Supporting Information

Synthesis, Biological Evaluation and Structure-Activity Relationship of 2-Phenylaminomethylene-cyclohexane-1,3-diones as Specific Anti-tuberculosis Agents

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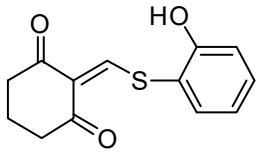
A. General information and representative procedure:

General. ^{1}H and ^{13}C NMR were recorded on 400 MHz BrukerDaltonics spectrometer. The chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as internal standard and coupling constants were measured in Hz. Mass spectra were recorded on BrukerDaltonics electro spray ionization apparatus. Column chromatography was carried out on silica gel (Qualigens, 60-120 mesh) and pre-coated silica gel thin layer chromatographic (TLC) plates were viewed with ultraviolet light at 254 nm for fluorescence quenching spots and at 366 nm for fluorescent spots. Ceric sulfate was used as visualizing agents.

Representative procedure for the synthesis of most active compound 39: A clean and dry 50 mL round bottom flask fitted with reflux condenser was charged with 5,5-dimethyl1,3-cyclohexanedione (625 mg, 4.46 mmol), 2-hydroxyaniline (487 mg, 4.46 mmol) and triethylorthoformate (1.1 ml, 6.69 mmol). The reaction mixture was stirred for 2 h at 120 ^{o}C. The crude solid material formed was then purified by silica gel column chromatography (eluted with ethylacetate: hexane, 20:80 v/v) to afford the pure white solid compound **39** (1010 mg) 90% yield.

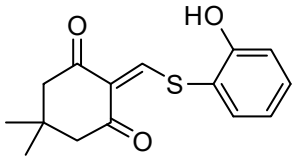
B. NMR data of compounds 5-43.

2-(((2-hydroxyphenyl)thio)methylene)cyclohexane-1,3-dione (5):



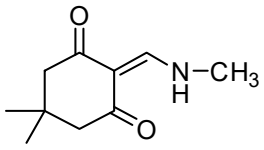
White solid; m.p. 230 ºC; TLC Rf value, 0.90 (in EtOAc:Hexane, 60:40); IR (neat) 3210, 2990, 2910, 1670, 1610, 1210 cm^{-1} ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.19 (IH, s), 7.29-7.24 (1H, m), 7.07-7.01 (1H, m), 6.88-6.74 (2H, m), 4.70 (1H, s, -OH), 2.50-2.28 (4H, m), 1.33-1.15 (2H, m); ^{13}C NMR (101 MHz, $CD_3)_2SO$) δ 195.3, 192.2, 165.7, 160.0, 140.0, 131.6, 118.8, 115.9, 115.1, 111.3, 50.6, 46.2, 19.5; ESI-MS: 249.06 $[M+H]^+$.

2-(((2-hydroxyphenyl)thio)methylene)-5,5-dimethyl cyclohexane-1,3-dione (6):



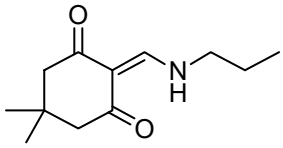
White solid; m.p. 225 ºC; TLC Rf value, 0.91 (in EtOAc:Hexane, 60:40); IR (neat) 3212, 2988, 2912, 1676, 1608, 1377, 1660, 1210 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.58 (IH, s), 7.38-7.27 (1H, m), 7.25-7.01 (1H, m), 6.88-6.74 (2H, m), 4.76 (1H, s, -OH), 2.58 (4H, bs), 1.04 (6H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 195.2, 191.0, 165.3, 160.1, 140.2, 131.6, 118.8, 115.9, 115.8, 111.3, 50.6, 46.2, 32.5, 28.8 (2C); ESI-MS: 277.09 $[M+H]^+$.

5,5-dimethyl-2-((methylamino)methylene)cyclohexane-1,3-dione (7):



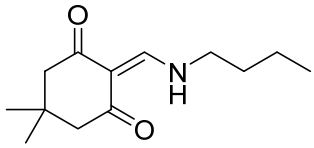
White solid; m.p. 210 ºC; TLC Rf value, 0.77 (in EtOAc:Hexane, 60:40); IR (neat) 3312, 3055, 2977, 2916, 1665, 1598, 1570, 1210, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (1H, s), 3.16 (3H, s), 2.40 (4H, s), 1.02 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 196.0, 165.5, 114.7, 51.4, 50.5, 41.4, 25.4, 22.7 (2C); ESI-MS: 204.08 $[M+Na]^+$.

5,5-dimethyl-2-((propylamino)methylene)cyclohexane-1,3-dione (8):



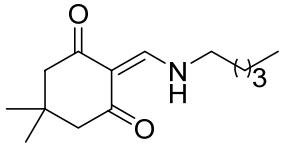
White solid; m.p. 149 ºC; TLC Rf value, 0.38 (in EtOAc:Hexane, 60:40); IR (neat) 3260, 3033, 2988, 2925, 1687, 1596, 1505, 1338, 1312 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, s), 3.18-3.14 (2H, m), 2.40 (4H, s), 1.57-1.53 (2H, m), 1.14 (6H, s), 1.02 (3H, t, J = 4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 197.3, 165.8, 113.1, 51.4, 50.5, 41.4, 32.4, 27.1 (2C), 25.5, 22.1; ESI-MS: 210.11 $[M+H]^+$.

2-((butylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione (9):



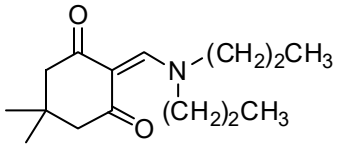
White solid; m.p. 193 ºC; TLC Rf value, 0.91 (in EtOAc:Hexane, 60:40); IR (neat) 2982, 2933, 1678, 1582, 1570, 1272, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ11.09 (1H, s), 8.10 (1H, d, J = 16 Hz), 3.37-3.32 (2H, m), 2.34 (2H, s), 2.31 (2H, s), 1.75-1.64 (4H, m), 1.23 (6H, s), 0.95 (3H, t, J = 8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 188.2, 161.0, 114.5, 64.1, 61.7, 46.0, 26.8, 24.1 (2C), 18.9, 17.1, 14.5; ESI-MS: m/z 224.13 $[M+H]^+$.

5,5-dimethyl-2-((pentylamino)methylene)cyclohexane-1,3-dione (10):



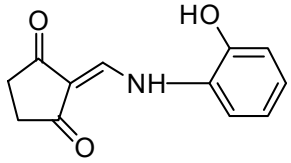
White solid; m.p. 116 ºC; TLC Rf value, 0.77 (in EtOAc:Hexane, 60:40); IR (neat) 2990, 2940, 1690, 1590, 1575, 1365 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (1H, s), 3.14-3.11 (2H, t), 2.27 (4H, s), 1.56-1.50 (4H, m), 1.39-1.32 (2H, m), 1.11 (6H, s), 0.99 (3H, t, J = 4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.7, 158.4, 115.8, 51.3 (2C), 46.1, 32.5, 30.5, 28.8 (2C), 20.2, 14.0; ESI-MS: 238.16 $[M+H]^+$.

2-((dipropylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione (11):



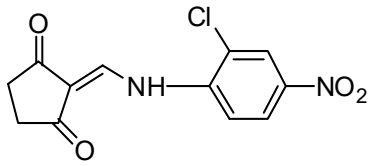
White solid; m.p. 224 ºC; TLC Rf value, 0.69 (in EtOAc:Hexane, 60:40); IR (neat) 3344, 2977, 2912, 1666, 1578, 1376, 1266, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, s), 3.24-3.21 (2H, m), 3.10-3.08 (2H, m), 2.65 (4H, s), 1.65-1.61 (4H, m), 1.13 (6H, s), 1.05-1.02 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 197.7, 165.8, 113.1, 51.4, 50.5, 43.2, 40.9, 32.4, 30.9, 29.5, 28.1, 27.1, 22.1 (2C); ESI-MS: 252.15 $[M+H]^+$.

2-(((2-hydroxyphenyl)amino)methylene)cyclopentane-1,3-dione (12):



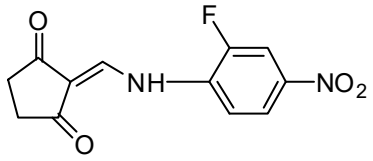
White solid; m.p. 220 ºC; TLC Rf value, 0.68 (in EtOAc:Hexane, 60:40); IR (neat) 3315, 2990, 2987, 2886, 1676, 1370, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, s), 7.29-7.25 (1H, m), 7.07-7.01 (1H, m), 6.88-6.65 (3H, m), 4.61 (1H, s), 2.65- 2.61 (4H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 195.3, 193.2, 165.8, 160.6, 140.3, 131.6, 118.8, 115.9, 115.1, 111.3, 34.9, 33.7; ESI-MS: 240.04 $[M+Na]^+$.

2-(((2-chloro-4-nitrophenyl)amino)methylene)cyclopentane-1,3-dione (13):



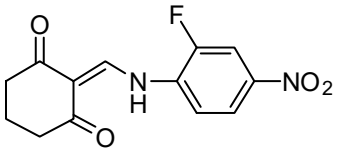
Yellow solid; m.p. 160 ºC; TLC Rf value, 0.51 (in EtOAc:Hexane, 60:40); IR (neat) 3230, 3087, 2933, 2909, 1672, 1578, 1505, 1235, 1202 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.61 (1H, s), 8.25 (1H, s), 8.15 (1H, d, J = 8 Hz), 7.91 (1H, d, J = 8 Hz), 2.65-2.25 (4H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 205.5, 201.0, 151.3, 145.9, 144.7, 135.9, 125.6, 119.9, 113.5, 110.8, 34.6, 33.6; ESI-MS: 303.00 $[M+Na]^+$.

2-(((2-fluoro-4-nitrophenyl)amino)methylene)cyclopentane-1,3-dione (14):



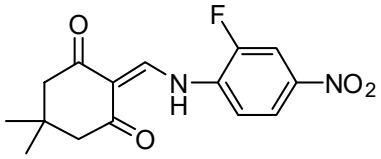
Yellow solid; m.p. 205 ºC; TLC Rf value, 0.70 (in EtOAc:Hexane, 60:40); IR (neat) 3310, 2990, 1670, 1376, 1155 cm^{-1}; IR...; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.90 (1H, s), 8.35 (1H, dd, J = 4, 4 Hz), 8.23-8.14 (2H, m), 2.63-2.45 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8, 201.7, 155.4, 153.3, 142.6, 141.5, 121.3, 120.5, 111.9, 110.4, 33.4 (2C); ESI-MS: m/z 265.03 $[M+H]^+$.

2-(((2-fluoro-4-nitrophenyl)amino)methylene)cyclohexane-1,3-dione (15):



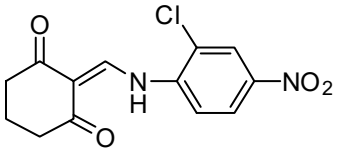
White solid; m.p. 128 ºC; TLC Rf value, 0.62 (in EtOAc:Hexane, 60:40); IR (neat) 2976, 2910, 1666, 1577, 1555, 1279 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 13.03 (1H, d, J = 12 Hz), 8.65 (1H, d, J = 12 Hz), 8.33-8.29 (1H, m), 7.91-7.86 (2H, m), 2.58-2.47 (4H, m), 1.97-1.91 (2H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 201.4, 195.7, 149.5, 144.5, 133.3, 121.2, 118.2, 112.3, 112.1, 111.9, 37.7, 37.3, 18.7; ESI-MS: 279.02 $[M+H]^+$.

2-(((2-fluoro-4-nitrophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (16):



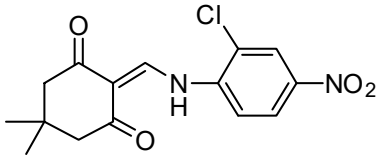
White solid; m.p. 224 ºC; TLC Rf value, 0.66 (in EtOAc:Hexane, 60:40); IR (neat): 3360, 2950, 2820, 1676, 1610, 1370, 1280, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.98 (1H, d, J = 12 Hz), 8.61 (1H, d, J = 12 Hz), 8.31-8.28 (1H, m), 8.15-8.07 (2H, m), 2.50 (2H, s), 2.41 (2H, s), 1.00 (6H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 200.8, 195.2, 149.0, 144.0, 133.2, 121.1, 118.1, 112.3, 112.0, 110.6, 51.0, 50.7, 30.6 (2C), 27.9; ESI-MS: 329.05 $[M+Na]^+$.

2-(((2-chloro-4-nitrophenyl)amino)methylene)cyclohexane-1,3-dione (17):



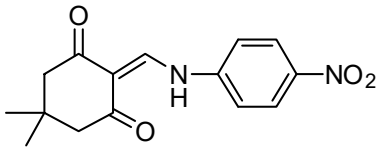
Yellow solid; m.p. 164 ºC; TLC Rf value, 0.66 (in EtOAc:Hexane, 60:40); IR (neat) 3090, 2967, 2810, 1688, 1592, 1588, 1533, 1272 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 13.22 (1H, d, J = 12 Hz), 8.65 (1H, d, J = 12 Hz), 8.24 (1H, d), 8.09 (1H, s), 7.93 (1H, d, J =), 2.61-2.48 (4H, m), 1.33-1.15 (2H, m);^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 201.5, 195.8, 151.4, 149.0, 144.0, 141.1, 135.9, 117.6, 113.6, 112.2, 37.8, 37.4, 30.7; ESI-MS: 295.01 $[M+H]^+$.

2-(((2-chloro-4-nitrophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (18):



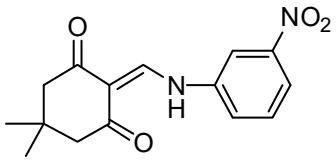
White solid; m.p. 217 ºC; TLC Rf value, 0.73 (in EtOAc:Hexane, 60:40); IR (neat) 3244, 2978, 2954, 1672, 1612, 1505, 1395, 1290, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, s), 8.07 (1H, s), 7.9 (1H, d, J = 8 Hz), 6.90 (1H, d, J = 8 Hz), 2.46 (4H, s), 1.17 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.7, 148.9, 144.0, 142.1, 125.0, 123.6, 122.4, 120.9, 115.4, 51.3 (2C), 32.5, 28.8 (2C); ESI-MS: 323.06 $[M+H]^+$.

5,5-dimethyl-2-(((4-nitrophenyl)amino)methylene)cyclohexane-1,3-dione (19):



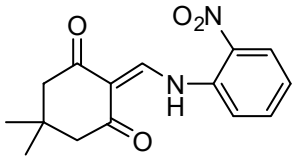
Gummy; TLC Rf value, 0.70 (in EtOAc:Hexane, 60:40);); IR (neat) 3240, 2988, 1666, 1290, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, d, J = 12 Hz), 8.26 (2H, d, J = 12 Hz), 7.35 (2H, d, J = 8 Hz), 2.47 (2H, s), 2.43 (2H, s), 1.07 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 196.2, 149.0, 145.1, 143.8, 125.9 (2C), 117.7, 110.3, 51.8, 51.3 (2C), 31.0, 28.5 (2C); ESI-MS: 289.09 $[M+H]^+$.

5,5-dimethyl-2-(((3-nitrophenyl)amino)methylene)cyclohexane-1,3-dione (20):



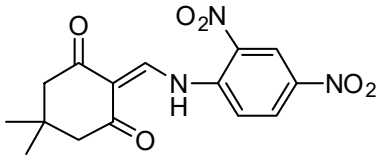
Gummy; TLC Rf value, 0.70 (in EtOAc:Hexane, 60:40);); IR (neat) 3255, 2956, 1670, 1615, 1395, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, d, J = 12 Hz), 8.11 (1H, s), 8.07 (IH, d, J = 8 Hz), 7.61-7.54 (2H, m), 2.47 (2H, s), 2.42 (2H, s), 1.08 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 196.4, 149.9, 148.8, 140.1, 131.1, 123.7, 120.7, 113.0, 110.0, 51.9, 51.5, 31.3, 28.7 (2C); ESI-MS: 289.07 $[M+H]^+$.

2-(((2-nitrophenyl)amino)methylene)cyclohexane-1,3-dione (21):



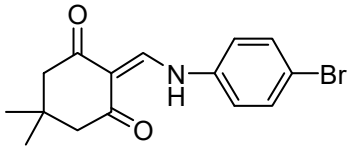
White solid; m.p. 139 ºC;; TLC Rf value, 0.72 (in EtOAc:Hexane, 60:40); IR (neat) 2980, 2910, 1682, 1579 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.72 (1H, s), 8.30 (1H, d, J = 8 Hz), 7.86-7.82 (2H, m), 7.45-7.41 (1H, m), 2.53 (2H, s), 2.47 (2H, s), 1.10 (6H, s); ^{13}C NMR (101 MHz, $CD_3OD/CDCl_3$) δ 201.4, 199.1, 150.6, 140.2, 137.1, 135.8, 127.5, 127.0, 119.7, 112.0, 52.4, 52.2, 31.8, 28.8 (2C); ESI-MS: 289.07 $[M+H]^+$.

2-(((2,4-dinitrophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (**22**):



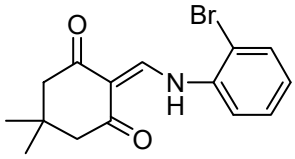
Yellowish gummy compound; TLC Rf value, 0.66 (in EtOAc:Hexane, 60:40);); IR (neat) 3256, 1665, 1505, 1290 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (1H, s), 8.35-8.33 (1H, m), 8.09 (1H, s), 7.17 (1H, d, J = 8 Hz), 2.58 (4H, s), 1.14 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.7, 148.9, 142.1, 141.8, 136.7, 129.3, 123.2, 120.2, 115.4, 51.3, 32.5, 31.7, 28.8 (2C); ESI-MS: 356.04 $[M+Na]^+$.

2-(((4-bromophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (23):



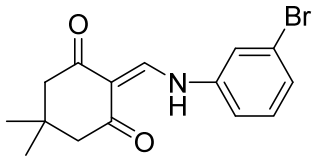
Gummy compound; TLC Rf value, 0.82 (in EtOAc:Hexane, 60:40); IR (neat) 3200, 2980, 1668, 1612, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.83 (1H, d, J = 12 Hz), 8.52 (1H, m), 7.50 (2H, dd, J = 16, 4 Hz), 7.12 (2H, d, J = 12 Hz), 2.44 (2H, s), 2.39 (2H, s), 1.06 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 196.2, 150.0, 137.5, 133.0 (2C), 133.0, 119.4 (2C), 109.1, 51.6, 51.3, 31.1, 28.5 (2C); ESI-MS: 322.03 $[M+H]^+$.

2-(((2-bromophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (24):



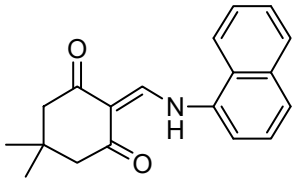
Gummy compound; TLC Rf value, 0.80 (in EtOAc:Hexane, 60:40); IR (neat) 3210, 2977, 1670, 1612, 1525 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (1H, d, J = 12 Hz), 7.61 (1H, d, J = 8 Hz), 7.45-7.35 (2H, m), 7.10-7.06 (1H, m), 2.48 (2H, s), 2.41 (2H, s), 1.08 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 196.6, 149.5, 137.4, 133.9, 129.1, 127.3, 117.1, 114.7, 109.9, 51.9, 51.6, 31.3, 28.8 (2C); ESI-MS: 322.01 $[M+H]^+$.

2-(((3-bromophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (25):



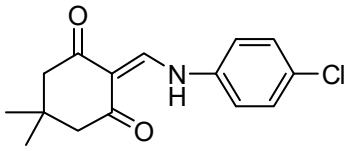
Gummy compound; TLC Rf value, 0.81 (in EtOAc:Hexane, 60:40); IR (neat) 3218, 2980, 1665, 1610, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.78 (1H, d, J = 16 Hz), 8.51 (1H, d, J = 12 Hz), 7.42 (1H, s), 7.35 (1H, d, J = 8 Hz), 7.27-7.23 (1H, m), 7.17 (1H, d, J = 8 Hz), 2.45 (2H, s), 2.40 (2H, s), 1.07 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 196.5, 150.3, 140.0, 131.4, 129.5, 123.9, 121.3, 117.0, 109.5, 51.9, 51.5, 31.3, 28.7 (2C);ESI-MS: 322.03 $[M+H]^+$.

5,5-dimethyl-2-((naphthalen-1-ylamino)methylene)cyclohexane-1,3-dione (26):



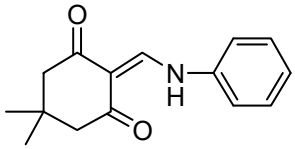
Oily compound; TLC Rf value, 0.92 (in EtOAc:Hexane, 60:40);); IR (neat) 3240, 1672, 1612, 1508, 1395, 1296, 1206 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 13.69 (1H, d, J = 12 Hz), 8.67 (1H, d, J = 416 Hz), 8.05-8.03 (2H, m), 7.99-7.57 (5H, m), 2.51 (2H, s), 2.39 (2H, s), 1.04 (6H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 199.9, 195.0, 151.4, 134.3, 133.9, 128.8, 127.5, 126.9, 126.6, 126.2, 124.7, 119.9, 114.8, 109.2, 50.9, 50.7, 30.8, 28.1 (2C); ESI-MS: 294.11 $[M+H]^+$.

2-(((4-chlorophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (27):



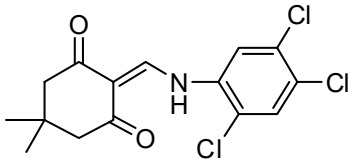
Gummy compound; TLC Rf value, 0.78 (in EtOAc:Hexane, 60:40); IR (neat) 3244, 1670, 1624, 1510 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.45-8.27 (1H, d, J = 12 Hz), 7.62-7.36 (4H, m), 2.50 (2H, s) 2.42 (2H, s), 2.35 (1H, s), 2.08 (6H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 198.9, 195.0, 149.8, 137.7, 129.5 (2C), 128.7, 120.7, 120.4, 108.7, 51.0, 50.7, 30.6, 28.0 (2C); ESI-MS: m/z 278.06 $[M+H]^+$.

5,5-dimethyl-2-((phenylamino)methylene)cyclohexane-1,3-dione (28):



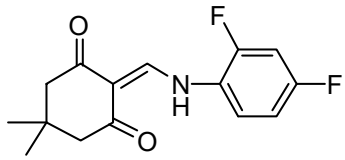
Gummy compound; TLC Rf value, 0.80 (in EtOAc:Hexane, 60:40); IR (neat) 3240, 1665, 1620, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.85 (1H, d, J = 12 Hz), 8.60 (1H, d, J = 16 Hz), 7.40-7.36 (2H, m), 7.23-7.19 (3H, m), 2.43 (2H, s), 2.39 (2H, s), 1.06 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 196.5, 150.7, 138.6, 130.1 (2C), 126.6, 118.3 (2C), 109.0, 51.8, 51.5, 31.3, 28.7 (2C); ESI-MS: 266.08 $[M+Na]^+$.

5,5-dimethyl-2-(((2,4,5-trichlorophenyl)amino)methylene)cyclohexane-1,3-dione (29):



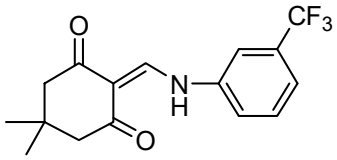
Gummy compound; TLC Rf value, 0.88 (in EtOAc:Hexane, 60:40); IR (neat) 3090, 2960, 2820, 1680, 1590, 1533, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (1H, s), 8.29 (1H, s), 8.07 (1H, s), 2.45(2H, s), 2.39 (2H, s), 1.07 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 197.4, 172.1, 165.9, 139.6, 138.1, 134.2, 132.4, 115.5, 113.1, 51.5, 50.5, 27.2, 22.1 (2C); ESI-MS: 346.00 $[M+H]^+$.

2-(((2,4-difluorophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (30):



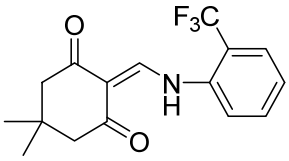
Gummy compound; TLC Rf value, 0.80 (in EtOAc:Hexane, 60:40); IR (neat) 3090, 2960, 1680, 1590, 1570, 1530, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (1H, d, J = 12 Hz), 7.40-7.34 (1H, m), 6.96-6.92 (2H, m), 2.45 (2H, s), 2.40 (2H, s), 1.07 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 196.5, 150.4, 118.8, 118.7, 112.7, 109.9, 105.4, 105.3, 105.2, 51.8, 51.5, 31.3, 28.7 (2C); ESI-MS: 280.10 $[M+H]^+$.

5,5-dimethyl-2-(((3-(trifluoromethyl)phenyl)amino)methylene)cyclohexane-1,3-dione (31):



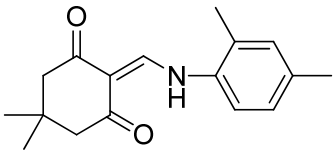
Gummy compound; TLC Rf value, 0.76 (in EtOAc:Hexane, 60:40); IR (neat) 3090, 1678, 1592, 1588, 1272 cm^{-1};...; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (IH, s), 7.07-6.65 (4H, m), 2.97 (2H, s), 2.51 (2H, s), 1.17 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 193.5, 148.9, 140.8, 128.4, 125.1, 123.0, 121.0, 120.9, 119.1, 113.9, 44.8 (2C), 28.6 (2C), 20.9; ESI-MS: 312.09 $[M+H]^+$.

5,5-dimethyl-2-(((2-(trifluoromethyl)phenyl)amino)methylene)cyclohexane-1,3-dione (**32**):



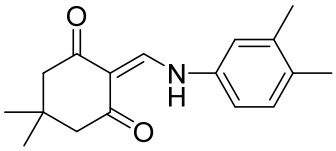
Gummy compound; TLC Rf value, 0.75 (in EtOAc:Hexane, 60:40); IR (neat) 3090, 2810, 1688, 1590, 1588, 1533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (1H, s), 8.29 (1H, d, J = 8 Hz), 7.88-7.82 (2H, m), 7.43 (1H, m), 2.53 (2H, s), 2.47 (2H, s), 1.10 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.7, 148.9, 139.9, 134.1, 127.2, 127.1, 126.3, 123.7, 123.7, 115.4, 51.3 (2C), 32.5, 28.8 (2C); ESI-MS: 312.10 $[M+H]^+$.

2-(((2,4-dimethylphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (33):



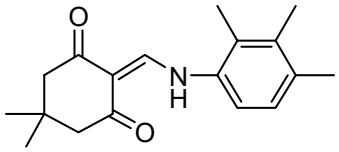
Gummy compound; TLC Rf value, 0.84 (in EtOAc:Hexane, 60:40); ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s), 8.62 (IH, s), 6.90-6.84 (2H, m), 6.55 (1H, d, J = 8 Hz), 2.44 (2H, s), 2.33 (2H, s), 2.24 (6H, s), 1.16 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.3, 148.9, 136.7, 131.2, 128.9, 126.1, 125.6, 118.3, 115.4, 51.3, 32.5, 28.8, 21.2, 18.1; ESI-MS: 272.14 $[M+H]^+$.

2-(((3,4-dimethylphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (34):



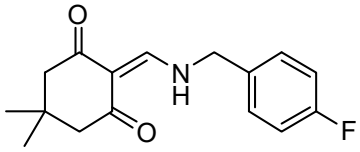
Gummy compound; TLC Rf value, 0.83 (in EtOAc:Hexane, 60:40); IR (neat) 3096, 2810, 1680, 1592, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (1H, s), 6.90 (1H, d, J = 8 Hz), 6.60 (1H, s), 6.47 (1H, d, J = 8 Hz), 2.44 (4H, s), 2.35 (3H, s), 2.31 (3H, s), 1.16 (6H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 196.6, 194.1, 150.0, 138.2, 137.1, 133.0, 129.5, 119.5, 119.3, 113.4, 51.3 (2C), 32.5, 28.8 (2C), 20.3, 19.4; ESI-MS: 272.14 $[M+H]^+$.

5,5-dimethyl-2-(((2,3,4-trimethylphenyl)amino)methylene)cyclohexane-1,3-dione (**35**):



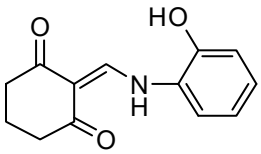
Gummy compound; TLC Rf value, 0.85 (in EtOAc:Hexane, 60:40); IR (neat) 3092, 2810, 1680, 1588, 1533 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.62 (IH, s), 6.80 (1H, d, J = 4 Hz), 6.42 (1H, d, J = 8 Hz), 2.35-2.29 (13 H, m), 1.13 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.7, 148.9, 136.4, 134.2, 131.8, 126.3, 125.7, 115.6, 115.4, 51.3 (2C), 32.5, 28.8 (2C), 19.7, 16.6, 14.3; ESI-MS: 286.34 $[M+H]^+$.

