Electronic Supplementary Material (ESI) for Green Chemistry.

Synthesis of spiro[2,3-dihydrofuran-3,3′-oxindole] via a multi-component cascade reaction of α-diazo esters, water, isatins and malononitrile/ethyl cyanoacetate

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General information

All reactions were carried out under air with magnetic stirring. All ^{1}H NMR, and ^{13}C NMR spectra were recorded using a Brucker-400 MHz spectrometer in CD_3OD unless otherwise noted. Tetramethylsilane (TMS) served as an internal standard (δ = 0) for ^{1}H NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). HRMS (ESI) were recorded on IonSpec FT-ICR mass spectrometer. Metal catalysts and starting materials such as isatin derivatives, amino acid derivatives, and malononitrile are all commercially available.

General procedure of the synthesis of *α*-diazo esters

Two methods were adopted to synthesize the α-diazo esters according to reported procedures[1].

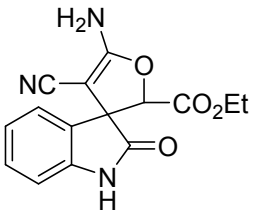
Method I: Ethyl 2-methyl-3-oxobutanoate (10 mmol, 1.0 equiv) and *p*-ABSA (11 mmol, 1.1 equiv) were dissolved in a 100 mL flask with 40 mL CH_2Cl_2. After the mixture was stirred in ice bath for 10 min, 20 mL solution of DBU (20 mmol, 2.0 equiv) in DCM was added dropwise. When the reaction was complete as monitored by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 ^{o}C and stirred for 10 min. Then the resulting mixture was extracted with diethyl ether (20 mL×3). The combination of organic phase was washed with 60 mL brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed to afford the crude product (The temperature cannot be higher than 30 ^{o}C due to the volatile property of the products). The crude product was then purified by the chromatography column on silica gel. Using petroleum ether with low boiling point (30 ^{o}C) as the elution, the pure products were obtained.

Method II: To the mixture of 50 mL of water and dichloromethane (v/v = 1/1), 2-ethoxy-2-oxoethanaminium chloride (10 mmol) and sodium nitrite (10 mmol) were added. Then 1 M sulfuric acid (0.1 mmol) was added dropwise with funnel at 0 ^{o}C. When the reaction was finished, the resulting yellow DCM solution was washed with $NaHCO_3$ to eliminate the remaining acid. Then the resulting mixture was extracted with diethyl ether (20 mL×3). The combination of organic phase was washed with 60 mL brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed to afford the crude product (The

temperature cannot be higher than 30 °C due to the volatile property of the products). The crude product was then purified by the chromatography column on silica gel. Using petroleum ether with low boiling point (30 °C) as the elution, the pure products were obtained.

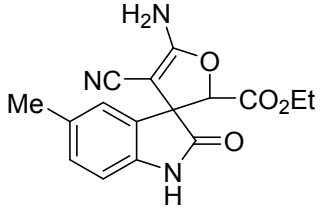
General procedure for synthesis of 6

A mixture of glycine ethyl ester hydrochloride (**1a**) and sodium nitrite in 5 mL EtOAc and 5 mL water, was added H_2SO_4 dropwise at -5 ℃. Then the EtOAc layer was syringed to the mixture of in situ-generated isatylidene malononitriles **5** (0.5 mmol) from **3** and **4** at 80 ℃, and $Cu(OTf)_2$ in 5 mL water over one hour via syringe pump at 80 ℃. When the reaction was complete as monitored by TLC, the reaction mixture was separated by funnel, then the aqueous phase was extracted with ethyl acetate (5 mL×3). The combined organic layers were dried with Na_2SO_4. After filtration, the crude product was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 3:1 to 1:1) to provide the corresponding products *trans*-**6** (R_f = 0.25 when PE: EA = 1:1) and *cis*-**6** (R_f = 0.2 when PE: EA = 1:1).



98%, *trans*-**6a**: *cis*-**6a** =45:55

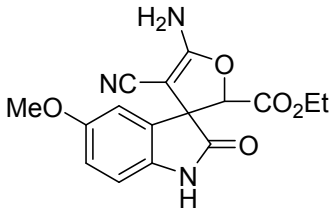
Column chromatography afforded the desired product **6a** in 98% yield as colorless solid, *trans*-**6a**: *cis*-**6a** = 45:55. *Trans*-**6a**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.39 (d, *J* = 7.4 Hz, 1 H), 7.30-7.28 (m, 1H), 7.13-7.10 (m, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.35 (s, 1H), 4.24-4.16 (m, 1H), 4.07-4.03 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.0, 170.8, 168.1, 143.2, 132.0, 130.6, 125.1, 124.2, 118.0, 111.2, 86.2, 62.9, 61.8, 56.0, 14.0. HRMS: calcd for $C_{15}H_{13}N_3O_4Na$ $[M+Na]^+$, 322.0804，found 322.0813. *Cis*-**6a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.77 (s, 2H), 7.26 (ddd, *J* = 7.8, 7.1, 1.9 Hz, 1H), 7.10-6.93 (m, 2H), 6.88 (dt, *J* = 7.7, 0.9 Hz, 1H), 5.26 (s, 1H), 3.72 (qd, *J* = 7.2, 2.4 Hz, 2H), 0.62 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) 177.6, 168.7, 166.1, 142.0, 130.0, 129.0, 124.6, 122.6, 117.4, 110.3, 84.2, 61.2, 59.9, 54.6, 13.4. HRMS: calcd for $C_{15}H_{14}N_3O_4$ $[M+H]^+$, 300.0984，found 300.0998.



90%, *trans*-**6b**: *cis*-**6b** = 44:56

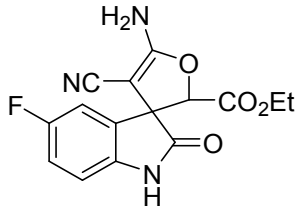
Column chromatography afforded the desired product **6b** in 90% yield as colorless solid, *trans*-**6b**:*cis*-**6b** = 44:56. *Trans*-**6b**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.21 (s, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.33 (s, 1H), 4.22-4.16 (m, 1H), 4.09-4.03 (m, 1H), 2.34 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.0,

170.8, 168.2, 140.6, 134.0, 132.1, 130.9, 125.7, 118.1, 111.0, 86.2, 62.9, 61.8, 56.1, 21.2, 14.0. HRMS: calcd for $C_{16}H_{15}N_3O_4Na$ $[M+Na]^+$, 336.0960，found 336.0954. *Cis*-**6b**: ^1H NMR (400 MHz, CD_3OD): δ 7.09 (d, *J* = 7.9 Hz, 1H), 6.91 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.26 (s, 1H), 3.86-3.71 (m, 2H), 2.29 (s, 3H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR(100 MHz, CD_3OD): δ 180.0, 170.7, 167.4, 140.2, 133.7, 131.2, 129.6, 126.5, 117.9, 111.1, 85.9, 62.6, 61.8, 55.8, 21.0, 13.8. HRMS: calcd for $C_{16}H_{15}N_3O_4Na$ $[M+Na]^+$, 336.0960，found 336.0950.



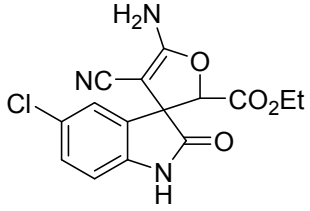
88%, *trans*-**6c**: *cis*-**6c** = 42:58

Column chromatography afforded the desired product **3c** in 88% yield as colorless solid, *trans*-**6c**:*cis*-**6c** = 42:58. *Trans*-**6c**: ^1H NMR (400 MHz, CD_3OD): δ 7.03 (d, *J* = 2.1 Hz, 1H), 6.87-6.81 (m, 2H), 5.36 (s, 1H), 4.24-4.07 (m, 2H), 3.79 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.0, 170.8, 168.1, 158.0, 136.3, 133.2, 118.0, 115.7, 113.8, 111.8, 86.1, 62.9, 62.2, 56.3, 56.1, 14.0. HRMS: calcd for $C_{16}H_{16}N_3O_5$ $[M+H]^+$330.1090，found 330.1085. *Cis*-**6c**: ^1H NMR (400 MHz, CD_3OD): δ 6.85 (d, *J* = 2.4 Hz, 2H), 6.69 (s, 1H), 5.27 (s, 1H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 0.77 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR(100 MHz, CD_3OD): δ 179.9, 170.7, 167.4, 157.7, 135.9, 131.0, 117.8, 115.9, 112.6, 111.90, 85.8, 62.6, 62.2, 56.3, 55.8, 13.8. HRMS: calcd for $C_{16}H_{15}N_3O_5Na$ $[M+Na]^+$ 352.0909，found 352.0910.



93%, *trans*-**6d**: *cis*-**6d** = 48:52

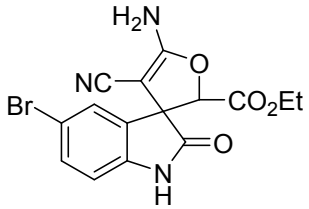
Column chromatography afforded the desired product **6d** in 93% yield as colorless solid, *trans*-**6d**: *cis*-**6d** = 48:52. *Trans*-**6d**: ^1H NMR (400 MHz, CD_3OD): δ 7.26-7.24 (m, 1H), 7.08-7.03 (m, 1H), 6.93-6.90 (m, 1H), 5.41 (s, 1H), 4.25-4.21 (m, 1H), 4.10-4.07 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.0, 170.9, 167.9, 162.1, 159.7, 139.3, 133.6, 117.1, 113.1, 112.1, 85.8, 63.0, 62.2, 55.8, 14.0. HRMS: calcd for $C_{15}H_{12}N_3O_4FNa$ $[M+Na]^+$340.0710，found 340.0726. *Cis*-**6d**: ^1H NMR (400 MHz, CD_3OD): δ 7.07-7.02 (m, 1H), 6.92-6.88 (m, 1H), 6.87-6.84 (m, 1H), 5.29 (s, 1H), 3.85 (q, *J* = 7.1 Hz, 2H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 179.7, 170.7, 167.2, 161.7, 159.3, 138.8, 131.6, 117.4, 113.5, 112.2, 85.7, 62.7, 62.2, 55.5, 13.8. HRMS: calcd for $C_{15}H_{12}N_3O_4FNa$ $[M+Na]^+$ 340.0710，found 340.0693.



92%, *trans*-**6e**: *cis*-**6e** = 50:50

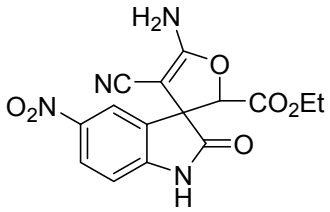
Column chromatography afforded the desired product **6e** in 92% yield as colorless solid, *trans*-**6e**:*cis*-**6e** = 50:50. *Trans*-**6e**: ^1H NMR (400 MHz, CD_3OD): δ 7.44 (d, *J* = 1.6 Hz, 1H), 7.35-7.23 (m, 1H), 6.89 (d, *J* = 8.3

Hz, 1H), 5.40 (s, 1H), 4.24-4.00 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 179.7, 170.9, 167.9, 142.0, 133.8, 130.6, 129.4, 125.7, 117.8, 112.4, 85.8, 63.0, 61.8, 55.7, 14.0. HRMS: calcd for $C_{15}H_{12}N_3O_4NaCl$ $[M+Na]^+$ 356.0414，found 356.0397. *Cis*-**6e**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.29 (dd, J = 8.3, 1.5 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.28 (s, 1H), 3.98-3.74 (m, 2H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 179.4, 170.8, 167.2, 141.6, 131.8, 130.9, 129.0, 126.1, 117.5, 112.6, 85.7, 62.8, 61.8, 55.4, 13.8. HRMS: calcd for $C_{15}H_{12}N_3O_4NaCl[M+Na]^+$ 356.0414，found 356.0406.



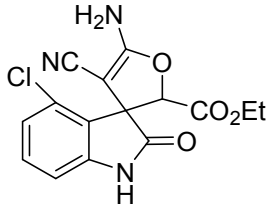
92%, *trans*-**6f**: *cis*-**6f** = 48:52

Column chromatography afforded the desired product **6f** in 92% yield as colorless solid, *trans*-**6f**:*cis*-**6f** = 48:52. *Trans*-**6f**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.56 (d, J = 1.8 Hz, 1H), 7.44 (dd, J = 8.3, 1.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 5.40 (s, 1H), 4.23-4.03 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 179.6, 170.9, 167.9, 142.5, 134.1, 133.6, 128.5, 117.8, 116.4, 112.9, 85.8, 63.0, 61.8, 55.6, 14.0. HRMS: calcd for $C_{15}H_{12}N_3O_4NaBr[M+Na]^+$ 399.9909，found 399.9891. *Cis*-**6f**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.44 (dd, J = 8.3, 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 5.28 (s, 1H), 3.87 (t, J = 7.1 Hz, 2H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 179.3, 170.8, 167.2, 142.0, 133.9, 132.2, 128.9, 117.5, 116.0, 113.0, 85.7, 62.8, 61.8, 55.4, 13.9. HRMS: calcd for $C_{15}H_{12}N_3O_4NaBr$ $[M+Na]^+$399.9909，found 399.9889.



91%, *trans*-**6g**: *cis*-**6g** = 49:51

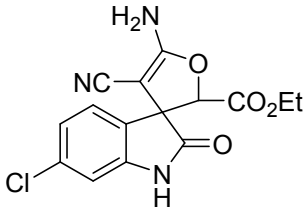
Column chromatography afforded the desired product **6g** in 91% yield as colorless solid, *trans*-**6g**: *cis*-**6g** = 49:51. *Trans*-**6g**: ^{1}H NMR (400 MHz, CD_3OD): δ 8.35 (d, J = 2.0 Hz, 1H), 8.28 (dd, J = 8.6, 2.0 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 5.53 (s, 1H), 4.23-4.05 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.1, 171.0, 167.7, 149.4, 145.2, 132.9, 127.6, 121.3, 117.6, 111.2, 85.6, 63.1, 61.6, 55.4, 14.0. HRMS: calcd for $C_{15}H_{12}N_4O_6Na$ $[M+Na]^+$ 367.0655，found 367.0670.*Cis*-**6g**: ^{1}H NMR (400 MHz, CD_3OD): δ 8.28 (dd, J = 8.6, 1.5 Hz, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 5.35 (s, 1H), 3.85 (q, J = 7.1 Hz, 2H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 179.7, 170.9, 167.1, 149.0, 144.8, 131.0, 128.0, 121.4, 117.3, 111.5, 85.7, 63.0, 61.6, 55.0, 13.9. HRMS: calcd for $C_{15}H_{12}N_4O_6Na$ $[M+Na]^+$ 367.0655，found 367.0658.



90%, *trans*-**6h**: *cis*-**6h** = 50:50

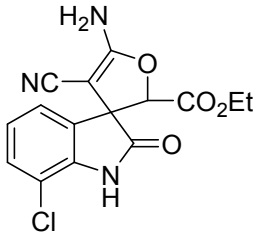
Column chromatography afforded the desired product **6h** in 90% yield as colorless solid, *trans*-**6h**:*cis*-**6h** = 50:50. *trans*-**6h**: ^{1}H NMR (400

MHz, CD_3OD): δ 7.31-7.28 (m, 1H), 7.09-7.07 (m, 1H), 6.89-6.87 (m, 1H), 5.56 (s, 1H), 4.23-4.18 (m, 1H), 4.11-4.07 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 178.9, 171.5, 168.4, 145.1, 132.4, 127.5, 125.0, 117.9, 110.2, 85.6, 82.8, 63.1, 62.6, 53.5, 14.2. HRMS: calcd for $C_{15}H_{12}N_3O_4NaCl$ $[M+Na]^+$356.0414，found 356.0424. *cis*-**6h**: ^1H NMR (400 MHz, CD_3OD): δ 7.26 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.32 (s, 1H), 4.02-3.77 (m, 2H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 178.9, 171.1, 167.0, 144.7, 132.9, 132.1, 127.1, 124.8, 110.0, 101.4, 85.4, 62.8, 62.7, 52.7, 13.8. HRMS: calcd for $C_{15}H_{12}N_3O_4NaCl$ $[M+Na]^+$ 356.0414, found 356.0406..



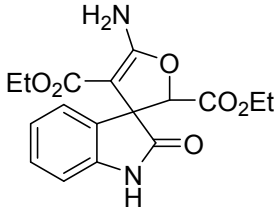
93%, *trans*-**6i:** *cis*-**6i** = 46: 54

Column chromatography afforded the desired product **6i** in 93% yield as colorless solid, *trans*-**6i**:*cis*-**6i** = 46:54. ^1H NMR (400 MHz, CD_3OD): δ 7.38 (d, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 5.37 (s, 1H), 4.23-4.18 (m, 1H), 4.09-4.04 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 178.5, 169.4, 166.5, 143.2, 134.8, 129.1, 125.1, 122.6, 116.4, 110.2, 84.4, 61.5, 60.0, 54.2, 12.6. HRMS: calcd for $C_{15}H_{13}N_3O_4Cl$ $[M+H]^+$ 334.0595，found 334.0609. *trans*-**6i** = 46:54. *cis*-**6i**: ^1H NMR (400 MHz, CD_3OD): δ 7.06 (s, 2H), 6.94 (s, 1H), 5.27 (s, 1H), 3.83 (q, *J* = 7.1 Hz, 2H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 179.7, 170.7, 167.2, 144.2, 136.6, 128.5, 127.1, 123.7, 117.6, 111.7, 85.8, 62.7, 61.6, 55.4, 13.8. HRMS: calcd for $C_{15}H_{12}N_3O_4NaCl$ $[M+Na]^+$ 356.0414，found 356.0419.



94%, *trans*-**6j**: *cis*-**6j** = 46:54

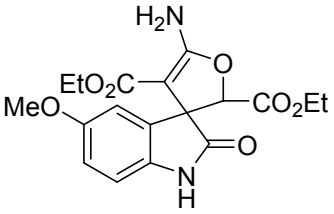
Column chromatography afforded the desired product **6j** in 94% yield as colorless solid, *trans*-**6j**:*cis*-**6j** = 46:54. *trans*-**6j**: ^1H NMR (400 MHz, CD_3OD): δ 7.36-7.29 (m, 2H), 7.13-7.09 (m, 1H), 5.37 (s, 1H), 4.23-4.19 (m, 1H), 4.09-4.06 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR(100 MHz, CD_3OD): δ 179.6, 170.9, 167.8, 141.0, 133.7, 130.6, 125.1, 123.7, 117.8, 116.4, 86.1, 63.0, 62.4, 55.8, 14.0. HRMS: calcd for $C_{15}H_{12}N_3O_4NaCl[M+Na]^+$ 356.0414，found 356.0419. *cis*-**6j**: ^1H NMR (400 MHz, CD_3OD): δ 7.31-7.29 (m, 2H), 7.04-7.02 (m, 1H), 5.29 (s, 1H), 3.81 (q, *J* = 7.1 Hz, 2H), 0.76 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 179.4, 170.7, 167.0, 140.6, 131.8, 130.9, 124.8, 124.3, 117.6, 116.6, 86.0, 62.6, 62.5, 55.5, 13.8. HRMS: calcd for $C_{15}H_{13}N_3O_4Cl$ $[M+H]^+$ 334.0595，found 334.0594.



96%, *trans*-**6k:** *cis*-**6k** = 60:40

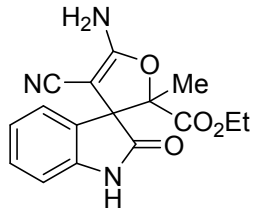
Column chromatography afforded the desired product **6k** in 96% yield as colorless solid, *trans*-**6k**:*cis*-**6k** = 60:40. *trans*-**6k**: ^1H NMR (400

MHz, CD_3OD) δ 7.20 (d, *J* = 7.7 Hz, 1H), 6.96-6.92 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.23 (s, 1H), 3.90-3.73 (m, 4H), 3.74 (d, *J* = 7.1 Hz, 2H), 0.90-0.76 (m, 3H), 0.72 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 180.0, 170.7, 167.3, 142.7, 130.9, 129.9, 125.9, 123.9, 117.8, 111.3, 85.9, 62.6, 61.8, 55.7, 13.8. HRMS: calcd for $C_{17}H_{18}N_2O_6Na$ $[M+Na]^+$, 369.1063，found 369.1068. *cis*-**6k**: ^1H NMR (400 MHz, CD_3OD) δ 7.22 (t, *J* = 7.8 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 5.23 (s, 1H), 4.22-4.17 (m, 1H), 4.10-4.06 (m, 1H), 3.88-3.62 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.90-0.75 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.4, 167.2, 142.0, 133.6, 128.2, 122.7, 122.3, 109.2, 84.8, 61.3, 58.2, 12.7. HRMS: calcd for $C_{17}H_{18}N_2O_6Na$ $[M+Na]^+$, 369.1063, found 369.1069.



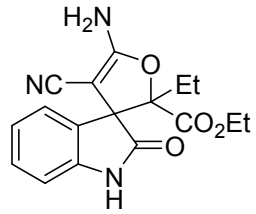
60%, *trans*-**6l**: *cis*-**6l** = 70:30

Column chromatography afforded the desired product **6l** in 60% yield as colorless solid, *trans*-**6l**:*cis*-**6l** = 70:30. *trans*-**6l**: ^1H NMR (400 MHz, CD_3OD) δ 6.79 (d, *J* = 1.2 Hz, 2H), 6.59 (s, 1H), 5.23 (s, 1H), 3.88-3.75 (m, 4H), 3.71 (s, 3H), 0.95-0.80 (m, 3H), 0.76 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 167.8, 157.3, 136.5, 114.9, 112.1, 111.1, 86.0, 62.5, 56.3, 54.8, 13.8. HRMS: calcd for $C_{18}H_{20}N_2O_7Na$ $[M+ Na]^+$, 399.1168，found 399.1167. *cis*-**6l**: ^1H NMR (400 MHz, CD_3OD) δ 6.87 (s, 1H), 6.79 (d, *J* = 1.5 Hz, 2H), 5.24 (d, *J* = 4.1 Hz, 1H), 4.22-4.17 (m, 1H), 4.10-4.07 (m, 1H), 3.88-3.71 (m, 5H), 1.28 (t, *J* = 8.6 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.6, 157.8, 136.7, 114.6, 112.1, 111.1, 86.3, 62.8, 59.8, 56.3, 14.1. HRMS: calcd for $C_{18}H_{20}N_2O_7Na$ $[M+Na]^+$, 399.1168，found 399.1176.



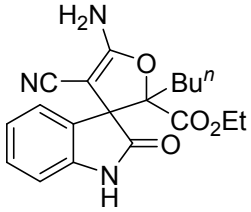
82%, *trans*-**6m**: *cis*-**6m**= 45:55

Column chromatography afforded the desired product **6m** in 82% yield as colorless solid, *trans*-**6m**:*cis*-**6m** = 45:55. *trans*-**6m**: ^1H NMR (400 MHz, CD_3OD) δ 7.18 (t, *J* = 7.5 Hz, 1H), 6.98-6.90 (m, 2H), 6.80 (d, *J* = 7.7 Hz, 1H), 3.82-3.77 (m, 1H), 3.64-3.60 (m, 1H), 1.62 (s, 3H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.7, 171.0, 169.2, 143.0, 130.8, 130.2, 125.8, 123.5, 118.6, 111.0, 92.4, 63.4, 62.8, 54.7, 20.9, 13.8. *cis*-**6m**: ^1H NMR (400 MHz, CD_3OD) δ 7.27 (d, *J* = 7.6 Hz, 1H), 7.18-7.16 (m, 1H), 6.99-6.96 (m, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 4.06-3.92 (m, 2H), 1.45 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 180.9, 171.3, 170.3, 143.7, 130.8, 128.6, 128.0, 123.4, 118.5, 111.4, 91.7, 64.7, 63.1, 55.4, 23.5, 14.0. HRMS: calcd for $C_{16}H_{15}N_3O_4Na$ $[M+H]^+$, 336.0960，found 336.0945.HRMS: calcd for $C_{16}H_{15}N_3O_4Na$$[M+Na]^+$, 336.0960, found 336.0963.



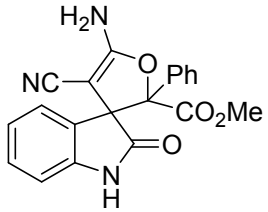
83%, *trans*-**6n**: *cis*-**6n** = 44:56

Column chromatography afforded the desired product **6n** in 83% yield as colorless solid, *trans*-**6n**:*cis*-**6n** = 44:56. *trans*-**6n**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.26-7.22 (m, 1H), 7.05-6.96 (m, 2H), 6.87 (d, *J* = 7.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.67-3.61 (m, 1H), 2.46-2.42 (m, 1H), 1.90-1.85 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.5, 170.6, 169.3, 142.8, 130.8, 125.7, 123.5, 118.6, 111.0, 96.2, 63.6, 62.8, 55.2, 30.7, 28.4, 13.8, 9.0. HRMS: calcd for $C_{17}H_{17}N_3O_4Na$ $[M+Na]^+$, 350.1117， found 350.1101.



78%, *trans*-**6o**: *cis*-**6o** = 42:58

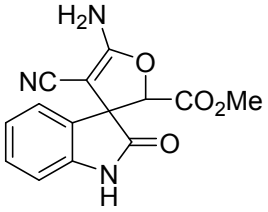
Column chromatography afforded the desired product **6o** in 78% yield as colorless solid, *trans*-**6o**:*cis*-**6o** = 42:58. *trans*-**6o**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.26-7.22 (m, 1H), 7.06-6.95 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 3.88-3.81 (m, 1H), 3.68-3.57 (m, 1H), 1.32-1.25 (m, 6H), 0.90-0.83 (m, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.5, 170.7, 169.4, 142.8, 130.8, 130.7, 125.8, 123.4, 118.6, 111.0, 95.7, 63.7, 62.7, 55.1, 34.8, 33.1, 30.8, 27.7, 23.7, 14.1. HRMS: calcd for $C_{19}H_{22}N_3O_4$ $[M+H]^+$, 356.1610， found 356.1609. *cis*-**6o**:^{1}H NMR (400 MHz, CD_3OD) δ 7.37-7.28 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 1.34-1.27 (m, 6H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 180.9, 170.4, 143.7, 130.8, 128.5, 128.3, 123.3, 118.5, 111.5, 94.5, 65.1, 63.0, 55.6, 37.4, 33.3, 30.8, 27.2, 23.6, 14.1. HRMS: calcd for $C_{19}H_{22}N_3O_4$ $[M+H]^+$, 356.1610， found 356.1594.



52%, *trans*-**6p**: *cis*-**6p** = 48:52

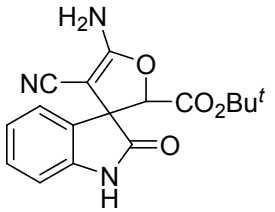
Column chromatography afforded the desired product **6p** in 52% yield as colorless solid, *trans*-**6p**:*cis*-**6p** = 48:52. *trans*-**6p**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.45 (d, *J* = 2.2 Hz, 1H), 7.96 (d, *J* = 2.5 Hz, 2H), 7.37–7.28 (m, 4H), 7.24–7.18 (m, 2H), 7.12–7.02 (m, 2H), 6.92 (d, *J* = 7.7 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.7, 169.5, 168.2, 143.0, 135.8, 130.4, 128.8, 128.2, 126.9, 126.1, 125.8, 122.4, 117.7, 110.6, 92.6, 64.1, 54.6, 53.4. HRMS: calcd for $C_{20}H_{16}N_3O_4$ $[M+H]^+$, 362.1063, found 362.1069. *cis*-**6p**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.60 (s, 1H), 8.00 (s, 2H), 7.48-7.34 (m, 3H), 7.20-7.05 (m, 3H), 6.83 (ddd, *J* = 7.7, 1.0, 0.5 Hz, 1H), 6.55 (td, *J* = 7.6, 1.1 Hz, 1H), 5.51–5.35 (m, 1H), 3.68 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6):

δ 179.6, 168.8, 168.7, 143.2, 134.6, 129.8, 129.7, 128.7, 126.7, 126.3, 126.3, 121.4, 117.5, 110.2, 93.0, 64.1, 55.4, 53.2. HRMS: calcd for $C_{20}H_{16}N_3O_4$ $[M+H]^+$, 362.1063, found 362.1071.



