Selective Synthesis of Polyfunctionalized Hydroisoquinoline Derivatives via Three-Component Domino Reaction

Juan-Juan Zhang[a], Jun-Die Hu[a], Cheng-Pao Cao[a], Guo-Lan Dou[b], Lei Fu[a], Zhi-Bin Huang[a], Da-Qing Shi*[,a]

[a] *Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China.*

[b]*School of Safety Engineering, China University of Mining & Technology, Xuzhou 221116, P. R. China*

E-mail: dqshi@suda.edu.cn

Table of Contents

1. Experimental section

Melting points were determined using an XT-5 melting point apparatus and are uncorrected. IR spectra were recorded (cm^{-1}) with a Varian F-1000 spectrometer, using KBr. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Varian Inova-400 MHz spectrometer, in DMSO-d_6 solution. J values are in hertz. Chemical shifts are expressed in parts million downfield from TMS as an internal standard. HRMS of all the compounds were obtained using a Bruker MicrOTOF-QII mass spectrometer with an ESI resource. General Methods. Microwave irradiation experiments were conducted in an Initiator 2.5 Microwave system (Biotage, Uppsala, Sweden). The reaction temperatures were measured using an infrared detector during the microwave heating stages. All chemicals and solvents were used without further purification, unless otherwise stated.

2. General procedure

General procedure for the synthesis of compounds 4

Glutaraldehyde (**1**, 50% solution, 0.200 g, 1 mmol), malononitrile (**2**, 0.132 g, 2 mmol) and acyclic 1,3-dicarbonyl compounds (**3**, 1 mmol) were placed in a 10 mL Initiator reactor vial, followed by NaOH (0.004 g, 0.1 mmol) and EtOH (2 mL). The reaction vial was then sealed and prestirred for 10 s before being irradiated in the microwave (time, 10 min; temperature, 100 ℃; absorption level, high; fixed hold time) until TLC (3:1 mixture of petroleum ether and acetone) revealed the complete consumption of the starting materials. The reaction mixture was then cooled to room temperature and diluted with cold water (20 mL) to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the desired product. The products were further identified using FTIR and NMR spectroscopies, and HRMS.

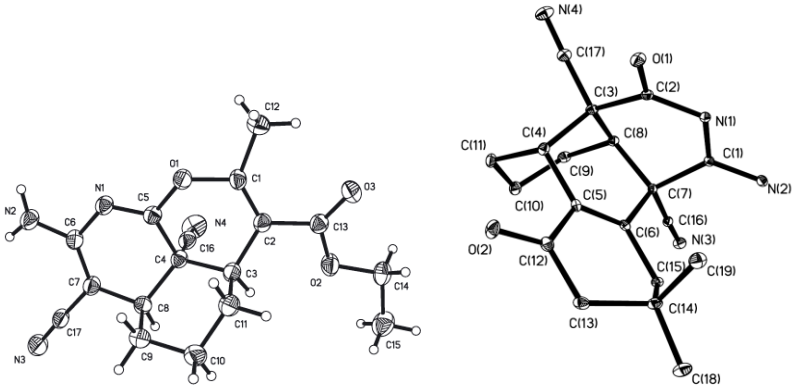
General procedure for the synthesis of compounds 6

Glutaraldehyde (**1**, 50% solution, 0.200 g, 1 mmol), malononitrile (**2**, 0.132 g, 2 mmol) and cyclic 1,3-dicarbonyl compounds (**5**, 1 mmol) were placed in a 10-mL Initiator reactor vial, followed by NaOH (0.004 g, 0.1 mmol) and and EtOH (2 mL)

The reaction vial was then sealed and prestirred for 10 s before being irradiated in the microwave (time, 10 min; temperature, 100 ℃; absorption level, high; fixed hold time) until TLC (petroleum ether/ acetone 3/1) revealed the complete consumption of the starting materials. The reaction mixture was then cooled to room temperature and diluted with cold water (20 mL) to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the desired product. The products were further identified using FTIR and NMR spectroscopies, and HRMS.

3.Analytical data of polyfunctionalized hydroisoquinoline derivatives

Crystal date of compound 4a and **6a**



4a **6a**

Table 1 Crystallographic Data of Compound **4a**

Empirical formula	$C_{17}H_{18}N_4O_3$	
Formula weight	326.35	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
space group	P-1	
Unit cell dimensions	a = 7.9219(8) Å	α = 108.694(2) °
	b = 10.2365(13) Å	β = 105.2940(10) °
	c = 11.9557(14) Å	γ = 100.3700(10) °
Volume	847.90(17) $Å^3$	
Z	2	
Calculated density	1.278 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	344	

Crystal size	0.32 × 0.30 × 0.23 mm
Theta range for data collection	2.78 to 25.02 °
Limiting indices	$-9 \le h \le 8$, $-12 \le k \le 9$, $-9 \le l \le 14$
Independent reflections	2490 [R(int) = 0.0383]
Data / restraints / parameters	2940 / 0 / 220
Goodness-of-fit on F2	0.969
Final R indices [I>2σ(I)]	$R_1 = 0.0549$, $wR_2 = 0.1125$
R indices (all data)	$R_1 = 0.1167$, $wR_2 = 0.1396$
Largest diff. peak and hole	0.178 and -0.201 e. $Å^{-3}$

Table 2 Selected bond lengths (Å) of compound **4a**

Bond	Bond Lengths	Bond	Bond Lengths	Bond	Bond Lengths
N(1)-C(5)	1.264(3)	C(1)-C(2)	1.327(4)	C(7)-C(17)	1.417(4)
N(1)-C(6)	1.417(3)	C(1)-C(12)	1.490(4)	C(7)-C(8)	1.514(4)
N(2)-C(6)	1.344(3)	C(2)-C(13)	1.486(4)	C(8)-C(9)	1.535(4)
N(3)-C(17)	1.143(3)	C(2)-C(3)	1.508(4)	C(9)-C(10)	1.521(4)
N(4)-C(16)	1.139(4)	C(3)-C(11)	1.528(4)	C(10)-C(11)	1.510(4)
O(1)-C(5)	1.359(3)	C(3)-C(4)	1.544(4)	C(14)-C(15)	1.502(4)
O(1)-C(1)	1.410(3)	C(4)-C(16)	1.494(4)		
O(2)-C(13)	1.336(3)	C(4)-C(5)	1.513(4)		
O(2)-C(14)	1.445(3)	C(4)-C(8)	1.551(4)		
O(3)-C(13)	1.200(3)	C(6)-C(7)	1.358(4)		

Table 3 Selected bond angles (°) of compound **4a**

Angles	(°)	Angles	(°)
C(5)-N(1)-C(6)	117.2(2)	O(1)-C(5)-C(4)	118.2(2)
C(5)-O(1)-C(1)	121.4(2)	N(2)-C(6)-C(7)	125.9(3)
C(13)-O(2)-C(14)	117.3(2)	N(2)-C(6)-N(1)	112.0(2)
C(2)-C(1)-O(1)	120.9(3)	C(7)-C(6)-N(1)	122.1(3)
C(2)-C(1)-C(12)	131.3(3)	C(6)-C(7)-C(17)	121.2(3)
O(1)-C(1)-C(12)	107.7(2)	C(6)-C(7)-C(8)	120.3(3)
C(1)-C(2)-C(13)	121.6(3)	C(17)-C(7)-C(8)	118.0(2)
C(1)-C(2)-C(3)	119.3(3)	C(7)-C(8)-C(9)	111.2(2)
C(13)-C(2)-C(3)	118.9(2)	C(7)-C(8)-C(4)	108.5(2)
C(2)-C(3)-C(11)	109.6(2)	C(9)-C(8)-C(4)	112.0(2)
C(2)-C(3)-C(4)	109.7(2)	C(10)-C(9)-C(8)	112.4(3)
C(11)-C(3)-C(4)	112.4(2)	C(11)-C(10)-C(9)	109.3(3)
C(16)-C(4)-C(5)	105.0(2)	C(10)-C(11)-C(3)	112.0(3)
C(16)-C(4)-C(3)	108.6(2)	O(3)-C(13)-O(2)	123.7(3)
C(5)-C(4)-C(3)	111.7(2)	O(3)-C(13)-C(2)	126.8(3)
C(16)-C(4)-C(8)	109.6(2)	O(2)-C(13)-C(2)	109.5(3)

C(5)-C(4)-C(8)	108.5(2)	O(2)-C(14)-C(15)	105.9(3)
C(3)-C(4)-C(8)	113.2(2)	N(4)-C(16)-C(4)	178.3(4)
N(1)-C(5)-O(1)	115.3(2)	N(3)-C(17)-C(7)	177.8(3)
N(1)-C(5)-C(4)	126.4(3)		

Table 1 Crystallographic Data of Compound **6a**

Empirical formula	$C_{19}H_{20}N_4O_2$	
Formula weight	336.39	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
space group	$P2_1/c$	
Unit cell dimensions	a = 7.7983(8) Å	α =90 °
	b = 15.7822(14) Å	β = 98.5090(10) °
	c = 14.3700(13) Å	γ =90 °
Volume	1749.1(3) $Å^3$	
Z	4	
Calculated density	1.277 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	712	
Crystal size	0.23 ×0.18 ×0.15 mm	
Theta range for data collection	2.58 to 25.02 °	
Limiting indices	$-9 \le h \le 8$, $-15 \le k \le 18$, $-15 \le l \le 17$	
Independent reflections	3081 [R(int) = 0.0546]	
Data / restraints / parameters	3081 / 0 / 228	
Goodness-of-fit on F2	1.032	
Final R indices [I>2σ(I)]	R_1 = 0.0578, wR_2 = 0.0975	
R indices (all data)	R_1 = 0.1009, wR_2 = 0.1226	
Largest diff. peak and hole	0.199 and -0.233 e. $Å^{-3}$	

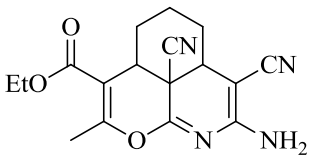
Table 2 Selected bond lengths (Å) of compound **6a**

Bond	Bond Lengths	Bond	Bond Lengths	Bond	Bond Lengths
N(1)-C(1)	1.315(3)	C(3)-C(8)	1.537(4)	C(8)-C(9)	1.531(4)
N(1)-C(2)	1.373(3)	C(3)-C(4)	1.561(3)	C(9)-C(10)	1.524(4)
N(2)-C(1)	1.314(3)	C(4)-C(5)	1.511(4)	C(10)-C(11)	1.530(4)
N(3)-C(16)	1.143(3)	C(4)-C(11)	1.540(4)	C(12)-C(13)	1.487(4)
N(4)-C(17)	1.143(3)	C(5)-C(6)	1.334(4)	C(13)-C(14)	1.528(4)
O(1)-C(2)	1.225(3)	C(5)-C(12)	1.493(3)	C(14)-C(18)	1.529(4)
O(2)-C(12)	1.229(3)	C(6)-C(15)	1.508(3)	C(14)-C(19)	1.534(4)
C(1)-C(7)	1.539(4)	C(6)-C(7)	1.541(3)	C(14)-C(15)	1.540(3)
C(2)-C(3)	1.550(4)	C(7)-C(16)	1.478(3)		

C(3)-C(17)	1.480(4)	C(7)-C(8)	1.555(3)		

Table 3 Selected bond angles (°) of compound **6a**

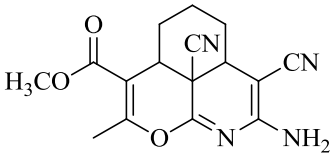
Angles	(°)	Angles	(°)
C(1)-N(1)-C(2)	120.4(2)	C(16)-C(7)-C(8)	109.1(2)
N(2)-C(1)-N(1)	120.3(3)	C(1)-C(7)-C(8)	105.05(19)
N(2)-C(1)-C(7)	119.5(2)	C(6)-C(7)-C(8)	114.4(2)
N(1)-C(1)-C(7)	120.1(2)	C(9)-C(8)-C(3)	112.7(2)
O(1)-C(2)-N(1)	121.3(3)	C(9)-C(8)-C(7)	115.8(2)
O(1)-C(2)-C(3)	118.3(3)	C(3)-C(8)-C(7)	104.4(2)
N(1)-C(2)-C(3)	120.4(2)	C(10)-C(9)-C(8)	114.2(2)
C(17)-C(3)-C(8)	111.5(2)	C(9)-C(10)-C(11)	111.4(2)
C(17)-C(3)-C(2)	106.3(2)	C(10)-C(11)-C(4)	110.9(2)
C(8)-C(3)-C(2)	111.8(2)	O(2)-C(12)-C(13)	121.7(2)
C(17)-C(3)-C(4)	110.4(2)	O(2)-C(12)-C(5)	119.2(3)
C(8)-C(3)-C(4)	107.4(2)	C(13)-C(12)-C(5)	119.1(3)
C(2)-C(3)-C(4)	109.4(2)	C(12)-C(13)-C(14)	114.9(2)
C(5)-C(4)-C(11)	111.0(2)	C(13)-C(14)-C(18)	109.9(2)
C(5)-C(4)-C(3)	108.0(2)	C(13)-C(14)-C(19)	110.9(2)
C(11)-C(4)-C(3)	110.4(2)	C(18)-C(14)-C(19)	108.8(3)
C(6)-C(5)-C(12)	118.8(2)	C(13)-C(14)-C(15)	107.2(2)
C(6)-C(5)-C(4)	123.8(2)	C(18)-C(14)-C(15)	109.5(2)
C(12)-C(5)-C(4)	117.3(2)	C(19)-C(14)-C(15)	110.6(2)
C(5)-C(6)-C(15)	123.2(2)	C(6)-C(15)-C(14)	112.4(2)
C(5)-C(6)-C(7)	120.2(2)	N(3)-C(16)-C(7)	177.1(3)
C(15)-C(6)-C(7)	116.4(2)	N(4)-C(17)-C(3)	178.3(3)
C(16)-C(7)-C(1)	110.7(2)	C(16)-C(7)-C(6)	112.0(2)
C(1)-C(7)-C(6)	105.3(2)		



Ethyl 8-amino-3a^1,7-dicyano-2-methyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4a)

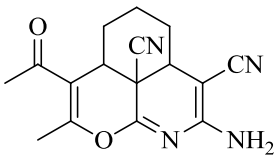
Yellow solid, 0.245 g, yield 75%; mp 188–190 ℃. IR (KBr): 3389, 2964, 2167, 1650, 1638, 1560, 1543, 1323, 1320, 1230, 1175, 1000, 878, 746 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.95 (s, 2H, NH_2), 4.30–4.17 (m, 2H, CH_2O), 3.22–3.16 (m, 1H, CH), 2.98–2.94 (m, 1H, CH), 2.38 (s, 3H, CH_3), 1.91–1.82 (m, 2H, 2 × CH), 1.49–1.46 (m, 1H, CH), 1.28–1.25 (m, 4H, CH_3 and CH), 1.04–0.98 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 196.8, 159.4, 159.1, 156.5,

120.5, 120.4, 117.7, 59.9, 37.8, 35.6, 30.5, 29.6, 28.6, 20.5, 19.4; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{19}N_4O_3$ [$(M+H)^+$], 327.1457; found, 327.1460.



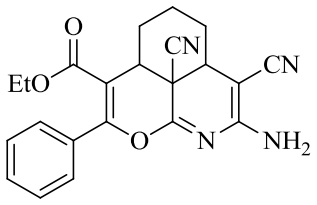
Methyl 8-amino-3a[1],7-dicyano-2-methyl-3a,3a[1],4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4b)

Yellow solid, 0.219 g, yield 70%; mp 228–230 ℃. IR (KBr): 3394, 2958, 2189, 1655, 1584, 1443, 1368, 1320, 1258, 1134, 1103, 885, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.96 (s, 2H, NH_2), 3.76 (s, 3H, CH_3O), 3.24–3.20 (m, 1H, CH), 2.98–2.93 (m, 1H, CH), 2.38 (s, 3H, CH_3), 1.92–1.82 (m, 2H, 2 × CH), 1.48–1.45 (m, 1H, CH), 1.32–1.23 (m, 1H, CH), 1.07–0.95 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.5, 160.4, 159.2, 156.4, 120.4, 117.7, 111.7, 60.0, 52.7, 39.3, 37.6, 35.6, 29.6, 28.6, 20.3, 18.8; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}N_4O_3$ [$(M+H)^+$], 313.1301; found, 313.1298.



3-Acetyl-8-amino-2-methyl-3a,3a[1],4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3a[1],7-dicarbonitrile (4c)

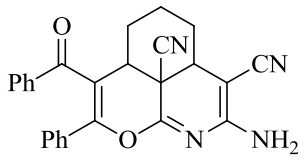
Yellow solid, 0.213 g, yield 72%; mp 258–260 ℃. IR (KBr): 3356, 2964, 2177, 1642, 1669, 1559, 1551, 1332, 1326, 1238, 1115, 1004, 876, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.93 (s, 2H, NH_2), 3.31–3.28 (m, 1H, CH), 2.90–2.87 (m, 1H, CH), 2.39 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.95–1.78 (m, 2H, 2 × CH), 1.49–1.46 (m, 1H, CH), 1.34–1.24 (m, 1H, CH), 1.05–0.96 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.1, 160.2, 159.2, 156.4, 120.4, 117.8, 111.8, 61.52, 60.0, 39.3, 37.6, 35.7, 29.7, 28.7, 20.3, 18.9, 14.5; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}N_4O_2$ [$(M+H)^+$], 297.1352; found, 297.1327.



Ethyl 8-amino-3a[1],7-dicyano-2-phenyl-3a,3a[1],4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4d)

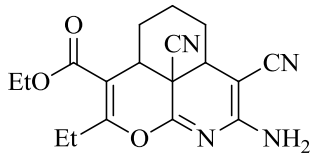
Yellow solid, 0.311 g, yield 80%; mp 228–230 ℃. IR (KBr): 3356, 2956, 2167, 1652, 1649, 1579, 1571, 1392, 1326, 1249, 1123, 1000, 879, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.53–7.34 (m, 5H, ArH), 7.01 (s, 2H,

NH_2), 4.01 (q, *J* = 6.8 Hz, 2H, CH_2O), 3.34–3.23 (m, 1H, CH), 3.02 (d, *J* = 8.4 Hz, 1H, CH), 2.09 (d, *J* = 11.4 Hz, 1H, CH), 1.88 (d, *J* = 11.8 Hz, 1H, CH), 1.55–1.52 (m, 1H, CH), 1.36–1.19 (m, 2H, 2 × CH), 1.12–1.03 (m, 1H, CH), 0.91 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.5, 159.4 , 157.3, 156.36 , 132.3, 131.1, 129.0, 128.7, 120.4, 117.7, 113.4, 61.5, 60.1, 39.5, 37.6, 36.8, 29.6, 28.7, 20.3, 13.8; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_4O_3$ [$(M+H)^+$], 389.1614; found, 389.1609.