2-(((4-fluorobenzyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (36):



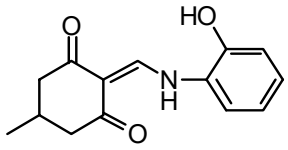
Oily compound; TLC Rf value, 0.75 (in EtOAc:Hexane, 60:40); IR (neat) 3092, 1688, 1580, 1533, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (1H, s), 7.26-7.23 (2H, m), 7.04-7.01 (2H, m), 4.46 (2H, s), 2.41 (4H, s), 1.14 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 194.7, 162.9, 160.8, 159.8, 135.5, 135.5, 129.6, 129.5, 115.9, 115.3, 51.3, 48.3, 32.5, 28.8 (2C); ESI-MS: 276.12 $[M+H]^+$.

2-(((2-hydroxyphenyl)amino)methylene)cyclohexane-1,3-dione (37):



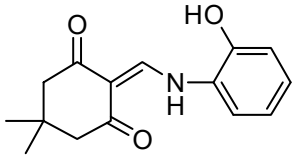
Yellowish solid; m.p. 240 ^oC; TLC Rf value, 0.45 (in EtOAc:Hexane, 60:40);); IR (neat) 2982, 2950, 1672, 1292 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 8.73 (1H, s), 7.44 (1H, d, J = 8.0 Hz), 7.12-7.08 (IH, m), 6.95-6.91 (2H, m), 3.33 (1H, s, -OH), 2.60-2.52 (4H, m), 2.07-2.01 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$/ CD_3OD) δ 201.7, 199.6, 150.9, 149.1, 128.4, 127.3, 121.3, 116.9, 116.9, 110.7, 38.5, 38.2, 20.7; HRMS calcd for $C_{13}H_{14}NO_3$ (M+H) 232.0968; found: 232.0969.

2-(((2-hydroxyphenyl)amino)methylene)-5-methylcyclohexane-1,3-dione (38):



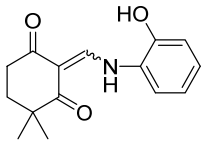
Yellowish solid; m.p. 238 ºC; TLC Rf value, 0.46 (in EtOAc:Hexane, 60:40);); IR (neat) 2982, 2950, 1670, 1582, 1290 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 12.89 (1H, d, J = 12.0 Hz), 10.55 (1H, s), 8.54 (1H, d, J = 16.0 Hz), 7.54 (1H, d, J = 8.0 Hz), 7.08-6.86 (3H, m), 2.50-2.43 (4H, m), 2.32-2.08 (4H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 199.0, 195.2, 148.5, 147.3, 126.6, 126.2, 120.1, 116.1, 115.9, 109.0, 45.5, 45.3, 26.4, 20.8; HRMS calcd for $C_{14}H_{16}NO_3$ (M+H) 246.1125; found: 246.1126.

2-(((2-hydroxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (39):



White solid; m.p. 249 ºC; TLC Rf value, 0.48 (in EtOAc:Hexane,60:40); IR (neat) 2980, 2950, 1678, 1040 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 9.86 (1H, bs), 8.66 (1H, d, J = 16.0 Hz), 7.46-7.34 (1H, m), 7.07-6.84 (3H, m), 2.46 (2H, s), 2.41 (2H, s), 1.10 (3H, s), 1.09 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 197.2, 149.6, 149.3, 147.8, 127.2, 126.6, 120.6, 120.3, 108.8, 51.5, 49.6, 31.4, 28.6 (2C); HRMS calcd for $C_{15}H_{18}NO_3$ (M+H) 260.1281; found: 260.1297.

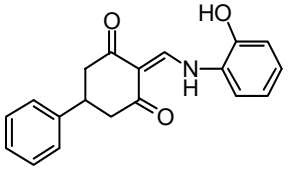
2-(((2-hydroxyphenyl)amino)methylene)-4,4-dimethylcyclohexane-1,3-dione (40): (*E:Z* mixture)



White solid; m.p180 ºC; TLC Rf value, 0.48 (in EtOAc:Hexane,60:40); IR 2980, 2955, 1678, 1580, 1290 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 13.04-12.94 (1H, m), 10.53 (1H, s), 8.58 (1H, m), 7.53 (1H, m), 7.09-6.87 (3H, m), 2.51-2.46 (2H, m), 1.81-1.80 (2H, m), 1.14 (3H, s), 1.11 (3H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 205.7, 199.7, 198.7, 195.0, 149.5, 149.5, 147.3,

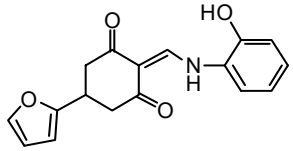
147.3, 126.5, 126.3, 120.0, 116.0, 116.0, 115.8, 107.8, 107.8, 33.7, 33.7, 32.9, 25.0, 24.8; HRMS calcd for $C_{15}H_{18}NO_3$ (M+H) 260.1281; found: 260.1297.

2-(((2-hydroxyphenyl)amino)methylene)-5-phenylcyclohexane-1,3-dione (41):



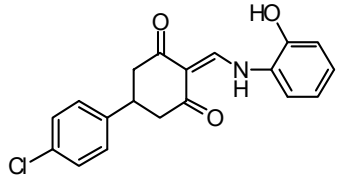
Yellow solid; m.p. 261 ºC; TLC Rf value, 0.59 (in EtOAc:Hexane,60:40); IR 3040, 2610, 1674, 1580, 1440, 1272, 1255, 1025 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 12.98 (1H, d, J = 12.0 Hz), 10.62 (1H, s), 8.61 (1H, d, J = 16.0 Hz), 7.60-6.98 (9H, m), 2.92-2.50 (5H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 198.1, 194.3, 148.7, 147.4, 143.5, 128.1, 127.4, 126.8 (2C), 126.1 (2C), 125.2, 120.1, 116.2, 115.9, 109.0, 44.4, 44.2, 36.0; HRMS calcd for $C_{19}H_{18}NO_3$ (M+H) 308.1281; found: 308.1290.

5-(furan-2-yl)-2-(((2-hydroxyphenyl)amino)methylene)cyclohexane-1,3-dione (42):



Brownish solid; m.p. 236 ºC; TLC Rf value, 0.52 (in EtOAc:Hexane,60:40); IR (neat) 2988, 2945, 1672, 1592, 1570, 1266, 1254 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 12.90 (1H, d, J = 16 Hz), 10.58 (1H, s), 8.56 (1H, d, J = 16 Hz), 7.55 (2H, m), 7.07-6.86 (3H, m), 6.35 (1H, s), 6.13 (1H, s), 2.88-2.50 (5H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ197.5, 193.7, 156.3, 148.6, 147.4, 141.9, 126.7, 126.1, 120.1, 116.1, 115.8, 110.4, 109.2, 104.9, 41.5, 41.3, 30.4; ESI-MS: 298.09 $[M+H]^+$.

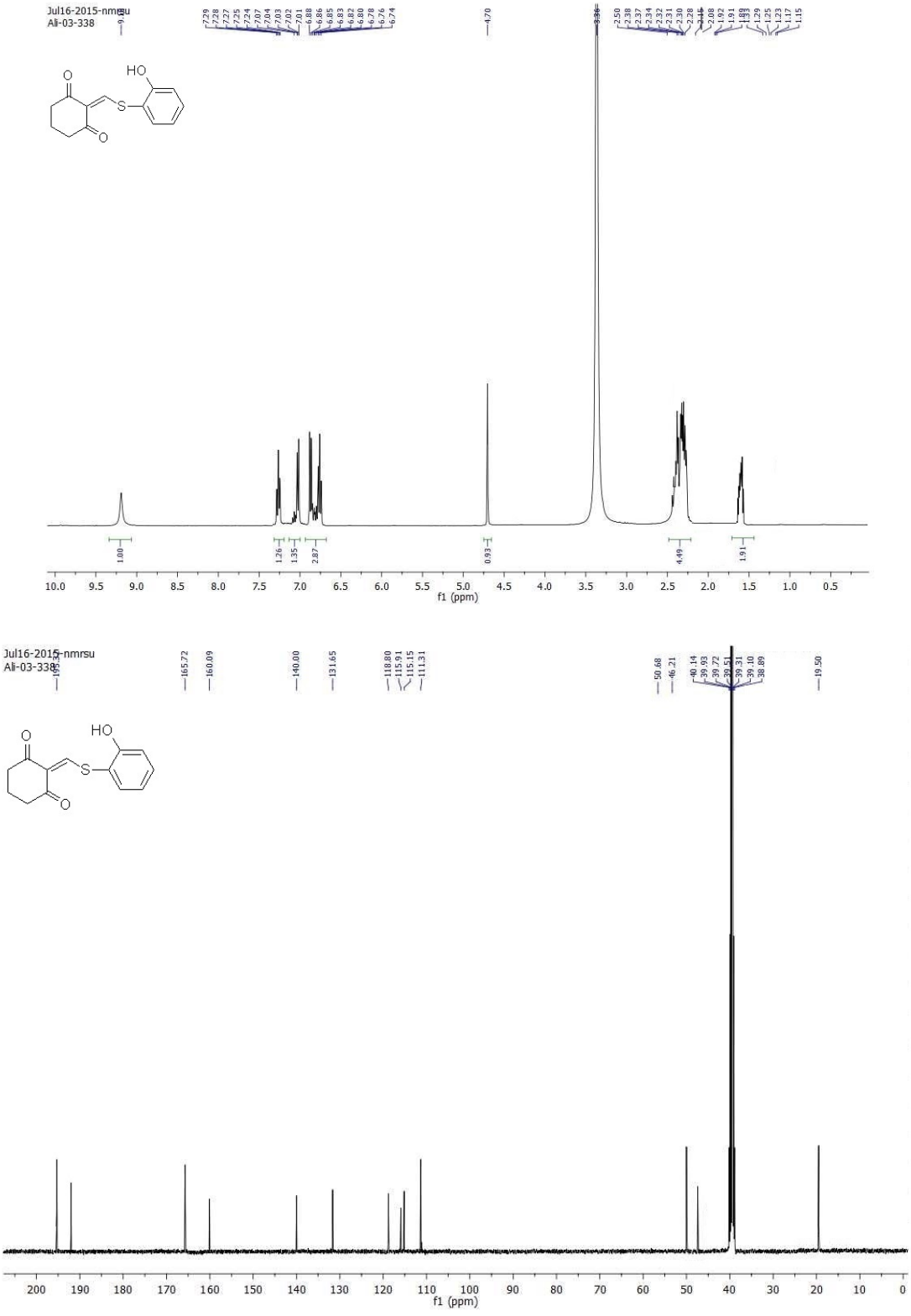
5-(4-chlorophenyl)-2-(((2-hydroxyphenyl)amino)methylene)cyclohexane-1,3-dione (43):



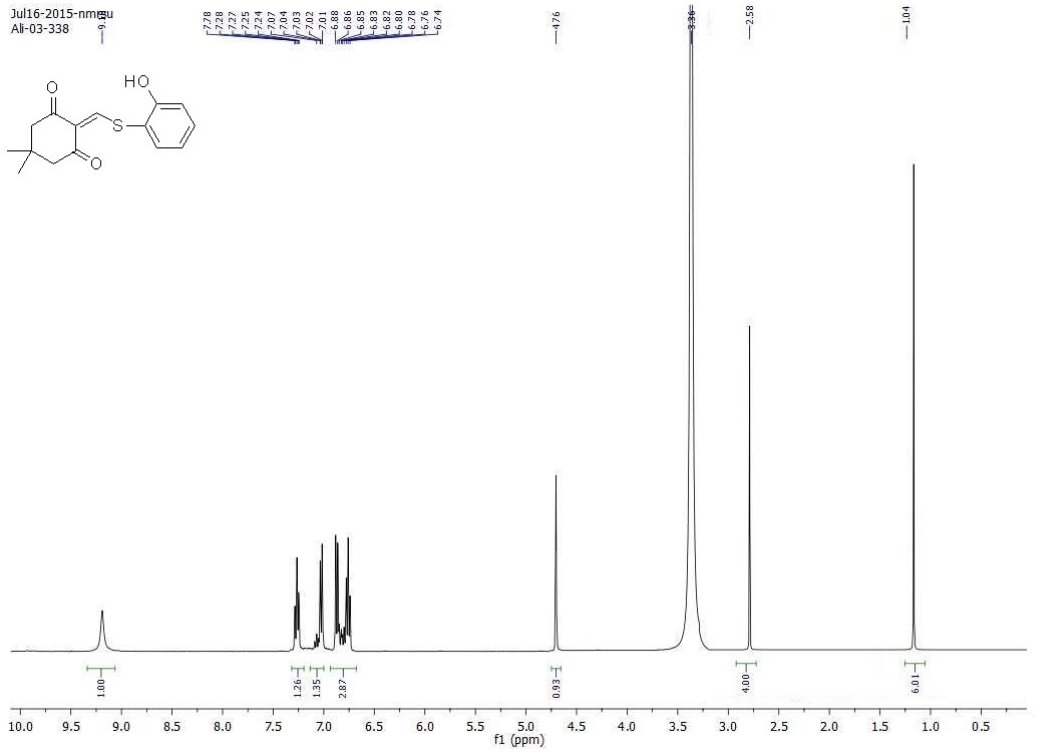
Light brown solid; m.p. 102 ºC; TLC Rf value, 0.59 (EtOAc:Hexane,60:40); IR 2995, 2920, 2892, 1680, 1612, 1493, 1182, 820 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 14.28 (1H, s),11.92 (1H, s), 9.94 (1H, d, J = 16.0 Hz), 8.92-8.23 (8H, m), 4.23-3.83 (5H, m); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 198.4, 194.3, 148.7, 147.4, 142.9, 142.5, 142.1, 131.1, 128.8, 128.5, 126.8, 126.1, 120.1, 116.2, 115.9, 109.1, 44.4, 44.2, 36.0; HRMS calcd for $C_{19}H_{17}ClNO_3$ (M+H) 342.0891; found: 342.0888.

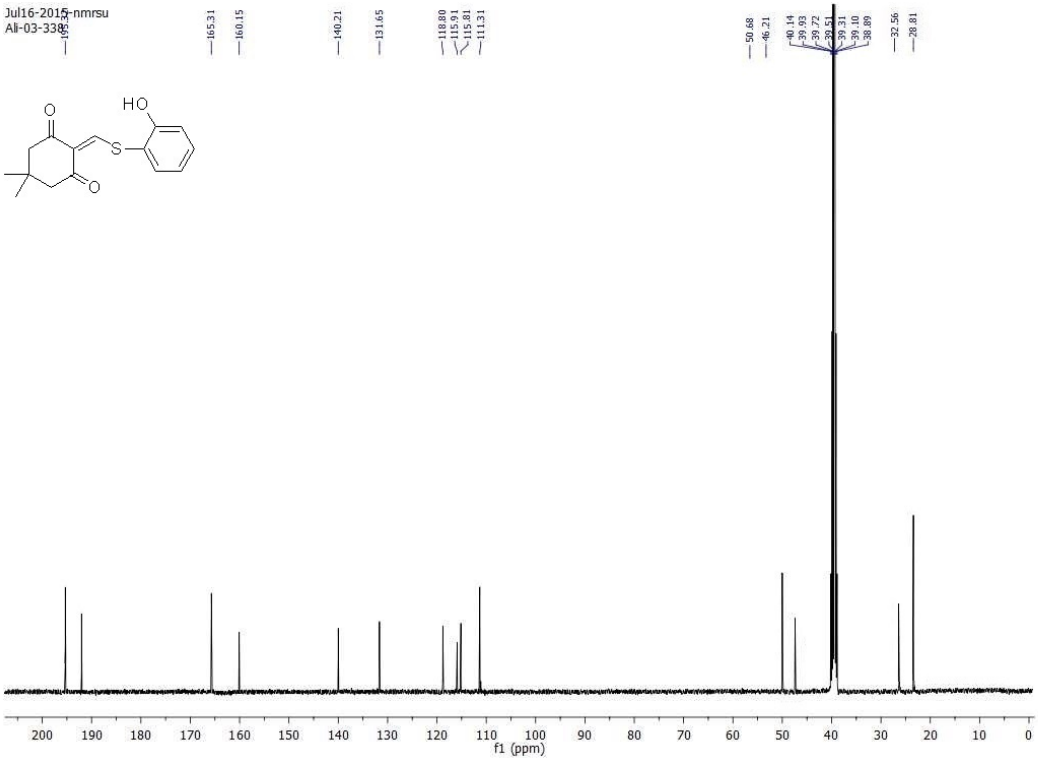
C. ^{1}H and ^{13}C NMR spectra of compounds 5-43

^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **5**

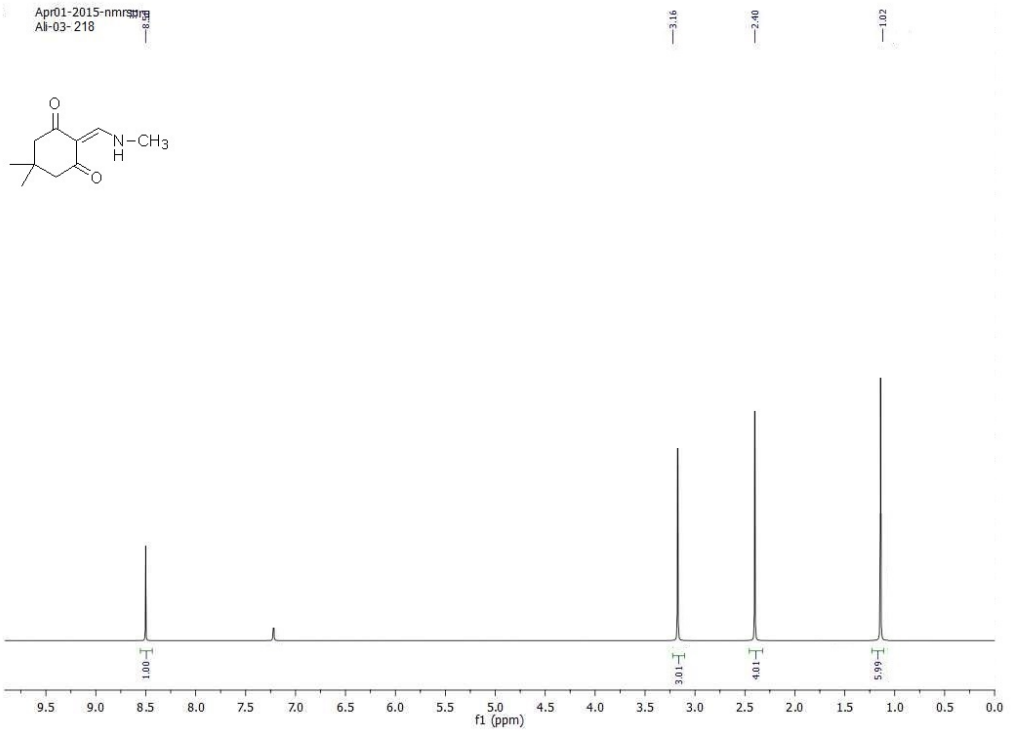


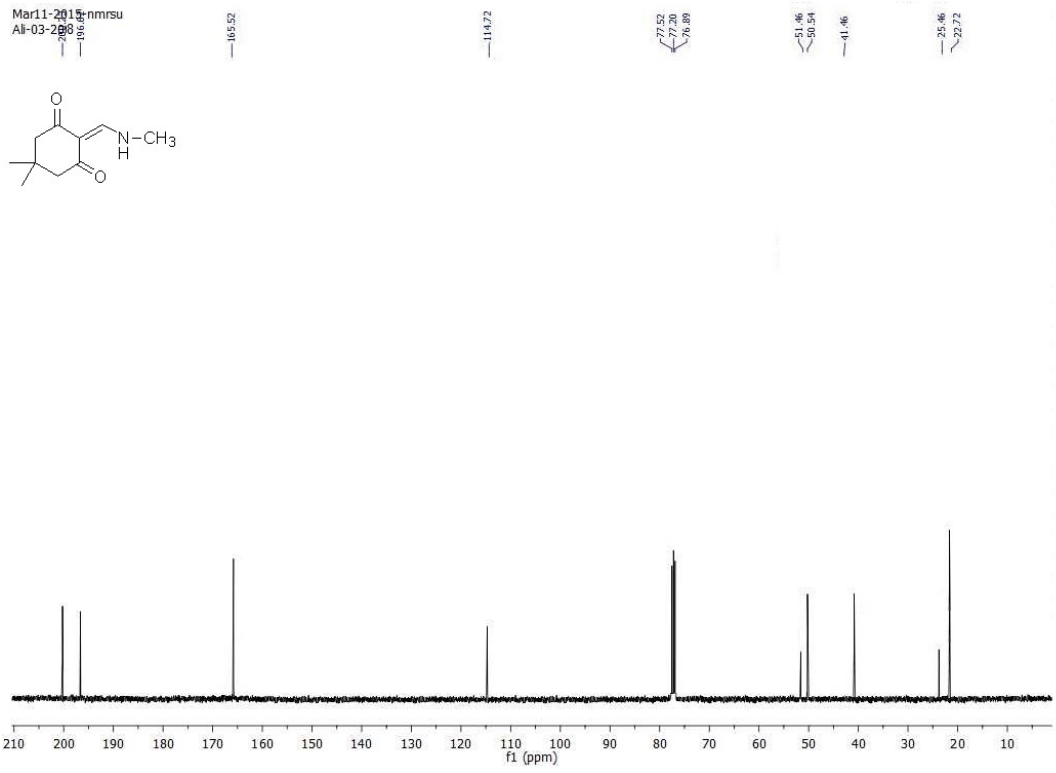
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **6**



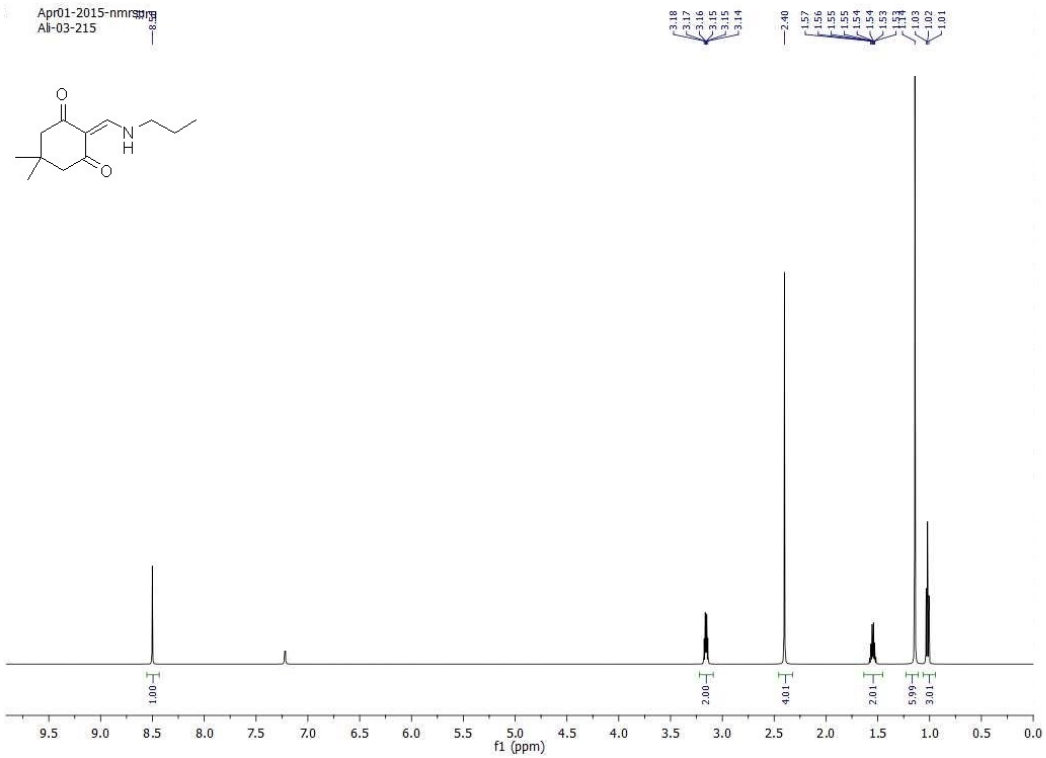


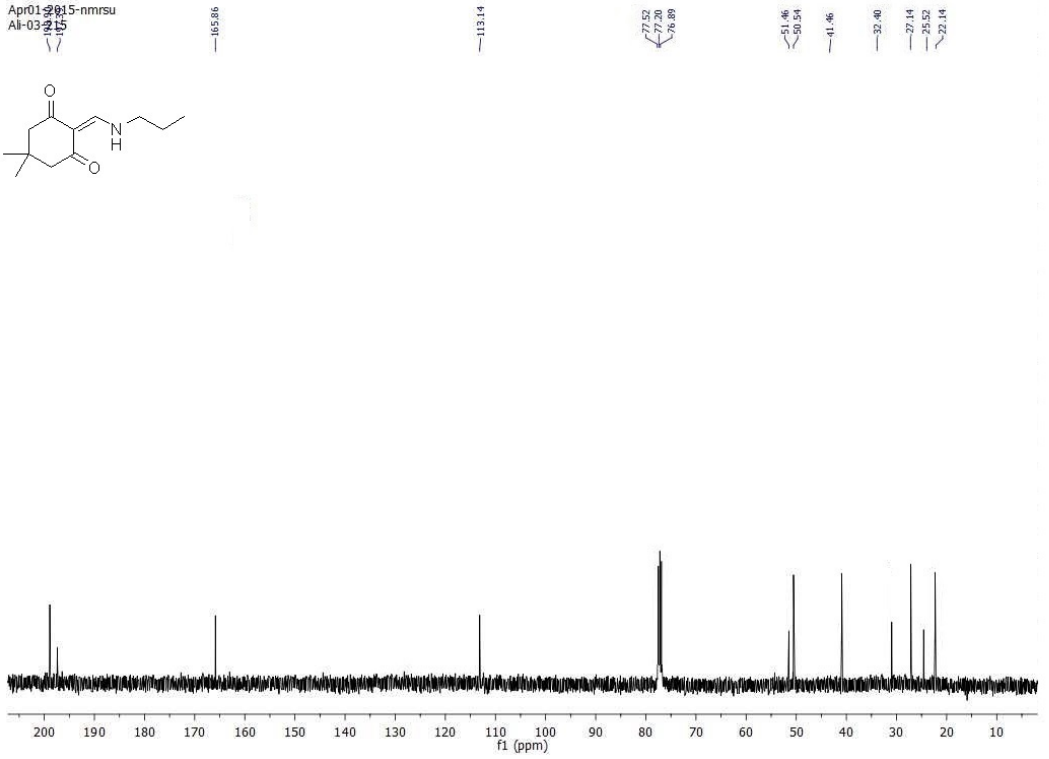
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **7**



