Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Intramolecular cross dehydrogenative coupling of 4-substituted coumarins: rapid and efficient access to coumestans and indole[3,2-*c*]coumarins

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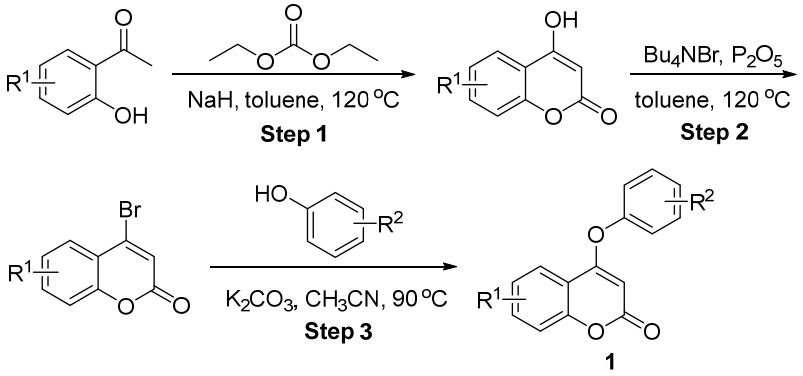
1. General

NMR spectra were recorded on a Mercury 300 spectrometer (300 MHz for ^{1}H), and Varian spectrometer (125 MHz or 150 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.16), DMSO-*d* (δ 39.52) for ^{13}C NMR. HRMS were recorded on a Q-TOF mass spectrometer with ESI resource or Magnetic Sector for EI. Melting point determinations were performed by the open capillary method.

2. General procedure for the synthesis of 4-aryloxy coumarin 1[1-3]



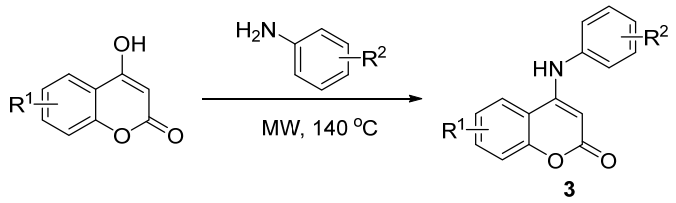
Step 1: A solution of substituted *o*-hydroxy acetophenone (9 mmol, 1 equiv) in toluene (15 mL) was added dropwise to a dry round-bottom flask containing sodium hydride (60% w/w suspension,27 mmol, 3 equiv) in toluene (10 mL) at 0 ºC. The mixture was stirred at the same temperature for 15 min followed by the dropwise addition of diethylcarbonate (13.5 mmol, 1.5 equiv) in toluene (10 mL). Then, the reaction mixture was heated at 120 °C and monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature. The solvents were removed under reduced pressure and resulting mixture residue was quenched at ice bath temperature by slow addition of water (20 mL) and acidified with 2 N HCl. The solid precipitate was filtered, washed with water, and dried under vacuum to afford the crude product (substituted 4-hydroxy coumarin)[1] which was directly used in the next step.

Step 2: to a round bottom flask equipped with a magnetic stir bar and a reflux condenser was added the substituted 4-hydroxy coumarin (2.0 mmol) and toluene (8 mL). The reaction mixture was heated at 120 °C for 10 min and then Bu_4NBr (3.0 equiv) was added in two portions over 5 min. The reaction mixture was stirred vigorously for 10 min until the starting material completely dissolved. P_2O_5 (4.8 mmol) was then added in two portions over 10 min and the reaction was heated for 3-5 h until reaction completion. The reaction mixture was cooled to 23 °C and quenched with a saturated aqueous $NaHCO_3$ solution. Then the reaction mixture was extracted with toluene (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give substituted 4-bromo coumarin.[2]

Step 3: a solution of substituted 4-bromo coumarin (1.5 mmol), substituted phenol (1.5 mmol) and K_2CO_3 (3.0 mmol) in acetonitrile (3 mL) was stirred at 90 ºC for 1-2 h. The reaction was allowed

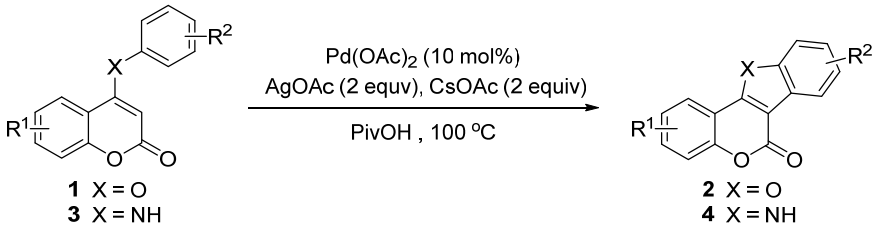
to cool to ambient temperature. After quenching the reaction by addition of water (2 ml), white precipitates formed immediately. Filtration of the mixture afforded the precipitates as crude product which was then purified by column chromatography on silica gel (typically using DCM/PE as the eluent) to yield product **1**.[3]

3. General procedure for the synthesis of 4-arylamino coumarins 3[4]



A mixture of substituted 4-hydroxycoumarin (2.0 mmol) and the corresponding amine (2.4-3 mmol) was placed in a 10 mL high pressure glass tube and placed into the microwave reactor for 10-30 min, the reaction mixture was allowed to cool to ambient temperature. Ice-cold acetone (10 mL) was added and the separated crystals were filtered off to give chromatographically (TLC) pure product **3**.

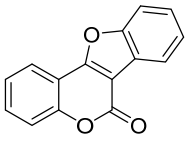
4. General procedure for coumestans 2 and indole[3,2-*c*]coumarins 4



Coumarin substrate **1** or **3** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv) and CsOAc (2 equiv) were combined in PivOH (1.0 mL). Then the reaction mixture was heated to 100 °C for 5-38 h as monitored by TLC (CH_2Cl_2/PE=1/1 as the mobile phase for substrate **1**; CH_2Cl_2/MeOH=100/1 as the mobile phase for substrate **3**). The reaction mixture was then diluted with CH_2Cl_2 and excess $NaHCO_3$ (aq.) was added to neutralize PivOH. After stirring the mixture for 10 min, the residue was washed with aqueous $NaHCO_3$. The isolated organic layer was dried over Na_2SO_4. After removal of solvent, the residue was purified by silica gel column chromatography (using CH_2Cl_2/PE as the eluent to get product **2**; CH_2Cl_2/MeOH as the eluent for product **4**) to give desired product **2** or **4**. In the work-up procedure for indole[3,2-*c*]coumarin **4**, the drying up step of the organic layer over Na_2SO_4 is omitted due to the relatively poor solubility of **4**. Compounds **2a**,[3] **2g**,[5] **2h**,[5] **2s**,[5] **4a**[6] and **4e**[7] are known compounds.

5. Characterization data of products 2 and 4

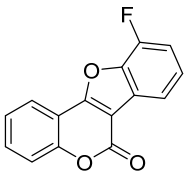
6*H*-benzofuro[3,2-*c*]chromen-6-one (2a).



2a

White solid, 40.6 mg, 86%. mp 181-182 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17-8.14 (m, 1H), 8.05 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.70-7.65 (m, 1H), 7.61 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.54-7.40 (m, 4H).

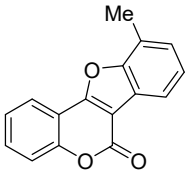
10-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2b).



2b

White solid, 43.4 mg, 85%. mp 238-240 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.68-7.63 (m, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.47-7.38 (m, 2H), 7.27-7.21 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 157.9, 153.9, 148.0 (d, J_{CF} = 250.5 Hz), 142.5 (d, J_{CF} = 12.0 Hz), 132.6, 126.9, 126.3 (d, J_{CF} = 6.0 Hz), 125.0, 122.2, 117.7, 117.6 (d, J_{CF} = 3.0 Hz), 113.5 (d, J_{CF} = 13.5 Hz), 112.4, 106.2. HRMS (EI): calcd for $C_{15}H_7FO_3$: 254.0379; found: 254.0374.

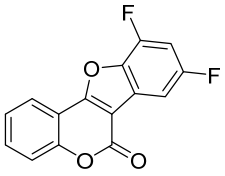
10-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2c).



2c

White solid, 42.1 mg, 84%. mp 174-176 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.61-7.56 (m, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.42-7.30 (m, *J* = 20.0, 7.6 Hz, 2H), 7.26-7.24 (m, 1H), 2.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 158.3, 154.6, 153.7, 131.9, 127.9, 125.3, 124.7, 123.0, 122.2, 121.9, 119.3, 117.5, 112.8, 106.2, 15.1. HRMS (EI): calcd for $C_{16}H_{10}O_3$: 250.0630; found: 250.0633.

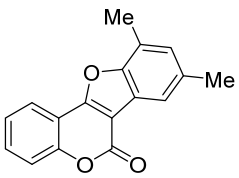
8,10-difluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2d).



2d

White solid, 45.2 mg, 83%. mp 234-236 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.71-7.63 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.04 (ddd, *J* = 10.2, 9.3, 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.2 (dd, J_{CF} = 244.4, 8.8 Hz), 157.5, 154.1, 146.3 (dd, J_{CF} = 252.9, 13.5 Hz), 139.1 (dd, J_{CF} = 11.8, 2.1 Hz), 133.0, 126.9 (dd, J_{CF} = 12.9, 3.3 Hz), 125.2, 122.3, 117.8, 112.3, 106.2 (t, J_{CF} = 3.6 Hz), 103.8 (dd, J_{CF} = 26.0, 4.4 Hz), 102.9 (dd, J_{CF} = 29.5, 19.7 Hz). HRMS (EI): calcd for $C_{15}H_6F_2O_3$: 272.0285; found: 272.0283.

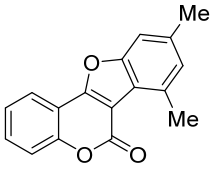
8,10-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2e).



2e

White solid, 45.2 mg, 86%. mp 228-230 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.61 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.10 (s, 1H), 2.60 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 158.5, 153.6, 153.2, 135.3, 131.7, 129.3, 124.6, 123.1, 121.9, 121.6, 119.2, 117.6, 113.0, 106.1, 21.4, 15.1. HRMS (EI): calcd for $C_{17}H_{12}O_3$: 264.0786; found: 264.0787.

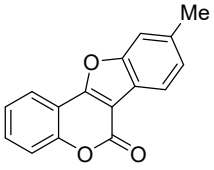
7,9-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2f).



2f

Light yellow solid, 52.6 mg, 99%. mp 199-200 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.23 (s, 1H), 6.99 (s, 1H), 2.92 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 158.1, 156.2, 153.5, 137.6, 133.7, 131.6, 128.3, 124.5, 121.8, 120.3, 117.1, 112.7, 109.4, 106.6, 21.7, 21.2. HRMS (EI): calcd for $C_{17}H_{12}O_3$: 264.0786; found: 264.0786.

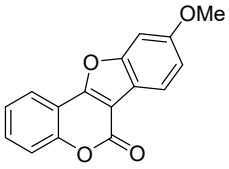
9-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2g).



2g

Light yellow solid, 36.7 mg, 73%. mp 200-202 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.7, 3.3 Hz, 2H), 7.56 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.45-7.34 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 1H), 2.51 (s, 3H).

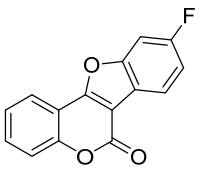
9-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2h).



2h

White solid, 45.8 mg, 86%. mp 215-217 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.58-7.53 (m, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 7.5, 7.5 Hz , 1H), 7.16 (d, *J* = 1.3 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H).

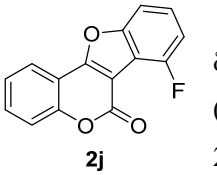
9-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2i).



2i

White solid, 33.1 mg, 65%. mp 248-250 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.61 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.44-7.38 (m, 2H), 7.25-7.18 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1 (d, J_{CF} = 246.0 Hz), 160.7 (d, J_{CF} = 3.0 Hz), 158.0, 155.7 (d, J_{CF} = 13.5 Hz), 153.6, 132.1, 124.9, 122.6 (d, J_{CF} = 10.5 Hz), 121.9, 119.9, 117.7, 113.7 (d, J_{CF} = 24.0 Hz), 112.6, 105.8, 100.2 (d, J_{CF} = 27.0 Hz). HRMS (EI): calcd for $C_{15}H_7FO_3$: 254.0379; found: 254.0382.

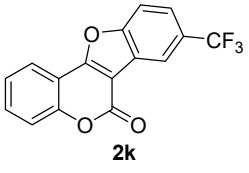
7-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2j).



2j

Light yellow solid, 16.0 mg, 31%. mp 218-220 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.52-7.36 (m, 4H), 7.16 (dd, *J* = 7.5, 7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 156.4 (d, J_{CF} = 255.0 Hz), 157.1 (d, J_{CF} = 9.0 Hz), 156.8, 154.1, 132.6, 127.9 (d, J_{CF} = 7.5 Hz), 124.9, 122.2, 117.6, 112.7 (d, J_{CF} = 21.0 Hz), 112.2, 112.0 (d, J_{CF} = 19.5 Hz), 108.1 (d, J_{CF} = 4.5 Hz), 104.8 (d, J_{CF} = 4.5 Hz). HRMS (EI): calcd for $C_{15}H_7FO_3$: 254.0379; found: 254.0382.

8-(trifluoromethyl)-6*H*-benzofuro[3,2-*c*]chromen-6-one (2k).

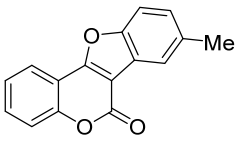


2k

White solid, 49.6 mg, 82%. mp 152-154 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.78-7.72 (m, 2H), 7.67 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 157.6, 156.8, 154.0, 132.9, 128.2 (q, J_{CF}

= 32.5 Hz), 125.1, 124.1 (q, J_{CF} = 3.0 Hz), 123.9, 123.3, 122.2, 119.7 (q, J_{CF} = 4.5 Hz), 117.8, 112.4, 112.2, 105.7. HRMS (EI): calcd for $C_{16}H_7F_3O_3$: 304.0347; found: 304.0346.

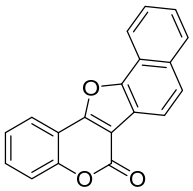
8-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2l).



2l

Light yellow solid, 41.7 mg, 83%. mp 201-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.95 (s, 1H), 7.63-7.50 (m, 3H), 7.42 (ddd, *J* = 7.7, 7.4, 0.9 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.3, 154.1, 153.7, 135.3, 131.9, 128.0, 124.7, 123.5, 121.9, 121.8, 117.6, 112.9, 111.3, 105.8, 21.5. HRMS (EI): calcd for $C_{16}H_{10}O_3$: 250.0630; found: 250.0626.

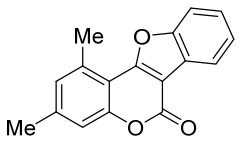
6*H*-naphtho[2',1':4,5]furo[3,2-*c*]chromen-6-one (2m).



2m

Light yellow solid, 52.8 mg, 92%. mp 213-215 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.10 (dd, *J* = 9.0, 9.0 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.58-7.47 (m, 3H), 7.42 (dd, *J* = 7.8, 7.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 158.4, 153.4, 151.5, 132.6, 131.5, 128.7, 127.2, 126.5, 126.0, 124.8, 121.7, 120.8, 120.0, 119.6, 119.0, 117.6, 112.9, 107.0. HRMS (EI): calcd for $C_{19}H_{10}O_3$: 286.0630; found: 286.0623.

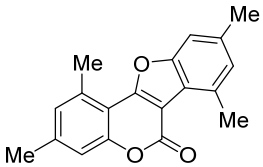
1,3-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2n).



2n

White solid, 43.1 mg, 82%. mp 258-260 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 5.4, 3.4 Hz, 1H), 7.64 (dd, *J* = 6.2, 2.8 Hz, 1H), 7.44 (dd, *J* = 5.9, 3.2 Hz, 2H), 7.12 (s, 1H), 6.98 (s, 1H), 2.86 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 158.5, 155.4, 154.7, 142.6, 135.0, 128.1, 126.4, 125.2, 123.3, 121.8, 115.5, 111.7, 109.6, 105.2, 21.8, 21.3. HRMS (EI): calcd for $C_{17}H_{12}O_3$: 264.0786; found: 264.0783.

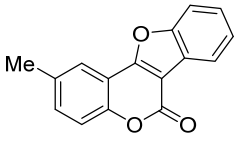
1,3,7,9-tetramethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2o).



2o

White solid, 42.7 mg, 86%. mp 192-194 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 2.93 (s, 3H), 2.82 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 158.2, 155.9, 154.4, 141.9, 136.9, 134.7, 133.4, 128.2, 127.9, 119.8, 115.0, 109.4, 109.2, 105.8, 21.7, 21.6, 21.4, 21.3. HRMS (EI): calcd for $C_{19}H_{16}O_3$: 292.1099; found: 292.1095.

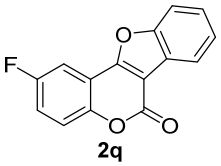
2-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2p).



2p

White solid, 47.2 mg, 94%. mp 171-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16-8.13 (m, 1H), 7.83 (s, 1H), 7.68-7.65 (m, 1H), 7.51-7.44 (m, 2H), 7.41 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 158.4, 155.6, 152.0, 134.7, 133.1, 126.8, 125.3, 123.7, 121.9, 121.6, 117.3, 112.4, 111.8, 105.9, 21.1. HRMS (EI): calcd for $C_{16}H_{10}O_3$: 250.0630; found: 250.0626.

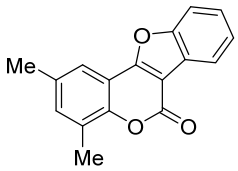
2-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2q).



2q

White solid, 43.4 mg, 85%. mp 211-213 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.2 Hz, 1H), 7.71-7.67 (m, 2H), 7.54-7.45 (m, 3H), 7.32 (ddd, *J* = 8.6, 8.4, 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (d, J_{CF} = 245.0 Hz), 159.2 (d, J_{CF} = 2.5 Hz), 157.8, 155.6, 149.9, 127.4, 125.6, 123.3, 122.2, 119.5(d, J_{CF} = 36.3 Hz), 119.4 (d, J_{CF} = 2.5 Hz), 113.5 (d, J_{CF} = 8.8 Hz), 112.0, 107.8 (d, J_{CF} = 25.0 Hz), 106.7. HRMS (EI): calcd for $C_{15}H_7FO_3$: 254.0379; found: 254.0384.

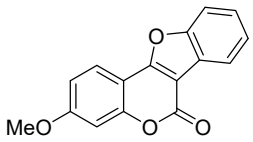
2,4-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2r).



2r

White solid, 48.0 mg, 91%. mp 249-250 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.11 (m, 1H), 7.64-7.61 (m, 2H), 7.48-7.41 (m, 2H), 7.21 (s, 1H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 158.4, 155.6, 150.4, 134.6, 134.1, 126.8, 126.6, 125.2, 123.8, 121.9, 119.2, 112.1, 111.7, 105.6, 21.0, 16.1. HRMS (EI): calcd for $C_{17}H_{12}O_3$: 264.0786; found: 264.0782.

