Supporting Information

One-pot construction of functionalized aziridines and maleimides *via* a novel *pseudo*-Knoevenagel cascade reaction†

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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.

Table S1. Optimization for synthesizing compound *cis*-**6a**.

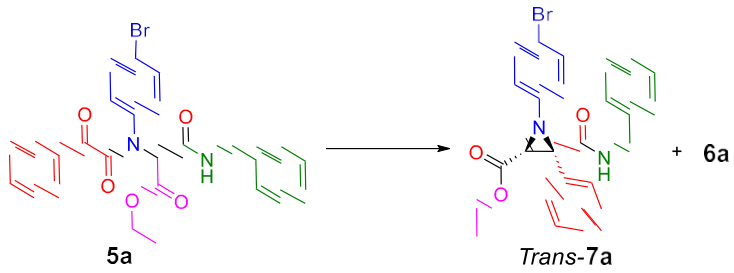
entry	solvt.	cat.	eq.	temp. (°C)	time (min)	yield (%) *cis*-**6a**[a]
1	DMF	DBU	2.0	MW 150	10	NR
2	DMF	Et_3N	2.0	MW 110	10	5
3	DMF	TEOA	2.0	MW 110	10	8
4	DMF	TEOA	2.0	MW 130	10	45
5	**DMF**	**TEOA**	**5.0**	**MW 130**	**10**	**72**
6	DMF	TEOA	8.0	MW 130	10	65
7	DMF	TEOA	5.0	MW 150	10	33
8	DMF	TEOA	5.0	MW 170	10	3
9	MeCN	TEOA	5.0	MW 130	10	29
10	DMSO	TEOA	5.0	MW 130	10	35
11	THF	TEOA	5.0	MW 130	10	NR
12	DCE	TEOA	5.0	MW 130	10	NR

[a] Yield of isolated product. MW = microwave irradiation. Reaction conditions: **5a** (0.2 mmol), base (relative equiv.) in solvent (1.0 mL) under microwave irradiation.

General procedures for compound *cis*-6.

A solution of benzoylformic acid (1.0 mmol), isocyanide (1.0 mmol), aniline (1.0 mmol) and ethyl glyoxylate (2.0 mmol) was 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 crude residue was subjected to triethanolamine (TEOA) (5.0 equiv.) and DMF (3.0 mL) solution under microwave irradiation condition at 130 °C for 10 min. After the microwave vial was cooled to room temperature, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product *cis*-**6**.

Table S2. Optimization for synthesizing compound **7a**.



entry	solvt.	cat.	eq.	temp. (°C)	time (min)	yield (%) **7a**[a]	yield (%) **6a**[a]
1	DMF	TEOA	5.0	MW 130	10	12	72
2	DMF	TEOA	2.0	MW 130	10	43	45
3	DMF	TEOA	2.0	MW 140	10	37	47
4	DMF	TEOA	1.0	MW 140	10	32	24
5	DMF	TEOA	2.0	MW 150	10	28	19
6	DMSO	TEA	2.0	MW 140	10	36	25
7	DCE	TEA	2.0	MW 140	10	Trace	5
8	**MeCN**	**TEA**	**2.0**	**MW 140**	**10**	**68**	**9**
9	MeCN	TEA	2.0	MW 140	20	61	17
10	MeCN	TEA	2.0	MW 150	10	50	14
11	MeCN	DIPEA	2.0	MW 140	10	33	32
12	MeCN	DIPA	2.0	MW 140	10	37	51

[a] Yield of isolated product. MW = microwave irradiation. Reaction conditions: **5a** (0.2 mmol), base (relative equiv.) in solvent (1.0 mL) under microwave irradiation.

General procedures for compound *trans*-7.

A solution of benzoylformic acid (1.0 mmol), isocyanide (1.0 mmol), aniline (1.0 mmol) and ethyl glyoxylate (2.0 mmol) was 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 crude residue was subjected to TEA (2.0 equiv.) and MeCN (3.0 mL) solution under microwave irradiation condition at 140 °C for 10 min. After the microwave vial was cooled to room temperature, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product

trans-**7**.

Table S3. Optimization for synthesizing compound **8a**.

Entry	Solvt.	Cat.	Eq.	Temp. (°C)	Time (min)	Yield (%) **8a**[a]
1[b]	10%TFA/DCE			MW 120	10	NR
2[b]	10%HCl/AcOH			MW 120	10	NR
3	DMF	K_2CO_3	2.0	MW 120	10	NR
4	DMF	EtONa	2.0	MW 120	30	NR
5	DMF	NaOH	2.0	MW 120	10	NR
6	DMF	KOAc	2.0	MW 120	10	NR
7	DMF	DIPA	2.0	MW 120	10	20
9	DMF	DIPEA	2.0	MW 120	10	32
10	DMF	DABCO	2.0	MW 120	10	50
11	DMF	DBU	2.0	MW 120	10	57
12	DMF	DBU	2.0	MW 120	10	63
13	**DMF**	**DBU**	**2.0**	**MW 140**	**10**	**75**
14	DMF	DBU	2.0	MW 150	10	60

[a] Yield of isolated product. MW = microwave irradiation. Reaction conditions: **5a** (0.2 mmol), base (0.4 mmol) in DMF (1.0 mL) under microwave irradiation. [b] The solvent was used as 1.0 mL.

General procedure for compound 8a from compound *cis*-6a

In a solution of compound *cis*-**6a** (86 mg, 0.2 mmol) in DMF (3.0 mL), DBU (60 mg, 0.4 mmol) was added and treated in microwave at 170 °C for 10 min. After the microwave vial was cooled to room temperature, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product **8a** with 81% yield.

General procedures for compound 8.

A solution of benzoylformic acid (1.0 mmol), isocyanide (1.0 mmol), aniline (1.0 mmol) and ethyl glyoxylate (2.0 mmol) was stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When no isonitrile

was left, the solvent was removed under nitrogen blowing and the crude residue was dissolved in DBU (2.0 equiv.) and DMF (3.0 mL) solution and treated in microwave at 140 °C for 10 min. After the microwave vial was cooled to room temperature, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na_2CO_3 and brine. The organic layer was drie d over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product **8**.

General procedures for compound 10.

A solution of benzoylformic acid (1.0 mmol), benzyl lsocyanide (1.0 mmol), 4-bromoaniline (1.0 mmol) and cyclohexanone (1.0 mmol) was stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-20%) to afford the relative targeted product **10** with 67% yield.

Density functional theory (DFT) calculations

The mechanism was investigated via DFT using the B3LYP functional[1] with the 6-31G* basis sets[2] as implemented in Gaussian 09 package,[3] which was used in the geometric optimizations of intermediates (IMs) and transition states (TSs). To considerate the weak interaction, the D3 version of Grimme's dispersion with Becke-Johnson damping were employed during the optimization[4]. To check the IMs and TSs structures, vibrational frequency calculations at the same level of theory were performed. Intrinsic reaction coordinates (IRC)[5] were performed to confirm the transition states connecting with the corresponding reactant and product intermediates. According to reaction conditions, the solvent effect of *N*, *N*-dimethylformamide (ε = 37.2) was evaluated using the Polarizable Continuum Model (PCM).[6] Natural charges were calculated via natural population analysis at the same level as that used for geometry optimization.

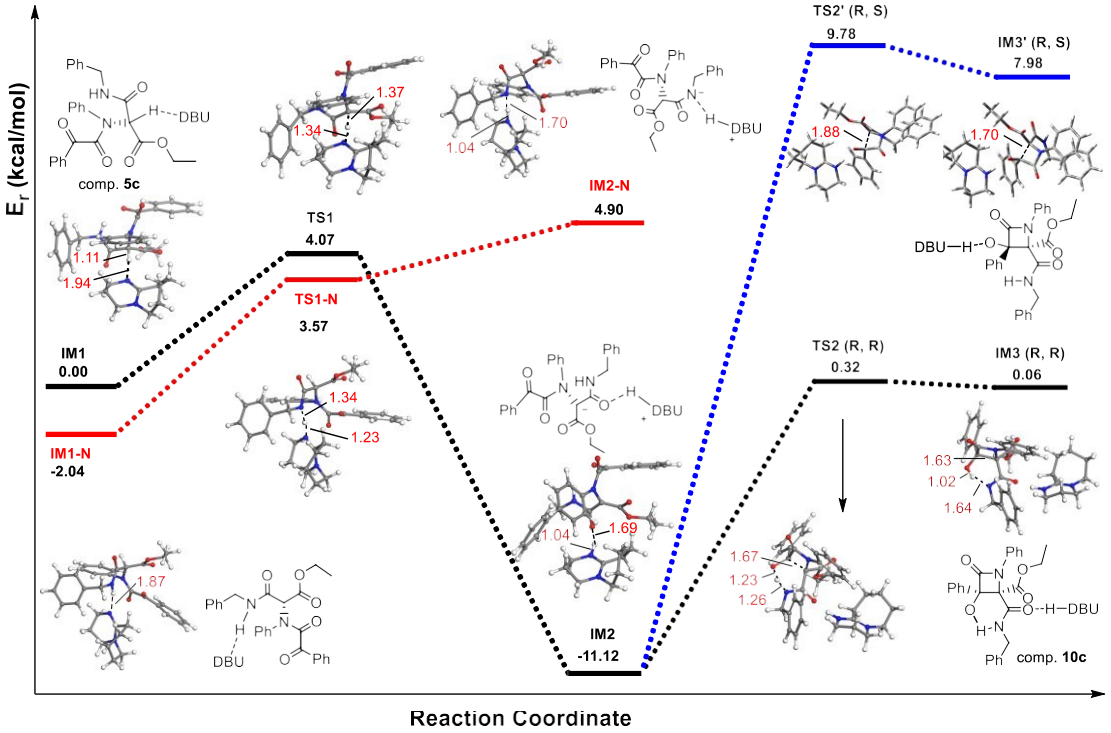


Figure S1. Calculated activation modes and potential energy profiles of the post-Ugi cascade reaction.

As shown in Figure 1, carbanion formation is exothermic (-11.12 kcal/mol), while amide anionic formation is endothermic (+4.90 kcal/mol). Further, the energy barrier for carbanion formation (4.07 kcal/mol) is lower than that of amide anionic formation (5.61 kcal/mol). Therefore, the formation of the carbanion is favourable thermodynamically and kinetically. The negative charge of the carbanion can delocalize between two adjacent carbonyls, while the amide anion can only delocalize to one carbonyl. Most importantly the α-amino group of compound **5** is neutralized with the substitutions of two adjacent carbonyl and a benzyl functional groups, which would further stabilize the enolate ion (carbanion). For the formation of the 4-membered azetidin-2-one ring **11**, the energy barrier of isomer IM3 (R, R) (0.06 kcal/mol) is lower than another IM3' (R, S) (7.98 kcal/mol). Therefore, the DFT results supported the formation of IM3 (R, R) would be the major pathway and also proved the reversible formation of compound *cis*-**6**.

1. a) A. D. Becke, Phys. Rev. A, 1988, 38, 3098; b) B. Miehlich, A. Savin, H. Stoll, and H. Preuss, *Chem. Phys. Lett.* 1989, **157**, 200.
2. R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* 1971, **54**, 724.
3. Gaussian 09, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, et al, Gaussian, Inc., Wallingford CT, 2009.
4. S. Grimme, S. Ehrlich and L. Goerigk, *J. Comp. Chem.* 2011, **32**, 1456.
5. a) K. Fukui, *Acc. Chem. Res.* 1981, **14**, 363; b) H. P. Hratchian and H. B. Schlegel, in Theory and Applications of Computational Chemistry: The First 40 Years, Ed. C. E. Dykstra, G. Frenking, K. S. Kim, and G. Scuseria (Elsevier, Amsterdam, 2005) 195-249.
6. G. Scalmani and M. J. Frisch, *J. Chem. Phys.* 2010, **132**, 114110.

Materials and methods

1. cell lines and culture

The human tumor cells (Huh-7, Hep3B, A549, H460, LN229, DU145, PC3, MDA-MB-468, MCF-7, PANC, SW1990, HCT116, SW620, Hela) were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). The Huh-7, Hep3B, LN229, DU145, MDA-MB-468, MCF-7, SW1990, SW620 and Hela cells were cultured with high-glucose DMEM (Hyclone, SH30022.01, USA) medium supplemented with 10% fetal bovine serum (FBS, Gibco, 10099, Australia origin). The A549 and PC3 cells were cultured in the Ham's F-12K (Kaighn's) Medium (GIBCO, 21127022, USA) with 10% FBS. The H460 and PANC cells were cultured with the RPMI 1640 Medium (GIBCO, 61870044, USA) added with 10% FBS. The cells were cultured in an incubator at the 37 ^{o}C and 5% CO_2 with humidified atmosphere.

2. MTT assay

The anticancer activity and the IC_{50} value of compound **8i** in the human tumor cells were measured by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT, Beyotime, ST316, Shanghai, China) assay. Briefly, the tumor cells were counted and seeded into the 96-well plate with density of 1×10^3 cells per well

containing 100 μL complete medium. After incubation for 24 h, added another 100 μL complete medium containing 10 μM compounds and incubated with 3 days for the initial screening. To further evaluate the IC_{50} of compound **8i**, tumor cells were incubated with various concentrations (0, 2.5, 5, 10, 20, 40, 80, 160, 320 μM) of compound **8i** for 7 days. Then, 20 μL MTT (5 mg/mL) was added to each well and incubated with 4 h. After incubation, removed the medium and added 200 μL DMSO into each well to dissolve the formazan product. The absorbance was measured at 570 nm (Bio-Tek, Winooski, VT, USA) and the inhibition values of compounds or IC_{50} values were analyzed by GraphPad Prism 8.

(Inhibition values%) 10 μM concentration of compounds was used for the following cell lines.															
Entry	**name**	**Huh7**	**Hep3B**	**A549**	**H460**	**LN229**	**DU145**	**PC3**	**MDA-MB-468**	**MCF7**	**PANC**	**SW1990**	**HCT116**	**SW620**	**Hela**
1	**8a**	6.6	17.9	14.8	11.5	13.8	6.7	11.6	5.0	19.4	16.8	25.4	12.7	24.0	29.7
2	**8b**	22.4	7.8	12.1	22.6	5.8	10.5	9.8	15.9	24.3	28.9	21.5	17.7	6.9	26.1
3	**8c**	20.5	14.5	18.9	28.6	15.8	13.1	9.4	24.0	23.5	22.5	12.2	26.0	20.6	22.2
4	**8d**	5.1	10.4	10.7	17.6	7.4	5.9	27.6	27.6	22.8	25.4	15.0	15.4	23.9	17.4
5	**8e**	13.7	10.7	29.3	19.0	10.9	15.8	21.2	21.2	5.9	13.4	29.2	27.6	20.7	5.7
6	**8f**	15.3	18.9	28.2	15.7	12.7	10.5	27.5	8.2	23.9	16.6	9.0	21.2	10.6	15.9
7	**8g**	15.4	8.0	11.0	27.1	13.4	13.9	24.0	11.3	24.9	11.2	24.0	24.0	12.2	9.4
8	**8h**	18.5	6.6	10.9	20.5	6.4	11.0	24.9	6.4	17.4	18.0	18.1	15.9	24.0	9.8
9	**8i**	56.2	50.3	28.1	12.9	11.8	13.8	5.7	17.0	13.9	29.2	23.8	24.9	25.9	11.6
10	**8l**	29.2	5.2	11.6	8.3	17.3	6.7	8.2	18.9	24.5	25.7	17.3	27.5	26.4	24.0
11	**8m**	13.6	13.0	8.4	4.7	13.1	18.5	15.9	10.5	5.7	25.6	24.3	8.2	23.6	27.5
12	**8n**	7.8	23.5	15.2	9.8	10.4	6.7	16.1	22.7	9.8	25.1	17.4	19.7	21.6	30.1

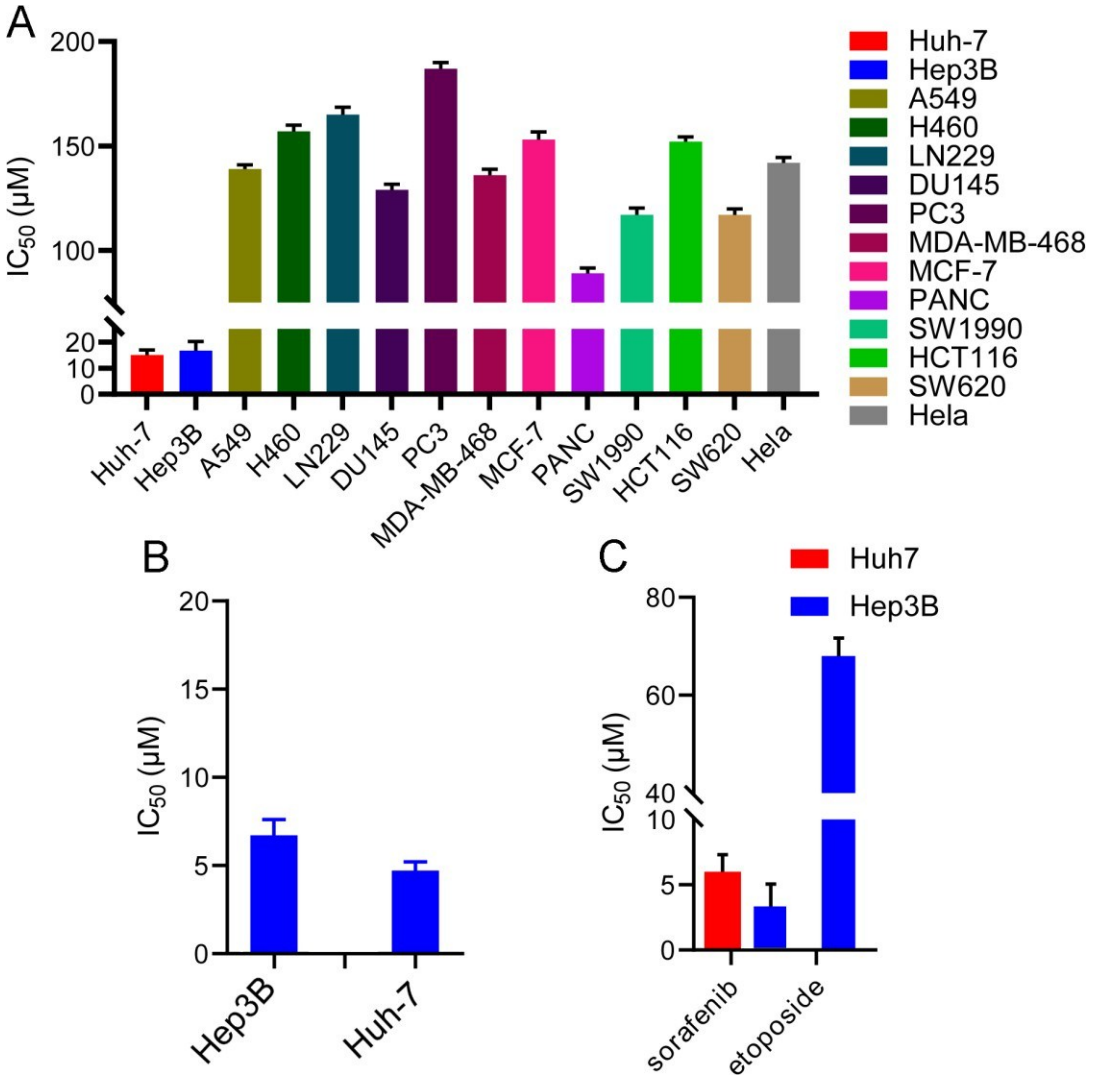
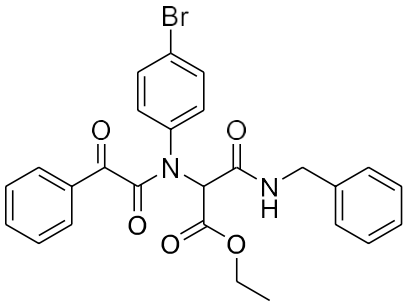


Figure 2. Anticancer activities IC_{50} (μM) of compound **8i**. A) Screening and activity analysis of compound **8i** in cancer cell lines using MTT assay for 3 days. B) The IC_{50} values of compound **8i** against Huh-7 and Hep3B (7days). C) Data Compare.[7]

7. (a) S. H. Yoo, Y. G. Yoon, J. S. Lee, Y. S. Song, J. S. Oh, B. S. Park, T. K. Kwon, C. Park, Y. H. Choi, Y. H. Yoo, *Int. J. Oncol*., 2012, **41**, 1443; (b) J. Liu, Y. Liu, L. Meng, B. Ji, D. Yan, *Int. J. Med. Sci.*, 2017, **14**, 523.

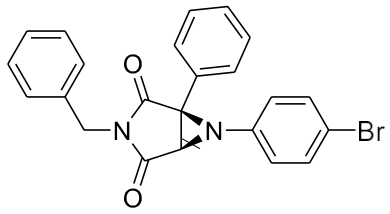
NMR Characterization Data and Figures of Products

Ethyl 3-(benzylamino)-2-(*N*-(4-bromophenyl)-2-oxo-2-phenylacetamido)-3-oxopropanoate



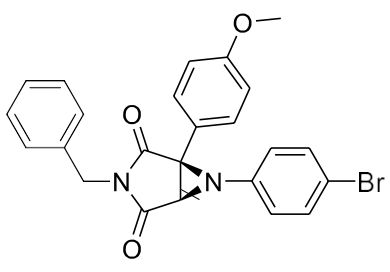
Compound **5a** (white solid, 520 mg, yield 78%, R_f = 0.29 (EA/Hex=25%)) ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.06 (t, *J* = 5.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.38-7.19 (m, 5H), 7.13 (d, *J* = 7.9 Hz, 2H), 5.71 (s, 1H), 4.33-4.16 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 190.4, 167.1, 167.0, 163.5, 138.6, 136.8, 135.8, 132.8, 132.5, 131.9, 129.7,129.6, 128.7, 127.8, 127.4, 122.7, 64.3, 62.4, 43.2, 14.3. HRMS (ESI) m/z calcd for $C_{26}H_{24}BrN_2O_5^+$ $(M+H)^+$ 523.0863, found 523.0864.

3-benzyl-6-(4-bromophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-Dione



Compound *cis*-**6a** (white solid, 290 mg, yield 67%, R_f = 0.35 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.47-7.40 (m, 3H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 7.4 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 4.37 (s, 2H), 3.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.74, 167.53, 142.61, 133.62, 131.38, 129.10, 128.26, 127.80, 127.75, 127.51, 126.78, 126.52, 119.99, 116.65, 51.19, 46.71, 41.00. HRMS (ESI) m/z calcd for $C_{23}H_{18}BrN_2O_2^+$ $(M+H)^+$ 433.0546, found 433.0544.

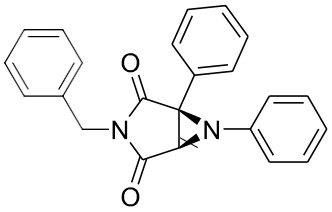
6-(4-Bromophenyl)-1-(4-methoxyphenyl)-3-(4-methylbenzyl)-3,6-diazabicyclo [3.1.0]hexane-2,4-dione



Compound *cis*-**6b** (white solid, 331 mg, yield 72%, R_f= 0.33 (EA/Hex=15%)). ^{1}H NMR (400 MHz,

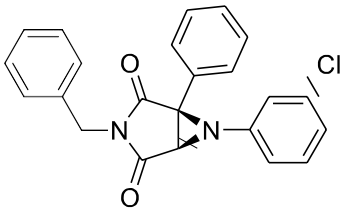
$CDCl_3$) δ 7.49-7.44 (m, 2H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 2H), 7.09-7.04 (m, 2H), 6.94 (t, *J* = 5.8 Hz, 2H), 6.91 (d, *J* = 7.4 Hz, 2H), 6.69 (t, *J* = 5.8 Hz, 2H), 4.36 (s, 2H), 3.83 (s, 3H), 3.71 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.07, 168.72, 160.39, 143.79, 134.70, 132.38, 129.16, 128.76, 128.52, 127.52, 121.93, 121.02, 117.57, 114.31, 55.41, 52.02, 47.57, 41.98. HRMS (ESI) m/z calcd for $C_{24}H_{20}BrN_2O_3^+$ $(M+H)^+$ 463.0652, found 463.0649.

3-Benzyl-1,6-diphenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



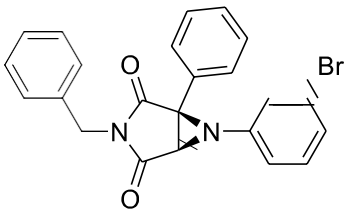
Compound *cis*-**6c** (white solid, 212 mg, yield 60%, R_f = 0.34 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.54 (m, 2H), 7.43 (dd, *J* = 5.0, 2.3 Hz, 3H), 7.13 (ddd, *J* = 15.8, 8.2, 5.7 Hz, 6H), 6.99-6.87 (m, 5H), 4.27 (s, 2H), 3.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.17, 169.01, 144.69, 135.03, 130.50, 129.52, 129.15, 128.76, 128.56, 127.91, 127.48, 124.68, 119.44, 52.34, 47.93, 41.87. HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2O_2^+$ $(M+H)^+$ 355.1441, found 355.1442.

3-Benzyl-6-(3-chlorophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



Compound *cis*-**6d** (white solid, 252 mg, yield 65%, R_f = 0.30 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.43 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.18-7.09 (m, 3H), 6.97 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.93-6.83 (m, 2H), 6.80-6.69 (m, 2H), 4.35 (s, 2H), 3.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.80, 168.57, 145.74, 135.04, 134.96, 130.44, 130.02, 129.32, 128.84, 128.50, 127.86, 127.68, 125.16, 119.55, 117.66, 52.07, 47.64, 41.91. HRMS (ESI) m/z calcd for $C_{23}H_{17}ClN_2O_2^+$ $(M+Na)^+$ 411.0871, found 411.0969.

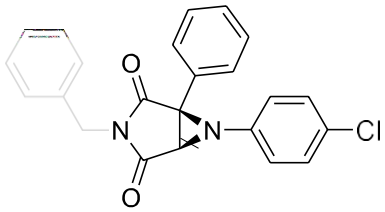
3-Benzyl-6-(3-bromophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



Compound *cis*-**6e** (white solid, 260 mg, yield 60%, R_f = 0.34 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ

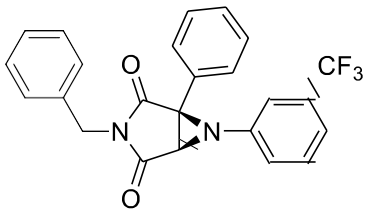
7.54 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.49-7.40 (m, 3H), 7.19-7.12 (m, 3H), 7.01 (s, 1H), 6.97 (dd, *J* = 6.4, 2.6 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.83 (t, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.36 (s, 2H), 3.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.77, 168.53, 145.83, 134.93, 130.67, 129.99, 129.32, 128.84, 128.51, 128.08, 127.84, 127.67, 123.07, 122.37, 118.09, 52.06, 47.64, 41.91. HRMS (ESI) m/z calcd for $C_{23}H_{18}BrN_2O_2^+$ $(M+H)^+$ 433.0546, found 433.0613.

3-Benzyl-6-(4-chlorophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



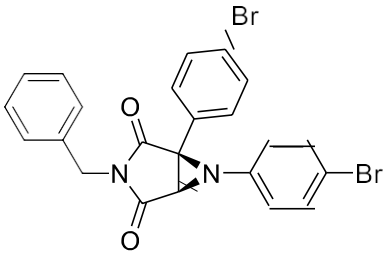
Compound *cis*-**6f** (white solid, 264 mg, yield 68%, R_f = 0.31 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.46-7.40 (m, 3H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 2H), 6.96-6.86 (m, 4H), 6.75 (d, *J* = 8.7 Hz, 2H), 4.37 (s, 2H), 3.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.80, 168.59, 143.13, 134.66, 130.16, 129.83, 129.51, 129.28, 128.82, 128.48, 127.82, 127.51, 120.63, 52.26, 47.79, 42.00. HRMS (ESI) m/z calcd for $C_{23}H_{18}ClN_2O_2^+$ $(M+H)^+$ 389.1051, found 389.1045.

3-Benzyl-1-phenyl-6-(3-(trifluoromethyl)phenyl)-3,6-diazabicyclo[3.1.0]hexane-2, 4-dione



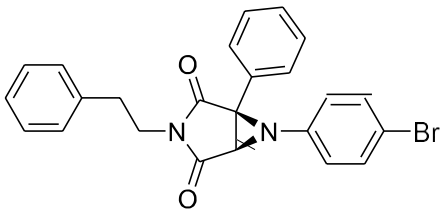
Compound *cis*-**6g** (white solid, 282 mg, yield 67%, R_f = 0.30 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.44 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.13-7.03 (m, 6H), 6.99 (dd, *J* = 5.5, 3.4 Hz, 1H), 6.96-6.90 (m, 2H), 4.33 (s, 2H), 3.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.71, 168.45, 145.10, 134.87, 129.97, 129.40, 128.89, 128.55, 127.81, 127.60, 124.80, 122.55, 121.52, 116.30, 52.10, 47.70, 41.89. HRMS (ESI) m/z calcd for $C_{24}H_{18}F_3N_2O_2^+$ $(M+H)^+$ 423.1315, found 423.1307.

3-Benzyl-1,6-bis(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



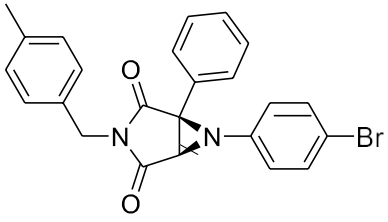
Compound *cis*-**6h** (white solid, 312 mg, yield 61%, R_f = 0.33 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.36 (s, 2H), 3.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.36, 168.19, 143.31, 134.50, 132.47, 132.03, 129.41, 129.25, 128.79, 128.57, 127.62, 123.60, 120.95, 117.89, 51.60, 47.91, 42.08. HRMS (ESI) m/z calcd for $C_{23}H_{17}Br_2N_2O^+$ $(M+H)^+$ 510.9651, found 510.9653.

6-(4-Bromophenyl)-3-phenethyl-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



Compound *cis*-**6i** (white solid, 280 mg, yield 63%, R_f = 0.32 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.49 (m, 3H), 7.44 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.25 (s, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 1H), 3.38 (ddd, *J* = 9.4, 7.1, 3.8 Hz, 2H), 2.13 (td, *J* = 7.1, 4.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.78, 168.67, 144.44, 137.45, 132.55, 131.52, 129.31, 128.85, 128.57, 127.78, 126.67, 121.52, 117.28, 52.42, 47.97, 39.04, 32.96. HRMS (ESI) m/z calcd for $C_{24}H_{20}BrN_2O_2^+$ $(M+H)^+$ 447.0703, found 447.0702.

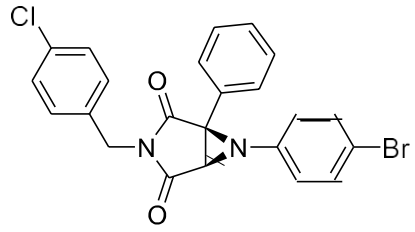
6-(4-Bromophenyl)-3-(4-methylbenzyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



Compound *cis*-**6j** (white solid, 315 mg, yield 71%, R_f = 0.31 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.43 (dd, *J* = 5.0, 1.7 Hz, 3H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.9 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 4.33 (s, 2H), 3.74 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.82, 168.64,

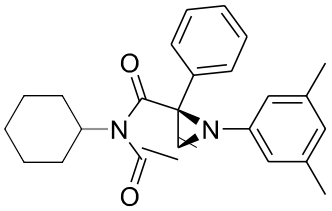
143.62, 137.50, 132.25, 129.26, 128.81, 128.63, 127.81, 121.46, 121.00, 117.81, 52.15, 47.68, 41.74, 21.36. HRMS (ESI) m/z calcd for $C_{24}H_{20}BrN_2O_2^+$ $(M+H)^+$ 447.0703, found 447.0701.

6-(4-Bromophenyl)-3-(4-chlorobenzyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2, 4-dione



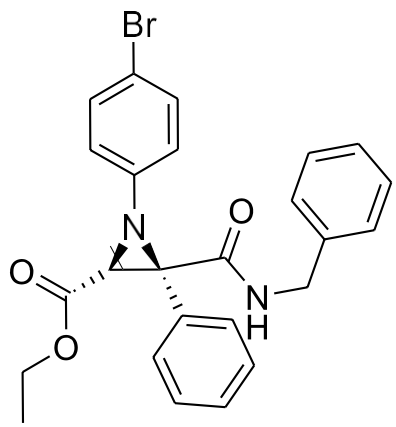
Compound *cis*-**6k** (white solid, 270 mg, yield 58%, R_f = 0.33 (EA/Hex=3%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.44 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.08 (d, *J* = 8.8 Hz, 3H), 6.96 (m, 1H), 6.75-6.61 (m, 4H), 4.36 (s, 2H), 3.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.69, 168.43, 143.50, 136.90, 132.34, 130.10, 129.36, 128.86, 127.79, 124.50, 120.97, 52.16, 47.65, 41.32. HRMS (ESI) m/z calcd for $C_{23}H_{17}BrClN_2O_2^+$ $(M+H)^+$ 467.0156, found 467.0160.

3-cyclohexyl-6-(3,5-dimethylphenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione



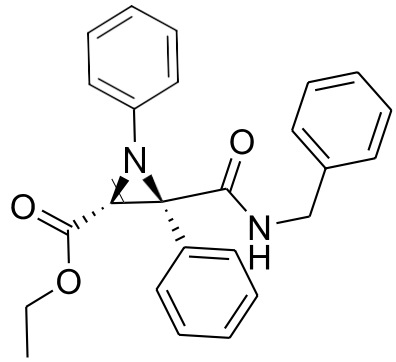
Compound *cis*-**6l** (light yellow solid, 259 mg, yield 71%, Rf = 0.35 (EA/Hex=15%)) ^{1}H NMR (400 MHz, CDCl3) δ 7.58 – 7.52 (m, 2H), 7.42 (tt, J = 6.6, 3.4 Hz, 3H), 6.67 (s, 1H), 6.58 (s, 2H), 3.62 (d, J = 0.9 Hz, 1H), 3.59 – 3.48 (m, 1H), 2.21 (s, 6H), 1.72 – 1.58 (m, 4H), 1.51 (s, 1H), 1.06 (t, J = 10.2 Hz, 3H), 0.86 (d, J = 10.9 Hz, 1H), 0.76 (d, J = 12.7 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 170.29, 169.39, 145.06, 139.26, 130.93, 128.90, 128.64, 127.87, 125.87, 117.60, 109.99, 51.69, 51.19, 47.75, 28.58, 28.32, 25.79, 25.75, 24.87, 21.14. HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_2^+$ $(M+H)^+$ 375.2067, found 375.2072.

