Electronic Supplementary Material (ESI) for RSC Advances

Novel Atom Economic Reaction: Comprehensive Utilization of *S*-Alkylisothiouronium Salt in the Synthesis of Thioether and Guanidinium Salt

Pengchao Gao, Penglin Leng, Qi Sun, Xin Wang, Zemei Ge* and Runtao Li*

State key laboratory of natural and biomimetic drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing, 100191, China

E-mail: zmge@bjmu.edu.cn; lirt@mail.bjmu.edu.cn;

Fax: 86 10 82716956; Tel: 86 82801504

1. Experimental part

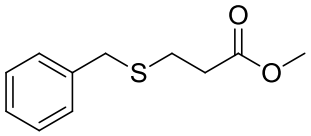
All reagents were commercially available. The waste free reactions were monitored by thin layer chromatography. ^{1}H NMR spectra were recorded on 400MHz Bruker spectrometers with TMS as an internal standard

Compounds**1a-f**[5], **2a-c**[19], **3a-c**[10,17], **4a-r**[19-26], **5a-e**[15-18], **6**[28], **7**[29], **8**[29], **9**[30], **10**[31], **11**[32]are known. **12** is a new compound. Characterization data (^{1}H NMR, ^{13}C NMR, MP, ESI-MS) are reported below.

Typical procedure for the symbiotic reaction

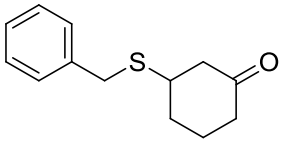
To the mixed solvent (10 mL, H_2O/EtOH = 1:1) was added the *S*-alkylisothiouronium salt (4.4 mmol), the amine (4.0 mmol) and the Michael receptor (4.0 mmol), TEA (4.0 mmol). The mixture was stirred at 30 °C for 6 h, then 5 mL H_2O was added and the mixture was extracted with EtOAc (15 mL × 3). The remaining aqueous layer was concentrated under reduced pressure using a rotary evaporator and the resulting solid was washed with a small amount of ethanol, then recrystallized from hot water to give the corresponding guanidinium salt (**5**). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford the corresponding thia-Michael addition product (**4**).

Methyl 3-(benzylthio)propanoate(4a)



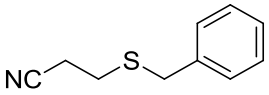
Isolated in 83.4% yield, yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 7.25 (m, 5H), 3.66 (s, 2H), 3.61 (s, 3H), 2.61 (t, 2H, J = 7.3Hz), 2.48 (t, 2H, J = 7.3Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 172.37, 138.05, 128.85, 128.57, 127.11, 51.80, 36.30, 34.29, 26.19

3-(Benzylthio)cyclohexanone(4b)



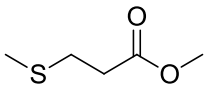
Isolated in 82.3% yield, yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 7.18 (m 5H), 3.67 (s, 2H), 2.85 (m 1H), 2.57 (m, 1H), 2.26 (m, 3H), 1.99 (m, 2H), 1.61 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ 208.68, 137.93, 128.75, 128.62, 127.16, 47.80, 41,97, 40.95, 34.93, 31.28, 24.12

3-(Benzylthio)propanenitrile(4c)



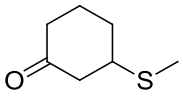
Isolated in 80.1% yield, yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 7.24 (m, 5H), 3.69 (s, 2H), 2.54 (t, 2H, J = 7.2Hz), 2.38 (t, 2H, J = 7.2Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 137.43, 128.93, 128.79, 127.48, 118.50, 36.30, 26,64, 18.61

Methyl 3-(methylthio)propanoate(4d)



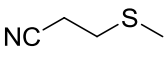
Isolated in 61.8% yield, pale yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 3.63 (s, 3H), 2.70 (t, 2H, J = 7.4Hz), 2.56 (t, 2H, J = 7.4Hz), 2.05 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 171.38, 50.75, 33.22, 28.06, 14.46

3-(Methylthio)cyclohexanone(4e)



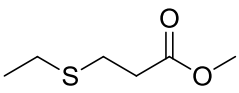
Isolated in 72.6% yield, yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 2.90-2.93 (m, 1H), δ 2.61-2.66 (m, 1H), δ 2.26-2.34 (m, 3H), δ 2.05-2.10 (m, 5H), δ 1.63-1.68 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 208.73, 47.50, 44.12, 40.86, 30.90, 24.05, 13.48

3-(Methylthio)propanenitrile(4f)



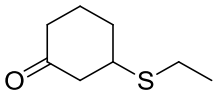
Isolated in 58.9% yield, colorless oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 2.71 (t, 2H, J = 7.5Hz), 2.60 (t, 2H, J = 7.5Hz), 2.13 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 117.39, 28.65, 17.43, 14.58

Methyl 3-(ethylthio)propanoate(4g)



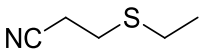
Isolated in 68.5% yield, pale yellow oil, Lit[20], ^{1}H NMR (400MHz, $CDCl_3$): δ 3.63 (s, 3H), 2.71-2.75 (m, 2H), 2.48-2.55 (m, 4H), 1.17-1.21 (m, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 172.45, 51.75, 34.65, 26.49, 25.94, 14.64

3-(Ethylthio)cyclohexanone(4h)



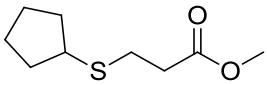
Isolated in 81.5% yield, brown oil, Lit[21], ^{1}H NMR (400MHz, $CDCl_3$): δ 3.03 (m, 1H), 2.61-2.65 (m, 1H), 2.50 (q, 2H, J = 7.4Hz), 2.28-2.30 (m, 3H), 2.06-2.09 (m, 2H), 1.63-1.68 (m, 2H), 1.19 (t, 3H, J = 7.4Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 207.93, 47.14, 41.34, 39.96, 30.55, 23.40, 23.23, 13.78

3-(Ethylthio)propanenitrile(4i)



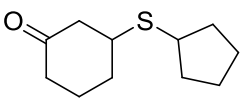
Isolated in 77.1% yield, colorless oil, Lit[22], ^{1}H NMR (400MHz, $CDCl_3$): δ 2.74 (t, 2H, J = 7.1Hz), 2.57 (m, 4H), 1.22 (t, 3H, J = 7.4Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 118.52, 27.09, 26.00, 18.86, 14.56

Methyl 3-(cyclopentylthio)propanoate(4j)



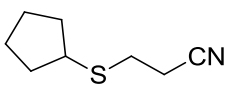
Isolated in 68.1% yield, pale yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 3.72 (s, 3H), 2.81 (t, 2H, J = 7.4Hz), 2.63 (t, 2H, J = 7.4Hz), 2.55 (m, 1H), 1.63 (m, 2H), 1.36(m, 6H).^{13}C NMR (100MHz, $CDCl_3$): δ 171.40, 59.57, 50.70, 33.71, 28.24, 25.94, 21.30

3-(Cyclopentylthio)cyclohexanone(4k)



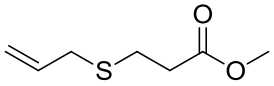
Isolated in 75.7% yield, yellow oil, Lit[19], ^{1}H NMR(400MHz,$CDCl_3$): δ 2.98 (m, 1H), 2.60-2.65 (m, 1H), 2.45 (m, 2H), 2.27-2.33 (m, 3H), 2.04-2.08 (m, 2H), 1.62-1.67 (m, 2H), 1.49-1.57 (m, 2H), 1.24-1.29 (m, 3H), 0.82 (t, 2H, J = 7.0Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 208.76, 48.16, 42.68, 40.90, 31.57, 31.04, 30.43, 24.18, 22.22

3-(Cyclopentylthio)propanenitrile(4l)



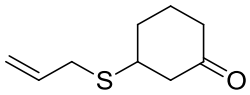
Isolated in 68.1% yield, pale yellow oil, Lit[19], ^{1}H NMR (400MHz, $CDCl_3$): δ 2.71 (t, 2H, J = 7.2Hz), 2.57 (t, 2H, J = 7.2Hz), 2.52 (m, 1H), 1.53 (m, 2H), 1.28(m, 6H). ^{13}C NMR (100MHz, $CDCl_3$): δ 118.45, 30.90, 29.11, 27.59, 22.24, 18.91

Methyl 3-(allylthio)propanoate(4m)



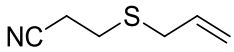
Isolated in 71.2% yield, pale yellow oil, Lit[23], ^{1}H NMR (400MHz, $CDCl_3$): δ 5.61-5.80 (m, 1H), 5.05 (d, 2H, J = 18.7Hz), 3.62 (s, 3H), 3.08 (d, 2H, J = 6.9Hz), 2.66 (t, 2H, J = 7.2Hz), 2.52 (t, 2H, J = 7.2Hz). ^{13}CNMR (100MHz, $CDCl_3$): δ 172.27, 134.13, 117.18, 51.69, 34.76, 34.37, 25.53

3-(Allylthio)cyclohexanone(4n)



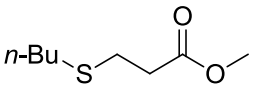
Isolated in 82.8% yield, pale yellow oil, Lit[23], ^{1}H NMR (400MHz, $CDCl_3$): δ 5.91-5.64 (m, 1H), 5.11 (d, 2H, J = 13.9Hz), 3.19 (d, 2H, J = 7.1Hz), 3.09-2.95 (m, 1H), 2.68 (dd, 1H, J = 14.3, 4.5Hz), 2.45-2.25 (m, 3H), 2.18-2.01 (m, 2H), 1.78-1.60 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ 208.86, 134.23, 117.24, 47.92, 41.40, 40.97, 33.58, 31.36, 24.21

3-(Allylthio)propanenitrile(4o)



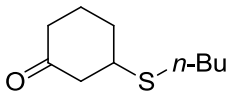
Isolated in 66.5% yield, pale red oil, Lit[24], ^{1}H NMR (400MHz, $CDCl_3$): δ 5.72 (m, 1H), 5.09 (d, 2H, J = 12.8Hz), 3.15 (d, 2H, J = 7.2Hz), 2.66 (t, 2H, J = 7.0Hz), 2.56 (t, 2H, J = 7.0Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 133.63, 118.41, 118.01, 34.75, 25.86, 18.66

Methyl 3-(butylthio)propanoate(4p)



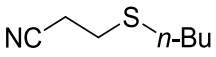
Isolated in 78.8% yield, pale yellow oil, Lit[25], ^{1}H NMR(400MHz,$CDCl_3$): δ 3.67 (s, 3H), 2.75 (t, 2H, J = 7.4Hz), 2.58 (t, 2H, J = 7.3Hz), 2.50 (t, 2H, J = 7.3Hz), 1.54 (m, 2H), 1.37 (m, 2H), 0.89 (s, 3H, J = 7.4Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 172.37, 51.66, 54.69, 31.79, 31.59, 36.92, 21.90, 13.59

3-(Butylthio)cyclohexanone(4q)



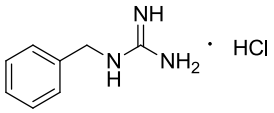
Isolated in 72.4% yield, yellow oil, Lit[25], ^{1}H NMR(400MHz,$CDCl_3$): δ 2.62-2.65 (m, 1H), 2.48 (m, 3H), 2.28-2.31 (m, 3H), 2.07-2.09 (m, 2H), 1.64-1.67 (m, 2H), 1.48 (m, 2H), 1.32 (m, 2H), 0.84 (t, 3H, J = 7.1Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 207.91, 47.25, 41.76, 39.95, 30.78, 30.66, 29.21, 23.26, 21.03, 12.64

3-(Butylthio)propanenitrile(4r)



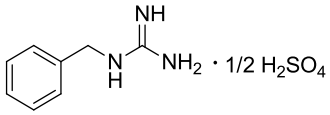
Isolated in 63.5% yield, yellow oil, Lit[26], ^{1}H NMR (400MHz, $CDCl_3$): δ 2.71 (t, 2H, J = 6.9Hz), 2.51-2.58 (dt, 4H, J = 14.6Hz, 7.2Hz), 1.51 (m, 2H), 1.36 (m, 2H), 0.86 (t, 3H, J = 7.2Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 117.38, 30.96, 30.49, 26.61, 20.86, 17.91, 12.60

1-Benzylguanidine hydrochloride (5a)



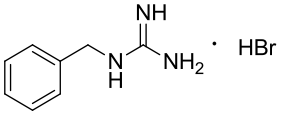
Mp 175-178 ^{o}C, Lit[16,18], Mp 173-174^{o}C, ^{1}H NMR (400MHz, D_2O): δ 7.43 (m, 5H), 4.43 (s, 2H). ES ($[M+H]^+$) calculated: 150.24(100)

1-Benzylguanidine Half Sulfate(5b)



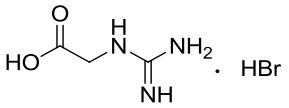
Mp 204-205 ^{o}C, Lit[15], Mp 208-209 ^{o}C, ^{1}H NMR (400MHz, D_2O): δ 7.38 (m, 5H), 4.42 (s, 2H). ES ($[M+H]^+$) calculated: 150.24(100)

1-Benzylguanidine Hydrobromate(5c)



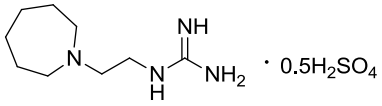
Mp 110-113^{o}C, ^{1}H NMR (400MHz, D_2O): δ 7.42 (m, 5H), 4.43 (s, 2H). ES ($[M+H]^+$) calculated: 150.24(100)

2-Guanidinoacetic Hydrobromate (5d)



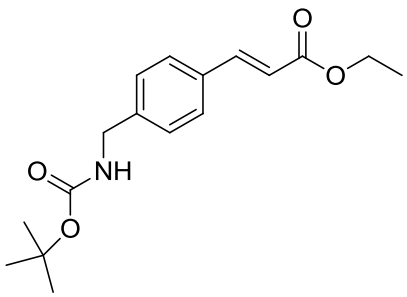
Carbonized at 284 °C, Lit[18] Carbonized at 280-284°C, ^{1}H NMR (400MHz, D_2O) : δ 3.69 (s, 2H). ES([M+H]$^+$) calculated: 118.07(100)

Ismelin Half Sulfate (5e)



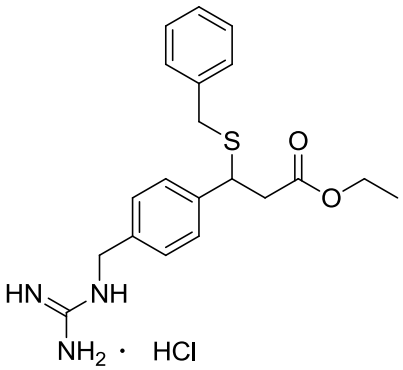
Mp 270-271 °C, Lit[17], Mp 276-281°C. ^{1}H NMR (400MHz, D_2O) : δ 3.36 (t, 2H, J = 6.4Hz), 3.31 (m, 6H), 1.80 (s, 4H), 1.60 (s, 4H). ^{13}C NMR (100MHz, D_2O): δ 156.98, 55.10, 54.66, 36.28, 25.91, 22.99. ES([M+H]$^+$) calculated: 185.26 (100)

Ethyl 3-(4-tert-butoxycarbonylaminomethylphenyl) acrylate (10)



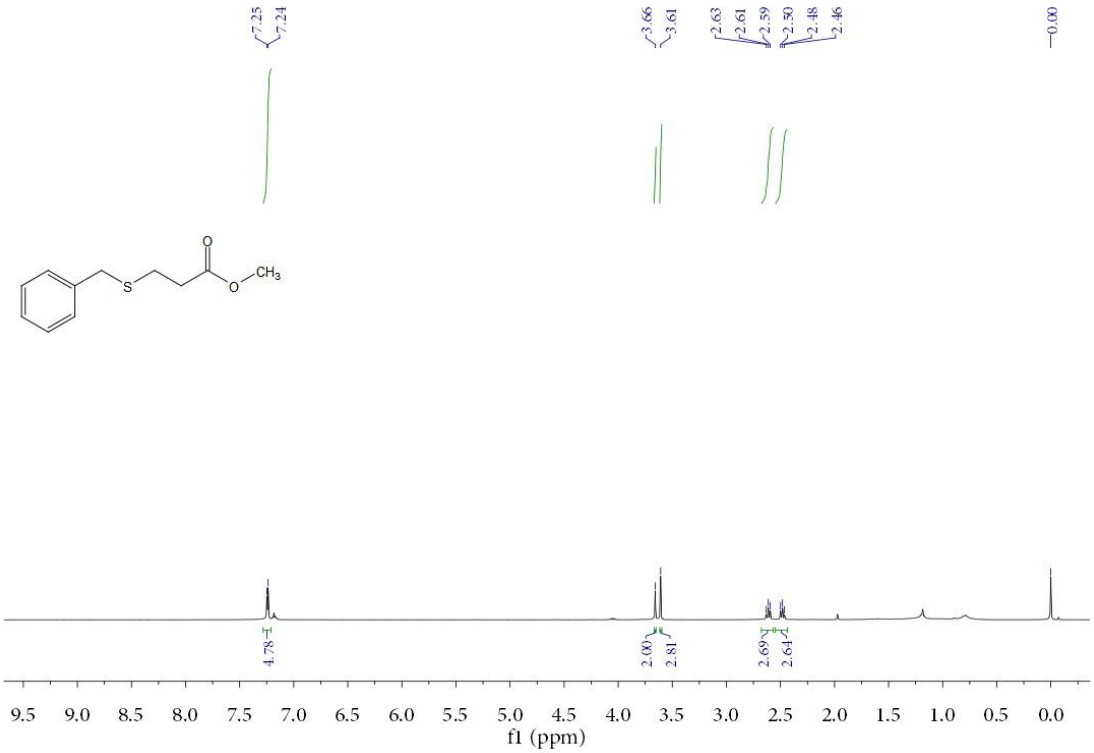
Isolated in 20.5% overall yield as a brown oil, Lit[31], ^{1}H NMR (400MHz, $CDCl_3$) δ 7.59 (d, 1H, J = 16.0Hz), 7.40 (d, 2H, J = 8.2Hz), 7.22 (d, 2H, J = 8.2Hz), 6.34 (d, 2H, J = 16.0Hz), 4.71 (s, 2H), 4.19 (q, 2H, J = 7.1Hz), 1.38 (s, 9H), 1.26 (t, 3H, J = 7.1Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 166.99, 151.49, 143.21, 139.91, 132.33, 127.07, 126.66, 117.01, 81.68, 59.43, 48.22, 26.99, 13.31

