TETRABROMOMETHANE-MEDIATED DESULFURIZATION FOR SYNTHESIS OF
ISOTHIOCYANATES FROM AMINES

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จุฬาลงกรณ์มหาวิทยาลัย
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เอ็กซเรย์ สเปกโทรสโกปี (SEM/EDX) หลักฐานนี้ให้กลไกที่เสนอแนะว่า คาร์บอนเตตระโบรไมด์ทำหน้าที่เป็นอิ
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Saharat Techapanalai : TETRABROMOMETHANE-MEDIATED DESULFURIZATION FOR SYNTHESIS OF ISOTHIOCYANATES FROM AMINES. Advisor: Prof. SUMRIT WACHARASINDHU, Ph.D. Co-advisor: Prof. MONGKOL SUKWATTANASINITT, Ph.D.

Isothiocyanate considered as an important building block for pharmaceutical industry. Traditional methods for preparation of isothiocyanate involved the desulfurization of dithiocarbamate salt from amine using oxidizing agent. Although those methods are efficient, however, all of them require the use of toxic reagent, strong oxidizing agent, multiple step synthesis, harsh condition and large amount of metal catalyst. Therefore, in this research, we develop two mild methods to synthesize isothiocyanates from amines using low toxic reagent. For the first process, we were able to demonstrate the use of photocatalyst, safranin O to convert dithiocarbamate salt of 4-bromoaniline into 4-brophenyl isothiocyanate in 48% yield in one-pot under white LED irradiation. For the second process, commercially and low toxic CBr_4 was used for desulfurization process. Based on our optimize investigation, we found that the use of CBr_4 1.5 equivalences in the presence of 3.0 equivalences of DBU as base in acetonitrile give the optimized condition. Under this condition, we were able to synthesize 32 examples of isothiocyanates in moderate to excellent yields. Moreover, we were able to extend this methodology to prepare unsymmetrical thioureas via the *in situ* generation of isothiocyanate in one-pot. The synthesis of isothiocyanates and unsymmetrical thioureas were able to prepare a one-gram scale in good yields. The mechanistic study revealed that $CHBr_3$ and sulfur were detected by NMR and SEM/EDX. This evidence suggests that CBr_4 act as an electrophile to induce the desulfurization process. The benefit of this reaction includes one-pot synthesis, open air condition and low toxic desulfurizing agent.

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^{1}H-NMR	proton nuclear magnetic resonance
13C-NMR	carbon nuclear magnetic resonance
19F-NMR	fluorine nuclear magnetic resonance
$CDCl_3$	deuterated chloroform solvent
DMSO-d6	deuterated dimethyl sulfoxide solvent
CH_3CN	acetonitrile
EtOAc	ethyl acetate
EtOH	ethanol
i-PrOH	isopropanol
DMSO	dimethyl sulfoxide
CH_2Cl_2	dichloromethane
DMF	*N, N*-dimethyl formamide
THF	tetrahydrofuran
DMAP	dimethyl aminopyridine
DBU	1,8-dizabicyclo undec-7-ene
Et_3N	triethylamine
DABCO	1,4-diazabicyclo octane
DIPEA	diisopropyl ethylamine
K_2CO_3	potassium carbonate
Cs_2CO_3	cesium carbonate
NaOAc	sodium acetate
$NaHCO_3$	sodium carbonate
KOH	potassium hydroxide
$Ru(bpy)_2Cl_2$	cis-dichlorobis(bipyridine)ruthenium (II)
Eosin Y	disodium 2- (2,4,5,7-tetrabromo-3-oxido-6-oxoxanthen-9- yl)benzoate
Roes Bengal	4,5,6,7-Tetrachloro-3′,6′-dihydroxy-2′,4′,5′,7′-tetraiodo-3 H -spiro [[2]benzofuran-1,9′-xanthen]-3-one

Safranin O	3,7-diamino-5-phenylphenazin-5-ium
	Pyrene benzo(d,e,f)phenanthrene
mmol	millimole
mL	milliliter
nm	nanometer
GC-MS	gas chromatography mass spectrometer
HRMS	high resolution mass spectroscopy
ppm	part per million
cm	centimeter (s)
s	singlet (NMR)
d	doublet (NMR)
dd	doublet of doublet (NMR)
Hz	hertz
h	hour (s)
min	minute
j	coupling constant
m	miltiplet (NMR)
mg	milligram
m/s	mass per charge
TLC	thin layer chromatography
% yield	percentage yield
ee	enantiomeric excess
°C	degree Celsius
LED	light emitting diode
UV	ultraviolet

CHAPTER I

INTRODUCTION

1.1 Overview

Isothiocyanates are important building block for construction sulfur-containing heterocyclic compounds. They are found in various applications such as pharmaceuticals, natural products and organic materials. Traditionally, isothiocyanates were prepared from direct thiocarbonylation between amine with various thiocarbonyl transfer reagents. However, the reaction required anhydrous solvent, strong exothermic and required the use of toxic reagent. In recent years, the oxidative desulfurization between amine and carbon disulfide to deliver isothiocyanate has been tremendously studied due to their benefit such as high atom economy and ease of practical operation. However, such method involves the use of heavy metals and strong oxidizing agents. Therefore, the safe and efficient method for preparation of isothiocyanate is still challenged. In this work, we replace the toxic oxidizing agent into carbon tetrabromide which is a commercially available, cheap and less hazardous reagent to prepare isothiocyanate from amines as shown in **scheme 1.1**.
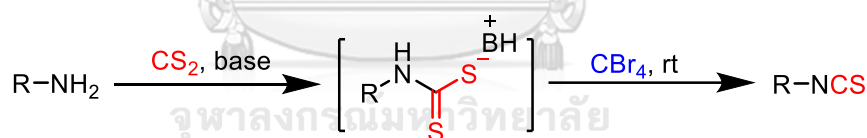
Scheme 1.1 Synthesis of isothiocyanate using carbon tetrabromide.

1.2 Introduction to isothiocyanate

Isothiocyanates have been known as important class of organic compounds and they are common subunits in various natural products and bioactive compounds. For example, sulforaphane (**1**) was isolated from Japanese wasabi spice[1, 2] which shown antioxidant and anti-cancer activity. Moreover, moringa isothiocyanate[3, 4] (**2**) processed high inflammatory bioactivity. In addition, the simple isothiocyanate such as phenyl (**3**), benzyl (**4**), phenylethyl (**5**) and allyl isothiocyanates (**6**) was found in the brassicale vegetables showing antibiotic[5], anticancer[6-9] and antitumor[10, 11] activities (**Figure 1.1**).
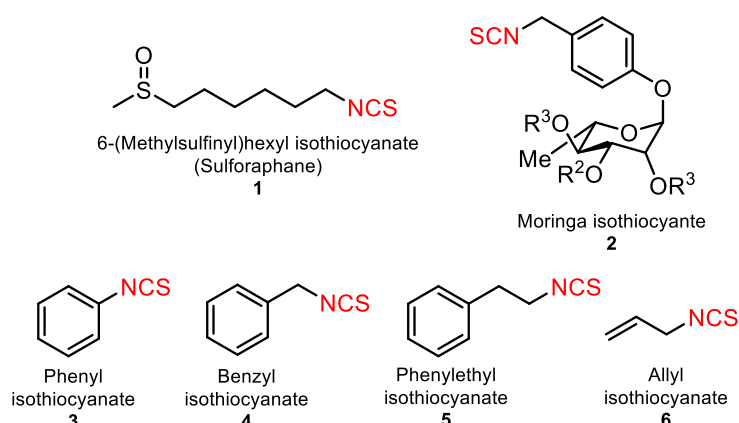
Figure 1.1 Natural and bioactive compounds of isothiocyanates.

Moreover, isothiocyanate was used fluorescence biomarkers for biomolecule in medical and biological diagnostics[12-14]. In addition, in organic synthesis, isothiocyanates are useful building block for construction of sulfur-containing heterocyclic compounds to prepare various therapeutic drugs, natural products and bioactive compounds[15-18] as shown in **Figure 1.2.**
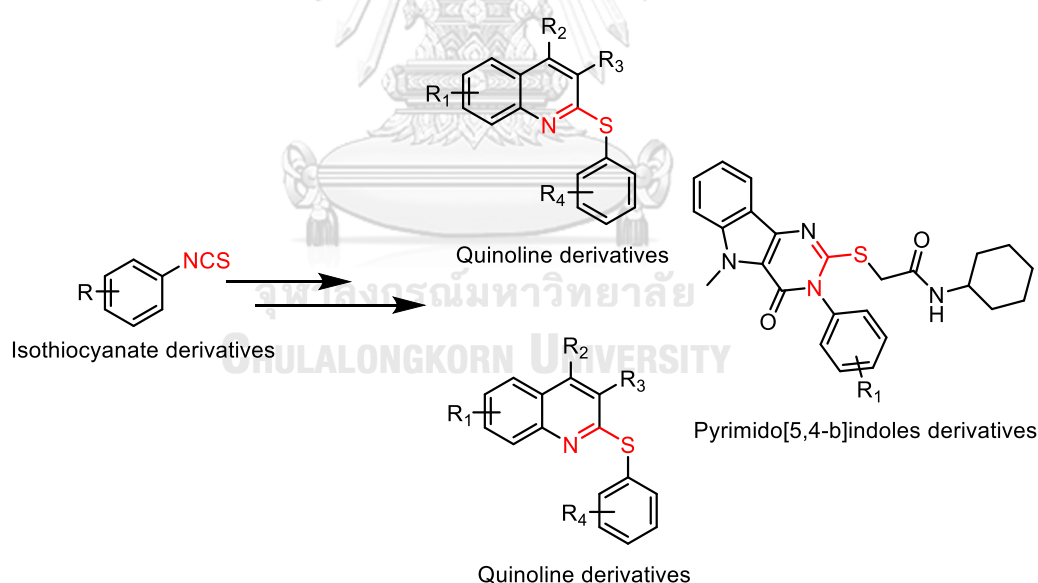
Figure 1. 2 The example of sulfur-containing heterocyclic compounds from isothiocyanates

1.3 **Reviews on synthesis of isothiocyanates**

In general, isothiocyanates can be prepared from 8 different staring material such as 1) isocyanide (**8**) 2) amide (**9**) 3) aldoxime (**10**) 4) Iminophosphorane (**11**) 5)

phosphoramidate (**12**) 6) isocyanate (**13**) 7) N-formamide (**14**) and 8) amine (**7**) as summarize in **Scheme 1.1**. We will discuss each substrate in the following section.
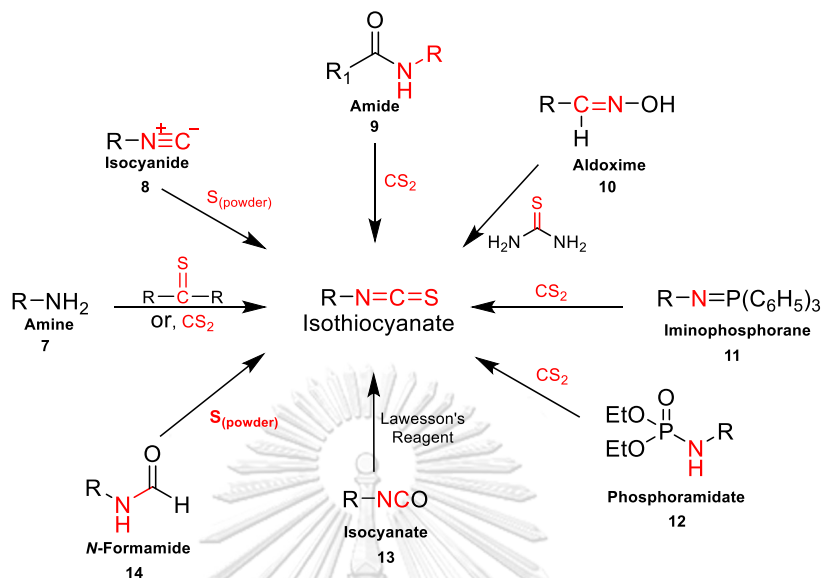
Scheme 1.2 A various substrate for synthesis of isothiocyanates

1. **Isocyanide** (**8**)

In 1991, Fujiwara and coworker[19] reported the use corresponding isocyanide (**8**) with element sulfur in the presence element as a catalytic amount. Triethylamine was used as a base in THF. Aliphatic and aromatic isothiocyanates were isolated in good to excellent yield as shown in **Scheme 1.3.**

$$R-NC \xrightarrow[\text{reflux, 0.5 - 7.5 h.}]{\substack{\text{Se (5\% mol), S(1.2 eq.),} \\ \text{Et}_3\text{N (2.4 eq.) THF,}}} R-NCS$$

R−NC **8**   R−NCS 62-95%
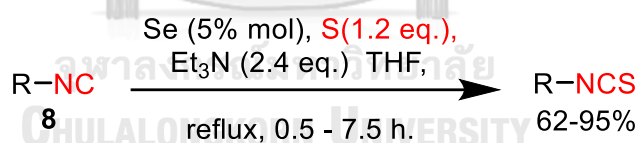
Scheme 1. 3 Synthesis of isothiocyanate from isocyanide

2. **Amide** (**9**)

In 1991, Penso and coworker[20] reported the use of amide derivatives (**9**) as starting material to react with carbon disulfide in presence of the mixture between potassium carbonate and sodium hydroxide. Aliphatic and aromatic isothiocyanates were generated in low to excellent yields as shown in **scheme 1.4**.

$$\xrightarrow[\text{CH}_3\text{CN, 0.5-3 h, rt.}]{\substack{\text{K}_2\text{CO}_3 \text{ (1.5 eq.), NaOH (1.0 eq.)} \\ \text{CS}_2 \text{ (4.0 eq.)}}} R-NCS$$

9   R−NCS 26-82%
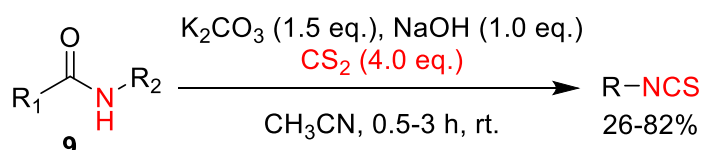
Scheme 1. 4 Synthesis of isothiocyanate from amide

3. **Aldoxime (10)**

In 1997, Kim and coworker[21] reported the two methods for synthesis of isothiocyanates from the reaction between aldoxime (**10**) with ether *N*-chlorosuccinimide (**Method I**) or mixture of HCl, DMF, Oxone (**Method II**) to generate chloro-oxime (**10'**) intermediate. The treatment of thioureas with intermediate gave isothiocyanates in good to excellent yields as shown in **Scheme 1.5**.
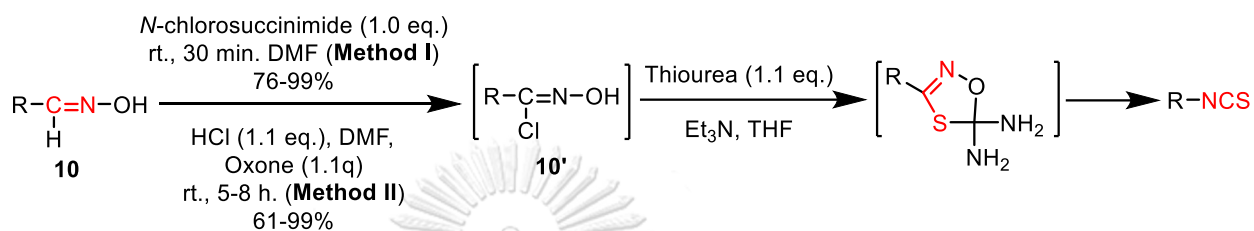
Scheme 1.5 Synthesis of isothiocyanate from aldoxime

4. **Iminophosphorane (11)**

In 1982, Molina and coworker[22] reported the use of Iminophosphorane (**11**) as starting material which were generated from amines with triphenylphosphine dibromide. Then intermediate **11** can reacted with either CO_2 or CS_2 to provide isocyanate (**13**) and isothiocyanate in good to excellent yields as shown in **scheme 1.6**.
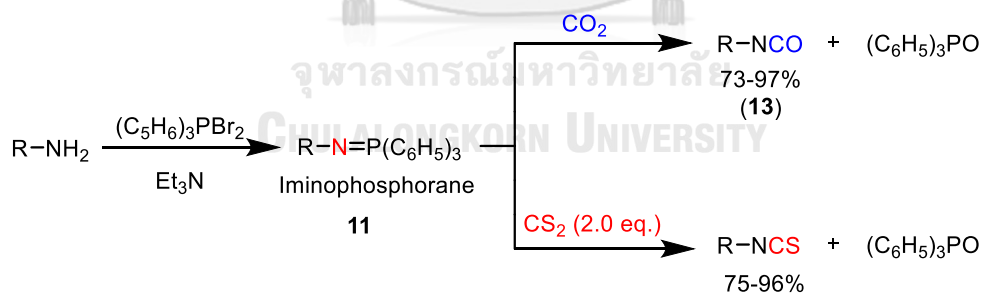
Scheme 1.6 Synthesis of isothiocyanate from iminophosphorane

5. **Phosphoramidate (12)**

In 1989, Zwierzak and coworker[23] reported the preparation of aliphatic and aromatic isocyanates from phosphoramidate (**12**) derivatives. It reacted with NaH to undergo deprotonation and reacting further with CS_2 to generate isothiocyanate in good to excellent yields under reflux condition as shown in **scheme 1.7**.
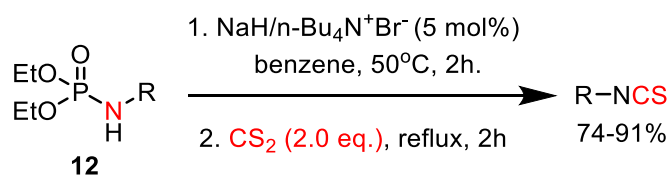
Scheme 1.7 Synthesis of isothiocyanate from phosphoramidate

6. **Isocyanate (13)**

In 2005, Populian and coworker[24] reported the utilization of isocyanate (**13**) as staring material. It reacted with Lawesson's reagent under solvent-free condition mediating by microwave irradiation to provide aliphatic and aromatic isothiocyanates in moderate to excellent yield as shown in **Scheme 1.8**.
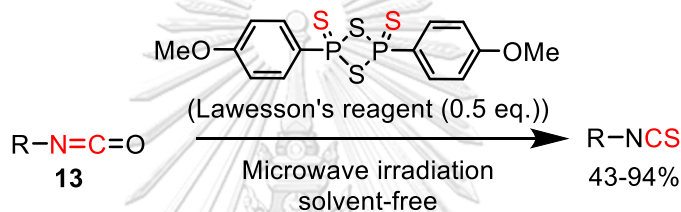
Scheme 1.8 Synthesis of isothiocyanate from isocyanate

7. **Formamide (14)**

In 2004, Liang and coworker[25] reported the preparation of isothiocyanate from formamide derivatives (**14**) and sulfur powder in presence of bis(trichloromethy) carbonate (BTC) and selenium powder. They obtained isothiocyanate in good to excellent yield as shown in **scheme 1.9**.
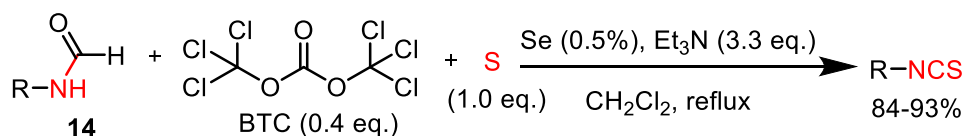
Scheme 1.9 Synthesis of isothiocyanate from formamide

Even though above reports demonstrated highly efficient synthesis of isothiocyanates, most of processes required multiple steps synthesis of starting materials. Unlike above starting materials, amine was considered as one of the most highly available starting material. However, many methods for the preparation of isothiocyanate has been extensively studied until now and we will discuss the details in next section.

1.3.1 Synthesis of isothiocyanates from amine

The typical synthesis of isothiocyanates from amine involve two strategies (**Scheme 1.10**). The first method (**Scheme 1.10, Top**) is the direct thiocarbonylation of amine with thiocarbonyl transfer reagent to deliver isothiocyanates in one step. The Second method (**Scheme 1.10, Bottom**) is the treatment of amine with carbon disulfide in presence of base following of desulfurization to give isothiocyanate.
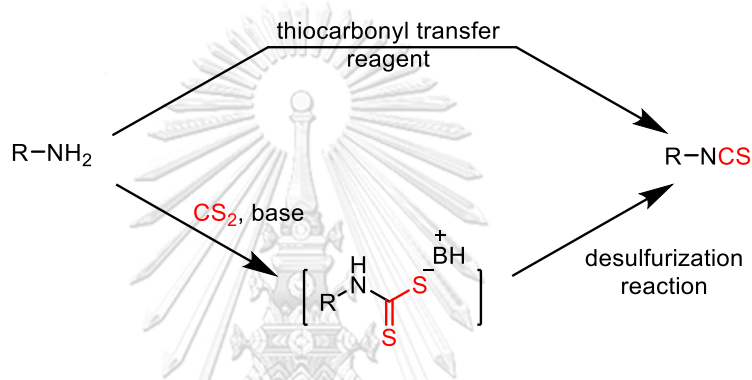
Scheme 1.10 Two strategies for the synthesis of isothiocyanates from amine

1.3.1.1 Reviews on thiocarbonylation transfer reagents

The direct synthesis of isothiocyanate via thiocarbonyl transfer reagents in one pot method was summarized in **Scheme 1.11**. In 1932, Johnson and Dyer[26] first reported the use of thiophosgene (**15**) as a thiocarbonyl reagent to provide corresponding isothiocyanate in good yield. The first step is attacking of amine to the thiophosgene along with the leaving of chloride ion. Then the elimination takes place to generate isothiocyanate. With the same concept, there are various thiocarbonyl transfer reagents were reported such as *N,N*-thiocarbonyl-di-imidazole (**16**)[27], thiocarbonyl-2,2'-pyridine (**17**)[28], (Thiocarbonyldioxy)dibenzotriazole (**18**), chlorothionoformate (**19**)[29] and (Me$_4$N)SCF (**20**)[30].

Although, various thiocarbonyl transfer reagents gave high yields of isothiocyanates in one pot fashion. Due to the high reactive property of those thiocarbonyl transfer reagents. However, most of them therefore generate high

temperature from strong exothermic property, toxic reagent and required anhydrous condition.
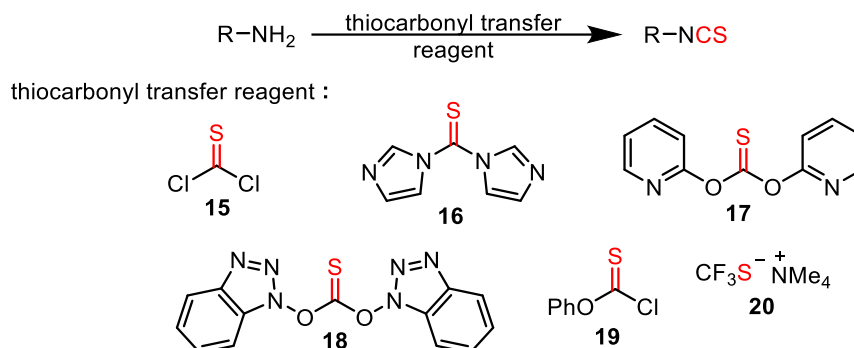
Scheme 1.11 The thiocarbonylation of amine with various thiocarbonyl transfer reagent

    1.3.1.2 Reviews on oxidative desulfurization

    The alternative method is treatment of amine with carbon disulfide in presence of base to form dithiocarbamate salt (**X**) following by desulfurization to give isothiocyanate in two pot fashion (**Scheme 1.12**). Although, it required two steps synthesis. However, the carbon and sulfur atom in final product came from CS_2 which is cheap and highly available. Therefore, this method is more atom economy and has been studied extensively. The desulfurization can be divided into two processes including the use of **1**) non-metal oxidizing agents and **2**) metal oxidizing agents.
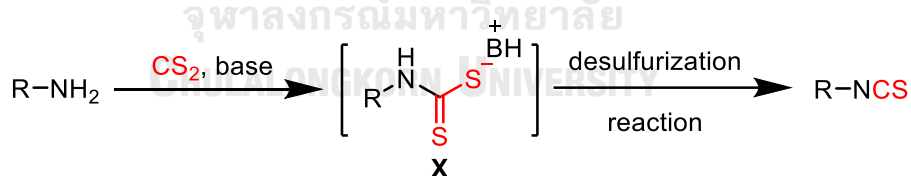
Desulfurizing agents : 1) *non*-metal oxidizing agent 2) metal oxidizing agent

Scheme 1.12 Desulfurization of dithiocarbamate salt with desulfurizing agent

    1.3.1.2.1 Reviews on non-metal oxidative desulfurization (**Table 1.1**)

In 1997, Li and coworker[31] reported the use of hydrogen peroxide (**21**) as an oxidizing agent for desulfurization of dithiocarbamate salt (**X**) in stoichiometric amount to produce corresponding aromatic isothiocyanate in good to excellent yields as shown in **Table 1.1, entry 1**. Later, in 2005, Su and cosorker[32] used bis(trichloromethyl)carbonate (BTC) (**22**) and trichloromethyl chloroformate (TCF) (**23**)
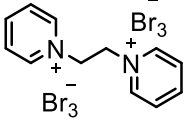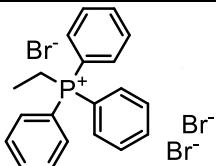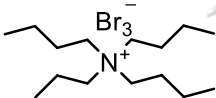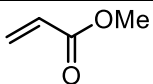
as activator to provide isothiocyanate product in low to excellent yield as shown in **Table 1.1, entry 2**. In 2007, Wong and Dolman[33] utilize tosyl chloride (TsCl) **(24)** for oxidative desulfurization of dithiocarbamate salt **(X)** as seen in **Table 1.1, entry 3**. Under this condition, intermediate dithiocarbamate salt **(X)** reacted with tosyl chloride to provide isothiocyanate in moderate to excellent yields. In 2008, Much and coworker[34] reported the use of tertiary butyl dicarbamate (Boc$_2$O) **(25)** as reagent for desulfurizing agent in one-pot fashion to provide isothiocyanate product in moderate to quantitative yields as shown in **Table 1.1, entry 4**. In 2007, Lai and coworker[35] demonstrated the desulfurization using chlorosilane derivatives **(26)** as decomposition reagent of dithiocarbamate salt **(X)** via one-pot and two-pots methods as shown in **Table 1.1, entry 5**. In 2008, Patel and coworker[36] reported the use of (diacetoxyiodo)benzene (DIB) **(27)** for oxidative desulfurization of dithiocarbamate salt **(X)** as seen in **Table 1.1**, **entry 6**. This process provided the desired isothiocyanates in moderate to excellent yields. Later, same group[37] reported similar method but used iodine **(28)** as an activator to produce corresponding isothiocyanate in good to excellent yields as shown in **Table 1.1, entry 7.** Moreover, the same group[38] also reported the utilization of 1,10-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) **(29)** for oxidative desulfurization of dithiocarbamate salt **(X)** as shown in **Table 1.1, entry 8**. Under this condition, 1,10-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) **(29)** can generate bromine (Br$_2$) *in situ* then reacted with dithiocarbamate salt **(X)** following by desulfurization to provide isothiocyanates in good to excellent yields. Similarly, Jamir and coworker[38] reported the use of ethyl triphenyl phosphonium tribromide (ETPPTB) **(30)** as activator to produce corresponding isothiocyanate in good to excellent yields as shown in **Table 1.1, entry 9**. Recently, in 2017, Kuotsu and coworker[39] demonstrated the similarly method using tetrapropylammonium tribromide (TPATB) **(31)** as activator to provide isothiocyanates in good to excellent yields as shown in **Table 1.1, entry 10**. In addition, the reactions on water for desulfurization were developed by Patel[40] and Fu[41] using methyl arylate **(32)** and Na$_2$S$_2$O$_8$ **(33)**, respectively to provide isothiocyanates in good to excellent yields as seen in **Table 1.1, entries 11 and 12**. Moreover, the desulfurization in the absent of desulfurizing agents were

demonstrated using ball milling[42] under solvent-free condition (**Table 1.1 , entry 13**) and microwave irradiation[43] in dichloromethane at 90 $^\circ$ C (**Table 1.1, entry 14**). In contrast, ball milling method limited to only aromatic isothiocyanate substrates while microwave irradiation method provided low to excellent yields of isothiocyanate substrates.

Table 1.1 Review on non-metal oxidative desulfurization
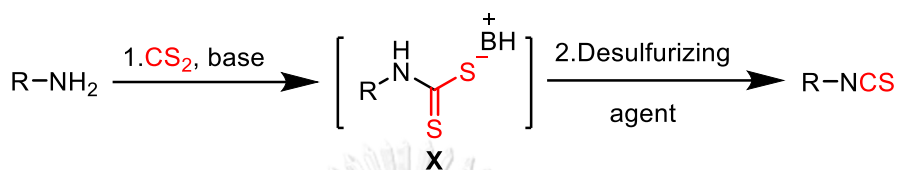
Entry	Desulfurizing agent	Condition	Process	Yield
1	H$_2$O$_2$ **21** (Hydrogen peroxide)	**21** (1-6 eq.), THF, 0-40 $^\circ$C, 2h	one-pot	84-95%
2	Cl$_3$C–O–C(=O)–O–CCl$_3$ **22** (*bis*-(trichloromethyl) carbonate) or Cl–C(=O)–O–CCl$_3$ **23** (Trichloromethyl chloroformates)	**22** or **23** (0.3 eq.), CH$_2$Cl$_2$, 4-6 h., 0°C-rt	one-pot	25-86% or 65-95%
3	Cl–S(=O)$_2$–C$_6$H$_4$–CH$_3$ **24** (Tosyl chloride)	**24** (1.1 eq.), THF, 1h, rt	one-pot	34-99%
4	**25** (di-tert-butyl carbamate)	**25** (1.0 eq.), DMAP (1-3% mol), EtOH, 20 min, rt	one-pot	63-quant.
5	R$^2_{4-n}$SiCl$_n$ **26** (Chlorosilane derivatives)	**26** (2.0 eq.), DABCO or Et$_3$N (2.0 eq.), 4-20 h, 0°C-rt	one-pot and two-pots	31-92%
6	**27** I(OAc)$_2$	**27** (1.0 eq.), THF, 1h, rt	two-pots	34-99%

	27 ((Diacetoxyiodo) benzene)			
7	I_2 **28** (Iodine)	**28 (**1.0 eq.), H_2O/EtOAc, NaHCO$_3$, 15-30 min, rt	two-pots	77-92%
8	**29** (dipyridinium bistribromide)	**29** (0.5 eq.), Et$_3$N (2.0 eq.), CH$_3$CN, 10 min, 0°C	two-pots	70-96%
9	**30** (ethyltriphenyl phosphonium tribromide)	**30** (1.0 eq.), Et$_3$N (1.5 eq.), CH$_3$CN, 0°C	two-pots	65-87%
10	**31** (tetrapropylammonium Tribromide)	**31** (1.0 eq.), NaHCO$_3$ (2.0 eq.), EtOAc/H$_2$O, 10-15 min, 0°C	two-pots	77-92%
11	**32** (Methyl acrylate)	**32** (1.6 eq.), H$_2$O, 1.5 h, rt	two-pots	67-91%
12	$Na_2S_2O_8$ **33** (Sodium persulfate)	**33** (1.0 eq.), K$_2$CO$_3$ (1.0 eq.), H$_2$O, 1h, rt	one-pot and two- pots	20-99%
13	-	**Ball milling**, KOH (1.0 eq.), vibrated around 1,800 round per minute, rt.	one-pot	52-97%
14	-	**Microwave irradiation**, 20 min., 90°C	two-pots	25-98%

From literature review, although there are many reports on the synthesis of isothiocyanate using various reagents in desulfurization process in one-pot or two pots fashion, most of them required the stepwise reaction or stochiometric amount of strong oxidizing agents or harsh condition.

1.3.1.2.2 Review on metal catalyst as an oxidizing agent (**Table 1.2**)

Besides, the use of organic activators, there are report on metal catalyst as an oxidizing agent for desulfurization of dithiocarbamate salt (**X**). The dithiocarbamate salts (**X**) were prepared *in situ* from reaction of amine and CS_2 in presence of base following by the addition of metal catalysts such as cobalt (II) chloride[44] ($CoCl_2$) (**34**) (**Table 1.2, entry 1**), copper (II) sulfate[45] ($CuSO_4$) (**35**) (**Table 1.2, entry 2**), iron (III) sulfate[46] ($Fe_2(SO_4)_3$) (**36**) (**Table 1.2, entry 3**) and iron(III) chloride[47] ($FeCl_3$) (**37**) (**Table 1.2, entry 4**). Although, all reactions proceed at room temperature to provide corresponding isothiocyanates in moderate to excellent yields. However, those reactions required large amount of metal catalyst at 50% mol.

Table 1.2 Review on metal catalyst as an oxidizing agent.
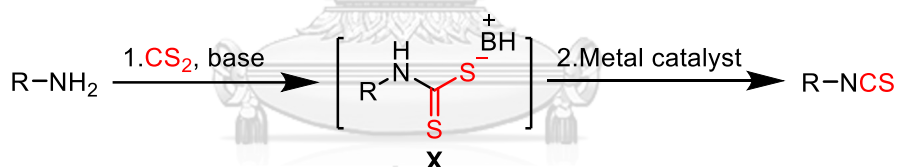
Entry	Condition	Yield
1	1. CS_2 (10 eq.), NaHCO$_3$ (2.0 eq.), 1h., rt. 2. **CoCl$_2$** (50 mol%), EtOAc, 3h., rt.	50-95%
2	1. CS_2 (10 eq.), Et$_3$N (1.0 eq.), EtOAc/H$_2$O 1h., rt. 2. **CuSO$_4$** (50 mol%), Et$_3$N (1.0 eq.), 2 h., rt.	34-99%
3	1. CS_2 (10 eq.), NaOAc (1.0 eq.), DMSO, 1h., rt. 2. **Fe$_2$(SO$_4$)$_3$** (50 mol%), NaOAc (1.0 eq.) H$_2$O, 2h., rt.	60-97%
4	1. CS_2 (10 eq.), NaOAc (1.0 eq.), Acetone, 2h., rt. 2. **FeCl$_3$** (50 mol%), NaOAc (1.0 eq.), 2h., rt.	65-98%

1.4 Introduction to Carbon tetrabromide

Carbon tetrabromide (CBr_4), also known as tetra bromomethane, is a commercially available white solid which is stable at room temperature, easy to handle and low toxic reagent. In addition, carbon tetrabromide has been reported as a brominating agent, catalyst or mediator to prepare various chemicals. For example, in combination of carbon tetrabromide with tertiary phosphine, it has been used for the bromination of various functional groups such as alcohol (Appel reaction)[48-51], *N*-heterocycle[52] and ether[53]. Moreover, carbon tetrabromide was reported as a catalyst in many organic transformation reactions including, acetalization and tetrahydropyranylation[54].

1.4.1 Reviews for carbon tetrabromide with organosulfur

From above benefits, carbon tetrabromide also has been utilized to functionalize various organosulfur. In 2007, Wu and coworker[55] reported the use of carbon tetrabromide in catalytic amount to promote the acetylation of phenol, alcohol and thiol derivatives with acid anhydride in low to excellent yields as shown in **Scheme 1.13**.
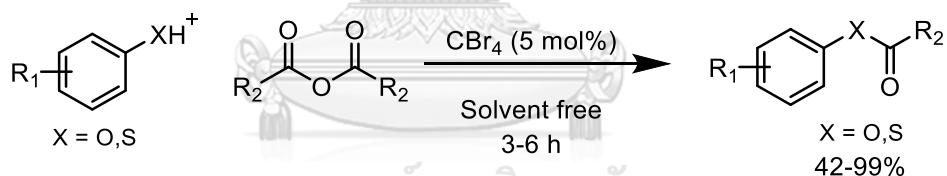
Scheme 1.13 Acetylation using CBr_4 as a catalyst

In 2008, Yuan and coworker[56] reported the multi-component reaction between secondary amine (**1'**), CS_2 and active methylenes (**2'**) using carbon tetrabromide as a mediator to provide dithiocarbamates (**3'**) in good to excellent yields as seen in **Scheme 1.14**. The key step reaction is the treatment of amine with CS_2 to generate dithiocarbamate salt (**X**) following by nucleophilic attack of sulfur on CBr_4 to form sulfenyl bromide (**4'**) electrophilic species.
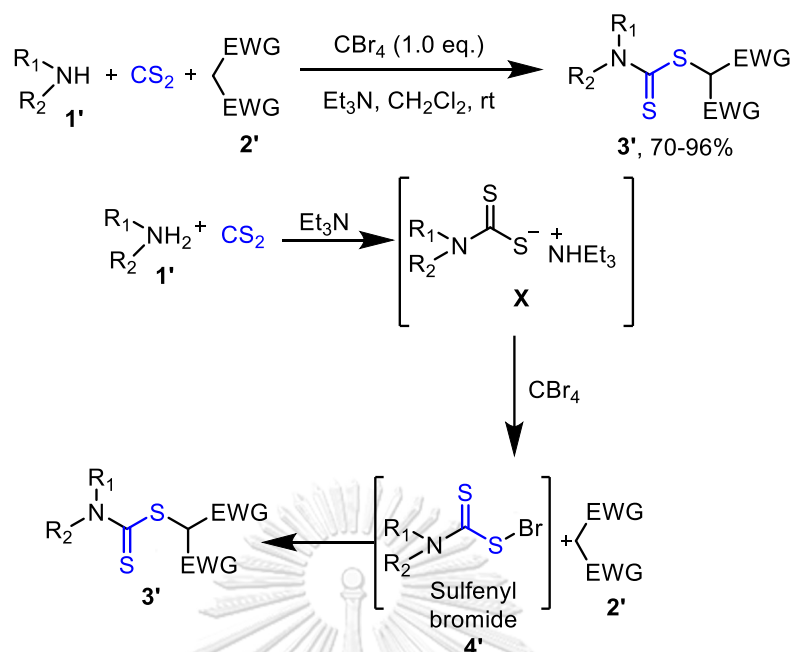
Scheme 1.14 Synthesis of dithiocarbamates (**3'**) using CBr_4.

In 2015, Yadav and coworker[57] reported the use of carbon tetrabromide as a mediator for preparation of 2-aminobenzothiazole (**7'**) from the reaction of ketones (**5'**) and thioureas (**6'**) in moderate to excellent yields as shown in **Scheme 1.15**. From proposed mechanism, it is important to note that CBr_4 can promote the formation of sulfenyl bromide (**4'**) which is the key step in the present of hetero-cyclization reaction to provide target products.
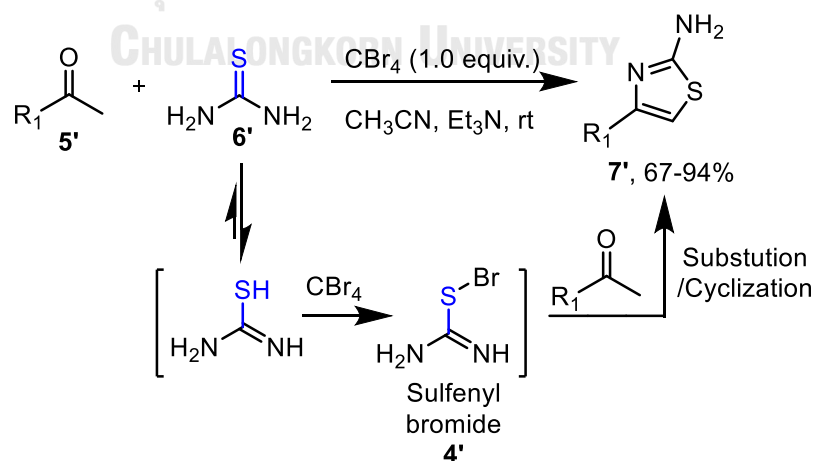
Scheme 1.15 Synthesis of 2-aminobenzothiazole using CBr_4

In addition, carbon tetrabromide also has been reported in desulfurization reaction. In 2008, liu and coworker[58] reported the preparation of symmetrical thioureas (**8'**) and thiuram disulfide (**9'**) from amine (**Scheme 1.16**). In this work, CBr_4 was used as mediator to prepare sulfenyl bromide (**4'**). The addition of primary amine led to target thioureas in good to excellent yields (**Scheme 1.16, eq. 1**) while the addition of secondary amines led to thiuram disulfides in moderate to excellent yields (**Scheme 1.16, equation 2**).
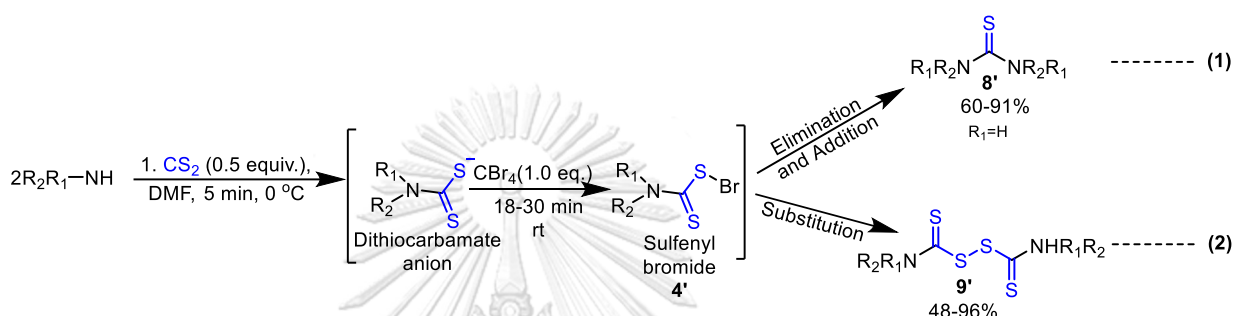
Scheme 1.16 Synthesis of symmetric thioureas and thiuram disulfides using CBr_4

1.4.2 Reviews for carbon tetrabromide with Vilsmeier-Haack reagent

Besides, the use of carbon tetrabromide as a mediator, there are reported the use of carbon tetrabromide under photochemical method to prepare carboxylic acid[59, 60] and dibromo acetophenone[61] under aerobic condition. Later, carbon tetrabromide has been used to replace conventional Vilsmeier-Haack reaction. Typically, Vilsmeier-Haack reaction[62, 63] is a chemical reaction of a substituted amide with phosphorus oxychloride to generate Vilsmeier-Haack reagent (**Y**) *in situ* and reacted with an electron-rich aromatic hydrocarbon to produce an aryl aldehyde or ketone as shown in **Scheme 1.17a**. However, generating of the Vilsmeier-Haack reagent (**Y**) required toxic phosphorus oxychloride and high temperature condition. For the past decade, the new Vilsmeier-Haack reagents (**Y**) were modified by the reduction of CX_4 to form the intermediate such as carbene, radical reacting with amide derivatives to generate Vilsmeier-Haack reagent (**Y**) as demonstrate in **Scheme 1.17b**.

a.) Previous method
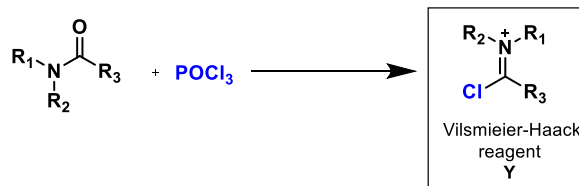
b.) Recently method
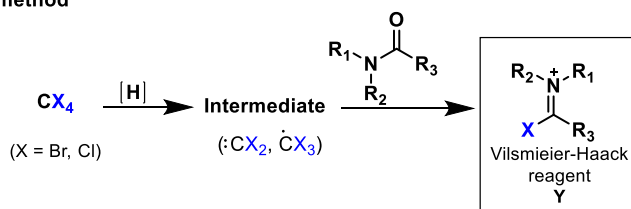
Scheme 1.17 The comparison of a) traditional and b)new Vilsmeier-Haack reagent

In 2011, Stephenson and Coworker[64] first reported a visible-light-mediated conversion of alcohols into halides with Vilsmeier-Haack type reagent (**Y**) from the reaction between CBr_4 and DMF in good to excellent yield as shown in **Scheme 1.18, Route A.** Later, in 2012, the same research group[65] reported a visible light mediated for preparation of acid anhydride derivatives with Vilsmeier-Haack reagent (**Y**) from cross-coupling of carboxylic acid derivatives as shown in **Scheme 1.18, Route B**. Similarly, in 2014, Yadav and coworkers[66] provided the new preparation of amide derivatives from the activation of keto oximes by using eosin Y as photocatalyst via Beckmann rearrangement as shown in **Scheme 1.18, Route C.** In 2015, Mccallum and Barriault[67] reported the preparation of amides from corresponding carboxylic acids with amines via Vilsmeier-Haack reagent using only UVA light (365 nm. LED) without any photocatalyst in moderate to excellent yields as shown in **Scheme 1.18 (route D)**
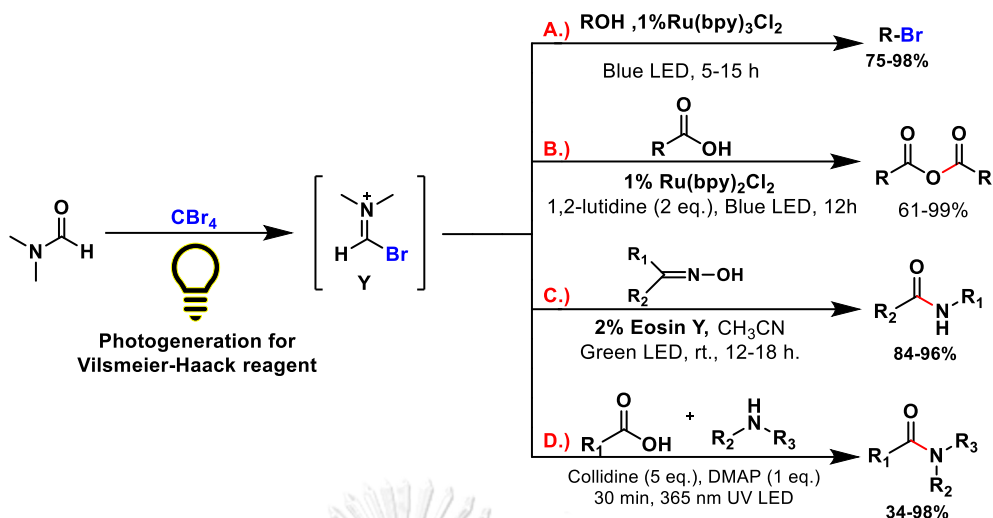
Scheme 1.18 Light-mediated Vilsmeier-Haack reagent for synthesis of organic compounds.

Based on above review on oxidative desulfurization to prepare isothiocyanate derivatives from amines, most of them require stepwise synthesis, large amount of strong oxidizing agents and harsh condition. To avoid the use of strong oxidizing agent and harsh condition, we intended to replace the process with carbon tetrabromide under **1**) photo-organic synthesis mediating by Vilsmeier-Haack reagent or **2**) mediating agent due to their low toxic reagent and easy to handle which has never been reported before.

1.5 Objective of this research

In this research, we aim to develop one-pot synthesis of isothiocyanates from amines via the oxidative desulfurization of dithiocarbamate salt (**X**). We plan to use two oxidative desulfurization process including 1) photo reaction with Vilsmeier-Haack reagent (**Method I**) and 2) carbon tetrabromide mediator (**Method II**) as shown in **Scheme 1.19**.
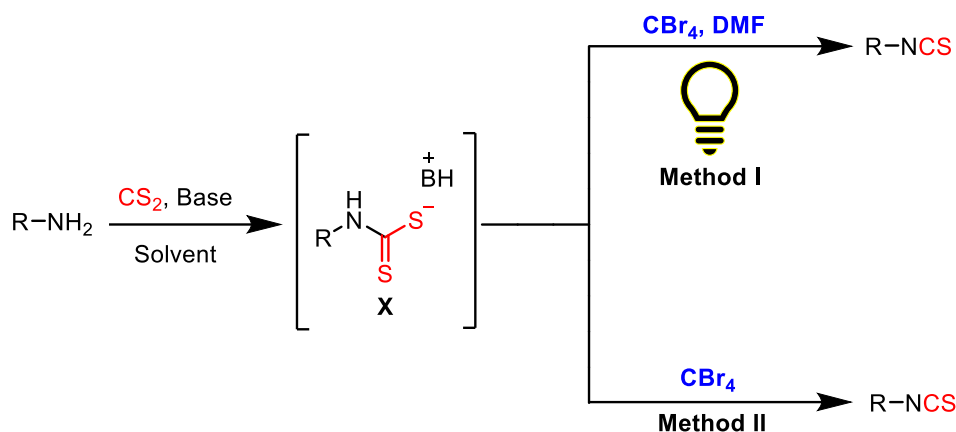
Scheme 1.19 Synthesis plan of isothiocyanate from amines in our research

      For **Method I**, various parameters such as light source and amount of DMF will be investigated. For **Method II**, the reaction parameters including solvent, base, amount of carbon disulfide, amount of carbon tetrabromide, temperature and reaction time will be studied to determine the optimized condition. Then, the substrate scope of amines including aryl amines, benzylamines, aliphatic amines, chiral amine, phenolic amines and NH-protected or OH-protected amines will be tested to grade reaction generality. Finally, the mechanistic studies will be conducted to propose the mechanism process of oxidative desulfurization process using nuclear magnetic resonance spectroscopy (NMR) and scanning electron microscope (SEM) equipped with x-ray spectroscopy (EDX).

CHAPTER II

EXPRIMENTAL

2.1   Chemical reagents, equipment and instrument for synthesis and Characterization

All chemicals and solvents were obtained from commercially available suppliers such as Sigma-Aldrich and TCI (Japan) and were used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed with precoated Merck silica gel 60 F254 plates(0.25 mm for thick layer) and visualized at 254 nm using an ultraviolet lamp. Column chromatography was performed with Silicycle silica gel 60-200 μm. (70-230 mesh). ^{1}HNMR, ^{13}C-NMR and ^{19}F spectra were obtained with JEOL JNM-ECZ500R/S1 NMR spectrometers operating at 500 MHz for ^{1}H or 125 MHz for ^{13}C or 470 MHz for ^{19}F nuclei. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) with a MicroTOF Bruker mass spectrometer and electron spray ionization (ESI) with Gas chromatography mass spectrometer. White LED (Philip LED 19W Durable Brightness Daylight E27) and green LED (SMD 5050 LED, 12W) were used as the visible light source. 254 nm. UV and 365 nm. UV LEDs (8X6W) were used as the ultraviolet light source.

2.2   General procedure for synthesis of isothiocyanate via light mediated Vilsmeier-Haack reagent

2.2.1   General procedure for synthesis of isothiocyanate from amines (**1a**) under visible light source
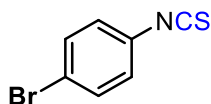
1-Bromo-4-isothiocyanatobenzene (**2a***)* A mixture of 4-bromoaniline **1a** (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (20 mL.) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) and *N, N-*dimethyl formamide (2.0 eq., 1.16 mmol) were added and stirred at room

temperature under white or green LED irradiation for 16 hours. After reaction complete, the reaction mixture was washed with water (1x4 mL) and the organic portion was extracted with EtOAc (3x5 mL). The organic layer was eliminated water by Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography to afford **2a** the results were summarized in Table **3.1**. ^{1}H-NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 – 7.37 (m, 2H), 7.19 – 6.99 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 137.0, 132.8, 130.6, 127.3, 120.9. GC-MS: m/z: 215.0 (calced for C_7H_4BrNS: 214.9).
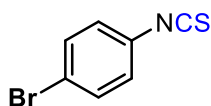
    2.2.2 General procedure for synthesis of isothiocyanate from amines (1a) under ultraviolet light source

1-Bromo-4-isothiocyanatobenzene (2a). A mixture of 4-bromoaniline **1a** (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (20 mL.) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) and *N, N*-dimethyl formamide (2.0 eq., 1.16 mmol) were added and stirred at room temperature under 254 nm or 365 nm. UV LED irradiation for 2-6 hours. After reaction complete, the reaction mixture was washed with water (1x4 mL) and the organic portion was extracted with EtOAc (3x5 mL). The organic layer was eliminated water by Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography to afford **2a** and the results were summarized in Table **3.1**. ^{1}H-NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 – 7.37 (m, 2H), 7.19 – 6.99 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 137.0, 132.8, 130.6, 127.3, 120.9. GC-MS: m/z: 215.0 (calced for C_7H_4BrNS: 214.9).

2.3   General procedure for synthesis of isothiocyanate using photocatalysts
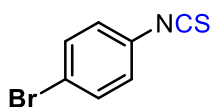
1-bromo-4-isothiocyanatobenzene (**2a**) A mixture of 4-bromoaniline **1a** (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) was dissolved by acetonitrile (20 mL.) in Pyrex glass tube. The mixture was stirred at room temperature for 20 hours. Then, photocatalysts (0.05 eq., 0.029 mmol) was added and at room temperature under green or white LEDs for 16 hours. After reaction complete, the reaction mixture was washed with water (1x4 mL) and the organic portion was extracted with EtOAc (3x5 mL). The organic layer was eliminated water by Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography to afford **2a** and the results were summarized in Table **3.2**. ^{1}H-NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 – 7.37 (m, 2H), 7.19 – 6.99 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 137.0, 132.8, 130.6, 127.3, 120.9. GC-MS: m/z: 213.0 : 215.0 (1:1) (calced for C_7H_4BrNS: 212.9 : 214.9 (1:1)).