Ethyl 3-(benzylcarbamoyl)-1-(4-bromophenyl)-3-phenylaziridine-2-carboxylate



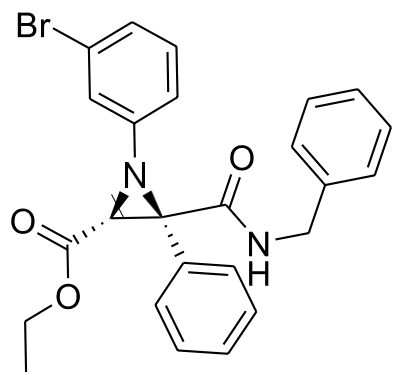
Compound *trans*-**7a** (white solid, 325 mg, yield 68%, R_f = 0.18 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.48-7.37 (m, 3H), 7.31-7.26 (m, 5H), 7.05 (dd, *J* = 6.8, 2.5 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.07 (t, *J* = 5.7 Hz, 1H), 4.43 (dd, *J* = 14.8, 6.5 Hz, 1H), 4.24 (s, 1H), 4.17 (dd, *J* = 14.8, 5.6 Hz, 1H), 4.07-3.85 (m, 2H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.84, 164.46, 146.63, 137.45, 133.15, 131.93, 129.38, 129.01, 128.68, 127.78, 121.05, 116.06, 61.26, 56.01, 47.23, 44.35, 13.81. HRMS (ESI) m/z calcd for $C_{25}H_{24}BrN_2O_3^+$ $(M+H)^+$ 479.0965, found 479.0960.

Ethyl 3-(benzylcarbamoyl)-1,3-diphenylaziridine-2-carboxylate



Compound *trans*-**7c** (white solid, 245 mg, yield 61%, R_f = 0.21 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 6.6 Hz, 3H), 7.26 (d, *J* = 13.0 Hz, 5H), 7.06 (dd, *J* = 9.9, 4.6 Hz, 3H), 6.96 (d, *J* = 7.5 Hz, 2H), 6.03 (t, *J* = 5.5 Hz, 1H), 4.43 (dd, *J* = 14.8, 6.5 Hz, 1H), 4.29 (s, 1H), 4.18 (dd, *J* = 14.9, 5.5 Hz, 1H), 3.96 (ddd, *J* = 34.8, 10.8, 7.1 Hz, 2H), 0.93 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.09, 164.94, 147.54, 137.76, 133.81, 129.21, 128.97, 128.94, 128.87, 127.89, 127.51, 123.23, 119.45, 61.37, 55.54, 46.84, 43.88, 13.48. HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_3^+$ $(M+H)^+$ 401.1859, found 401.1859.

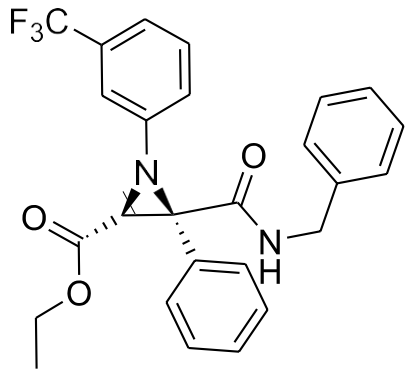
Ethyl 3-(benzylcarbamoyl)-1-(3-bromophenyl)-3-phenylaziridine-2-carboxylate



Compound *trans*-**7e** (white solid, 286 mg, yield 60%, R_f = 0.19 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.41 (q, *J* =

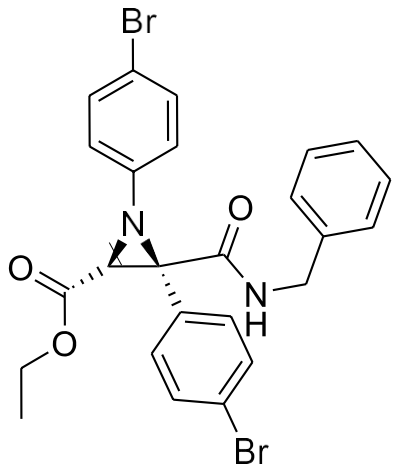
5.3 Hz, 3H), 7.33 – 7.21 (m, 4H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.10 (dd, *J* = 7.1, 5.7 Hz, 3H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.13 (t, *J* = 5.6 Hz, 1H), 4.46 (dd, *J* = 14.9, 6.6 Hz, 1H), 4.25 (s, 1H), 4.19 (dd, *J* = 14.9, 5.4 Hz, 1H), 4.03 – 3.85 (m, 2H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.98, 162.36, 149.28, 137.23, 132.87, 130.38, 129.48, 129.23, 128.50, 128.29, 127.74, 126.35, 122.95, 122.42, 118.56, 118.35, 61.47, 55.88, 47.41, 44.27, 13.74. HRMS (ESI) m/z calcd for $C_{25}H_{24}BrN_2O_3^+$ $(M+H)^+$ 479.0965, found 479.0981.

Ethyl 3-(benzylcarbamoyl)-3-phenyl-1-(3-(trifluoromethyl)phenyl)aziridine-2-carboxylate



Compound *trans*-**7g** (white solid, 318 mg, yield 68%, R_f = 0.16 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (m, 2H), 7.43 (q, *J* = 5.4 Hz, 3H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.32-7.27 (m, 3H), 7.21 (s, 1H), 7.13-7.04 (m, 3H), 6.11 (t, *J* = 5.5 Hz, 1H), 4.38 (dd, *J* = 14.9, 6.2 Hz, 1H), 4.29 (s, 1H), 4.25 (dd, *J* = 14.9, 5.6 Hz, 1H), 4.06-3.89 (m, 2H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69, 164.35, 148.27, 137.24, 132.88, 129.55, 129.09, 128.74, 127.70, 122.49, 120.08, 116.07, 61.35, 55.94, 47.46, 44.37, 13.81. HRMS (ESI) m/z calcd for $C_{26}H_{24}F_3N_2O_3^+$ $(M+H)^+$ 469.1734, found 469.1734.

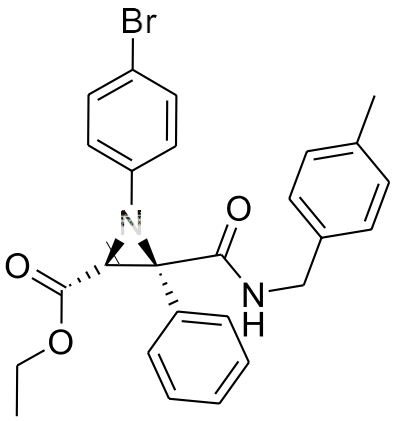
Ethyl 3-(benzylcarbamoyl)-1,3-bis(4-bromophenyl)aziridine-2-carboxylate



Compound *trans*-**7h** (white solid, 320 mg, yield 58%, R_f = 0.20 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 6.4, 1.8 Hz, 5H), 7.06 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.00 (s, 1H), 4.44 (dd, *J* = 14.7, 6.6 Hz, 1H), 4.24 (s, 1H), 4.16 (dd, *J* = 14.7, 5.5 Hz, 1H), 4.07 – 3.89 (m, 2H),

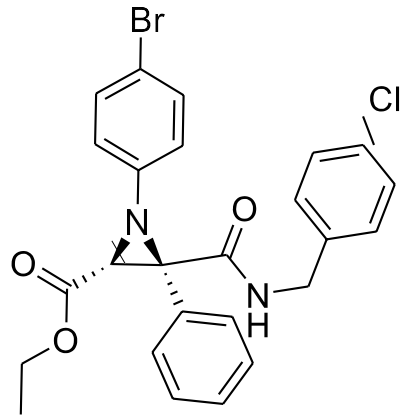
1.00 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.45, 163.34, 146.54, 137.65, 132.58, 132.37, 131.65, 130.94, 129.27, 128.28, 127.83, 123.51, 121.35, 60.82, 54.81, 46.41, 43.76, 13.27. HRMS (ESI) m/z calcd for $C_{25}H_{23}Br_2N_2O_3^+$ $(M+H)^+$ 557.0070, found 557.0077.

Ethyl 1-(4-bromophenyl)-3-((4-methylbenzyl)carbamoyl)-3-phenylaziridine-2-carboxylate



Compound *trans*-**7j** (white solid, 295 mg, yield 60%, R_f = 0.15 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 30.0 Hz, 2H), 7.41 (d, J = 19.2 Hz, 3H), 7.28 (dd, J = 10.9, 8.0 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.99 – 6.88 (m, 2H), 6.81 (t, J = 5.7 Hz, 2H), 6.04 (s, 1H), 4.38 (dd, J = 14.7, 6.5 Hz, 1H), 4.26 (s, 1H), 4.12 (dd, J = 14.6, 5.4 Hz, 1H), 4.06 – 3.83 (m, 2H), 2.36 (s, 3H), 0.94 (t, J = 4.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.65, 164.17, 146.02, 137.05, 134.60, 132.60, 131.91,131.57, 129.35, 129.11, 128.15, 127.62, 121.17, 116.45, 60.79, 55.52, 47.59, 44.64, 20.26, 12.54. HRMS (ESI) m/z calcd for $C_{26}H_{26}BrN_2O_3^+$ $(M+H)^+$ 493.1121, found 493.1129.

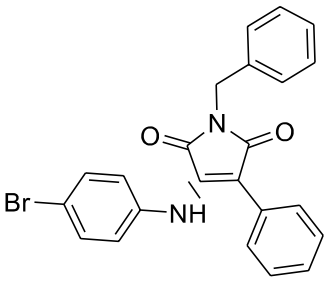
Ethyl 1-(4-bromophenyl)-3-((4-chlorobenzyl)carbamoyl)-3-phenylaziridine-2-carboxylate



Compound *trans*-**7k** (white solid, 328 mg, yield 64%, R_f = 0.22 (EA/Hex=20%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.5, 1.8 Hz, 2H), 7.47-7.39 (m, 3H), 7.32 (d, J = 8.7 Hz, 2H), 7.26-7.19 (m, 1H), 6.96 (td, J = 8.4, 2.1 Hz, 1H), 6.87-6.72 (m, 4H), 6.09 (t, J = 5.9 Hz, 1H), 4.42 (dd, J = 15.0, 6.6 Hz, 1H), 4.23 (s, 1H), 4.15 (dd, J = 15.0, 5.8 Hz, 1H), 3.90-4.03 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.77, 164.64, 146.52, 140.03, 133.07, 131.98, 129.47, 129.09, 123.30, 121.03, 116.18, 114.73, 61.30, 55.93, 47.20, 43.77,

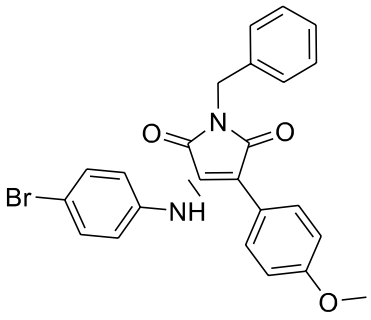
13.81. HRMS (ESI) m/z calcd for $C_{25}H_{23}BrClN\ O^+$ $(M+H)^+$ 513.0575, found 513.0600.

1-Benzyl-3-((4-bromophenyl)amino)-4-phenyl-1*H*-pyrrole-2,5-dione



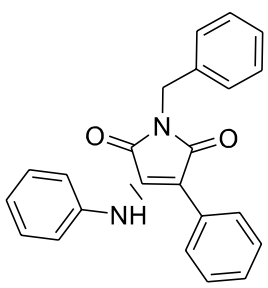
Compound **8a** (yellow solid, 307 mg, yield 71%, R_f = 0.27 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.38-7.27 (m, 3H), 7.21-7.17 (m, 2H), 7.16-7.11 (m, 3H), 7.03 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.48 (d, *J* = 8.7 Hz, 2H), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.54, 168.08, 136.44, 135.56, 135.44, 131.31, 129.77, 129.04, 128.70, 127.86, 127.80, 127.50, 122.76, 117.36, 103.71, 41.91. HRMS (ESI) m/z calcd for $C_{23}H_{17}BrN_2O_2^+$ $(M+H)^+$ 433.0546, found 433.0546.

1-Benzyl-3-((4-bromophenyl)amino)-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione



Compound **8b** (yellow solid, 345 mg, yield 75%, R_f = 0.24 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 2H), 7.36-7.27 (m, 3H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.12 (s, 1H), 7.06-6.94 (m, 2H), 6.77-6.65 (m, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.81, 168.35, 159.27, 136.52, 135.64, 134.34, 131.34, 131.13, 128.70, 127.84, 122.51, 121.50, 117.01, 113.10, 104.22, 55.32, 41.88. HRMS (ESI) m/z calcd for $C_{24}H_{19}BrN_2O_3^+$ $(M+H)^+$ 463.0652, found 463.0653.

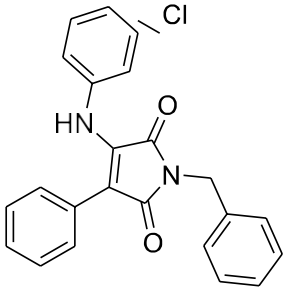
1-Benzyl-3-phenyl-4-(phenylamino)-1*H*-pyrrole-2,5-dione



Compound **8c** (light yellow solid, 260 mg, yield 73%, R_f= 0.23 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.0 Hz, 2H), 7.38-7.27 (m, 3H), 7.15 -7.06 (m, 3H), 7.05-6.95 (m, 5H), 6.62 (d, *J* = 7.6 Hz, 2H), 4.78 (s, 2H). ^{13}C

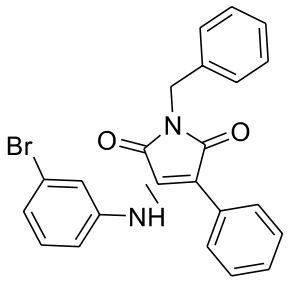
NMR (100 MHz, $CDCl_3$) δ 171.81, 168.25, 136.59, 136.28, 136.13, 129.74, 129.32, 128.69, 128.67, 128.31, 127.81, 127.34, 127.27, 124.55, 121.55, 102.79, 41.87. HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2O_2^+$ $(M+H)^+$ 355.1441, found 355.1441.

1-Benzyl-3-((3-chlororinphenyl)amino)-4-phenyl-1*H*-pyrrole-2,5-dione



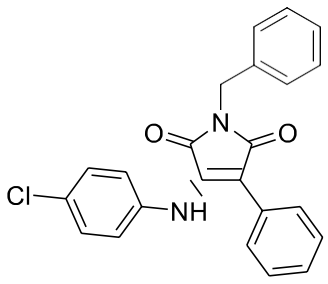
Compound **8d** (white solid, 325 mg, yield 61%, Rf = 0.20 (EA/Hex=15%)). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.9 Hz, 2H), 7.38-7.28 (m, 3H), 7.21-7.14 (m, 3H), 7.04 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.97-6.91 (m, 2H), 6.58 (s, 1H), 6.52 (dt, *J* = 6.7, 2.3 Hz, 1H), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 168.08, 137.46, 136.43, 135.50, 134.23, 129.72, 129.20, 129.02, 128.70, 128.64, 127.90, 127.86, 127.48, 124.36, 121.79, 119.32, 104.25, 41.93. HRMS (ESI) m/z calcd for $C_{23}H_{18}ClN_2O_2^+$ $(M+H)^+$ 389.1051, found 389.1051.

1-Benzyl-3-((3-bromophenyl)amino)-4-phenyl-1*H*-pyrrole-2,5-dione



Compound **8e** (white solid, 325 mg, yield 75%, R_f = 0.20 (EA/Hex=15%)) ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.38-7.27 (m, 3H), 7.22-7.16 (m, 3H), 6.89 (t, *J* = 8.0 Hz, 1H), 6.73 (t, *J* = 1.9 Hz, 1H), 6.58 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 168.07, 137.54, 136.43, 135.42, 129.74, 129.46, 128.99, 128.71, 127.98, 127.52, 127.27, 124.72, 122.10, 119.74, 104.29, 41.94. HRMS (ESI) m/z calcd for $C_{23}H_{18}BrN_2O_2^+$ $(M+H)^+$ 433.0546, found 433.0546.

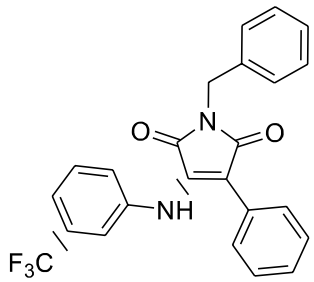
1-Benzyl-3-((4-chlorophenyl)amino)-4-phenyl-1*H*-pyrrole-2,5-dione



Compound **8f** (yellow solid, 264 mg, yield 68%, R_f = 0.28 (EA/Hex=15%)) ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 2H), 7.37-7.28 (m, 3H), 7.21 (s, 1H), 7.20-7.12

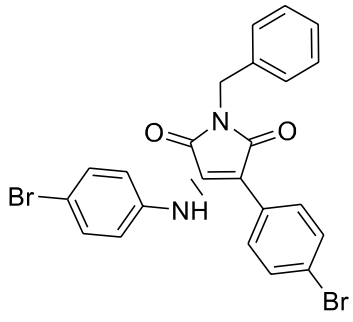
(m, 3H), 7.02 (dd, *J* = 7.9, 1.3 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.54 (d, *J* = 8.7 Hz, 2H), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.57, 168.09, 136.46, 135.69, 134.93, 129.79, 129.77, 129.05, 128.71, 128.67, 128.37, 127.87, 127.77, 127.48, 122.49, 103.54, 41.91. HRMS (ESI) m/z calcd for $C_{23}H_{18}ClN_2O_2^+$ $(M+H)^+$ 389.1051, found 389.1051.

1-Benzyl-3-phenyl-4-((3-(trifluoromethyl)phenyl)amino)-1*H*-pyrrole-2,5-dione



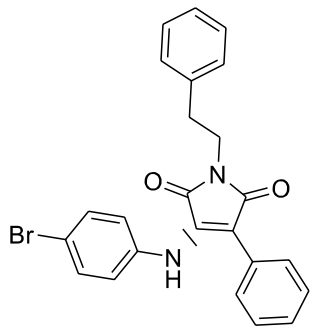
Compound **8g** (yellow solid, 330 mg, yield 78%, R_f = 0.29 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.33 (dd, *J* = 13.9, 6.6 Hz, 3H), 7.22-7.09 (m, 5H), 7.02 (d, *J* = 6.9 Hz, 2H), 6.92-6.84 (m, 1H), 6.75 (s, 1H), 4.79 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.43, 168.07, 136.85, 136.39, 135.31, 131.02, 130.69, 129.67, 128.96, 128.68, 128.01, 127.91, 127.56, 124.69, 124.01, 120.78, 118.00, 117.97, 104.69, 41.97. HRMS (ESI) m/z calcd for $C_{24}H_{18}F_3N_2O_2^+$ $(M+H)^+$ 423.1315, found 423.1315.

1-Benzyl-3-(4-bromophenyl)-4-((4-bromophenyl)amino)-1*H*-pyrrole-2,5-dione



Compound **8h** (light yellow solid, 285 mg, yield 56%, R_f = 0.31 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.36-7.27 (m, 5H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.51 (d, *J* = 8.7 Hz, 2H), 4.76 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.24, 167.78, 136.27, 135.70, 135.21, 131.57, 131.22, 130.66, 128.73, 127.94, 122.88, 122.00, 117.87, 102.34, 41.99. HRMS (ESI) m/z calcd for $C_{23}H_{17}Br_2N_2O_2^+$ $(M+H)^+$ 510.9651, found 510.9649.

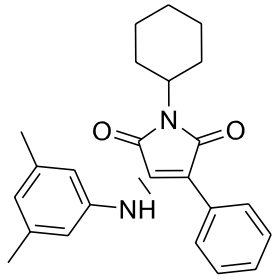
3-((4-Bromophenyl)amino)-1-phenethyl-4-phenyl-1*H*-pyrrole-2,5-dione



Compound **8i** (light yellow solid, 320 mg, yield 72%, R_f = 0.20 (EA/Hex=15%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 3H), 7.19 (s, 2H), 7.16 (dd, *J* = 10.0, 8.2 Hz,

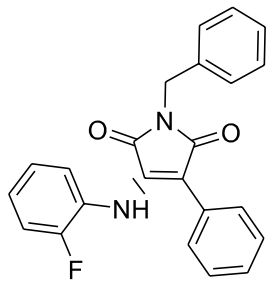
5H), 7.03 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.49 (d, *J* = 8.7 Hz, 2H), 3.89-3.83 (dd, *J* = 8.6, 6.9 Hz, 2H), 3.08-2.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.74, 168.19, 138.11, 135.52, 131.32, 129.78, 129.12, 128.89, 128.59, 127.80, 127.53, 126.67, 122.74, 117.31, 103.68, 39.62, 34.79. HRMS (ESI) m/z calcd for $C_{24}H_{20}BrN_2O_2^+$ $(M+H)^+$ 447.0703, found 447.0703.

1-cyclohexyl-3-((3,5-dimethylphenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione



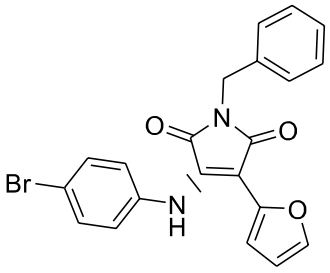
Compound **8l** (yellow solid, 243 mg, yield 69%, R_f = 0.40 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 5.2, 2.1 Hz, 3H), 7.02 – 6.97 (m, 2H), 6.57 (s, 1H), 6.21 (s, 2H), 4.06 – 3.95 (m, 1H), 2.11 (dt, *J* = 15.7, 10.9 Hz, 2H), 1.98 (s, 6H), 1.84 (d, *J* = 13.4 Hz, 2H), 1.75 (d, *J* = 10.7 Hz, 2H), 1.67 (d, *J* = 12.0 Hz, 2H), 1.35 (dd, *J* = 13.1, 3.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.23, 168.34, 137.98, 135.91, 135.76, 129.92, 128.64, 127.87, 127.09, 127.02, 125.83, 119.41, 117.59, 50.81, 30.10, 25.99, 25.14, 20.88. HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_2^+$ $(M+H)^+$ 375.2067, found 375.2071.

1-Benzyl-3-((2-fluorophenyl)amino)-4-phenyl-1*H*-pyrrole-2,5-dione



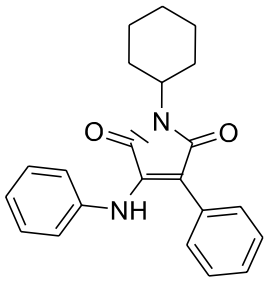
Compound **8m** (yellow solid, 257 mg, yield 69%, R_f = 0.26 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 2H), 7.37-7.28 (m, 3H), 7.15-7.10 (m, 3H), 7.06-7.01 (m, 2H), 7.01-6.96 (m, 1H), 6.96-6.89 (m, 1H), 6.60 (t, *J* = 7.7 Hz, 1H), 6.28 (td, *J* = 8.2, 1.4 Hz, 1H), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.51, 167.91, 155.72, 153.26, 136.49, 135.77, 129.65, 128.97, 128.69, 127.84, 127.62, 127.38, 125.36, 115.36, 115.17, 104.35, 41.90. HRMS (ESI) m/z calcd for $C_{23}H_{18}FN_2O_2^+$ $(M+H)^+$ 373.1347, found 373.1347.

1-Benzyl-3-((4-bromophenyl)amino)-4-(furan-2-yl)-1*H*-pyrrole-2,5-dione



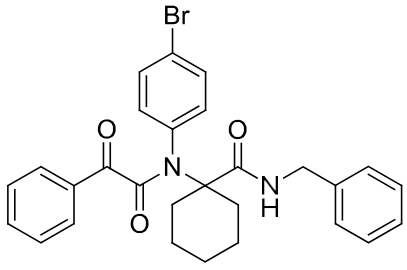
Compound **8n** (white solid, 300mg, yield 71%, R_f = 0.24 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.33-7.27 (m, 5H), 7.20 (d, *J* = 1.7 Hz, 1H), 6.84-6.77 (m, 2H), 6.74 (d, *J* = 3.4 Hz, 1H), 6.42 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.72 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.48, 167.19, 144.26, 142.59, 136.90, 136.32, 134.52, 131.62, 128.71, 128.55, 127.88, 123.07, 118.00, 111.76, 111.44, 97.65, 41.77. HRMS (ESI) m/z calcd for $C_{21}H_{16}BrN_2O_3^+$ $(M+H)^+$ 423.0339, found 423.0331.

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

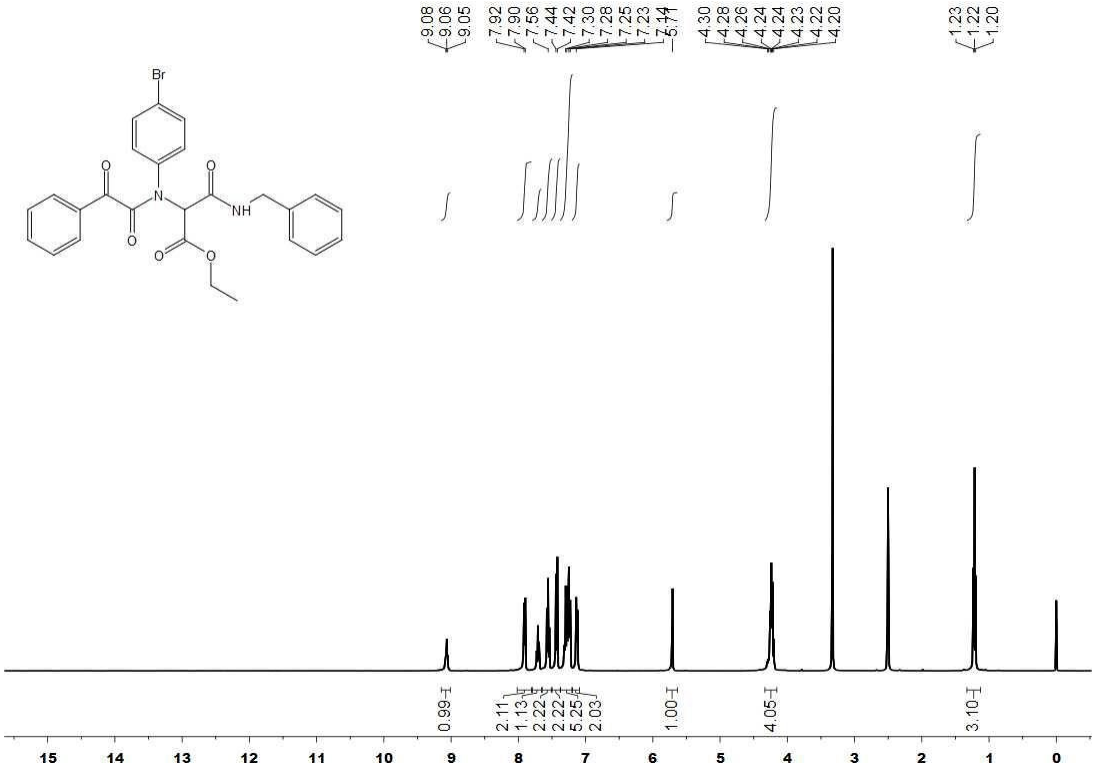


Compound **8o** (light yellow solid, 266 mg, yield 77%, R_f = 0.28 (EA/Hex=15%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 12.0 Hz, 1H), 7.06 (d, *J* = 12.6 Hz, 7H), 6.64 (s, 2H), 4.02 (s, 1H), 2.13 (d, *J* = 10.4 Hz, 2H), 1.75 (m, 5H), 1.32 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.12, 168.40, 136.53, 135.96, 129.78, 129.59, 128.22, 127.21, 127.17, 124.31, 121.51, 102.27, 50.95, 30.16, 26.04 , 25.20. HRMS (ESI) m/z calcd for $C_{22}H_{23}N_2O_2^+$ $(M+H)^+$ 347.1754, found 347.1752.

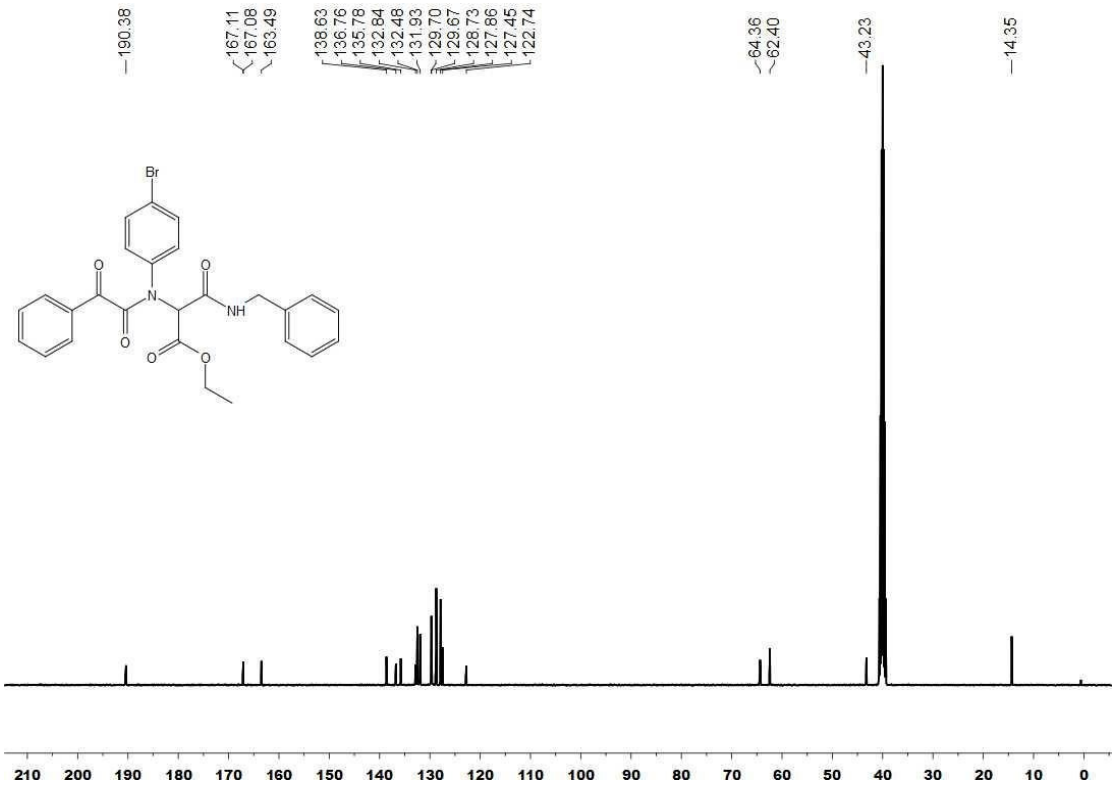
***N*-benzyl-1-(*N*-(4-bromophenyl)-2-oxo-2-phenylacetamido)cyclohexanecarboxamide,** Compound **9** (white solid, 350 mg, yield 67%, R_f = 0.42 (EA/Hex=20%)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.43 – 7.35 (m, 6H), 7.31 – 7.26 (m, 5H), 6.76 (t, *J* = 5.1 Hz, 1H), 4.62 (d, *J* = 5.6 Hz, 2H), 2.27 – 2.20 (m, 2H), 1.93 – 1.86 (m, 2H), 1.53 – 1.52 (m, 4H), 1.40 – 1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 173.1, 168.6, 138.2, 135.7, 134.3, 133.7, 133.1, 131.8, 129.5, 128.8, 128.7, 127.9, 127.5, 123.3, 66.7, 44.3, 33.5, 25.2, 22.5. HRMS (ESI) m/z calcd for $C_{28}H_{28}BrN_2O_3^+$ $(M+H)^+$ 519.1278, found 519.1274.



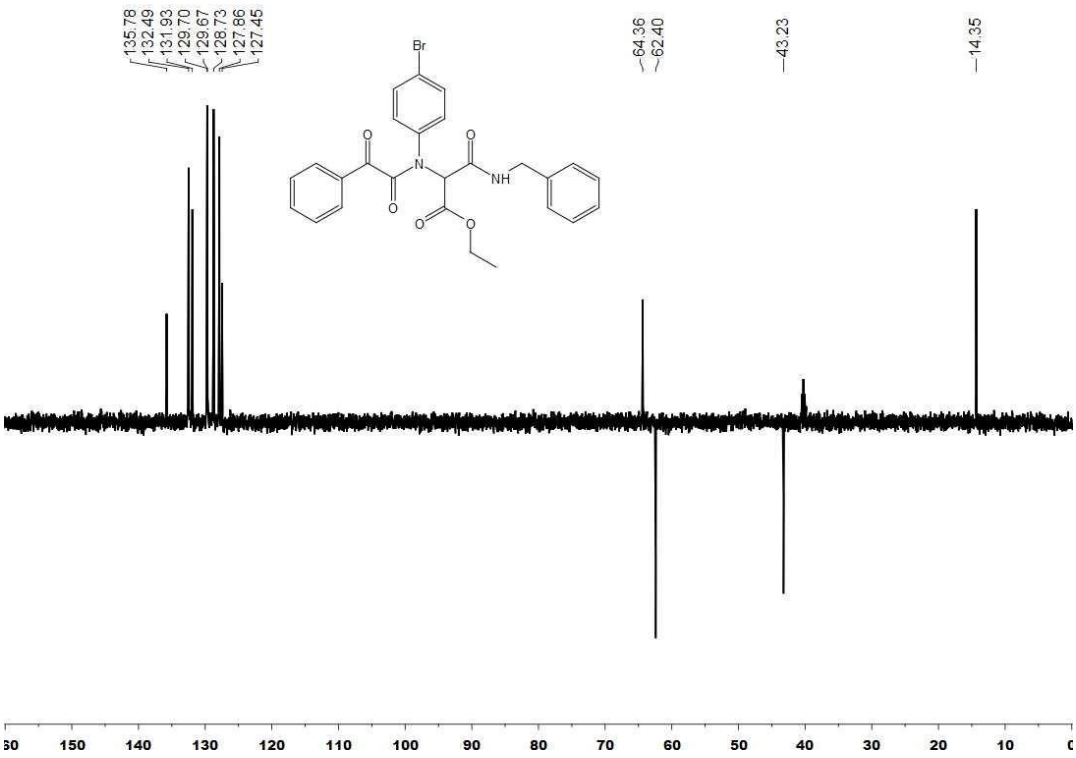
NMR spectrum of **5a**.