99%, (80% in gram scale)
trans-**6q**: *cis*-**6q** = 48:52

Column chromatography afforded the desired product **6q** in 99% yield as colorless solid, *trans*-**6q**:*cis*-**6q** = 48:52. *trans*-**6q**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.28 (s, 1H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.0, 170.8, 168.7, 143.1, 132.1, 130.7, 125.1, 124.3, 117.9, 111.3, 86.3, 61.8, 56.1, 52.9. HRMS: calcd for $C_{14}H_{12}N_3O_4[M+H]^+$, 286.0828，found 286.0822. *cis*-**6q**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.30-7.27 (m, 1H), 7.11-7.08 (m, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.32 (s, 1H), 3.34 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.0, 170.8, 167.9, 142.6, 131.0, 129.7, 125.7, 123.8, 117.8, 111.3, 86.0, 61.8, 55.6, 52.6. HRMS: calcd for $C_{14}H_{12}N_3O_4[M+H]^+$, 286.0828，found 286.0825.



92%, *trans*-**6r**: *cis*-**6r**= 42:58

Column chromatography afforded the desired product **6r** in 92% yield as colorless solid, *trans*-**6r**:*cis*-**6r** = 42:58. *trans*-**6r**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.16 (s, 1H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.4, 169.1, 164.6, 141.4, 129.5, 128.9, 124.8, 122.6, 116.4, 109.9, 84.6, 83.1, 60.4, 54.4, 26.2. HRMS: calcd for $C_{17}H_{17}N_3O_4Na$ $[M+ Na]^+$, 350.1117，found 350.1131. *cis*-**6r**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, *J* = 7.4 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 5.25 (s, 1H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 180.2, 170.9, 166.8, 143.2, 131.8, 130.5, 125.2, 124.1, 118.1, 111.1, 86.2, 84.7, 61.5, 55.7, 28.0. HRMS: calcd for $C_{17}H_{17}N_3O_4Na$ $[M+Na]^+$, 350.1117，found 350.1100.

Procedure for the scale-up synthesis of 6q.

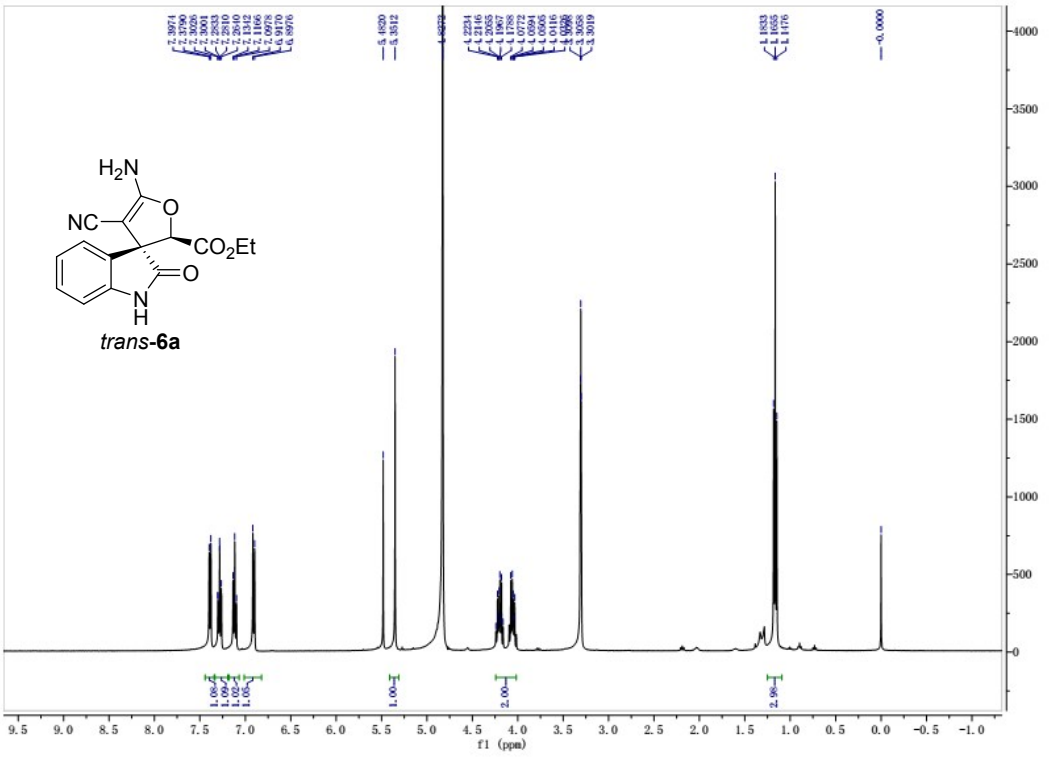
To the 400 mL aqueous solution of **1q** (154 mmol) and sodium nitrite, was added 100 mL EtOAc and 100 mL water. Then 1 M sulfuric acid (1.54 mmol) was added dropwise with funnel at -5 °C. The resulting yellow EtOAc solution was washed with $NaHCO_3$ to eliminate the remaining acid. In the other 1000 mL flask, 200 mL EtOAc/H_2O mixture with isatin **3a** (38.60 mmol) was mixed with 200 mL EtOAc/H_2O mixture with malononitrile **4a** at 80 °C

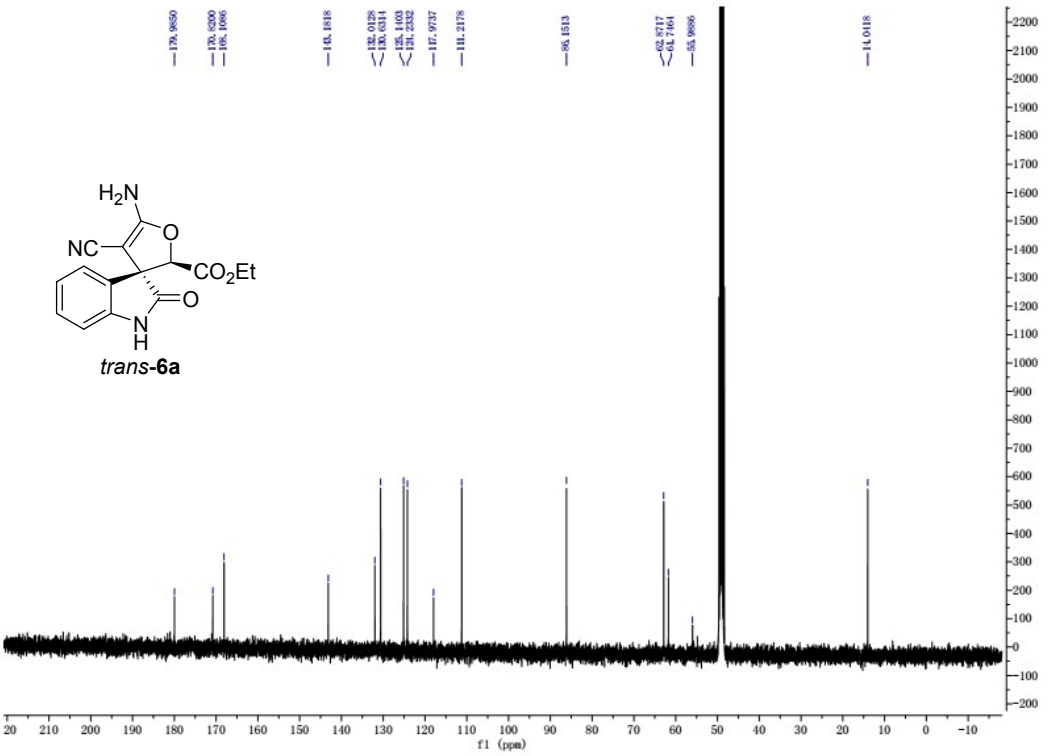
for 1 h. Then the *in situ*-generated methyl diazoacetate **2q** was added slowly to the solution of isatylidene malononitrile **5a** with 20 mol% $Cu(OTf)_2$ in 400 mL water. After all the methyl diazoacetate added within 2 h, the crude product in organic phase was separated with a funnel and the aqueous phase was extracted with EtOAc (50 mL×3). The combined organic phases were washed with Na_2CO_3, and then brine. Then anhydrous Na_2SO_4 (50 g) was added to the final product solution. After filtration, the solvent was removed to afford solid crude product, which then underwent recrystallization in the mixture of EtOAc and petroleum ether. Eventually, **6q** was obtained (11.4 g, 80% yield) as yellowish white solid.

References

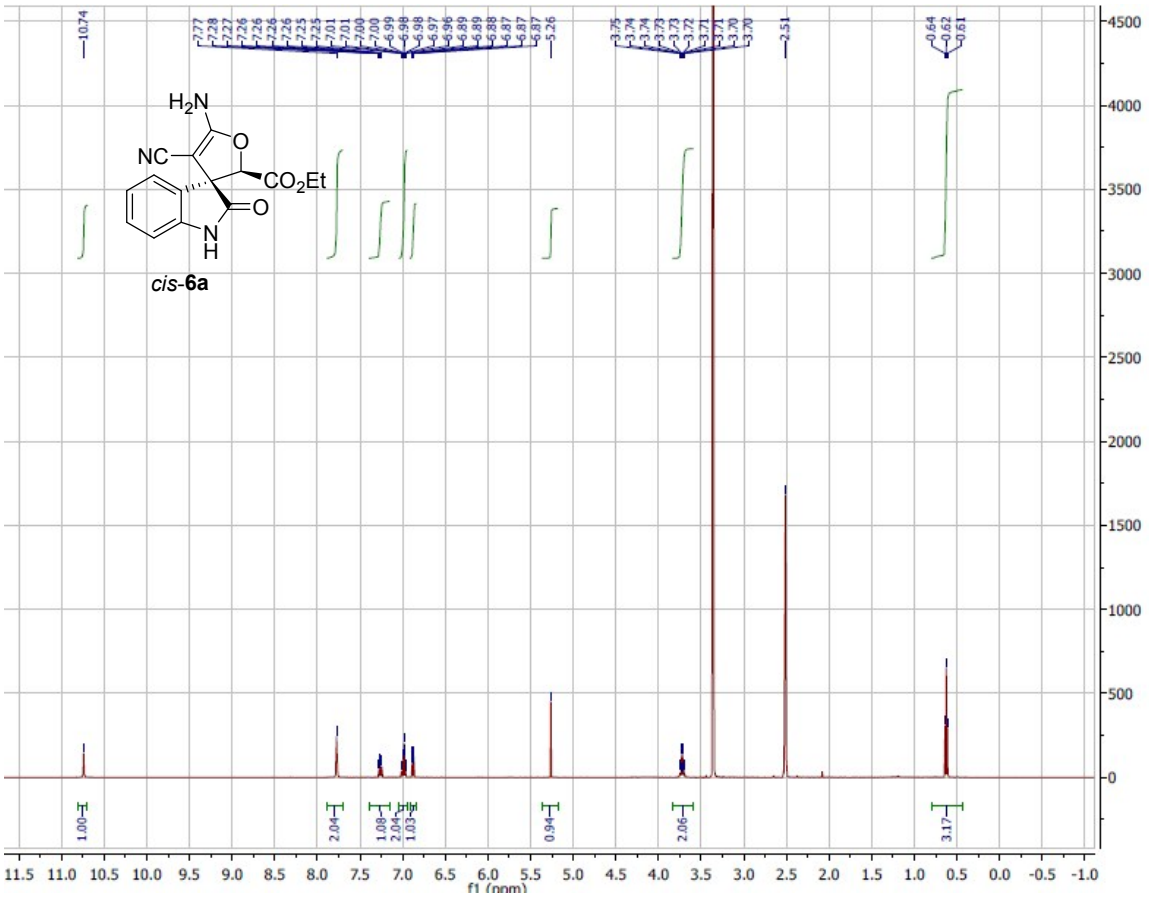
1. a) Z. Q. Guo, T. D Shi, J. Jiang, L. Yang and W. H. Hu, *Org. Biomol. Chem.*, 2009, **7**, 5028; b) Y. Qian, X. F. Xu, L. Q. Jiang, D. Prajapati and W. H. Hu, *J. Org. Chem.*, 2010, **75**, 7483; c) Y. Qian; C. C Jing; T. D. Shi, J. J. Ji, M. Tang, J. Zhou, C. W. Zhai and W. H. Hu, *Chemcatchem.*, 2011, **3**, 653.

NMR spectra for the products

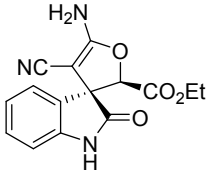




trans-**6a**



cis-**6a**



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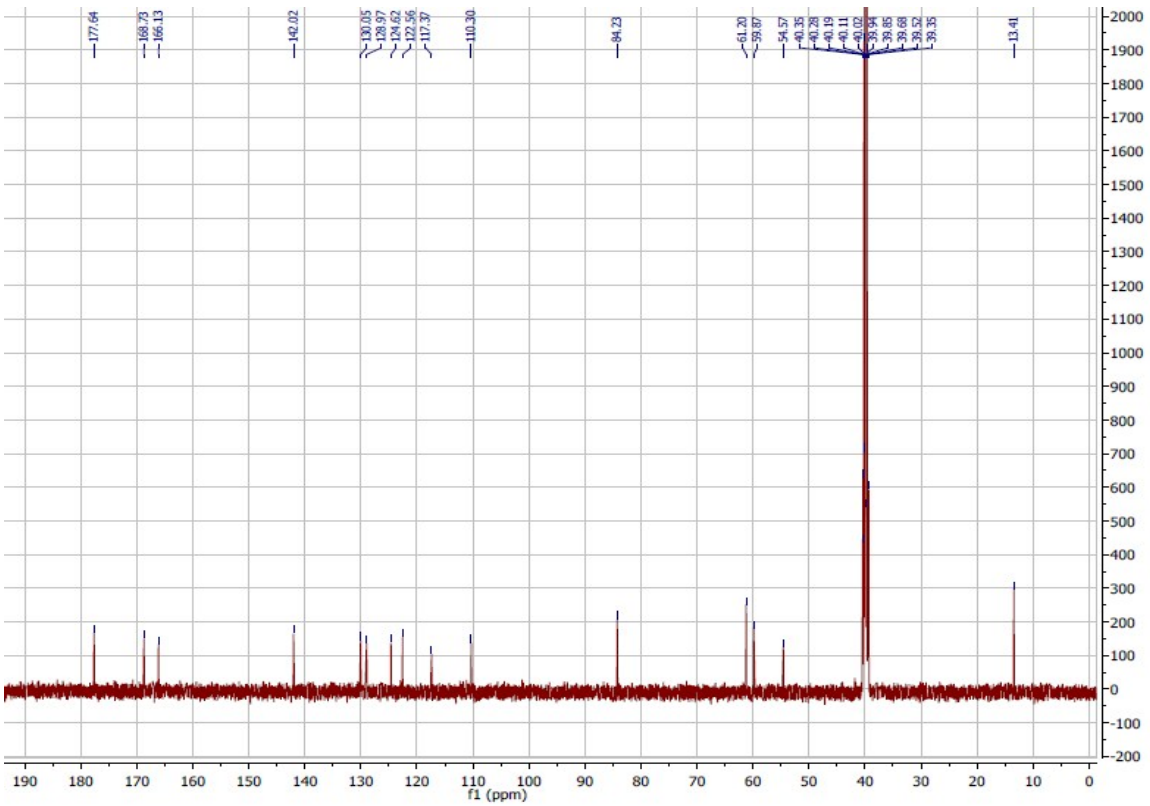
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59.87
54.57
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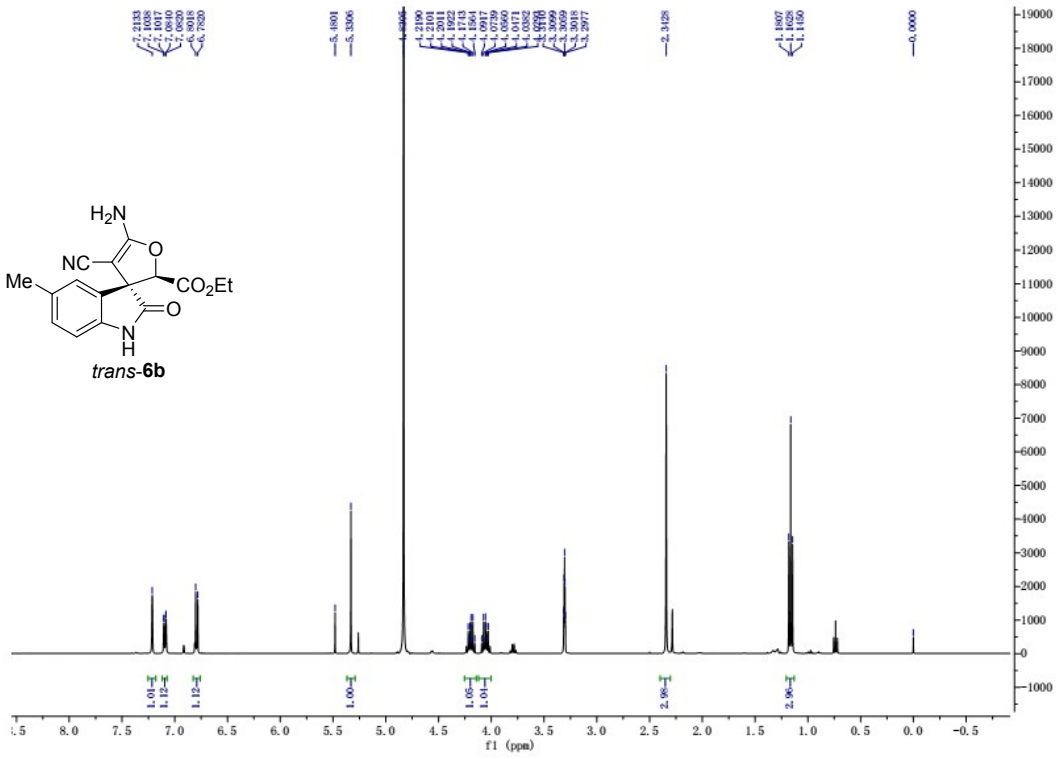
40.11
40.02
39.94
39.85
39.68
39.52
39.35
13.41
f1 (ppm)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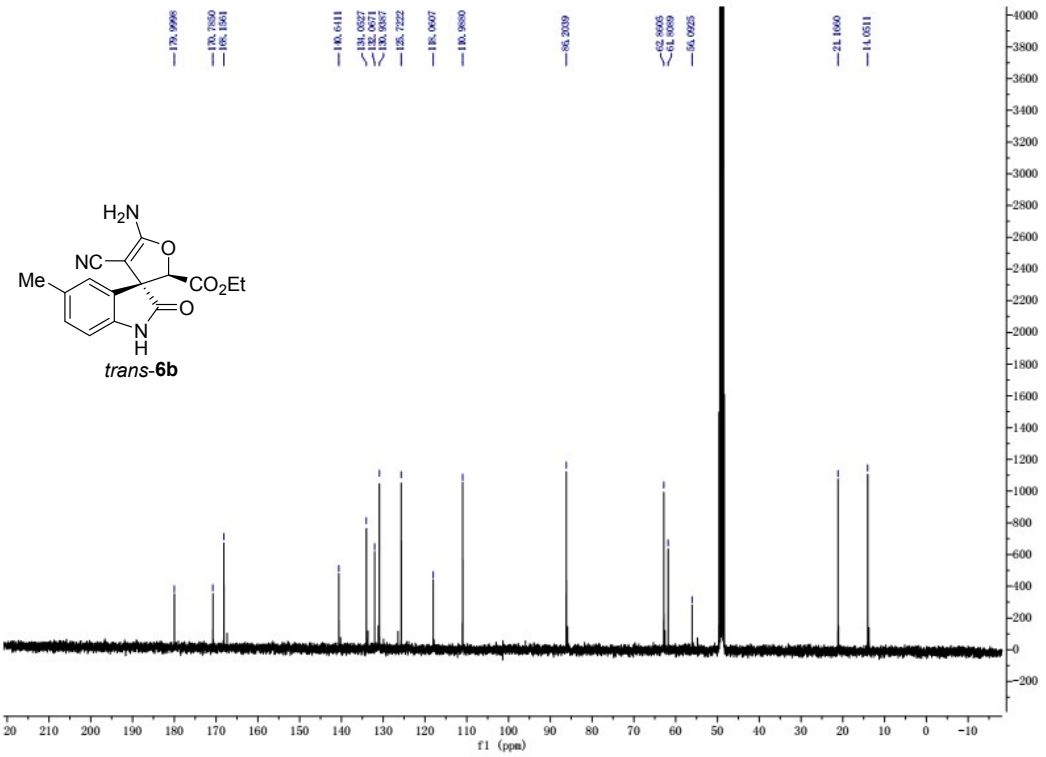
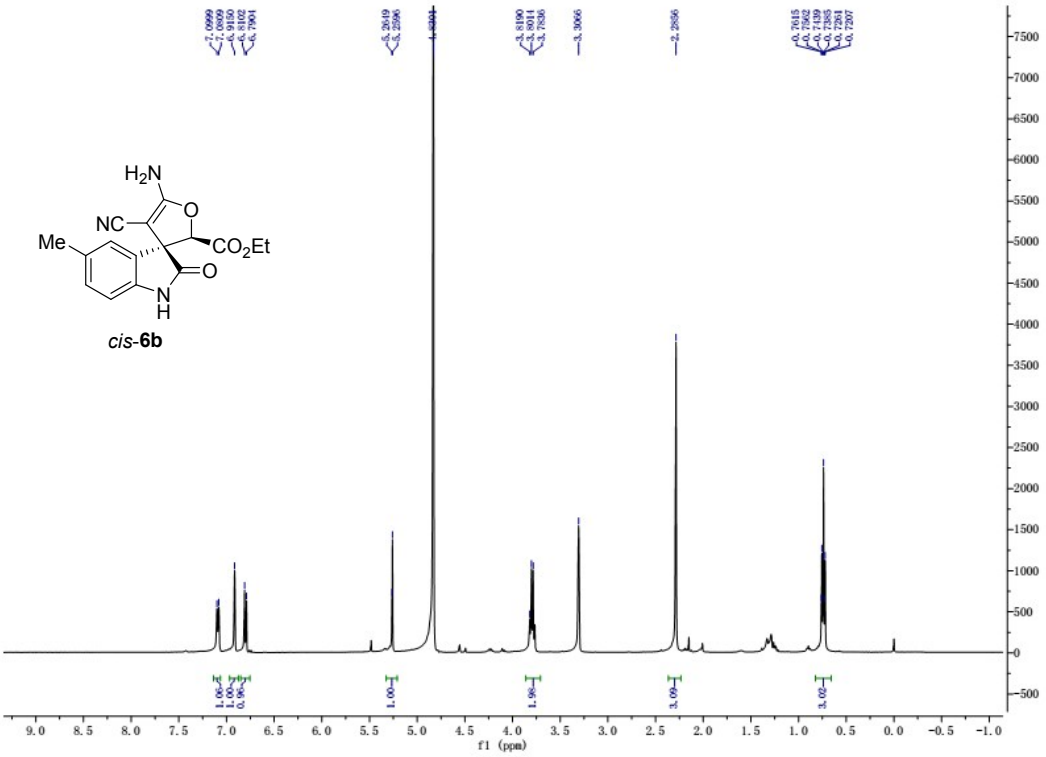
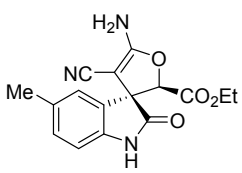
trans-**6b**



