SUPPORTING INFORMATION

Highly diastereo- and enantioselective organocatalytic synthesis of new heterocyclic hybrids isoindolinone-imidate and isoindolinone-phthalide.

Antonia Di Mola, Francesco Scorzelli, Guglielmo Monaco, Laura Palombi and Antonio Massa*

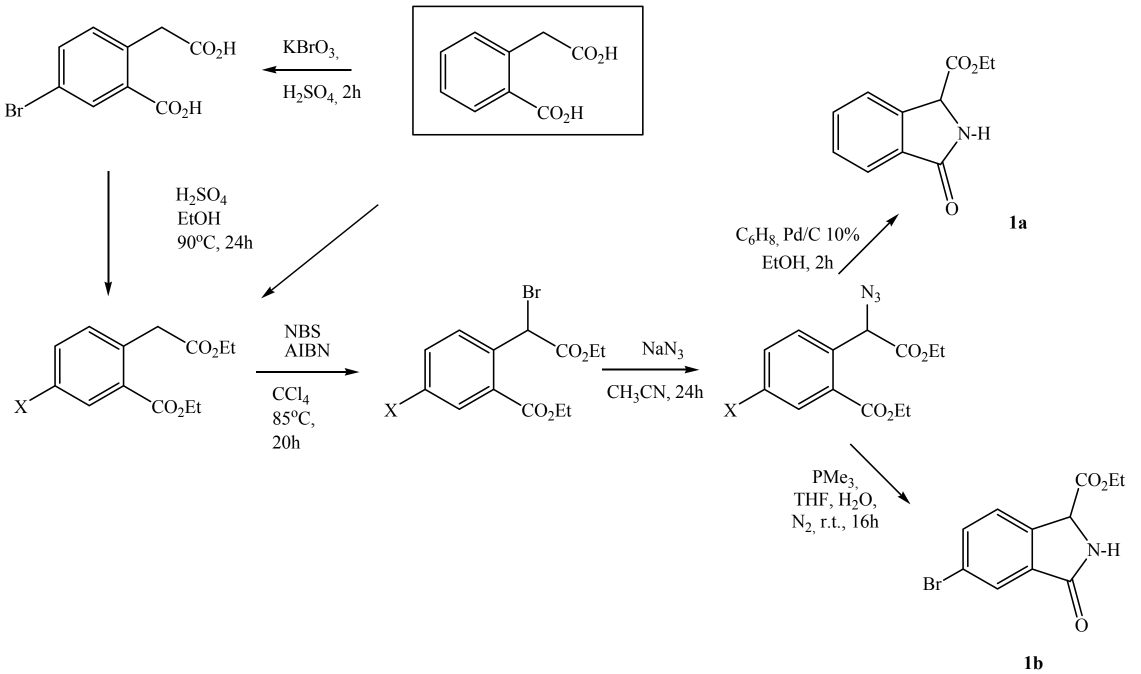
[a] *Dipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II, 132, 84084-Fisciano, SA, Italy.*
E-mail: amassa@unisa.it; Fax: +39-089-969603; Tel: +39-089-969565

1. General

All reactions were performed using commercially available compounds without further purification. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ^{1}H; 100 MHz, 75 MHz, 62.5 MHz ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Coupling constants *J* are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. High resolution mass spectral analysis were carried out using a FT-ICR-MS Solarix XR (Bruker) equipped with electrospray and MALDI source. Low resolution mass spectral analyses were carried out using an electrospray spectrometer Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus.

2. Procedures for the synthesis of 3-carboethoxy-isoindolinones 1a,b

Isoindolinone **1a** was synthesized according to reported procedures as described in Scheme S1.[1] Isoindolinone **1b** was obtained by a modification of the main route consisting of bromination of homophthalic acid with potassium bromated in sulfuric acid to give the brominated diacid,[2,3] by Fischer esterification, radical bromination and reduction of the corresponding azide by Staudinger reaction.



Scheme S1

Ethyl 2-((ethoxycarbonyl)azidomethyl)-5-bromobenzoate

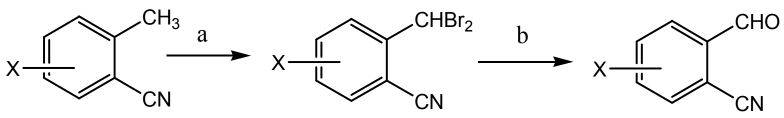
Prepared according to the literature procedure.[1] Pale oil. Yield: 91%. ^{1}H-NMR (250 MHz): 8.14 (s, 1H), 7.66 (dd, 1H, *J*= 2.0, 8.4 Hz), 7.43 (d, 1H, *J*= 8.4 Hz), 6.09 (s, 1H), 4.37-4.31 (q, 2H, *J*= 7.1 Hz), 4.24-4.19 (q, 2H, *J*= 7.1 Hz), 1.38 (t, 3H, *J*= 7.1 Hz), 1.24 (t, 3H, , *J*= 7.1 Hz). ^{13}C-NMR (60 MHz): 169.1, 165.7, 135.8, 134.8, 124.0, 130.9, 130.1, 122.8, 62.4, 62.3, 62.1, 14.4, 14.2. MS (ESI): m/z = 356 (M+ H) $^+$. Anal. calcd for $C_{18}H_{14}BrNO_3$: C, 43.84; H, 3.96; N, 11.80. Found: : C, 43.89; H, 3.78; N, 11.67.

Ethyl 5-bromo-3-oxoisoindoline-1-carboxylate 1b

To a solution of ethyl 2-((ethoxycarbonyl)azidomethyl)-5-bromobenzoate (70 mg, 0.197 mmol, 1 equiv.) in THF/H_2O (2 mL/200 μL) under nitrogen atmosphere, trimethylphosphine (1M in THF, 235 μL, 1.2 equiv) was added and the mixture was stirred for 16h at room temperature. After evaporation of the solvent, the crude was taken up with dichloromethane and washed with water. Purification by chromatography (Ethyl acetate 3/Hexane 7) gave a white solid. Yield: 55%. Mp 163-165°C. ^{1}H-NMR (300 MHz): 7.99 (s, 1H), 7.73 (d, 1H, J=8.1 Hz), 7.60 (d, 1H, J=8.1 Hz), 7.14 (bs, 1H, NH), 5.21 (s, 1H), 4.32-4.24 (m, 2H), 1.32 (t, 3H, J=7.2 Hz). ^{13}C-NMR (100 MHz): 170.6, 169.1, 140.7, 136.6, 134.5, 128.4, 126.5, 124.7, 63.8, 59.6, 15.3. HRMS (ESI): *m/z* calcd for $C_{11}H_{10}BrNO_3 + H^+$ 283.99168, found 283.99168. Anal. calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.53; H, 3.41; N, 5.04.

3. General procedure for the synthesis of 2-formylbenzonitriles (2-cyano benzaldehydes) 4a-i

2-formylbenzonitriles **4a-i** were prepared according the procedure reported in literature starting from 2-methyl benzonitriles by hydrolysis of benzal bromides in water/dioxane system.[4]

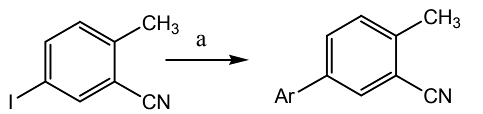


4a-i

X= H, 5-F, 5-Br, 5-Cl, 5-I, 5-OCH_3, 5-NO_2, 5-Ph, 5-α Napht

Reagents and conditions: a) *N*-bromosuccinimide, dibenzoyl peroxide, CCl_4, reflux; b) dioxane/water (1/1), reflux, 24 h.

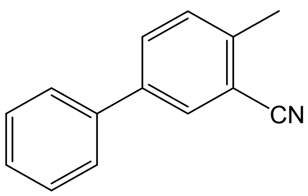
Scheme S2



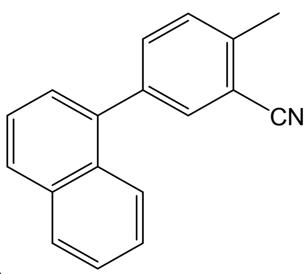
Ar= Ph, α-Napth

Reagents and conditions. a) phenyl boronic acid or α–napthyl boronic acid, $Pd(PPh_3)_4$, EtOH, K_2CO_3, reflux.

Scheme S3

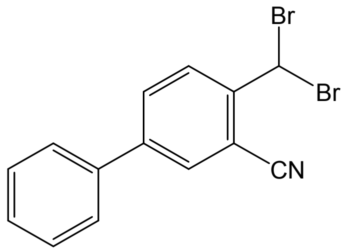


5-phenyl-2-methylbenzonitrile. Prepared from 5-iodo 2-methyl benzonitrile according to the procedure reported in literature using phenyl boronic acid.[4,5] White solid. Yield: 80%. Mp.: 88-89 °C (Ethyl acetate/Hexane). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.83 (d, 1H, *J*= 3.0 Hz), 7.71 (dd, 1H, *J*= 2.1 Hz, 8.1 Hz), 7.56 (dd, 2H, *J*= 2.1 Hz, 8.1 Hz), 7.50-7.45 (m, 2H), 7.42-7.38 (m, 2H), 2.60 (s, 3H). ^{13}C-NMR (75 MHz): 140.6, 139.5, 138.8, 138.7, 131.2, 130.8, 130.6, 129.0, 128.0, 126.8, 118.1, 113.2, 20.0. MS (ESI): m/z = 194 (M+ H)$^+$. Anal. calcd for:$C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.35; H, 5.83; N, 7.56.

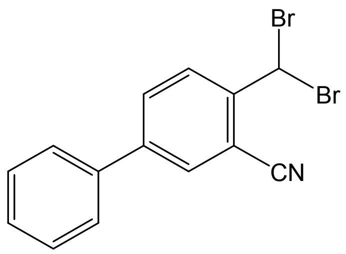


,

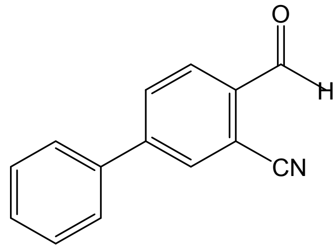
5-(1-naphtyl)-2-methylbenzonitrile. Prepared from 5-iodo 2-methyl benzonitrile according to the procedure reported in literature using 1-naphtyl boronic acid.[4,5] Pale oil. Yield: 78%. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.90 (t, 2H, *J*= 8.4 Hz), 7.77-7.61 (m, 2H), 7.57 (d, 1H, *J*= 6.9 Hz), 7.54-7.44 (m, 4H), 7.39 (d, 1H, *J*= 6.6 Hz), 2.67 (s, 3H). ^{13}C-NMR (75 MHz): 141.0, 139.2, 137.8 134.5, 133.9, 133.8, 131.4, 130.5, 128.7, 128.6, 127.3, 126.7, 126.3, 125.5, 125.4, 118.3, 113.1, 20.4. MS (ESI): m/z = 244 (M+ H)$^{+}$. Anal. calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39; N, 5.75. Found: C, 88.66; H, 5.61; N, 5.68.



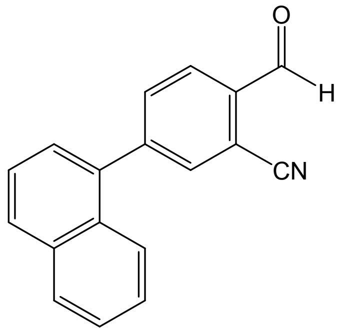
2-(Dibromomethyl)-5-phenylbenzonitrile. Prepared according to the procedure reported in literature using 4.5 equivalents of NBS.[3] Pale oil Yield: 87%. ^{1}H-NMR (250 MHz): 8.09 (d, 1H, *J*= 8.2 Hz), 7.89 (dd, 1H, *J*= 1.7 Hz, 8.2 Hz), 7.80 (d, 1H, *J*= 1.7 Hz), 7.58-7.44 (m, 5H), 7.00 (s, 1H). ^{13}C-NMR (60 MHz) : 143.6, 142.9, 137.9, 132.8, 132.6, 130.8, 130.6, 129.5, 129.2, 127.3, 116.2, 109.2, 35.8. MS (EI): m/z = 351 [M]$^{+}$. Anal. calcd for:$C_{14}H_9Br_2N$: C, 47.90; H, 2.58; N, 3.99. Found: C, 47.65; H, 2.78; N, 3.69.



2-(Dibromomethyl)-5-phenylbenzonitrile. Prepared according to the procedure reported in literature using 4.5 equivalents of NBS.[3] Pale oil Yield: 87%. ^{1}H-NMR (250 MHz): 8.09 (d, 1H, *J*= 8.2 Hz), 7.89 (dd, 1H, *J*= 1.7 Hz, 8.2 Hz), 7.80 (d, 1H, *J*= 1.7 Hz), 7.58-7.44 (m, 5H), 7.00 (s, 1H). ^{13}C-NMR (60 MHz) : 143.6, 142.9, 137.9, 132.8, 132.6, 130.8, 130.6, 129.5, 129.2, 127.3, 116.2, 109.2, 35.8. MS (EI): m/z = 351 [M]$^{+}$. Anal. calcd for:$C_{14}H_9Br_2N$: C, 47.90; H, 2.58; N, 3.99. Found: C, 47.65; H, 2.78; N, 3.69.



2-formyl 5-phenyl benzonitrile 4h. Prepared according to the procedure reported in literature.[3] White solid. Yield: 76%. Mp.: 132-133°C (Ethyl acetate /Hexane). ^{1}H-NMR (250MHz): 10.35 (s, 1H), 8.10 (d, 1H, *J*= 8.1 Hz), 8.02-7.95 (m, 2H), 7.62 (dd, 2H, *J* =2.0 Hz, 8.1 Hz), 7.53-7.48 (m, 3H). ^{13}C-NMR (60 MHz): 188.5, 147.6, 137.6, 135.4, 132.7, 131.8, 130.4, 129.8, 129.6, 127.5, 116.3, 114.6. MS (ESI): m/z = 208 (M+ H)$^{+}$. Anal. calcd for:$C_{14}H_{9}NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.35; H, 4.28; N, 6.66.



2-formyl 5-(1-naphtyl)- benzonitrile 4i. Prepared according to the procedure reported in literature.[3] White waxy solid. Yield: 96%. ^{1}H-NMR (250 MHz): 10.44 (s, 1H), 8.17 (d, 1H, *J*= 8.2 Hz), 7.98-7.90 (m, 4H), 7.73 (d, 1H, *J*= 8.2 Hz), 7.60-7.50 (m, 3H), 7.43 (d, 1H, *J*= 7.2 Hz). ^{13}C-NMR (60 MHz): 188.2, 147.4, 143.5, 136.3, 135.3, 134.7, 133.7, 130.5, 129.6, 129.5, 128.6, 127.5, 127.2, 127.0, 126.3, 125.2, 124.5, 115.9, 113.9. MS (ESI): m/z = 258 (M+ H)$^{+}$. Anal. calcd for $C_{18}H_{11}NO$: C, 84.03; H, 4.31; N, 5.44. Found: C, 84.21; H, 4.54; N, 5.09.

4. Pathway A: Procedure for the preparation of racemic pthalide from 2-carbomethoxybenzaldehyde 3

A solution of isoindolinone **1** (0.1 mmol), potassium carbonate (0.5 equiv.) and 2-carbomethoxybenzaldehyde **2** (1.1 equiv.) in CH_3CN (2 mL) was stirred at room temperature for 1 h. The mixture was evaporated under reduced pressure, giving a white solid which was purified by chromatography on silica gel (Hexane/Ethyl acetate 8/2). Yield: 88%.

6. Pathway B: General procedure for the preparation of racemic imidates rac-5a-i from 2-formylbenzonitriles and phtalides by hydrolysis of imidates a rac-3a-j

A solution of isoindolinone **1** (0.1 mmol), potassium carbonate (0.5 equiv.) and 2-formylbenzonitriles **4a-i** (1.1 equiv.) in CH_3CN (2 mL) was stirred at room temperature till starting material disappeared (1-2h). The mixture was filtered, evaporated under reduced pressure, then suspended in THF (2 mL)/ HCl 0.5M (1 mL) and the reaction mixture was stirred at room temperature for 2h. The solvent was removed under reduced pressure and extracted three times with dichlorometane affording a white solid which was purified by chromatography on silica gel (Hexane/Ethyl acetate 7/3). Yields for the obtained hybrids are in the range 75-93%.

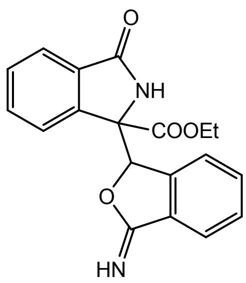
7. General procedure for organocatalytic asymmetric synthesis of imidates 5a-j

A solution of isoindolinone **1** (0.058 mmol), Takemoto catalyst **8** (10% mol) and 2-formylbenzonitriles **4a-i** (1.1 equiv.) in p-xylene (2.5 mL) were stirred at 20°C till starting material disappeared. The mixture was directly purified by chromatography on silica gel (Hexane/Ethyl acetate 8/2 to Ethyl acetate).

8. General procedure for the preparation of chiral pthalides 3a-i by hydrolysis of imidates 5a-i

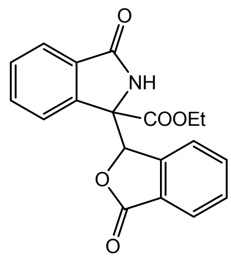
Imidates **5a-i** were suspended in THF (2 mL) and HCl 0.5M (1 mL) was added and the reaction mixture was stirred at room temperature for 2h. Solvent was removed under reduced pressure and extracted three times with dichlorometane affording a white solid which was purified by chromatography on silica gel (Hexane/Ethyl acetate 7/3).

9. Characterization of the imidate 5a

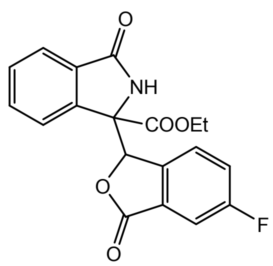


Ethyl 1-(1,3-dihydro-1-iminoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 5a. White solid. Yield: 90%. Mp.: 198°C decomp. ($CHCl_3$/Hexane). $[\alpha]_D^{14}$: + 220 (c 0.1, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): 7.94 (d, 1H, *J*= 7.5 Hz), 7.83 (d, 1H, *J*= 7.5 Hz), 7.74 (t, 1H, *J*= 7.4 Hz), 7.67-7.64 (m, 2H), 7.19 (bt, 1H, *J*= 8.0 Hz), 7.06 (t, 1H, *J*= 7.5 Hz), 6.36 (s, 1H), 5.62 (d, 1H, *J*= 7.7 Hz), 4.41-4.31 (m, 2H), 1.36 (t, 3H, *J*= 7.1 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): 169.6, 168.5, 166.8, 140.5, 140.1, 132.5, 132.4, 131.7, 130.4, 129.9, 129.8, 124.5, 124.3, 123.9, 121.1, 85.8, 69.9, 63.0, 14.0. HRMS (ESI) calcd for $C_{19}H_{16}N_2O_4 + H^+$: 337.11828, found 337.11820. Enantiomeric excesses were determined after hydrolysis.

