Supporting Information

Synthesis of indoline-piperidinones *via* a novel Ugi, ring expansion, *pseudo*-Dieckmann condensation and rearrangement cascade reaction

Jie Lei,[a,b] Gui-Ting Song,[a] Ya-Fei Luo,[a] Dian-Yong Tang,[a] Wei Yan,[b] Hong-yu Li,*[b] Zhong-Zhu Chen,*[a] Zhi-Gang Xu*[a]

[a]College of Pharmacy, National & Local Joint Engineering Research Center of Targeted and Innovative Therapeutics, Chongqing Key Laboratory of Kinase Modulators as Innovative Medicine, Chongqing University of Arts and Sciences, Chongqing 402160, China.

[b]Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

*e-mail: HLi2@uams.edu;18883138277@163.com; xzg@cqwu.edu.cn

Table of Contents **Page**

General Experimental

^{1}H and ^{13}C NMR were recorded on a Bruker 400 spectrometer. ^{1}H NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), relative intensity. ^{13}C NMR data are reported as follows: chemical shift in ppm (δ). LC/MS analyses were performed on a Shimadzu-2020 LC-MS instrument using the following conditions: Shim-pack VP-ODS C18 column (reverse phase, 150 x 4.6 mm); a linear gradient from 10% water and 90% acetonitrile to 75% acetonitrile and 25% water over 6.0 min; flow rate of 0.5 mL/min; UV photodiode array detection from 200 to 400 nm. High-resolution mass spectra (HRMS) were recorded on Thermo Scientific Exactive Plus System. The products were purified by Biotage Isolera™ Spektra Systems and hexane/EtOAc solvent systems. All reagents and solvents were obtained from commercial sources and used without further purification. All microwave irradiation experiments were carried out in a Biotage® Initiator Classic microwave apparatus with continuous irradiation power from 0 to 400W with utilization of the standard absorbance level of 250W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to 50 ^{o}C with gas jet cooling.

Experimental Sections

(a) **General procedures for compound 7**.

Glyoxylate acid (1.0 mmol), isonitrile (1.0 mmol), ethyl glyoxylate (2.0 mmol) and methyl-2-aminobenzoate (1.0 mmol) were mixed and stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under nitrogen blowing. Then the crude residue was subjected to DBU (2.0 equiv.) and DMF (3.0 mL) solution under microwave irradiation condition at 80 ^{o}C for 10 min. After the microwave vial was cooled to room temperature, the residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product **7**.

(b) **General procedures for compound 10**.

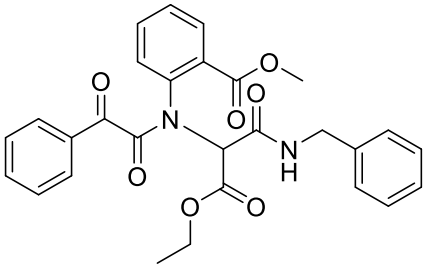
Benzoylformic acid (1.0 mmol), formaldehyde (4.0 mmol), benzyl isocyanide (1.0 mmol), and methyl-2-aminobenzoate (1.0 mmol) were mixed and stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure and the product **9a** was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) (350 mg of white solid was obtained and the yield was 82%). Then, the product **9a** (86 mg, 0.2 mmol) was subjected to DBU (0.4 mmol, 2.0 equiv.) and DMF (1.0 mL) solution under microwave irradiation condition at 140 ^{o}C for 10 min. After the microwave vial was cooled to room temperature, the residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (20-100%) to afford the relative targeted product **10** (64 mg, 78% yield) as yellow solid.

(c) **General procedures for compound 12**.

1a (1.0 mmol), **2** (2.0 mmol), **3** (1.0 mmol), and aniline **11** (1.0 mmol) were mixed and stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. Then, the product **5v** was subjected to DBU (2.0 mmol, 2.0 equiv.) and DMF (5.0 mL) solution under microwave irradiation condition at 80 ^{o}C for 10 min. After the microwave vial was cooled to room temperature, the residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford final product **12** (217 mg, 59% yield) as yellow solid.

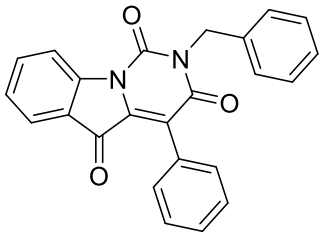
NMR Characterization Data and Figures of Products

Methyl 2-(*N*-(1-(benzylamino)-3-ethoxy-1,3-dioxopropan-2-yl)-2-oxo-2-phenyl acetamido)benzoate



Compound **5a** (white solid, 421 mg, yield 87%, R_f = 0.20 (EA/Hex= 20%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 2H), 7.83 – 7.78 (m, 1H), 7.64 (d, *J* = 4.3 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.42 – 7.35 (m, 4H), 7.20 – 7.13 (m, 3H), 6.81 (d, *J* = 6.8 Hz, 2H), 5.77 (s, 1H), 4.49 – 4.41 (m, 2H), 4.24 (dd, *J* = 14.3, 7.2 Hz, 1H), 3.94 (dd, *J* = 14.3, 4.3 Hz, 1H), 3.78 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.53, 167.44, 167.15, 166.63, 163.01, 136.94, 135.81, 134.48, 133.10, 132.87, 131.57, 130.64, 130.36, 130.06, 129.77, 129.51, 129.31, 128.59, 128.00, 127.34, 65.09, 62.52, 52.82, 43.88, 14.15. HRMS (ESI) m/z calcd for $C_{28}H_{27}N_2O_7^+$ $(M+H)^+$ 503.1813, found 503.1811.

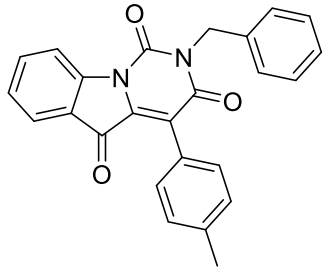
2-Benzyl-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7a** (dark yellow solid, 262 mg, yield 69%, R_f = 0.29 (EA/Hex=15%)) ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.36 (d, *J* = 8.2 Hz, 1H), 7.88-7.82 (m, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.46-7.39 (m, 8H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 182.35, 163.25, 147.57, 146.58, 137.98, 136.98, 136.09, 131.21,129.29, 129.13, 128.85, 128.26, 127.96, 127.83, 126.40, 125.11, 123.80, 118.11, 116.74, 44.71. HRMS (ESI) m/z calcd for

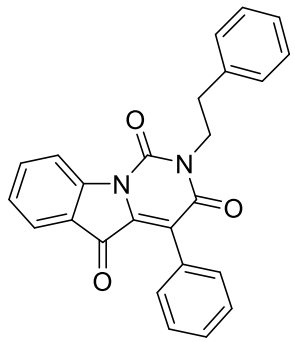
$C_{24}H_{17}N_2O_3^+$ $(M+H)^+$ 381.1234, found 381.1238.

2-Benzyl-4-(*p*-tolyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



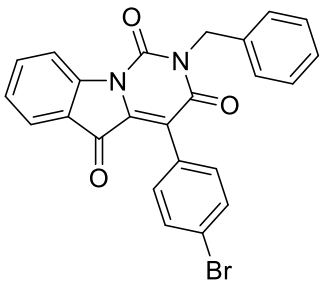
Compound **7b** (dark yellow solid, 288 mg, yield 73%, R_f = 0.21 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.79-7.68 (m, 2H), 7.60-7.54 (m, 2H), 7.35-7.27 (m, 7H), 7.26 (s, 1H), 5.26 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.79, 163.03, 147.28, 146.40, 139.91, 137.53, 136.23, 134.60, 130.46, 129.54, 128.81, 128.56, 128.01, 126.03, 125.01, 124.66, 123.49, 119.98, 117.09, 45.06, 21.56. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_3^+$ $(M+H)^+$ 395.1390, found 395.1391.

2-Phenethyl-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



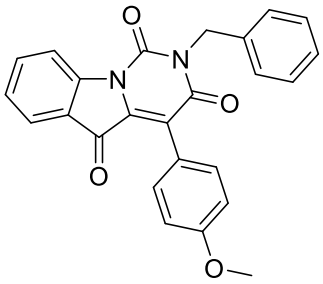
Compound **7c** (light yellow solid, 251 mg, yield 64%, R_f = 0.24 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.85-7.69 (m, 2H), 7.48 (dd, *J* = 4.2, 2.3 Hz, 3H), 7.44-7.39 (m, 2H), 7.37-7.29 (m, 5H), 7.25-7.21 (m, 1H), 4.35-4.24 (m, 2H), 3.09-2.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.81, 162.78, 147.09, 146.50, 138.10, 137.65, 134.79, 130.47, 129.68, 129.02, 128.62, 128.05, 127.70, 126.69, 126.09, 125.09, 123.42, 119.69, 117.04, 43.33, 33.82. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_3^+$ $(M+H)^+$ 395.1390, found 395.1391.

2-Benzyl-4-(4-bromophenyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



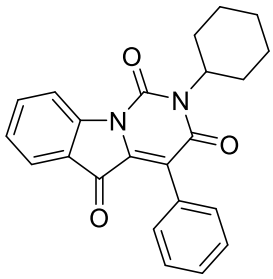
Compound **7d** (dark yellow solid, 275 mg, yield 61%, R_f = 0.23 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.81-7.69 (m, 2H), 7.62-7.53 (m, 4H), 7.36-7.27 (m, 6H), 5.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.71, 162.62, 147.12, 146.47, 137.79, 136.03, 134.89, 132.26, 131.30, 129.52, 128.60, 128.10, 126.51, 126.23, 125.16, 124.27, 123.23, 118.45, 117.13, 45.13. HRMS (ESI) m/z calcd for $C_{24}H_{16}BrN_2O_3^+$ $(M+H)^+$ 459.0339, found 459.0335.

2-Benzyl-4-(4-methoxyphenyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



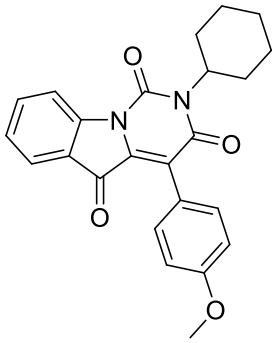
Compound **7e** (light yellow solid, 308 mg, yield 75%, R_f = 0.23 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.75-7.69 (m, 1H), 7.60-7.55 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.32 (qd, *J* = 8.6, 3.9 Hz, 4H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.26 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.82, 163.14, 160.89, 147.25, 146.30, 137.48, 136.22, 134.27, 132.29, 129.51, 128.56, 128.01, 126.01, 124.98, 123.56, 119.82, 119.64, 117.09, 113.53, 55.32, 45.08. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_4^+$ $(M+H)^+$ 411.1339, found 411.1339.

2-Cyclohexyl-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



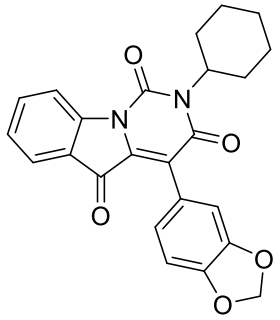
Compound **7f** (dark yellow solid, 253 mg, yield 68%, R_f = 0.22 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.81-7.68 (m, 2H), 7.44 (m, 5H), 7.32 (t, *J* = 7.3 Hz, 1H), 4.93-4.86 (m, 1H), 2.49 (qd, *J* = 12.4, 3.3 Hz, 2H), 1.88 (d, *J* = 13.2 Hz, 2H), 1.78-1.70 (m, 2H), 1.47-1.34 (m, 2H), 1.33-1.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.03, 163.37, 147.42, 146.75, 137.55, 134.64, 130.53, 129.53, 128.08, 127.97, 125.89, 124.96, 123.47, 119.86, 117.17, 55.47, 28.67, 26.40, 25.27. HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2O_3^+$ $(M+H)^+$ 373.1547, found 373.1546.

2-Cyclohexyl-4-(4-methoxyphenyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



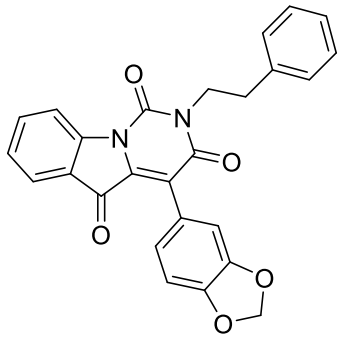
Compound **7g** (dark yellow solid, 260 mg, yield 65%, R_f = 0.30 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (t, *J* = 8.9 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 1H), 3.78 (s, 3H), 1.89 (dd, *J* = 12.3, 3.0 Hz, 1H), 1.80 (d, *J* = 10.1 Hz, 2H), 1.69-1.63 (m, 3H), 1.40-1.24 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.06, 162.53, 159.74, 146.35, 145.53, 136.37, 132.89, 131.27, 124.76, 123.84, 122.58, 118.95, 116.11, 112.78, 112.42, 54.28, 47.37, 31.70, 27.64, 25.37, 24.26, 23.74. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_4^+$ $(M+H)^+$ 403.1652, found 403.1653.

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-cyclohexylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



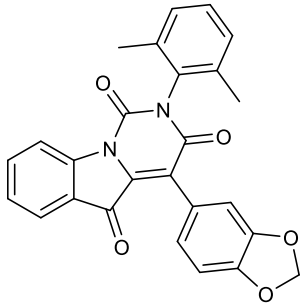
Compound **7h** (red solid, yield 67%, 280 mg, R_f = 0.15 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.96-6.88 (m, 3H), 6.03 (s, 2H), 4.90-4.83 (m, 1H), 2.53-2.43 (m, 2H), 1.88 (d, *J* = 10.3 Hz, 2H), 1.73 (d, *J* = 9.6 Hz, 3H), 1.45-1.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.99, 163.39, 148.85, 147.42, 147.33, 146.58, 137.50, 134.48, 125.86, 125.07, 124.94, 123.50, 121.29, 119.61, 117.15, 111.04, 108.07, 101.41, 55.46, 28.64, 26.37, 25.26. HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_5^+$ $(M+H)^+$ 417.1445, found 417.1448.

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenethylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



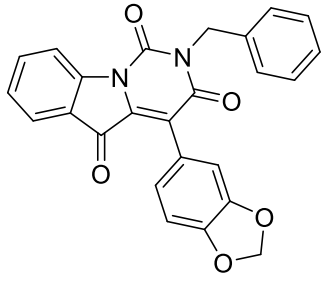
Compound **7i** (red solid, yield 74%, 322 mg, R_f = 0.18 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.38-7.29 (m, 5H), 7.24 (dd, *J* = 6.0, 2.9 Hz, 1H), 6.96-6.91 (m, 2H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.04 (s, 2H), 4.39-4.21 (m, 2H), 3.07-2.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.79, 162.83, 149.00, 147.50, 147.01, 146.34, 138.08, 137.62, 134.63, 129.02, 128.62, 126.70, 126.08, 125.08, 123.47, 120.98, 119.47, 117.03, 110.97, 108.17, 101.47, 43.34, 33.81. HRMS (ESI) m/z calcd for $C_{26}H_{19}N_2O_5^+$ $(M+H)^+$ 439.1288, found 439.1281.

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(2,6-dimethylphenyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7j** (red solid, yield 59%, 258 mg, R_f = 0.20 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.32-7.27 (m, 1H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.03 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.98 (d, *J* = 1.5 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.70, 162.16, 149.15, 147.43, 146.29, 146.18, 137.72, 135.37, 135.28, 132.83, 129.31, 128.76, 126.19, 125.44, 125.12, 123.62, 120.63, 119.74, 117.22, 111.19, 108.06, 101.49, 17.86. HRMS (ESI) m/z calcd for $C_{26}H_{19}N_2O_5^+$ $(M+H)^+$ 439.1288, found 439.1289.

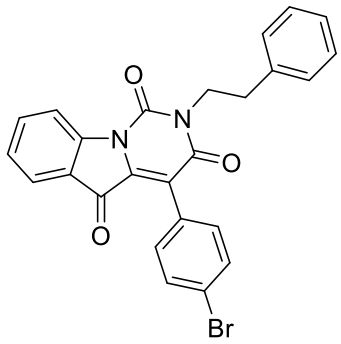
4-(Benzo[*d*][1,3]dioxol-5-yl)-2-benzylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7k** (red solid, 264 mg, yield 62%, R_f = 0.32 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.57 (d, *J* = 6.7 Hz, 2H), 7.31 (dd, *J* = 15.3, 8.3 Hz, 4H), 6.94 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.03 (s, 2H), 5.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.71, 162.98, 148.99, 147.47, 147.19, 146.30, 137.57, 136.15, 134.67, 129.53, 128.57, 128.04, 126.08, 125.13, 125.04, 123.44, 120.96, 119.51, 117.09, 111.00, 108.14, 101.46, 45.10. HRMS (ESI) m/z calcd for $C_{25}H_{17}N_2O_5^+$ $(M+H)^+$

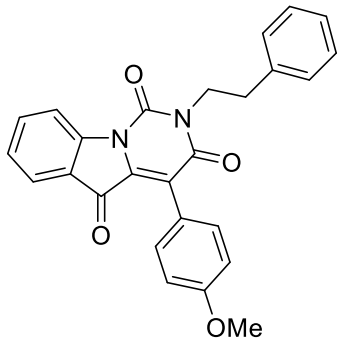
425.1132, found 425.1131.

4-(4-Bromophenyl)-2-phenethylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7l** (red solid, 303 mg, yield 64%, R_f = 0.27 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.38-7.32 (m, 5H), 7.30 (d, *J* = 8.4 Hz, 3H), 4.31-4.27 (m, 2H), 3.04-2.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.79, 162.46, 146.93, 146.50, 137.97, 137.84, 134.84, 132.21, 131.31, 129.00, 128.63, 126.72, 126.52, 126.23, 125.20, 124.25, 123.25, 118.39, 117.07, 43.43, 33.30. HRMS (ESI) m/z calcd for $C_{25}H_{18}BrN_2O_3^+$ $(M+H)^+$ 473.0495, found 473.0492.

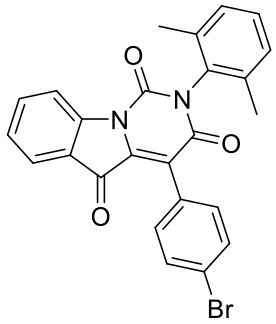
4-(4-methoxyphenyl)-2-phenethylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7m** (red solid, 285 mg, yield 67%, R_f = 0.21 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.36-7.30 (m, 5H), 7.23 (d, *J* = 6.9 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 4.34-4.24 (m, 2H), 3.88 (s, 3H), 3.06-2.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.87, 162.97, 160.88, 147.05,

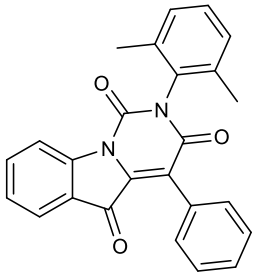
146.31, 138.13, 137.51, 133.91, 132.26, 129.02, 128.75, 128.61, 126.70, 126.67, 126.00, 125.00, 123.56, 119.65, 117.00, 113.53, 55.33, 43.33, 33.83. HRMS (ESI) m/z calcd for $C_{26}H_{21}N_2O_4^+$ $(M+H)^+$ 425.1496, found 425.1492.

4-(4-Bromophenyl)-2-(2,6-dimethylphenyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7n** (red solid, 330 mg, yield 70%, R_f = 0.23 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 3H), 7.33-7.24 (m, 2H), 7.21 (d, *J* = 7.4 Hz, 2H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.69, 161.81, 146.46, 146.11, 137.96, 135.59, 135.33, 132.68, 132.43, 131.21, 129.39, 128.80, 126.36, 126.17, 125.25, 124.43, 123.40, 118.64, 117.26, 17.86. HRMS (ESI) m/z calcd for $C_{25}H_{18}BrN_2O_3^+$ $(M+H)^+$ 473.0495, found 473.0497.

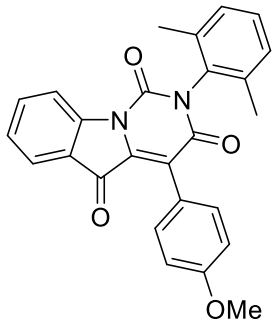
2-(2,6-Dimethylphenyl)-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7o** (red solid, 280 mg, yield 71%, R_f = 0.25 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 2.2 Hz, 5H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.34-7.27 (m, 1H), 7.21 (d, *J* = 7.5 Hz, 2H), 2.22 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.73, 162.10, 146.46, 146.26, 137.77, 135.51, 135.38, 132.82, 130.70,

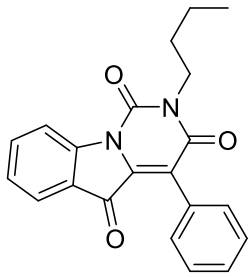
129.84, 129.30, 128.76, 127.94, 127.32, 126.21, 125.14, 123.55, 119.96, 117.23, 17.86. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_3^+$ $(M+H)^+$ 395.1390, found 395.1392.