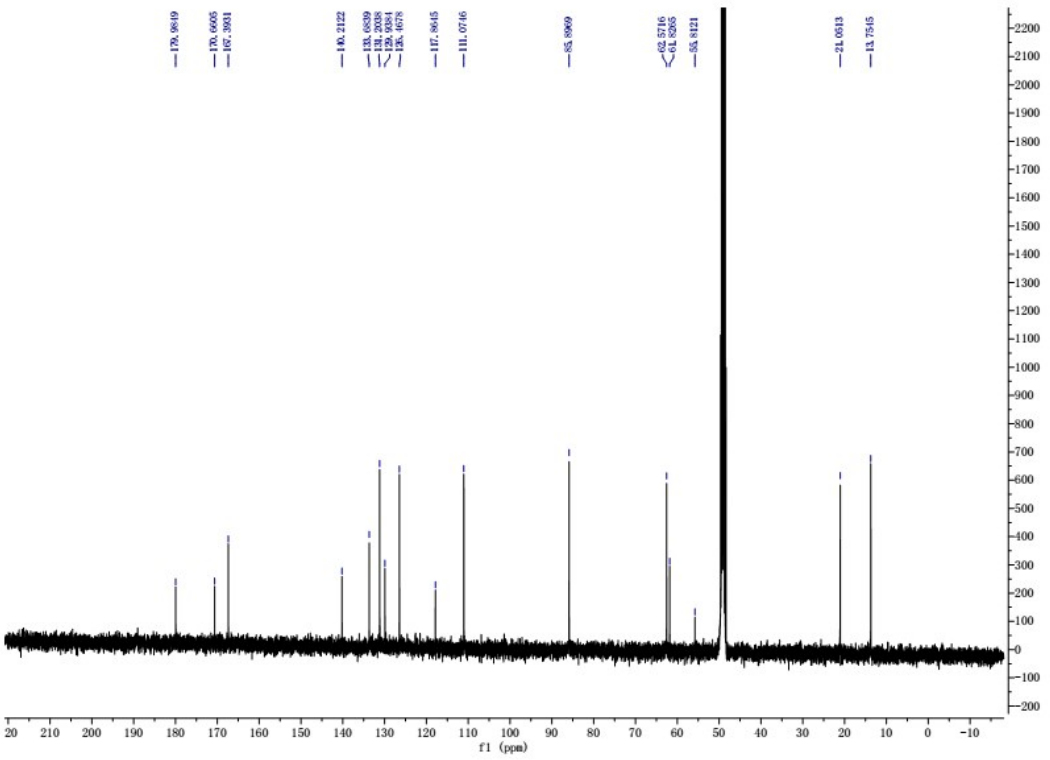
trans-**6b**



cis-**6b**



cis-**6b**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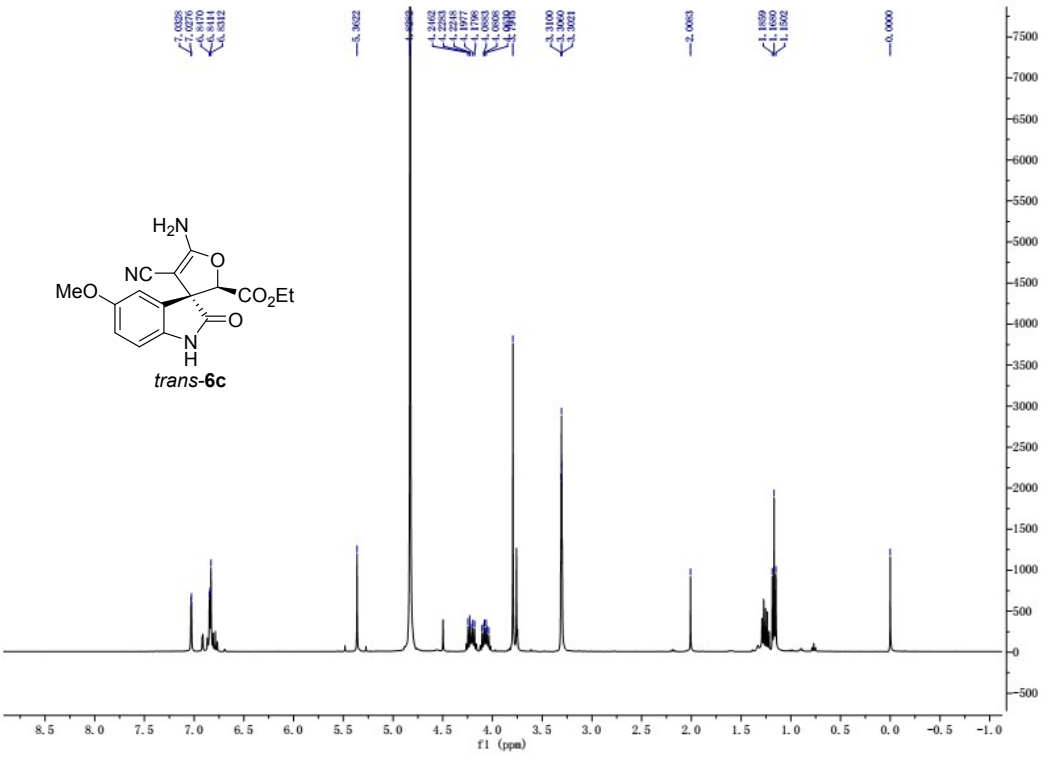
f1 (ppm)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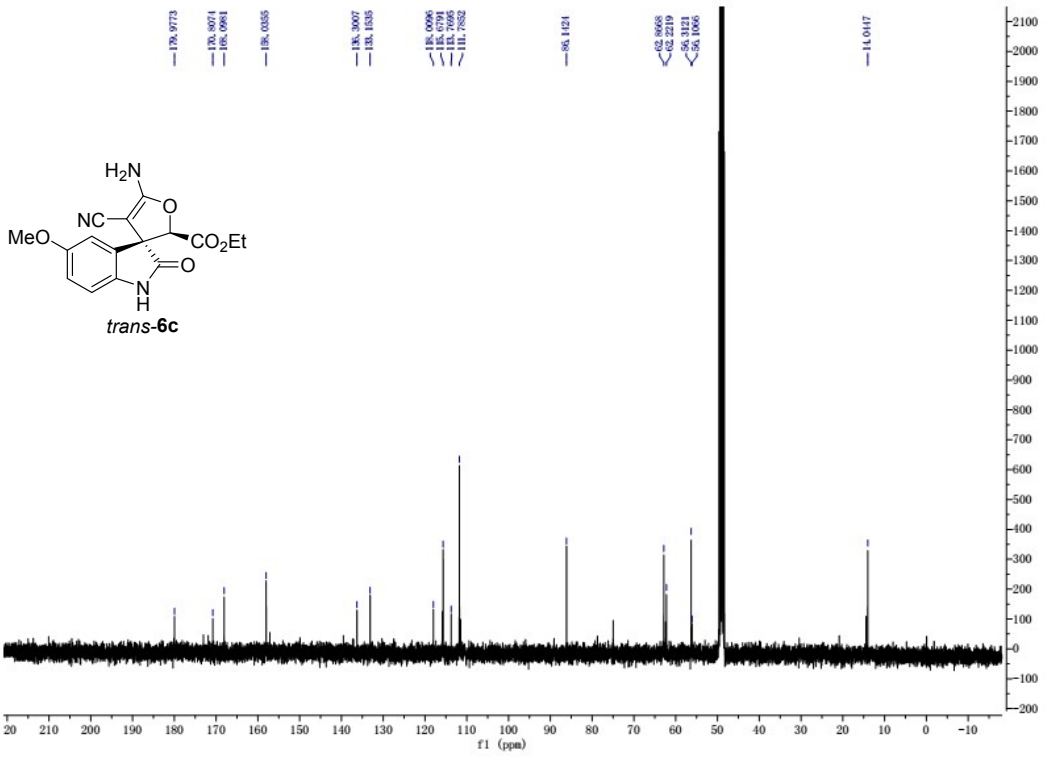
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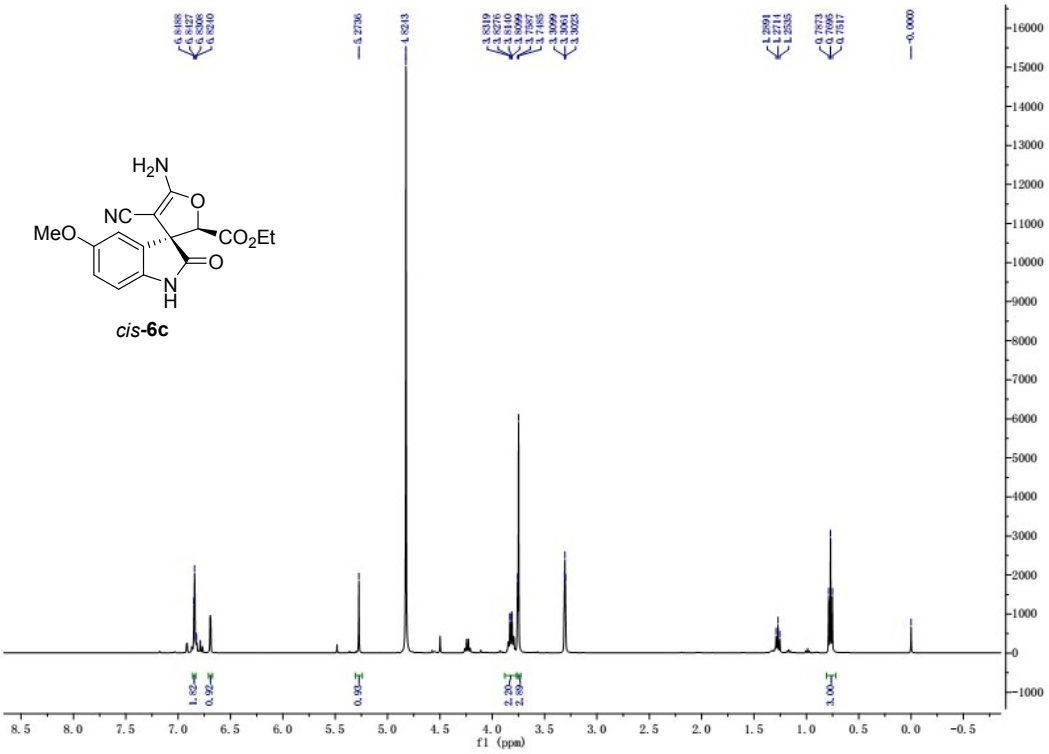
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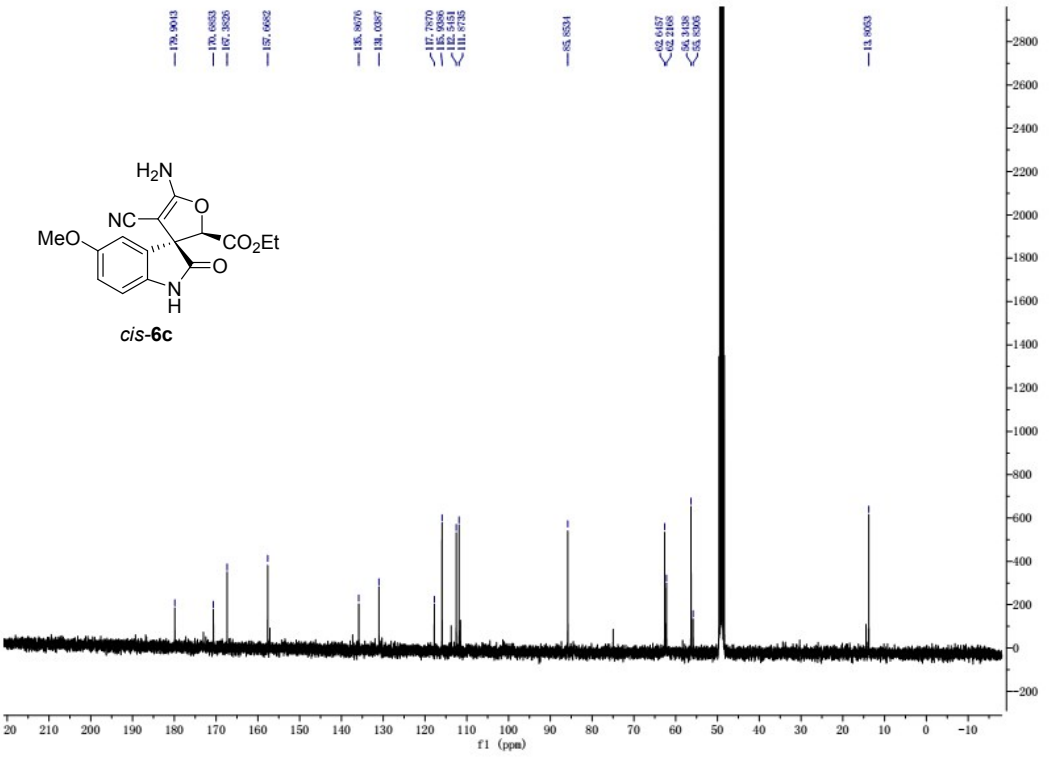
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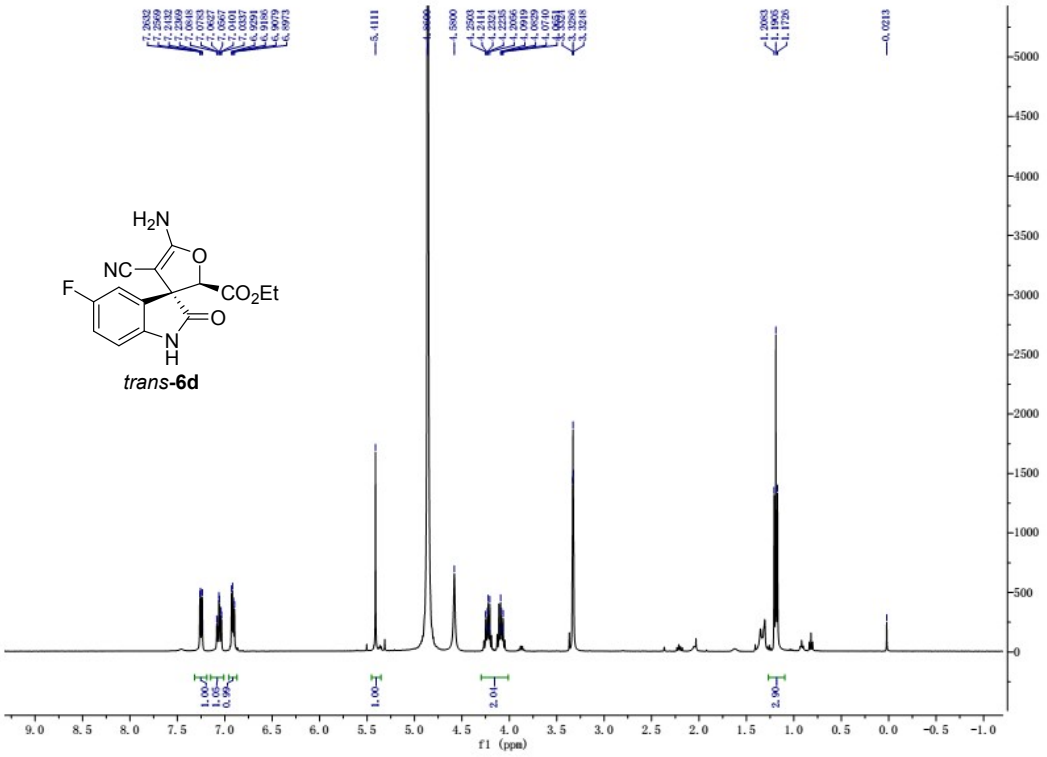
f1 (ppm)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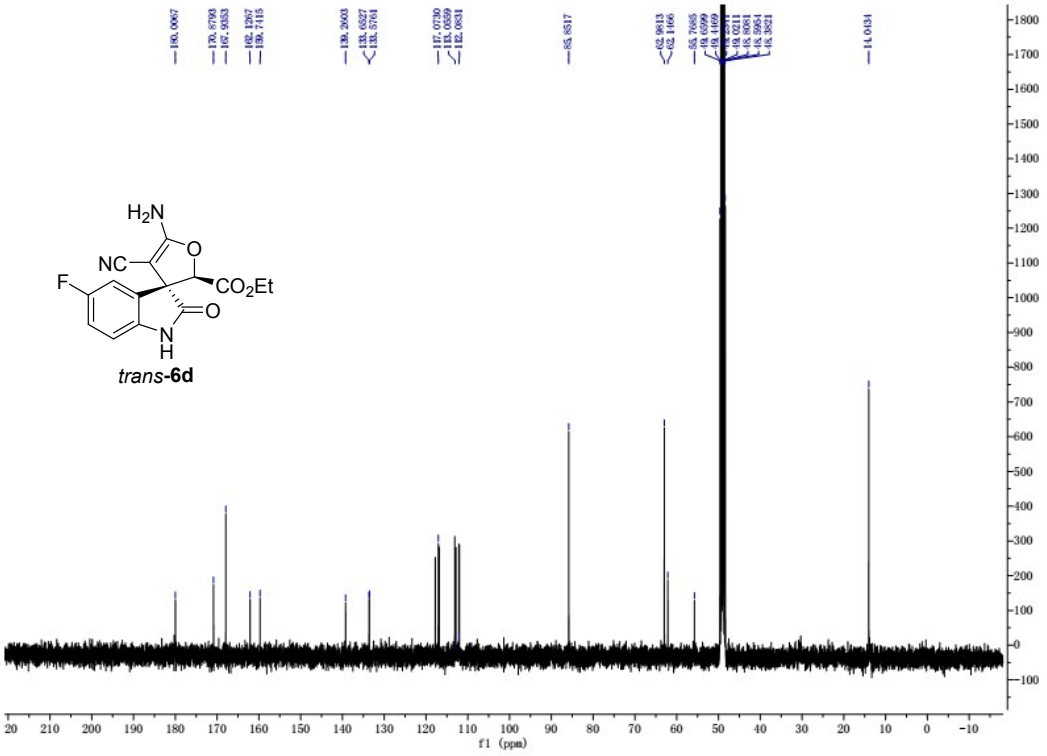
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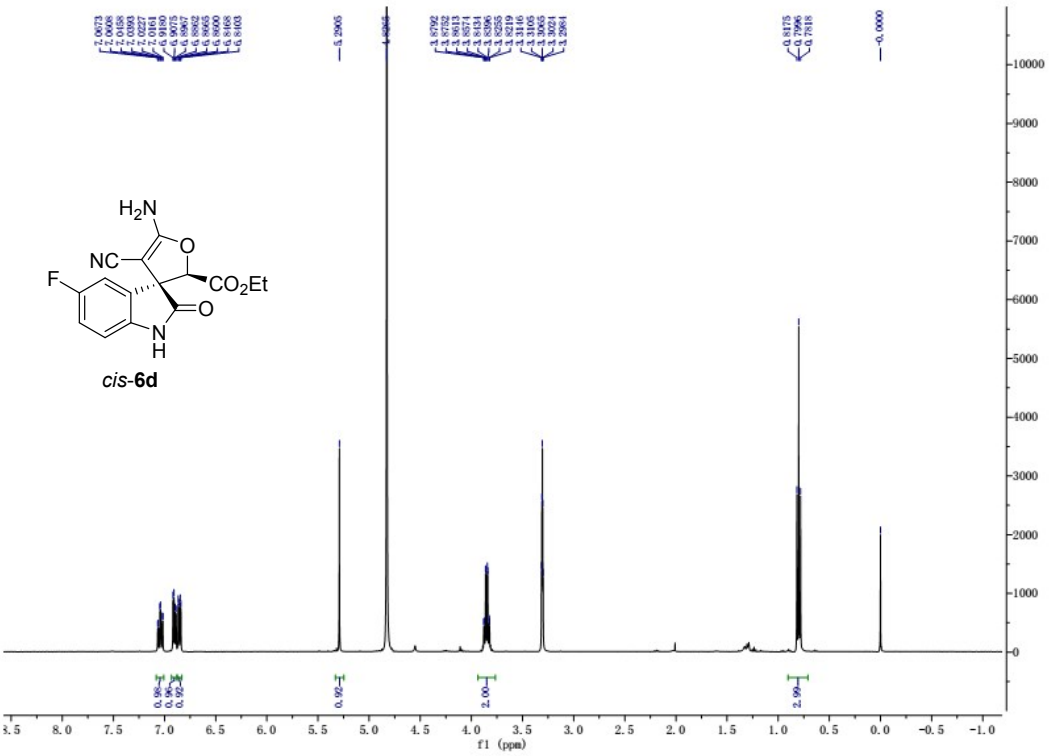
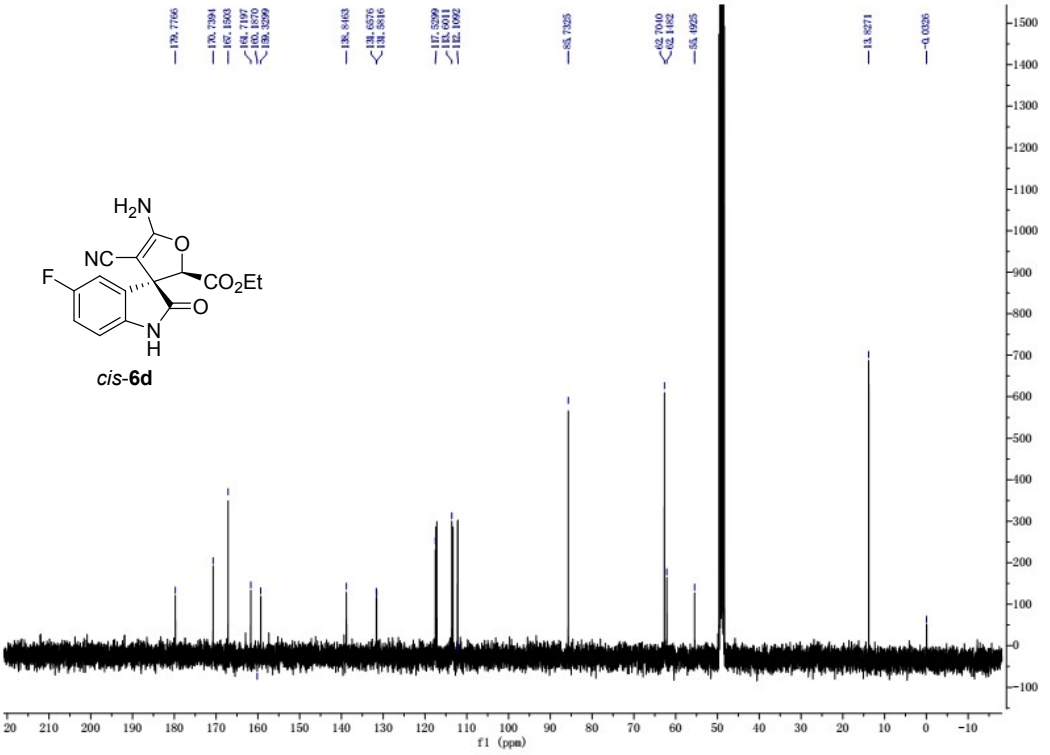
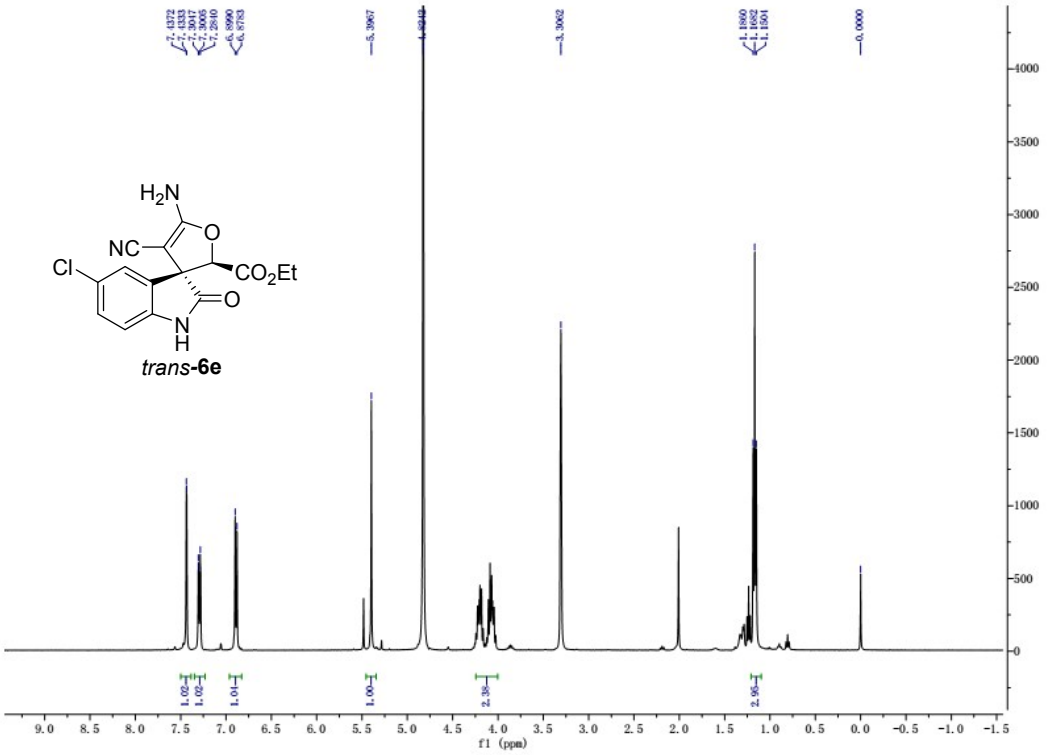
O
F
CO2Et
O
N
H
trans-6d
f1 (ppm)


H2N
NC
O
F
CO2Et
O
N
H
cis-6d
f1 (ppm)


