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PAPER

Facile aromatic nucleophilic substitution reactions (S_NAr) in ionic liquid: An electrophile-nucleophile dual activation by [Omim]Br for the reaction

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Xiao Zhang, Guo-ping Lu*, Chun Cai

A facile aromatic nucleophilic substitution reaction (S_NAr) in recyclable [Omim]Br under relatively mild conditions has been described. An electrophile-nucleophile dual activation by [Omim]Br is also discovered based on control experiments, ^1H NMR and IR spectroscopies. This chemistry provides an efficient and metal-free approach for the generation of C_{aryl}-X (X = S, N, O) bonds, many of which are significant synthetic intermediates or drugs rendering this methodology attractive to both synthetic and medicinal chemistry.

Introduction

Recently, ionic liquids (ILs) have become tunable and multipurpose materials for a variety of applications, such as organic synthesis, catalysis, chemical separation, material and energy science, due to their unique chemical or biological properties.[1] Among them, the imidazolium-based ILs that are one of the first to find applications on an industrial scale, are the most commonly investigated group for organic synthesis.[2] Both imidazolium-based IL cations' H-atoms of C-2 position and anions' lone pairs can form hydrogen bondings (HBs) with each other or other subtracts during the reactions,[3] by which some transformations can be further enhanced.[4] Therefore, the exploration of organic reactions in imidazolium-based ILs, in which HBs between ILs and substrates are formed to promote the reaction, is an appealing and greener alternative to organic synthesis.

Aromatic nucleophilic substitution reactions (S_NAr) are one of the powerful tools in medicine and chemical industry owing to their atom economy and metal-free conditions.[5] However, a major drawback is that dipolar, aprotic solvents such as DMF, DMAc, NMP and DMSO, are often required.[6] These solvents may cause significant health issues,[7] meanwhile an aqueous work-up procedure for the wastewater contain these solvents are also required.[8] To resolve the issue, several attempts have been made to use water in place of these solvents, in which the use of surfactants[9] and the formation of HBs between substrates and water[10] can accelerate the S_NAr reactions because of high local concentrations and the improvement of substrates' electrophile and nucleophile. Although most of nitroaryl fluorides are applied in these protocols under mild conditions and the aqueous medium can be also recycled by simple extraction, electron-deficient fluoroarenes without nitro group and most of electron-deficient chloroarenes fail to provide the desired products in water.

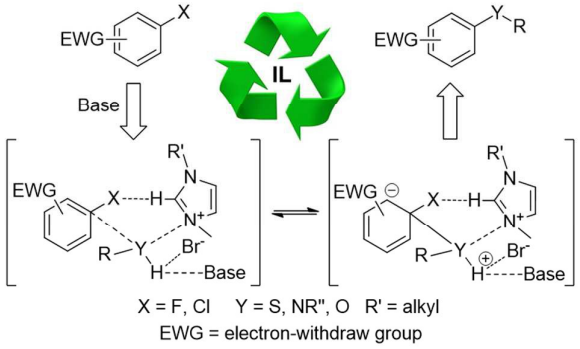

Fig. 1 Working hypothesis: an electrophile-nucleophile dual activation by ILs in S_NAr reactions.

Similarly, imidazolium-based ILs can also form HBs with electron-deficient aryl halides and nucleophiles, and be recycled by simple extraction. Furthermore, they have better solubility for substrates and higher boiling points than water, which are beneficial to S_NAr reactions. On the basis of these results, we reasoned that imidazolium-based ILs could be ideal solvents for S_NAr reactions, by which an electrophile-nucleophile dual activation is triggered to promote S_NAr reactions (Fig. 1). To our best knowledge, there is no report on the S_NAr reactions in ILs and exploring the activation mechanism of ILs in the transformation. Alone this line, we describe an efficient S_NAr reaction in [Omim]Br for the construction of C_{aryl}-X (X = S, N, O) bonds, in which the promotion of [Omim]Br on the reaction is investigated.

Chemical Engineering College, Nanjing University of Science & Technology
Xiaolingwei 200, Nanjing, 210094 (China)
* E-mail: glu@njust.edu.cn
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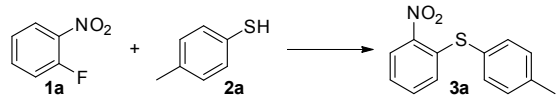
Moreover, the chemistry provides several advantages including free of metal catalysts, relatively mild conditions, the use of recyclable solvents, high yields and broad substrate scope that are in alignments with the principles of green chemistry.[11]

Results and discussion

To probe the feasibility of our working hypothesis, we started our investigation by reacting 1-fluoro-2-nitrobenzene **1a** with 4-methylbenzenethiol **2a** (Table 1). After screening different solvents, [Omim]Br proved to be the best choice for the reaction (entry 1). Bases were also necessary for the reaction as the acid-accepters. Although Cs_2CO_3, DBU and K_3PO_4 provided excellent yield of the product **3a** (entries 15, 18, 19), only K_3PO_4 could afford full conversion when the amount of base was reduced to 1.1 equiv. Only moderate yields were afforded at lower temperatures (entry 19). Moreover, K_3PO_4 have lower toxic and cost than the other two bases.

After comparing with different ILs, it was found that C-2 hydrogen of [Omim]Br might enhance the reaction by forming HBs with substrates (entries 19 *vs* 20).[4] Anions of ILs had a certain influence on the process. A slight lower yield was observed in [Omim]I (entries 19 *vs* 21) presumably owing to the weaker hydrogen bond acceptor (HBA) (β scale) property.[12] The acidic IL could inhibit the reaction since the base was consumed by IL (entry 26). The length of alkyl groups had no evident effect on the chemistry, but [Omim]Br emerged as the best option owing to better flowability than [Hmim]Br and [Bmim]Br (entries 19, 25, 26).

Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Base	Yield (%)[b]
1	[Omim]Br	K_2CO_3	92
2	MeCN	K_2CO_3	52
3	EtOH	K_2CO_3	75
4	water	K_2CO_3	29
5	THF	K_2CO_3	41
6	DMSO	K_2CO_3	74
7	DMF	K_2CO_3	65
8	Hexane	K_2CO_3	32
9	[Omim]Br	NaOH	85
10	[Omim]Br	NEt_3	62
11	[Omim]Br	KOH	83
12	[Omim]Br	Na_2CO_3	64
13	[Omim]Br	*t*-BuOK	77
14	[Omim]Br	$NH_3{\cdot}H_2O$	66
15	[Omim]Br	$C_{S2}CO_3$	96
16	[Omim]Br	Piperidine	88
17	[Omim]Br	DABCO	81
18	[Omim]Br	DBU	97
19	[Omim]Br	K_3PO_4	>99, >99,[c] 68,[d] 51[e]
20	[Ommim]Br[f]	K_3PO_4	73
21	[Omim]Cl	K_3PO_4	98
22	[Omim]I	K_3PO_4	89
23	[Omim]OAc	K_3PO_4	97
24	[Omim]HSO_4	K_3PO_4	trace
25	[Hmim]Br	K_3PO_4	96
26	[Bmim]Br	K_3PO_4	93
27	[Omim]Br	/	trace

[a] Conditions: **1a** 1.0 mmol, **2a** 1.2 mmol, base 3.0 equiv, solvent 1.0 mL, 80 °C, 12 h. [b] GC yields, [c] K_3PO_4 was 1.1 equiv. [d] At 50 °C. [e] At room temperature. [f] [Ommim]Br was 1,2-dimethyl-3-octyl-1H-imidazol-3-ium bromide.

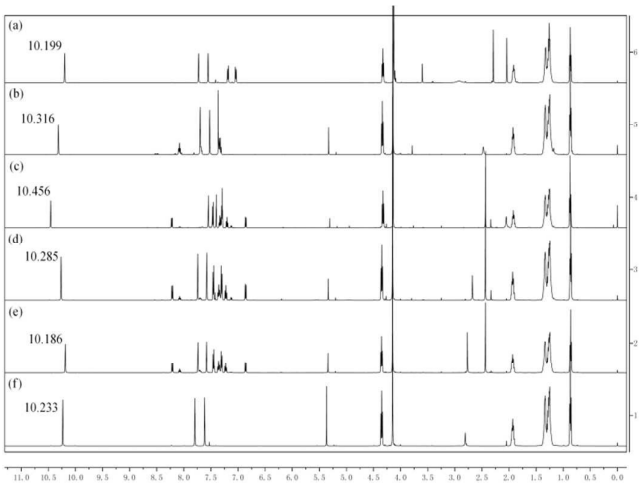
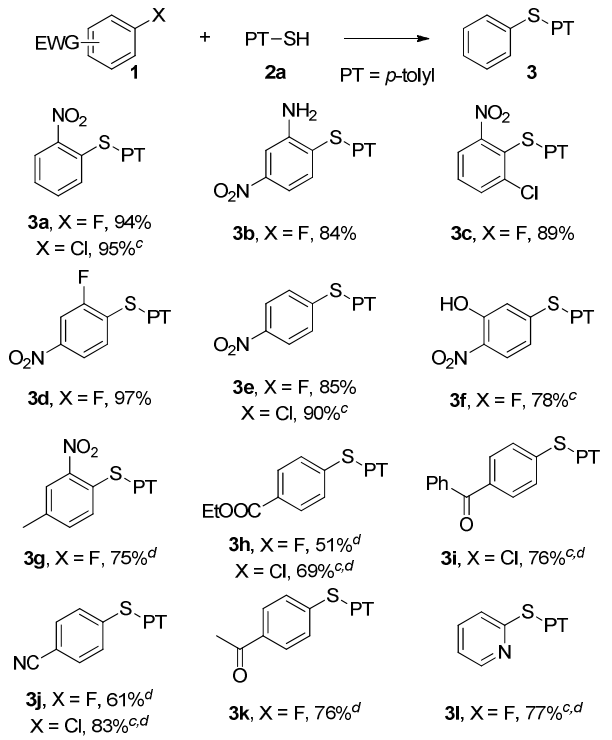


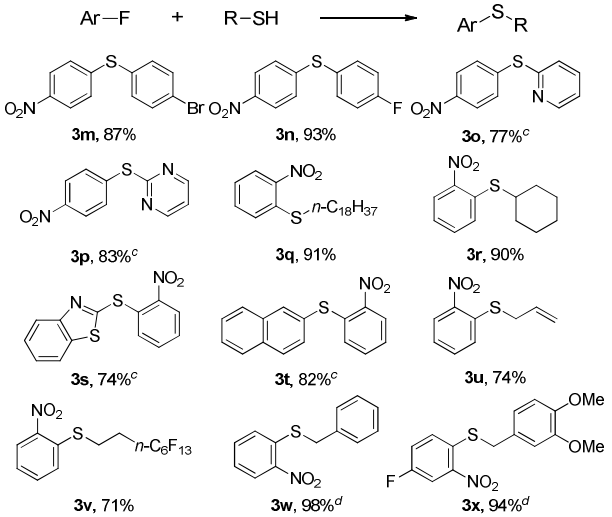
Fig. 2 ^{1}H NMR spectra of (a) The mixing of **2a** and [Omim]Br after 30 min, (b) The mixing of **1a** and [Omim]Br after 30 min, (c-e) The reaction of **1a** and **2a** in [Omim]Br with K_3PO_4 after 12 h (c), 1 h (d), 30 min (e). (f) [Omim]Br.

Further experiments were also performed to investigate the hypothetical interaction between [Omim]Br and substrates (**1a**, **2a**). The model reaction was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ (Fig. 2). Based on these results, it was found that the proton at the C-2 position of the imidazolium moiety shifted from 10.233 (f) to 10.186 (30 min, e), 10.285 (1 h, d) and 10.456 (12 h, c), which could be considered as evidences of the electrophile–nucleophile dual activation by [Omim]Br. Firstly, the charge-charge interaction between the quaternary N atom of [Omim]Br and the S atom of **2a** and HB formation between Br^- and thiol S-H hydrogen can increase the charge density of imidazole ring (nucleophilic activation),[3,13] so the proton shifted from 10.233 to 10.186.[14]

Then, HB is generated between the C-2 hydrogen and F atom, resulting in an electrophilic activation of the C-F bond's carbon.[4,13] Meanwhile, the charge-charge interaction of the quaternary nitrogen atom and S atom decreases along with the formation of the C-S bond in reaction. Thus, the charge density of imidazole ring is reduced, making C-2 proton shift to low field (10.186 to 10.285). Finally, the F atom separates from **1a** to be the anion of IL, which further drops the charge density of imidazole ring (10.285 to 10.456). Based on these results, it can be concluded the electrophile-nucleophile dual activation by [Omim]Br may be a stepwise process or a pathway between stepwise mechanism and synergistic mechanism unlike the previous literature.[4,10] The results of interactions between IL and subtrates (**1a**, **2a**) were also



Scheme 1 The S_NAr reactions of electron-deficient aryl halides with *p*-tolylthiol in [Omim]Br.[a,b] [a] Conditions: **1** 1.0 mmol, **2a** 1.1 mmol, K_3PO_4 1.1 mmol, [Omim]Br 1 mL, 80 °C, 12 h. [b] Isolated yields. [c] At 120 °C. [d] 24 h.

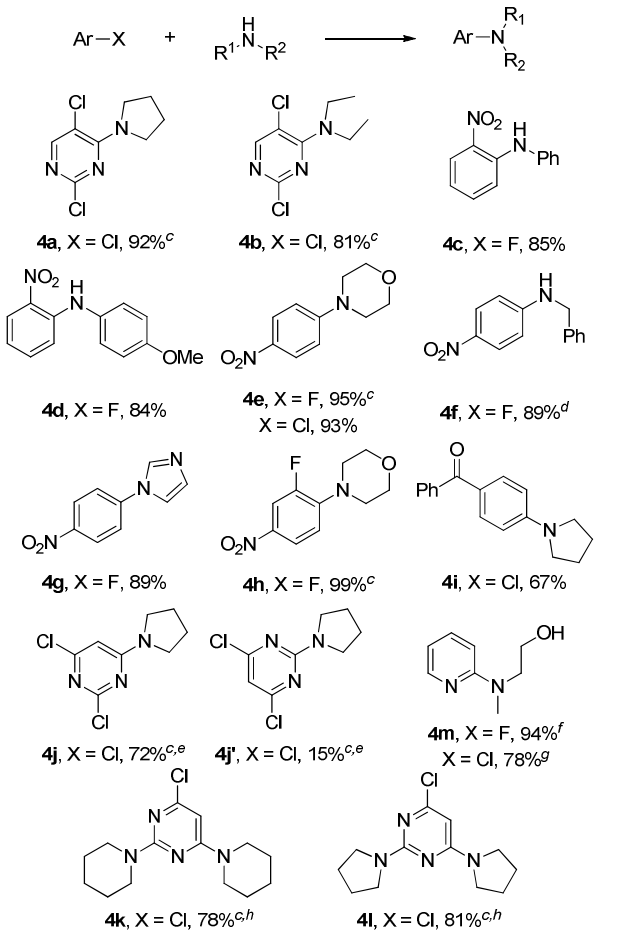


Scheme 2 The S_NAr reactions of nitroaryl fluorides with thiols in [Omim]Br.[a,b] [a] Conditions: **1** 1.0 mmol, **2** 1.1 mmol, K_3PO_4 1.1 mmol, [Omim]Br 1 mL, 80 °C, 12 h. [b] Isolated yields. [c] 24 h. [d] At 50 °C.

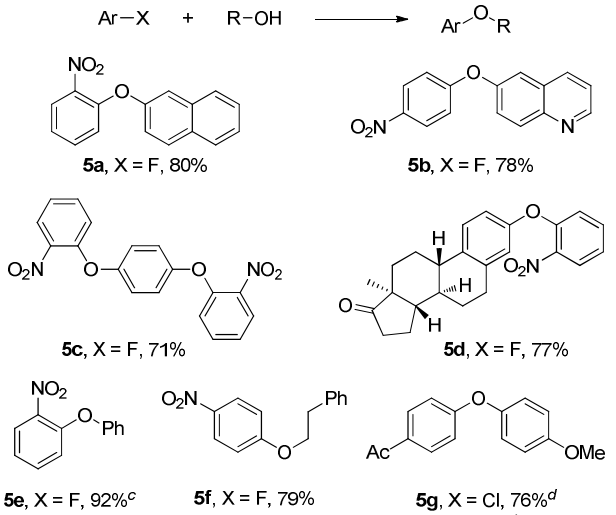
according with our assumptions (a, b *vs* f). Additionally, the reaction was examined by IR spectroscopy, and similar results were obtained (see ESI). Clarification of the detailed mechanism is a goal in our future research by experiments and quantum chemical calculations.

With the optimized conditions in hands, a series of electron-deficient aryl halides **1** were applied to establish the scope and generality of the protocol (Scheme 1). Generally, *para*- or *ortho*-nitroaryl fluorides could react with **2a** smoothly to yield the desired products **3a**-**3e**. Prolonging reaction time to 24 h or increasing temperature to 120 °C were required using nitroaryl fluorides containing electron-donating groups (EDGs) as the starting materials (**3f**, **3g**). To our delight, fluoroarenes with other electron-withdrawing groups (EWGs) could also applied in the approach for longer reaction time (**3h**, **3j**, **3k**). Satisfactory yields were provided at higher temperature (120 °C) when electron-deficient aryl chlorides were employed (**3a**, **3e**, **3h**-**3j**), and a 77% yield of **3l** was also afforded from 2-fluoropyridine at 120 °C for 24 h. Likewise, substituted phenyl, heteroaryl and naphthyl thiols could react with nitroaryl fluorides to produce the corresponding aryl sulfides (Scheme 2, **3m**-**3p**, **3s**, **3t**). Good to excellent yields were provided in the reactions of alkyl and allyl thiols and nitroaryl fluorides under optimized conditions (**3q**, **3r**, **3u**, **3v**). Lower temperature (50 °C) was demanded in the cases of benzyl thiols (**3w**, **3x**).

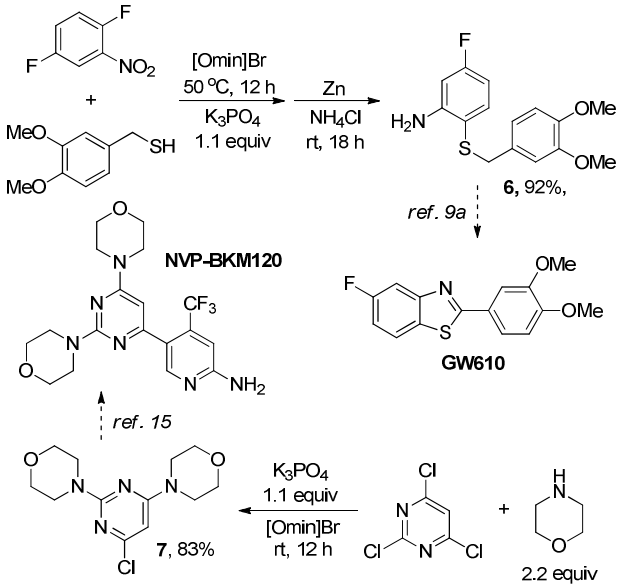
To further broaden the scope of the reaction, we also focused on employing amines to the protocol (Scheme 3). Secondary amines and benzyl amine have higher reactivity



Scheme 3 The S_NAr reactions of aryl halides with amines in [Omim]Br.[a,b] [a] Conditions: aryl halide 1.0 mmol, amines 1.1 mmol, K_3PO_4 1.1 mmol, [Omim]Br 1 mL, 80 °C, 12 h. [b] Isolated yields. [c] At rt for 6 h. [d] At rt for 12 h. [e] The use of 0.9 equiv of pyrrolidine. [f] At 50 °C for 24 h. [g] At 80 °C for 24 h. [h] The use of 2.2 equiv of amines.



Scheme 4 The S_NAr reactions of aryl halides with arenols in [Omim]Br[a,b] [a] Conditions: aryl halide 1.0 mmol, arenol 1.1 mmol, K_3PO_4 1.1 mmol, [Omim]Br 1 mL, 80 °C, 24 h. [b] Isolated yields. [c] 12 h. [d] At 120 °C for 18 h.



Scheme 5 The synthesis of drug Intermediates **6** and **7** by the S_NAr reactions in [Omim]Br

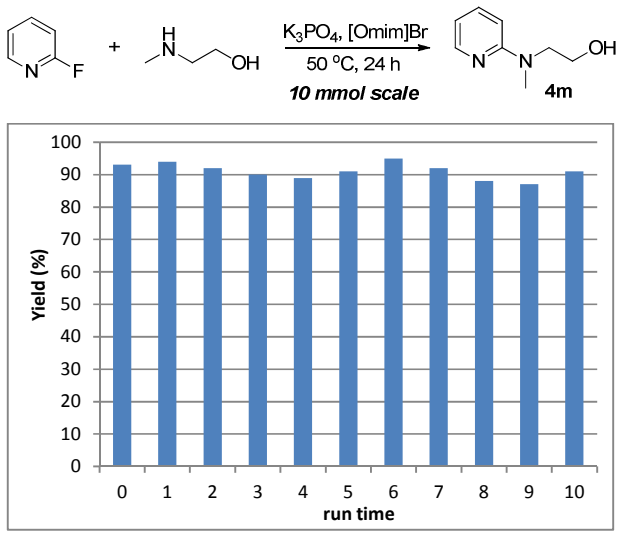


Fig. 3 Recycle studies.[a,b] [a] Conditions: 2-fluoropyridine 10 mmol, 2-(methylamino)ethanol 11 mmol, K_3PO_4 11 mmol, [Omim]Br 10 mL, 50 °C, 24 h. [b] Isolated yields.

than aryl amines, so the reactions of them with fluoroarenes could be completed at room temperature (**4a, 4b**, **4e**, **4f**, **4h**, **4j**-**4l**). Aryl amines were also employed in the reaction successfully (**4c**, **4d**). Notably, iminazole reacted with 4-fluoronitrobenzene to yield the desired product **4g**. The reactions of electron-deficient aryl chlorides with amine also took place (**4a**, **4b**, **4e**, **4i**-**4m**). In the cases of 2,4,6-trichloro-pyrimidine, the selectivity between mono-substituted product (**4j**) and di-substituted one (**4k**) could be controlled by changing the amount of amines. However, a 15% yield of 2-substituted product (**4j'**) was produced. Moreover, 2-fluoropyridine worked well at 50 °C with 2-(methylamino)-ethanol to derive **4m**, which was an important intermediate of rosiglitazone.[15]

To our delight, a series of arenols also provided the final products (**5a**-**5e**) under similar conditions (Scheme 4). As expected, alkyl alcohol was yielded the final product **5f**. Higher temperature was needed in the case of 4-chloroacetophenone (**5g**). To further demonstrate the potential of this methodology, two compounds (**6** and **7**) were synthesized by S_NAr reactions in [Omim]Br, which were significant intermediates of antitumor agents (**GW610**[9b] and **NVP-BKM120**[16]) (Scheme 5). A one-pot sequence involving an initial S_NAr reaction followed by NO_2 reduction occurred smoothly in the case of **6**.

Finally, investigations were also conducted to assess the potential for recycling of the reaction medium and the reaction of 2-fluoropyridine and 2-(methylamino)ethanol was selected as the model reaction. Meanwhile, we scaled up the model reaction to 10 mmol to show the possibility for large-scale operations. After completion of reaction, the product undergoes in-flask extraction with minimum amounts of an organic solvent (MTBE). The phase of [Omim]Br was separated by simple extraction and reuse for next run. The process could be repeated 10 times without an obvious change in yields, but the flowability of [Omim]Br was decreasing along with the increase of inorganic salts' amount (Fig. 3).

Experimental section

General remarks: All chemical reagents were obtained from commercial suppliers and used without further purification. All known compounds were identified by appropriate technique such as ^1H NMR and ^{13}C NMR and MS. All unknown compounds were characterized by ^1H NMR, ^{13}C NMR, MS and elemental analyses. Analytical thin-layer chromatography was performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm). GC analyses were performed on an Agilent 7890A instrument

(Column: Agilent 19091J-413: 30 m×320 μm×0.25 μm. H. FID. detection). IR was taken on a Thermo Fisher Nicolet iS10 spectrometer. All NMR spectra were recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in $CDCl_3$, respectively, and chemical shifts were reported in ppm. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

General procedure for the S_NAr in [Omim]Br: A mixture of aryl halides 1.0 mmol, nucleophile (thiols, amines and arenols) 1.1 mmol and K_3PO_4 1.1 mmol was added in [Omim]Br (1 mL), which was stirred at a certain temperature (rt to 120 ^oC) for 6 h to 24 h. Upon completion, the reaction mixture was extracted by methyl tert-butyl ether (MTBE) (3×2 mL). The organic phase was collected and filtered through a bed of silica gel layered over Celite. The volatiles were removed in *vacuo* to afford the crude product. Further column chromatography on silica gel was needed to afford the pure product **(3-5)**.

The synthesis of 6: A mixture of 1,4-difluoro-2-nitrobenzene 1.0 mmol, (3,4-dimethoxyphenyl)methanethiol 1.1 mmol, K_3PO_4 1.1 mmol was added in [Omim]Br (1.0 mL), which was stirred at 50 ^oC for 12 h. After reaction completed, Zn dust (4.0 equiv) and NH_4Cl (4.0 equiv) were weighted to the mixture. The solution was vigorously stirred at room temperature overnight (18 h). Upon completion, the reaction mixture was extracted by methyl tert-butyl ether (MTBE) (3×2 mL). The organic phase was collected and filtered through a bed of silica gel layered over Celite. The volatiles were removed in *vacuo* to afford the crude product. Further column chromatography on silica gel was needed to afford the pure product **6**.

The synthesis of 7: A mixture of 2,4,6-trichloropyrimidine 1.0 mmol, morpholine 2.2 equiv and K_3PO_4 1.1 mmol was added in [Omim]Br (1.0 mL), which was stirred at rt for 12 h. Upon completion, the reaction mixture was extracted by methyl tert-butyl ether (MTBE) (3×2 mL). The organic phase was collected and filtered through a bed of silica gel layered over Celite. The volatiles were removed in *vacuo* to afford the crude product. Further column chromatography on silica gel was needed to afforded the pure product **7**.

The procedure of recycling [Omim]Br: After reaction completion, the mixture was then extracted with MTBE (3×10 mL). The organic layer was collected and filtered through a bed of silica gel layered over Celite. The volatiles were removed in *vacuo* to afford the crude product **4m**. To the phase of IL, K_3PO_4 10.0 mmol was added, followed by 2-fluoropyridine 10.0 mmol and 2-(methylamino)ethanol 10.0 mmol at room temperature and the reaction stirred for 24 h at 50 ^oC. The extraction cycle was then repeated for the separation of **4m**.

Conclusions

In summary, we disclose an efficient protocol for the formation of C_{aryl}-heteroatom (S, N, O) bonds through S_NAr reactions in [Omim]Br. The reaction can be promoted by an electrophile-nucleophile dual activation which is mainly triggered by HBs between IL and substrates based on further investigations. Electron-deficient fluoroarenes without nitro group and various electron-deficient chloroarenes were also applied in the chemistry. These metal-free reactions take place in recyclable [Omim]Br under relatively mild conditions with high yields and broad substrate scope, thereby making it more environmentally friendly and suitable for large-scale operations, and offering considerable applications to complex targets in organic and medicinal chemistry. Other transformations in ILs are ongoing in our group.

Acknowledgements

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Notes and references

1 (a) R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792; (b) V. I. Pârvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615; (c) M. Armand, F. Endres, D. R. MacFarlane, H. Ohno and B. Scrosati, *Nat. Mater.*, 2009, **8**, 621; (d) A. S. Amarasekara, *Chem. Rev.*, 2016, **116**, 6133; (e) P. C. Marr and A. C. Marr, *Green Chem.*, 2016, **18**, 105.

2 (a) N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123; (b) K. L. Luska, P. Migowski and W. Leitner, *Green Chem.*, 2015, **17**, 3195; (c) P. Lozano, J. M. Bernal, E. Garcia-Verdugo, G. Sanchez-Gomez, M. Vaultier, M. I. Burguete and S. V. Luis, *Green Chem.*, 2015, **17**, 3706.

3 (a) R. Hayes, G. G. Warr and R. Atkin, *Chem. Rev.*, 2015, **115**, 6357; (b) P. A. Hunt, C. R. Ashworth and R. P. Matthews, *Chem. Soc. Rev.*, 2015, **44**, 1257; (c) R. Lungwitz and S. Spange, *New J. Chem.*, 2008, **32**, 392.

4 (a) P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138; (b) A. Sarkar, S. R. Roy and A. K. Chakraborti, *Chem. Commun.*, 2011, **47**, 4538; (c) R. Kumar, Saima, A. Shard, N. H. Andhare, Richa and A. K. Sinha, *Angew. Chem. Int.Ed.* 2015, **54**, 828.

5 (a) T. Terrier, In *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH: Weinheim, 2013; (b) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (c) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2013, **9**, 2265; (d) S. L. Gaonkar and H. Shimizu, *Tetrahedron*, 2010, **66**, 3314.

6 (a) X. Jia, L. Yu, J. Liu, Q. Xu, M. Sickert, L. Chen and M. Lautens, *Green Chem.*, 2014, **16**, 3444; (b) C. P. Ashcroft, P. J. Dunn, J. D. Hayler and A. S. Wells, *Org. Process Res. Dev.*, 2015, **19**, 740.

7 (a) T. Laird, *Org. Process Res. Dev.* 2012, **16**, 1; (b) C. Jimenez-Gonzales and D. J. Constable, In *Green Chemistry and Engineering: A Practical Approach*, Wiley: New York, 2011.

8 (a) M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter and H. F. Sneddon, *J. Med. Chem.*, 2013, **56**, 6007; (b) W. J. W. Watson, *Green Chem.*, 2012, **14**, 251.

9 (a) N. A. Isley, R. T. H. Linstadt, S. M. Kelly, F. Gallou and B. H. Lipshutz, *Org. Lett.*, 2015, **17**, 4734; (b) G.-p. Lu and C. Cai, *RSC Adv.*, 2014, **4**, 59990.

10 (a) M. Imoto, Y. Matsui, M. Takeda, A. Tamaki, H. Taniguchi, K. Mizuno and H. Ikeda, *J. Org. Chem.*, 2011, **76**, 6356; (b) D. N. Kommi, P. S. Jadhavar, D. Kumar and A. K. Chakraborti,

Green Chem., 2013, **15**, 798. (c) B. Tanwar, P. Purohit, B. N. Raju, D. Kumar, D. N. Kommi and A. K. Chakraborti, *RSC Adv.*, 2015, **5**, 11873.

11 (*a*) P. T. Anastas and J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press: Oxford, UK, 1998; (*b*) P. T. Anastas and T. Williamson, in *Green Chemistry, Frontiers in Benign Chemical Synthesis and Process*, Oxford University of Press: Oxford, UK, 1998; (*c*) P. G. Jessop, *Green Chem.*, 2011, **13**, 1391; (c) G.-p. Lu, C. Cai and B. H. Lipshutz, *Green Chem.*, 2013, **15**, 105; (d) G.-p. Lu, C. Cai, F. Chen, R.-l. Ye and B.-j. Zhou, *ACS Sustain. Chem. Eng.*, 2016, **4**, 1804.

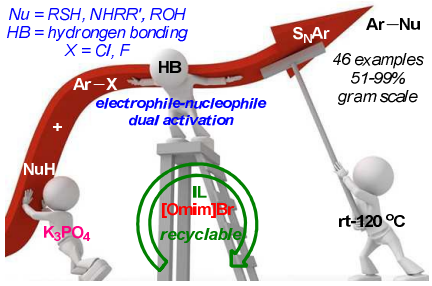
12 M. J. Kamlet, J. L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, 1983, **48**, 2877.

13 (a) G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 2433; (b) A. K. Chakraborti, L. Sharma and M. K. Nayak, *J. Org. Chem.*, 2002, **67**, 2541; (c) A. K. Chakraborti, S. Rudrawar, K. B. Jadhav, G. Kaur and S. V. Chankeshwara, *Green Chem.*, 2007, **9**, 1335.

14 The use of bases can also enhance the nucleophilicity of thiols by capturing of their proton, which may be another reason for that the proton shifted from 10.233 to 10.186.

15 (a) S. L. Gaonkar and H. Shimizu, *Tetrahedron*, 2010, **66**, 3314; (b) D. V. Jawale, U. R. Pratap and R. A. Mane, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 924.

16 W. Zhu, Y. Liu, Y. Zhao, H. Wang, L. Tan, W. Fan and P. Gong, *Arch. Pharm.*, 2012, **345**, 812.



Aromatic nucleophilic substitution reaction in ionic liquid is promoted by an electrophile-nucleophile dual activation

Facile aromatic nucleophilic substitution reactions (S_NAr) in ionic liquid: An electrophile-nucleophile dual activation by [Omim]Br for the reaction

Xiao Zhang, Guo-ping Lu*, Chun Cai

Chemical Engineering College, Nanjing University of Science & Technology, Nanjing, Jiangsu 210094, P. R. China

* Corresponding Author E-mail: glu@njust.edu.cn

1 Experimental

General procedures for the synthesis of ionic liquids[1]: *N*-Methylimidazole or 1,2-dimethyl-imidazole 40 mmol, 1-haloalkane 48 mmol and ethyl acetate 10 mL were heated under reflux for 24 h. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethyl acetate (3 × 10 mL), and dried under vacuum to give 1-octyl-3-methylimidazolium bromide as a colourless liquid. [Omim]OAc and [Omim]HSO_4 are synthesized by exchanging the bromide ion of [Omim]Br with AcO^- or HSO_4^- in acid-base neutralization with NaOAc and $NaHSO_4$ respectively.

Experimental Procedure for IR Studies

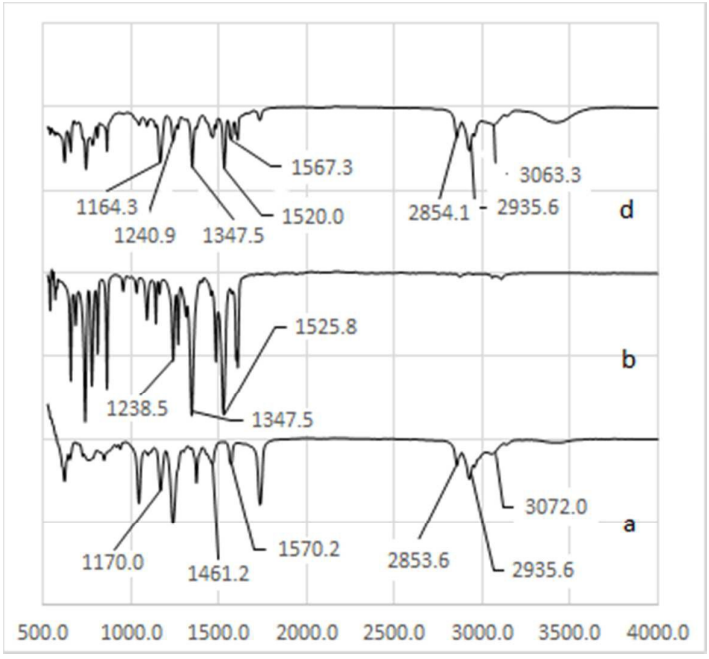


Figure S1 IR spectrum of (a) [Omim]Br, (b) 1-Fluoro-2-nitrobenzene **1a**, (d) the mixing of **1a** and [Omim]Br after 30 min.

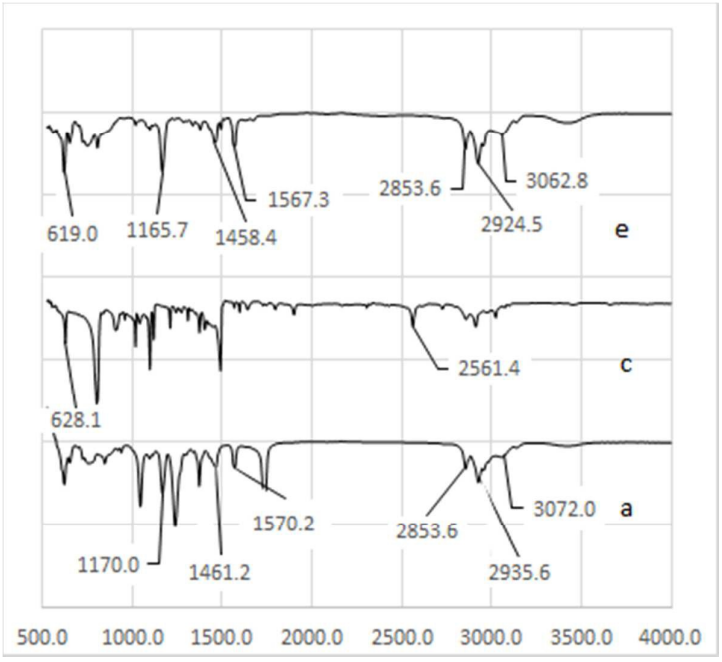


Figure S2 IR spectrum of (a) [Omim]Br, (c) 4-Tolyl mercaptan **2a**, (e) the mixing of **2a** and [Omim]Br after 30 min.

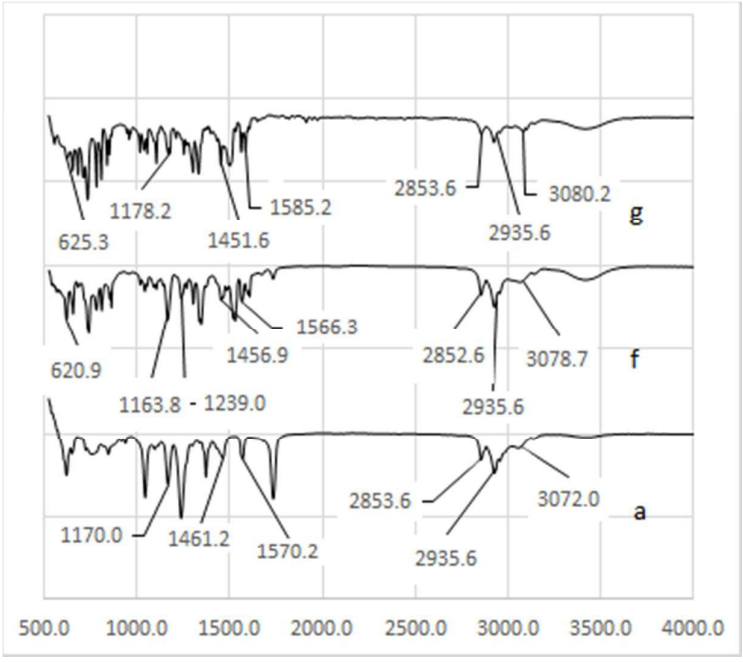


Figure S3 IR spectrum of (a) [Omim]Br. (f) the mixing of **1a** and **2a** in [Omim]Br after 30 min. (g) the mixing of **1a** and **2a** in [Omim]Br after 2 h.