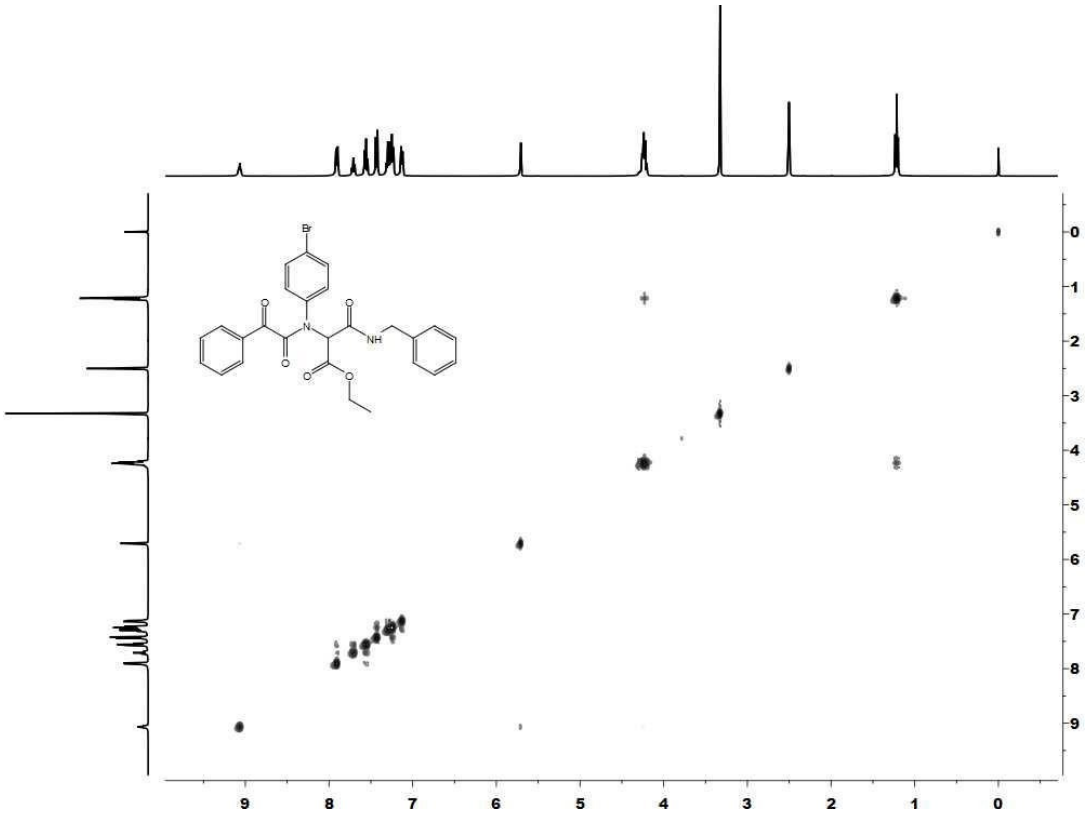
^{1}H NMR spectrum of **5a**



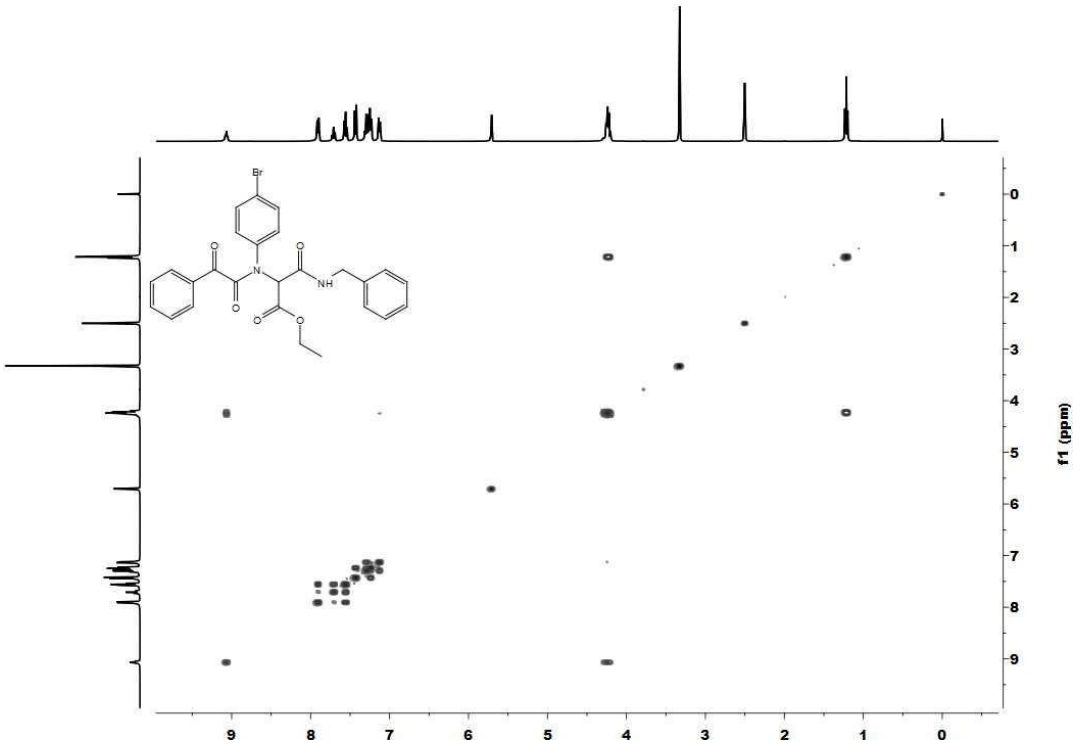
^{13}C NMR spectrum of **5a**



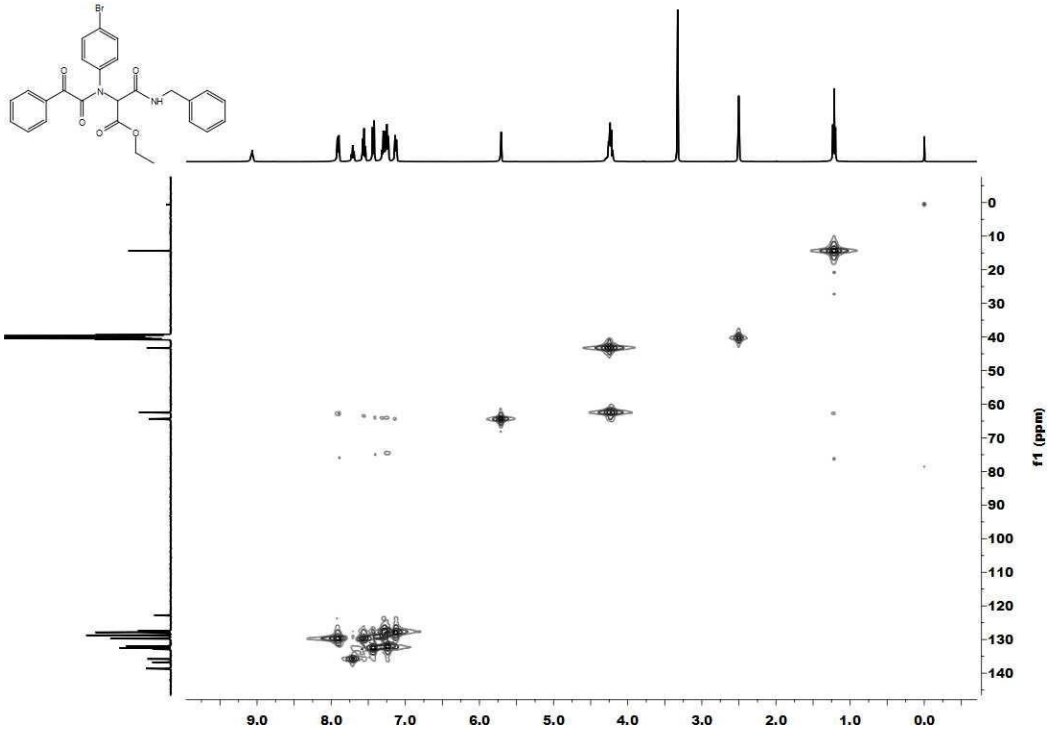
DEPT (135°) spectrum of **5a**



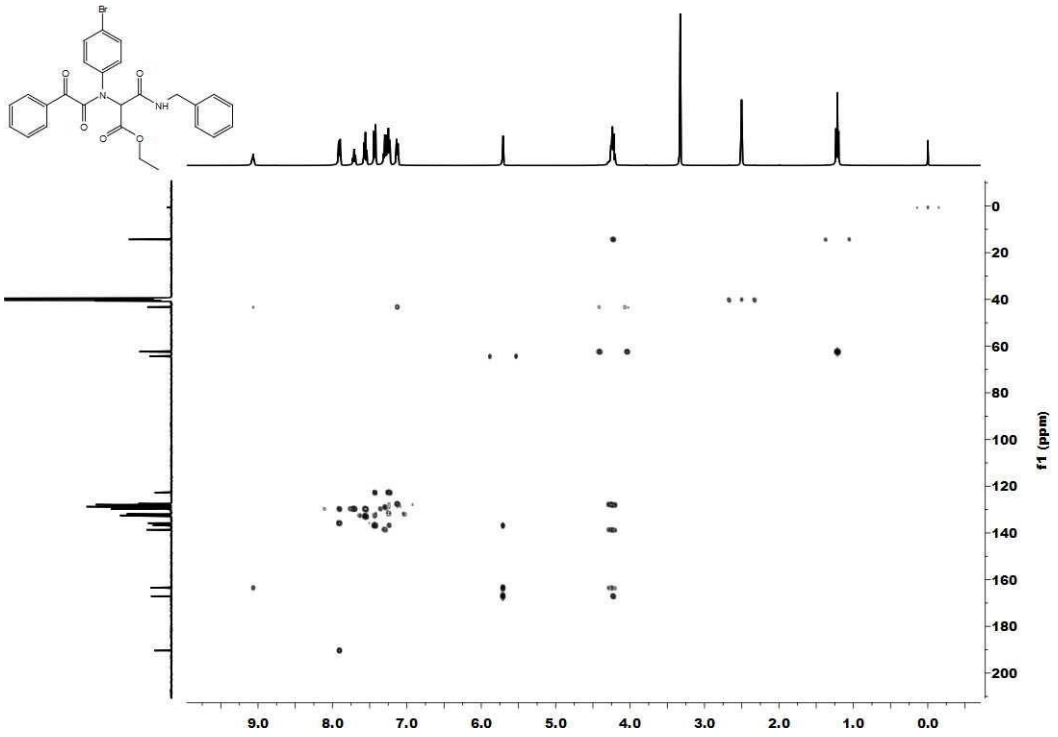
^{1}H-^{1}H COSY spectrum of **5a**



^{1}H-^{1}H NOESY spectrum of **5a**

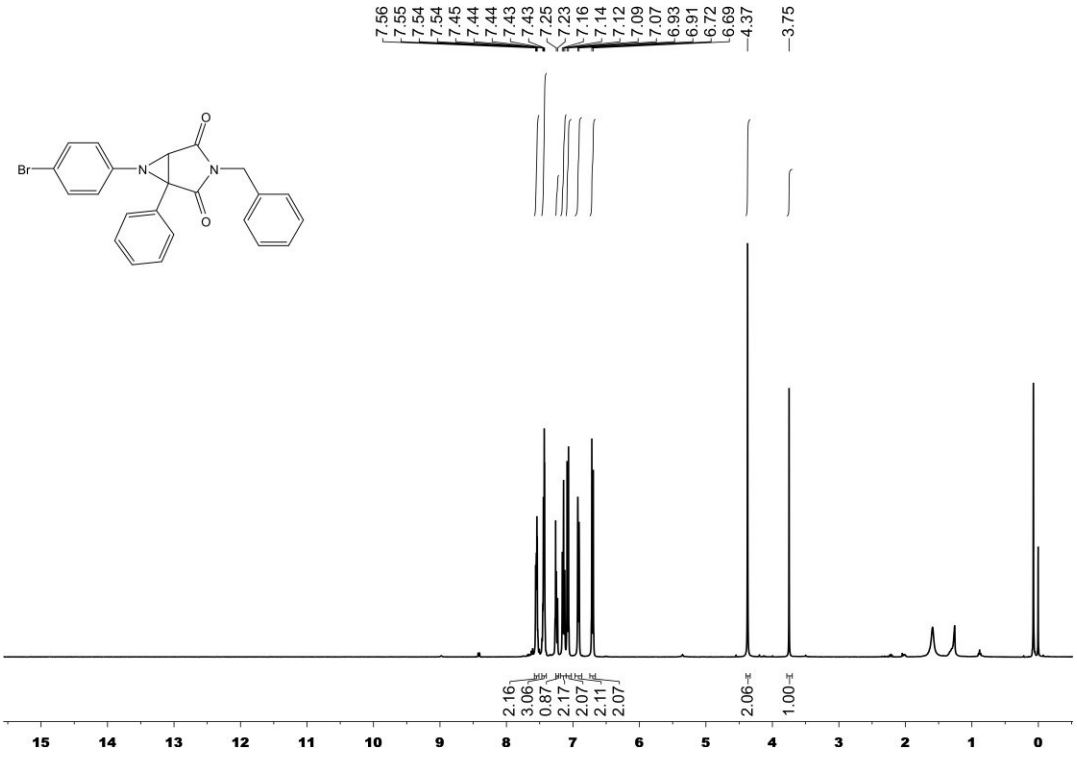


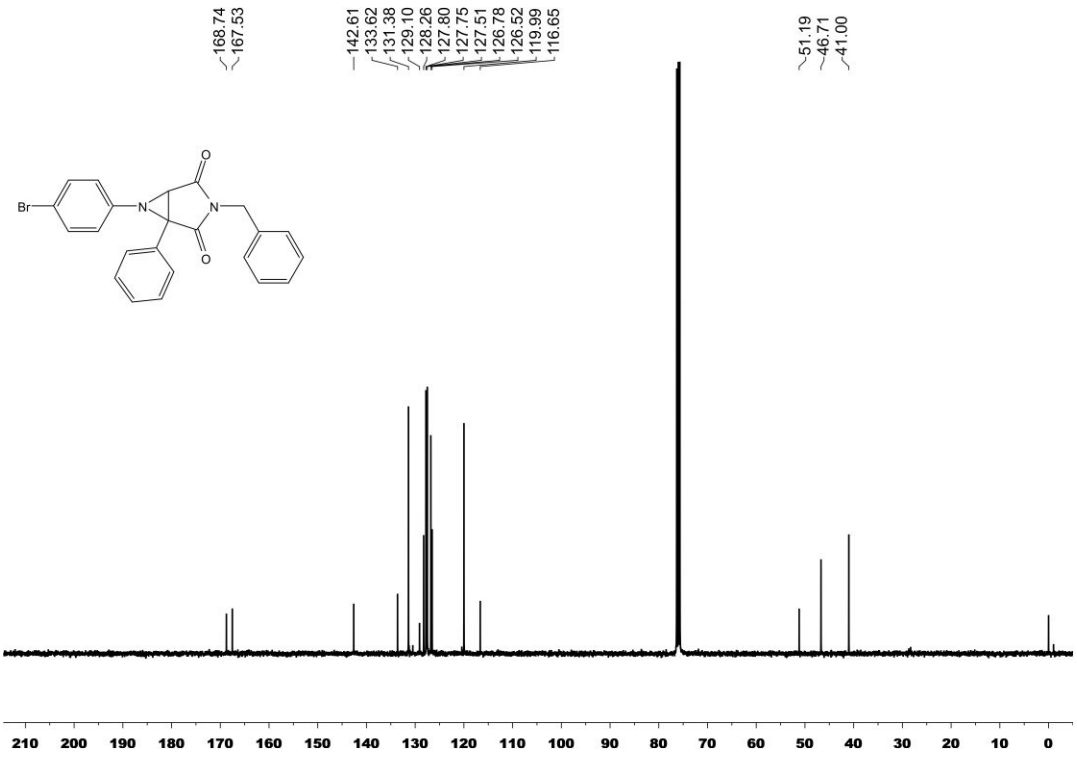
^{13}C-^{1}H HMQC spectrum of **5a**



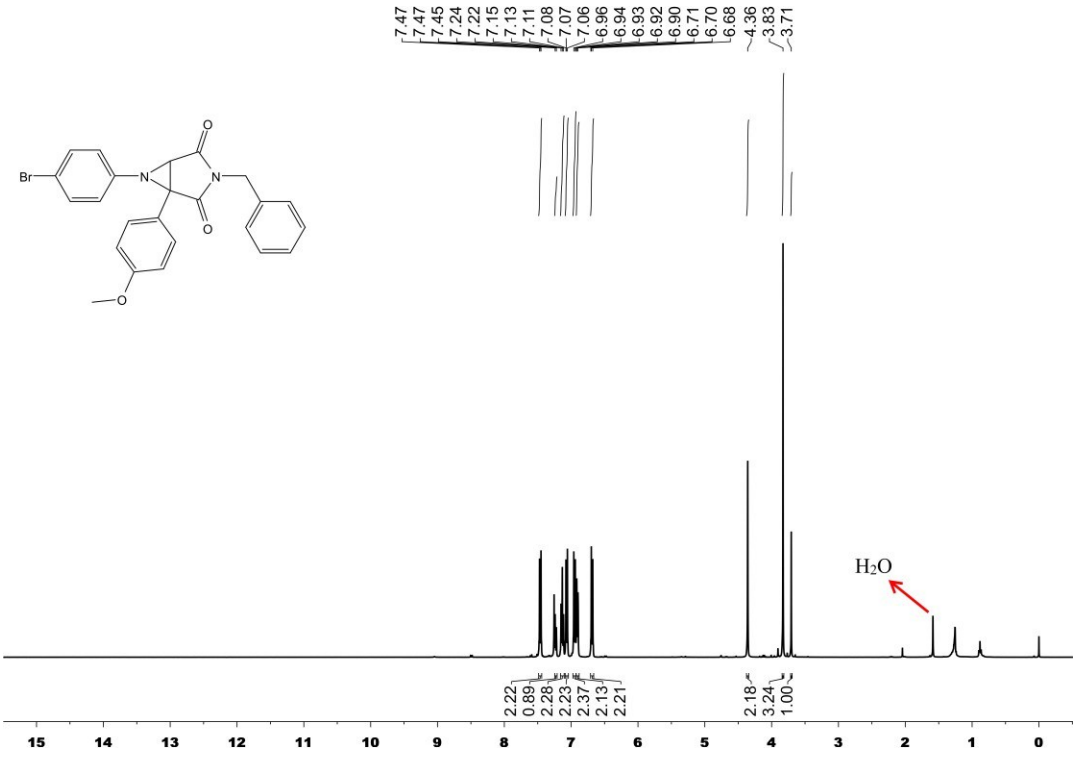
^{13}C-^{1}H HMBC spectrum of **5a**

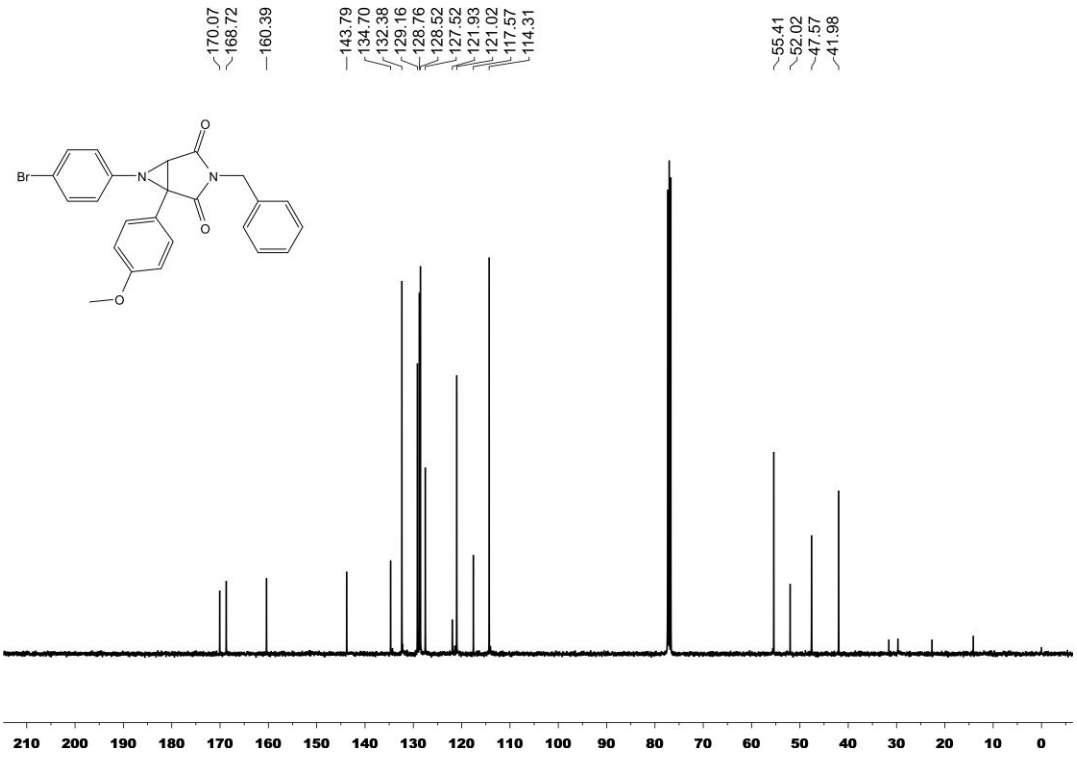
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6a**.



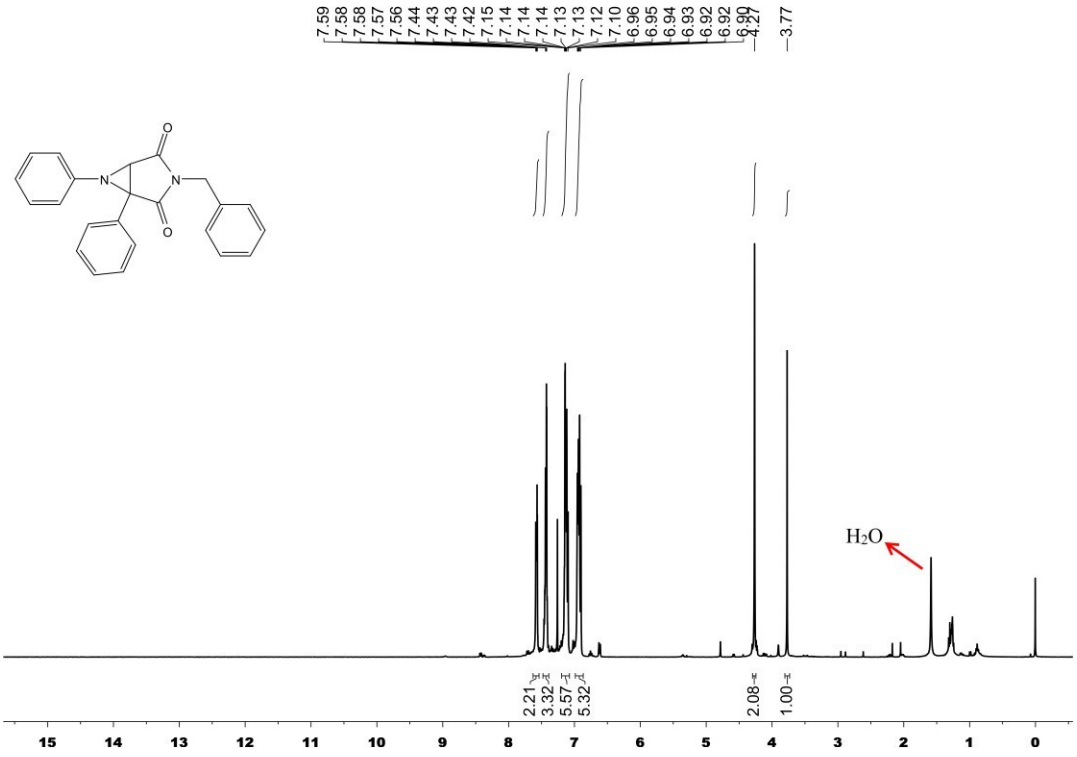


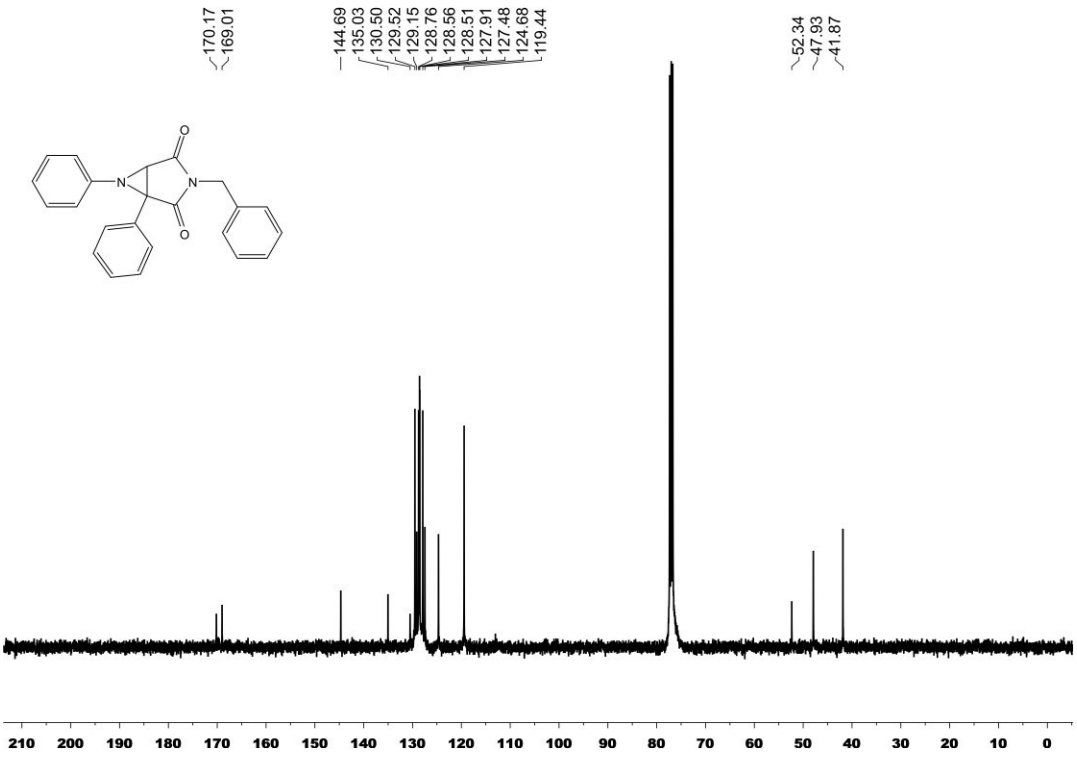
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6b**.



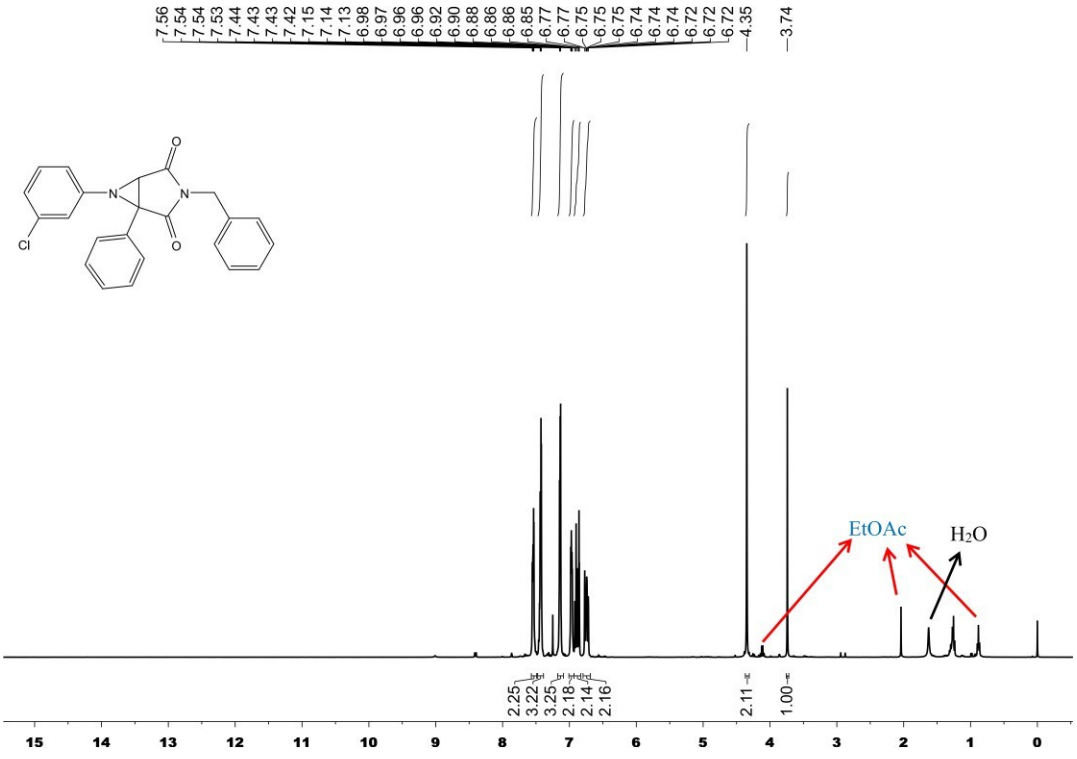


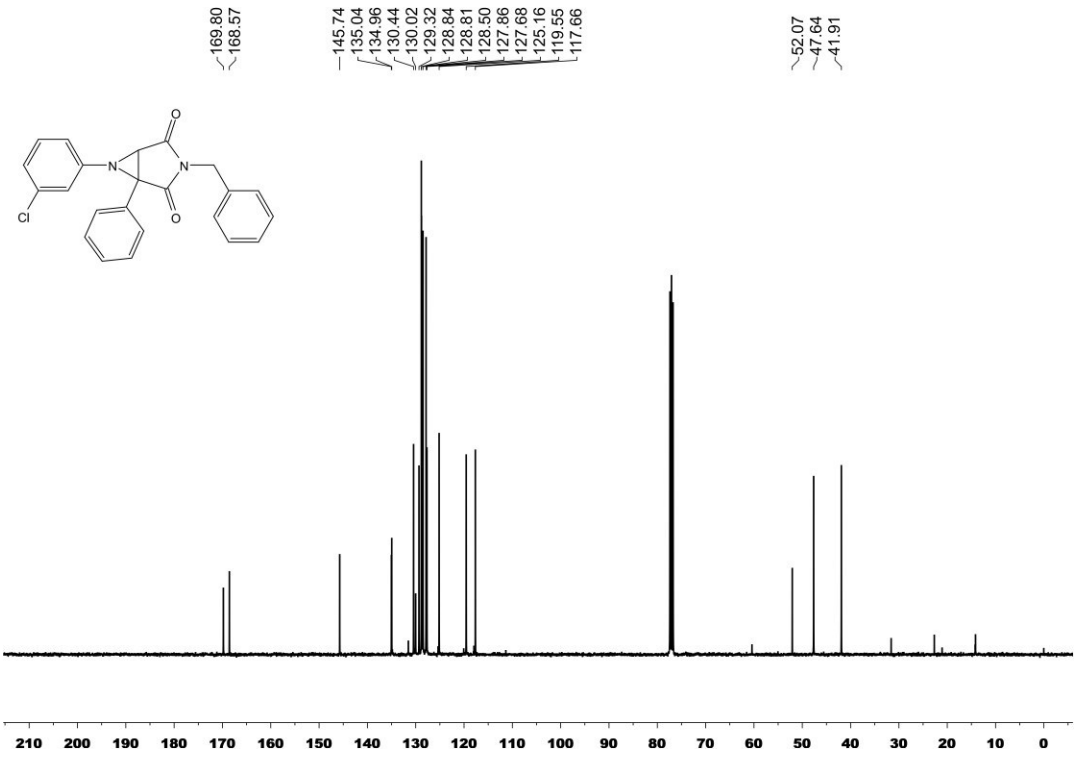
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6c**.



