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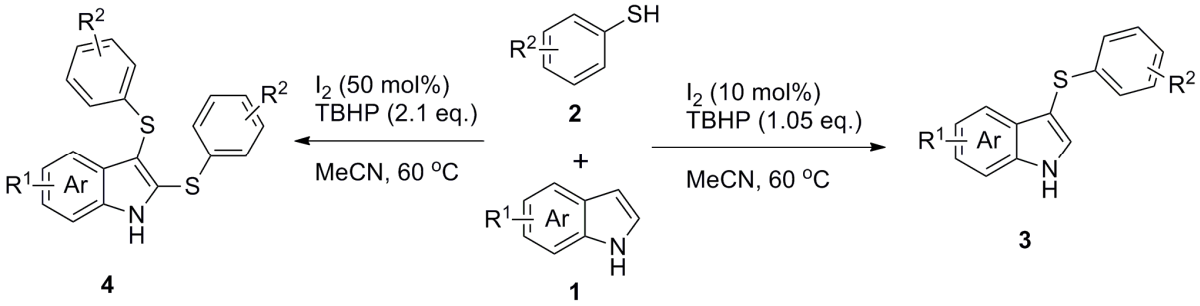

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ABSTRACT

A versatile method for the synthesis of mono- and bis-arylthioindoles *via* I_2 catalysed direct oxidative sulfenylation of indoles with thiophenols (especially mercaptobenzoic acids) has been presented. This system features environmental friendliness, easy operation, and mild reaction conditions, and shows a broad functional group tolerance furnishing good to excellent yields.

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1. Introduction

The significance of sulfur-bearing indoles is well reflected in the myriad constructive and functional building blocks in medicinal chemistry, materials science and natural products.[1] Among a wide range of sulfur-modified indole derivatives known, the wide spectrum of therapeutic value of numerous sulfenylated indoles which constitutes a constant source of fascination, has been recently revealed to have dramatic effects on bacterial infection, HIV, cardiovascular diseases, cancer, affective and respiratory disorders, to name but a few,[2] since the discovery of 3-sulfenylindoles that can serve as an orally active inhibitor of 5-lipoxygenase in 1993.[3]

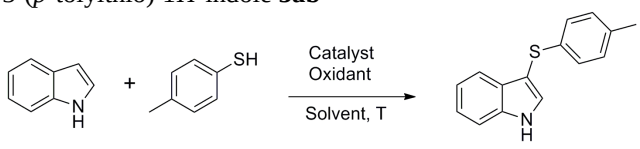
On account of the intriguing synthetic value and varying pronounced bioactivities of these compounds, the synthetic repertoire has currently enjoyed a resurgence of interest after the initial studies in 1980s,[4] and resulted in the development of two major synthetic strategies. The first route is achieved by cyclization reactions of 2-alkynylanilines,[5] *o*-ethenylaryl isocyanides,[6] 2-(*gem*-dibromo(chloro)vinyl) anilines[7] or phenylhydrazine hydrochloride,[8] whereas the other method involves the direct sulfenylation of a pre-existing indole ring owing to its nucleophilic nature,[9-16] using arylsulfenyl halides,[4a,17b,c] diaryl disulfides,[9] aryl-*N*-thioimides,[10] aryl thiols,[11] arylsulfonyl chlorides,[12] sulfonyl hydrazides,[13] quinone mono-*O*,*S*-acetals,[14] arylsulfonium salts[15] and sulfinic acids[16] as sources of the sulfenylating agents. Nevertheless, many of these sulfur-transfer reagents are either difficult to prepare or air and moisture sensitive. Moreover, the existing methodologies frequently require harsh reaction conditions, excess additives and transition metal catalysts, suffer from a narrow substrate scope, or yield by-products unfriendly to the environment.

Although many methods have been successfully demonstrated to construct structurally diverse mono-sulfenyl indoles, synthesis of arylthioindoles having acidic proton functional groups (peculiarly CO_2H) has not been well documented to date.[9g,11e] Moreover, methodologies that can accomplish double C–H sulfenylation in indoles at 2- and 3-positions have remained elusive. In the context of step- and atom-economy points of view in industrial and green chemistry, especially the low threshold residual tolerance of harmful ingredients for pharmaceuticals, there is a highly urgent demand for organic chemists to explore alternative sustainable processes for mono- and bis-arylthioindoles from simple and readily exploitable precursors under mild reaction conditions. To the best of our knowledge, there is no report on I_2/TBHP catalyzed mono- and bis-sulfenylation of indoles with thiophenols. Herein, we detail an efficient and generally applicable methodology for the synthesis of diversely substituted mono- and bis-arylthioindoles. Unlike the previously reported sulfenylation of indoles with thiophenols, the protocol here has an extremely broad substrate scope, simple reaction conditions, and excellent yields. Notably, in this transformation, no metal salts, ligands or additives were added and without exclusion of air and moisture.

2. Results and Discussion

To acquire the optimized reaction conditions, the preliminary investigation was initiated from the model reaction of indole **1a** and *p*-toluenethiol **2b** in the presence of various iodo-containing catalysts and 1.05 equiv of *tert*-butyl hydroperoxide (TBHP). Pleasingly, I_2 (10 mol%) exhibited the best performance to produce the expected product **3ab**, 3-(*p*-tolylthio)-*1H*-indole, in 72% yield at 40 °C under air (Table 1, entry 2). Increasing the temperature to 60 °C caused an increase to 92% yield (Table 1, entry 5). The influence of the stoichiometric oxidant on the reaction system was subsequently assessed; nonetheless, better yield could not be obtained (Table 1, entries 6-8). Replacement of MeCN with other common solvents such as DMSO, MeOH and H_2O all decreased the reaction yield to varying degrees (Table 1, entries 9-11). By screening the catalyst loading, it was indicated that reducing the loading to 5 mol% gave rise to a much lower yield (Table 1, entry 12) and no product was formed without the presence of iodine catalyst (Table 1, entry 13).

Table 1. Optimization of reaction conditions for the synthesis of 3-(*p*-tolylthio)-*1H*-indole **3ab**[a,b]



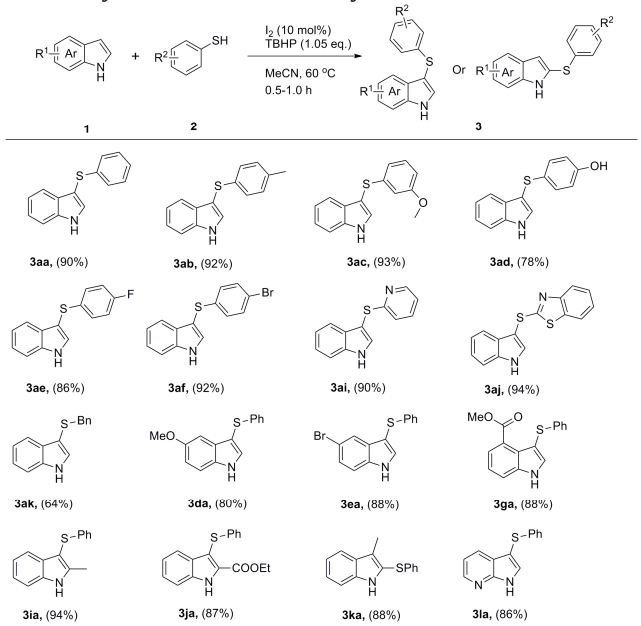
1a 2b 3ab

Entry	Catalyst	Oxidant	Solvent	T (°C)	Yield (%)[b]
1	NIS	TBHP	MeCN	40	70
2	I_2	TBHP	MeCN	40	73
3	KI	TBHP	MeCN	40	13
4	TBAI	TBHP	MeCN	40	Trace
5	I_2	TBHP	MeCN	60	92
6	I_2	H_2O_2	MeCN	60	78
7	I_2	$(NH_4)_2S_2O_8$	MeCN	60	83
8	I_2	DTBP	MeCN	60	Trace
9	I_2	TBHP	DMSO	60	81
10	I_2	TBHP	MeOH	60	63
11	I_2	TBHP	H_2O	60	74
12[c]	I_2	TBHP	MeCN	60	71
13	-	TBHP	MeCN	80	-

[a] Reaction conditions: indole **1a** (0.50 mmol), *p*-toluenethiol **2b** (0.505 mmol), catalyst (10 mol%), oxidant (0.525 mmol), solvent (2.0 mL), open to air. [b] Isolated yield. [c] 5 mol% iodine was used.

With the optimal reaction conditions in hand, a systematic investigation was conducted to evaluate the generality of the

Scheme 1 Synthesis of monosulfenyl indoles[a,b]



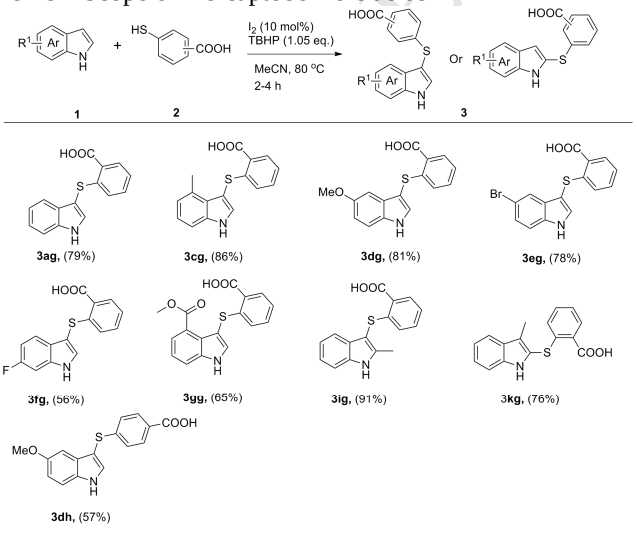
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.51 mmol), I_2 (0.05 mmol), TBHP (0.525 mmol), MeCN (2 mL) under air. [b] Isolated yield.

facile transformation. As outlined in Scheme 1, a vast variety of aryl- and heteroarylthiols smoothly underwent sulfenylation with indoles to generate structurally diverse thioethers in high yields with extremely high regioselectivity (Scheme 1, **3a-j**). In addition, sulfenylation reaction using benzyl mercaptan successfully took place under present catalytic conditions (Scheme 1, **3ak**). Indoles bearing functional groups such as alkoxyl, halide and ester all displayed satisfactory tolerance to the protocol and provided corresponding products with good to excellent yields (Scheme 1, **3da-3ga**). Furthermore, we were delighted to disclose that high yields were also obtained from 7-aza, 2- and 3-substituted indoles (Scheme 1, **3ia-3la**).

In the existing literature, very few synthetic pathways enabling the preparation of the sulfenylindoles using mercaptobenzoic acids as sulfur-transfer reagents were found because of the strong electron-withdrawing feature of carboxy group.[9g,11e] Within this scenario, the optimized reaction conditions prompted us to validate a further useful application by reacting two sorts of mercaptobenzoic acids with various indoles to furnish the corresponding arylthioindoles. By comparing with previously reported results,[9g,11e] it could be easily discerned that the new method not only considerably reduced the reaction time and temperature, but above all markedly increased the yield of the products. In particular, under our experimental conditions, methyl indole-4-carboxylate and 3-methylindole smoothly went through sulfenylation to afford the relevant derivatives in good yields (Scheme 2, **3gg**, **3kg**). Among the mercaptobenzoic acids tested, 4-mercaptobenzoic acid **2h** which exhibited worse reactivity compared with **3dg** could be explained mainly by taking into account the formation of different active species of mercaptobenzoic acids proposed by Li.[11e]

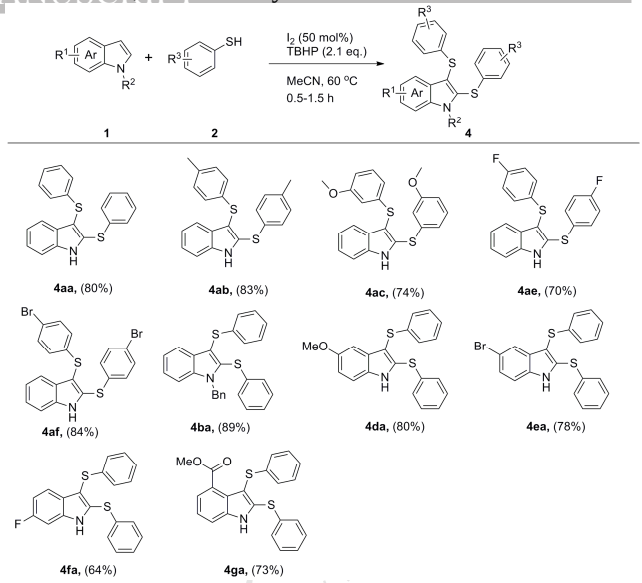
Previously, the synthesis of 2,3-bis-sulfenyl indoles had been attained by Hamel *et al* utilizing aryl sulfenyl chlorides and diaryl disulfides as the sulfur source.[17] To the best of our knowledge, there is no report in the literature on the synthesis of 2,3-bis-sulfenyl indoles under mild reaction conditions and using readily available thiols as yet. Additionally, the sulfenylation reaction generally took place at the C-3 position of the indole ring owing to its electron-rich nature. However, the C-2 position of the indole ring may also be the reaction site of choice when the C-3 position was occupied by the sulfenylation. To testify our hypothesis, indole **1a** (1.0 equiv) and *p*-toluenethiol **2b** (2.1 equiv) were selected as the starting materials in the presence of different

Scheme 2 Scope of mercaptobenzoic acids[a,b]



[a] Reaction conditions: **1** (5.5 mmol), **2** (5.0 mmol), I_2 (0.5 mmol), TBHP (5.25 mmol), MeCN (20 mL) under air. [b] Isolated yield.

Scheme 3 2,3-Bis-sulfenylation of indoles [a,b]

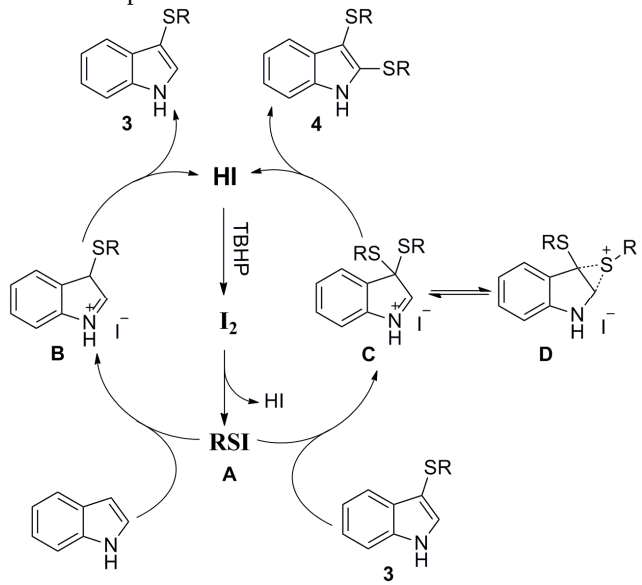


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.05 mmol), I_2 (0.25 mmol), TBHP (1.05 mmol), MeCN (2 mL) under air. [b] Isolated yield.

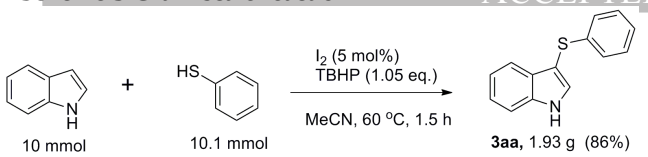
kinds and loadings of oxidants and iodine-containing catalysts. Ultimately, 0.5 equiv of I_2 and 2.1 equiv of TBHP were found to be optimum for the maximum yield (83%) of 2,3-bis-sulfenylindole **4ab** (Scheme 3). As illustrated by Scheme 3, it is noteworthy that both electron-withdrawing and electron-donating groups were introduced into the 2,3-sulfenylation products by employing various indoles and thiols bearing such groups on the aromatic ring to give the respective 2,3-bis-sulfenyl indoles in moderate to high yields.

Based on the above experimental results and formerly published similar examples,[9d,17c] a plausible reaction mechanism for mono- and bis-sulfenylation of indoles is depicted in Scheme 4. Firstly, RSH reacts with I_2 to form an electrophilic species RSI **A**, which can provide the electrophile RS^+ and react with indole moiety to produce intermediate **B**. Deprotonation of **B** gives the desired monosulfenyl indole and HI. Then the second sulfenylation of indole occurs predominantly, if not completely, by initial addition at the 3-position of the indole ring, leading to a 3,3-disubstituted indolenine intermediate **C**, followed by

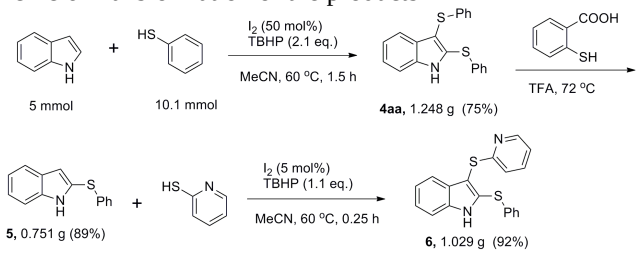
Scheme 4 Proposed mechanism



Scheme 5 Gram-scale reaction



Scheme 6 Transformation of the products



migration of one of the sulfide groups to the 2-position, as has been suggested by Préville.[17c] In the end, I_2 is regenerated by the oxidation of TBHP with the formation of water and *tert*-butanol.

