理 學 碩 士 學 位 論 文

광촉매작용을 이용한 친환경적 조건에서 설파이드와 설폭사이드의 One-pot 합성

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指 導 敎 授 우 상 국

이 論文을 理學碩士 學位論文으로 提出함

2021年 8月

蔚 山 大 學 校 大 學 院

化 學 科

朴 鎭

朴　鎭의 理學碩士 學位論文을 認准함

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1. Abstract

A facile and efficient protocol for one-pot synthesis of sulfides and sulfoxides via visible-light induced coupling of alkylthiomethylsilanes with activated alkenes has been developed. The developed method is performed under mild conditions. Diverse sulfides and sulfoxides were obtained in moderate to good yields.

2. Introduction

Organosulfur compounds are attracting attention in a wide range of research fields such as pharmaceutical and biological industry. Sulfides and sulfoxides are very valuable building blocks that are found in many natural products, bioactive molecules, and drug candidates as the major structural motifs. Consequently, the synthesis of sulfur-containing compounds is of great interest in organic chemistry.[1,2]

Visible light has been known as an ideal energy source for chemical reaction due to its clean and inexpensive properties. The photoredox-catalysis has been used as an effective tool for formation of C–C and C-heteroatom bonds in organic synthesis. The photoredox catalyzed Giese reaction of olefins with α-alkylthiomethyl radical is useful reaction for synthesis of sulfides. However, previous method for generation of α-alkylthiomethyl radical have drawbacks. The potassium trifluoroborate, which exists in a salt state, is difficult to purify and handle. Also, carboxylic acid has the disadvantage of reacting with alkene by adding a base to form a carboxylate.[3]

Traditionally, the approaches for the synthesis of sulfoxides rely on the oxidation of sulfides using a stoichiometric amount of peroxides and hypervalent iodine reagents with the assistance of various transition-metal catalysts such as iron, vanadium, copper, titanium, cobalt, magnesium, silver and zinc salts. Nevertheless, due to the use of metal reagents and hazardous oxidizing agents, these methods have several drawbacks, such as the generation of stoichiometric amounts of toxic waste, limited functional group tolerance, or over-oxidation of sulfoxides to sulfones (Scheme 1b).[4–10]

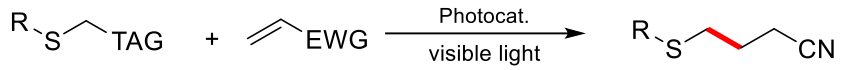
Recently, a visible light-induced tandem reaction to construct sulfoxides directly from commercially available thiols has been reported. Yadav, Alemάn, and Wei group reported the visible light-promoted sulfoxidation of alkenes with thiols to obtain β-keto sulfoxide or sulfoxide. However, the developed method has achieved a limited substrate scope (Scheme 1c).[11]

Fortunately, green and photocatalytic one-pot reaction have been developed to synthesize the corresponding sulfides and sulfoxide in ethanol and buffer solutions as solvents under mild conditions. This reaction is carried out under mild and environmental conditions and can provide a variety of sulfides and sulfoxides in good to excellent yields with good functional tolerance (Scheme 1d).

Scheme 1. Synthesis approach to sulfides and sulfoxides.

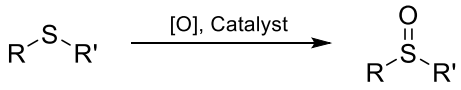
Previous work:

(a) Giese reaction

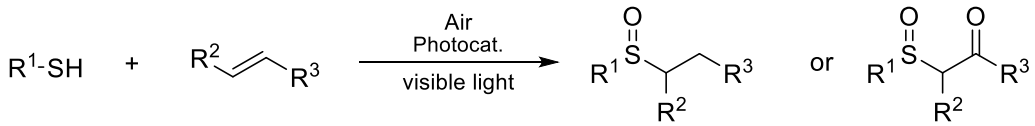


TAG = $-CO_2H$, $-BF_3K$

(b) Oxidation: General approach

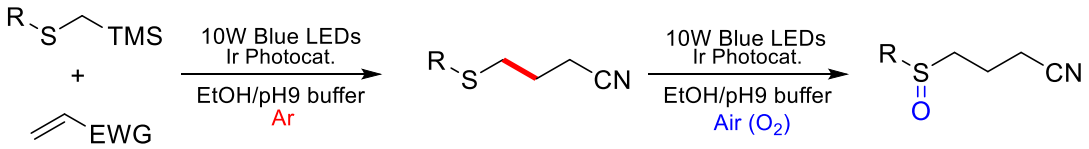


(c) Oxidative thiol-ene reaction : Photocatalytic C-S bond formation



This work:

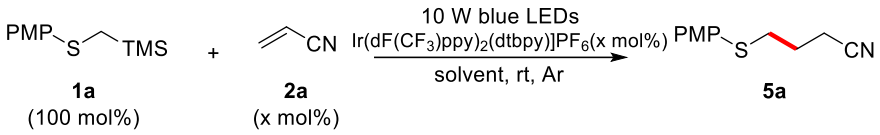
(d) One-pot reaction : Giese reaction and Sulfoxidation

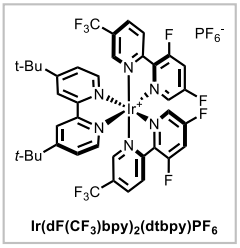


3. Results and Discussions

a. Optimization of the Reaction Conditions

Table 1. Optimization of the Reaction Conditions[a]





entry	catalyst	alkene	solvent (0.1 M)	additive	time	yield (%)
1	1 mol%	2 eq	MeCN	-	14 h	36
2	1 mol%	2 eq	EtOAc	-	14 h	30
3	1 mol%	2 eq	MeOH	-	14 h	50
4	1 mol%	2 eq	MeOH	$NaHCO_3$ (1 eq)	2 h	75
5	1 mol%	2 eq	EtOH	$NaHCO_3$ (1 eq)	3 h	66
6	1 mol%	2 eq	EtOH/H_2O (5:1)	$NaHCO_3$ (1 eq)	3 h	85
7	1 mol%	2 eq	EtOH/pH9 Buffer (5:1)	-	3 h	95
8	0.5 mol%	2 eq	EtOH/pH9 Buffer (5:1)	-	4 h	92
9	0.1 mol%	2 eq	EtOH/pH9 Buffer (5:1)	-	20 h	86
10	0.5 mol%	1.5 eq	EtOH/pH9 Buffer (5:1)	-	8 h	58
11	0.5 mol%	1.2 eq	EtOH/pH9 Buffer (5:1)	-	20 h	30

[a]Reaction conditions : **1a** (0.20 mmol), **2a** (quantity noted), catalyst (quantity noted), solvent (0.1 M) with 10 W blue LEDs irradiation at room temperature under Ar gas. [b]Isolated yield by flash column chromatography.

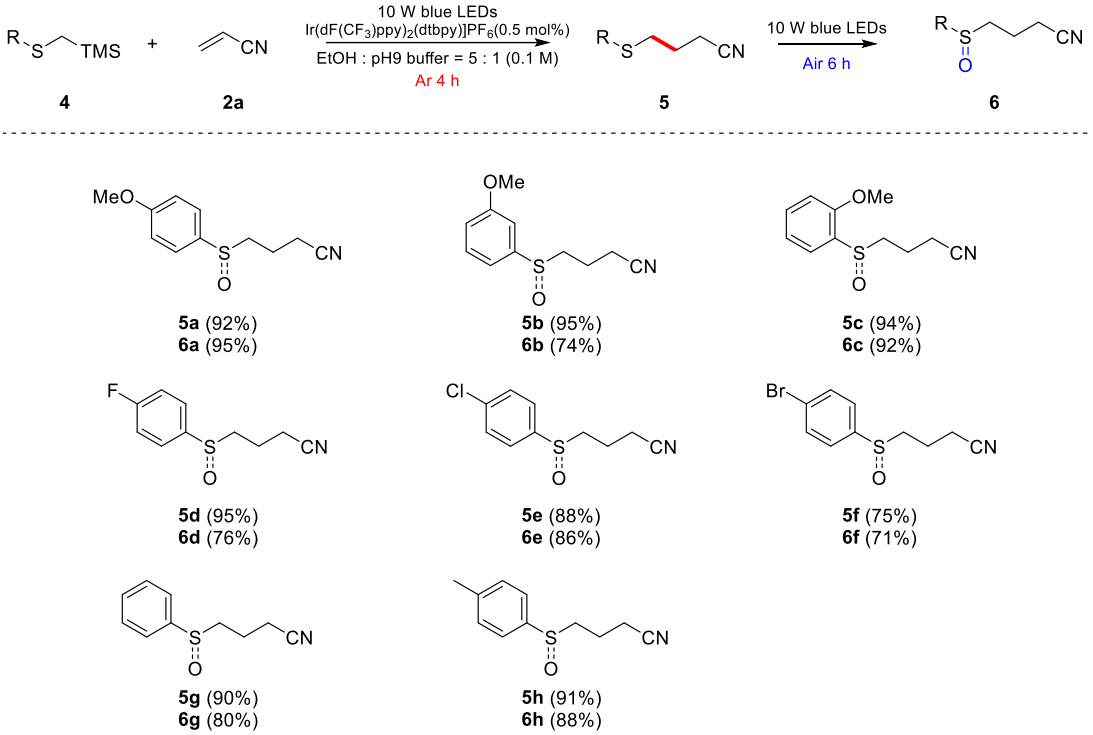
In early studies, we selected $PMPSCH_2TMS$ **1a** as thiomethyl radical precusor. The oxidation potential of $PMPSCH_2TMS$ **1a** was measured at +0.976 V. This valu is low than nomarl sulfide due to the β-silicon effect, The oxidation potential of the $Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ photoredox catalyst ($E_{1/2}^{red}$ ($PC^*/PC^{\bullet -}$) = +1.21 V vs SCE) was sufficient to oxidize $PMPSCH_2TMS$ **1a**. The reaction of $PMPSCH_2TMS$ **1a** with acrylonitrile **2a** was first perfomed in MeCN using 1 mol% $Ir(dF\text{-}CF_3ppy)_2(dtb\text{-}bpy)PF_6$ photoredox catalyst under irratdiation with 10W blue LEDs for 14 h. The

desired sulfide product **5a** was obtained in 36% (Table 1, entry 1). Optimization was performed to improve yield. First, solvent changes, catalyst loading, partner equivalents and additives were investigated to optimize reaction conditions. Methanol was considered optimal compared to other solvents (Table 1, entries 2-3). The effect of the base on the reaction efficiency was notable. (Table 1, entry 4-6). In particular, the EtOH/pH9 buffer co-solvent, which is considered an eco-friendly solvent, gave a good yield of 95% yield (Table 1, entry 7). When reduced the amount of acylronitrile **2a** and catalyst loading, unfortunately the yield decreased (Table 1, entries 8-11). After screening the reaction conditions, the optimal result is that $PMPSCH_2TMS$ **1a** and 2.0 equivalents of acrylonitrile **2a** were reacted with 0.5 mol% $Ir(dF\text{-}CF_3ppy)_2(dtb\text{-}bpy)PF_6$ catalyst in EtOH/pH9 buffer at room temperature, and a 10W blue LED was irradiated under an argon atmosphere to obtain the desired product **5a** in 92% yield (Table 1, entry 8).

b. Substrate Scope

Next, we explored the substrate with various alkylthiomethylsilanes **4** to examine the eletronic effect for desilylative Gises addition under optimized condition. And we have developed direct oxidiation sulfide **5** to sulfoxide **6** by photoxoidation using air as thermial oxidant. We used a variety of substituents on arylthiomethylsilanes **4**, including electron-rich groups (*p*-, m-, o-OMe, *p*-Me), Halogens (*p*-F, Br and Cl). *p*-, m-, o-MeO substituted arylthiomethylsilanes (**4a-4c**) that gave sulfides (**5a-5c**) and also sulfoxides (**6a-6c**) in good to excellent yields (74%-95%). Halogen-substituted arylthiomethylsilanes (**4d-4f**) proceeded, and the corresponding coupled products (**5d-5f**) and oxidation products (**6d-6f**) were obtained in good yields (71%-86%). Phenylthiosilane provided corresponding products **5g** and **6g**, 90% and 80% respectively. And p-toyl thiosilane provided corresponding products **5h** (91%) and **6h** (88%).

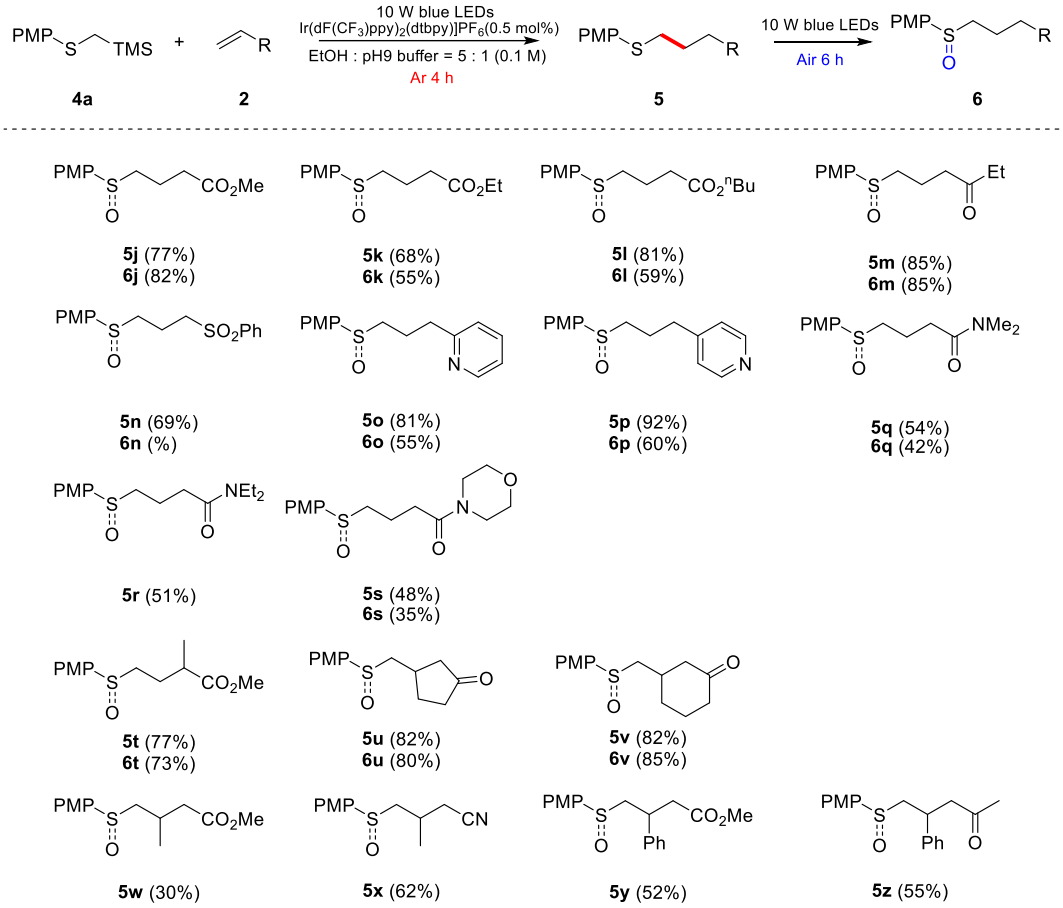
Scheme 2. Substrate Scope of α-thiomethyl silanes[a]



[a]Reaction conditions : **1a** (0.20 mmol), **2a** (0.40 mmol), catalyst (0.05 mol%), solvent (0.1 M) with 10 W blue LEDs irradiation at room temperature under Ar gas. [b]Isolated yield by flash column chromatography. See Experimental section for details.

PMPSCH$_2$TMS **4a** was added to a diverse range of alkene derivatives contaning nitrile, ester, ketone, amide and sulfone to form sulfides (**5j-5z**) and sulfoxides (**6j-6v**). In particular, acrylates containing methyl, ethyl and *n*-butyl groups produced sulfides (**5j-5l**) and sulfoxides (**6j-6l**) in good yields. Ethyl vinyl ketone, phenyl vinyl sulfone, *o*-vinyl pyridine and *p*-vinyl pyridine reacted provibed corresponding products in good yields (60%-92%). α-methyl acrylate affored the sulfide (**5t**) and sulfoxide (**6t**) in 77% and 73% yield. Alkenes containing amides (**5q-5s, 6q-6s**) and α-, β-substituted alkenes slightly obtained lower yields (**5w-5z**).

Scheme 3. Substrate Scope of Various Alkenes[a]

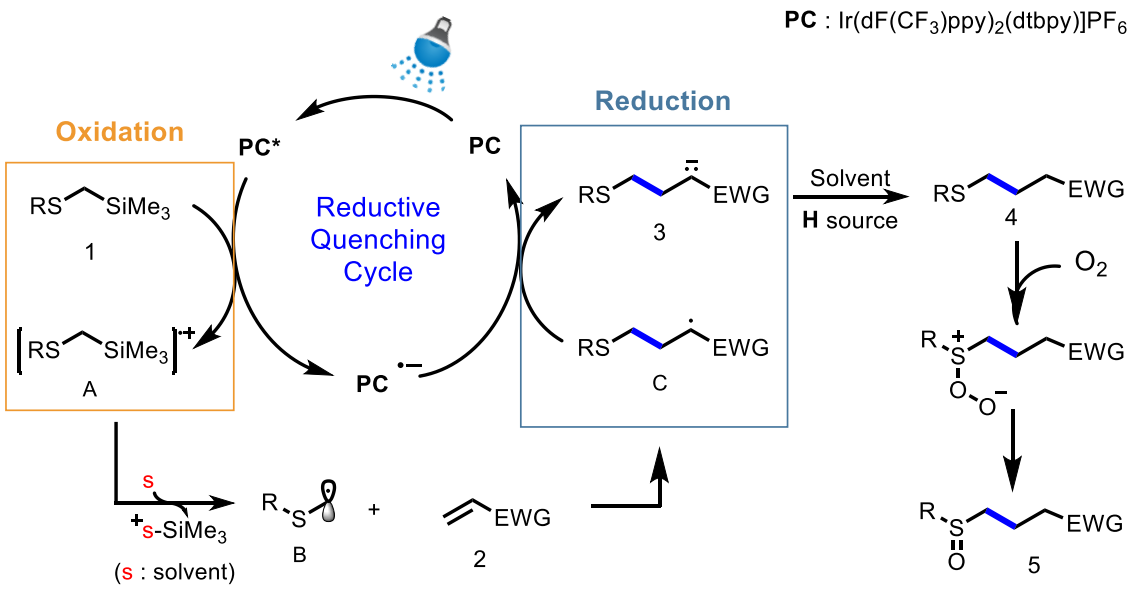


[a]Reaction conditions : **1a** (0.20 mmol), **2a** (0.40 mmol), catalyst (0.05 mol%), solvent (0.1 M) with 10 W blue LEDs irradiation at room temperature under Ar gas. [b]Isolated yield by flash column chromatography. See Experimental section for details.

c. Plausible Mechanism for a Photoredox Catalysis

A plausible reaction mechanism was proposed as illustrated in **Scheme 4**. Initially, the photocatalyst was excited by blue LEDs irradiation. Then, oxidation of alkylthiomethyl silane **1** by excited photocatalyst generates a cation radical **A**, which is desilylated with solvent to produce the alkylthiomethyl radical **B**. The coupling of alkylthiomethyl radical with activated alkene **2** would lead to the formation of the sulfide radical **C**. Reduction of sulfide radical **C** by reduced photoredox catalyst provides sulfide anion **3**. Sulfide **4** is produced by the protonation of anion with solvent. Finally, the oxidation of sulfide **4** by O_2 produced the desired sulfoxide **5**.

Scheme 4. Proposed mechanism



4. Conclusion

In conclusion, we have developed visible light induced one-pot reaction of alkenes and silanes under mild conditions to produce sulfides and sulfoxides. The developed method produces products in excellent yields using simple and readily available materials. This method has great value in terms of green chemistry in organic synthesis because it is easy to operate using environmentally friendly energy sources and green solvents.

5. Experiment Section

a. Reagent

All reactions were run under an atmosphere of argon and open air unless otherwise indicated. EtOH and pH9 buffer solution were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Reagents were purchased from Daejung, Alfa, across and Aldrich degassed by bubbling of nitrogen gas for 30 minutes. Pressure tubes (13 x 100 mm, PYREXPLUS, and 50 mL flask, purchased from Chem Glass) were dried in oven for overnight and cooled under a stream of nitrogen prior to use. All commercial reagents were used directly without further purification. Confirmation of the reaction progress was performed using a TLC plate (Merck 5554 Kiesel gel 60 F254), and Column chromatography was performed with hexane-EtOAc (v/v) or dichloromethane-methanol (v/v) and silica gel (Merck 9385 Kiesel gel 60).

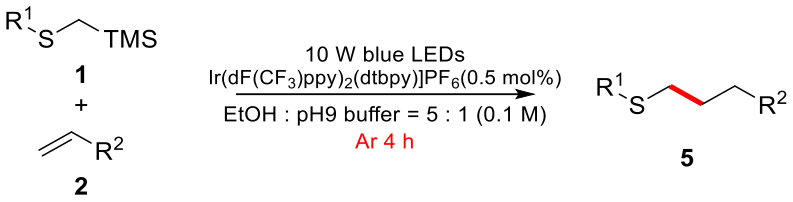
b. Instruments

Infrared spectra were recorded on a Shimadzu (IRaffinity-1S). High-resolution mass spectra (EI) were obtained on a Jeol JMS 700 HRMS at the Korea Basic Science Center (KBSI), Daegu, Korea. Accurate masses are reported for the molecular ion [M+] or [M+H]+. Nuclear magnetic resonance spectra (1H NMR, 13C NMR) were recorded with a Bruker 300 MHz spectrometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. The following abbreviations are used: m (multiplet), s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd

(doublet of doublets), etc. Absorption spectra of the photocatalysts and emission spectra of the visible light sources were measured on a Varian Carry 100, Horiba Fluoromax-4P spectrophotometer, and Ocean Optics QE65000. Cyclic voltammograms were recorded on a Bio-Logic (SP-300 model).

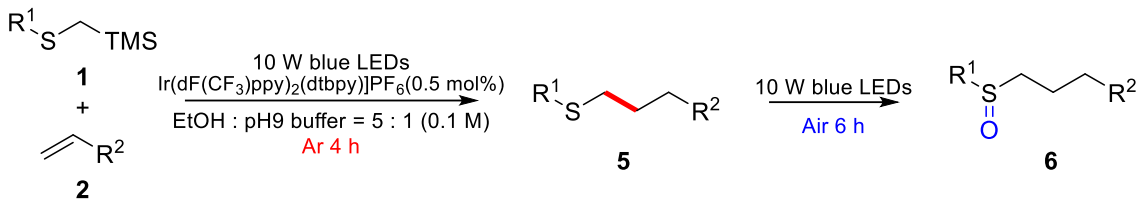
c. Synthesis of Compound.

- General Procedure for Sulfides



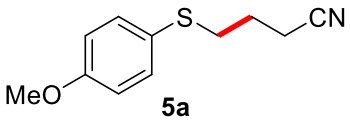
To a re-sealable pressure tube (13 x 100 mm) with a tiny magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv) and $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (1.2mg, 0.0010 mmol, 0.05 mol%) under argon atmosphere. Then, a mixture of degassed solvents (2 mL, 0.1 M for **1**) of EtOH/pH9 buffer in a ratio of 5:1 was added to that pressure tube. The resultant light greenish-yellow mixture was irradiating with 2 x 5W blue LEDs under constant stirring condition at room temperature for 4 h. After finishing the stipulated time, the solvent was removed under reduced pressure and residue was purified by flash column chromatography on silica gel to afford the corresponding sulfide product.

- General Procedures for Sulfoxides.