2.4   General procedure for synthesis of isothiocyanates and unsymmetric thioureas using carbon tetrabromide

2.4.1   Reaction optimization

We studied optimized condition by working reaction on different parameter which were listed below

Solvent: Ethyl acetate, Ethanol, *i*-propanol, Acetone, *N, N*-dimethyl sulfoxide, acetonitrile

Base: DBU, TEA, DIPEA, K_2CO_3, Cs_2CO_3, NaOAc

Amount of carbon disulfide: 1.5-3 equivalent

Amount of carbon tetrabromide: 0-2 equivalent

**2.5 The substrate scopes of isothiocyanates and unsymmetric thioureas**

    2.5.1 General experiment procedure A: isothiocyanates **2a – 2ff**

    A mixture of amine (**1**) (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. After reaction complete, the reaction mixture was washed with water (1x4 mL) and the organic portion was extracted with EtOAc (3x5 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography to afford isothiocyanates **2a – 2ff**

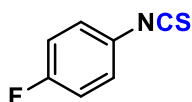   **2.5.2 General experiment procedure B**: unsymmetric thioureas **3a – 3i**

    A mixture of *p*-toluidine (**1f**) (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, secondary amine (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 hours. After reaction complete, the reaction mixture was washed with water (1x6 mL) and the organic portion was extracted with EtOAc (3x10 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography to afford unsymmetric thioureas **3a – 3i**

    2.5.3 Synthesis of isothiocyanate derivatives
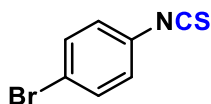
1-bromo-4-isothiocyanatobenzene (**2a**). According to the general experiment procedure A, the reaction was performed by using 4-bromoaniline (**1a**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and

stirred at room temperature for 1 hour afford 2a in 105.4 mg, 85% yield as a white solid: ^{1}H-NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 – 7.37 (m, 2H), 7.19 – 6.99 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 137.0, 132.8, 130.6, 127.3, 120.9. GC-MS: m/z: 213.0 : 215.0 (1:1) (calced for C$_7$H$_4$BrNS: 212.9 : 214.9 (1:1)).

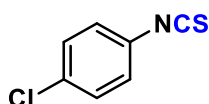**1-fluoro-4-isothiocyanatobenzene (2b)**. According to the general experiment procedure A, the reaction was performed by using 4-fluoroaniline (**1b**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, c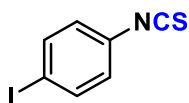arbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2b** in 79.8 mg, 90% yield as a colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.23 – 7.12 (m, 2H), 7.08 – 6.96 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 162.1, 160.2, 136.0, 127.4, 116.7. ^{19}F-NMR (470 MHz, CDCl3): δ -110.19. GC-MS: m/z: 153.0 (calced for C$_7$H$_4$ClNS: 153.1).
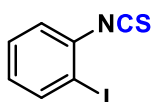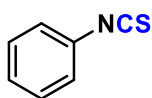

1-chloro-4-isothiocyanatobenzene (2c). According to the general experiment procedure A, the reaction was performed by using 4-chloroaniline (**1c**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2c** in 73.5 mg, 75% yield as a white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.23 – 7.12 (m), 7.08 – 6.96 (m). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 136.9, 133.0,130.0, 123.0, 127.0. GC-MS: m/z: 169.1 : 171.1 (3:1) (calced for C$_7$H$_4$FNS: 169.0 : 171.0 (3:1)).

1-iodo-4-isothiocyanatobenzene (2d). According to the general experiment procedure A, the reaction was performed by using 4-iodoaniline (**1d**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2d** in 142 mg, 94% yield as a white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.23 – 7.12 (m), 7.08 – 6.96 (m). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 138.8, 137.1, 131.3, 127.5, 92.0. GC-MS: m/z: 261.0 (calced for C$_7$H$_4$INS: 260.9).
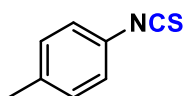

1-iodo-2-isothiocyanatobenzene (2e). According to the general experiment procedure A, the reaction was performed by using 4-iodoaniline (**1d**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2d** in 113.5 mg, 75% yield as yellow oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.92 – 7.65 (m, 1H), 7.32 (td, 1H, J = 7.9, 1.3 Hz), 7.28 – 7.21 (m, 1H), 6.96 (td, 1H, J = 7.6, 1.5 Hz). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 162.2, 160.2, 136.0, 127.4, 116.7. GC-MS: m/z: 261.0 (calced for C$_7$H$_4$INS: 260.9).
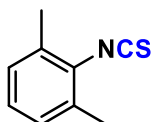

isothiocyanatobenzene (2f). According to the general experiment procedure A, the reaction was performed by using aniline (**1f**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2f** in 75 mg, 84% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.37 – 7.31 (m, 2H), 7.31 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H). ^{13}C-NMR

(125 MHz, CDCl$_3$): δ 135.4, 131.3, 129.6, 127.4, 125.8. GC-MS: m/z: 135.1 (calced for C$_7$H$_5$NS: 135.0).

1-isothiocyanato-4-methylbenzene (2g). According to the general experiment procedure A, the reaction was performed by using p-toluidine (**1g**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2g** in 82.1 mg, 95% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.11 (m, 4H, J = 6.2, 5.2 Hz), 2.34 (s, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 137.6, 134.5, 130.2, 128.4, 125.6, 21.3. GC-MS: m/z: 149.1 (calced for C$_7$H$_4$NS: 149.2).
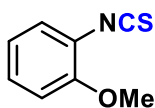

2-isothiocyanato-1,3-dimethylbenzene (2h). According to the general experiment procedure A, the reaction was performed by using 2,6-dimethylaniline (**1h**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2h** in 89.7 mg, 95% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.16 – 6.94 (m, 3H), 2.37 (s, 6H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 136.6, 135.1, 129.6, 128.0, 127.0, 18.8. GC-MS: m/z: 163.1 (calced for C$_9$H$_9$NS: 163.2).
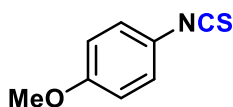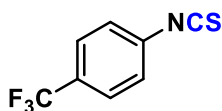

1-isothiocyanato-4-methoxybenzene (2i). According to the general experiment procedure A, the reaction was performed by using p-anisidine (**1i**, 1.0 eq., 0.58

mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2i** in 84.3 mg, 88% yield as yellow oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.18 – 7.05 (m, 2H), 6.87 – 6.69 (m, 2H), 3.79 (s, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 158.6, 134.0, 127.0, 123.6, 114.9, 55.6. GC-MS: m/z: 165.1 (calced for C$_8$H$_7$NOS: 165.0).
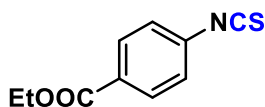

1-isothiocyanato-2-methoxybenzene (2j). According to the general experiment procedure A, the reaction was performed by using *o*-anisidine (**1j**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2j** in 89.1 mg, 93% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.24 – 7.18 (m, 2H), 7.09 (dd, 1H, *J* = 7.8, 1.6 Hz), 6.93 – 6.78 (m, 1H), 3.89 (s, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 156.0, 139.8, 128.3, 125.5, 120.7, 111.5, 56.0. GC-MS: m/z: 165.1 (calced for C$_8$H$_7$NOS: 165.0).
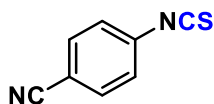

1-isothiocyanato-4-(trifluoromethyl) benzene (2k). According to the general experiment procedure A, the reaction was performed by using 4-(trifluoromethyl)-aniline (**1j**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2j** in 89.1 mg, 93% yield as white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.61 (d, 2H, *J* = 8.8 Hz), 7.37 – 7.27 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 138.3, 135.0, 129.5, 129.2, 129.0, 128.8, 126.9, 126.1, 124.7, 122.5, 120.4. ^{19}F-NMR (470 MHz, CDCl3): δ -62.5, GC-MS: m/z: 203.1 (calced for C$_8$H$_4$F$_3$NS: 203.0).

1-isothiocyanato-3-nitrobenzene (2l). According to the general experiment procedure A, the reaction was performed by using 3-nitroaniine (**1l**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2l** in 65.8 mg, 63% yield as yellow solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 8.14 – 8.09 (m, 1H), 8.06 (d, 1H, J = 1.9 Hz), 7.68 – 7.41 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 148.8, 139.7, 133.3, 131.6, 130.6, 121.9, 120.8. GC-MS: m/z: 180.1 (calced for C$_7$H$_4$N$_2$O$_2$S: 180.0).
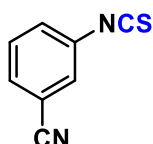

ethyl 4-isothiocyanatobenzoate (2m). According to the general experiment procedure A, the reaction was performed by using 4-ethylamino benzoate (**1m**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2m** in 90.0 mg, 75% yield as colorless solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 8.02 (dd, 2H, J = 8.7, 2.1 Hz), 7.36 – 7.07 (m, 2H), 4.36 (q, 2H), 1.37 (t, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 165.5, 137.8, 135.6, 131.1, 129.1, 125.7, 61.4, 14.3. GC-MS: m/z: 207.1 (calced for C$_{10}$H$_9$NO$_2$S: 207.0).
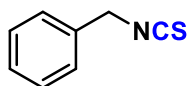

4-isothiocyanatobenzonitrile (2n). According to the general experiment procedure A, the reaction was performed by using 4-aminobenzonitrile (**1n**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at

room temperature for 1 hour to afford **2n** in 37.2 mg, 40% yield as white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.67 – 7.60 (m, 2H), 7.31 – 7.27 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 139.8, 136.2, 133.7, 126.6, 118.0, 110.7. GC-MS: m/z: 160.0 (calced for C$_8$H$_4$N$_2$S: 160.0).

3-isothiocyanatobenzonitrile (2o). According to the general experiment procedure A, the reaction was performed by using 3-aminobenzonitrile (**1o**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2o** in 58.4 mg, 63% yield as white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.56 – 7.51 (m, 1H), 7.49 – 7.45 (m, 2H), 7.45 – 7.41 (m, 1H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 139.4, 133.1, 130.8, 130.5, 130.1, 128.9, 117.3, 114.0. GC-MS: m/z: 160.1 (calced for C$_8$H$_4$N$_2$S: 160.0).
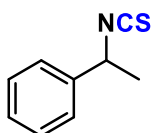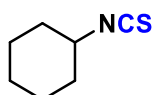

(isothiocyanatomethyl)benzene (2p). According to the general experiment procedure A, the reaction was performed by using benzylamine (**1p**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2p** in 63 mg, 73% yield as white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.41 – 7.37 (m, 2H), 7.34 (dd, 1H, J = 6.2, 3.9 Hz), 7.31 (dt, 2H, J = 7.3, 1.5 Hz), 4.70 (s). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 134.3, 131.6, 129.0, 128.4, 126.9, 48.7. GC-MS: m/z: 149.1 (calced for C$_8$H$_7$NS: 149.0).
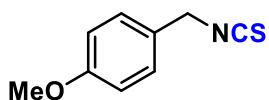
1-(isothiocyanatomethyl)-4-methoxybenzene (2q). According to the general experiment procedure A, the reaction was performed by using 4-methoxy benzylamine (**1q**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2q** in 67.5 mg, 65% yield as yellow oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.24 – 7.21 (m, 2H), 6.98 – 6.80 (m, 2H), 4.62 (s, 2H), 3.80 (s, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 134.3, 131.6, 129.1, 128.5, 126.9, 48.7. GC-MS: m/z: 179.1 (M), 121.1 (M-NCS) (calced for C$_9$H$_9$NOS: 179.0).
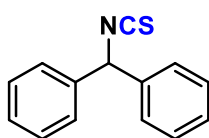
(isothiocyanatomethylene) dibenzene (2r). According to the general experiment procedure A, the reaction was performed by using diphenylmethanamine (**1r**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2r** in 92.3 mg, 71% yield as yellow oil: HNMR (500 MHz, CDCl$_3$): δ 7.40 – 7.34 (m, 4H), 7.34 – 7.29 (m, 6H), 5.99 (s, 1H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 139.3, 134.6, 132.0, 130.2, 129.0, 128.4, 126.7, 64.7. GC-MS: m/z: 224.1 (M-1), 167.1 (M-NCS) (calced for C$_{14}$H$_{11}$NS: 225.1).
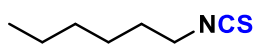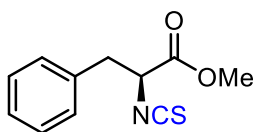

(1-isothiocyanatoethyl) benzene (2s). According to the general experiment procedure A, the reaction was performed by using 1-phenylethan-1-amine (**1s**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in

acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2s** in 79.4 mg, 84% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.41 − 7.35 (m, 2H), 7.33 (dd, 3H), 4.91 (q, 1H), 1.67 (d, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 140.3, 132.4, 129.0, 128.3, 125.5, 57.1, 25.1. GC-MS: m/z: 163.1 (M), 105.1 (M-NCS) (calced for C$_9$H$_9$NS: 163.0).
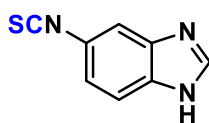

isothiocyanatocyclohexane (2t). According to the general experiment procedure A, the reaction was performed by using cyclohexylamine (**1t**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2t** in 65.4 mg, 80% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 3.74 − 3.58 (m, 1H), 1.96 − 1.81 (m, 2H), 1.79 − 1.57 (m, 4H), 1.52 − 1.42 (m, 1H), 1.43 − 1.30 (m, 3H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 127.2, 55.5, 33.3, 29.8, 25.1, 23.3. GC-MS: m/z: 141.1 (calced for C$_7$H$_{11}$NS: 141.1).
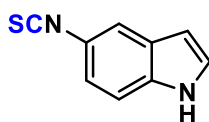

1-isothiocyanatohexane (2u). According to the general experiment procedure A, the reaction was performed by using hexylamine (**1u**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2u** in 78.8 mg, 95% yield as colorless oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 3.48 (t, 2H), 1.71 − 1.61 (m, 2H), 1.43 − 1.35 (m, 2H), 1.35 − 1.21 (m, 4H), 0.91 − 0.84 (m, 3H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 129.5, 45.1, 31.0, 30.0, 26.3, 22.5, 14.0. GC-MS: m/z: 115.1 (M-C$_2$H$_4$) (calced for C$_7$H$_{13}$NS: 143.1).

Methyl (S)-2-isothiocyanato-3-phenylpropanoate (2v). According to the general experiment procedure A, the reaction was performed by using L-phenylalanine methyl ester hydrochloride (**1v**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2v** in 43.6 mg, 34% yield as orange oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.38 – 7.28 (3H, m), 7.24 – 7.21 (2H, m), 4.48 (1H, dd, J = 8.4, 4.8 Hz), 3.80 (3H, s), 3.25 (1H, dd, J = 13.8, 4.7 Hz), 3.13 (1H, dd, J = 13.8, 8.4 Hz). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 168.5, 138.0, 135.1, 129.4, 128.8, 127.7, 60.9, 53.2, 39.8.

5-Isothiocyanato-1H-benzo[d]imidazole (2w). According to the general experiment procedure A, the reaction was performed by using 5-aminobenzimidazole (**1w**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2w** in 72 mg, 71% yield as yellow oil: ^{1}HNMR (500 MHz, DMSO-d6): 8.34 (s, 1H), 7.68 (d, 1H), 7.60 (d, 1H), 7.24 (dd, 1H, J = 8.5, 1.3 Hz). ^{13}C-NMR (125 MHz, DMSO-d6): δ 144.7, 138.2, 137.0, 132.5, 124.6, 121.3, 116.7, 113.6. GC-MS: m/z: 175.1 (calced for C$_8$H$_5$N$_3$S: 175.0).
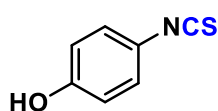

5-isothiocyanato-1H-indole (2x). According to the general experiment procedure A, the reaction was performed by using 5-aminoindole (**1w**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4
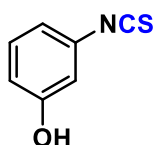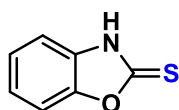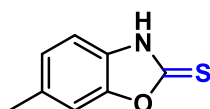
hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2w** in 81.7 mg, 81% yield as yellow solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 8.28 (s, 1H), 7.51 (t, 1H), 7.33 (d, 1H), 7.28 – 7.25 (m, 1H), 7.07 (dt, 1H, J = 8.6, 4.4 Hz), 6.53 (t, 1H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 134.4, 128.1, 126.2, 123.1, 120.2, 118.1, 112.0, 103.1. GC-MS: m/z: 174.1 (calced for C$_9$H$_6$N$_2$S: 174.0).
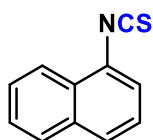
1 -isothiocyanatonaphthalene (2y). According to the general experiment procedure A, the reaction was performed by using napthelene-1amine (**1y**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2y** in 82.6 mg, 77% yield as white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 8.09 (dd, 1H, J = 8.4, 0.5 Hz), 7.86 (dd, 1H, J = 8.1, 0.6 Hz), 7.76 (p, 1H, J = 3.5 Hz), 7.62 – 7.51 (m, 2H), 7.42 – 7.36 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 136.1, 134.1, 129.3, 128.5, 127.8, 127.5, 127.5, 127.2, 125.5, 123.5, 122.8. GC-MS: m/z: 185.1 (calced for C$_9$H$_9$NS: 185.0).

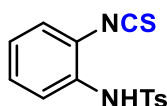**4-isothiocyanatophenol (2z).** According to the general experiment procedure A, the reaction was performed by using 4-aminophenol (**1z**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2z** in 68.3 mg, 78% yield as yellow oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.18 – 7.00 (m, 2H), 6.87 – 6.65 (m, 2H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 154.8, 134.0, 127.3, 123.8, 116.4. GC-MS: m/z: 151.1 (calced for C$_7$H$_5$NOS: 151.0).

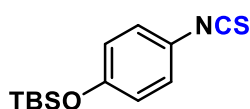**3-isothiocyanatophenol (2aa).** According to the general experiment procedure A, the reaction was performed by using 3-aminophenol (**1aa**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1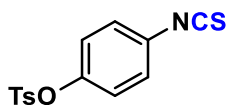.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2aa** in 73.5 mg, 84% yield as yellow oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 6.81 – 6.77 (m, 1H), 6.77 – 6.72 (m, 2H), 6.68 (t, 1H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 156.4, 135.5, 132.2, 130.6, 118.5, 114.9, 112.8. GC-MS: m/z: 151.1 (calced for C$_7$H$_5$NOS: 151.0).

benzo[d]oxazole-2(3H)-thione (2bb). According to the general experiment procedure A, the reaction was performed by using 3-aminophenol (**1aa**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2aa** in 71.0 mg, 84% yield as yellow solid: ^{1}HNMR (500 MHz, DMSO-d6): δ 11.26 (s, 1H), 7.36 (d, 1H), 7.27 (dd, 2H, J = 10.6, 4.4 Hz), 7.24 (t, 1H).^{13}C-NMR (125 MHz, DMSO-d6): δ 180.6, 148.7, 131.8, 125.7, 124.3, 111.0, 110.5. GC-MS: m/z: 151.1 (calced for C$_7$H$_5$NOS: 151.0).

6-methylbenzo[d]oxazole-2(3H)-thione (2cc). According to the general experiment procedure A, the reaction was performed by using 3-aminophenol (**1aa**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and

stirred at room temperature for 1 hour to afford **2aa** in 77.5 mg, 81% yield as yellow solid: ^{1}HNMR (500 MHz, DMSO-d6): δ 7.33 (d, 1H, J = 8.8 Hz), 7.02 (d, 2H, J = 7.1 Hz), 2.32 (s, 3H).^{13}C-NMR (125 MHz, DMSO-d6): δ 180.7, 146.9, 135.4, 131.7, 124.9, 111.1, 110.0, 21.3. GC-MS: m/z: 165.1 (calced for C_8H_7NOS: 165.0).

_N_-(2-isothiocyanatophenyl)-4-methylbenzenesulfonamide (2dd). According to the general experiment procedure A, the reaction was performed by using _N_-(2-aminophenyl)-4-methylbenzenesulfonamide (**1dd**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2dd** in 95.2 mg, 54% yield as white solid: ^{1}HNMR (500 MHz, DMSO): δ 7.98 – 7.94 (m, 1H), 7.92 (d, 2H), 7.41 (d, 2H), 7.31 – 7.24 (m, 2H), 7.16 – 7.11 (m, 1H), 2.40 – 2.27 (s, 3H).^{13}C-NMR (125 MHz, CDCl$_3$): 169.1, 146.8, 134.1, 131.5, 131.2, 130.3, 128.8, 126.0, 124.1, 114.0, 110.7, 21.7. HRMS: [M+2H+Na] 329.1654 (calced for $C_{14}H_{12}N_2O_2S_2$: 304.0340).

tert-butyl(4-isothiocyanatophenoxy) dimethylsilane (2ee). According to the general experiment procedure A, the reaction was performed by using 4-((_tert_-butyldimethylsilyl)oxy)aniline (**1ee**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2ee** in 133.7 mg, 87% yield as dark-brown oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.16 – 6.98 (m, 2H), 6.85 – 6.65 (m, 2H), 0.96 (m, 9H), 0.18 (m, 6H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 155.0, 134.0, 127.0, 124.2, 121.1, 25.7, -4.38. GC-MS: m/z: 265.2 (calced for $C_{13}H_{19}NOSSi$: 265.1).

4-isothiocyanatophenyl 4-methylbenzenesulfonate (2ff). According to the general experiment procedure A, the reaction was performed by using 4-((*tert*-butyldimethylsilyl)oxy)aniline (**1ff**, 1.0 eq., 0.58 mmol), DBU (3.0 eq., 1.74 mmol), carbon disulfide (3.0 eq., 1.74 mmol) in acetonitrile 2 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 0.58 mmol) was added and stirred at room temperature for 1 hour to afford **2ee** in 122.1 mg, 69% yield as yellow solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.67 (d, 2H, *J* = 8.3 Hz), 7.32 – 7.29 (m, 2H), 7.18 – 7.04 (m, 2H), 7.02 – 6.85 (m, 2H), 2.44 (s, 3H).^{13}C-NMR (125 MHz, CDCl$_3$): δ 147.9, 145.9, 137.1, 132.0, 130.4, 130.0, 128.6, 127.0, 123.9, 21.8. HRMS: [M+Na] 328.0084 (calced for C$_{14}$H$_{11}$NNaO$_3$S$_2$: 328.0078).

2.5.4 Synthesis derivatives of unsymmetric thiourea
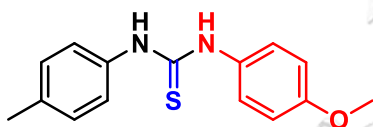
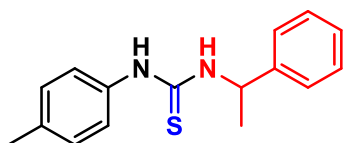**1-(4-methoxyphenyl)-3-(p-tolyl) thiourea (3a).** According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, *p*-anisidine (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 h to afford **3a** in 138.8 mg, 88% yield as yellow solid: ^{1}HNMR (500 MHz, DMSO): δ 7.80 (s, 1H), 7.27 – 7.21 (m, 4H), 7.17 (d, 2H, *J* = 8.2 Hz), 6.98 – 6.80 (m, 2H), 3.79 (s, 3H), 2.33 (s, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): 180.1, 158.7, 137.7, 134.7, 130.2, 127.7, 125.6, 114.8, 55.6, 21.1. HRMS: [M+Na] 295.0866 (calced for C$_{15}$H$_{16}$N$_2$NaOS: 295.0881).
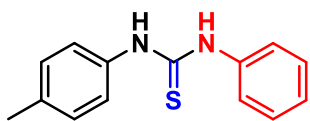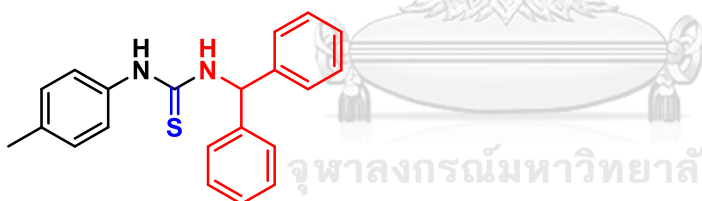
1-phenyl-3-(p-tolyl) thiourea (3b). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL.) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour Next, aniline (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 h to afford **3b** in 92.6 mg, 66% yield as white solid: ^{1}HNMR (500 MHz, DMSO-d6): δ 9.64 (s, 2H), 7.44 (d, 2H, J = 7.9 Hz), 7.34 – 7.21 (m, 4H), 7.16 – 7.01 (m, 3H), 2.24 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d6): 180.1, 140.6, 137.4, 133.6, 129.4, 128.9, 124.8, 124.4, 124.1, 21.0. HRMS: [M+Na] 265.0769 (calced for $C_{14}H_{14}N_2NaS$: 265.0775).
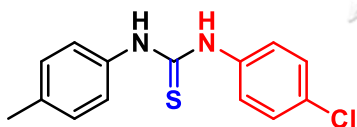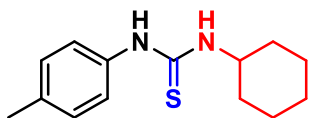

1-(4-chlorophenyl)-3-(p-tolyl) thiourea (3c). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL.) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, 4-chloroaniline (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 hours to afford **3c** in 112 mg, 70% yield as white solid: ^{1}HNMR (500 MHz, DMSO-d6): δ 9.74 (s, 1H), 9.71 (s, 1H), 7.52 – 7.42 (m, 2H), 7.33 (dd, 2H, J = 9.3, 2.4 Hz), 7.28 (d, 2H, J = 8.3 Hz), 7.09 (d, 2H, J = 8.2 Hz), 2.24 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d6): 180.1, 148.2, 139.0, 137.1, 134.4, 129.5, 129.0, 128.8, 128.6, 125.8, 125.8, 124.4, 119.1 115.6, 20.8. HRMS: [M+Na] 299.0375 (calced for $C_{14}H_{13}ClN_2$-NaS: 299.0386).
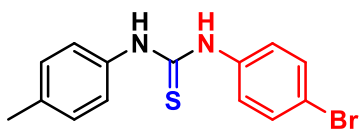
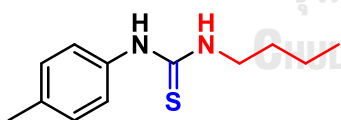**1-(4-bromophenyl)-3-(p-tolyl) thiourea (3d).** According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, 4-bromoaniline (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 hours to afford **3d** in 112 mg, 70% yield as white solid: ^{1}HNMR (500 MHz, DMSO-d6): δ 7 9.74 (s, 1H), 9.71 (s, 1H), 7.52 – 7.42 (m, 2H), 7.33 (dd, 2H, J = 9.3, 2.4 Hz), 7.28 (d, 2H, J = 8.3 Hz), 7.09 (t, 2H, J = 8.3 Hz), 2.24 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d6): 180.2, 139.5, 137.1, 134.4, 129.5, 128.8, 125.8, 124.6, 21.0. HRMS: [M-H] 319.0578 (calced for $C_{14}H_{12}BrN_2NaS$: 318.9905).
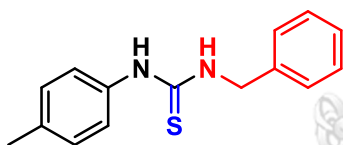
1-benzyl-3-(p-tolyl) thiourea (3e). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, benzylamine (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 hours to afford **3e** in 111.4 mg, 70% yield as white solid: ^{1}HNMR (500 MHz, CDCl₃): δ 7.91 (s, 1H), 7.34 – 7.28 (m,2H), 7.26 (dd, 3H, J = 9.4, 4.5 Hz), 7.18 (d, 2H, J = 8.2 Hz), 7.10 – 7.05 (m, 2H), 6.28 (s, 1H), 4.84 (s, 2H), 2.32 (s, 3H). ^{13}C-NMR (125 MHz, CDCl₃): 181.0, 137.9, 137.3, 133.0, 130.9, 128.9, 127.8, 127.7, 125.7, 49.5, 21.1. HRMS: [M+K-2H] 293.1091 (calced for $C_{15}H_{14}KN_2S$: 293.0515).

1-(1-phenylethyl)-3-(p-tolyl) thiourea (3f). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, 1-phenylethylamine (1.5 eq., 0.87 mmol) was added in the mixture and stirred for 3 hours to afford **3f** in 90.8 mg, 58% yield as yellow oil: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.77 (s,1H), 7.34 – 7.30 (m, 2H), 7.29 – 7.22 (m, 3H), 7.18 (d, 2H, *J* = 8.1 Hz), 7.05 (d, 2H, *J* = 8.2 Hz), 6.27 (s, 1H), 5.64 (s, 1H), 2.33 (s, 3H), 1.51 (d, 3H, *J* = 6.9 Hz). ^{13}C-NMR (125 MHz, CDCl$_3$): 179.5, 142.3, 137.6, 133.3, 130.8, 130.4, 129.2, 128.2, 129.1, 127.6, 126.1, 126.0, 125.6, 125.5, 54.4, 21.4. HRMS: [M+Na] 293.1091 (calced for C$_{16}$H$_{18}$N$_2$NaS: 293.1088).

1-benzhydryl-3-(p-tolyl) thiourea (3g). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, diphenylmethanamine (3.0 eq., 1.74 mmol) was added in the mixture and stirred for 3 hours to afford **3g** in 80.8 mg, 42% yield as white solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.74 (s, 1H), 7.31 (t, 4H, , *J* = 7.3 Hz), 7.29 – 7.22 (m, 3H), 7.18 (dd, 5H, *J* = 7.3, 5.3 Hz), 7.07 (d, 2H, *J* = 8.3 Hz), 6.83 (s, 1H), 6.56 (s, 1H), 2.33

(s, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): 180.4, 140.8, 137.7, 133.2, 130.9, 129.0, 128.8, 128.7, 127.7, 127.5, 127.4, 127.3, 127.2, 125.5, 62.5, 21.2. HRMS: [M-H] 331.1264 (calced for C$_{21}$H$_{20}$N$_2$S: 332.1347).

1-cyclohexyl-3-(p-tolyl) thiourea (3h). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, cyclohexylamine (3.0 eq., 1.74 mmol) was added in the mixture and stirred for 3 hours to afford **3h** in 103.5 mg, 72% yield as yellow solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 7.63 (s, 1H), 7.21 (d, 2H, *J* = 8.1 Hz), 7.05 (d, 2H, *J* = 8.2 Hz), 5.83 (s, 1H), 4.24 (s, 1H), 2.35 (s, 3H), 2.00 (m, 2H), 1.68 − 1.54 (m, 3H), 1.48 − 1.30 (m, 2H), 1.15 − 1.04 (m, 3H). ^{13}C-NMR (125 MHz, CDCl$_3$): 178.9, 137.5, 133.3, 130.9, 125.4, 54.1, 32.8, 32.6, 25.5, 24.7, 21.1. HRMS: [M+Na] 271.1237 (calced for C$_{14}$H$_{20}$N$_2$NaS: 271.1245).

1-butyl-3-(p-tolyl) thiourea (3i). According to the general experiment procedure B. A mixture of *p*-toluidine (1.0 eq, 0.58 mmol), carbon disulfide (3.0 eq., 1.74 mmol) and DBU (3.0 eq., 1.74 mmol) were dissolved by acetonitrile (2 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 0.87 mmol) was added and stirred at room temperature for 1 hour. Next, butylamine (3.0 eq., 1.74 mmol) was added in the mixture and stirred for 3 hours to afford **3i** in 109.4 mg, 85% yield as yellow solid: ^{1}HNMR (500 MHz, CDCl$_3$): δ 8.01 (s), 7.25 - 7.16 (m, 4H), 7.06 (d, 2H, *J* = 8.2 Hz), 5.95 (s, 1H), 3.58 (t, 2H, *J* = 7.2

Hz), 1.55 – 1.44 (m, 2H), 1.34 – 1.24 (m, 2H), 0.88 (t, 3H, J = 7.4 Hz). ^{13}C-NMR (125 MHz, CDCl$_3$): 180.3, 137.6, 133.3, 130.8, 125.6, 45.3, 31.1, 21.1, 20.1, 13.7. HRMS: [M+H] 223.1224 (calced for C$_{12}$H$_{18}$N$_2$S: 222.1191).

2.5.5 Gram-scale synthesis

2.5.5.1 Gram-scale synthesis of isothiocyanate

General procedure A was followed, the reaction was performed by 4-bromoaniline (**1a**, 1.0 eq., 5.8 mmol), DBU (3.0 eq., 17.4 mmol), carbon disulfide (3.0 eq., 17.4 mmol) in acetonitrile 20 mL for 4 hours. Then, carbon tetrabromide (1.0 eq., 5.8 mmol) was added and stirred at room temperature for 1 hour afford **2a** in 980 mg, 79% yield as a white solid: ^{1}H-NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 – 7.37 (m, 2H), 7.19 – 6.99 (m, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ 136.9, 132.8, 130.5, 127.2, 120.8. GC-MS: m/z: 213.0 : 215.0 (1:1) (calced for C$_7$H$_4$BrNS: 212.9 : 214.9 (1:1)).

2.5.5.1 Gram-scale synthesis of unsymmetric thiourea

General procedure B was followed, A mixture of *p*-toluidine (**1f**) (1.0 eq, 9.33 mmol), carbon disulfide (3.0 eq., 28.0 mmol) and DBU (3.0 eq., 28.0 mmol) were dissolved by acetonitrile (20 mL) in Pyrex glass tube. The mixture was stirred at room temperature for 4 hours. Then, carbon tetrabromide (1.5 eq., 14 mmol) was added and stirred at room temperature for 1 hour. Next, *p*-anisidine (**1i**) (1.5 eq., 14 mmol) was added in the mixture and stirred for 3 h to afford **3a** in 1.75 g, 69% yield as yellow solid: ^{1}HNMR (500 MHz, DMSO): δ 9.64 (s, 2H), 7.44 (d, 2H, J = 8.2 Hz), 7.34 – 7.21 (m, 4H), 7.16 – 7.01 (m, 3H), 2.24 (s, 3H). ^{13}C-NMR (125 MHz, DMSO): 180.1, 140.6, 137.4, 133.6, 129.4, 128.9, 124.8, 124.4, 124.1, 21.0. HRMS: [M+Na] 265.0769 (calced for C$_{14}$H$_{14}$N$_2$NaS: 265.0775).

CHAPTER III

RESULT & DISCCUSION

In this work, we developed the synthesis of isothiocyanate from amines in one pot fashion. The first step involves the formation of dithiocarbamate salt (**X**) via the treatment of CS_2. The second step is the desulfurization of dithiocarbamate salt (**X**) into the target isothiocyanate. Our work will focus on developing the method for desulfurization process using various desulfurizing agents.
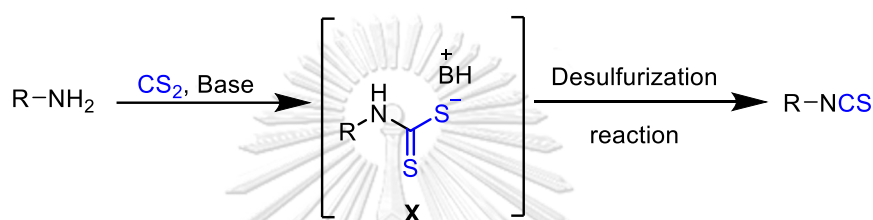
Scheme 3.1 Synthesis of isothiocyanate via desulfurization process.

3.1 Synthesis of isothiocyanate via light mediated Vilsmeier-Haack reagent

The first desulfurization method that we plan to use was photochemical reaction via Vilsmeier-Haack reagent. Therefore, we first built our photoreactors equipped by either 1) Visible light or 2) Ultraviolet (UV) bulb. There are two light sources for visible photo reactor including 19W white LED (**Picture 3.1, A**) and SMD 5050 LED, 12W green LED (**Picture 3.1 ,B**). The reaction vessel that used for visible light photo reaction was made from simple borosilicate glass. On the other hand, the UV photo reactor were equipped with either 254 nm UV lamp (**Picture 3.1 ,C**) or 365 nm UV lamp (**Picture 3.1 ,D**). Importantly, the quartz was used as reaction vessel due to it excels at transmitting UV light.
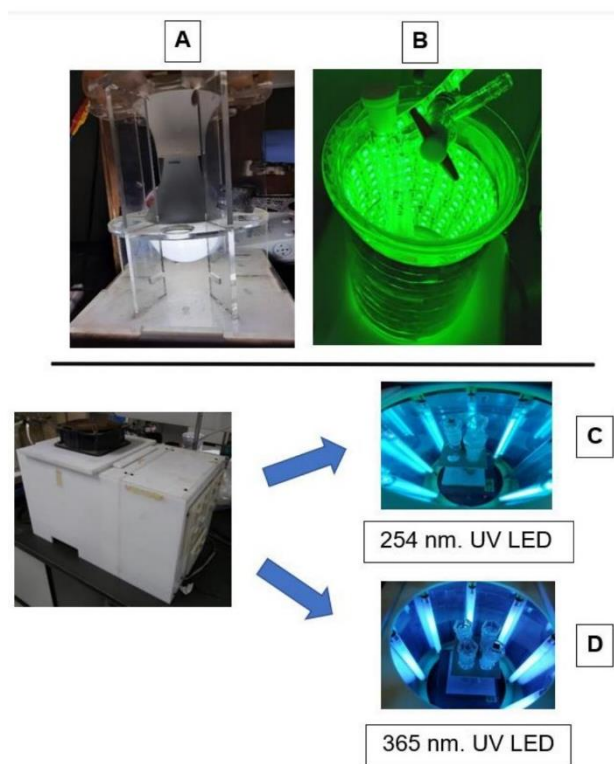
Picture 3.1 Our photoreactor in this study **A,B**) Visible light. **C,D**) Ultraviolet light.

    3.1.1 Effect of light sources for desulfurization via Vilsmeier-Haack reagent

4-Bromoaniline (**1a**) was used as a model substrate for optimized study for preparation of isothiocyanate (**Scheme 3.2**). The first step was the formation of dithiocarbamate salt (**X**) from the reaction between 4-bromoaniline **1a** and CS_2 in presence of DBU as base. The second step was desulfurization via Vilsmeier-Haack light- mediated by using carbon tetrabromide and *N,N*-dimethyl formamide (DMF) to provide isothiocyanate **2a**. The parameter that we focus on this study was the light source.
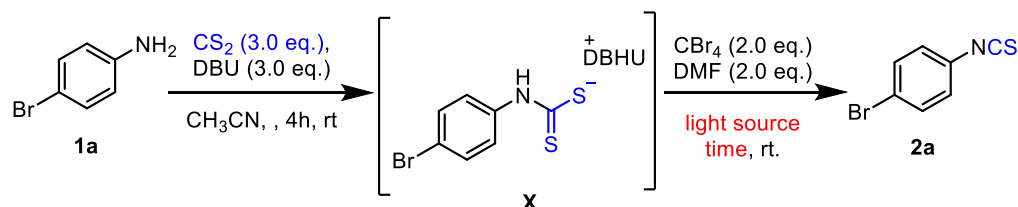
Scheme 3.2 The study for synthesis of isothiocyanate from 4-bromoaniline

    First, we tested the light source irradiation including white LED, green LED, 254 nm. UV. and 365 nm. UV. The treatment of CS_2 in the presence of DBU to **1a**

leaded to the complete consume of starting material (**1a**) within 20 hours. Under visible light irradiation for 16 hours by white LED (**Table 3.1, entry 1**) and green LED (**Table 3.1, entry 2**) with the addition of 2.0 equivalences of CBr$_4$ and 2.0 equivalence of DMF in acetonitrile, the isothiocyanate **2a** was isolated in 61% and 51% yields, respectively. The low yield of product **2a** was probably due to the decomposition of product under the long irradiation time. Switching the visible light sources to ultraviolet light sources, after the reaction provided product **2a** in 65-80% yields in case of 254 nm UV irradiation (**Table 3.1, entry 2-4**). While using 365 nm UV irradiation, the product **2a** was received in slightly better yields (70-77%, **Table3.1, entry 6-8**) under the same irradiation time. To test the stability of product **2a** under UV irradiation, we irradiated isothiocyanate **2a** under both ultraviolet light sources for 4 hours. Both reactions were monitored by ^{1}HNMR spectroscopy to check the decomposition of isothiocyanate product (**Figure 3.1**). From NMR result, we found newly unidentified peak at aromatic region (7.4-7.5 ppm) and down field peak at 9.97 ppm indicating the composition from 254 nm. UV irradiation case (**Figure 3.1, TOP**). while UV 365 nm. gave clean NMR spectrum of isothiocyanate **2a** (**Figure 3.1, Bottom**). Therefore, UV 365 nm. LED light is suitable light source for further study.

Table 3.1 light source screening[a]
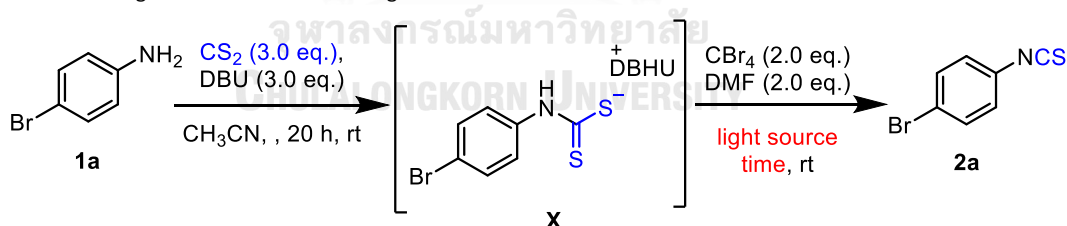
Entry	Light source	Time	%Yield[a]
1	White LED	16	61
2	Green LED	16	51
3	UV 254 nm	2	68
4	UV 254 nm	4	80
5	UV 254 nm	6	65
6	UV 365 nm	2	70

7	UV 365 nm	4	77
8	UV 365 nm	6	76
[a]Reaction condition: 4-bromoamiline (1.0 eq., 0.58 mmol), CS_2 (3.0 eq., 1.74 mmol), DBU (1.74 mmol), CBr_4 (2.0 eq., 1.16 mmol), DMF (2.0 eq., 1.16 mmol), MeCN (2 mL), Isolated yield.			
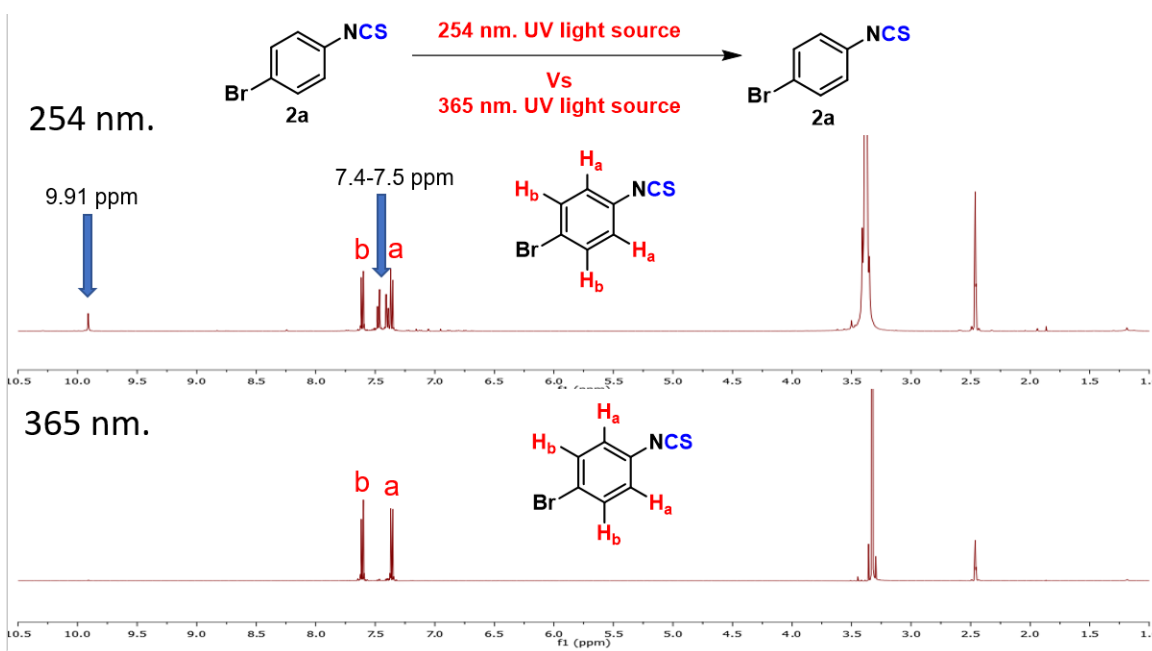
Figure 3.1 Comparison ^{1}HNMR spectrum from irradiation of isothiocyanate using UV 254 nm (**TOP**) and UV 365 nm (**Bottom**) light source

Next, we tested the necessity of the light source and CBr_4/DMF. We therefore ran the control experiment when the reaction test tube was covered by aluminum foil and carried in parallel with the reaction irradiated by 365 nm UV LED (**Table 3.2, entry 1-2**). Moderate yield of isothiocyanate **2a** was obtained. This result suggested that light had little effect on the reaction. When we carried in the absence of CBr_4 and DMF under irradiation by 254 nm and 365 nm UV LED, isothiocyanate **2a** was isolated in 16% and 26% yields respectively (**Table 3.2, entries 3, 4**). This finding that suggested that CBr_4 and DMF is crucial factor in our reaction. Next, we ran the reaction under daylight condition and reduced the equivalence of CBr_4 from 2.0

equivalence to 1.0 equivalence. Isothiocyanate **2a** was isolated in good yield (**Table 3.2, entry 5**). This information indicated that light source has no effect and 1.0 equivalent of CBr_4 is sufficient. Moreover, we reduced the time of dithiocarbamate salt (**X**) formation from 20 hours to 4 hours. The target isothiocyanate **2a** was isolated in 78% yield (**Table 3.2, entry 6**). Finally, we carried the reaction without the addition of DMF at the second step. As expected, isothiocyanate **2a** was isolated in 76% yield (**Table 3.2, entry 7**).

Table 3.2 Effect of light and DMF[a]

Entry	Light Source	CBr_4 (eq.)	DMF (eq.)	%Yield[a]
1	UV 365 nm.	2.0	2.0	77
2	Covered with Aluminium foil	2.0	2.0	52
3	UV 254 nm	-	2.0	16
4	UV 365 nm	-	2.0	26
5	Daylight	1.0	2.0	76
6[b]	Daylight	1.0	2.0	78
7	Daylight	1.0	-	76
[a]Reaction condition: 4-bromoamiline (1.0 eq., 0.58 mmol), CS_2 (3.0 eq., 1.74 mmol), DBU (1.74 mmol), CBr_4 (2.0 eq., 1.16 mmol), DMF (2.0 eq., 1.16 mmol), CH_3CN (2 mL), isolated yield. [b]1 h. in first step				

This observation suggested two knowledges. The first one is the use of CBr_4 under visible light is not required. Therefore, in **section 3.2** we studied the possibility to use other photocatalysts in the absence of CBr_4. On the other hand, such result suggested that CBr_4 can use for desulfurization directly. We therefore turned our attention to use CBr_4 as only reagent without the need of light and DMF (Vilsmeier-Haack) and the result will be discussed further in **Section 3.3**.

3.2 Synthesis of isthiocyanate using photocatalysts

In this section, we planed to study the synthesis of isothiocyanate via photochemical using dye as photocatalyst. In recently years, our group reported the funtionalization of organosulfur using photocatalysts to perform oxidative cross coupling thiol to disulfide compounds[68] and oxidative desulfurization to convert thiol to 2-aminobenzoxazole[69] and guadinine[70] derivatives (**Scheme 3.3**). For disulfide synthesis, the singlet oxygen as act as an oxidizing agent to generate the corresponding thiol radical (**A**) which can undergo homocoupling to provide disulfide products (**Scheme 3.3, eq. 1**). Interestingly, in oxidative desulfurization reaction, the transformation of thiol in to thiol radical (**A**) via singlet elctron transfer which can undergo coupling with superoxide to produce peroxysulfur (**B**) intermediate. The elimination of organosulfur took place by substitution by amines to obtaine target 2-aminobenzoxazole or guadinine derivatives (**Scheme 3.3, eq. 2 and 3**).

Previous methods from our group
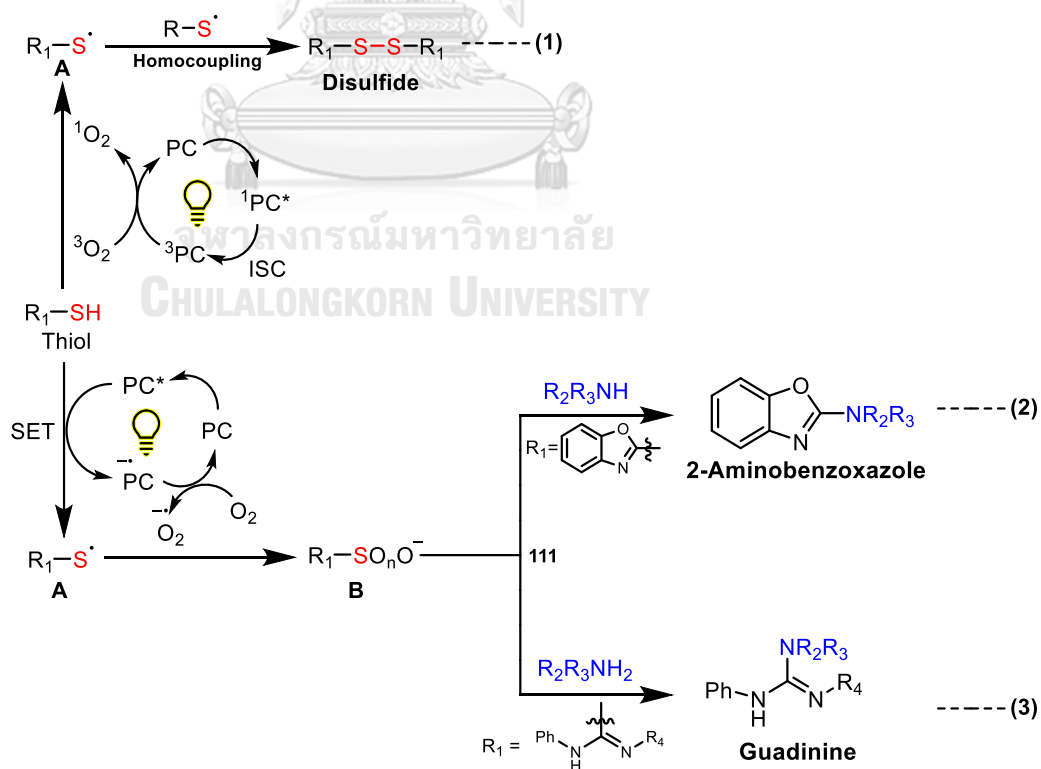
Scheme 3.3 Reviews on organosulfur of previous where method from our group

Based on above idea, we planned to investigate the synthesis of isothiocyanate using photocatalyst. We hypothesized that under photochemical and photocatalytic system, the dithiocarbamate radical **A** was formed via by singlet electron transfer (SET) under photochemical reaction and generating superoxide. Then, the coupling reaction of superoxide and dithiocarbamate radical **A** produces peroxysulfur (**B**) intermediate followed by desulfurization to obtain target isothiocyanate (**Scheme 3.4**).
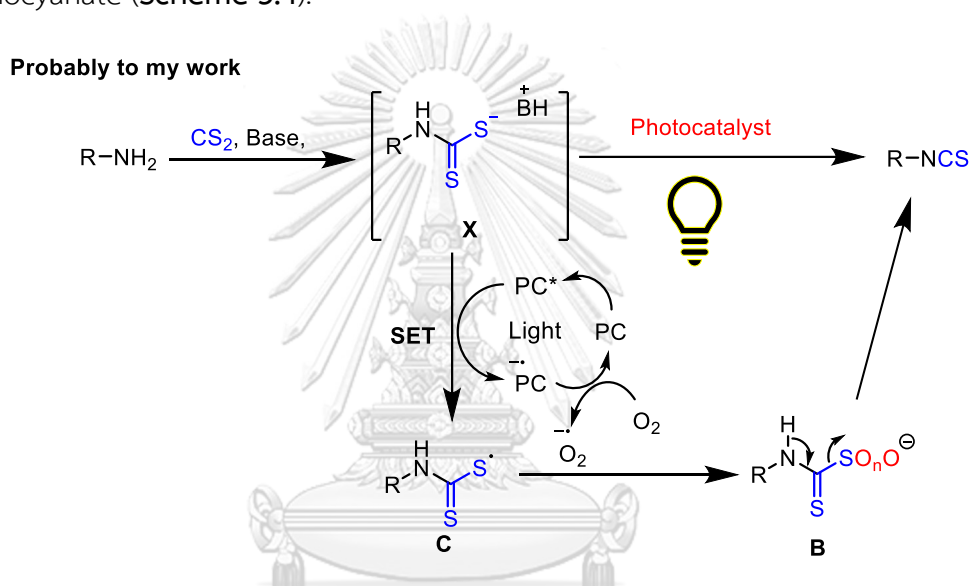
Scheme 3.4 Synthesis of isothiocyanate using photocatalyst

3.2.1 Photocatalyst and light sources screening

4-Bromoaniline (**1a**) and carbon disulfide were used as a model substrate for optimized study for preparation of isothiocyanate under visible light irradiation in presence of photocatalysts. We tried the reaction using Ru(bpy)$_3$Cl$_2$ as catalyst with white LED. After the formation of dithiocarbamate salt (**X**), we added 5 mol% of Ru(bpy)$_3$Cl$_2$ and irradiated by white LED for 16 hours. The product **2a** was formed in 38% (**Table 3.3, entry 2**) along with recovered staring material **1a** 31% yield. With this promising result, other photocatalyst including Eosin Y, Rose Bengal, Safranin O and pyrene (**Table 3.3**) were screened under similar condition. We found that Safranin O gave the best result providing compound **2a** in 48% yield (**Table 3.3, entry 5**). We would like to note that the recovering starting material **1a** was received

in 30-40% even though the formation of dithiocarbamate salt (**X**) was completely occurred (observing from TLC). We therefore suspected that the dithiocarbamate salt (**X**) was decomposed to starting material during the desulfurization. Moreover, we ran the control experiment which Ru(bpy)$_3$Cl$_2$ was used as catalyst and carried the photoreaction by covering with aluminium foil (**Table 3.3, entry 1**). Isothiocyanate **2a** was isolated in 6% yield along with recovered starting material **1a** 61%. Finally, the control experiment in without photocatalyst was irradiated by white LED. Isothiocyanate **2a** was obtained in 9% yield along with recovered starting material **1a** in 52% (**Table 3.3, Entry 3**)

Table 3.3 Photocatalysts and light sources screening[a]
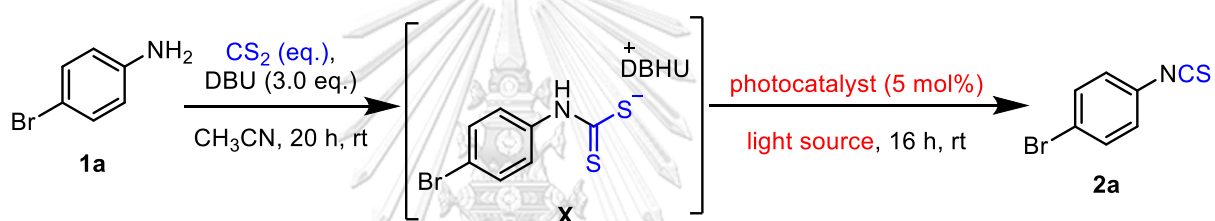
Entry	Photocatalyst (5 mol%)	Light source	%Yield[a] (2a)	Starting material 1a (% recovery)
1	Ru(bpy)$_2$Cl$_2$	Covered with aluminium foil	6	61
2	Ru(bpy)$_2$Cl$_2$	White LED	38	31
3	-	White LED	9	52
4	EosinY	Green LED	29	35
5	Roes Bengal	White LED	22	32
6	Safranin O	White LED	48	mixture compounds
7	Pyrene	White LED	24	38
8[b]	Ru(bpy)$_2$Cl$_2$	White LED	35	42
[a]Reaction condition: 4-bromoamiline (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), DBU (1.74 mmol), Photocatalyst (0.05 eq., 0.029 mmol), MeCN (2 mL), Isolated yield. [b]1% of Ru(bpy)$_2$Cl$_2$				

Although the moderate yields were received, this is the first example to prepare isothiocyanate in catalytic version which we plan to further investigate in the near future.

