Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

A versatile synthesis of "tafuramycin A": a potent anticancer and parasite attenuating agent

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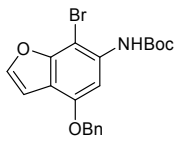
Supporting Information

Contents

EXPERIMENTAL SECTION

General information: Reagents and dry solvents purchased from commercial sources were used without further purification. Anhydrous reactions were carried out under an atmosphere of argon, using oven-dried glassware. Reactions were monitored using thin layer chromatography (TLC) on aluminium plates precoated with Silica Gel 60 F254 (E. Merck). Developed plates were observed under UV light at 254 nm. Flash chromatography was performed on Silica Gel 60 (0.040–0.063mm) using distilled solvents. All melting points were recorded on a Sanyo Gallenkamp apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a Bruker Avance 300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), relative to the residual solvent peak as internal reference [$CDCl_3$: 7.26 (s) for ^{1}H, 77.0 (t) for ^{13}C; d_6-DMSO: 2.50 (pent) for ^{1}H, 39.51 (hept) for ^{13}C]. 2D COSY and HSQC experiments were run to support assignments. Infrared spectra were run neat on a Bruker alpha FT-IR spectrometer. Low-resolution mass spectra (LRMS) were recorded, in electrospray ionization mode, on a Bruker Daltonics Esquire 3000 ESI spectrometer, using positive mode. High-resolution mass spectrometry (HRMS) was carried out by the University of Queensland FTMS Facility on a Bruker Daltonics Apex III 4.7e Fourier Transform micrOTOF-Q70 MS. HPLC purification was performed on an Agilent HP1100 instrument using a Synergi Fusion Phenomenex C18 column (250 × 10 mm) at a flow rate of 3mL/min and column temperature of 37 °C using solvents as indicated. The purities of all synthetic intermediates after chromatographic purification were judged to be >90% by ^{1}H and ^{13}C NMR. The purity of final products **3**, **12**, **15** and **16** was ≥95% by HPLC analysis. Intermediates **5**, **6**, **7**, **9** and **11** were prepared according to literature.[1]

4-Benzyloxy-7-bromo-6-[*N*-(*tert*-butyloxycarbonyl)amino]benzofuran (8).

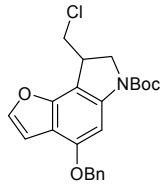


8

A solution of NBS (1.15 g, 6.48 mmol) in DCM (25 mL) was added in a dropwise manner to a solution of intermediate **7** (2.0 g, 5.89 mmol) and DMAP (0.72 g, 5.89 mmol) in DCM (25 mL) at 0 ºC. The reaction mixture was stirred at 0 °C for 1 h, then concentrated under reduced pressure and purified by flash

chromatography (EtOAc/hexanes, 1:20) to yield compound **8** (2.27 g, 92%) as a white waxy solid. mp = 117–9 ºC (Lit. 86–90 ºC)[1]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H, *t*-butyl-3CH_3), 5.21 (s, 2H, benz-CH_2), 6.90 (d, *J* = 2.2 Hz, 1H, Ar-H-3), 7.04 (s, 1H, NH), 7.31–7.58 (m, 6H, Ar), 7.85 (s, 1H, Ar-H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.34 (*t*-butyl-3CH_3), 70.51 (Bn-CH_2), 81.12 (*t*-butyl-$\underline{C}CH_3$), 85.96 (Ar q carbon), 98.37 (Ar), 105.11 (Ar), 114.11 (Ar q carbon), 127.83 (Ar), 128.11 (Ar), 128.53 (Ar), 134.15 (Ar q carbon), 136.49 (Ar q carbon), 143.52 (Ar), 151.93 (Ar q carbon), 152.65 (Ar q carbon), 152.92 (CO); FTIR (solid) υ = 3412, 2978, 1729, 1597, 1542, 1353, 1228, 1154, 1081, 726 cm^{-1}; LRMS [$C_{20}H_{20}BrNO_4$] (*m/z*): (+ve ion mode) 440.1 $[M+Na]^+$, 442.1.

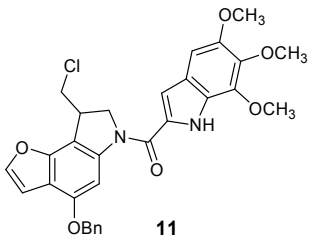
4-(Benzyloxy)-6-(*tert*-butoxycarbonyl)-8-(chloromethyl)-7,8-dihydrofuro[2,3-*e*]indole (10).



10

A solution of intermediate **9** (1.0 g, 2.03 mmol, mixture of *Z* and *E* isomers) and AIBN (33 mg, 0.203 mmol), in toluene (10 mL) was degassed with argon for 15 minutes. To this solution and under argon atmosphere was added Bu_3SnH (0.55 mL, 2.03 mmol), and the mixtue was heated under reflux for 1 h. The reaction mixture was left to cool down to rt, then concentrated under reduced pressure and purified by flash column (EtOAc/hexanes, 1:20) to yield compound **10** (0.75 g, 89%) as a white solid. mp = 133–135 ºC (Lit. Oil)[1]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 9H, *t*-butyl-3CH_3), 3.61 (dd, *J* = 10.7, 9.1 Hz, 1H, C$\underline{H}$N), 3.93–4.15 (m, 3H, C$\underline{H}$N, C$\underline{H}$Cl, C$\underline{H}CH_2Cl$), 4.22 (dd, *J* = 11.6, 9.5 Hz, 1H, C$\underline{H}$Cl), 5.20 (s, 2H, benz-CH_2), 6.85 (d, *J* = 2.2 Hz, 1H, Ar), 7.30–7.76 (m, 7H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.46 (*t*-butyl-3CH_3), 40.18 ($\underline{C}HCH_2Cl$), 46.12 ($\underline{C}H_2N$), 53.22 ($\underline{C}H_2Cl$), 70.41 (Bn-CH_2), 80.34 (*t*-butyl-$\underline{C}CH_3$), 95.01 (Ar), 106.55 (Ar), 114.65 (Ar q carbon), 124.57 (Ar q carbon), 127.57 (Ar), 128.08 (Ar), 128.55 (Ar), 136.51 (Ar q carbon), 137.34 (Ar q carbon), 152.06 (Ar q carbon), 152.27 (CO); FTIR (solid) υ = 2976, 1701, 1490, 1417, 1342, 1140, 731 cm^{-1}; LRMS [$C_{23}H_{24}ClNO_4$] (*m/z*): (+ve ion mode) 436.2 $[M+Na]^+$.

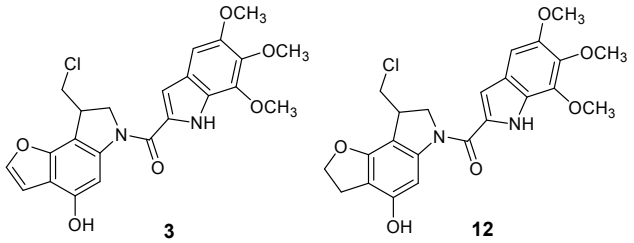
4-(Benzyloxy)-8-(chloromethyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-7,8-dihydrofuro[2,3-*e*]indole (11).



11

Concentrated HCl (3.6 mL) was added slowly while stirring to a solution of **10** (500 mg, 1.2 mmol) in anhydrous THF (10 mL) at 0 ºC. The mixture was stirred in an ice bath for 15 min, then at rt o/n. The reaction was quenched with saturated aq. $NaHCO_3$ (80 mL) and extracted with EtOAc (100 mL × 2). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure to yield the crude amine as brown oil. To this crude amine was added 5,6,7,-trimethoxy-*1H*-indole-2-carboxylic acid (360 mg, 1.44 mmol) and EDCI (558 mg, 3.6 mmol) and the mixture was suspended in anhydrous DMF (15 mL) and stirred under argon o/n at rt. Upon reaction completion (monitored by TLC), DMF was removed under reduced pressure, and the mixture was taken in DCM and purified by flash chromatography (EtOAc/hexanes, 1:3) to yield compound **11** (545 mg, 83%) as a white solid. mp = 183–5 ºC (Lit. 170–4 ºC)[1]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (t, *J* = 11.0 Hz, 1H, C<u>H</u>N), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.16–4.24 (m, 2H, C<u>H</u>N, C<u>H</u>CH_2Cl), 4.59 (dd, *J* = 10.8, 4.7 Hz, 1H, C<u>H</u>Cl), 4.75 (dd, *J* = 10.9, 8.9 Hz, 1H, C<u>H</u>Cl), 5.26 (s, 2H, benz-CH_2), 6.83–7.03 (m, 3H, Ar), 7.28–7.60 (m, 6H, Ar), 8.07 (s, 1H, Ar), 9.43 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.71 (<u>C</u>HCH_2Cl), 45.95 (<u>C</u>H_2N), 55.29 (<u>C</u>H_2Cl), 56.30 (OCH_3), 61.13 (OCH_3), 61.49 (OCH_3), 70.40 (Bn-CH_2), 96.94 (Ar), 97.70 (Ar), 104.89 (Ar), 106.27 (Ar q carbon), 106.44 (Ar), 115.21 (Ar q carbon), 123.67 (Ar q carbon), 125.50 (Ar q carbon), 127.60 (Ar), 128.05 (Ar), 128.57 (Ar), 129.95 (Ar q carbon), 136.69 (Ar q carbon), 138.85 (Ar q carbon), 140.56 (Ar q carbon), 142.76 (Ar q carbon), 143.49 (Ar), 150.18 (Ar q carbon), 151.40 (Ar q carbon), 153.03 (Ar q carbon), 160.11 (CO); LRMS [$C_{30}H_{27}ClN_2O_6$] (*m/z*): (+ve ion mode) 569.2 [M+Na]$^+$, 547.2.

4-(Hydroxy)-8-(chloromethyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-7,8-dihydrofuro[2,3-*e*]indole (3) and 4-(Hydroxy)-8-(chloromethyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-2,3,7,8-tetrahydrofuro[2,3-*e*]indole (12).



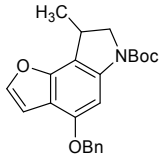
To a mixture of compound **11** (500 mg, 0.91 mmol) and 10% Pd/C (170 mg) was added 25% aq. NH_4HCO_2 (4 mL) and THF (16 mL). The mixture was flushed with H_2 gas and stirred under H_2 atmosphere o/n. Upon reaction completion (monitored by TLC), the mixture was filtered over celite. The filtrate was then concentrated under reduced pressure and purified by flash chromatography (acetone/hexanes, 1:3) to yield a mixture of compound **3** and its dihydro-derivative **12** (370 mg, 89%, calculated as for **3**) as a buff powder. The mixture of compounds **3** and **12** was resolved with RP-HPLC (isocratic elution with THF/acetonitrile/water, 5:45:50, retention time; **3**: 25.67 min and **12**: 22.27 min).

Compound 3. mp = 291–3 ºC (Lit. 250 ºC)[1]; ^{1}H NMR (300 MHz, d_6-DMSO): δ 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.92–3.98 (m, 4H, OCH_3, C<u>H</u>N), 4.07 (dd, *J* = 10.9, 3.3 Hz, 1H, C<u>H</u>N), 4.15 (m, 1H, C<u>H</u>CH_2Cl), 4.37 (dd, *J* = 11.0, 4.8 Hz, 1H, C<u>H</u>Cl), 4.70 (dd, *J* = 10.9, 9.3 Hz, 1H, C<u>H</u>Cl), 6.89–7.06 (m, 3H, Ar), 7.65 (s, 1H, Ar), 7.82 (d, *J* = 2.2 Hz, 1H, Ar), 10.12 (s, 1H, NH); ^{13}C NMR (75 MHz, d_6-DMSO): δ 40.12 (<u>C</u>HCH_2Cl), 46.59 (<u>C</u>H_2N), 54.88 (<u>C</u>H_2Cl), 55.91 (OCH_3), 60.90 (OCH_3), 61.07 (OCH_3), 98.00 (Ar), 98.93 (Ar), 104.66 (Ar), 104.76 (Ar q carbon), 105.84 (Ar), 113.07 (Ar q carbon), 123.12 (Ar q carbon), 125.21 (Ar q carbon), 131.08 (Ar q carbon), 139.02 (Ar q carbon), 139.76 (Ar q carbon), 142.47 (Ar q carbon), 143.73 (Ar), 149.10 (Ar q carbon), 151.03 (Ar q carbon), 151.26 (Ar q carbon), 159.96 (CO); FTIR (solid) υ = 3430, 2362, 1698, 1508, 1423, 1310, 1107, 832, 744 cm^{-1}; LRMS [$C_{23}H_{21}ClN_2O_6$] (*m/z*): (+ve ion mode) 478.9 $[M+Na]^+$.

Compound 12. mp = 281–3 ºC; ^{1}H NMR (300 MHz, d_6-DMSO): δ 3.02 (t, *J* = 8.6 Hz, 2H, C<u>H</u>$_2$-CH_2-O), 3.71–3.81 (m, 8H, 2 OCH_3, C<u>H</u>N, C<u>H</u>CH_2Cl), 3.88–3.93 (m, 4H, OCH_3, C<u>H</u>N), 4.26 (dd, *J* = 10.9, 4.1 Hz, 1H, C<u>H</u>Cl), 4.53–4.61 (m, 3H, C<u>H</u>$_2$-O, C<u>H</u>Cl), 6.91–7.02 (m, 2H, Ar), 7.29 (s, 1H, Ar), 9.57 (s, 1H, NH);

^{13}C NMR (75 MHz, d_6-DMSO): δ 26.51 (C-3), 46.43 (<u>C</u>H$_2$N), 54.58 (<u>C</u>H$_2$Cl), 55.90 (OCH$_3$), 60.89 (OCH$_3$), 61.06 (OCH$_3$), 72.14 (C-2), 97.74 (Ar), 98.00 (Ar), 103.10 (Ar q carbon), 105.72 (Ar), 108.16 (Ar q carbon), 123.10 (Ar q carbon), 125.14 (Ar q carbon), 131.07 (Ar q carbon), 138.98 (Ar q carbon), 139.71 (Ar q carbon), 144.76 (Ar q carbon), 149.07 (Ar q carbon), 153.99 (Ar q carbon), 156.44 (Ar q carbon), 159.86 (CO); FTIR (solid) υ = 3435, 2362, 1698, 1522, 1489, 1396, 1309, 745 cm^{-1}; LRMS [$C_{23}H_{23}ClN_2O_6$] (*m/z*): (+ve ion mode) 480.9 [M+Na]$^+$; HRMS (API) (*m/z*): [M+H]$^+$ calcd for $C_{23}H_{24}ClN_2O_6$ [M+H]$^+$ 459.1317; found, 459.1319.

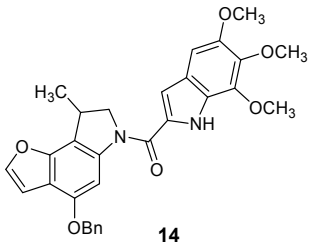
4-(Benzyloxy)-6-(*tert*-butoxycarbonyl)-8-(methyl)-7,8-dihydrofuro[2,3-*e*]indole (13).



13

A solution of intermediate **9** (500 mg, 1.01 mmol) and AIBN (50 mg, 0.303 mmol), in toluene (5.0 mL) was degassed with argon for 15 minutes. To this solution and under argon atmosphere was added Bu_3SnH (0.82 mL, 3.03 mmol), and the mixtue was heated under reflux for 1 h. The reaction mixture was left to cool down to rt, then concentrated under reduced pressure and purified by flash column (EtOAc/hexanes, 1:20) to yield compound **13** (350 mg, 91% mmol) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, J = 6.6 Hz, 3H, CH$_3$), 1.58 (s, 9H, *t*-butyl-3CH$_3$), 3.58–3.75 (m, 2H, C<u>H</u>N, CH$_3$C<u>H</u>), 4.24 (t, J = 9.8 Hz, 1H, C<u>H</u>N), 5.20 (s, 2H, Bn-CH$_2$), 6.84 (d, J = 2.2 Hz, 1H, Ar), 7.30–7.81 (m, 7H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.97 (CH$_3$), 28.54 (*t*-butyl-3CH$_3$), 32.10 (CH$_3$<u>C</u>H), 56.96 (<u>C</u>H$_2$N), 70.34 (Bn-CH$_2$), 80.44 (*t*-butyl-<u>C</u>CH$_3$), 94.52 (Ar), 104.51 (Ar), 113.51 (Ar q carbon), 127.58 (Ar), 127.92 (Ar), 128.51 (Ar), 137.06 (Ar q carbon), 142.60 (Ar), 152.00 (Ar q carbon), 152.22 (Ar q carbon), 152.54 (CO); FTIR (solid) υ = 2972, 1697, 1489, 1338, 1131, 732 cm^{-1}; LRMS [$C_{23}H_{25}NO_4$] (*m/z*): (+ve ion mode) 402.0 [M+Na]$^+$; HRMS (API) (*m/z*): [M+Na]$^+$ calcd for $C_{23}H_{25}NNaO_4$ [M+Na]$^+$ 402.1676; found, 402.1674.

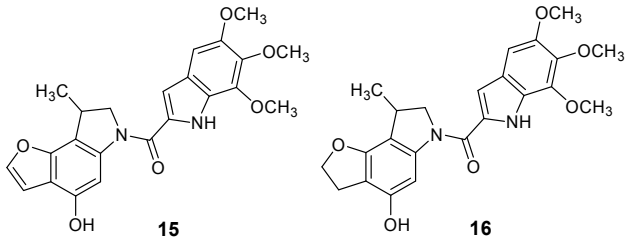
4-(Benzyloxy)-8-(methyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-7,8-dihydrofuro[2,3-*e*]indole (14).



14

Concentrated HCl (2.4 mL) was added slowly while stirring to a solution of **13** (300 mg, 0.79 mmol) in anhydrous THF (7.0 mL) at 0 ºC. The mixture was stirred in an ice bath for 15 min, then at rt o/n. The reaction was quenched with saturated aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (50 mL × 2). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (EtOAc/hexanes, 1:5) to yield the pure amine as a greenish oil (187 mg, 85%). A mixture of the crude amine (150 mg, 0.54 mmol), 5,6,7,-trimethoxy-*1H*-indole-2-carboxylic acid (300 mg, 0.65 mmol) and EDCI (250 mg, 1.62 mmol) was suspended in anhydrous DMF (5 mL) and stirred under argon o/n at rt. Upon reaction completion (monitored by TLC), DMF was removed under reduced pressure, and the mixture was taken in DCM and purified by flash chromatography (EtOAc/hexanes, 1:3) to yield compound **14** (220 mg, 79%) as a yellowish white solid that was recrystallized from ethanol for X-ray crystallography. mp = 212–4 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (d, *J* = 6.7 Hz, 3H, CH_3), 3.86–3.91 (m, 4H, OCH_3, $CH_3C\underline{H}$), 3.95 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.15 (dd, *J* = 10.1, 5.8 Hz, 1H, C<u>H</u>N), 4.78 (t, *J* = 9.7 Hz, 1H, C<u>H</u>N), 5.26 (s, 2H, Bn-CH_2), 6.86 (s, 1H, Ar), 6.92 (dd, *J* = 6.5, 2.3 Hz, 2H, Ar), 7.29–7.53 (m, 6H, Ar), 8.06 (s, 1H, Ar), 9.42 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.86 (CH_3), 33.58 ($CH_3C\underline{H}$), 56.31 (OCH_3), 59.09 ($\underline{C}H_2N$), 61.12 (OCH_3), 61.49 (OCH_3), 70.36 (Bn-CH_2), 96.85 (Ar), 97.64 (Ar), 104.70 (Ar), 106.13 (Ar), 112.16 (Ar q carbon), 115.29 (Ar q carbon), 123.66 (Ar q carbon), 125.34 (Ar q carbon), 127.58 (Ar), 127.95 (Ar), 128.53 (Ar), 130.37 (Ar q carbon), 136.95 (Ar q carbon), 138.89 (Ar q carbon), 140.43 (Ar q carbon), 141.63 (Ar q carbon), 143.36 (Ar), 150.10 (Ar q carbon), 151.50 (Ar q carbon), 152.02 (Ar q carbon), 159.95 (CO); FTIR (solid) υ = 2934, 1619, 1524, 1407, 1306, 1222, 1108, 997, 734 cm^{-1}; LRMS [$C_{30}H_{28}N_2O_6$] (*m/z*): (+ve ion mode) 534.9 $[M+Na]^+$, 512.9.

4-(Hydroxy)-8-(methyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-7,8-dihydrofuro[2,3-*e*]indole (15) and 4-(Hydroxy)-8-(methyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-2,3,7,8-tetrahydrofuro[2,3-*e*]indole (16).



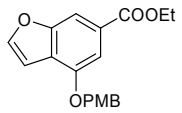
To a mixture of compound **14** (150 mg, 0.29 mmol) and 10% Pd/C (55 mg) was added 25% aq. NH_4HCO_2 (1.5 mL) and THF (6 mL). The mixture was flushed with H_2 gas and stirred under H_2 atmosphere o/n. Upon reaction completion (monitored by TLC), the mixture was filtered over celite. The filtrate was then concentrated under reduced pressure and purified by flash chromatography (acetone/hexanes, 1:3) to yield a mixture of compound **15** and its dihydro-derivative **16** (113 mg, 92%, calculated as for **15**) as a buff powder. The mixture of compounds **15** and **16** was resolved with RP-HPLC (isocratic elution with water/acetonitrile, 40:60, retention time; **15**: 13.43 min and **16**: 11.53 min).

Compound 15. mp = 293–4 ºC; ^{1}H NMR (300 MHz, d_6-DMSO): δ 1.40 (d, J = 6.7 Hz, 3H, CH_3), 3.68-3.84 (m, 7H, 2 OC$\underline{H}_3$, $CH_3C\underline{H}$), 3.92 (s, 3H, OCH_3), 4.04 (dd, J = 10.6, 6.1 Hz, 1H, C$\underline{H}$N), 4.68 (dd, J = 10.6, 9.2 Hz, 1H, C$\underline{H}$N), 6.88–6.97 (m, 2H, Ar), 7.00 (d, J = 2.2 Hz, 1H, Ar), 7.64 (s, 1H, Ar), 7.79 (d, J = 2.2 Hz, 1H, Ar), 9.95 (s, 1H, NH); ^{13}C NMR (75 MHz, d_6-DMSO): δ 19.33 (CH_3), 32.57 ($CH_3C\underline{H}$), 55.91 (OCH_3), 58.80 ($\underline{C}H_2N$), 60.90 (OCH_3), 61.06 (OCH_3), 97.95 (Ar), 98.90 (Ar), 104.57 (Ar), 105.83 (Ar), 110.18 (Ar q carbon), 113.15 (Ar q carbon), 123.14 (Ar q carbon), 125.13 (Ar q carbon), 131.27 (Ar q carbon), 139.00 (Ar q carbon), 139.66 (Ar q carbon), 141.26 (Ar q carbon), 143.57 (Ar), 149.04 (Ar q carbon), 150.07 (Ar q carbon), 151.23 (Ar q carbon), 159.90 (CO); FTIR (solid) υ = 3442, 2930, 2361, 1625, 1490, 1429, 1309, 1106, 744 cm^{-1}; LRMS [$C_{23}H_{22}N_2O_6$] (*m/z*): (+ve ion mode) 445.0 [M+Na]$^+$; HRMS (API) (*m/z*): [M+H]$^+$ calcd for $C_{23}H_{23}N_2O_6$ [M+H]$^+$ 423.1551; found, 423.1550.