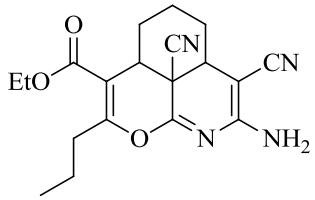
8-Amino-3-benzoyl-2-phenyl-2,3,3a,3a^1,4,5,6,6a-octahydropyrano[4,3,2-*ij*]isoquinoline-3a^1,7-dicarbonitrile (4e)

Yellow solid, 0.215 g, yield 51%; mp 238–240 ℃. IR (KBr): 3359, 2952, 2166, 1663, 1638, 1587, 1564, 1383, 1333, 1247, 1124, 1004, 875, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.66–7.64 (m, 2H, ArH), 7.39–7.36 (m, 1H, ArH), 7.28–7.18 (m, 7H, ArH), 7.04 (s, 2H, NH_2), 3.32–3.29 (m, 1H, CH), 3.04–3.00 (m, 1H, CH), 2.25–2.23 (m, 1H, CH), 1.92–1.89 (m, 1H, CH), 1.57–1.55 (m, 1H, CH), 1.46–1.31 (m, 2H, 2 × CH), 1.16–1.07 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.5, 193.3, 165.0, 151.6, 136.9, 136.8, 129.8, 129.5, 129.4, 128.4, 120.1, 118.2, 58.3, 56.8, 39.9, 39.7, 39.5, 39.3, 39.1, 28.8, 25.10, 24.9; HRMS (ESI): *m*/*z* calcd for $C_{26}H_{23}N_4O_2$ [$(M+H)^+$], 423.1821; found, 423.1834.



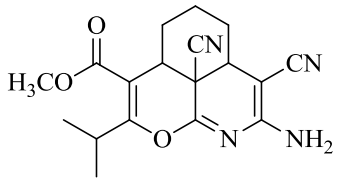
Ethyl 8-amino-3a^1,7-dicyano-2-ethyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-ij]isoquinoline-3-carboxylate (4f)

Yellow solid, 0.231 g, yield 68%; mp 148–150 ℃. IR (KBr): 3344, 2967, 2168, 1666, 1649, 1569, 1541, 1392, 1346, 1258, 1135, 989, 877, 742 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.96 (s, 2H, NH_2), 4.24–4.21 (m, 2H, CH_2O), 3.22–3.17 (m, 1H, CH), 2.98–2.93 (m, 1H, CH), 2.87–2.82 (m, 1H, CH), 2.69–2.64 (m, 1H, CH), 1.92–1.82 (m, 2H, CH_2), 1.49–1.45 (m, 1H, CH), 1.29–1.23 (m, 4H, CH_3 and CH), 1.11 (t, *J* = 7.4 Hz, 3H, CH_3), 1.05–0.96 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 164.9, 164.3, 159.6, 156.4, 120.4, 117.7, 111.4, 61.6, 60.0, 39.3, 37.5, 35.60, 29.7, 28.7, 25.2, 20.4, 14.4, 11.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}N_4O_3$ [$(M+H)^+$], 341.1614; found, 341.1592.



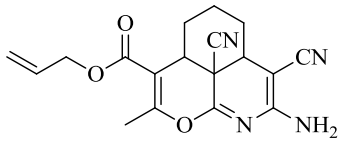
Ethyl 8-amino-3a^1,7-dicyano-2-propyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-ij]isoquinoline-3-carboxylate (4g)

Yellow solid, 0.234 g, yield 66%; mp 143–145 ℃. IR (KBr): 3339, 2956, 2164, 1655, 1645, 1556, 1575, 1333, 1216, 1148, 1025, 1000, 876, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.94 (s, 2H, NH_2), 4.25–4.19 (m, 2H, CH_2O), 3.24–3.18 (m, 1H, CH), 2.97–2.87 (m, 2H, CH_2), 2.67–2.60 (m, 1H, CH), 1.93–1.82 (m, 2H, CH_2), 1.62–1.46 (m, 3H, CH_3), 1.28–1.23 (m, 4H, 2 × CH_2), 1.10–0.95 (m, 2H, CH_2), 0.91 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.0, 163.0, 159.5, 156.4, 120.4, 117.8, 112.6, 61.6, 60.0, 39.3, 37.5, 35.8, 33.0, 29.7, 28.7, 20.4, 14.4, 13.4; HRMS (ESI): m/z calcd for $C_{19}H_{23}N_4O_3$ [(M+H)$^+$], 355.1770; found, 355.1750.



Methyl 8-amino-3a^1,7-dicyano-2-isopropyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3-carboxylate (4h)

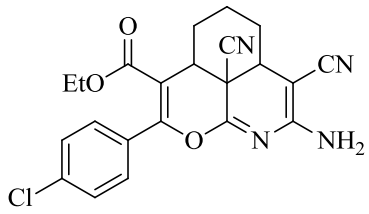
Yellow solid, 0.235 g, yield 69%; mp 238–240 ℃. IR (KBr): 3356, 2944, 2157, 1762, 1539, 1489, 1361, 1282, 1136, 1247, 1126, 1004, 889, 732 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.00 (s, 2H, NH_2), 3.85–3.79 (m, 1H, CH), 3.77 (s, 3H, CH_3O), 3.21–3.18 (m, 1H, CH), 2.97–2.92(m, 1H, CH), 1.94–1.82 (m, 2H, 2 × CH), 1.49–1.45 (m, 1H, CH), 1.29–1.23 (m, 1H, CH), 1.12–1.08 (m, 6H, 2 × CH_3), 1.03–0.97 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 166.5, 165.6, 160.2, 156.5, 120.5, 117.7, 110.7, 60.1, 52.9, 39.3, 37.4, 35.6, 29.6, 29.3, 28.4, 20.3, 19.4, 19.1; HRMS (ESI): m/z calcd for $C_{18}H_{21}N_4O_3$ [(M+H)$^+$], 341.1614; found, 341.1604.



***A*llyl 8-amino-3a^1,7-dicyano-2-methyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3-carboxylate (4i)**

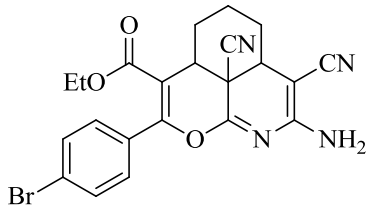
Yellow solid, 0.237 g, yield 70%; mp 248–250 ℃. IR (KBr): 3396, 2934, 2147, 1652, 1629, 1549, 1501, 1342, 1306, 1233, 1105, 1004, 875, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.94 (s, 2H, NH_2), 6.02–5.91 (m, 1H, CH), 5.36–5.24 (m, 2H, 2 × CH),

4.71 (d, J = 5.2 Hz, 2H, CH_2O), 3.26–3.20 (m, 1H, CH), 2.99–2.93 (m, 1H, CH), 2.38 (s, 3H, CH_3), 1.92–1.81 (m, 2H, 2 × CH), 1.50–1.47 (m, 1H, CH), 1.33–1.22 (m, 1H, CH), 1.09–0.97 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 166.5, 165.5, 160.0, 156.5, 120.4, 117.7, 110.7, 60.0, 52.9, 37.4, 35.6, 29.6, 29.30, 28.5, 20.3, 19.5, 19.1; HRMS (ESI): m/z calcd for $C_{18}H_{19}N_4O_3$ [$(M+H)^+$], 339.1457; found, 339.1485.



Ethyl 8-amino-2-(4-chlorophenyl)-3a^1,7-dicyano-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3-carboxylate (4j)

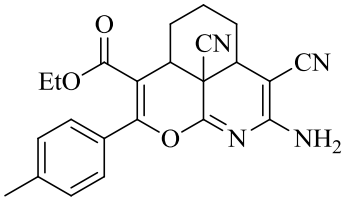
Yellow solid, 0.275 g, yield 65%; mp 120–122 ℃. IR (KBr): 2925, 2851, 2764, 2380, 2174, 1690, 1656, 1491, 1383, 1270, 1192, 1093, 1016, 844, 782, 730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.56–7.54 (m, 2H, ArH), 7.49–7.47 (m, 2H, ArH), 7.02 (s, 2H, NH_2), 4.04 (q, J = 6.8 Hz, 2H, CH_2O), 3.02 (dd, J_1 = 4.4, J_2 = 4.4 Hz, 1H, CH), 2.07 (d, J = 12.4 Hz, 1H, CH), 1.87 (d, J = 11.2 Hz, 1H, CH), 1.53 (d, J = 12.8 Hz, 1H, CH), 1.363–1.05 (m, 4H, 4 × CH), 0.95 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.1, 159.2, 156.3, 156.2, 135.8, 131.2, 131.1, 128.8, 120.3, 117.7, 113.8, 61.6, 60.0, 37.6, 36.7, 29.6, 28.6, 20.2, 13.9; HRMS (ESI): m/z calcd for $C_{22}H_{19}ClNaN_4O_3$ [$(M+Na)^+$], 445.1043; found, 445.1049.



Ethyl 8-amino-2-(4-bromophenyl)-3a^1,7-dicyano-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3-carboxylate (4k)

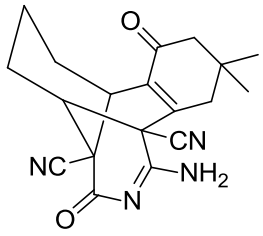
Yellow solid, 0.318 g, yield 68%; mp 216–218 ℃. IR (KBr): 2988, 2941, 2860, 2358, 2173, 1687, 1656, 1575, 1440, 1371, 1410, 1368, 1329, 1210, 1086, 834, 786, 722 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.71–7.67 (m, 2H, ArH), 7.42–7.39 (m, 2H, ArH), 7.02 (s, 2H, NH_2), 4.04 (q, J = 7.2 Hz, 2H, CH_2O), 3.02 (dd, J_1 = 4.8, J_2 = 4.8 Hz, 1H, CH), 2.07 (d, J = 11.2 Hz, 1H, CH), 1.87 (d, J = 11.2 Hz, 1H, CH), 1.53 (d, J = 13.2 Hz, 1H, CH), 1.39–0.94 (m, 4H, 4 × CH), 0.95 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.0, 159.1, 156.3, 156.2, 131.7, 131.5, 131.2,

124.6, 120.3, 117.6, 113.8, 61.6, 60.0, 37.6, 36.7, 29.6, 28.6, 20.2, 13.8; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}BrNaN_4O_3$ [$(M+Na)^+$], 489.0538; found, 489.0520.



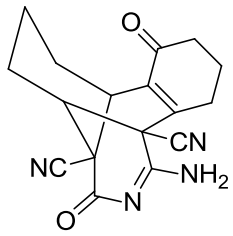
Ethyl 8-amino-3a^1,7-dicyano-2-(*p*-tolyl)-3a,3a^1,4,5,6,6a-hexa hydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4l)

Yellow solid, 0.306 g, yield 76%; mp 120–122 ℃. IR (KBr): 3336, 2985, 2935, 2864, 2362, 2175, 1692, 1658, 1578, 1446, 1373, 1411, 1373, 1331, 1219, 1088, 1015, 837, 824, 781, 721 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.33–7.27 (m, 4H, ArH), 7.00 (s, 2H, NH_2), 4.03 (q, J = 7.2 Hz, 2H, CH_2O), 3.01 (dd, J_1 = 4.0, J_2 = 4.4 Hz, 1H, CH), 2,37 (s, 3H, CH_3), 2.08 (d, J = 11.6 Hz, 1H, CH), 1.87 (d, J = 11.6 Hz, 1H, CH), 1.53 (d, J = 12.8 Hz, 1H, CH), 1.39–1.02 (m, 4H, 4 × CH), 0.95 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.6, 159.5, 157.3, 156.4, 141.1, 129.4, 129.2, 129.0, 120.4, 117.8, 112.9, 61.4, 60.0, 37.6, 36.9, 29.6, 28.7, 21.5, 20.3, 13.9; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}NaN_4O_3$ [$(M+Na)^+$], 425.1590; found, 425.1599.



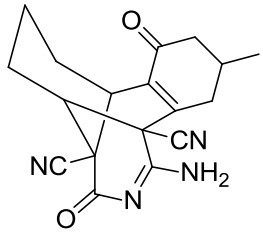
11-Amino-2,2-dimethyl-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decah ydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8] annulene-10,14-dicarbonitrile (6a)

White solid, 0.235 g, yield 70%; mp > 300 ℃. IR (KBr) 3416, 2174, 1675, 1642, 1536, 1448, 1382, 1290, 1129, 1051, 1038 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.44 (s, 1H, NH), 8.90 (s, 1H, NH), 3.20 (s, 2H, 2 × CH), 2.77–2.73 (m, 1H, CH), 2.46 (s, 1H, CH), 2.23–2.19 (m, 2H, 2 × CH), 2.08–2.04 (m, 1H, CH), 1.90–1.86 (m, 2H, 2 × CH), 1.52–1.49 (m, 2H, 2 × CH), 1.33–1.29 (s, 1H, CH), 1.04 (s, 3H, CH_3), 0.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 196.0, 146.5, 133.0, 119.2, 115.2, 56.5, 50.3, 49.3, 46.6, 37.9, 34.6, 33.49, 29.2, 26.0, 25.5, 24.8, 19.0, 16.0; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}N_4O_2$ [$(M)^+$], 336.1586; found, 336.1581.



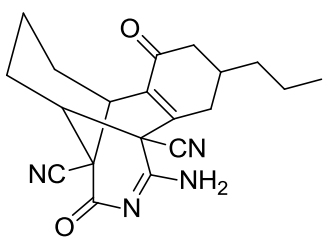
11-Amino-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6b)

White solid, 0.185 g, yiled 60%; mp 238–240 ℃. IR (KBr): 3410, 2175, 1670, 1630, 1538, 1420, 1380, 1280, 1123, 1042, 1036 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.42 (s, 1H, NH), 8.94 (s, 1H, NH), 3.13–3.19 (m, 2H, 2 × CH), 2.74–2.79 (m, 1H, CH), 2.34–2.47 (m, 3H, 3 × CH), 2.03–2.06 (m, 2H, 2 × CH), 1.83–1.92 (m, 3H, 3 × CH), 1.51–1.54 (m, 2H, 2 × CH), 1.30–1.37 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.7, 148.9, 133.9, 119.2, 115.4, 56.5, 49.1, 46.7, 37.9, 37.2, 34.6, 26.9, 26.0, 24.8, 22.3, 19.0, 15.8; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_4O_2$ [$(M)^+$], 308.1273; found, 308.1272.



11-Amino-2-methyl-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6c)

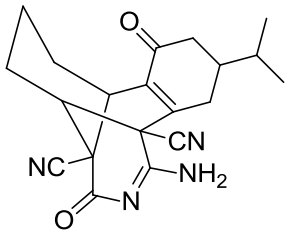
White solid, 0.219 g, yield 68%; mp 170–172 ℃. IR (KBr): 3417, 2173, 1681, 1637, 1617, 1533, 1384, 1294, 1123, 1041 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.40 (s, 1H, NH), 8.93 (s, 1H, NH), 3.19–3.16 (m, 2H, 2 × CH), 2.85–2.81 (m, 1H, CH), 2.54 (s, 1H, CH), 2.36–2.31 (m, 1H, CH), 2.22–2.03 (m, 2H, 2 × CH), 1.93–1.81 (m, 2H, 2 × CH), 1.52–1.50 (m, 2H, 2 × CH), 1.33–1.30 (m, 1H, CH), 1.03–1.01 (m, 1H, CH), 0.90 (d, *J* = 6.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.8, 147.3, 133.5, 119.2, 115.5, 46.7, 45.0, 44.6, 38.1, 34.5, 31.2, 30.1, 28.7, 26.0, 24.8, 21.1, 19.7, 15.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_4O_2$ [$(M)^+$], 322.1430; found, 322.1418.



11-Amino-4,13-dioxo-2-propyl-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6d)

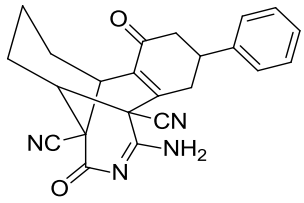
White solid, 0.228 g, yield 65%; mp 162–164 ℃. IR (KBr) 3413, 2172, 1675, 1542, 1444, 1297, 1290, 1134, 1002 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.44 (s, 1H, NH), 8.94 (s, 1H, NH), 3.18–3.13 (m, 2H, 2 × CH), 2.87–2.84 (m, 1H, CH), 2.56–2.53 (m, 1H, CH),

2.42–2.13 (m, 3H, 3 × CH), 2.07–2.03 (m, 1H, CH), 1.89–1.79 (m, 2H, CH_2), 1.52–1.49 (m, 2H, CH_2), 1.31–1.19 (m, 5H, 5 × CH), 0.85 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.7, 147.3, 133.7, 119.2, 115.5, 46.6, 43.4, 43.2, 38.1, 37.3, 35.9, 34.5, 33.3, 32.5, 26.0, 24.8, 19.7, 19.4, 15.8, 14.3; HRMS (ESI): m/z calcd for $C_{20}H_{22}N_4O_2$ [$(M)^+$], 350.1743; found, 350.1736.



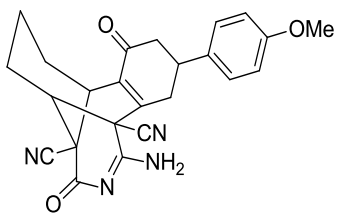
11-Amino-2-isopropyl-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6e)

White solid, 0.245 g, yield 70%; mp 170–172 ℃. IR (KBr): 3418, 2174, 1680, 1547, 1450, 1382, 1257, 1134, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.39 (s, 1H, NH), 8.96 (s, 1H, NH), 3.18–3.16 (m, 2H, 2 × CH), 2.84–2.80 (m, 1H, CH), 2.38–2.19 (m, 2H, 2 × CH), 2.07–2.04 (m, 1H, CH), 1.90–1.80 (m, 3H, 3 × CH), 1.58–1.45 (m, 3H, 3 × CH), 1.35–1.28 (m, 1H, CH), 0.91–0.84 (m, 7H, 3 × CH_3 and CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 196.0, 147.8, 133.8, 119.3, 115.6, 46.6, 41.4, 41.1, 38.2, 34.5, 31.6, 30.8, 25.9, 24.8, 20.2, 19.9, 19.69, 19.6, 15.8; HRMS (ESI): m/z calcd for $C_{20}H_{22}N_4O_2$ [$(M)^+$], 350.1743; found, 350.1742.