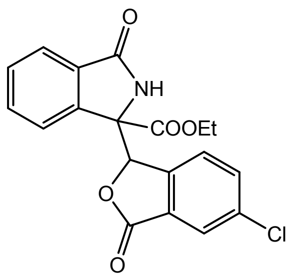
10. Characterization of the phtalides



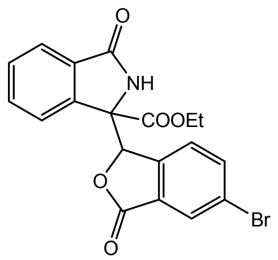
Ethyl 1-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3a. Yield after 2 steps: 86%. Mp.: 217°C (decomp.); $[\alpha]_D^{14}$: + 121.9 (c 0.12, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): 7.99 (d, 1H, *J*= 7.56 Hz), 7.88-7.68 (m, 4H), 7.45 (t, 1H, *J*= 7.81 Hz), 7.25 (t, 1H, *J*= 7.38 Hz), 6.46 (bs, 1H, NH), 6.37 (s, 1H), 5.79 (d, 1H, *J*= 7.62 Hz), 4.37-4.31 (m, 2H), 1.34 (t, 3H, *J*= 7.14 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): 169.3, 169.0, 168.0, 143.2, 140.2, 133.8, 132.9, 131.8, 130.7, 130.2, 126.8, 126.0, 124.7. 123.3, 121.7, 83.2, 69.0, 63.4, 13.9. HRMS (ESI): *m/z* calcd for $C_{19}H_{15}NO_5 + H^+$ 338.10231, found: 338.10240. Anal. Calcd for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15. Found: C 67.41, H 4.32, N 4.11.Chiral HPLC: IA-3 column, hexane-*i*PrOH (70:3), flow: 0.6 mL/min, t: 24.9 min and 31.7 min.



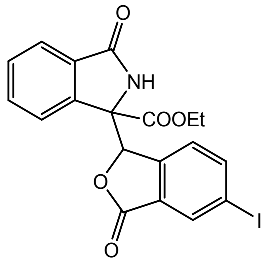
Ethyl 1-(6-fluoro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3b. Yield after 2 steps: 90%. Mp.: 173°C (decomp.); $[\alpha]_D^{20}$: + 149.1 (c 0.1, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): 7.97 (d, 1H, *J*= 10.0 Hz), 7.80 (q, 2H, *J*= 7.5 Hz), 7.69 (t, 1H, *J*= 7.5 Hz), 7.51 (d, 1H, *J*= 6.9 Hz), 6.99-6.93 (m, 1H), 6.52 (bs, 1H, NH), 6.35 (s, 1H), 5.74 (dd, 1H, *J*= 3.0 Hz, 8.1 Hz), 4.38-4.33 (m, 2H), 1.35 (t, 3H, *J*= 7.2 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): 169.5, 168.1, 168.0, 163.2 (J_1 C-F = 250 Hz), 140.3, 138.9, 133.3, 131.9, 131.2, 129.4 (J_3 C-F = 9 Hz), 125.1, 123.8 (J_3 C-F = 9 Hz), 123.5, 122.0 (J_2 C-F = 23 Hz), 112.8 (J_2 C-F = 23 Hz), 83.4, 69.1, 63.8, 14.2. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}FNO_5 + H^+$: 356.09288, found: 356.09281. Chiral HPLC: IA-3 column, hexane-*i*PrOH (70:30), flow: 0.6 mL/min, t: 30.1 min and 34.4 min. Anal. calcd for $C_{19}H_{14}FNO_5$: C 64.23, H 3.87, N 3.94. Found: C 64.31, H 3.62, N 3.71.



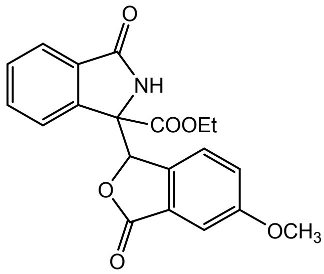
Ethyl 1-(6-chloro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3c
Yield after 2 steps: 93%. 224°C (decomp.); $[\alpha]_D^{20}$: + 128.3 (c 0.43, $CHCl_3$).. ^{1}HNMR (300 MHz, $CDCl_3$): 7.97 (d, 1H, *J*= 8.76 Hz), 7.85-7.83 (m, 3H), 7.77-7.72 (m, 1H), 7.19 (d, 1H, *J*= 8.76 Hz), 6.36 (bs, 1H, NH), 6.32 (s, 1H), 5.68 (d, 1H, *J*= 8.04 Hz), 4.38-4.33 (m, 2H), 1.35 (t, 3H, *J*= 7.17 Hz). ^{13}CNMR (60 MHz, $CDCl_3$): 169.6, 168.1, 167.8, 141.6, 140.3, 136.9, 134.5, 133.4, 131.9, 131.2, 129.0, 126.3, 125.2, 123.6, 123.2, 83.4, 69.1, 63.8, 14.3. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}ClNO_5 + H^+$: 372.06333, found: 372.06345. Chiral HPLC: AD column, hexane-*i*PrOH (8:2), flow: 0.6 mL/min, t: 38.7 min and 45.4 min. Anal. calcd for $C_{19}H_{14}ClNO_5$: C 61.38, H 3.80, N 3.77. Found: C 61.31, H 3.62, N 3.61



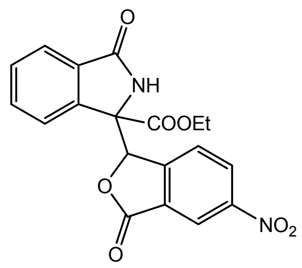
Ethyl 1-(6-bromo-1,3-dihydo-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3d.
Yield after 2 steps: 86%. Mp: 193-194°C; $[\alpha]_D^{14}$: + 107.8 (c 0.5, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): 7.97 (t, 1H, *J*= 7.65 Hz), 7.79-7.85 (m, 3H), 7.69-7.77 (m, 1H), 7.35 (dd, 1H, *J*= 1.74 Hz, 8.18 Hz), 6.43 (bs, 1H, NH), 6.33 (s, 1H), 5.63 (d, 1H, *J*= 8.19 Hz), 4.38-4.31 (m, 2H), 1.35 (t, 3H, *J*= 7.25 Hz). ^{13}CNMR (60 MHz, $CDCl_3$): 169.6, 168.1, 167.7, 142.1, 140.3, 137.2, 133.4, 131.9, 131.2, 129.3, 129.2, 125.2, 124.7, 123.6, 123.4, 83.5, 69.1, 63.8, 14.3. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}BrNO_5 + H^+$: 416.01281, found 416.01277. Anal. calcd for $C_{19}H_{14}BrNO_5$: C 54.83, H 3.39, N 3.37. Found: C 54.71, H 3.32, N 3.51. Chiral HPLC: IA-3 column, hexane-*i*PrOH (70:30), flow: 0.6 mL/min, t: 21.7 min and 24.7 min.



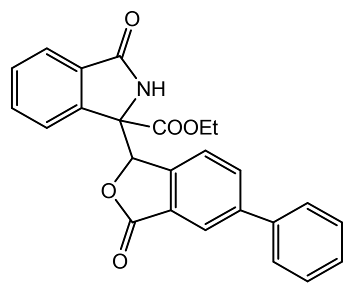
Ethyl 1-(6-iodo-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3e. Yield after 2 steps: 90%. Mp: 211-213°C; $[\alpha]_D^{18}$: + 81.4 (c 0.5, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): 8.18 (s, 1H), 7.96 (d, 1H, *J*= 7.6 Hz), 7.84-7.76 (m, 2H), 7.70-7.68 (m, 1H), 7.53 (d, 1H, *J*= 8.1 Hz), 6.50 (bs, 1H, NH), 6.32 (s, 1H), 5.49 (d, 1H, *J*= 8.2 Hz), 4.39-4.30 (m, 2H), 1.34 (t, 3H, *J*= 7.1 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): 169.3, 167.8, 167.3, 142.6, 142.5, 139.9, 135.0, 133.1, 131.7, 130.9, 128.9, 124.9, 123.3, 123.2, 95.6, 83.3, 68.7, 63.6, 13.9. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}INO_5$+ H^+: 463.99894, found: 463.99874. Chiral HPLC: IA-3 column, hexane-*i*PrOH (70:30), flow: 0.6 mL/min, t: 16.9 min and 20.0 min. Anal. calcd for $C_{19}H_{14}INO_5$: C 49.26, H 3.05, N 3.02. Found: C 49.41, H 3.22, N 3.35.



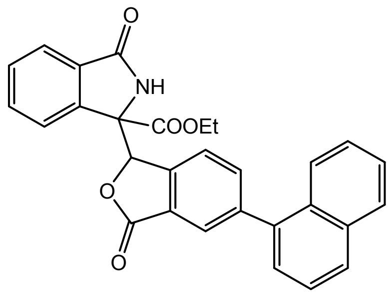
Ethyl 1-(6-methoxy-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3f. Yield after 2 steps: 93%. Mp.: 131-133°C; $[\alpha]_D^{20}$: + 77.2 (c 0.4, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): 7.76 (d, 1H, *J*= 6.3 Hz), 7.65-7.70 (m, 2H), 7.68-7.65 (m,1H), 7.28 (s, 1H), 6.78 (dd, 1H, *J*= 2.4 Hz, 8.4 Hz), 6.38 (bs, 1H, NH), 6.31 (s, 1H), 5.63 (d, 1H, *J*= 8.7 Hz), 4.40-4.29 (m, 2H), 3.78 (s, 3H), 1.35 (t, 3H, *J*= 6.9 Hz). ^{13}CNMR (60 MHz, $CDCl_3$): 169.3, 169.0, 168.0, 161.2, 140.2, 135.3, 132.8, 132.0, 131.8, 130.7, 128.5, 128.3, 124.7, 123.3, 107.9, 83.1, 68.9, 63.4, 55.6, 13.9. HRMS (ESI): *m/z* calcd $C_{20}H_{17}NO_6$ + H^+: 368.11286, found: 368.11282. Anal. calcd for $C_{20}H_{17}NO_6$: C 65.39, H 4.66, N 3.81. Found: C 65.31, H 4.52, N 3.75.Chiral HPLC: IA-3 column, hexane-*i*PrOH (70:30), flow: 0.6 mL/min, t: 25.6 min and 31.2 min.



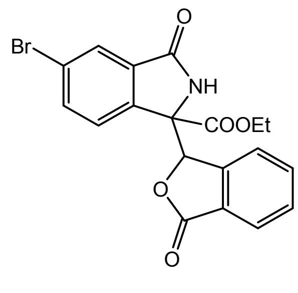
Ethyl 1-(6-nitro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3g. Yield after 2 steps: 80%. Mp.: 198°C (decomp.); $[\alpha]_D^{20}$: + 64.4 (c 0.9, $CHCl_3$). ^{1}HNMR (300 MHz, $CDCl_3$): 8.69 (s, 1H), 8.12 (dd, 1H, *J*= 1.8, 8.4 Hz), 8.01 (d, 1H, *J*= 7.6 Hz), 7.87-7.82 (m, 2H), 7.76-7.72 (m, 1H), 6.49 (s, 1H), 6.40 (bs, 1H, NH), 5.93 (d, 1H, *J*= 8.1 Hz), 4.43-4.33 (m, 2H), 1.37 (t, 3H, *J*= 7.1 Hz). ^{13}CNMR (60 MHz, $CDCl_3$): 169.4, 167.5, 166.5, 149.5, 148.5, 139.6, 133.3, 132.3, 131.7, 131.2, 129.2, 128.8, 125.1, 124.0, 123.6, 123.3, 123.1, 121.4, 83.4, 68.9, 63.8, 14.0. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}N_2O_7 + H^+$: 383.08738, found 383.08731. Chiral HPLC: AD column, hexane-*i*PrOH (70:30), flow: 0.8 mL/min, t: 25.9 min and 36.3 min. Anal. calcd for $C_{19}H_{14}N_2O_7$: C 59.69, H 3.69, N 7.33. Found: C 59.35, H 3.52, N 7.45.



Ethyl 1-(6-phenyl-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3h. Yield after 2 steps: 85%. Mp.: 195-196°C; $[\alpha]_D^{20}$: + 169.4 (c 0.43, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): 8.04 (t, 2H, *J*= 9.0 Hz), 7.84 (q, 2H, *J*= 9.0 Hz), 7.73 (t, 1H, *J*= 6.0 Hz), 7.51-7.44 (m, 6H), 6.49 (s, 1H), 6.48 (s, 1H), 5.84 (d, 1H, *J*= 8.0 Hz), 4.43-4.33 (m, 2H), 1.38 (t, 3H, *J*= 7.5 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): 169.6, 169.2, 168.3, 143.9 142.1, 140.1, 138.9, 133.2, 132.0, 131.0, 129.2, 128.5, 127.8, 127.4, 125.1, 124.4, 123.7, 122.3, 83.5, 69.3, 63.7, 14.2. HRMS (ESI): *m/z* calcd for $C_{25}H_{19}NO_5 + H^+$: 414.13367, found 414.13358. Anal. calcd for $C_{25}H_{19}NO_5$: C 72.63, H 4.63, N 3.39. Found: C 72.55, H 4.52, N 3.67. Chiral HPLC: IA-3 column, hexane-*i*PrOH (7:3), flow: 0.6 mL/min, t: 29.7 min and 49.6 min.



Ethyl 1-(6-(3,4 dimethoxy)phenyl-1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3i. Yield after 2 steps: 80% as a waxy solid; $[\alpha]_D^{20}$: + 48.4 (c 057, $CHCl_3$)..).. [1]HNMR (400 MHz, $CDCl_3$): 7.89 (t, 2H, *J*= 8.0 Hz), 7.87-7.84 (m, 3H), 7.81 (t, 1H, *J*= 8.0 Hz), 7.72 (t, 1H, *J*= 8.0 Hz), 7.64 (d, 1H, *J*= 8.0 Hz), 7.52-7.48 (m, 2H), 7.44-7.40 (m, 2H), 7.33 (d, 1H, *J*= 8.0 Hz), 6.43 (s, 2H), 5.92 (d, 1H, *J*= 8.0 Hz), 4.44-4.34 (m, 2H), 1.38 (t, 3H, *J*= 8.0 Hz). ^{13}C-NMR (100 MHz): 170.7, 170.2, 169.4, 144.5, 143.4, 141.6, 138.8, 137.2, 134.9, 134.3, 133.1, 132.2, 132.1, 131.3, 129.8, 129.7, 128.6, 128.5, 127.8, 127.3, 126.5, 126.3, 126.2, 124.7, 123.0, 84.6, 70.3, 64.8, 15.3. HRMS (ESI): *m/z* calcd for $C_{25}H_{21}NO_5 + H^+$: 464.14925, found 464.14933 Anal. calcd for $C_{29}H_{21}NO_5$: C 75.15, H 4.57, N 3.02. Found: C 75.38, H 4.49, N 3.27. Chiral HPLC: IA-3 column, hexane-*i*PrOH (8:2), flow: 0.8 mL/min, t: 30.0 min and 33.7 min.



Ethyl 5-bromo-1-(1,3-dihydro-1-oxoisobenzofuran-3-yl)-3-oxoisoindoline-1-carboxylate 3j. Yield after 2 steps: 81%. Mp.: 250°C (dec.) $[\alpha]_D^{20}$: + 168.0 (c 0.25, $CHCl_3$).. [1]HNMR (300 MHz, $CDCl_3$): 7.91-7.86 (m, 4), 7.50 (t, 1H, *J*= 7.5 Hz), 7.36 (t, 1H, *J*= 6.0 Hz), 6.46 (bs, 1H, NH), 6.34 (s, 1H), 5.97 (d, 1H, *J*= 9.0 Hz), 4.44-4.28 (m, 2H), 1.36 (t, 3H, *J*= 7.5 Hz). ^{13}CNMR (75 MHz, $CDCl_3$): 169.1, 168.0, 167.8, 143.2, 139.1, 136.2, 134.3, 134.0, 130.6, 128.2, 127.0, 126.5, 125.4, 125.2, 121.9, 83.1, 69.2, 63.9, 14.2. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}BrNO_5 + H^+$: 416.01281, found 416.01287. Chiral HPLC: IA-3 column, hexane-*i*PrOH (7:3), flow: 0.6 mL/min, t: 28.5 min and 31.6 min. Anal. calcd for $C_{19}H_{14}BrNO_5$: C 54.83, H 3.39, N 3.37. Found: C 54.79, H 3.32, N 3.49.

Ab initio calculations

A conformational search has been performed at the MMFF level using Spartan 04 for **3**-SR and **3**-SS. The 18 conformers lying in a window of 5 kcal mol^{-1} have then been optimized at the B3LYP/6-31G* level using Gaussian 09. Single point B3LYP/6-31+G** calculations have then been performed on the optimized structures to calculate energies and nuclear shieldings. Relative energies are gathered in Table S1.

Table S1. Relative B3LYP/6-31+G**//B3LYP/6-31G* energies in kcal mol^{-1}

Conf.#	**3**-SR	**3**-SS
1	0.000	0.558
2	0.363	1.248
3	0.625	1.412
4	0.741	1.515
5	1.089	1.861
6	1.171	2.120
7	2.378	2.356
8	2.714	2.366
9	2.881	2.512
10	3.244	2.649
11	3.264	3.060
12	3.484	3.066
13	3.921	3.101
14	4.051	3.923
15	4.206	4.081
16	4.209	4.211
17	4.834	4.606
18	5.254	4.892

For every proton H_i the isotropic nuclear shielding σ_i has been converted in the corresponding chemical shift δ_i by the relation

$$\delta_i = \frac{A - \sigma_i}{B},$$

where the constants A=31.643 ppm and B=1.0591 are reported in ref. 9 of the paper, and take into account the effect of the solvent.

In Table S2 we report the chemical shifts computed for the two diastereomers either Boltzmann-averaged on the 18 conformers, or obtained from the single lowest energy conformer. The close values computed for the methyl and methylene protons have been averaged. For each calculation, the chemical shifts assignable to experimental doublets and triplets have been sorted to get the best agreement.

Table S2. Comparison of calculated and experimental chemical shifts. Calculations are either the Boltzmann-averages over the 18 low energy conformers, or the values obtained for the lowest energy conformer. The standard deviation *s* of the differences between experimental and computed values is also reported. In case of incomplete experimental information, the proton selected to match the experimental values is indicated in square brackets (proton numbers are as in Scheme 1). All entries in ppm.