2-(2,6-Dimethylphenyl)-4-(4-methoxyphenyl)pyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7p** (dark yellow solid, 260 mg, yield 61%, R_f = 0.29 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.3-7.28 (m, 1H), 7.21 (d, *J* = 7.4 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.81, 162.34, 161.06, 146.29, 137.64, 135.40, 132.90, 132.54, 129.28, 128.76, 126.12, 125.06, 123.74, 120.05, 119.33, 117.22, 113.43, 55.33, 17.87. HRMS (ESI) m/z calcd for $C_{26}H_{21}N_2O_4^+$ $(M+H)^+$ 425.1496, found 425.1432.

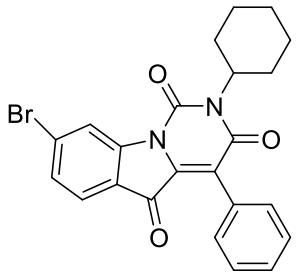
2-Butyl-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7q** (yellow solid, 264 mg, R^4=Me, yield 69%; R^4=Et, yield 65%, R_f = 0.35 (EA/Hex= 15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.69 (m, 2H), 7.46 (dd, *J* = 6.7, 2.8 Hz, 3H), 7.41 (dt, *J* = 3.9, 2.7 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 4.12 – 4.01 (m, 2H), 1.70 (tt, *J* = 7.7, 6.6 Hz, 2H), 1.42 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.87, 162.80, 147.19, 146.48, 137.59, 134.67, 130.46, 129.60, 127.96, 127.69, 125.99, 125.01, 123.34,

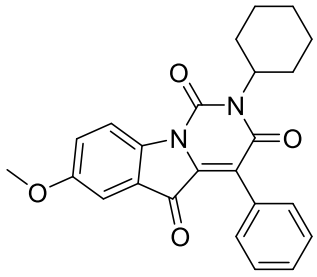
119.62, 116.99, 41.87, 29.68, 20.24, 13.72. HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3^+$ $(M+H)^+$ 374.1390, found 374.1391.

8-Bromo-2-cyclohexyl-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



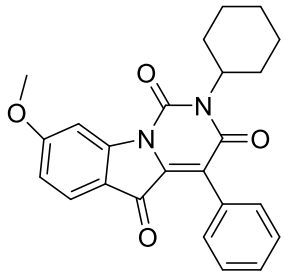
Compound **7r** (yellow solid, 280 mg, yield 72%, R_f = 0.28 (EA/Hex= 10%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.45 (dd, *J* = 5.2, 1.1 Hz, 4H), 7.41 – 7.37 (m, 2H), 4.85 (ddd, *J* = 12.0, 8.7, 3.6 Hz, 1H), 2.49 – 2.40 (m, 2H), 1.87 (d, *J* = 12.8 Hz, 2H), 1.70 (s, 2H), 1.43 – 1.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.76, 163.01, 132.80, 131.18, 130.42, 129.67, 129.33, 128.41, 127.95, 127.63, 125.71, 122.19, 120.56, 55.60, 29.56, 28.57, 26.44. HRMS (ESI) m/z calcd for $C_{23}H_{20}BrN_2O_3^+$ $(M+H)^+$ 451.0652, found 451.0649.

2-Cyclohexyl-7-methoxy-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



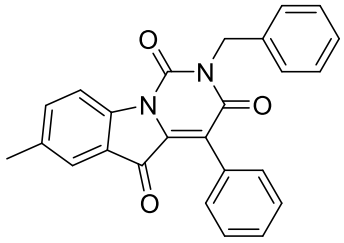
Compound **7s** (yellow solid, 174 mg, yield 52%, R_f = 0.30 (EA/Hex= 10%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.42 – 7.36 (m, 2H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 4.90 – 4.81 (m, 1H), 3.83 (s, 3H), 2.54 – 2.42 (m, 2H), 1.86 (d, *J* = 12.9 Hz, 2H), 1.72 (d, *J* = 13.5 Hz, 2H), 1.45 – 1.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.86, 163.29, 157.78, 141.00, 131.21, 130.29, 129.40, 127.90, 124.96, 118.12, 107.17, 55.84, 55.31, 29.62, 28.60, 26.33. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_3^+$ $(M+H)^+$ 403.1652, found 403.1652.

2-Cyclohexyl-8-methoxy-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



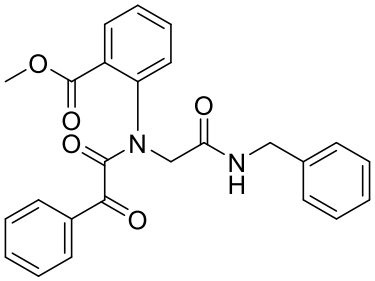
Compound **7t** (yellow solid, 167 mg, yield 50%, R_f = 0.35 (EA/Hex= 10%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.81-7.68 (m, 2H), 7.44 (m, 4H), 7.32 (t, *J* = 7.3 Hz, 1H), 4.93-4.86 (m, 1H), 3.78 (s, 3H), 2.49 (qd, *J* = 12.4, 3.3 Hz, 2H), 1.88 (d, *J* = 13.2 Hz, 2H), 1.78-1.70 (m, 2H), 1.47-1.34 (m, 2H), 1.33-1.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.03, 163.37, 147.42, 146.75, 137.55, 134.64, 130.53, 129.53, 128.08, 127.97, 125.89, 124.96, 123.47, 119.86, 117.17, 59.23, 55.47, 28.67, 26.40, 25.27. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_3^+$ $(M+H)^+$ 403.1652, found 403.1652.

2-Benzyl-7-methyl-4-phenylpyrimido[1,6-*a*]indole-1,3,5(2*H*)-trione



Compound **7u** (yellow solid, 151 mg, yield 57%, R_f = 0.35 (EA/Hex= 10%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.81 – 7.68 (m, 2H), 7.57 (d, *J* = 6.6 Hz, 2H), 7.30 (ddd, *J* = 16.7, 9.5, 3.8 Hz, 8H), 5.26 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.79, 163.03, 147.28, 146.40, 139.91, 137.53, 136.23, 134.60, 130.46, 129.54, 128.81, 128.56, 128.01, 126.03, 125.01, 124.66, 123.49, 119.98, 117.09, 45.06, 21.56. HRMS (ESI) m/z calcd for $C_{25}H_{19}N_2O_3^+$ $(M+H)^+$ 395.1390, found 395.1391.

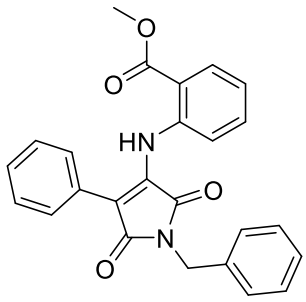
Methyl 2-(*N*-(2-(benzylamino)-2-oxoethyl)-2-oxo-2-phenylacetamido)benzoate



Compound **9a** (white solid, 350 mg, yield 82%, R_f = 0.25 (EA/Hex=30%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 10.1, 4.2 Hz, 3H), 7.52 (dd, *J* = 9.9, 4.1 Hz, 2H), 7.46-7.42 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.33 (d, *J* = 7.1 Hz, 2H), 7.30 (d, *J* = 3.2 Hz, 3H), 7.23-7.19 (m, 1H), 4.90 (d, *J* = 8.9 Hz, 1H), 4.52 (dd, *J* = 8.0, 4.7 Hz, 2H), 4.23 (t, *J* = 8.5 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.41, 167.68, 166.62, 165.69, 140.19, 138.02, 134.41, 133.59, 133.01, 131.62, 130.73, 130.28, 129.96, 128.99, 128.64，128.60, 127.77, 127.40, 53.74, 52.49, 43.64. HRMS (ESI) m/z calcd for $C_{25}H_{23}N_2O_5^+$ $(M+H)^+$ 431.1601, found 431.1607.

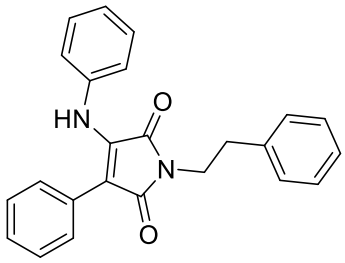
Methyl

2-((1-benzyl-2,5-dioxo-4-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)amino)benzoate



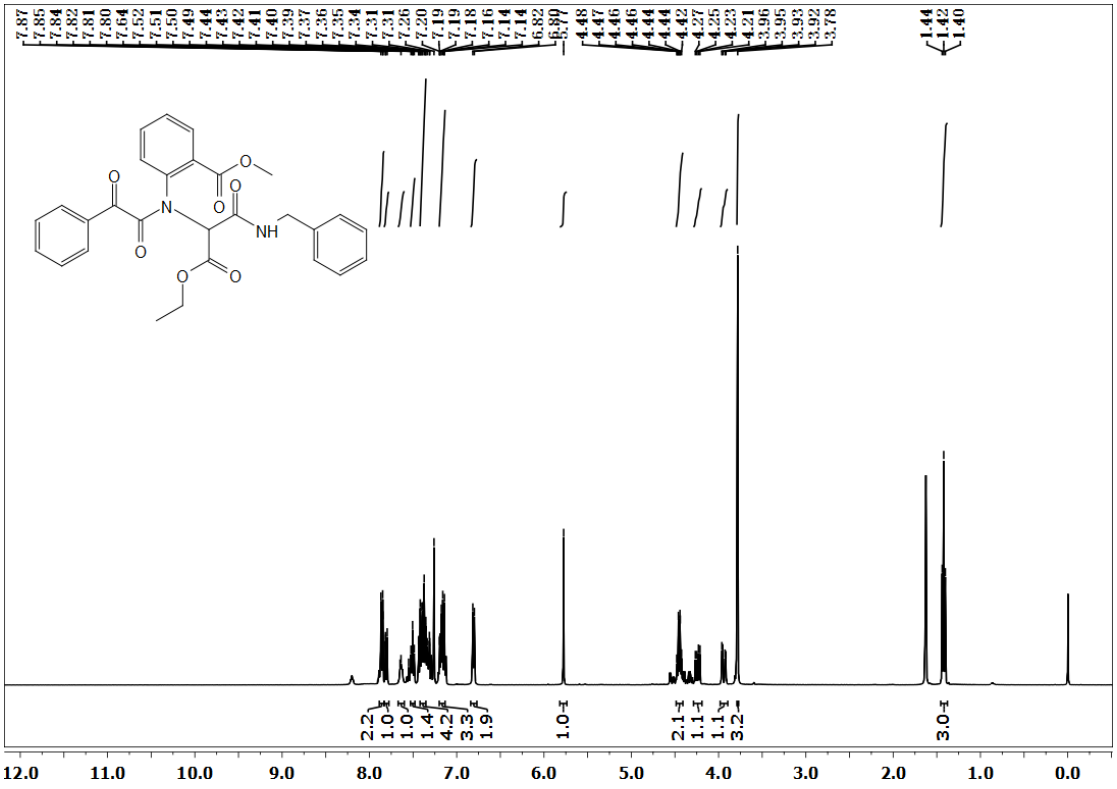
Compound **10** (yellow solid, 64 mg, yield 78%, R_f = 0.29 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.98 (s, 1H), 7.47 (d, *J* = 6.5 Hz, 2H), 7.37-7.29 (m, 2H), 7.26 (s, 1H), 7.19 (d, *J* = 6.5 Hz, 3H), 7.11 (s, 2H), 6.90 (s, 2H), 6.12 (s, 1H), 4.80 (s, 2H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.68, 168.13, 168.04, 138.96, 136.56, 134.87, 132.45, 130.90, 129.89, 129.71, 128.84, 128.66, 127.87, 127.80, 127.49, 122.02, 120.89, 116.98, 106.24, 52.47, 41.92. HRMS (ESI) m/z calcd for $C_{25}H_{21}N_2O_4^+$ $(M+H)^+$ 413.1496, found 413.1495.

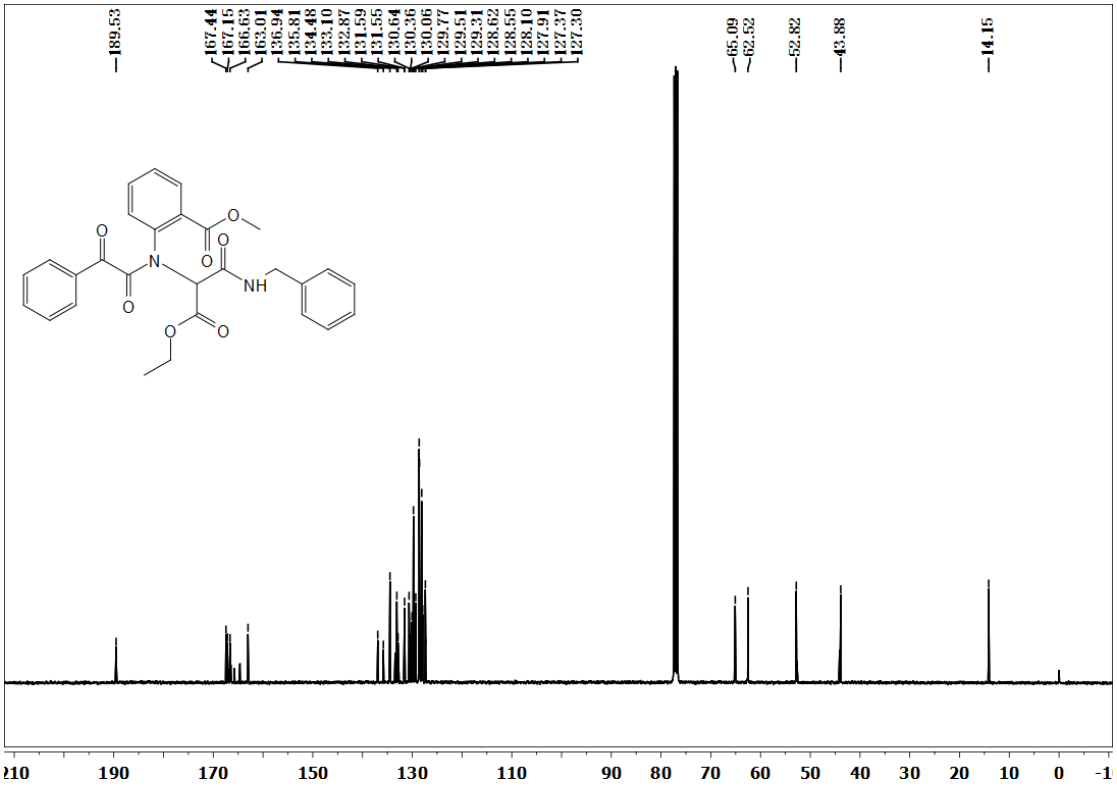
1-Phenethyl-3-phenyl-4-(phenylamino)-1*H*-pyrrole-2,5-dione



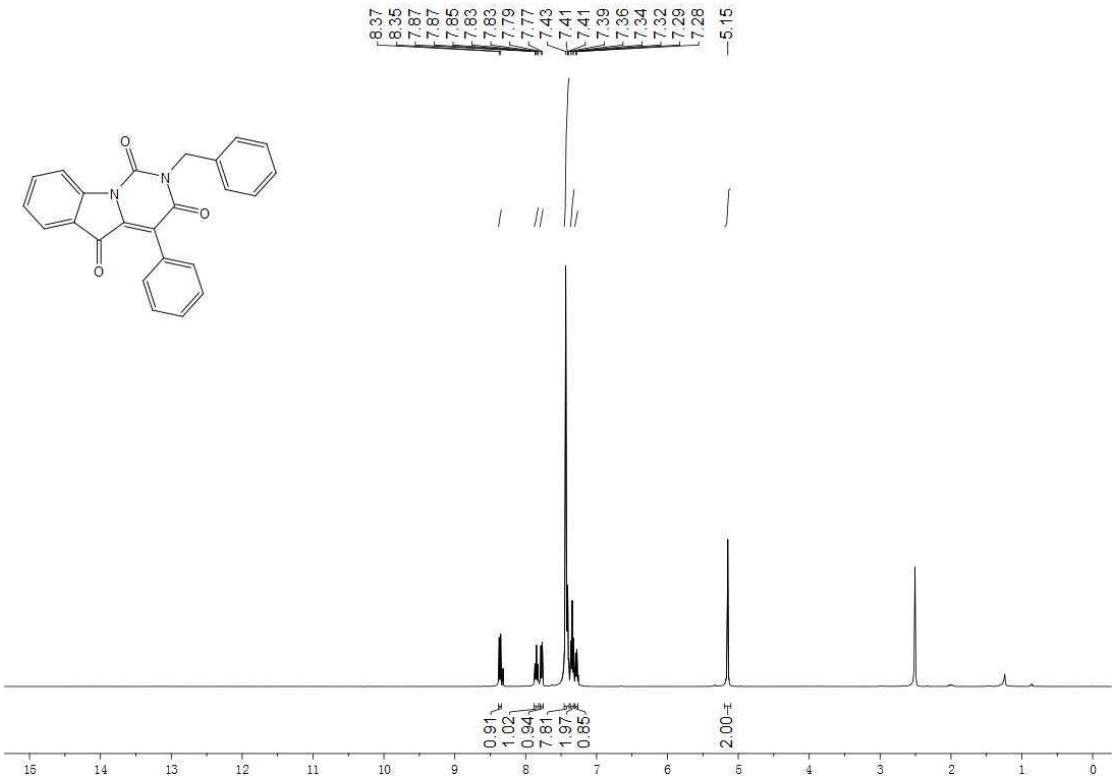
Compound **12** (yellow solid, 91 mg, yield 59%, R_f = 0.30 (EA/Hex= 10%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 6H), 7.16 – 7.08 (m, 3H), 7.06 – 6.93 (m, 5H), 6.63 (d, *J* = 7.5 Hz, 2H), 3.86 (dd, *J* = 8.7, 6.9 Hz, 2H), 3.06 – 2.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.03, 168.35, 138.19, 136.28, 135.97, 129.72, 129.33, 128.91, 128.58, 128.30, 127.32, 126.64, 124.49, 121.50, 102.64, 39.57, 34.85. HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_3^+$ $(M+H)^+$ 369.1598, found 369.1597.

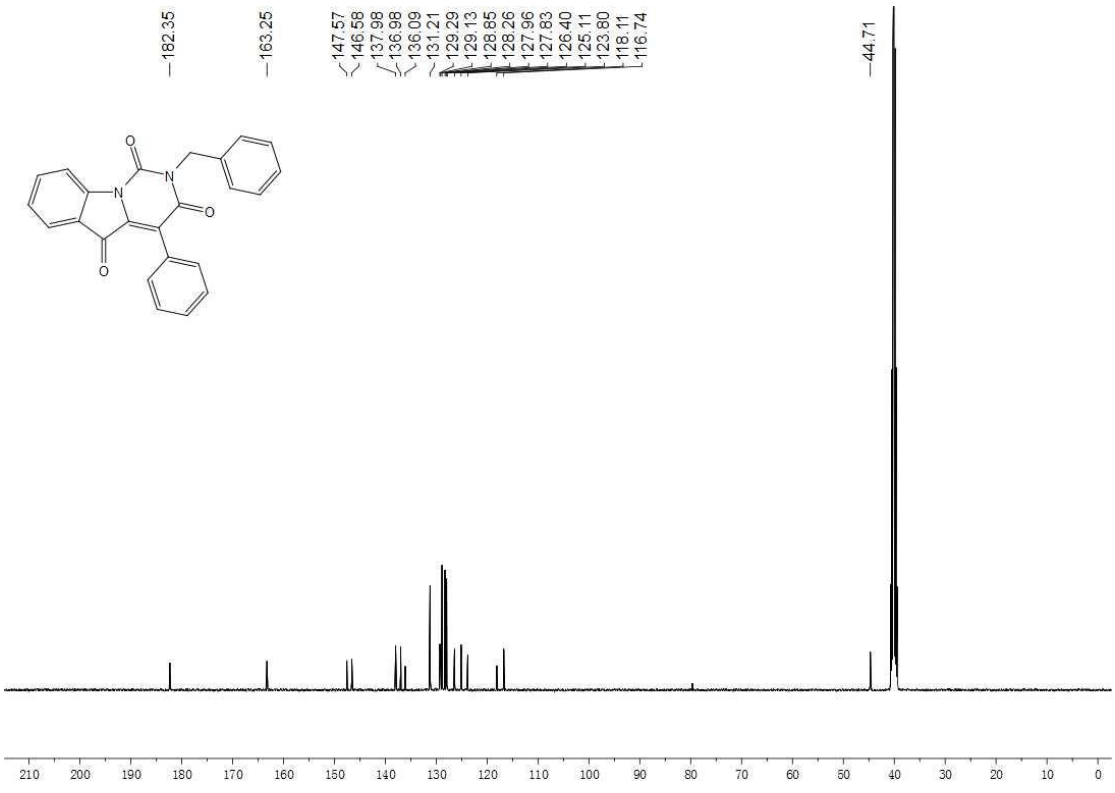
^{1}H NMR and ^{13}C NMR spectrum of **5a**.