To a re-sealable pressure tube (13 x 100 mm) with a tiny magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv) and $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (1.2mg, 0.0010 mmol, 0.05 mol%) under argon atmosphere. Then, a mixture of degassed solvents (2 mL, 0.1 M for **1**) of EtOH/pH9 buffer in a ratio of 5:1 was added to that pressure tube. The resultant light greenish-yellow mixture was irradiating with 2 x 5W blue LEDs under constant stirring condition at room temperature for 4 h. After 4h, open the cap of the tube and send 6h reaction in Air (open cap) condition. After finishing the stipulated time, the solvent was removed under reduced pressure and residue was purified by flash column chromatography on silica gel to afford the corresponding sulfoxide product.

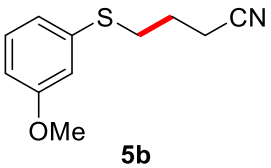
4-((4-methoxyphenyl)thio)butanenitrile (5a)



5a

Following the general procedures, **5a** were obtained as a colourless liquid in the yield of 92% (38.1 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.29 (m, 2H), 6.93 – 6.79 (m, 2H), 3.80 (s, 3H), 2.91 (t, *J* = 6.8 Hz, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 1.88 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 134.1, 124.8, 119.3, 114.9, 55.5, 34.7, 24.9, 15.9.

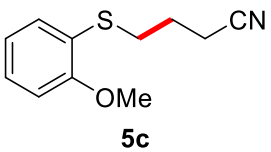
4-((3-methoxyphenyl)thio)butanenitrile (5b)



5b

Following the general procedures, **5b** were obtained as a colourless liquid in the yield of 95% (39.4 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 (t, *J* = 8.0 Hz, 1H), 6.97 – 6.85 (m, 2H), 6.76 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.80 (s, 3H), 3.04 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.97 (tt, *J* = 7.1 Hz, 6.8Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 136.1, 130.0, 121.9, 119.1, 115.3, 112.3, 55.4, 32.3, 24.9, 16.0.

4-((2-methoxyphenyl)thio)butanenitrile (5c)

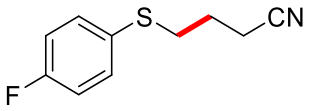


5c

Following the general procedures, **5c** were obtained as a colourless liquid in the yield of 94% (39.0 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloroform-

d) δ 7.32 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.25 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 6.97 – 6.84 (m, 2H), 3.90 (s, 3H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 1.92 (tt, *J* = 7.1, 6.8 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 131.7, 128.6, 122.4, 121.2, 119.4, 110.9, 55.9, 31.3, 25.0, 16.1.

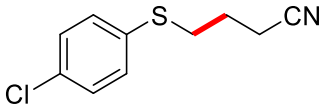
4-((4-fluorophenyl)thio)butanenitrile (5d)



5d

Following the general procedures, **5d** were obtained as a colourless liquid in the yield of 95% (37.1 mg). R_f = 0.20 (Hexane:EtOAc, 20:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.31 (m, 2H), 7.08 – 6.95 (m, 2H), 2.98 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.92 (tt, *J* = 6.9 Hz, 7.0Hz 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 133.3, 129.7, 119.1, 116.6, 116.3, 34.0, 29.8, 24.9, 16.0.

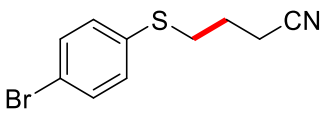
4-((4-chlorophenyl)thio)butanenitrile (5e)



5e

Following the general procedures, **5e** were obtained as a colourless liquid in the yield of 88% (37.3 mg). R_f = 0. (Hexane:EtOAc, 20:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (s, 4H), 3.02 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.95 (tt, *J* = 7.0 Hz, 6.9 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 133.0, 131.5, 129.4, 119.0, 32.9, 24.8, 16.0.

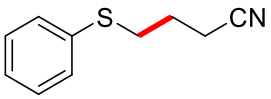
4-((4-bromophenyl)thio)butanenitrile (5f)



5f

Following the general procedures, **5f** were obtained as a colourless liquid in the yield of 75% (38.4 mg). R_f = 0.20 (Hexane:EtOAc, 20:1); R_f = 0.20 (EtOAc:Hexane, 1:4); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.38 (m, 2H), 7.25 – 7.19 (m, 2H), 3.02 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.95 (tt, *J* = 7.0 , 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 132.4, 131.7, 120.8, 119.0, 32.7, 24.8, 16.1.

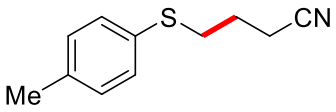
4-(phenylthio)butanenitrile (5g)



5g

Following the general procedures, **5g** were obtained as a colourless liquid in the yield of 90% (31.9 mg). R_f = 0.20 (Hexane:EtOAc, 20:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 4H), 7.26 – 7.19 (m, 1H), 3.04 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.96 (tt, *J* = 7.1, 6.8 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 130.3, 129.3, 126.9, 119.2, 32.7, 24.9, 16.0

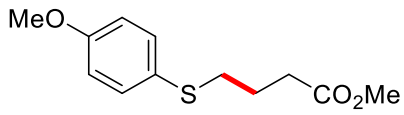
4-(p-tolylthio)butanenitrile (5h)



5h

Following the general procedures, **5h** were obtained as a colourless liquid in the yield of 91% (34.8 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.23 (m, 2H), 7.17 – 7.06 (m, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.92 (tt, *J* = 7.1, 6.8 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 131.1, 130.9, 130.1, 119.2, 33.4, 29.8, 24.9, 21.2, 16.0.

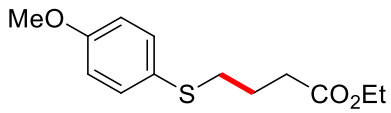
methyl 4-((4-methoxyphenyl)thio)butanoate (5j)



5j

Following the general procedures, **5j** were obtained as a colourless liquid in the yiel d of 77% (37.0 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloro form-*d*) δ 7.42 – 7.29 (m, 2H), 6.90 – 6.79 (m, 2H), 3.79 (s, 3H), 3.66 (s, 3 H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 1.88 (tt, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.65, 159.12, 133.53, 126.04, 114.72, 5 5.47, 51.75, 35.26, 32.67, 24.53.

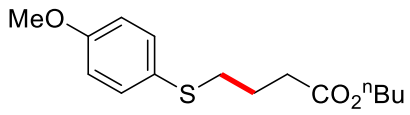
ethyl 4-((4-methoxyphenyl)thio)butanoate (5k)



5k

Following the general procedures, **5k** were obtained as a colourless liquid in the yield of 68% (34.6 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 2H), 6.89 – 6.79 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.88 (tt, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.17, 159.08, 133.48, 126.10, 114.69, 60.49, 55.43, 35.25, 32.94, 24.58, 14.33.

butyl 4-((4-methoxyphenyl)thio)butanoate (5l)

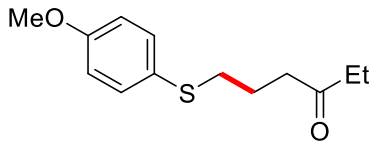


5l

Following the general procedures, **5l** were obtained as a colourless liquid in the yield of 81% (45.7 mg). R_f = 0.20 (Hexane:EtOAc, 5:1); ^{1}H NMR (300 MHz, Chloroform-

d) δ 7.41 – 7.29 (m, 2H), 6.89 – 6.78 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.87 (p, *J* = 7.2 Hz, 2H), 1.66 – 1.51 (m, 2H), 1.45 – 1.26 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.25, 159.08, 133.51, 126.08, 114.68, 64.42, 55.42, 35.27, 32.95, 30.75, 24.60, 19.24, 13.82.

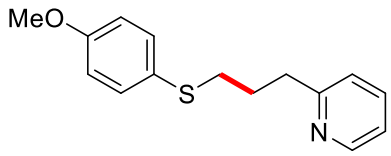
6-((4-methoxyphenyl)thio)hexan-3-one (5m)



5m

Following the general procedures, **5m** were obtained as a colourless liquid in the yield of 85% (40.5 mg). R_f = 0.20 (Hexane:EtOAc, 5:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 2H), 6.89 – 6.78 (m, 2H), 3.79 (s, 3H), 2.82 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.84 (tt, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.05, 159.05, 133.34, 126.20, 114.72, 55.47, 40.66, 36.14, 35.34, 23.30, 7.95.

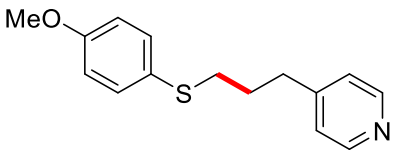
2-(3-((4-methoxyphenyl)thio)propyl)pyridine (5o)



5o

Following the general procedures, **5o** were obtained as a colourless liquid in the yield of 81% (42.0 mg). R_f = 0.30 (Hexane:EtOAc, 2:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.51 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.15 – 7.07 (m, 2H), 6.87 – 6.78 (m, 2H), 3.79 (s, 3H), 2.88 (dt, *J* = 14.3, 7.3 Hz, 4H), 2.09 – 1.95 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.28, 158.96, 149.41, 136.52, 133.28, 126.56, 123.08, 121.28, 114.67, 55.47, 37.07, 35.36, 29.35.

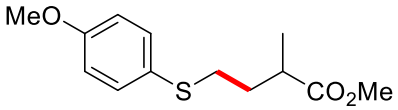
4-(3-((4-methoxyphenyl)thio)propyl)pyridine (5p)



5p

Following the general procedures, **5p** were obtained as a colourless liquid in the yield of 92% (47.7 mg). R_f = 0.20 (Hexane:EtOAc, 2:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.54 – 8.46 (m, 2H), 7.41 – 7.30 (m, 2H), 7.14 – 7.06 (m, 2H), 6.92 – 6.81 (m, 2H), 3.82 (s, 3H), 2.79 (dt, *J* = 24.1, 7.5 Hz, 4H), 1.91 (dtd, *J* = 9.0, 7.5, 6.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.05, 150.39, 149.78, 133.47, 125.93, 123.94, 114.63, 55.35, 35.09, 33.73, 29.61.

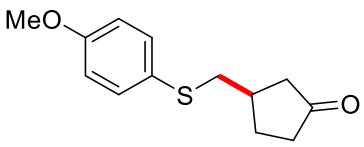
methyl 4-((4-methoxyphenyl)thio)-2-methylbutanoate (5t)



5t

Following the general procedures, **5t** were obtained as a colourless liquid in the yield of 77% (39.2 mg). R_f = 0.20 (Hexane:EtOAc, 10:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.28 (m, 2H), 6.90 – 6.79 (m, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 2.91 – 2.72 (m, 2H), 2.62 (ddd, *J* = 14.0, 7.0 Hz, 1H), 1.95 (dtd, *J* = 13.8, 8.0, 6.8 Hz, 1H), 1.74 – 1.58 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 159.1, 133.4, 126.2, 114.7, 55.5, 51.8, 38.4, 33.6, 33.2, 17.1.

(R)-3-(((4-methoxyphenyl)thio)methyl)cyclopentan-1-one (5u)

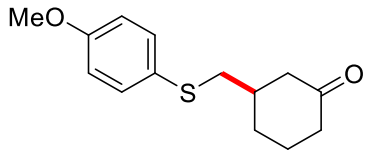


5u

Following the general procedures, **5u** were obtained as a colourless liquid in the yield of 82% (38.8 mg). R_f = 0.20 (Hexane:EtOAc, 5:1); ^{1}H NMR (300 MHz, Chloroform-

d) δ 7.42 – 7.31 (m, 2H), 6.91 – 6.79 (m, 2H), 3.80 (s, 3H), 3.01 – 2.83 (m, 2H), 2.52 – 2.06 (m, 5H), 2.06 – 1.88 (m, 1H), 1.77 – 1.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.61, 159.26, 133.65, 126.15, 114.82, 55.49, 44.61, 41.52, 38.46, 36.99, 28.90.

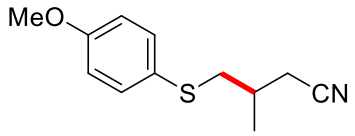
(R)-3-(((4-methoxyphenyl)thio)methyl)cyclohexan-1-one (5v)



5v

Following the general procedures, **5v** were obtained as a colourless liquid in the yield of 82% (41.1 mg). R_f = 0.20 (Hexane:EtOAc, 5:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 2H), 6.89 – 6.76 (m, 2H), 3.79 (s, 3H), 2.90 – 2.72 (m, 2H), 2.61 – 2.48 (m, 1H), 2.41 – 2.18 (m, 2H), 2.20 (s, 2H), 2.18 – 1.87 (m, 4H), 1.69 – 1.56 (m, 1H), 1.53 – 1.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.03, 159.15, 133.49, 126.38, 114.80, 55.47, 47.31, 42.60, 41.41, 38.75, 30.56, 24.94.

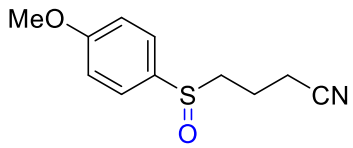
(R)-4-((4-methoxyphenyl)thio)-3-methylbutanenitrile (5x)



5x

Following the general procedures, **5x** were obtained as a colourless liquid in the yield of 62% (27.4 mg). R_f = 0.20 (Hexane:EtOAc, 10:1) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.30 (m, 2H), 6.92 – 6.79 (m, 2H), 3.80 (s, 3H), 2.87 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.77 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.55 (dd, *J* = 16.7, 5.2 Hz, 1H), 2.42 (dd, *J* = 16.7, 6.9 Hz, 1H), 2.08 – 1.91 (m, 1H), 1.16 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.44, 133.83, 125.45, 118.46, 114.94, 55.49, 41.98, 30.59, 23.18, 19.25.

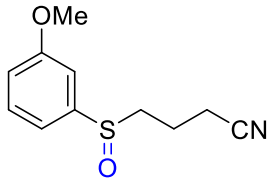
4-((4-methoxyphenyl)sulfinyl)butanenitrile (6a)



6a

Following the general procedures, **6a** were obtained as a colourless liquid in the yield of 95% (42.4 mg). R_f = 0.30 (EtOAc:Ether, 1:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.64 – 7.53 (m, 2H), 7.13 – 7.03 (m, 2H), 3.89 (s, 3H), 3.04 – 2.79 (m, 2H), 2.67 – 2.44 (m, 2H), 2.26 – 1.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.23, 133.60, 125.81, 118.48, 115.02, 55.60, 54.81, 18.58, 16.57.

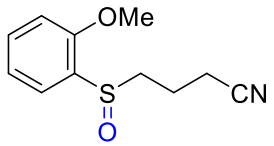
4-((3-methoxyphenyl)sulfinyl)butanenitrile (6b)



6b

Following the general procedures, **6b** were obtained as a colourless liquid in the yield of 74% (33.0 mg). R_f = 0.20 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.11 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.04 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.88 (s, 3H), 3.00 (ddd, *J* = 13.4, 8.9, 6.6 Hz, 1H), 2.85 (ddd, *J* = 13.4, 8.7, 5.7 Hz, 1H), 2.66 – 2.42 (m, 2H), 2.29 – 2.09 (m, 1H), 2.09 – 1.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.63, 144.31, 130.54, 118.54, 117.70, 115.89, 108.48, 55.70, 54.60, 18.48, 16.60.

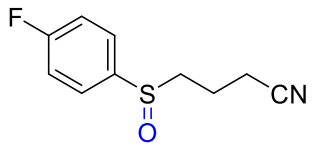
4-((2-methoxyphenyl)sulfinyl)butanenitrile (6c)



6c

Following the general procedures, **6c** were obtained as a colourless liquid in the yield of 92% (41.1 mg). R_f = 0.20 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.76 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.21 (td, *J* = 7.6, 0.9 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.0 Hz, 1H), 3.91 (s, 3H), 3.22 (ddd, *J* = 13.5, 8.3, 7.0 Hz, 1H), 2.93 (ddd, *J* = 13.6, 8.2, 5.7 Hz, 1H), 2.65 – 2.41 (m, 2H), 2.23 (dddd, *J* = 15.0, 13.7, 8.2, 6.8 Hz, 1H), 2.05 – 1.86 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 154.95, 132.46, 129.84, 125.53, 121.76, 118.74, 110.84, 55.89, 50.84, 18.40, 16.63.

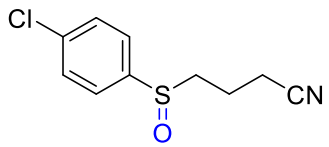
4-((4-fluorophenyl)sulfinyl)butanenitrile (6d)



6d

Following the general procedures, **6d** were obtained as a colourless liquid in the yield of 76% (32.1 mg). R_f = 0.30 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.70 – 7.58 (m, 2H), 7.39 – 7.20 (m, 2H), 3.07 – 2.77 (m, 2H), 2.68 – 2.45 (m, 2H), 2.31 – 2.09 (m, 1H), 2.11 – 1.88 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.26, 162.91, 138.38, 138.34, 126.37, 126.25, 118.46, 117.14, 116.84, 54.90, 54.88, 18.54, 16.61.

4-((4-chlorophenyl)sulfinyl)butanenitrile (6e)

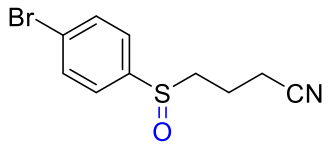


6e

Following the general procedures, **6e** were obtained as a colourless liquid in the yield of 86% (39.2 mg). R_f = 0.30 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.63 – 7.50 (m, 4H), 3.01 (ddd, *J* = 13.5, 8.9, 6.6 Hz, 1H), 2.84 (ddd, *J* = 13.5, 8.7, 5.6 Hz, 1H), 2.68 – 2.45 (m, 2H), 2.21 (ddq, *J* = 13.4, 8.8, 6.7 Hz, 1H), 2.10 – 1.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.44, 137.74, 129.89, 125.41, 118.43, 54.68,

18.46, 16.61.

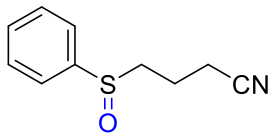
4-((4-bromophenyl)sulfinyl)butanenitrile (6f)



6f

Following the general procedures, **6f** were obtained as a colourless liquid in the yield of 71% (38.6 mg). R_f = 0.30 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80 – 7.65 (m, 2H), 7.59 – 7.41 (m, 2H), 3.01 (ddd, *J* = 13.4, 8.8, 6.5 Hz, 1H), 2.84 (ddd, *J* = 13.4, 8.7, 5.6 Hz, 1H), 2.72 – 2.45 (m, 2H), 2.32 – 2.11 (m, 1H), 2.09 – 1.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.09, 132.84, 126.01, 125.60, 118.43, 54.65, 18.47, 16.64.

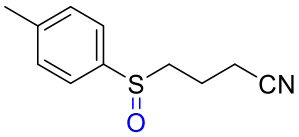
4-(phenylsulfinyl)butanenitrile (6g)



6g

Following the general procedures, **6g** were obtained as a colourless liquid in the yield of 80% (30.9 mg). R_f = 0.30 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 – 7.46 (m, 5H), 2.99 (ddd, *J* = 13.4, 8.8, 6.6 Hz, 1H), 2.84 (ddd, *J* = 13.4, 8.7, 5.7 Hz, 1H), 2.65 – 2.41 (m, 2H), 2.29 – 2.09 (m, 1H), 2.08 – 1.94 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.90, 131.48, 129.59, 123.97, 118.54, 54.64, 18.51, 16.64.

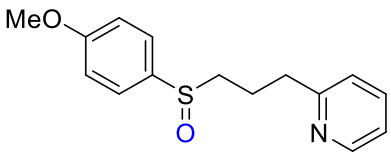
4-(p-tolylsulfinyl)butanenitrile (6h)



6h

Following the general procedures, **6h** were obtained as a colourless liquid in the yield of 88% (36.5 mg). R_f = 0.20 (Hexane:EtOAc, 1:2); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 7.44 (m, 2H), 7.41 – 7.28 (m, 2H), 2.95 (ddd, *J* = 13.3, 8.8, 6.7 Hz, 1H), 2.81 (ddd, *J* = 13.4, 8.6, 5.7 Hz, 1H), 2.62 – 2.42 (m, 2H), 2.41 (s, 3H), 2.25 – 2.05 (m, 1H), 2.05 – 1.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.99, 139.58, 130.23, 123.97, 118.56, 54.64, 21.49, 18.48, 16.59.

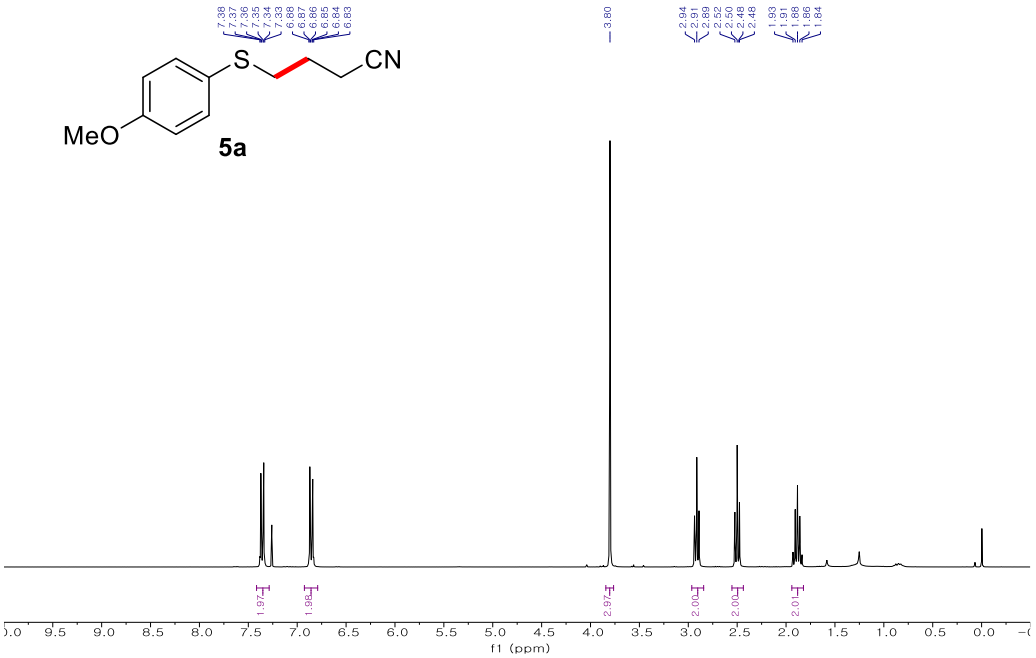
2-(3-((4-methoxyphenyl)sulfinyl)propyl)pyridine (6o)



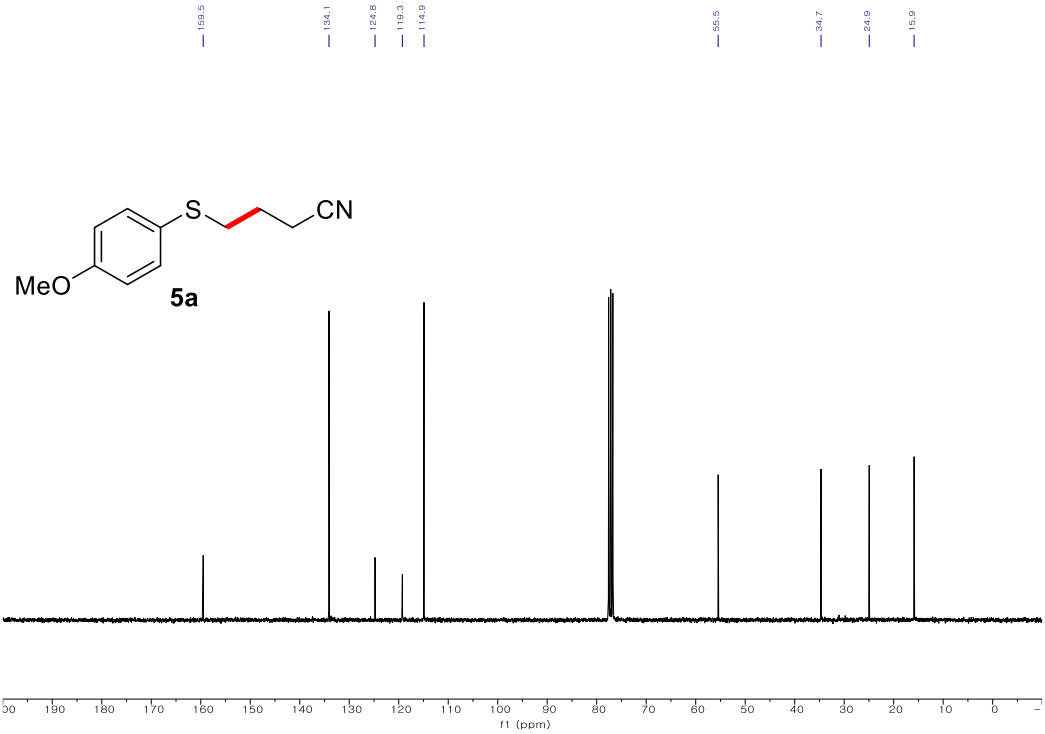
6o

Following the general procedures, **6o** were obtained as a colourless liquid in the yield of 55% (30.3 mg). R_f = 0.20 (EtOAc:Ether, 1:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.53 – 8.44 (m, 1H), 7.68 – 7.47 (m, 3H), 7.17 – 6.94 (m, 4H), 3.84 (s, 3H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.87 – 2.76 (m, 2H), 2.22 – 1.98 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.94, 160.24, 149.30, 136.64, 134.58, 125.99, 123.00, 121.47, 114.77, 56.54, 55.53, 36.77, 22.29.