H2N
NC
O
F
CO2Et
O
N
H
cis-6d
f1 (ppm)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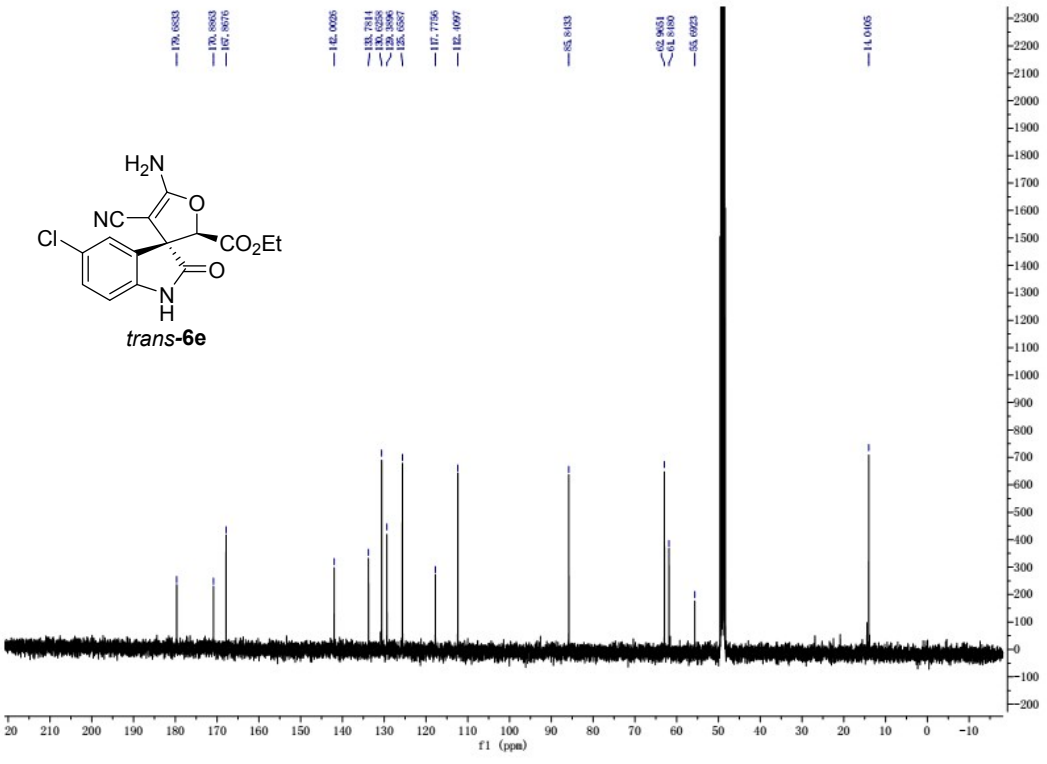
NC
O
Cl
CO2Et
O
N
H
trans-6e
f1 (ppm)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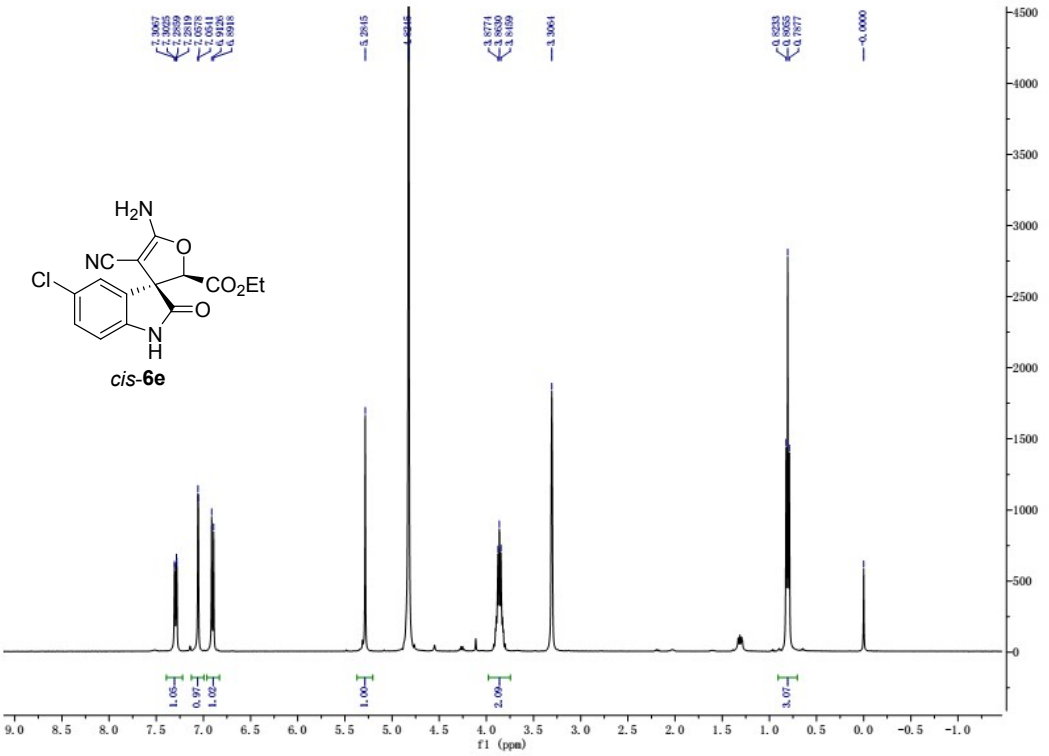
NC
O
Cl
CO2Et
O
N
H
trans-6e
f1 (ppm)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NC
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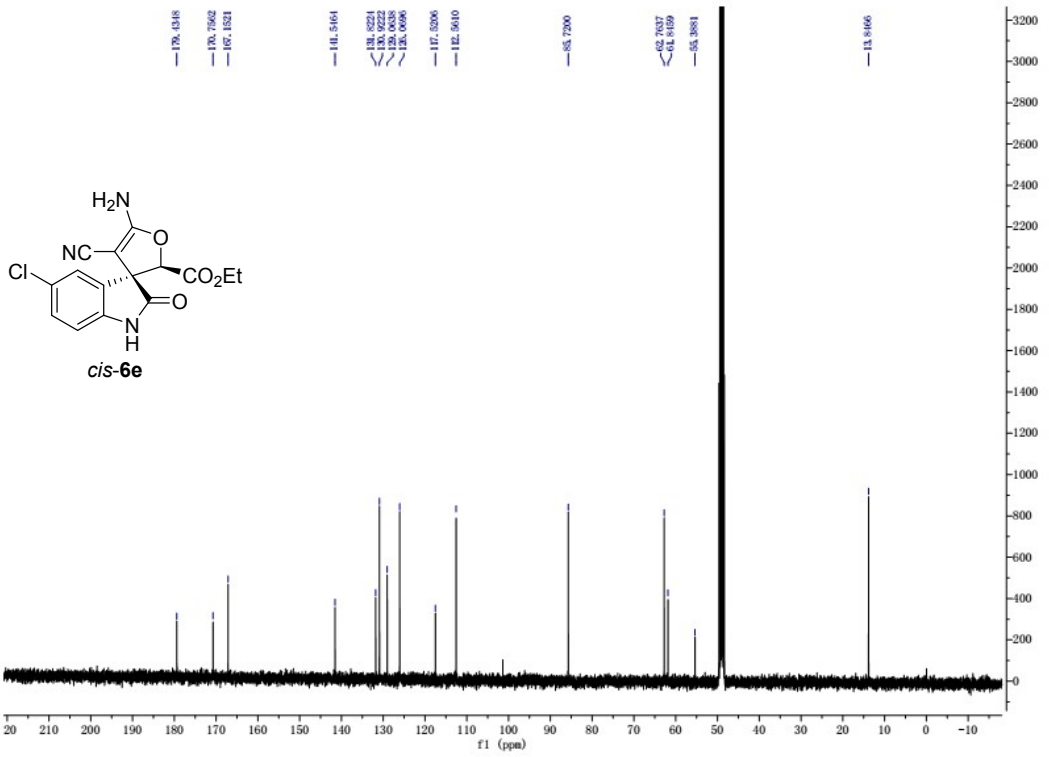
Cl
CO2Et
O
N
H
cis-6e
f1 (ppm)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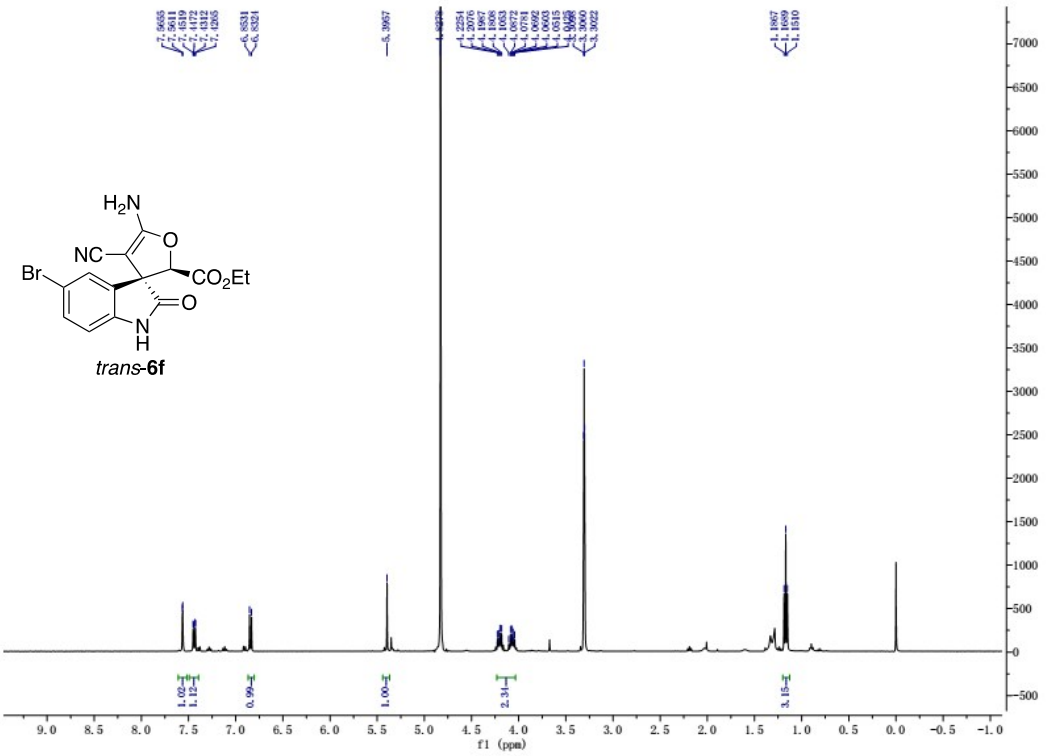
Cl
CO2Et
O
N
H
cis-6e
f1 (ppm)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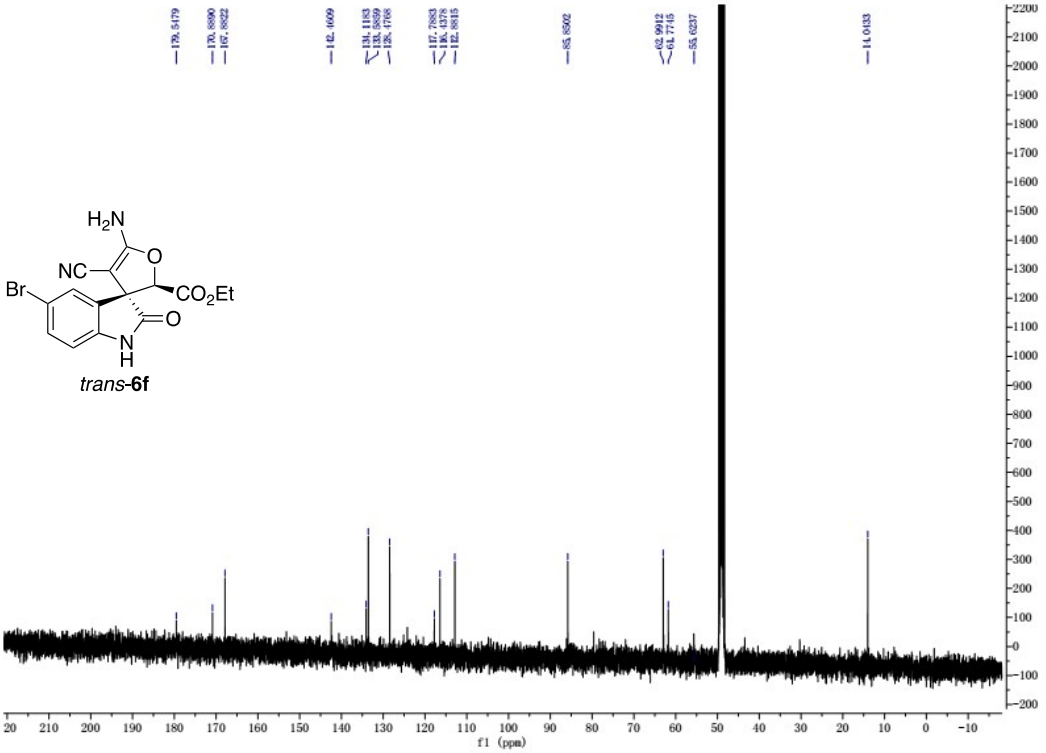
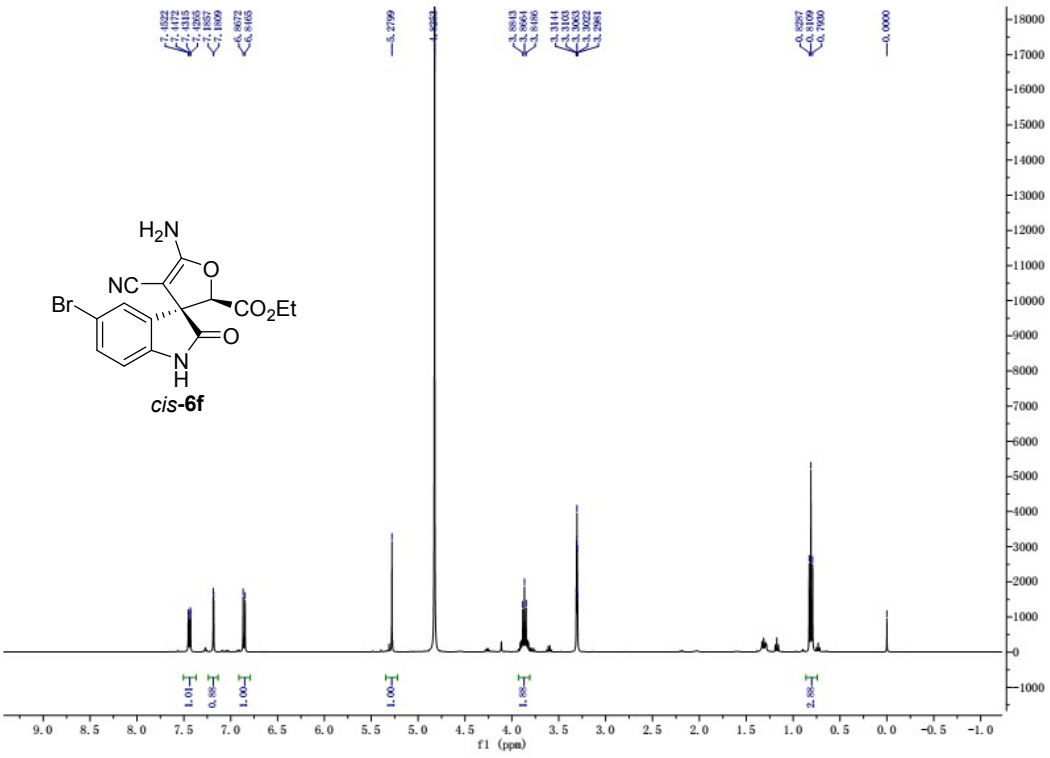
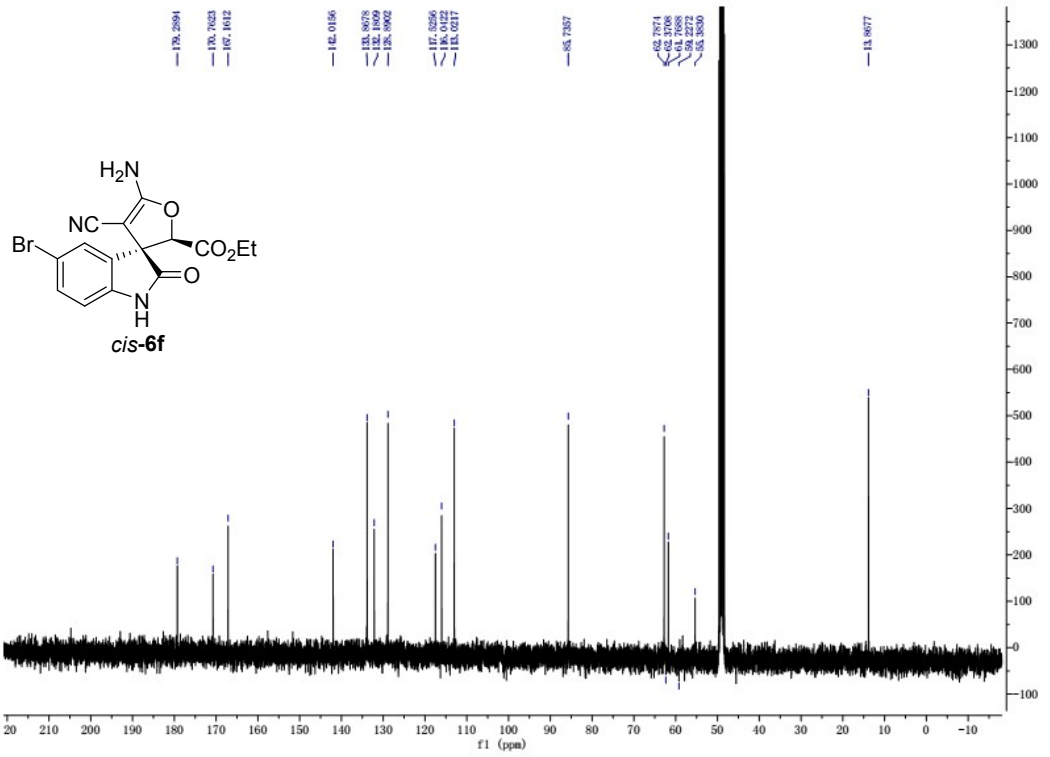
NC
O
Br
CO2Et
O
N
H
trans-6f
f1 (ppm)


H2N
NC
O
Br
CO2Et
O
N
H
trans-6f
f1 (ppm)


H2N
NC
O
Br
CO2Et
O
N
H
cis-6f
f1 (ppm)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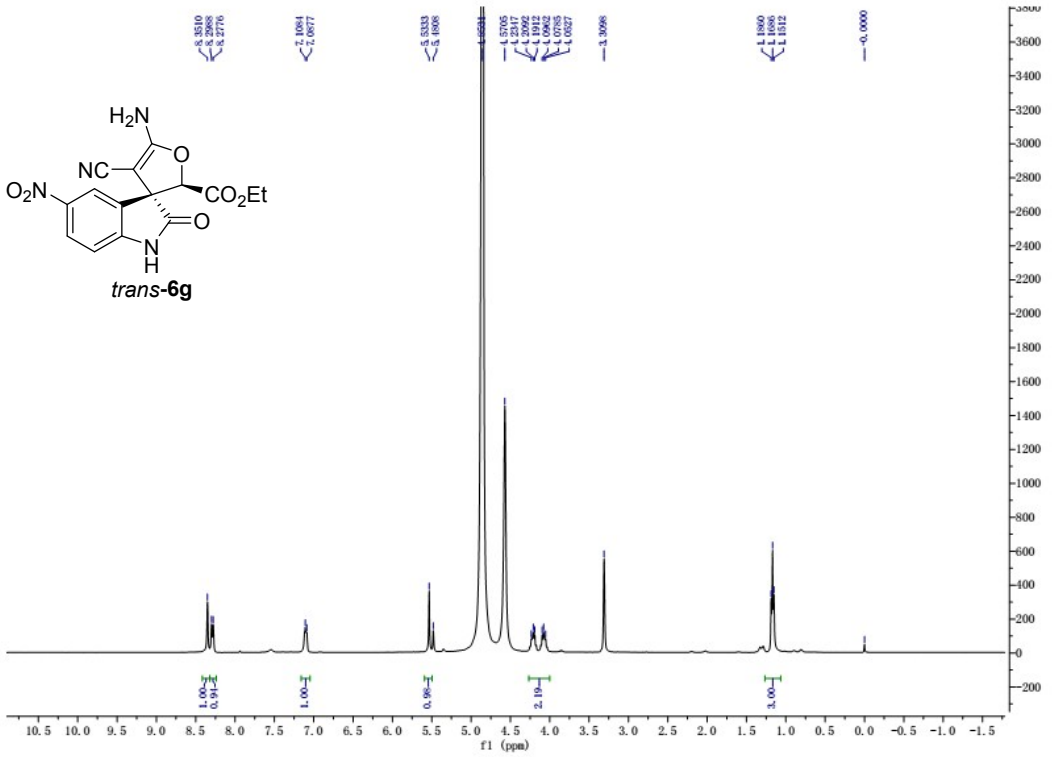
NC
O
Br
CO2Et
O
N
H
cis-6f
f1 (ppm)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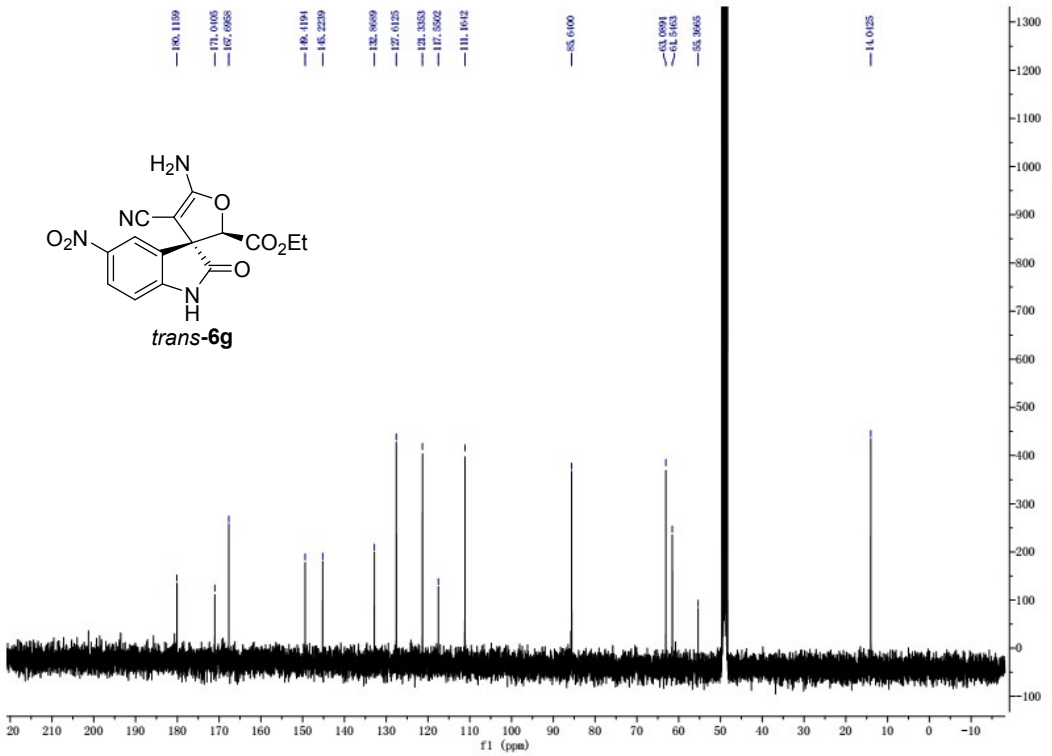
NC
O
O2N
CO2Et
O
N
H
trans-6g
f1 (ppm)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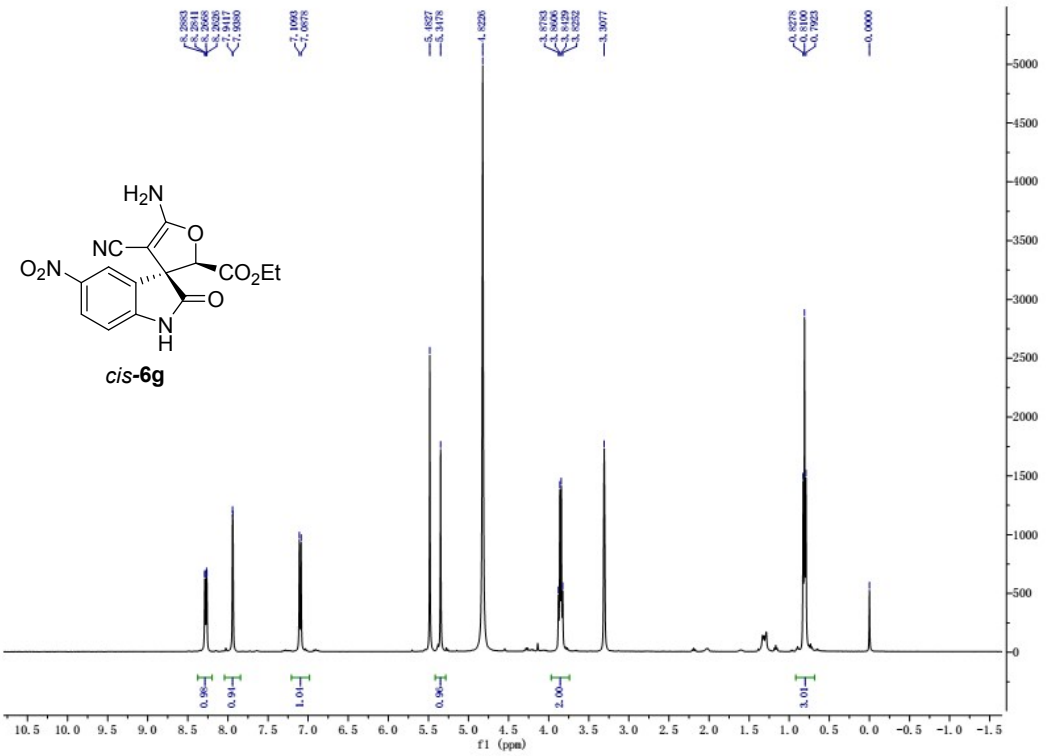
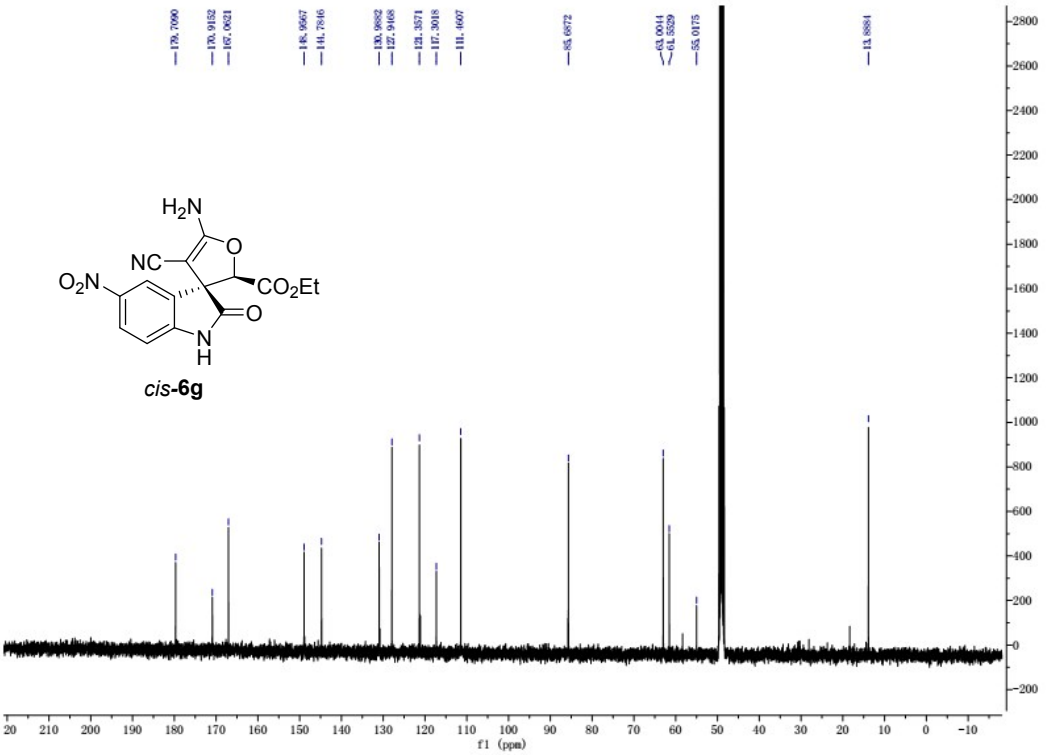
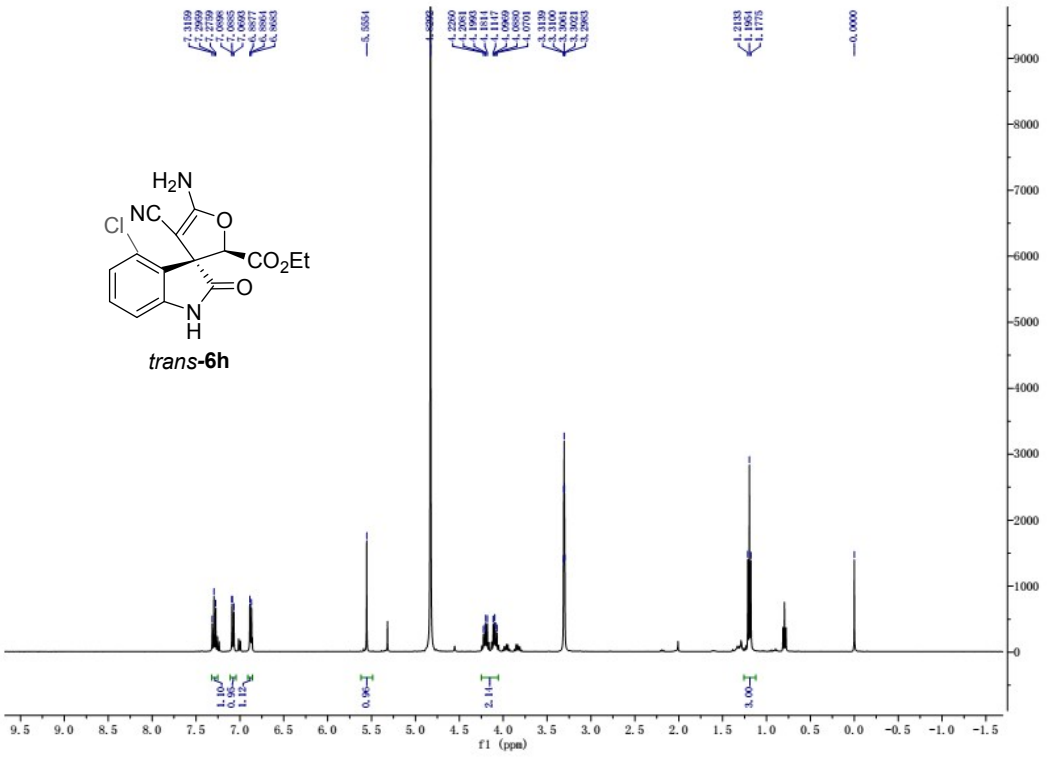
NC
O
O2N
CO2Et
O
N
H
trans-6g
f1 (ppm)