Compound 16. mp = 322–4 ºC; ^{1}H NMR (300 MHz, d_6-DMSO): δ 1.24 (d, J = 6.7 Hz, 3H, CH_3), 3.00 (dd, J = 9.3, 7.9 Hz, 2H, C$\underline{H}_2$-CH_2-O), 3.39 (dt, J = 9.1, 6.3 Hz, 1H, $CH_3C\underline{H}$), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.88–3.94 (m, 4H, OCH_3, CHN), 4.45–4.63 (m, 3H, C$\underline{H}_2$-O, CHN), 6.91 (s, 1H, Ar), 6.95 (d, J = 2.1

Hz, 1H, Ar), 7.27 (s, 1H, Ar), 9.40 (s, 1H, NH); ^{13}C NMR (75 MHz, d_6-DMSO): δ 19.29 (CH_3), 26.54 (C-3), 32.10 ($CH_3\underline{C}H$), 55.90 (OCH_3), 58.57 ($\underline{C}H_2N$), 60.89 (OCH_3), 61.05 (OCH_3), 71.74 (C-2), 97.66 (Ar), 97.94 (Ar), 105.71 (Ar), 108.21 (Ar q carbon), 108.64 (Ar q carbon), 123.11 (Ar q carbon), 125.06 (Ar q carbon), 131.27 (Ar q carbon), 138.97 (Ar q carbon), 139.61 (Ar q carbon), 143.81 (Ar q carbon), 149.00 (Ar q carbon), 153.03 (Ar q carbon), 156.17 (Ar q carbon), 159.81 (CO); FTIR (solid) υ = 3441, 2937, 2361, 1629, 1489, 1391, 1309, 1105, 827, 745 cm^{-1}; LRMS [$C_{23}H_{24}N_2O_6$] (*m/z*): (+ve ion mode) 447.0 [M+Na]$^+$; HRMS (API) (*m/z*): [M+Na]$^+$ calcd for $C_{23}H_{24}N_2NaO_6$ [M+Na]$^+$ 447.1527; found, 447.1526.

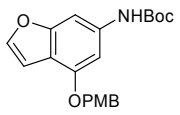
Ethyl 4-(4-methoxybenzyloxy)benzofuran-6-carboxylate (17).



17

To a mixture of the phenol **5** (2.4 g, 11.64 mmol), K_2CO_3 (2.28 g, 16.52 mmol) and TBAI (Cat., 20 mg) in DMF (30 mL) under argon and at rt, was added 4-methoxybenzyl chloride (2.05 mL, 15.13 mmol) while stirring. The reaction mixture was stirred at rt and under argon atmosphere o/n. Upon reaction completion (monitored by TLC) the solvent was removed under reduced pressure, and the residue was taken into DCM and purified by flash chromatography (EtOAc/hexanes, 1:10) to yield compound **17** (3.19 g, 84%) as a brown solid. mp = 94–5 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.1, Hz, 3H, $CH_2\underline{CH_3}$), 3.83 (s, 3H, OCH_3), 4.41 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 5.18 (s, 2H, Bn-CH_2), 6.87–6.98 (m, 3H, Ar), 7.42 (d, *J* = 8.8 Hz, 2H, PMB), 7.48 (d, *J* = 1.0 Hz, 1H, Ar), 7.65 (d, *J* = 2.2 Hz, 1H, Ar), 7.89 (t, *J* = 1.0 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.40 ($CH_2\underline{C}H_3$), 55.29 (OCH_3), 61.12 ($\underline{C}H_2CH_3$), 70.28 (Bn-$\underline{C}H_2$), 104.55 (Ar), 105.36 (Ar), 106.93 (Ar), 114.01 (Ar), 122.37 (Ar q carbon), 127.49 (Ar q carbon), 128.61 (Ar q carbon), 129.42 (Ar), 146.24 (Ar), 152.30 (Ar q carbon), 155.53 (Ar q carbon), 159.58 (Ar q carbon), 166.79 (CO); FTIR (solid) υ = 2981, 1709, 1597, 1456, 1332, 1310, 1074, 1025, 762, 696 cm^{-1}; LRMS [$C_{19}H_{18}O_6$] (*m/z*): (+ve ion mode) 348.9 [M+Na]$^+$; HRMS (API) (*m/z*): [M+Na]$^+$ calcd for $C_{19}H_{18}NaO_5$ [M+Na]$^+$ 349.1046; found, 349.1048.

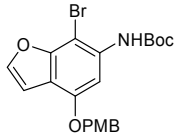
4-(4-Methoxybenzyloxy)-6-(*N*-(*tert*-butyloxycarbonyl)amino)benzofuran (18).



18

Compound **17** (3.0 g, 9.2 mmol) was stirred under reflux in a mixture of EtOH (50 mL) and 20% NaOH (50 mL) for 3h. After cooling down to rt, EtOH was evaporated under reduced pressure and the remaining suspension was chilled in an ice bath and acidified with 6M HCl to pH = 1. The resulted solid was filtered, washed with cold water and left to dry to yield the crude acid. Anhydrous diisopropylethylamine (2.40 mL, 13.8 mmol) and DPPA (3.0 mL, 13.8 mmol) were added to a solution of the crude acid in dry *t*-butanol (60 mL) under argon. The resulted mixture was stirred under reflux and under argon atmosphere o/n. After cooling to rt, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (EtOAc/hexanes, 1:9) to yield pure **18** as a yellowish white solid (2.55 g, 75%). mp = 137–9 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H, *t*-butyl-3CH_3), 3.83 (s, 3H, OCH_3), 5.09 (s, 2H, benz-CH_2), 6.80 (dd, *J* = 2.2, 1.0 Hz, 1H, Ar), 6.85 (brs, 1H, NH), 6.93 (d, *J* = 8.8 Hz, 2H, PMB), 7.23–7.29 (m, 2H, Ar), 7.39 (d, *J* = 8.8 Hz, 2H, PMB), 7.45 (d, *J* = 2.2 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.38 (*t*-butyl-3CH_3), 55.30 (OCH_3), 70.15 (benz-CH_2), 80.56 (*t*-butyl-$\underline{C}CH_3$), 95.22 (Ar), 97.52 (Ar), 104.03 (Ar), 113.63 (Ar q carbon), 113.97 (Ar), 128.82 (Ar q carbon), 129.27 (Ar), 136.31 (Ar q carbon), 143.09 (Ar), 152.54 (Ar q carbon), 152.79 (Ar q carbon), 156.47 (Ar q carbon), 159.48 (CO); FTIR (solid) υ = 2977, 2361, 1699, 1507, 1160, 764 cm^{-1}; LRMS [$C_{21}H_{23}NO_5$] (*m/z*): (+ve ion mode) 392.0 $[M+Na]^+$; HRMS (API) (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{23}NNaO_5$ $[M+Na]^+$ 392.1468; found, 392.1468.

7-Bromo-4-(4-methoxybenzyloxy)-6-(*N*-(*tert*-butyloxycarbonyl)amino)benzofuran (19).

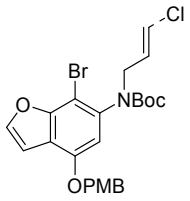


19

A solution of NBS (1.06 g, 5.95 mmol) in DCM (25 mL) was added in a dropwise manner to a solution of intermediate **18** (2.0 g, 5.41 mmol) and DMAP (0.66 g, 5.41 mmol) in DCM (25 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 1 h, then concentration under reduced pressure and purified by flash

chromatography (EtOAc/hexanes, 1:15) to yield compound **19** (2.0 g, 83%) as a white solid. mp = 116–7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 9H, *t*-butyl-3CH_3), 3.81 (s, 3H, OCH_3), 5.14 (s, 2H, benz-CH_2), 6.88 (dd, *J* = 2.2, 0.4 Hz, 1H, Ar), 6.93 (d, *J* = 8.6 Hz, 2H, PMB), 7.08 (s, 1H, NH), 7.42 (d, *J* = 8.6 Hz, 2H, PMB), 7.50 (d, *J* = 2.2 Hz, 1H, Ar), 7.86 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.38 (*t*-butyl-3CH_3), 55.25 (OCH_3), 70.34 (benz-CH_2), 81.07 (*t*-butyl-$\underline{C}CH_3$), 85.92 (Ar q carbon), 98.42 (Ar), 105.16 (Ar), 113.95 (Ar), 114.15 (Ar q carbon), 128.56 (Ar q carbon), 129.63 (Ar), 134.13 (Ar q carbon), 143.47 (Ar), 151.98 (Ar q carbon), 152.66 (Ar q carbon), 152.90 (Ar q carbon), 159.57 (CO); FTIR (solid) υ = 2977, 1731, 1518, 1231, 1157, 765 cm^{-1}; LRMS [$C_{21}H_{22}BrNO_5$] (*m/z*): (+ve ion mode) 471.9 [M+Na]$^+$; HRMS (API) (*m/z*): [M+Na]$^+$ calcd for $C_{21}H_{22}BrNNaO_5$ [M+Na]$^+$ 470.0574; found, 470.0578.

(*Z/E*) 4-(4-Methoxybenzyloxy)-7-bromo-6-[*N*-(3-chloro-2-popenyl)-*N*-(*tert*-butoxycarbonyl)amino] benzofuran (20).

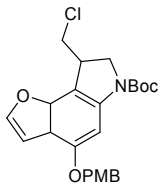


20

A mixture of compound **19** (1.0 g, 2.23 mmol), NaH (256 mg of 60% dispersion in mineral oil; 154 mg, 6.69 mmol) and TBAI (40 mg, 0.11 mmol) was suspended in anhydrous DMF (30 mL) at 0 ºC, and stirred under argon, in an ice bath for 2 h. To this mixture was added 1,3-dichloropropene (0.61 mL, 6.69 mmol), and the mixture was stirred at rt o/n. DMF was removed under reduced pressure, and the residue was taken in DCM and purified by flash chromatography (EtOAc/hexanes, 1:10) to yield a transparent oil that consists of a mix of *Z* and *E* isomers of **20** (1.15 g, 99%, *Z:E* ≡ 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H, *t*-butyl-3CH_3), 3.82 (s, 3H, OCH_3), 4.35 (dd, *J* = 15.9, 6.2 Hz, 1H, C$\underline{H}$N), 4.49 (dd, *J* = 16.5, 5.8 Hz, 1H, C$\underline{H}$N), 5.10 (q, *J* = 11.2 Hz, 2H, benz-CH_2), 5.94–6.05 (m, 2H, C$\underline{H}$=C$\underline{H}$-Cl), 6.64 (m, 1H, Ar), 6.91–6.94 (m, 3H, Ar), 7.37 (d, *J* = 8.5 Hz, 2H, PMB), 7.62 (d, *J* = 2.6 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.18 (*t*-butyl-3CH_3), 46.44 ($\underline{C}H_2$N), 55.31 (OCH_3), 70.45 (benz-CH_2), 80.68 (*t*-butyl-$\underline{C}CH_3$), 97.57 (Ar q carbon), 105.15 (Ar), 107.26 (Ar), 114.04 (Ar), 120.39 (CH=CH-Cl), 127.55 (CH=CH-Cl), 128.29 (Ar q carbon),

129.18 (Ar), 132.96 (Ar), 137.92 (Ar q carbon), 144.94 (Ar), 151.29 (Ar q carbon), 159.61 (CO); FTIR (solid) υ = 2976, 1733, 1541, 1366, 1251, 1173, 1033, 770 cm^{-1}; LRMS [$C_{24}H_{25}BrClNO_5$] (*m/z*): (+ve ion mode) 546.1 $[M+Na]^+$.

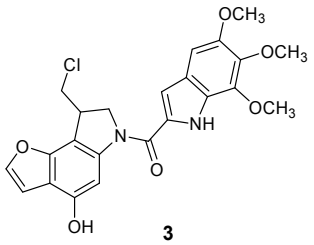
4-(4-Methoxybenzyloxy)-6-(*tert*-butoxycarbonyl)-8-(chloromethyl)-7,8-dihydrofuro[2,3-*e*]indole (21).



21

A solution of intermediate **20** (1.0 g, 1.91 mmol, mixture of *Z* and *E* isomers) and AIBN (314 mg, 1.91 mmol), in toluene (9 mL) was degassed with argon for 15 minutes. To this solution and under argon atmosphere was added Bu_3SnH (0.52 mL, 1.91 mmol), and the mixtue was heated under reflux for 2 h. The reaction mixture was left to cool down to rt, then concentrated under reduced pressure and purified by flash column (EtOAc/hexanes 1:12) to yield compound **21** (0.73 g, 86%) as a yellowish white solid. Mp = 145–7 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 9H, *t*-butyl-3CH_3), 3.61 (dd, *J* = 10.7, 9.2 Hz, 1H, C<u>H</u>N), 3.83 (s, 3H, OCH_3), 3.93–4.15 (m, 3H, C<u>H</u>N, C<u>H</u>Cl, C<u>H</u>CH_2Cl), 4.22 (dd, *J* = 11.7, 9.5 Hz, 1H, C<u>H</u>Cl), 5.12 (s, 2H, benz-CH_2), 6.82 (d, *J* = 2.2 Hz, 1H, Ar), 6.94 (d, *J* = 8.7 Hz, 2H, PMB-2H), 7.33–7.74 (m, 4H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.50 (*t*-butyl-3CH_3), 40.31 (<u>C</u>HCH_2Cl), 46.29 (<u>C</u>H_2N), 53.29 (<u>C</u>H_2Cl), 55.30 (OCH_3), 70.20 (Bn-CH_2), 80.96 (*t*-butyl-<u>C</u>CH_3), 94.48 (Ar), 104.71 (Ar), 113.44 (Ar q carbon), 113.94 (Ar), 128.83 (Ar q carbon), 129.40 (Ar), 142.64 (Ar), 151.87 (Ar q carbon), 152.35 (Ar q carbon), 153.31 (Ar q carbon), 159.50 (CO); FTIR (solid) υ = 2975, 1698, 1490, 1340, 1247, 1136, 730 cm^{-1}; LRMS [$C_{24}H_{26}ClNO_5$] (*m/z*): (+ve ion mode) 465.9 $[M+Na]^+$; HRMS (API) (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{26}ClNNaO_5$ $[M+Na]^+$ 466.13917; found, 466.13933.

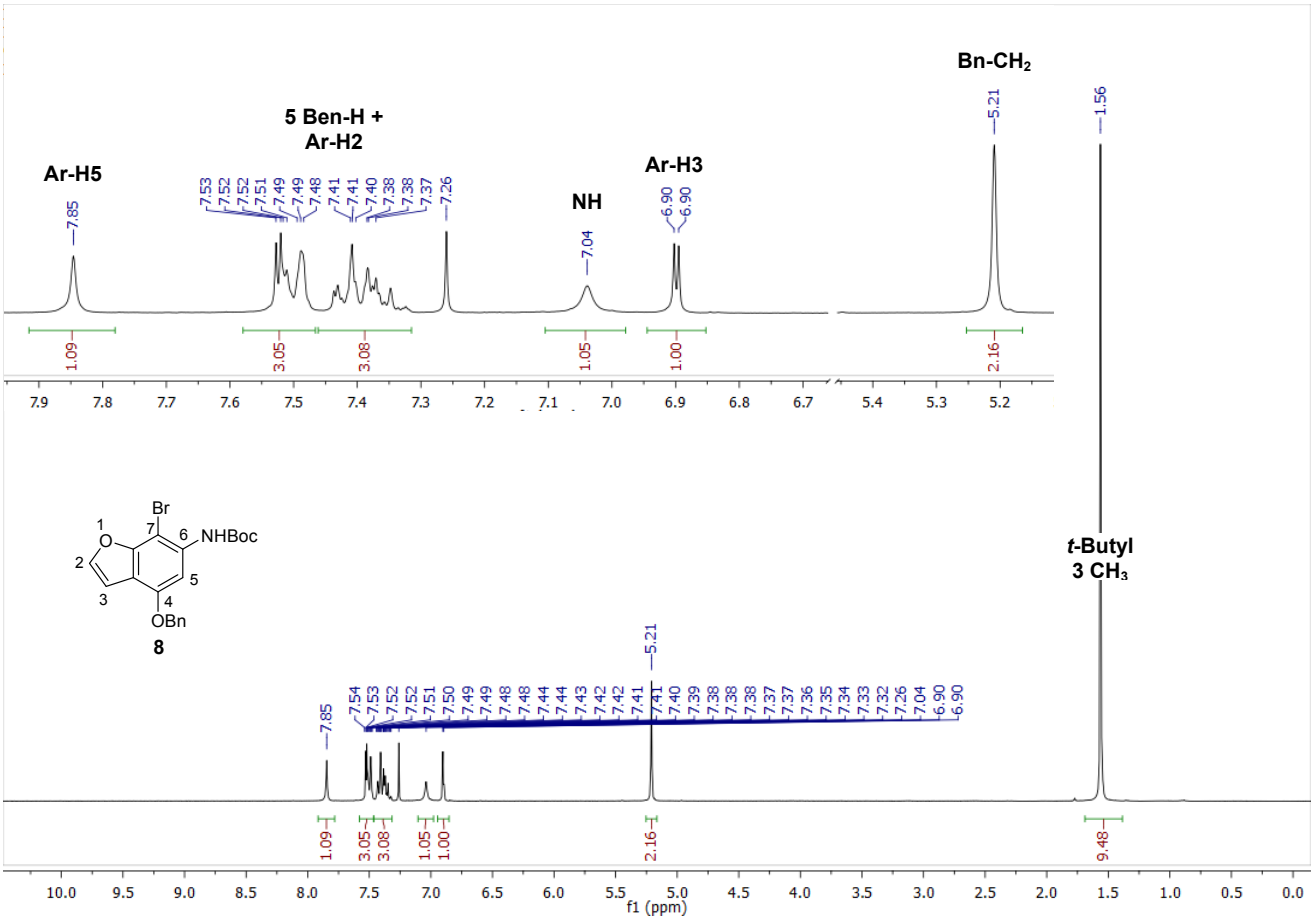
4-(Hydroxy)-8-(chloromethyl)-6-[(5,6,7-trimethoxy-*1H*-indol-2-yl)carbonyl]-7,8-dihydrofuro[2,3-*e*]indole (3).



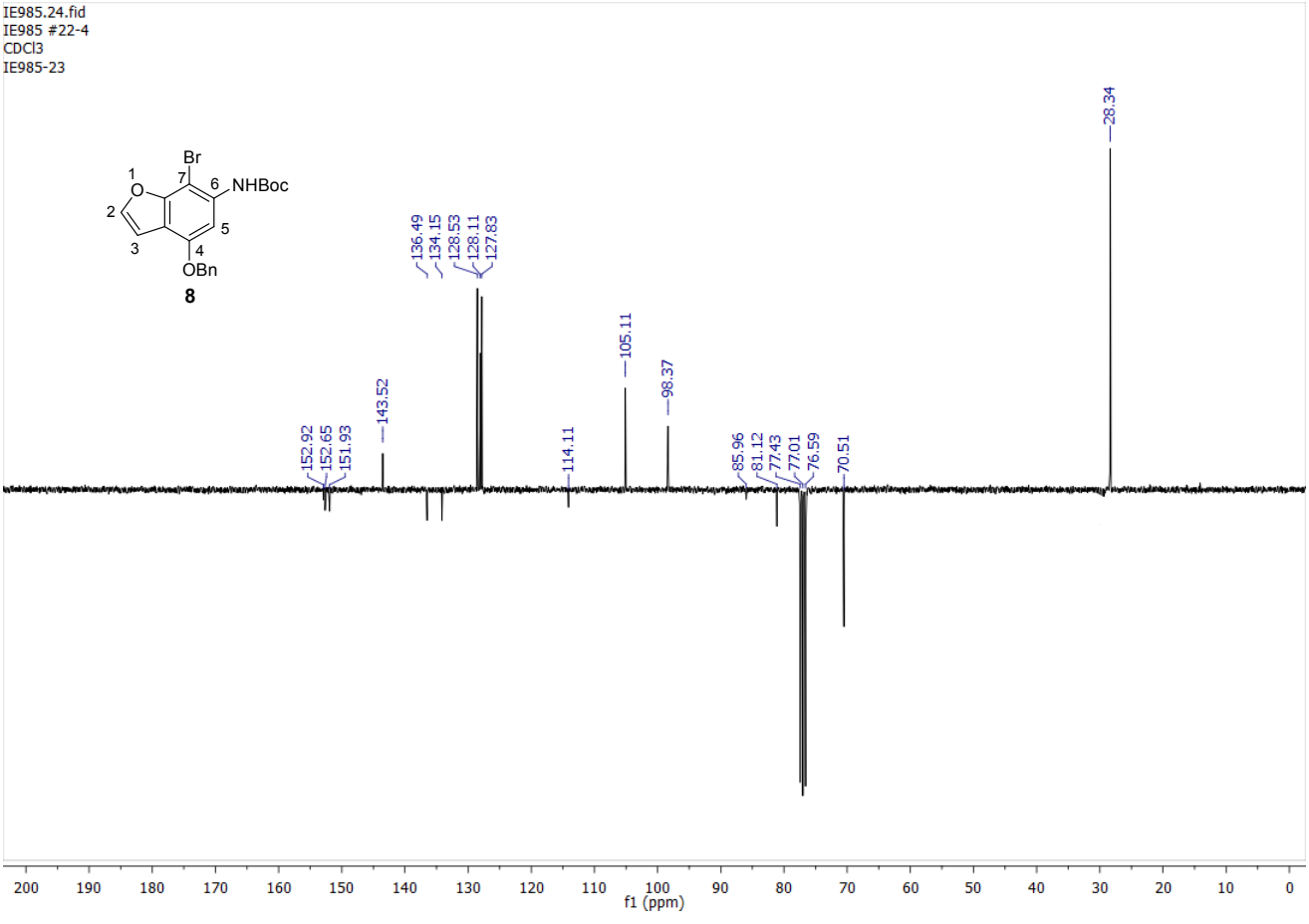
3

Concentrated HCl (0.70 mL) was added slowly while stirring to a solution of **21** (100 mg, 0.226 mmol) in anhydrous THF (2 mL) at 0 ºC. The mixture was stirred in an ice bath for 15 min, then at rt o/n. The reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (25 mL × 2). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure to yield the crude phenolic amine as a brown oil. To this crude product was added 5,6,7,-trimethoxy-*1H*-indole-2-carboxylic acid (68 mg, 0.27 mmol) and EDCI (105 mg, 0.68 mmol) and the reaction mixture was suspended in anhydrous DMF (3.0 mL) and stirred under argon o/n at rt. Upon reaction completion (monitored by TLC), DMF was removed under reduced pressure, and the mixture was taken in DCM and purified by flash chromatography (EtOAc/hexanes, 1:3) to yield compound **3** (71 mg, 69%) as a buff powder.