To demonstrate the practical applicability of the mono- and bis-sulfenylating process on a much larger scale, a gram-scale synthesis of **3aa** and **4aa** was subjected to the protocol. To our delight, with a lower catalyst loading (5 mol% instead of 10 mol% in Scheme 1), the reaction still proceeded smoothly, albeit expectedly slower, and the mono-sulfenylating product **3aa** was isolated in 86% yield, which is only marginally lower than that of the 0.5 mmol scale reaction (Scheme 5). Besides, the gram-scale synthesis of **4aa** was conducted with maintained efficiency and 2-indolyl sulfide **5** was acquired *via* the selective desulfenylation of **4aa**, using trifluoroacetic acid in the presence of 2-mercaptobenzoic acid as trapping agent (Scheme 6).[17b] Finally, the single mixed indole 2,3-bis(sulfides) **6**, which was a knotty problem by one-pot reaction, was synthesized in high yield under our developed experimental conditions (Scheme 6).

3. Conclusion

In summary, a simple and versatile oxidative system for the selective and controllable sulfenylation of indoles to the corresponding mono- and bis-sulfenylindoles in the presence of catalytic amounts of iodine using thiols as sulfenylation reagent in MeCN under mild conditions has been developed. In comparison with reported protocols, the present procedure not only can perform without metal and removal of moisture and air, but also has the superiority of short reaction time and high yields. Moreover, both diversely substituted indoles and thiols, peculiarly with acidic protons, like hydroxyl and carboxylic acid groups can be tolerated commendably. Last but not the least, the current study paves the way for the synthesis of 2,3-bis-sulfenyl indoles with the addition of a catalytic amount of iodine, making use of thiols as the sulfur source.

4. Experimental section

4.1. General experimental details

Unless otherwise noted, all reagents and chemicals (AR grade) were purchased from commercial suppliers and used without further purification. Petroleum ether (PE) refers to the fraction boiling in the 60-90 ℃ range. Unless otherwise noted, all reactions were carried out under air in oven-dried glassware with magnetic stirring. The progress of the reactions was monitored by TLC (silica gel, Polygram SILG/UV 254 plates). Column chromatography was performed on silica gel (100~200 mesh). All ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker Avance Ⅱ 400 MHz and Bruker Avance Ⅲ 471 MHz respectively, ^{13}C NMR spectra were recorded on a Bruker Avance Ⅱ 101 MHz or Bruker Avance Ⅲ 126 MHz. $CDCl_3$ and DMSO-d_6 were used for NMR spectroscopy, using singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, dd = doublet doublet, coupling constants in Hz, integration). Data for 13C NMR and 19F NMR are reported in terms of chemical shift (δ, ppm). HRMS (ESI) was determined by a HRMS/MS instrument (LTQ Orbitrap XL TM).

4.2. Experimental procedure for mono- and bis-sulfenylation of indoles

A mixture of indole **1** (0.5 mmol), thiol **2** (0.505 mmol) and TBHP (0.51 mmol) were dissolved in MeCN (2.0 mL) at 60 ℃ in a flask, then iodine (0.10 mmol, 10 mol%) was added. The reaction proceeded under an air atmosphere for 0.5-1.0 h until complete consumption of starting material as monitored by TLC. The reaction mixture was quenched by the addition of saturated aq $Na_2S_2O_3$ (5 mL) and then extracted with EtOAc (2 × 10 mL). The combined organic layer was separated, dried ($MgSO_4$), filtered and concentrated under vacuum and the crude product was purified by column chromatography using petroleum ether/ethyl acetate as eluent to provide the product **3**.

4.2.1. 3-(Phenylthio)-1H-indole ***(3aa)***[9c]

White solid, yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (brs, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.27-7.21 (m, 1H), 7.17-7.09 (m, 5H), 7.06-7.02 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$,): δ 139.3, 136.5, 130.7, 129.1, 128.7, 125.9, 124.8, 123.1, 121.0, 119.7, 111.6, 102.9.

4.2.2. 3-(p-Tolylthio)-1H-indole ***(3ab)***[9c]

White solid, yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (brs, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.32–7.30 (m, 2H), 7.24–7.20 (m, 1H), 7.15–7.11 (m, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 2.21 (s, 3H); ^{13} C NMR (126 MHz, $CDCl_3$) δ 136.5, 135.6, 134.8, 130.6, 129.6, 129.2, 126.4, 123.1, 120.9, 119.7, 111.7, 103.3, 20.9.

4.2.3. 3-(3-Methoxyphenylthio)-1H-indole ***(3ac)***[18a]

White solid, yield 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (brs, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.33-7.31 (m, 2H), 7.24-7.18 (m, 1H), 7.15–7.12 (m, 1H), 7.07-7.03 (m, 1H), 6.70-6.66 (m, 2H), 6.60-6.57 (m, 1H), 3.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 140.9, 136.5, 130.9, 129.7, 129.1, 123.1, 121.0, 119.6, 118.4, 111.8, 111.7, 110.4, 102.4, 55.2.

4.2.4. 3-(4-hydroxyphenylthio)-1H-indole ***(3ad)***[17d]

Off-white solid, yield 78%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 9.37 (s, 1H), 7.71 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.16 (m, 1H), 7.04 (d, *J* = 6.8 Hz, 3H), 6.67 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.7, 136.6, 131.4, 129.0, 128.7, 127.0, 122.0, 119.9, 118.5, 116.0, 112.2, 102.3.

4.2.5. 3-(4-Fluorophenylthio)-1H-indole ***(3ae)***[11f]

White solid, yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (brs, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.39–7.35 (m, 2H), 7.26–7.22 (m, 1H), 7.19–7.13 (m, 1H), 7.09–7.04 (m, 2H), 6.85–6.81 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -118.10; ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9 (d, $^1J_{C\text{-}F}$ = 243 Hz), 136.5, 134.0, 130.5, 128.9, 128.0 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 123.2, 121.0, 119.6, 115.8 (d, $^2J_{C\text{-}F}$ = 22 Hz), 111.7, 103.4.

4.2.6. 3-(4-Bromophenylthio)-1H-indole ***(3af)*** [11f]

White solid, yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (brs, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.40-7.38 (m, 2H), 7.28-7.22

(m, 3H), 7.18-7.14 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, CDCl3) δ 138.6, 136.5, 131.7, 130.8, 128.8, 127.5, 123.3, 121.1, 119.5, 118.4, 111.8, 102.3.

4.2.7. 3-[(2-Carboxyphenyl)thio]-1H-indole ***(3ag)*** [9g]

Light brown solid, yield 79%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (brs, 1H), 11.77 (s, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.24-7.20 (m, 2H), 7.14-7.07 (m, 2H), 6.75 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.5, 143.8, 137.0, 132.7, 132.0, 131.0, 128.7, 126.7, 125.6, 123.7, 122.2, 120.2, 118.3, 112.4, 100.0.

4.2.8. 3-(Pyridin-2-ylthio)-1H-indole ***(3ai)*** [18b]

Pale-yellow solid, yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (brs, 1H), 8.36-8.34 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.41-7.37 (m, 2H), 7.33-7.29 (m, 1H), 7.24-7.20 (m, 1H), 7.16-7.12 (m, 1H), 6.94-6.90 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 148.9, 136.9, 131.7, 128.9, 123.0, 120.9, 120.2, 119.5, 119.3, 112.1, 100.2.

4.2.9. 3-(Benzothiazole-2-ylthio)-1H-indol ***(3aj)*** [18c]

White solid, yield 94%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (brs, 1H), 8.08 (d, *J* = 2.8 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.67-7.62 (m, 2H), 7.43-7.39 (m, 1H), 7.31-7.24 (m, 2H), 7.21-7.17 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.3, 154.2, 136.8, 135.0, 133.8, 128.0, 126.1, 123.9, 122.6, 121.5, 121.1, 120.8, 118.1, 112.7, 97.3.

4.2.10. 3-(Benzylthio)-1H-indole ***(3ak)*** [9c]

Yellow solid, yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (brs, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.24-7.15 (m, 5H), 7.08-7.05 (m, 2H), 6.95 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 136.2, 129.9, 129.3, 129.0, 128.3, 126.8, 122.7, 120.5, 119.3, 111.5, 105.3, 41.0.

4.2.11. 4-Methyl-3-[(2-Carboxyphenyl)thio]-1H-indole ***(3cg)*** [9g]

White solid, yield 86%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.01 (d, *J* = 6.8 Hz, 1H), 7.71 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.26-7.24 (m, 1H), 7.14-7.07 (m, 2H), 6.84-6.79 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.0, 146.5, 138.0, 133.6, 132.6, 131.4, 130.7, 127.2, 126.9, 126.4, 124.0, 122.7, 122.1, 110.8, 100.7, 18.4.

4.2.12. 3-(5-Methoxyphenylthio)-1H-indole ***(3da)*** [9c]

White solid, yield 80%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (brs, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H) 7.20-7.16 (m, 2H), 7.08-7.02 (m, 3H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.90-6.87 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.4, 139.4, 132.9, 131.7, 129.6, 128.8, 125.2, 124.6, 113.2, 112.3, 99.9, 98.9, 55.2.

4.2.13. 5-Methoxyl-3-[(4-Carboxyphenyl)thio]-1H-indole ***(3dg)*** [9g]

White solid, yield 81%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (brs, 1H), 11.63 (brs, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.72 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.15-7.11 (m, 1H), 6.89-6.84 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8, 159.6, 149.1, 138.3, 137.3, 137.1, 136.2, 134.8, 131.9, 130.8, 128.9, 118.5, 117.6, 105.0, 104.7, 60.5.

4.2.14. 5-Methoxyl -3-[(4-Carboxyphenyl)thio]-1H-indole ***(3dh)*** [9g]

Light yellow solid, yield 57%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (brs, 1H), 11.74 (brs, 1H), 7.87-7.82 (m, 3H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 2H), 6.93 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.6, 155.0, 146.5, 133.7, 132.2, 130.3, 129.8, 127.5, 124.9, 113.8, 113.0, 100.2, 97.8, 55.7.

4.2.15. 5-Bromo-3-(phenylthio)-1H-indole ***(3ea)*** [9c]

White solid, yield 88%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (brs, 1H), 7.89 (s, 1H), 7.57-7.52 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.23-7.20 (m, 2H), 7.10-7.06 (m, 3H) ^{13}C NMR (126 MHz, DMSO-d_6) δ 138.7, 135.5, 134.1, 130.6, 128.9, 125.4, 125.0, 124.8, 120.4, 114.5, 113.0, 99.3.

4.2.16. 5-Bromo-3-[(2-Carboxyphenyl)thio]-1H-indole ***(3eg)*** [9g]

Yellow solid, yield 78%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (brs, 1H), 12.00 (s, 1H), 8.00 (d, *J* = 7.2 Hz, 1H), 7.88 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.30-7.26 (m, 1H), 7.18-7.15 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 143.2 135.7, 134.3, 132.2, 131.1, 130.7, 126.7, 125.5, 124.8, 123.9, 120.4, 114.6, 113.0, 99.9.

4.2.17. 6-Fluoro-3-[(2-Carboxyphenyl)thio]-1H-indole ***(3fg)*** [9g]

Light purple solid, yield 56%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (brs, 1H), 11.83 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.38-7.32 (m, 2H), 7.27-7.23 (m, 1H), 7.16-7.12 (m, 1H), 6.98-6.93 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.5, 159.3 (d, $^{1}J_{C\text{-}F}$ = 236 Hz), 143.4, 136.9, 133.4, 132.1, 131.0, 126.7, 125.6, 125.3, 123.8, 119.5, 108.8, 108.6, 100.5, 98.6, 98.4.

4.2.18. Methyl 1-methyl-3-(Phenylthio)-1H-indole-4-carboxylate ***(3ga)***

Light yellow liquid, yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (brs, 1H), 7.46-7.42 (m, 2H), 7.34 (d, *J* = 2.8 Hz, 1H), 7.22-7.17 (m, 1H), 7.12-7.08 (m, 2H), 7.02-6.97 (m, 3H), 3.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 140.2, 137.7, 134.1, 128.6, 125.6, 125.4, 125.2, 124.7, 122.1, 122.0, 115.4, 101.7, 52.0; HRMS (ESI) Calcd. for $C_{16}H_{14}NO_2S$ ($[M+H]^+$) 284.0740, Found 284.0739.

4.2.19. Methyl 1-methyl-3-[(2-Carboxyphenyl)thio]-1H-indole-4-carboxylate ***(3gg)***

Light yellow solid, yield 65%, mp: 233.7-235.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (brs, 1H), 12.13 (brs, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.34-7.23 (m, 3H), 7.14-7.10 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.33 (s, 3H); $_{13}$C NMR (126 MHz, DMSO-d_6) δ 168.6, 167.5, 145.0, 137.9, 135.8, 131.8, 130.6, 126.2, 126.0, 125.1, 124.8, 123.4, 121.4, 121.0, 115.5, 99.8, 50.9; HRMS (ESI) Calcd. for $C_{17}H_{14}NO_4S$ ($[M+H]^+$) 328.0638, Found 328.0649.

4.2.20. 2-Methyl-3-(phenylthio)-1H-indole ***(3ia)*** [9c]

White solid, Yield 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (brs, 1H), 7.53 (d, *J* = 6 Hz, 1H), 7.18-6.95 (m, 8H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 139.5, 135.6, 130.4, 128.9, 125.7, 124.80, 122.3, 120.9, 119.0, 111.0, 99.2.

4.2.21. 2-Methyl-3-[(2-Carboxyphenyl)thio]-1H-indole ***(3ig)***

Light yellow solid, yield 91%, mp: 190.5-191.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (brs, 1H), 11.71 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.23-7.19 (m, 1H), 7.16-7.09 (m, 2H), 7.05-7.01 (m, 1H), 6.67 (d, *J* = 8 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.6, 143.5, 142.3, 135.9, 132.0, 131.1, 129.7, 126.9, 125.2, 123.6, 121.4, 119.9, 117.6, 111.3, 96.9, 11.6; HRMS (ESI) Calcd. for $C_{16}H_{14}NO_2S$ ($[M+H]^+$) 284.0740, Found 284.0742.

4.2.22. Ethyl 3-(phenylthio)-1H-indole-2-carboxylate ***(3ja)*** [9f]

White solid, yield 88%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (brs, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.37-7.33 (m, 1H), 7.23-7.20 (m, 2H), 7.15-7.08 (m, 4H), 4.37-4.31 (m, 2H), 1.28-1.24 (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.4, 137.9, 136.3, 129.3, 129.2, 128.8, 126.4, 125.4, 125.1, 121.1, 120.3, 113.2, 107.4, 60.7, 14.0.

4.2.23. 3-Methyl-2-(phenylthio)-1H-indole ***(3ka)*** [18b]

White solid, yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (brs, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.19-7.15 (m, 1H), 7.12-7.07 (m, 4H), 7.04-7.00 (m, 1H), 6.98-6.95 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 137.1, 129.3, 128.7, 126.7, 125.89, 123.7, 121.7, 120.1, 119.9, 119.7, 111.2, 9.7.

4.2.24. 3-Methyl-2-[(2-Carboxyphenyl)thio]-1H-indole ***(3kg)*** [9g]

Light yellow solid, yield 77%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (brs, 1H), 11.37 (s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.39-7.32 (m, 2H), 7.23-7.18 (m, 2H), 7.10-7.06 (m, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 141.8, 137.3, 132.7, 131.2, 127.8, 126.7, 125.7, 124.5, 122.8, 121.4, 119.1, 118.8, 118.4, 111.3, 9.04.

4.2.25. 3-(Phenylthio)-1H-pyrrolo[2,3-b]pyridine ***(3la)*** [9f]

Light yellow solid, yield 86%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (brs, 1H), 8.35-8.30 (m, 1H), 7.97 (s, 1H), 7.83-7.70 (m, 1H), 7.22-7.07 (m, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.9, 148.0, 143.7, 143.7, 138.6, 133.2, 130.4, 128.9, 128.0, 126.7, 125.6, 125.0, 122.0, 121.0, 116.5, 116.4, 98.7.

4.2.26. 2,3-bis(phenylthio)-1H-indole ***(4aa)*** [17d]

Colorless oil, yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (brs, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.26-7.16 (m, 7H), 7.14-7.08 (m, 5H), 7.04-7.01 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 136.9, 134.5, 133.6, 130.0, 129.7, 129.5, 128.8, 127.3, 126.7, 125.2, 124.0, 121.3, 120.0, 111.3, 109.3.

4.2.27. 2,3-bis[(4-methylphenyl)thio]-1H-indole ***(4ab)***

Colorless oil, yield 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (brs, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.20-7.15 (m, 4H), 7.11-7.07 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 4H), 6.92 (d, *J* = 7.6 Hz, 2H), 2.27 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 136.8, 135.0, 134.6, 130.7, 130.3, 130.2, 129.6, 127.0, 123.6, 121.2, 119.8, 111.1, 108.5, 21.2, 21.0; HRMS (ESI) Calcd. for $C_{22}H_{20}NS_2$ ($[M+H]^+$) 362.1032, Found 362.1018.

4.2.28. 2,3-bis[(3-methoxyphenyl)thio]-1H-indole ***(4ac)***

Colorless oil, yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (brs, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.26-7.19 (m, 2H), 7.15-7.09 (m, 2H), 7.05-7.01 (m, 1H), 6.82-6.77 (m, 2H), 6.72-6.66 (m, 3H), 6.59-6.57 (m, 1H), 3.65 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 159.9, 139.6, 137.0, 135.6, 133.5, 130.2, 130.0, 129.6, 124.0, 121.9, 121.3, 119.9, 118.9, 115.0, 113.2, 112.1, 111.3, 110.8, 109.0, 55.3, 55.2; HRMS (ESI) Calcd. for $C_{22}H_{20}NO_2S_2$ ($[M+H]^+$) 394.0930, Found 394.0925.