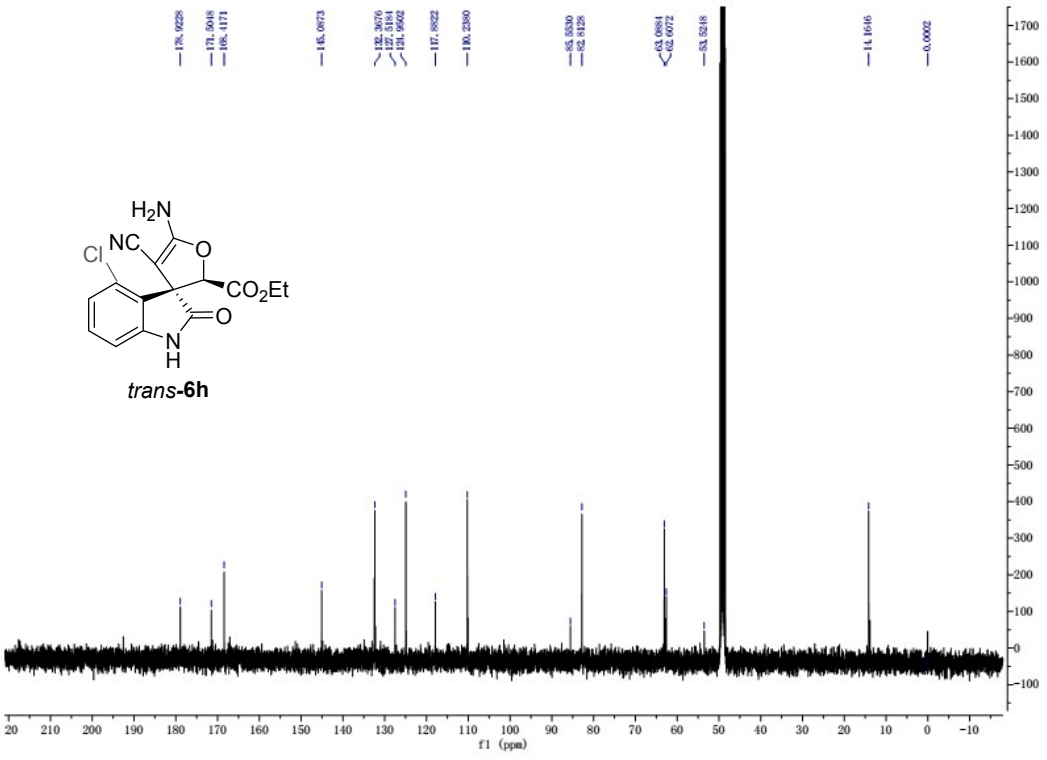
cis-**6g**



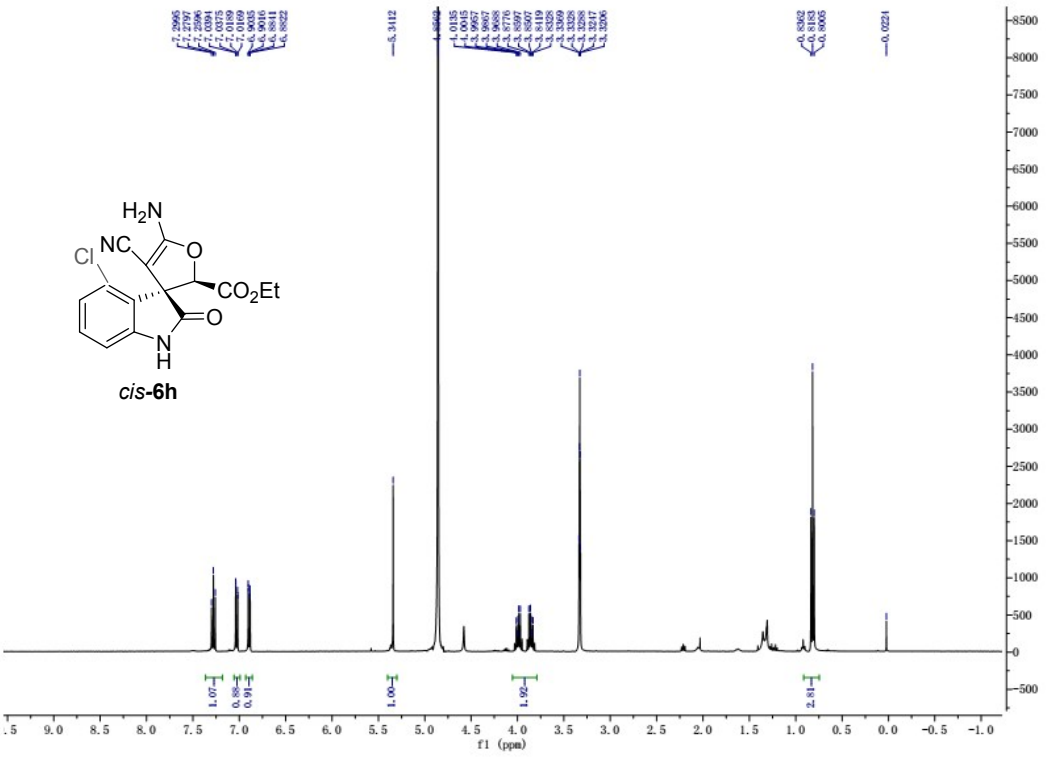
cis-**6g**

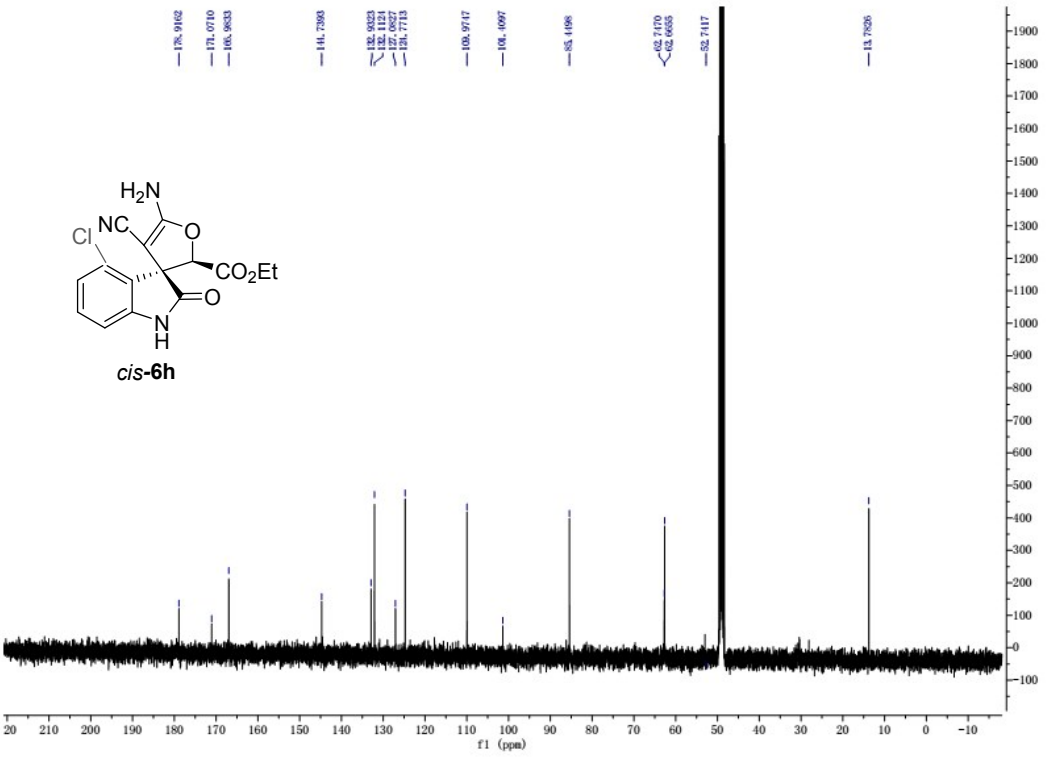


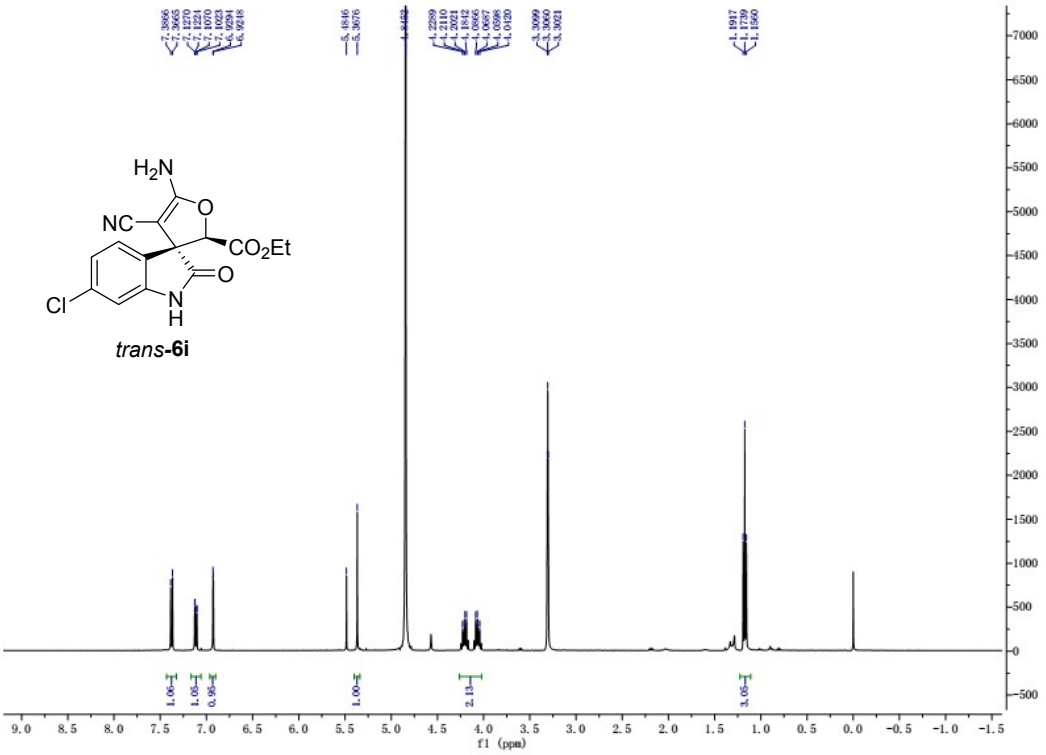
trans-**6h**



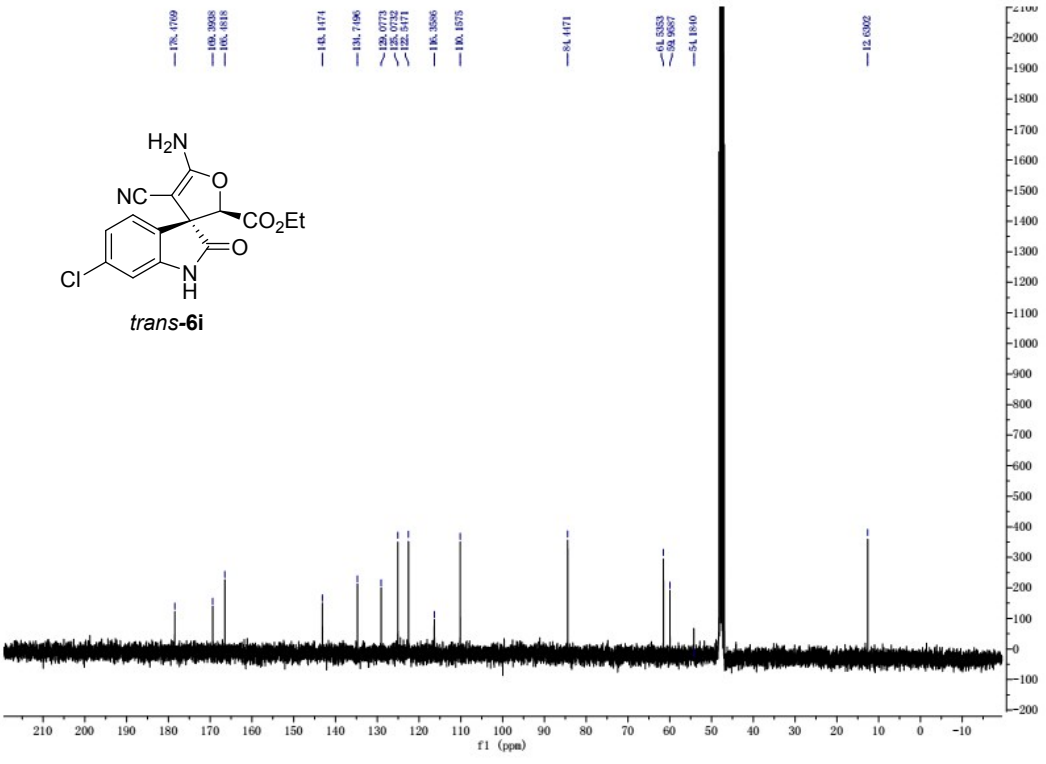
trans-**6h**


H2N
NC
Cl
O
CO2Et
O
N
H
cis-6h
f1 (ppm)

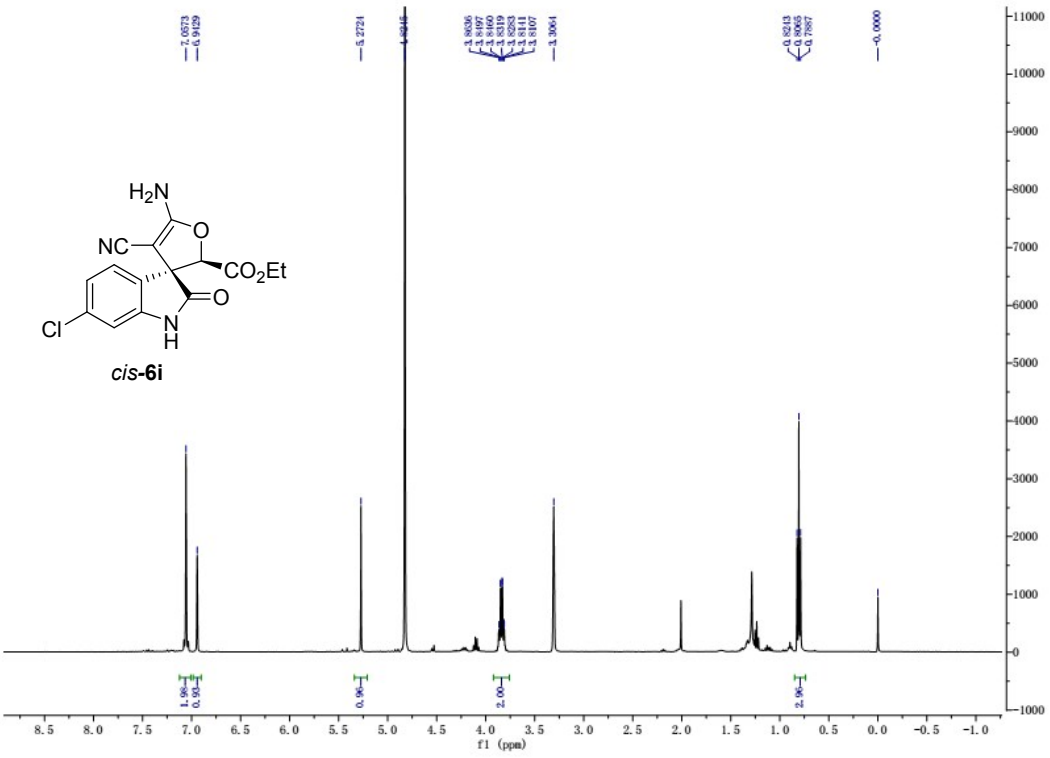

H2N
NC
Cl
O
CO2Et
O
N
H
cis-6h
f1 (ppm)

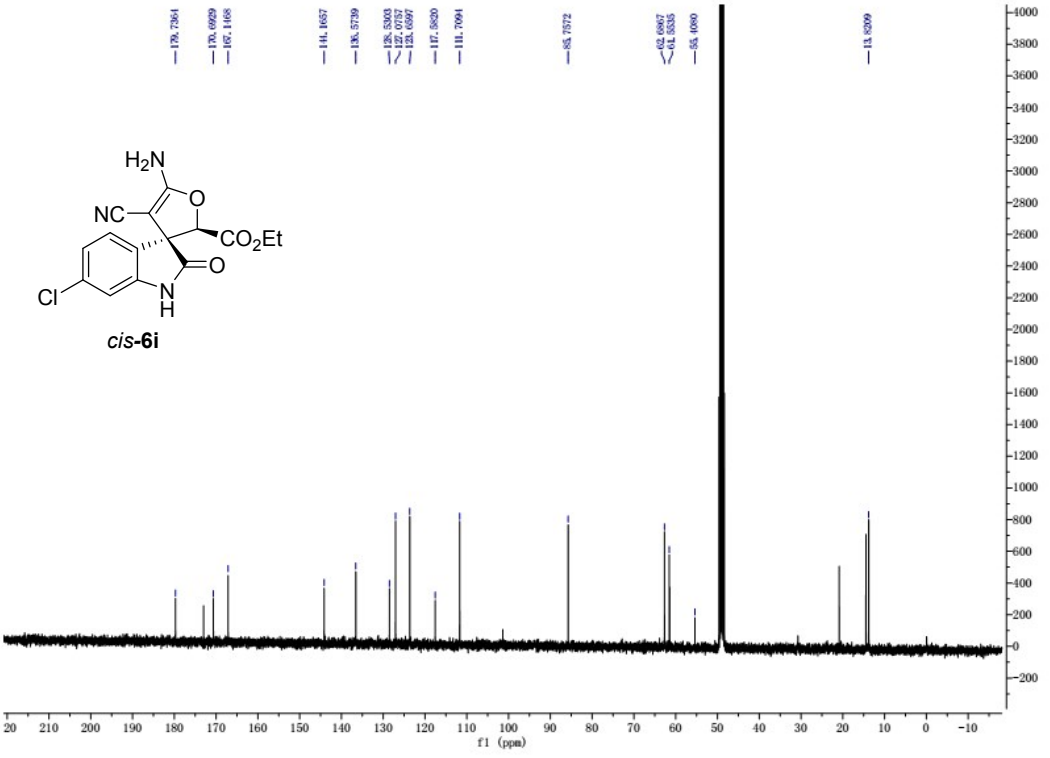


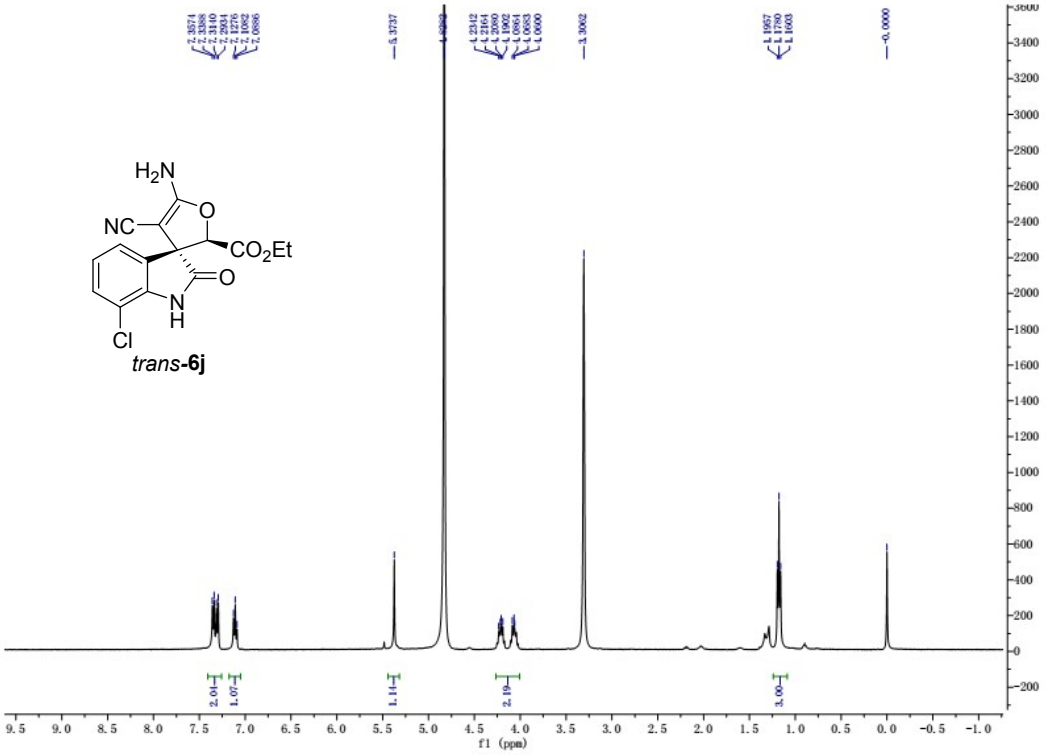
trans-**6i**

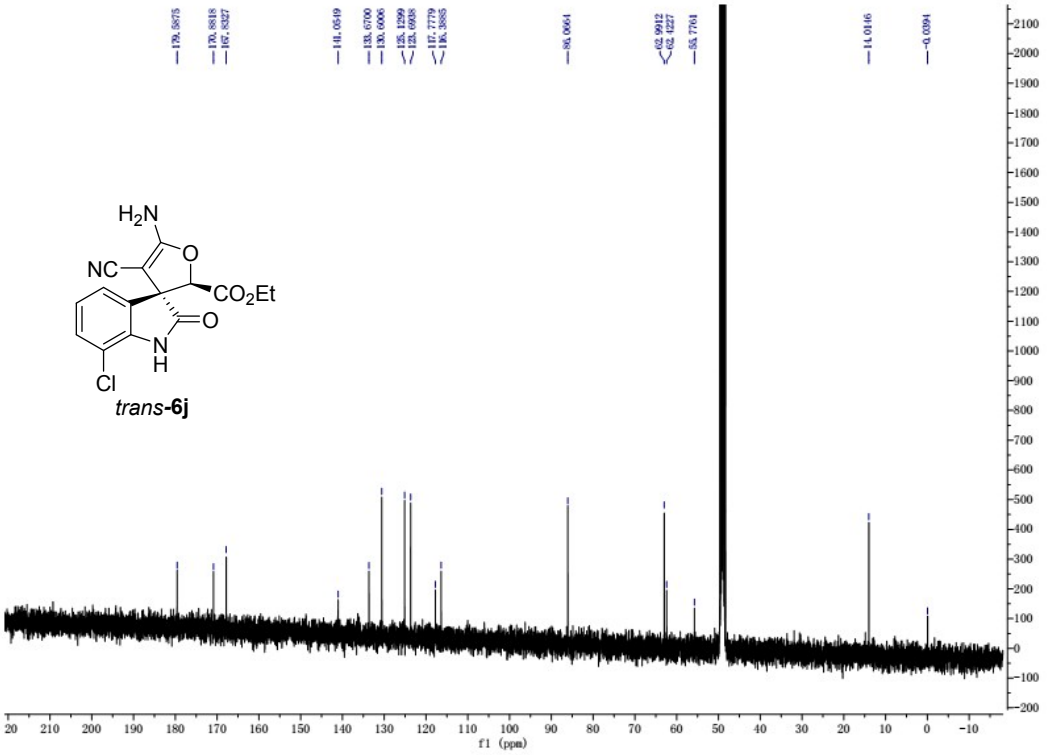


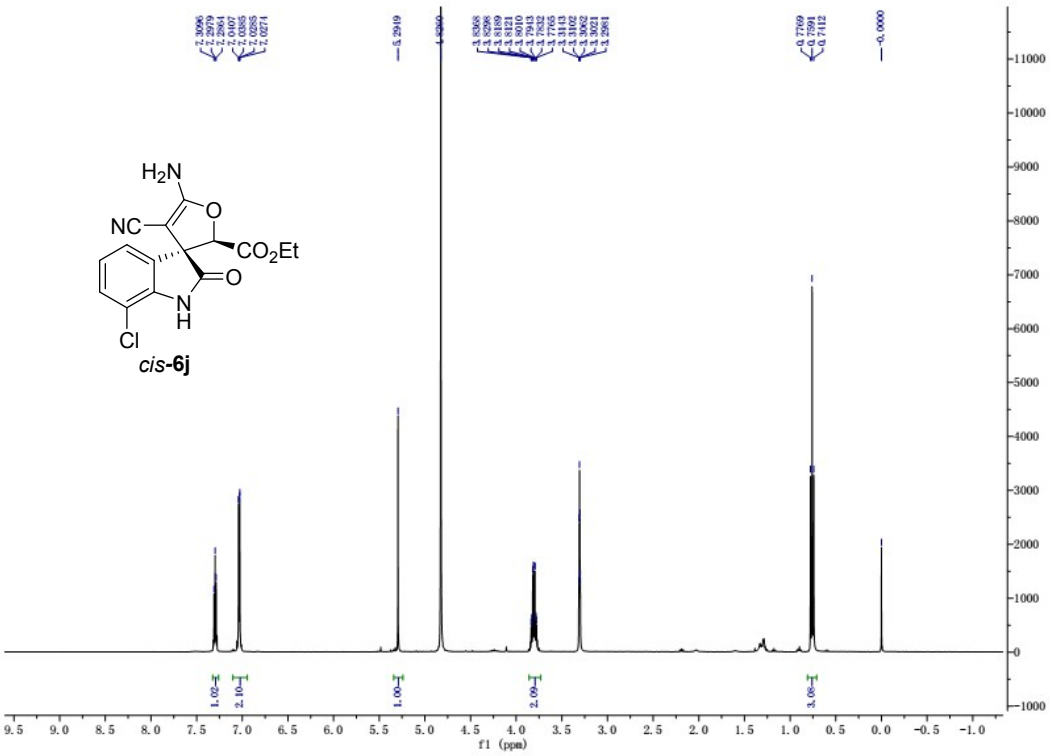
trans-**6i**

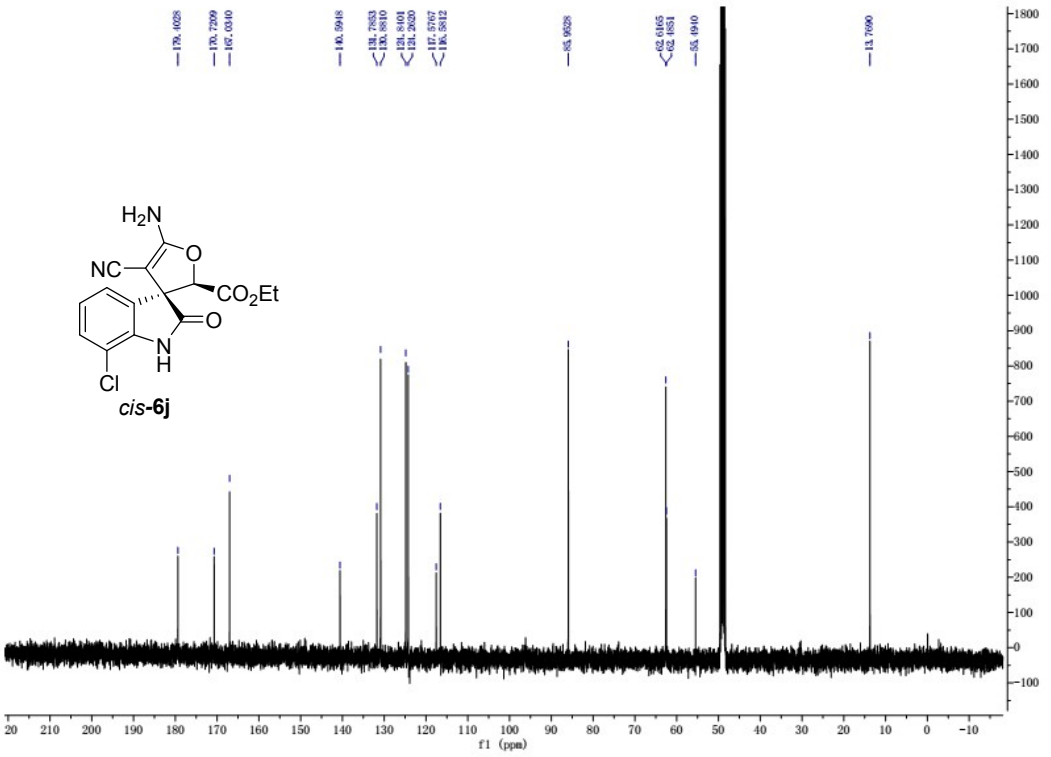

H2N
NC
O
CO2Et
O
Cl
N
H
cis-6i
f1 (ppm)