3.3 Synthesis of isthiocyanate by using carbon tetrabromide

Based on results from section **3.1**, the use of CBr$_4$ alone was possible as seen in **Table 3.1, entry 7**. We hypothesized that the desulfurization of dithiocarbamate salt (**X**) for prepration the corresponding isothiocyanate (**2**) can proceed through **Scheme 3.5**. Therefore, we began to investigate this reaction as presented in the following section.
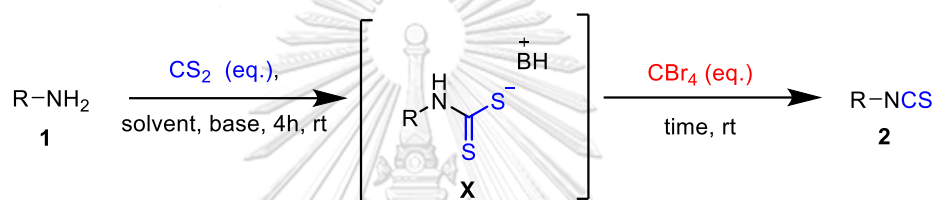
Scheme 3.5 Synthesis of isothiocyanate using CBr$_4$

3.2.1 Optimized condition

The optimization of isothiocyanate was studied using 4-bromoaniline (**1a**) as a model starting material for desulfurization operated with carbon tetrabromide as desulfurizing agent. We planned to investigate various parameters including type of solvents, amount of carbon disulfide, base, reaction times and amount of carbon tetrabromide to provide 4-bromophenyl isothiocyanate (**2a**) as shown in **Scheme 3.6**. The yield of this reaction was obtained from the purification by column chromatography and confirmed by mass spectroscopy which those data were shown in next subtopic.
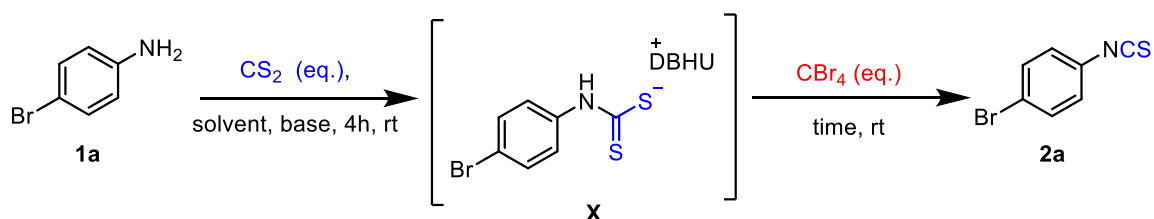
Scheme 3.6 The optimized condition with various parameters

3.2.1.1 Solvent screening[a]

Various solvents such as CH_3CN, EtOAc, EtOH, *i*-propanol, acetone and DMSO were tested and the yields of isothiocyanate were presented in **Table 3.4**. Initially, the formation of dithiocarbamate (**X**) were carried under various solvents in the presence of CS_2 and DBU 3.0 equivalences followed by the treatment of CBr_4 1.0 equivalence for 2 hours. We found that CH_3CN gave the best result and provide isothiocyanate in 74% (**Table 3.4, entry 6**). In other solvent systems, the starting material (**1a**) was remained due to the poor solubility in such solvent. Therefore, acetonitrile was used for further study.

Table 3.4 Effect of solvent type[a]
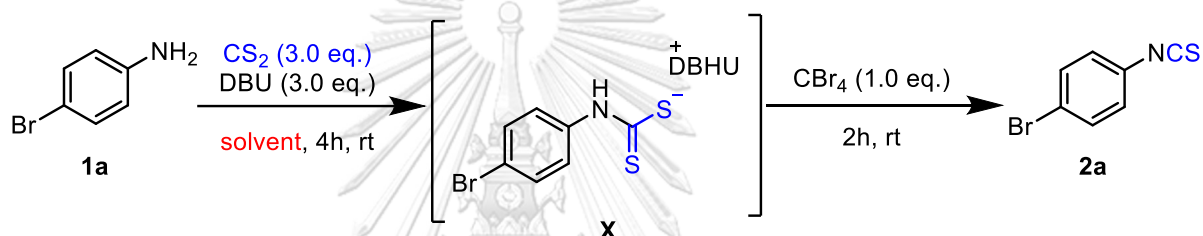
| Entry	Solvent	%Yield[b]
1	EtOAc	52
2	EtOH	10
3	*i*-Propanol	18
4	Acetone	22
5	DMSO	46
6	CH_3CN	74

[a]Reaction condition: 4-bromoaniline (1.0 eq., 0.58 mmol), CS_2 (3.0 eq., 1.74 mmol), CBr_4 (1.0 eq., 0.58 mmol) DBU (3.0 eq., 1.74 mmol), Solvent (2.0 mL).
[b]Isolated yield

3.2.1.2 Base Screening[a]

Next, organic and inorganic bases were investigated and summarized in **Table 3.4**. We performed the reaction in acetonitrile using carbon disulfide 3.0 equivalences and CBr$_4$ 1.0 equivalence. Among organic bases, DBU gave the high yield of isothiocyanate (**2a**) in 74% (**Table 3.5, entry 1-3**). On the other hand, when we switched to inorganic base such as K$_2$CO$_3$, Cs$_2$CO$_3$ and NaOAc, the isothiocyanates were obtained in lower yields, respectively (43-0%, **Table 3.5, entry 4-6**). We found that it is probably due to the poor formation of dithiocarbamate salt (**X**) in the first step causing poor solubility of those bases. Based on these results, we selected DBU (**Table 3.5, entry 1**) as base for further study.

Table 3.5 Effect of Base[a]
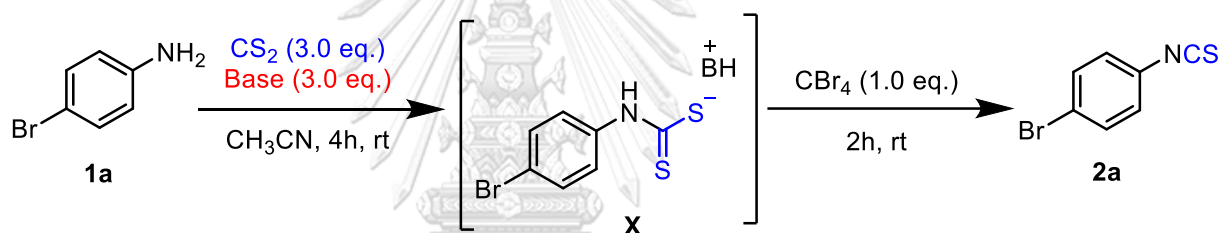
| Entry	Base	%Yield[a]
1	DBU	74
2	Et$_3$N	58
3	DIPEA	22
4	K$_2$CO$_3$	43
5	Cs$_2$CO$_3$	48
6	NaOAc	0
[a]Reaction condition: 4-bromoaniline (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.0 eq., 0.58 mmol) Base (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL). [b]Isolated yield		

3.2.1.3 Amount of CS_2 and CBr_4[a]

In this section, we would like to investigate the amount of CS_2 which used for the formation of dithiocarbamate salt (**X**) and the amount of CBr_4 which used for desulfurization during the second step (**Table 3.6**). We carried the reaction using 3.0 equivalences of DBU in acetonitrile. When only 1.5 equivalences of carbon disulfide were used, we observed the remaining starting material **1a** and only 53% of isothiocyanate was produced (**Table 3.6, entry 1**). To ensure the complete conversion of **1a** into the corresponding thiocarbamate salt (**X**), 3.0 equivalences of carbon disulfide was added (**Table 3.6, entry 2**). The product **2a** was isolated in 74% yield without the remaining starting material. On the other hand, increasing the amount of CS_2 to 5.0 equivalences gave no significant improvement (**Table 3.6, entry 3**). Therefore, the use of 3.0 equivalence of CS_2 was sufficient to convert amine **1a** to dithiocarbamate salt (**X**) and was used for further study. Then, we studied the amount of CBr_4 for desulfurization step using 3.0 equivalences of CS_2 (**Table 3.6, entry 4-6**). When the reaction was performed without CBr_4, only 12% of isothiocyanate was isolated (**Table 3.6, entry 4**). Using 1.5 equivalence of CBr_4, the isothiocyanate were produced in 85% after 2 hours (**Table 3.6, entry 6**). During the addition of CBr_4 we observed the increase of temperature which could result in the decomposition of the intermediate or product. Therefore, we carried the desulfurization step at $0^{\circ}C$. However, the isothiocyanates was isolated in slightly lower yield (78%) (**Table 3.6, entry 7**). We hypothesized that there were remaining unreacted dithiocarbamate salt (**X**). Then, when we reduced the desulfurization time from 2 to 1 hour, we received the similar yield of isothiocyanate **2a** (**Table 3.6, entry 8**). Therefore, this condition was used as our optimize condition for further study.

Table 3.6 The amount of CS_2 and CBr_4[a]
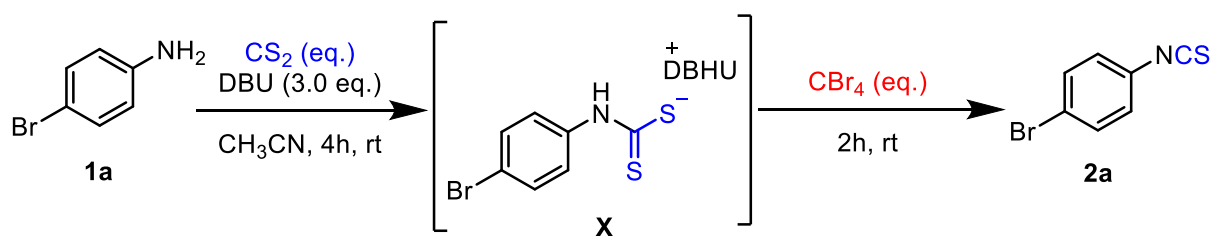
Entry	CS_2 (eq.)	CBr_4 (eq.)	%Yield[a]
1	1.5	1.0	53
2	3.0	1.0	74
3	5.0	1.0	75
4	3.0	-	12
5	3.0	0.5	53
6	3.0	1.5	85
7[c]	3.0	1.5	78
8[d]	3.0	1.5	85
[a]Reaction condition: 4-bromoaniline (1.0 eq., 0.58 mmol), CS_2 (1.5-5.0 eq., 0.87-0.29 mmol), CBr_4 (0-1.5 eq., 0-0.87 mmol) DBU (3.0 eq., 1.74 mmol), CH_3CN (2.0 mL). [b]Isolated yield. [c]The reaction was perform under 0-5 °C. [d]the desulfurization time for 1 h.			

3.2.2 Substrate scope of amines

With the optimized condition in our hands as presented in **Table 3.6**, **entry 8**, we next expanded the scope of our reaction. Various amines such as aryl amines, benzyl amines, bicyclic amines, aliphatic amines and amino phenols were tested under our optimized condition to prepare the corresponding isothiocyanates.

3.2.2.1 Aromatic amines carrying halogen groups[a].

Aryl amines containing halogen atoms such as 4-bromo (**1a**), 4-fluoro (**1b**), 4-chloro (**1c**), 4-iodo (**1d**) and 2-iodo (**1e**) were subjected to optimize condition and isothiocyanates (**2a-2e**) were isolated in good to excellent yields (**Scheme 3.7**).
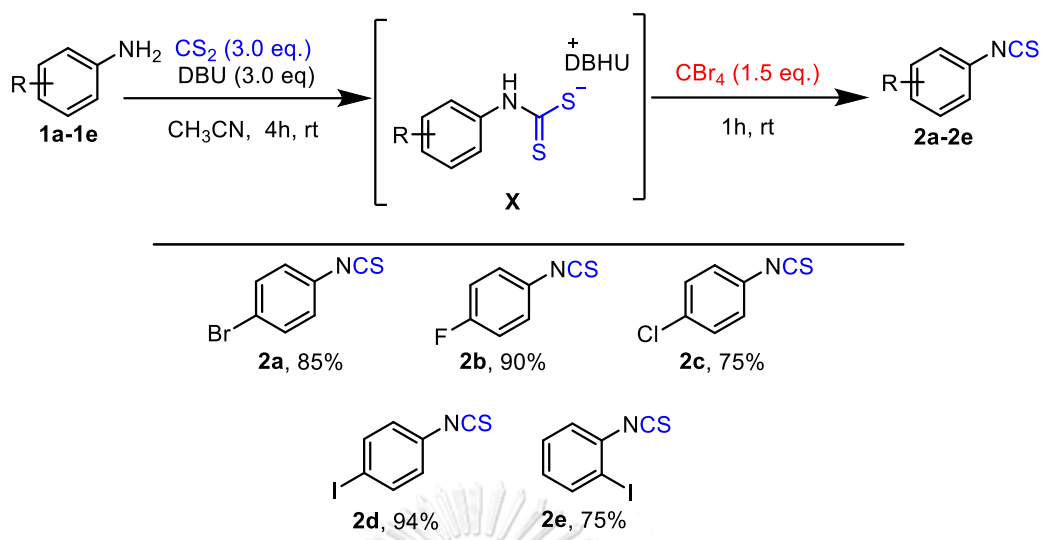
aReaction condition: amine (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL), isolated yield.

Scheme 3.7 Aromatic amines carrying halogen groups[a].

3.2.2.2 Aromatic amines carrying electron donating groups[a]

First, aniline (**1f**) was first tested, and we were able to isolate isothiocyanate (**2f**) in 84% yield (**Scheme 3.8**). Then, various aryl amines carrying electron donating groups such methyl (**1g**), 2,6-dimethyl (**1h**), 4-methoxy (**1i**) and 2-methoxy (**1j**) were studied. The isothiocyanate derivatives (**2g-2j**) were isolated in 88-95% yields. Interestingly, aromatic amine carrying NH-Ts (**1dd**) group tolerated under our condition and provided the target isothiocyanate (**2dd**) in 54% yield (**Scheme 3.8**).
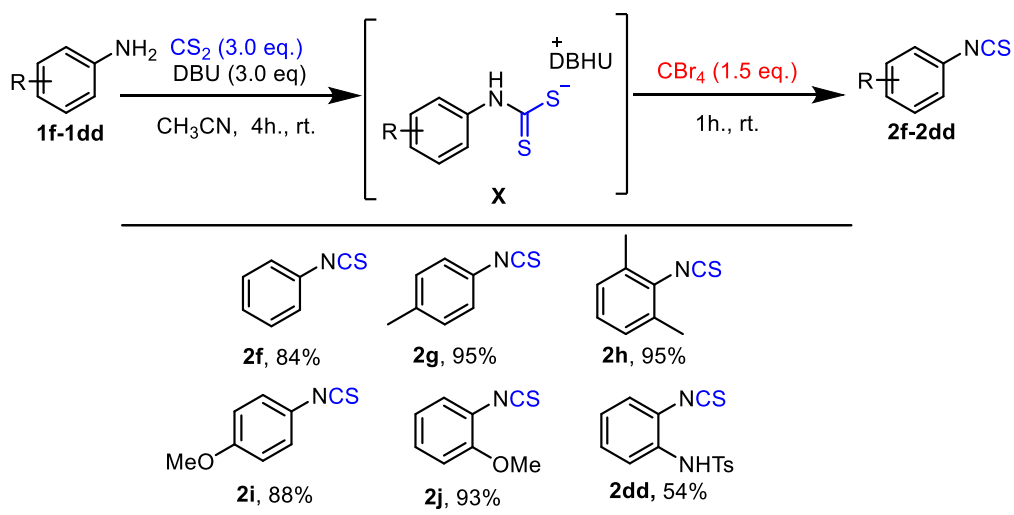
[a]Reaction condition: amine (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL), isolated yield.

Scheme 3.8 Aromatic amines carrying electron donating groups[a]

3.2.2.3 Aromatic amine carrying electron withdrawing groups[a]

Aromatic amines containing with electron withdrawing groups such as 4-trifluoromethyl (**1k**), nitro (**1l**), ethyl benzoate (**1m**) and 4-cyano (**1n**) and 3-cyano (**1o**) groups had strong effect on the reaction efficiency providing low to moderate yields of isothiocyanates (**2k-2o**) as shown in **Scheme 3.9**. We observed the remaining starting materials in all cases indicating that the formation of dithiocarbamate salt (**X**) is poor in our reaction. So, we increased the amount of CS$_2$ from 3.0 equivalences to 5.0 equivalences. Fortunately, the yield of target isothiocyanates (**2k-2o**) were dramatically increased (**Scheme 3.9**). Therefore, we hypothesized that the first step which is the formation of dithiocarbamate salt (**X**) is the rate determining step in our process.
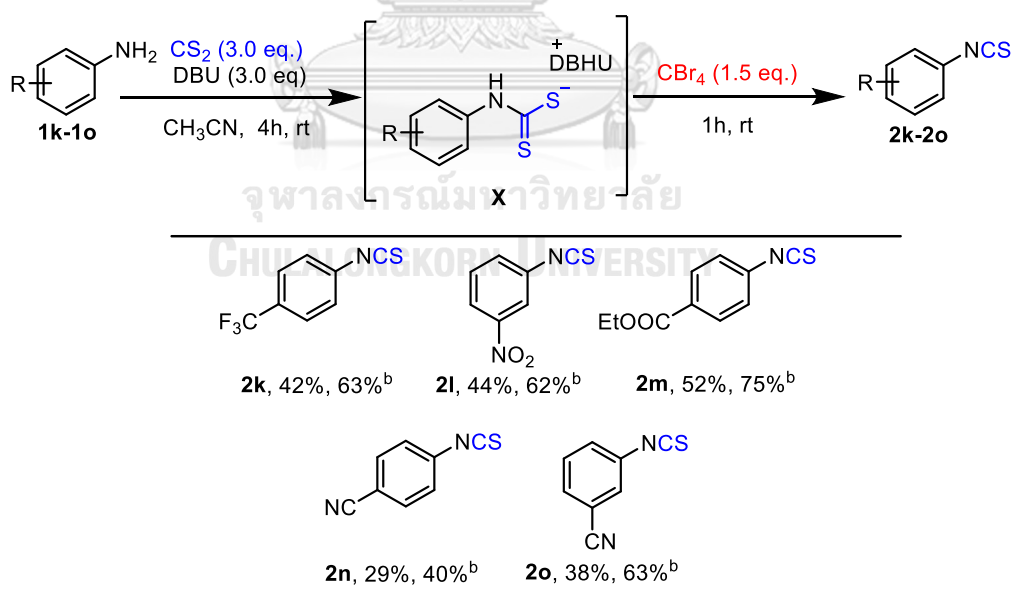
[a]Reaction condition: amine (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL), isolated yield. [b]5.0 eq. of CS$_2$

Scheme 3.9 Aromatic amine carrying electron withdrawing groups[a]

3.2.2.4 Benzylamines scope[a]

Next, we expanded amine substrates into benzylamine derivatives as shown in **Scheme 3.10**. Under optimized condition, benzylamine (**1p**) can be converted into isothiocyanate (**2p**) in 73% yield as shown in **Scheme 3.10.** Similarly, 4-methoxy benzylamine (**1q**), benzhydryl amine (**1r**) and 1-phenylethylamine (**1s**) were subjected to the thiocarbamate formation following by desulfurization to provide corresponding isothiocyanates (**2q-2s**) in 65-84% yields as shown in **Scheme 3.10**.
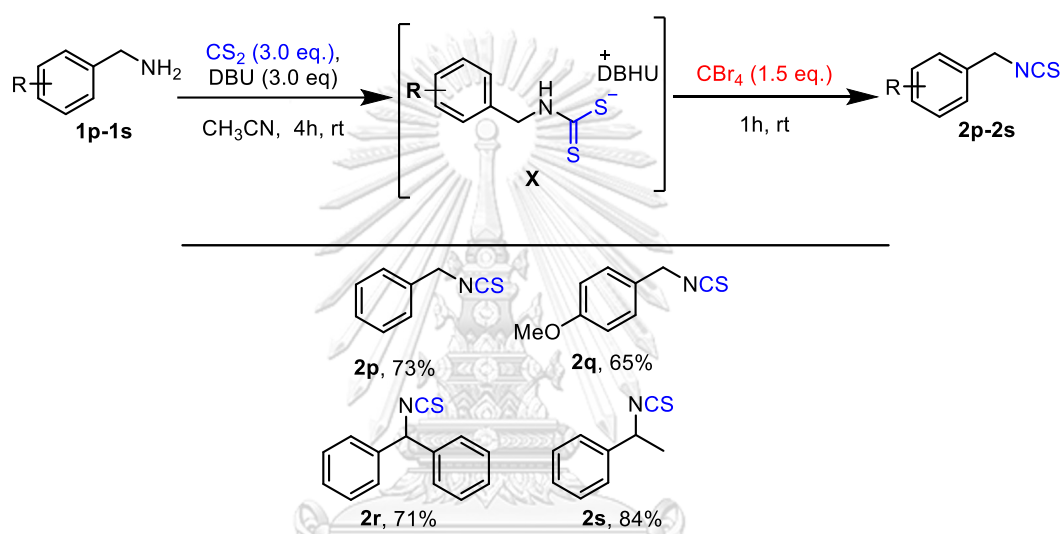
[a]Reaction condition: Amine (1.0 eq., 0.58 mmol), CS_2 (3.0 eq., 1.74 mmol), CBr_4 (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH_3CN (2.0 mL), isolated yield.

Scheme 3.10 Benzylamines scope[a]

3.2.2.5 Aliphatic amines scope[a]

Then, we extended our methodology to prepare isothiocyanates from aliphatic amines. Primary aliphatic amines such as cyclohexylamine (**1t)** and hexylamine (**1u)** were converted into corresponding isothiocyanate in excellent yields under optimized condition as shown in **Scheme 3.11**. Then, the chiral amino acid L-phenylalanine methyl ester hydrochloride was carried under the optimal condition and provided target isothiocyanate **2v** in 34% as seen in **Scheme 3.11**. Although, the yield of this transformation was moderate due to the poor solubility of L-phenylalanine methyl ester hydrochloride in acetonitrile.
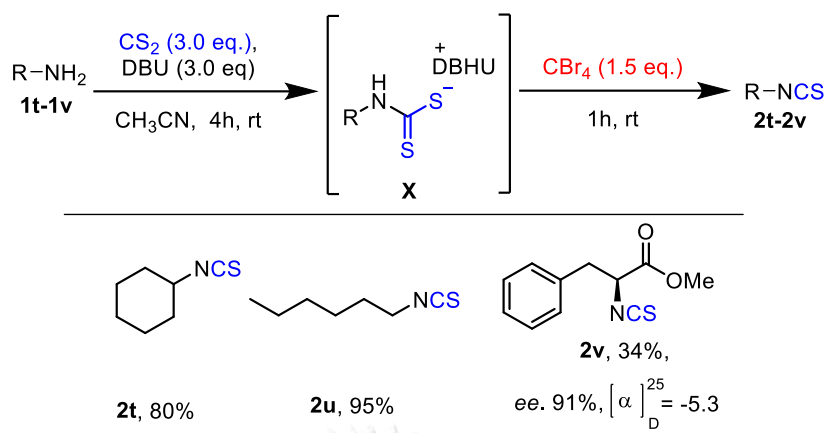
^aReaction condition: amine (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL), isolated yield.

Scheme 3.11 Aliphatic amines scope^a

3.2.2.6 Hetero and homocyclic amines scope^a

Next, we expanded amine substrates into bicyclic amine derivatives such as 5-aminobenzimidazole (**1w**), 5-aminoindole (**1x**) and 1-napthylamine (**1y**) as shown in **Scheme 3.12**. The corresponding isothiocyanates (**2w-2y**) were isolated in 71-81% yields as shown in **Scheme 3.12**. We would like to note that the nitrogen containing heterocycle in substrate **1w** and **1x** were easy to undergo oxidation.
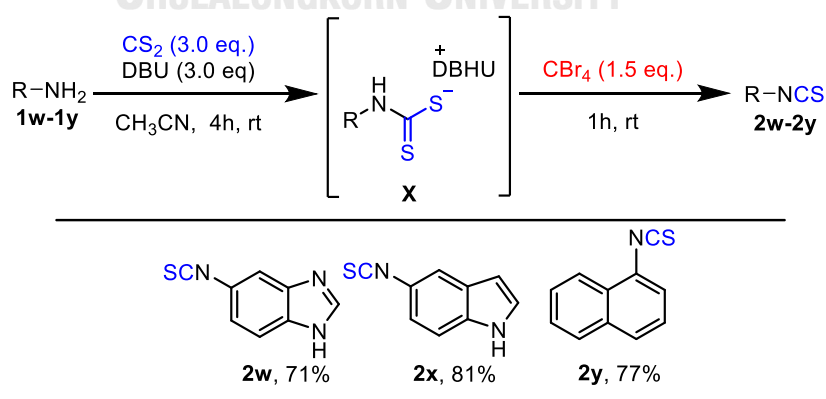
^aReaction condition: Amine (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL), isolated yield.

Scheme 3.12 Hetero and Homocyclic amines scope^a

3.2.2.7 Amino phenols and its derivatives scope[a]

Next, we extended our scope into aryl amine bearing hydroxy group in various positions such as 4-aminophenol (**1z**), 3-aminophenol (**1aa**), 2-aminophenol (**1bb**) and 2-amino-5-methylphenol (**1bb**) as shown in **Scheme 3.13**. For 4-aminophenol (**1z**) and 3-aminophenol (**1aa**) were reacted with CS_2/CBr_4 providing the corresponding isothiocyanates **2z** and **2aa** in good to excellent yields (**Scheme 3.13**). This observation suggested that the phenolic group can tolerate to our reaction condition. Interestingly, when 2-hydroxyaniline derivatives such as **1bb** and **1cc** were subjected to our reaction condition, we did not observe expected isothiocyanates **2bbx** and **2ccx**. Mercaptobenzoxales **2bb** and **2cc** were isolated in excellent yields (**Scheme 3.13**). We believe that the intermediate of isothiocyanates **2bbx** and **2ccx** were rapidly underwent intramolecular cyclization with adjacent phenolic groups. Although, the phenol group can be survived in the reaction, we would like to test our condition to other common alcohol protecting groups. Therefore, 4-aminophenols with *tert*-butyl silyl (**1ee**) and tosyl groups protecting (**1ff**) were subjected to our reaction condition providing the expected isothiocyanates **2ee** and **2ff** in good to excellent yields. Importantly, we did not observed the free phenol isothiocyanate (**2z**) indicating that such protecting groups are tolerated in our reaction condition (**Scheme 3.13**).
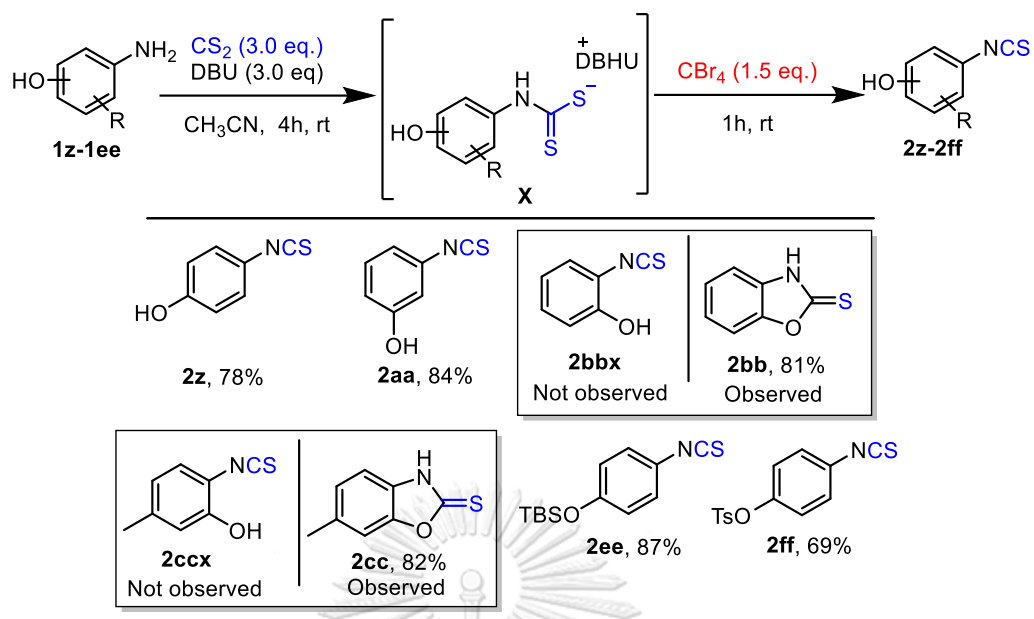
aReaction condition: 4-bromoaniline (1.0 eq., 0.58 mmol), CS$_2$ (3.0 eq., 1.74 mmol), CBr$_4$ (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH$_3$CN (2.0 mL), isolated yield.

Scheme 3.13 Amino phenols and its derivatives scope[a]

3.2.3 Substrate scopes for unsymmetric thiourea

With the successful in desulfurization of dithiocarbamate salt (**X**) to synthesize isothiocyanates, we would like to extend our method to prepare unsymmetrical thiourea in one-pot fashion from amines. The reason is because thiourea derivatives are important for bioactive compounds and important building block in medicinal chemistry. Following by our developed methodology, we plan to add amines into *in situ* generated isothiocyanate to provide unsymmetric thioureas (**Scheme 3.14**). *p*-toluidine (**1f**) was chosen as a model to convert into *p*-tolyl isothiocyanate (**2f**) *in situ* which was future reacted with 1.5 equivalence of amines. Aromatic amines such as *p*-anisidine (**1i**), aniline (**1f**), 4-choloroaniline (**1c**), 4-bromoaniline (**1a**), benzylamine (**1p**), 1-phenylethylamine (**1s**) and benzhydryl amine (**1r**) and aliphatic amines such as cyclohexyl amine (**1t**) and butylamine (**1u**) were reacted smoothly providing the unsymmetrical thioureas (**3a-3i**) in 34-88% yields (**Scheme 3.14**). However, bulky amines such as benzhydryl amine and cyclohexylamine and poor nucleophile such as butylamine gave low yields of target thioureas. Therefore, the amount of amines

was increased to 3.0 equivalences. Fortunately, we were able to prepare unsymmetrical thioureas **3g-3i** in much better yields (42-85%) (**Scheme 3.14**)
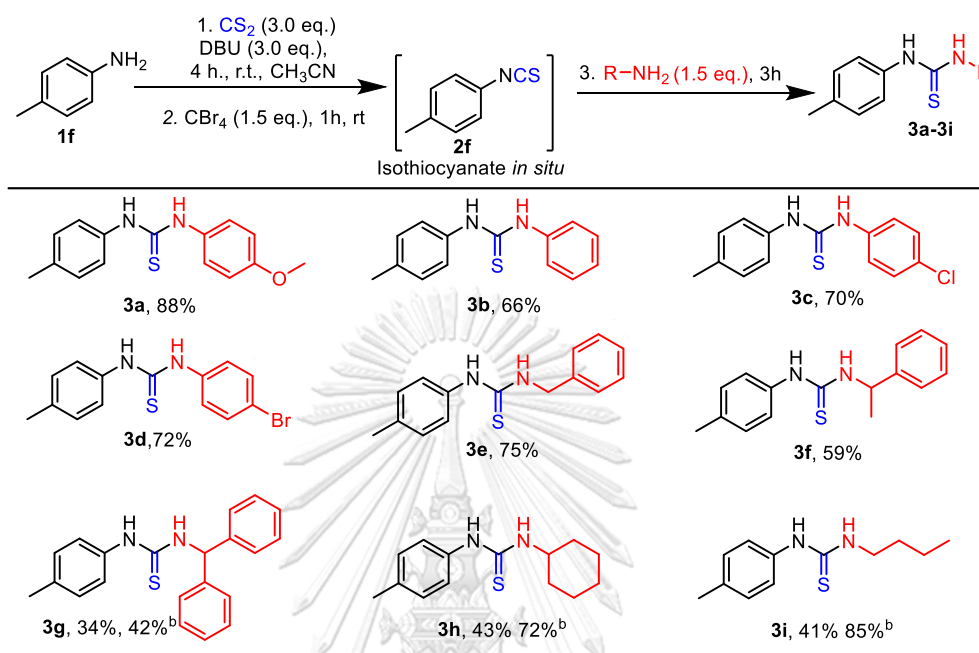
aReaction condition: *p*-toluidine **1f** (1.0 eq., 0.58 mmol), CS_2 (3.0 eq., 1.74 mmol), CBr_4 (1.5 eq., 0.87 mmol), DBU (3.0 eq., 1.74 mmol), CH_3CN (2.0 mL), secondary amine (1.5 eq., 0.87 mmol), Isolated yield. b1.74 mmol of second amine was perform.

Scheme 3.14 Unsymmetric thioureas scope[a]

3.2.4 Gram-scale synthesis of isothiocyanate and unsymmetric thiourea

After the successful preparation of isothiocyanates and unsymmetrical thioureas in laboratory scale, the gram-scale preparation isothiocyanate was considered (**Scheme 3.15 , eq. 1**). 1.0 gram of 4-bromoaniline **1a** was subjected to our optimized condition providing isothiocyanate in 79% yield. Moreover, 1.0 gram of *p*-toluidine was converted into thiourea (**X**) in one-pot fashion via **1**) formation of dithiocarbamate with CS_2 **2**) desulfurization with CBr_4 and **3**) addition with p-anisidine to provide thiourea in 69% yield (**Scheme 3.15, eq. 2**).
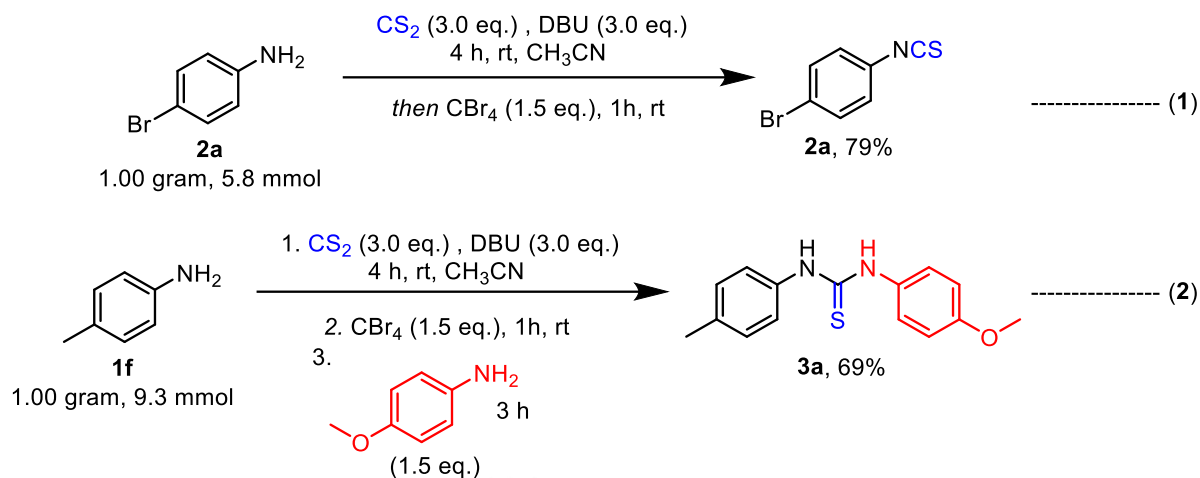
Scheme 3.15 Gram-scale synthesis

3.2.5 By-product detection by SEM/EDX

We hypothesized that the by-product of our reaction must contain sulfur which came from desulfurization reaction under the optimized condition as shown in **Scheme 3.16**. Therefore, we set the reaction and filtrate the solid precipitate. After filtration, it washed with acetonitrile and dried over high vacuum. The solid was exposed to characterize with scanning electron microscope (SEM) equipped with x-ray spectroscopy (EDX). The SEM/EDX results indicated that the particles contain with sulfur, carbon and bromine as a main element distributing in surface on particle (**Picture 3.2**). Importantly, the element distribution revealed that carbon and bromide elements bind together as they both are located in the same area while the sulfur atom displayed independently in another surface area. The result suggests that the formation of S_8 atom as the most stable form[71] as shown in **Picture 3.2**.
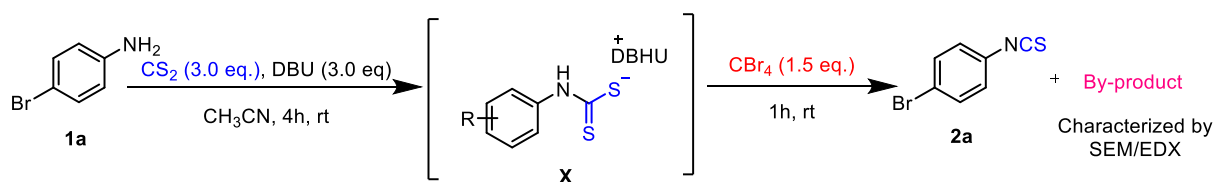
Scheme 3.16 By-product detection

By-product particle   Carbon   Bromine   Sulfur

SEM image   EDX image
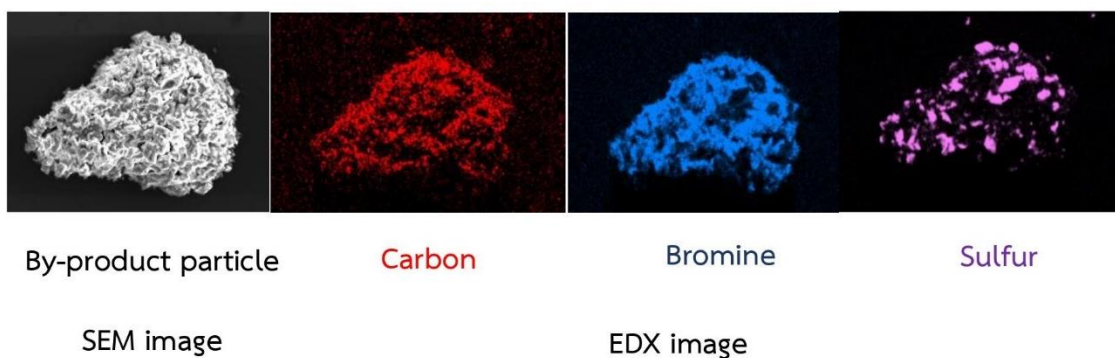
Picture 3.2 SEM-EDX results from by-product detection

    3.2.6 Proposed mechanism

    Based on the results from mechanistic study and reviews[56-58]. We proposed the reaction mechanism of our reaction as shown in **Scheme 3.17** . Initially, the amine reacted with carbon disulfide in presence of DBU to generate dithiocarbamate salt (**X**) intermediate which undergo nucleophilic attack to bromine atom of carbon tetrabromide leading to the formation of intermediate of sulfenyl bromide (**4'**). Then, sulfur atom that attached to bromine was eliminated to give isothiocyanate (**Scheme 3.17**). The by-product of this reaction is bromoform ($CHBr_3$) which was identified by NMR spectroscopy (singlet at δ = 6.82 ppm.) along with S_8 and DBU-Br salt were detected in SEM/EDX experiment.
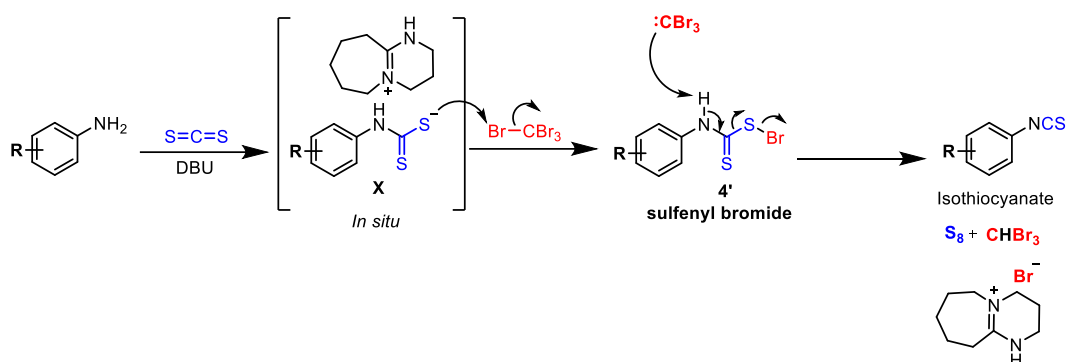
Scheme 3.17 Proposed mechanism

CHAPTER IV

CONCLUSION

In conclusion, we developed 2 methods including photocatalytic and stoichiometry desulfurization process of dithiocarbamate salt (**X**). For photocatalysis, we could prepare 4-bromophenyl isothiocyanate in 48% yield from 4-bromoaniline in the present of safranin O as photocatalyst as shown in **Scheme 4.1**. However, generality of this method was limited. Therefore, we decided to investigate this photocatalytic method in the near future. For stoichiometry desulfurization process, we successfully synthesize isothiocyanate derivatives by using CBr_4 as a mediator. Under optimize condition, a various amine carrying halogen atom, electron donating, electron withdrawing group, heterocyclic, aliphatic, phenolic and protecting group are able to tolerate under our optimize condition. In addition, isothiocyanate derivatives were obtained in moderate to excellent yield for 32 examples. Moreover, we also prepare unsymmetrical thiourea from the generating of isothiocyanate *in situ* which are able to react with aliphatic and aromatic amine in moderate to excellent yield for 9 examples as shown in **Scheme 4.1**. Gram-scale synthesis of isothiocyanates and unsymmetric thioureas are accomplished under optimize condition in good yield. Based on mechanistic study including NMR monitoring and SEM/EDX, we proposed the mechanism involving **1**) the nucleophilic attack dithiocarbamate salt (**X**) to bromine atom of carbon tetrabromide **2**) the formation of intermediate of sulfenyl bromide intermediate **3**) desulfurization process. Importantly, our condition offers several advantages such as the use of low toxic reagent, easy procedure in open-air condition, one-pot fashion and gram scalability.
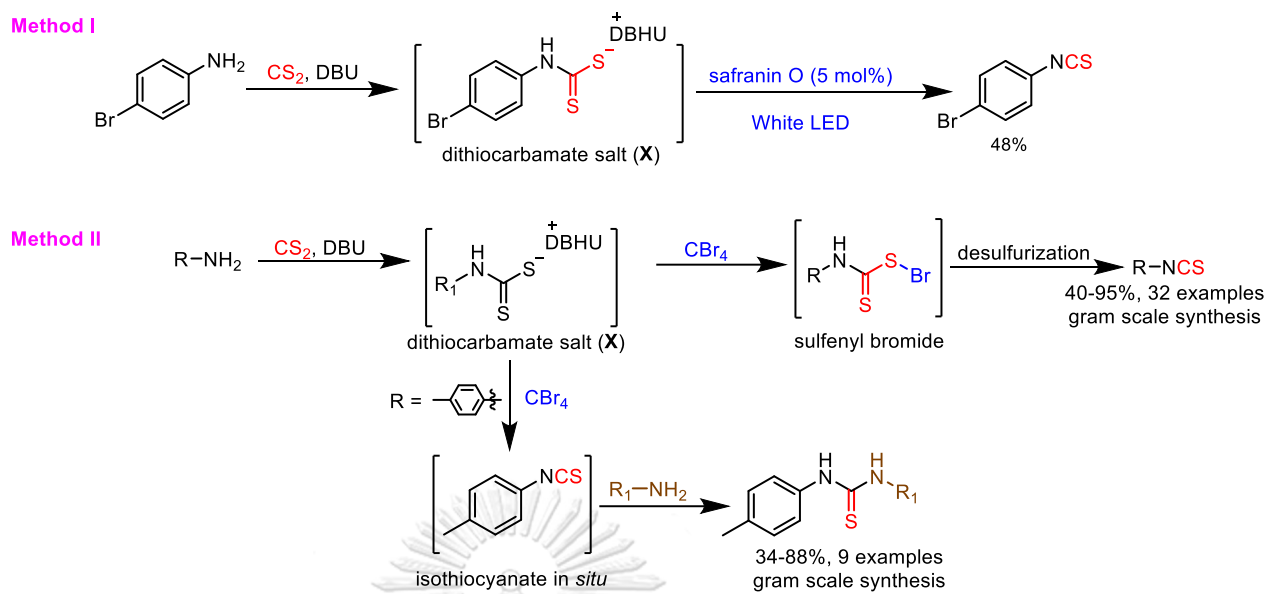
Scheme 4.1 Synthesis of isothiocyanate using **1**) photocatalyst **2**) CBr$_4$ mediator