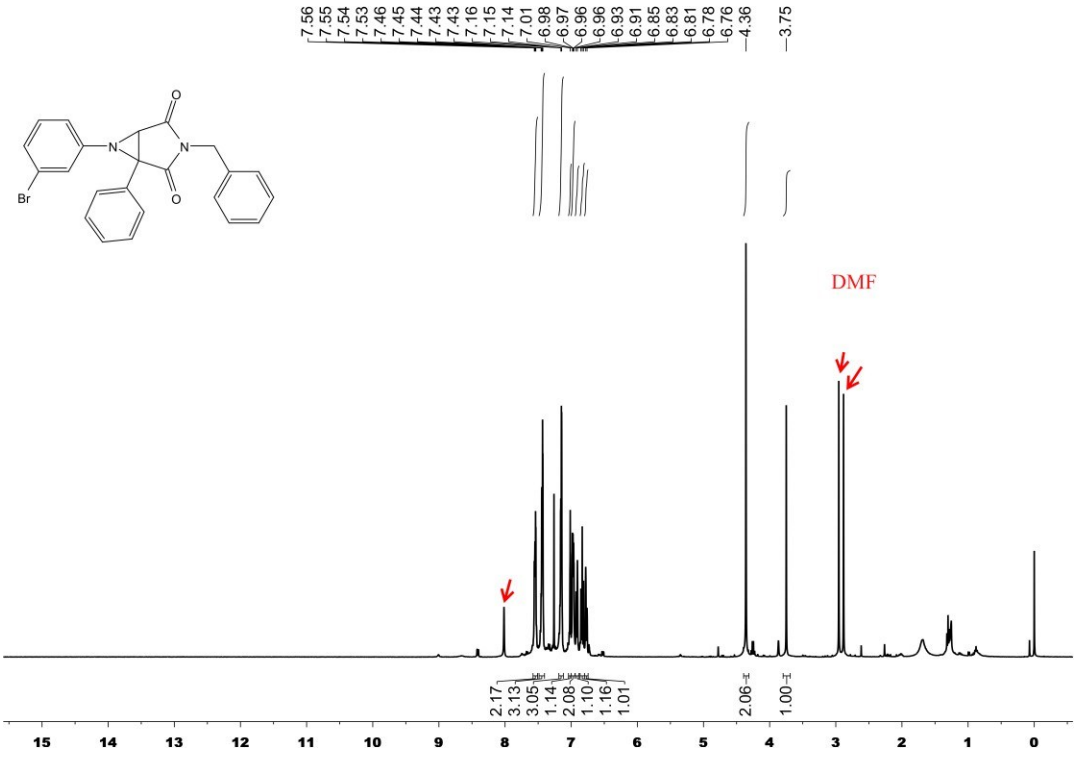


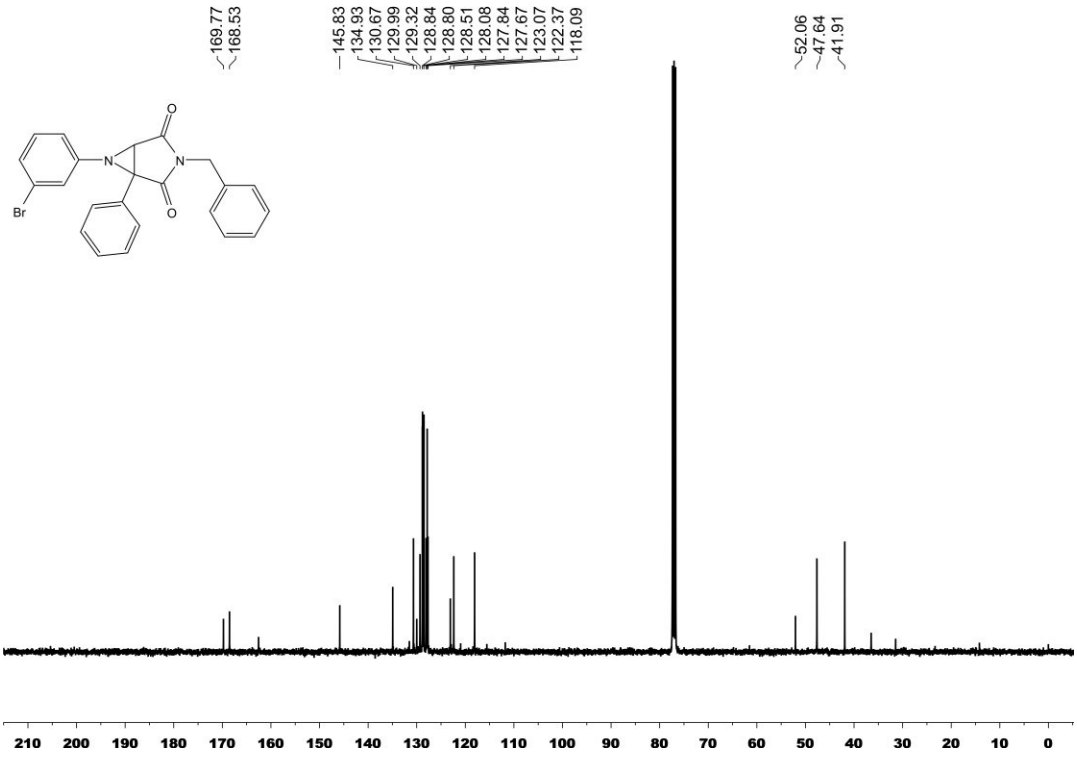
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6d**.



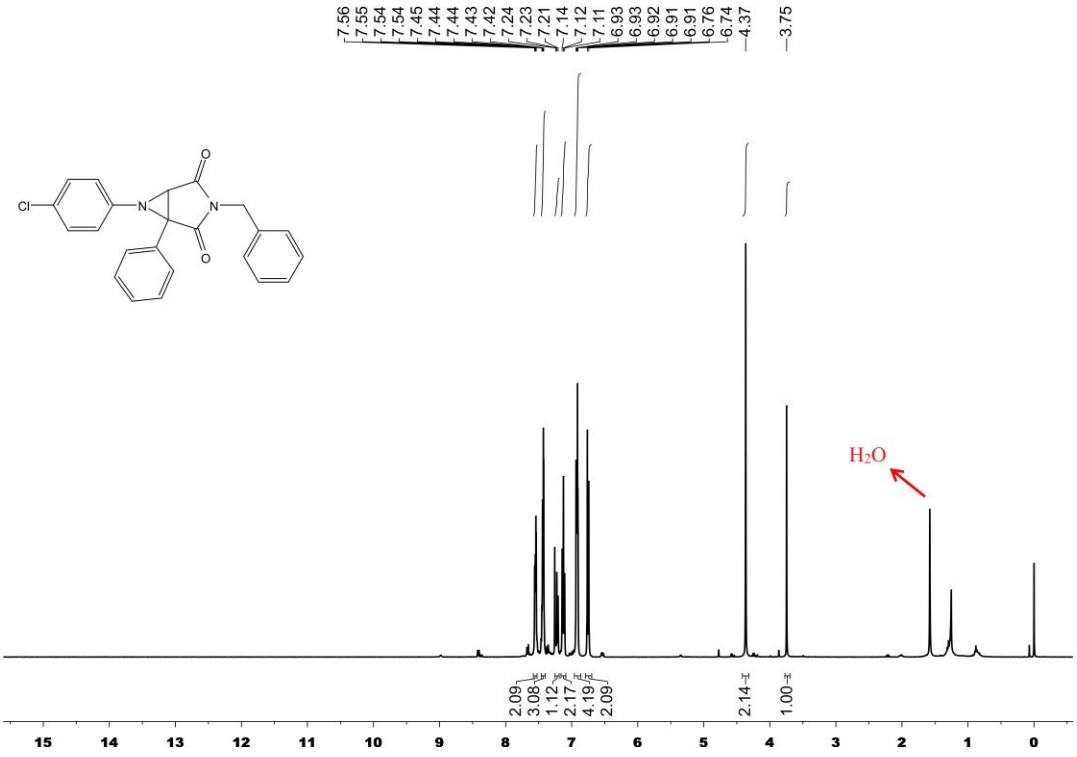


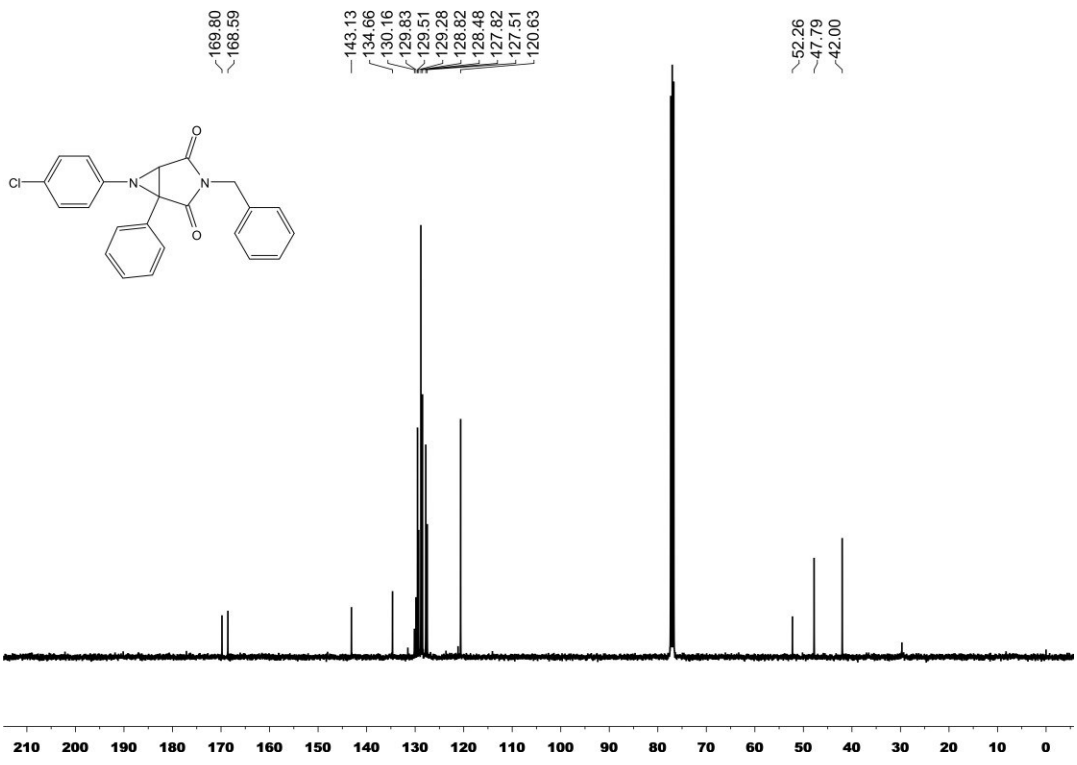
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6e**.



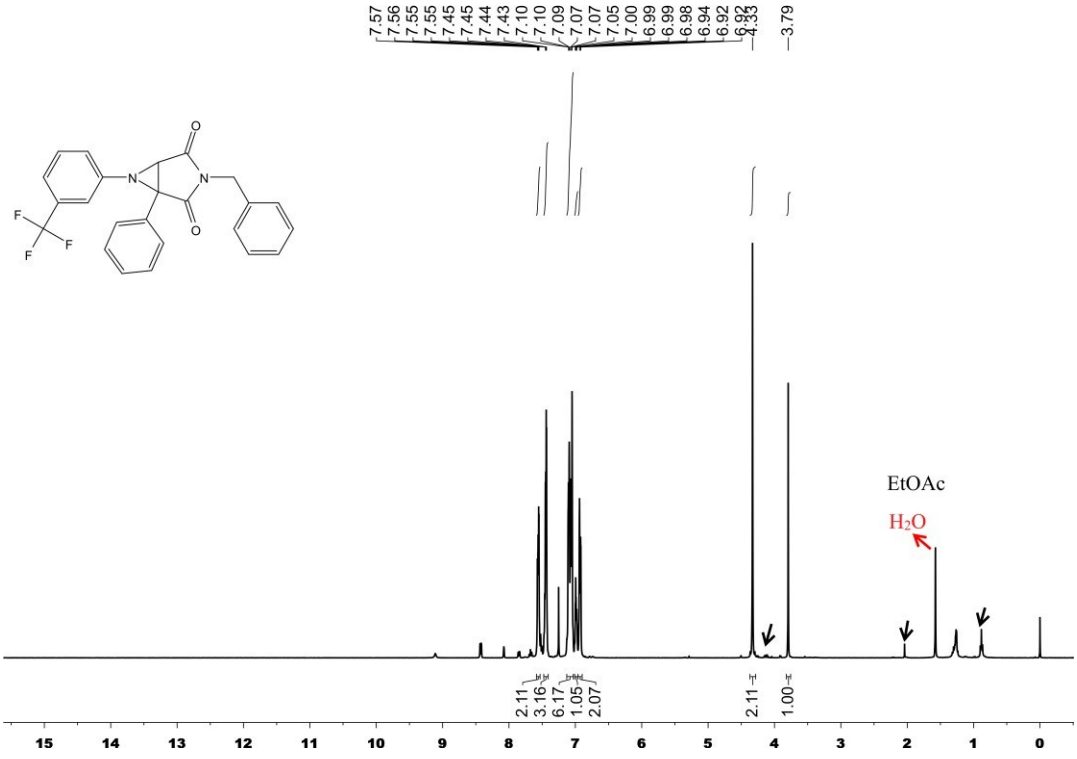


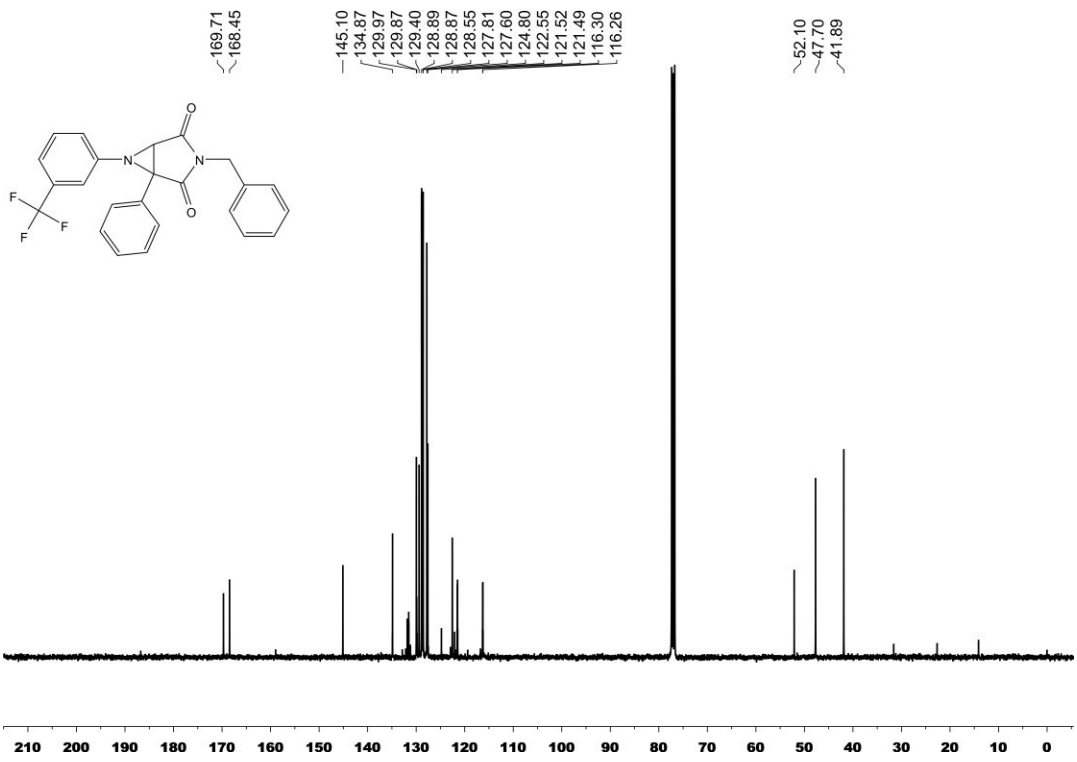
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6f**.



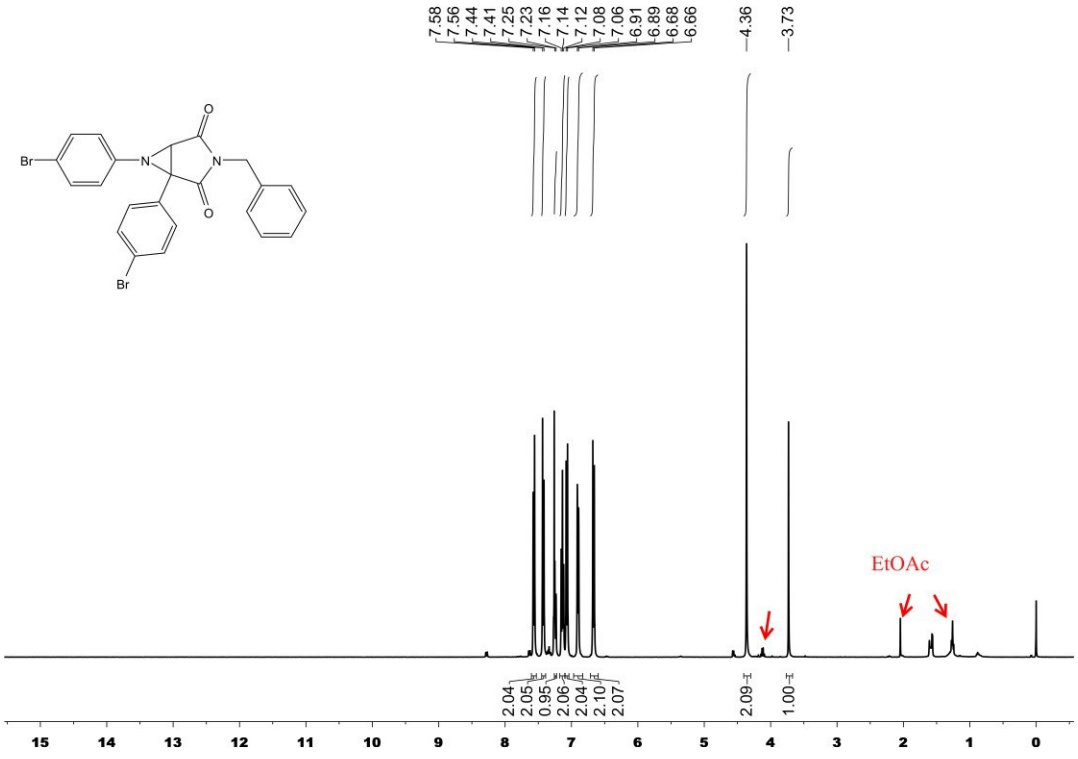


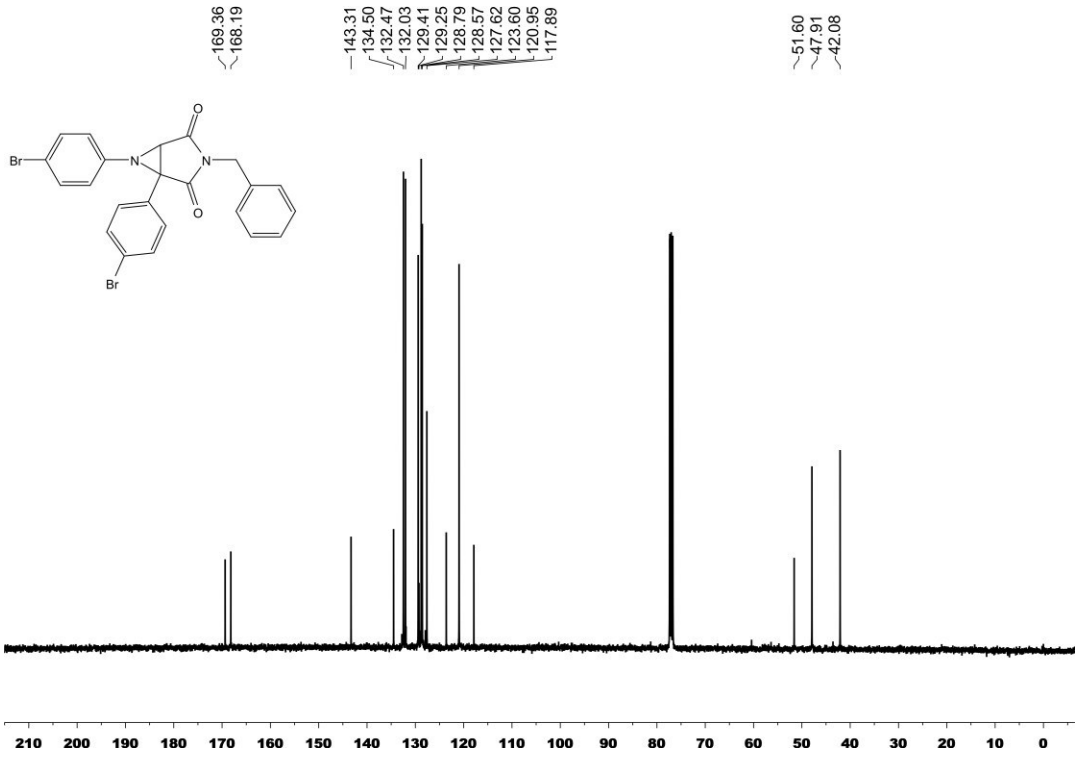
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6g**.



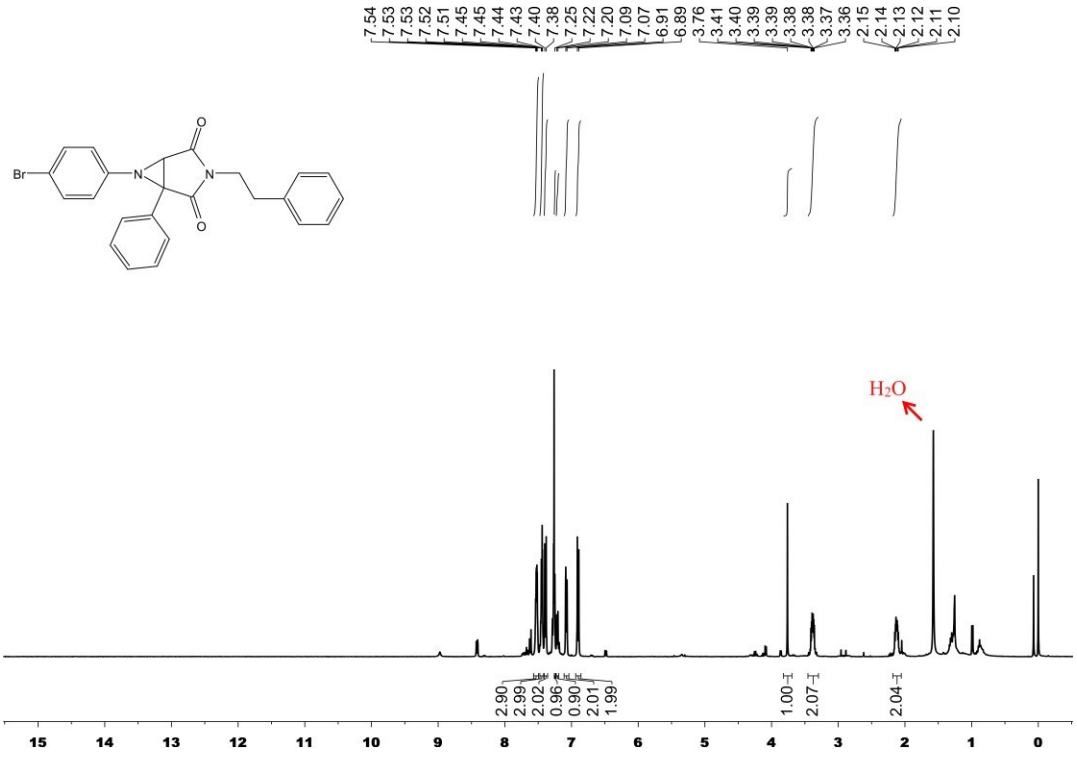


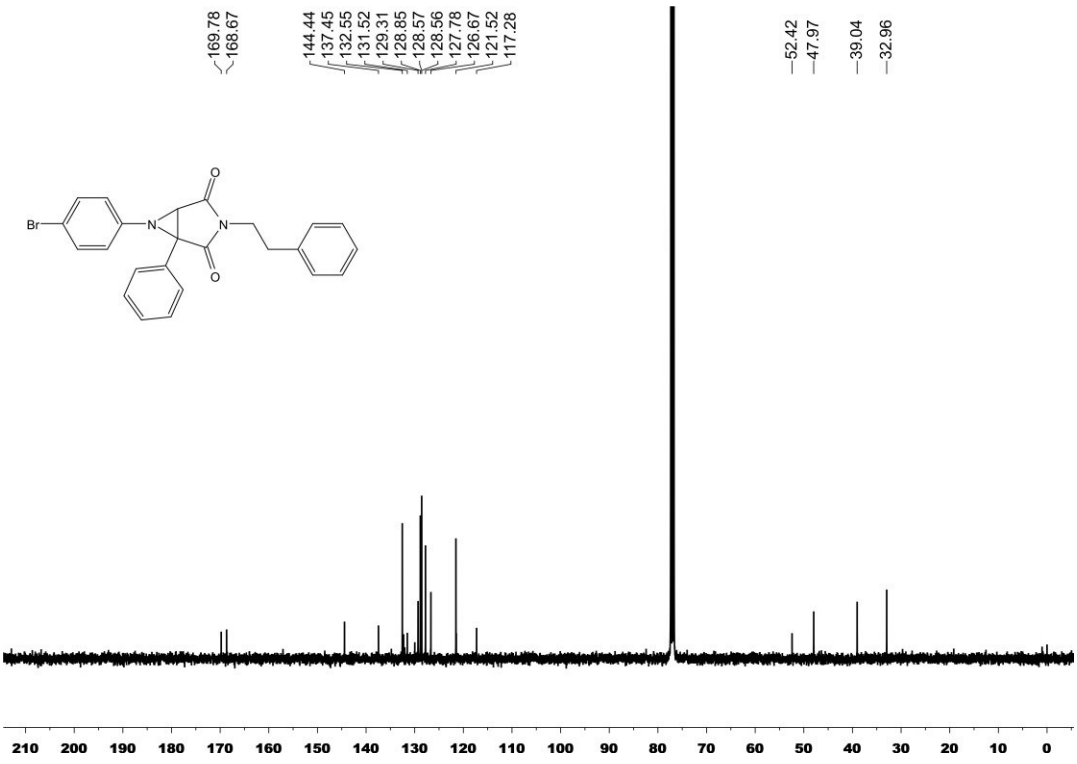
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6h**.



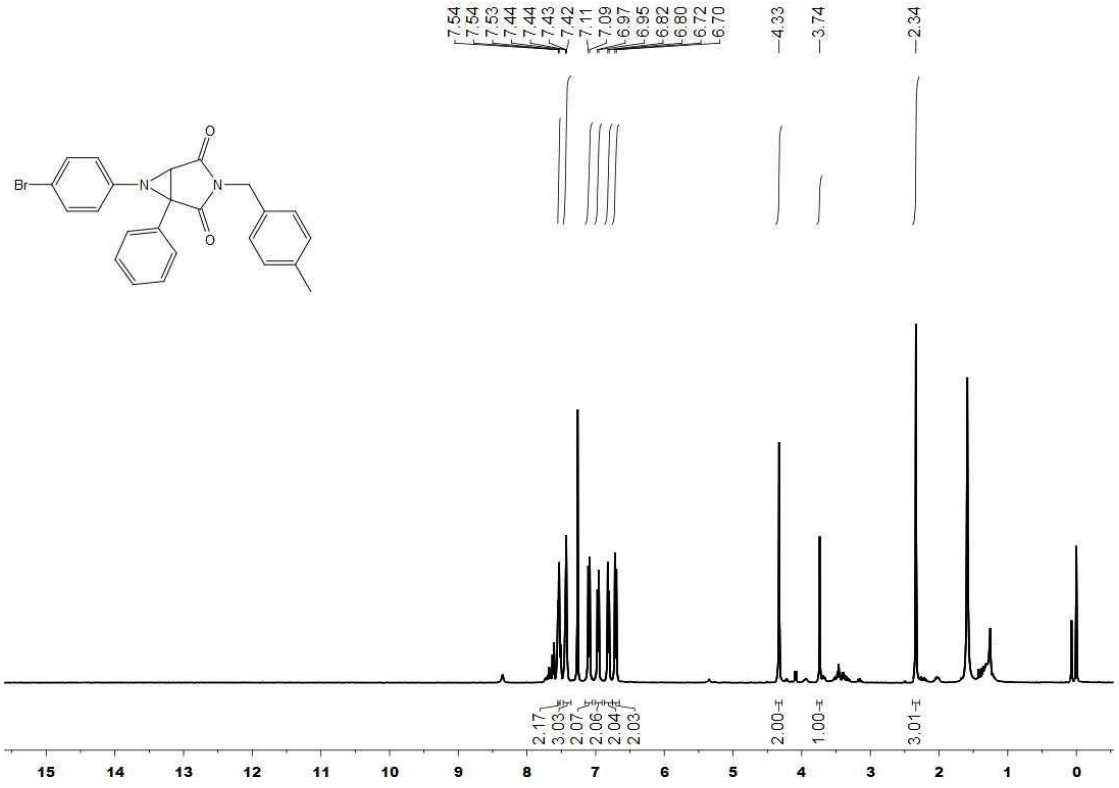


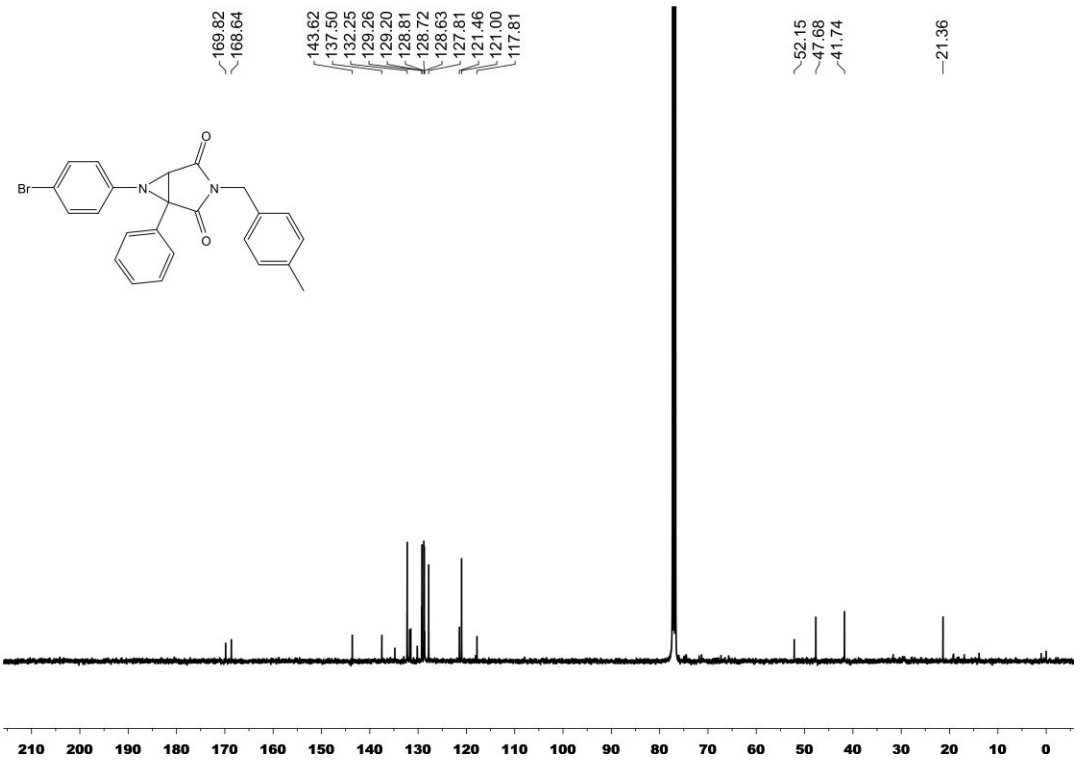
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6i**.



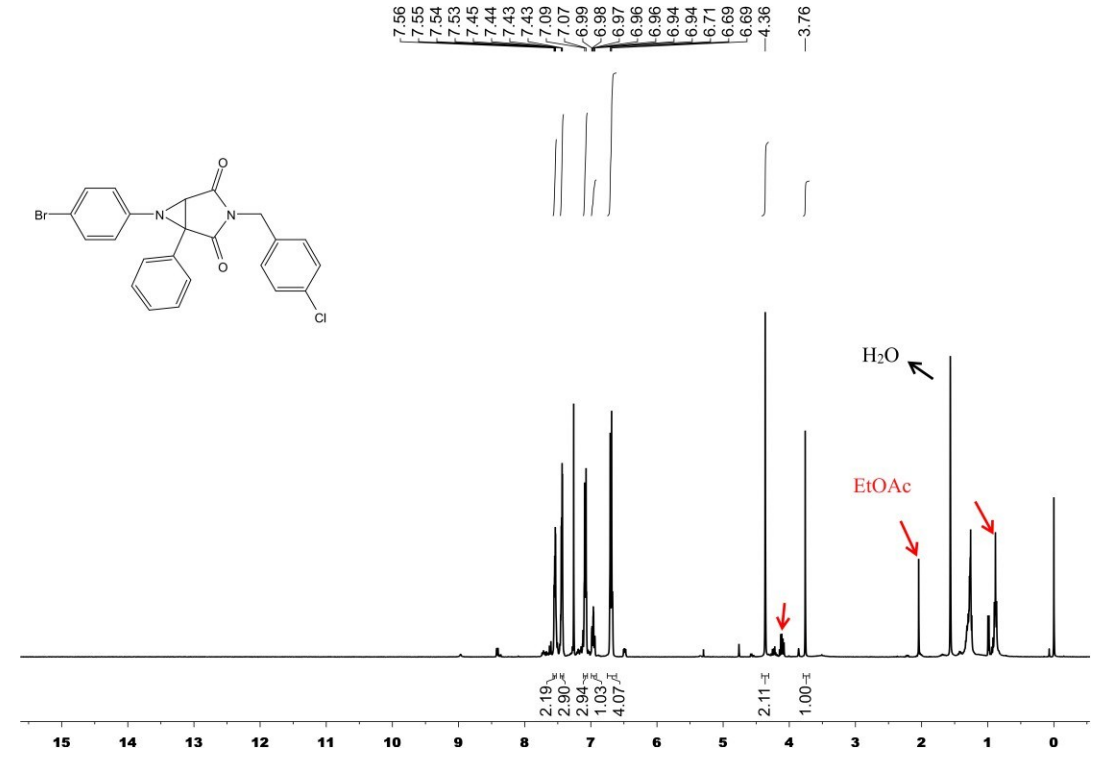


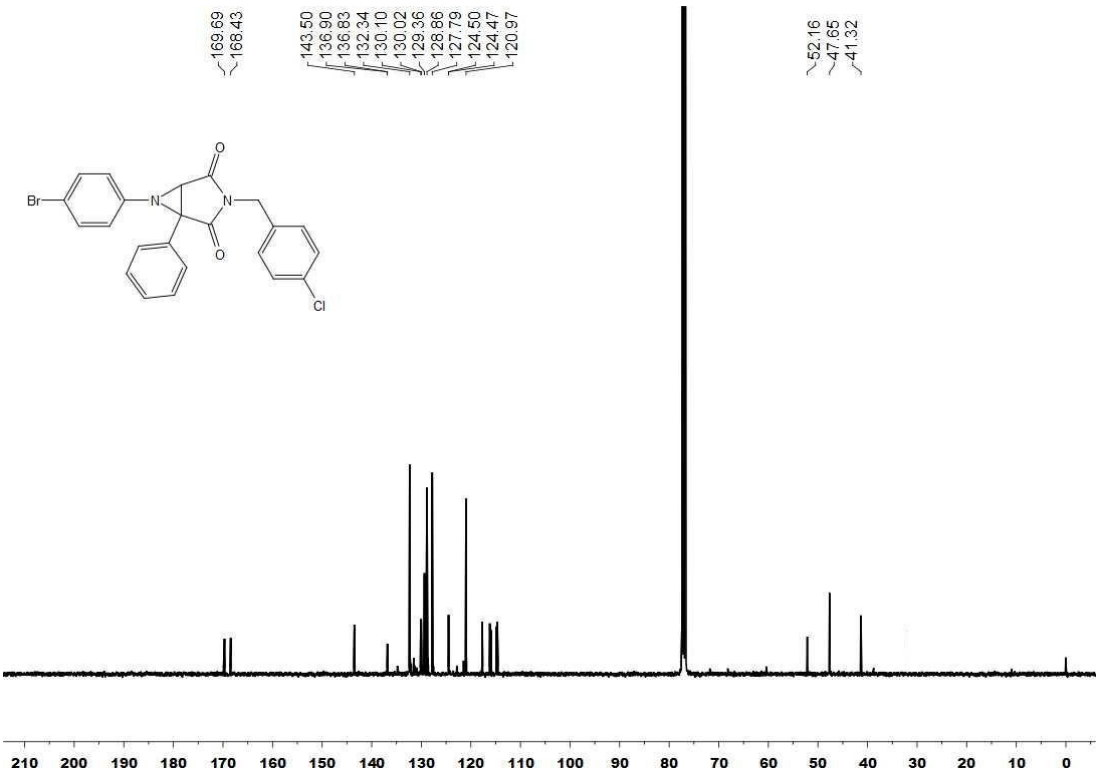
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6j**.