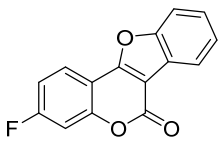
3-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2s).



2s

White solid, 44.7mg, 85%. mp 199-200 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 5.7, 3.1 Hz, 1H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.61 (dd, *J* = 5.8, 3.2 Hz, 1H), 7.42 (dd, *J* = 5.9, 3.1 Hz, 2H), 6.97-6.95 (m, 2H), 3.90 (s, 3H).

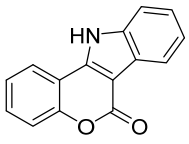
3-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2t).



2t

White solid, 44.2 mg, 87%. mp 231-232 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12-8.10 (m, 1H), 8.02 (dd, *J* = 8.3, 6.2 Hz, 1H), 7.67-7.64 (m, 1H), 7.51-7.44 (m, 2H), 7.24-7.14 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8 (d, J_{CF} = 252.5 Hz), 159.7, 157.8, 155.6, 155.0 (d, J_{CF} = 13.8 Hz), 127.0, 125.5, 123.7(d, J_{CF} = 10.0 Hz), 123.4, 121.9, 113.1 (d, J_{CF} = 22.5 Hz), 111.9, 109.5(d, J_{CF} = 2.5 Hz), 105.4 (d, J_{CF} = 26.3 Hz), 105.0 (d, J_{CF} = 2.5 Hz). HRMS (EI): calcd for $C_{15}H_7FO_3$: 254.0379; found: 254.0372.

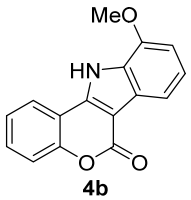
chromeno[4,3-*b*]indol-6(11*H*)-one (4a).



4a

Light yellow solid, 43.1 mg, 92%. mp >300 ºC. ^{1}H NMR (300 MHz, DMSO) δ 13.02 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.55-7.31 (m, 4H).

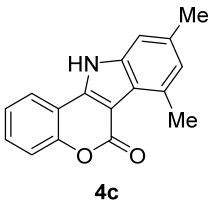
10-methoxychromeno[4,3-*b*]indol-6(11*H*)-one (4b).



4b

Light yellow solid**,** 41.1 mg, 78%. mp 285-287 ºC. ^{1}H NMR (300 MHz, DMSO) δ 13.11 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 7.64-7.50 (m, 3H), 7.44 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.27 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 158.0, 152.6, 146.4, 141.3, 130.7, 127.8, 125.7, 124.3, 123.3, 123.2, 117.1, 113.4, 112.6, 105.5, 100.6, 55.5. HRMS (ESI): *m/z* $[M-H]^-$ calcd for $C_{16}H_{11}NO_3$: 264.0666; found: 264.0663.

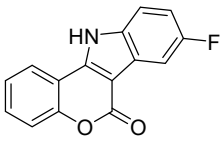
7,9-dimethylchromeno[4,3-*b*]indol-6(11*H*)-one (4c).



4c

Yellow solid, 45.9 mg, 86%. mp >300 ºC. ^{1}H NMR (300 MHz, DMSO) δ 12.82 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.62-7.41 (m, 3H), 7.23 (s, 1H), 6.89 (s, 1H), 2.90 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 157.7, 152.4, 141.6, 138.7, 134.5, 131.3, 130.4, 125.8, 124.0, 122.4, 121.5, 116.7, 113.0, 109.6, 100.6, 21.6, 21.1. HRMS (ESI): *m/z* [M-H]$^-$ calcd for $C_{17}H_{13}NO_2$: 262.0874; found: 262.0868.

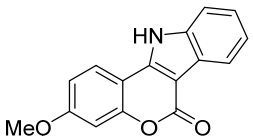
8-fluorochromeno[4,3-*b*]indol-6(11*H*)-one (4d).



4d

Light yellow solid, 32.0 mg, 63%. mp >300 ºC. ^{1}H NMR (300 MHz, DMSO) δ 13.13 (s, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.71-7.62 (m, 3H), 7.55-7.46 (m, 2H), 7.28 (ddd, *J* = 9.3, 9.2, 3.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 158.5 (d, J_{CF} = 235.0 Hz), 157.7, 152.8, 143.1, 134.3, 131.1, 125.0 (d, J_{CF} = 11.3 Hz), 124.4, 122.8, 117.3, 113.8(d, J_{CF} = 10.0 Hz), 113.0, 112.8 (d, J_{CF} = 25.0 Hz), 105.2 (d, J_{CF} = 25.0 Hz), 100.1 (d, J_{CF} = 3.8 Hz). HRMS (ESI): *m/z* [M-H]$^-$ calcd for $C_{15}H_8FNO_2$: 252.0466; found: 252.0459.

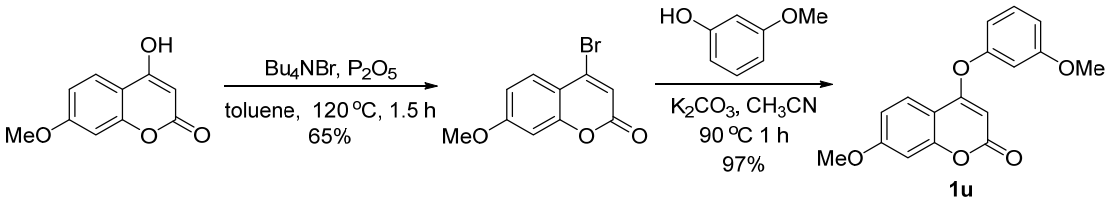
3-methoxychromeno[4,3-*b*]indol-6(11*H*)-one (4e).



4e

Light yellow solid, 45.9 mg, 87%. mp >300 ºC. ^{1}H NMR (300 MHz, DMSO) δ 12.83 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.40-7.28 (m, 2H), 7.11-7.07 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 161.6, 158.0, 154.5, 142.6, 137.6, 124.5, 124.3, 123.7, 122.2, 119.9, 112.24, 112.20, 106.2, 101.6, 98.1, 55.8.

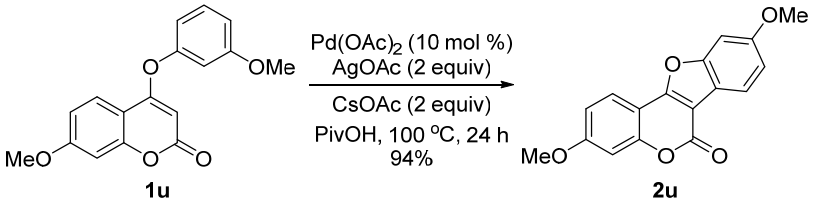
6. Synthesis of coumestrol[8]



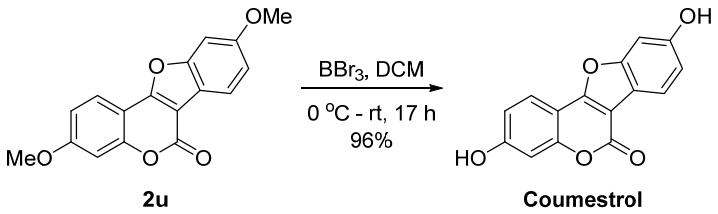
1u

To a round bottom flask equipped with a magnetic stir bar and a reflux condenser was added the 4-hydroxy-7-methoxy-2*H*-chromen-2-one (2.0 mmol) and toluene (8 mL). The reaction mixture was heated at 120 °C for 10 min and then Bu_4NBr (3.0 equiv) was added in 2 portions over 5 min. The reaction mixture was stirred vigorously for 10 min until the starting material completely dissolved. P_2O_5 (4.8 mmol) was then added in 2 portions over 10 min and the reaction was heated for 1.5 h. The reaction mixture was cooled to 23 °C and quenched with a saturated aqueous $NaHCO_3$ solution. Then the reaction mixture was extracted with toluene (3 × 10 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give 4-bromo-7-methoxy-2H-chromen-2-one as a light yellow solid (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 3.90 (s, 3H).

A solution of 4-bromo-7-methoxy-2*H*-chromen-2-one (1.5 mmol), 3-methoxyphenol (1.5 mmol) and K_2CO_3 (3.0 mmol) in acetonitrile (3 mL) was stirred at 90 °C for 1 h. The reaction was allowed to cool to ambient temperature. After quenching the reaction by addition of water (2 ml), white precipitates formed immediately. Filtration of the mixture afforded the precipitates as crude product which was then purified by column chromatography on silica gel to yield product **1u** as a white solid (97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 1H), 7.36 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.93-6.85 (m, 3H), 6.77-6.70 (m, 2H), 5.33 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H).

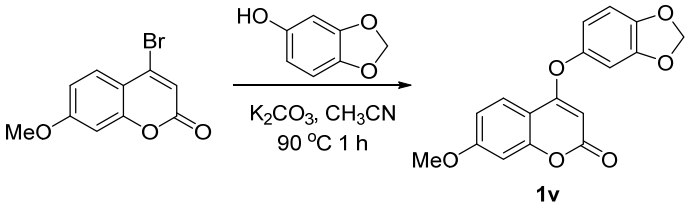


2u[5] was synthesized from **1u** following the general procedure for coumestans as a white solid (94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 9.3 Hz, 1H), 7.15 (s, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.97-6.95 (m, 2H), 3.90 (s, 6H).



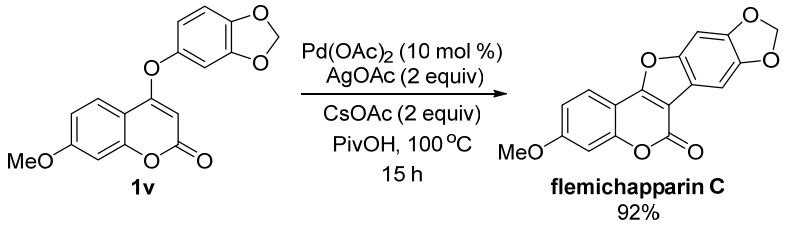
3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (**2u**) (59.2 mg, 0.2 mmol) was dissolved in 2 mL of dry CH_2Cl_2, and the solution was cooled to 0 °C. A solution of BBr_3 in CH_2Cl_2 (1.0 M, 0.6 mL) was added via syringe. The reaction mixture was allowed to attain room temperature overnight. The reaction mixture was monitored by TLC using (DCM/MeOH = 20/1) as the mobile phase. Then hydrolyzed by ice water and filtered to give coumestrol. Light yellow solid, 96%, mp >300 °C. ^{1}H NMR (300 MHz, DMSO) δ 10.70 (s, 1H), 10.03 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 6.95-6.91 (m, 3H).

7. Synthesis of flemichapparin C[2b] **and 5**[9]

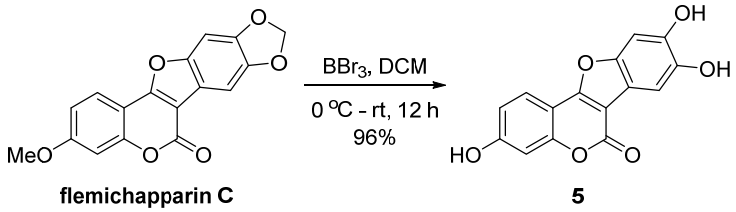


A solution of 4-bromo-7-methoxy-2*H*-chromen-2-one (1.5 mmol), benzo[*d*][1,3]dioxol-5-ol (1.5 mmol) and K_2CO_3 (3.0 mmol) in acetonitrile (3 mL) was stirred at reflux for 1 h. The reaction was allowed to cool to ambient temperature. After quenching the reaction by addition of water (2 ml),

white precipitates formed immediately. Filtration of the mixture afforded the precipitates as crude product which was then purified by column chromatography on silica gel to yield product **1v** as a white solid (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 1H), 6.92-6.83 (m, 3H), 6.65-6.60 (m, 2H), 6.05 (s, 2H), 5.32 (s, 1H), 3.90 (s, 3H).

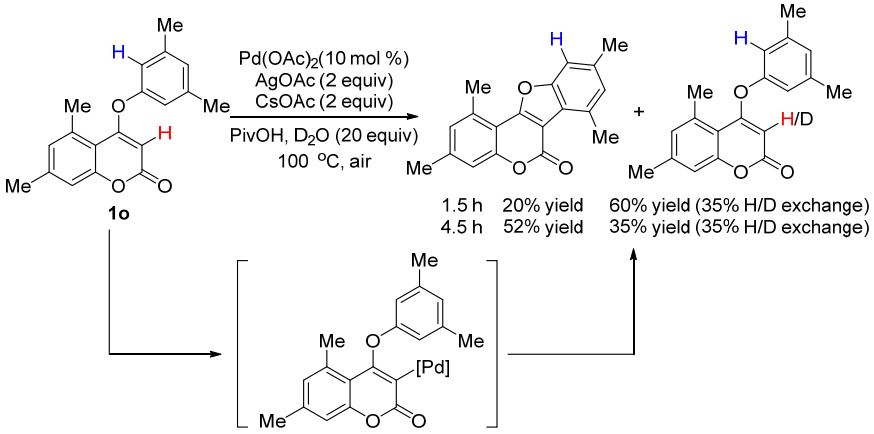


Flemichapparin C was synthesized from **1v** following the general procedure for coumestans. White solid, 92%, mp 270-272 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 9.4 Hz, 1H), 7.46 (s, 1H), 7.11 (s, 1H), 6.98-6.95 (m, 2H), 6.07 (s, 2H), 3.91 (s, 3H).



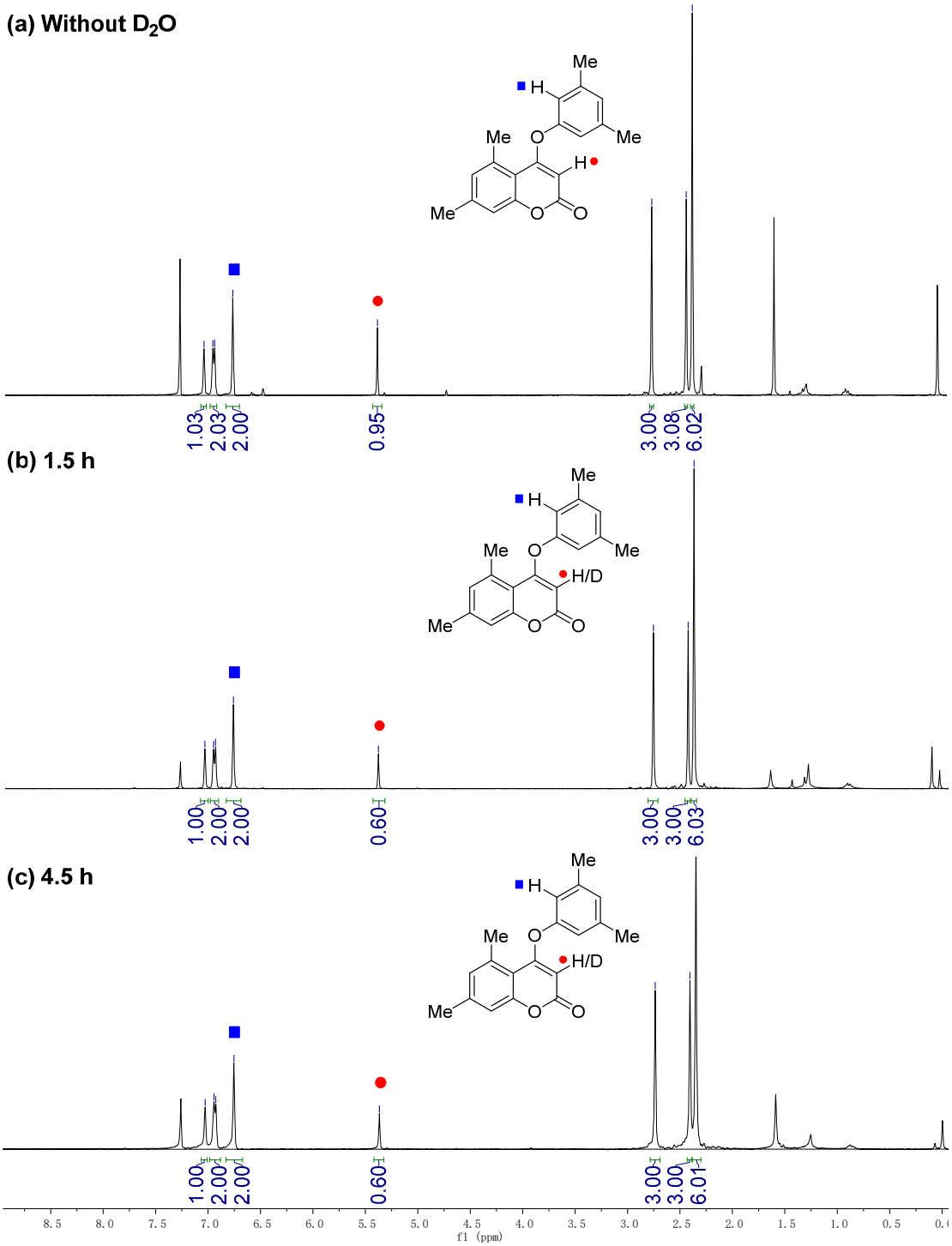
Compound **5** was synthesized following the procedure of synthesizing coumestrol from **2u**. Light yellow solid, 96%. ^{1}H NMR (300 MHz, DMSO) δ 10.64 (s, 1H), 9.49 (s, 1H), 9.41 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 6.93-6.90 (m, 2H).

8. H/D exchange experimental study



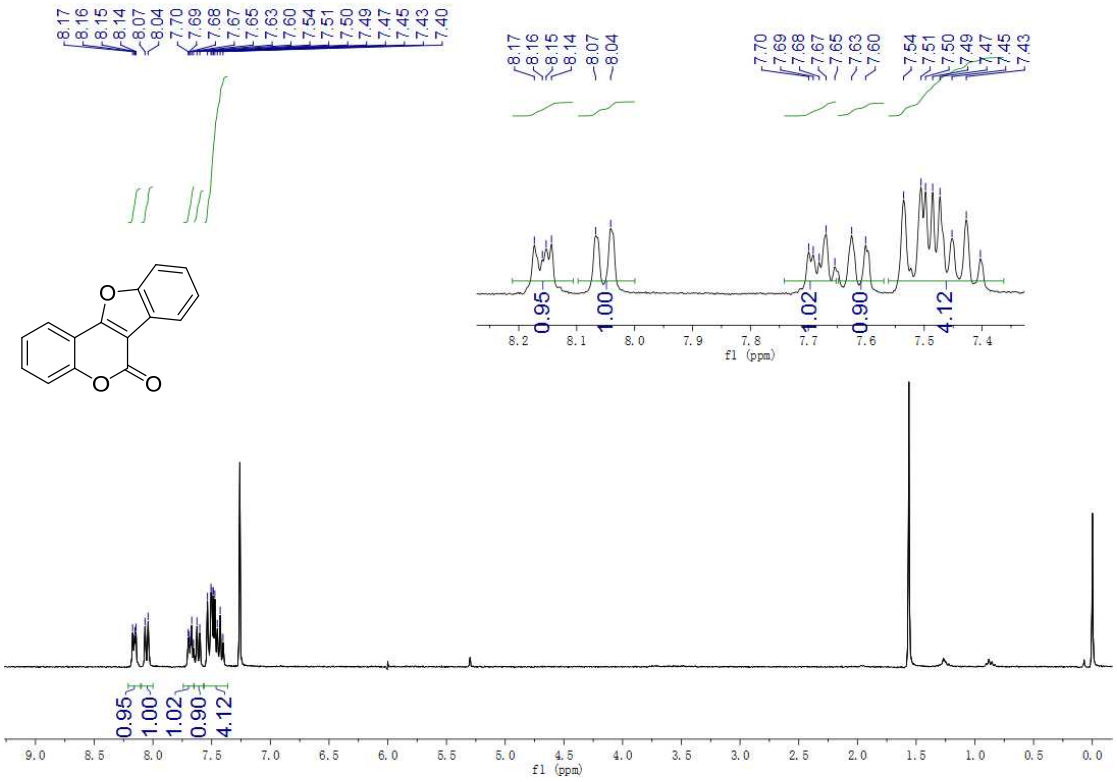
4-(3,5-dimethylphenoxy)-5,7-dimethyl-2*H*-chromen-2-one (**1o**) (0.1 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv) and CsOAc (2 equiv) were combined in PivOH (0.5 mL). Subsequently, D_2O (2 mmol, 20 equiv) was added and the reaction mixture was heated to 100 °C for specified time (1.5 h or 4.5 h). Then the reaction mixture was diluted with CH_2Cl_2 and the excess $NaHCO_3$ (aq.) was added to neutralize PivOH. After stirring the mixture for 10 min, the residue was washed with

aqueous $NaHCO_3$ and the isolated organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using CH_2Cl_2/PE as the eluent to give product **2o**. The starting material **1o** was recovered and subjected to ^1H NMR analysis.

