Supporting Information

For

Synthesis of Highly Substituted 2-Hydroxybenzophenones through Skeletal Clipping of 3-Benzofuranones

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1. General experimental information

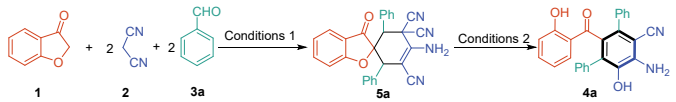
Reactions were monitored by thin layer chromatography (TLC) and the developed chromatogram was visualized under ultraviolet light. All reagents were purchased from commercial supplier without any further purification. The forced-flow column chromatography was performed on QingDao Haiyang Chemical Co. silica gel (HG-/T2354) eluting with ethyl acetate, dichloromethane and petroleum ether. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ or DMSO-d_6 solutions were measured on 400 and 100 MHz or at 500 and 125 MHz (Bruker Avance) respectively and chemical shift (δ) is given in parts per million (ppm) relatives to tetramethylsilane (TMS). Coupling constants for NMR are reported in Hertz (Hz), as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). High resolution mass spectra (HRMS) were measured on a Q-TOF-Premier mass spectrometer. The X-ray crystal-structure determinations (XRD) of intermediate **e** and **4c** were obtained on a Bruker APEX DUO system. All melting points were measured by using a SGW X-4 melting apparatus, which were uncorrected.

2. Optimization of the Reaction Conditions

Firstly, for step 1, the model reaction catalyzed by simple inorganic/organic base, was carried out in acetonitrile at 40 °C (entries 1-7, Table 1). When sodium carbonate was employed as the catalyst, the desired intermediate **5a** was isolated in 61% yield (entry 1). Subsequently, other easily available inorganic or organic base were evaluated (entries 2-7), among which potassium carbonate proved to be the best catalyst in terms of isolated yield (entry 2). After identifying the optimal catalyst, a series of solvents were evaluated by using potassium carbonate (20 mol%) as the catalyst and the results were listed in Table 1 (entries 8-13). The results revealed that yields are greatly variable with solvents. When the reaction was conducted in less polar solvent such as dichloromethane, the desired product intermediate **5a** was obtained in excellent yield (94%, Table 1, entry 9). Moderate results were observed when the reaction was carried out in polar solvent such as DMF and DMSO (Table1, entry 12 and 13). Those results indicated that dichloromethane delivered the highest yield at 40 ^{o}C, and was chosen as a suitable candidate solvent for further screening (entry 9). Through those screenings, the optimized reaction conditions for the one-pot five component

reactions involve the use of potassium carbonate (20 mol%) in dichloromethane at 40 °C with 1.0 equiv. benzofuranone, 2.0 equiv. malononitrile and 2.0 equiv. benzaldehyde (entry 9).

Table S1. Optimization of the Reaction Conditions[a]

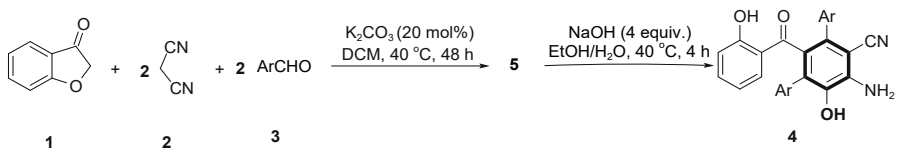


Entry	Conditions		Yield (%)
1	conditions **1**	Na_2CO_3 (20 mol%), CH_3CN, 40 °C, 48 h	61[b]
2		K_2CO_3 (20 mol%), CH_3CN, 40 °C, 48 h	80[b]
3		Cs_2CO_3 (20 mol%), CH_3CN, 40 °C, 48 h	51[b]
4		DABCO (20 mol%), CH_3CN, 40 °C, 48 h	64[b]
5		DBU (20 mol%), CH_3CN, 40 °C, 48 h	52[b]
6		DMAP (20 mol%), CH_3CN, 40 °C, 48 h	71[b]
7		Et_3N (20 mol%), CH_3CN, 40 °C, 48 h	78[b]
8		K_2CO_3 (20 mol%), toluene, 40 °C, 48 h	18[b]
9		K_2CO_3 (20 mol%), CH_2Cl_2, 40 °C, 48 h	94[b]
10		K_2CO_3 (20 mol%), $CHCl_3$, 40 °C, 48 h	31[b]
11		K_2CO_3 (20 mol%), THF, 40 °C, 48 h	62[b]
12		K_2CO_3 (20 mol%), 1,4-dioxane, 40 °C, 48 h	48[b]
13		K_2CO_3(20 mol%), DMF, 40 °C, 48 h	35[b]
14		K_2CO_3 (20 mol%), DMSO, 40 °C, 48 h	48[b]
15[c]	conditions **2**	NaOH (1.0 equiv), EtOH/H_2O, 40 °C, 4 h	26[d]
16[c]		NaOH (2.0 equiv), EtOH/H_2O, 40 °C, 4 h	39[d]
17[c]		NaOH (3.0 equiv), EtOH/H_2O, 40 °C, 4 h	79[d]
18[c]		NaOH (4.0 equiv), EtOH/H_2O, 40 °C, 4 h	90[d]

[a] Unless otherwise specified, all reaction carried out with benzofuran-3-one (0.15 mmol, 1.0 equiv), malononitrile (**2**, 0.30 mmol, 2.0 equiv), benzaldehyde (**3a**, 0.30 mmol, 2.0 equiv), solvent (1.0 mL) and catalysts (20 mol%) at 40 °C. [b] Isolated yields of step 1. [c] Unless otherwise specified, all reaction carried out with intermediate (0.10 mmol, 1.0 equiv), NaOH and EtOH/H_2O (0.09 M, v/v = 10 : 1) at 40 °C. [d] Isolated yields of step 2

Subsequently, the reaction conditions of step 2 were optimized, mainly screening the amount of sodium hydroxide. And the results revealed that the 4.0 equiv. sodium hydroxide could give the product **4a** in excellent yield (90% yield, entry 17). Thus, 4.0 equiv. sodium hydroxide was chosen as suitable for this transformation of step 2.

3. General experimental procedures for synthesis of compounds 4 and characterization data

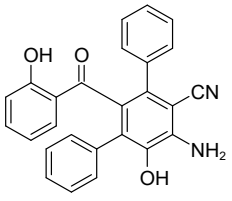


General procedure for synthesis of compounds 4:

Step 1: A stirred solution of benzofuran-3-one (**1**, 0.40 mmol, 1.0 equiv.), malononitriles (0.80 mmol, 2.0 equiv.), benzaldehyde (0.80 mmol, 2.0 equiv.) and K_2CO_3 (0.08 mmol, 0.2 equiv.) in CH_2Cl_2 (6.0 mL) was stirred at 40 °C for 48 h. After the complete consumption of benzofuran-3-one as monitored by TLC, to the reaction solution, H_2O (10 mL) was added. Then, the reaction solution was extracted with CH_2Cl_2 (15 mL×3). The organic phase was dried with $MgSO_4$, filtered and concentrated *in-vacuo*. The residue was purified by column chromatography on silica gel (eluent PE/EtOAc/DCM = 8:1:1 to 5:1:1) to afford pure intermediate compounds **5**.

Step 2: a mixture of intermediate spiro product (1.0 equiv.), sodium hydroxide (4.0 equiv.) was dissolved in the mixture solvent of EtOH/H_2O (0.09 M, V/V = 10 : 1) were added to a sealed reaction tube equipped with a stir bar. The tube was then sealed and the resulting mixture was stirred at 40 °C for the 4 h. Upon completion (monitored by TLC, visualized by UV light), to the reaction solution, H_2O (5 mL) was added. And then, the pH of mixture was adjusted to 5 with 0.5 N HCl in fume hood. The mixture was extracted with CH_2Cl_2 (15 mL×3). The aqueous layer was discarded after basified with sodium hypochlorite solution. The organic phase was dried with $MgSO_4$, filtered and concentrated *in-vacuo*. The residue was purified by column chromatography on silica gel to afford pure products **4**.

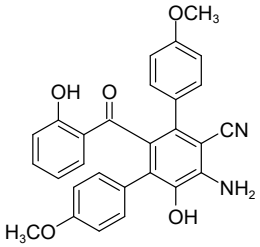
5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4a)



The reaction was performed utilizing corresponding compound **3a** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.35 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 94% yield, (166.4 mg, step 1), 90% yield (136.0 mg, step 2); m.p. 155.3 – 156.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.88 (s, 1H), 7.32 – 7.14 (m, 10H), 7.12 (d, J = 7.1 Hz, 2H), 6.70 – 6.64 (m, 1H), 6.60 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.02 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.7, 160.4, 143.8, 139.8, 136.9, 136.1, 134.8,

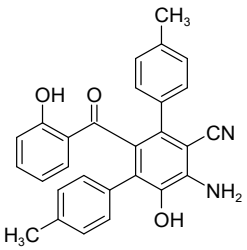
133.9, 133.0, 130.7, 129.9, 129.5, 128.0, 127.8, 127.7, 127.6, 127.4, 121.5, 118.9, 116.9, 116.8, 94.3. HRMS (ESI) calcd. for $C_{26}H_{19}N_2O_3$ $[M + H]^+$ 407.1390, found: 407.1391.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-4'-carbonitrile (4b)



The reaction was performed utilizing corresponding compound **3b** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent, Rf = 0.20 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 89 % yield (132.7 mg, step 1), 58% yield (96.3 mg, step 2); m.p. 236.9 – 237.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.76 (s, 1H), 7.34 – 7.17 (m, 2H), 7.14 – 6.92 (m, 4H), 6.82 – 6.54 (m, 6H), 5.93 (s, 2H), 3.73 – 3.57 (m, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 202.2, 160.6, 158.8, 158.6, 143.6, 139.8, 136.2, 133.6, 133.0, 131.2, 130.8, 130.4, 129.1, 127.9, 127.7, 126.8, 121.4, 119.0, 117.0, 113.4, 113.3, 94.5, 55.1, 55.0. HRMS (ESI) calcd. for $C_{28}H_{23}N_2O_5$ $[M + H]^+$ 467.1601, found: 467.1600.

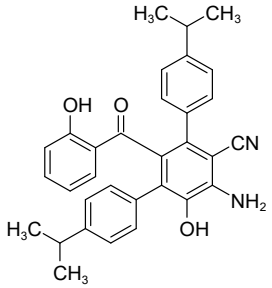
5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-4,4''-dimethyl-[1,1':3',1''-terphenyl]-4'-carbonitrile (4c)



The reaction was performed utilizing corresponding compound **3c** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.45 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 95 % yield (178.8 mg, step 1), 82% yield (135.4 mg, step 2); m.p. 176.7 – 177.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.38 (s, 1H), 7.25 – 7.09 (m, 3H), 7.05 (d, J = 7.7 Hz, 3H), 6.94 (d, J = 7.8 Hz, 3H), 6.88-6.85 (m, 1H), 6.60 – 6.51 (m, 2H), 5.29 (s, 1H), 4.82 (s, 2H), 2.19 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 160.9, 139.6, 139.5, 138.2, 137.6, 137.2, 135.1, 134.1, 132.2, 131.8, 129.2, 128.4, 128.0, 127.9, 127.6,

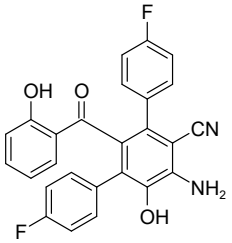
126.7, 120.1, 117.4, 116.5, 115.5, 95.3, 20.19, 20.16. HRMS (ESI) calcd. for $C_{28}H_{23}N_2O_3$ $[M + H]^+$ 435.1703, found: 435.1700.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-4,4''-diisopropyl-[1,1':3',1''-terphenyl]-4'-carbonitrile (4d)



The reaction was performed utilizing corresponding compound **3d** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.60 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 63 % yield (160.8 mg, step 1), 49% yield (60.6 mg, step 2); m.p. 225.0 – 226.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.38 (s, 1H), 7.16 – 7.11 (m, 3H), 7.06 (d, *J* = 7.8 Hz, 4H), 6.70 – 6.47 (m, 2H), 5.33 (s, 1H), 4.91 (s, 2H), 2.87 – 2.81 (m, 1H), 2.81 – 2.75 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 161.7, 150.0, 148.9, 140.7, 138.6, 135.9, 135.4, 133.6, 132.7, 129.5, 129.4, 128.8, 128.0, 127.6, 126.2, 121.3, 118.43, 118.40, 117.3, 116.5, 96.2, 33.8, 33.7, 23.68, 23.66. HRMS (ESI) calcd. for $C_{32}H_{31}N_2O_3$ $[M + H]^+$ 491.2329, found: 491.2327.

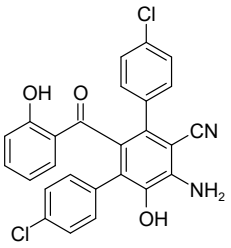
5'-amino-4,4''-difluoro-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4e)



The reaction was performed utilizing corresponding compound **3e** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.35 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 84 % yield (160.8 mg, step 1), 56% yield (83.2 mg, step 2); m.p. 122.5 – 123.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.07 (s, 1H), 8.98 (s, 1H), 7.31 – 6.94 (m, 10H), 6.72 – 6.51 (m, 2H), 6.06 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ

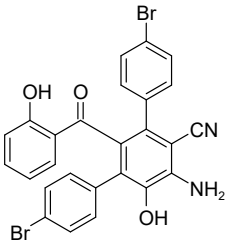
201.2, 161.8 (d, J = 245.2 Hz), 161.6 (d, J = 244.4 Hz), 160.2, 143.9, 140.2, 136.3, 133.3 (d, J = 3.2 Hz), 132.9, 132.8, 132.1 (d, J = 8.3 Hz), 131.8 (d, J = 8.3 Hz), 131.1 (d, J = 3.2 Hz), 129.6, 128.0, 121.8, 119.1, 117.1, 116.8, 114.9 (d, J = 21.5 Hz), 114.8 (d, J = 21.5 Hz), 94.5. HRMS (ESI) calcd. for $C_{26}H_{17}F_2N_2O_3$ $[M + H]^+$ 443.1202, found: 443.1200.

5'-amino-4,4''-dichloro-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4f)



The reaction was performed utilizing corresponding compound **3f** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.45 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 64 % yield (130.9 mg, step 1), 76% yield (92.5 mg, step 2); m.p. 162.4 – 163.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.05 (s, 1H), 7.32 – 7.30 (m,2H), 7.29-7.26 (m， 3H), 7.25 – 7.18 (m, 3H), 7.13 (d, J = 8.2 Hz, 2H), 6.71 – 6.61 (m, 2H), 6.10 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 200.7, 160.1, 143.9, 140.2, 136.2, 135.8, 133.7, 132.9, 132.7, 132.6, 132.5, 131.8, 131.3, 129.3, 128.0, 127.9, 127.6, 121.8, 119.0, 117.0, 116.6, 94.3. HRMS (ESI) calcd. for $C_{26}H_{17}Cl_2N_2O_3$ $[M + H]^+$ 475.0611, found: 475.0609.

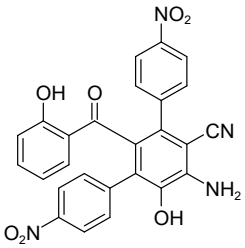
5'-amino-4,4''-dibromo-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4g)



The reaction was performed utilizing corresponding compound **3g** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.35 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 57 % yield (136.9 mg, step 1), 58% yield (74.6 mg, step 2); m.p. 153.9 – 154.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.28 (s, 1H), 7.51 – 7.33 (m, 2H), 7.32 – 7.15 (m, 4H), 7.09 – 7.01 (m, 3H), 6.96 – 6.80 (m, 1H), 6.63 (d, J = 8.3 Hz, 1H),

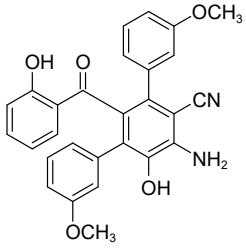
6.60 – 6.53 (m, 1H), 5.27 (s, 1H), 4.90 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 161.1, 140.1, 137.8, 135.8, 133.9, 132.8, 131.7, 131.3, 130.5, 130.1, 129.8, 126.4, 126.3, 122.9, 122.1, 119.8, 117.7, 117.0, 114.9, 95.1. HRMS (ESI) calcd. for $C_{26}H_{17}Br_2N_2O_3$ $[M + H]^+$ 562.9600, found: 562.9610.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-4,4''-dinitro-[1,1':3',1''-terphenyl]-4'-carbonitrile (4h)



The reaction was performed utilizing corresponding compound **3h** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent, Rf = 0.22 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 65 % yield (138.4 mg, step 1), 67% yield (86.5 mg, step 2); m.p. 117.6 – 118.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.08-8.02 (m, 4H), 7.49-7.38 (m, 4H), 7.26 – 7.00 (m, 2H), 6.62-6.57 (m, 2H), 6.21 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.2, 159.6, 147.3, 147.1, 144.6, 144.3, 142.7, 141.0, 136.3, 132.5, 132.3, 131.8, 131.4, 129.0, 128.3, 123.3, 123.2, 123.0, 119.4, 117.3, 116.7, 94.3. HRMS (ESI) calcd. for $C_{26}H_{17}N_4O_7$ $[M + H]^+$ 497.1092, found: 497.1100.

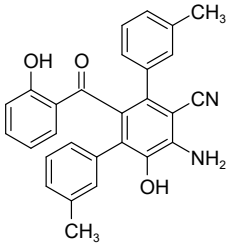
5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-3,3''-dimethoxy-[1,1':3',1''-terphenyl]-4'-carbonitrile (4i)



The reaction was performed utilizing corresponding compound **3i** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.40 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 71 % yield (142.7 mg, step 1), 80% yield (106.0 mg, step 2); m.p. 188.4 – 188.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.89 (s, 1H), 7.30-7.26 (m, 2H), 7.18 – 7.02 (m, 2H), 6.71 (m, 6.63 – 6.78, 8H), 6.00 (s, 2H), 3.57-3.55 (m,

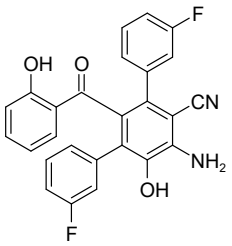
6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.6, 160.3, 158.6, 158.5, 143.9, 139.9, 139.8, 138.2, 136.2, 136.0, 133.6, 133.1, 130.4, 129.1, 129.0, 127.4, 122.3, 122.0, 118.9, 117.0, 116.8, 115.4, 115.1, 113.8, 113.7, 94.2, 54.9, 54.8. HRMS (ESI) calcd. for $C_{28}H_{23}N_2O_5$ $[M + H]^+$ 467.1601, found: 467.1601.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-3,3''-dimethyl-[1,1':3',1''-terphenyl]-4'-carbonitrile (4j)



The reaction was performed utilizing corresponding compound **3j** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.40 (petroleum ether/ethyl acetate = 3:1). Brownish yellow solid; 72 % yield (135.5 mg, step 1), 73% yield (91.3 mg, step 2); m.p. 188.5 – 188.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.13 (s, 1H), 8.81 (s, 1H), 7.29 – 7.21 (m, 2H), 7.12 – 7.04 (m, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.97 – 6.95 (m, 4H), 6.94 (s, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 5.97 (s, 2H), 2.16 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.6, 160.2, 143.7, 139.6, 136.8, 136.7, 136.6, 135.9, 134.6, 133.9, 132.8, 130.7, 130.6, 130.2, 128.5, 128.1, 127.7, 127.6, 127.4, 126.9, 126.5, 121.6, 118.6, 116.8, 116.7, 94.2, 20.8.82, 20.79. HRMS (ESI) calcd. for $C_{28}H_{23}N_2O_3Na$ $[M + Na]^+$ 435.1703, found: 435.1707.

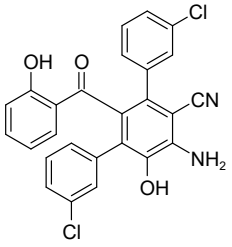
5'-amino-3,3''-difluoro-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4k)



The reaction was performed utilizing corresponding compound **3k** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.40 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 91 % yield (174.2 mg, step 1), 86% yield

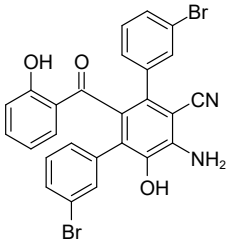
(138.5 mg, step 2); m.p. 202.5 – 203.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 9.12 (s, 1H), 7.30 – 7.22 (m, 7H), 7.18-7.13 (m, 2H), 7.05 (s, 1H), 6.70-6.65 (m, 2H), 6.15 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 200.4, 161.4 (d, J = 244.1 Hz), 161.2 (d, J = 244.8 Hz), 159.9, 143.9, 140.1, 139.2 (d, J = 8.2 Hz), 137.1 (d, J = 8.2 Hz), 136.1, 132.7, 132.4 (d, J = 2.0 Hz), 130.0 (d, J = 8.6 Hz), 129.8 (d, J = 8.6 Hz), 129.1 (d, J = 1.9 Hz), 127.6, 126.0 (d, J = 2.7 Hz), 125.8 (d, J = 2.8 Hz), 121.9, 118.9, 116.93 (d, J = 21.9 Hz), 116.91, 116.52, 116.50 (d, J = 21.9 Hz), 114.9 (d, J = 20.7 Hz), 114.5 (d, J = 21.0 Hz), 94.2. HRMS (ESI) calcd. for $C_{26}H_{17}F_2N_2O_3$ $[M + H]^+$ 443.1202, found: 443.1199.

5'-amino-3,3''-dichloro-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4l)



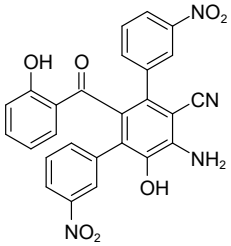
The reaction was performed utilizing corresponding compound **3l** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.45 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 88 % yield (180.0 mg, step 1), 59% yield (98.7 mg, step 2); m.p. 183.3 – 183.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.11 (s, 1H), 7.31 – 7.25 (m, 3H), 7.25 – 7.19 (m, 4H), 7.15-7.12 (m, 2H), 7.05-7.03 (m, 1H), 6.70 – 6.64 (m, 2H), 6.12 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 200.1, 159.7, 144.0, 140.2, 138.9, 136.9, 136.0, 132.5, 132.43, 132.38, 132.3, 129.8, 129.7, 129.6, 129.3, 129.0, 128.5, 128.3, 128.0, 127.8, 127.5, 122.2, 118.9, 116.9, 116.5, 94.2. HRMS (ESI) calcd. for $C_{26}H_{16}Cl_2N_2O_3Na$ $[M + Na]^+$ 497.0430, found: 497.0432.

5'-amino-3,3''-dibromo-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4m)



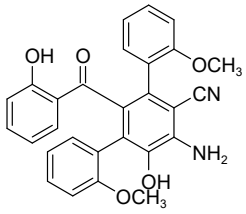
The reaction was performed utilizing corresponding compound **3m** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.35 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 86 % yield (206.5 mg, step 1), 76% yield (147.5 mg, step 2); m.p. 118.4 – 119.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.11 (s, 1H), 7.43-7.41 (m, 1H), 7.39 – 7.33 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 – 7.14 (m, 4H), 7.08 (d, J = 7.7 Hz, 1H), 6.74 – 6.59 (m, 2H), 6.14 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 200.3, 159.9, 157.1, 144.2, 140.4, 139.3, 137.3, 136.2, 132.8, 132.6, 132.33, 132.30, 131.0, 130.6, 130.2, 130.1, 129.2, 129.0, 128.8, 128.1, 122.3, 121.2, 119.1, 117.1, 116.8, 94.3. HRMS (ESI) calcd. for $C_{26}H_{17}Br_2N_2O_3$ $[M + H]^+$ 562.9600, found: 562.9596.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-3,3''-dinitro-[1,1':3',1''-terphenyl]-4'-carbonitrile (4n)



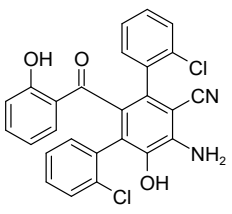
The reaction was performed utilizing corresponding compound **3n** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent, Rf = 0.22 (petroleum ether/ethyl acetate = 3:1). Reddish brown solid; 68 % yield (144.8 mg, step 1), 75% yield (101.3 mg, step 2); m.p. 189.1 – 190.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.32 (s, 1H), 8.11 (dd, J = 8.2, 2.3 Hz, 1H), 8.07 – 8.04 (m, 2H), 7.98-7.97 (m, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.21 – 7.14 (m, 2H), 6.61 – 6.58 (m, 2H), 6.29 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.5, 158.9, 147.1, 147.0, 144.2, 140.6, 138.6, 136.7, 136.6, 136.2, 135.6, 131.7, 129.7, 129.5, 128.9, 128.2, 124.8, 124.1, 123.3, 122.9, 122.5, 119.0, 116.9, 116.4, 94.2. HRMS (ESI) calcd. for $C_{26}H_{17}N_4O_7$ $[M + H]^+$ 497.1092, found: 497.1096.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-2,2''-dimethoxy-[1,1':3',1''-terphenyl]-4'-carbonitrile (4o)



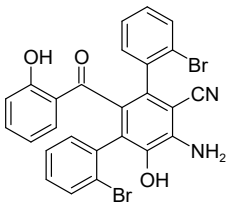
The reaction was performed utilizing corresponding compound **3o** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent, Rf = 0.30 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 85% yield (170.9 mg, step 1), 66% yield (104.7 mg, step 2); m.p. 200.5 – 201.4 °C. The ratio of **4o**-A/**4o**-B was 1:0.75 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 11.25 (s, 1H, isomer A), 11.22 (s, 1H, isomer B), 8.72 (s, 1H for isomer A and 1H for isomer B, overlapped), 7.37 – 7.33 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.28-7.23 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.19-7.13 (m, 2H for isomer A and 2H for isomer B, overlapped), 7.03-7.01 (m, 2H, isomer A), 6.90-6.80 (m, 2H for isomer A and 5H for isomer B, overlapped), 6.76 – 6.63 (m, 3H for isomer A and 2H for isomer B, overlapped), 6.59-6.54 (m, 1H for isomer A and 1H for isomer B, overlapped), 5.84 (s, 2H for isomer A and 2H for isomer B, overlapped), 3.68 (s, 3H, isomer B), 3.63 (s, 3H, isomer B), 3.51 (s, 3H, isomer A), 3.36 (s, 3H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6, a mixture of two isomers) δ 202.0, 201.8, 160.6, 160.4, 156.4, 156.2, 142.9, 142.3, 140.6, 140.5, 135.9, 135.8, 133.5, 133.0, 131.8, 131.4, 130.7, 130.6, 130.0, 129.9, 129.63, 129.59, 128.0, 127.9, 127.4, 127.3, 125.7, 125.4, 123.4, 123.1, 121.2, 120.3, 119.84, 119.81, 119.17, 119.7, 118.2, 117.6, 116.93, 119.91, 116.6, 116.4, 111.2, 111.0, 110.9, 110.7, 95.5, 95.3, 55.3, 55.1, 54.9, 54.6. HRMS (ESI) calcd. for $C_{28}H_{23}N_2O_5$ $[M + H]^+$ 467.1601, found: 467.1605.

5'-amino-2,2''-dichloro-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4p)



The reaction was performed utilizing corresponding compound **3p** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.50 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 71 % yield (145.2 mg, step 1), 65% yield (87.7 mg, step 2); m.p. 203.4 – 204.6 °C; The ratio of **4p**-A/**4p**-B was 1:0.07 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.25 (s, 1H), 7.42-7.40 (m, 1H), 7.37 – 7.33 (m, 1H), 7.31 – 7.23 (m, 5H), 7.21 – 7.16 (m, 3H), 6.70 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 6.14 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 200.6, 160.5, 143.7, 141.4, 136.8, 135.5, 133.9, 133.7, 133.6, 133.5, 132.9, 132.8, 131.1, 130.6, 130.2, 129.63, 129.58, 129.5, 128.1, 127.6, 127.0, 126.8, 121.4, 118.8, 117.1, 116.7, 95.6. HRMS (ESI) calcd. for $C_{26}H_{16}Cl_2N_2O_3Na$ $[M+Na]^+$ 497.0432, found: 497.0434.

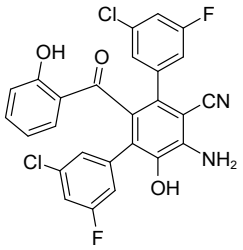
5'-amino-2,2''-dibromo-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4q)



The reaction was performed utilizing corresponding compound **3q** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.40 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 81 % yield (194.5 mg, step 1), 79% yield (144.4 mg, step 2); m.p. 124.7 – 125.2 °C. The ratio of **4q**-A/**4q**-B was 1:0.23 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 11.01 (s, 1H, isomer A), 10.93 (s, 1H, isomer B), 9.24 (s, 1H for isomer A and 1H for isomer B, overlapped), 7.56 (d, J = 7.9 Hz, 1H, isomer B), 7.54 – 7.50 (m, 2H for isomer A and 1H for isomer B, overlapped), 7.48 (d, J = 1.8 Hz, 1H, isomer B), 7.46 (d, J = 7.7 Hz, 1H, isomer A), 7.30 – 7.28 (m, 1H, isomer A), 7.27-7.25 (m, 2H for isomer A and 1H for isomer B, overlapped), 7.22 – 7.19 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.18 – 7.13 (m, 2H for isomer A and 3H for isomer B, overlapped), 7.12-7.10 (m, 1H, isomer A), 7.09 (d, J = 1.8 Hz, 1H, isomer B), 7.06-7.04 (m, 1H, isomer B), 6.76 – 6.73 (m, 1H, isomer B), 6.70 (t, J = 7.6 Hz, 1H, isomer A), 6.61 – 6.58 (m, 1H for isomer A and 1H for isomer B, overlapped), 6.13 (s, 2H, isomer B), 6.11 (s, 2H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6, a mixture of two isomers) δ 200.4, 200.1, 160.0, 159.9, 143.2, 143.1, 140.8, 140.7, 137.0,

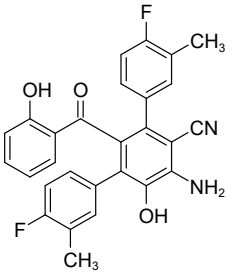
136.3, 136.2, 135.5, 135.3, 133.6, 133.2, 132.5, 132.4, 132.35, 132.31, 132.2, 132.1, 130.2, 129.8, 128.5, 127.4, 127.2, 127.1, 127.0, 126.9, 124.5, 124.3, 124.1, 123.8, 121.4, 121.1, 121.0, 118.7, 118.6, 118.4, 116.7, 116.6, 116.3, 116.2, 95.3. HRMS (ESI) calcd. for $C_{26}H_{17}Br_2N_2O_3$ $[M + H]^+$ 562.9600, found: 562.9606.

5'-amino-3,3''-dichloro-5,5''-difluoro-6'-hydroxy-2'-(2-hydroxybenzoyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4r)



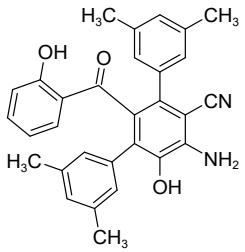
The reaction was performed utilizing corresponding compound **3r** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.40 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 43 % yield (94.1 mg, step 1), 75% yield (66.0 mg, step 2); m.p. 114.5 – 115.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 9.29 (s, 1H), 7.35 – 7.23 (m, 3H), 7.20 (dd, J = 8.3, 1.8 Hz, 1H), 7.09 (t, J = 1.5 Hz, 1H), 7.06-7.03 (m, 1H), 6.98 (s, 1H), 6.93-6.90 (m, 1H), 6.70-6.67 (m, 2H), 6.24 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.6, 161.5 (d, J = 247.8 Hz), 161.2 (d, J = 248.9 Hz), 159.1, 144.1, 140.5 (d, J = 9.2 Hz), 140.5, 138.5 (d, J = 9.4 Hz), 135.8, 133.4 (d, J = 10.1 Hz), 133.3 (d, J = 10.1 Hz), 132.0, 131.1 (d, J = 2.1 Hz), 128.2, 127.6, 126.3 (d, J = 2.8 Hz), 125.9 (d, J = 3.4 Hz), 123.0, 119.0, 116.9, 116.3, 116.0 (d, J = 21.8 Hz), 115.7 (d, J = 2.7 Hz), 115.6, 115.2 (d, J = 25.1 Hz), 93.9. HRMS (ESI) calcd. for $C_{26}H_{15}Cl_2F_2N_2O_3$ $[M + H]^+$ 511.0422, found: 511.0426.

5'-amino-4,4''-difluoro-6'-hydroxy-2'-(2-hydroxybenzoyl)-3,3''-dimethyl-[1,1':3',1''-terphenyl]-4'-carbonitrile (4s)



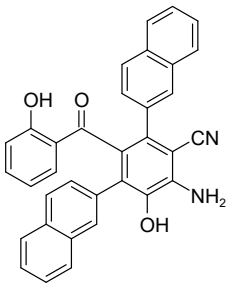
The reaction was performed utilizing corresponding compound **3s** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent, Rf = 0.35 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 59 % yield (119.5 mg, step 1), 61% yield (67.7 mg, step 2); m.p. 101.5 – 102.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.89 (s, 1H), 7.30-7.26 (m, 1H), 7.22 – 7.19 (m, 1H), 7.11 – 7.08 (m, 1H), 7.03 – 6.90 (m, 5H), 6.67-6.64 (m, 2H), 6.03 (s, 2H), 2.13 – 1.98 (m, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.0, 160.2 (d, J = 244.2 Hz), 160.1 (d, J = 243.7 Hz), 160.0, 143.7, 140.0, 136.0, 133.5, 133.4, 133.0 (d, J = 3.7 Hz), 132.9, 132.8, 132.7, 130.8 (d, J = 3.8 Hz), 129.6, 129.2 (d, J = 8.3 Hz), 128.9 (d, J = 8.5 Hz), 123.7, 123.6, 123.4, 122.0, 118.9, 116.9, 114.5 (d, J = 22.5 Hz), 114.4 (d, J = 22.1 Hz), 94.3, 14.04, 14.02. HRMS (ESI) calcd. for $C_{28}H_{21}F_2N_2O_3$ $[M + H]^+$ 471.1515, found: 471.1514.

5'-amino-6'-hydroxy-2'-(2-hydroxybenzoyl)-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-4'-carbonitrile (4t)



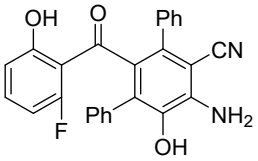
The reaction was performed utilizing corresponding compound **3t** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.45 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 67 % yield (133.6 mg, step 1), 71% yield (88.0 mg, step 2); m.p. 230.5 – 231.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.76 (s, 1H), 7.29-7.26 (m, 1H), 7.21-7.19 (m, 1H), 6.82 (s, 1H), 6.80 – 6.74 (m, 3H), 6.72 – 6.66 (m, 3H), 6.63 (d, J = 8.3 Hz, 1H), 5.93 (s, 2H), 2.11 (s, 6H), 2.08 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.6, 160.2, 143.6, 139.5, 136.8, 136.6, 136.5, 135.8, 134.5, 133.9, 132.8, 130.7, 129.3, 128.9, 127.8, 127.4, 121.8, 118.5, 116.9, 116.7, 94.0, 20.8, 20.7. HRMS (ESI) calcd. for $C_{30}H_{27}N_2O_3$ $[M + H]^+$ 463.2016, found: 463.2010.

2-amino-3-hydroxy-5-(2-hydroxybenzoyl)-4,6-di(naphthalen-2-yl)benzonitrile (4v)



The reaction was performed utilizing corresponding compound **3v** (0.80 mmol). Purified by column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent, Rf = 0.50 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 63% yield (136.7 mg, step 1), 76% yield (97.0 mg, step 2); m.p. 203.5 – 204.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.04 (s, 1H), 7.85 – 7.74 (m, 7H), 7.68 (s, 1H), 7.50 – 7.43 (m, 4H), 7.40 – 7.34 (m, 2H), 7.31 (d, J = 8.5 Hz, 1H), 7.17-7.14 (m, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 8.3 Hz, 1H), 6.12 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.9, 160.6, 144.3, 140.7, 136.5, 134.9, 134.2, 133.3, 132.90, 132.87, 132.7, 132.61, 132.58, 130.8, 129.7, 129.3, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.0, 126.9, 126.8, 126.6, 122.0, 119.3, 117.4, 117.3, 95.0, 40.5, 40.4, 40.3, 40.25, 40.16, 40.1, 40.0, 39.9, 39.8, 39.6, 39.5. HRMS (ESI) calcd. for $C_{34}H_{23}N_2O_3$ $[M + H]^+$ 507.1703, found: 507.1703.

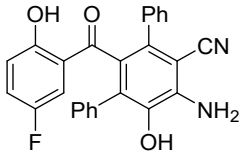
5'-amino-2'-(2-fluoro-6-hydroxybenzoyl)-6'-hydroxy-[1,1':3',1''-terphenyl]-4'-carbonitrile (4w)



The reaction was performed utilizing corresponding compound **3a** (0.80 mmol). Purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent. Rf = 0.30 (petroleum ether/ethyl acetate = 3:1). White solid; 73% yield (134.4 mg, step 1), 53% yield (65.6 mg, step 2); m.p. 218.7 – 219.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.74 (s, 1H), 7.25 – 7.22 (m, 4H), 7.21 – 7.16 (m, 4H), 7.14 (d, J = 7.7 Hz, 3H), 6.41 (d, J = 8.4 Hz, 1H), 6.34 (dd, J = 11.0, 8.2 Hz, 1H), 6.02 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.4, 160.8 (d, J = 254.1 Hz, 1C), 159.5 (d, J = 4.0 Hz, 1C), 143.9, 139.6, 137.3, 135.2, 135.1, 134.3, 131.0 (d, J = 12.7 Hz, 1C), 129.7, 129.3, 127.9, 127.87, 127.4, 116.9, 114.4 (d, J = 11.7 Hz, 1C), 112.8 (d, J = 3.0 Hz, 1C), 106.0 (d, J = 22.8 Hz, 1C), 94.3. HRMS (ESI-TOF) calcd. for

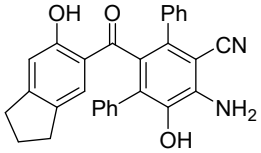
$C_{26}H_{18}FN_2O_3$ $[M + H]^+$ 425.1296, found: 425.1295.

5'-amino-2'-(5-fluoro-2-hydroxybenzoyl)-6'-hydroxy-[1,1':3',1''-terphenyl]-4'-carbonitrile (4x)



The reaction was performed utilizing corresponding compound **3a** (0.80 mmol). Purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent. Rf = 0.35 (petroleum ether/ethyl acetate = 3:1). White solid; 66 % yield (121.5 mg, step 1), 55% yield (61.6 mg, step 2); m.p. 212.9 – 214.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.88 (s, 1H), 7.27 – 7.20 (m, 7H), 7.18 (d, J = 6.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.10 (dd, J = 8.5, 3.2 Hz, 1H), 6.90 (dd, J = 9.0, 3.2 Hz, 1H), 6.63 (dd, J = 9.1, 4.4 Hz, 1H), 6.04 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 199.5, 156.0, 154.1 (d, J = 234.6 Hz, 1C), 144.0, 139.8, 137.1, 135.0, 134.3, 130.9, 129.9, 129.6, 128.0 (d, J = 7.2 Hz, 1C), 127.98, 127.9, 127.6, 123.0 (d, J = 23.7 Hz, 1C), 122.5, 118.6 (d, J = 7.2 Hz, 1C), 116.9, 116.87 (d, J = 23.1 Hz, 1C), 94.4. HRMS (ESI-TOF) calcd. for $C_{26}H_{18}FN_2O_3$ $[M + H]^+$ 425.1296, found: 425.1305.

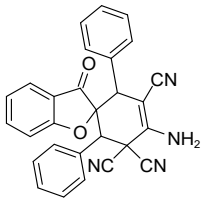
5'-amino-6'-hydroxy-2'-(6-hydroxy-2,3-dihydro-1H-indene-5-carbonyl)-[1,1':3',1''-terphenyl]-4'-carbonitrile (4y)



The reaction was performed utilizing corresponding compound **3a** (0.80 mmol). Purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent. Rf = 0.45 (petroleum ether/ethyl acetate = 3:1). Yellow solid; 54 % yield (104.2 mg, step 1), 60% yield (57.8 mg, step 2); m.p. 235.1 – 235.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.87 (s, 1H), 7.25 – 7.15 (m, 8H), 7.12 (d, J = 7.5 Hz, 2H), 7.07 (s, 1H), 6.46 (s, 1H), 6.02 (s, 2H), 2.70 – 2.64 (m, 4H), 1.88 (p, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 201.45, 160.42, 153.97, 143.79, 139.78, 137.07, 134.96, 134.16, 133.97, 130.87, 129.90, 129.51, 127.97, 127.85, 127.82, 127.72, 127.57, 127.34, 119.34, 116.87, 112.30, 94.38, 32.94, 30.87, 24.93. HRMS (ESI-TOF) calcd. for $C_{29}H_{23}N_2O_3$ $[M + H]^+$ 447.1707 found: 447.1704.

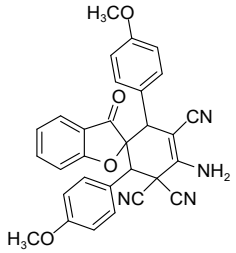
4'-amino-2',6'-diphenyl-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-

tricarbonitrile (**5a**)



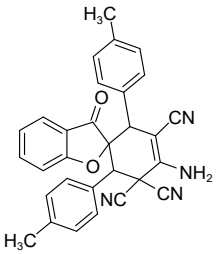
The compound **5a** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.45 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 140.7 – 141.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 3H), 7.27 – 7.21 (m, 2H), 7.20 – 7.11 (m, 3H), 7.10 – 6.99 (m, 5H), 6.76 (t, *J* = 7.4 Hz, 1H), 5.14 (s, 2H), 4.31 (s, 1H), 3.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 171.6, 144.2, 138.8, 132.5, 130.2, 130.1, 129.9, 129.2, 128.7, 128.3, 124.0, 122.6, 121.4, 116.0, 112.8, 112.04, 112.01, 87.2, 83.5, 50.7, 49.4, 40.7. HRMS (ESI-TOF) calcd. for $C_{28}H_{18}N_4O_2Na$ $[M + Na]^+$ 465.1322, found: 465.1324.

4'-amino-2',6'-bis(4-methoxyphenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5b)



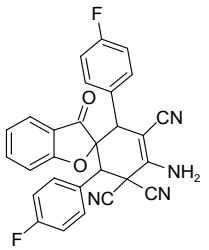
The compound **5b** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent. Rf = 0.30 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 142.1 – 142.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.60 (m, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.21-7.19 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.94 (s, 4H), 6.67-6.65 (m, 2H), 5.06 (s, 2H), 3.91 (s, 1H), 3.83 (s, 3H), 3.74 (s, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 170.1, 160.6, 160.1, 143.3, 138.8, 131.1, 130.7, 125.0, 124.7, 123.4, 122.1, 121.3, 116.4, 114.5, 114.4, 113.9, 112.6, 111.8, 87.8, 84.0, 55.3, 55.1, 50.1, 45.6, 41.4. HRMS (ESI-TOF) calcd. for $C_{30}H_{22}N_4O_4Na$ $[M + Na]^+$ 525.1533, found: 525.1538.

4'-amino-2',6'-di-p-tolyl-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5c)



The compound **5c** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.55 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 258.8 – 259.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.44 – 7.30 (m, 1H), 7.22 – 7.18 (m, 2H), 7.07 – 7.03 (m, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.92 – 6.68 (m, 7H), 5.06 (s, 2H), 4.21 (s, 1H), 3.85 (s, 1H), 2.14 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 170.6, 143.0, 139.1, 137.6, 137.3, 128.8, 128.6, 128.5, 127.9, 126.1, 123.0, 121.5, 120.4, 115.0, 111.8, 111.2, 111.1, 86.4, 82.9, 49.4, 48.1, 39.9, 20.1, 20.0. HRMS (ESI-TOF) calcd. for $C_{30}H_{22}N_4O_2Na$ $[M + Na]^+$ 493.1635, found: 493.1624.

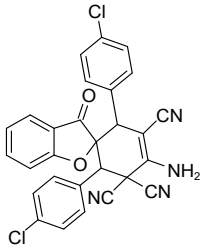
4'-amino-2',6'-bis(4-fluorophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5e)



The compound **5e** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.50 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 148.3 – 148.9 °C. The ratio of **5e**-A/**5e**-B was 1:0.30 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 7.87 (t, *J* = 7.8 Hz, 1H, isomer A), 7.71 (s, 2H, isomer B), 7.67 (d, *J* = 7.8 Hz, 1H, isomer B), 7.64 (s, 2H, isomer A), 7.51 (d, *J* = 8.4 Hz, 1H, isomer A), 7.47 (d, *J* = 7.7 Hz, 1H, isomer A), 7.43 – 7.39 (m, 3H, isomer B), 7.37-7.34 (m, 2H, isomer A), 7.29 (t, *J* = 8.6 Hz, 2H, isomer B), 7.25 – 7.17 (m, 5H, isomer A), 7.15 (d, *J* = 8.4 Hz, 1H, isomer B), 7.07 (t, *J* = 8.4 Hz, 2H for isomer A and 2H for isomer B, overlapped), 7.04 (d, *J* = 7.5 Hz, 1H, isomer B), 6.96 (t, *J* = 8.7 Hz, 2H, isomer B), 4.74 (s, 1H, isomer B), 4.22 (s, 1H, isomer B), 4.14 (s, 1H, isomer A), 4.11 (s, 1H, isomer A).^{13}C NMR (125 MHz, DMSO-d_6) δ 195.6, 195.4, 169.9, 169.4, 162.6 (d, *J* = 246.1 Hz), 162.5 (d, *J* = 244.9 Hz), 161.9 (d, *J* = 243.4 Hz), 161.6

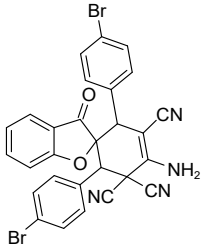
(d, J = 243.6 Hz), 145.6, 144.8, 139.5, 139.1, 133.6 (d, J = 9.7 Hz), 132.2 (d, J = 8.0 Hz), 132.1 (d, J = 8.2 Hz), 131.9 (d, J = 7.9 Hz), 131.1 (d, J = 2.8 Hz), 130.1 (d, J = 3.3 Hz), 127.7 (d, J = 3.1 Hz), 127.4 (d, J = 3.2 Hz), 124.6, 124.3, 123.6, 122.9, 120.9, 120.0, 117.8, 117.2, 115.7 (d, J = 21.6 Hz), 115.3 (d, J = 21.6 Hz), 114.9 (d, J = 21.4 Hz), 113.9, 113.4, 113.2, 112.4 (d, J = 25.8 Hz), 111.7, 87.4, 86.1, 77.1, 76.5, 49.3, 48.7, 44.6, 42.2, 40.6, 39.0. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}F_2N_4O_2Na$ $[M + Na]^+$ 501.1134, found: 501.1142.