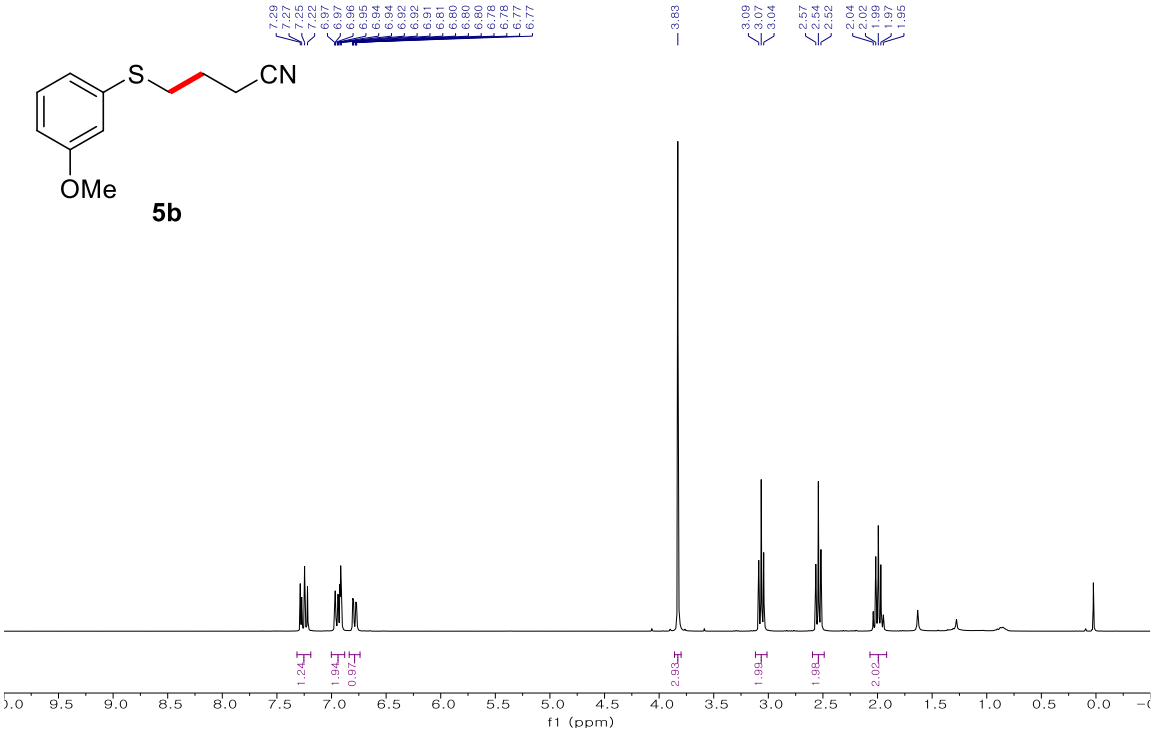
d. ^{1}H, ^{13}C NMR Spectrum analysis



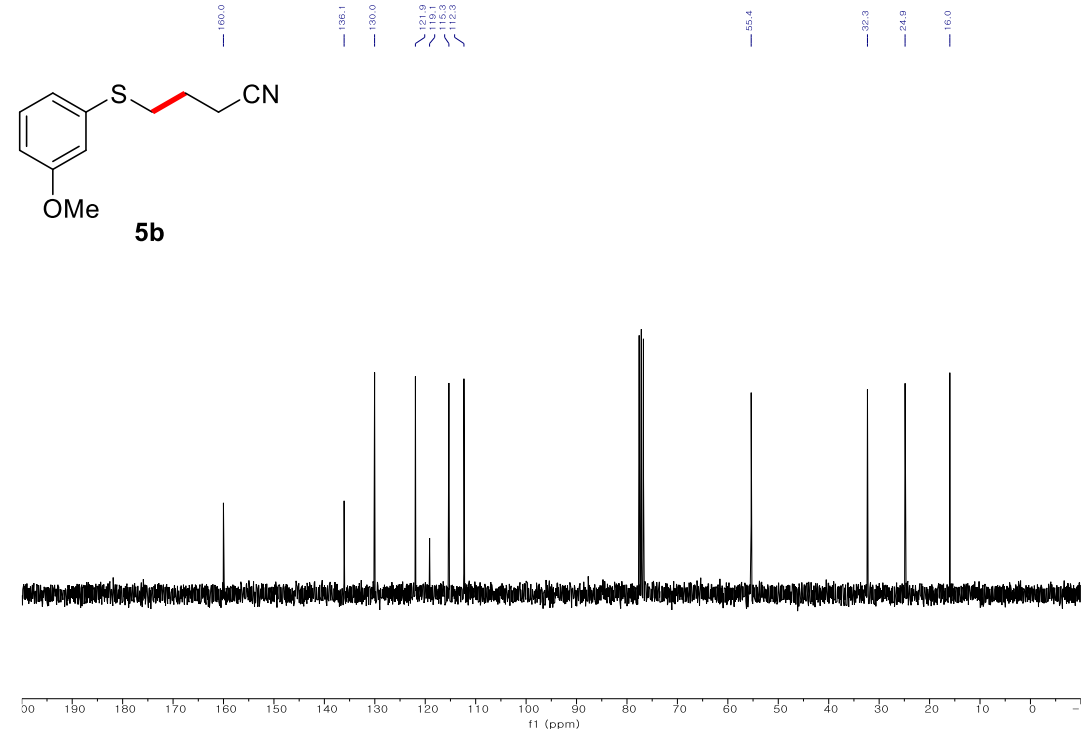
^{1}H-NMR (300 MHz, CDCl3) of **5a**



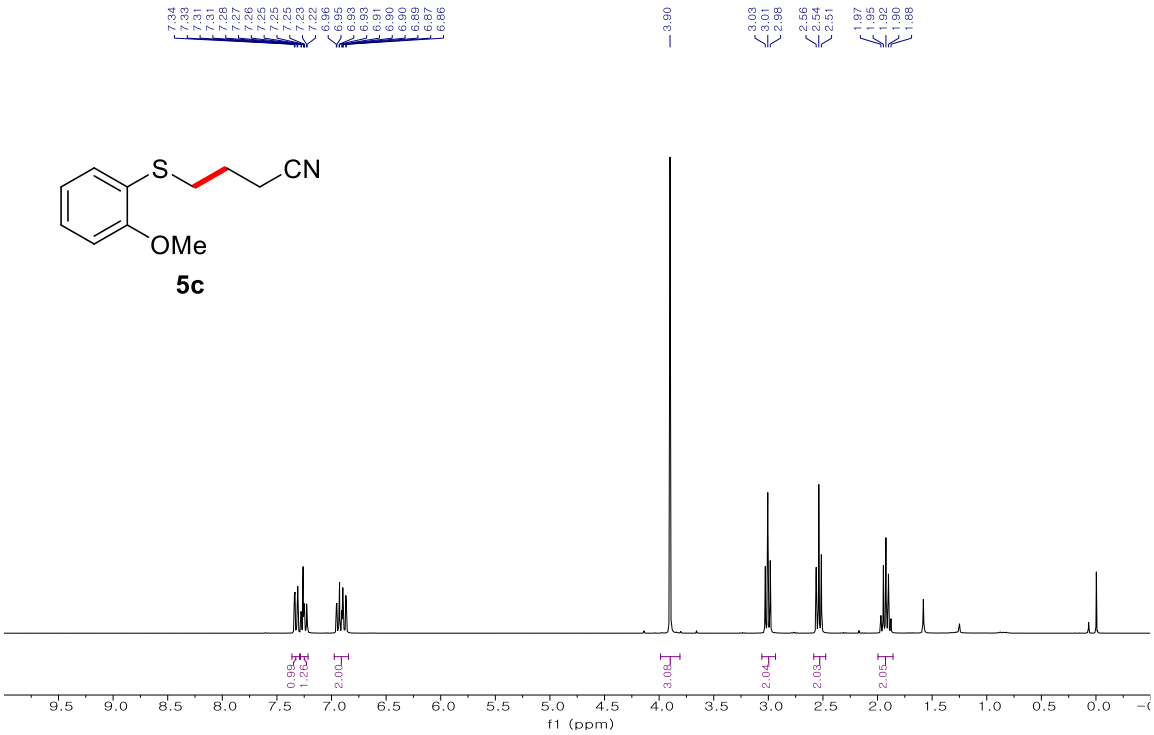
^{13}C-NMR (75 MHz, CDCl3) of **5a**



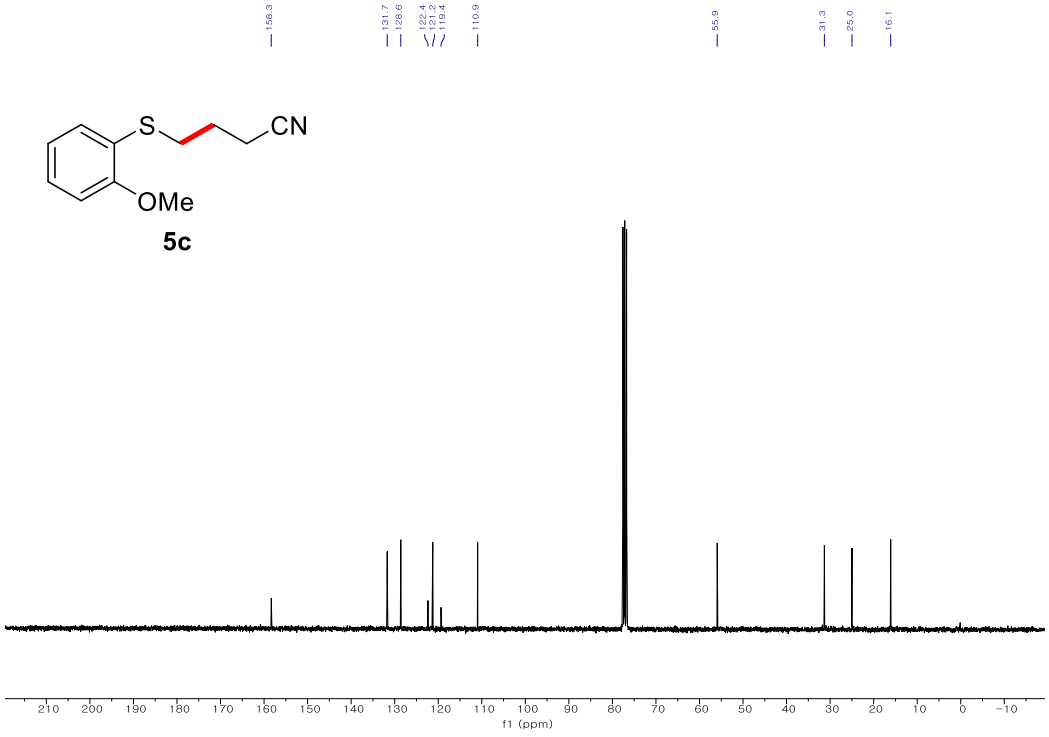
^{1}H-NMR (300 MHz, CDCl3) of **5b**



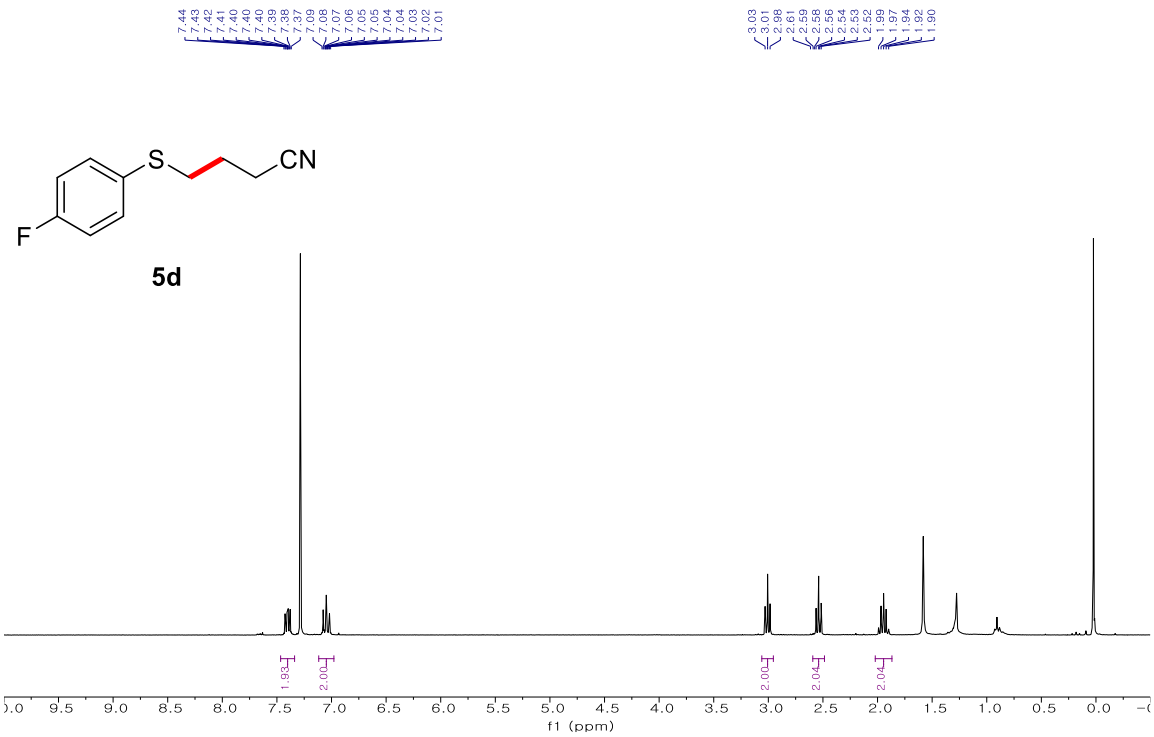
^{13}C-NMR (75 MHz, CDCl3) of **5b**



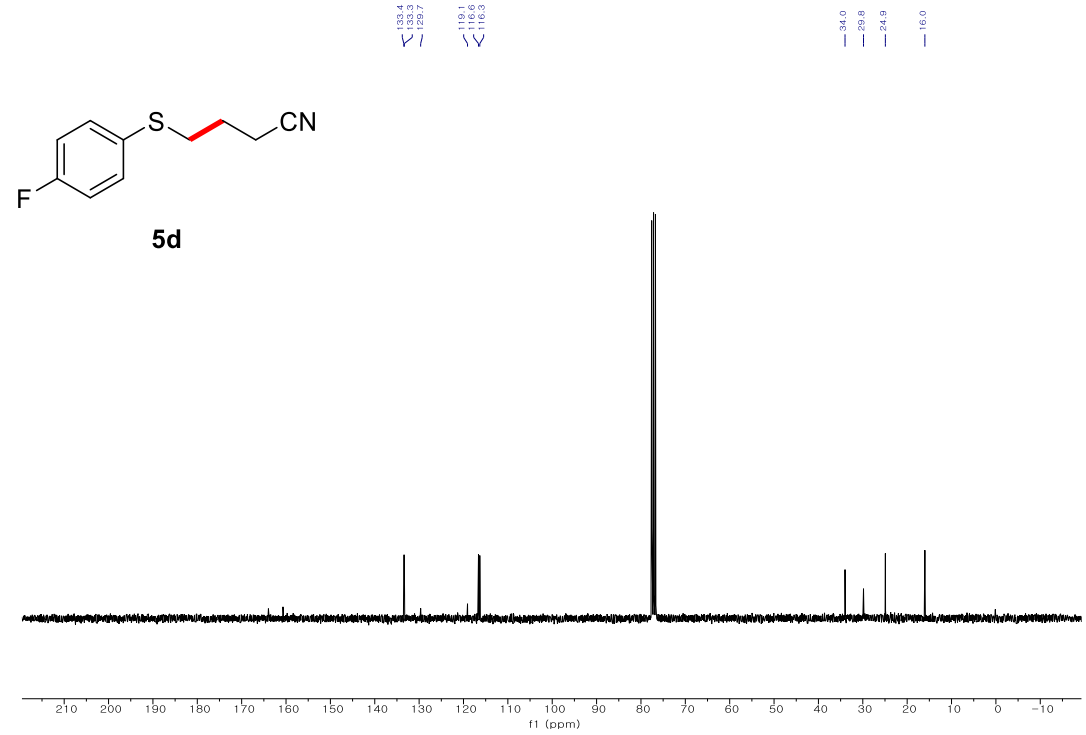
^{1}H-NMR (300 MHz, CDCl3) of **5c**



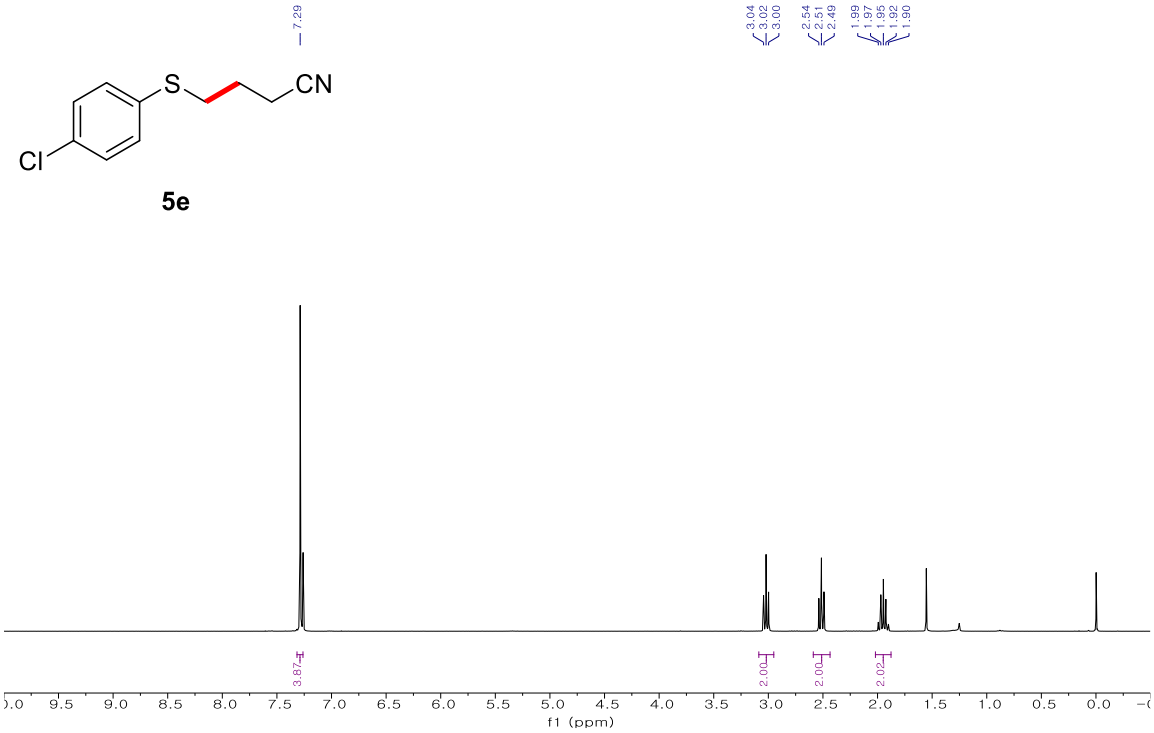
^{13}C-NMR (75 MHz, CDCl3) of **5c**



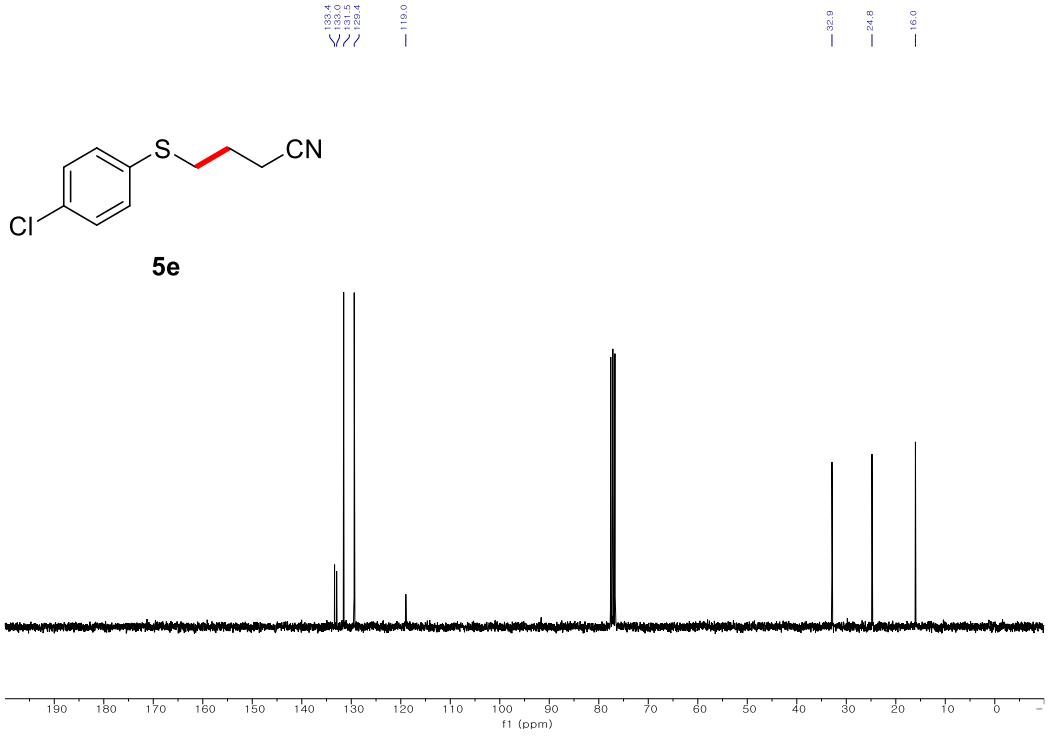
^{1}H-NMR (300 MHz, CDCl3) of **5d**



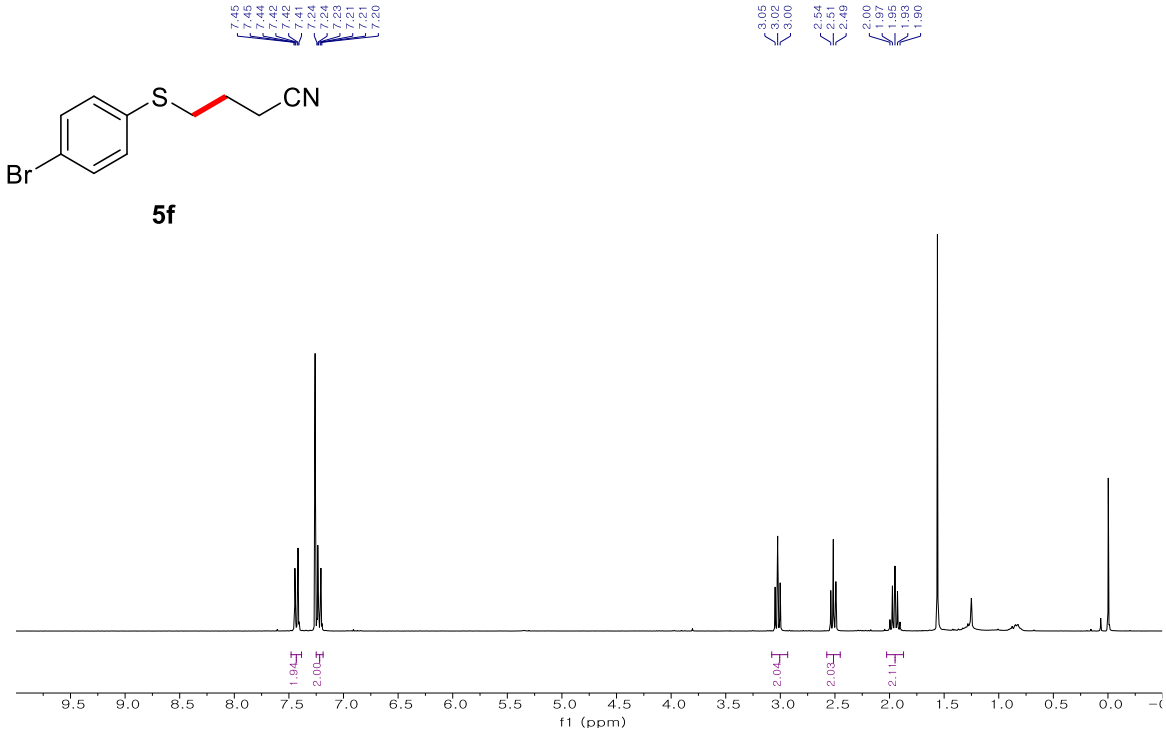
^{13}C-NMR (75 MHz, CDCl3) of **5d**