Table S1 The characteristic frequency of compounds in IR

characteristic frequency	chemical bond	compound
1170.0 cm^{-1}	C-N stretching imidazole ring	[Omim]Br
1461.2-1570.2 cm^{-1}	skeleton vibration of imidazole ring	
2853.6-2935.6 cm^{-1}	saturated C-H stretching vibration	
3072.0 cm^{-1}	C-H stretching vibration of imidazole ring	
1238.5 cm^{-1}	C-F stretching vibration of benzene	1-fluoro-2-nitrobenzene
1347.5-1525.8 cm^{-1}	C-NO_2 stretching vibration of benzene	**1a**
628.1 cm^{-1}	C-S stretching vibration of benzene	4-tolyl mercaptan
2561.4 cm^{-1}	S-H stretching vibration	**2a**

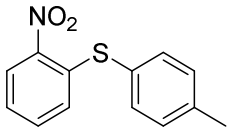
Results and Conclusions:

(1) The formation of HB between the C-2 hydrogen of [Omim]Br and F atom of **1a** is evidenced by the facts that $\nu_{C\text{-}H}$ of imidazole ring in [Omim]Br is shifted from 3072.0 to 3063.3 and $\nu_{C\text{-}F}$ of **1a** is shifted from 1238.5 to 1240.9. (Figure S1)

(2) The interaction between [Omim]Br and **2a** is evidenced by the facts that $\nu_{C\text{-}H}$ of imidazole ring in [Omim]Br is shifted from 3072.0 to 3062.8 and $\nu_{C\text{-}S}$ of **2a** is shifted from 628.1 to 619.0. (Figure S2)

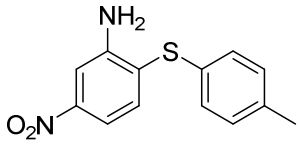
(3) The interaction between [Omim]Br and substrates (**1a** and **2a**) is evidenced by the facts that $\nu_{C\text{-}H}$ of imidazole ring in [Omim]Br is shifted from 3072.0 to 3078.7 (f) and 3080.2 (g). (Figure S3)

2 Characterization Data



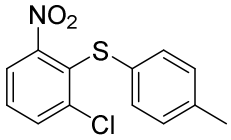
Chemical Formula: $C_{13}H_{11}NO_2S$
Mass: 245

(2-Nitrophenyl)(*p*-tolyl)sulfane **3a**,[2] yellow solid, mp: 87-88 °C (lit. 89-90 °C), yield 94%, 230.3 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.85 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.28-7.34 (m, 3H), 7.46 (d, J = 8.0 Hz, 2H), 8.22 (d, J = 8,5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 124.8, 125.9, 127.4, 128.3, 131.0, 133.5, 136.1, 140.2, 140.6, 145.0. MS (ESI) *m/z*: 245.



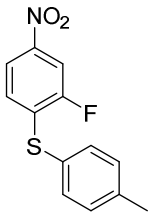
Chemical Formula: $C_{13}H_{12}N_2O_2S$
Mass: 260

5-Nitro-2-(*p*-tolylthio)aniline **3b**,[3] yellow solid, 111-113 °C, yield 84%, 218.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.49 (s, 2H), 7.12-7.17 (m, 4H), 7.32 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 109.3, 113.1, 126.0, 129.5, 130.3, 130.5, 134.3, 137.9, 147.2, 148.6. MS (ESI) *m/z*: 260.



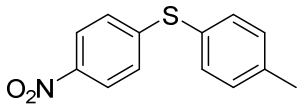
Chemical Formula: $C_{13}H_{10}ClNO_2S$
Mass: 279

(2-Chloro-6-nitrophenyl)(*p*-tolyl)sulfane **3c**,[4] yellow solid, mp: 72-74 °C (lit. 69-70 °C), yield 89%, 248.3 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 3H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 122.3, 124.5, 127.7, 130.1, 130.3, 133.5, 136.0, 137.7, 141.5, 155.6. MS (ESI) *m/z*: 279.



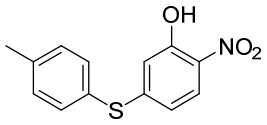
Chemical Formula: $C_{13}H_{10}FNO_2S$
Exact Mass: 263.0416
Elemental Analysis: C, 59.31; H, 3.83; F, 7.22; N, 5.32; O, 12.15; S, 12.18

(2-Fluoro-4-nitrophenyl)(*p*-tolyl)sulfane **3d**, pale yellow solid, mp: 91-93 °C, yield 97%, 255.1 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 6.97 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 110.7-111.0 (d, *J* = 26 Hz, 1C), 119.7, 124.6, 127.4, 131.2, 135.6, 137.6, 140.8, 145.8, 156.4-158.4 (d, *J* = 248 Hz, 1C). MS (ESI) *m/z*: 263.0416. Anal. Calcd for $C_{13}H_{10}FNO_2S$: C, 59.31%; H, 3.83%; N, 5.32%. Found: C, 59.17%; H, 4.12; N, 5.04%.



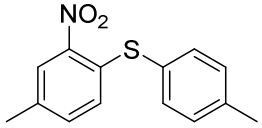
Chemical Formula: $C_{13}H_{11}NO_2S$
Mass: 245

(4-Nitrophenyl)(*p*-tolyl)sulfane **3e**,[2] yellow solid, mp: 78-80 °C (lit. 81.5 °C), yield 90%, 220.5 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.13 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 124.1, 126.3, 126.6, 131.0, 135.2, 140.4, 145.3, 149.5. MS (ESI) *m/z*: 245.



Chemical Formula: $C_{13}H_{11}NO_3S$
Exact Mass: 261.0460
Elemental Analysis: C, 59.76; H, 4.24; N, 5.36; O, 18.37; S, 12.27

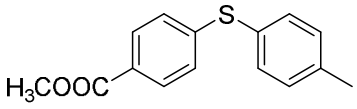
2-Nitro-5-(*p*-tolylthio)phenol **3f**, yellow solid, 118-120 °C, yield 78%, 203.6 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.63-6.67 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 1H), 10.76 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 115.0, 117.8, 125.3, 125.6, 130.8, 131.0, 135.5, 140.7, 135.6, 155.5. MS (ESI) *m/z*: 261.0460. Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.76%; H, 4.24; N, 5.36%. Found: C, 59.45%; H, 4.62; N, 5.15%.



Chemical Formula: $C_{14}H_{13}NO_2S$
Mass: 259

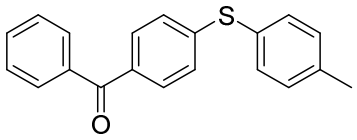
(4-Methyl-2-nitrophenyl)(*p*-tolyl)sulfane **3g**,[5] yellow solid, 105-107 °C, yield 75%, 194.3 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2,27 (s, 3H), 2.34 (s, 3H), 6.66 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.0 Hz,

1H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.95 (s, 1H).[13]C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.5, 125.9, 127.8, 128.3, 130.9, 134.7, 135.4, 135.9, 136.6, 140.3, 144.9. MS (ESI) *m/z*: 259.



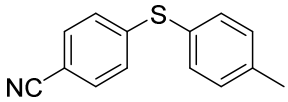
Chemical Formula: $C_{15}H_{14}O_2S$
Mass: 258

Methyl 4-(*p*-tolylthio)benzoate **3h**,[6] white solid, mp: 101-103 °C, yield 51%, 131.6 mg. [1]H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.88 (s, 3H),7.14 (d, *J* = 7.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H),7.87 (d, *J* = 8.0 Hz, 2H). [13]C NMR (125 MHz, $CDCl_3$) δ 21.4, 52.2, 126.8, 127.2, 128.3, 130.1, 130.6, 134.5, 139.3, 145.5, 166.9. MS (ESI) *m/z*: 258.



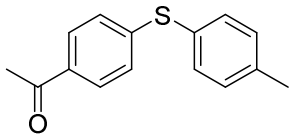
Chemical Formula: $C_{20}H_{16}OS$
Mass: 304

Phenyl(4-(*p*-tolylthio)phenyl)methanone **3i**,[7] pale yellow solid, 123-125 °C, yield 76%, 231.0 mg. [1]H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.43-7.48 (m, 4H), 7.57 (t, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H). [13]C NMR (125 MHz, $CDCl_3$) δ 21.3, 126.5, 128.0, 128.3, 129.9, 130.6, 130.8, 132.3, 134.4, 134.5, 137.8, 139.3, 145.3, 195.8. MS (ESI) *m/z*: 304.



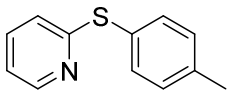
Chemical Formula: $C_{14}H_{11}NS$
Mass: 225

4-(*p*-Tolylthio)benzonitrile **3j**,[8] white solid, mp: 100-102 °C (lit. 102-103 °C), yield 83%, 186.8 mg. [1]H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H). [13]C NMR (125 MHz, $CDCl_3$) δ 21.4, 108.3, 118.9, 126.7, 126.8, 130.8, 132.3, 135.0, 140.0, 146.6. MS (ESI) *m/z*: 225.



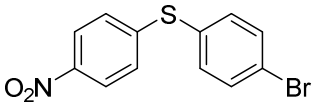
Chemical Formula: $C_{15}H_{14}OS$
Mass: 242

1-(4-(*p*-Tolylthio)phenyl)ethan-1-one **3k**,[9] pale yellow solid, mp: 88-90 °C (lit. 90-92 °C), yield 76%, 183.9 mg. [1]H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.54 (s, 3H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H). [13]C NMR (125 MHz, $CDCl_3$) δ 21.4, 26.6, 126.8, 128.0, 129.0, 130.7, 134.3, 134.6, 139.5, 146.1, 197.3. MS (ESI) *m/z*: 242.



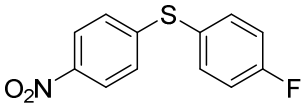
Chemical Formula: $C_{12}H_{11}NS$
Mass: 201

2-(*p*-Tolylthio)pyridine **3l**,[10] pale yellow oil, yield 77%, 154.8 mg. [1]H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 8.41 (d, *J* = 5.0 Hz, 1H). [13]C NMR (125 MHz, $CDCl_3$) δ 21.5, 119.7, 121.0, 127.4, 130.6, 135.4, 136.7, 139.6, 149.6, 162.3. MS (ESI) *m/z*: 201.



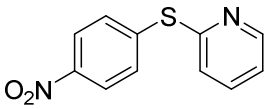
Chemical Formula: $C_{12}H_8BrNO_2S$
Mass: 310

(4-Bromophenyl)(4-nitrophenyl)sulfane **3m**,[11] pale yellow solid, mp: 94-96 °C (lit. 92-94 °C), yield 87%, 269.7 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.3, 127.2, 130.0, 133.4, 136.1, 145.8, 147.5. MS (ESI) *m/z*: 310.



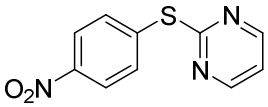
Chemical Formula: $C_{12}H_8FNO_2S$
Mass: 249

(4-Fluorophenyl)(4-nitrophenyl)sulfane **3n**,[9] pale yellow solid, 82-84 °C, yield 93%, 231.6 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12-7.18 (m, 4H), 7.53-7.56 (m, 2H), 8.06 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 117.6, 124.2, 125.6, 126.4, 137.3, 145.5, 148.6, 162.8-164.8 (d, *J* = 250 Hz, 1C). MS (ESI) *m/z*: 249.



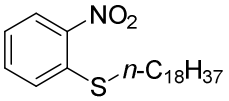
Chemical Formula: $C_{11}H_8N_2O_2S$
Mass: 232

2-((4-Nitrophenyl)thio)pyridine **3o**,[12] pale yellow solid, mp: 84-86 °C (lit. 84-85 °C), yield 77%, 178.6 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.59-7.65 (m, 3H), 8.18 (d, *J* = 9.0 Hz, 2H), 8.52 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.2, 124.3, 125.0, 132.0, 137.5, 142.5, 147.1, 150.6, 156.7. MS (ESI) *m/z*: 232.



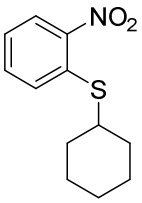
Chemical Formula: $C_{10}H_7N_3O_2S$
Mass: 233

2-((4-Nitrophenyl)thio)pyrimidine **3p**,[13] yellow solid, mp: 108-110 °C (lit. 108-113 °C), yield 83%, 193.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.0 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 8.24 (d, *J* = 8.5 Hz, 2H), 8.52 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.1, 124.1, 134.9, 138.7, 148.0, 157.9, 170.9. MS (ESI) *m/z*: 233.



Chemical Formula: $C_{24}H_{41}NO_2S$
Mass: 407

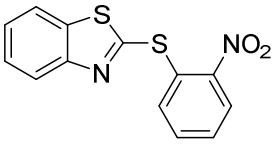
(2-Nitrophenyl)(octadecyl)sulfane **3q**,[14] yellow solid, mp: 52-54 °C (lit. 58-59 °C), yield 91%, 370.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.20-1.33 (m, 28H), 1.45-1.51 (m, 2H), 1.70-1.76 (m, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.8, 28.0, 29.3 (2C), 29.5, 29.6, 29.7, 29.8, 32.1, 32.5, 124.3, 126.3, 126.7, 133.5, 138.5, 146.1. MS (ESI) *m/z*: 407.



Chemical Formula: $C_{12}H_{15}NO_2S$
Mass: 237

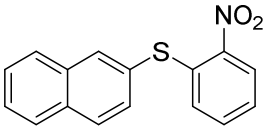
Cyclohexyl(2-nitrophenyl)sulfane **3r**,[15] yellow oil, yield 90%, 213.3 mg. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 1.27-1.47 (m, 5H), 1.66 (d, *J* = 10.0 Hz, 1H), 1.80 (d, *J* = 10.0 Hz, 2H), 2.05 (d, *J* = 11.0 Hz, 2H), 3.27-3.31 (m, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.45-7.52 (m, 2H), 8.07 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 26.1, 32.7, 44.4, 124.9, 126.0, 128.5, 133.1, 136.0, 147.6. MS (ESI) *m/z*: 237.



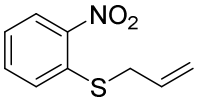
Chemical Formula: $C_{13}H_8N_2O_2S_2$
Mass: 288

2-((2-Nitrophenyl)thio)benzo[d]thiazole **3s**,[16] yellow solid, mp: 104-106 °C (lit. 106 °C), yield 74%, 213.1 mg. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.44 (m, 2H), 7.46-7.51 (m, 2H), 7.55 (t, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.6, 123.8, 125.8, 126.4, 126.9, 127.6, 130.8, 133.3, 134.0, 137.7, 146.8, 153.8, 161.0. MS (ESI) *m/z*: 288.



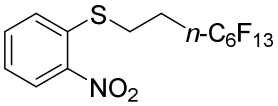
Chemical Formula: $C_{16}H_{11}NO_2S$
Mass: 281

Naphthalen-2-yl(2-nitrophenyl)sulfane **3t**,[17] yellow solid, mp: 92-94 °C (lit. 92-93 °C), yield 82%, 230.4 mg. ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.5 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.62-7.67 (m, 2H), 7.82-7.98 (m, 3H), 8.22 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.2, 125.9, 127.2, 127.8, 128.0, 128.2, 128.3, 128.8, 130.1, 131.7, 133.6, 133.7, 134.1, 136.1, 139.5, 145.2. MS (ESI) *m/z*: 281.



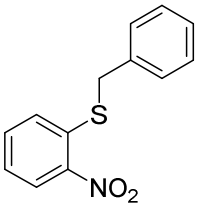
Chemical Formula: $C_9H_9NO_2S$
Mass: 195

Allyl(2-nitrophenyl)sulfane **3u**,[18] light yellow oil, yield 74%, 144,3 mg. ^1H NMR (500 MHz, $CDCl_3$) δ 3.65 (d, *J* = 6.5 Hz, 2H), 5.25 (d, *J* = 10.0 Hz, 1H), 5.37 (d, *J* = 16.5 Hz, 1H)， 5.89-5.94 (m, 1H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 8.20 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.6, 119.5, 124.7, 126.0, 127.2, 131.8, 133.3, 137.1, 146.4. MS (ESI) *m/z*: 195.



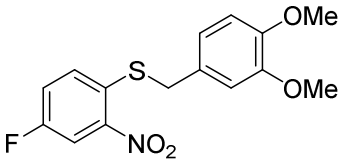
Chemical Formula: $C_{14}H_8F_{13}NO_2S$
Mass: 501

(2-Nitrophenyl)(nonyl)sulfane **3v**,[19] Light yellow oil, yield 71%, 385.8 mg. ^1H NMR (500 MHz, $CDCl_3$) δ 2.44-2.55 (m, 2H), 3.22 (t, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.62-7.65 (m, 1H), 8.23-8.25 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.2, 29.3-29.7 (m), 124.6, 125.3, 125.6, 133.0, 134.5, 145.7. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -126.1, -123.3, -122.8, -121.8, -114.2, -80.8. MS (ESI) *m/z*: 501.



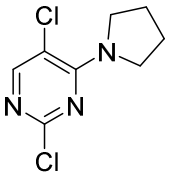
Chemical Formula: $C_{13}H_{11}NO_2S$
Mass: 245

Benzyl(2-nitrophenyl)sulfane **3w**,[20] yellow solid, mp: 82-84 °C (lit. 82-83 °C), yield 98%, 240.1 mg. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.20 (s, 2H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.29 (t, *J* = 7.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 8.20 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.7, 124.9, 126.2, 127.1, 127.9, 129.0, 129.2, 133.7, 135.1, 137.9, 146.0. MS (ESI) *m/z*: 245.



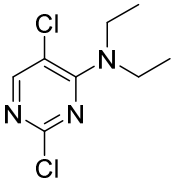
Chemical Formula: $C_{15}H_{14}FNO_4S$
Mass: 323

(3,4-Dimethoxybenzyl)(4-fluoro-2-nitrophenyl)sulfane **3x**,[21] Light yellow solid, mp: 92-94 °C (lit. 92-94 °C), yield 94%, 303.6 mg. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97 (s, 6H), 4.25 (s, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.36-7.40 (m, 1H), 7.52-7.55 (m, 1H), 7.98-8.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.0, 54.9 (2C), 110.3, 111.0, 112.0-112.2 (d, *J* = 26 Hz, 1C), 120.1, 120.2-120.4 (d, *J* = 25 Hz, 1C), 126.1, 128.3, 131.7, 145.7, 147.8, 148.3, 157.4-159.4 (d, *J* = 248 Hz, 1C). MS (ESI) *m/z*: 323.



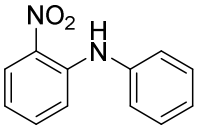
Chemical Formula: $C_8H_9Cl_2N_3$
Mass: 217

2,5-Dichloro-4-(pyrrolidin-1-yl)pyrimidine **4a**,[17] white solid, 78-80 °C, yield 92%, 200.6 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (s, 4H), 3.77 (s, 4H), 7.91 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 49.8, 112.4, 156.7, 157.3, 157.6. MS (ESI) *m/z*: 217.



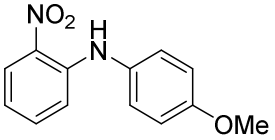
Chemical Formula: $C_8H_{11}Cl_2N_3$
Mass: 219

2,5-Dichloro-*N,N*-diethylpyrimidin-4-amine **4b**,[22] colorless oil, yield 81%, 177.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, *J* = 8.0 Hz, 6H), 3.61-3.65 (m, 4H), 7.91 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 44.5, 112.2, 157.5, 157.9, 158.3. MS (ESI) *m/z*: 219.



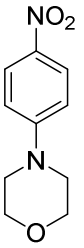
Chemical Formula: $C_{12}H_{10}N_2O_2$
Mass: 214

2-Nitro-*N*-phenylaniline **4c**,[23] red solid, mp: 70-72 °C (lit. 75 °C), yield 85%, 181.9 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (t, *J* = 9.0 Hz, 1H), 7.13-7.20 (m, 4H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 1H), 9.41 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.2, 117.6, 124.5, 125.8, 126.8, 129.9, 133.4, 135.8, 138.9, 143.2. MS (ESI) *m/z*: 214.



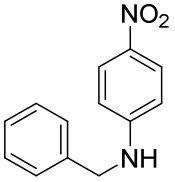
Chemical Formula: $C_{13}H_{12}N_2O_3$
Mass: 244

N-(4-Methoxyphenyl)-2-nitroaniline **4d**,[24] red solid, mp: 88-90 °C (lit. 89 °C), yield 84%, 205.0 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 2H), 7.32 (t, *J* = 7.0 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 9.41 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7, 115.1, 115.9, 116.9, 126.7, 127.2, 131.3, 132.6, 135.9, 144.6, 158.1. MS (ESI) *m/z*: 244.



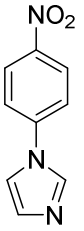
Chemical Formula:$C_{10}H_{12}N_2O_3$
Mass: 208

4-(4-Nitrophenyl)morpholine **4e**,[25] yellow solid, mp: 147-149 °C (lit. 149-150 °C), yield 95%, 197.6 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (t, *J* = 5.0 Hz, 4H), 3.84 (t, *J* = 5.0 Hz, 4H), 6.81 (d, *J* = 9.5 Hz, 2H), 8.10 (d, *J* = 9.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.2, 66.5, 112.7, 126.0, 139.1, 155.1. MS (ESI) *m/z*: 208.



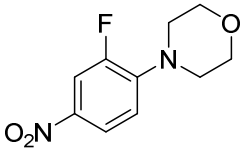
Chemical Formula:$C_{13}H_{12}N_2O_2$
Mass: 228

N-Benzyl-4-nitroaniline **4f**,[26] yellow solid, mp: 144-146 °C (lit. 147 °C), yield 89%, 202.9 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (d, *J* = 5.5 Hz, 2H), 4.94 (s, 1H),6.57 (d, *J* = 9.0 Hz, 2H), 7.30-7.39 (m, 5H), 8.07 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.8, 111.5, 126.5, 127.5, 128.0, 129.1, 137.5, 138.4, 153.2. MS (ESI) *m/z*: 228.



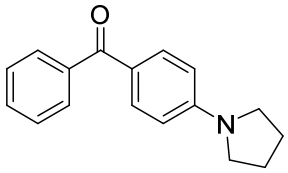
Chemical Formula:$C_9H_7N_3O_2$
Mass: 189

1-(4-Nitrophenyl)-1H-imidazole **4g**,[27] pale yellow solid, mp: 193-195 °C (lit. 195-198 °C), yield 89%, 168.2 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.37 (s, 1H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.98 (s, 1H), 8.37 (d, *J* = 9.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 117.8, 121.2, 125.9, 131.8, 135.5, 142.1, 146.4. MS (ESI) *m/z*: 189.



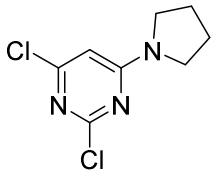
Chemical Formula:$C_{10}H_{11}FN_2O_3$
Mass: 226

4-(2-Fluoro-4-nitrophenyl)morpholin **4h**,[28] yellow solid, mp: 110-112 °C (lit. 112-113 °C), yield 99%, 223.7 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 (t, *J* = 9.5 Hz, 4H), 3.84 (t, *J* = 5.0 Hz, 4H), 6.89 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 10.5 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.0, 66.7, 112.7, 117.0, 121.1, 140.8, 145.6, 152.2-154.2 (d, *J* = 248 Hz, 1C). MS (ESI) *m/z*: 226.



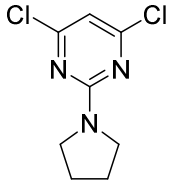
Chemical Formula: $C_{17}H_{17}NO$
Mass: 251

Phenyl(4-(pyrrolidin-1-yl)phenyl)methanone **4i**,[29] pale yellow solid, mp: 134-136 °C (lit. 138 °C), yield 67%, 168.2 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (t, *J* = 6.5 Hz, 4H), 3.37 (t, *J* = 6.5 Hz, 4H), 6.53 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 47.7, 110.7, 124.3, 128.1, 129.5, 131.1, 133.1, 139.6, 151.0, 195.2. MS (ESI) *m/z*: 251.



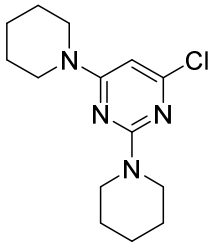
Chemical Formula: $C_8H_9Cl_2N_3$
Mass: 217

2,4-Dichloro-6-(pyrrolidin-1-yl)pyrimidine **4j**,[30] white solid, 84-86 °C, yield 72%, 156.2 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91-1.97 (m, 2H), 2.01-20.6 (m, 2H), 3.29 (t, *J* = 7.0 Hz, 2H), 3.57 (t, *J* = 6.5 Hz, 2H), 6.15 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8-25.5 (d, *J* = 86 Hz, 1C), 46.9-47.4 (d, *J* = 65 Hz, 1C), 100.5, 159.1, 159.6, 161.4. MS (ESI) *m/z*: 217.



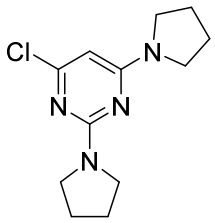
Chemical Formula: $C_8H_9Cl_2N_3$
Mass: 217

4,6-Dichloro-2-(pyrrolidin-1-yl)pyrimidine **4j'**,[31] white solid, 87-89 °C, yield 15%, 32.6 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96-1.98 (m, 4H), 3.56 (t, *J* = 7.0 Hz, 4H), 6.49 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 47.2, 107.2, 159.4, 161.4. MS (ESI) *m/z*: 217.



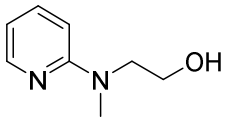
Chemical Formula: $C_{14}H_{21}ClN_4$
Mass: 280

4-Chloro-2,6-di(piperidin-1-yl)pyrimidine **4k**,[32] pale yellow solid, mp: 93-95 °C (lit. 95-96 °C), yield 78%, 218.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52-1.58 (m, 8H), 1.59-1.64 (m, 4H), 3.50 (t, *J* = 5.0 Hz, 4H), 3.69 (t, *J* = 5.0 Hz, 4H), 5.79 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8-25.0 (d, *J* = 23 Hz, 1C), 25.6-25.9 (d, *J* = 35 Hz, 1C), 44.9-45.3 (d, *J* = 51 Hz, 1C), 90.2, 160.4, 161.1, 163.2. MS (ESI) *m/z*: 280.



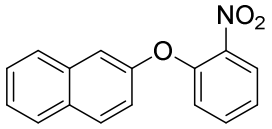
Chemical Formula: $C_{12}H_{17}ClN_4$
Mass: 252

4-Chloro-2,6-di(pyrrolidin-1-yl)pyrimidine **4l**,[32] pale yellow solid, mp: 78-80 °C (lit. 79-82 °C), yield 81%, 204.1 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88-1.94 (m, 8H), 3.52 (t, *J* = 7.0 Hz, 8H), 5.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 46.3-46.6 (d, *J* = 41 Hz, 1C), 90.7, 159.0, 159.9, 161.4. MS (ESI) *m/z*: 252.



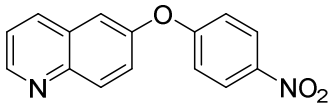
Chemical Formula: $C_8H_{12}N_2O$
Mass: 152

2-(Methyl(pyridin-2-yl)amino)ethan-1-ol **4m**,[33] pale yellow oil, yield 94%, 142.9 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.69 (t, *J* = 5.5 Hz, 2H), 3.83 (t, *J* = 5.0 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 1H), 6.56 (t, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.0, 54.5, 63.1, 106.5, 112.4, 137.9, 147.2, 159.4. MS (ESI) *m/z*: 152.



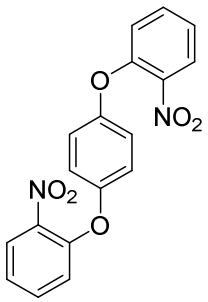
Chemical Formula: $C_{16}H_{11}NO_3$
Mass: 265

2-(2-Nitrophenoxy)naphthalene **5a**,[34] brown solid, mp: 55-57 °C (lit. 58 °C), yield 80%, 212 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 1H), 7.25-7.33 (m, 2H), 7.42 (s, 1H), 7.47-7.56 (m, 3H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.88-7.93 (m, 2H), 8.03 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.2, 119.8, 120.9, 123.5, 125.5, 126.0, 127.0, 127.4, 128.0, 130.5, 130.9, 134.3, 134.4, 141.6, 150.8, 153.7. MS (ESI) *m/z*: 265.



Chemical Formula: $C_{15}H_{10}N_2O_3$
Mass: 266

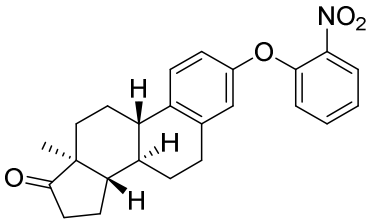
6-(4-Nitrophenoxy)quinoline **5b**,[35] red solid, 69-71 °C, yield 78%, 207.5 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 9.0 Hz, 2H), 7.42-7.49 (m, 3H), 8.09 (d, *J* = 9.0 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 1H), 8.90 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.4, 117.9, 122.1, 123.8, 126.2, 129.2, 132.3, 135.6, 143.3, 146.0, 150.3, 152.9, 162.9. MS (ESI) *m/z*: 266.



Chemical Formula: $C_{18}H_{12}N_2O_6$
Mass: 352

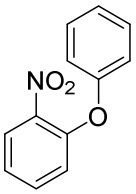
1,4-Bis(2-nitrophenoxy)benzene **5c**,[36] brown solid, mp: 158-160 °C (lit. 159-160 °C), yield 71%, 249.9 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 4H), 7.22 (t, *J* = 7.5 Hz,

2H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.4, 120.9, 123.5, 125.9, 134.4, 141.4, 150.8, 152.4. MS (ESI) *m/z*: 352.



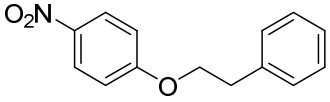
Chemical Formula: $C_{24}H_{25}NO_4$
Mass: 391

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-3-(2-nitrophenoxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclop enta[a]phenanthren-17-one **5d**,[37] yellow solid, >250 °C, yield 77%, 301.1 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.49-1.64 (m, 7H), 1.96-2.17 (m, 3H), 2.27-2.31 (m, 1H), 2.39-2.42 (m, 1H), 2.49-2.54 (m, 1H), 2.88-2.90 (m, 2H), 6.79 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.48 (t, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.7, 26.0, 26.5, 29.6, 31.7, 36.0, 38.3, 44.2, 48.1, 50.6, 60.5, 116.6, 119.4, 120.5, 122.9, 125.8, 127.0, 134.1, 136.3, 138.8, 141.4, 151.1, 153.8. MS (ESI) *m/z*: 391.



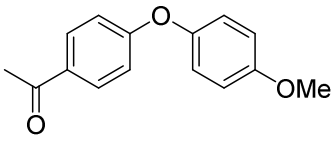
Chemical Formula: $C_{12}H_9NO_3$
Mass: 215

1-Nitro-2-(*p*-tolyloxy)benzene **5e**,[38] yellow oil, yield 92%, 197.8 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 7.16-7.20 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.9, 120.6, 123.3, 124.7, 125.9, 130.2, 134.3, 141.5, 150.9, 155.9. MS (ESI) *m/z*: 215.



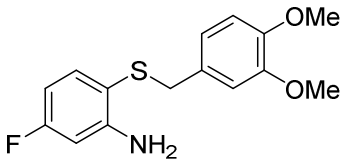
Chemical Formula: $C_{14}H_{13}NO_3$
Mass: 243

1-Nitro-4-phenethoxybenzene **5f**,[39] pale yellow solid, mp: 54-56 °C (lit. 56-57 °C), yield 79%, 192.0 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.15 (t, *J* = 7.0 Hz, 2H), 4.26-4.30 (m, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 7.22-7.36 (m, 5H), 8.18 (d, *J* = 9.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.6, 69.6, 114.6, 126.0, 126.9, 128.8, 129.1, 137.6, 141.6, 164.0. MS (ESI) *m/z*: 243.



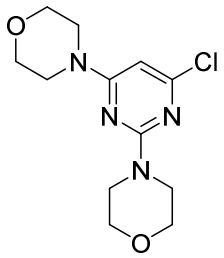
Chemical Formula: $C_{15}H_{14}O_3$
Mass: 242

1-(4-(4-Methoxyphenoxy)phenyl)ethan-1-one **5g**,[38] pale yellow solid, mp: 60-62 °C (lit. 60-61 °C), yield 76%, 183.9 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55(s, 3H), 3.82 (s, 3H), 6.92 (t, *J* = 7.5 Hz, 4H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 55.8, 115.2, 116.5, 121.8, 130.7, 131.5, 148.6, 156.8, 163.1, 196.9. MS (ESI) *m/z*: 242.



Chemical Formula: $C_{15}H_{16}FNO_2S$
Mass: 293

2-((3,4-Dimethoxybenzyl)thio)-5-fluoroaniline **6**,[40] light yellow oil, yield 92%, 269.6 mg. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (s, 3H), 3.74 (s, 2H), 3.79 (s, 3H), 4.44 (s, 2H), 6.27-6.34 (m, 1H), 6.35-6.36 (m, 1H), 6.53 (d, *J* = 1.5 Hz, 1H), 6.61-6.62 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 7.07-7.10 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.2, 54.3, 54.5, 99.8-100.0 (d, *J* = 25 Hz, 1C), 103.7-103.8 (d, *J* = 22 Hz, 1C), 109.8, 110.8-110.9 (d, *J* = 22 Hz, 1C), 119.8, 129.5, 137.3, 137.4, 146.8-147.3 (d, *J* = 65 Hz, 1C), 149.3-149.4 (d, *J* = 11 Hz, 1C), 162.0, 164.0. MS (ESI) *m/z*: 293.



Chemical Formula: $C_{12}H_{17}ClN_4O_2$
Mass: 284

4,4'-(6-Chloropyrimidine-2,4-diyl)dimorpholine **7**,[30] white solid, mp: 139-141 °C (lit. 139-142 °C), yield 83%, 235.7 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (s, 4H), 3.68-3.72 (m, 12H), 5.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.4, 66.6-66.9 (d, *J* = 39 Hz, 1C), 91.2, 160.6, 160.9, 163.9. MS (ESI) *m/z*: 284.

[1] (a) Simon, L. D, Simon, W. R. David, J. C. Aqueous-biphasic hydroformylation of alkenes promoted by"weak" surfactants. *Green Chemistry* **2009**, 11(5), 630-637. (b) Rather, M. A.; Rather, G. M.; Pandit, S. A.; Bhat, S. A.; Bhat, M. A., Determination of cmc of imidazolium based surface active ionic liquids through probe-less UV–vis spectrophotometry. *Talanta* **2015,** *131*, 55-58.

[2] Liang L.; Hongyang, M.; Yuqiang, D., Iridium and phosphine promoted C–F bond activation: the C–S cross-coupling of aryl fluorides with diaryl disulfides to synthesize thioethers. *Tetrahedron Letters* **2015**, 56(46), 6405–6408.

[3] Commercial chemical, CAS number: 91955-35-0.

[4] Commercial chemical, CAS number: 870241-04-7.

[5] Rockway, T. W.; Betebenner, D. A.; Krueger, A.; Iwasaki, N.; Cooper, C. S.; Anderson, D. D.; Kempf, D. J.; Madigan, D. L.; Motter, C. E.; Shanley, J. P., Preparation of 1,6- and 1,8-naphthyridines as antiviral compounds for treatment of HCV infections. *The International Application according to the Patent Cooperation Treaty* **2007**, WO 2007076035.

[6] Suguru, Y.; Yasuyuki, S.; Yuki, H.; Yoshitake, N.; Takahisa, Y.; Shigeomi, S.; Takamitsu, H., A mild and facile synthesis of aryl and alkenyl sulfides via copper-catalyzed deborylthiolation of organoborons with thiosulfonates. *Chemical Communications* **2015**, 51(93), 16613-16616

[7] Nicolaou, K. C.; Koumbis, A. E.; Snyder, S. A.; Simonsen, K. B. Novel reactions initiated by titanocene methylidenes: deoxygenation of sulfoxides, N-oxides, and selenoxides. *Angewandte Chemie International Edition* **2000**, 39(14), 2529-2533.

[8] Anns, M. T.; Sujatha, A.; K, S. S.; Gopinathan, A., A general and inexpensive protocol for the

Cu-catalyzed C-S cross-coupling reaction between aryl halides and thiols. *Tetrahedron Letters* **2015,** 56(47), 6560-6564.

[9] K, S. S.; Amrutha, P.; Thankachan, A.; Maria, T.; Gopinathan, A., An efficient iron-catalyzed S-arylation of aryl and alkylthiols with aryl halides in the presence of water under aerobic conditions. *Tetrahedron Letters* **2015,** 56(34), 4923-4926.

[10] Gogoi, P., Role of TBATB in nano indium oxide catalyzed C-S bond formation. *Scientific Reports* **2015**, 5, 13873.

[11] Mei-jie, B.; Guo-ping, L.; Chun, C., Ascorbic Acid Promoted Metal-Free Synthesis of Aryl Sulfides with Anilines Nitrosated in Situ by tert-Butyl Nitrite. *Synlett* **2015**, 26(13), 1841-1846.

[12] Rahul, S.; Bharat, K. A.; Neetu, S.; Kumkum,, K.; Satish, K. S.; Krishna, N. S., Nickel-Catalyzed C-S Bond Formation: Synthesis of Aryl Sulfides from Arylsulfonyl Hydrazides and Boronic Acids. *Advanced Synthesis & Catalysis* **2015**, 357(6), 1181 -1186.