4'-amino-2',6'-bis(4-chlorophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5f)



The compound **5f** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.55 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 200.6 – 201.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.45 (m, 1H), 7.35-7.33 (m, 2H), 7.19-7.16 (m, 4H), 7.11-7.03 (m, 4H), 6.88 (t, J = 7.5 Hz, 1H), 5.17 (s, 2H), 4.30 (s, 1H), 3.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 171.4, 144.0, 139.3, 136.6, 134.9, 131.1, 130.9, 129.5, 128.6, 128.3, 124.3, 123.2, 121.0, 115.6, 112.8, 111.7, 111.6, 86.8, 83.0, 50.0, 48.7, 40.4. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}Cl_2N_4O_2Na$ $[M + Na]^+$ 533.0543, found: 533.0527.

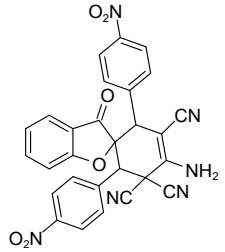
4'-amino-2',6'-bis(4-bromophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5g)



The compound **5g** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.55 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 173.2 – 174.0 °C. The ratio of **5g**-A/**5g**-B/**5g**-C/**5g**-D was 1:0.95:0.09:0.05 as determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of four isomers) δ 7.79 – 7.75 (m,

1H, isomer A), 7.73-7.71 (m, 1H, isomer C), 7.61 – 7.59 (m, 3H for isomer C), 7.55 (d, *J* = 8.3 Hz, 2H, isomer A), 7.52-7.47 (m, 1H for isomer B and 2H for isomer C, overlapped),7.45 (s, 1H, isomer C), 7.39 – 7.30 (m, 3H for isomer A, 4H for isomer B, overlapped), 7.28 (s, 4H, isomer C), 7.21 – 7.15 (m, 3H for isomer A, 3H for isomer B and 1H for isomer C, overlapped), 7.12 – 7.01 (m, 1H for isomer A and 2H for isomer B, overlapped), 6.94 – 6.81 (m, 2H for isomer A and 1H for isomer B, overlapped), 6.62 (d, *J* = 8.6 Hz, 1H, isomer B), 5.40 (s, 2H, isomer C), 5.33 (s, 2H, isomer B), 5.25 (s, 2H, isomer A), 4.30 (s, 1H, isomer A), 4.16 (s, 1H, isomer D), 4.06 (s, 1H, isomer B), 3.93 (s, 1H, isomer C), 3.84 (s, 1H, isomer B), 3.82 (s, 1H, isomer C), 3.76 (s, 1H, isomer A), 3.58 (s, 1H, isomer D). ^{13}C NMR (100 MHz, $CDCl_3$, a mixture of isomers A and B) δ 198.3, 194.8, 171.0, 170.0, 145.1, 143.7, 139.4, 139.2, 132.5, 132.3, 132.2, 131.9, 131.4, 131.2, 131.1, 129.0, 128.3, 125.2, 124.9, 124.7, 123.9, 123.6, 123.2, 122.9, 122.0, 121.0, 116.1, 115.9, 114.0, 112.9, 112.4, 112.2, 111.3, 110.4, 87.0, 85.8, 82.4, 81.5, 53.0, 50.2, 49.2, 45.9, 42.2, 40.7. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}Br_2N_4O_2Na$ $[M + Na]^+$ 620.9532, found: 620.9529.

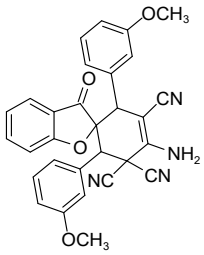
4'-amino-2',6'-bis(4-nitrophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5h)



The compound **5h** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent. Rf = 0.25 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 160.5 – 161.1 °C. The ratio of **5h**-A/**5h**-B was 1:0.31 as determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of isomers A and B) δ 8.31 (d, *J* = 8.8 Hz, 2H, isomer B), 8.09-8.00 (m, 4H for isomer A and 2H for isomer B, overlapped), 7.87 – 7.82 (m, 2H, isomer B), 7.63 (d, *J* = 9.0 Hz, 2H for isomer A and 1H for isomer B, overlapped), 7.56 – 7.48 (m, 2H for isomer A and 1H for isomer B, overlapped), 7.44 (d, *J* = 8.4 Hz, 2H, isomer B), 7.26 – 7.21 (m, 1H for isomer A and 2H for isomer B, overlapped), 7.17 – 7.15 (m, 1H, isomer A), 7.09 (d, *J* = 8.4 Hz, 1H, isomer A), 6.92 – 6.89 (m, 1H, isomer A), 5.41 (s, 2H, isomer B), 5.38 (s, 2H, isomer A), 4.48 (s, 1H, isomer A), 4.13 (s, 1H, isomer A), 3.95 (s, 2H, isomer B). ^{13}C NMR (100 MHz, $CDCl_3$, a

mixture of isomers A and B) δ 196.7, 194.6, 171.1, 170.1, 149.0, 148.4, 148.0, 144.3, 143.9, 140.1, 140.0, 139.7, 139.5, 136.3, 136.3, 131.0, 130.9, 130.5, 125.3, 124.5, 124.4, 124.3, 124.29, 123.9, 123.5, 120.6, 120.5, 115.7, 115.3, 114.2, 112.8, 111.7, 111.2, 110.8, 86.5, 86.2, 81.4, 81.3, 50.2, 50.0, 49.0, 46.2, 40.1, 39.8. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}N_6O_6Na$ $[M + Na]^+$ 555.1024, found: 555.1010.

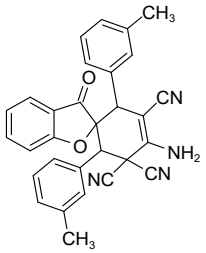
4'-amino-2',6'-bis(3-methoxyphenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5i)



The compound **5i** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.50 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 145.2 – 146.0 °C. The ratio of **5i**-A/**5i**-B was 1:0.31 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 7.87 (t, J = 7.6 Hz, 1H, isomer A), 7.66 (d, J = 4.5 Hz, 3H, isomer B), 7.62 (s, 2H, isomer A), 7.51 (t, J = 7.2 Hz, 2H, isomer A), 7.47 (d, J = 7.6 Hz, 1H, isomer B), 7.38 (t, J = 8.0 Hz, 1H, isomer B), 7.34 (t, J = 7.9 Hz, 1H, isomer A), 7.21 (t, J = 7.5 Hz, 1H, isomer A), 7.13 (t, J = 8.1 Hz, 1H for isomer A and 1H for isomer B, overlapped), 7.08-7.03 (m, 1H, isomer A), 6.95-6.91 (m, 1H for isomer A and 1H for isomer B, overlapped), 6.89 – 6.82 (m, 1H for isomer A and 3H for isomer B, overlapped), 6.81 (d, J = 1.9 Hz, 1H for isomer A and 1H for isomer B, overlapped), 6.74 (d, J = 7.7 Hz, 1H, isomer A), 6.69-6.67 (m, 1H, isomer B), 6.65 (s, 1H for isomer A and 1H for isomer B, overlapped), 6.59 (s, 1H, isomer B), 4.56 (s, 1H, isomer B), 4.18 (s, 1H, isomer B), 4.05 (s, 1H, isomer A), 4.03 (s, 1H, isomer A), 3.74 (s, 3H for isomer A and 3H for isomer B, overlapped), 3.60 (s, 3H, isomer B), 3.42 (s, 3H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6, a mixture of two isomers) δ 195.7, 195.1, 169.8, 169.4, 159.0, 159.0, 158.9, 158.6, 145.8, 144.8, 139.3, 139.0, 136.4, 135.6, 132.7, 132.4, 130.1, 129.9, 129.8, 129.6, 129.6, 129.1, 124.7, 124.43, 124.40, 123.5, 122.9, 122.4, 121.75, 121.72, 121.2, 120.1, 117.9, 117.3, 116.30, 116.29, 115.8, 115.4, 114.1, 113.8, 113.6, 113.5, 113.1, 112.9, 112.3, 111.7, 87.4, 86.0,

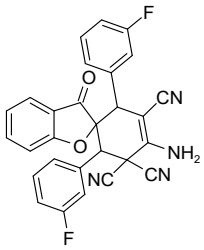
77.1, 76.6, 55.05, 55.03, 54.99, 54.7, 50.1, 49.5, 45.7, 43.3, 40.7, 40.1. HRMS (ESI-TOF) calcd for $C_{30}H_{22}N_4O_4Na$ $[M+Na]^+$: 525.1533, found: 525.1550.

4'-amino-2',6'-di-m-toly-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5j)



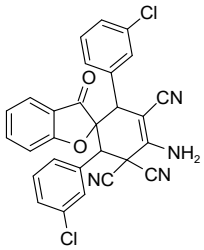
The compound **5j** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.55 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 180.4 – 181.2 °C. The ratio of **5j**-A/**5j**-B was 1:0.19 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 7.87 (t, J = 7.8 Hz, 1H, isomer A), 7.65 (d, J = 7.7 Hz, 1H, isomer B), 7.63-7.60 (m, 2H for isomer A and 2H for isomer B, overlapped), 7.52 (d, J = 8.4 Hz, 1H, isomer A), 7.47 (d, J = 7.7 Hz, 1H, isomer A), 7.44 (d, J = 7.6 Hz, 1H, isomer B), 7.33 (t, J = 7.6 Hz, 1H, isomer B), 7.30-7.25 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.21 – 7.16 (m, 2H, isomer A), 7.13 (d, J = 8.2 Hz, 2H, isomer B), 7.09-7.06 (m, 1H for isomer A and 3H for isomer B, overlapped), 7.06 – 6.99 (m, 3H for isomer A and 1H for isomer B, overlapped), 6.92-6.91 (m, 2H, isomer A), 6.87-6.86 (m, 2H, isomer B), 4.51 (s, 1H, isomer B), 4.14 (s, 1H, isomer B), 3.99 (s, 1H, isomer A), 3.97 (s, 1H, isomer A), 2.32 (s, 3H, isomer A), 2.31 (s, 3H, isomer B), 2.12 (s, 3H, isomer B), 2.07 (s, 3H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.7, 195.1, 169.8, 169.5, 145.7, 144.8, 139.3, 138.9, 137.9, 137.7, 137.5, 137.0, 134.8, 134.1, 131.3, 131.1, 130.8, 130.34, 130.31, 130.2, 129.0, 128.7, 128.5, 128.4, 127.9, 127.2, 127.0, 126.8, 124.6, 124.4, 124.1, 123.43, 123.40, 122.8, 121.1, 120.2, 118.0, 117.4, 113.8, 113.7, 113.1, 112.9, 112.2, 111.7, 87.5, 86.2, 77.5, 76.8, 50.2, 49.6, 45.7, 43.1, 40.8, 39.4, 21.22, 21.19, 20.9, 20.8. HRMS (ESI-TOF) calcd for $C_{30}H_{22}N_4O_2Na$ $[M+Na]^+$: 493.1635, found: 493.1627.

4'-amino-2',6'-bis(3-fluorophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5k)



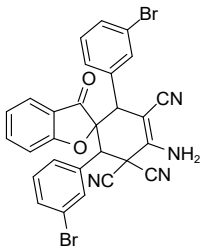
The compound **5k** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 4:1:1 as eluent. Rf = 0.45 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 162.4 – 163.2 °C. The ratio of **5k**-A/**5k**-B was 1:0.56 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 7.89 (t, J = 7.8 Hz, 1H, isomer A), 7.75 (s, 2H, isomer B), 7.69 – 7.66 (m, 2H for isomer A and 1H for isomer B, overlapped), 7.58-7.51 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.49-7.40 (m, 2H for isomer A and 1H for isomer B, overlapped), 7.31-7.25 (m, 1H, isomer B), 7.29 – 7.23 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.22 – 7.15 (m, 5H for isomer A and 1H for isomer B, overlapped), 7.13-7.10 (m, 3H, isomer B), 7.06 (t, J = 7.4 Hz, 1H, isomer B), 7.02 (d, J = 7.9 Hz, 1H, isomer A), 6.96 – 6.85 (m, 1H for isomer A and 2H for isomer B, overlapped), 4.75 (s, 1H, isomer B), 4.29 (s, 1H, isomer B), 4.22 (s, 1H, isomer A), 4.18 (s, 1H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6) 195.5, 195.3, 169.9, 169.4, 161.9 (d, J = 242.2 Hz), 161.5 (d, J = 243.3 Hz), 161.4 (d, J = 242.1 Hz), 160.9 (d, J = 244.2 Hz), 145.7, 144.9, 139.6, 139.2, 137.8 (d, J = 7.1 Hz), 136.7 (d, J = 7.1 Hz), 133.8 (d, J = 7.6 Hz), 133.6 (d, J = 7.4 Hz), 130.8 (d, J = 8.2 Hz), 130.79 (d, J = 8.4 Hz), 130.34 (d, J = 8.3 Hz), 130.28 (d, J = 4.2 Hz), 130.1 (d, J = 3.9 Hz), 130.0 (d, J = 8.6 Hz), 126.4 (d, J = 2.4 Hz), 125.9 (d, J = 3.5 Hz), 124.7, 124.5, 123.7, 123.1, 120.9, 120.0, 117.8, 117.2, 117.1, 116.9, 116.8, 116.7, 116.54 (d, J = 20.5 Hz), 116.51 (d, J = 21.4 Hz), 115.2 (d, J = 20.8 Hz), 115.1 (d, J = 21.9 Hz), 113.9, 113.2 (d, J = 20.0 Hz), 113.1 (d, J = 22.4 Hz), 112.30 (d, J = 13.8 Hz), 112.28 (d, J = 14.8 Hz), 111.6, 87.2, 85.8, 76.8, 76.2, 49.6, 49.1, 44.7, 42.7, 40.4, 38.8. HRMS (ESI-TOF) calcd for $C_{28}H_{17}F_2N_4O_2$ $[M+H]^+$: 479.1314, found: 479.1316.

4'-amino-2',6'-bis(3-chlorophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5l)



The compound **5l** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.50 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 146.0 – 147.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.4 Hz, 1H), 7.28 – 7.13 (m, 6H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.82 (t, *J* = 7.5 Hz, 2H), 5.19 (s, 2H), 4.21 (s, 1H), 3.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 171.4, 144.2, 139.4, 132.5, 131.9, 131.6, 131.5, 131.4, 131.3, 129.4, 129.2, 128.9, 125.0, 124.4, 123.3, 123.1, 121.1, 115.7, 112.8, 111.8, 111.7, 86.7, 82.5, 50.1, 48.8, 40.3. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}Cl_2N_4O_2Na$ [M + Na]$^{+}$ 533.0543, found: 533.0556.

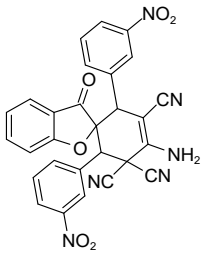
4'-amino-2',6'-bis(3-bromophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5m)



The compound **5m** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.50 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 214.9 – 215.8 °C. The ratio of **5m**-A/**5m**-B was 1:0.53 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 7.89 (t, *J* = 7.8 Hz, 1H, isomer A), 7.78 (s, 2H, isomer B), 7.70-7.67 (m, 2H for isomer A and 2H for isomer B, overlapped), 7.59 (s, 1H, isomer A), 7.55 – 7.50 (m, 2H for isomer A and 3H for isomer B, overlapped), 7.48 – 7.45 (m, 1H for isomer A and 2H for isomer B, overlapped), 7.40 (s, 1H for isomer A and 1H for isomer B, overlapped), 7.36 (t, *J* = 7.8 Hz, 1H, isomer A), 7.31 (t, *J* = 6.8 Hz, 1H for isomer A and 1H for isomer B, overlapped), 7.27 – 7.15 (m, 3H for isomer A and 2H for isomer B, overlapped), 7.11-7.05 (m, 1H for isomer A and 1H for isomer B, overlapped), 4.74 (s, 1H, isomer B), 4.24 (s, 1H, isomer B), 4.21 (s, 1H, isomer A), 4.18 (s, 1H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.5,

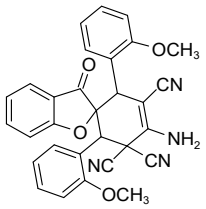
195.4, 170.0, 169.4, 145.8, 144.9, 139.7, 139.3, 137.7, 136.5, 133.8, 133.5, 132.7, 132.5, 131.2, 131.0, 130.8, 130.6, 130.2, 129.3, 124.7, 124.5, 123.7, 123.1, 121.8, 121.6, 121.0, 120.9, 120.0, 117.8, 117.1, 113.8, 113.2, 113.0, 112.3, 112.2, 111.6, 87.1, 85.8, 76.6, 76.1, 49.3, 48.8, 44.6, 42.7, 40.4, 38.8. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}Br_2N_4O_2Na$ $[M + Na]^+$ 620.9532, found: 620.9534.

4'-amino-2',6'-bis(3-nitrophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5n)



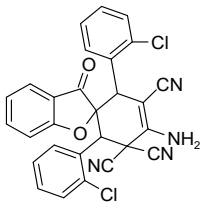
The compound **5n** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent. Rf = 0.25 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 257.8 – 258.5 °C. The ratio of **5n**-A/**5n**-B was 1:0.32 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 8.37 – 8.35 (m, 1H for isomer A and 1H for isomer B, overlapped), 8.27 (s, 1H, isomer B), 8.20 (d, J = 7.9 Hz, 1H, isomer A), 8.15-8.14 (m, 1H, isomer A), 8.08 (s, 1H, isomer A), 7.98 (d, J = 8.2 Hz, 1H, isomer B), 7.93 – 7.90 (m, 2H, isomer A), 7.84-7.80 (m, 3H for isomer A and 2H for isomer B, overlapped), 7.76-7.74 (m, 3H, isomer B), 7.71-7.67 (m, 1H for isomer A and 1H for isomer B, overlapped), 7.59 – 7.53 (m, 2H for isomer A and 1H for isomer B, overlapped), 7.47 – 7.42 (m, 1H for isomer A and 2H for isomer B, overlapped), 7.20 (t, J = 7.5 Hz, 1H, isomer A), 7.16 (d, J = 8.4 Hz, 1H, isomer B), 7.04 (t, J = 7.5 Hz, 1H, isomer B), 5.07 (s, 1H, isomer B), 4.56 (s, 1H, isomer B), 4.54 (s, 1H, isomer A), 4.50 (s, 1H, isomer A). ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.7, 195.4, 170.3, 169.4, 147.9, 147.5, 147.2, 145.9, 145.3, 140.1, 139.6, 137.1, 137.06, 136.99, 136.98, 136.2, 133.15, 133.12, 130.6, 130.5, 129.92, 129.87, 124.9, 124.7, 124.60, 124.58, 123.9, 123.42, 123.38, 123.3, 120.9, 119.9, 117.7, 117.1, 114.0, 113.1, 112.2, 112.0, 111.7, 87.1, 85.7, 76.2, 75.5, 49.2, 48.4, 44.1, 42.4, 40.3, 38.8. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}N_6O_6Na$ $[M + Na]^+$ 555.1024, found: 555.1028.

4'-amino-2',6'-bis(2-methoxyphenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5o)



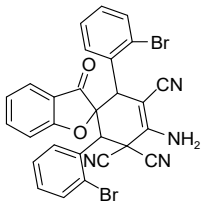
The compound **5o** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 3:1:1 as eluent. Rf = 0.35 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 232.5 – 233.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (t, J = 7.8 Hz, 1H), 7.64 (s, 2H), 7.51-7.47 (m, 2H), 7.39 (t, J = 8.1 Hz, 1H), 7.21 (t, J = 7.7 Hz, 2H), 7.18-7.14 (m, 3H), 6.98-6.95 (m, 2H), 6.63 (t, J = 7.7 Hz, 1H), 4.79 (s, 1H), 4.03 (s, 1H), 3.63 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 194.2, 168.8, 157.6, 157.3, 145.9, 138.7, 130.9, 130.0, 128.2, 127.9, 123.9, 123.3, 122.1, 121.4, 120.9, 120.5, 120.2, 118.1, 113.8, 112.4, 112.2, 111.0, 87.7, 75.2, 56.5, 54.6, 44.0, 40.1, 35.1. HRMS (ESI-TOF) calcd for $C_{30}H_{22}N_4O_4Na$ $[M+Na]^+$: 525.1533, found: 525.1539.

4'-amino-2',6'-bis(2-chlorophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5p)



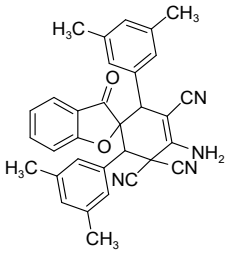
The compound **5p** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.60 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 150.3 – 151.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 1H), 7.57 – 7.46 (m, 2H), 7.43 – 7.30 (m, 6H), 7.21 – 7.15 (m, 1H), 7.15 – 7.07 (m, 1H), 6.97-6.93 (m, 1H), 5.15 (s, 2H), 5.07 (s, 1H), 4.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 171.0, 144.2, 138.8, 136.2, 134.4, 132.1, 131.3, 130.8, 130.7, 130.0, 129.7, 129.1, 128.0, 127.5, 126.7, 124.5, 123.0, 120.9, 115.7, 112.7, 112.0, 111.1, 86.7, 83.6, 44.2, 43.9, 39.7. HRMS (ESI-TOF) calcd. for $C_{28}H_{16}Cl_2N_4O_3Na$ $[M + Na]^+$ 533.0543, found: 533.0540.

4'-amino-2',6'-bis(2-bromophenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5q)



The compound **5q** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.55 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 164.5 – 165.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88-7.85 (m, 3H), 7.68-7.95 (m, 3H), 7.54 (d, J = 8.4 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.38 (t, J = 7.7 Hz, 1H), 7.22-7.18 (m, 2H), 7.11 (t, J = 7.7 Hz, 1H), 4.97 (s, 1H), 4.30 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 194.6, 169.9, 145.9, 139.9, 134.1, 133.3, 133.2, 132.3, 131.2, 130.8, 130.1, 129.5, 129.2, 128.5, 127.8, 127.1, 124.8, 124.4, 121.7, 118.1, 114.1, 112.5, 112.1, 87.4, 75.7, 50.3, 42.7, 39.8. HRMS (ESI-TOF) calcd for $C_{28}H_{16}Br_2N_4O_2Na$ ([M+Na]$^+$): 620.5932, found: 620.5933.

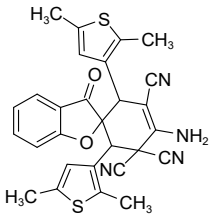
4'-amino-2',6'-bis(3,5-dimethylphenyl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5t)



The compound **5t** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.60 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 292.8– 293.6 °C. The ratio of **5t**-A/**5t**-B was 1:0.36 as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-d_6, a mixture of two isomers) δ 7.87 (t, J = 7.8 Hz, 1H, isomer A), 7.65 (t, J = 7.8 Hz, 1H, isomer B), 7.57 (s, 2H for isomer A and 2H for isomer B, overlapped), 7.53 – 7.45 (m, 2H for isomer A and 2H for isomer B, overlapped), 7.19 (t, J = 7.5 Hz, 1H, isomer A), 7.12 (d, J = 8.4 Hz, 1H, isomer B), 7.07 (s, 1H, isomer B), 7.03 (t, J = 7.5 Hz, 1H, isomer B), 6.98 (s, 1H, isomer A), 6.88 (s, 1H for isomer A and 2H for isomer B, overlapped), 6.82 (s, 2H, isomer A), 6.73 (s, 1H, isomer B), 6.73-6.68 (m, 2H for isomer A and 2H for isomer B, overlapped), 4.40 (s, 1H, isomer B), 4.10 (s, 1H, isomer B), 3.93 (s, 1H, isomer A), 3.92 (s, 1H, isomer A), 2.28 (s, 6H, isomer A), 2.26 (s, 6H, isomer B), 2.09 (s, 6H, isomer B), 2.00 (s, 6H, isomer A). ^{13}C NMR (125 MHz,

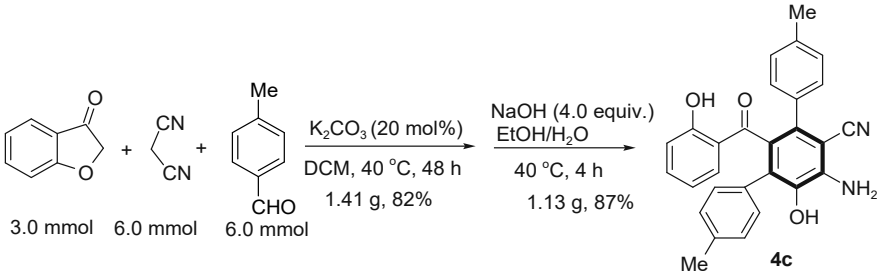
DMSO-d_6) δ 195.8, 195.0, 169.8, 169.5, 145.6, 144.7, 139.2, 138.8, 137.6, 137.5, 137.3, 136.8, 134.5, 134.2, 131.2, 131.01, 130.99, 130.97, 129.9, 129.5, 127.9, 124.6, 124.4, 123.3, 122.8, 121.2, 120.2, 118.0, 117.4, 113.7, 113.6, 113.0, 112.2, 111.7, 87.5, 86.1, 77.6, 77.0, 50.2, 49.5, 45.7, 43.1, 40.8, 39.5, 21.11, 21.08, 20.7, 20.6. HRMS (ESI-TOF) calcd. for $C_{32}H_{26}N_4O_2Na$ $[M + Na]^+$ 521.1948, found: 521.1955.

4'-amino-2',6'-bis(2,5-dimethylthiophen-3-yl)-3-oxo-3H-spiro[benzofuran-2,1'-cyclohexan]-4'-ene-3',3',5'-tricarbonitrile (5u)

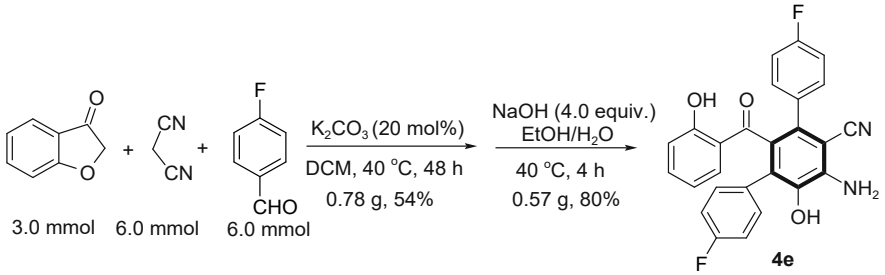


The compound **5u** was purified by silica gel column chromatography using petroleum ether/ ethyl acetate/dichloromethane = 8:1:1 to 5:1:1 as eluent. Rf = 0.45 (petroleum ether/ethyl acetate = 5:1 for twice). m.p. 145.3 – 146.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 (t, J = 7.8 Hz, 1H), 7.42 (s, 1H), 7.41 (s, 2H), 6.96 – 6.87 (m, 2H), 6.29 (s, 1H), 6.21 (s, 1H), 4.99 (s, 1H), 4.84 (s, 1H), 2.51 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.6, 170.4, 145.5, 139.0, 138.6, 135.7, 134.9, 134.1, 129.8, 126.1, 126.0, 124.0, 123.0, 122.2, 121.9, 117.7, 113.8, 111.9, 111.7, 87.6, 76.4, 43.1, 41.4, 40.9, 14.7, 14.6, 13.0, 12.9. HRMS (ESI-TOF) calcd. for $C_{28}H_{22}N_4O_2S_2Na$ $[M + Na]^+$ 533.1076, found: 533.1080.

4. Experimental procedures for gram-scale synthesis of compound 4c and 4e



Experiment procedure for gram-scale synthesis of compound 4c: A stirred solution of benzofuran-3-one (**1**, 402.4 mg, 3.0 mmol, 1.0 equiv.), malononitriles (**2**, 396.3 mg, 6.0 mmol, 2.0 equiv.), benzaldehyde (**3c**, 564.7 mg, 6.0 mmol, 2.0 equiv.) and K_2CO_3 (82.9 mg, 0.60 mmol, 0.2 equiv.) in CH_2Cl_2 (20 mL) was stirred at 40 °C for 48 h. After the benzofuran-3-one was consumed as indicated monitored by TLC, the reaction solution was added H_2O (20 mL, then extracted with CH_2Cl_2 (50 mL×3). The organic phase was dried with $MgSO_4$, filtered and concentrated *in-vacuo*. The residue was purified by column chromatography on silica gel (eluent PE/EtOAc/DCM = 8:1:1 to 5:1:1) to afford pure intermediate (1.41g, 82% yield). Proceed with the ring-opening and benzannulation reaction (step 2), a mixture of spiro intermediate (1.41 g, 1.0 equiv.), sodium hydroxide (12.0 mmol, 478.8 mg, 4.0 equiv.) was dissolved in the mixture solvent of EtOH/H_2O H_2O (3 mL) and ethanol (30 mL) were added to a sealed reaction tube equipped with a stir bar. The tube was then sealed and the resulting mixture was stirred at 40 °C for the 4 h. Upon completion (monitored by TLC, visualized by UV light), the reaction solution was added H_2O (5 mL), adjust the pH to 5 with 0.5 N HCl in fume hood, then extracted with CH_2Cl_2 (60 mL×3). The aqueous layer was discarded after basified with sodium hypochlorite solution. The organic phase was dried with $MgSO_4$, filtered and concentrated *in-vacuo*. The residue was purified by column chromatography on silica gel (eluent PE/EtOAc/DCM = 6:1:1 to 3:1:1) to afford pure product **4c** (1.13 g, 87% yield).



Experiment procedure for gram-scale synthesis of compound 4e: A stirred solution of benzofuran-3-one (**1**, 402.4 mg, 3.0 mmol, 1.0 equiv.), malononitriles (**2**, 396.3 mg, 6.0 mmol, 2.0 equiv.), benzaldehyde (**3e**, 744.2 mg, 6.0 mmol, 2.0 equiv.) and K_2CO_3 (82.9 mg, 0.60 mmol, 0.2 equiv.) in CH_2Cl_2 (0.15 M) was stirred at 40 °C for 48 h. After the complete consumption of benzofuran-3-one as monitored by TLC, to the reaction solution, H_2O (20 mL) was added. Then, the solution was extracted with CH_2Cl_2 (50 mL×3). The organic phase was dried with $MgSO_4$, filtered and concentrated *in-vacuo*. The residue was purified by column chromatography on silica gel (eluent PE/EtOAc/DCM = 8:1:1 to 5:1:1) to afford pure spiro intermediate **5e** (0.78 g, 54% yield). Proceed with the ring-opening and benzannulation reaction (step 2), a mixture of spiro intermediate **5e** (0.78 g, 1.0 equiv.), sodium hydroxide (12.0 mmol, 478.8 mg, 4.0 equiv.) was dissolved in the mixture solvent of EtOH/H_2O (0.09M, v/v = 100:1) were added to a sealed reaction tube equipped with a stir bar. The tube was then sealed and the resulting mixture was stirred at 40 °C for the 4 h. Upon completion (monitored by TLC, visualized by UV light), to the reaction mixture, H_2O (30 mL) was added. Then, the pH of solution was adjusted to 5 with 0.5 N HCl in fume hood. Subsequently, the solution was extracted with CH_2Cl_2 (60 mL×3). The aqueous layer was discarded after basified with sodium hypochlorite solution. The organic phase was dried with $MgSO_4$, filtered and concentrated *in-vacuo*. The residue was purified by column chromatography on silica gel (eluent PE/EtOAc/DCM = 6:1:1 to 3:1:1) to afford pure product **4e** (0.57 g, 80% yield).

5. X-ray crystal structure of compound 4c

Preparation of the single crystals of compound **4c**: pure compound **4c** (8 mg) was dissolved in dichloromethane (5 mL). The bottle was sealed by a parafilm with several tiny holes, and then placed in a refrigerator, allowing slow evaporation of the solvents. Several weeks later, some small particles were observed on the wall and at the bottom of the bottle. Then, the crystals were carefully chosen and subjected to the crystal X-ray diffraction analysis to determine the structure of compound **4c**.

Crystal data for compound **4c**: $C_{28}H_{22}N_2O_3$, M = 434.47, a = 16.1597(16) Å, b = 10.6689(10) Å, c = 13.0214(13) Å, α = 90°, β = 90°, γ = 90°, V = 2245.0(4) Å^3, T = 100(2) K, space group *Pca*21, Z = 4, μ(MoKα) = 0.084 mm^{-1}, 24137 reflections measured, 6691 independent reflections (R_{int} = 0.0285). The final R_1 values were 0.0354 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0869 ($I > 2\sigma(I)$). The final R_1 values were 0.0409 (all data). The final $wR(F^2)$ values were 0.0909 (all data). The goodness of fit on F^2 was 1.025. Flack parameter = 0.4(3)

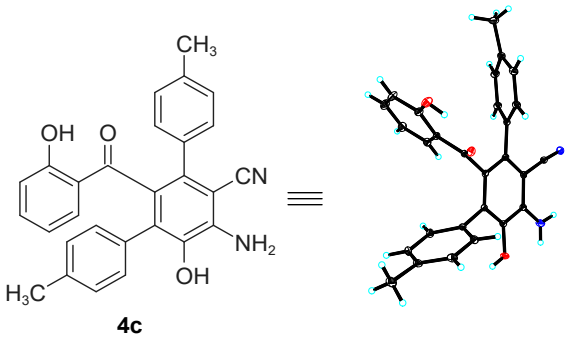


Figure S1. View of a molecule of compound **4c** with the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

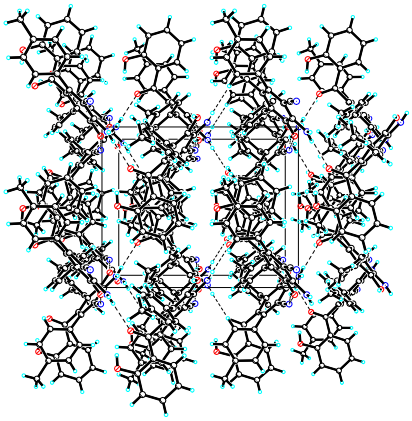


Figure S2. View of the pack drawing of compound **4c**.

Hydrogen-bonds are shown as dashed lines.

Table S2. Crystal data and structure refinement for compound **4c**.

Identification code	mo_hd_fjys1_0m	
Empirical formula	C28 H22 N2 O3	
Formula weight	434.47	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pca2_1$	
Unit cell dimensions	a = 16.1597(16) Å	α= 90°.
	b = 10.6689(10) Å	β= 90°.
	c = 13.0214(13) Å	γ = 90°.
Volume	2245.0(4) $Å^3$	
Z	4	
Density (calculated)	1.285 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	912	
Crystal size	0.750 x 0.700 x 0.170 mm^3	
Theta range for data collection	1.909 to 31.115°.	
Index ranges	-23<=h<=22, -15<=k<=15, -18<=l<=18	
Reflections collected	24137	
Independent reflections	6691 [R(int) = 0.0285]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6691 / 4 / 312	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0869	
R indices (all data)	R1 = 0.0409, wR2 = 0.0909	
Absolute structure parameter	0.4(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.313 and -0.209 e.$Å^{-3}$	

6. X-ray crystal structure of 5e

Preparation of the single crystals of **5e**: pure intermediate **5e** (15 mg) was dissolved in dichloromethane (10 mL). The bottle was sealed by a parafilm with several tiny holes, allowing slow evaporation of the solvents at room temperature. Several weeks later, some small particles were observed on the wall and at the bottom of the bottle. Then, the crystals were carefully chosen and subjected to the crystal X-ray diffraction analysis to determine the structure of intermediate **5e**.

Crystal data for intermediate **e**: $C_{28}H_{16}O_2F_2N_4$, M = 478.45, a = 8.9992(9) Å, b = 11.0091(12) Å, c = 29.001(3) Å, α = 90°, β = 91.719°, γ = 90°, V = 2871.93(52) Å^3, T = 296 K, space group $P\ 1\ 21/c\ 1$, Z = 4, μ(Mo Kα) = 0.081 mm^{-1}, 14496 reflections measured, 5097 independent reflections (R_{int} = 0.0411). The final R_1 values were 0.0485 ($I > = 2\sigma(I)$). The final $wR(F^2)$ values were 0.1237 ($I > = 2\sigma(I)$). The final R_1 values were 0.0994 (all data). The final $wR(F^2)$ values were 0.1498 (all data). The goodness of fit on F^2 was 0.999. Largest diff. peak/hole / e Å-3 0.18/-0.19.

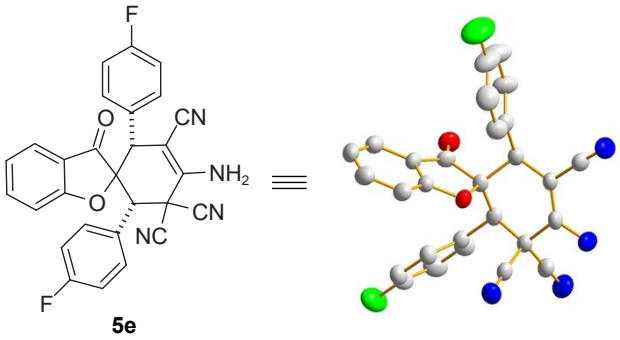


Figure S3. View of a molecule of intermediate **5e** with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table S3. Crystal data and structure refinement for intermediate **5e**

Identification code	MPT8752_0m
Empirical formula	$C_{28}H_{16}F_2N_4O_2$
Formula weight	478.45
Temperature/K	296.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.9992(9)

b/Å	11.0091(12)
c/Å	29.001(3)
α/°	90
β/°	91.719(2)
γ/°	90
Volume/Å^3	2871.9(5)
Z	4
ρ_{calc}g/cm^3	1.107
μ/mm^{-1}	0.081
F(000)	984.0
Crystal size/mm^3	0.41 × 0.22 × 0.18
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.646 to 50.198
Index ranges	$-10 \leq h \leq 10$, $-12 \leq k \leq 13$, $-34 \leq l \leq 31$
Reflections collected	14496
Independent reflections	5097 [R_{int} = 0.0411, R_{sigma} = 0.0509]
Data/restraints/parameters	5097/15/326
Goodness-of-fit on F^2	0.999
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.1237
Final R indexes [all data]	R_1 = 0.0994, wR_2 = 0.1498
Largest diff. peak/hole / e Å^{-3}	0.18/-0.19

7. Biological assay

The experiment of biological assay was conducted at Shenyang Research Institute of Chemical Industry.

7.1 The preparation of medicinal solution

Each of the test compounds was first dissolved in acetone (with a content of 5% of the drug solution). Subsequently, to this solution, water containing 0.1% Tween 80 was added preparing the drug solution for investigating the antifungal activity on live seedlings.

7.2 Inoculate pathogenic bacteria

A spore suspension (5-8 × 10^6 /mL) of cucumber downy mildew and corn rust was sprayed on the host crops, and then the crops were moved to the phytotron for cultivation (24 ± 2 ℃, RH>90, no light). After 24 hours, the crops were moved to the hothouse for routine management.

A spore suspension of cucumber powdery mildew pathogen (5-8 × 10^6/mL) was sprayed on the host crops, and then moved to the hothouse for routine management.

A spore of wheat powdery mildew was shaken off onto the wheat and placed in a hothouse for routine management.

The experimental materials were cultivated for 5-15 days, and the antifungal activity of the compounds was investigated separately.

7.3 Experiment results

According to "A Manual of Assessment Keys for Plant Diseases" (published by American College of Plant Diseases), the antifungal activity of the test samples was ascertained by a visual section method, which was based on the degree of incidence of the control group.

Table S4. Antifungal activity of part of compounds **4** at 400 mg/L

Compound	CDM	CSR	CPM
4a	85	75	70
4b	100	95	30
4e	100	85	50
4f	90	0	0
4g	95	80	0
4h	85	90	0
4i	98	70	0
4j	60	75	40
4k	70	0	0
4l	60	60	0

4m	90	50	0
4n	90	50	90
4o	75	60	30
4p	90	80	0
4q	70	95	75
cyazofamid	100		-
azoxystrobin	-		100
ethirimol	-	100	-

8. Computational Details

Geometry optimizations were carried out with the B3LYP[1] functional and the 6-31G(d,P)[2] basis set and SMD[3] solvent model and dispersion corrections by Grimme with Becke-Johnson damping (D3BJ)[4], which is termed as B3LYP+D3BJ/6-31G(d,P) (SMD,Solvent=Dichloromethane). Vibrational frequency calculations were performed at the same level of theory to confirm the stationary points as transition states (only one imaginary frequency) or minima (no imaginary frequencies) and used to obtain the zero-point energy (ZPE)-corrected enthalpies and free energies at 298.15 K and 1 atm. Intrinsic reaction coordinate (IRC)[5] analysis was conducted to evaluate the correct connections between the transition states and corresponding minima if necessary. The energetics was further improved by using the larger basis set 6-311++G(2d,p) [6]single point calculations, which included solvation effect of Ethanol with the SMD[4] solvent model, denoted as B3LYP+D3BJ/6-311++G(2d,p)(SMD, Solvent = Dichloromethane) //B3LYP+D3BJ/6-31G(d,P)(SMD, Solvent = Dichloromethane). Gibbs free energies (in kcal/mol) are used in the following discussion, and the electronic energies without ZPE corrections are also given in the related schemes for reference. All calculations were performed by using the Gaussian 16 program[7].

References

[1]. a) D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652.; b) C. Lee, *Phys. Rev. B* 1988, *37*, 785-789.

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J. L.Sonnenberg, D.Williams-Young, F.Ding, F.Lipparini, F.Egidi, J.Goings, B.Peng, A.Petrone, T.Henderson, D.Ranasinghe, V. G.Zakrzewski, J.Gao, N.Rega, G.Zheng, W.Liang, M.Hada, M.Ehara, K.Toyota, R.Fukuda, J.Hasegawa, M.Ishida, T.Nakajima, Y.Honda, O.Kitao, H.Nakai, T.Vreven, K.Throssell, J. A.Montgomery Jr., J. E.Peralta, F.Ogliaro, M. J.Bearpark, J. J.Heyd, E. N.Brothers, K. N.Kudin, V. N.Staroverov, T. A.Keith, R.Kobayashi, J.Normand, K.Raghavachari, A. P.Rendell, J. C.Burant, S. S.Iyengar, J.Tomasi, M.Cossi, J. M.Millam, M.Klene, C.Adamo, R.Cammi, J. W.Ochterski, R. L.Martin, K.Morokuma, O.Farkas, J. B.Foresman and D. J. Fox, **2016**.

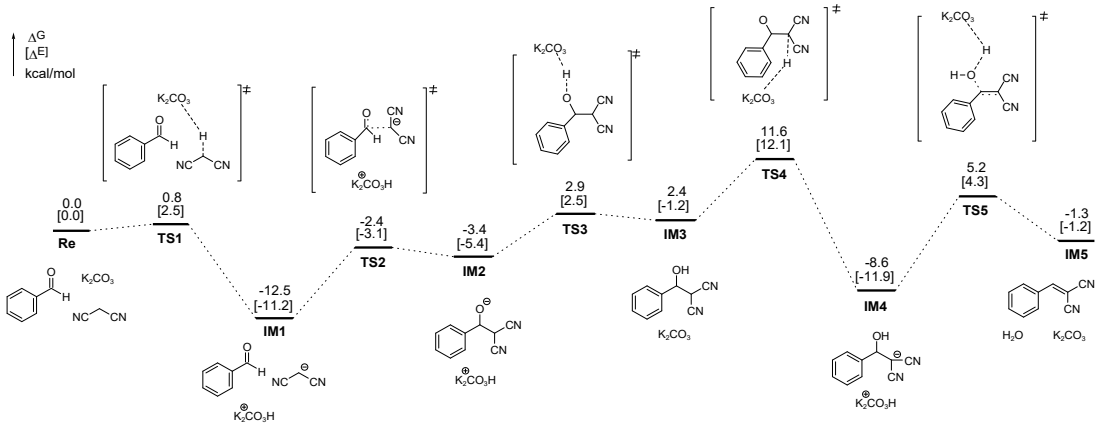


Figure S4. Free energy and electronic energy profile for the stage I at B3LYP-D3(BJ) /6-311++G(2d, p) (SMD, Solvent = Dichloromethane)//B3LYP-D3(BJ)/6-31G(d, p) (SMD, Solvent= Dichloromethane) level.