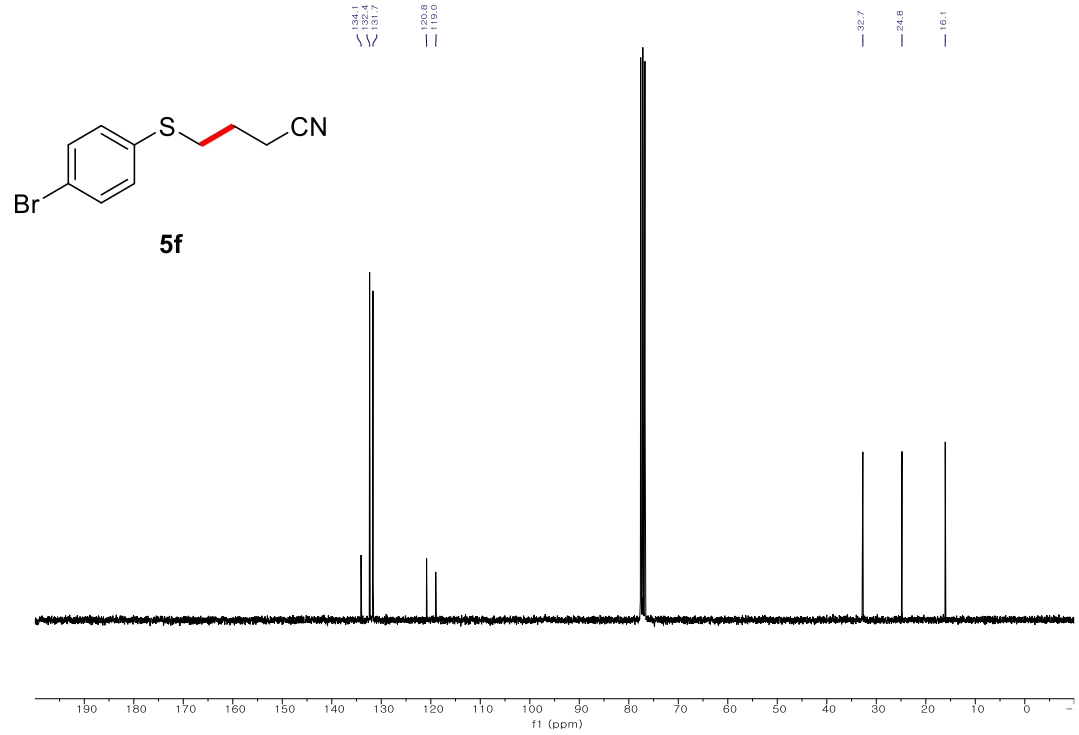
^{1}H-NMR (300 MHz, CDCl3) of **5e**



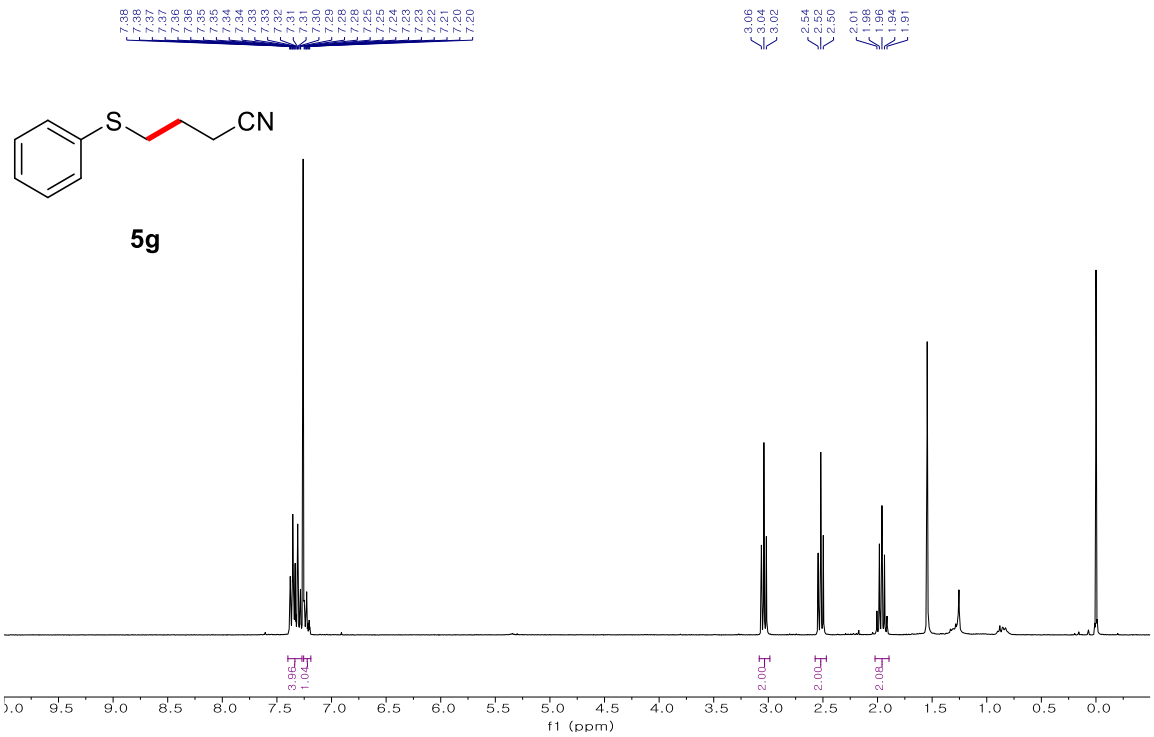
^{13}C-NMR (75 MHz, CDCl3) of **5e**



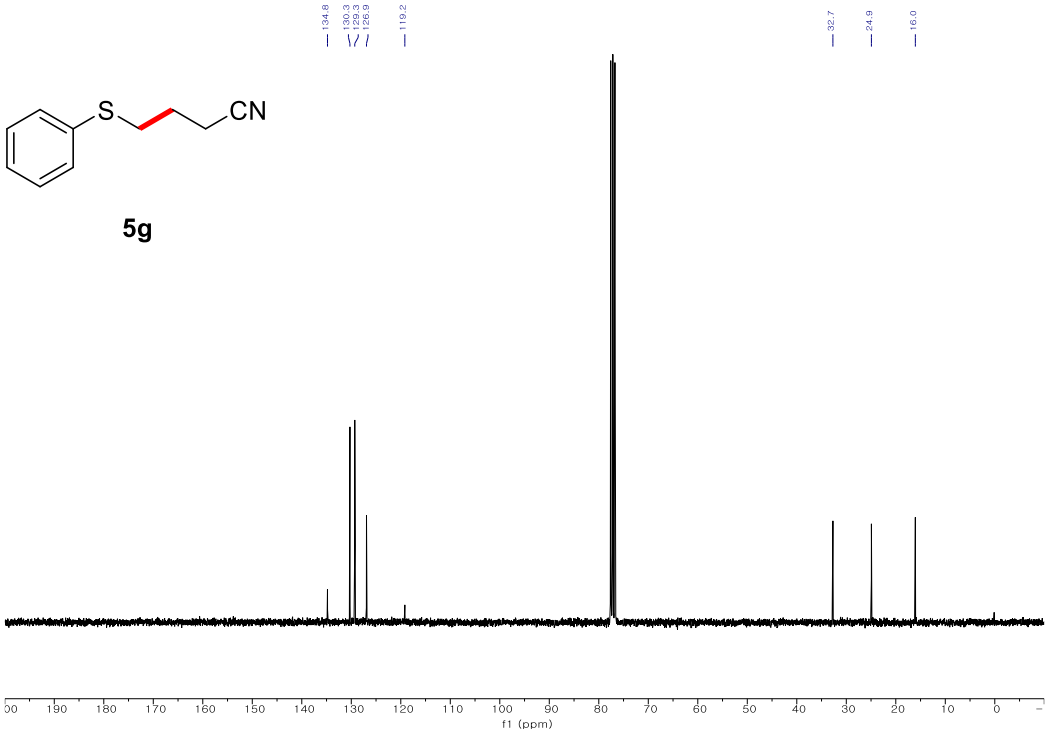
^{1}H-NMR (300 MHz, CDCl3) of **5f**



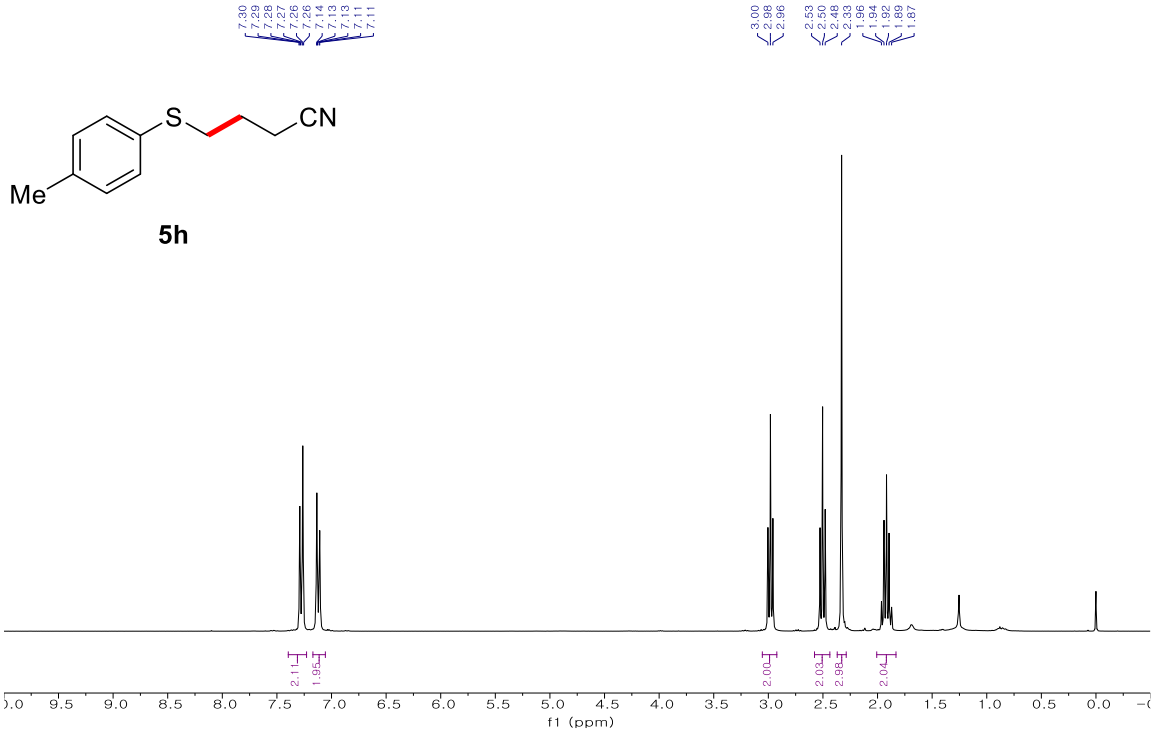
^{13}C-NMR (75 MHz, CDCl3) of **5f**



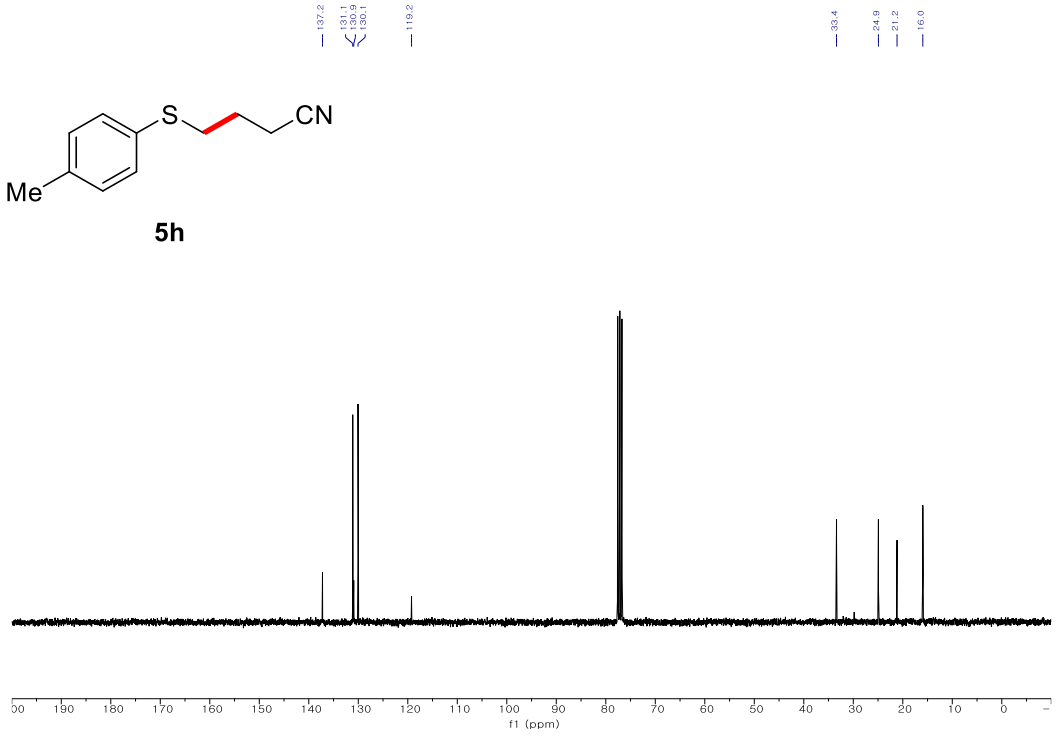
^{1}H-NMR (300 MHz, CDCl3) of **5g**



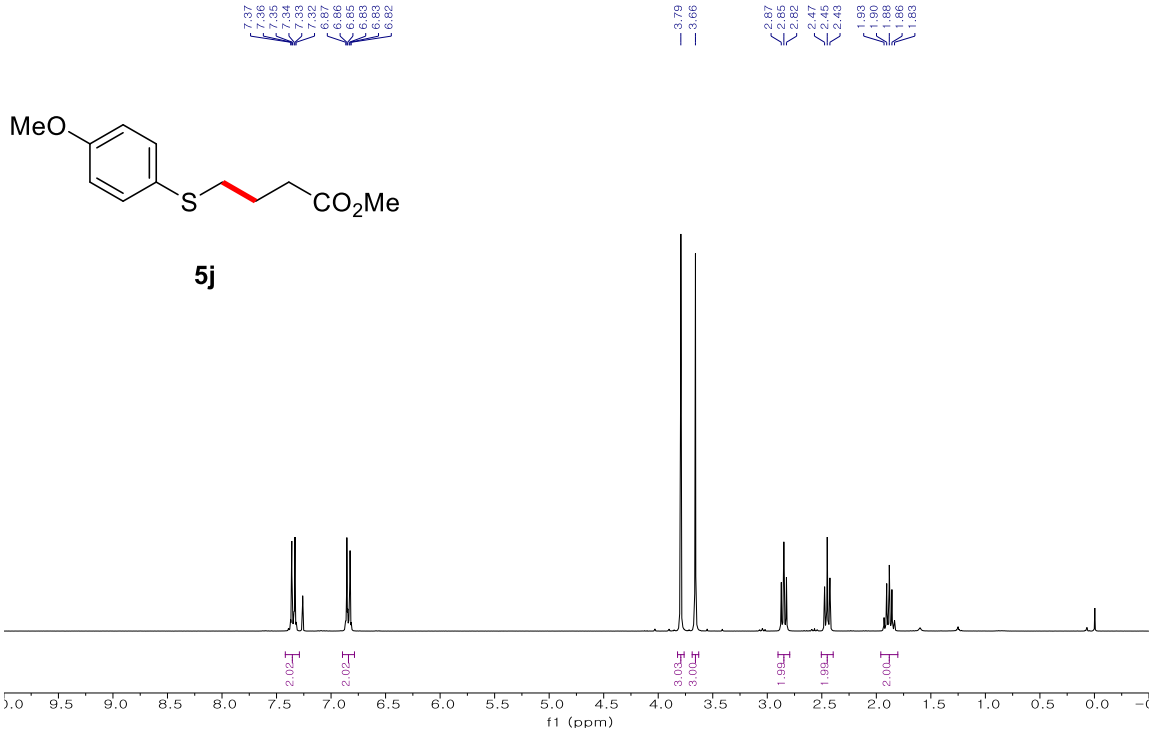
^{13}C-NMR (75 MHz, CDCl3) of **5g**



^{1}H-NMR (300 MHz, CDCl3) of **5h**



^{13}C-NMR (75 MHz, CDCl3) of **5h**



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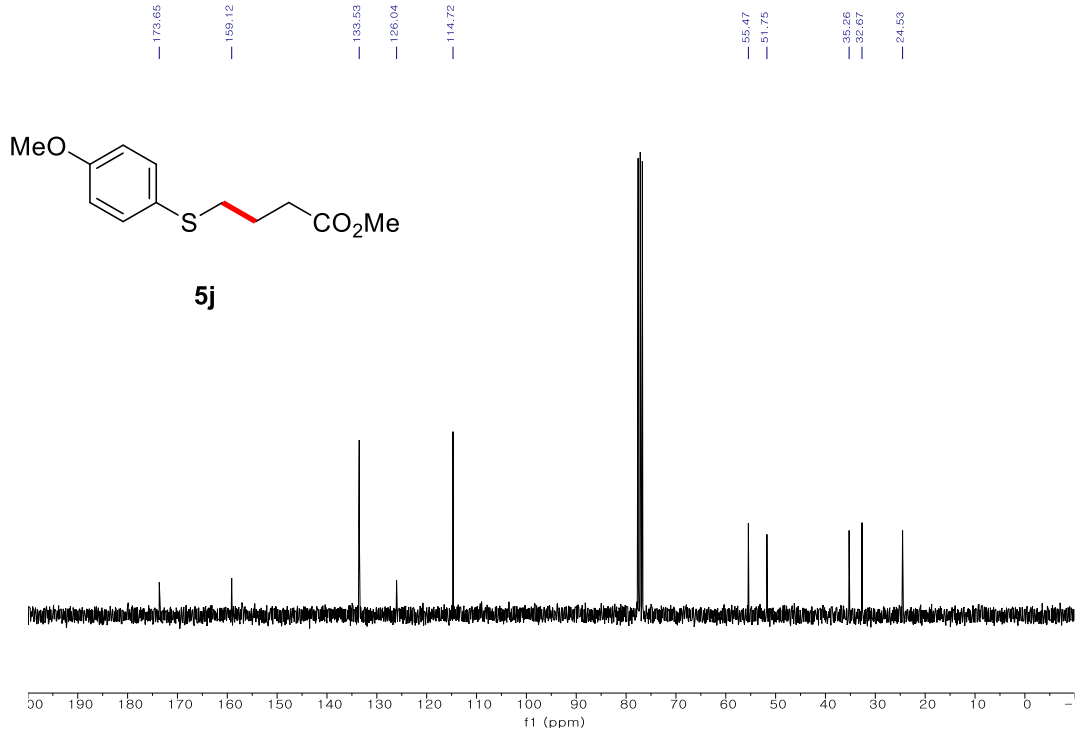

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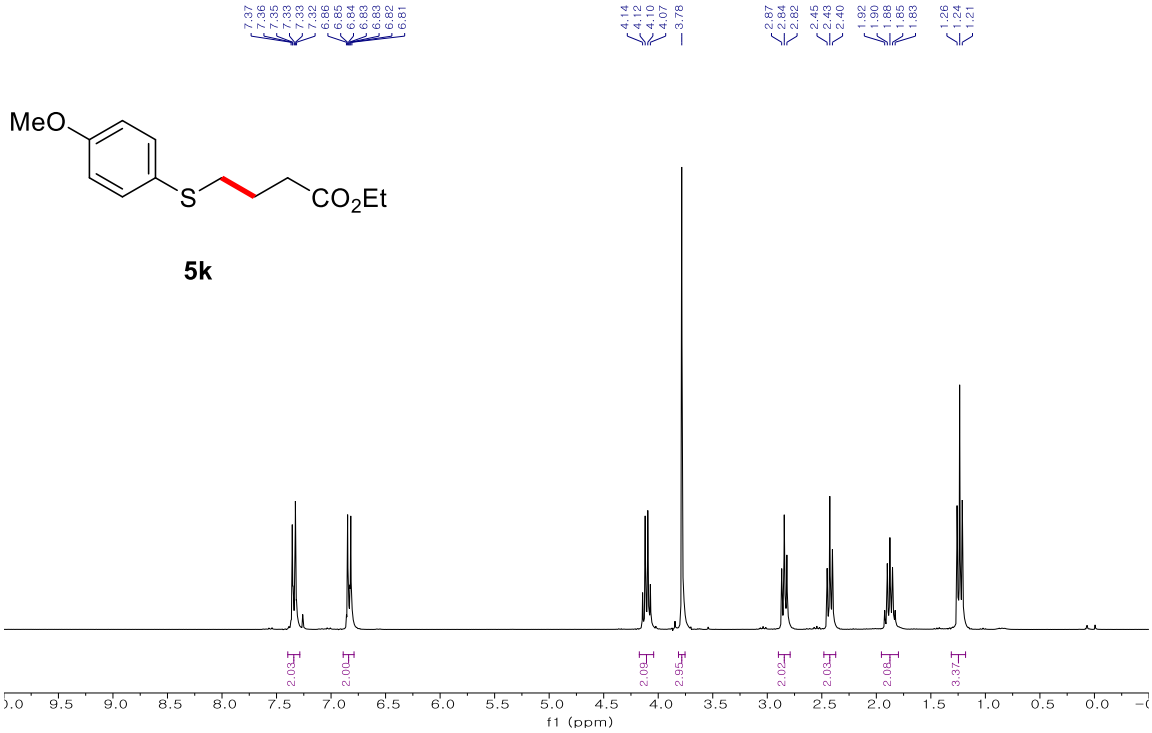

