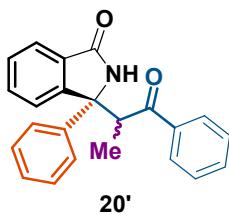


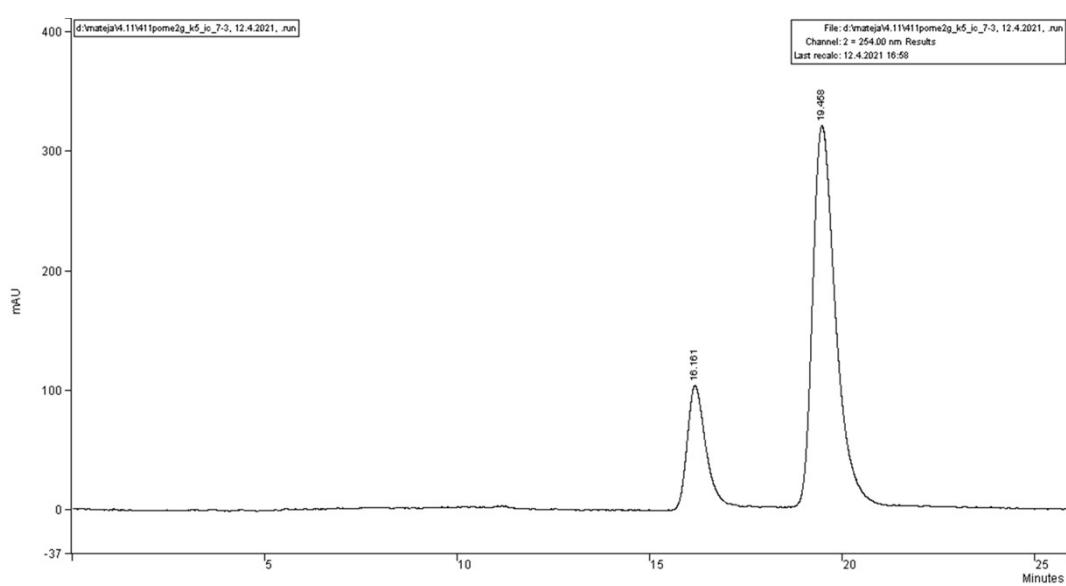
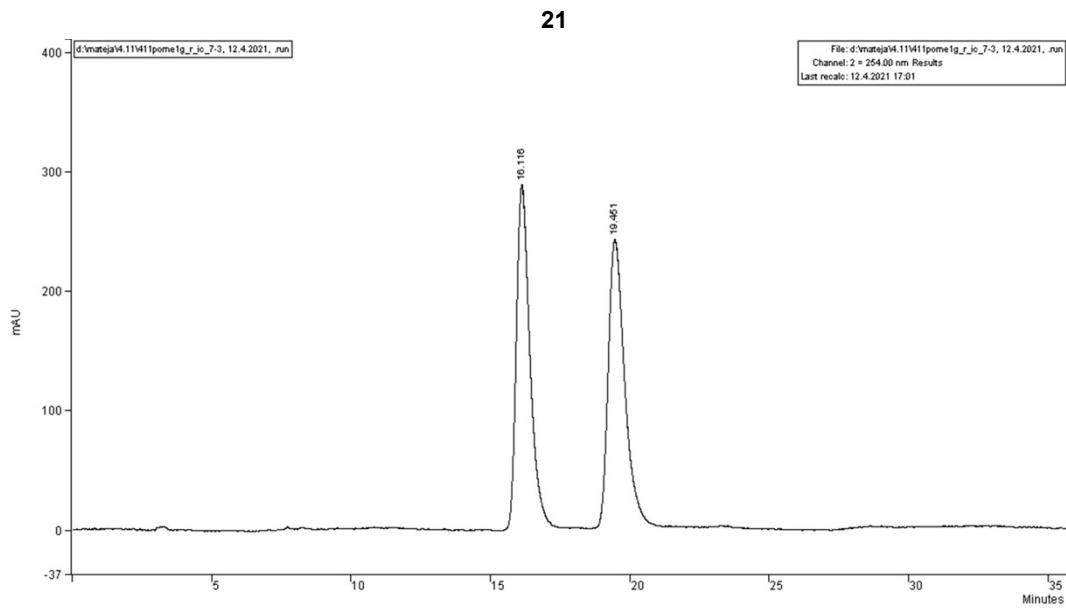
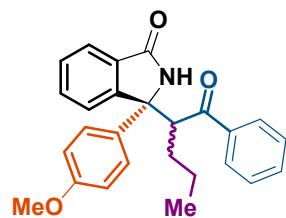


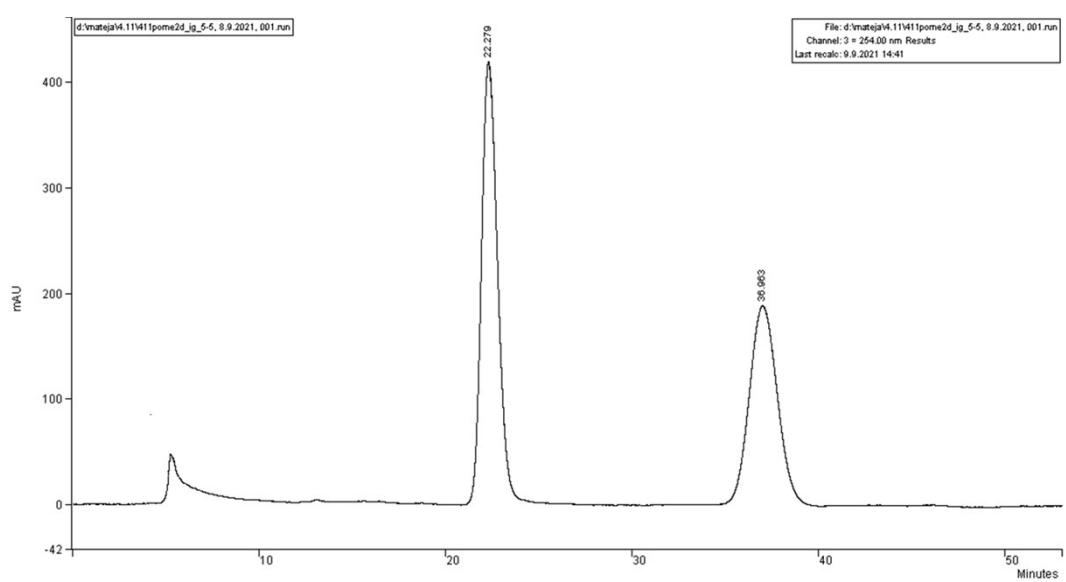
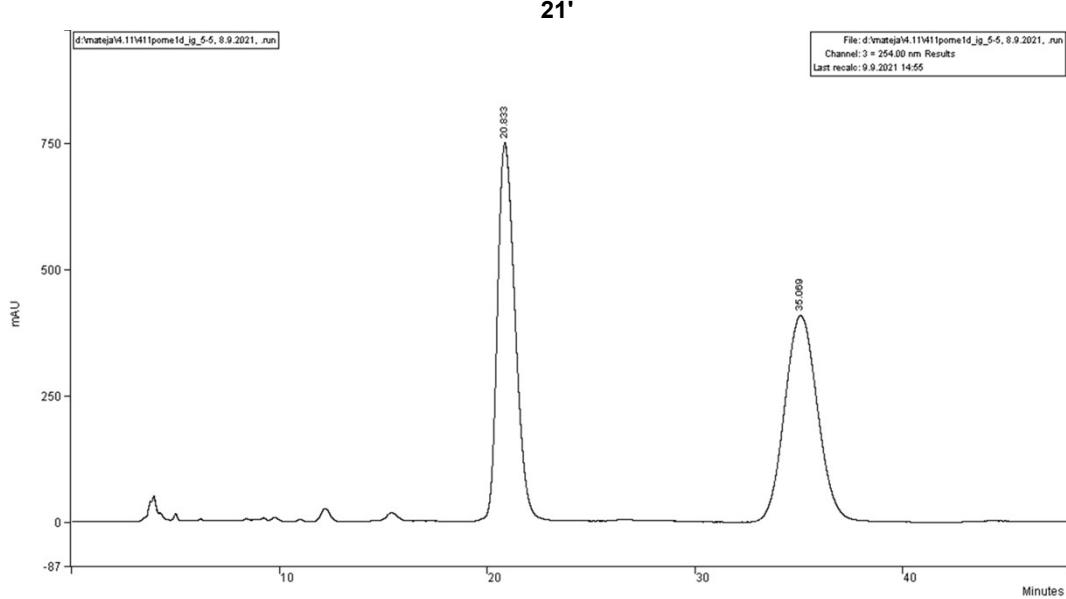
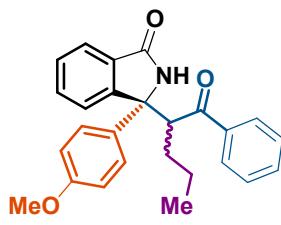