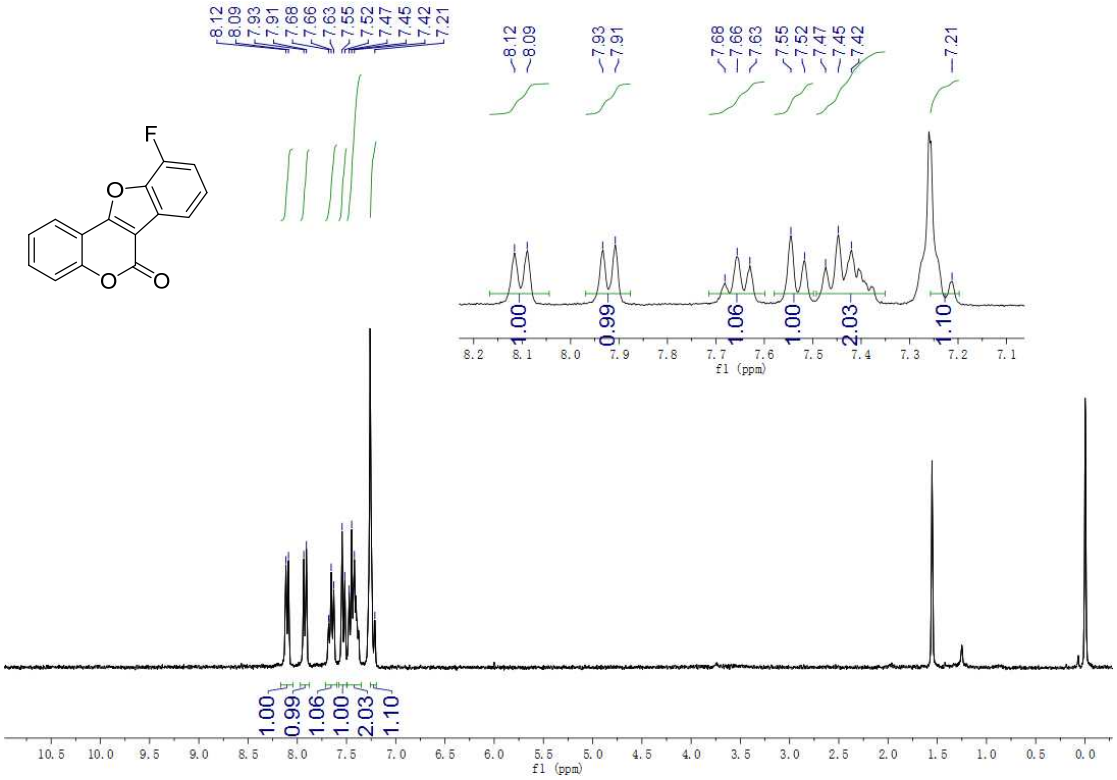


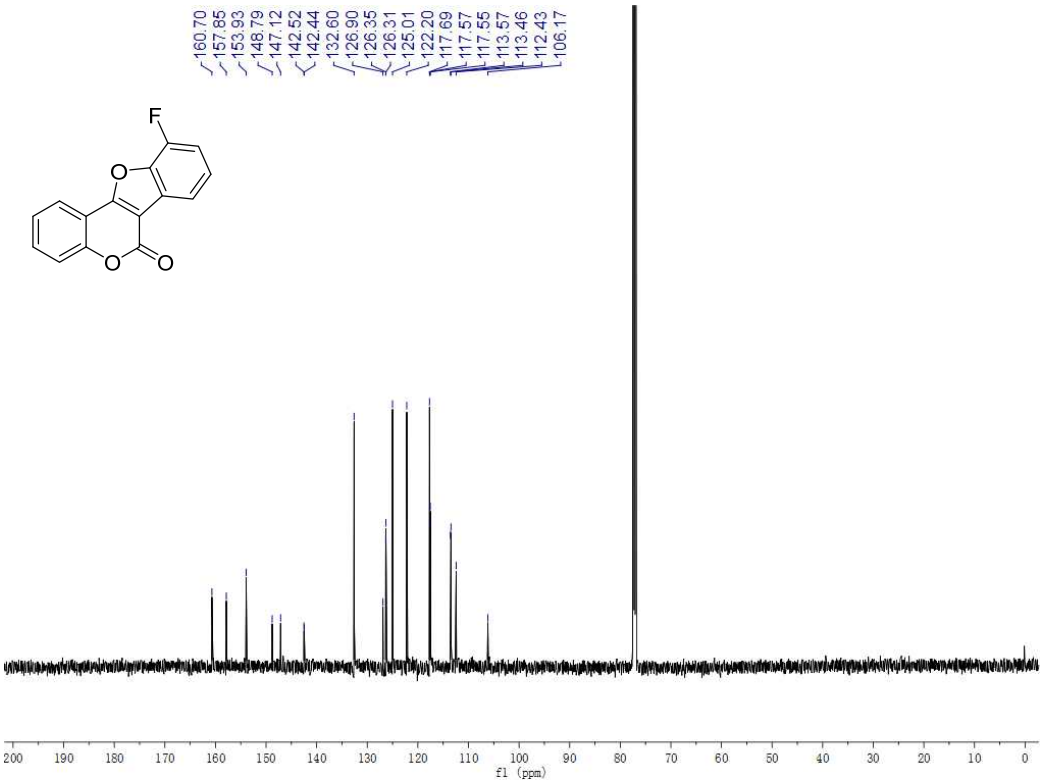
9. Copies of ^{1}H NMR and ^{13}C NMR spectra

6*H*-benzofuro[3,2-*c*]chromen-6-one (2a)

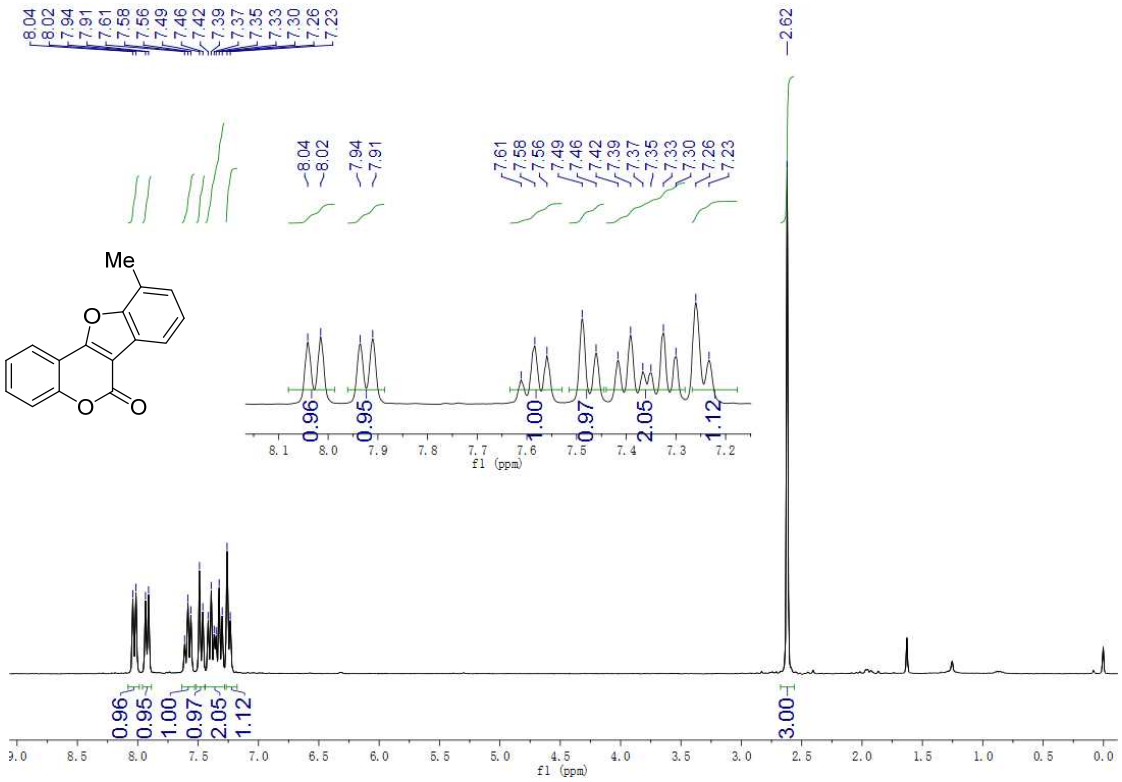


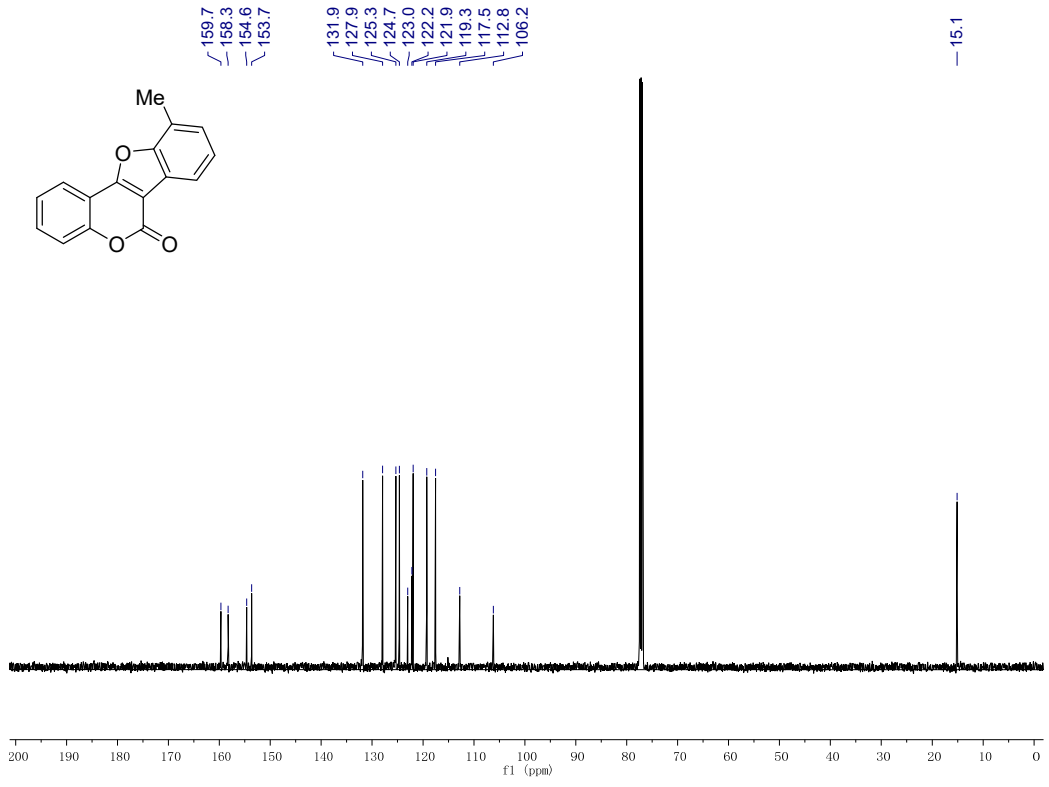
10-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2b)



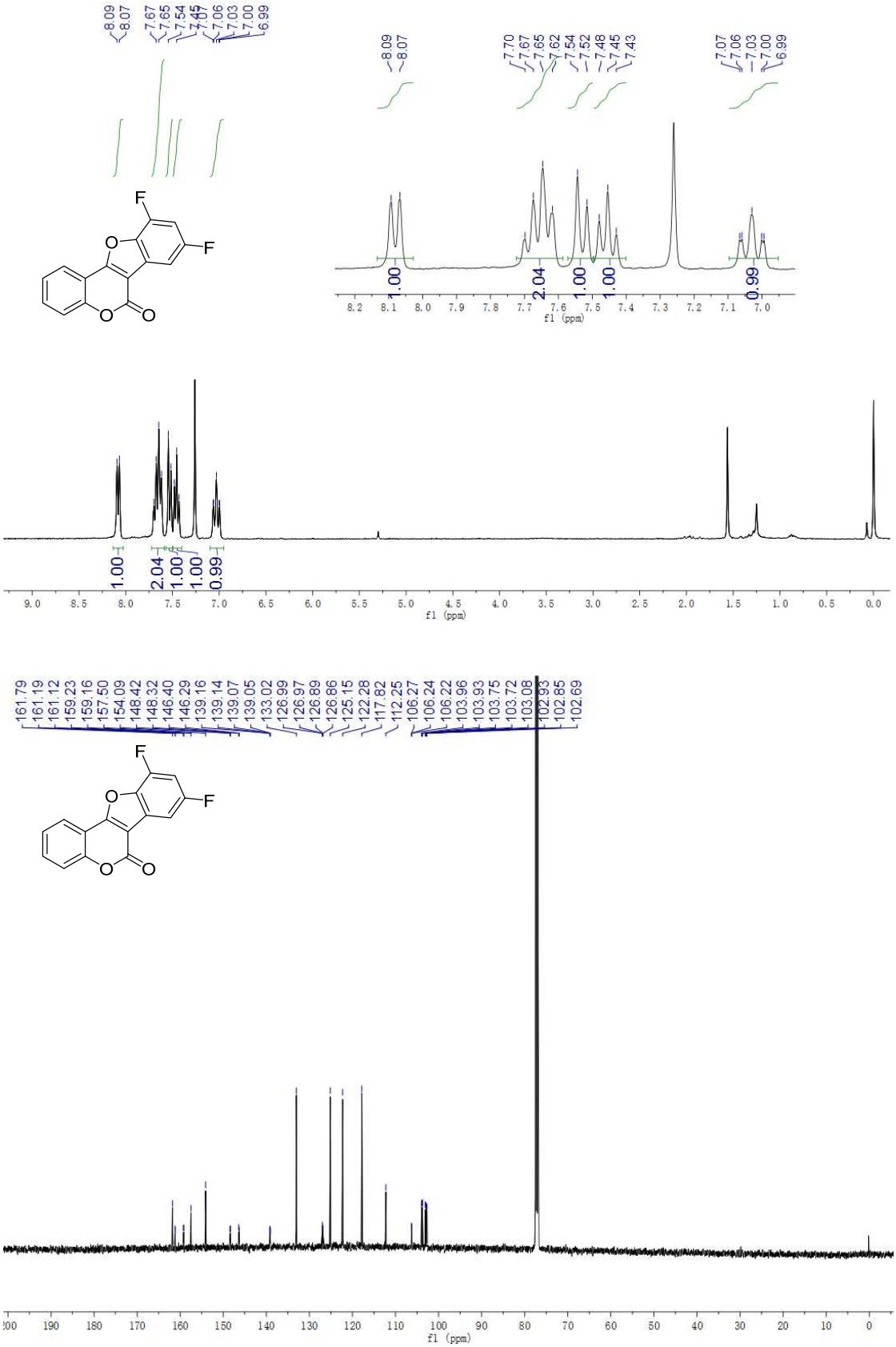


10-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2c)

