Supporting Information

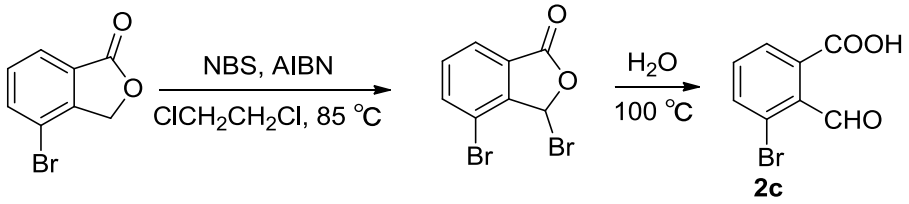
Facile construction of pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-ones *via* a redox-amination-aromatization-Friedel-Crafts acylation cascade reaction and discovery of novel topoisomerase inhibitors

Shanchao Wu,[†,$] Na Liu,[†,$] Guoqiang Dong,[†,$] Lin Ma,[†] Shengzheng Wang,[†] Wencai Shi,[§] Kun Fang,[†,≠] Shuqiang Chen[†], Jian Li,[≠] Wannian Zhang,[†,*] Chunquan Sheng[†,*] and Wei Wang[‡,≠,*]

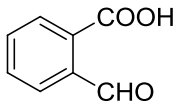
Table of contents

General Information: All starting materials are commercially available and analytical pure. Microwave reactions were carried out in a Biotage (initiator-type) reactor. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE II 300 or AVANCE II 600 Nuclear Magnetic Resonance spectrometer (Bruker Company, Germany), using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts (δ values) and coupling constants (J values) are given in ppm (δ) and Hz, respectively. The mass spectra were recorded on an Esquire 3000 LC-MS mass spectrometer. High resolution mass spectrometry (HRMS) was recorded on an Agilent 6538 UHD Accurate-Mass Q-TOF LC/MS spectrometer. Silica gel thin-layer chromatography was performed on precoated plates GF-254 (Qingdao Haiyang Chemical, China) and compounds were visualized with a UV light at 254 and 365 nm. Silica gel column chromatography was performed with Silica gel 60G (Qindao Haiyang Chemical, China). Structural determination of the products was determined by X-ray and NMR.

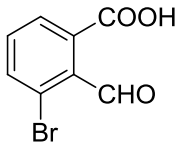
General procedure for the preparation of substrates 2c-e.



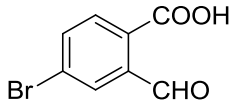
A mixture of 1,2-dichloroethane (25 mL), 4-bromoisobenzofuran-1(3*H*)-one (0.95 g, 4.5 mmol, 1.0 equiv), *N*-bromosuccinimide (0.89 g, 5.0 mmol, 1.1 equiv) and azobisisobutyronitrile (0.04 g, 0.2 mmol, 0.04 equiv) was refluxed for 1 h. The reaction mixture was kept in an ice bath for 2 h then filtered. The solvent was removed under reduced pressure. Water (10 mL) was added and the resulting mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and extracted with EtOAc. The combined organic phases were dried and concentrated under reduced pressure to give compound **2c** as a white solid (0.78 g, 76.2% yield). The synthetic method for substrates **2a** and **2d-e** were similar to the synthesis of substrate **2c**. Substrates **2b** and **2f** are commercially available.



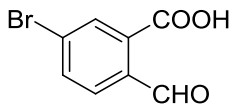
2-Formylbenzoic acid (2a): White solid (0.55g), yield: 82.1%. ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ = 8.18 (s, 1H), 7.77-7.85 (m, 2H), 7.64-7.69 (m, 2H), 6.67 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 168.92, 147.90, 134.97, 130.98, 127.04, 124.98, 124.19, 98.76; HRMS (ESI) calcd for $C_8H_5O_3$ $[M-H]^-$ = 149.0244, found 149.0243.



3-Bromo-2-formylbenzoic acid (2c): White solid (0.78 g), yield: 76.2%. ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ = 8.28 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 6.61 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 168.38, 147.05, 138.94, 133.75, 129.95, 125.03, 118.41, 99.23; HRMS (ESI) calcd for $C_8H_4BrO_3$ $[M-H]^-$ = 226.9349, found 226.9350.



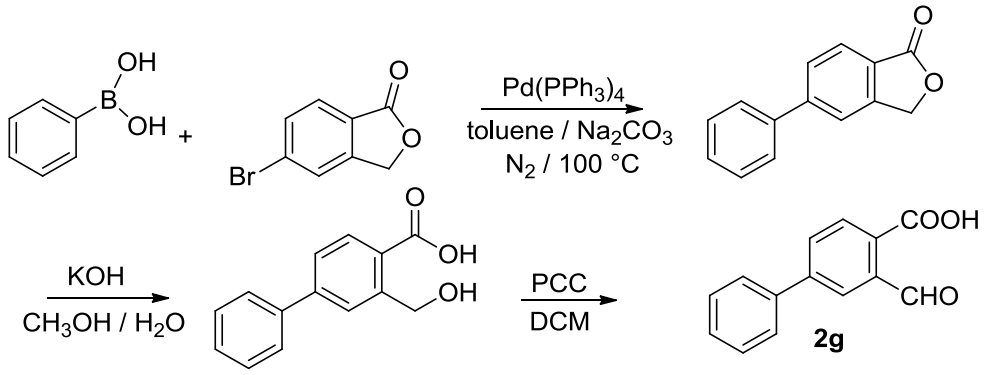
4-Bromo-2-formylbenzoic acid (2d): White solid (0.68 g), yield: 56.3%. ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ = 7.90-7.91 (m, 1H), 7.84 (dd, J = 1.5, 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 168.38, 147.05, 138.94, 133.75, 129.95, 125.03, 118.41, 99.23; HRMS (ESI) calcd for $C_8H_4BrO_3$ $[M-H]^-$ = 226.9349, found 226.9348.



5-Bromo-2-formylbenzoic acid (2e): White solid (0.65 g), yield: 63.4%. ^{1}H NMR (600 MHz, DMSO-d_6, TMS): δ = 8.27 (dd, J = 4.1 Hz, 1H), 7.96-8.00 (m, 2H), 7.63 (d, J = 7.7 Hz, 2H), 6.65 (d, J = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 167.57, 149.41, 133.74, 128.45, 126.97, 126.42, 125.81, 97.66; HRMS (ESI) calcd

for $C_8H_4BrO_3$ $[M-H]^-$ = 226.9349, found 226.9349.

General procedure for the preparation of substrates 2g-i.



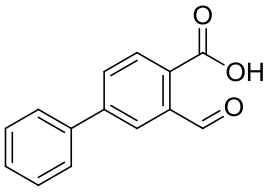
Phenylboronic acid (1.9 g, 15 mmol, 1.5 equiv), 5-bromoisobenzofuran-1(3*H*)-one (2.3 g, 10 mmol, 1.0 equiv) and terakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (1.0 g, 0.8 mmol, 0.08 equiv) were added to a mixed solvent of toluene (20 mL) and 2 M Na_2CO_3 solution (16 mL). The resulted solution was stirred at 100 °C for 3 h under nitrogen atmosphere. Then the reaction mixture was extracted with EtOAc (3 × 30 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc = 8:1, v/v) afforded 5-phenylisobenzofuran-1(3*H*)-one (2.0 g, 63.5% yield) as white solid.

5-Phenylisobenzofuran-1(3*H*)-one (1.5 g, 7.1 mmol, 1.0 equiv) and KOH (0.6 g, 11 mmol, 1.5 equiv) were added to the mixed solvent of methanol (17 mL) and water (3 mL) (methanol/water = 85:15, v/v). The resulted solution was stirred at 50 °C for 2 h, and the pH value was adjusted to 4 by saturated $KHSO_4$ aqueous solution. After filtration, product **2g** was dried at 50 °C as a white solid (1.62 g, 80.2% yield).

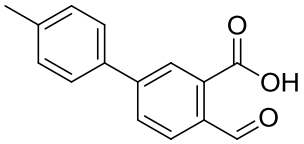
3-(Hydroxymethyl)-[1,1'-biphenyl]-4-carboxylic acid (0.60 g, 2.6 mmol, 1.0 equiv) was dissolved into dichloromethane (8 mL), pyridinium chlorochromate (PCC) (1.1 g, 5.2 mmol, 2.0 equiv) was added, and the solution was stirred for 2 h at room temperature. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 4: 1-1:1, v/v) to give the substrate **2g** (0.13 g, yield: 21.9%) as a white solid.

The synthetic method for substrates **2h** and **2i** was similar to the synthesis of

substrate **2g**. Substrate **2h** was obtained as crude compound by a simple purification procedure through flash column chromatography on silica gel.

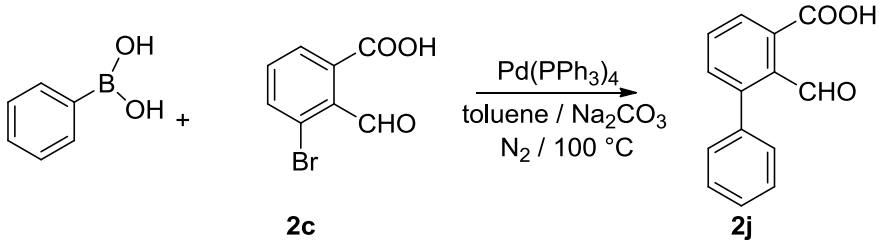


3-Formyl-[1,1'-biphenyl]-4-carboxylic acid (2g): White solid (0.13 g), yield: 21.9%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.97 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 6.9 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.1 Hz, 2H), 7.47-7.49 (m, 1H), 6.71 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 168.45, 148.17, 147.07, 139.37, 130.20, 129.17, 128.82, 127.52, 125.88, 125.55, 121.92, 97.23; HRMS (ESI) calcd for $C_{14}H_9O_3$ $[M-H]^-$ = 225.0553, found 225.0552.



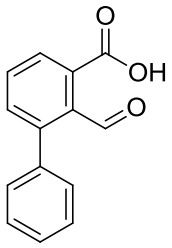
4-Formyl-4'-methyl-[1,1'-biphenyl]-3-carboxylic acid (2i): White solid (0.82 g), yield: 13.2 %. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.09 (d, *J* = 1.0 Hz, 1H), 7.96 (dd, *J* = 1.6, 7.9 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.32-7.35 (m, 2H), 6.70 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 168.64, 144.60, 144.55, 138.48, 136.26, 133.47, 129.87, 127.68, 127.14, 123.66, 123.51, 97.36, 29.70; HRMS (ESI) calcd for $C_{15}H_{11}O_3$ $[M-H]^-$ = 239.0714, found 239.0715.

General procedure for the preparation of substrates 2j-t

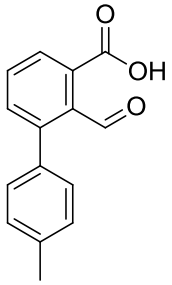


2c **2j**

Phenylboronic acid (0.26 g, 2.1 mmol, 1.2 equiv), 3-bromo-2-formylbenzoic acid **2c** (0.4g, 1.7 mmol, 1.0 equiv) and ($Pd(PPh_3)_4$) (0.18g, 0.14 mmol, 0.08 equiv) were added to the mixed solvent of toluene (4.8 mL) and 2 M Na_2CO_3 solution (6.0 mL). The resulted solution was stirred at 100 °C for 3 h under nitrogen atmosphere. Then the reaction mixture was extracted with EtOAc (3 × 30 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc = 8:1, v/v) afforded 2-formyl-[1,1'-biphenyl]-3-carboxylic acid **2j** (0.48 g, 47.1% yield) as a white solid. The synthetic method for substrates **2k-t** were similar to the synthesis of substrate **2j**.

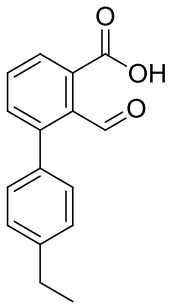


2-Formyl-[1,1'-biphenyl]-3-carboxylic acid (2j): White solid (0.18 g), yield: 47.1%. ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ = 7.91 (d, J = 8.2 Hz, 1H), 7.82 (dd, J = 0.9, 7.4 Hz, 1H), 7.80 (1.0, 7.6 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.63-7.65 (m, 2H), 7.46-7.49 (m, 2H), 7.40-7.42 (m, 1H), 7.04 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 168.48, 144.41, 138.04, 137.36, 134.90, 131.16, 128.61, 128.48, 127.98, 127.33, 123.54, 98.26; HRMS (ESI) calcd for $C_{14}H_9O_3$ $[M-H]^-$ = 225.0557, found 225.0559.

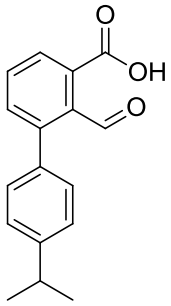


2-Formyl-4'-methyl-[1,1'-biphenyl]-3-carboxylic acid (2k): White solid (0.24 g), yield: 59.5%. ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ = 7.92 (s, 1H), 7.71-7.83 (m,

3H), 7.56 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.06 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 169.85, 145.59, 139.32, 138.70, 136.03, 135.76, 132.43, 130.52, 129.67, 128.61, 124.59, 99.65, 22.02; HRMS (ESI) calcd for $C_{15}H_{11}O_3$ $[M-H]^-$ = 239.0714, found 239.0715.

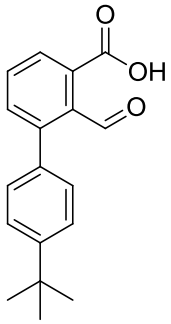


4'-Ethyl-2-formyl-[1,1'-biphenyl]-3-carboxylic acid (2l): White solid (0.11 g), yield: 26.1%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.88 (dd, J = 1.3, 6.9 Hz, 1H), 7.65-7.74 (m, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 7.4 Hz, 1H), 2.74 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 168.70, 144.65, 143.20, 139.04, 135.28, 134.54, 131.43, 128.52, 128.37, 127.39, 124.18, 97.14, 28.57, 12.38; HRMS (ESI) calcd for $C_{16}H_{13}O_3$ $[M-H]^-$ = 253.0870, found 253.0870.

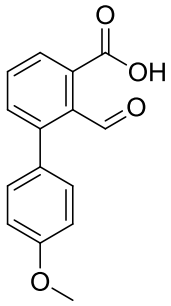


2-Formyl-4'-isopropyl-[1,1'-biphenyl]-3-carboxylic acid (2m): Yellow solid (0.31 g), yield: 60.3%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.88 (d, J = 7.4 Hz, 1H), 7.74 (dd, J = 0.8, 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 6.87 (s, 1H), 2.99-3.04 (m, 1H), 1.34 (d, J = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 168.86, 149.20, 143.25, 139.04, 135.29, 134.65, 131.37, 128.54, 127.37, 126.93, 124.13, 97.28, 33.85, 23.89; HRMS (ESI) calcd for

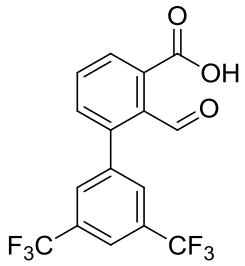
$C_{17}H_{15}O_3$ $[M-H]^-$ = 267.1027, found 267.1029.



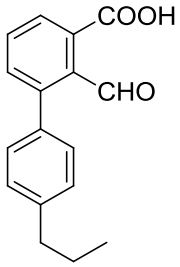
4'-(*Tert*-butyl)-2-formyl-[1,1'-biphenyl]-3-carboxylic acid (2n): Yellow oil (0.33 g), yield: 62%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.87 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.53 (s, 4H), 7.50 (d, *J* = 8.2 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ = 170.80, 169.03, 150.87, 144.77, 138.42, 135.34, 134.97, 131.62, 128.69, 127.80, 125.92, 123.80, 98.77, 60.22, 34.81; HRMS (ESI) calcd for $C_{18}H_{17}O_3$ $[M-H]^-$ = 281.1183, found 281.1182.



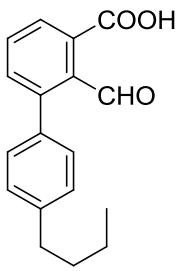
2-Formyl-4'-methoxy-[1,1'-biphenyl]-3-carboxylic acid (2o): White solid (0.11 g), yield: 25.3%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.80 (dd, *J* = 1.3, 7.3 Hz, 1H), 7.59-7.69 (m, 2H), 7.47-7.52 (m, 2H), 7.09-7.18 (m, 1H), 6.96-7.01 (m, 2H), 6.80 (s, 1H), 3.84 (s, 3H); HRMS (ESI) calcd for $C_{15}H_{12}NaO_4$ $[M+Na]^+$ = 279.0628, found 279.0629.



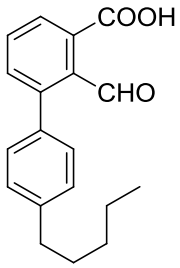
2-Formyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylic acid (2p): White solid (0.18 g), yield: 28.7%. ^{1}H NMR (300 MHz, CD_3OD, TMS): δ = 8.38 (s, 2H), 8.21 (s, 1H), 8.14 (s, 1H), 7.95-8.02 (m, 2H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.09 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD, TMS): δ = 169.43, 146.19, 141.16, 136.80, 136.08, 132.75, 132.10, 131.67, 130.82, 128.73, 126.35, 99.47; HRMS (ESI) calcd for $C_{16}H_7F_6O_3$ $[M-H]^-$ = 361.0305, found 361.0307.



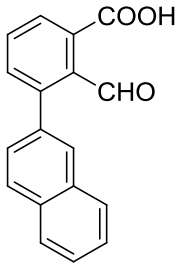
2-Formyl-4'-propyl-[1,1'-biphenyl]-3-carboxylic acid (2q): White solid (0.10 g), yield: 22.4%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.85 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.69 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.45 (dt, *J* = 2.0, 4.0, 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 3.6 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.65-1.72 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 168.68, 143.22, 139.08, 135.27, 134.56, 131.42, 128.96, 128.45, 127.41, 124.18, 97.14, 37.76, 29.71, 24.41, 13.90; HRMS (ESI) calcd for $C_{17}H_{15}O_3$ $[M-H]^-$ = 267.1027, found 267.1028.



4'-Butyl-2-formyl-[1,1'-biphenyl]-3-carboxylic acid (2r): White solid (0.21 g), yield: 43.5%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.87 (s, 1H), 7.77 (t, *J* = 6.9 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.54-1.60 (m, 2H), 1.29-1.35 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 169.03, 144.78, 142.74, 138.53, 135.27, 135.19, 131.62, 129.04, 128.88, 127.83, 123.78, 98.81, 34.97, 33.48, 22.31; HRMS (ESI) calcd for $C_{18}H_{17}O_3$ $[M-H]^-$ = 281.1183, found 281.1184.



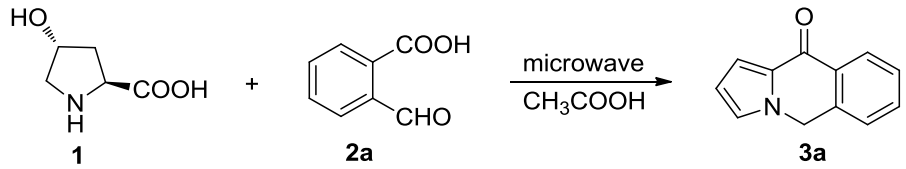
2-Formyl-4'-pentyl-[1,1'-biphenyl]-3-carboxylic acid (2s): White solid (0.26 g), yield: 52.5%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.86 (dd, *J* = 1.0, 7.4 Hz, 1H), 7.71 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.47 (dt, *J* = 2.0, 4.0, 8.3 Hz, 2H), 7.29 (dt, *J* = 2.0, 4.0, 8.3 Hz, 2H), 6.83 (d, *J* = 7.2 Hz, 1H), 3.76 (d, *J* = 7.7 Hz, 1H), 2.67 (t, *J* = 7.7 Hz, 2H), 1.65-1.69 (m, 2H), 1.35-1.39 (m, 4H), 0.91-0.94 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 168.23, 142.93, 142.74, 138.58, 134.77, 134.02, 130.91, 128.39, 127.97, 126.91, 123.66, 96.69, 35.16, 31.08, 30.53, 22.05, 13.53; HRMS (ESI) calcd for $C_{19}H_{19}O_3$ $[M-H]^-$ = 295.1340, found 295.1342.



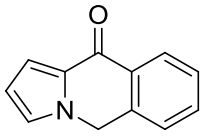
2-Formyl-3-(naphthalen-2-yl)benzoic acid (2t): Gray solid (0.10 g), yield: 22.4%. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.03 (d, *J* = 1.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.89-7.93 (m, 3H), 7.82 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.65

(dd, *J* = 1.8, 8.4 Hz, 1H), 7.54-7.57 (m, 2H), 6.89 (d, *J* = 6.3 Hz, 1H), 3.69 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 168.05, 143.02, 138.56, 135.04, 134.19, 132.81, 132.43, 131.02, 128.09, 127.78, 127.48, 127.29, 127.06, 126.26, 125.71, 124.01, 96.57; HRMS (ESI) calcd for $C_{18}H_{11}O_3$ $[M-H]^-$ = 275.0714, found 275.0716.

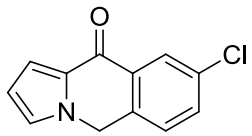
General procedure for the preparation of target compounds 3a-f



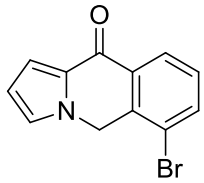
A 10 mL microwave reaction tube was charged with *trans*-4-hydroxy-*L*-proline **1** (0.16 g, 1.2 mmol, 1.2 equiv), 2-formylbenzoic acid **2a** (0.15 g, 1.0 mmol, 1.0 equiv), and CH_3COOH (2.0 mL). The reaction tube was sealed with a Teflon-lined snap cap and heated in the microwave reactor at 170 °C at very high absorption level for 20 min. After cooling, the crude reaction mixture was evaporated in vacuo and the crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 8: 1, v/v) to give **3a** (0.13 g, 71.7% yield) as a white solid. The synthetic method for compounds **3b-f** was similar to the synthesis of compound **3a**.



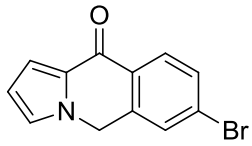
Pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3a): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.18 (d, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz,1H), 7.13-7.14 (m, 1H), 7.01-7.01 (m, 1H), 6.38 (dd, *J* = 2.5, 4.2 Hz, 1H), 5.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 174.80, 135.60, 132.46, 130.69, 129.76, 127.99, 127.23, 125.68, 125.57, 113.77, 111.71, 46.98; HRMS (ESI) calcd for $C_{12}H_{10}NO$ $[M+H]^+$ = 184.0758, found 184.0759.



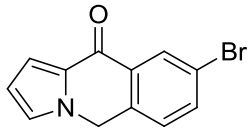
8-Chloropyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3b): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.27 (d, *J* = 2.2 Hz, 1H), 7.53 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.22 (dd, *J* = 1.3, 4.0 Hz, 1H), 7.10 (s, 1H), 6.46 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.37 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 173.49, 134.55, 133.84, 132.61, 132.28, 129.40, 127.34, 127.21, 126.12, 114.46, 112.22, 46.77; HRMS (ESI) calcd for $C_{12}H_9ClNO$ $[M+H]^+$ = 218.0.367, found 218.0369.



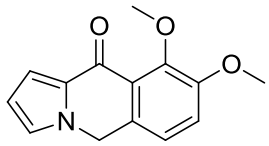
6-Bromopyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3c): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.35 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.83 (dd, *J* = 1.0, 7.3 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 1.4, 4.1 Hz, 1H), 7.20-7.21 (m, 1H), 6.52 (dd, *J* = 2.4, 4.1 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 173.45, 136.30, 134.85, 132.87, 129.19, 128.58, 126.51, 125.17, 121.32, 114.12, 112.19, 48.27; HRMS (ESI) calcd for $C_{12}H_9BrNO$ $[M+H]^+$ = 261.9862, found 261.9863.



7-Bromopyrrolo[1,2-b]isoquinolin-10(5H)-one (3d): ^{1}H-NMR (600 MHz, $CDCl_3$, TMS): δ = 8.18 (d, *J* = 8.4 Hz, 1H), 7.63 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.53 (s, 1H), 7.23 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.10 (s, 1H), 6.47 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 173.74, 139.23, 137.15, 131.44, 129.56, 128.90, 128.62, 127.39, 125.76, 114.18, 112.01, 46.45; HRMS (ESI) calcd for $C_{12}H_9BrNO$ $[M+H]^+$ = 261.9862, found 261.9863.

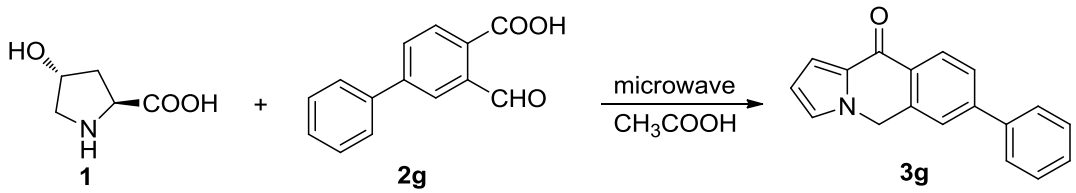


8-Bromopyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3e): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.43 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.22-7.24 (m, 2H), 7.10 (s, 1H), 6.46 (s, 1H), 5.35 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 173.35, 135.44, 134.33, 132.45, 130.23, 129.36, 127.55, 126.12, 122.37, 114.46, 112.23, 46.80; HRMS (ESI) calcd for $C_{12}H_8BrNNaO$ $[M+Na]^+$ = 261.9862, found 261.9860.



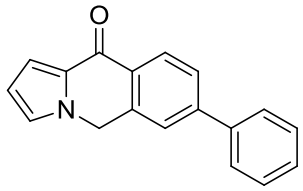
8,9-Dimethoxypyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3f): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.12-7.13 (m, 2H), 7.05 (dt, *J* = 0.9, 1.8, 8.4 Hz, 1H), 6.97-6.98 (m, 1H), 6.38 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.28 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.77, 153.38, 150.75, 130.96, 129.07, 125.12, 124.38, 121.42, 116.60, 113.48, 111.50, 61.49, 56.44, 46.73; HRMS (ESI) calcd for $C_{14}H_{14}NO_3$ $[M+H]^+$ = 244.0968, found 244.0969.

General procedure for the preparation of target compounds 3g-t

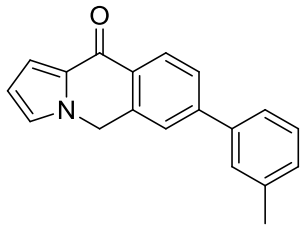


A 10 mL microwave reaction tube was charged with *trans*-4-hydroxy-*L*-proline **1** (0.13 g, 1.0 mmol, 1.0 equiv), 3-formyl-[1,1'-biphenyl]-4-carboxylic acid **2g** (0.27 g, 1.2 mmol, 1.2 equiv), and CH_3COOH (2.0 mL). The reaction tube was sealed with a Teflon-lined snap cap and heated in the microwave reactor at 170 °C at very high absorption level for 20 min. After cooling, the crude reaction mixture was evaporated in vacuo and the crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 16:1-14:1, v/v) to give **3g** (0.078 g, 30.0% yield) as a white

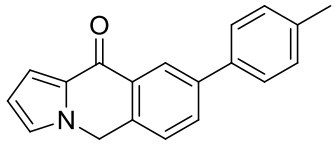
solid. The synthetic method for compounds **3h-t** were similar to the synthesis of compound **3g**.



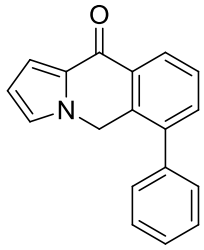
7-Phenylpyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3g): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.38 (d, *J* = 8.1 Hz, 1H), 7.71 (dt, *J* = 0.9, 1.7, 8.1 Hz, 1H), 7.63-7.65 (m, 2H), 7.55 (d, *J* = 0.9 Hz, 1H), 7.47-7.50 (m, 2H), 7.42 (tt, *J* = 1.2, 2.4, 6.9 Hz, 1H), 7.23 (dd, *J* = 1.5, 3.9 Hz, 3H), 7.10-7.11 (m, 1H), 6.46 (dd, *J* = 2.4, 4.0 Hz, 1H), 5.47 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.60, 145.33, 139.66, 136.14, 129.88, 129.56, 129.04, 128.43, 127.85, 127.30, 126.89, 125.63, 124.19, 113.17, 111.75, 47.16; HRMS (ESI) calcd for $C_{18}H_{14}NO$ $[M+H]^+$ = 260.1070, found 260. 1071.



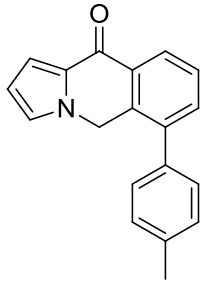
7-(*M*-tolyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3h): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.37 (d, *J* = 8.0 Hz, 1H), 7.69-7.71 (m, 1H), 7.54 (s, 1H), 7.42-7.45 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.23-7.24 (m, 2H), 7.11 (s, 1H), 6.46 (dd, *J* = 2.4 , 3.9 Hz, 1H), 5.47 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.16, 144.98, 138.22, 135.58, 129.38, 128.96, 128.68, 128.45, 127.55, 127.29, 126.41, 125.12, 123.91, 123.68, 123.02, 115.42, 113.25, 111.24, 46.66, 31.12; HRMS (ESI) calcd for $C_{19}H_{16}NO$ $[M+H]^+$ = 274.1226, found 274.1228.



8-(*P*-tolyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3i): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.58 (s, 1H), 7.83 (dd, *J* = 1.3, 7.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.14 (s, 1H), 6.49-6.50 (m, 1H), 5.46 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.80, 140.87, 137.77, 136.72, 134.11, 130.93, 129.80, 129.65, 126.92, 126.21, 125.67, 125.12, 113.85, 111.75, 46.85, 21.13; HRMS (ESI) calcd for $C_{19}H_{16}NO$ $[M+H]^+$ = 274.1226, found 274.1228.