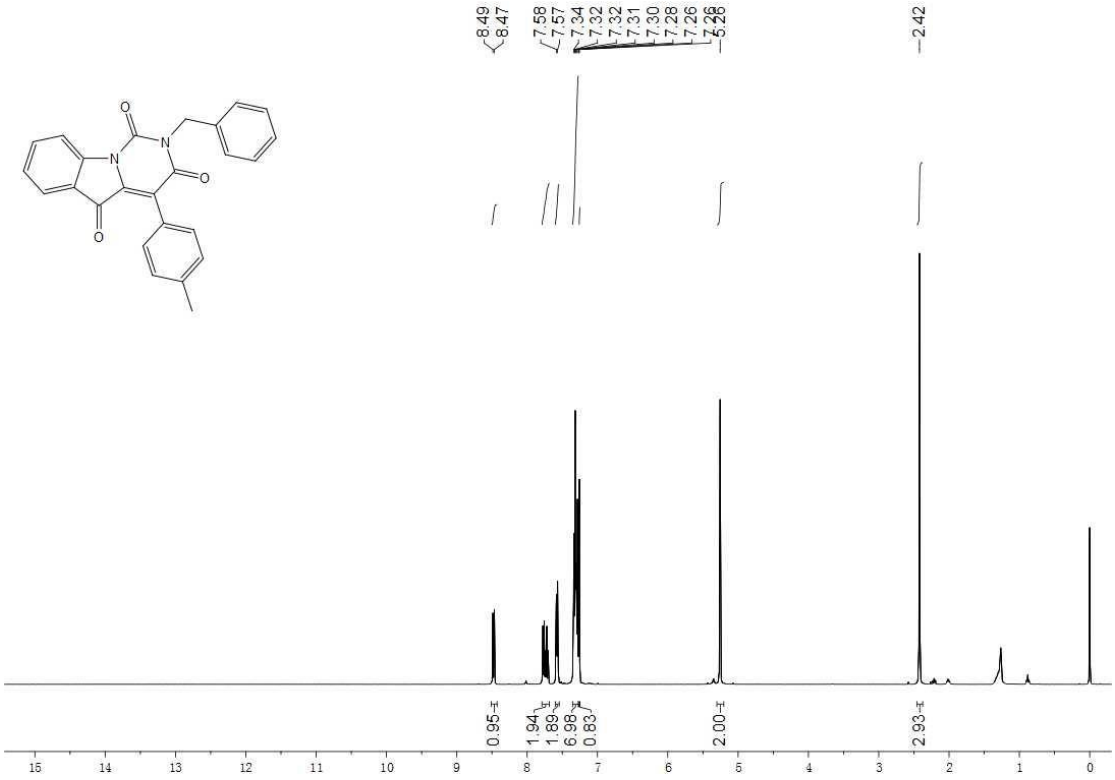


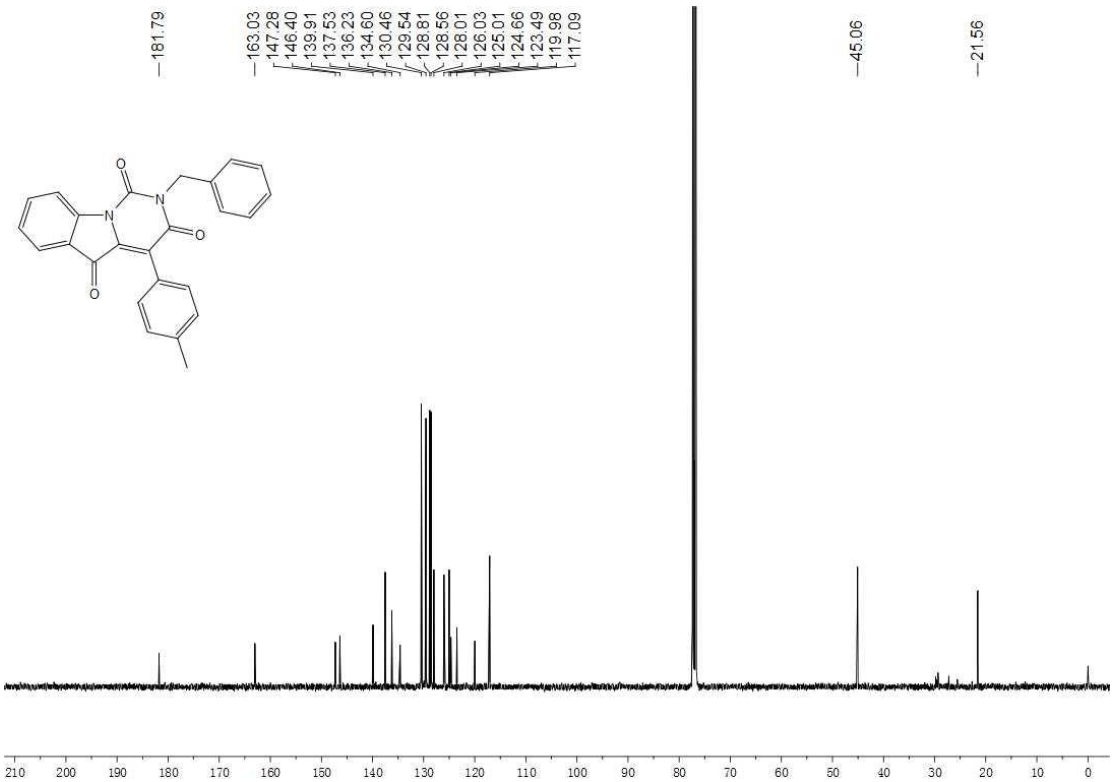
^{1}H NMR and ^{13}C NMR spectrum of **7a**.



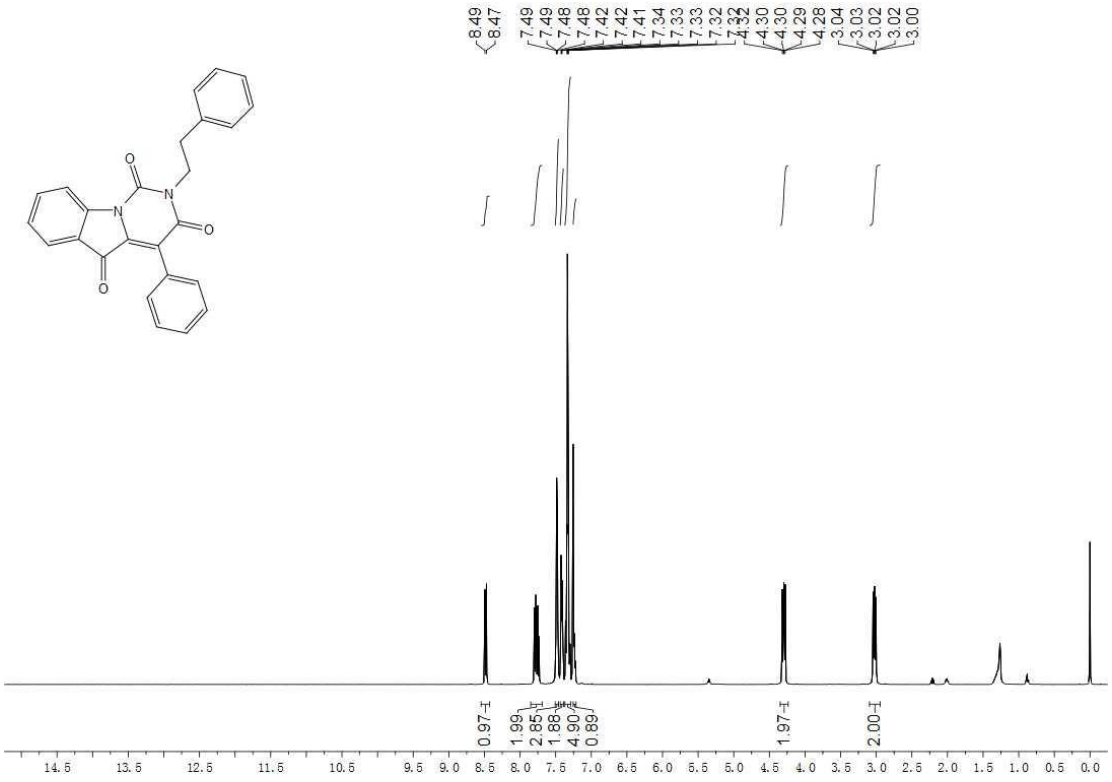


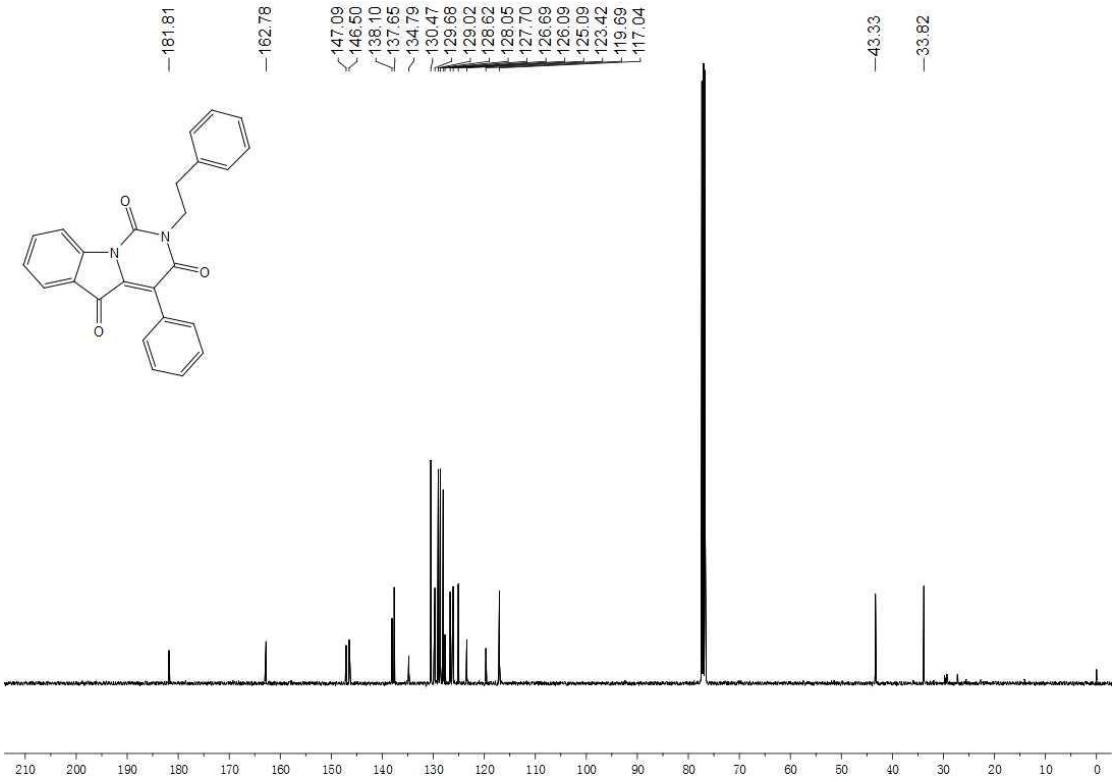
^{1}H NMR and ^{13}C NMR spectrum of **7b**.



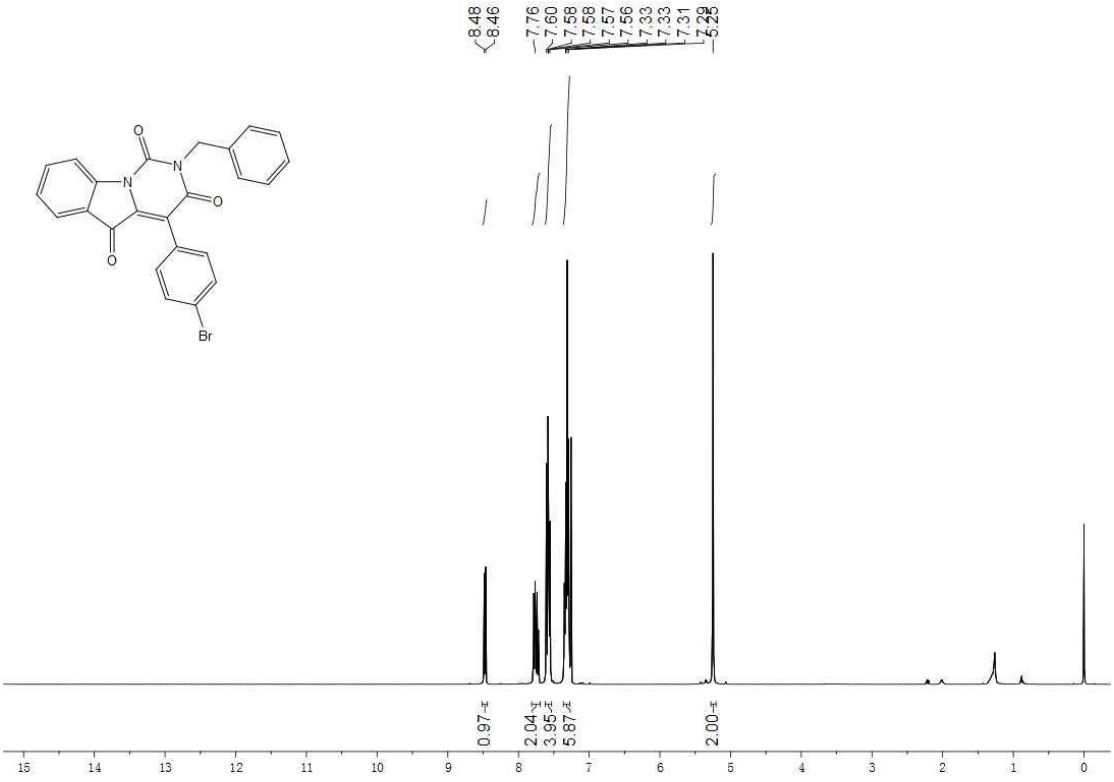


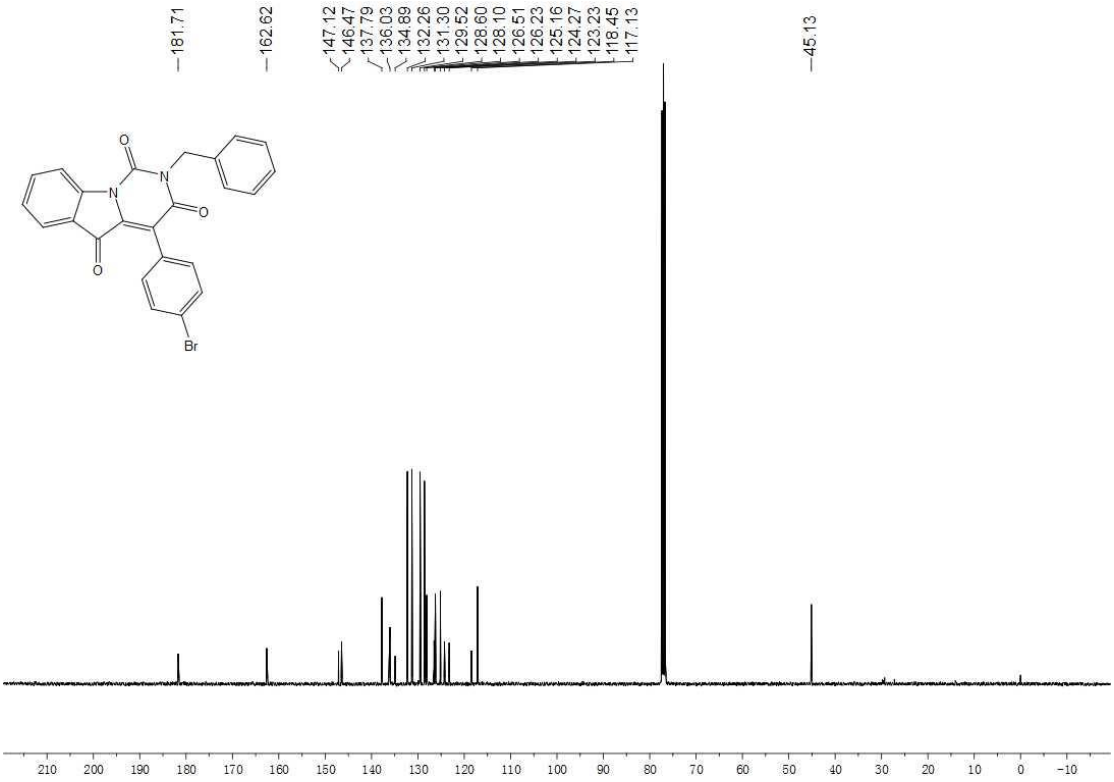
^{1}H NMR and ^{13}C NMR spectrum of **7c**.



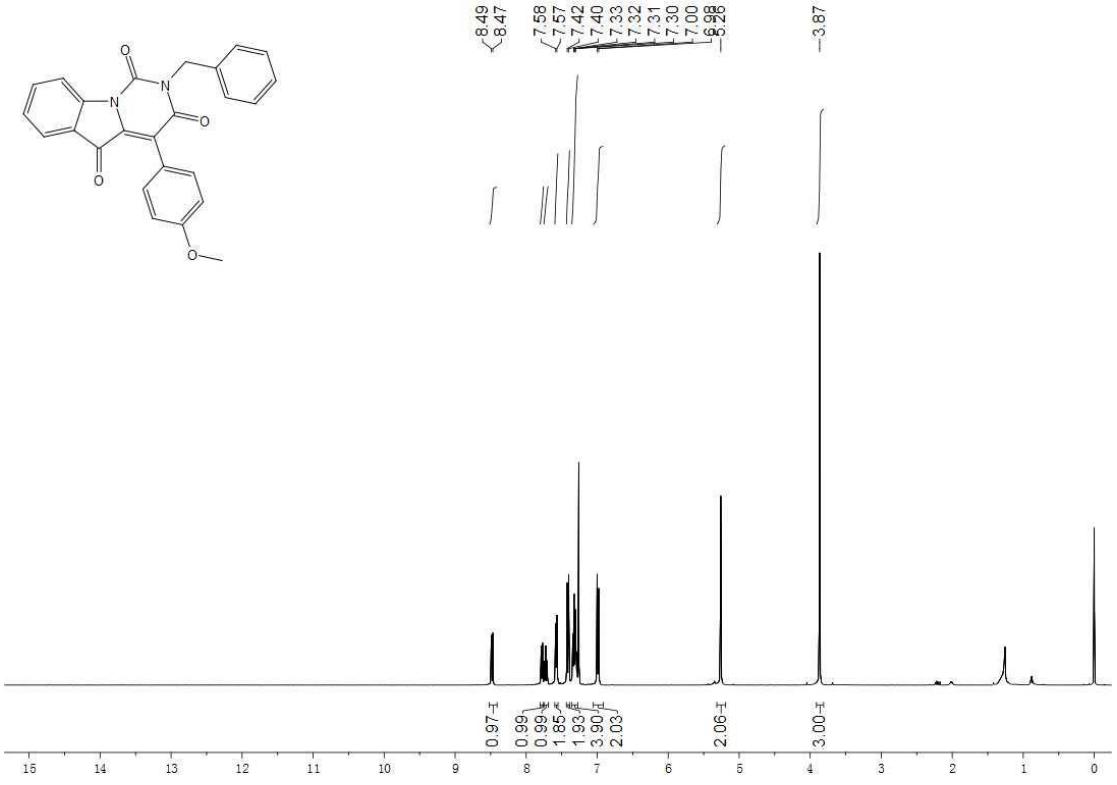


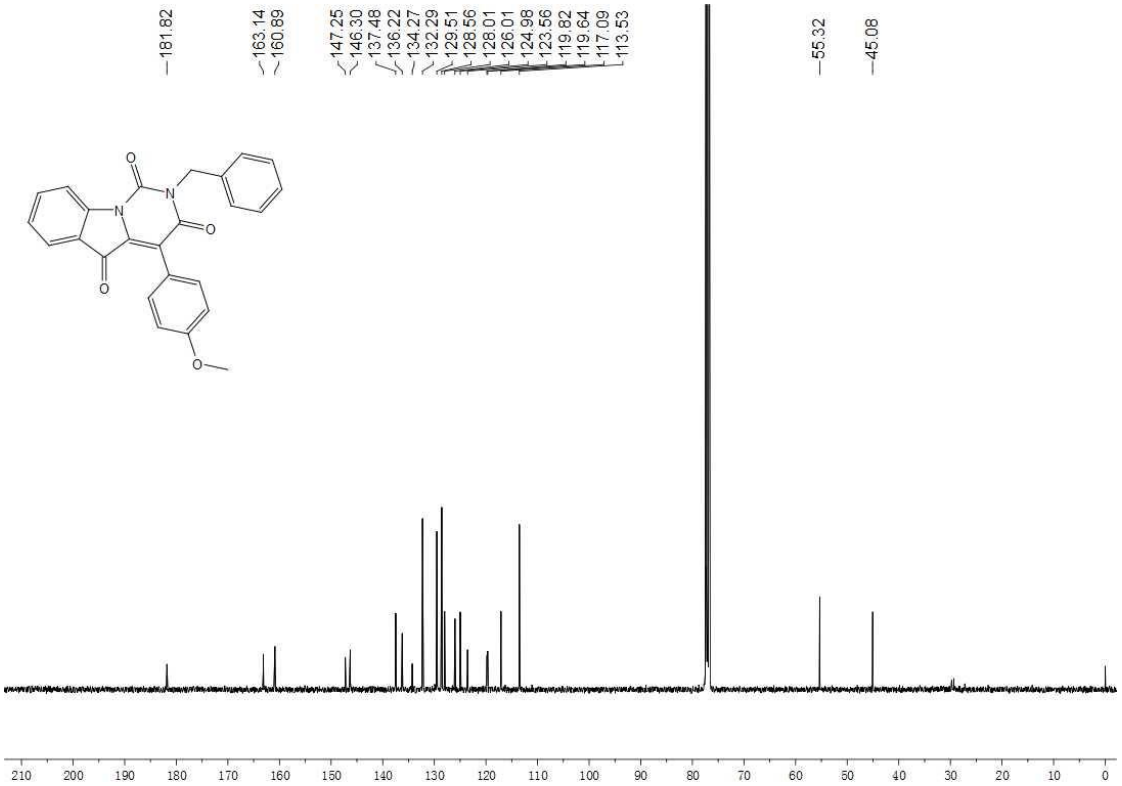
^{1}H NMR and ^{13}C NMR spectrum of **7d**.