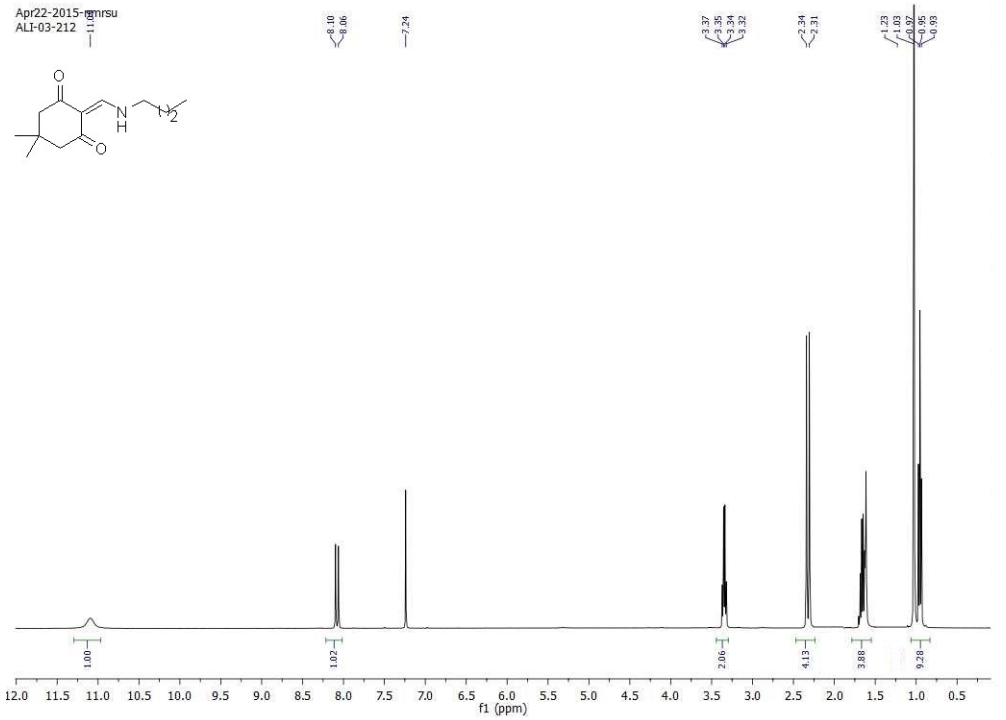


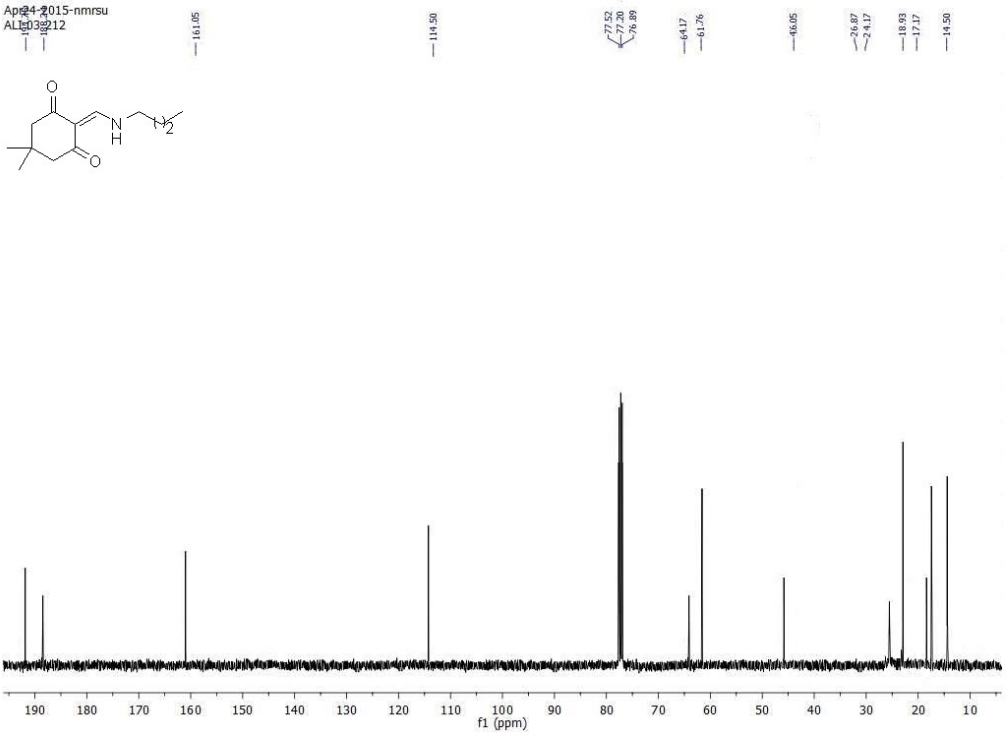
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **8**



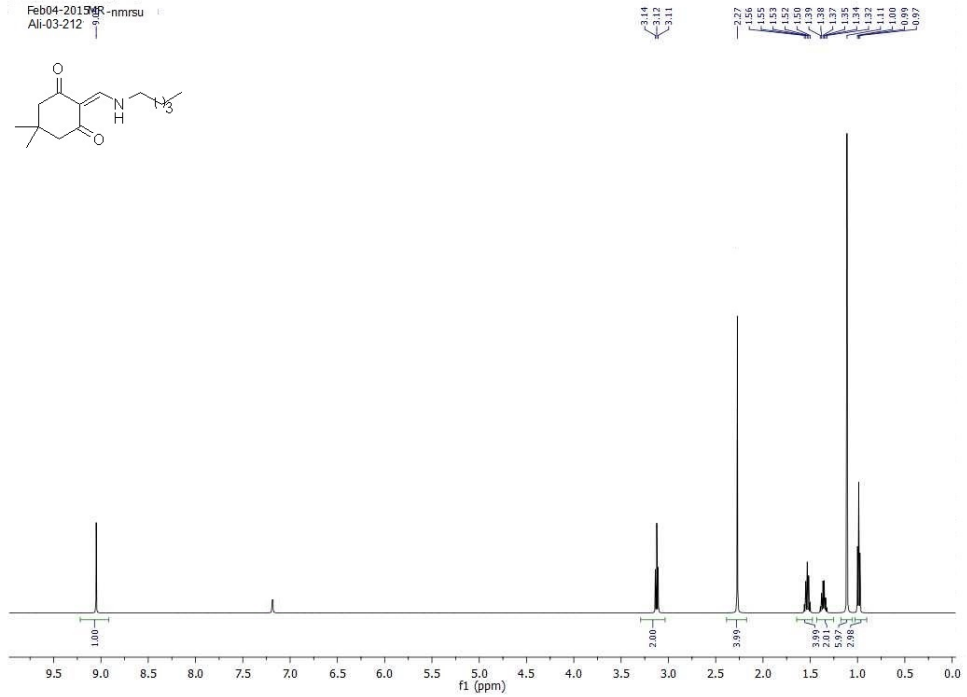


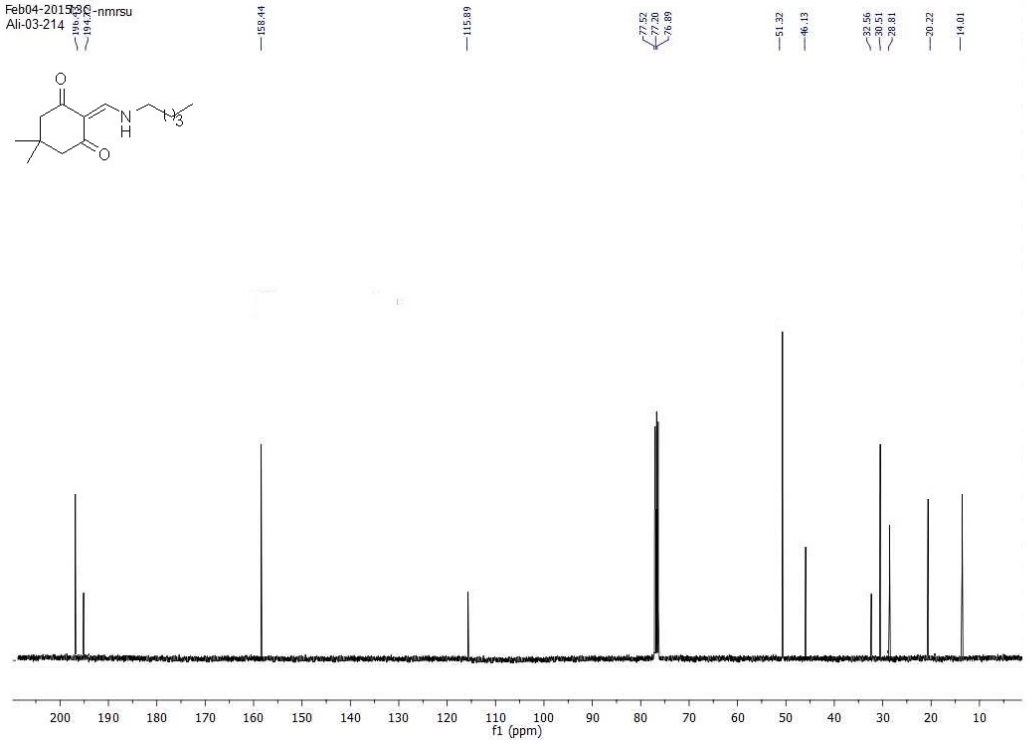
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **9**



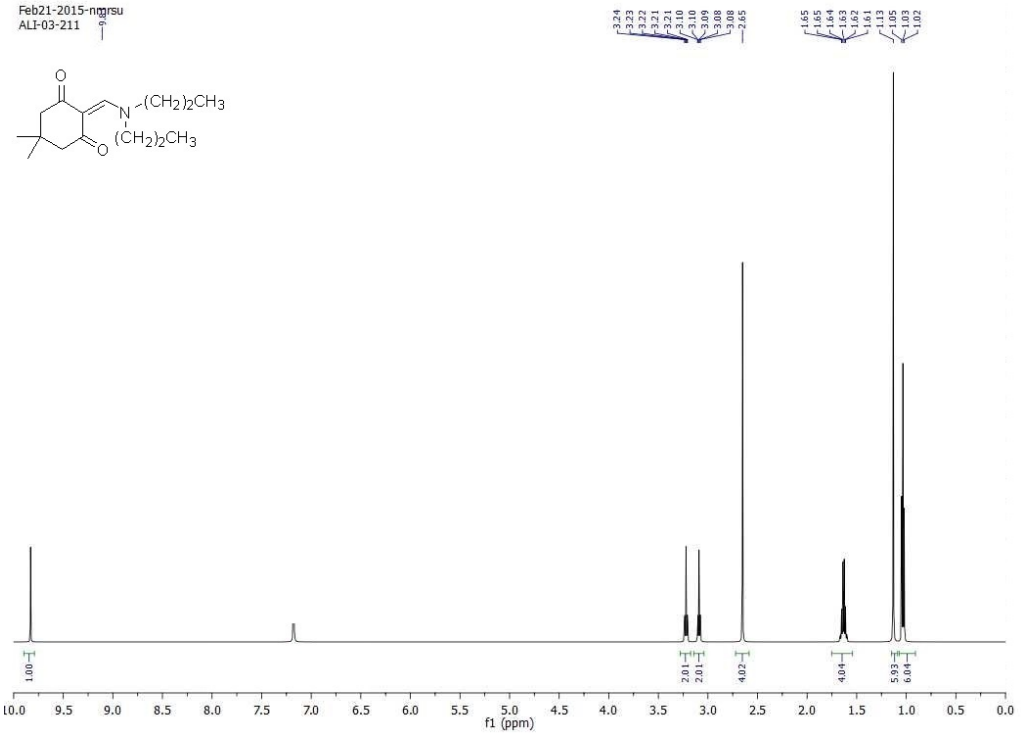


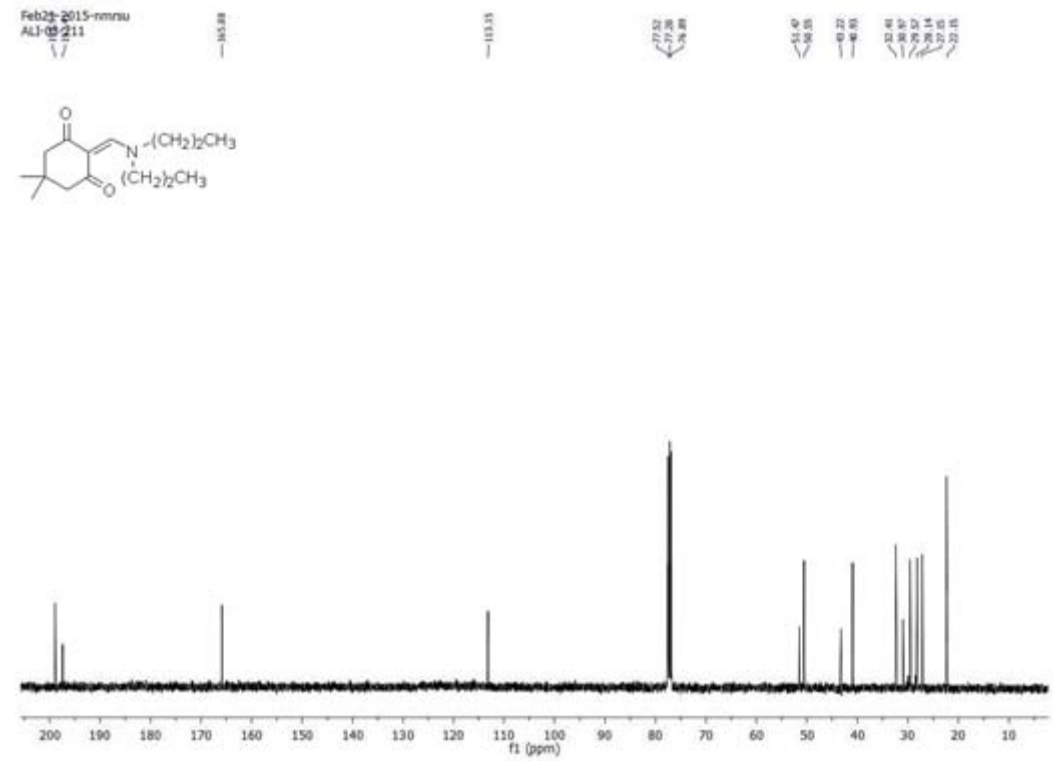
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **10**



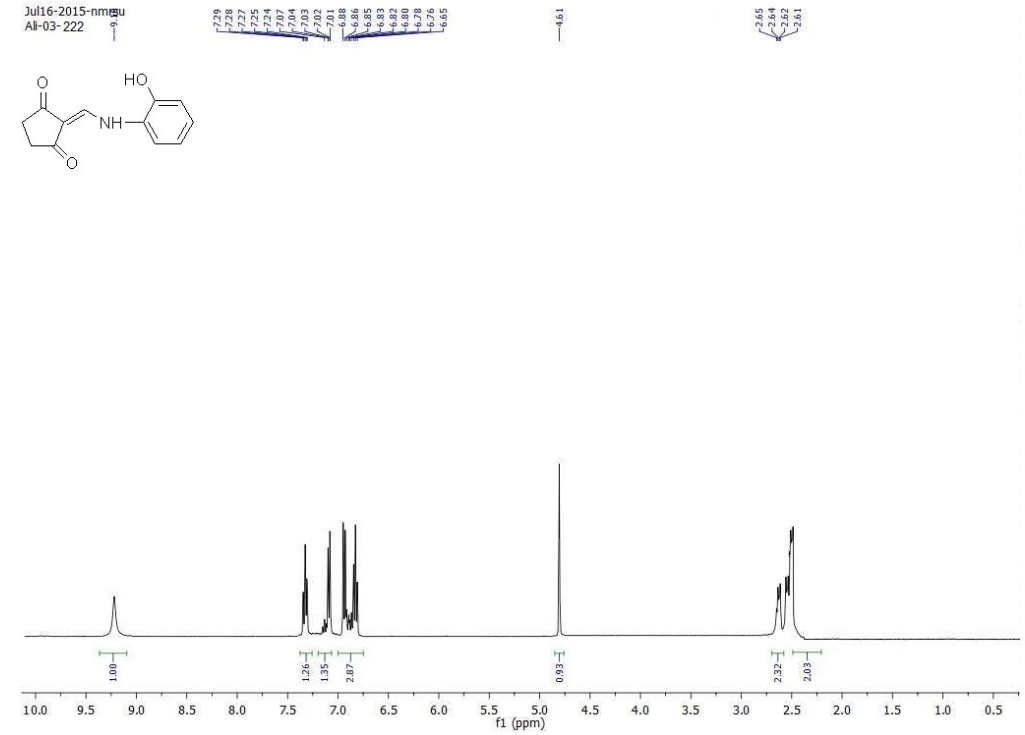


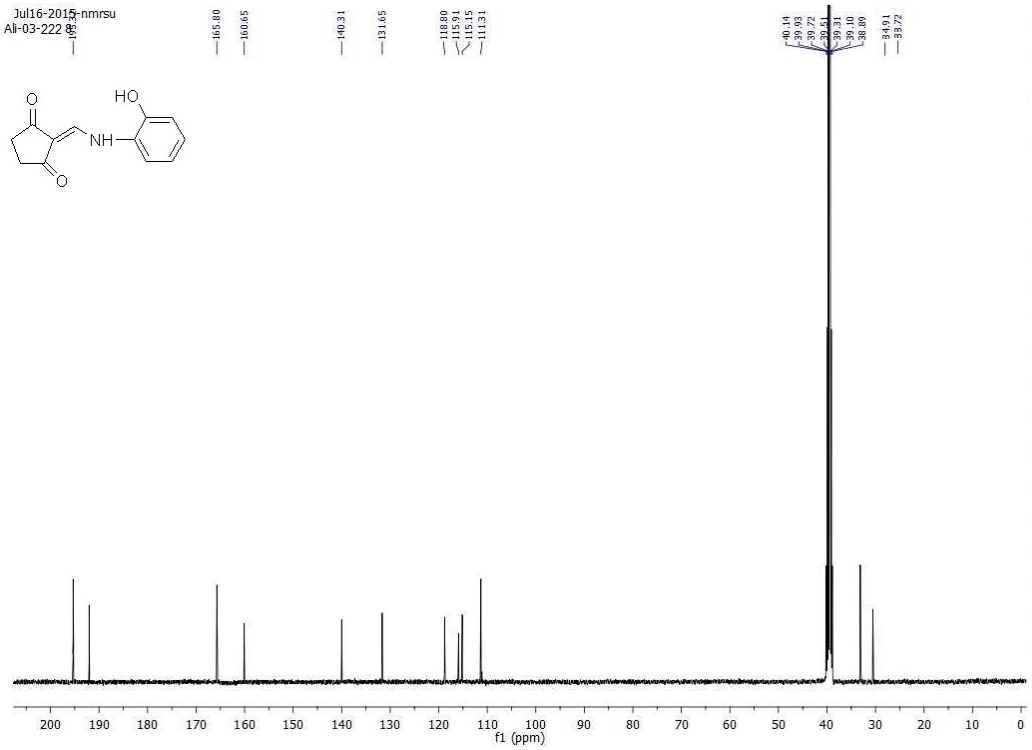
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **11**



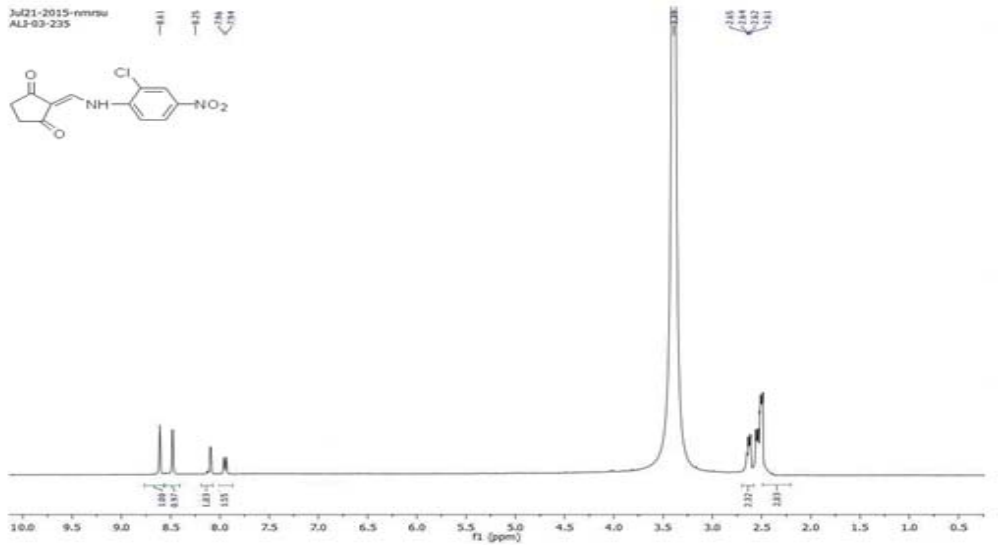


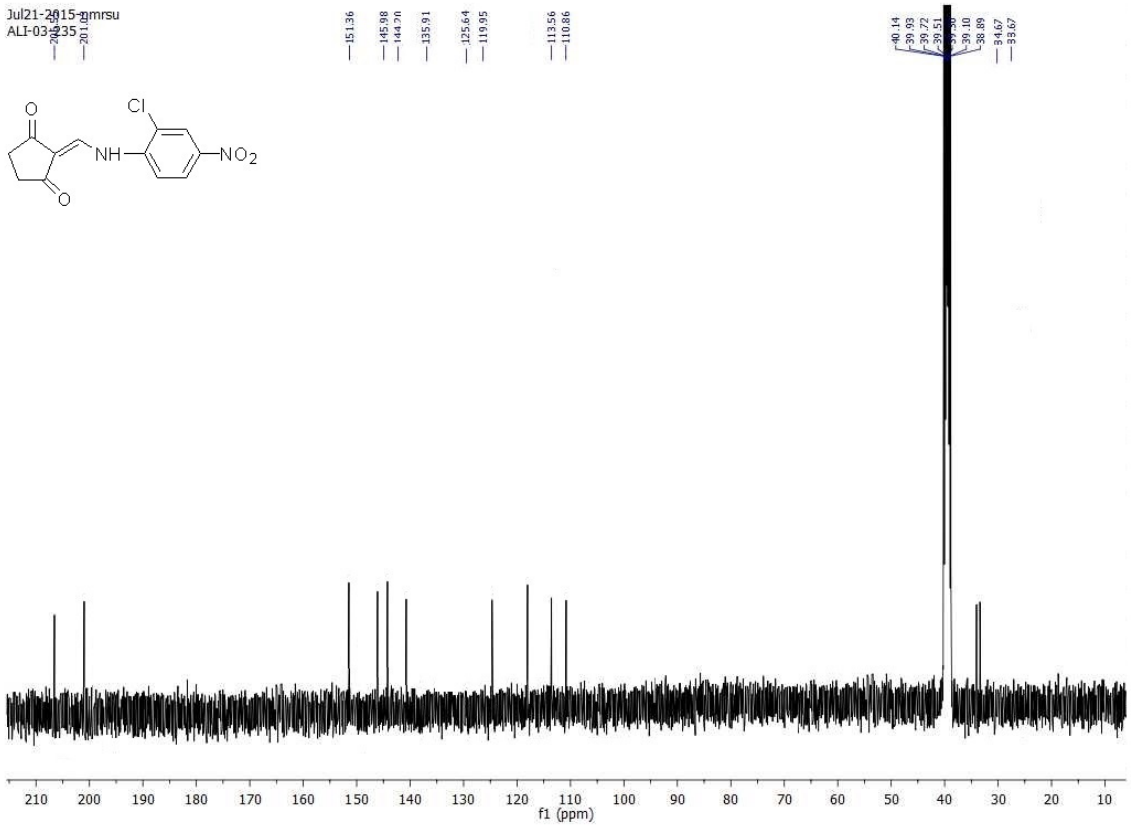
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **12**



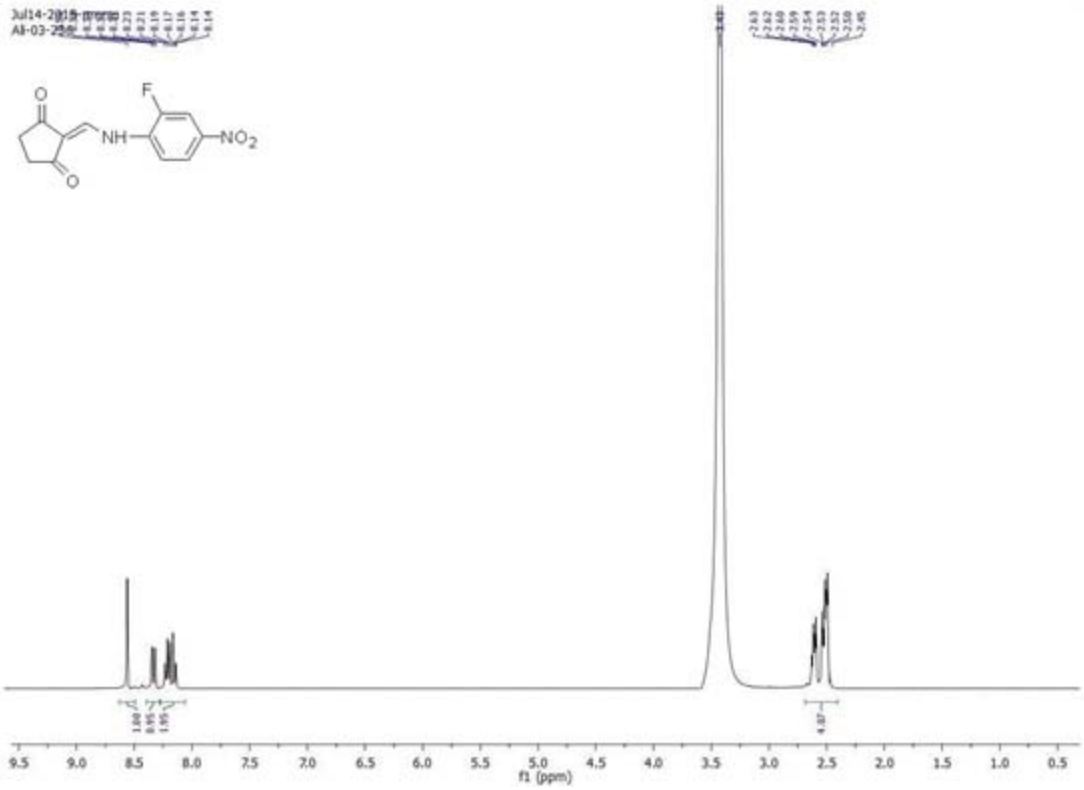


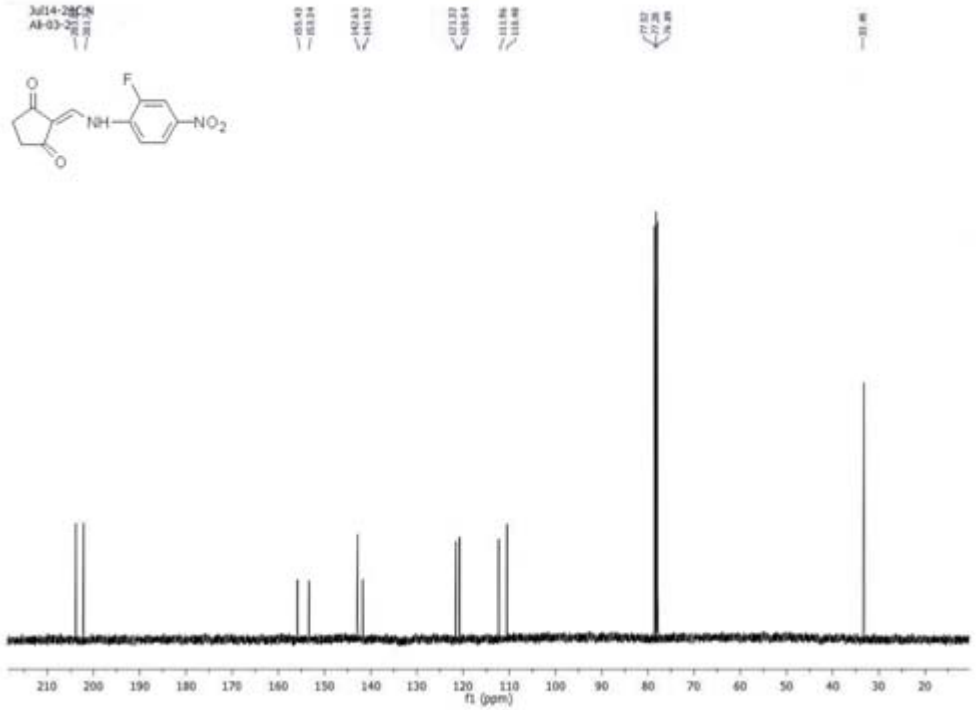
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **13**