[13] Feng, L.; Qingqing, M.; Huansheng, C.; Zhiming, L.; Quanrui, Wang., Synthesis of Diaryl Ethers, Diaryl Sulfides, Heteroaryl Ethers and Heteroaryl Sulfides under Microwave Dielectric Heating. *Synthesis* **2005,** 8, 1305-1313.

[14] Commercial chemical, CAS number: 1031899067-8.

[15] Zhongyu, D.; Sadananda, R.; Pengfei, Z.; Xiaogang, L., Synthesis of Aryl Sulfides by Decarboxylative C-S Cross-Couplings. *Chemistry-A European Journal* **2009**, 15(15), 3666-3669.

[16] Guozhen, H.; Yuan, H.; Yao, T.; Jie, Z.; Dan, Z.; Shuangli, Z.; Shiqing, H., Substrate-promoted ligand-free CuI catalyzed S-arylation of 2-mercaptobenzothiazoles with aryl iodides in water. *Tetrahedron Letters* **2013,** 54(39), 5318-5321.

[17] Nicholas, A. I.; Roscoe, T. H. L.; Sean, M. K.; Fabrice, G.; Bruce, H. L., Nucleophilic Aromatic Substitution Reactions in Water Enabled by Micellar Catalysis. *Organic Letters* **2015,** 17 (19), 4734-4737.

[18] Peter, K. D.; Kevin, G. M. K.; K, N. Houk.; Vy M. D., Dynamic Kinetic Resolution of Allylic Sulfoxides by Rh-Catalyzed Hydrogenation: A Combined Theoretical and Experimental Mechanistic Study. J*ournal of Americal Chemistry Society* **2014**, 136(1), 291−298.

[19] Commercial chemical, CAS number: 1642142-77-5.

[20] Prasanta, G.; Sukanya, H.; Manas, J. S.; Kuladip, S.; Pranjit, B., Nickel-Schiff base complex catalyzed C-S cross-coupling of thiols with organic chlorides. *Tetrahedron Letters* **2014,** 70(41), 7484-7489.

[21] Guoping, L.; Yamei, L., Preparation of polysubstituted 2-arylbenzothiazole with thiourea as sulfur source. *Faming Zhuanli Shenqing* **2015**, CN 104892545.

[22] Commercial chemical, CAS number: 1531745-71-7.

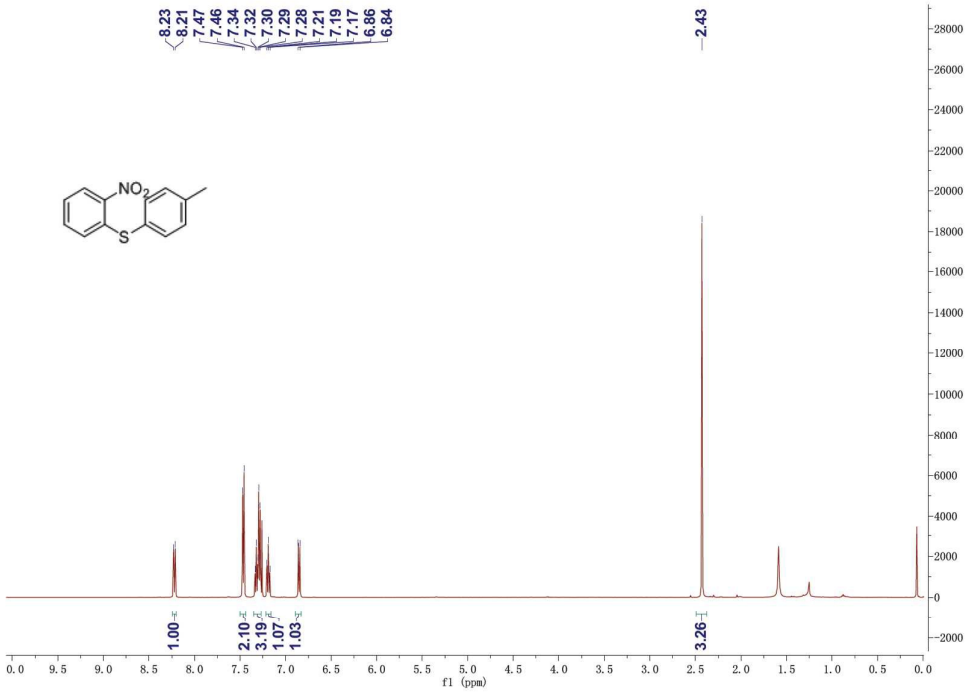
[23] Reddy, P. L.; Arundhathi, R.; Rawat, D. S., Cu(0)@Al2O3/SiO2 NPs: an efficient reusable catalyst for the cross coupling reactions of aryl chlorides with amines and anilines. *RSC Advances* **2015**, 5(112), 92121-92127.

[24] Liang-Zhu, H.; Pan, H.; You-Qiang, L.; Ying-Meng, X.; Tao, Z.; Zhen-Ting, D., A Facile and Efficient Synthesis of Diaryl Amines or Ethers under Microwave Irradiation at Presence of KF/Al_2O_3 without Solvent and Their Anti-Fungal Biological Activities against Six Phytopathogens. *International Journal of Molecular Sciences* **2013**, 14(9), 18850-18860.

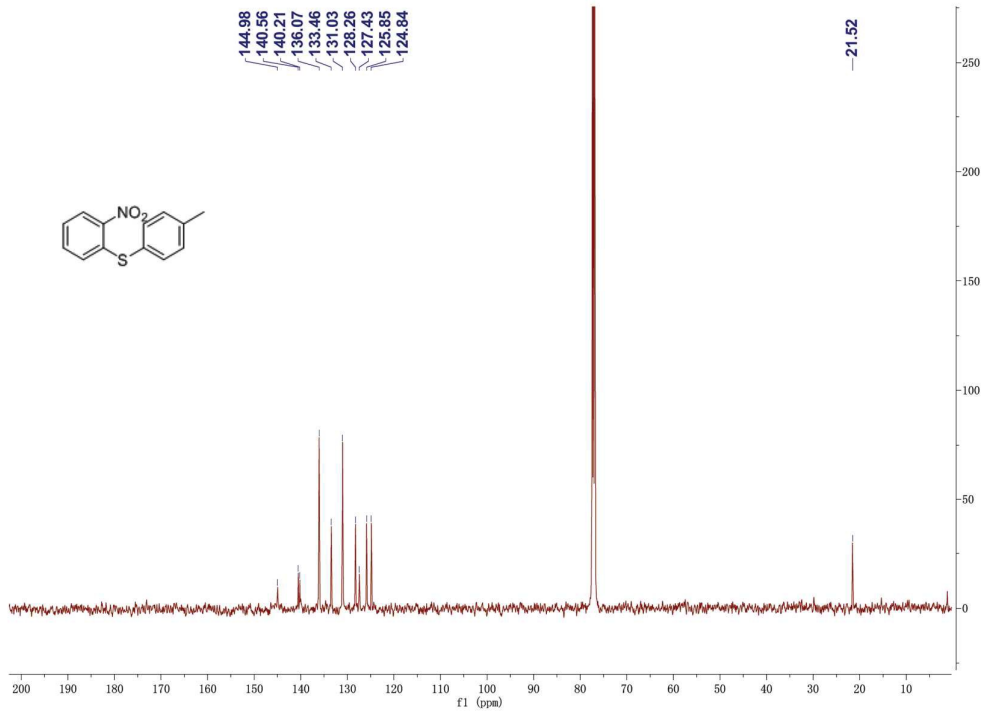
[25] Sheng-Huei, H.; Ying-Hsiu, H.; Yu-Ruei, K., Synthesis and characterization of new redox-active and electrochromic polyimides with (4-morpholinyl)triphenylamine units. *Journal of Electroanalytical Chemistry* **2016**, 764, 31-37.

[26] Valerio, F.; James, E. R.; Michael, J. I., $B(C_6F_5)_3$-Catalyzed Reductive Amination using Hydrosilanes. *ACS Catalysis* **2016**, 6(3), 1793−1798.
[27] Jie-hua, S.; Jiong-jie, W., An efficient method for N-arylation of nitrogen-containing heterocycles catalyzed by CuCl2/Al2O3. *Zhejiang Gongye Daxue Xuebao* **2013**, 41(2), 126-132.
[28] Paulen, A.; Gasser, V.; Hoegy, F.; Perraud, Q.; Pesset, B.; Schalk, Isabelle. J.; Mislin, G. L. A., Synthesis and antibiotic activity of oxazolidinone-catechol conjugates against Pseudomonas aeruginosa. *Organic & Biomolecular Chemistry* **2015**, 13(47), 11567-11579.
[29] Zhi, H. C.; Zi, H. M.; Yan, Q. M.; Peng, W.; Qi, W.; Lin, M. Z.; Ke, J. Cu.; Fang, Y.; Zhi, B. X., Amination of electron deficient aryl chlorides promoted by nano sized Mg(OH)2 under transition metals free condition. *Chinese Chemical Letters* **2012**, 23(2), 137-140.
[30] Ping, G; Yanfang, Z; Yajing, L; Xin, Z; Wufu, Zhu. Preparation of pyrimidine and triazine derivatives for treating cancer. *Faming Zhuanli Shenqing* **2012**, CN 102659765 .
[31] Padilla, A. G.; Pearlman, B. A. Highly Selective Hydrolysis of Chloropyrimidines to Pyrimidones in 12 N Hydrochloric Acid. *Organic Process Research & Development* **2006**, 10(5), 921-926.
[32] Prevost, G; Liberatore, A; Bigg, D; Pons, D. Preparation of triaminopyrimidine derivatives as phosphatase Cdc25 inhibitors and their use in treatment of diseases, especially neoplasm. *The International Application according to the Patent Cooperation Treaty* **2008**, WO 2008152223.
[33] Ge, M; Meilin, Z; Mengshu, D; Yang, G; Aqun, Zheng; Zhenyu, L; Ruizhi, Hu. Synthetic optimization of rosiglitazone and related intermediates for industrial purposes. *Research on Chemical Intermediates* **2016**, 42(3), 2023-2033.
[34] Jungwun, H.; Dial, B. E.; Ping, L.; Kozik, M. E.; Smith, M. D.; Shimizu, K. D., How important are dispersion interactions to the strength of aromatic stacking interactions in solution? *Chemical Science* **2015**, 6(7), 4358-4364.
[35] Teno, N.; Gohda, K.; Wanaka, K.; Tsuda, Y.; Sueda, T.; Yamashita, Y.; Otsubo, T., Pyrrolopyrimidine-inhibitors with hydantoin moiety as spacer can explore P4/S4 interaction on plasmin. *Bioorganic & Medicinal Chemistry* **2014**, 22(7), 2339-2352.
[36] Okazaki, T.; Nakagawa, M.; Futemma, T.; Kitagawa, T., NMR and DFT studies on persistent carbocations derived from benzo[kl]xanthene, dibenzo[d,d']benzo[1,2-b:4,3-b']difuran and dibenzo[d,d']benzo[1,2-b:4,5-b']difuran in superacidic media. *Journal of Physical Organic Chemistry* **2016**, 29(2), 107-111.
[37] Commercial chemical, CAS number: 1034358-12-7.
[38] Pillaiyar, P.; Wha-Seung, A., Synthesis of copper nanoparticles supported on a microporous covalent triazine polymer: an efficient and reusable catalyst for O-arylation reaction. *Catalysis Science & Technology* **2016**, 6(6), 1701-1709.
[39] Buonomo, J. A.; Aldrich, C. C., Mitsunobu Reactions Catalytic in Phosphine and a Fully Catalytic System. *Angewandte Chemie International Edition* **2015**, 54(44), 13041-13044.
[40] Guoping, L; Yamei, L. Preparation of polysubstituted 2-arylbenzothiazole with thiourea as sulfur source. *Faming Zhuanli Shenqing* **2015**, CN 104892545.

3 NMR Spectra of All Products



^{1}H NMR of 3a



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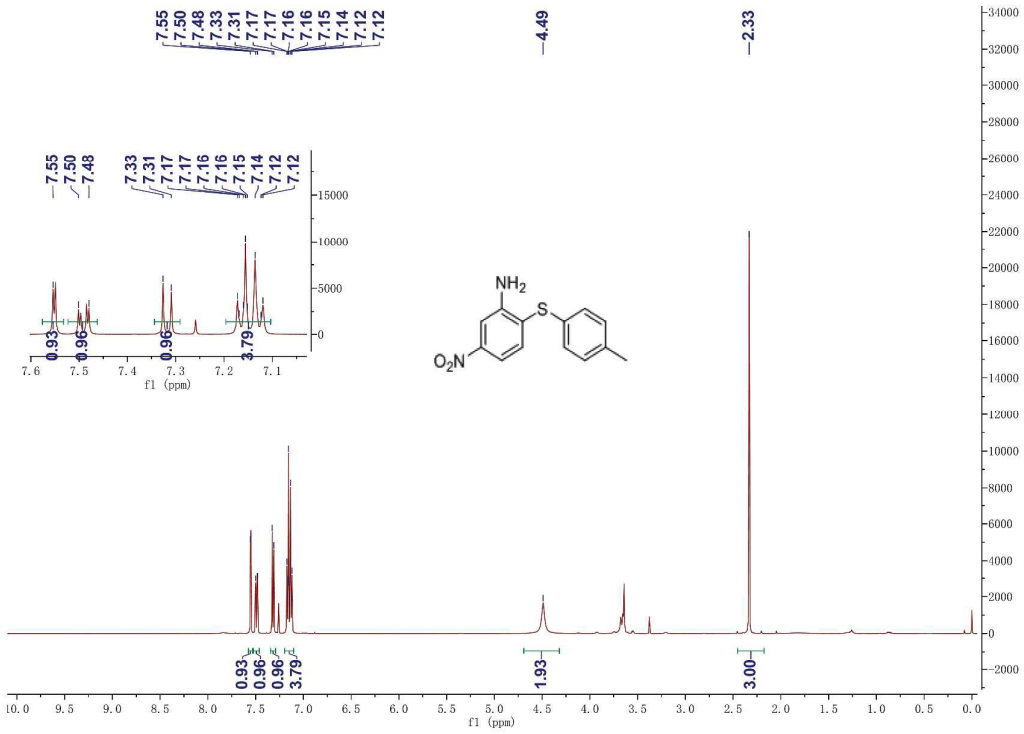
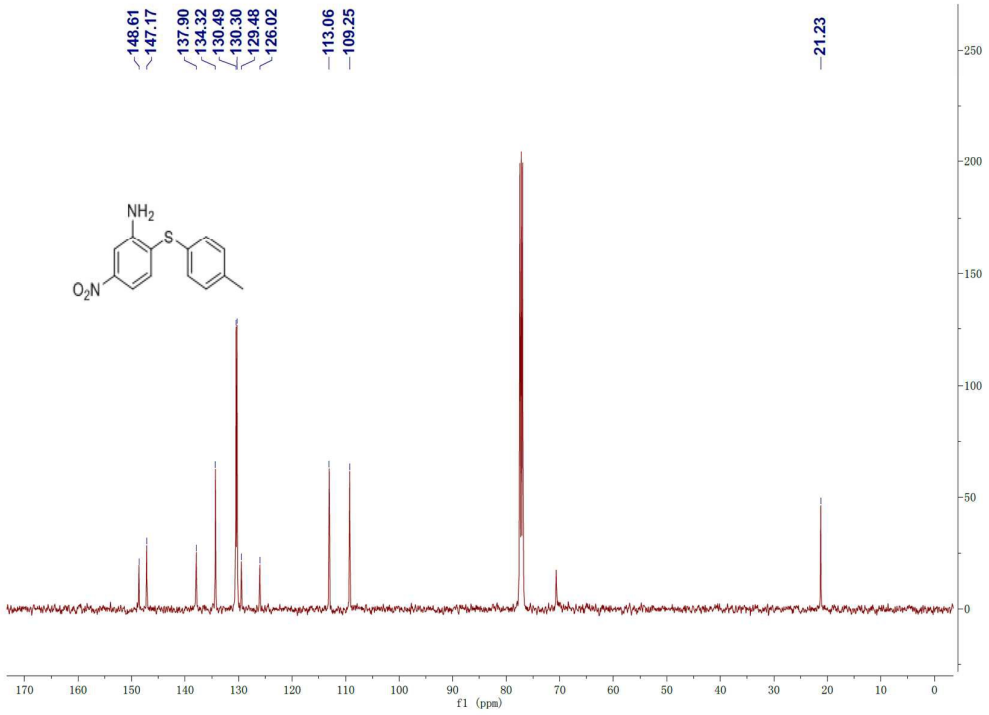


^{1}H NMR of 3b



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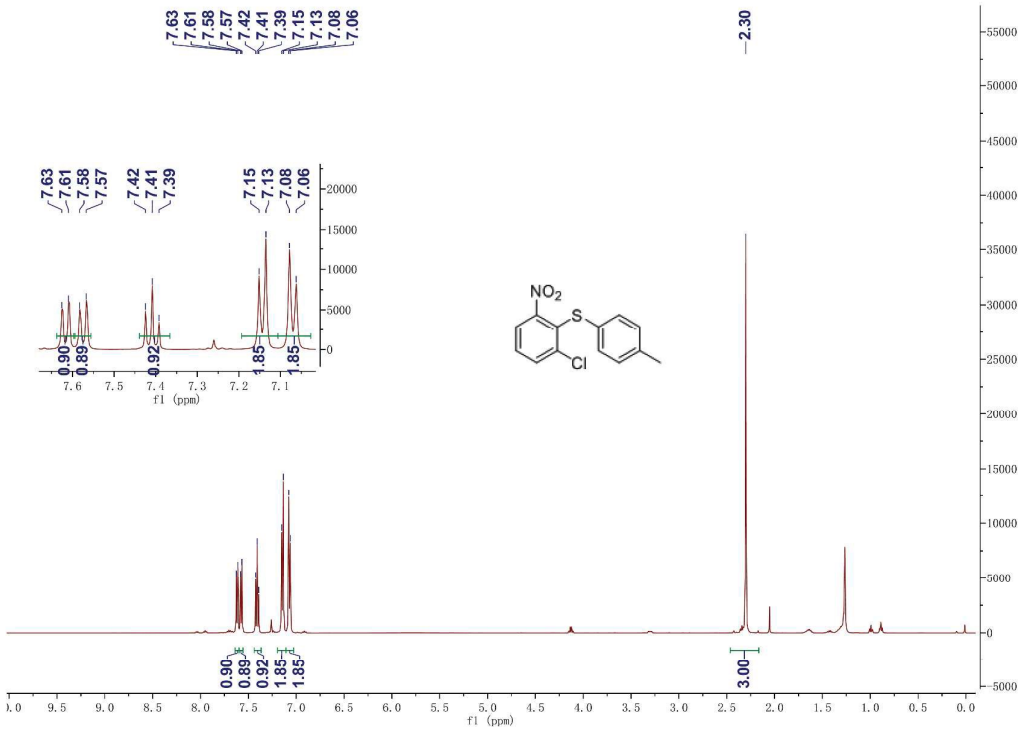

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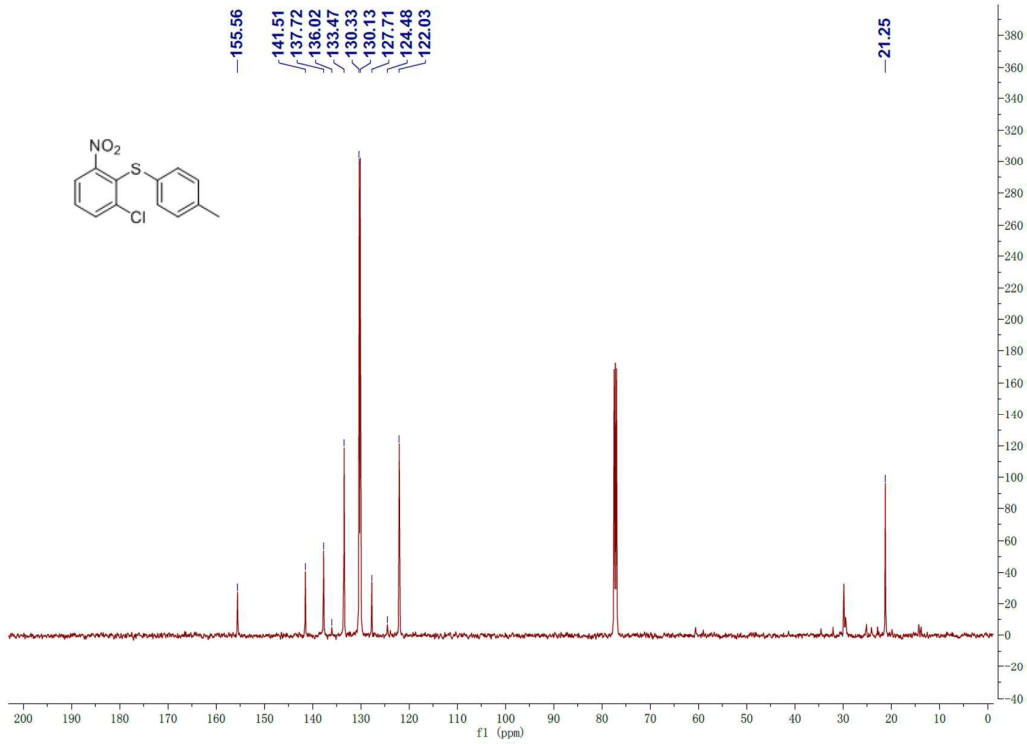

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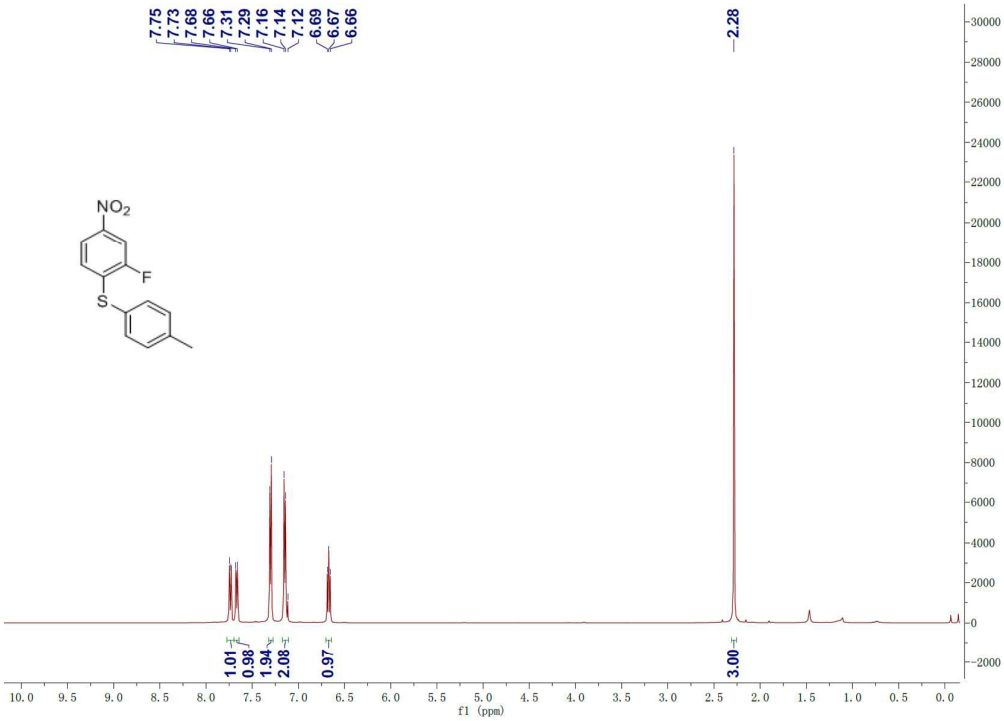

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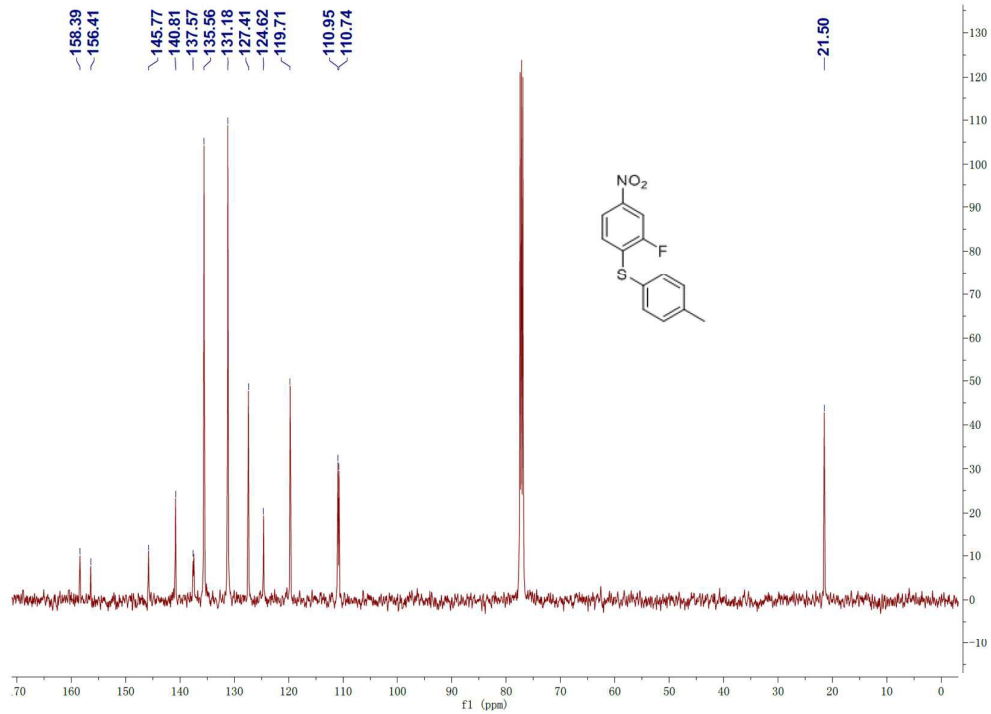
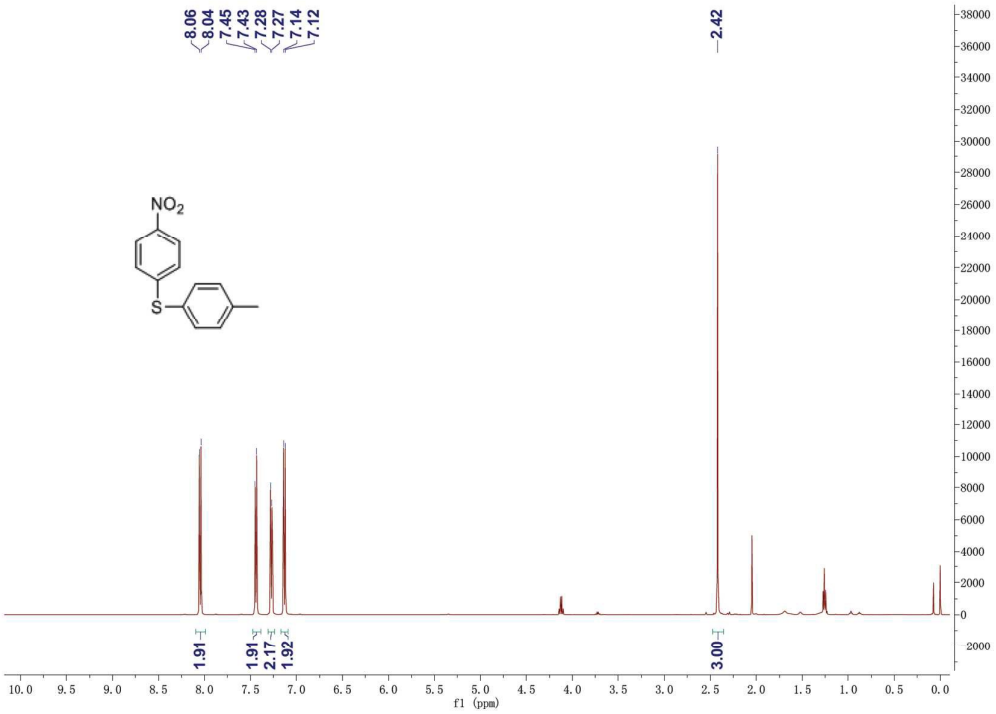
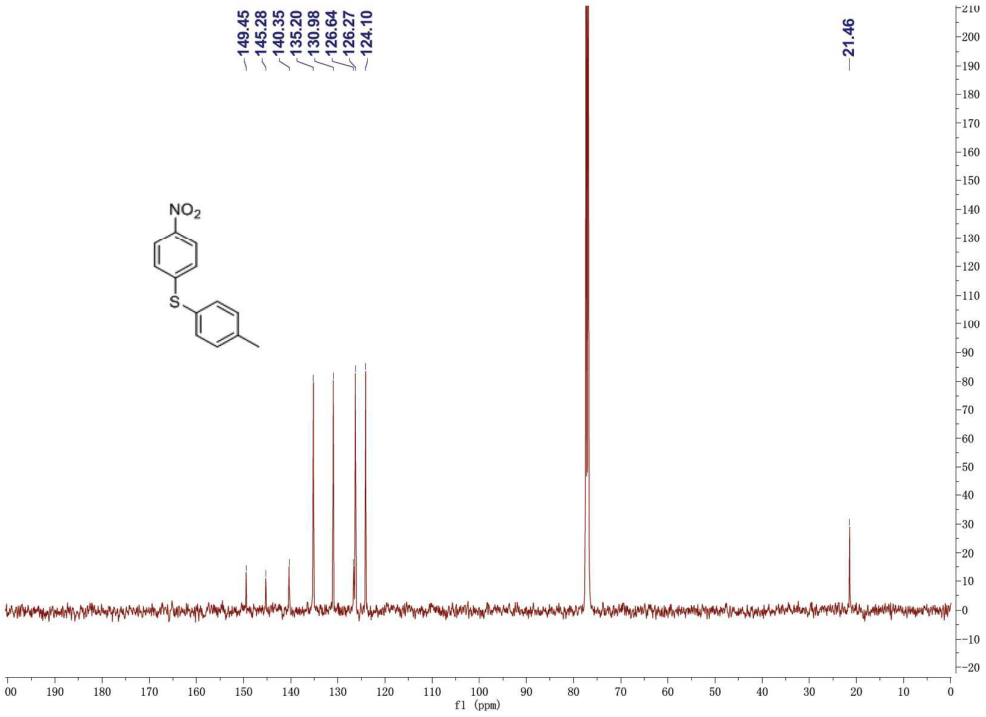