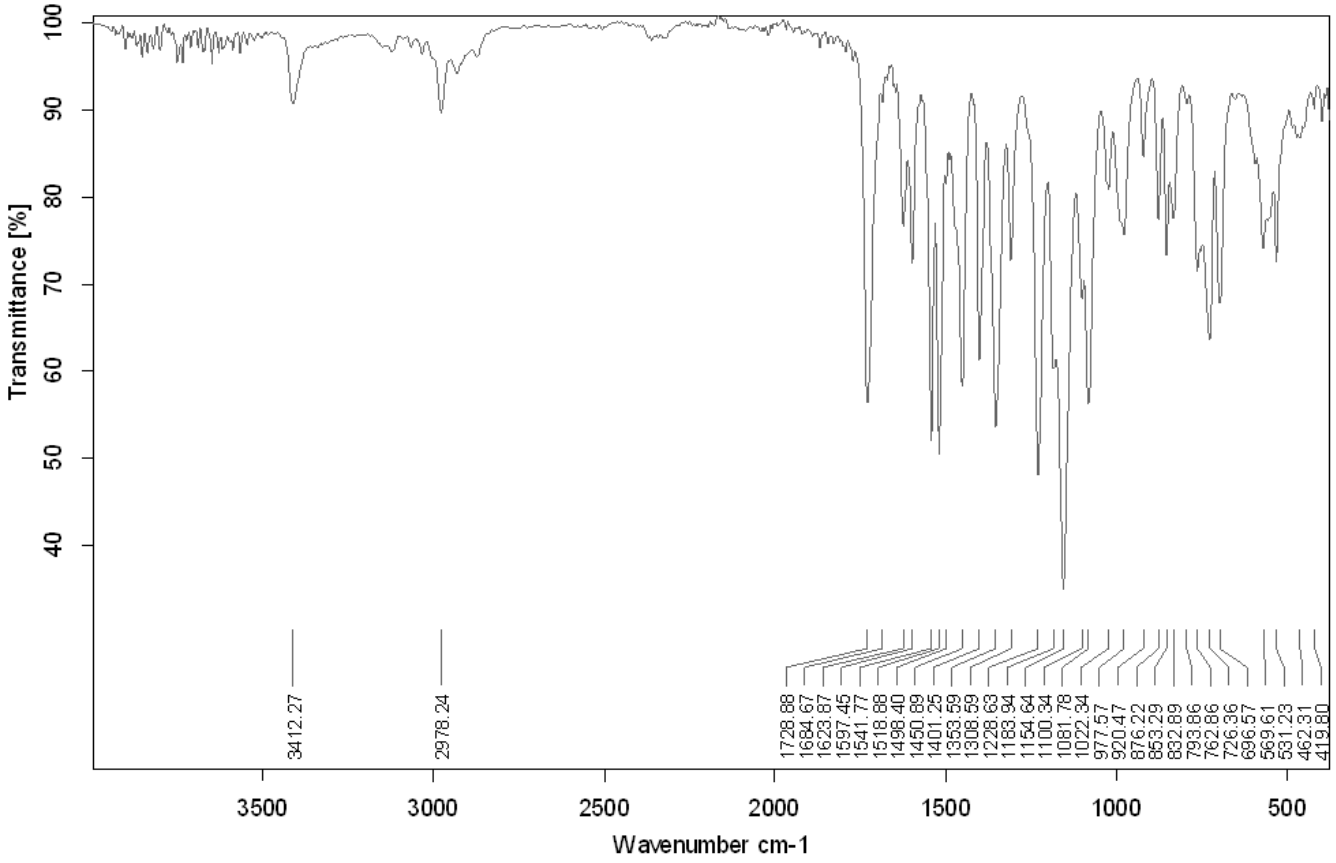
^{1}H NMR spectrum of 8 (300 MHz, $CDCl_3$)



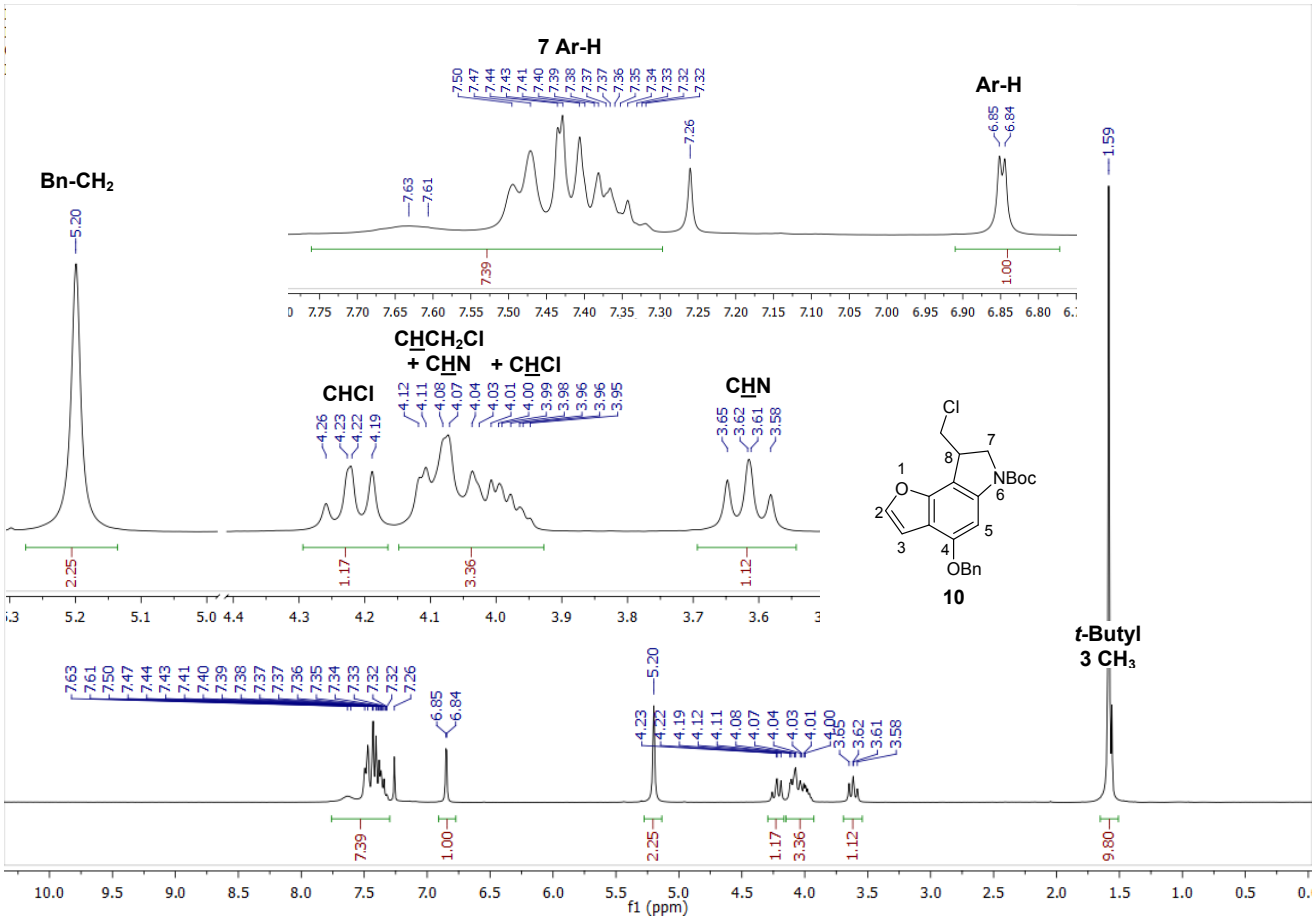
^{13}C NMR spectrum of 8 (75 MHz, $CDCl_3$)



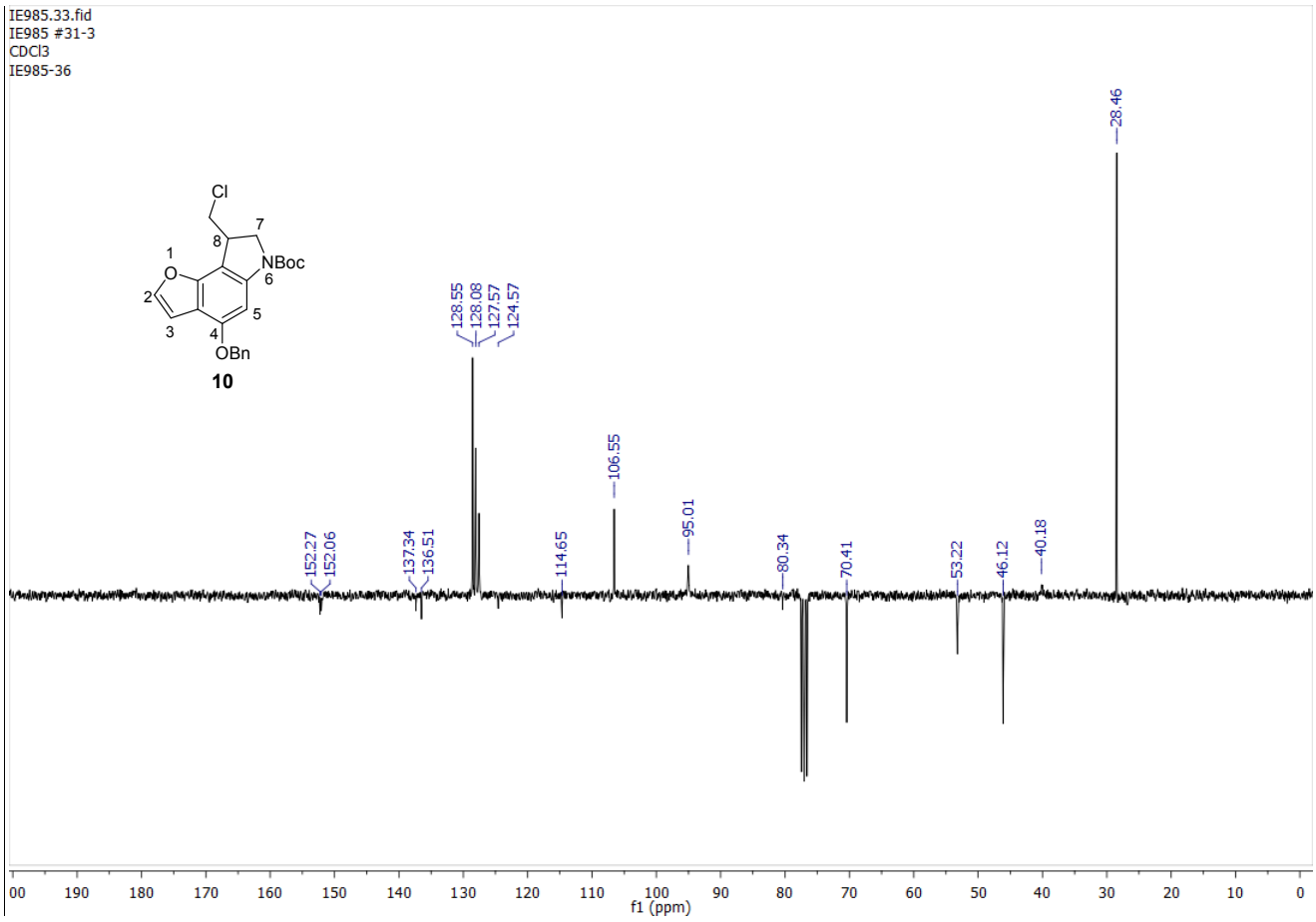
FT-IR spectrum of 8



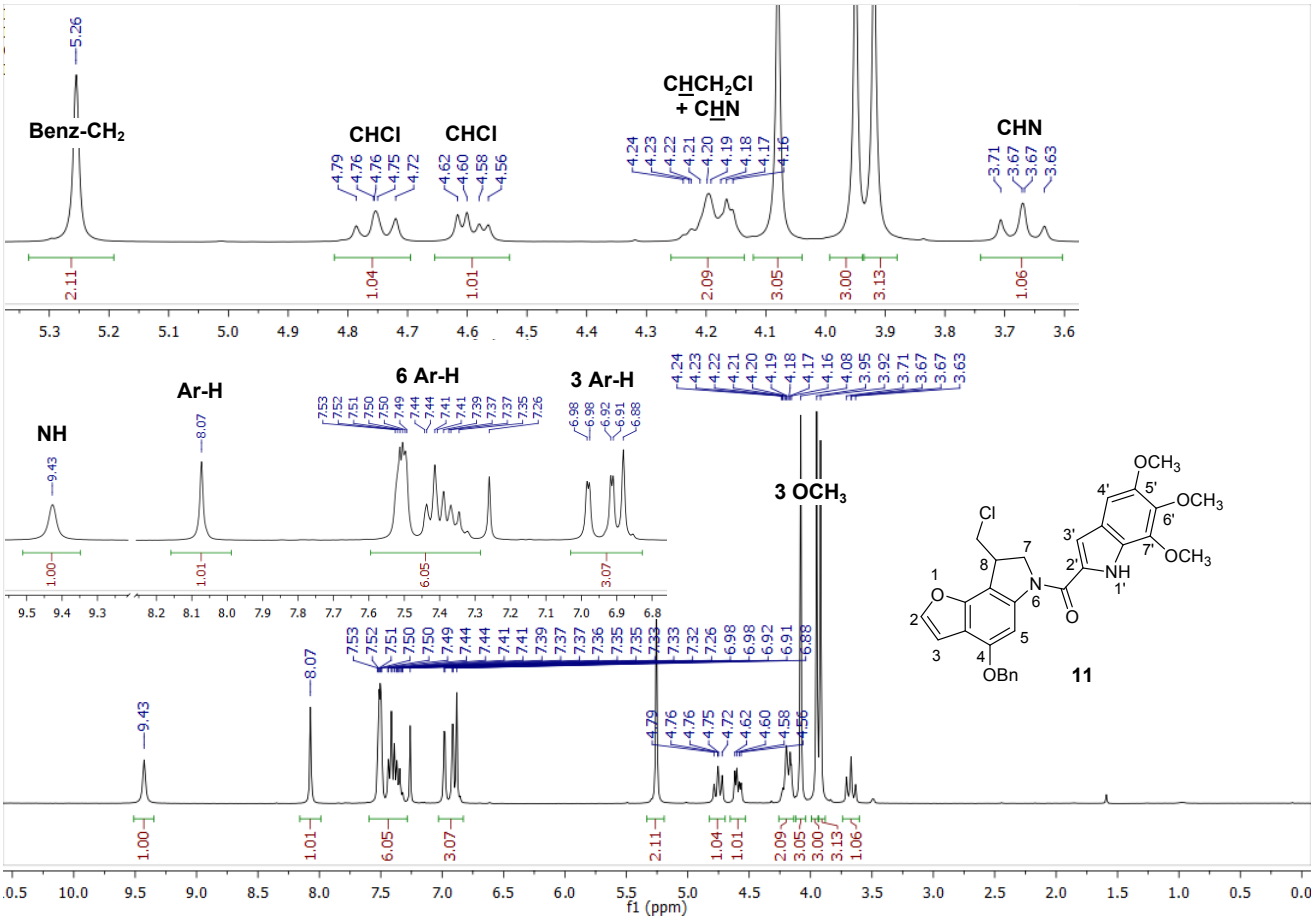
^{1}H NMR spectrum of 10 (300 MHz, $CDCl_3$)



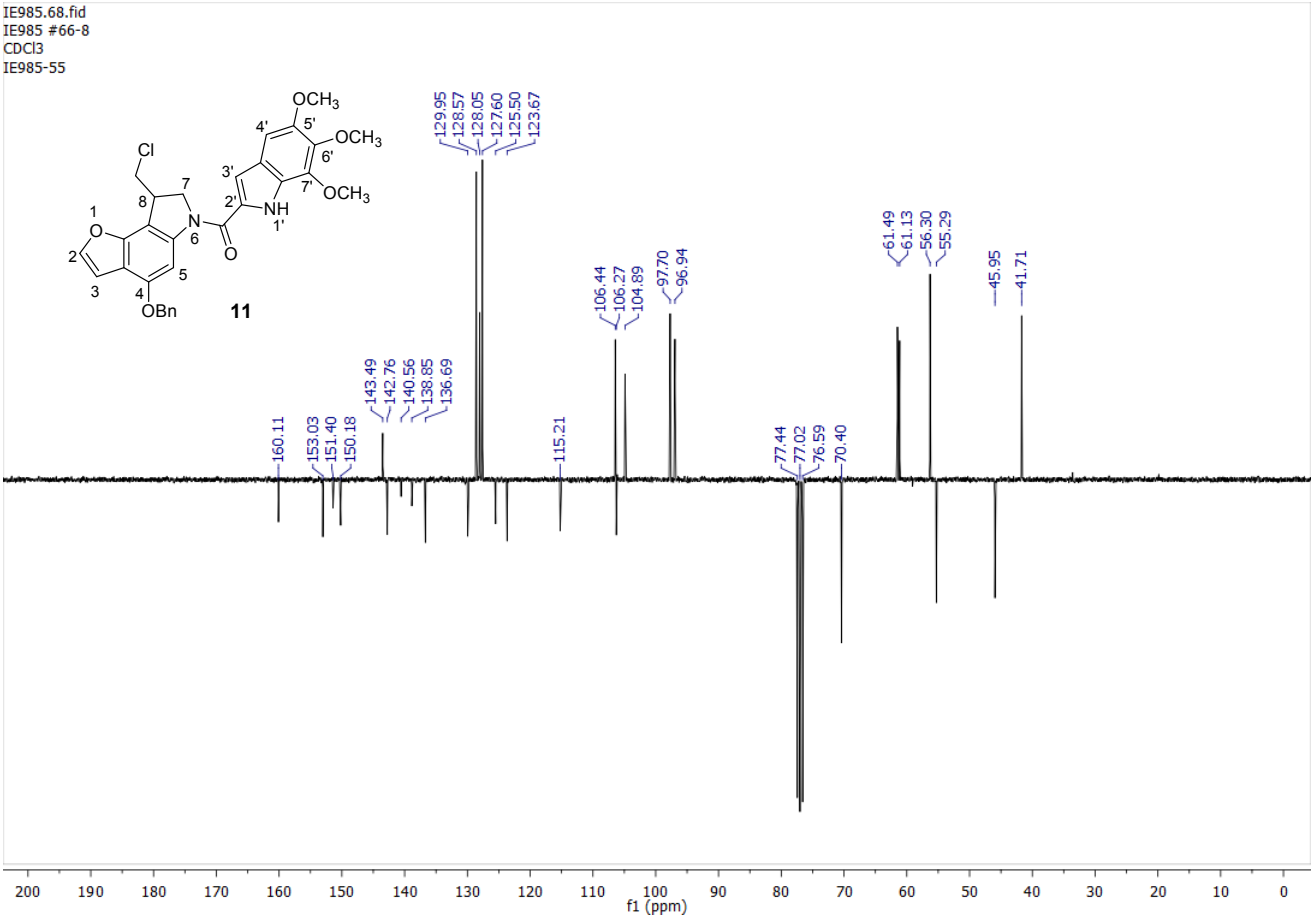
^{13}C NMR spectrum of 10 (75 MHz, $CDCl_3$)



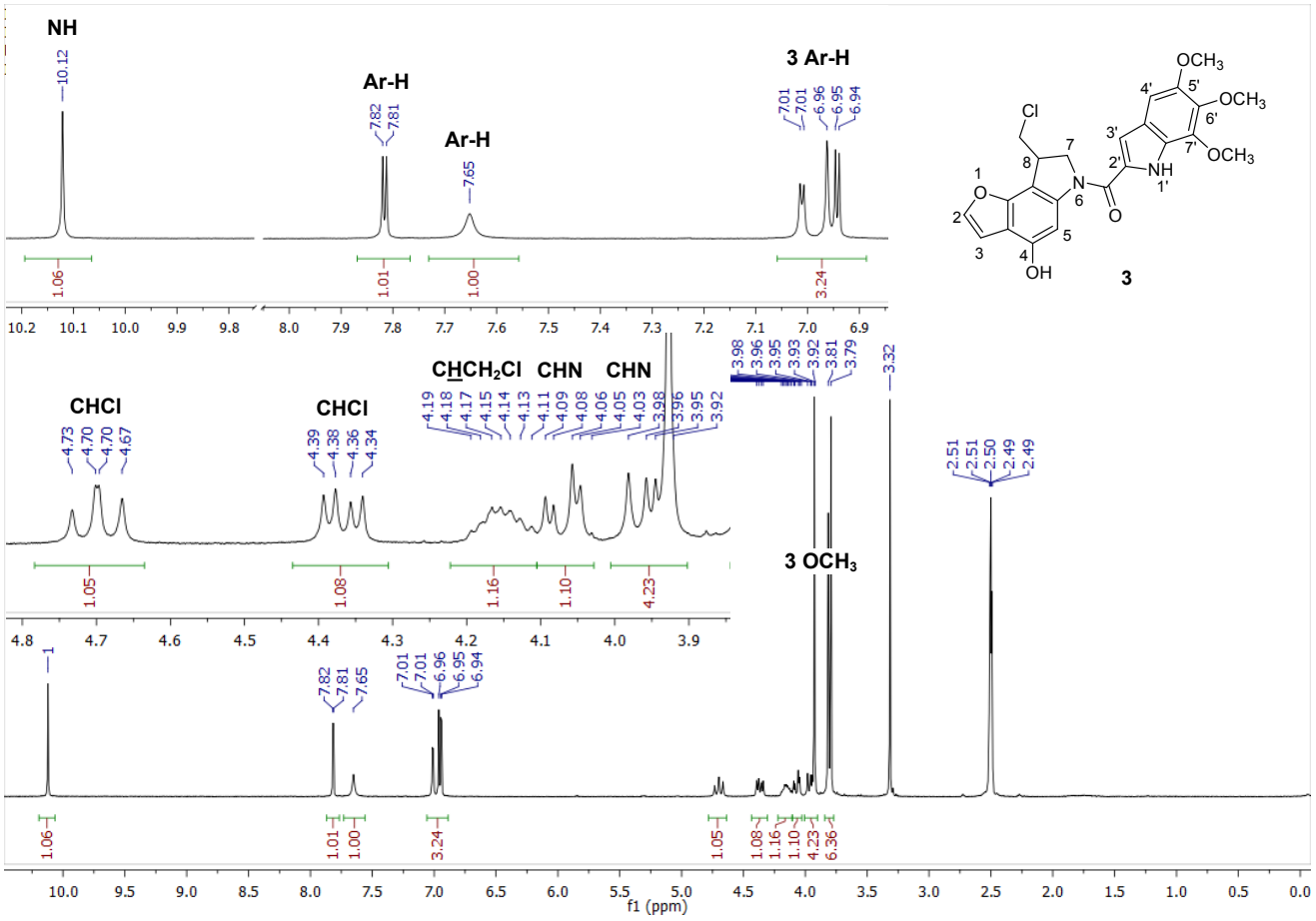
^{1}H NMR spectrum of 11 (300 MHz, $CDCl_3$)