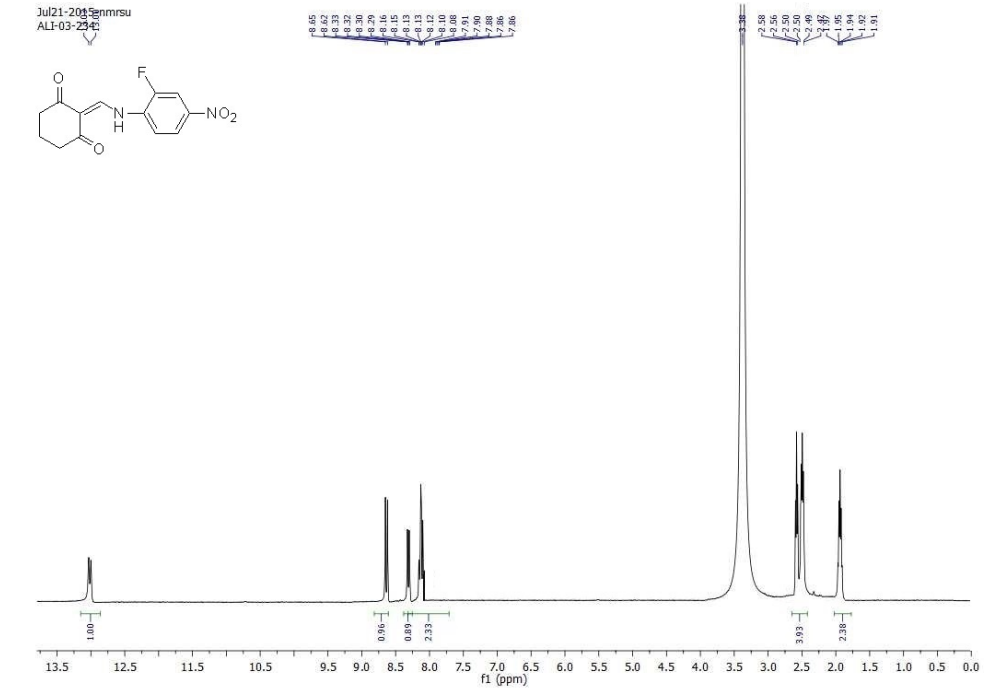


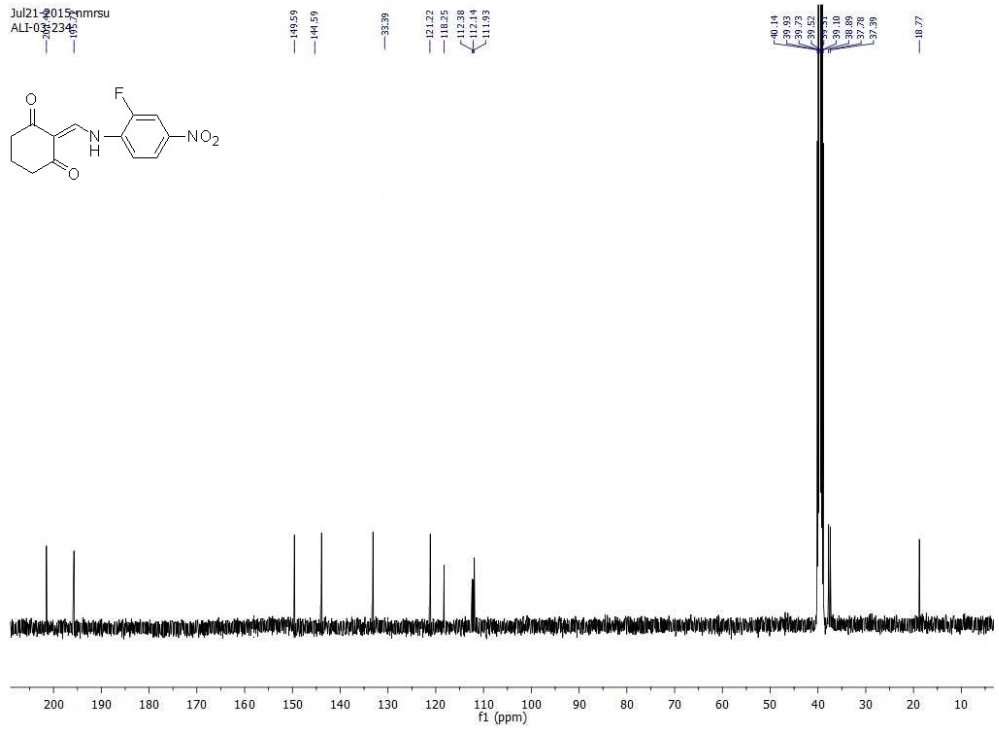
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **14**



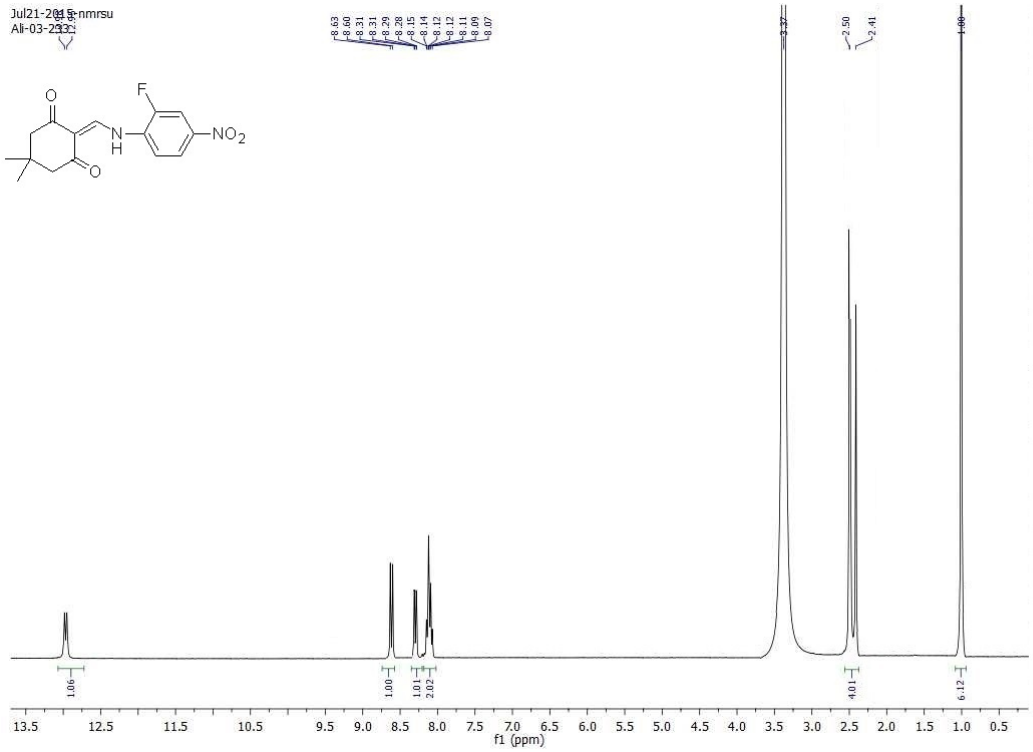


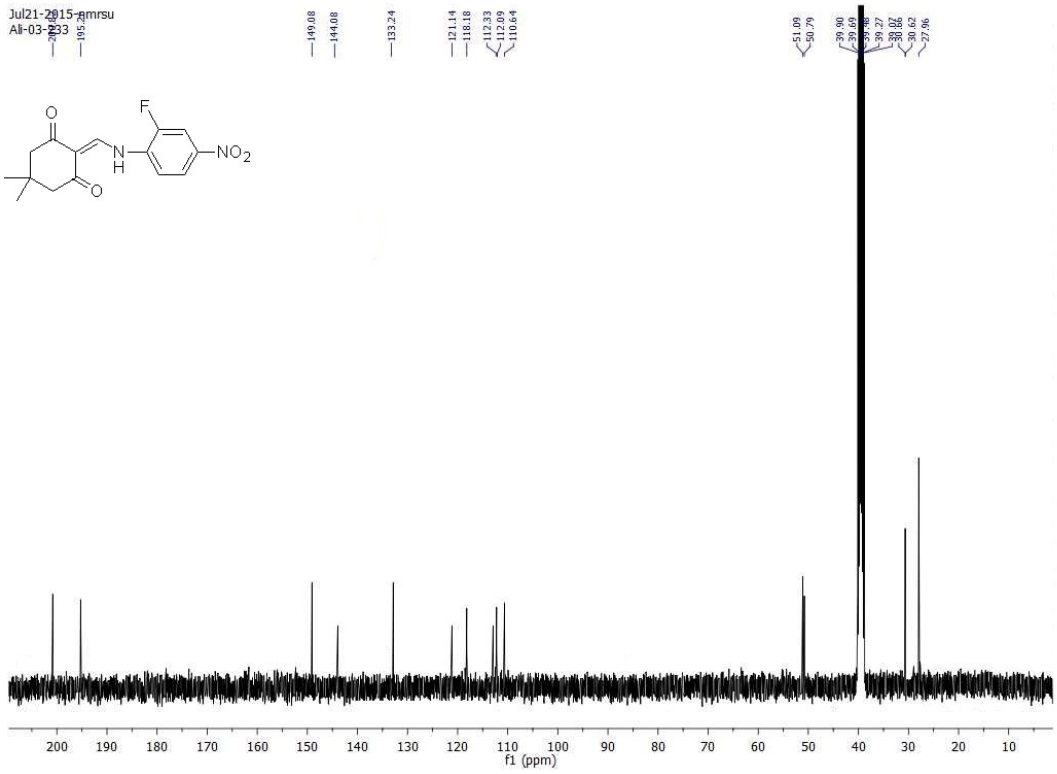
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **15**



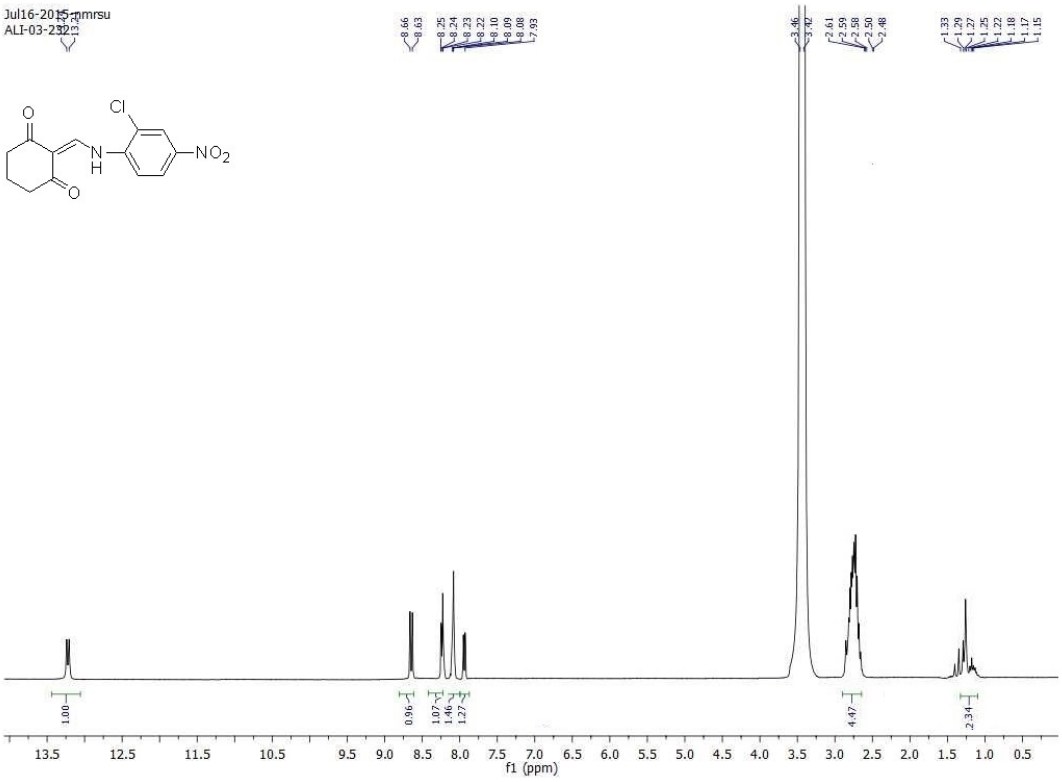


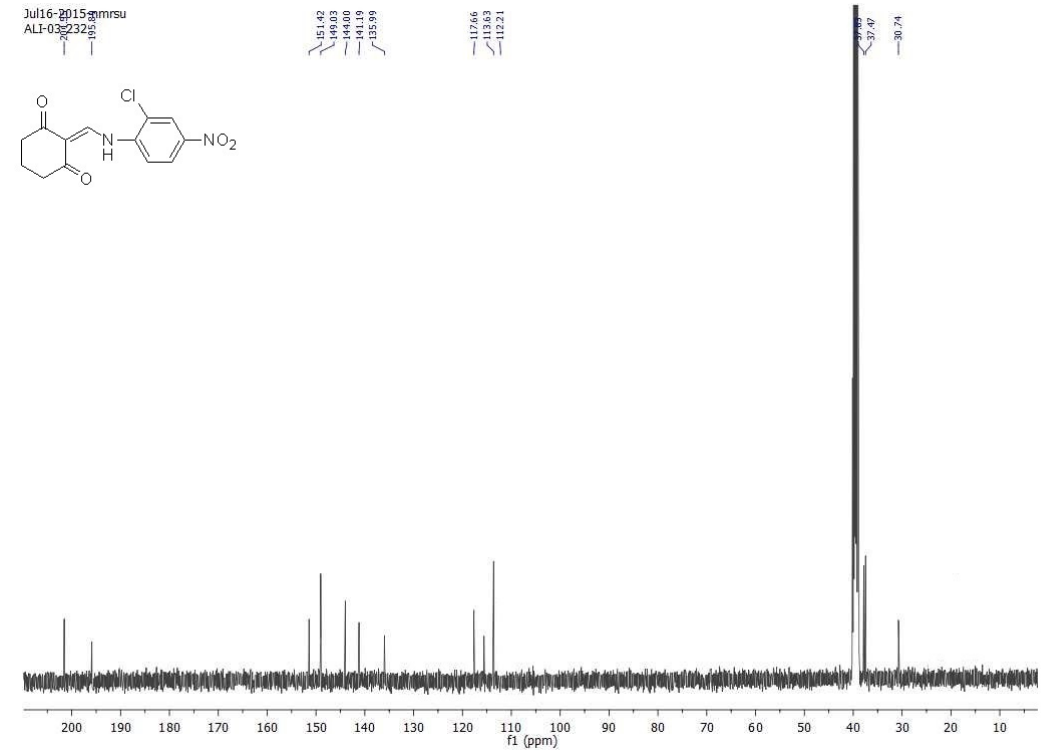
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **16**



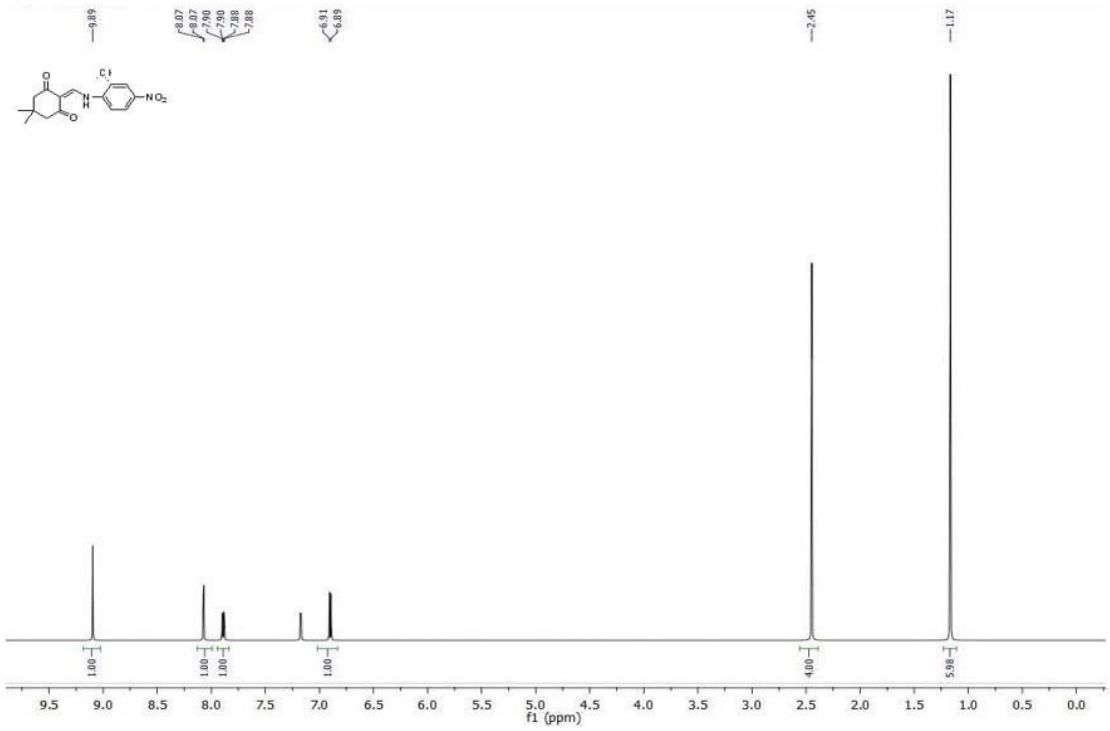


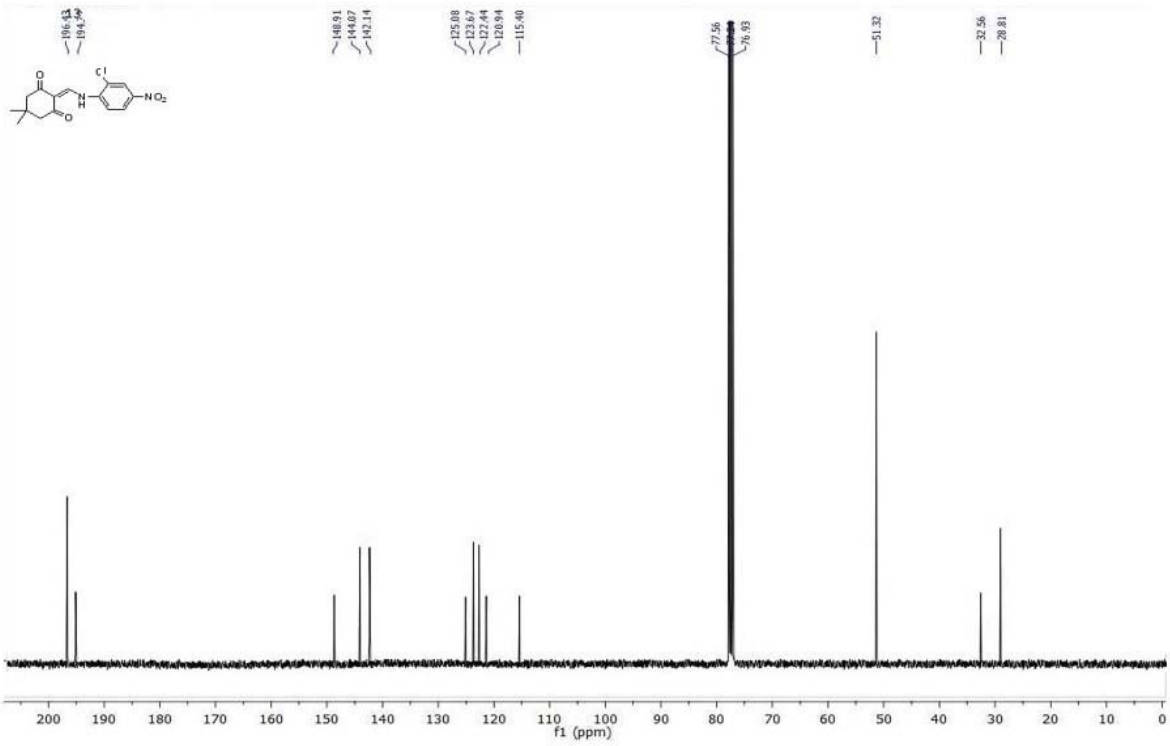
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **17**



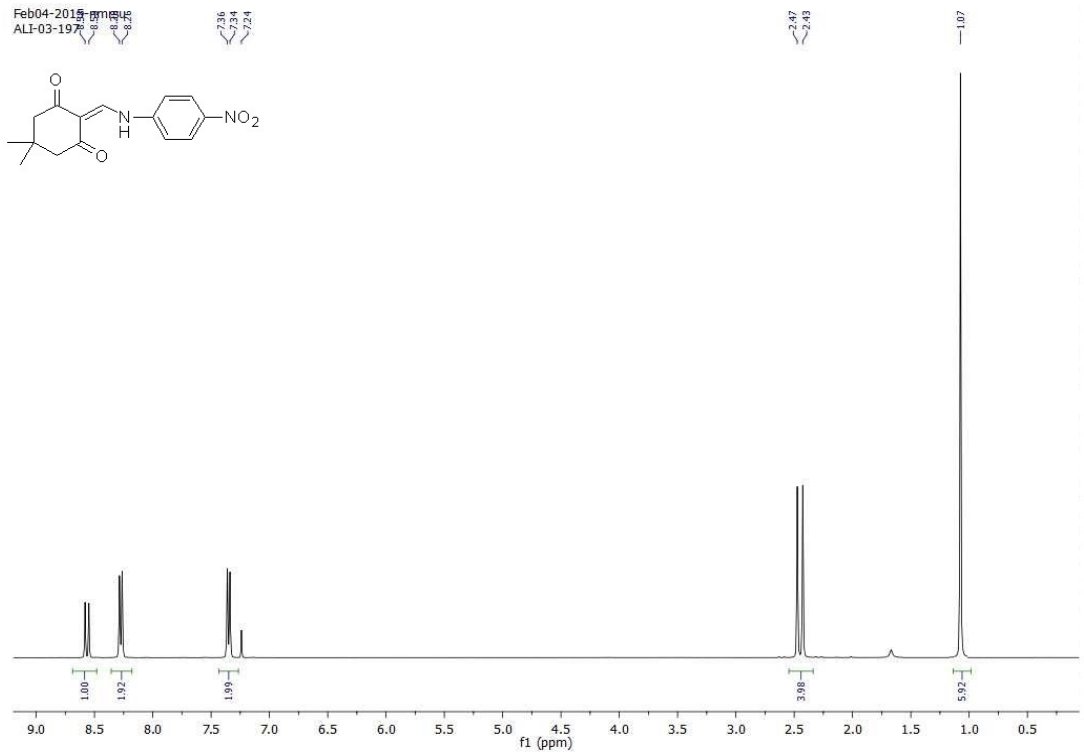


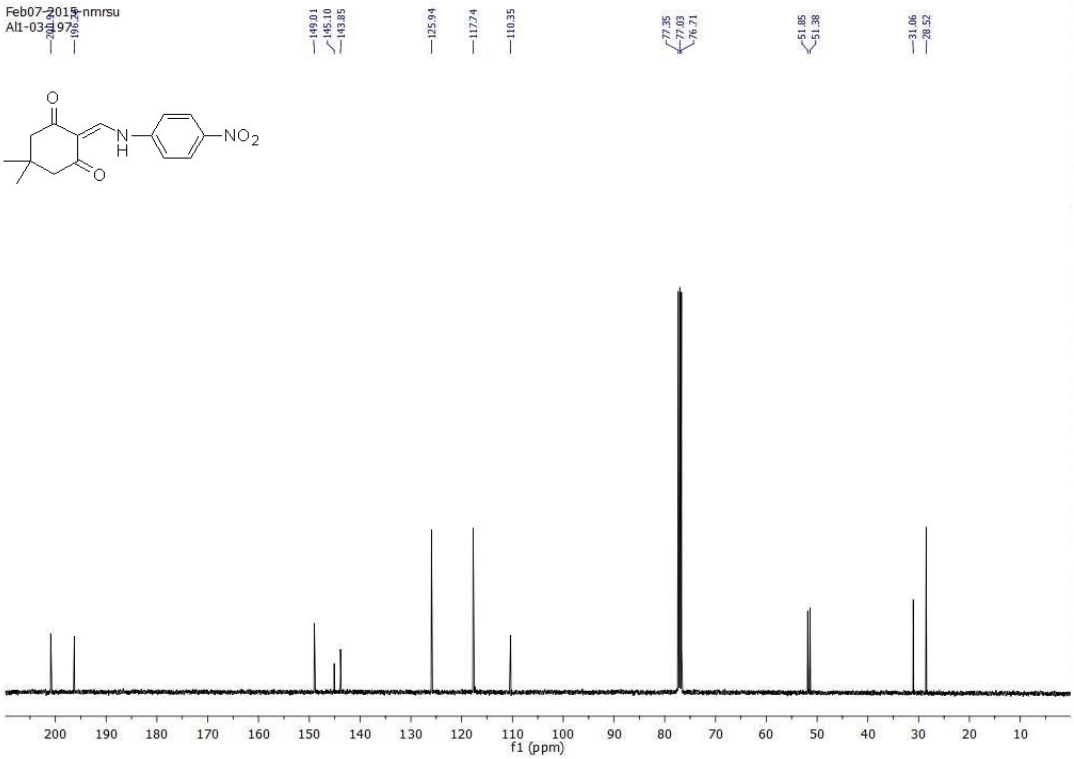
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **18**