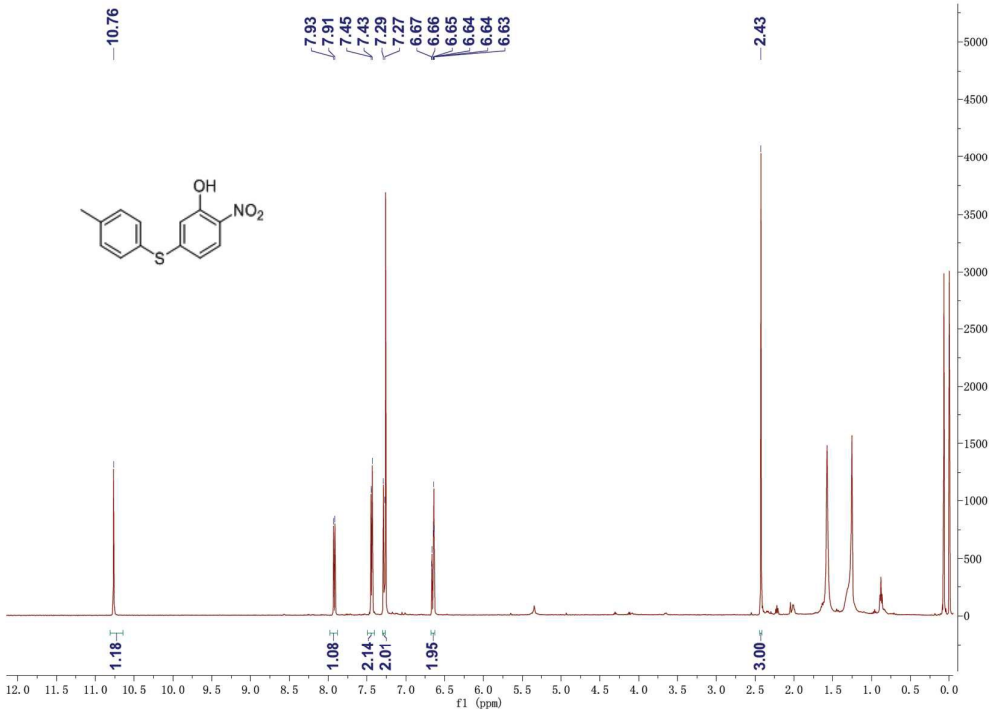
^{13}C NMR of 3d



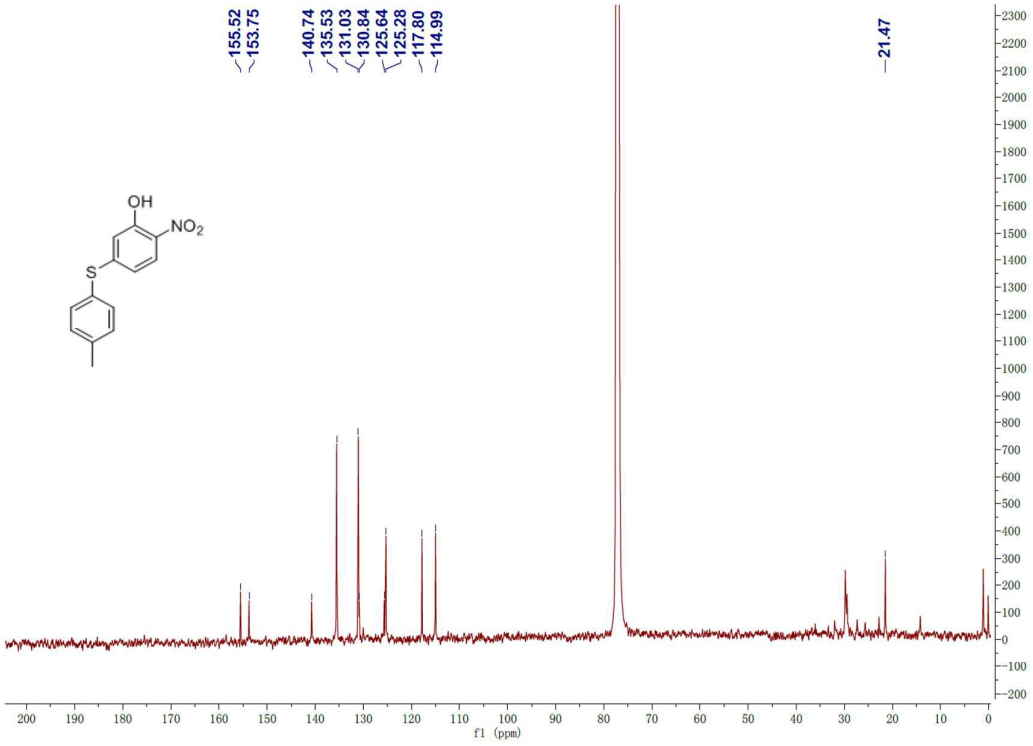
^{1}H NMR of 3e



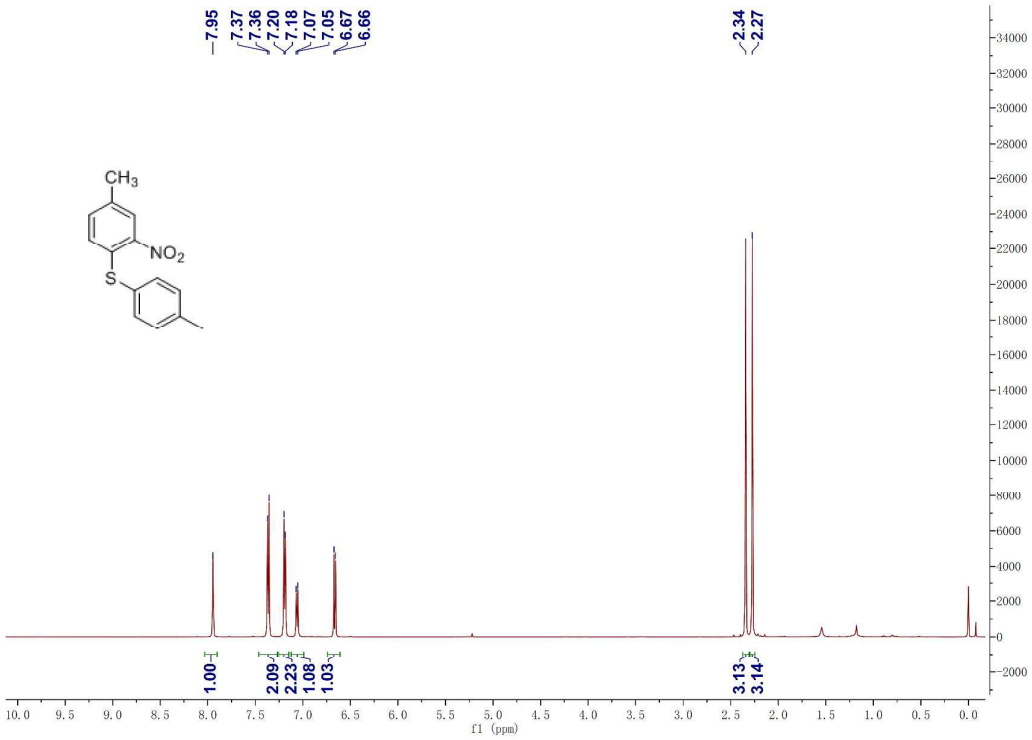
^{13}C NMR of 3e



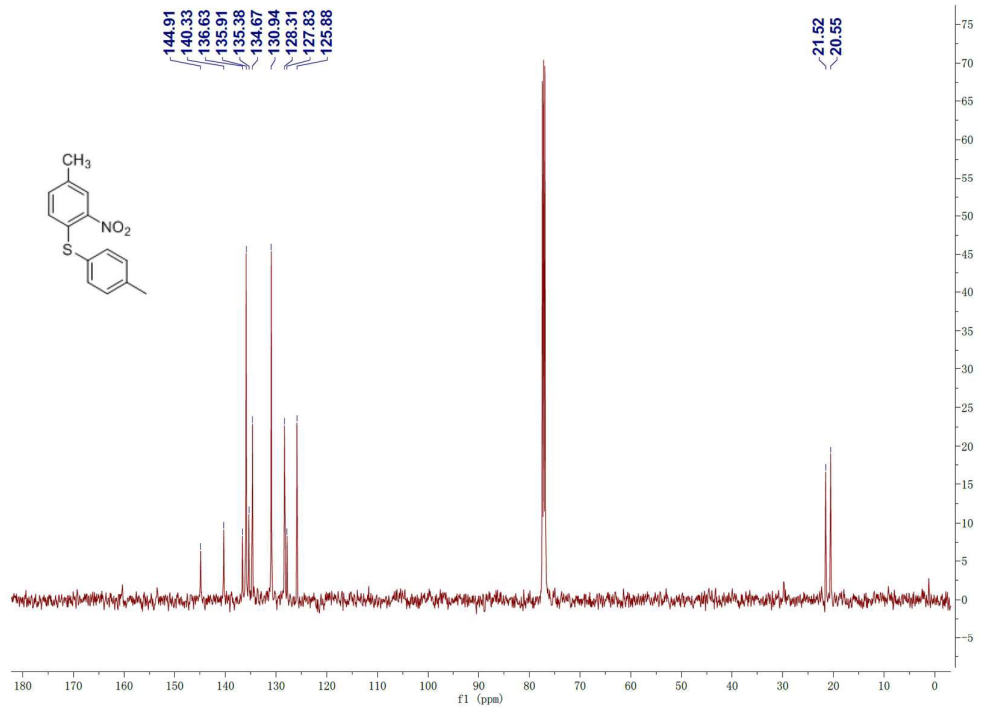
^{1}H NMR of 3f



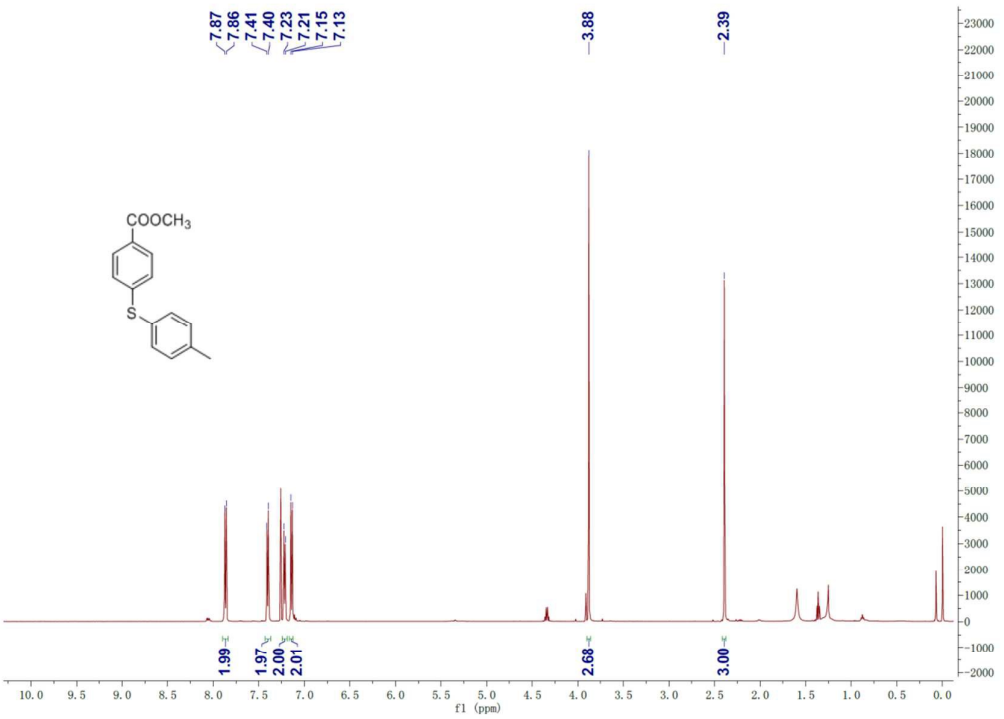
^{13}C NMR of 3f



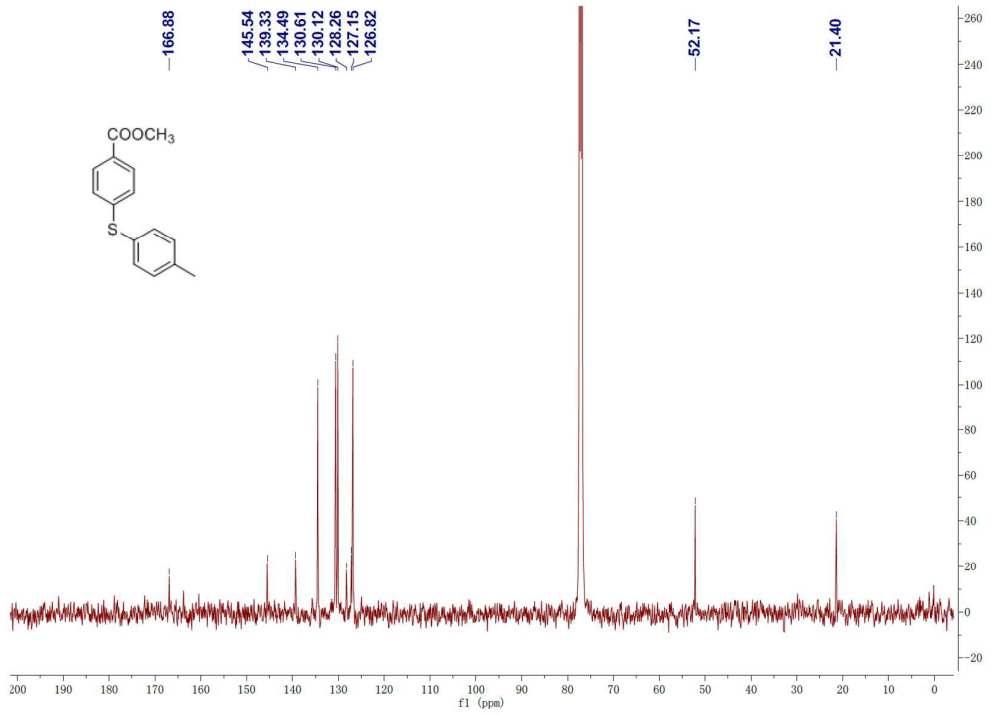
^{1}H NMR of 3g



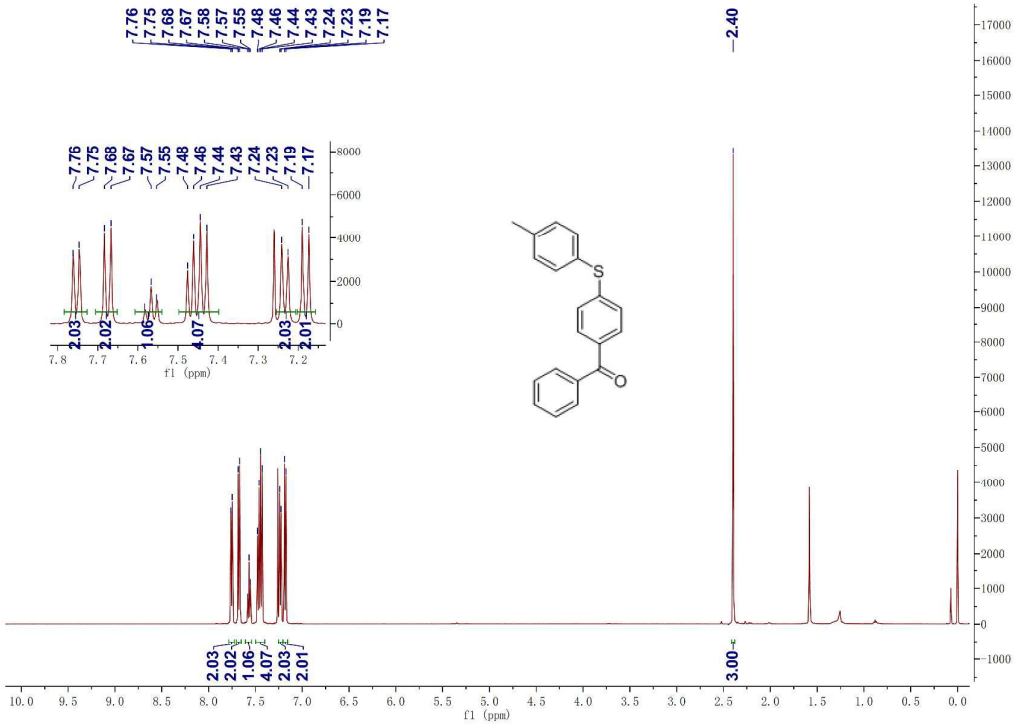
^{13}C NMR of 3g



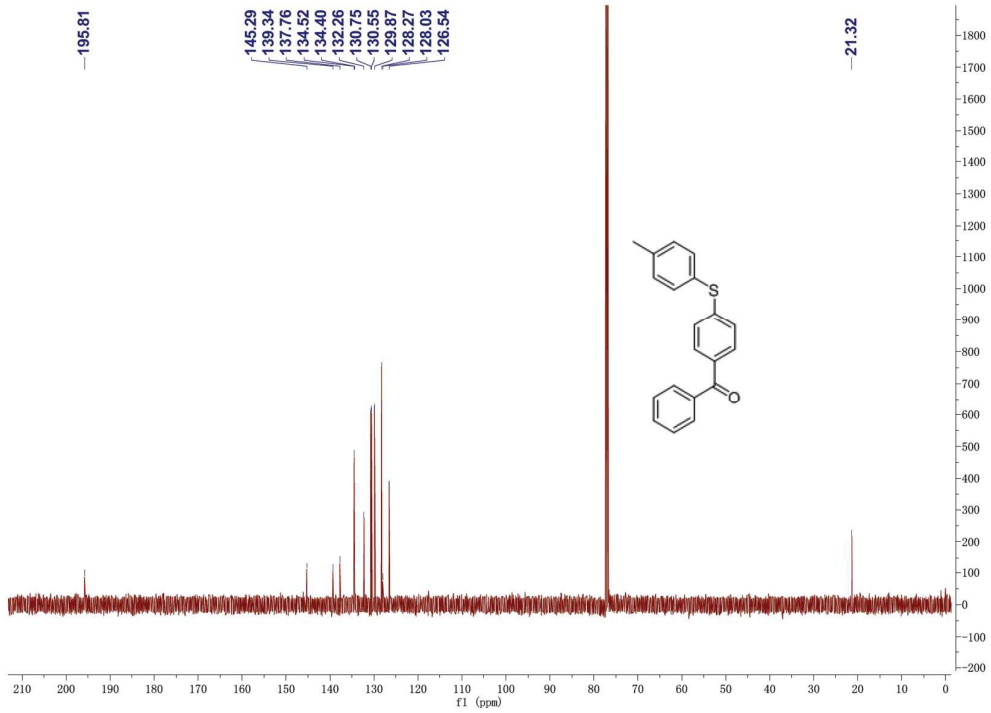
^{1}H NMR of 3h



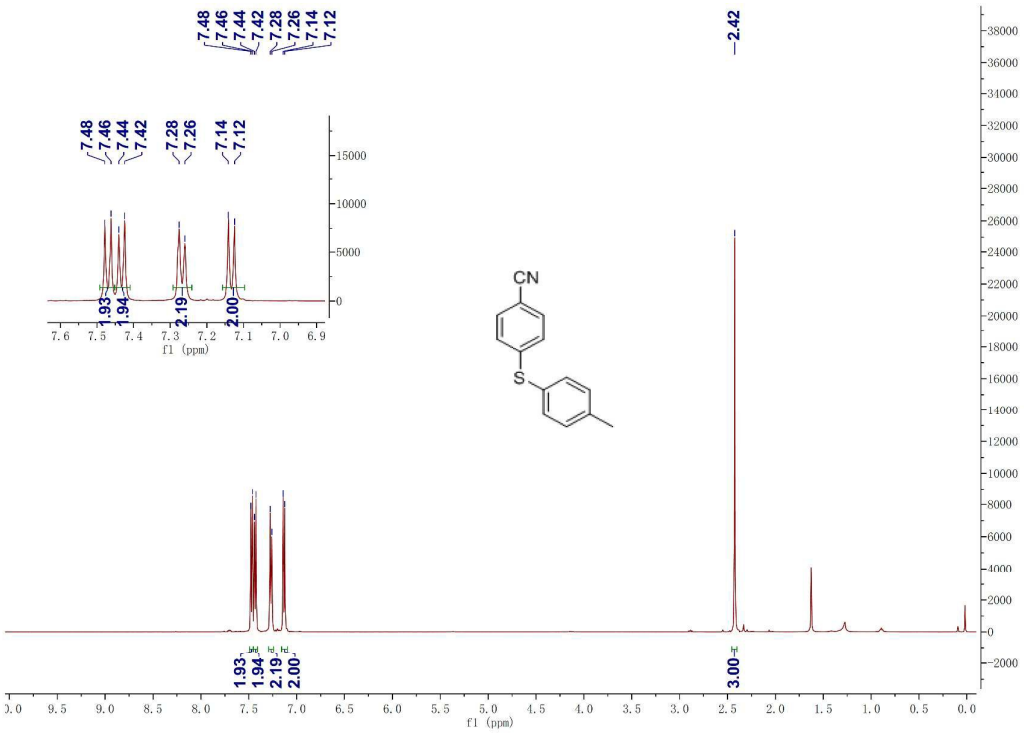
^{13}C NMR of 3h



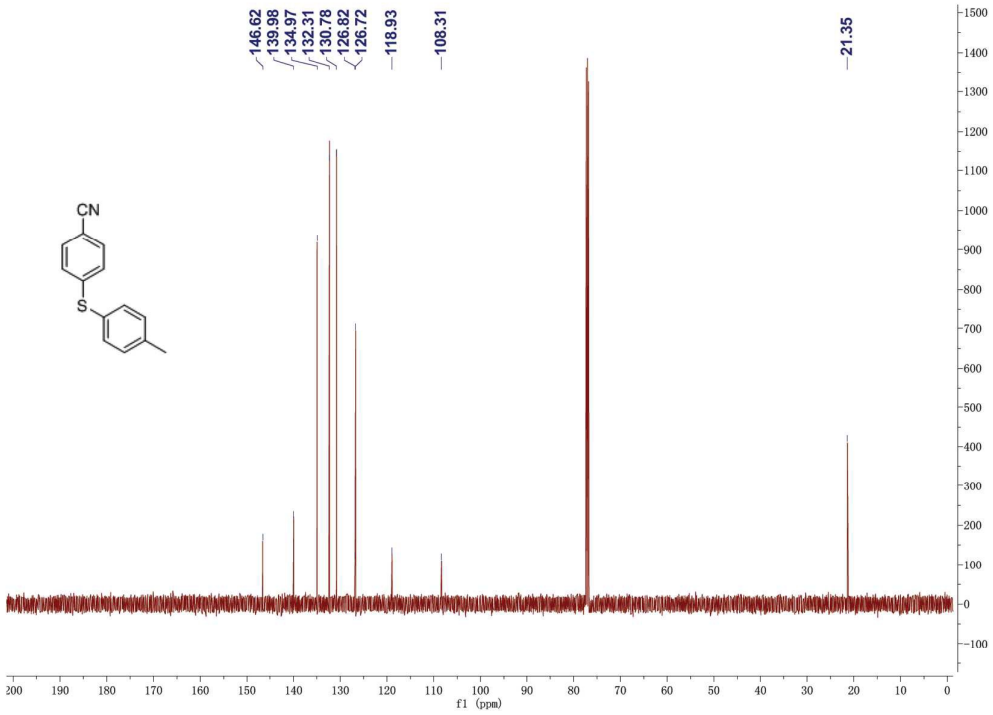
^{1}H NMR of 3i



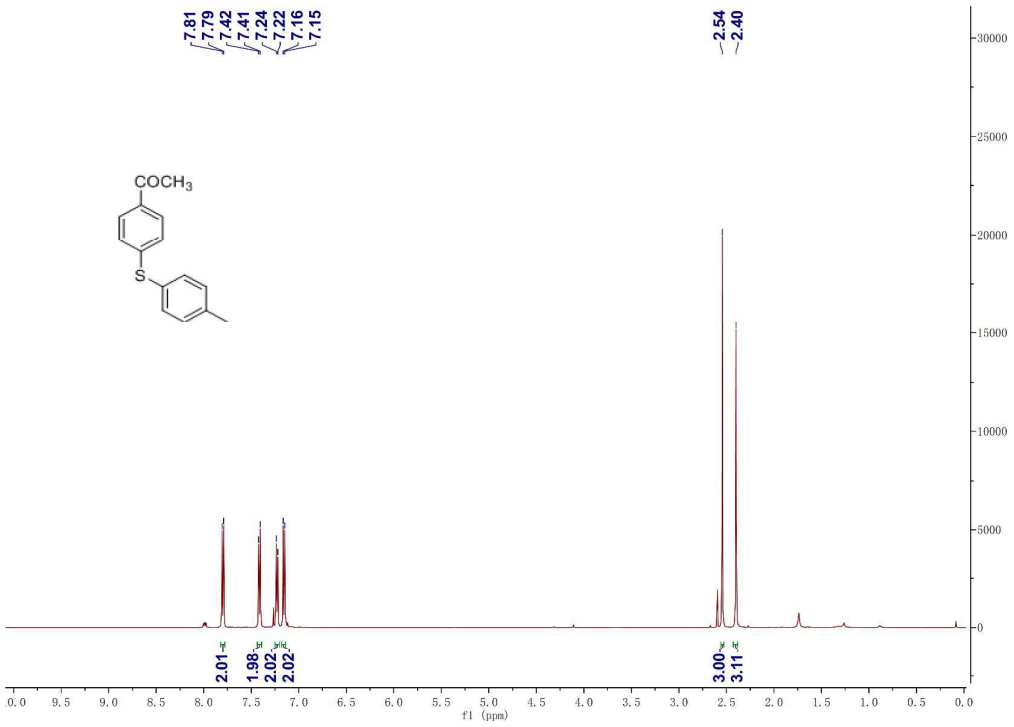
^{13}C NMR of 3i



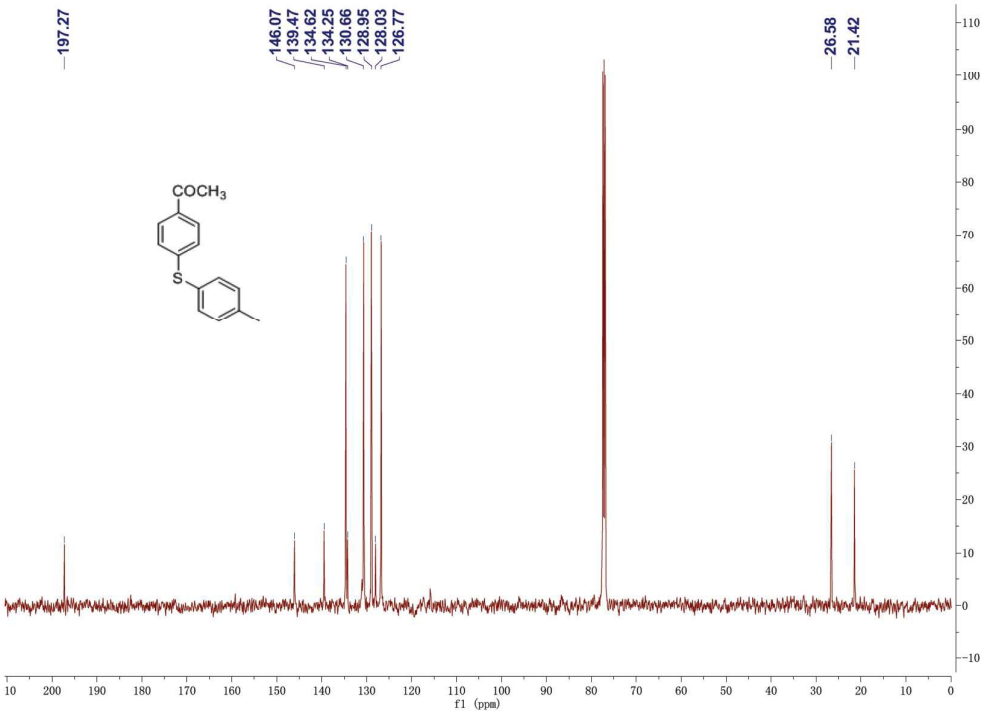
^{1}H NMR of 3j



^{13}C NMR of 3j



^{1}H NMR of 3k



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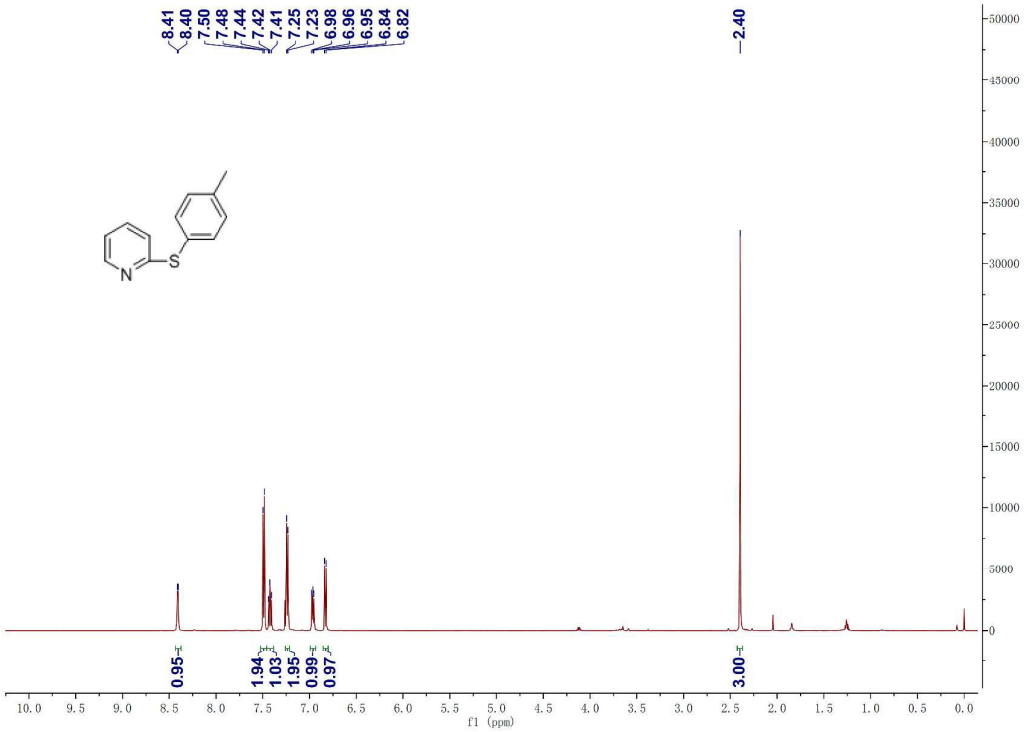
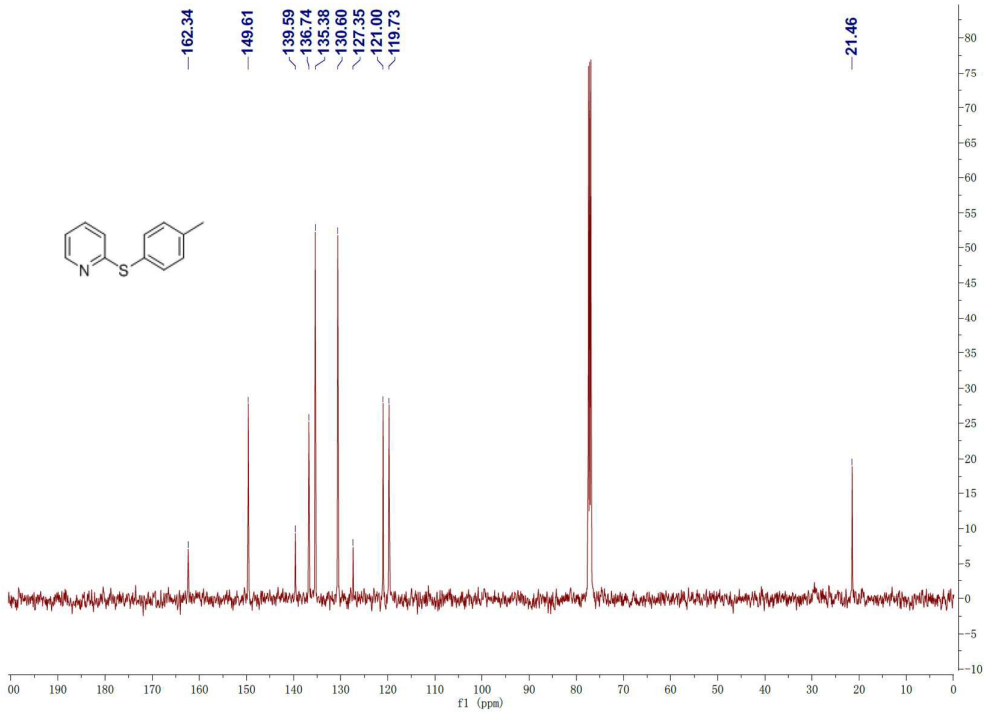
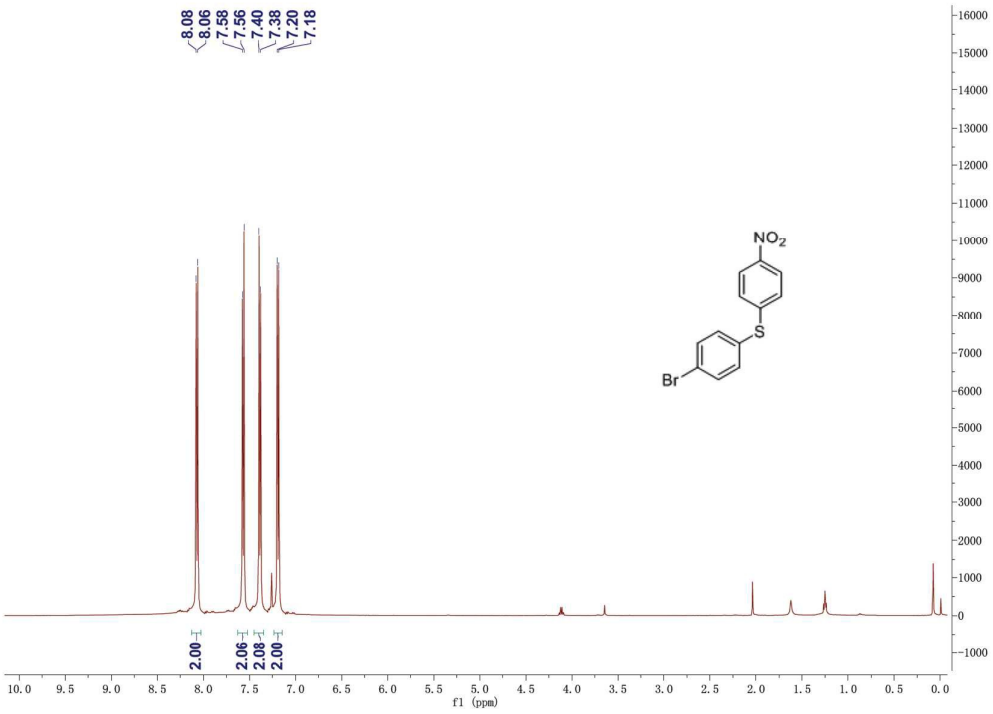