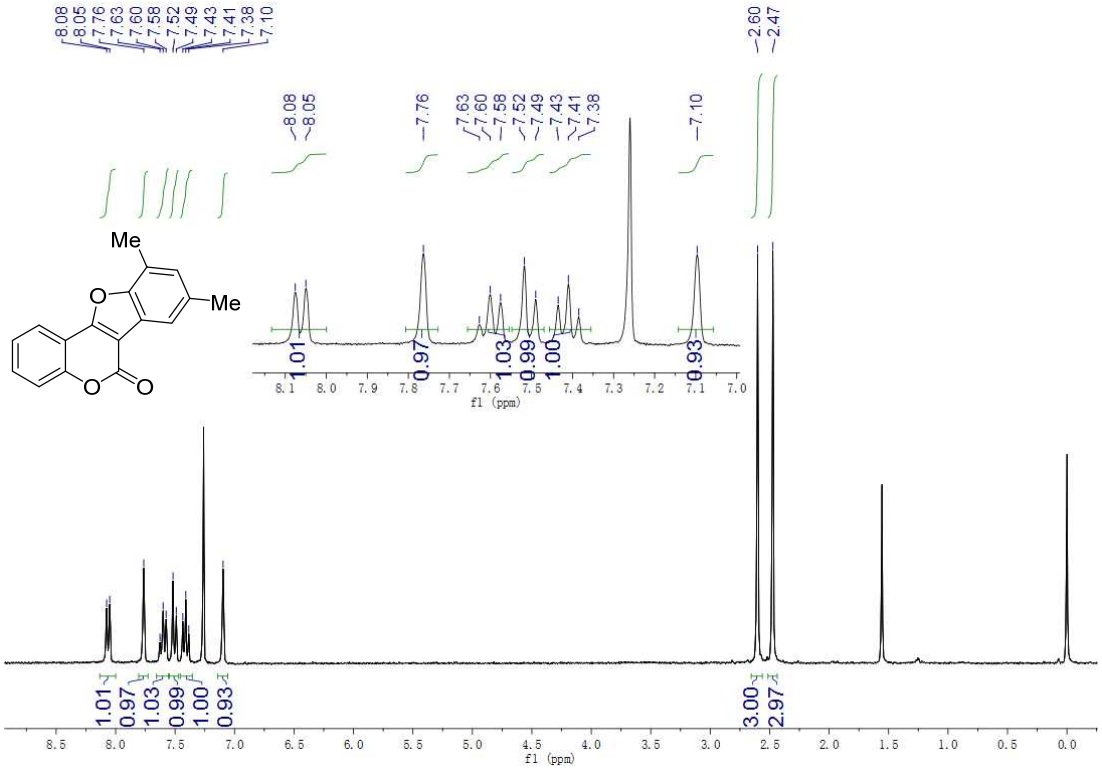


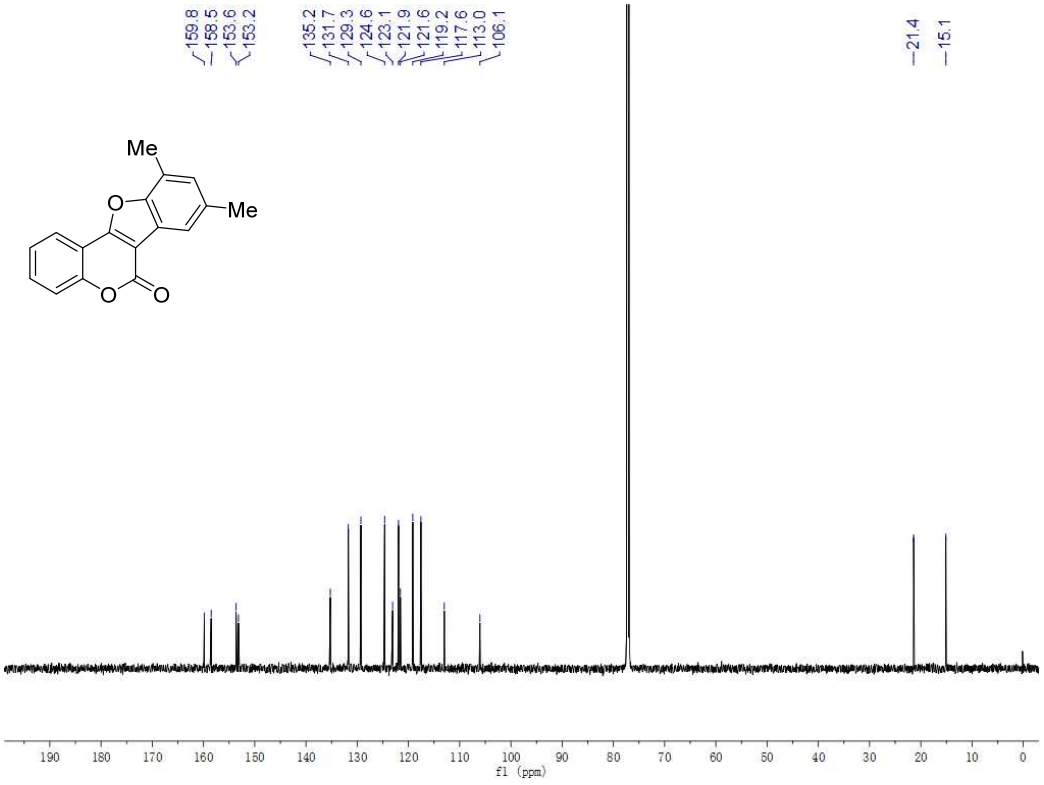


8,10-difluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2d)

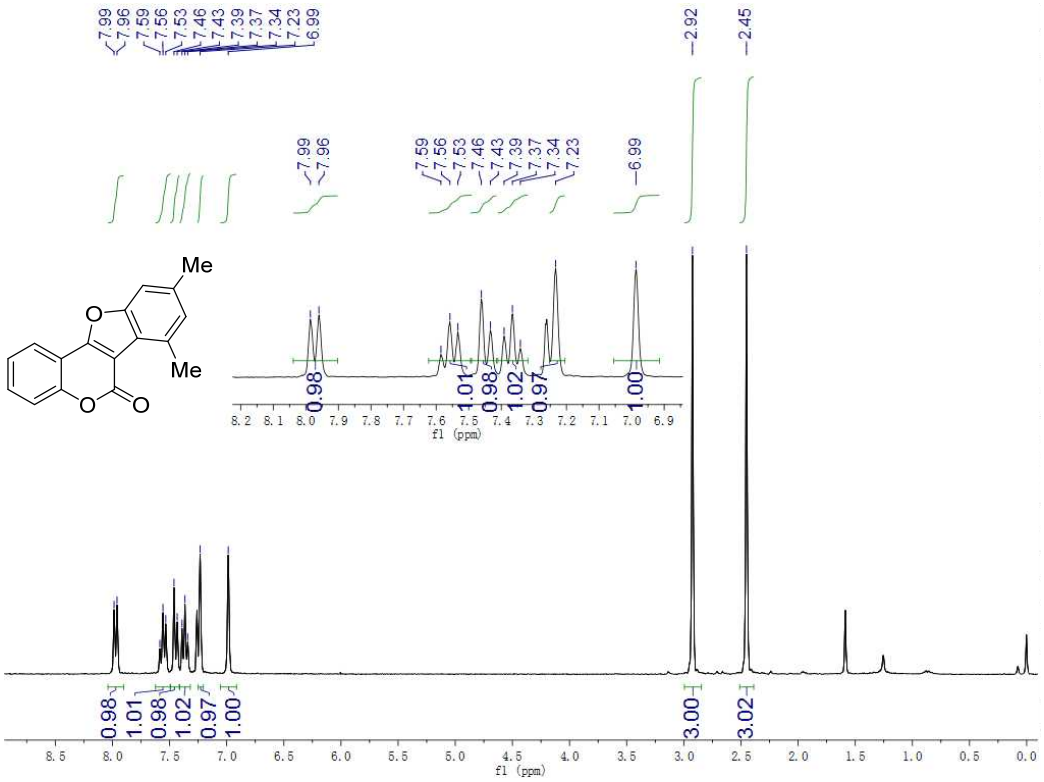


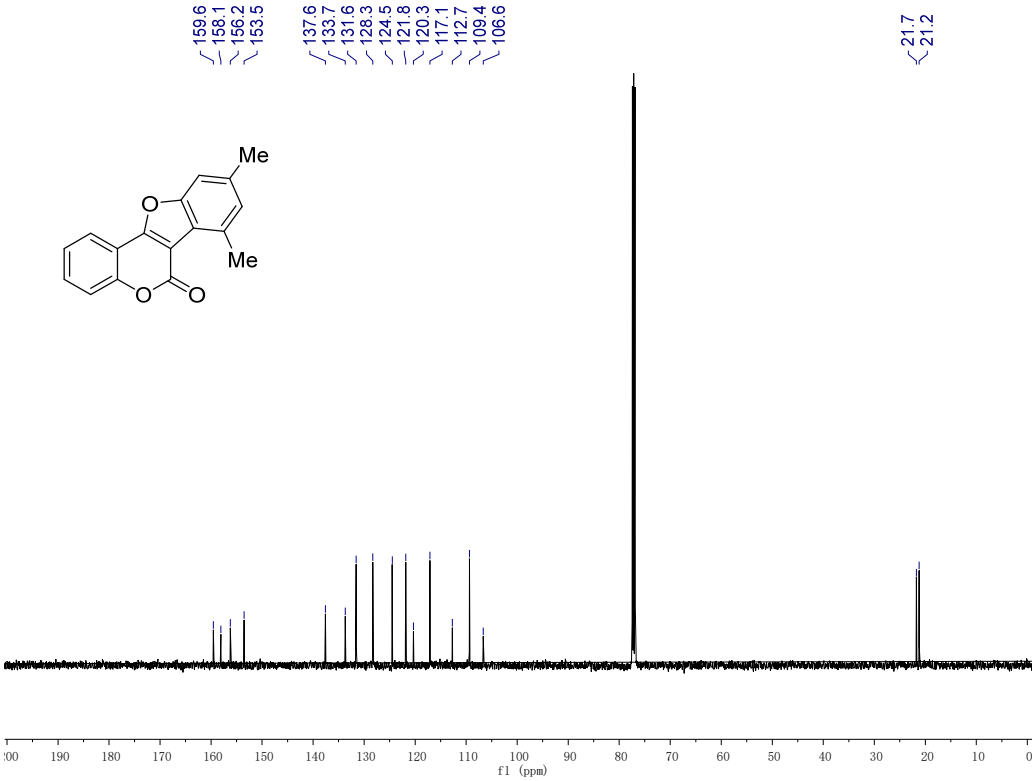
8,10-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2e)



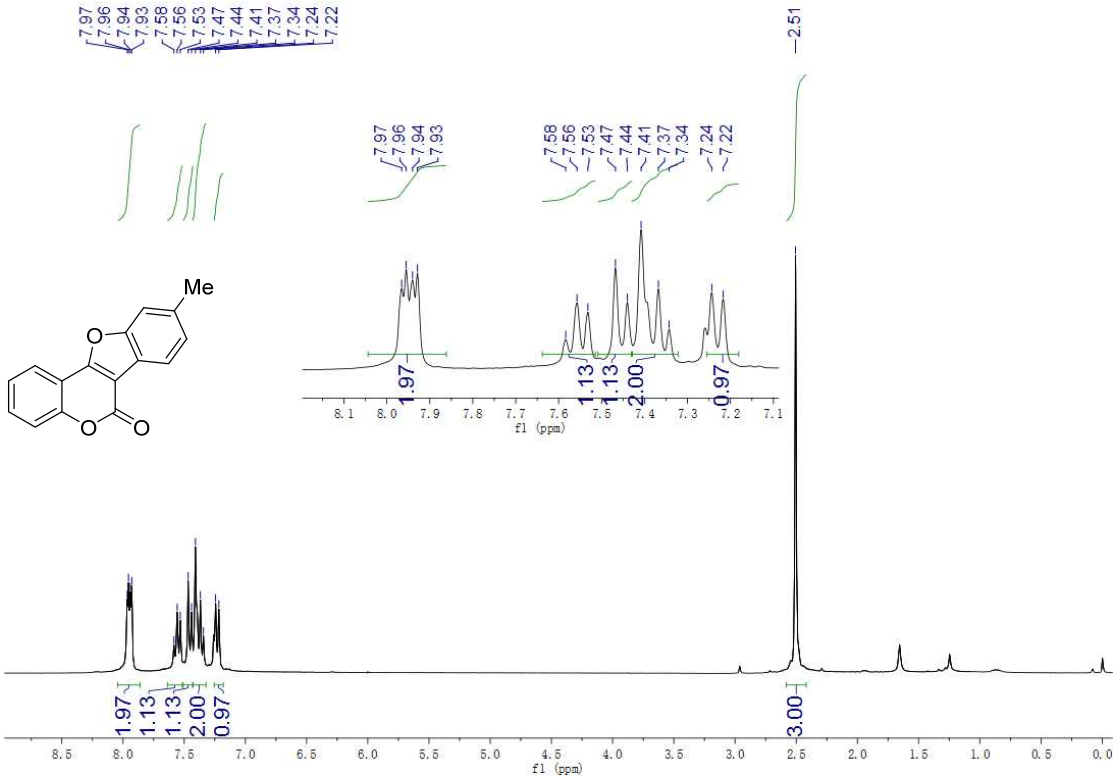


7,9-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2f)

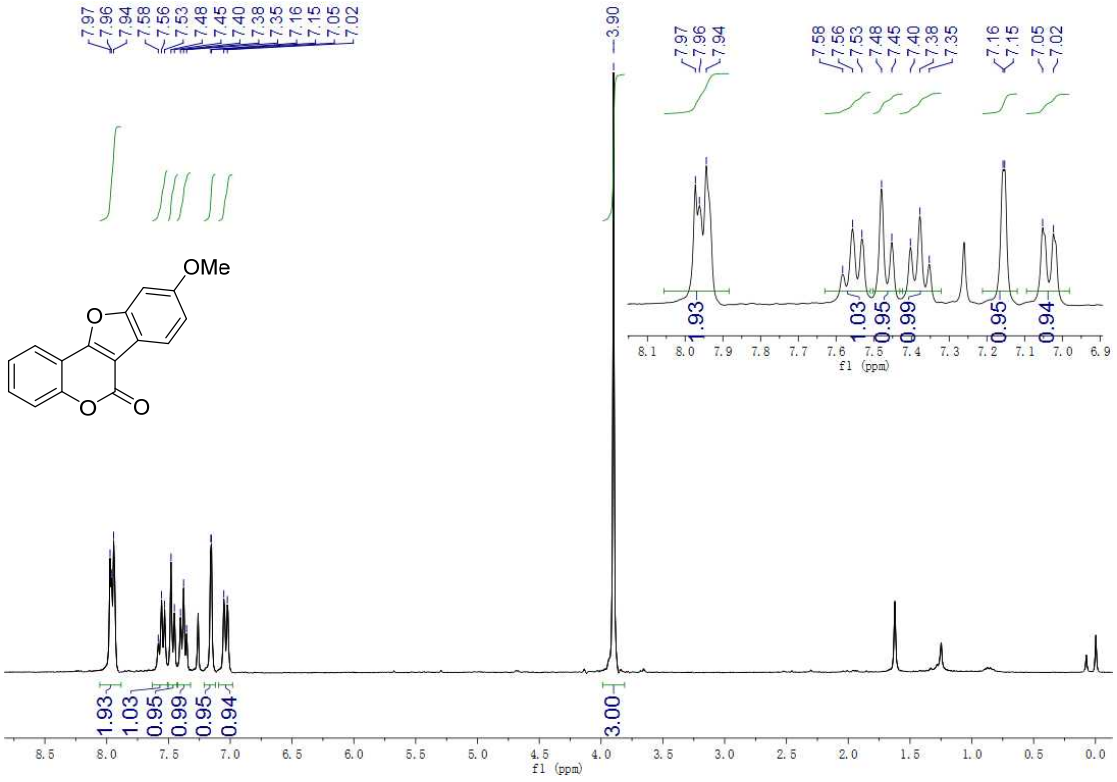




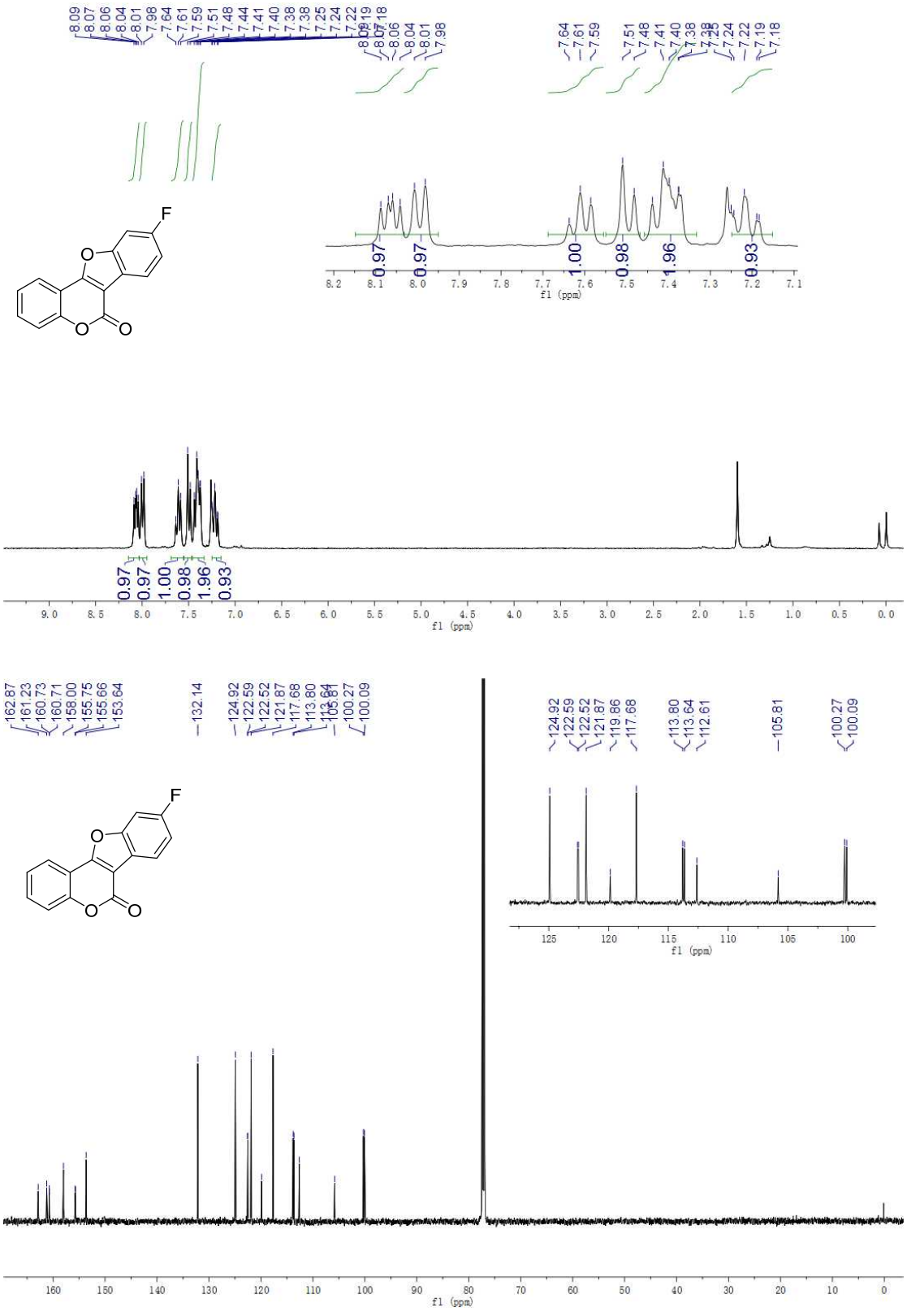
9-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2g)



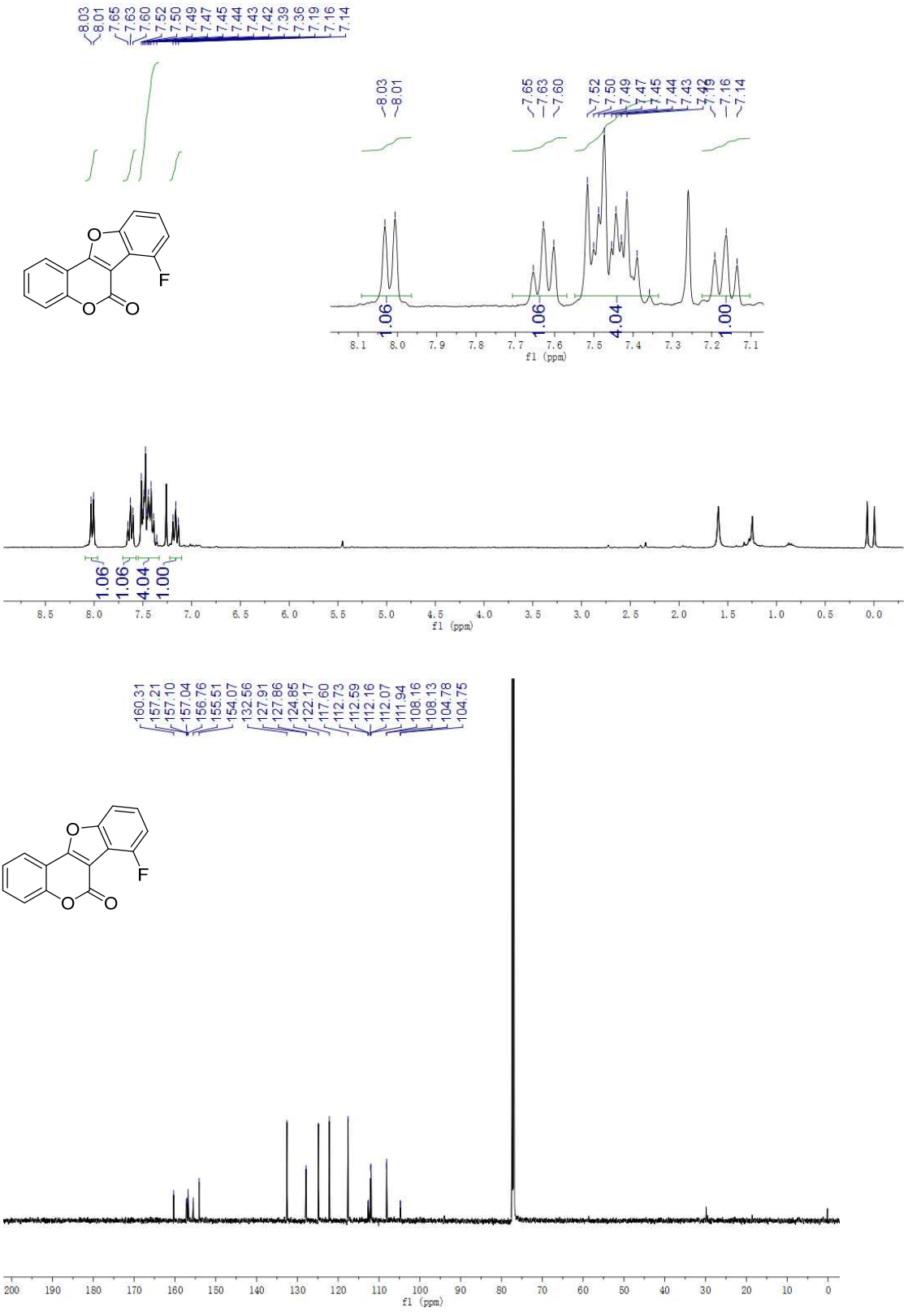
9-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2h)