4.2.29. 2,3-bis[(4-fluorophenyl)thio]-1H-indole ***(4ae)***

Colorless oil, yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (brs, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26-7.22 (m, 3H), 7.17-7.13 (m, 1H), 7.09-7.05 (m, 2H), 6.94, 6.9-6.90 (m, 2H), 6.85-6.81 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.5, -117.3; ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 161.2 (d, $^1J_{C\text{-}F}$ = 244,4 Hz), 136.8, 133.8, 132.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 132.3 (d, $^2J_{C\text{-}F}$ = 8,8 Hz), 129.9, 129.1 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 128.8 (d, $^2J_{C\text{-}F}$ = 7.6 Hz), 124.1, 121.5, 119.8, 116.7, 116.5, 115.9, 115.8, 111.3, 109.5; HRMS (ESI) Calcd. for $C_{20}H_{14}F_2NS_2$ ($[M+H]^+$) 370.0530, Found 370.0519.

4.2.30. 2,3-bis[(4-bromophenyl)thio]-1H-indole ***(4af)***

Colorless oil, yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.36 (brs, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.31-7.23 (m, 4H), 7.21-7.14 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 138.6, 136.6, 131.7, 130.8, 128.8, 127.5, 123.3, 121.1, 119.5, 118.4, 111.8, 102.3; HRMS (ESI) Calcd. for $C_{20}H_{12}Br_2NS_2$ ($[M-H]^-$) 489.8757, Found 489.8750.

4.2.31. 2,3-bis(phenylthio)-1-benzyl-indole ***(4ba)***

Colorless oil, Yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.66 (d, *J* = 8.0 Hz, 1H), 7.25-7.05 (m, 11H), 7.03-6.96 (m, 5H), 6.94-6.92 (m, 2H), 5.46 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 138.4, 138.4, 137.2, 135.7, 134.6, 129.6, 129.2, 128.9, 128.8, 128.0, 127.6, 126.8, 126.6, 126.5, 125.3, 124.5, 121.5, 120.7, 112.4, 111.3, 48.5; HRMS (ESI) Calcd. for $C_{27}H_{22}NS_2$ ($[M+H]^+$) 424.1188, Found 424.1175.

4.2.32. 2,3-bis(phenylthio)-5-methoxy-1H-indole ***(4da)***

Colorless oil, Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.32 (brs, 1H), 7.21-7.16 (m, 5H), 7.15-7.08 (m, 5H), 7.05-7.00 (m, 2H), 6.89-6.86 (m, 1H), 3.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 155.3, 138.2, 134.6, 133.8, 131.9, 130.9, 129.5, 129.4, 128.8, 127.2, 126.4, 125.1, 114.6, 112.2, 108.6, 101.0, 55.8; HRMS (ESI) Calcd. for $C_{21}H_{18}NOS_2$ ($[M+H]^+$) 364.0824, Found 364.0813.

4.2.33. 2,3-bis(phenylthio)-5-bromo-1H-indole ***(4ea)***

Colorless oil, yield 78%; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 12.49 (brs, 1H), 7.57-7.04 (m, 13H); ^{13}C NMR (126 MHz, DMSO-d_6) *δ* 137.5, 136.2, 134.7, 130.9, 129.4, 129.0, 128.3, 126.8, 126.1, 125.9, 125.3, 120.8, 114.3, 113.5, 106.9; HRMS (ESI) Calcd. for $C_{21}H_{18}NOS_2$ ($[M+H]^+$) 411.9824, Found 411.9813.

4.2.34. 2,3-bis(phenylthio)-6-fluoro-1H-indole ***(4fa)***

Colorless oil, Yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.29 (brs, 1H), 7.47-7.44 (m, 1H), 7.25-7.14 (m, 5H), 7.12-7.02 (m, 5H), 6.95- 6.92 (m, 1H), 6.90-6.85 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ* -117.7; ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 160..9 (d, $^1J_{C\text{-}F}$ = 241 Hz), 137.8, 136.97, 136.8, 134.4, 133.6 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 129.6, 129.5, 128.9, 127.4, 126.9, 126.4, 125.4, 121.0 (d, $^2J_{C\text{-}F}$ = 10.0 Hz), 110.3, 110.1, 109.9, 97.9, 97.7; HRMS (ESI) Calcd. for $C_{20}H_{15}FNS_2$ ($[M+H]^+$) 352.0624, Found 352.0619.

4.2.35. Methyl 1-methyl-2,3-bis(phenylthio)-5-bromo-1H-indole-4-carboxylate ***(4ga)***

Light yellow solid, yield 73%, mp: 230.1-231.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 12.58 (brs, 1H), 7.65-7.63 (m, 1H), 7.32-7.29 (m, 4H), 7.25-7.20 (m, 3H), 7.18-7.15 (m, 2H), 7.06-7.02 (m, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 3.50 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) *δ* 168.4, 139.1, 138.1, 136.6, 134.4, 129.4, 128.6, 128.5, 126.9, 125.5, 125.1, 124.6, 122.5, 121.1, 114.9, 105.6, 51.5; HRMS (ESI) Calcd. for $C_{22}H_{18}NO_2S_2$ ($[M+H]^+$) 392.0773, Found 392.0768.

4.2.36. 2-(Phenylthio)-1H-indole ***(5)*** [17a]

White solid, yield 93%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.83 (brs, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.19-7.13 (m, 4H), 7.11-7.06 (m, 4H), 6.81 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 137.8, 136.9, 129.3, 128.6, 127.6, 126.4, 125.3, 123.4, 120.9, 120.5, 111.7, 111.1.

4.2.37. 2-(phenylthio)-3-(pyridin-2-ylthio)-1H-indole ***(6)***

White solid, yield 90%, mp: 161.8-162.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (brs, 1H), 8.35 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.43-7.39 (m, 1H), 7.28-7.24 (m, 5H), 7.15 (d, J = 6.4 Hz, 2H), 6.99 (m, 1H), 6.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 161.4, 149.7, 138.2, 137.3, 135.9, 133.4, 129.8, 129.7, 128.4, 127.0, 124.1, 121.4, 120.2, 119.8, 119.4, 112.8, 106.9; HRMS (ESI) Calcd. for $C_{19}H_{15}N_2S_2$ ($[M+H]^+$) 335.0671, Found 335.0667.

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Supporting Information

Iodine-Catalyzed Versatile Sulfenylation of Indoles with Thiophenols: Controllable Synthesis of mono- and bis-Arylthioindoles

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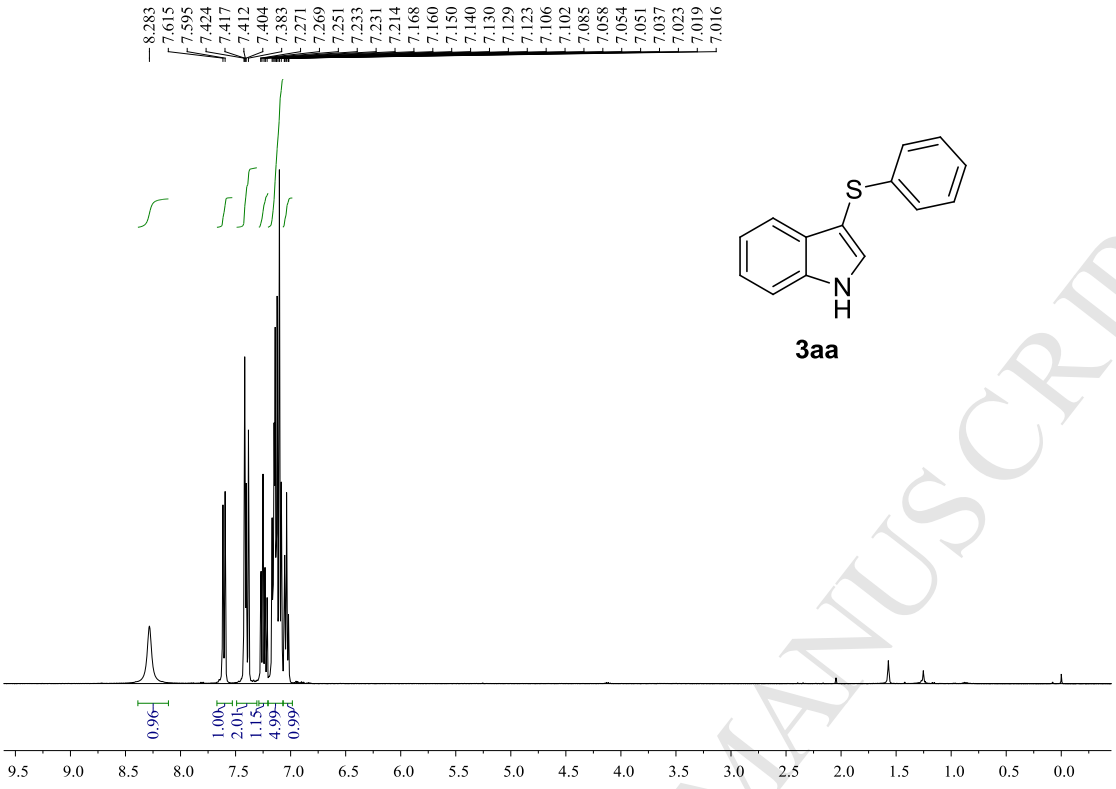

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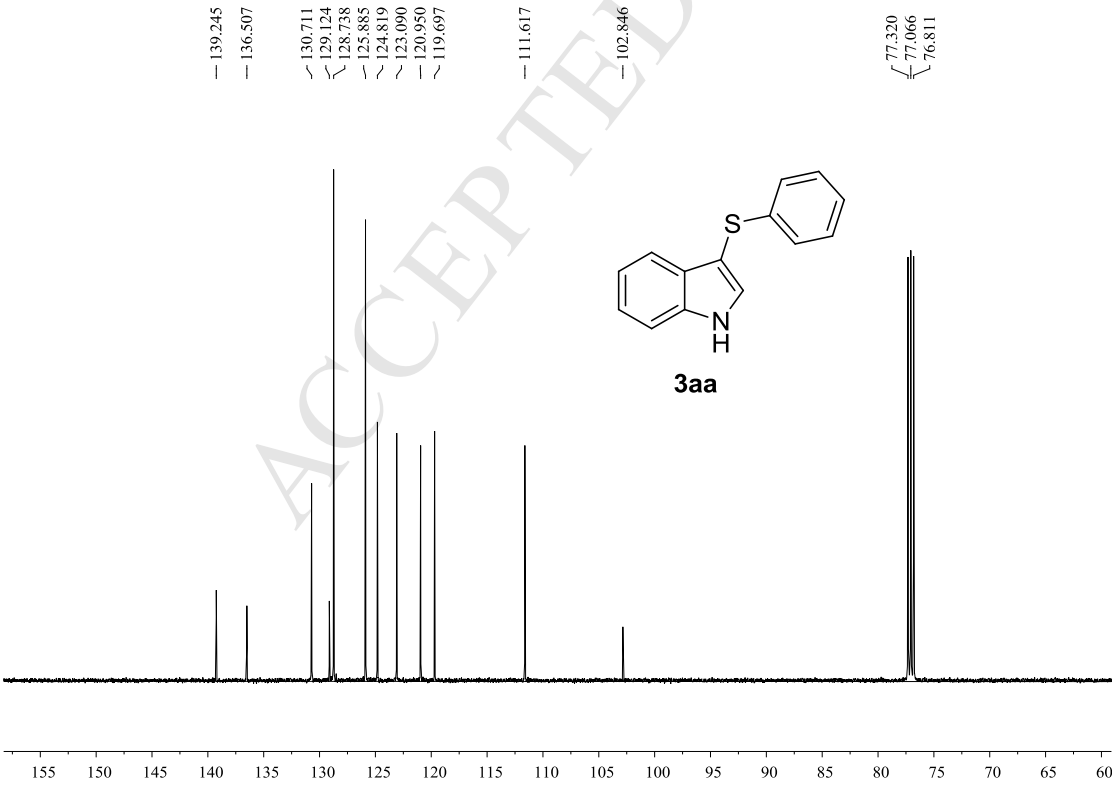

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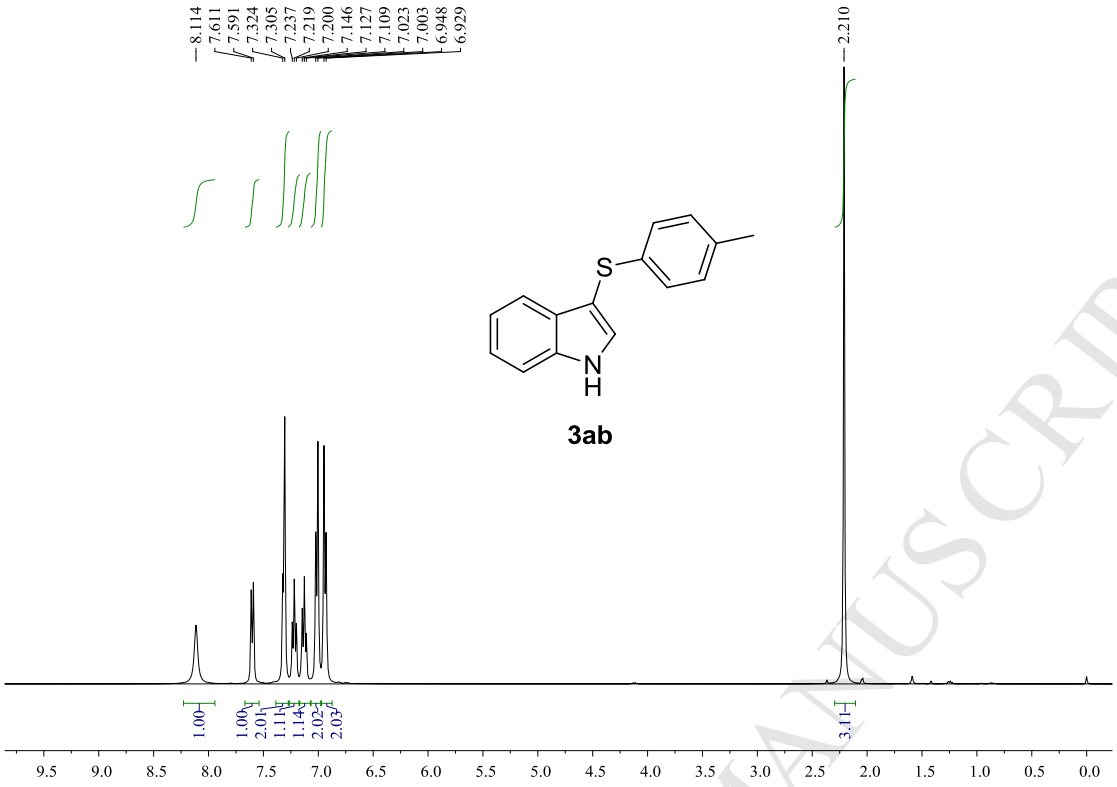

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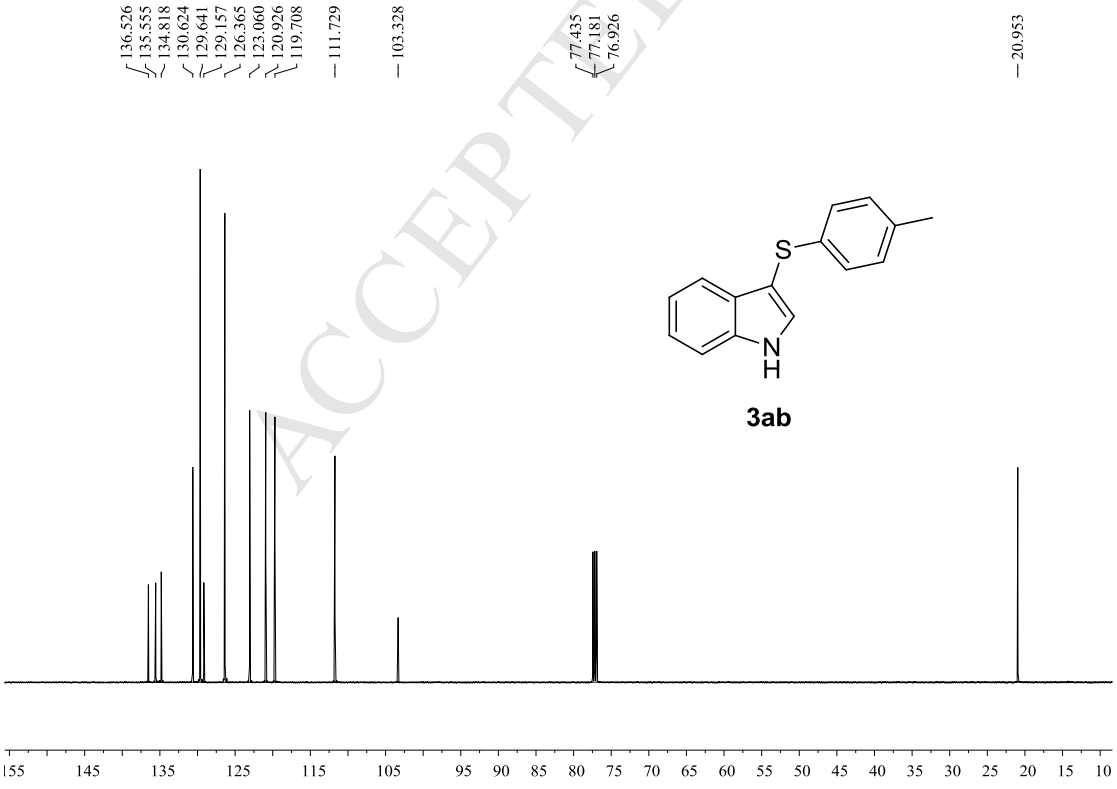