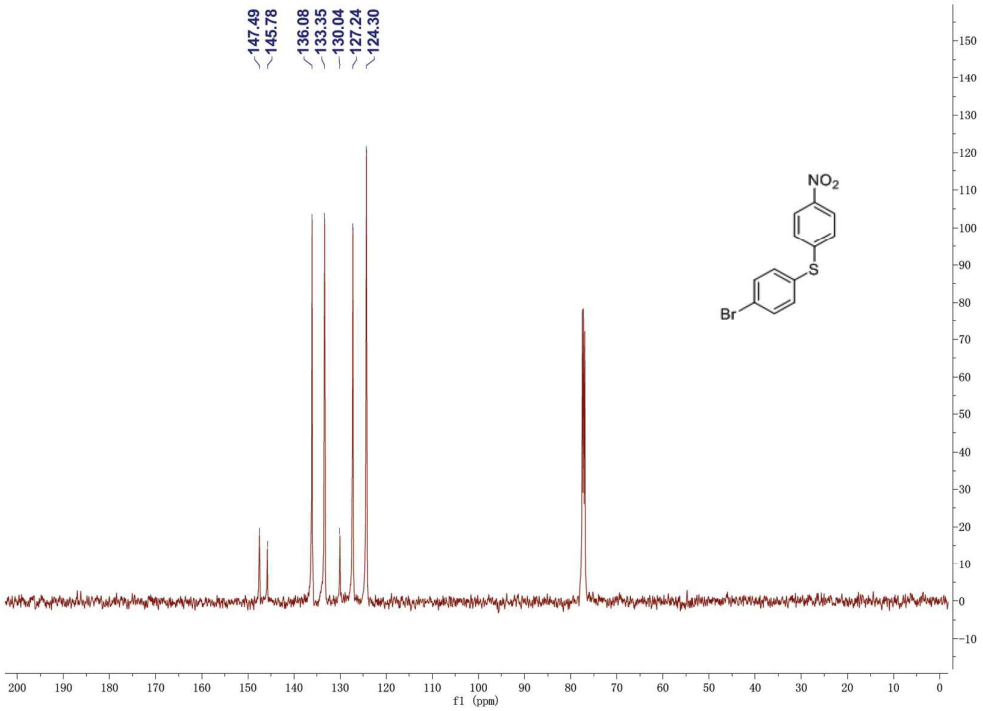
^{1}H NMR of 3l



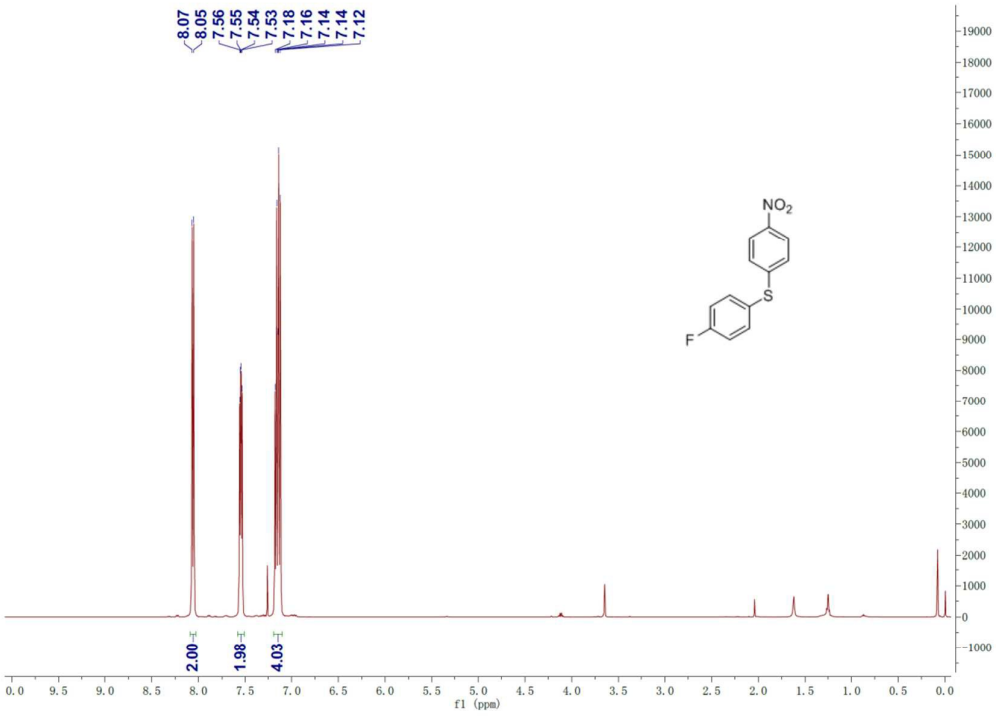
^{13}C NMR of 3l



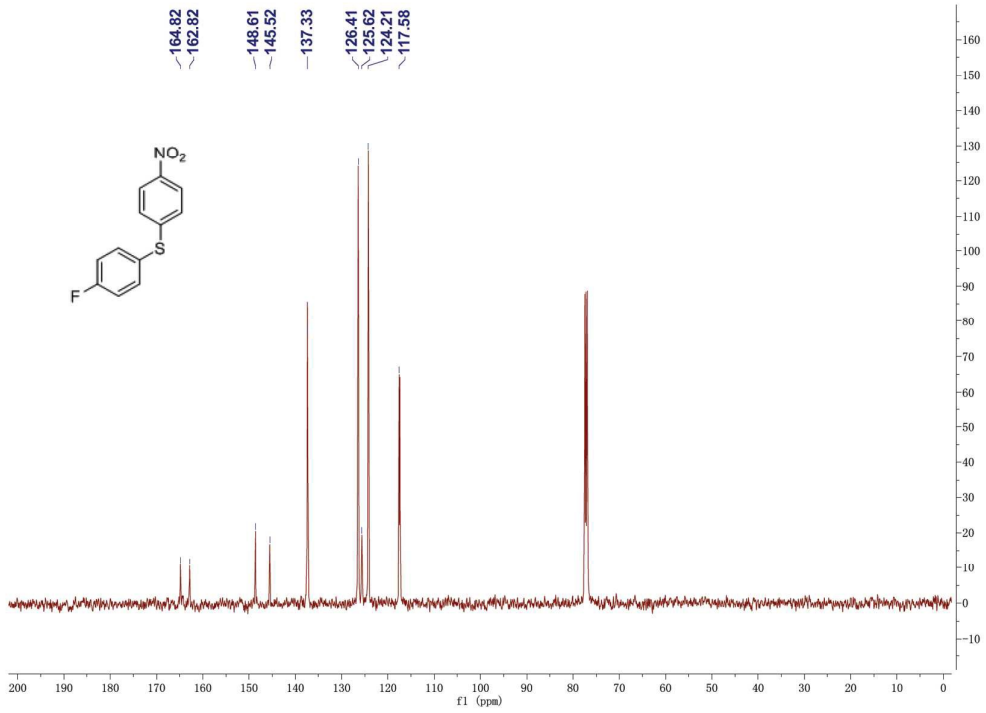
^{1}H NMR of 3m



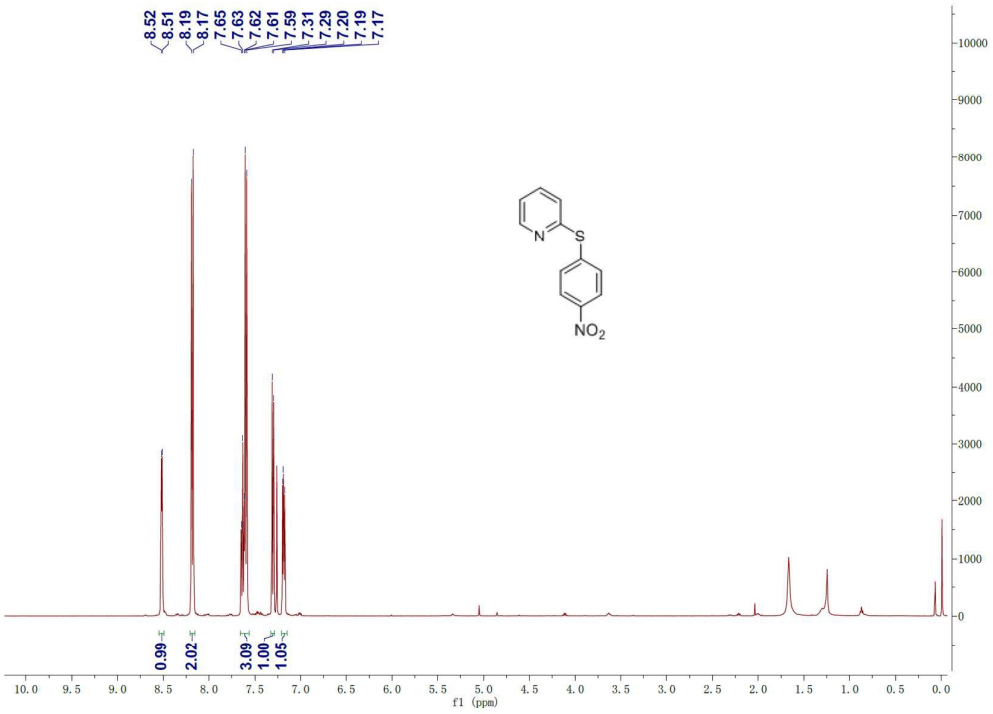
^{13}C NMR of 3m



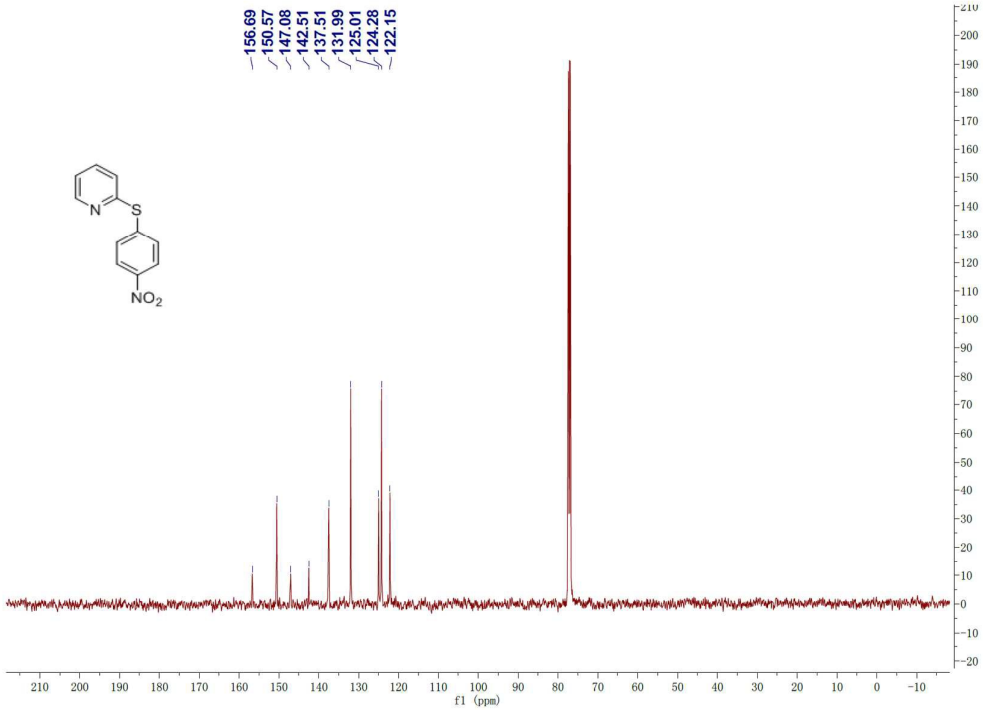
^{1}H NMR of 3n



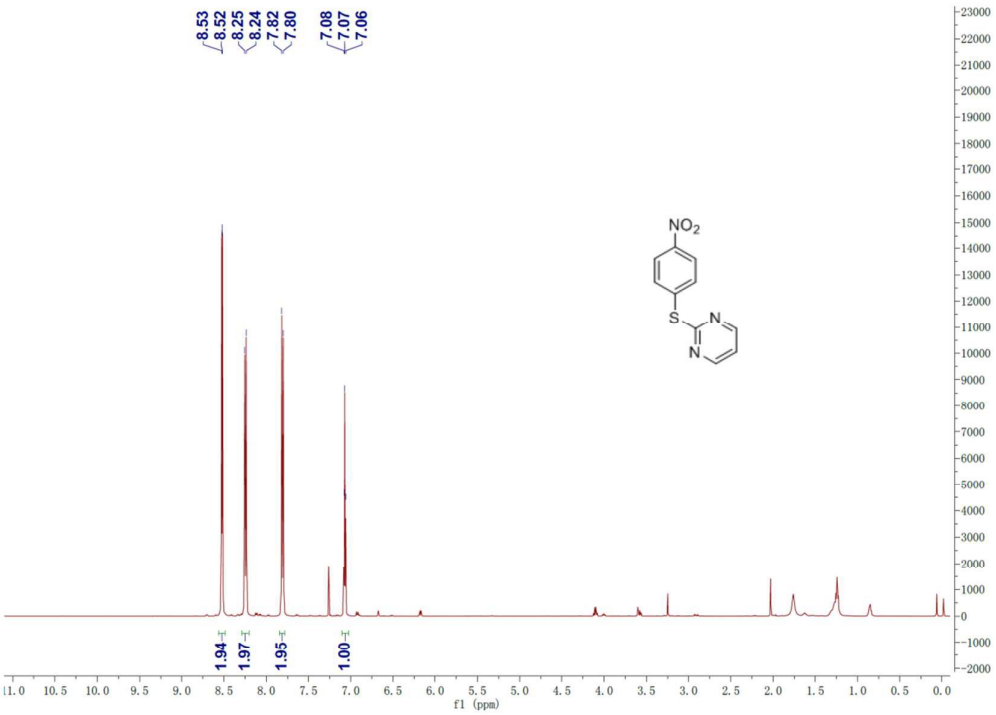
^{13}C NMR of 3n



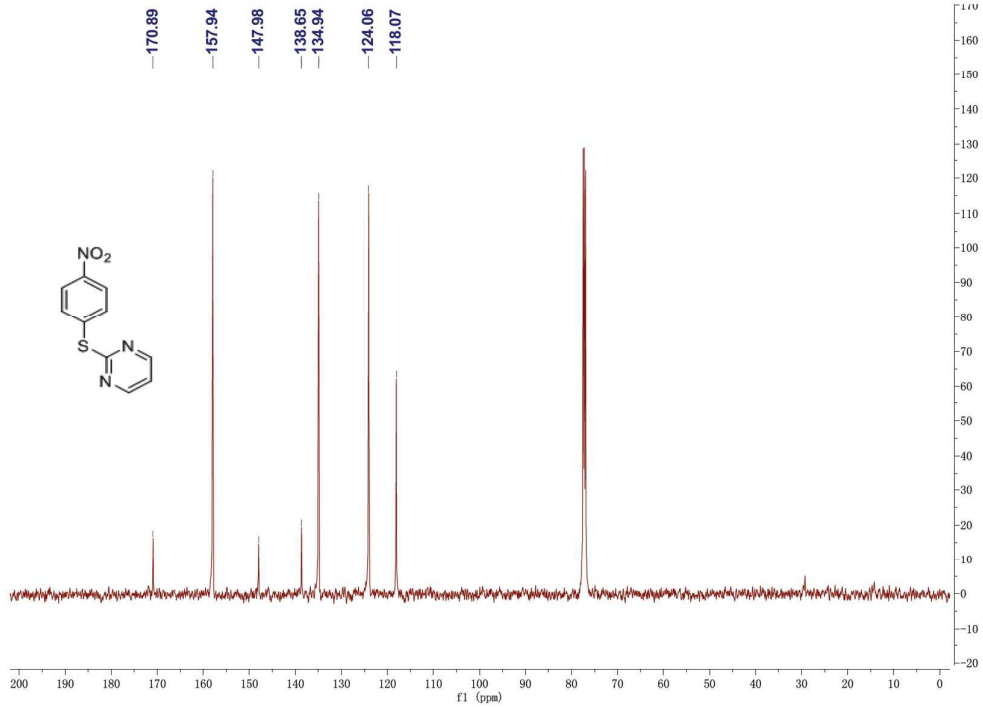
^{1}H NMR of 3o



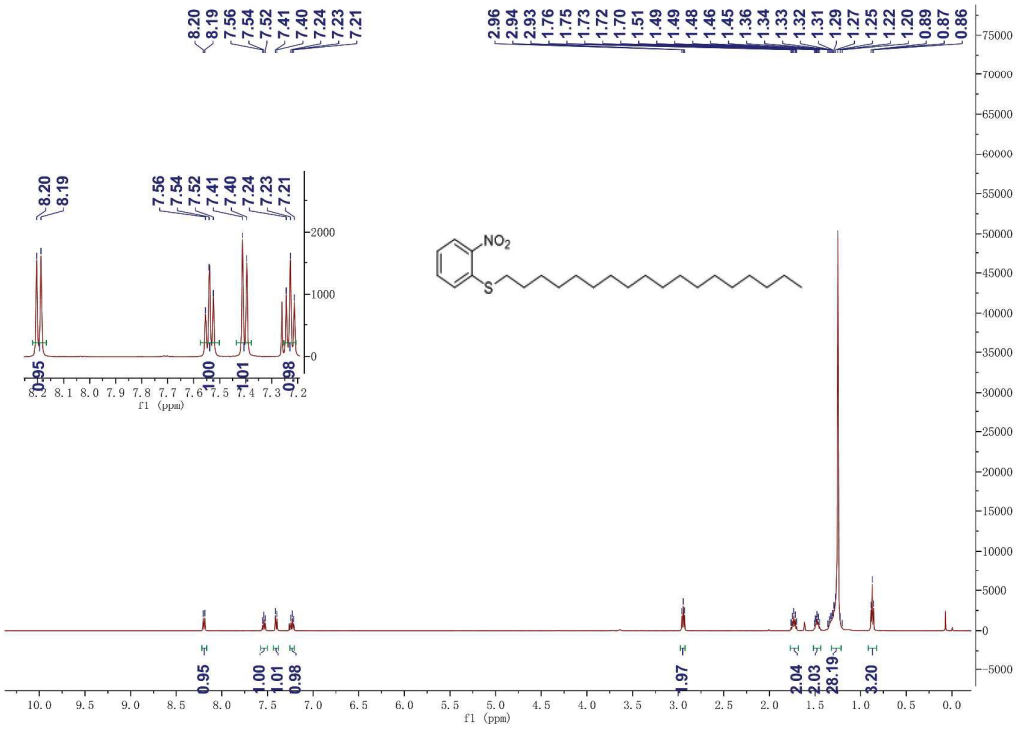
^{13}C NMR of 3o



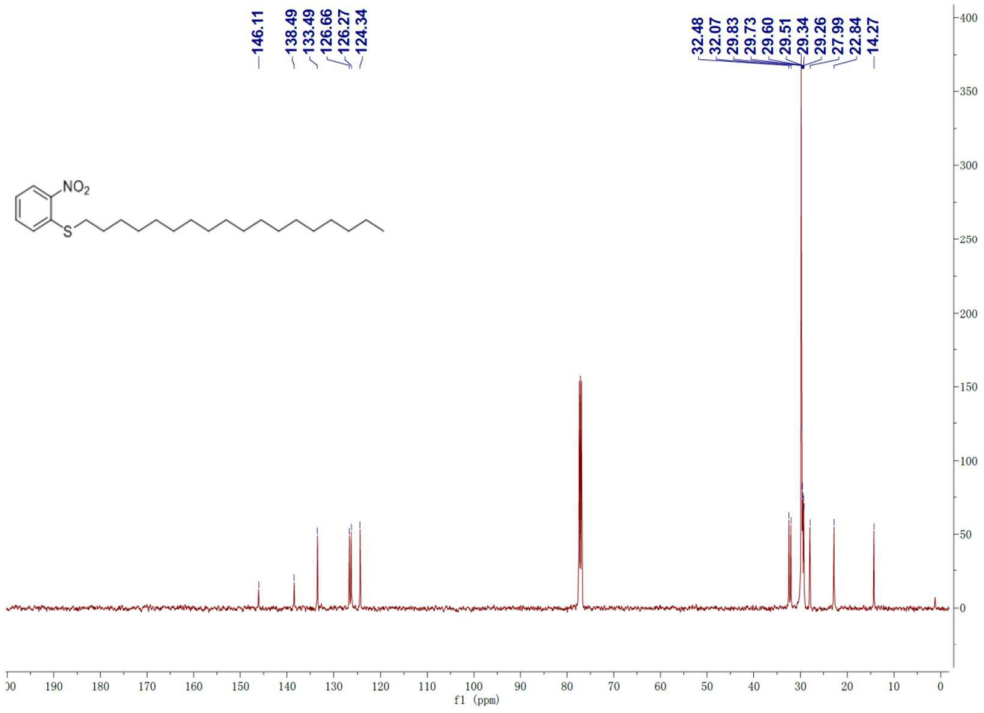
^{1}H NMR of 3p



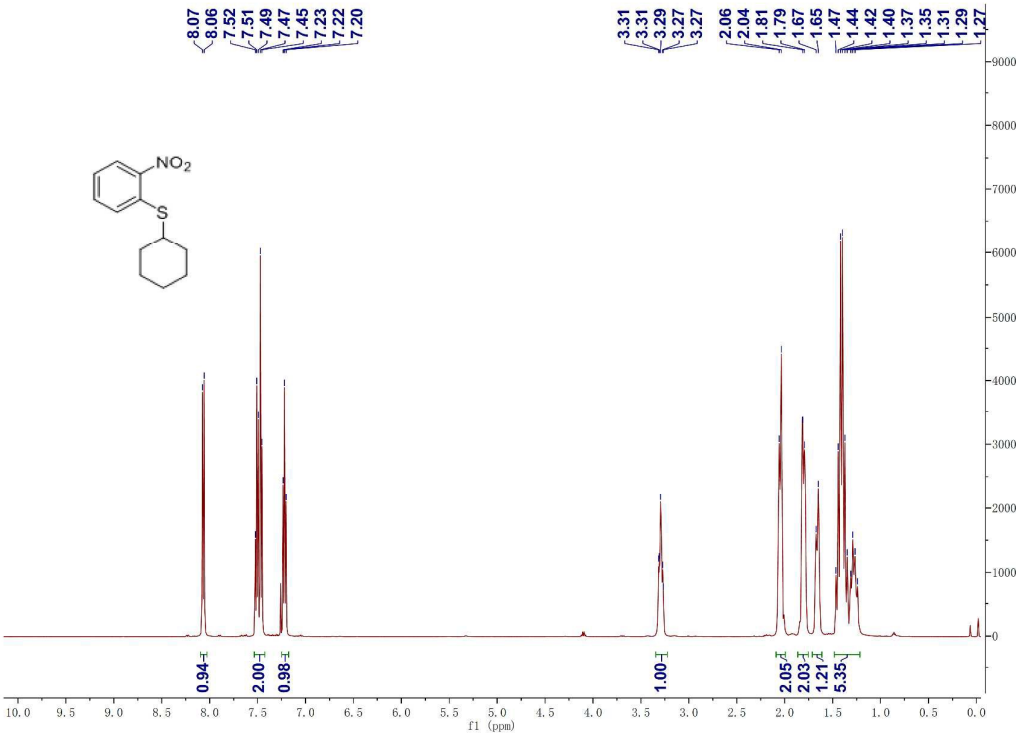
^{13}C NMR of 3p



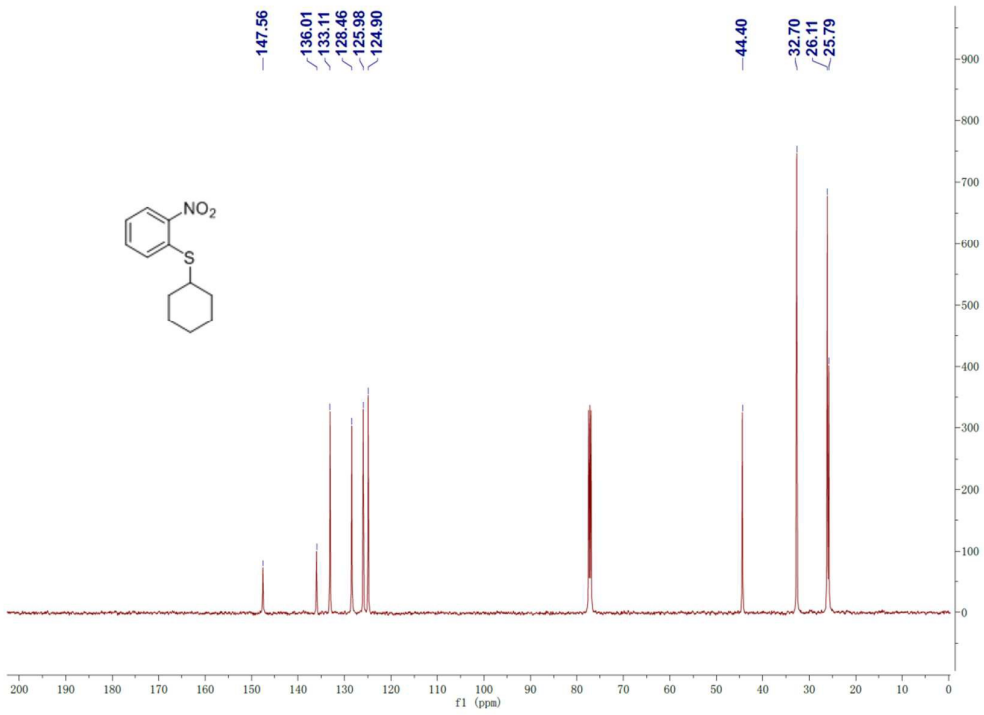
^{1}H NMR of 3q



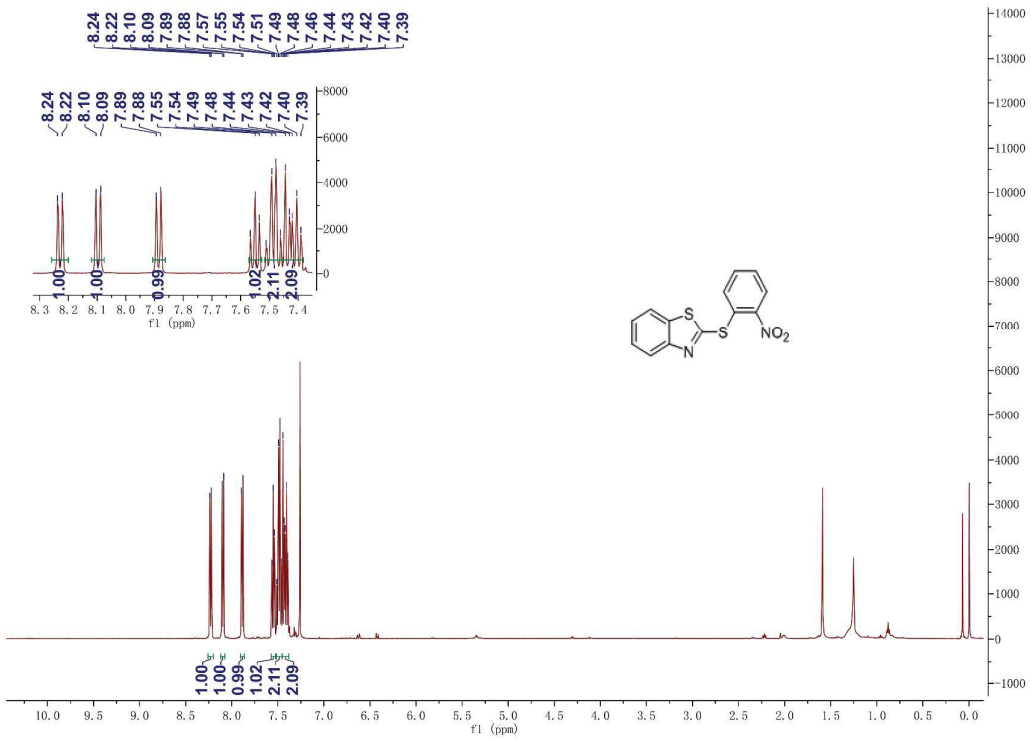
^{13}C NMR of 3q



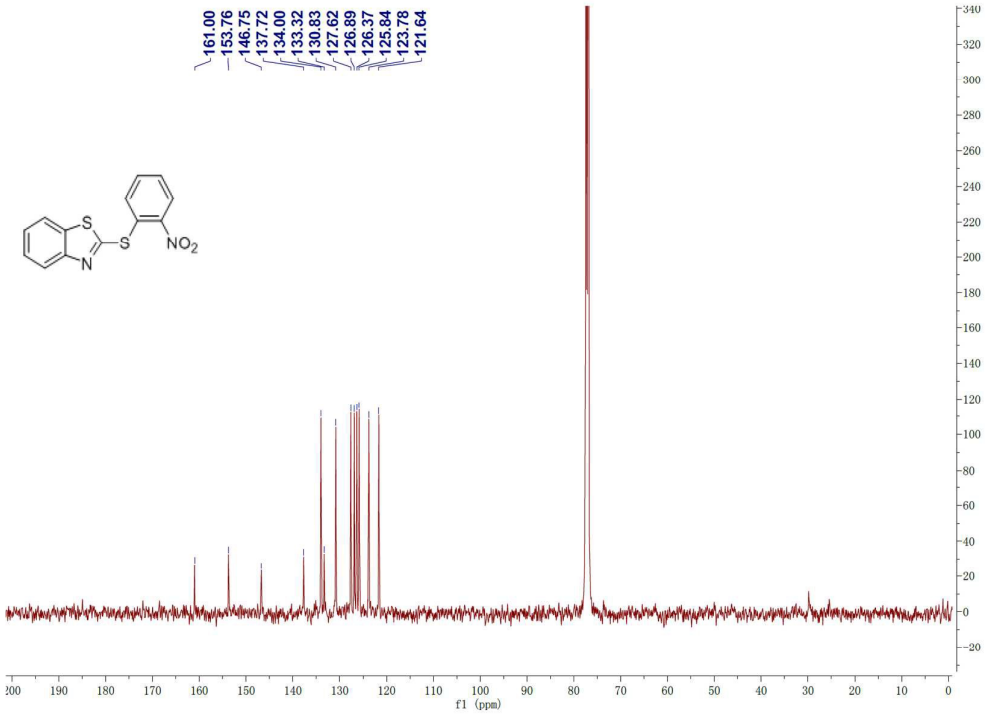
^{1}H NMR of 3r



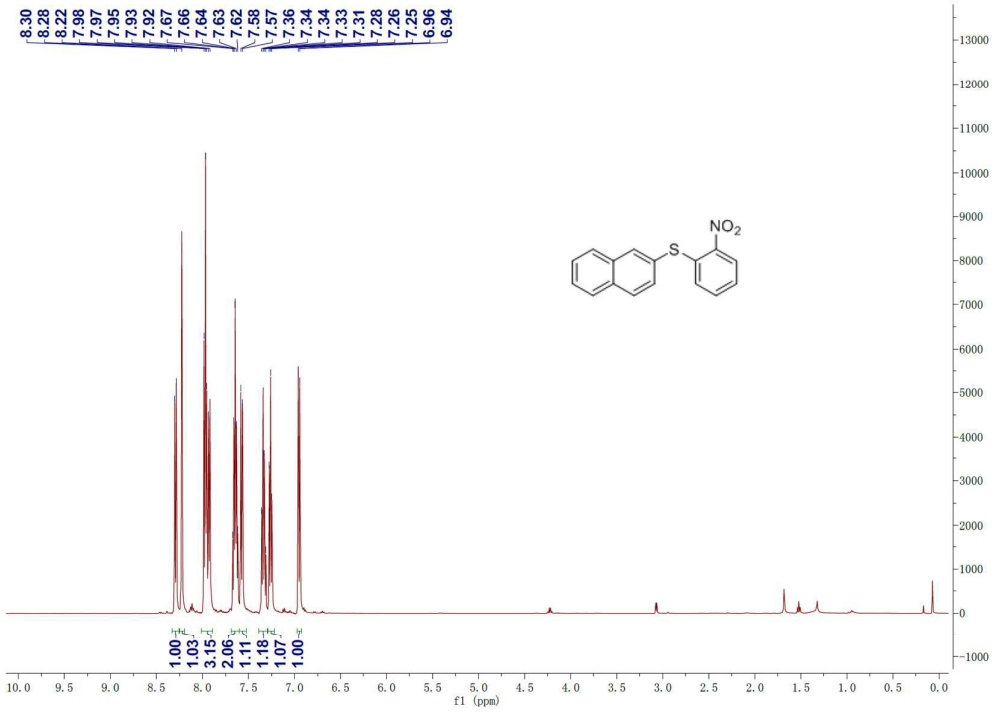
^{13}C NMR of 3r



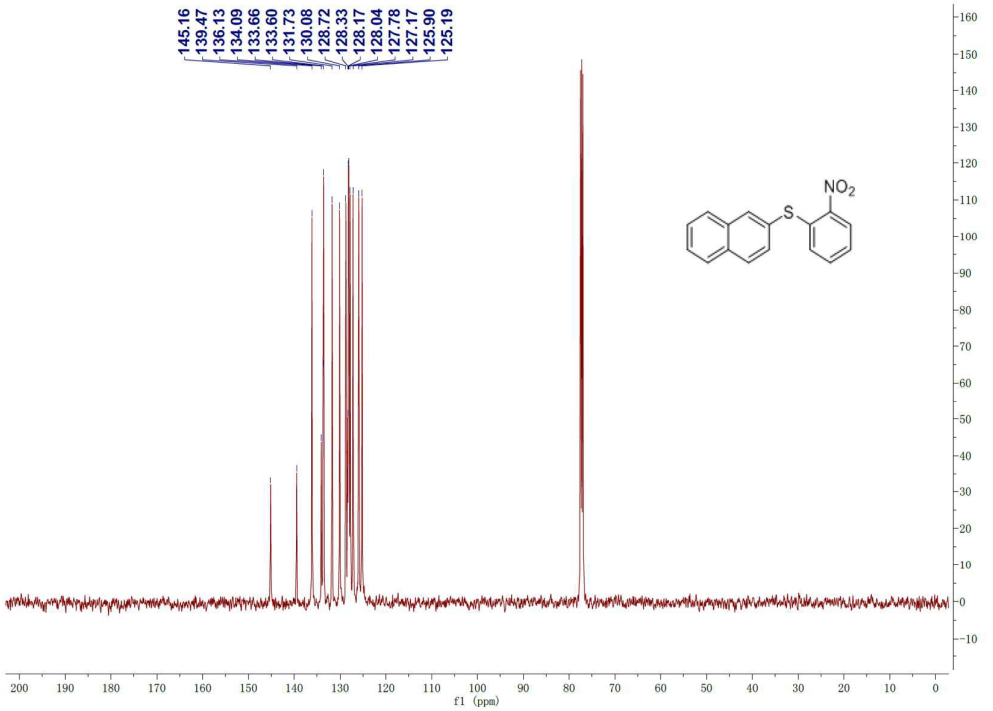
^{1}H NMR of 3s



^{13}C NMR of 3s



^{1}H NMR of 3t



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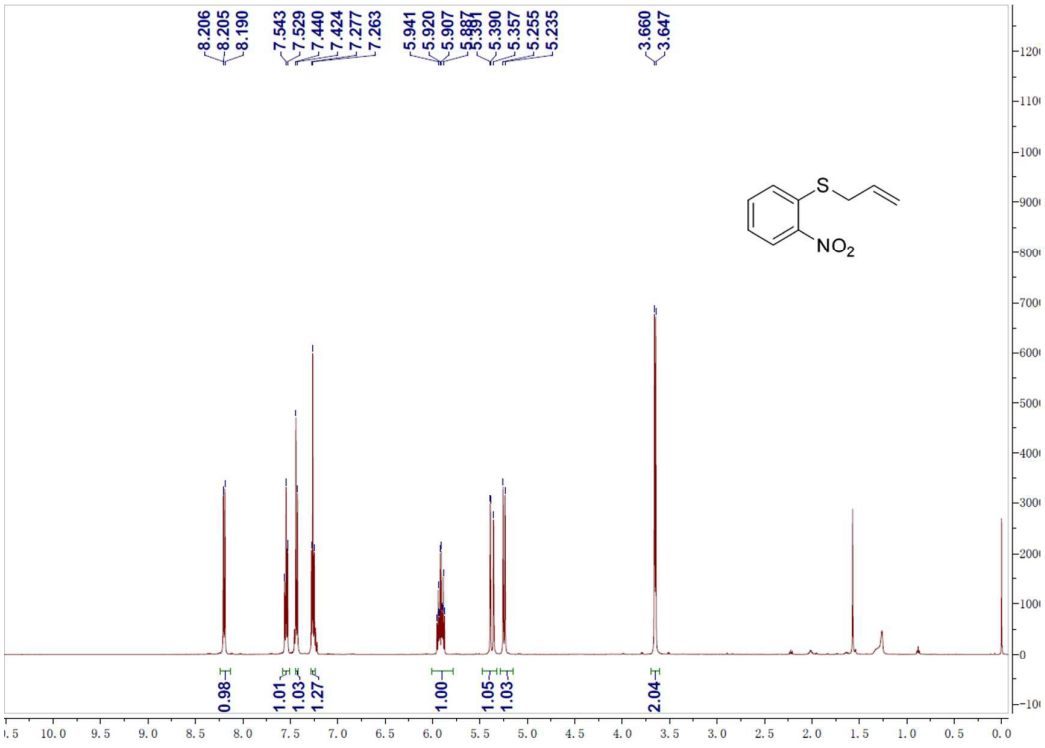
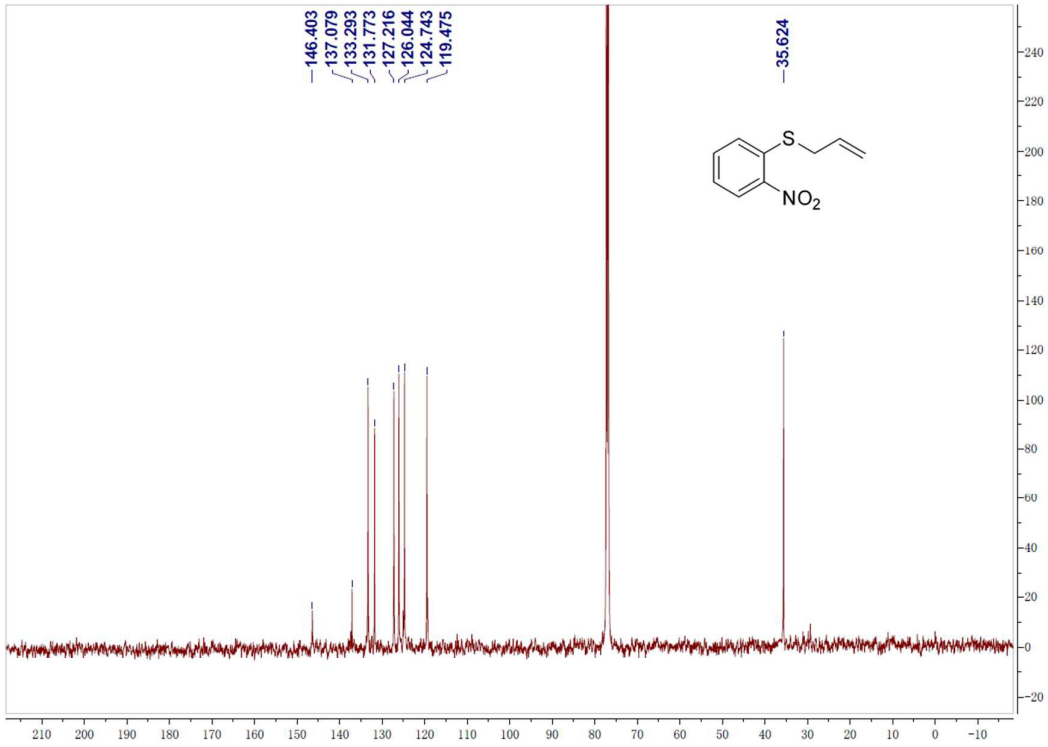
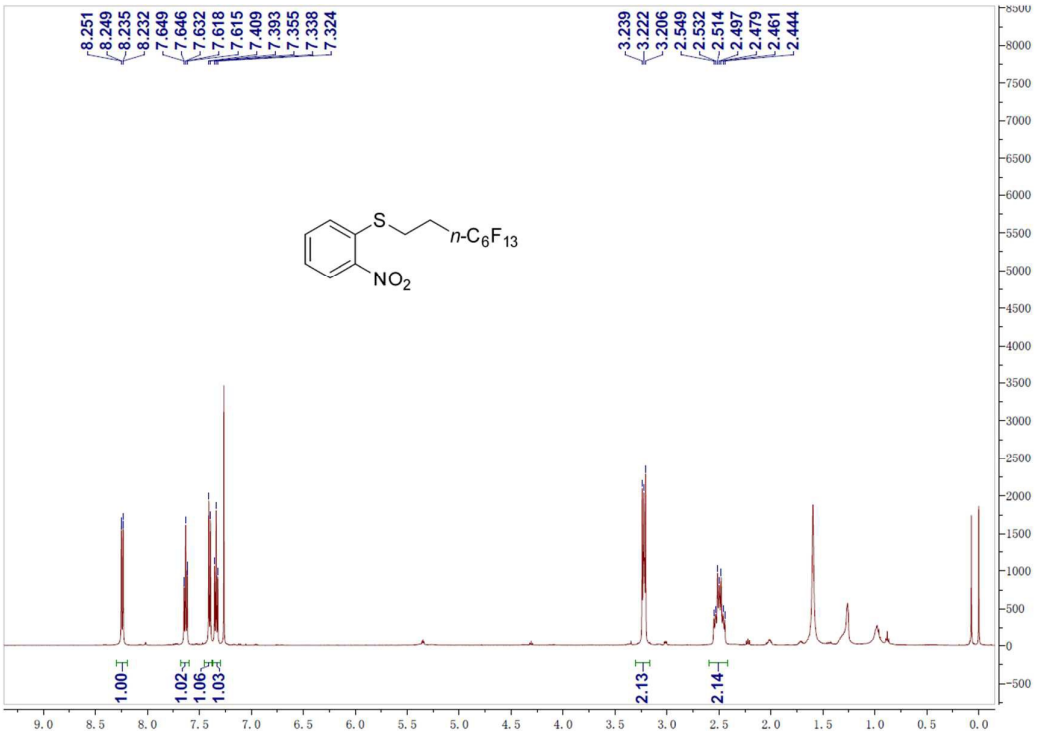