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APPENDIX
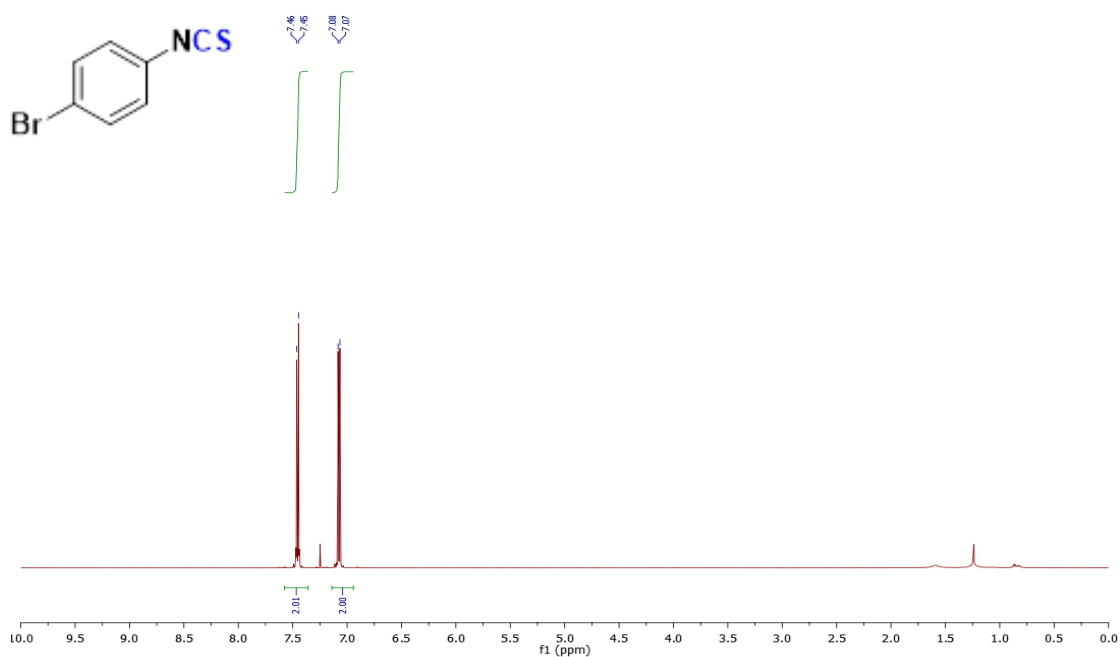
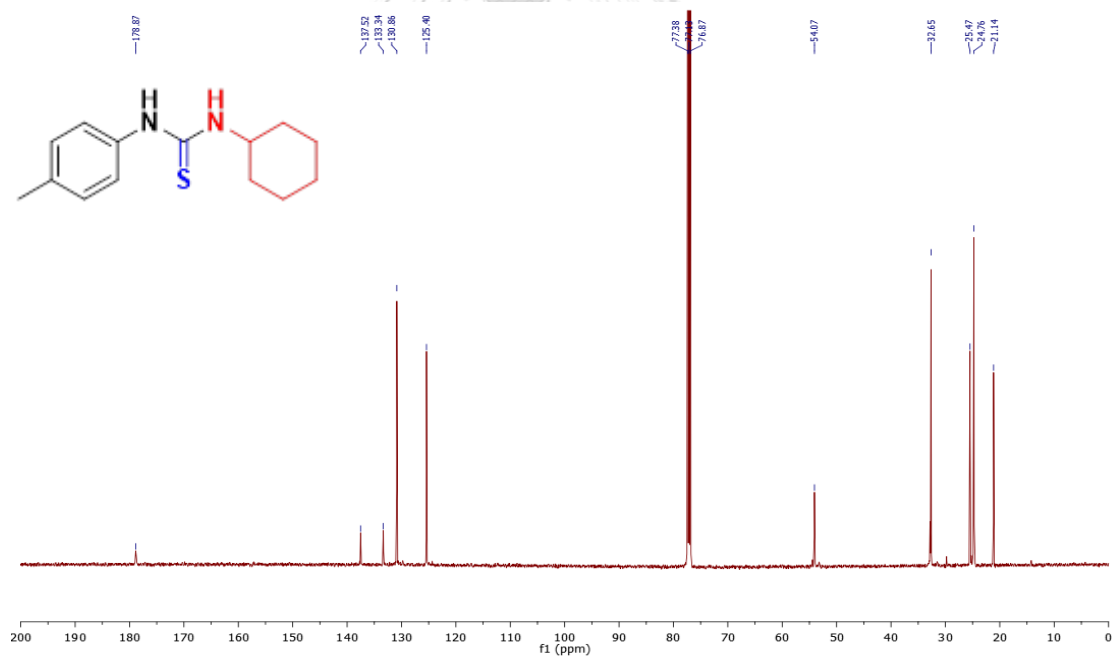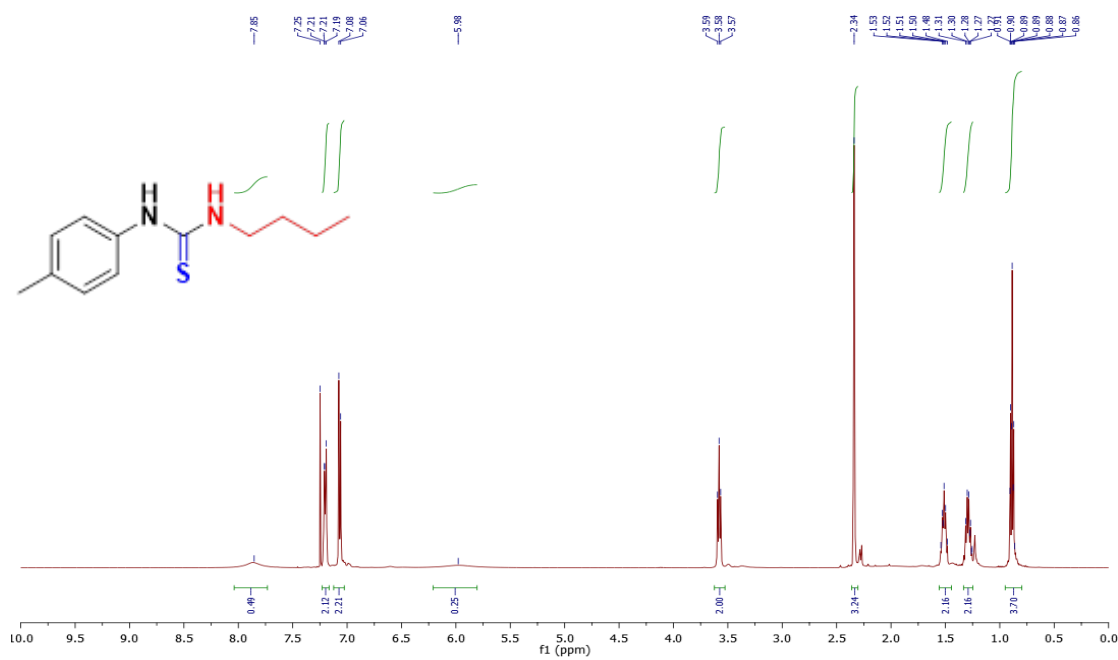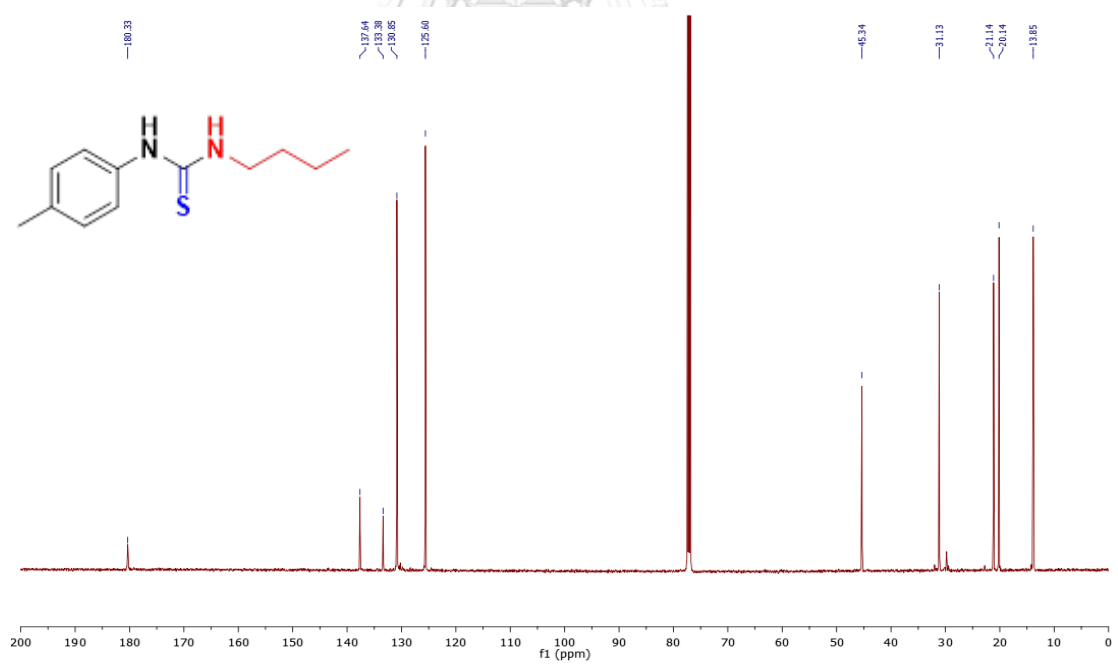**Figure A1** ^{1}H-NMR spectrum of **2a** (CDCl$_3$, 500 MHz)
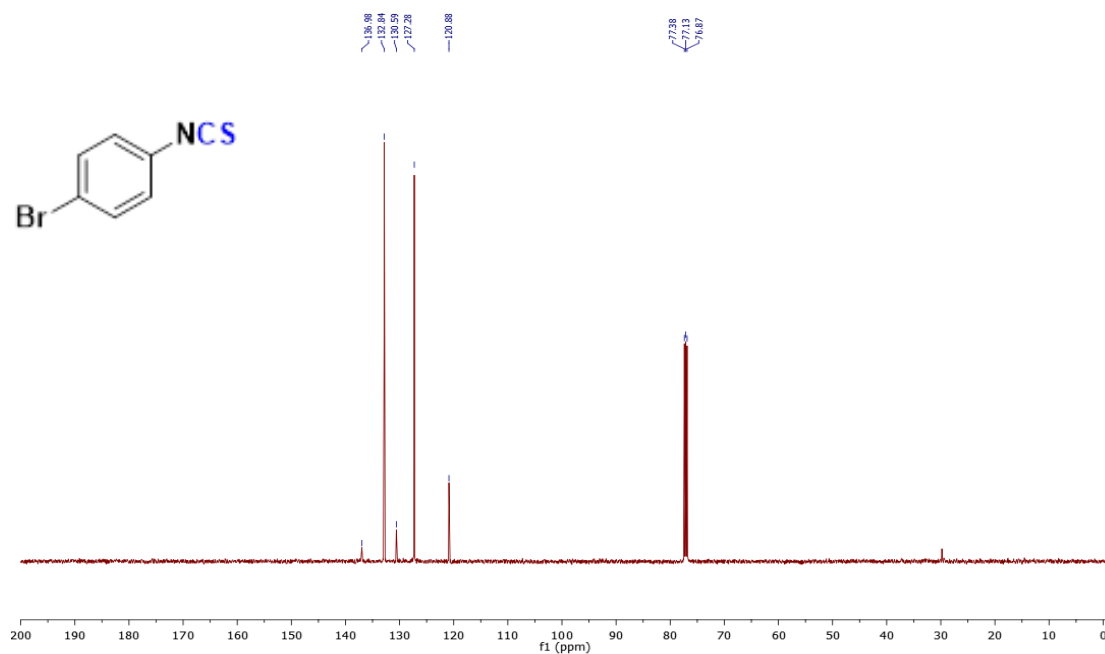
Figure A2 ^{13}C-NMR spectrum of **2a** (CDCl$_3$, 125 MHz)
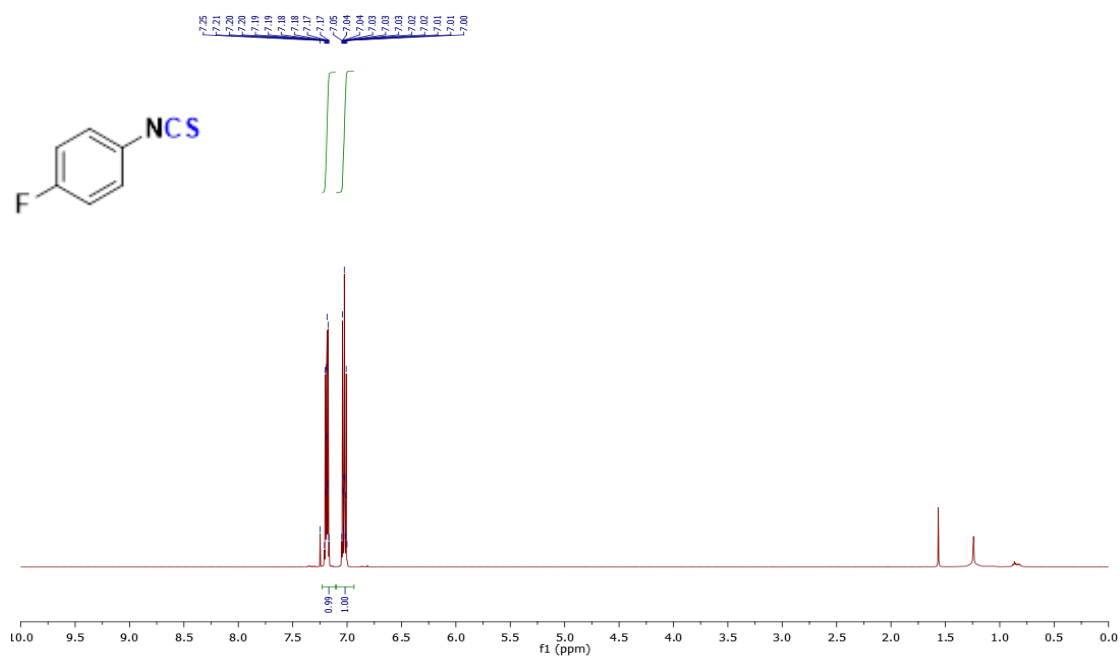
Figure A3 ¹H-NMR spectrum of **2b** (CDCl₃, 500 MHz)
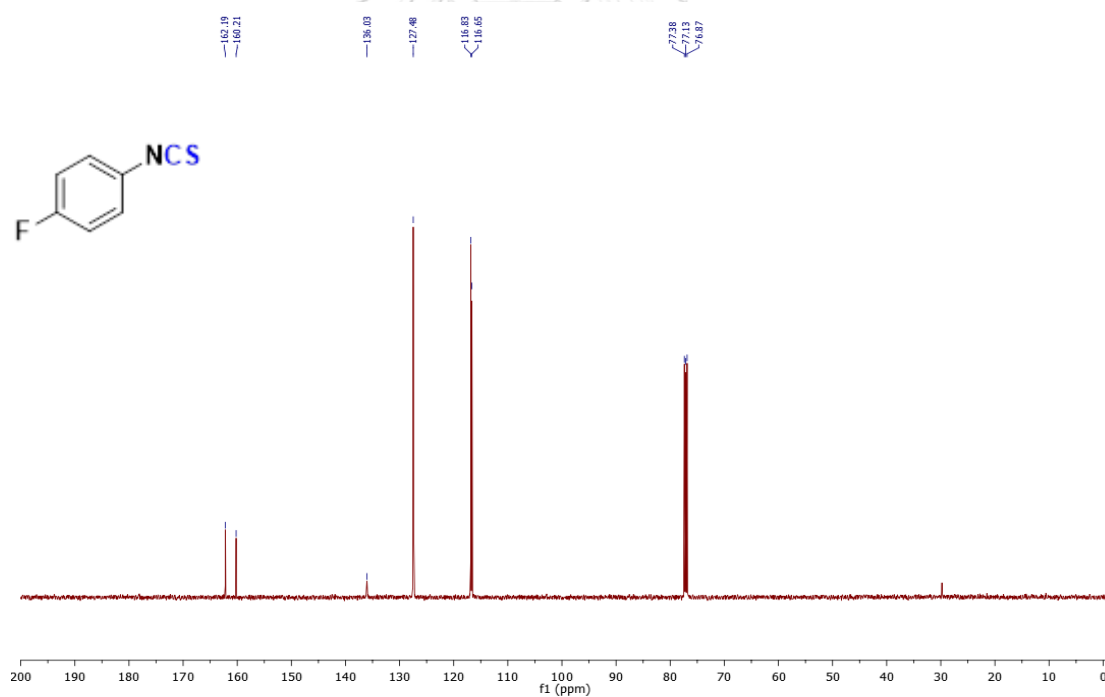