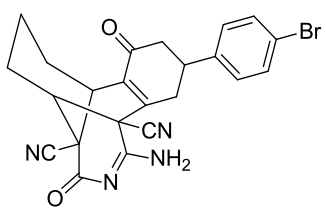
11-Amino-4,13-dioxo-2-phenyl-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6f)

White solid, 0.250 g, yield 65%; mp 278–280 ℃. IR (KBr) 3404, 2173, 1678, 1538, 1448, 1378, 1294, 1145, 1027 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.34 (s, 1H, NH), 8.88 (s, 1H, NH), 7.35–7.27 (m, 5H, ArH), 3.55–3.49 (m, 1H, CH), 3.24–3.18 (m, 2H, 2 × CH), 2.96–2.84 (m, 2H, 2 × CH), 2.66–2.55 (m, 2H, 2 × CH), 2.11–1.83 (m, 3H, 3 × CH), 1.58–1.39 (m, 3H, 3 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.4, 147.5, 143.2, 133.9, 129.1, 127.4, 119.3, 115.7, 115.1, 49.5, 46.7, 46.6, 43.8, 43.6, 39.2, 38.2, 34.8, 34.5, 26.0, 24.9, 15.8; HRMS (ESI): m/z calcd for $C_{23}H_{20}N_4O_2$ [$(M)^+$], 384.1586; found, 384.1585.



11-Amino-2-(4-methoxyphenyl)-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6g)

White solid, 0.273 g, yield 66%; mp > 300 ℃. IR (KBr): 3396, 2174, 1678, 1544, 1448, 1380, 1294, 1138, 1072, 1030 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.31 (s, 1H, NH), 8.87 (s, 1H, NH), 7.26 (s, 2H, ArH), 6.89 (s, 2H, ArH), 3.72 (s, 3H, CH_3O), 3.45 (s, 1H, CH), 3.23–3.17 (m, 2H, 2 × CH), 2.89–2.80 (m, 2H, 2 × CH), 2.61–2.56 (m, 2H, 2 × CH), 2.10–1.86 (m, 3H, 3 × CH), 1.57–1.41 (m, 3H, 3 × CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.5, 158.6, 147.6, 135.2, 133.8, 128.4, 119.3, 115.7, 114.4, 55.5, 46.7, 44.2, 44.0, 38.5, 38.2, 35.1, 34.5, 34.3, 26.0, 24.9, 15.8, 15.5; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_4O_3$ [$(M)^+$], 414.1692; found, 414.1695.

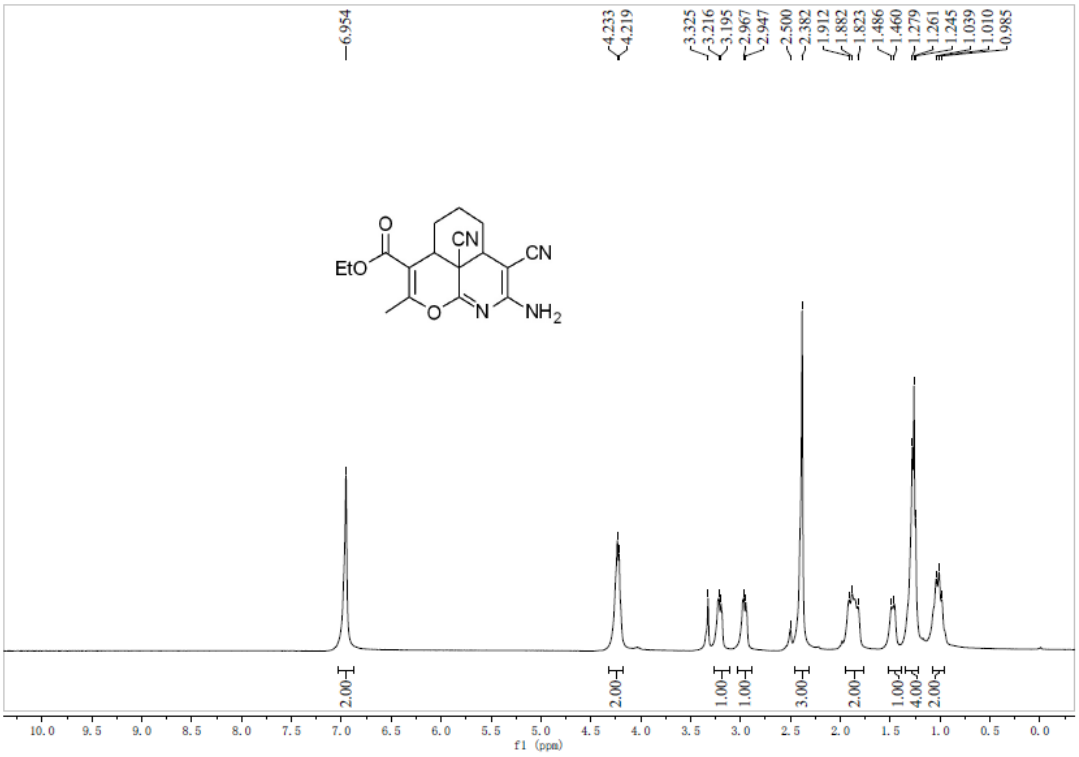


11-Amino-2-(4-bromophenyl)-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenomethano)benzo[8]annulene-10,14-dicarbonitrile (6h)

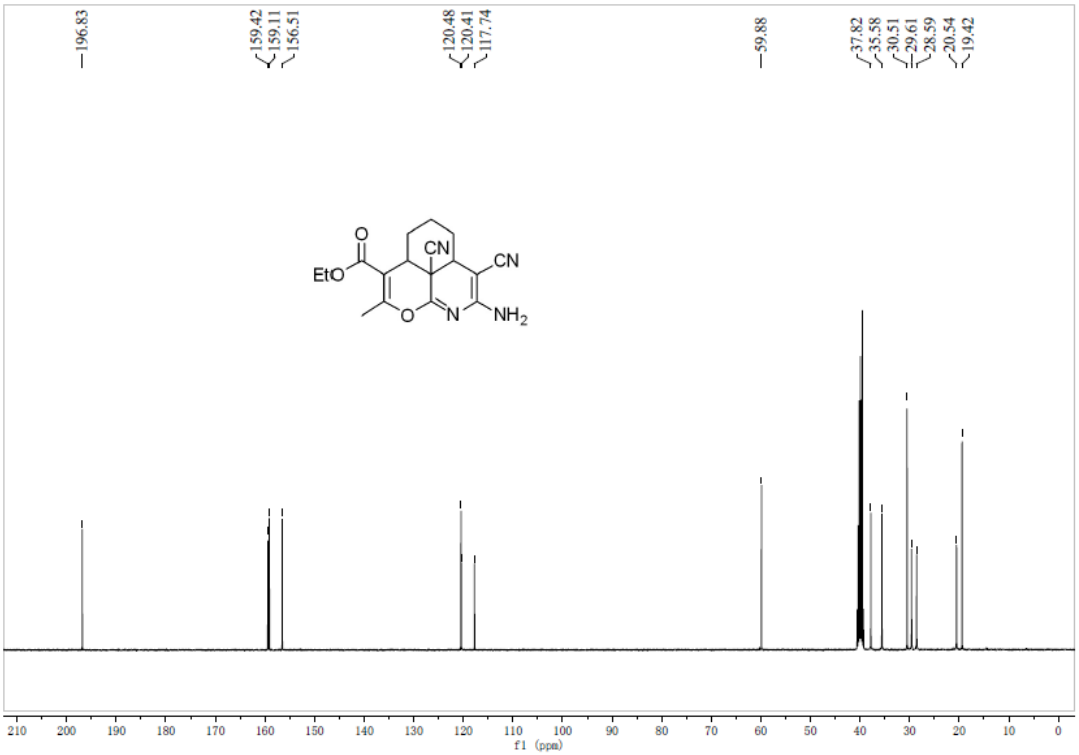
White solid, 0.283 g, yield 61%; mp > 300 ℃. IR (KBr): 3416, 2172, 1673, 1604, 1515, 1382, 1292, 1235, 1182, 1114, 1032 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.31 (s, 1H, NH), 8.86 (s, 1H, NH), 7.52 (s, 2H, ArH), 7.33(s, 2H, ArH), 3.54 (s, 1H, CH), 3.23–3.18 (m, 2H, 2 × CH), 2.91–2.87 (m, 2H, 2 × CH), 2.66–2.59 (m, 2H, 2 × CH), 2.10–1.86 (m, 3H, 3 × CH), 1.57–1.43 (m, 3H, 3 × CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.3, 146.5, 141.7, 132.97, 131.0, 128.9, 119.5, 118.4, 114.7, 48.6, 45.8, 42.7, 42.4, 37.7, 37.3, 33.6, 33.5, 25.1, 24.0, 14.9, 14.6; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}BrN_4O_2$ [$(M)^+$], 462.0691; found, 462.0691.