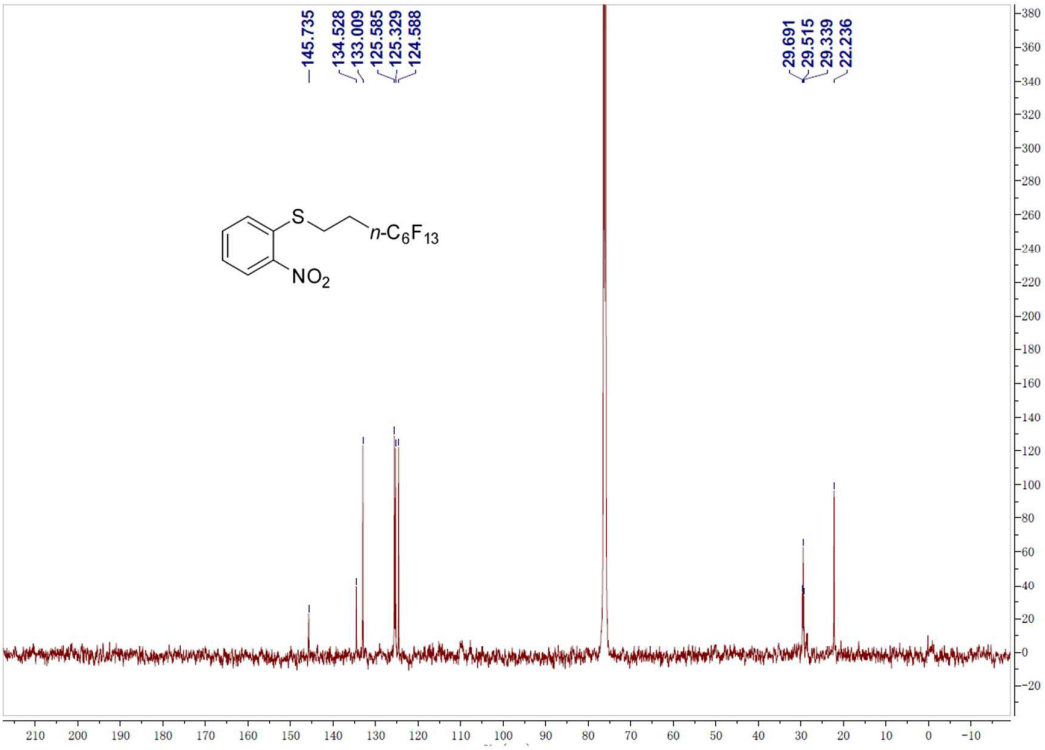
^{1}H NMR of 3u



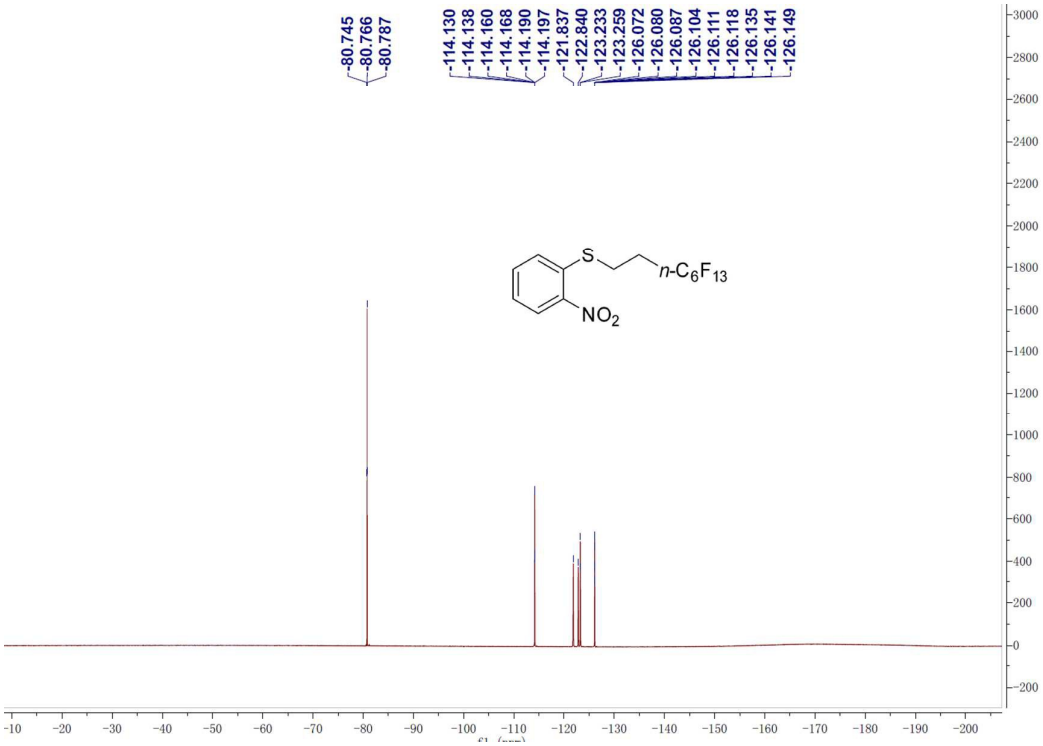
^{13}C NMR of 3u



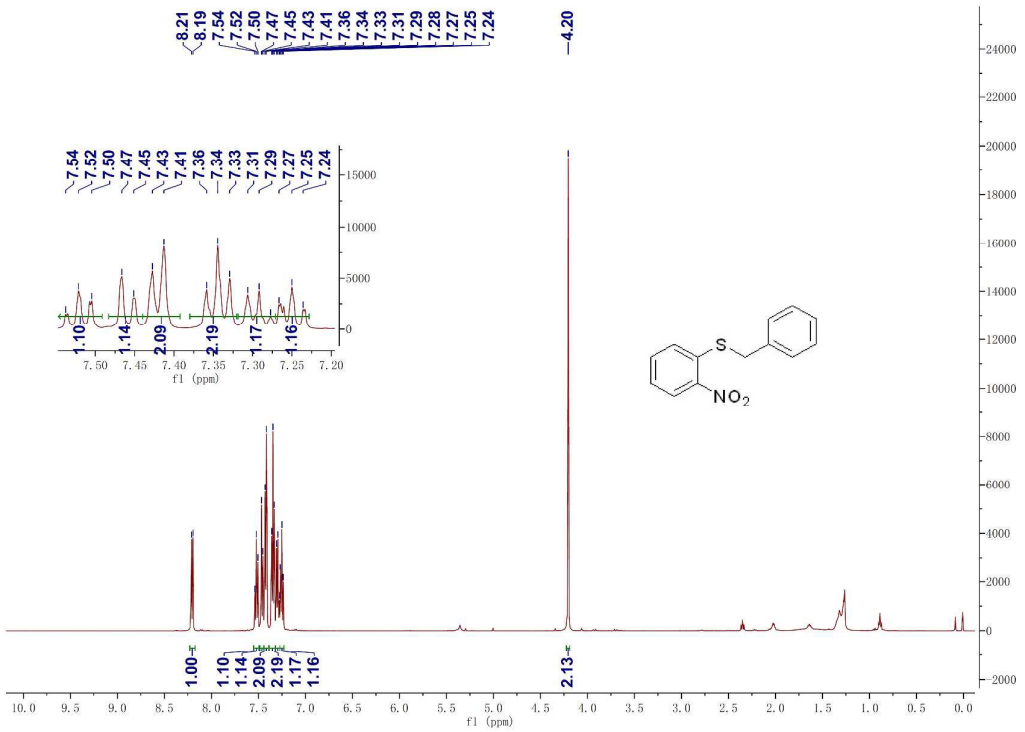
^{1}H NMR of 3v



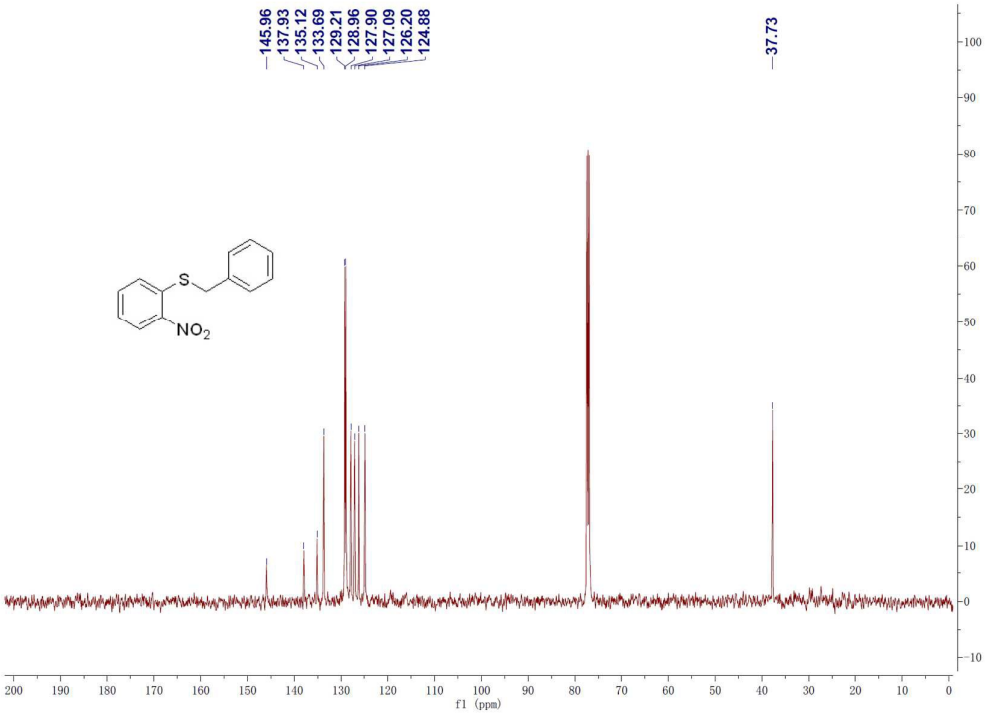
^{13}C NMR of 3v



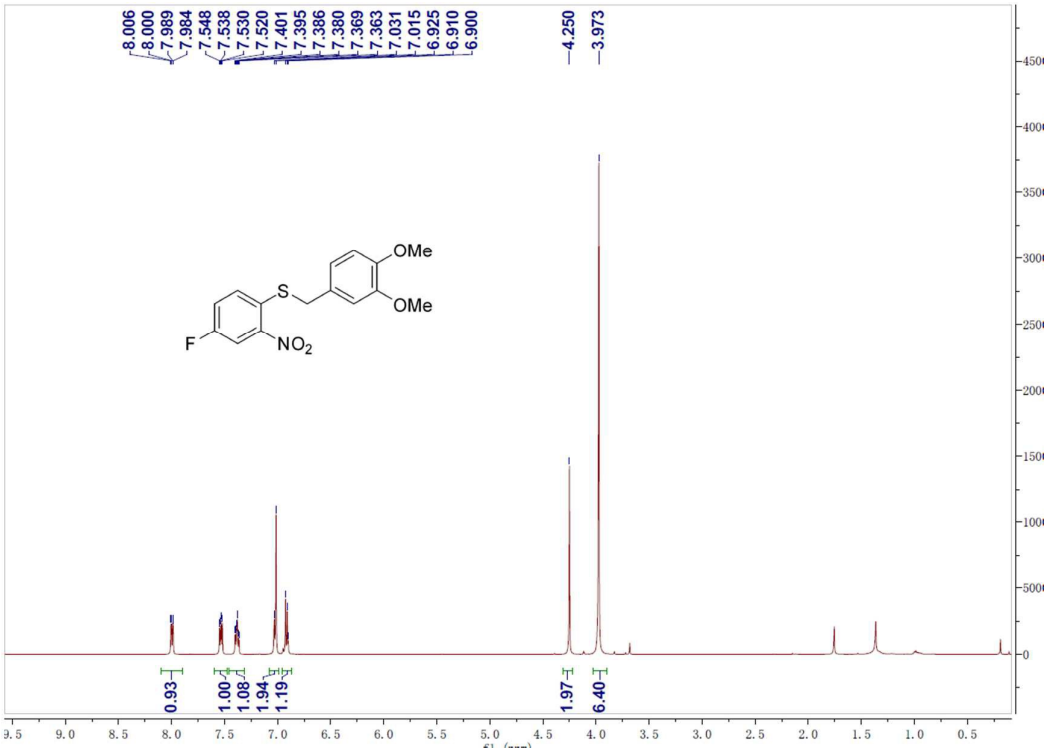
^{19}F NMR of 3v



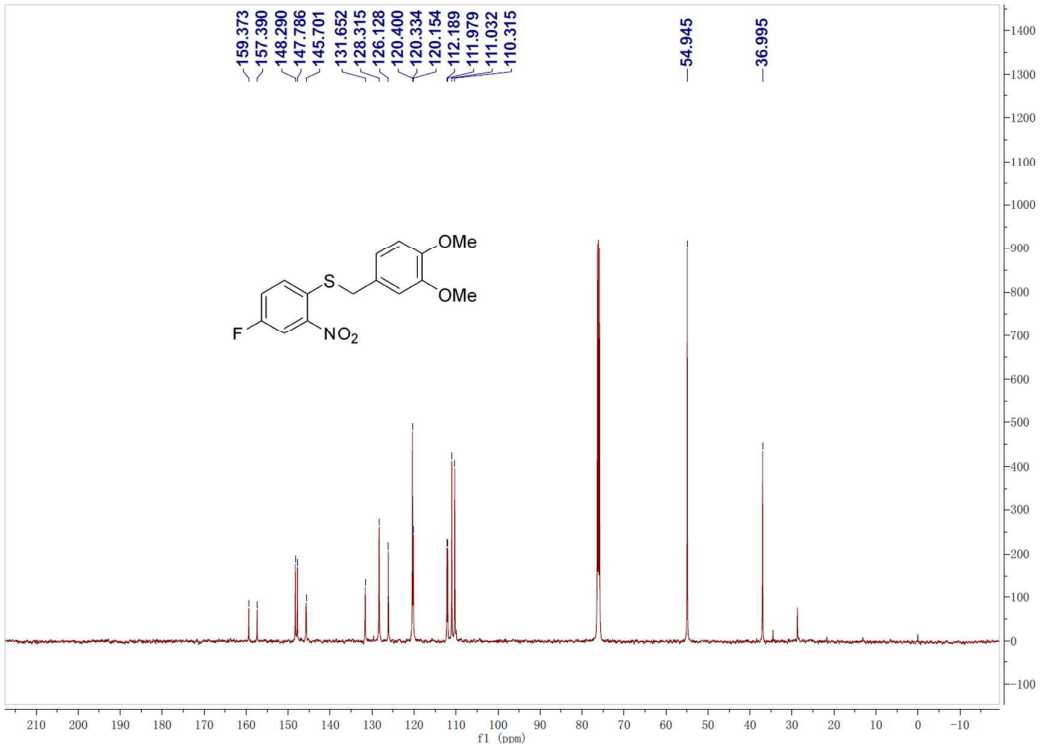
^{1}H NMR of 3w



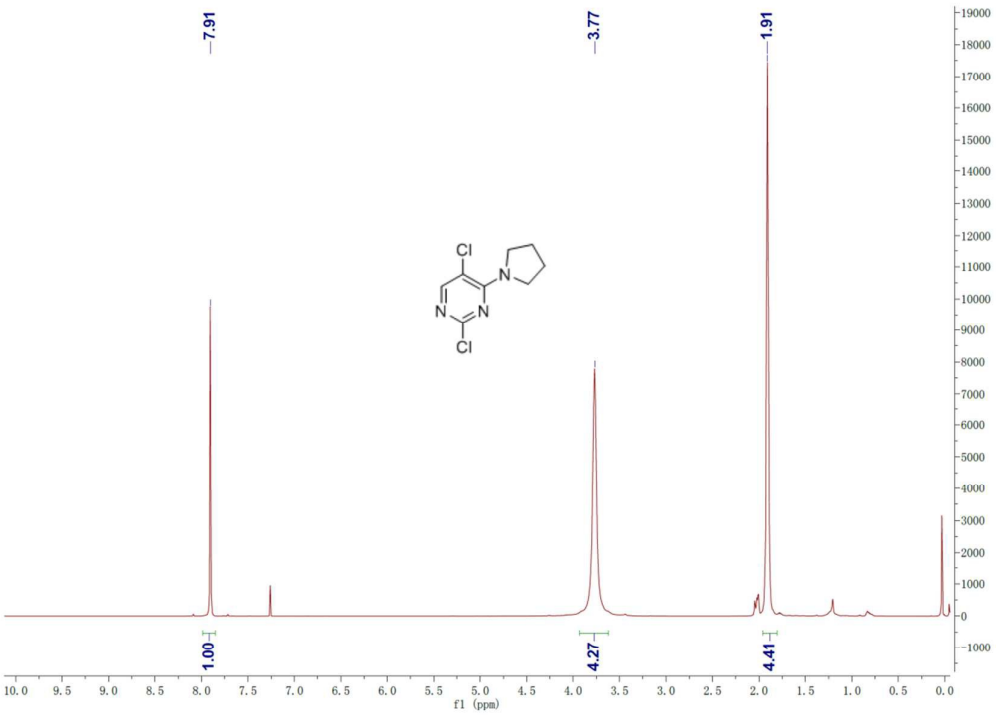
^{13}C NMR of 3w



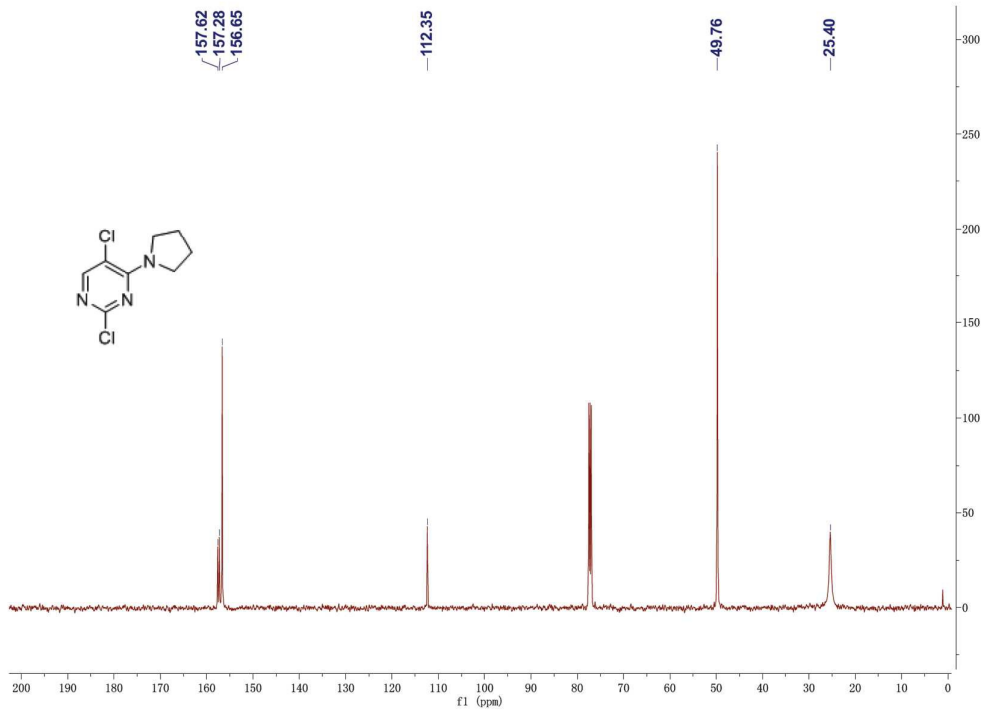
^{1}H NMR of 3x



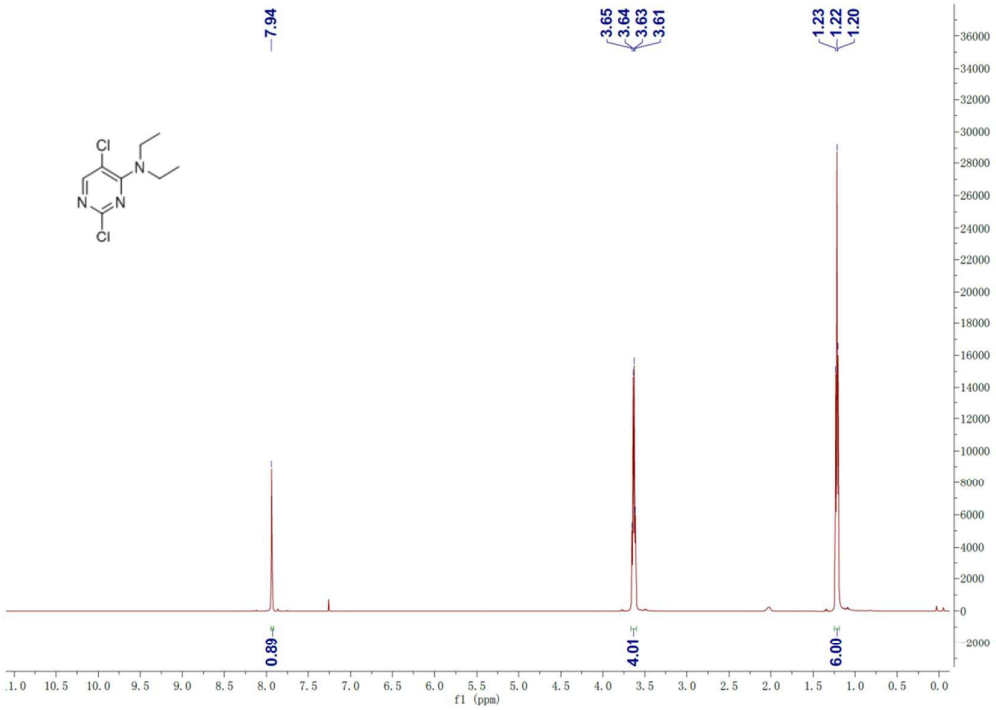
^{13}C NMR of 3x



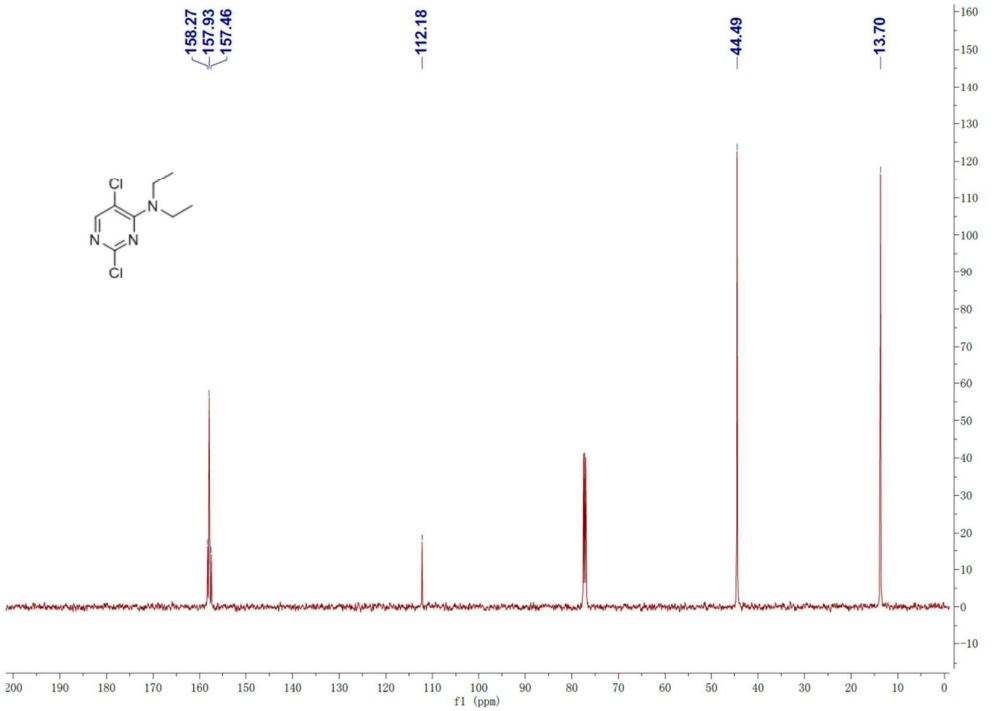
^{1}H NMR of 4a



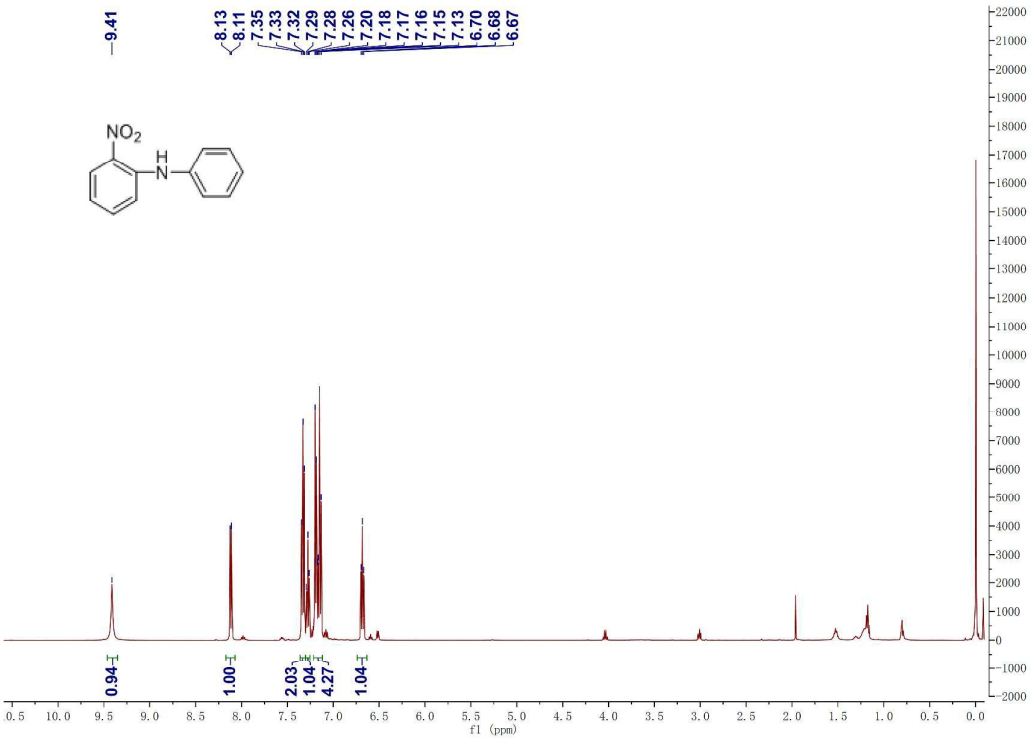
^{13}C NMR of 4a



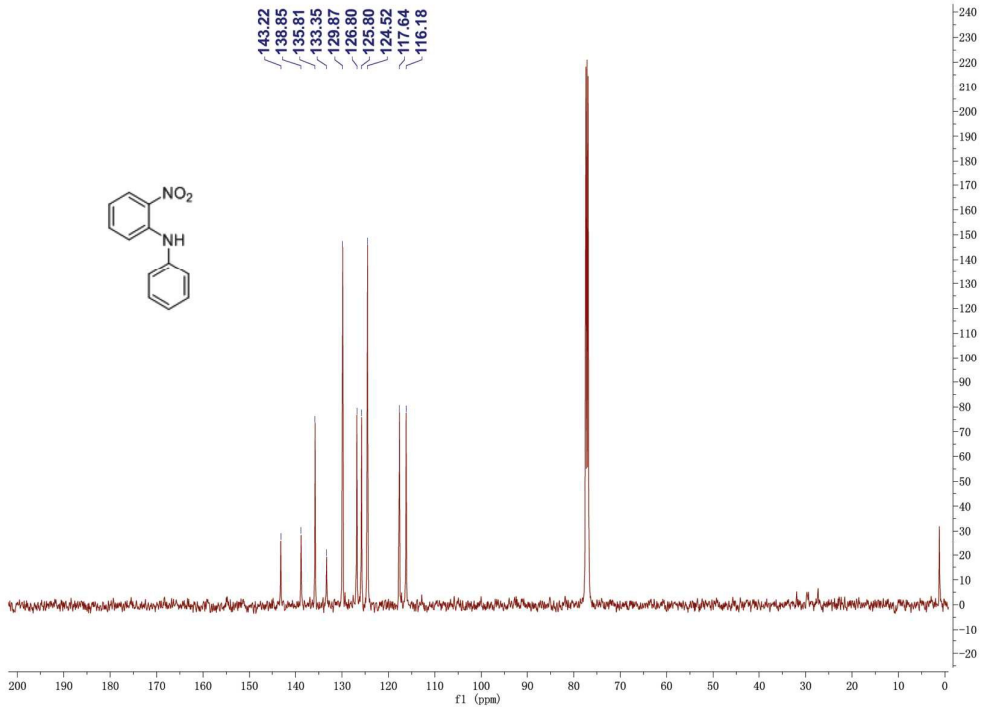
^{1}H NMR of 4b



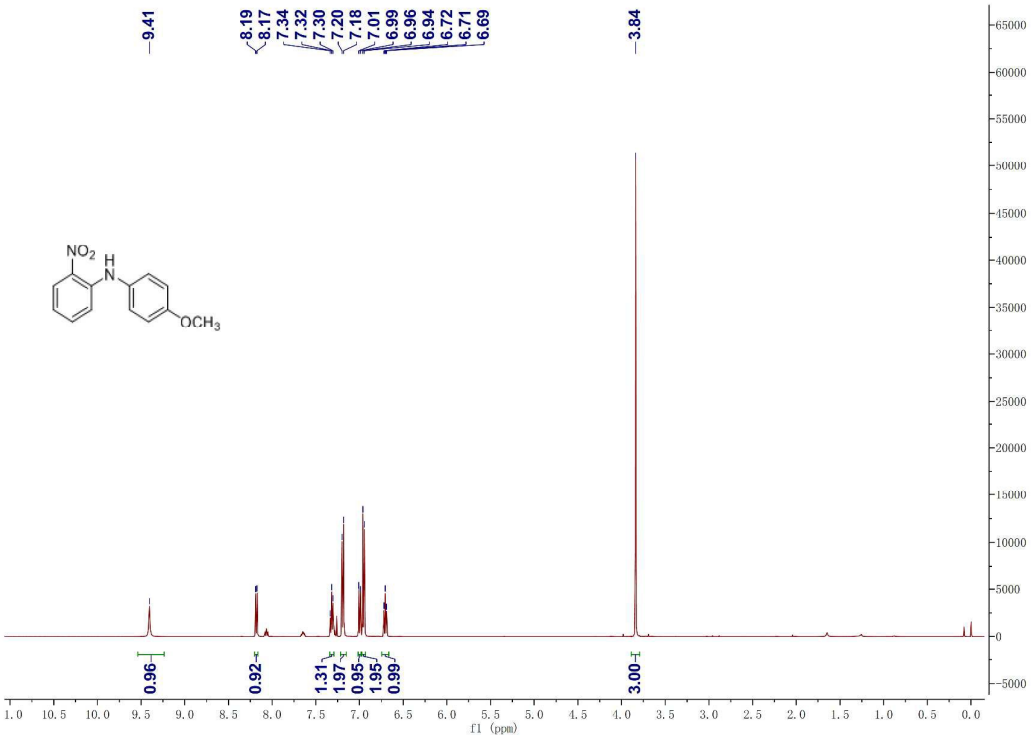
^{13}C NMR of 4b



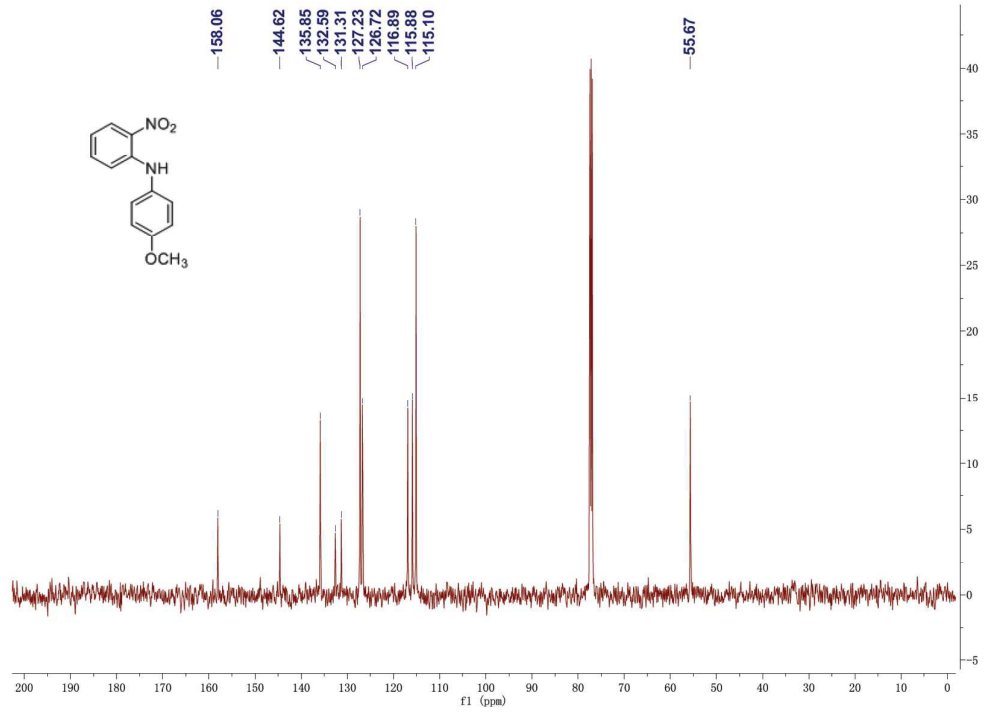
^{1}H NMR of 4c



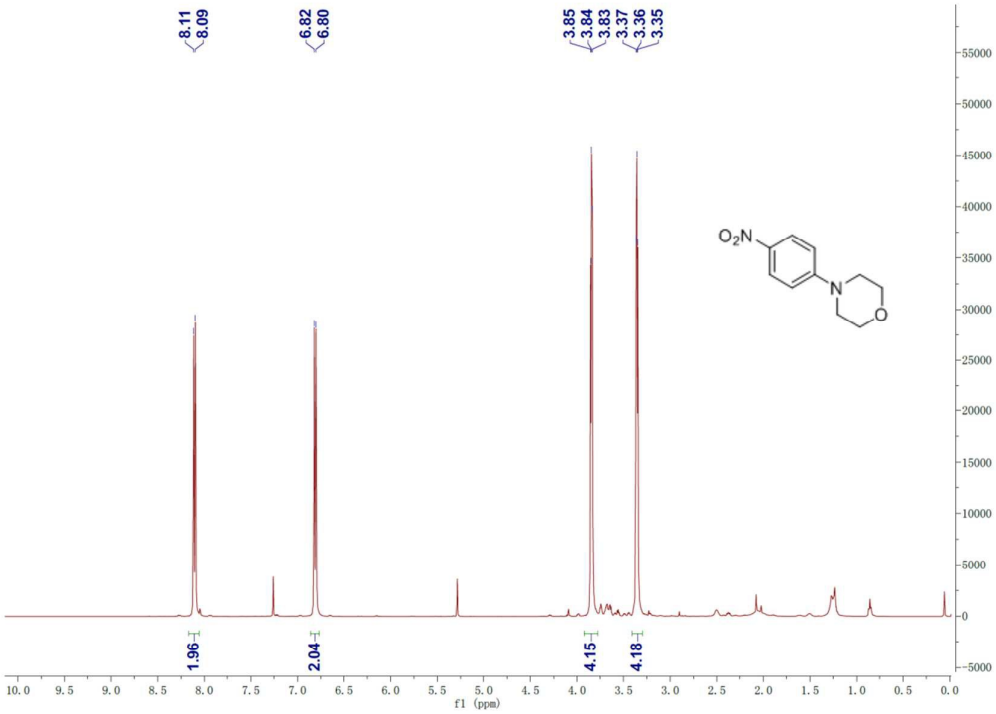
^{13}C NMR of 4c



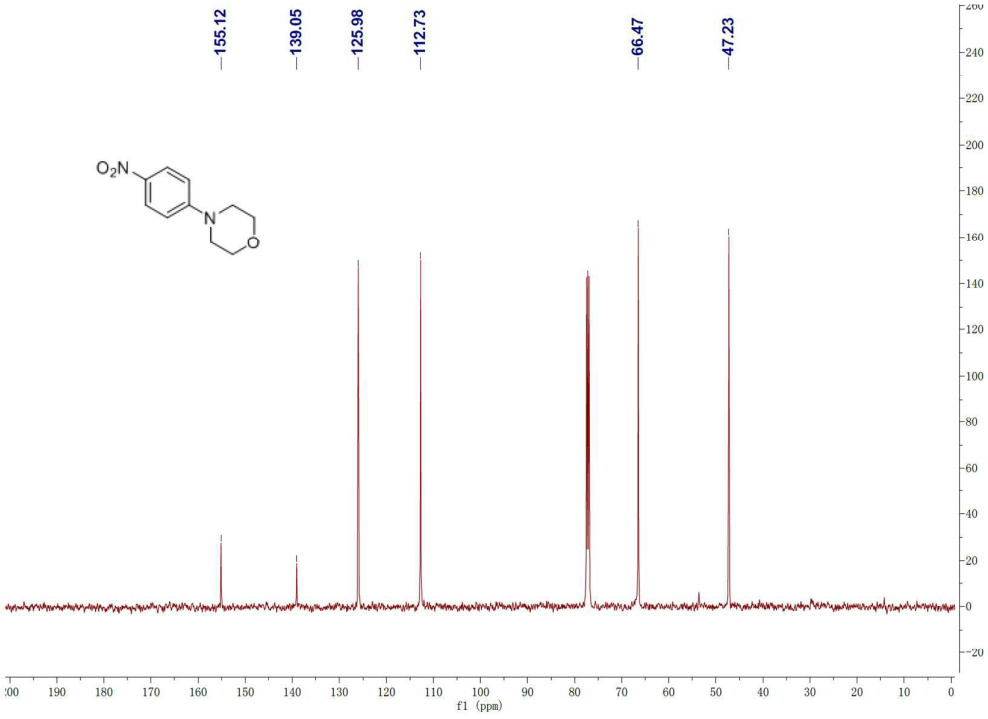
^{1}H NMR of 4d



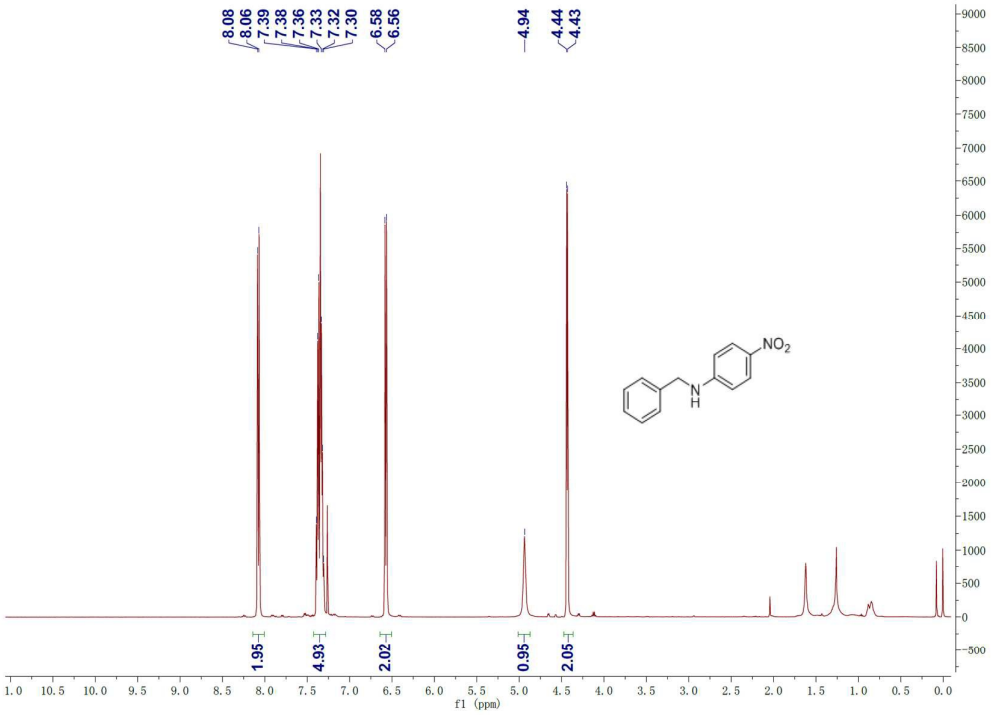