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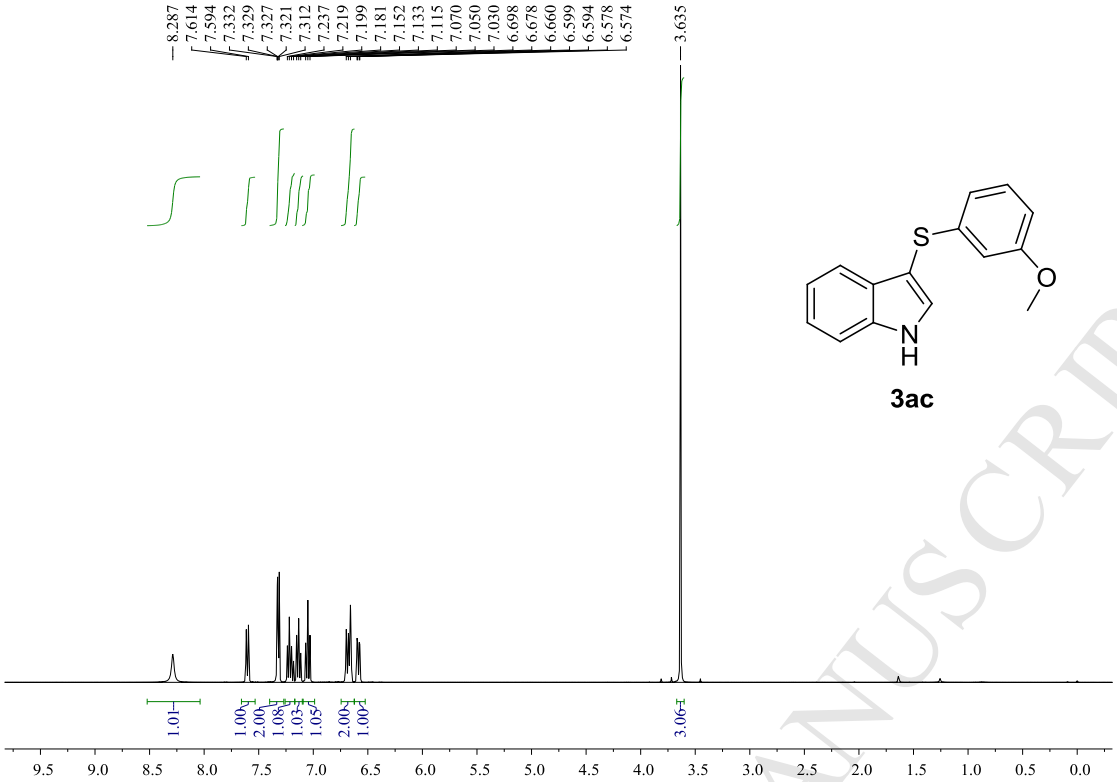

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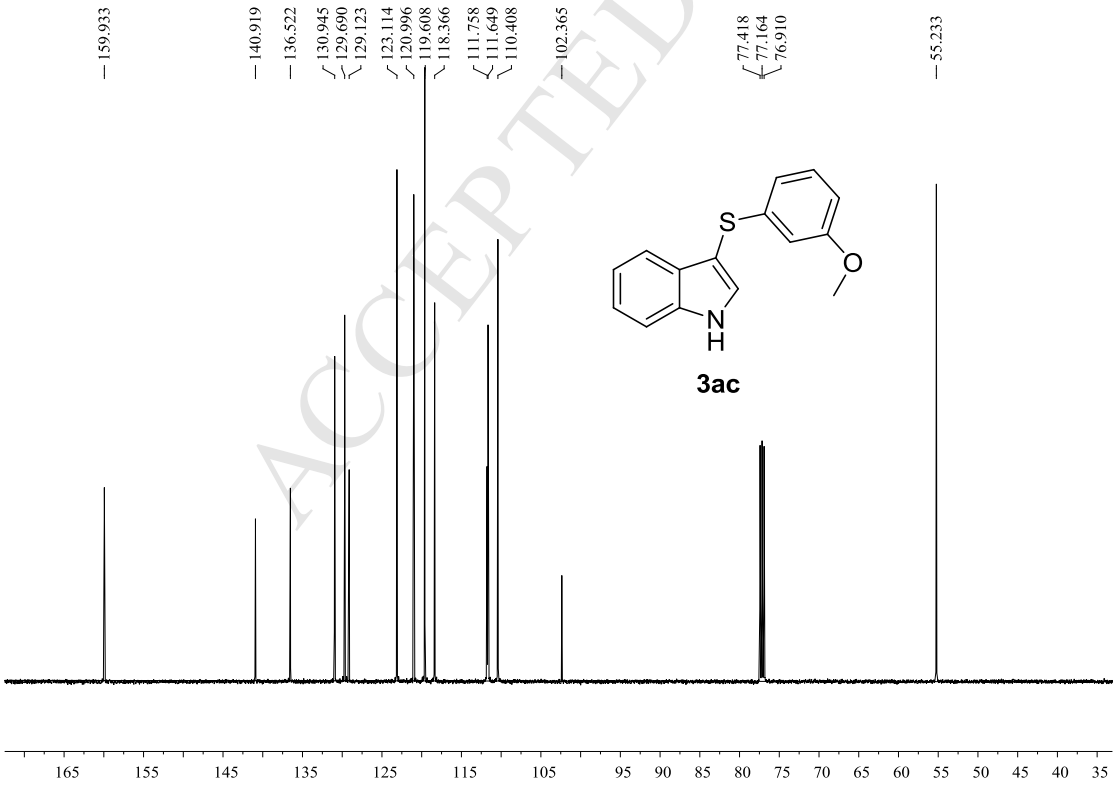

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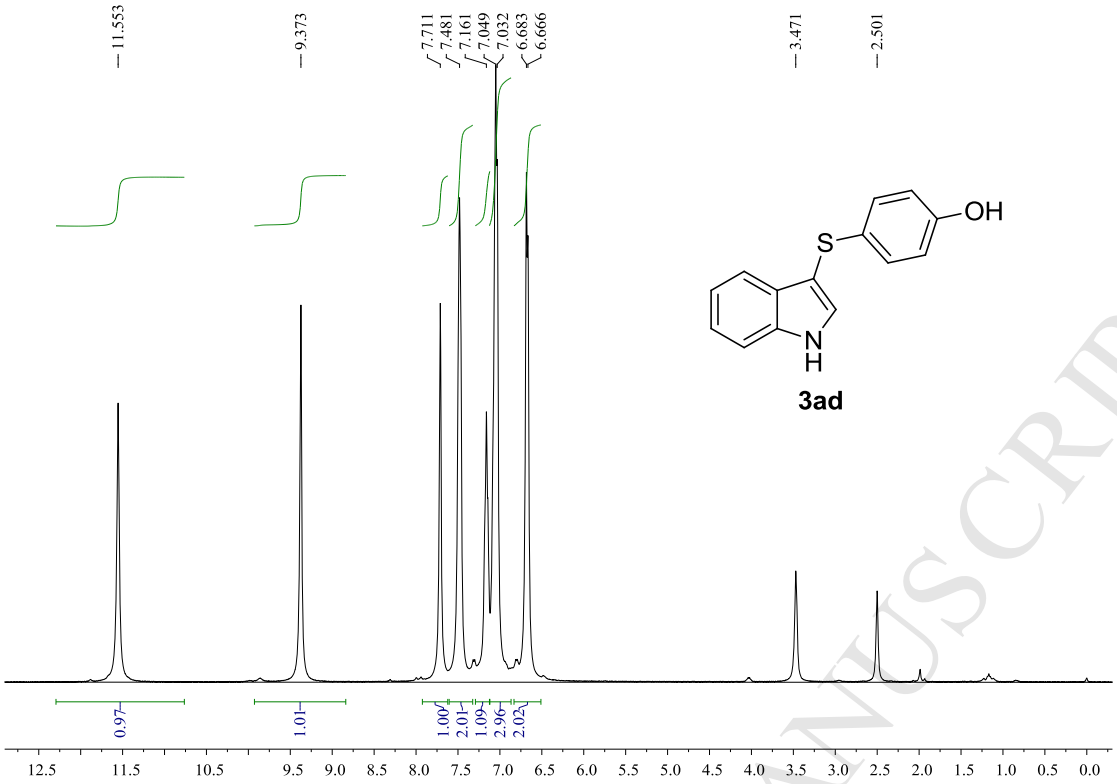

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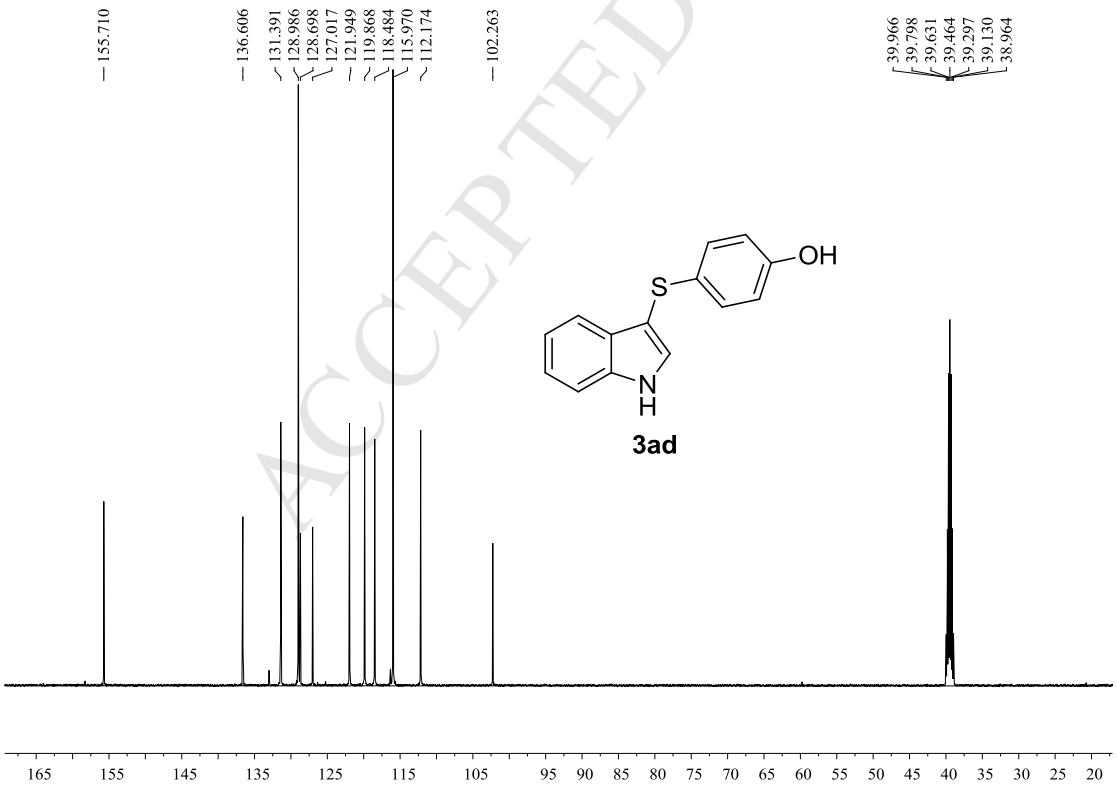

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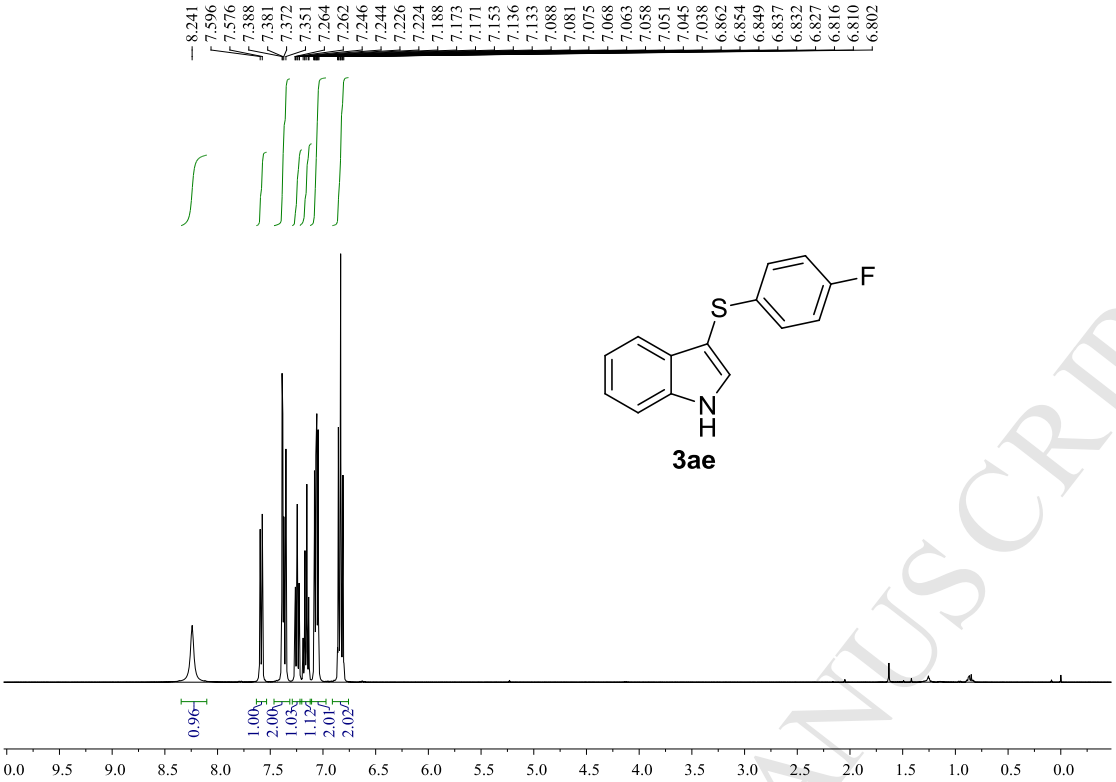

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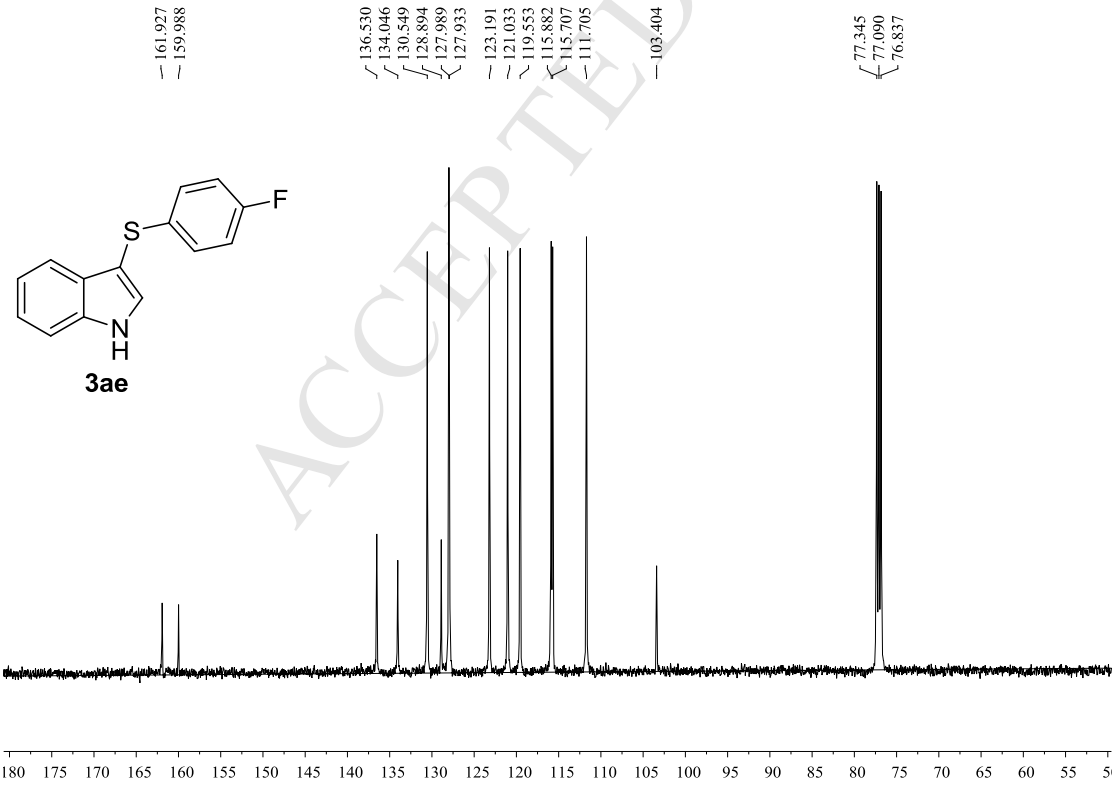