	18 conf.s		1 conf.		
H	3-SR	3-SS	3-SR	3-SS	Exp.
CH_3	1.35	1.21	1.35	1.15	1.34
CH_2O	4.24	4.14	4.14	4.00	4.34
d	6.03 [4]	7.39 [4]	5.93 [4]	7.40 [4]	5.79
CH phtalide	6.26	6.32	6.26	6.46	6.37
NH	5.59	4.91	5.60	4.74	6.46
T	7.15 [3]	7.49 [7]	7.09 [3]	7.52 [7]	7.25
t	7.34 [2]	7.52 [2]	7.34 [2]	7.58 [6]	7.45
t	7.55 [7]	7.55 [6]	7.55 [7]	7.59 [2]	7.67
t	7.70 [6]	7.57 [3]	7.71 [6]	7.59 [3]	7.83
d	7.68 [5]	7.73 [5]	7.66 [8]	7.76 [5]	7.83
d	7.74 [8]	7.75 [8]	7.70 [1]	7.79 [8]	7.83
d	7.97 [1]	7.76 [1]	8.00 [5]	7.81 [1]	7.99
s	0.28	0.66	0.26	0.69	-

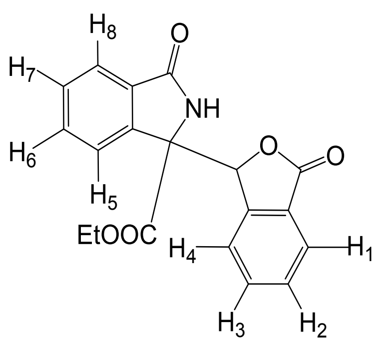


Figure S1

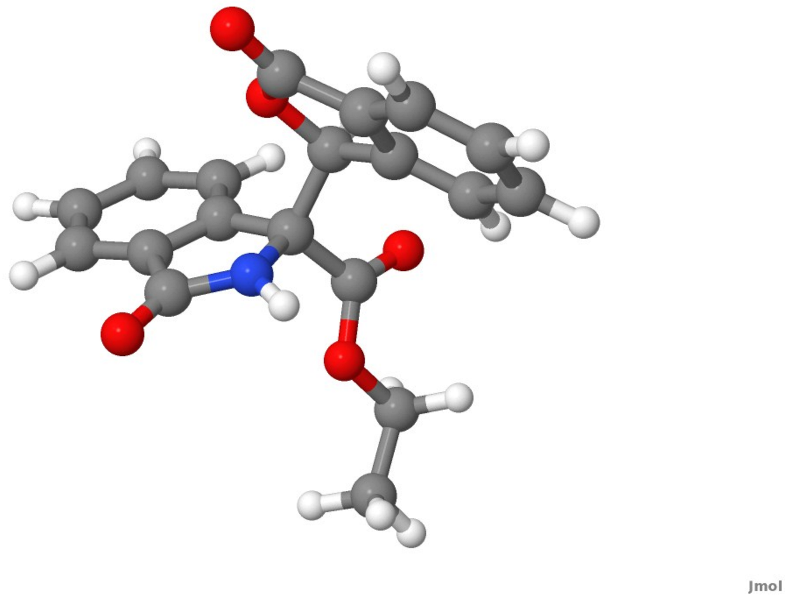
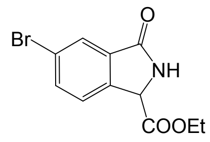


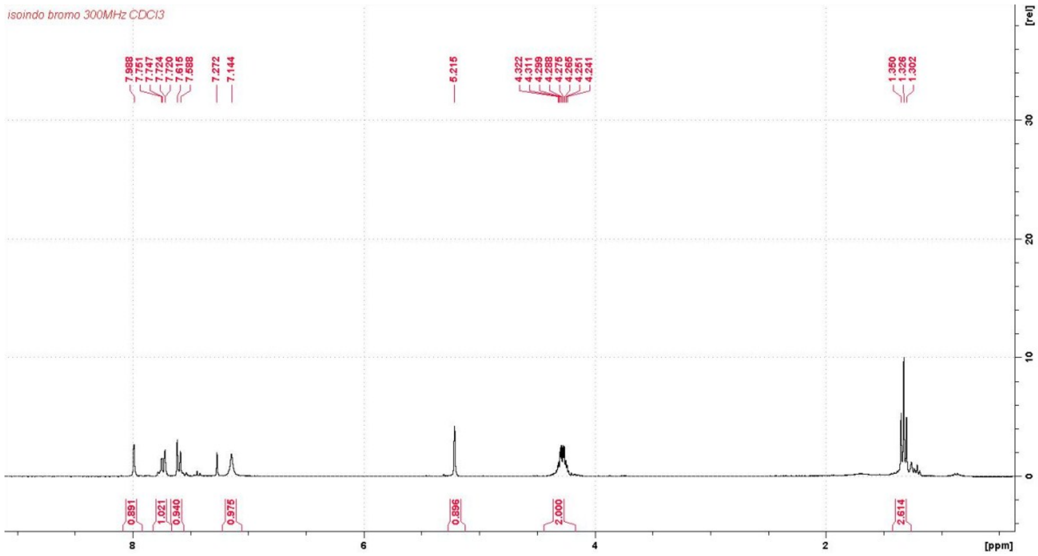
Figure S2. Model of the lowest energy conformer of **3**-SS.

References

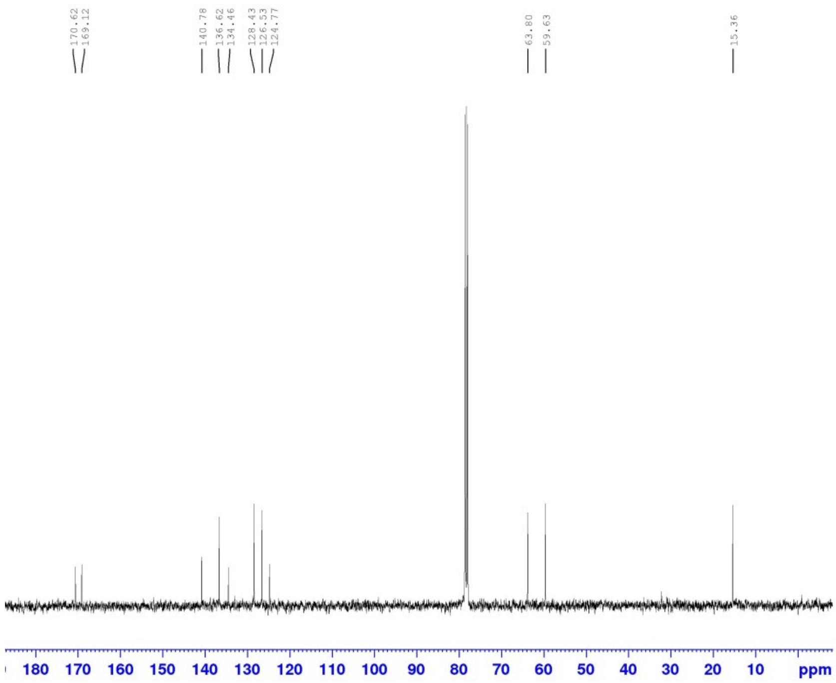
[1]E. L. Conn, D. Hepworth, Y. Qi, B. N. Rocke, R. B. Ruggeri, Y. Zhang PCT WO 2011/ 145022 A1.
[2]Harrison, J. J.; Pellegrini, J. P.; Selwitz, C. M. *J. Org. Chem.* **1981**, *46*, 2169.
[3]M.K. Deliömeroğlu, S. Özcan, M. Balcia *ARKIVOC* **2010**, 148-160
[4]A. Di Mola, T. Caruso, P. De Caprariis, A. Massa *ARKIVOC* **2016** (*iv*) 9.
[5]Billamboz, M.; Fabrice, B.; Barreca, M. L.; De Luca, L.; Mouscadet, J-F.; Calmels, C.; Andreola, M-L.; Witvrouw, M.; Christ, F.; Debyser, Z.; Cotelle, P. *J. Med. Chem.* **2008**, *51,* 7717.



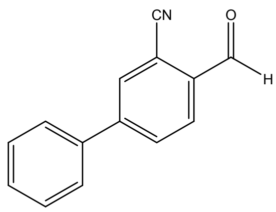
1b



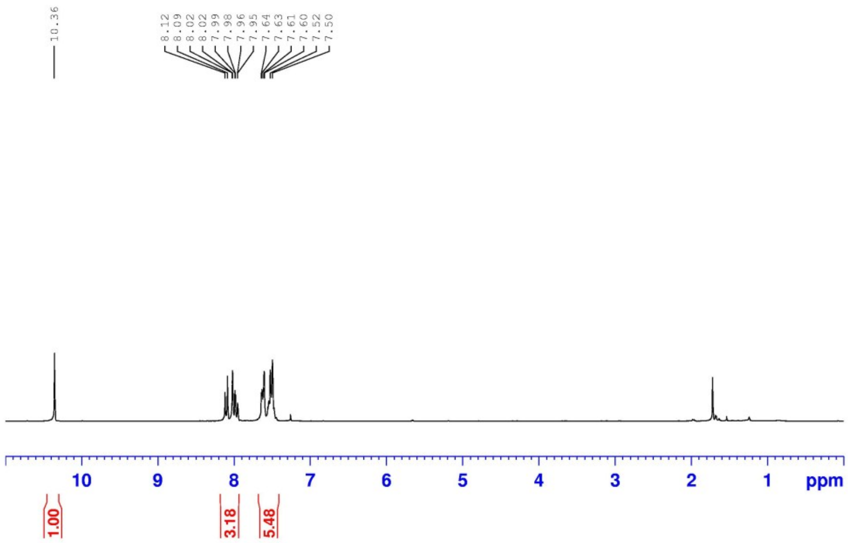
isoindo bromo 300MHz CDCl3
7.988
7.751
7.747
7.724
7.720
7.615
7.588
7.272
7.144
5.215
4.322
4.311
4.299
4.288
4.275
4.265
4.251
4.241
1.350
1.326
1.302
0.891
1.021
0.940
0.975
0.896
2.000
2.614
[rel]
[ppm]



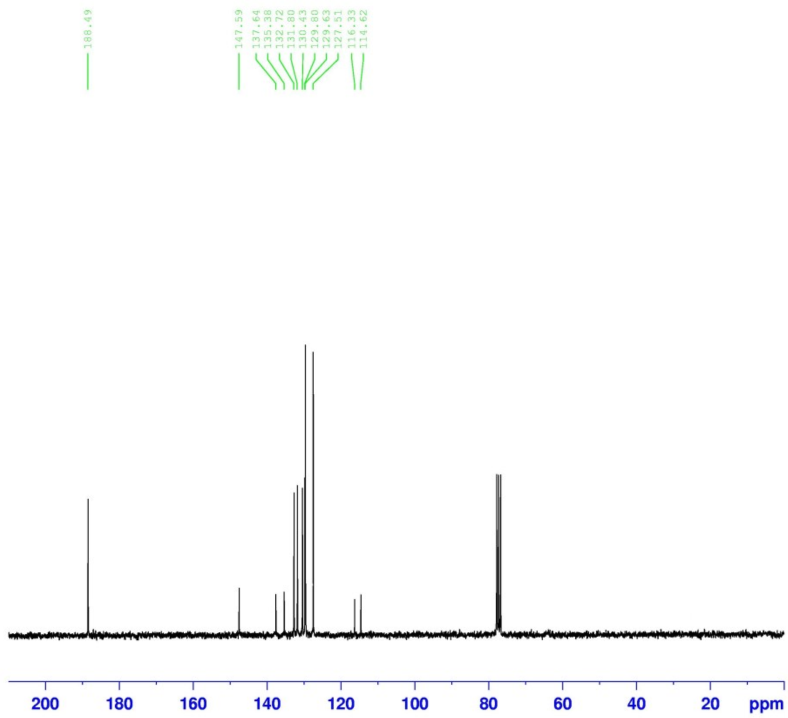
170.62
169.12
140.78
136.62
134.46
128.43
126.53
124.77
63.80
59.63
15.36
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



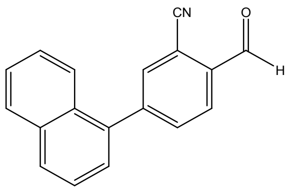
CN
O
H

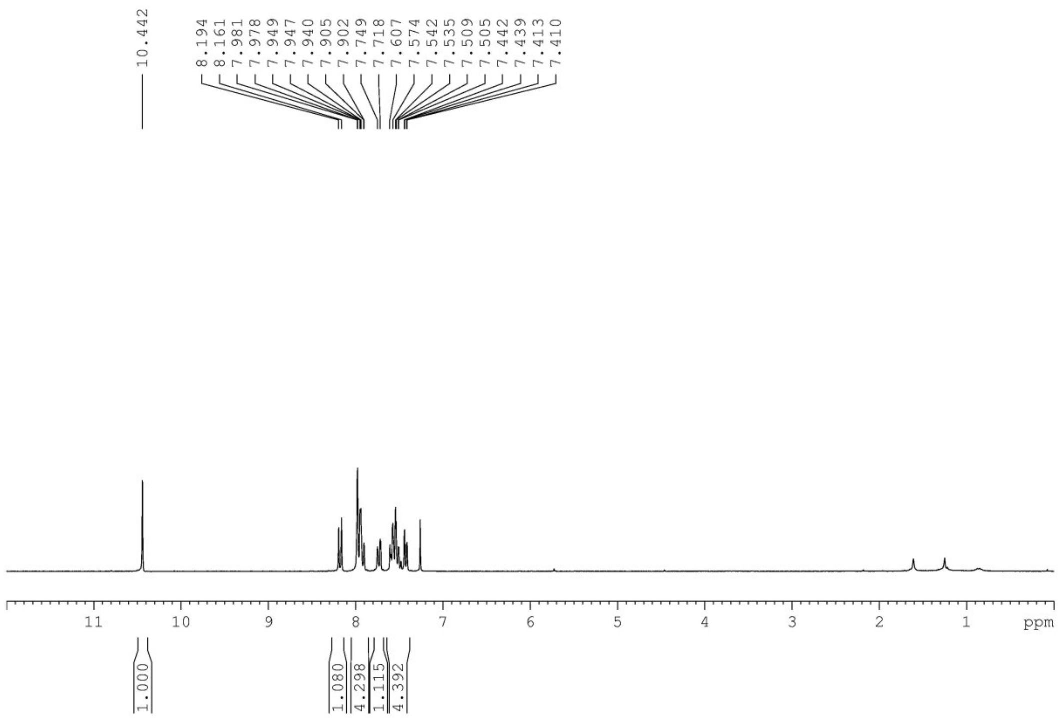


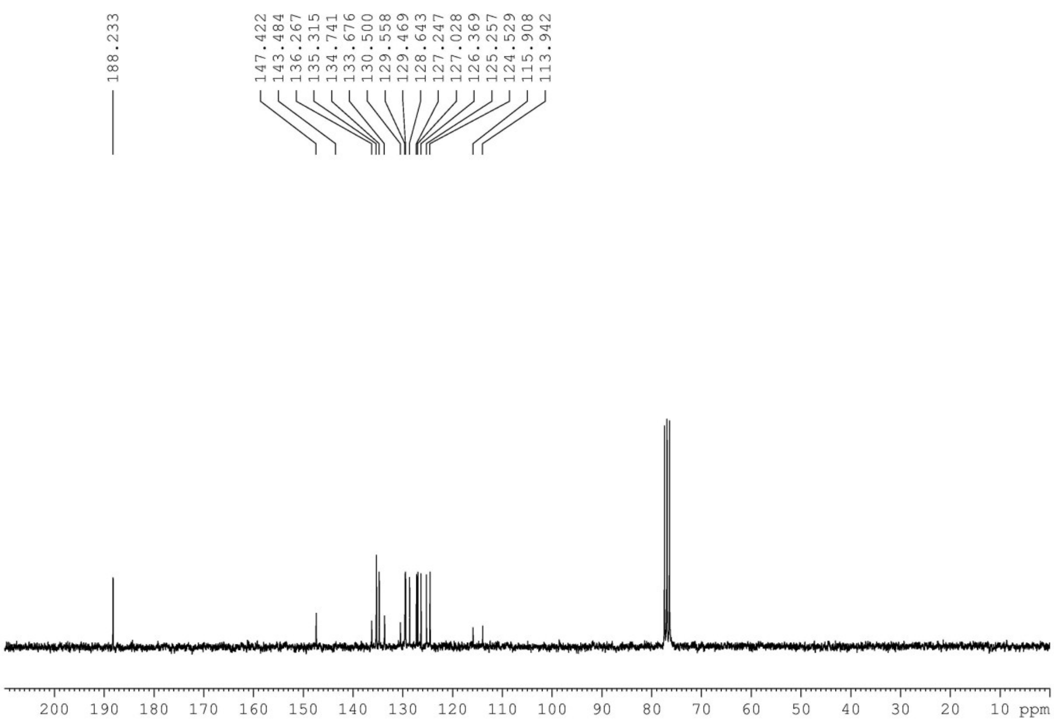
10.36
8.12
8.09
8.02
8.02
7.99
7.98
7.96
7.95
7.64
7.63
7.61
7.60
7.52
7.50
10
9
8
7
6
5
4
3
2
1
ppm
1.00
3.18
5.48

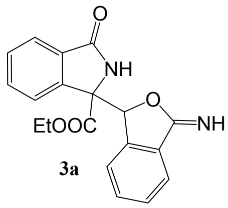


188.49
147.59
137.64
135.38
132.72
131.80
130.43
129.80
129.63
127.51
116.33
114.62
200
180
160
140
120
100
80
60
40
20
ppm