Ethyl 3-benzylthio-3-(4-guanidinomethylphenyl) propanoate Hydrochloride (12)

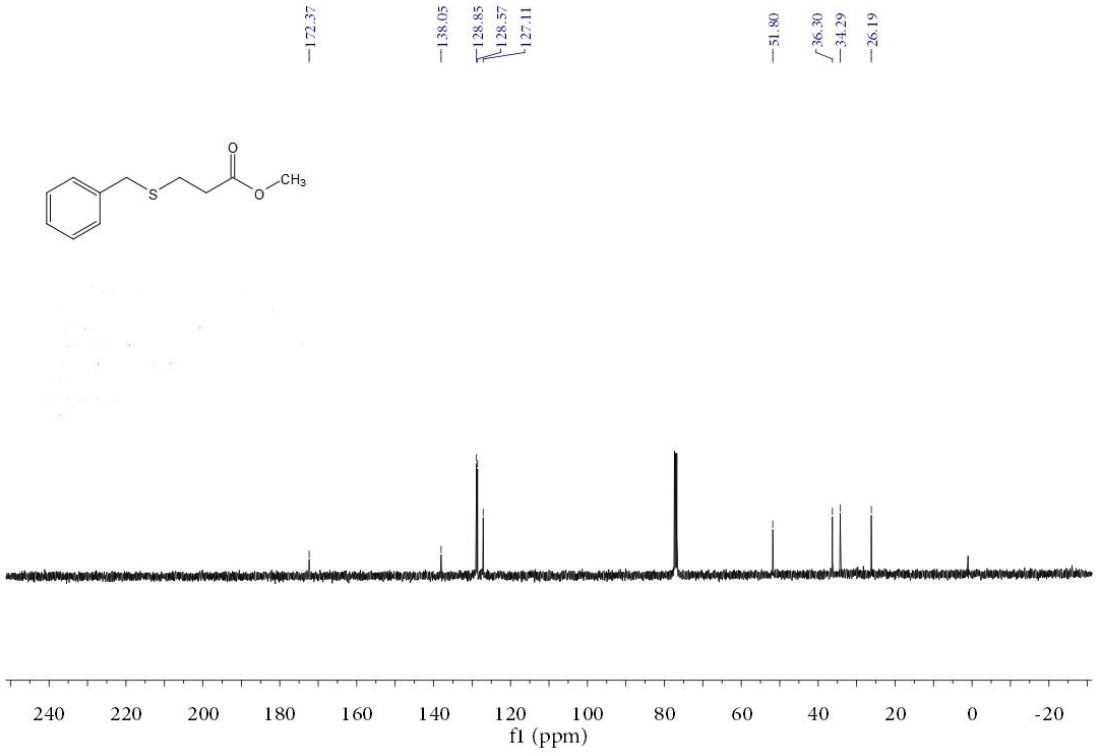


Isolated by column chromatography (Ethyl Acetate/MeOH = 5:1) in 42.1% yield. Yellow solid, Mp 176.1-179.6°C, ^{1}H NMR (400MHz, CD_3OD) δ 7.34 (m, 9H), 4.33 (s, 1H), 4.16 (q, 2H, J = 7.1Hz), 3.91 (m, 2H), 2.74 (m, 2H), 1.22 (t, 3H, J = 7.1Hz). ^{13}C NMR (100MHz, DMSO-d_6): δ 170.43, 163.47, 137.78, 129.84, 129.55, 129.26, 128.87, 128.23, 127.77, 127.41, 60.54, 44.64, 42.25, 42.07, 35.31, 14.67, HR ESI MS m/z calcd for $C_{20}H_{25}N_3O_2S$, ($[M+H]^+$) 372.17451.

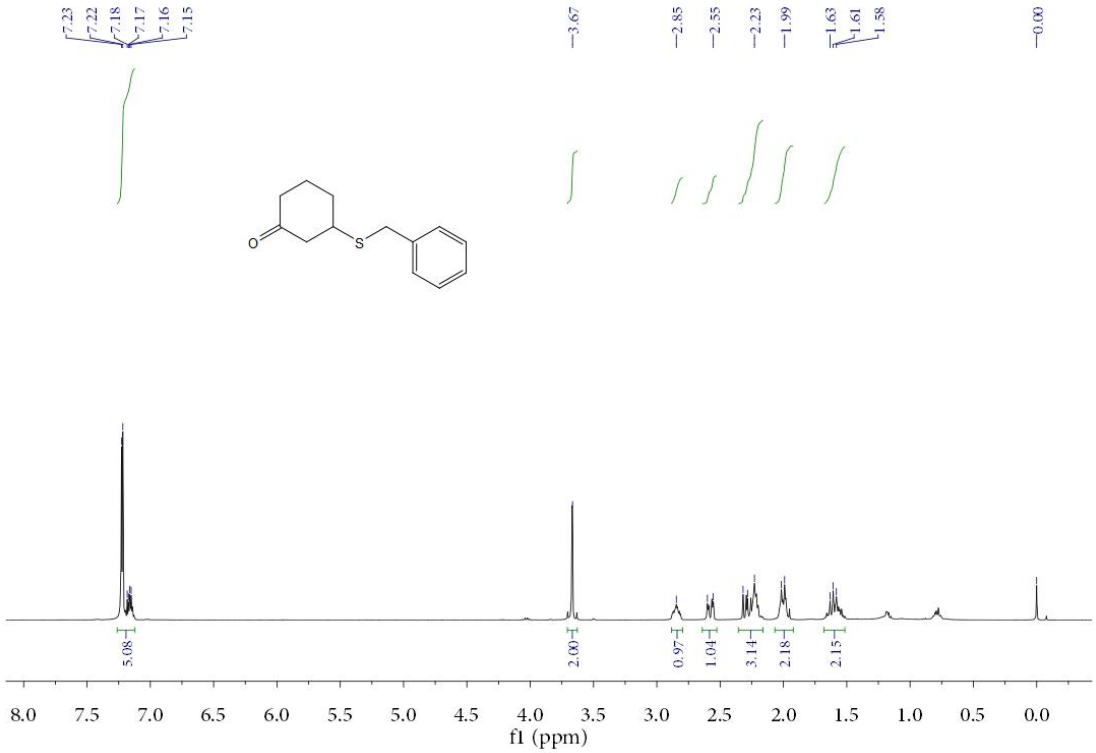
2. **Spectra of compounds**



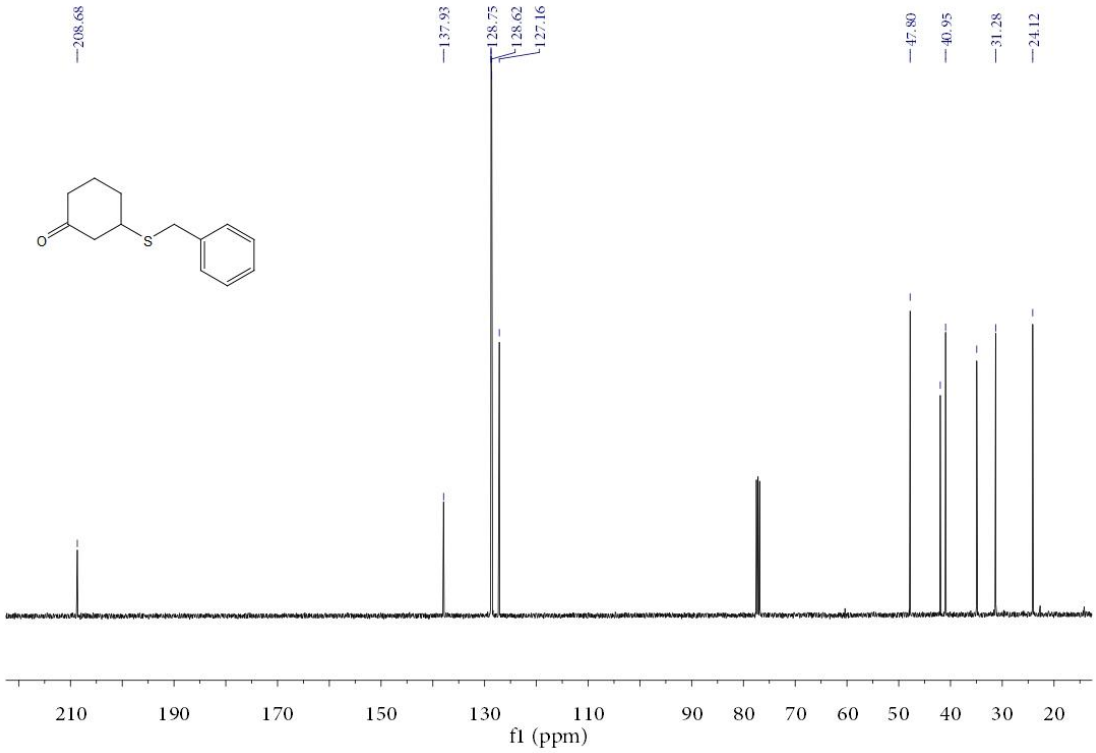
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4a**



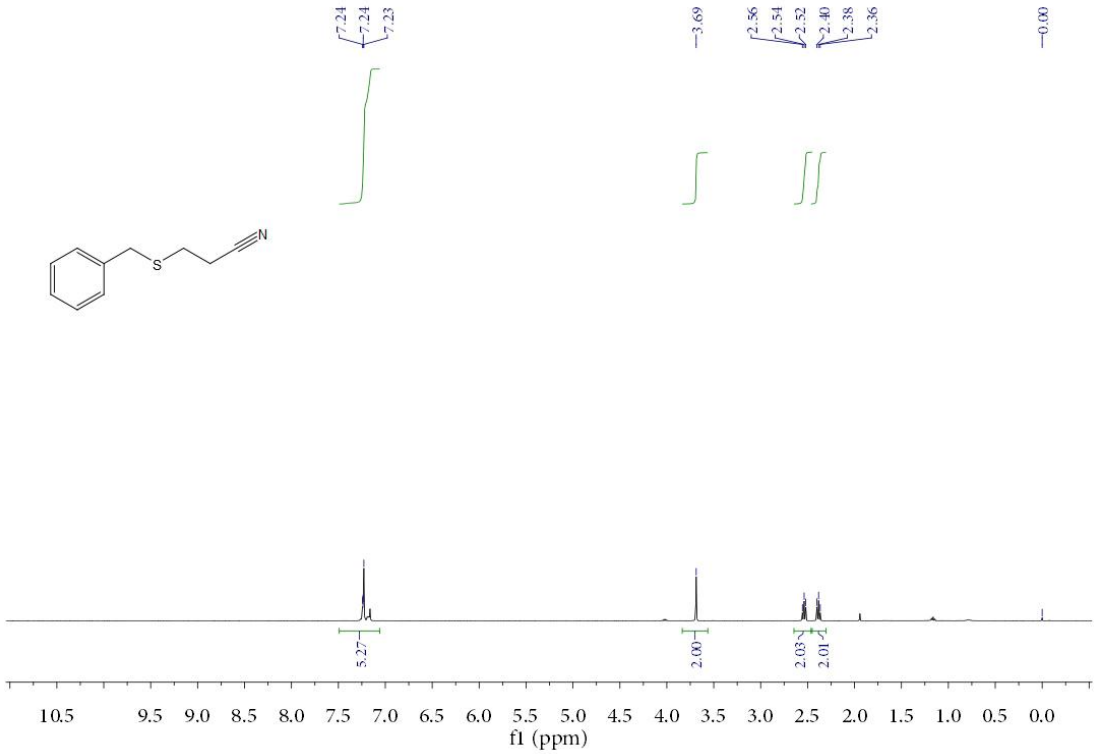
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4a**



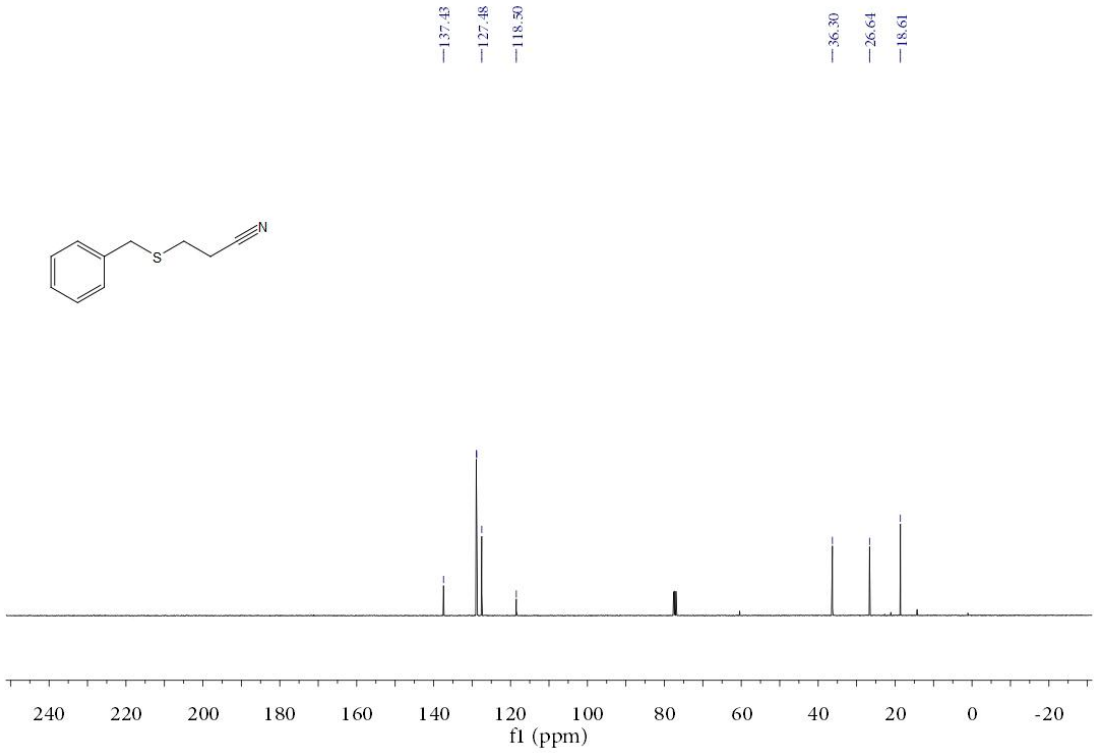
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4b**



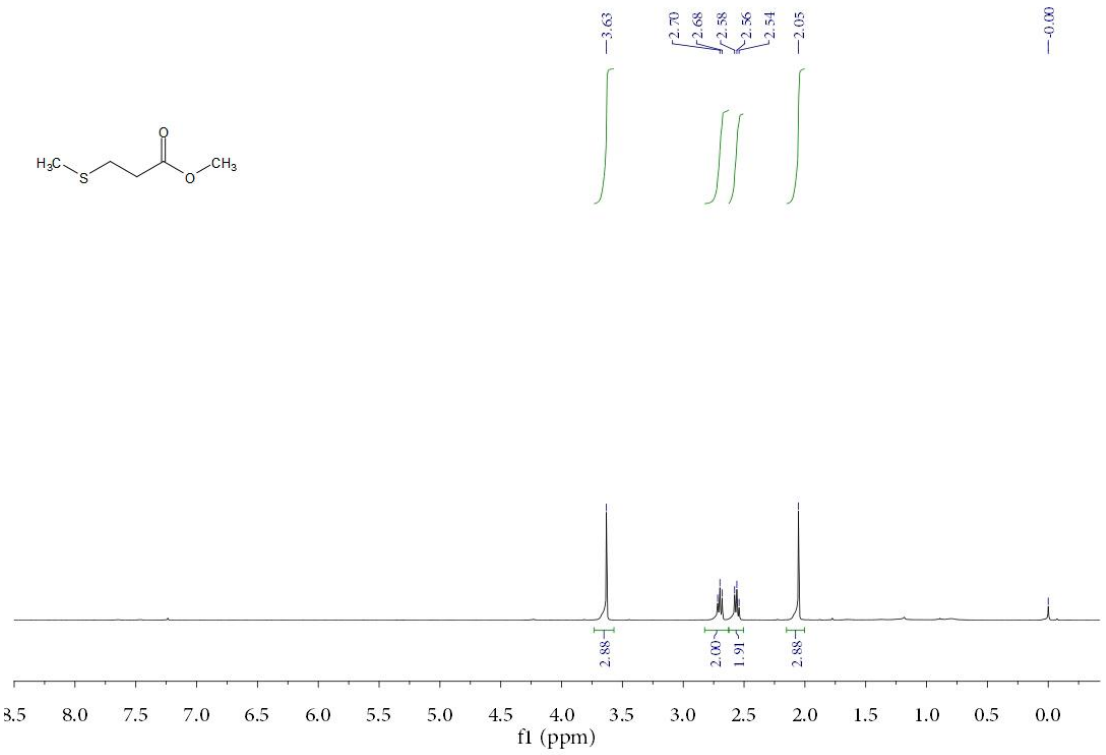
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4b**