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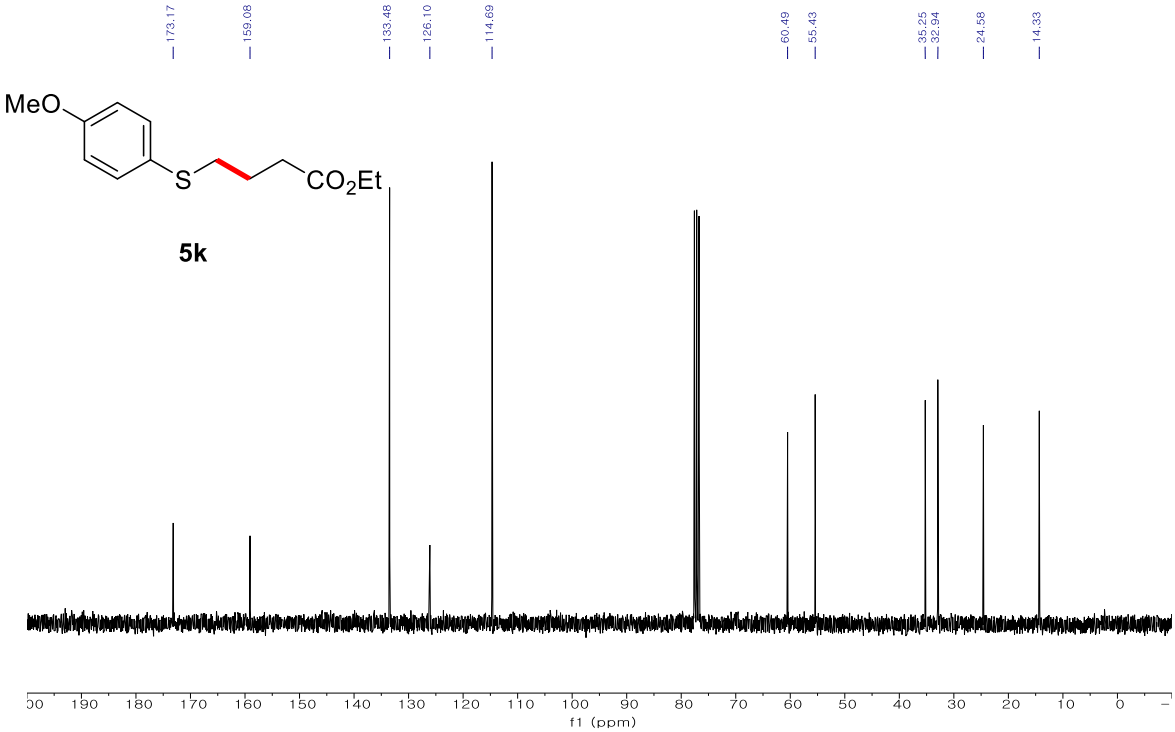
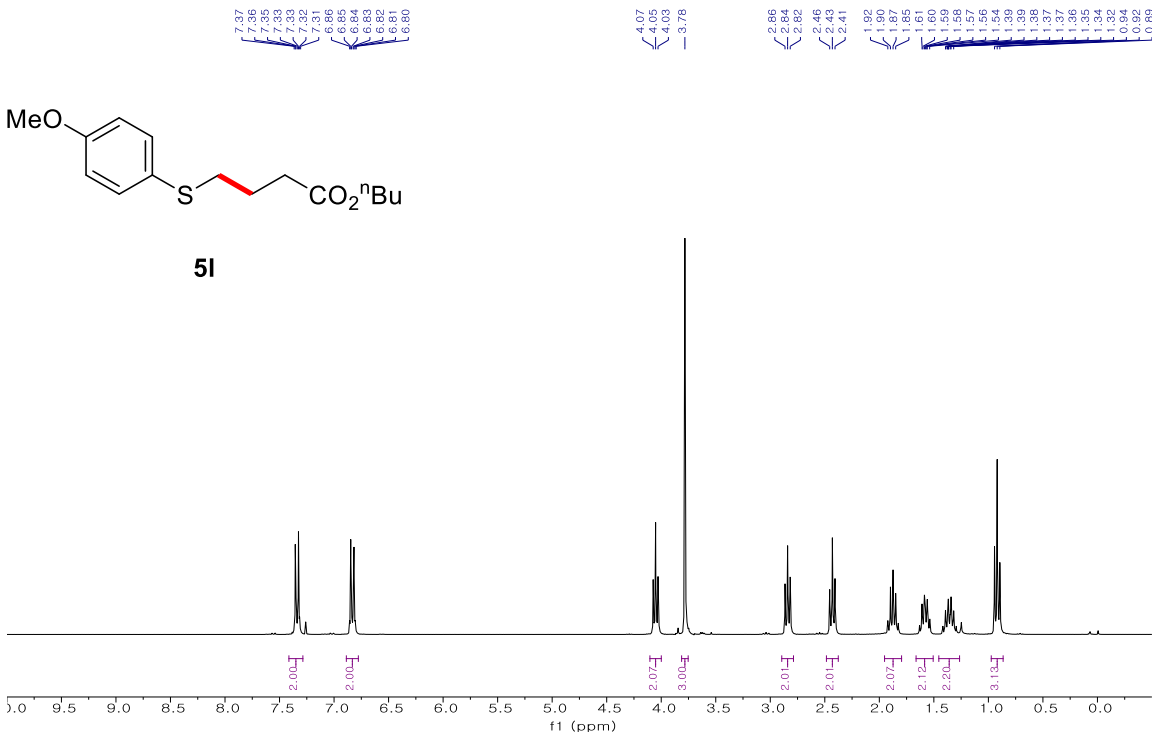
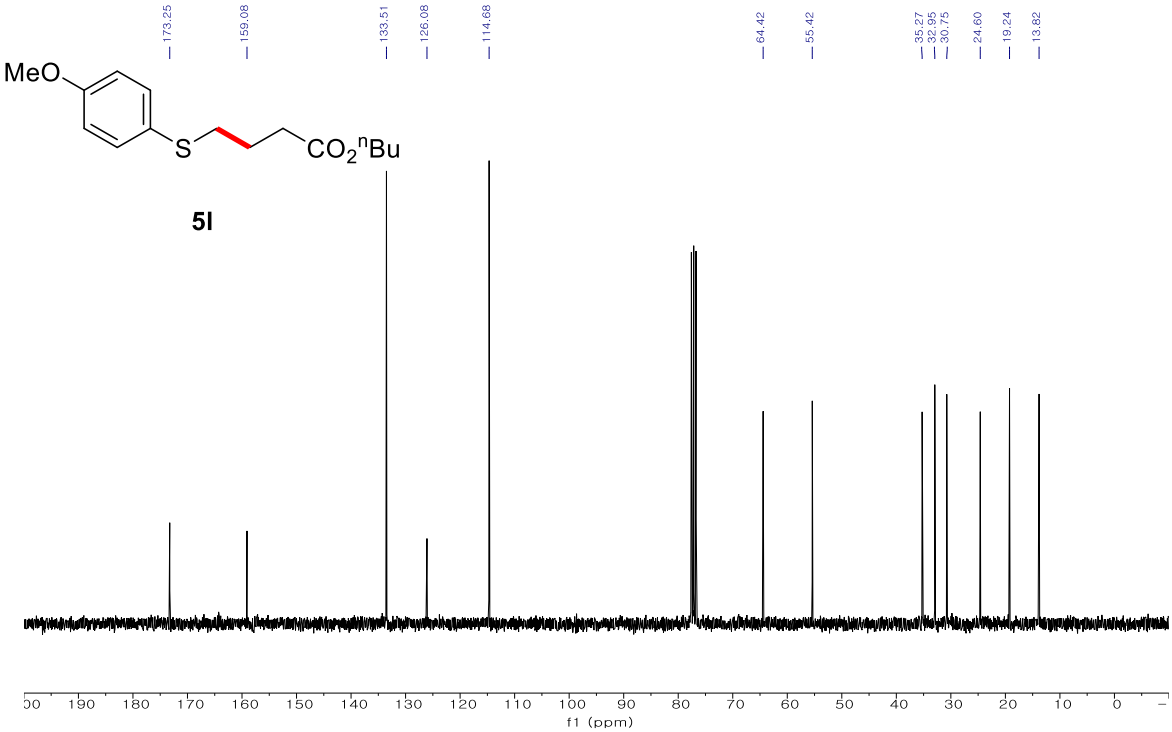