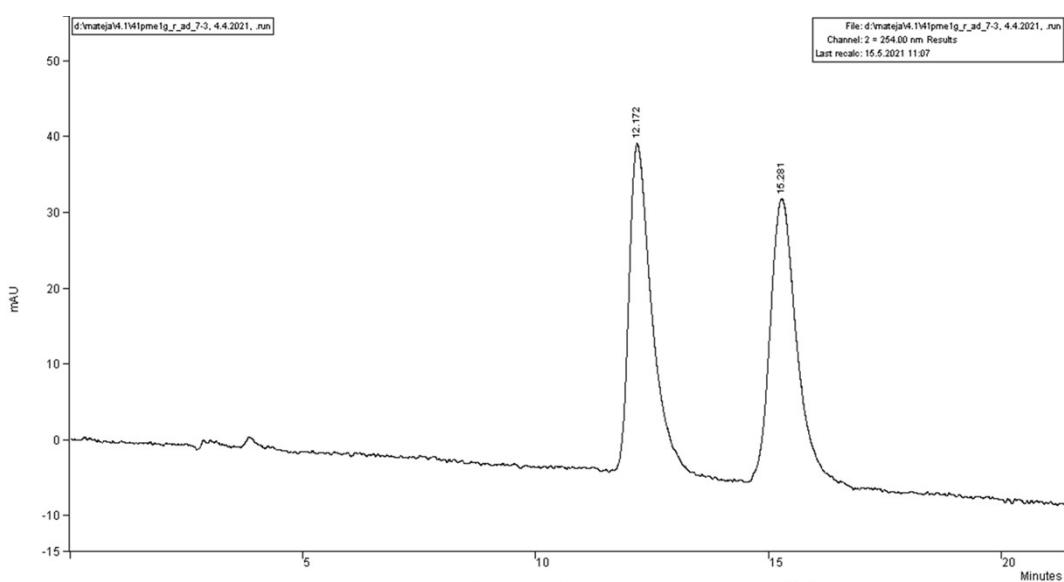
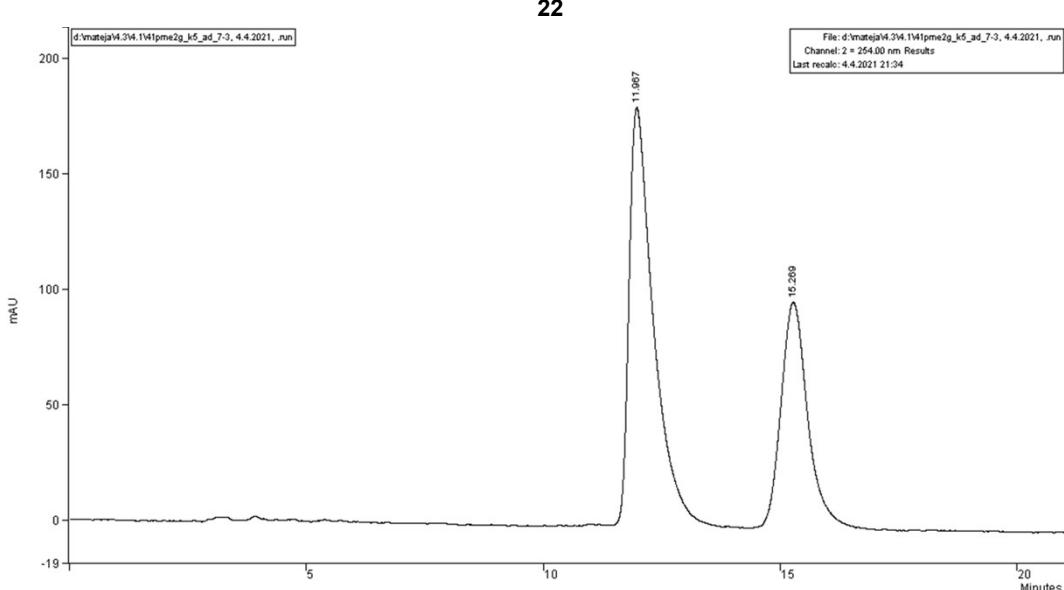
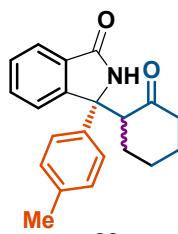