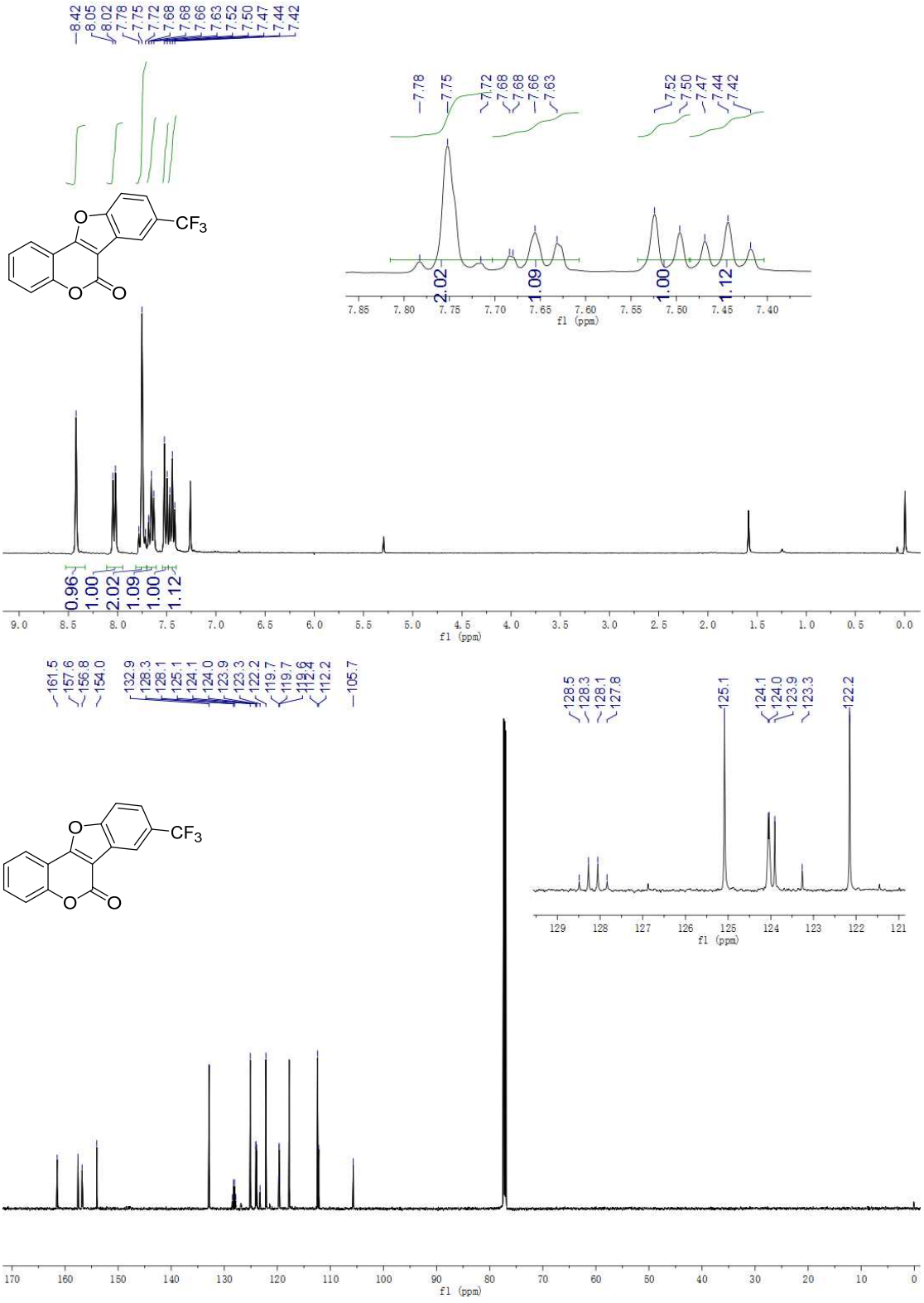
9-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2i)



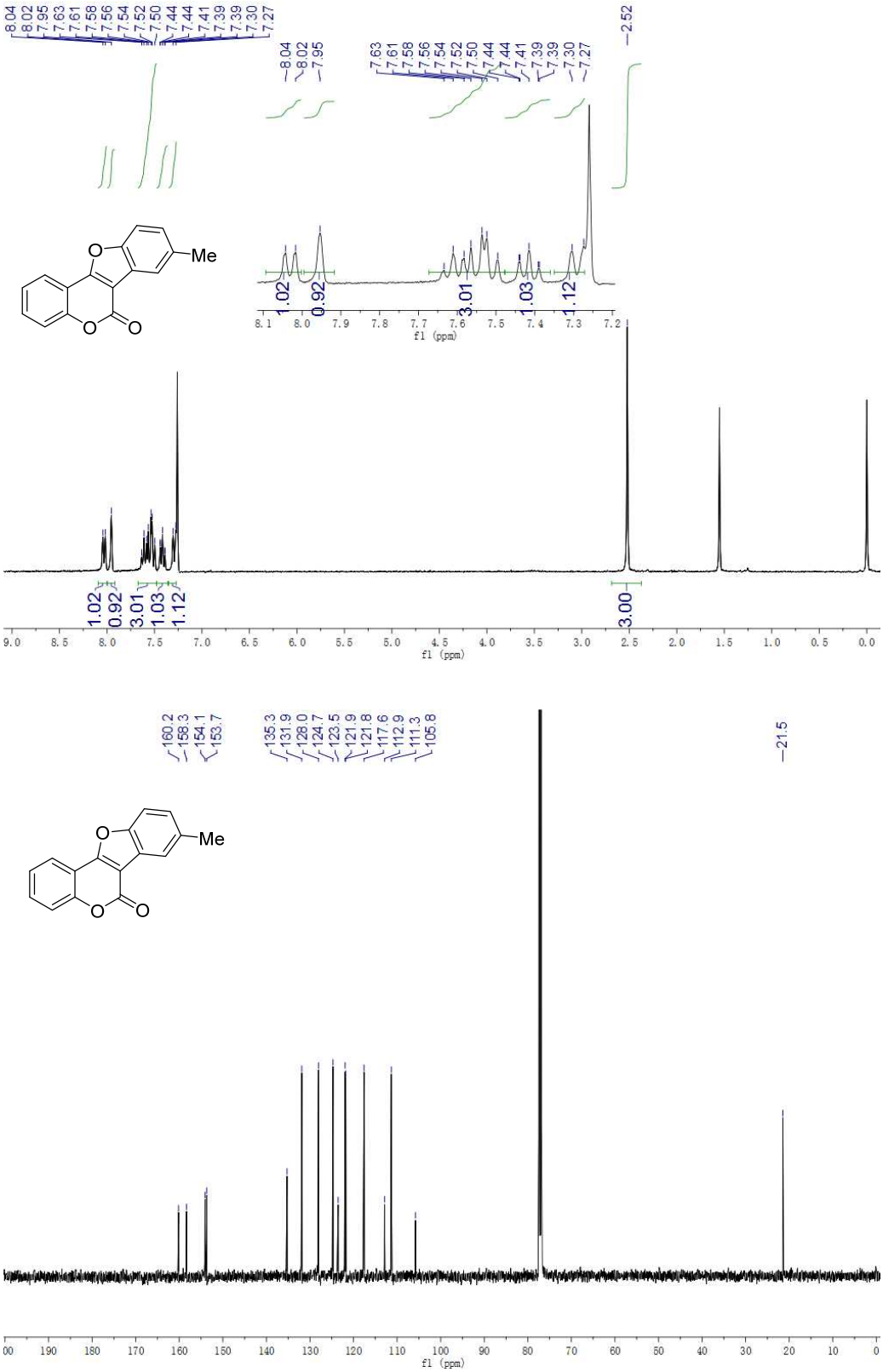
7-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2j)



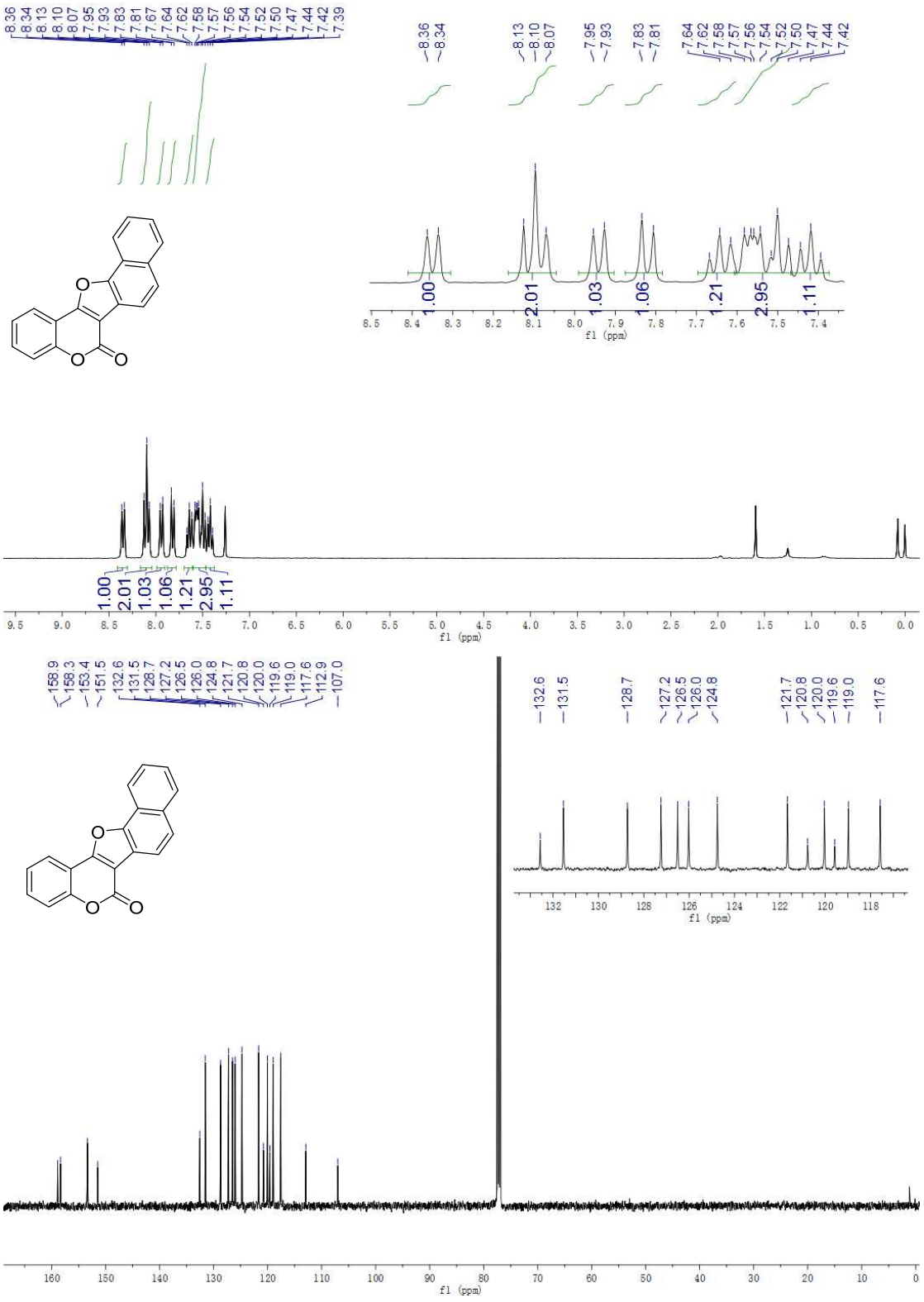
8-(trifluoromethyl)-6*H*-benzofuro[3,2-*c*]chromen-6-one (2k)



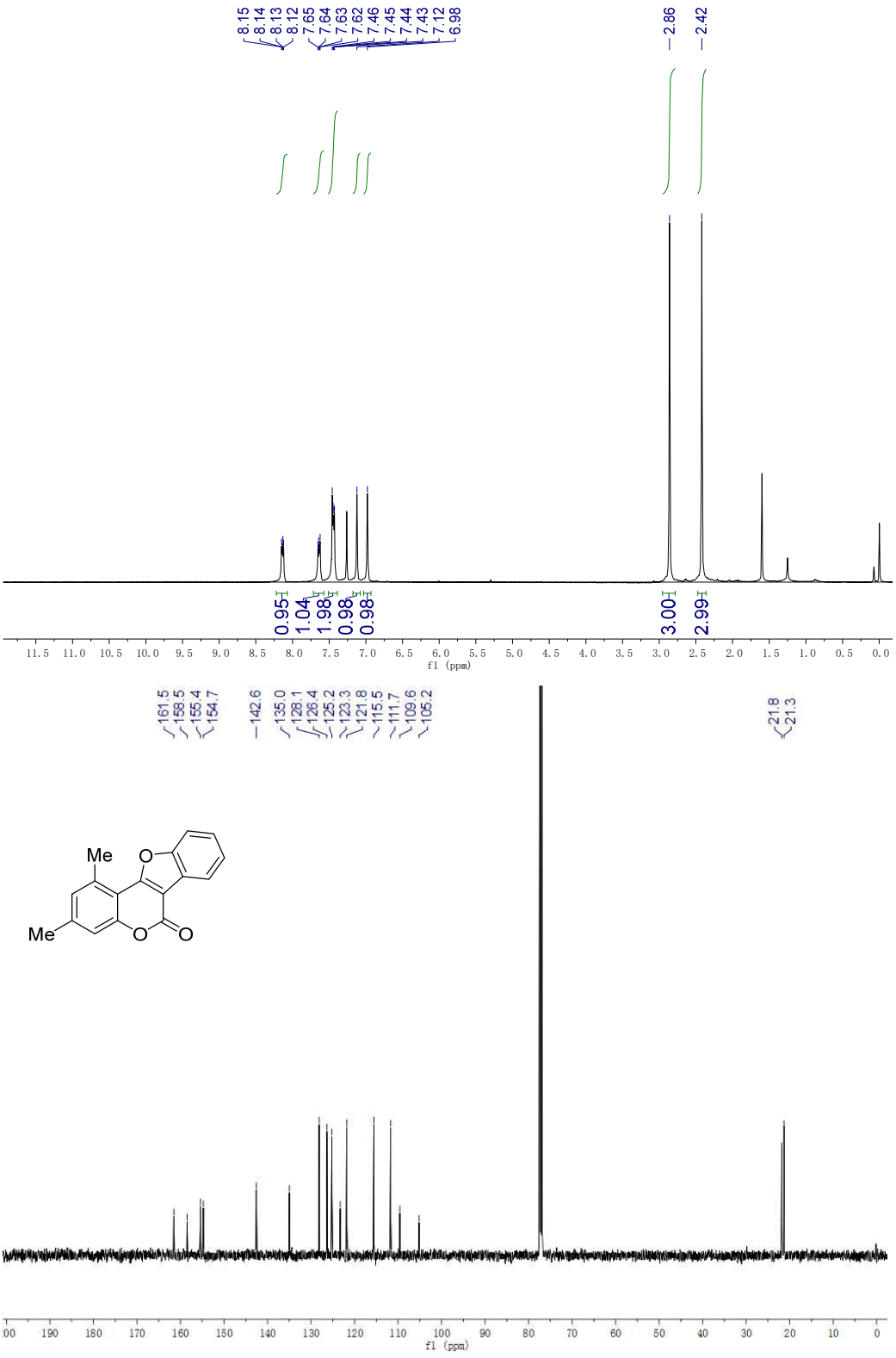
8-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2l)



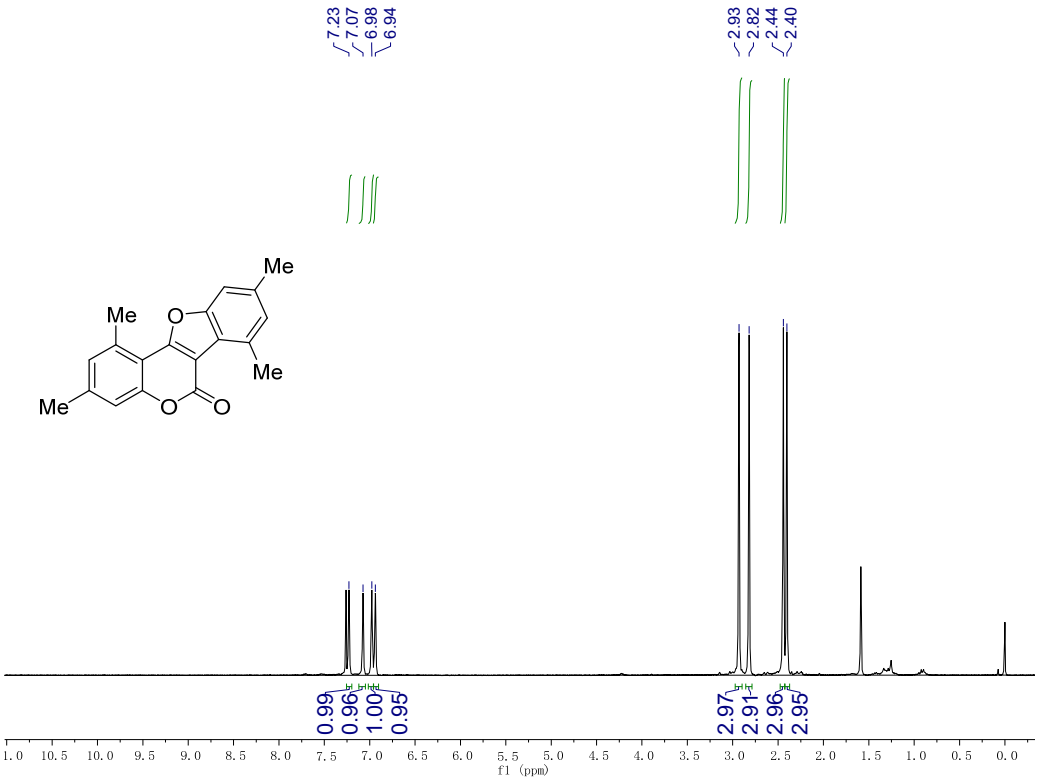
6*H*-naphtho[2',1':4,5]furo[3,2-*c*]chromen-6-one (2m)