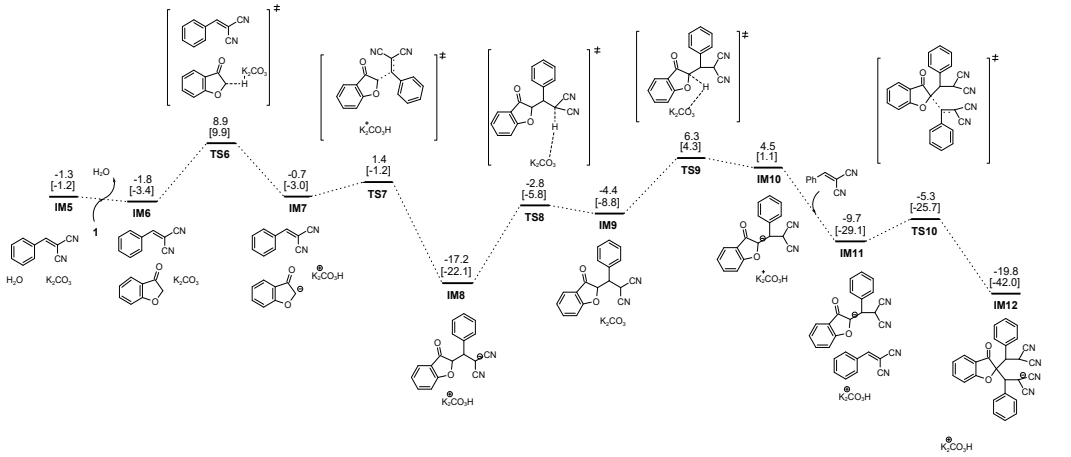


Figure S5. Free energy and electronic energy profile for the stage II at B3LYP-D3(BJ) /6-311++G(2d,p) (SMD, Solvent = Dichloromethane)//B3LYP-D3(BJ)/6-31G(d, p) (SMD, Solvent = Dichloromethane) level.

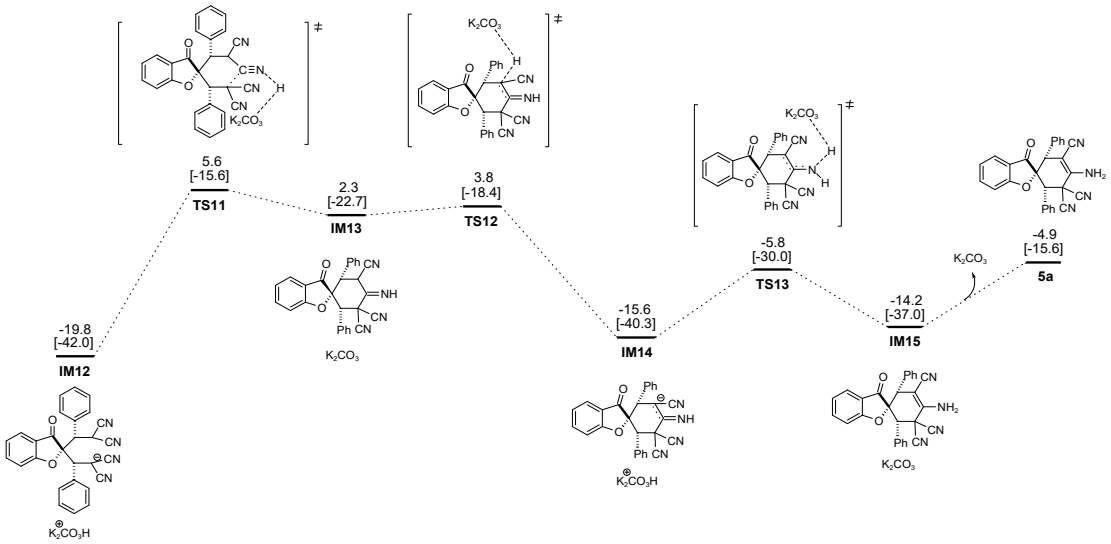


Figure S6. Free energy and electronic energy profile for the stage III at B3LYP-D3(BJ) /6-311++G(2d, p) (SMD, Solvent = Dichloromethane)//B3LYP-D3(BJ)/6-31G(d,p) (SMD, Solvent = Dichloromethane) level.

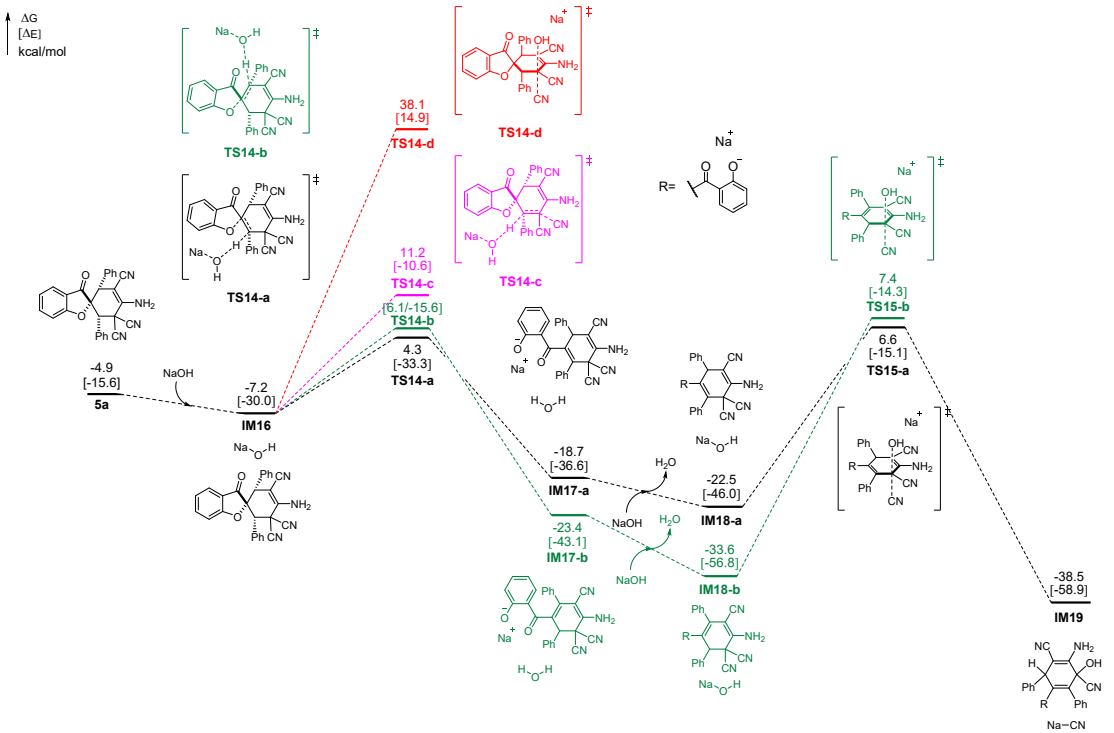


Figure S7. Free energy and electronic energy profile for the stage IV at B3LYP-D3(BJ) /6-311++G(2d, p) (SMD, Solvent = Ethanol)//B3LYP-D3(BJ)/6-31G(d, p)(SMD, Solvent=Ethanol) level.

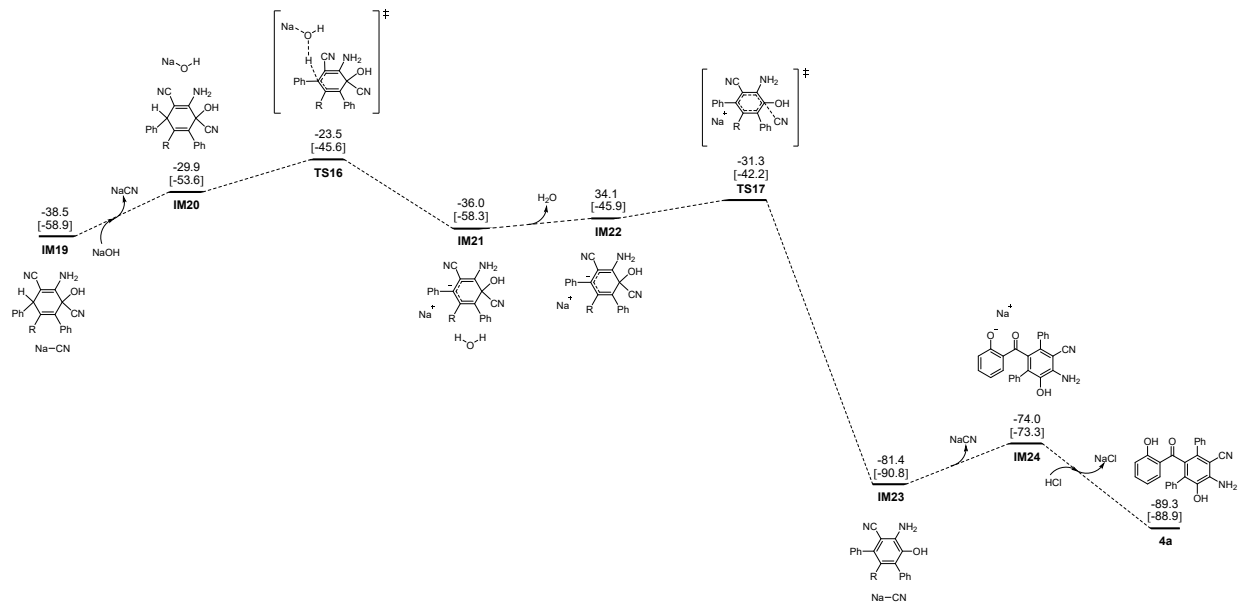


Figure S8. Free energy and electronic energy profile for the stage V at B3LYP-D3(BJ)/6-311++G(2d, p) (SMD, Solvent = Ethanol)//B3LYP-D3(BJ)/6-31G(d, p)

Table S5. Coordinates and free energies and electronic energies (in hatree) of the calculated structures at the B3LYP-D3(BJ) /6-311++G(2d,p) (SMD, Solvent = Ethanol) //B3LYP-D3(BJ)/6-31G(d,p) (SMD, Solvent = Ethanol) level

Re

Free energy：-2034.613016

Energy：-2034.730468

C	4.914100000	0.199610000	0.910970000
C	3.970125000	1.068713000	0.360445000
C	2.736441000	0.574343000	-0.058724000
C	2.449955000	-0.792878000	0.066309000
C	3.406305000	-1.664232000	0.615522000
C	4.632595000	-1.167167000	1.038945000
H	5.874973000	0.584680000	1.240390000
H	4.192463000	2.125591000	0.254363000
H	2.005583000	1.244566000	-0.497286000
H	3.161891000	-2.718412000	0.698153000
H	5.373851000	-1.835642000	1.466675000
C	1.146592000	-1.301806000	-0.386226000
H	0.409856000	-0.555637000	-0.742274000
O	0.841818000	-2.495126000	-0.379639000

C	-0.881856000	2.362135000	-1.205535000
C	0.333604000	2.788803000	-1.896782000
N	1.312614000	3.081370000	-2.449372000
C	-0.681158000	2.309139000	0.243041000
N	-0.484722000	2.226115000	1.386163000
C	-2.588474000	-0.134986000	-0.357536000
O	-3.097693000	1.012561000	-0.097942000
O	-1.834165000	-0.304966000	-1.417859000
O	-2.751465000	-1.139032000	0.470591000
K	-1.755630000	-2.837870000	-1.124025000
K	-2.758811000	0.608088000	2.355293000
H	-1.729665000	3.013620000	-1.433283000
H	-1.207161000	1.317144000	-1.522172000

TS1

Free energy：-2034.605425

Energy：-2034.718813

C	-4.324749000	0.721836000	-0.461548000
C	-3.472567000	0.102815000	0.462037000
C	-2.931108000	-1.161384000	0.181891000
C	-4.634175000	0.085805000	-1.662388000
C	-3.241690000	-1.794076000	-1.016984000
C	-4.092115000	-1.172003000	-1.938716000
H	-5.293244000	0.565125000	-2.379879000
H	-4.735858000	1.703335000	-0.237898000
H	-2.265708000	-1.619526000	0.904695000
H	-2.823931000	-2.772210000	-1.236417000
H	-4.333698000	-1.670003000	-2.873589000
C	-3.134104000	0.794072000	1.723393000
C	0.580284000	0.610160000	1.683030000
C	0.451766000	-0.789573000	1.329782000
N	0.394496000	-1.898247000	0.977553000
C	-0.124314000	1.454417000	0.738758000
N	-0.556377000	2.158893000	-0.082651000
H	-3.634704000	1.777048000	1.864495000
H	1.756606000	0.952260000	1.465656000
C	3.296496000	0.206651000	0.206414000
O	3.649633000	-0.715162000	0.998902000
O	2.887094000	1.376263000	0.689103000
O	3.211543000	0.022670000	-1.087869000
K	2.085699000	2.271755000	-1.549122000
K	2.804141000	-2.496582000	-0.518770000
O	-2.367093000	0.361404000	2.566552000

H	0.264970000	0.797437000	2.711066000

IM1

Free energy：-2034.634626

Energy：-2034.750916

C	-4.800769000	-0.018254000	1.154806000
C	-4.582771000	-0.734729000	-0.022784000
C	-3.535181000	-0.376580000	-0.868621000
C	-2.694541000	0.693177000	-0.527946000
C	-2.917712000	1.409078000	0.661009000
C	-3.968952000	1.056558000	1.496661000
H	-5.617562000	-0.297821000	1.814126000
H	-5.214206000	-1.579720000	-0.276186000
H	-3.342707000	-0.953830000	-1.766303000
H	-2.261149000	2.238226000	0.903046000
H	-4.145026000	1.608316000	2.415323000
C	-1.574321000	1.047347000	-1.408376000
H	-1.496637000	0.460726000	-2.341256000
O	-0.763691000	1.943978000	-1.171256000
C	-0.020082000	-1.620231000	-0.774322000
H	3.113133000	0.822348000	-2.373255000
C	-1.098678000	-2.505581000	-0.925958000
N	-2.012520000	-3.224502000	-1.074264000
C	0.214663000	-0.930138000	0.397679000
N	0.505147000	-0.312981000	1.368780000
C	3.496624000	0.315317000	-0.576517000
O	3.650344000	-0.853540000	-0.992508000
O	3.153768000	1.288547000	-1.525276000
O	3.535736000	0.751477000	0.604852000
K	1.309993000	2.227796000	0.414939000
K	2.957910000	-1.758370000	1.383790000
H	0.706697000	-1.514433000	-1.573237000

TS2

Free energy： -2034.621354

Energy：-2034.74174368

C	2.126793000	-2.855877000	-1.420446000
C	2.957825000	-2.522733000	-0.348143000
C	2.602516000	-1.489423000	0.517041000
C	1.415053000	-0.769210000	0.314367000
C	0.586935000	-1.108278000	-0.768618000
C	0.939950000	-2.147152000	-1.627122000

H	2.402603000	-3.663034000	-2.092674000
H	3.885352000	-3.063900000	-0.188357000
H	3.256807000	-1.222260000	1.340707000
H	-0.335767000	-0.564258000	-0.931360000
H	0.286261000	-2.407579000	-2.454385000
C	1.014183000	0.307212000	1.268558000
H	1.621380000	0.323261000	2.189784000
O	-0.189352000	0.723118000	1.310698000
C	2.267111000	1.966532000	0.575182000
H	2.138247000	2.578082000	1.467144000
C	3.596065000	1.508125000	0.361770000
N	4.662197000	1.047257000	0.246709000
C	1.520208000	2.434456000	-0.530126000
N	0.781375000	2.770632000	-1.373842000
C	-3.111560000	-0.509417000	-0.545442000
O	-2.914755000	-1.740324000	-0.479543000
O	-2.925365000	0.097891000	-1.797613000
O	-3.372974000	0.307029000	0.378253000
K	-1.726004000	2.235014000	-0.396948000
K	-1.901669000	-1.291367000	1.917450000
H	-2.705016000	-0.621944000	-2.406959000

IM2

Free energy： -2034.621482

Energy：-2034.74311954

C	-2.735839000	2.706814000	1.270431000
C	-3.108902000	2.545982000	-0.064686000
C	-2.607740000	1.472757000	-0.807960000
C	-1.725437000	0.551869000	-0.231859000
C	-1.358835000	0.722017000	1.113239000
C	-1.863699000	1.785740000	1.860851000
H	-3.124662000	3.538957000	1.849882000
H	-3.790892000	3.252950000	-0.528511000
H	-2.903948000	1.347214000	-1.846679000
H	-0.668575000	0.018236000	1.565834000
H	-1.576408000	1.898129000	2.902557000
C	-1.068601000	-0.550156000	-1.076205000
H	-1.405760000	-0.393565000	-2.126831000
O	0.252692000	-0.648577000	-0.904079000
C	-1.792932000	-2.005208000	-0.758207000
C	-3.251119000	-1.957694000	-0.798819000
N	-4.404099000	-1.846170000	-0.879642000
C	-1.273332000	-2.537098000	0.499475000
N	-0.745387000	-2.916205000	1.463189000

C	3.641456000	0.585680000	-0.056557000
O	3.769736000	1.453712000	-0.943694000
O	4.399998000	-0.591235000	-0.202946000
O	2.861800000	0.561458000	0.932685000
K	1.940633000	-1.864625000	0.618810000
K	1.144307000	1.899339000	-0.623741000
H	-1.429929000	-2.659970000	-1.558875000
H	4.928781000	-0.451960000	-1.002449000

TS3

Free energy： -2034.60971

Energy：-2034.73031656

C	-4.983235000	-1.626591000	-0.670722000
C	-4.876714000	-0.377739000	-1.285747000
C	-3.648728000	0.282208000	-1.321747000
C	-2.512517000	-0.291751000	-0.737068000
C	-2.626683000	-1.547573000	-0.132884000
C	-3.852897000	-2.211430000	-0.097346000
H	-5.938544000	-2.142885000	-0.644760000
H	-5.748689000	0.082557000	-1.741057000
H	-3.573119000	1.254081000	-1.800532000
H	-1.740712000	-2.005421000	0.290506000
H	-3.925643000	-3.187927000	0.373962000
C	-1.182623000	0.444328000	-0.745708000
H	-1.123068000	1.055718000	-1.663598000
O	-0.105723000	-0.387660000	-0.580596000
C	-1.136581000	1.568809000	0.431909000
H	-0.172620000	2.079120000	0.292055000
C	-2.216451000	2.551376000	0.377802000
N	-3.072299000	3.328115000	0.271582000
C	-1.065985000	0.888579000	1.727310000
N	-0.928268000	0.267310000	2.699396000
C	3.012398000	0.575658000	-0.222780000
O	3.945988000	1.371188000	-0.523501000
O	1.771238000	1.026438000	-0.096796000
O	3.222368000	-0.700186000	-0.009513000
K	1.219713000	-1.368830000	1.453143000
K	5.581029000	-0.451782000	-0.911753000
H	0.881385000	0.274936000	-0.444688000

IM3

Free energy： -2034.612584

Energy：-2034.73765739

C	-4.922030000	-0.525799000	0.923258000
C	-3.824792000	-1.319878000	1.261672000
C	-2.612048000	-1.161795000	0.591429000
C	-2.480739000	-0.208989000	-0.424451000
C	-3.586767000	0.579804000	-0.762365000
C	-4.799687000	0.424879000	-0.091392000
C	-1.152600000	0.002077000	-1.124693000
O	-0.395830000	-1.165849000	-1.129747000
C	-0.302553000	1.161053000	-0.434572000
C	0.152297000	0.753021000	0.898476000
N	0.607196000	0.386406000	1.903993000
C	-0.984379000	2.452554000	-0.396347000
N	-1.528255000	3.477990000	-0.412935000
H	0.536937000	-1.000067000	-1.566344000
H	0.655463000	1.266791000	-1.008267000
C	2.657420000	-0.245359000	-0.973078000
O	1.995167000	-1.050292000	-1.760091000
O	2.512489000	1.034133000	-1.071079000
O	3.390006000	-0.757643000	-0.023943000
K	3.585023000	1.475378000	1.171659000
K	1.593891000	-2.607985000	0.245534000

TS4

Free energy：-2034.59662

Energy：-2034.71867566

C	-4.721637000	-0.271795000	1.343248000
C	-4.074829000	-1.406877000	0.857332000
C	-2.987609000	-1.280482000	-0.011339000
C	-2.531828000	-0.016325000	-0.398427000
C	-3.194998000	1.121602000	0.083838000
C	-4.279381000	0.993722000	0.948942000
H	-5.567218000	-0.369651000	2.017664000
H	-4.418938000	-2.395922000	1.147385000
H	-2.504092000	-2.164630000	-0.409893000
H	-2.858010000	2.110348000	-0.213437000
H	-4.780407000	1.884844000	1.315364000
C	-1.336537000	0.147785000	-1.321626000
O	-0.834425000	-1.144034000	-1.669142000
C	-0.180328000	1.024669000	-0.723556000
C	0.148340000	0.698507000	0.645107000
N	0.523984000	0.329809000	1.688036000
C	-0.335453000	2.442874000	-0.936289000
N	-0.472639000	3.579696000	-1.146347000

H	0.027481000	-0.995443000	-2.104603000
H	-1.656432000	0.673006000	-2.232566000
H	0.871348000	0.536789000	-1.328470000
C	2.762785000	-0.151257000	-0.800375000
O	1.751608000	-0.421201000	-1.648825000
O	3.138130000	1.046783000	-0.672149000
O	3.205712000	-1.124918000	-0.068838000
K	3.517062000	0.747658000	1.776404000
K	1.052806000	-2.500997000	-0.072865000

IM4

Free energy： -2034.633157

Energy：-2034.75506700

C	2.461875000	2.740313000	1.718791000
C	1.234688000	2.071866000	1.684451000
C	1.051287000	0.980974000	0.832472000
C	2.090497000	0.540168000	-0.005879000
C	3.313806000	1.219590000	0.038083000
C	3.501940000	2.305796000	0.895554000
H	2.607059000	3.585979000	2.384572000
H	0.418271000	2.392540000	2.326317000
H	0.098562000	0.464143000	0.822059000
H	4.128209000	0.890729000	-0.602199000
H	4.461191000	2.815046000	0.916051000
C	1.903763000	-0.630815000	-0.953035000
O	0.766637000	-0.271040000	-1.838398000
C	1.700248000	-1.973114000	-0.316115000
C	0.721418000	-2.148254000	0.656354000
N	-0.131480000	-2.237396000	1.464985000
C	2.439820000	-3.079049000	-0.782578000
N	3.071379000	-3.974662000	-1.196328000
H	0.443932000	-1.128720000	-2.153216000
H	2.795748000	-0.706021000	-1.584416000
C	-3.261024000	0.422233000	-0.441331000
O	-3.309958000	1.001341000	-1.725108000
O	-4.076419000	-0.485907000	-0.200226000
O	-2.347316000	0.898857000	0.286927000
K	-2.579533000	-1.328610000	1.839436000
K	-0.721411000	1.896024000	-1.520882000
H	-4.027787000	0.545588000	-2.188454000

TS5

Free energy：-2034.603619

Energy：-2034.72664486

C	-5.041197000	0.467994000	0.191610000
C	-4.957004000	-0.905486000	-0.039989000
C	-3.710314000	-1.528317000	-0.104264000
C	-2.536178000	-0.777271000	0.040696000
C	-2.627452000	0.601833000	0.291328000
C	-3.873648000	1.217186000	0.365252000
H	-6.011815000	0.951513000	0.249348000
H	-5.860768000	-1.494646000	-0.162799000
H	-3.645065000	-2.598622000	-0.279463000
H	-1.714041000	1.158846000	0.468626000
H	-3.937267000	2.282328000	0.568487000
C	-1.226098000	-1.452535000	-0.067821000
O	-0.565409000	-1.017689000	1.895839000
C	-0.243938000	-1.043339000	-0.963829000
C	-0.279319000	0.207780000	-1.635971000
N	-0.293838000	1.227127000	-2.205666000
C	0.929400000	-1.814171000	-1.182385000
N	1.908071000	-2.412763000	-1.399173000
H	-1.186328000	-2.489110000	0.242740000
H	0.058316000	-0.163516000	1.719130000
C	2.025794000	0.514421000	1.093502000
O	0.789245000	0.968216000	1.274141000
O	2.422425000	-0.515300000	1.714011000
O	2.779690000	1.132472000	0.220095000
K	4.071744000	-1.104133000	-0.058964000
K	1.094590000	2.886150000	-0.399556000
H	-1.330902000	-0.675816000	2.378211000

IM5

Free energy： -2034.622139

Energy：-2034.74579915

C	-4.655264000	-0.316005000	0.085769000
C	-4.078525000	0.915253000	-0.242097000
C	-2.764022000	0.976897000	-0.696530000
C	-1.992658000	-0.201283000	-0.816622000
C	-2.598191000	-1.439770000	-0.509488000
C	-3.913630000	-1.490659000	-0.059699000
H	-5.682377000	-0.358030000	0.436765000
H	-4.660634000	1.828700000	-0.162188000
H	-2.353772000	1.938114000	-0.978104000
H	-2.008507000	-2.345272000	-0.614440000
H	-4.360658000	-2.450876000	0.178414000
C	-0.602821000	-0.240811000	-1.253135000

O	-0.057408000	-3.235373000	-0.285589000
C	0.272492000	0.801537000	-1.438342000
C	0.043829000	2.135815000	-0.977827000
N	-0.134996000	3.194156000	-0.521175000
C	1.588295000	0.584098000	-1.951650000
N	2.666427000	0.488979000	-2.383389000
H	0.895265000	-3.045750000	-0.382979000
H	-0.207752000	-1.239569000	-1.433597000
C	1.403694000	-0.799683000	1.005225000
O	0.166300000	-1.050940000	1.323943000
O	2.112651000	-1.651038000	0.353427000
O	1.903153000	0.379281000	1.305377000
K	4.077702000	-0.138242000	0.028852000
K	-0.307491000	1.265931000	2.200745000
H	-0.192368000	-2.623142000	0.474843000

IM6

Free energy： -2417.128656

Energy：-2417.339372

C	2.055118000	-2.089721000	-0.340125000
C	2.417807000	-1.331791000	0.930979000
C	3.650369000	-0.619659000	0.610394000
C	4.428155000	0.280854000	1.344226000
C	5.538759000	0.845328000	0.728020000
C	5.859584000	0.504007000	-0.602266000
C	5.092715000	-0.391497000	-1.345156000
C	3.977066000	-0.946555000	-0.712815000
H	4.149059000	0.527884000	2.363830000
H	6.164335000	1.551014000	1.264683000
H	6.732126000	0.955909000	-1.065583000
H	5.335498000	-0.647427000	-2.370233000
O	3.108800000	-1.798775000	-1.299757000
O	1.781735000	-1.326634000	1.982828000
H	1.075243000	-1.762608000	-0.726444000
C	1.462679000	1.024244000	-1.870699000
C	0.075809000	0.951568000	-1.802142000
C	-0.622901000	1.738265000	-0.863481000
C	0.094432000	2.585949000	0.002476000
C	1.482445000	2.654079000	-0.078453000
C	2.168099000	1.875148000	-1.014413000
H	1.999668000	0.391197000	-2.569432000
H	-0.491709000	0.243394000	-2.396888000
H	-0.434502000	3.213237000	0.711940000
H	2.029625000	3.318500000	0.583267000

H	3.251451000	1.919324000	-1.065369000
C	-2.072396000	1.638019000	-0.843549000
C	-2.894827000	1.735252000	0.251179000
C	-4.297852000	1.549044000	0.071407000
N	-5.430915000	1.354433000	-0.122855000
C	-2.422385000	1.752517000	1.597574000
N	-2.024370000	1.712441000	2.692697000
H	-2.556866000	1.421528000	-1.786956000
C	-2.035093000	-1.293729000	-0.517830000
O	-2.490613000	-0.910231000	-1.674811000
O	-0.779244000	-1.466318000	-0.314847000
O	-2.879522000	-1.450260000	0.479686000
K	-0.924295000	-1.149325000	2.202025000
K	-4.905665000	-1.407497000	-1.013544000
H	2.027558000	-3.170641000	-0.169595000

TS6

Free energy：-2417.11425

Energy：-2417.318375

C	-2.593394000	0.002319000	-1.098355000
C	-3.086345000	-0.775344000	0.028364000
C	-4.540754000	-0.738066000	-0.095390000
C	-5.578832000	-1.228125000	0.705361000
C	-6.887928000	-1.041803000	0.278073000
C	-7.153350000	-0.372811000	-0.936301000
C	-6.133747000	0.119468000	-1.745379000
C	-4.820944000	-0.084164000	-1.307264000
H	-5.348793000	-1.742249000	1.634359000
H	-7.716285000	-1.409231000	0.876185000
H	-8.185058000	-0.240039000	-1.250272000
H	-6.334576000	0.633445000	-2.678951000
O	-3.710566000	0.309936000	-1.958027000
O	-2.412680000	-1.260114000	0.981046000
H	-1.742990000	-0.345783000	-1.681974000
C	1.388795000	-2.992310000	0.629667000
C	2.766347000	-2.943683000	0.448666000
C	3.365918000	-1.838766000	-0.196771000
C	2.530794000	-0.820309000	-0.706654000
C	1.153218000	-0.878148000	-0.534456000
C	0.576421000	-1.959858000	0.145768000
H	0.941503000	-3.840420000	1.139388000
H	3.394116000	-3.748259000	0.822663000
H	2.954683000	-0.001834000	-1.275141000
H	0.545033000	-0.066202000	-0.923754000

H	-0.501195000	-1.982268000	0.301216000
C	4.810294000	-1.821678000	-0.288683000
C	5.665030000	-0.764306000	-0.462327000
C	7.079539000	-0.977276000	-0.536244000
N	8.228291000	-1.151935000	-0.595124000
C	5.240009000	0.600030000	-0.501783000
N	4.892771000	1.710735000	-0.500436000
H	-2.106822000	1.110888000	-0.457482000
H	5.301467000	-2.785008000	-0.167067000
C	-0.307239000	2.094068000	0.245268000
O	0.203120000	2.161527000	-0.916267000
O	-1.609934000	1.872629000	0.400149000
O	0.394895000	2.182825000	1.333438000
K	-1.199292000	0.481599000	2.532071000
K	2.419808000	3.039217000	0.003596000

IM7

Free energy：-2417.136637

Energy：-2417.345101

C	2.255657000	0.540250000	-2.118611000
C	1.501850000	1.262618000	-1.203598000
C	2.427133000	1.461262000	-0.072085000
C	2.312270000	2.099745000	1.167879000
C	3.395583000	2.064587000	2.042639000
C	4.588160000	1.405511000	1.689887000
C	4.730201000	0.776064000	0.452325000
C	3.636469000	0.830643000	-0.407347000
O	3.566982000	0.263252000	-1.649154000
O	0.264652000	1.643183000	-1.245213000
C	-4.809674000	1.040599000	0.486949000
C	-3.655461000	0.414489000	0.944778000
C	-2.406080000	1.062151000	0.829857000
C	-2.350625000	2.341809000	0.226732000
C	-3.512871000	2.959994000	-0.225501000
C	-4.745343000	2.312631000	-0.092214000
C	-1.133842000	0.486116000	1.227927000
H	-0.271980000	1.049929000	0.881439000
C	-0.854036000	-0.670446000	1.901807000
C	-1.801435000	-1.622120000	2.394495000
N	-2.530230000	-2.435665000	2.797298000
C	0.511614000	-1.063683000	2.075345000
N	1.616024000	-1.421160000	2.168904000
C	-1.094300000	-2.364373000	-1.004094000
O	-0.660467000	-3.278832000	-0.039864000

O	-2.253989000	-1.915095000	-0.897482000
O	-0.203744000	-2.064425000	-1.847612000
K	-1.529791000	0.201453000	-2.416633000
K	2.083533000	-2.116681000	-0.603355000
H	-1.414545000	-3.435978000	0.549335000

TS7

Free energy：-2417.121774

Energy：-2417.334843

C	0.784293000	-0.326243000	-0.750851000
C	1.508538000	0.848092000	-1.055711000
C	2.880529000	0.526456000	-0.627195000
C	4.065194000	1.266310000	-0.559239000
C	5.216653000	0.633384000	-0.095779000
C	5.189075000	-0.718783000	0.295073000
C	4.016251000	-1.474244000	0.233530000
C	2.883366000	-0.822256000	-0.238141000
H	4.069630000	2.308751000	-0.862686000
H	6.148981000	1.185920000	-0.029357000
H	6.099752000	-1.186642000	0.657089000
H	3.979935000	-2.512918000	0.544184000
O	1.635559000	-1.381385000	-0.369121000
O	1.055761000	1.944974000	-1.500750000
C	-2.306246000	3.145177000	1.019924000
C	-1.886975000	1.830644000	1.213522000
C	-0.512437000	1.532475000	1.365347000
C	0.410346000	2.597511000	1.287101000
C	-0.016230000	3.909968000	1.104954000
C	-1.376198000	4.191656000	0.971395000
H	-3.367357000	3.350802000	0.910896000
H	-2.627714000	1.043009000	1.202633000
H	1.471571000	2.384187000	1.363425000
H	0.716789000	4.708562000	1.050669000
H	-1.711978000	5.214660000	0.827928000
C	0.014813000	0.183786000	1.546596000
H	1.090401000	0.117009000	1.661016000
C	-0.687084000	-0.957732000	1.972590000
C	-2.089633000	-1.063928000	2.168463000
N	-3.236745000	-1.223858000	2.323790000
C	-0.014251000	-2.204248000	2.091064000
N	0.468147000	-3.270620000	2.095783000
C	-2.758320000	-1.062587000	-1.320238000
O	-3.090248000	-2.170828000	-0.536626000
O	-3.347432000	0.011654000	-1.093344000

O	-1.829791000	-1.297865000	-2.149337000
K	-1.510295000	1.625444000	-2.158608000
K	-0.593956000	-3.295259000	-0.781056000
H	-3.656469000	-1.852964000	0.188527000
H	-0.173476000	-0.637586000	-1.138726000

IM8

Free energy：-2417.15195

Energy：-2417.367145

C	-1.191066000	0.641833000	0.707927000
C	-2.076933000	1.881979000	0.455082000
C	-1.138267000	2.933684000	0.053549000
C	-1.344949000	4.239699000	-0.400510000
C	-0.227842000	5.001423000	-0.727433000
C	1.064919000	4.456171000	-0.604688000
C	1.290546000	3.155123000	-0.149425000
C	0.154362000	2.422398000	0.181114000
H	-2.355347000	4.625304000	-0.492802000
H	-0.347816000	6.017669000	-1.089183000
H	1.921541000	5.063948000	-0.881904000
H	2.283089000	2.715254000	-0.082586000
O	0.177321000	1.134108000	0.664356000
O	-3.289677000	1.919237000	0.546475000
C	-5.064724000	-1.283674000	-1.037725000
C	-3.788809000	-0.731715000	-1.154710000
C	-2.776324000	-1.071855000	-0.252461000
C	-3.068439000	-1.973688000	0.779623000
C	-4.343868000	-2.522728000	0.902559000
C	-5.346670000	-2.180387000	-0.007310000
H	-5.837938000	-1.009003000	-1.749292000
H	-3.578863000	-0.022892000	-1.950914000
H	-2.292532000	-2.259693000	1.483995000
H	-4.553832000	-3.221461000	1.707449000
H	-6.339744000	-2.609993000	0.087172000
C	-1.389347000	-0.454862000	-0.383367000
C	-0.241219000	-1.454028000	-0.365261000
C	0.250583000	-2.017506000	0.808422000
N	0.734972000	-2.468227000	1.789257000
C	0.546840000	-1.690981000	-1.484824000
N	1.287039000	-1.944643000	-2.370687000
H	-1.367114000	0.218016000	1.701207000
H	-1.332082000	0.060294000	-1.348691000
H	2.731489000	-0.355474000	-2.054791000
C	3.474224000	0.180872000	-0.380248000

O	3.722467000	1.163239000	0.351886000
O	3.132608000	0.448262000	-1.674694000
O	3.459575000	-1.042191000	-0.004273000
K	3.021004000	-3.370074000	-0.723417000
K	2.273660000	-0.024856000	2.198599000

TS8

Free energy：-2417.123165

Energy：-2417.336352

C	-0.867100000	1.015322000	0.788103000
C	-1.456515000	2.378079000	0.347925000
C	-0.300909000	3.126475000	-0.145278000
C	-0.202804000	4.367910000	-0.783653000
C	1.054628000	4.787604000	-1.201254000
C	2.181737000	3.964854000	-0.999759000
C	2.103817000	2.725249000	-0.363453000
C	0.838179000	2.346948000	0.073503000
H	-1.095467000	4.963537000	-0.946574000
H	1.171497000	5.742091000	-1.704873000
H	3.147681000	4.299605000	-1.368068000
H	2.936832000	2.030259000	-0.267489000
O	0.570308000	1.181169000	0.751940000
O	-2.634983000	2.679563000	0.378112000
C	-4.994891000	-0.436340000	-0.994726000
C	-3.638666000	-0.128533000	-1.099493000
C	-2.752117000	-0.447115000	-0.066045000
C	-3.249881000	-1.078295000	1.082677000
C	-4.604975000	-1.386660000	1.188875000
C	-5.481633000	-1.067029000	0.150164000
H	-5.669530000	-0.181336000	-1.806510000
H	-3.264841000	0.370170000	-1.989341000
H	-2.578953000	-1.335362000	1.896975000
H	-4.975961000	-1.877426000	2.083842000
H	-6.537244000	-1.307887000	0.233922000
C	-1.280442000	-0.103986000	-0.201751000
C	-0.304141000	-1.314084000	-0.049648000
C	-0.021908000	-1.665171000	1.328018000
N	0.227597000	-1.817745000	2.455913000
C	-0.648834000	-2.474762000	-0.845502000
N	-0.756848000	-3.390497000	-1.557834000
H	-1.156887000	0.758067000	1.809660000
H	-1.095392000	0.278655000	-1.211559000
H	0.758380000	-0.963297000	-0.582950000
C	2.860442000	-0.810269000	-0.342558000

O	3.626057000	0.124610000	0.046674000
O	1.966960000	-0.624376000	-1.308589000
O	2.853688000	-1.977593000	0.243783000
K	2.206043000	-3.182498000	-1.913770000
K	2.825771000	-0.511583000	2.412411000

IM9

Free energy： -2417.124792

Energy：-2417.339382

C	-0.876351000	1.040282000	0.788923000
C	-1.414581000	2.420402000	0.335061000
C	-0.227445000	3.127941000	-0.141026000
C	-0.077972000	4.362994000	-0.782952000
C	1.198919000	4.736521000	-1.184111000
C	2.294553000	3.876361000	-0.963315000
C	2.166753000	2.642540000	-0.323828000
C	0.882290000	2.311670000	0.094843000
H	-0.947039000	4.988460000	-0.960718000
H	1.355717000	5.684279000	-1.689679000
H	3.276344000	4.176837000	-1.319024000
H	2.975388000	1.919180000	-0.208262000
O	0.564357000	1.154981000	0.771730000
O	-2.584628000	2.754826000	0.342545000
C	-5.021259000	-0.396843000	-1.019447000
C	-3.663118000	-0.096809000	-1.119670000
C	-2.785755000	-0.398070000	-0.072835000
C	-3.295235000	-1.003039000	1.085008000
C	-4.652291000	-1.305394000	1.185427000
C	-5.519292000	-1.003492000	0.133624000
H	-5.688463000	-0.154528000	-1.841108000
H	-3.280468000	0.382824000	-2.016153000
H	-2.634280000	-1.243724000	1.911947000
H	-5.032211000	-1.776101000	2.087318000
H	-6.576492000	-1.238245000	0.213948000
C	-1.313749000	-0.062852000	-0.208776000
C	-0.339282000	-1.281512000	-0.080655000
C	-0.104973000	-1.688647000	1.302051000
N	0.080713000	-1.888243000	2.432485000
C	-0.704107000	-2.421387000	-0.916485000
N	-0.847673000	-3.315725000	-1.645470000
H	-1.190441000	0.794224000	1.806063000
H	-1.127662000	0.322931000	-1.216930000
H	0.665955000	-0.947337000	-0.527058000
C	2.867574000	-0.837563000	-0.314209000

O	3.640429000	0.054007000	0.175022000
O	2.121261000	-0.618254000	-1.368851000
O	2.736455000	-2.004961000	0.283533000
K	2.245515000	-3.131170000	-1.950325000
K	2.768238000	-0.623799000	2.467849000

TS9

Free energy：-2417.166579

Energy：-2417.377734

C	1.113941000	0.345625000	0.147986000
C	1.832836000	-0.930743000	0.113727000
C	3.235644000	-0.571410000	-0.120228000
C	4.388624000	-1.340472000	-0.313745000
C	5.599965000	-0.680972000	-0.492840000
C	5.654250000	0.727915000	-0.484414000
C	4.515092000	1.508258000	-0.298182000
C	3.310655000	0.828747000	-0.105041000
H	4.326406000	-2.424778000	-0.322155000
H	6.512836000	-1.248185000	-0.644550000
H	6.611622000	1.220621000	-0.626636000
H	4.555577000	2.592131000	-0.292750000
O	2.106750000	1.409119000	0.095993000
O	1.342457000	-2.083893000	0.129308000
C	-1.263646000	-2.166860000	3.336995000
C	-0.516008000	-1.071600000	2.901192000
C	-0.766994000	-0.473437000	1.661546000
C	-1.797887000	-0.997330000	0.870476000
C	-2.554754000	-2.087759000	1.303238000
C	-2.286553000	-2.680897000	2.539429000
H	-1.048122000	-2.613959000	4.302614000
H	0.277662000	-0.678511000	3.529902000
H	-2.015347000	-0.567490000	-0.098827000
H	-3.354137000	-2.470572000	0.673592000
H	-2.873790000	-3.528459000	2.879143000
C	0.104840000	0.693463000	1.236454000
C	-0.697835000	1.995230000	0.782434000
C	-2.120062000	2.008177000	1.131856000
N	-3.273472000	1.982701000	1.265254000
C	-0.046346000	3.215729000	1.257938000
N	0.481882000	4.178702000	1.630653000
H	0.489799000	0.246826000	-1.157797000
H	0.667976000	0.995355000	2.125025000
H	-0.725723000	2.022445000	-0.329005000
C	-1.325968000	0.314860000	-2.208649000

O	-1.596995000	1.535566000	-1.965995000
O	-0.049512000	-0.096108000	-2.157557000
O	-2.217608000	-0.574701000	-2.440323000
K	-0.570633000	-2.620489000	-1.645297000
K	-4.105322000	1.040792000	-1.468510000

IM10

Free energy：-2417.197398

Energy：-2417.408868

C	-0.307464000	-1.350812000	-0.988697000
C	0.435574000	-0.248580000	-1.415550000
C	1.832566000	-0.730975000	-1.358217000
C	3.065362000	-0.096468000	-1.555283000
C	4.231652000	-0.823015000	-1.311778000
C	4.173842000	-2.166084000	-0.887518000
C	2.951790000	-2.818331000	-0.695329000
C	1.802082000	-2.071718000	-0.940948000
H	3.100308000	0.944891000	-1.861525000
H	5.200377000	-0.350649000	-1.444452000
H	5.097030000	-2.706671000	-0.702349000
H	2.897407000	-3.849818000	-0.362156000
O	0.521482000	-2.485105000	-0.748044000
O	0.078870000	0.929968000	-1.773414000
C	-3.880258000	1.430858000	-1.619185000
C	-3.162729000	0.236723000	-1.693660000
C	-2.542493000	-0.301716000	-0.559891000
C	-2.664390000	0.375600000	0.660722000
C	-3.399823000	1.563308000	0.745156000
C	-4.006020000	2.098967000	-0.396006000
H	-4.349618000	1.834333000	-2.511288000
H	-3.072061000	-0.281747000	-2.643553000
H	-2.188651000	-0.002567000	1.558421000
H	-3.495060000	2.066795000	1.702933000
H	-4.577710000	3.019954000	-0.330620000
C	-1.752862000	-1.595259000	-0.711441000
C	-1.878221000	-2.568427000	0.537983000
C	-1.013410000	-2.165082000	1.656097000
N	-0.282756000	-1.843016000	2.497157000
C	-3.267954000	-2.737558000	0.971323000
N	-4.377634000	-2.871898000	1.278794000
H	-2.231334000	-2.175105000	-1.514216000
H	-1.506951000	-3.546622000	0.212202000
C	1.990858000	2.581991000	1.208675000
O	3.130784000	2.114799000	1.415736000

O	1.905389000	3.749920000	0.442996000
O	0.871046000	2.130412000	1.568977000
K	-0.565513000	2.962713000	-0.506187000
K	1.998496000	-0.284866000	1.777538000
H	2.813143000	3.972020000	0.180554000

IM11

Free energy：-2911.347195

Energy：-2911.675729

C	0.626504000	0.335307000	-0.839926000
C	1.609507000	-0.185000000	-1.676503000
C	1.322339000	-1.631528000	-1.702323000
C	1.942155000	-2.715457000	-2.329795000
C	1.407750000	-3.989401000	-2.143110000
C	0.265411000	-4.181283000	-1.344328000
C	-0.367299000	-3.110721000	-0.708757000
C	0.195375000	-1.850850000	-0.899771000
H	2.817560000	-2.547252000	-2.950597000
H	1.870046000	-4.847645000	-2.622348000
H	-0.135280000	-5.182268000	-1.216115000
H	-1.241717000	-3.254990000	-0.083539000
O	-0.246453000	-0.675028000	-0.343261000
O	2.581852000	0.419040000	-2.255970000
C	2.713680000	4.620539000	0.230042000
C	1.714169000	3.864867000	-0.385443000
C	1.396284000	2.584716000	0.081191000
C	2.093953000	2.075254000	1.184888000
C	3.088889000	2.832188000	1.808417000
C	3.405168000	4.107089000	1.328951000
H	2.951497000	5.609672000	-0.150014000
H	1.180588000	4.269587000	-1.240988000
H	1.892240000	1.068450000	1.530736000
H	3.612951000	2.421064000	2.667148000
H	4.180200000	4.696170000	1.810694000
C	0.293949000	1.774632000	-0.598004000
C	-1.077136000	1.910080000	0.162476000
C	-1.004620000	1.449116000	1.556646000
N	-0.928760000	1.035438000	2.637519000
C	-1.605975000	3.278660000	0.093714000
N	-2.035769000	4.350663000	-0.010967000
H	0.103537000	2.252422000	-1.570058000
H	-1.793678000	1.255367000	-0.343628000
C	-3.258089000	1.846016000	-2.858226000
C	-4.122235000	1.503508000	-1.824687000