Figure A4 ¹³C-NMR spectrum of **2b** (CDCl₃, 125 MHz)
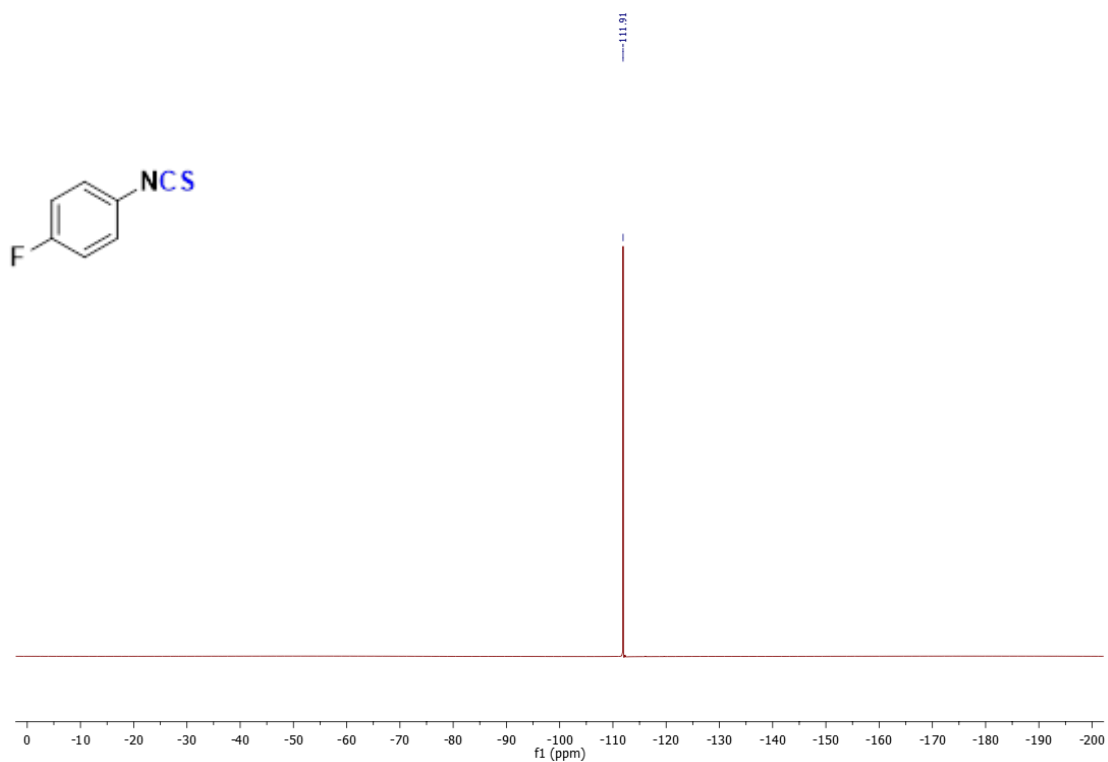
Figure A5 ^{19}F-NMR spectrum of **2b** (CDCl$_3$, 470 MHz)
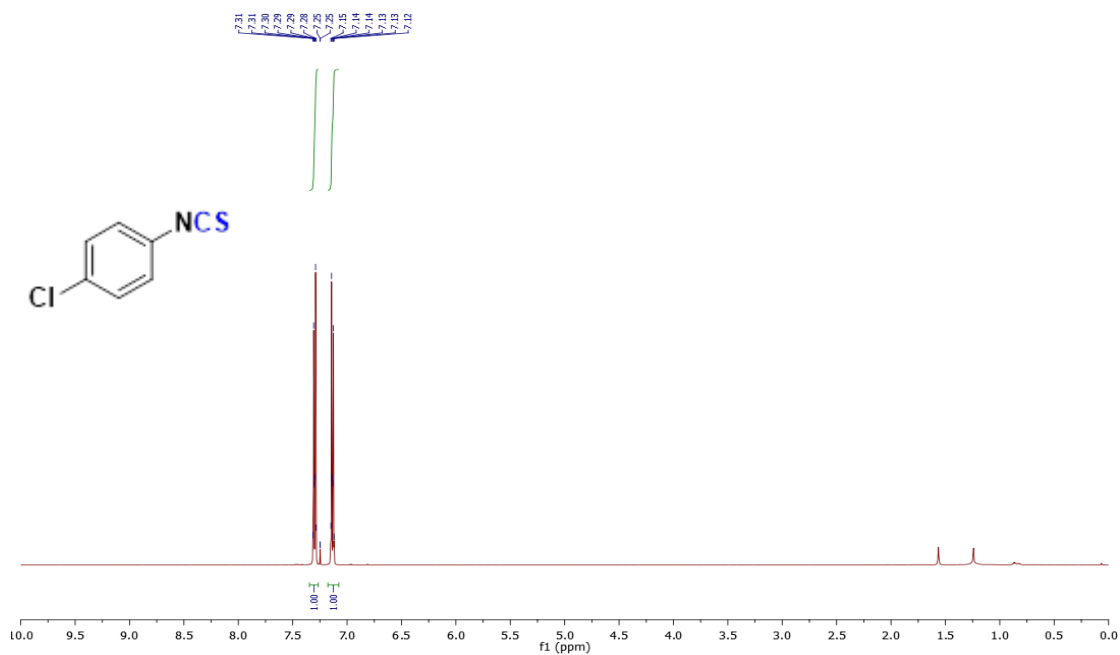
Figure A6 ^{1}H-NMR spectrum of **2c** (CDCl$_3$, 500 MHz)
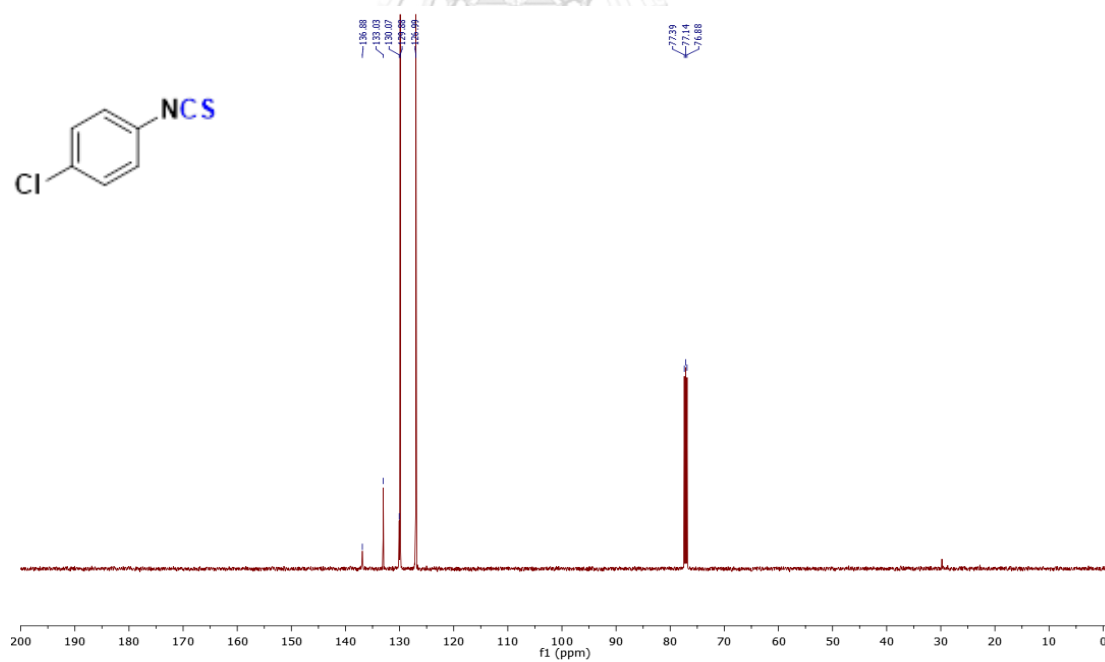
Figure A7 ^{13}C-NMR spectrum of **2c** (CDCl$_3$, 125 MHz)
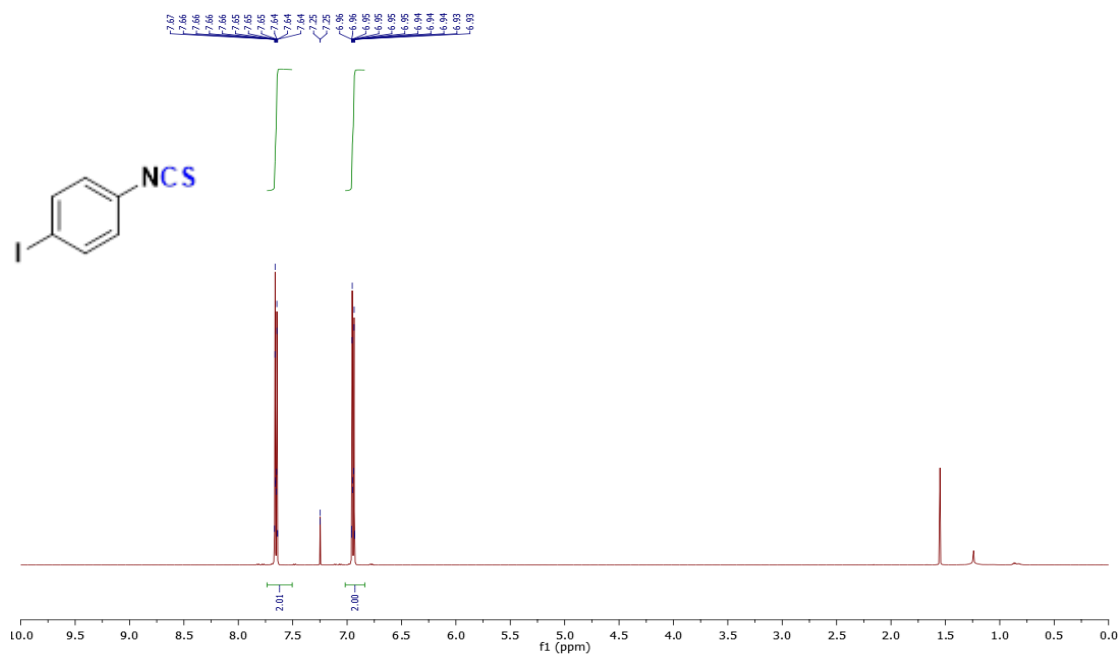
Figure A8 ^{1}H-NMR spectrum of **2d** (CDCl$_3$, 500 MHz)
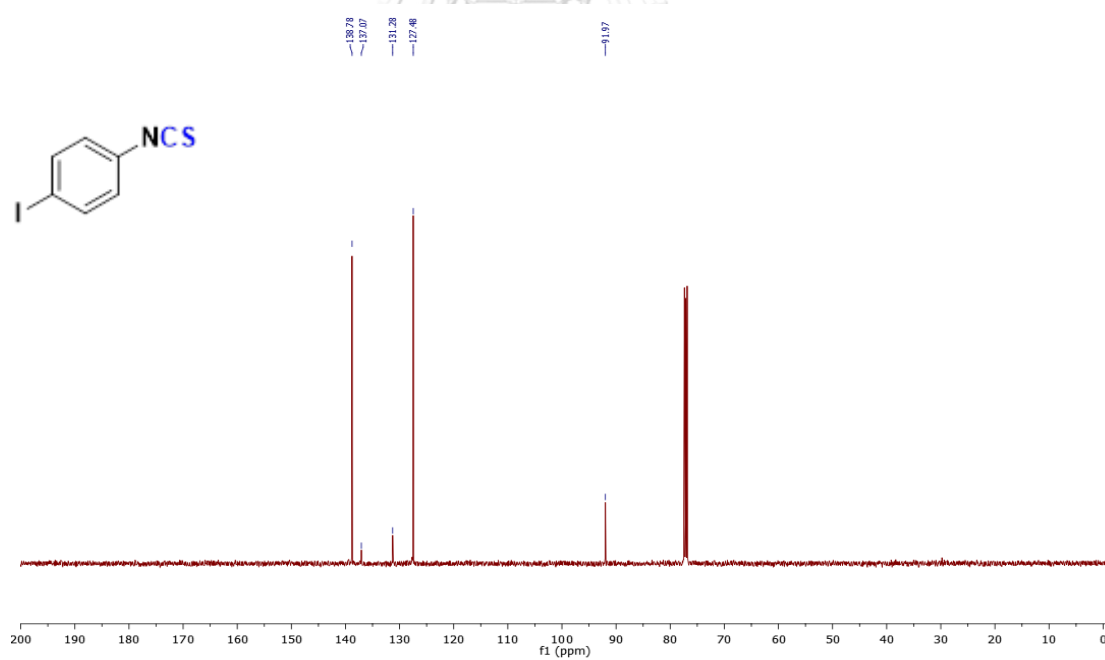
Figure A9 ^{13}C-NMR spectrum of **2d** (CDCl$_3$, 125 MHz)
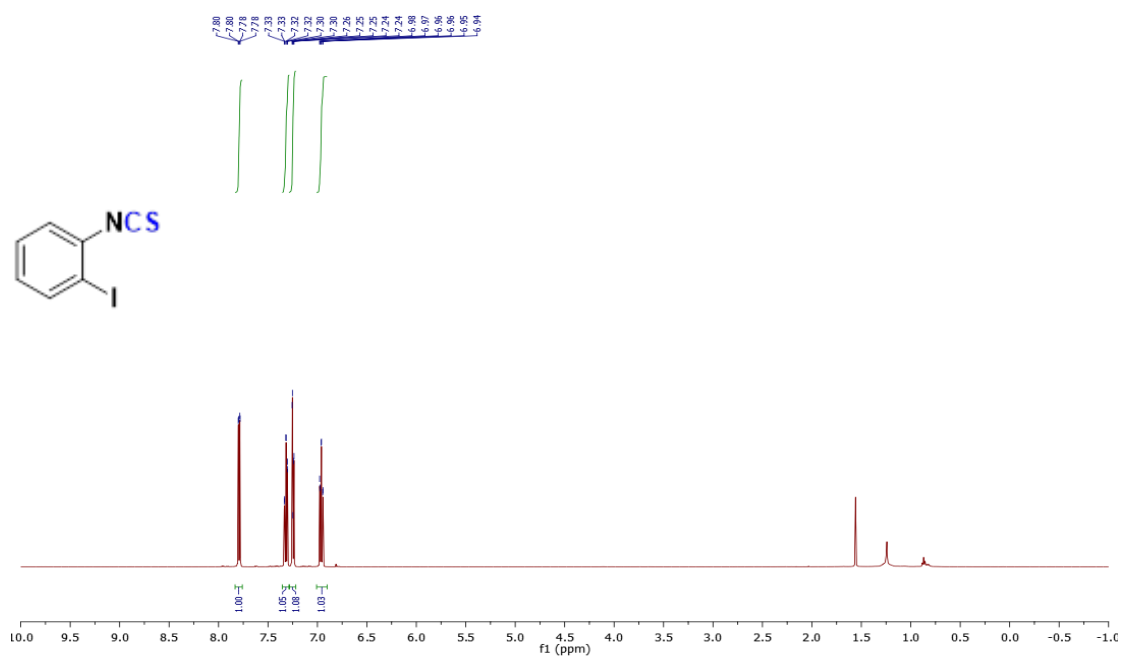
Figure A10 ^{1}H-NMR spectrum of 2e (CDCl$_3$, 500 MHz)
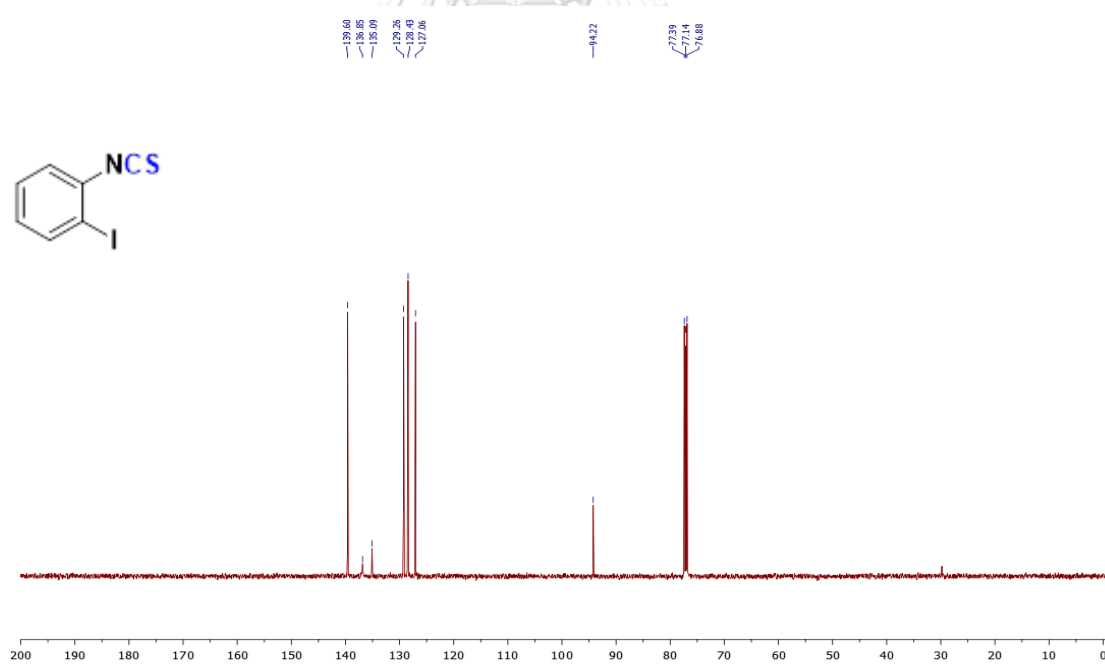
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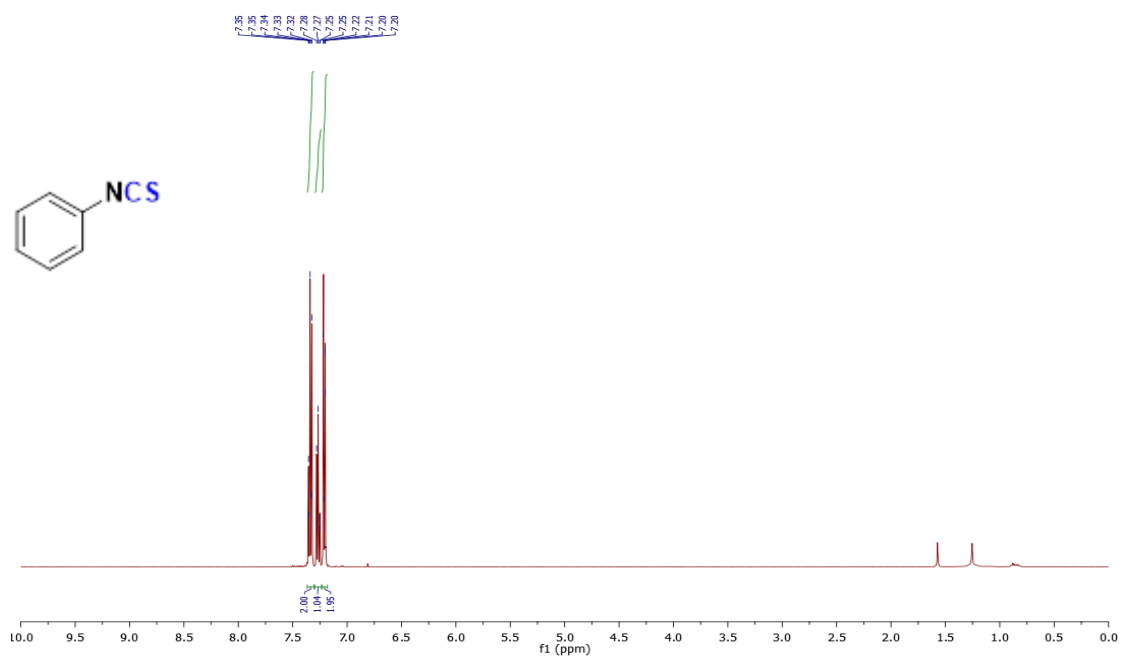
Figure A12 ^{1}H-NMR spectrum of **2f** (CDCl$_3$, 500 MHz)
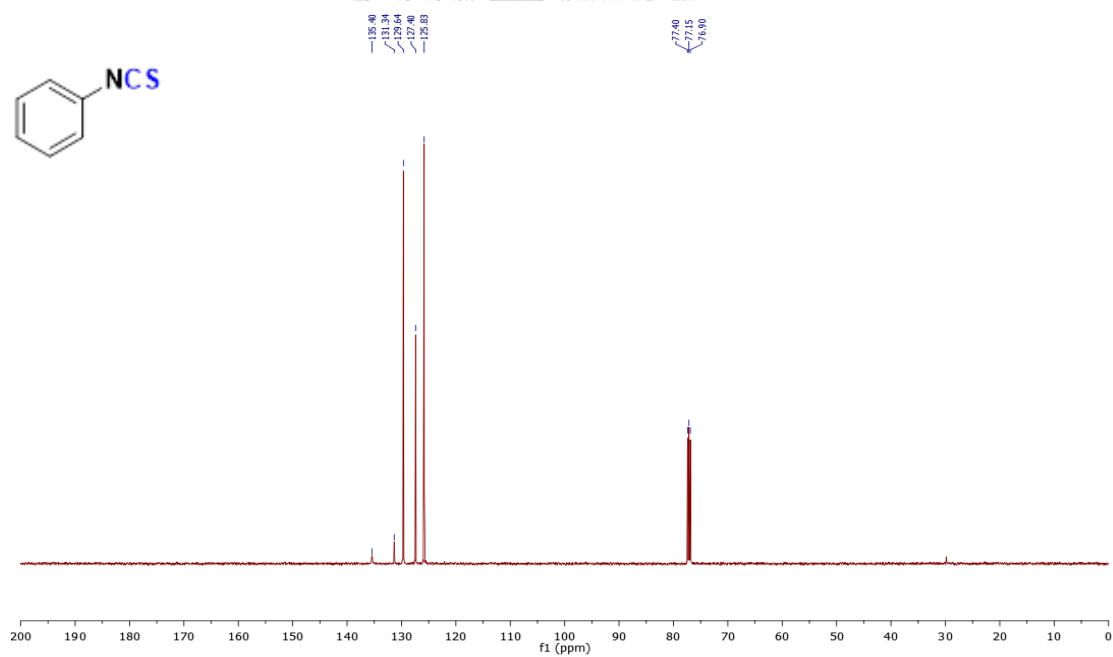
Figure A13 ^{13}C-NMR spectrum of **2f** (CDCl$_3$, 125 MHz)
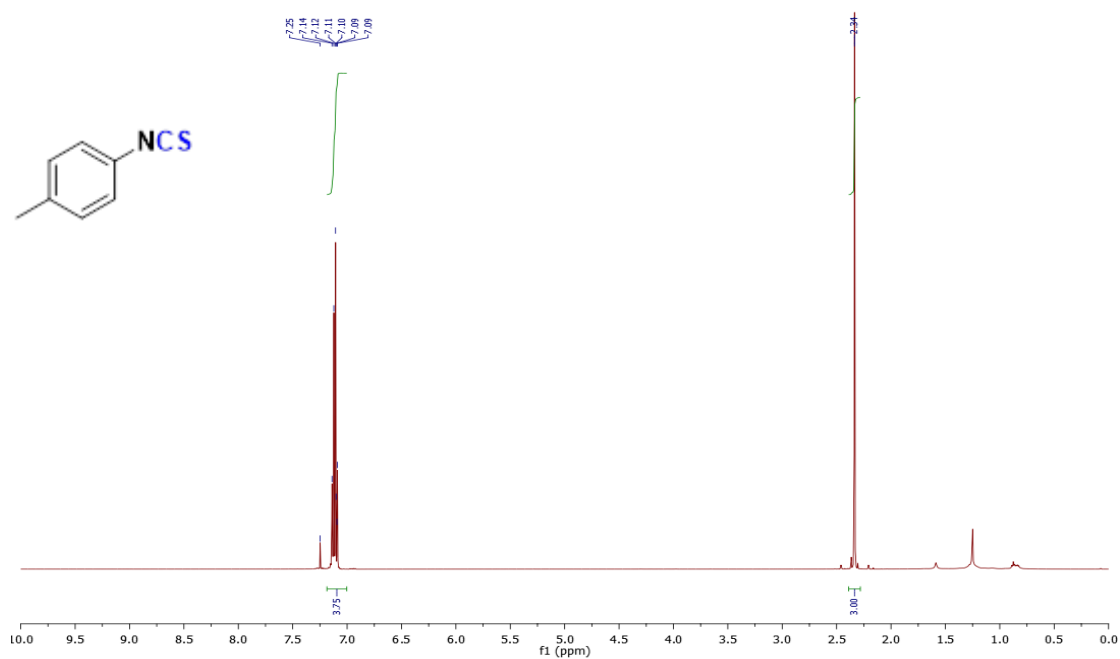
Figure A14 ^{1}H-NMR spectrum of **2g** (CDCl$_3$, 500 MHz)
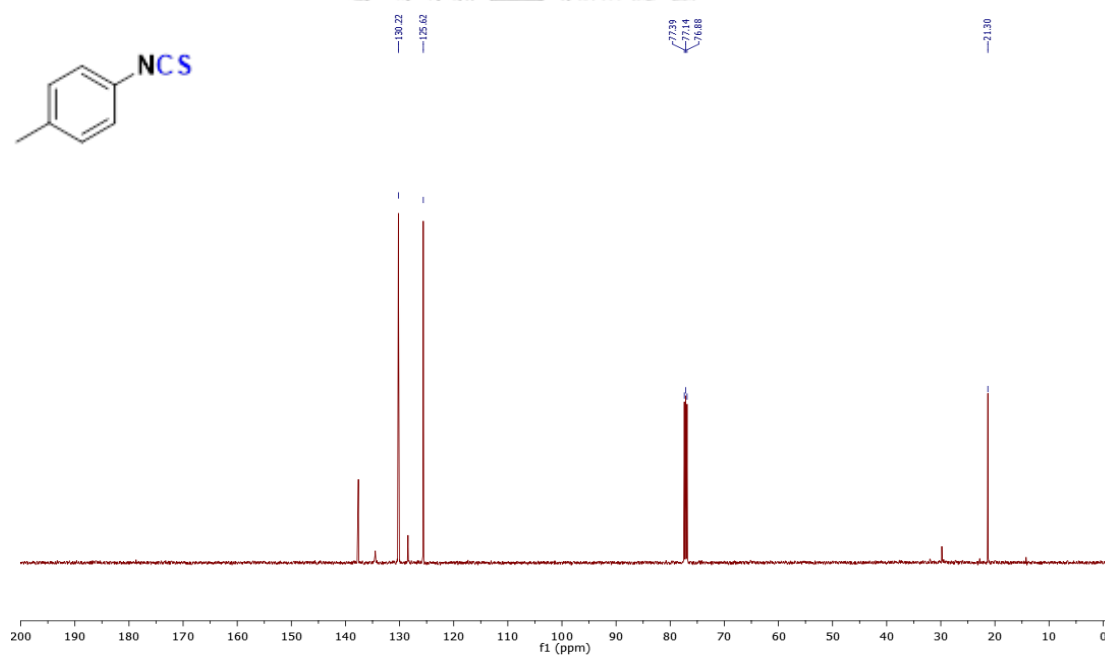
Figure A15 ^{13}C-NMR spectrum of **2g** (CDCl$_3$, 125 MHz)
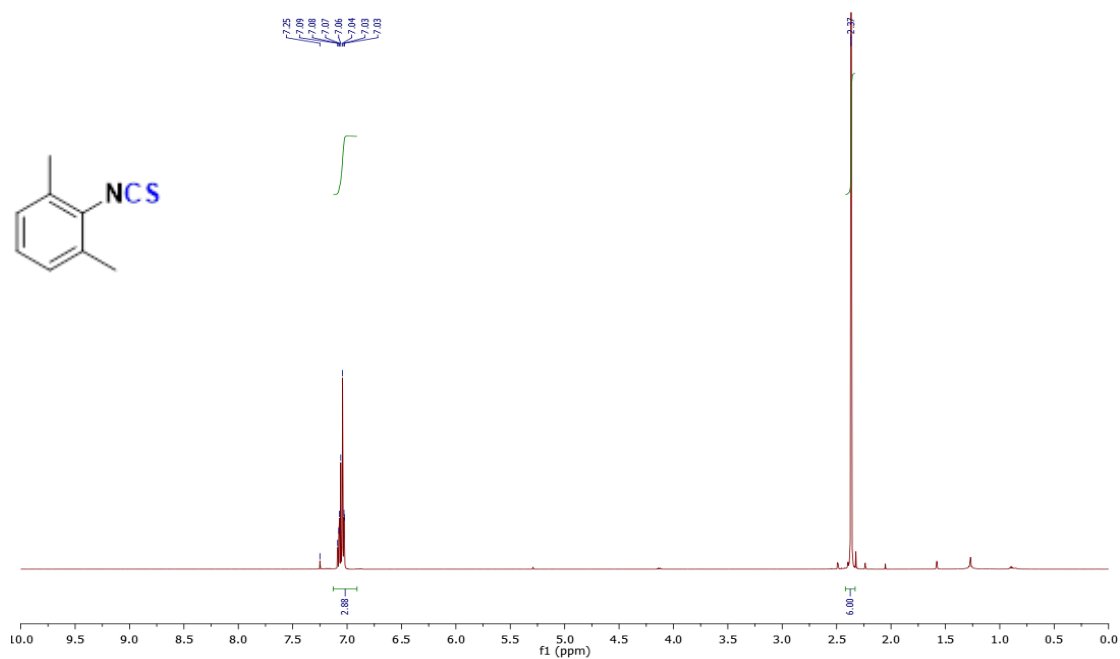
Figure A16 ^{1}H-NMR spectrum of **2h** (CDCl$_3$, 500 MHz)
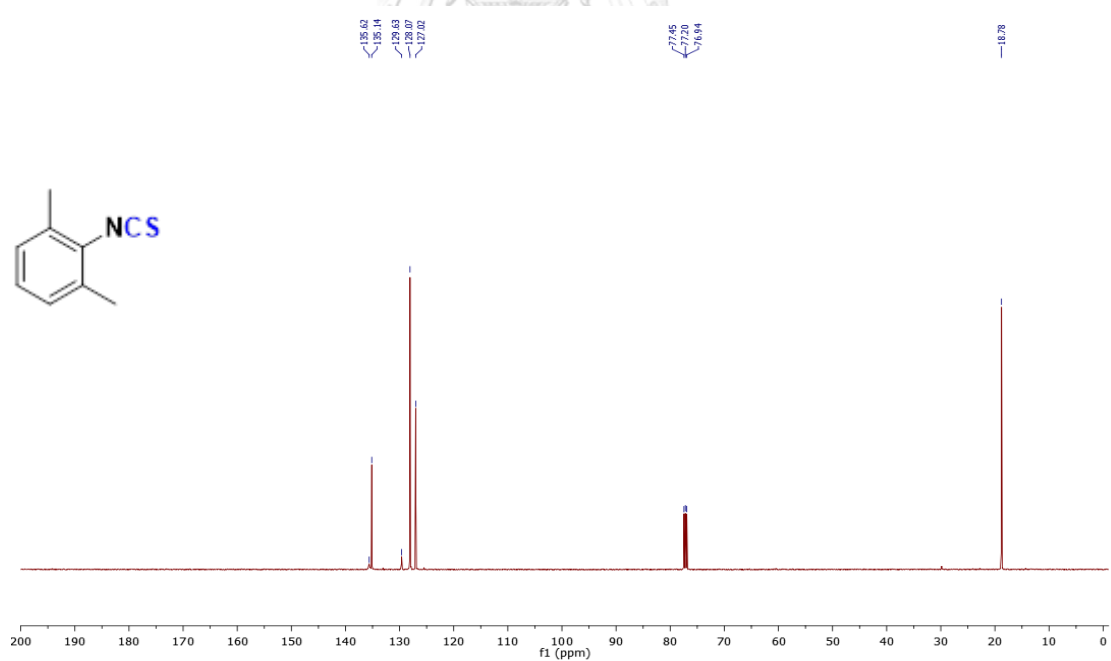
Figure A17 ^{13}C-NMR spectrum of **2h** (CDCl$_3$, 125 MHz)
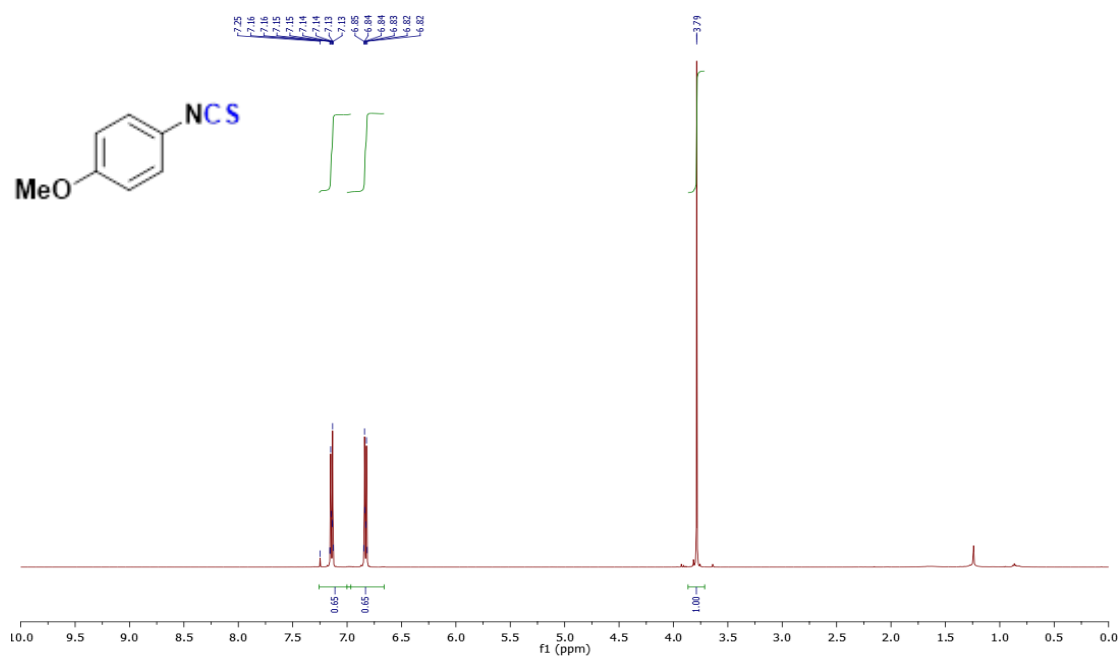
Figure A18 ^{1}H-NMR spectrum of **2i** (CDCl$_3$, 500 MHz)
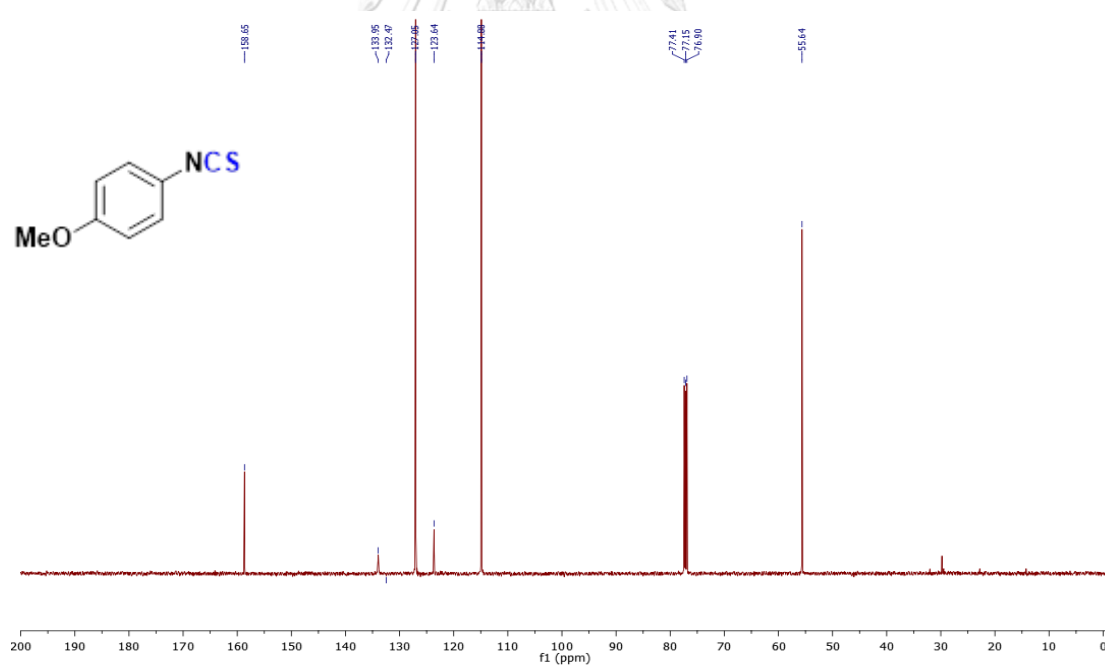
Figure A19 ^{13}C-NMR spectrum of **2i** (CDCl$_3$, 125 MHz)
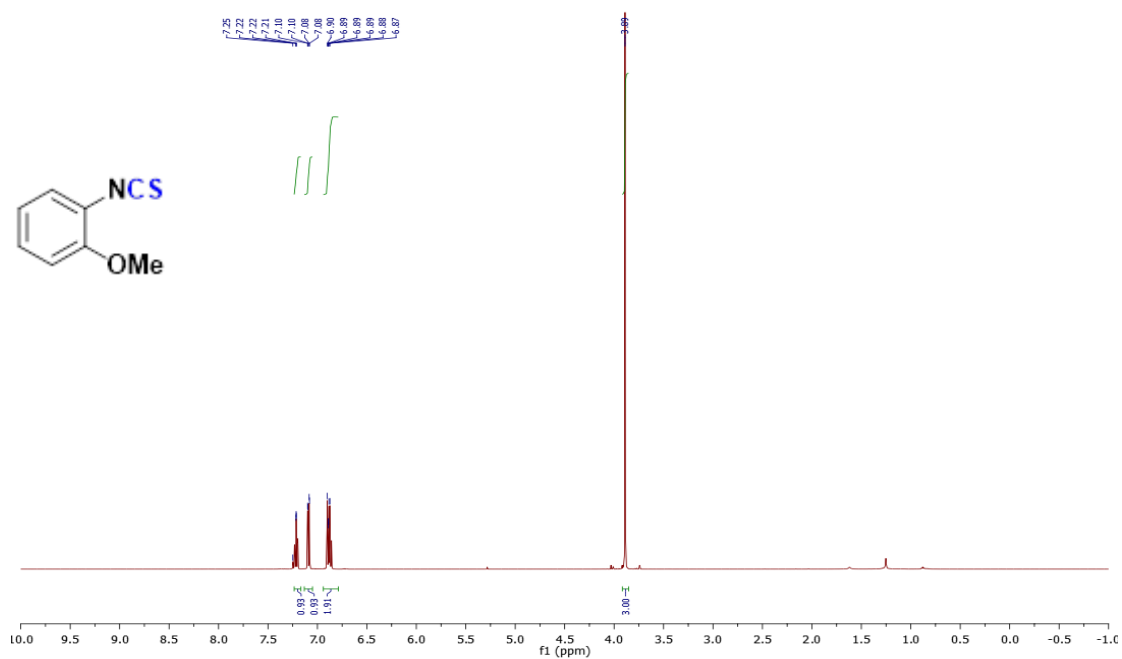
Figure A20 ^{1}H-NMR spectrum of **2j** (CDCl$_3$, 500 MHz)
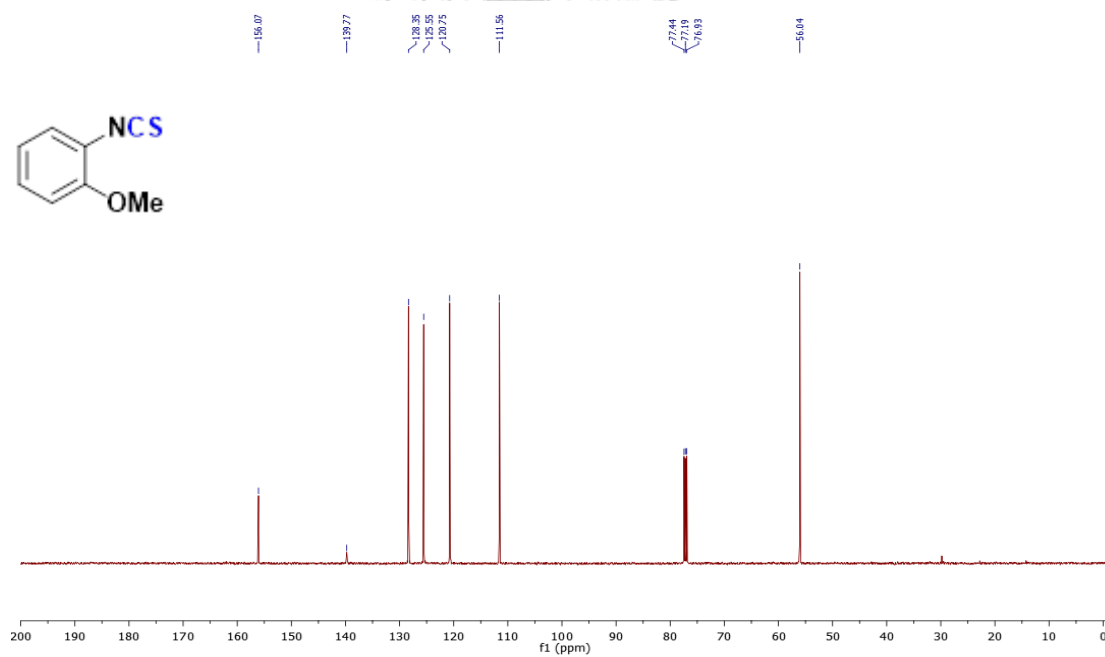
Figure A21 ^{13}C-NMR spectrum of **2j** (CDCl$_3$, 125 MHz)
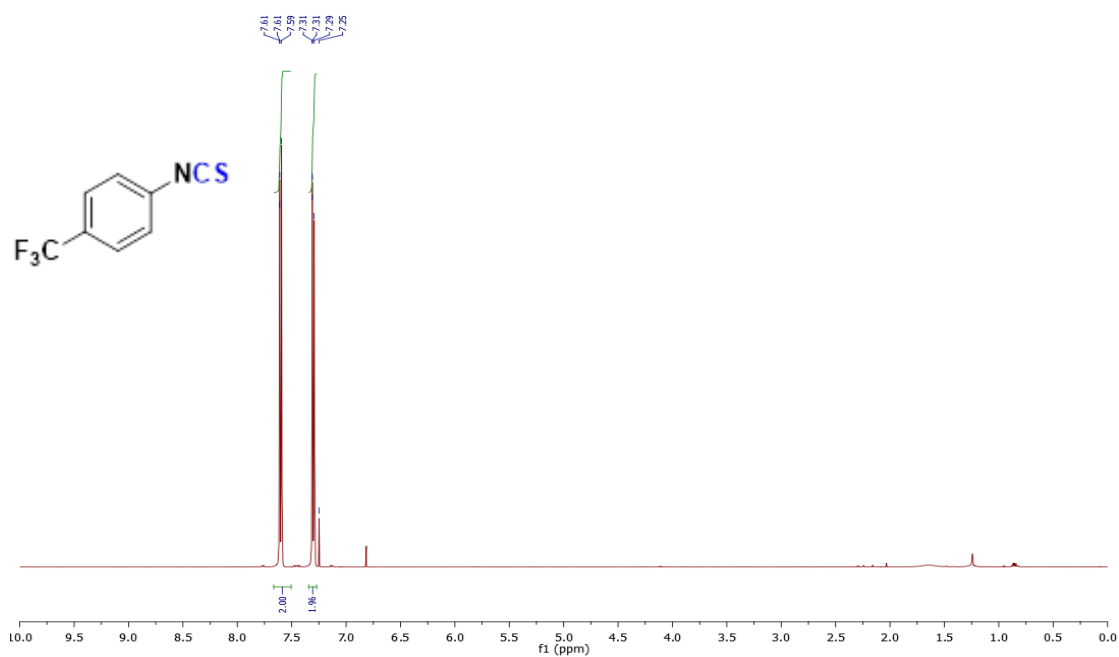
Figure A22 ^{1}H-NMR spectrum of **2k** (CDCl$_3$, 500 MHz)
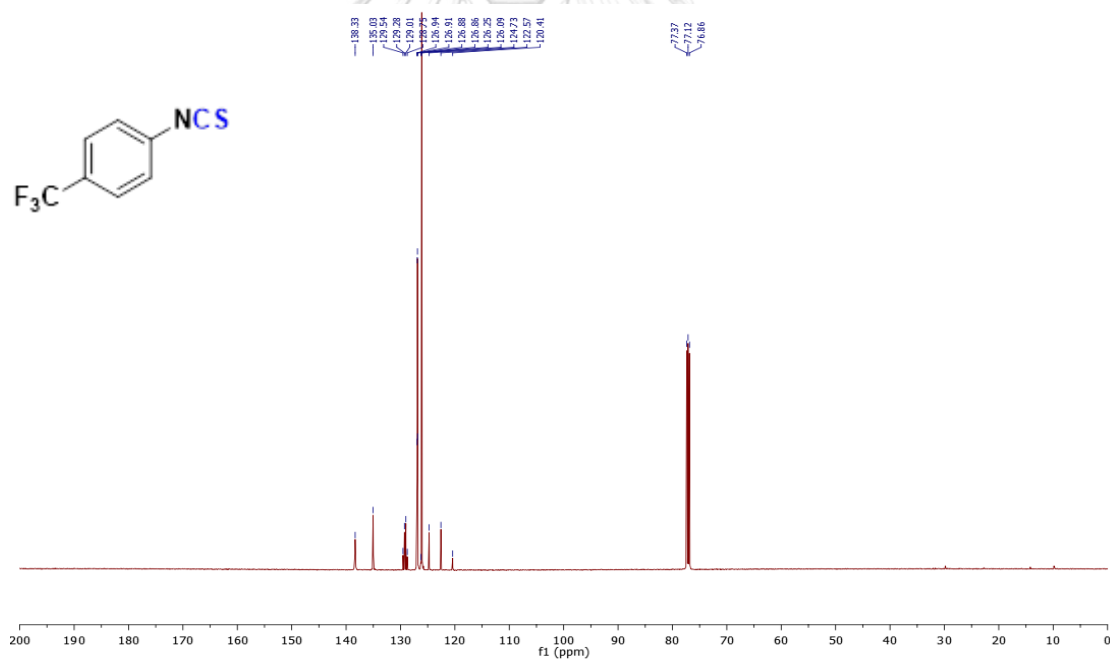
Figure A23 ^{13}C-NMR spectrum of **2k** (CDCl$_3$, 125 MHz)
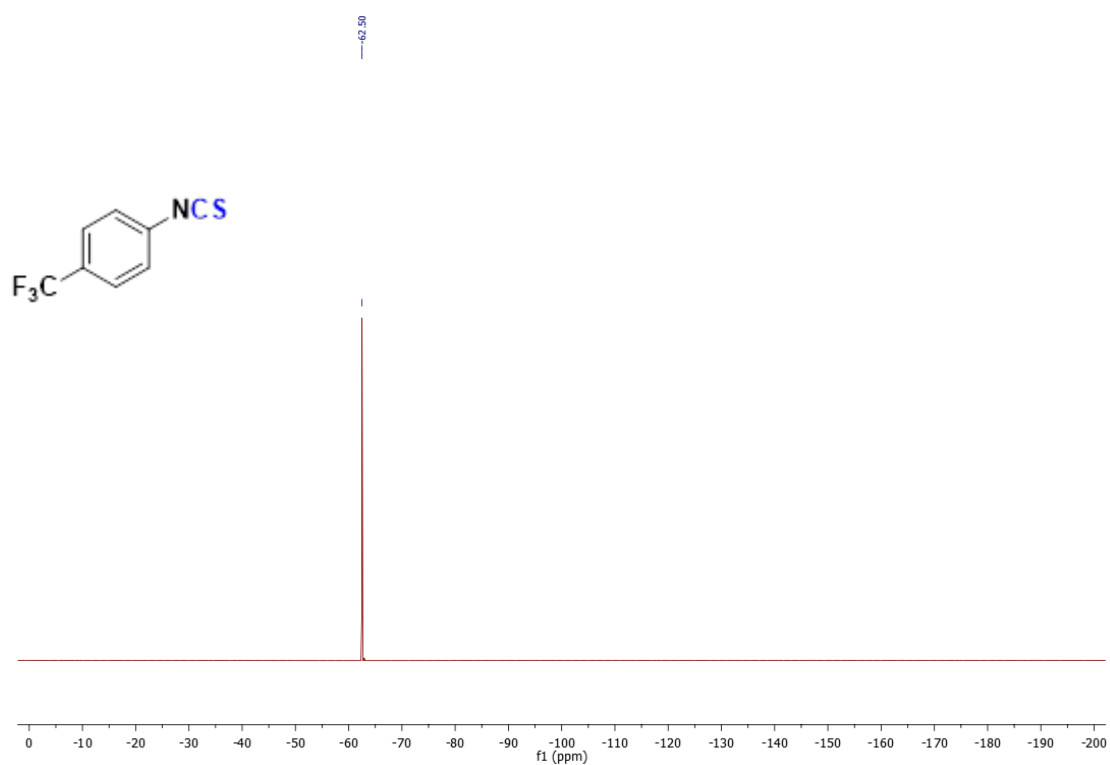
Figure A24 ^{19}F-NMR spectrum of **2k** (CDCl$_3$, 470 MHz)
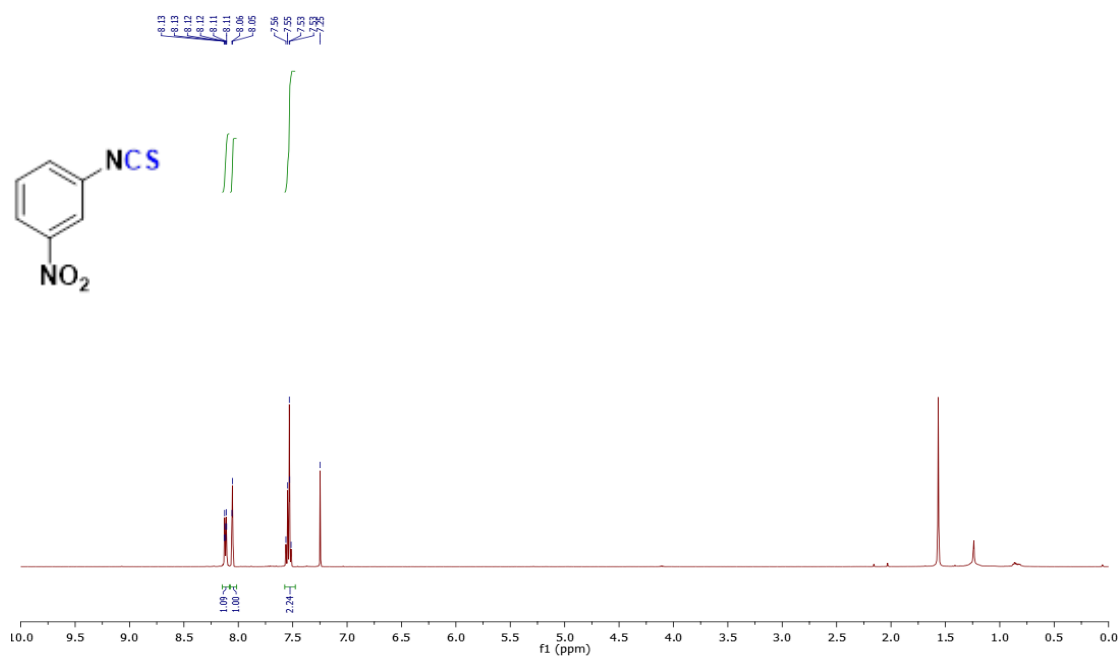
Figure A25 ^{1}H-NMR spectrum of **2l** (CDCl$_3$, 500 MHz)
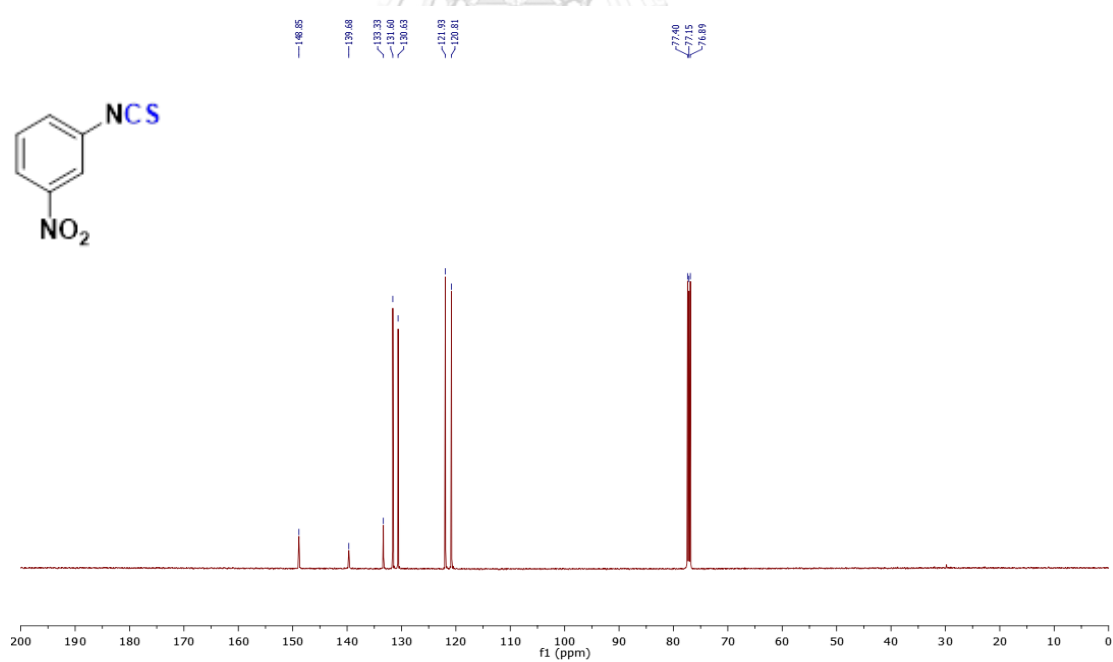
Figure A26 ^{13}C-NMR spectrum of **2l** (CDCl$_3$, 125 MHz)
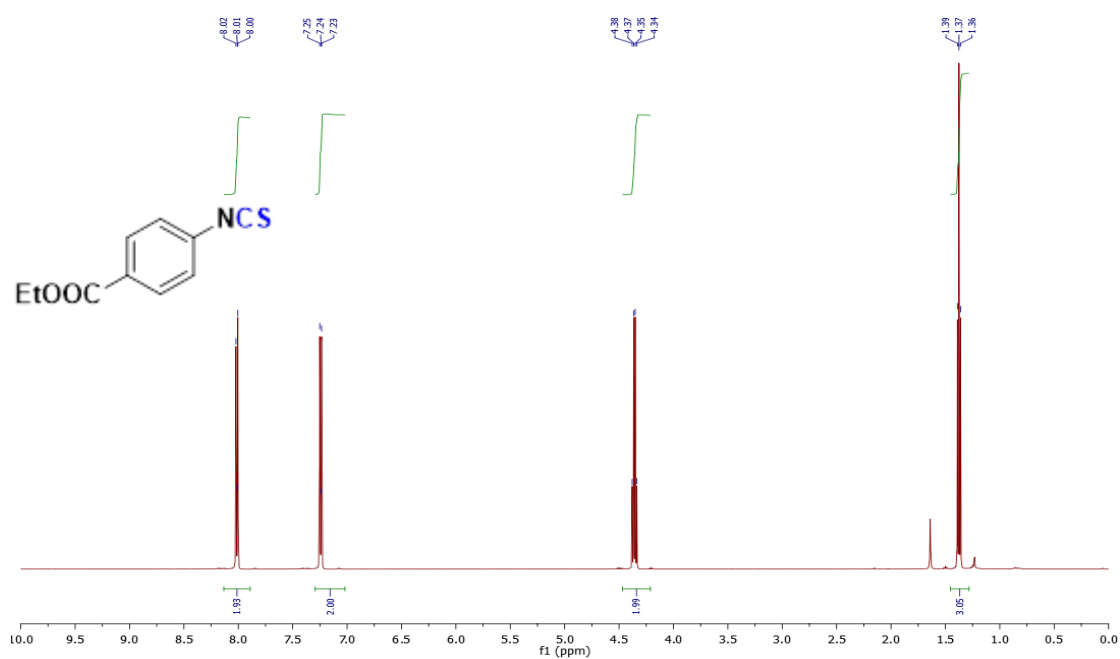
Figure A27 ^{1}H-NMR spectrum of **2m** (CDCl$_3$, 500 MHz)
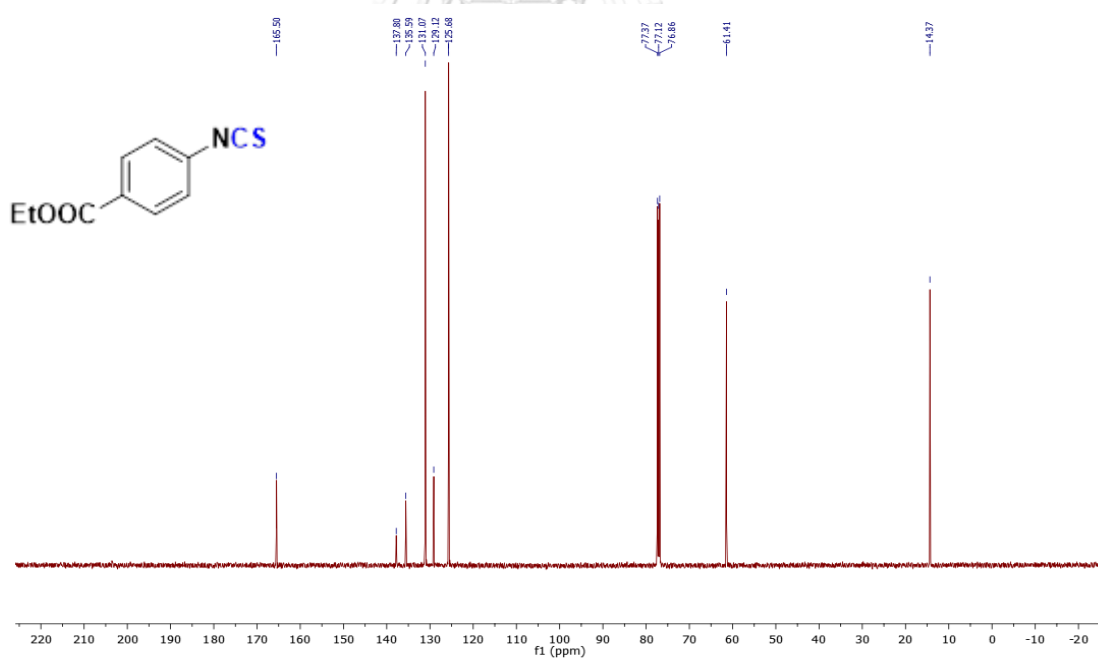
Figure A28 ^{13}C-NMR spectrum of **2m** (CDCl$_3$, 125 MHz)
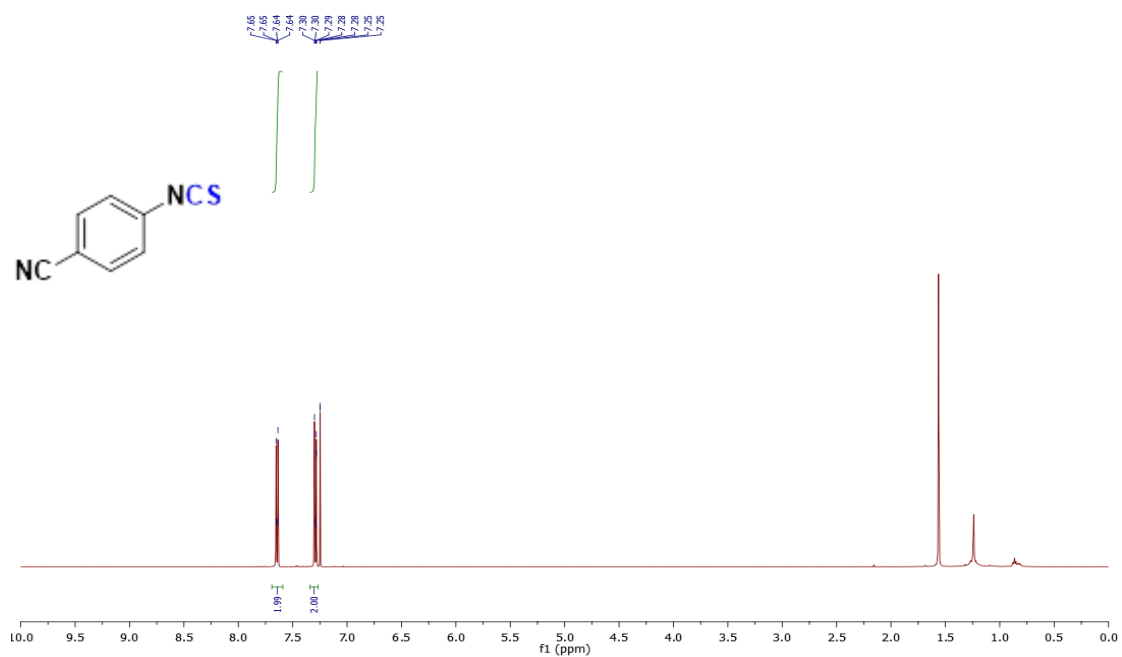
Figure A29 ^{1}H-NMR spectrum of **2n** (CDCl$_3$, 500 MHz)
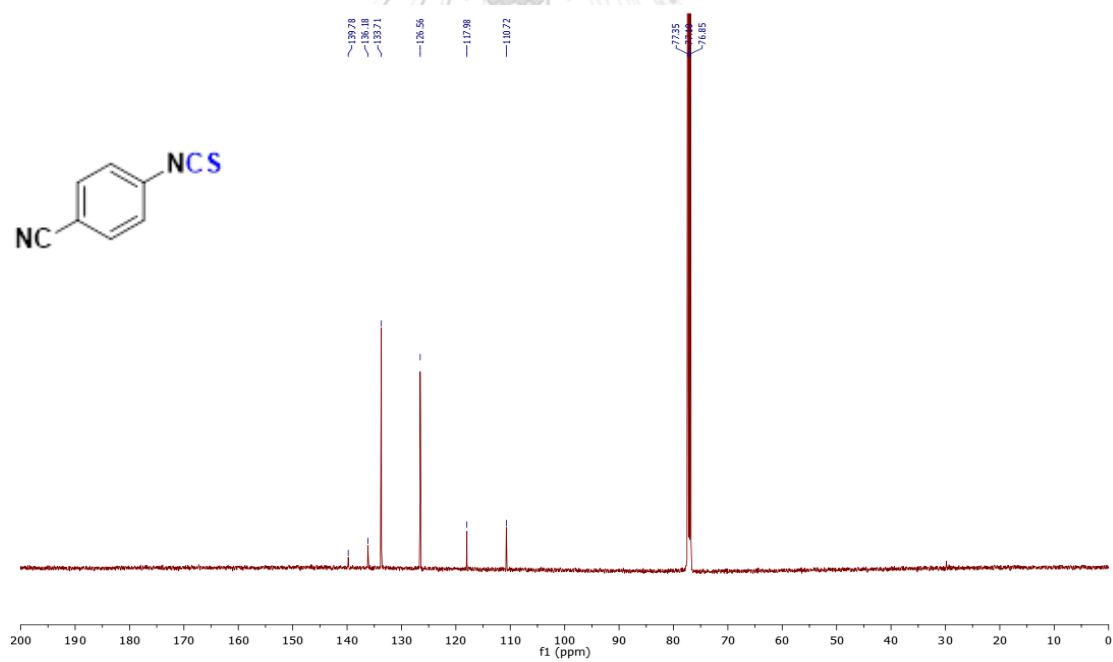