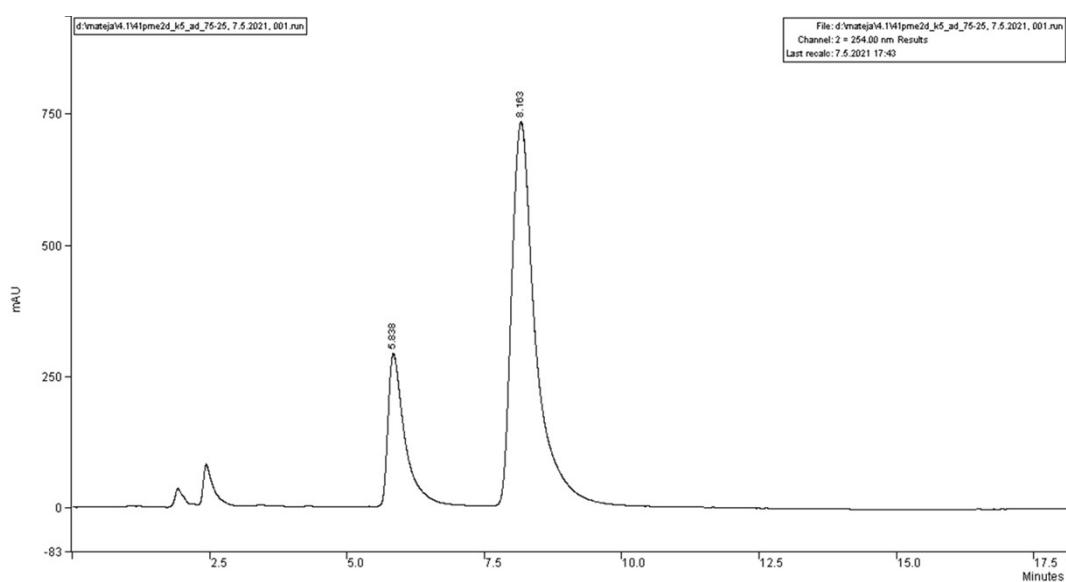
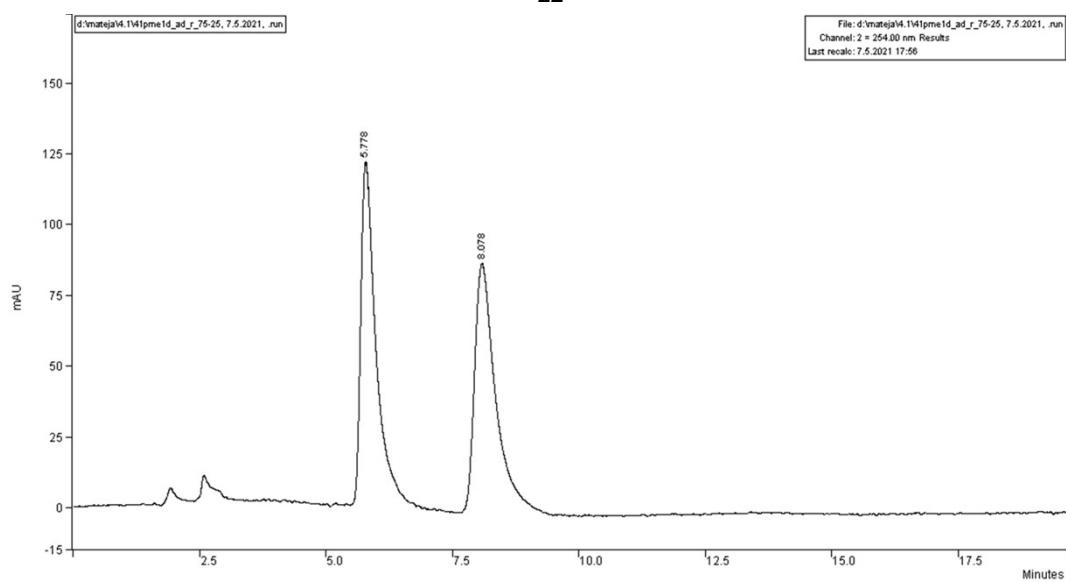
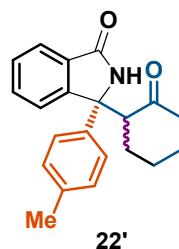


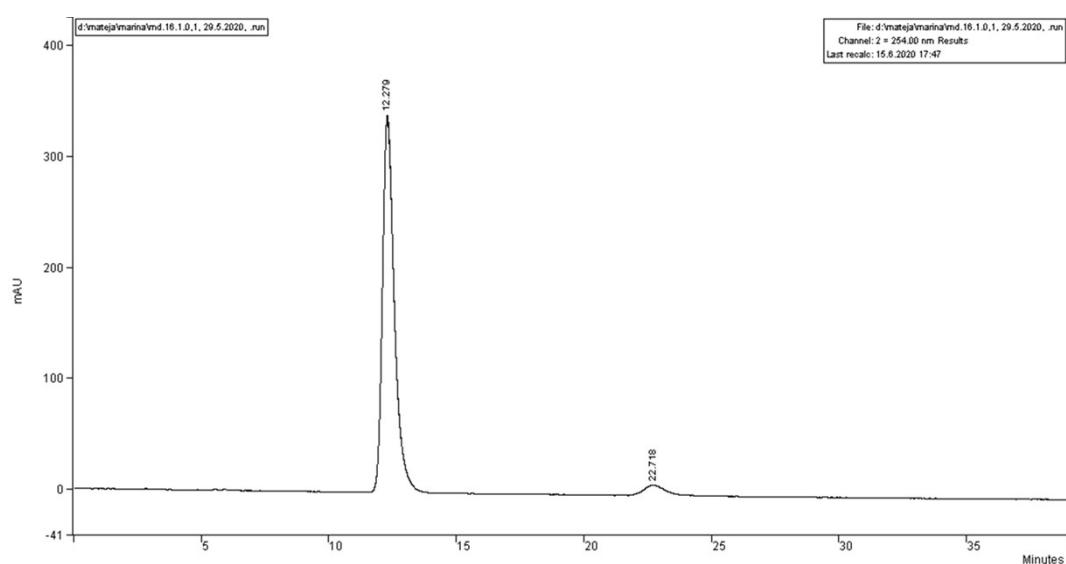
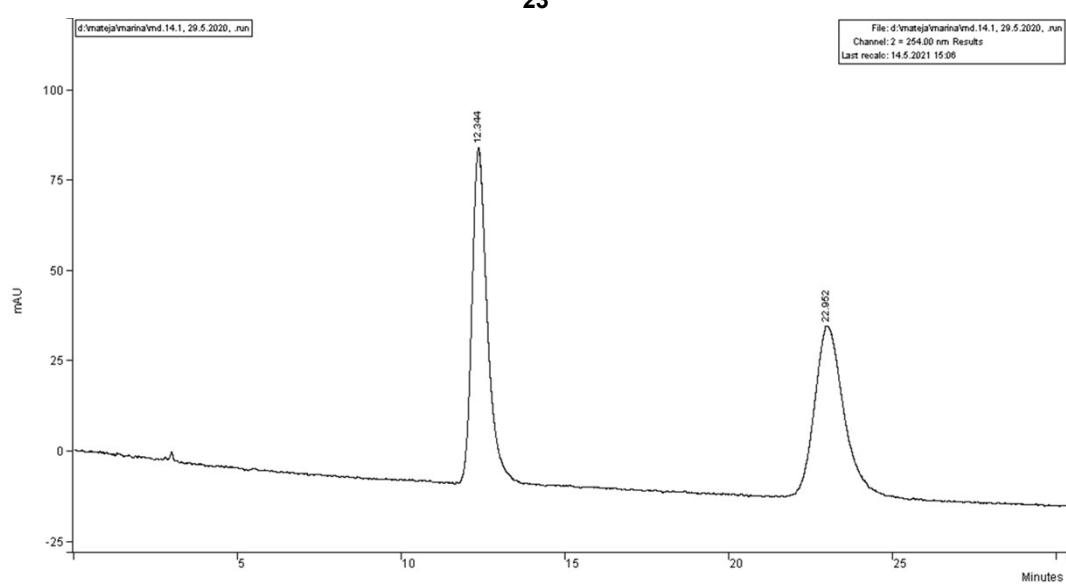
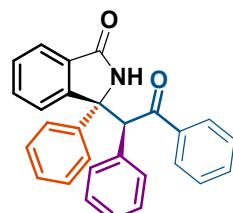