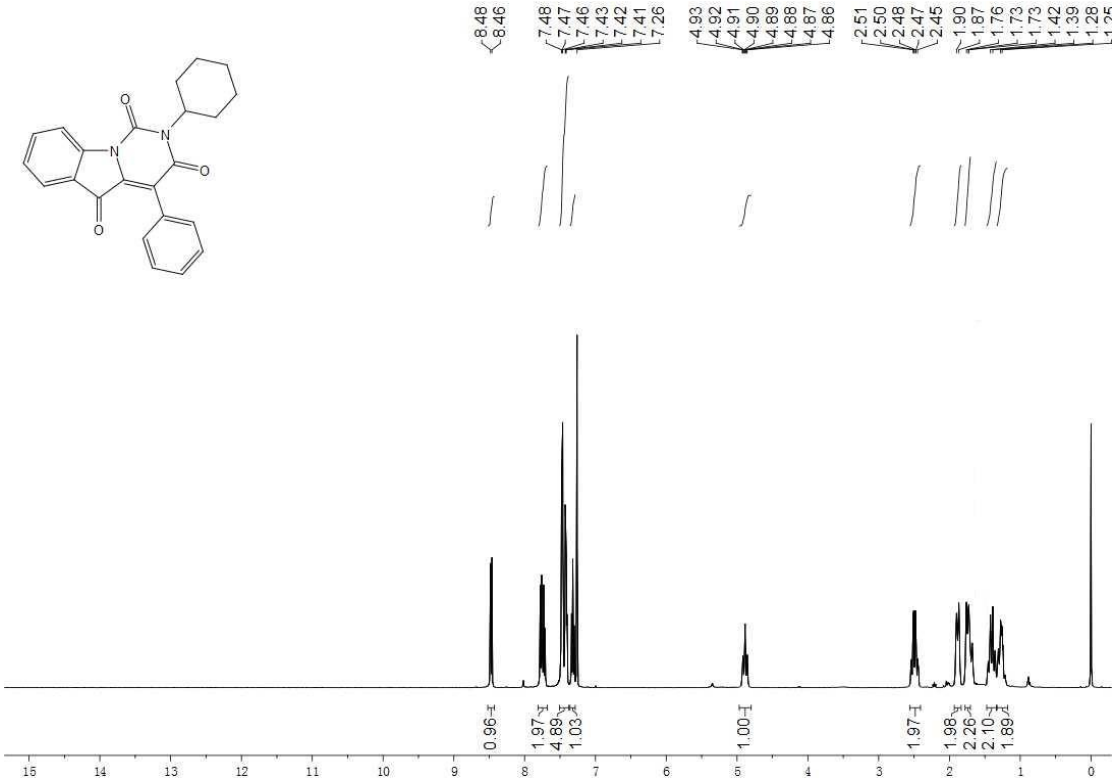


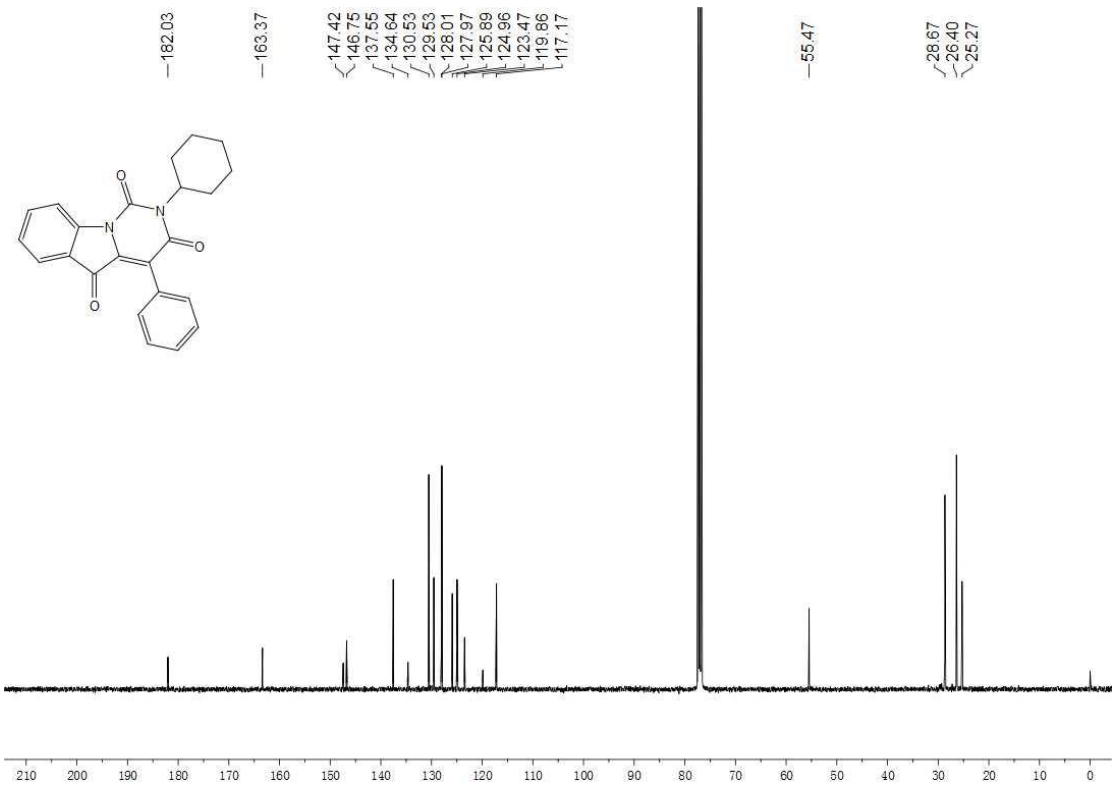
^{1}H NMR and ^{13}C NMR spectrum of **7e**.



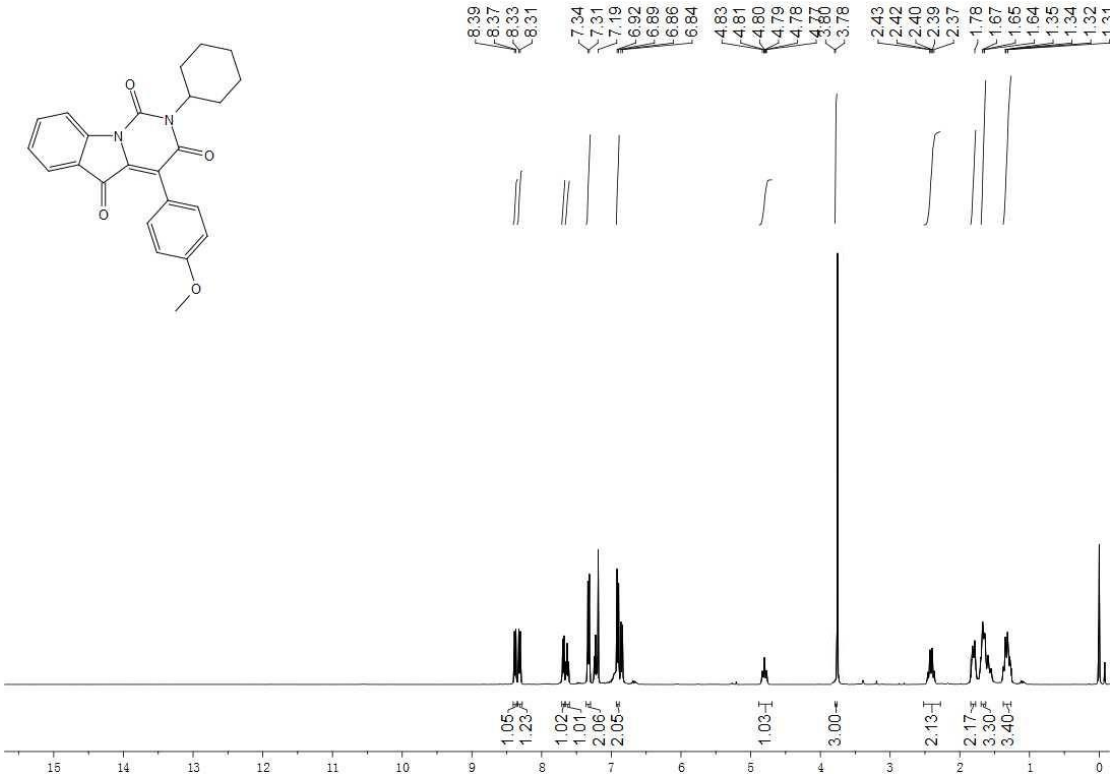


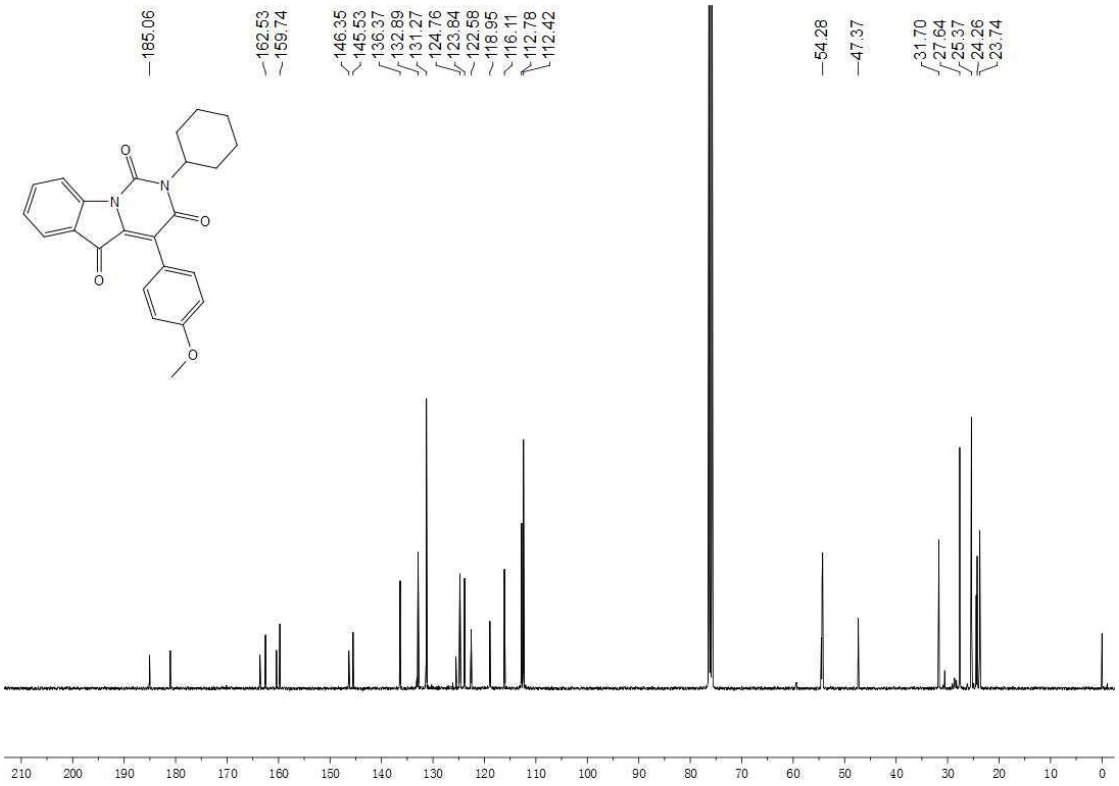
^{1}H NMR and ^{13}C NMR spectrum of **7f**.



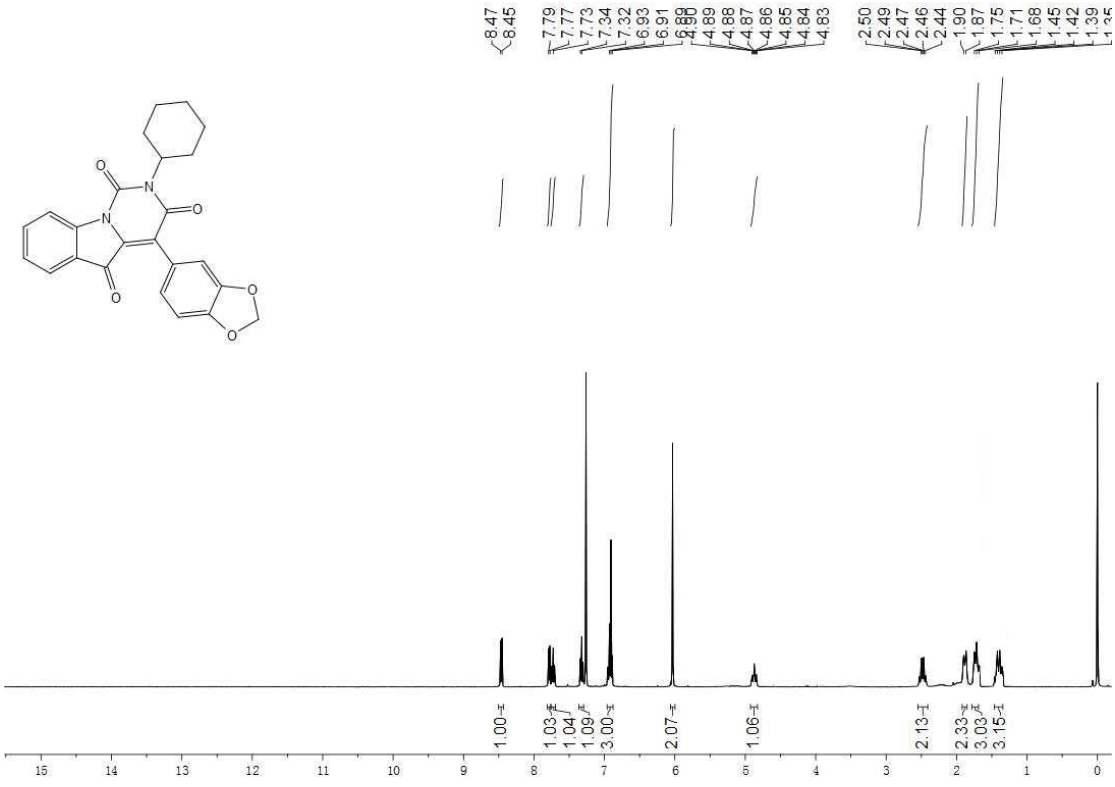


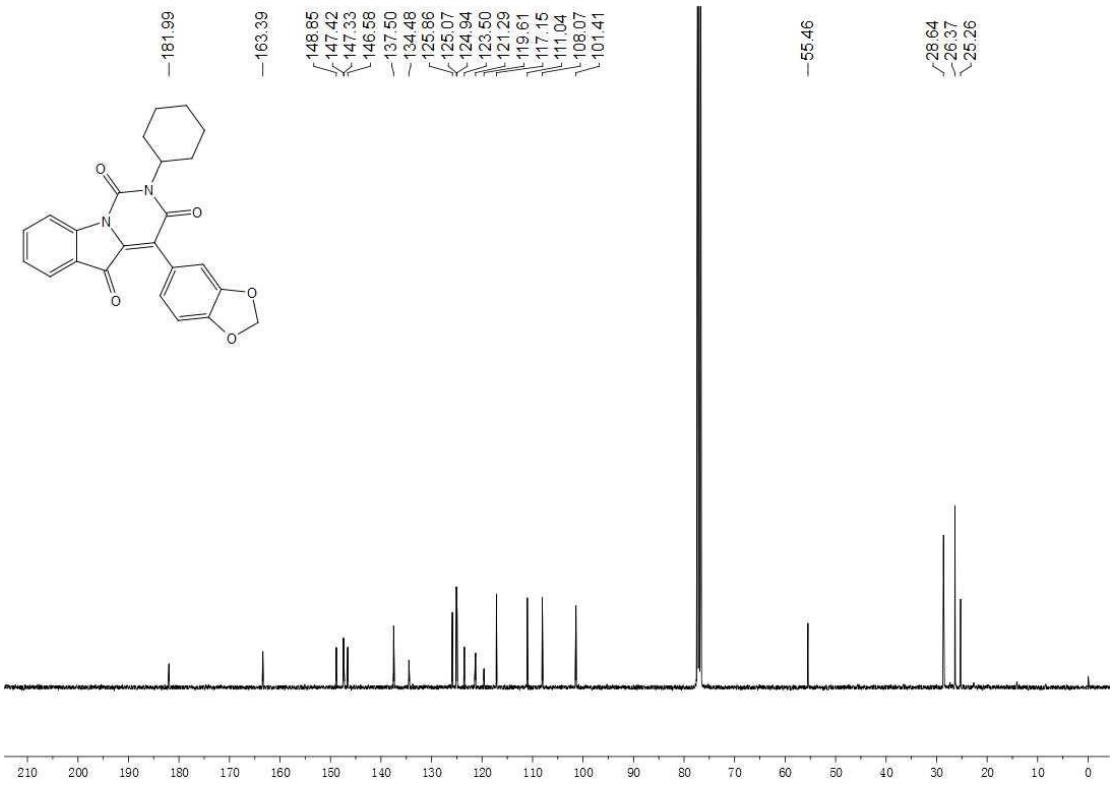
^{1}H NMR and ^{13}C NMR spectrum of **7g**.