4. NMR Spectra of Products

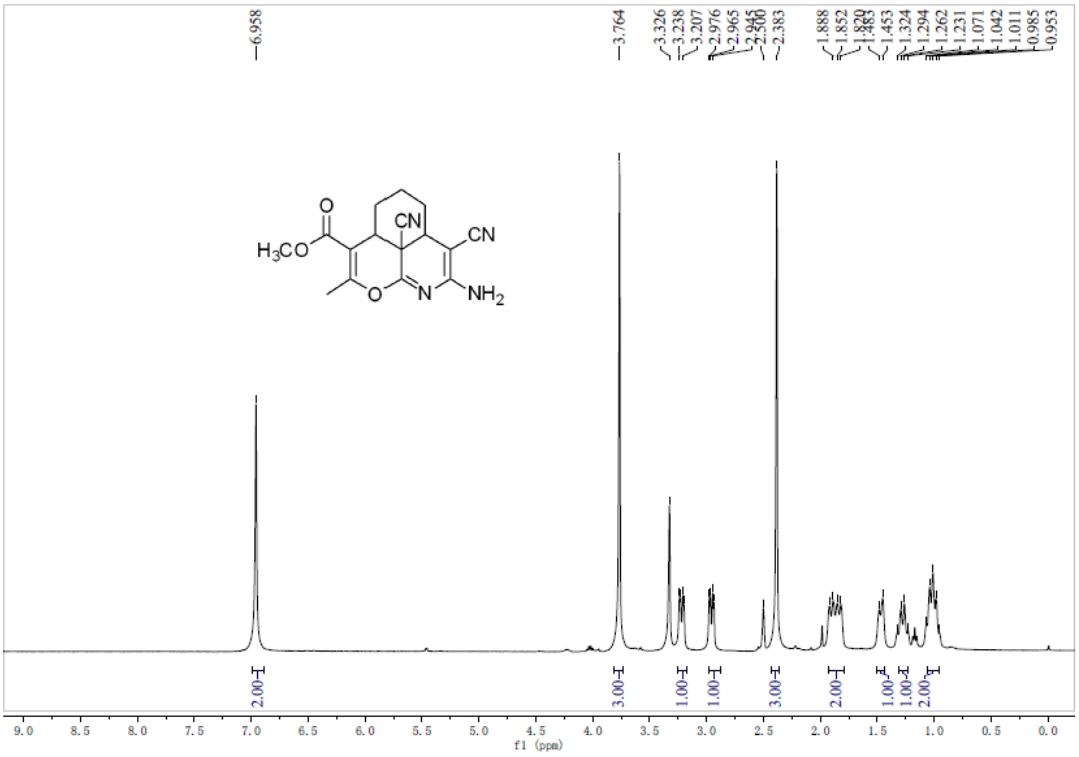
^{1}H NMR of compound **(4a)**



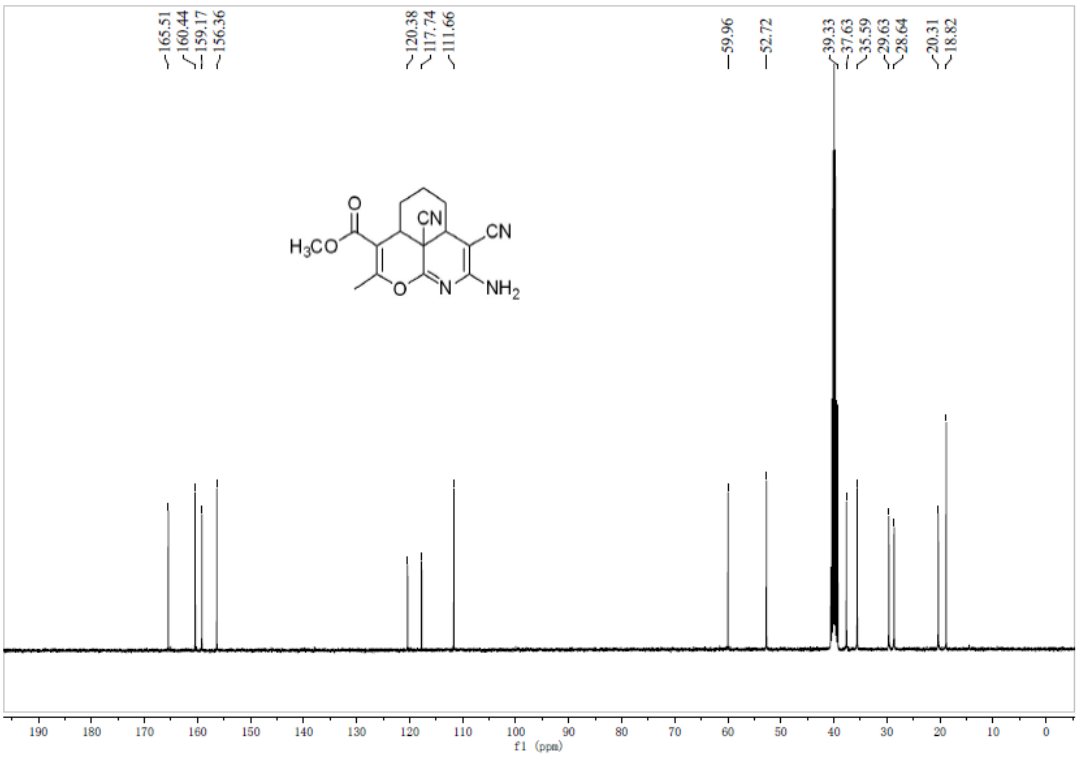
^{13}C NMR of compound **(4a)**



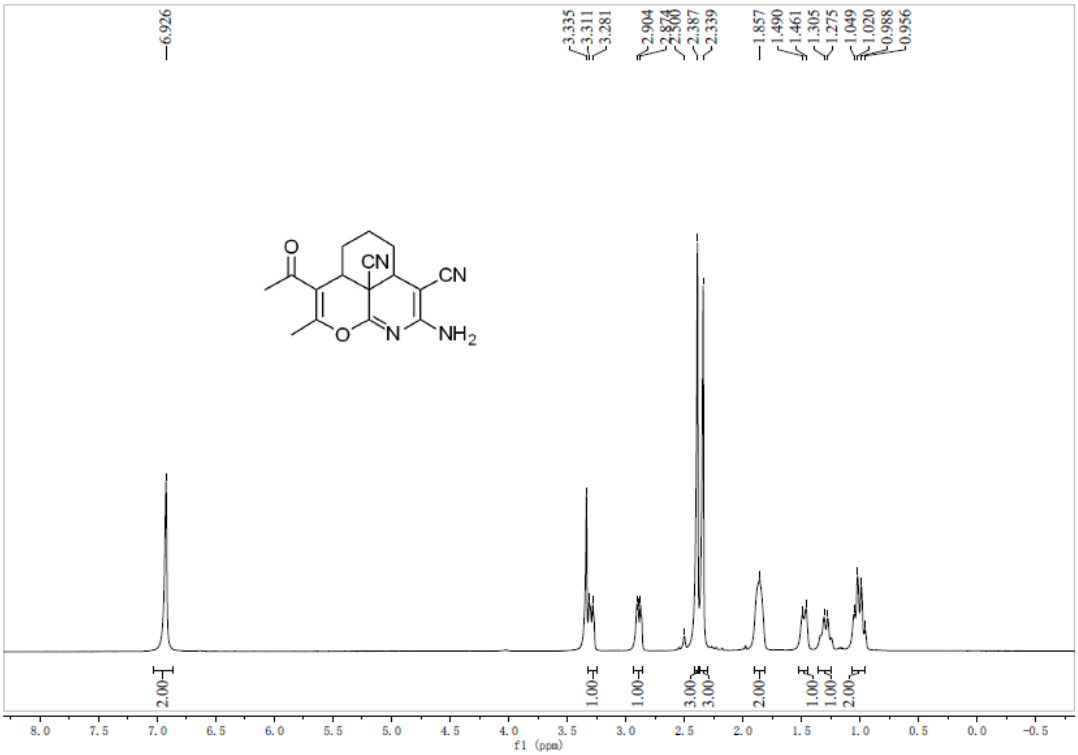
^{1}H NMR of compound **(4b)**



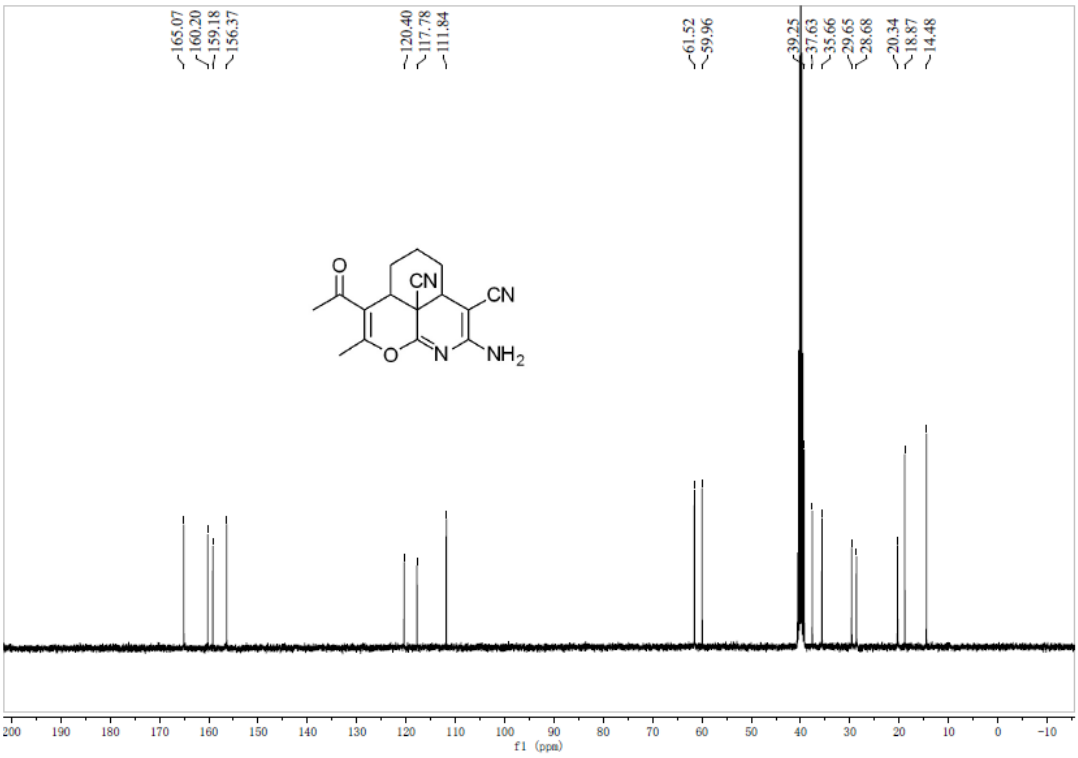
^{13}**C** NMR of compound **(4b)**



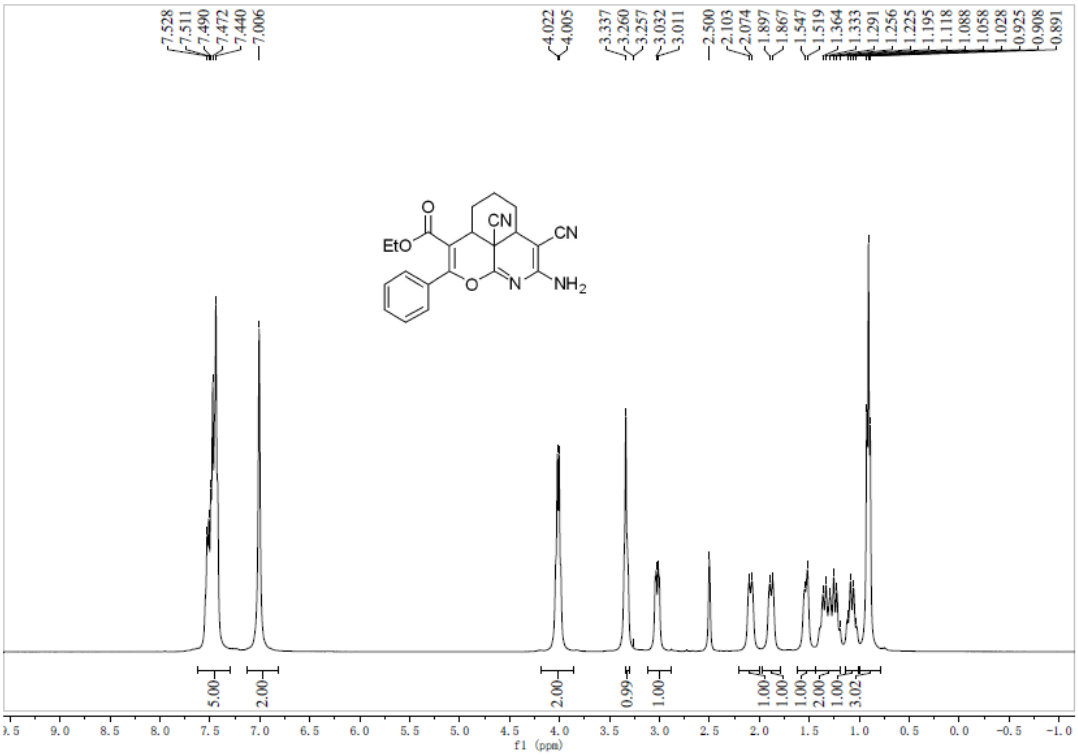
^{1}H NMR of compound **(4c)**



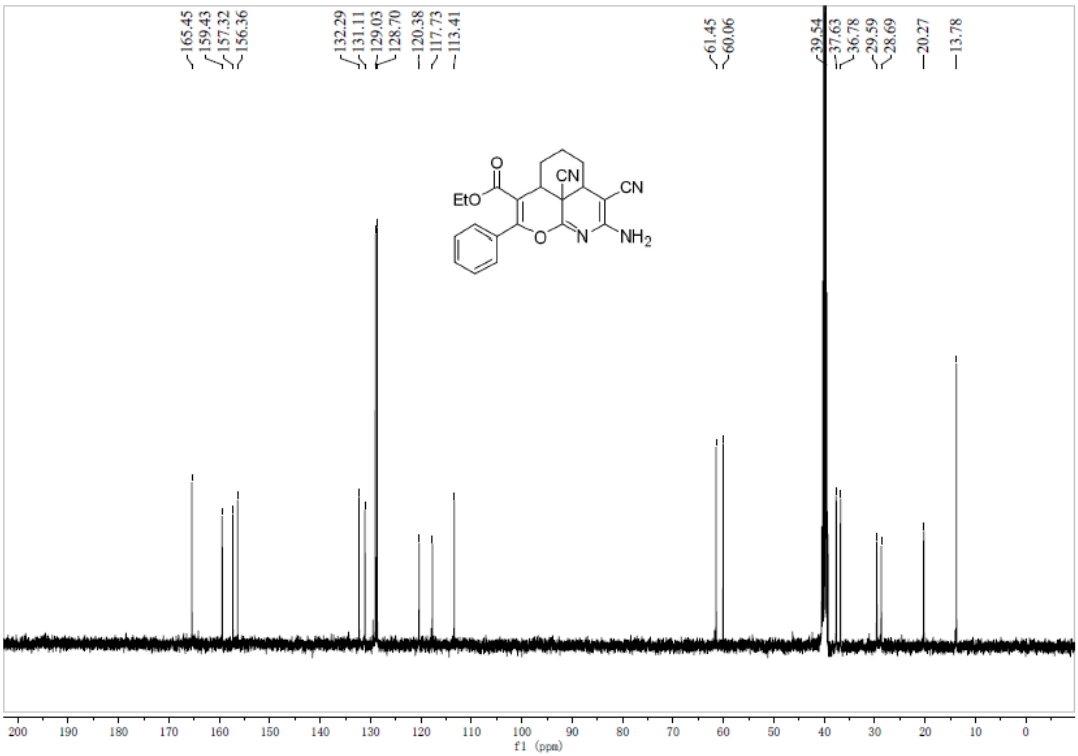
^{13}**C** NMR of compound **(4c)**



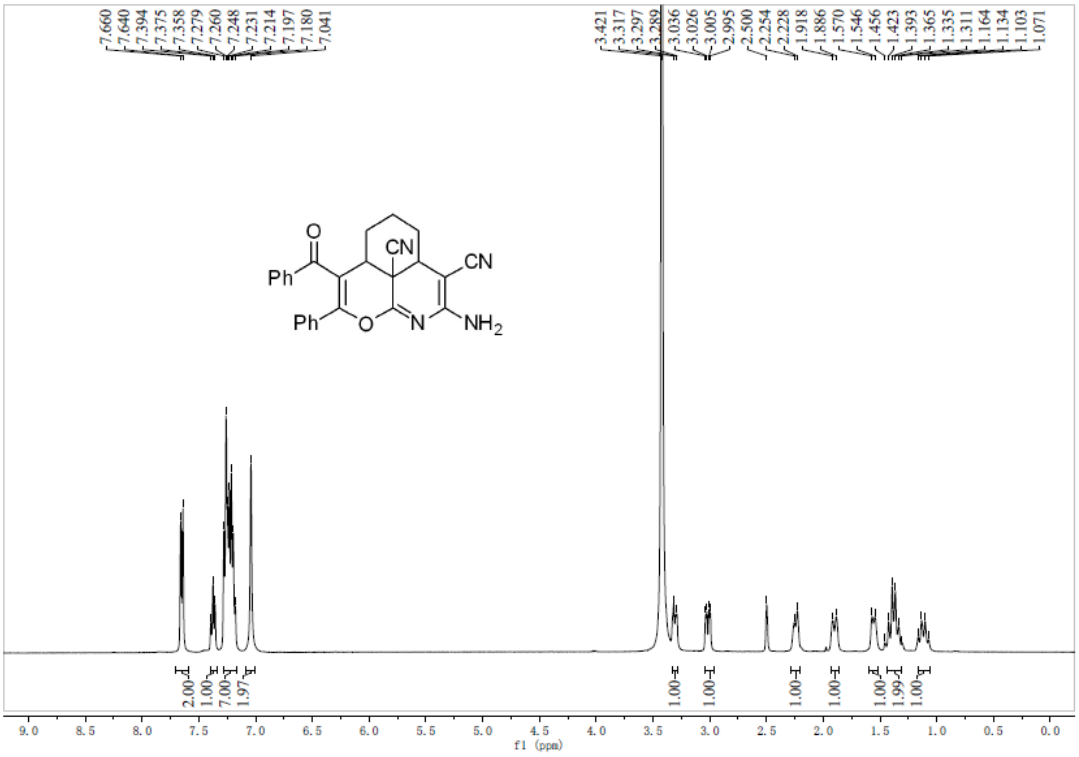
^{1}H NMR of compound **(4d)**



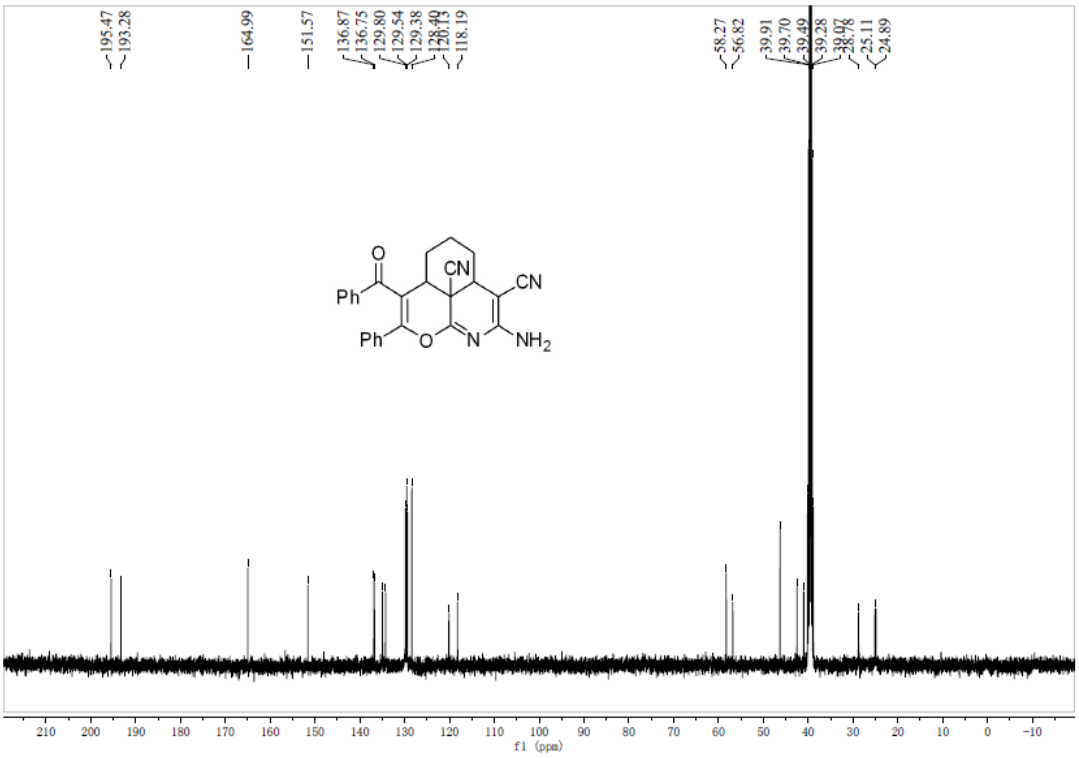