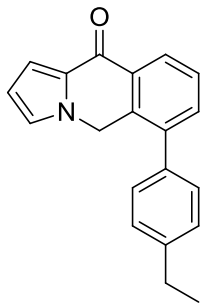


6-Phenylpyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3j): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.39 (dd, *J* = 1.0, 7.7 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.50-7.53 (m, 2H), 7.47-7.49 (m, 2H), 7.34-7.35 (m, 2H), 7.21 (dd, *J* = 1.1, 3.9 Hz, 1H), 6.96-6.97 (m, 1H), 6.42 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 176.26, 141.45, 140.76, 135.20, 134.61, 132.44, 130.58, 130.29, 130.11, 129.46, 129.11, 127.94, 127.28, 115.03, 113.17, 47.70; HRMS (ESI) calcd for $C_{18}H_{14}NO$ $[M+H]^+$ = 260.1070, found 260.1068.

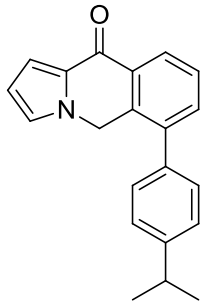


6-(*P*-tolyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3k): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.41 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 1.5, 3.9 Hz, 1H), 7.01-7.02 (m, 1H), 6.46 (dd, *J* = 2.4, 4.0 Hz, 1H), 5.26 (s, 2H), 2.52 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.92, 140.06, 137.91, 136.40, 133.90, 133.32, 131.03, 129.54, 129.21, 128.58, 127.67, 126.38, 125.81, 113.57, 11.72, 46.32, 29.71, 21.27; HRMS (ESI) calcd for $C_{19}H_{16}NO$ $[M+H]^+$ = 274.1226, found 274.1227.

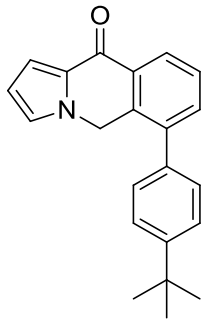


6-(4-Ethylphenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3l): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.39 (dd, *J* = 0.9, 7.7 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 1.2, 7.4 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.28-7.30 (m, 2H), 7.23 (dd, *J* = 1.3, 3.9 Hz, 1H), 7.00 (t, *J* = 1.8 Hz, 1H), 6.43 (dd, *J* = 2.4, 3.9 Hz, 1H), 5.25 (s, 2H), 2.80 (q, *J* = 7.6 Hz, 2H), 1.38 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.92, 144.15, 140.07, 136.56, 133.92, 130.97, 129.16, 128.62, 128.31, 127.64, 126.32, 125.85, 113.55, 111.70, 46.32, 28.61, 15.45; HRMS (ESI) calcd for $C_{20}H_{18}NO$ $[M+H]^+$ = 288.1383, found 288.1385.

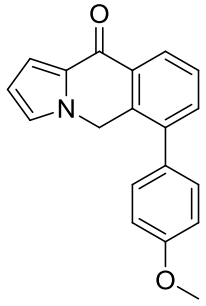


6-(4-Isopropylphenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3m): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.40 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.50 (dd, *J* = 1.2, 7.4 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.30 (s, 1H), 7.29 (s, 1H), 7.24 (dd, *J* = 1.3, 3.9 Hz, 1H), 7.02 (t, *J* = 1.88 Hz, 1H), 6.44 (dd, *J* = 2.4, 3.9 Hz, 1H), 5.26 (s, 2H), 3.03-3.07 (m, 1H), 1.38 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 175.58, 149.39, 140.73, 137.33, 14.59, 133.95, 131.68, 129.86, 129.25, 128.29,

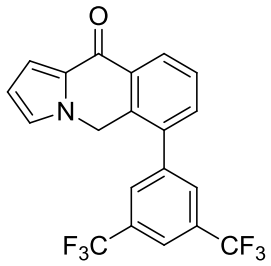
127.53, 126.99, 126.44, 114.19, 112.33, 46.98, 34.55, 24.62; HRMS (ESI) calcd for $C_{21}H_{20}NO$ $[M+H]^+$ = 302.1539, found 302.1540.



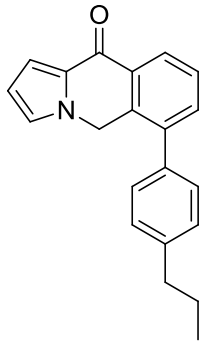
6-(4-(*Tert*-butyl)phenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3n): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.40 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.54-7.59 (m, 3H), 7.49 (dd, *J* = 1.2, 7.4 Hz, 1H), 7.31 (t, *J* = 2.2 Hz, 1H), 7.23 (dd, *J* = 1.3, 3.9 Hz, 1H), 7.02 (t, *J* = 1.8 Hz, 1H), 6.44 (dd, *J* = 2.5, 4.4 Hz, 1H), 5.27 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.96, 151.07, 140.04, 136.32, 133.98, 133.34, 131.05, 129.24, 128.38, 127.66, 126.36, 125.84, 125.76, 113.56, 111.70, 46.37, 34.73, 31.40; HRMS (ESI) calcd for $C_{21}H_{22}NO$ $[M+H]^+$ = 316.1696, found 316.1697.



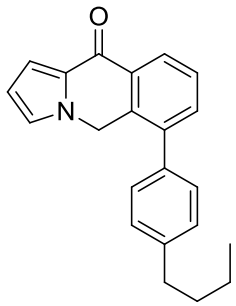
6-(4-Methoxyphenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3o): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.34 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.44 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.26 (t, *J* = 2.9 Hz, 1H), 7.24 (t, *J* = 2.8 Hz, 1H), 7.19 (dd, *J* = 1.5, 4.0 Hz, 1H), 7.03 (t, *J* = 2.9 Hz, 1H), 7.02 (t, *J* = 2.9 Hz, 1H), 6.95-6.96 (m, 1H), 6.40 (dd, *J* = 2.4, 3.9 Hz, 1H), 5.19 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.45, 158.93, 139.26, 133.54, 133.01, 130.54, 129.34, 128.69, 127.15, 125.81, 125.33, 113.76, 113.08, 111.23, 54.89, 45.85; HRMS (ESI) calcd for $C_{19}H_{16}NO_2$ $[M+H]^+$ = 290.1176, found 290.1178.



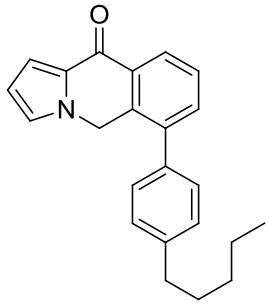
6-(3,5-Bis(trifluoromethyl)phenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3p): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.49 (dd, *J* = 1.1, 7.8 Hz, 1H), 8.07 (s, 1H), 7.90 (s, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52 (dd, *J* = 1.1, 7.3 Hz, 1H), 7.26 (dd, *J* = 1.3, 3.9 Hz, 1H), 7.05 (s, 1H), 6.49 (t, *J* = 2.5, 4.0 Hz, 1H), 5.19 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.05, 141.42, 136.79, 133.59, 132.81, 132.60, 132.38, 131.46, 129.02, 128.96, 128.22, 127.91, 126.11, 123.99, 122.24, 122.18, 114.15, 114.06, 112.15, 46.00; ^{19}F NMR (282 MHz, $CDCl_3$, TMS): δ = -62.72 (s, 6F); HRMS (ESI) calcd for $C_{20}H_{12}F_6NO$ $[M+H]^+$ = 396.0818, found 396.0819.



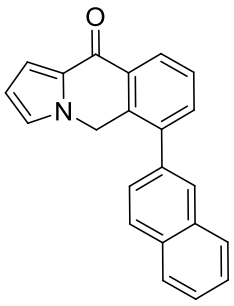
6-(4-Propylphenyl)pyrrolo[1,2-*b*]isoquinolin-10(5H)-one (3q): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.39 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.50 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.27-7.29 (m, 2H), 7.23 (dd, *J* = 1.4, 3.9 Hz, 1H), 7.01 (s, 1H), 6.44 (dd, *J* = 2.4, 3.9 Hz, 1H), 5.25 (s, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 1.74-1.81 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.94, 142.65, 140.08, 136.57, 133.94, 133.30, 130.99, 129.18, 128.88, 128.53, 127.64, 126.34, 125.84, 113.57, 111.70, 46.31, 37.80, 24.49, 13.94; HRMS (ESI) calcd for $C_{21}H_{20}NO$ $[M+H]^+$ = 302.1539, found 302.1540.



6-(4-Butylphenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3r): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.36 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.46 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.20 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.97 (t, *J* = 1.6 Hz, 1H), 6.41 (dd, *J* = 2.4, 3.9 Hz, 1H), 5.21 (s, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.67-1.72 (m, 2H), 1.42-1.43 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.44, 142.40, 139.61, 136.06, 133.44, 132.82, 130.54, 128.73, 128.35, 128.06, 127.16, 125.86, 125.32, 113.06, 111.20, 45.84, 34.94, 33.09, 29.21, 21.99, 13.50; HRMS (ESI) calcd for $C_{22}H_{21}NO$ $[M+H]^+$ = 316.1696, found 316.1697.

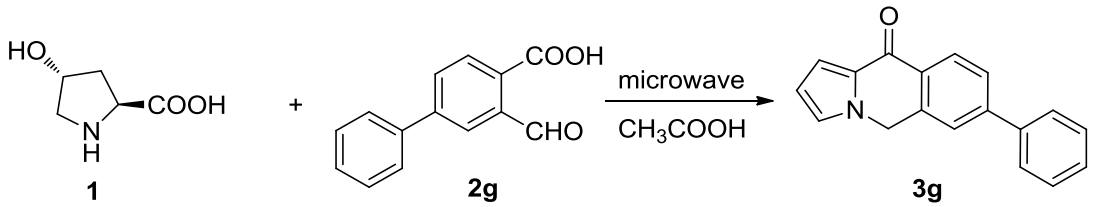


6-(4-Pentylphenyl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3s): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.36 (dt, *J* = 1.1, 2.3, 7.8 Hz, 1H), 7.52-7.55 (m, 1H), 7.46 (dd, *J* = 0.7, 7.4 Hz, 1H), 7.30-7.33 (m, 2H), 7.24 (dt, *J* = 1.7, 3.6, 8.0 Hz, 2H), 7.20 (dt, *J* = 1.1, 2.4, 4.0 Hz, 1H), 6.96-6.97 (m, 1H), 6.40-6.41 (m, 1H), 5.21 (s, 2H), 2.70 (t, *J* = 7.7 Hz, 2), 1.69-1.74 (m, 2H), 1.38-1.43 (m, 4H), 0.93-0.96 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.44, 142.45, 139.61, 136.05, 133.44, 132.82, 130.54, 128.72, 128.33, 128.06, 127.15, 125.86, 125.32, 113.06, 111.20, 45.84, 35.23, 31.15, 30.63, 29.21, 22.08, 13.57; HRMS (ESI) calcd for $C_{23}H_{24}NO$ $[M+H]^+$ = 330.1852, found 330.1853.



6-(Naphthalen-2-yl)pyrrolo[1,2-*b*]isoquinolin-10(5*H*)-one (3t): ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.42 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.96 (dd, *J* = 3.1, 5.9 Hz, 1H), 7.90 (dd, *J* = 3.4, 6.1 Hz, 1H), 7.82 (d, *J* = 0.7 Hz, 1H), 7.55-7.61 (m, 4H), 7.46 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.21 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.91 (dd, *J* = 1.6, 2.1 Hz, 1H), 6.40 (dd, *J* = 2.4, 4.0 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 174.35, 139.50, 136.27, 133.42, 132.95, 132.83, 132.30, 130.62, 128.71, 128.14, 127.56, 127.38, 127.27, 127.22, 126.34, 126.16, 126.09, 125.35, 113.17, 111.28, 45.91, 29.21; HRMS (ESI) calcd for $C_{22}H_{16}NO$ $[M+H]^+$ = 310.1226, found 310.1228.

Table S1. Further exploration of the optimized reaction condition of diphenyl substituted substrate 2g.[a]



Entry	Product	1 : 2 (equivalence ratio)	Time (min)	Yield[b] (%)
1	**3g**	1.2:1	20	20%
2	**3g**	1:1	20	18%
3	**3g**	1:1.2	20	25%
4	**3g**	1:1.2	40	30%

[a]Microwave reaction conditions (unless otherwise specified): solvent (2.0 mL), reaction mixture was heated in the microwave reactor at 170 °C for the appropriate time. [b] Yield of isolated product after column chromatography.

X-ray structure of 3j

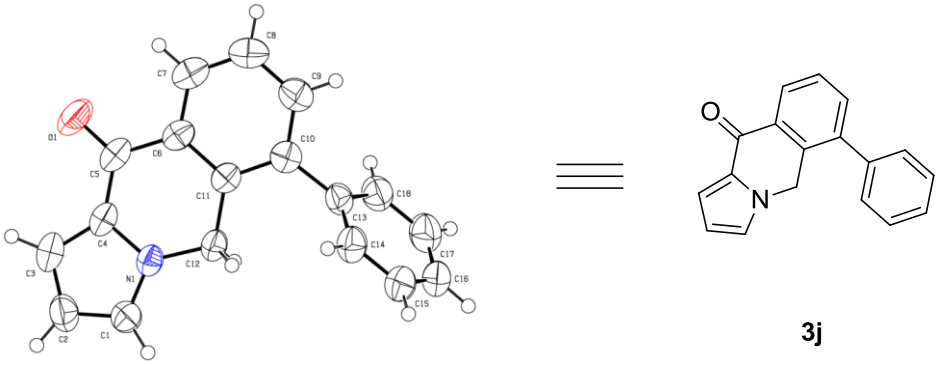


Table 1. Crystal data and structure refinement for a51209b (compound **3j**).

Identification code	a51209b
Empirical formula	C18H13NO
Formula weight	259.29
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 10.016(4) Å α = 90°.
	b = 9.223(3) Å β = 94.662(4)°.
	c = 13.978(5) Å γ = 90°.
Volume	1287.0(8) $Å^3$
Z	4
Density (calculated)	1.338 Mg/m^3
Absorption coefficient	0.083 mm^{-1}

F(000)	544
Crystal size	0.200 x 0.120 x 0.100 mm^3
Theta range for data collection	2.040 to 25.998°.
Index ranges	-10<=h<=12, -11<=k<=9, -17<=l<=16
Reflections collected	5708
Independent reflections	2525 [R(int) = 0.0566]
Completeness to theta = 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.328
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2525 / 0 / 182
Goodness-of-fit on F^2	0.927
Final R indices [I>2sigma(I)]	R1 = 0.0488, wR2 = 0.1156
R indices (all data)	R1 = 0.0716, wR2 = 0.1226
Extinction coefficient	0.018(3)
Largest diff. peak and hole	0.174 and -0.166 e.$Å^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for a51209b (compound **3j**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	5859(1)	1675(1)	4833(1)	43(1)
O(1)	6071(1)	3067(2)	7222(1)	76(1)
C(1)	6750(2)	877(2)	4390(1)	53(1)
C(2)	7821(2)	580(2)	5037(1)	60(1)
C(3)	7566(2)	1208(2)	5901(1)	57(1)
C(4)	6350(2)	1905(2)	5772(1)	46(1)
C(5)	5666(2)	2864(2)	6376(1)	51(1)
C(6)	4467(2)	3625(2)	5935(1)	46(1)
C(7)	3858(2)	4670(2)	6465(1)	58(1)
C(8)	2711(2)	5358(2)	6099(1)	63(1)
C(9)	2122(2)	4932(2)	5215(1)	58(1)
C(10)	2685(2)	3875(2)	4669(1)	47(1)
C(11)	3906(2)	3250(2)	5015(1)	42(1)
C(12)	4569(2)	2169(2)	4406(1)	45(1)
C(13)	1927(2)	3355(2)	3767(1)	47(1)
C(14)	2385(2)	3536(2)	2867(1)	56(1)
C(15)	1676(2)	2980(2)	2062(1)	66(1)
C(16)	507(2)	2228(2)	2143(2)	70(1)
C(17)	25(2)	2065(2)	3030(2)	71(1)
C(18)	728(2)	2626(2)	3834(1)	58(1)

Table 3. Bond lengths [Å] and angles [°] for a51209b (compound **3j**).

N(1)-C(1)	1.345(2)
N(1)-C(4)	1.3805(19)
N(1)-C(12)	1.4515(19)
O(1)-C(5)	1.2336(19)
C(1)-C(2)	1.374(2)
C(2)-C(3)	1.383(3)
C(3)-C(4)	1.376(2)
C(4)-C(5)	1.435(2)
C(5)-C(6)	1.481(2)
C(6)-C(7)	1.387(2)
C(6)-C(11)	1.404(2)
C(7)-C(8)	1.374(3)
C(8)-C(9)	1.383(2)
C(9)-C(10)	1.386(2)
C(10)-C(11)	1.402(2)
C(10)-C(13)	1.498(2)
C(11)-C(12)	1.500(2)
C(13)-C(14)	1.383(2)
C(13)-C(18)	1.387(2)
C(14)-C(15)	1.381(3)
C(15)-C(16)	1.373(3)
C(16)-C(17)	1.375(3)
C(17)-C(18)	1.377(3)
C(1)-N(1)-C(4)	108.89(13)
C(1)-N(1)-C(12)	125.72(13)
C(4)-N(1)-C(12)	125.35(13)
N(1)-C(1)-C(2)	108.53(15)

C(1)-C(2)-C(3)	107.56(16)
C(4)-C(3)-C(2)	107.81(15)
C(3)-C(4)-N(1)	107.21(15)
C(3)-C(4)-C(5)	132.14(15)
N(1)-C(4)-C(5)	120.26(14)
O(1)-C(5)-C(4)	121.46(16)
O(1)-C(5)-C(6)	121.32(16)
C(4)-C(5)-C(6)	117.21(13)
C(7)-C(6)-C(11)	120.02(16)
C(7)-C(6)-C(5)	118.92(14)
C(11)-C(6)-C(5)	120.99(14)
C(8)-C(7)-C(6)	120.83(16)
C(7)-C(8)-C(9)	119.01(17)
C(8)-C(9)-C(10)	121.88(16)
C(9)-C(10)-C(11)	118.84(15)
C(9)-C(10)-C(13)	119.16(15)
C(11)-C(10)-C(13)	121.84(14)
C(10)-C(11)-C(6)	119.17(14)
C(10)-C(11)-C(12)	119.44(13)
C(6)-C(11)-C(12)	121.38(14)
N(1)-C(12)-C(11)	113.33(12)
C(14)-C(13)-C(18)	118.25(16)
C(14)-C(13)-C(10)	122.99(15)
C(18)-C(13)-C(10)	118.74(15)
C(15)-C(14)-C(13)	120.67(18)
C(16)-C(15)-C(14)	120.35(19)
C(15)-C(16)-C(17)	119.66(18)
C(16)-C(17)-C(18)	120.04(18)
C(17)-C(18)-C(13)	120.99(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for a51209b (compound **3j**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	43(1)	50(1)	36(1)	4(1)	-3(1)	-1(1)
O(1)	92(1)	90(1)	42(1)	-13(1)	-16(1)	1(1)
C(1)	53(1)	63(1)	44(1)	1(1)	3(1)	8(1)
C(2)	48(1)	72(1)	59(1)	10(1)	-2(1)	10(1)
C(3)	51(1)	66(1)	52(1)	8(1)	-14(1)	-8(1)
C(4)	48(1)	53(1)	37(1)	3(1)	-6(1)	-9(1)
C(5)	59(1)	54(1)	37(1)	-1(1)	-5(1)	-14(1)
C(6)	52(1)	46(1)	40(1)	-2(1)	6(1)	-11(1)
C(7)	70(1)	56(1)	47(1)	-7(1)	7(1)	-11(1)
C(8)	74(1)	53(1)	64(1)	-10(1)	18(1)	0(1)
C(9)	58(1)	54(1)	62(1)	2(1)	9(1)	6(1)
C(10)	50(1)	45(1)	46(1)	6(1)	7(1)	-3(1)
C(11)	46(1)	42(1)	38(1)	3(1)	4(1)	-6(1)
C(12)	44(1)	52(1)	37(1)	2(1)	-5(1)	0(1)
C(13)	44(1)	46(1)	50(1)	4(1)	-2(1)	8(1)
C(14)	51(1)	65(1)	52(1)	10(1)	-2(1)	0(1)
C(15)	66(1)	79(1)	50(1)	2(1)	-6(1)	14(1)
C(16)	56(1)	80(1)	70(1)	-17(1)	-18(1)	14(1)
C(17)	47(1)	81(1)	85(2)	-9(1)	-4(1)	-2(1)
C(18)	48(1)	66(1)	60(1)	2(1)	3(1)	4(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for a51209b (compound **3j**).

	x	y	z	U(eq)
H(1)	6656	577	3753	64
H(2)	8580	51	4915	72
H(3)	8118	1168	6468	69
H(7)	4231	4909	7076	69
H(8)	2337	6099	6441	76
H(9)	1324	5368	4979	69
H(12A)	3983	1338	4297	54
H(12B)	4691	2604	3788	54
H(14)	3179	4036	2805	67
H(15)	1991	3115	1460	79
H(16)	45	1831	1602	84
H(17)	-777	1575	3087	85
H(18)	393	2513	4431	70

Table 6. Torsion angles [°] for a51209b (compound **3j**).

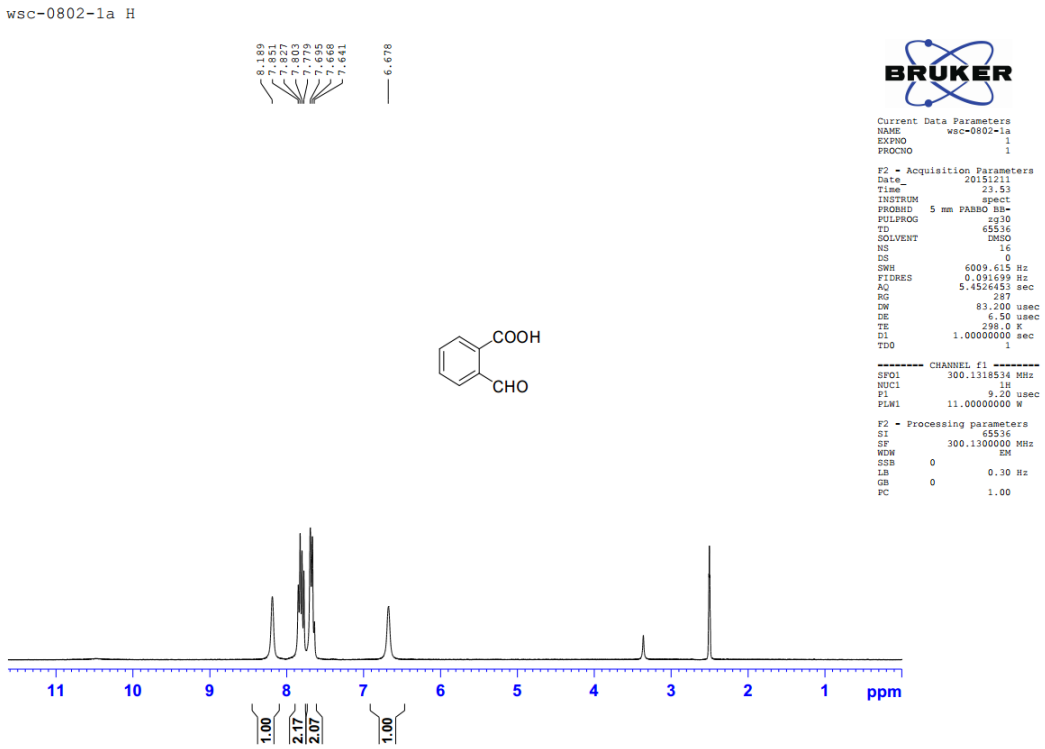
C(4)-N(1)-C(1)-C(2)	0.16(19)
C(12)-N(1)-C(1)-C(2)	-177.68(15)
N(1)-C(1)-C(2)-C(3)	0.5(2)
C(1)-C(2)-C(3)-C(4)	-0.9(2)
C(2)-C(3)-C(4)-N(1)	1.02(19)
C(2)-C(3)-C(4)-C(5)	-171.60(17)
C(1)-N(1)-C(4)-C(3)	-0.74(18)
C(12)-N(1)-C(4)-C(3)	177.12(14)
C(1)-N(1)-C(4)-C(5)	172.93(14)
C(12)-N(1)-C(4)-C(5)	-9.2(2)
C(3)-C(4)-C(5)-O(1)	-9.5(3)
N(1)-C(4)-C(5)-O(1)	178.68(15)
C(3)-C(4)-C(5)-C(6)	169.33(17)
N(1)-C(4)-C(5)-C(6)	-2.5(2)
O(1)-C(5)-C(6)-C(7)	5.3(2)
C(4)-C(5)-C(6)-C(7)	-173.53(14)
O(1)-C(5)-C(6)-C(11)	-171.45(15)
C(4)-C(5)-C(6)-C(11)	9.7(2)
C(11)-C(6)-C(7)-C(8)	-0.4(3)
C(5)-C(6)-C(7)-C(8)	-177.22(15)
C(6)-C(7)-C(8)-C(9)	3.9(3)
C(7)-C(8)-C(9)-C(10)	-2.8(3)
C(8)-C(9)-C(10)-C(11)	-1.7(3)
C(8)-C(9)-C(10)-C(13)	173.75(16)
C(9)-C(10)-C(11)-C(6)	5.1(2)
C(13)-C(10)-C(11)-C(6)	-170.25(14)
C(9)-C(10)-C(11)-C(12)	-176.39(14)
C(13)-C(10)-C(11)-C(12)	8.3(2)

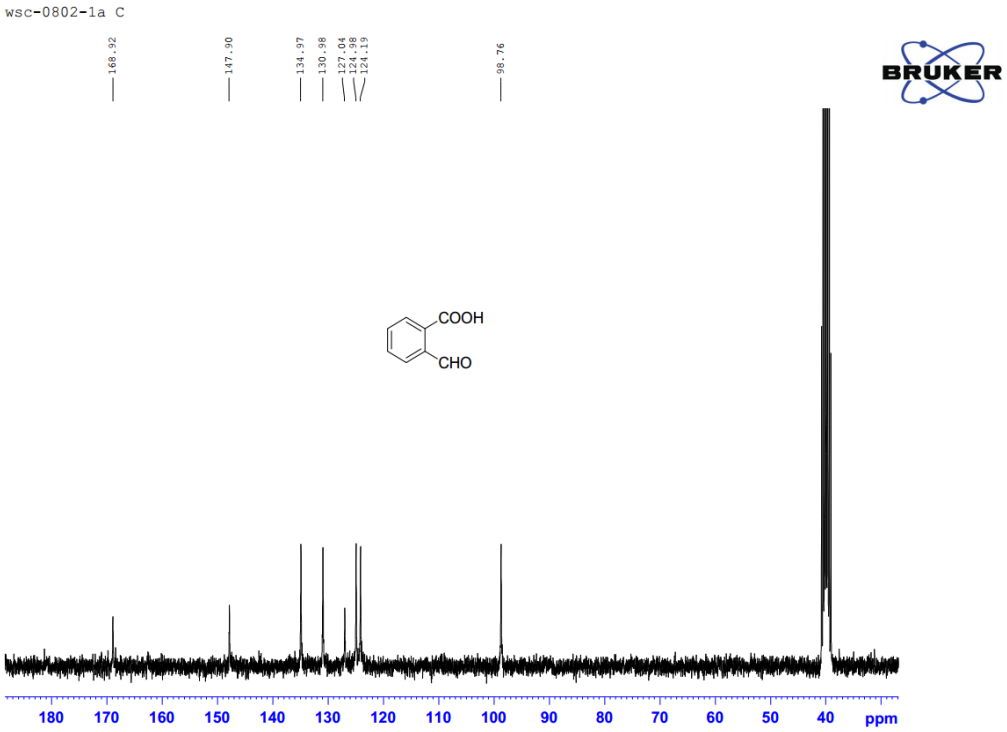
C(7)-C(6)-C(11)-C(10)	-4.1(2)
C(5)-C(6)-C(11)-C(10)	172.62(14)
C(7)-C(6)-C(11)-C(12)	177.44(14)
C(5)-C(6)-C(11)-C(12)	-5.8(2)
C(1)-N(1)-C(12)-C(11)	-169.85(14)
C(4)-N(1)-C(12)-C(11)	12.6(2)
C(10)-C(11)-C(12)-N(1)	176.78(13)
C(6)-C(11)-C(12)-N(1)	-4.8(2)
C(9)-C(10)-C(13)-C(14)	116.81(18)
C(11)-C(10)-C(13)-C(14)	-67.8(2)
C(9)-C(10)-C(13)-C(18)	-65.0(2)
C(11)-C(10)-C(13)-C(18)	110.39(18)
C(18)-C(13)-C(14)-C(15)	-1.1(3)
C(10)-C(13)-C(14)-C(15)	177.13(15)
C(13)-C(14)-C(15)-C(16)	-0.5(3)
C(14)-C(15)-C(16)-C(17)	1.8(3)
C(15)-C(16)-C(17)-C(18)	-1.4(3)
C(16)-C(17)-C(18)-C(13)	-0.2(3)
C(14)-C(13)-C(18)-C(17)	1.5(3)
C(10)-C(13)-C(18)-C(17)	-176.83(16)

Symmetry transformations used to generate equivalent atoms:

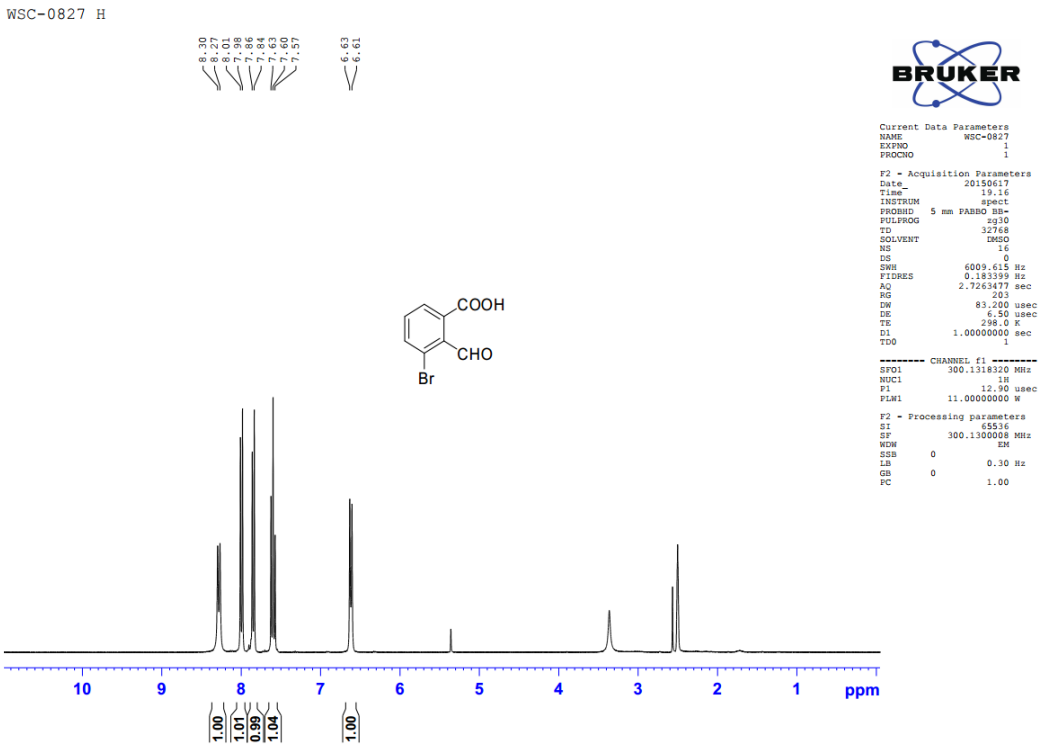
NMR Spectra

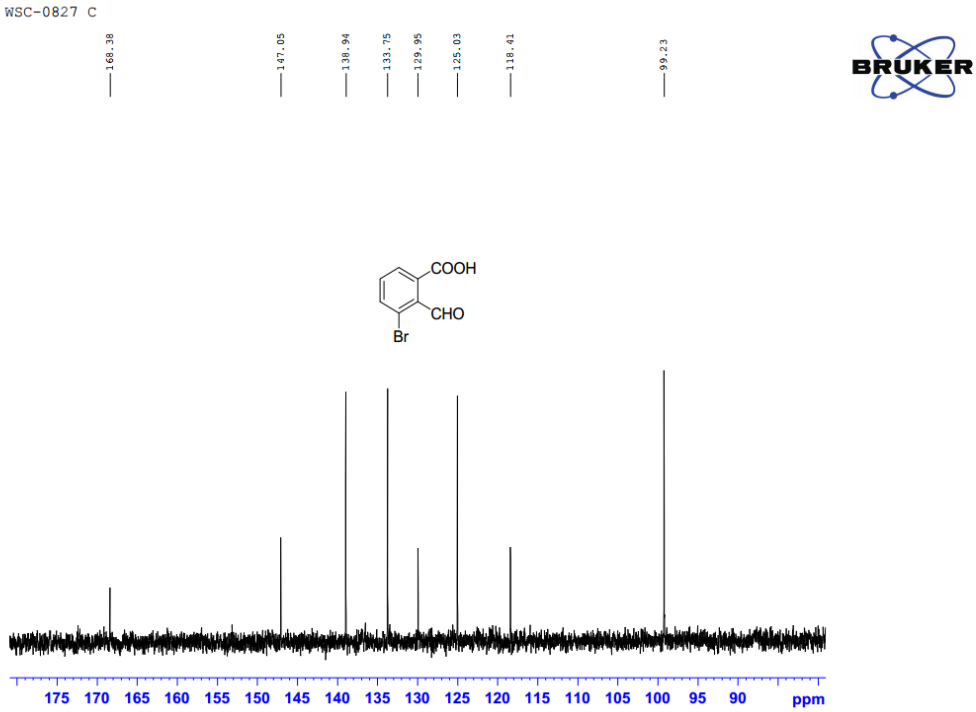
NMR of compound **2a**



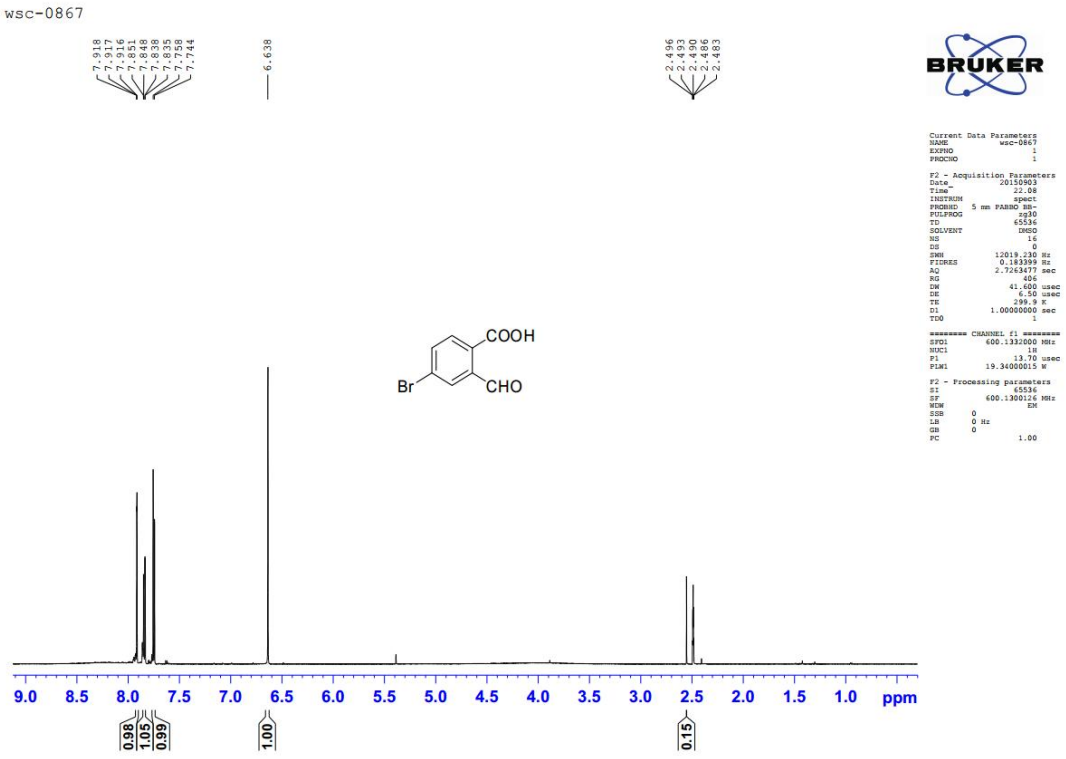


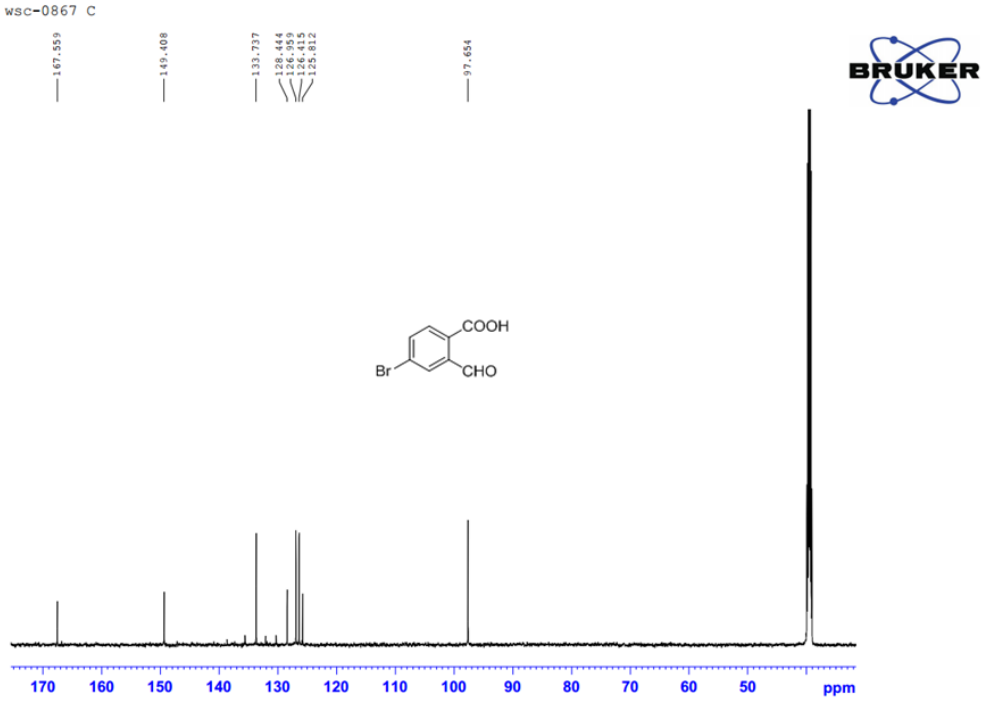
NMR of compound **2c**



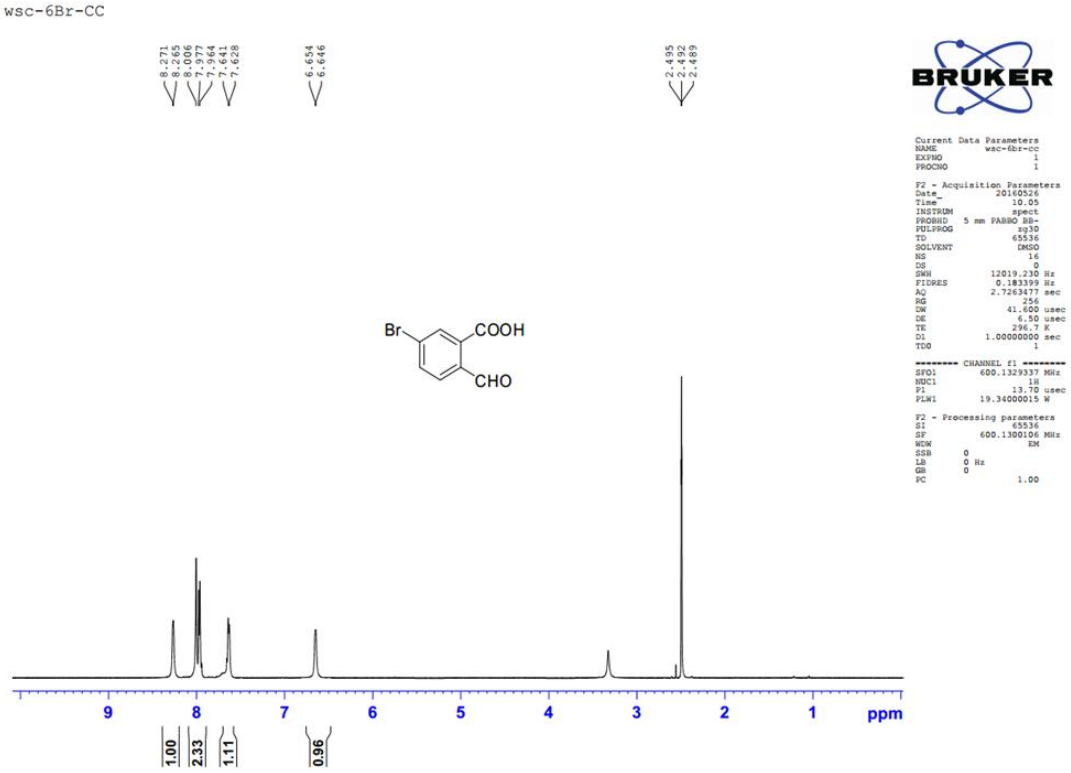


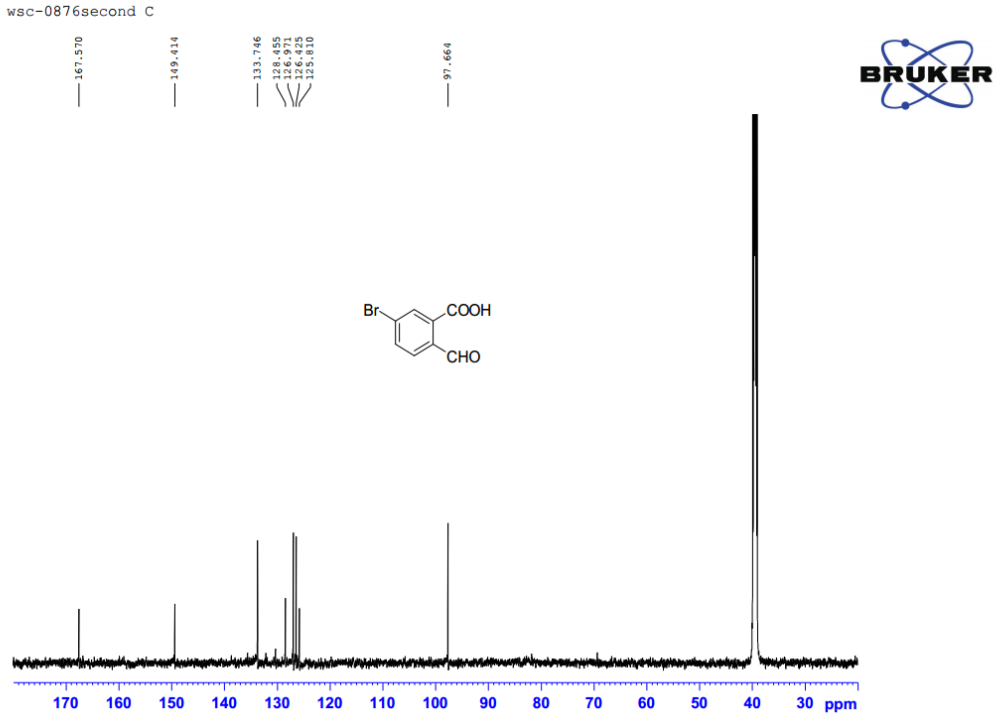
NMR of compound **2d**



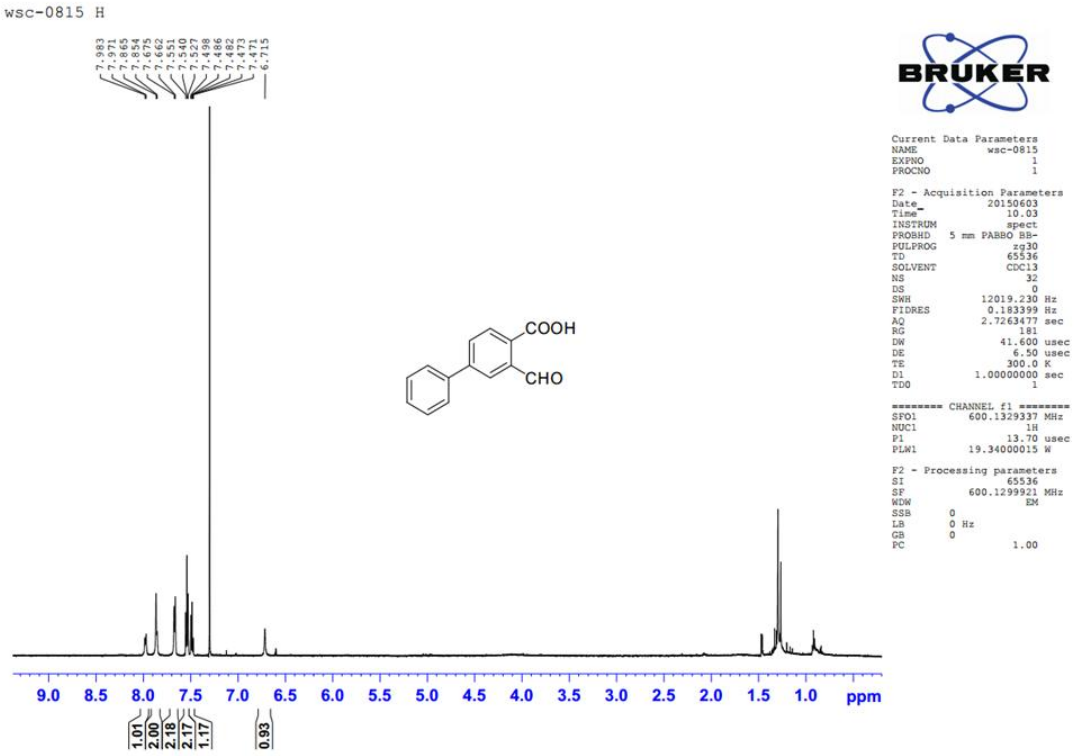


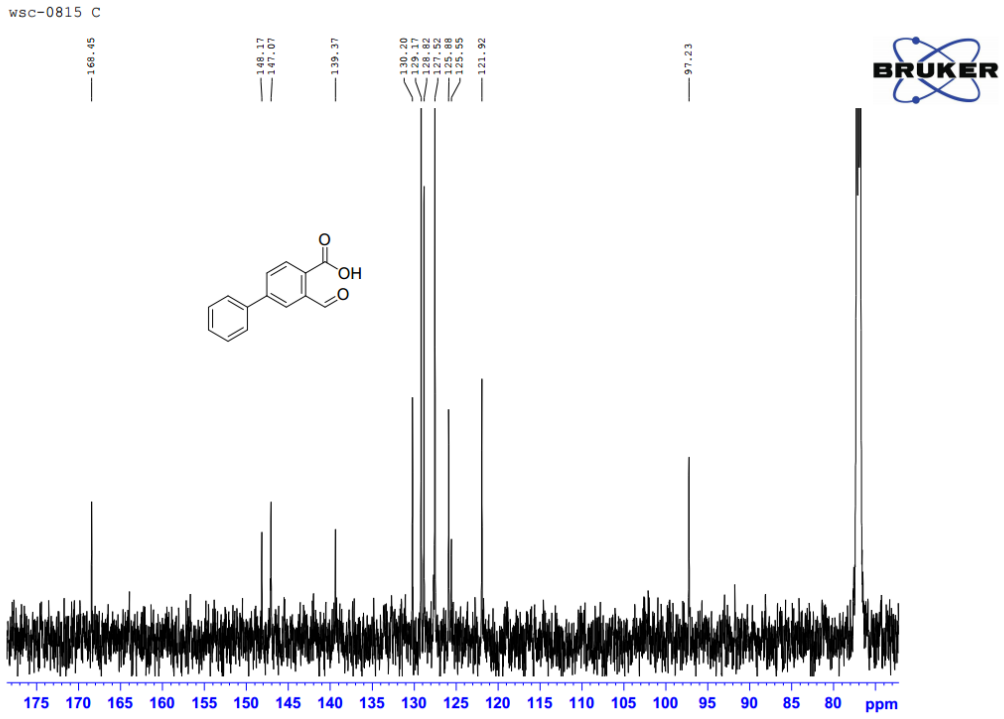
NMR of compound **2e**



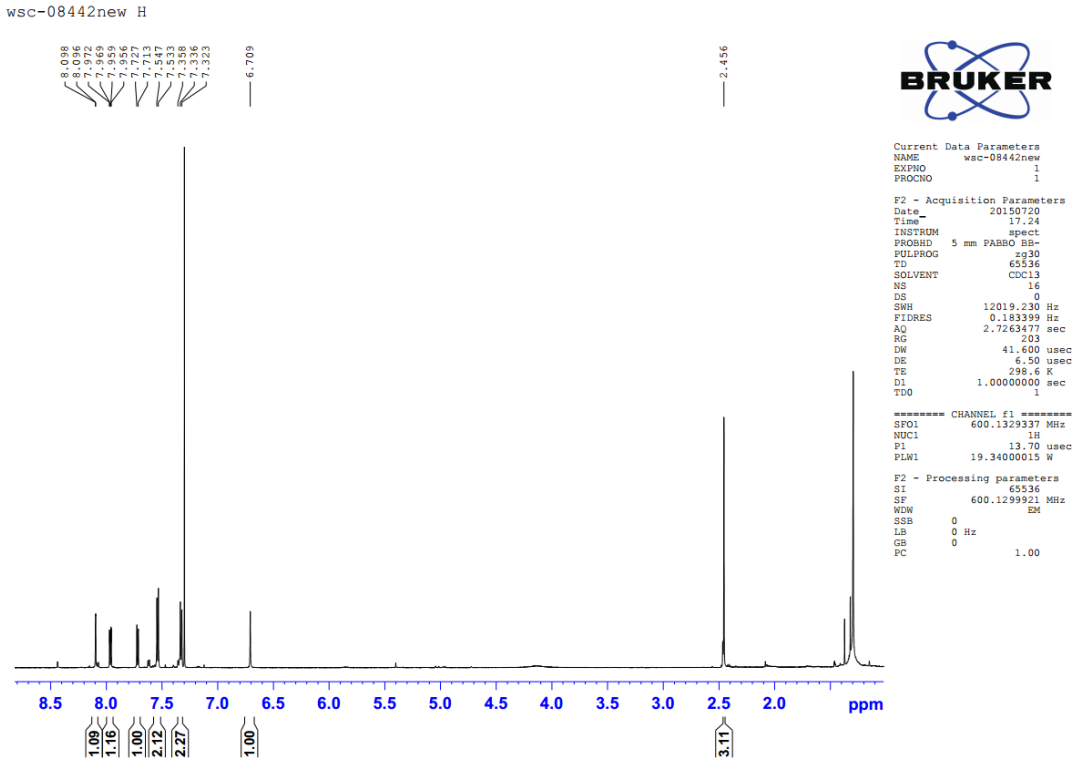


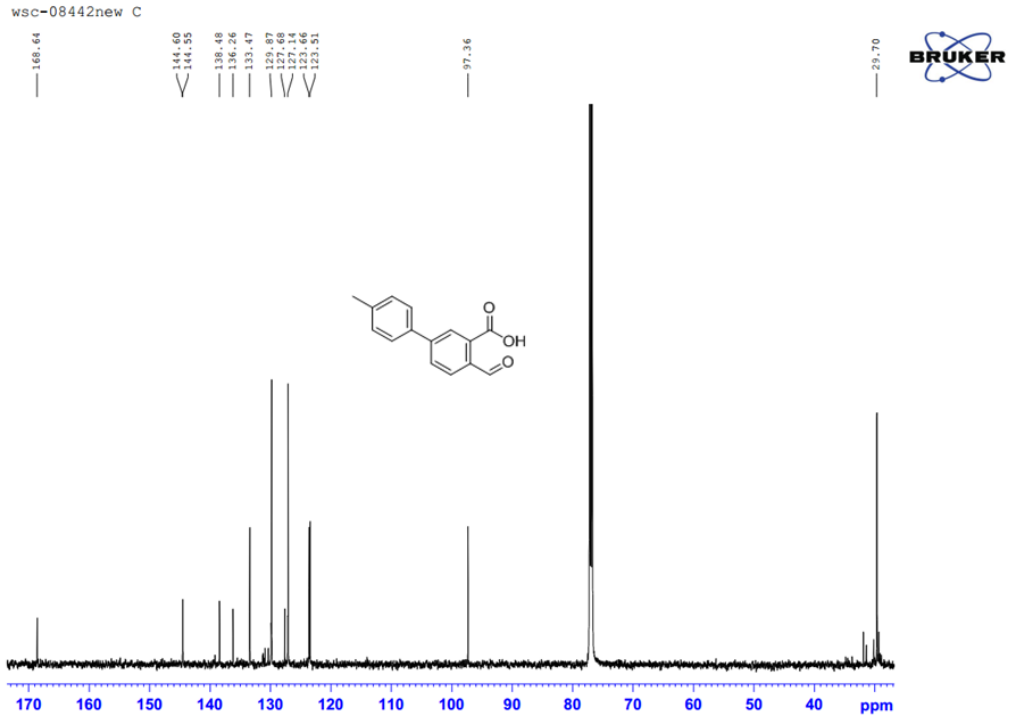
NMR of compound **2g**



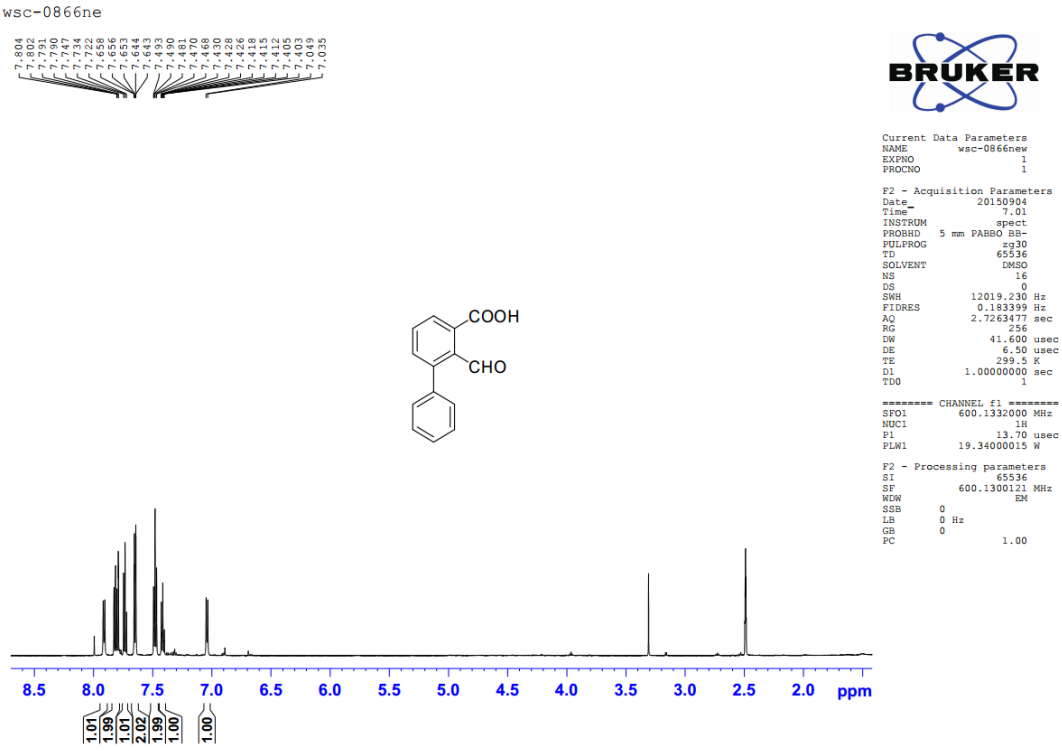


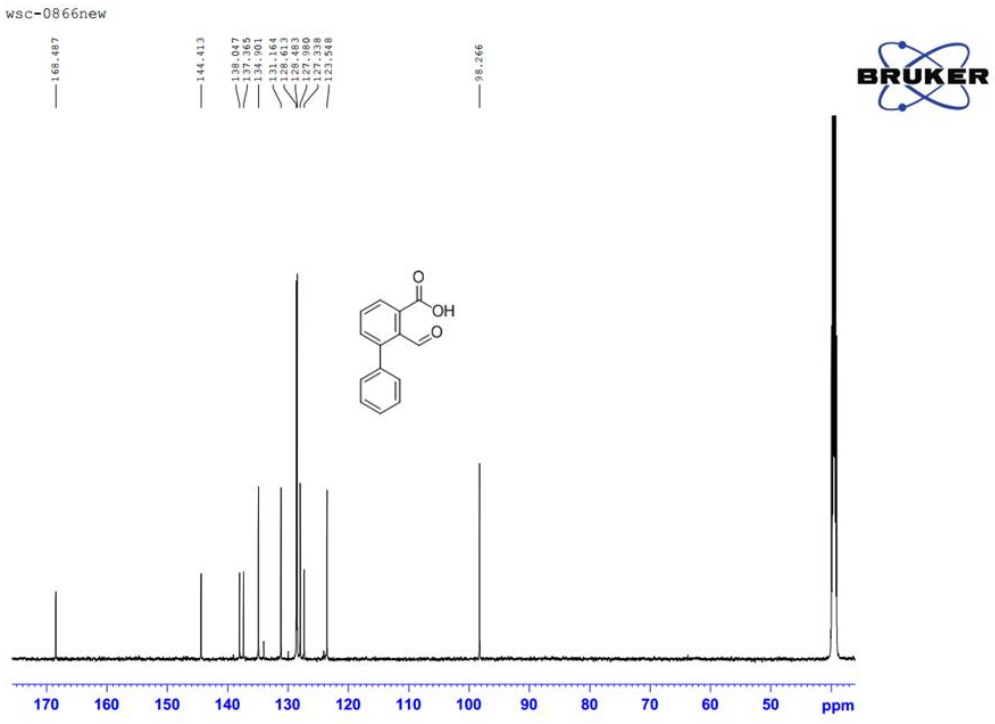
NMR of compound **2i**



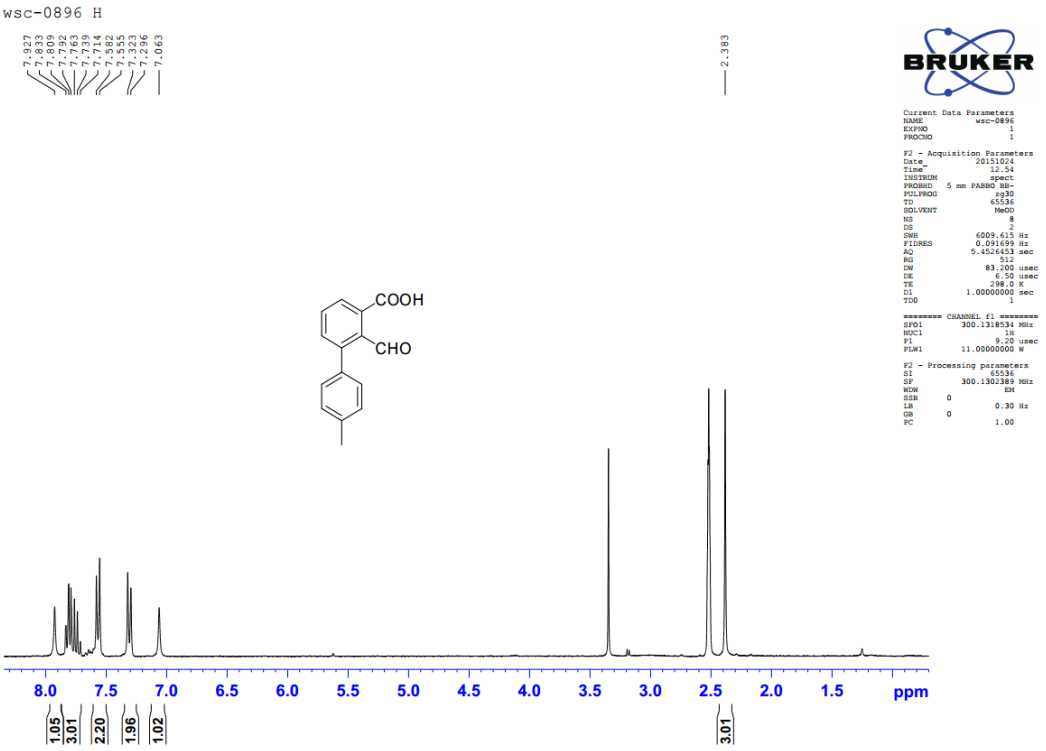


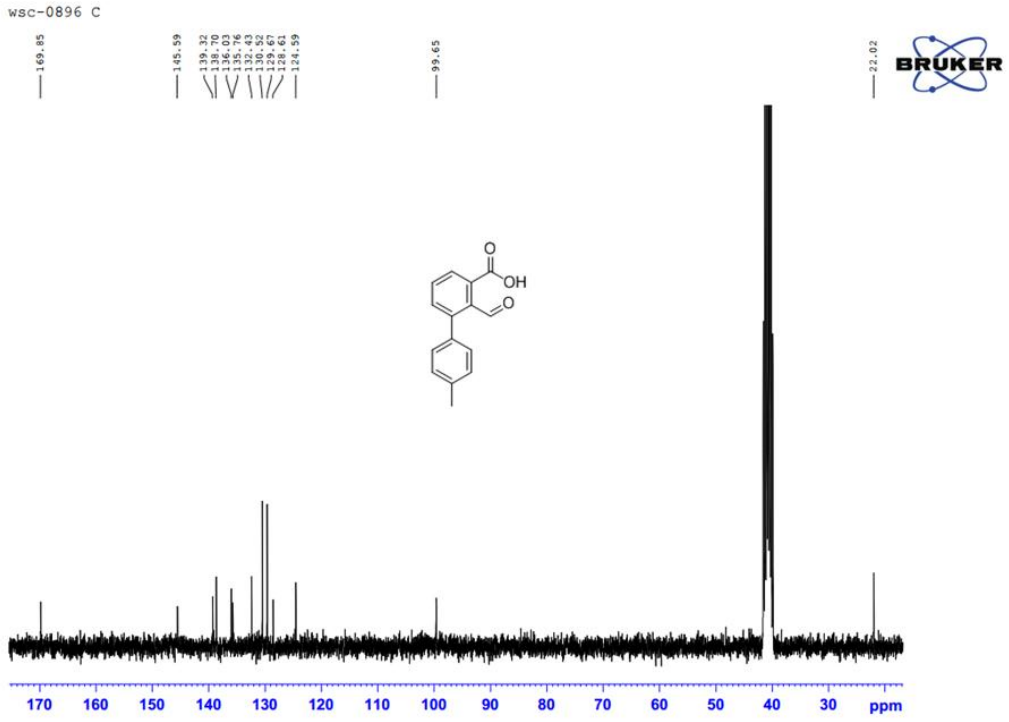
NMR of compound **2j**



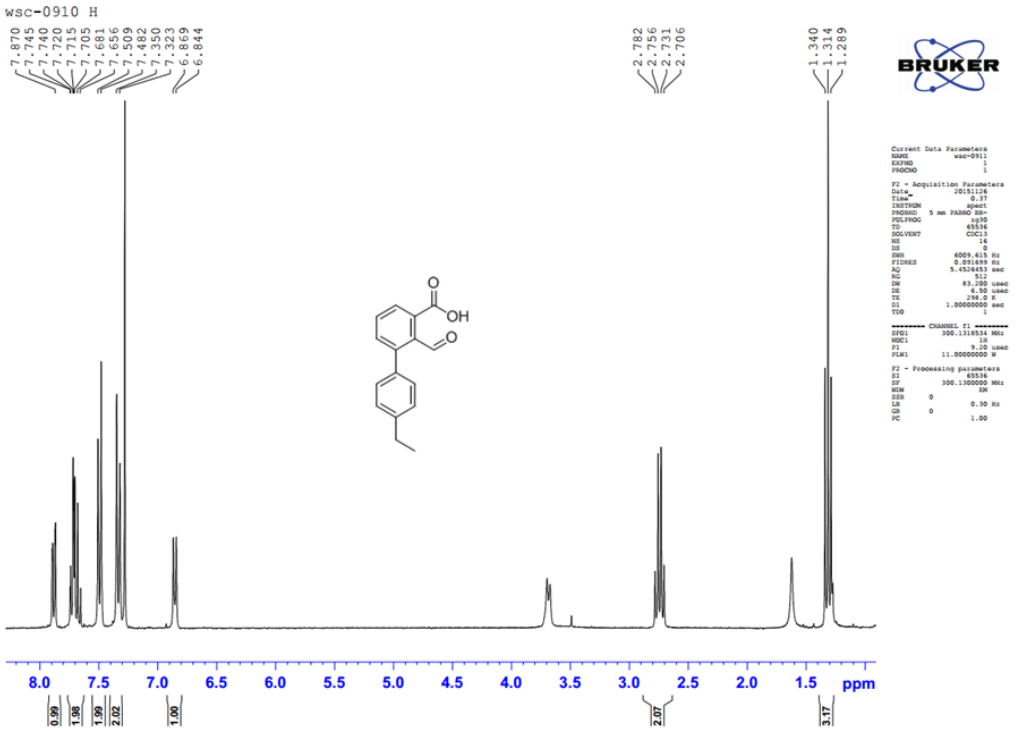


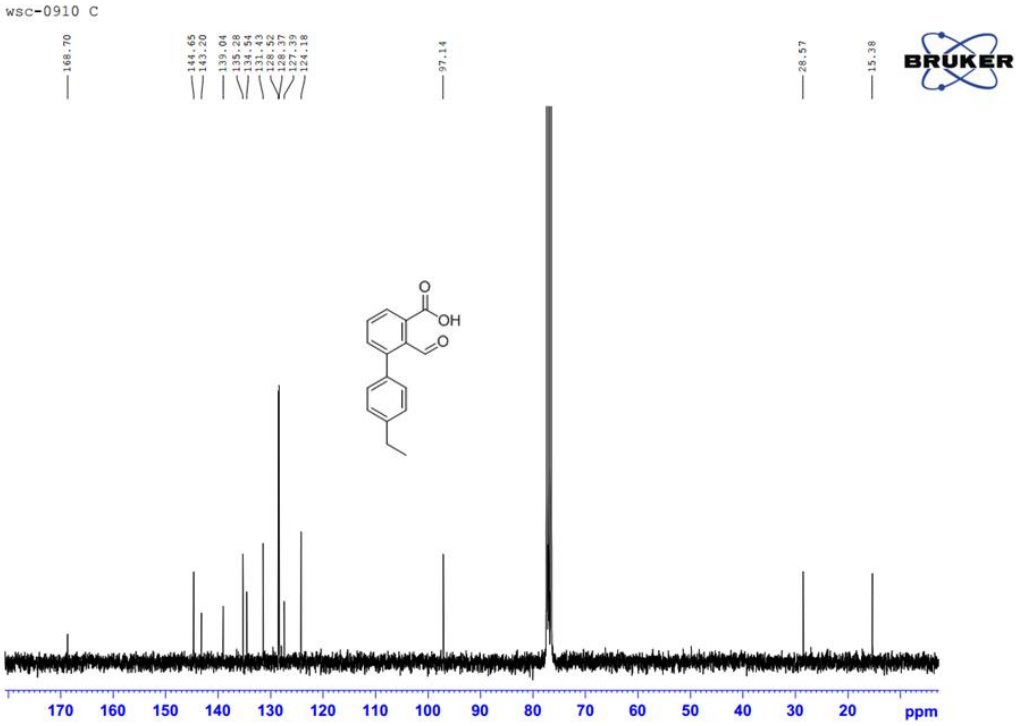
NMR of compound **2k**



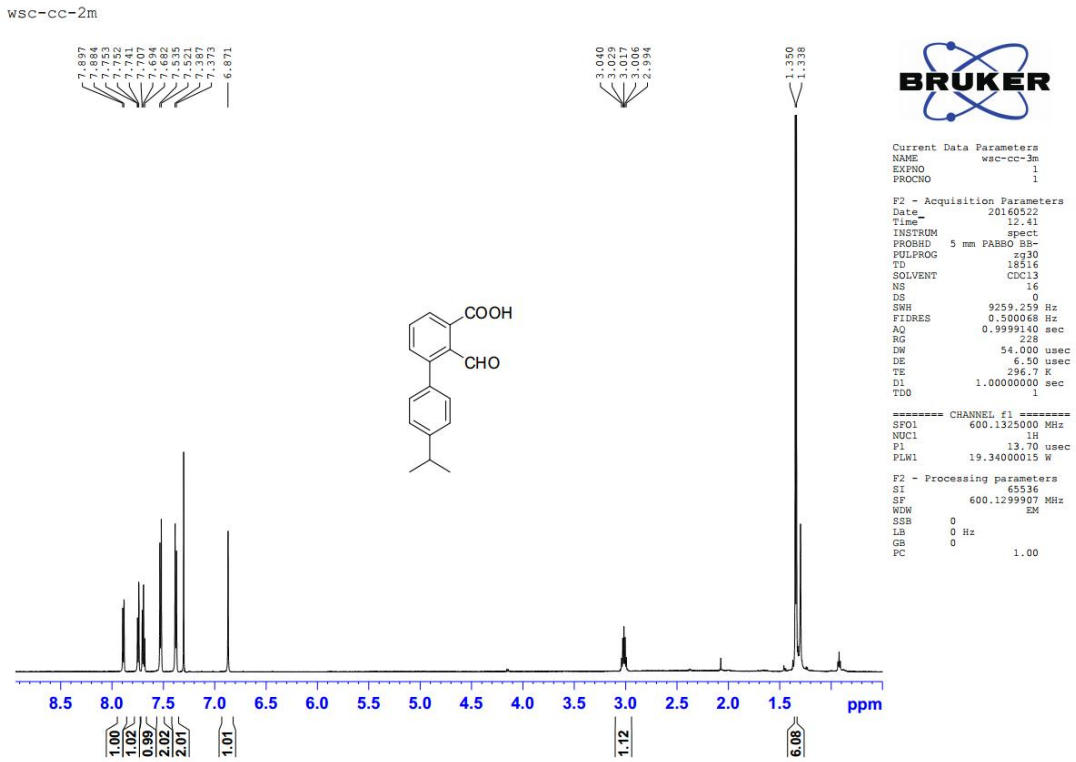


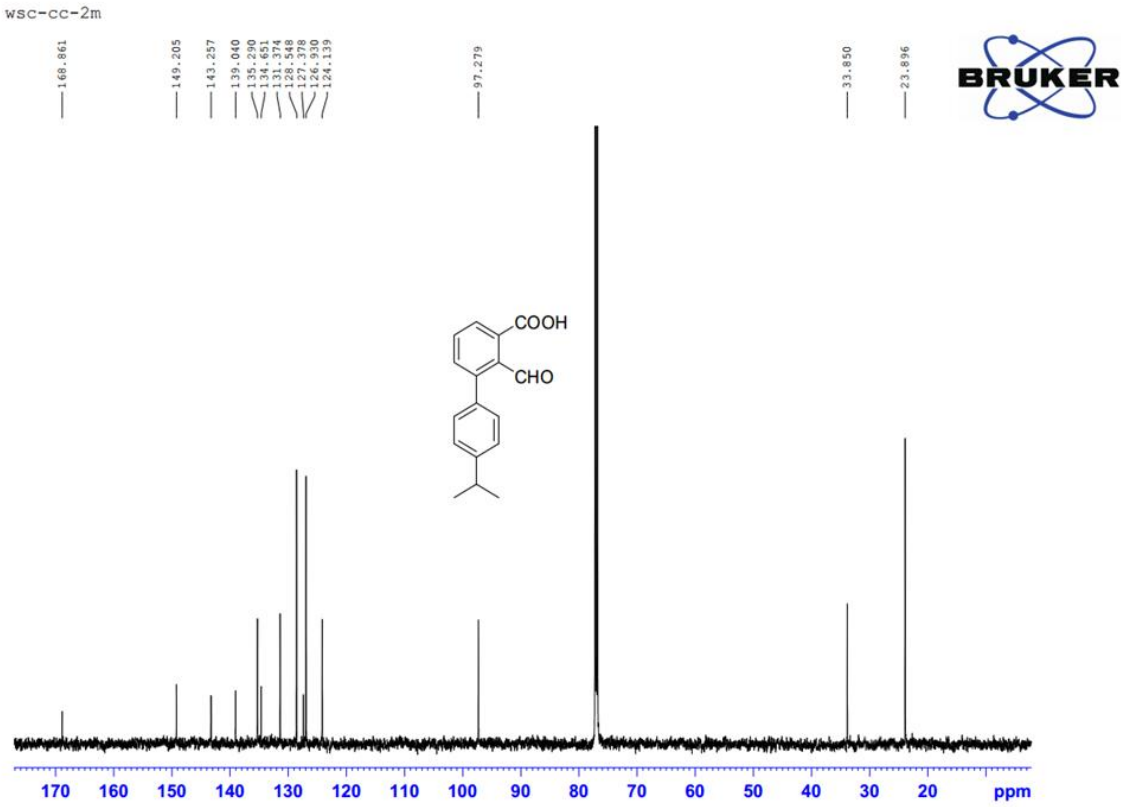
NMR of compound **2l**



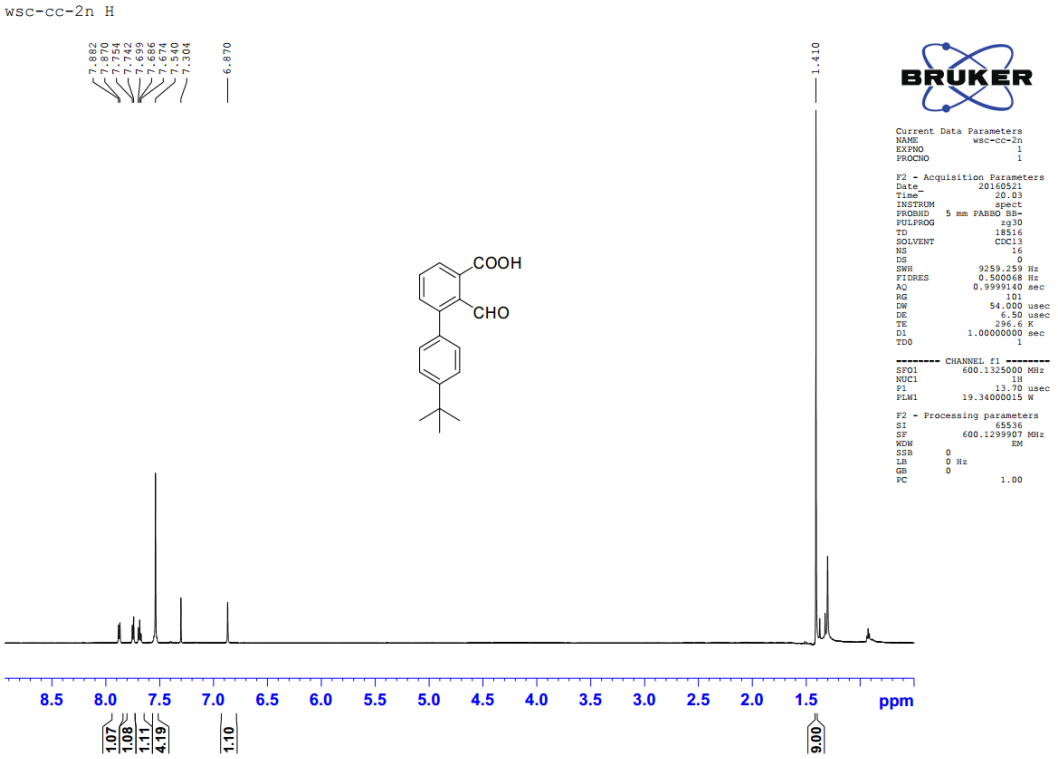


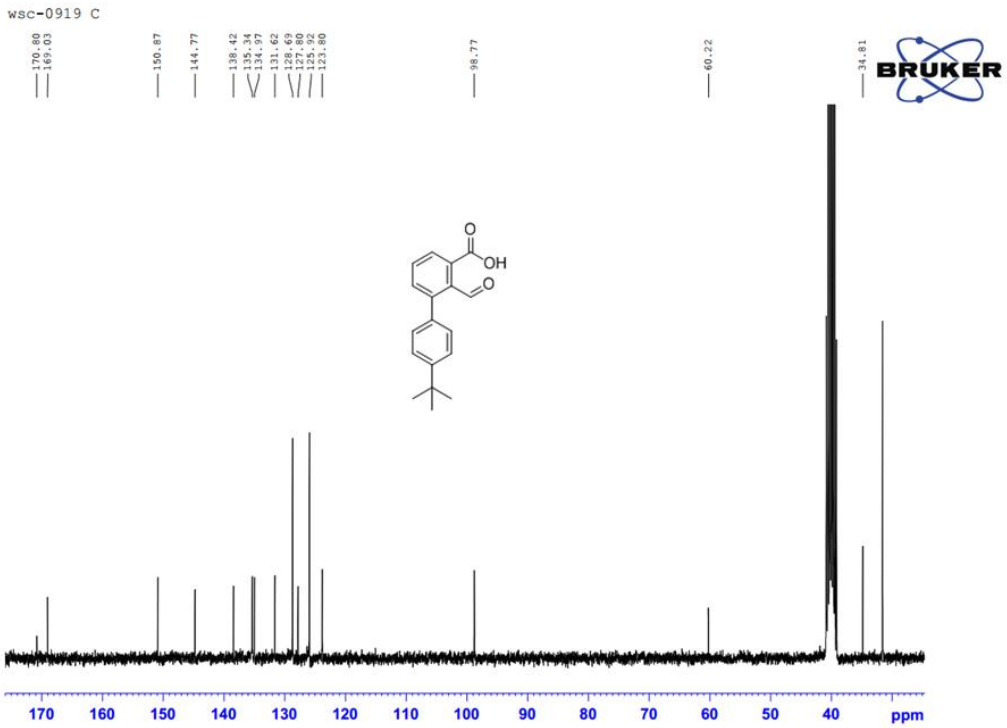
NMR of compound **2m**



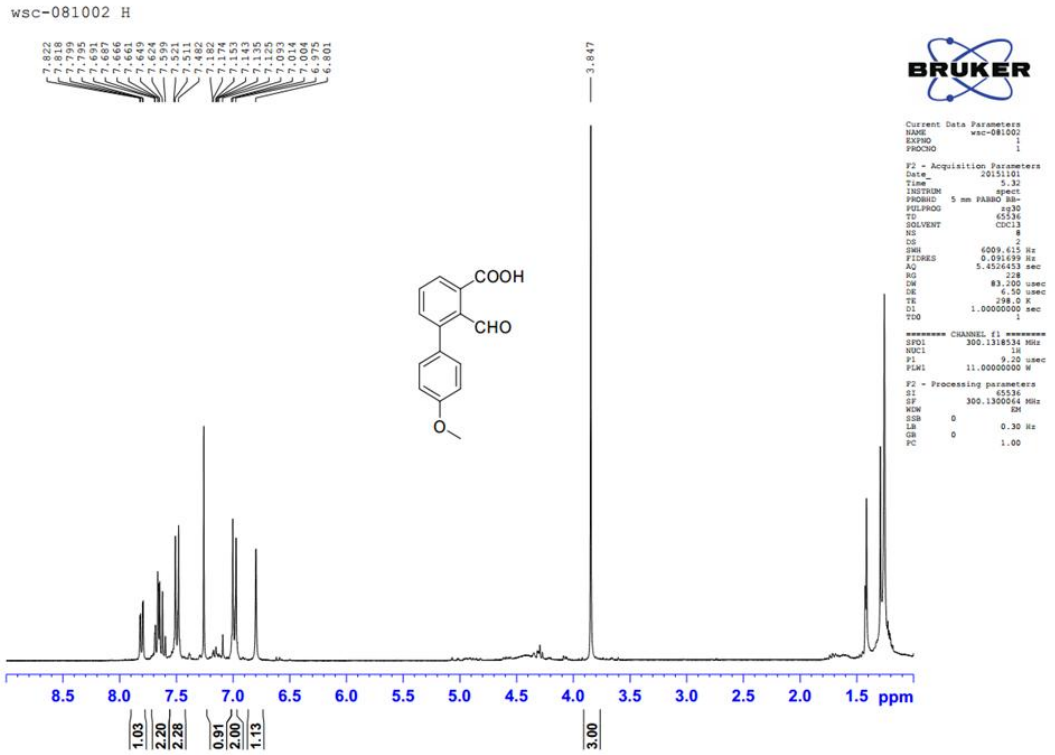


NMR of compound **2n**

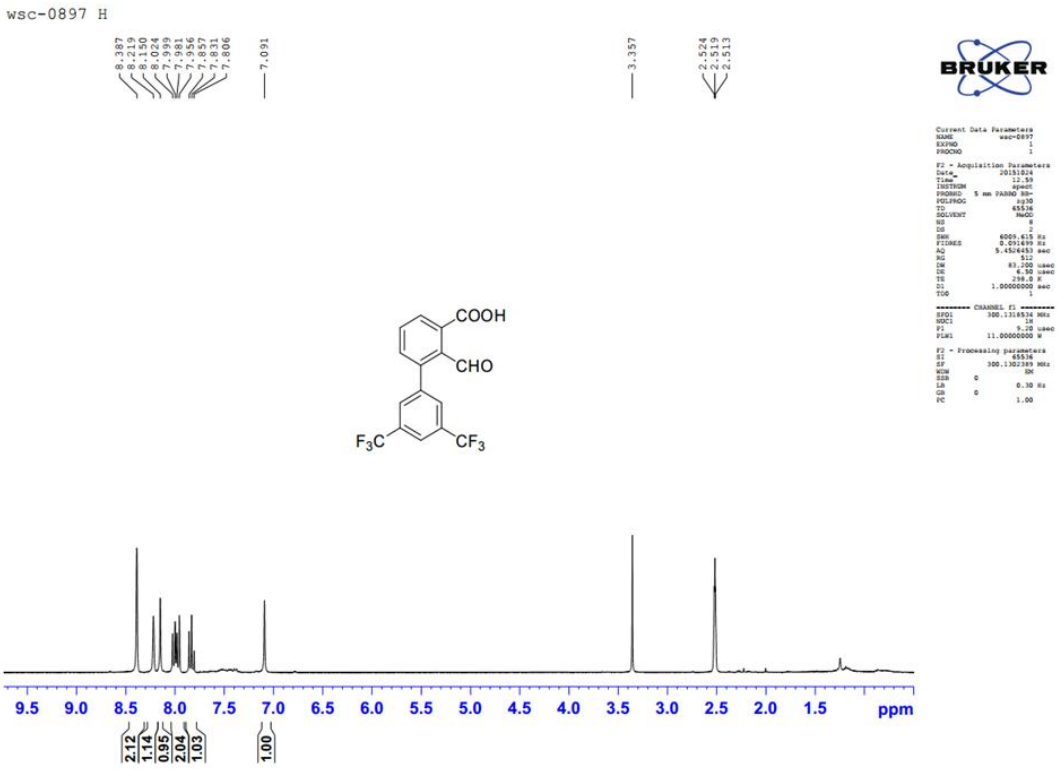