C	-3.982124000	0.268989000	-1.150481000
C	-2.992541000	-0.636972000	-1.587467000
C	-2.151219000	-0.299659000	-2.643991000
C	-2.269536000	0.943820000	-3.268496000
H	-3.351734000	2.813176000	-3.340758000
H	-4.884440000	2.206493000	-1.501424000
H	-2.876056000	-1.599479000	-1.105561000
H	-1.379493000	-0.995274000	-2.954250000
H	-1.590871000	1.208494000	-4.073181000
C	-4.861624000	0.022125000	-0.021611000
H	-5.806050000	0.561995000	-0.035177000
C	-4.662607000	-0.753176000	1.086845000
C	-3.442952000	-1.429691000	1.409402000
N	-2.464423000	-1.961643000	1.743914000
C	-5.693952000	-0.866513000	2.077058000
N	-6.532558000	-0.961941000	2.877459000
C	3.060646000	-2.203089000	1.305845000
O	2.352677000	-3.174824000	1.631547000
O	4.050011000	-2.432134000	0.335023000
O	3.007263000	-1.005130000	1.699670000
K	4.264106000	0.233885000	-0.344774000
K	0.392024000	-1.617000000	2.441562000
H	3.888797000	-3.331190000	0.013187000

TS10

Free energy：-2911.307063

Energy：-2911.642182

C	-1.006488000	0.512151000	-0.668789000
C	-2.315023000	0.865976000	-1.228389000
C	-2.241030000	2.324659000	-1.455046000
C	-3.198965000	3.244588000	-1.879097000
C	-2.821041000	4.579850000	-2.007479000
C	-1.507874000	4.977738000	-1.703962000
C	-0.542509000	4.062608000	-1.276354000
C	-0.937385000	2.731347000	-1.177314000
H	-4.207229000	2.904733000	-2.094497000
H	-3.542148000	5.323048000	-2.332709000
H	-1.234188000	6.024833000	-1.793956000
H	0.453978000	4.395463000	-1.007895000
O	-0.145784000	1.674344000	-0.788415000
O	-3.309825000	0.152077000	-1.392072000
C	-1.390675000	-3.653100000	-3.251743000
C	-0.713089000	-2.514702000	-2.812230000
C	-1.057872000	-1.899982000	-1.602666000

C	-2.097515000	-2.441900000	-0.837105000
C	-2.772679000	-3.577623000	-1.274685000
C	-2.422515000	-4.187757000	-2.480882000
H	-1.113064000	-4.116267000	-4.194085000
H	0.090404000	-2.101019000	-3.417001000
H	-2.386753000	-1.972141000	0.091438000
H	-3.578891000	-3.979855000	-0.669177000
H	-2.953451000	-5.072819000	-2.819481000
C	-0.243941000	-0.709111000	-1.131949000
C	0.905610000	-1.183096000	-0.115490000
C	0.519720000	-2.254856000	0.810531000
N	0.241856000	-3.132406000	1.514776000
C	2.053330000	-1.658332000	-0.901424000
N	2.941241000	-1.995001000	-1.567158000
H	0.333131000	-0.352739000	-1.996580000
H	1.255118000	-0.331739000	0.479961000
C	-3.026997000	-2.277640000	2.973836000
C	-2.095366000	-1.280777000	2.705141000
C	-2.450734000	-0.154298000	1.936954000
C	-3.783007000	-0.050437000	1.483117000
C	-4.712472000	-1.049711000	1.757492000
C	-4.336682000	-2.171685000	2.496720000
H	-2.722539000	-3.145098000	3.550678000
H	-1.088011000	-1.398286000	3.077750000
H	-4.083574000	0.807555000	0.895068000
H	-5.726881000	-0.953244000	1.383458000
H	-5.058290000	-2.956437000	2.704482000
C	-1.519766000	0.920461000	1.575717000
H	-2.013373000	1.801055000	1.181774000
C	-0.292711000	1.243413000	2.217849000
C	0.542452000	0.363310000	2.945722000
N	1.311195000	-0.319002000	3.505575000
C	0.273264000	2.527367000	2.033207000
N	0.796484000	3.562184000	1.858482000
C	4.328101000	0.027039000	0.826212000
O	3.279171000	0.536609000	1.583066000
O	4.907994000	-0.996923000	1.229987000
O	4.529744000	0.680814000	-0.244204000
K	5.657518000	-1.537711000	-1.183398000
K	2.581170000	2.489065000	-0.049782000
H	3.098002000	-0.031567000	2.355219000

IM12

Free energy： -2911.328751

Energy：-2911.662172

C	-1.823467000	0.502452000	-0.171725000
C	-3.316785000	0.048041000	-0.239637000
C	-4.046408000	1.202299000	-0.761932000
C	-5.409747000	1.406168000	-0.997622000
C	-5.807598000	2.632367000	-1.518251000
C	-4.851438000	3.629349000	-1.797289000
C	-3.489209000	3.435982000	-1.570191000
C	-3.112716000	2.199588000	-1.048363000
H	-6.119497000	0.616861000	-0.770961000
H	-6.856965000	2.829882000	-1.710899000
H	-5.184857000	4.580728000	-2.201547000
H	-2.749340000	4.199928000	-1.779439000
O	-1.830768000	1.839756000	-0.777982000
O	-3.739682000	-1.045073000	0.080946000
C	-2.161012000	-3.783932000	-2.332028000
C	-1.960193000	-2.408805000	-2.233965000
C	-1.181195000	-1.861659000	-1.204546000
C	-0.596237000	-2.732162000	-0.279265000
C	-0.795526000	-4.109040000	-0.373705000
C	-1.577888000	-4.641147000	-1.398407000
H	-2.773042000	-4.182805000	-3.135293000
H	-2.423877000	-1.749290000	-2.963172000
H	-0.000951000	-2.347309000	0.533642000
H	-0.343975000	-4.762821000	0.366482000
H	-1.734730000	-5.713492000	-1.467264000
C	-0.995807000	-0.350853000	-1.188091000
C	0.500105000	0.110672000	-1.303454000
C	1.440098000	-0.333674000	-0.255985000
N	2.337965000	-0.773352000	0.342466000
C	1.099481000	-0.371758000	-2.564983000
N	1.667104000	-0.761236000	-3.500130000
H	-1.411796000	0.000832000	-2.138265000
H	0.525955000	1.209414000	-1.325526000
C	-0.718402000	-2.329122000	3.513404000
C	-0.509980000	-1.271240000	2.627574000
C	-1.558419000	-0.411661000	2.273928000
C	-2.813317000	-0.629305000	2.860264000
C	-3.027360000	-1.687062000	3.740852000
C	-1.978355000	-2.546774000	4.068328000
H	0.114122000	-2.975910000	3.774745000
H	0.485645000	-1.112708000	2.234029000
H	-3.637690000	0.035284000	2.620775000
H	-4.012266000	-1.834809000	4.173613000

H	-2.139192000	-3.369638000	4.758728000
C	-1.390287000	0.773535000	1.325428000
H	-2.156258000	1.502727000	1.629899000
C	-0.020063000	1.442073000	1.417063000
C	0.858424000	1.300563000	2.502762000
N	1.728082000	1.253515000	3.294323000
C	0.397781000	2.515031000	0.613232000
N	0.919346000	3.338489000	-0.049911000
C	5.767842000	0.479938000	-0.236192000
O	6.169387000	1.110900000	0.946891000
O	6.389177000	-0.548265000	-0.576954000
O	4.778181000	1.029735000	-0.792625000
K	4.373282000	-1.208667000	-2.127556000
K	3.589235000	2.194825000	1.267144000
H	6.899149000	0.578610000	1.295598000

TS11

Free energy：-2911.318076

Energy：-2911.65237

C	-3.585606000	0.973204000	-0.184401000
C	-2.967801000	0.974911000	1.070776000
O	-1.700134000	0.479054000	1.066284000
C	-1.370848000	0.077816000	-0.287931000
C	-2.621758000	0.437622000	-1.133384000
C	-4.891923000	1.444315000	-0.343673000
C	-5.560088000	1.915754000	0.780288000
C	-4.922567000	1.913418000	2.036290000
C	-3.619628000	1.446567000	2.207121000
O	-2.681848000	0.301516000	-2.344401000
C	-0.189649000	0.896918000	-0.858564000
C	1.190836000	0.226617000	-0.558973000
C	1.224014000	-1.331484000	-1.317820000
C	-0.229331000	-1.848231000	-1.470517000
C	-1.097058000	-1.450779000	-0.243503000
C	-2.388772000	-2.225253000	-0.040536000
C	-0.295916000	2.381105000	-0.549236000
C	-2.805473000	-2.504783000	1.266490000
C	-4.017425000	-3.151249000	1.506182000
C	-4.827917000	-3.532862000	0.436489000
C	-4.418755000	-3.262719000	-0.870286000
C	-3.209716000	-2.611083000	-1.108474000
C	-0.643526000	3.260262000	-1.582463000
C	-0.774816000	4.628277000	-1.342459000
C	-0.556604000	5.135670000	-0.061870000

C	-0.211530000	4.266452000	0.975311000
C	-0.084071000	2.898956000	0.737118000
N	2.246403000	-1.914197000	-1.651778000
C	-0.200588000	-3.302376000	-1.658260000
N	-0.239961000	-4.452203000	-1.803647000
C	2.237073000	1.045038000	-1.161567000
N	3.033518000	1.729539000	-1.657506000
C	1.476172000	0.075859000	0.861340000
N	1.695483000	-0.048968000	1.996655000
H	-5.353684000	1.431863000	-1.325589000
H	-6.575834000	2.287728000	0.696910000
H	-5.462478000	2.286780000	2.901710000
H	-3.128266000	1.442548000	3.173181000
H	-0.297598000	0.792460000	-1.943172000
H	-0.480796000	-1.613791000	0.646206000
H	-2.176477000	-2.204085000	2.099490000
H	-4.324602000	-3.360777000	2.526643000
H	-5.769796000	-4.041777000	0.619076000
H	-5.040006000	-3.561401000	-1.709219000
H	-2.910846000	-2.395562000	-2.128038000
H	-0.821476000	2.867354000	-2.579588000
H	-1.045841000	5.294080000	-2.156332000
H	-0.657244000	6.200150000	0.128547000
H	-0.046671000	4.653049000	1.976930000
H	0.164322000	2.231929000	1.553214000
H	-0.680502000	-1.417043000	-2.374018000
C	4.624947000	-1.251436000	0.361894000
O	4.008997000	-2.177509000	0.954116000
O	4.486104000	-1.097028000	-0.960444000
O	5.364813000	-0.371336000	0.972837000
K	5.731093000	1.085028000	-1.117807000
K	4.092732000	-1.021299000	3.156596000
H	3.413497000	-1.540159000	-1.328433000

IM13

Free energy：-2911.323474

Energy：-2911.664452

C	3.134040000	0.581657000	-0.892968000
C	3.406607000	0.219902000	0.427545000
O	2.295934000	-0.049204000	1.167045000
C	1.118557000	0.130600000	0.329937000
C	1.686224000	0.529208000	-1.069292000
C	4.166722000	0.890366000	-1.781097000
C	5.475142000	0.828489000	-1.312623000

C	5.732685000	0.458660000	0.021124000
C	4.708606000	0.146014000	0.915627000
O	1.012764000	0.695841000	-2.065596000
C	0.339509000	-1.185900000	0.132492000
C	-0.592071000	-1.494549000	1.359376000
C	-1.671419000	-0.375323000	1.483787000
C	-1.235135000	0.950397000	0.884732000
C	0.274977000	1.247264000	1.036639000
C	0.646283000	2.644166000	0.572629000
C	1.196204000	-2.353028000	-0.313514000
C	1.579329000	3.384448000	1.306616000
C	1.967839000	4.656012000	0.883584000
C	1.421227000	5.200248000	-0.279037000
C	0.491193000	4.464998000	-1.017474000
C	0.103309000	3.192425000	-0.600637000
C	0.987093000	-2.857694000	-1.604380000
C	1.751474000	-3.923510000	-2.078190000
C	2.728122000	-4.500274000	-1.264848000
C	2.936566000	-4.006620000	0.024347000
C	2.177427000	-2.937791000	0.500112000
N	-2.773640000	-0.665311000	2.043169000
C	-2.120228000	2.017385000	1.335576000
N	-2.951389000	2.786537000	1.603123000
C	-1.265184000	-2.792419000	1.168664000
N	-1.814005000	-3.802548000	1.017200000
C	0.134637000	-1.545553000	2.645843000
N	0.695761000	-1.546738000	3.661118000
H	3.932127000	1.166859000	-2.803969000
H	6.304137000	1.061584000	-1.972769000
H	6.761562000	0.413091000	0.366610000
H	4.903486000	-0.141928000	1.942305000
H	-0.385954000	-0.982680000	-0.669368000
H	0.538099000	1.159698000	2.095120000
H	2.005807000	2.958306000	2.210681000
H	2.693020000	5.219655000	1.463149000
H	1.720405000	6.190605000	-0.610008000
H	0.071721000	4.878695000	-1.930123000
H	-0.592868000	2.612090000	-1.199935000
H	0.219222000	-2.406816000	-2.226237000
H	1.581840000	-4.303494000	-3.081435000
H	3.323330000	-5.331228000	-1.632552000
H	3.694069000	-4.452105000	0.662569000
H	2.353601000	-2.553504000	1.497701000
C	-3.100333000	-0.143781000	-1.371755000

O	-2.568814000	1.030661000	-1.561179000
O	-2.348588000	-1.182041000	-1.235207000
O	-4.398234000	-0.242472000	-1.225471000
K	-4.166907000	-2.648211000	-0.284587000
K	-4.641113000	2.305100000	-0.955531000
H	-3.382331000	0.155250000	2.102444000
H	-1.506860000	0.894379000	-0.217837000

TS12

Free energy： -2911.321223

Energy：-2911.659348

C	-3.101020000	-0.552258000	-0.920734000
C	-3.387668000	-0.185602000	0.395705000
O	-2.285903000	0.080882000	1.146805000
C	-1.097841000	-0.111129000	0.325693000
C	-1.651164000	-0.504438000	-1.079370000
C	-4.124379000	-0.859478000	-1.820219000
C	-5.437982000	-0.791654000	-1.367625000
C	-5.709965000	-0.416984000	-0.037932000
C	-4.695624000	-0.105496000	0.867650000
O	-0.967948000	-0.671915000	-2.069885000
C	-0.306930000	1.199315000	0.140815000
C	0.645953000	1.480414000	1.360192000
C	1.716614000	0.348707000	1.451841000
C	1.239740000	-0.959273000	0.937167000
C	-0.272677000	-1.230179000	1.050971000
C	-0.667107000	-2.628598000	0.608787000
C	-1.154725000	2.383134000	-0.278408000
C	-1.577963000	-3.358961000	1.379866000
C	-1.983553000	-4.634690000	0.985615000
C	-1.477567000	-5.195264000	-0.187310000
C	-0.570676000	-4.470928000	-0.964434000
C	-0.166222000	-3.195370000	-0.573907000
C	-0.955816000	2.903818000	-1.564451000
C	-1.713055000	3.985535000	-2.013233000
C	-2.671685000	4.562618000	-1.179089000
C	-2.869105000	4.053515000	0.105874000
C	-2.117529000	2.968625000	0.556421000
N	2.880445000	0.667667000	1.881692000
C	2.114548000	-2.030446000	1.326503000
N	2.959720000	-2.816060000	1.510781000
C	1.322595000	2.777963000	1.176648000
N	1.877033000	3.784498000	1.021002000
C	-0.062965000	1.519465000	2.656507000

N	-0.611172000	1.511747000	3.678821000
H	-3.878829000	-1.139601000	-2.839554000
H	-6.259992000	-1.023747000	-2.036828000
H	-6.742742000	-0.366771000	0.295133000
H	-4.901637000	0.185948000	1.891159000
H	0.398983000	0.999129000	-0.675316000
H	-0.565769000	-1.126597000	2.100980000
H	-1.973188000	-2.921495000	2.292683000
H	-2.691002000	-5.188660000	1.595710000
H	-1.790325000	-6.188486000	-0.496467000
H	-0.183592000	-4.896271000	-1.886243000
H	0.507297000	-2.621757000	-1.202006000
H	-0.199825000	2.454403000	-2.201691000
H	-1.551264000	4.378044000	-3.012960000
H	-3.261150000	5.406083000	-1.527094000
H	-3.612248000	4.499540000	0.760425000
H	-2.285355000	2.571935000	1.550536000
C	3.015226000	0.194153000	-1.449429000
O	2.364353000	-0.976380000	-1.415294000
O	2.348132000	1.272625000	-1.383082000
O	4.306362000	0.158505000	-1.457196000
K	4.218467000	2.526462000	-0.204608000
K	4.431094000	-2.409114000	-0.994497000
H	3.469909000	-0.166385000	1.950853000
H	1.628148000	-0.908706000	-0.333849000

IM14

Free energy：-2911.350572

Energy：-2911.688712

C	-1.095776000	-2.235171000	-0.917333000
C	-1.916771000	-2.346653000	0.212468000
O	-1.936145000	-1.236956000	0.989663000
C	-1.052682000	-0.241283000	0.404767000
C	-0.542770000	-0.898597000	-0.901372000
C	-0.961408000	-3.296763000	-1.820079000
C	-1.663981000	-4.465901000	-1.560757000
C	-2.488672000	-4.560666000	-0.420456000
C	-2.633103000	-3.510731000	0.484124000
O	0.136160000	-0.316443000	-1.742974000
C	-1.821919000	1.042695000	-0.029308000
C	-1.537167000	2.287579000	0.890432000
C	0.005222000	2.511459000	0.987017000
C	0.736979000	1.338050000	1.334755000
C	0.066932000	-0.013499000	1.486546000

C	1.033025000	-1.194897000	1.482207000
C	-3.279224000	0.795740000	-0.372363000
C	0.839171000	-2.258028000	2.369770000
C	1.669800000	-3.381120000	2.336209000
C	2.706890000	-3.460651000	1.406254000
C	2.909829000	-2.405338000	0.511208000
C	2.083420000	-1.282114000	0.554185000
C	-3.682488000	0.916119000	-1.707360000
C	-5.008738000	0.693494000	-2.077479000
C	-5.951731000	0.350455000	-1.109491000
C	-5.559613000	0.228591000	0.225256000
C	-4.233164000	0.444016000	0.593897000
N	0.404916000	3.722809000	0.726619000
C	2.045792000	1.501972000	1.790114000
N	3.146505000	1.649279000	2.179737000
C	-2.194089000	3.451081000	0.263306000
N	-2.765221000	4.291093000	-0.295091000
C	-2.068074000	2.106536000	2.255238000
N	-2.461283000	1.915539000	3.330149000
H	-0.320351000	-3.189596000	-2.689142000
H	-1.585376000	-5.312501000	-2.234532000
H	-3.032528000	-5.483614000	-0.241035000
H	-3.269221000	-3.581588000	1.358507000
H	-1.333348000	1.341920000	-0.960465000
H	-0.495711000	-0.062165000	2.428924000
H	0.025591000	-2.207929000	3.087565000
H	1.501170000	-4.195368000	3.034878000
H	3.345918000	-4.338471000	1.373038000
H	3.695981000	-2.453374000	-0.238656000
H	2.253498000	-0.467141000	-0.138879000
H	-2.952598000	1.191624000	-2.464249000
H	-5.302838000	0.794890000	-3.117781000
H	-6.986583000	0.180793000	-1.391764000
H	-6.288600000	-0.037097000	0.984955000
H	-3.938714000	0.332713000	1.629704000
C	3.965775000	0.521698000	-2.172412000
O	3.389460000	0.498074000	-3.269343000
O	4.910408000	-0.488934000	-1.899745000
O	3.817159000	1.321156000	-1.203536000
K	5.164402000	0.542869000	0.831969000
K	1.429747000	2.070052000	-1.999302000
H	1.417381000	3.788459000	0.874006000
H	4.937938000	-1.041720000	-2.694241000

TS13

Free energy：-2911.334655

Energy：-2911.67487

C	-2.783134000	0.564207000	1.080162000
C	-3.283709000	0.216936000	-0.180321000
O	-2.325244000	-0.073607000	-1.087993000
C	-1.015375000	0.084236000	-0.462309000
C	-1.342240000	0.466494000	1.001881000
C	-3.645614000	0.899449000	2.131010000
C	-5.011834000	0.876866000	1.887753000
C	-5.499593000	0.519911000	0.612730000
C	-4.653119000	0.184237000	-0.441154000
O	-0.506538000	0.603587000	1.892496000
C	-0.197787000	-1.224952000	-0.436940000
C	0.706800000	-1.389517000	-1.717030000
C	1.699088000	-0.204007000	-1.746959000
C	1.173597000	1.034559000	-1.403490000
C	-0.324878000	1.237723000	-1.296256000
C	-0.802229000	2.606504000	-0.843362000
C	-0.968963000	-2.471568000	-0.050814000
C	-1.879713000	3.199744000	-1.512951000
C	-2.398009000	4.424106000	-1.091169000
C	-1.839007000	5.077657000	0.007531000
C	-0.763375000	4.496427000	0.681365000
C	-0.251690000	3.268562000	0.263605000
C	-0.485402000	-3.229476000	1.026204000
C	-1.143045000	-4.390442000	1.430780000
C	-2.287416000	-4.816867000	0.755341000
C	-2.753772000	-4.088500000	-0.340019000
C	-2.097923000	-2.926635000	-0.747414000
N	2.971632000	-0.487431000	-2.071434000
C	2.120120000	2.054677000	-1.186219000
N	3.009360000	2.790896000	-0.977796000
C	1.411776000	-2.684621000	-1.678323000
N	1.893821000	-3.737889000	-1.689820000
C	-0.100419000	-1.364551000	-2.956381000
N	-0.765295000	-1.295172000	-3.905058000
H	-3.238978000	1.170315000	3.100175000
H	-5.713003000	1.132099000	2.675200000
H	-6.572829000	0.505697000	0.446303000
H	-5.026488000	-0.090135000	-1.420807000
H	0.567547000	-1.057557000	0.325357000
H	-0.746043000	1.076814000	-2.294402000
H	-2.317850000	2.690914000	-2.366851000

H	-3.234369000	4.867340000	-1.623549000
H	-2.236734000	6.033617000	0.335295000
H	-0.320507000	4.999401000	1.536280000
H	0.569662000	2.816322000	0.806922000
H	0.447939000	-2.933797000	1.495990000
H	-0.749807000	-4.971912000	2.259879000
H	-2.800299000	-5.722156000	1.067043000
H	-3.627314000	-4.429512000	-0.887966000
H	-2.456990000	-2.379069000	-1.609312000
C	3.520505000	-0.832129000	0.982075000
O	2.435395000	-1.508848000	0.979190000
O	4.333946000	-0.877743000	-0.055816000
O	3.831546000	-0.037362000	1.963186000
K	5.147666000	1.541314000	0.448806000
K	1.581316000	-0.403878000	3.129237000
H	3.478270000	0.373696000	-2.270017000
H	3.585818000	-0.968616000	-1.194058000

IM15

Free energy：-2911.336626

Energy：-2911.677292

C	-3.591508000	1.013364000	-0.345589000
C	-3.075143000	1.141991000	0.946582000
O	-1.814382000	0.651309000	1.089337000
C	-1.387329000	0.092064000	-0.182101000
C	-2.554789000	0.396408000	-1.162707000
C	-4.876594000	1.465428000	-0.654950000
C	-5.629297000	2.046133000	0.359983000
C	-5.093170000	2.171144000	1.655996000
C	-3.810504000	1.725487000	1.975096000
O	-2.514563000	0.187356000	-2.361746000
C	-0.138699000	0.806703000	-0.741909000
C	1.201183000	0.043556000	-0.343300000
C	1.103723000	-1.347826000	-1.013326000
C	-0.086473000	-2.013461000	-0.817943000
C	-1.158003000	-1.438501000	0.091850000
C	-2.483612000	-2.181198000	0.138966000
C	-0.139255000	2.307700000	-0.527977000
C	-3.101293000	-2.381495000	1.379194000
C	-4.352226000	-2.992661000	1.464617000
C	-5.001128000	-3.416537000	0.304662000
C	-4.392991000	-3.221924000	-0.936794000
C	-3.145595000	-2.605858000	-1.021770000
C	-0.295047000	3.136391000	-1.646634000

C	-0.316705000	4.524160000	-1.509952000
C	-0.176604000	5.102366000	-0.248360000
C	-0.023602000	4.284460000	0.872934000
C	-0.009558000	2.896986000	0.738590000
N	2.098794000	-1.691912000	-1.850495000
C	-0.224494000	-3.289925000	-1.415847000
N	-0.278184000	-4.332563000	-1.939604000
C	2.326669000	0.852154000	-0.852487000
N	3.161881000	1.569823000	-1.212567000
C	1.355036000	-0.026860000	1.127003000
N	1.390963000	0.033929000	2.285887000
H	-5.258117000	1.354057000	-1.664717000
H	-6.633052000	2.405905000	0.159299000
H	-5.696949000	2.629428000	2.434095000
H	-3.396353000	1.820105000	2.972288000
H	-0.196029000	0.624023000	-1.819316000
H	-0.770529000	-1.442231000	1.117540000
H	-2.599266000	-2.046443000	2.282760000
H	-4.816124000	-3.139441000	2.435759000
H	-5.973326000	-3.896902000	0.367095000
H	-4.889715000	-3.549760000	-1.845018000
H	-2.690745000	-2.440894000	-1.991113000
H	-0.409494000	2.688371000	-2.629602000
H	-0.441949000	5.149917000	-2.388505000
H	-0.191637000	6.182756000	-0.138077000
H	0.077164000	4.727284000	1.859644000
H	0.084132000	2.272358000	1.617325000
C	4.467014000	-1.234825000	0.243418000
O	3.460214000	-1.786401000	0.817561000
O	4.576023000	-1.268897000	-1.058027000
O	5.356551000	-0.568348000	0.937035000
K	5.945486000	0.825388000	-1.131985000
K	4.015016000	-0.989816000	3.101374000
H	1.966852000	-2.604453000	-2.274566000
H	3.120648000	-1.517594000	-1.552598000

4a

Free energy：-1447.459945

Energy：-1447.794767

C	0.60321600	-2.25500700	-0.37221700
C	0.64293400	-1.67452500	0.90042400
O	0.27373800	-0.35983700	0.91359700
C	0.02417900	0.05774300	-0.44985600

C	0.18866100	-1.22305600	-1.30485400
C	0.94299100	-3.60092800	-0.55529000
C	1.31912100	-4.33616800	0.56136400
C	1.35298200	-3.73208400	1.83363300
C	1.01722900	-2.39233100	2.02987200
O	0.01219300	-1.26272200	-2.51423000
C	-1.39105900	0.62888400	-0.57373100
C	-1.56609600	1.85530600	0.39658900
C	-0.39131700	2.85036300	0.29760400
C	0.78130300	2.46713100	-0.28840900
C	1.07528100	1.10063100	-0.88523600
C	-2.51392100	-0.38457200	-0.46280300
C	-3.42738200	-0.47411800	-1.52101500
C	-4.47184100	-1.39693600	-1.48471000
C	-4.61388600	-2.24644600	-0.38686200
C	-3.70799000	-2.16477500	0.67154900
C	-2.66414200	-1.24050000	0.63824600
C	-1.70062600	1.46322200	1.81699000
N	-1.80602900	1.20523700	2.94157900
H	0.91144300	-4.04137900	-1.54653000
H	1.59153600	-5.38120100	0.46008200
H	1.65133600	-4.32701000	2.69146900
H	1.04446400	-1.92722500	3.00848000
H	-1.43439600	1.06284000	-1.57589900
H	-3.31576400	0.18308700	-2.37824400
H	-5.16999200	-1.45273800	-2.31431600
H	-5.42468000	-2.96810000	-0.35632400
H	-3.80947900	-2.82347100	1.52864400
H	-1.97410600	-1.19613800	1.46996600
C	-2.82482400	2.52543100	0.00559800
N	-3.80702100	3.04440100	-0.32366300
N	-0.60775400	4.04470500	0.89936400
H	0.08962900	4.77320300	0.81280500
H	-1.55116200	4.36678200	1.06849300
C	1.81564000	3.43287900	-0.38288500
N	2.65632800	4.23819200	-0.46095900
H	0.96902700	1.16697400	-1.97476800
C	2.48114500	0.60549800	-0.58731600
C	3.21936700	-0.02213300	-1.59608500
C	3.02854500	0.70616100	0.69763500
C	4.48256100	-0.54961200	-1.32549300
H	2.79762600	-0.10445800	-2.59364300
C	4.29049200	0.17958600	0.96876400
H	2.46176800	1.18913300	1.48657400

C	5.01995800	-0.45177900	-0.04135000
H	5.04501600	-1.03436700	-2.11786900
H	4.70357500	0.26123100	1.96975900
H	6.00291100	-0.86159400	0.17120100

IM16

Free energy：-1685.684357

Energy：-1686.026139

C	1.02200200	2.18477500	0.17698800
C	1.09910800	1.62841900	-1.10789300
O	0.53129300	0.39553000	-1.19940100
C	0.09460800	-0.01066600	0.12739200
C	0.35150800	1.22445100	1.01723600
C	1.54796800	3.45809800	0.44081900
C	2.14536300	4.14316500	-0.60647200
C	2.21148900	3.56564400	-1.89185200
C	1.69251700	2.30215300	-2.16948900
O	0.04375800	1.30218700	2.20832900
C	-1.37366100	-0.43540300	0.11846500
C	-1.59836100	-1.55304000	-0.96054800
C	-0.51105900	-2.64597700	-0.90736100
C	0.62651400	-2.45030300	-0.17634500
C	0.96958200	-1.19348400	0.60666100
C	-2.38961300	0.68558700	0.03301900
C	-3.44966400	0.68057900	0.95224200
C	-4.39966200	1.70202200	0.95155200
C	-4.30264500	2.74332300	0.02724800
C	-3.25833900	2.75014300	-0.89918700
C	-2.30931000	1.72748000	-0.90197900
C	-1.66179900	-1.01960600	-2.33892000
N	-1.71770500	-0.61550400	-3.42352100
H	1.48583600	3.87931400	1.43886100
H	2.56776200	5.12871700	-0.44371200
H	2.68471200	4.12324300	-2.69423700
H	1.74497100	1.85977700	-3.15740000
H	-1.53034800	-0.96479700	1.08676600
H	-3.52367500	-0.13568400	1.66511700
H	-5.21307700	1.68213500	1.67073500
H	-5.03792800	3.54233700	0.02551400
H	-3.18016400	3.55323100	-1.62580000
H	-1.51443900	1.74779800	-1.63638600
C	-2.91120200	-2.16512200	-0.65853400
N	-3.93450500	-2.64273200	-0.39912800

N	-0.76432900	-3.73399200	-1.67285800
H	-0.13974800	-4.52868200	-1.62385600
H	-1.70704900	-3.93784400	-1.97644200
C	1.55845200	-3.51674500	-0.11248400
N	2.31275100	-4.40589600	-0.06352800
Na	-1.34929100	0.14940000	3.54712100
O	-1.77838400	-1.77397600	2.78357100
H	-2.72153400	-1.93821600	2.64708500
H	0.68652200	-1.35091100	1.65393600
C	2.44497700	-0.83725600	0.56720700
C	3.07709200	-0.40973900	1.73982700
C	3.17054100	-0.85892300	-0.63046200
C	4.40918500	0.00410800	1.71640400
H	2.51828600	-0.39612500	2.67148900
C	4.50171000	-0.44526200	-0.65473000
H	2.68938800	-1.19023400	-1.54444700
C	5.12348200	-0.00928700	0.51740800
H	4.88776600	0.33377600	2.63374000
H	5.05322400	-0.46229500	-1.59000000
H	6.16018800	0.31320000	0.49669200

TS14-a

Free energy：-1685.665984

Energy：-1686.006458

C	-1.20931800	-2.06284600	0.11014800
C	-1.40094900	-1.47416700	-1.16539600
O	-0.78199200	-0.33385600	-1.37810800
C	0.00159700	0.06139500	0.17957900
C	-0.35098800	-1.24044400	0.90844500
C	-1.81105500	-3.28618600	0.45587200
C	-2.61195300	-3.91923900	-0.47608300
C	-2.80635700	-3.33259300	-1.74925600
C	-2.21906600	-2.12966300	-2.10953700
O	0.05371100	-1.47906400	2.06041600
C	1.38558400	0.34829700	0.02801600
C	1.70779000	1.59670300	-0.80921000
C	0.65931000	2.71960900	-0.70716500
C	-0.49401100	2.52227600	-0.00597300
C	-0.88528300	1.22243900	0.66820900
C	2.35665000	-0.78241500	-0.13586900
C	3.58034700	-0.79199400	0.56643500
C	4.46245000	-1.87049400	0.47221800
C	4.14517100	-2.97012800	-0.32866200

C	2.94998000	-2.96866800	-1.04956100
C	2.07521000	-1.88453000	-0.96467700
C	1.83324400	1.22064900	-2.24828800
N	1.90457200	0.83962600	-3.34225700
H	-1.64568300	-3.70666400	1.44341100
H	-3.09655900	-4.86054000	-0.23956900
H	-3.44154700	-3.84210400	-2.46877600
H	-2.37782300	-1.68784500	-3.08738800
H	1.70365900	1.06834700	1.78169800
H	3.84153100	0.05302700	1.19693900
H	5.39442400	-1.85129100	1.02998100
H	4.82658300	-3.81278700	-0.39681800
H	2.70034300	-3.80894800	-1.69129500
H	1.16924800	-1.88182400	-1.55760900
C	3.00811000	2.16722600	-0.37756400
N	4.00796700	2.62320800	-0.00658300
N	0.96721400	3.84772800	-1.39438800
H	0.37318600	4.66123000	-1.29876200
H	1.92499900	4.03670500	-1.65738800
C	-1.37481600	3.62317400	0.13987200
N	-2.08378300	4.54301600	0.25869100
Na	1.91878400	-0.94707700	3.12990800
O	1.94091300	1.25325000	2.73964000
H	2.78411900	1.72760000	2.69005200
H	-0.63120500	1.30404600	1.73367900
C	-2.37821000	0.93346200	0.61163000
C	-3.00089900	0.37508900	1.73280000
C	-3.13967000	1.16640800	-0.53963000
C	-4.35324100	0.03151000	1.70112200
H	-2.41721300	0.19725600	2.63212700
C	-4.49112100	0.82748100	-0.57342900
H	-2.66728300	1.59220800	-1.41764100
C	-5.10166700	0.25468100	0.54526000
H	-4.81909100	-0.40737800	2.57849700
H	-5.06798300	1.00823500	-1.47569800
H	-6.15420400	-0.01131200	0.51592000

TS14-b

Free energy：-1685.663261

Energy：-1686.003180

C	-0.40286700	-2.34968300	0.04338400
C	-0.36731400	-1.88649300	-1.29340000
O	-0.08760500	-0.60546300	-1.45000100

C	-0.06232600	0.06019200	0.15070200
C	-0.16082200	-1.25381500	0.93132500
C	-0.65911700	-3.69833700	0.34814600
C	-0.88483100	-4.57986800	-0.69305100
C	-0.85331700	-4.11458200	-2.02879600
C	-0.60174500	-2.78808300	-2.34859200
O	-0.03341100	-1.29816500	2.16593900
C	1.32294600	0.71591200	0.21739400
C	1.47606900	1.83133700	-0.88112700
C	0.24414700	2.74244400	-0.90000100
C	-0.92521600	2.28553500	-0.35137600
C	-1.15410100	0.97680500	0.27998800
C	2.51127000	-0.21832500	0.31566400
C	3.31899500	-0.13486200	1.45803900
C	4.41378100	-0.98235600	1.62525200
C	4.71838600	-1.92613200	0.64343300
C	3.92585000	-2.01011900	-0.50254100
C	2.82966800	-1.16363100	-0.66929200
C	1.72367500	1.33478900	-2.25494400
N	1.91482100	1.00694700	-3.35057900
H	-0.68018200	-4.02289200	1.38413000
H	-1.08800000	-5.62687200	-0.49511600
H	-1.03058000	-4.82261900	-2.83356800
H	-0.57627900	-2.44282900	-3.37636300
H	-0.94302600	1.57060700	2.04902500
H	3.09062100	0.60819500	2.21774900
H	5.02676200	-0.90226700	2.51793900
H	5.56872200	-2.58964300	0.76879300
H	4.15788000	-2.73954900	-1.27265700
H	2.22515100	-1.24407500	-1.56218100
C	2.66926200	2.61824400	-0.49911000
N	3.58493100	3.25178700	-0.17606700
N	0.42048200	3.93626600	-1.59172400
H	-0.40414200	4.52696000	-1.62079500
H	1.23411500	4.47942600	-1.31380600
C	-2.01688400	3.20814900	-0.34782000
N	-2.89426800	3.97514900	-0.33592400
Na	0.24608300	0.10857000	3.82887500
O	-0.78853500	1.87709900	2.99711400
H	-1.67607800	2.06965800	3.33385200
C	-2.53309200	0.40333200	0.22382500
C	-3.11911800	-0.21234600	1.34359300
C	-3.27469000	0.42803300	-0.97217500
C	-4.38433700	-0.79508100	1.26803000

H	-2.57756600	-0.22447600	2.28379900
C	-4.54735700	-0.13673100	-1.04567700
H	-2.83456400	0.88051700	-1.85596000
C	-5.10687000	-0.75726500	0.07377300
H	-4.81253000	-1.26666800	2.14840000
H	-5.09712700	-0.10534900	-1.98243200
H	-6.09539100	-1.20345200	0.01634600
H	1.29966500	1.29989000	1.14299600

TS14-c

Free energy：-1685.654996

Energy：-1685.995229

C	1.19006400	2.09697400	0.04857400
C	1.32152500	1.45791300	-1.19549400
O	0.66150300	0.28267600	-1.27841900
C	0.07589100	-0.02354600	0.06249600
C	0.36499000	1.25635400	0.87495600
C	1.80360200	3.33475500	0.29432400
C	2.54685800	3.90667800	-0.72602600
C	2.66887600	3.25183100	-1.97090200
C	2.06454100	2.02475800	-2.23035200
O	-0.02738400	1.45031000	2.03106100
C	-1.37482200	-0.38561700	-0.03331200
C	-1.65298800	-1.60120200	-0.71551500
C	-0.63288200	-2.71269100	-0.64507800
C	0.55758200	-2.49407100	-0.00833800
C	0.90962300	-1.18577100	0.67516900
C	-2.37924700	0.71481700	-0.05977400
C	-3.56933300	0.65267400	0.69549200
C	-4.47133300	1.71874900	0.71310400
C	-4.21073800	2.87398100	-0.02755500
C	-3.05215700	2.94125200	-0.80305400
C	-2.15402800	1.87386400	-0.82734800
C	-1.71443700	-1.31803600	-2.60608000
N	-1.76574500	-0.60515900	-3.53496000
H	1.69491100	3.81560800	1.26121700
H	3.04147300	4.86005800	-0.57484800
H	3.25675000	3.72054100	-2.75439900
H	2.16233200	1.52450400	-3.18687600
H	-1.70096300	-1.29661900	1.87663000
H	-3.78568100	-0.23632700	1.28009300
H	-5.37549400	1.64442500	1.31042900
H	-4.90777600	3.70615900	-0.00834700

H	-2.84858100	3.82378900	-1.40271400
H	-1.28098100	1.93319200	-1.46537500
C	-3.02210400	-2.09099200	-0.59163800
N	-4.10322000	-2.49744100	-0.47845800
N	-1.01469000	-3.90055800	-1.18408600
H	-0.30733100	-4.61552000	-1.30253600
H	-1.70041200	-3.86895000	-1.92886000
C	1.47582800	-3.56566500	0.08755900
N	2.21835600	-4.46467100	0.15708100
Na	-1.85581500	0.87404500	3.14689500
O	-1.87915300	-1.34391300	2.84450300
H	-2.71197600	-1.83391300	2.91626800
H	0.58547500	-1.23466700	1.72204900
C	2.39780200	-0.88329300	0.67658300
C	2.99143100	-0.37392000	1.83684900
C	3.18089100	-1.03866600	-0.47441600
C	4.33804200	-0.00887500	1.84558200
H	2.39055100	-0.25471400	2.73419800
C	4.52626800	-0.67364000	-0.46762300
H	2.73181800	-1.43099300	-1.38017400
C	5.10818800	-0.15414500	0.69091400
H	4.78354800	0.38707800	2.75336700
H	5.11995300	-0.79347300	-1.36900900
H	6.15609300	0.13073800	0.69426700

TS14-d

Free energy：-1685.612251

Energy：-1685.954521

C	1.28615300	2.09137100	0.65568800
C	1.15928700	1.81097500	-0.71660600
O	0.49545700	0.65500600	-0.98337800
C	0.14259100	0.04015500	0.27267800
C	0.64757400	1.01268000	1.35792900
C	1.94920400	3.24926900	1.09294700
C	2.47039400	4.10117400	0.13233600
C	2.33218600	3.80098800	-1.24000700
C	1.67886100	2.65656800	-1.69127900
O	0.48786200	0.79914600	2.56578800
C	-1.38372200	-0.09387500	0.44536400
C	-1.91628200	-1.47534200	0.03391900
C	-1.03991800	-2.58264500	-0.44761700
C	0.31865000	-2.41965800	-0.37894900
C	0.93614900	-1.29313800	0.42191600

C	-2.21364200	1.11792700	0.03599300
C	-3.10319300	1.61483800	0.99960900
C	-3.90067800	2.72896900	0.73949700
C	-3.81057400	3.37383000	-0.49356200
C	-2.92513700	2.89107000	-1.45865200
C	-2.13480800	1.77119700	-1.20224500
C	-2.24004300	-1.04814300	-2.07181000
N	-2.36516400	-1.02040500	-3.23598600
H	2.04440600	3.45713600	2.15361300
H	2.99059500	5.00540700	0.42895000
H	2.75107000	4.48556800	-1.97119300
H	1.57693400	2.42681300	-2.74546100
H	-1.51616000	-0.11474400	1.52104800
H	-3.17388500	1.12095300	1.96519200
H	-4.58452100	3.09157800	1.50095700
H	-4.42393500	4.24545900	-0.70185700
H	-2.84698700	3.38647600	-2.42180500
H	-1.46506200	1.40928400	-1.96683000
C	-3.34062300	-1.67244500	0.15875500
N	-4.48900900	-1.81061500	0.26623200
N	-1.66680700	-3.71250600	-0.86503700
H	-1.09358200	-4.42924200	-1.29372600
H	-2.58590900	-3.61937400	-1.28051700
C	1.14586000	-3.45788800	-0.85804700
N	1.80594100	-4.33147300	-1.26688100
Na	-0.62594900	-1.07329800	3.45879000
O	-1.74211900	-2.13852600	1.89475800
H	-1.90975100	-3.09207500	1.85441700
H	0.85122300	-1.56362500	1.48006800
C	2.41131400	-1.06279300	0.14979700
C	3.28820600	-0.89818700	1.22717700
C	2.90770300	-0.95430500	-1.15565100
C	4.63778300	-0.61894600	1.00839600
H	2.90785900	-0.98219400	2.24171500
C	4.25556700	-0.67553100	-1.37532100
H	2.23597600	-1.07551700	-1.99810900
C	5.12370100	-0.50419000	-0.29447800
H	5.30666400	-0.49301600	1.85448000
H	4.62758700	-0.59025800	-2.39191000
H	6.17322000	-0.28591300	-0.46803000

IM17-a

Free energy：-1685.702780

Energy：-1686.036540

C	0.59686300	2.13636700	-0.12259400
C	1.54389500	3.20852300	-0.40411600
O	2.23559800	3.29700500	-1.48167400
C	-0.44490200	-0.14163800	-0.67103200
C	0.26850600	1.13112100	-1.09897500
C	-0.01458800	2.06660400	1.16111100
C	0.19887200	3.01858200	2.12982300
C	1.07241300	4.09569000	1.84685300
C	1.71697300	4.18628400	0.63507400
O	0.56717900	1.15747200	-2.31701100
C	0.30846500	-1.10525600	-0.13237600
C	-0.26857100	-2.49337200	0.19309400
C	-1.72810500	-2.69673400	-0.24828200
C	-2.42247900	-1.67371900	-0.82006700
C	-1.89820100	-0.27515800	-1.04366000
C	1.76666000	-0.90155700	0.11680400
C	2.67476600	-1.08418300	-0.93816300
C	4.03359400	-0.81590600	-0.75429200
C	4.49436600	-0.36802200	0.48688800
C	3.59658600	-0.20140000	1.54409000
C	2.23800400	-0.46798000	1.36238200
C	0.55979600	-3.51597400	-0.49196400
N	1.20032000	-4.27673300	-1.08667600
H	-0.68426900	1.24271800	1.37199600
H	-0.29725800	2.94796000	3.09195100
H	1.24443000	4.85827300	2.60278300
H	2.40313200	5.00289700	0.42706400
H	2.31110600	-1.43676700	-1.89889500
H	4.72933000	-0.96542500	-1.57502800
H	5.54923100	-0.15631800	0.63109000
H	3.95063000	0.14600600	2.50953900
H	1.53952100	-0.31381400	2.17703500
C	-0.18911800	-2.70096400	1.65916100
N	-0.16096300	-2.80374800	2.81314900
N	-2.19578000	-3.95587800	-0.06916700
C	-3.76671100	-1.91003000	-1.20434000
N	-4.87200200	-2.10730000	-1.52124100
Na	2.71269500	1.61432600	-2.76396000
O	2.99324300	-3.69315600	1.57963500
H	3.10448300	-2.76819700	1.84294600
H	-1.72137700	-4.59343600	0.55616300
H	-3.18095800	-4.13865600	-0.21248400
H	-1.96226100	-0.04129300	-2.11457300