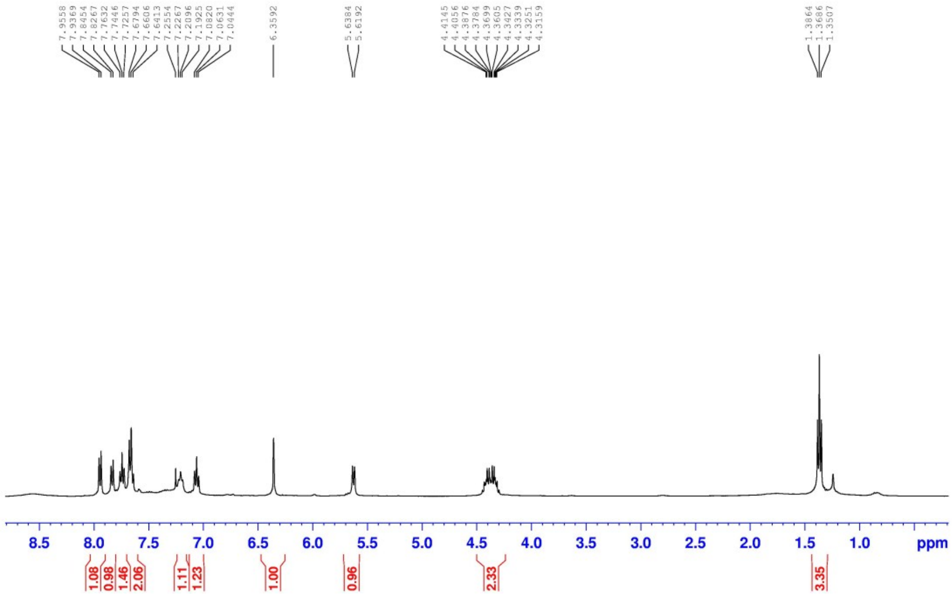

CN
O
H

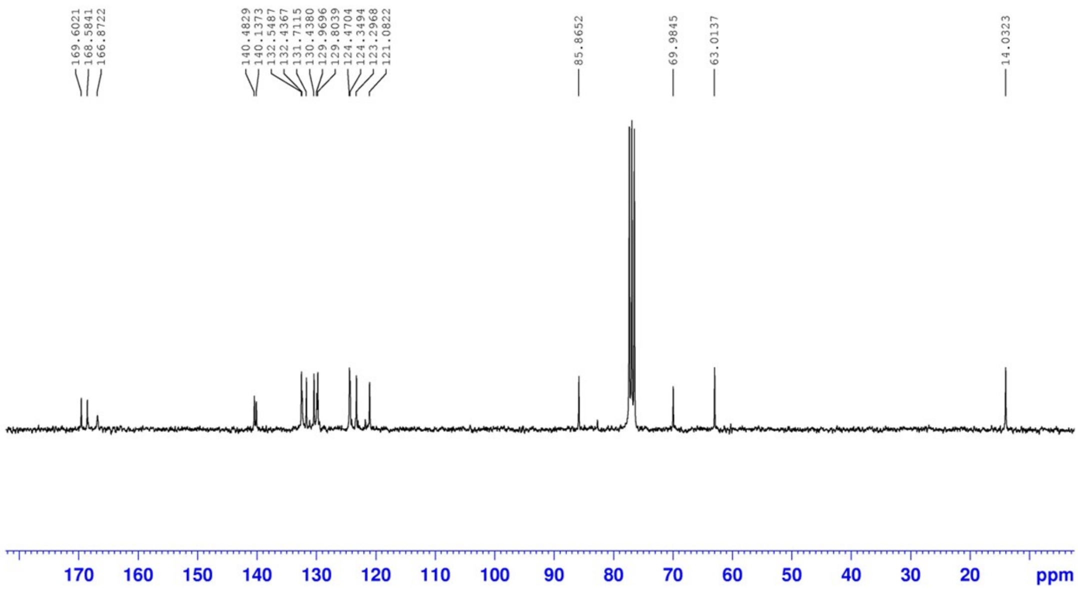

10.442
8.194
8.161
7.981
7.978
7.949
7.947
7.940
7.905
7.902
7.749
7.718
7.607
7.574
7.542
7.535
7.509
7.505
7.442
7.439
7.413
7.410
11
10
9
8
7
6
5
4
3
2
1
ppm
1.000
1.080
4.298
1.115
4.392

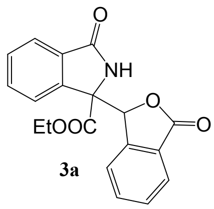

188.233
147.422
143.484
136.267
135.315
134.741
133.676
130.500
129.558
129.469
128.643
127.247
127.028
126.369
125.257
124.529
115.908
113.942
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm


O
NH
O
NH
EtOOC

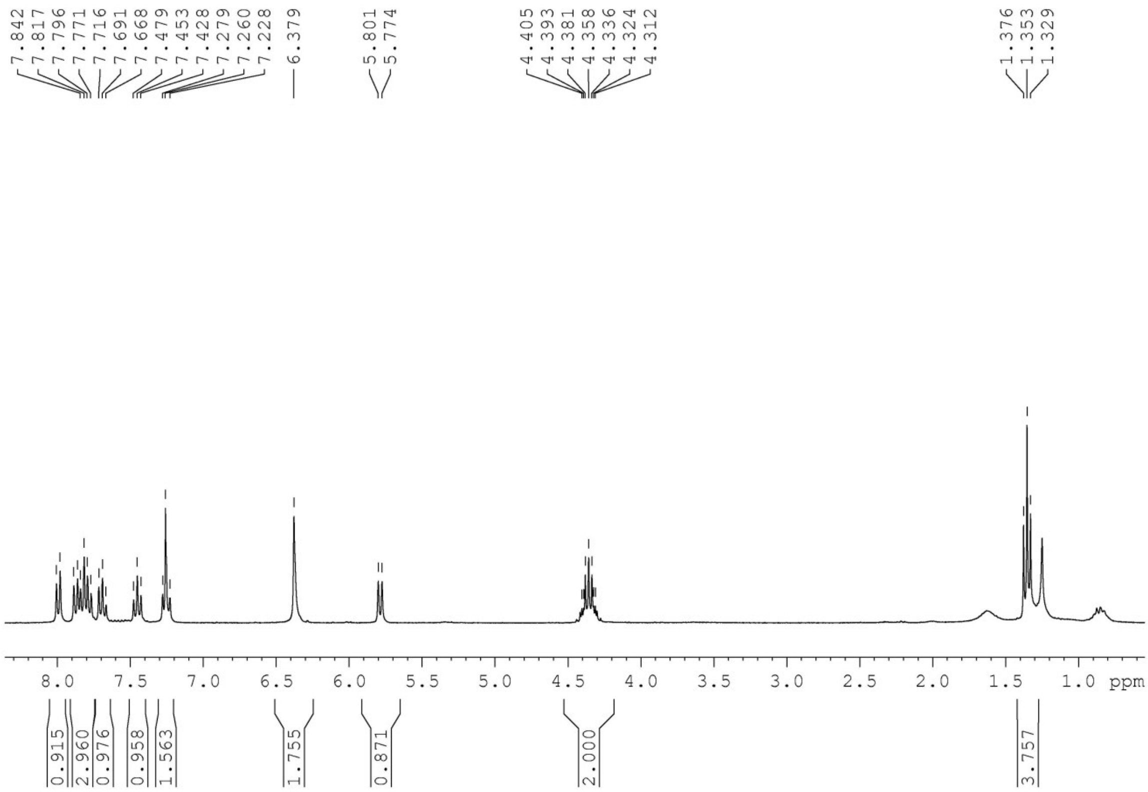
3a

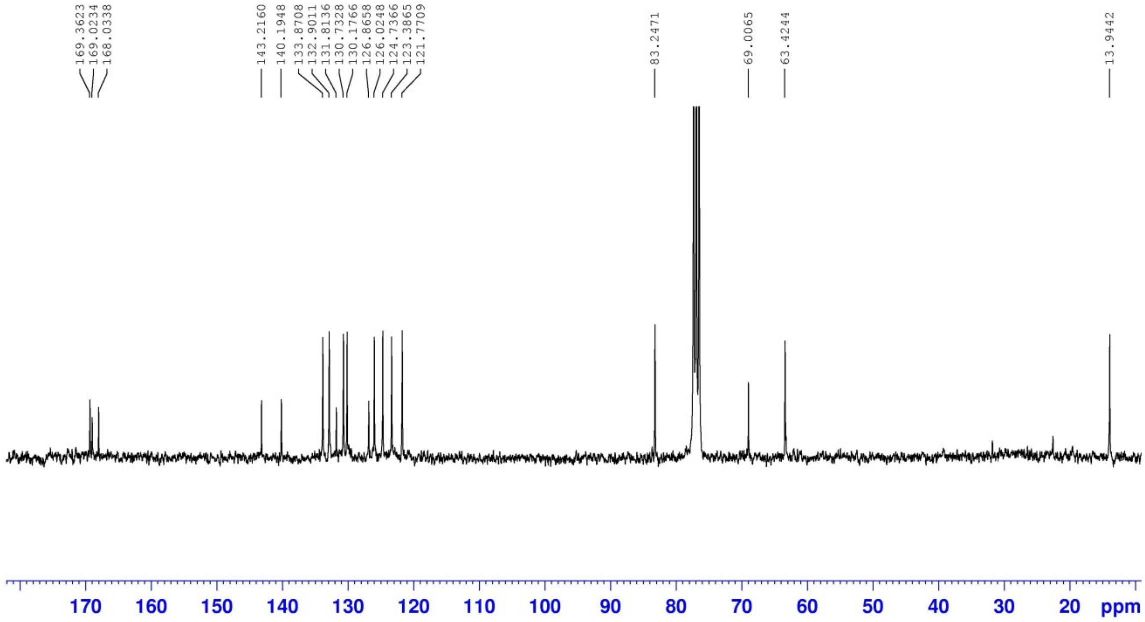

7.9558
7.9369
7.8454
7.8267
7.7632
7.7446
7.7257
7.6794
7.6606
7.6413
7.2354
7.2267
7.2096
7.1925
7.0820
7.0631
7.0444
6.3592
5.6384
5.6192
4.4145
4.4056
4.3876
4.3784
4.3699
4.3605
4.3427
4.3339
4.3251
4.3159
1.3864
1.3686
1.3507
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.08
0.98
1.46
2.06
1.11
1.23
1.00
0.96
2.33
3.35


169.6021
168.5841
166.8722
140.4829
140.1373
132.5487
132.4367
131.7115
130.4380
129.9696
129.8039
124.4704
124.3494
123.2968
121.0822
85.8652
69.9845
63.0137
14.0323
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

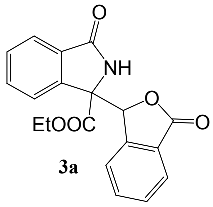

O
NH
O
O
EtOOC

3a

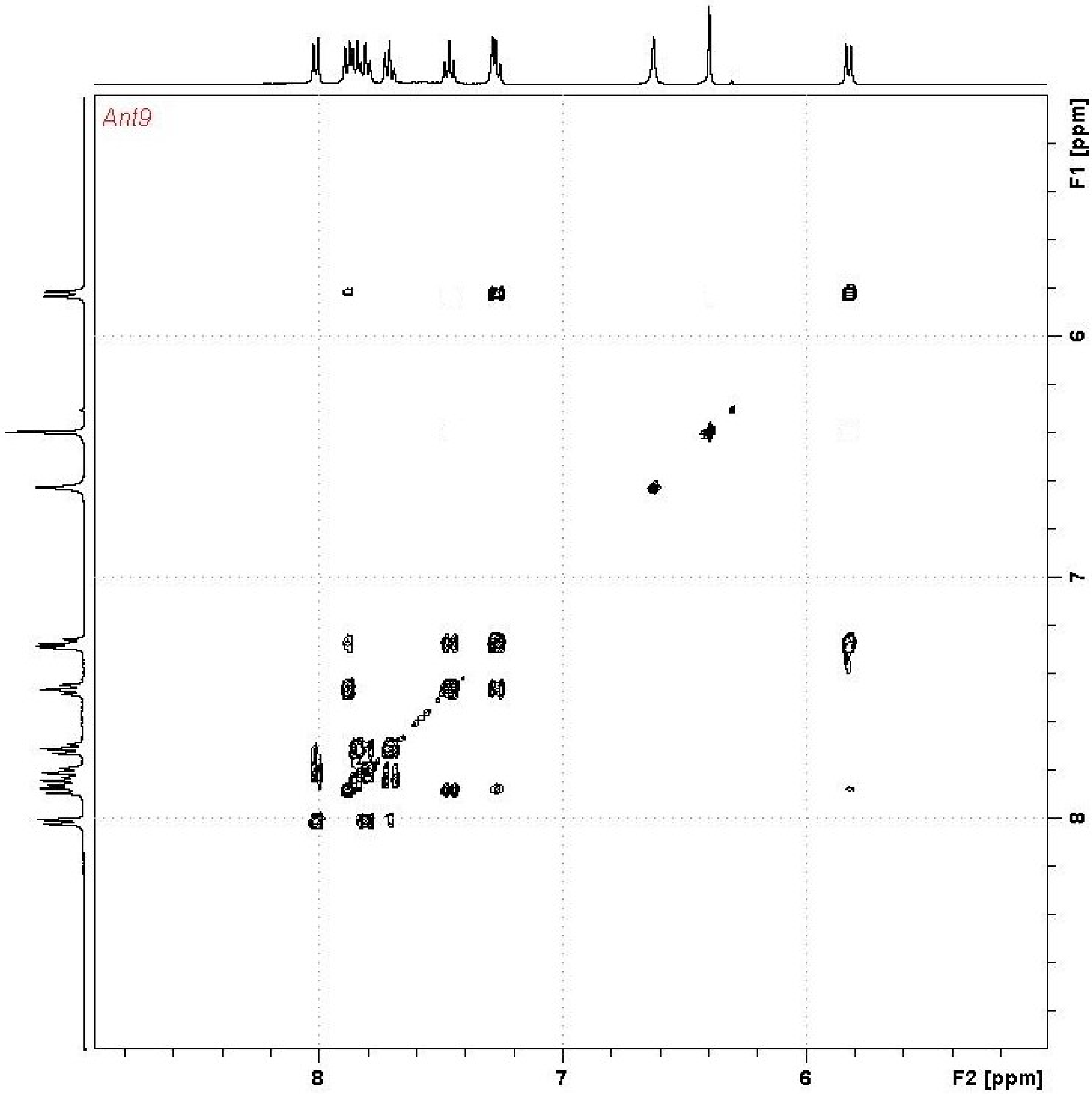

7.842
7.817
7.796
7.771
7.716
7.691
7.668
7.479
7.453
7.428
7.279
7.260
7.228
6.379
5.801
5.774
4.405
4.393
4.381
4.358
4.336
4.324
4.312
1.376
1.353
1.329
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.915
2.960
0.976
0.958
1.563
1.755
0.871
2.000
3.757

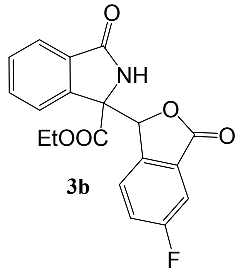

169.3623
169.0234
168.0338
143.2160
140.1948
133.8708
132.9011
131.8136
130.7328
130.1766
126.8658
126.0248
124.7366
123.3865
121.7709
83.2471
69.0065
63.4244
13.9442
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