^{13}**C** NMR of compound **(4d)**



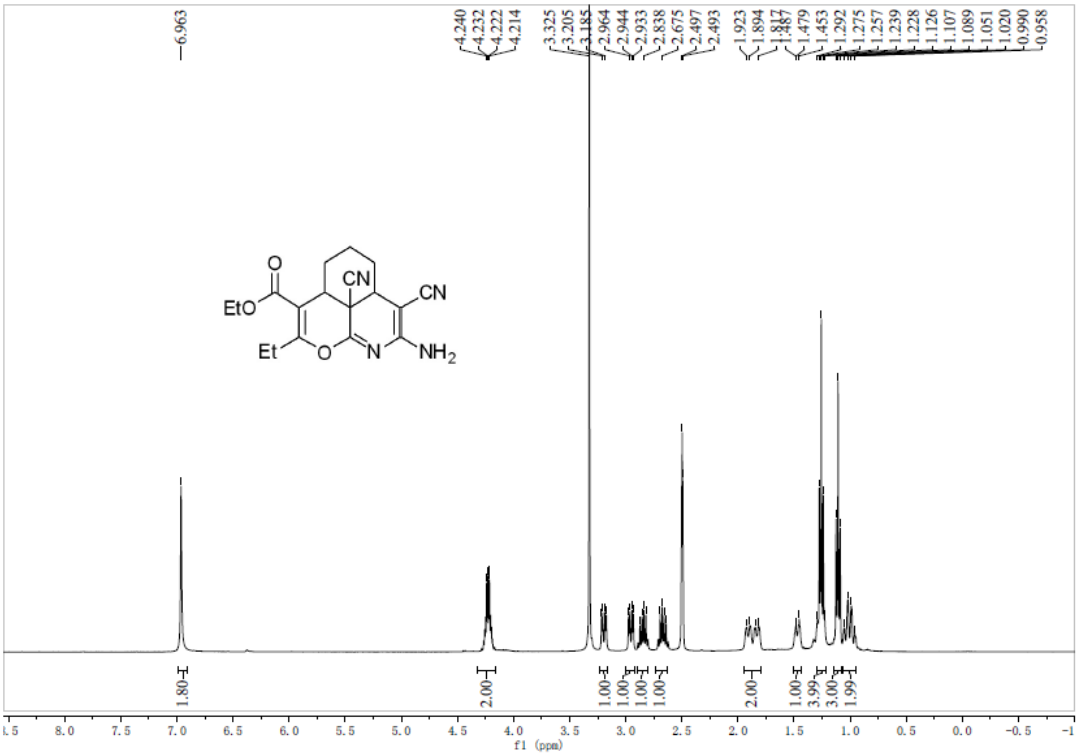
^{1}H NMR of compound **(4e)**



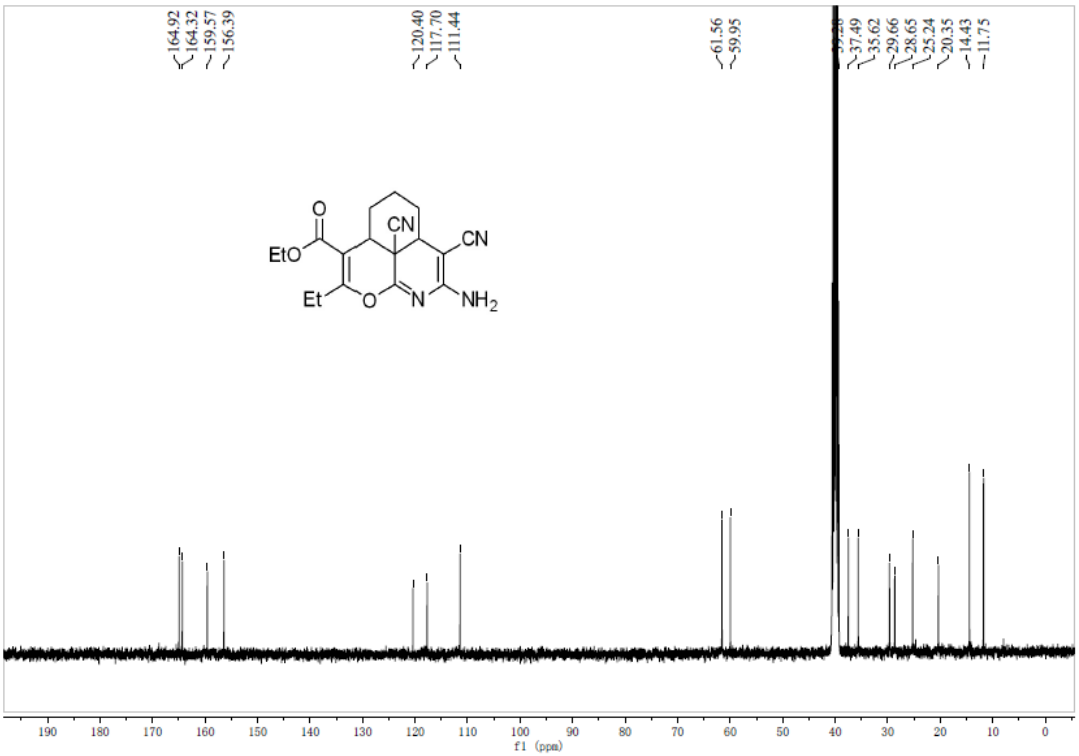
^{13}**C** NMR of compound **(4e)**



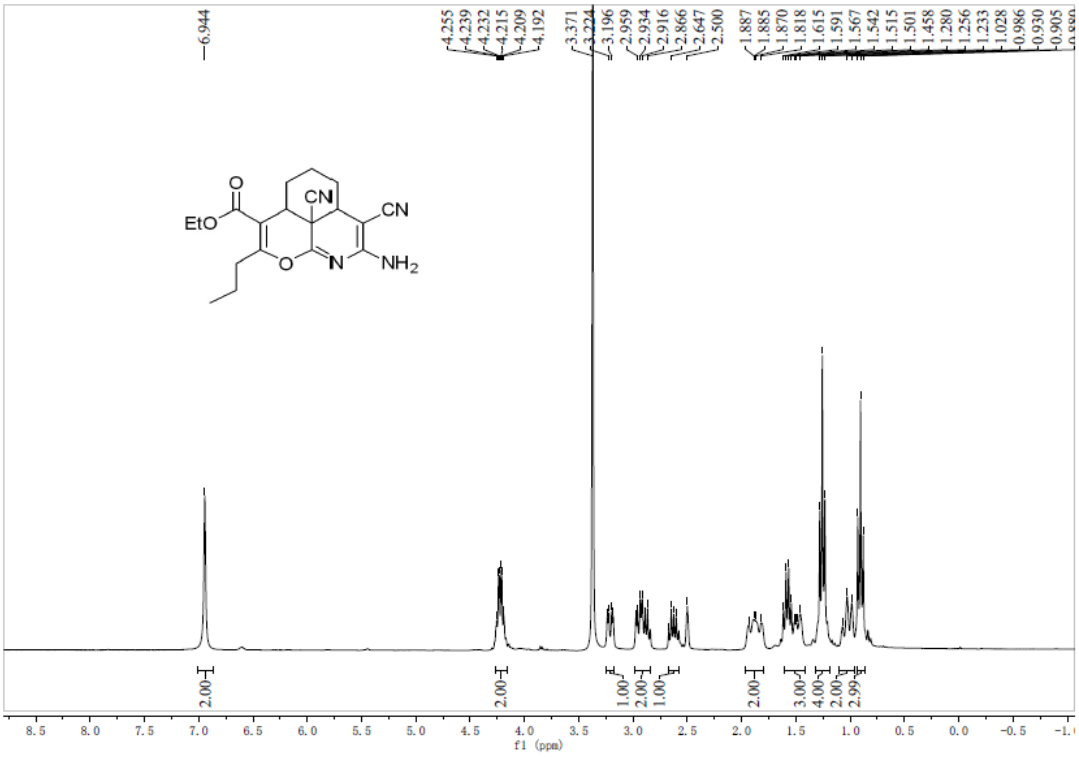
^{1}H NMR of compound **(4f)**



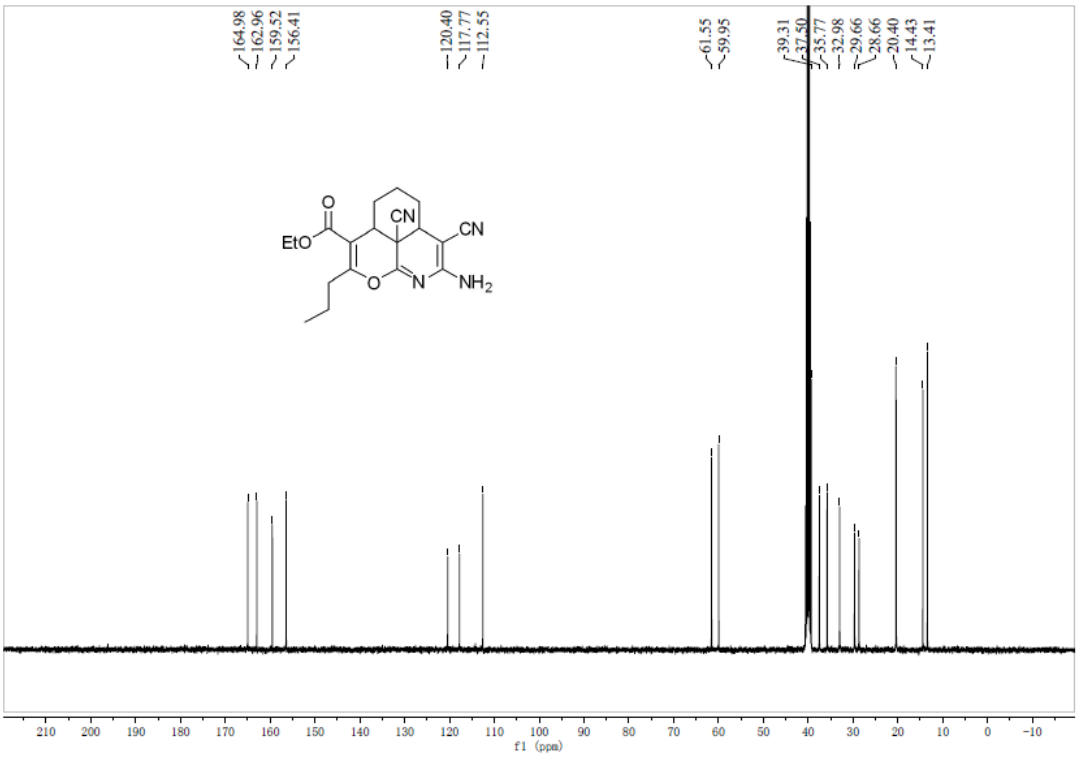
^{13}**C** NMR of compound **(4f)**



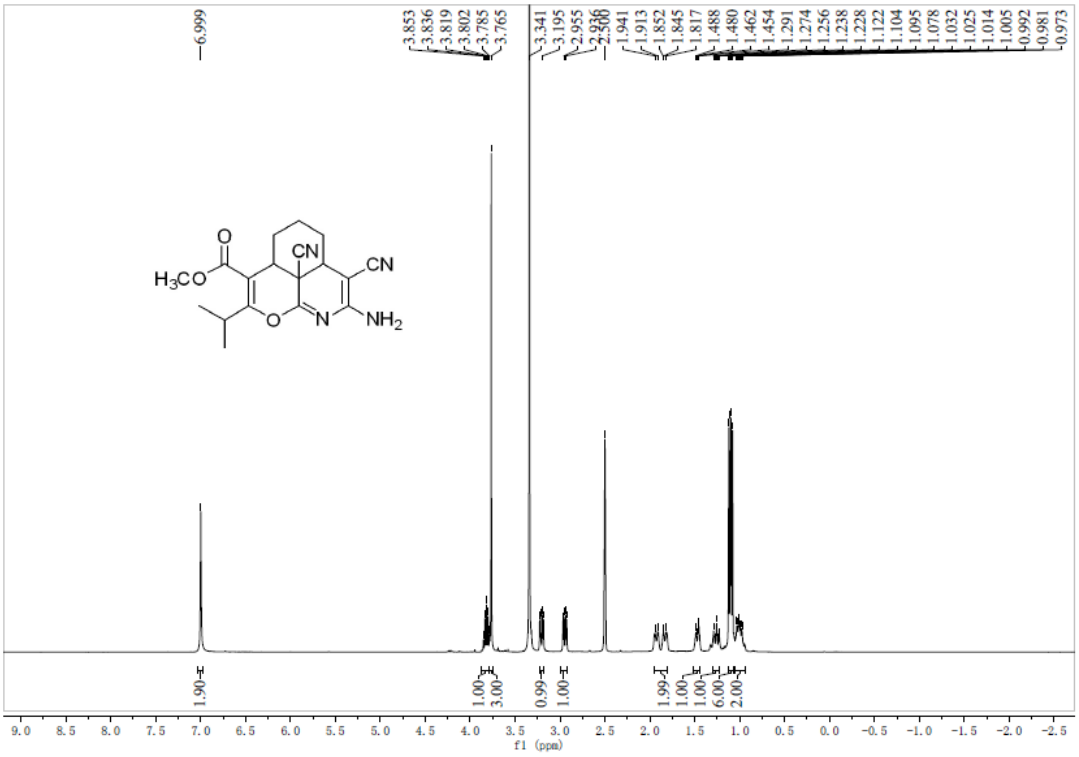
^{1}H NMR of compound **(4g)**



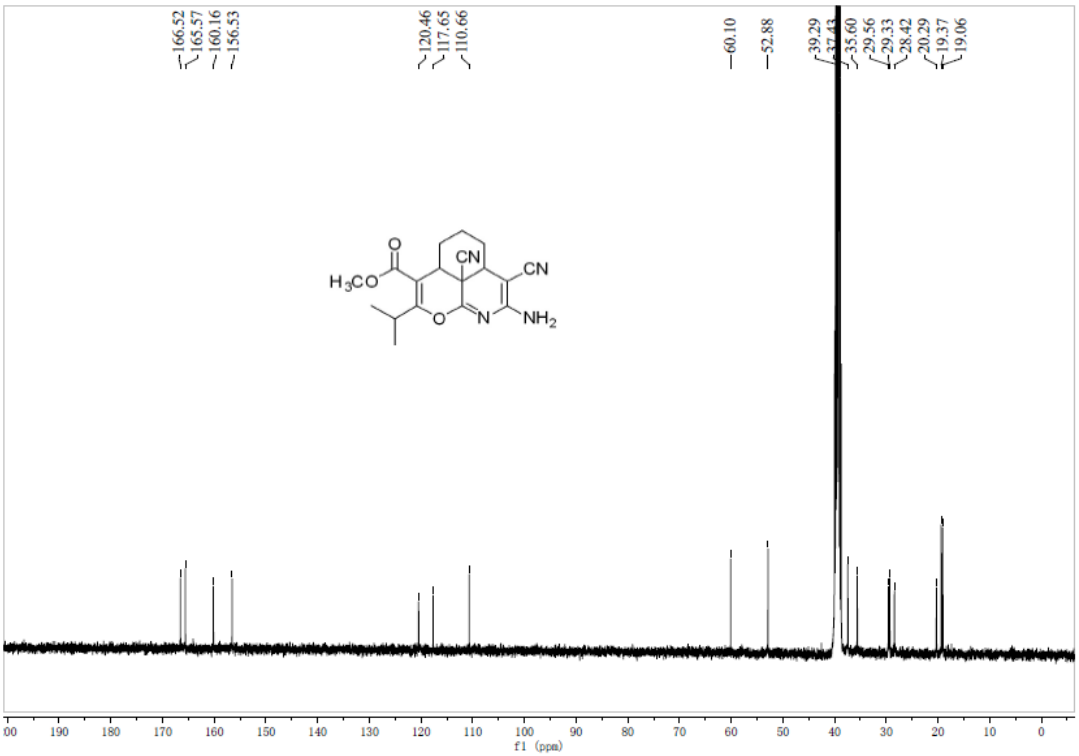
^{13}**C** NMR of compound **(4g)**



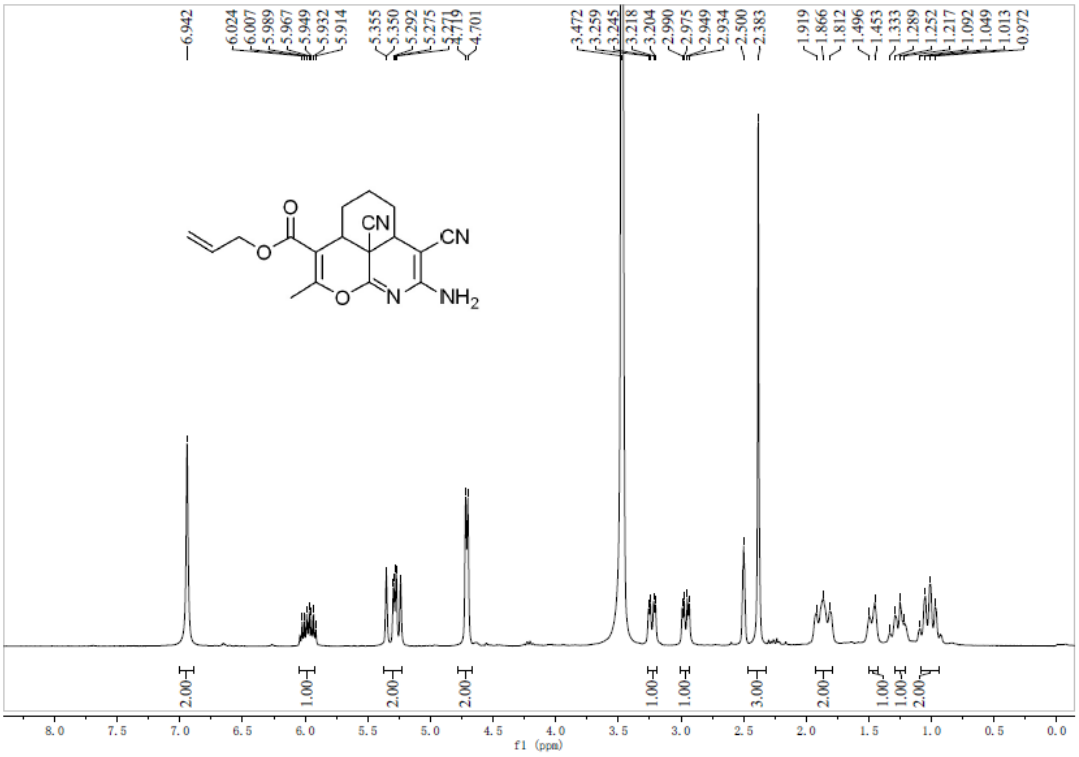
^{1}H NMR of compound **(4h)**