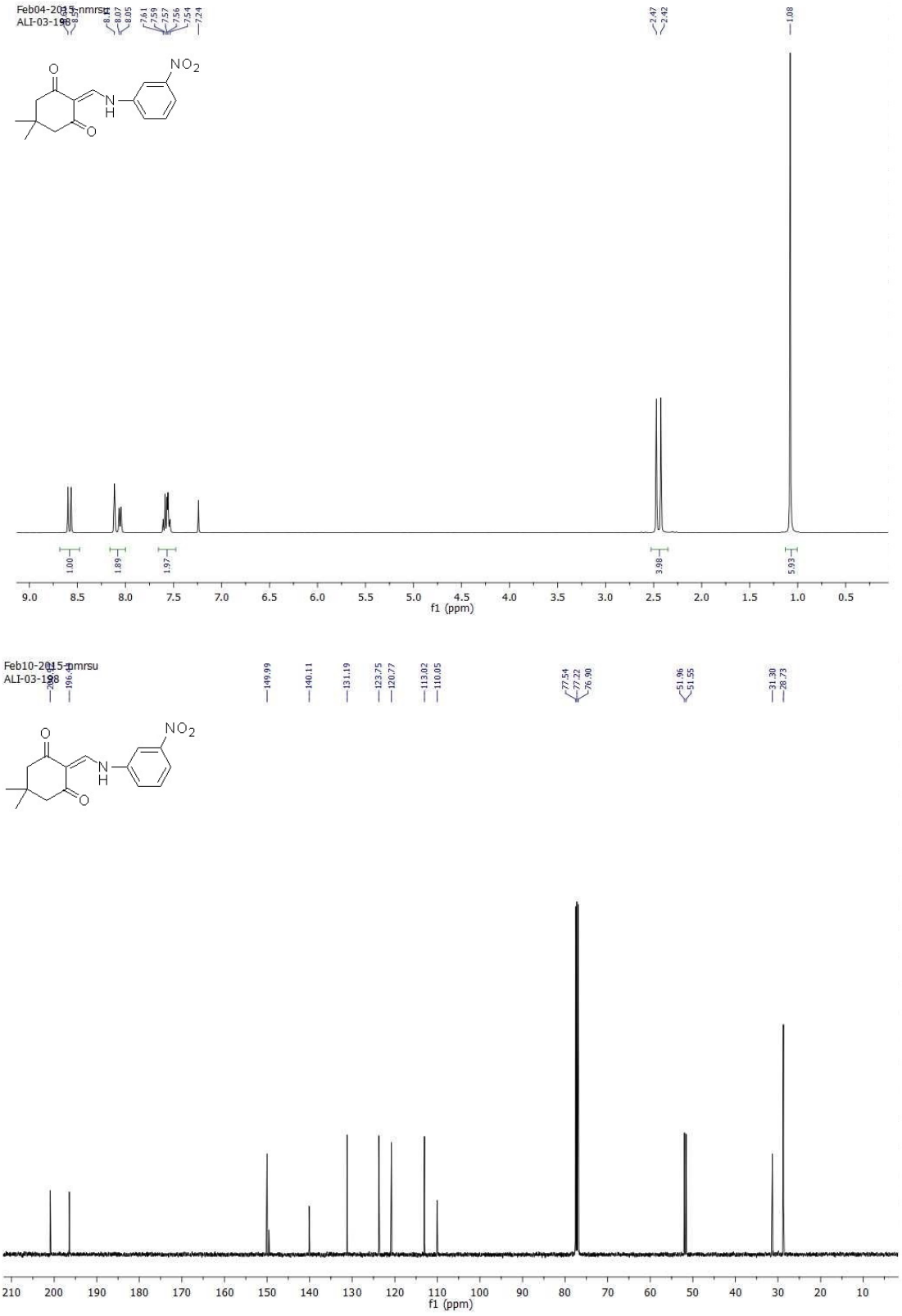


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **19**

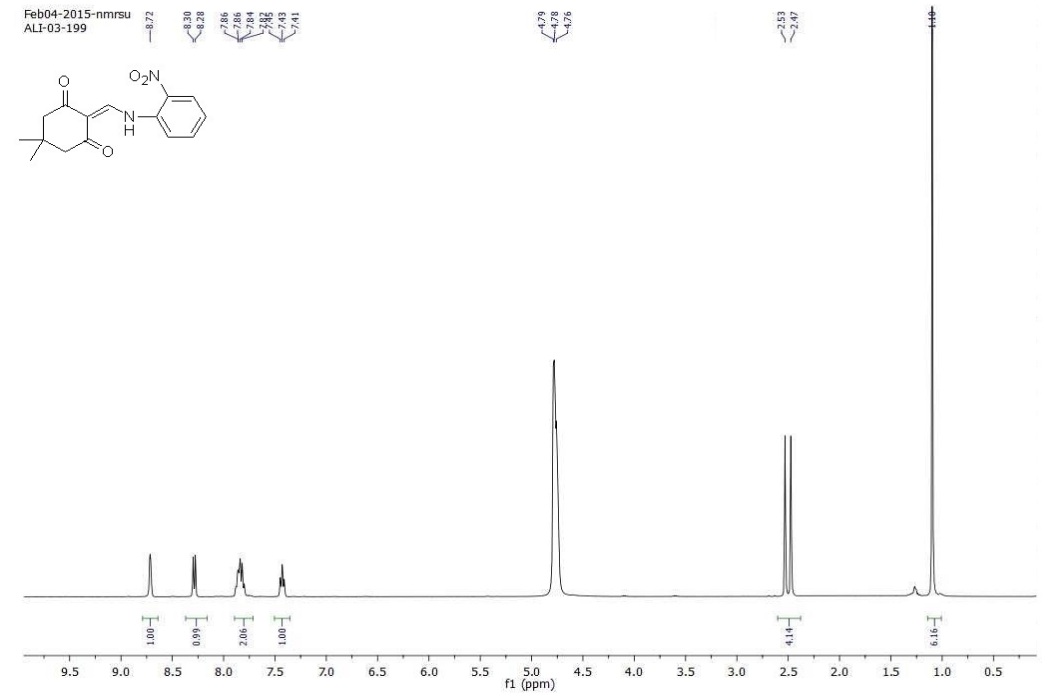


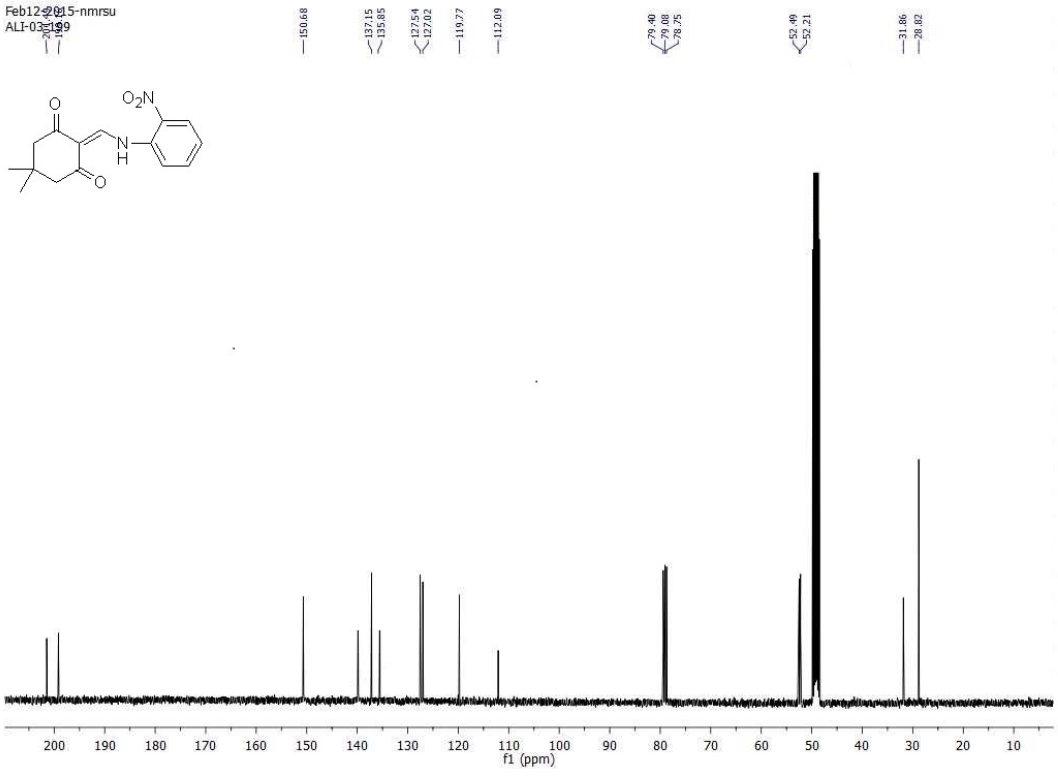


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **20**

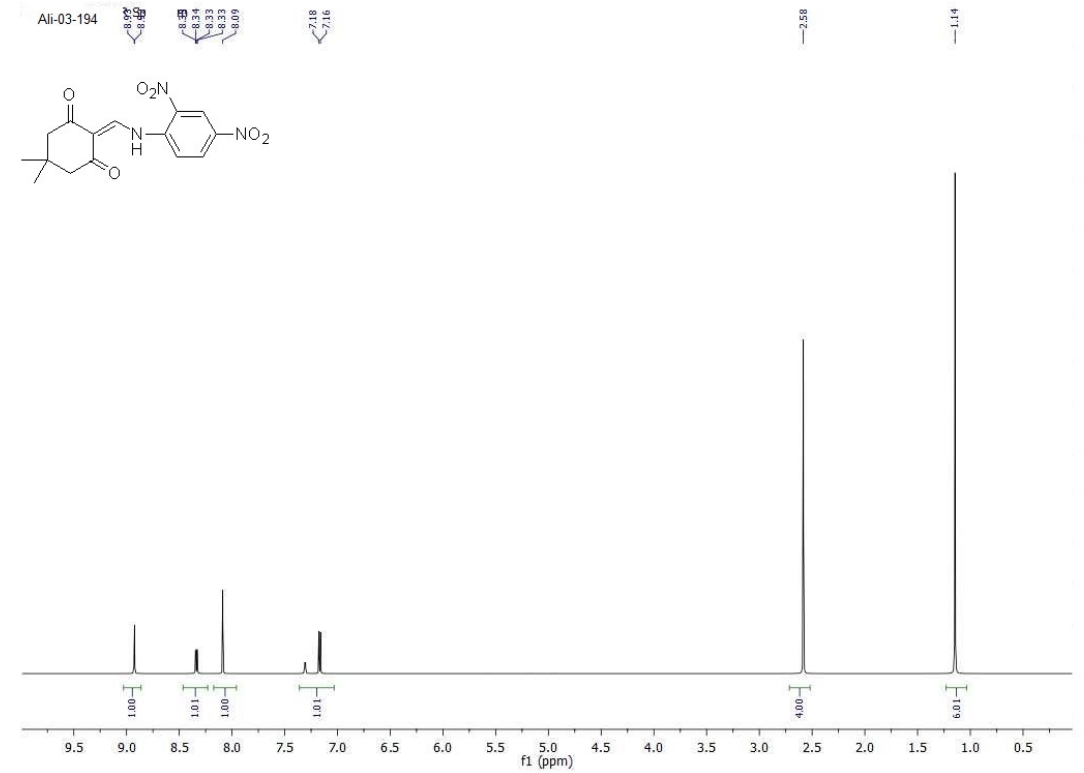


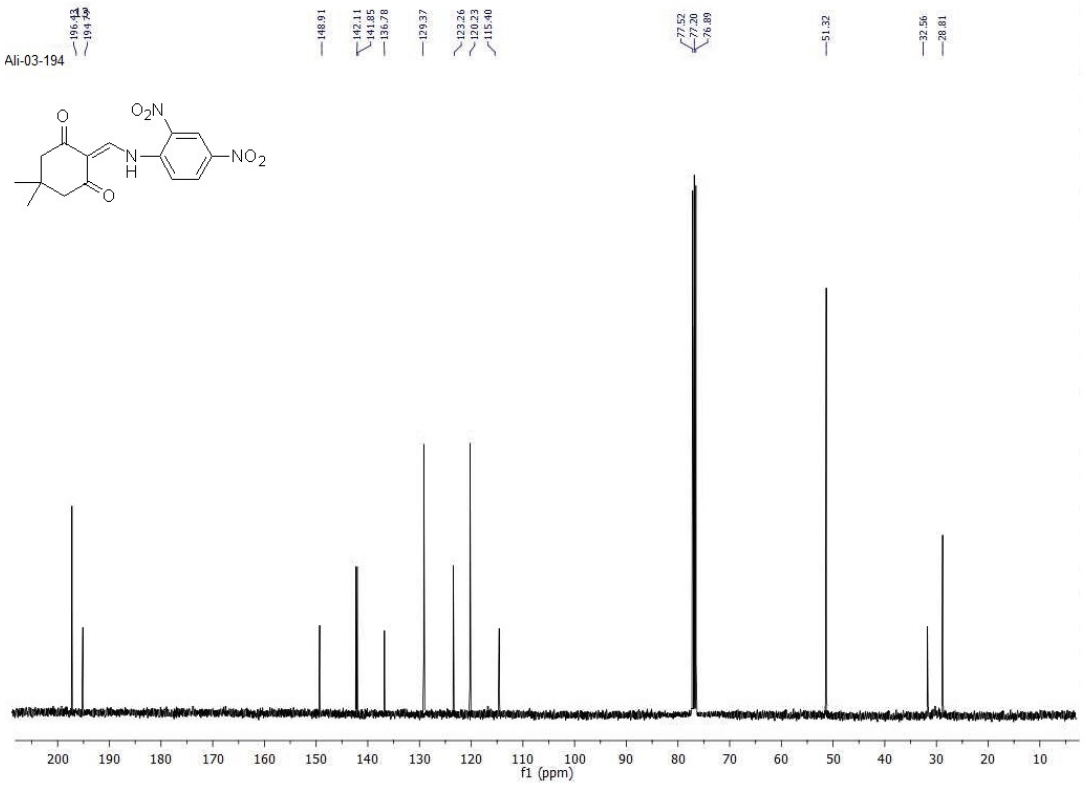
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (101 MHz, $CD_3OD/CDCl_3$) of compound **21**



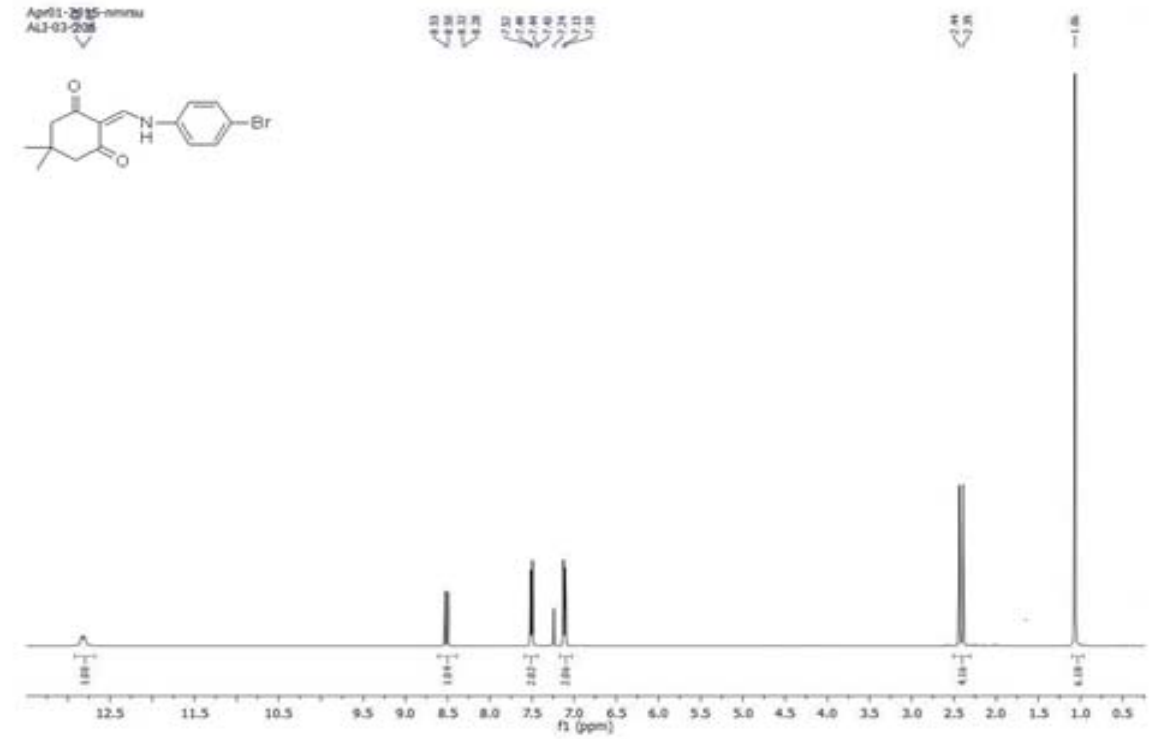


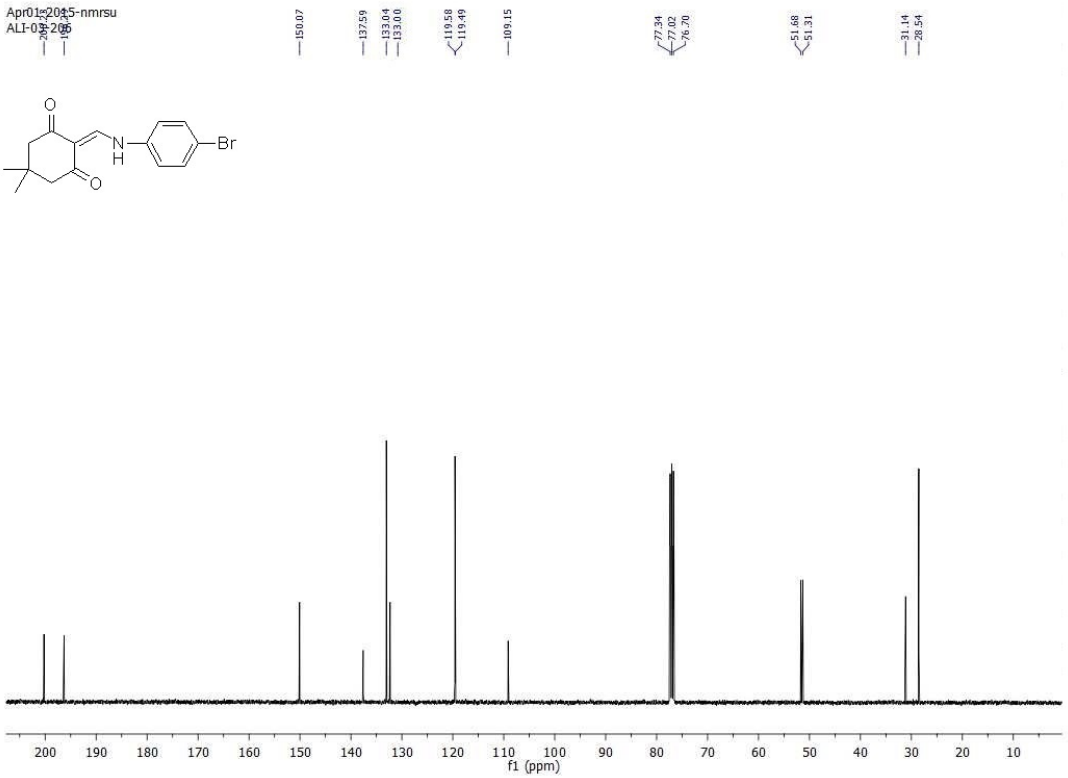
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **22**



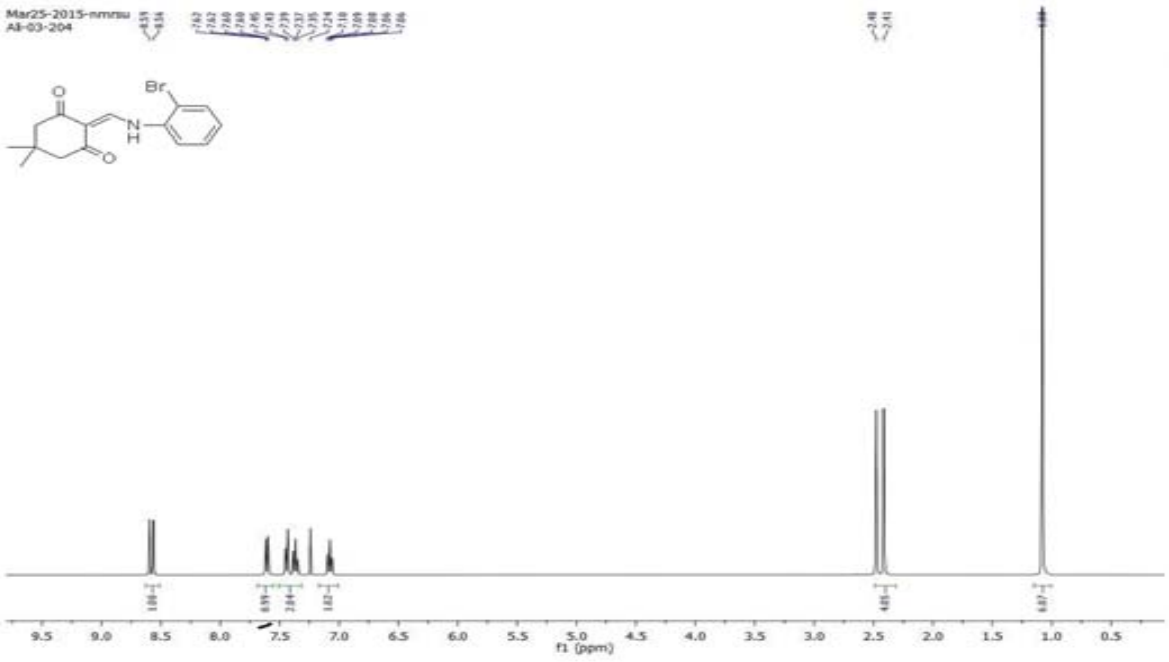


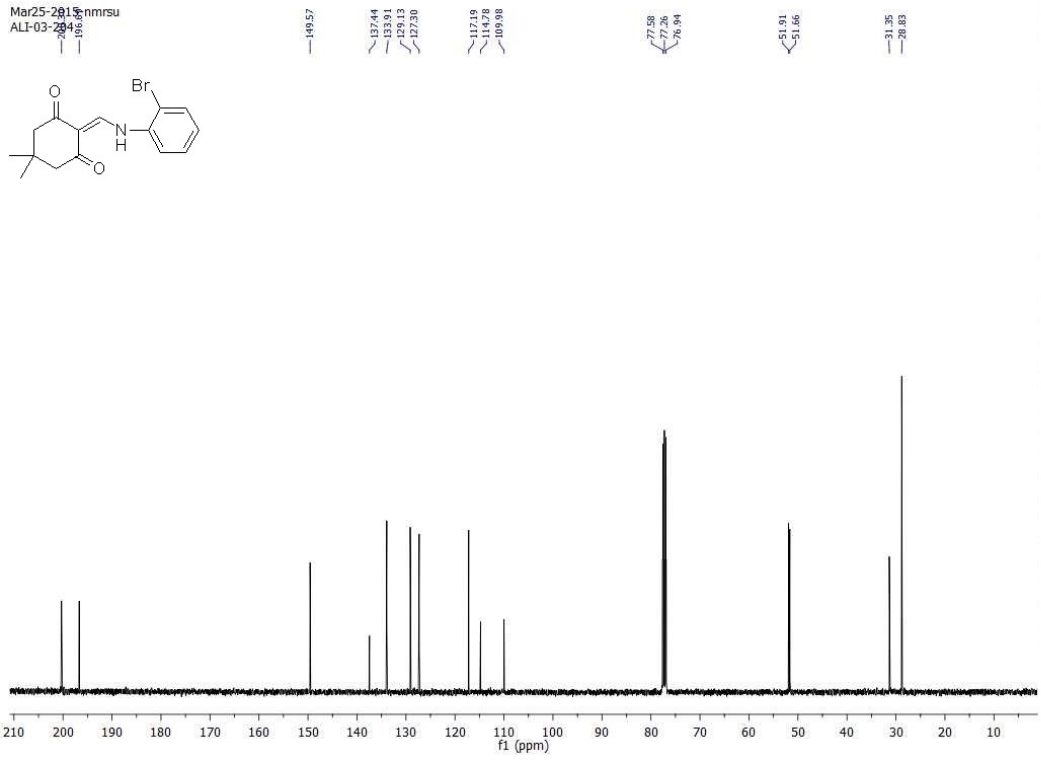
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **23**



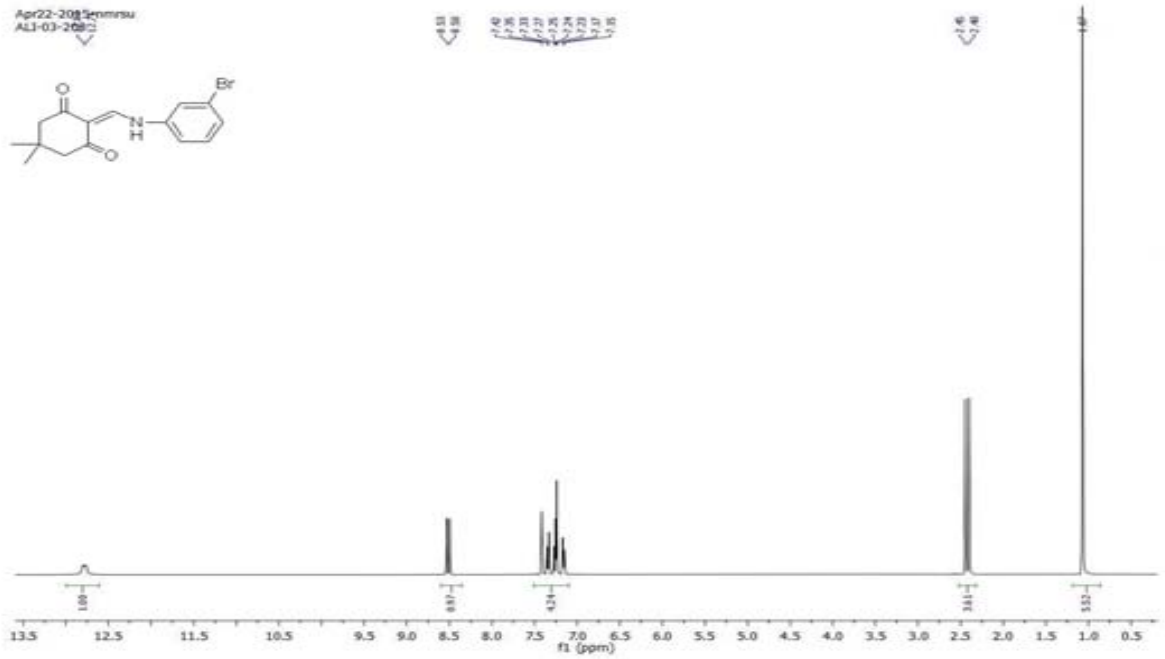


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **24**

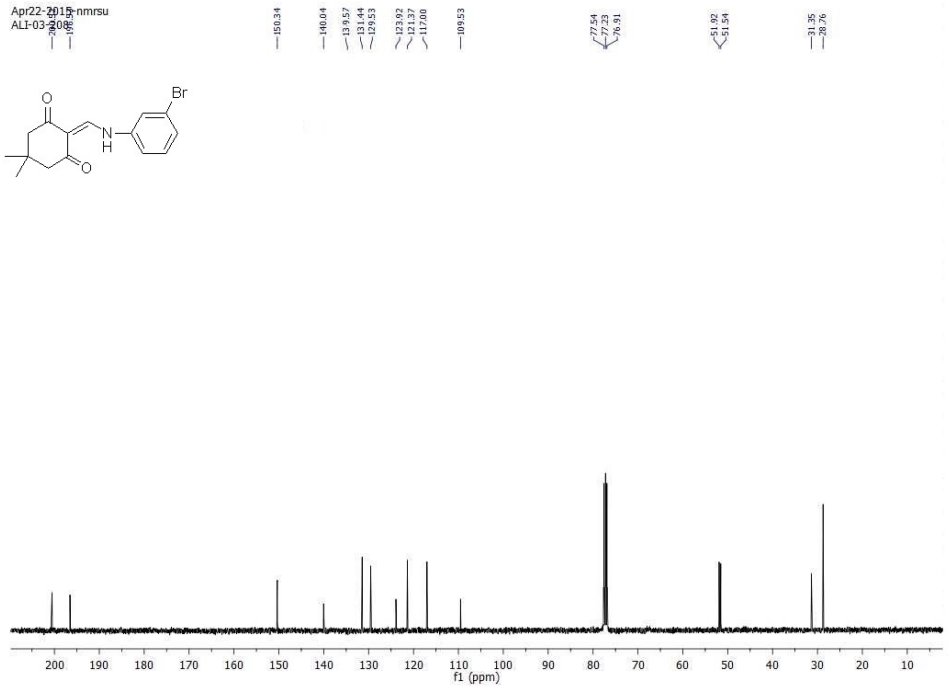




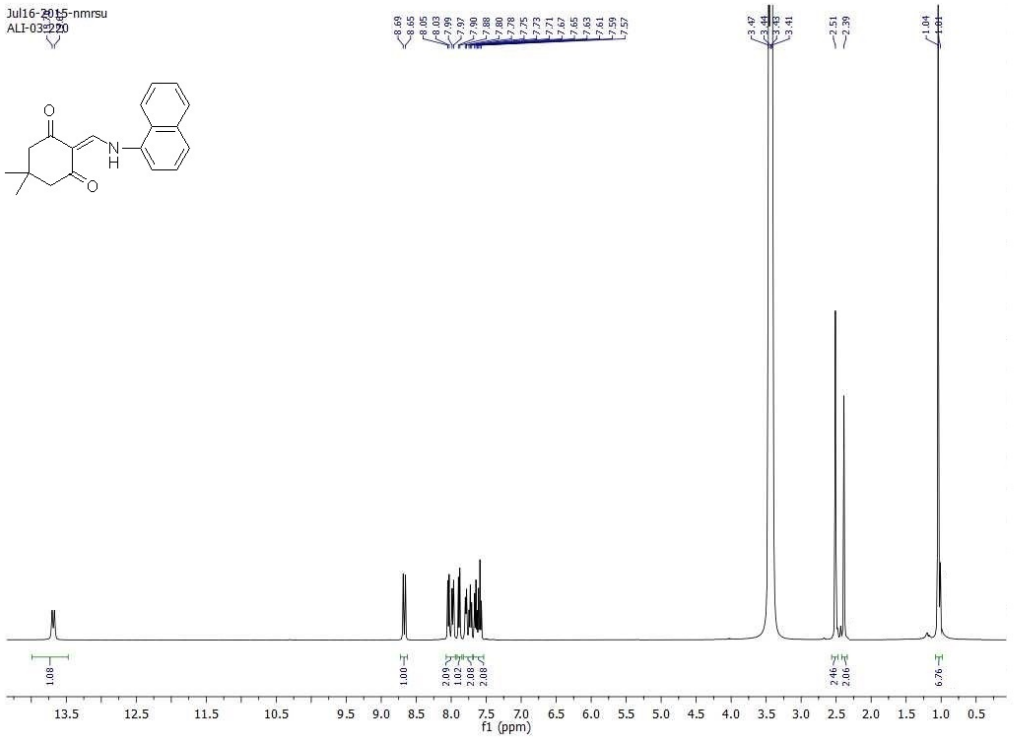
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **25**