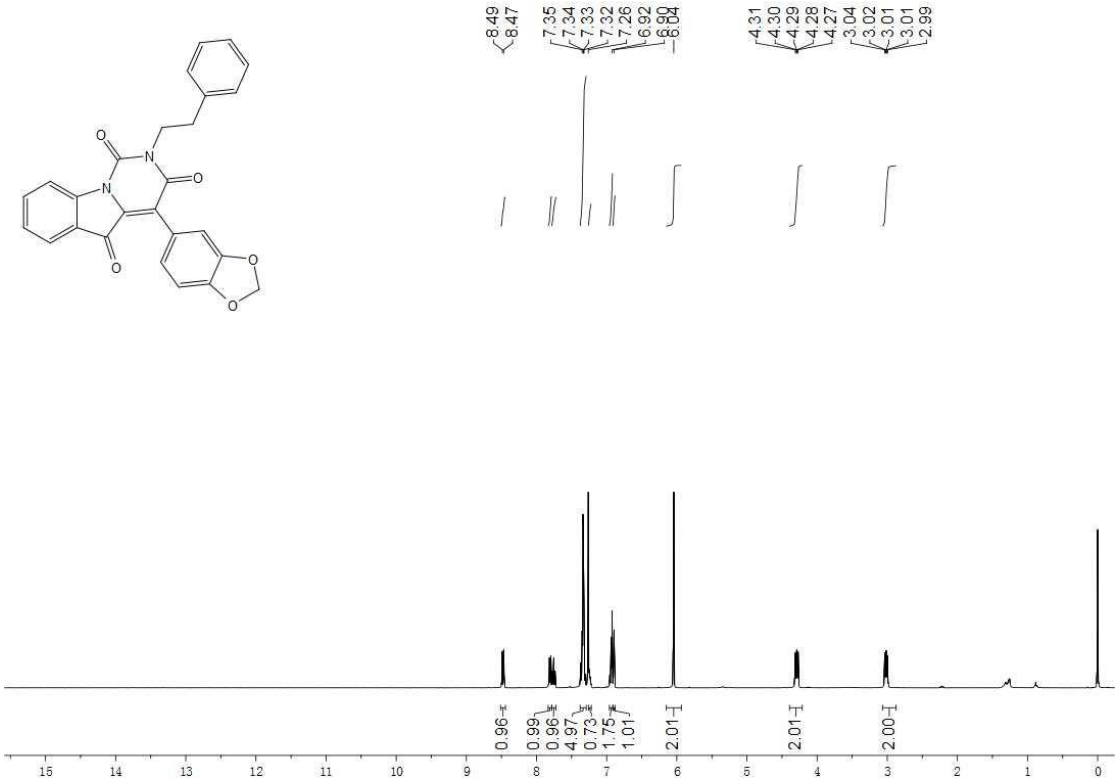


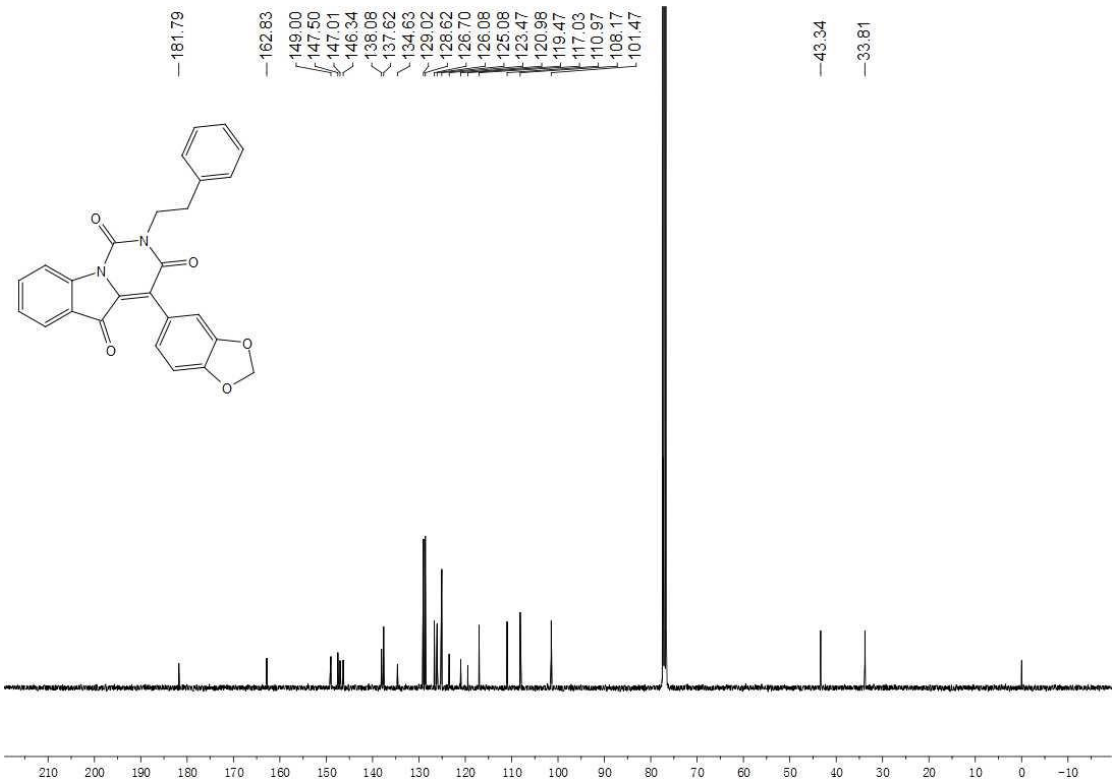
^{1}H NMR and ^{13}C NMR spectrum of **7h**.



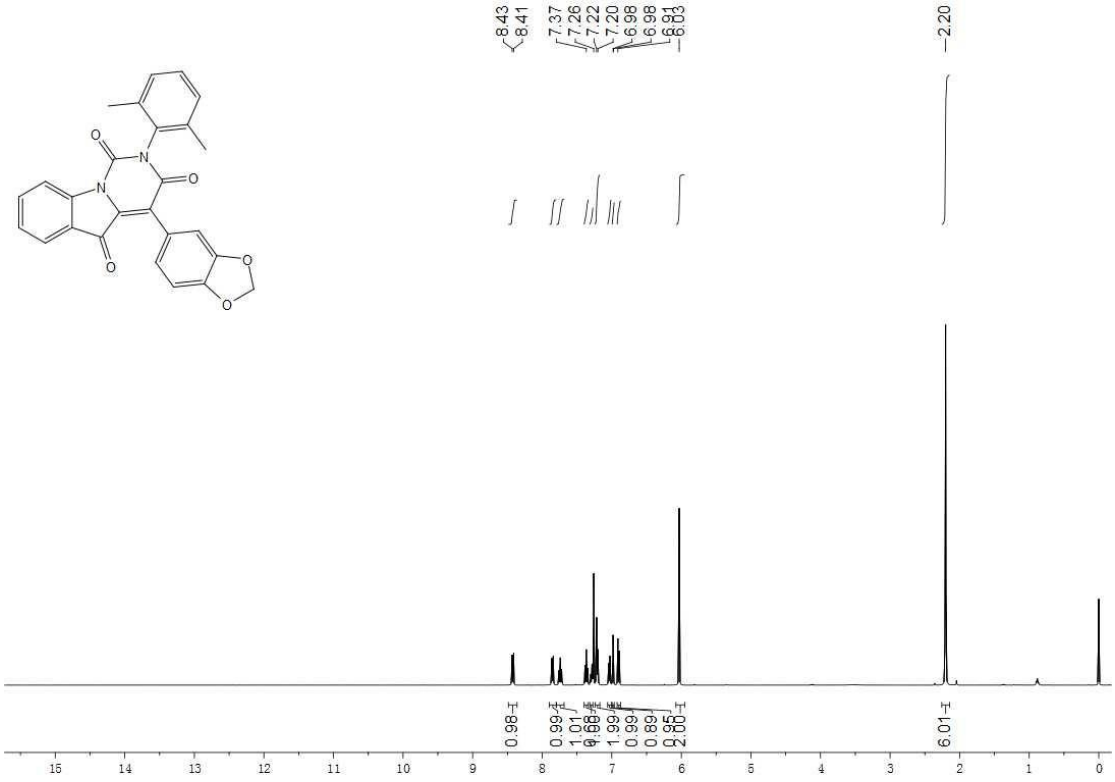


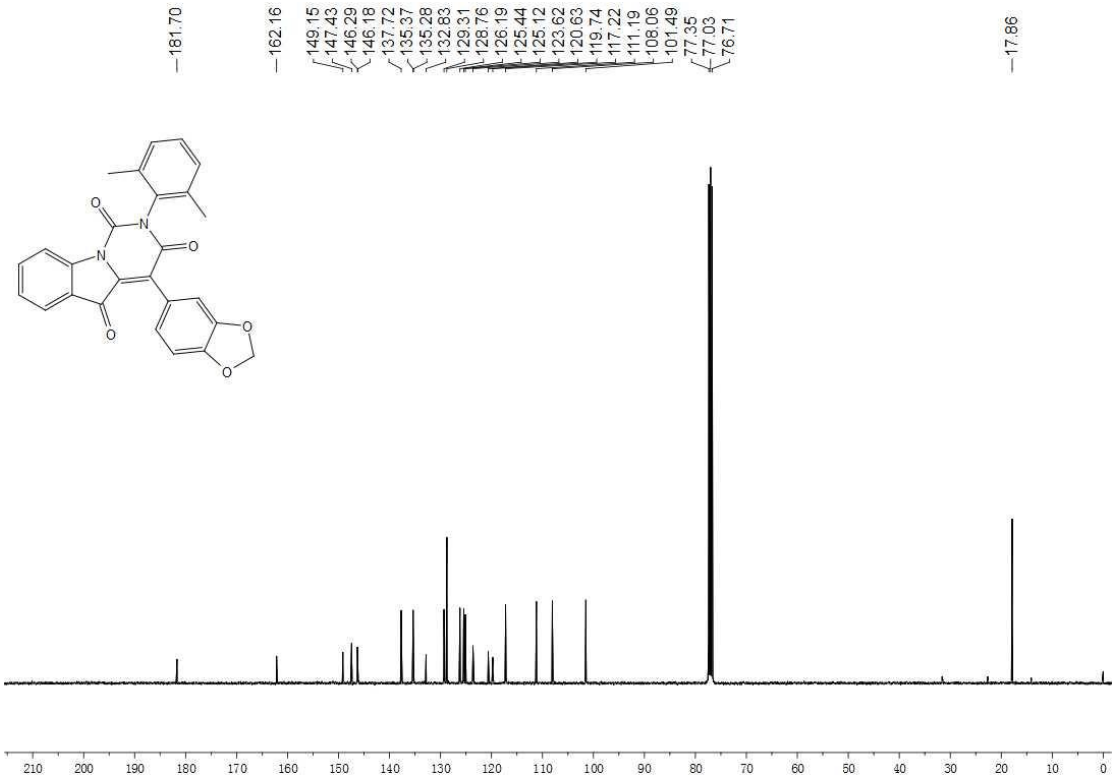
^{1}H NMR and ^{13}C NMR spectrum of **7i**.



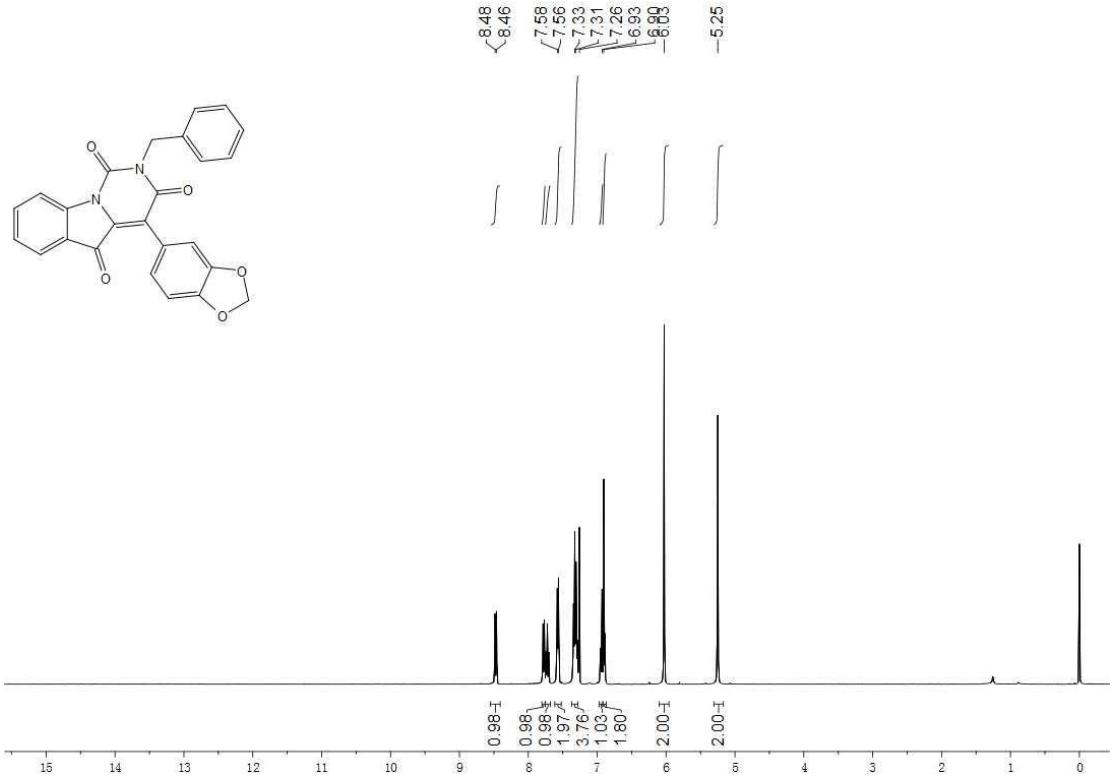


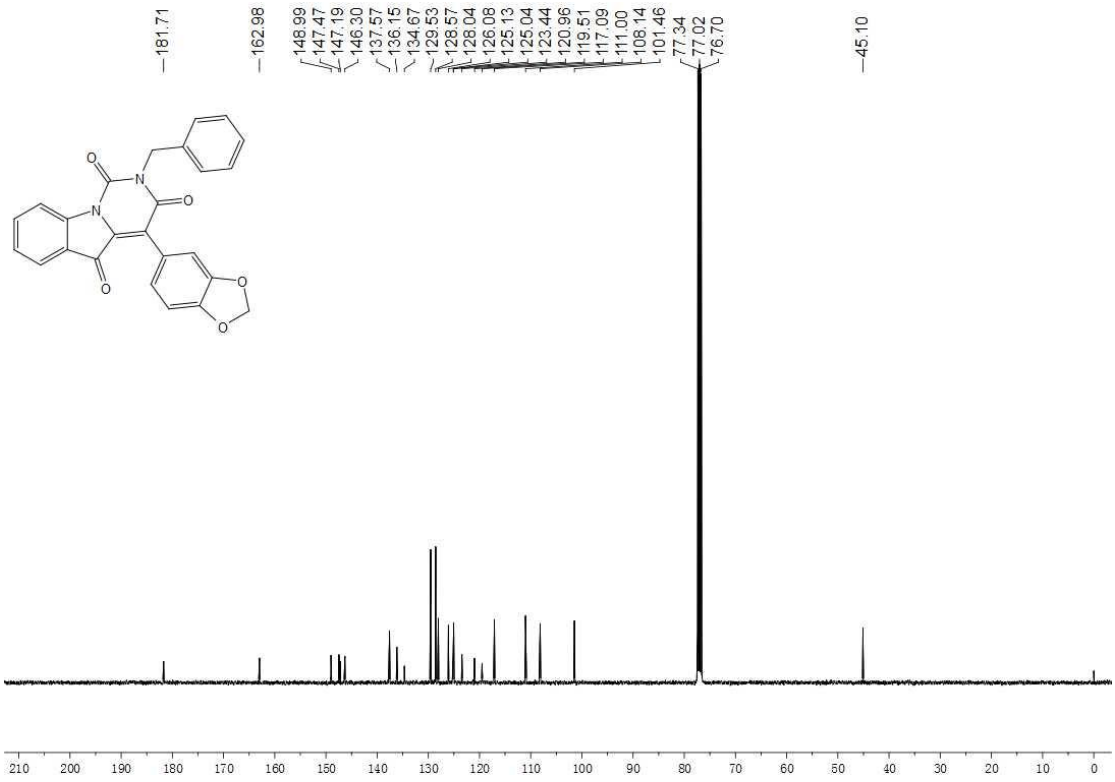
^{1}H NMR and ^{13}C NMR spectrum of **7j**.



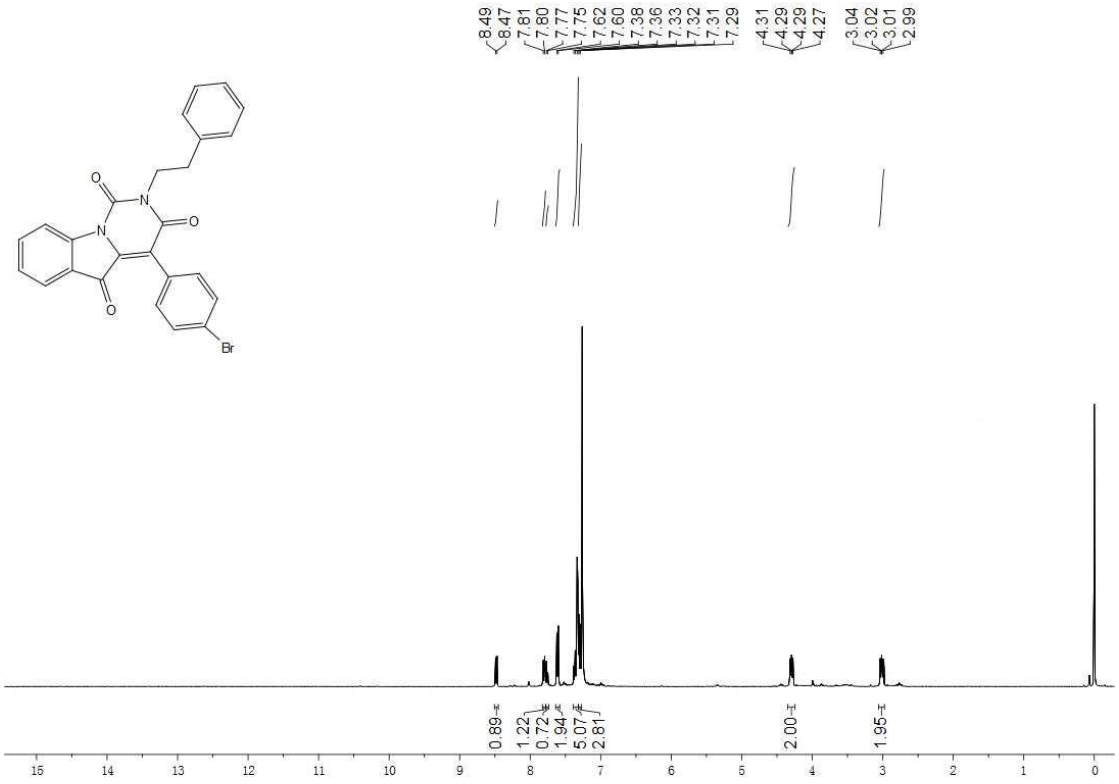


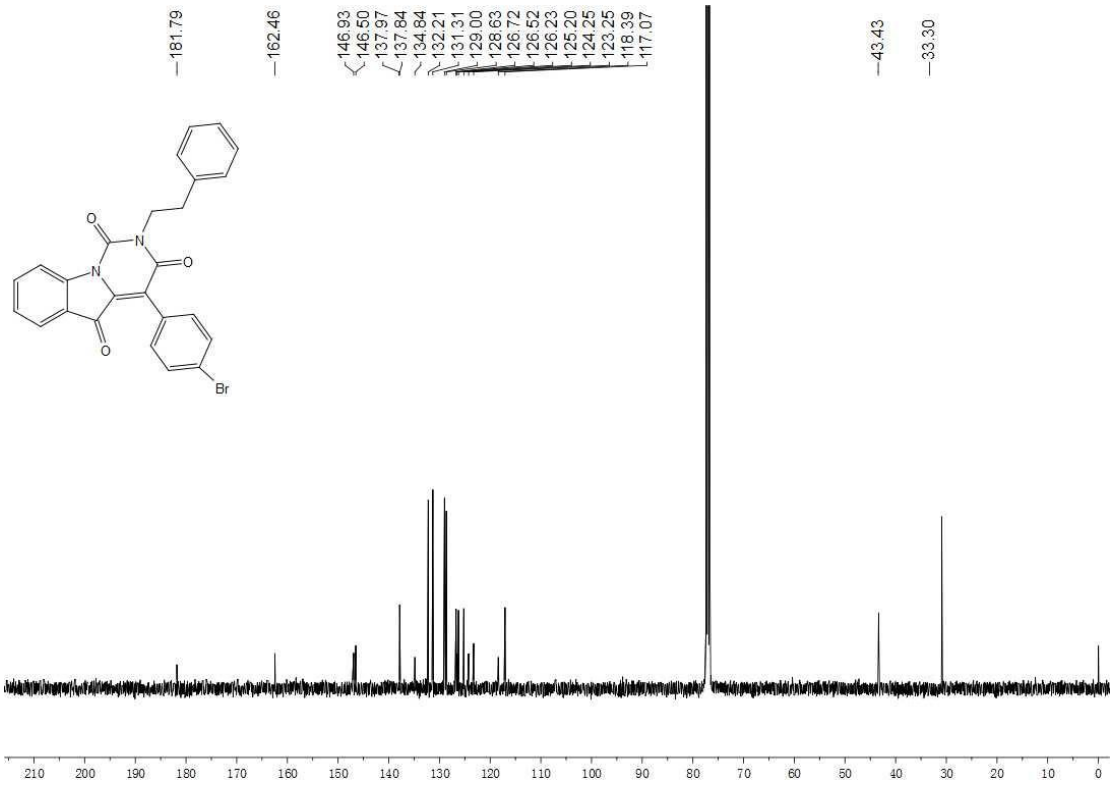
^{1}H NMR and ^{13}C NMR spectrum of **7k**.