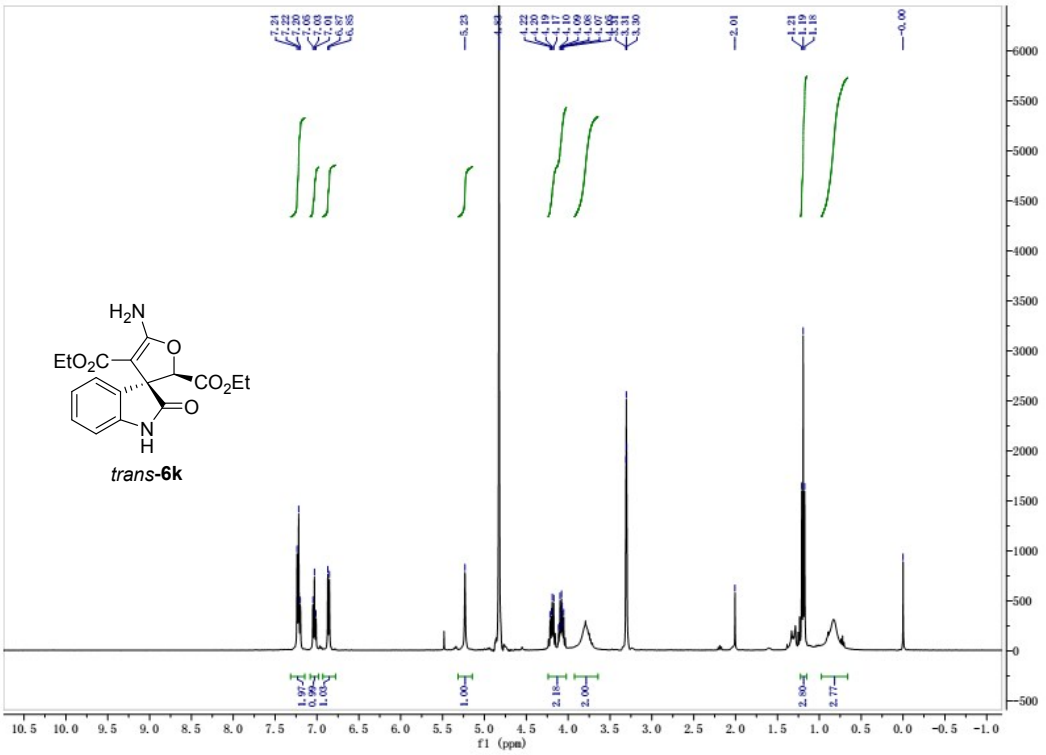

H2N
NC
O
CO2Et
O
Cl
N
H
cis-6i
f1 (ppm)

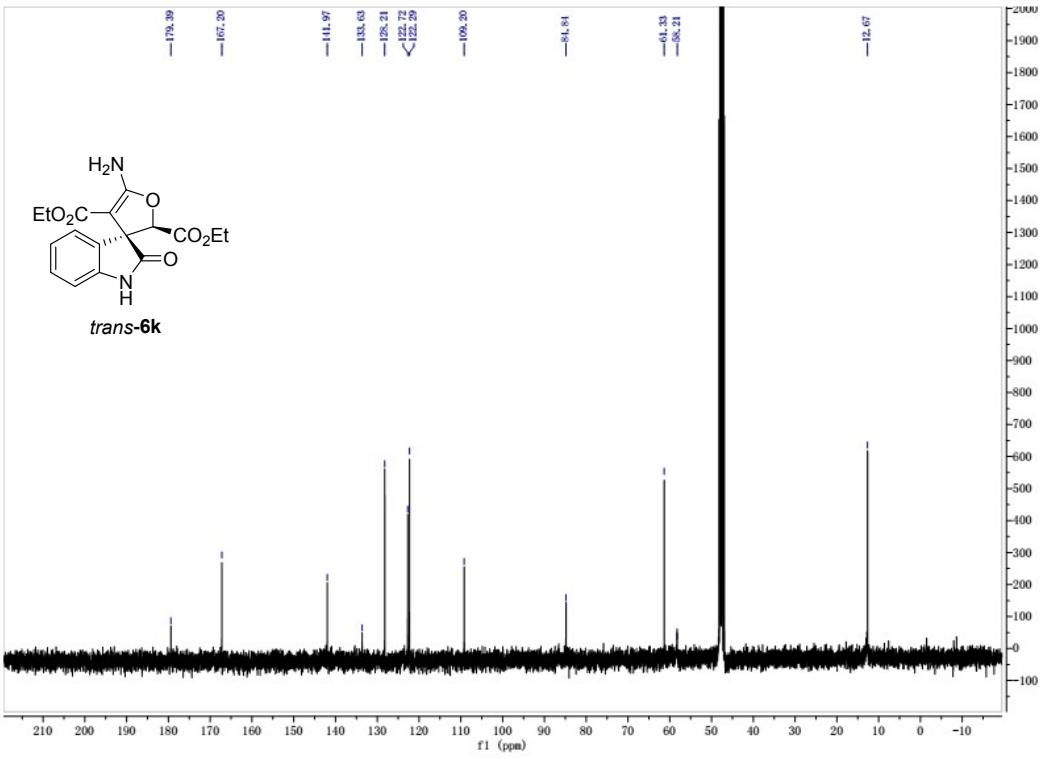

H2N
NC
O
CO2Et
O
N
H
Cl
trans-6j
f1 (ppm)

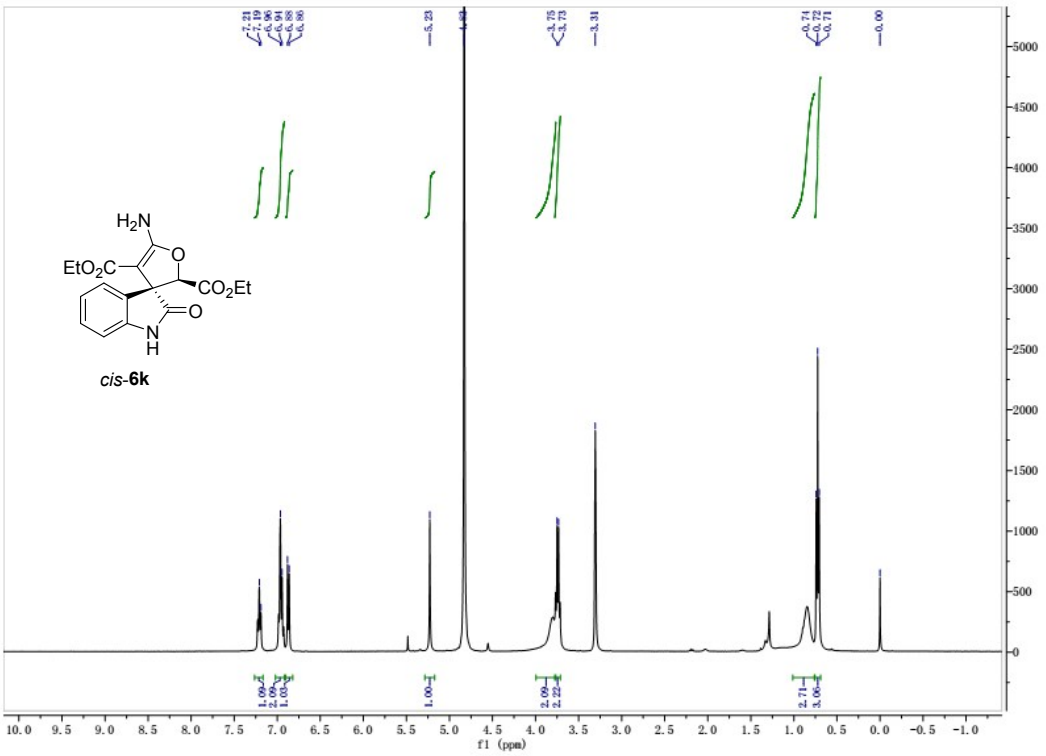

H2N
NC
O
CO2Et
O
N
H
Cl
trans-6j
f1 (ppm)

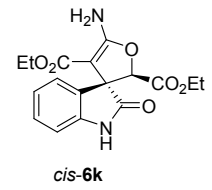

H2N
NC
O
CO2Et
O
N
H
Cl
cis-6j
f1 (ppm)


H2N
NC
O
CO2Et
O
N
H
Cl
cis-6j
f1 (ppm)


H2N
EtO2C
O
CO2Et
O
N
H
trans-6k
f1 (ppm)


H2N
EtO2C
O
CO2Et
O
N
H
trans-6k
f1 (ppm)


7.21
7.19
6.96
6.94
6.88
6.86
5.23
4.33
3.75
3.73
3.31
0.74
0.72
0.71
0.00
1.09
2.09
1.03
1.00
2.09
2.22
2.71
3.06
f1 (ppm)

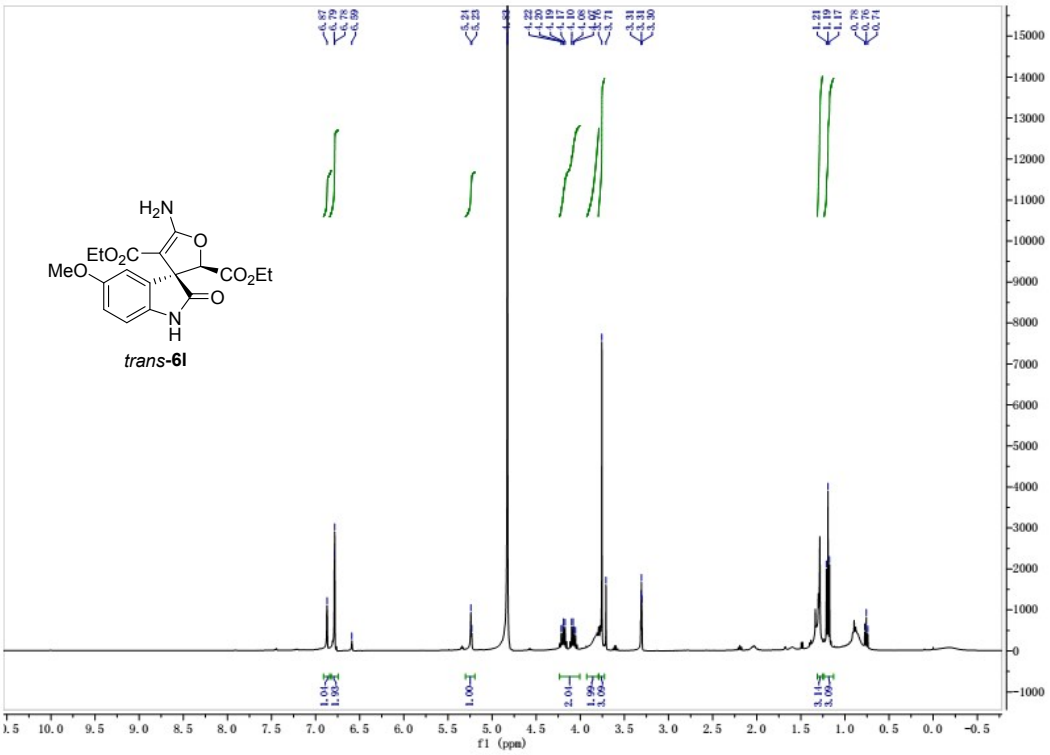

H2N
EtO2C
O
CO2Et
O
N
H

cis-**6k**

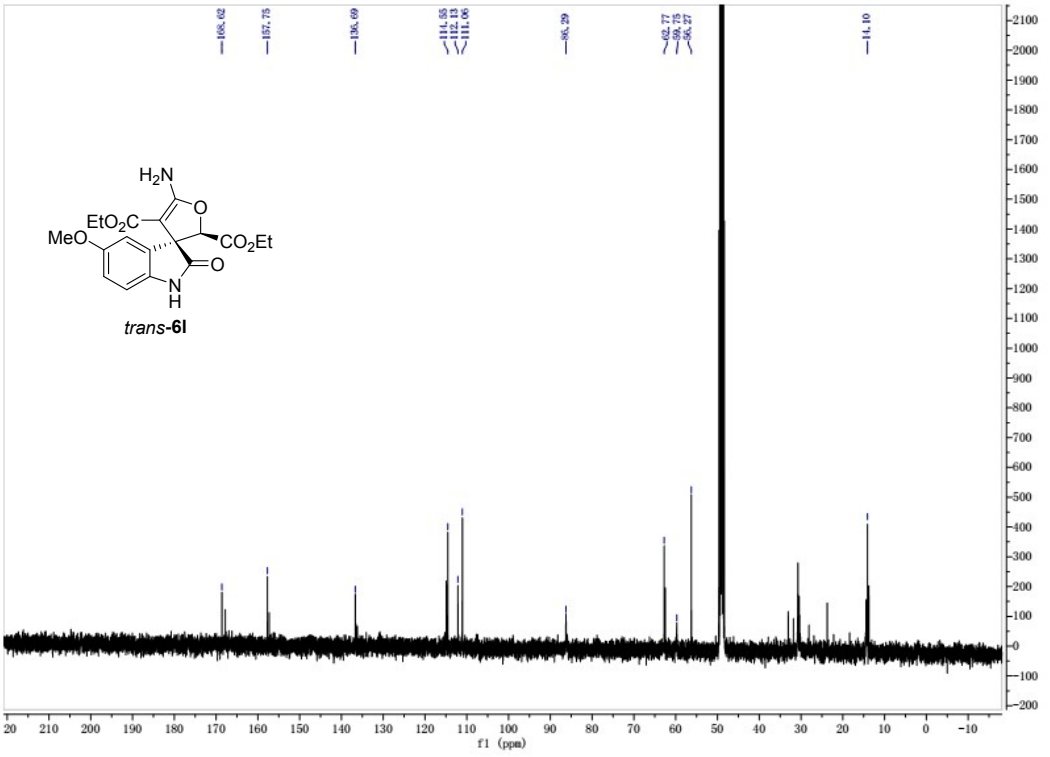
179.96
170.69
167.32
142.74
130.95
129.91
125.88
123.87
117.79
111.31
85.90
62.56
61.78
55.71
13.76
f1 (ppm)

H2N
EtO2C
O
CO2Et
O
N
H

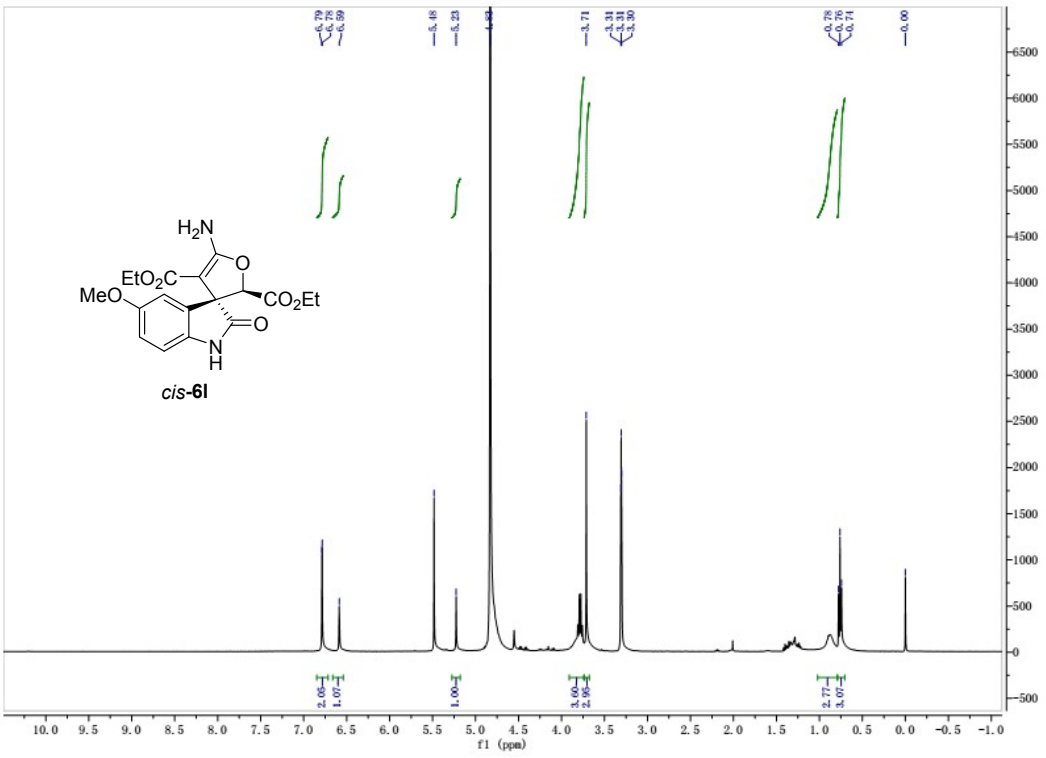
cis-**6k**

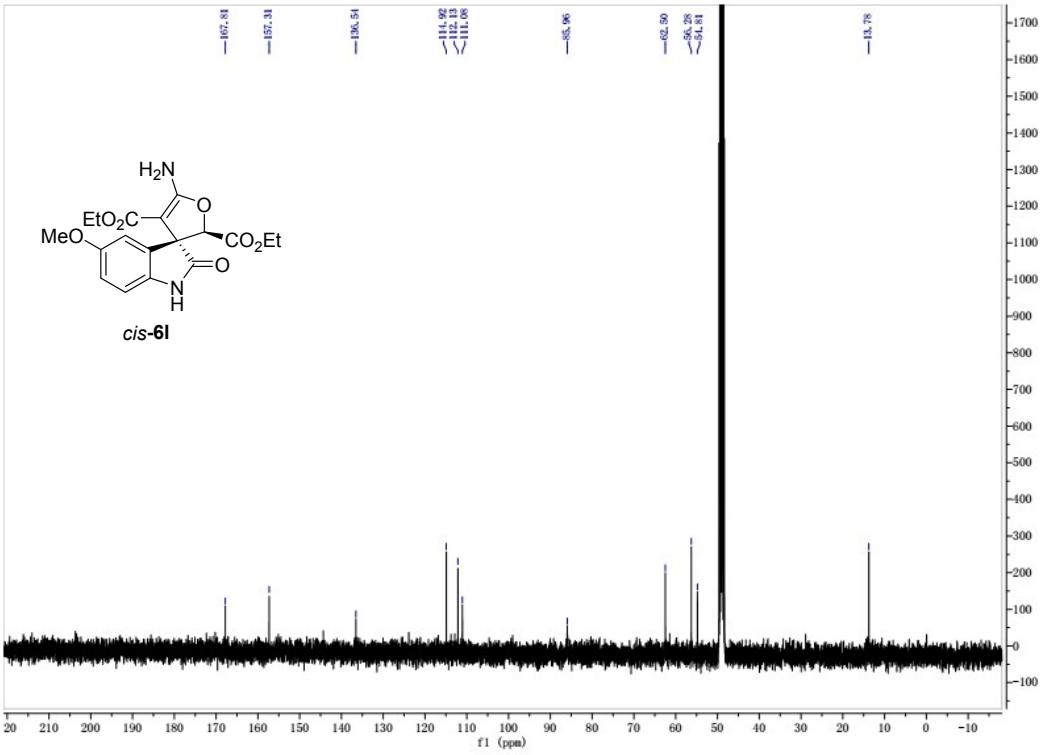


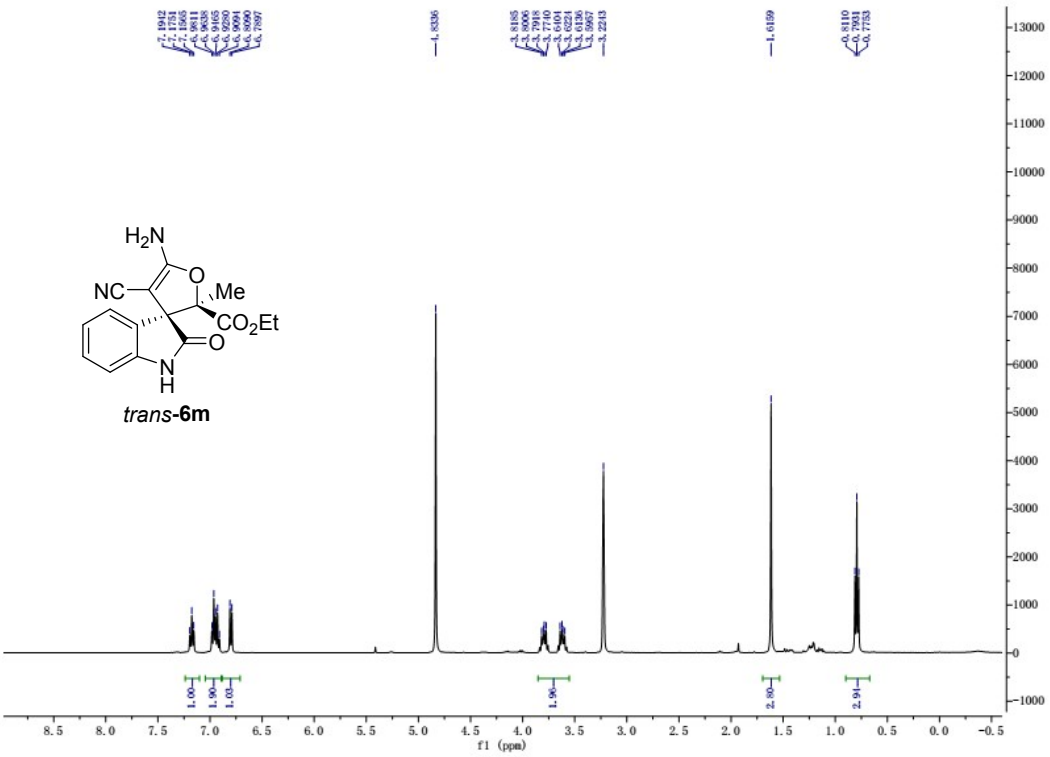
trans-**6l**

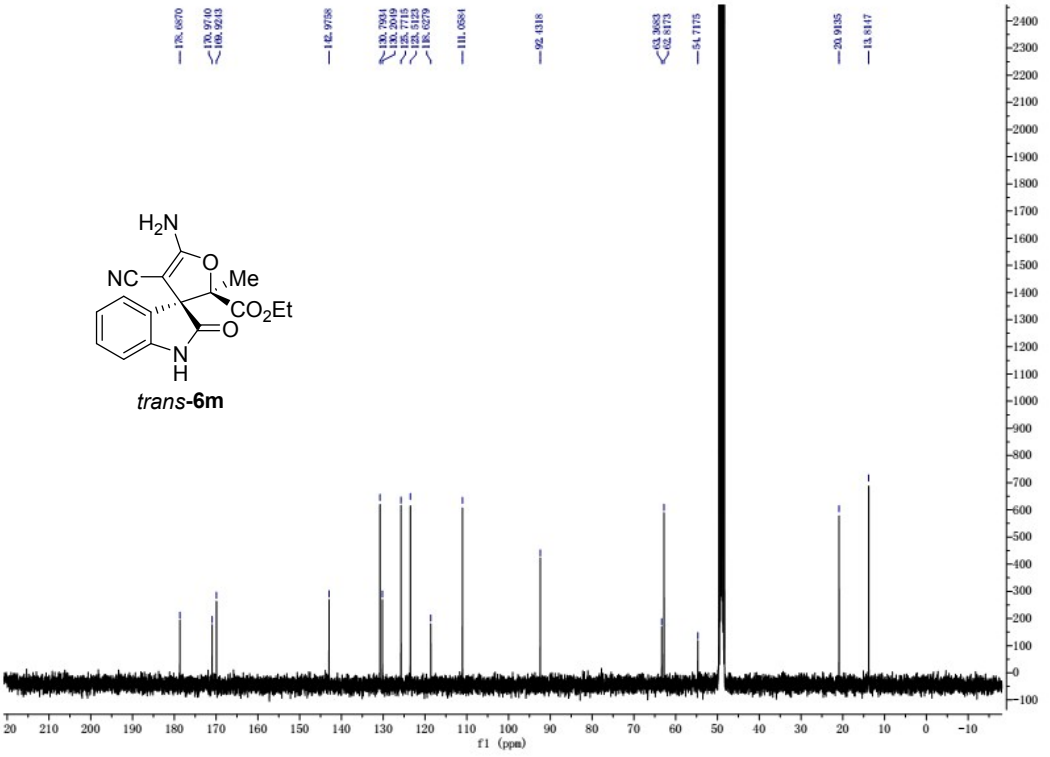


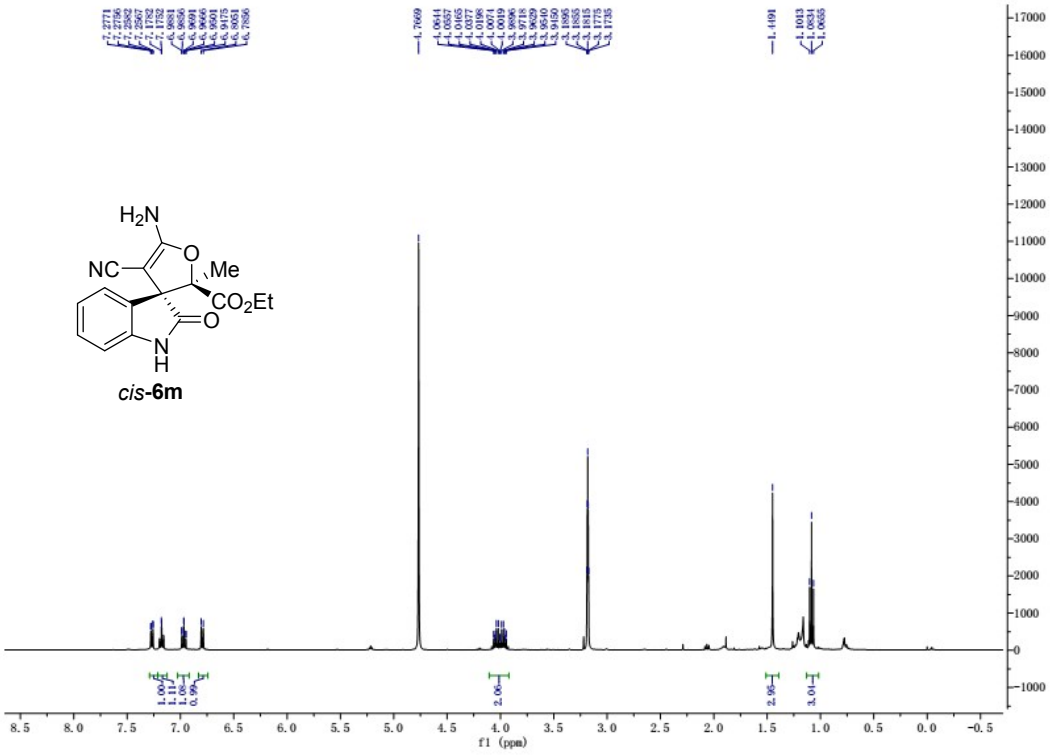
trans-**6l**

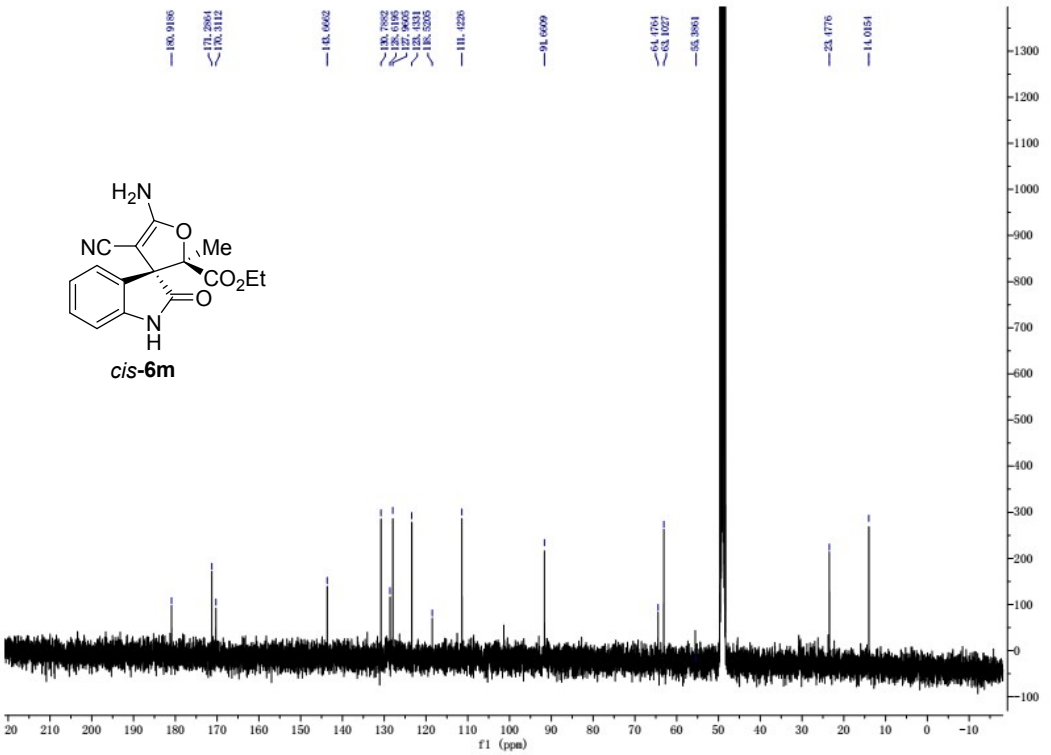

H2N
EtO2C
MeO
CO2Et
O
N
H
cis-6l
f1 (ppm)