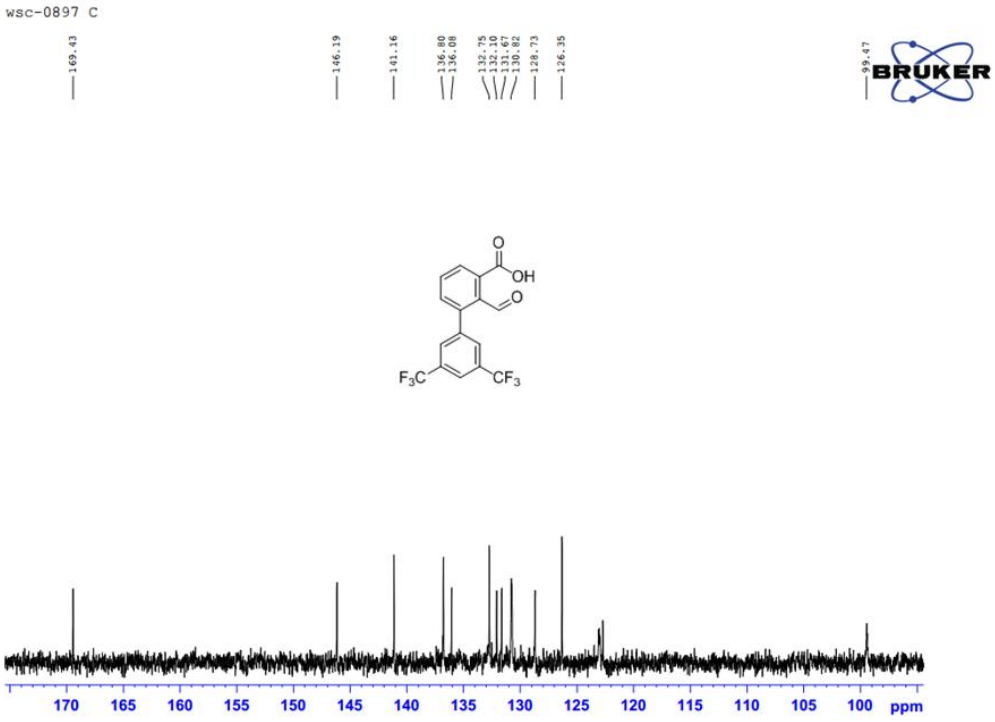


NMR of compound **2o**

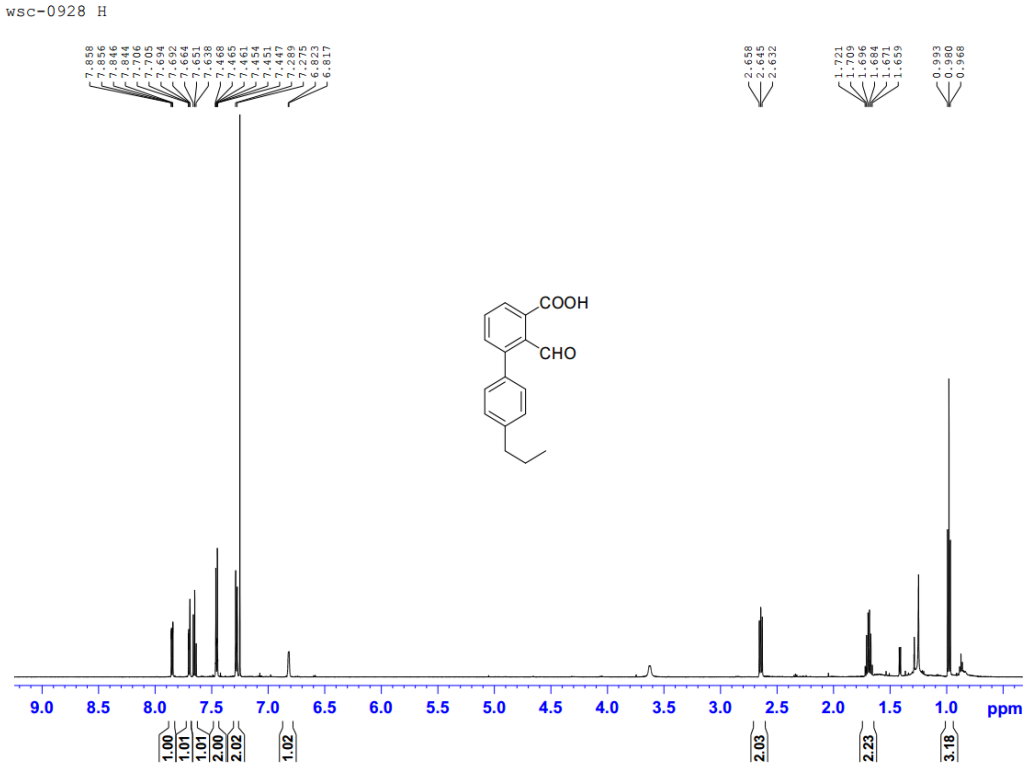


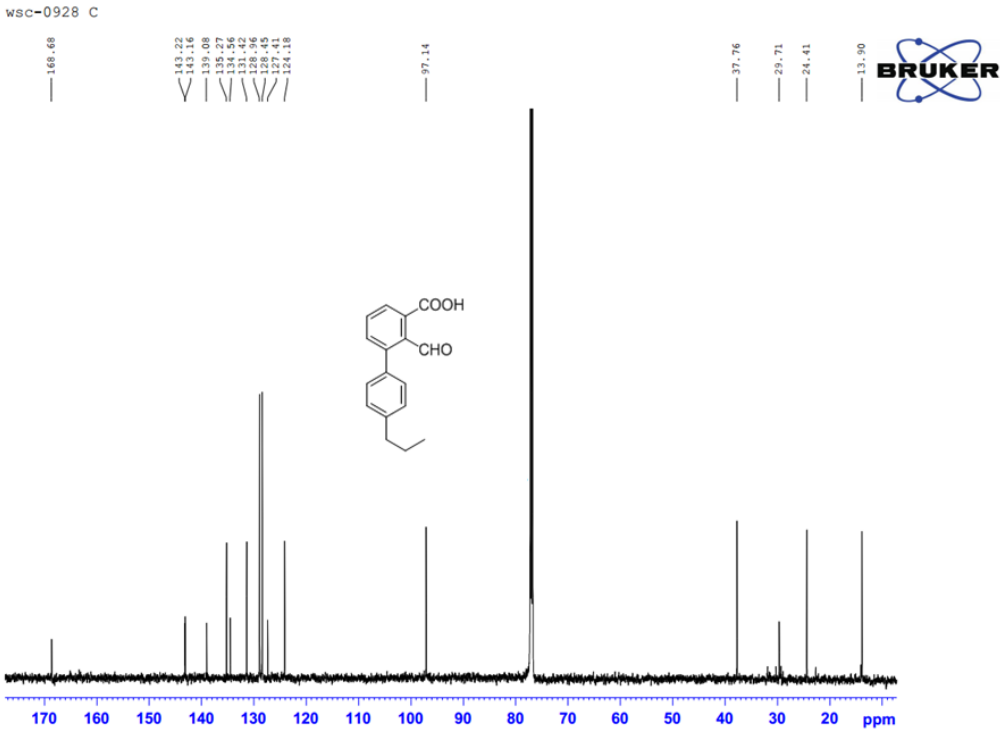
NMR of compound **2p**



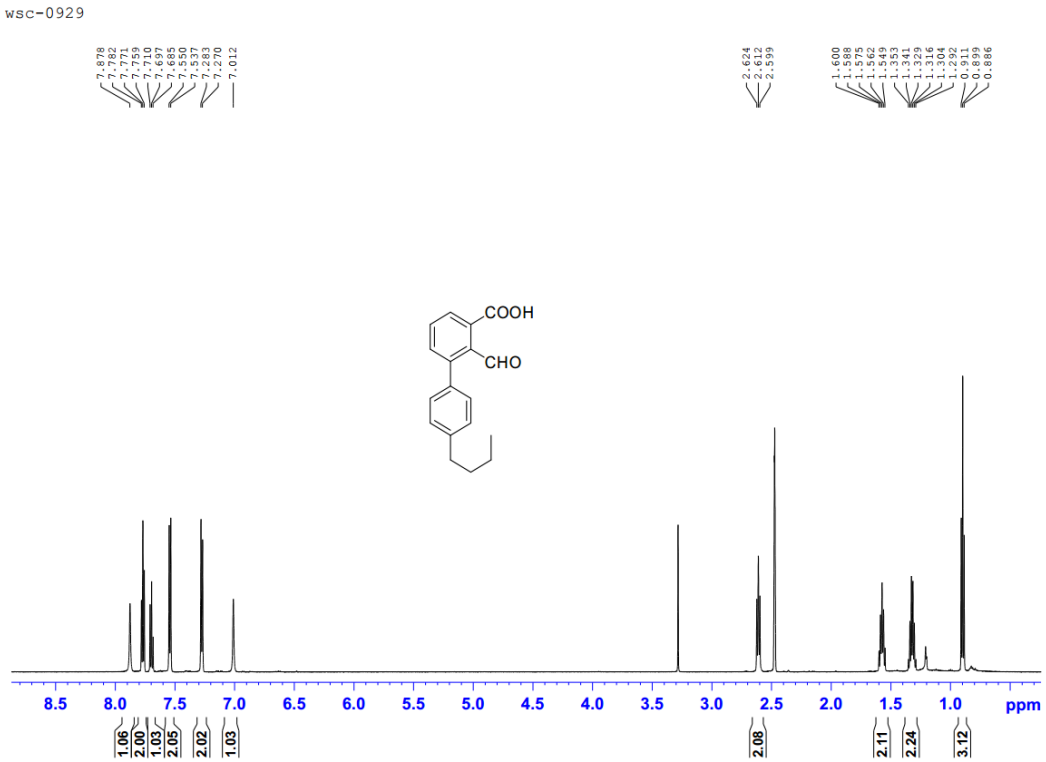


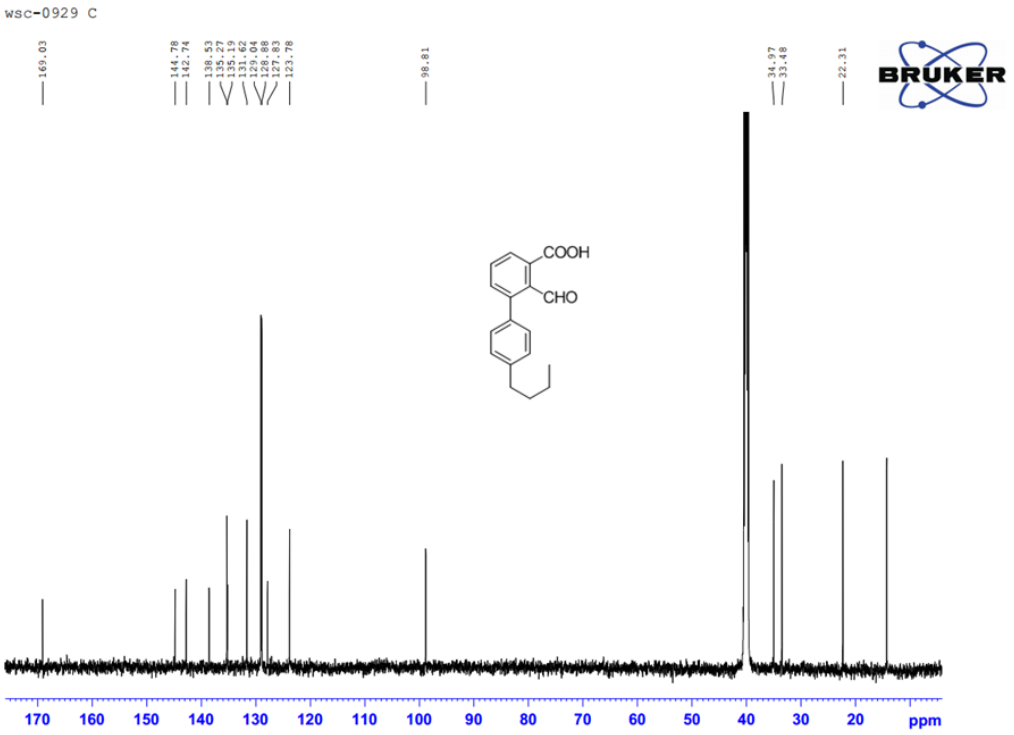
NMR of compound **2q**



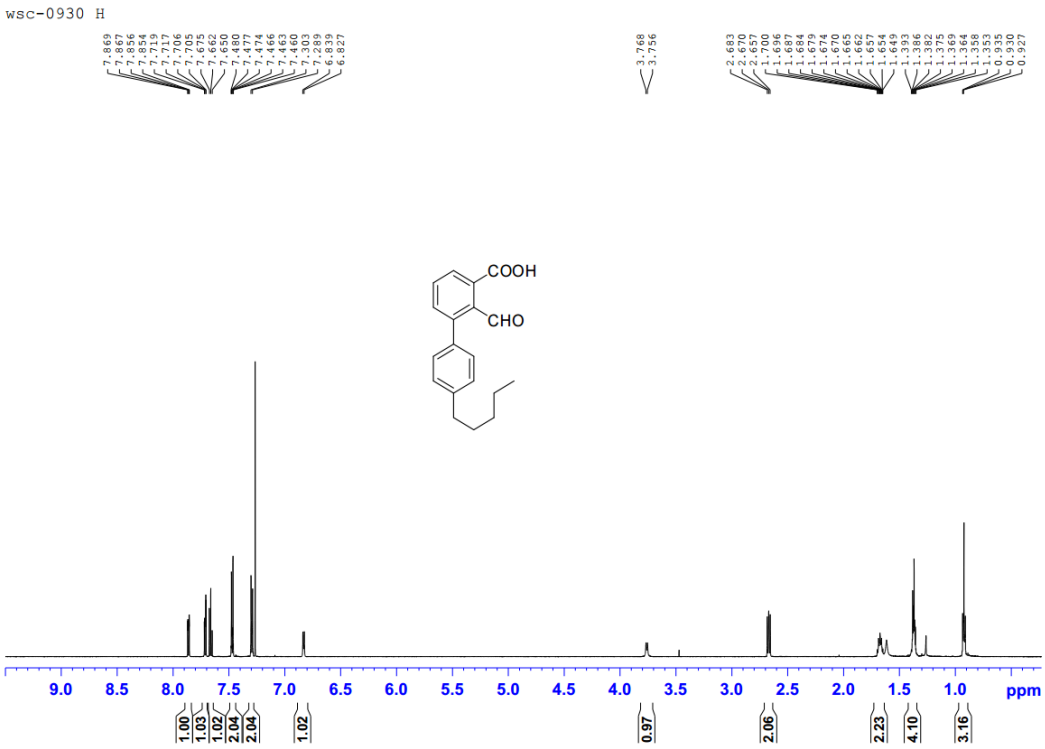


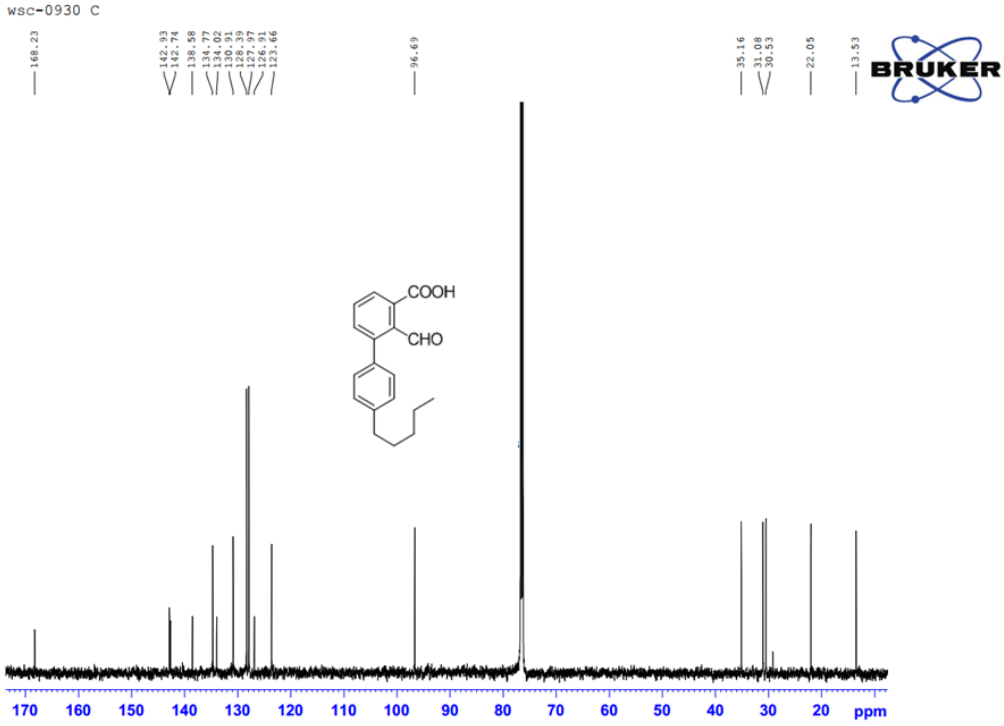
NMR of compound **2r**



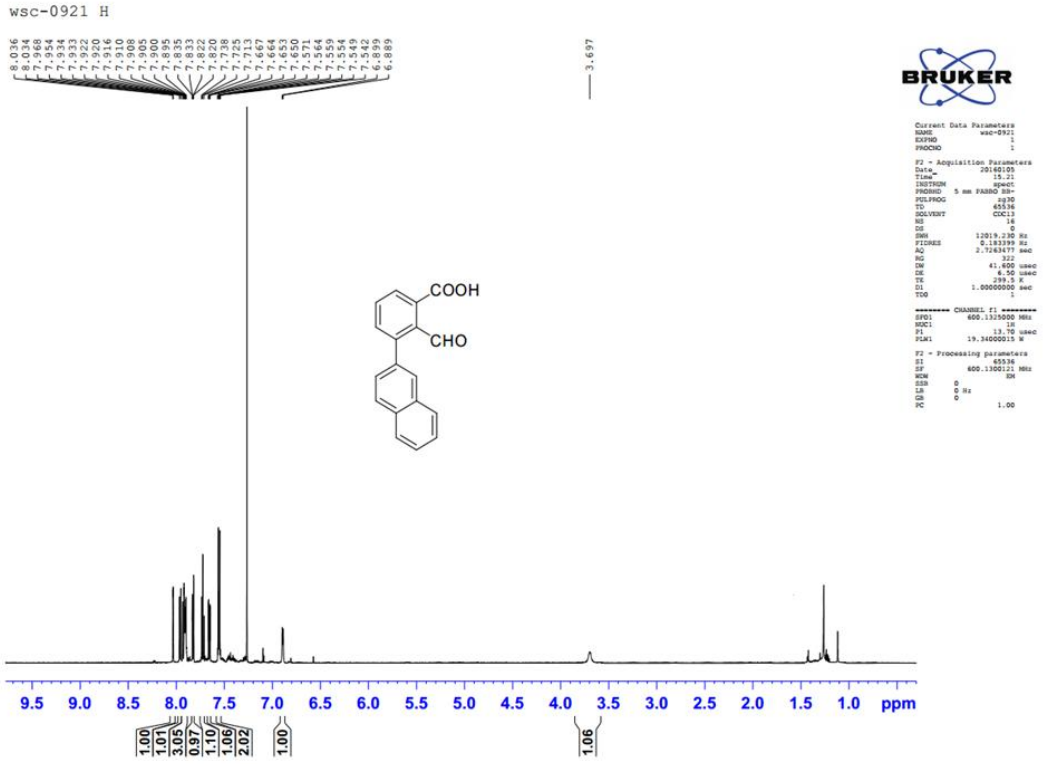


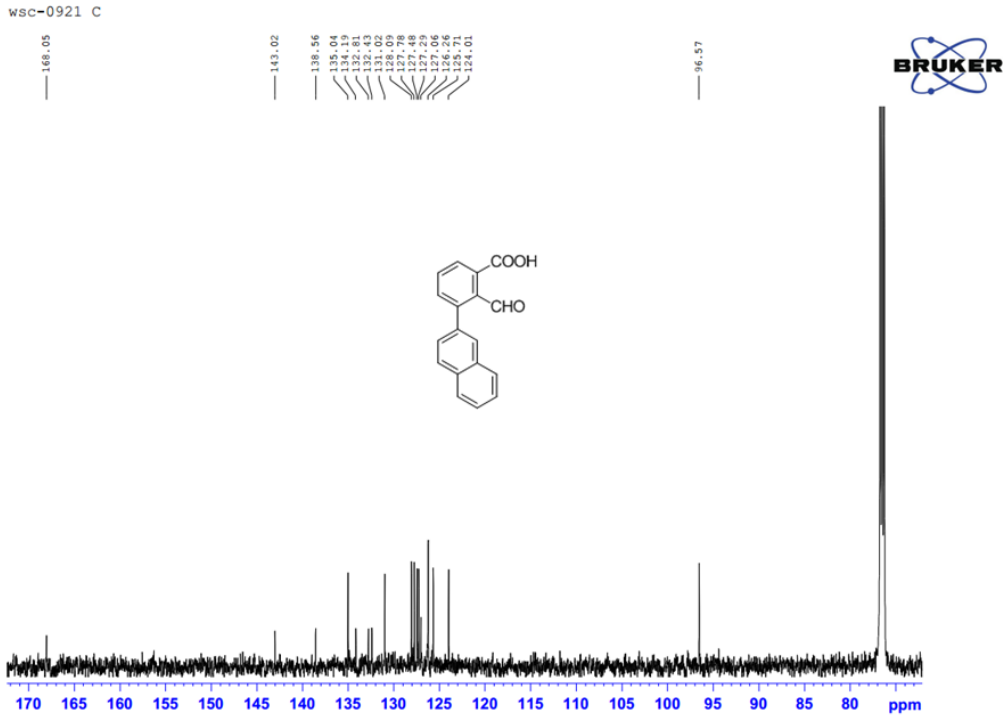
NMR of compound **2s**



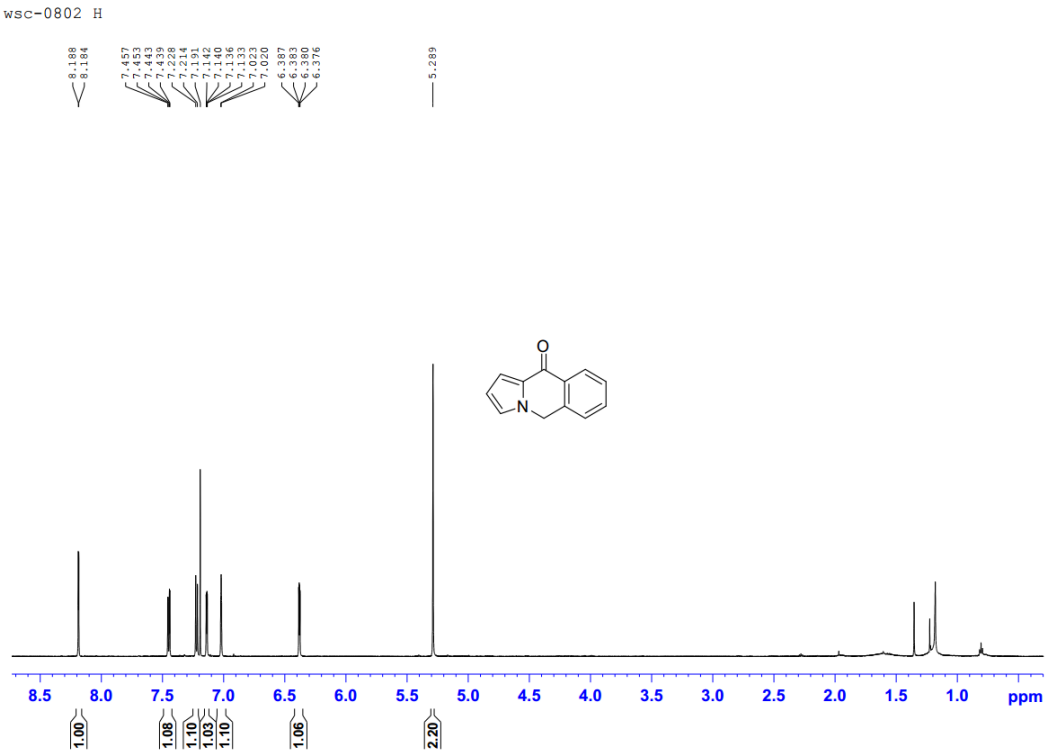


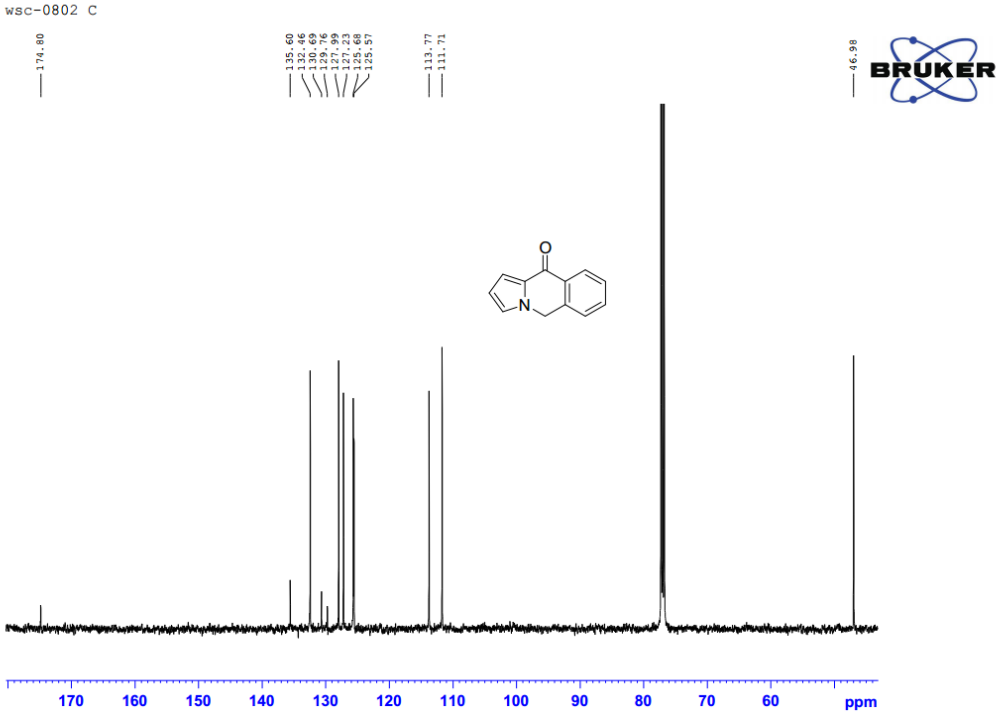
NMR of compound **2t**



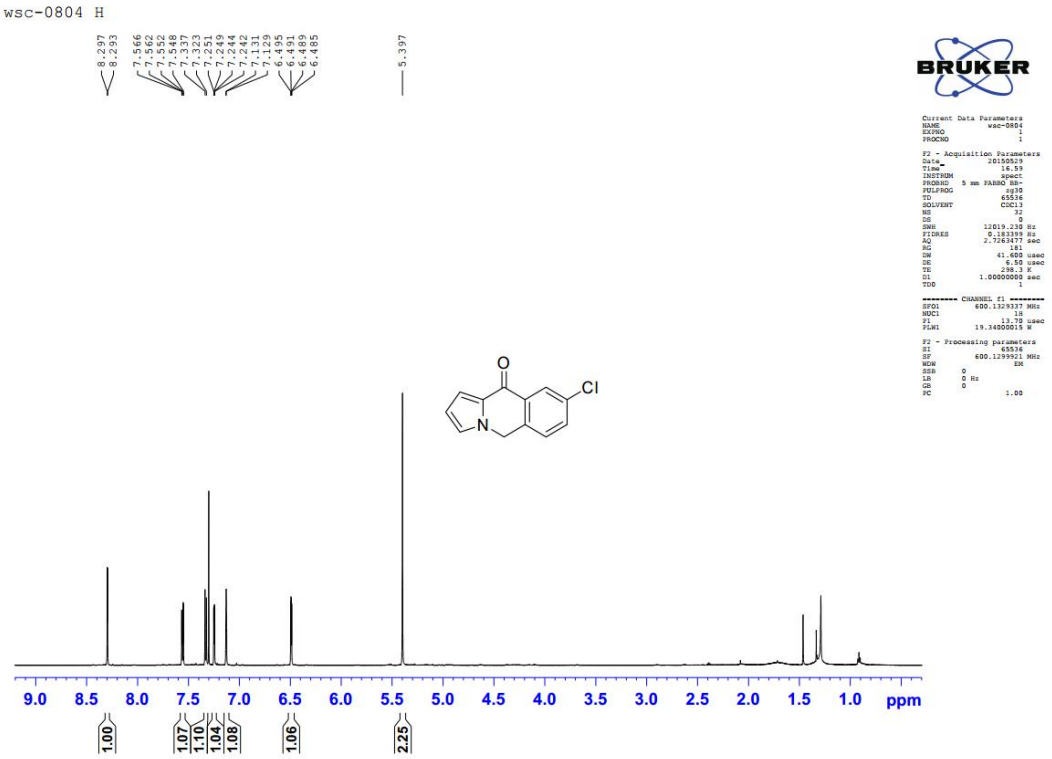


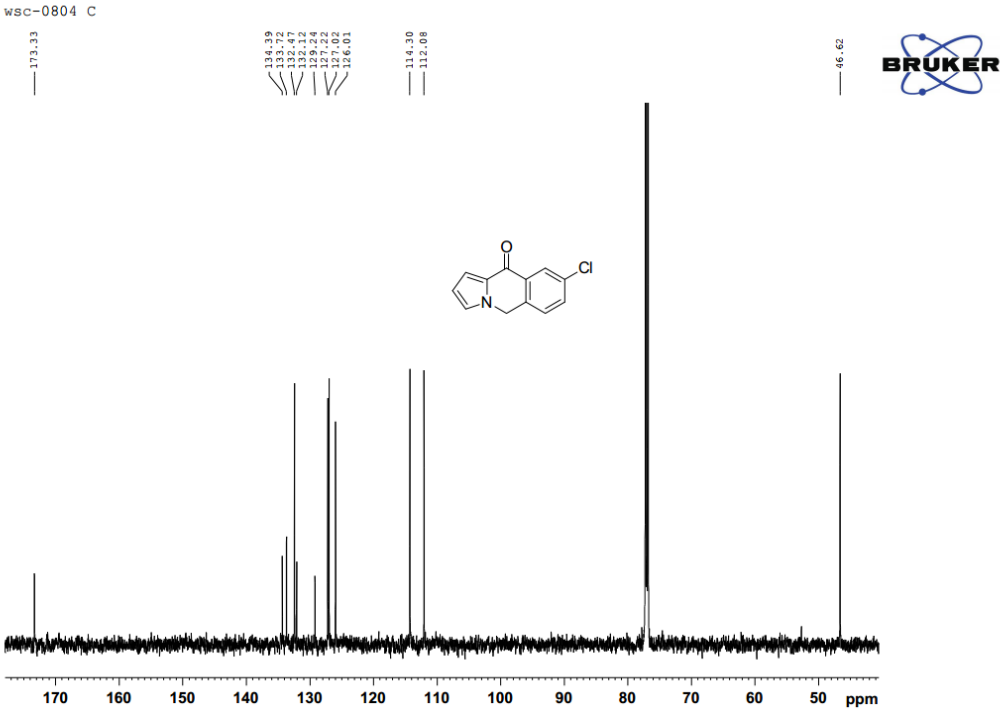
NMR of compound **3a**



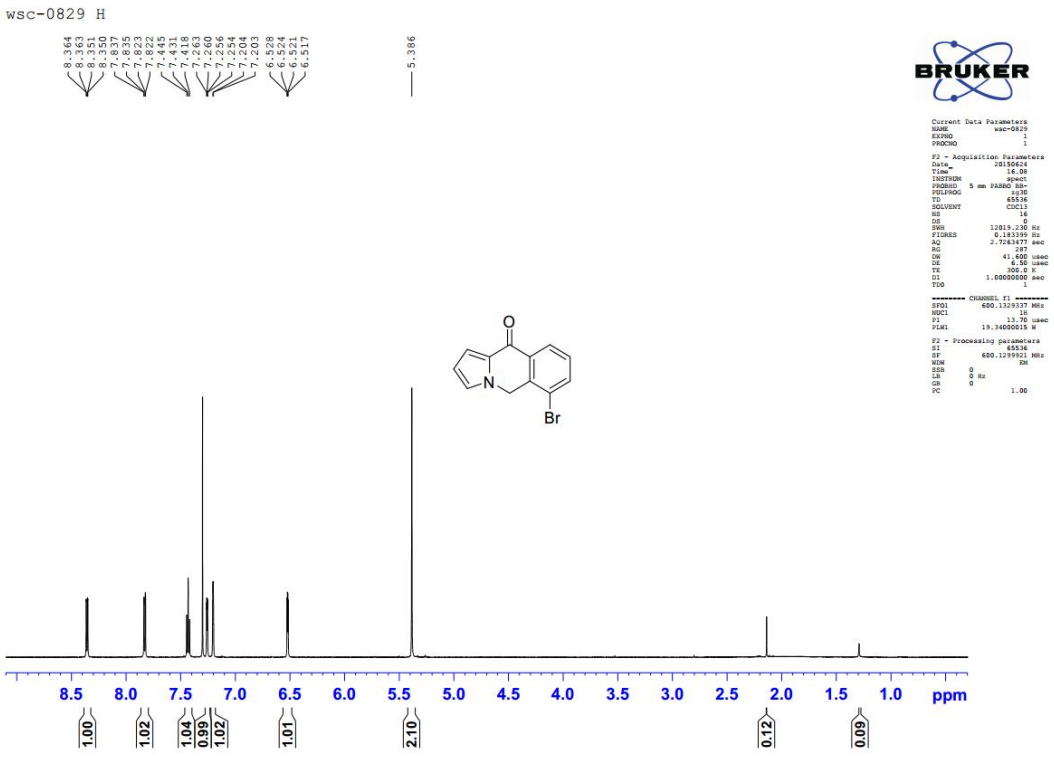


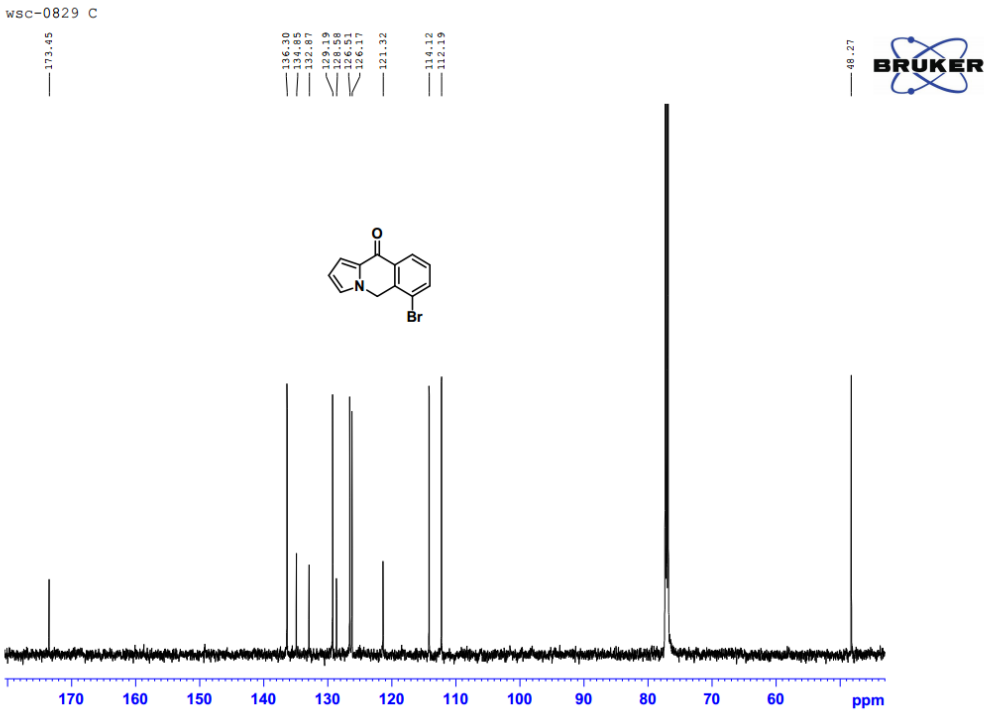
NMR of compound **3b**



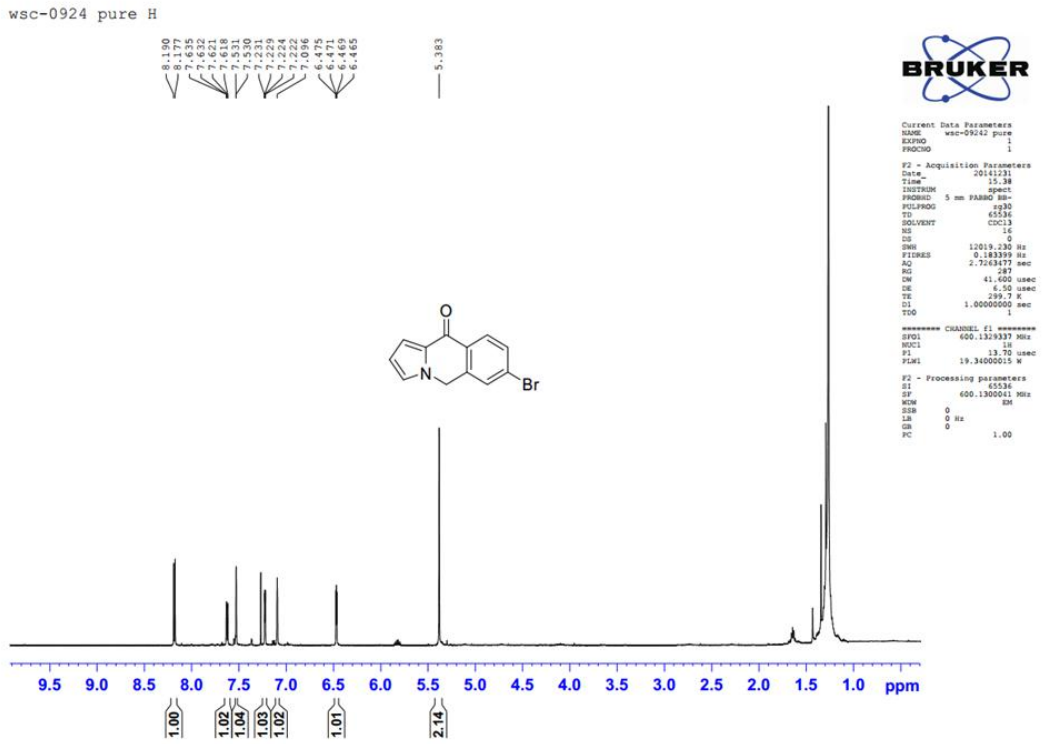


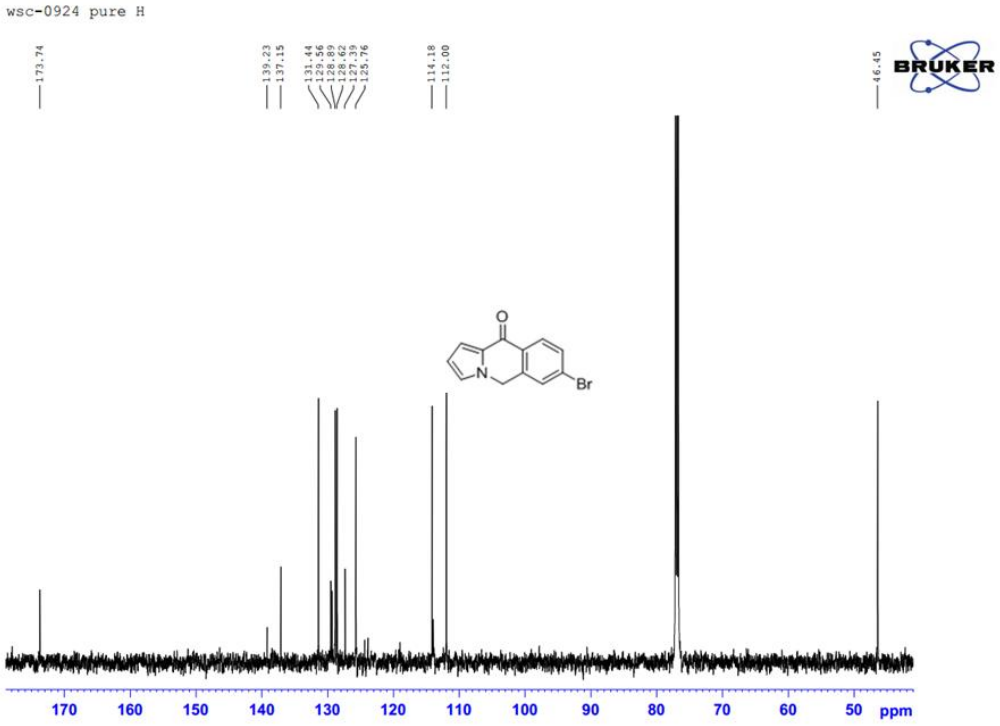
NMR of compound **3c**



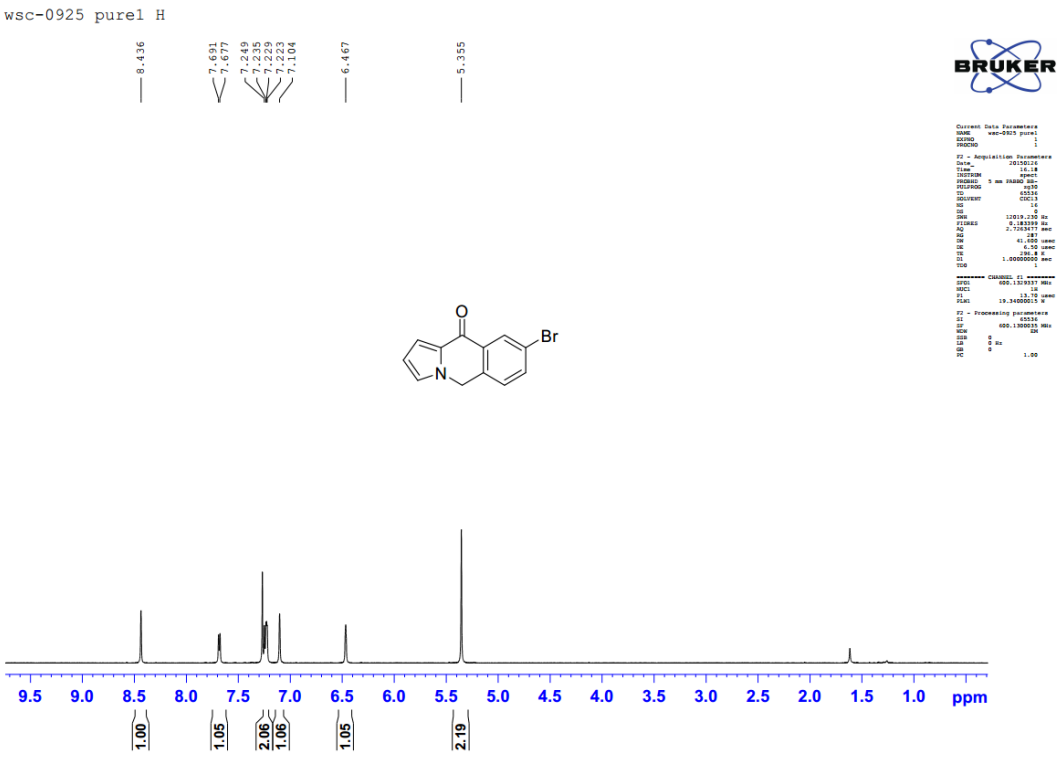


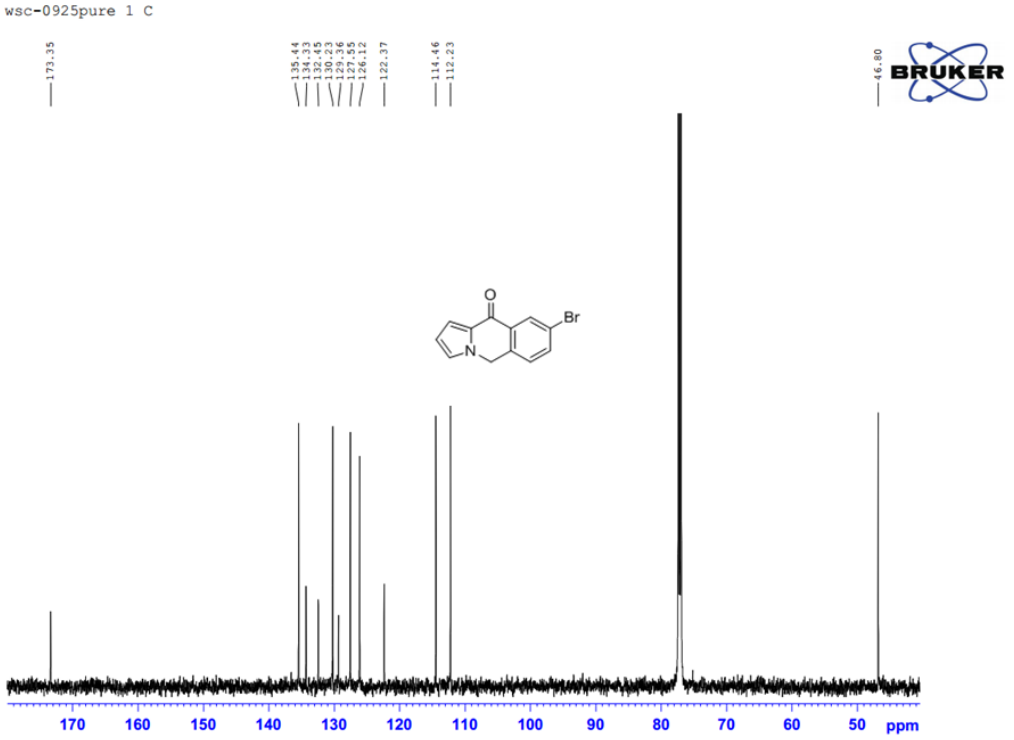
NMR of compound **3d**



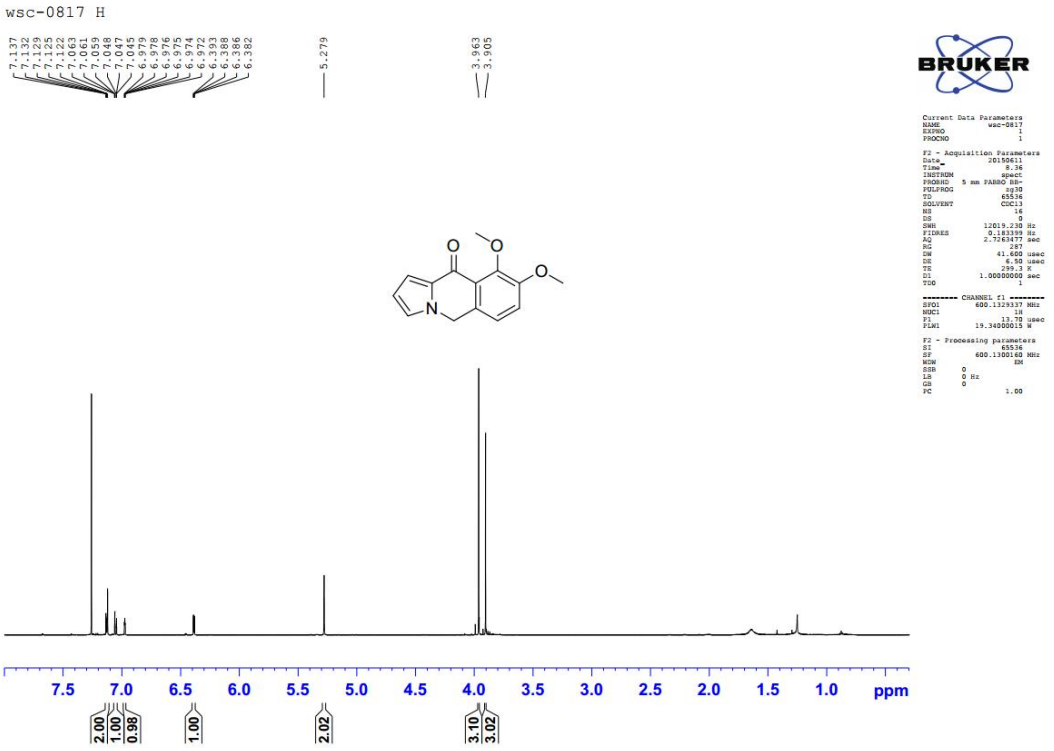


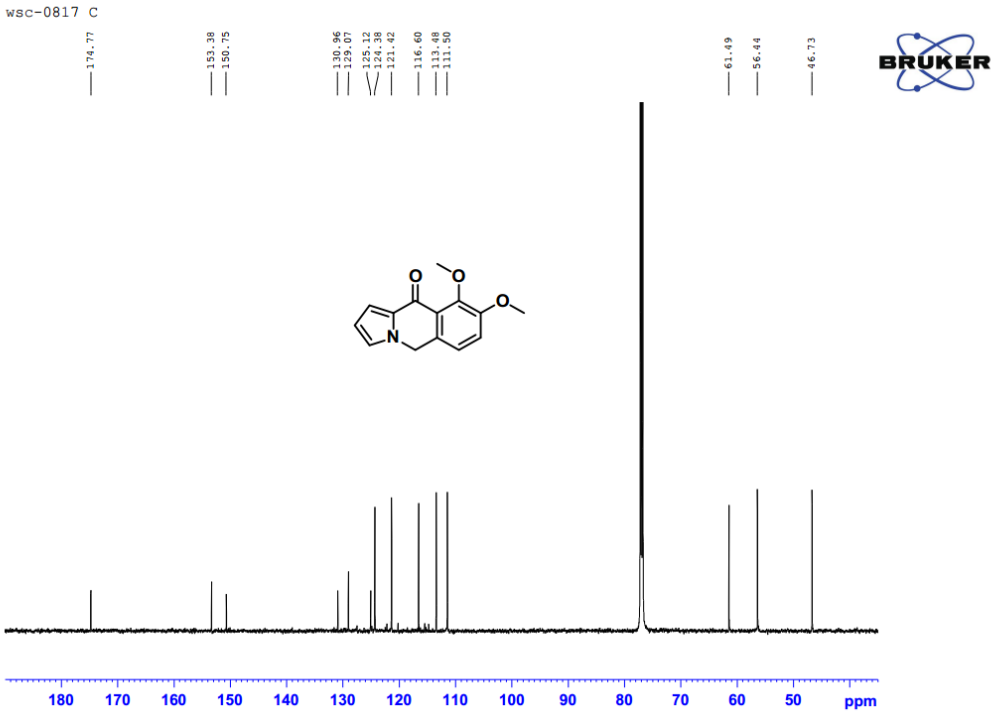
NMR of compound **3e**