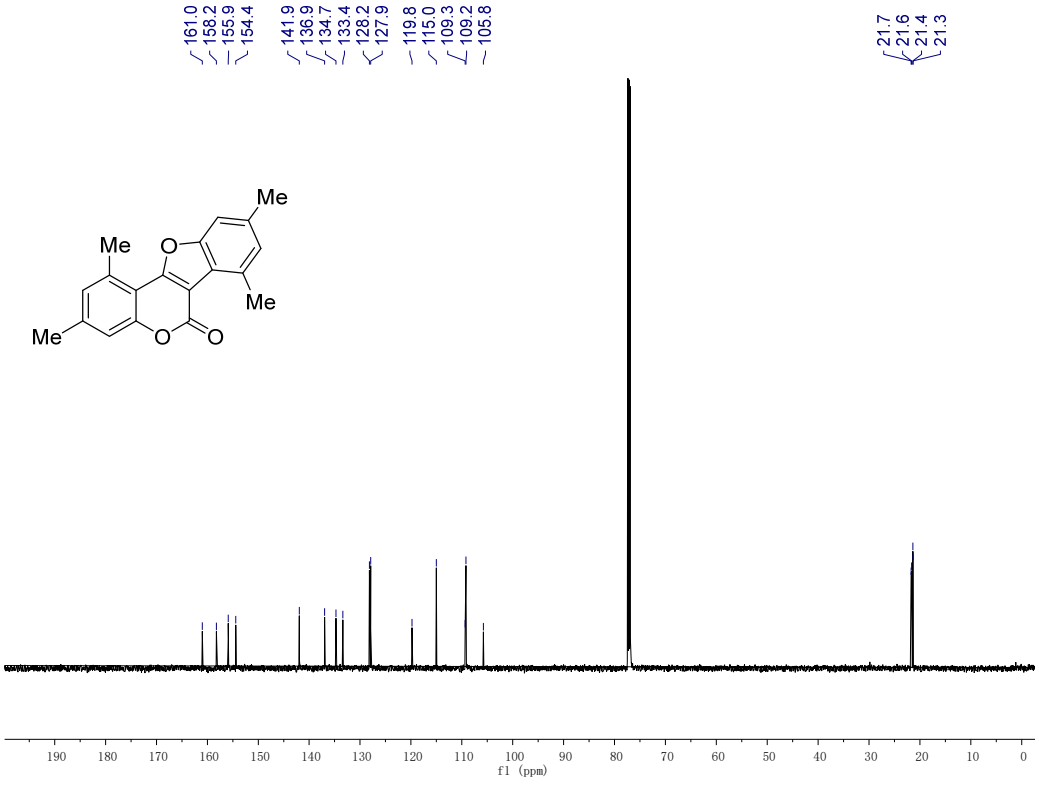


1,3-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2n)

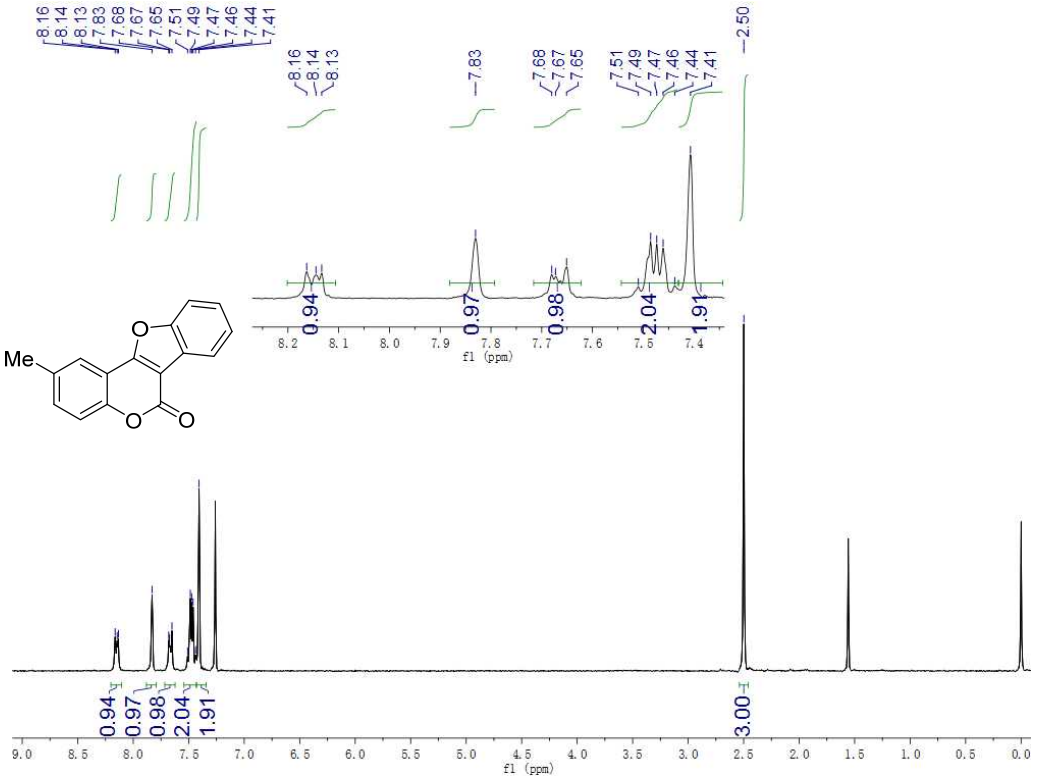


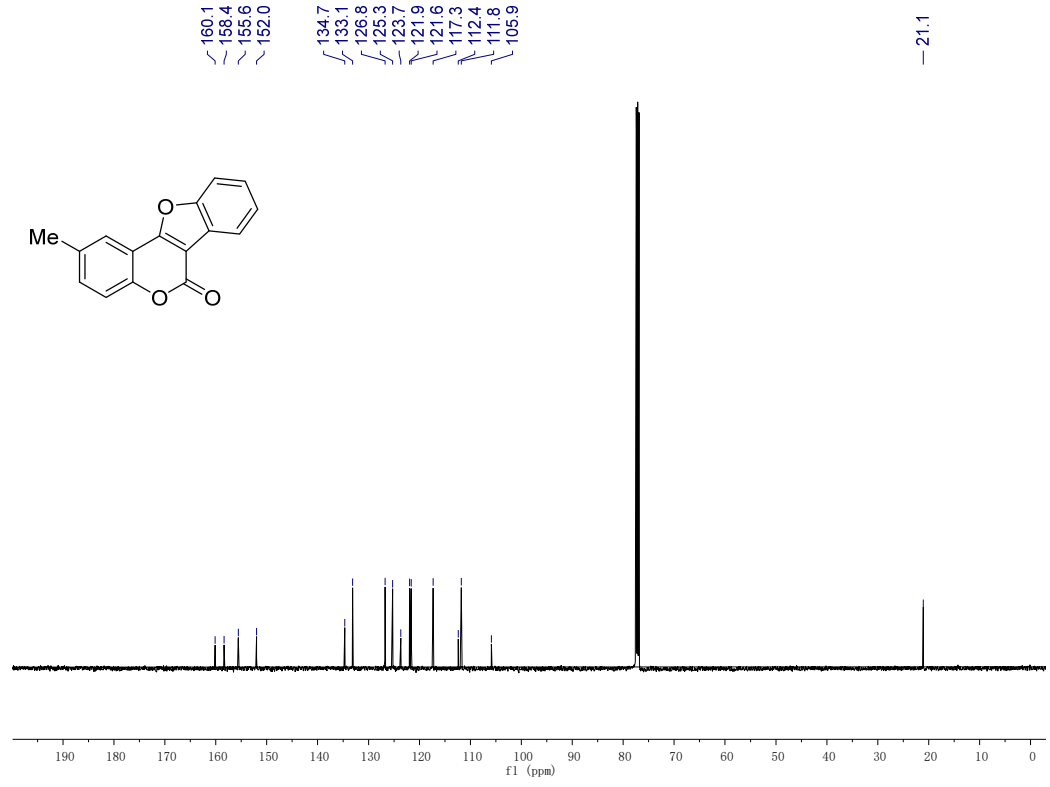
1,3,7,9-tetramethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2o)



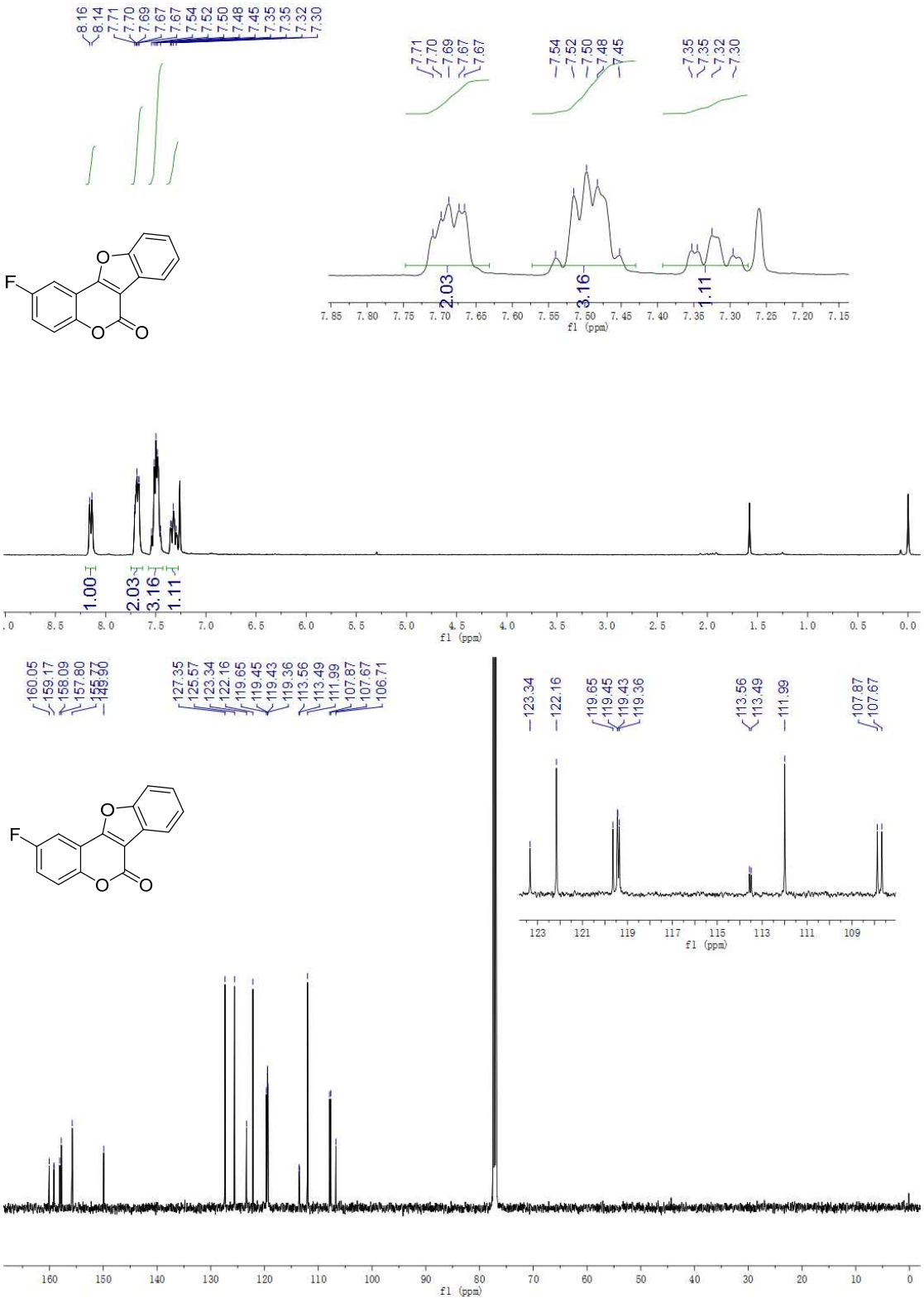


2-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one(2p)

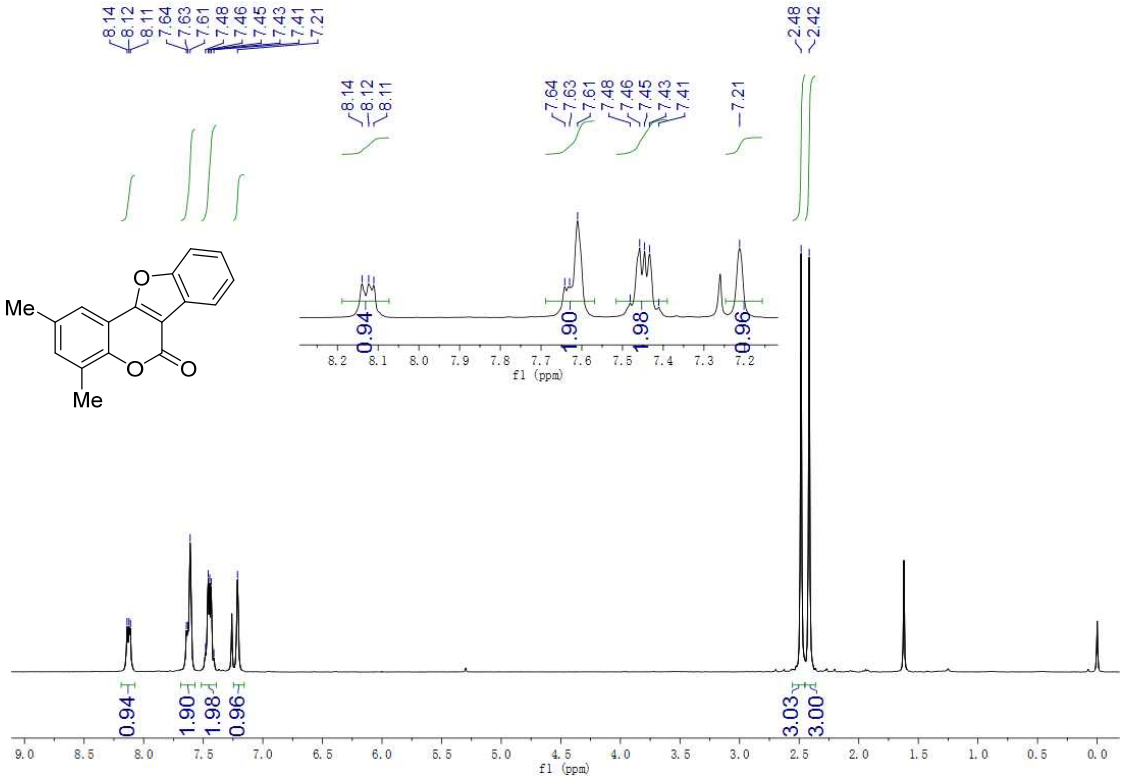


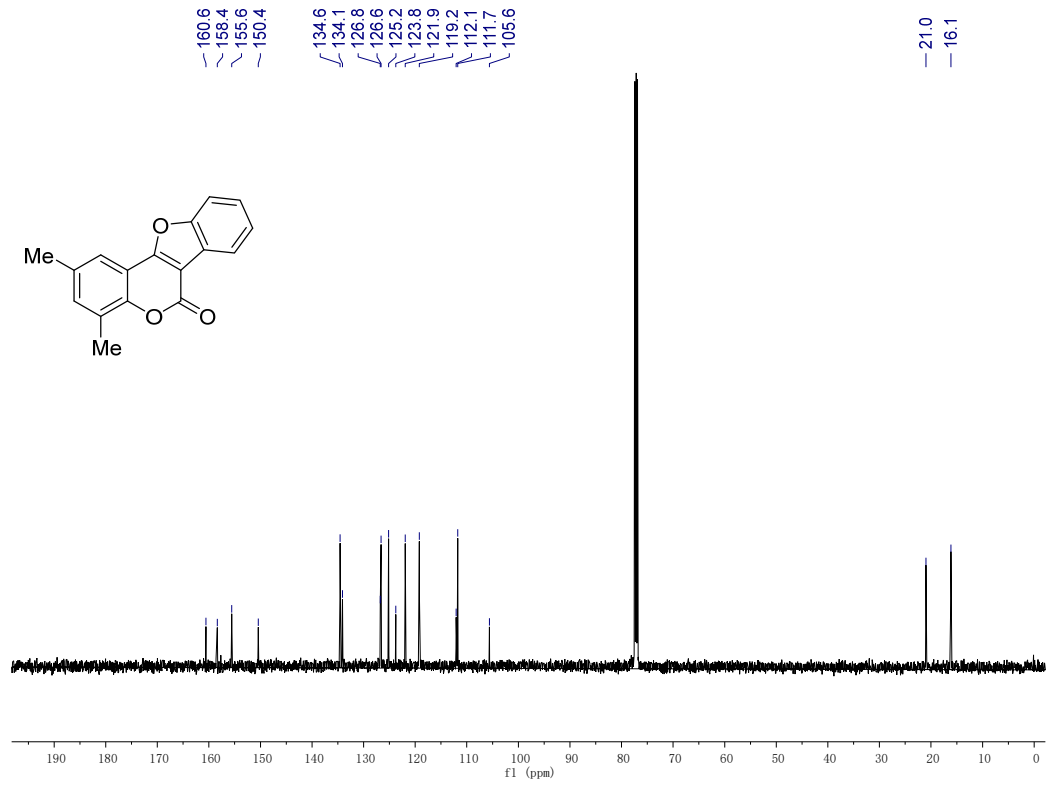


2-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2q)