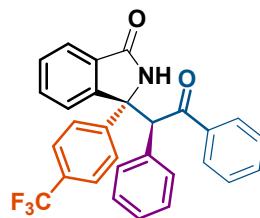
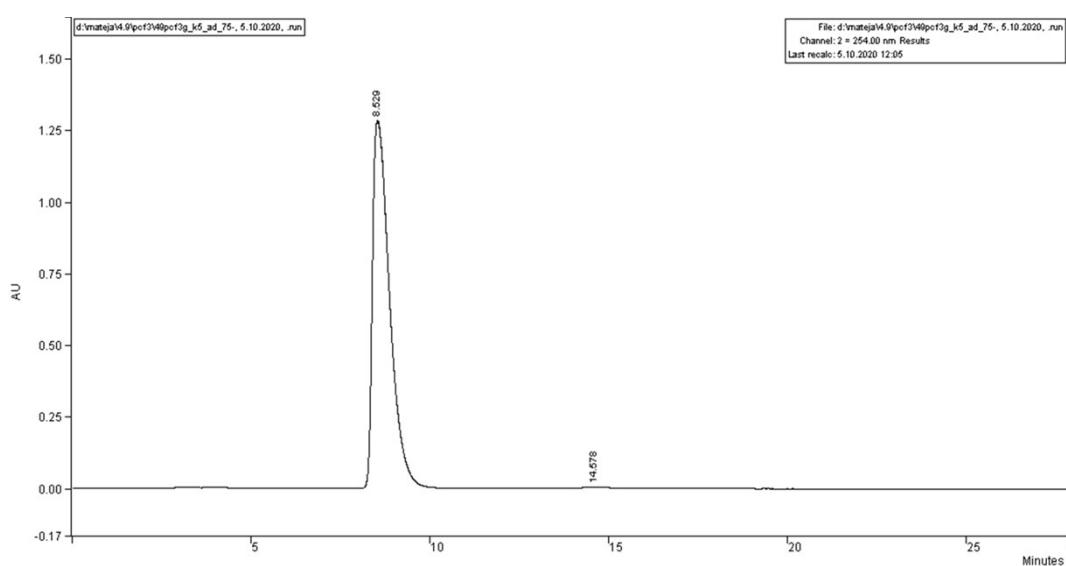
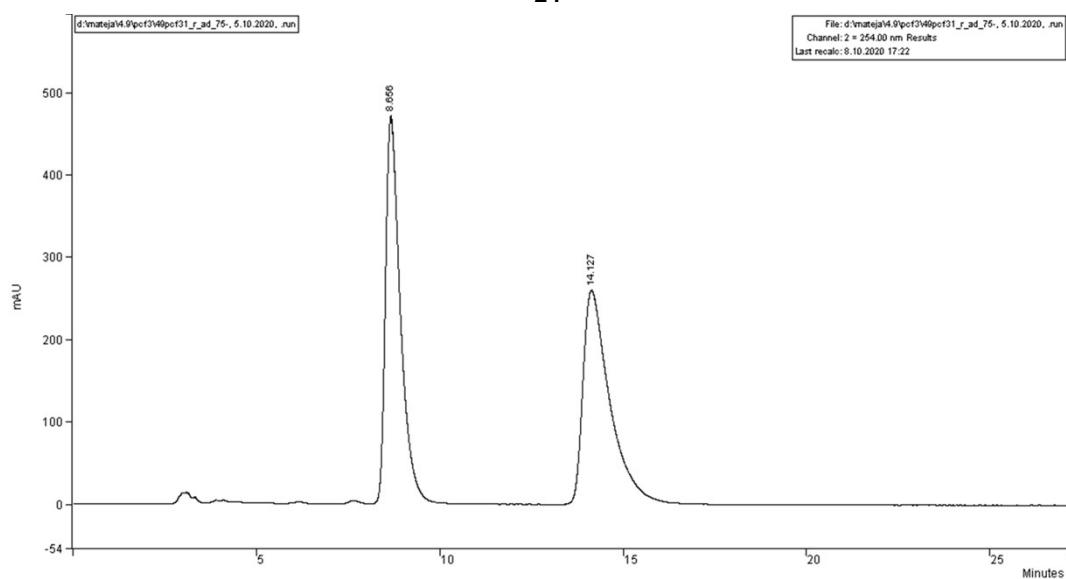