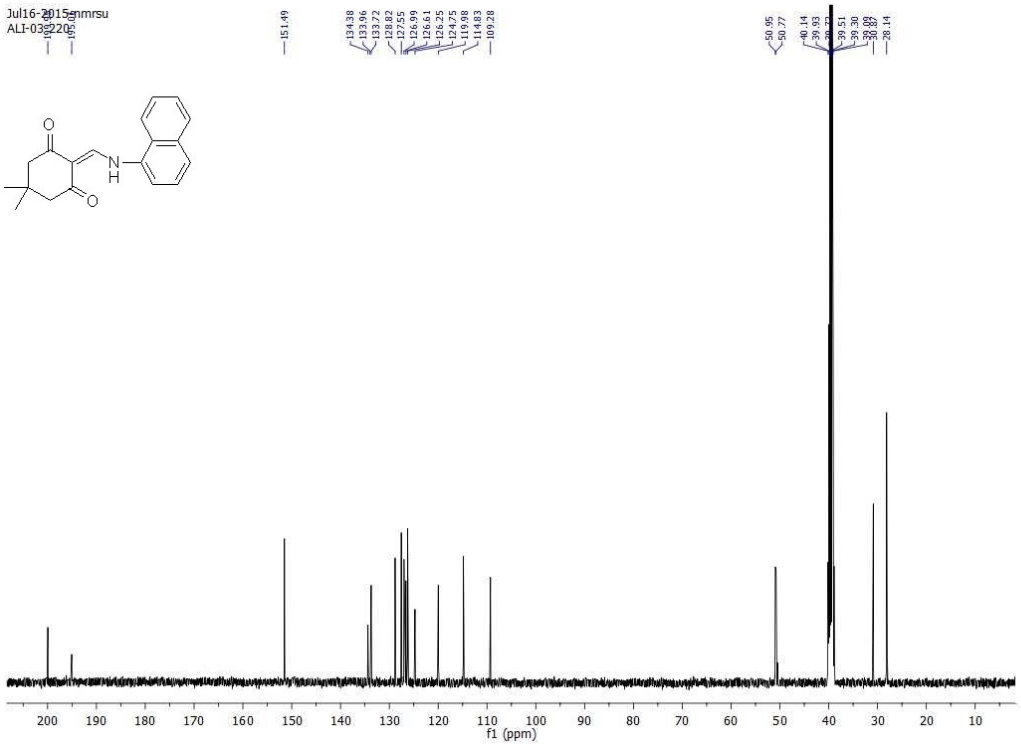


Sa S

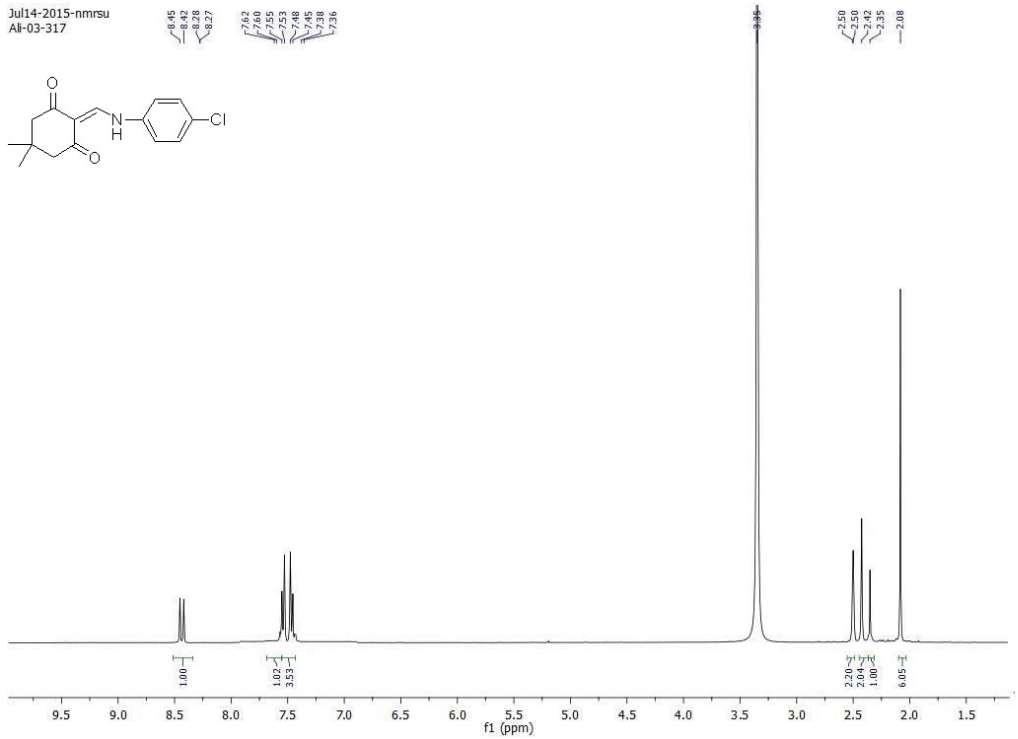


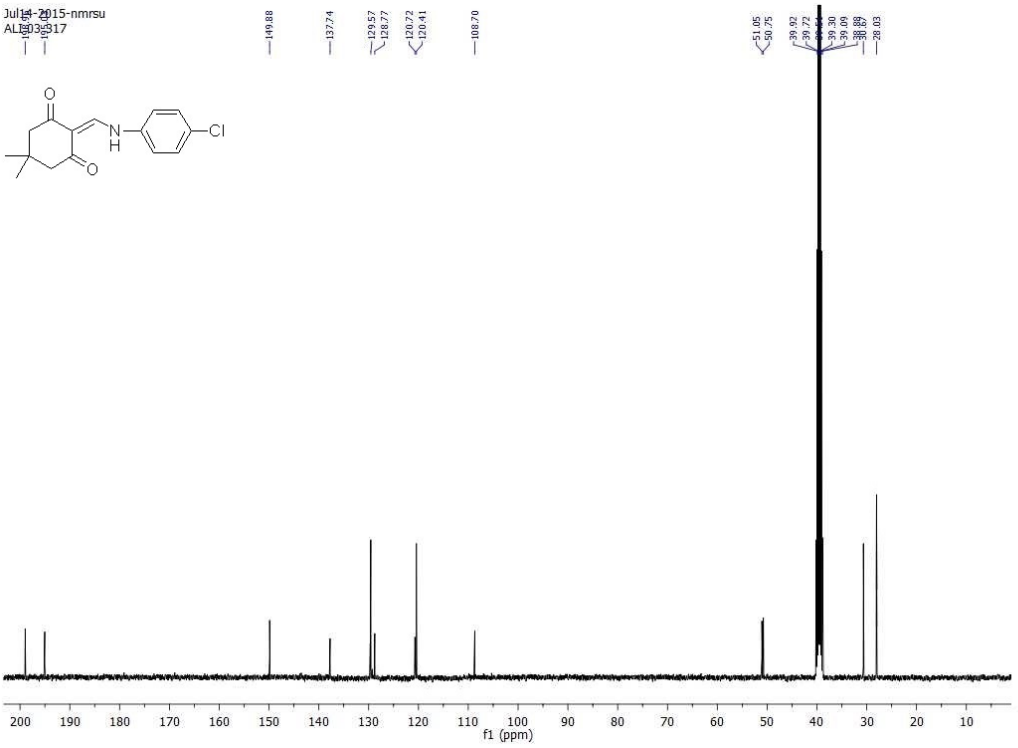
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **26**



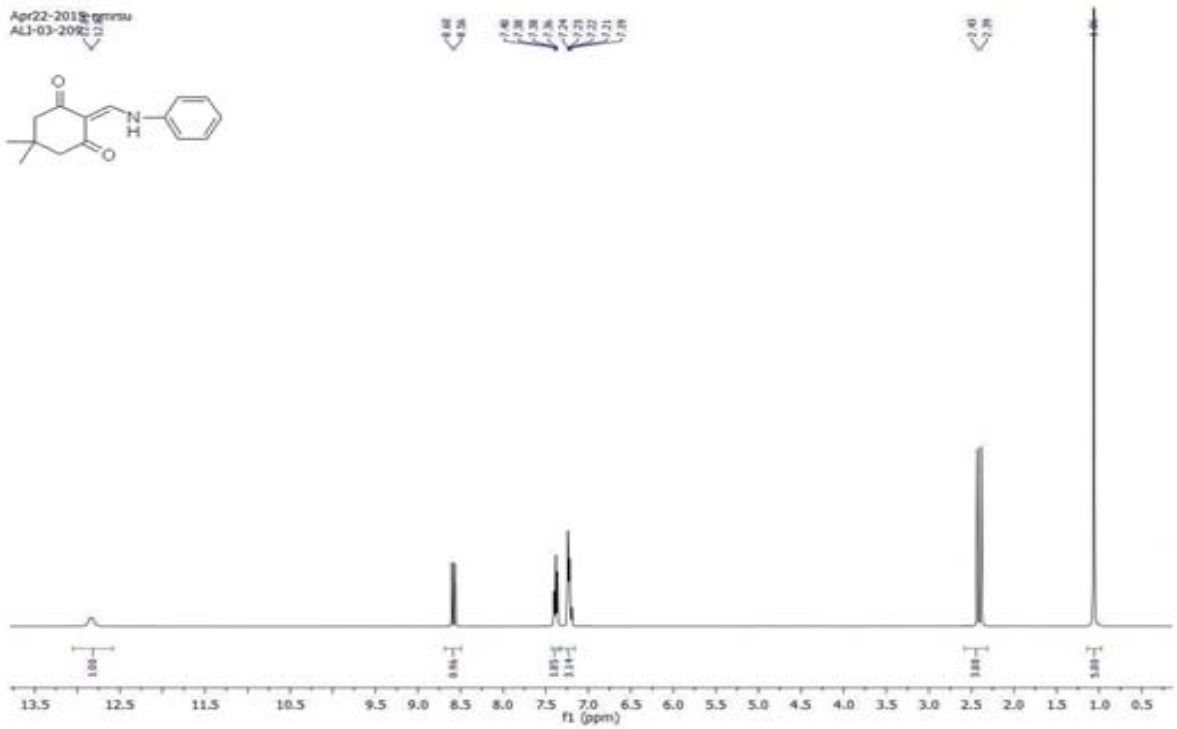


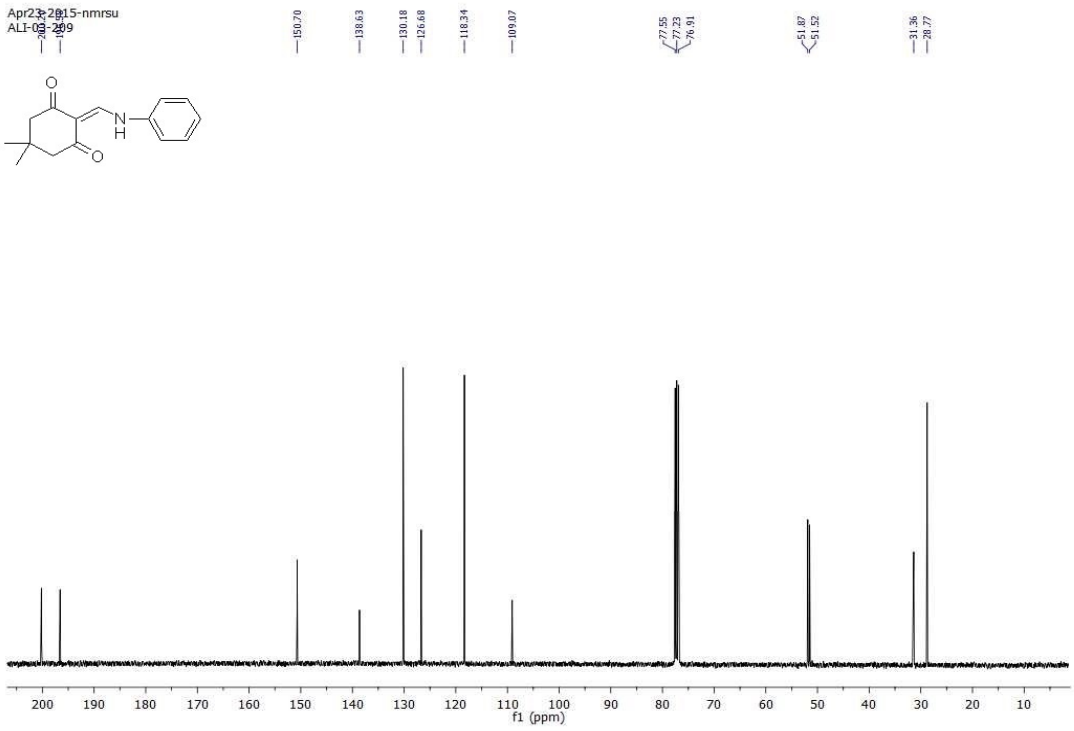
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **27**



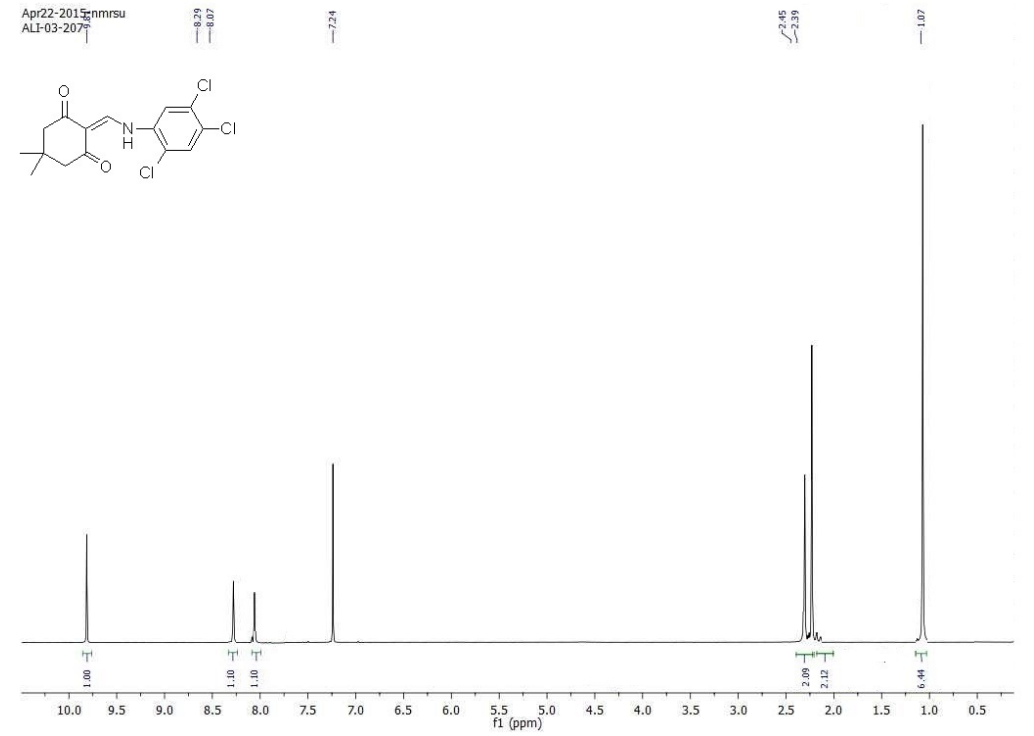


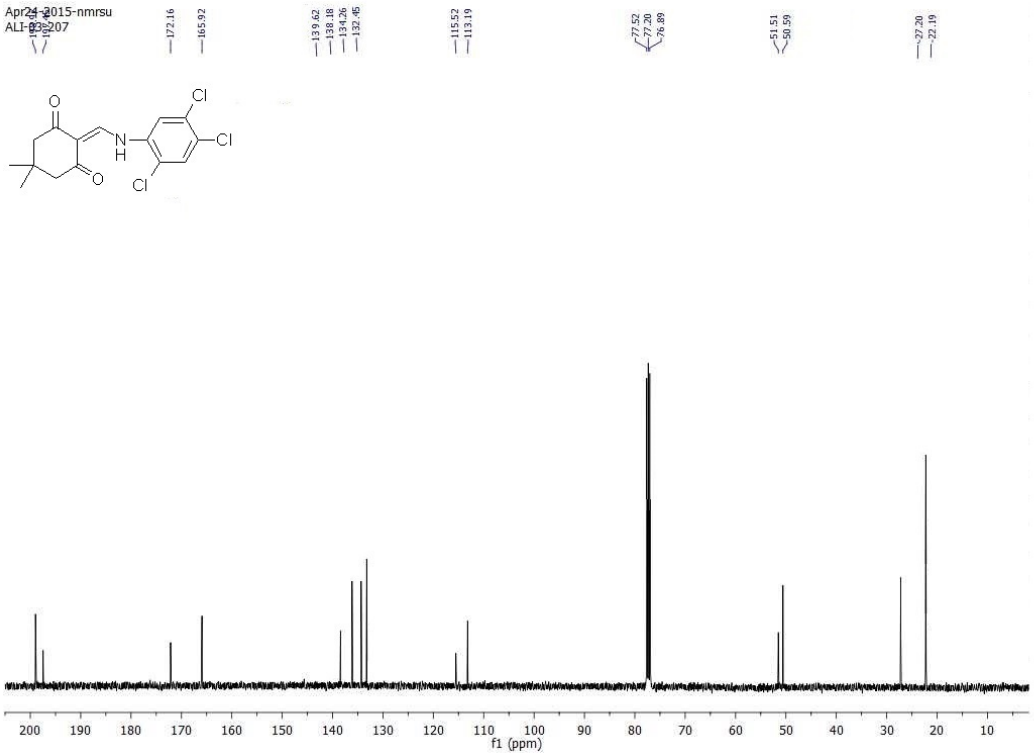
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101MHz, $CDCl_3$) of compound **28**



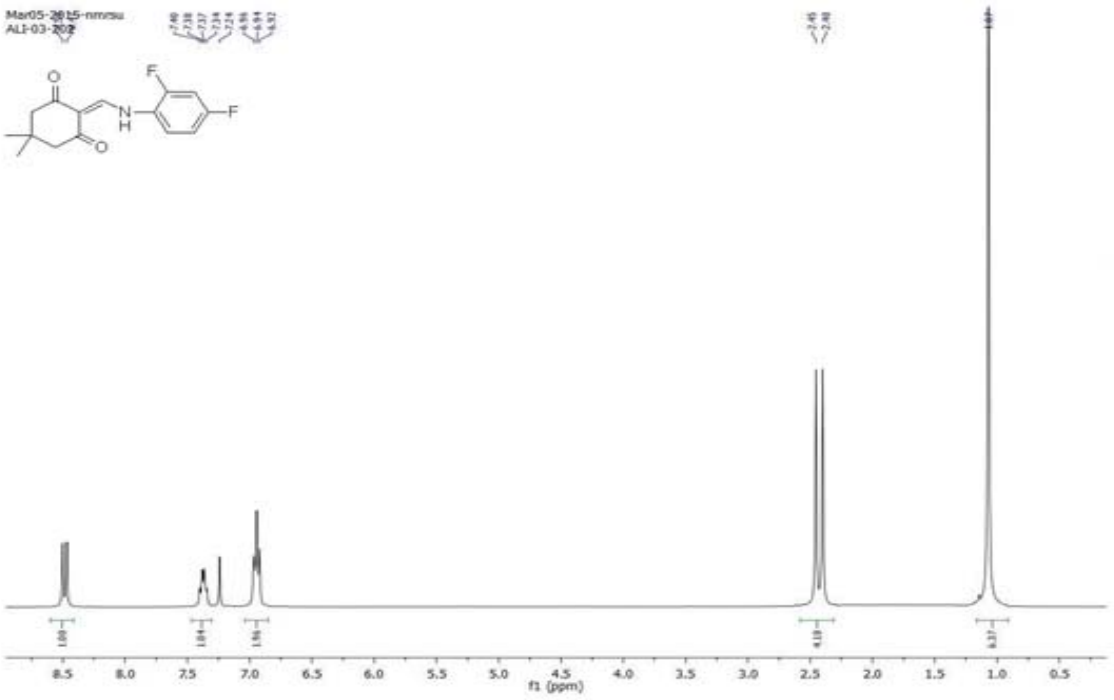


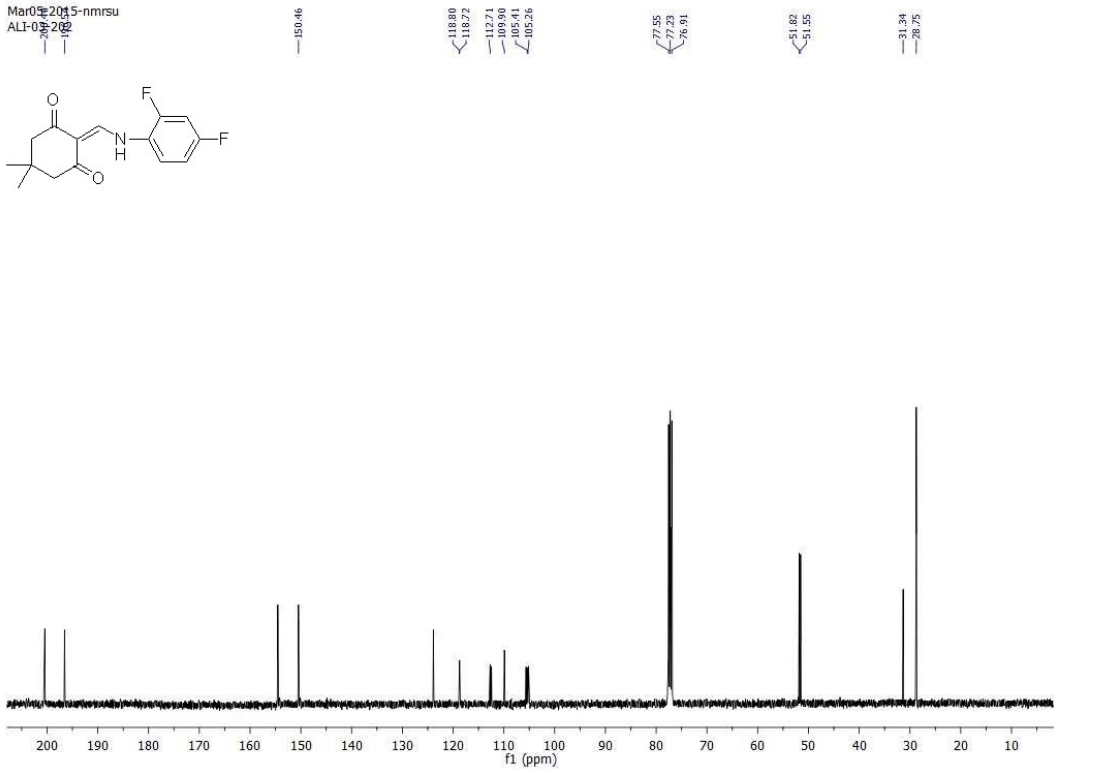
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **29**



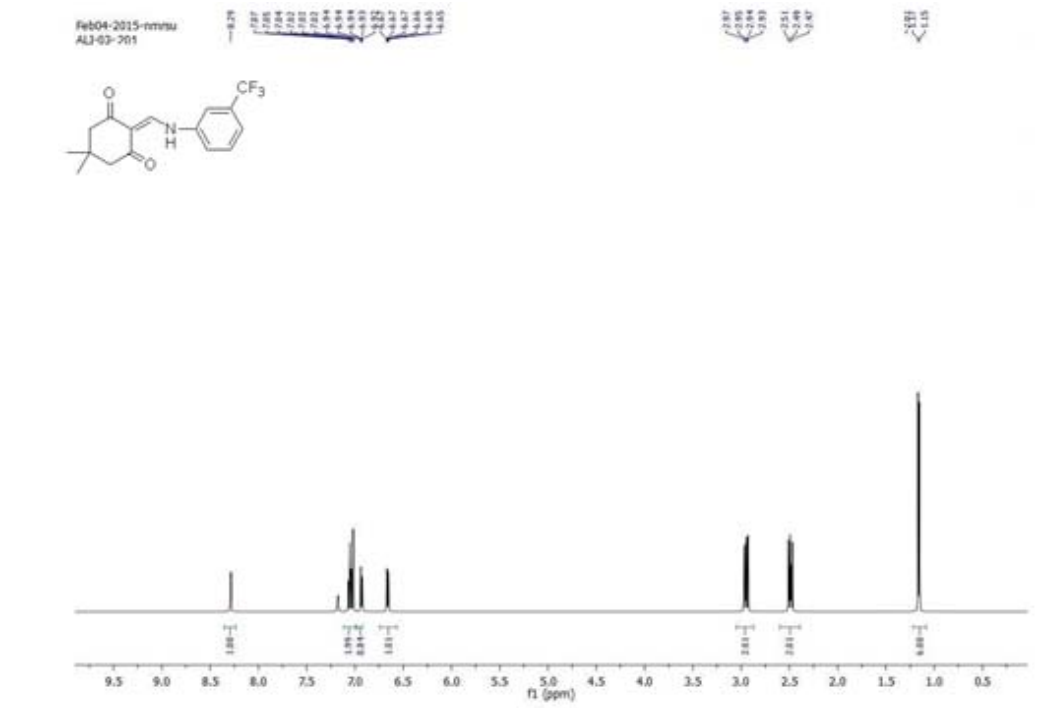


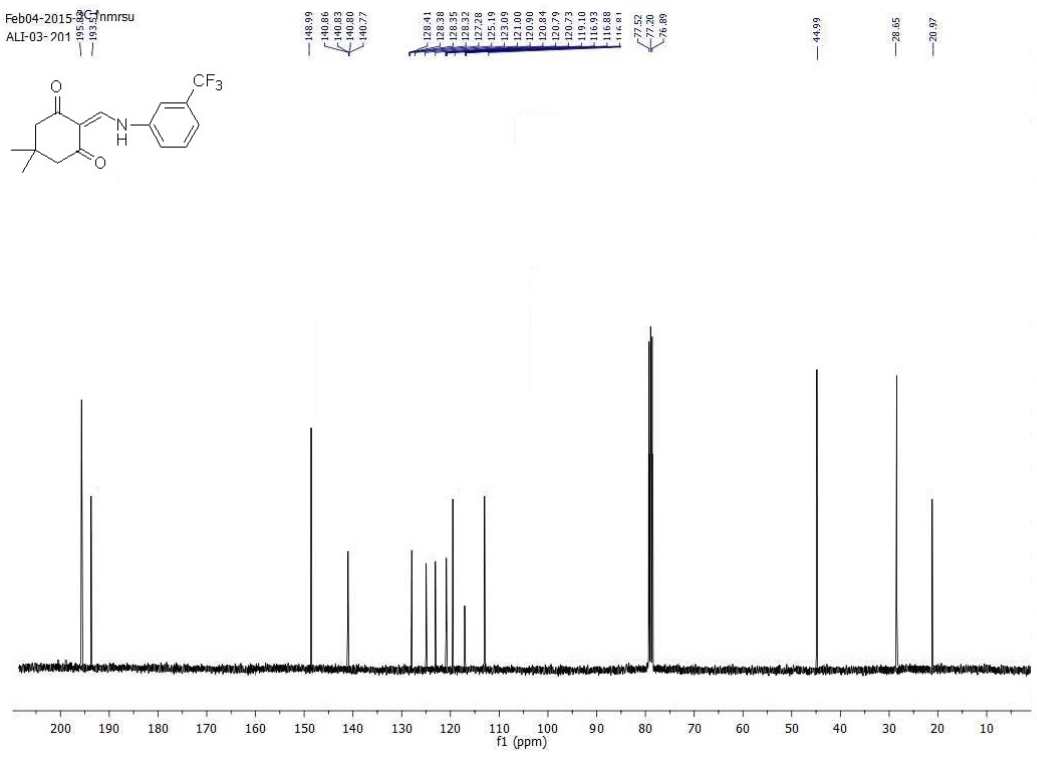
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **30**



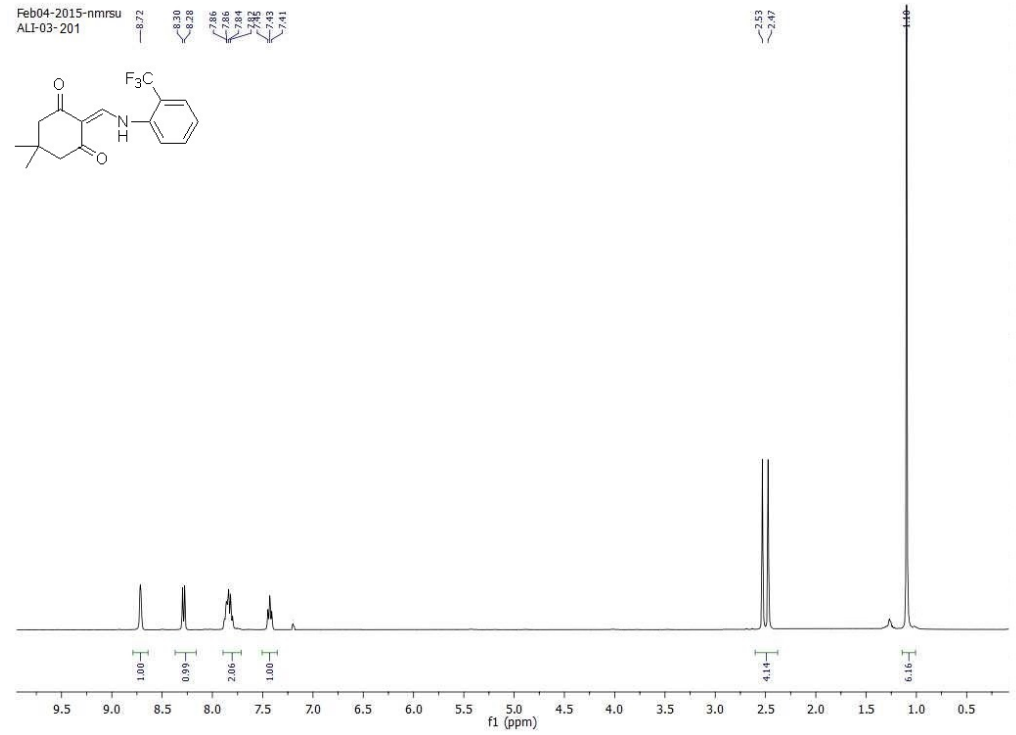


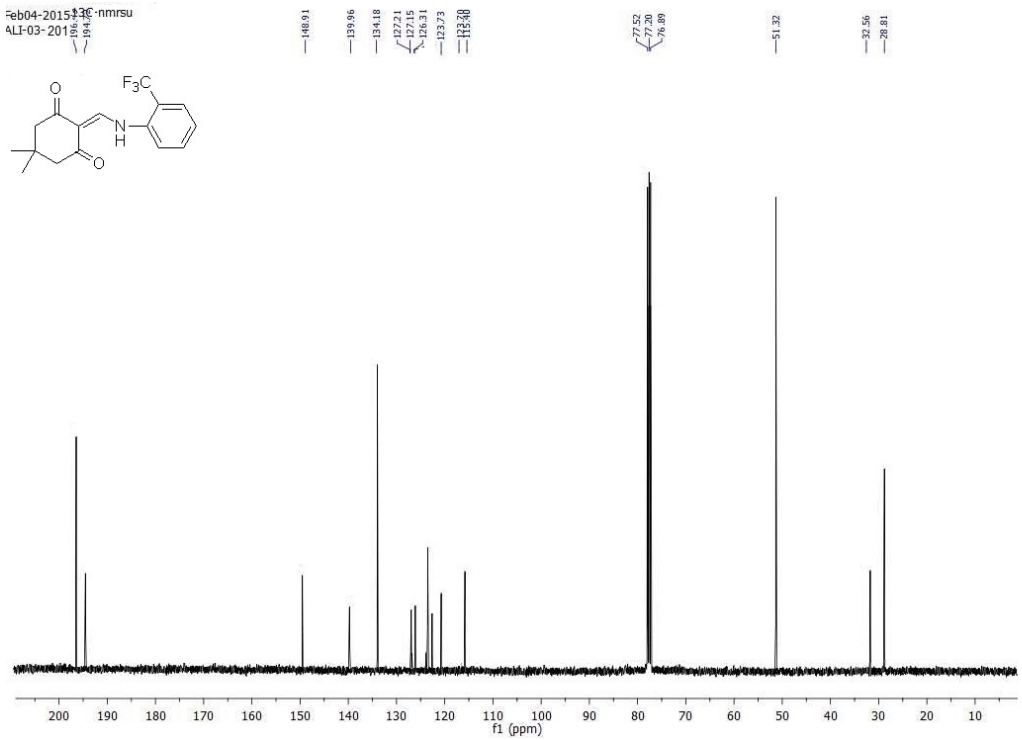
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **31**