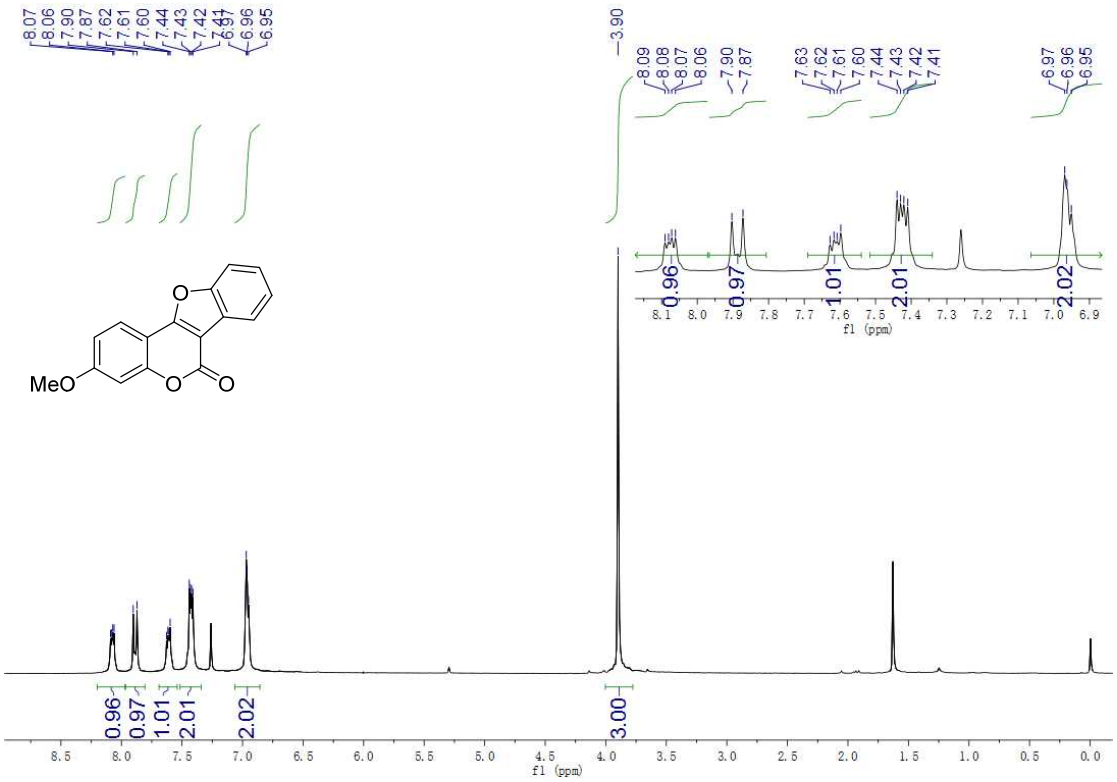


2,4-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (2r)

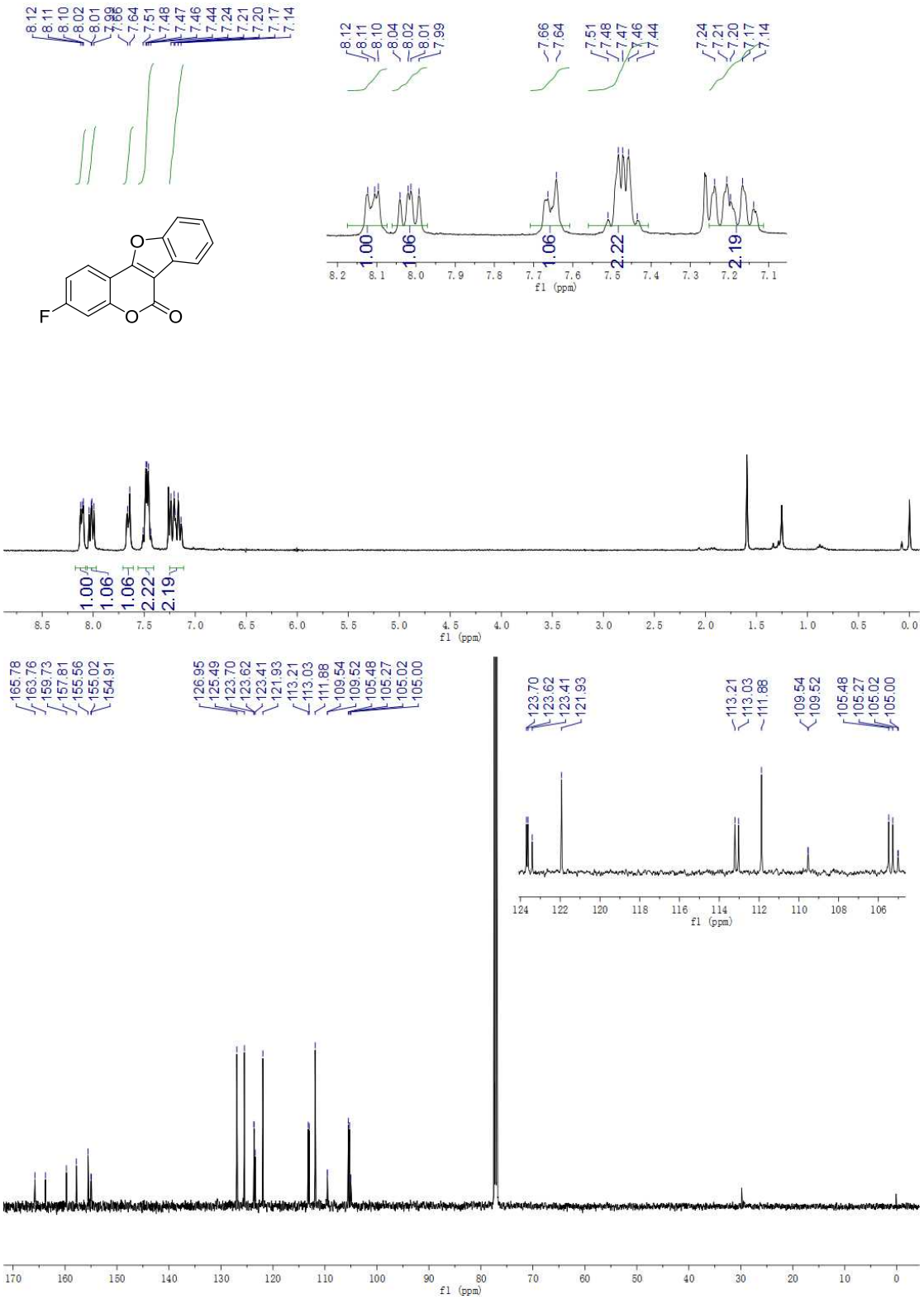




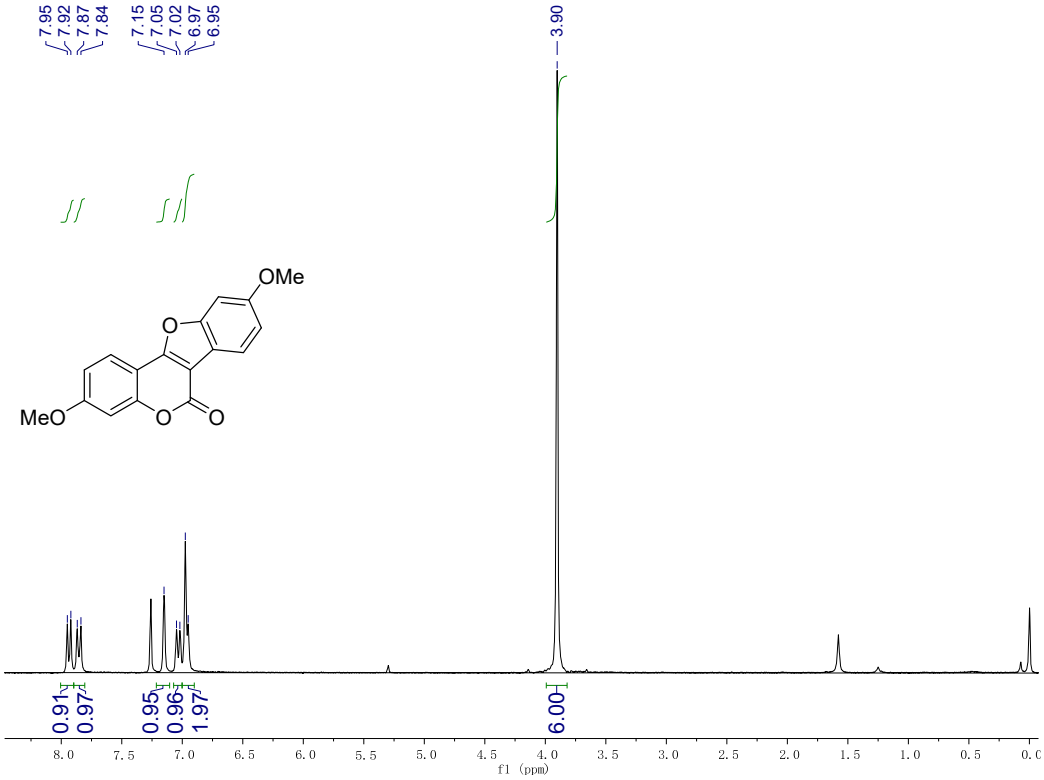
3-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2s)



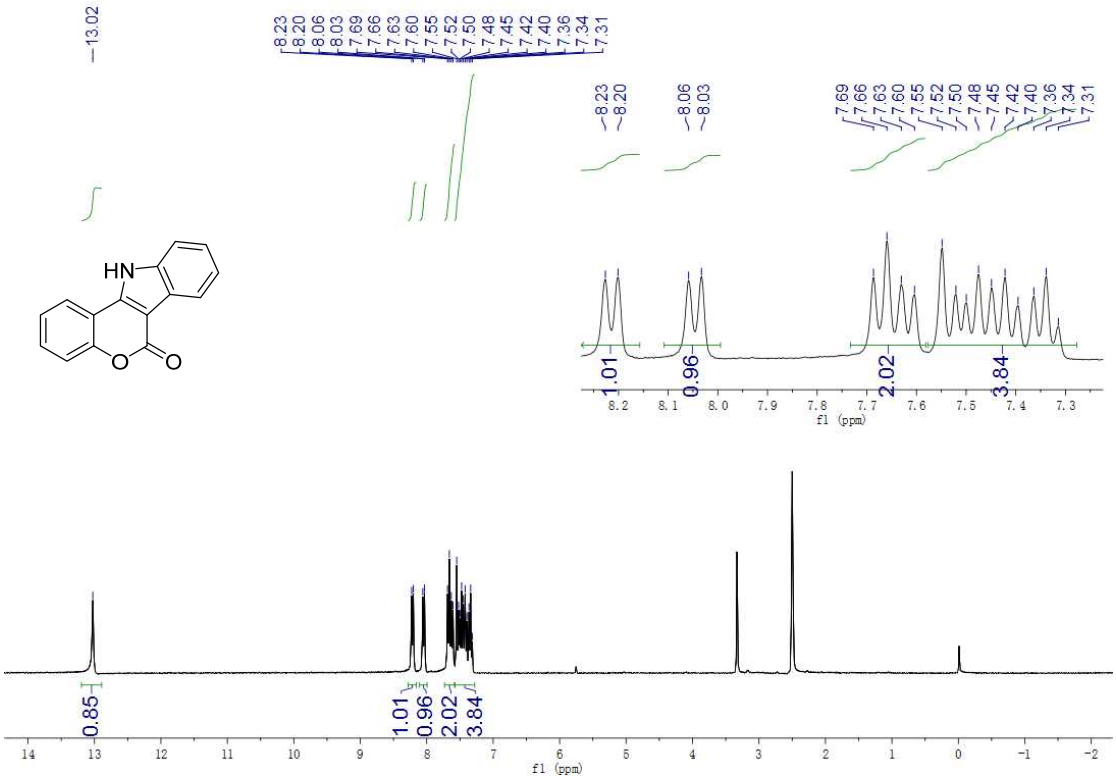
3-fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (2t)


8.12
8.11
8.10
8.02
8.01
7.99
7.66
7.64
7.51
7.48
7.47
7.46
7.44
7.24
7.21
7.20
7.17
7.14
1.00
1.06
1.06
2.22
2.19
f1 (ppm)
F
O
O
O
165.78
163.76
159.73
157.81
155.56
155.02
154.91
126.95
125.49
123.70
123.62
123.41
121.93
113.21
113.03
111.88
109.54
109.52
105.48
105.27
105.02
105.00

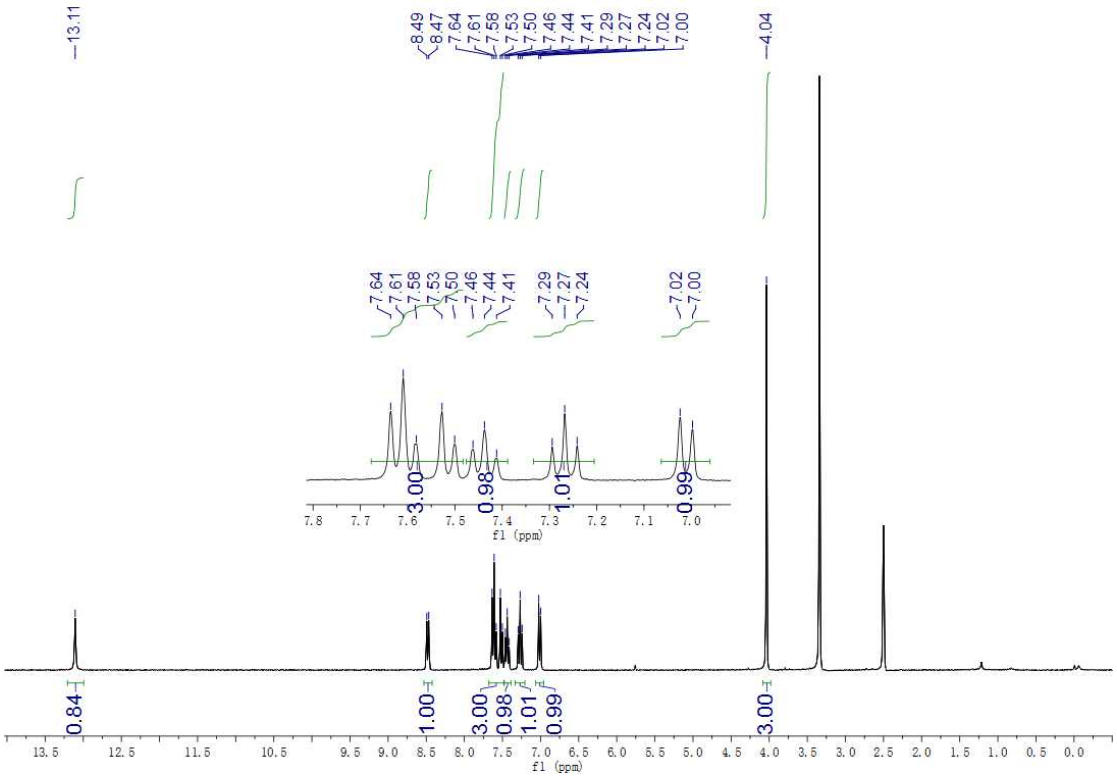
3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2u)

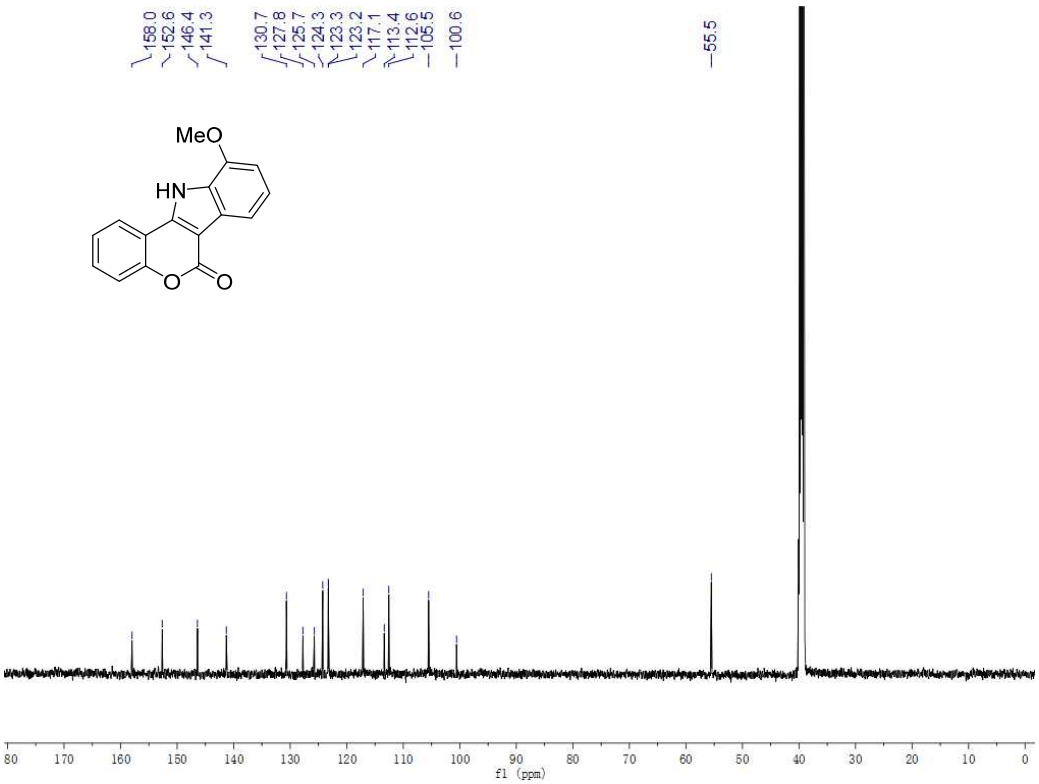


chromeno[4,3-*b*]indol-6(11*H*)-one (4a) (in DMSO-*d*)