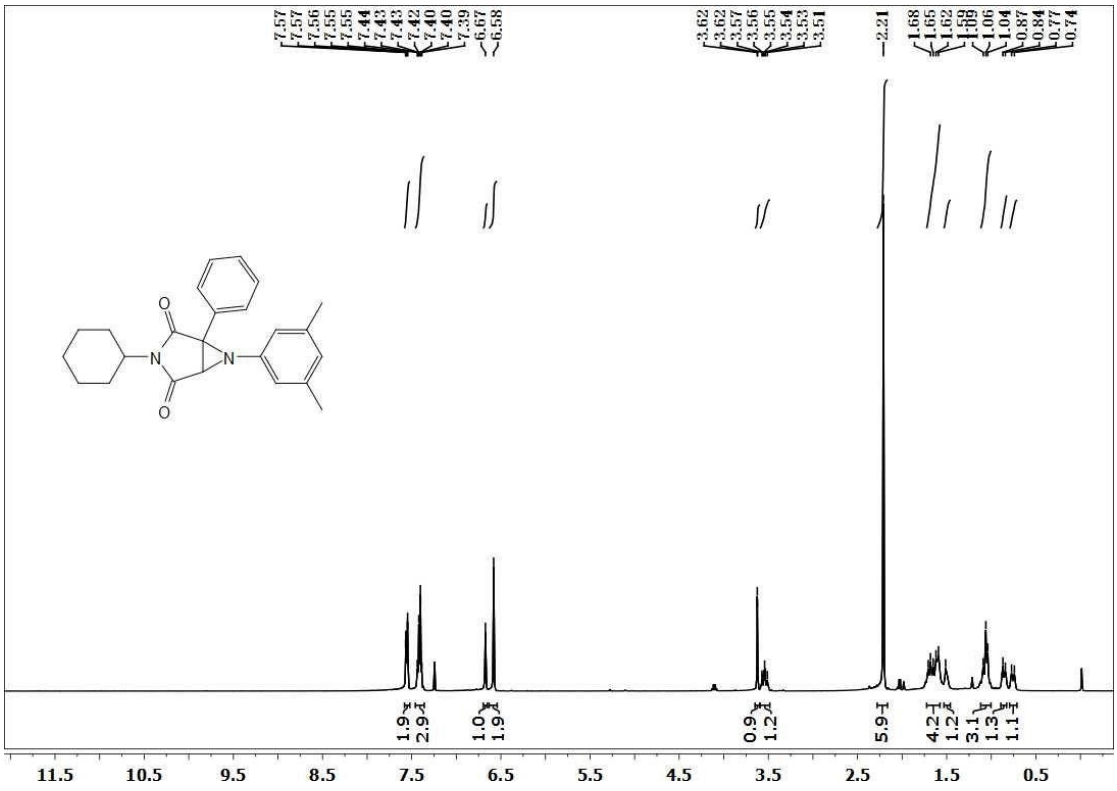


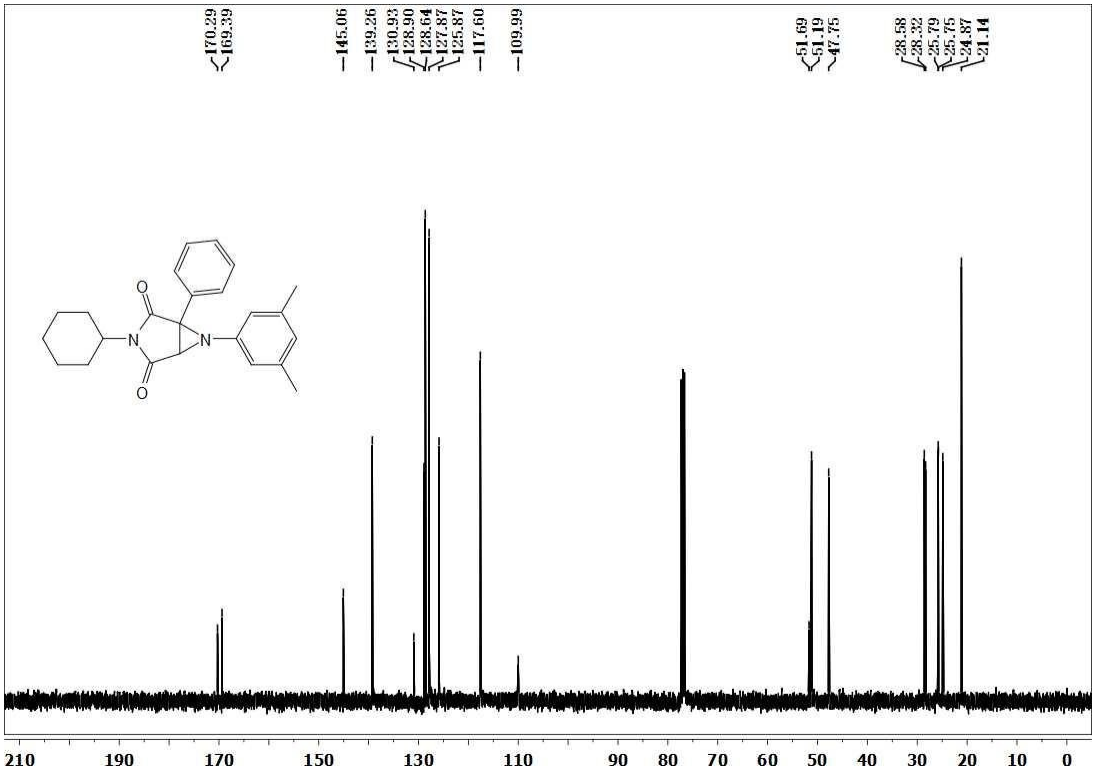
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6k**.



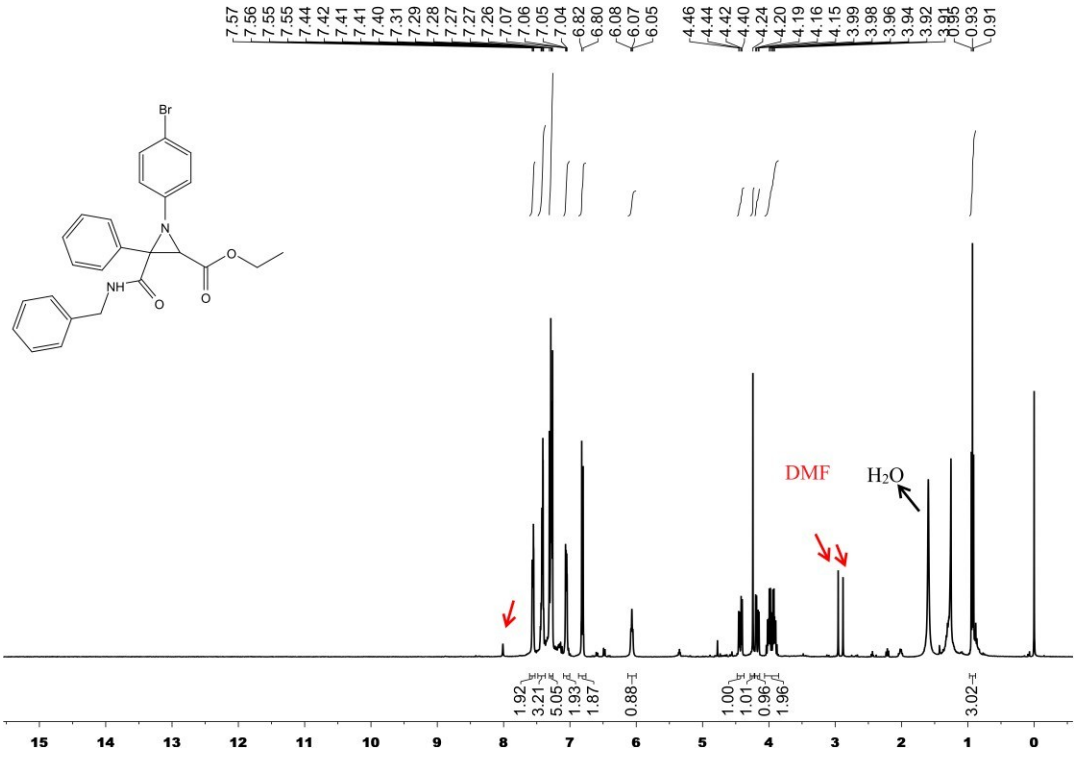


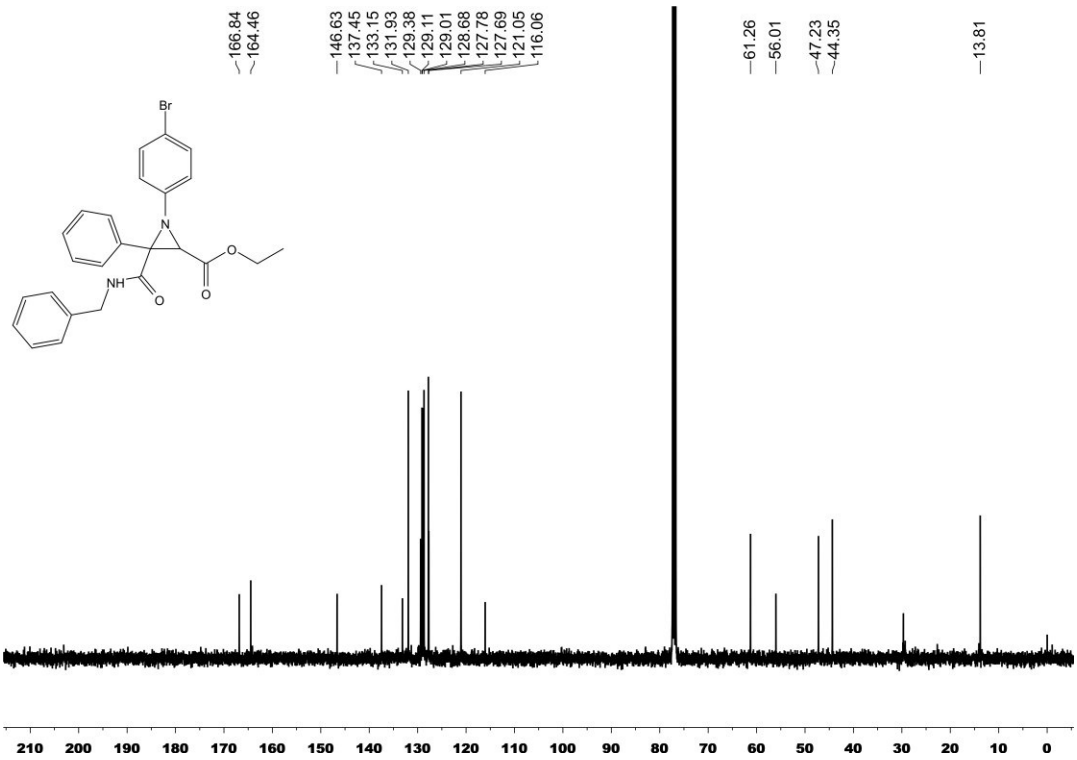
^{1}H NMR and ^{13}C NMR spectrum of *cis*-**6l**.



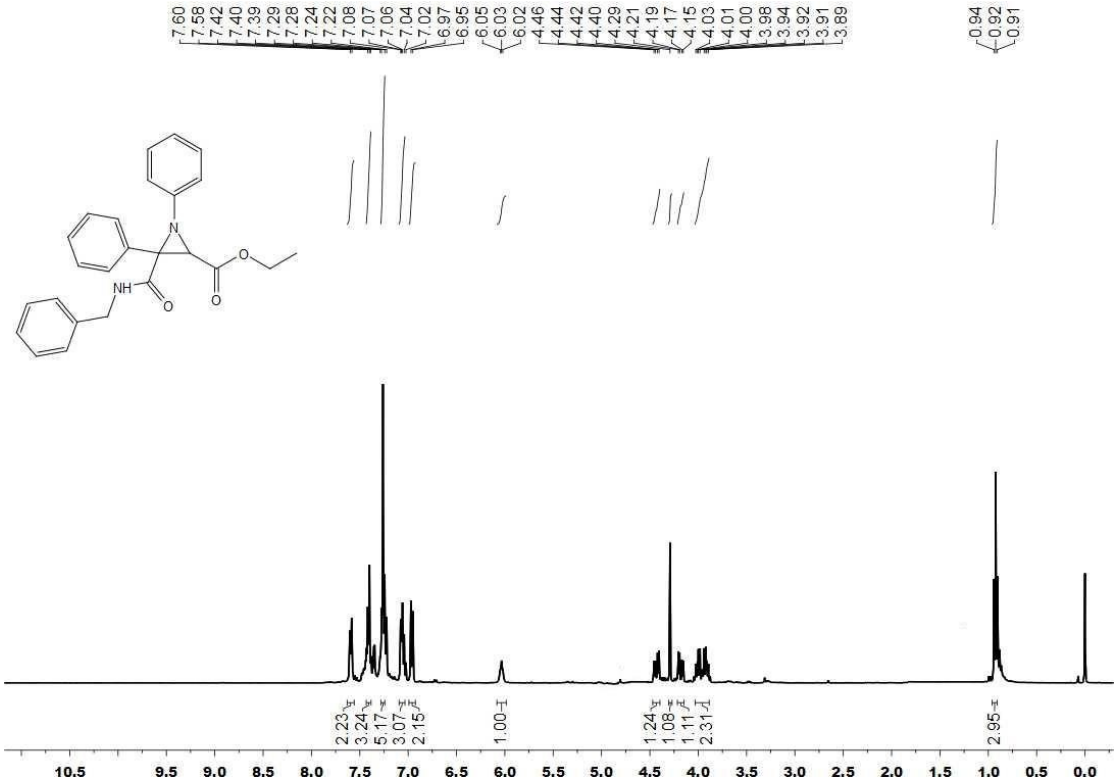


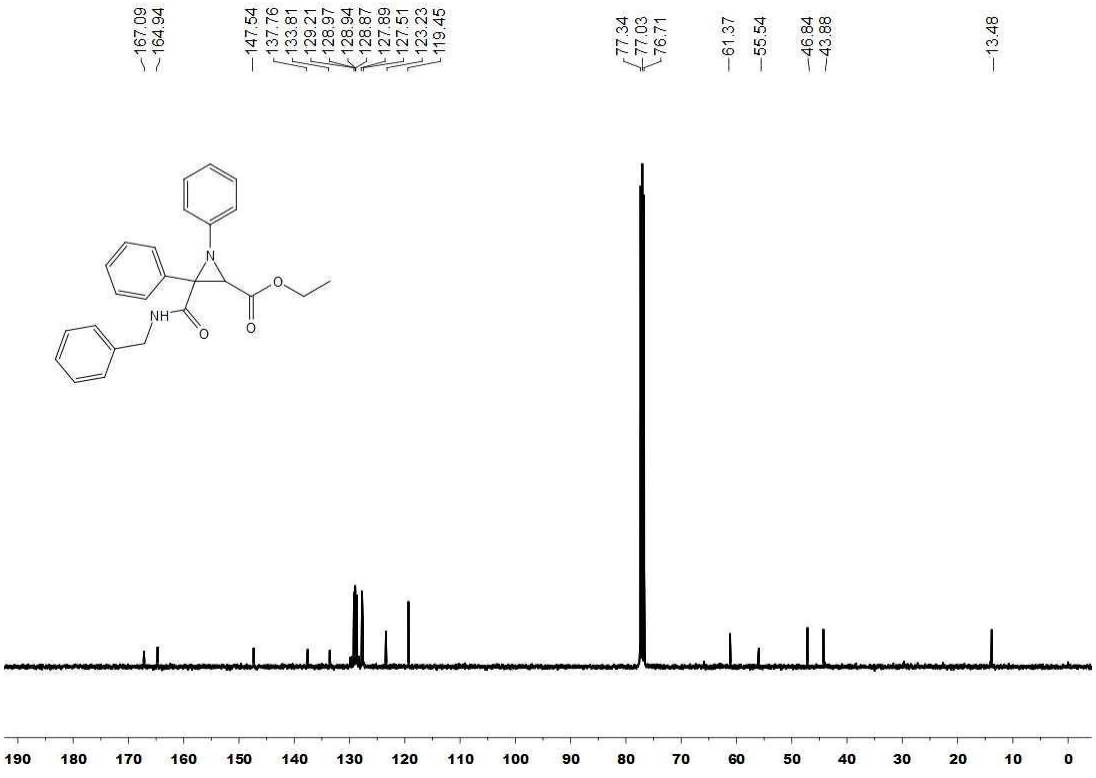
^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7a**.



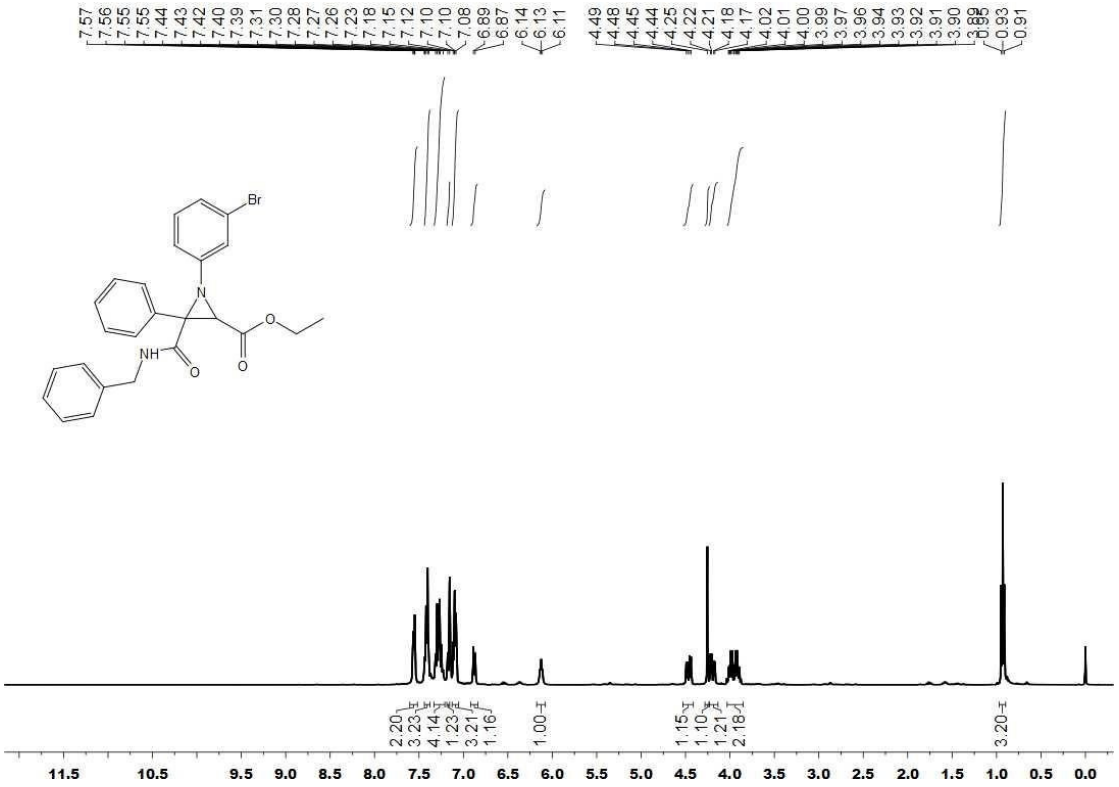


^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7c**.

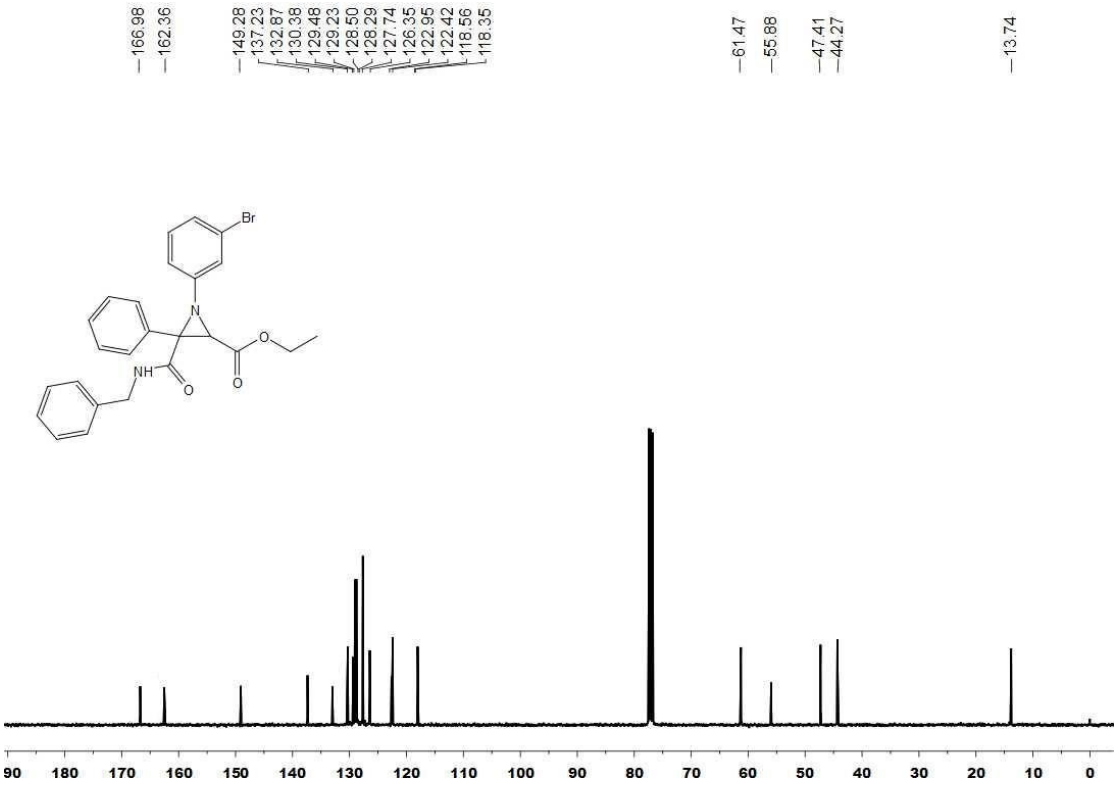




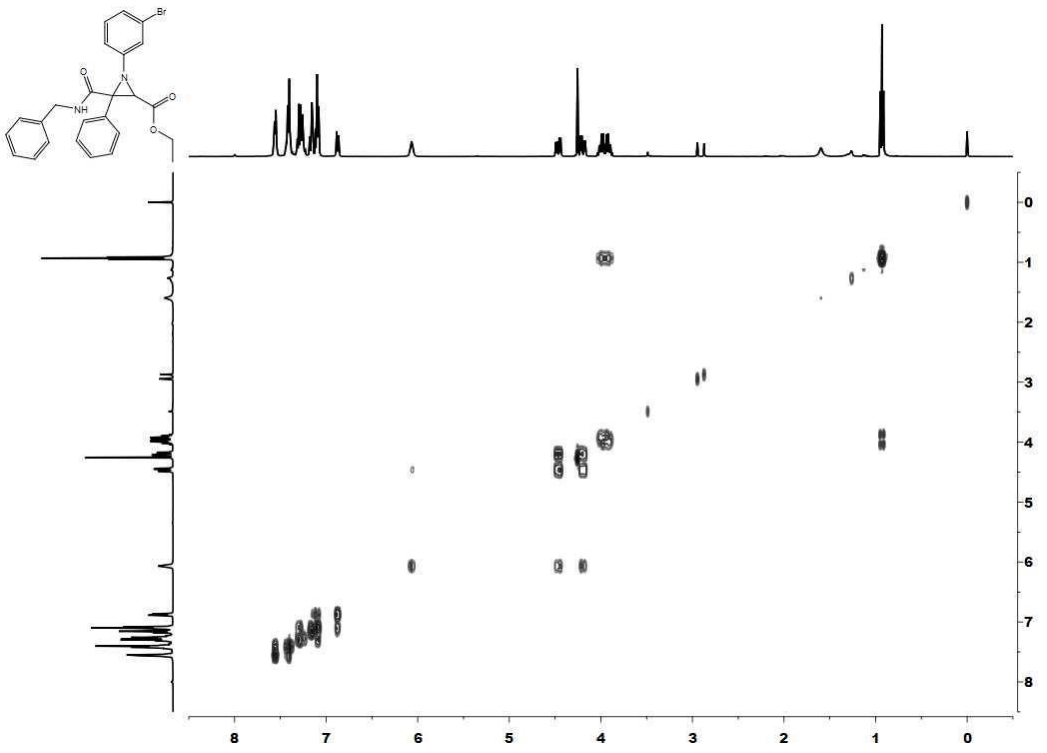
^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7e**.



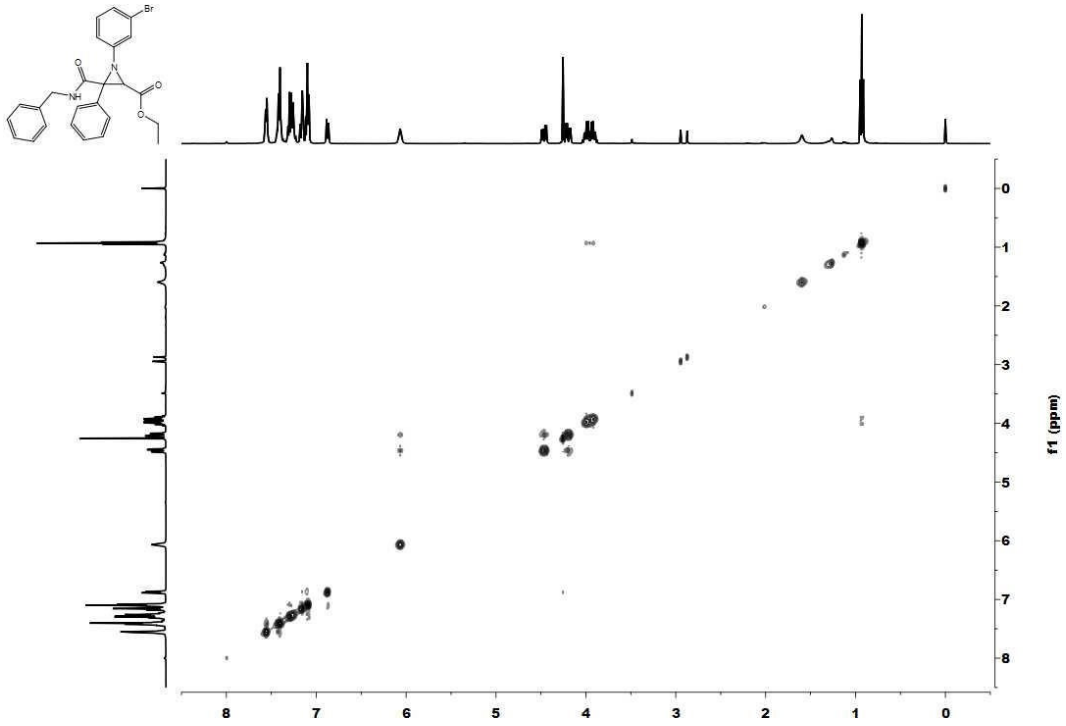
^{1}H NMR spectrum of *trans*-**7e**



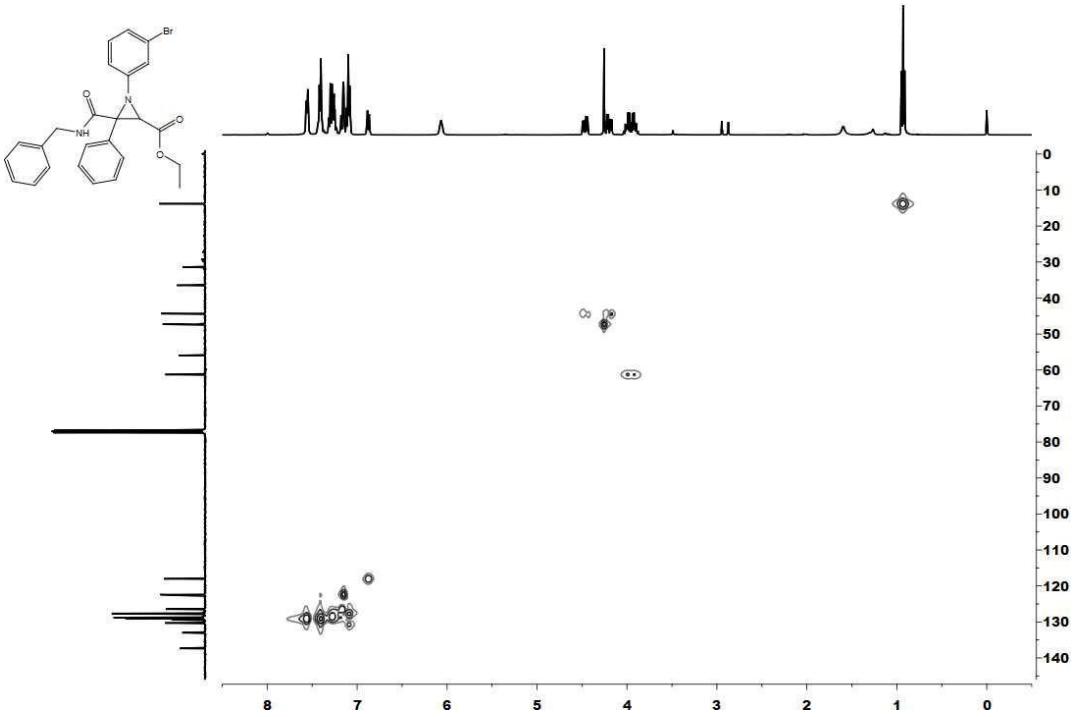
^{13}C NMR spectrum of *trans*-**7e**



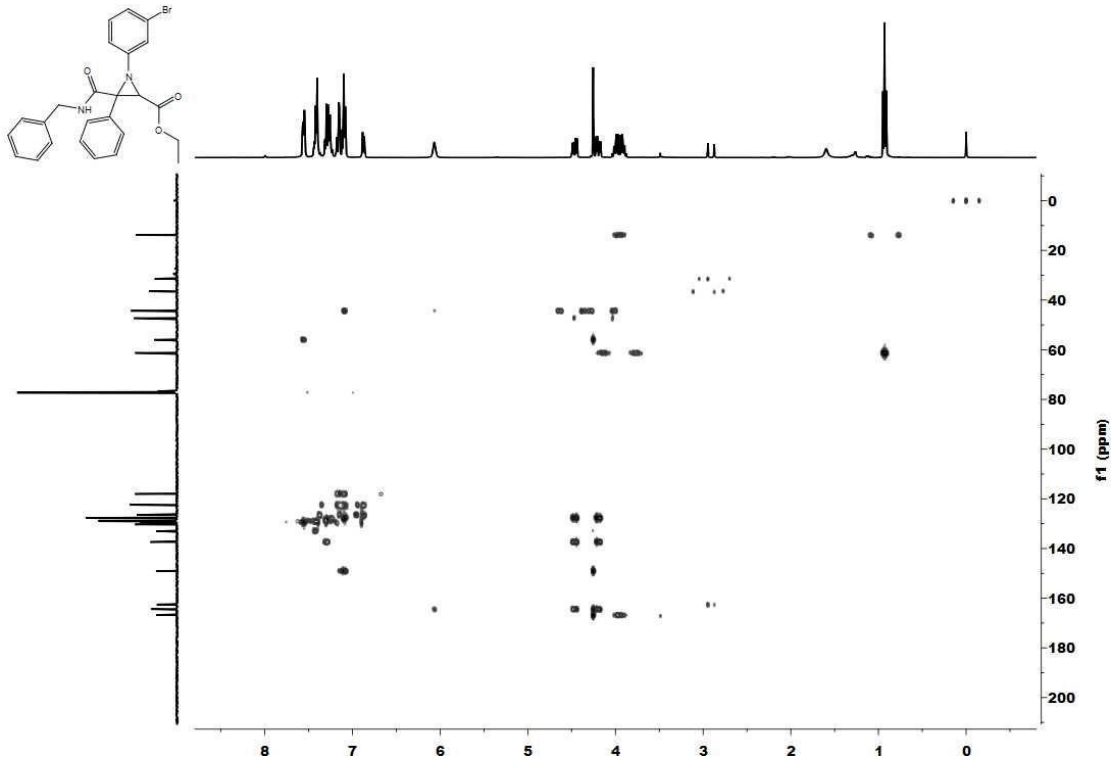
^{1}H-^{1}H COSY spectrum of *trans*-7**e**