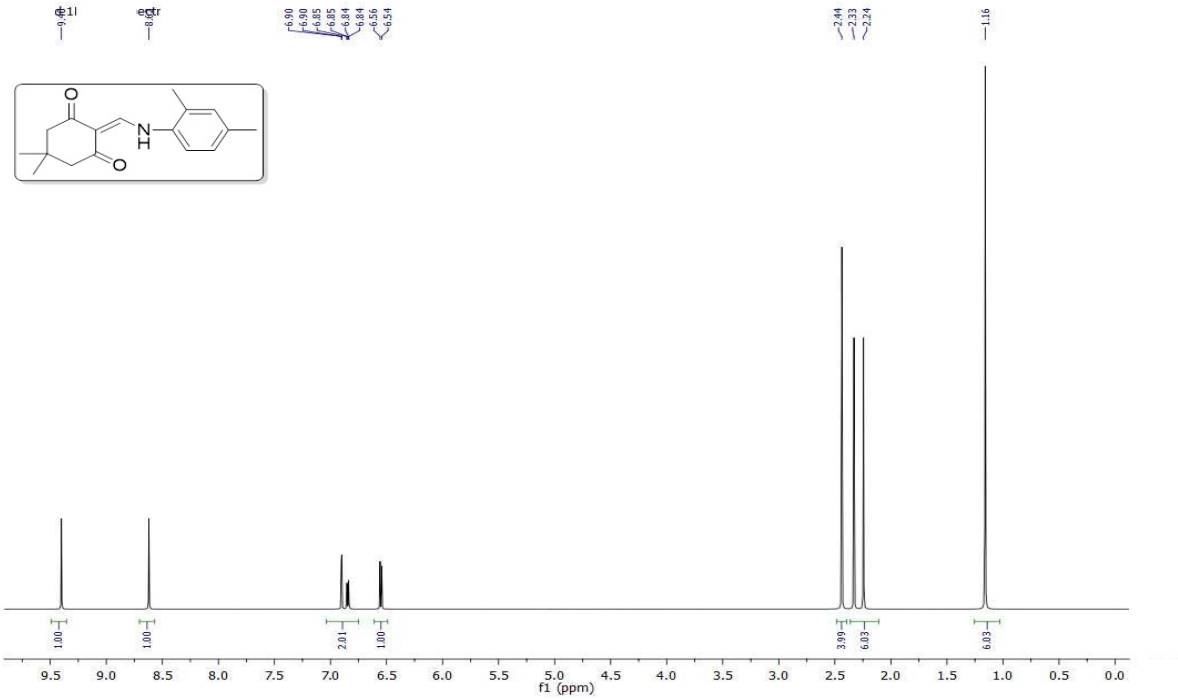


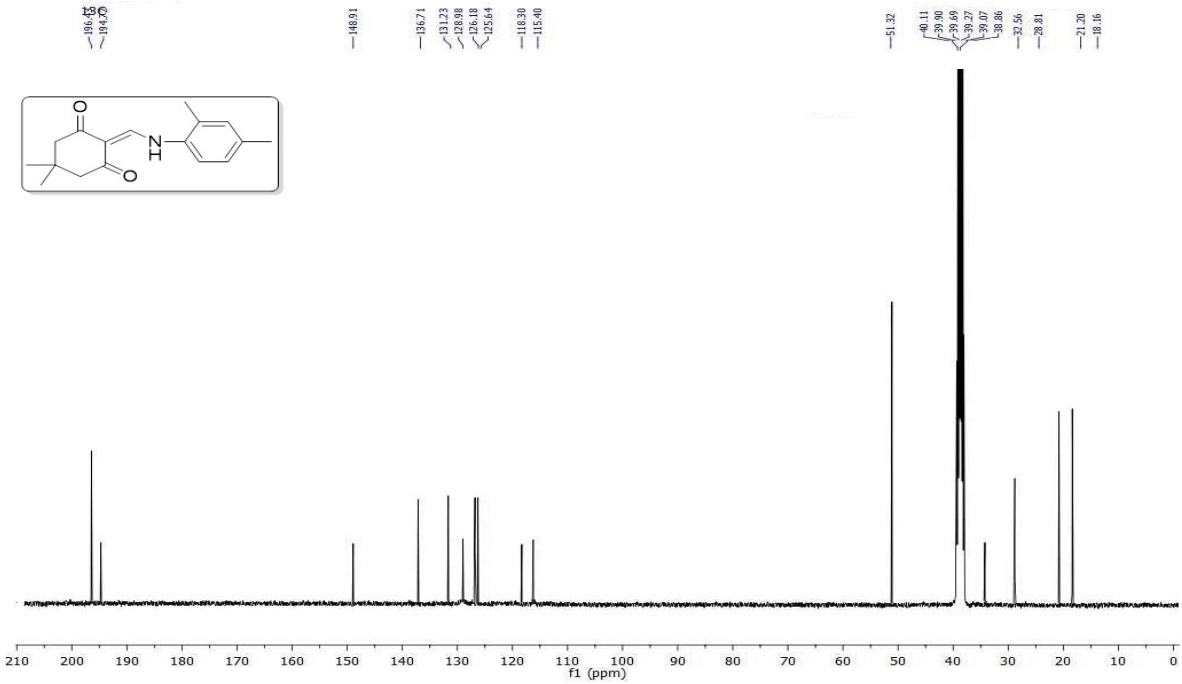
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **32**



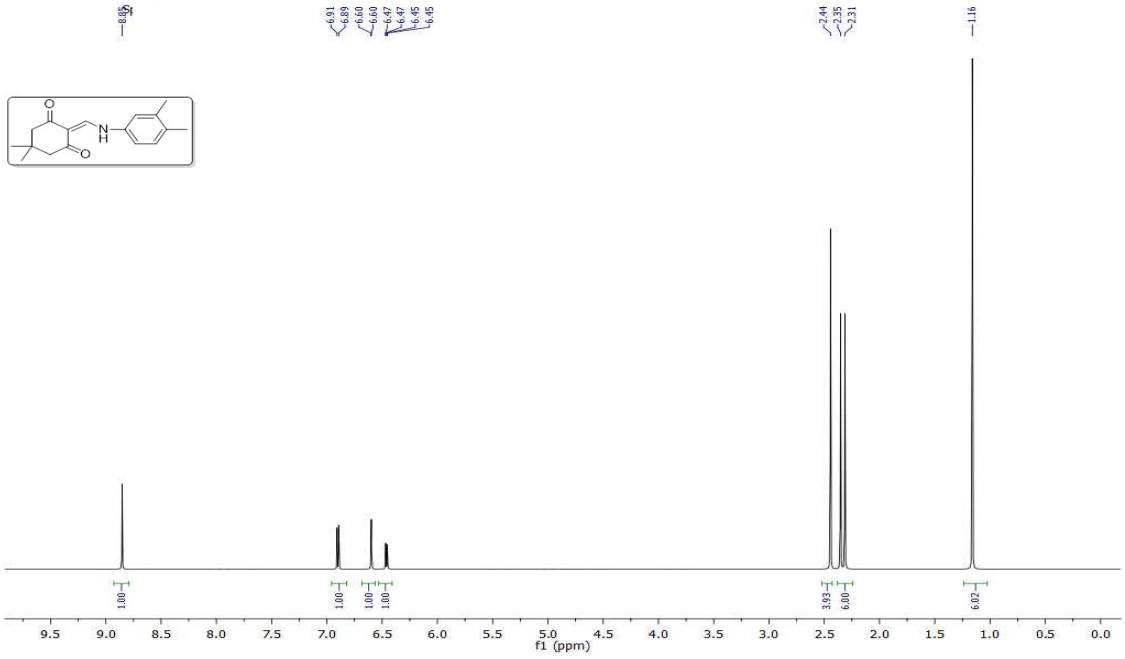


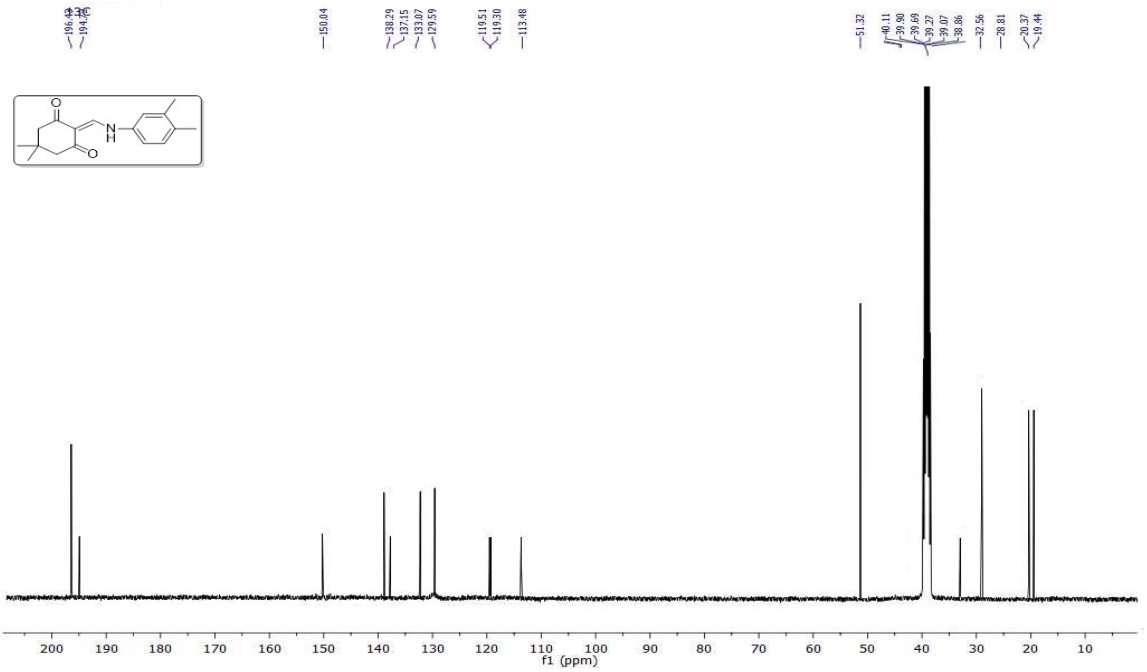
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) of compound **33**



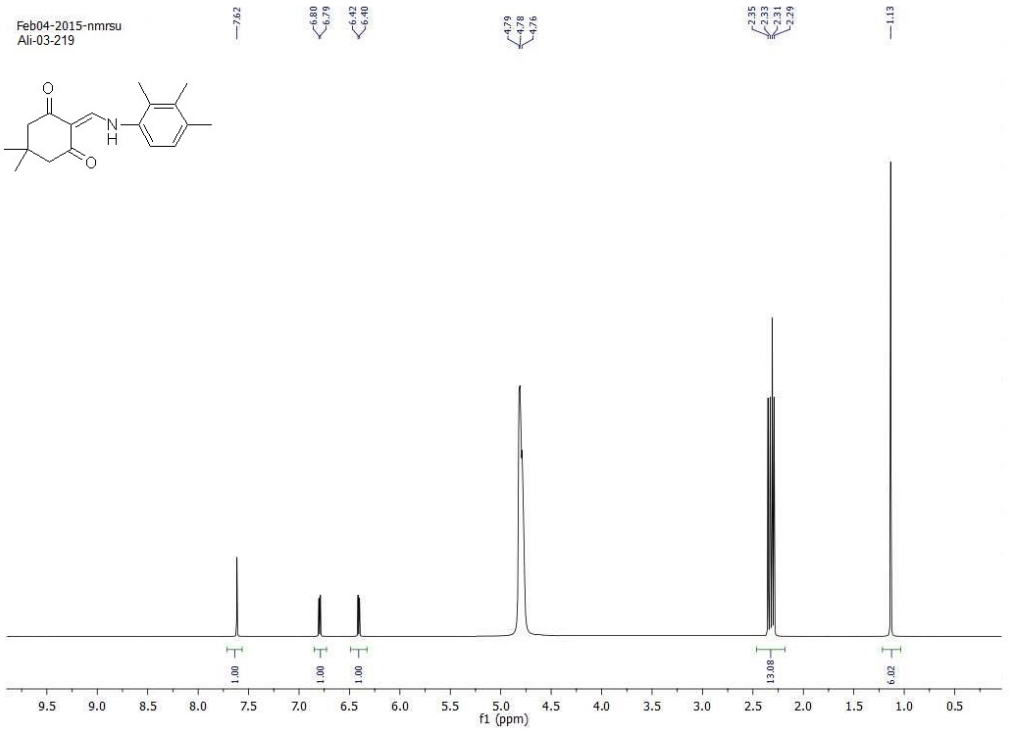


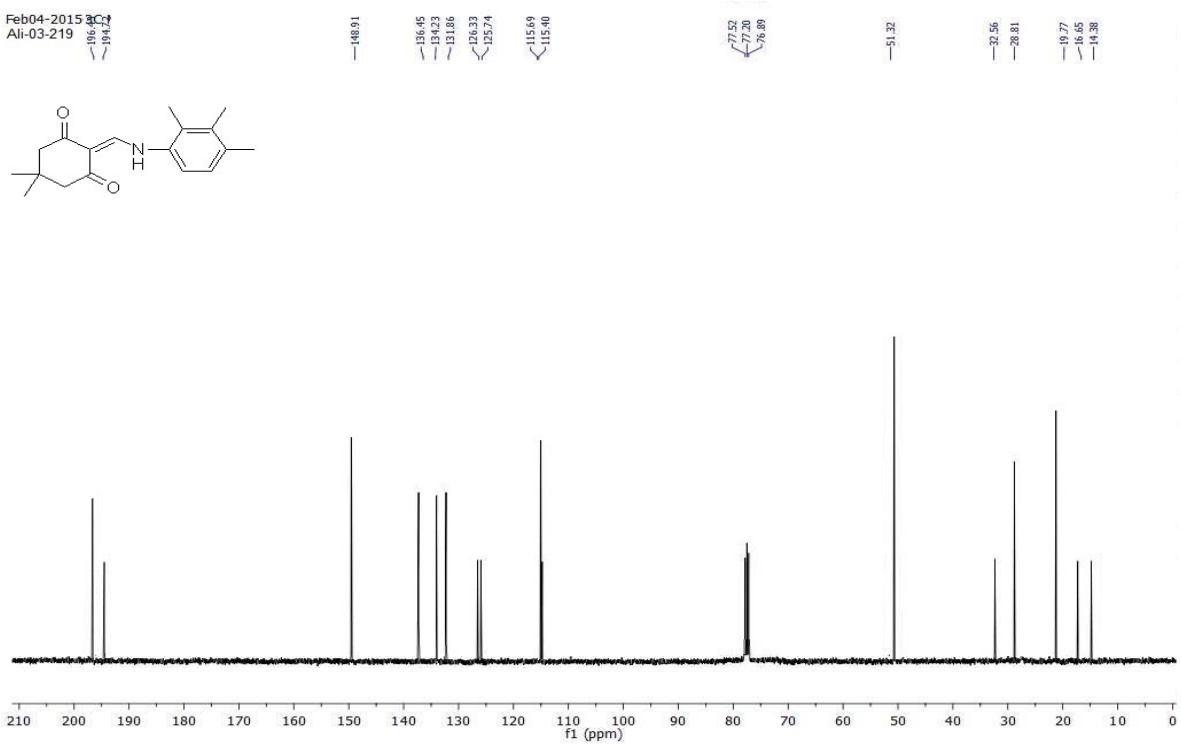
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$)) of compound **34**



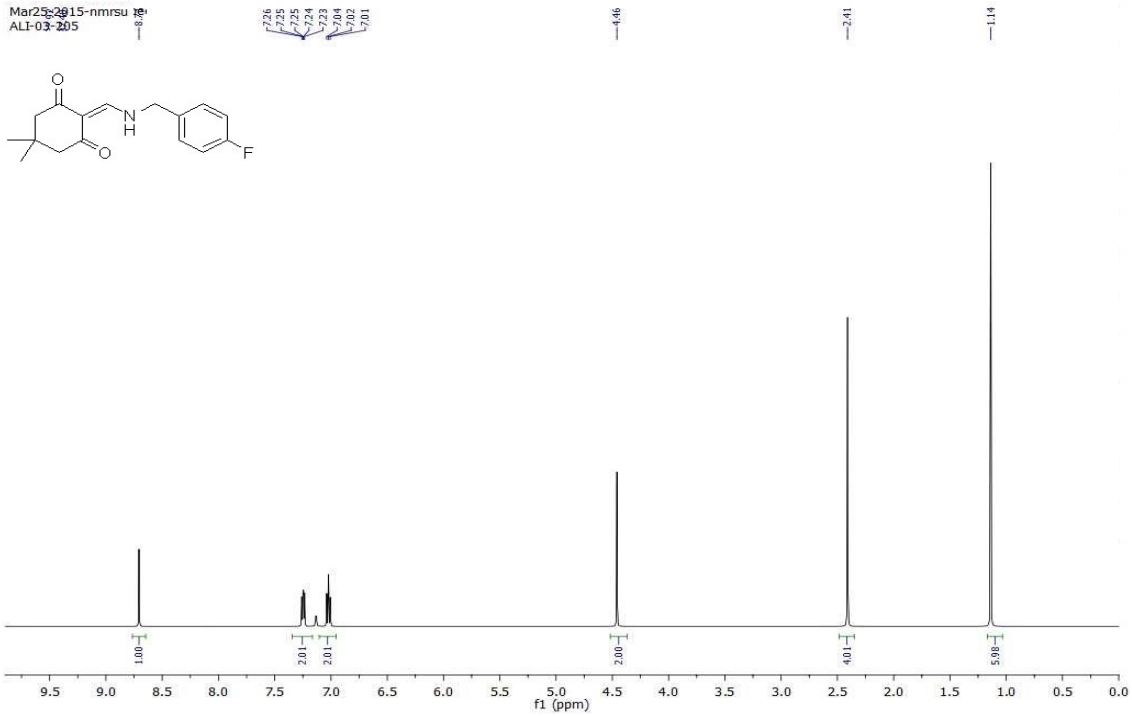


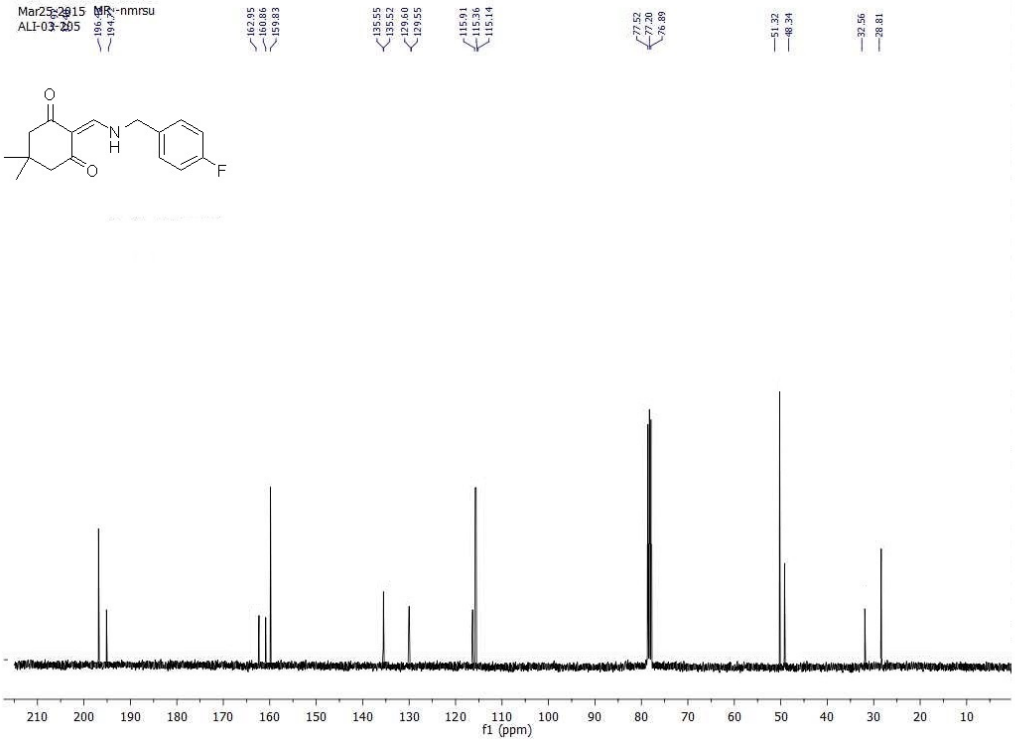
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **35**



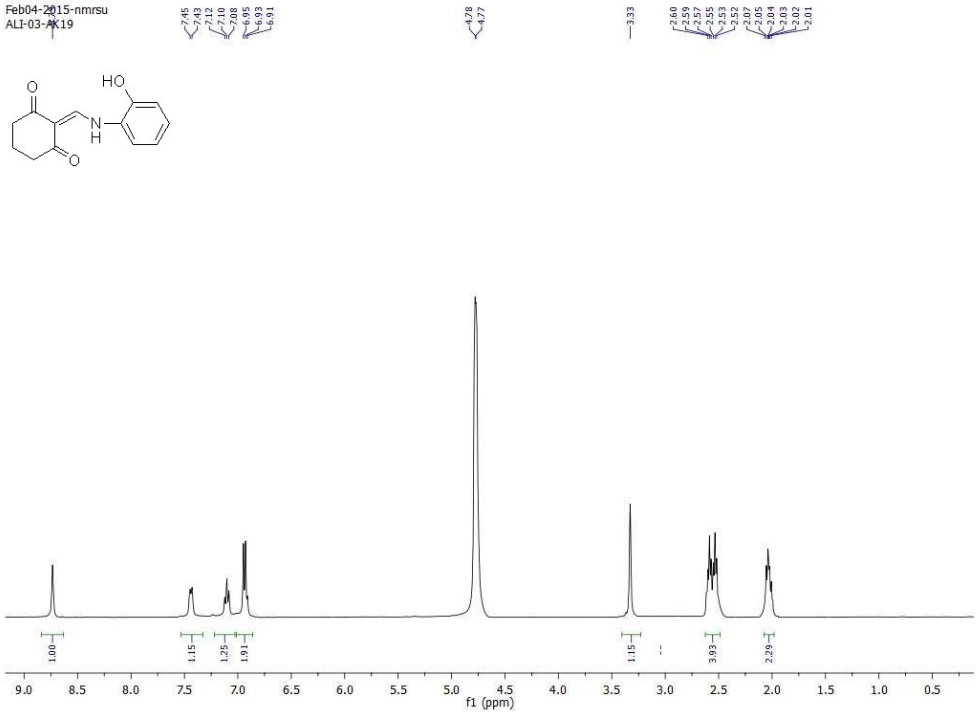


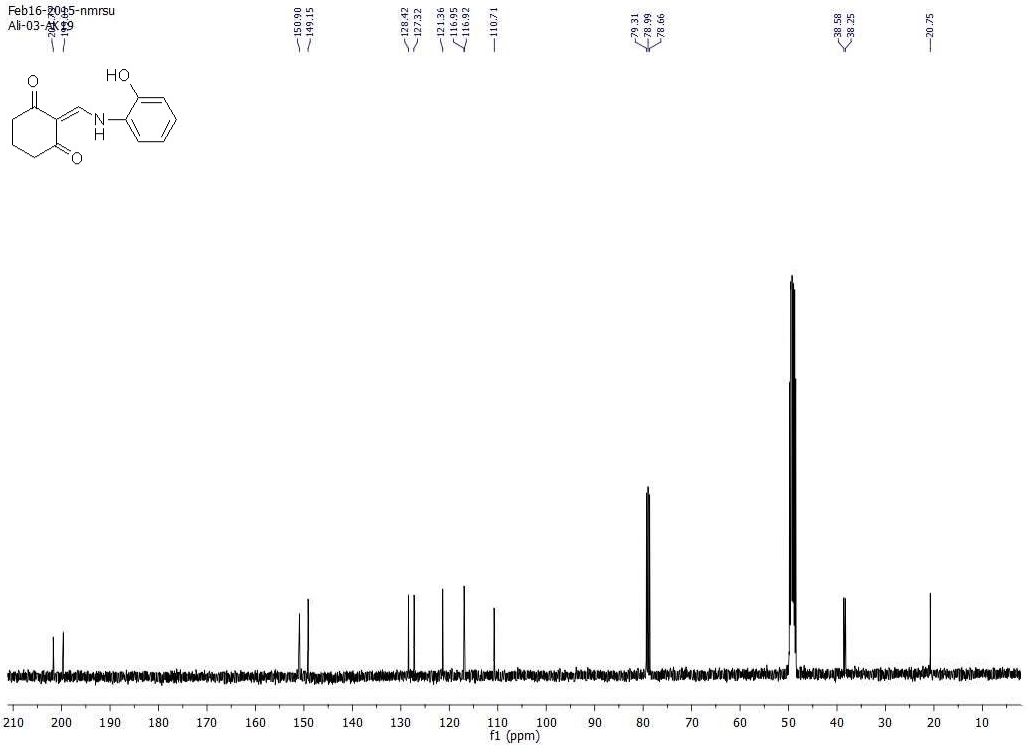
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **36**