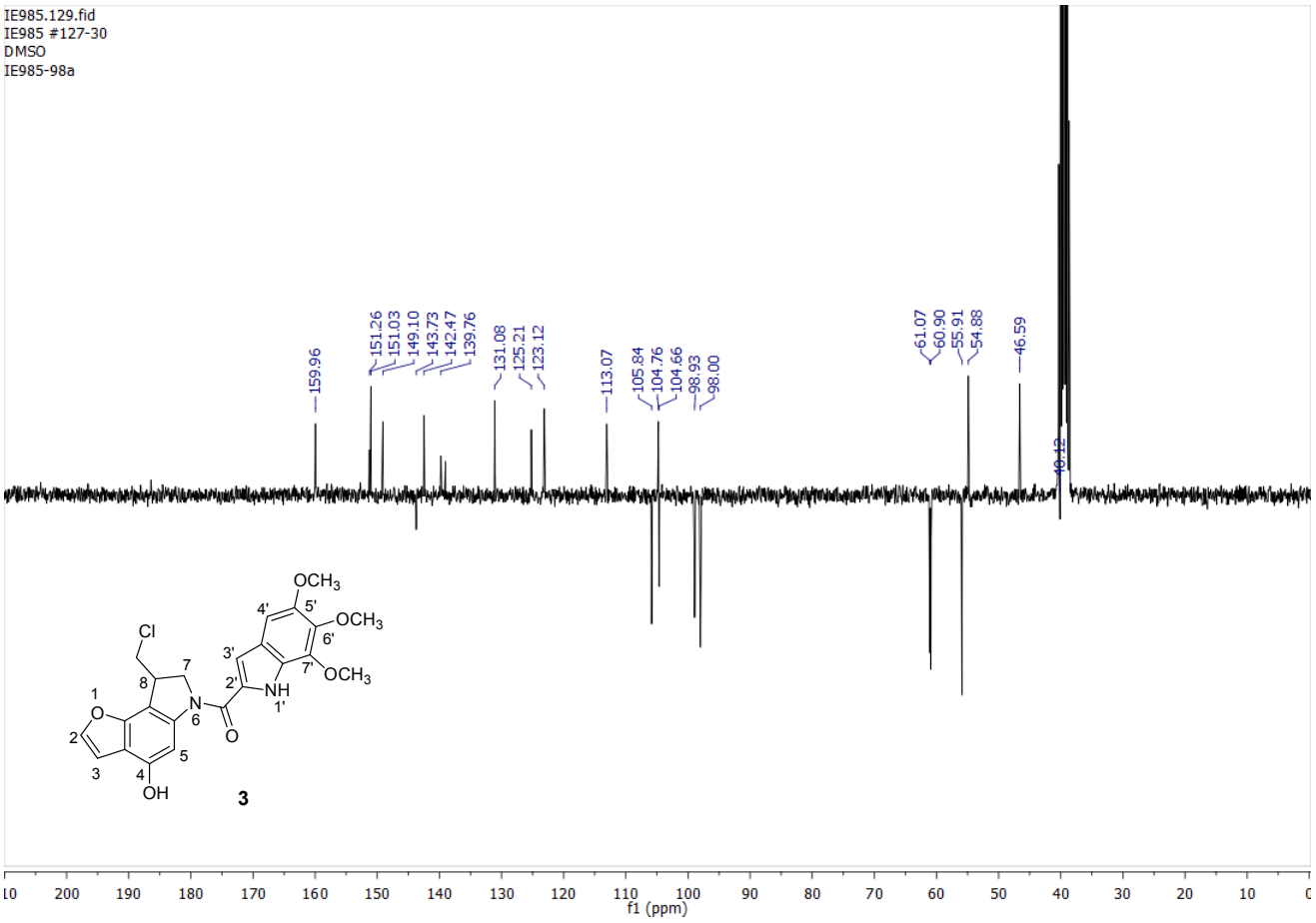
^{13}C NMR spectrum of 11 (75 MHz, $CDCl_3$)



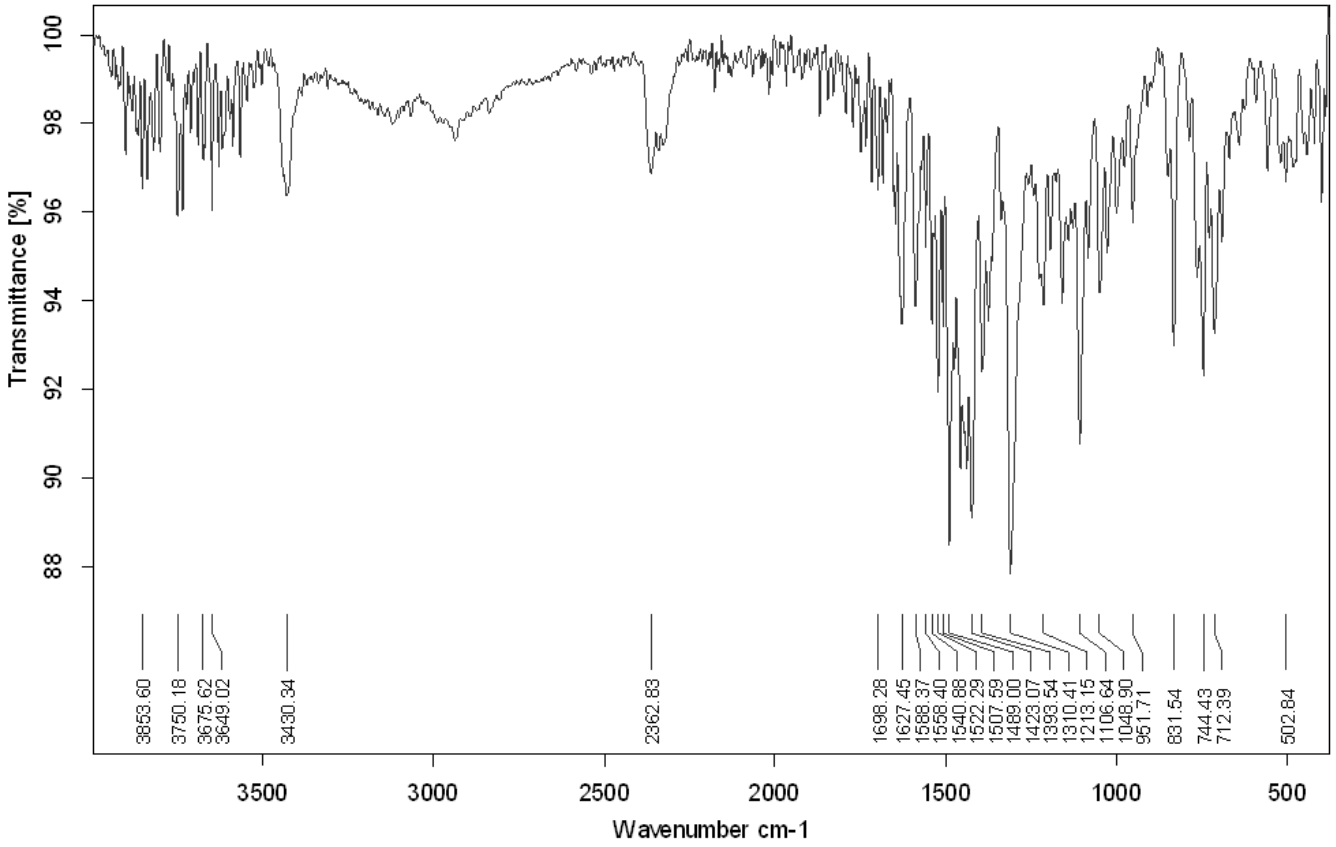
^{1}H NMR spectrum of 3 (300 MHz, d_6-DMSO)



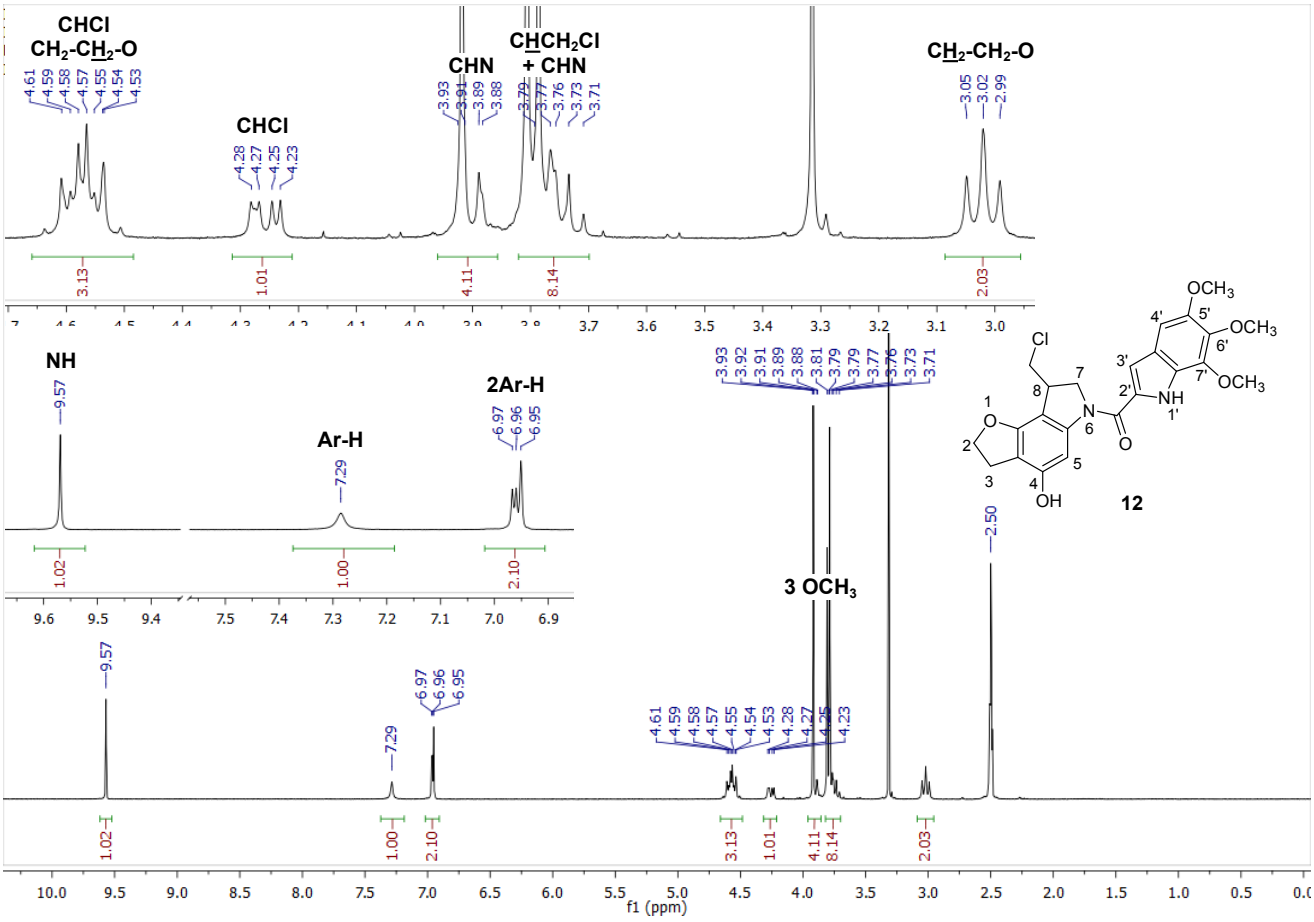
^{13}C NMR spectrum 3 (75 MHz, d_6-DMSO)



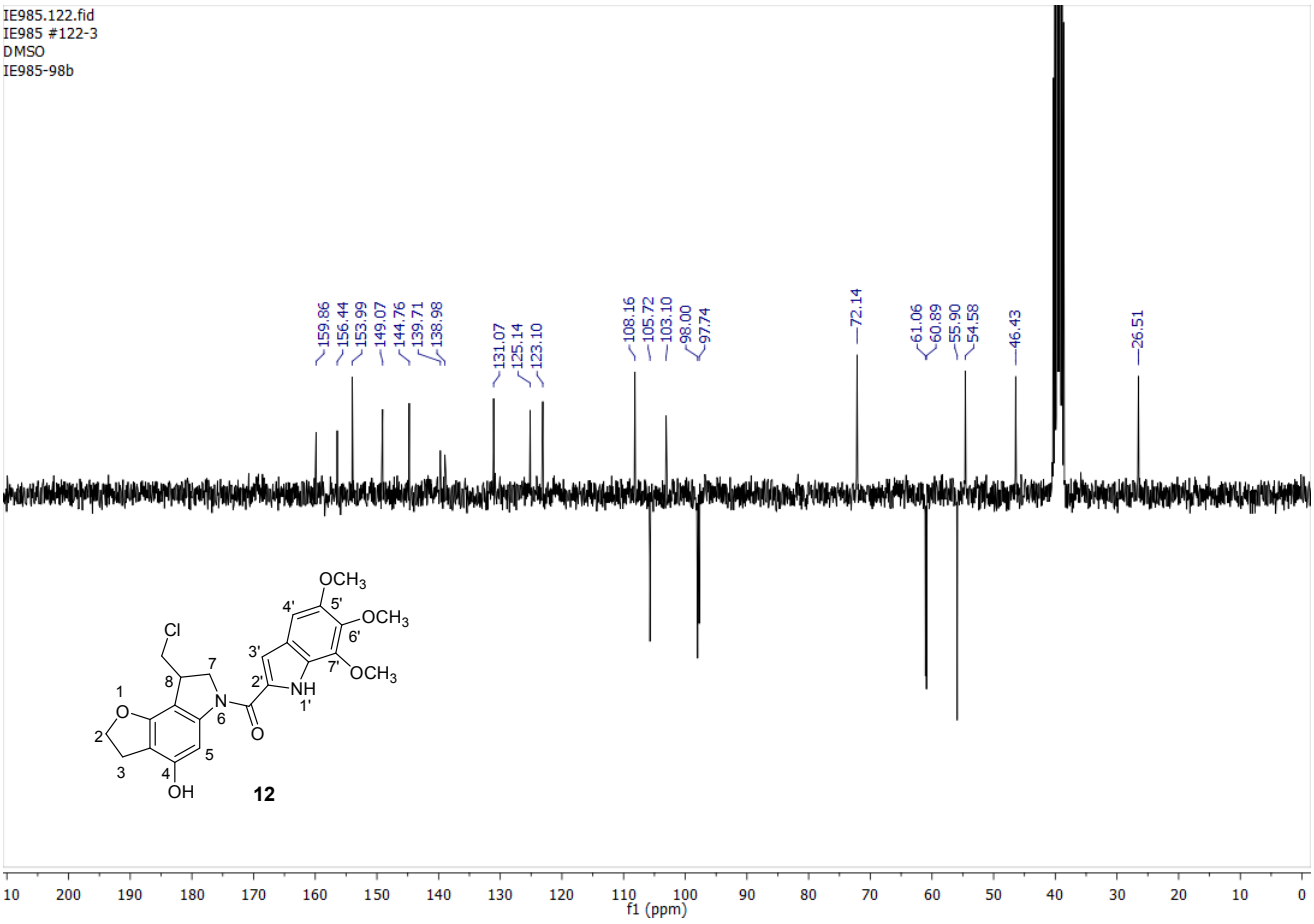
FT-IR spectrum of 3



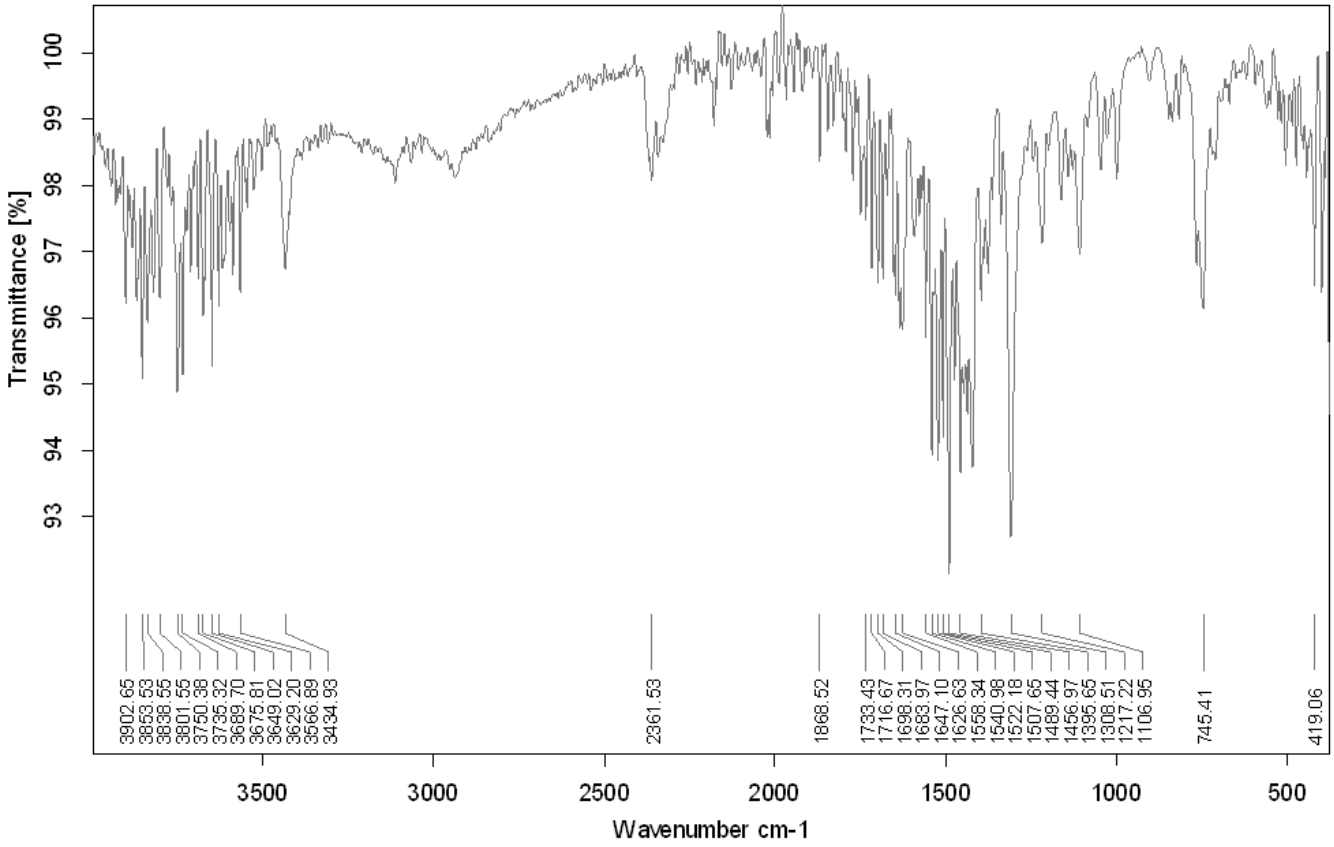
^{1}H NMR spectrum of 12 (300 MHz, d_6-DMSO)



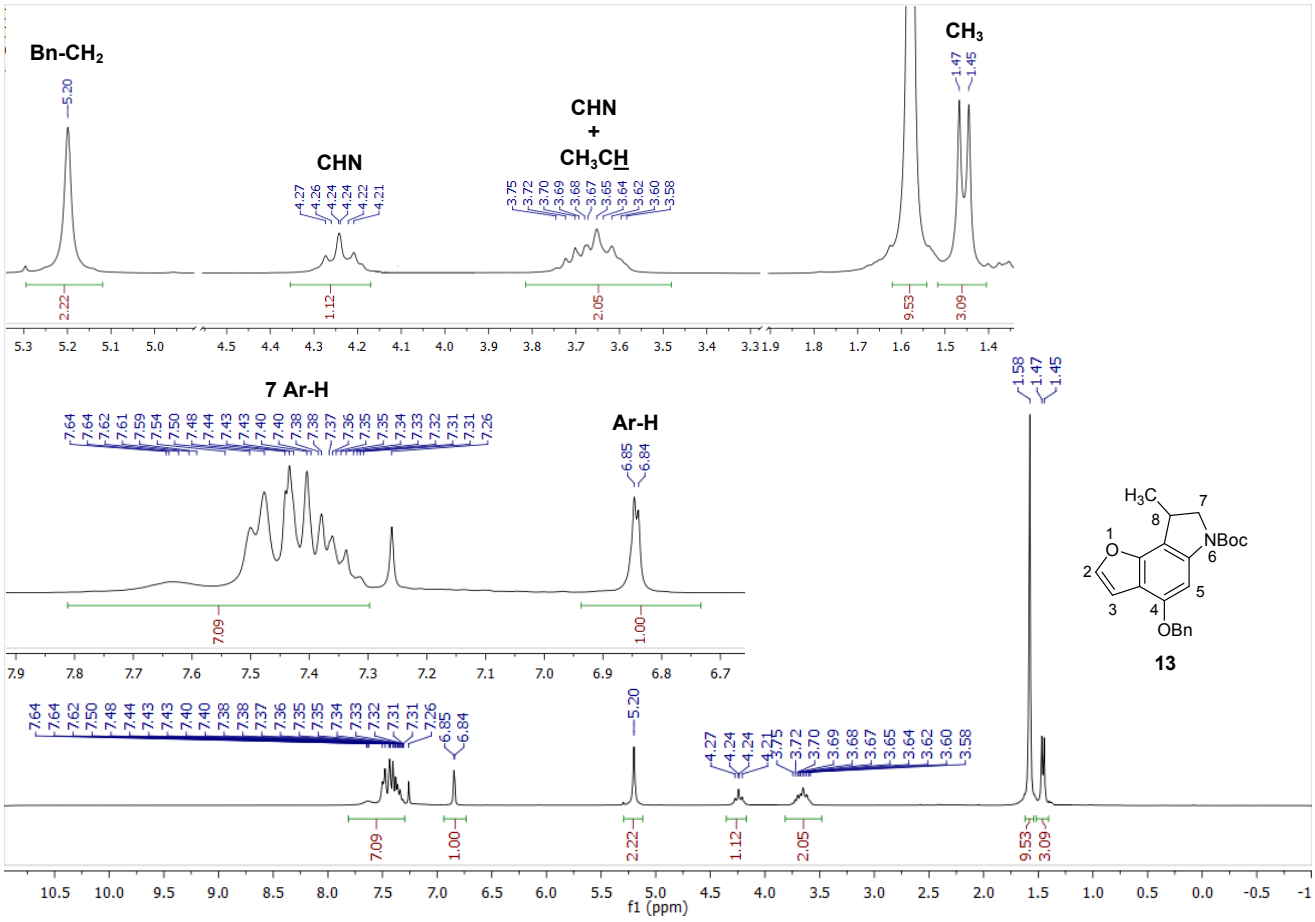
^{13}C NMR spectrum 12 (75 MHz, d_6-DMSO)