^{1}H-^{1}H NEOSY spectrum of *trans*-**7e**

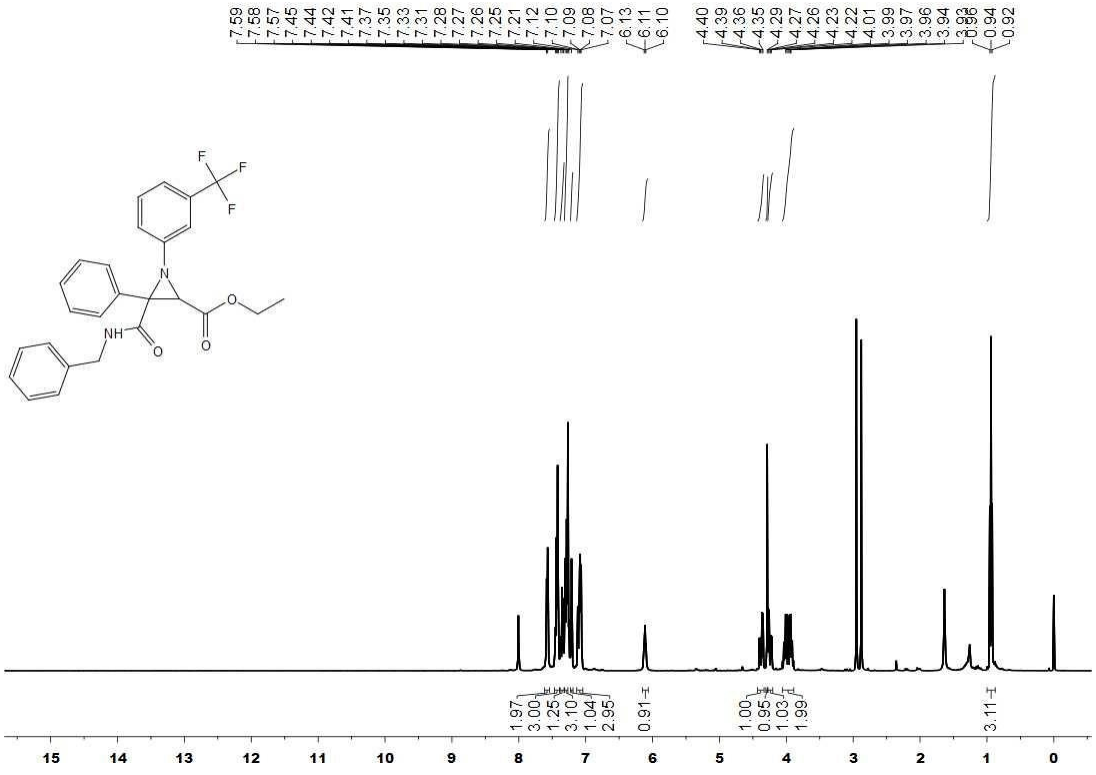


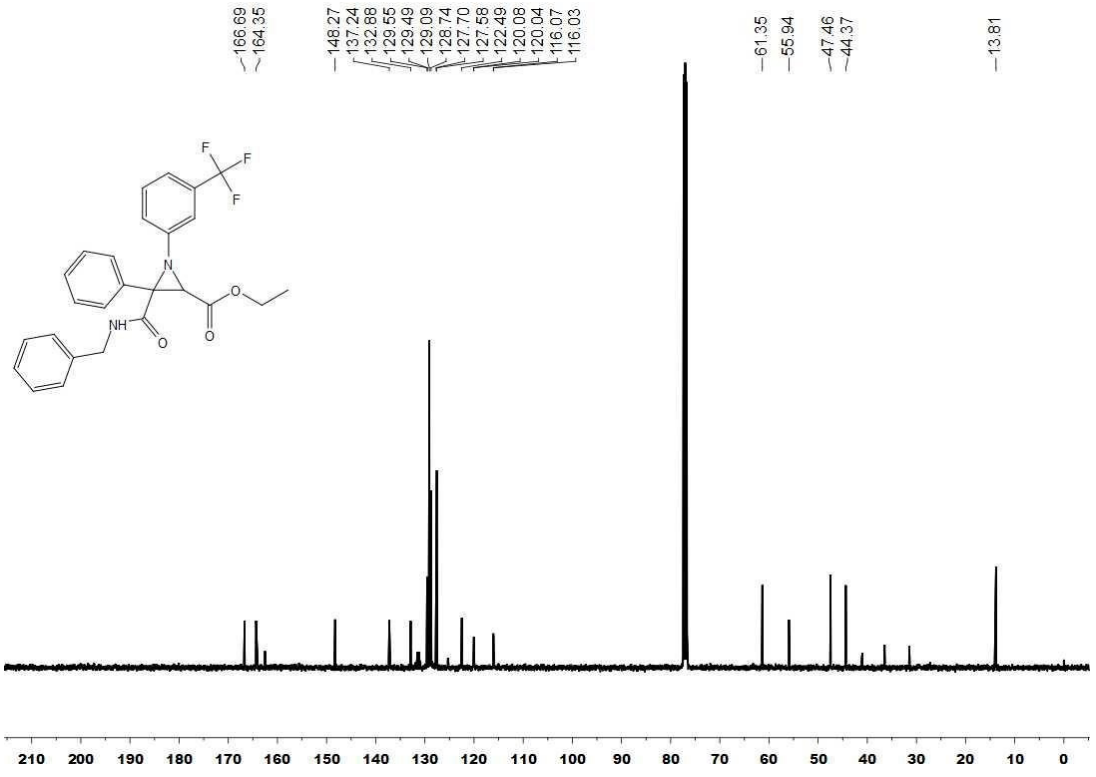
^{13}C-^{1}H HMQC spectrum of *trans*-7**e**



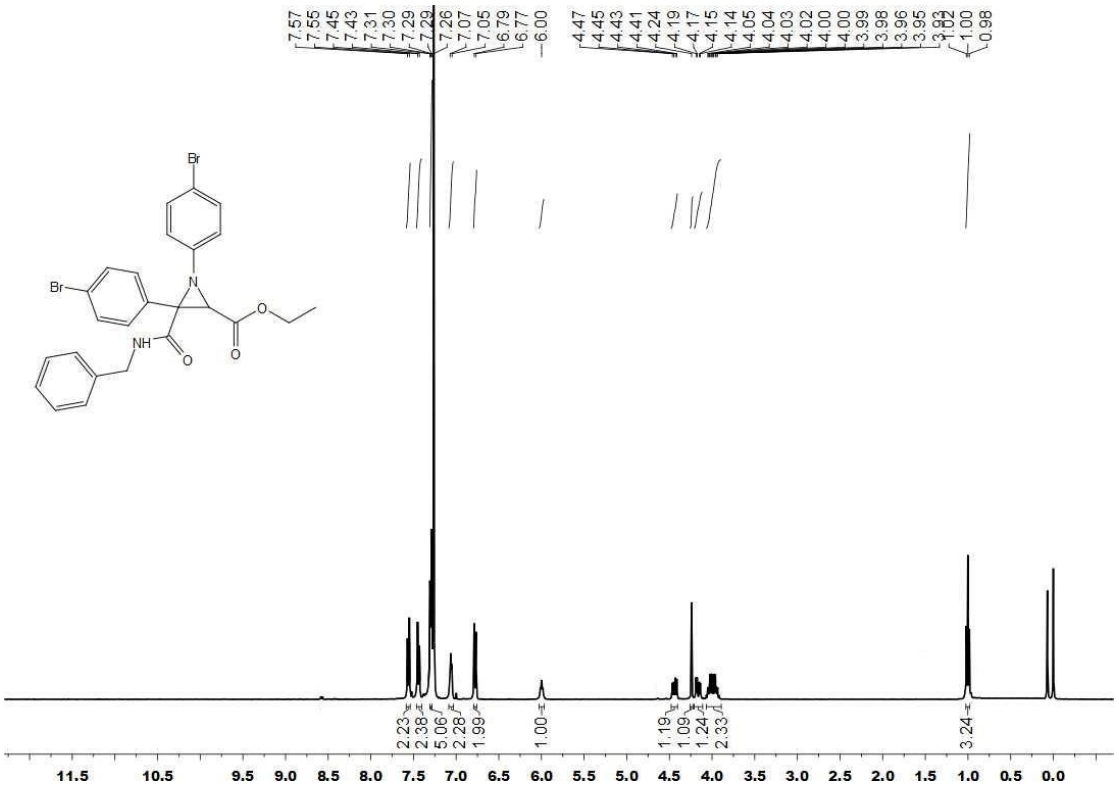
^{13}C-^{1}H HMBC spectrum of *trans*-**7e**

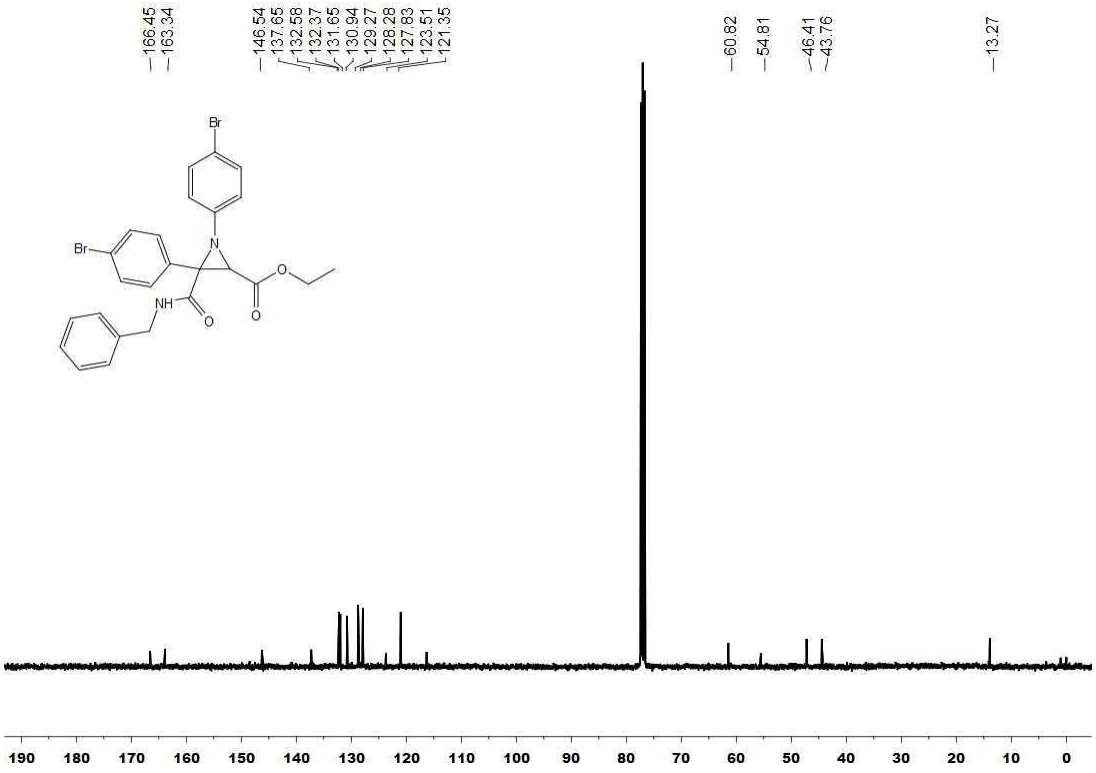
^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7g**.



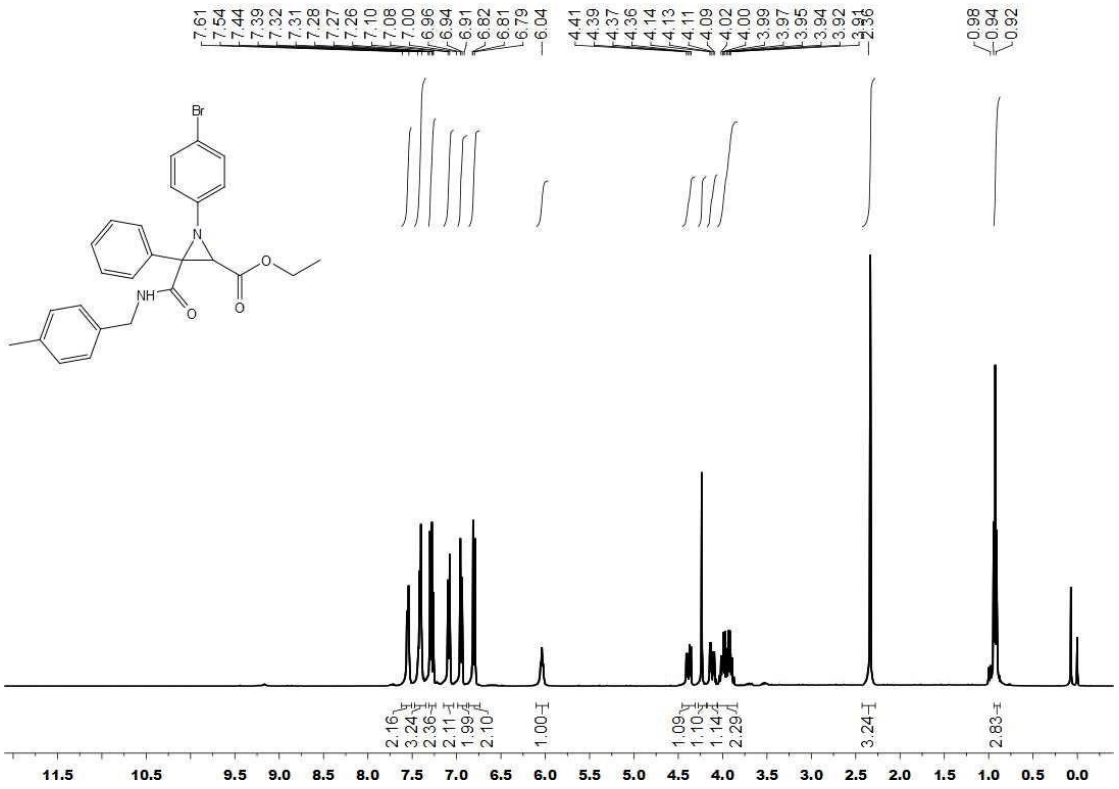


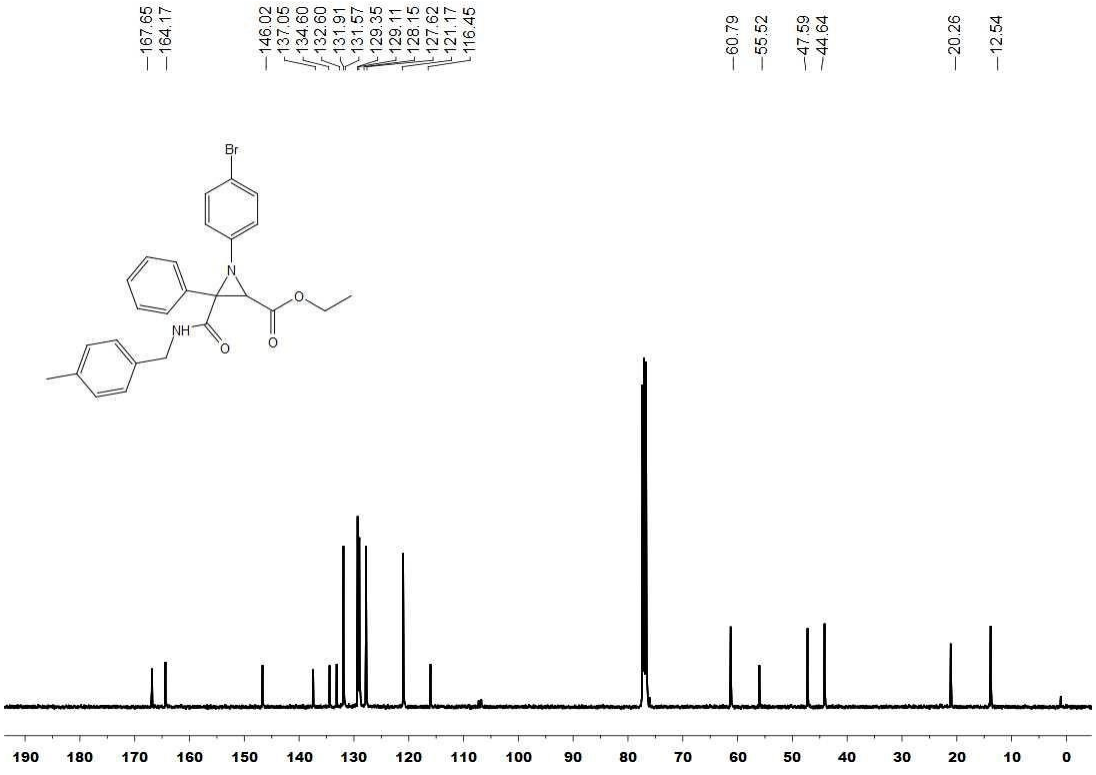
^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7h**.



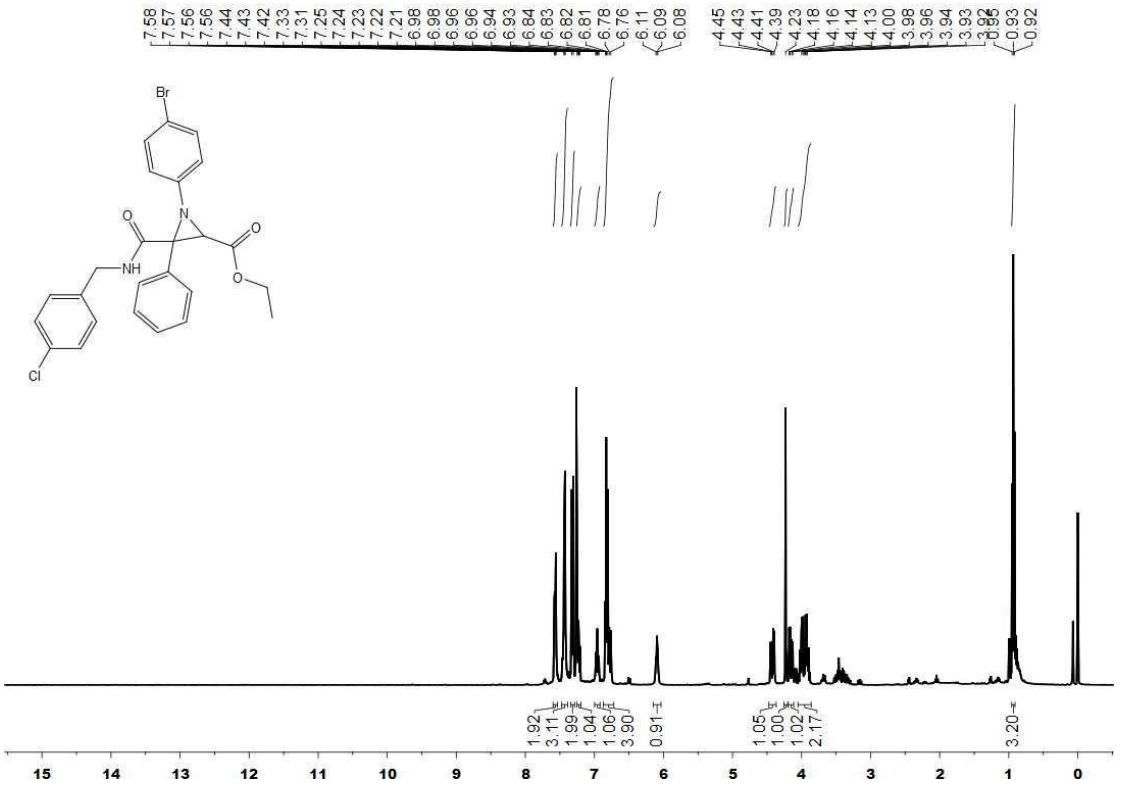


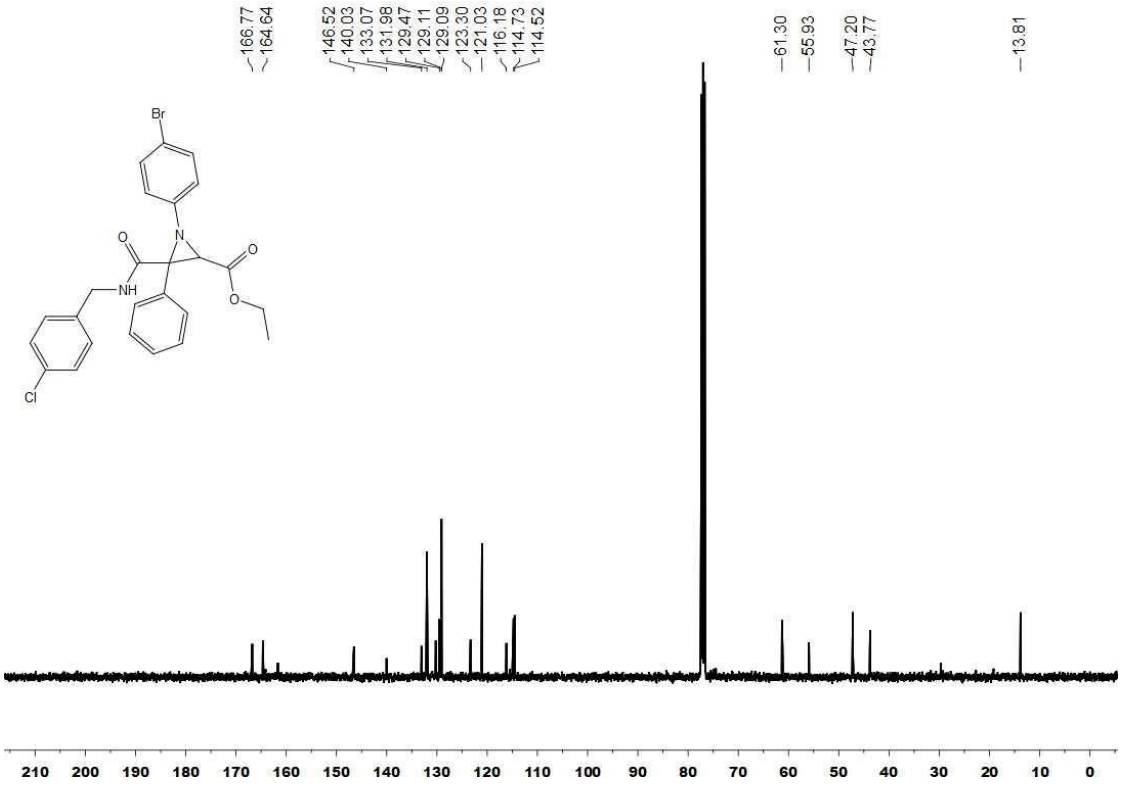
^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7j**.



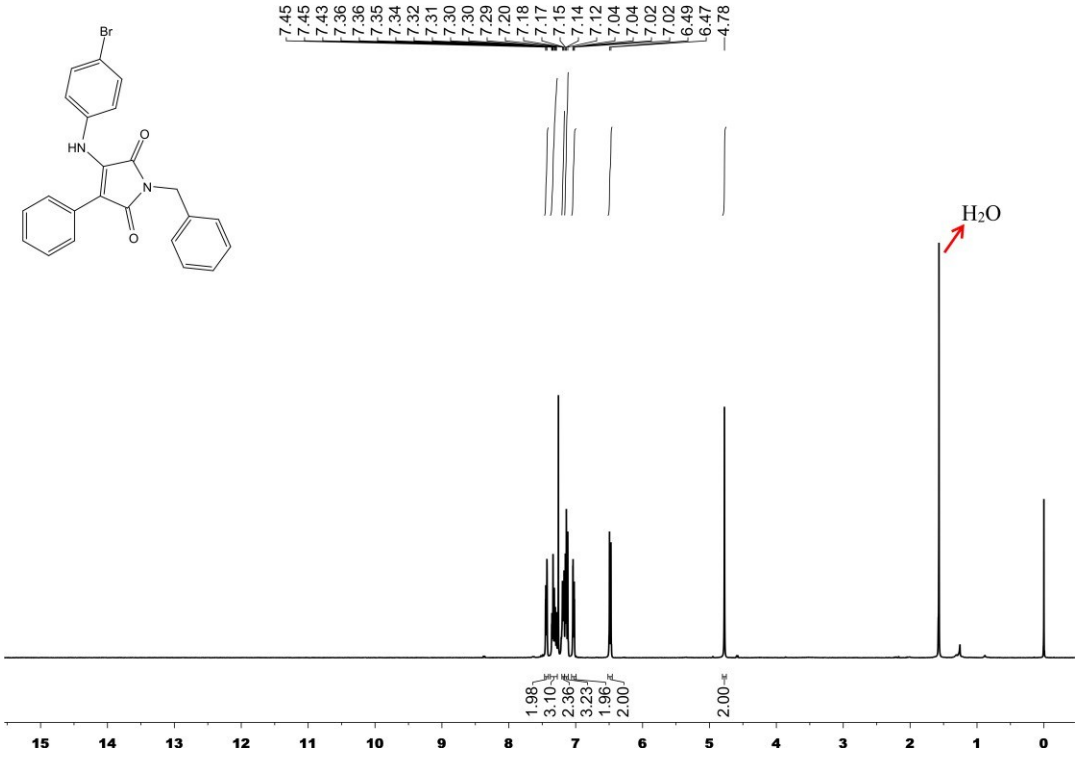


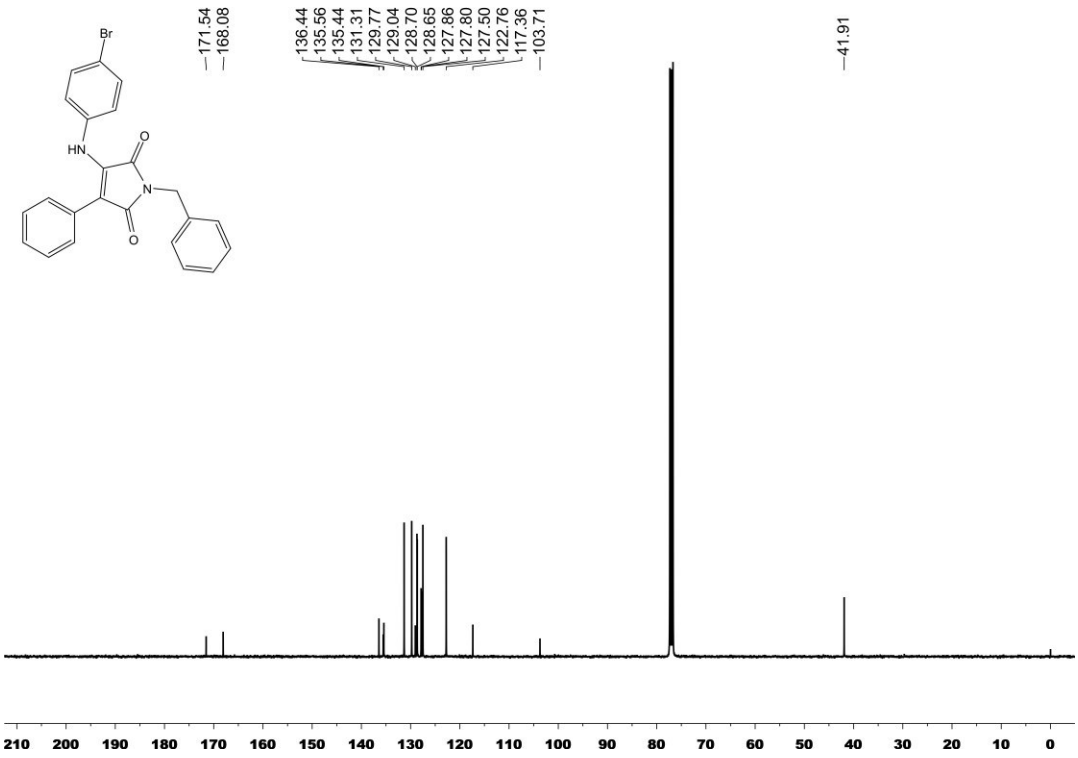
^{1}H NMR and ^{13}C NMR spectrum of *trans*-**7k**.



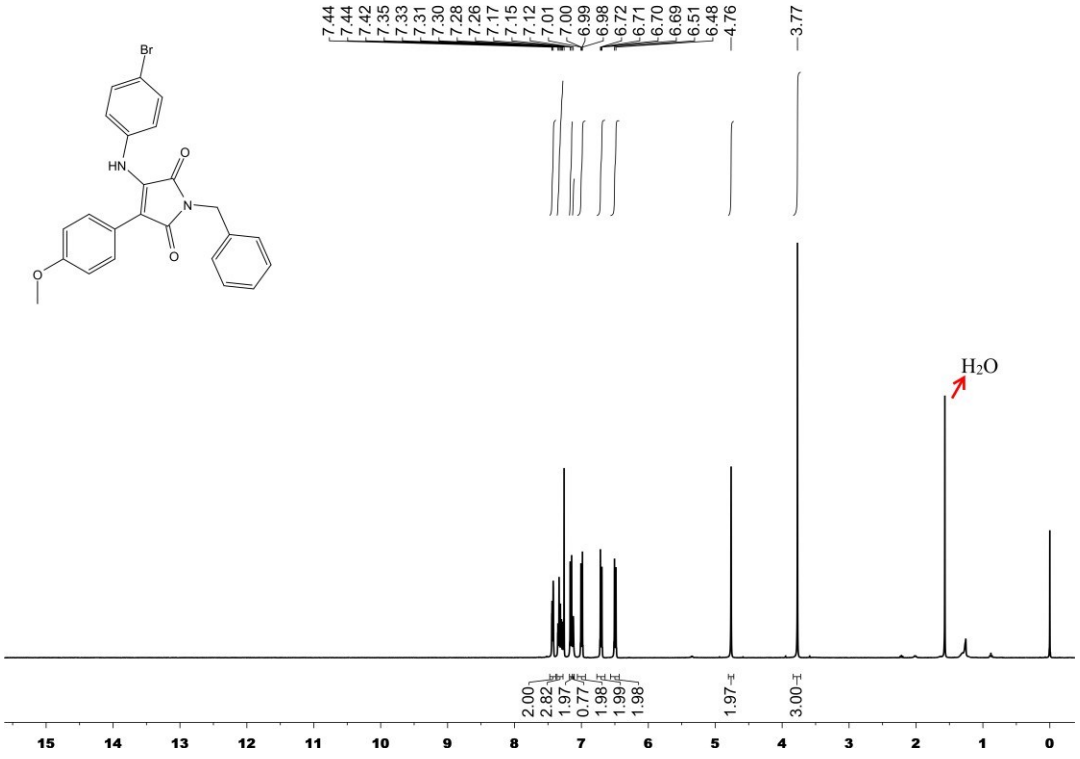


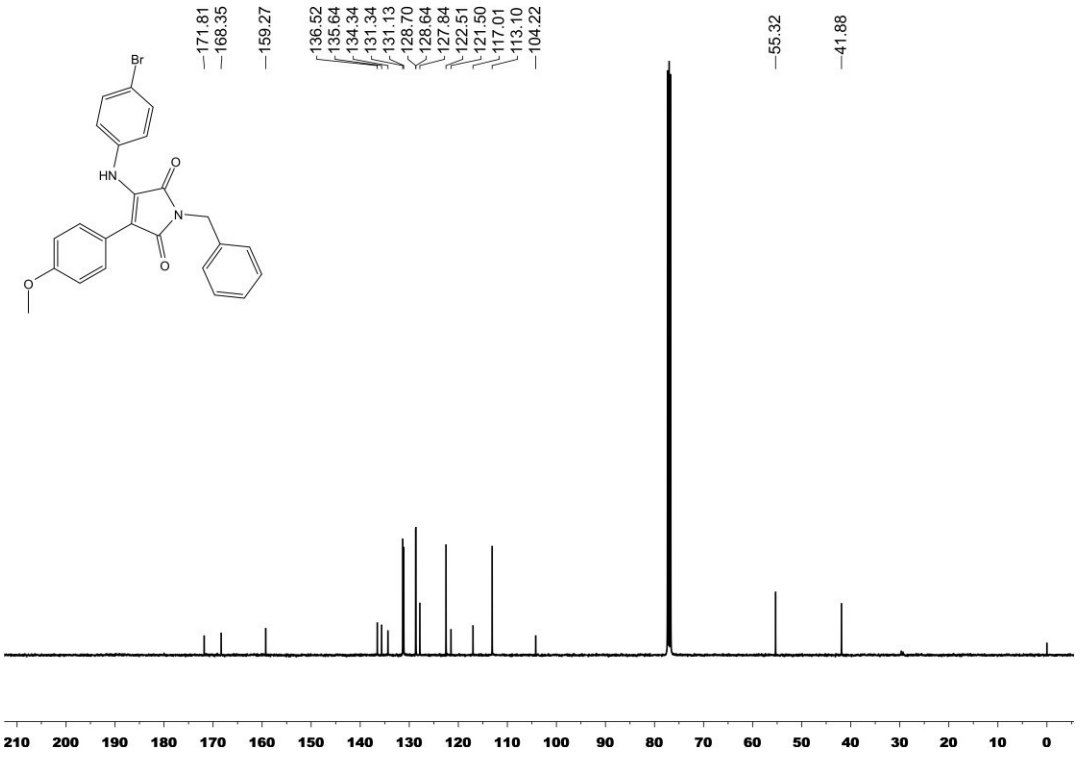
^{1}H NMR and ^{13}C NMR spectrum of **8a**.