C	-2.72201200	0.77849500	-0.30140600
C	-2.94505500	2.02510600	-0.89233600
C	-3.17817000	0.54411700	1.00032900
C	-3.60370100	3.03248700	-0.18610300
H	-2.59179500	2.20884700	-1.90320700
C	-3.84026200	1.54894500	1.70521500
H	-3.00259200	-0.42106000	1.46607000
C	-4.04996000	2.79754700	1.11545000
H	-3.76797600	3.99897100	-0.65317600
H	-4.18771300	1.35840100	2.71632600
H	-4.56168800	3.58130700	1.66585700
H	3.12964100	-3.66081600	0.62261400

IM17-b

Free energy：-1685.710267

Energy：-1686.047025

C	-0.58318000	-2.03540400	-0.29186100
C	-0.30463600	-3.46585500	-0.20397800
O	0.35668500	-4.02129700	0.74739500
C	-0.30794600	0.36020500	0.59220400
C	-0.23465500	-1.12831800	0.77894000
C	-1.17761400	-1.51990500	-1.47856000
C	-1.58668800	-2.33135800	-2.51131200
C	-1.39991300	-3.72918400	-2.39792800
C	-0.78595800	-4.27178700	-1.29301300
O	0.26003100	-1.47950200	1.88126900
C	1.03130700	1.07826400	0.72940200
C	1.04971100	2.29358800	-0.27119500
C	-0.15577300	3.20352600	0.04347300
C	-1.33364400	2.56802000	0.38319800
C	-1.43448700	1.10260600	0.48504500
C	2.25218800	0.18716500	0.60088700
C	3.16698900	0.13504800	1.65885800
C	4.24505300	-0.75475100	1.62891200
C	4.42324700	-1.60202700	0.52996500
C	3.52407900	-1.54092600	-0.54229500
C	2.44717900	-0.65009000	-0.50907800
C	2.32421200	3.00684000	-0.10504000
N	3.32508800	3.56245600	0.07428500
H	-1.30653100	-0.44949100	-1.56807800
H	-2.04245200	-1.90615800	-3.39940900
H	-1.73011200	-4.38180600	-3.20280900
H	-0.61637700	-5.34268400	-1.21780300

H	3.02017000	0.77692900	2.52212400
H	4.94020200	-0.78756700	2.46201200
H	5.25617500	-2.29777900	0.50463300
H	3.65368400	-2.19179000	-1.40124400
H	1.74608300	-0.64117800	-1.33398400
C	0.90606000	1.85635300	-1.67677700
N	0.73176300	1.51543700	-2.77030700
N	0.01184300	4.52075900	-0.10157300
C	-2.47061700	3.37714700	0.63555300
N	-3.37721200	4.08173600	0.84254500
Na	1.92552500	-2.96068600	1.85123300
O	4.17394200	1.52756900	-2.28618600
H	4.13571700	0.66902800	-1.84051200
H	0.90517100	4.92495700	-0.34615300
H	-0.75864600	5.15925300	0.05177500
C	-2.78923900	0.49591200	0.48261800
C	-3.15595000	-0.43700300	1.46337000
C	-3.71218900	0.82898300	-0.52127300
C	-4.41295000	-1.03913100	1.42926600
H	-2.45879600	-0.68112700	2.25765200
C	-4.96618900	0.22300100	-0.55517800
H	-3.43497200	1.54320000	-1.29030700
C	-5.31934400	-0.71402300	0.41873700
H	-4.68476700	-1.75875000	2.19556900
H	-5.66573200	0.47844800	-1.34531300
H	-6.29744000	-1.18483800	0.39188900
H	4.49076300	2.12074600	-1.59065700
H	1.06713200	1.55990800	1.71494400

IM18-a

Free energy：-1847.460294

Energy：-1847.787216

C	2.01793300	1.21728500	-0.31305500
C	3.40948600	1.31187600	-0.75091200
O	3.95382500	0.49146900	-1.57020900
C	-0.27697900	0.06543900	-0.30416700
C	1.09474400	0.30754400	-0.90826600
C	1.56933300	2.04383400	0.76217200
C	2.36968500	3.00623500	1.32343400
C	3.68826000	3.17760900	0.82824400
C	4.18696800	2.37016300	-0.16549900
O	1.31533500	-0.40628000	-1.93650000
C	-0.40608600	-1.02932500	0.45860600

C	-1.79330200	-1.47494000	0.94665200
C	-2.94156100	-0.97471800	0.05285800
C	-2.74471400	0.12066400	-0.73692000
C	-1.43368900	0.86717400	-0.87040600
C	0.78583900	-1.85031800	0.82998600
C	1.01423300	-3.07452400	0.17425200
C	2.21744300	-3.75884900	0.37088800
C	3.19688900	-3.23229000	1.22454400
C	2.95605800	-2.03307100	1.90165700
C	1.75468600	-1.34652900	1.70874300
C	-1.87694500	-2.94357100	1.13535100
N	-2.01185800	-4.03768200	1.49771600
H	0.56300700	1.90745400	1.13677800
H	1.99868500	3.63146200	2.12823800
H	4.32175200	3.95041800	1.25685000
H	5.20848700	2.48088900	-0.51832500
H	0.24745000	-3.45451100	-0.49594000
H	2.39169300	-4.69911800	-0.14424300
H	4.13404300	-3.76105300	1.36947400
H	3.70425800	-1.62771800	2.57548800
H	1.57819300	-0.40603000	2.21804600
C	-1.98890200	-0.88342200	2.29708200
N	-2.11192900	-0.38752300	3.33833700
N	-4.12498100	-1.60336200	0.23048200
C	-3.82244700	0.60305600	-1.51582000
N	-4.70580600	1.00009600	-2.16812000
Na	3.25035200	-1.59085900	-1.54309600
Na	-0.41078400	-1.75813800	-2.74816500
O	-1.56645600	-3.08626800	-1.58103300
H	-2.52300100	-2.96556000	-1.64070500
H	-4.15151300	-2.53487100	0.62275800
H	-4.90733400	-1.35461900	-0.36117600
H	-1.22680000	0.98283800	-1.94357700
C	-1.48614500	2.28528000	-0.30453900
C	-0.90759000	3.33576900	-1.02200700
C	-2.04257600	2.53726500	0.95400400
C	-0.86330700	4.62092600	-0.48034500
H	-0.47449500	3.14130200	-1.99930400
C	-1.99760000	3.82110200	1.49661400
H	-2.50300400	1.72923100	1.51199300
C	-1.40270000	4.86509400	0.78340600
H	-0.40573400	5.42841400	-1.04404600
H	-2.42666000	4.00609700	2.47697600
H	-1.36596800	5.86371600	1.20826600

IM18-b

Free energy：-1847.478061

Energy：-1847.804403

C	-0.46505500	-2.09962200	-0.35321700
C	-0.20107200	-3.51755800	-0.11076400
O	0.59231100	-3.95904700	0.79539000
C	-0.15166300	0.37804800	0.20578500
C	0.01901000	-1.07397400	0.52666800
C	-1.22350300	-1.72675900	-1.50440800
C	-1.79729400	-2.65555800	-2.33668300
C	-1.62707000	-4.03358800	-2.05174700
C	-0.86527700	-4.44620100	-0.98547800
O	0.69999000	-1.29753000	1.57969500
C	1.14606100	1.16889000	0.05232700
C	0.92649600	2.25589700	-1.05870900
C	-0.25028700	3.14903400	-0.61720800
C	-1.32750300	2.50278400	-0.04177200
C	-1.32780500	1.05364100	0.20928000
C	2.38416500	0.31969800	-0.16866000
C	3.43457900	0.42228500	0.75409800
C	4.53682700	-0.43395000	0.68026300
C	4.60871900	-1.39765500	-0.33251500
C	3.57765100	-1.48563800	-1.27681300
C	2.47276400	-0.63302300	-1.19562200
C	0.56343800	1.65800700	-2.36265600
N	0.24767000	1.17992800	-3.37038300
H	-1.34362500	-0.67425000	-1.72442200
H	-2.37200100	-2.34064200	-3.20122000
H	-2.09125300	-4.77494000	-2.69773900
H	-0.70959600	-5.50236100	-0.78315300
H	3.36103700	1.15844600	1.54888100
H	5.33561900	-0.34961700	1.41078300
H	5.46227800	-2.06611500	-0.39246600
H	3.62908900	-2.22304400	-2.07212200
H	1.67048000	-0.73902700	-1.91557400
C	2.17008600	3.02229700	-1.22005800
N	3.15627200	3.62200300	-1.32276100
N	-0.17191600	4.45558800	-0.87776300
H	-0.92233100	5.07894900	-0.60723800
H	0.65886300	4.87364700	-1.27368800
C	-2.44681800	3.28908600	0.33092100
N	-3.34059100	3.97839700	0.62680500

Na	2.38054500	-2.78635300	1.29229300
C	-2.63304400	0.39398600	0.46463500
C	-2.81421700	-0.44803900	1.57114700
C	-3.69937900	0.58245100	-0.42889500
C	-4.02878100	-1.10359600	1.76886900
H	-2.00678900	-0.58469600	2.28222500
C	-4.91079000	-0.07659800	-0.23162900
H	-3.56746600	1.22555300	-1.29343100
C	-5.07831700	-0.92341000	0.86642900
H	-4.15491200	-1.75239900	2.63036300
H	-5.72207800	0.06642700	-0.93896200
H	-6.02301500	-1.43629400	1.01976400
H	1.29932300	1.75764300	0.98655300
O	1.47049700	2.29209900	2.88877800
H	2.41457100	2.46254900	3.01211800
Na	1.05471300	0.24444100	3.21549100

TS15-a

Free energy：-1847.413946

Energy：-1847.737955

C	1.96714500	-1.23372000	0.23873700
C	3.35603400	-1.42808900	0.65350100
O	3.95619100	-0.67430500	1.49726900
C	-0.29172800	0.00898200	0.38134300
C	1.10235200	-0.31012400	0.89324900
C	1.46632000	-1.97421200	-0.87544700
C	2.20311500	-2.95394800	-1.48925200
C	3.50928200	-3.23412600	-1.00901500
C	4.06188600	-2.50792300	0.01800000
O	1.39601200	0.37272400	1.92791500
C	-0.43030500	1.18486000	-0.26315500
C	-1.77486700	1.78409300	-0.40719800
C	-2.97509500	1.05995000	0.09035400
C	-2.79547300	-0.14392500	0.71334500
C	-1.44963500	-0.80799900	0.93028500
C	0.76827500	1.96948400	-0.68529600
C	1.09433400	3.18620700	-0.05781100
C	2.31966800	3.80616400	-0.31789900
C	3.22625400	3.22746900	-1.21609500
C	2.88472000	2.04403200	-1.87799500
C	1.66114300	1.42228200	-1.61869600
C	-1.92106500	3.10862600	-0.96322500
N	-2.06693700	4.16771300	-1.41737300

H	0.47168900	-1.75223400	-1.23874100
H	1.79281200	-3.51055600	-2.32467000
H	4.09055600	-4.02448200	-1.47768100
H	5.07623500	-2.69798700	0.35736500
H	0.39197200	3.62268900	0.64376500
H	2.56687200	4.73768500	0.18243800
H	4.18093700	3.70626200	-1.41099400
H	3.57062300	1.60196200	-2.59366700
H	1.40290800	0.49992800	-2.12506300
C	-2.02686000	0.98587400	-2.40580300
N	-2.01841600	0.36585700	-3.40028400
N	-4.16902600	1.68697800	-0.06661300
C	-3.92706600	-0.83573500	1.20049000
N	-4.86243200	-1.40389200	1.60878300
Na	3.38221800	1.45442500	1.44119200
Na	-0.24377500	1.78197400	2.84162700
O	-1.57677000	2.73530500	1.41017400
H	-2.44803100	3.12691300	1.57113300
H	-4.26132000	2.36302900	-0.81397400
H	-5.00975400	1.15577000	0.12202700
H	-1.27870900	-0.90393900	2.01354100
C	-1.43848100	-2.23320400	0.37684700
C	-0.86943400	-3.26810200	1.12183100
C	-1.94271800	-2.50008500	-0.90196000
C	-0.78388300	-4.55555500	0.58957300
H	-0.47878200	-3.06141400	2.11443300
C	-1.85721000	-3.78591800	-1.43354300
H	-2.37724400	-1.69541700	-1.48676200
C	-1.27311100	-4.81587500	-0.69114700
H	-0.33426200	-5.35236500	1.17452300
H	-2.24250000	-3.98319000	-2.42956600
H	-1.20422800	-5.81634100	-1.10768000

TS15-b

Free energy：-1847.412621

Energy：-1847.736716

C	-2.08248300	-1.12026100	-0.06675900
C	-3.29030100	-1.75826000	0.45175800
O	-3.45583900	-2.12360700	1.67004000
C	0.15432200	0.10617900	0.28487300
C	-0.97374700	-0.76162500	0.77252400
C	-2.02363500	-0.78620500	-1.45237800
C	-3.06288500	-1.02629200	-2.31693100

C	-4.24740500	-1.61809400	-1.81597100
C	-4.35658500	-1.96352200	-0.49056400
O	-0.83537000	-1.13435300	1.98511200
C	1.51459400	-0.55214100	0.44814700
C	2.65768100	0.47676500	0.48413400
C	2.43764000	1.90371600	0.13004900
C	1.15273500	2.29873800	-0.21203100
C	-0.00138600	1.40970300	-0.05960100
C	1.68447200	-1.72808800	-0.50664200
C	2.17817300	-2.93651700	-0.00628700
C	2.31038300	-4.04969300	-0.83976600
C	1.93467600	-3.96443500	-2.18058600
C	1.43525600	-2.76068200	-2.68531700
C	1.31202500	-1.65015900	-1.85389800
C	3.48072400	0.25479500	-1.48696900
N	4.03746300	0.31584800	-2.51525200
H	-1.11911900	-0.32884700	-1.82751200
H	-2.97893300	-0.76470600	-3.36638300
H	-5.07999800	-1.80568500	-2.48976600
H	-5.26310900	-2.42115500	-0.10410000
H	2.46239100	-3.00507100	1.04034000
H	2.70121800	-4.98028900	-0.43913000
H	2.02887300	-4.82989100	-2.82974200
H	1.14246400	-2.68632400	-3.72833600
H	0.94548100	-0.71321200	-2.25564300
C	3.93020900	0.01669500	0.98644900
N	4.94821400	-0.38576000	1.37733400
N	3.49288600	2.73261100	0.19814200
H	3.39934600	3.68448100	-0.13206000
H	4.43158900	2.35567300	0.20445700
C	0.96614000	3.65776300	-0.56191400
N	0.87724200	4.78670700	-0.84803900
Na	-1.92282100	-2.77737700	3.01423400
C	-1.34883100	2.03395500	-0.21152300
C	-2.24012000	2.11116100	0.86639000
C	-1.74263300	2.54333400	-1.45688600
C	-3.50856100	2.66620900	0.69821500
H	-1.94552700	1.73382300	1.84055200
C	-3.01086100	3.09651100	-1.62509400
H	-1.06040100	2.48472600	-2.29926100
C	-3.89867400	3.15625200	-0.54911300
H	-4.19012200	2.71491600	1.54221700
H	-3.30757700	3.47449400	-2.59878400
H	-4.88770400	3.58445600	-0.68133000

H	1.54983100	-1.00280700	1.44085900
O	2.22904200	0.92662400	2.38372800
H	2.78209700	1.69386900	2.59039500
Na	0.39831000	0.32115900	3.33404300

IM19

Free energy：-1847.485896

Energy：-1847.807873

C	0.94535700	-1.09123700	-0.94944100
C	2.03528000	-2.04980000	-1.05517700
O	2.61356600	-2.58655500	-0.02104000
C	-0.64397300	0.36477500	0.42147300
C	0.46351000	-0.64808500	0.33811700
C	0.34184500	-0.59797900	-2.14156000
C	0.77633700	-0.97940800	-3.38831400
C	1.85767600	-1.88484800	-3.49435400
C	2.46508200	-2.40145200	-2.37119100
O	0.86804600	-1.09774600	1.44853100
C	-0.43284900	1.64199500	0.08105900
C	-1.53097300	2.68477600	0.21539100
C	-2.91872900	2.09889900	0.49396500
C	-3.06881000	0.79023300	0.85182700
C	-1.91863500	-0.17184400	1.03399400
C	0.93970000	2.10985100	-0.27304100
C	1.92300900	2.09067200	0.73098100
C	3.24621500	2.42316100	0.43665500
C	3.60000900	2.78241700	-0.86624000
C	2.62435900	2.82184700	-1.86410900
C	1.30078500	2.49035700	-1.57214900
C	-1.61245000	3.46992000	-1.05239700
N	-1.70261700	4.10186400	-2.02101600
H	-0.48782000	0.09138900	-2.05501700
H	0.29722300	-0.59099900	-4.28038900
H	2.21061100	-2.18367400	-4.47792600
H	3.28870800	-3.10481200	-2.44967200
H	1.64100700	1.81730700	1.74344300
H	3.99372400	2.39810400	1.22335300
H	4.62946400	3.03628300	-1.09995400
H	2.89451600	3.09924700	-2.87844800
H	0.56065400	2.49328100	-2.36329900
C	4.77063700	0.05641700	2.89891500
N	5.49398800	0.65399700	3.60463400
N	-3.92801000	3.00938300	0.47386800

C	-4.36859600	0.30716900	1.14435600
N	-5.44443400	-0.08218400	1.37477800
Na	0.91528400	-3.39663100	1.22083500
Na	3.21279900	-0.90600700	1.39295200
O	-1.13282700	3.55423900	1.27042100
H	-1.84603300	4.19279800	1.43864500
H	-3.84490400	3.83132700	-0.11100300
H	-4.87664600	2.68358500	0.61155600
H	-1.70923900	-0.26777700	2.10906700
C	-2.20704000	-1.57902100	0.52284900
C	-2.03877300	-2.67757300	1.37625400
C	-2.54636300	-1.80019800	-0.81548100
C	-2.16495000	-3.98264300	0.88615000
H	-1.80557700	-2.50848800	2.42509800
C	-2.67504000	-3.10009700	-1.30623200
H	-2.69385700	-0.95225500	-1.47707200
C	-2.47005700	-4.19427800	-0.46262200
H	-2.04397400	-4.82758700	1.55916500
H	-2.92855300	-3.25858400	-2.34997400
H	-2.56636700	-5.20520000	-0.84643300

IM20

Free energy：-1830.450748

Energy：-1830.783173

C	-1.52646200	1.55668600	0.20681700
C	-2.79304800	2.11967600	0.67317900
O	-3.54134400	1.56215200	1.55048500
C	0.28819000	-0.25476600	0.22495600
C	-0.91636100	0.43321000	0.84230700
C	-0.88499400	2.14060500	-0.92756500
C	-1.35178900	3.28557900	-1.52134600
C	-2.51737100	3.90370500	-0.99943100
C	-3.20671800	3.34886900	0.05161300
O	-1.33842300	-0.12089600	1.90422400
C	0.03333600	-1.32453000	-0.54415600
C	1.15114300	-2.15189200	-1.16728000
C	2.50098500	-1.96147700	-0.48090500
C	2.70171400	-0.91124400	0.36324800
C	1.67383100	0.15127800	0.68264000
C	-1.37430600	-1.75618500	-0.80818900
C	-1.92799000	-2.79892900	-0.04369800
C	-3.28955500	-3.10226300	-0.14176300
C	-4.10907800	-2.36685900	-1.00798400

C	-3.55599000	-1.35039000	-1.79307800
C	-2.19540000	-1.04999500	-1.69850400
H	0.00340000	1.66661000	-1.32238100
H	-0.83377100	3.71621700	-2.37135200
H	-2.88177000	4.82269600	-1.45210600
H	-4.11883200	3.80427200	0.42709900
H	-1.29605700	-3.34970000	0.64608900
H	-3.70892500	-3.90430400	0.45839800
H	-5.16841800	-2.59395300	-1.07746500
H	-4.18499700	-0.78529000	-2.47356400
H	-1.77340200	-0.24544700	-2.28996600
N	3.43328500	-2.87322700	-0.85411700
H	4.31234400	-2.90203600	-0.35329300
H	3.09518200	-3.76011500	-1.20375400
C	3.96604500	-0.76525800	0.98616100
N	5.01271700	-0.64518200	1.48806100
Na	-3.54885900	-0.63504200	1.65968600
Na	-0.04727000	-1.49443700	3.14515600
O	1.92261200	-1.05489400	3.76093600
H	1.87557800	-0.15175600	4.10554600
C	1.29053000	-1.70727800	-2.58490300
N	1.36611800	-1.33347600	-3.68116500
H	1.63703300	0.21307400	1.78091400
C	2.06867200	1.52636900	0.15307300
C	1.86712600	2.65763100	0.94750600
C	2.56338700	1.67922700	-1.14737700
C	2.13454700	3.93130200	0.44329000
H	1.48466600	2.53867300	1.95753900
C	2.83099600	2.95105000	-1.65221200
H	2.72260200	0.80286400	-1.76843900
C	2.61153500	4.08105100	-0.85971700
H	1.96857200	4.80450800	1.06722200
H	3.20798900	3.06083500	-2.66482400
H	2.81696100	5.07154600	-1.25459000
O	0.88810900	-3.54651400	-1.12799300
H	0.06894000	-3.73101900	-1.61508800

TS16

Free energy：-1830.440615

Energy：-1830.770576

C	-0.74353000	1.91012100	-0.30751200
C	-1.66666200	3.01347200	-0.05958400
O	-2.51579700	3.03441800	0.90179200

C	0.23053600	-0.39214800	0.19821700
C	-0.58198600	0.82260300	0.60917300
C	0.02601000	1.90329300	-1.50899300
C	0.00575300	2.95136200	-2.39528400
C	-0.81650700	4.07146600	-2.11344300
C	-1.61677800	4.10298800	-0.99630000
O	-1.13658100	0.74706200	1.74853700
C	-0.50494400	-1.44090100	-0.25866100
C	0.13063200	-2.72089200	-0.74681400
C	1.63866900	-2.74540800	-0.58476800
C	2.31083000	-1.68555500	-0.04436500
C	1.67073700	-0.44830200	0.49015500
C	-1.99905400	-1.36278600	-0.30668900
C	-2.77044300	-1.97025600	0.70120600
C	-4.15468500	-1.77770500	0.75790400
C	-4.78960800	-0.97526700	-0.19877900
C	-4.03491200	-0.39041500	-1.22276100
C	-2.65264400	-0.58973600	-1.27990800
H	0.65085500	1.04368300	-1.71661300
H	0.61302200	2.92758900	-3.29377200
H	-0.82599500	4.91293400	-2.80209900
H	-2.26849400	4.94940800	-0.79771000
H	-2.28120600	-2.57783600	1.45725000
H	-4.73297100	-2.24566900	1.54885900
H	-5.86270800	-0.81660500	-0.15267100
H	-4.52165300	0.22307400	-1.97463000
H	-2.06978100	-0.12198200	-2.06526900
N	2.21349700	-3.89999300	-1.05836600
H	3.18631300	-4.05503800	-0.82156200
H	1.64160700	-4.73104900	-0.96537400
C	3.70920600	-1.84031000	0.16458700
N	4.85456600	-1.98532100	0.33351900
Na	-3.37143300	1.12528000	1.56027100
Na	-0.43910500	-0.80908600	3.22743900
O	1.70254400	-0.96341000	3.08508600
H	2.14541900	-0.19302100	3.46889900
C	-0.20153700	-2.87620400	-2.19729300
N	-0.49499100	-2.93065000	-3.31985900
H	1.69721100	-0.66381000	1.78104500
C	2.44199900	0.83517900	0.29690900
C	2.33326100	1.86056800	1.24846100
C	3.25024100	1.05781300	-0.82781200
C	2.98654700	3.07943300	1.06869700
H	1.72715800	1.70044100	2.13520500

C	3.91799200	2.27019900	-1.00270900
H	3.33990200	0.28376100	-1.58402800
C	3.78302700	3.29004100	-0.05891200
H	2.87977000	3.86215800	1.81449400
H	4.53417000	2.42184600	-1.88456700
H	4.29608500	4.23701300	-0.19829400
O	-0.34627700	-3.89619900	-0.05882300
H	-1.28830800	-4.01417300	-0.26209200

IM21

Free energy：-1830.460523

Energy：-1830.790738

C	0.88393300	-1.41422500	0.38959800
C	1.29148200	-2.81334300	0.28936400
O	0.89677200	-3.61960000	-0.62363800
C	-0.55868000	0.57043300	-0.37416000
C	0.10492000	-0.76034200	-0.65917000
C	1.22060700	-0.67943400	1.56071500
C	2.03068800	-1.19810600	2.55740800
C	2.51874600	-2.52223700	2.41835600
C	2.16778700	-3.29193700	1.33077200
O	-0.13029900	-1.28776900	-1.76825600
C	-1.93132400	0.47861500	-0.12713000
C	-2.76869300	1.67580200	0.14291000
C	-1.95225300	2.92028700	0.31274900
C	-0.59379600	2.94160800	0.04485500
C	0.17133000	1.76951700	-0.31823400
C	1.60667200	1.84728200	-0.61234900
C	-2.60536600	-0.85281700	-0.13546600
C	2.49868500	2.57372000	0.21624900
C	3.86416700	2.64787000	-0.06869100
C	4.39908400	1.97831900	-1.18002100
C	3.53723000	1.23882100	-2.00349400
C	2.16792100	1.18082400	-1.72993600
C	-3.44599100	-1.23200400	-1.19944400
C	-3.98827900	-2.51928400	-1.26867900
C	-3.69994500	-3.45917800	-0.27019400
C	-2.88543800	-3.08986900	0.80758900
C	-2.35498700	-1.79824200	0.87667600
H	0.83847400	0.33052300	1.65813400
H	2.26842600	-0.60964800	3.43757500
H	3.16392100	-2.93970700	3.18725600
H	2.51425800	-4.31802600	1.24113600

H	4.61584800	-2.81663100	0.02937600
H	2.11800700	3.06847100	1.10319400
H	4.51610900	3.21856000	0.58680800
H	5.45987300	2.03759100	-1.40264500
H	3.92958200	0.72089100	-2.87418200
H	1.51654200	0.63609700	-2.40354700
H	-3.64148600	-0.52063700	-1.99510000
H	-4.62540800	-2.79222700	-2.10493000
H	-4.11414600	-4.46147200	-0.32564100
H	-2.66809200	-3.80524400	1.59537300
H	-1.72458100	-1.51939900	1.71388000
N	-2.68740500	4.01706000	0.75103900
H	-2.20001100	4.90575100	0.72358900
H	-3.59837500	4.08298600	0.30950700
C	0.02056600	4.22801900	0.05455500
N	0.47258000	5.30359400	0.05985100
Na	-1.00665800	-3.35455200	-1.70762600
Na	3.71379600	-0.30244700	0.51637700
O	5.04458300	-1.96147100	-0.12957700
H	5.90867000	-2.03934500	0.30192800
O	-3.76784700	2.00321200	-0.92536300
H	-4.49192300	1.35915900	-0.86421900
C	-3.58957300	1.43951100	1.37449900
N	-4.15186400	1.17315700	2.35839400

IM22

Free energy：-1753.988213

Energy：-1754.298232

C	0.86387200	-1.70507700	0.37355600
C	1.04946900	-3.14191000	0.17454800
O	0.42762900	-3.83929200	-0.69834500
C	-0.28040200	0.53363300	-0.23790600
C	0.09857700	-0.89302900	-0.57143700
C	1.40822900	-1.09265500	1.53591500
C	2.23726800	-1.77151200	2.41477200
C	2.54171300	-3.13256900	2.15180300
C	1.98648500	-3.78269100	1.06801900
O	-0.33617800	-1.34437300	-1.65361300
C	-1.65448800	0.74612100	-0.02281300
C	-2.19265900	2.12914200	-0.08866100
C	-1.17350500	3.11888400	0.41526200
C	0.17621900	2.85660300	0.22512300
C	0.67208000	1.56061700	-0.19062400

C	2.07914500	1.35287200	-0.56498300
C	-2.58317800	-0.40120300	0.07634600
C	3.14780900	1.80245000	0.24792700
C	4.47904300	1.57269700	-0.10532300
C	4.79440400	0.86493100	-1.27649800
C	3.75032000	0.40410600	-2.09288800
C	2.41786800	0.65230600	-1.74745600
C	-3.67479500	-0.54572800	-0.80566900
C	-4.45815300	-1.70096500	-0.80276500
C	-4.17858300	-2.74769700	0.08616600
C	-3.12721300	-2.60314700	1.00110900
C	-2.35262900	-1.43972900	1.00352700
H	1.17679000	-0.04984400	1.71914900
H	2.63686300	-1.27518600	3.29265300
H	3.20877600	-3.67243400	2.81906800
H	2.19220400	-4.83396500	0.88656400
H	2.93122100	2.31266900	1.17968700
H	5.27406200	1.93107000	0.54223900
H	5.82940300	0.69057500	-1.55367500
H	3.97421300	-0.13123600	-3.01133300
H	1.62732000	0.31724200	-2.40915800
H	-3.87762300	0.24276400	-1.52245100
H	-5.28067800	-1.79294900	-1.50630400
H	-4.78382500	-3.64917200	0.08198300
H	-2.91883700	-3.39021900	1.72063600
H	-1.55103000	-1.33316200	1.72553800
N	-1.65919200	4.27220500	1.01784800
H	-0.96266100	4.97960400	1.22419100
H	-2.47980400	4.67939200	0.58123800
C	1.06290000	3.95104100	0.42325700
N	1.74638300	4.88383900	0.58417200
Na	-1.54840800	-3.21813900	-1.51296400
Na	3.75894200	-1.30093400	0.19608500
O	-2.58543600	2.46001500	-1.48881900
H	-2.91230000	3.37599400	-1.50974000
C	-3.44014500	2.22744300	0.71407900
N	-4.42233100	2.30227900	1.33016500

IM22’

Free energy：-1754.063603

Energy：-1754.371076

C	-0.72490100	-2.00642800	-0.41875600
C	-0.61052500	-3.42036200	-0.06330000

O	0.16458900	-3.86916100	0.85212300
C	-0.07976400	0.45550900	-0.14124500
C	-0.09819000	-0.97682600	0.34957100
C	-1.48116800	-1.64086200	-1.57426600
C	-2.18553200	-2.56202800	-2.30772000
C	-2.15513300	-3.92421300	-1.91319000
C	-1.40420300	-4.33534600	-0.83926900
O	0.53850000	-1.16418100	1.43308700
C	1.16733300	0.95628100	-0.56597400
C	1.29629900	2.30470500	-0.93080100
C	0.19271700	3.20170100	-0.85773300
C	-1.04921500	2.66670500	-0.41269400
C	-1.19321900	1.30780400	-0.06247300
C	-2.51606700	0.79334600	0.37946500
C	2.35210400	0.04883000	-0.58428400
C	-3.62878700	0.91309800	-0.46677100
C	-4.86358100	0.39293000	-0.08415900
C	-5.00362800	-0.24594100	1.14914100
C	-3.90301100	-0.36076200	2.00010100
C	-2.66460700	0.15236200	1.61777400
C	3.39334100	0.25135000	0.33583200
C	4.42156700	-0.68880400	0.44130700
C	4.43142100	-1.82161900	-0.38196300
C	3.41180100	-2.00470600	-1.32523300
C	2.37378900	-1.07384900	-1.42535000
H	-1.49928100	-0.60031500	-1.87462400
H	-2.76044100	-2.25513800	-3.17486400
H	-2.72312600	-4.65686500	-2.48132600
H	-1.35857800	-5.38303500	-0.55526000
H	-3.51809300	1.39093500	-1.43478900
H	-5.71371400	0.48092500	-0.75356200
H	-5.96568500	-0.65232800	1.44589800
H	-4.00626000	-0.85007800	2.96372900
H	-1.81812000	0.06259700	2.28970000
H	3.34951700	1.10675900	1.00999600
H	5.21178200	-0.53958600	1.17074600
H	5.23240900	-2.54994800	-0.29847100
H	3.42300400	-2.87091700	-1.97966200
H	1.57448600	-1.22560800	-2.14224000
C	2.54978400	2.80451100	-1.38521300
N	3.55309200	3.25650600	-1.76623500
N	0.31811600	4.49614200	-1.21133600
H	1.23174700	4.89387500	-1.37868000
H	-0.43819800	5.14582900	-1.04813700

C	-2.14302700	3.56845500	-0.27501900
N	-2.99394500	4.35755500	-0.17426900
Na	2.04504900	-2.85002100	1.33093200
Na	1.23174100	0.57127100	2.75779900
O	2.42425300	2.31158900	2.78864200
H	3.26069400	2.03669500	3.19091200

TS17

Free energy：-1753.983820

Energy：-1754.292447

C	-0.04637400	-1.79253100	0.33157300
C	-0.43907300	-3.19452700	0.20481600
O	-1.21044700	-3.64847200	-0.70807000
C	-0.06401000	0.64326400	-0.45530800
C	-0.32079600	-0.81838300	-0.72222600
C	0.59628600	-1.36029500	1.52593600
C	0.99710500	-2.24460800	2.51432700
C	0.74995500	-3.63096400	2.33215200
C	0.07937500	-4.08669100	1.21562600
O	-0.84792900	-1.11554400	-1.81634700
C	-1.22397500	1.40547000	-0.21369500
C	-1.12634900	2.73394200	0.34211900
C	0.17791500	3.38211100	0.10969900
C	1.29904800	2.61390600	-0.19112100
C	1.21858300	1.19569500	-0.42692600
C	2.43459100	0.39792500	-0.67295200
C	-2.55754300	0.73188600	-0.21295500
C	3.55060700	0.49186100	0.18883700
C	4.69672700	-0.27864300	-0.02346100
C	4.75820800	-1.17741200	-1.09942000
C	3.65911800	-1.28390500	-1.96490100
C	2.51748000	-0.50232900	-1.75847900
C	-3.44221800	0.87850300	-1.29334500
C	-4.62659700	0.13877300	-1.35793800
C	-4.95266500	-0.75848900	-0.33114500
C	-4.09391900	-0.89100100	0.76660100
C	-2.91068200	-0.14674400	0.82591300
H	0.78243600	-0.30043400	1.65572800
H	1.47760400	-1.88238500	3.41691100
H	1.08047100	-4.33897000	3.08781500
H	-0.13979400	-5.14363000	1.09241900
H	3.50662800	1.15751100	1.04448600
H	5.53838200	-0.18698200	0.65665000

H	5.64982200	-1.77336100	-1.26758000
H	3.69716300	-1.96331500	-2.81143800
H	1.68840800	-0.57701000	-2.45294800
H	-3.18054500	1.55507300	-2.10054500
H	-5.29253300	0.25714600	-2.20771500
H	-5.87078900	-1.33643900	-0.38089200
H	-4.34338900	-1.57328700	1.57406000
H	-2.24471500	-0.26001400	1.67409600
N	0.21165600	4.73051900	0.37816300
H	1.02151800	5.24434600	0.05260600
H	-0.66401500	5.20163400	0.18602600
C	2.53203000	3.30226800	-0.36672900
N	3.51995700	3.90767700	-0.50447100
Na	-2.72752400	-2.34209900	-1.66993800
Na	2.81136900	-2.56225100	0.51821300
O	-2.22461000	3.57525800	0.00074600
H	-2.58228300	3.92613300	0.83323400
C	-1.24137400	2.62204200	2.08538400
N	-0.89039800	2.10825400	3.08218700

TS17’

Free energy：-1753.984006

Energy：-1754.293999

C	0.83728500	-1.96228700	0.38934700
C	0.69145300	-3.41029800	0.29056100
O	0.05891900	-4.01835800	-0.65041700
C	0.24778900	0.41523400	-0.38611800
C	0.37151400	-1.07066800	-0.65646000
C	1.41918700	-1.40644000	1.56209300
C	1.93235500	-2.18597500	2.57508200
C	1.86585200	-3.59245300	2.45283600
C	1.27030800	-4.17796400	1.35858300
O	-0.05110600	-1.45847100	-1.77366600
C	-1.08409900	0.88280500	-0.26869600
C	-1.36968300	2.24251900	0.11823600
C	-0.22491100	3.15389700	0.07207800
C	1.06390200	2.66353900	-0.11848900
C	1.34513200	1.26938000	-0.32911000
C	2.73490000	0.79249400	-0.50541400
C	-2.21128600	-0.09546700	-0.29850700
C	3.73937100	1.14131300	0.41586600
C	5.04211900	0.66837500	0.26994700
C	5.37125100	-0.17273500	-0.79555600

C	4.38535600	-0.52825100	-1.71796300
C	3.08475500	-0.04489000	-1.57970800
C	-3.11850800	-0.14261600	-1.37636900
C	-4.12062100	-1.11983400	-1.43172700
C	-4.23103100	-2.07294100	-0.41031300
C	-3.34961300	-2.02515800	0.67686900
C	-2.35916400	-1.03956300	0.73689500
H	1.46369100	-0.32799700	1.64993400
H	2.38136600	-1.72843300	3.45057500
H	2.27698600	-4.22070000	3.23979300
H	1.19587600	-5.25927400	1.27636500
H	3.48862400	1.76664900	1.26689300
H	5.79851700	0.94610900	0.99849500
H	6.38501500	-0.54628500	-0.90543000
H	4.63060100	-1.17458800	-2.55597300
H	2.33342200	-0.30778100	-2.31637900
H	-3.01003200	0.56409100	-2.19327600
H	-4.80087200	-1.14632800	-2.27760300
H	-5.00045400	-2.83739600	-0.45766400
H	-3.43448600	-2.75227800	1.47885200
H	-1.67748200	-1.01068400	1.57927800
C	-2.09767400	2.30273100	1.65851900
N	-2.72481700	1.81605600	2.52340500
N	-0.52185800	4.46429200	0.37998600
H	-1.43715200	4.76410000	0.06886600
H	0.20138700	5.15069100	0.20004100
C	2.11097700	3.62800100	-0.17647200
N	2.92372100	4.46322400	-0.22307100
Na	-1.56990900	-3.09697700	-1.77179300
Na	-4.39616000	1.88830100	0.55754900
O	-2.57785500	2.82457300	-0.52355800
H	-2.42874900	2.75210500	-1.48325500

IM23

Free energy：-1754.063683

Energy：-1754.369819

C	-0.58688700	-1.33607100	-0.46523400
C	-1.06118200	-2.70659000	-0.26607700
O	-0.62964600	-3.49457100	0.64364100
C	0.92367100	0.63945800	0.15838900
C	0.27438200	-0.68107200	0.50344600
C	-0.97010500	-0.63318000	-1.64607000
C	-1.88286000	-1.14778300	-2.54745400

C	-2.44807700	-2.42516100	-2.29456200
C	-2.06311600	-3.16624700	-1.19744600
O	0.59868300	-1.17656800	1.60544600
C	2.31675800	0.58316700	-0.11001400
C	3.01368000	1.74449000	-0.40788100
C	2.36091800	3.00335800	-0.43411500
C	0.97979000	3.03592100	-0.13907900
C	0.24692100	1.85472400	0.15889100
C	-1.19900400	1.93929200	0.49951400
C	3.01256300	-0.73764100	-0.06406100
C	-2.11678300	2.52293500	-0.39074300
C	-3.47092500	2.61314400	-0.05856200
C	-3.92877100	2.12224100	1.17080000
C	-3.02355800	1.52779600	2.05914800
C	-1.66892900	1.43601300	1.72515800
C	3.85054500	-1.05582900	1.01550300
C	4.37369700	-2.34500300	1.14930500
C	4.06702700	-3.32896200	0.20150700
C	3.25285700	-3.00975400	-0.89262100
C	2.73366800	-1.72002300	-1.02741000
H	-0.53923900	0.34394300	-1.82977000
H	-2.16016200	-0.58798800	-3.43426100
H	-3.18679300	-2.82921400	-2.98188000
H	-2.47595400	-4.15561500	-1.02227300
H	-1.77140500	2.89522800	-1.34954200
H	-4.16778200	3.06467900	-0.75782600
H	-4.97980300	2.19744700	1.43140000
H	-3.36976400	1.14277000	3.01337900
H	-0.96997100	0.98768200	2.42266500
H	4.05948100	-0.30264700	1.76877800
H	5.01140000	-2.58324800	1.99493200
H	4.46835000	-4.33226300	0.30769600
H	3.02224300	-3.76431700	-1.63823000
H	2.09016000	-1.47876400	-1.86640800
N	3.07853200	4.11536300	-0.77519200
H	2.68999200	5.02014600	-0.54377900
H	4.08290300	4.04649600	-0.68338900
C	0.34864900	4.31109100	-0.09556300
N	-0.11417900	5.38031700	-0.06822600
Na	1.33226600	-3.28980100	1.62862100
Na	-3.52429200	-0.49709500	-0.14470000
O	4.34682600	1.77962600	-0.69425200
H	4.72129900	0.88542600	-0.63830400
C	-5.70027600	-1.35291900	0.16166400

N	-6.78542300	-1.76513400	0.33576000

IM24

Free energy：-1498.809729

Energy：-1499.117414

C	-0.55867500	-1.77770100	0.37633600
C	-1.48378500	-2.88769200	0.17218300
O	-2.37233400	-2.93176100	-0.75493700
C	0.24429000	0.60100900	-0.16143200
C	-0.48628700	-0.66834200	-0.54814100
C	0.27214000	-1.77177900	1.53144400
C	0.30200200	-2.81954500	2.42368900
C	-0.53583700	-3.93557900	2.19335700
C	-1.39201600	-3.96727400	1.11651700
O	-1.08351500	-0.62077200	-1.65086800
C	-0.58438900	1.71354000	0.14147500
C	-0.01720500	2.93910700	0.46000600
C	1.38832800	3.11460200	0.46650900
C	2.19157200	2.00110800	0.13571500
C	1.62988500	0.73295100	-0.17756300
C	2.50850900	-0.41585500	-0.51944800
C	-2.06863700	1.55403100	0.10987000
C	3.51836500	-0.82974400	0.36297400
C	4.31757900	-1.93011400	0.05777800
C	4.12083500	-2.63206900	-1.13325400
C	3.12228800	-2.22460100	-2.01948300
C	2.32211400	-1.12352600	-1.71654300
C	-2.81592500	2.12585200	-0.93175200
C	-4.18320300	1.86064100	-1.05121000
C	-4.81876600	1.02251100	-0.12699600
C	-4.08357800	0.46954300	0.92932900
C	-2.71818400	0.73861900	1.05025100
H	0.90717200	-0.91182300	1.70602100
H	0.95699100	-2.79091700	3.28821300
H	-0.51419300	-4.77437400	2.88532100
H	-2.05404600	-4.81387300	0.95446100
H	3.66104300	-0.30133700	1.30022100
H	5.08853800	-2.24429500	0.75496500
H	4.74193700	-3.49105300	-1.36891100
H	2.96710600	-2.76077400	-2.95099100
H	1.55453100	-0.80385100	-2.41296000
H	-2.31604000	2.74877500	-1.66707400
H	-4.74852200	2.30010600	-1.86717500

H	-5.87957700	0.81127100	-0.22190000
H	-4.57284400	-0.17075800	1.65682400
H	-2.14719200	0.29688100	1.85939100
N	1.90574000	4.33028200	0.82696500
H	2.86439200	4.52577700	0.56888400
H	1.27938500	5.11991400	0.74598400
C	3.59857000	2.20802200	0.07127000
N	4.73934000	2.44296200	0.02636300
Na	-3.25232400	-1.14341100	-1.65867600
O	-0.74144400	4.05135200	0.78271500
H	-1.69027600	3.84828400	0.74830900

5a

Free energy：-1337.025594

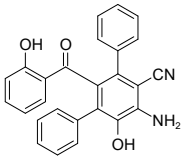
Energy：-1337.344387

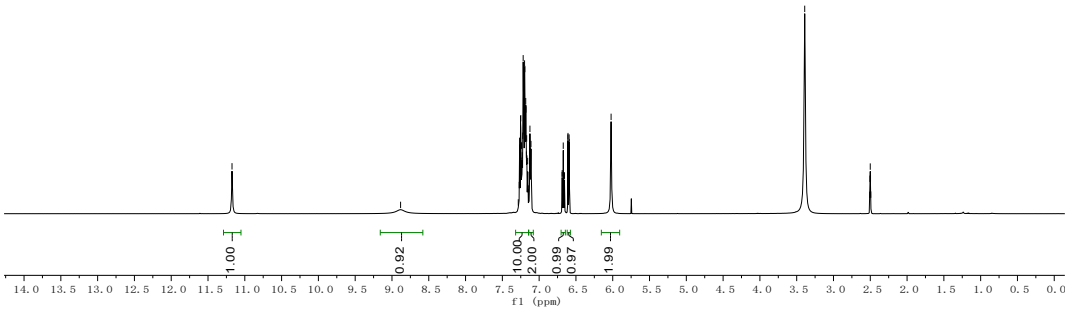
C	0.31699700	-1.89420900	0.29313500
C	0.52091100	-3.26005200	-0.04627800
O	0.28721600	-3.72443100	-1.28657000
C	-0.23852700	0.50325400	-0.39537600
C	-0.12788000	-0.95640000	-0.73271100
C	0.56646800	-1.47739300	1.61792300
C	1.01320000	-2.37126000	2.57496300
C	1.22425400	-3.71352600	2.21850600
C	0.98212200	-4.15791600	0.92645900
O	-0.42156600	-1.33845200	-1.88317500
C	-1.51898900	1.06046800	-0.16048400
C	-1.62560600	2.39827000	0.20442700
C	-0.48376800	3.22661500	0.32656400
C	0.77999300	2.64179200	0.08722100
C	0.91530100	1.27440600	-0.26371600
C	2.26051000	0.67133300	-0.45157200
C	-2.75548900	0.22709600	-0.20909800
C	3.20201500	0.70674900	0.58849500
C	4.44551800	0.09666700	0.43591500
C	4.76621100	-0.55477500	-0.75718100
C	3.83859200	-0.58781600	-1.79936600
C	2.59349400	0.02214200	-1.64963500
C	-3.26294900	-0.25546000	-1.42422000
C	-4.41836600	-1.03517200	-1.44307700
C	-5.08200200	-1.33819500	-0.25208000
C	-4.58835200	-0.85575100	0.96079800
C	-3.43232400	-0.07501200	0.98333000
H	0.39837300	-0.43902600	1.87903000