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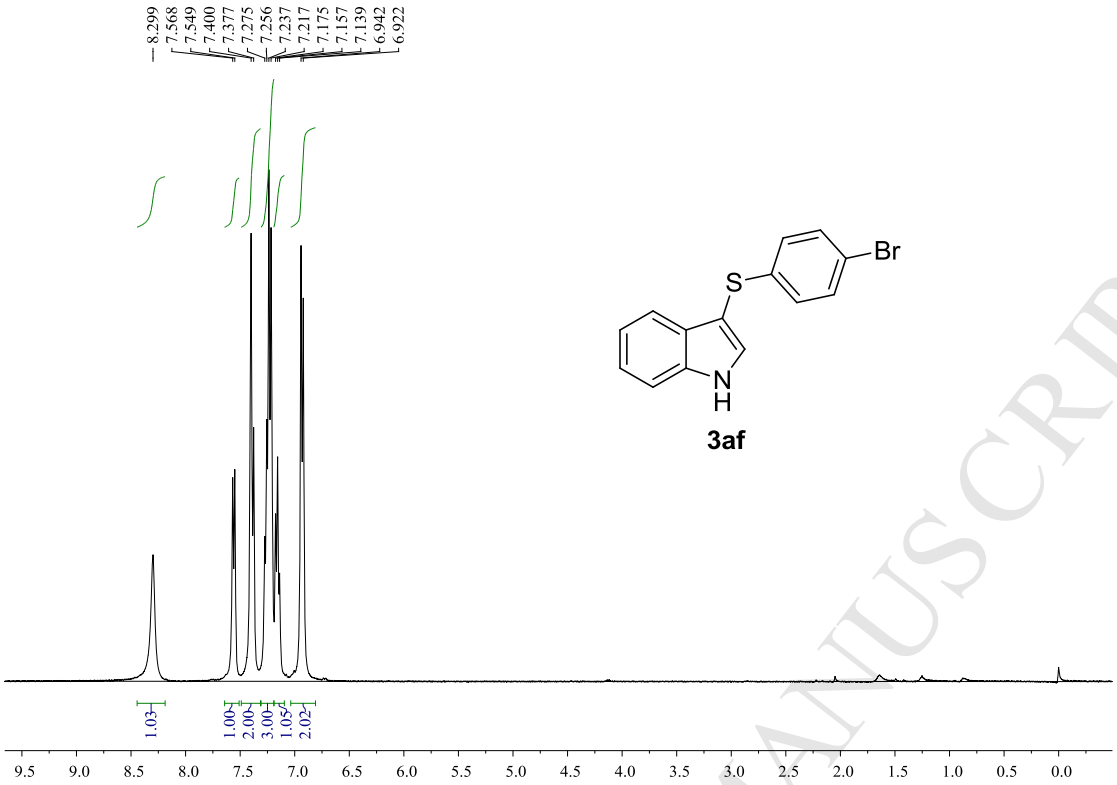

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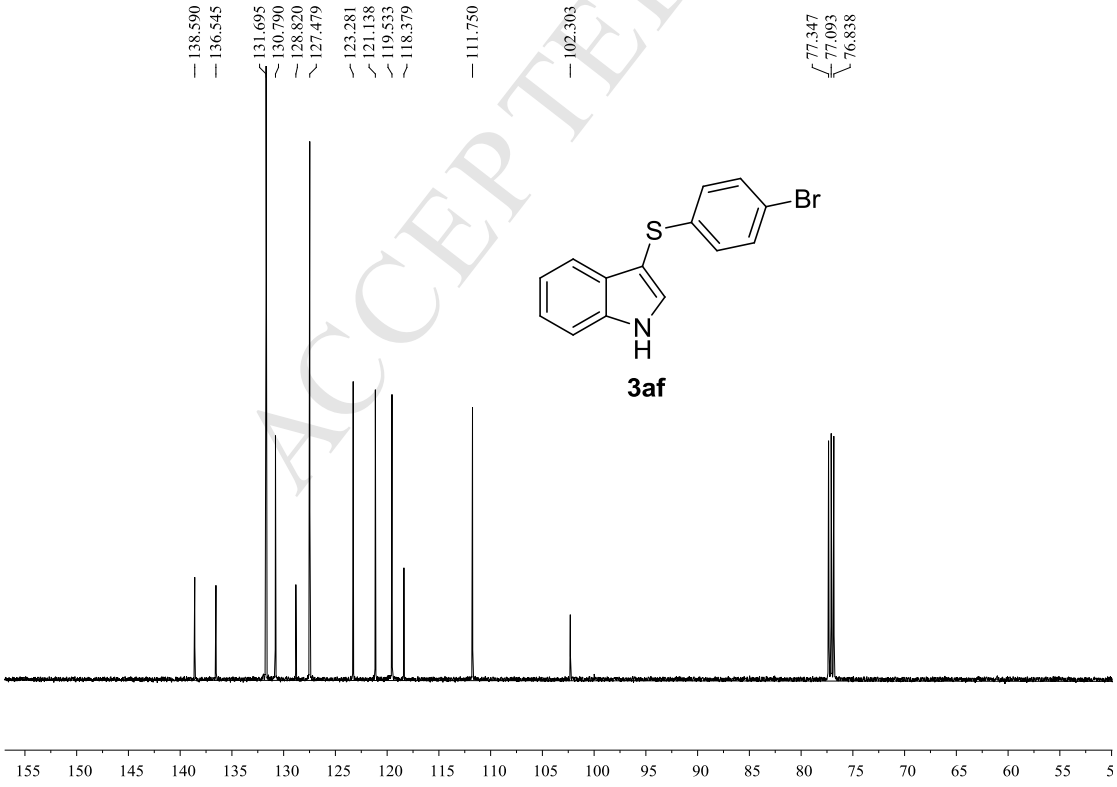

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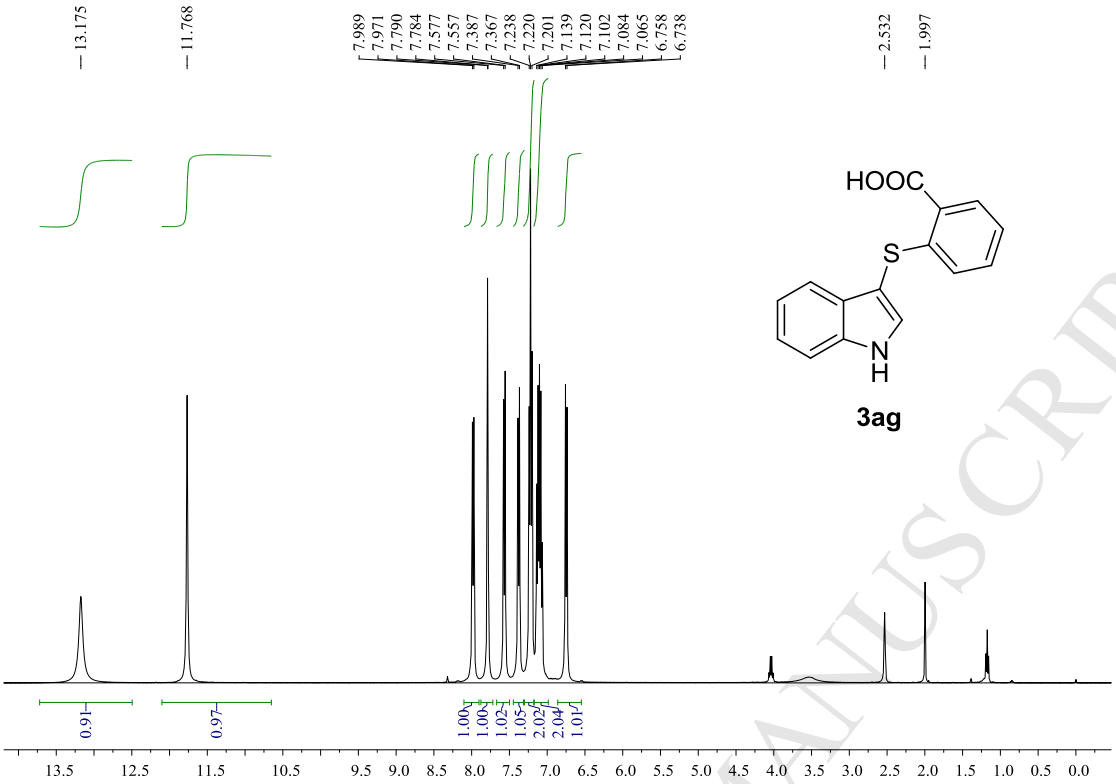

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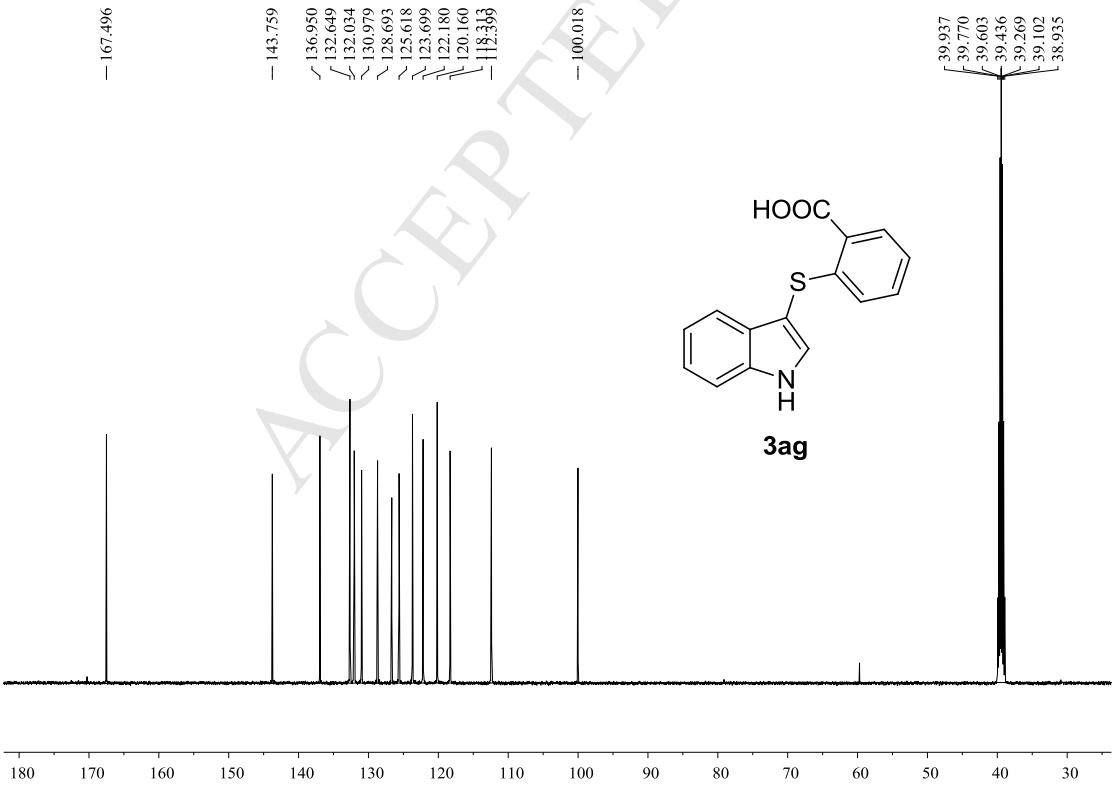

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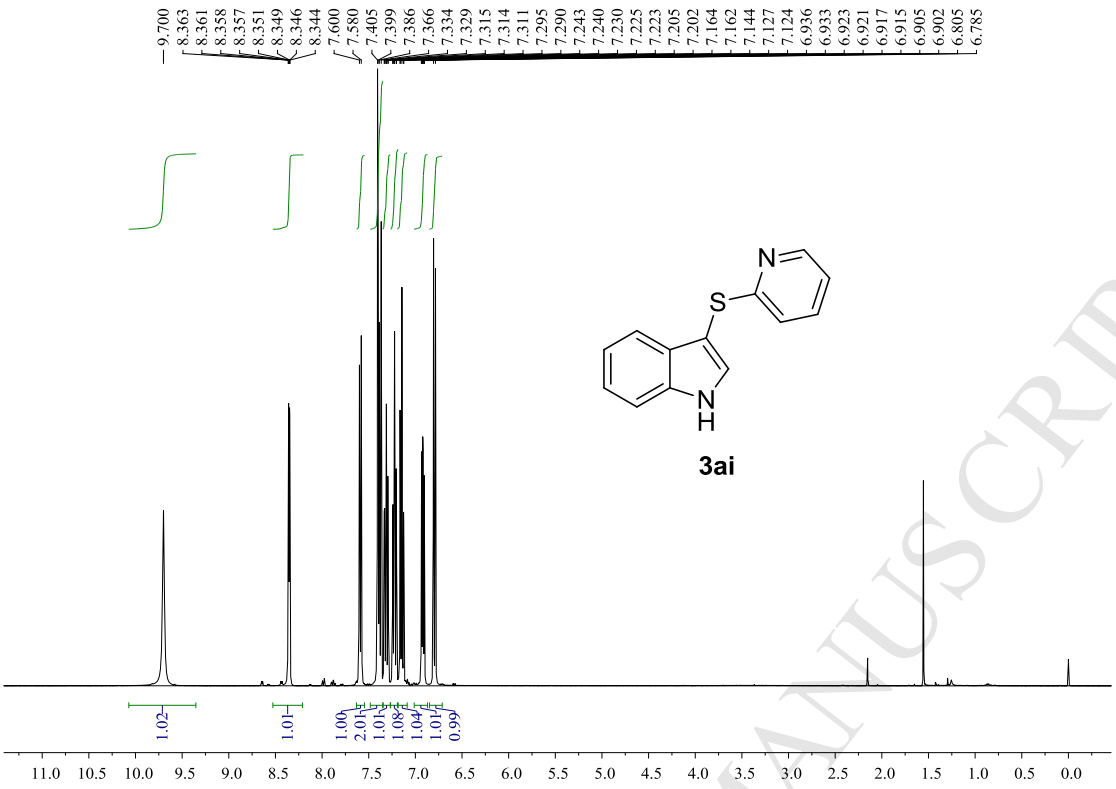

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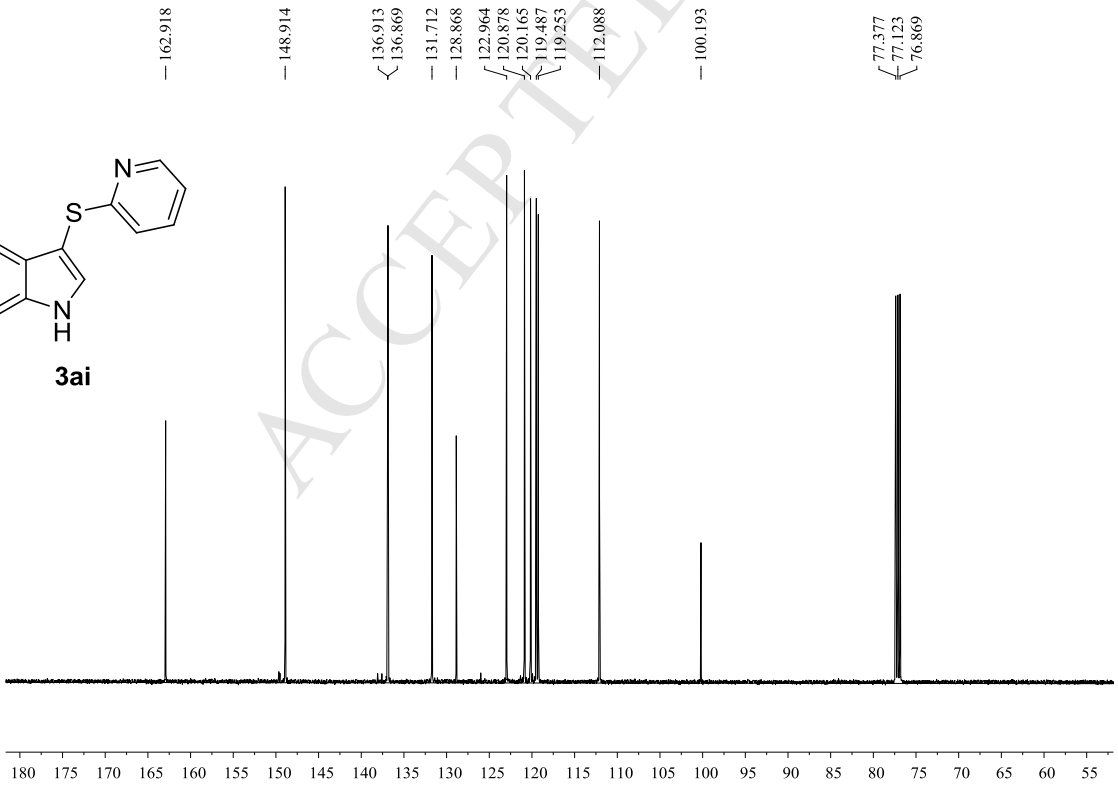