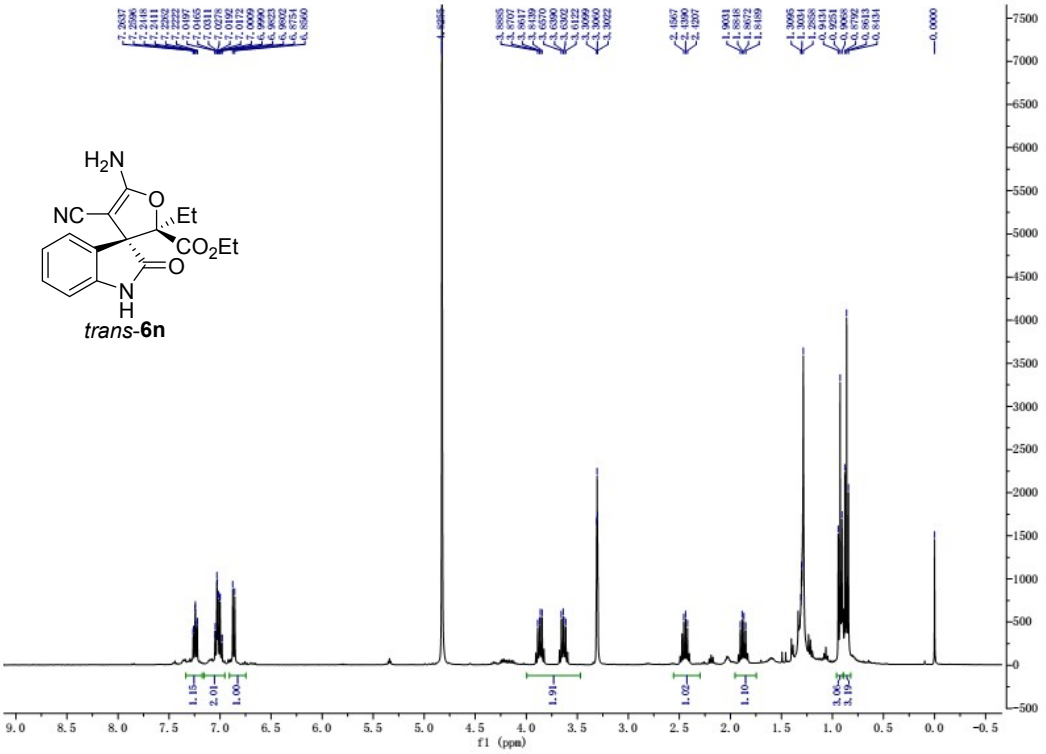

H2N
EtO2C
MeO
CO2Et
O
N
H
cis-6l
f1 (ppm)

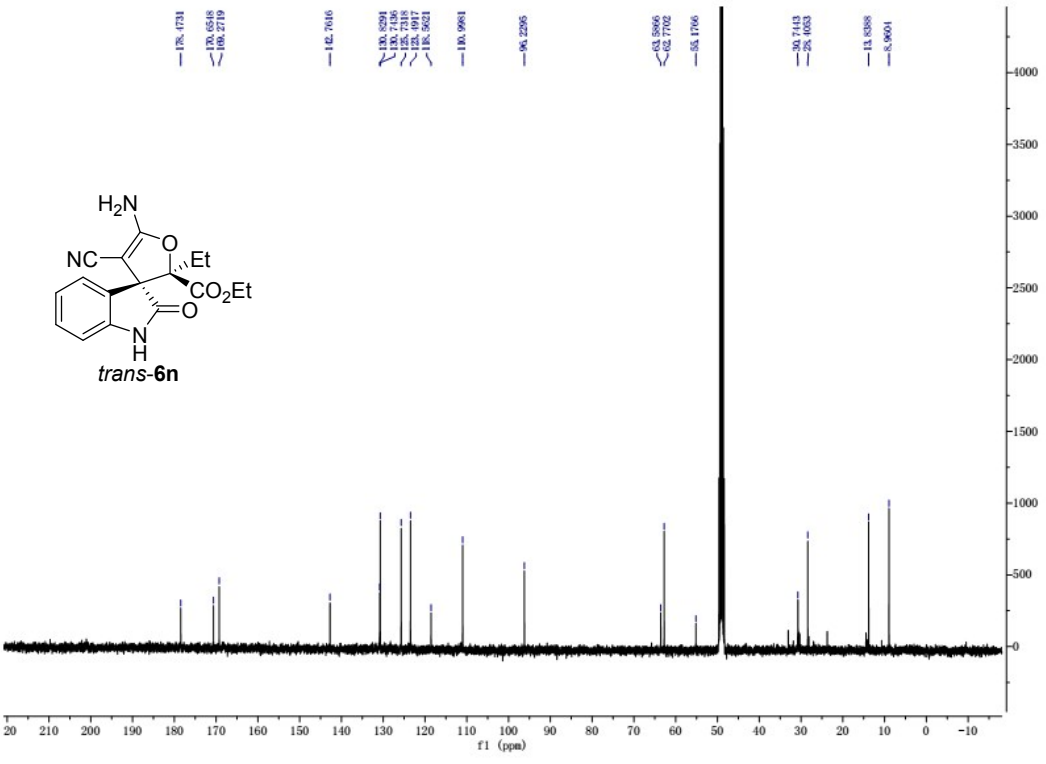

H2N
NC
O
Me
CO2Et
O
N
H
trans-6m
f1 (ppm)


H2N
NC
O
Me
CO2Et
O
N
H
trans-6m
f1 (ppm)


H2N
NC
O
Me
CO2Et
O
N
H
cis-6m
f1 (ppm)


H2N
NC
O
Me
CO2Et
O
N
H
cis-6m
f1 (ppm)


H2N
NC
O
Et
CO2Et
O
N
H
trans-6n
f1 (ppm)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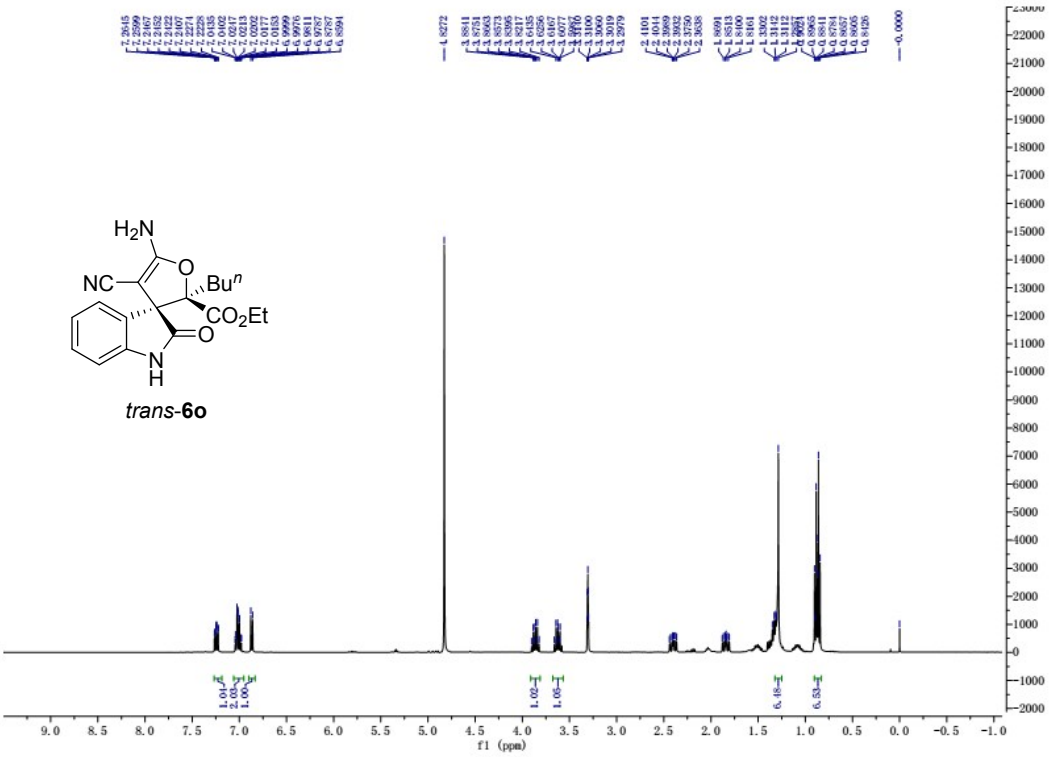
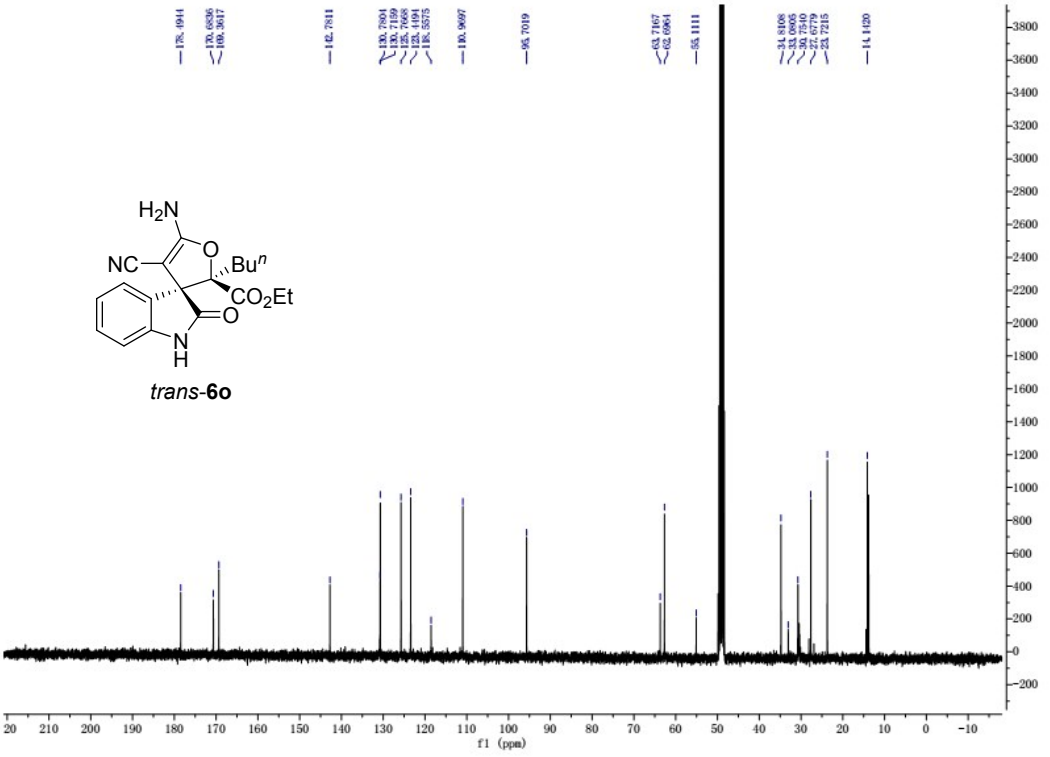
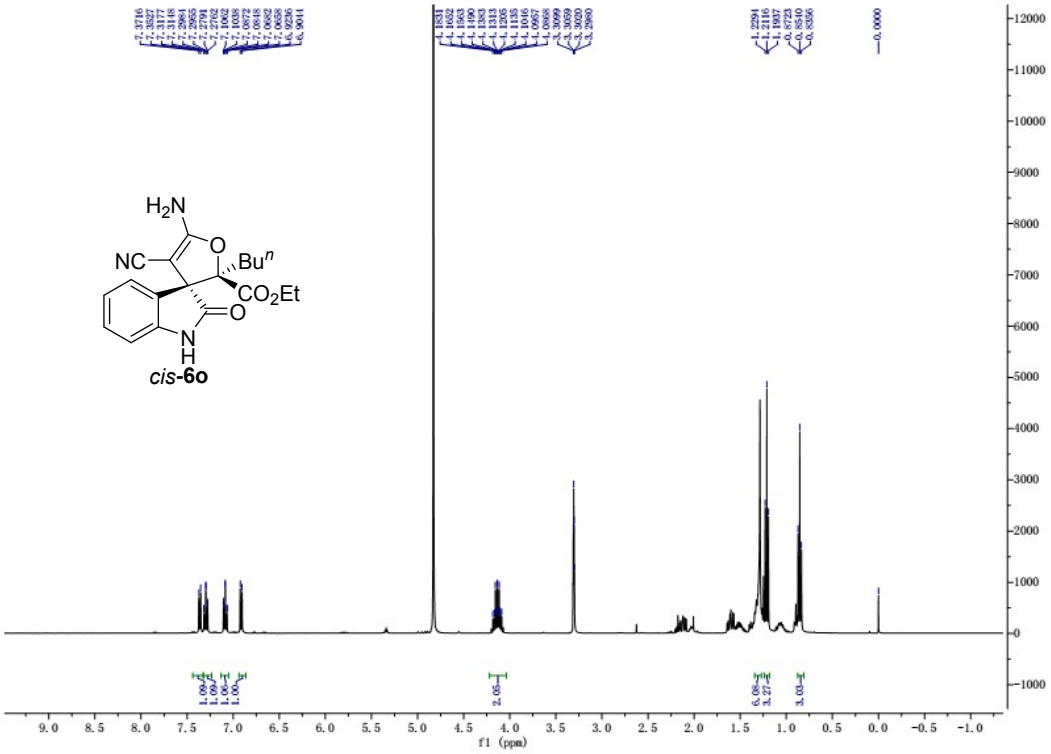
NC
O
Et
CO2Et
O
N
H
trans-6n
f1 (ppm)

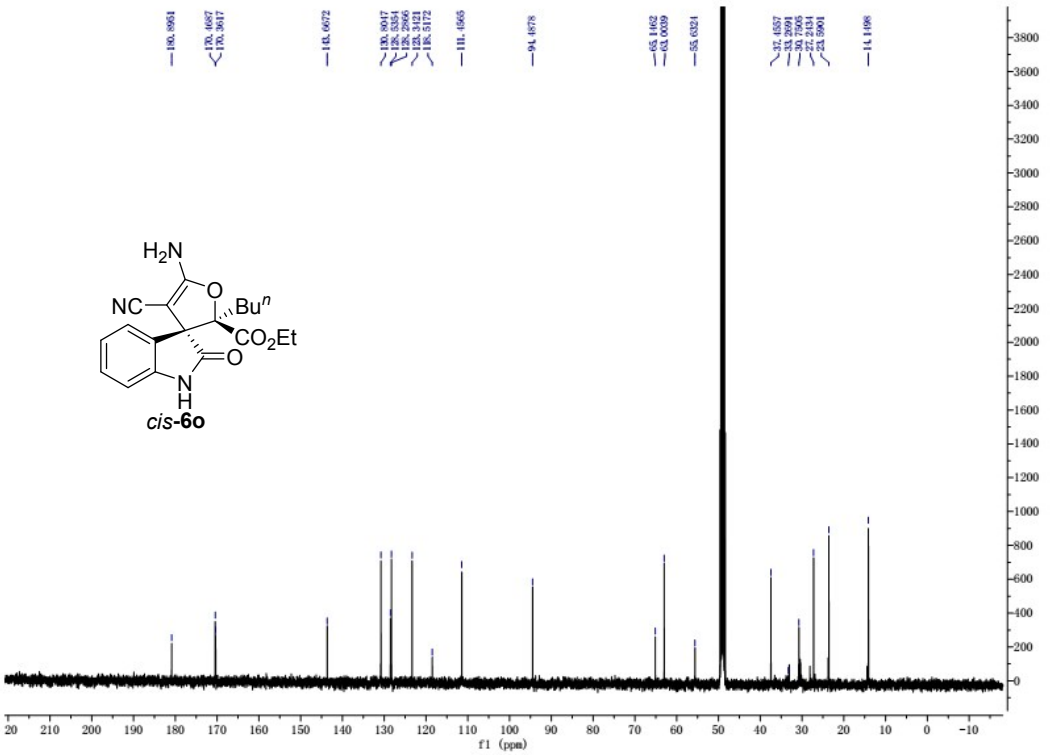


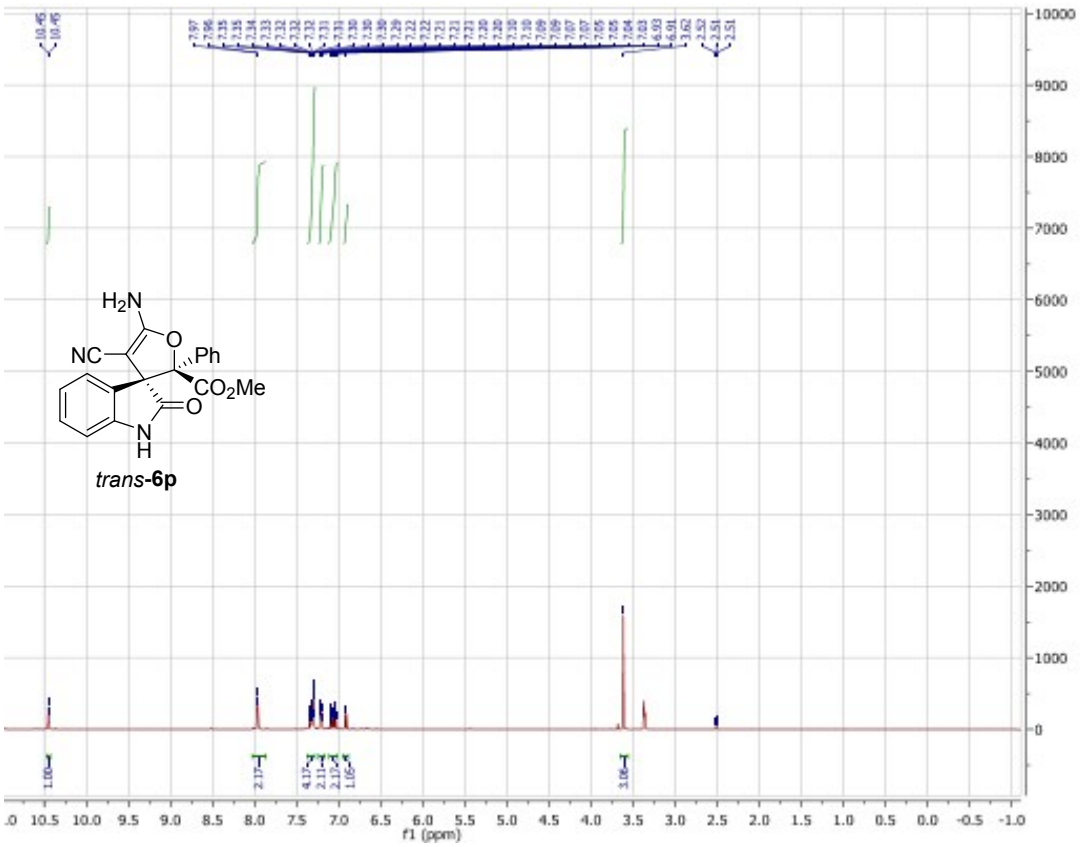
trans-**6o**



trans-**6o**


H2N
NC
O
Bu^n
CO2Et
O
N
H
cis-6o
f1 (ppm)