COSY-NMR

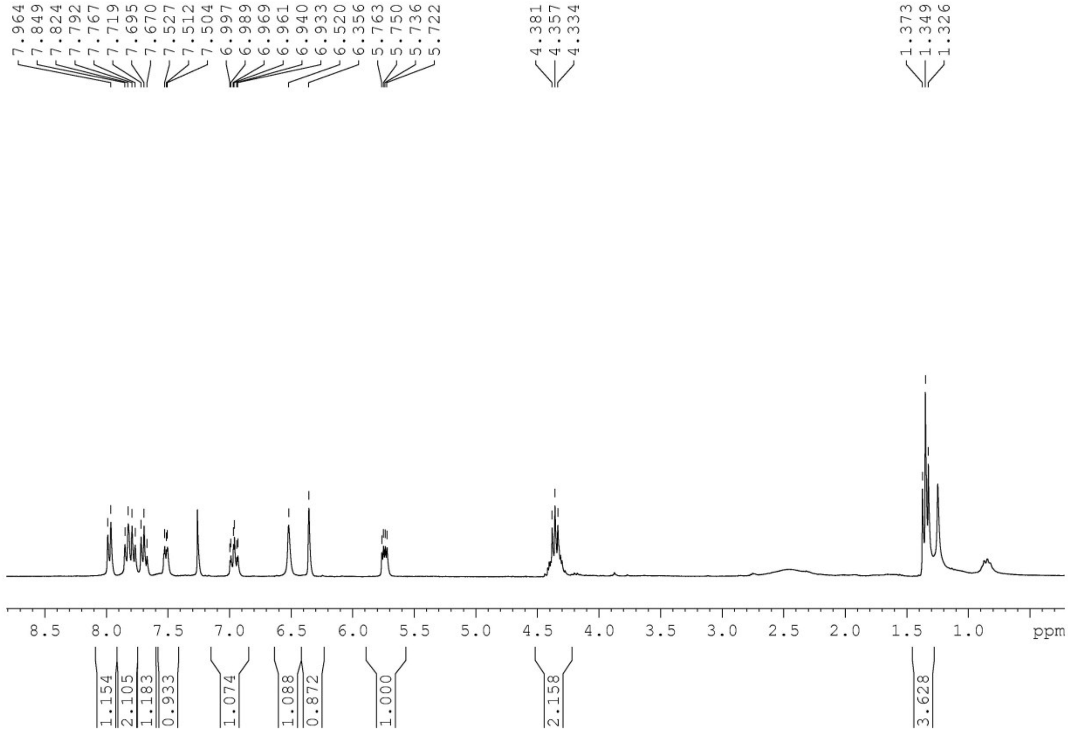


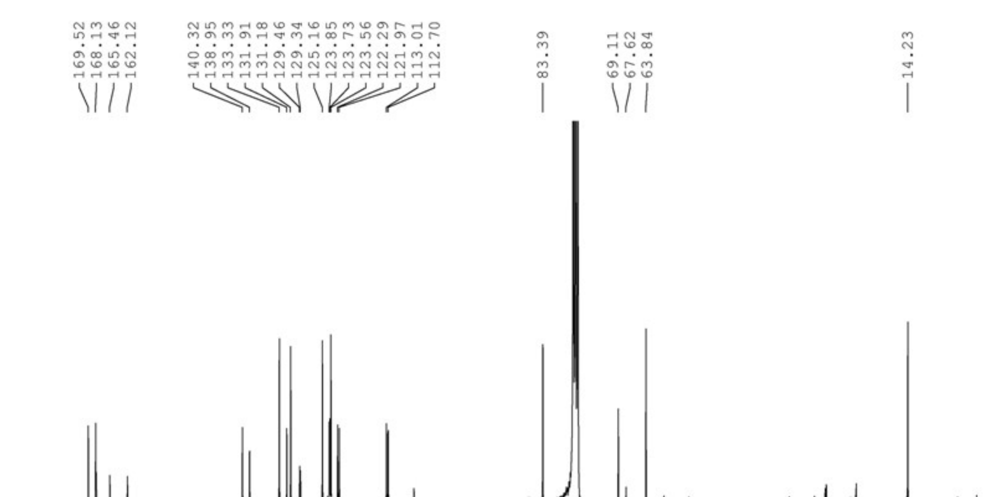
3a

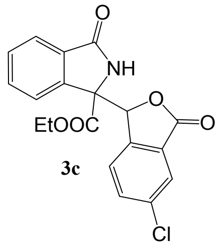




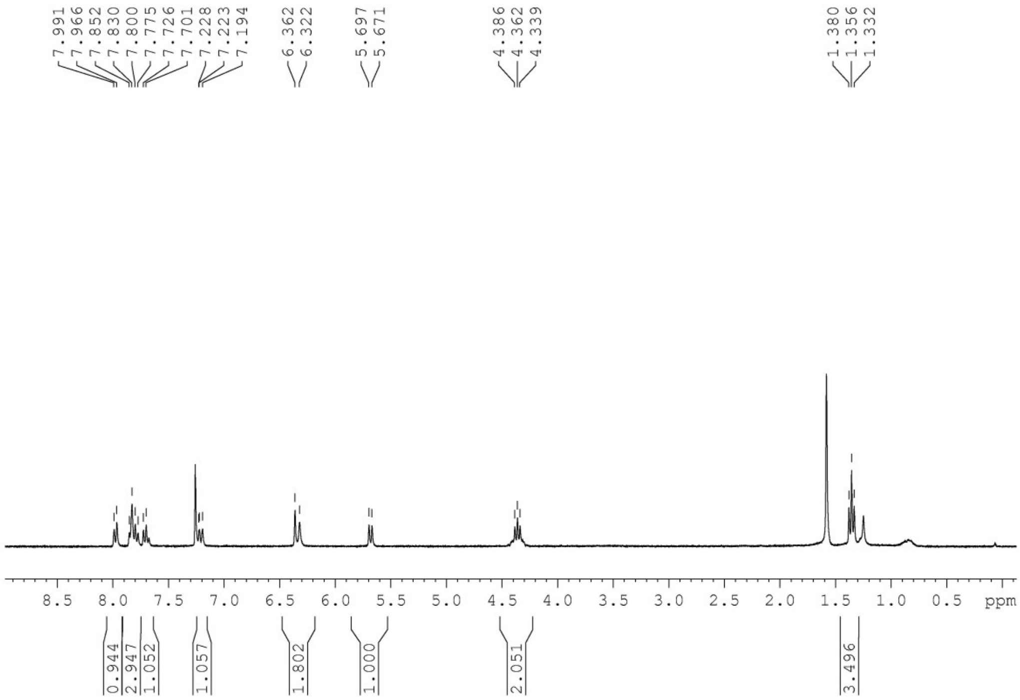
O
NH
EtOOC
O
O
F
3b

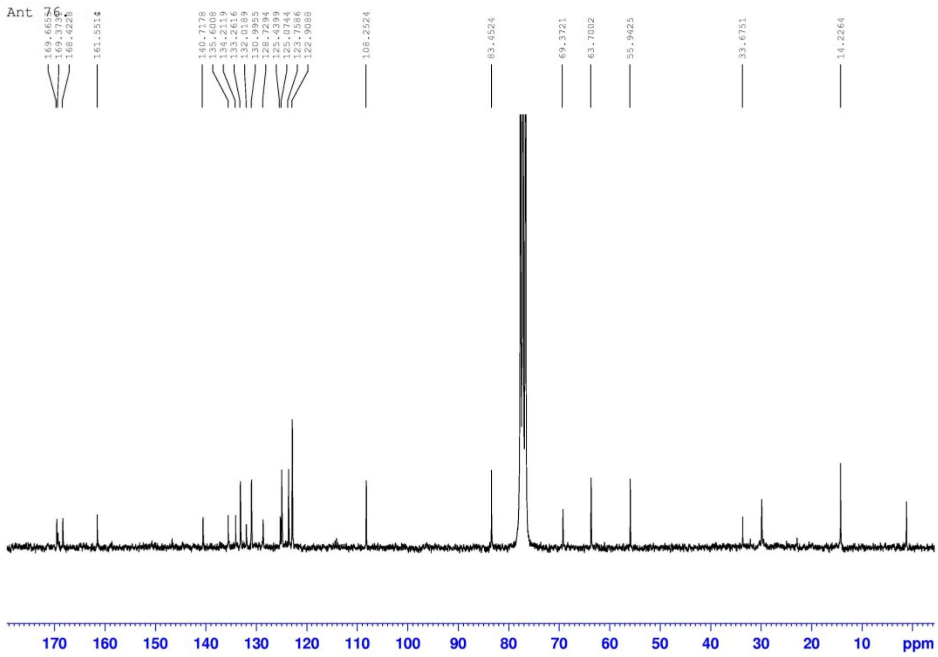


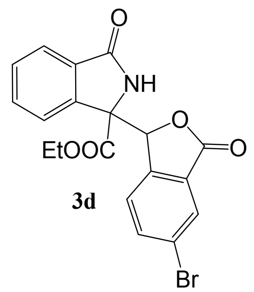



O
NH
O
O
EtOOC
Cl

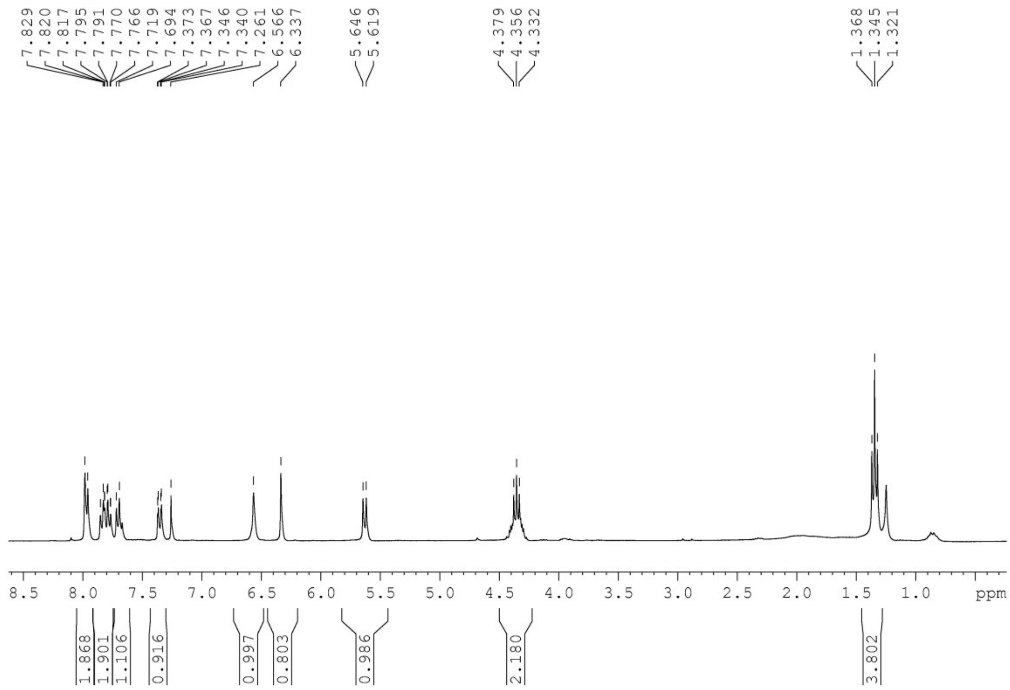
3c

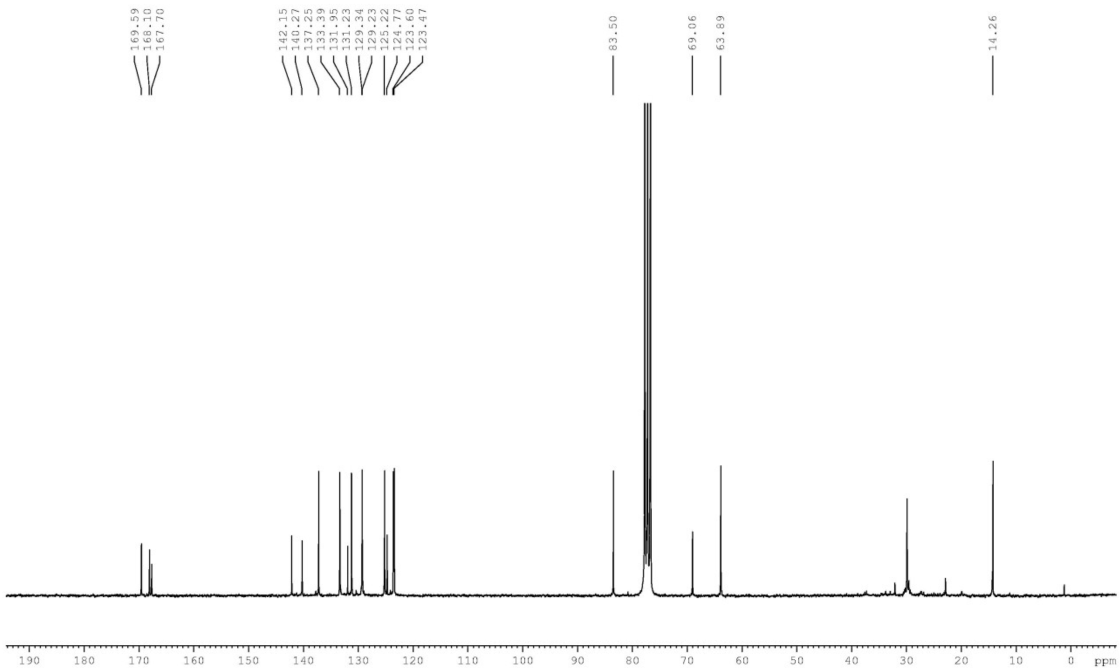

7.991
7.966
7.852
7.830
7.800
7.775
7.726
7.701
7.228
7.223
7.194
6.362
6.322
5.697
5.671
4.386
4.362
4.339
1.380
1.356
1.332
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.944
2.947
1.052
1.057
1.802
1.000
2.051
3.496

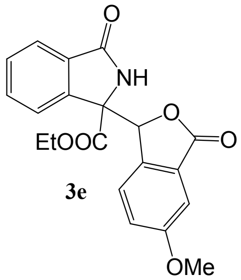

161.5514
140.7178
108.2524
83.4524
69.3721
63.7002
55.9425
33.6751
14.2264
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
NH
O
O
EtOOC
Br

3d

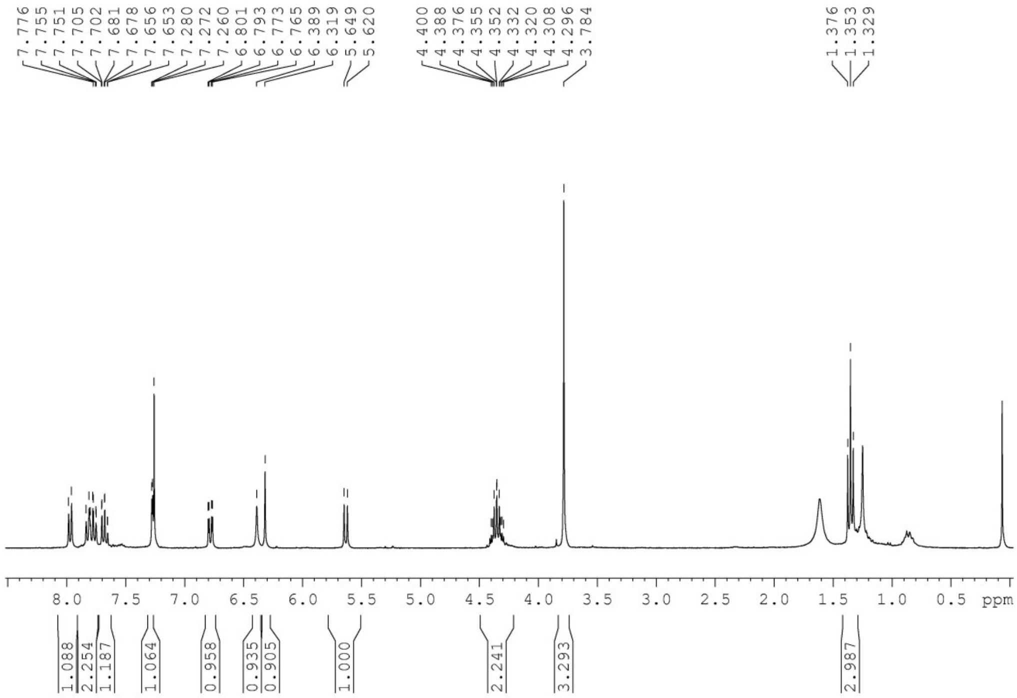

7.829
7.820
7.817
7.795
7.791
7.770
7.766
7.719
7.694
7.373
7.367
7.346
7.340
7.261
6.566
6.337
5.646
5.619
4.379
4.356
4.332
1.368
1.345
1.321
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.868
1.901
1.106
0.916
0.997
0.803
0.986
2.180
3.802


169.59
168.10
167.70
142.15
140.27
137.25
133.39
131.95
131.23
129.34
129.23
125.22
124.77
123.60
123.47
83.50
69.06
63.89
14.26
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

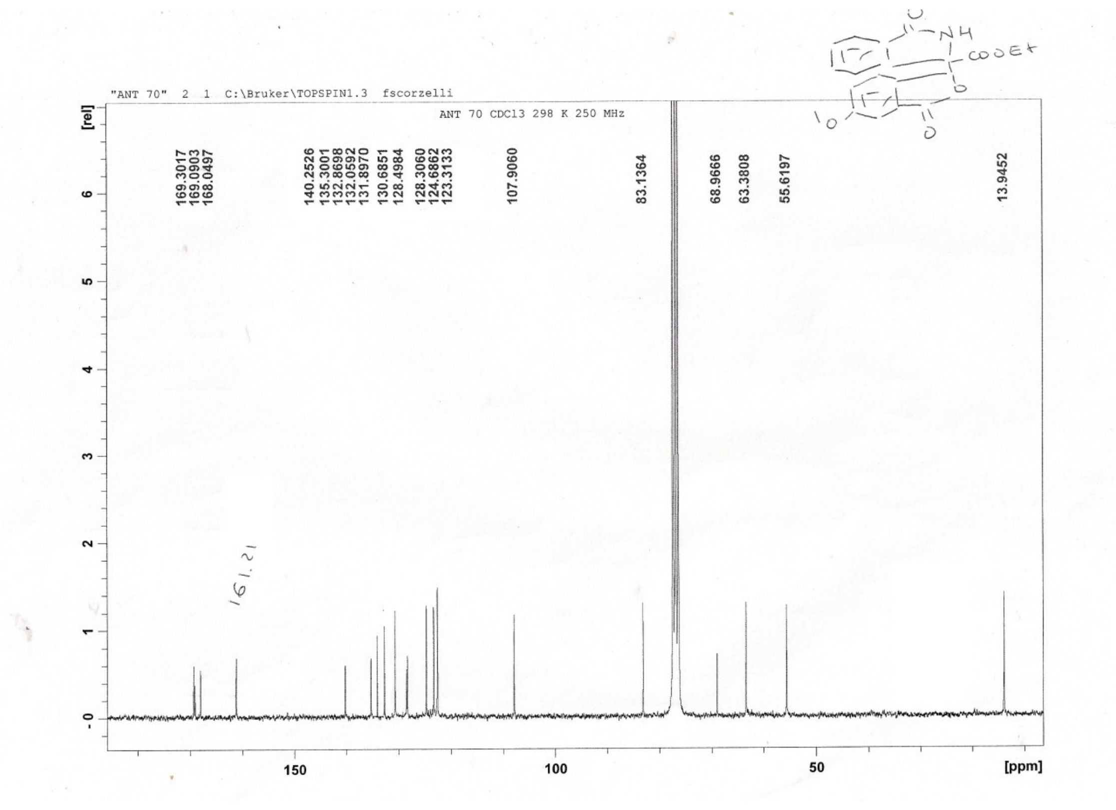


O
NH
EtOOC
O
O
OMe

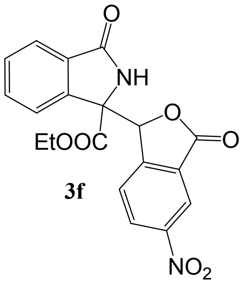
3e



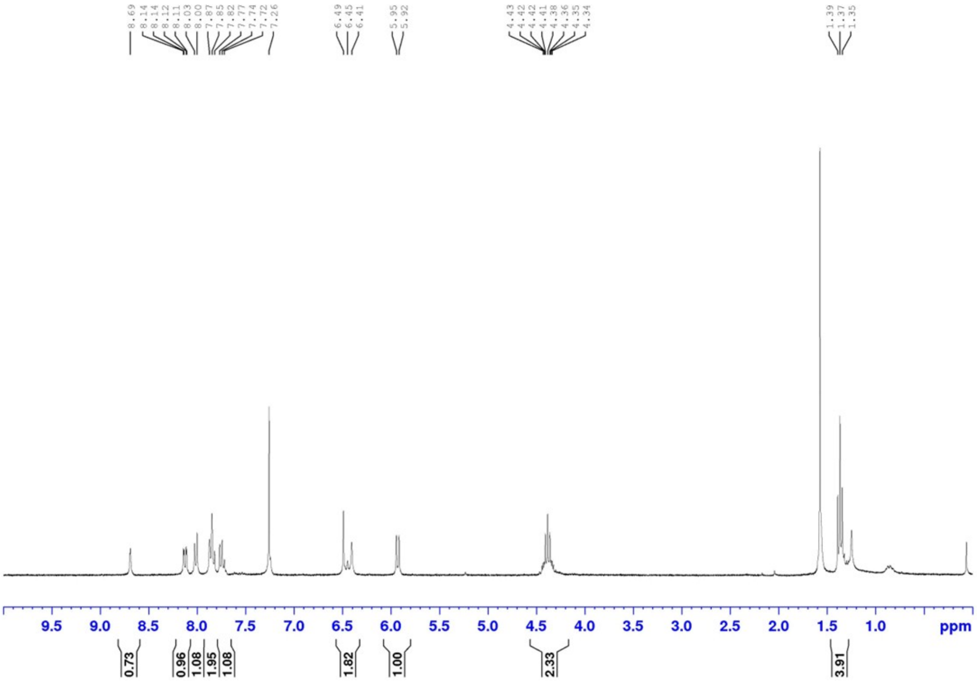
7.776
7.755
7.751
7.705
7.702
7.681
7.678
7.656
7.653
7.280
7.272
7.260
6.801
6.793
6.773
6.765
6.389
6.319
5.649
5.620
4.400
4.388
4.376
4.355
4.352
4.332
4.320
4.308
4.296
3.784
1.376
1.353
1.329
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.088
2.254
1.187
1.064
0.958
0.935
0.905
1.000
2.241
3.293
2.987

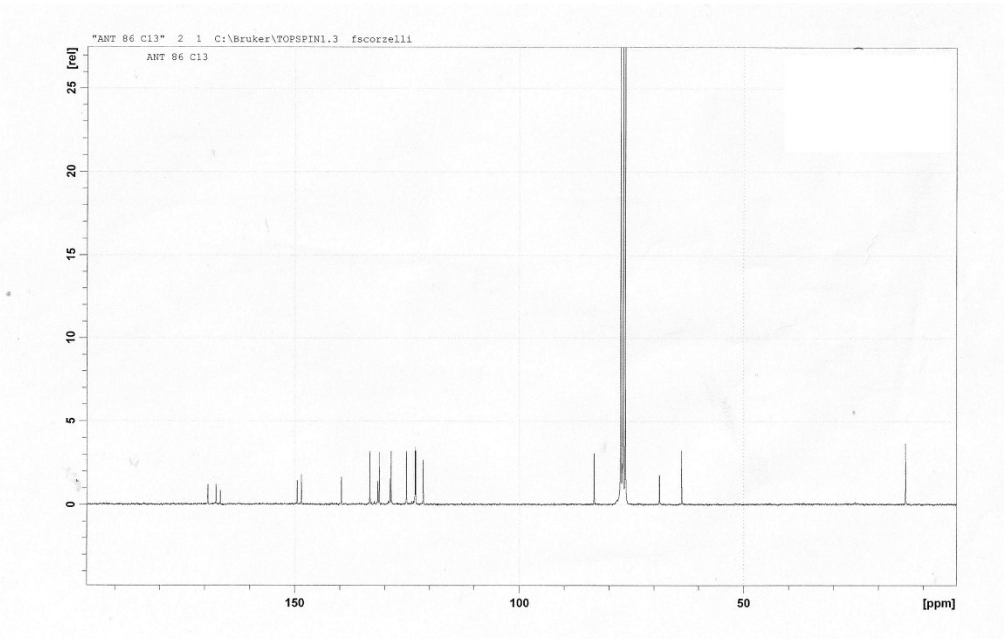


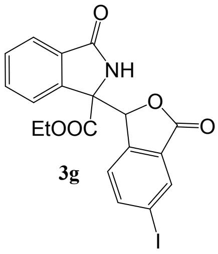
"ANT 70" 2 1 C:\Bruker\TOPSPIN1.3 fscorzelli
ANT 70 CDCl3 298 K 250 MHz
NH
COOEt
[rel]
169.3017
169.0903
168.0497
140.2526
135.3001
132.8698
132.0592
131.8970
130.6851
128.4984
128.3060
124.6862
123.3133
107.9060
83.1364
68.9666
63.3808
55.6197
13.9452
161.21
6
5
4
3
2
1
0
150
100
50
[ppm]