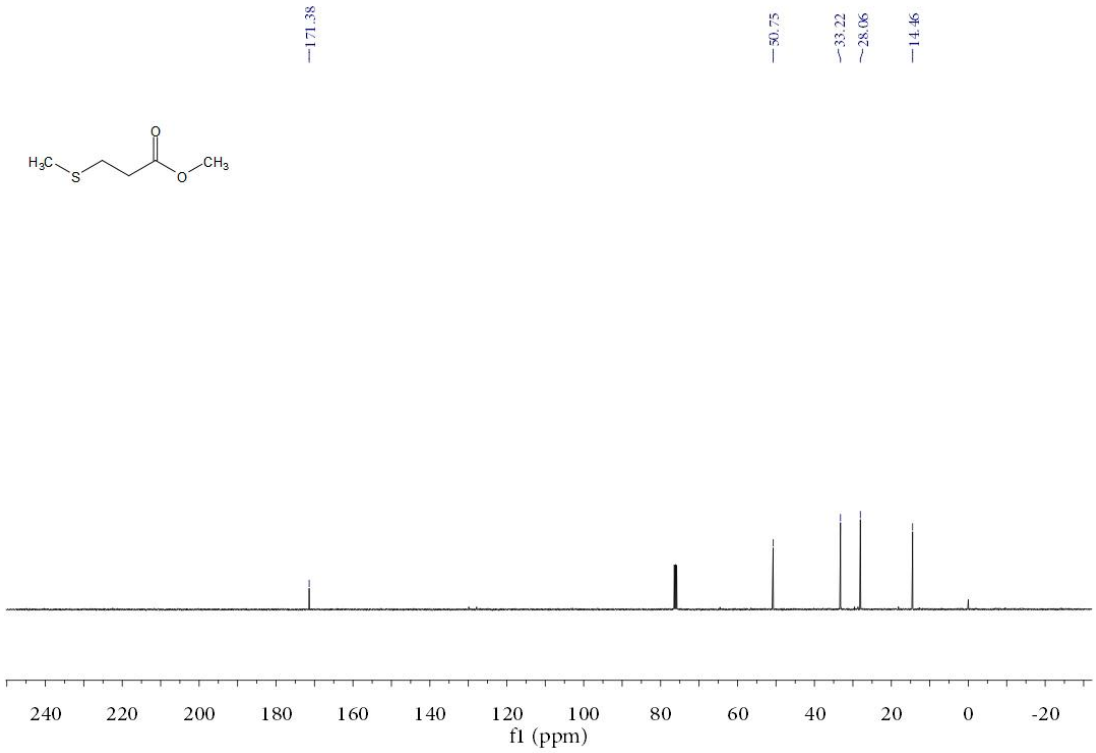
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4c**



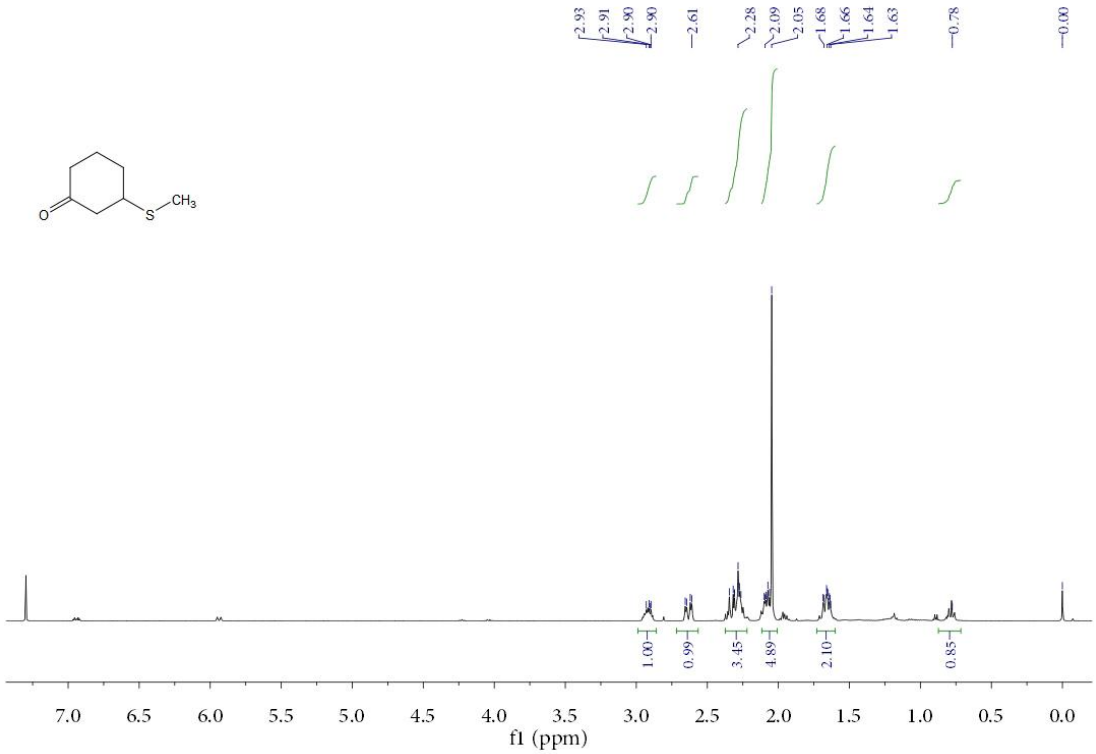
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4c**



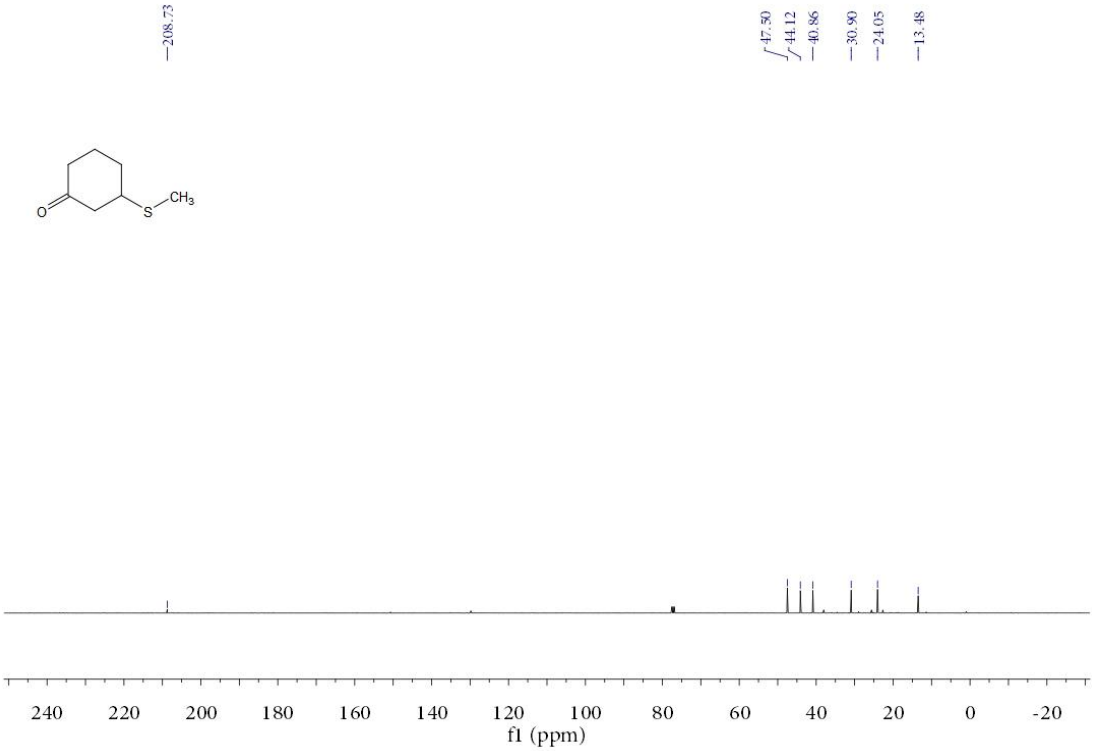
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4d**



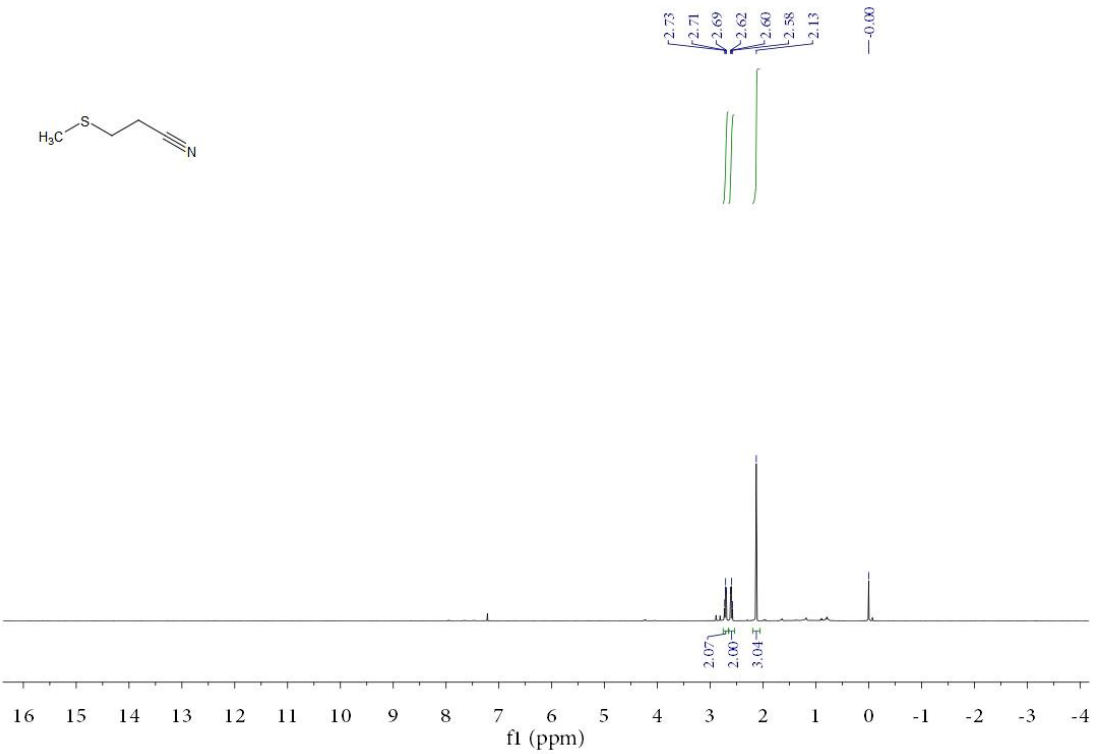
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4d**



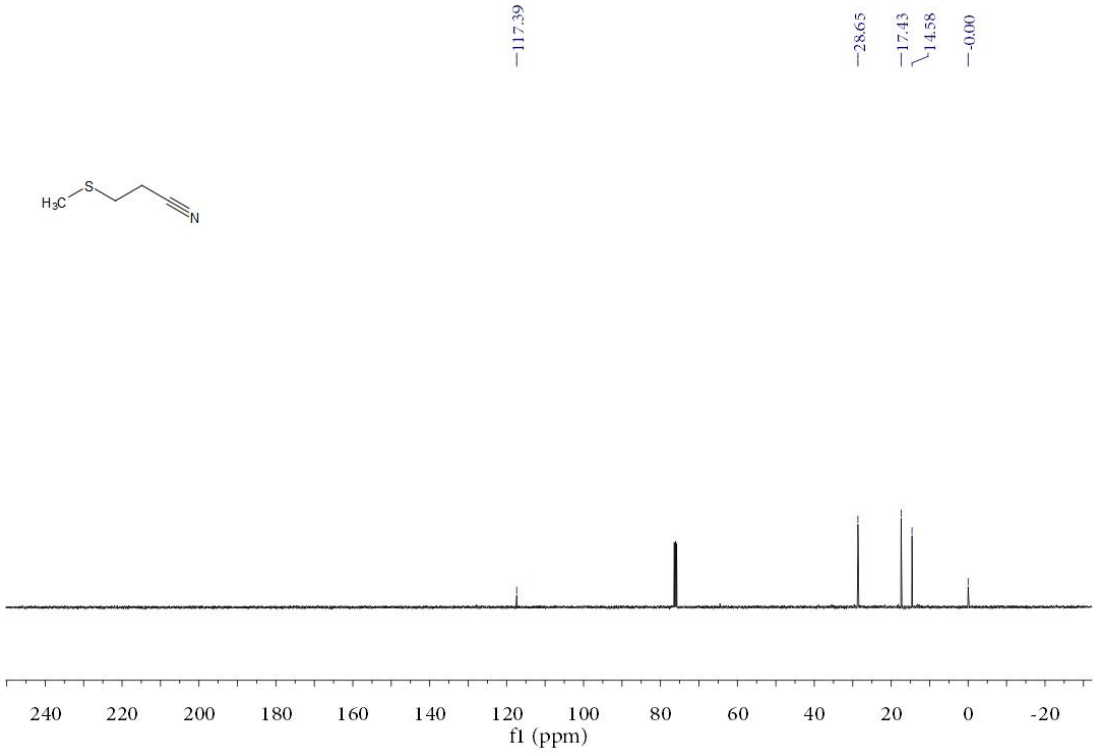
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4e**



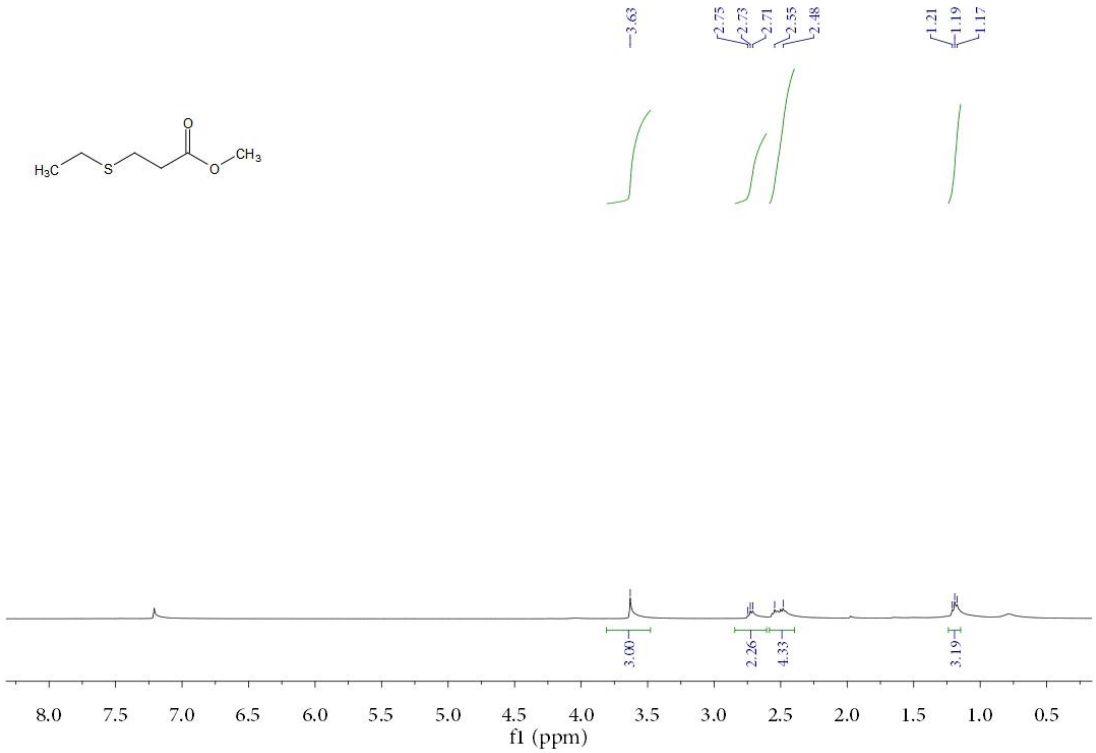
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4e**



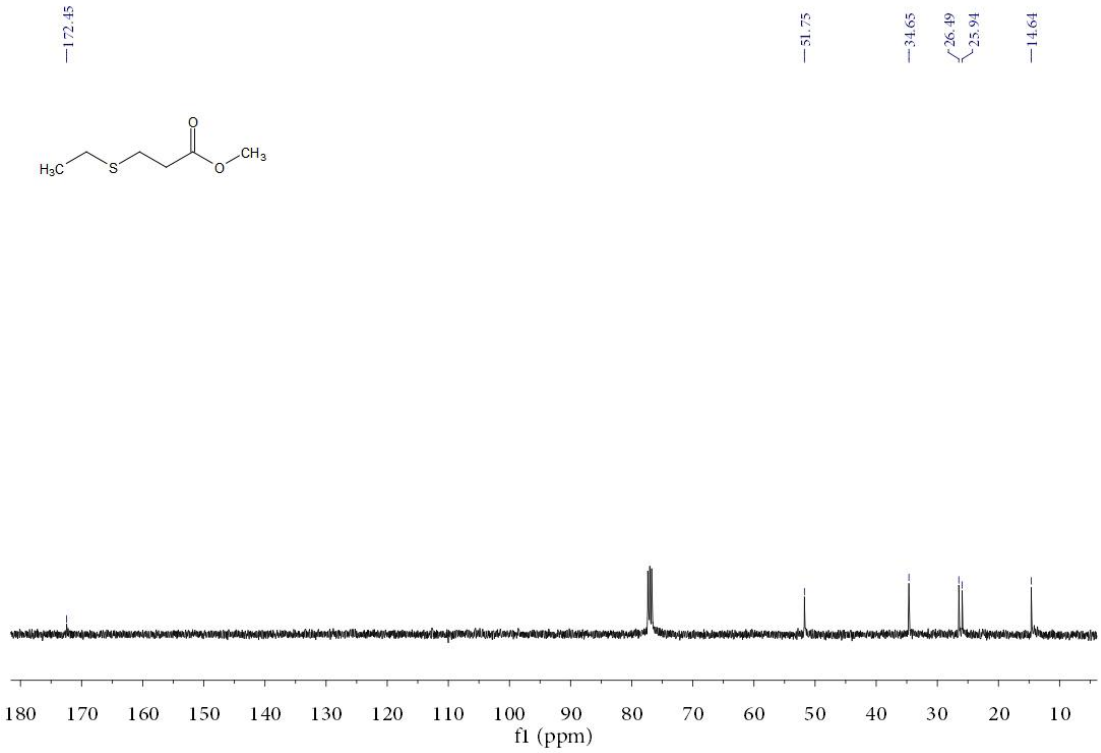
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4f**