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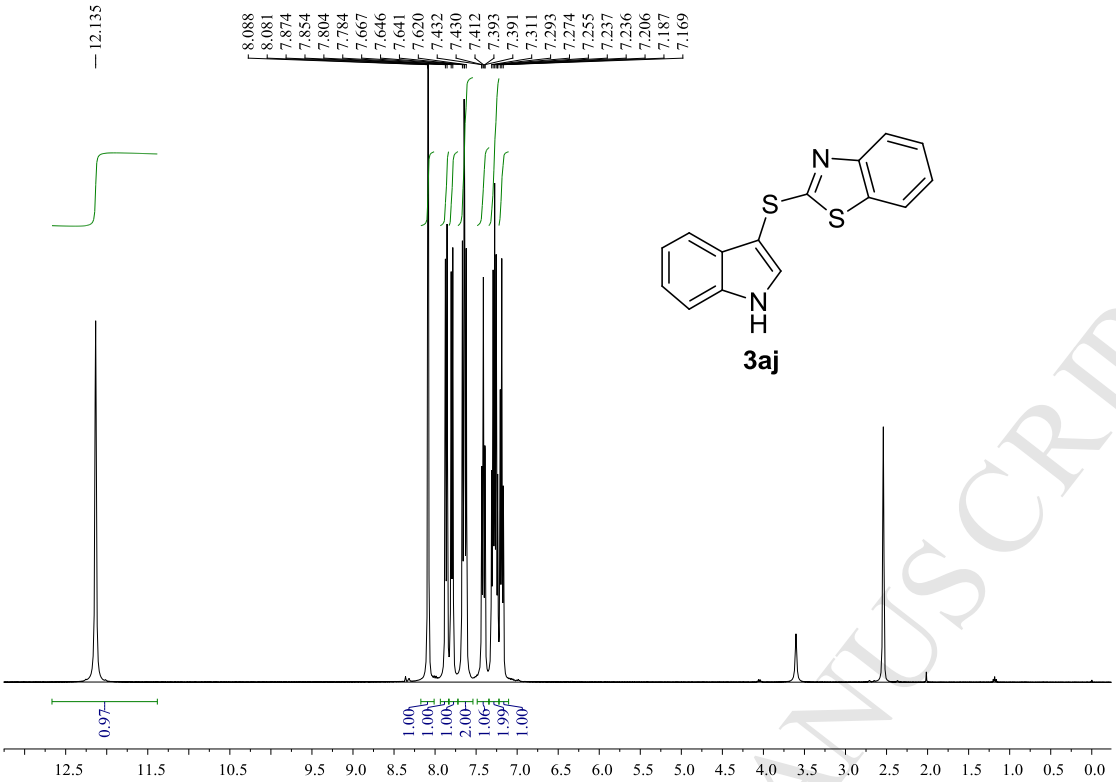

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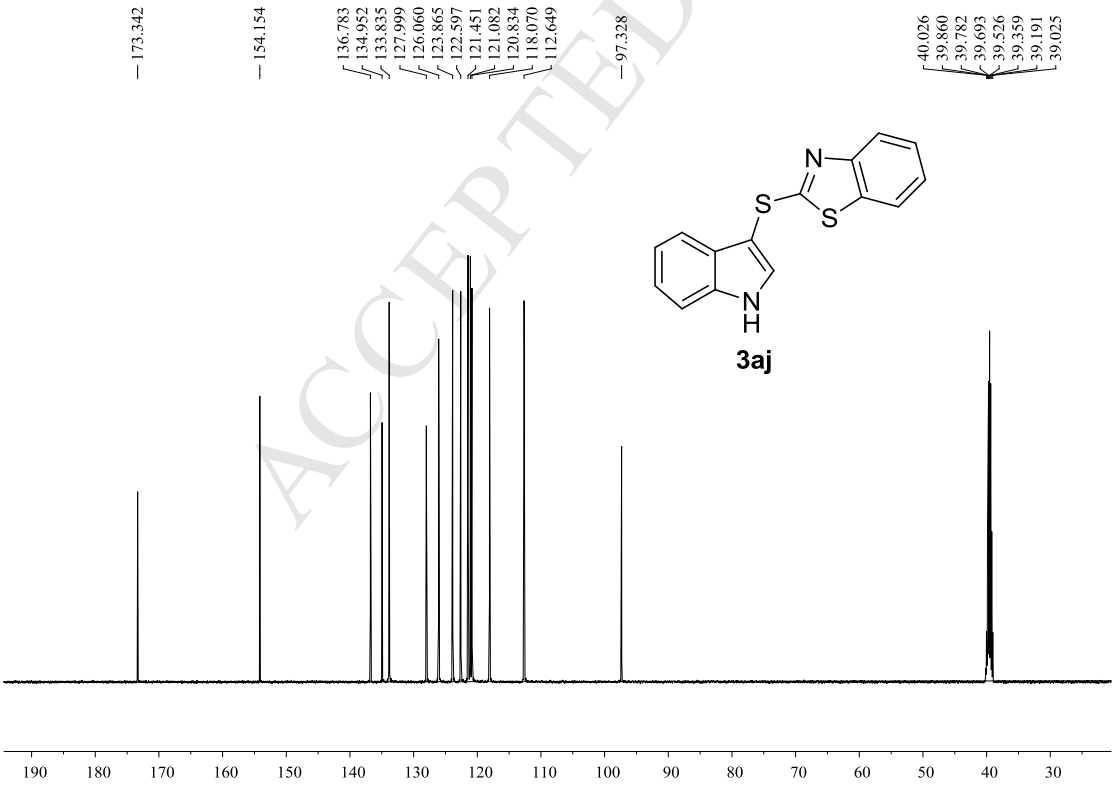

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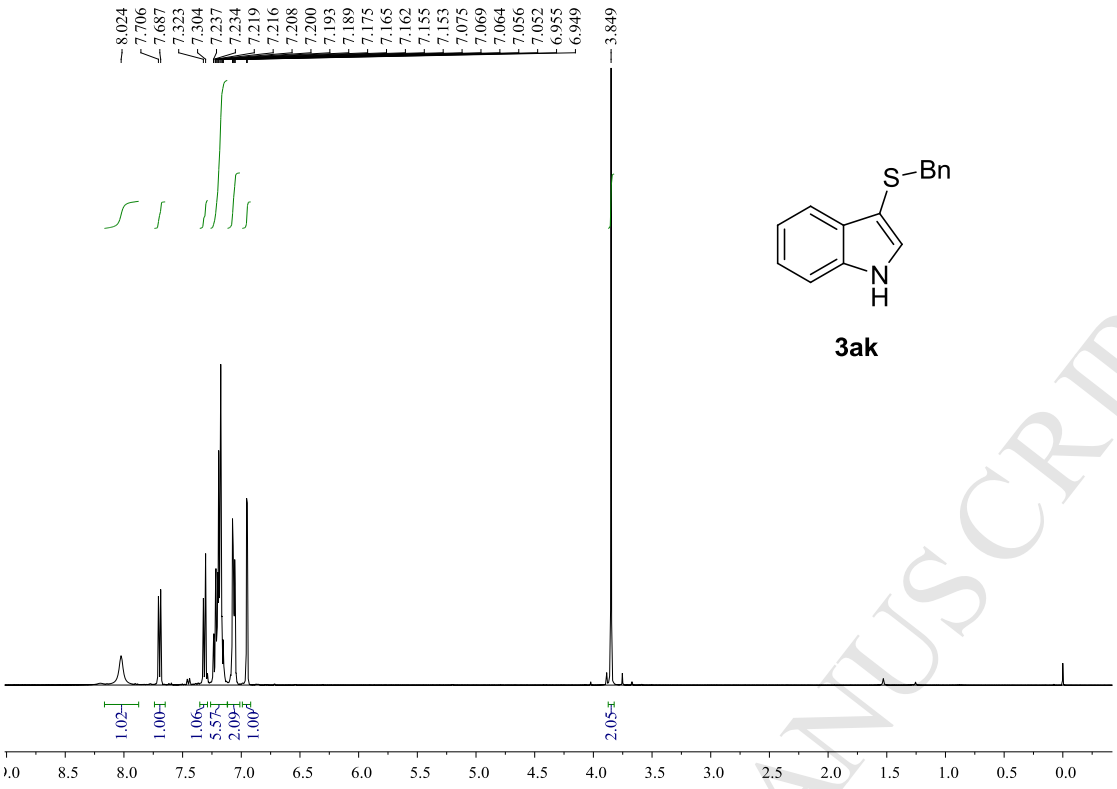

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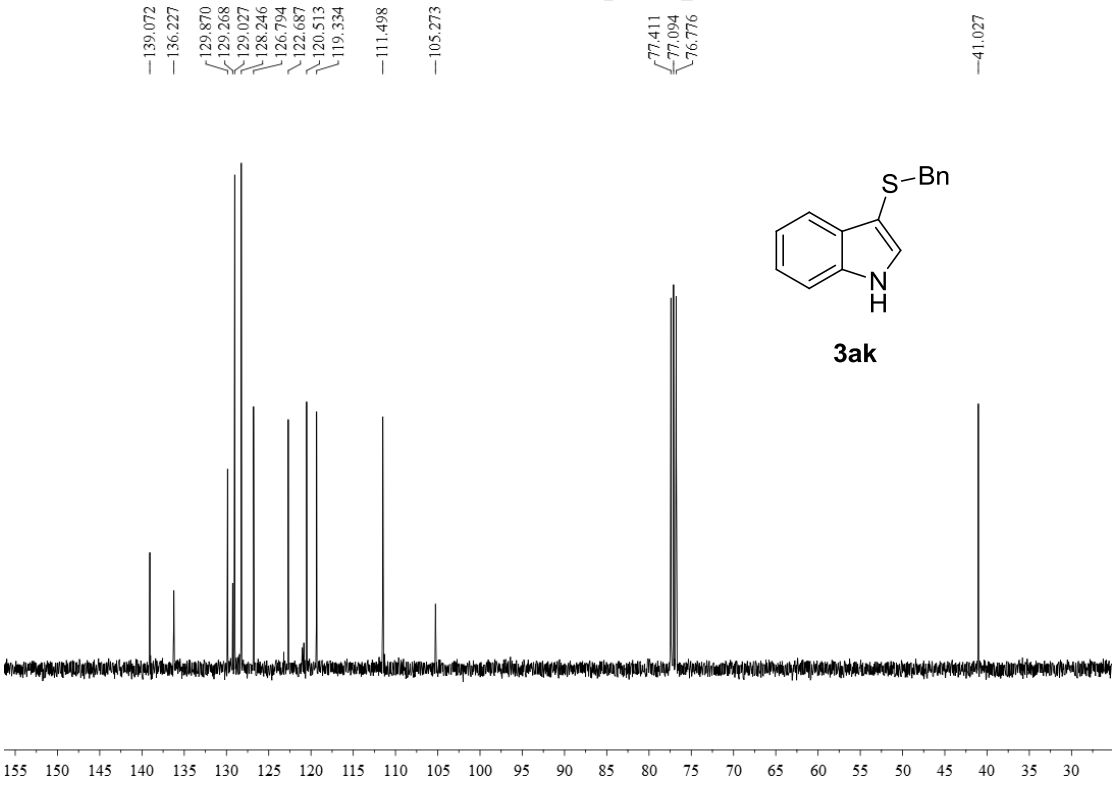

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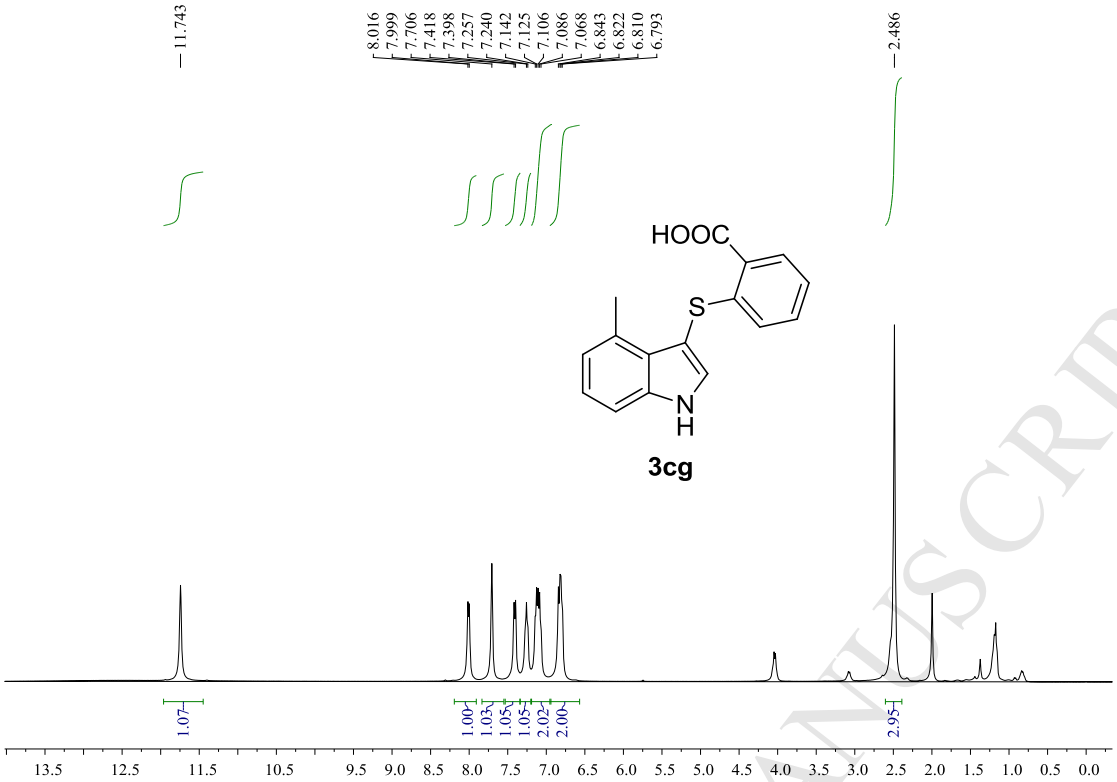

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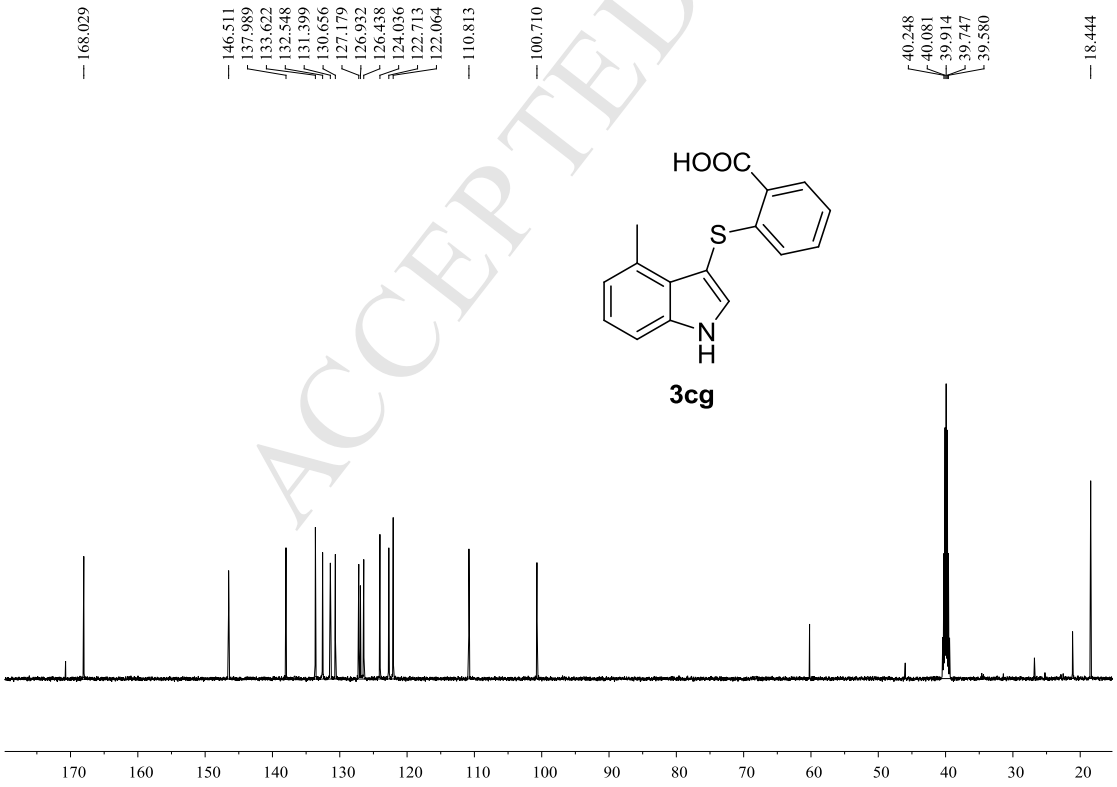

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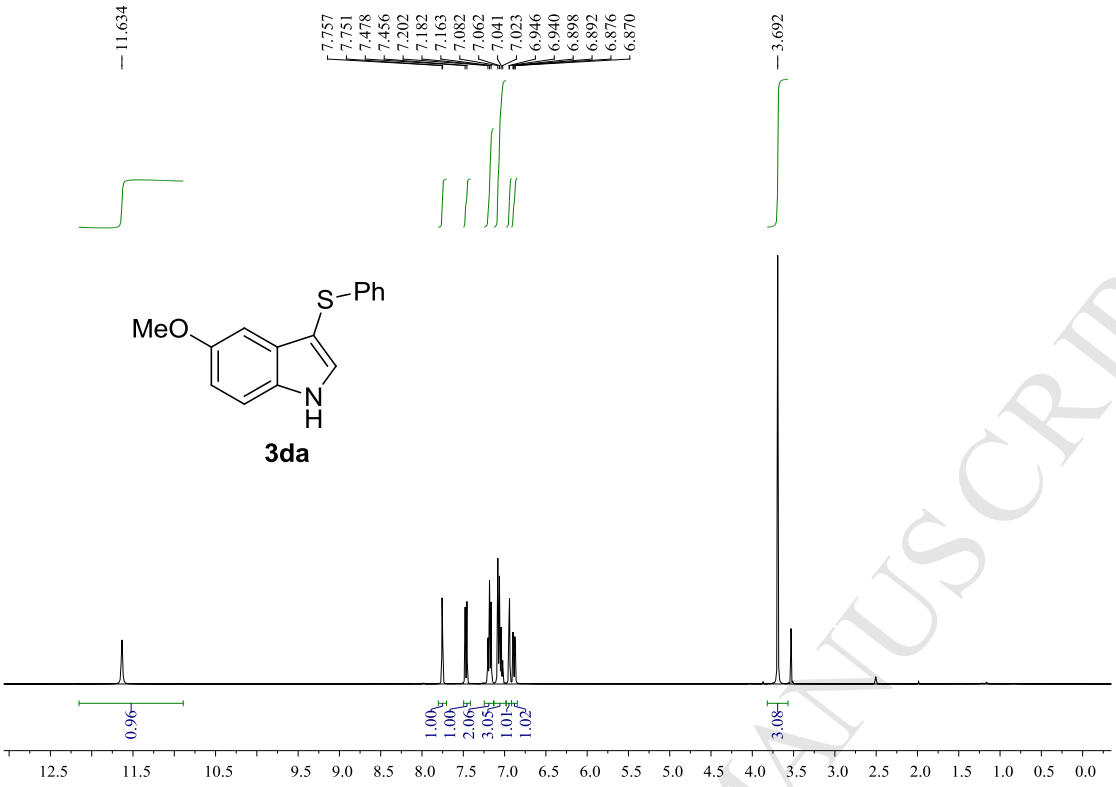