H	1.19979800	-2.03900200	3.59040400
H	1.57938800	-4.41914700	2.96380100
H	1.13799500	-5.19394100	0.64472200
H	2.94788100	1.19338900	1.52471600
H	5.16061200	0.12224100	1.25267500
H	5.73402200	-1.03314500	-0.87358400
H	4.08349700	-1.08636500	-2.73240100
H	1.87649300	-0.00072800	-2.46304100
H	-2.74512300	-0.02188700	-2.34750900
H	-4.80121900	-1.40547100	-2.38924700
H	-5.98060700	-1.94752700	-0.26989900
H	-5.09869900	-1.08929200	1.89029300
H	-3.04052800	0.29433500	1.92635300
N	-0.64358600	4.52786400	0.71122700
H	0.11991600	5.17049400	0.54734000
H	-1.56685200	4.92171100	0.59253000
C	1.92589200	3.48282500	0.16839800
N	2.82766700	4.21745200	0.24080100
O	-2.81575300	3.01705800	0.46016600
H	-3.54543800	2.40118700	0.28106700
H	-0.05060000	-2.95051300	-1.81283600

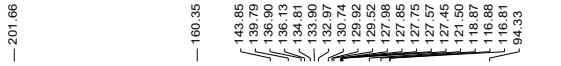
9. NMR spectra for compounds 4

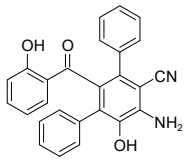
^{1}H NMR spectra for compound 4a (500 MHz, DMSO-d_6)

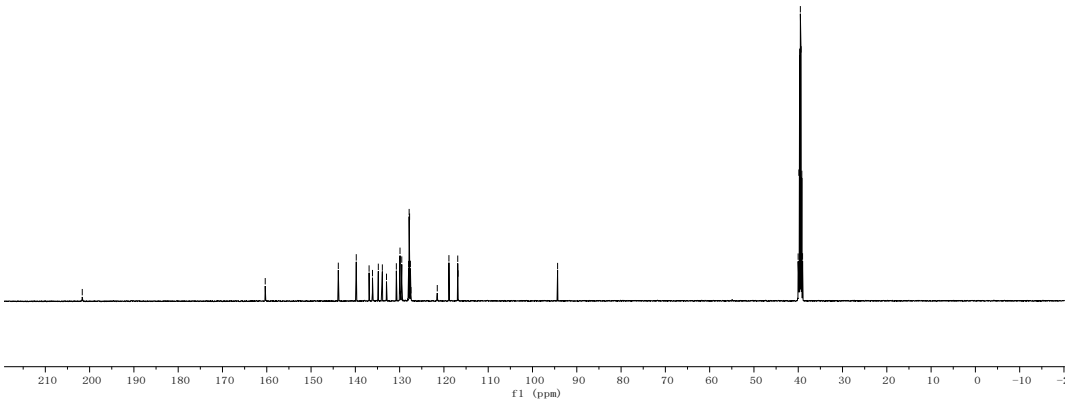




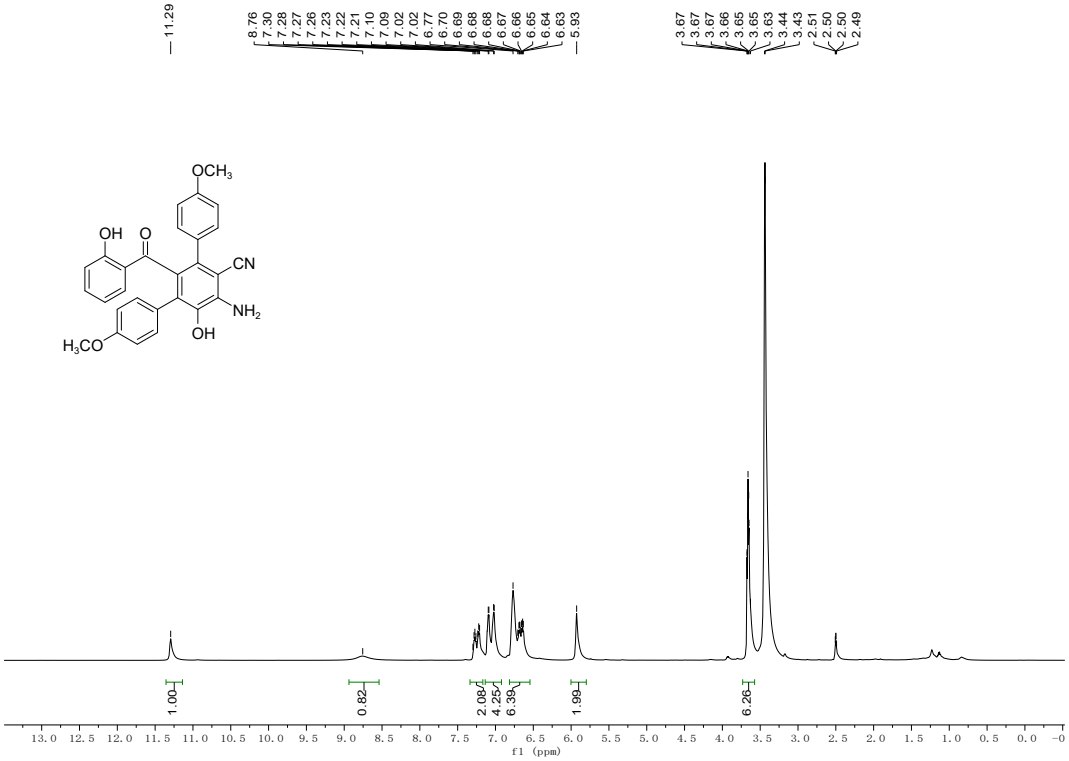
^{13}C NMR spectra for compound 4a (125 MHz, DMSO-d_6)



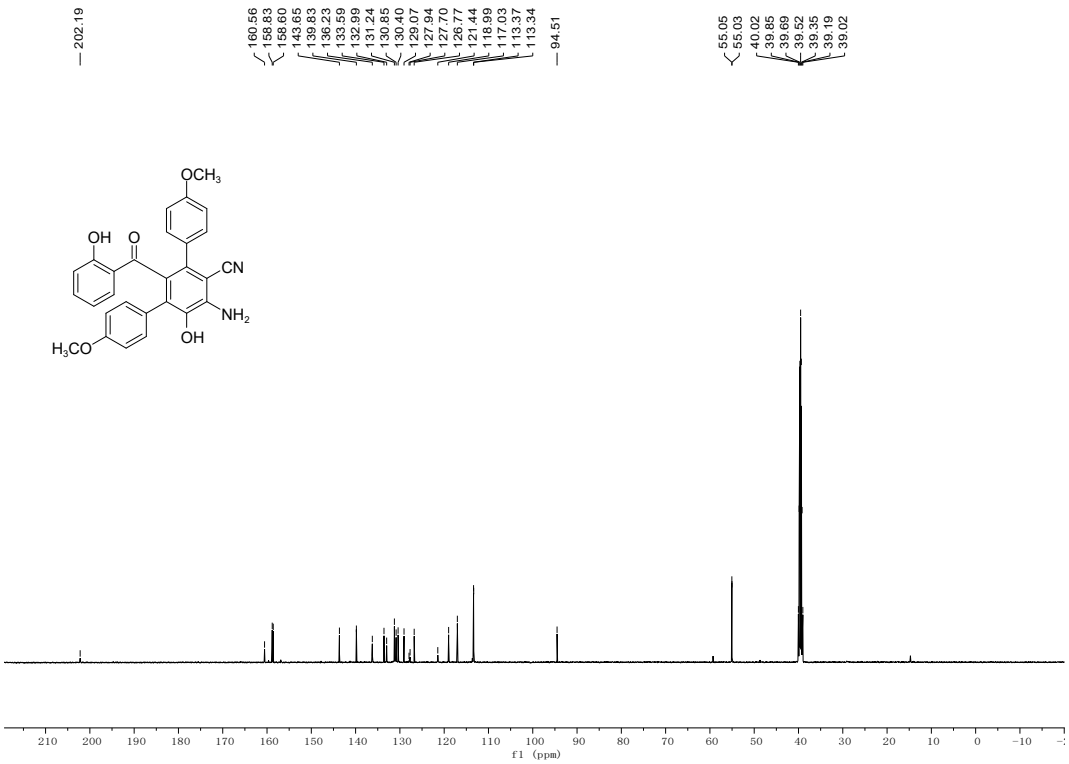




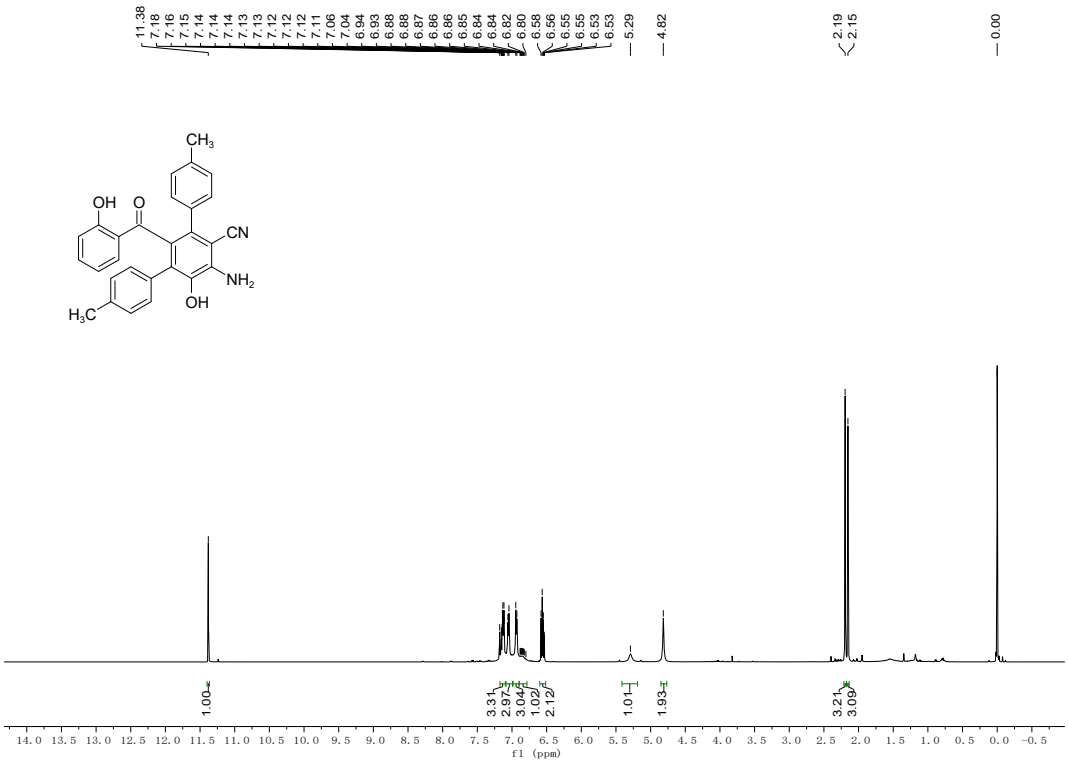
^{1}H NMR spectra for compound 4b (500 MHz, DMSO-d_6)



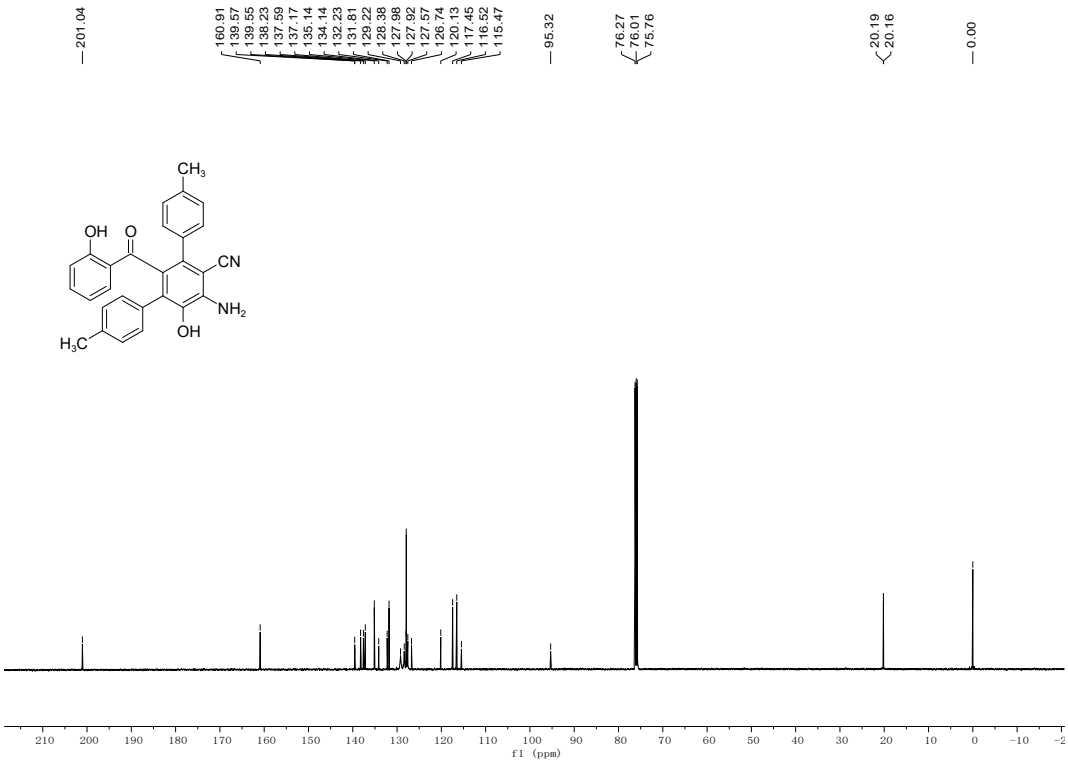
^{13}C NMR spectra for compound 4b (125 MHz, DMSO-d_6)



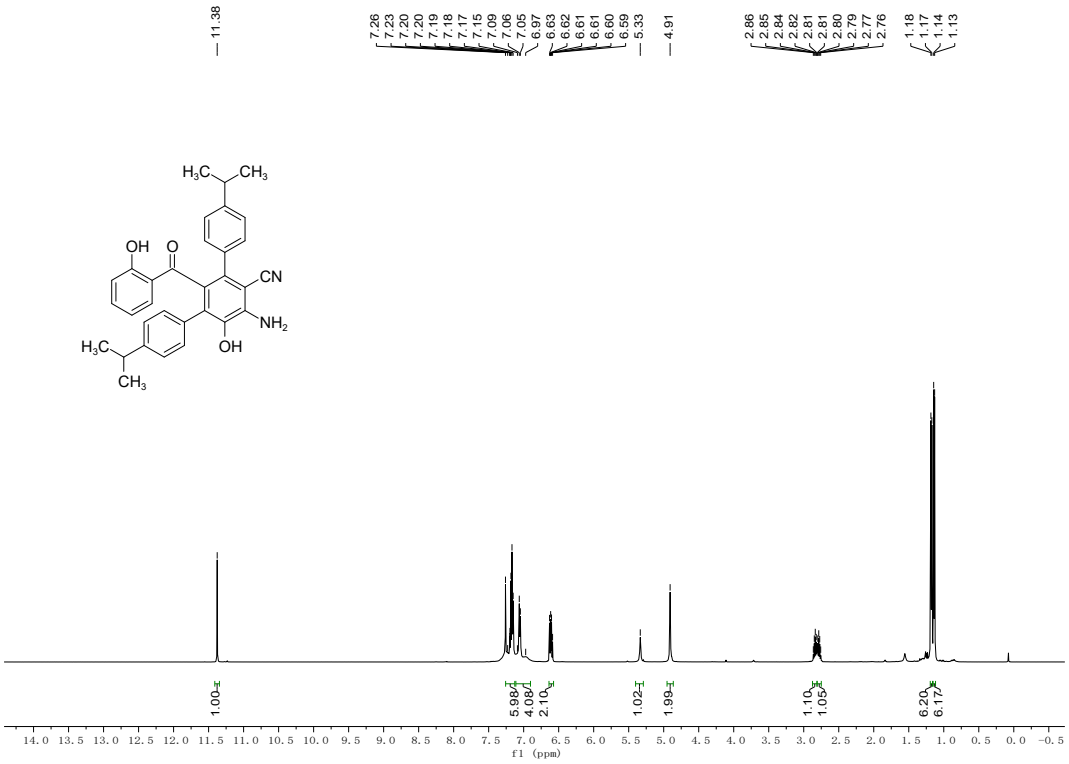
^{1}H NMR spectra for compound 4c (500 MHz, $CDCl_3$)



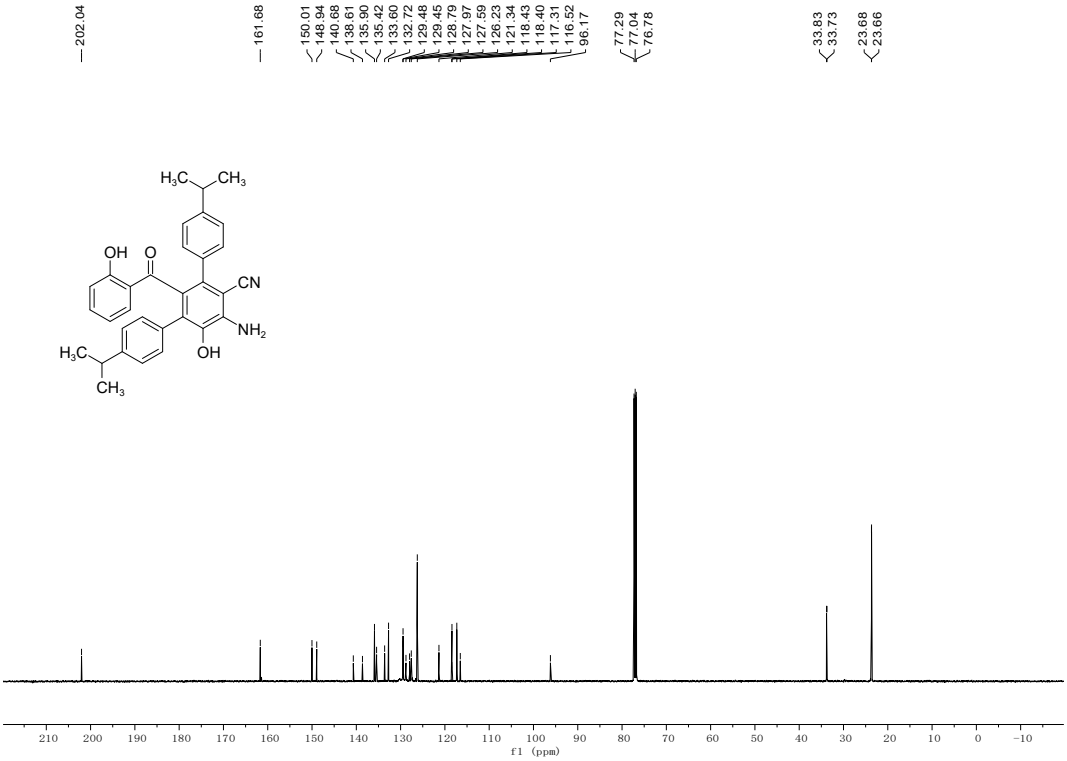
^{13}C NMR spectra for compound 4c (125 MHz, $CDCl_3$)



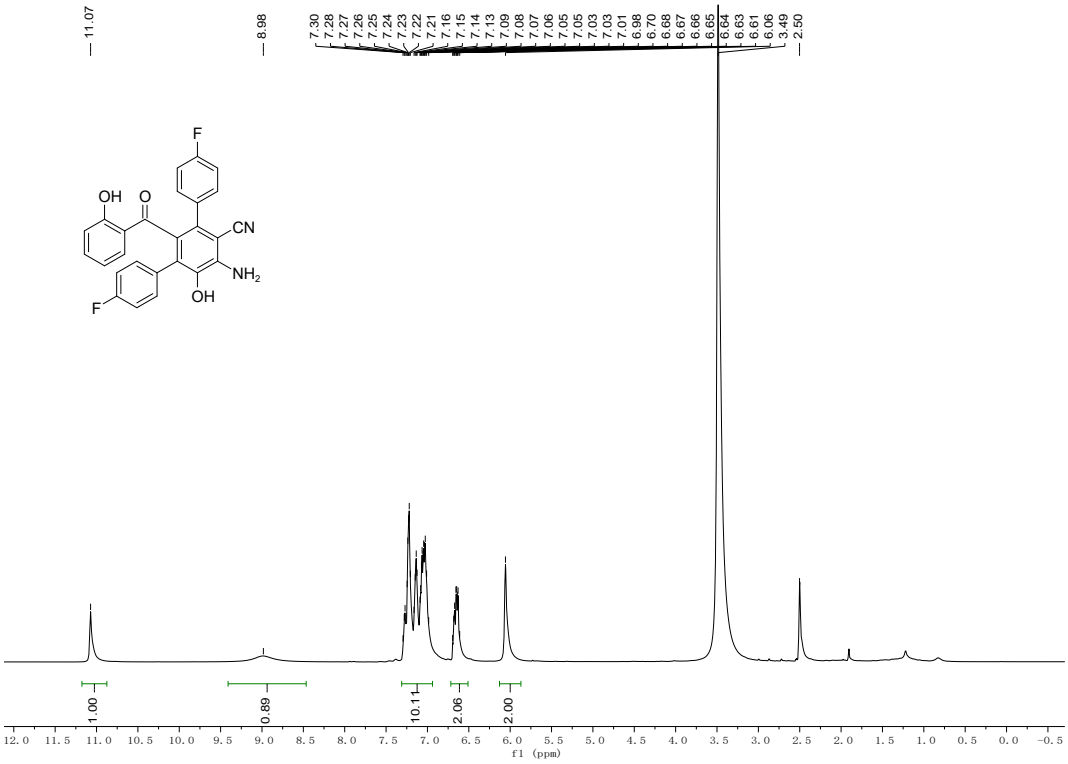
^{1}H NMR spectra for compound 4d (500 MHz, $CDCl_3$)



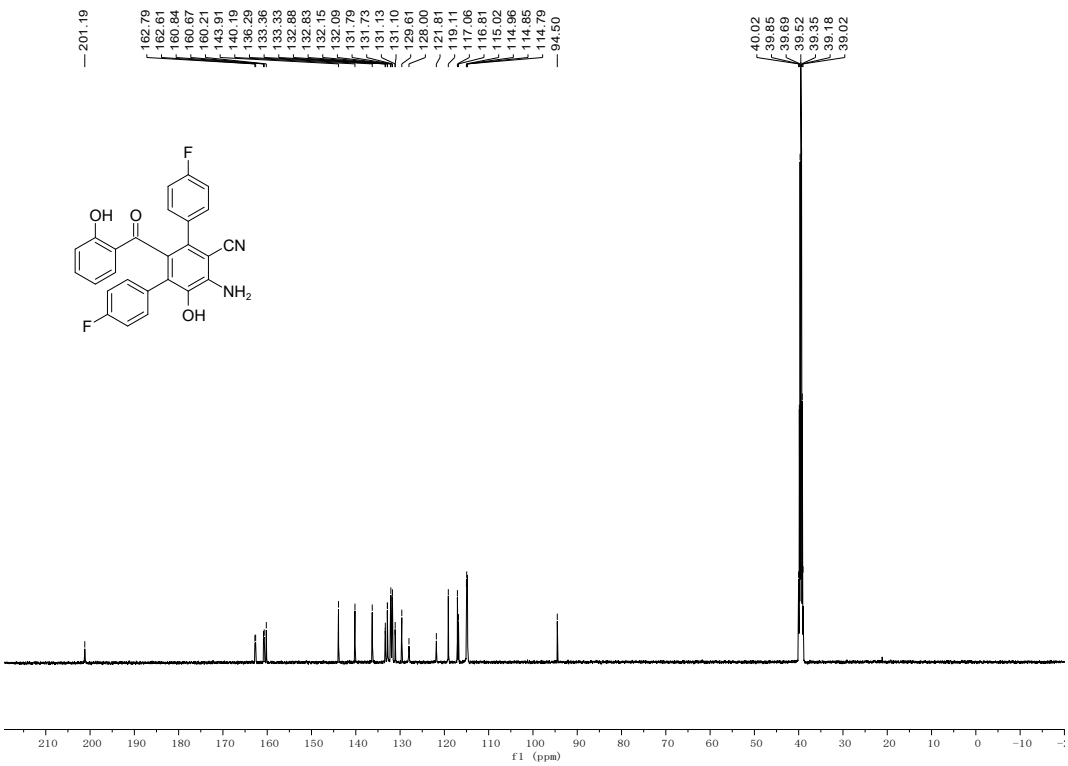
^{13}C NMR spectra for compound 4d (125 MHz, $CDCl_3$)



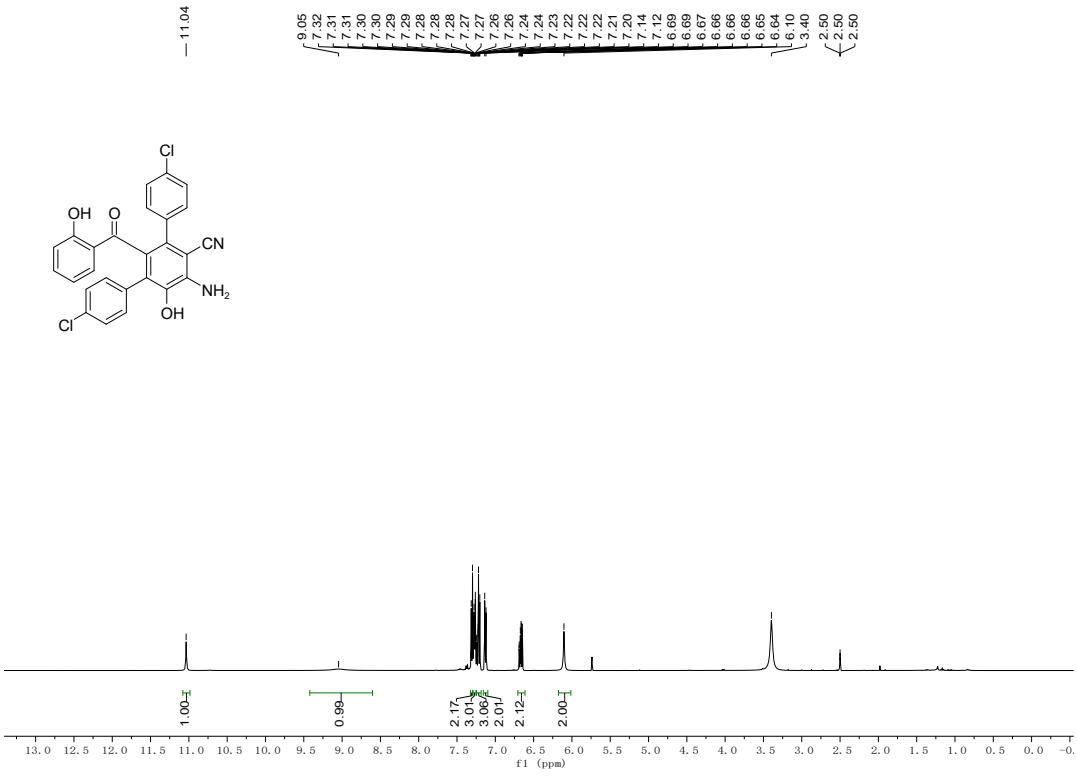
^{1}H NMR spectra for compound 4e (500 MHz, DMSO-d_6)



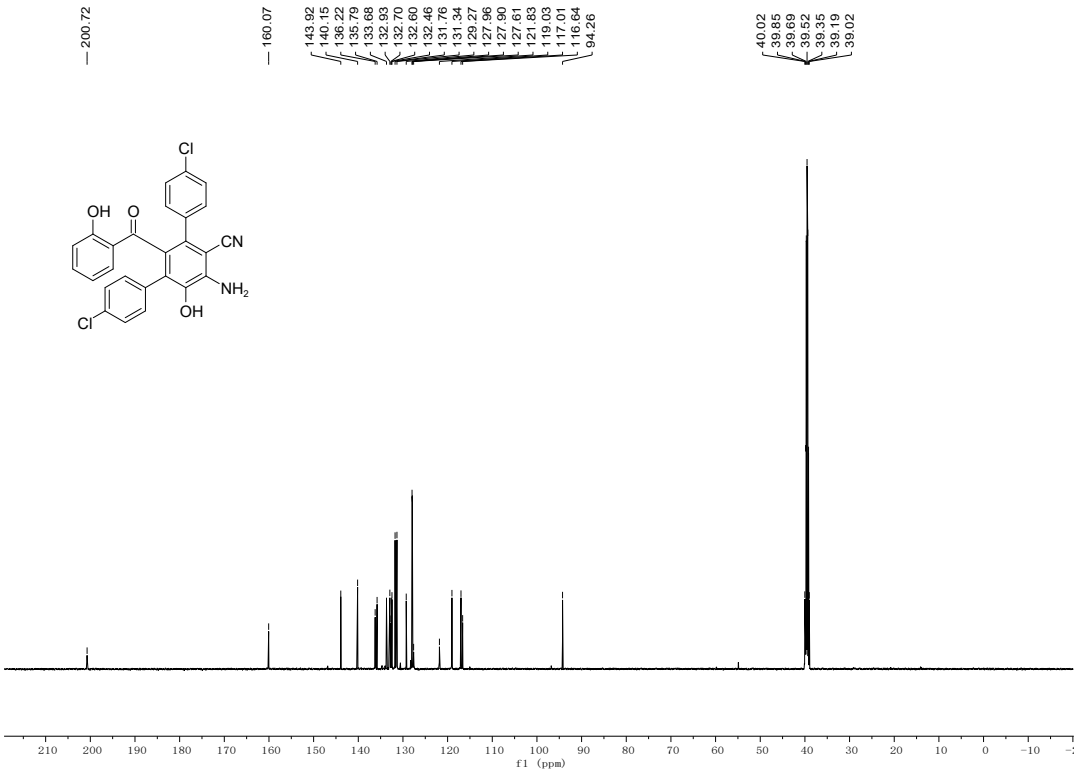
^{13}C NMR spectra for compound 4e (125 MHz, DMSO-d_6)



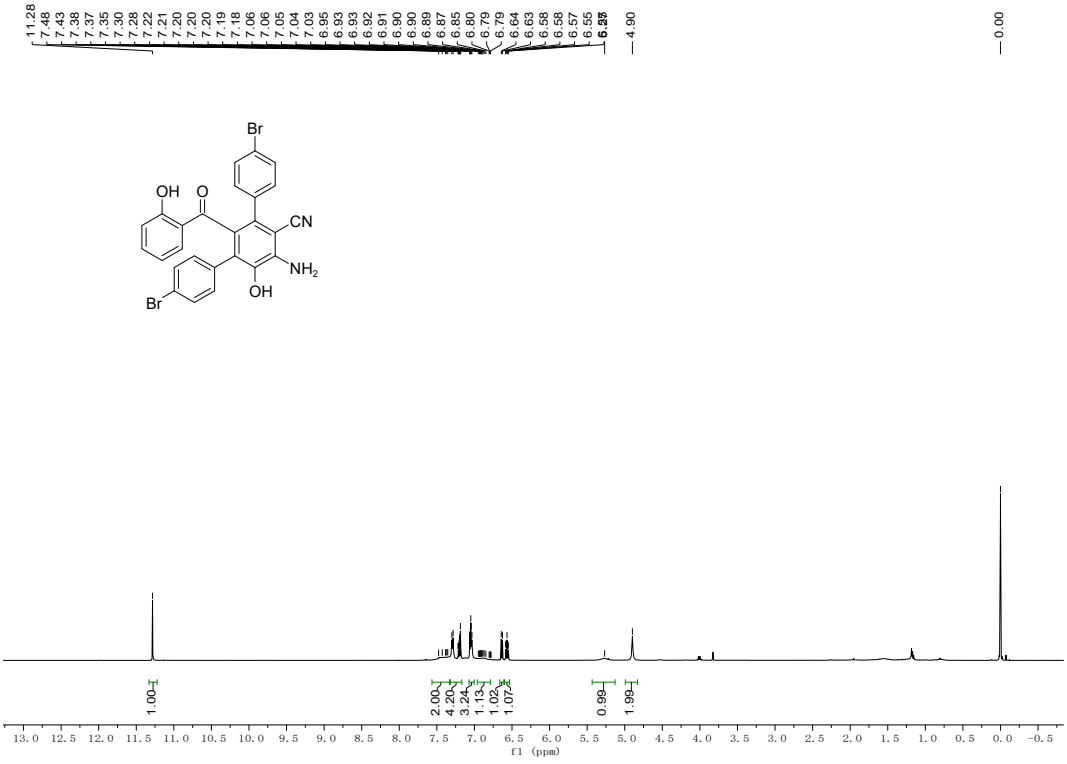
^{1}H NMR spectra for compound 4f (500 MHz, DMSO-d_6)



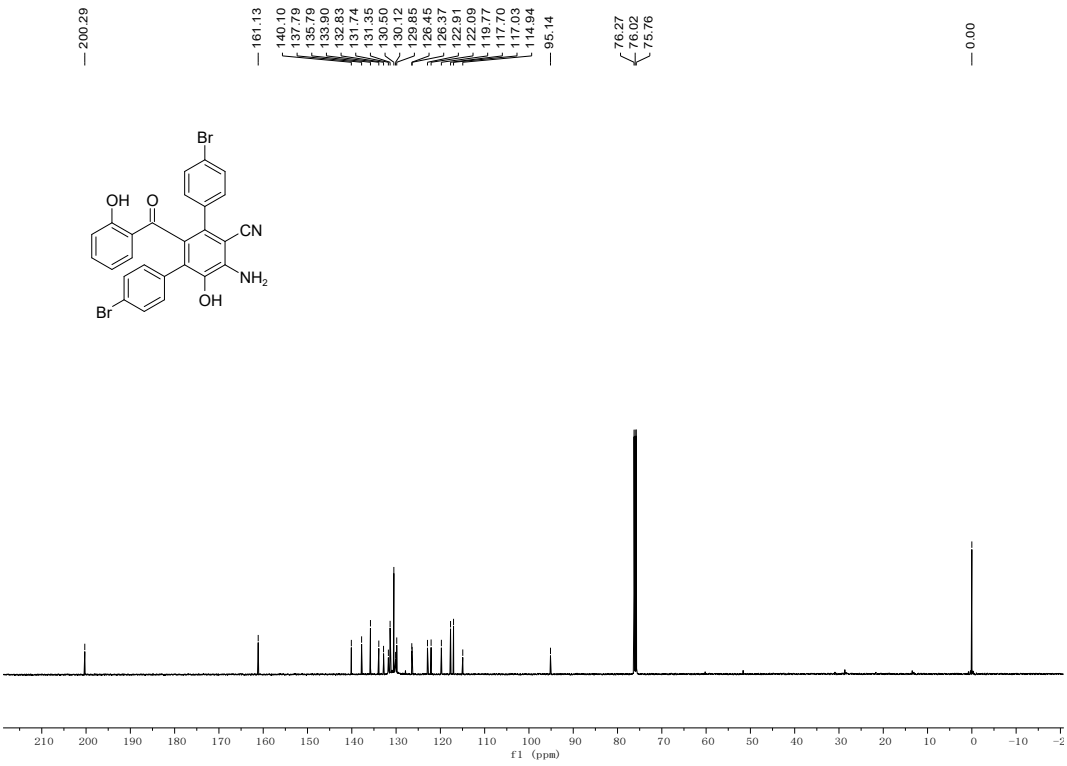
^{13}C NMR spectra for compound 4f (125 MHz, DMSO-d_6)



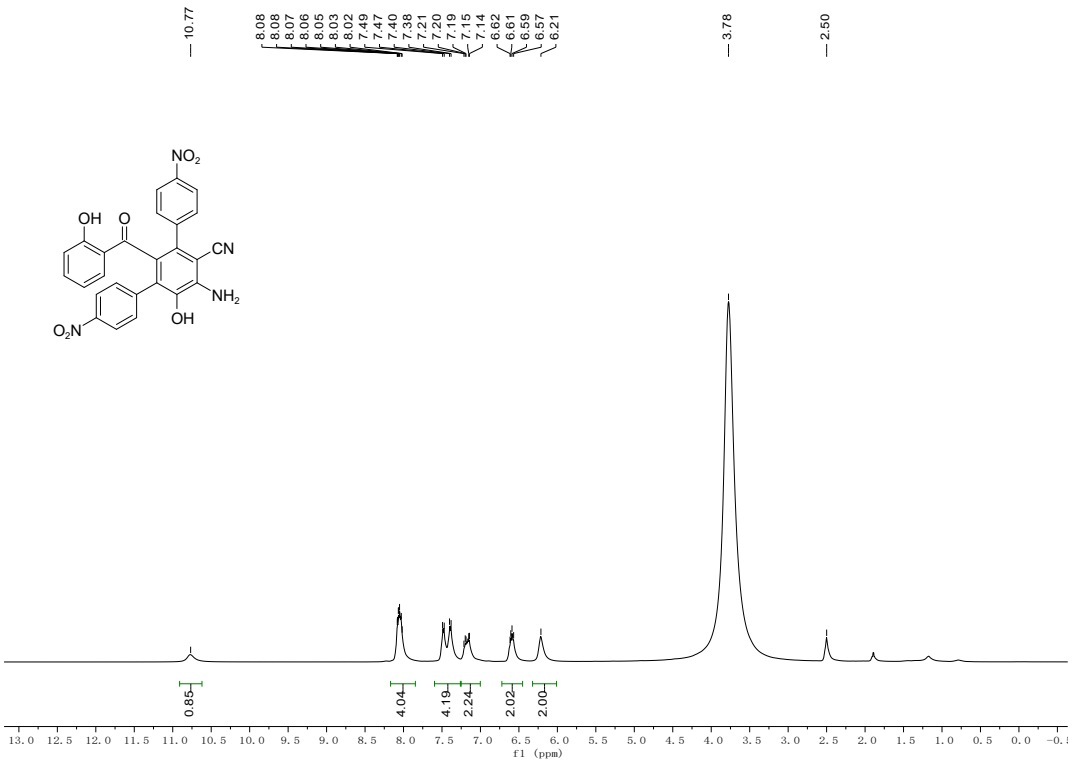
^{1}H NMR spectra for compound 4g (500 MHz, $CDCl_3$)



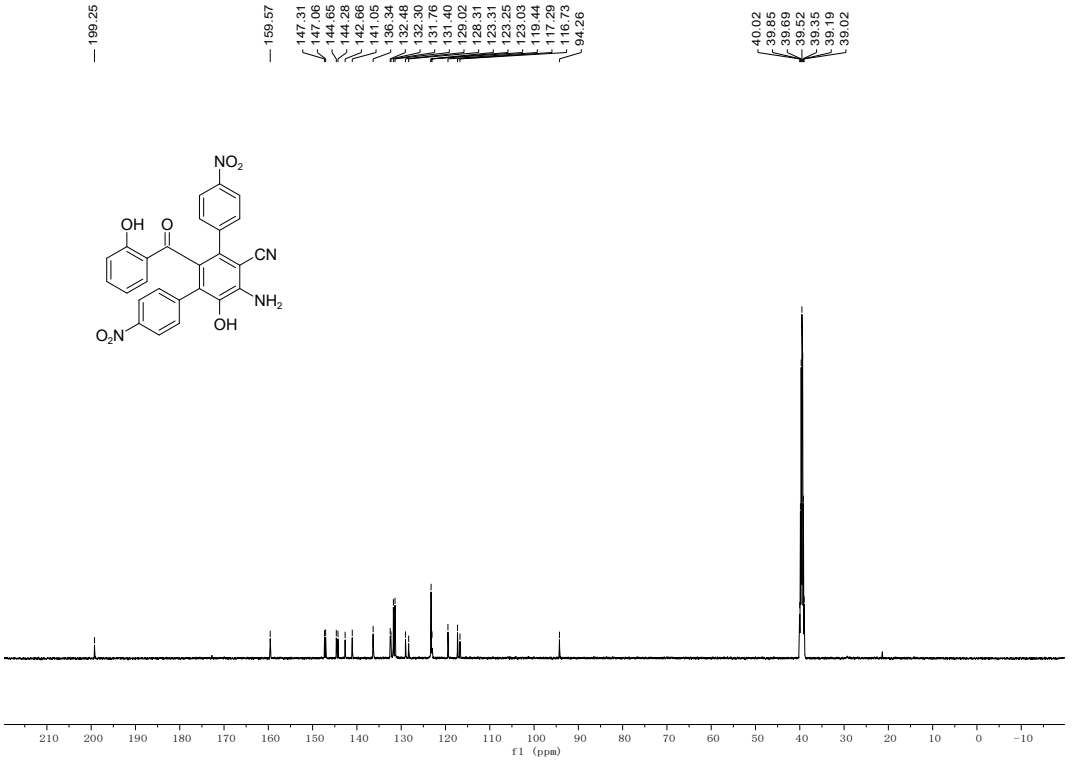
^{13}C NMR spectra for compound 4g (125 MHz, $CDCl_3$)



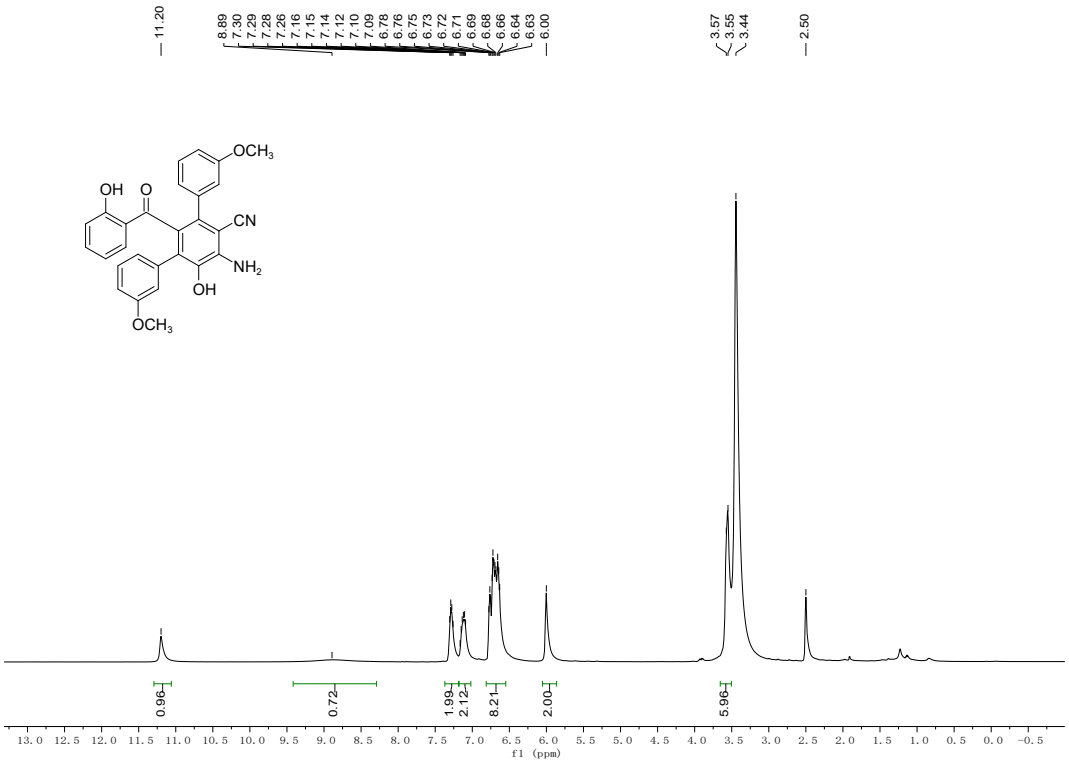
^{1}H NMR spectra for compound 4h (500 MHz, DMSO-d_6)