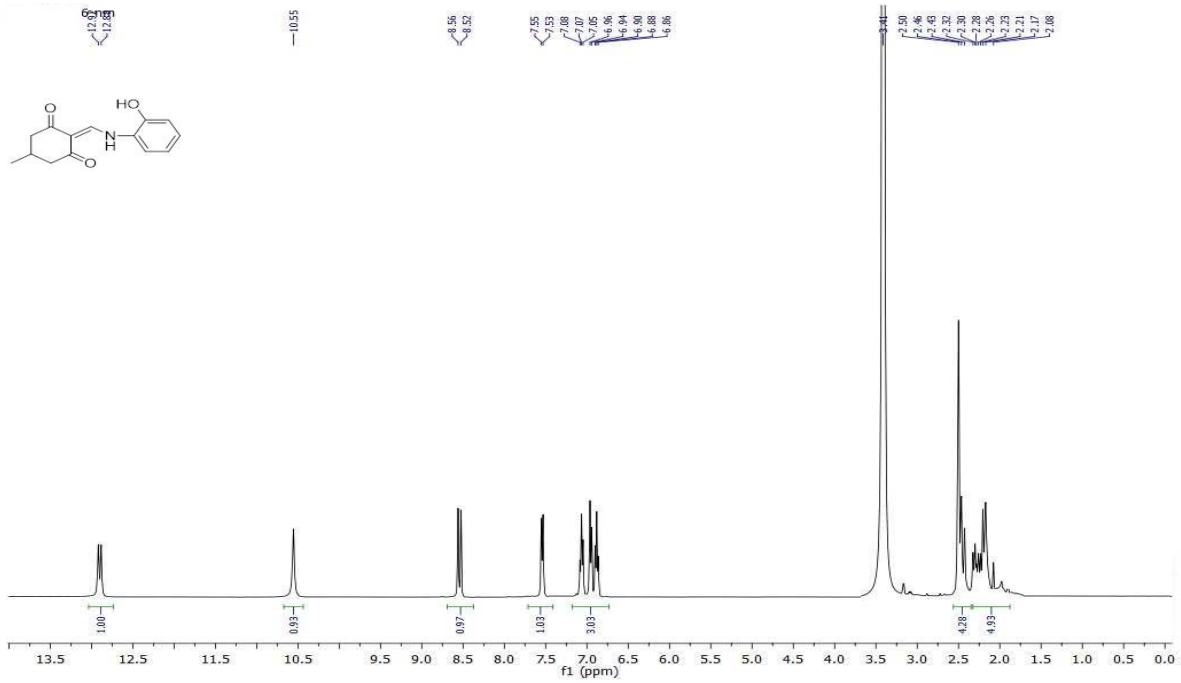


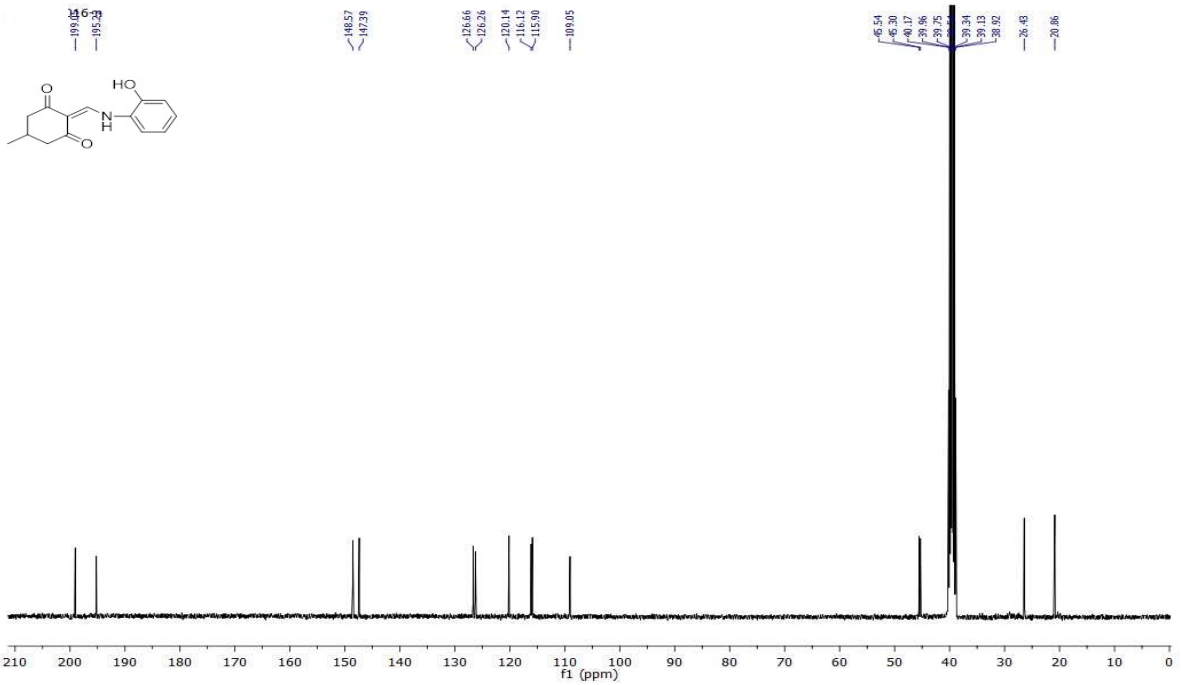
^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$) and ^{13}C NMR (101 MHz, $CD_3OD/CDCl_3$) of compound **37**



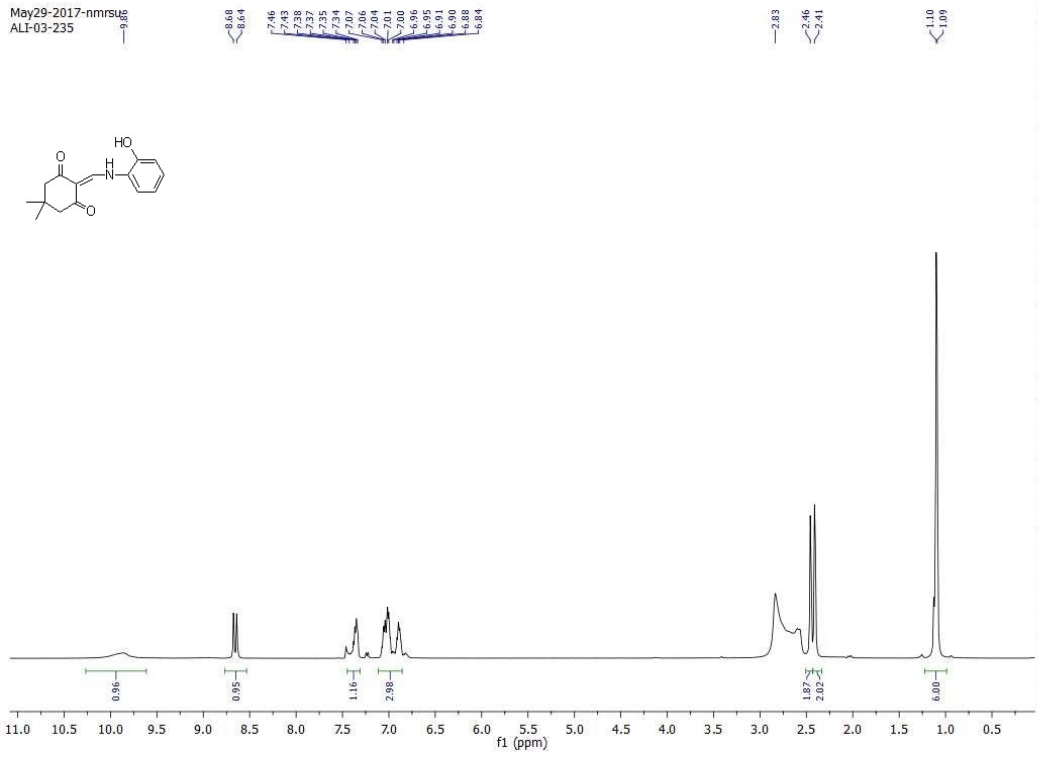


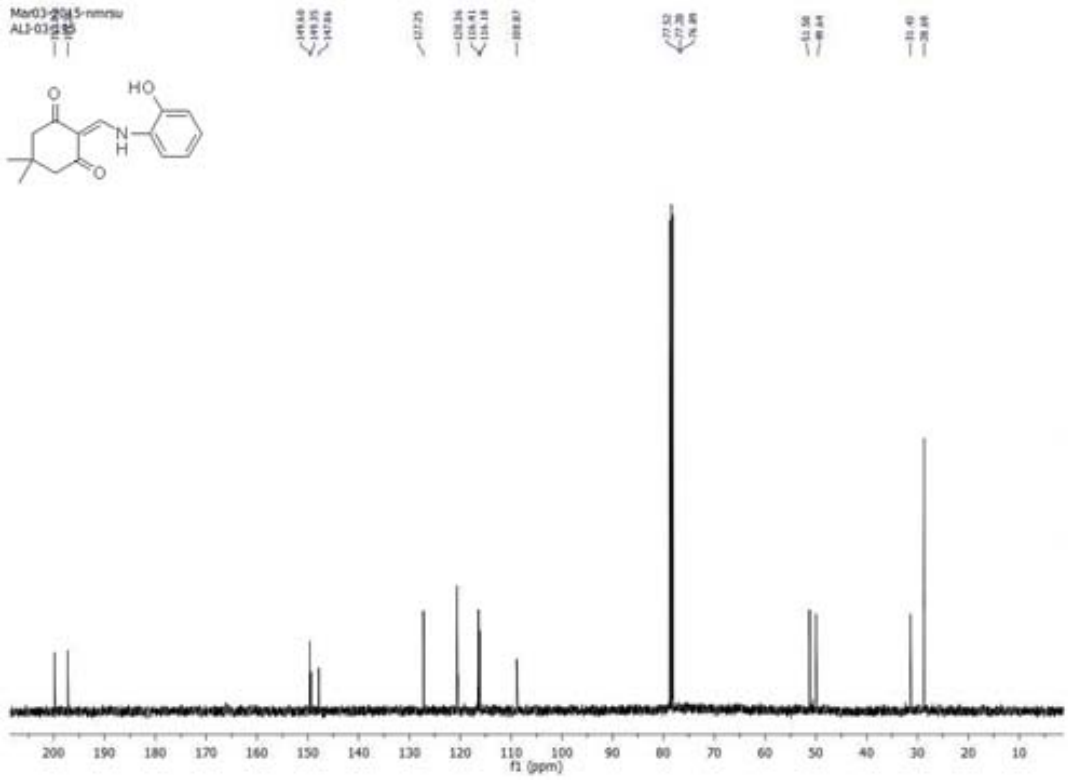
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101MHz, $(CD_3)_2SO$) of compound **38**



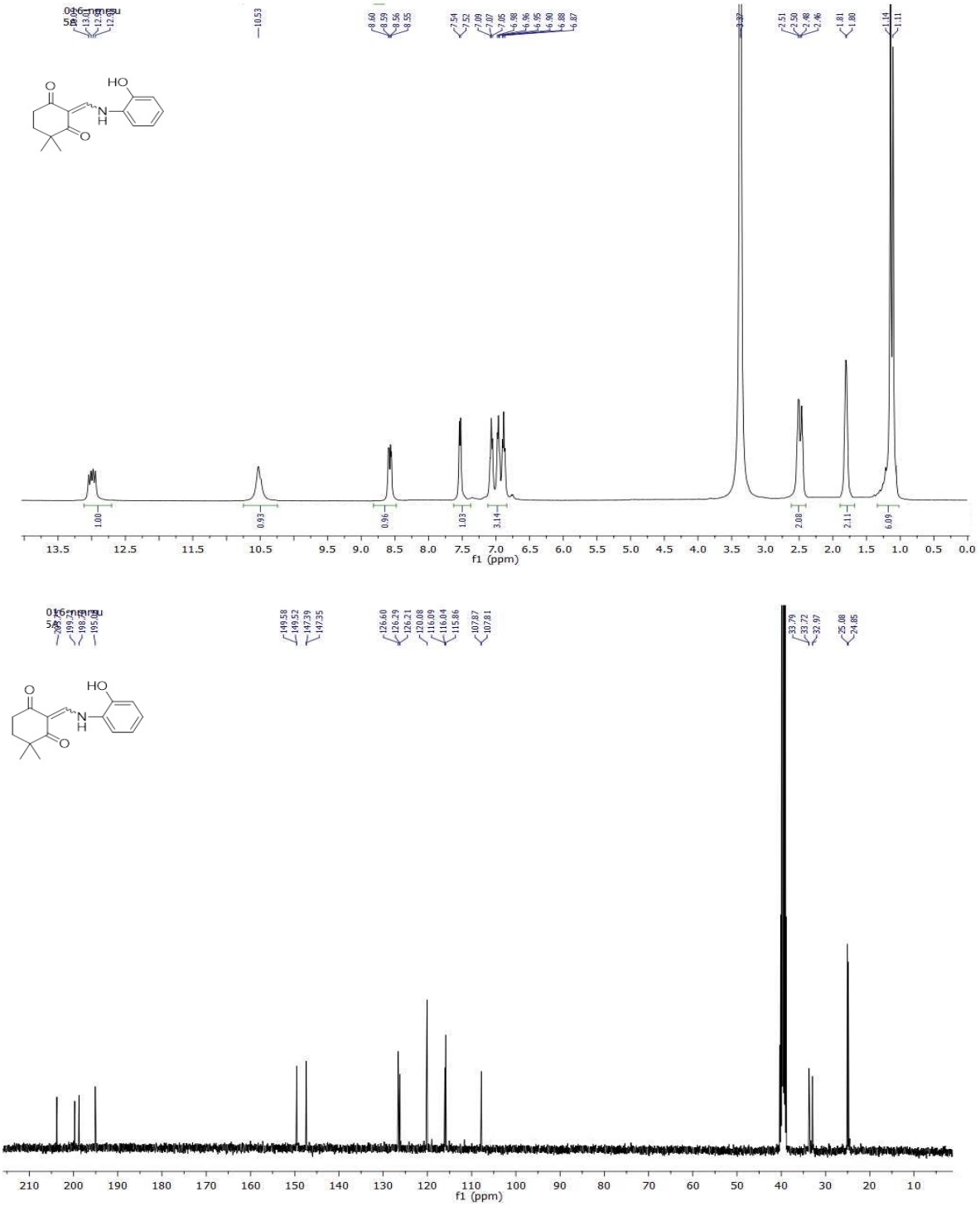


^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (101 MHz, $CDCl_3$) of compound **39**

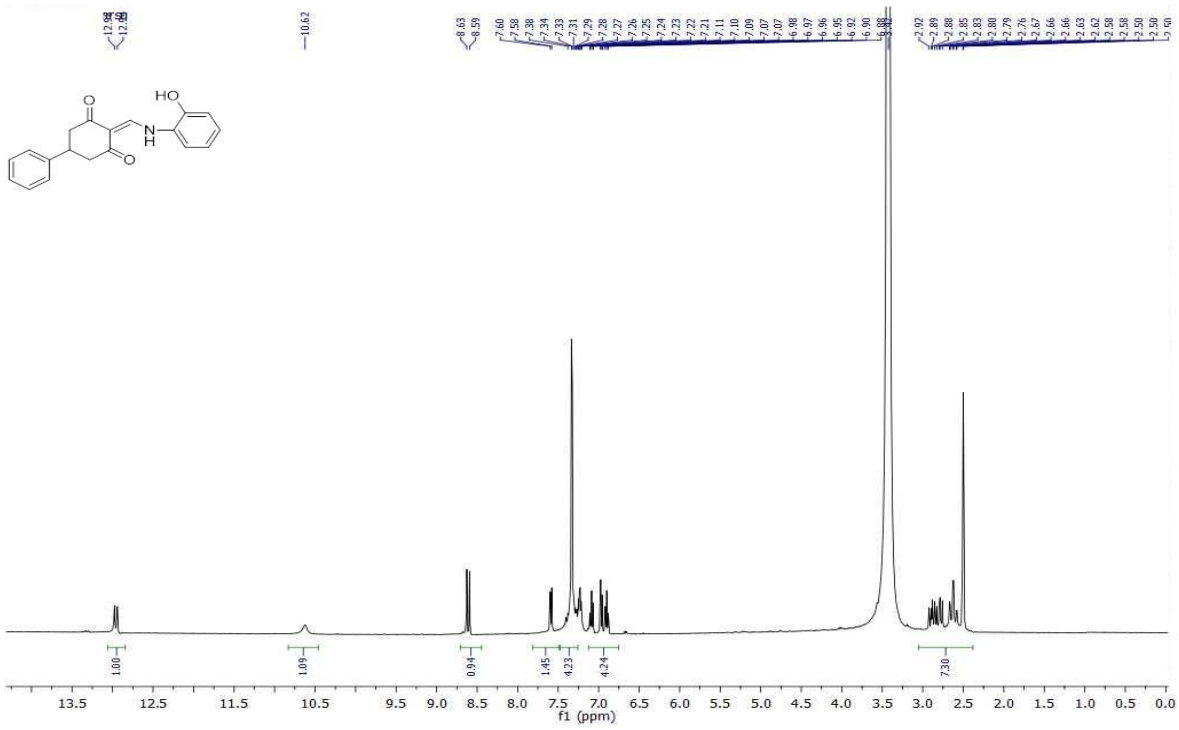


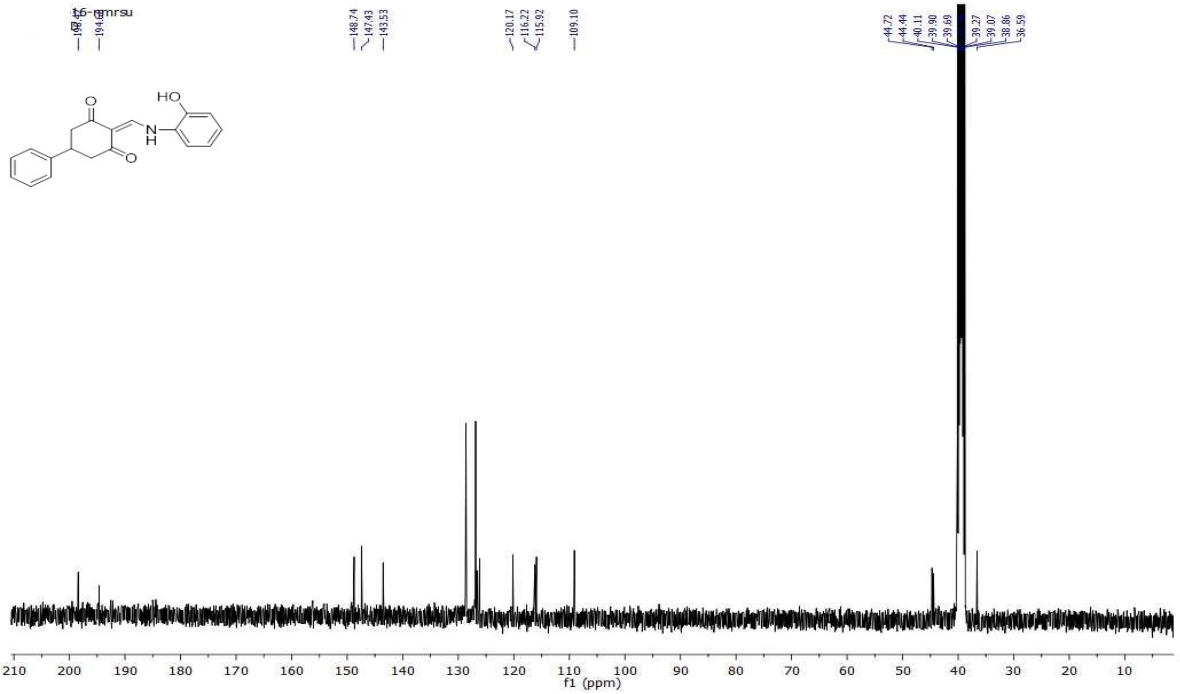


^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) ofcompound **40**

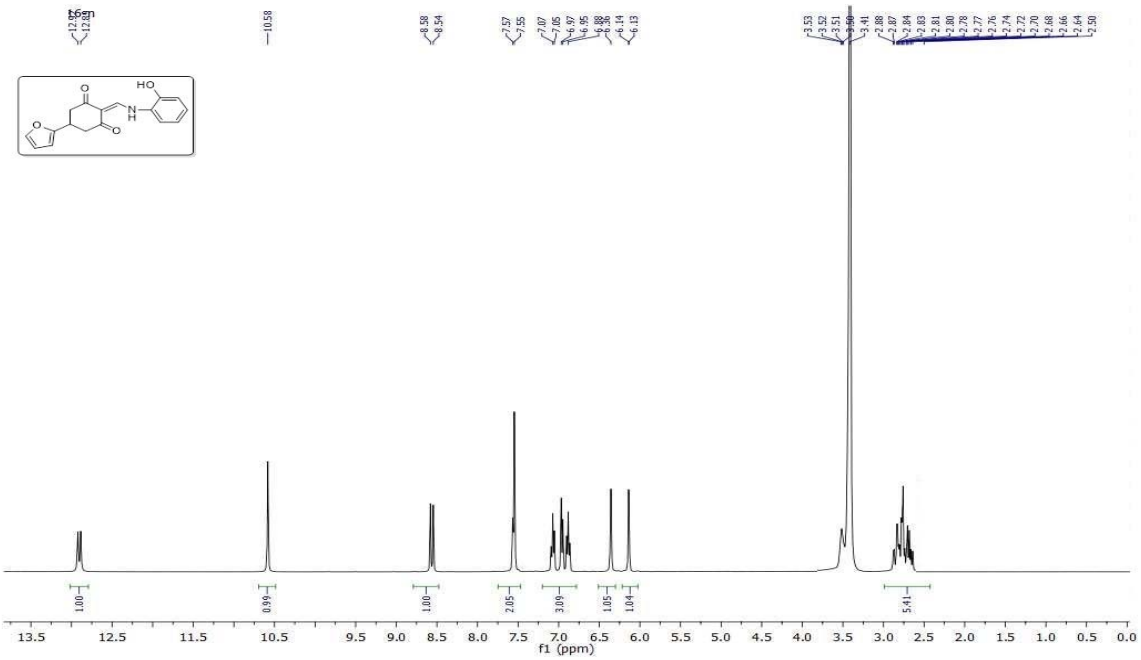


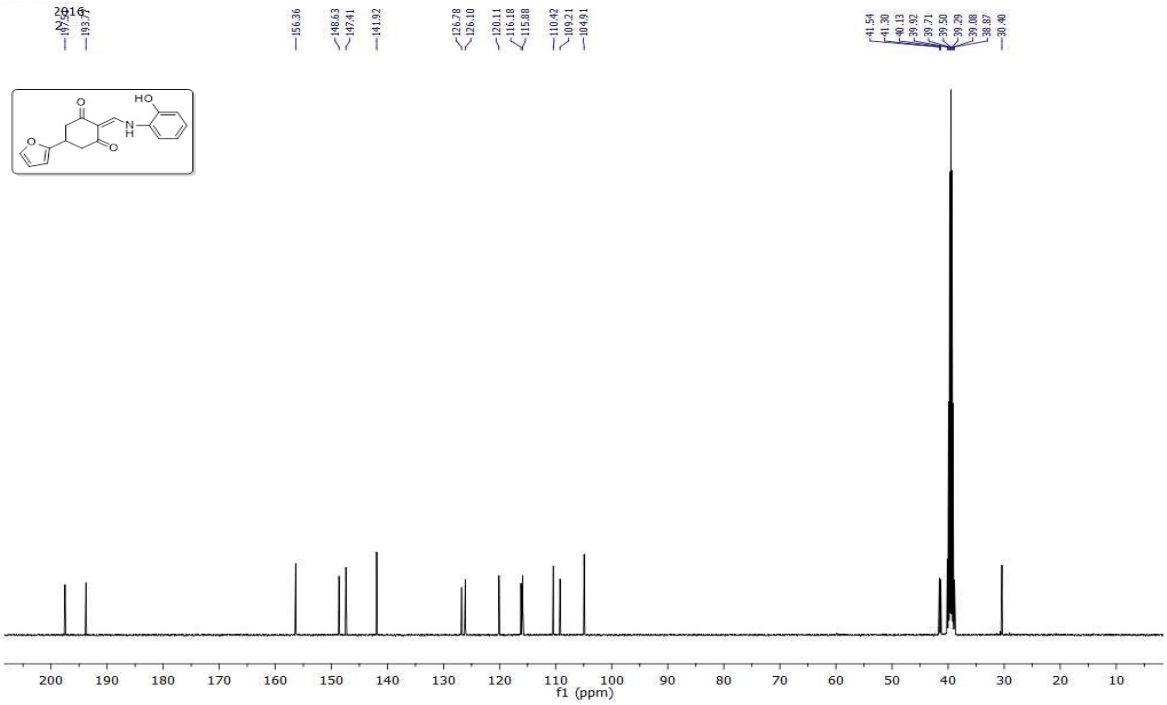
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) ofcompound **41**



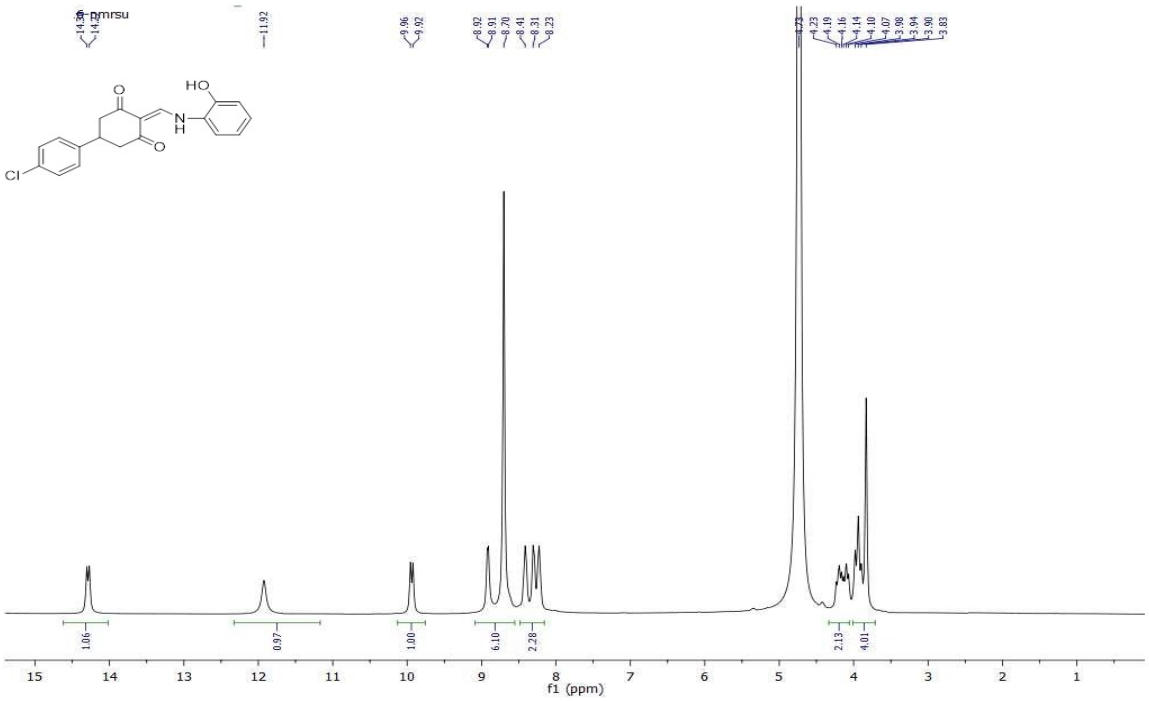


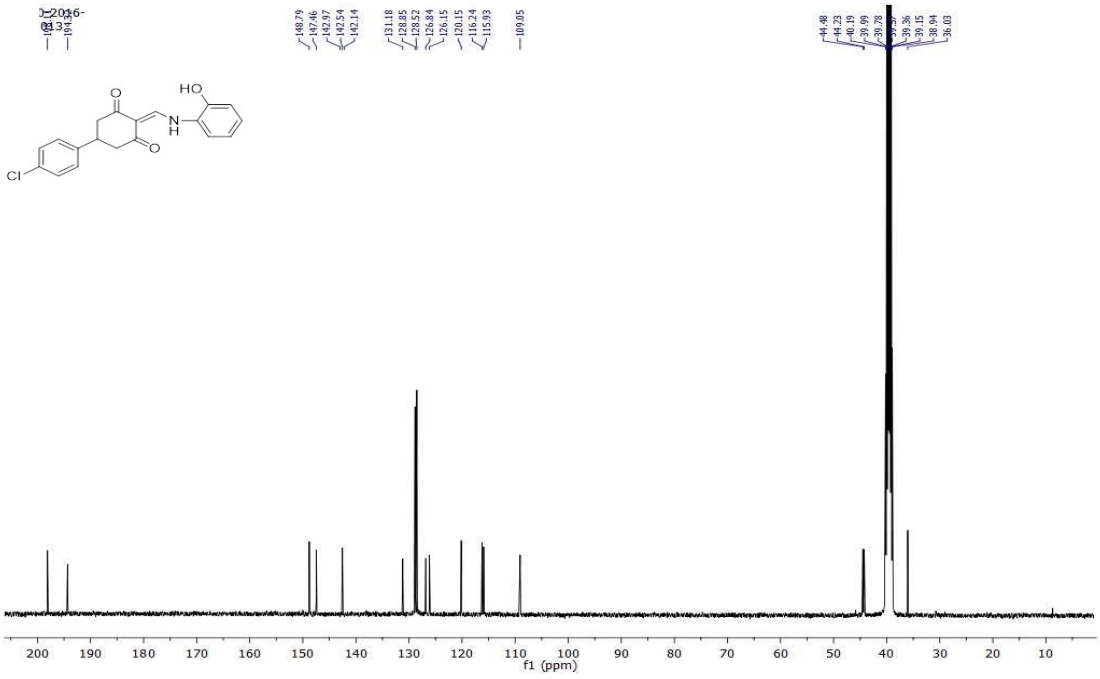
^{1}H NMR (400 MHz, $(CD_3)_2SO$) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) ofcompound **42**





^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (101 MHz, $(CD_3)_2SO$) ofcompound **43**





D. HPLC profile of active compound 39.

Solvent system; Acetonitrile : water (80:20)