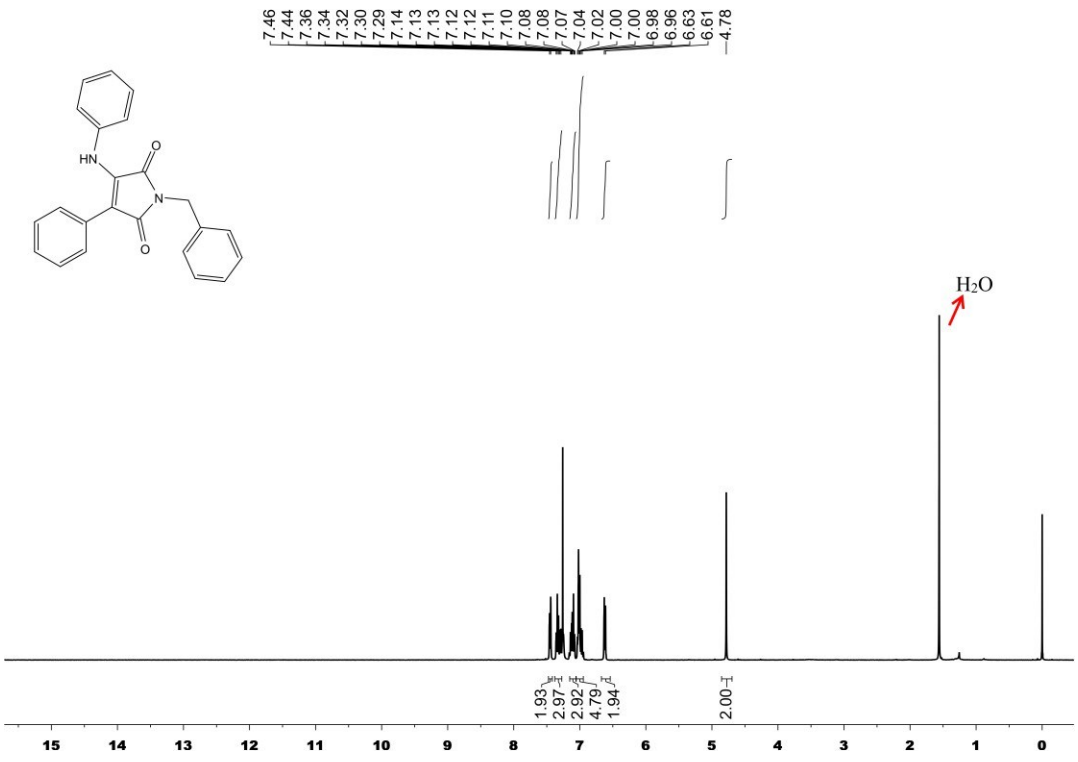


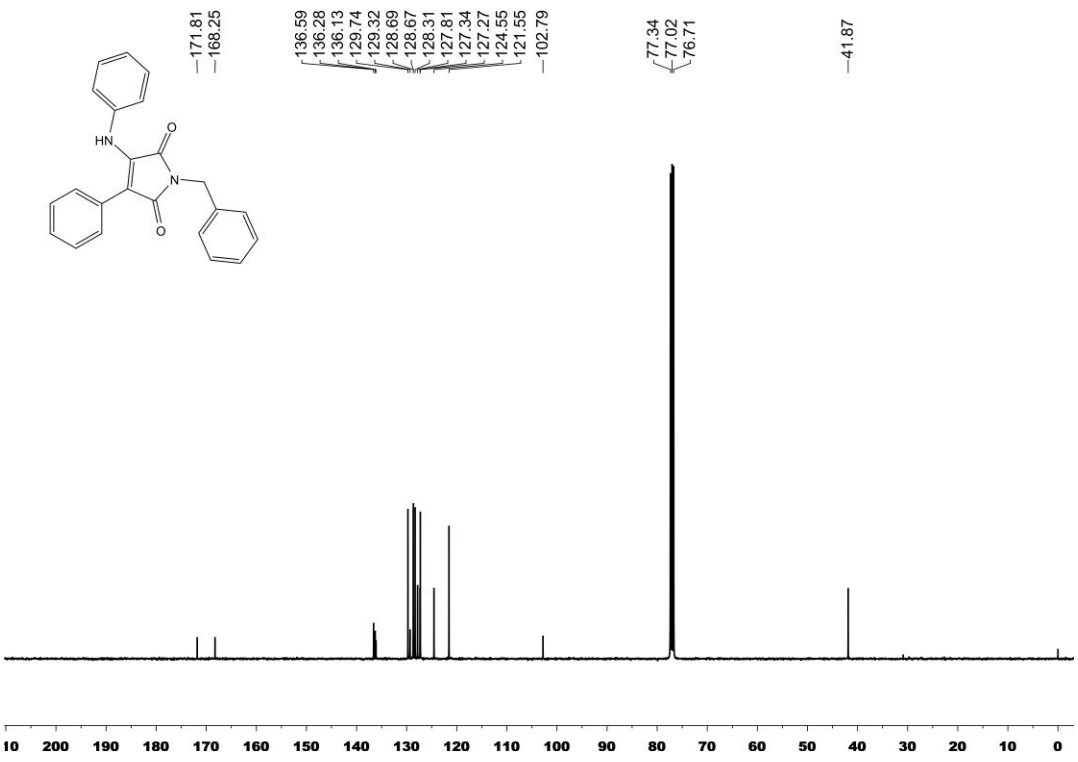
^{1}H NMR and ^{13}C NMR spectrum of **8b**.



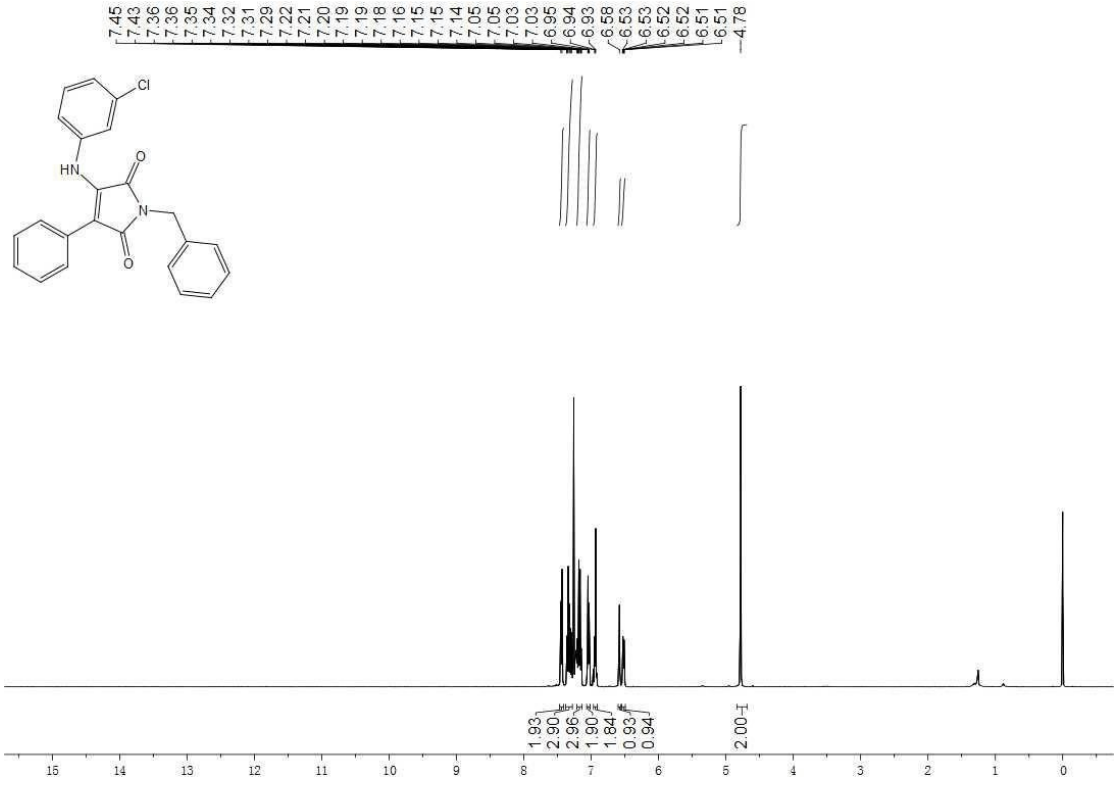


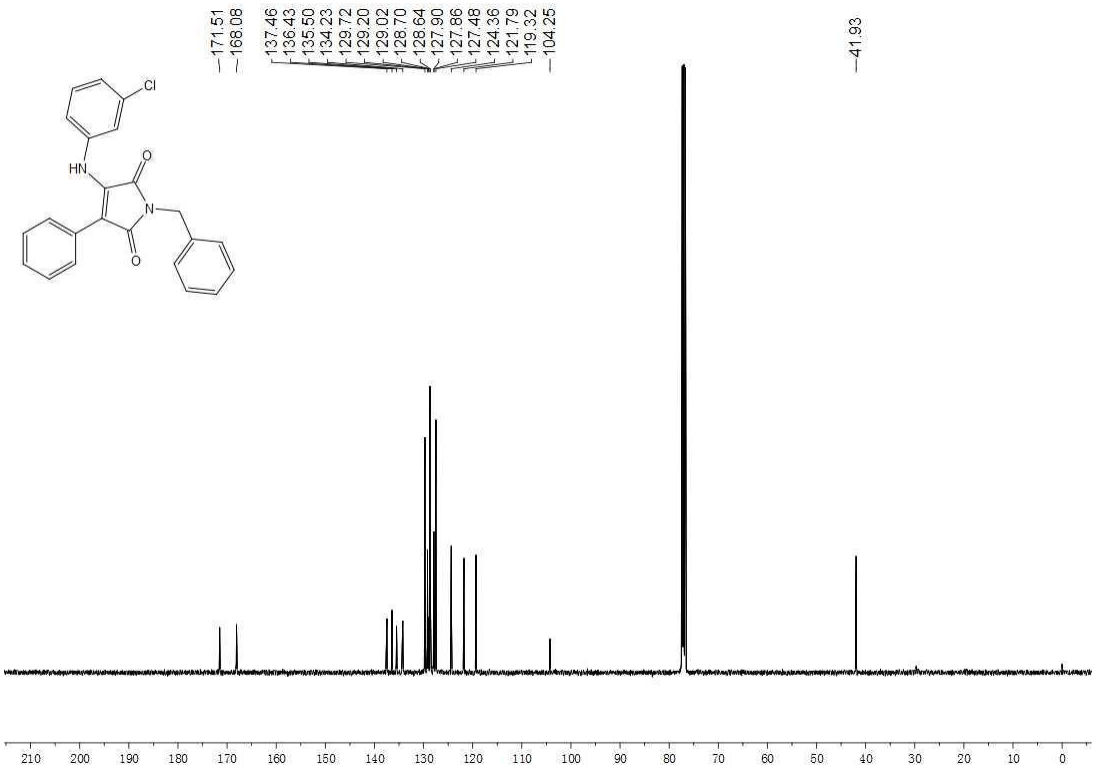
^{1}H NMR and ^{13}C NMR spectrum of **8c**.



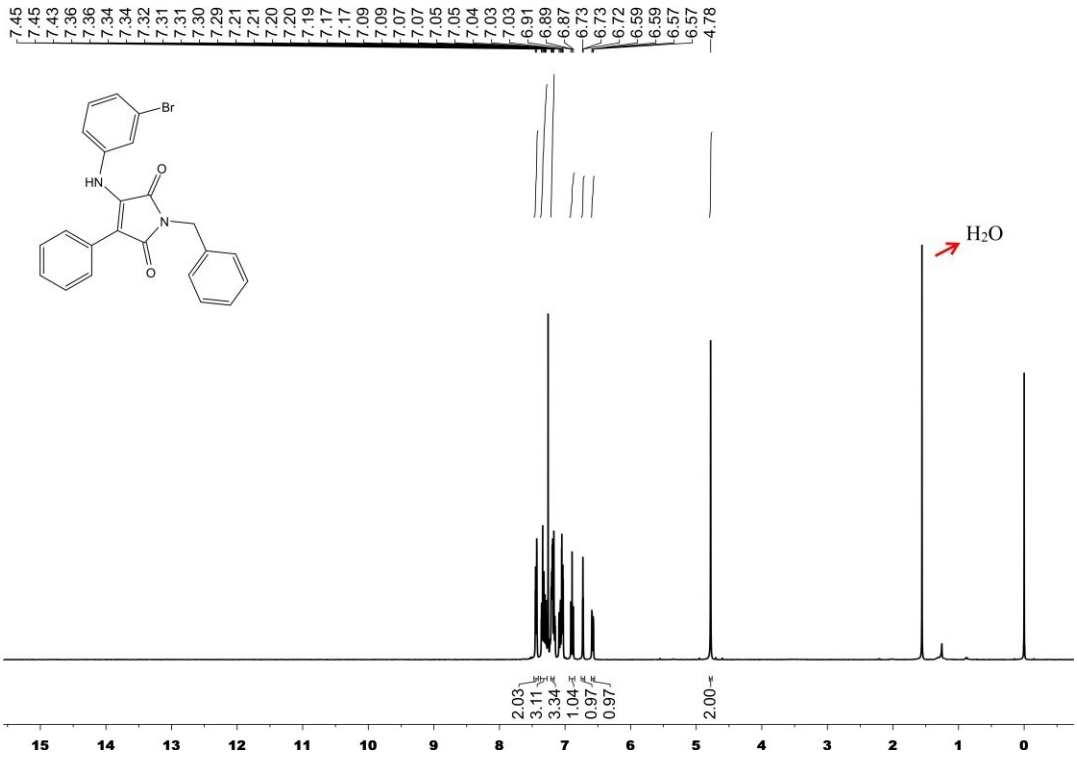


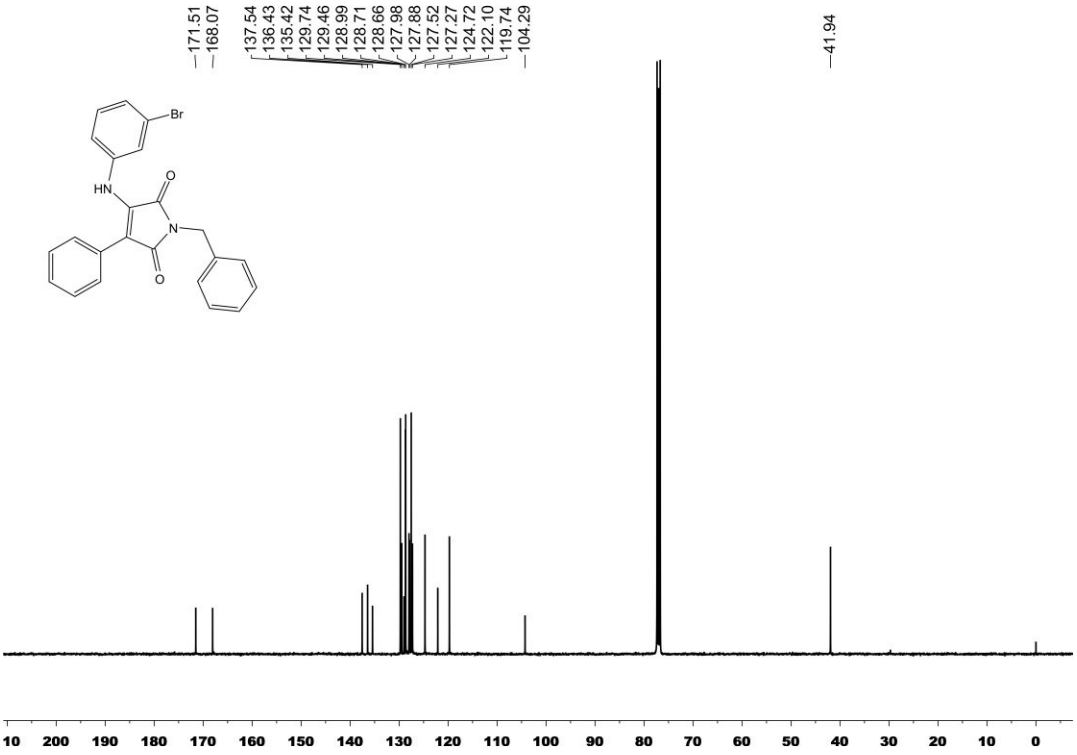
^{1}H NMR and ^{13}C NMR spectrum of **8d**.



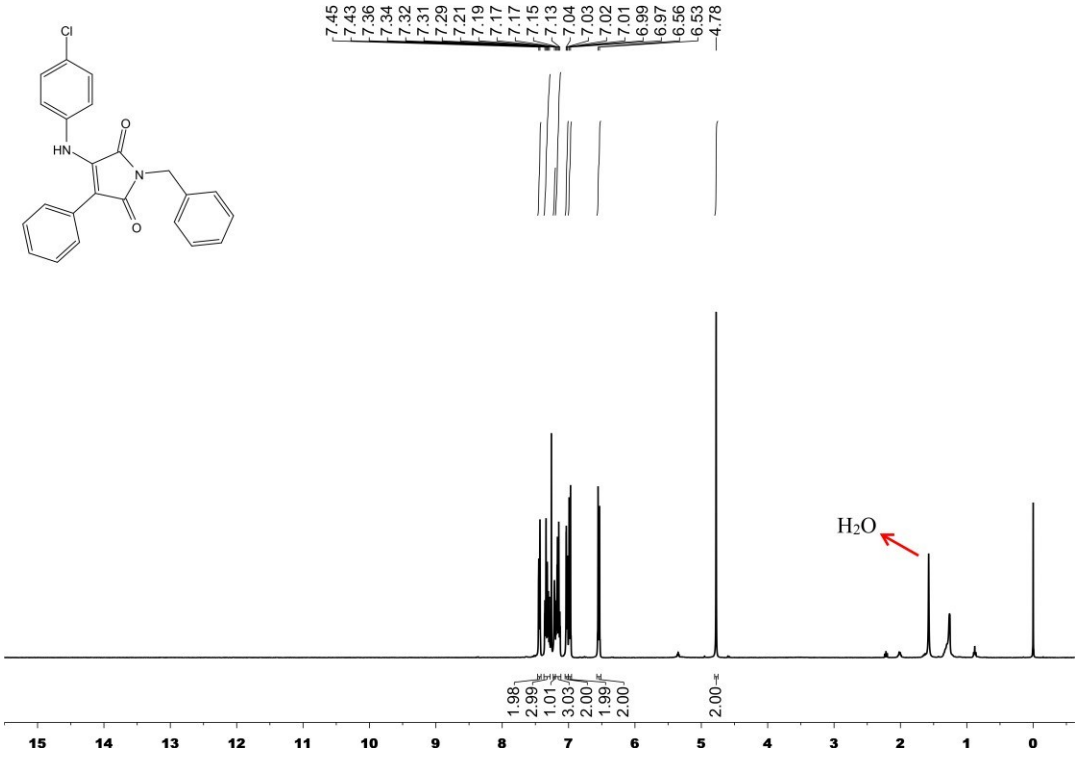


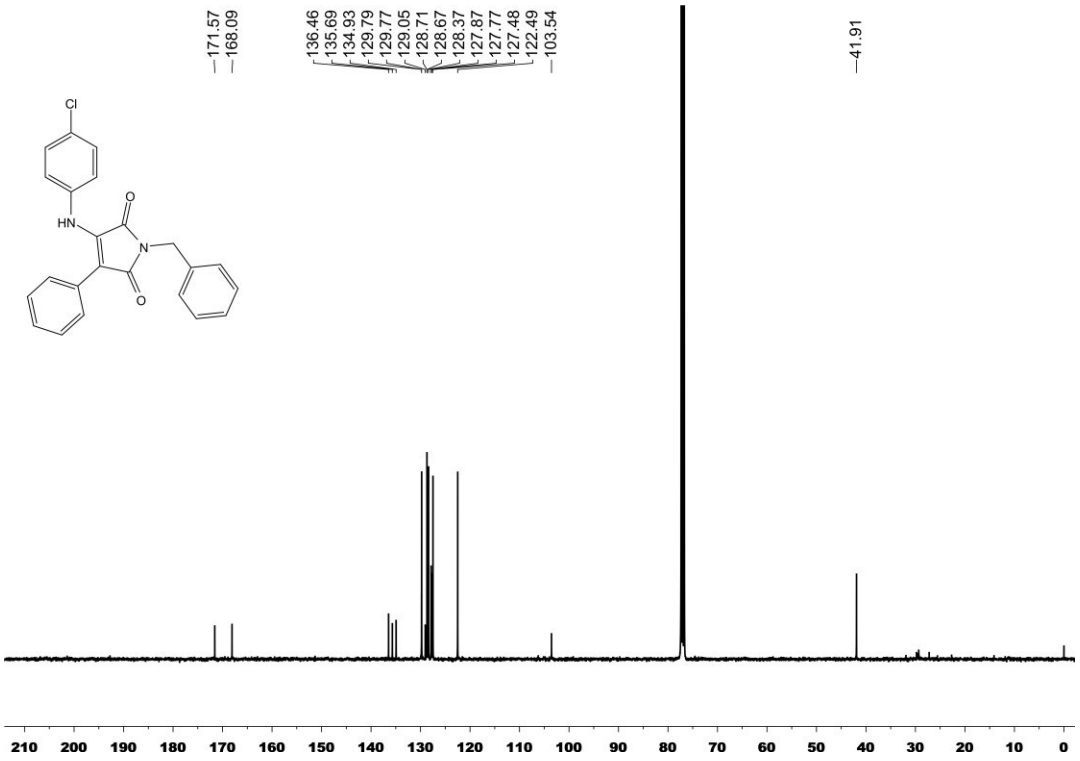
^{1}H NMR and ^{13}C NMR spectrum of **8e**.



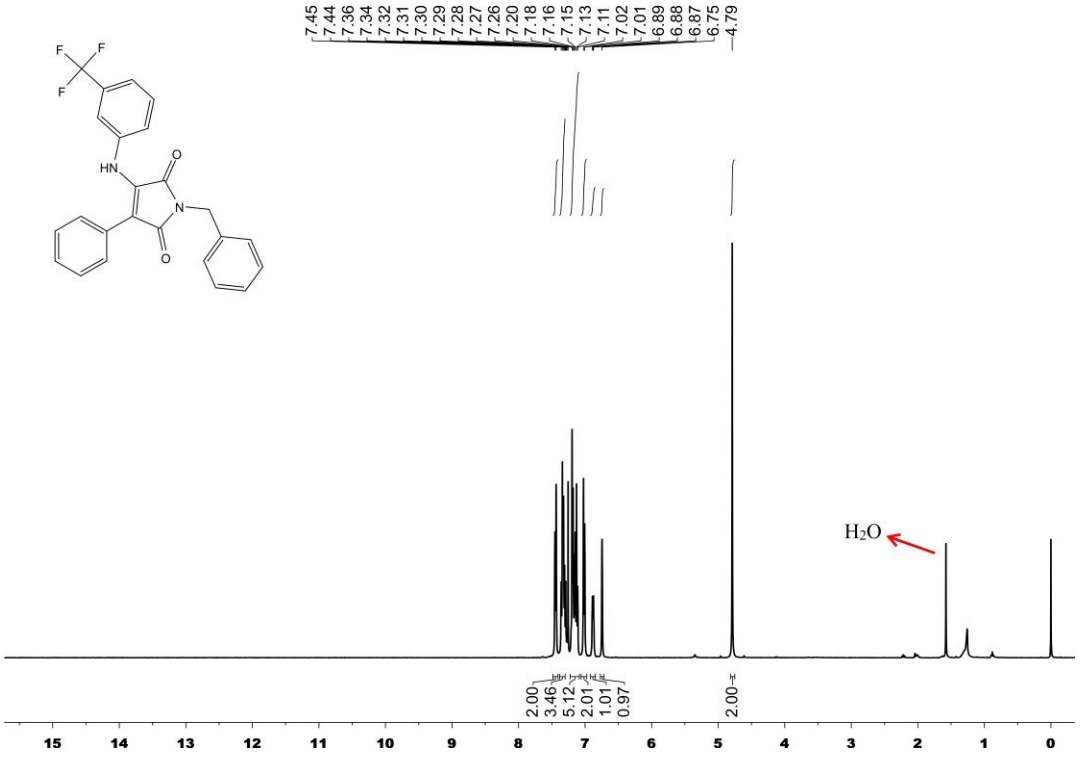


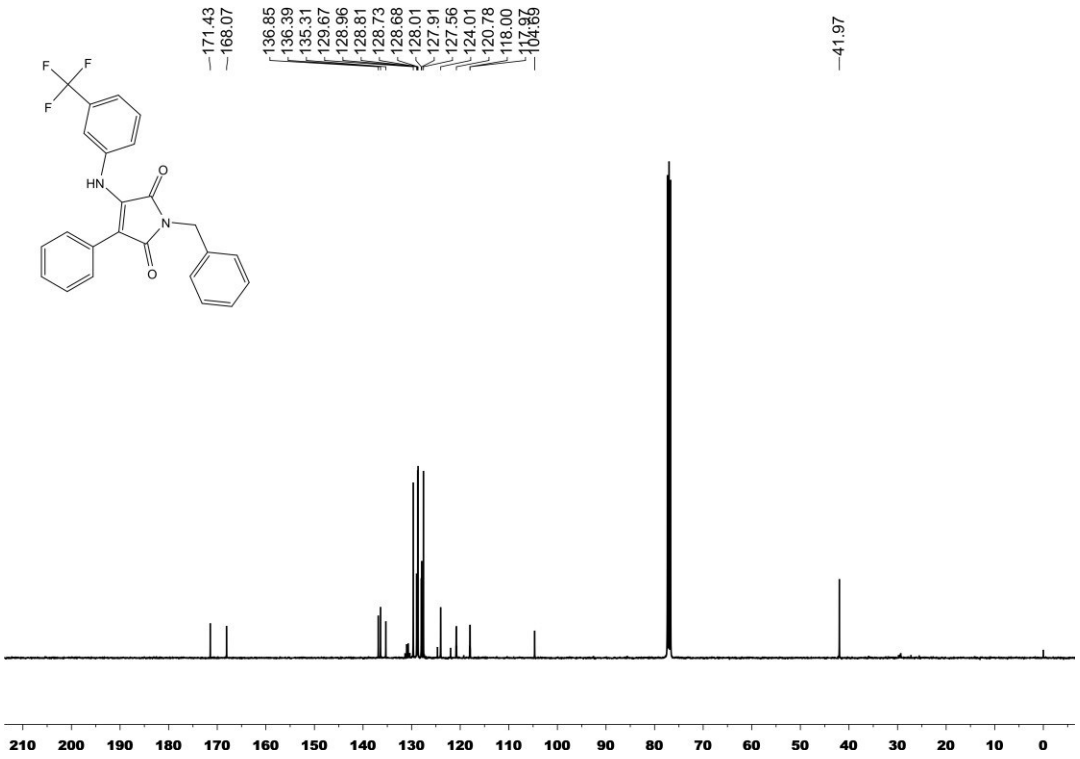
^{1}H NMR and ^{13}C NMR spectrum of **8f**.



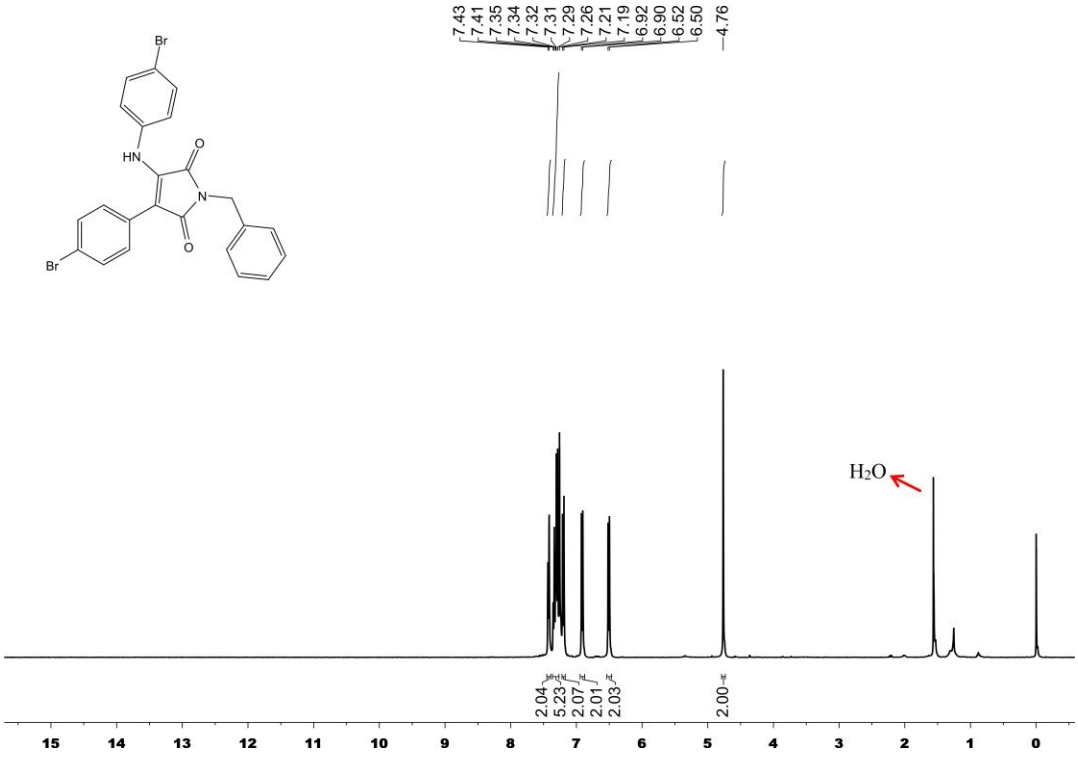


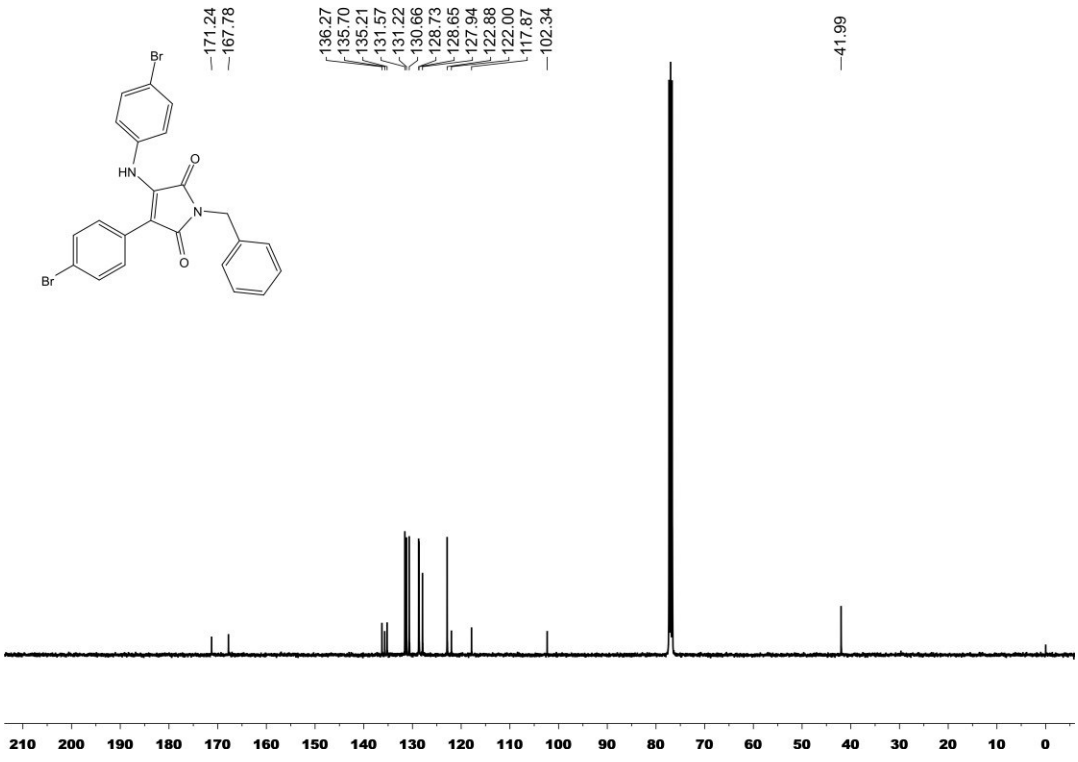
^{1}H NMR and ^{13}C NMR spectrum of **8g**.