O
NH
EtOOC
O
O
NO2

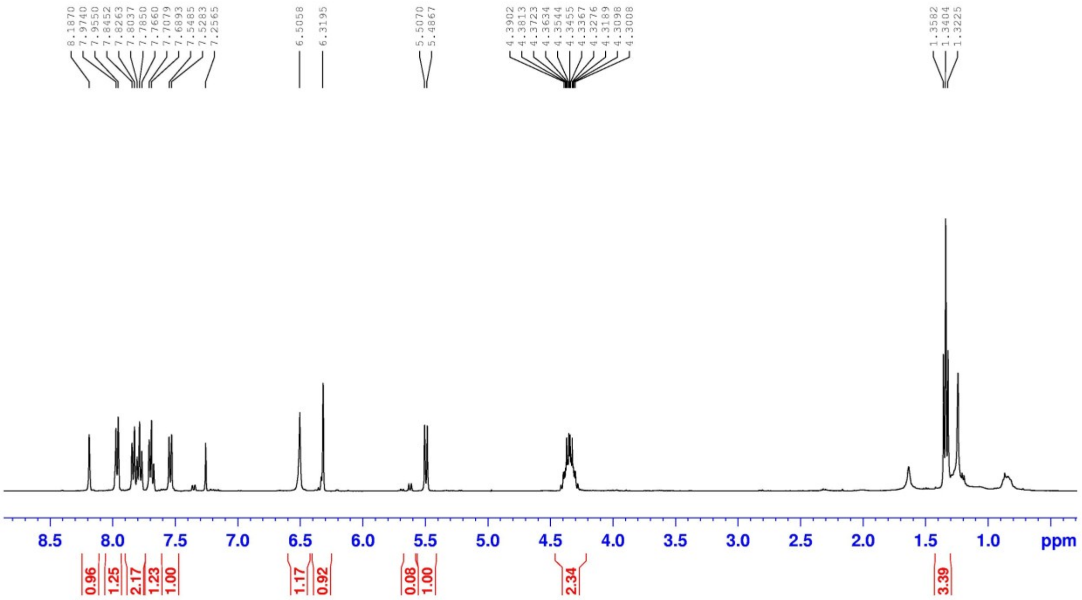
3f

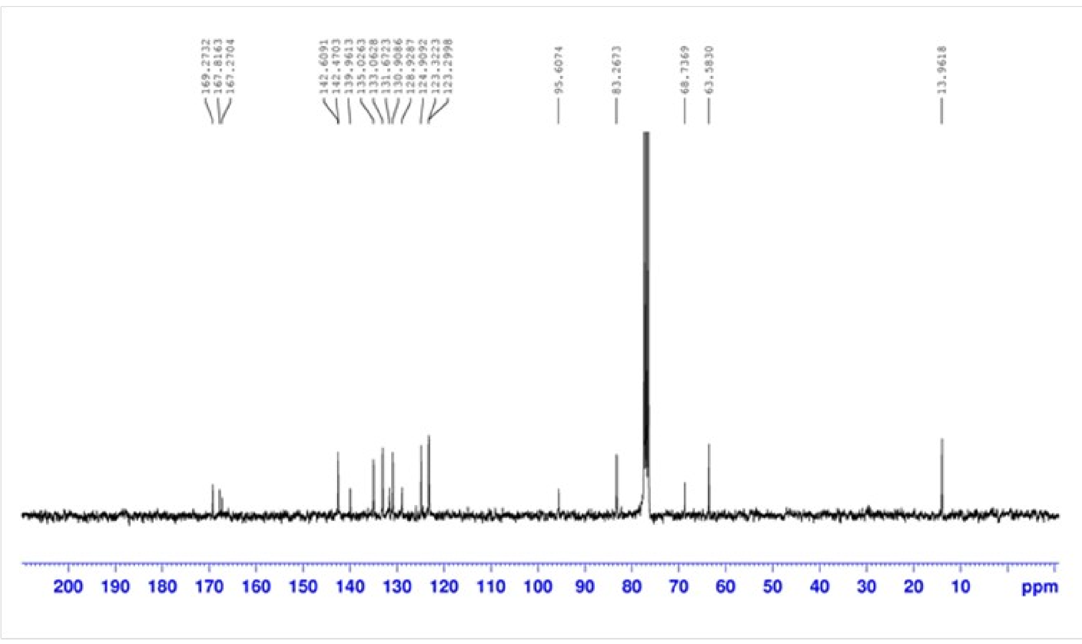

8.69
8.14
8.14
8.12
8.11
8.03
8.00
7.87
7.85
7.82
7.77
7.74
7.72
7.26
6.49
6.45
6.41
5.95
5.92
4.43
4.42
4.42
4.41
4.38
4.36
4.35
4.34
1.39
1.37
1.35
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.73
0.96
1.08
1.95
1.08
1.82
1.00
2.33
3.91

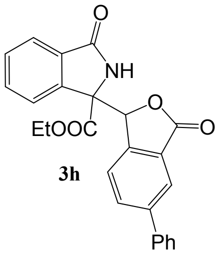

"ANT 86 C13" 2 1 C:\Bruker\TOPSPIN1.3 fscorzelli
ANT 86 C13
[rel]
25
20
15
10
5
0
150
100
50
[ppm]


O
NH
O
O
EtOOC
I

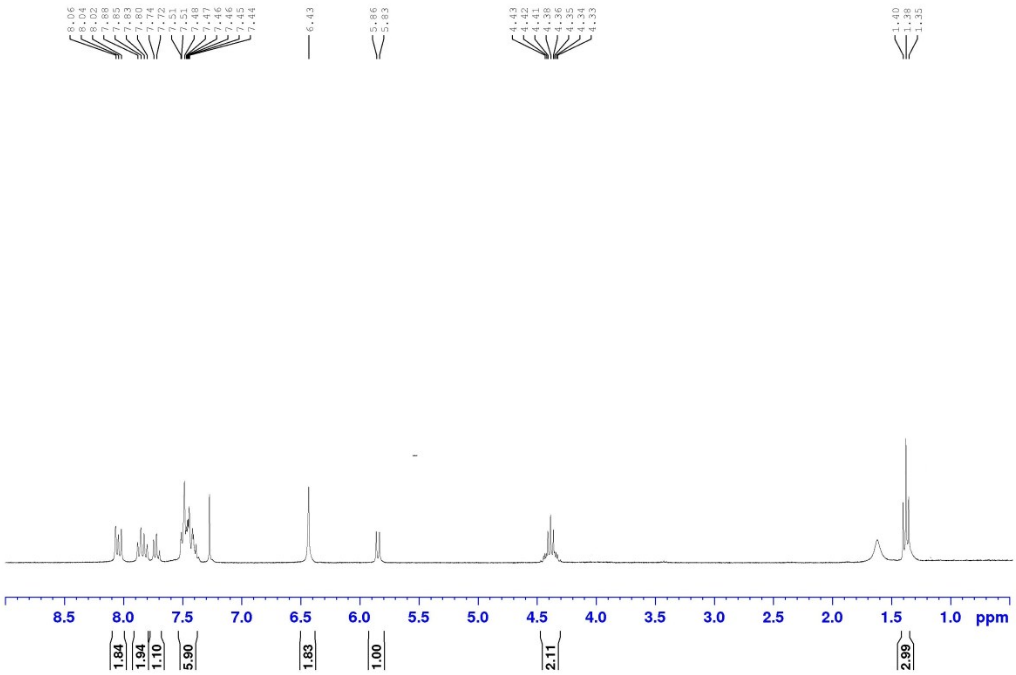
3g

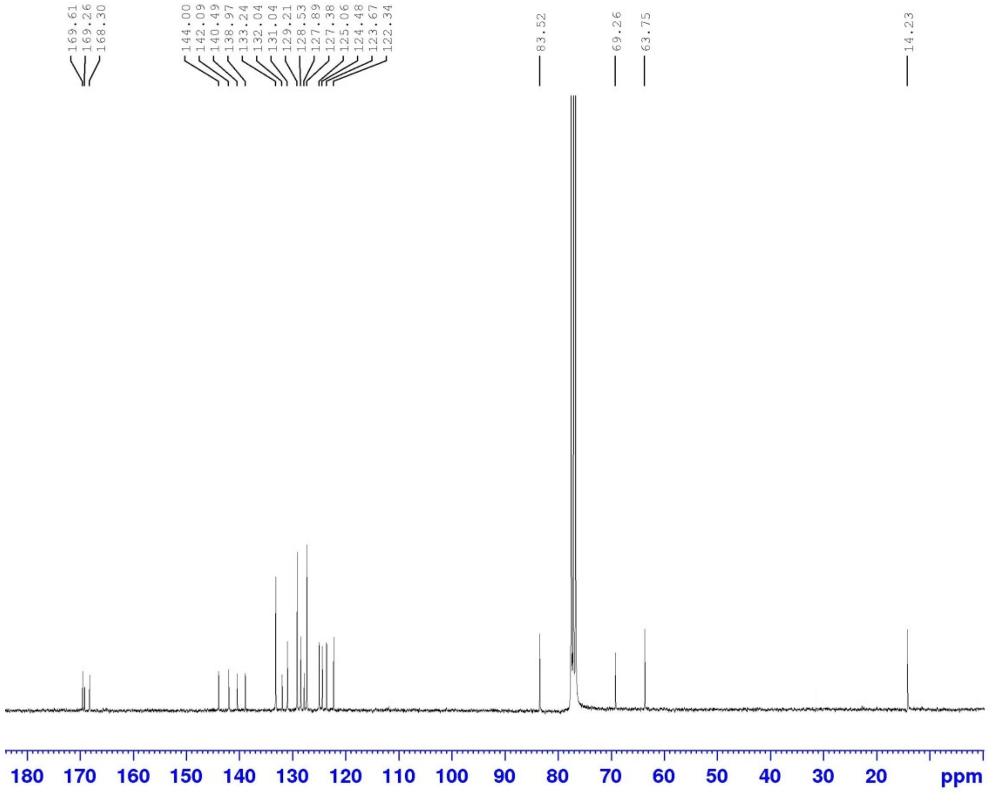

8.1870
7.9740
7.9550
7.8452
7.8263
7.8037
7.7850
7.7660
7.7079
7.6893
7.5485
7.5283
7.2565
6.5058
6.3195
5.5070
5.4867
4.3902
4.3813
4.3723
4.3634
4.3544
4.3455
4.3367
4.3276
4.3189
4.3098
4.3008
1.3582
1.3404
1.3225
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.96
1.25
2.17
1.23
1.00
1.17
0.92
0.08
1.00
2.34
3.39

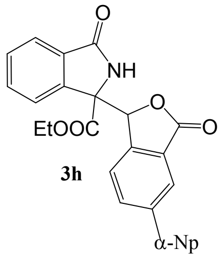

169.2732
167.8163
167.2704
142.6091
142.4703
139.9613
135.0263
133.0628
131.6723
130.9086
128.9287
124.9092
123.3223
123.2998
95.6074
83.2673
68.7369
63.5830
13.9618
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
NH
O
O
EtOOC
Ph

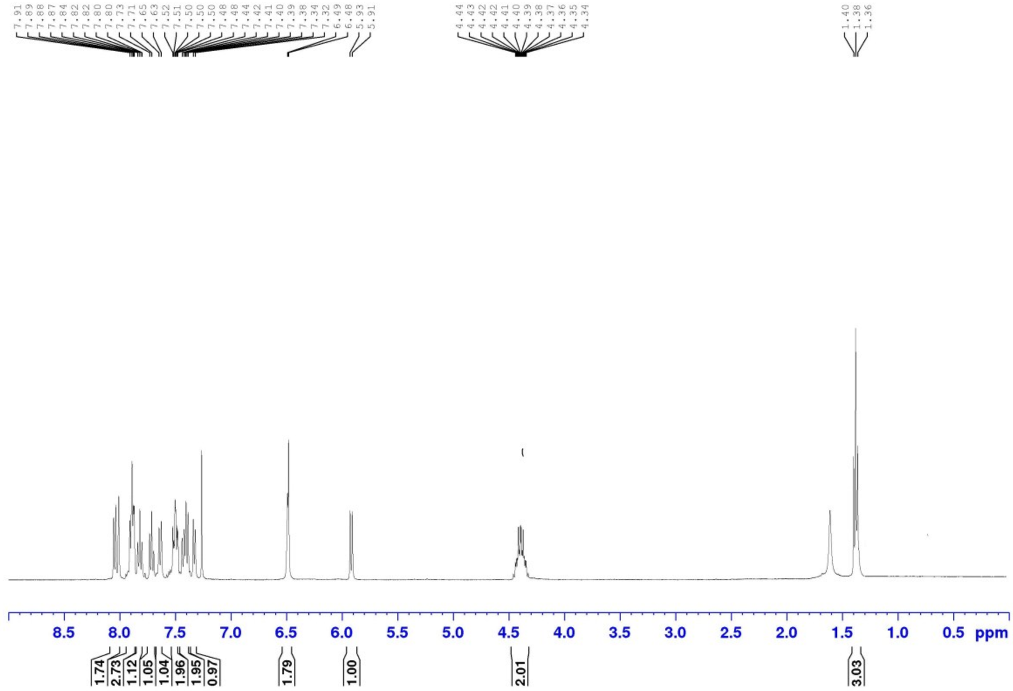
3h

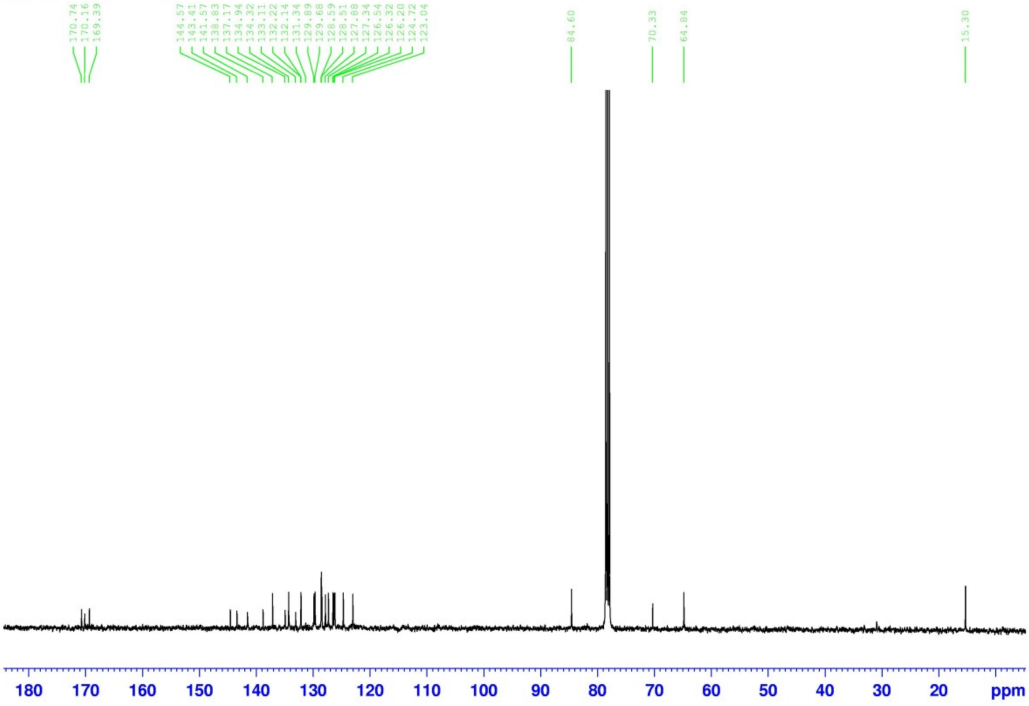

8.06 8.04 8.02 7.88 7.85 7.83 7.80 7.74 7.72 7.51 7.51 7.48 7.47 7.46 7.46 7.45 7.44
6.43
5.86 5.83
4.43 4.42 4.41 4.38 4.36 4.35 4.34 4.33
1.40 1.38 1.35
1.84 1.94 1.10 5.90 1.83 1.00 2.11 2.99
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

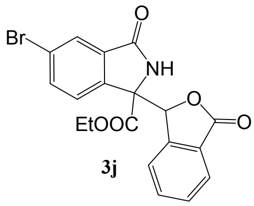

169.61 169.26 168.30
144.00 142.09 140.49 138.97 133.24 132.04 131.04 129.21 128.53 127.89 127.38 125.06 124.48 123.67 122.34
83.52
69.26
63.75
14.23
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