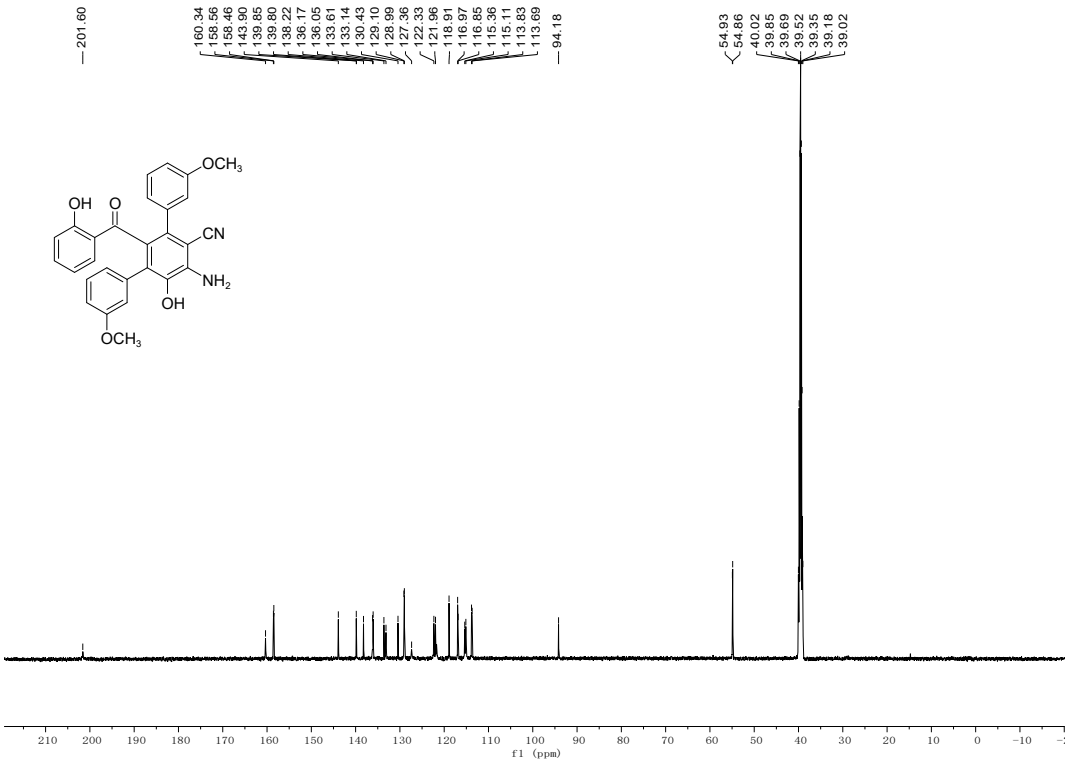
^{13}C NMR spectra for compound 4h (125 MHz, DMSO-d_6)



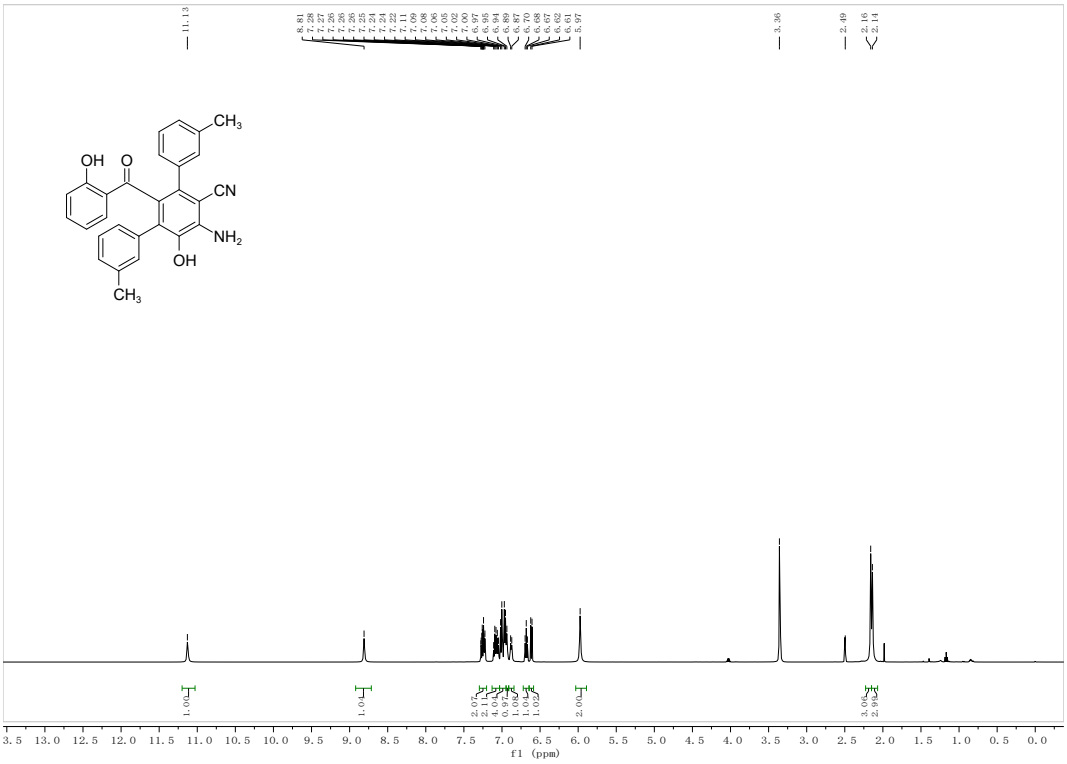
^{1}H NMR spectra for compound 4i (500 MHz, DMSO-d_6)



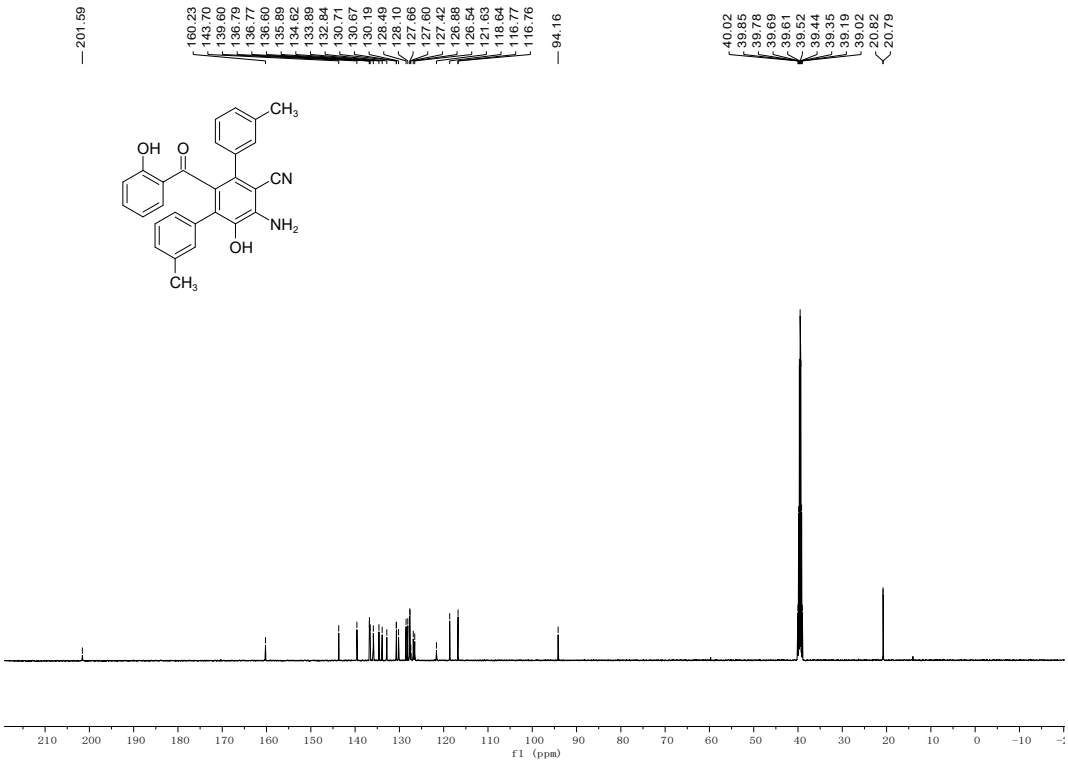
^{13}C NMR spectra for compound 4i (125 MHz, DMSO-d_6)



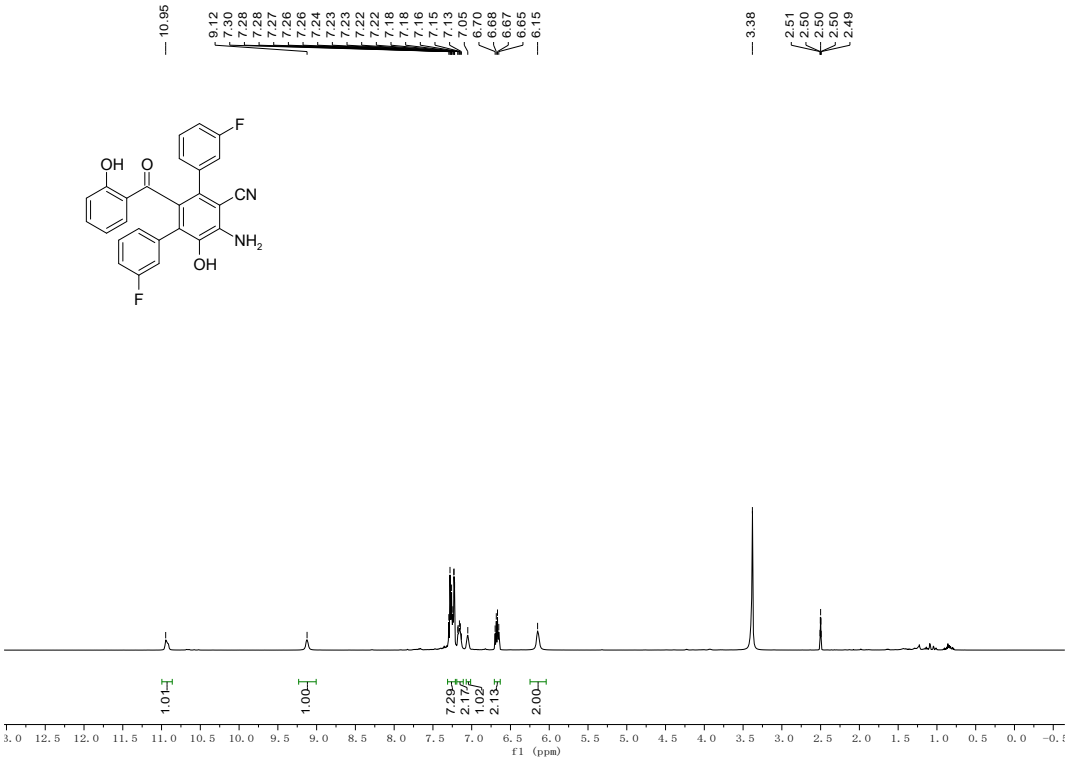
^{1}H NMR spectra for compound 4j (500 MHz, DMSO-d_6)



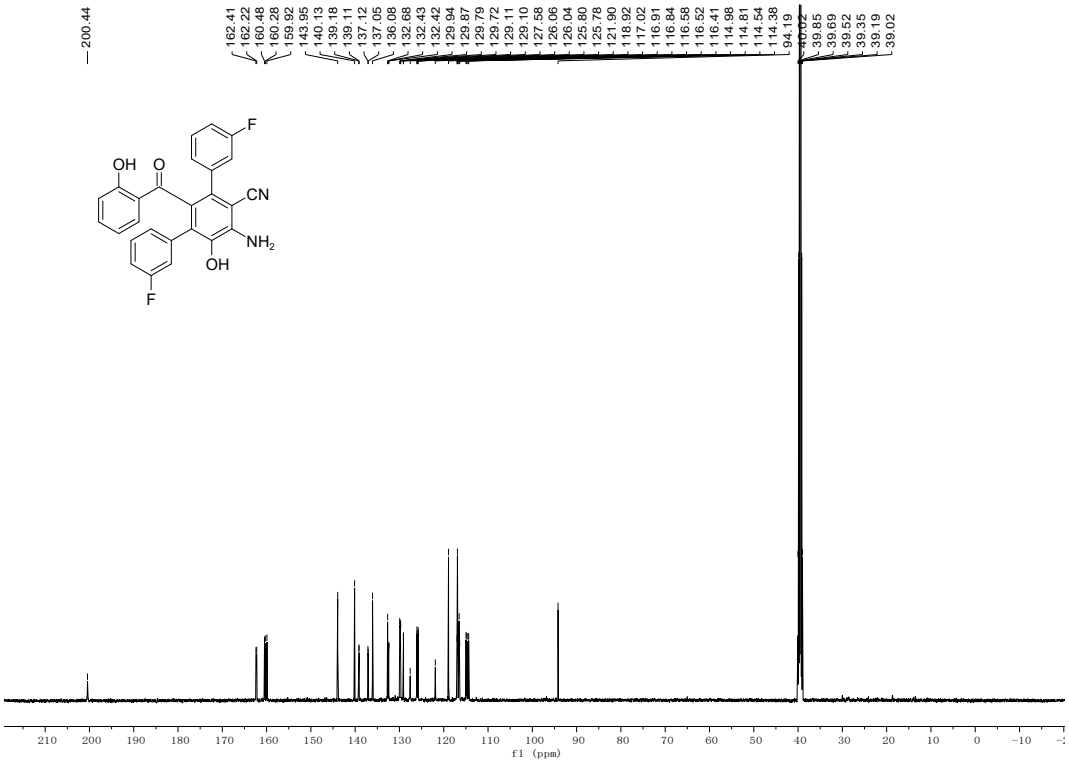
^{13}C NMR spectra for compound 4j (125 MHz, DMSO-d_6)



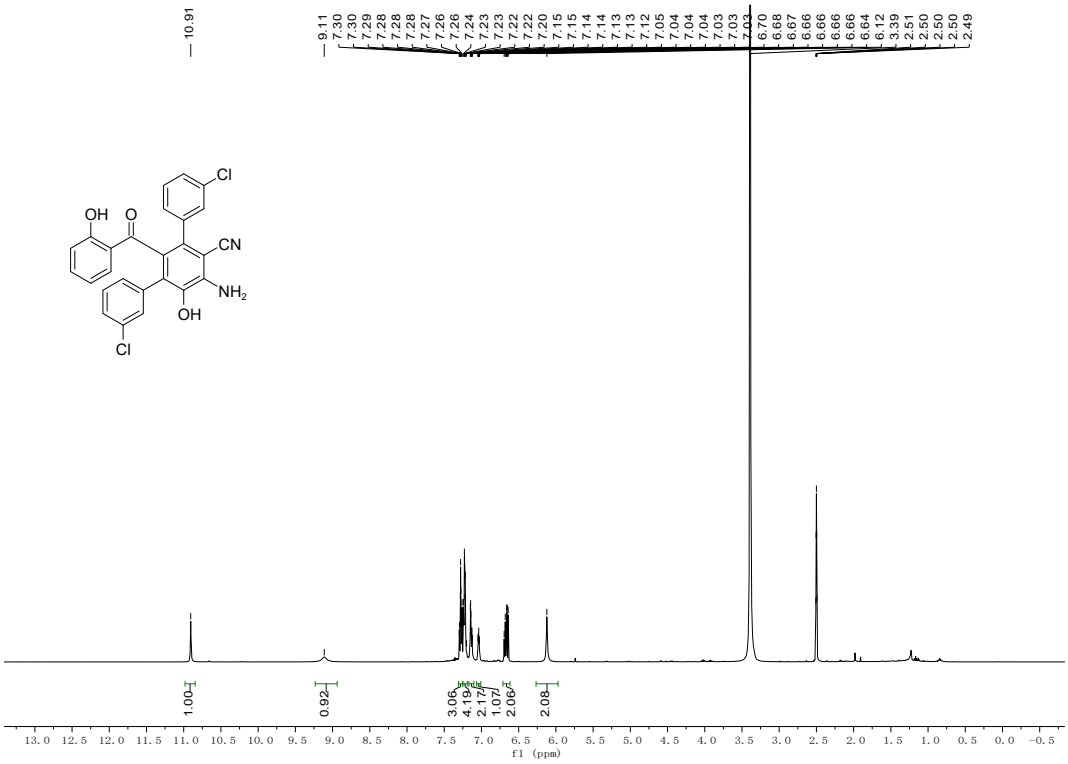
^{1}H NMR spectra for compound 4k (500 MHz, DMSO-d_6)



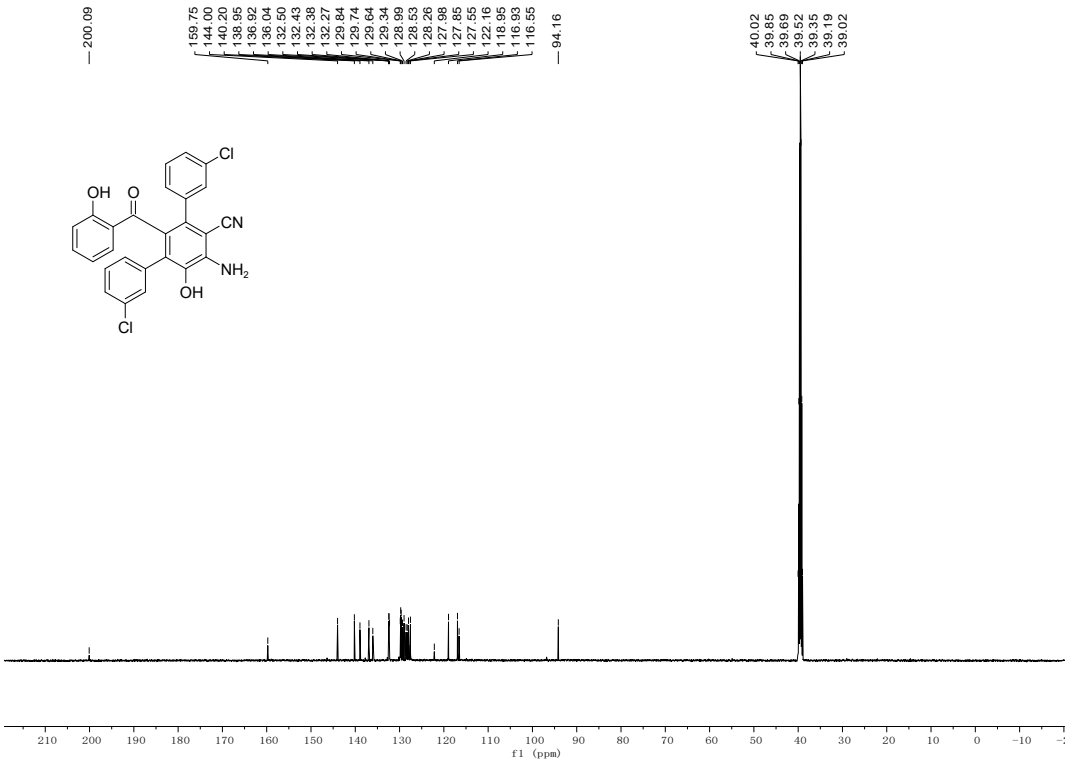
^{13}C NMR spectra for compound 4k (125 MHz, DMSO-d_6)



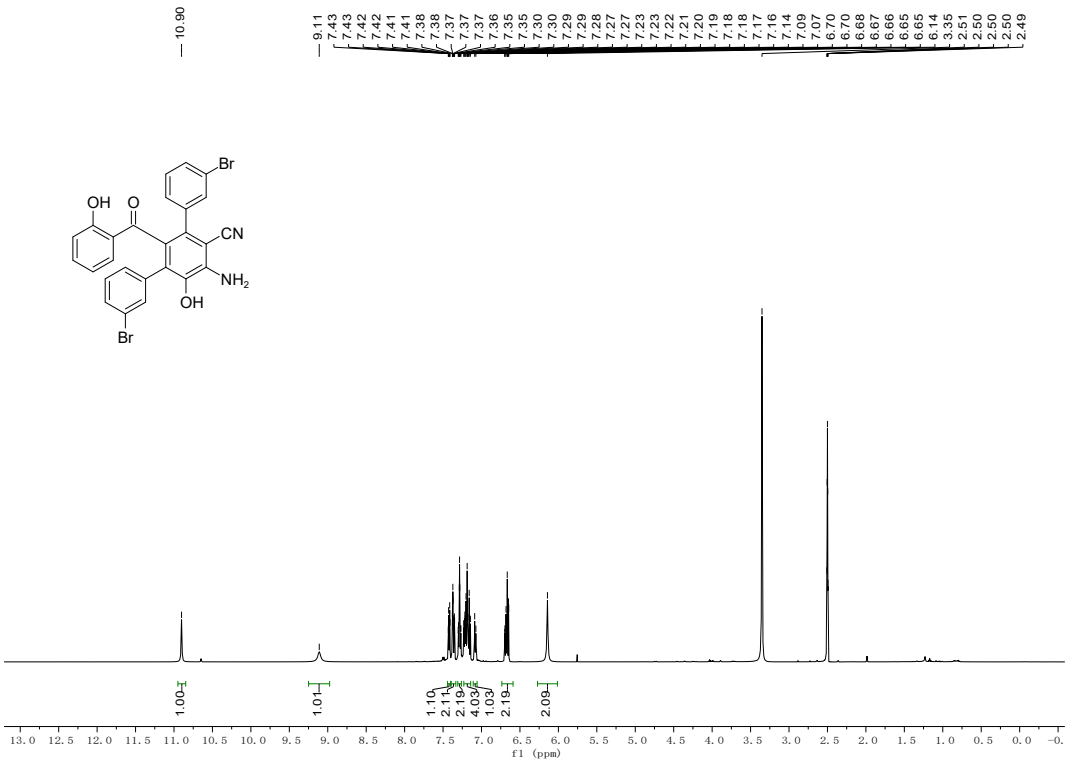
^{1}H NMR spectra for compound 4l (500 MHz, DMSO-d_6)



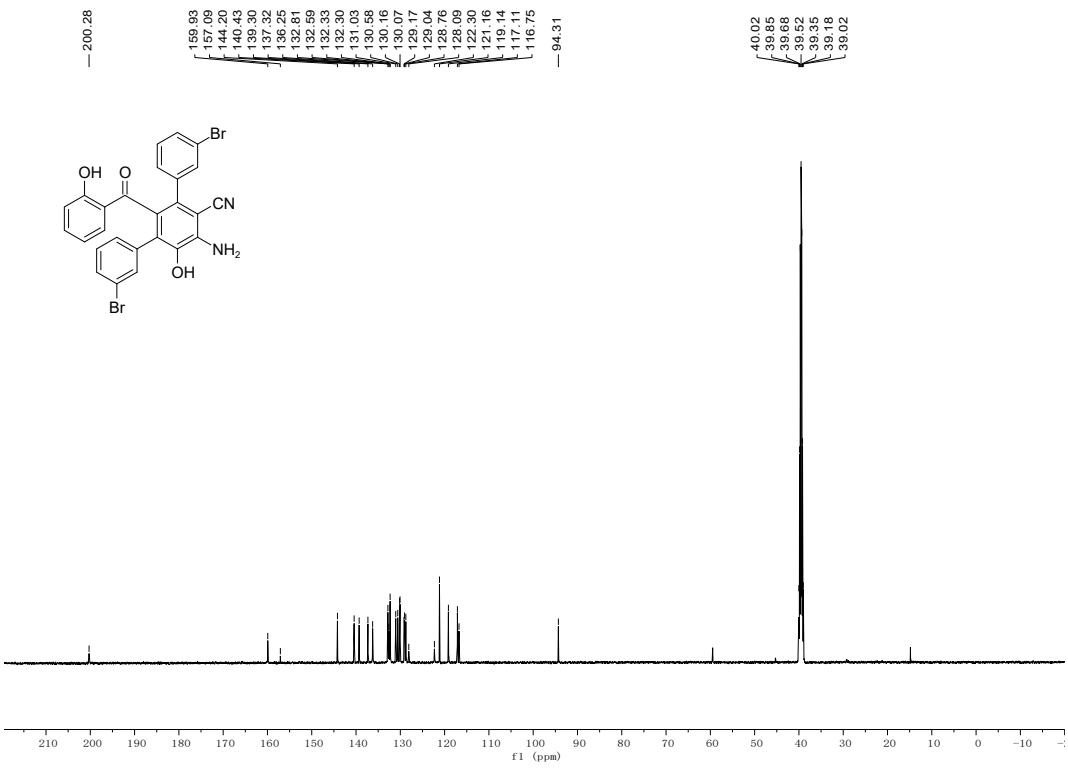
^{13}C NMR spectra for compound 4l (125 MHz, DMSO-d_6)



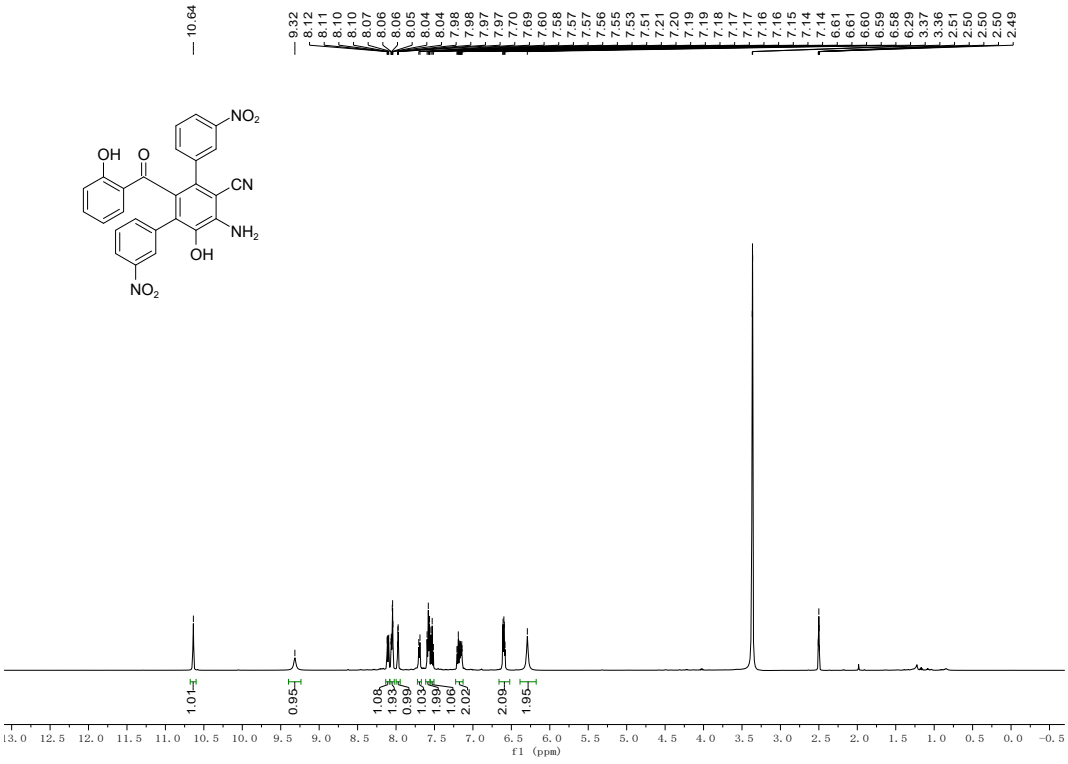
^{1}H NMR spectra for compound 4m (500 MHz, DMSO-d_6)



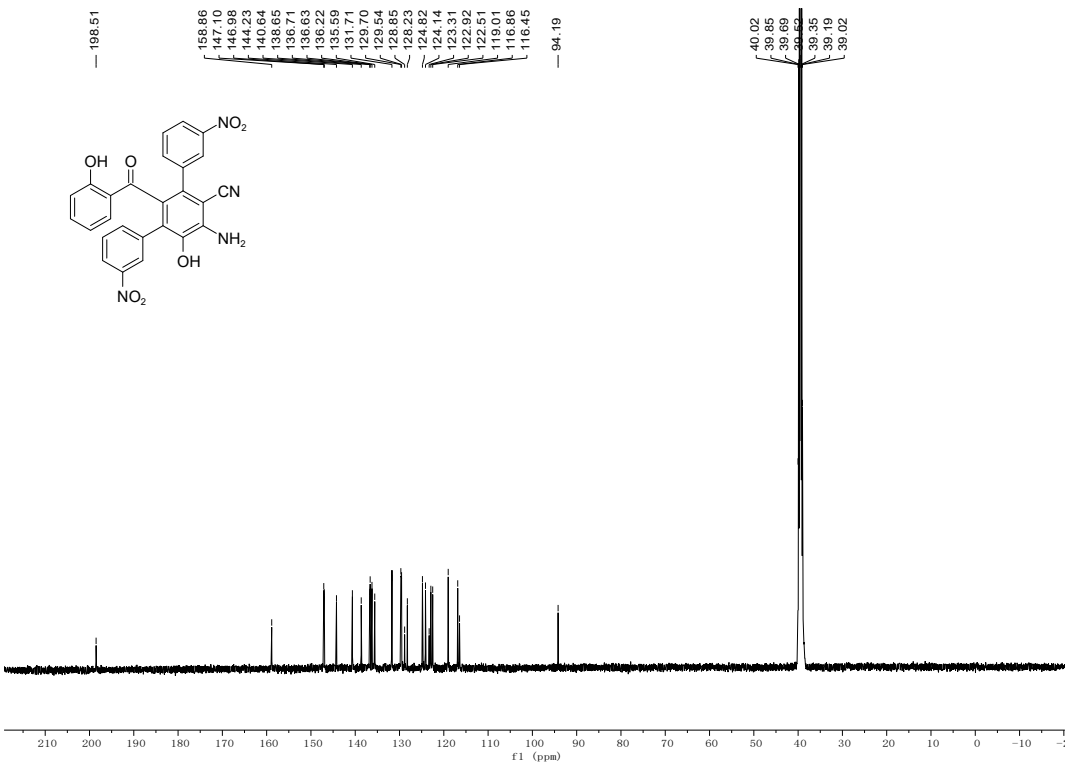
^{13}C NMR spectra for compound 4m (125 MHz, DMSO-d_6)



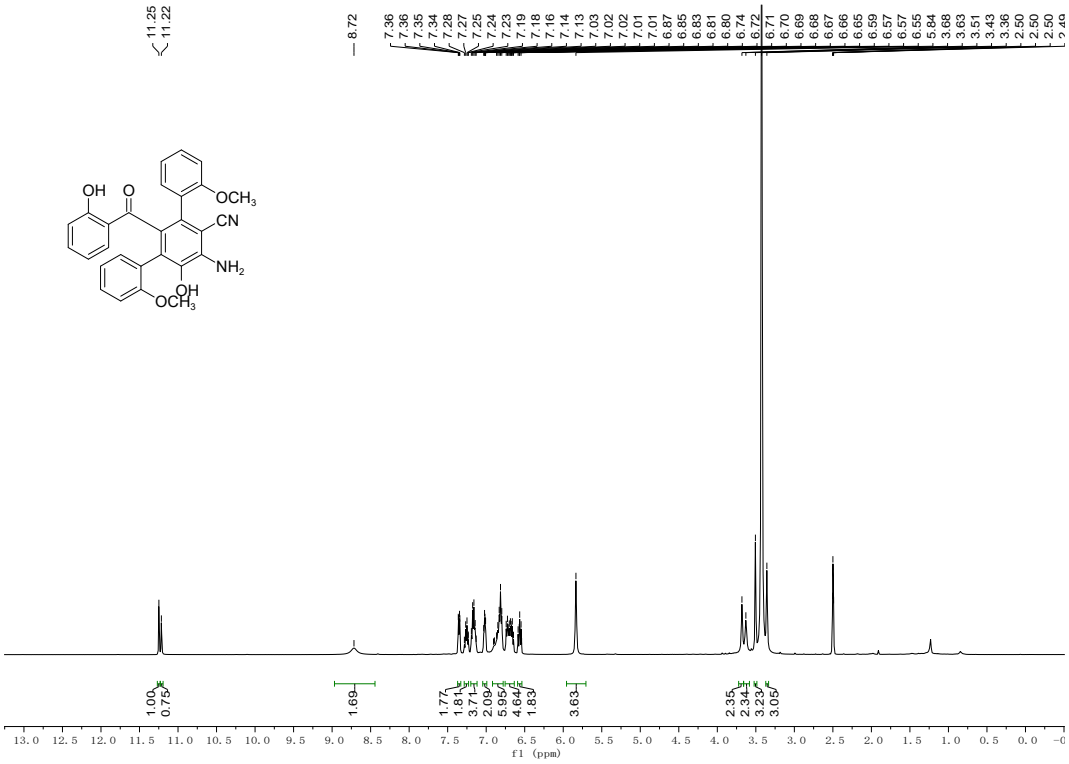
^{1}H NMR spectra for compound 4n (500 MHz, DMSO-d_6)



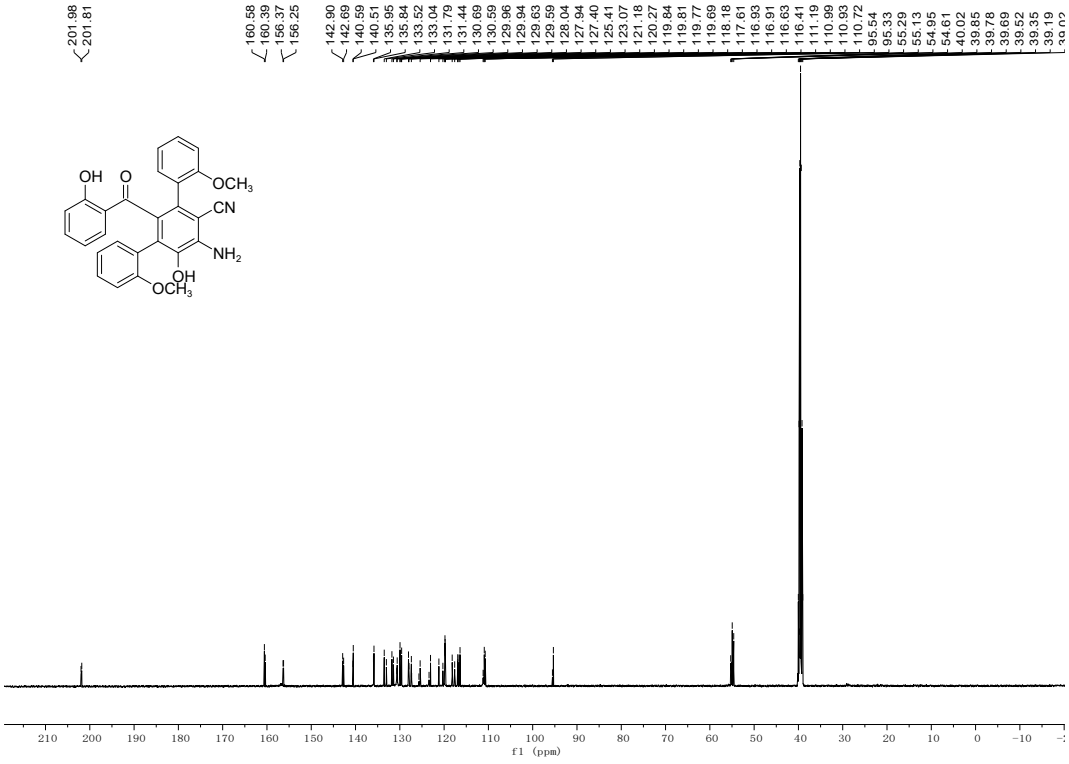
^{13}C NMR spectra for compound 4n (125 MHz, DMSO-d_6)



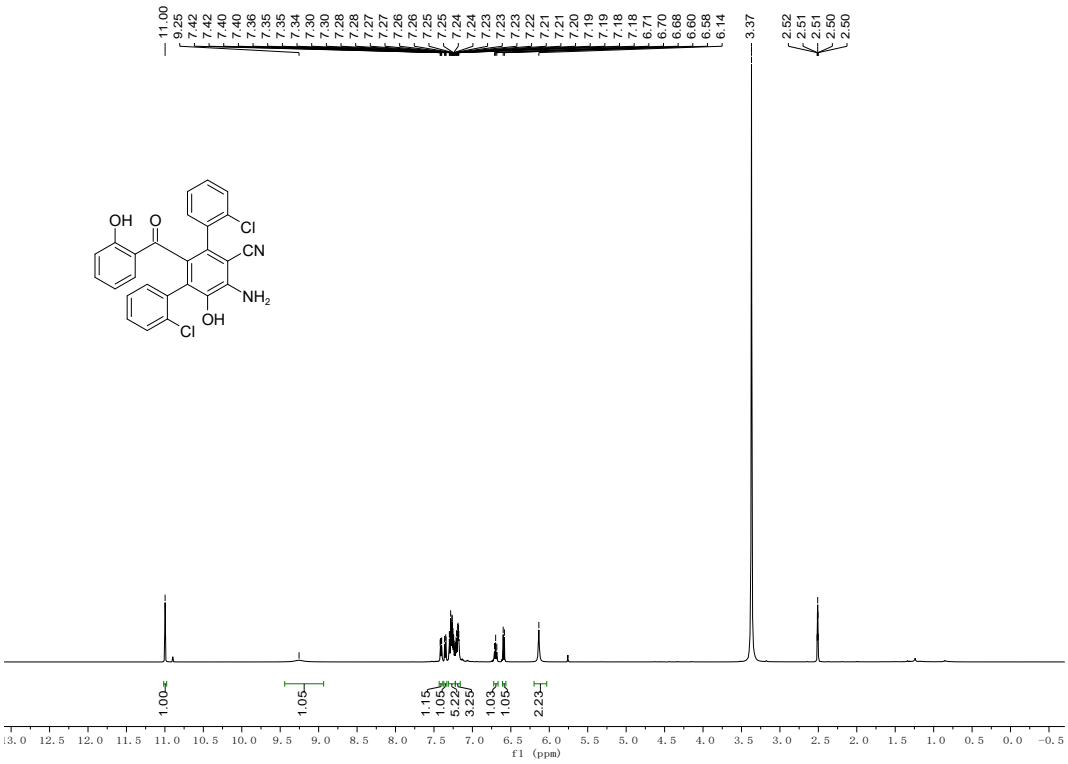
^{1}H NMR spectra for compound 4o (500 MHz, DMSO-d_6)



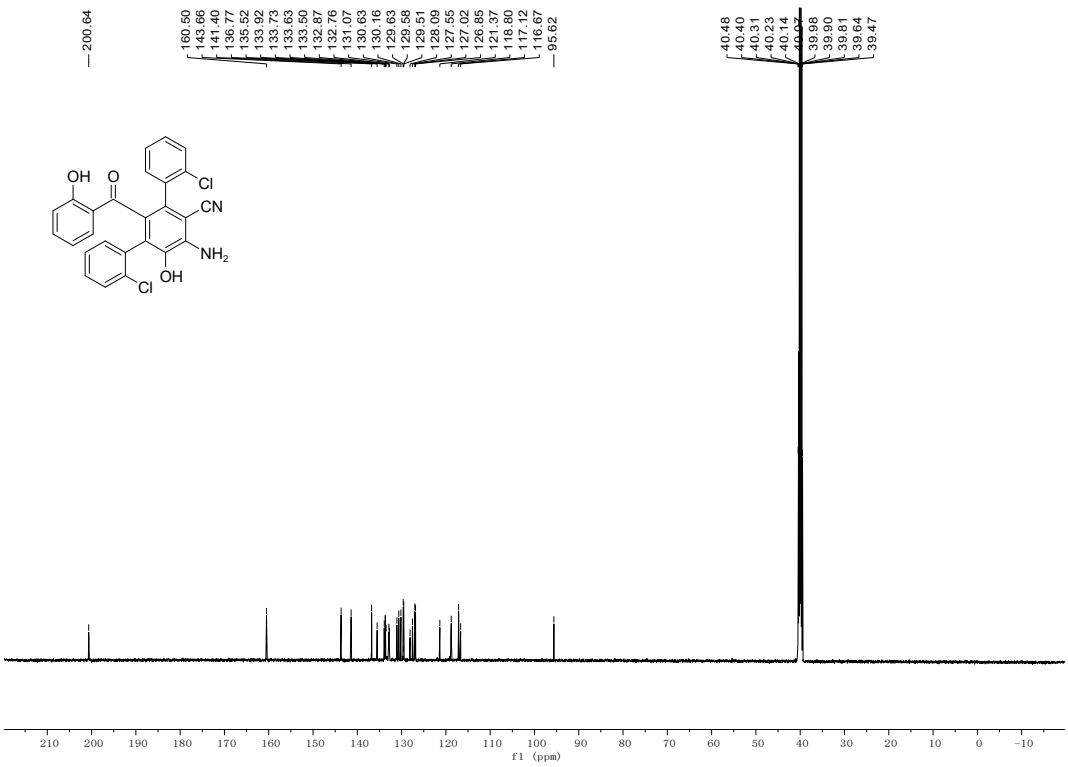
^{13}C NMR spectra for compound 4o (125 MHz, DMSO-d_6)



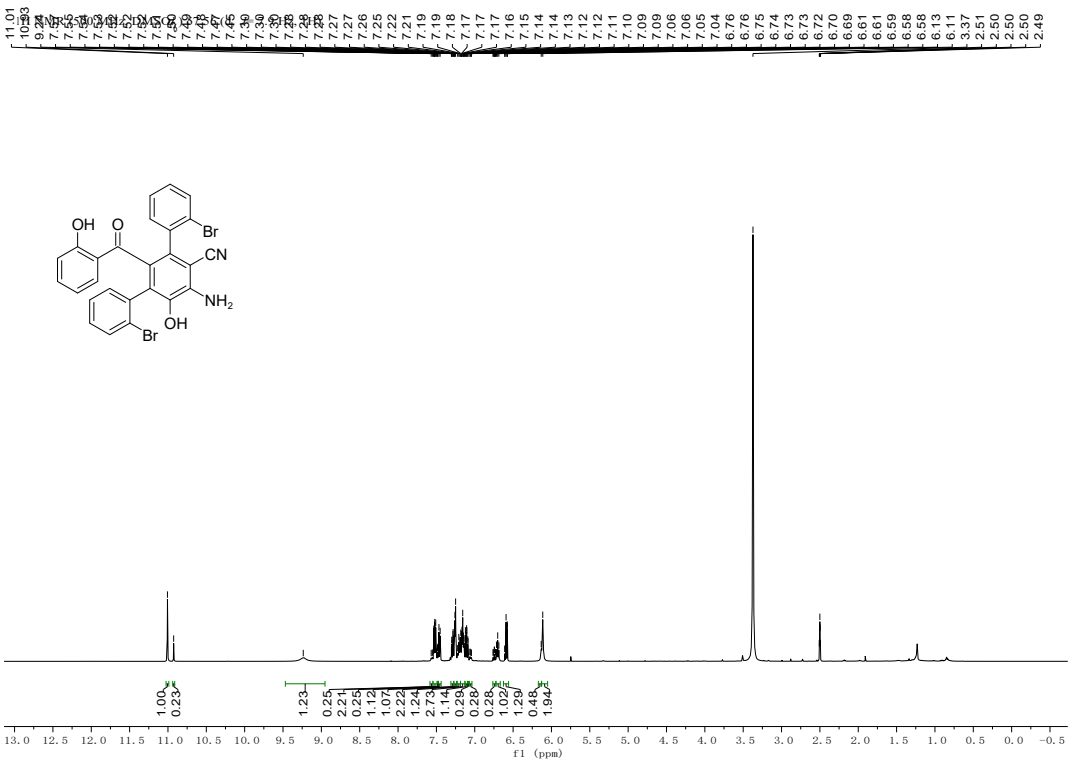
^{1}H NMR spectra for compound 4p (500 MHz, DMSO-d_6)



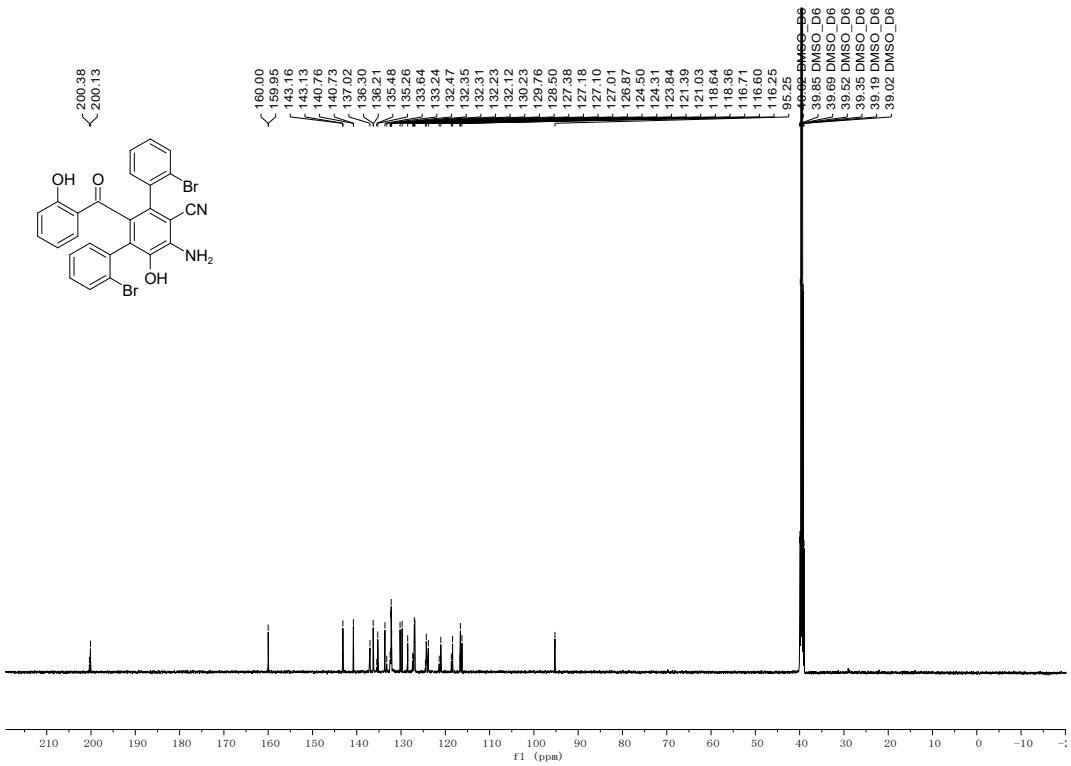
^{13}C NMR spectra for compound 4p (125 MHz, DMSO-d_6)