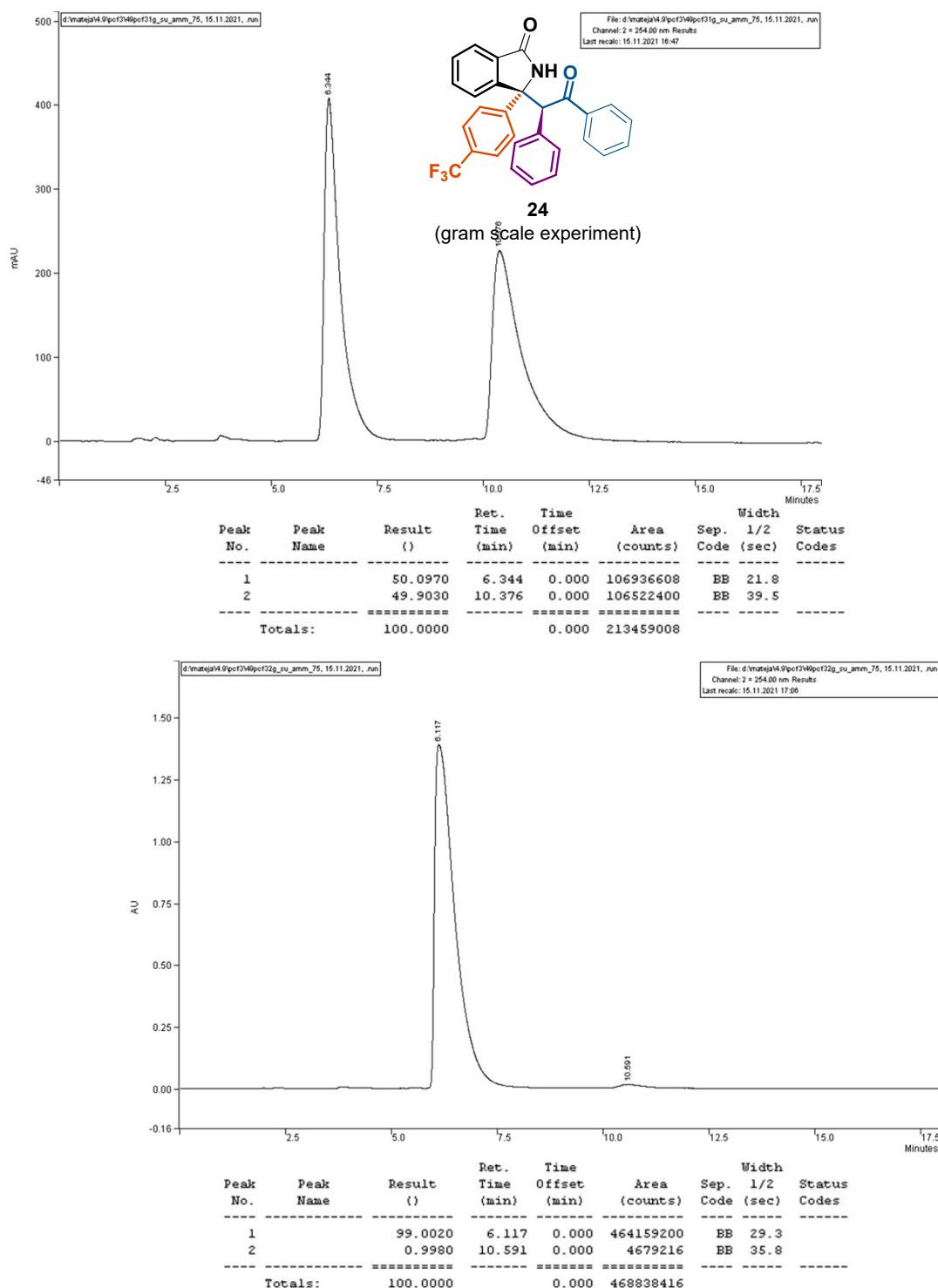


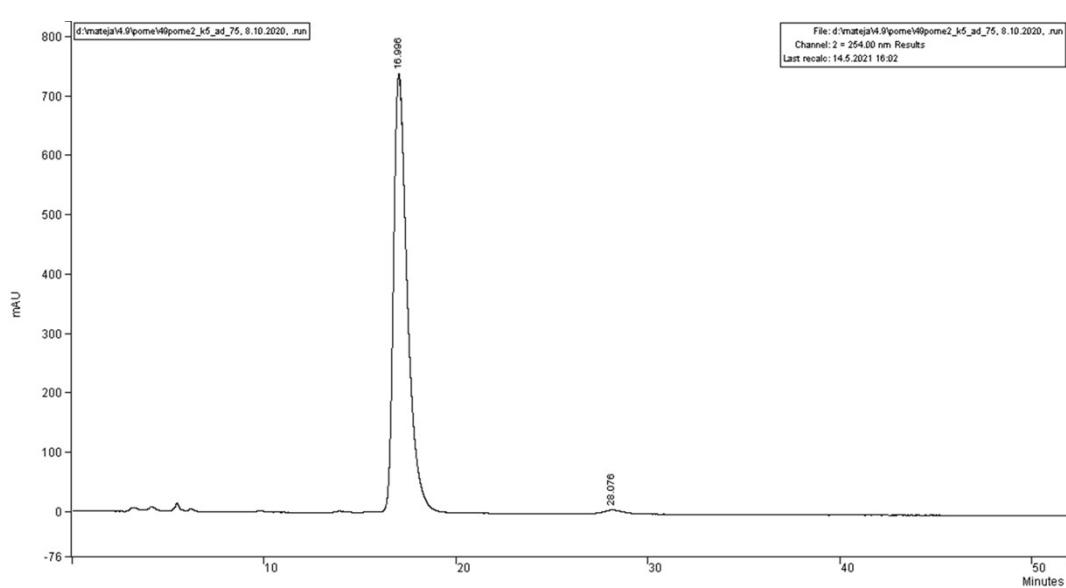
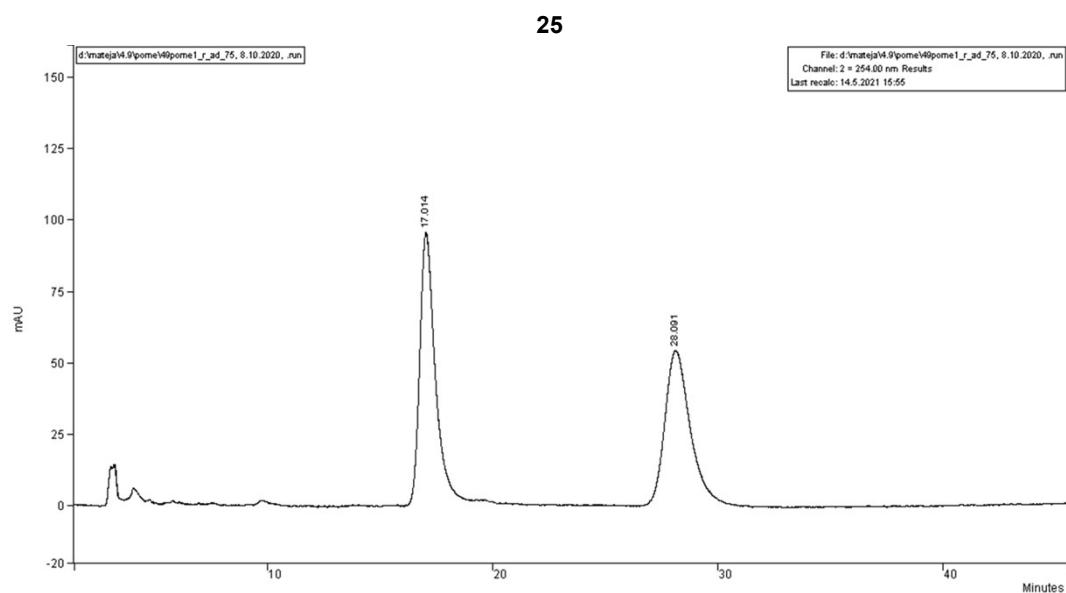
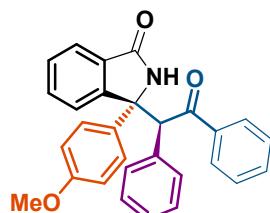


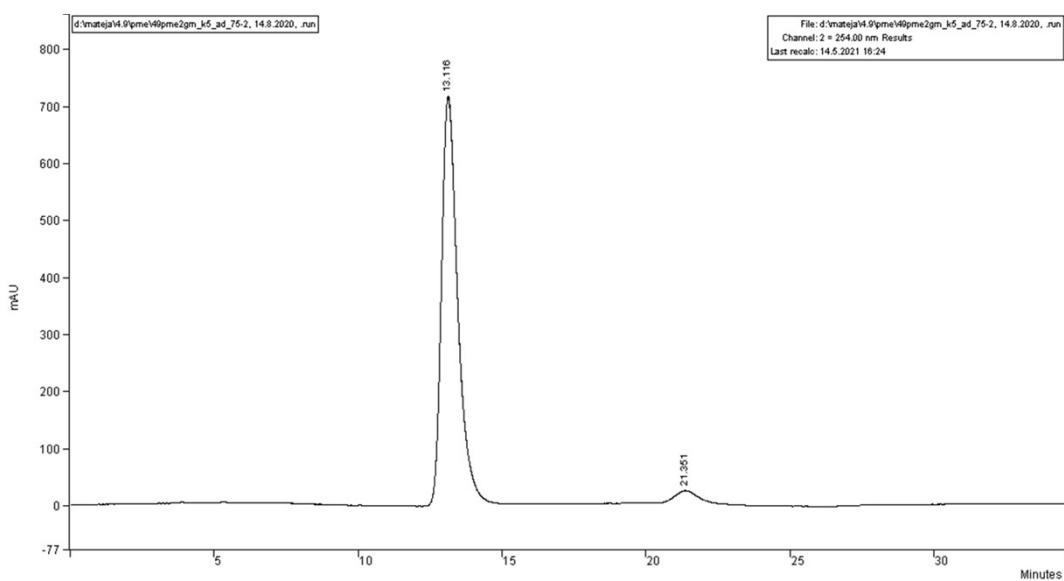
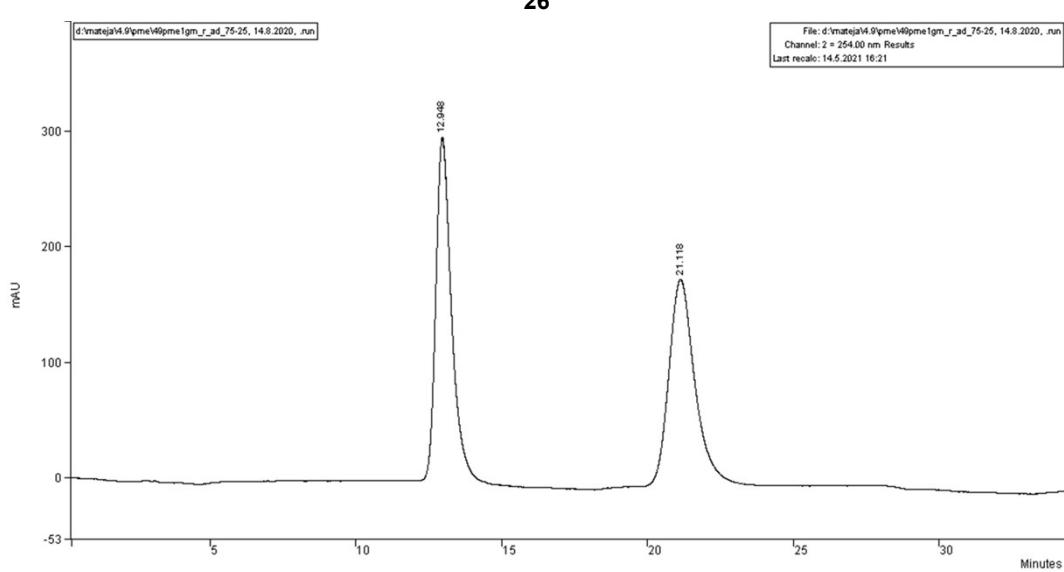
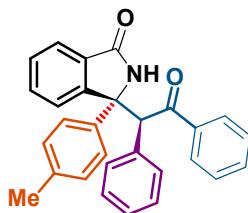