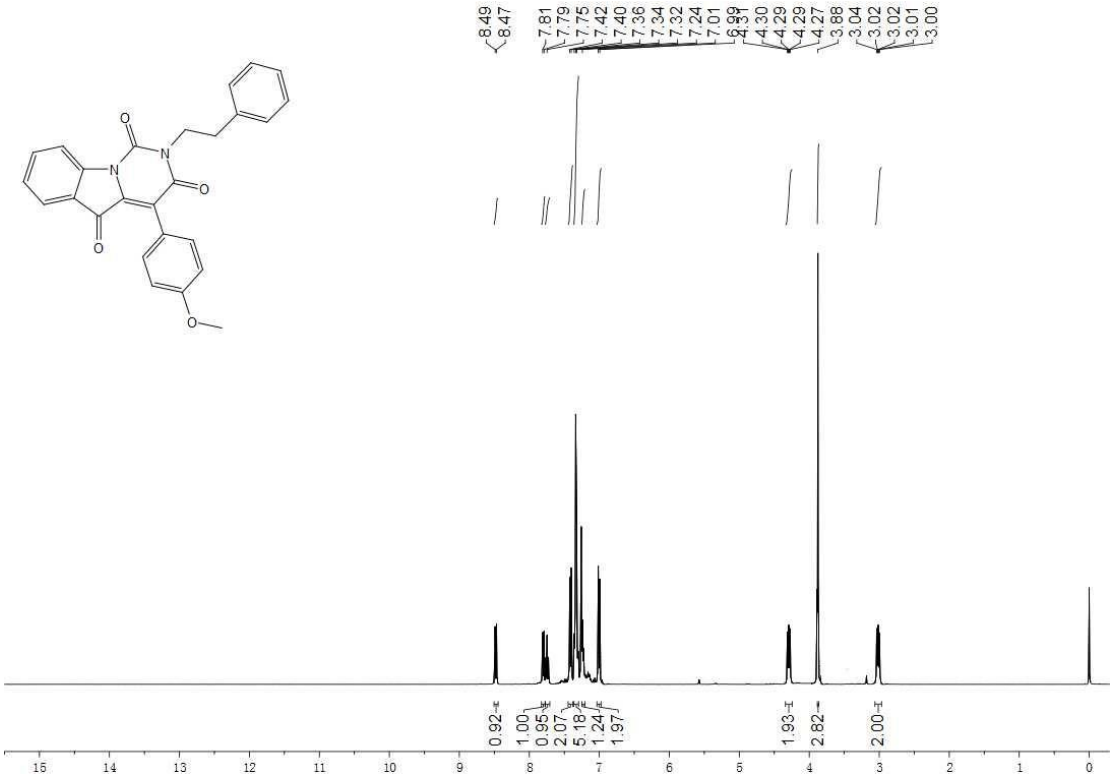


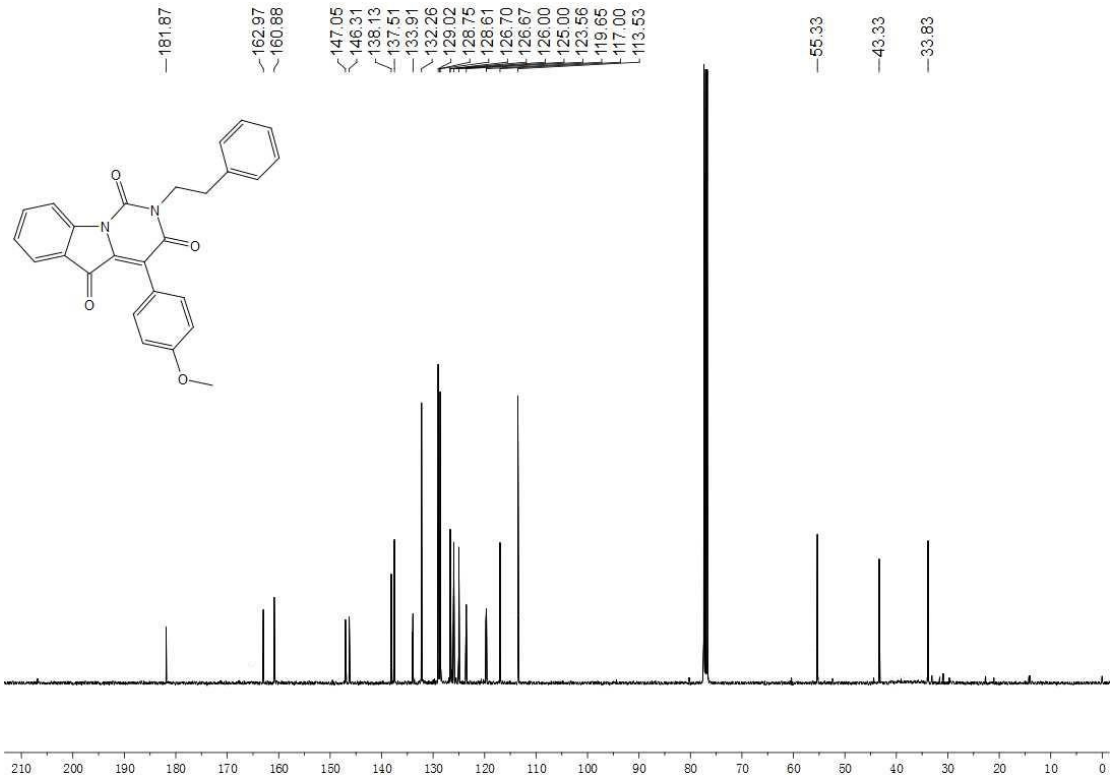
^{1}H NMR and ^{13}C NMR spectrum of **7l**.



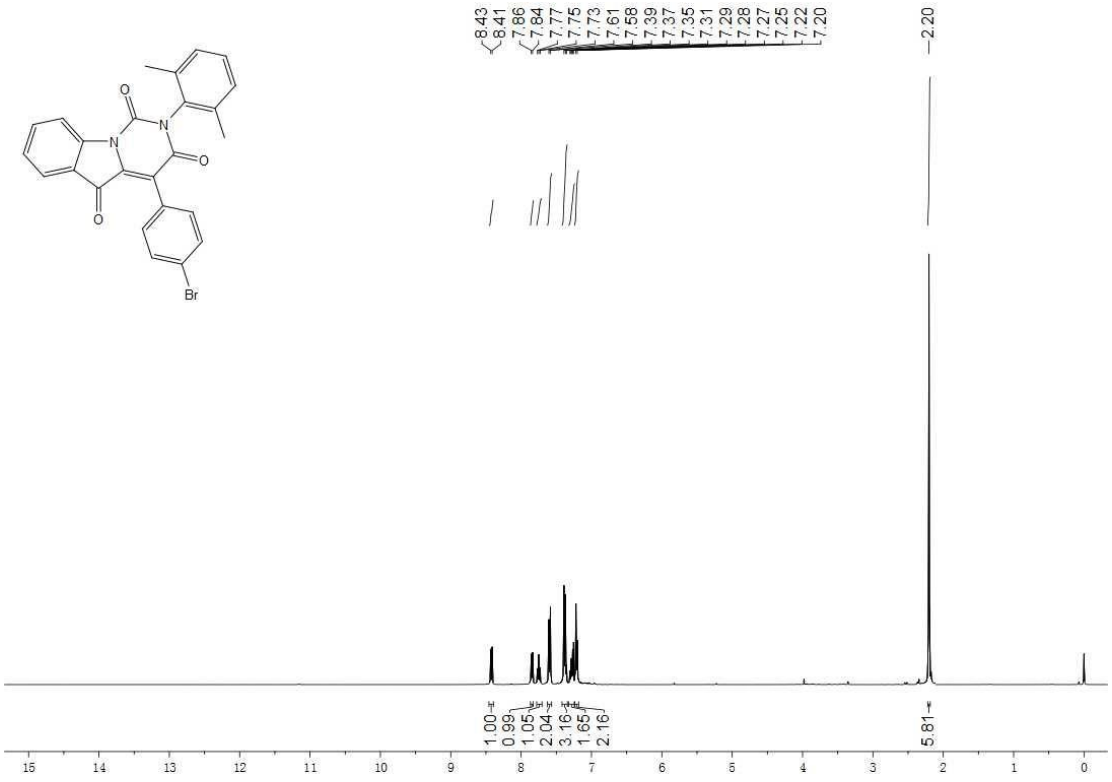


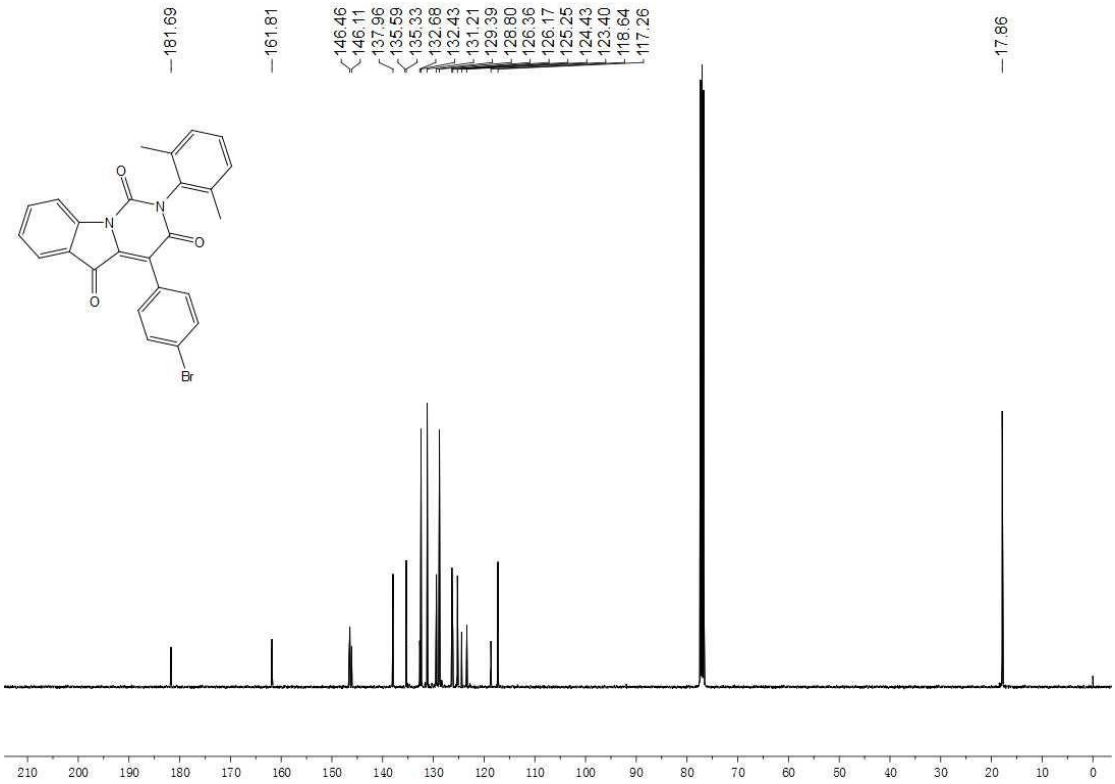
^{1}H NMR and ^{13}C NMR spectrum of **7m**.



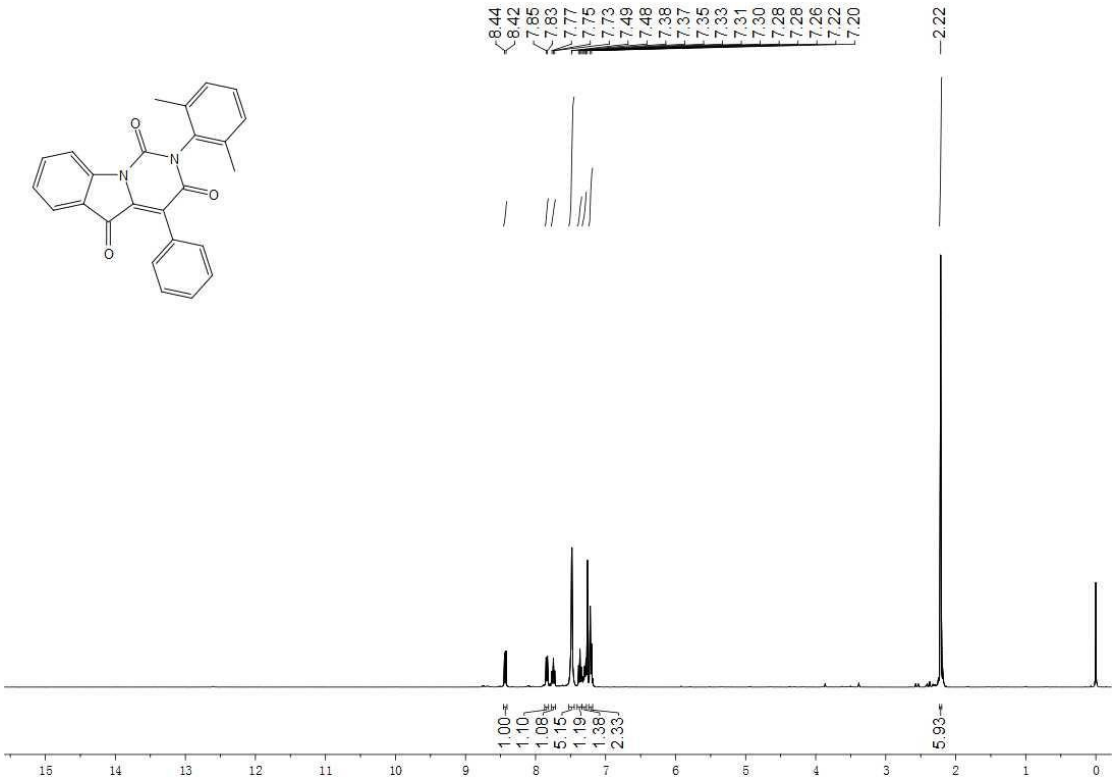


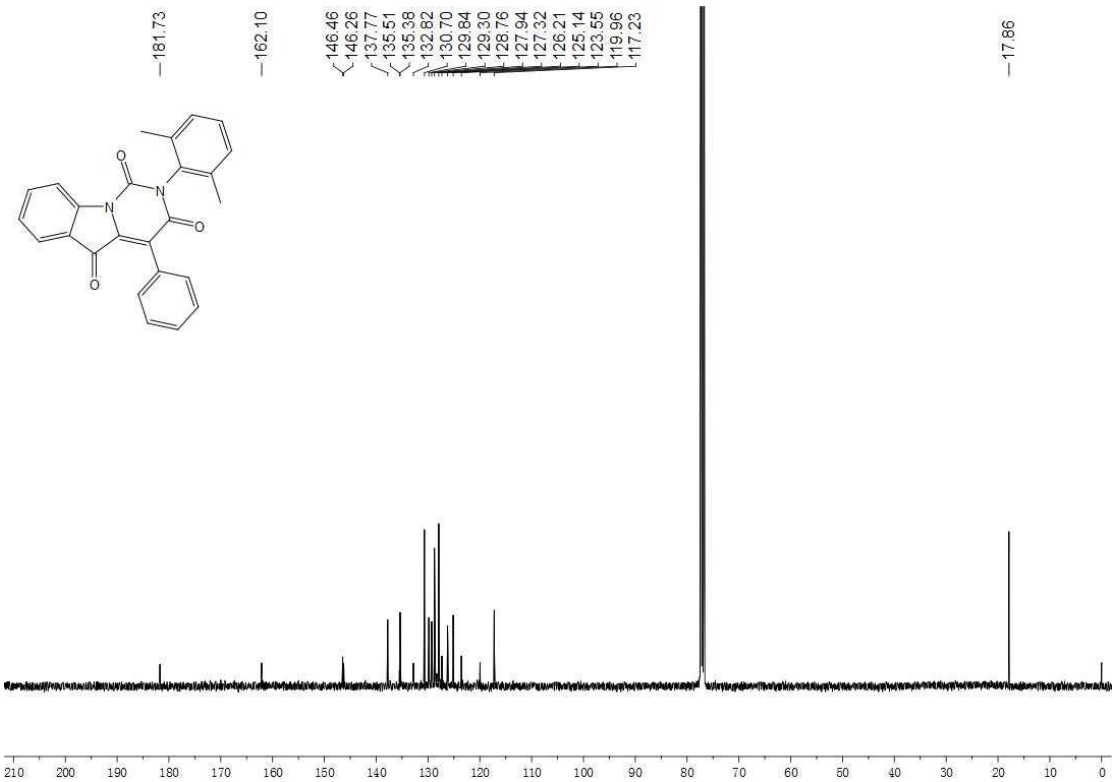
^{1}H NMR and ^{13}C NMR spectrum of **7n**.



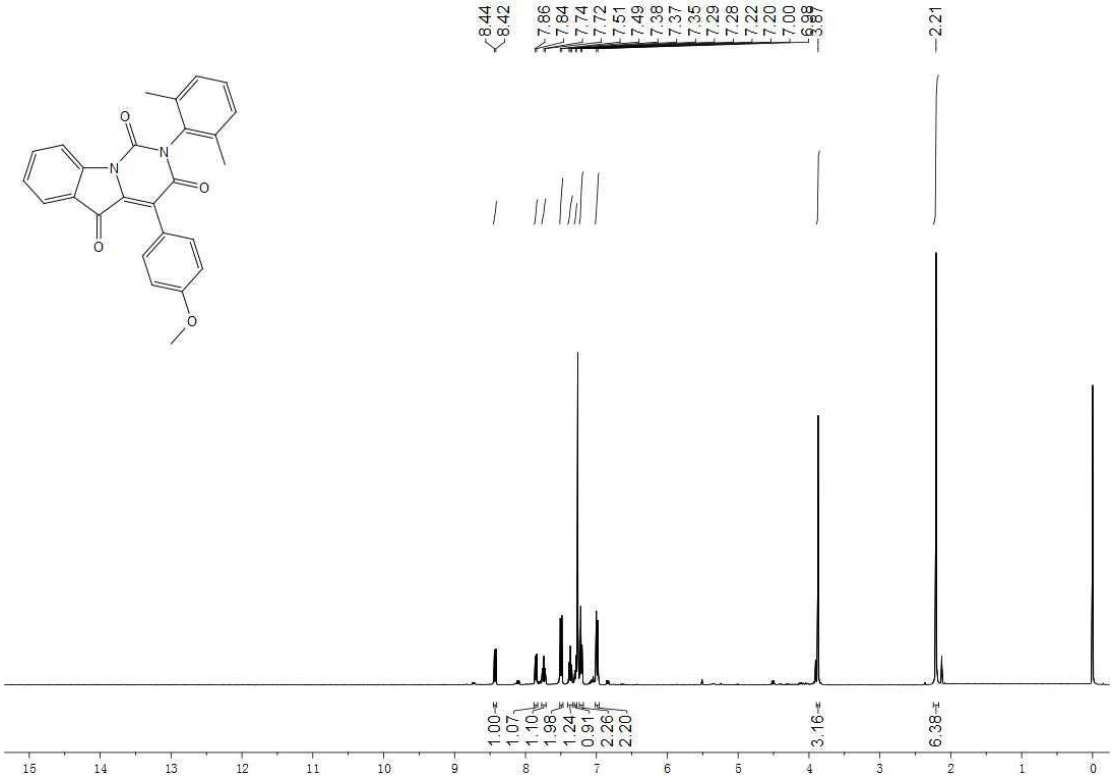


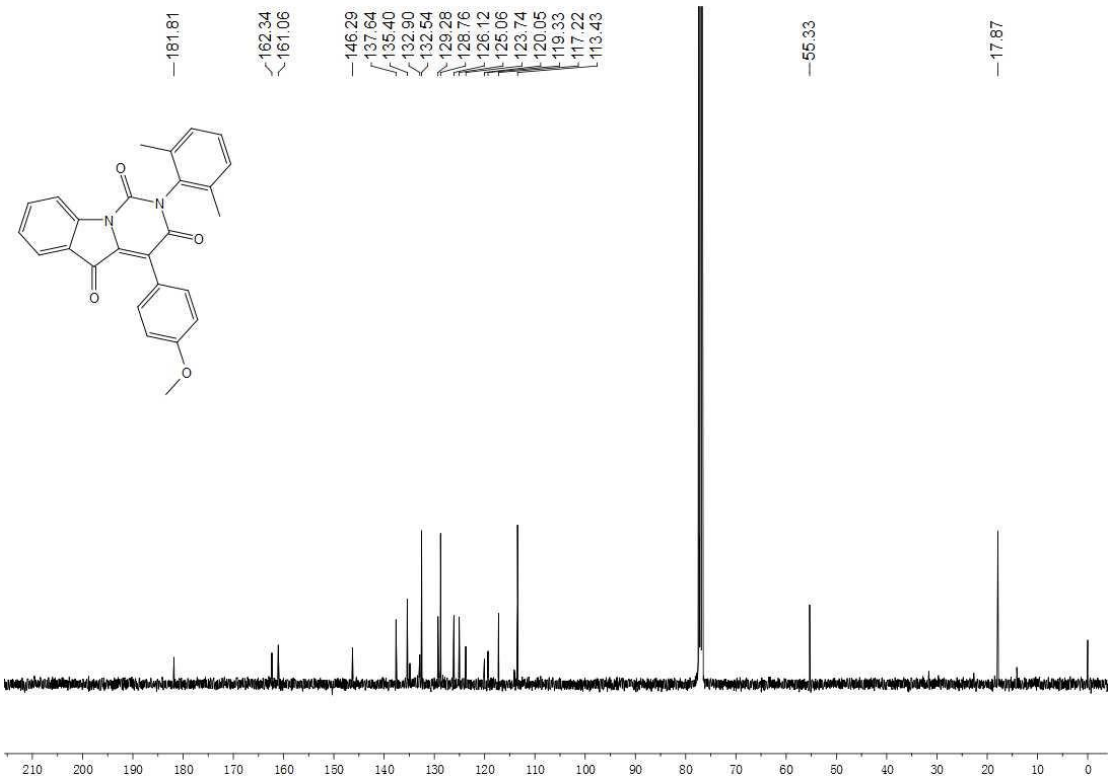
^{1}H NMR and ^{13}C NMR spectrum of **7o**.