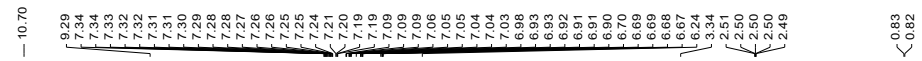
^{1}H NMR spectra for compound 4q (500 MHz, DMSO-d_6)

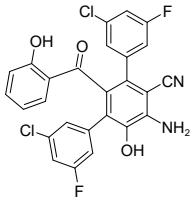


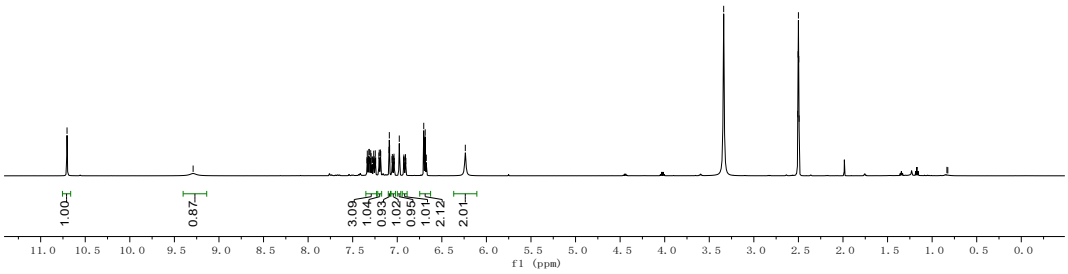
^{13}C NMR spectra for compound 4q (125 MHz, DMSO-d_6)



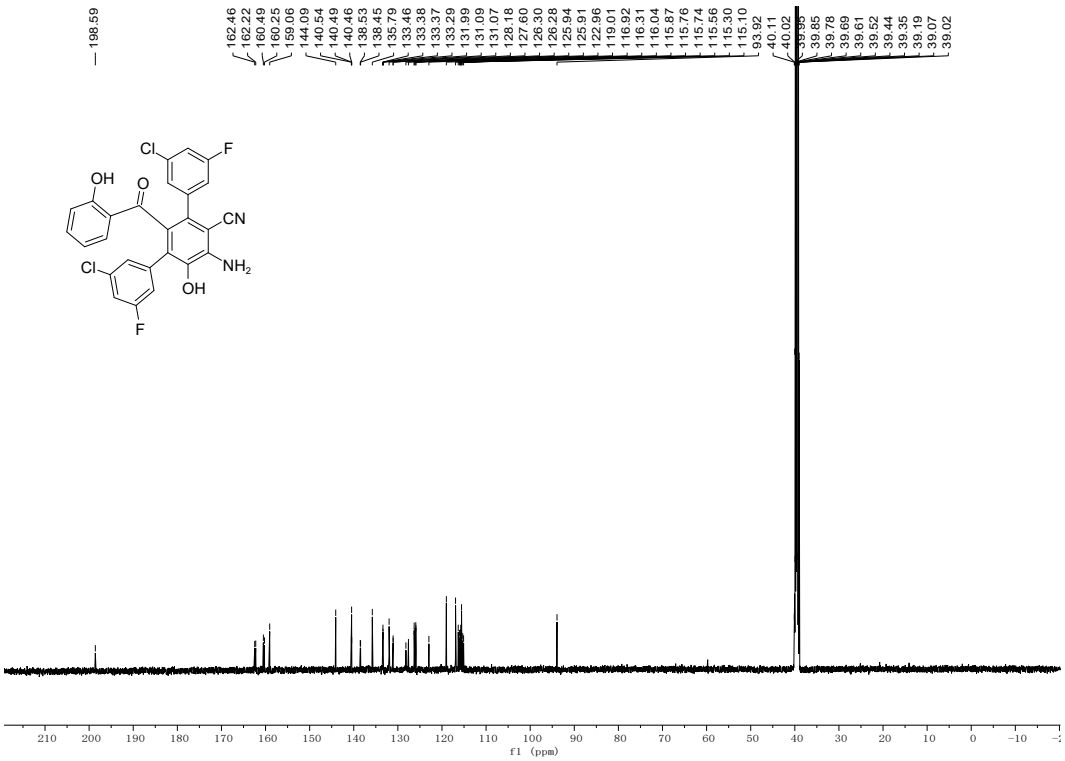
^{1}H NMR spectra for compound 4r (500 MHz, DMSO-d_6)



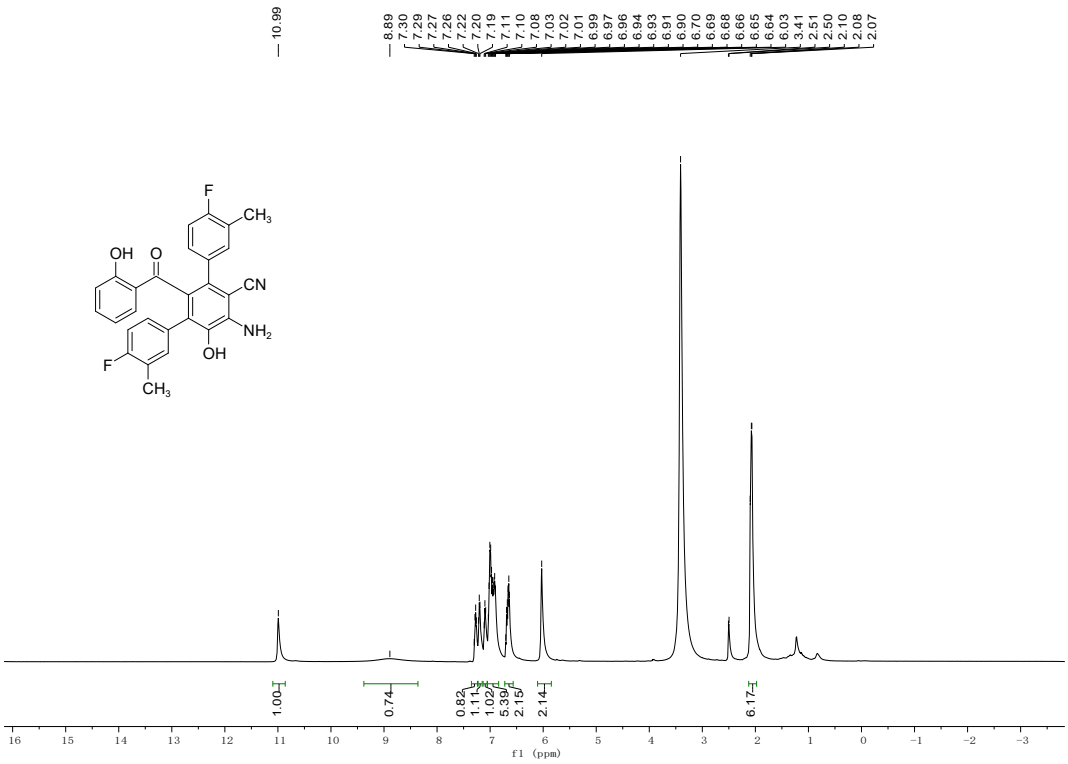




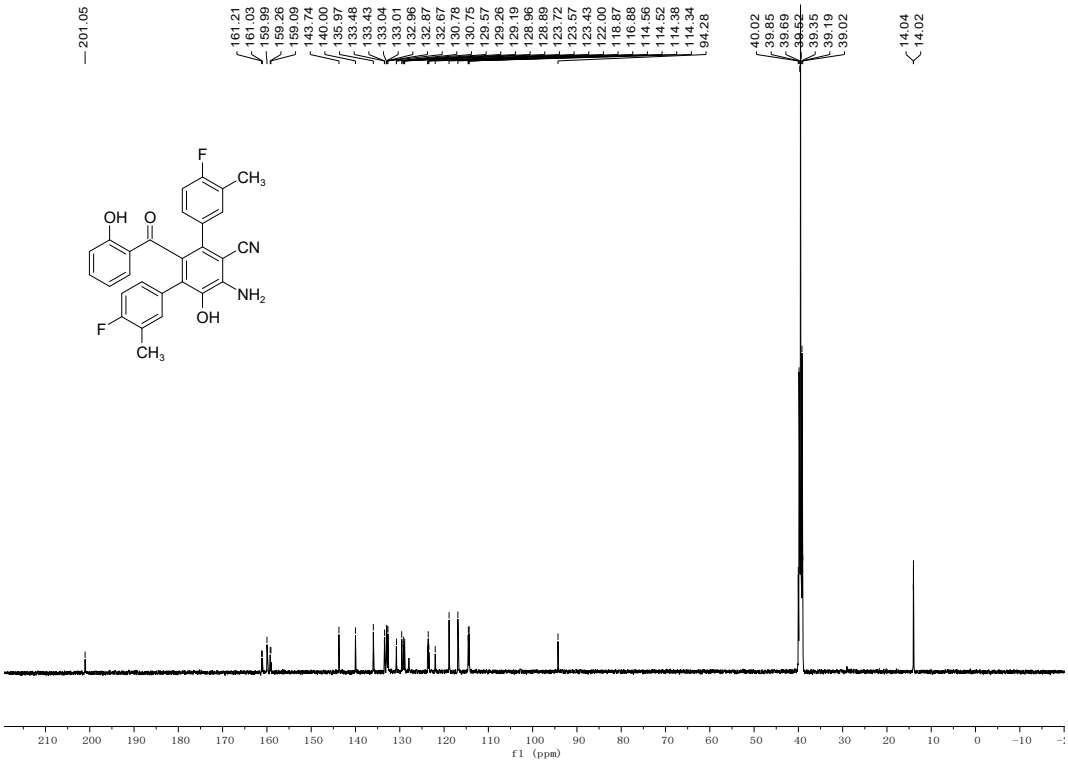
^{13}C NMR spectra for compound 4r (125 MHz, DMSO-d_6)



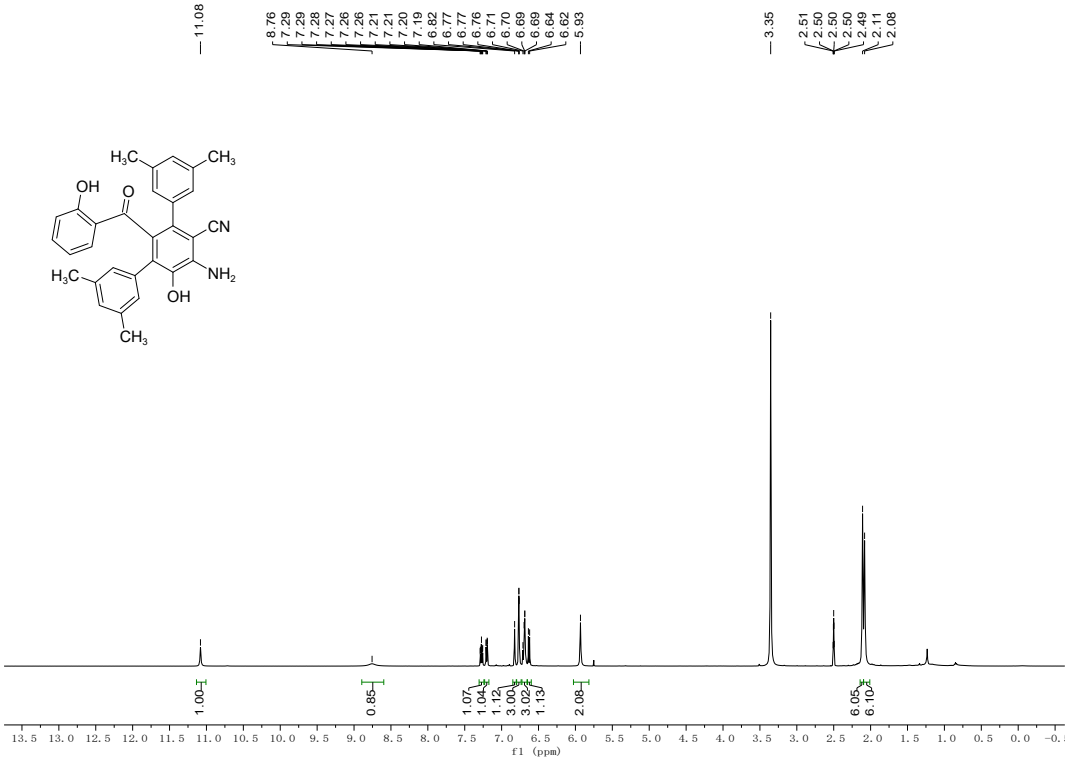
^{1}H NMR spectra for compound 4s (500 MHz, DMSO-d_6)



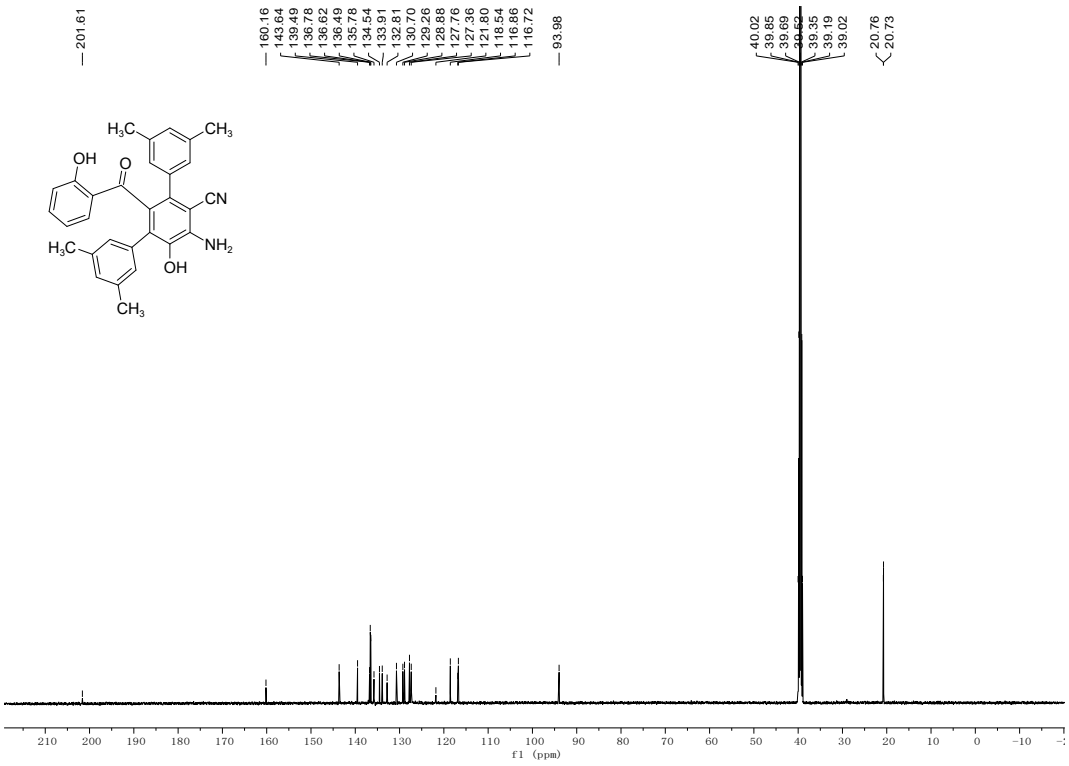
^{13}C NMR spectra for compound 4s (125 MHz, DMSO-d_6)



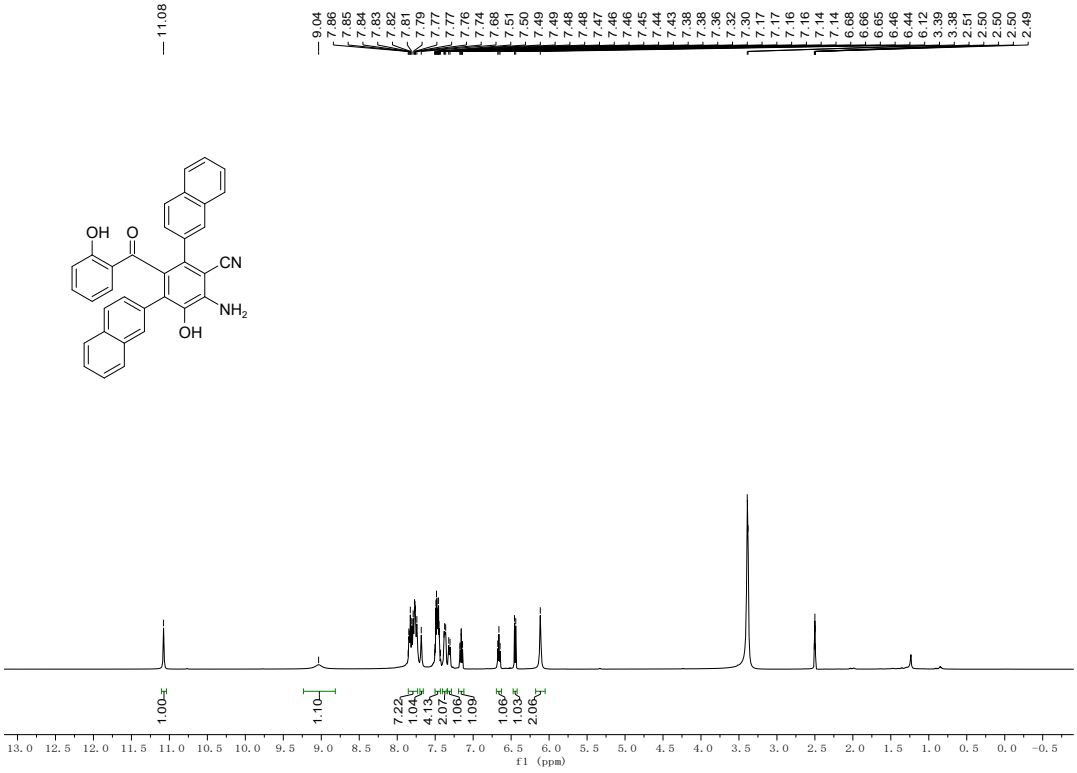
^{1}H NMR spectra for compound 4t (500 MHz, DMSO-d_6)



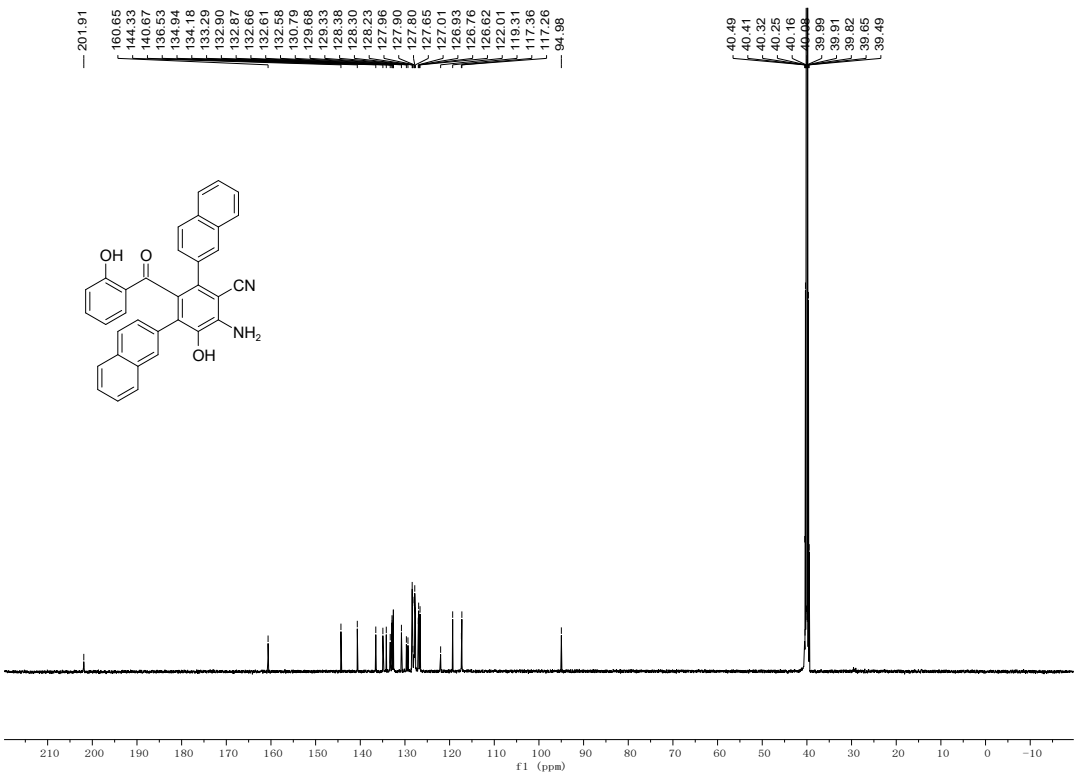
^{13}C NMR spectra for compound 4t (125 MHz, DMSO-d_6)



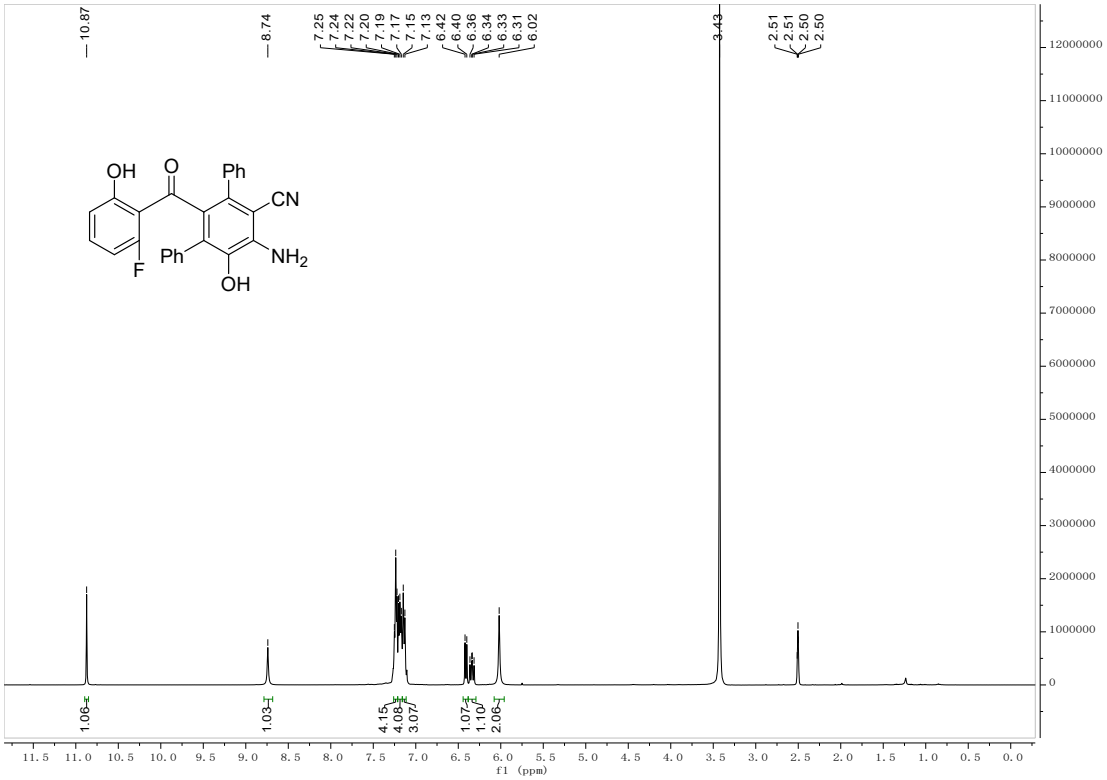
^{1}H NMR spectra for compound 4v (500 MHz, DMSO-d_6)



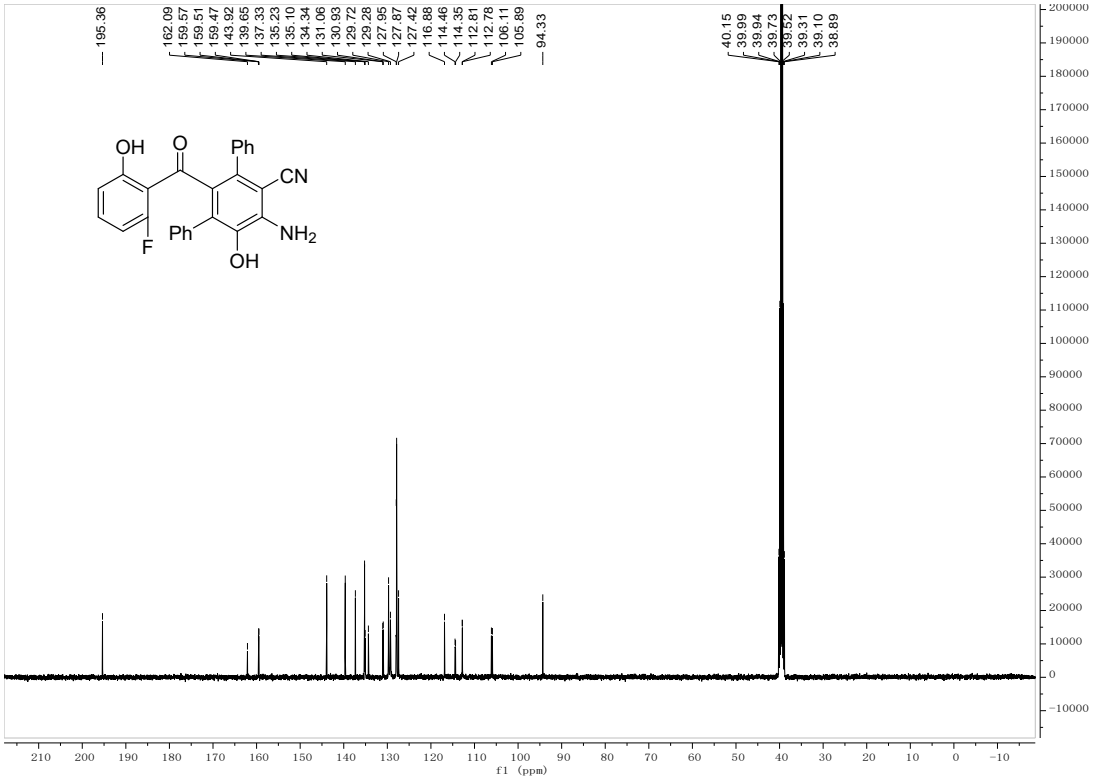
^{13}C NMR spectra for compound 4v (125 MHz, DMSO-d_6)



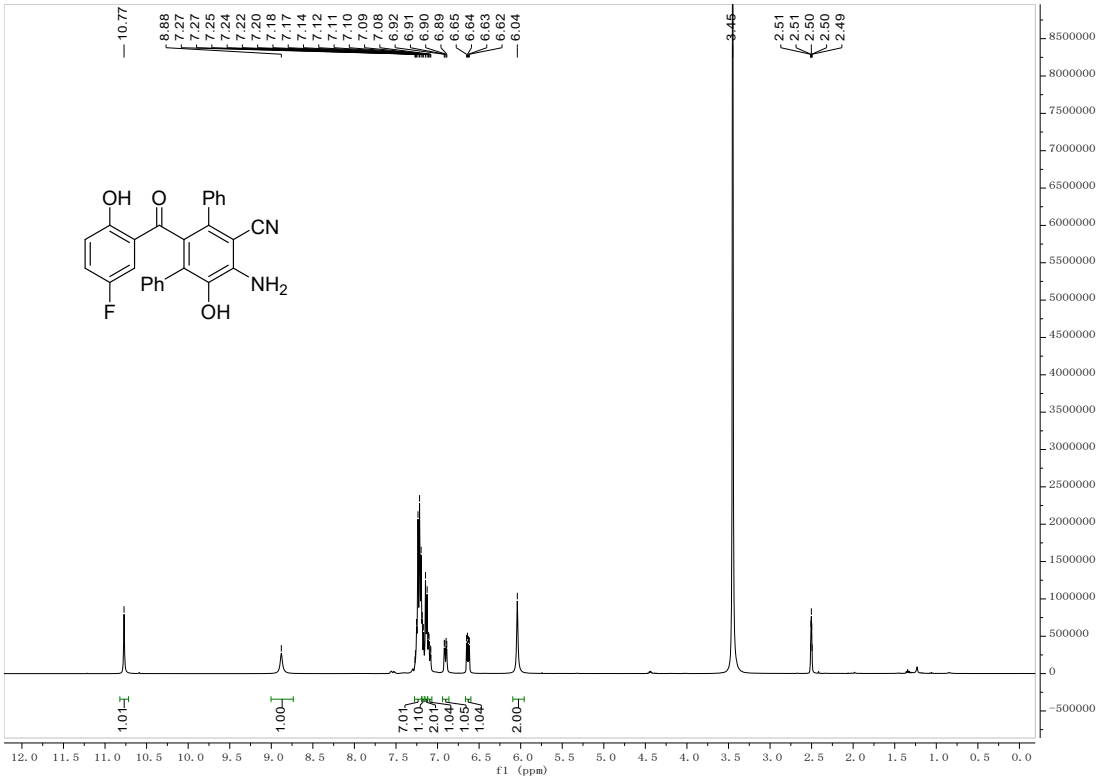
^{1}H NMR spectra for compound 4w (400 MHz, DMSO-d_6)



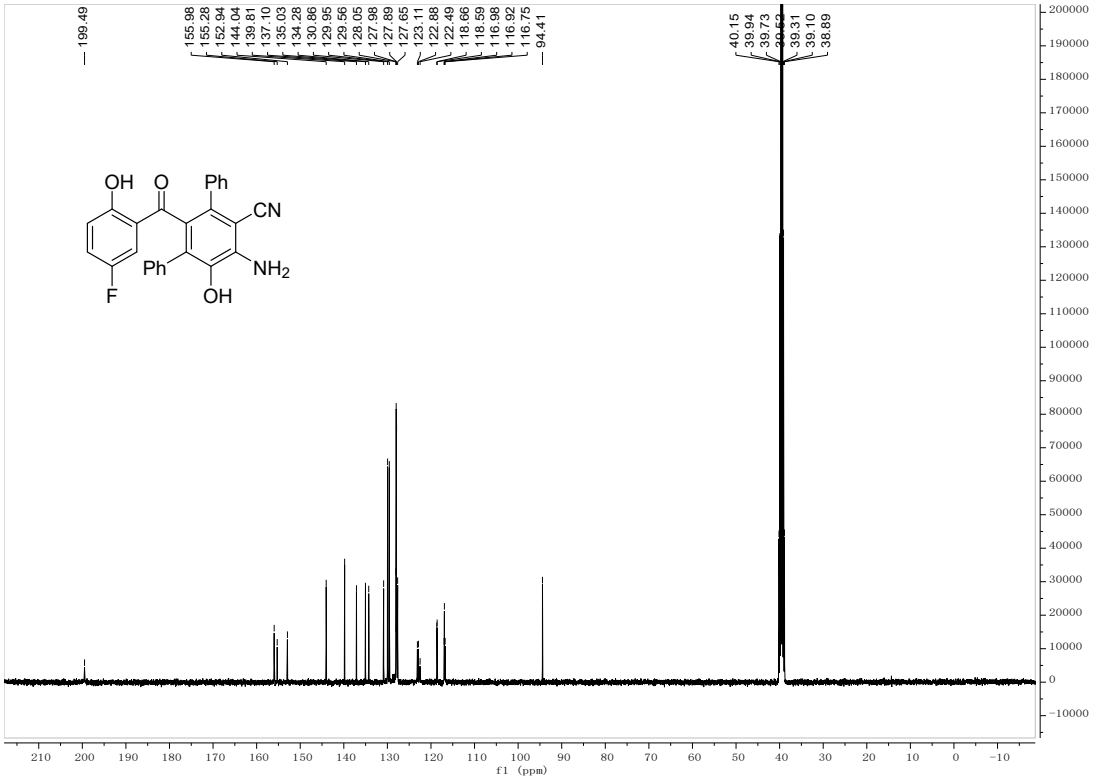
^{13}C NMR spectra for compound 4w (100 MHz, DMSO-d_6)



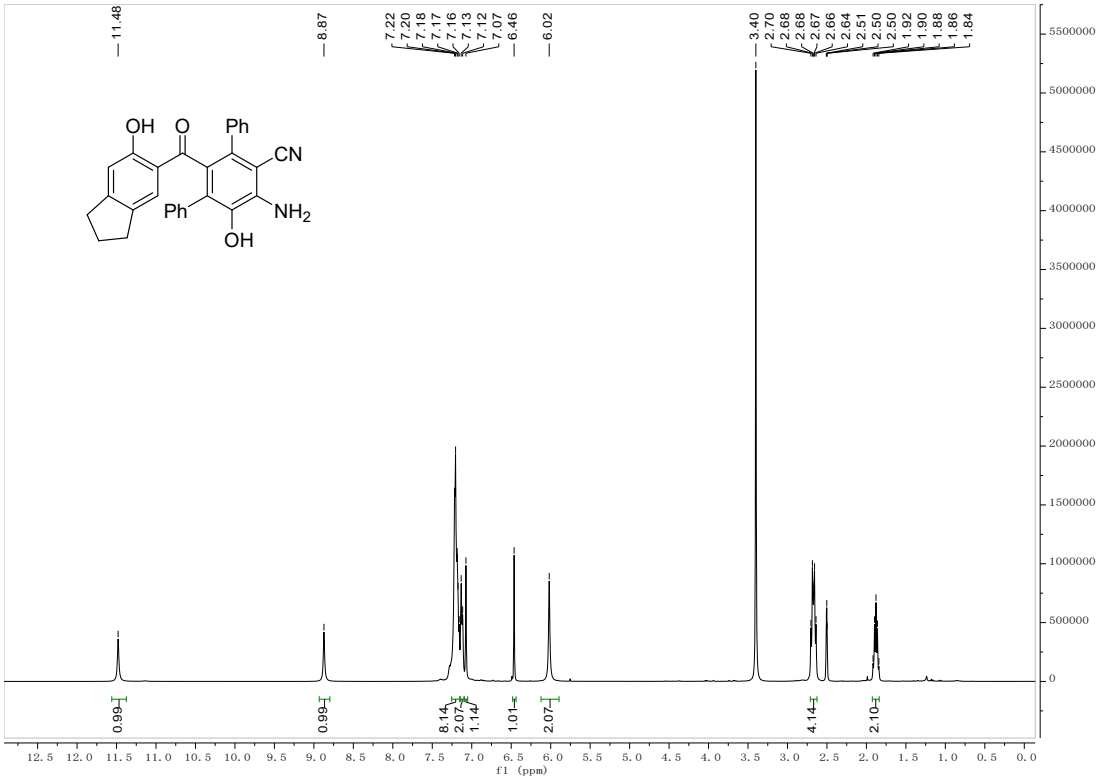
^{1}H NMR spectra for compound 4x (400 MHz, DMSO-d_6)



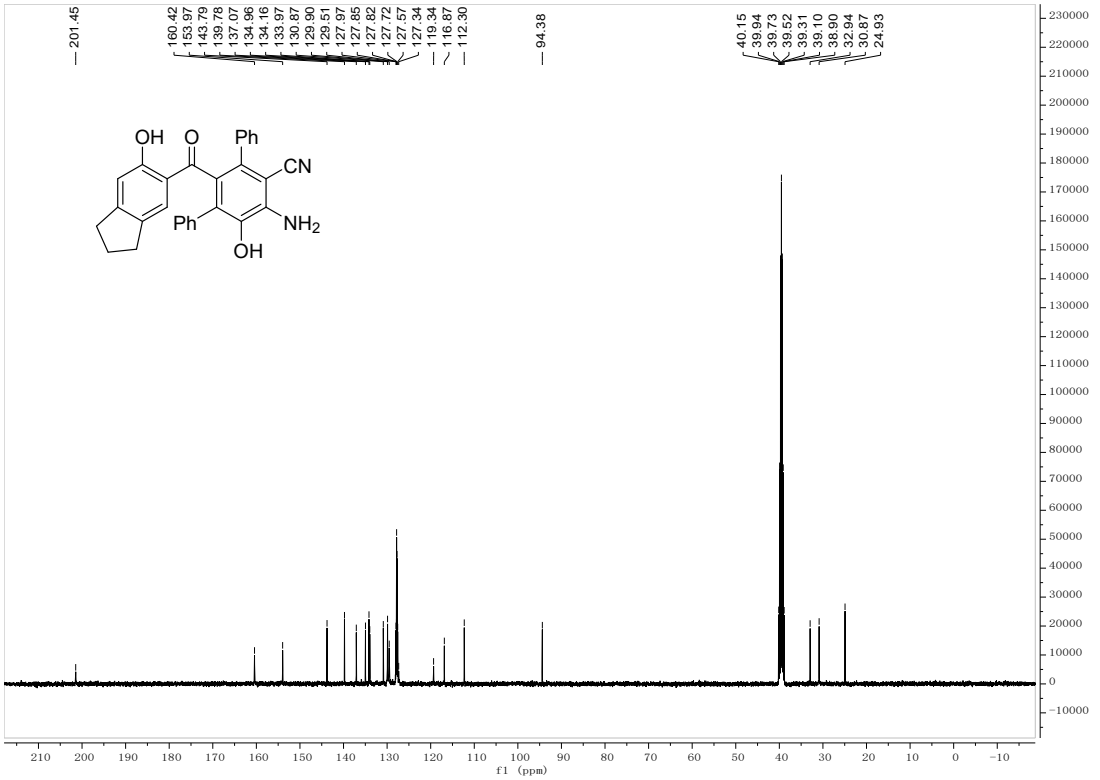
^{13}C NMR spectra for compound 4x (100 MHz, DMSO-d_6)



^{1}H NMR spectra for compound 4y (400 MHz, DMSO-d_6)

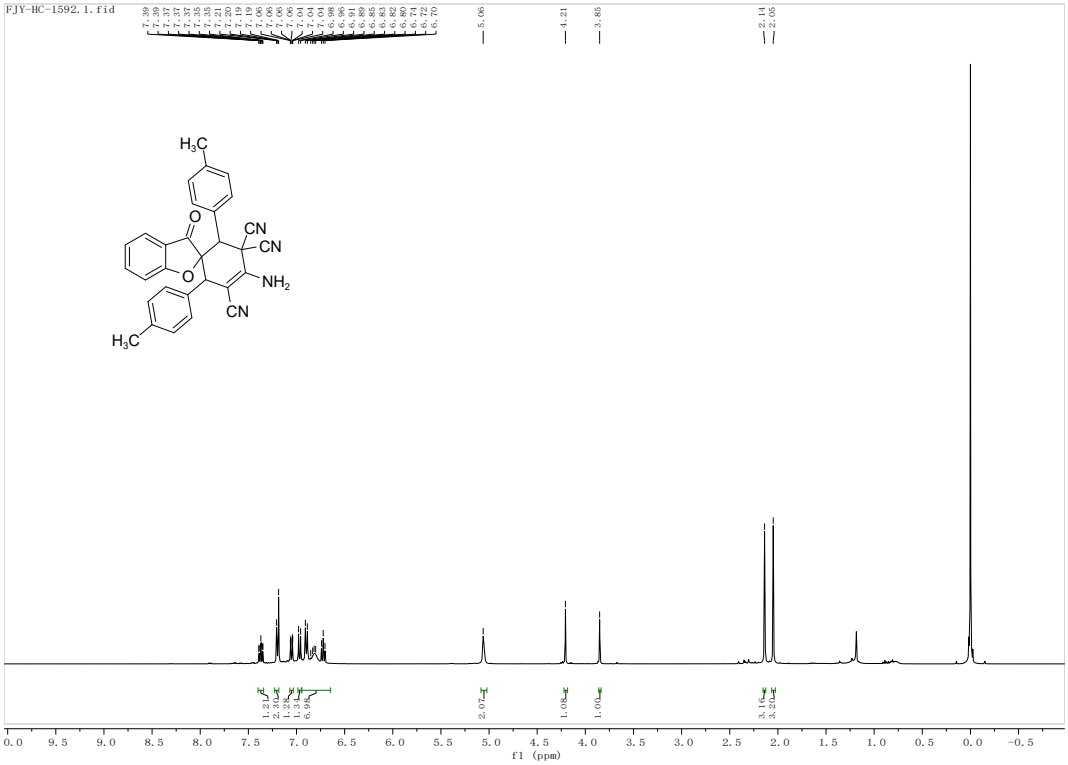


^{13}C NMR spectra for compound 4y (100 MHz, DMSO-d_6)

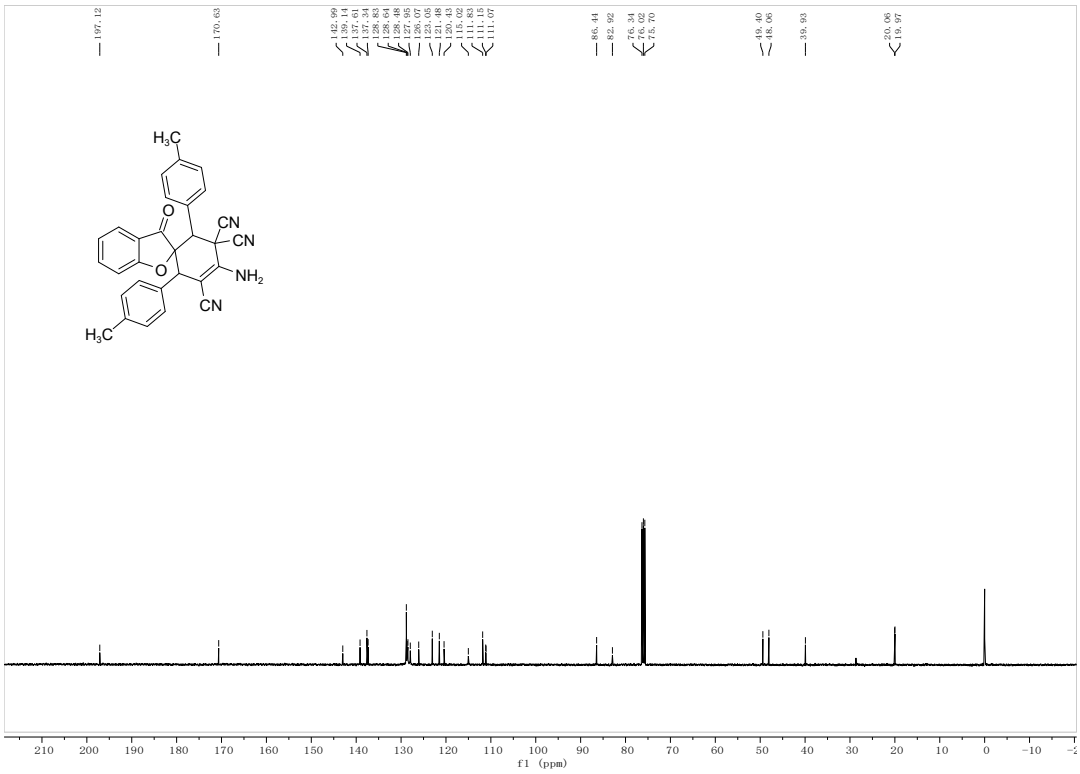


10. NMR spectra for compounds 5

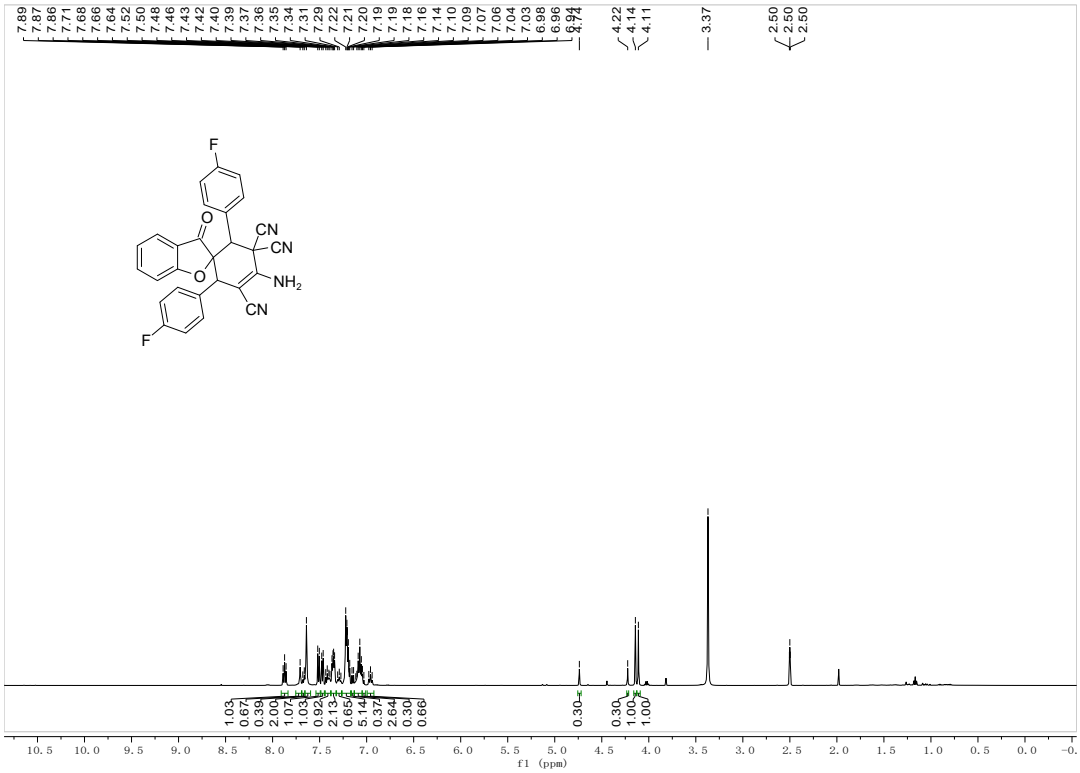
^{13}C NMR spectra for compound 5c (400 MHz, $CDCl_3$)



^{13}C NMR spectra for compound 5c (100 MHz, $CDCl_3$)



^{1}H NMR spectra for compound 5e (500 MHz, DMSO-d_6)



^{13}C NMR spectra for compound 5e (125 MHz, DMSO-d_6)