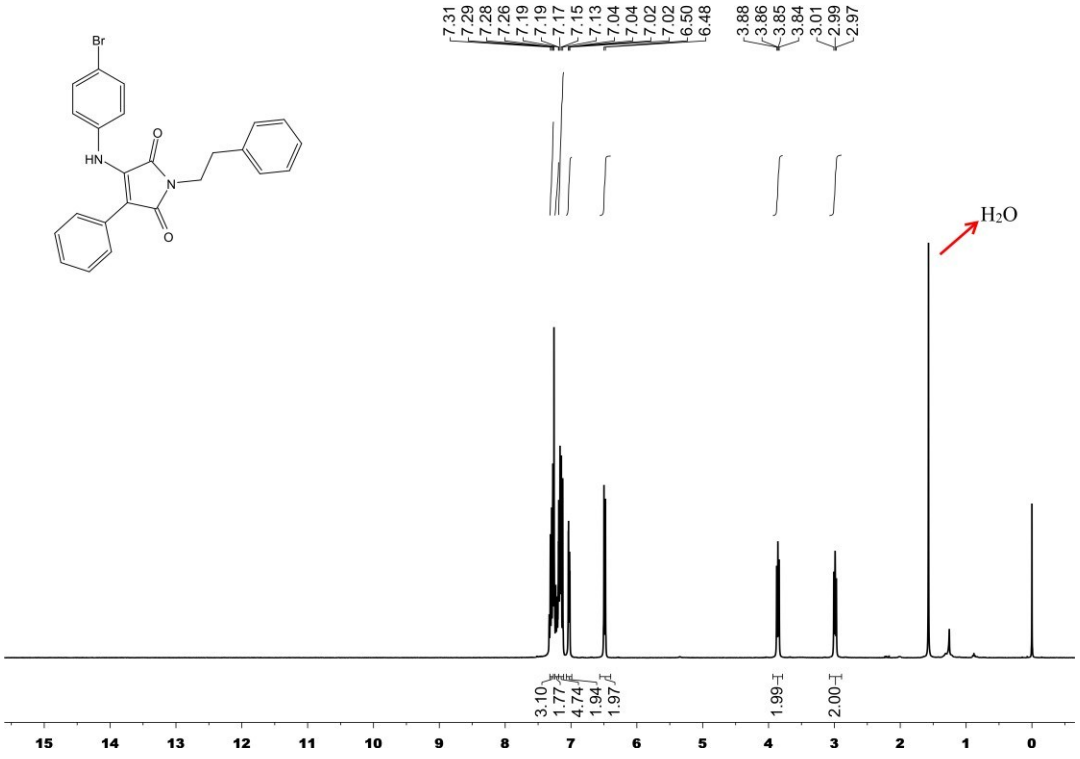


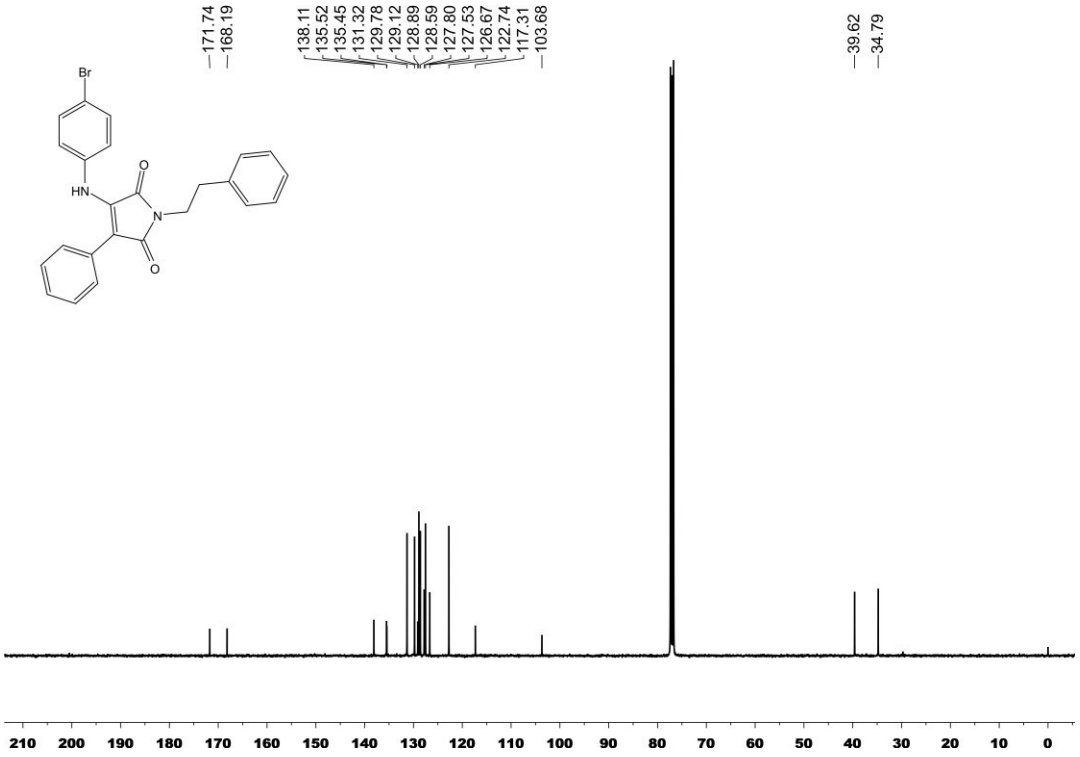
^{1}H NMR and ^{13}C NMR spectrum of **8h**.



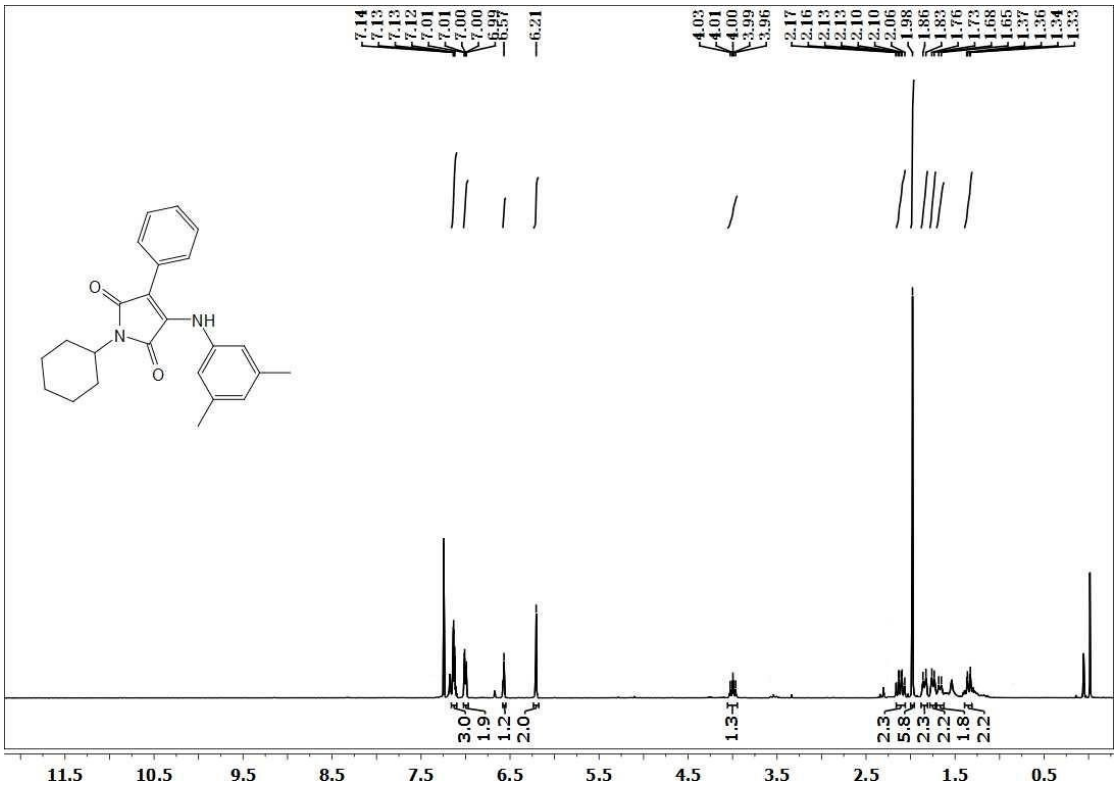


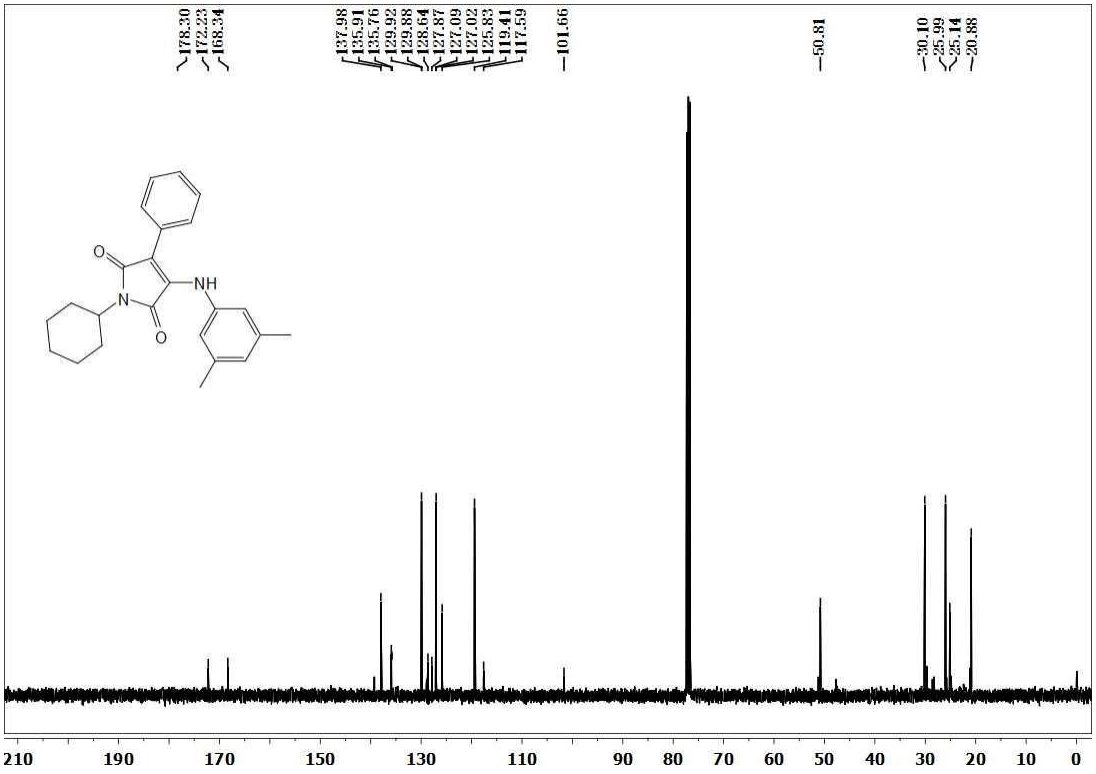
^{1}H NMR and ^{13}C NMR spectrum of **8i**.



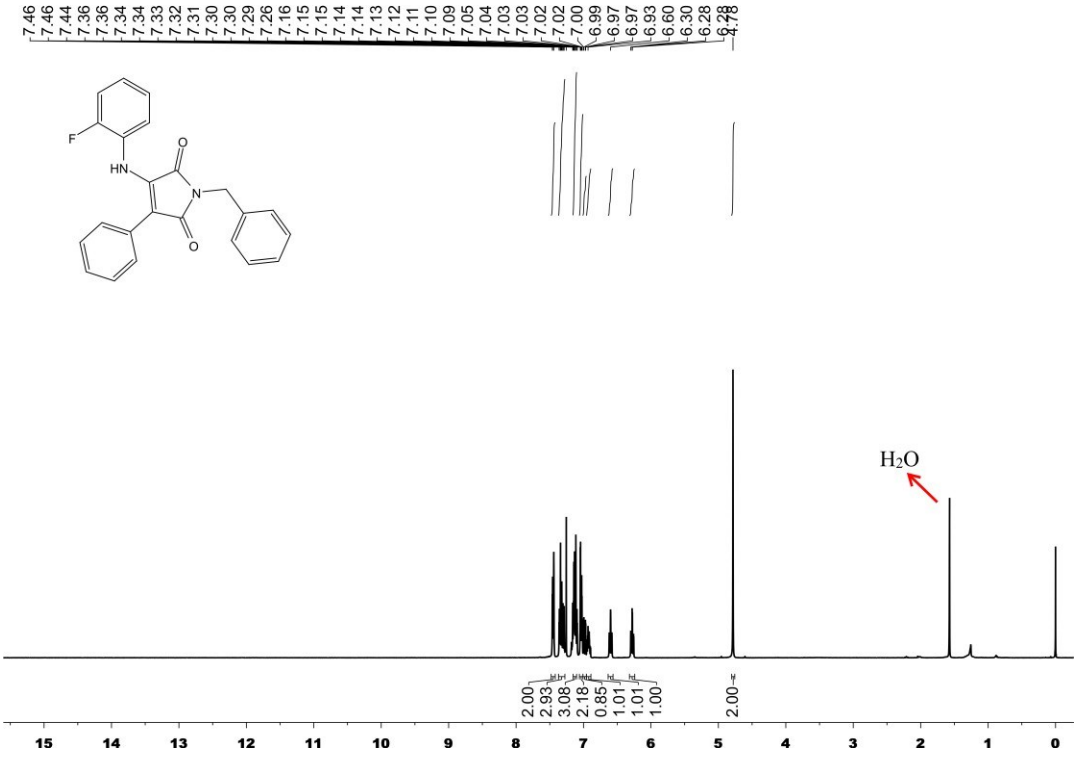


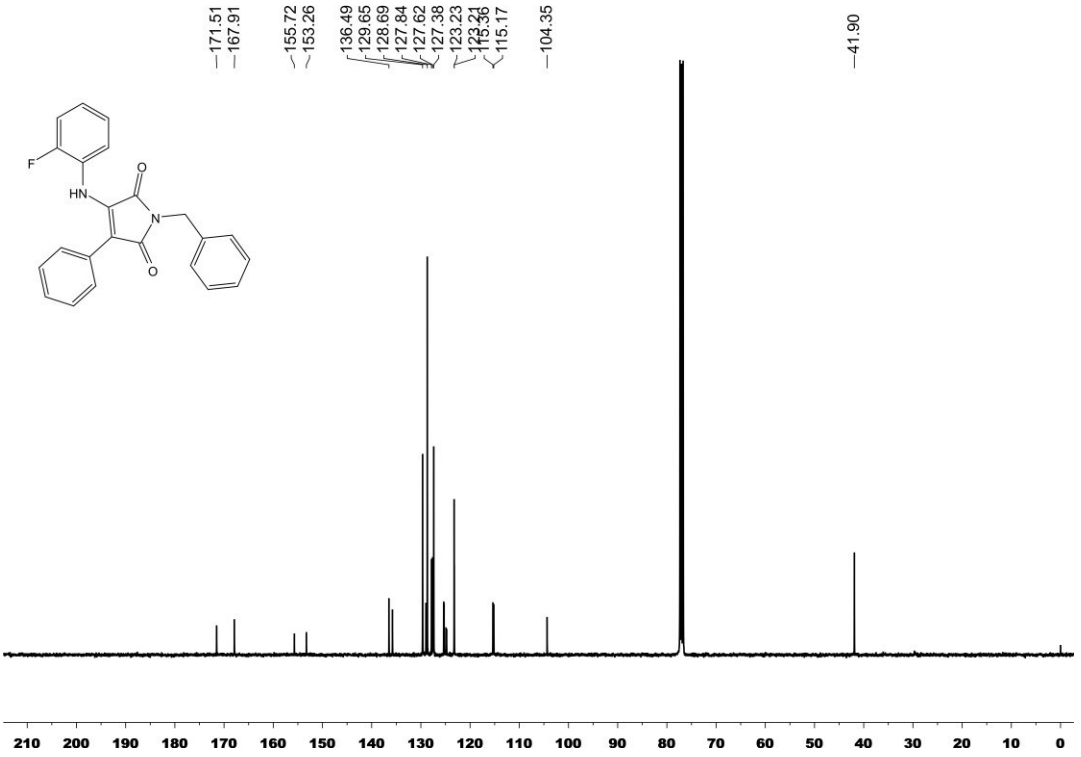
^{1}H NMR and ^{13}C NMR spectrum of **8l**.



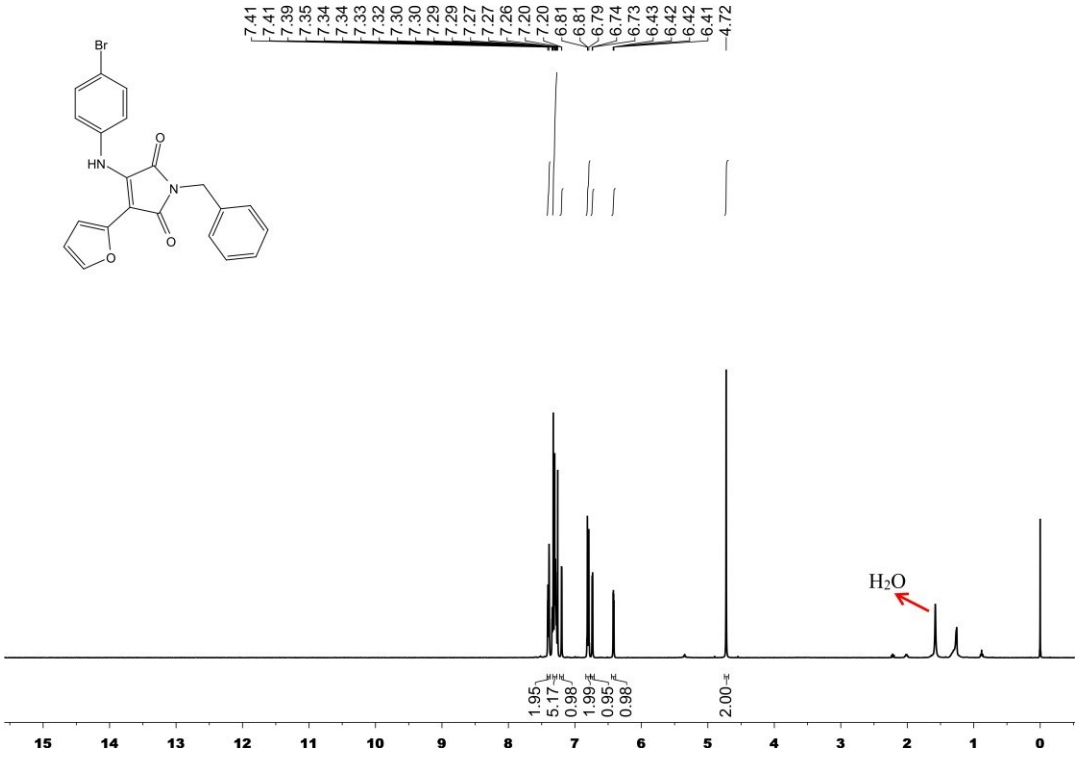


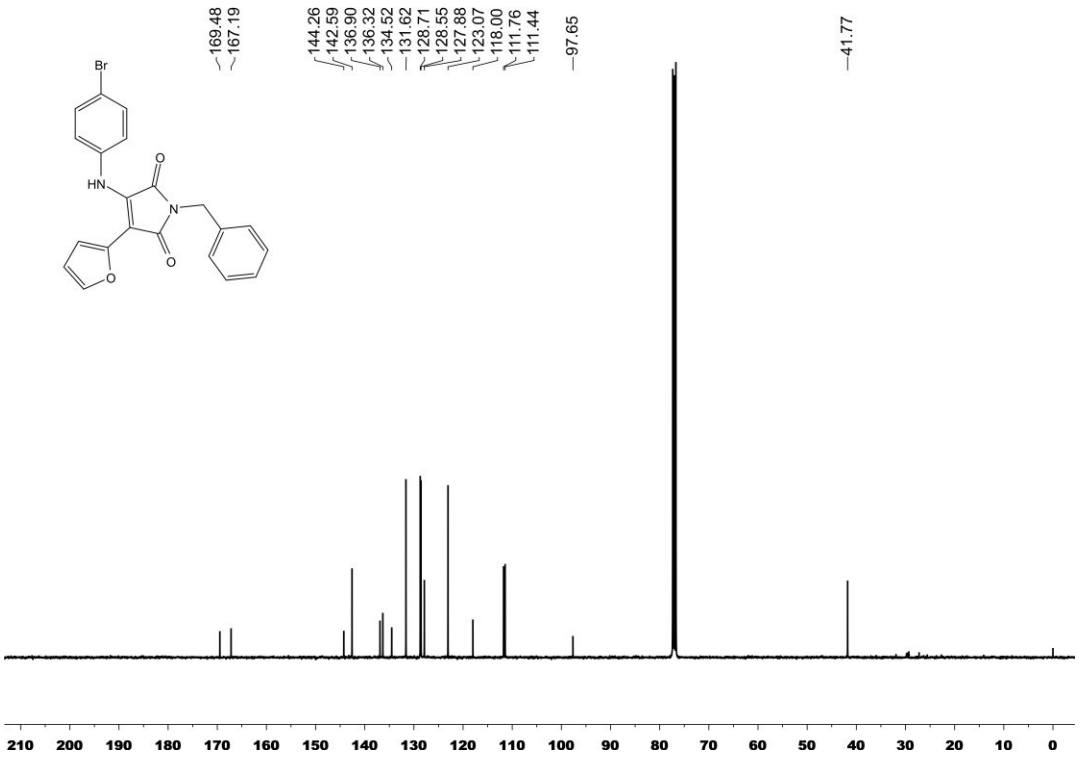
^{1}H NMR and ^{13}C NMR spectrum of **8m**.



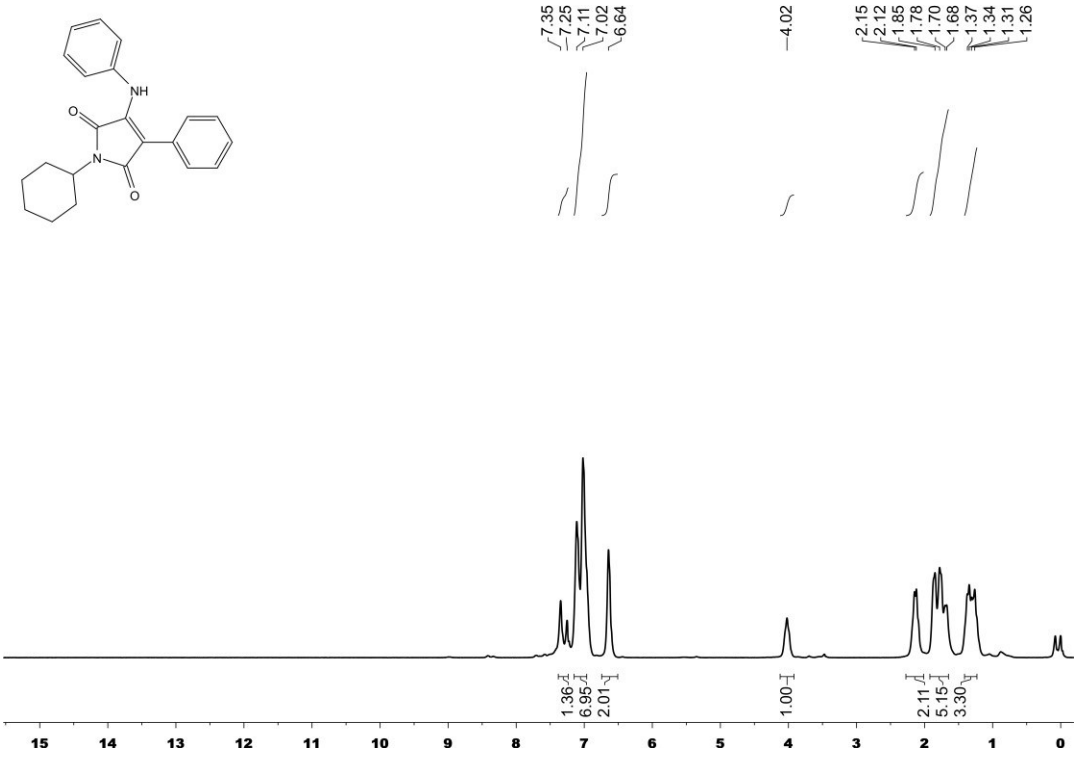


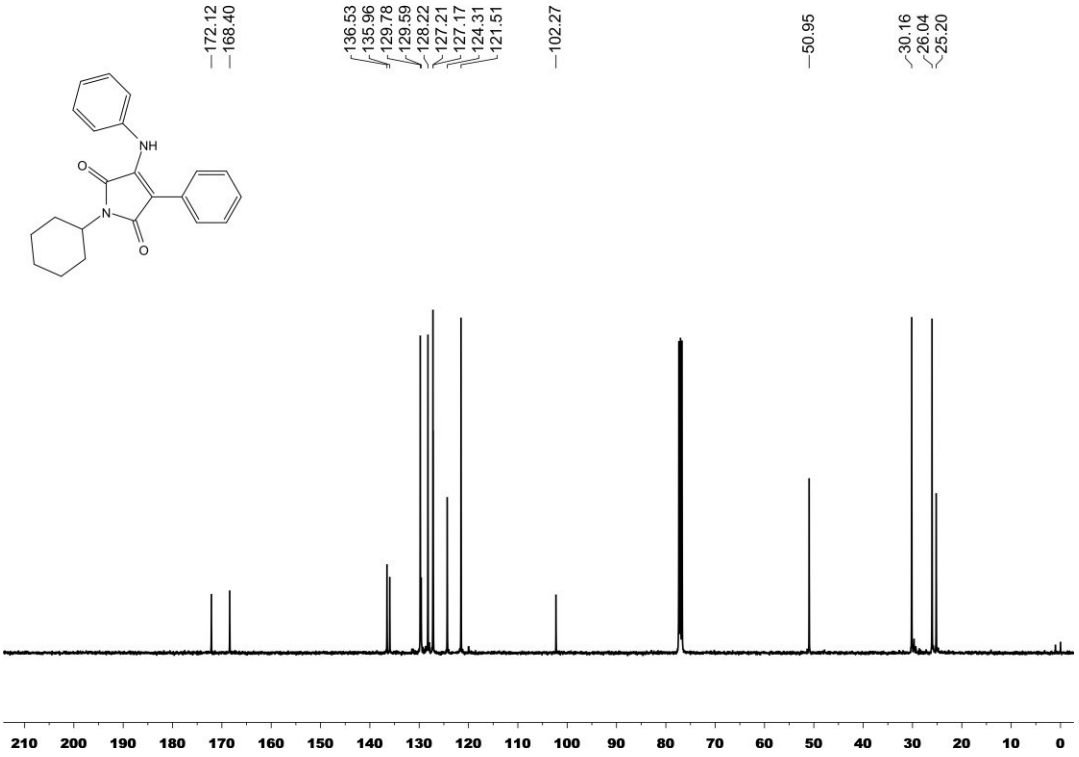
^{1}H NMR and ^{13}C NMR spectrum of **8n**.



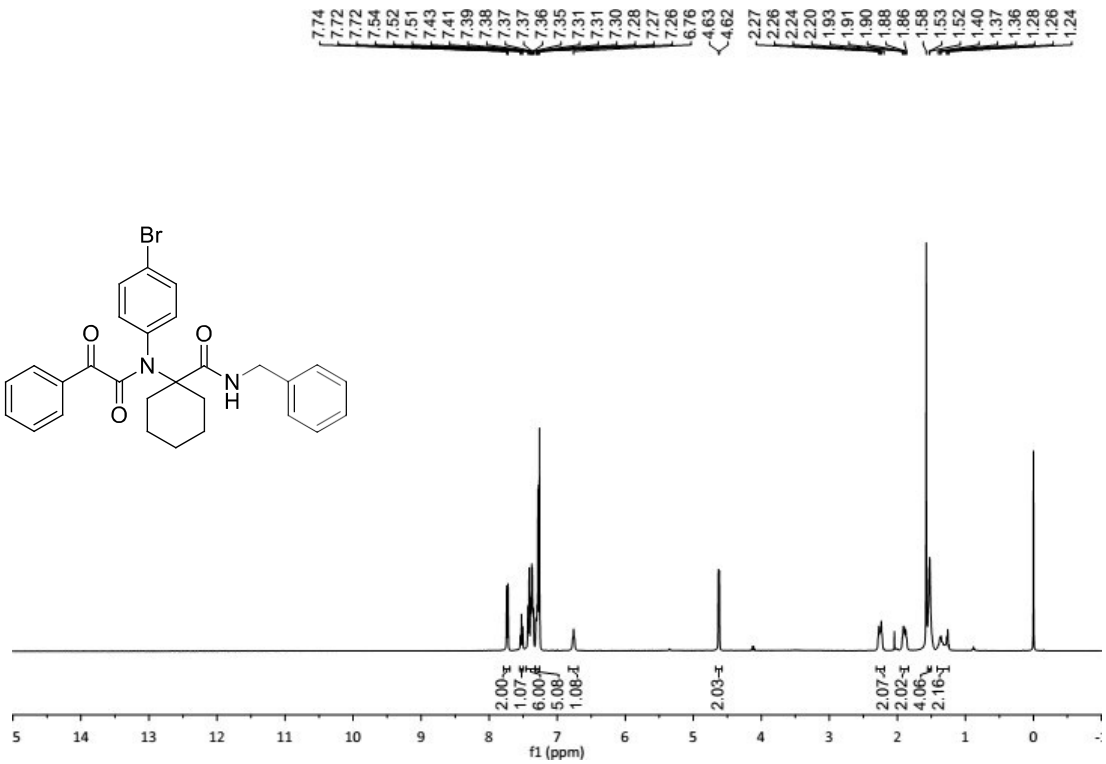


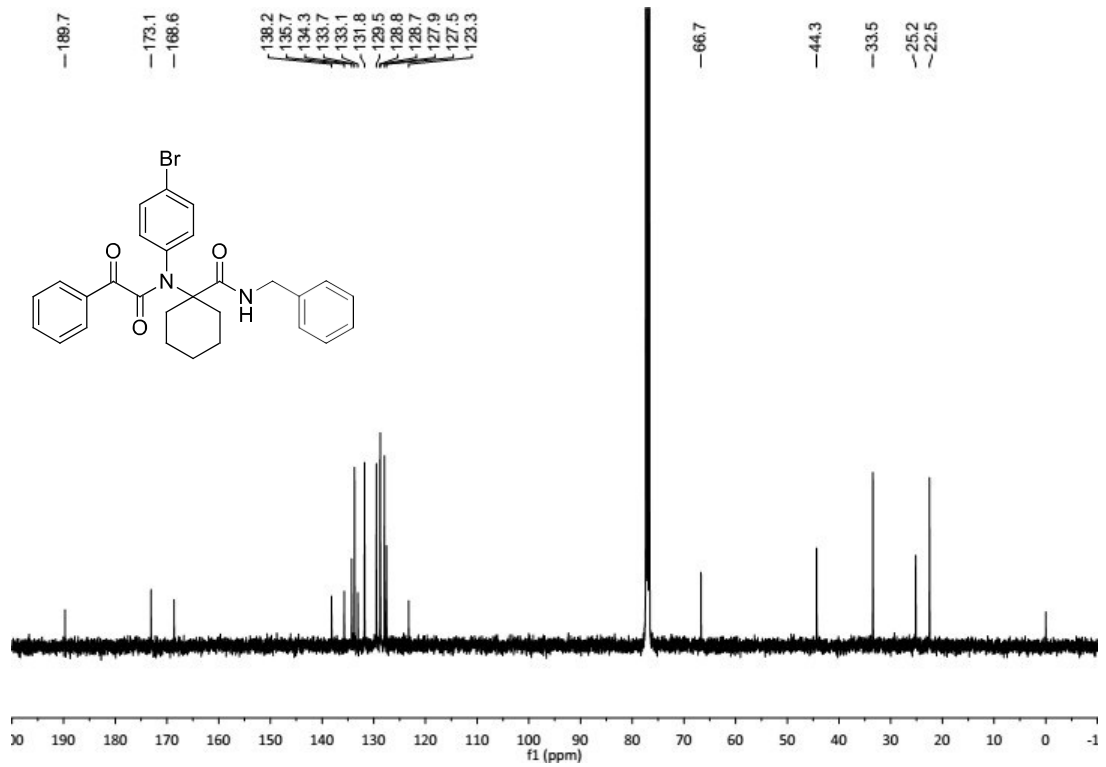
^{1}H NMR and ^{13}C NMR spectrum of **8o**.

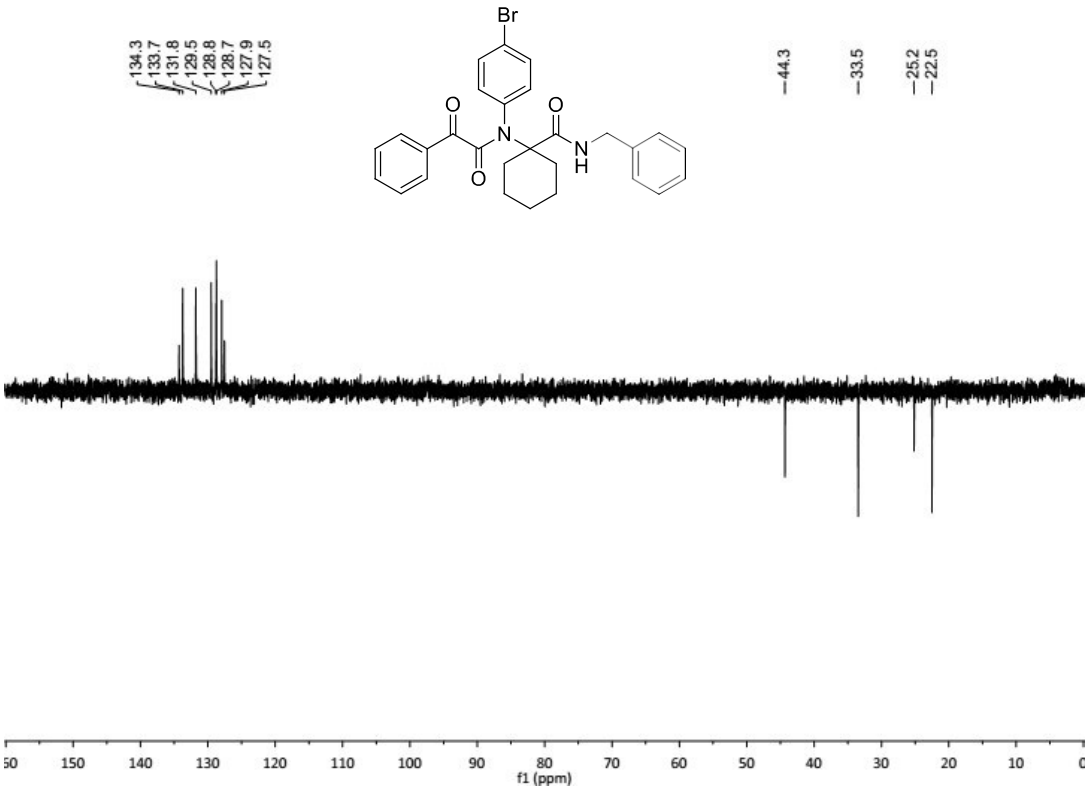




^{1}H NMR and ^{13}C NMR spectrum of **9**.



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133.7
131.8
129.5
128.8
128.7
127.9
127.5
44.3
33.5
25.2
22.5
Br
O
O
N
O
N
H
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)