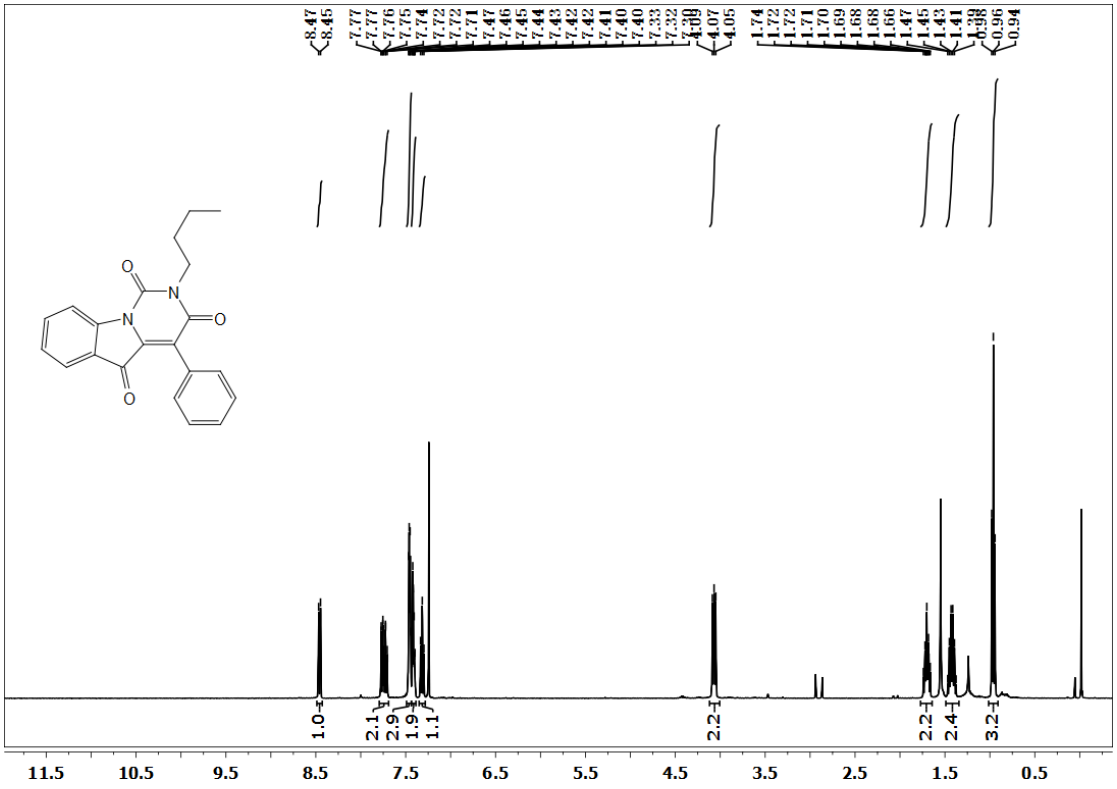


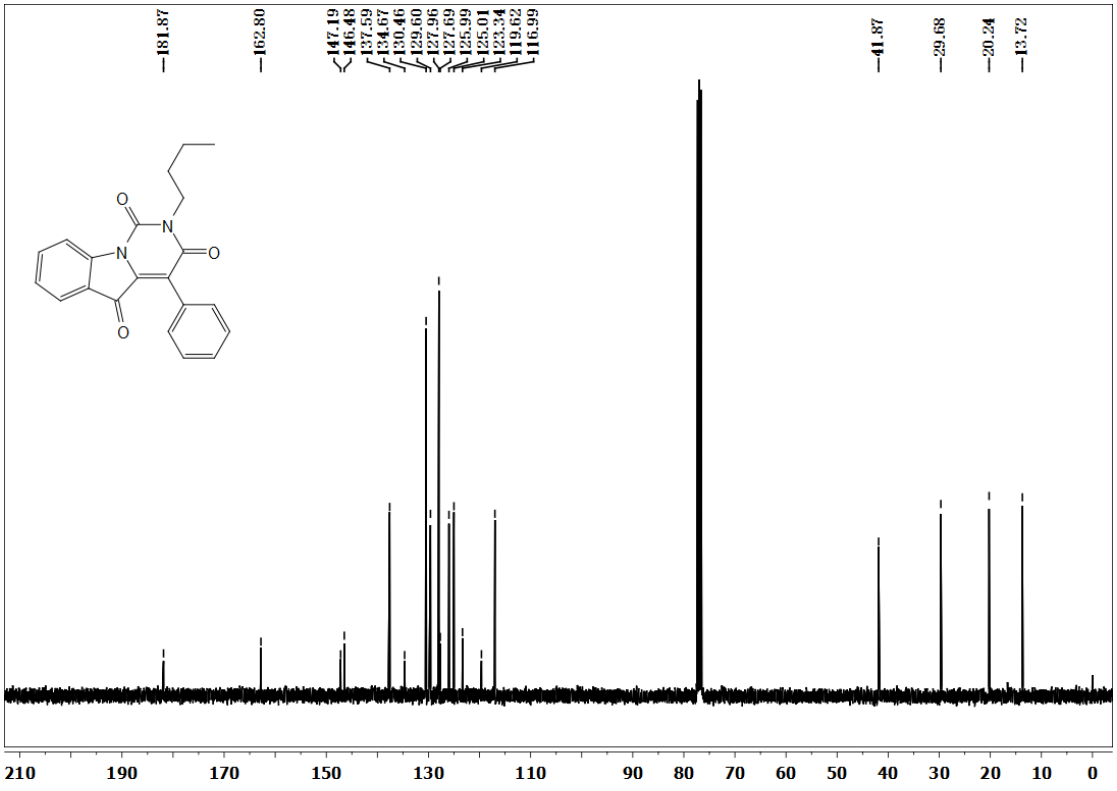
^{1}H NMR and ^{13}C NMR spectrum of **7p**.



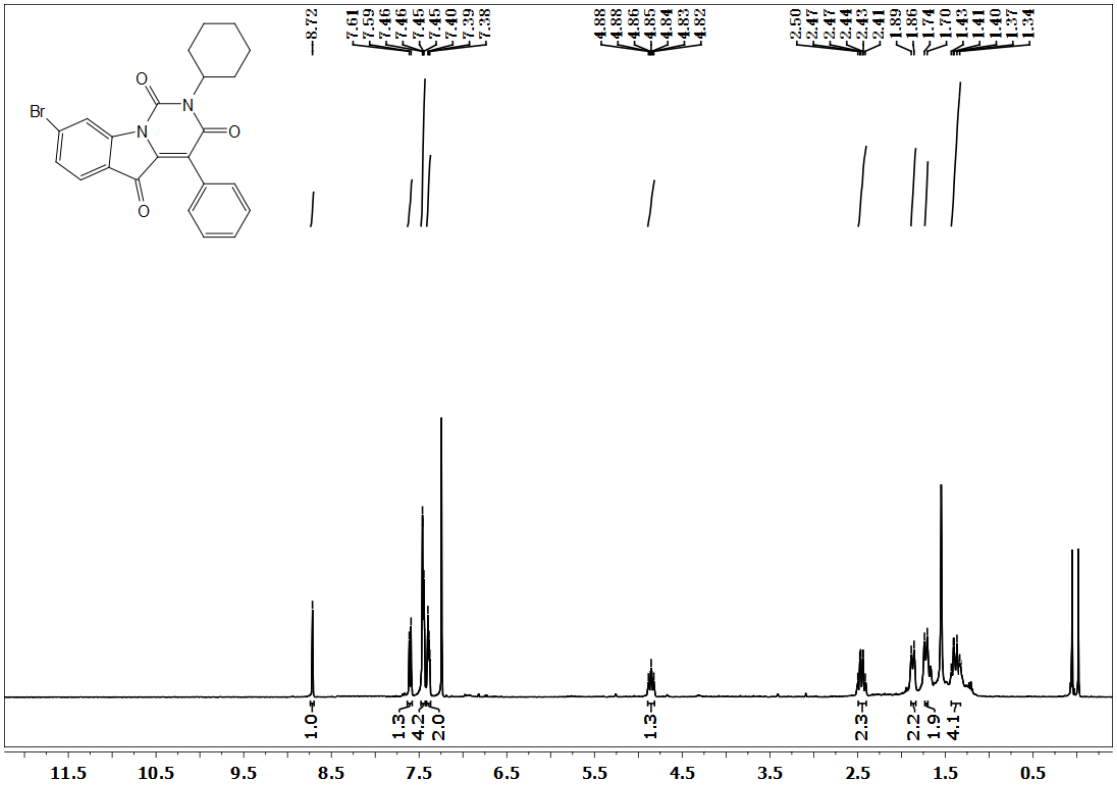


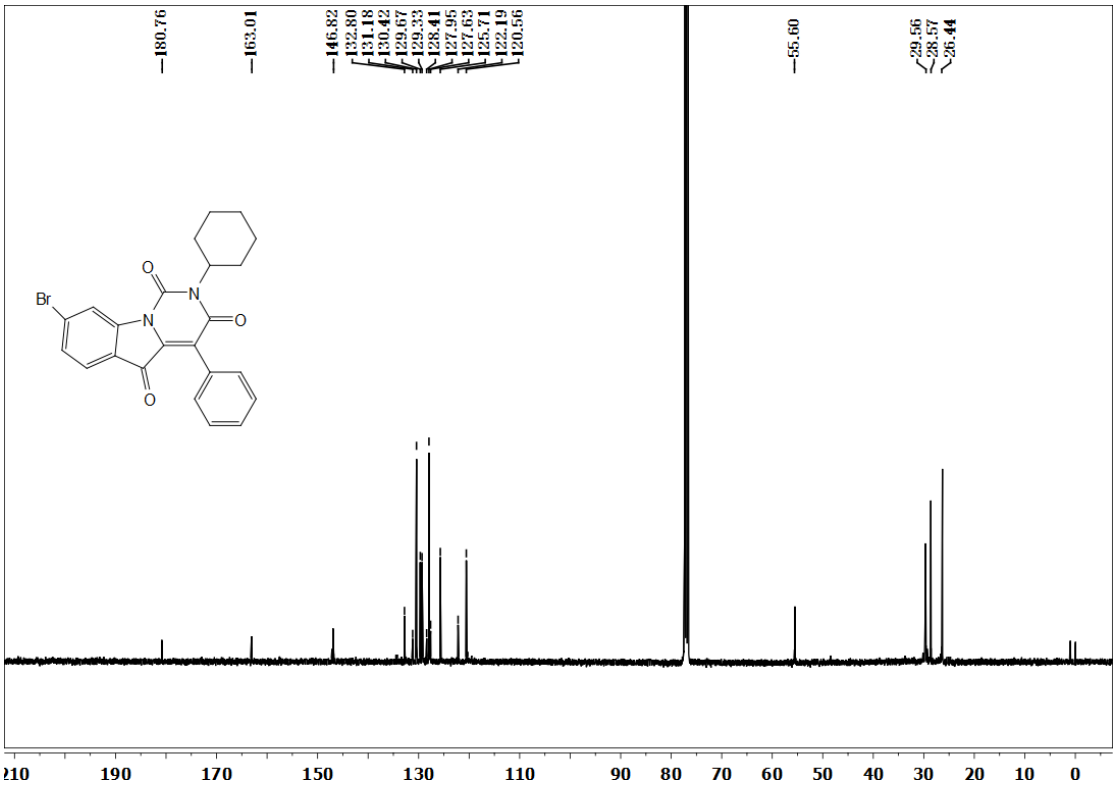
^{1}H NMR and ^{13}C NMR spectrum of **7q**.



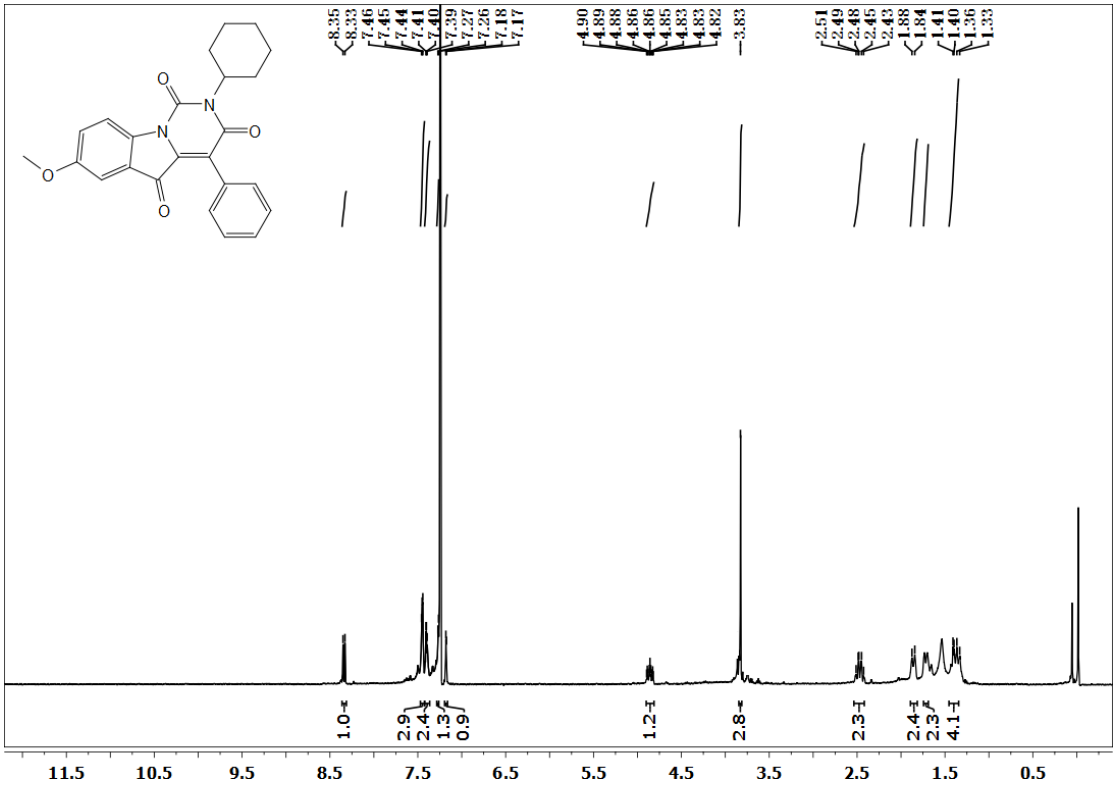


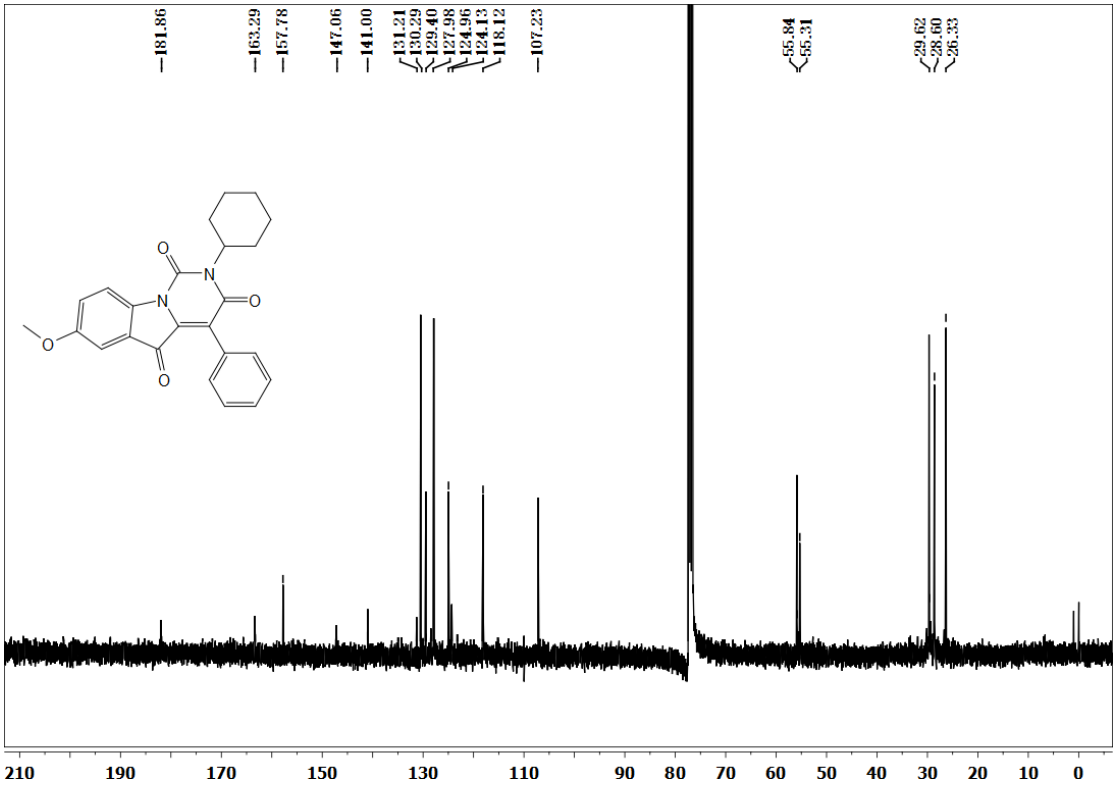
^{1}H NMR and ^{13}C NMR spectrum of **7r**.