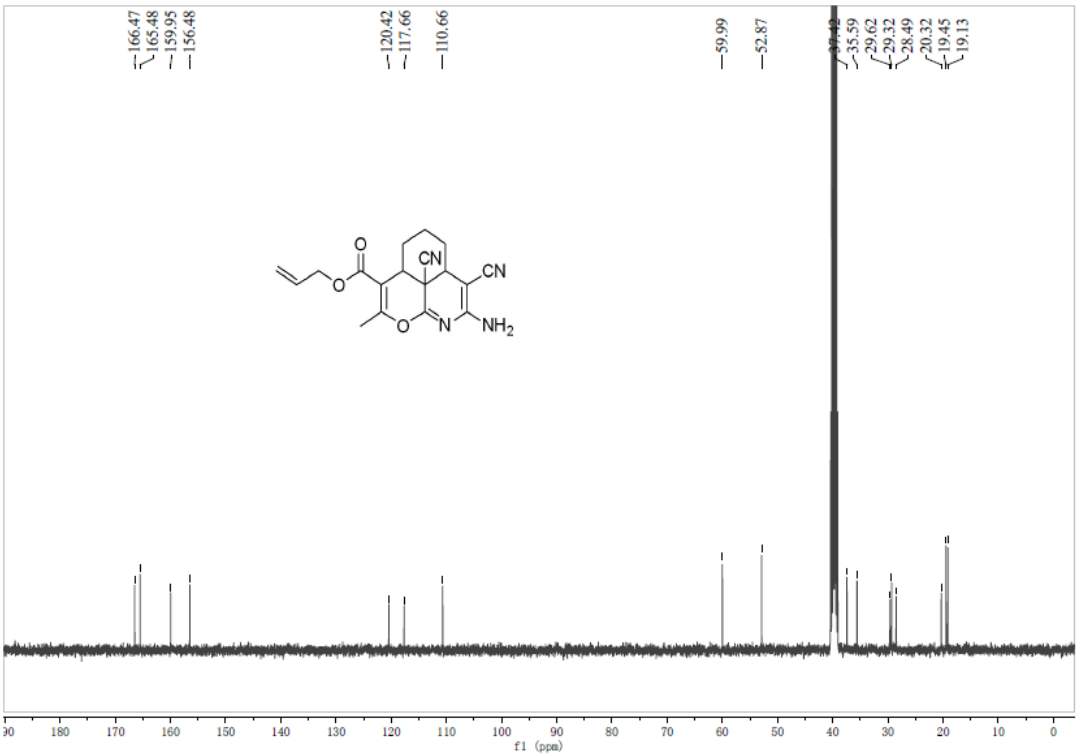
^{13}**C** NMR of compound **(4h)**



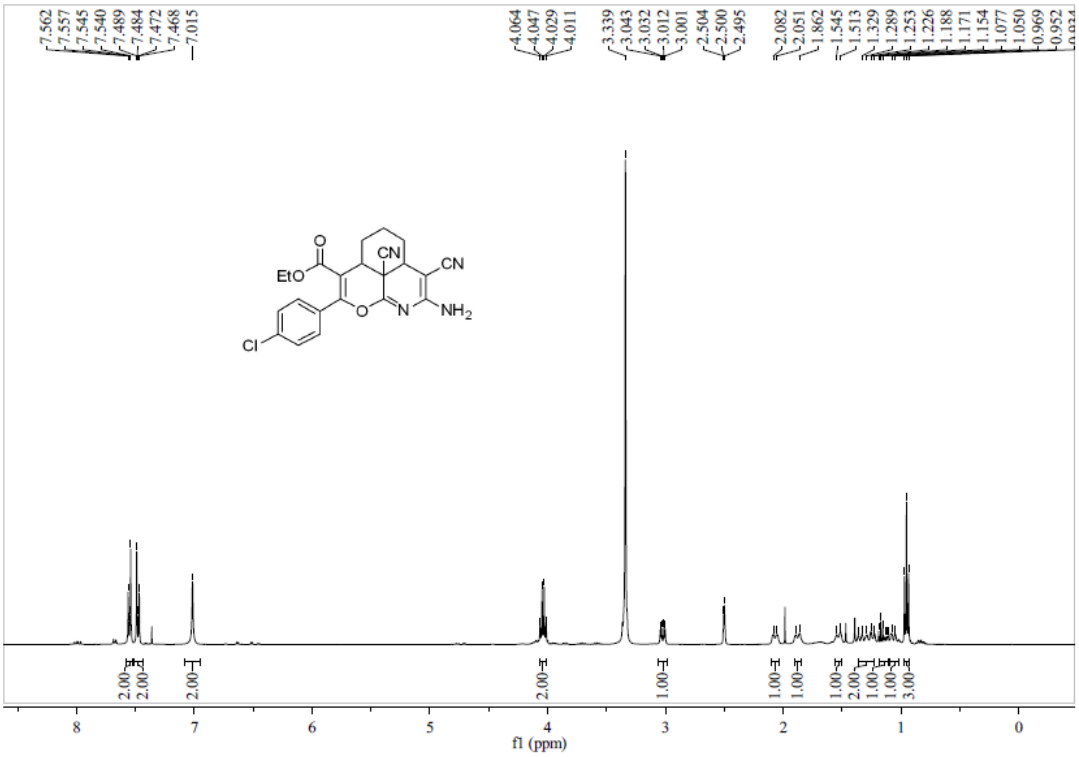
^{1}H NMR of compound **(4i)**



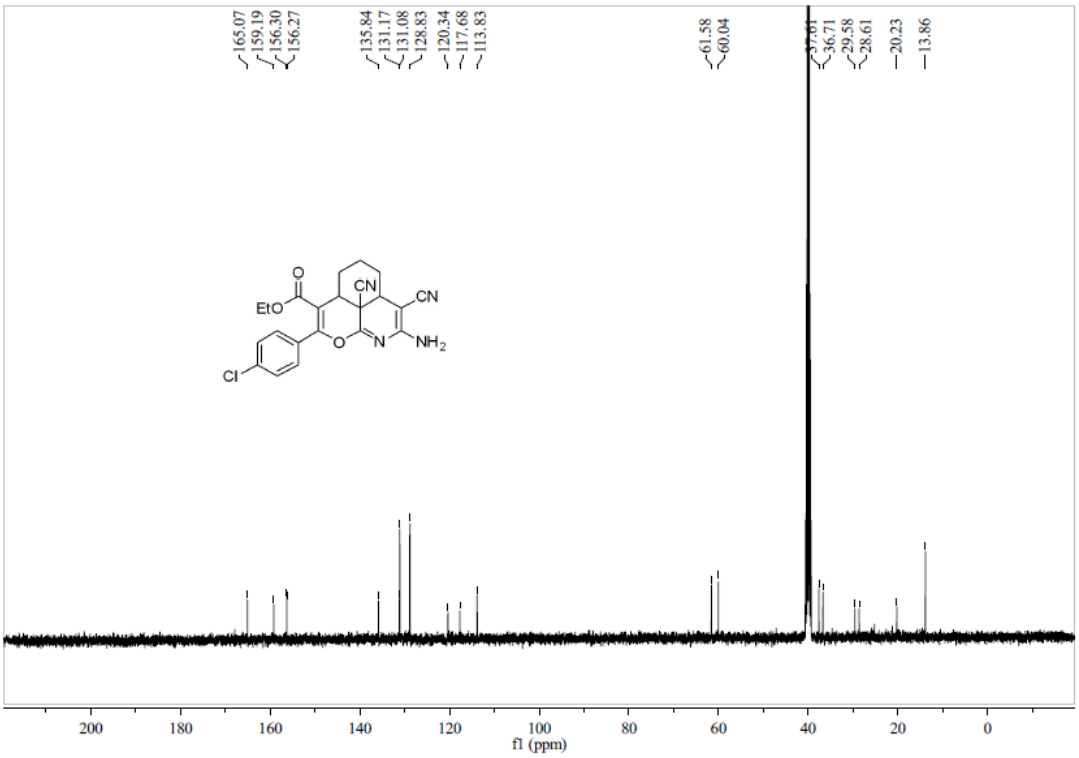
^{13}**C** NMR of compound **(4i)**



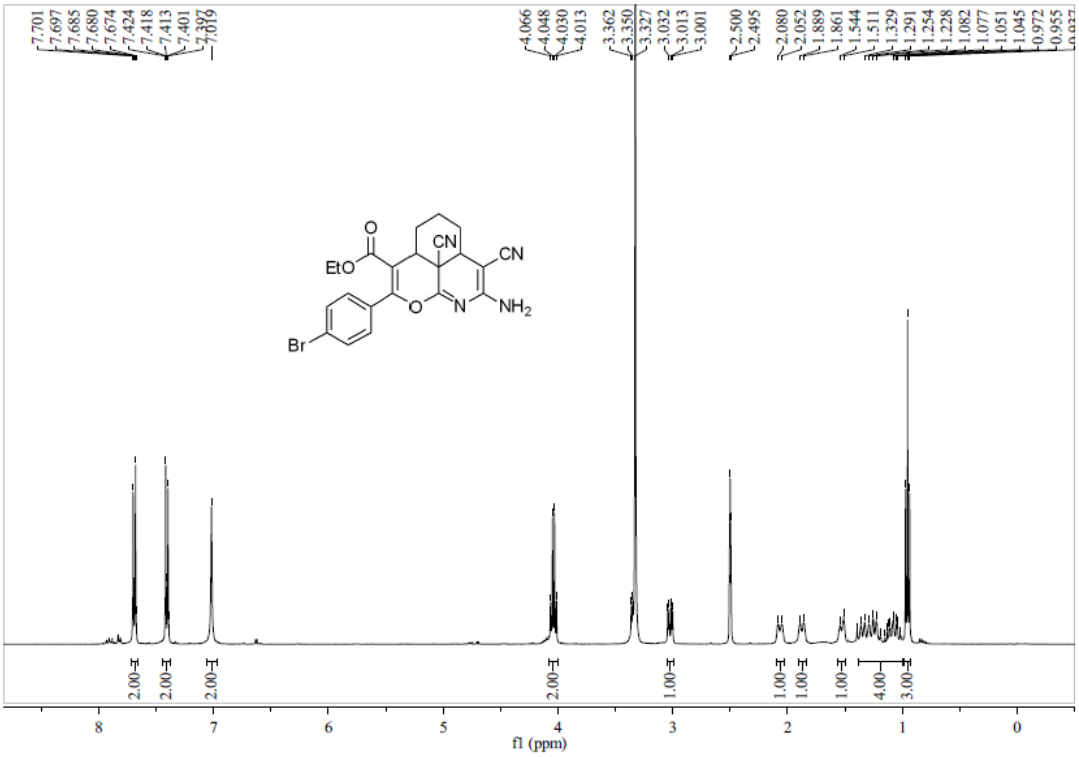
^{1}H NMR of compound **(4j)**



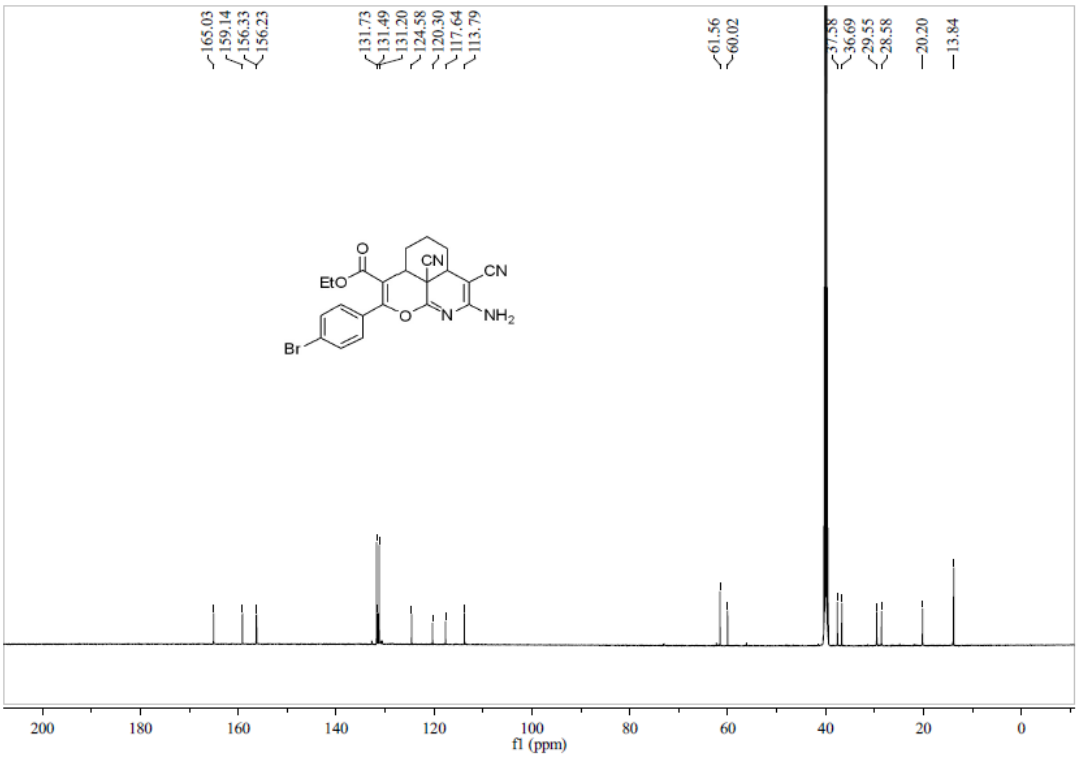
^{13}**C** NMR of compound **(4j)**



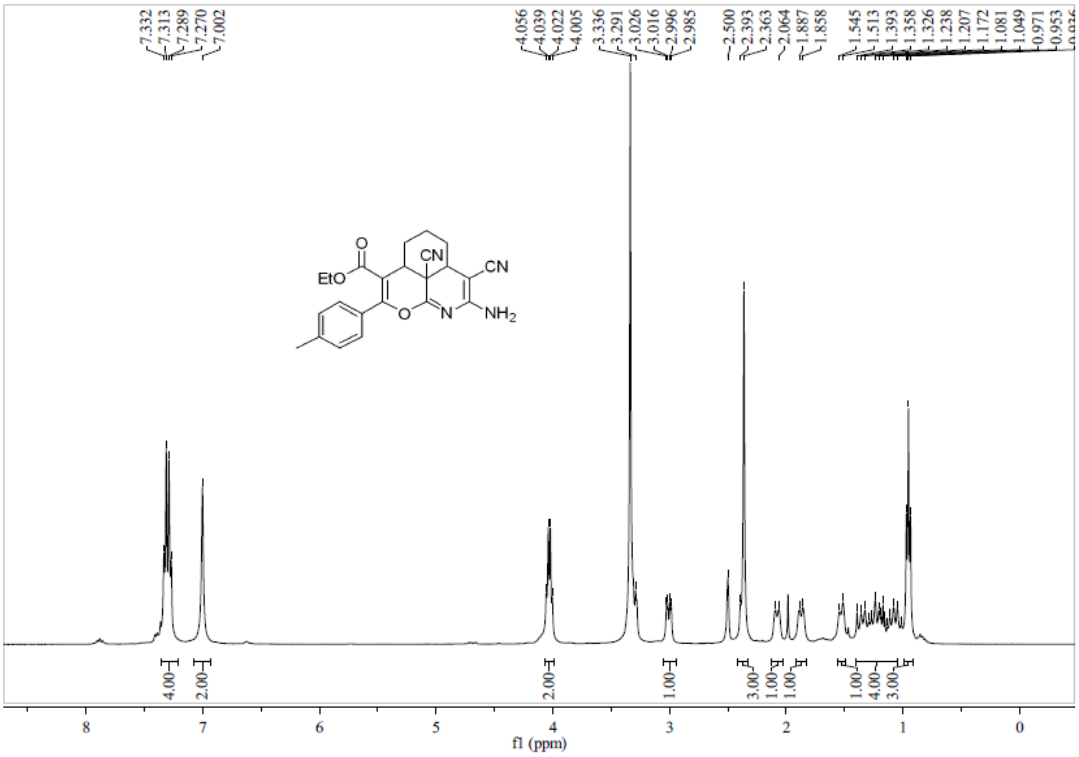
^{1}H NMR of compound **(4k)**



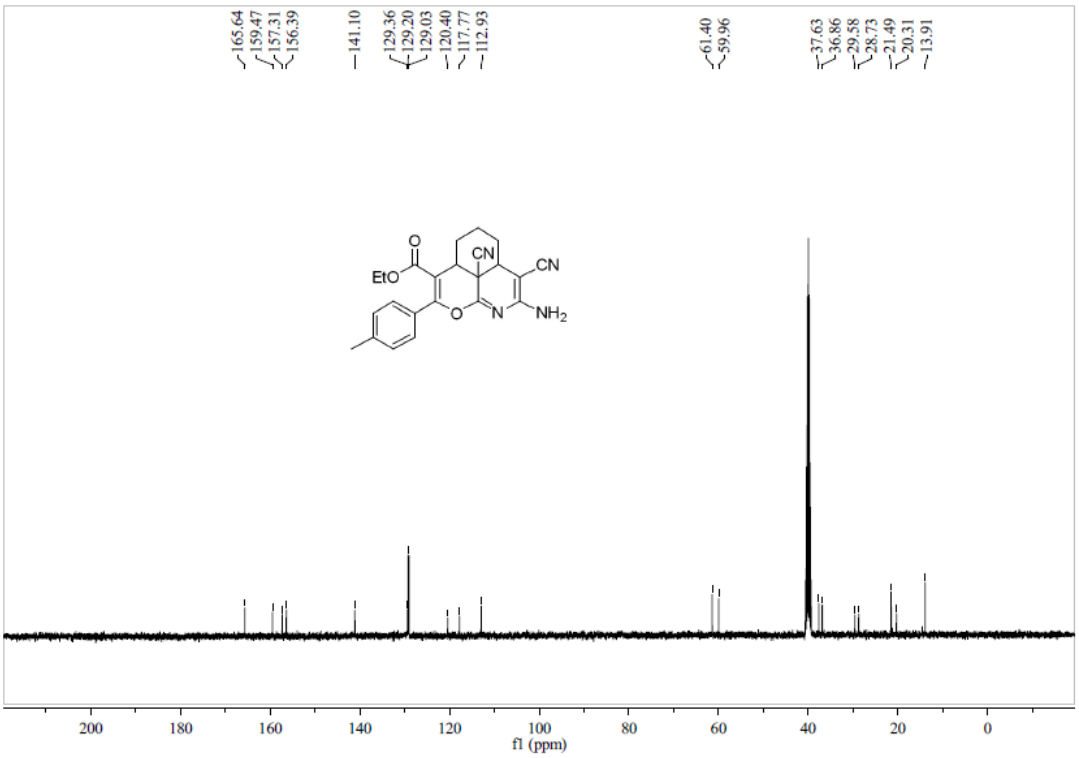
^{13}**C** NMR of compound **(4k)**



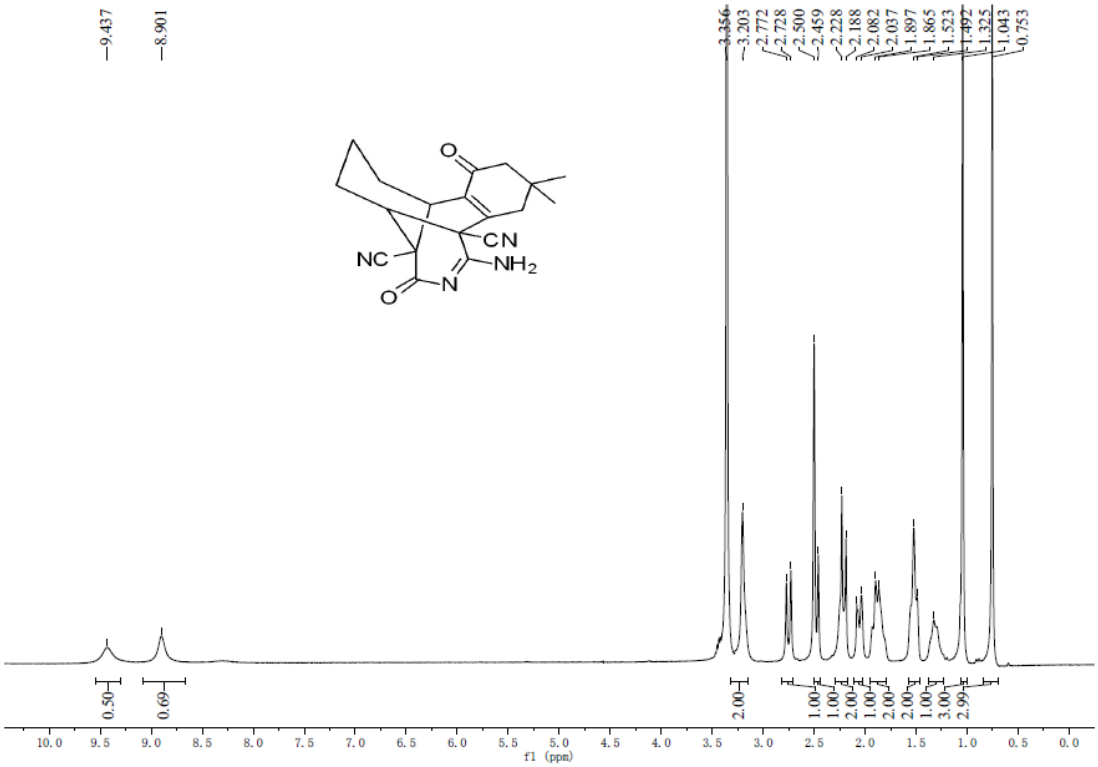
^{1}H NMR of compound **(4l)**