^{13}C NMR of 4d



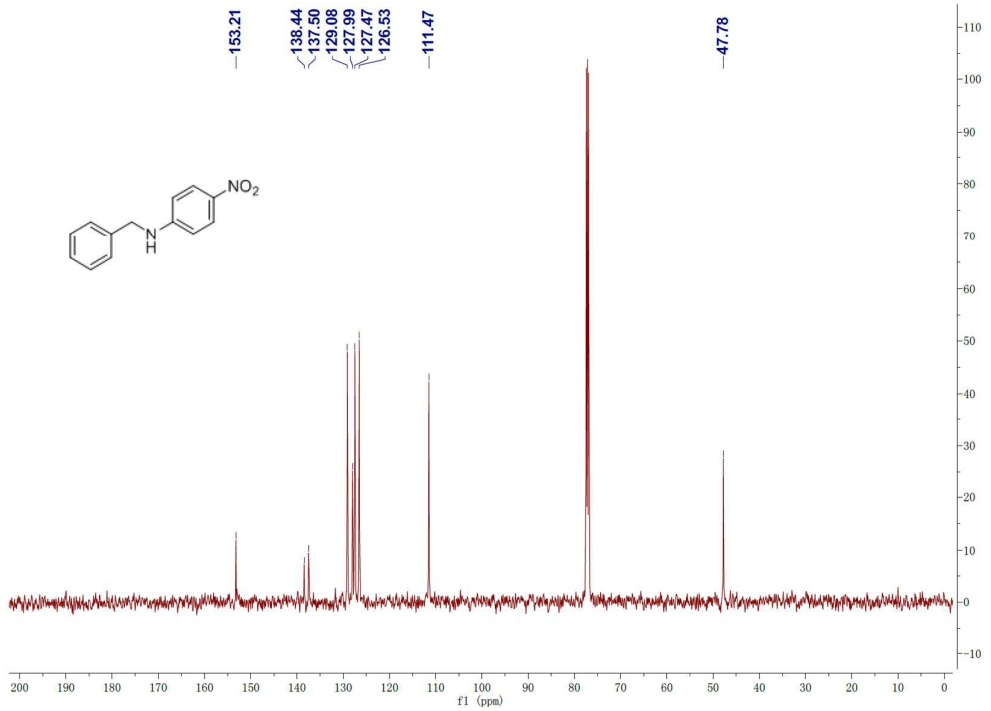
^{1}H NMR of 4e



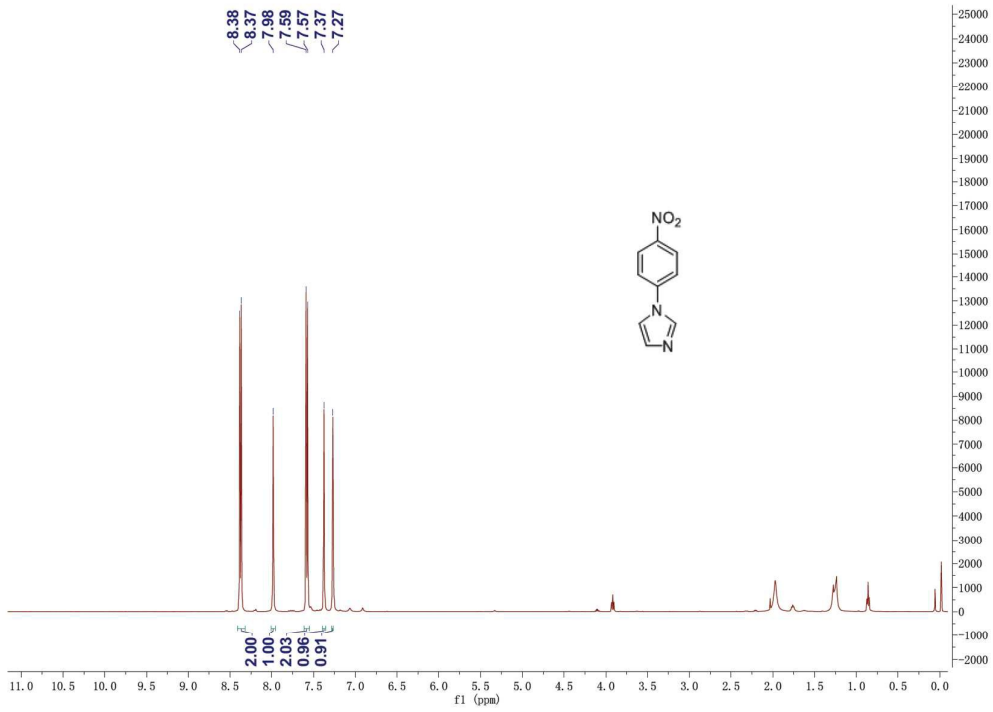
^{13}C NMR of 4e



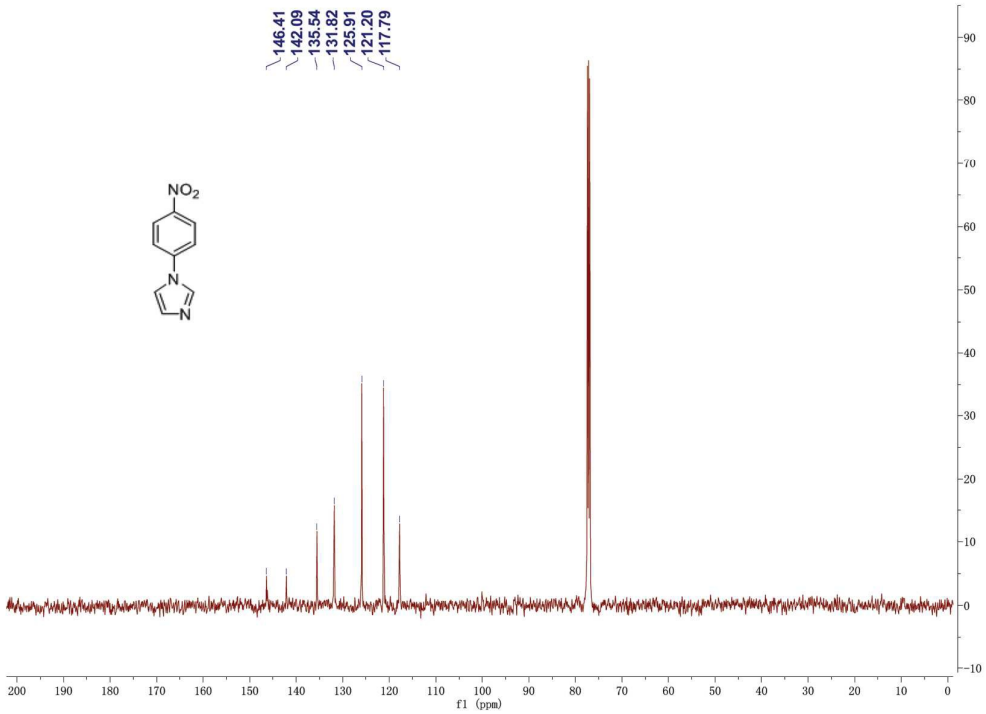
^{1}H NMR of 4f



^{13}C NMR of 4f



^{1}H NMR of 4g



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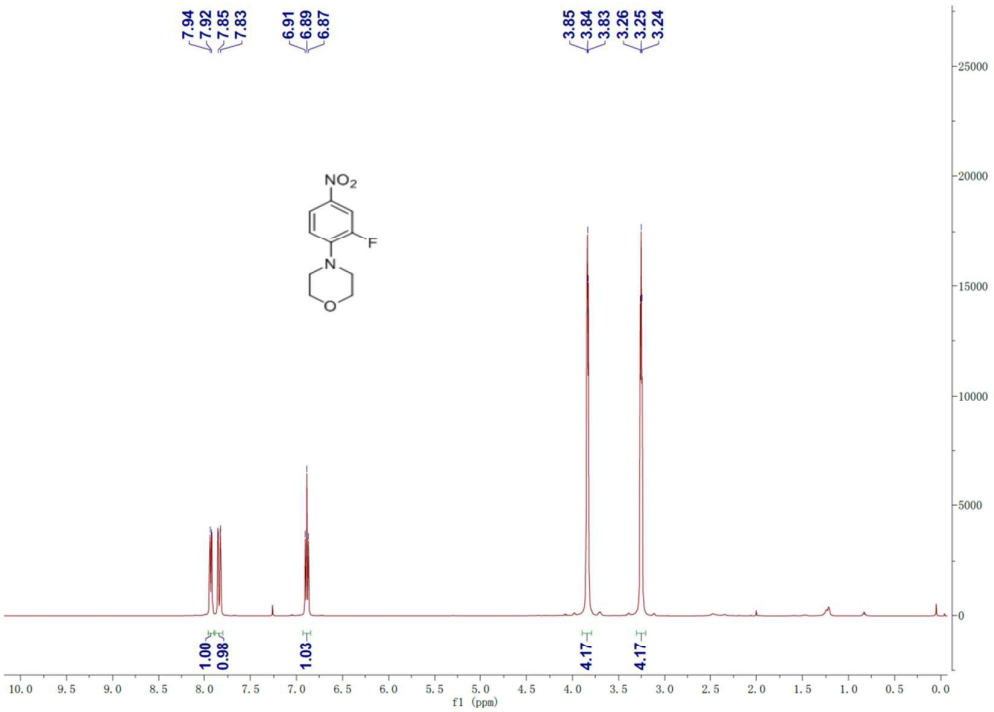
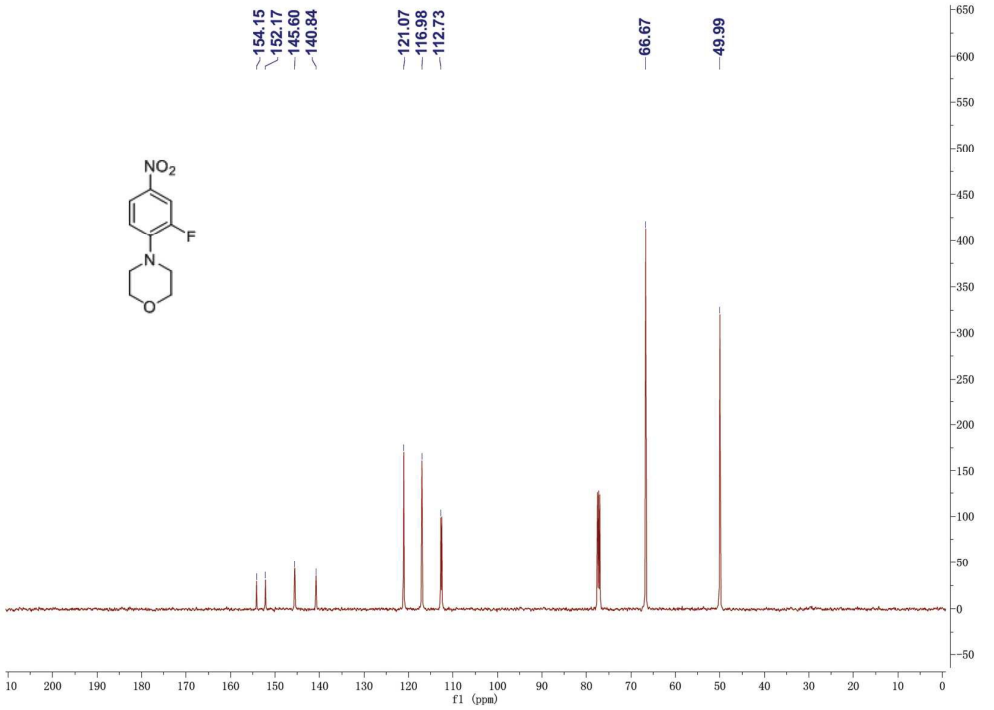
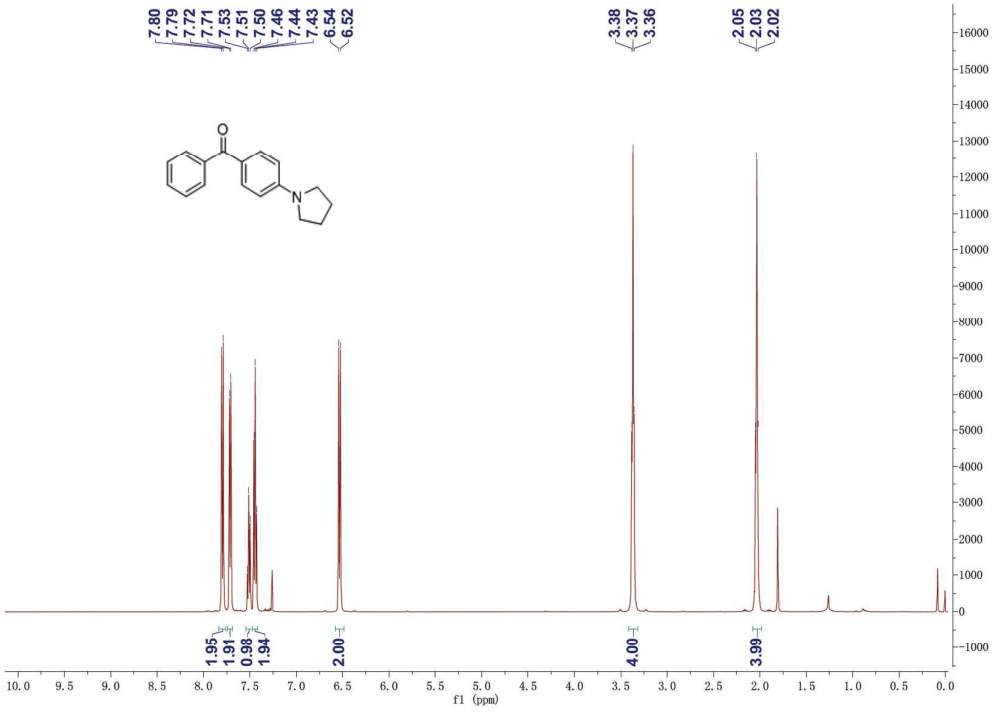


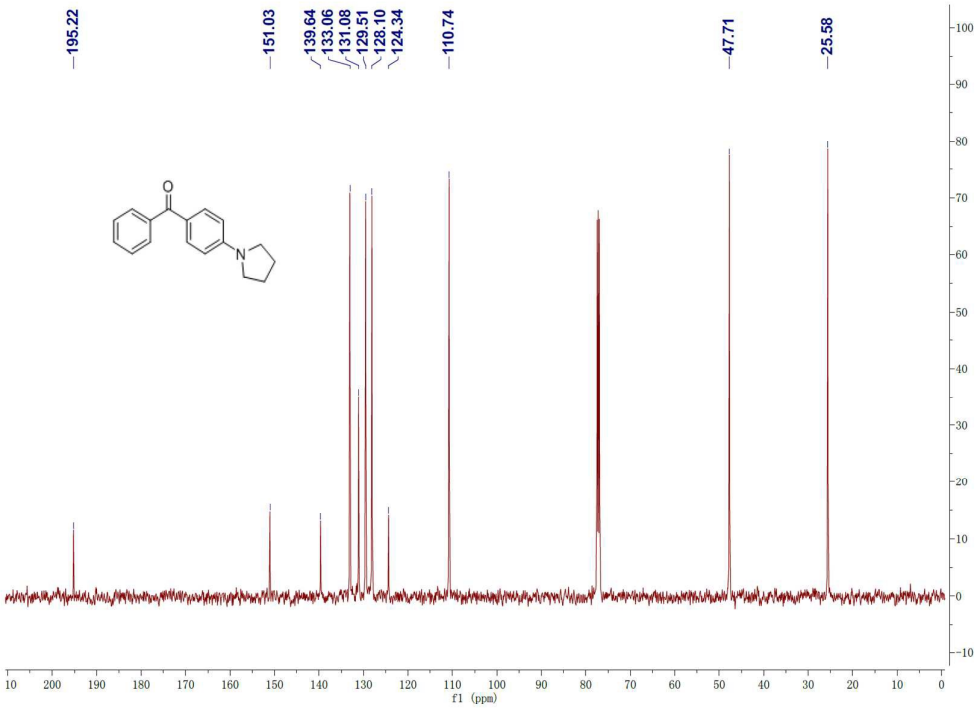
^{1}H NMR of 4h



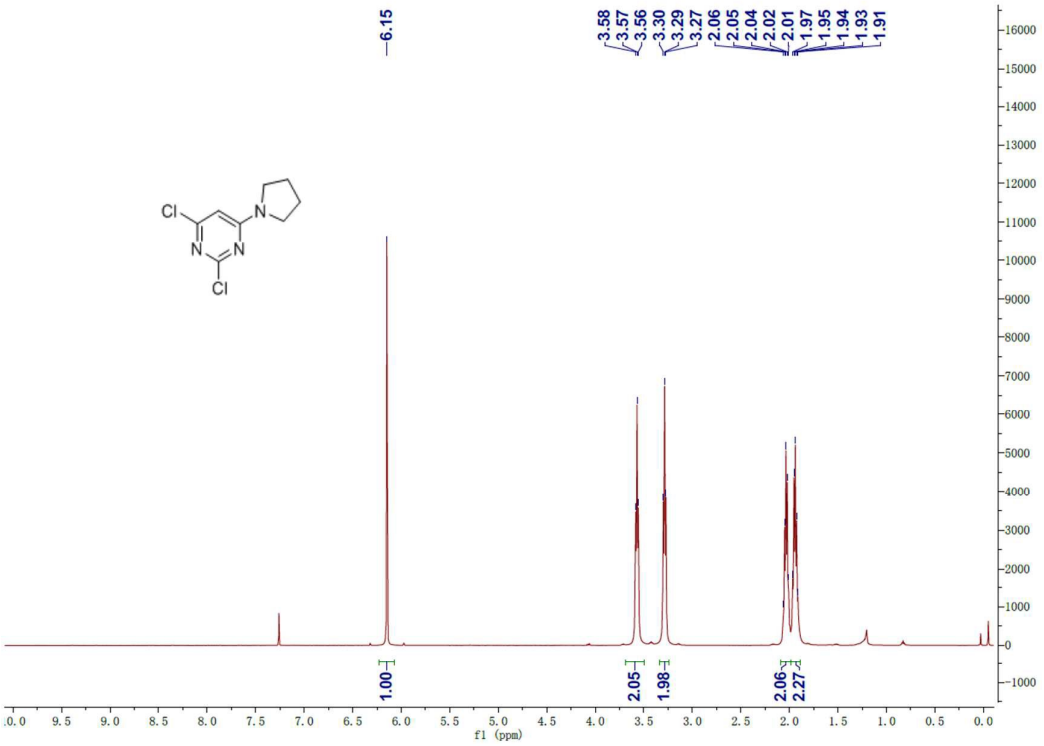
^{13}C NMR of 4h



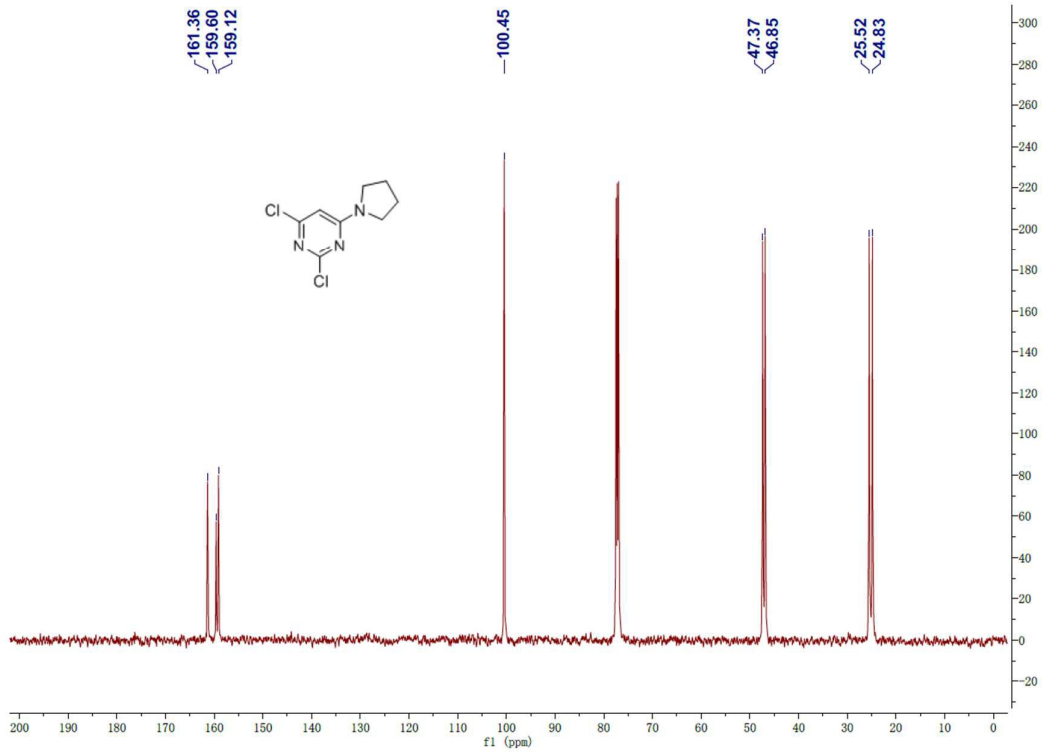
^{1}H NMR of 4i



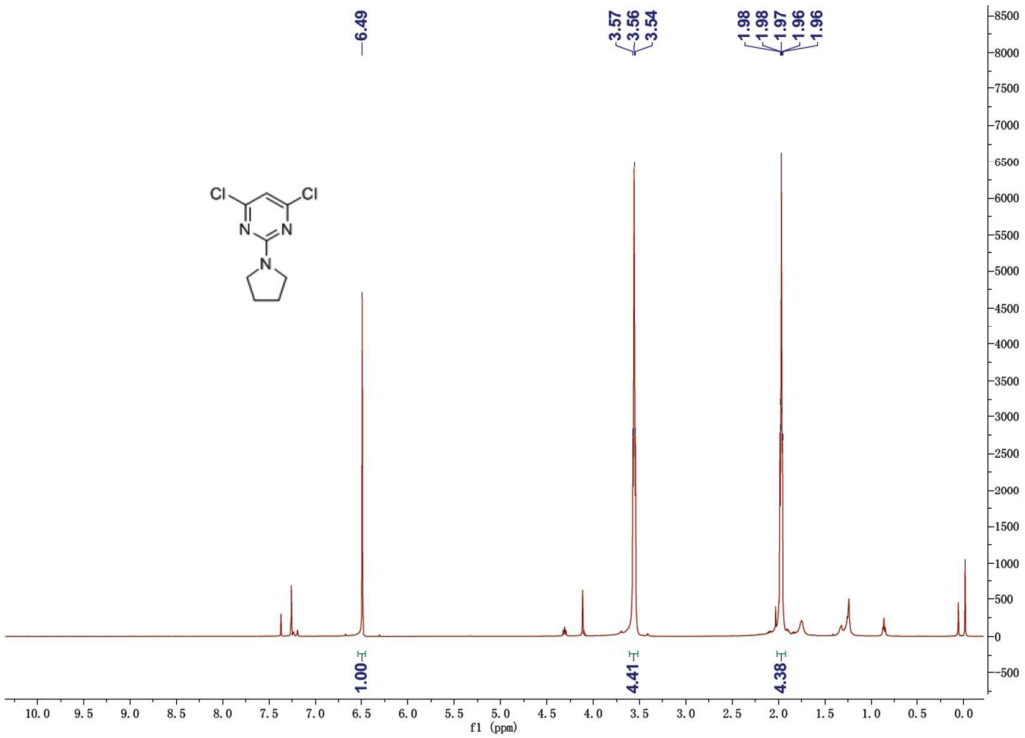
^{13}C NMR of 4i



^{1}H NMR of 4j



^{13}C NMR of 4j



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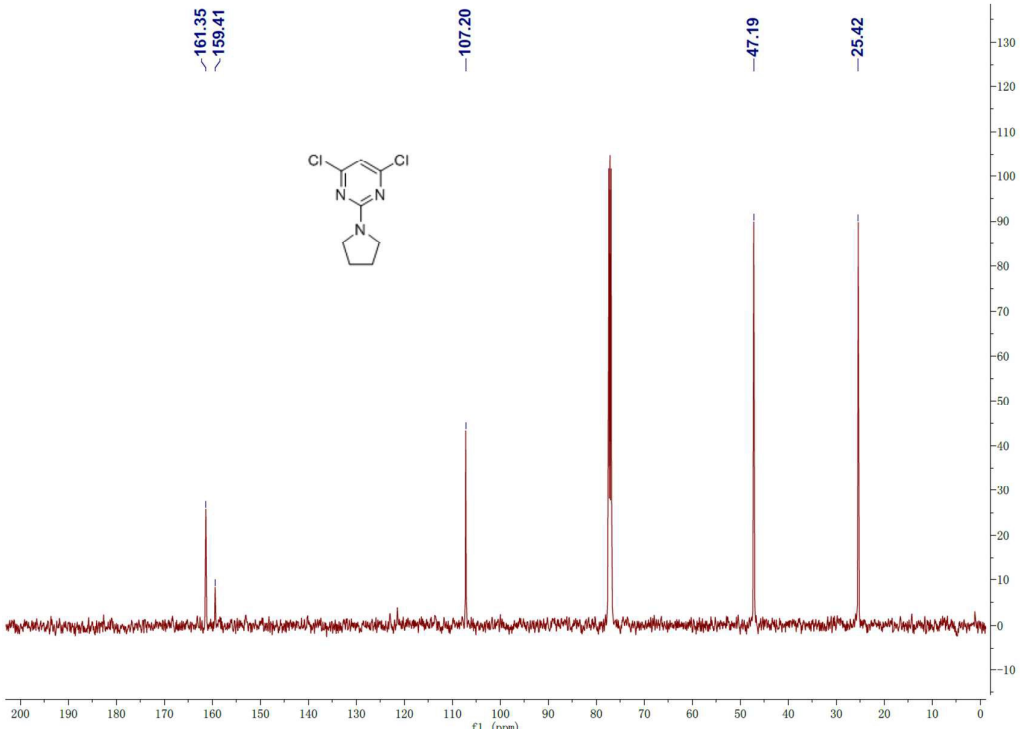

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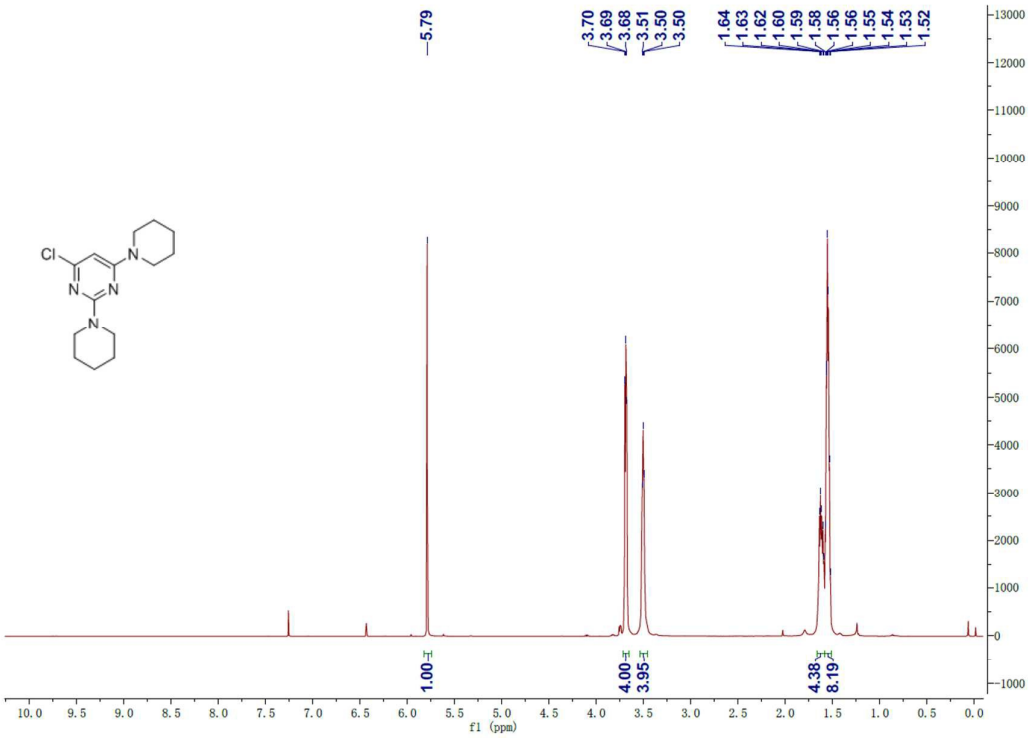
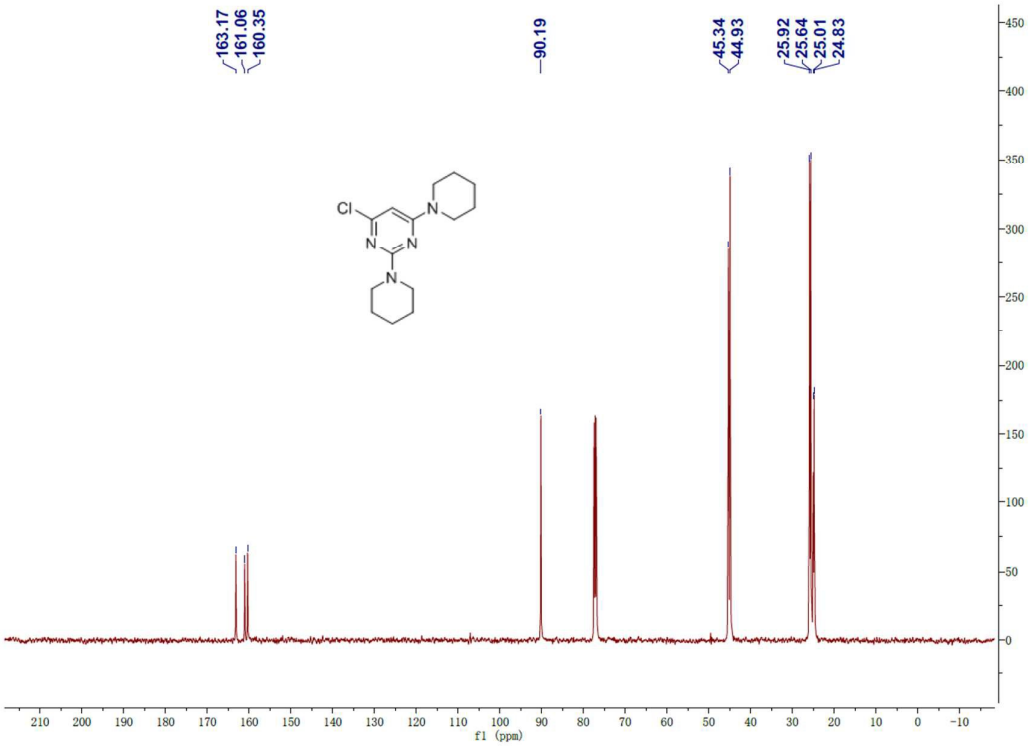
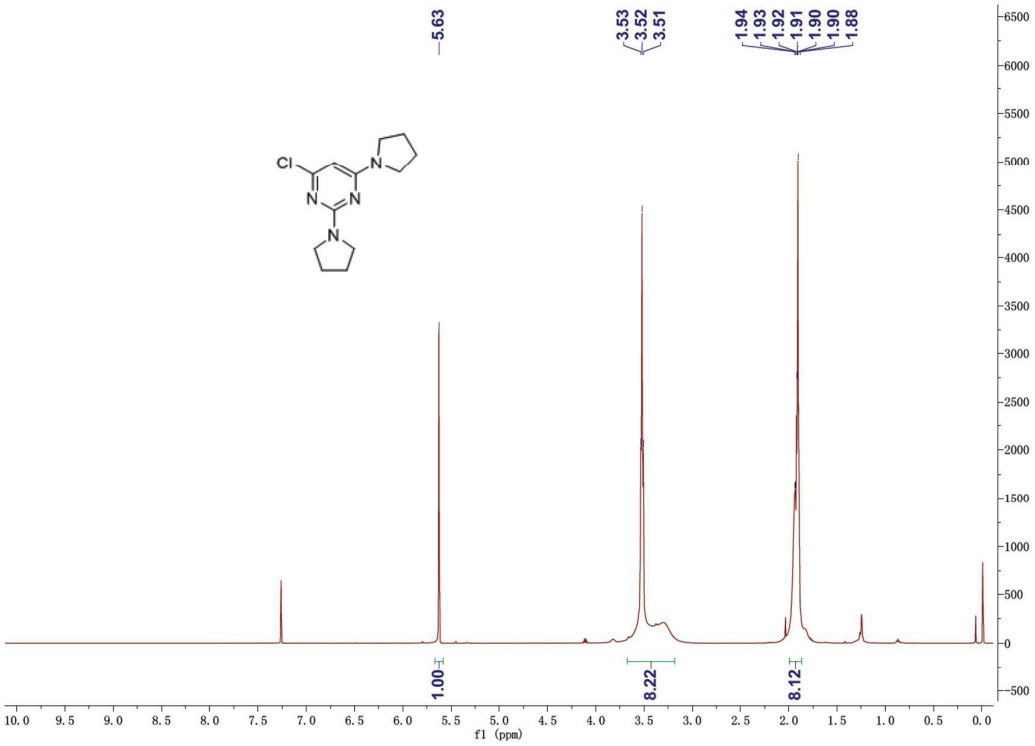