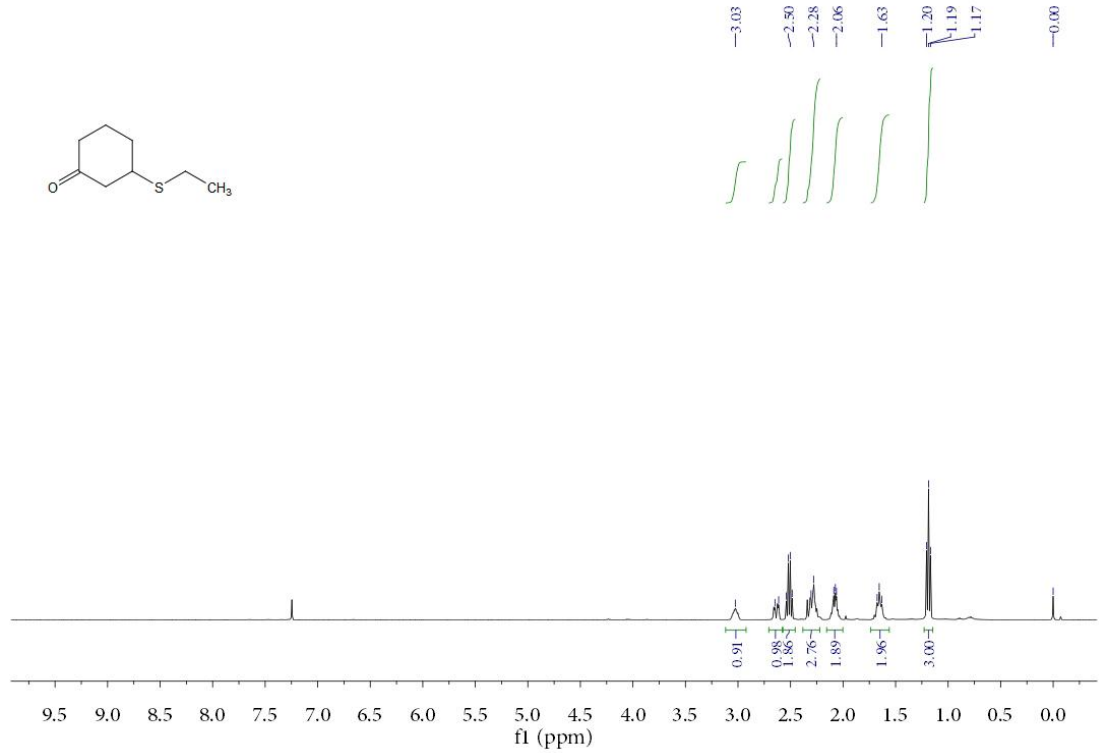
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4f**



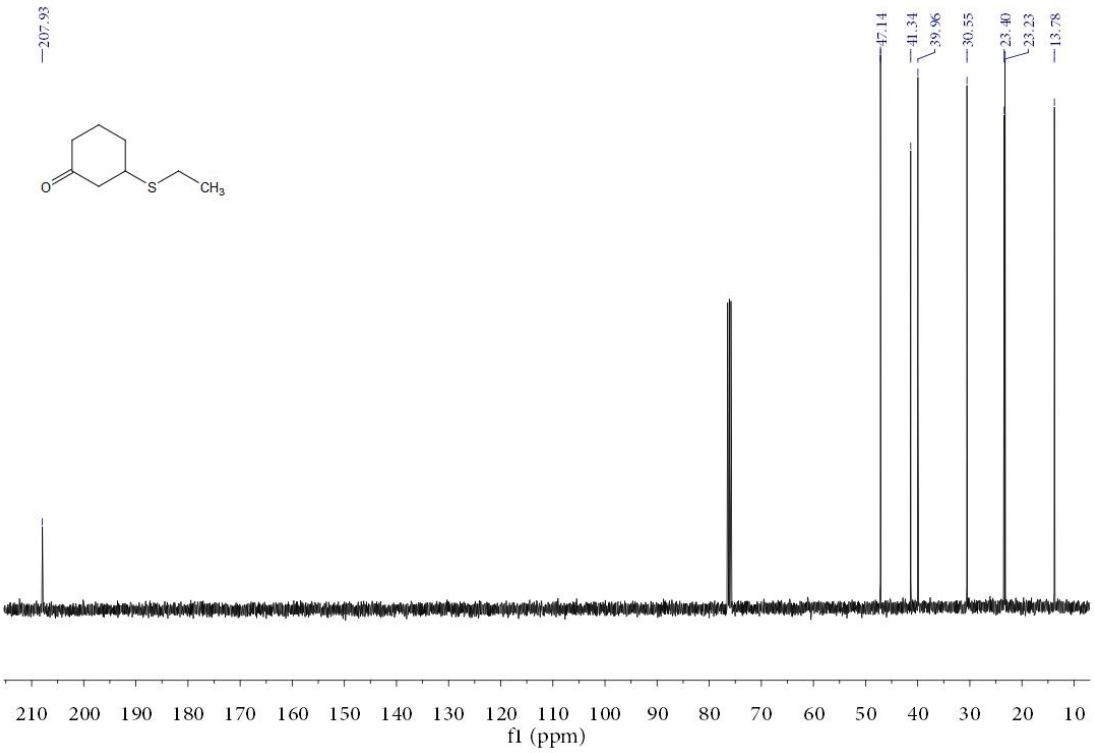
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4g**



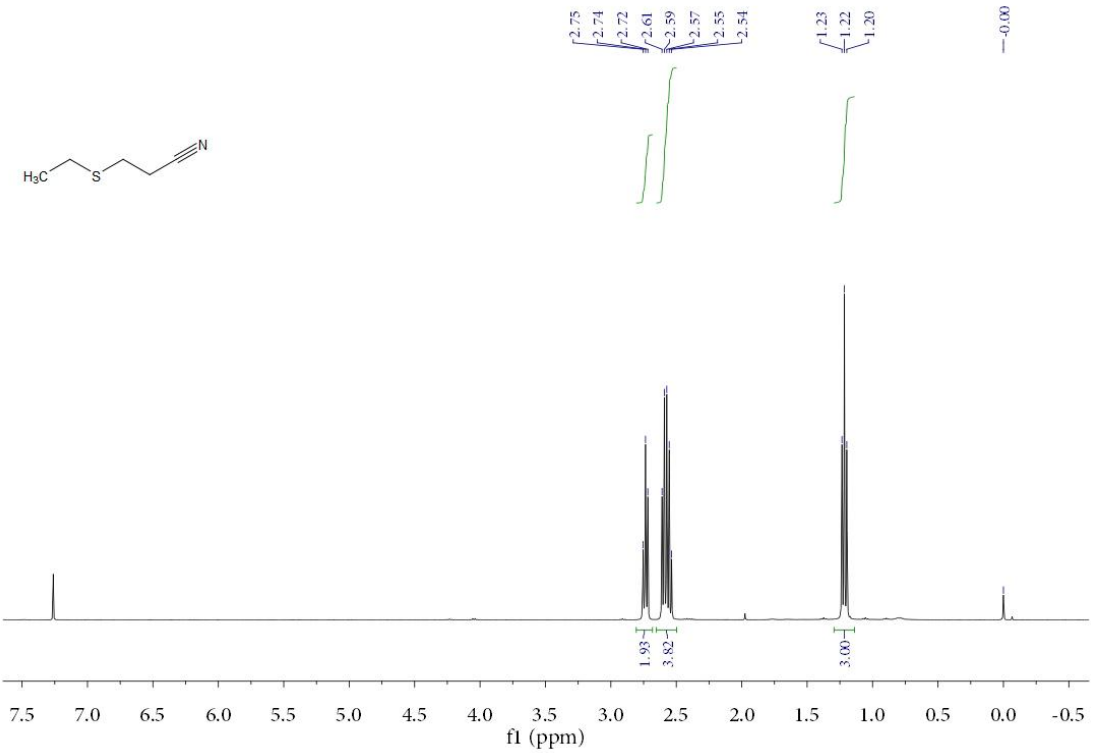
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4g**



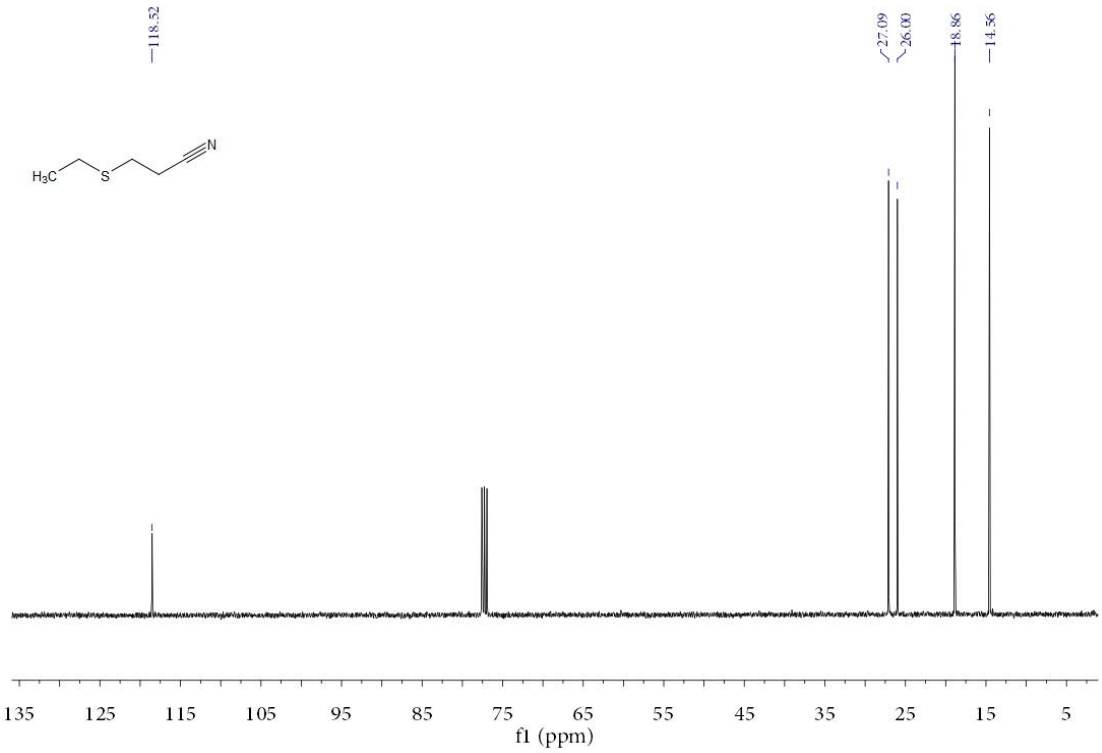
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4h**



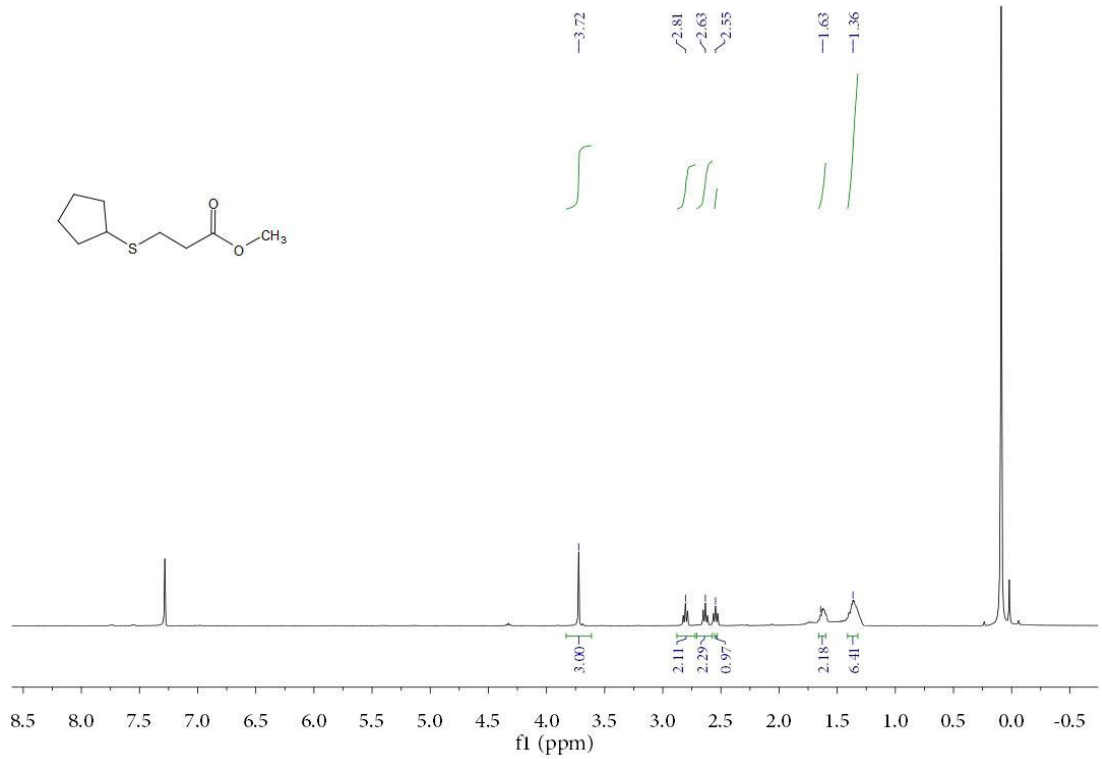
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4h**



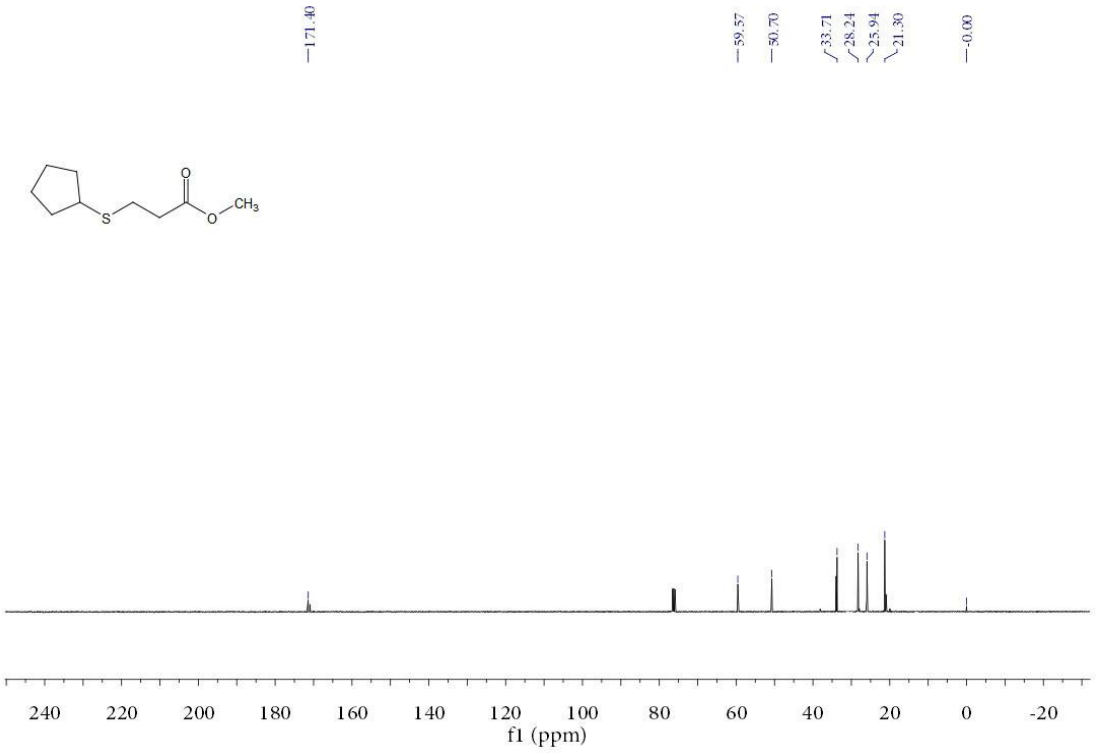
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4i**



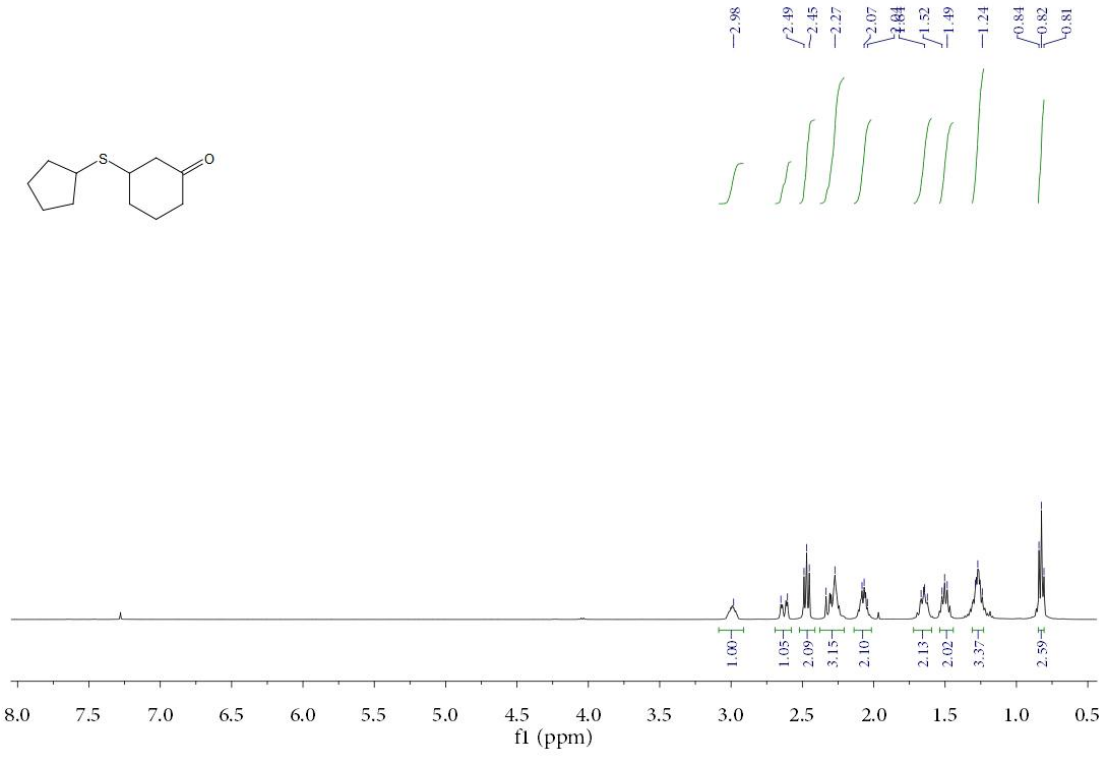
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4i**