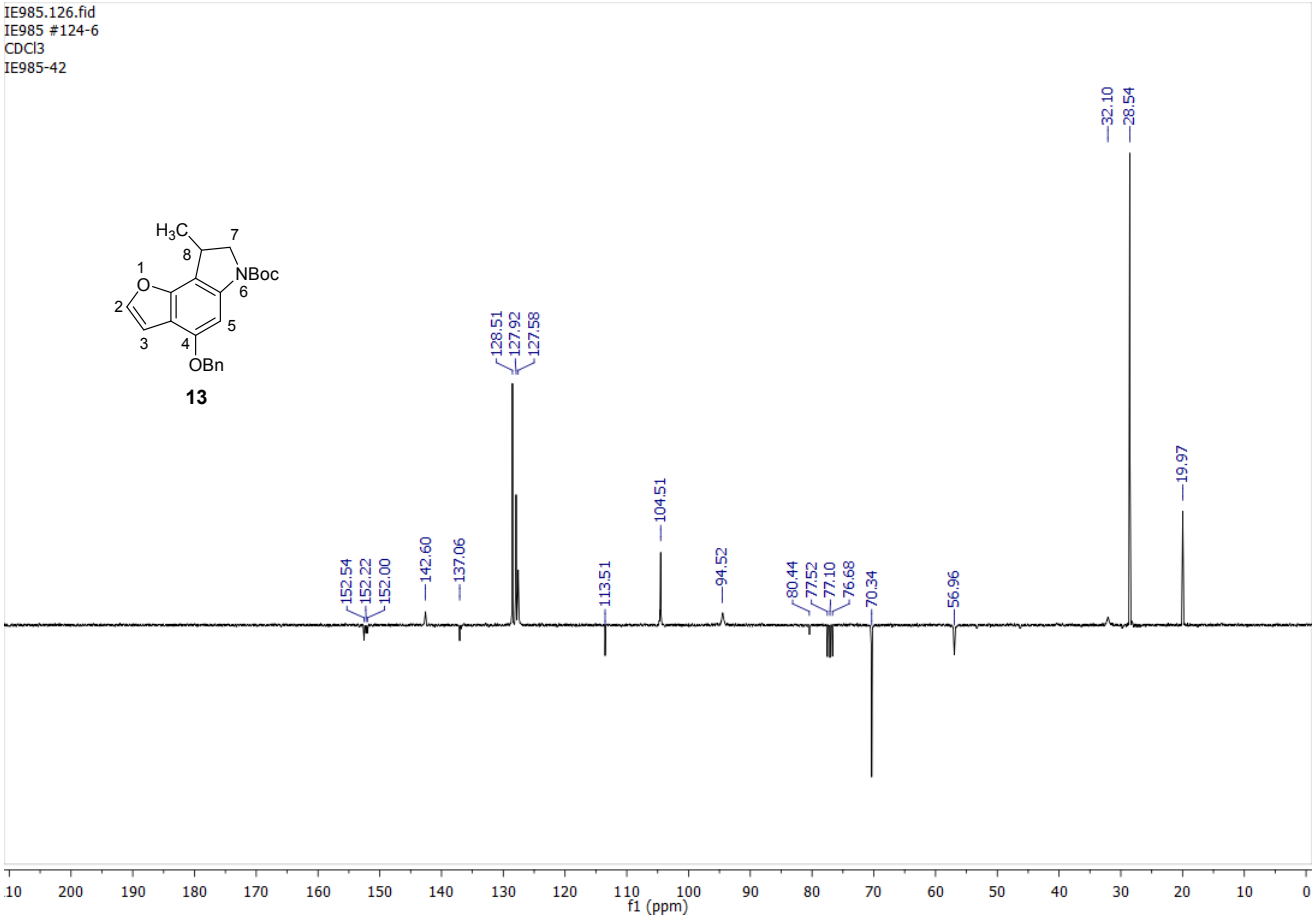
FT-IR spectrum of 12



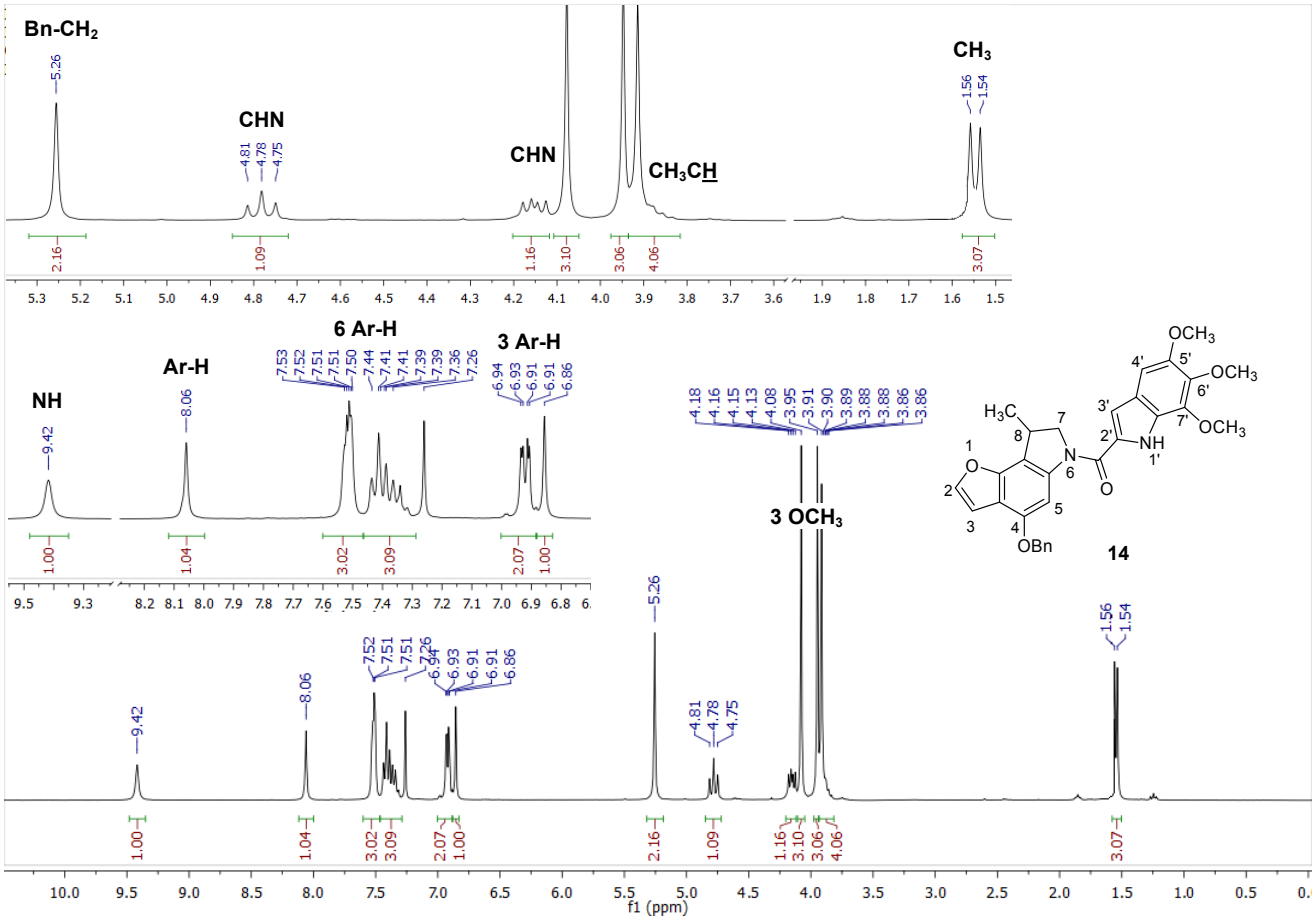
^{1}H NMR spectrum of 13 (300 MHz, $CDCl_3$)



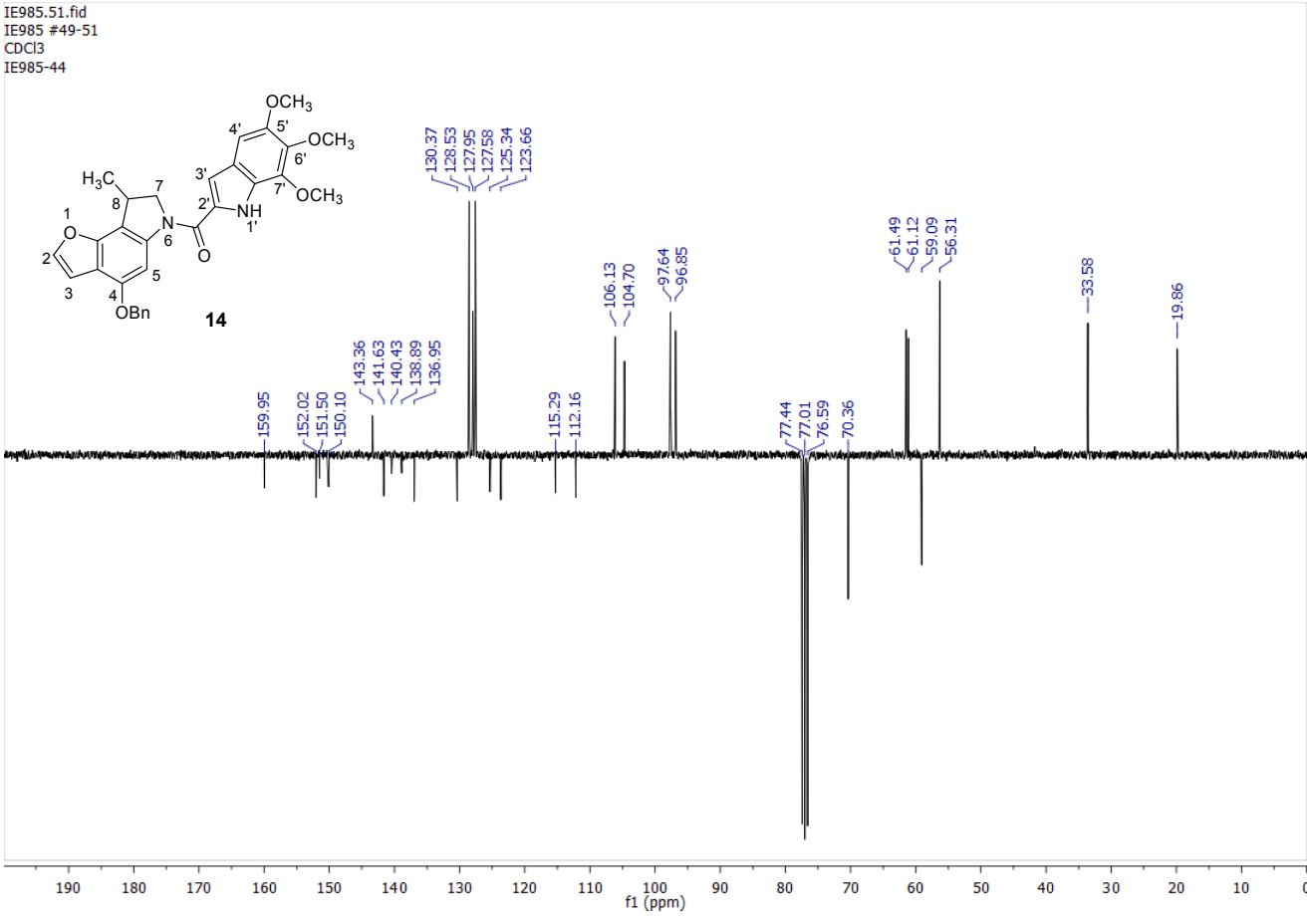
^{13}C NMR spectrum of 13 (75 MHz, $CDCl_3$)



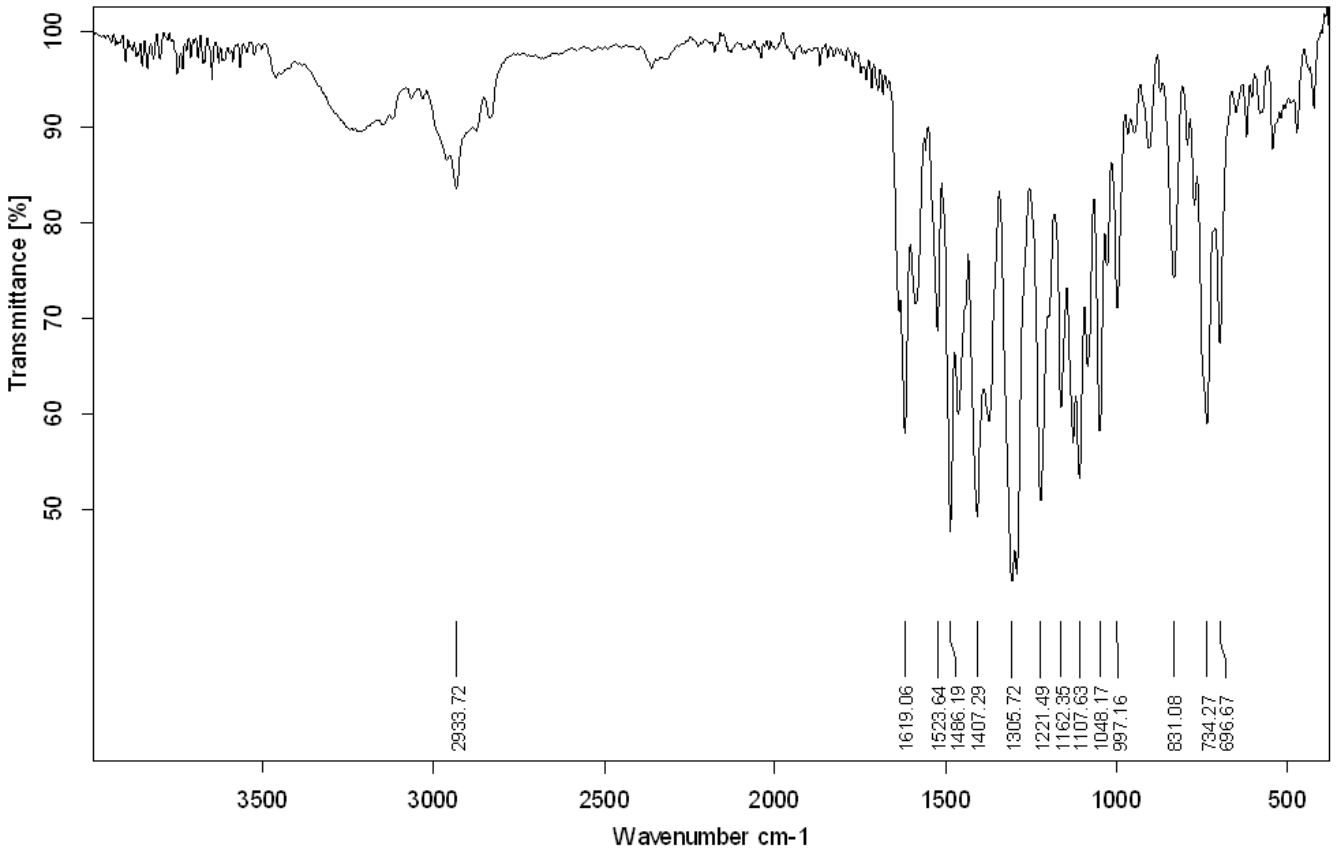
^{1}H NMR spectrum of 14 (300 MHz, $CDCl_3$)



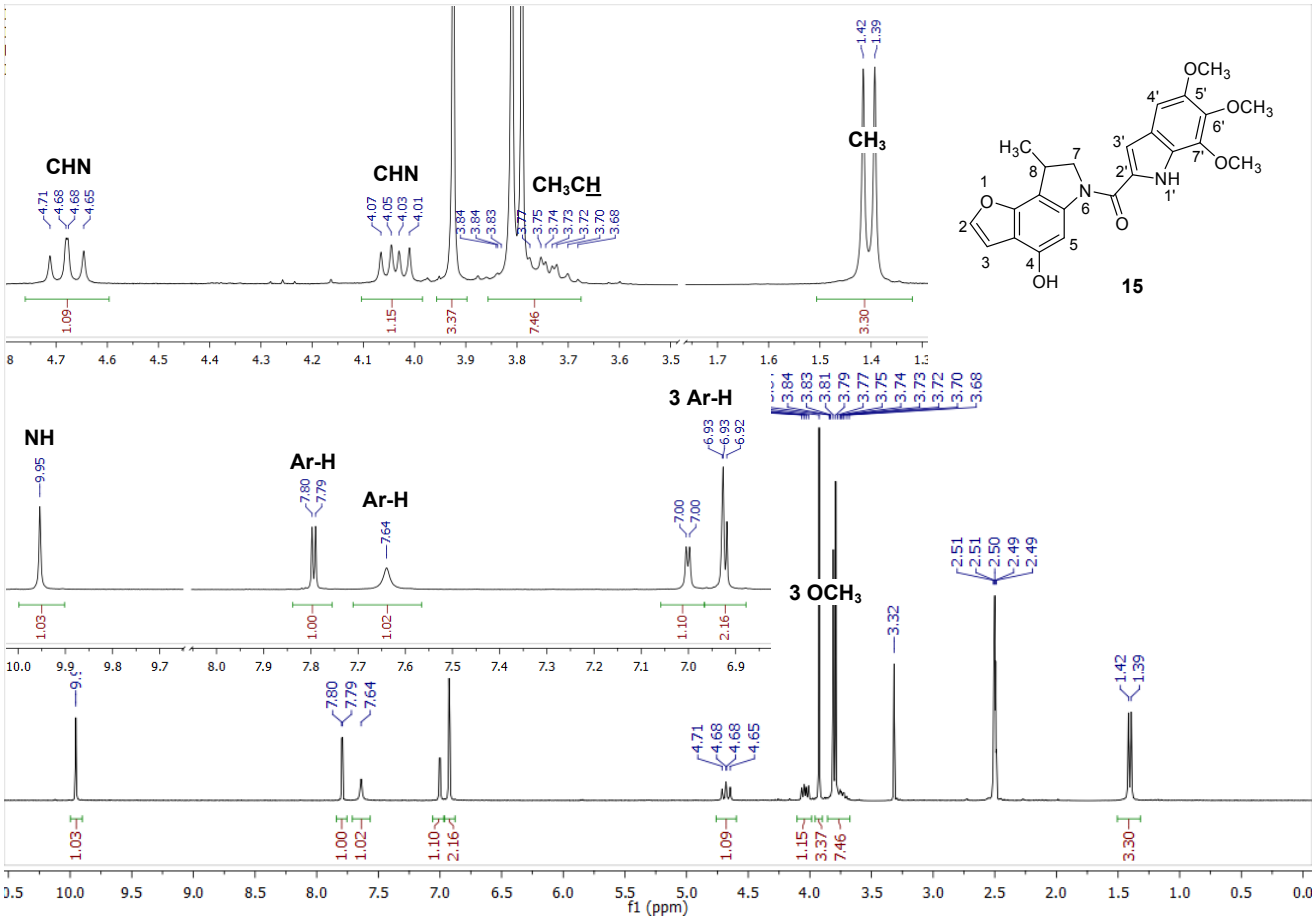
^{13}C NMR spectrum of 14 (75 MHz, $CDCl_3$)