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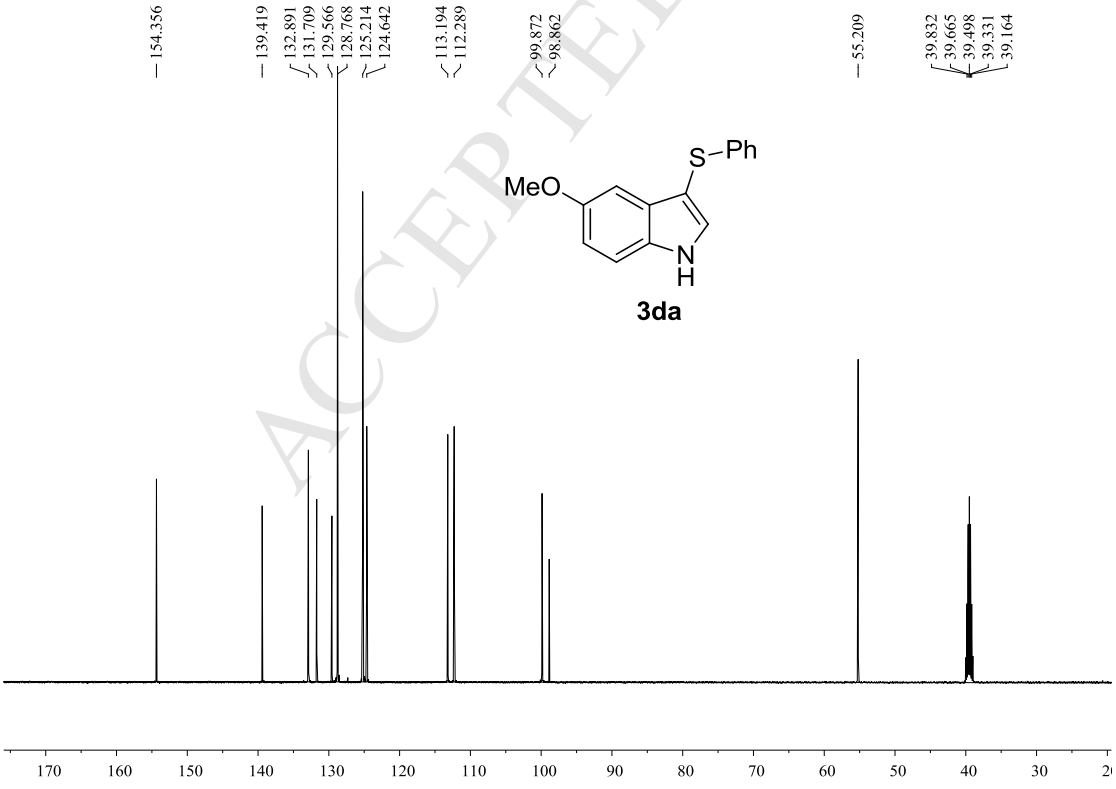

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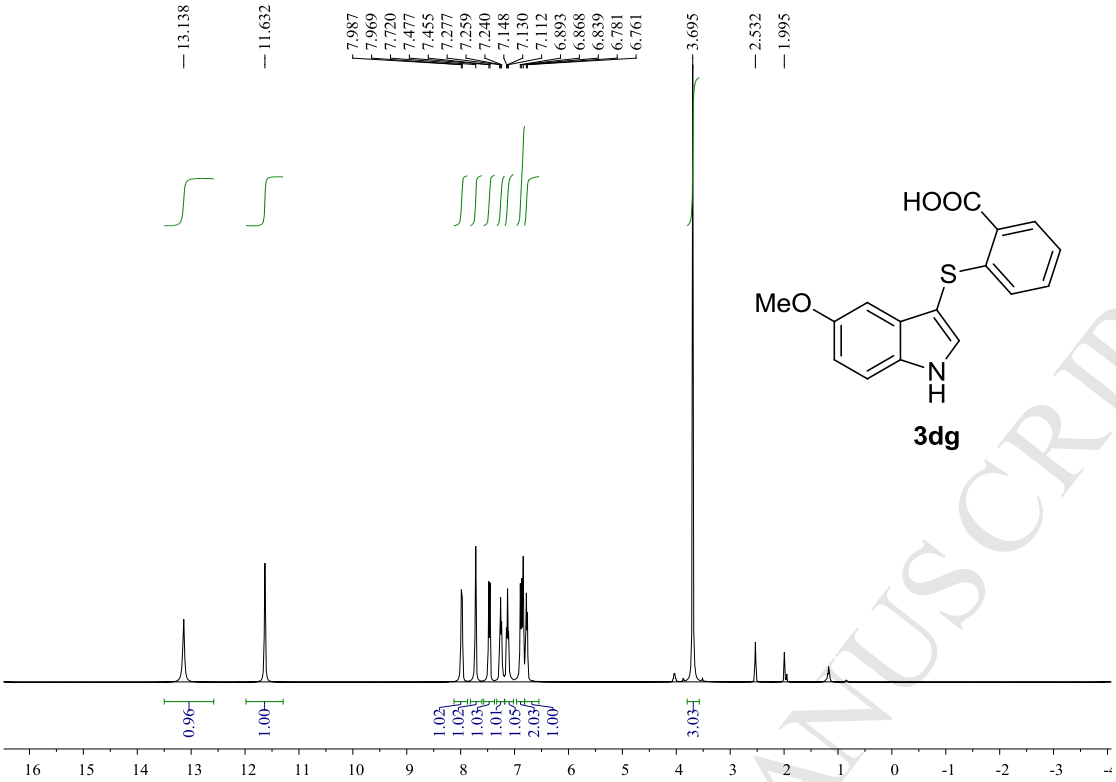

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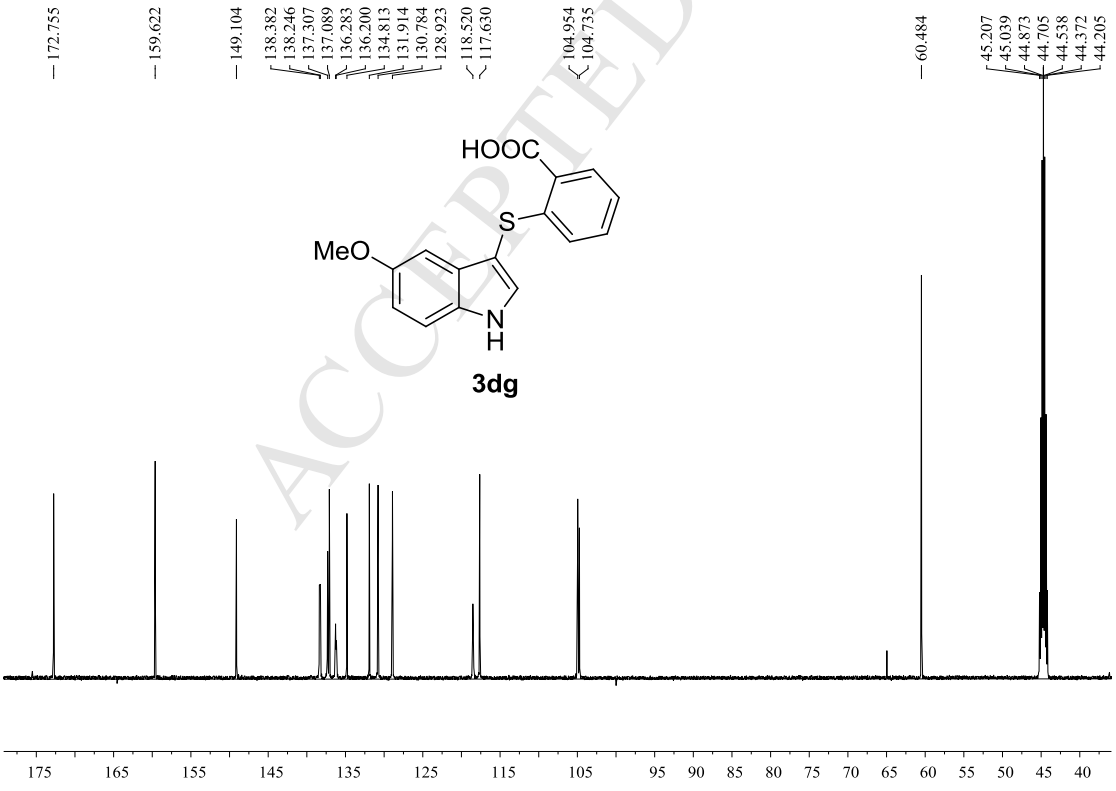

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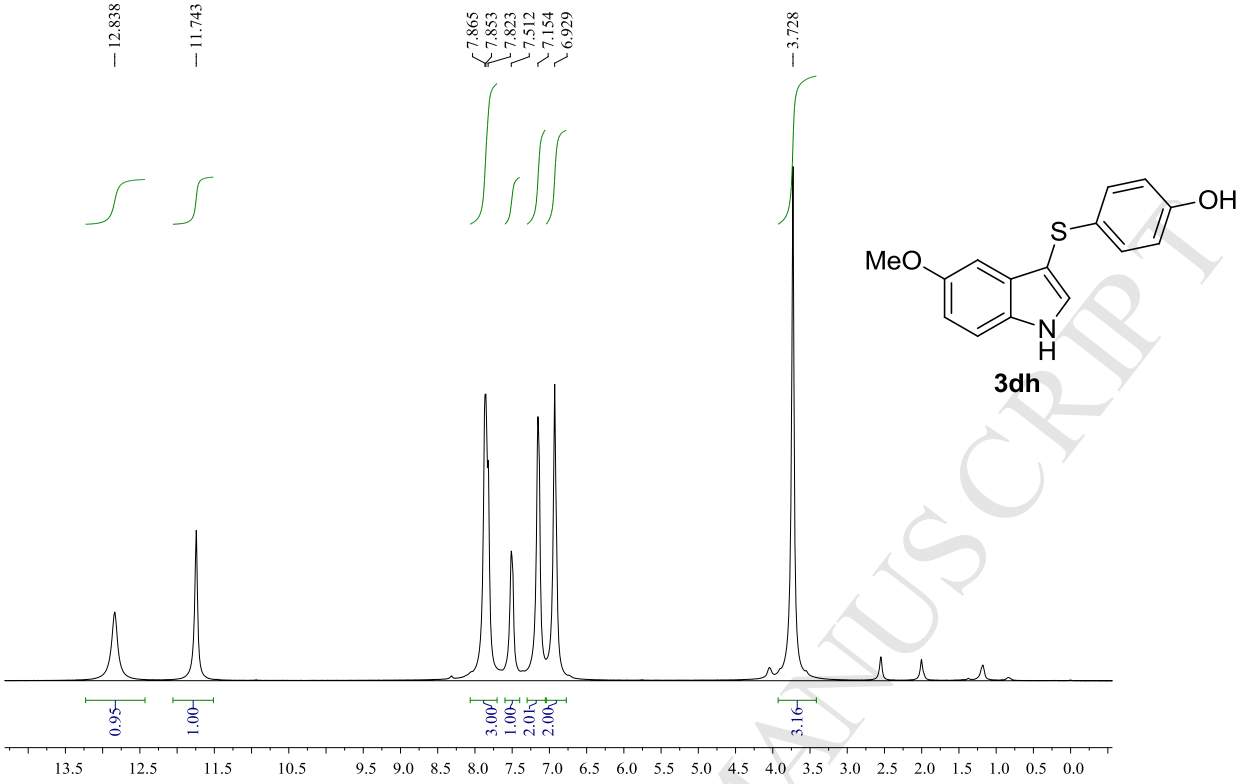

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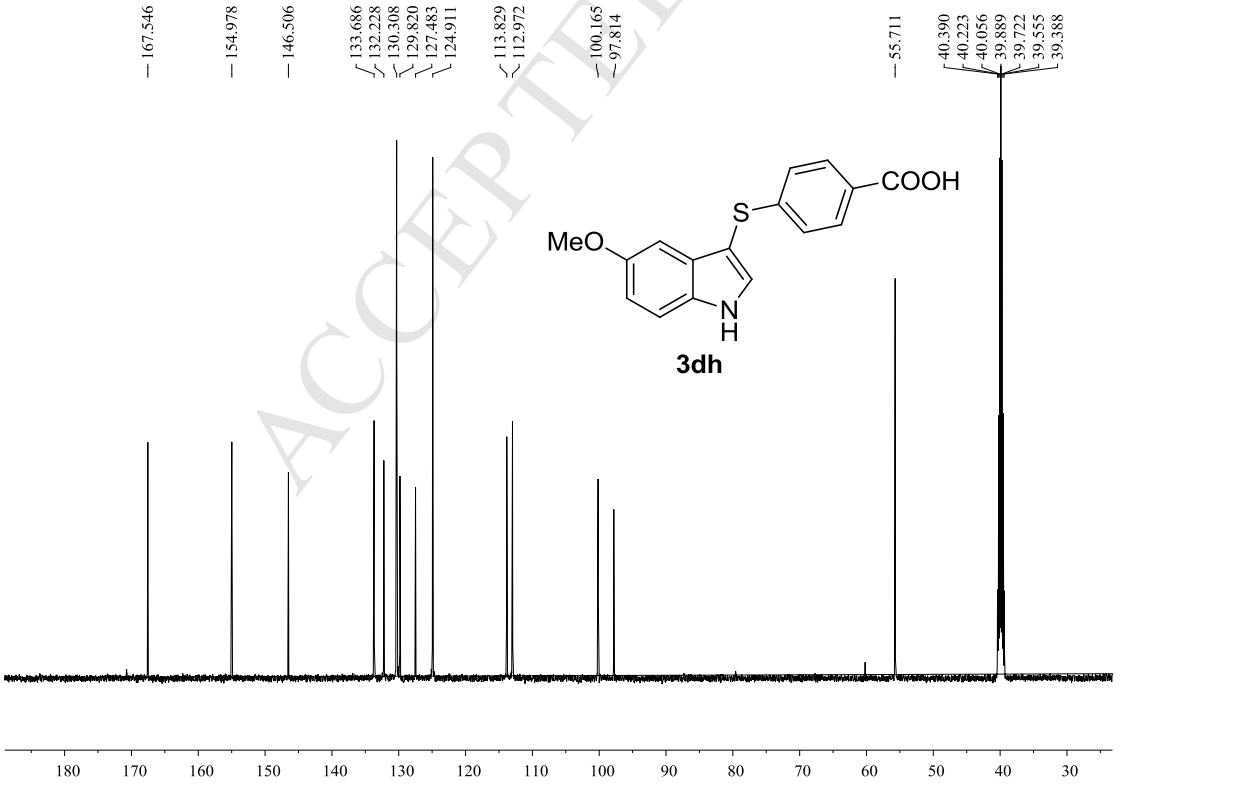

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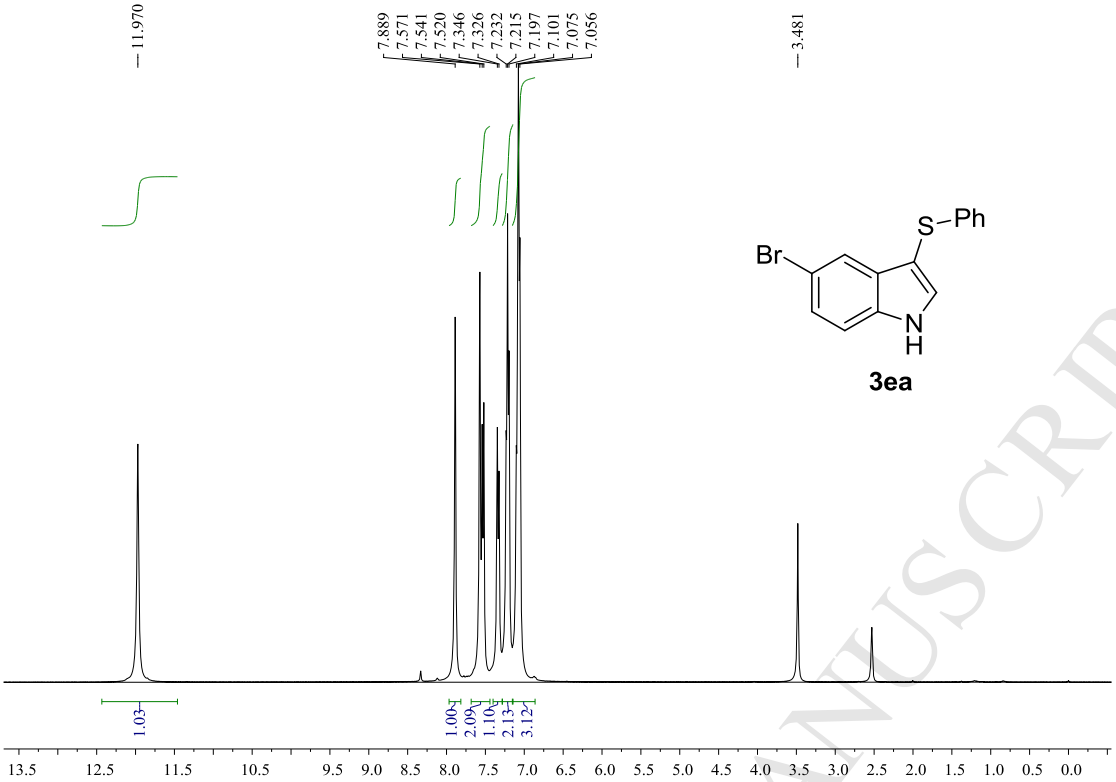