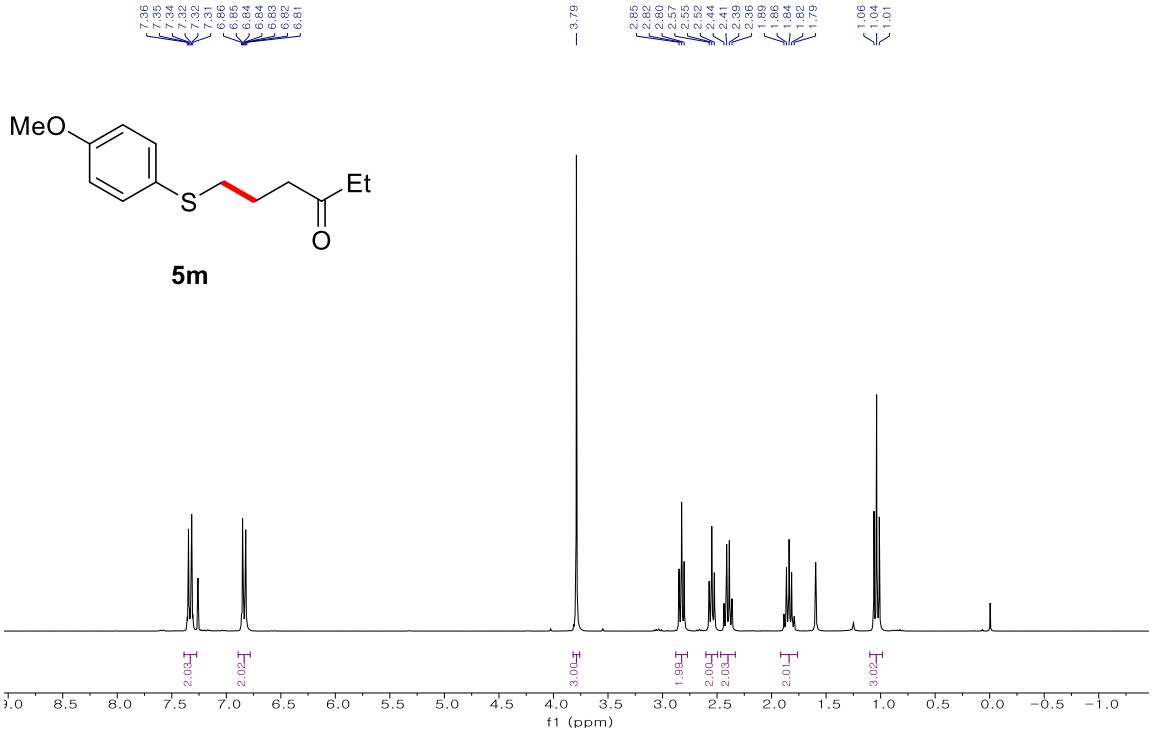
^{13}C-NMR (75 MHz, CDCl3) of **5k**



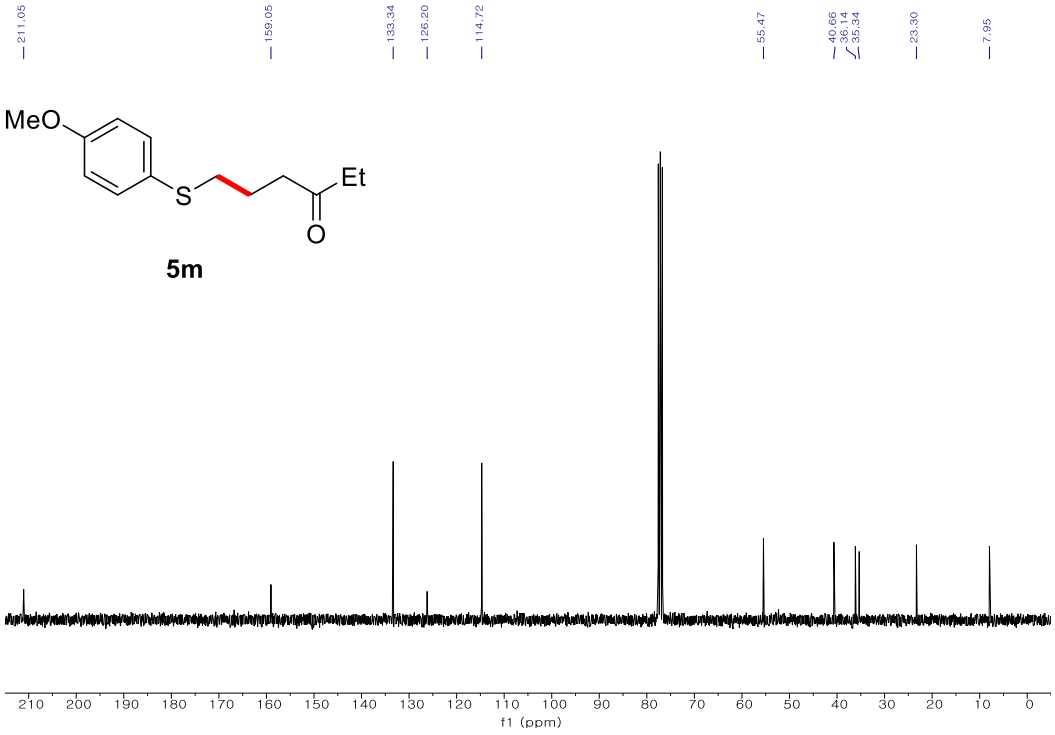
^{1}H-NMR (300 MHz, CDCl3) of **5l**



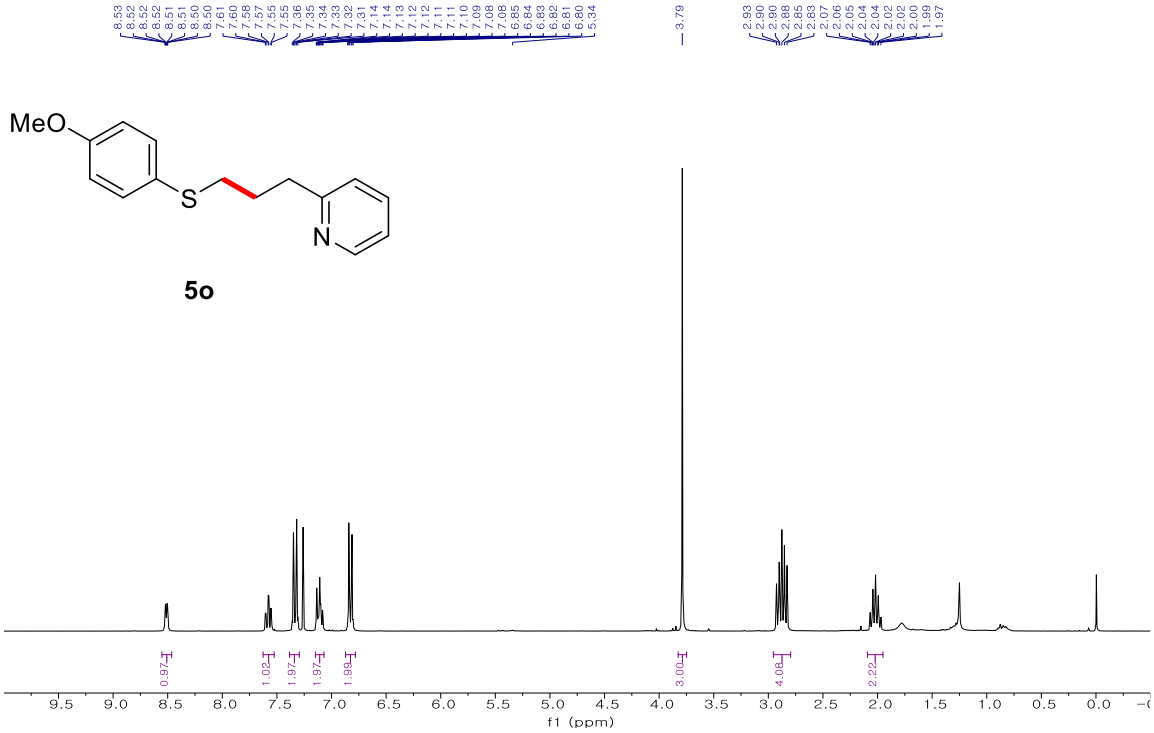
^{13}C-NMR (75 MHz, CDCl3) of **5l**



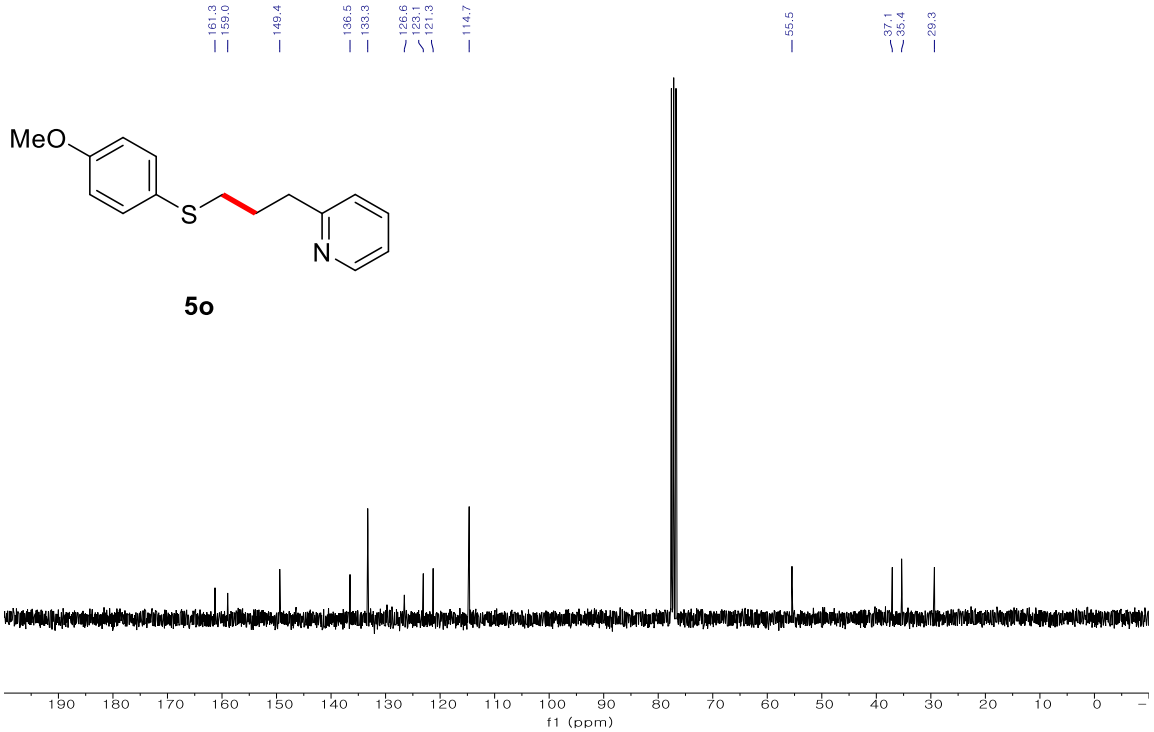
^{1}H-NMR (300 MHz, CDCl3) of **5m**



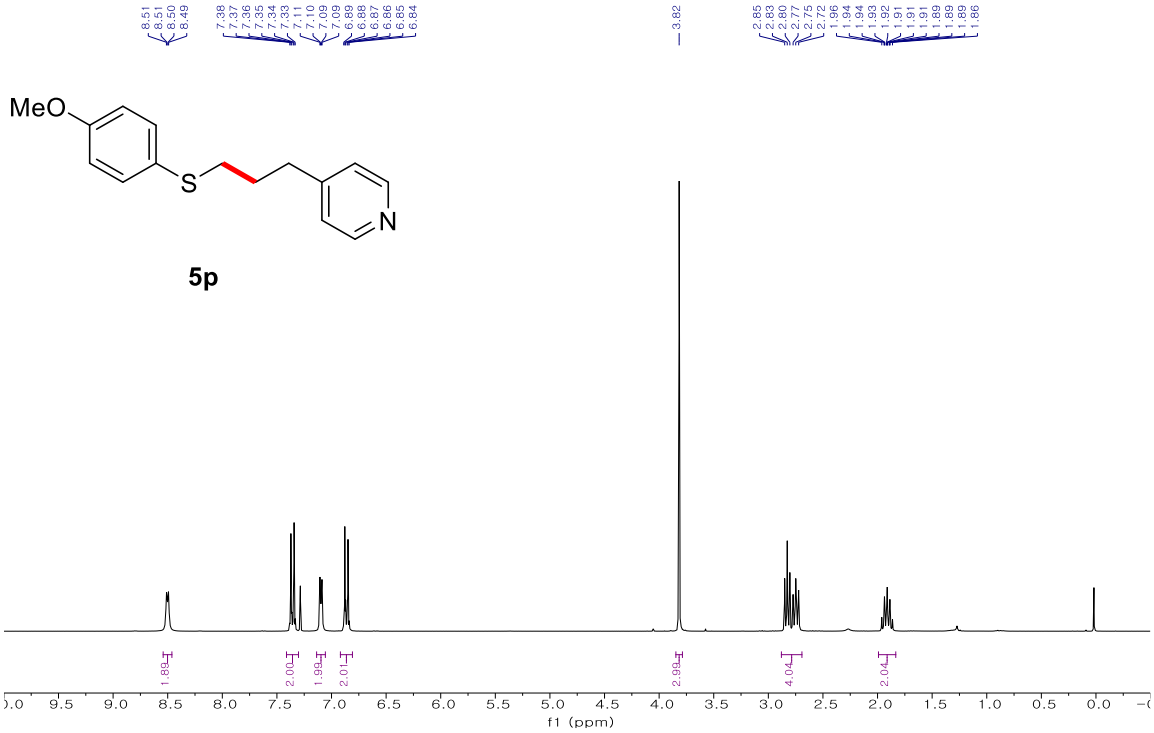
^{13}C-NMR (75 MHz, CDCl3) of **5m**



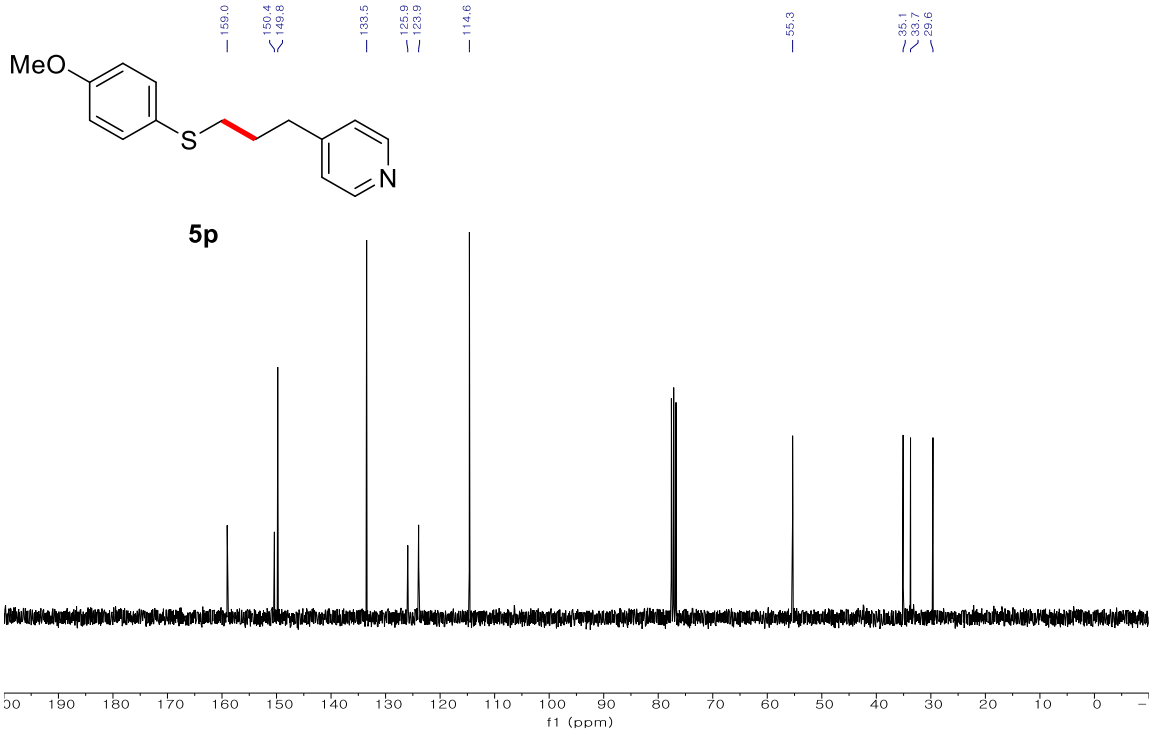
^{1}H-NMR (300 MHz, CDCl3) of **5o**



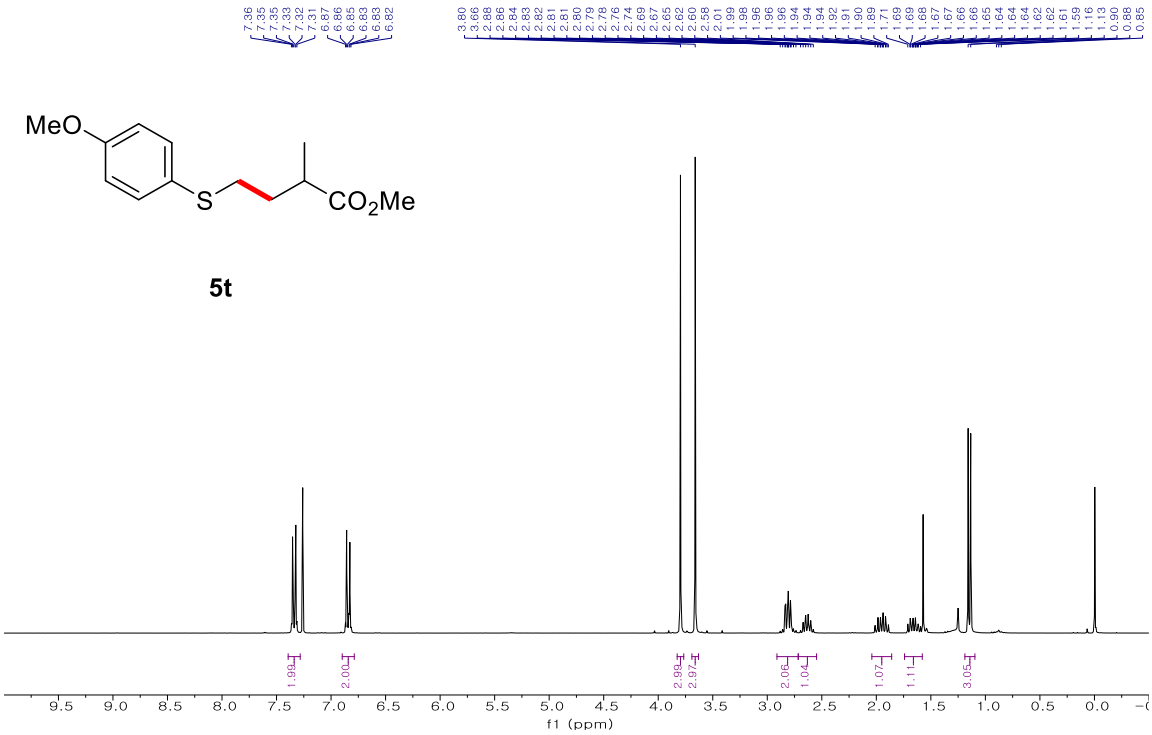
^{13}C-NMR (75 MHz, CDCl3) of **5o**



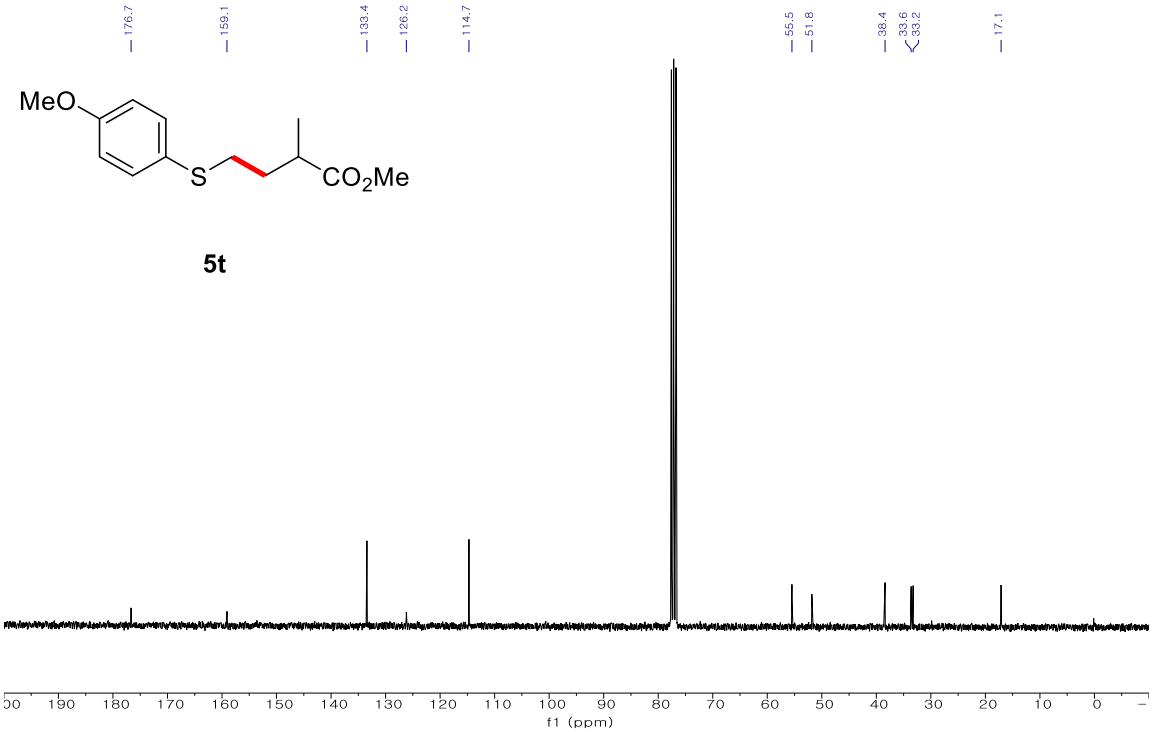
^{1}H-NMR (300 MHz, CDCl3) of **5p**



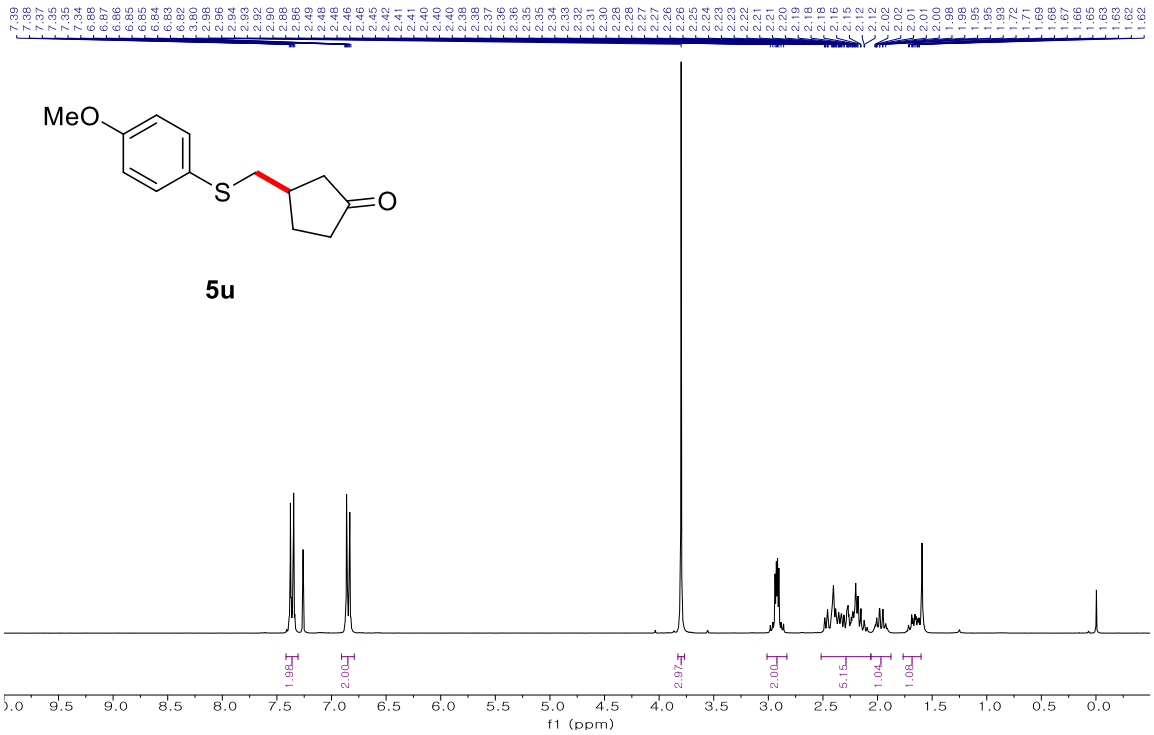
^{13}C-NMR (75 MHz, CDCl3) of **5p**



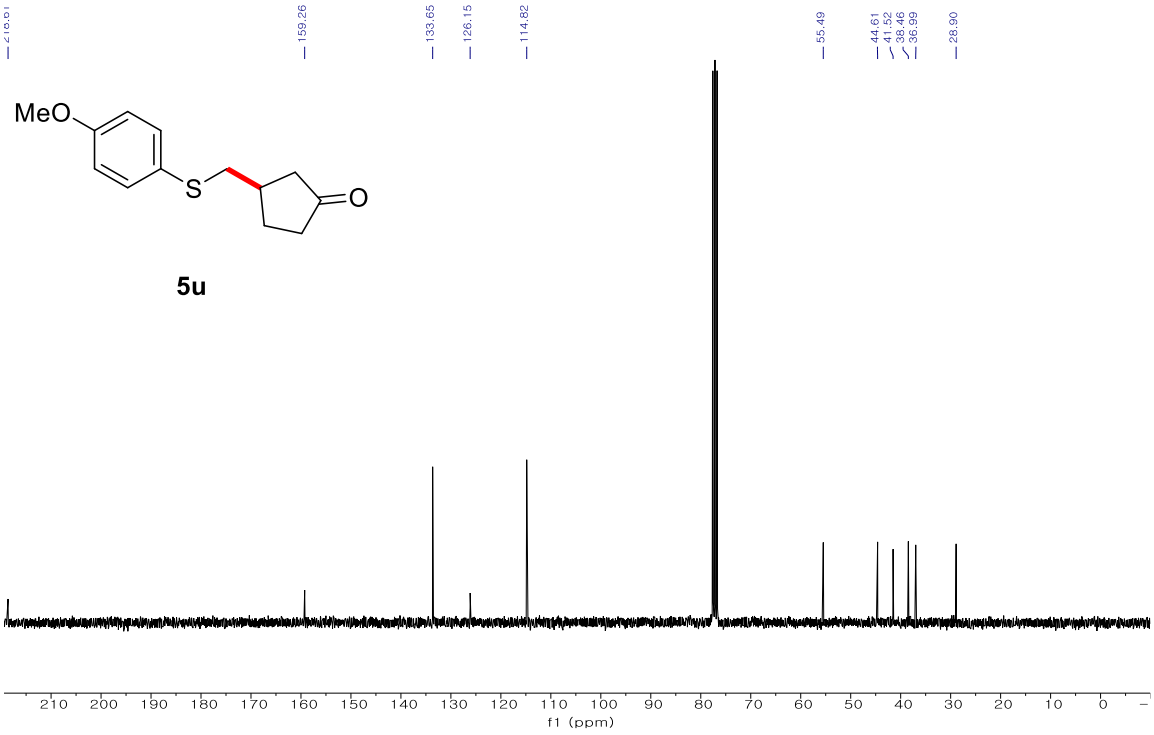
^{1}H-NMR (300 MHz, CDCl3) of **5t**



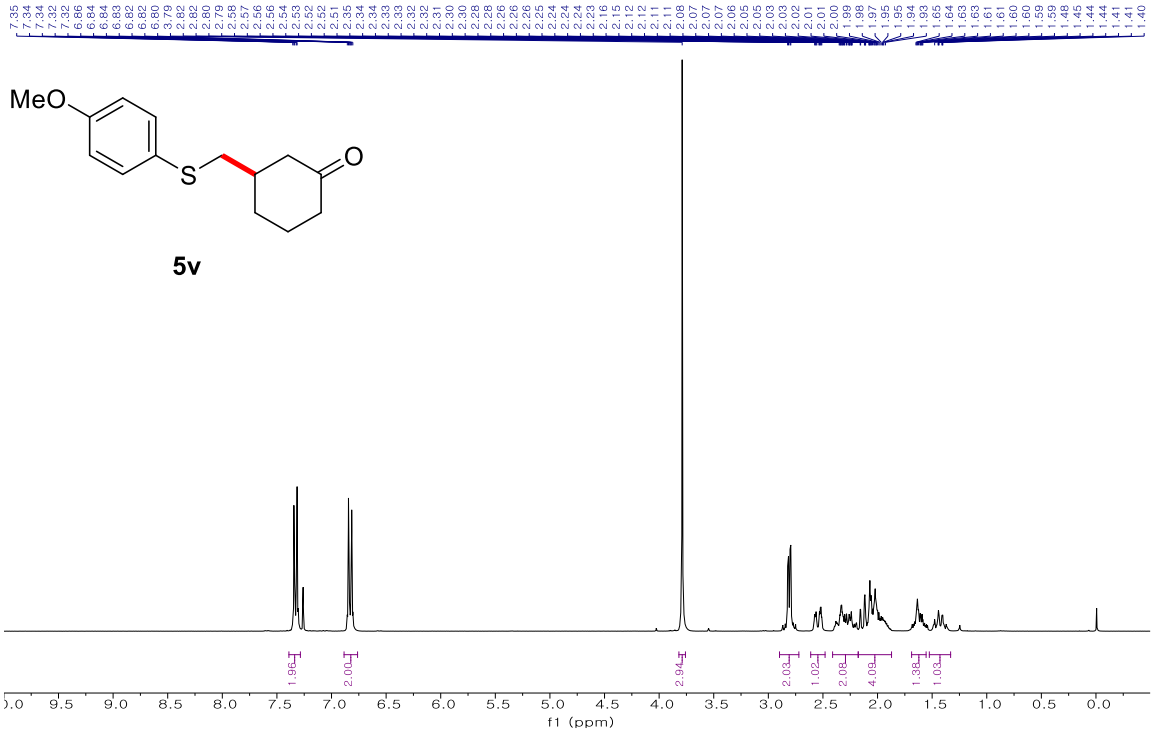
^{13}C-NMR (75 MHz, CDCl3) of **5t**



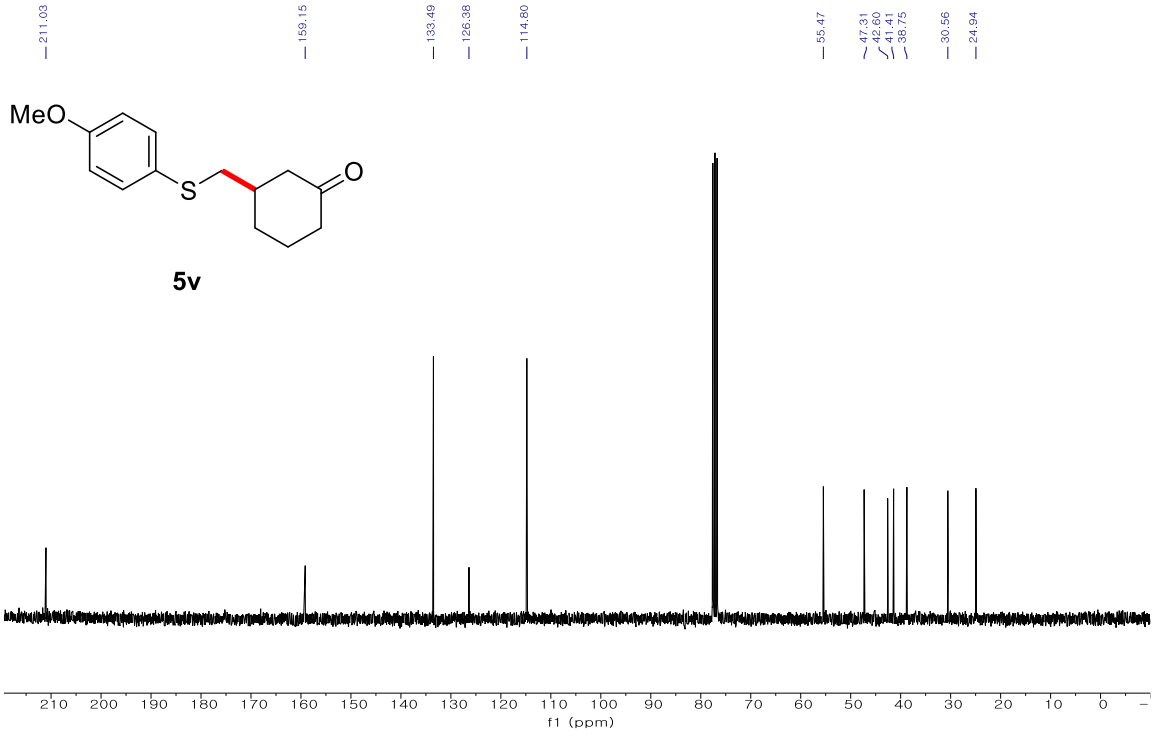