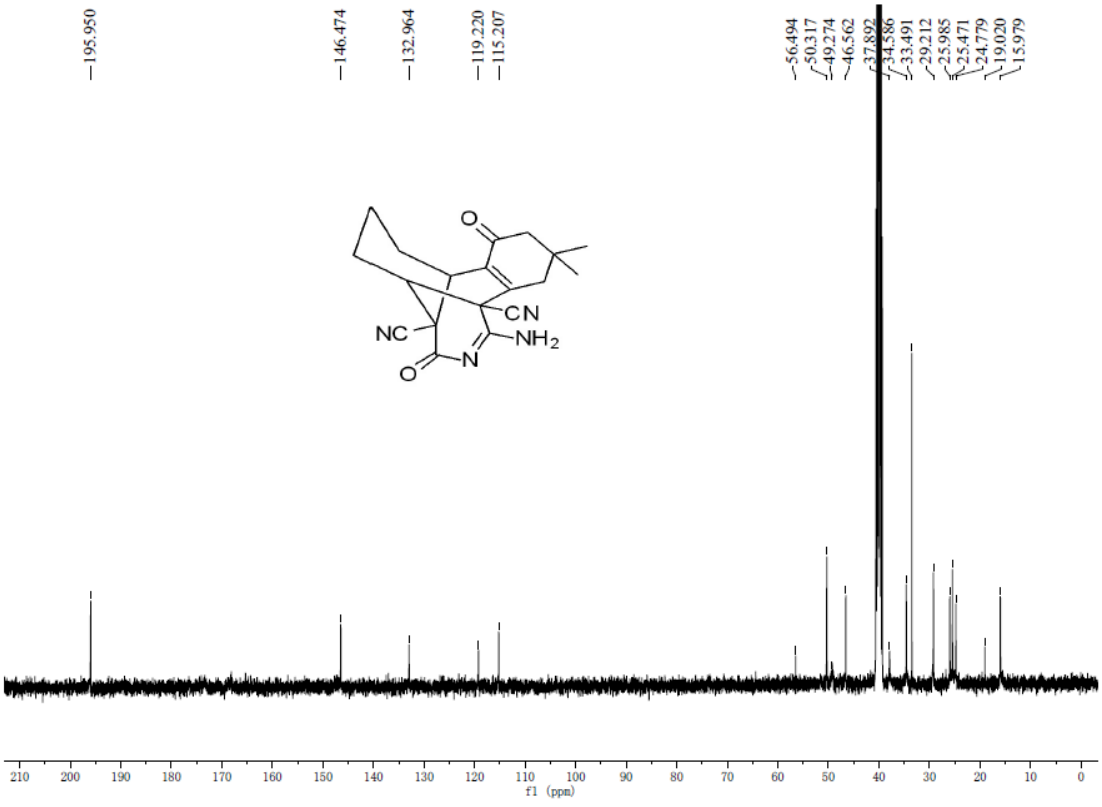
^{13}**C** NMR of compound **(4l)**



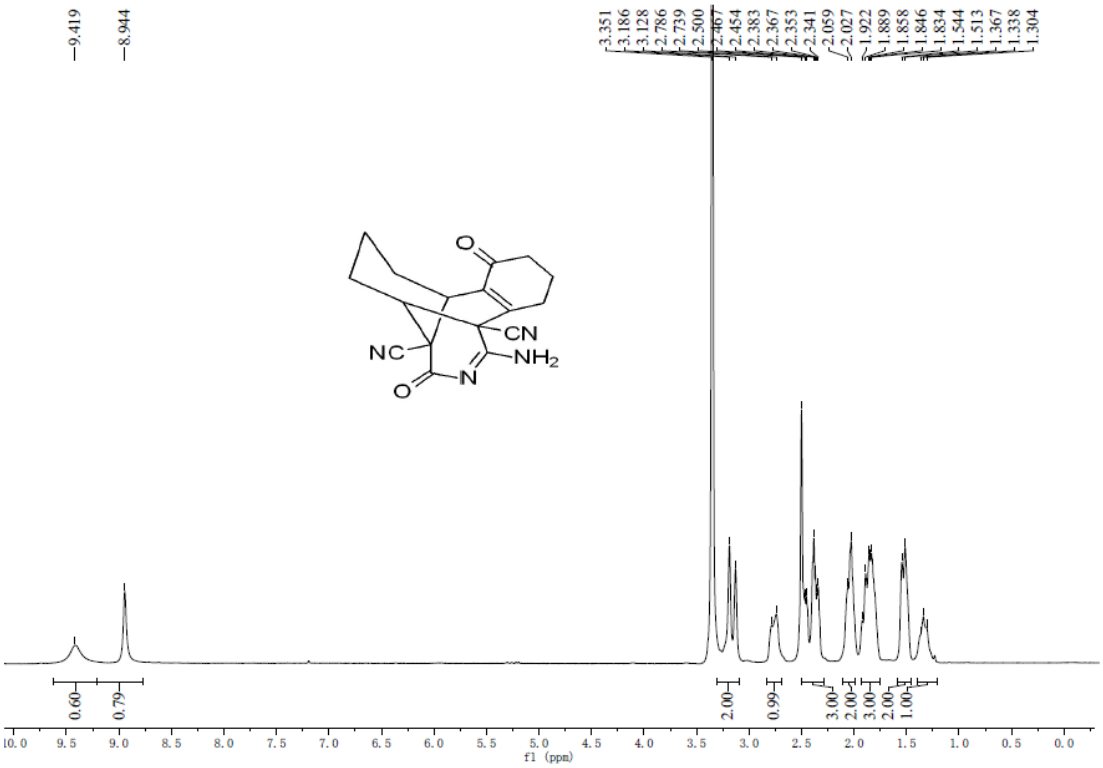
^{1}H NMR of compound **(6a)**



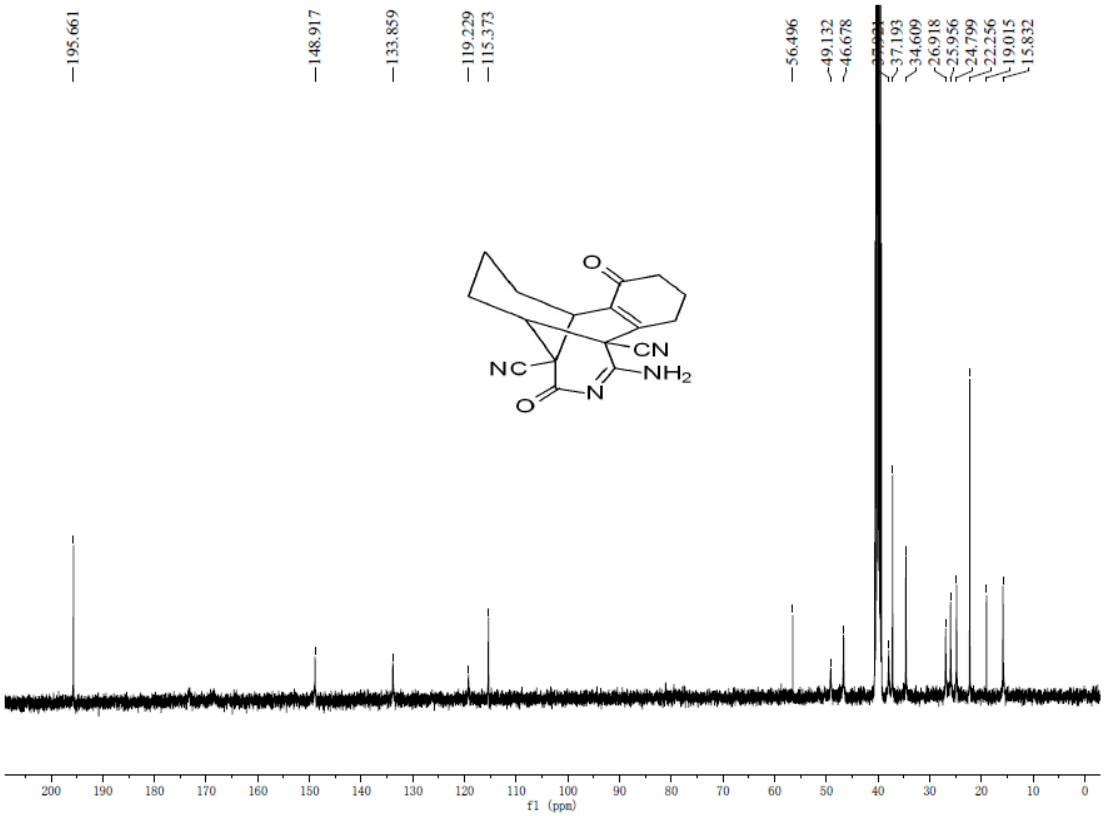
^{13}**C** NMR of compound **(6a)**



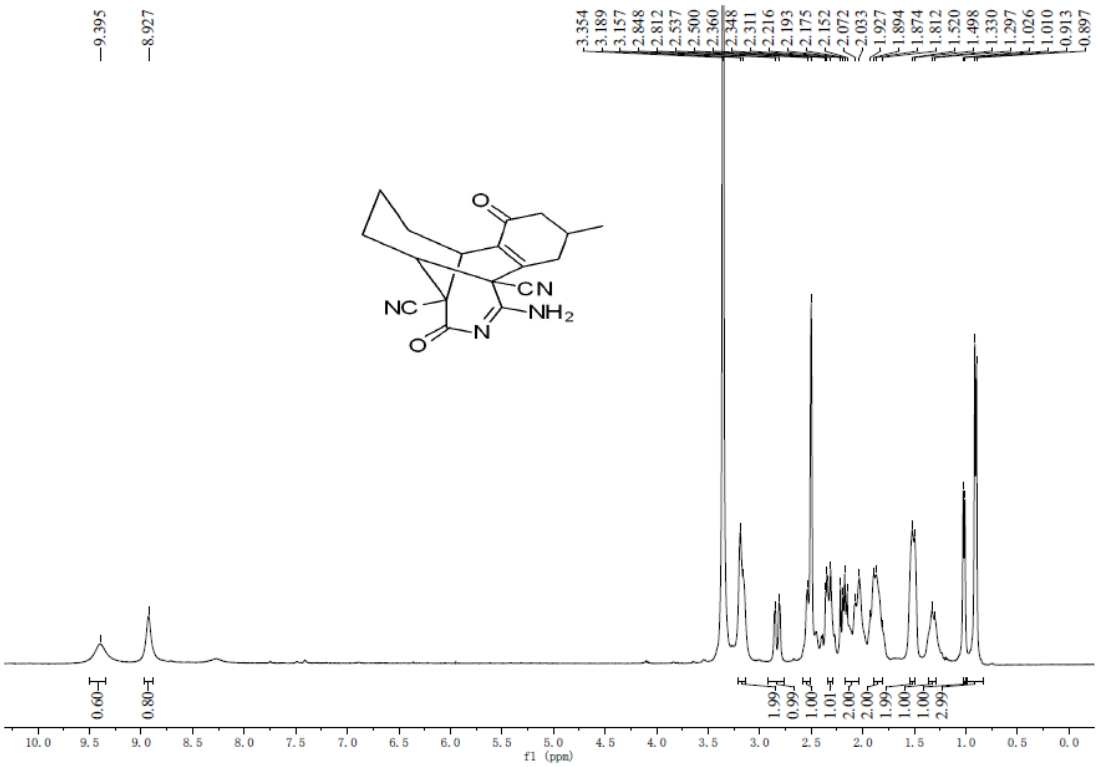
^{1}H NMR of compound **(6b)**



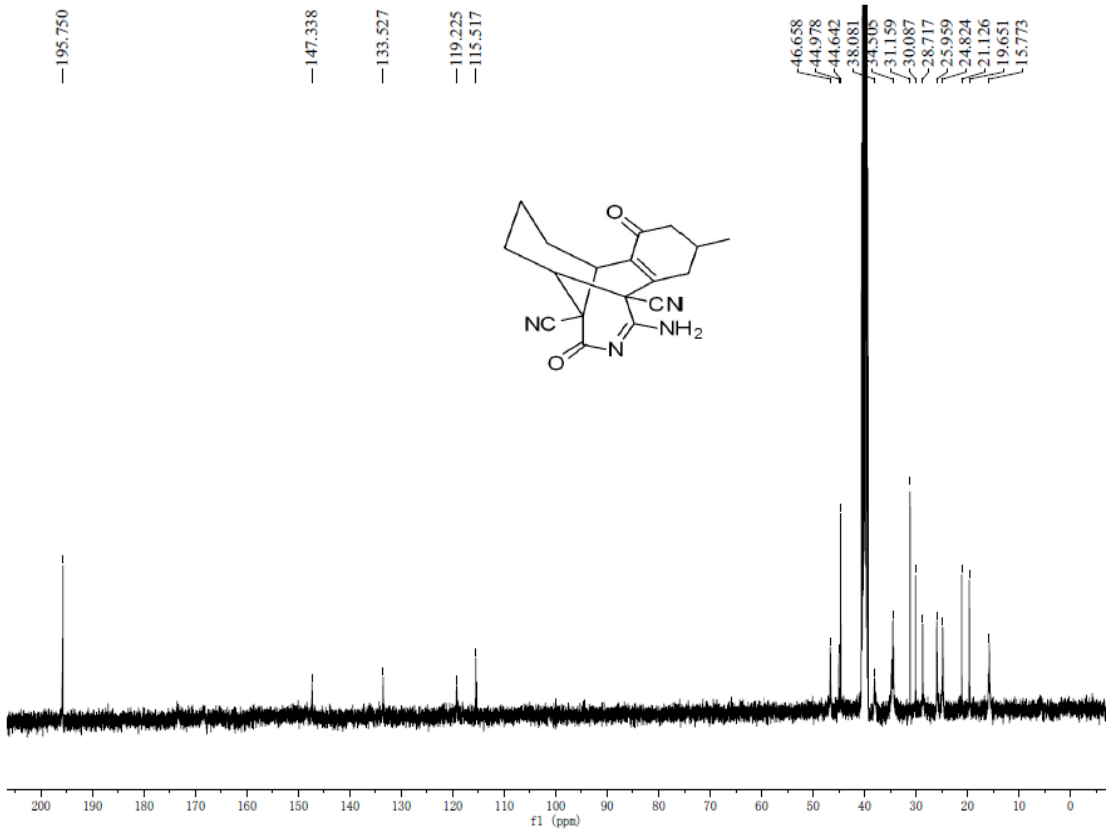
^{13}**C** NMR of compound **(6b)**



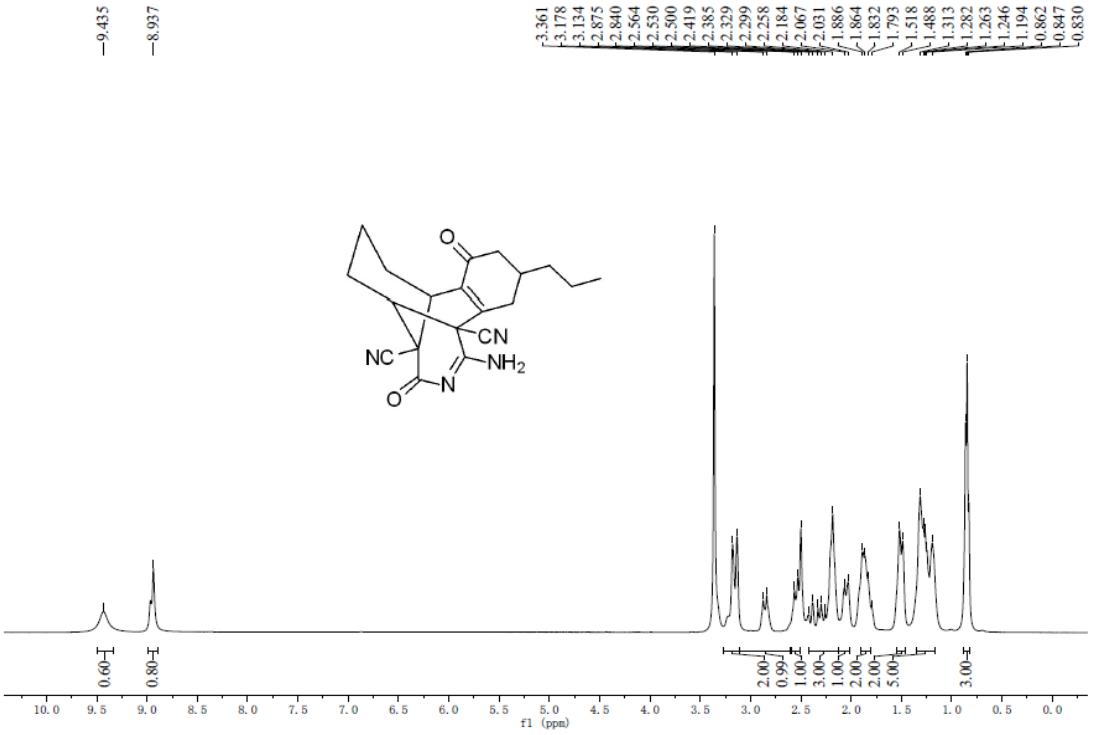
^{1}H NMR of compound **(6c)**



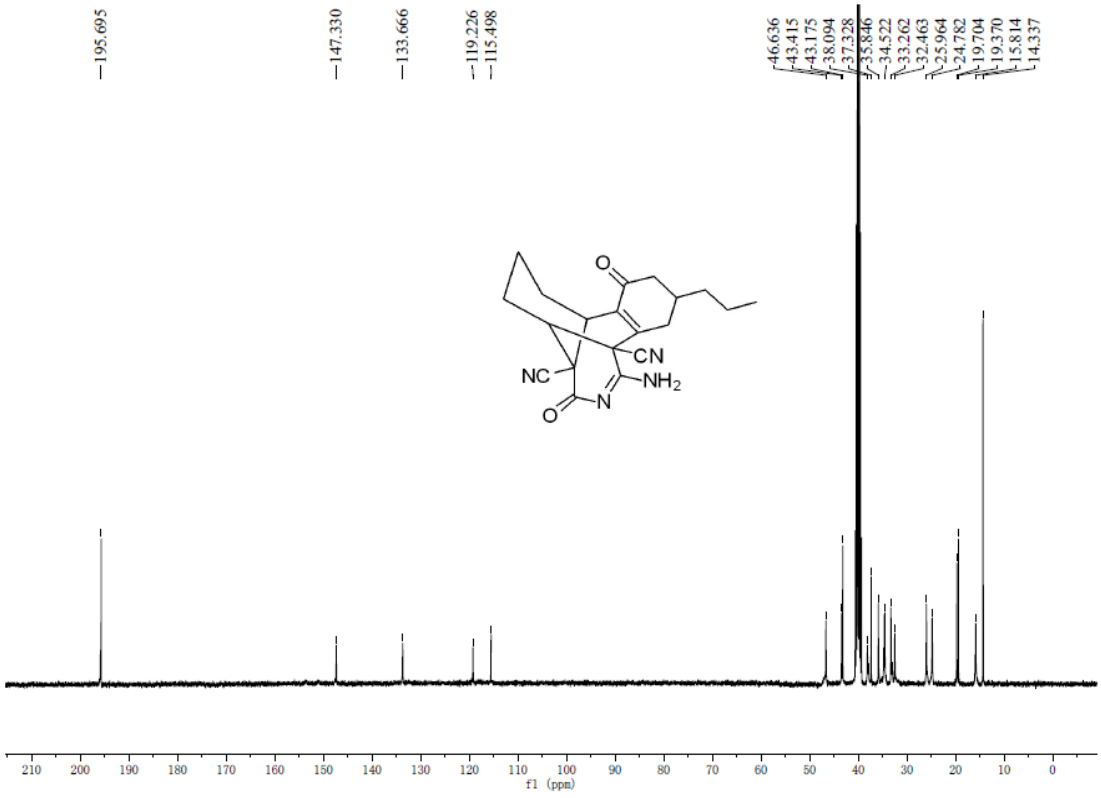
^{13}**C** NMR of compound **(6c)**



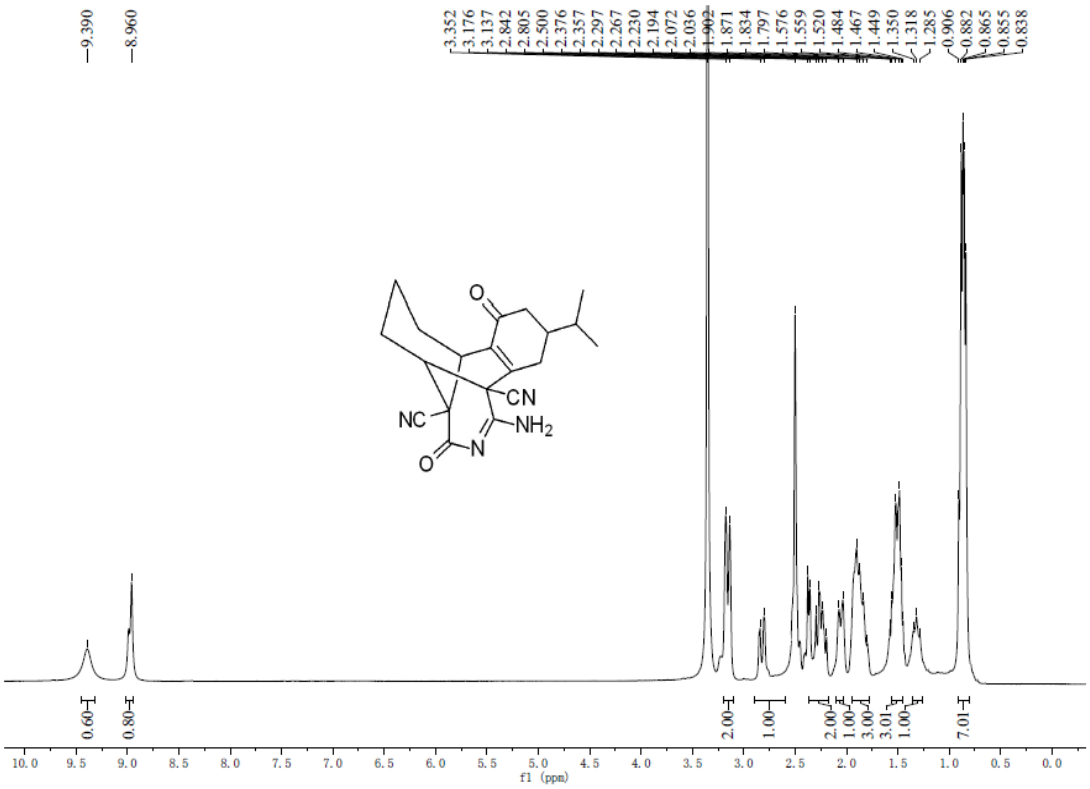