3h

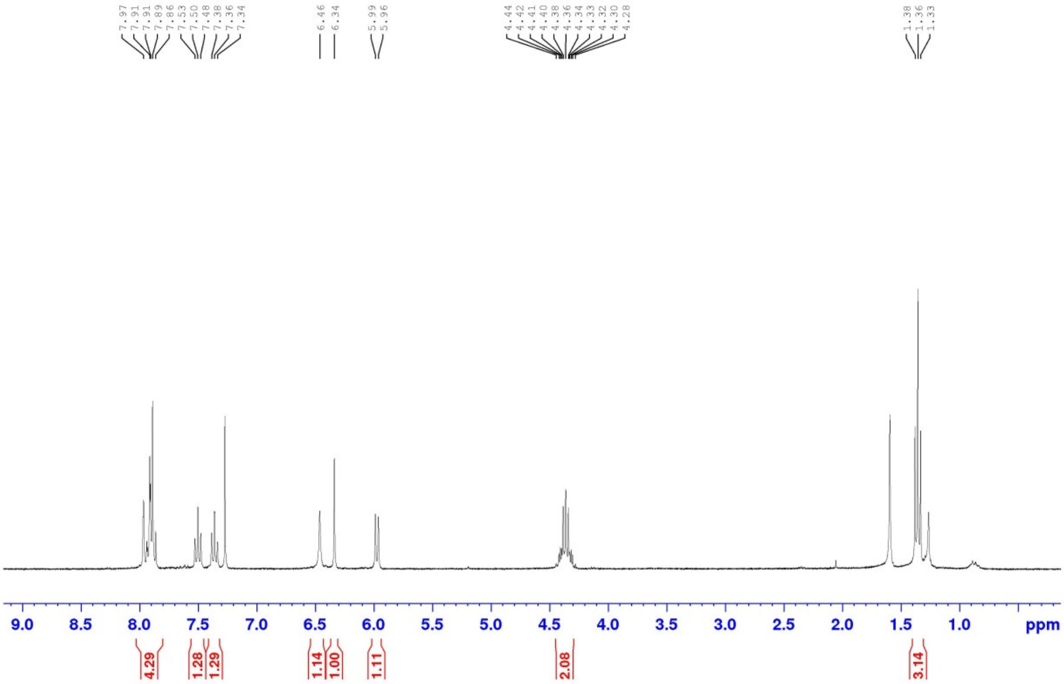




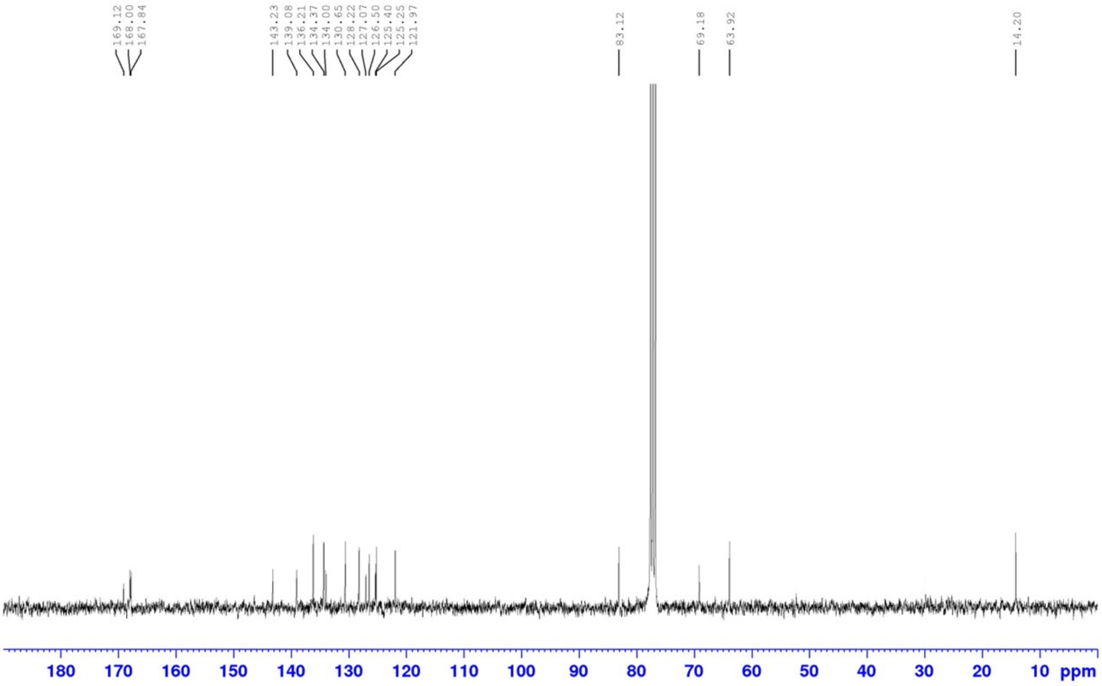


Br
O
NH
O
O
EtOOC

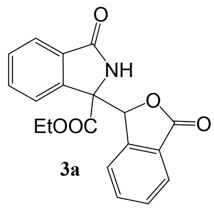
3j



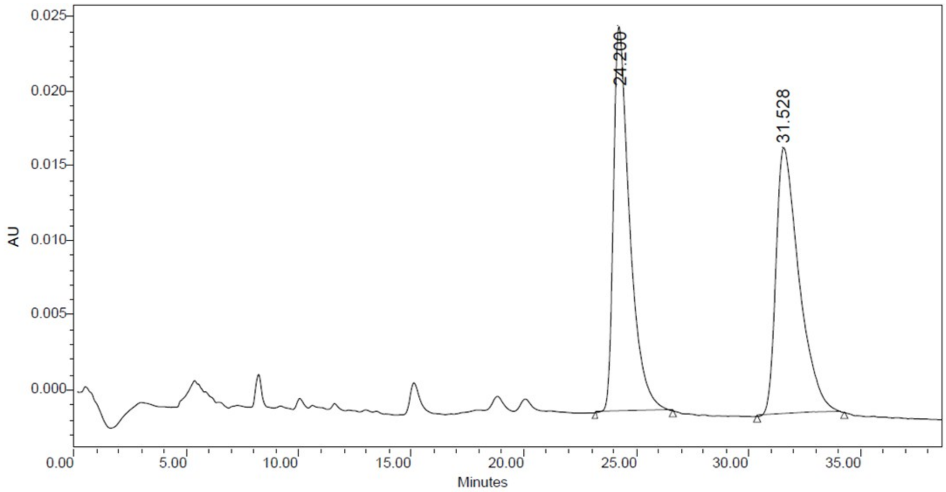
7.97 7.91 7.91 7.89 7.86 7.53 7.50 7.48 7.38 7.36 7.34
6.46 6.34
5.99 5.96
4.44 4.42 4.41 4.40 4.38 4.36 4.34 4.33 4.32 4.30 4.28
1.38 1.36 1.33
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.29 1.28 1.29 1.14 1.00 1.11 2.08 3.14



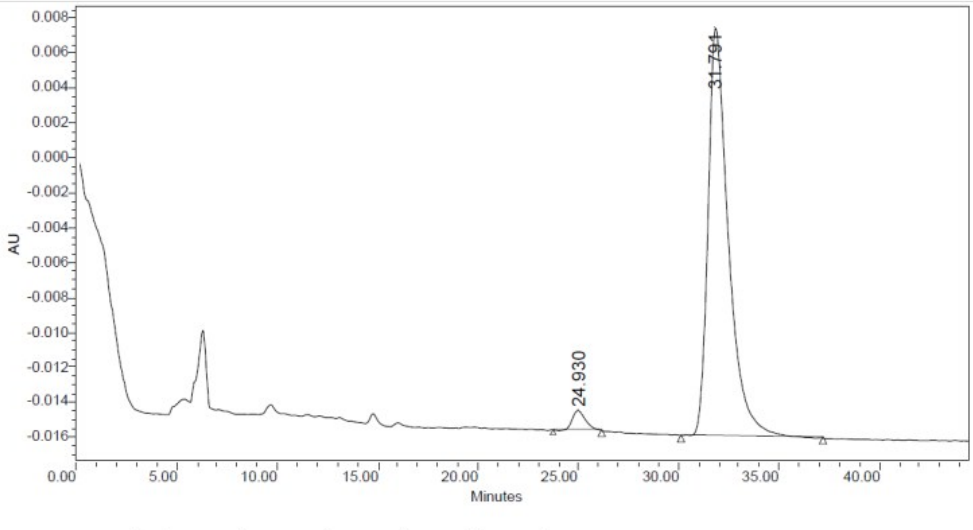
169.12 168.00 167.84
143.23 139.08 136.21 134.37 134.00 130.65 128.22 127.07 126.50 125.40 125.25 121.97
83.12
69.18
63.92
14.20
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



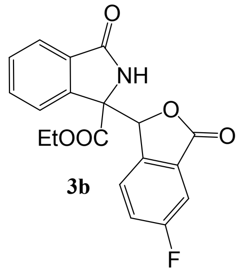
3a



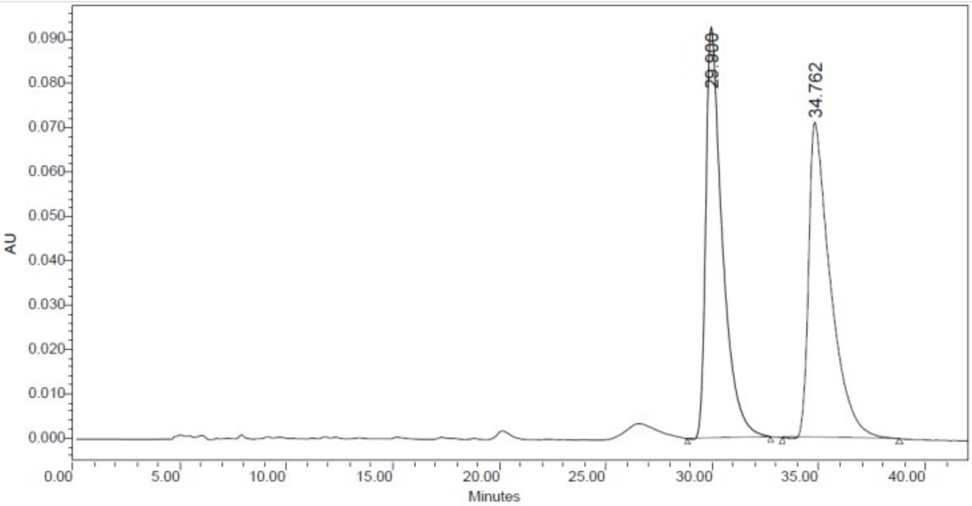
	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	24.200	1307691	49.02	25852	59.05
2	31.528	1360071	50.98	17926	40.95



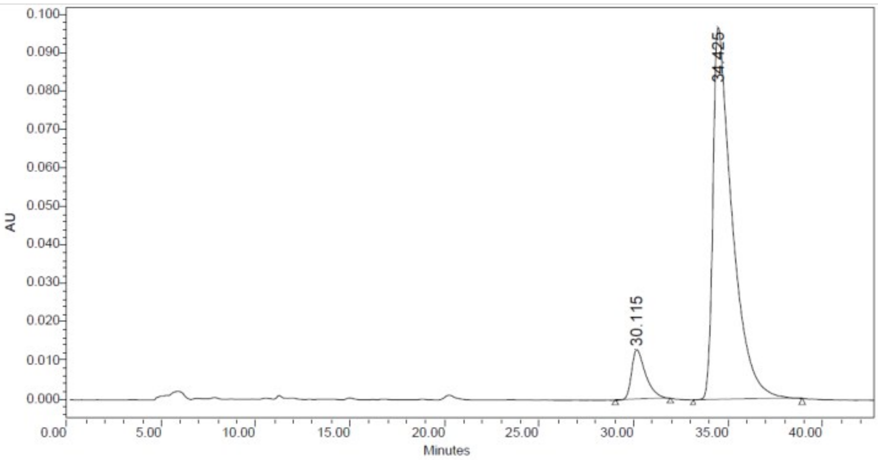
	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	24.930	53353	3.12	1128	4.61
2	31.791	1655764	96.88	23367	95.39



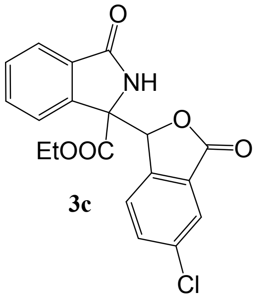
3b



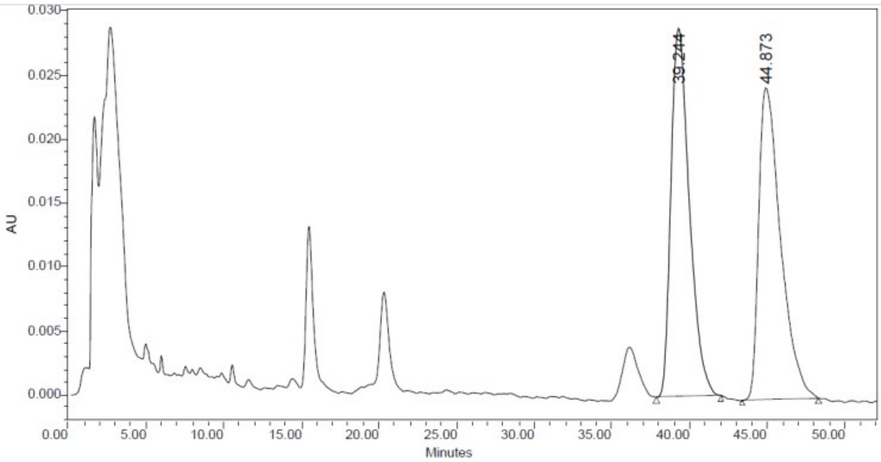
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	29.900	5014346	49.66	92809	56.54
2	34.762	5082021	50.34	71341	43.46



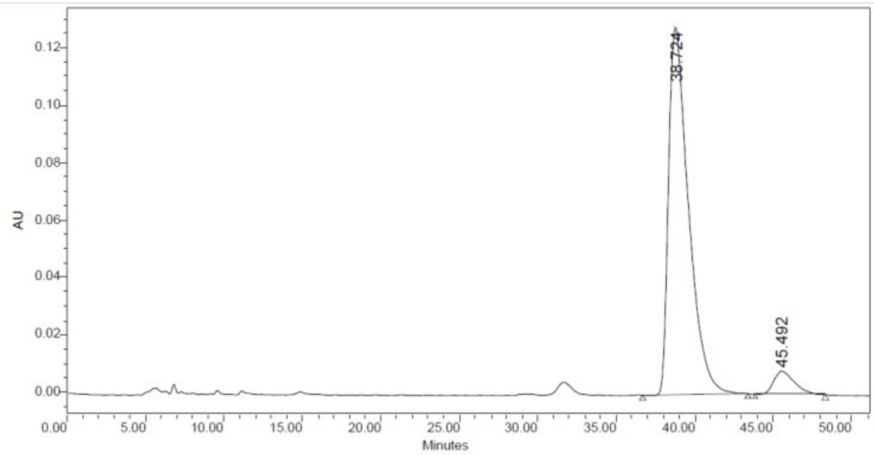
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	30.115	674814	8.96	12965	11.82
2	34.425	6858401	91.04	96740	88.18



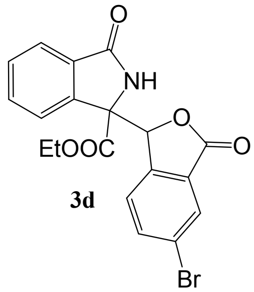
3c



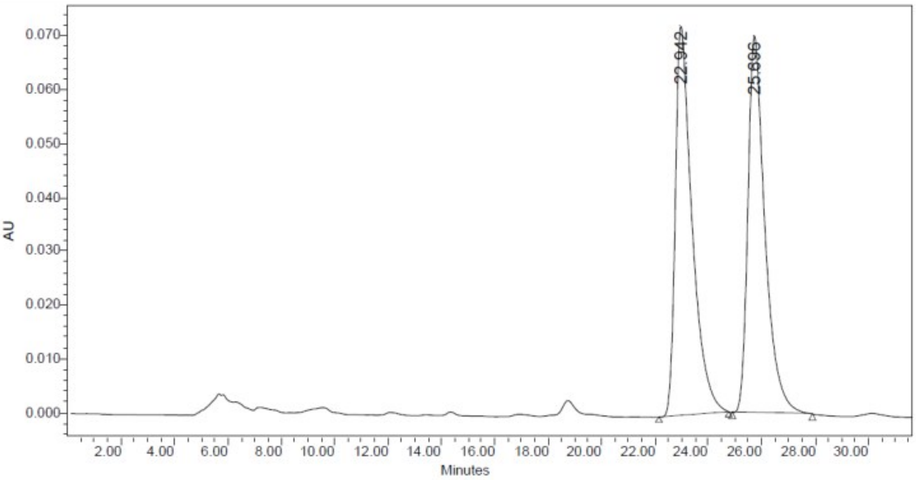
	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	39.244	2376219	49.74	28791	54.16
2	44.873	2400672	50.26	24371	45.84



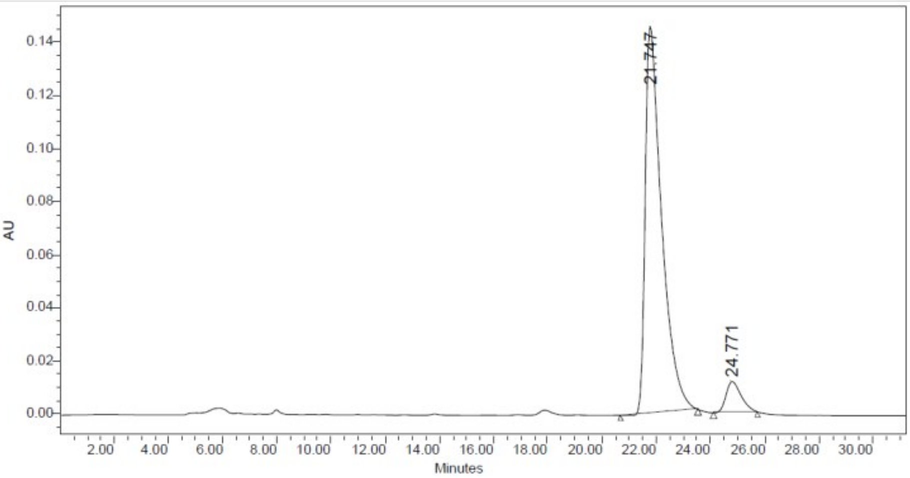
	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	38.724	11343947	93.90	127934	94.10
2	45.492	736707	6.10	8021	5.90



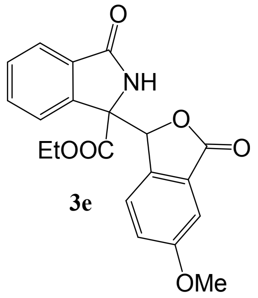
3d



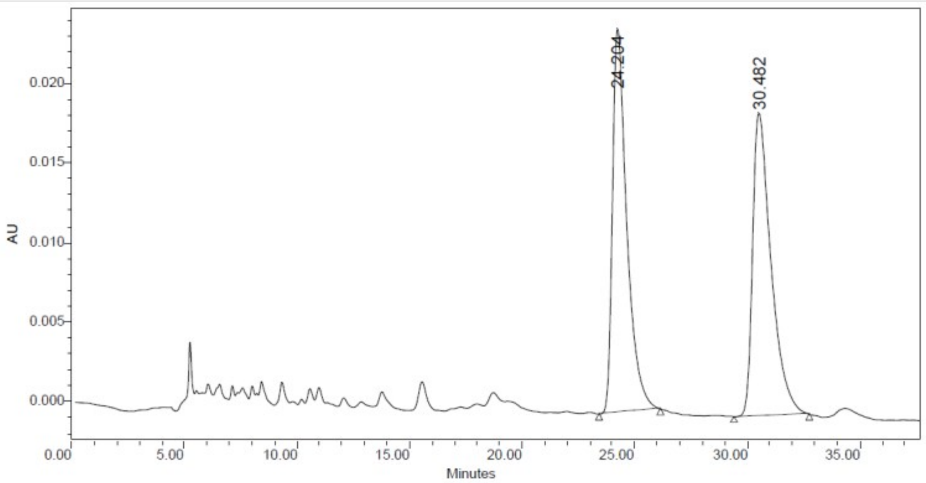
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	22.942	3166747	50.36	72418	50.81
2	25.696	3121610	49.64	70105	49.19