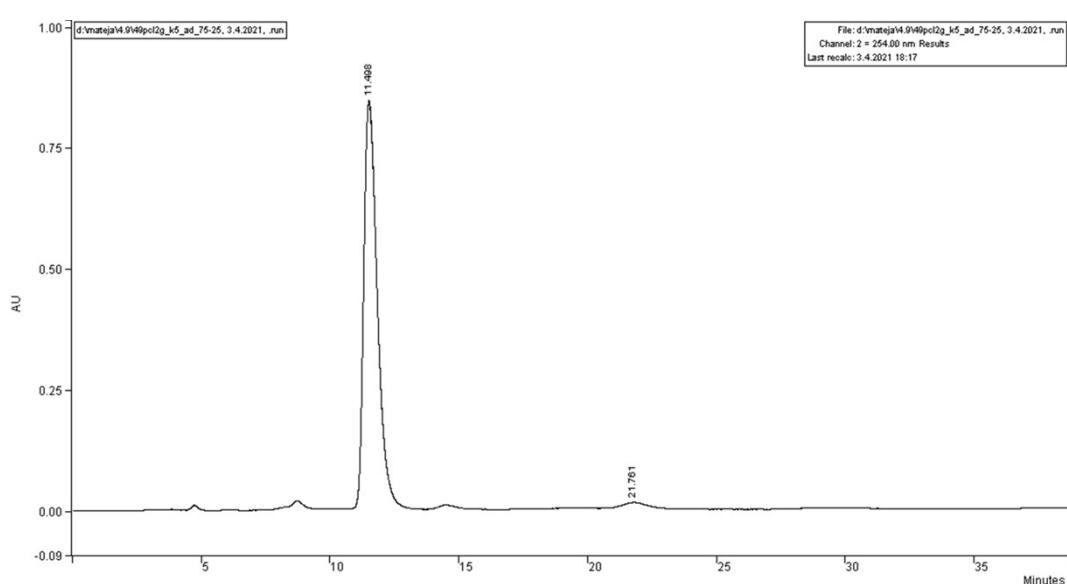
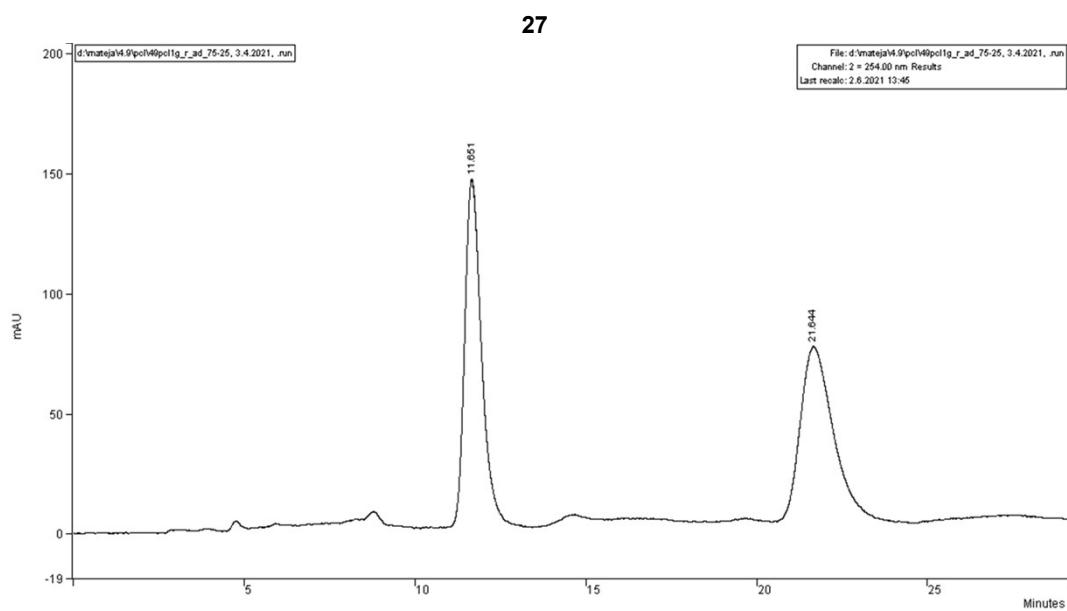
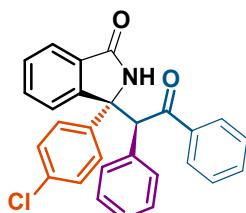
**24**

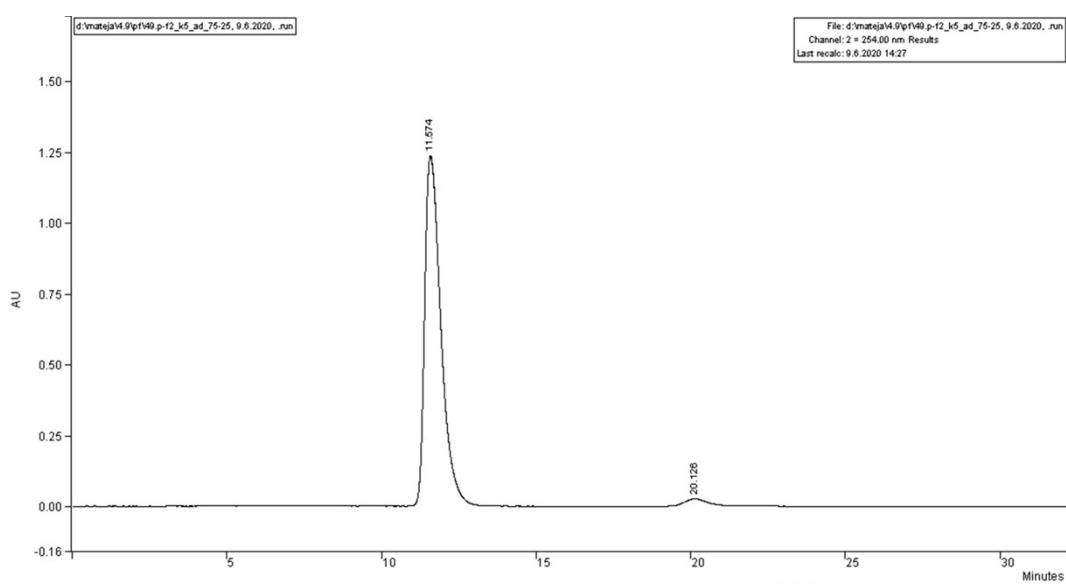
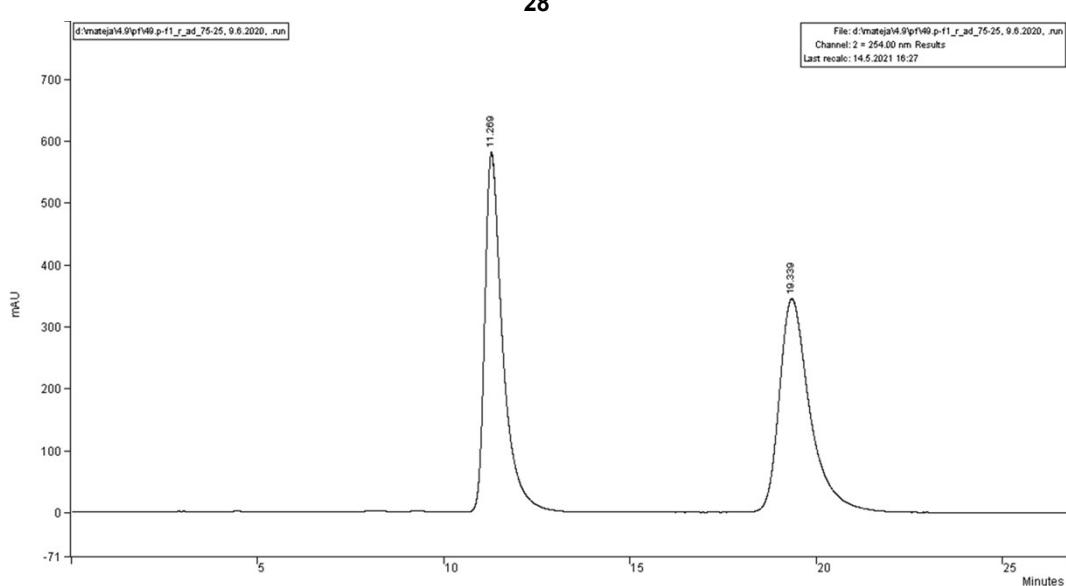
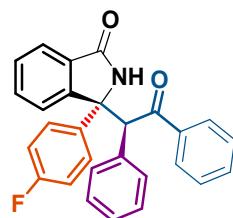
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Totals:			100.0000		0.000	431312627			