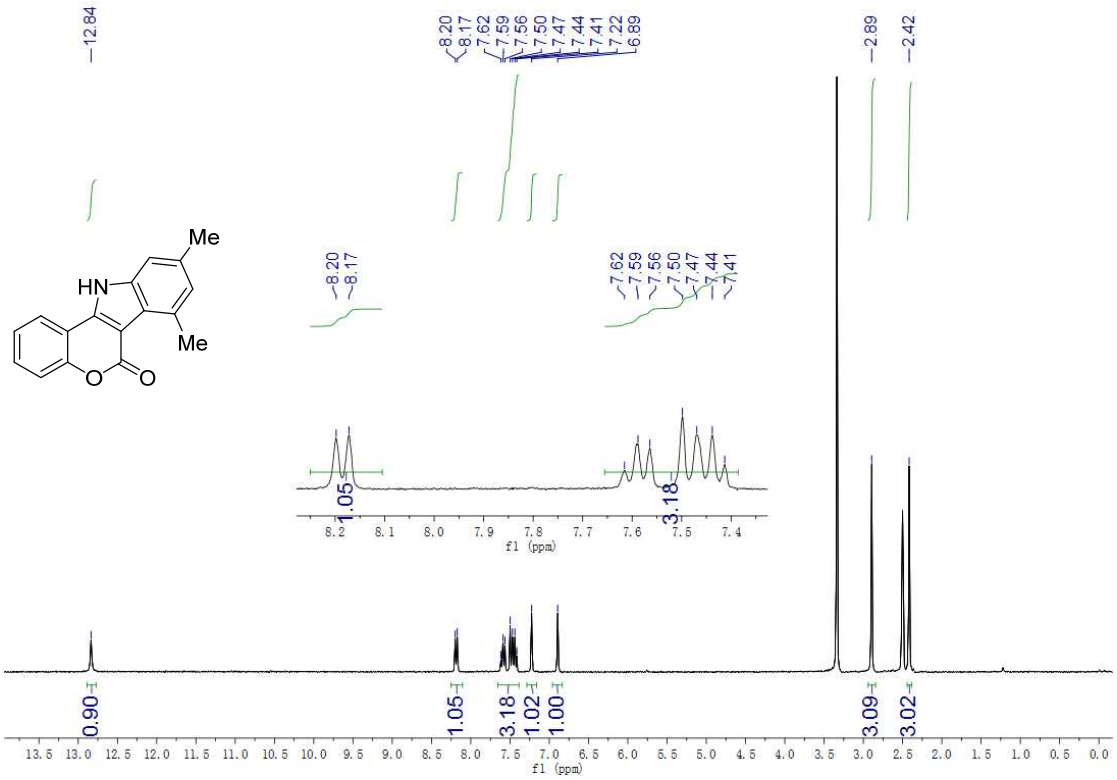


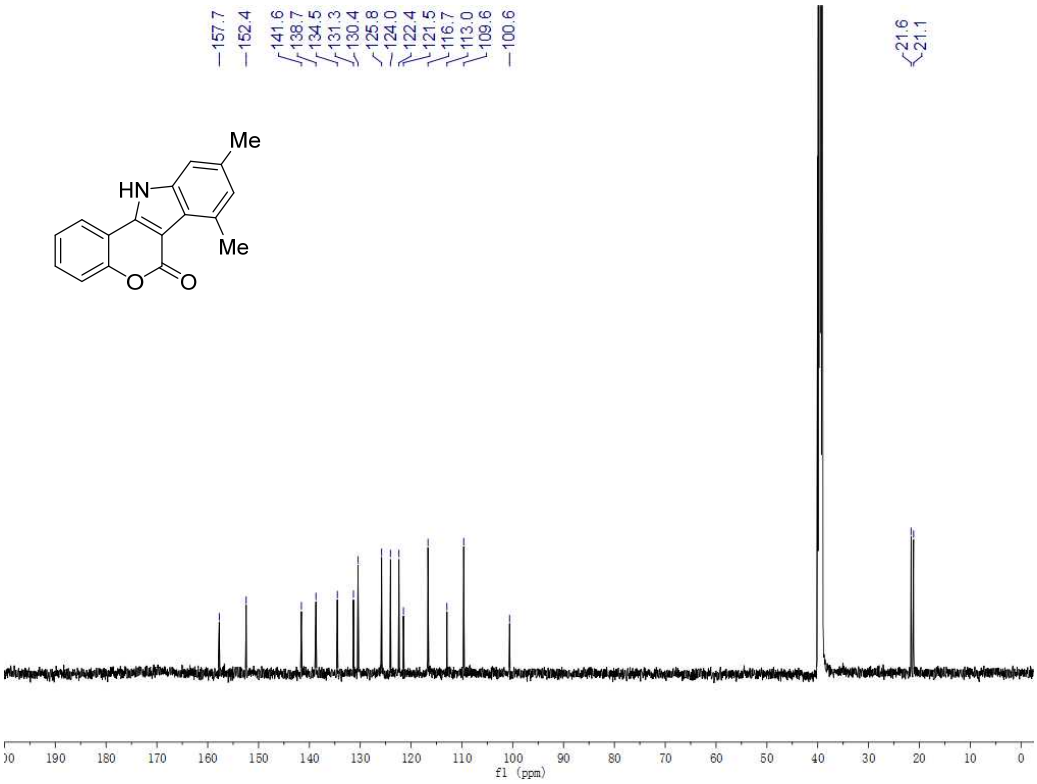
10-methoxychromeno[4,3-b]indol-6(11*H*)-one (4b) (in DMSO-*d*)



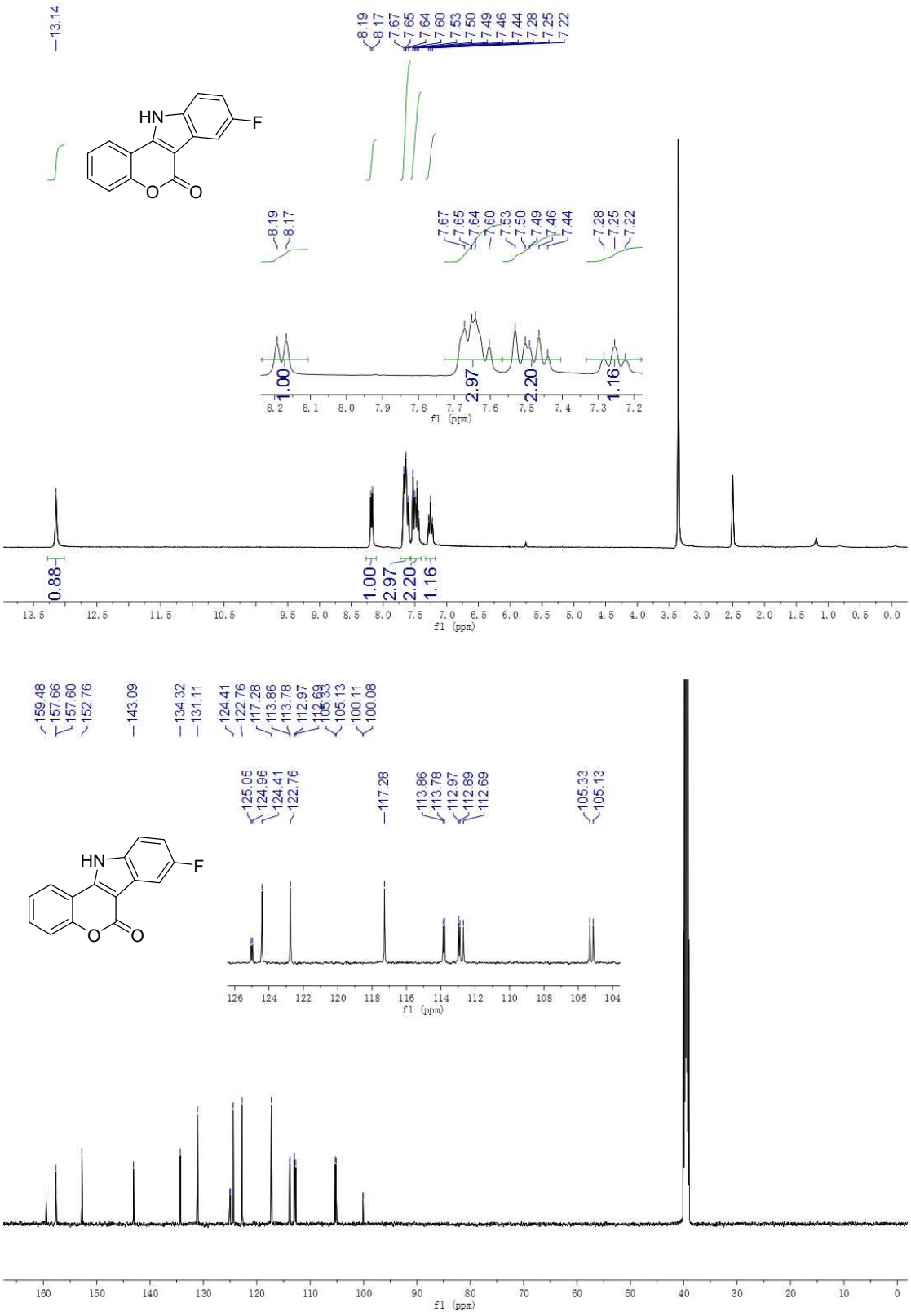


7,9-dimethylchromeno[4,3-*b*]indol-6(11*H*)-one (4c) (in DMSO-*d*)

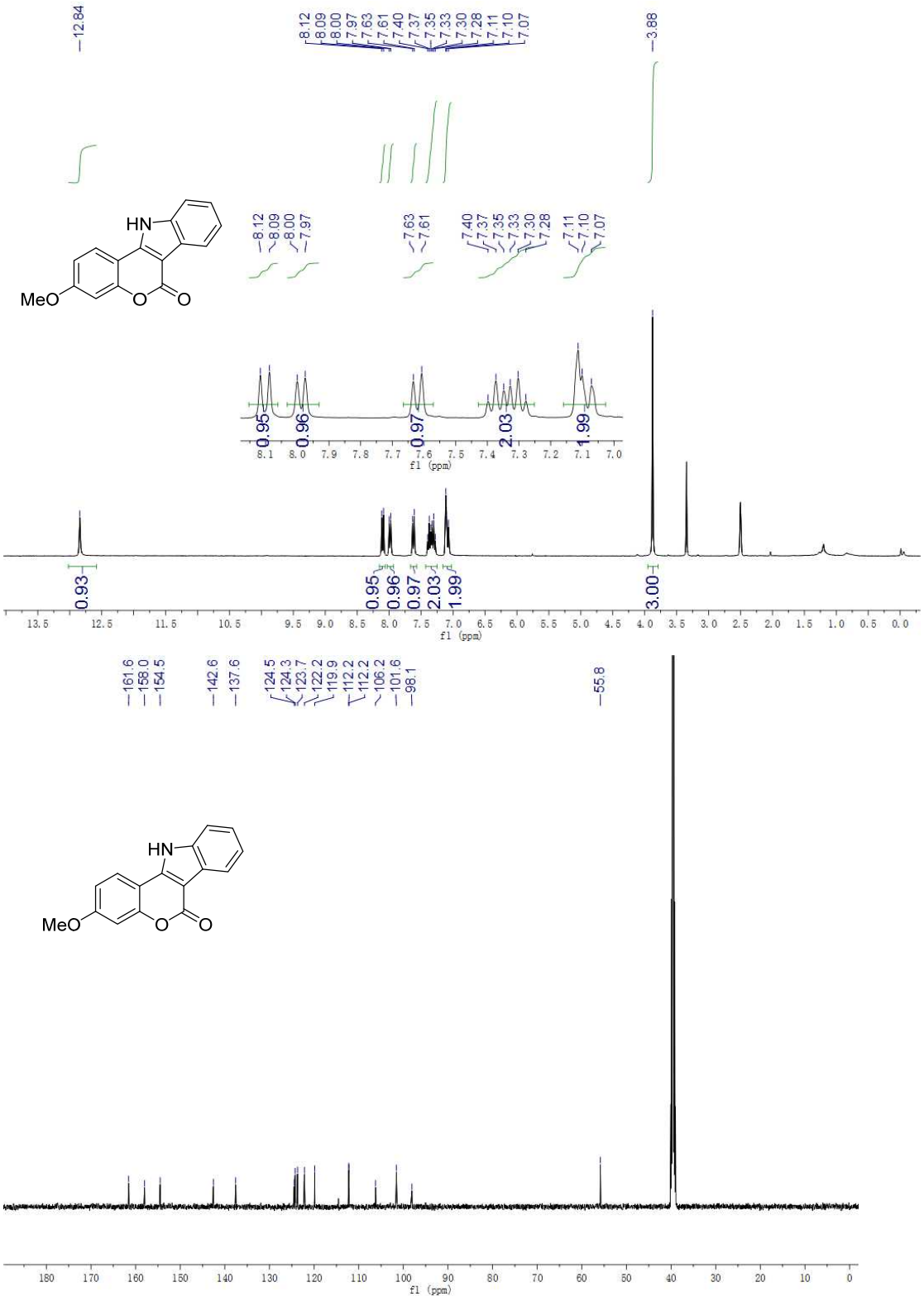




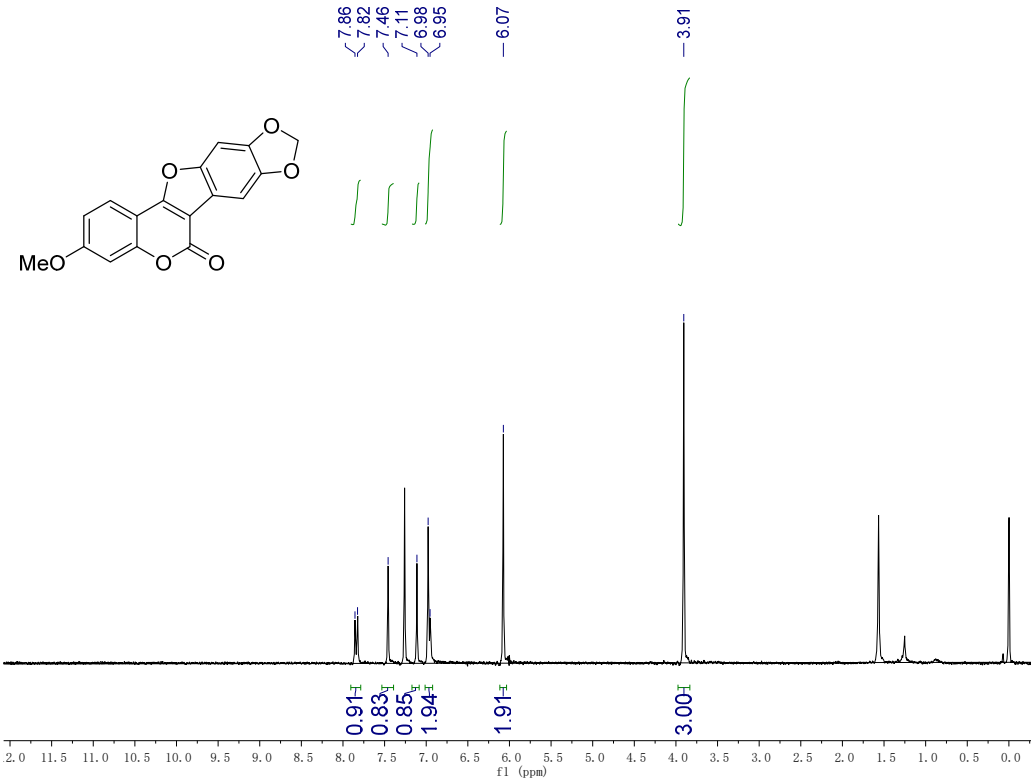
8-fluorochromeno[4,3-*b*]indol-6(11*H*)-one (4d) (in DMSO-*d*)



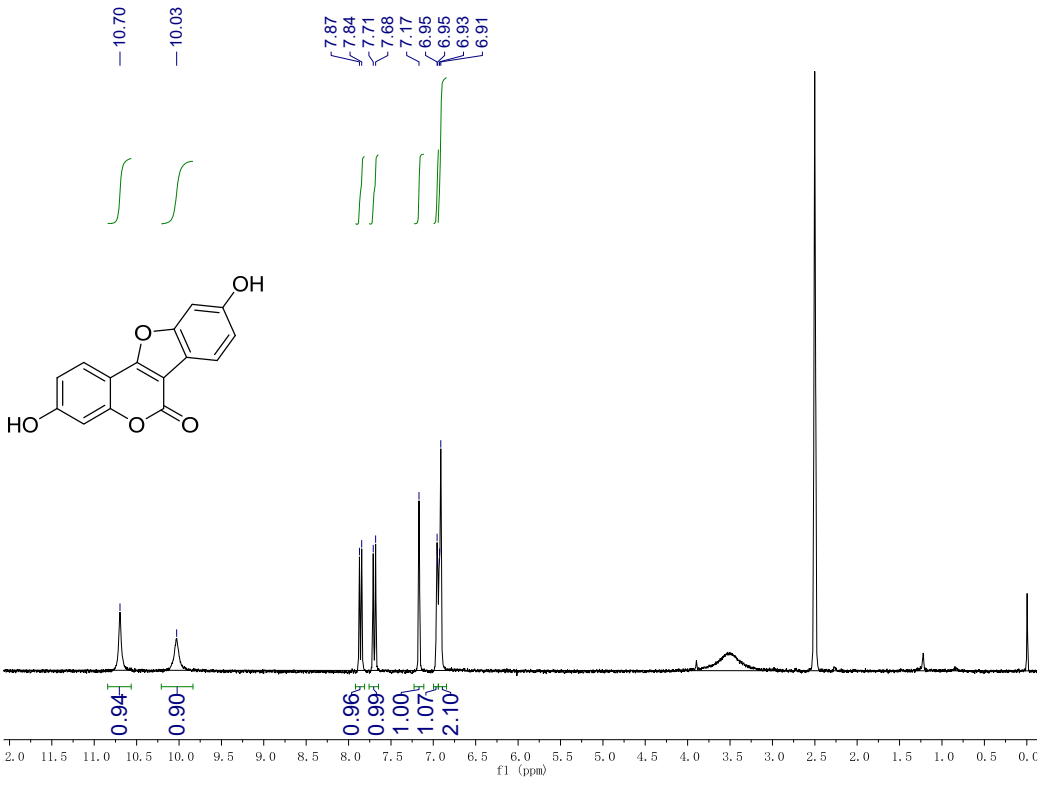
3-methoxychromeno[4,3-*b*]indol-6(11*H*)-one (4e) (in DMSO-*d*)



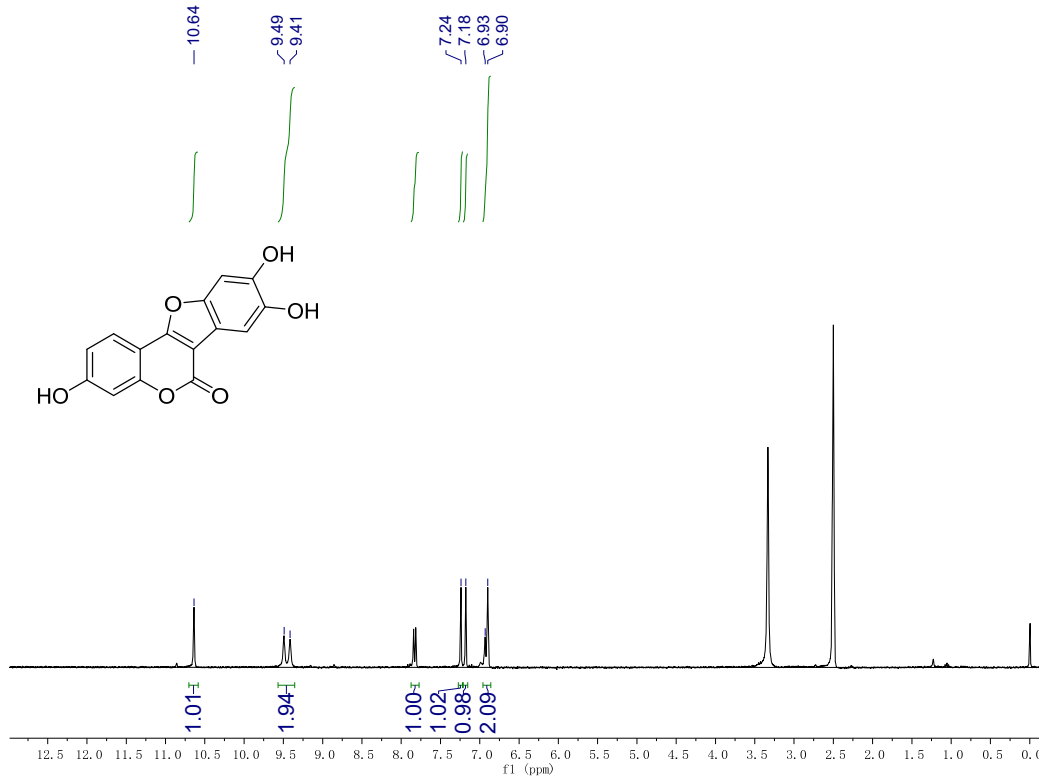
3-methoxy-6*H*-[1,3]dioxolo[4',5':5,6]benzofuro[3,2-*c*]chromen-6-one (flemichapparin C)



3,9-dihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (coumestrol) (in DMSO-*d*)



3,8,9-trihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (5) (in DMSO-*d*)



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