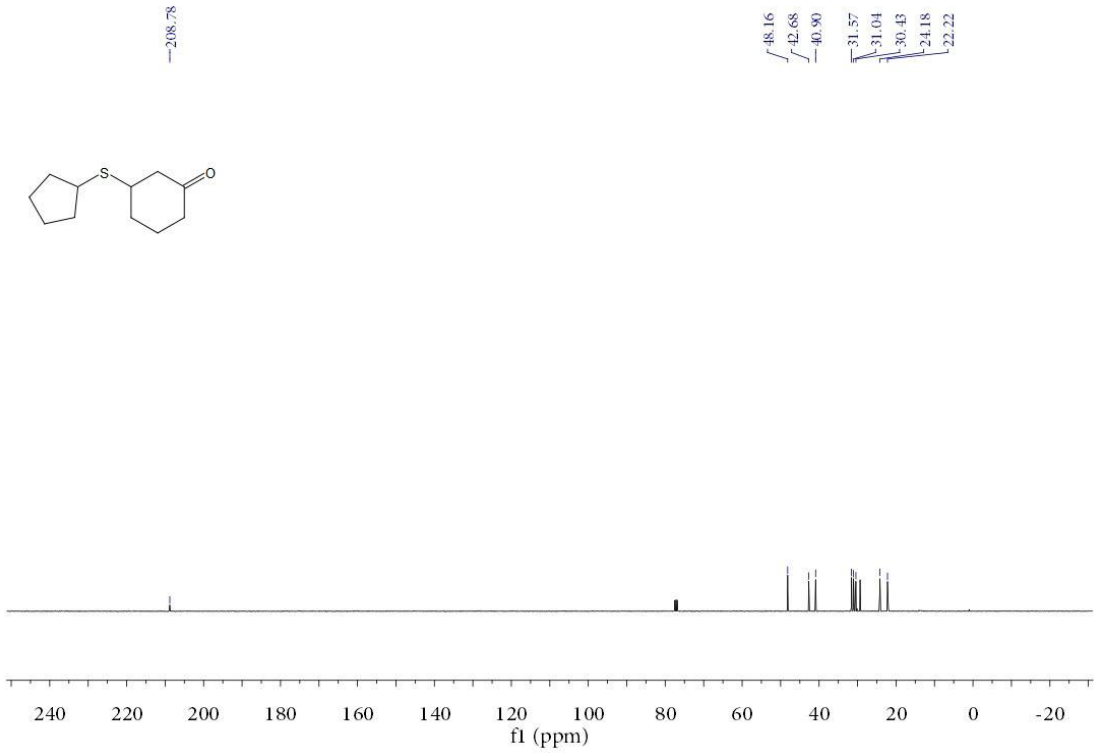
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4j**



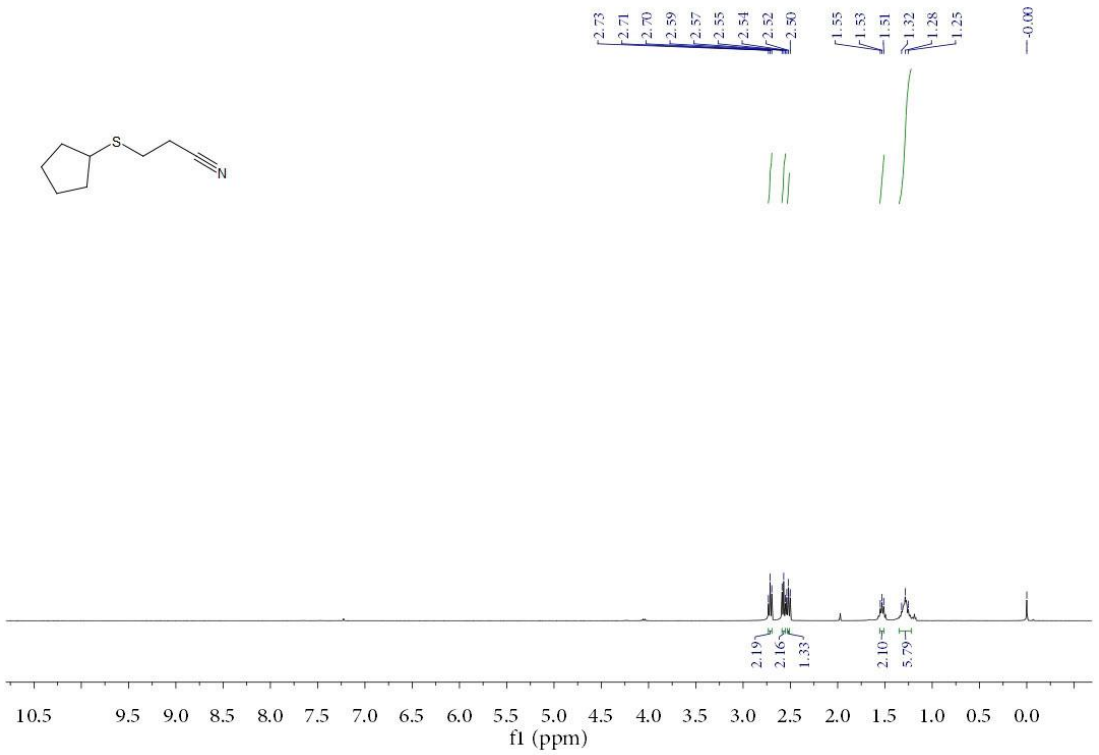
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4j**



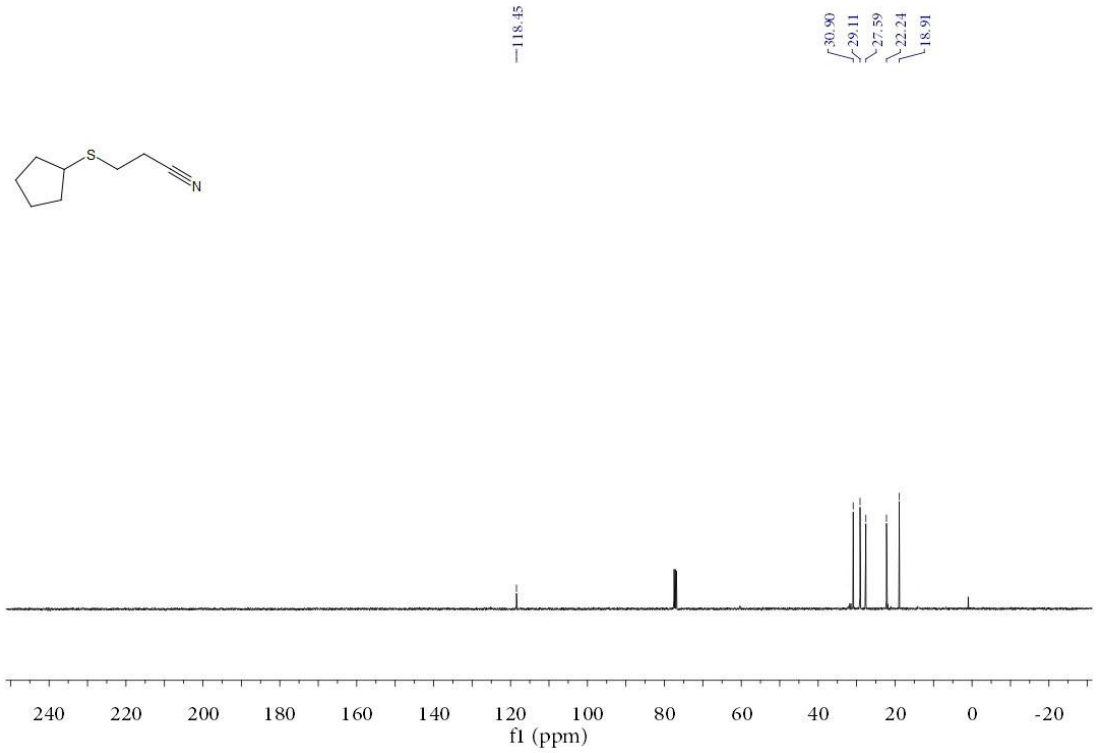
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4k**



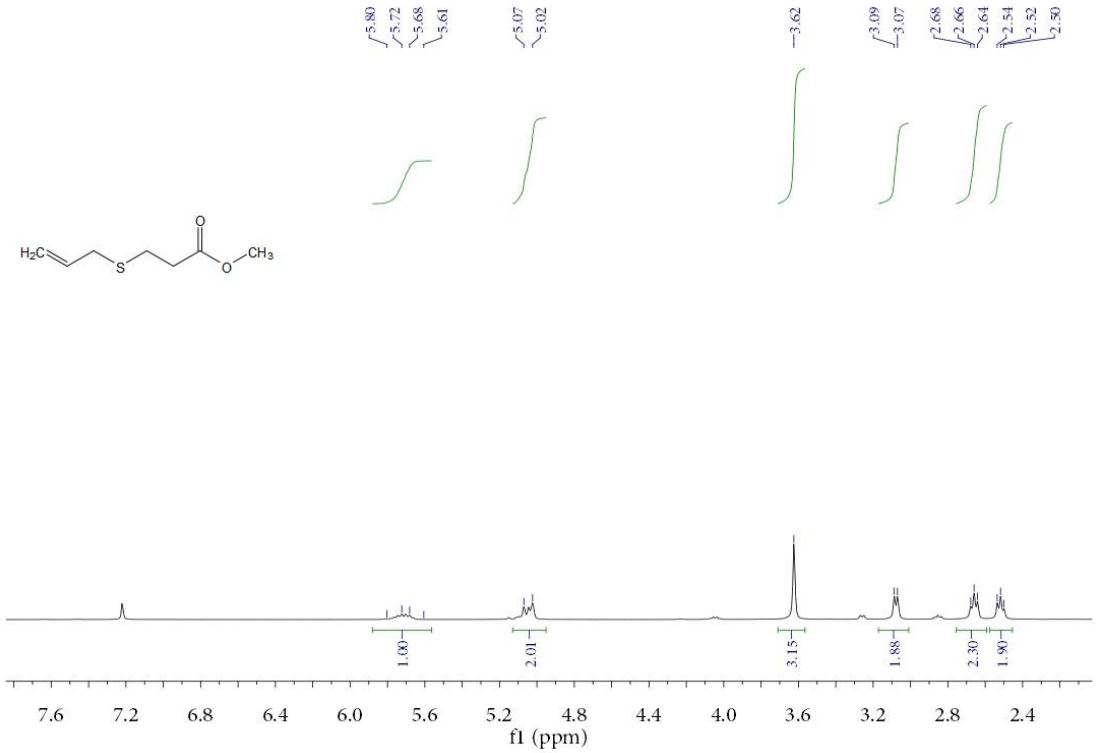
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4k**



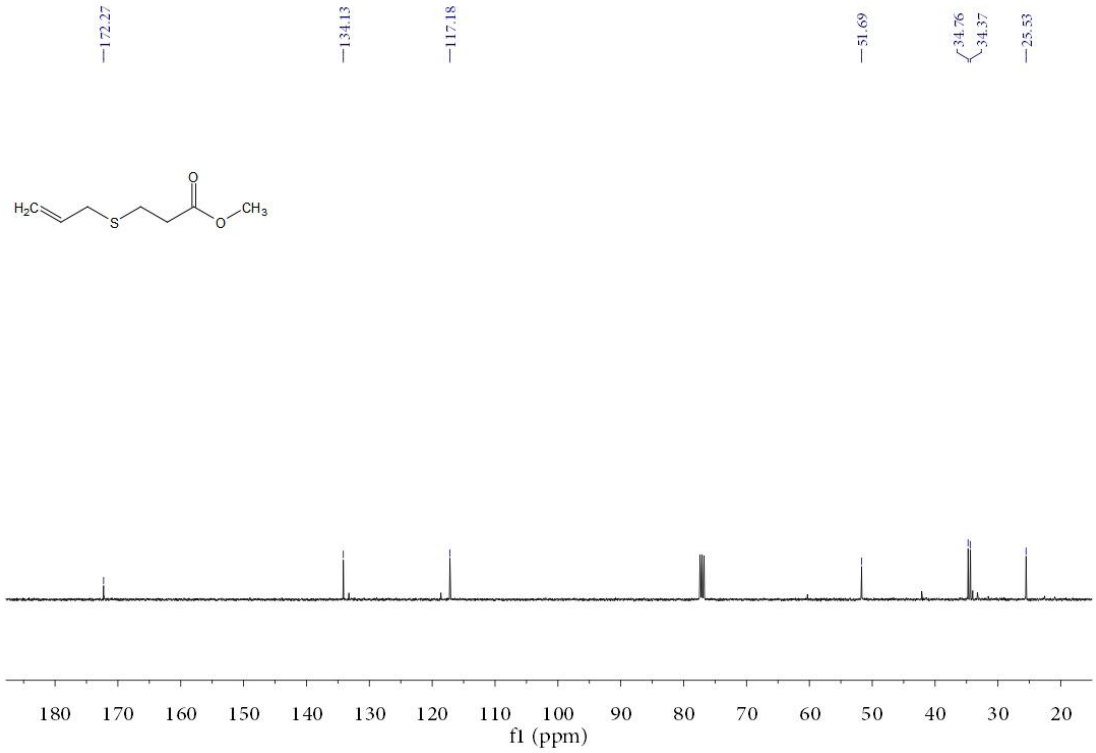
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4l**



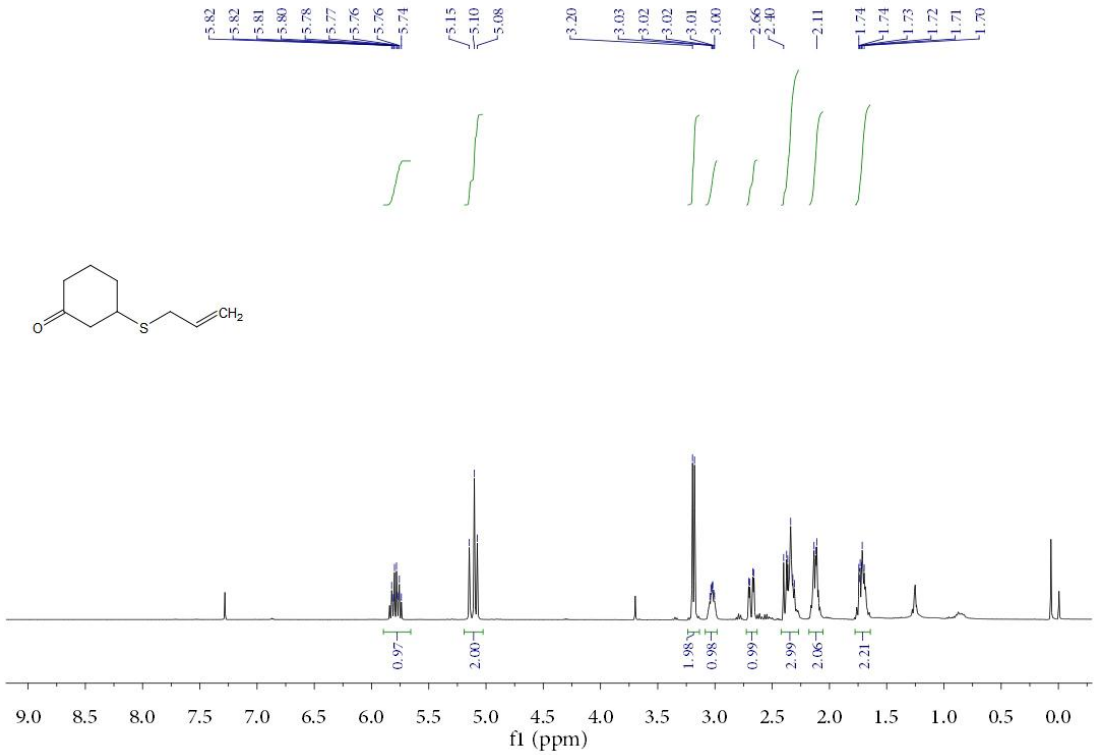
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4l**