^{1}H-NMR (300 MHz, CDCl3) of **5u**



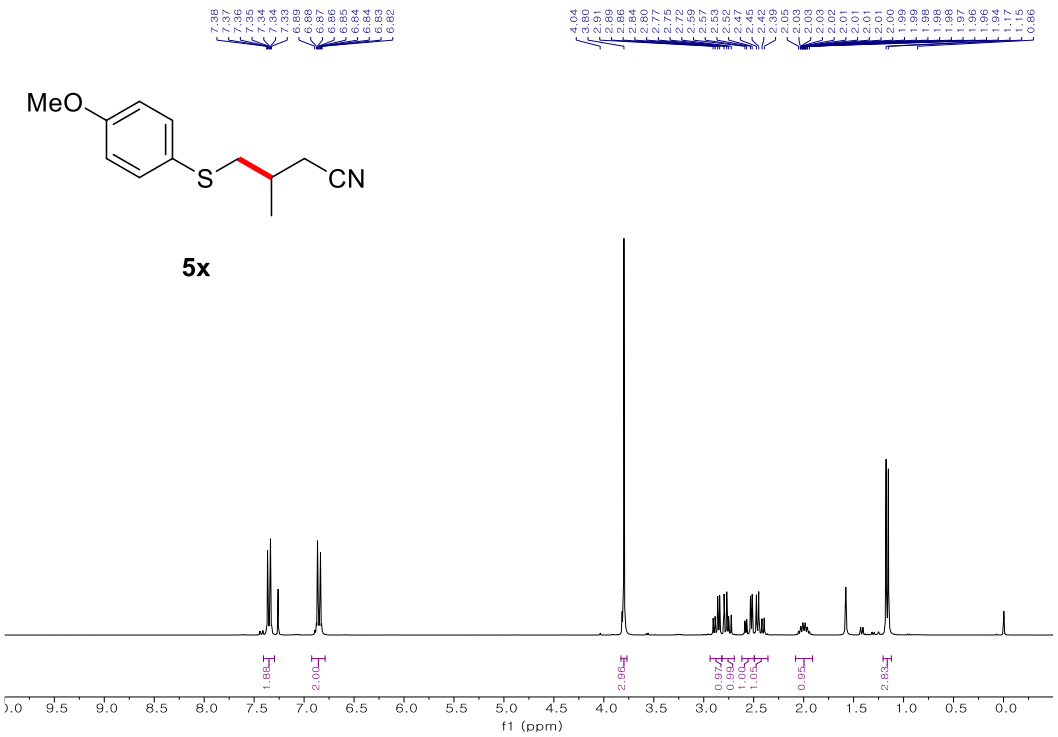
^{13}C-NMR (75 MHz, CDCl3) of **5u**



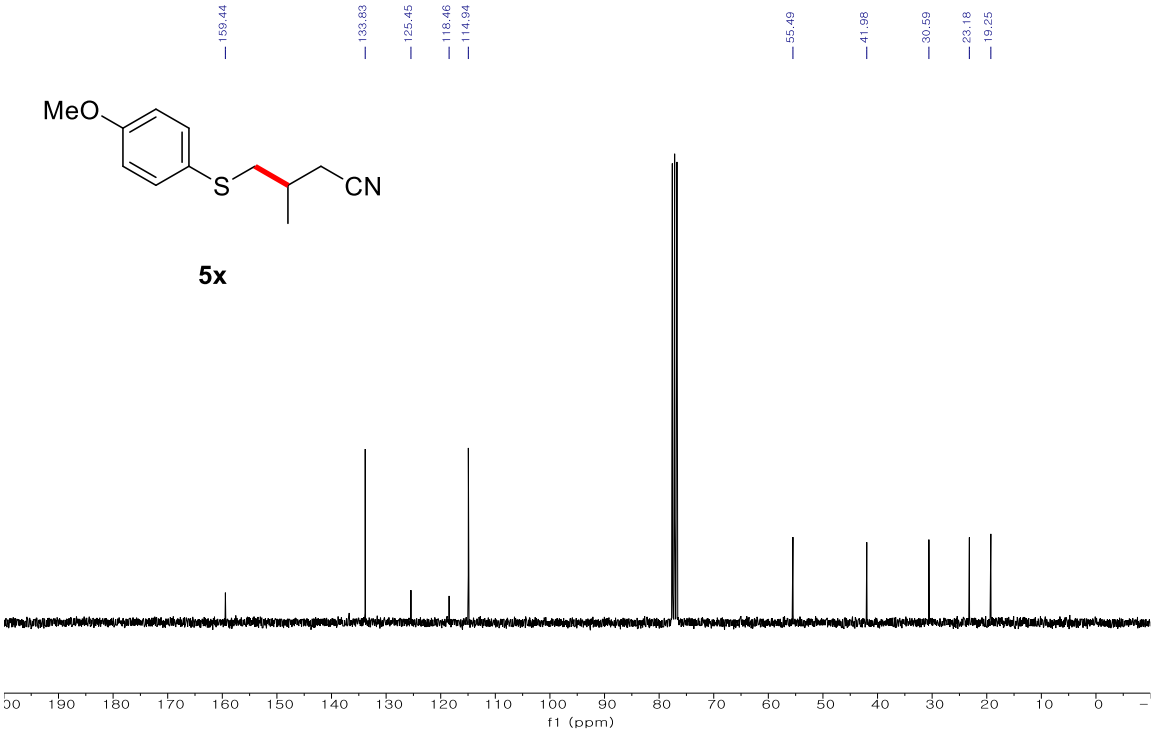
^{1}H-NMR (300 MHz, CDCl3) of **5v**



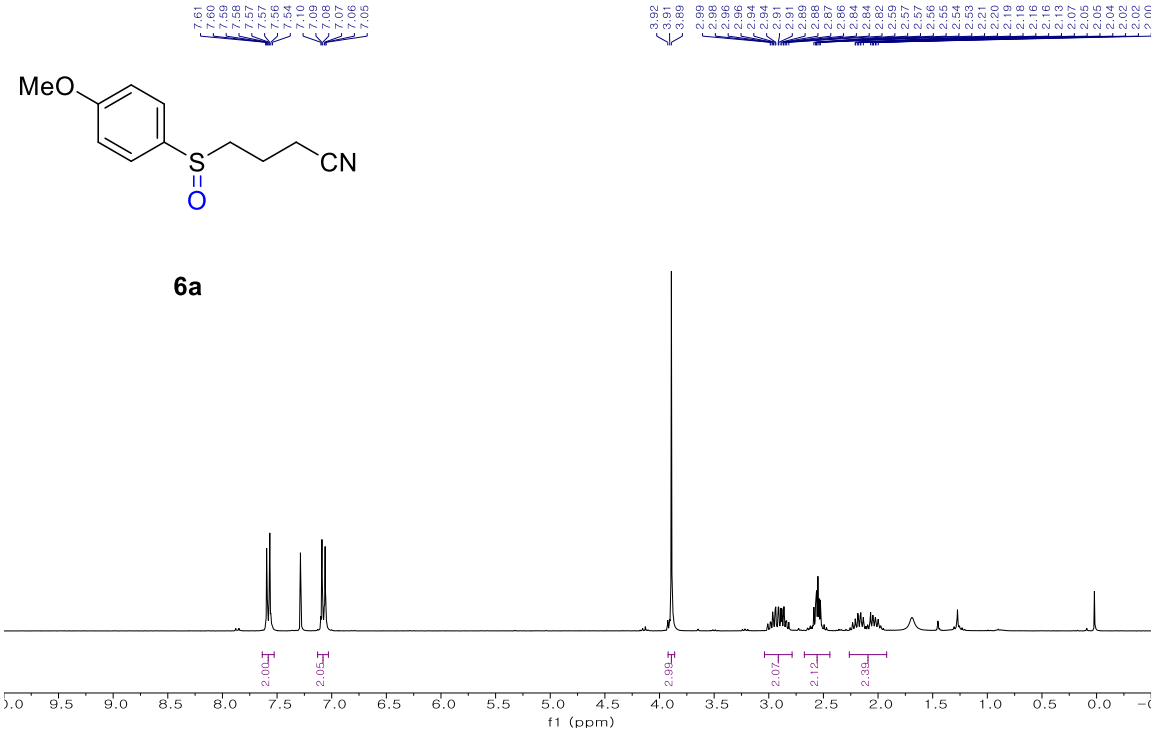
^{13}C-NMR (75 MHz, CDCl3) of **5v**



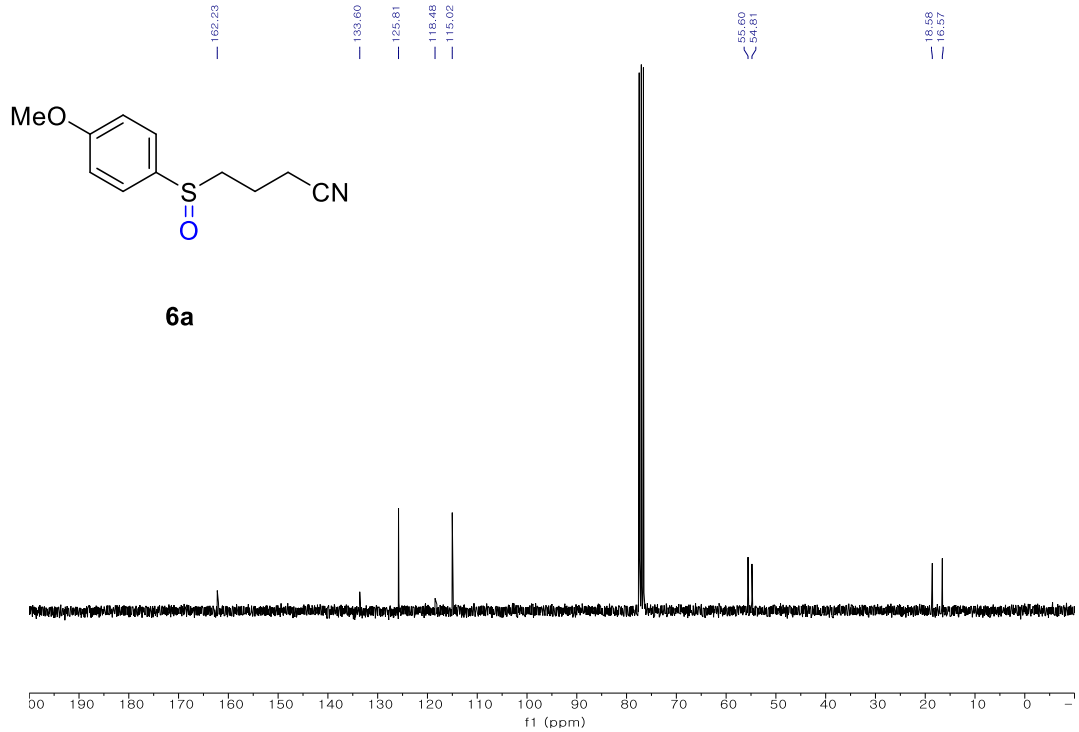
^{1}H-NMR (300 MHz, CDCl3) of **5x**



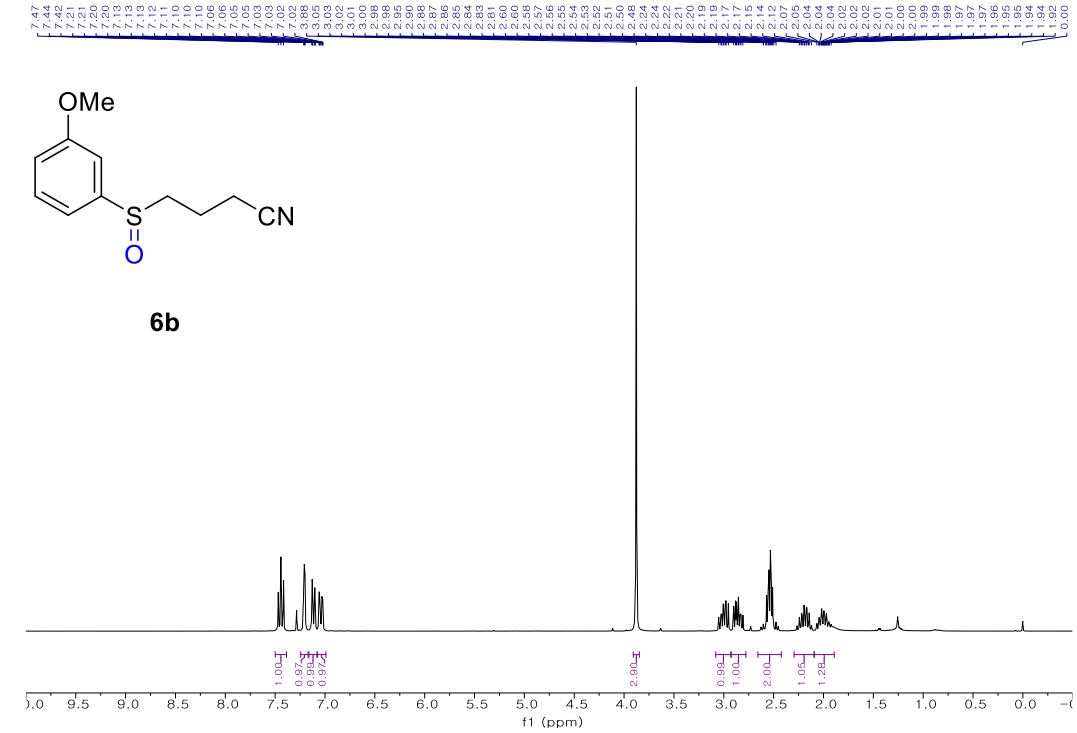
^{13}C-NMR (75 MHz, CDCl3) of **5x**



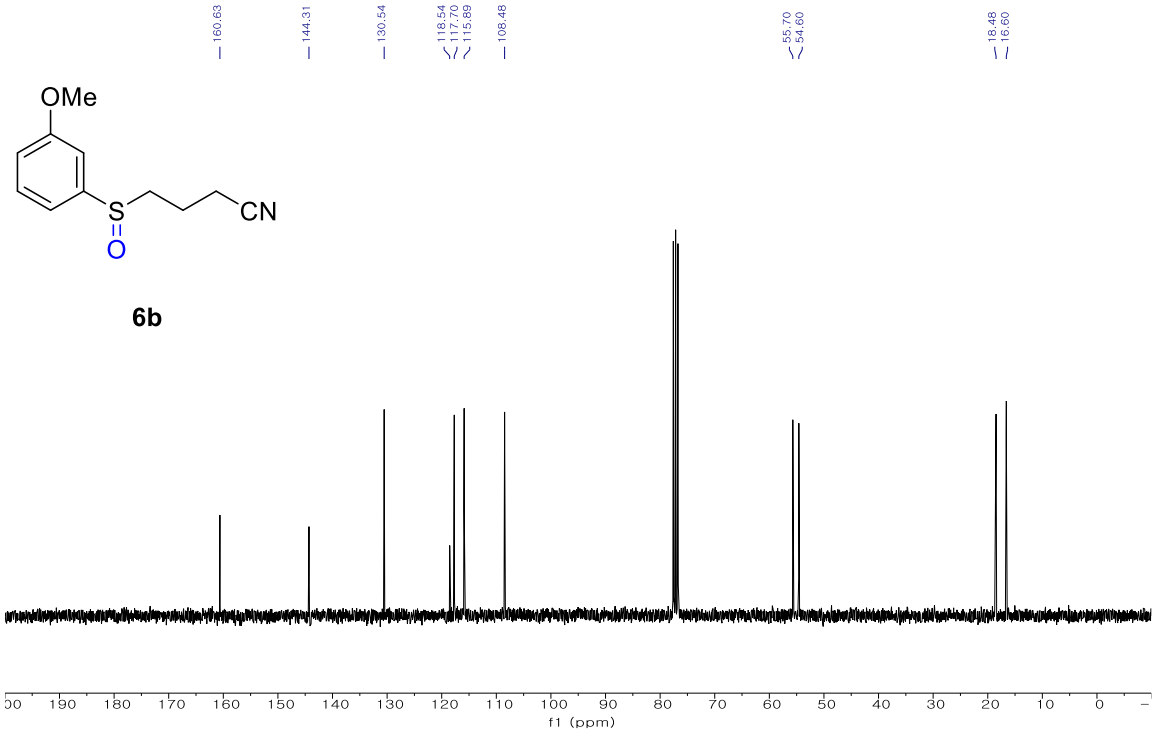
^{1}H-NMR (300 MHz, CDCl3) of **6a**



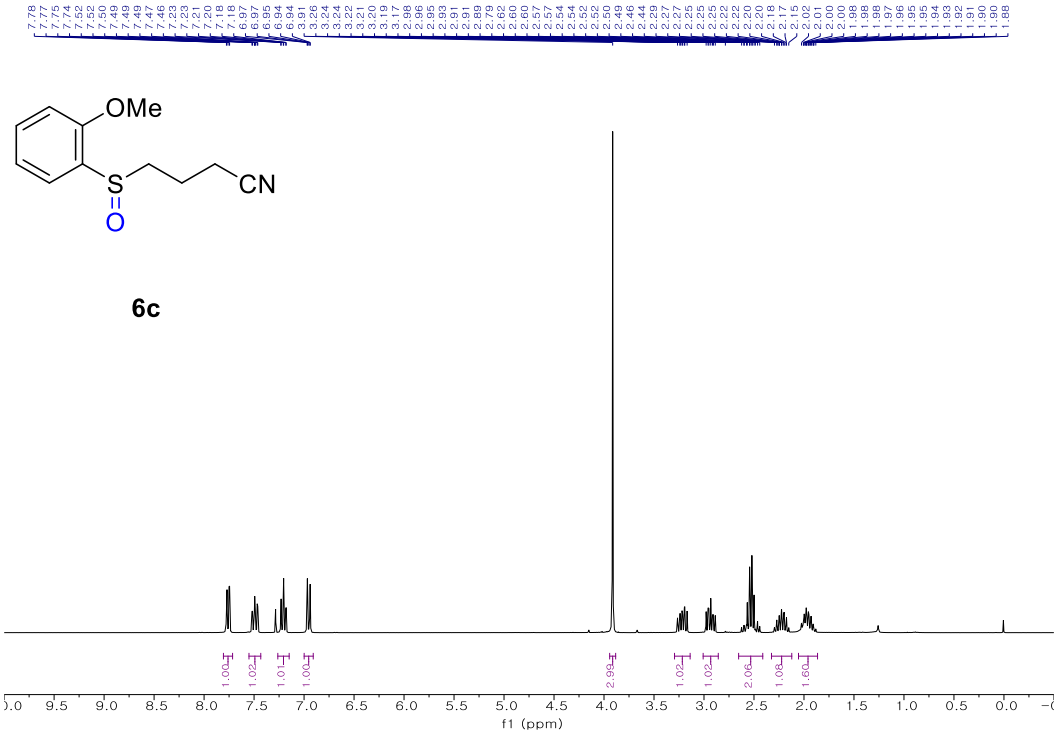
^{13}C-NMR (75 MHz, CDCl3) of **6a**



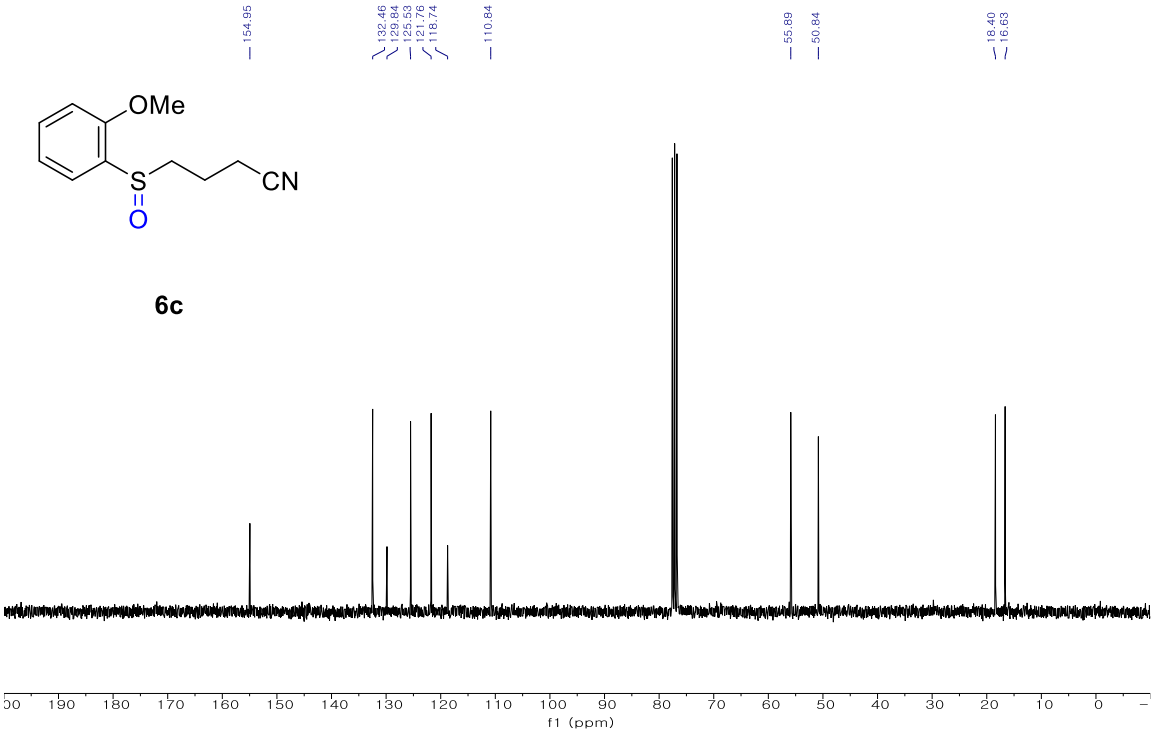
^{1}H-NMR (300 MHz, CDCl3) of **6b**



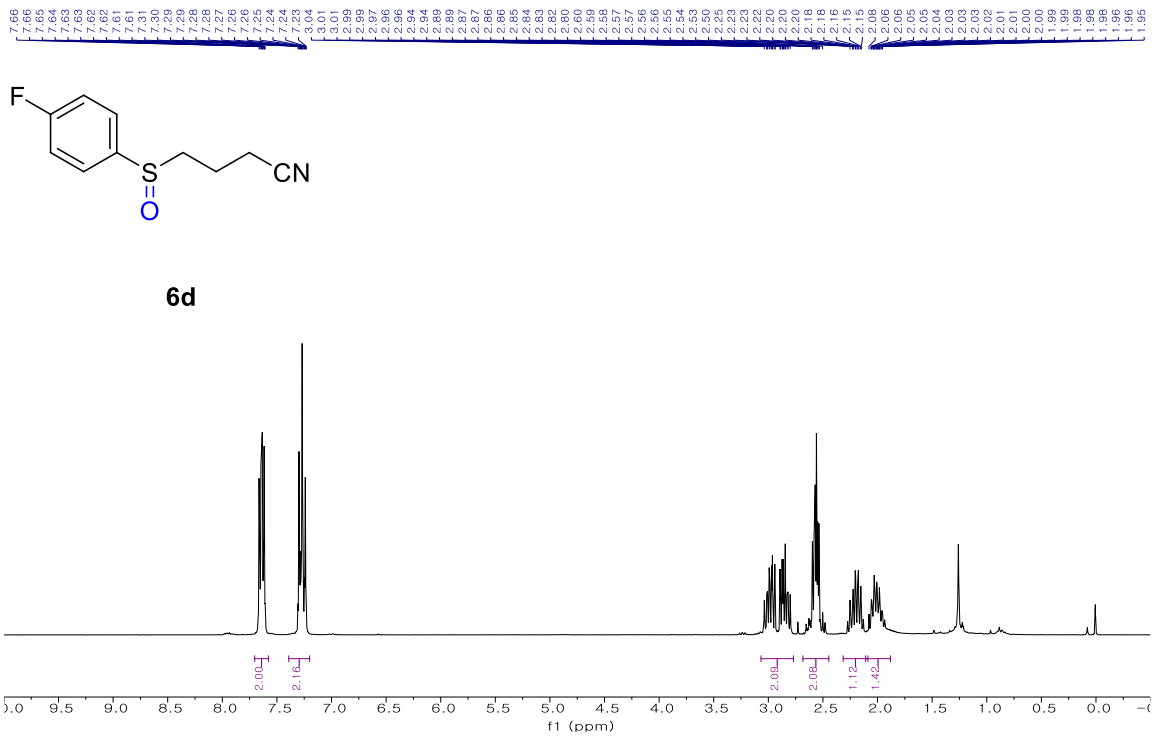
^{13}C-NMR (75 MHz, CDCl3) of **6b**



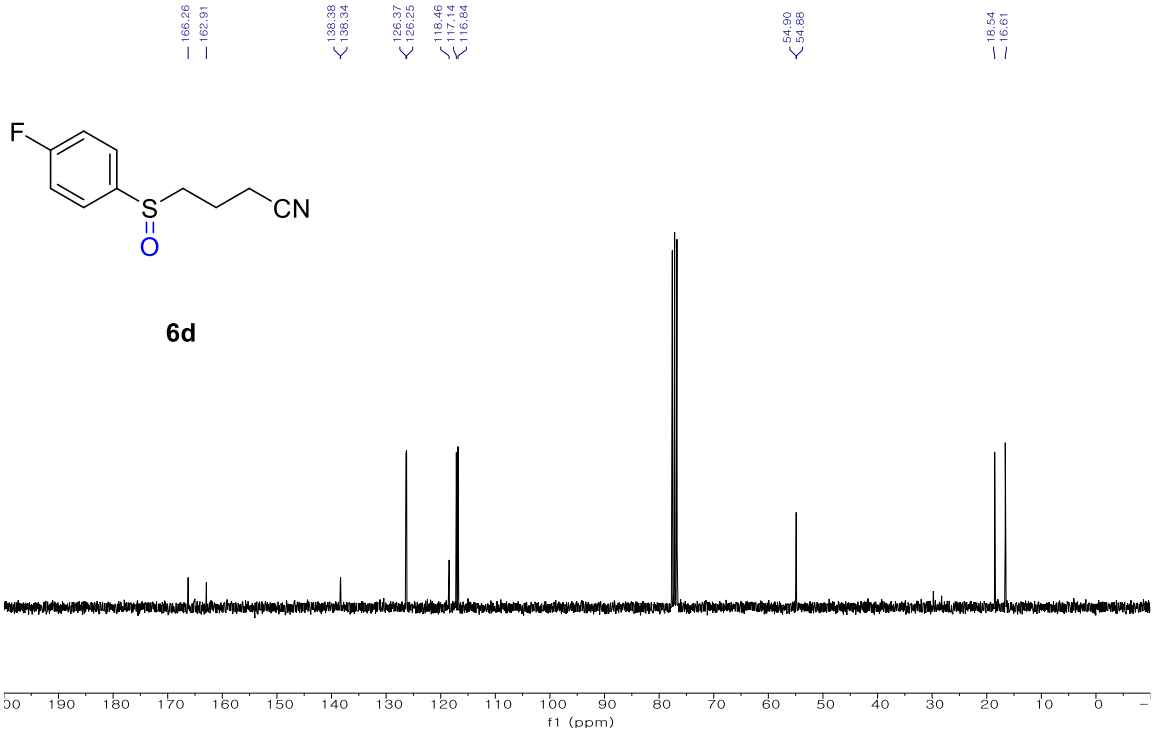
^{1}H-NMR (300 MHz, CDCl3) of **6c**



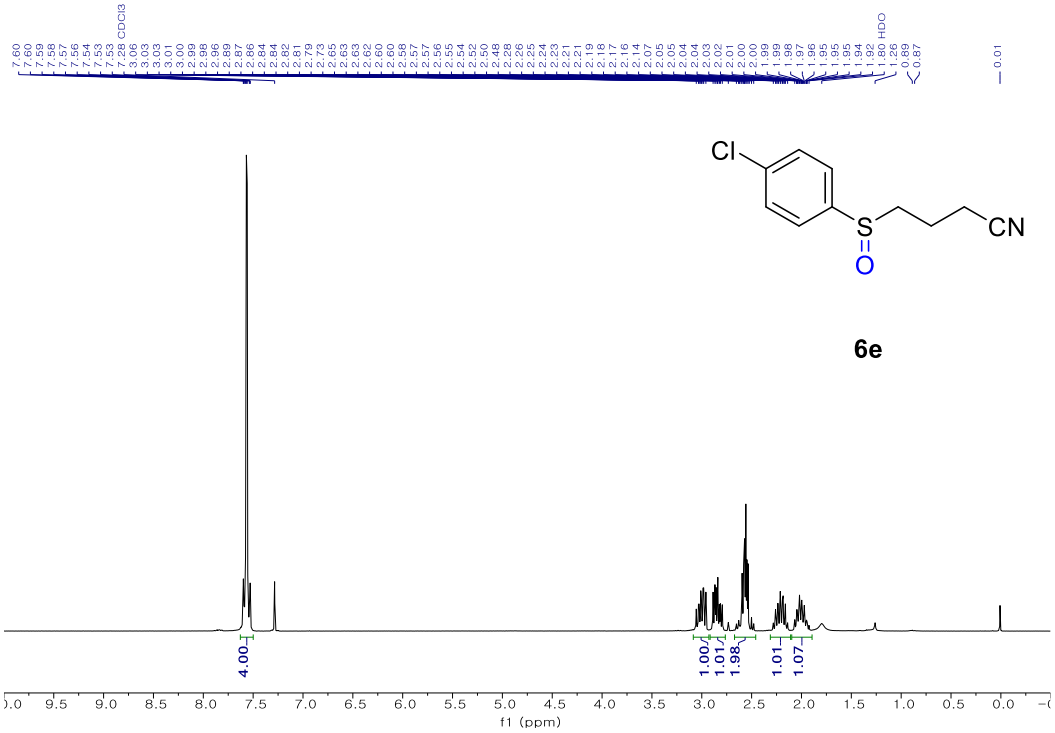