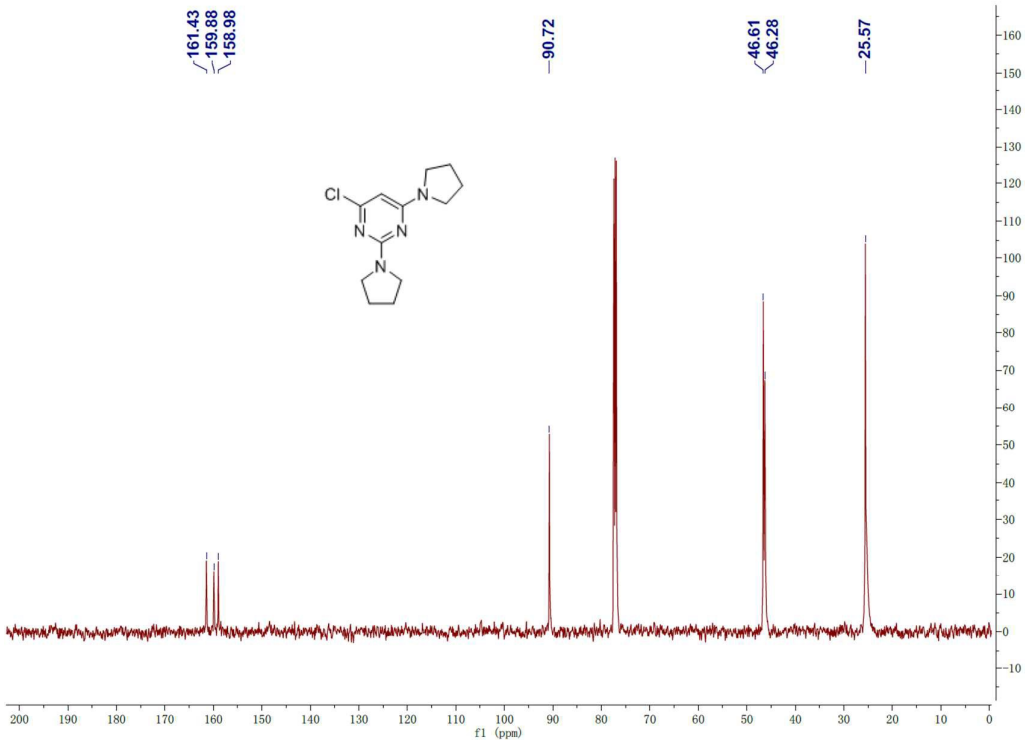
^{1}H NMR of 4k



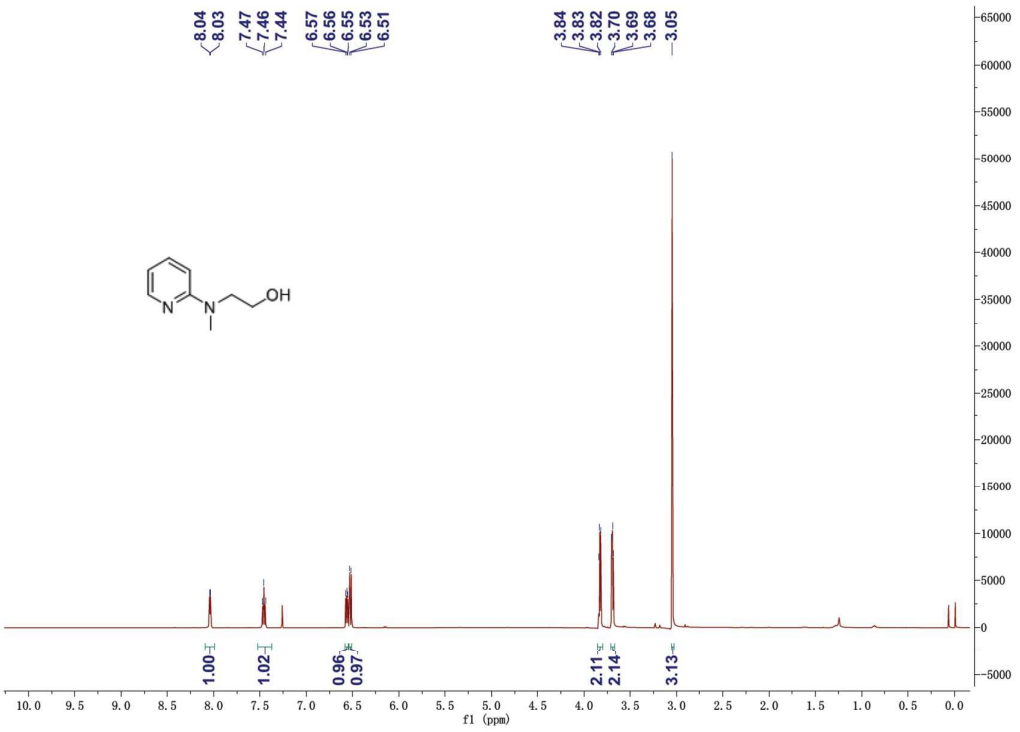
^{13}C NMR of 4k



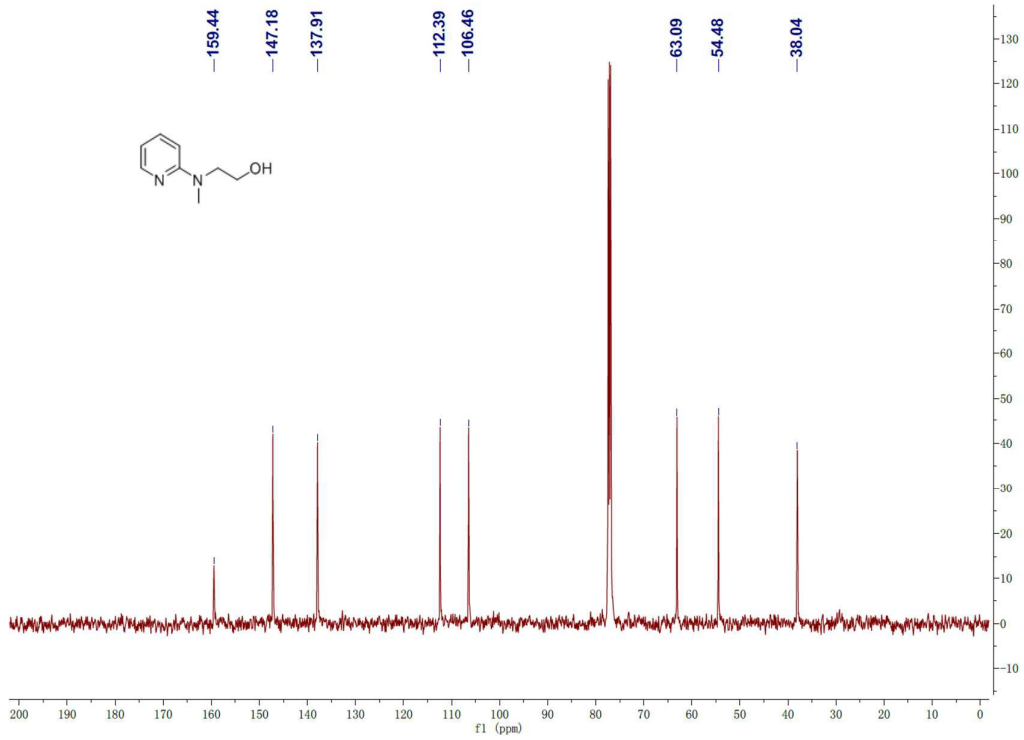
^{1}H NMR of 4l



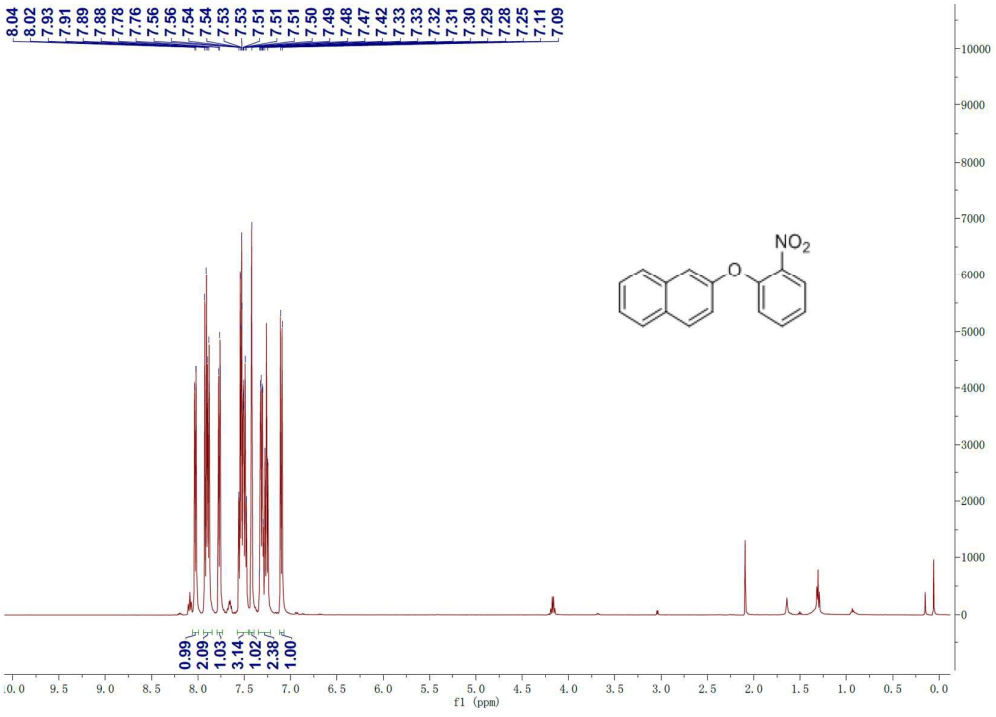
^{13}C NMR of 4l



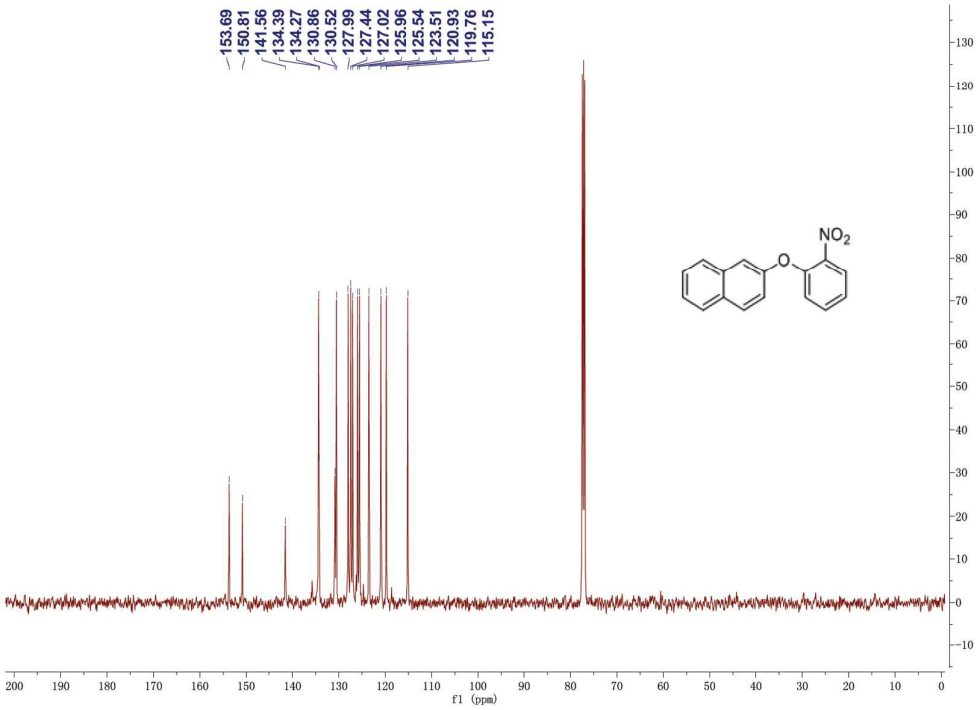
^{1}H NMR of 4m



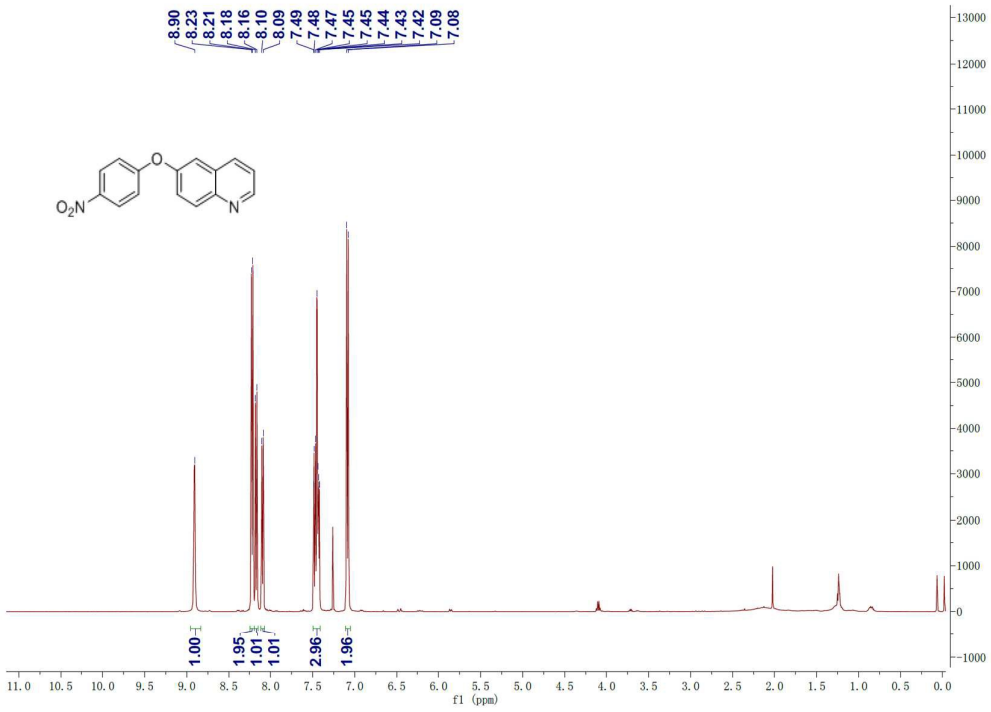
^{13}C NMR of 4m



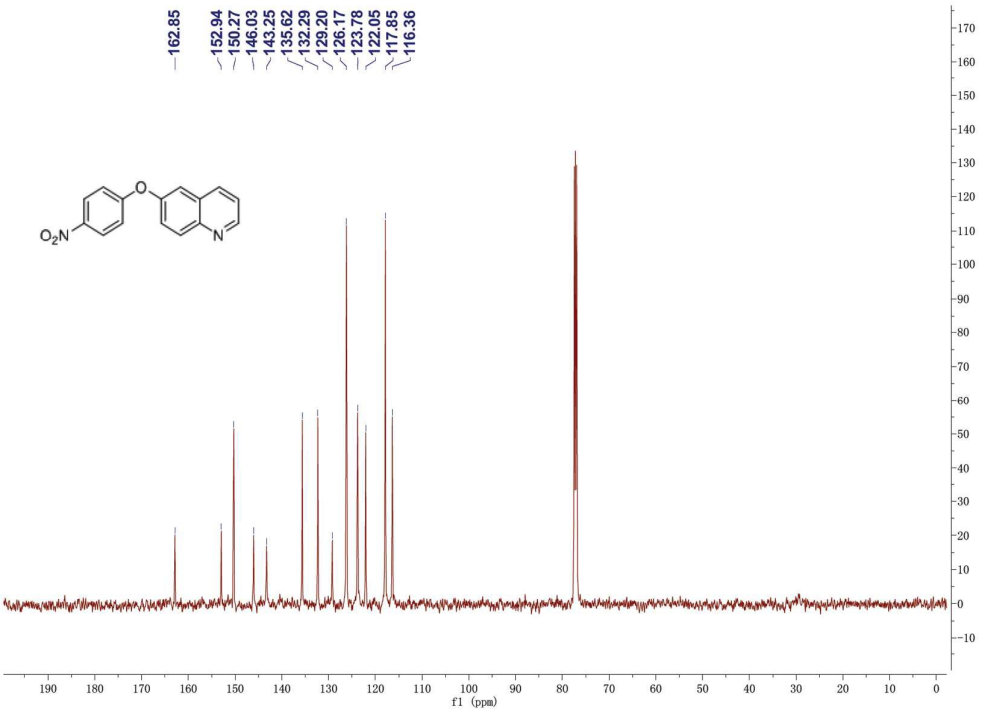
^{1}H NMR of 5a



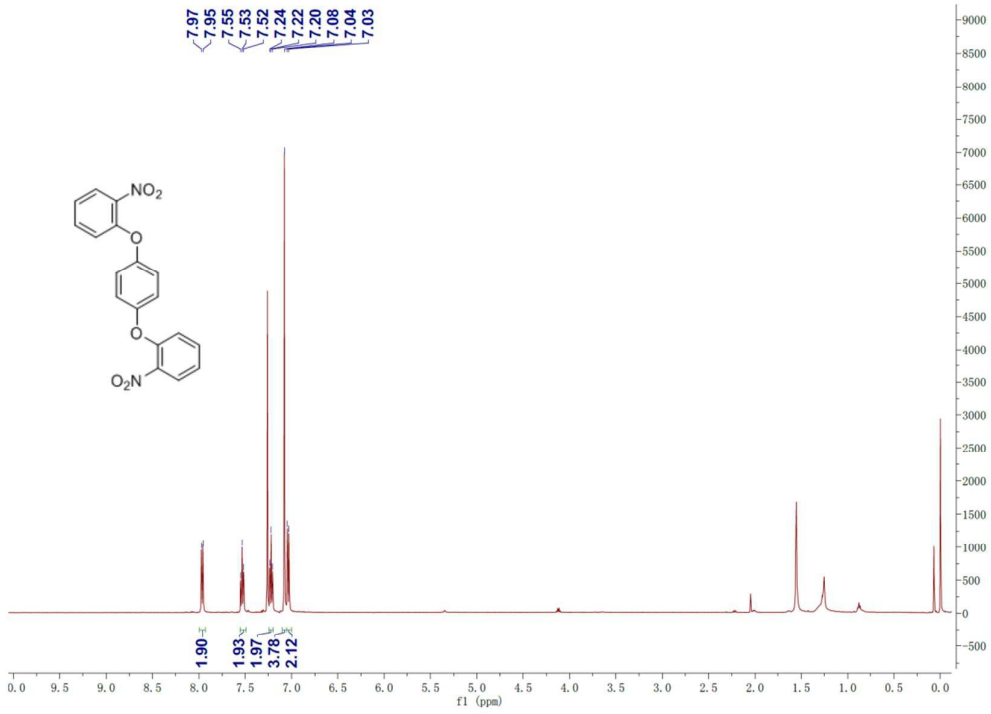
^{13}C NMR of 5a



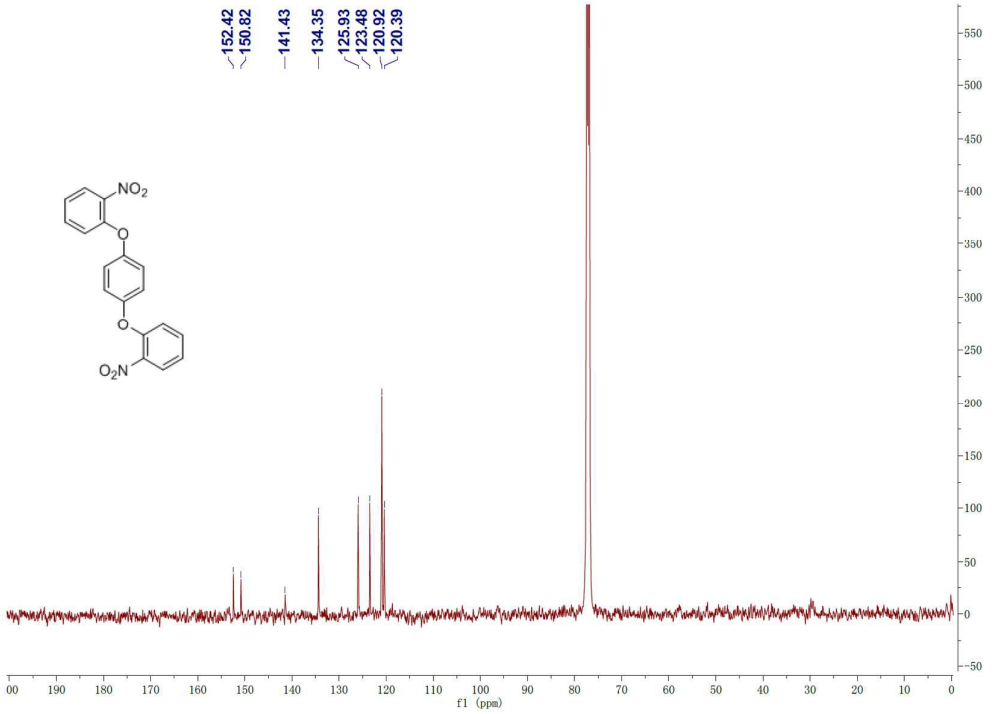
^{1}H NMR of 5b



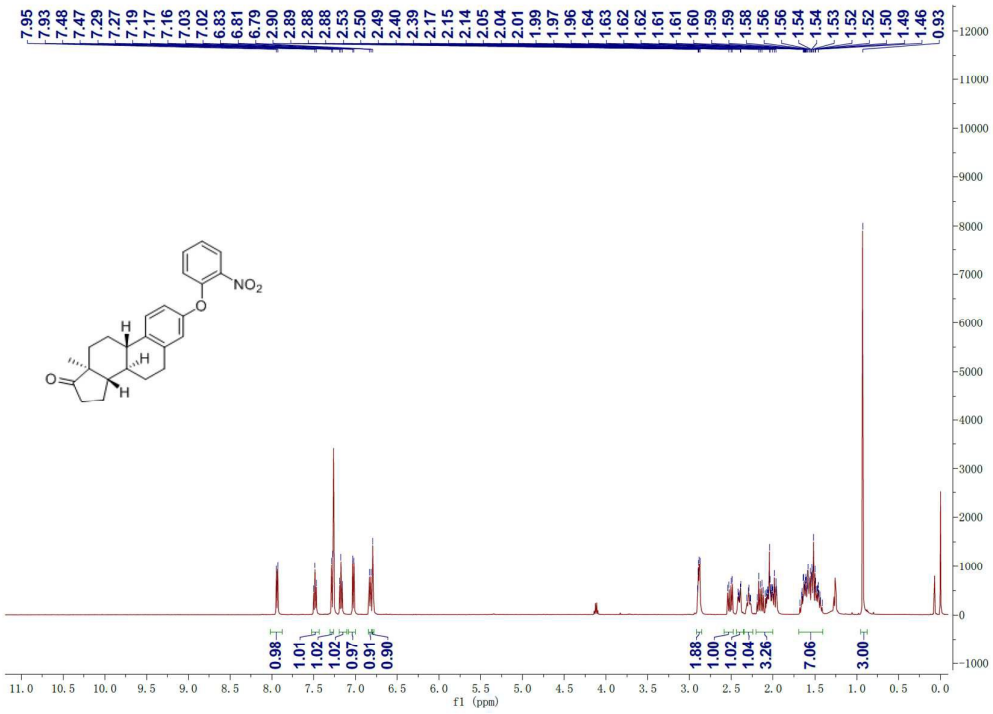
^{13}C NMR of 5b



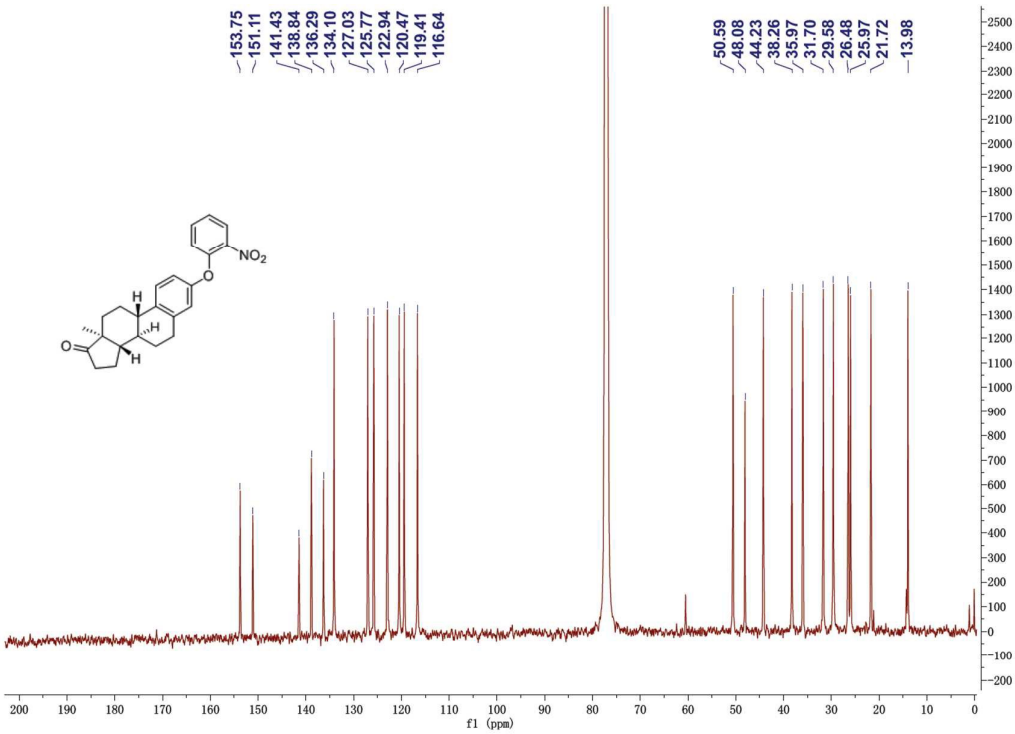
^{1}H NMR of 5c



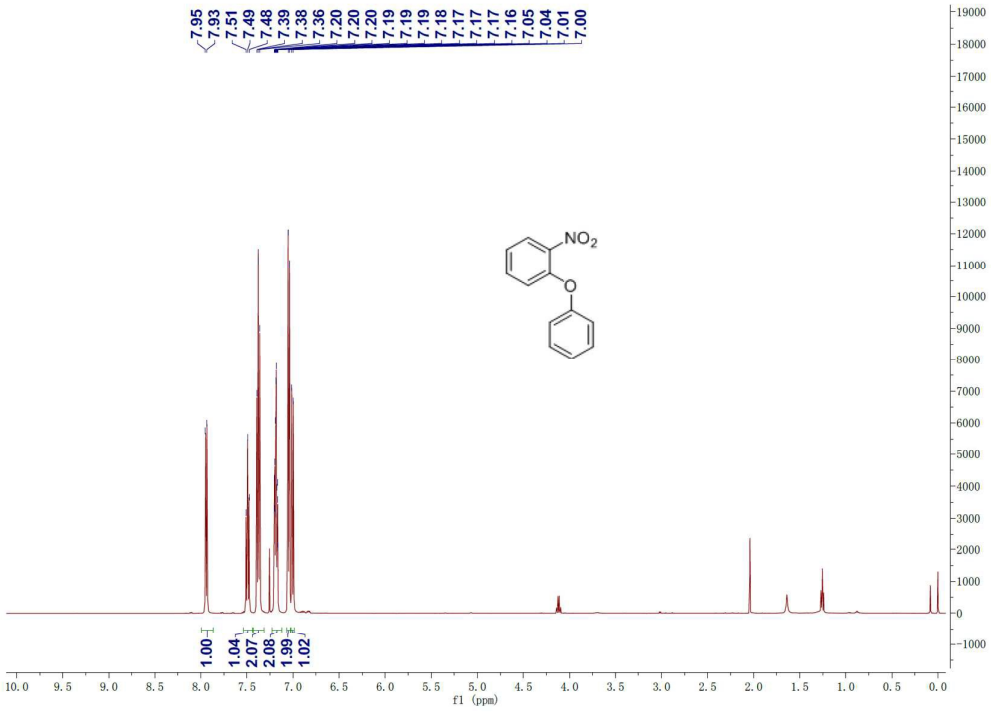
^{13}C NMR of 5c



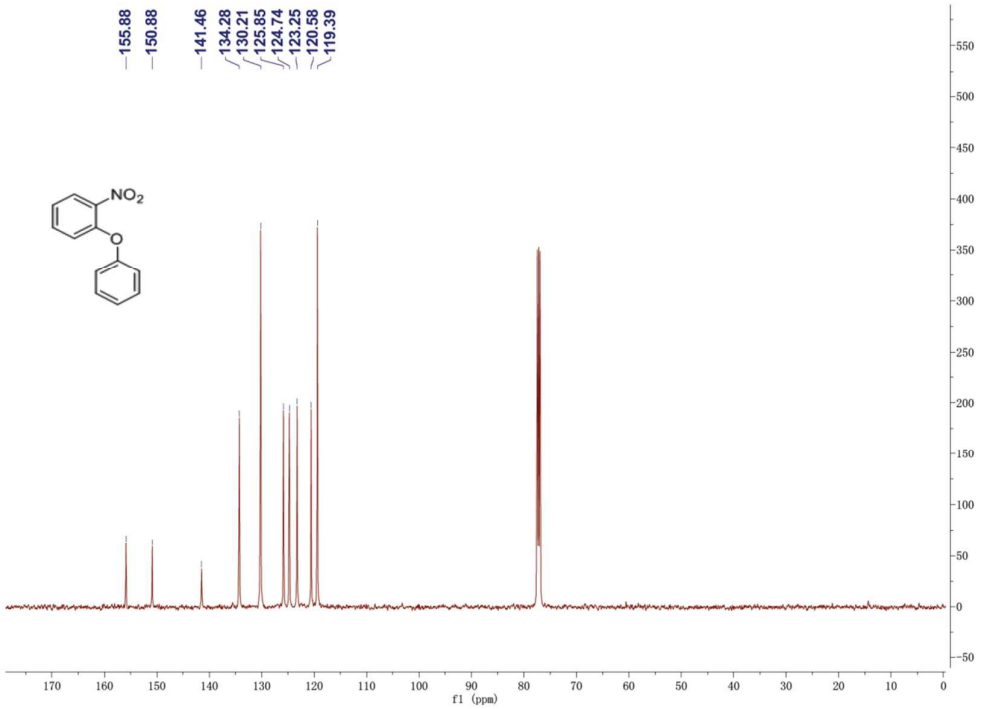
^{1}H NMR of 5d



^{13}C NMR of 5d



^{1}H NMR of 5e



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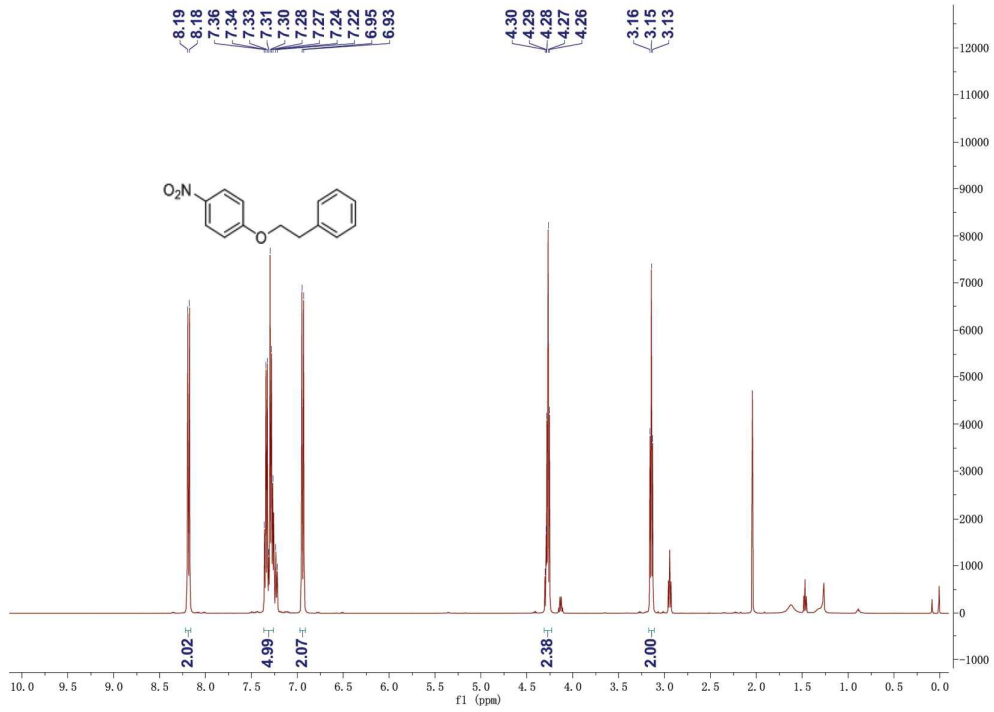
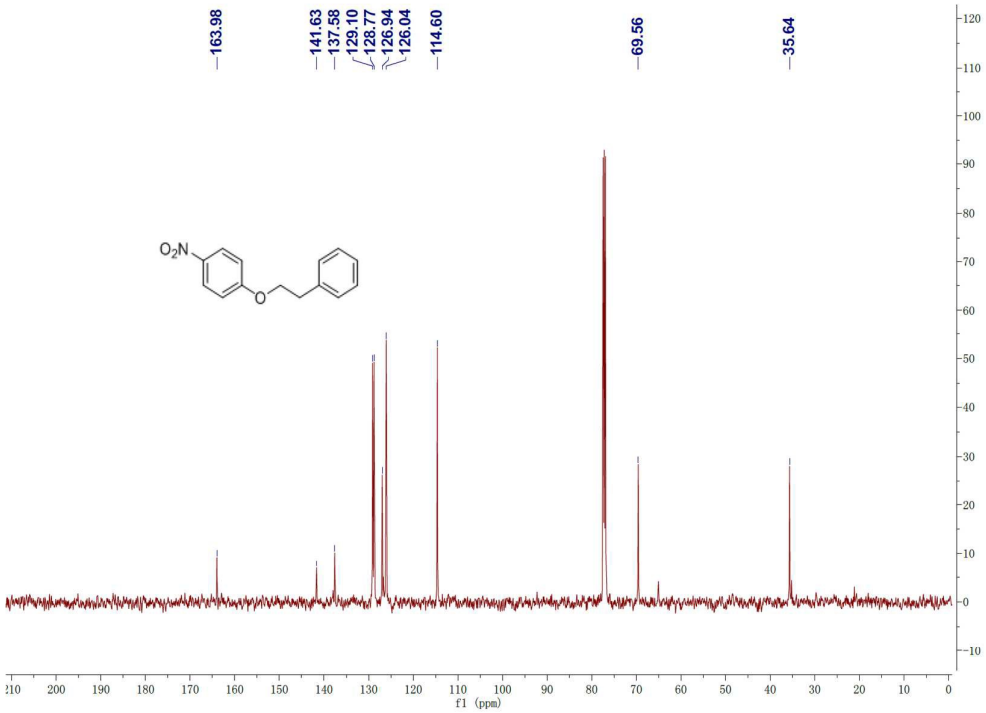
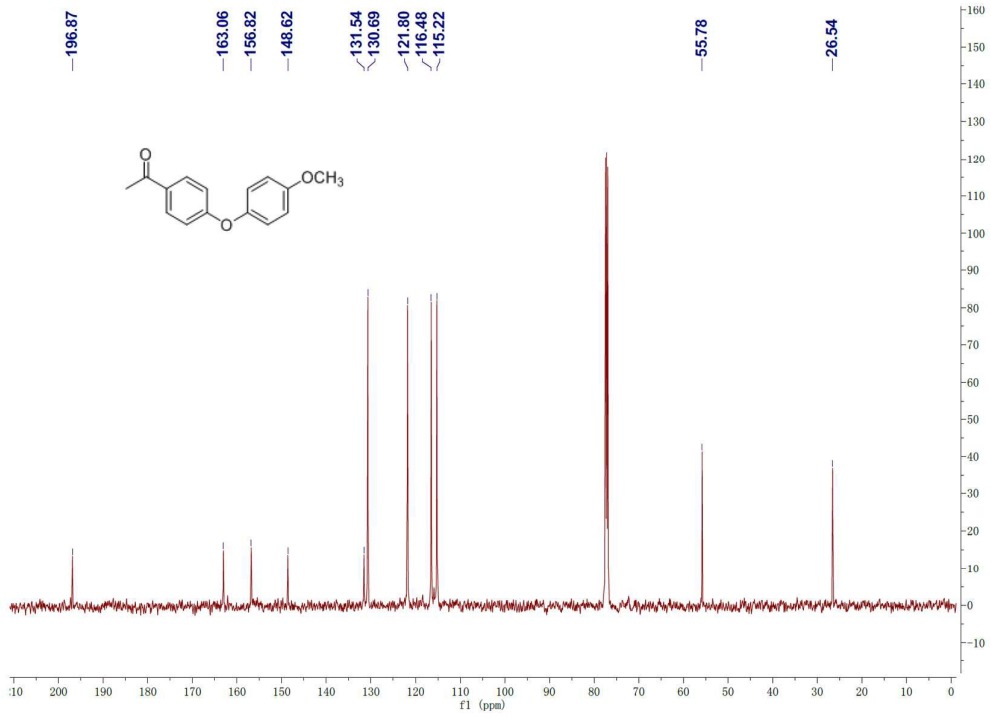


^{1}H NMR of 5f

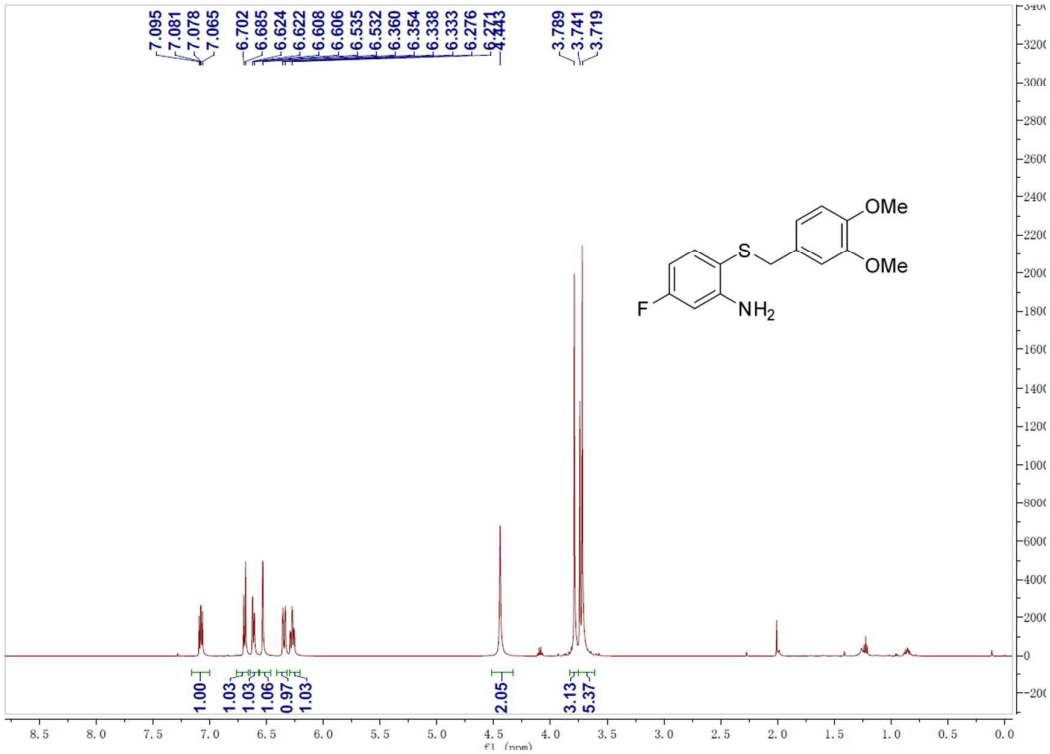


^{13}C NMR of 5f

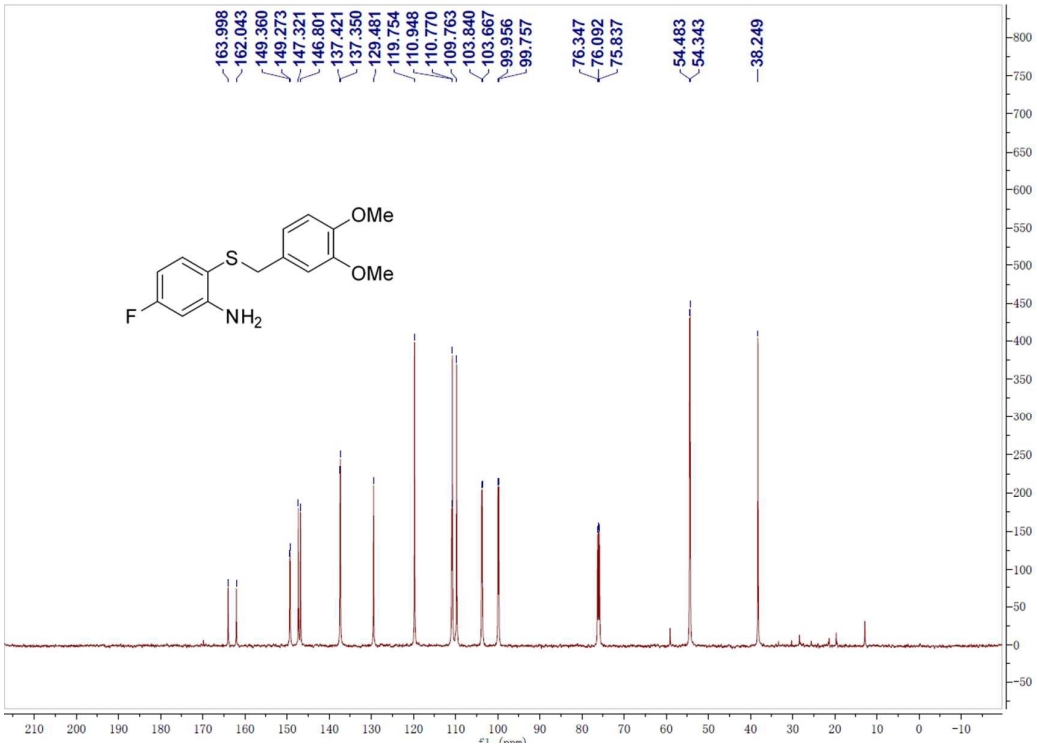
^{1}H NMR of 5g



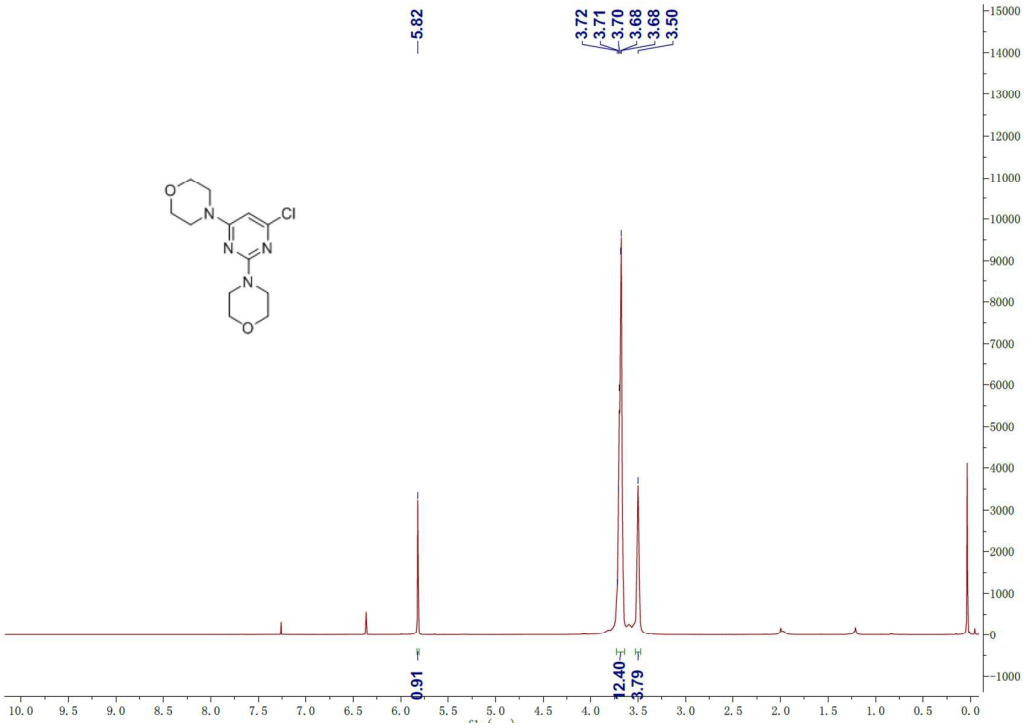
^{13}C NMR of 5g



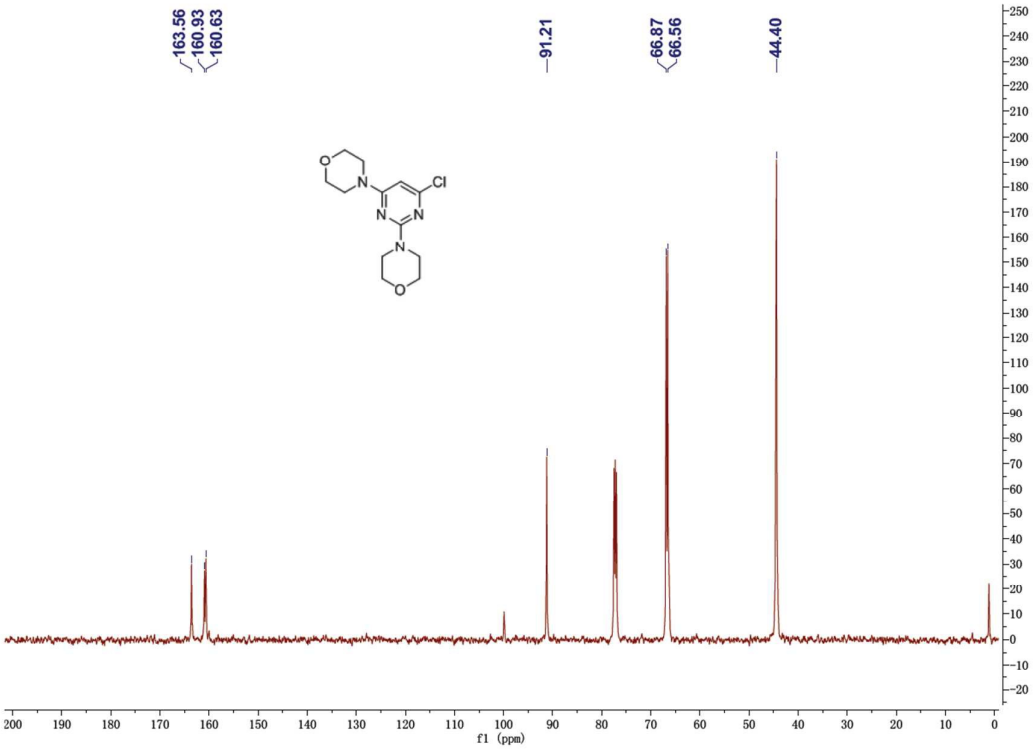
^{1}H NMR of 6



^{13}C NMR of 6



^{1}H NMR of 7



^{13}C NMR of 7