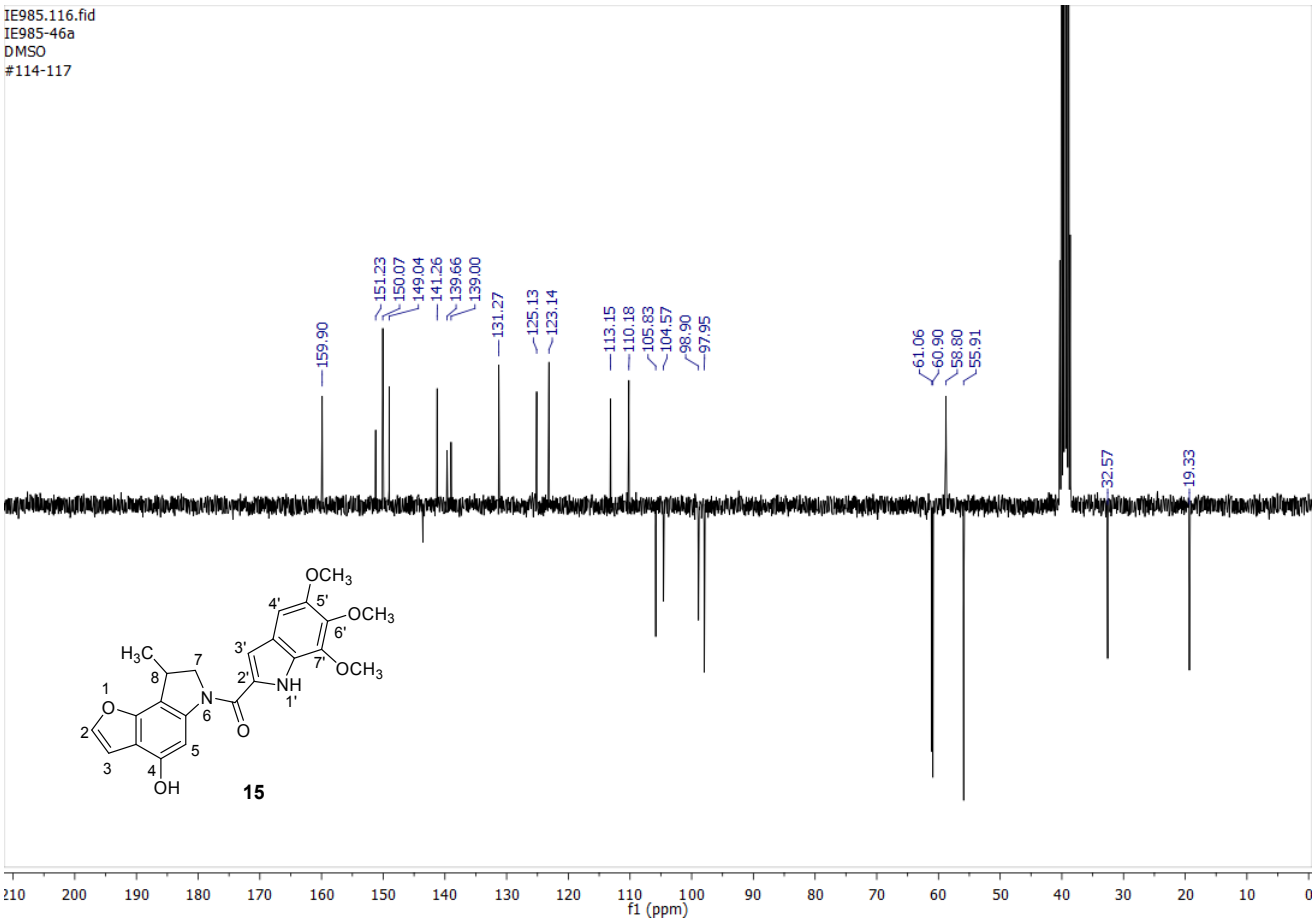
FT-IR spectrum of 14



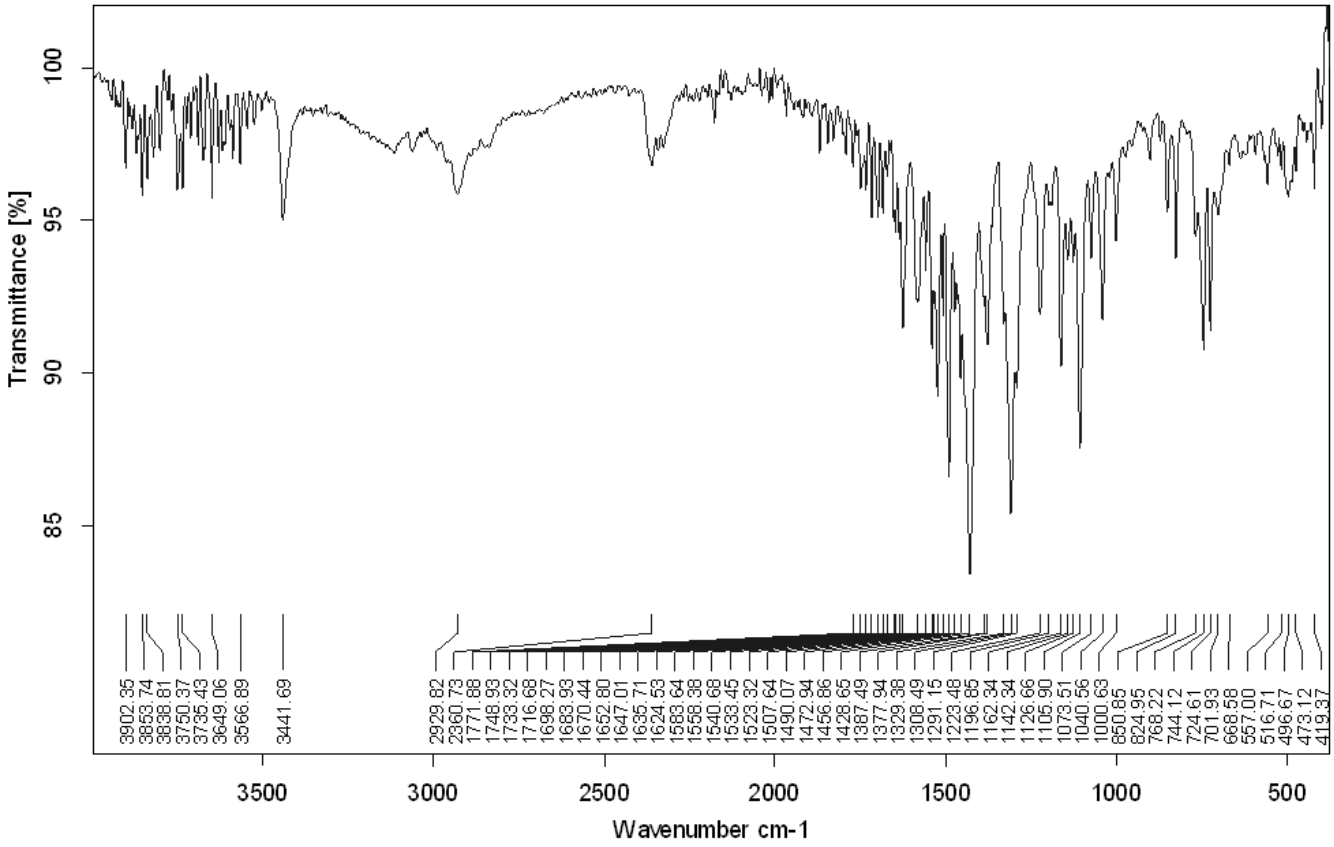
^{1}H NMR spectrum of 15 (300 MHz, d_6-DMSO)



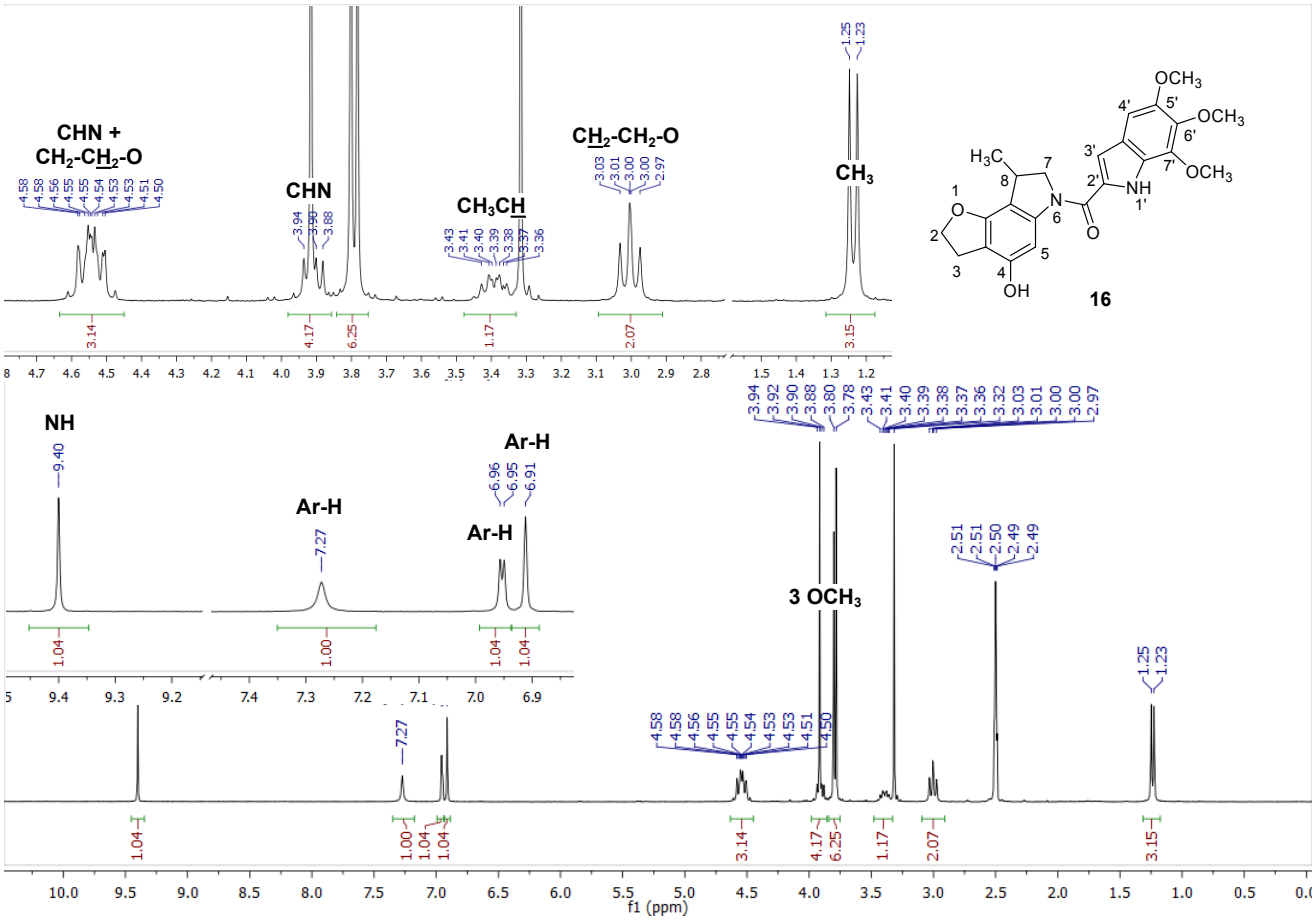
^{13}C NMR spectrum of 15 (75 MHz, d_6-DMSO)



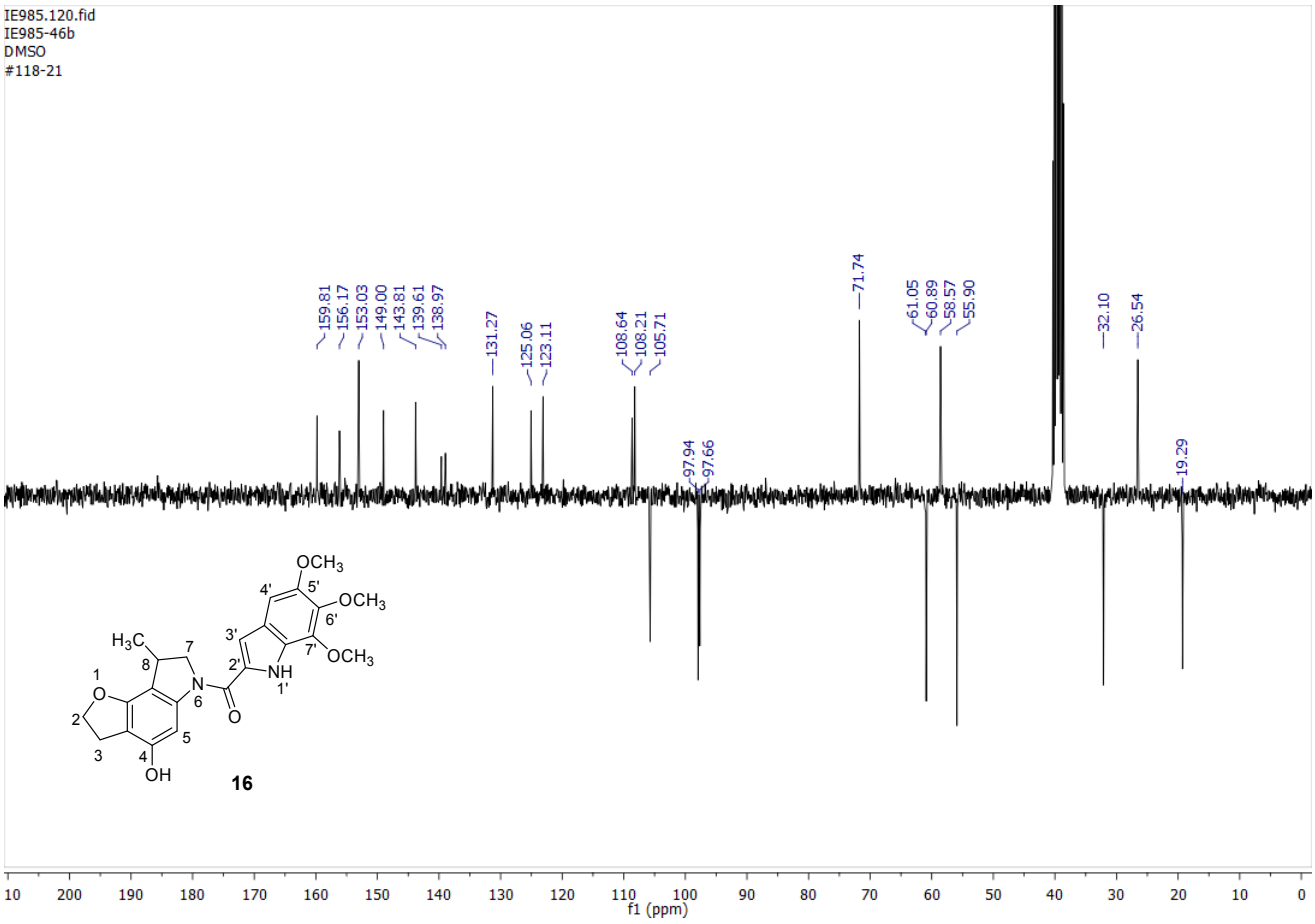
FT-IR spectrum of 15



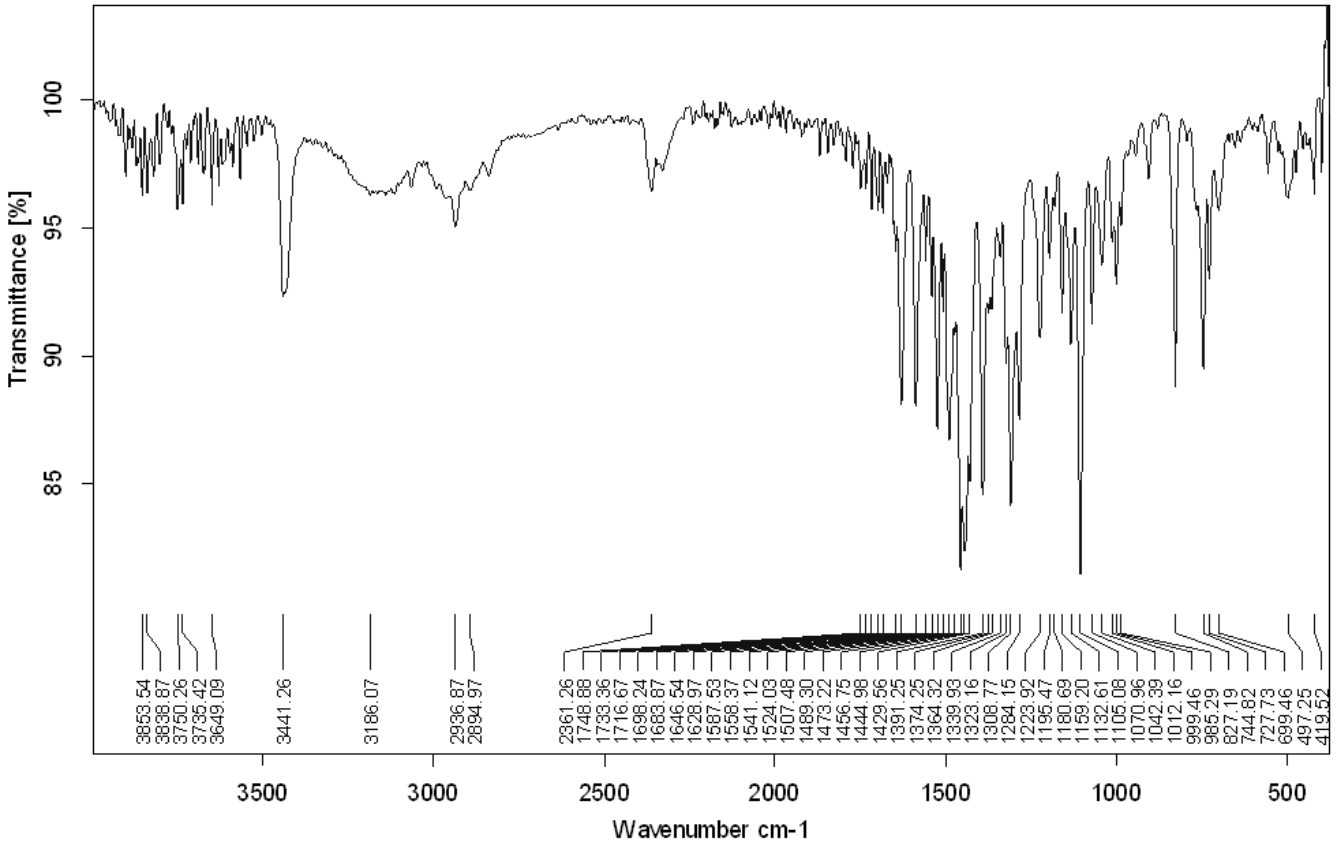
^{1}H NMR spectrum of 16 (300 MHz, d_6-DMSO)



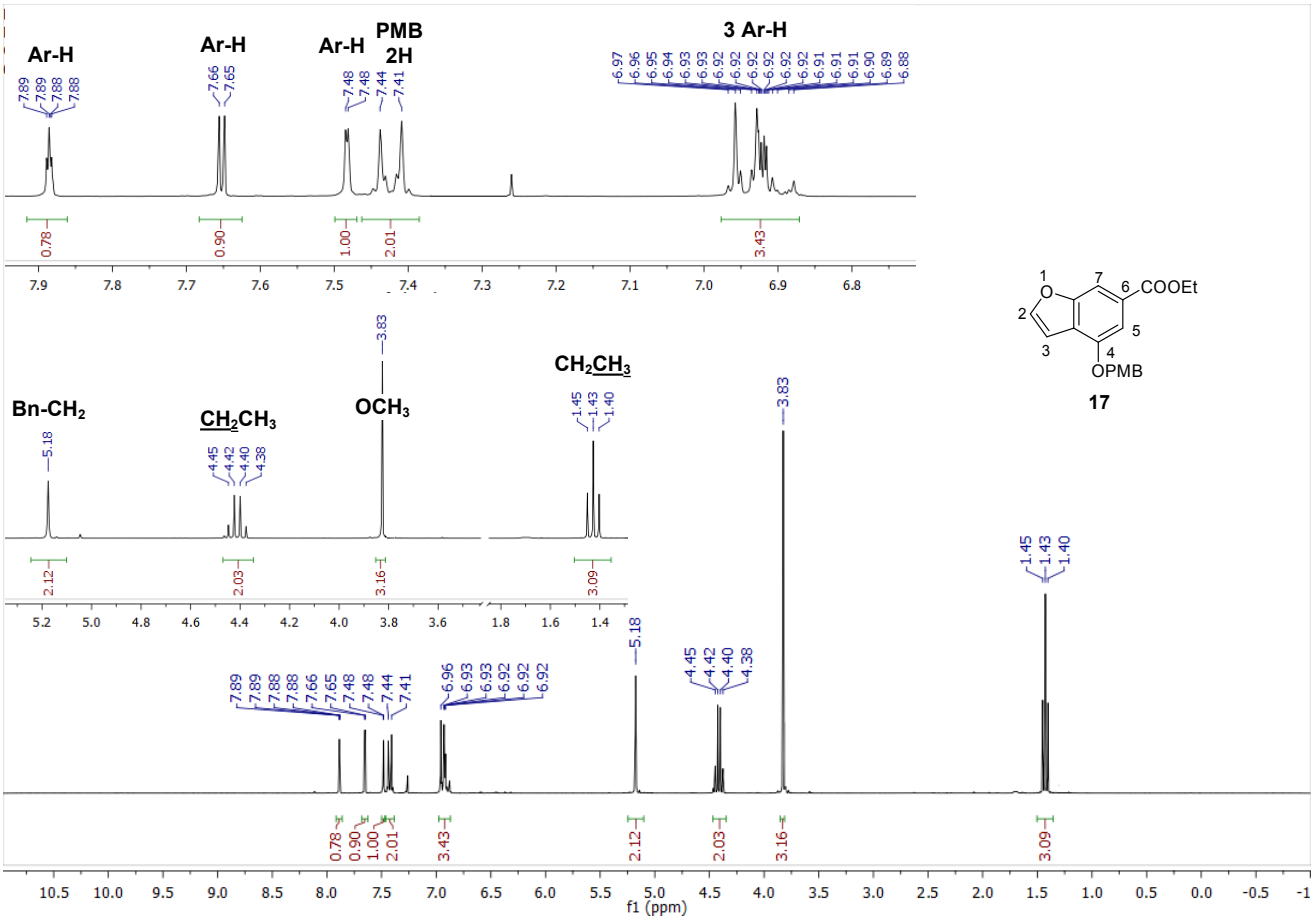
^{13}C NMR spectrum of 16 (75 MHz, d_6-DMSO)