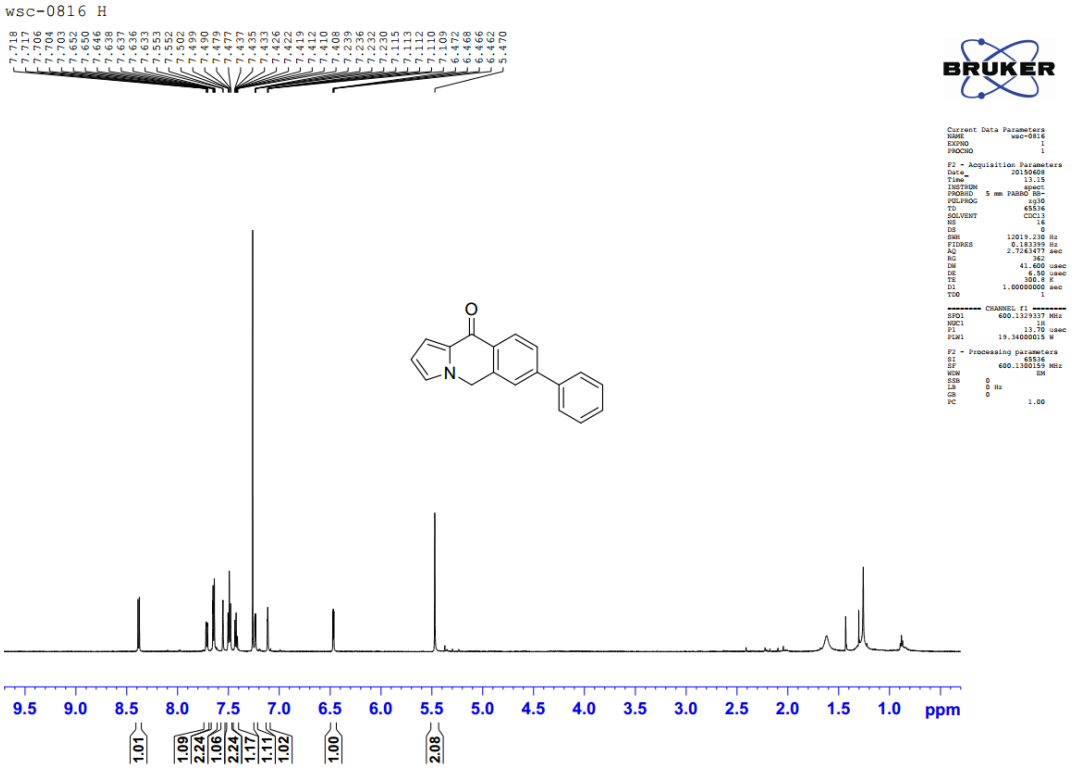


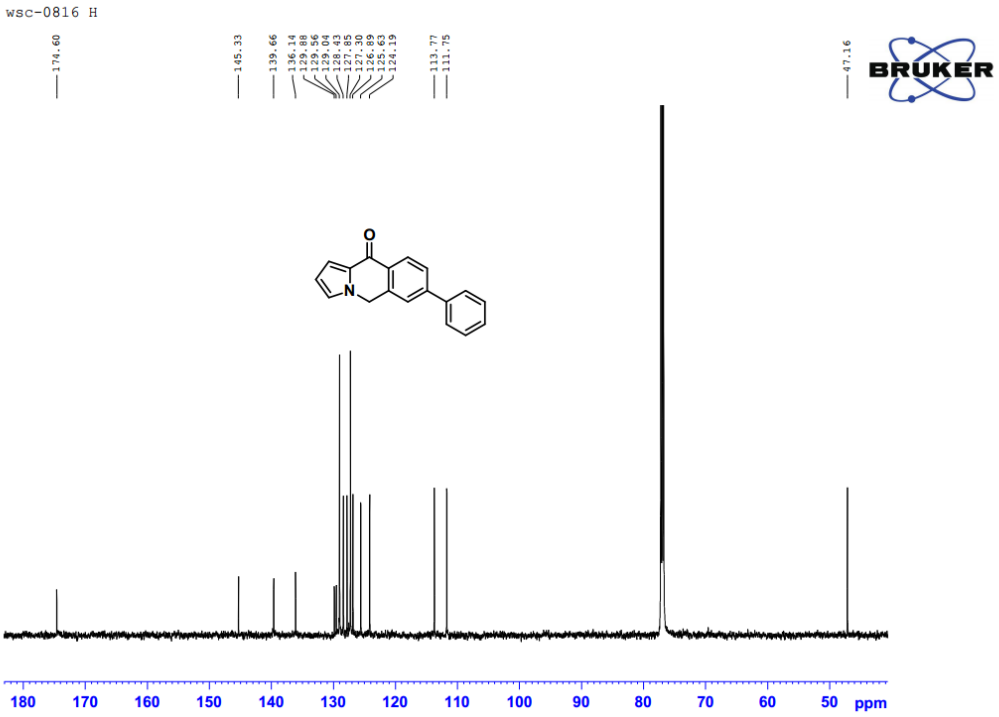
NMR of compound **3f**



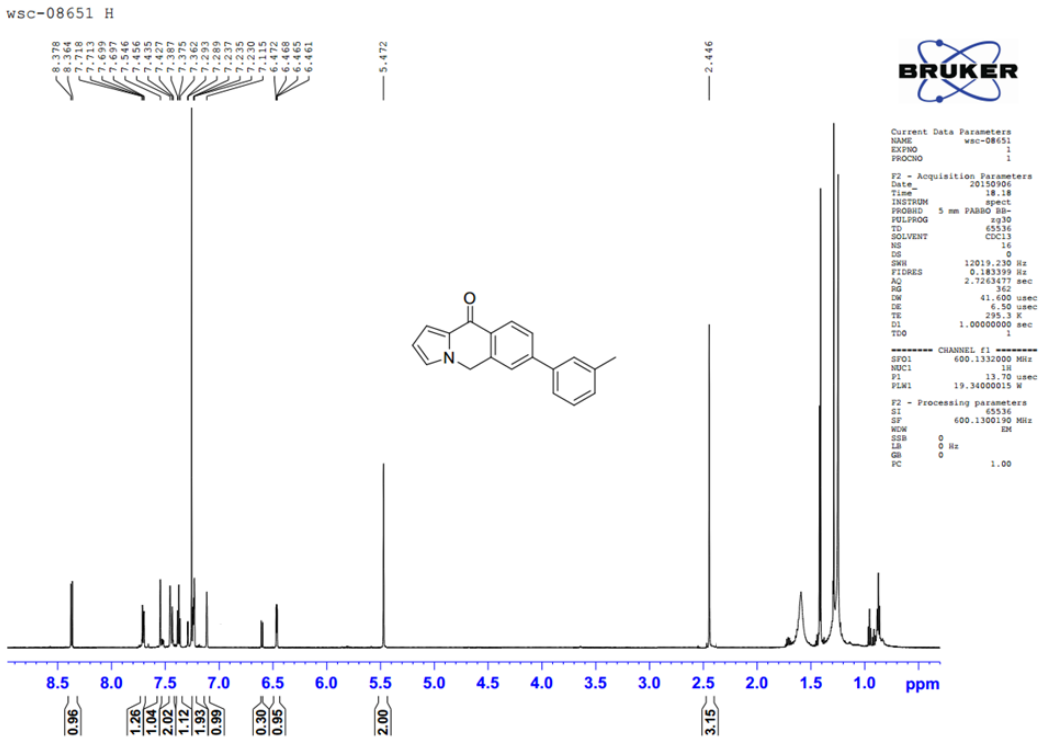


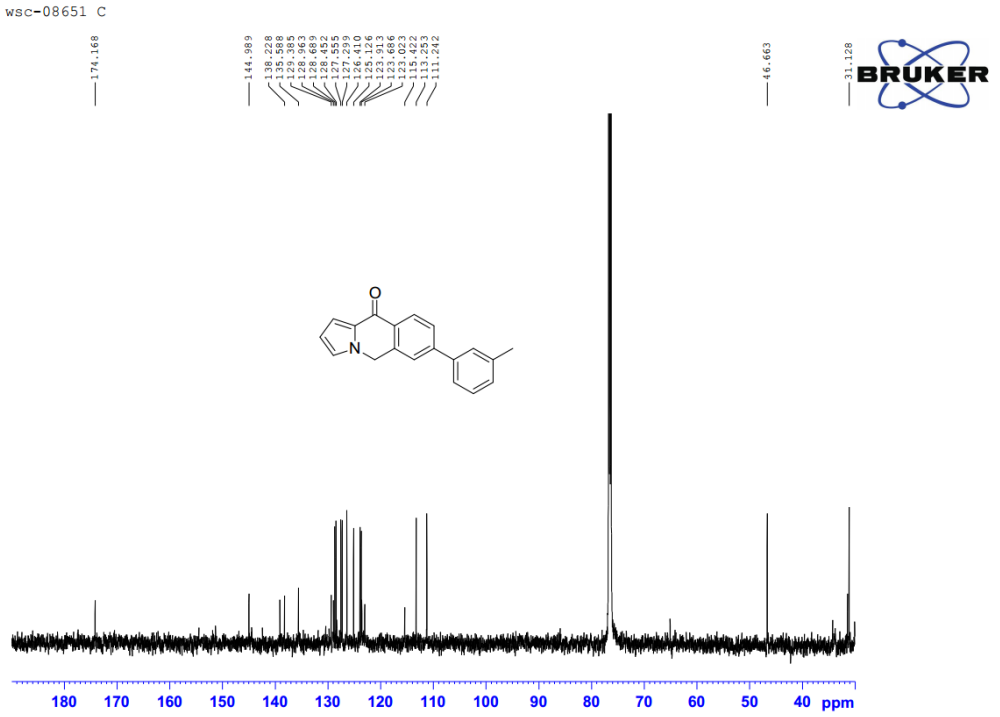
NMR of compound **3g**



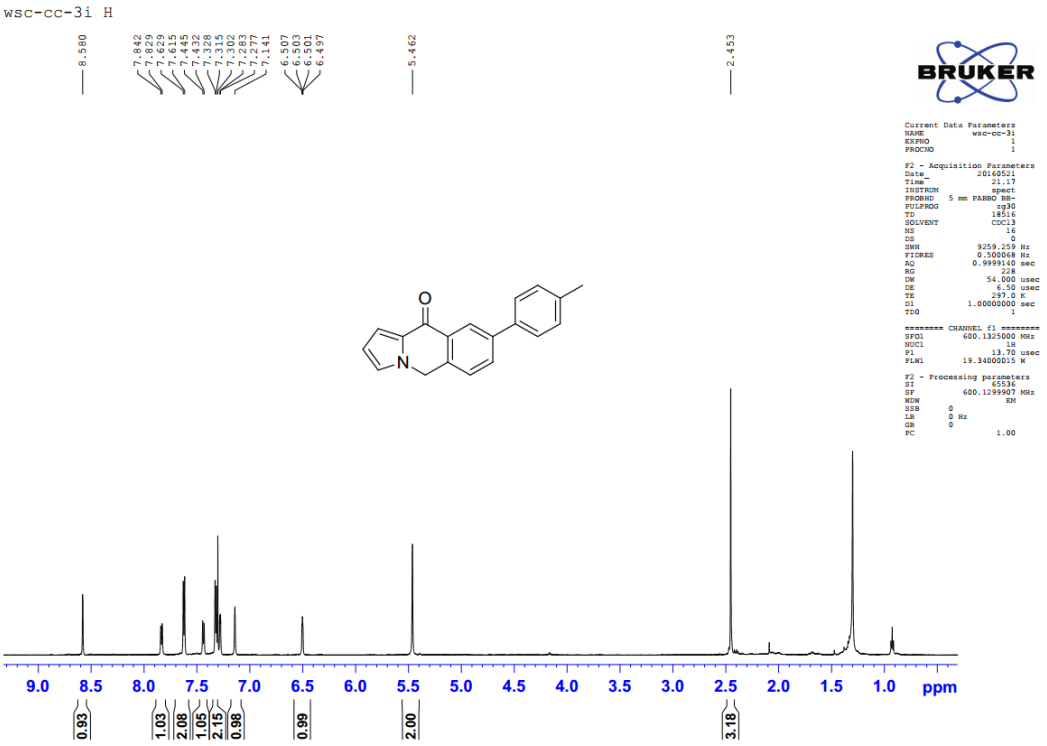


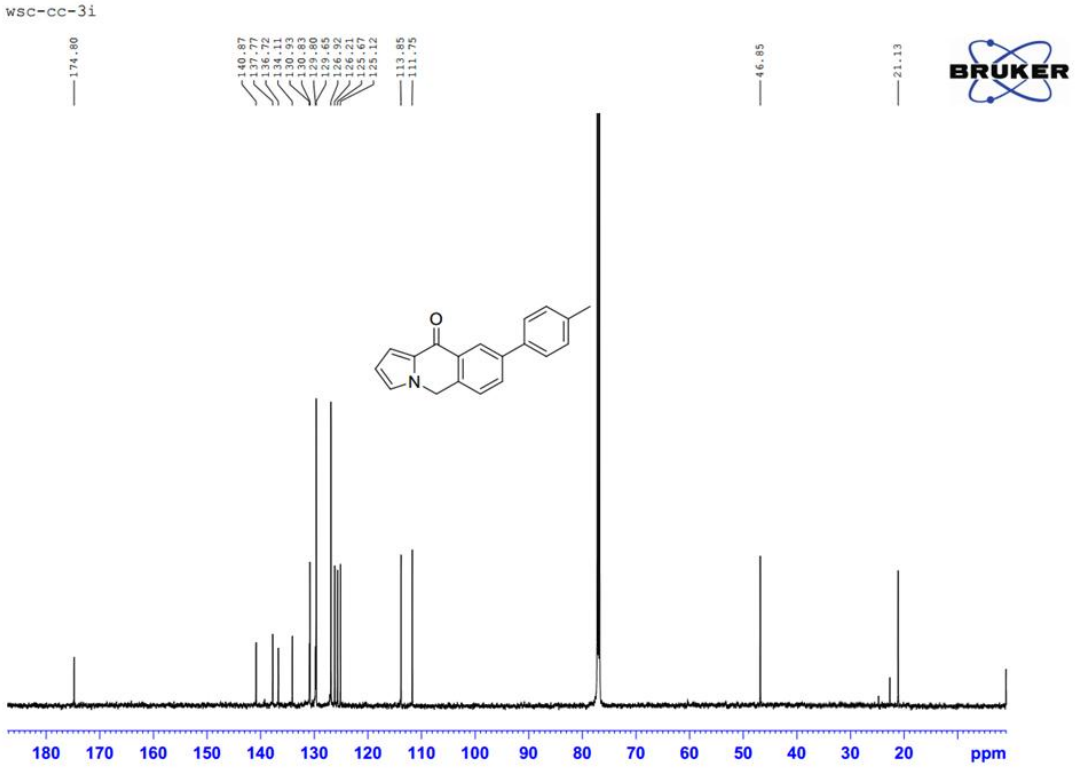
NMR of compound **3h**



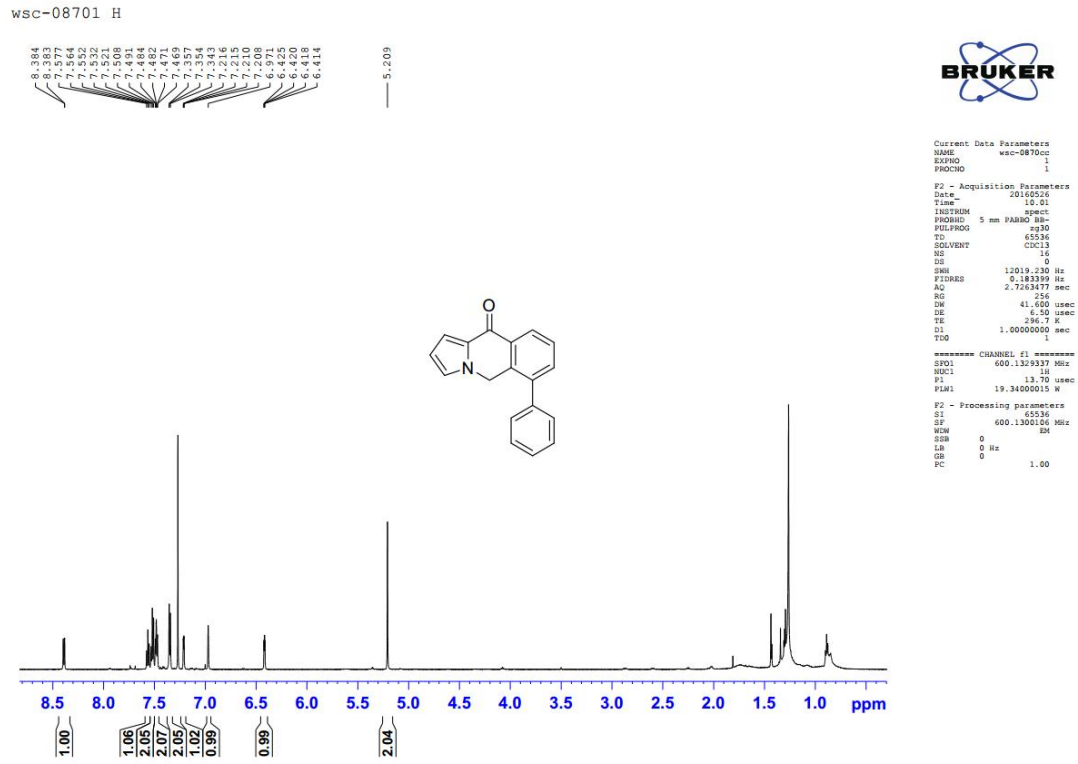


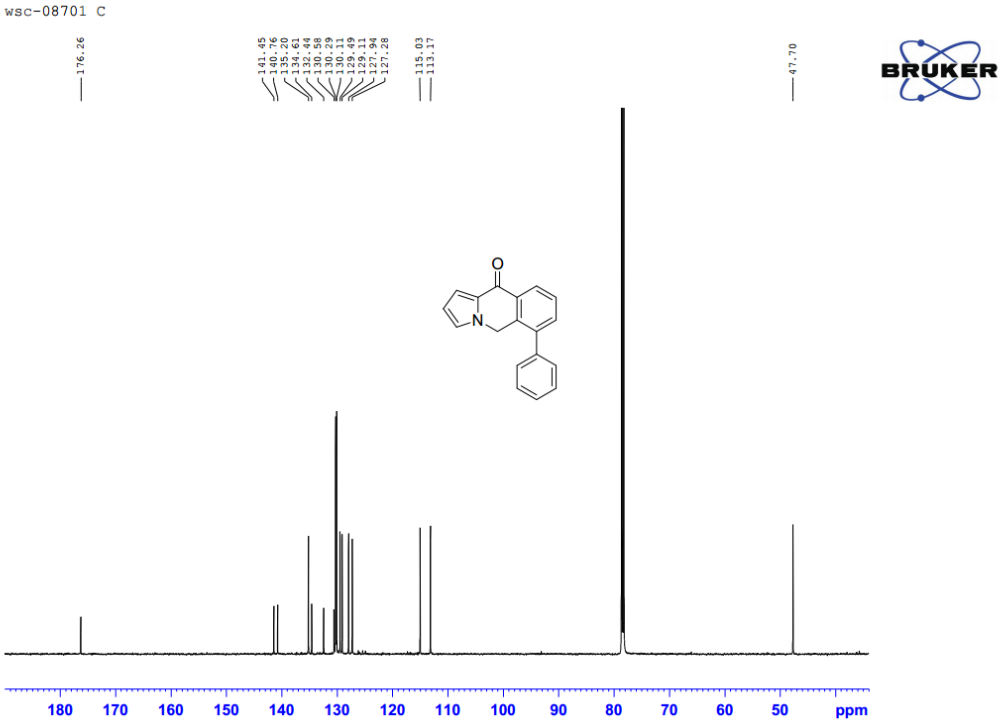
NMR of compound **3i**



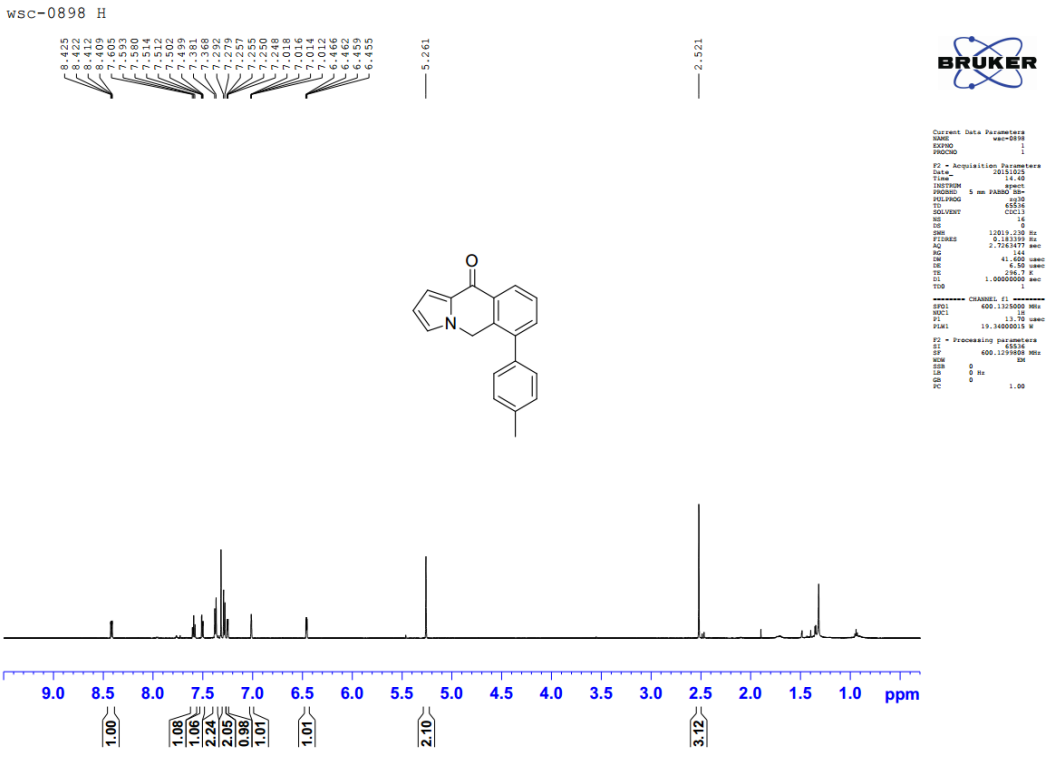


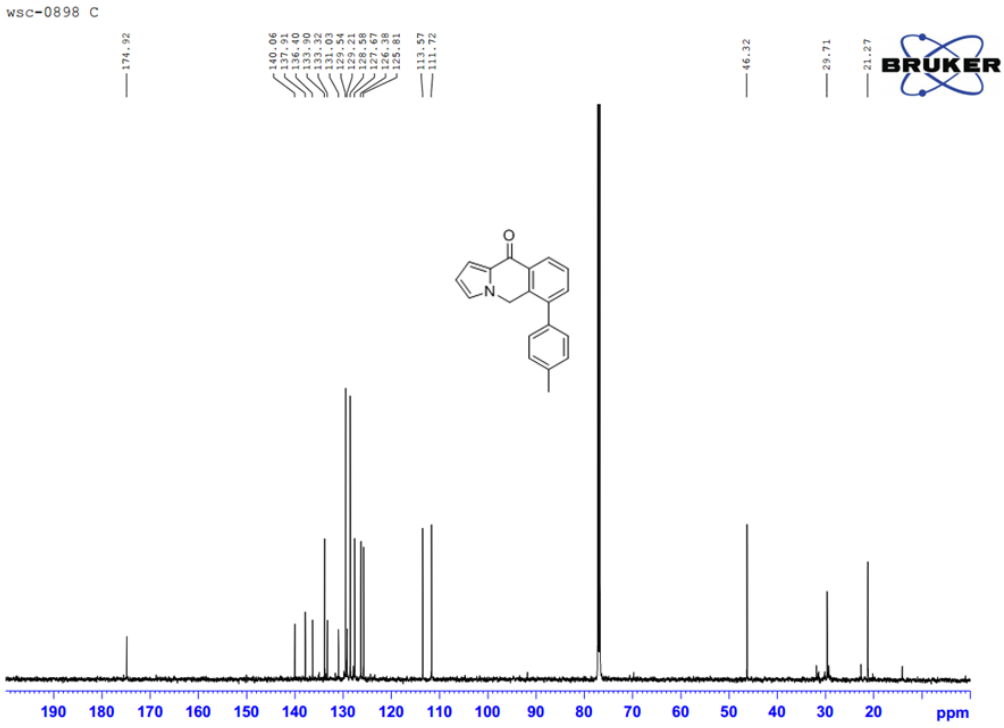
NMR of compound **3j**



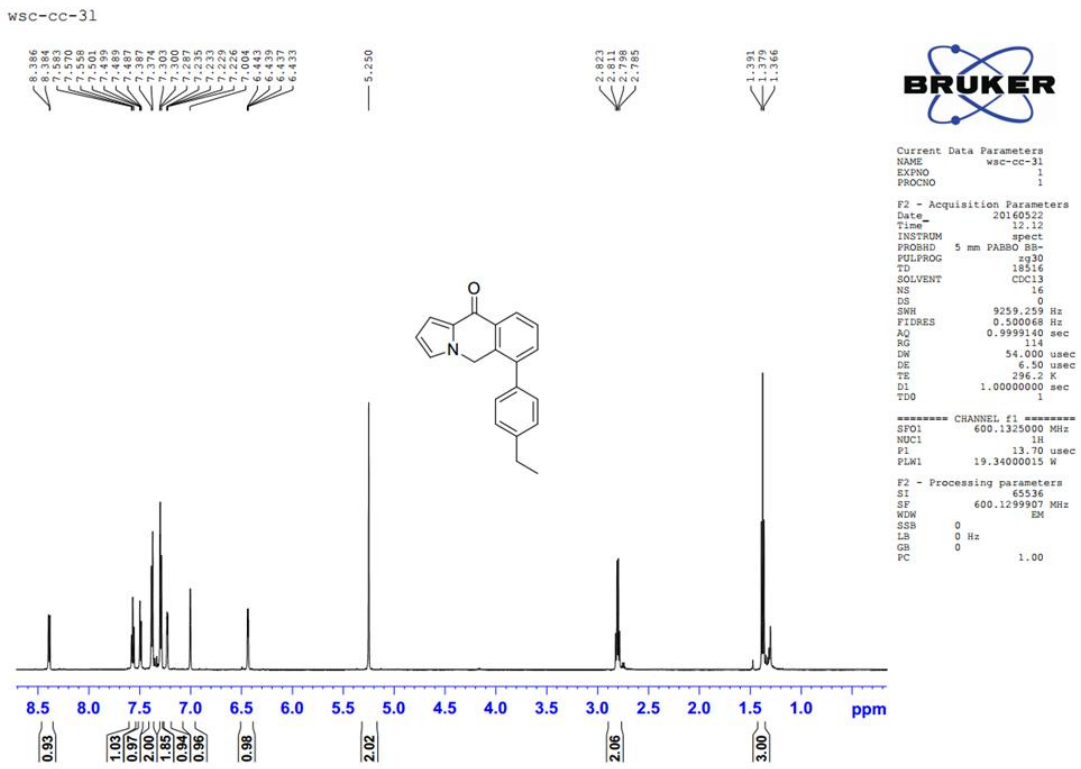


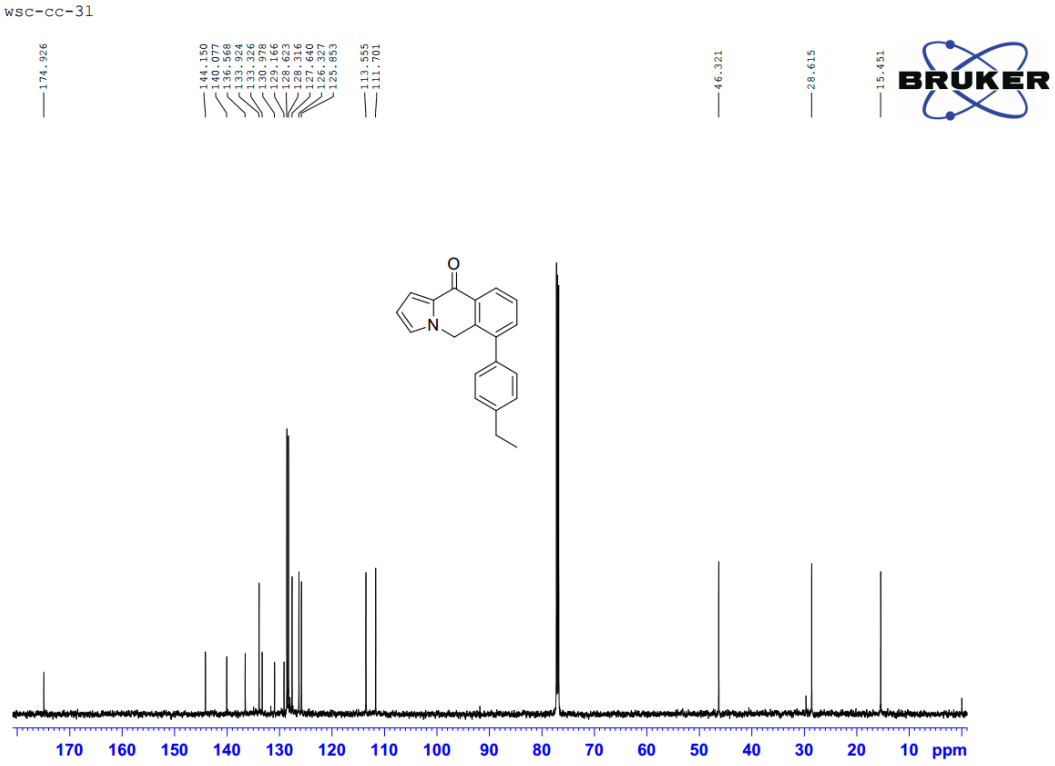
NMR of compound **3k**



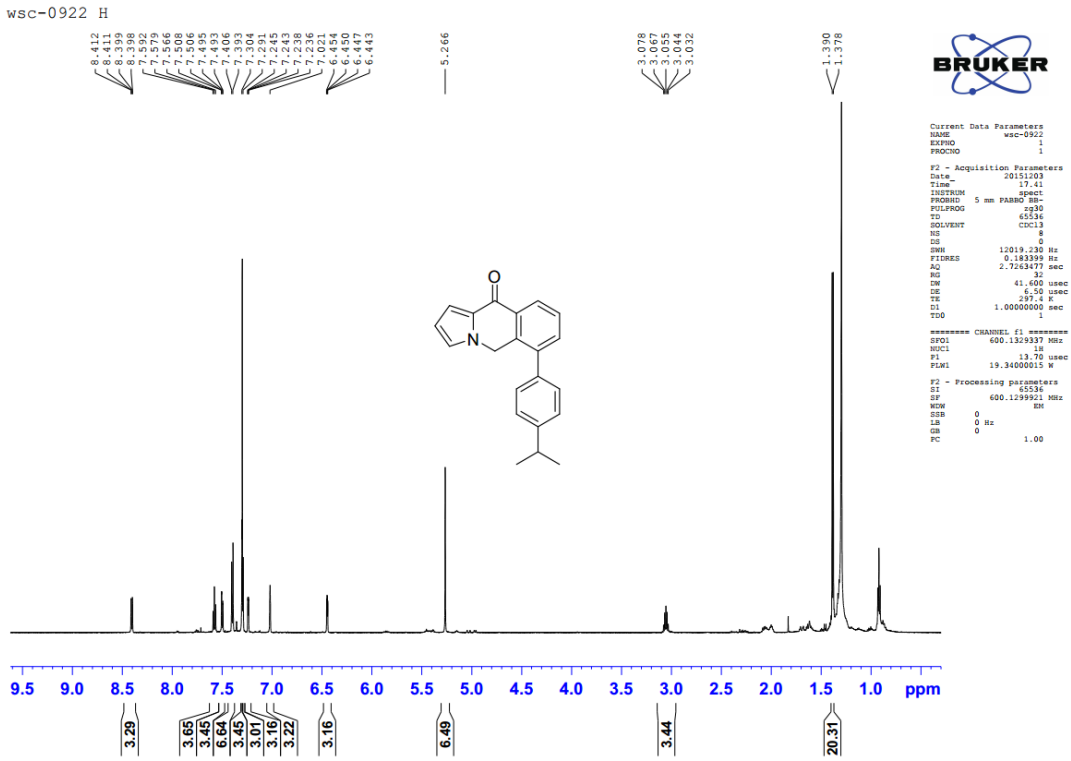


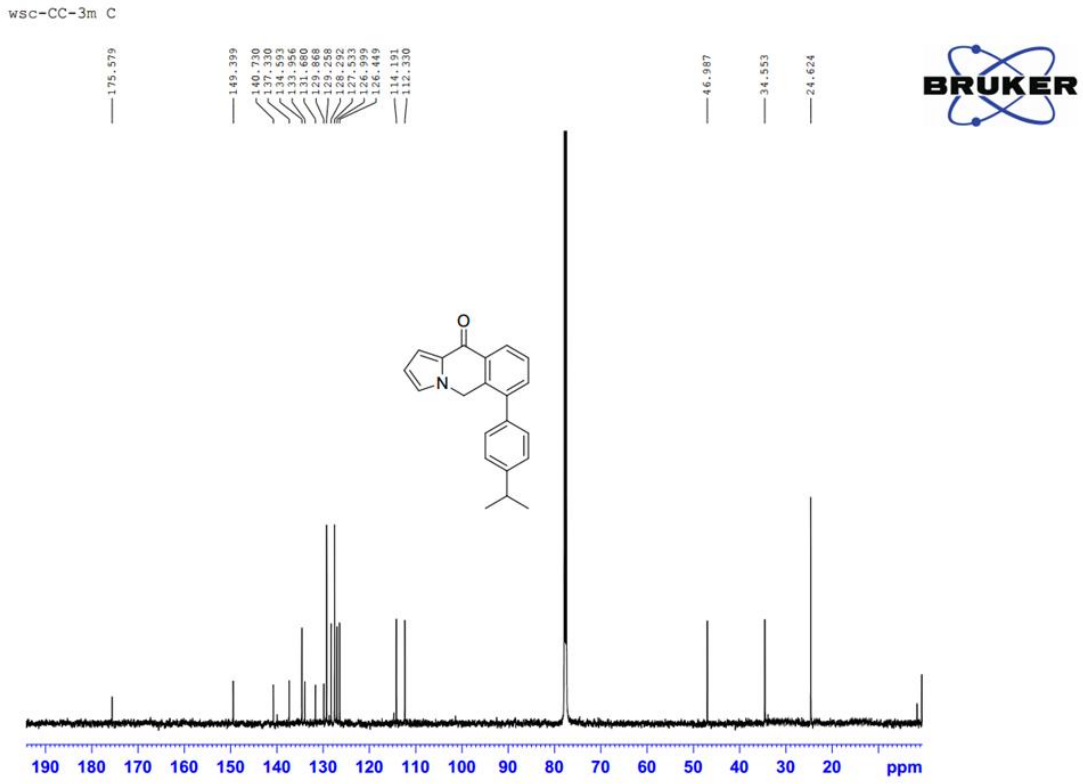
NMR of compound **3l**



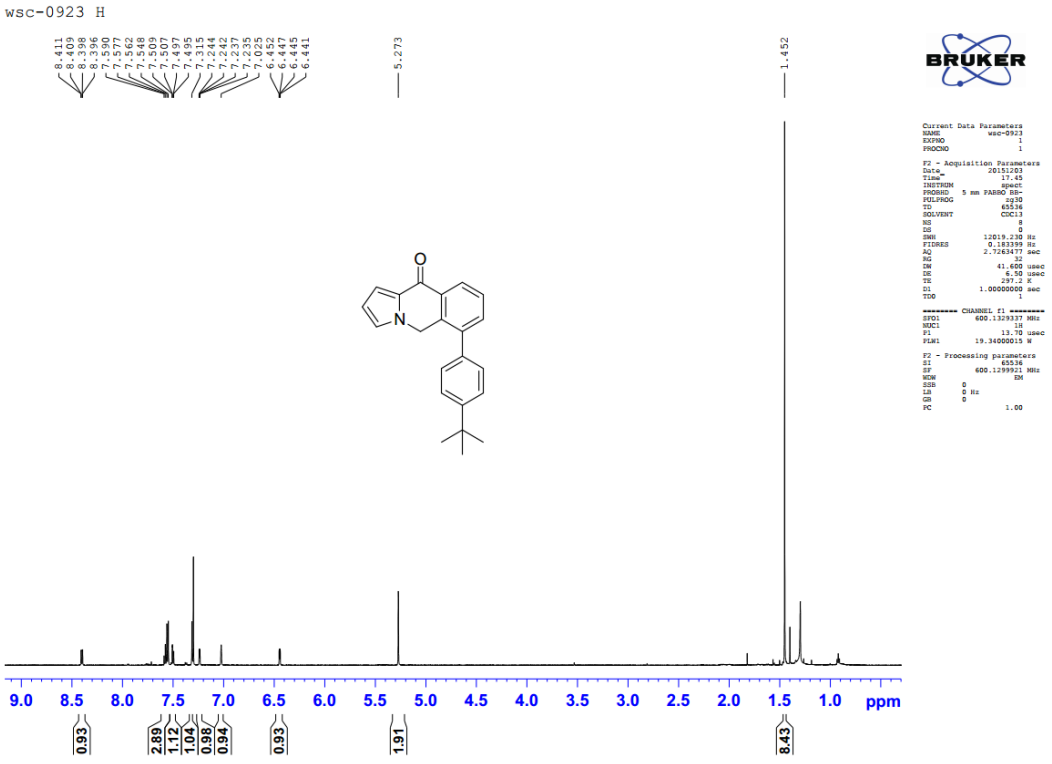


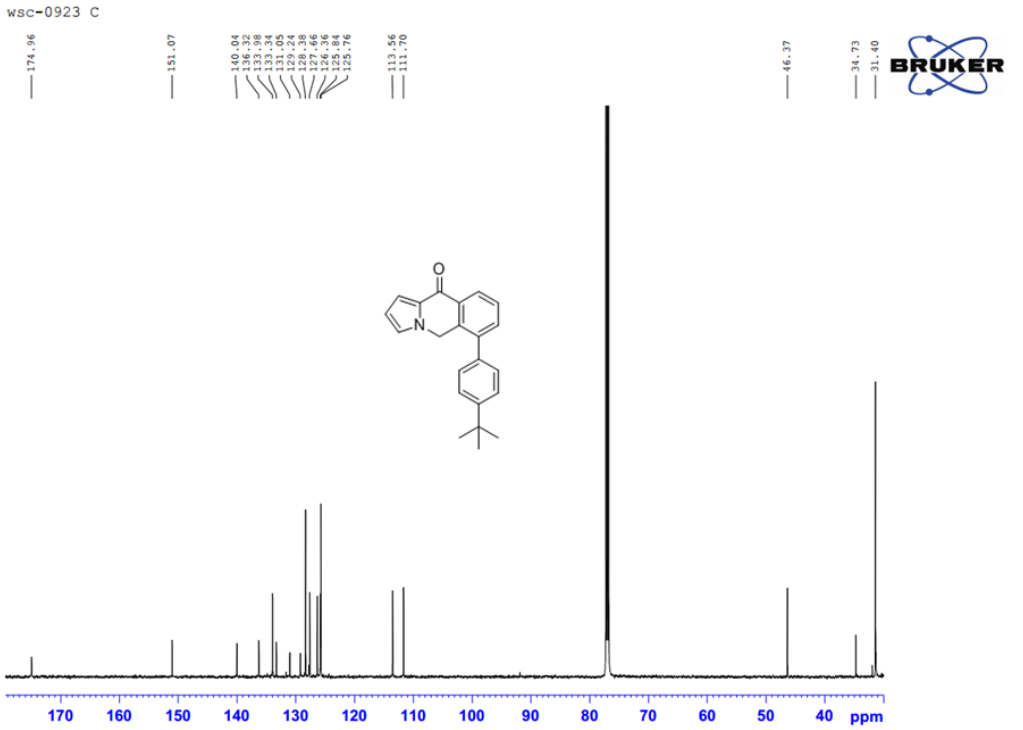
NMR of compound **3m**



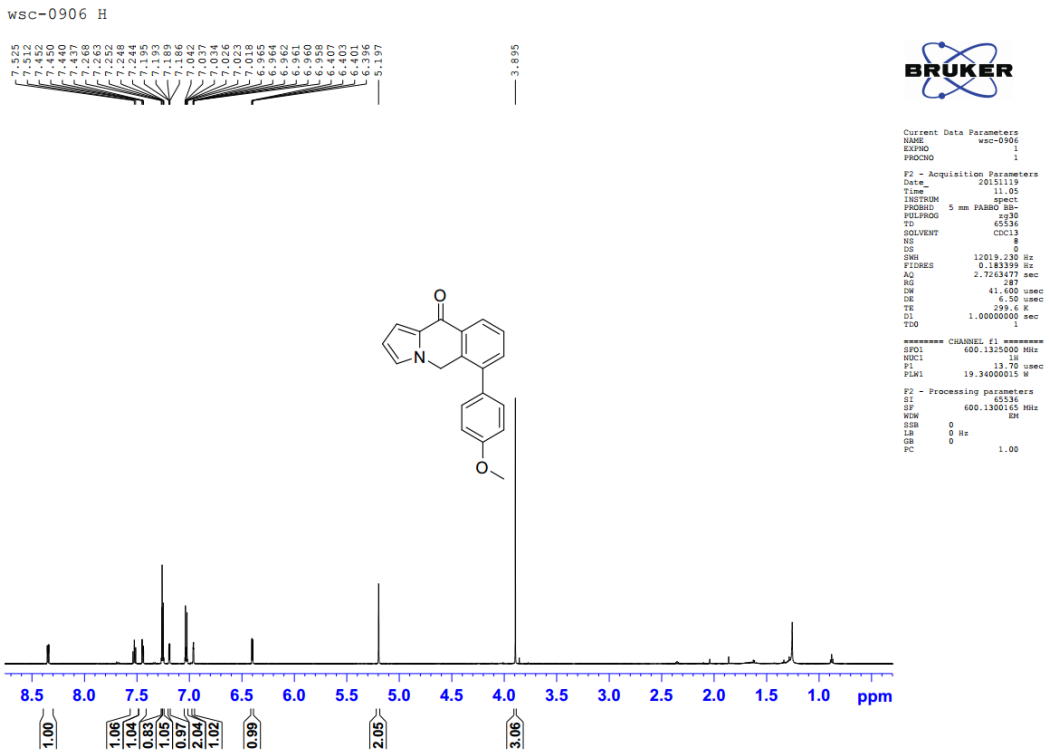


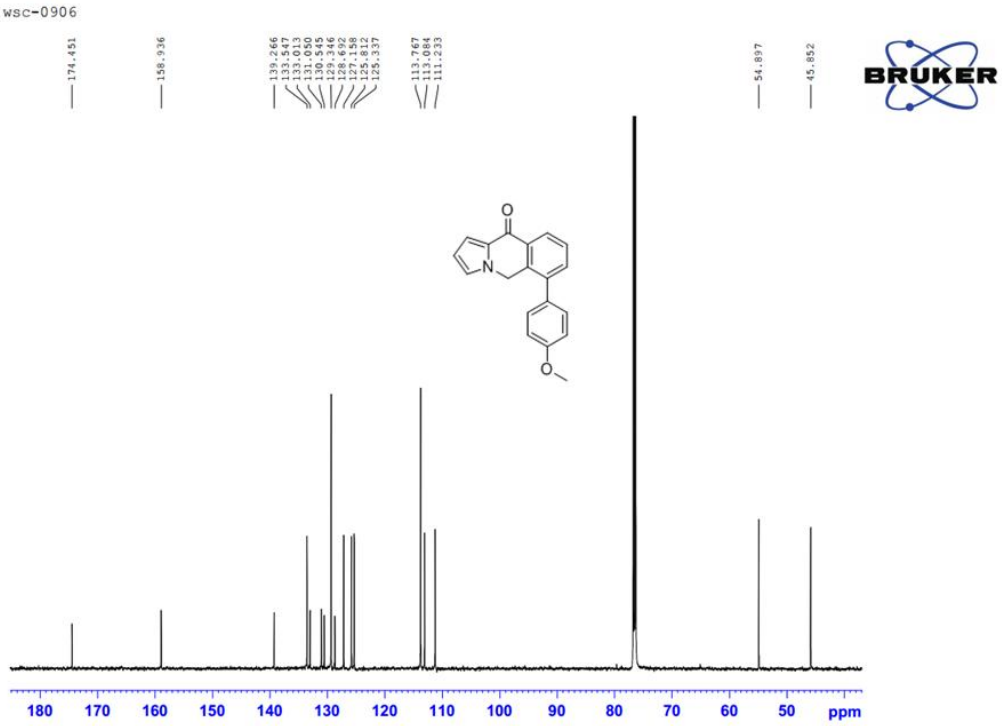
NMR of compound **3n**



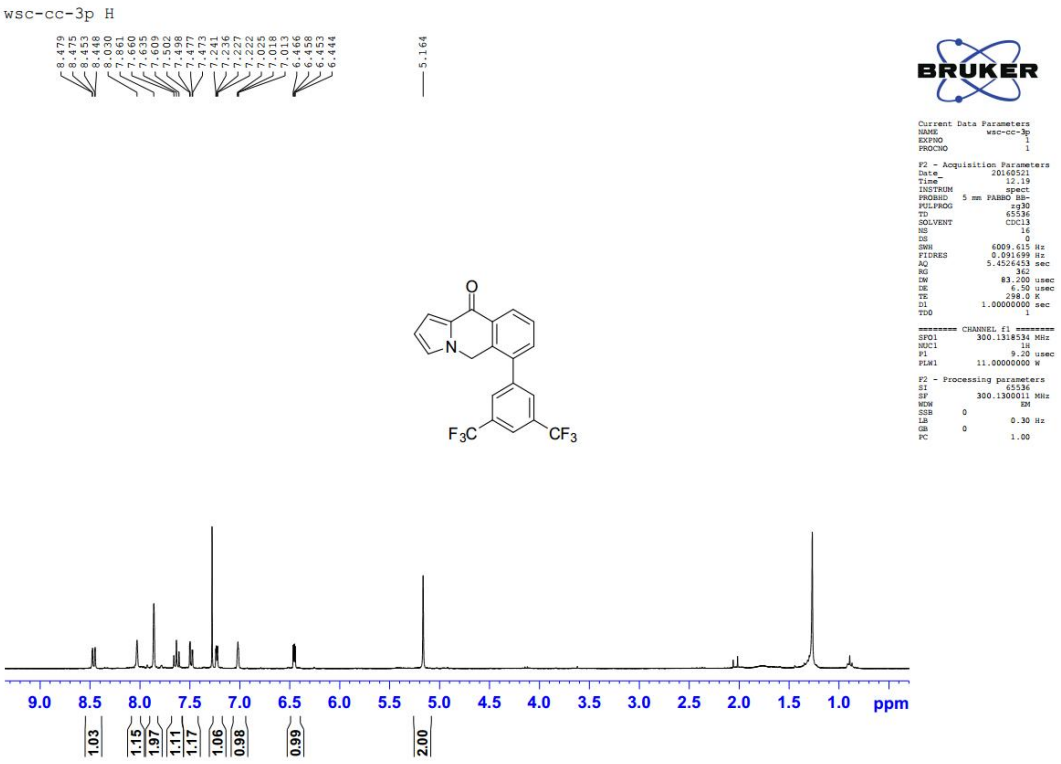


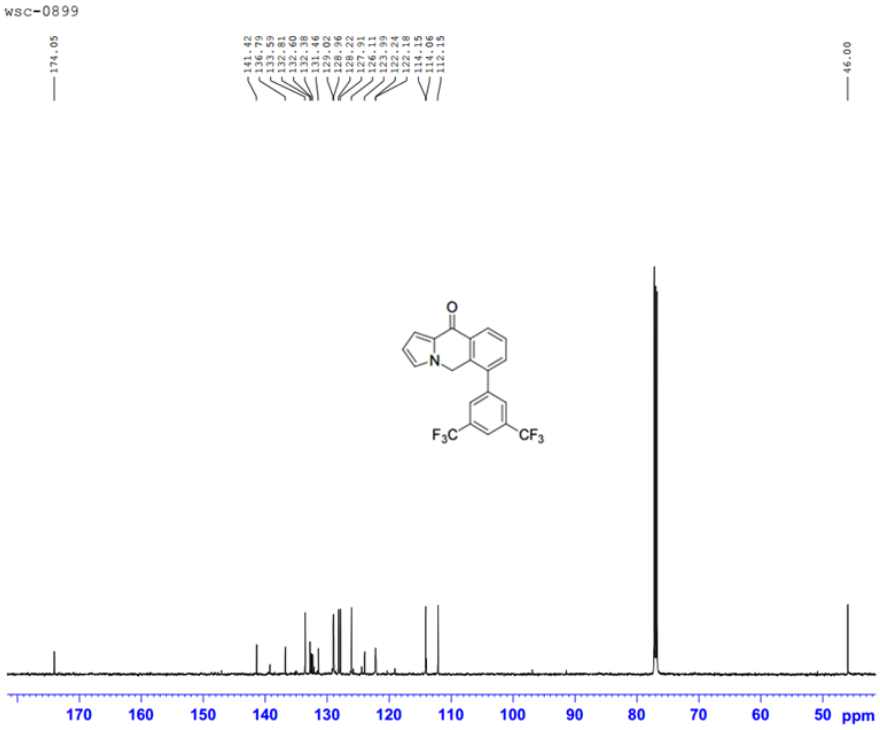
NMR of compound **3o**



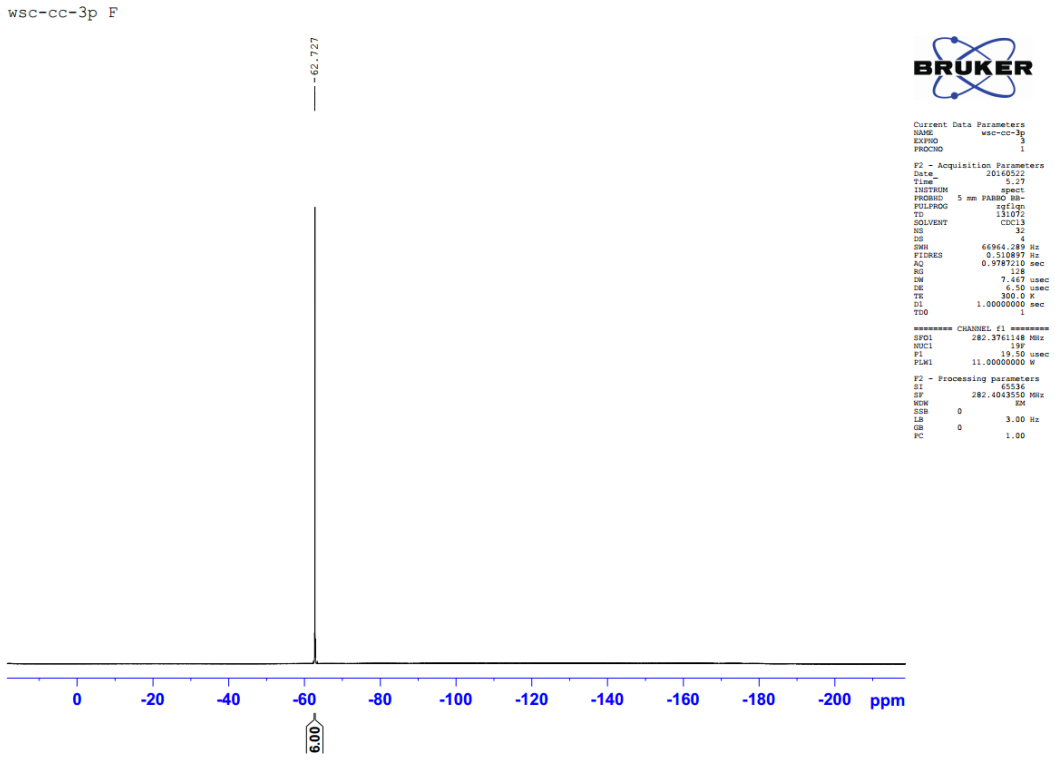


NMR of compound **3p**

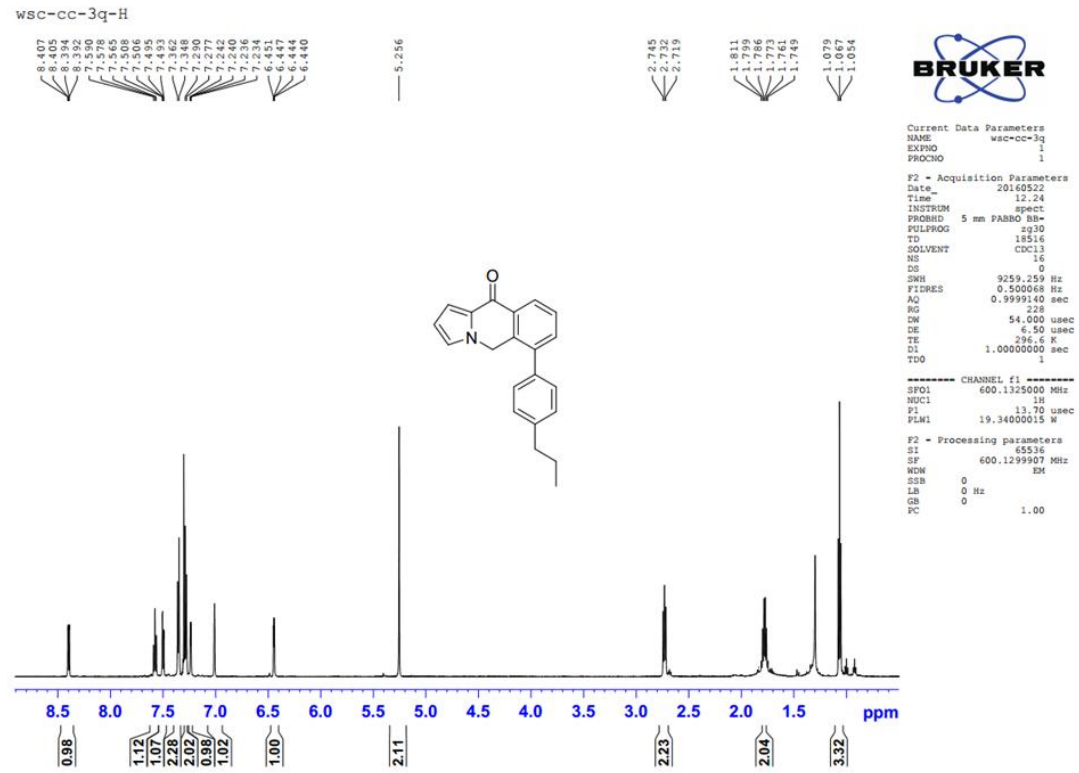