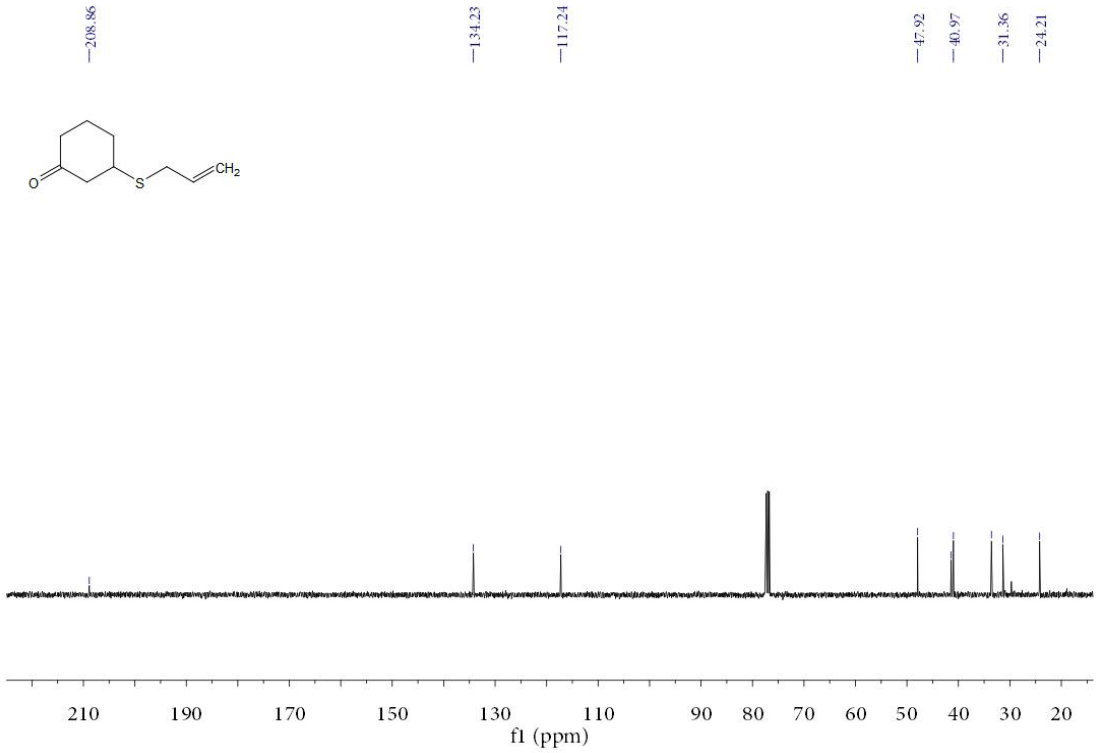
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4m**



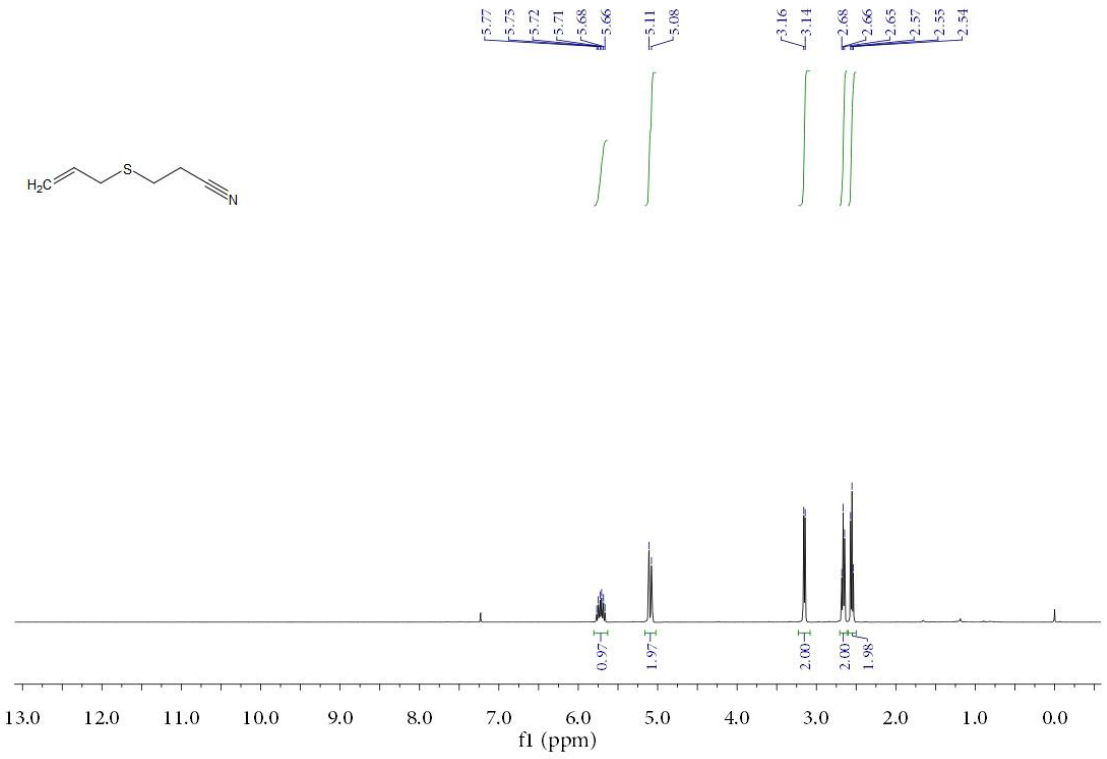
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4m**



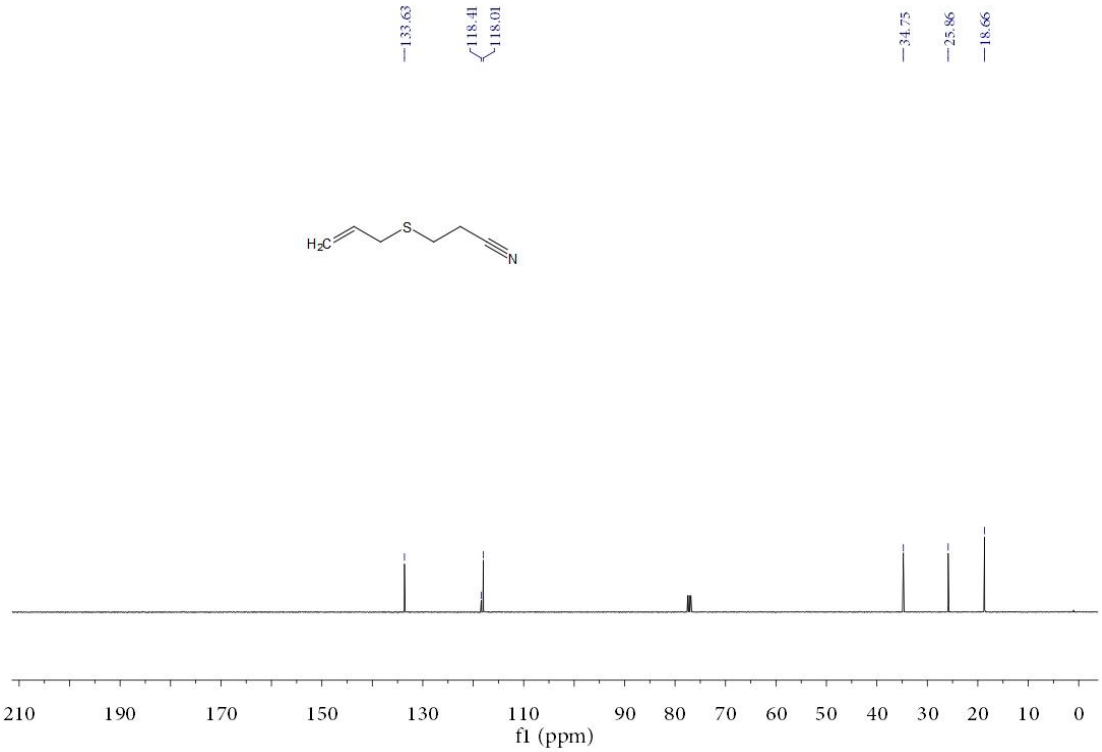
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4n**



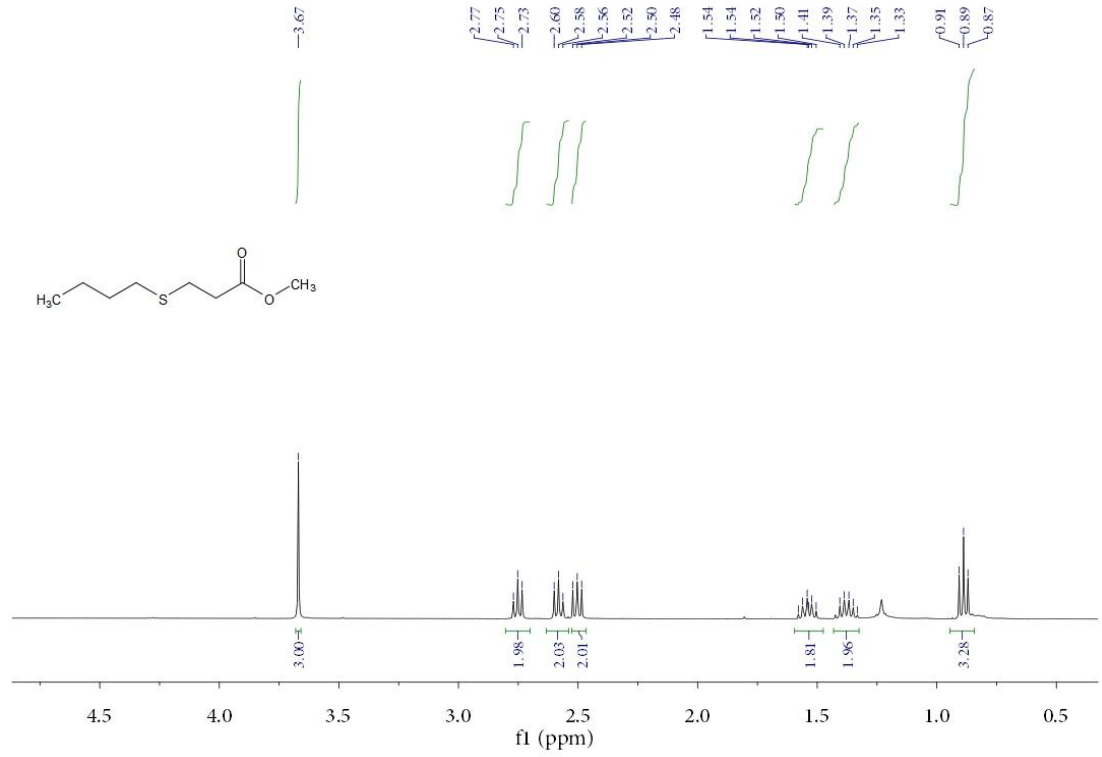
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4n**



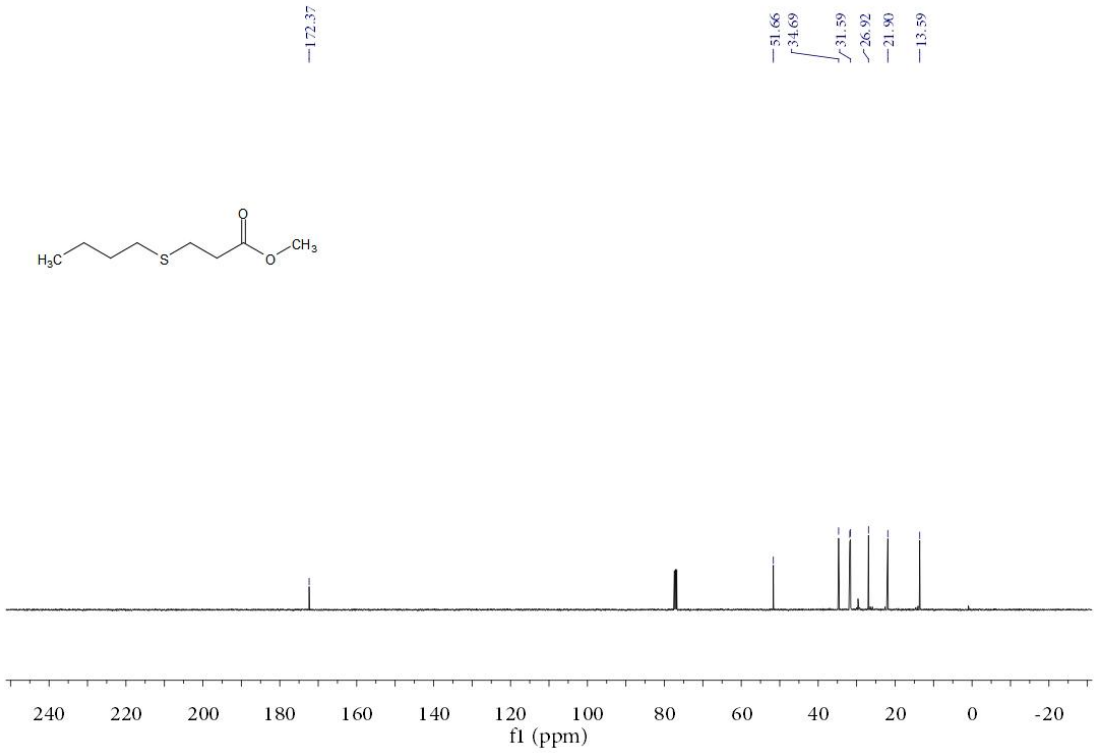
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4o**



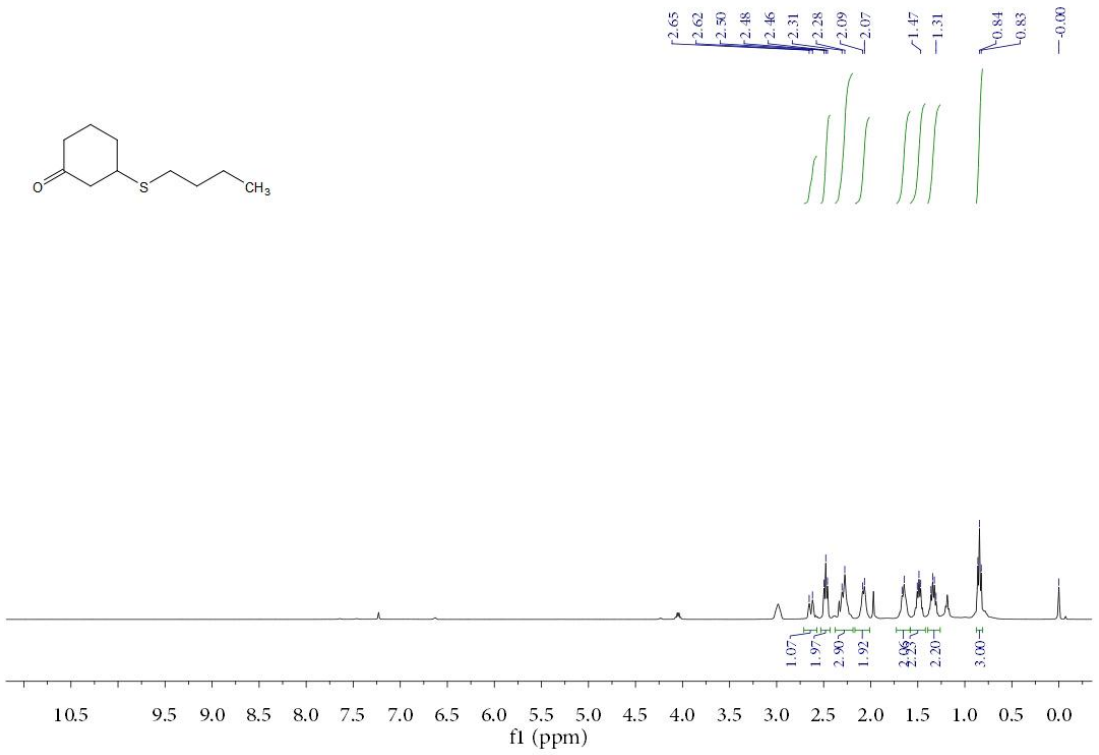
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4o**



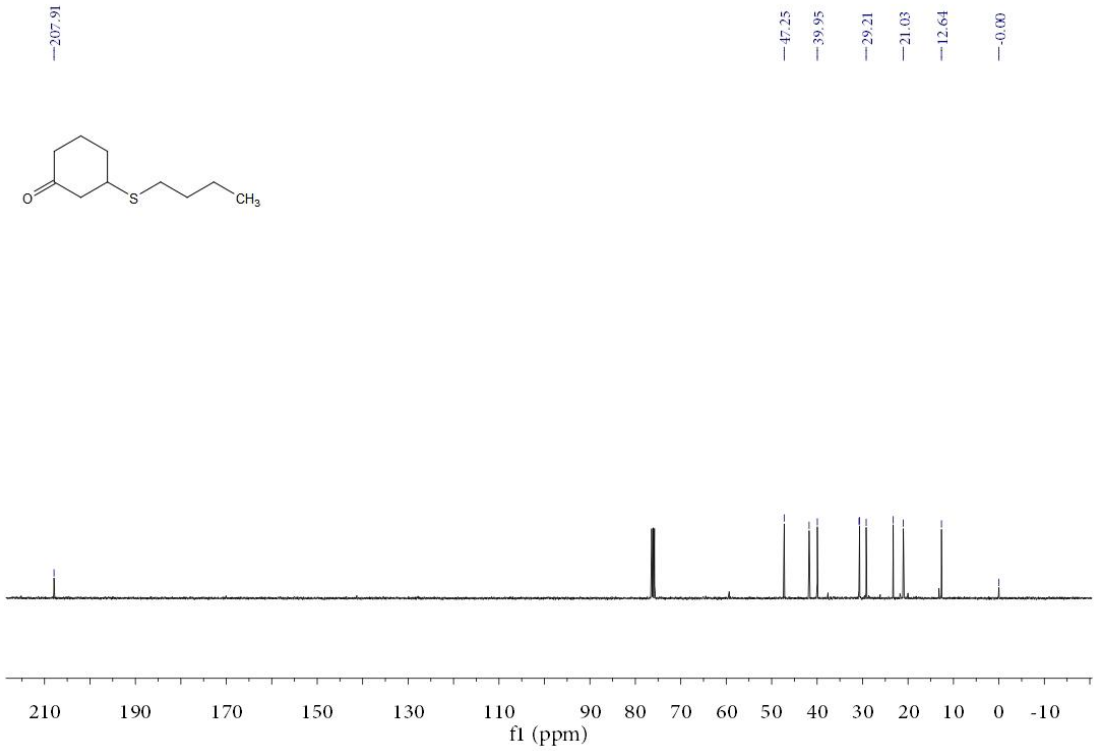
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4p**