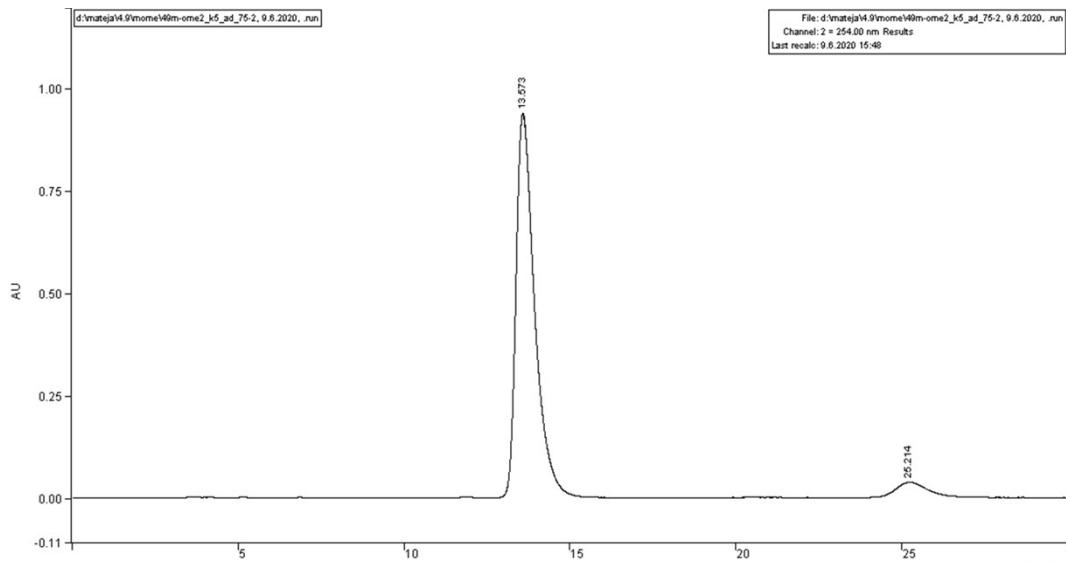
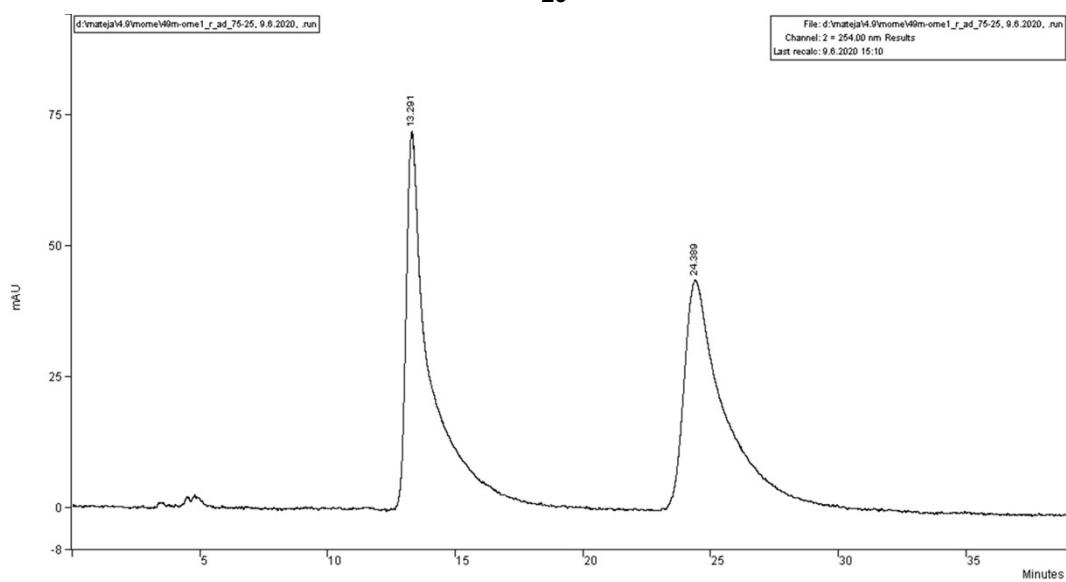
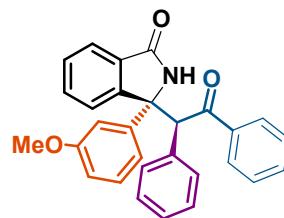