Figure A30 ^{13}C-NMR spectrum of **2n** (CDCl$_3$, 125 MHz)
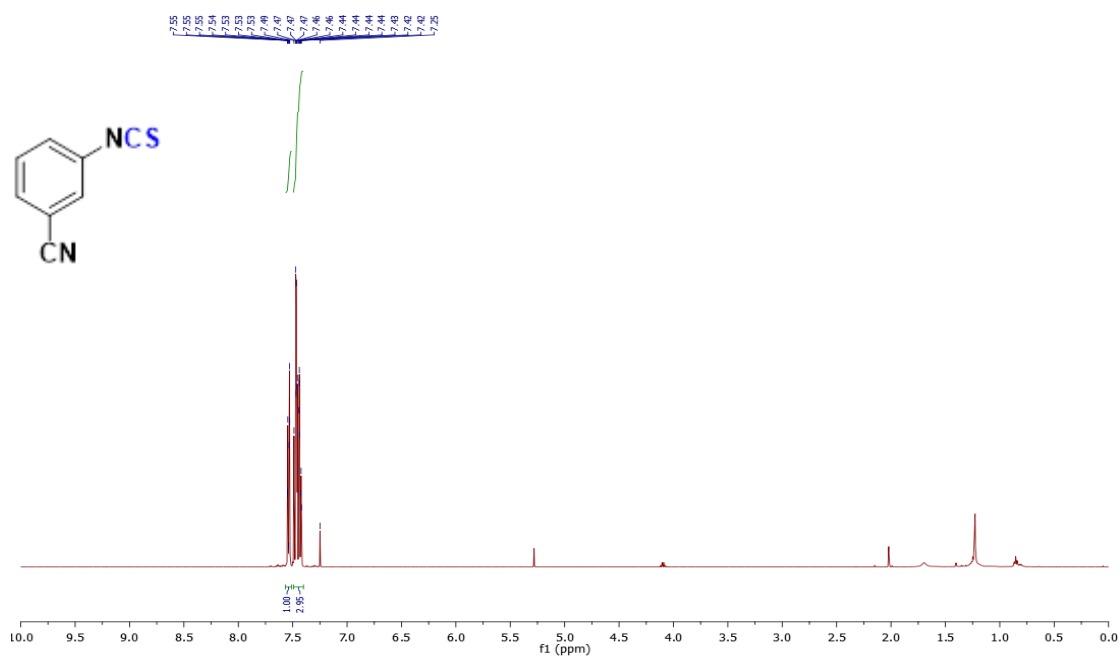
Figure A31 ^{1}H-NMR spectrum of **2o** (CDCl$_3$, 500 MHz)
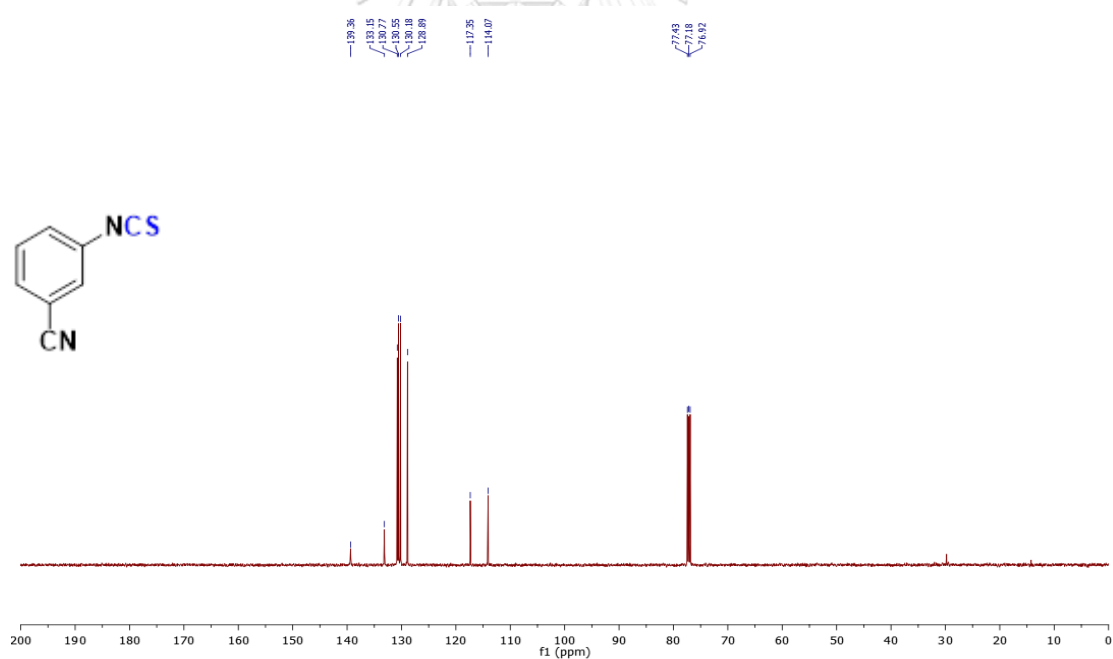
Figure A32 ^{13}C-NMR spectrum of **2o** (CDCl$_3$, 125 MHz)
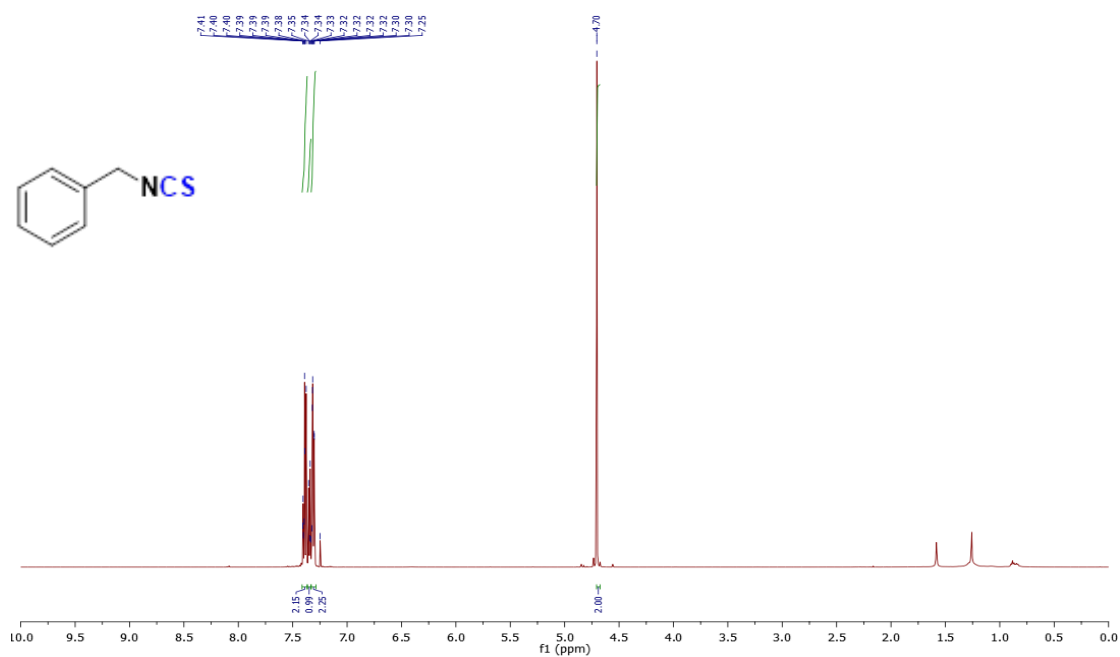
Figure A33 ^{1}H-NMR spectrum of 2p (CDCl$_3$, 500 MHz)
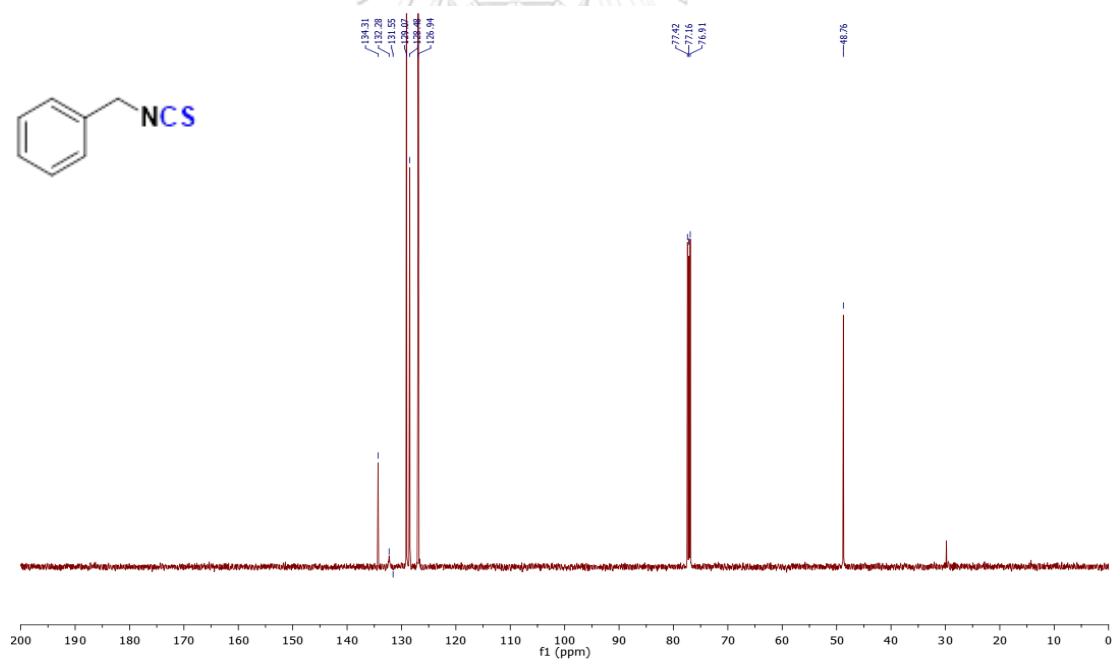
Figure A34 ^{13}C-NMR spectrum of 2p (CDCl$_3$, 125 MHz)
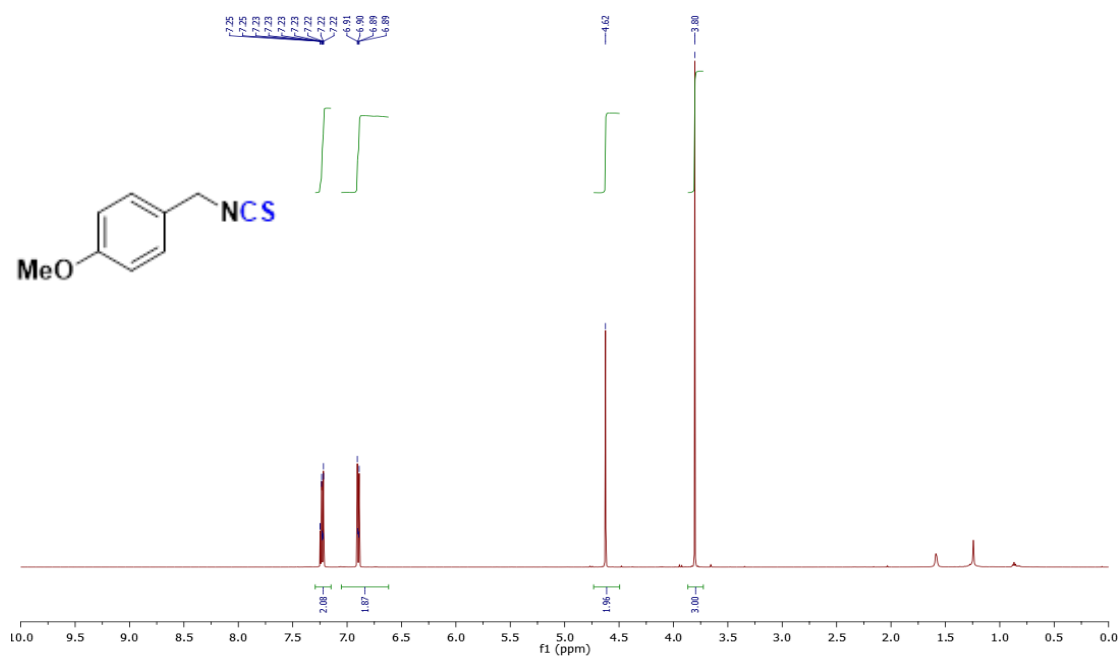
Figure A35 ^{1}H-NMR spectrum of **2q** (CDCl$_3$, 500 MHz)
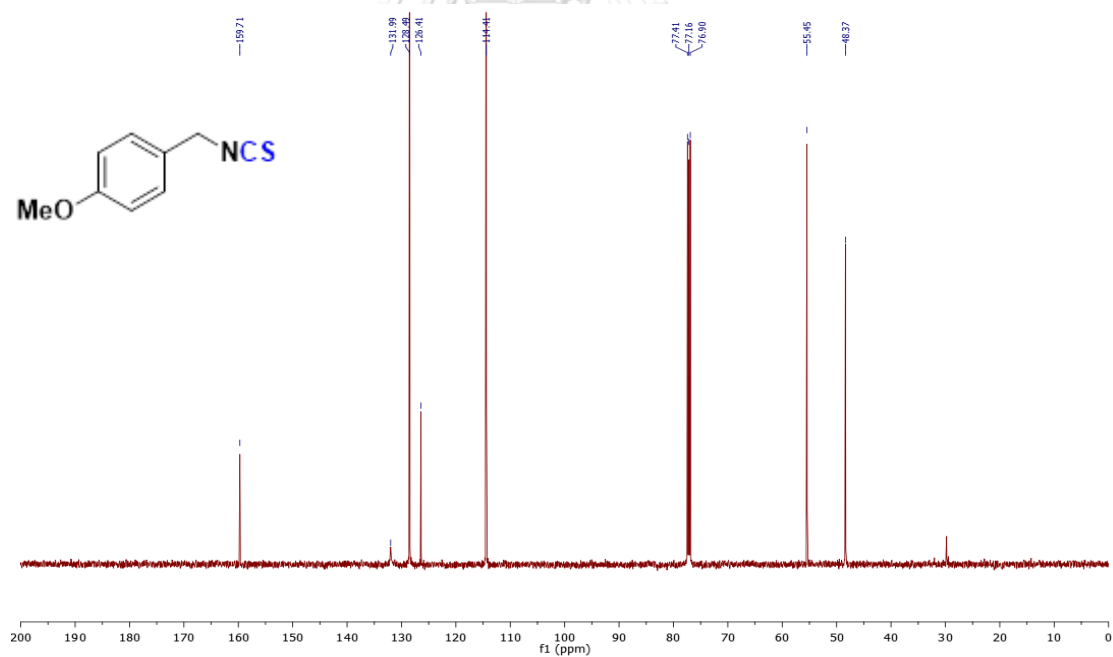
Figure A36 ^{13}C-NMR spectrum of **2q** (CDCl$_3$, 125 MHz)
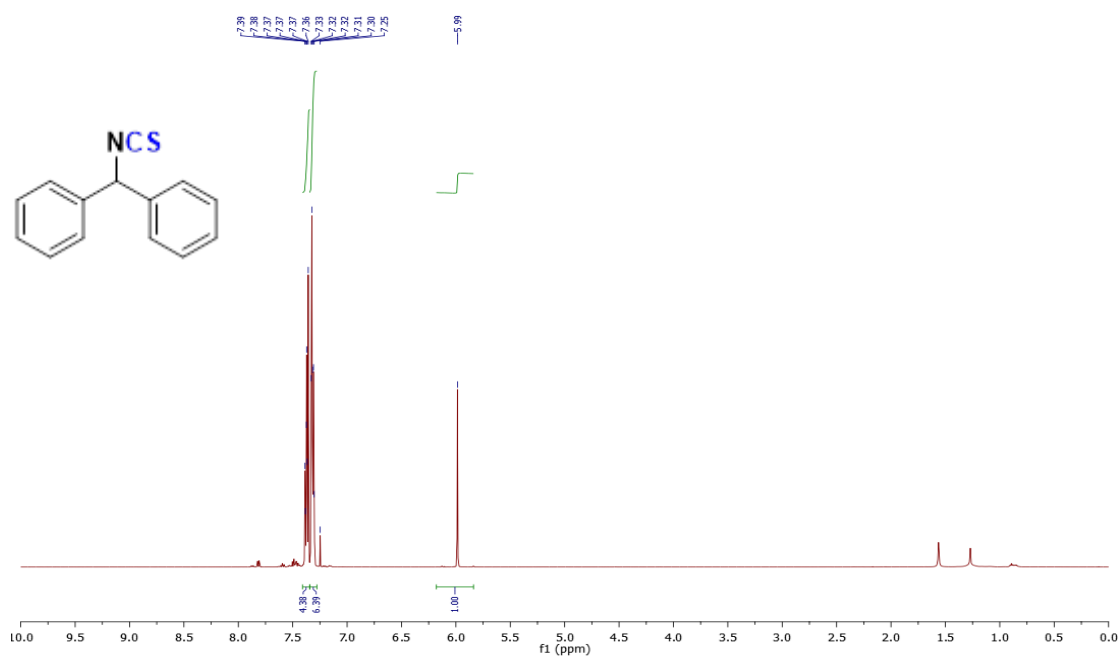
Figure A37 ^{1}H-NMR spectrum of **2r** (CDCl$_3$, 500 MHz)
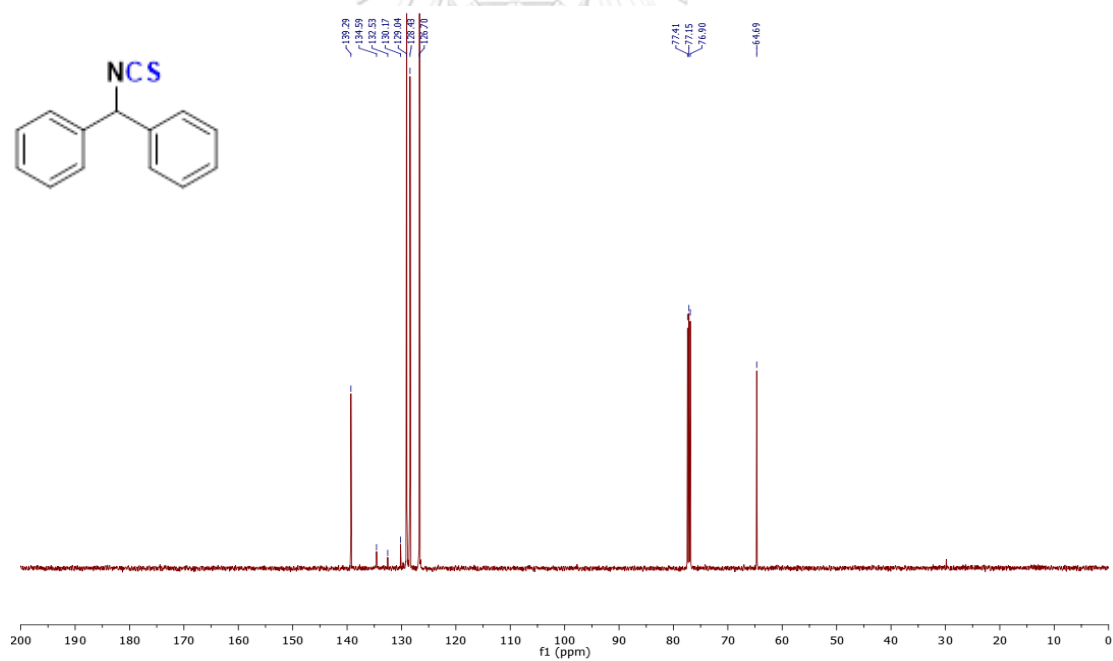
Figure A38 ^{13}C-NMR spectrum of **2r** (CDCl$_3$, 125 MHz)
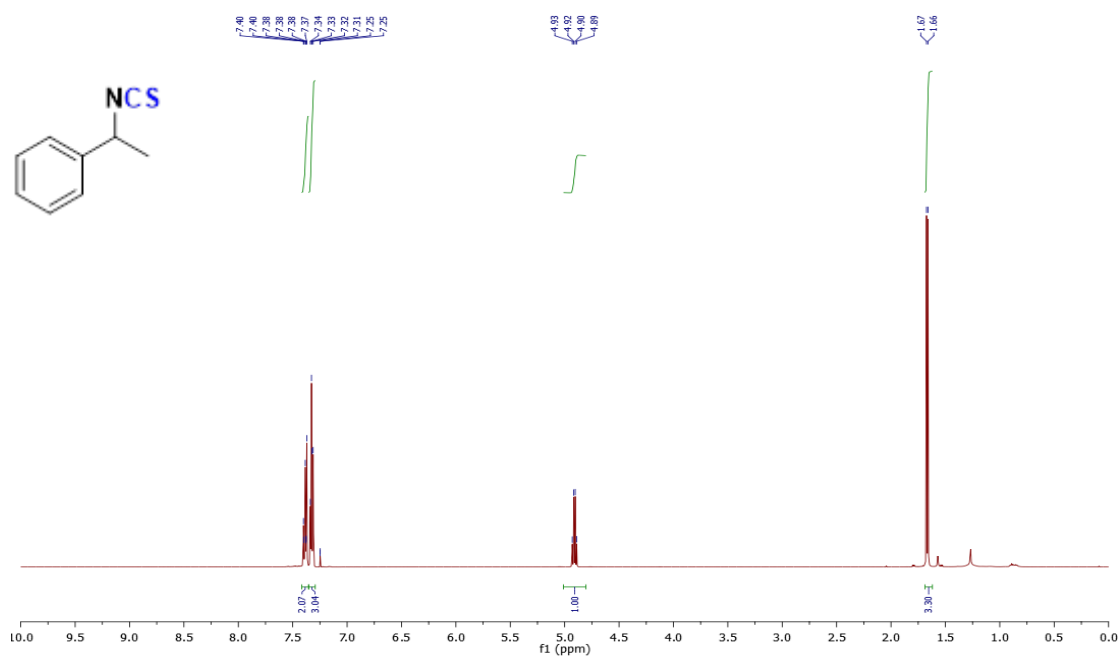
Figure A39 ¹H-NMR spectrum of **2s** (CDCl₃, 500 MHz)
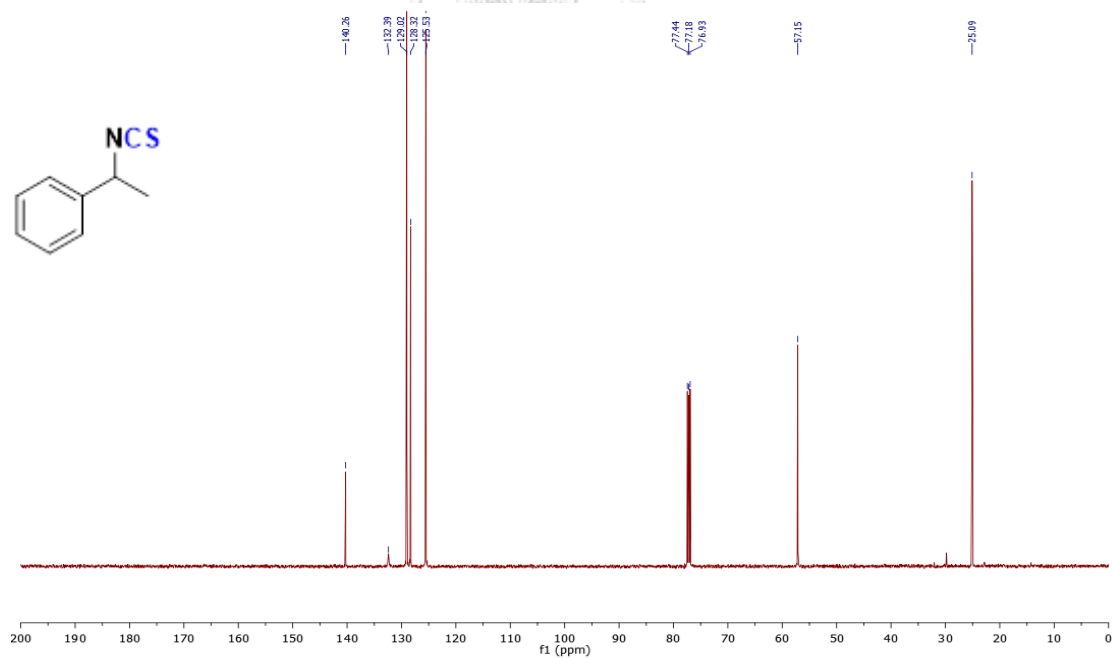
Figure A40 ¹³C-NMR spectrum of **2s** (CDCl₃, 125 MHz)
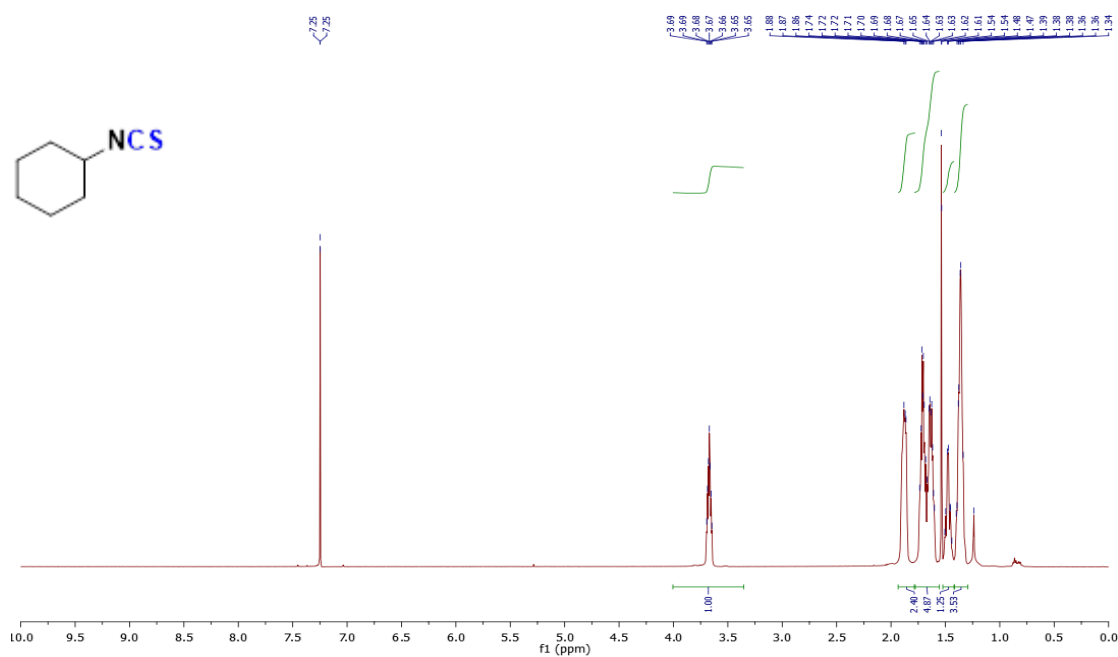
Figure A41 ^{1}H-NMR spectrum of **2t** (CDCl$_3$, 500 MHz)
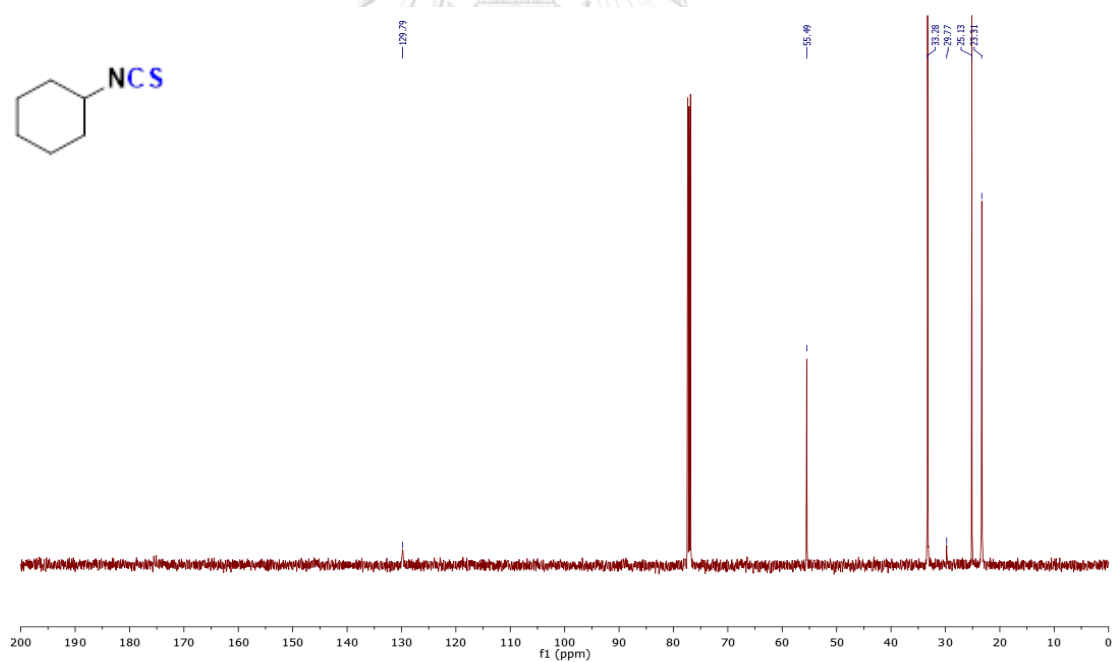
Figure A42 ^{13}C-NMR spectrum of **2t** (CDCl$_3$, 125 MHz)
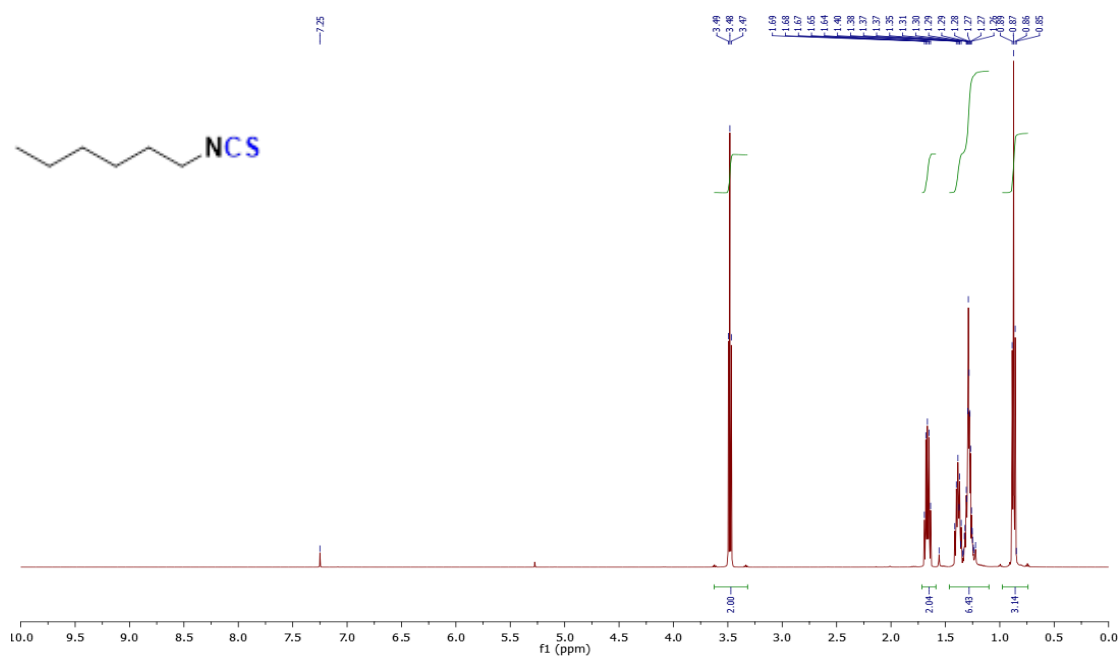
Figure A43 ^{1}H-NMR spectrum of **2u** (CDCl$_3$, 500 MHz)
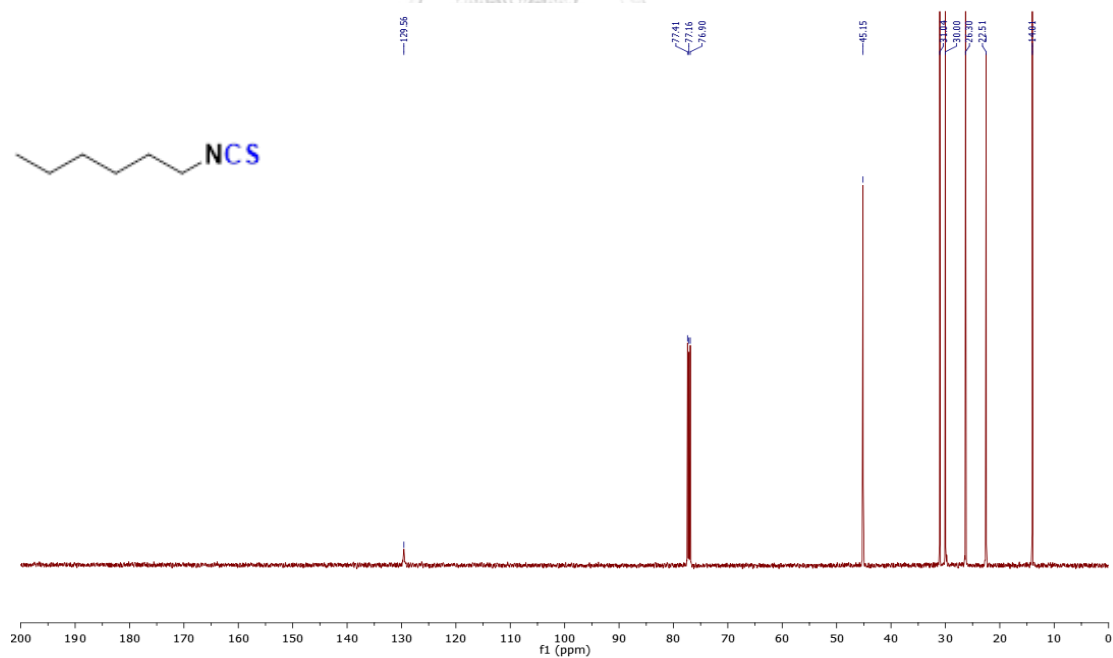
Figure A44 ^{13}C-NMR spectrum of **2u** (CDCl$_3$, 125 MHz)
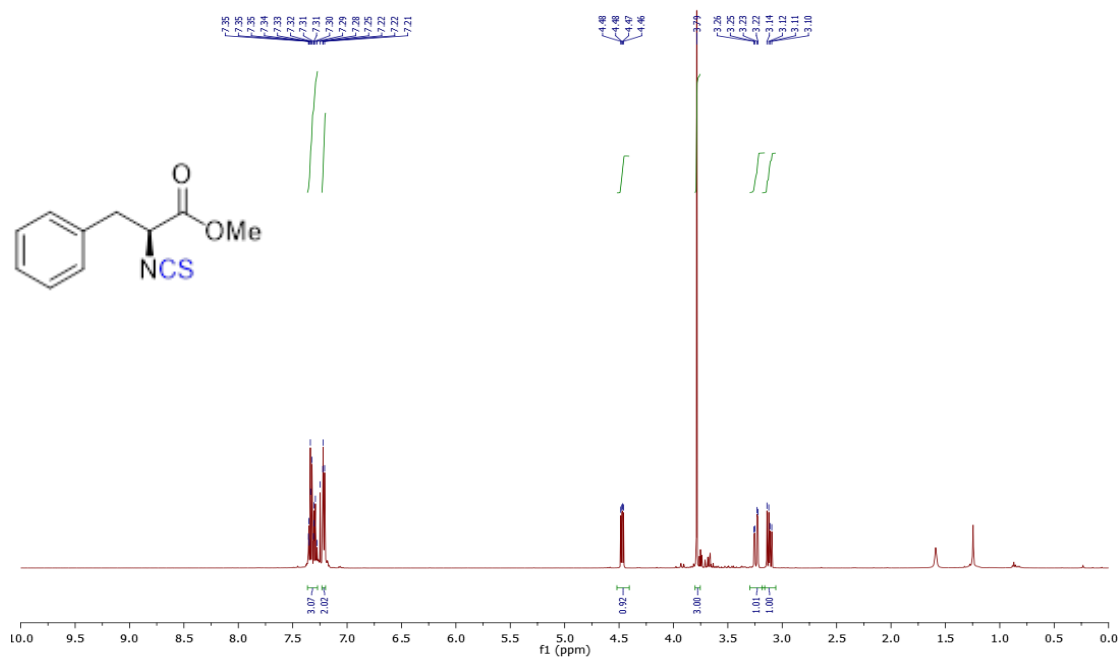
Figure A45 ^{1}H-NMR spectrum of **2v** (CDCl$_3$, 500 MHz)
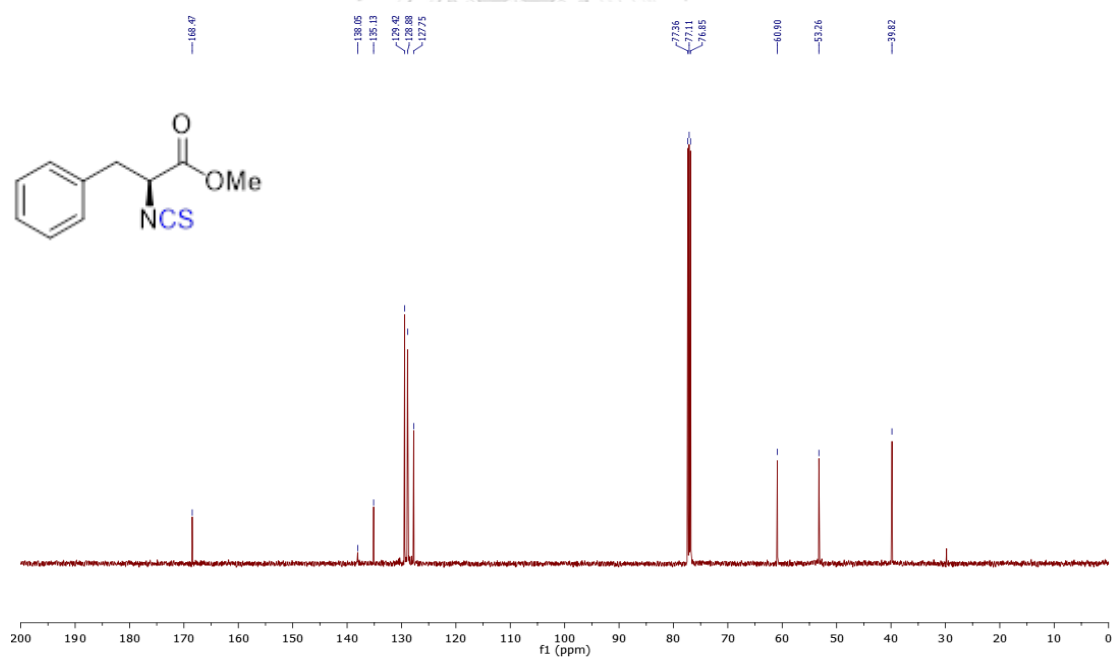
Figure A46 ^{13}C-NMR spectrum of **2v** (CDCl$_3$, 125 MHz)
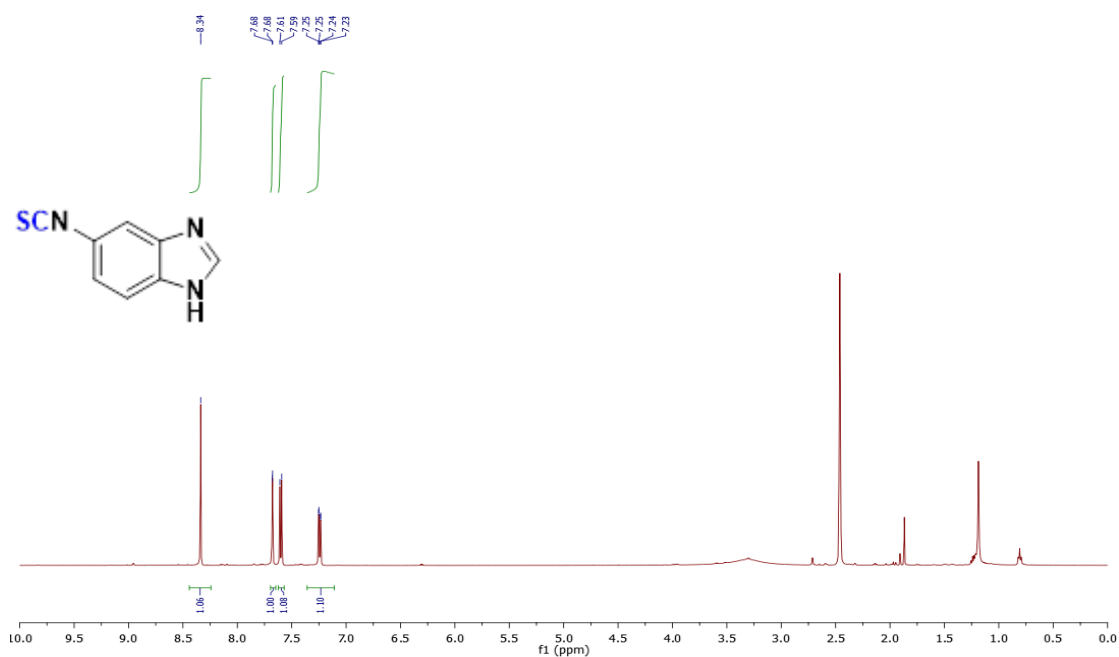
Figure A47 ^{1}H-NMR spectrum of **2w** (DMSO-d6, 500 MHz)
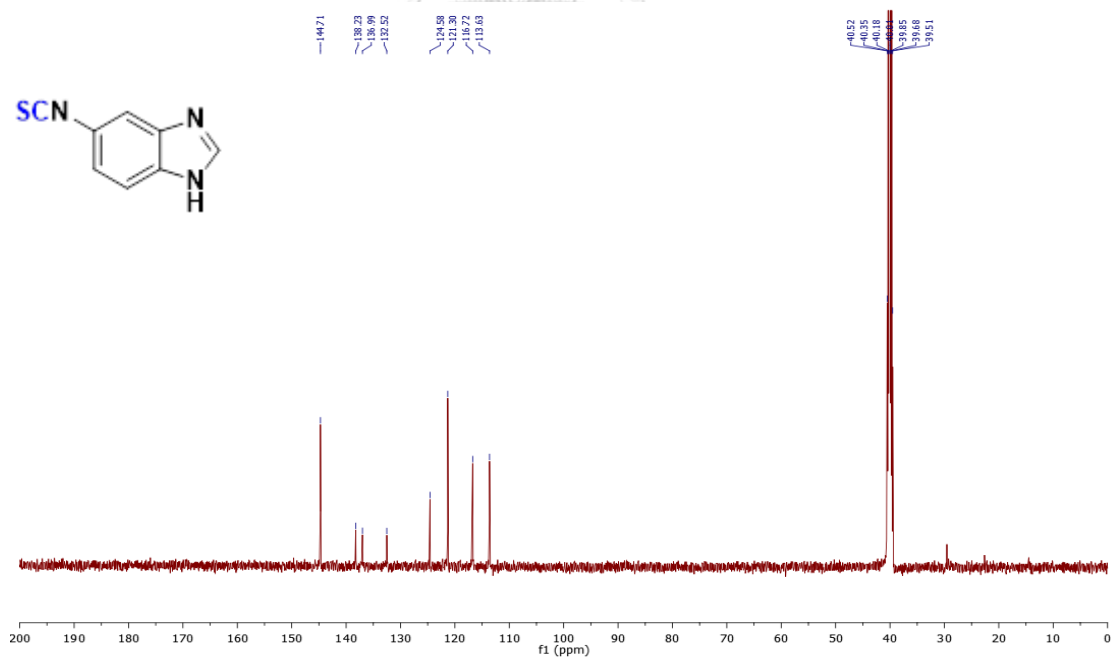
Figure A48 ^{1}H-NMR spectrum of **2w** (DMSO-d6, 500 MHz)
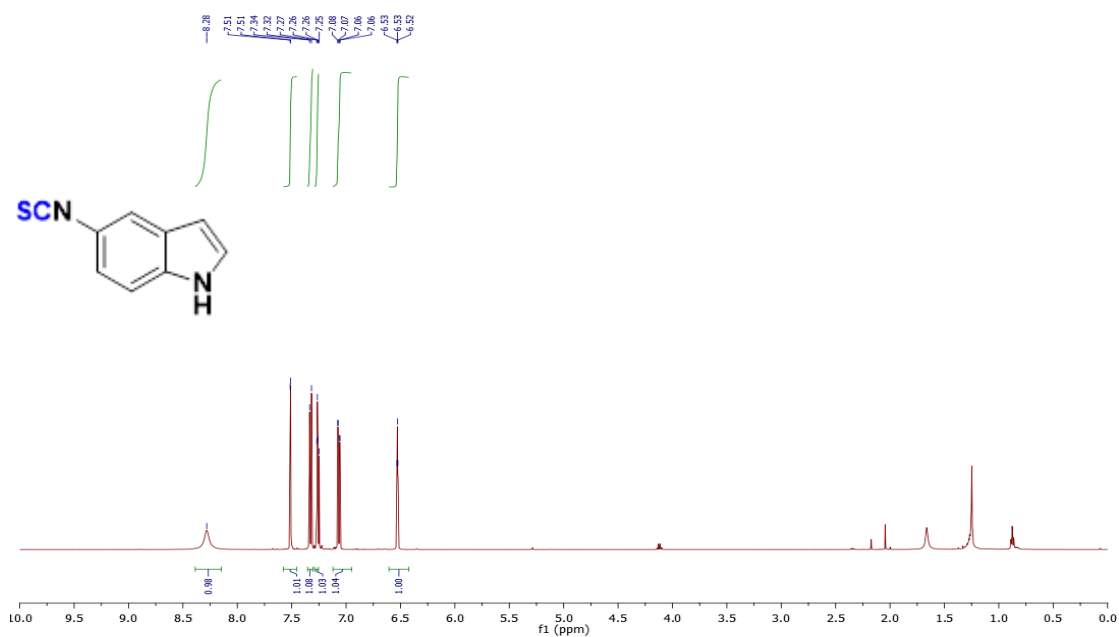
Figure A49 ^{1}H-NMR spectrum of **2x** (CDCl$_3$ 500 MHz)
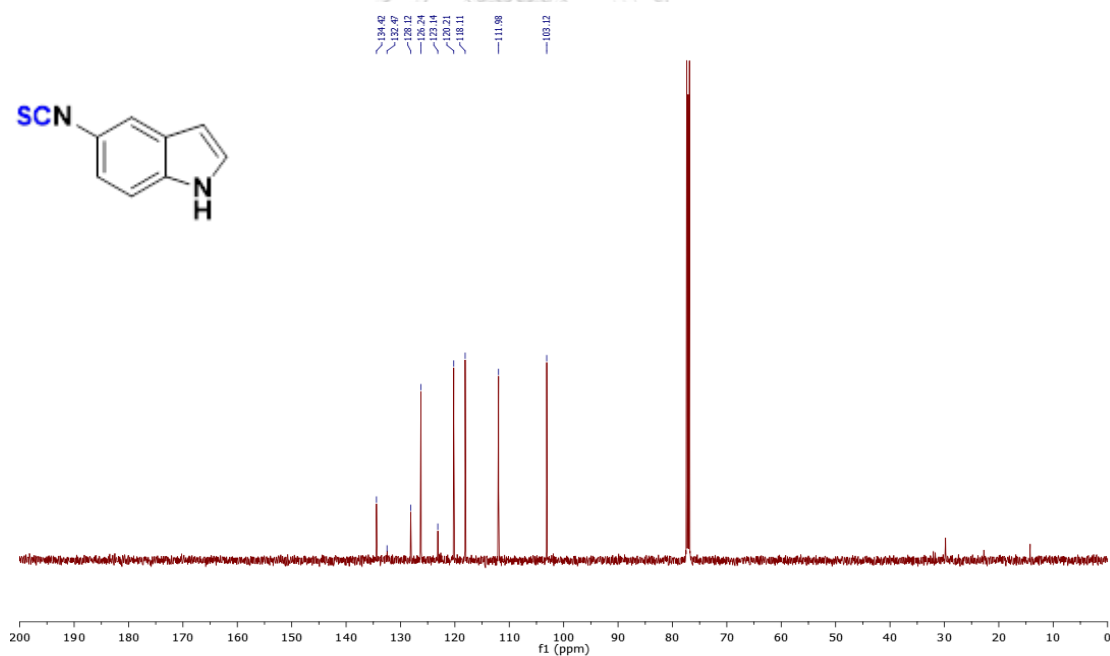
Figure A50 ^{13}C-NMR spectrum of **2x** (CDCl$_3$, 125 MHz)
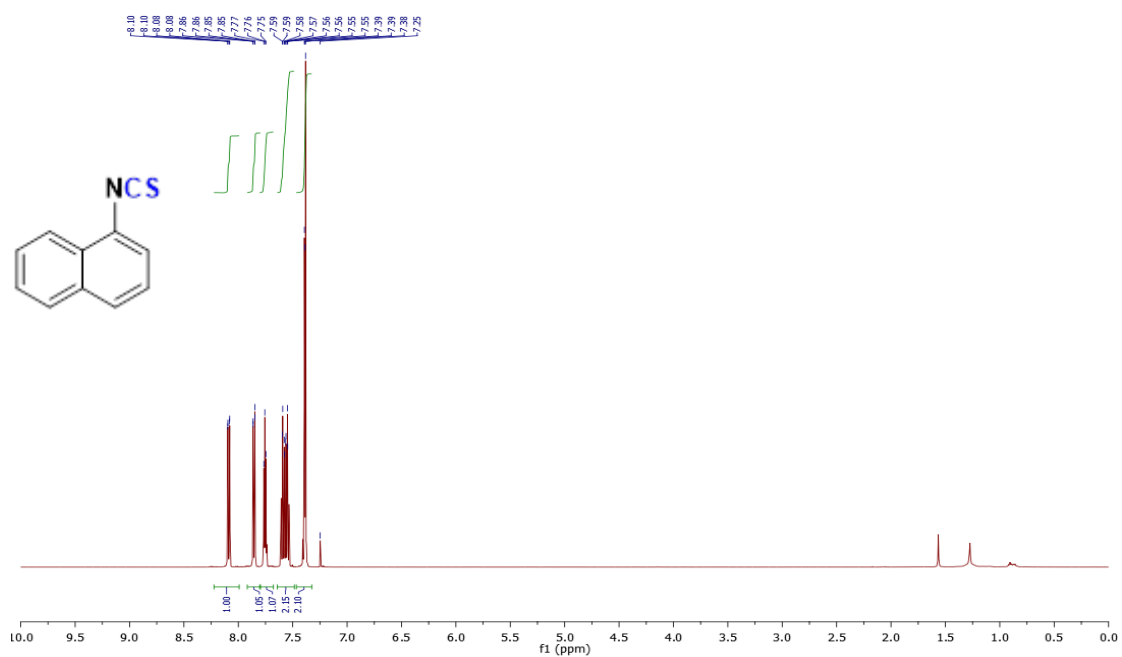
Figure A51 ^{1}H-NMR spectrum of **2y** (CDCl$_3$, 500 MHz)
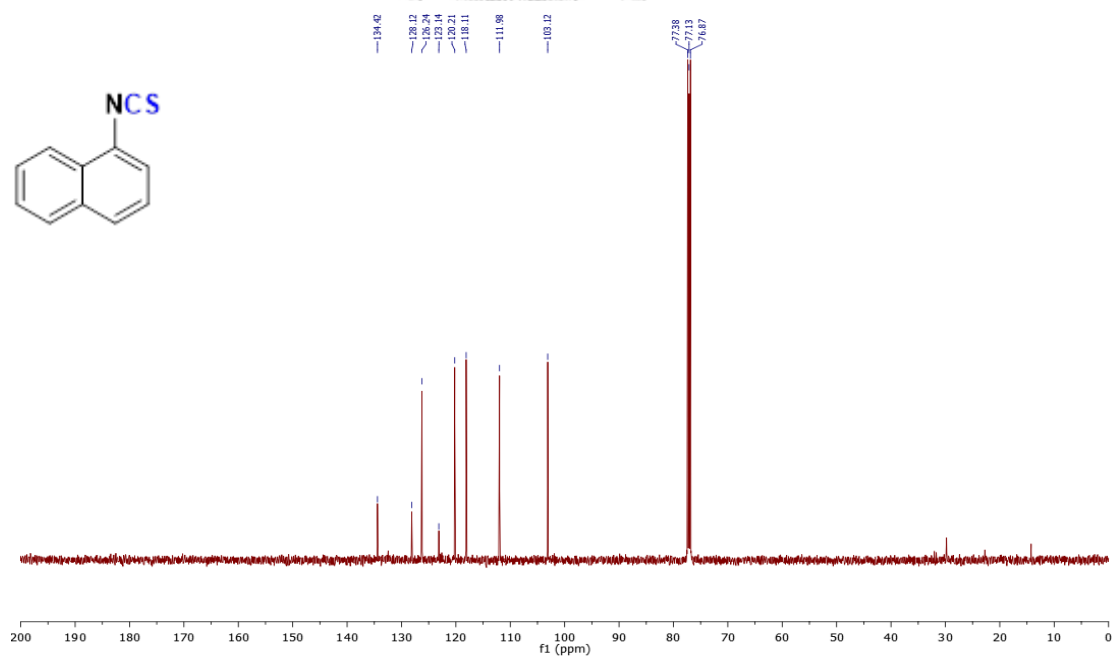
Figure A52 ^{13}C-NMR spectrum of **2y** (CDCl$_3$, 125 MHz)
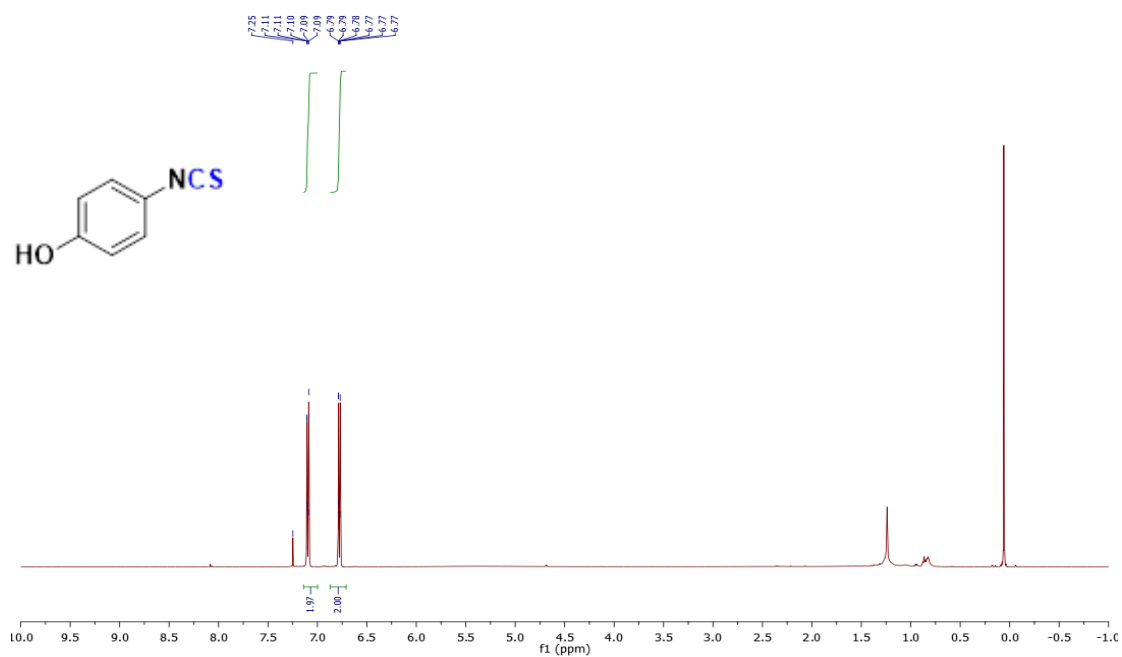
Figure A53 ^{1}H-NMR spectrum of **2z** (CDCl$_3$, 500 MHz)
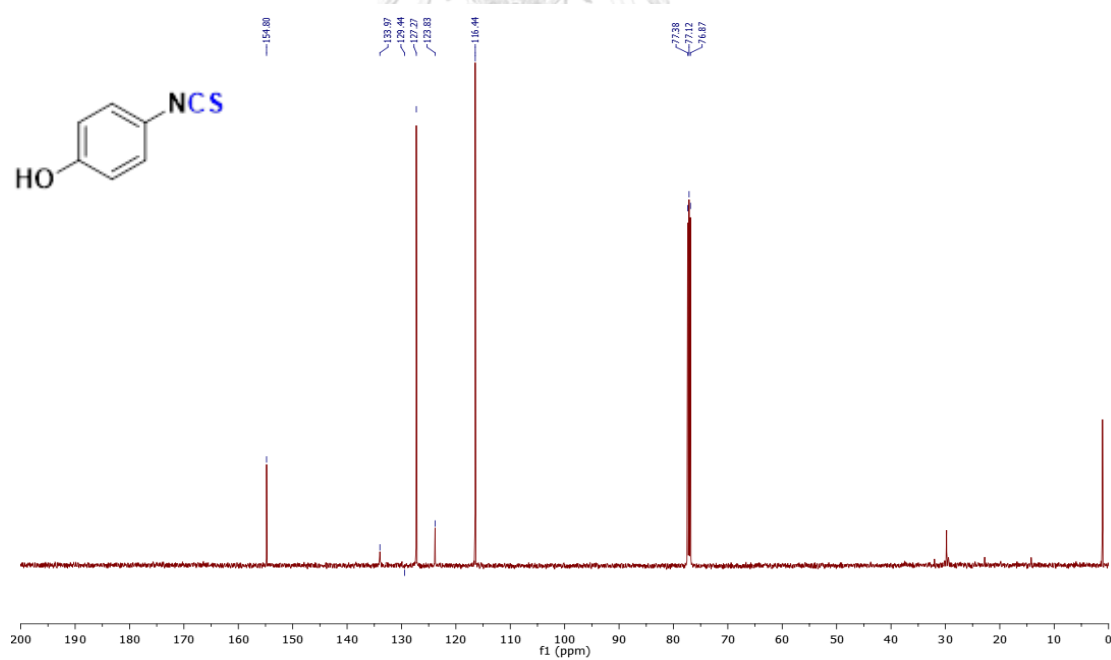
Figure A54 ^{13}C-NMR spectrum of **2z** (CDCl$_3$, 125 MHz)
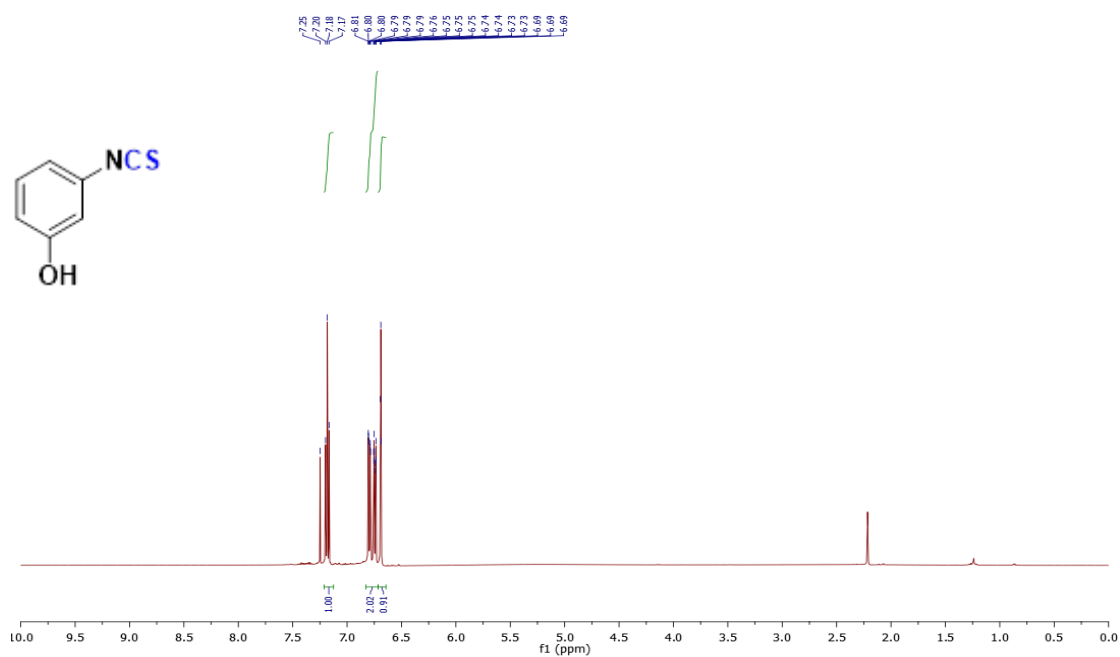
Figure A55 ^{1}H-NMR spectrum of **2aa** (CDCl$_3$ 500 MHz)