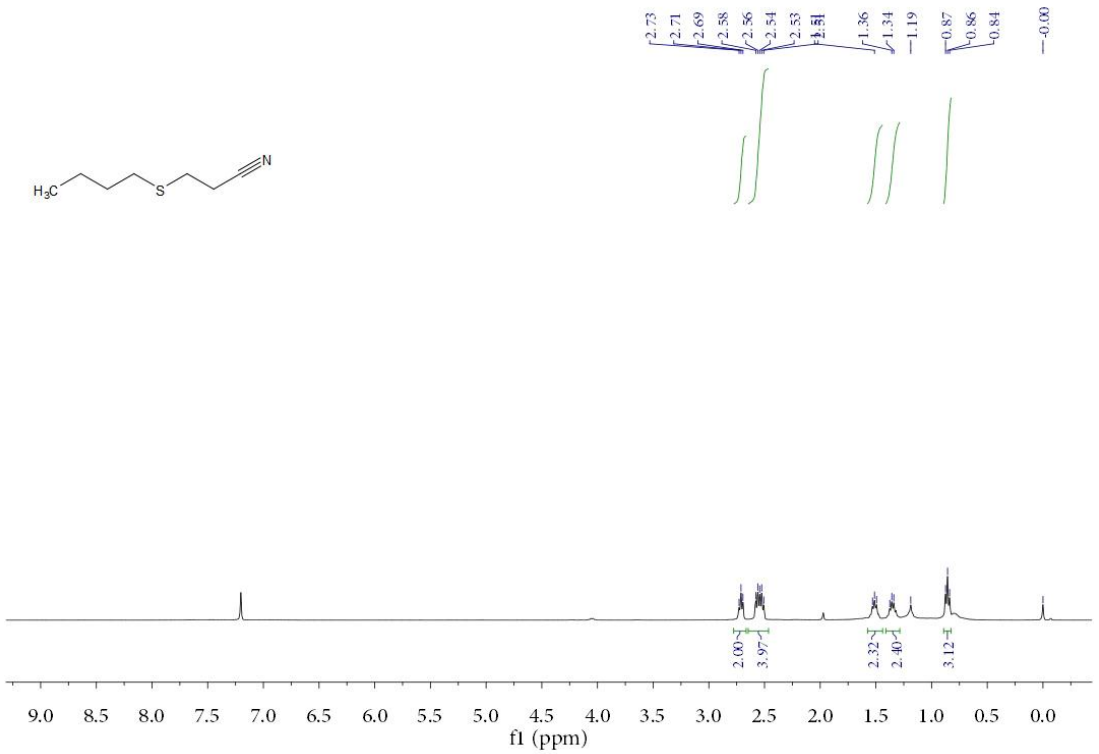
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4p**



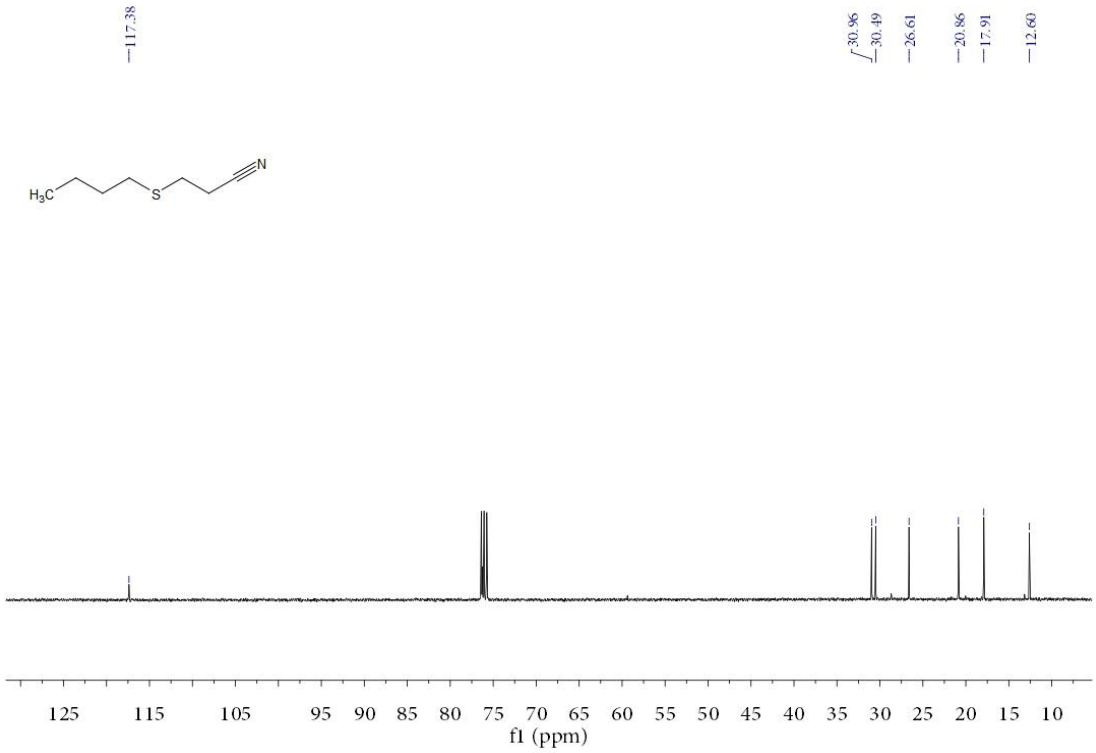
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4q**



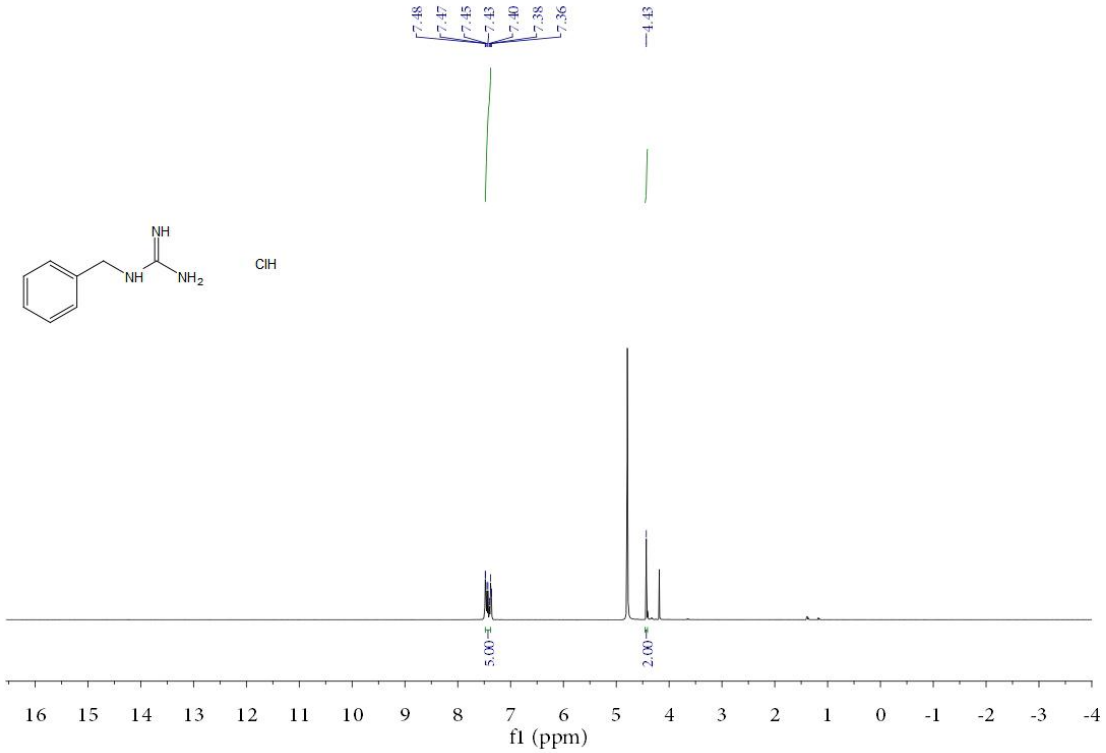
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4q**



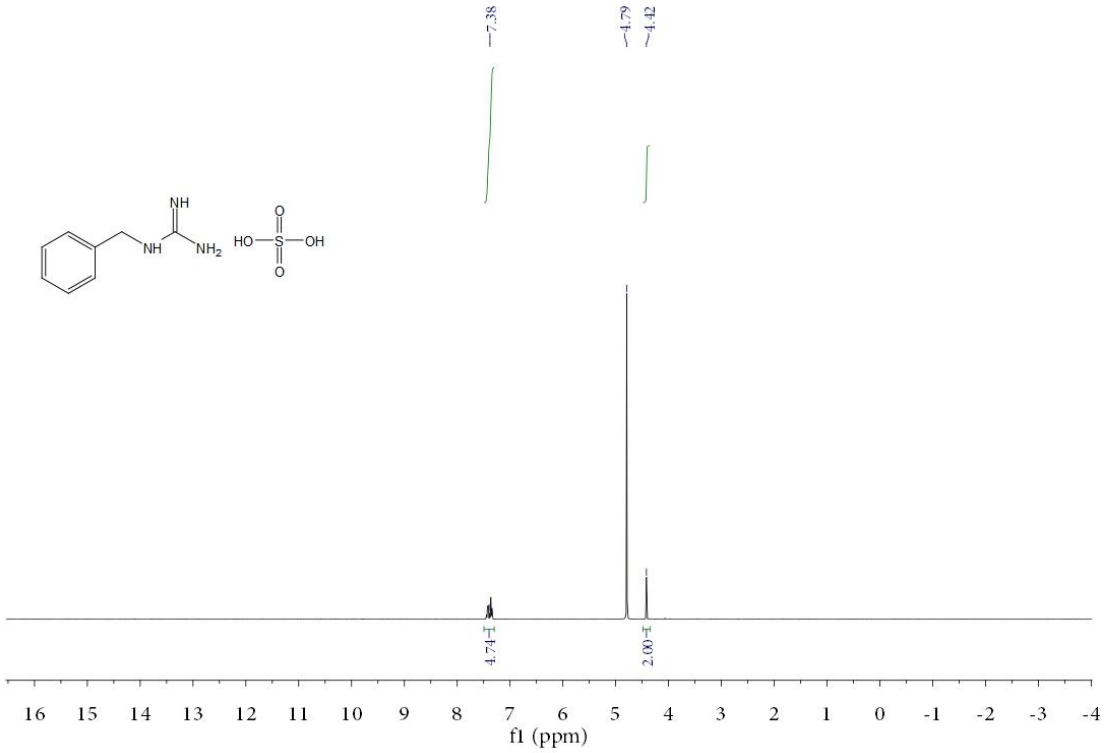
^{1}H NMR(400MHz, $CDCl_3$) of Compound **4r**



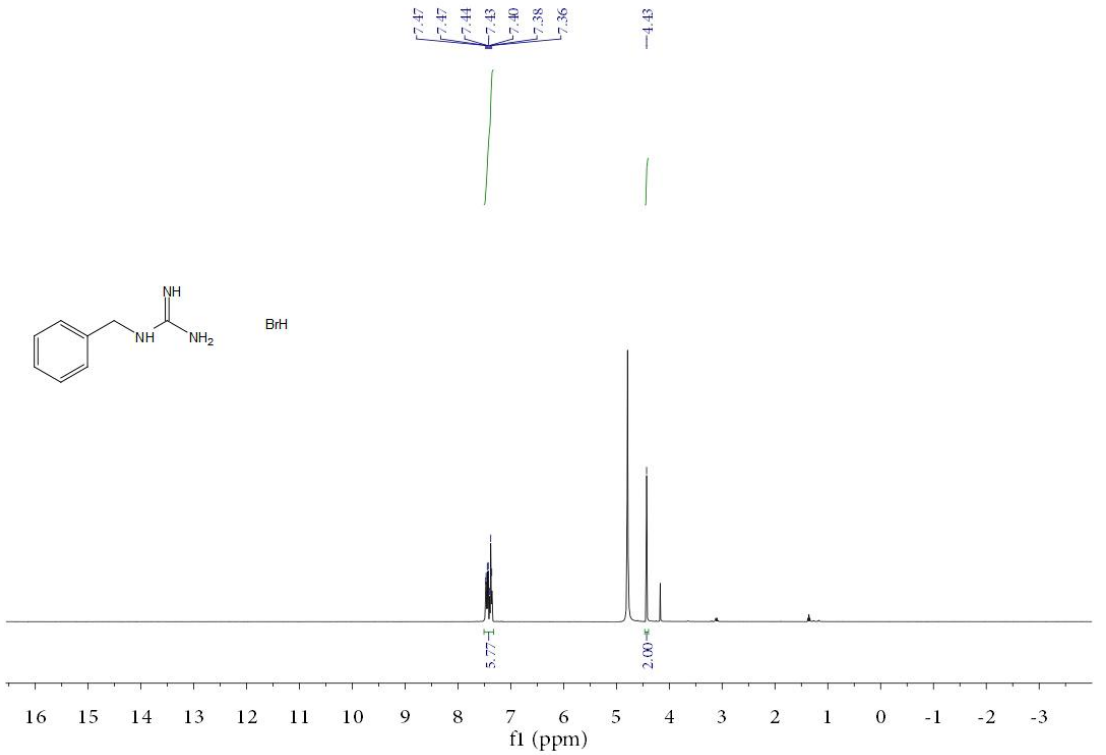
^{13}C NMR(100MHz, $CDCl_3$) of Compound **4r**



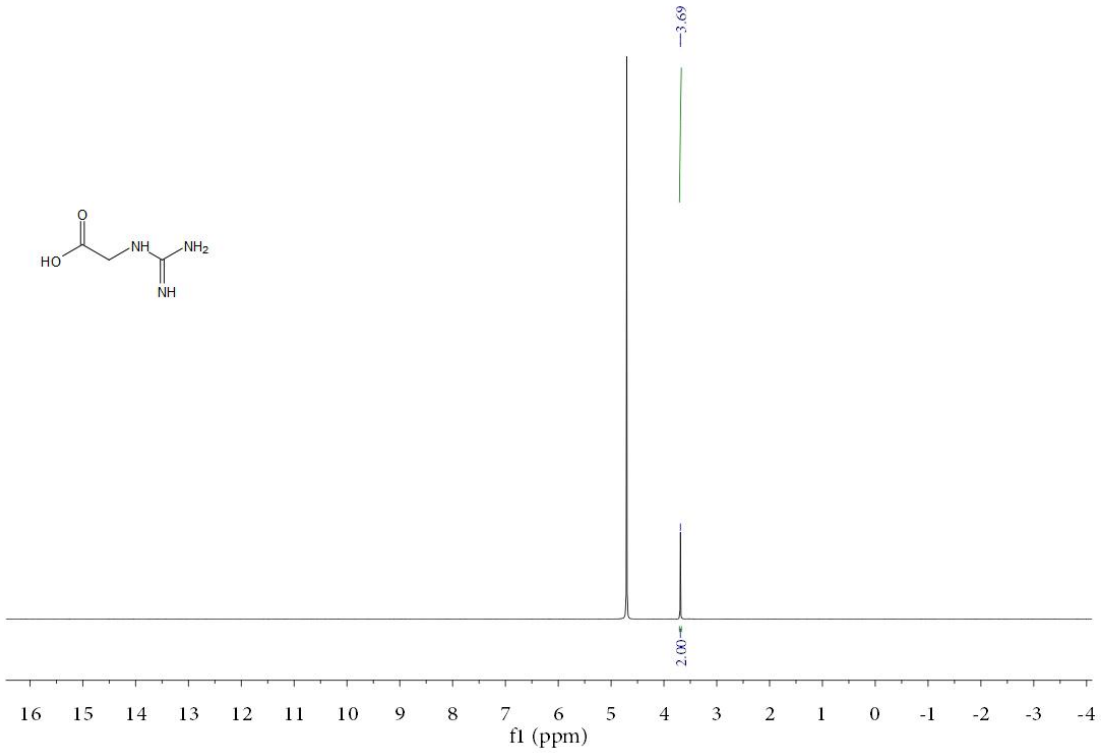
^{1}H NMR(400MHz, D_2O) of Compound **5a**



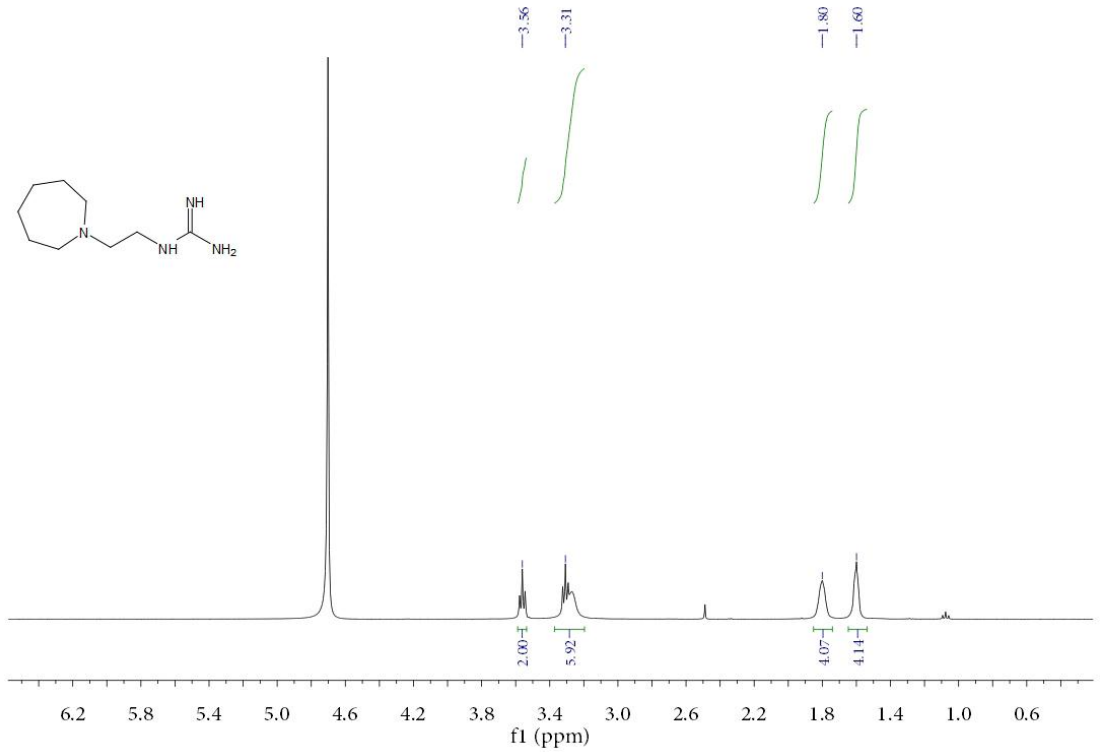
^{1}H NMR(400MHz, D_2O) of Compound **5b**