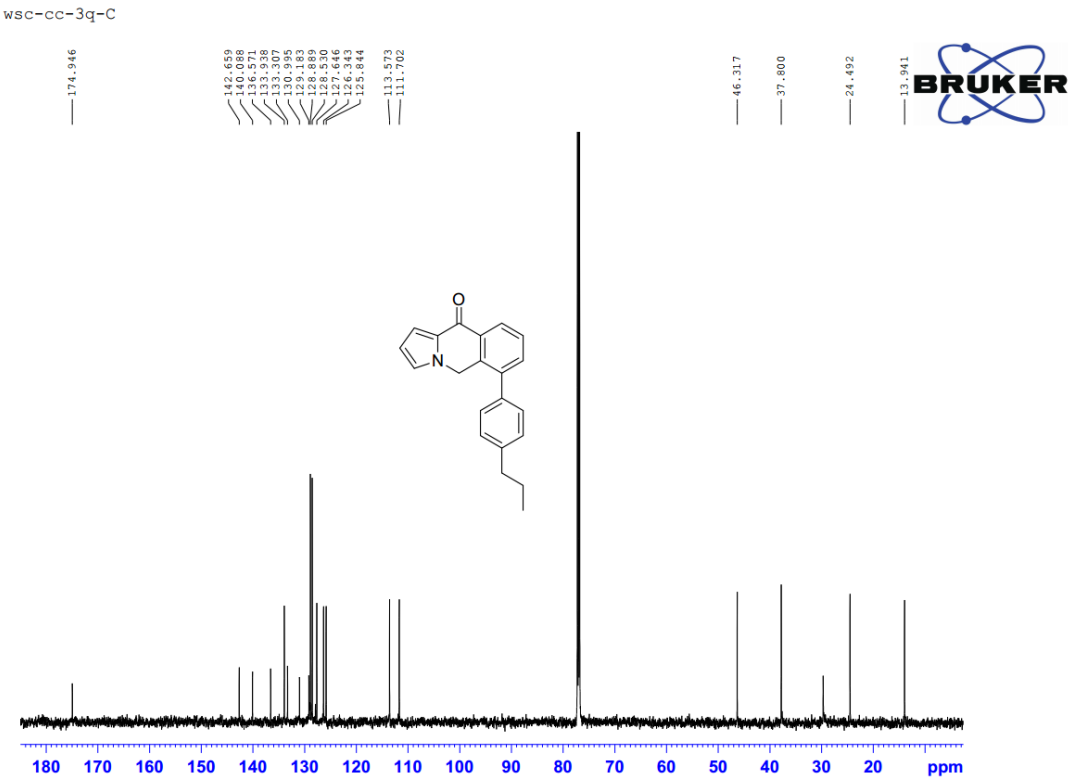


^{19}F NMR of compound **3p**

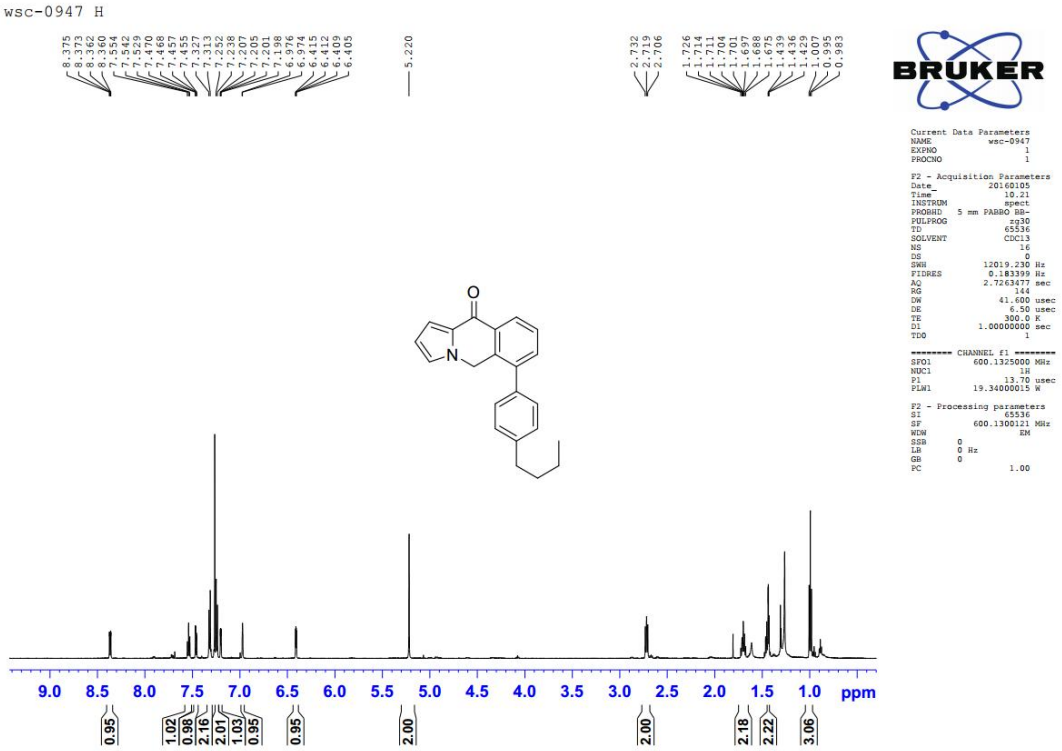


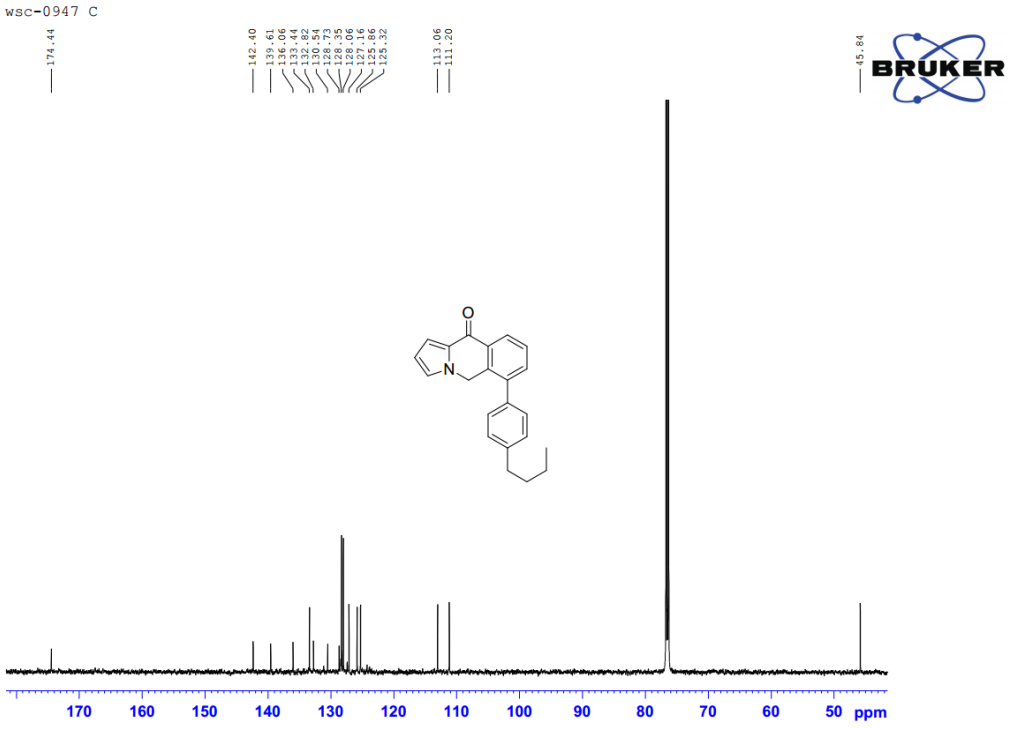
NMR of compound **3q**



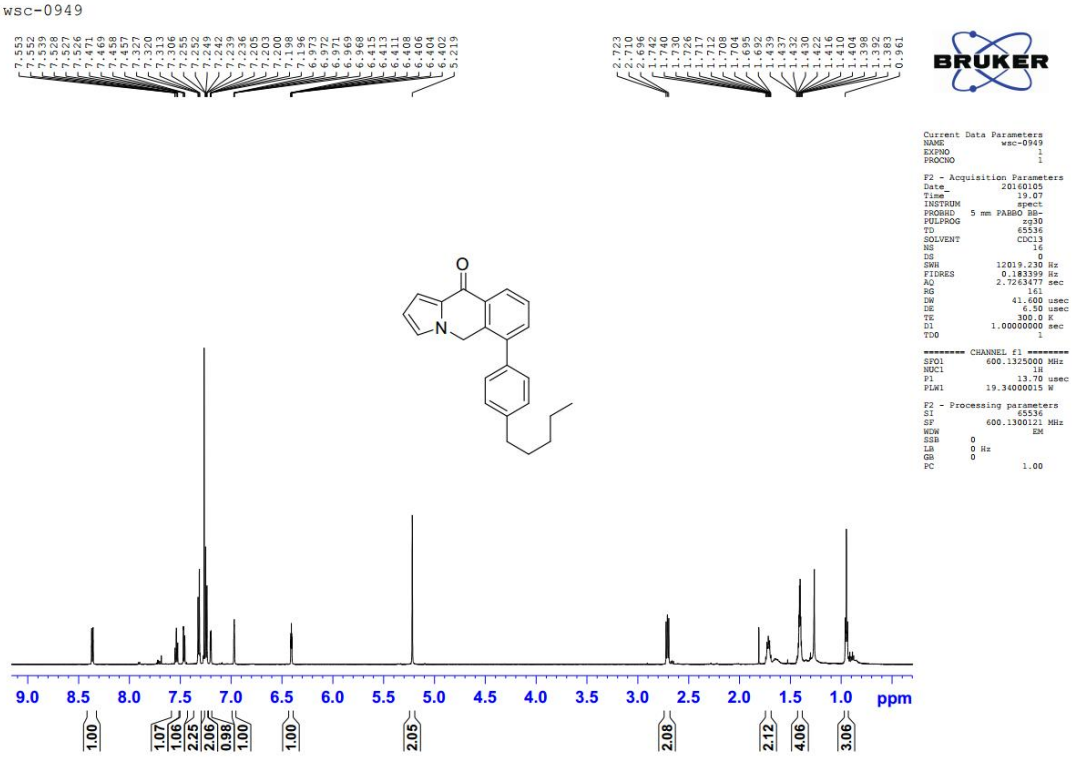


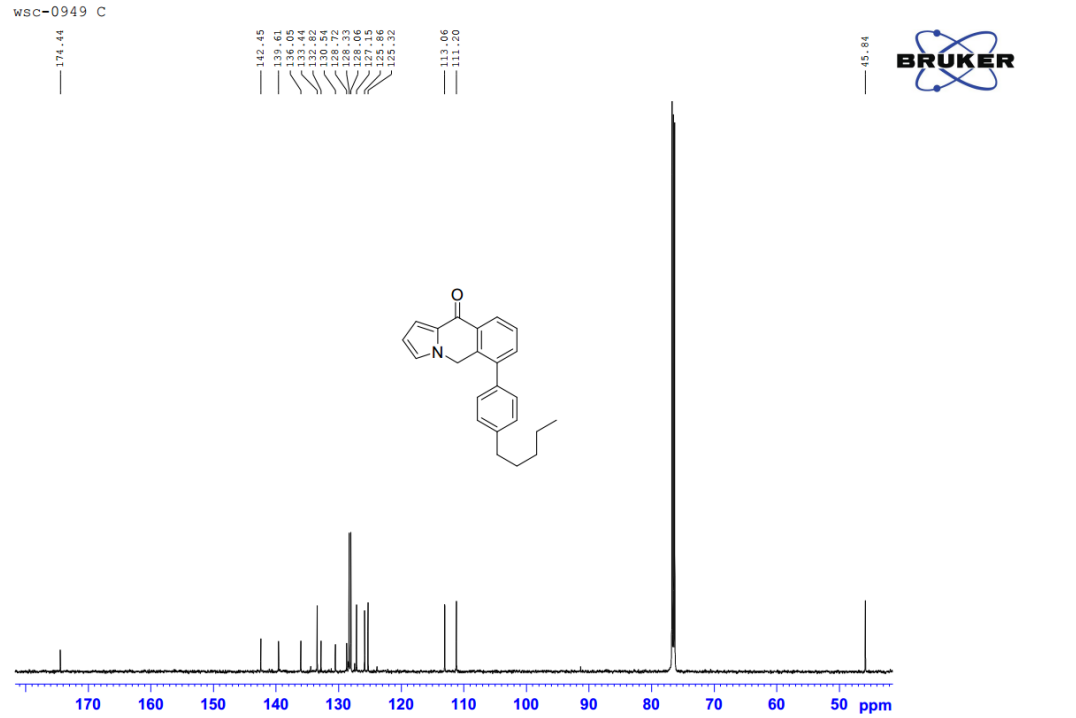
NMR of compound **3r**



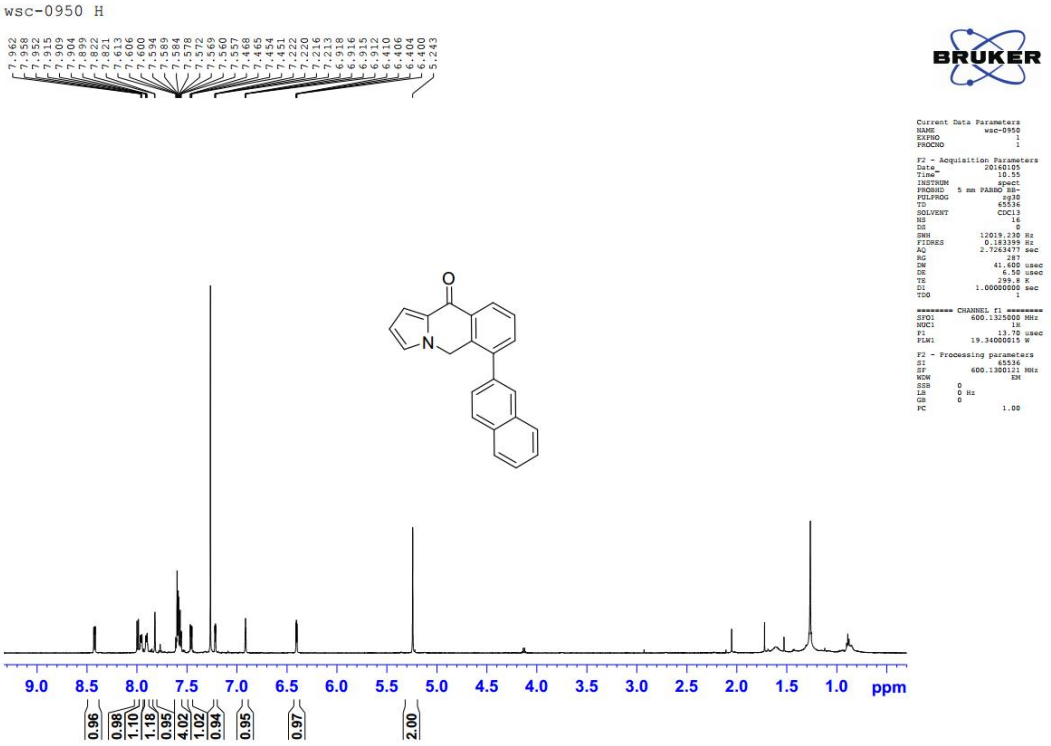


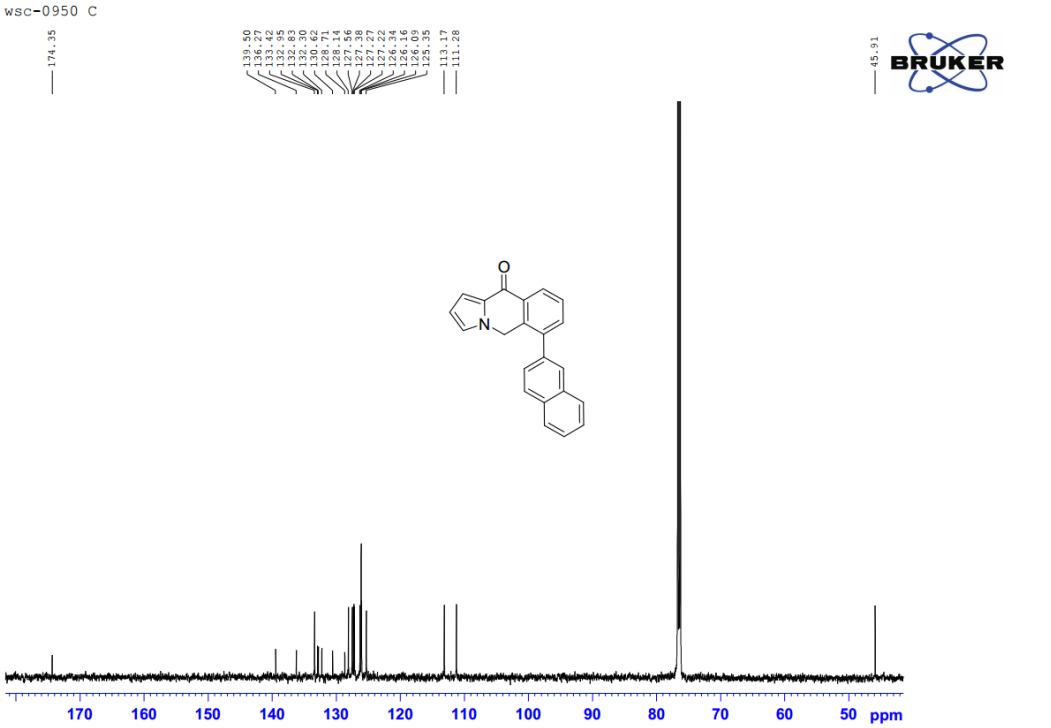
NMR of compound **3s**





NMR of compound **3t**





Top1 and Top2 Inhibitory Activity Assay

Top1 Inhibitory Activity Assay

DNA relaxation assays were employed according to the procedure described in previous studies[1]. The reaction mixture contained 35 mM Tris-HCl (pH 8.0), 72 mM KCl, 5 mM $MgCl_2$, 5 mM dithiothreitol, 5 mM spermidine, 0.1% bovine serum albumin (BSA), pBR322 plasmid DNA (0.25 μg), the indicated drug concentrations (1% DMSO), and 1 unit of Top1 (TaKaRa Biotechnology Co., Ltd., Dalian) in afinal volume of 20 μL. Reaction mixtures were incubated for 15 min at 37 °C and stopped by addition of 2 μL of 10× loading buffer (0.9% sodium dodecyl sulfate (SDS), 0.05% bromophenol blue, and 50% glycerol). Electrophoresis was carried out in a 0.8% agarose gel in TAE (Tris-acetate-EDTA) at 8 V/cm for 1 h. Gels were stained with ethidium bromide (0.5 μg/mL) for 60 min. The DNA band was visualized over UV light and photographed with Gel Doc Ez imager (Bio-Rad Laboratories Ltd.)