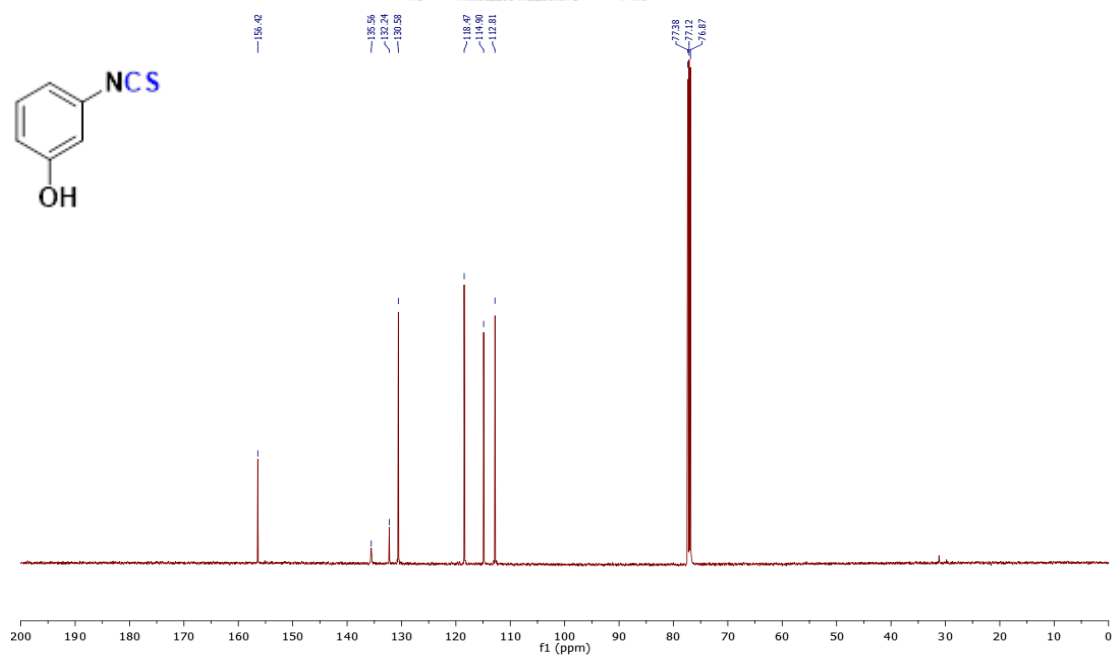
Figure A56 ^{13}C-NMR spectrum of **2aa** (CDCl$_3$, 125 MHz)
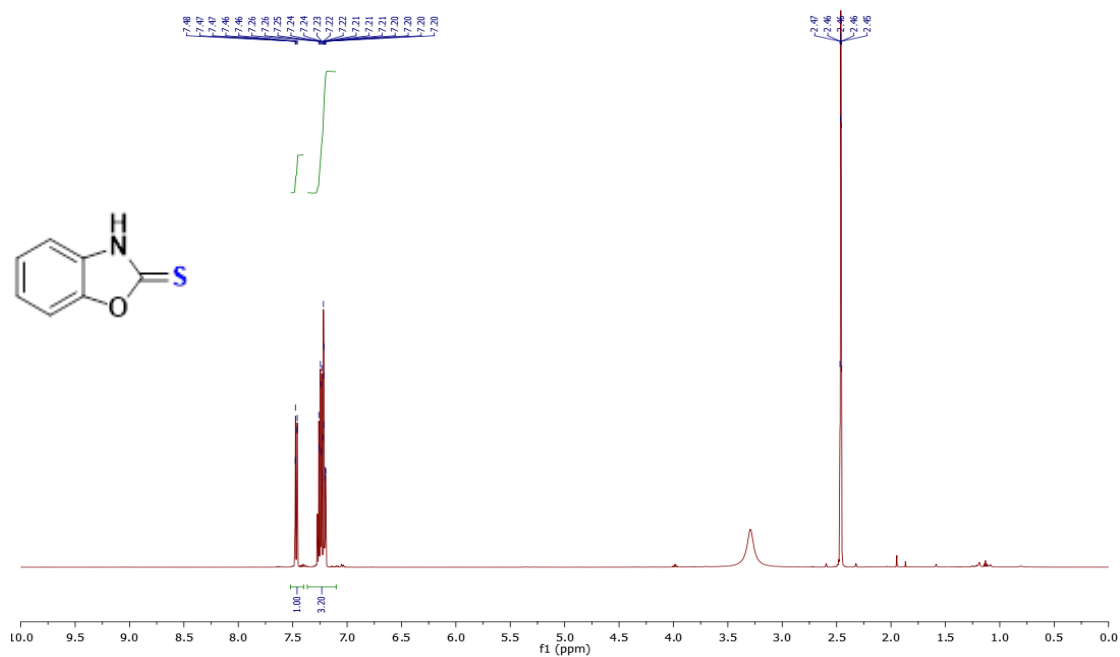
Figure A57 ^{1}H-NMR spectrum of **2bb** (DMSO-d6 500 MHz)
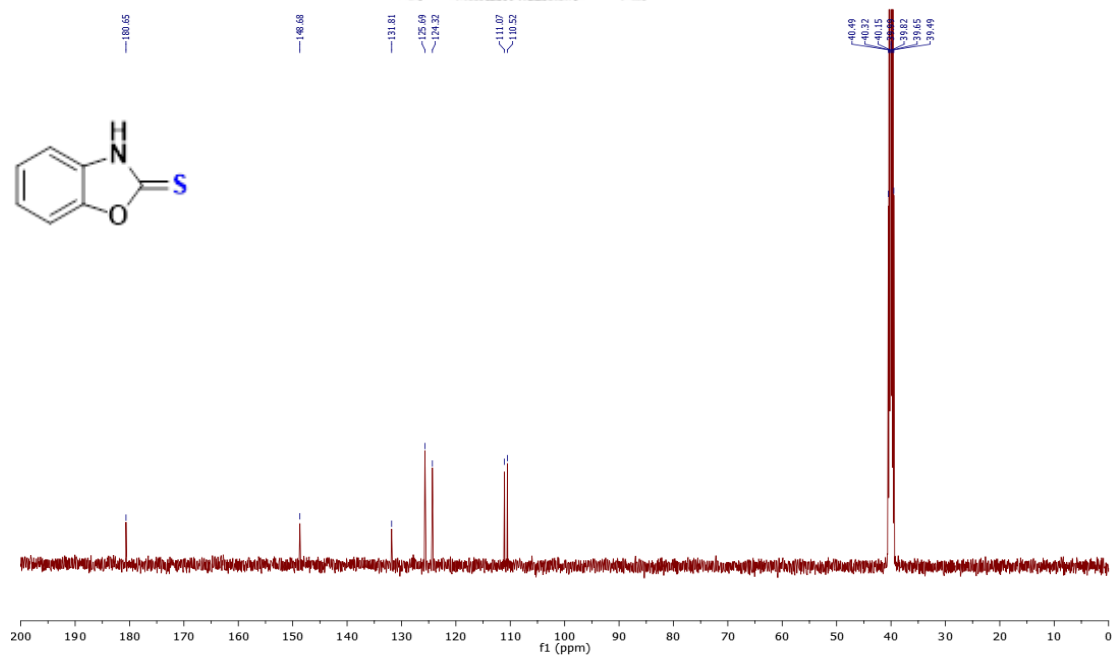
Figure A58 ^{13}C-NMR spectrum of **2bb** (DMSO, 125 MHz)
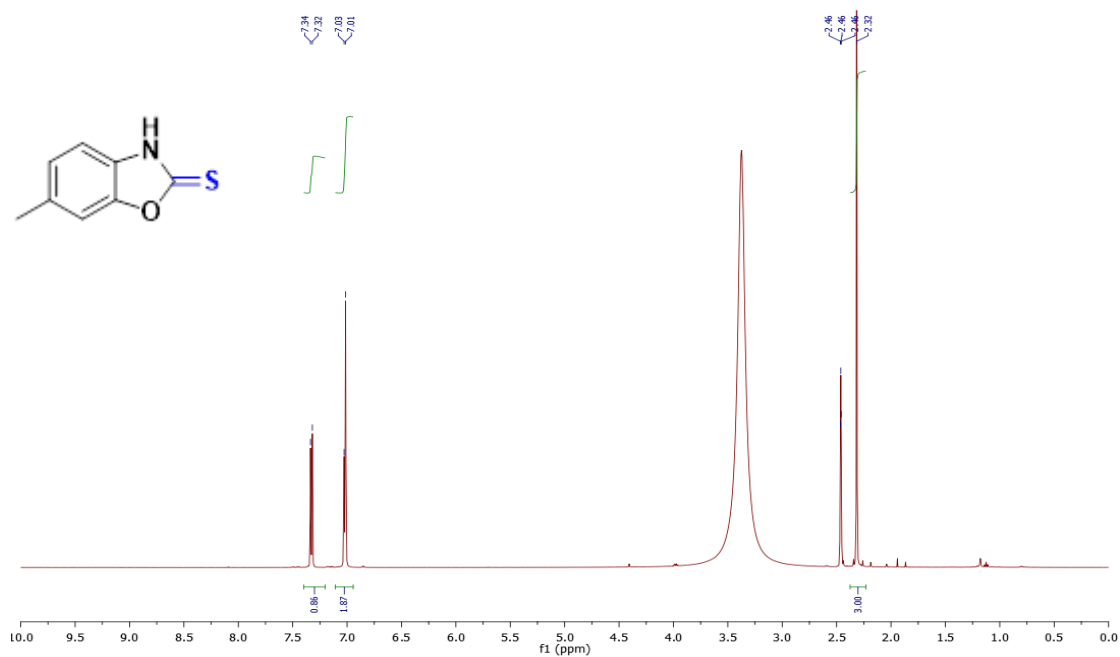
Figure A 59 ^{1}H-NMR spectrum of **2cc** (DMSO-d6 500 MHz)
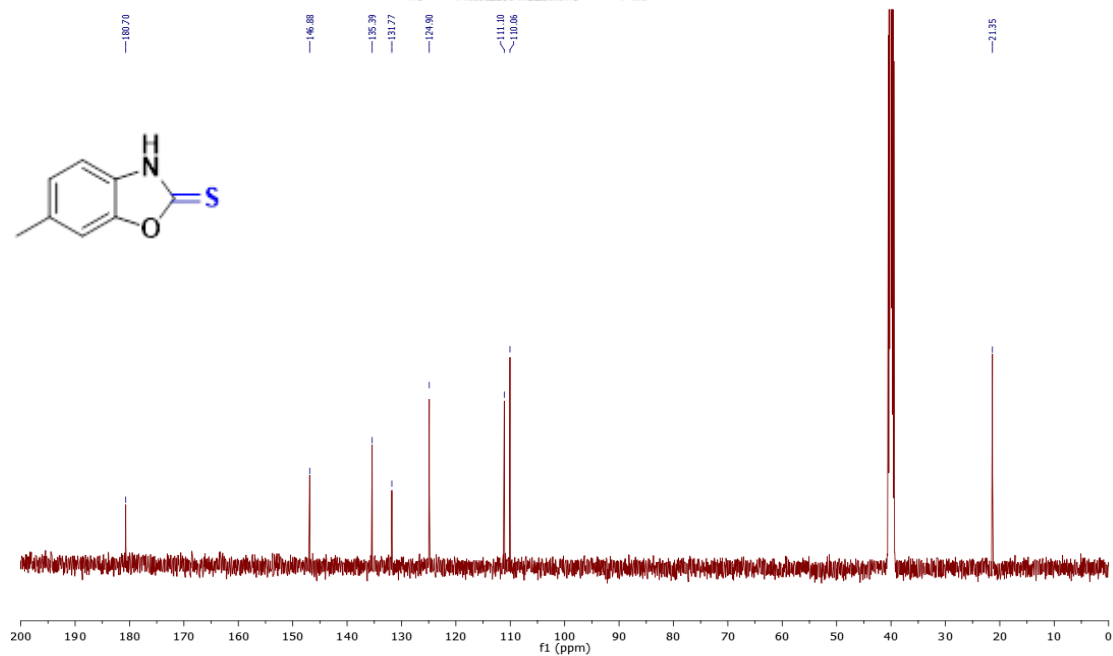
Figure A60 ^{13}C-NMR spectrum of **2cc** (DMSO, 125 MHz)
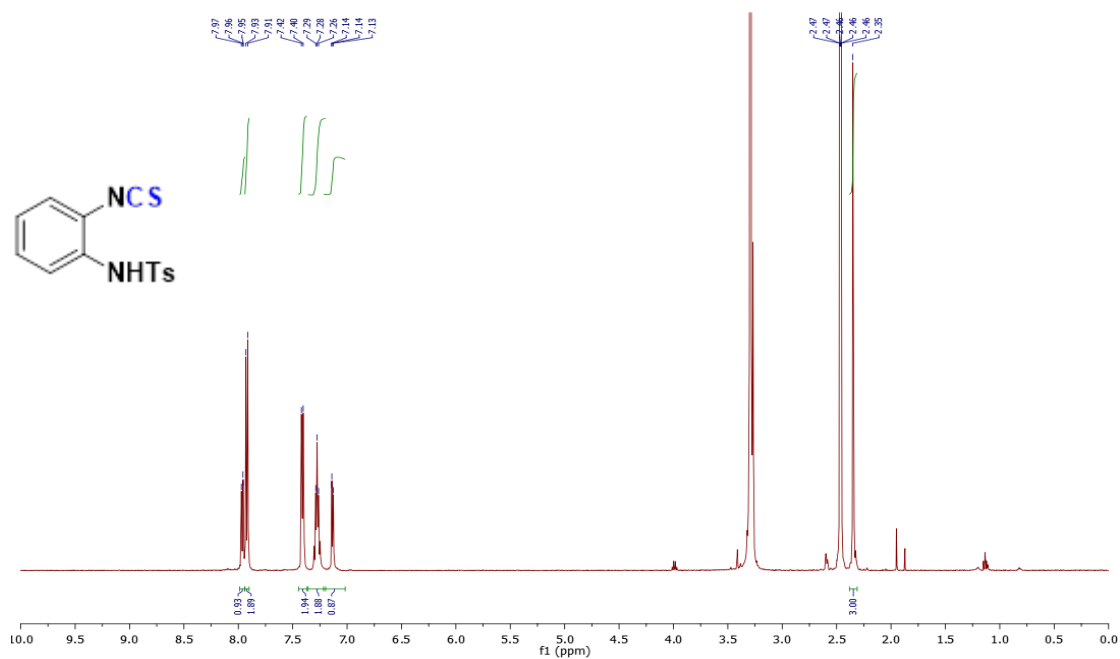
Figure A61 ^{1}H-NMR spectrum of **2dd** (DMSO-d6 500 MHz)
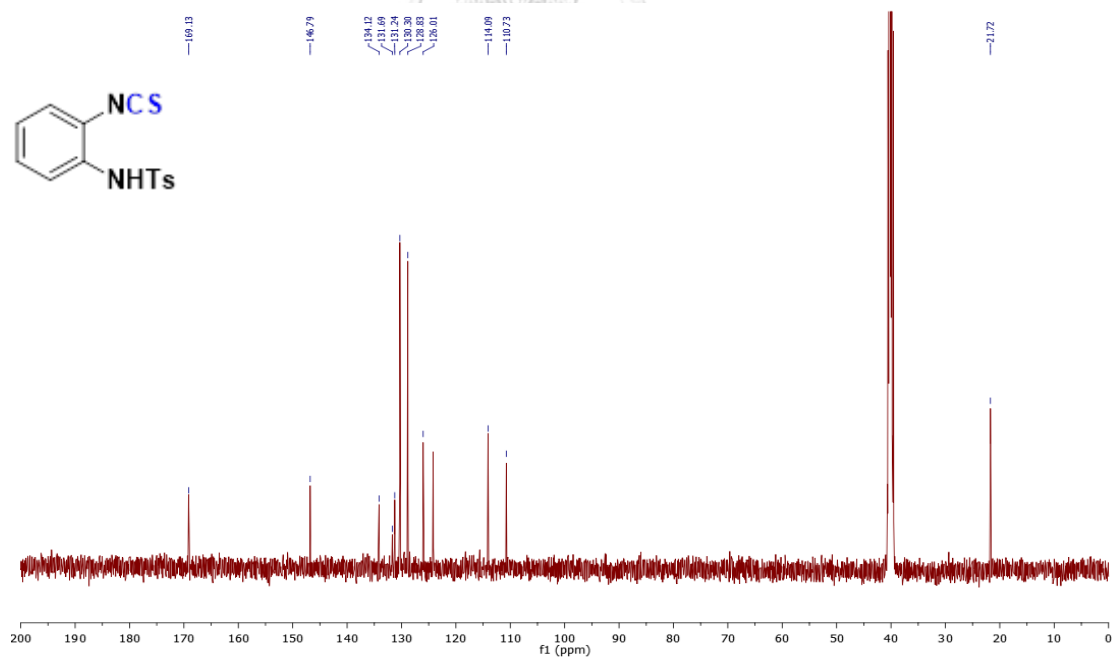
Figure A62 ^{13}C-NMR spectrum of **2dd** (DMSO, 125 MHz)
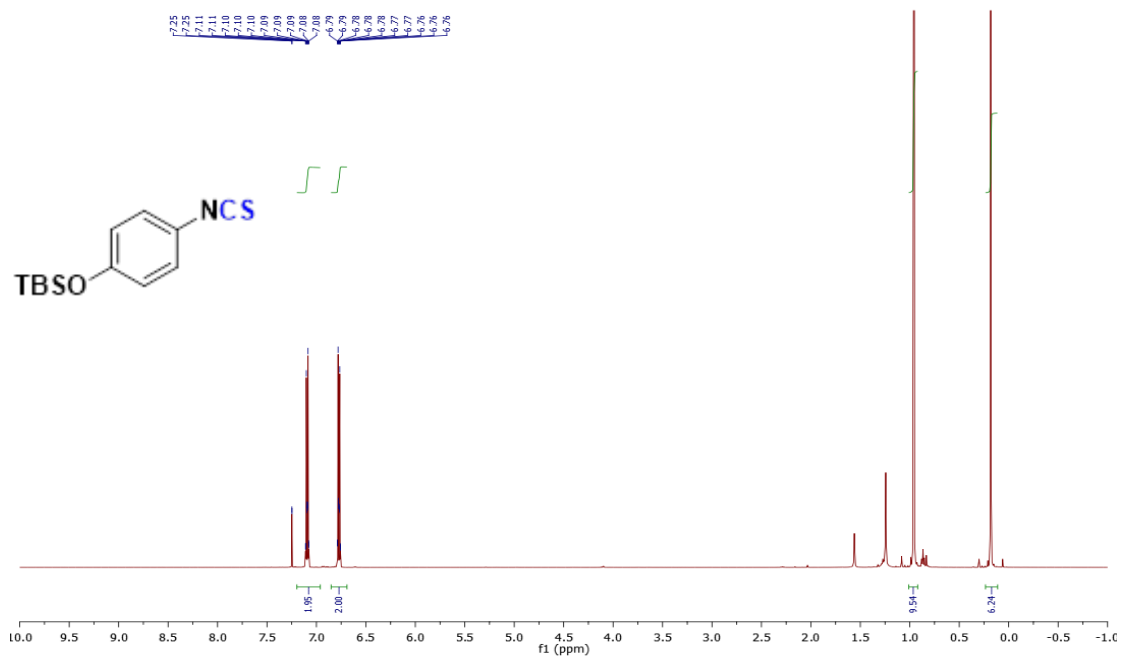
Figure A63 ^{1}H-NMR spectrum of **2ee** (CDCl$_3$, 500 MHz)
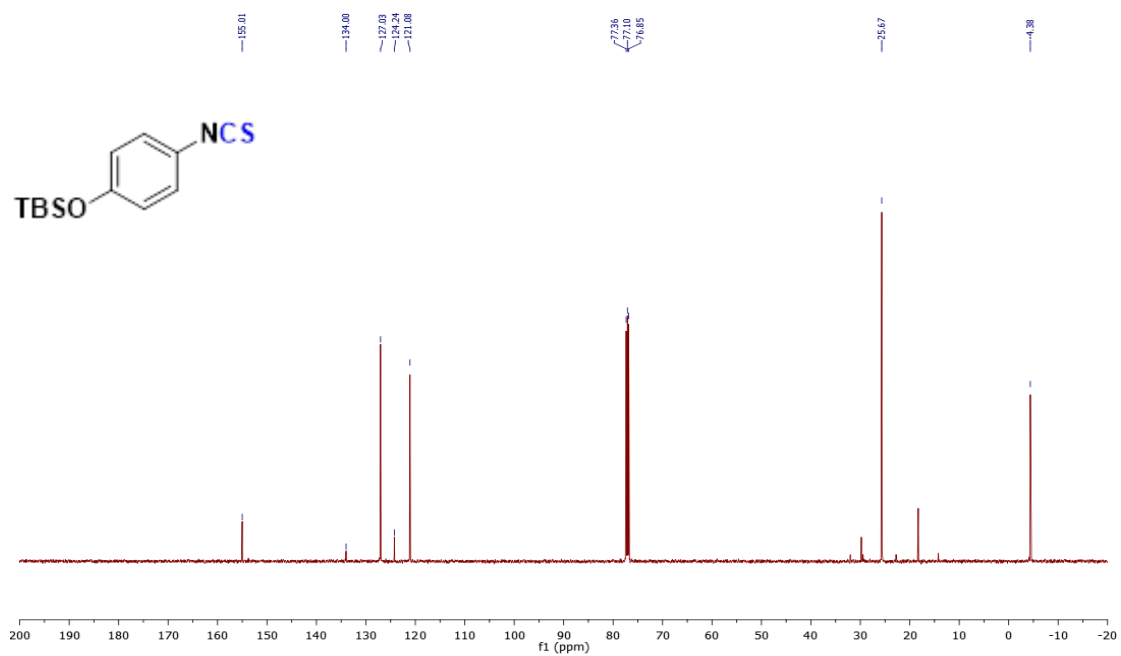
Figure A64 ^{13}C-NMR spectrum of **2ee** (CDCl$_3$, 125 MHz)
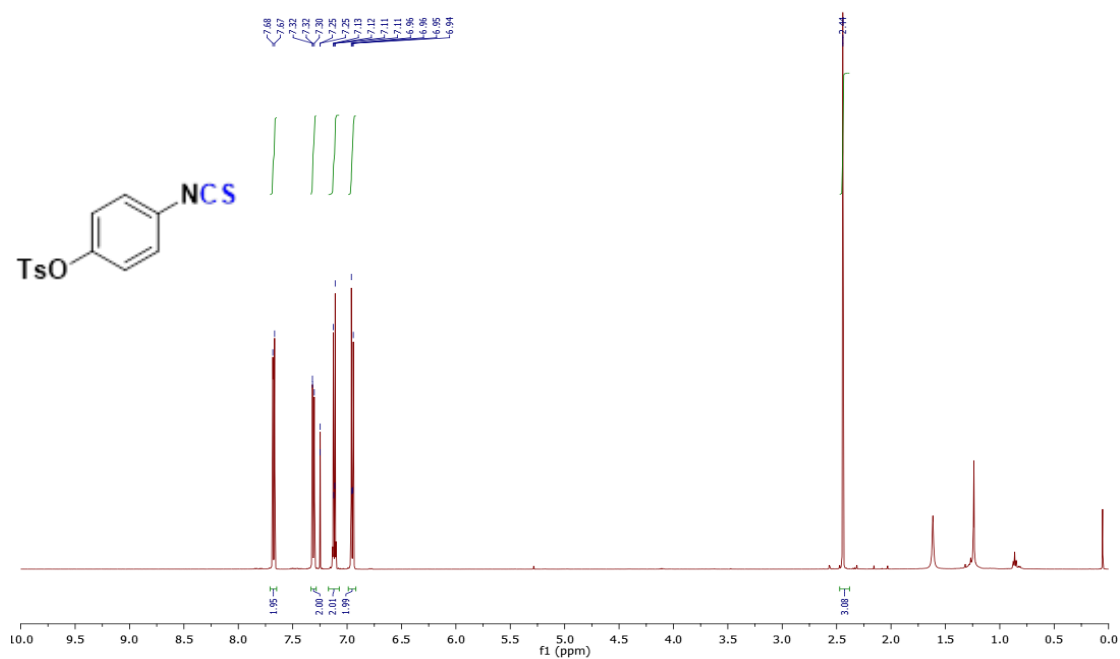
Figure A65 ^{1}H-NMR spectrum of **2ff** (CDCl$_3$, 500 MHz)
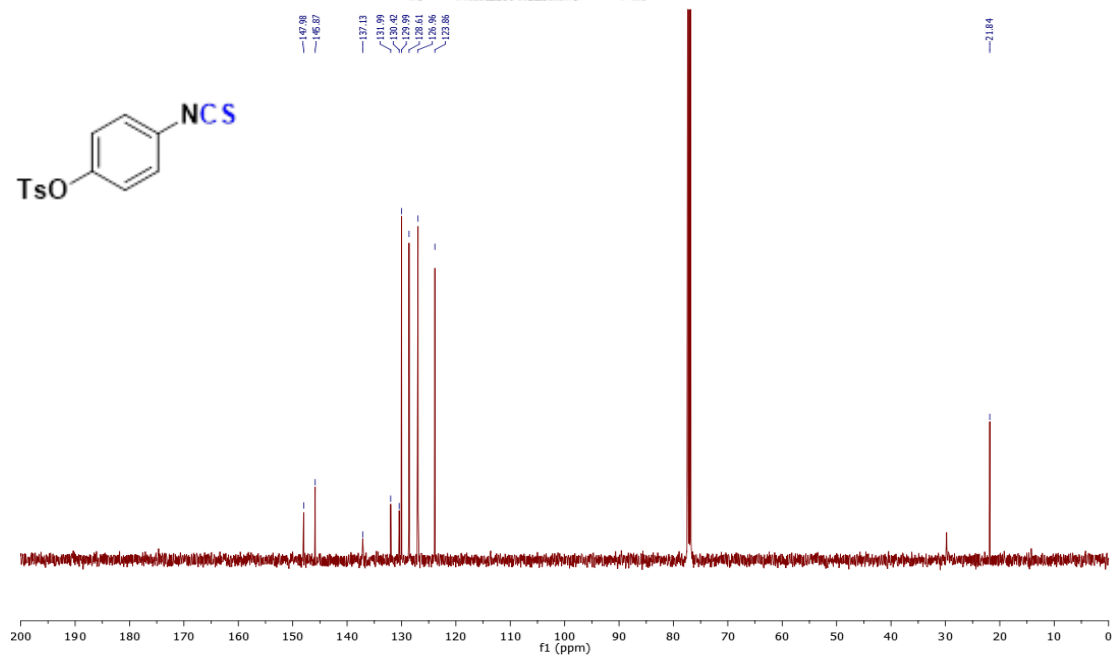
Figure A66 ^{13}C-NMR spectrum of **2ff** (CDCl$_3$, 125 MHz)
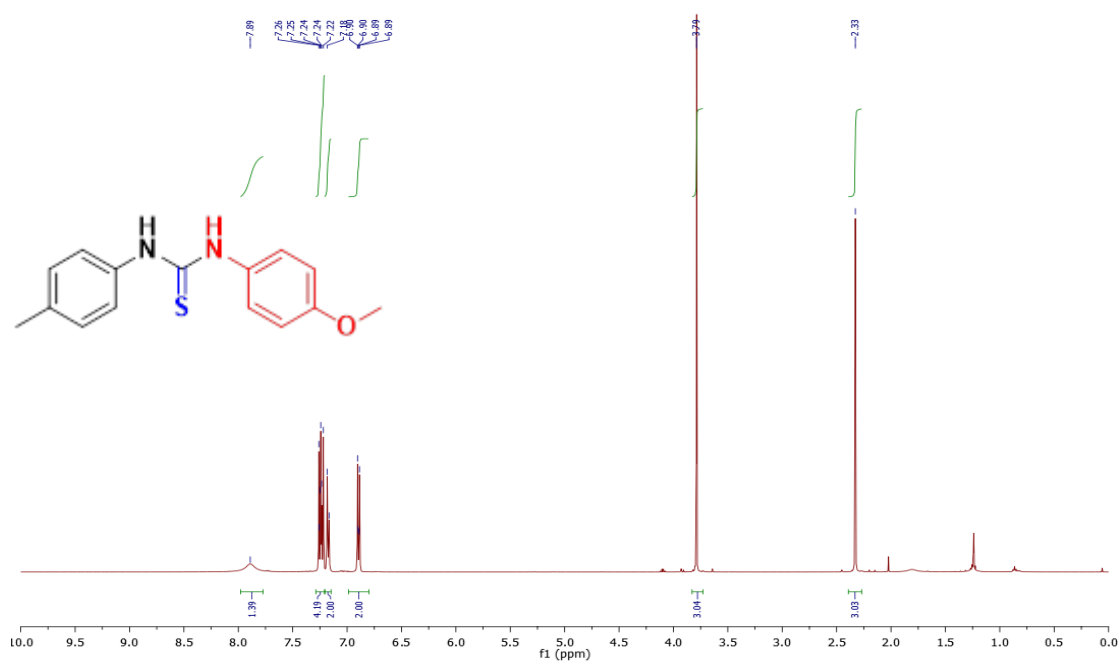
Figure A67 ^{1}H-NMR spectrum of **3a** (CDCl$_3$, 500 MHz)
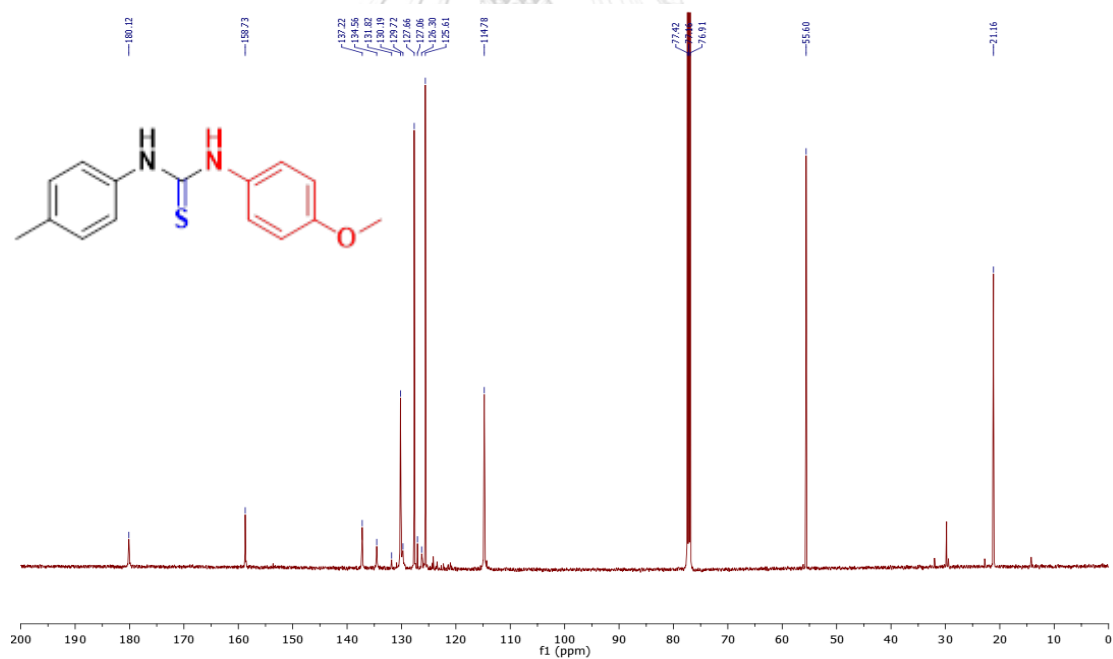
Figure A68 ^{13}C-NMR spectrum of **3a** (CDCl$_3$, 125 MHz)
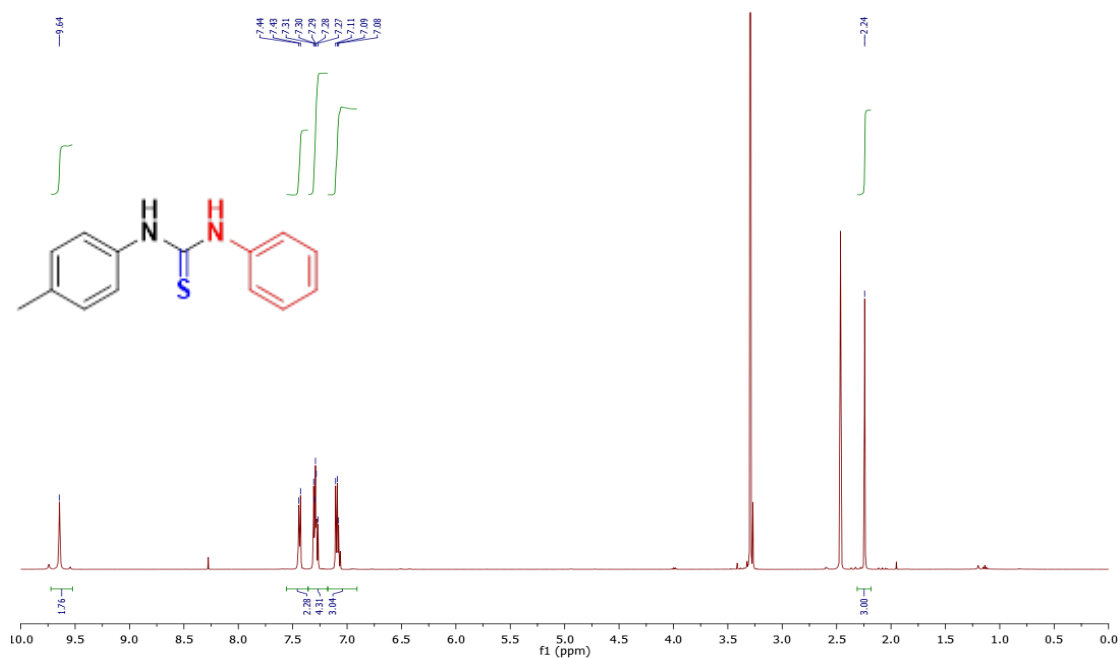
Figure A69 ^{1}H-NMR spectrum of **3b** (DMSO-d6 500 MHz)
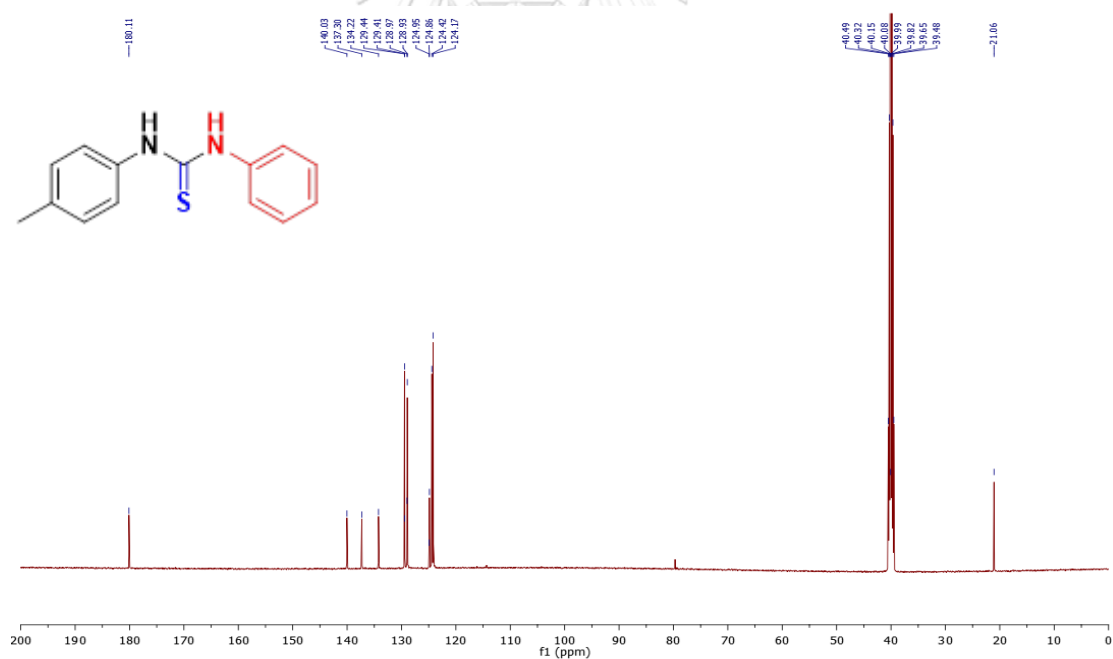
Figure A70 ^{13}C-NMR spectrum of **3b** (DMSO-d6, 125 MHz)
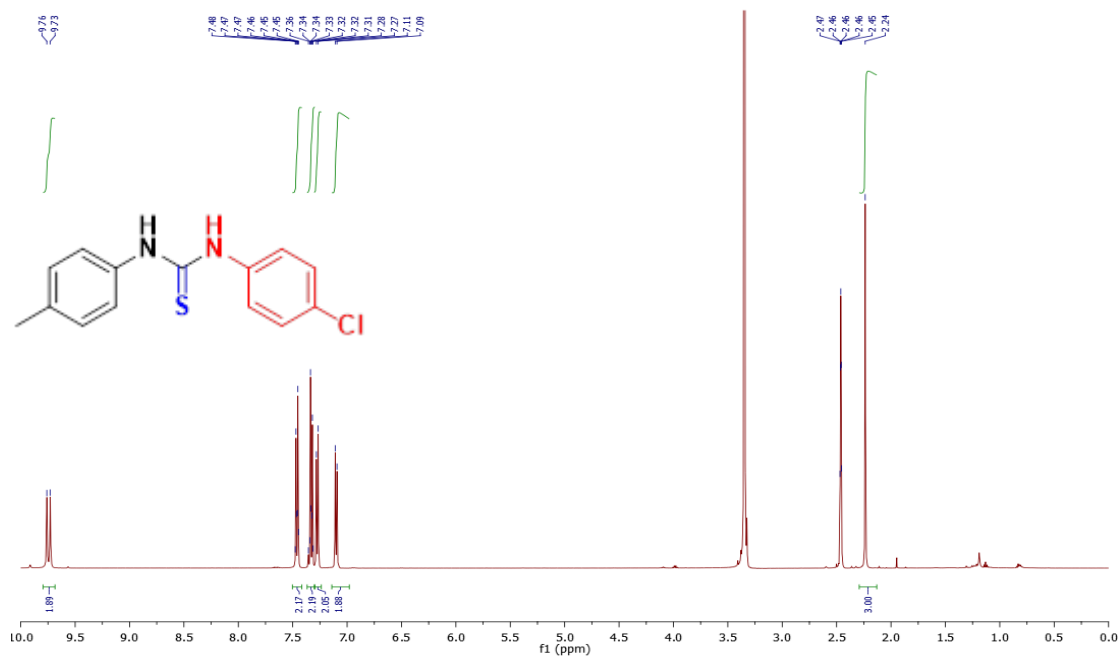
Figure A71 ¹H-NMR spectrum of **3c** (DMSO-d6 500 MHz)
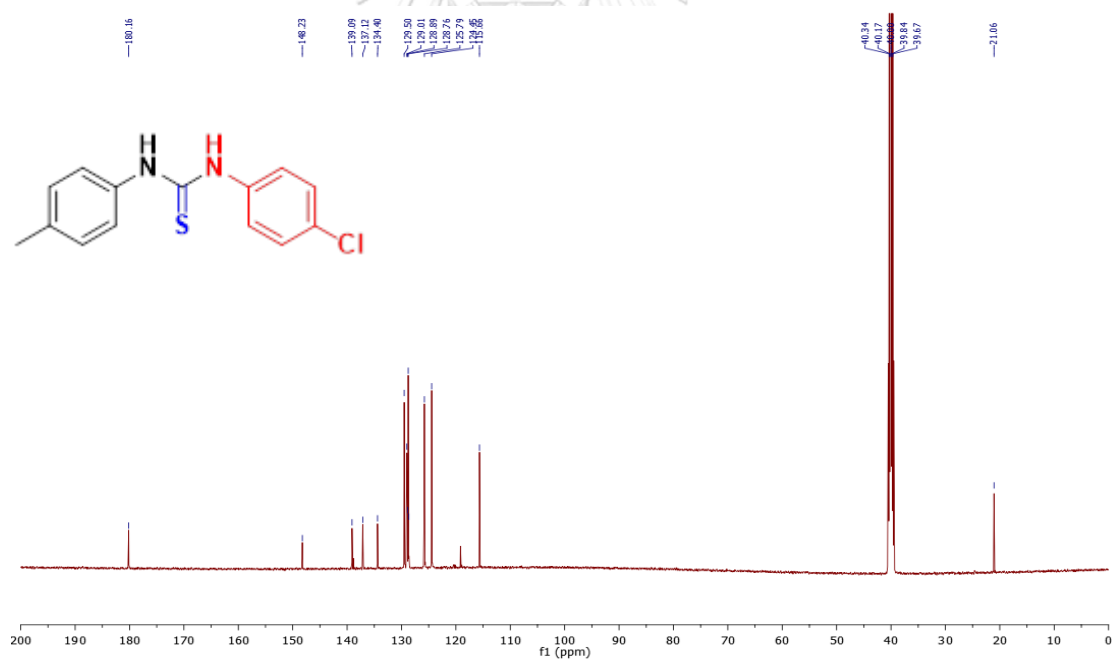
Figure A72 ¹³C-NMR spectrum of **3c** (DMSO-d6, 125 MHz)
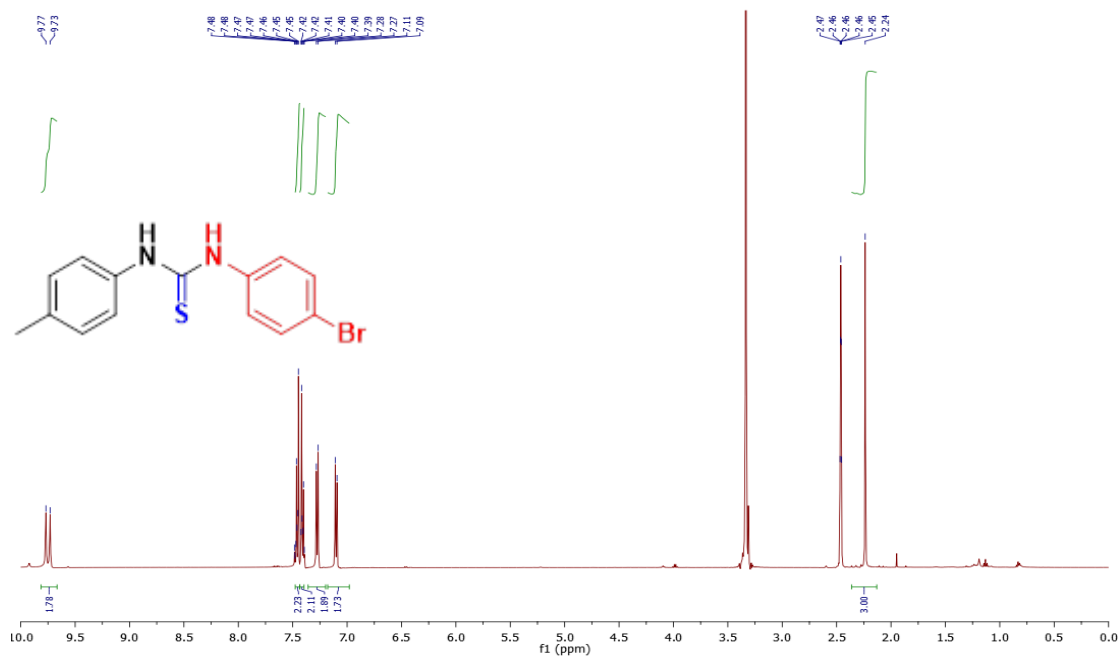
Figure A73 ^{1}H-NMR spectrum of **3d** (DMSO-d6 500 MHz)
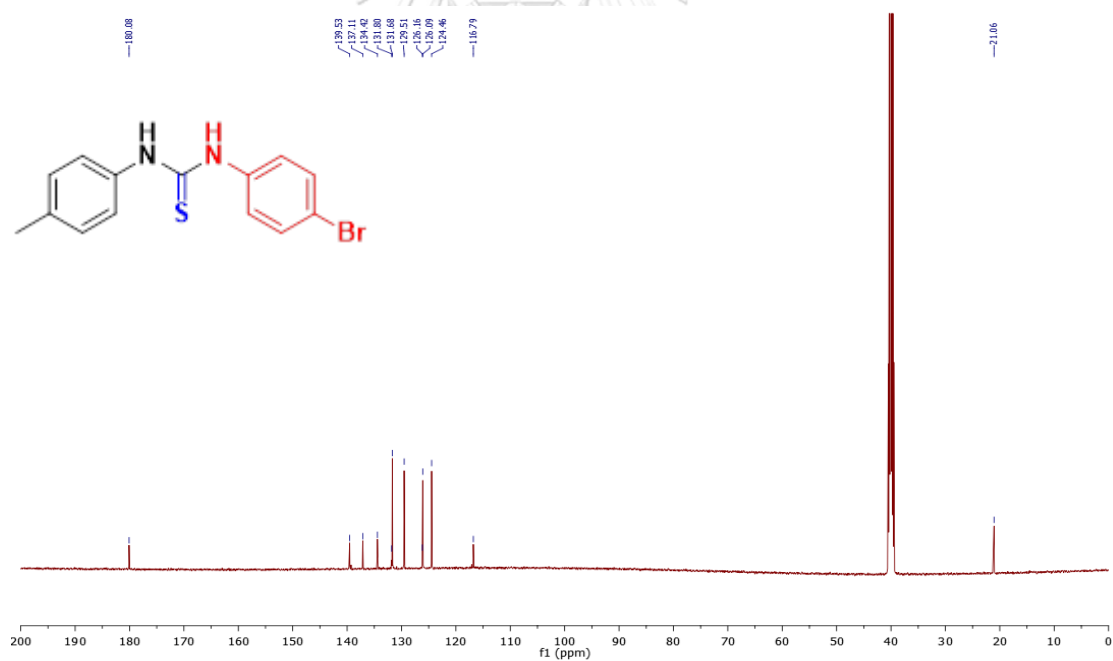
Figure A74 ^{13}C-NMR spectrum of **3d** (DMSO-d6, 125 MHz)
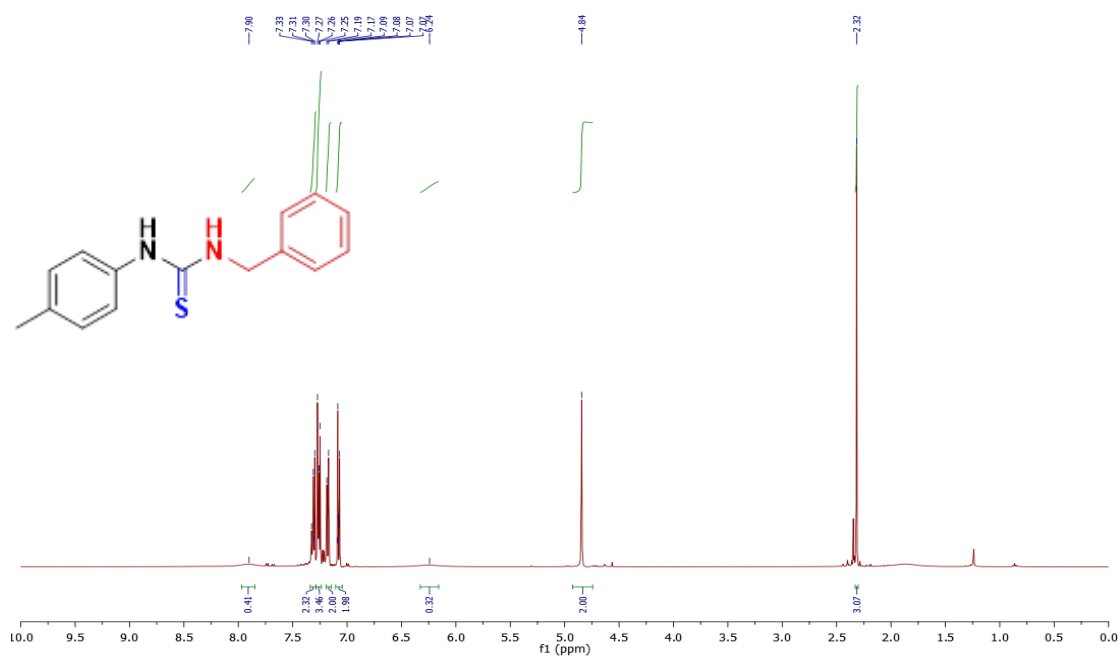
Figure A75 ^{1}H-NMR spectrum of **3e** (CDCl$_3$, 500 MHz)
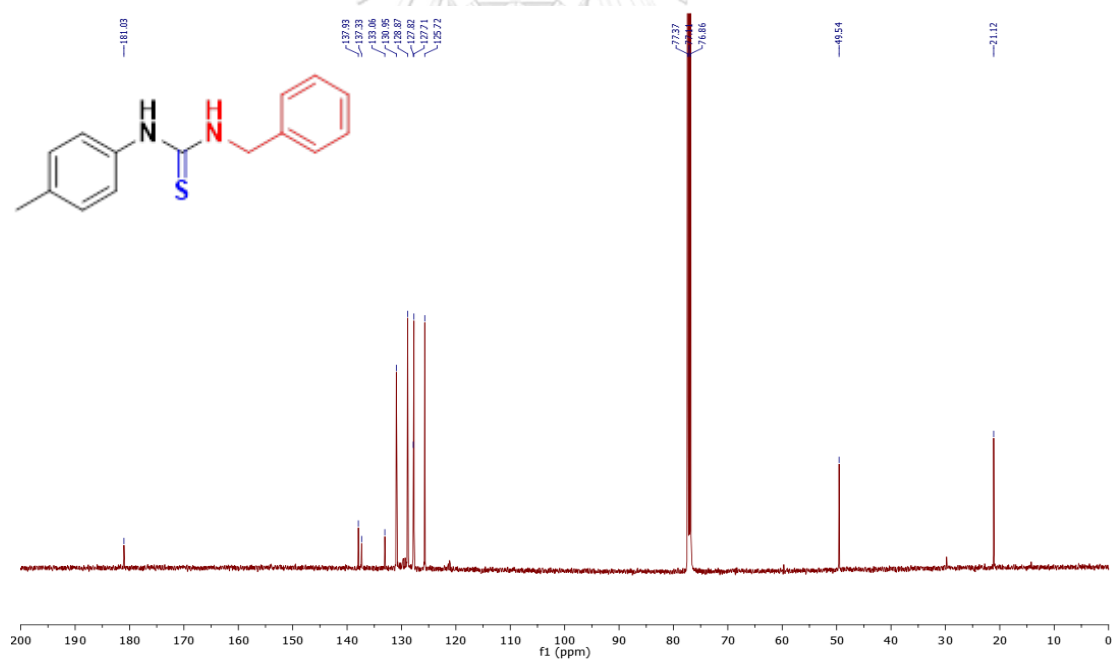
Figure A76 ^{13}C-NMR spectrum of **3e** (CDCl$_3$, 125 MHz)
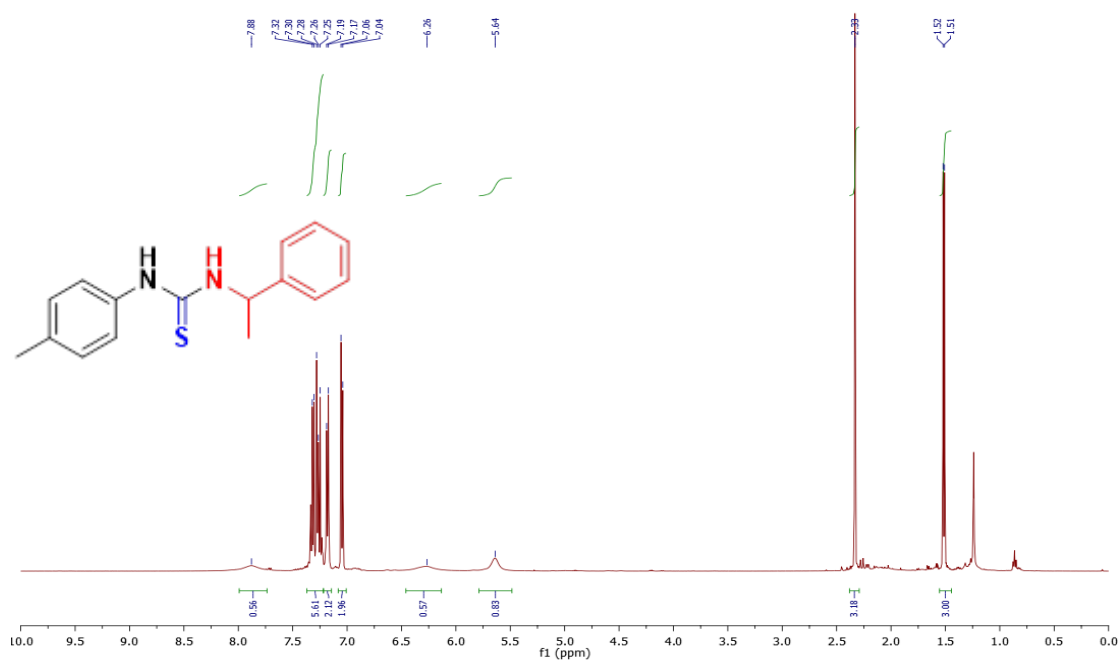
Figure A75 ^{1}H-NMR spectrum of **3f** (CDCl$_3$ 500 MHz)
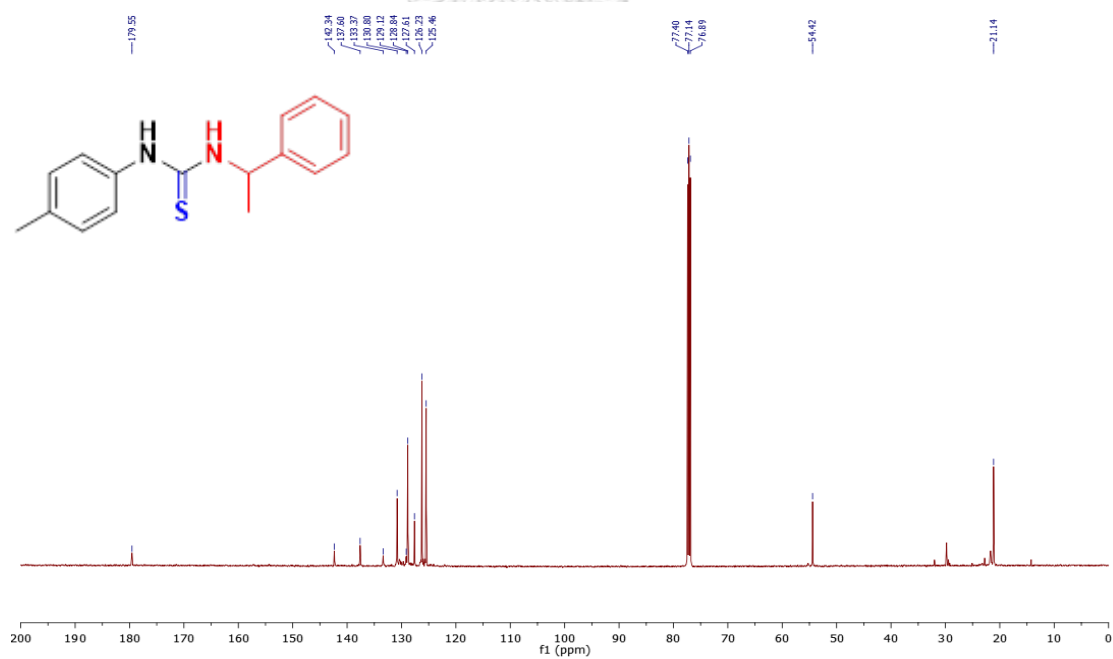
Figure A76 ^{13}C-NMR spectrum of **3f** (CDCl$_3$, 125 MHz)
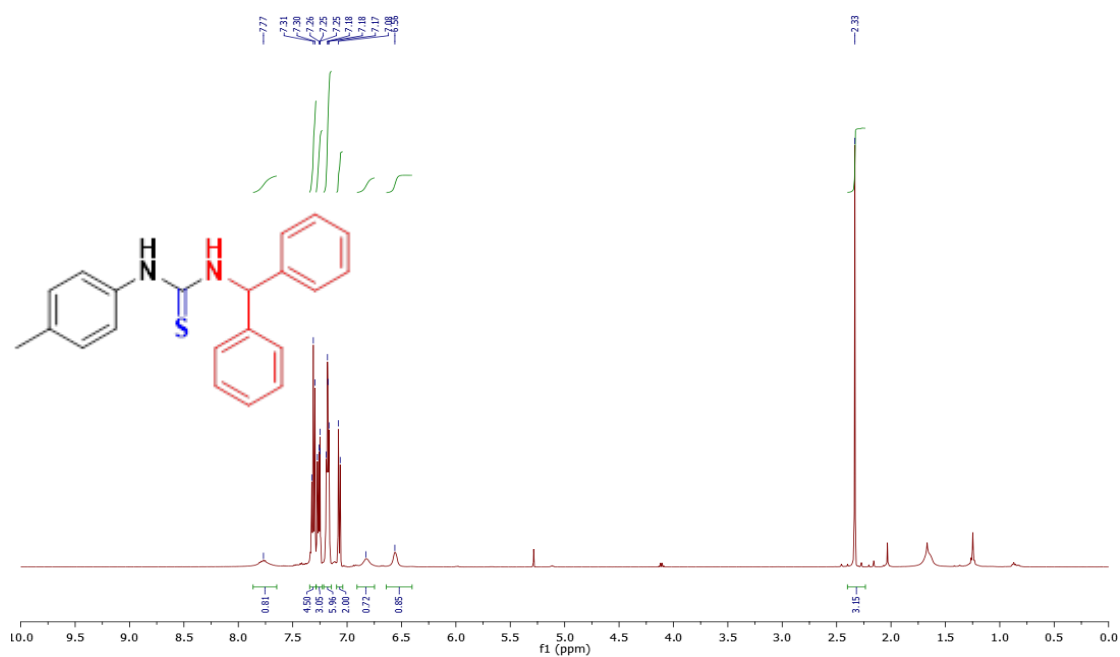
Figure A77 ^{1}H-NMR spectrum of **3g** (CDCl$_3$, 500 MHz)
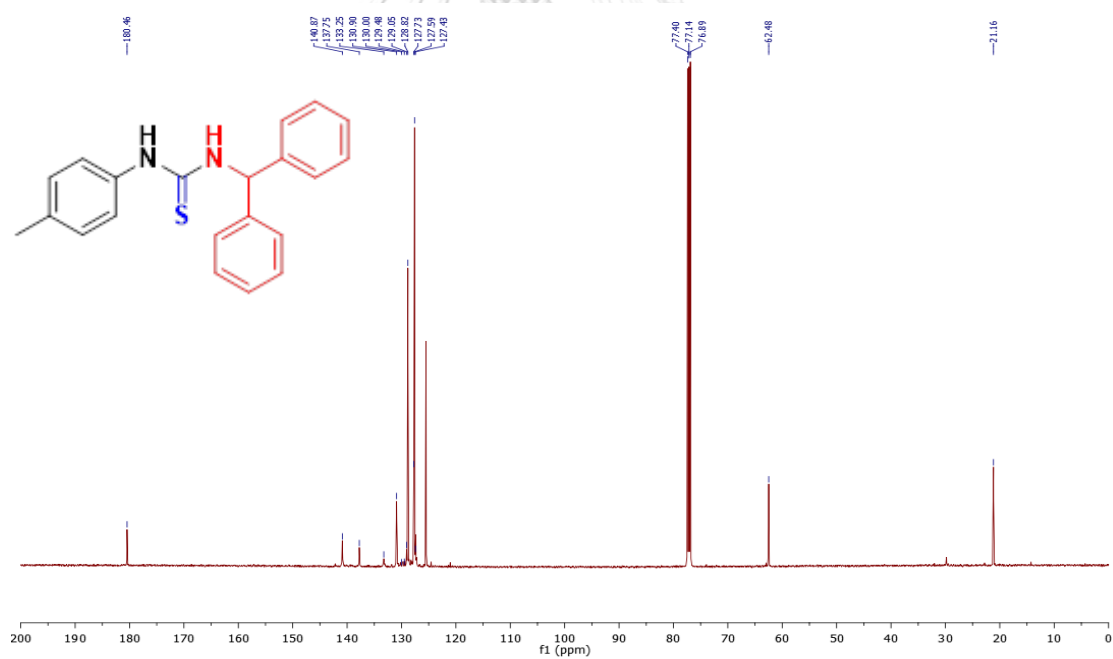
Figure A78 ^{13}C-NMR spectrum of **3g** (CDCl$_3$, 500 MHz)
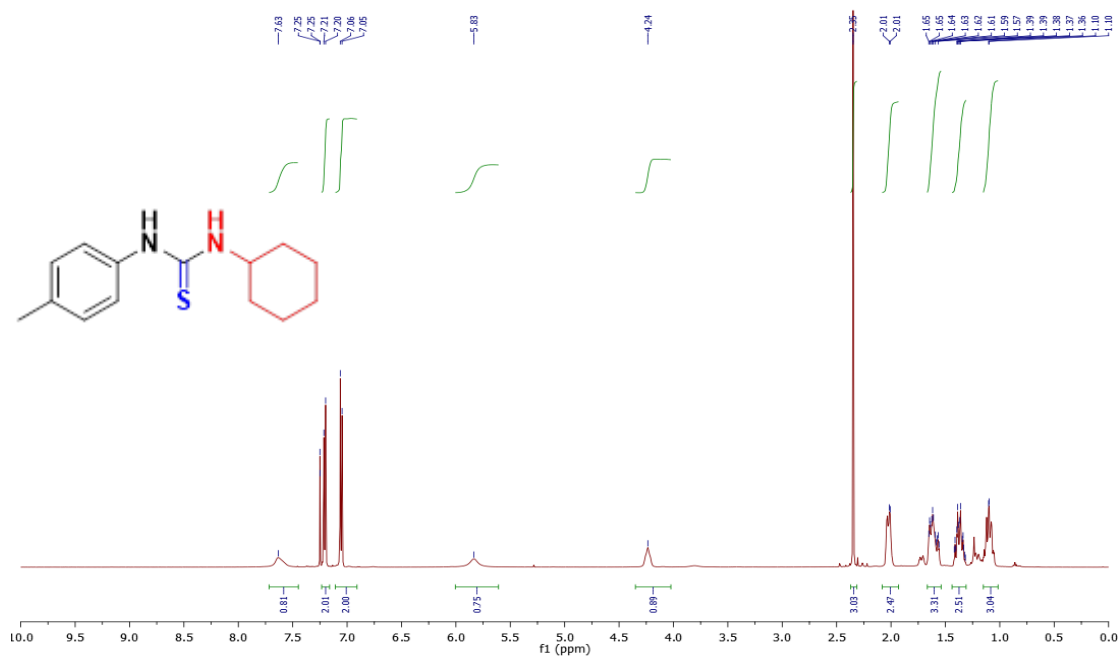
Figure A79 ^{1}H-NMR spectrum of **3h** (CDCl$_3$, 500 MHz)