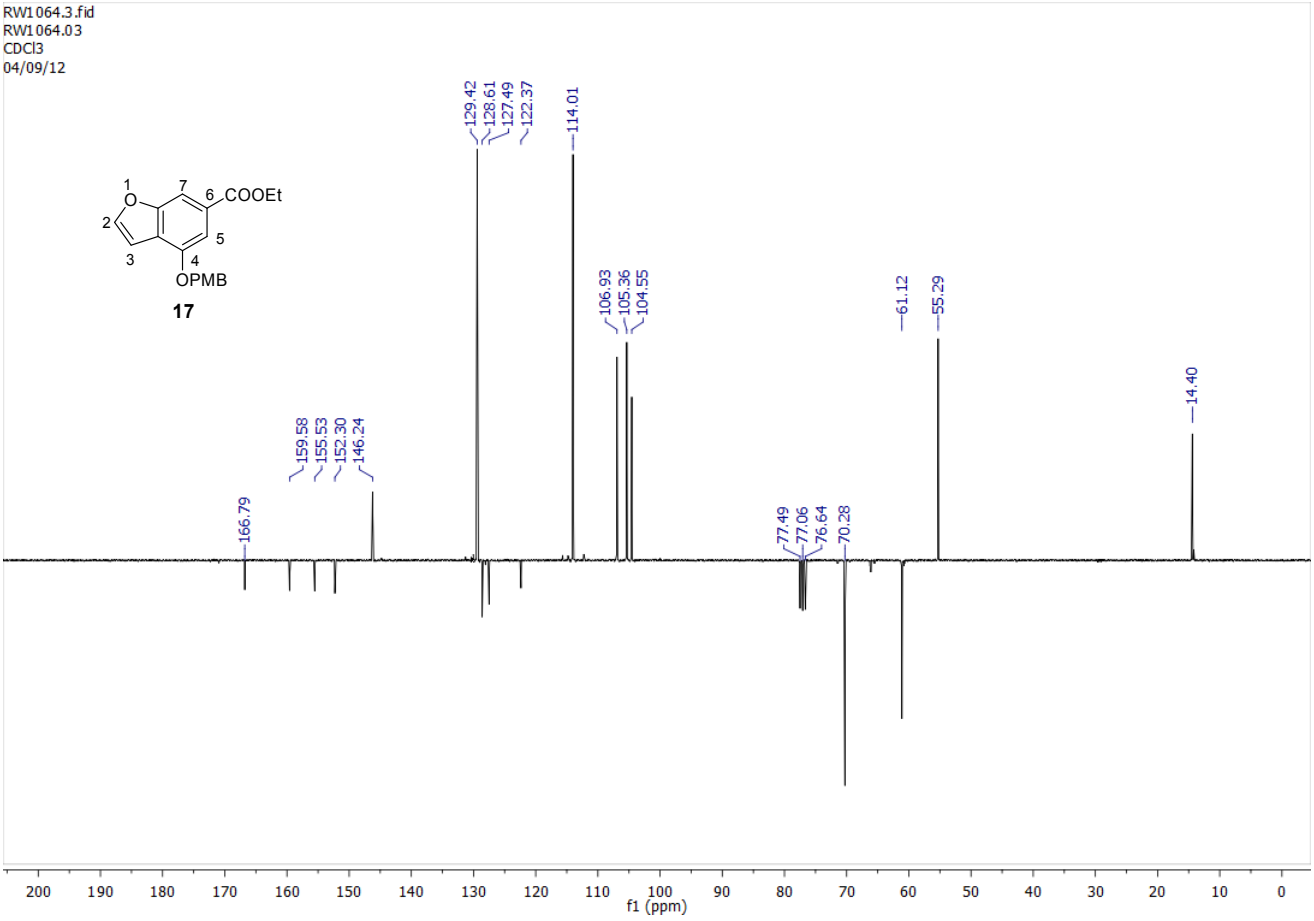
FT-IR spectrum of 16



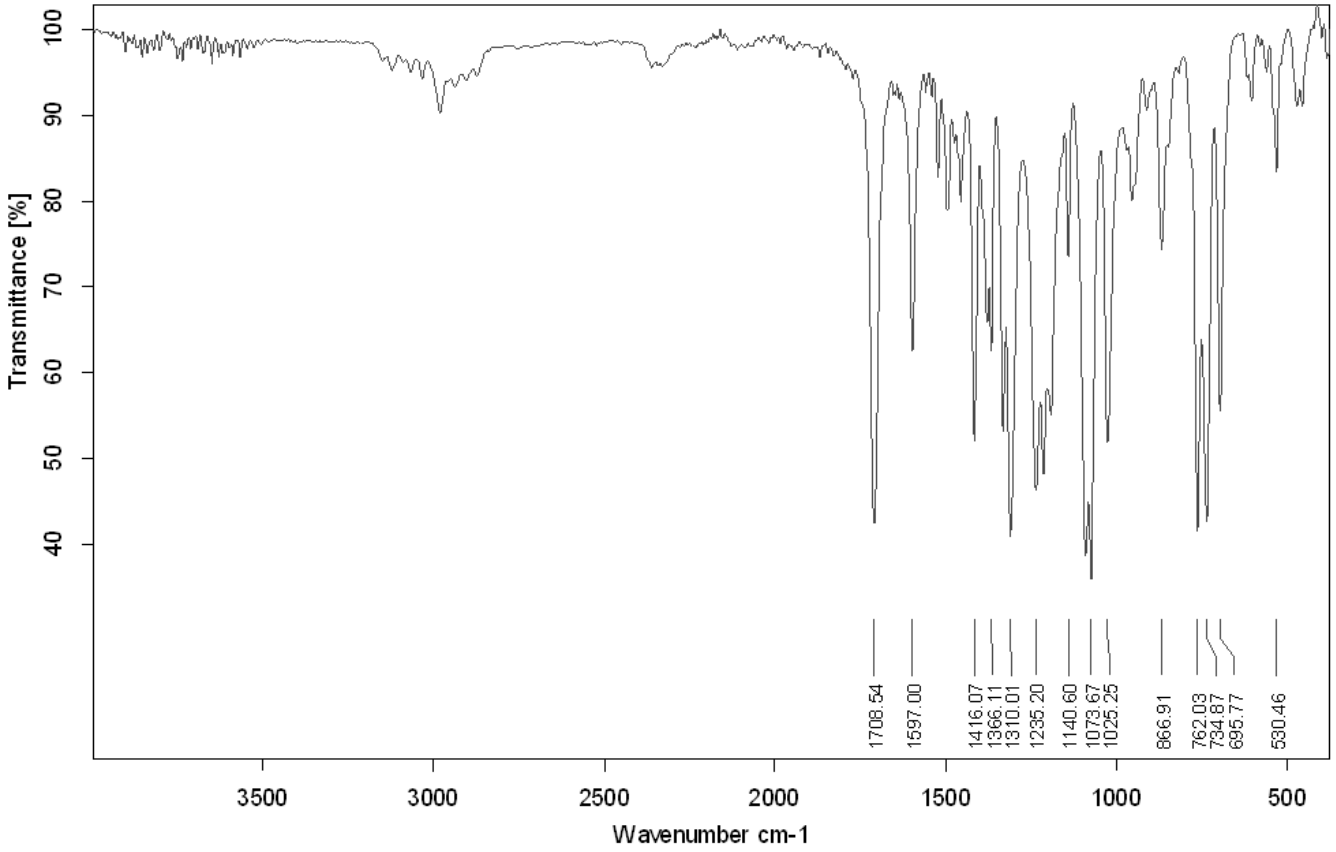
^{1}H NMR spectrum of 17 (300 MHz, $CDCl_3$)



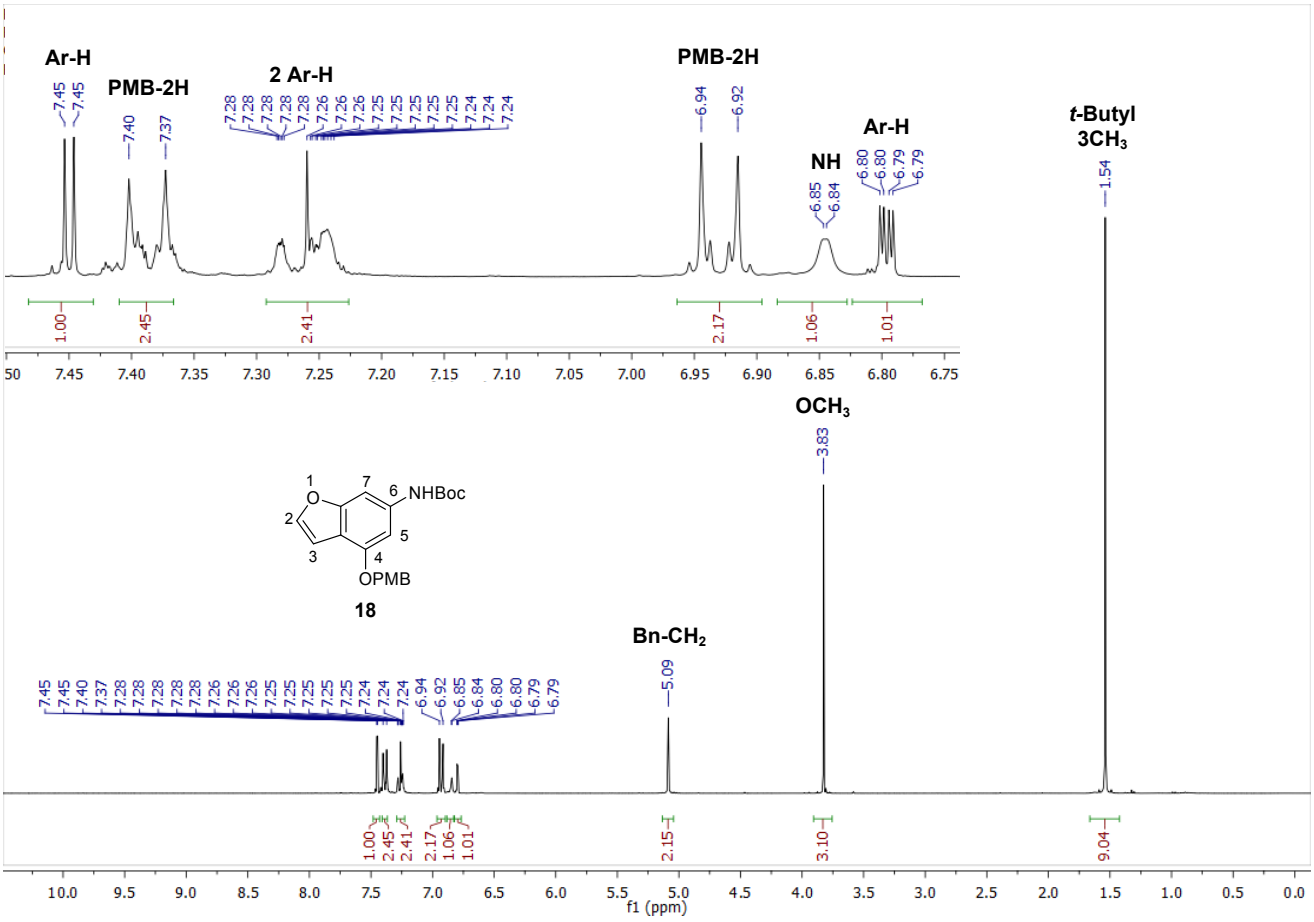
^{13}C NMR spectrum of 17 (75 MHz, $CDCl_3$)



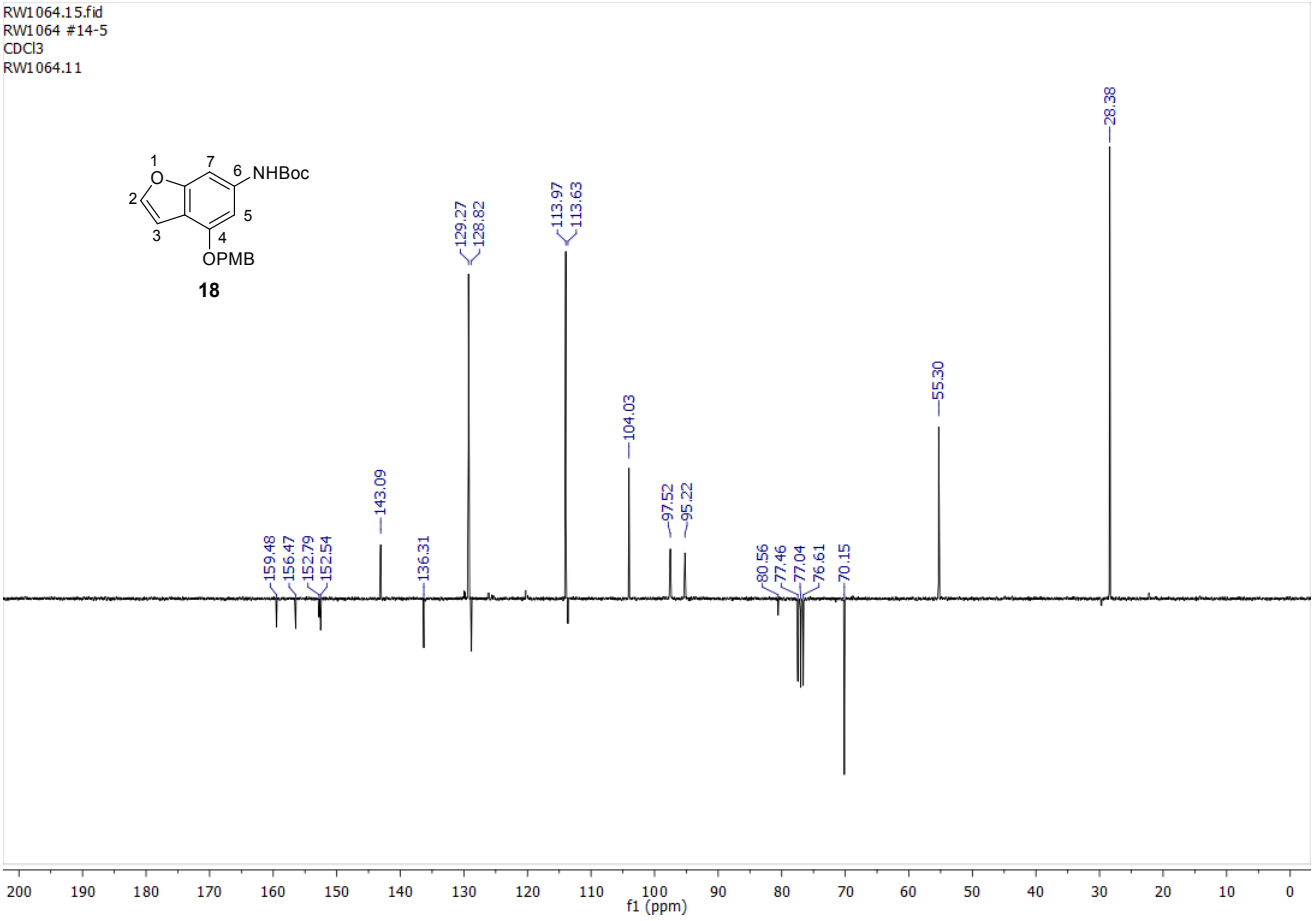
FT-IR spectrum of 17



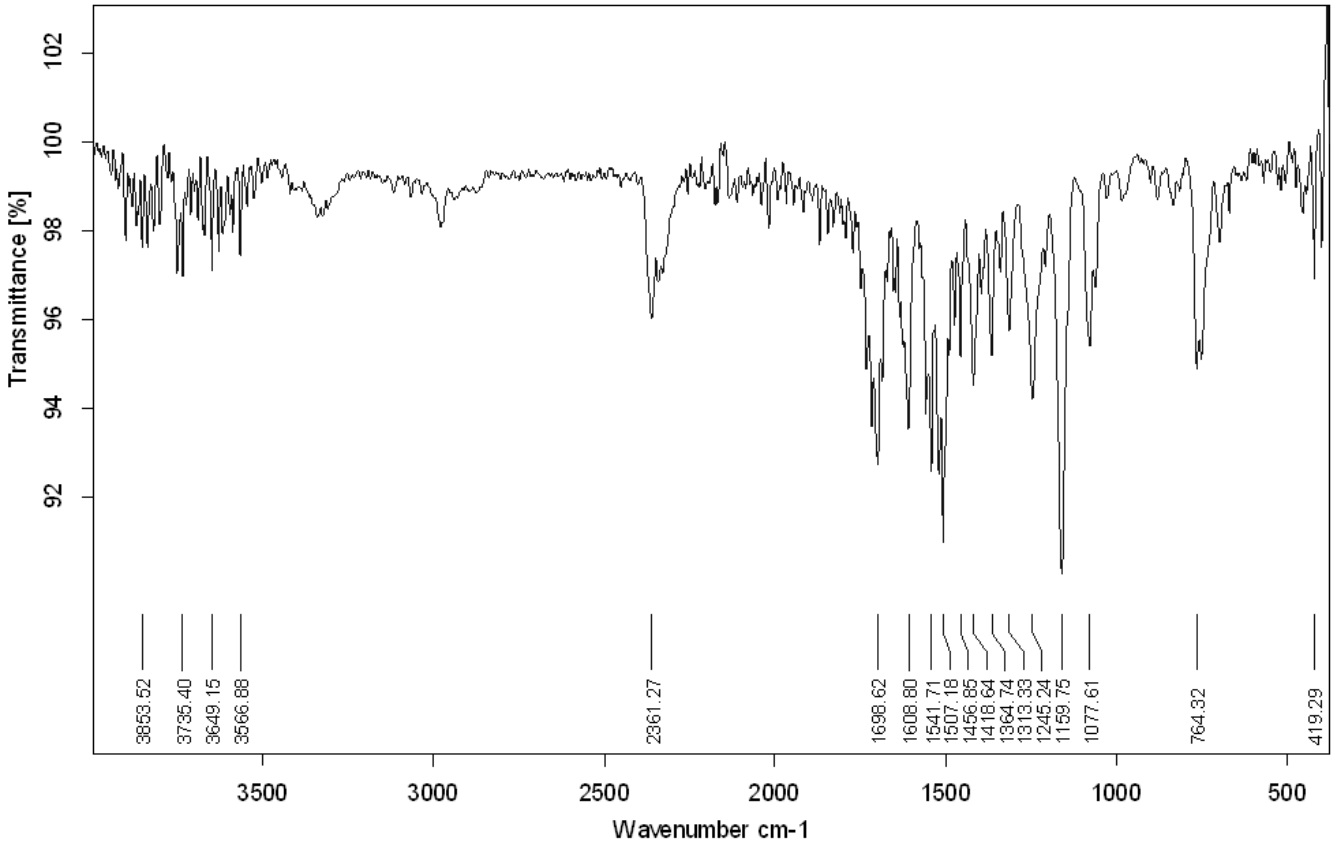
^{1}H NMR spectrum of 18 (300 MHz, $CDCl_3$)



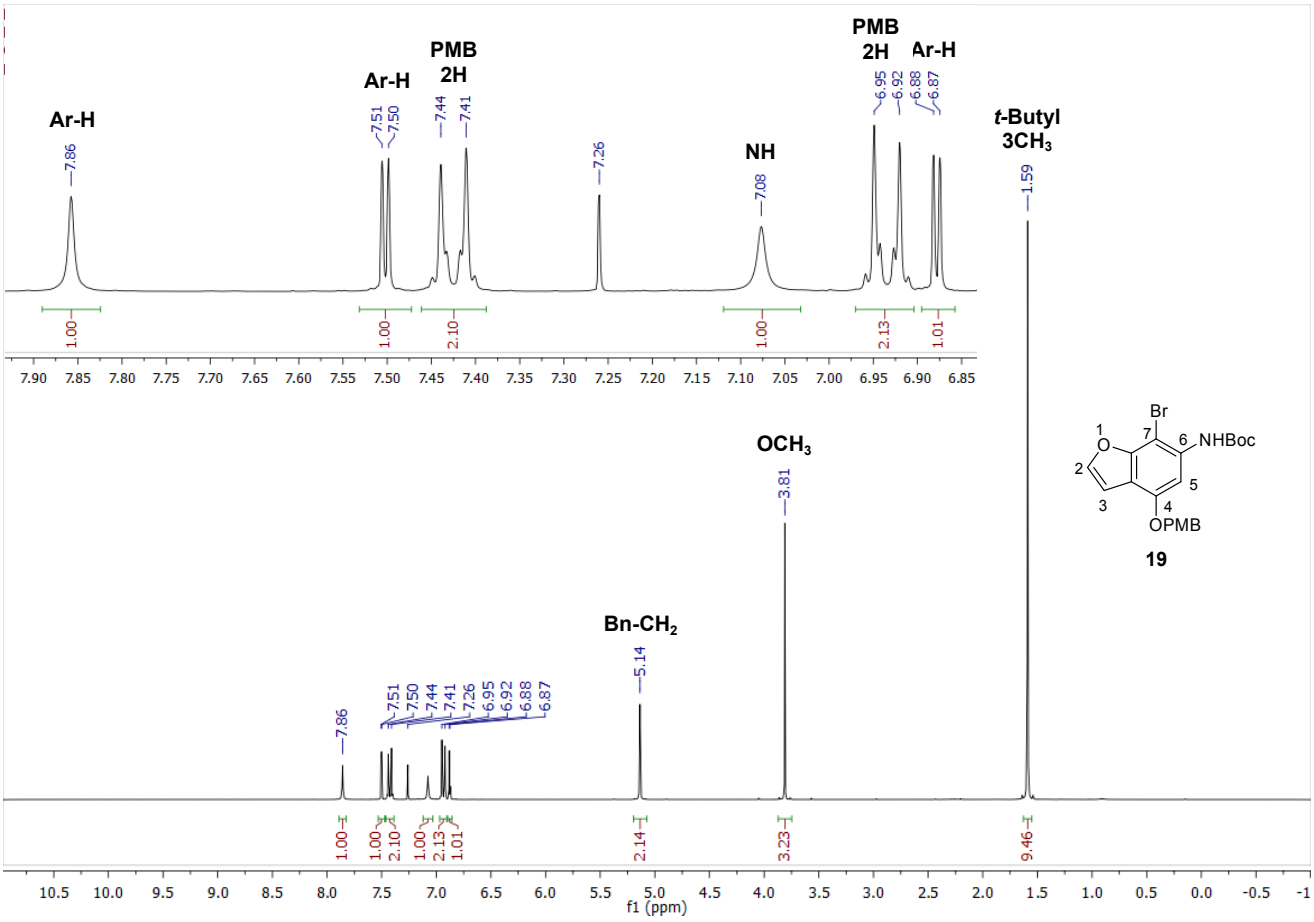
^{13}C NMR spectrum of 18 (75 MHz, $CDCl_3$)



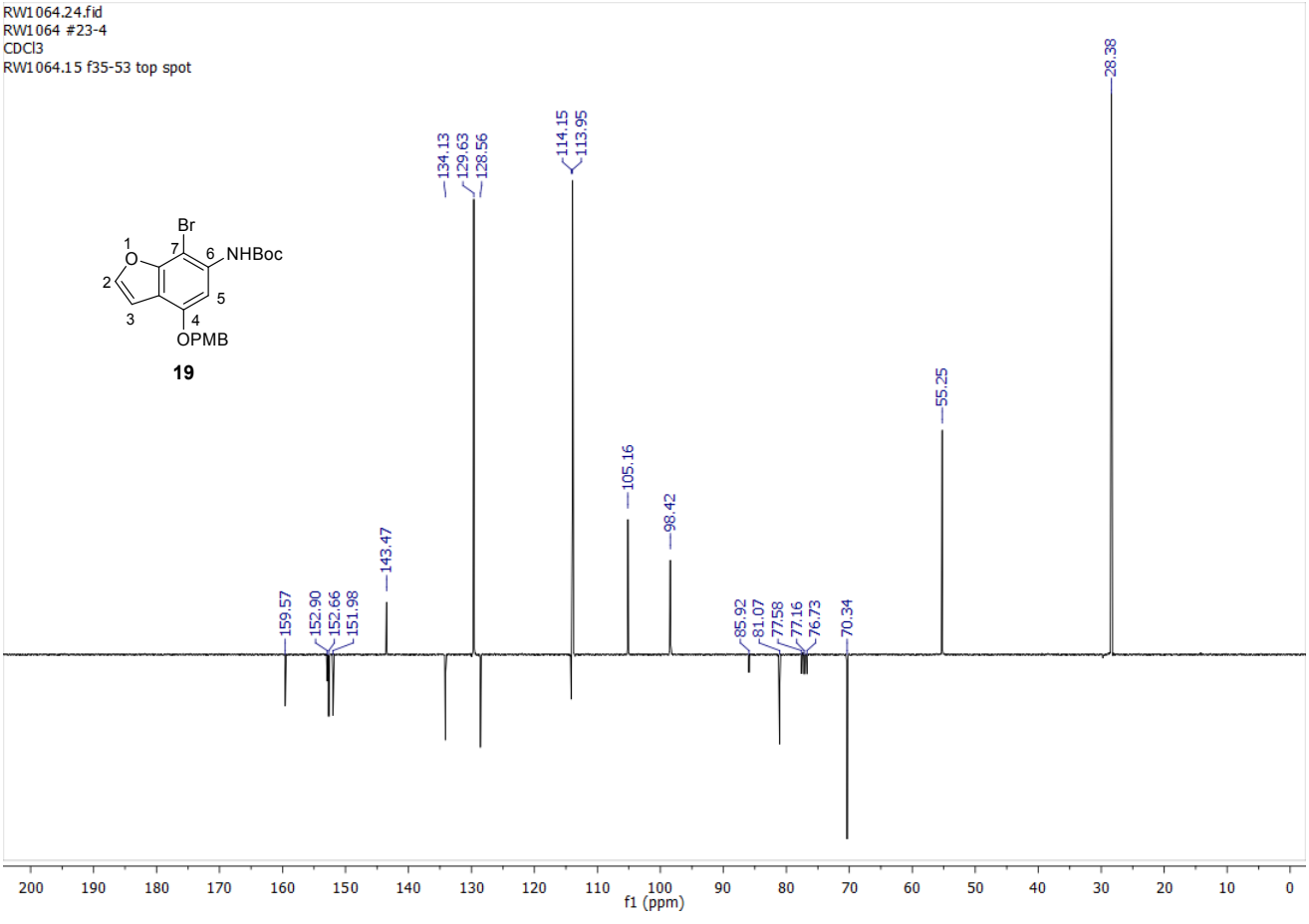
FT-IR spectrum of 18



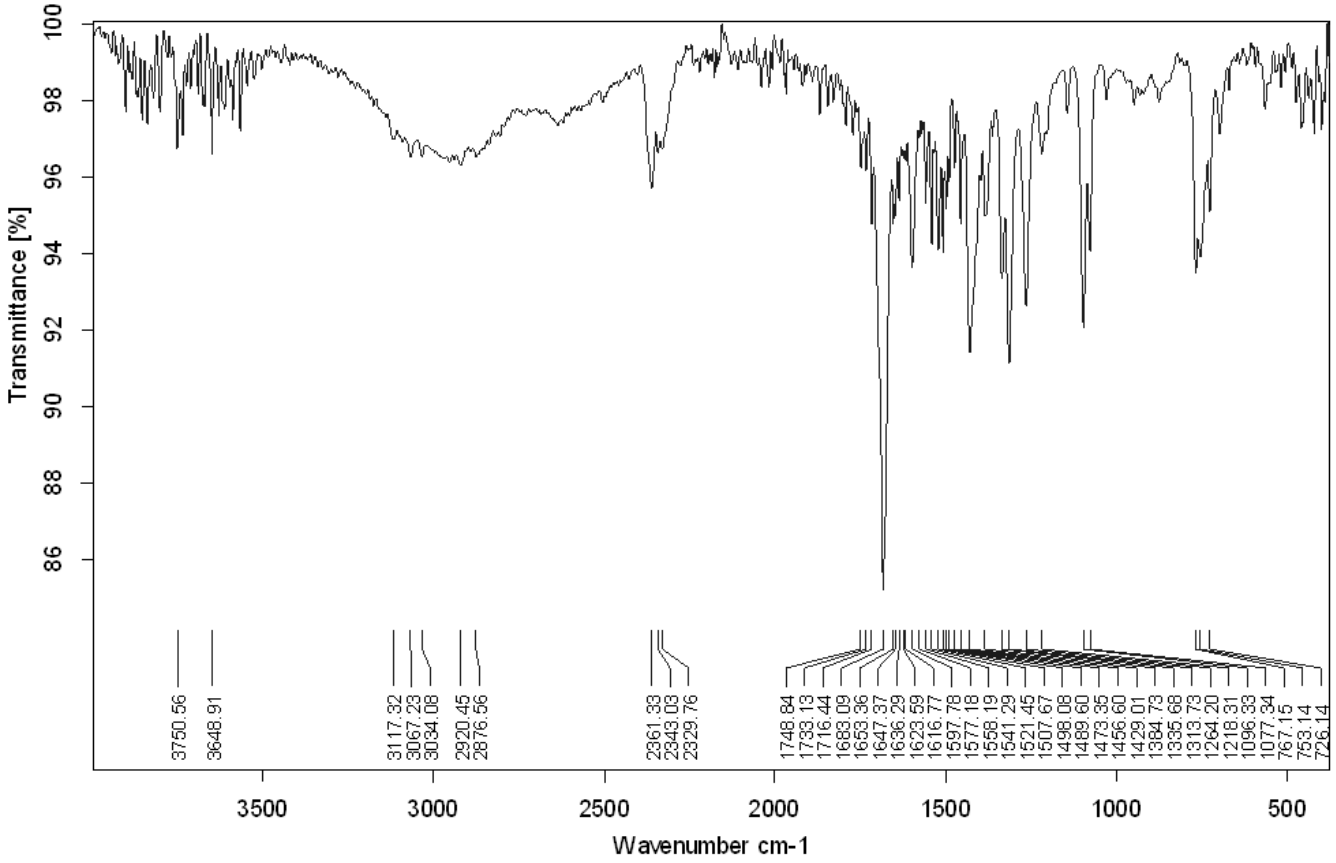
^{1}H NMR spectrum of 19 (300 MHz, $CDCl_3$)