Top2 Inhibitory Activity Assay

DNA Top2α inhibitory activity of the compounds was measured using Topoisomerase II Drug Screening Kit (TopoGEN, Inc.). The reaction mixture contained 50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 10 mM $MgCl_2$, 5 mM dithiothreitol, 30 μg/mL bovine serum albumin (BSA), 2 mM ATP, pBR322 plasmid DNA (0.25), the indicated drug concentrations (1% DMSO), and 0.75 unit of Top2α (TopoGEN, Inc.) in a final volume of 20 μL. Reaction mixtures were incubated for 30 min at 37°C and stopped by addition of 2 μL of 10% SDS. After that, 2 μL of 10× gel loading buffer (0.25% bromophenol blue, 50% glycerol) was added. The reaction products were analyzed on 1% agarose gel at 8 V/cm for 1 h with TAE (Tris acetate-EDTA) as the running buffer. Gels were stained with ethidium bromide (0.5μg/mL) for 60 min. The DNA band was visualized over UV light and photographed with Gel Doc Ez imager (Bio-Rad Laboratories Ltd.).

Biological assays

Cell cultures

Hela cells and HepG2 cells were cultured in DMEM medium (Hyclone), HCT116 cells were cultured in McCoy's 5A medium (Gibco) and A549 cells were cultured in RPMI 1640 medium (Gibco) with 10% fetal calf serum (Gibco), 100 U/ml penicillin

and 100μg/ml streptomycin (Invitrogen-Gibco, Karlsruhe, Germany). Cells were maintained in a humidified incubator with 5% CO_2 at 37 °C.

***In vitro* cytotoxicity assay**

5×10^3 cells were seeded on a 96-well culture transwell apparatus (Costar, Cambridge, MA, USA) and cultured in DMEM medium, RPMI 1640 medium or McCoy's 5A medium with 10% (*v/v*) fetal bovine serum (FBS), respectively. The tested compounds were diluted to different final concentration and the cells were incubated for 48 h in a CO_2 incubator at 37 °C. Above loading media were removed, and the cells were fed new medium, followed by 10 μL of Cell Counting Kit-8 (CCK-8) per 100 μL of medium and incubated for 1 h. The cell viability was then assessed by Cell-Counting Kit-8 assay (Dojindo Laboratories, Japan) following the manufacturers' protocol. The absorbance of each well was monitored by a spectrophotometer (Tecan, Switzerland) at 450 nm.

References

1. G. Dong, C. Sheng, S. Wang, Z. Miao, J. Yao and W. Zhang, *J. Med. Chem.*, 2010, **53**, 7521.