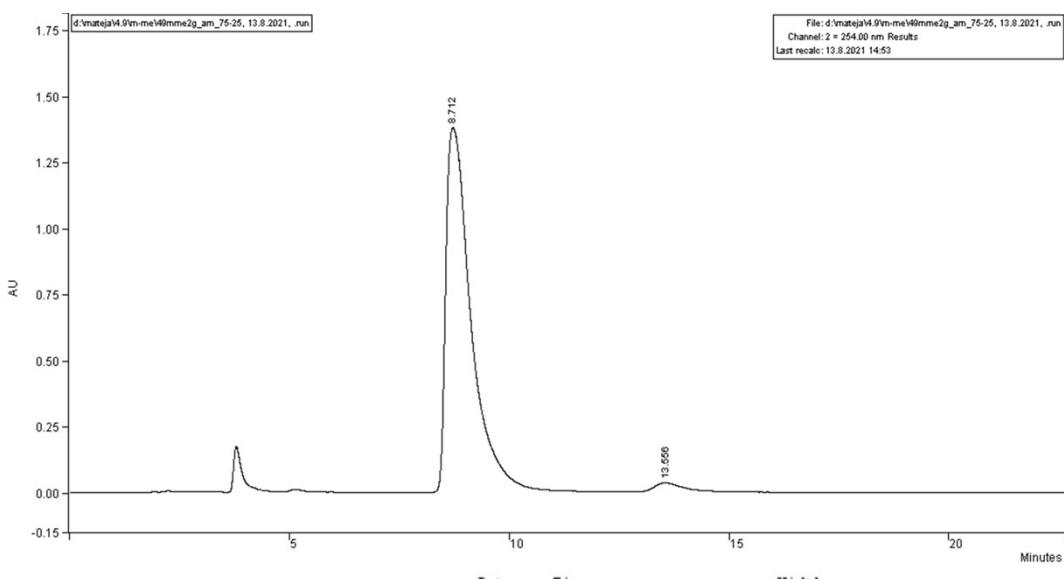
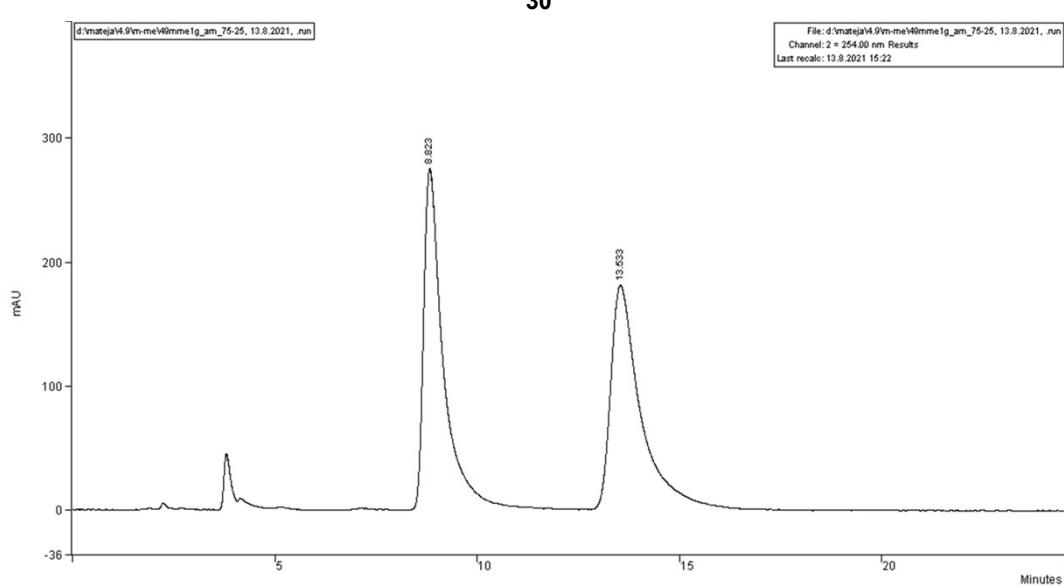
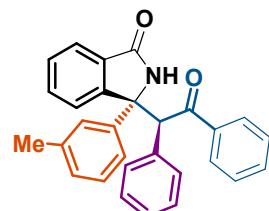


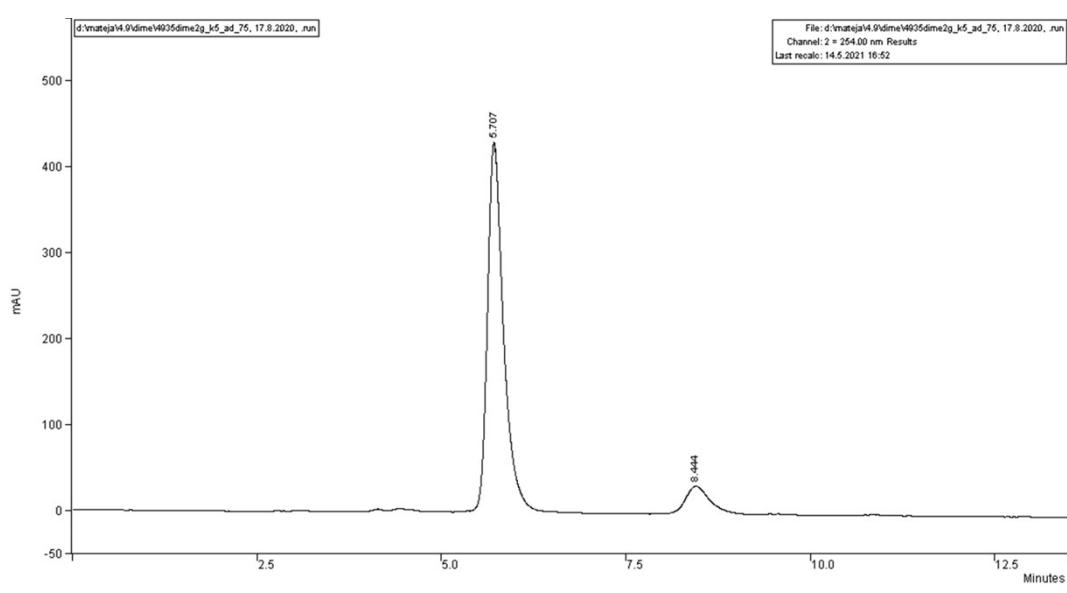
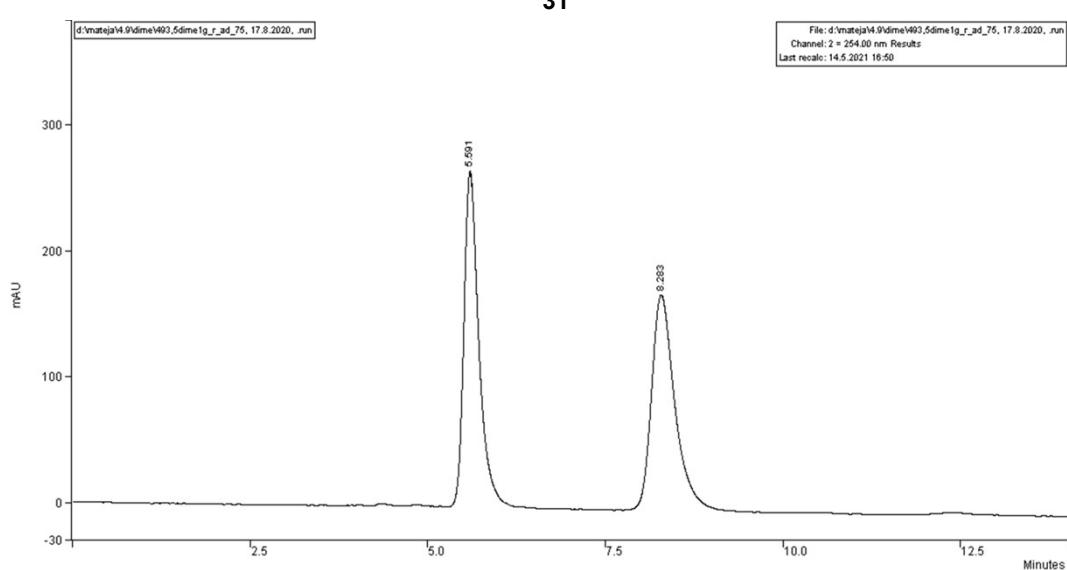
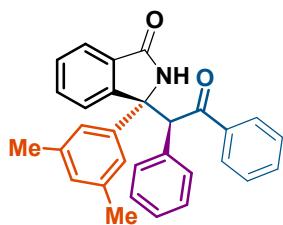


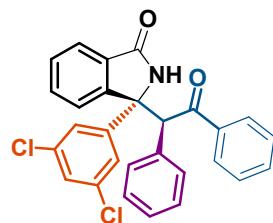










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