Figure A80 ^{13}C-NMR spectrum of **3h** (CDCl$_3$, 500 MHz)

Figure A81 ^{1}H-NMR spectrum of **3i** (CDCl$_3$, 500 MHz)

Figure A82 ^{13}C-NMR spectrum of **3i** (CDCl$_3$, 500 MHz)
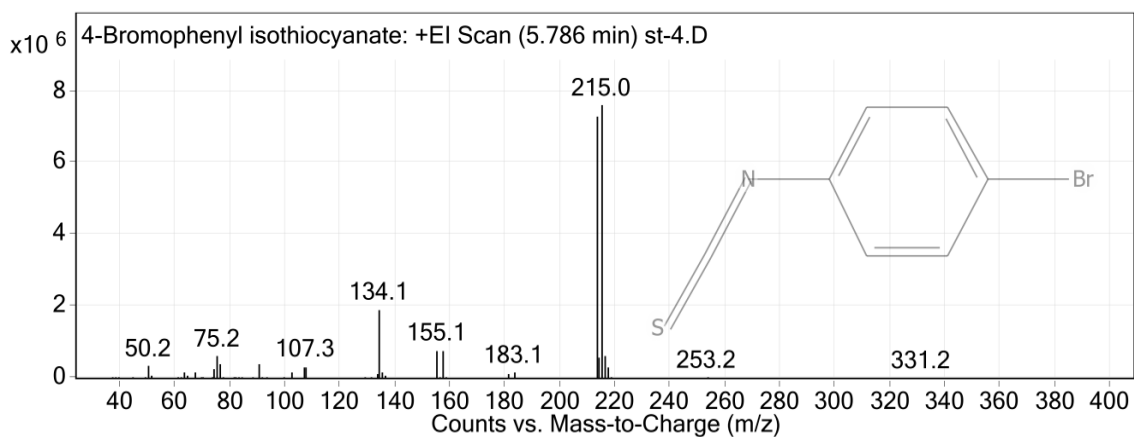
Figure A83 GC/MS spectrum of **2a**
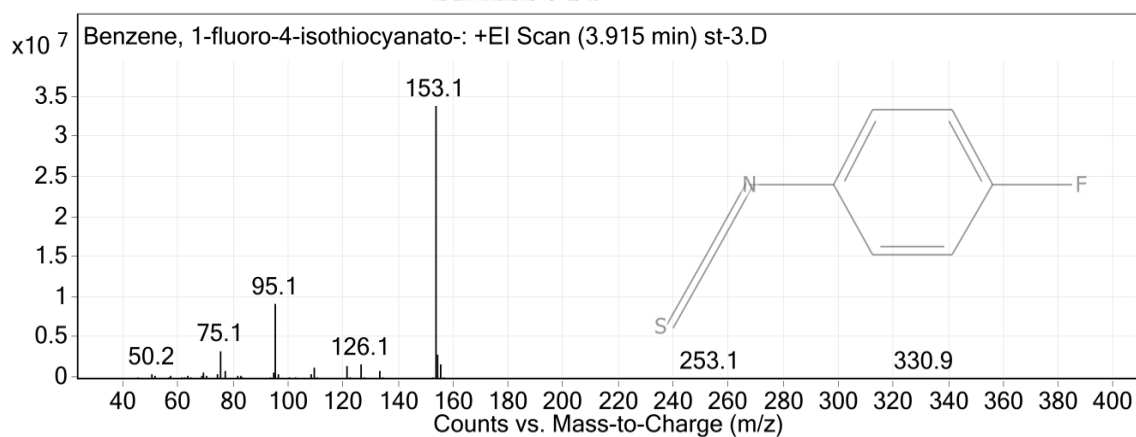
Figure A84 GC/MS spectrum of **2b**
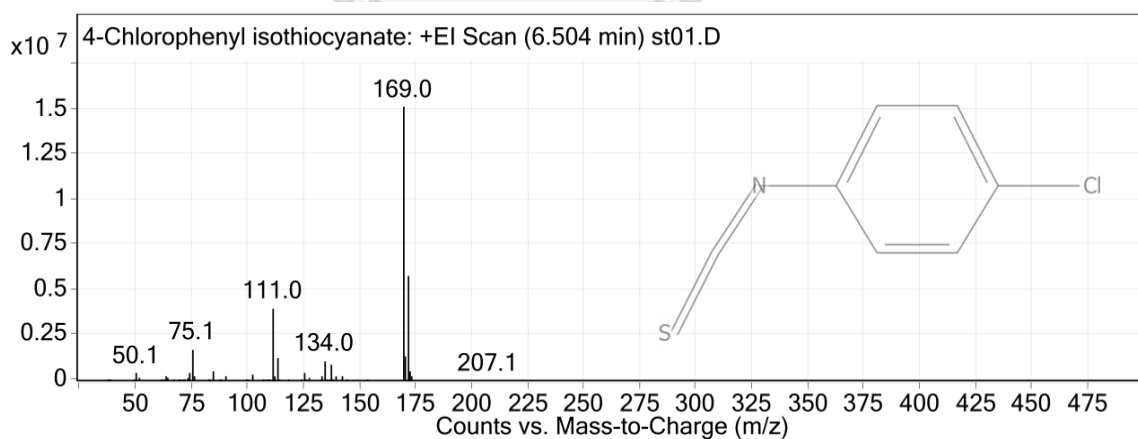
Figure A85 GC/MS spectrum of **2c**
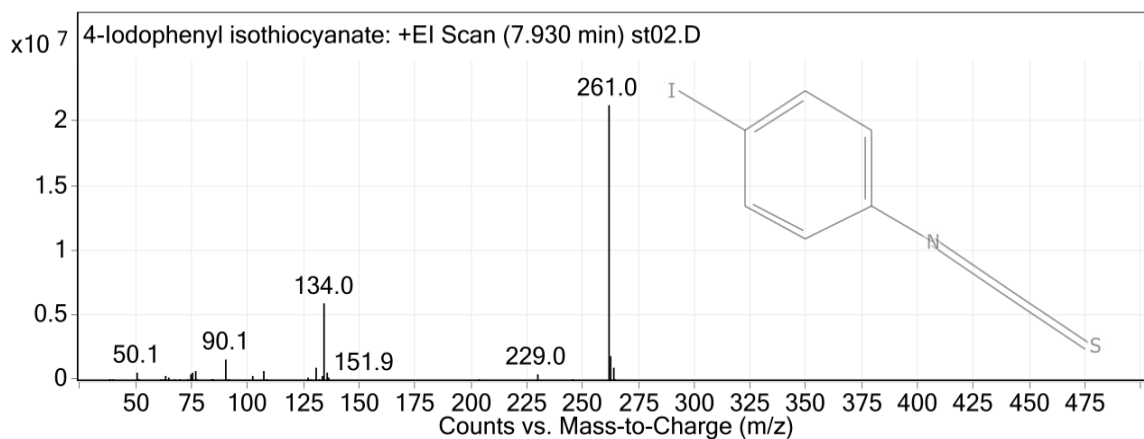
Figure A86 GC/MS spectrum of **2d**
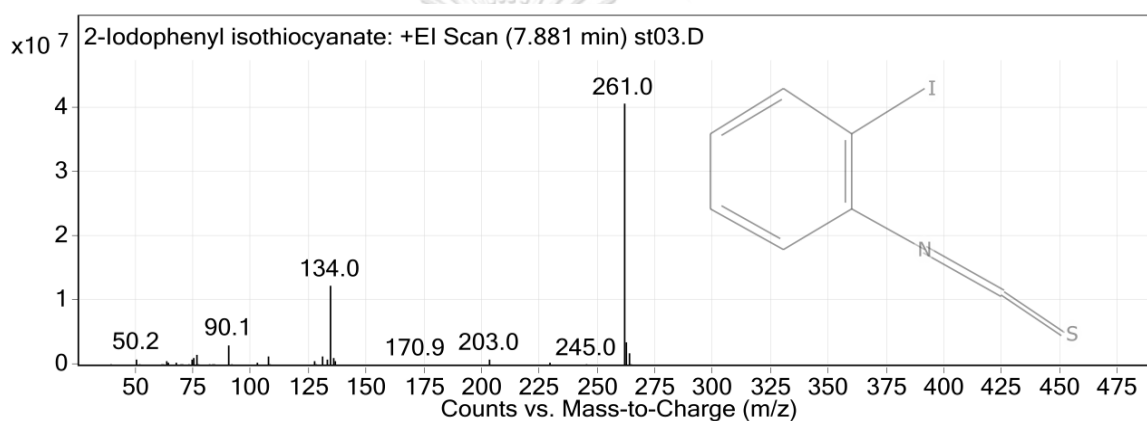
Figure A 87 GC/MS spectrum of **2e**
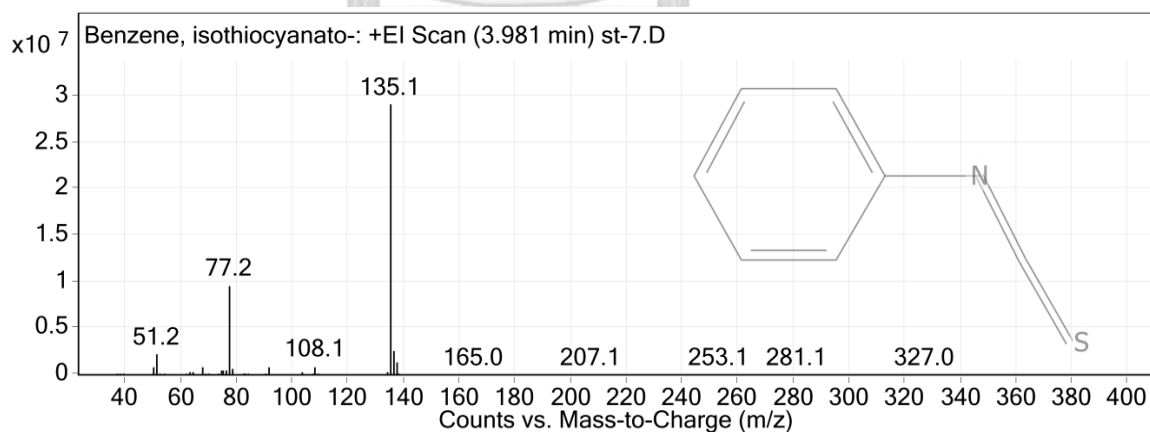
Figure A88 GC/MS spectrum of **2f**
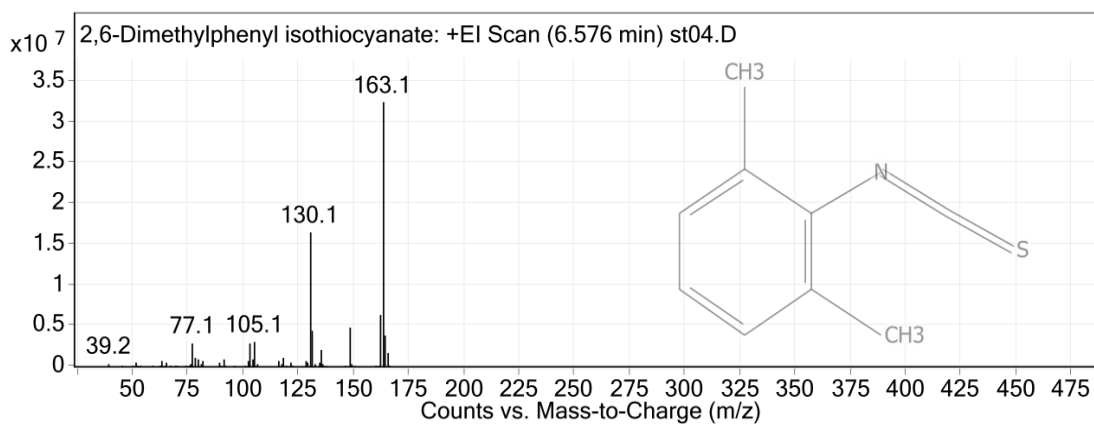
Figure A89 GC/MS spectrum of 2h
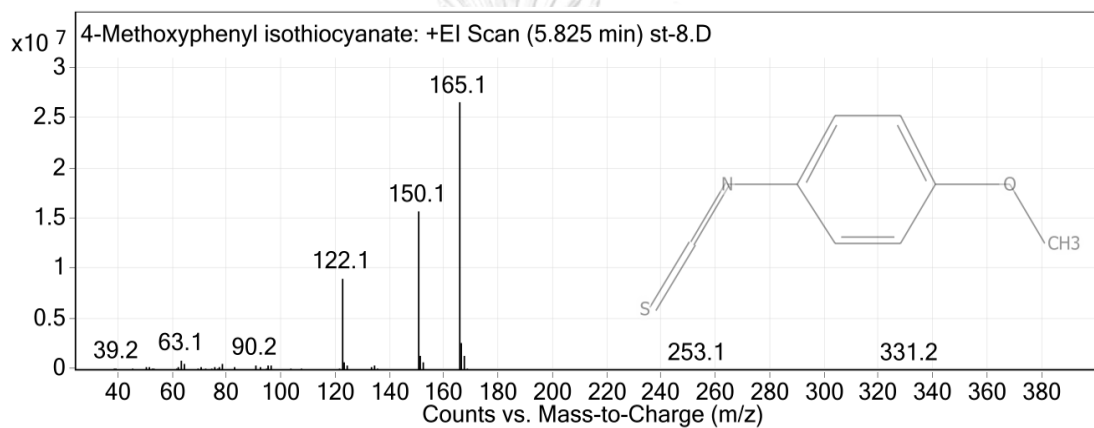
Figure A 90 GC/MS spectrum of 2i
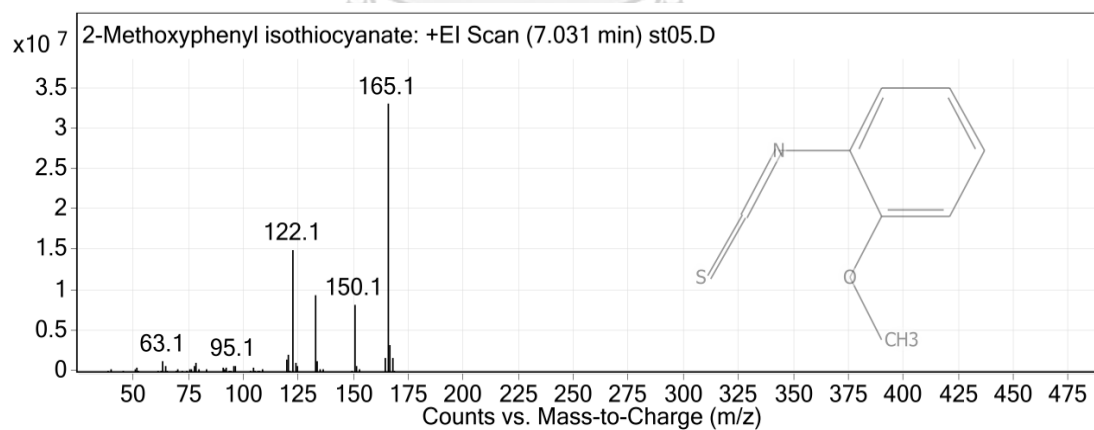
Figure A91 GC/MS spectrum of 2j
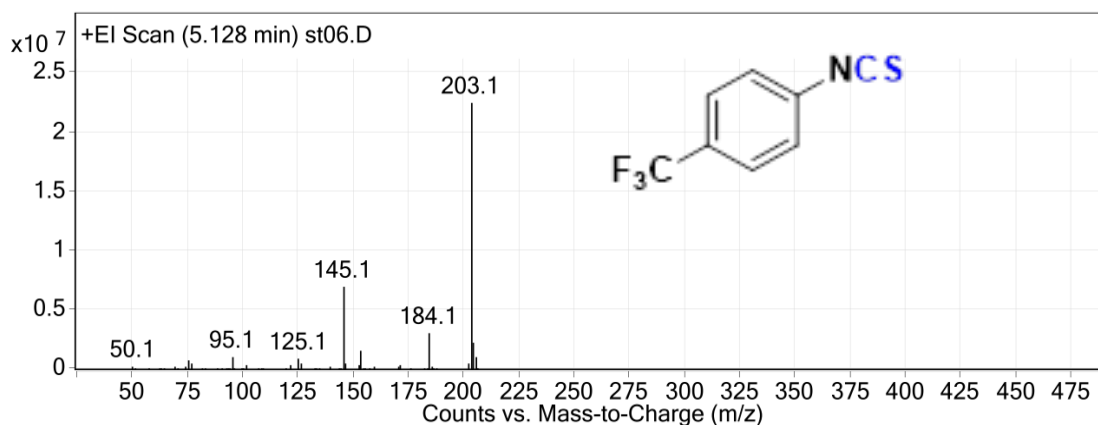
Figure A92 GC/MS spectrum of **2k**
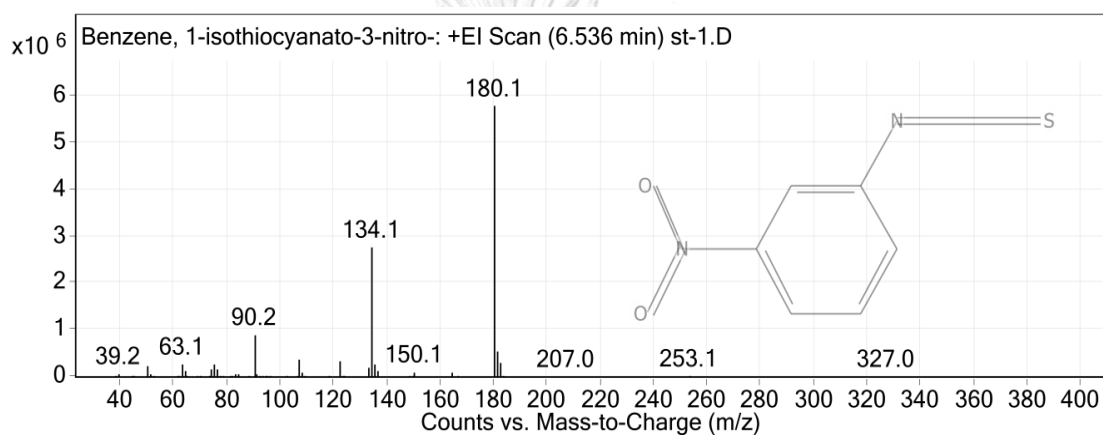
Figure A93 GC/MS spectrum of **2l**
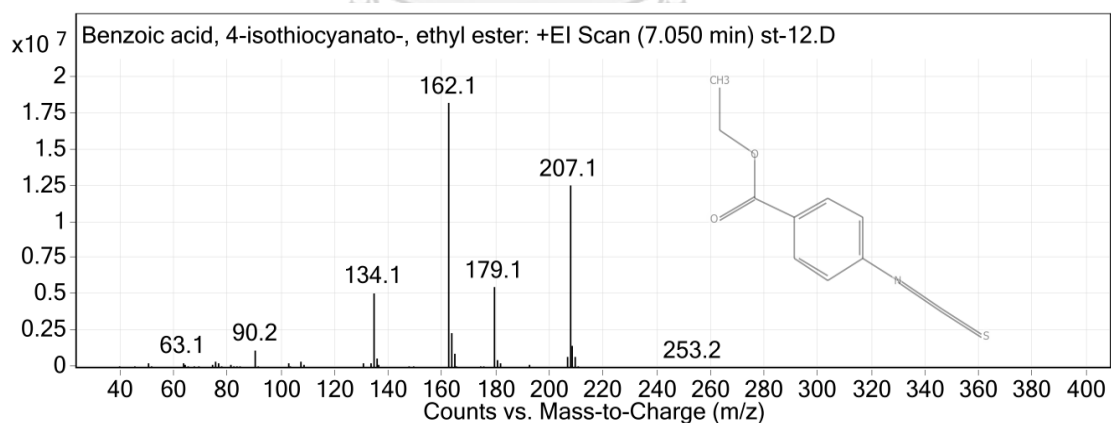
Figure A94 GC/MS spectrum of **2m**
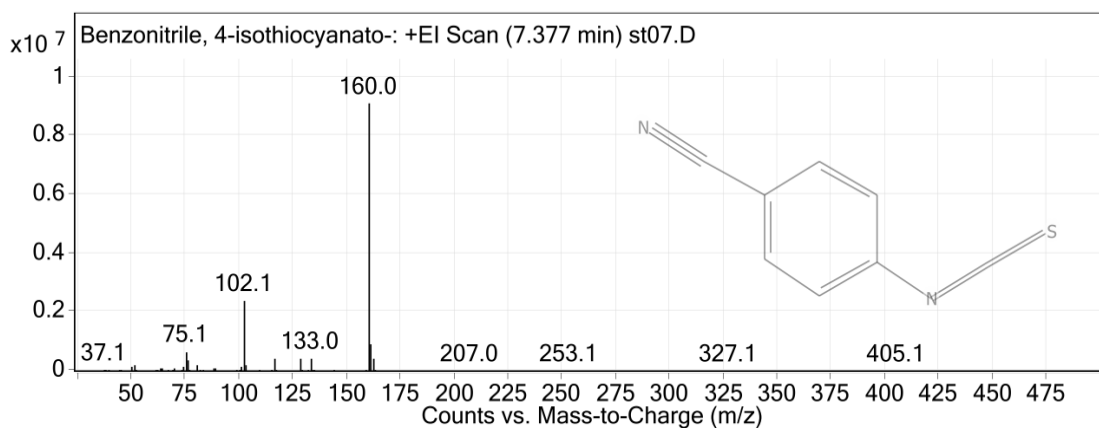
Figure A95 GC/MS spectrum of **2n**
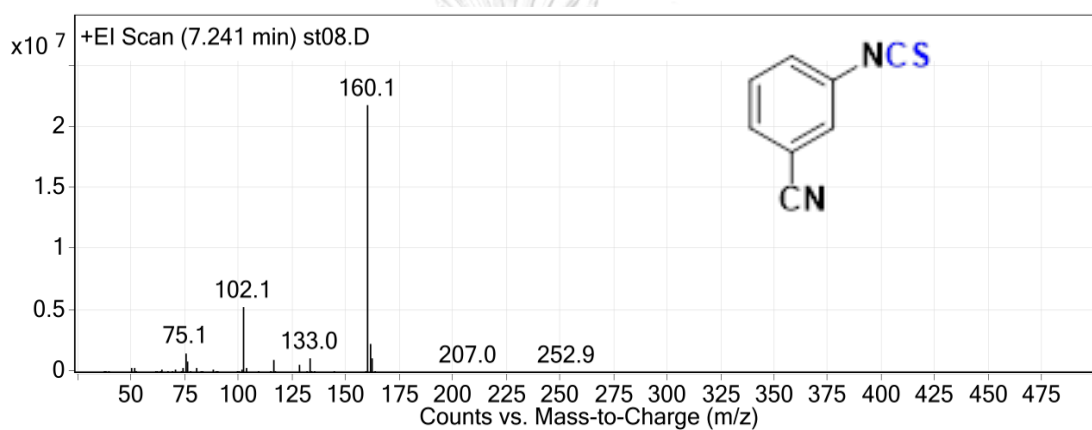
Figure A96 GC/MS spectrum of **2o**
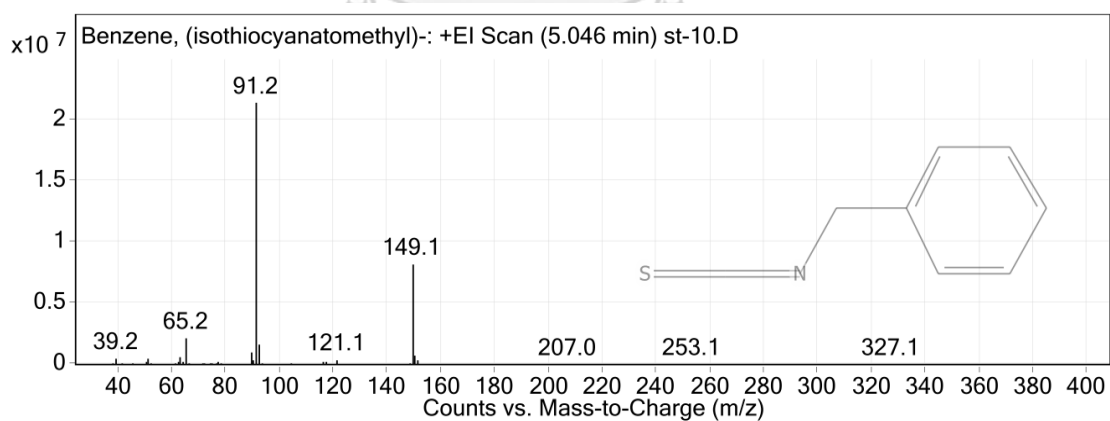
Figure A97 GC/MS spectrum of **2p**
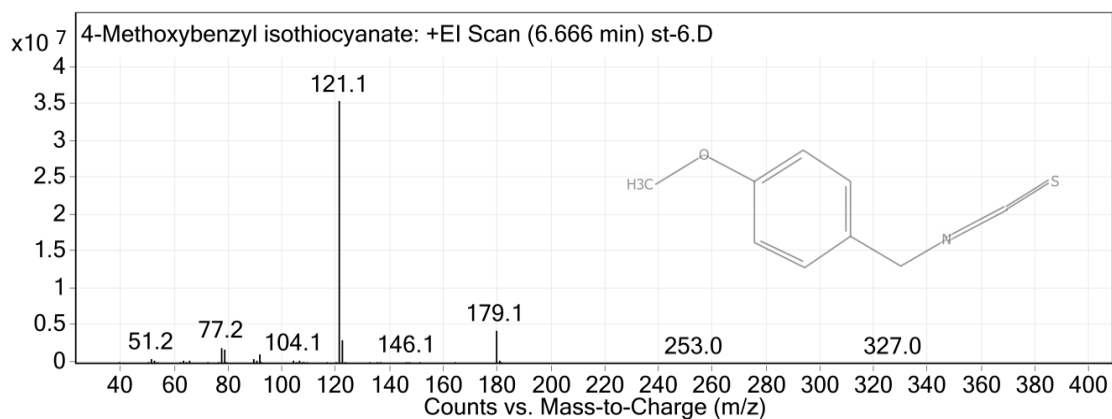
Figure A98 GC/MS spectrum of **2q**
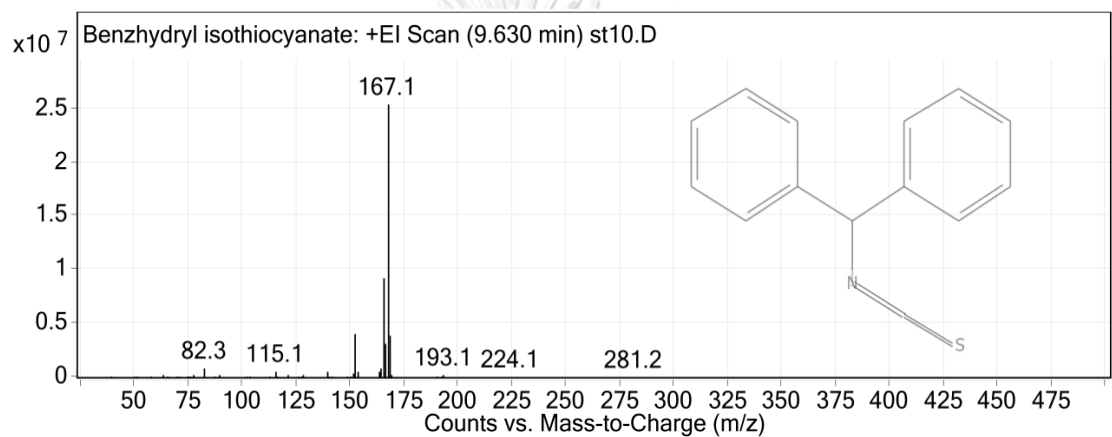
Figure A99 GC/MS spectrum of **2r**
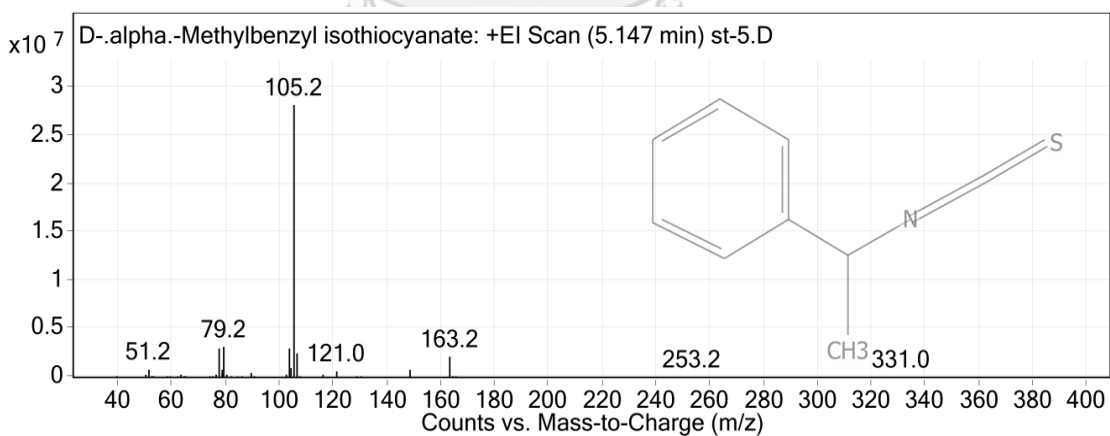
Figure A100 GC/MS spectrum of **2s**
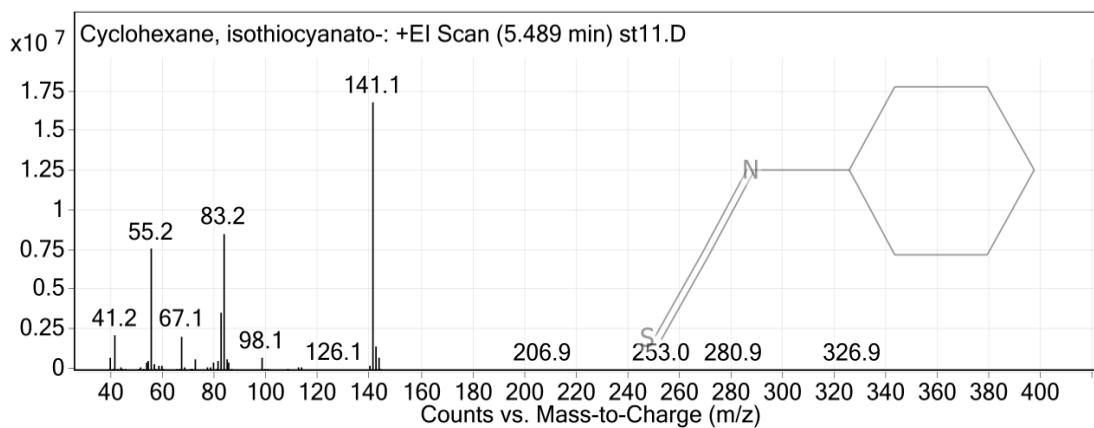
Figure A100 GC/MS spectrum of **2t**
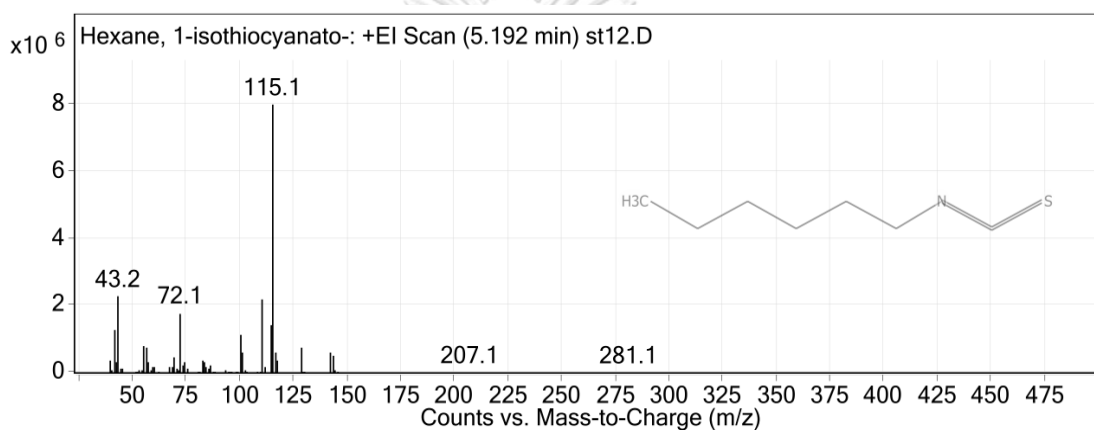
Figure A101 GC/MS spectrum of **2u**
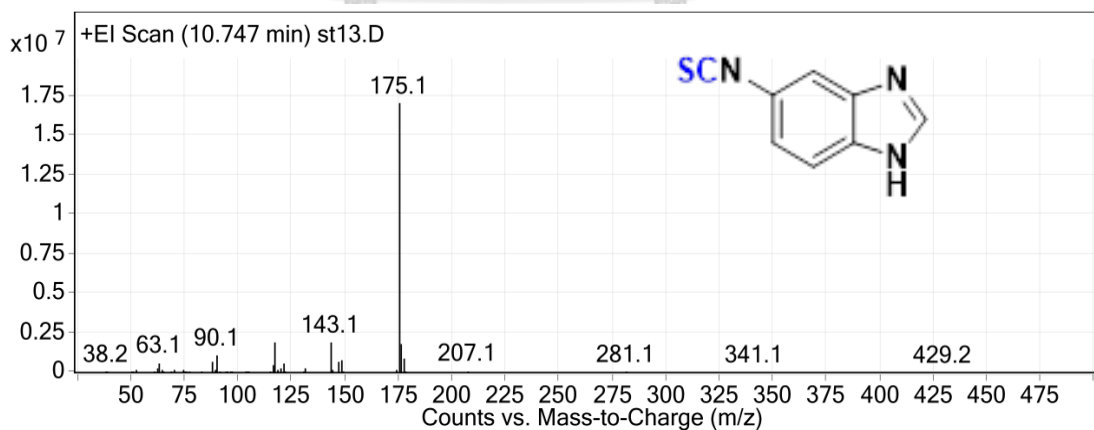
Figure A102 GC/MS spectrum of **2w**
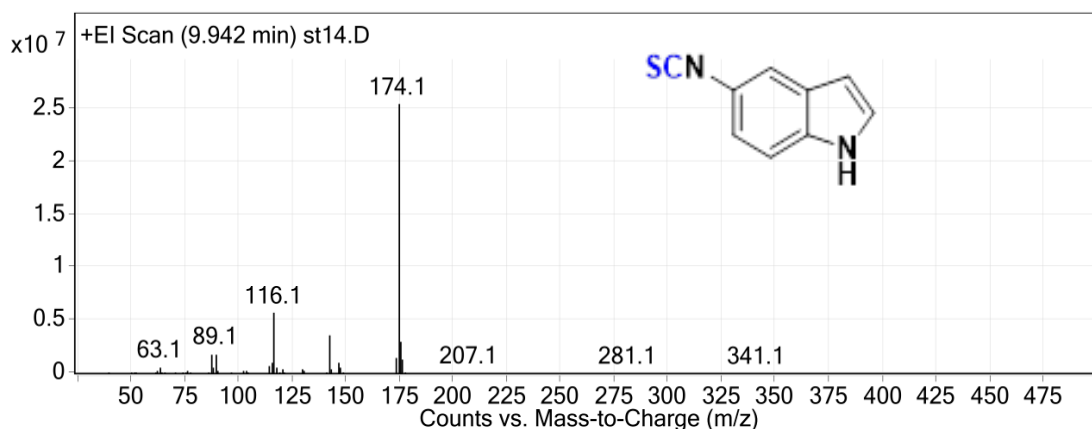
Figure A103 GC/MS spectrum of **2x**
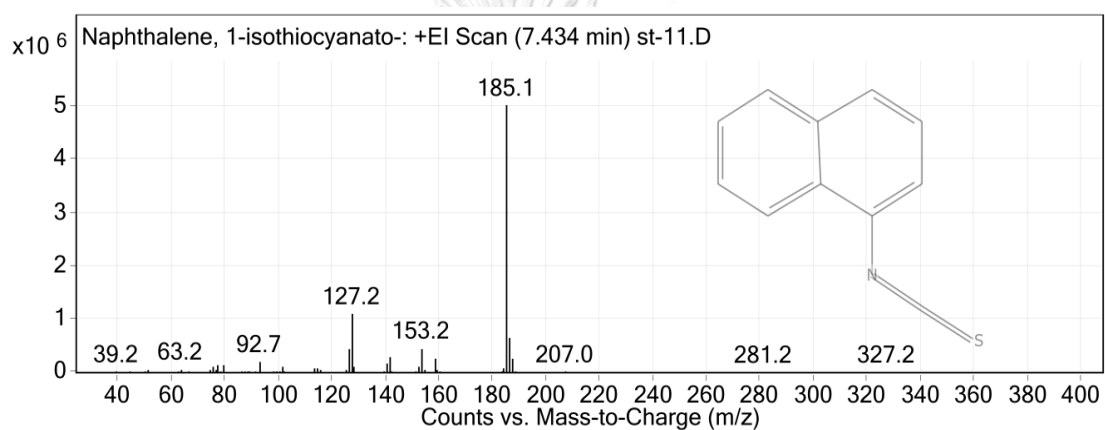
Figure A104 GC/MS spectrum of **2y**
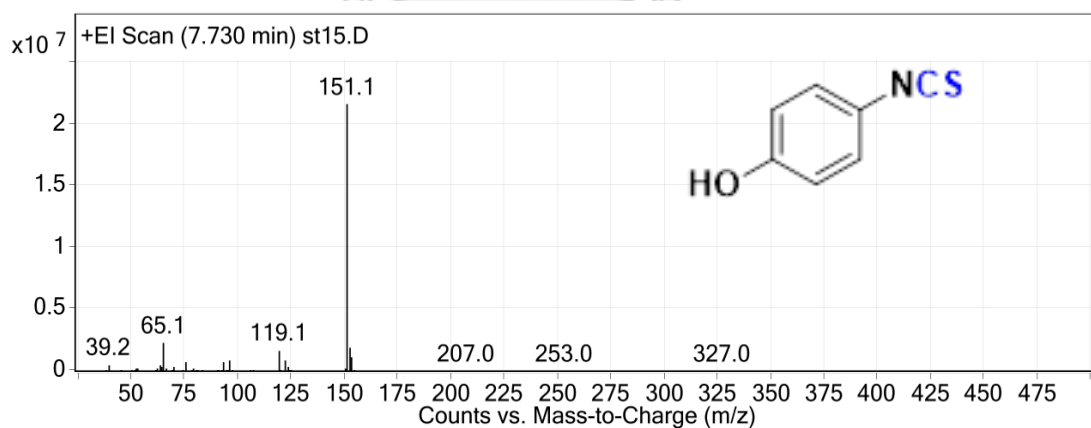
Figure A105 GC/MS spectrum of **2z**
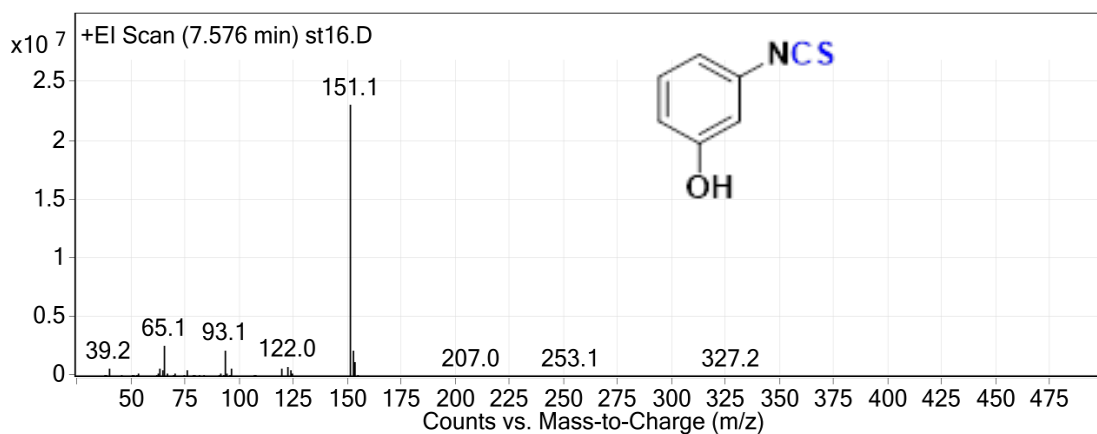
Figure A106 GC/MS spectrum of **2aa**
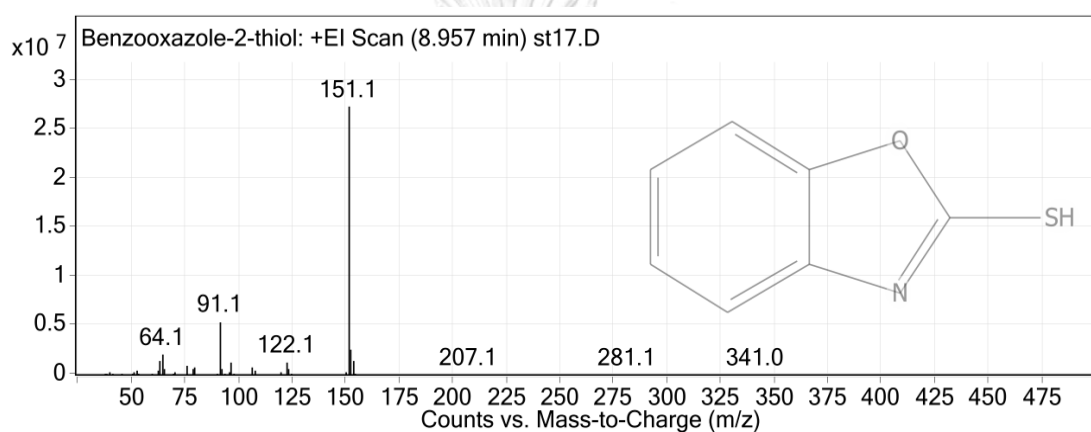
Figure A107 GC/MS spectrum of **2bb**
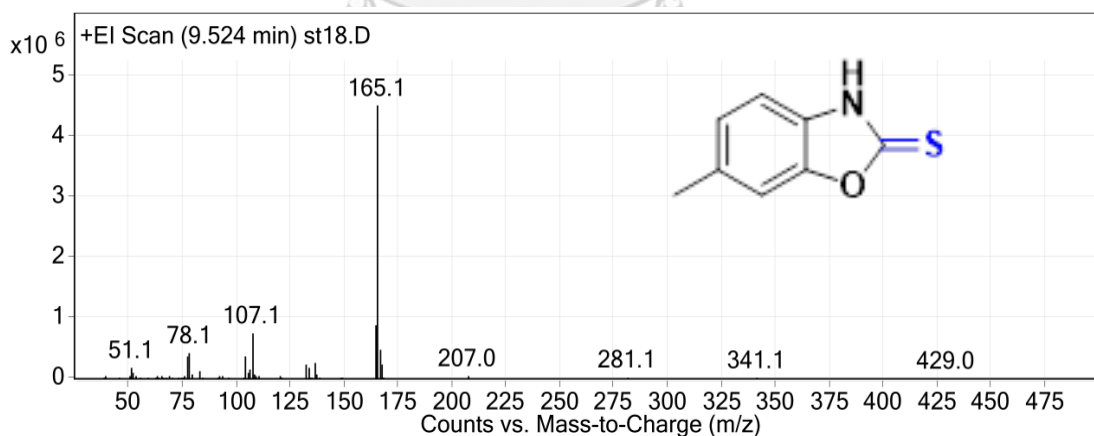
Figure A108 GC/MS spectrum of **2cc**
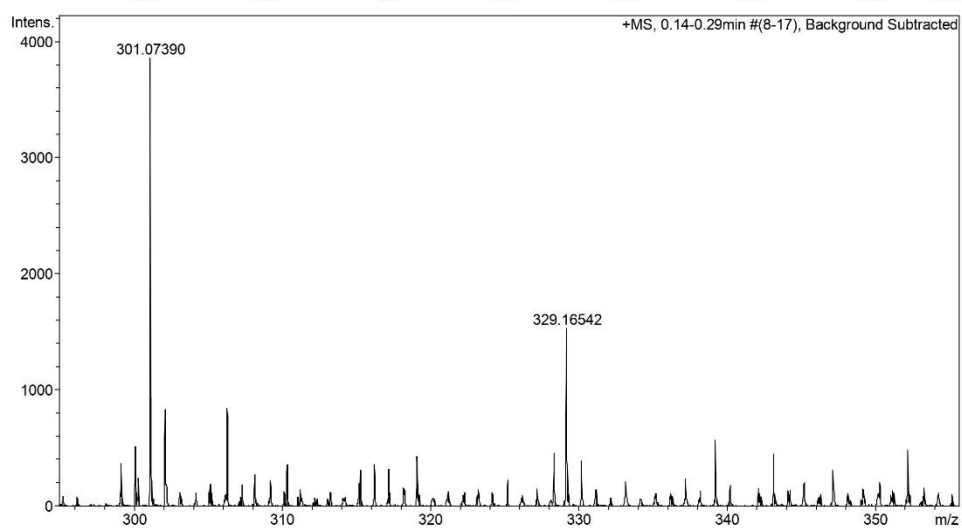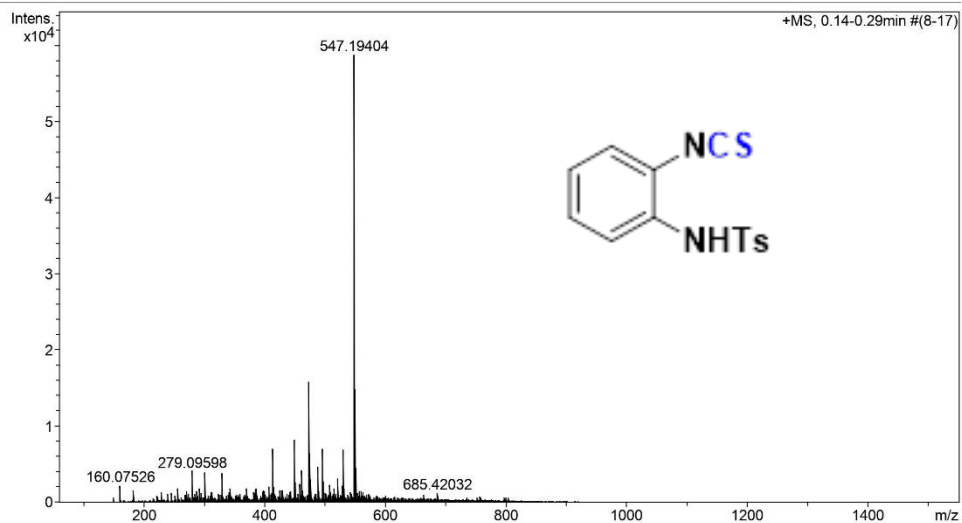
Figure A109 HRMS spectrum of **2dd**
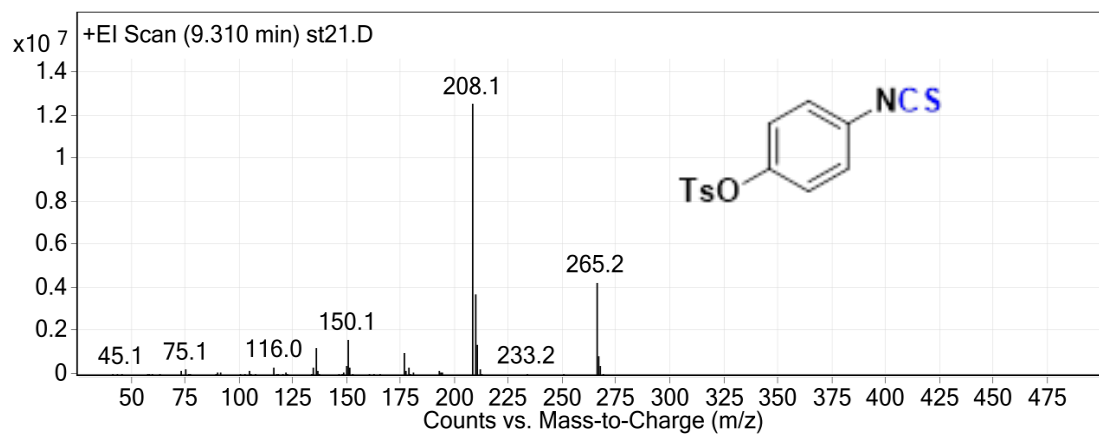
Figure A110 GC/MS spectrum of **2ee**

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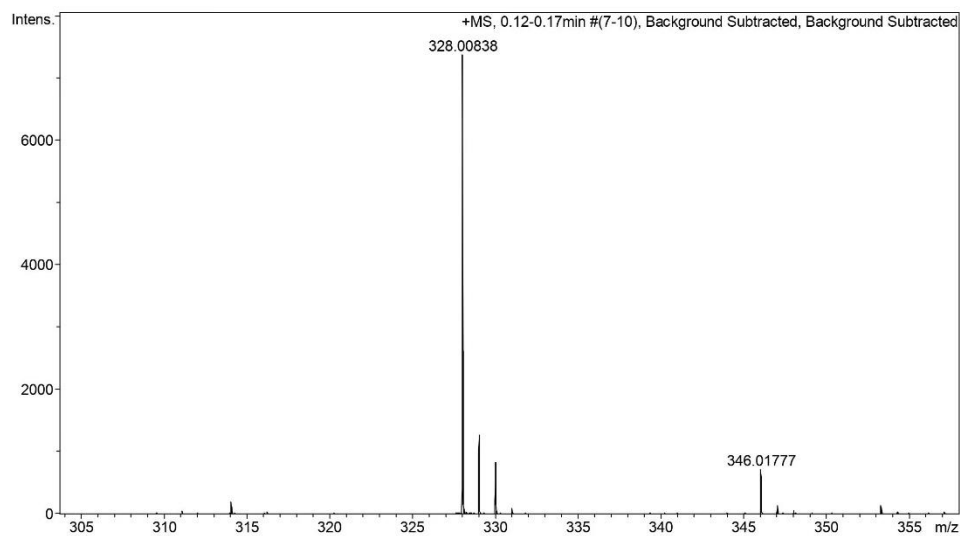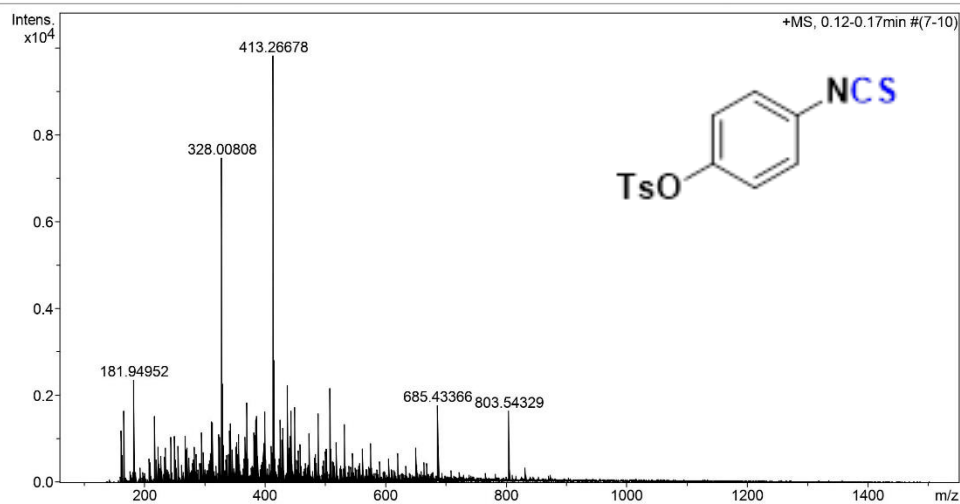
Figure A111 HRMS spectrum of **2ff**

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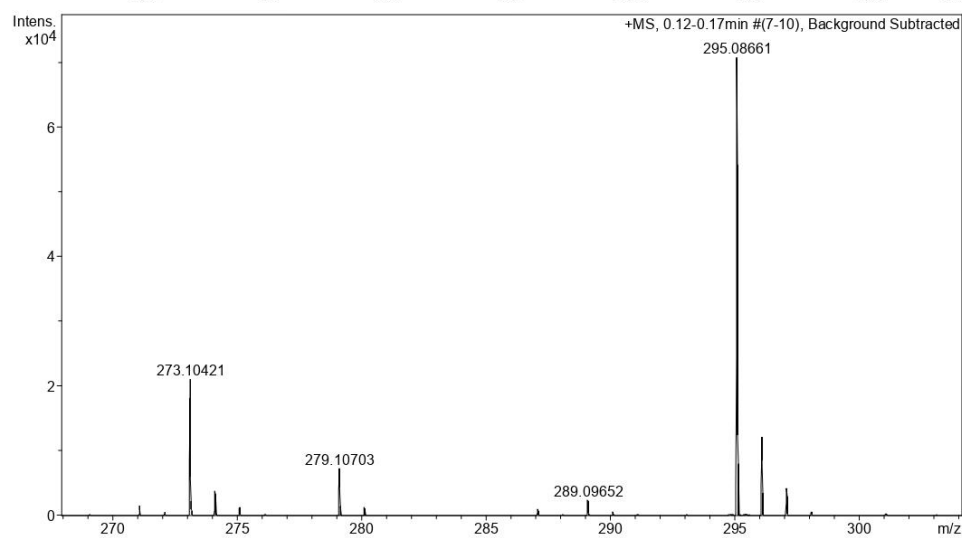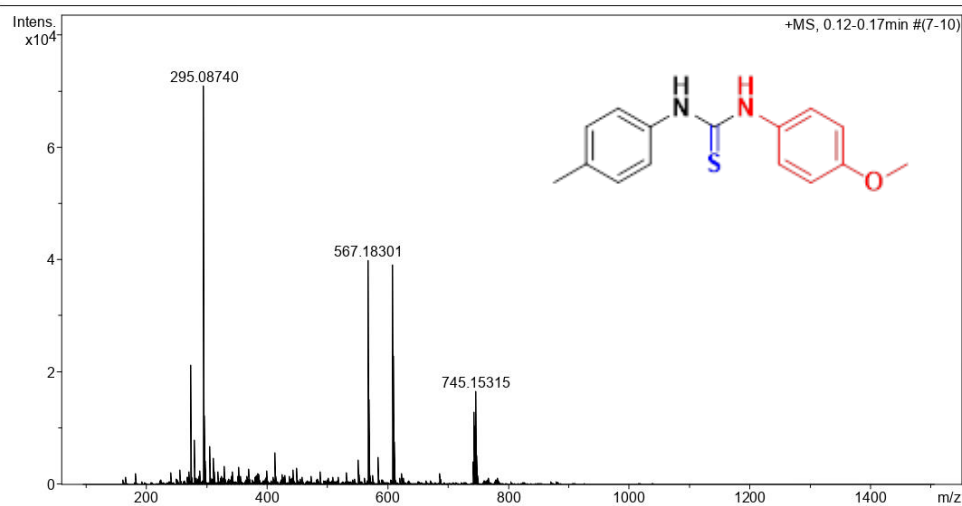
Figure A112 HRMS spectrum of **3a**
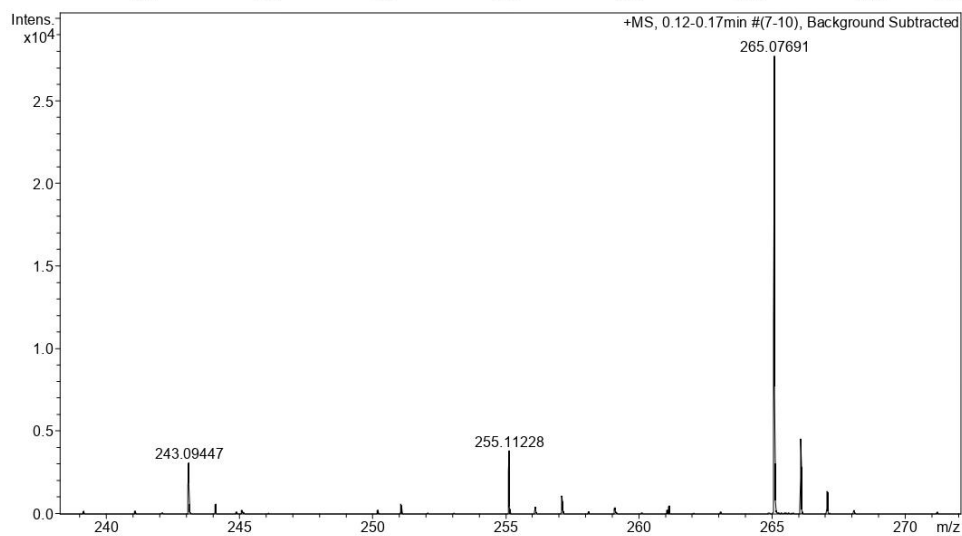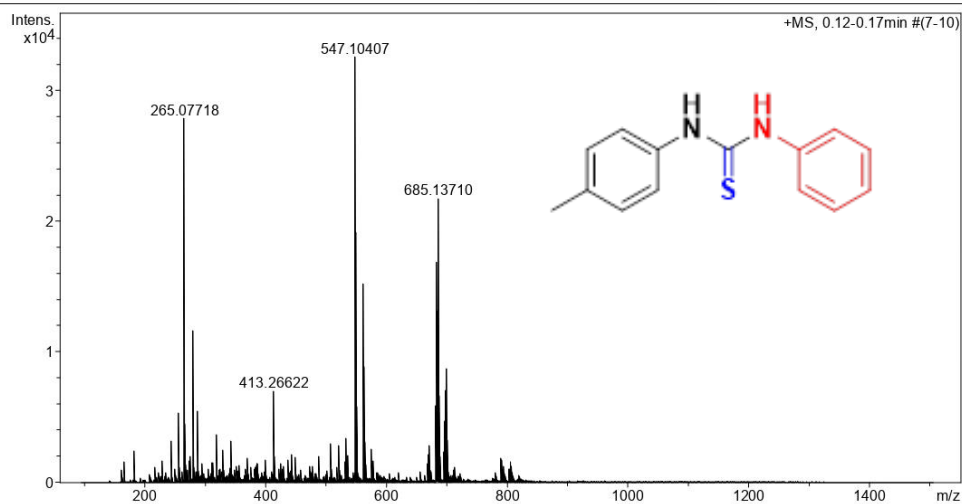
Figure A113 HRMS spectrum of 3b
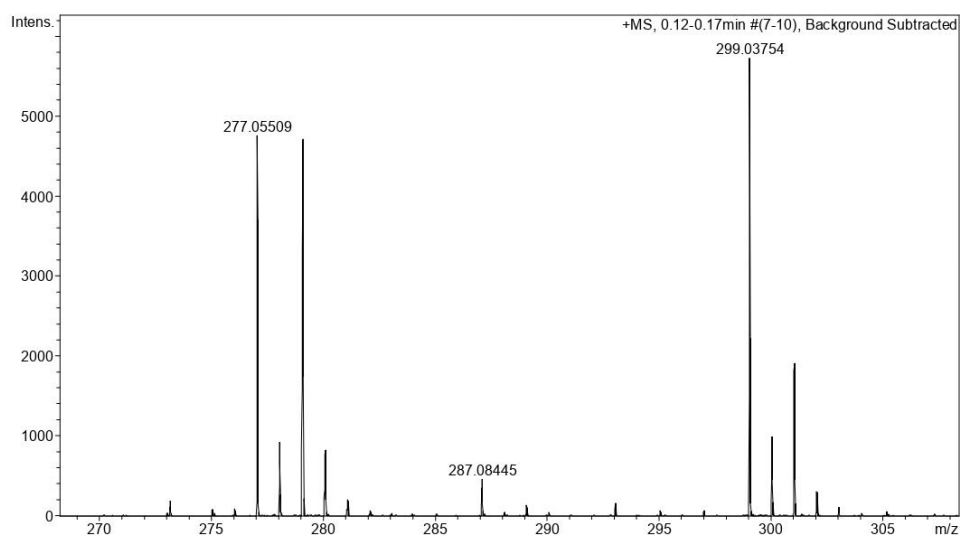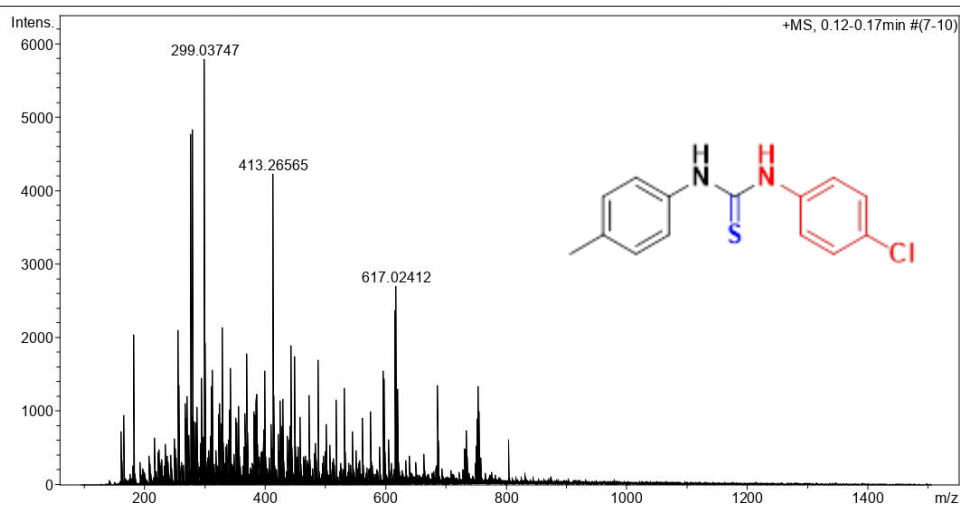
Figure A114 HRMS spectrum of 3c

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Figure A115 HRMS spectrum of **3d**

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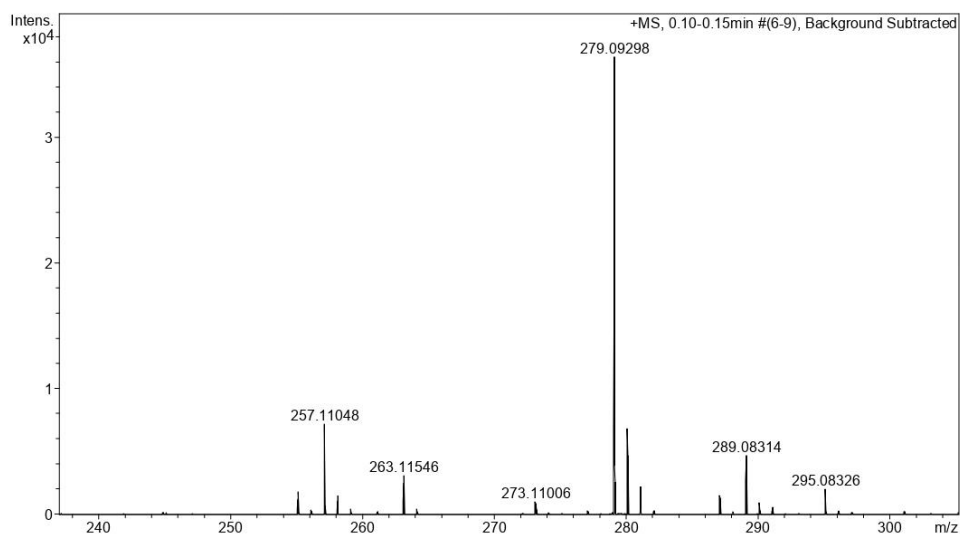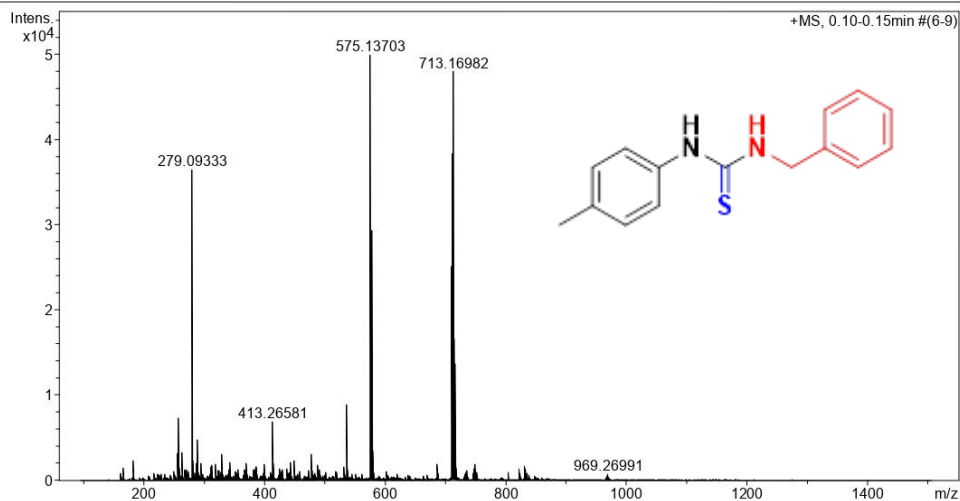
Figure A116 HRMS spectrum of **3e**
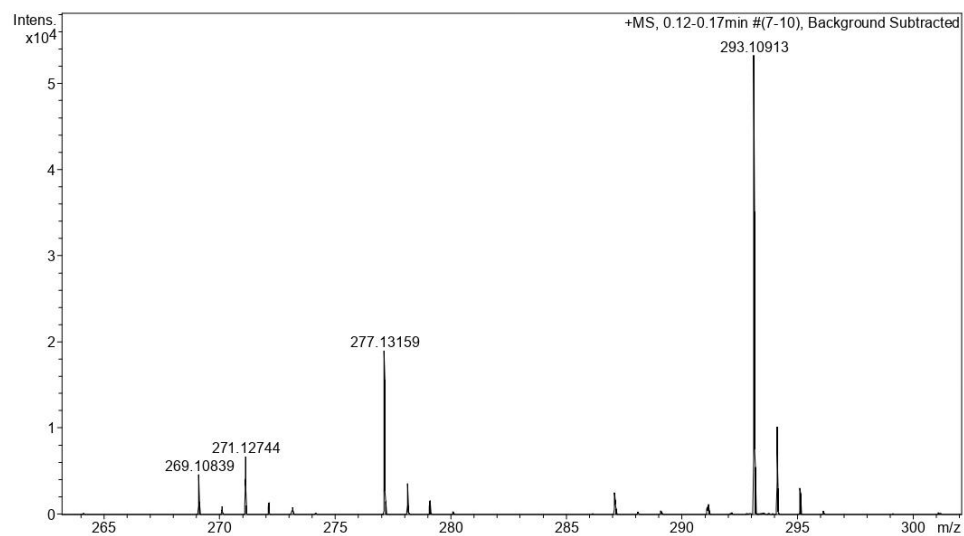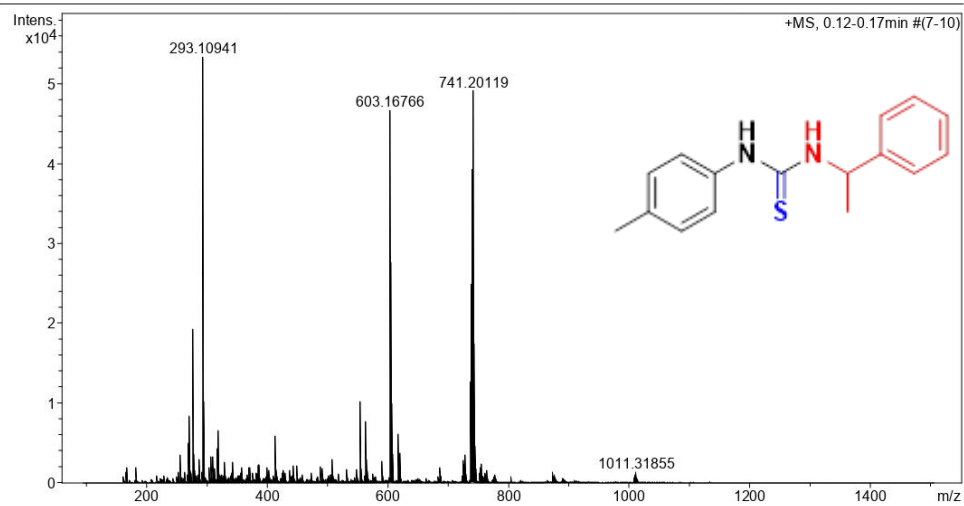
Figure A117 HRMS spectrum of 3f

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Figure A118 HRMS spectrum of **3g**

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Figure A119 HRMS spectrum of **3h**
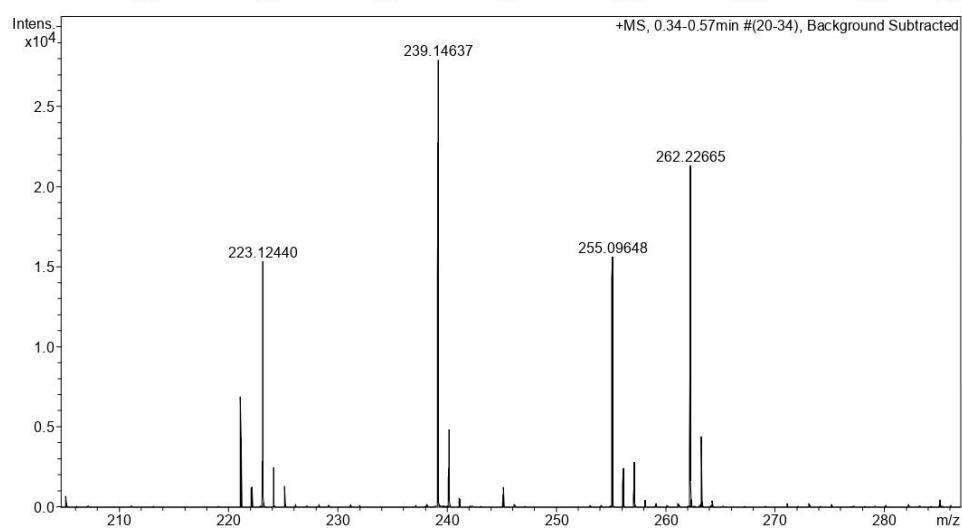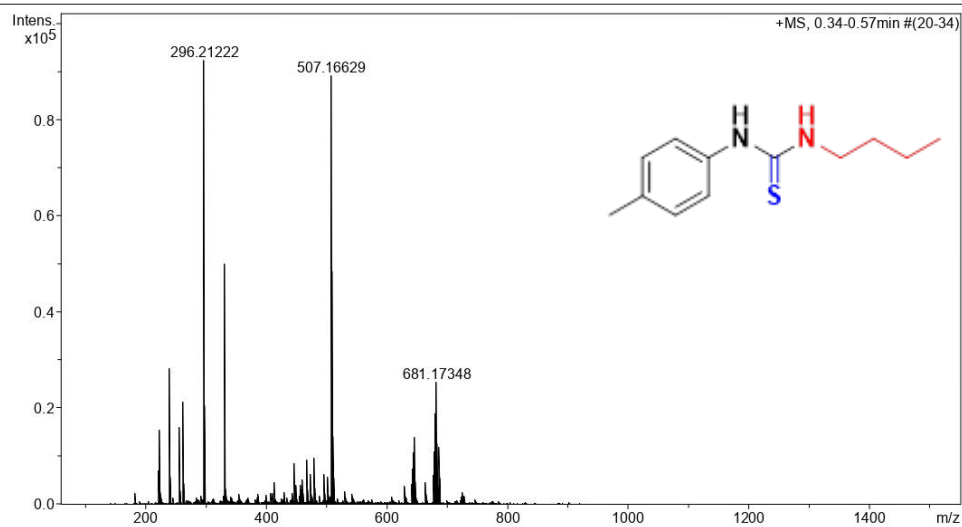
Figure A120 HRMS spectrum of **3i**

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