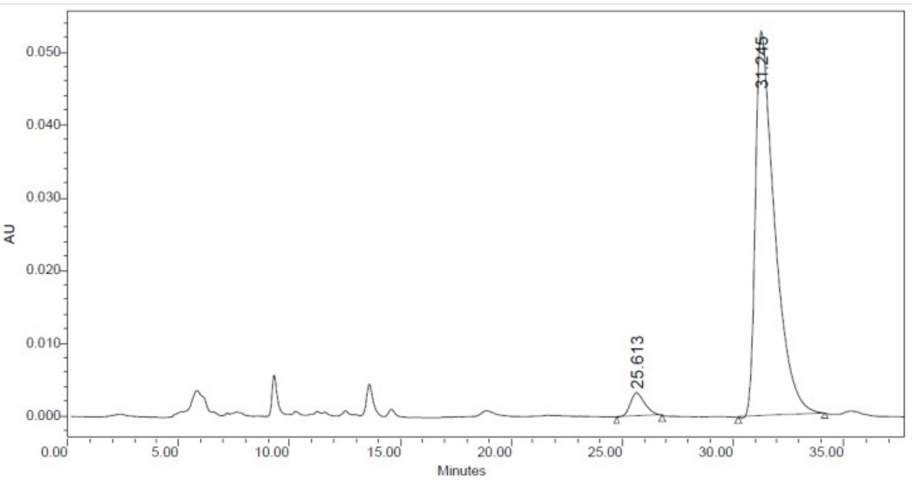
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.747	6155494	93.09	145240	92.58
2	24.771	456756	6.91	11644	7.42



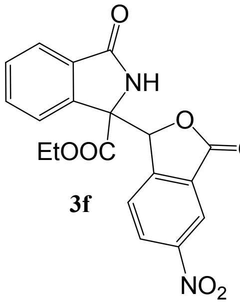
3e



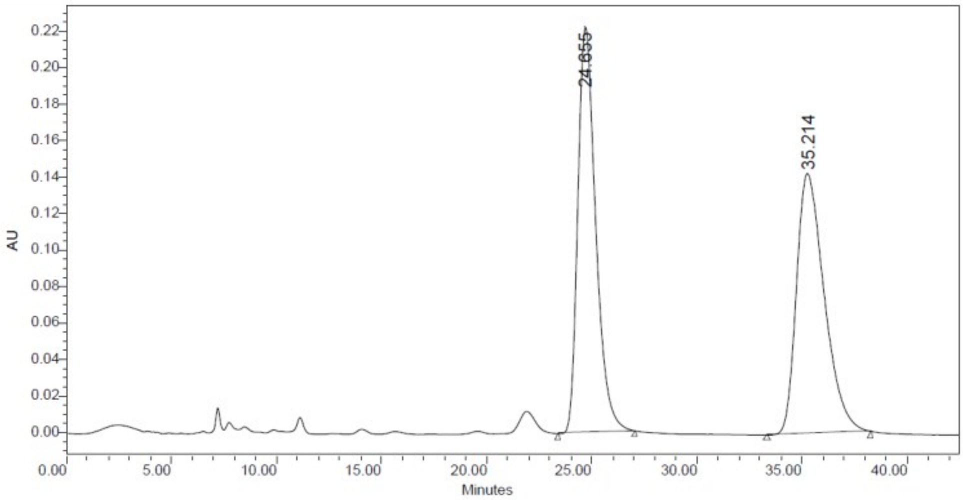
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	24.204	1070784	49.57	24127	55.88
2	30.482	1089210	50.43	19046	44.12



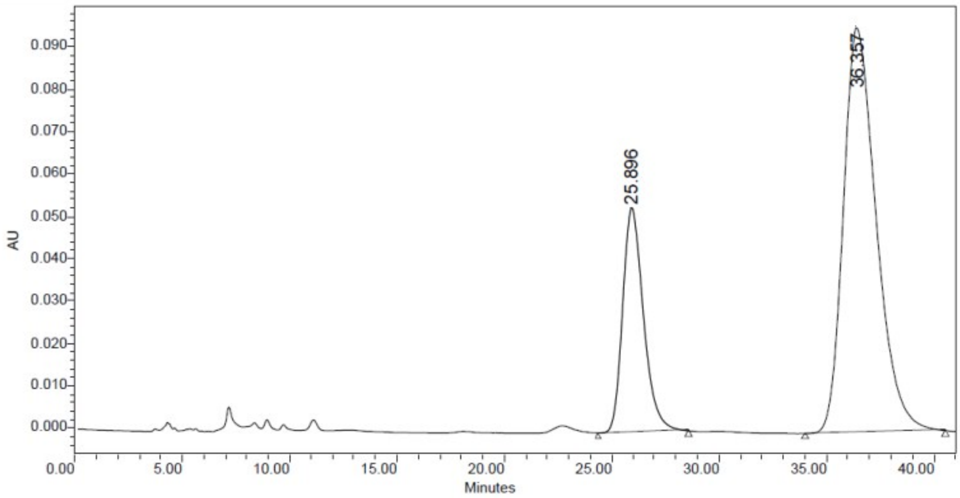
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	25.613	151495	4.50	3225	5.74
2	31.245	3217205	95.50	52949	94.26



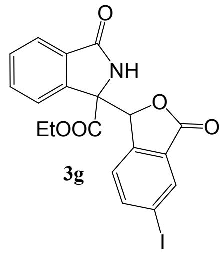
3f



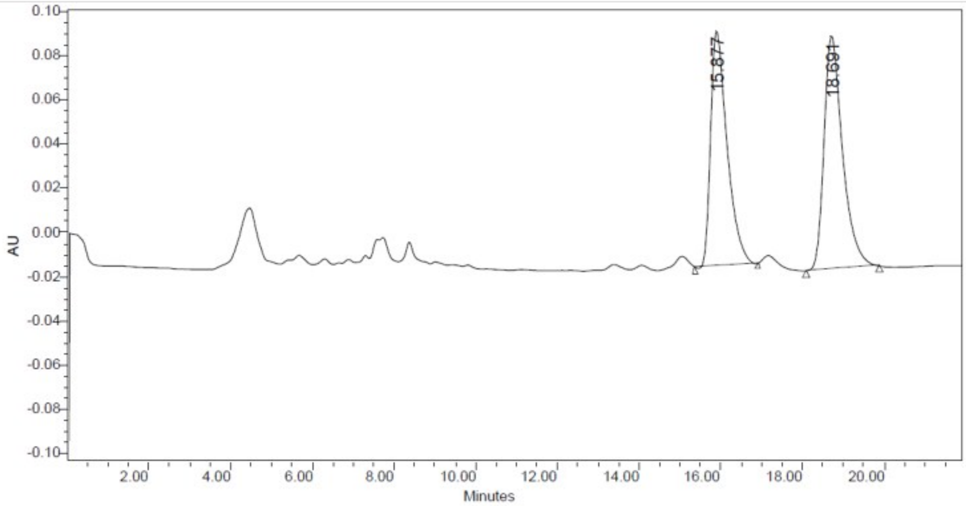
	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	24.655	13159891	50.05	222051	60.92
2	35.214	13132982	49.95	142428	39.08



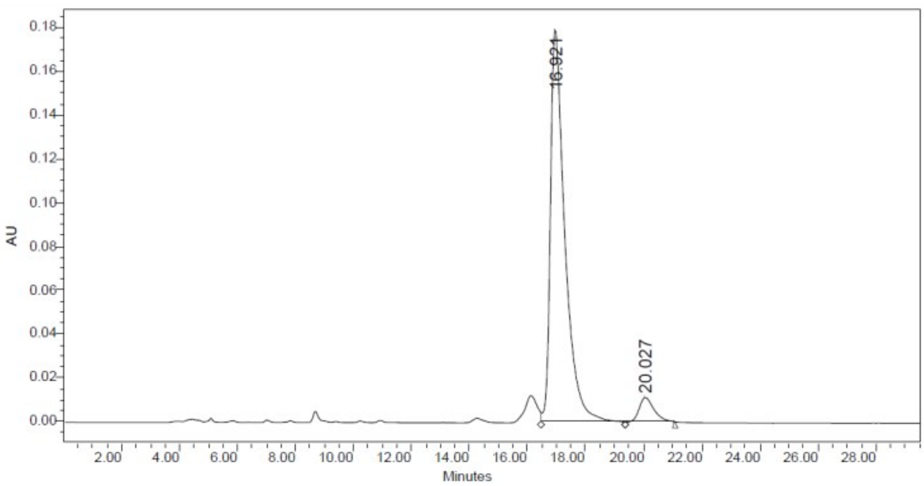
	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	25.896	3590492	26.06	53002	35.67
2	36.357	10186286	73.94	95575	64.33



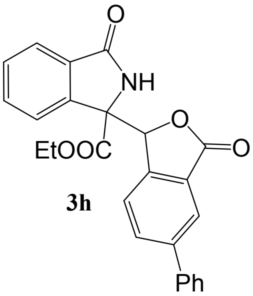
3g



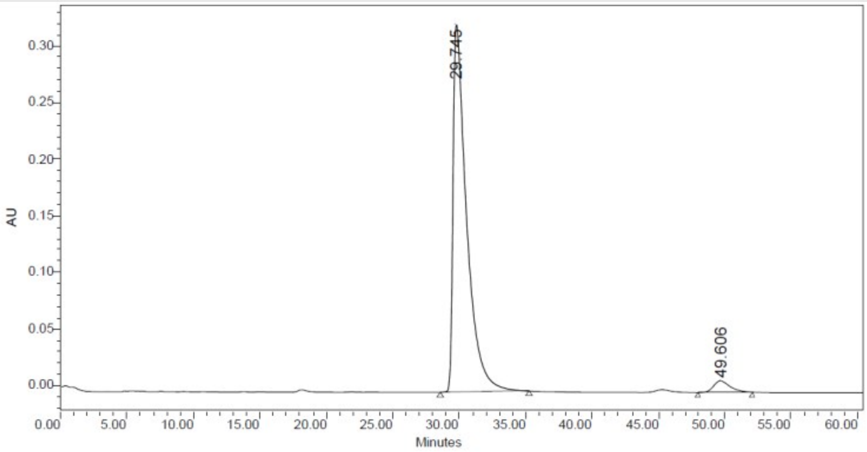
	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	15.877	2979019	47.11	106260	50.14
2	18.691	3345117	52.89	105672	49.86



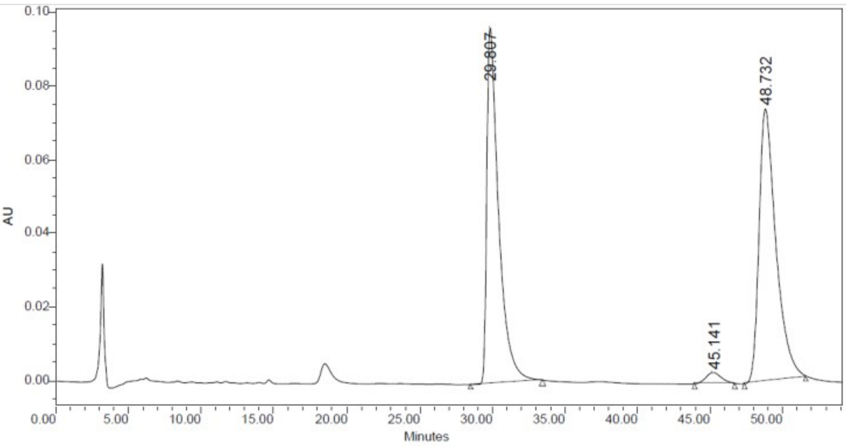
	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	16.921	6217159	93.90	179311	94.11
2	20.027	403898	6.10	11231	5.89



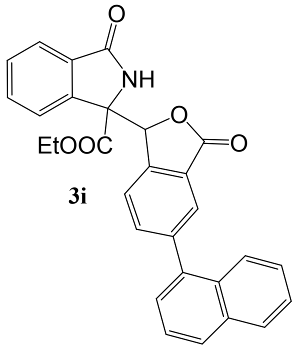
3h



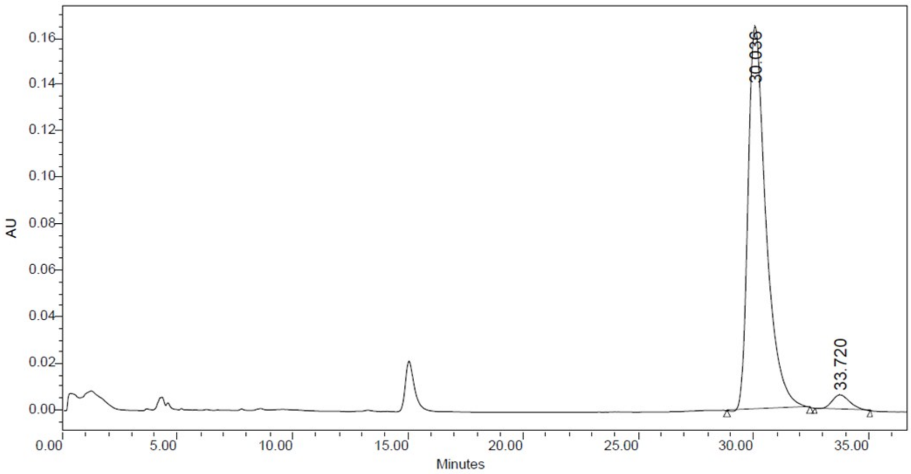
	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	29.745	22985396	96.29	324276	96.93
2	49.606	886016	3.71	10275	3.07



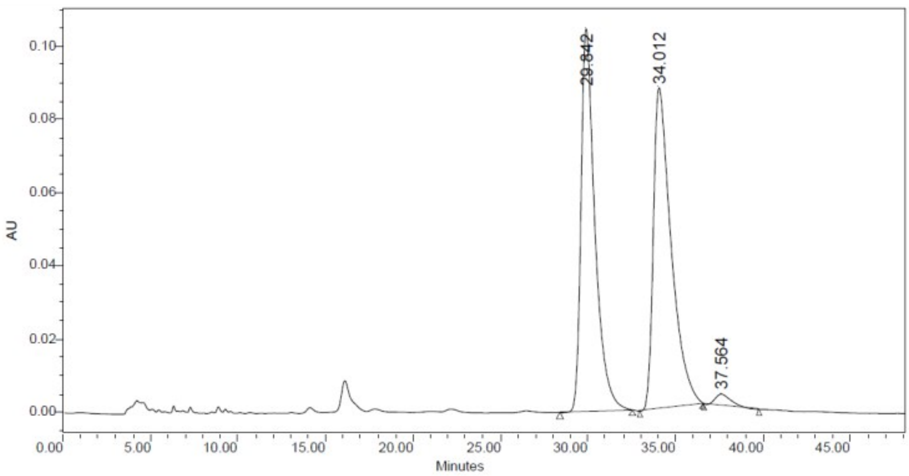
	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	29.807	5460469	46.86	96745	55.69
2	45.141	223469	1.92	3008	1.73
3	48.732	5969311	51.22	73964	42.58



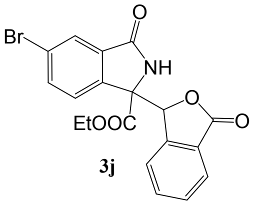
3i



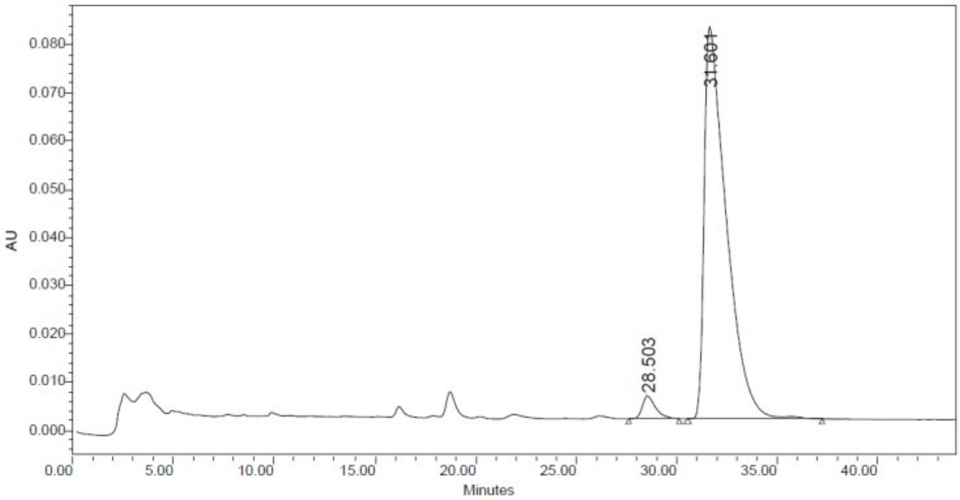
	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	30.036	9004761	96.36	165037	96.35
2	33.720	340202	3.64	6248	3.65



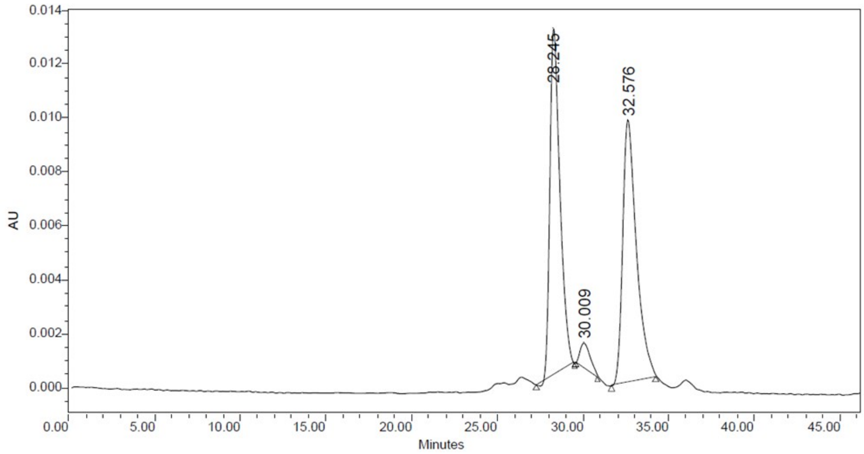
	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	29.842	5787948	47.45	104633	53.52
2	34.012	6210891	50.92	87721	44.87
3	37.564	198228	1.63	3149	1.61



3j



	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	28.503	213351	3.32	4713	5.49
2	31.601	6207116	96.68	81168	94.51



	RT (min)	Area (□V*sec)	% Area	Height (□V)	% Height
1	28.245	530541	47.72	12881	54.76
2	30.009	37054	3.33	897	3.81
3	32.576	544102	48.94	9745	41.43