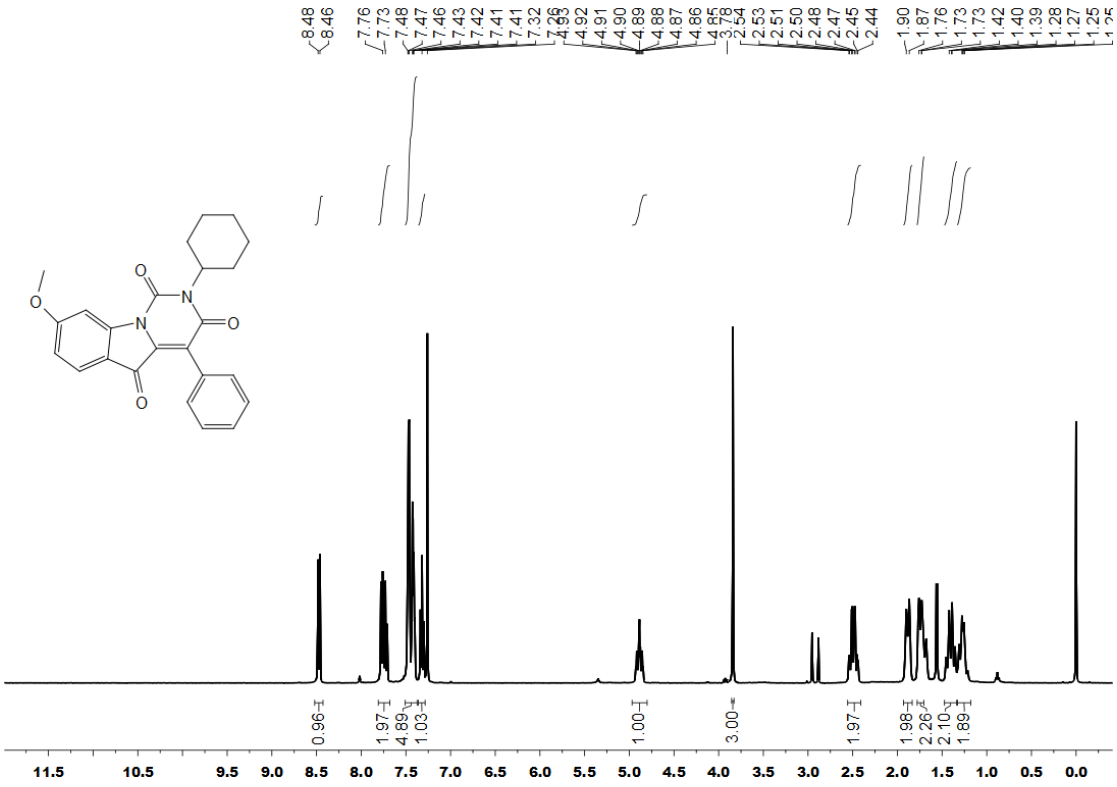


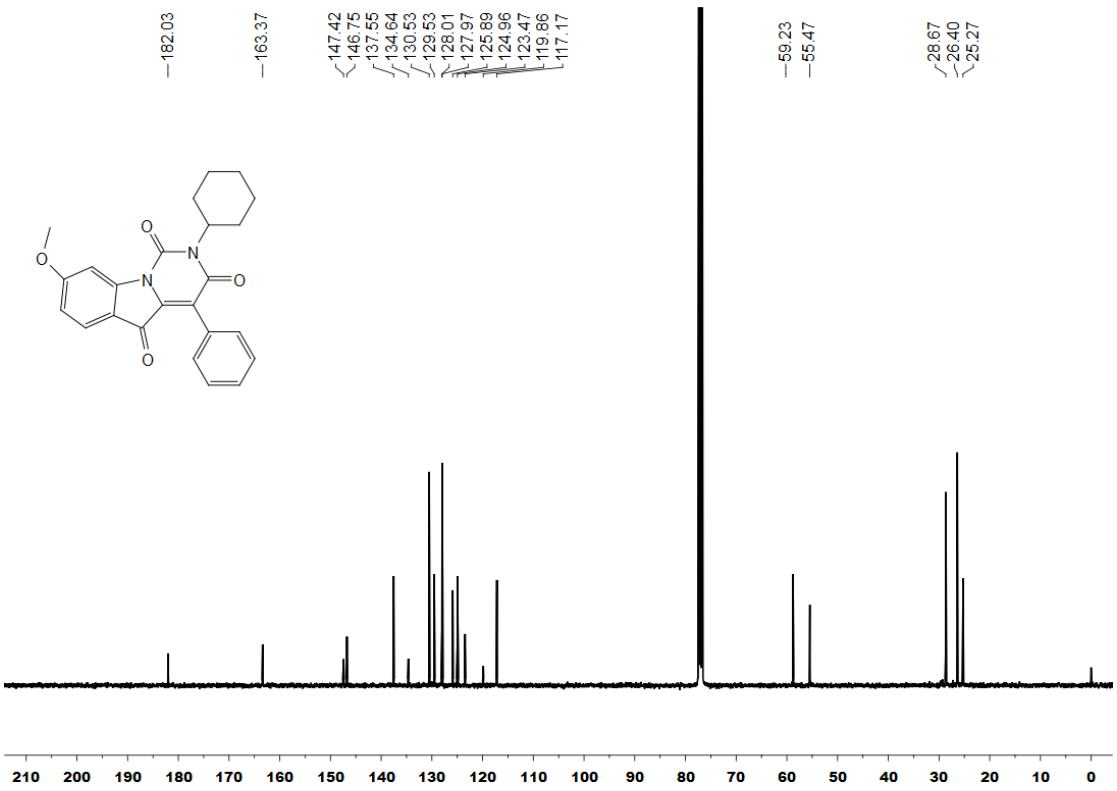
^{1}H NMR and ^{13}C NMR spectrum of **7s**.



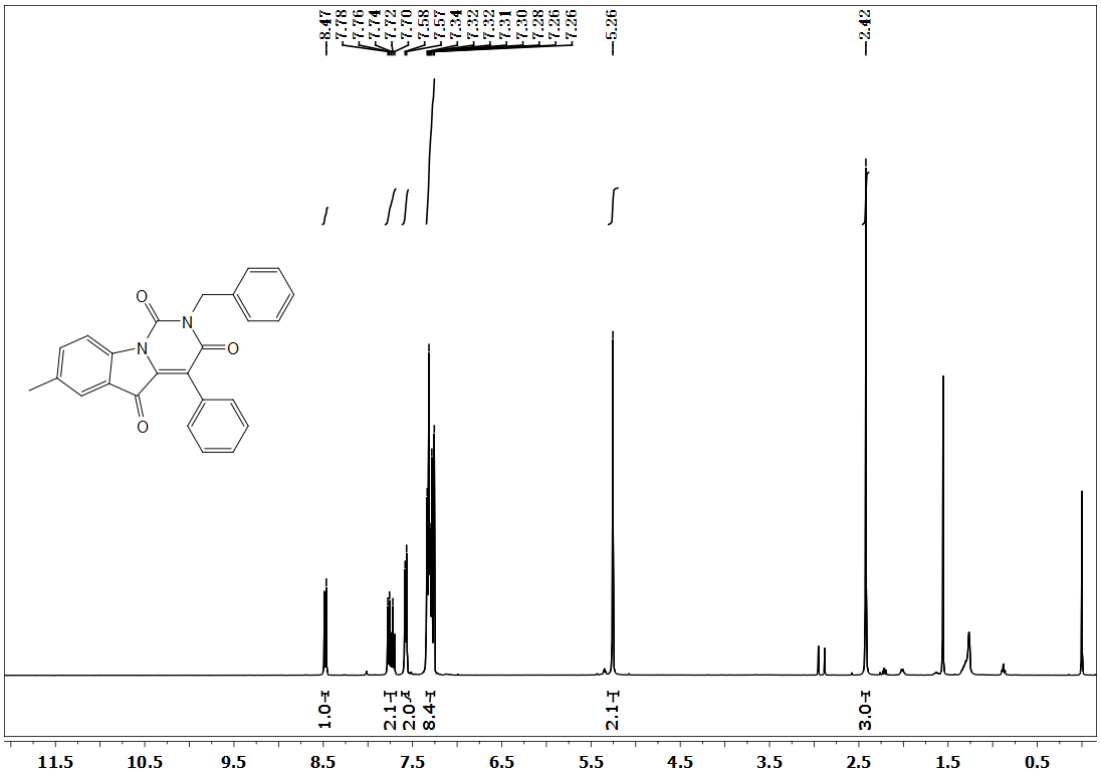


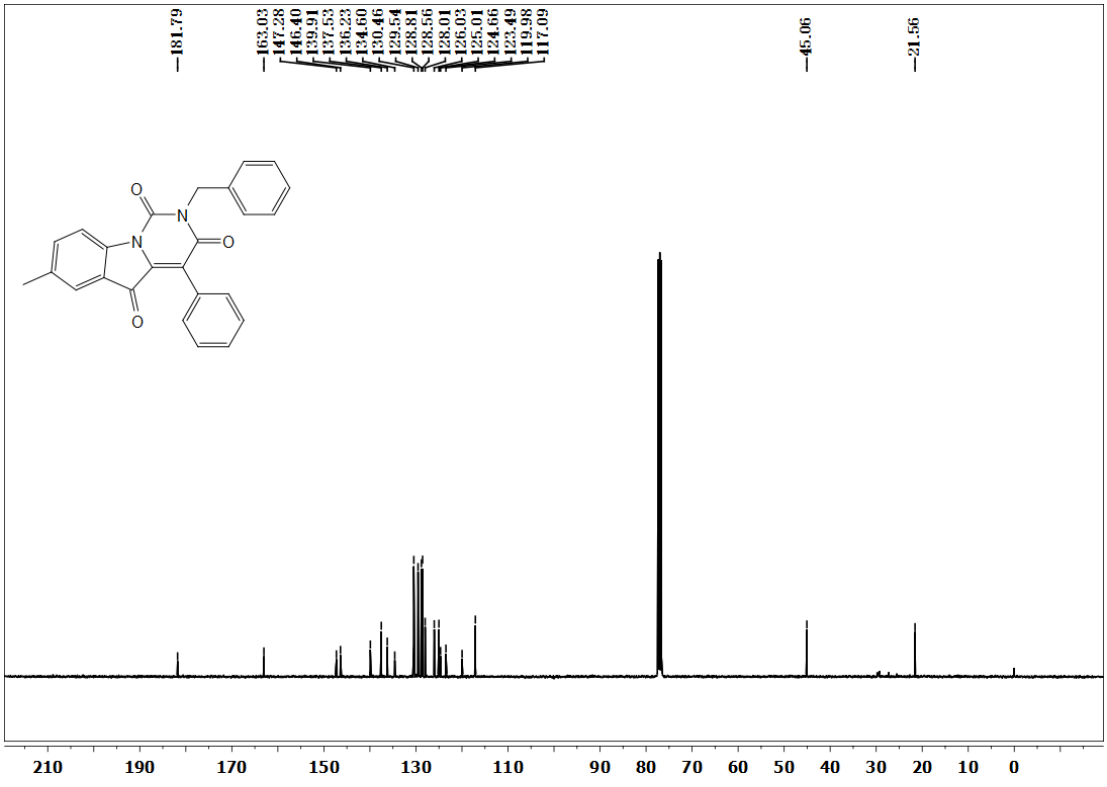
^{1}H NMR and ^{13}C NMR spectrum of **7t**.



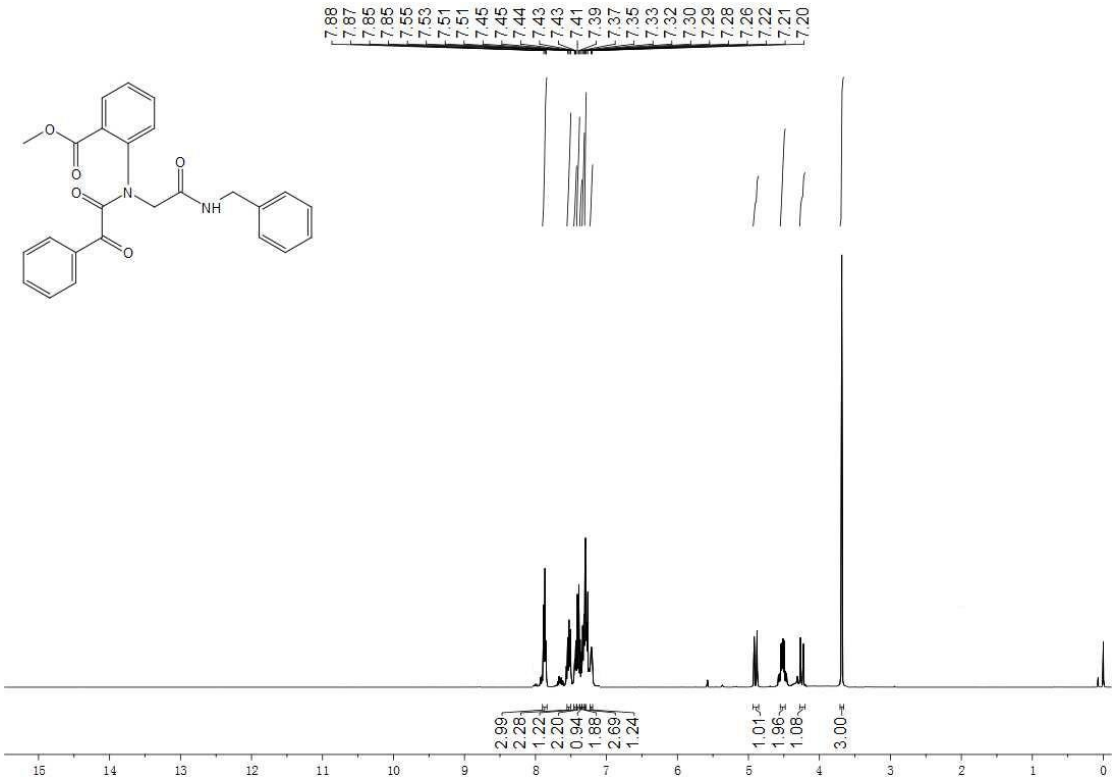


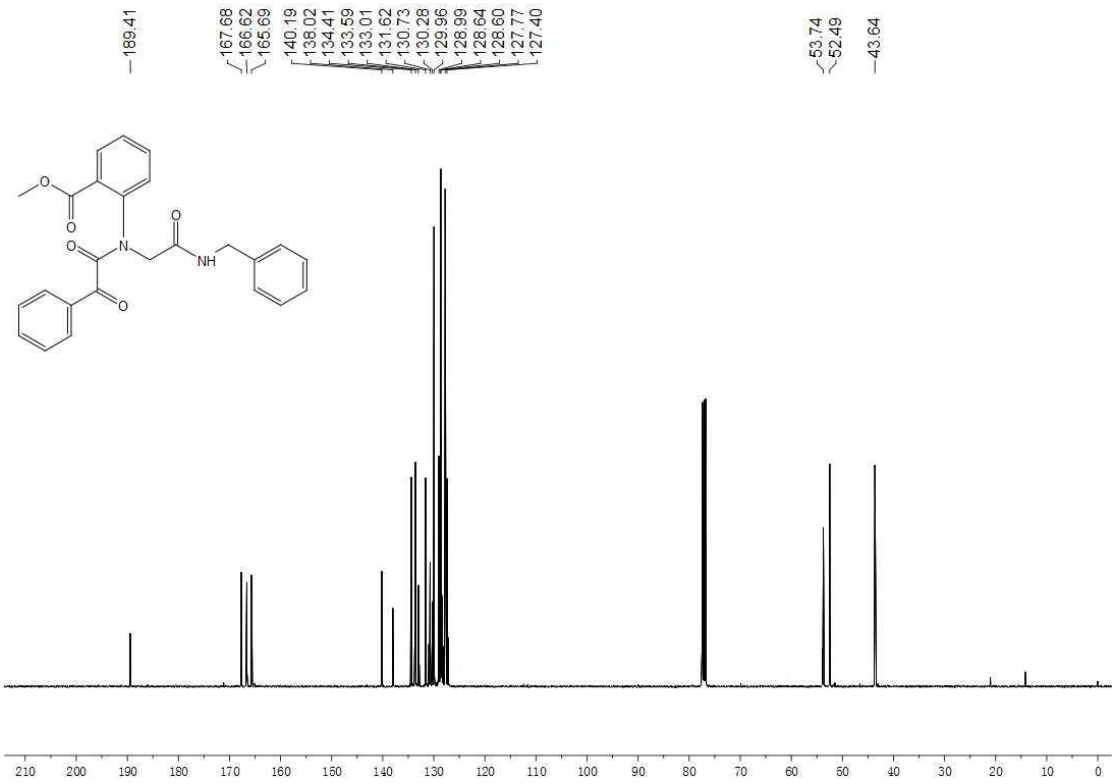
^{1}H NMR and ^{13}C NMR spectrum of **7u**.



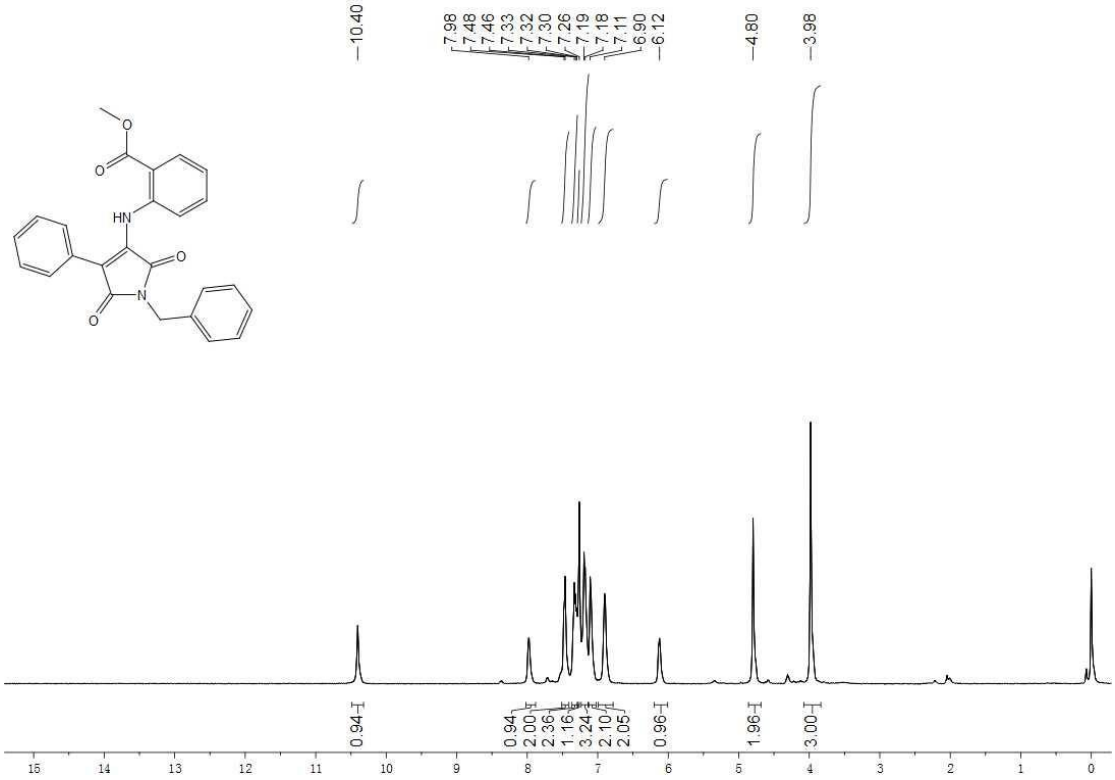


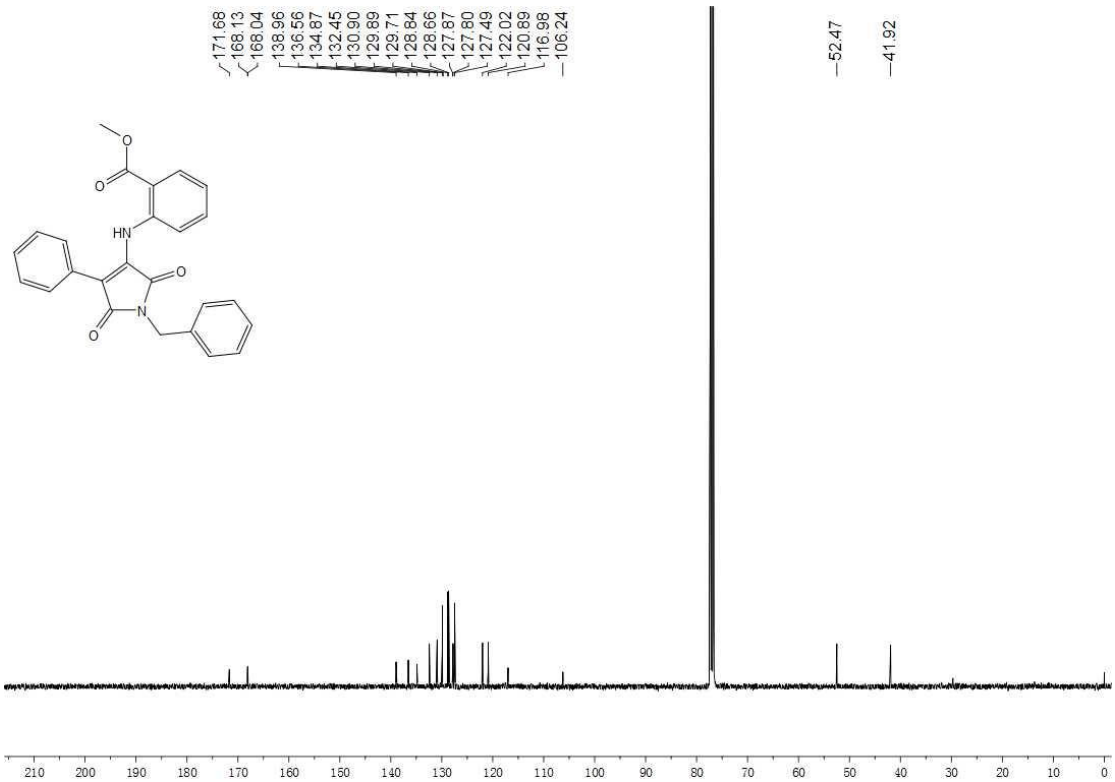
^{1}H NMR and ^{13}C NMR spectrum of **9a**.





^{1}H NMR and ^{13}C NMR spectrum of **10**.





^{1}H NMR and ^{13}C NMR spectrum of **12**.