^{13}C-NMR (75 MHz, CDCl3) of **6c**



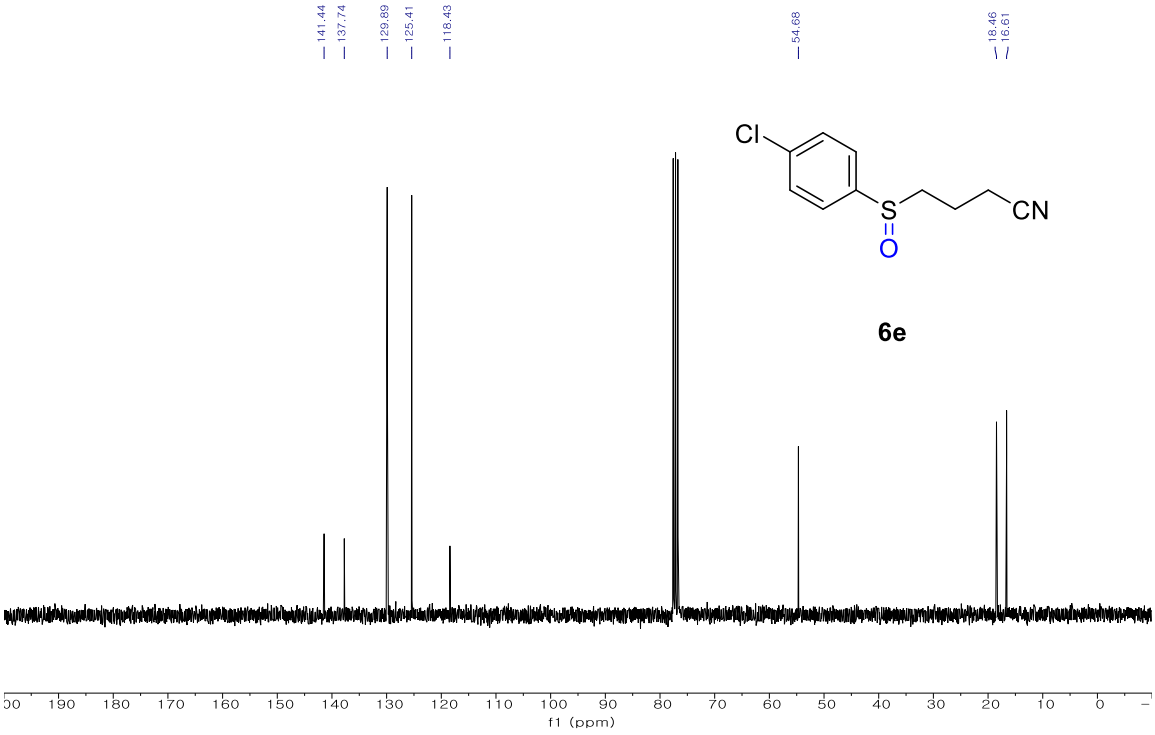
^{1}H-NMR (300 MHz, CDCl3) of **6d**



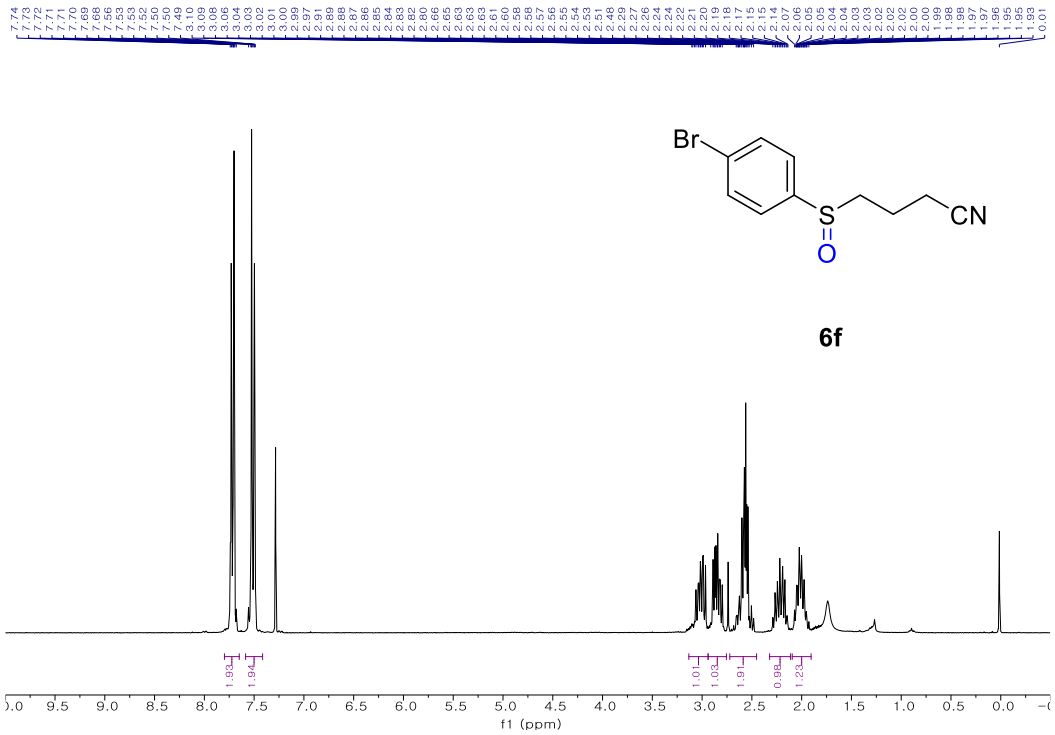
^{13}C-NMR (75 MHz, CDCl3) of **6d**



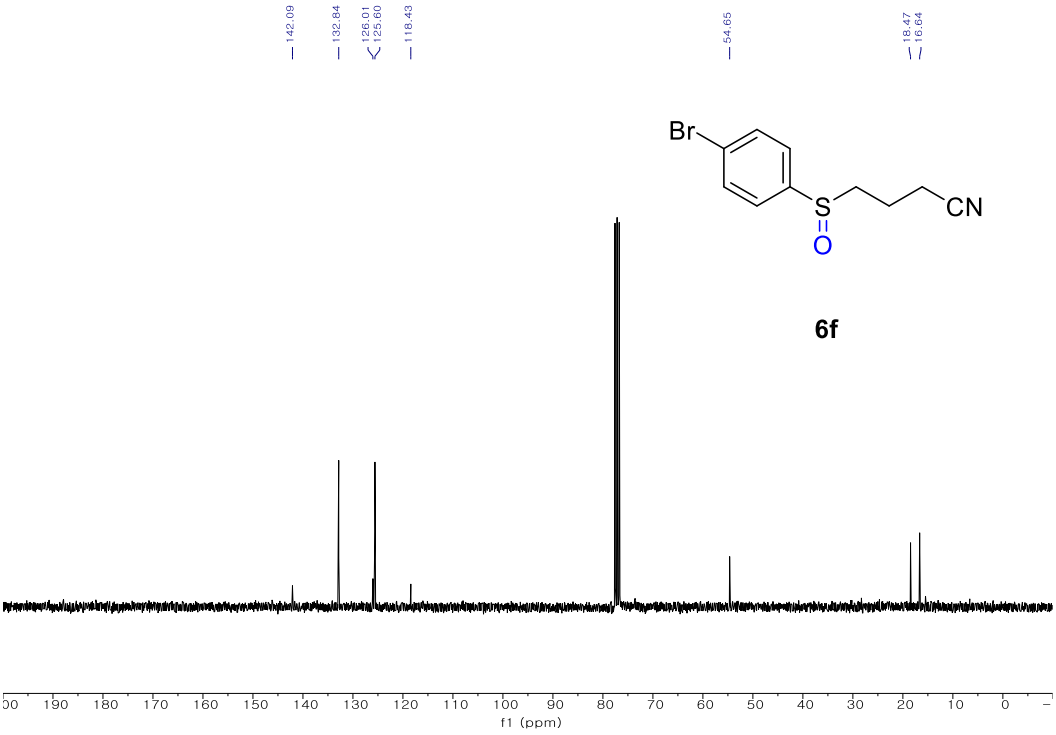
^{1}H-NMR (300 MHz, CDCl3) of **6e**



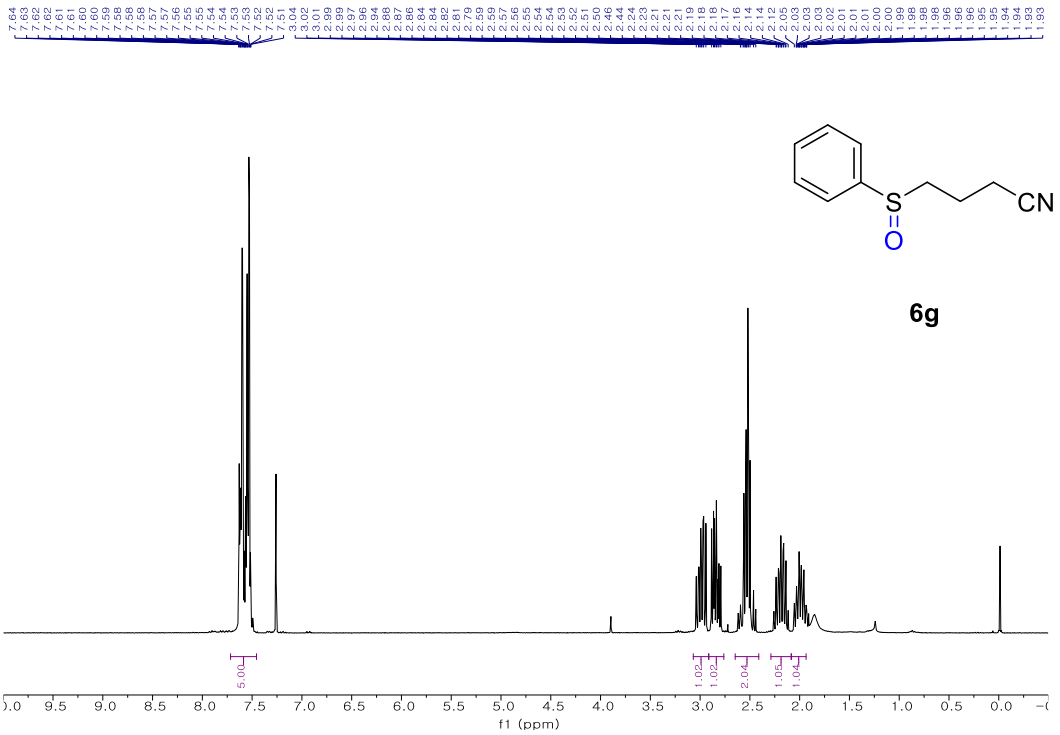
^{13}C-NMR (75 MHz, CDCl3) of **6e**



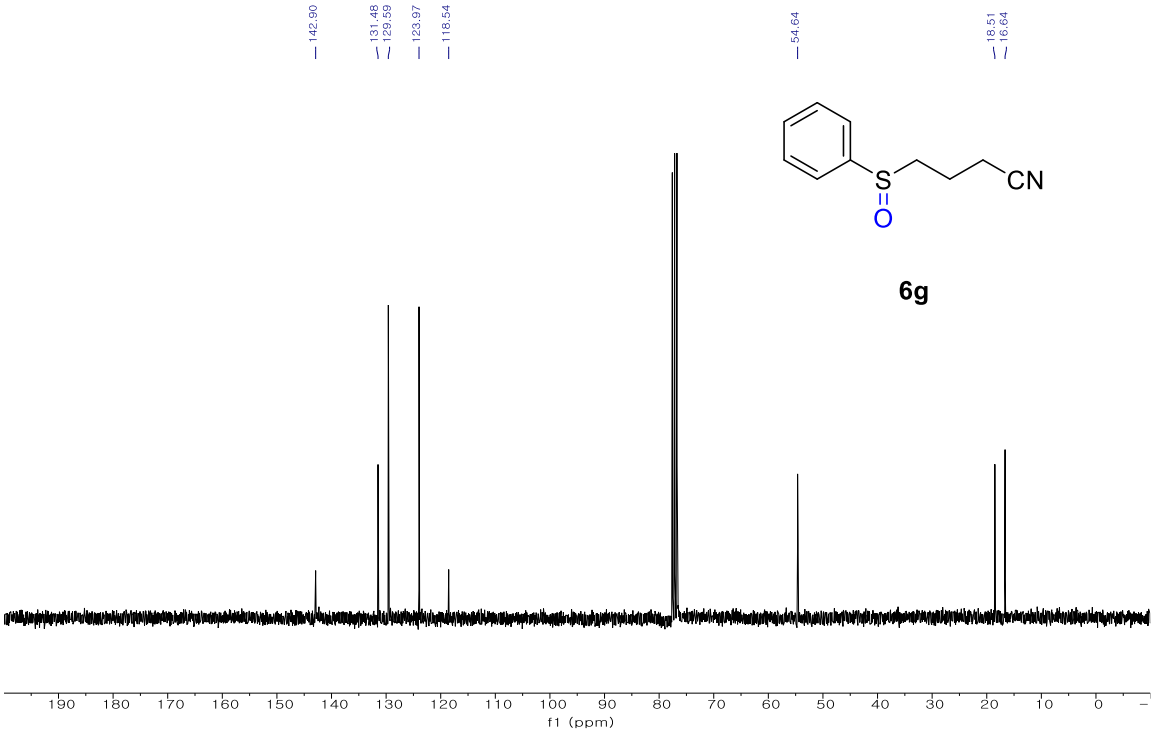
^{1}H-NMR (300 MHz, CDCl3) of **6f**



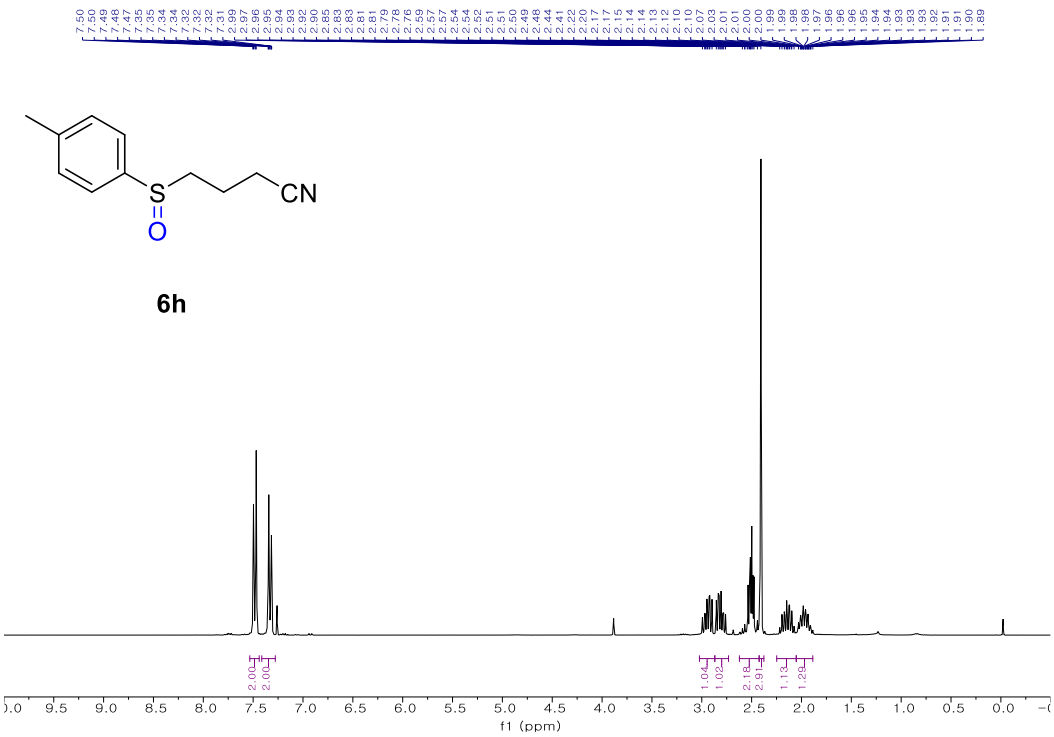
^{13}C-NMR (75 MHz, CDCl3) of **6f**



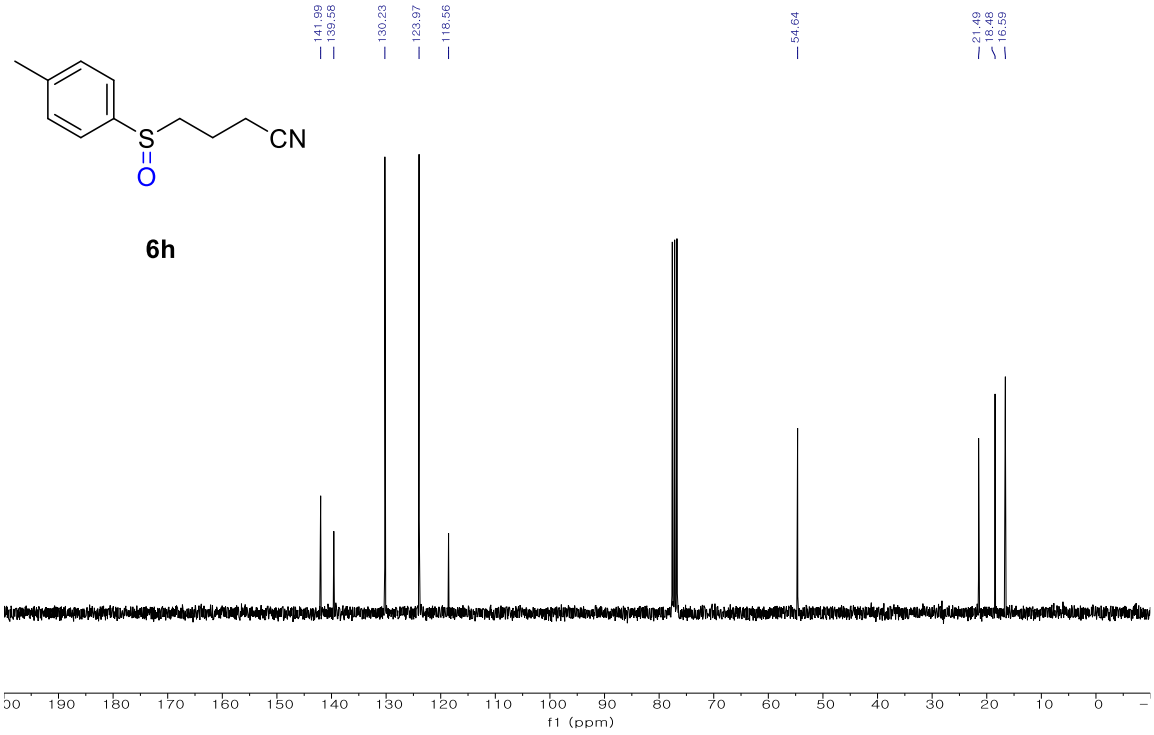
^{1}H-NMR (300 MHz, CDCl3) of **6g**



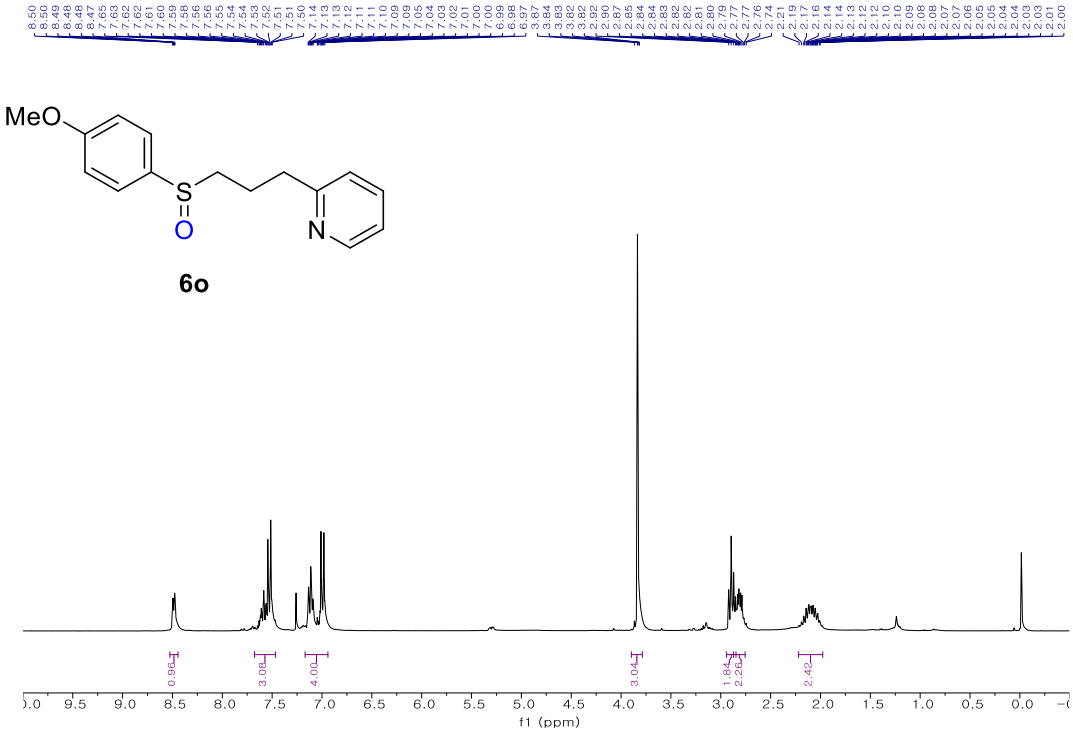
^{13}C-NMR (75 MHz, CDCl3) of **6g**



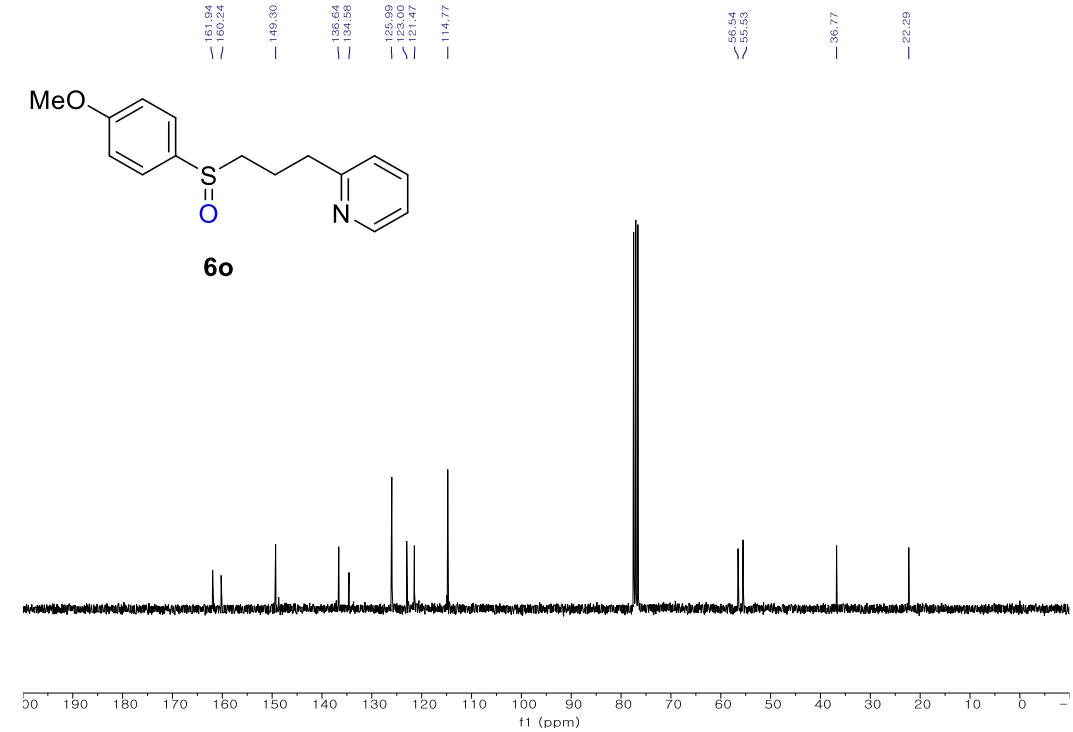
^{1}H-NMR (300 MHz, CDCl3) of **6h**



^{13}C-NMR (75 MHz, CDCl3) of **6h**



^{1}H-NMR (300 MHz, CDCl3) of **6o**



^{13}C-NMR (75 MHz, CDCl3) of **6o**

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