H2N
NC
O
Bu^n
CO2Et
O
N
H
cis-6o
f1 (ppm)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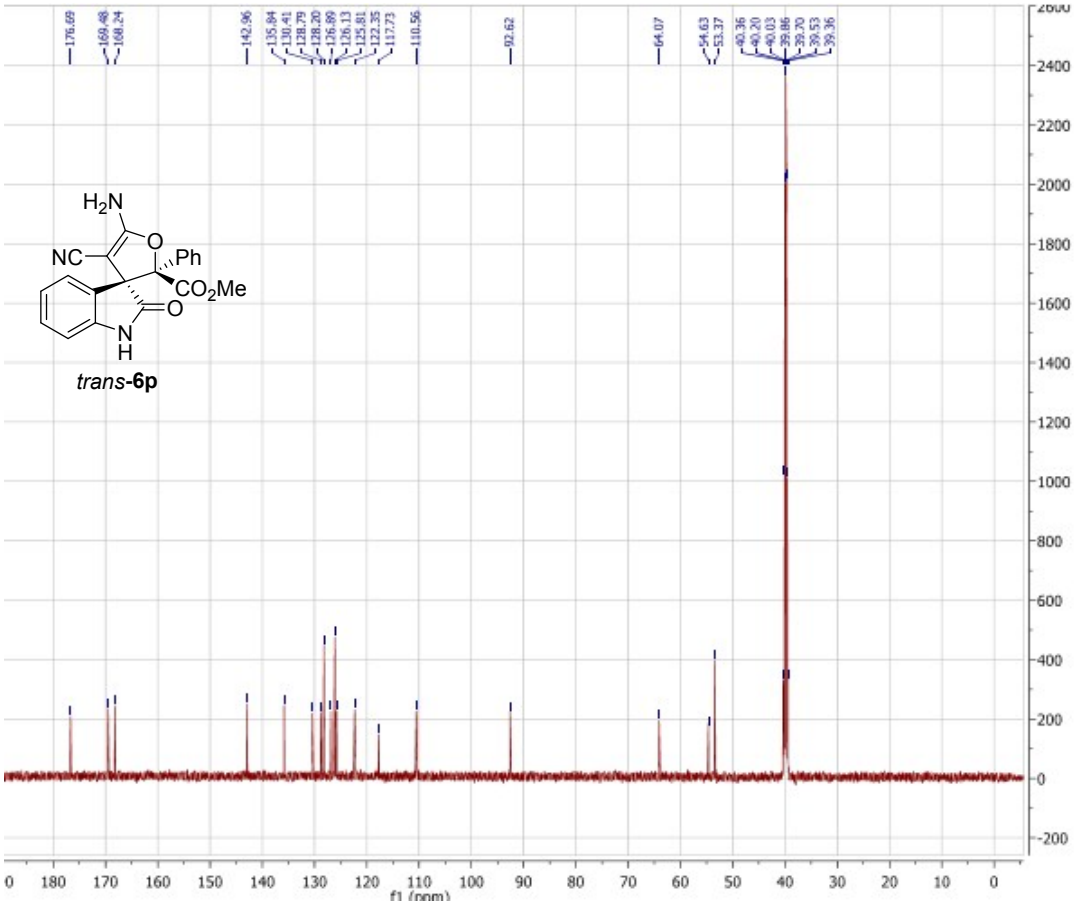
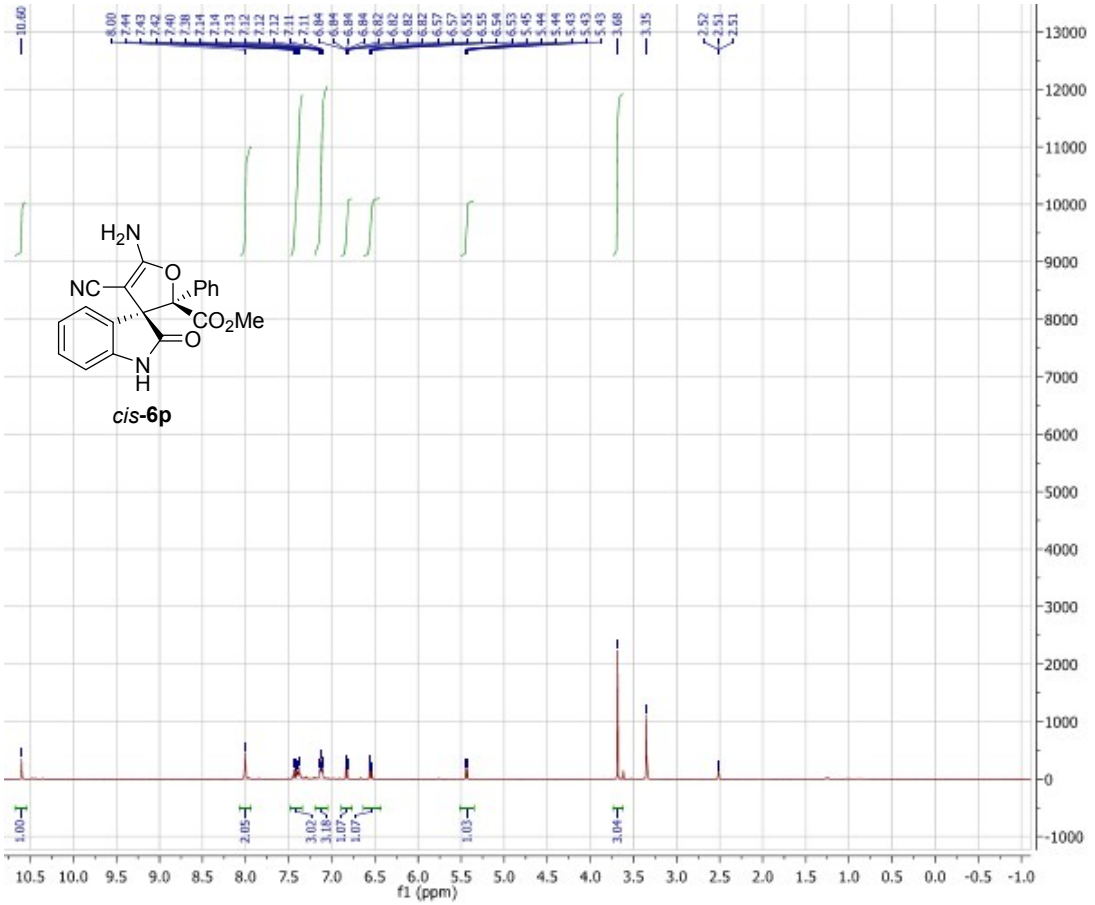
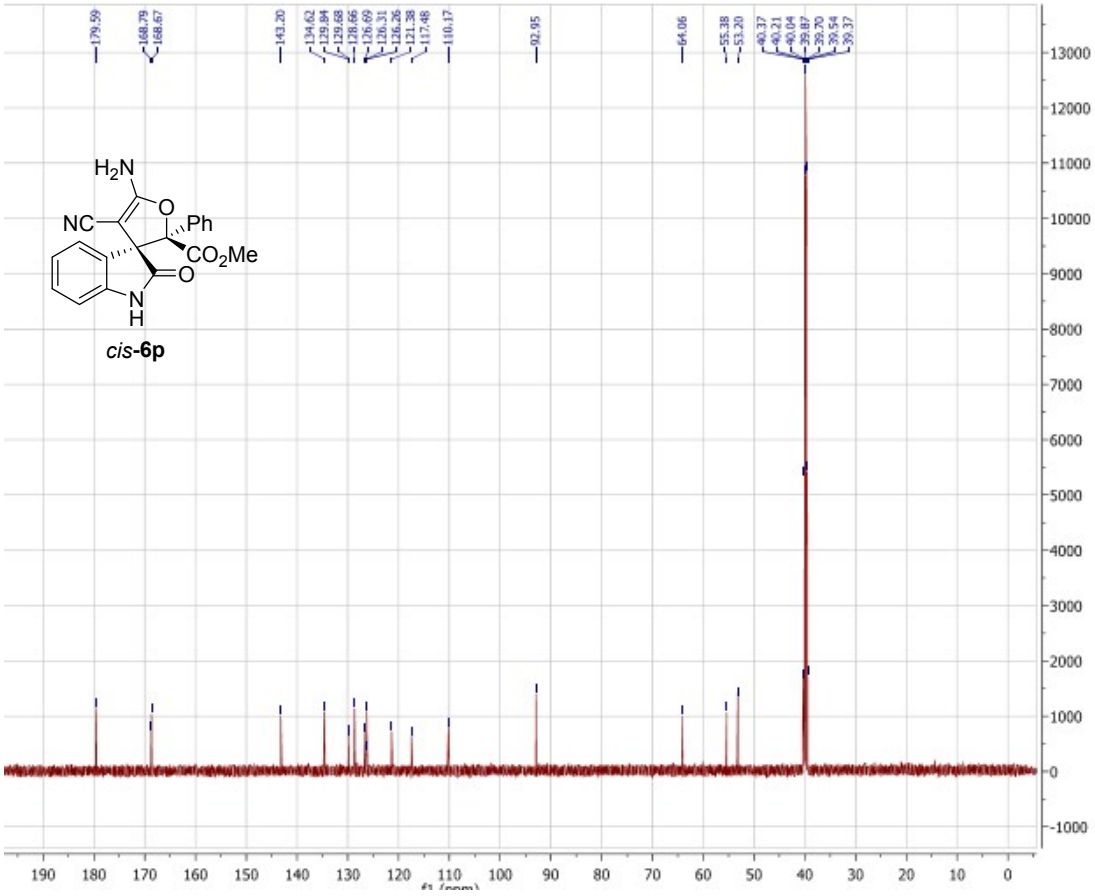
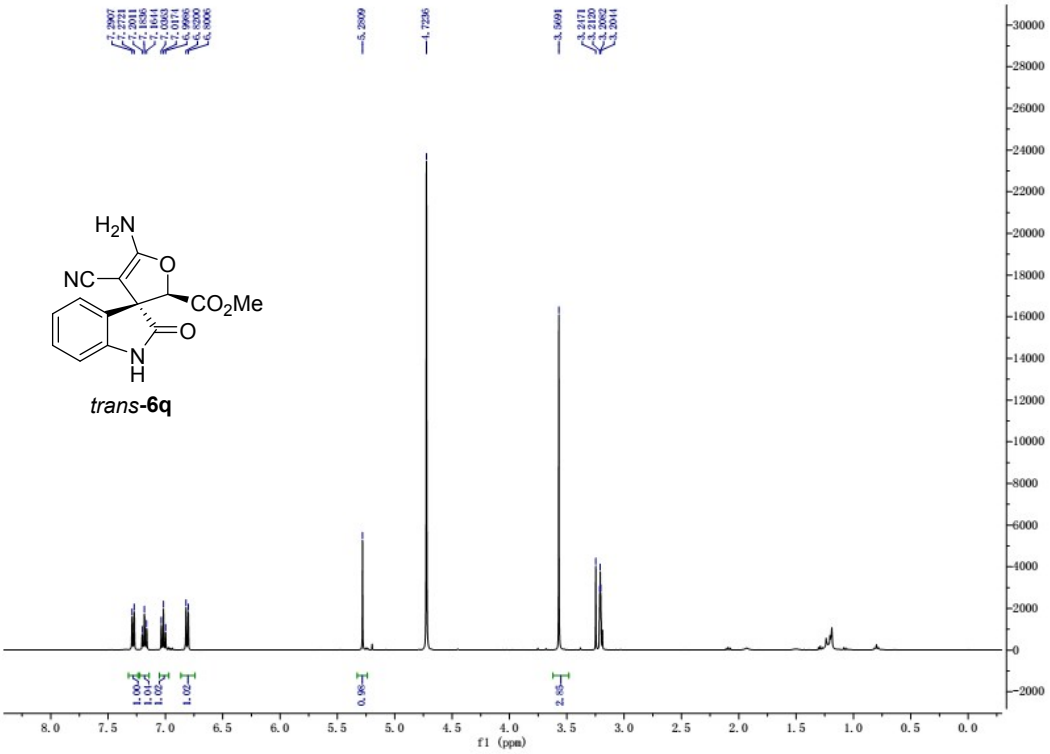
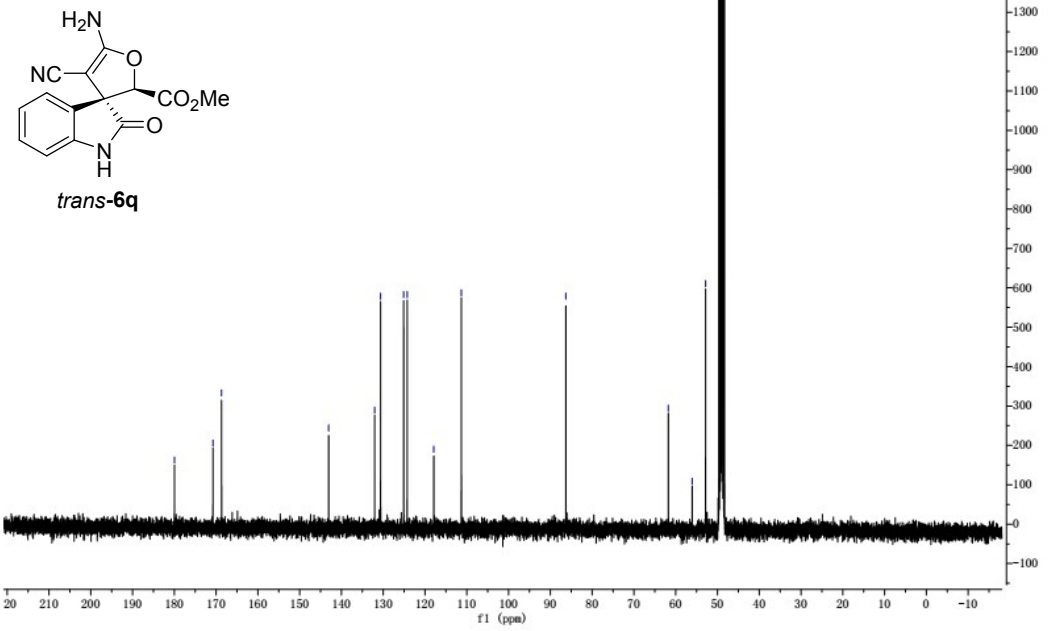
NC
O
Ph
CO2Me
O
N
H
trans-6p
f1 (ppm)

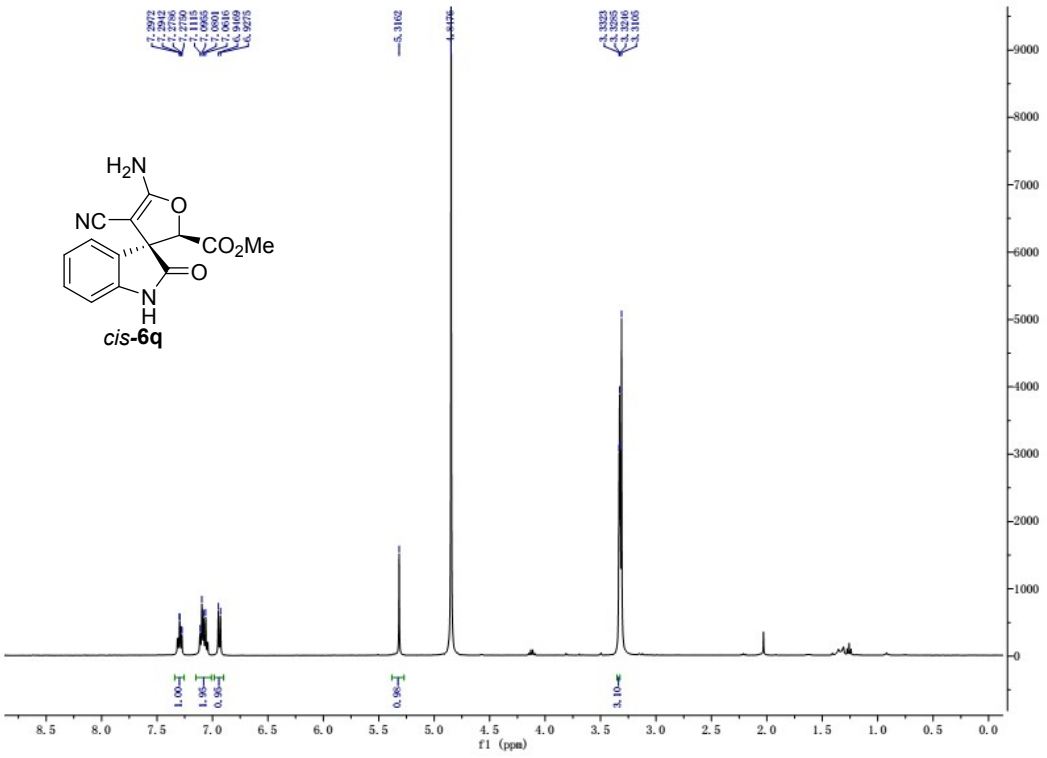

H2N
NC
O
Ph
CO2Me
O
N
H
trans-6p
f1 (ppm)

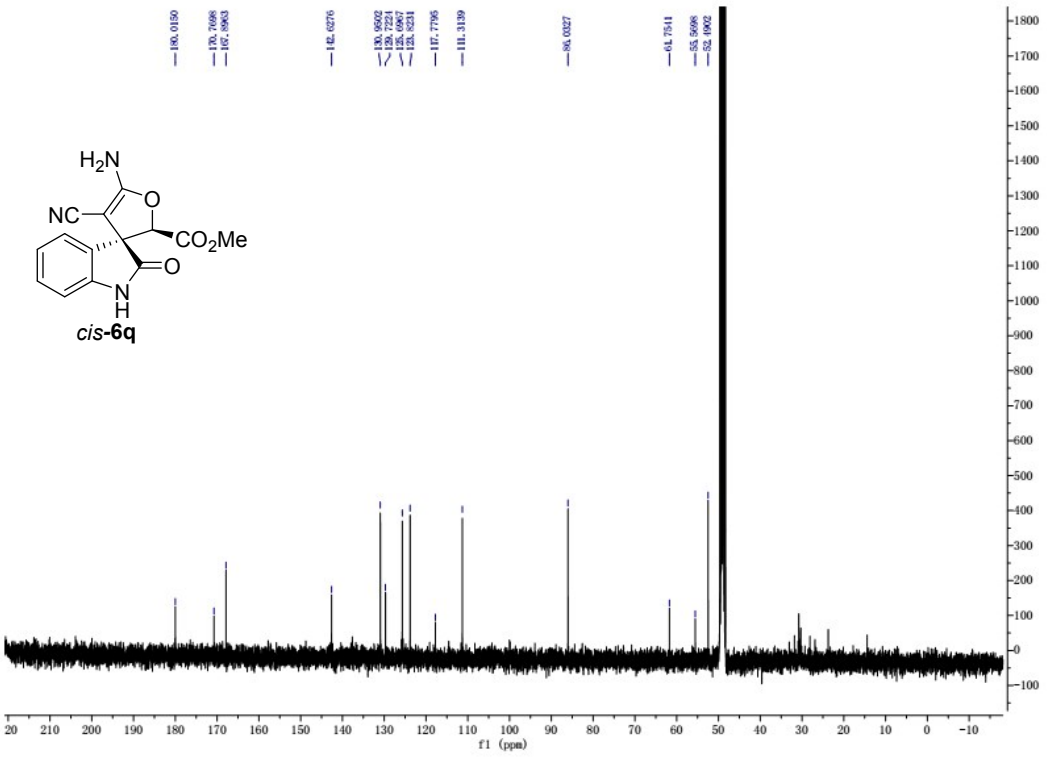

H2N
NC
O
Ph
CO2Me
O
N
H
cis-6p
f1 (ppm)

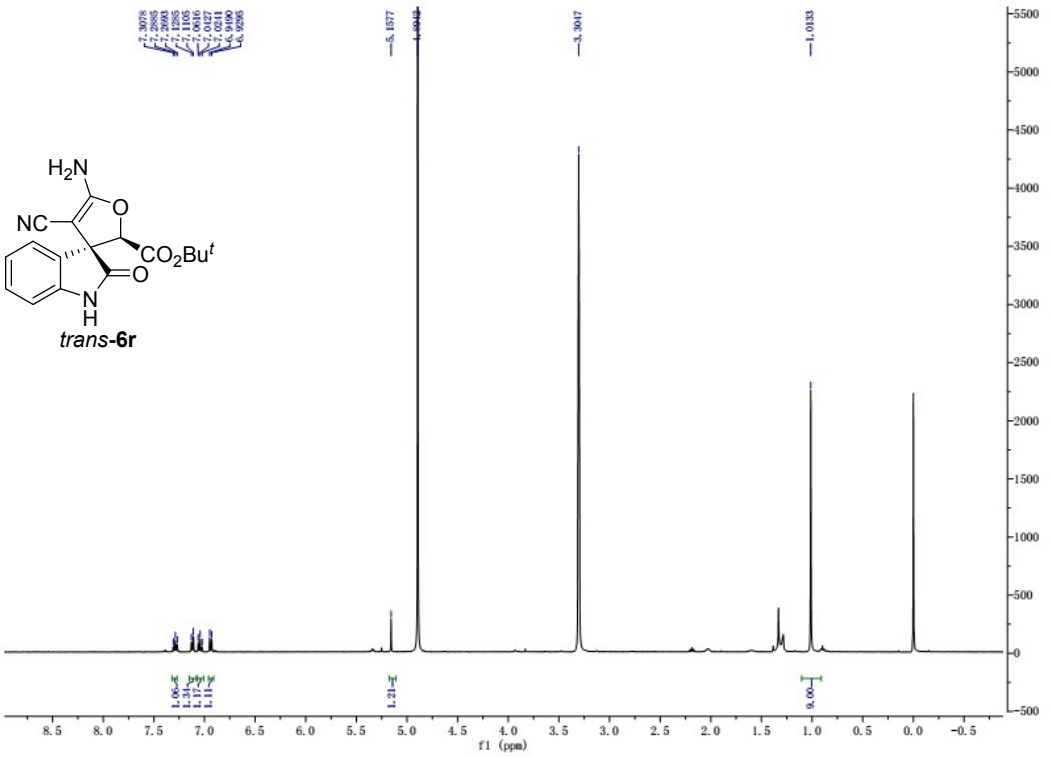

H2N
NC
O
Ph
CO2Me
O
N
H
cis-6p

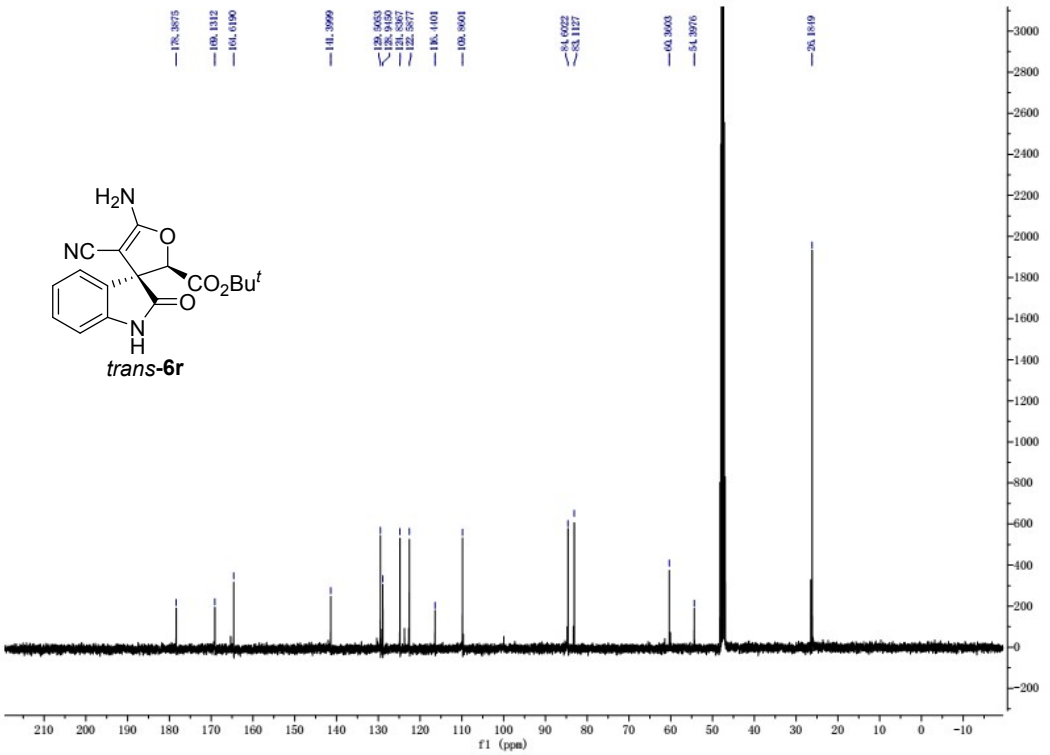

7.2997
7.2721
7.2011
7.1836
7.1641
7.1463
7.0171
6.9986
6.9200
6.8806
5.2809
4.7236
3.5691
3.2171
3.2120
3.2062
3.2014
1.00
1.04
1.05
1.02
0.98
2.83
f1 (ppm)

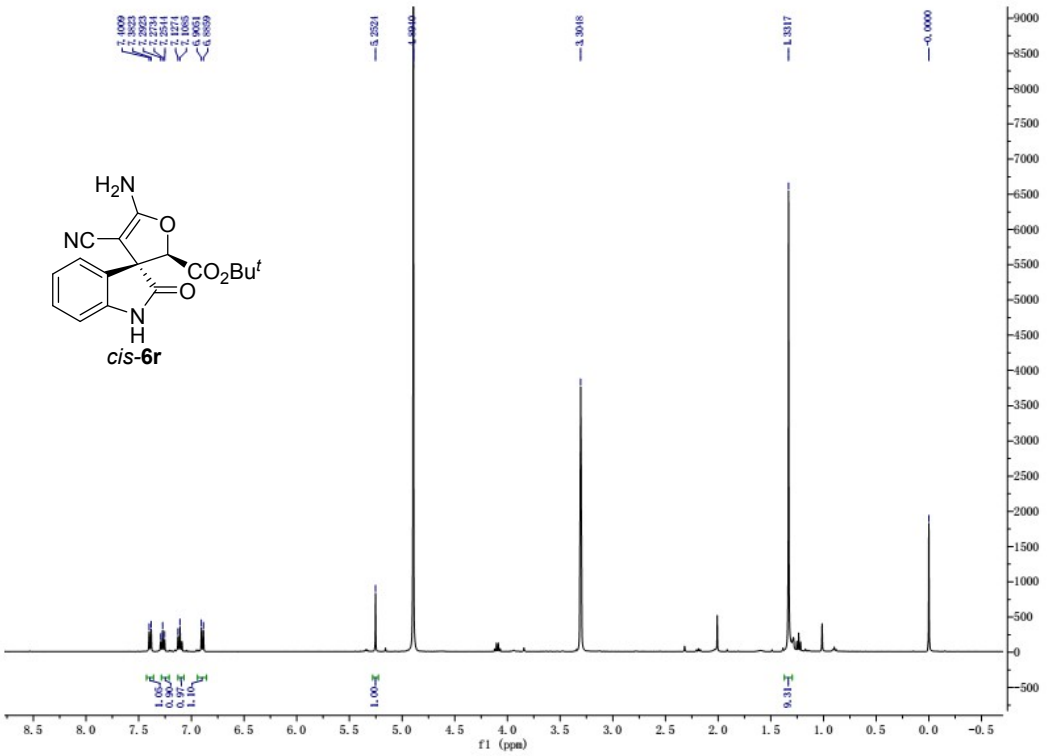

170.9811
170.7799
166.7667
143.0679
132.0702
130.6521
125.1177
121.2794
117.9204
111.3122
86.3065
61.7678
56.0664
52.8657
f1 (ppm)

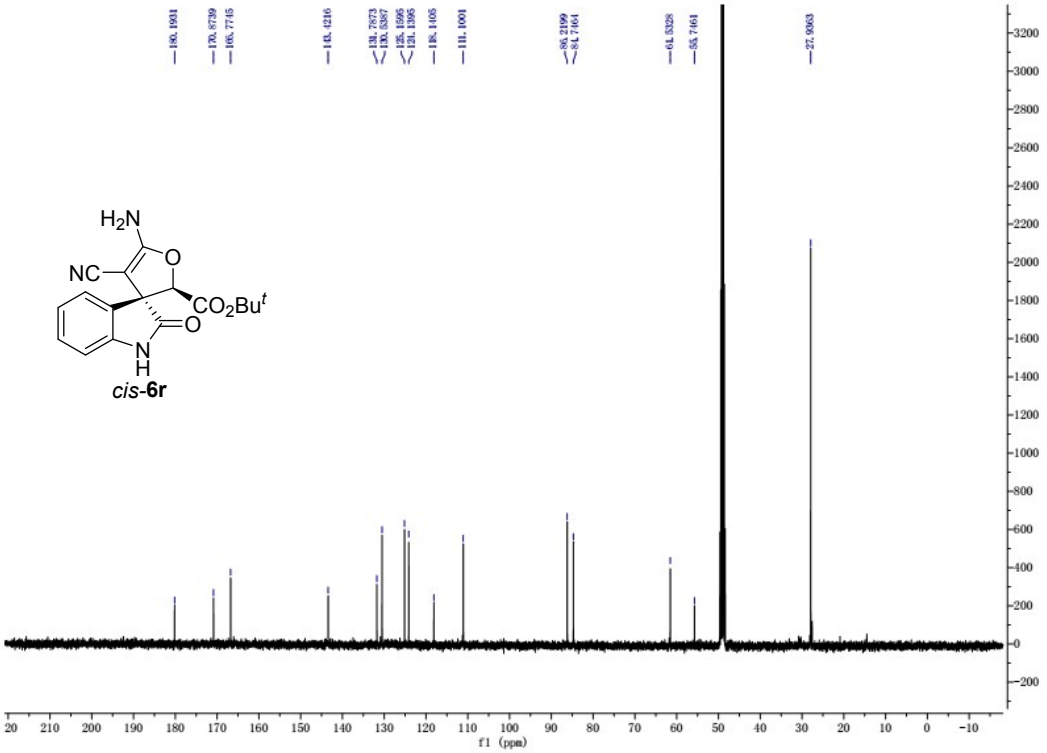

H2N
NC
O
CO2Me
O
N
H
cis-6q
f1 (ppm)


H2N
NC
O
CO2Me
O
N
H
cis-6q
f1 (ppm)

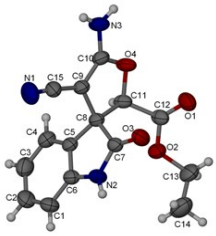

H2N
NC
O
CO2Bu^t
O
N
H
trans-6r
f1 (ppm)

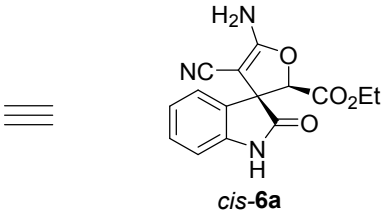

H2N
NC
O
CO2Bu^t
O
N
H
trans-6r
f1 (ppm)


H2N
NC
O
CO2Bu^t
O
N
H
cis-6r
f1 (ppm)


H2N
NC
O
CO2Bu^t
O
N
H
cis-6r
f1 (ppm)

X-ray crystal structure data of 6a and 6k

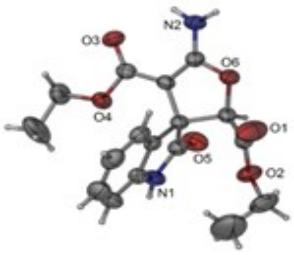




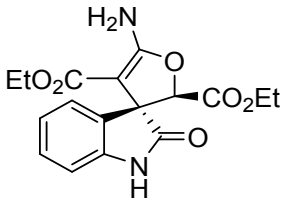
cis-**6a**

X-ray diffraction parameters and data (CCDC: 1899658)

```
Bond precision:       C-C = 0.0023 A                Wavelength=0.71073
Cell:        a=19.7660(14)     b=19.7660(14)     c=7.7429(6)
             alpha=90          beta=90           gamma=90
Temperature: 296 K
                    Calculated                          Reported
Volume              3025.1(5)                           3025.1(4)
Space group         P 4/n                               P4/n
Hall group          -P 4a                               ?
Moiety formula      C15 H13 N3 O4                       ?
Sum formula         C15 H13 N3 O4                       C1.97 H1.70 N0.39 O0.52
Mr                  299.28                              39.25
Dx,g cm-3           1.314                               1.314
Z                   8                                   61
Mu (mm-1)           0.098                               0.098
F000                1248.0                              1248.0
F000'               1248.63
h,k,lmax            23,23,9                             23,23,9
Nref                2676                                2673
Tmin,Tmax           0.954,0.965                         0.955,0.966
Tmin'               0.954
Correction method= MULTI-SCAN
Data completeness= 0.999          Theta(max)= 25.010
R(reflections)= 0.0379( 2412)         wR2(reflections)= 0.1001( 2673)
S = 1.036              Npar= 199
```



≡



trans-**6k**

X-ray diffraction parameters and data (CCDC: 1941034)

```
Bond precision:  C-C = 0.0041 A          Wavelength=0.71073

Cell:            a=19.0210(8)      b=19.0210(8)      c=8.7701(5)
                 alpha=90          beta=90           gamma=120
Temperature:     296 K

                 Calculated                Reported
Volume           2747.9(3)                 2747.9(2)
Space group      P 65                      P6(5)
Hall group       P 65                      ?
Moiety formula   C17 H18 N2 O6             ?
Sum formula      C17 H18 N2 O6             C17 H18 N2 O6
Mr               346.33                    346.33
Dx,g cm-3        1.256                     1.256
Z                6                         6
Mu (mm-1)        0.096                     0.096
F000             1092.0                    1092.0
F000'            1092.62
h,k,lmax         22,22,10                  22,22,10
Nref             3234[ 1733]               3143
Tmin,Tmax        0.978,0.989               0.964,0.988
Tmin'            0.964

Correction method= MULTI-SCAN

Data completeness= 1.81/0.97      Theta(max)= 25.000

R(reflections)= 0.0401( 2511)     wR2(reflections)= 0.0924( 3143)

S = 1.035                 Npar= 226
```