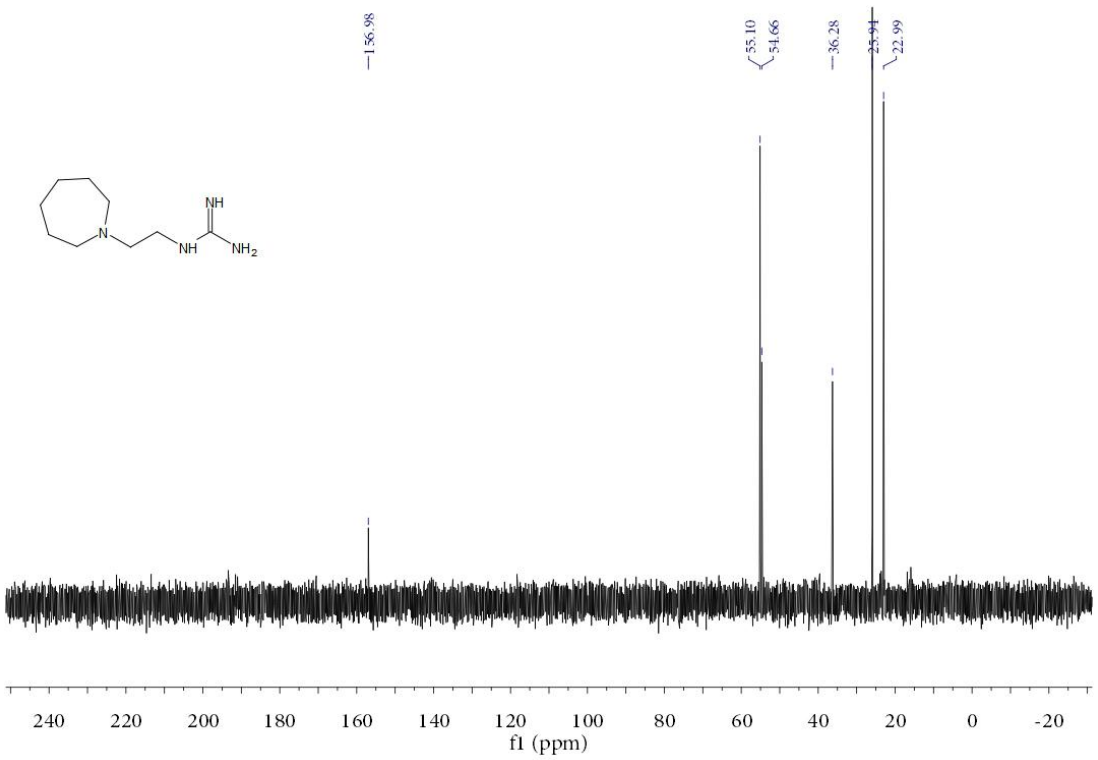
^{1}H NMR(400MHz, D_2O) of Compound **5c**



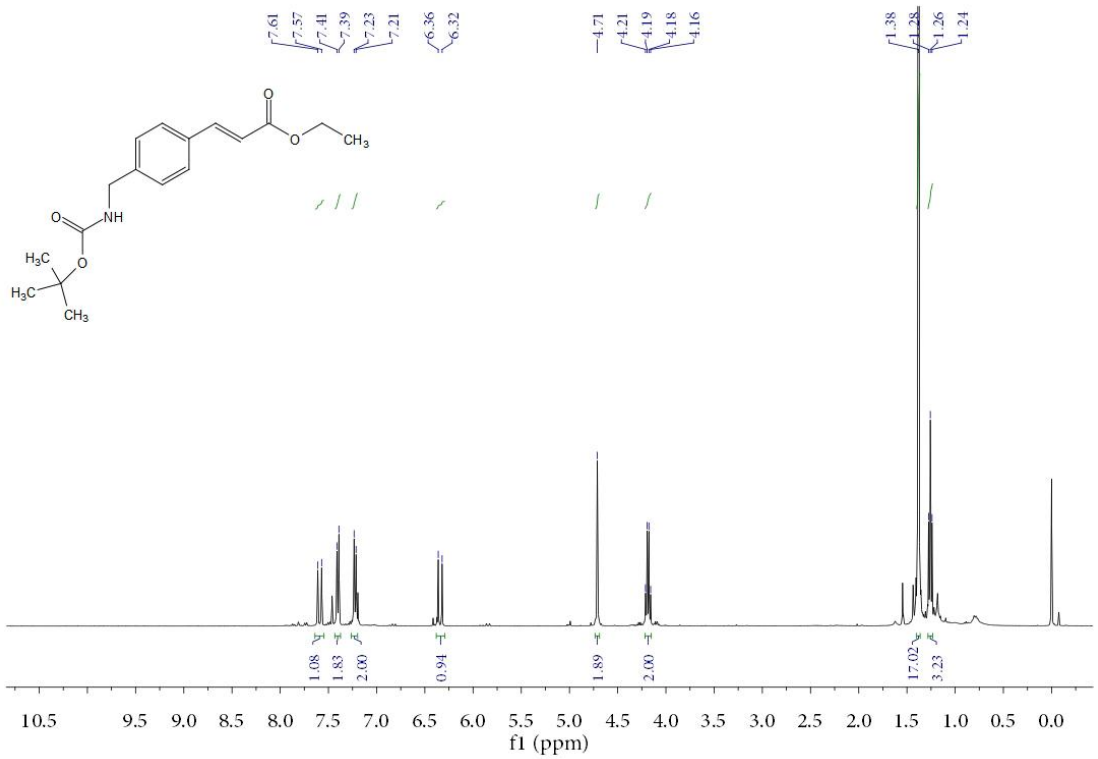
^{1}H NMR(400MHz, D_2O) of Compound **Glucocyamine**



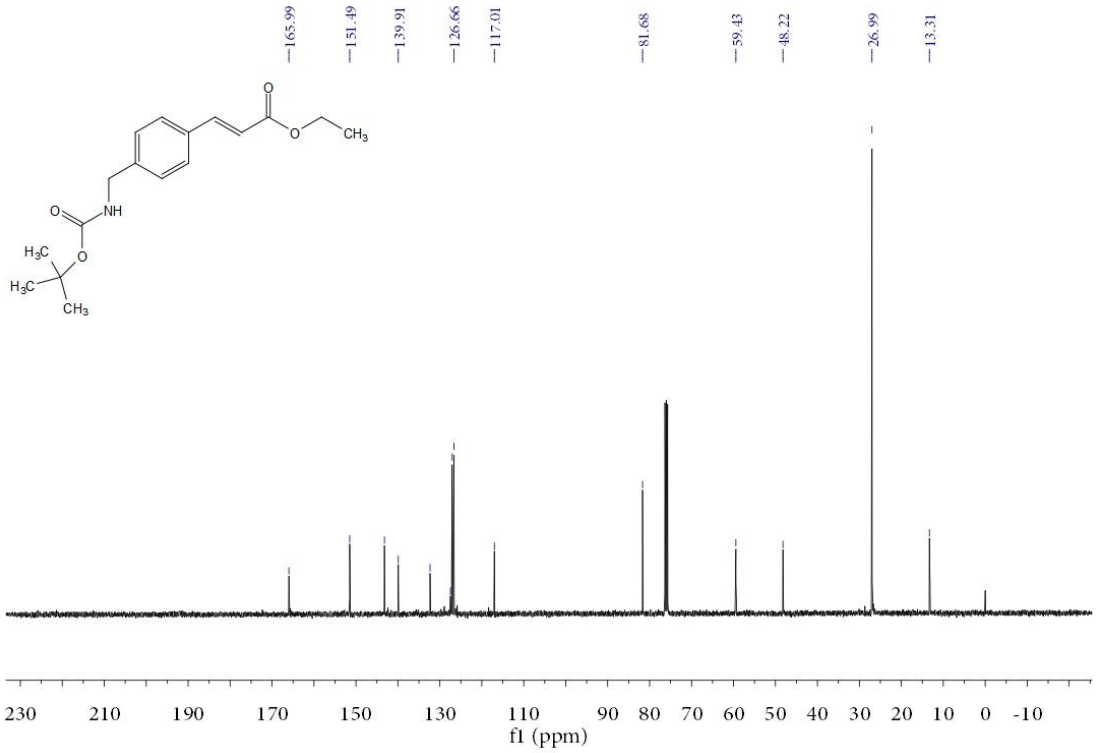
^{1}H NMR(400MHz, D_2O) of Compound **Ismelin**



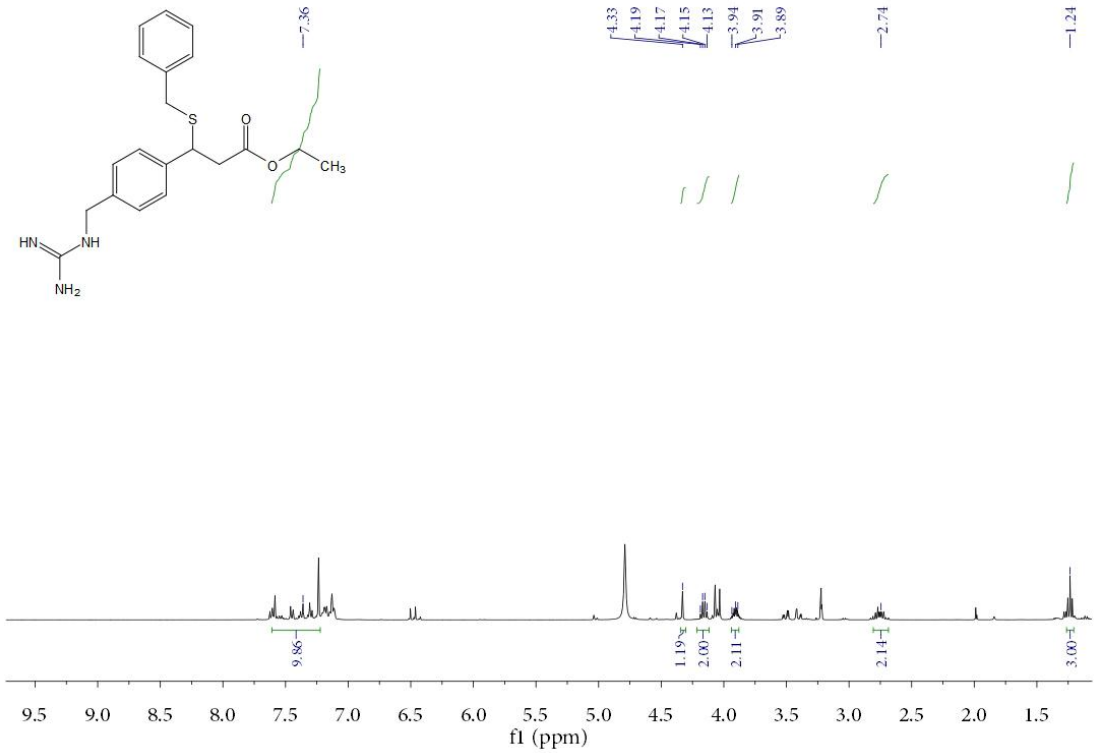
^{13}C NMR(100MHz, D_2O) of Compound **Ismelin.**



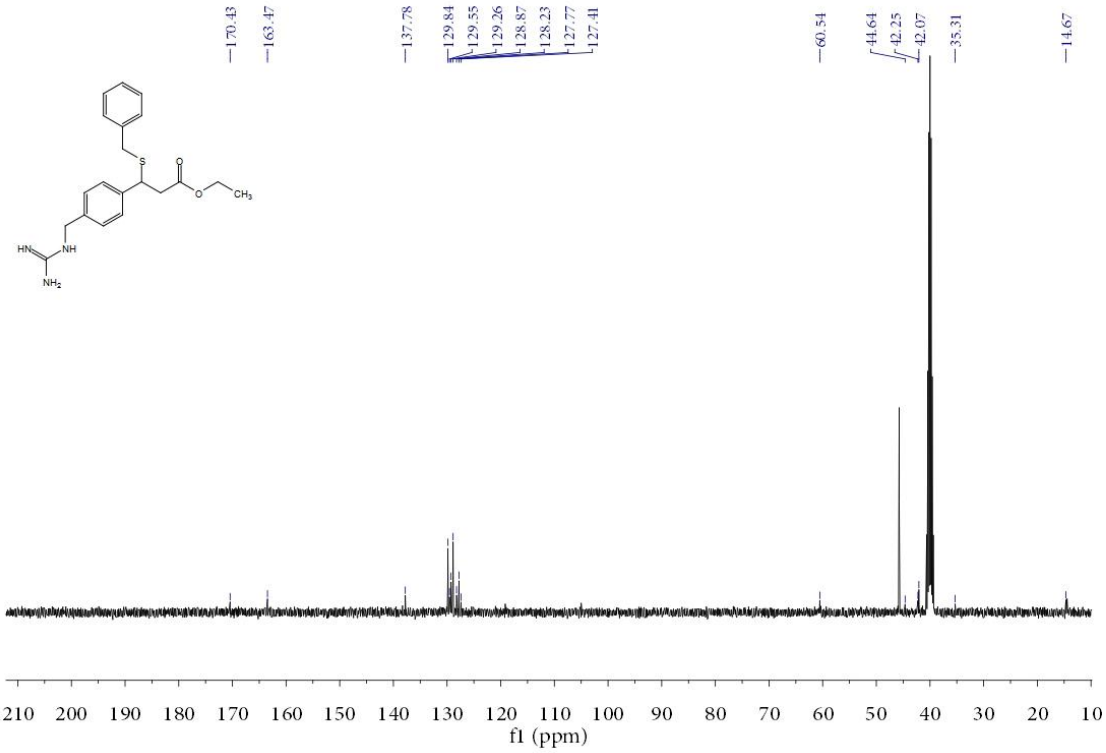
^{1}H NMR(400MHz, $CDCl_3$) of Compound **10**



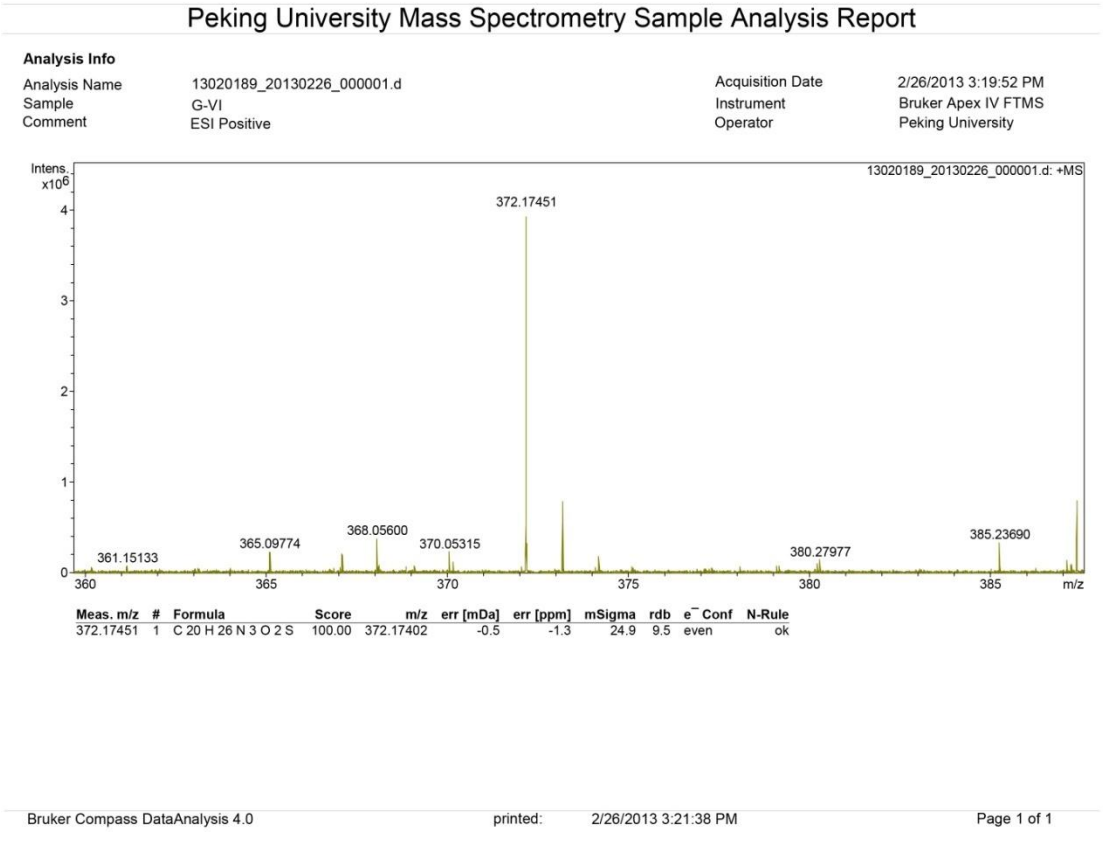
^{13}C NMR(100MHz, $CDCl_3$) of Compound **10**



^{1}H NMR(400MHz,CD_3OD) of Compound **12**



^{13}C NMR(100MHz, DMSO-d_6) of Compound **12**



ESI of compound **12**