^{1}H NMR of compound **(6d)**



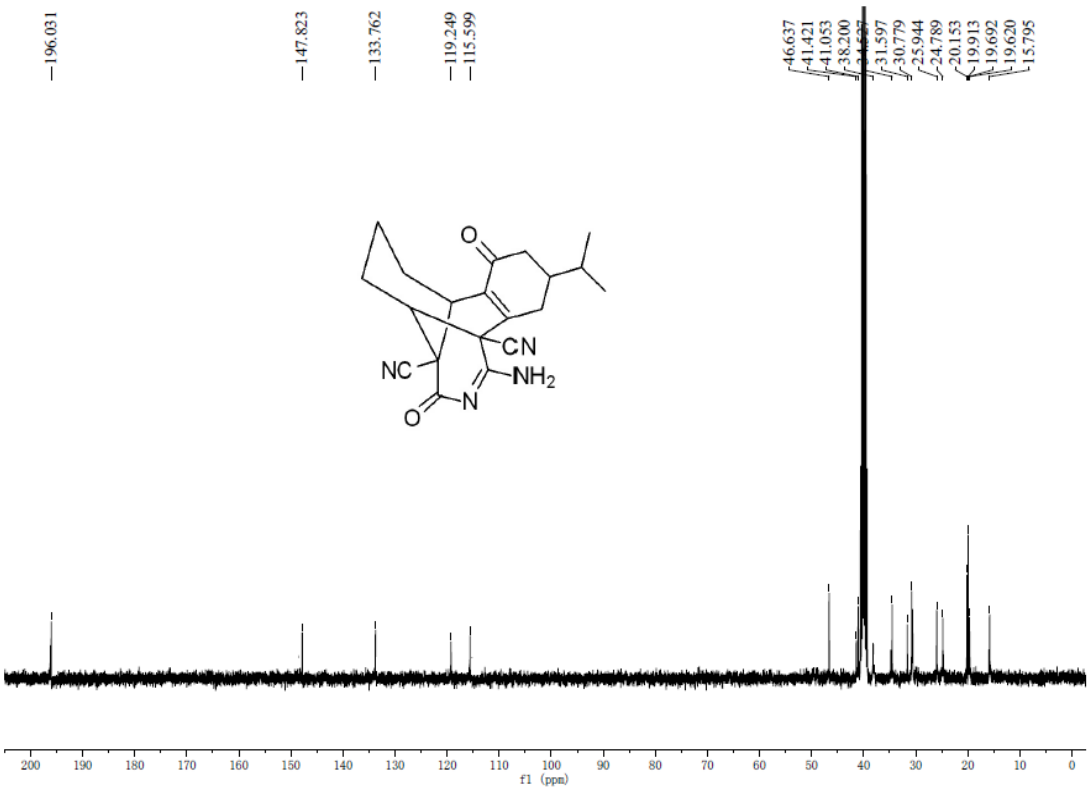
^{13}**C** NMR of compound **(6d)**



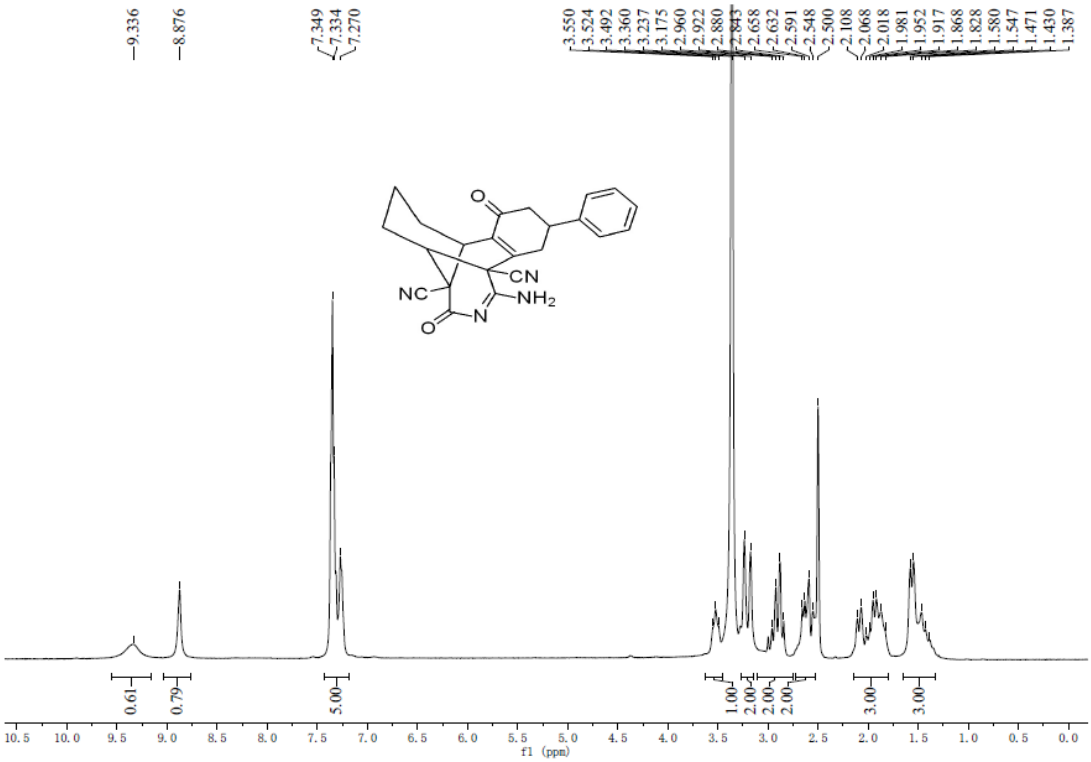
^{1}H NMR of compound **(6e)**



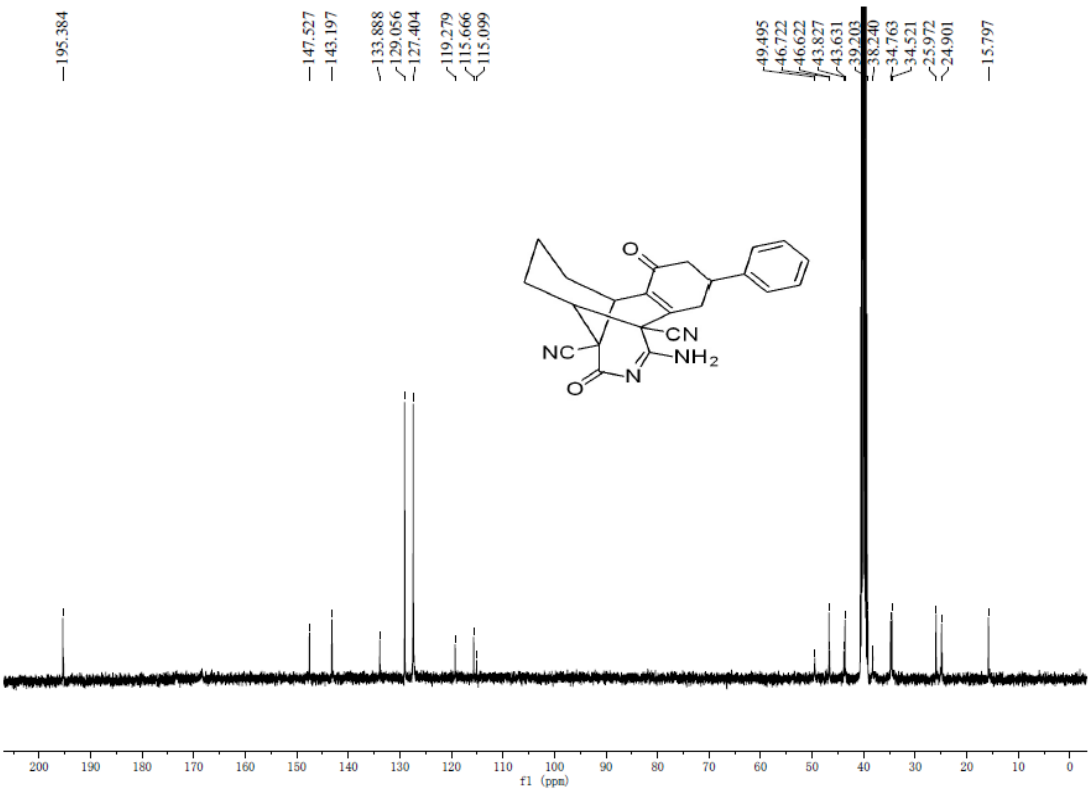
^{13}**C** NMR of compound **(6e)**



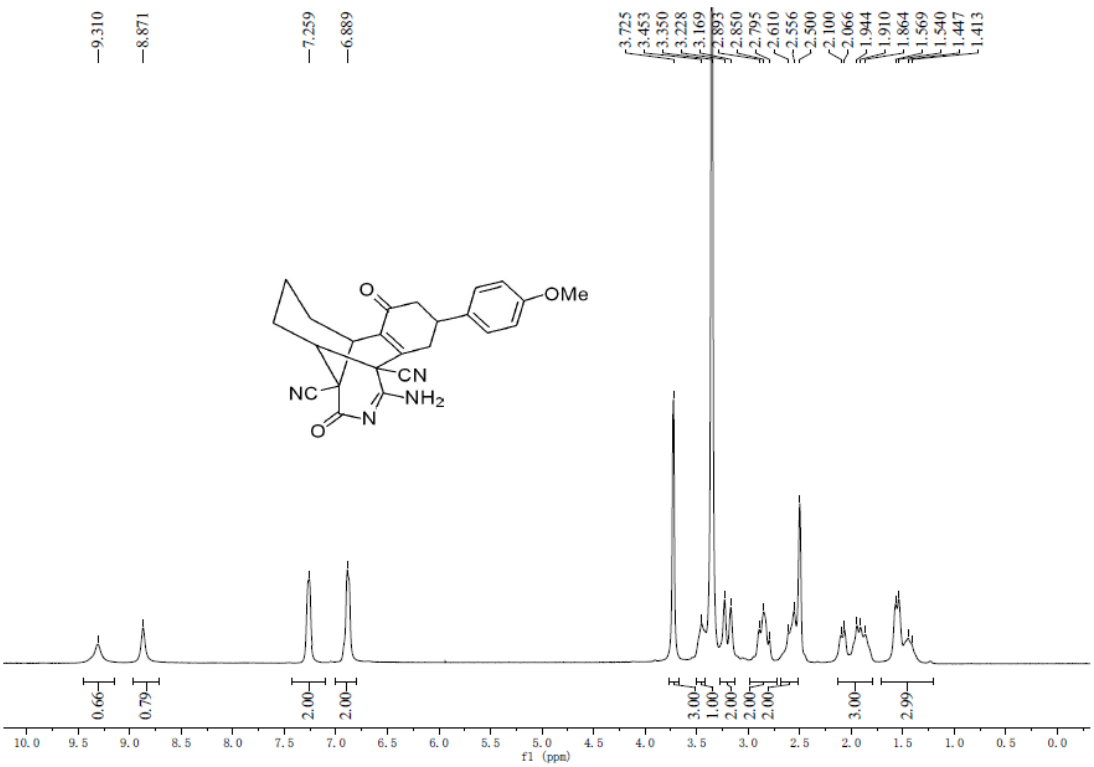
^{1}H NMR of compound **(6f)**



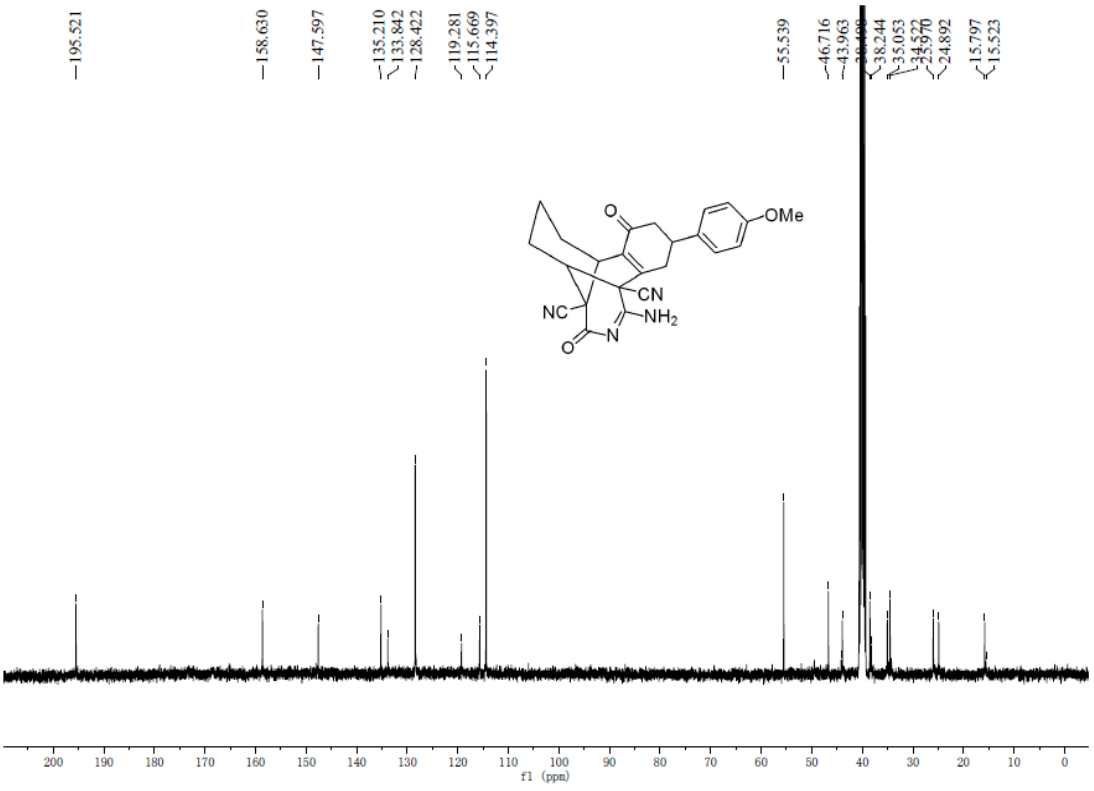
^{13}**C** NMR of compound **(6f)**



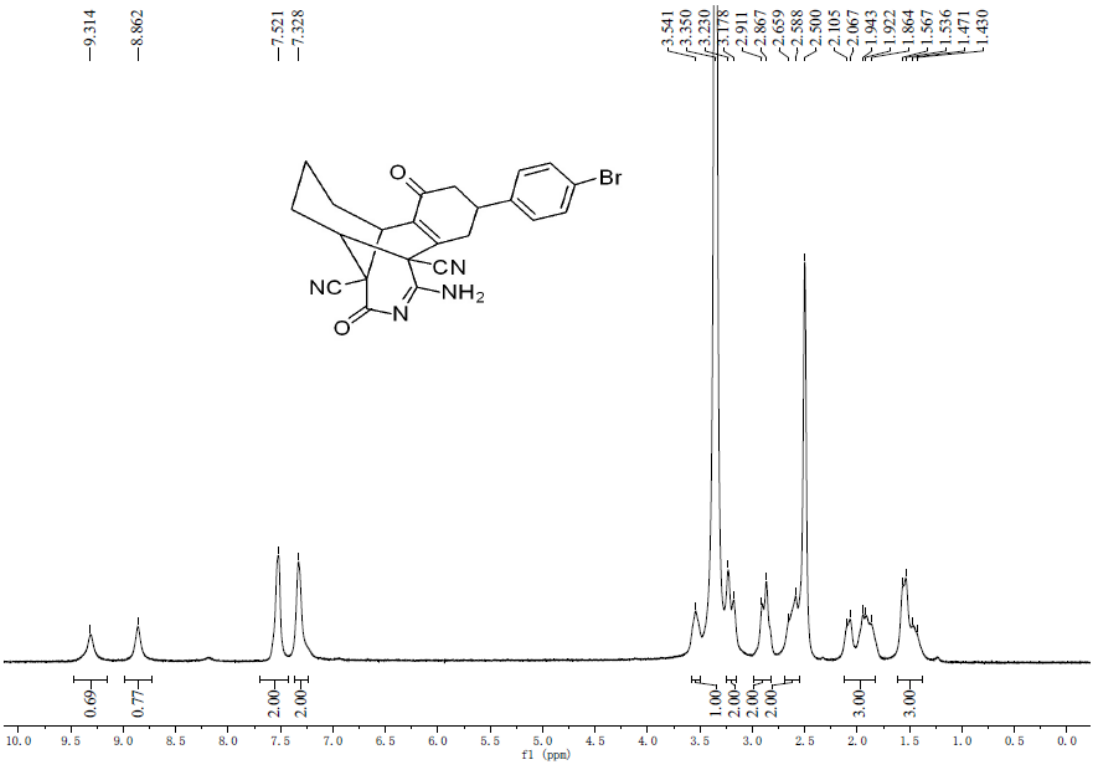
^{1}H NMR of compound **(6g)**



^{13}**C** NMR of compound **(6g)**



^{1}H NMR of compound **(6h)**



^{13}**C** NMR of compound **(6h)**