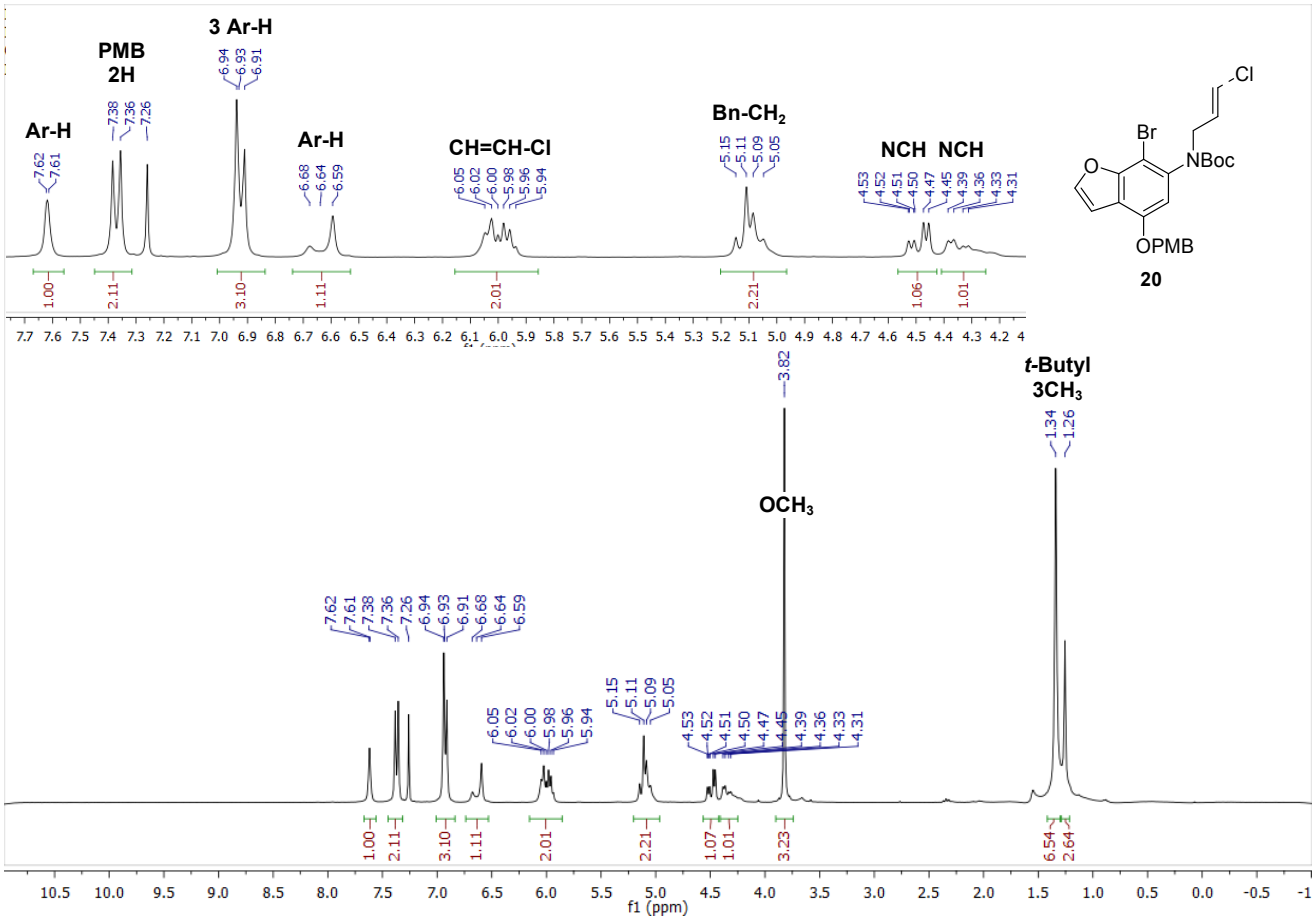
^{13}C NMR spectrum of 19 (75 MHz, $CDCl_3$)



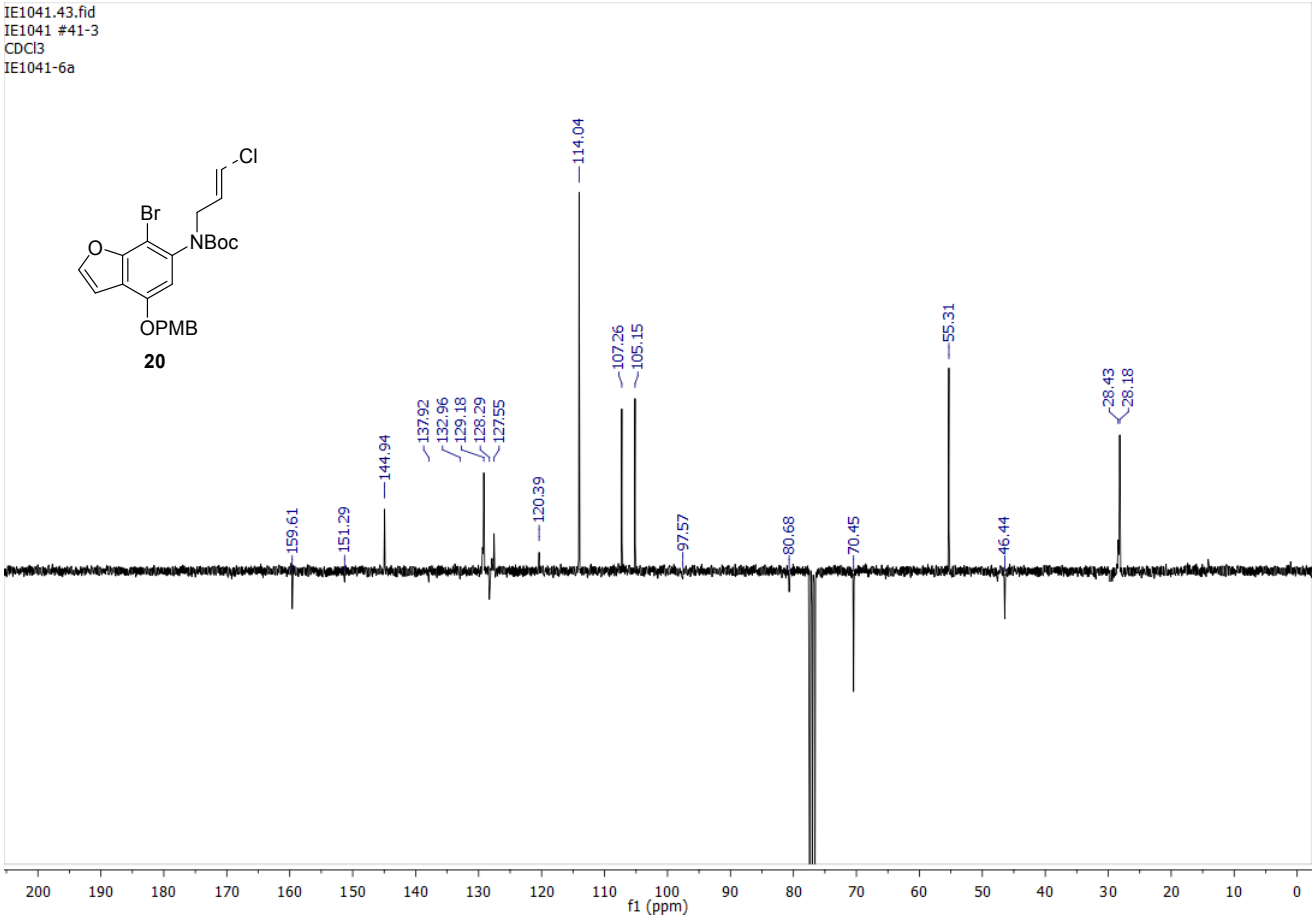
FT-IR spectrum of 19



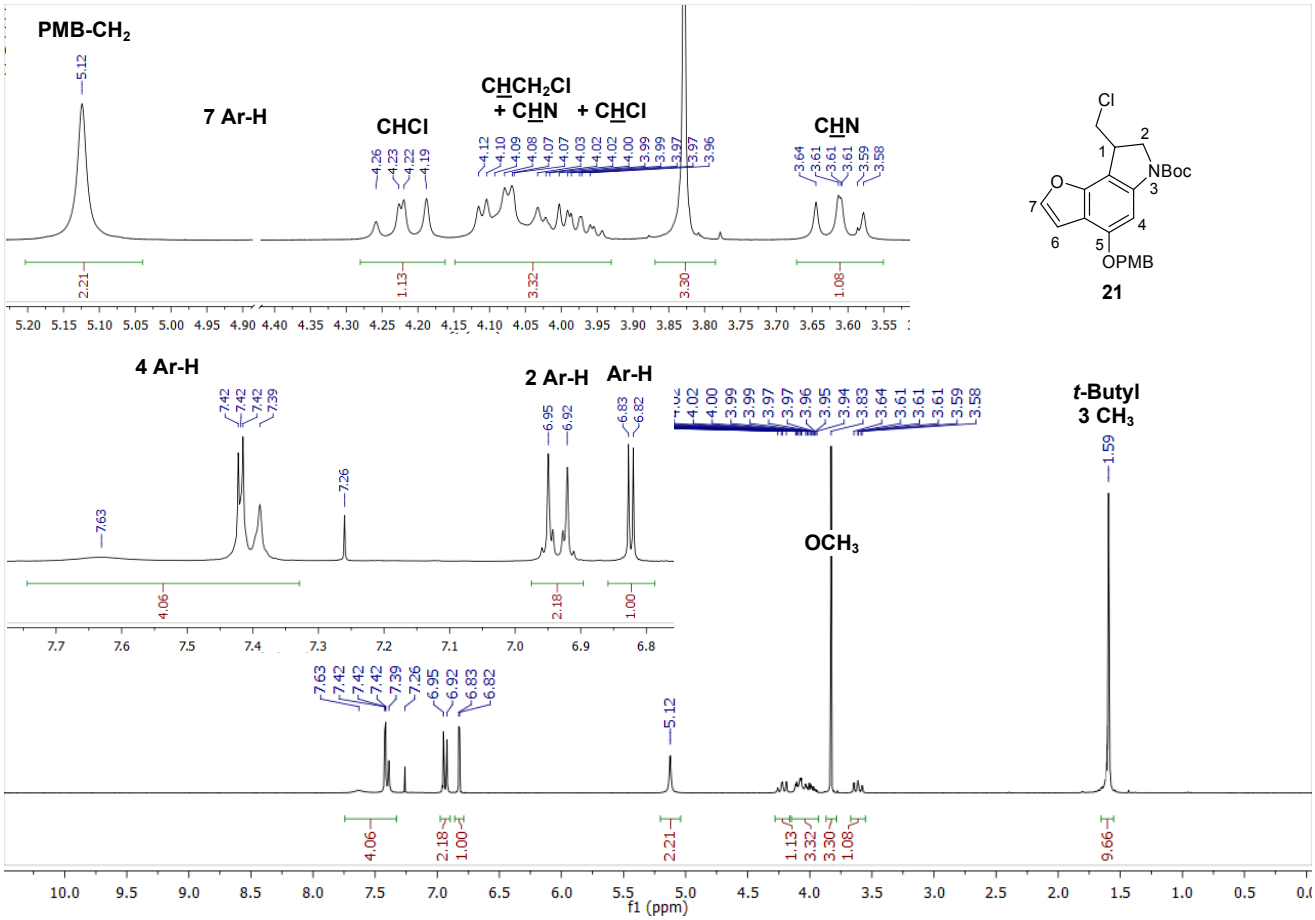
^{1}H NMR spectrum of 20 (300 MHz, $CDCl_3$)



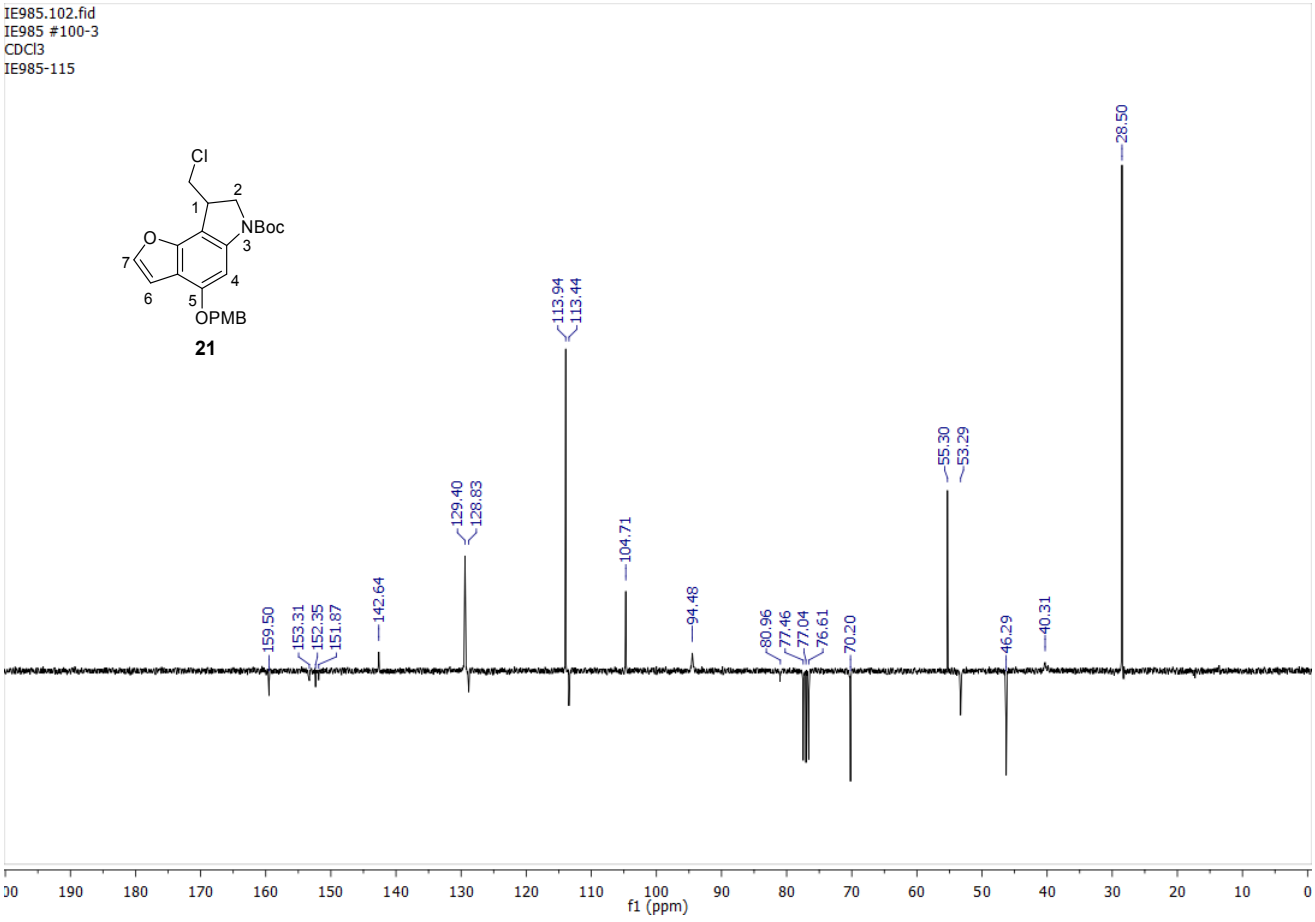
^{13}C NMR spectrum of 20 (75 MHz, $CDCl_3$)



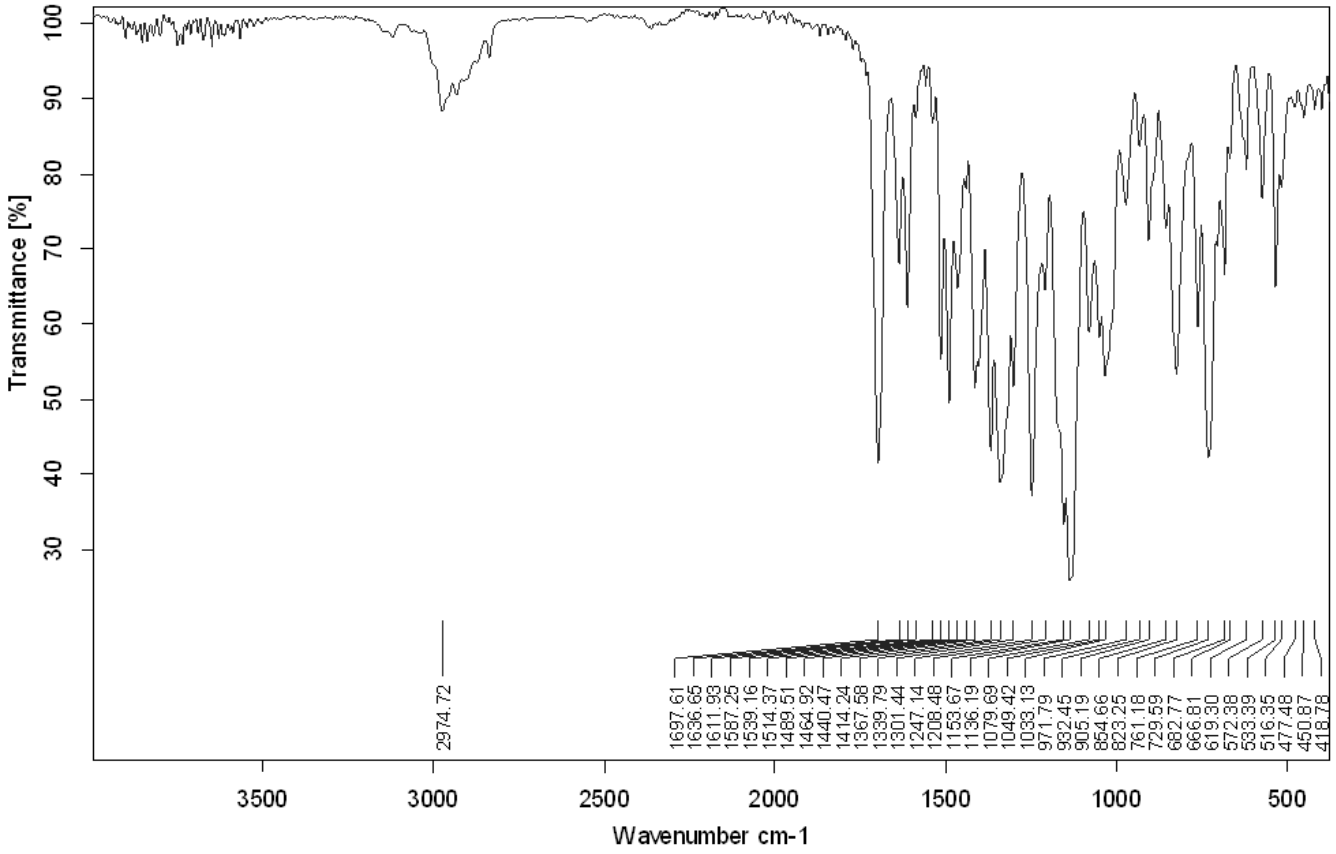
^{1}H NMR spectrum of 21 (300 MHz, $CDCl_3$)



^{13}C NMR spectrum of 21 (75 MHz, $CDCl_3$)



FT-IR spectrum of 21



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1. Howard, T. T.; Lingerfelt, B. M.; Purnell, B. L.; Scott, A. E.; Price, C. A.; Townes, H. M.; McNulty, L.; Handl, H. L.; Summerville, K.; Hudson, S. J.; Bowen, J. P.; Kiakos, K.; Hartley, J. A.; Lee, M. *Bioorg. Med. Chem.* **2002**, *10*, 2941.