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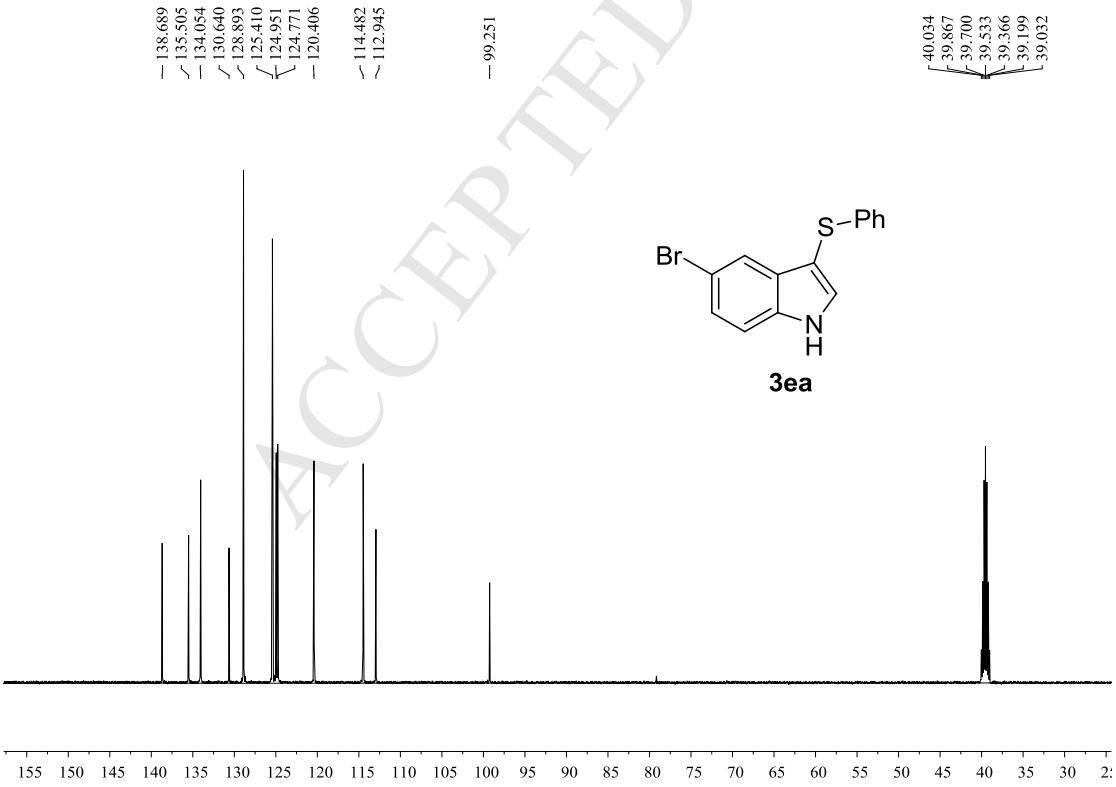

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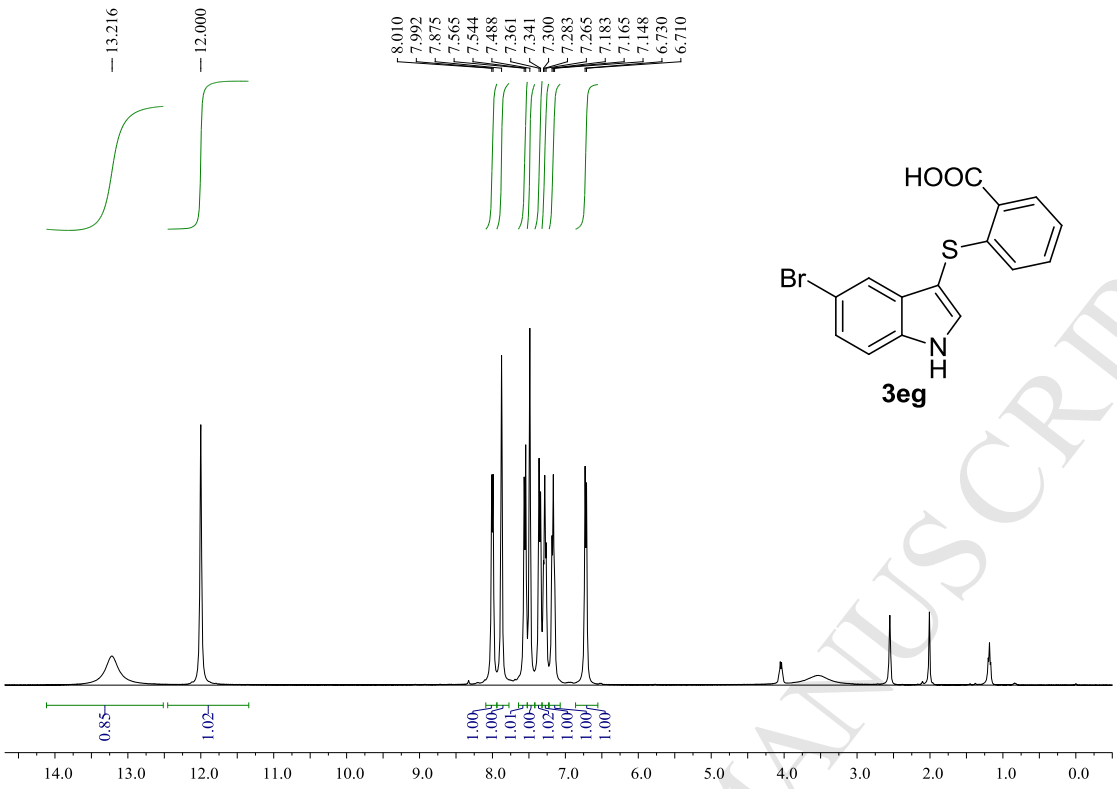

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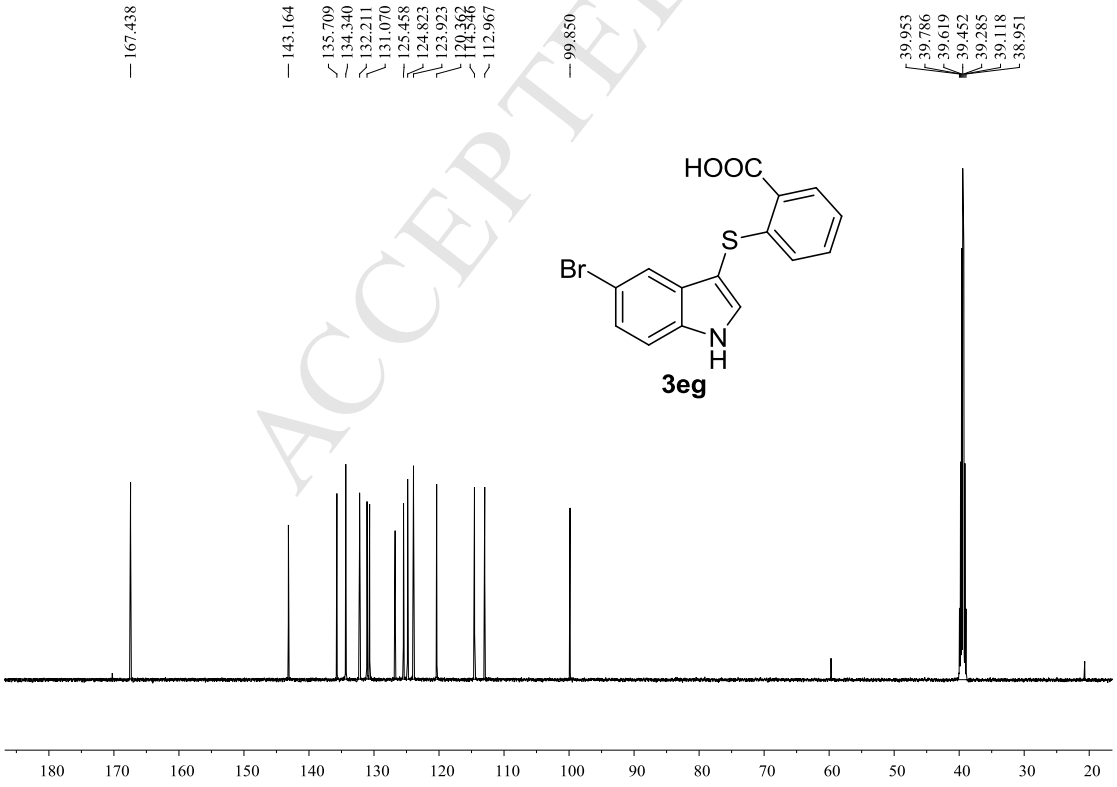

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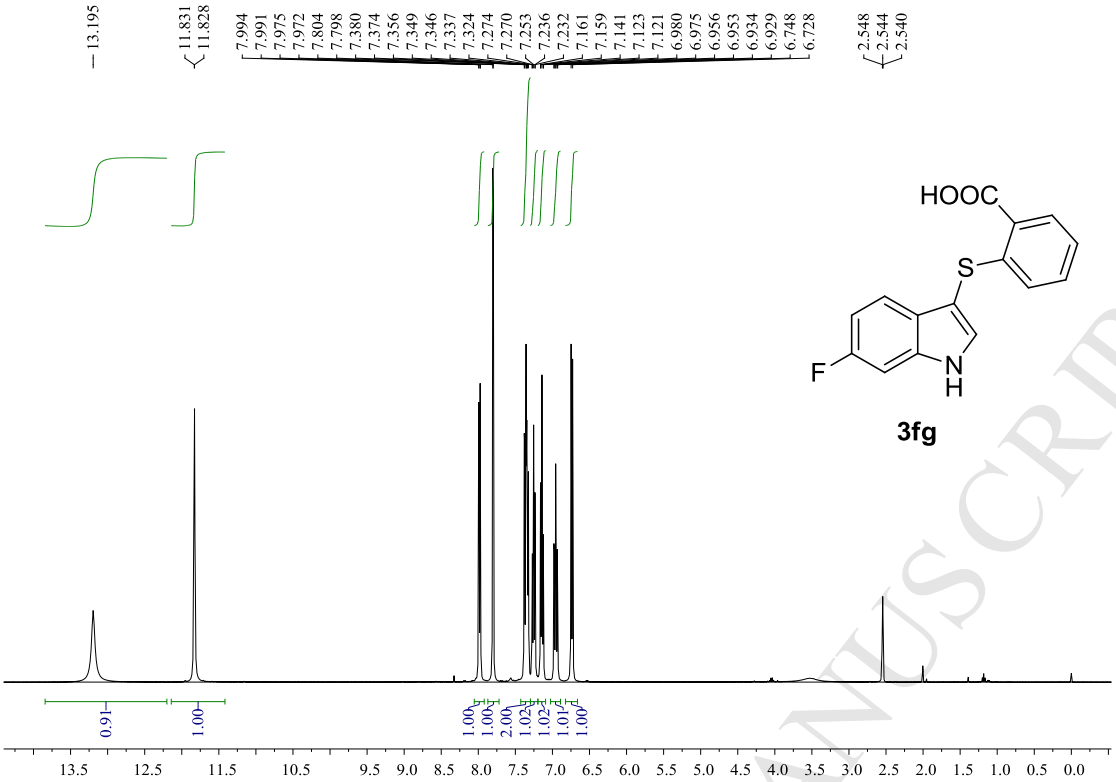

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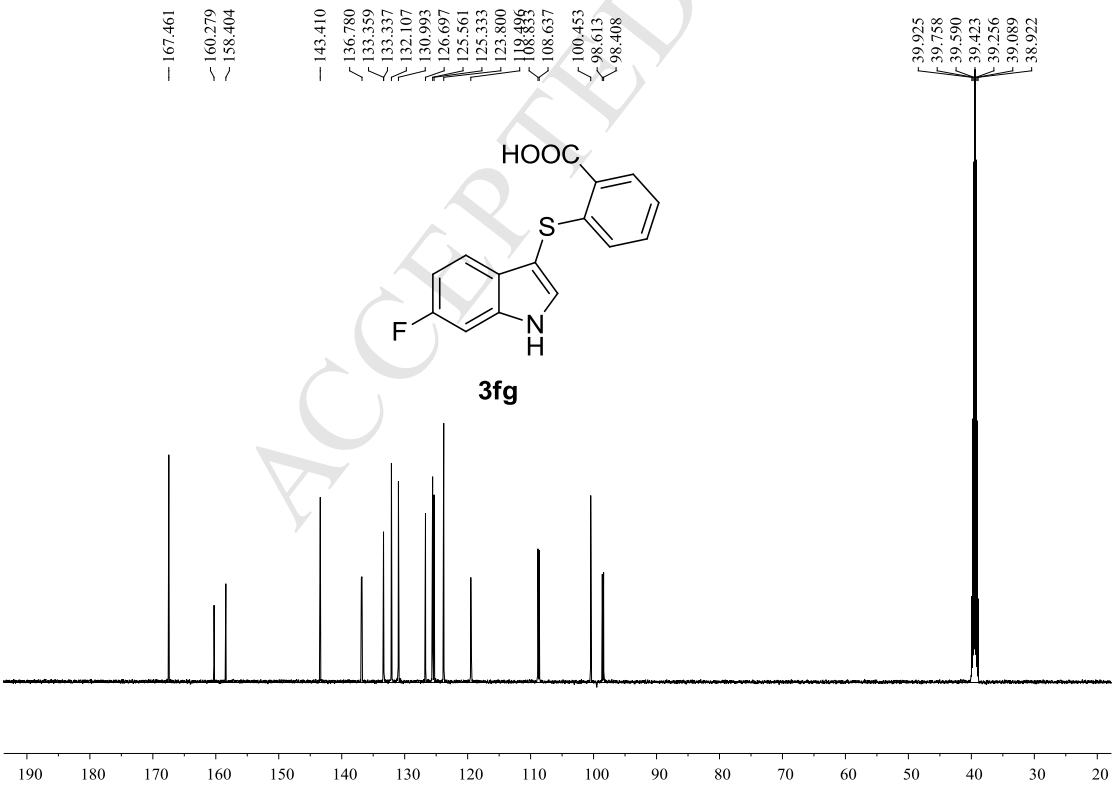

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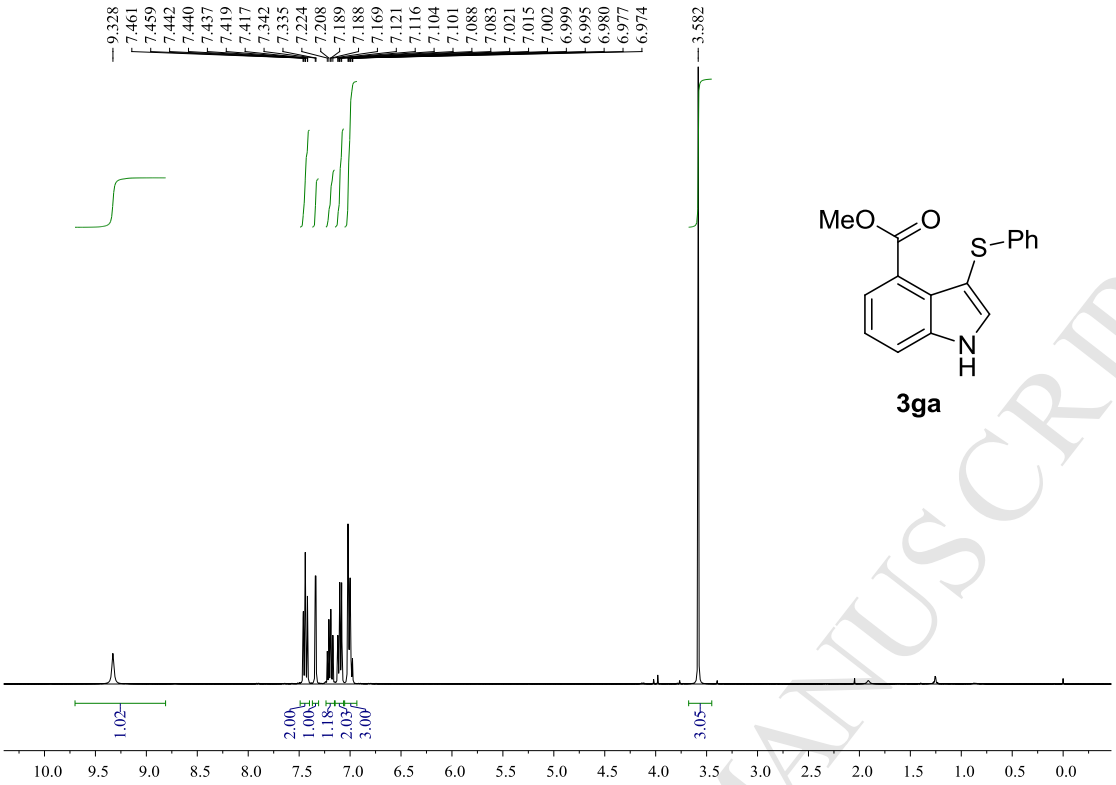

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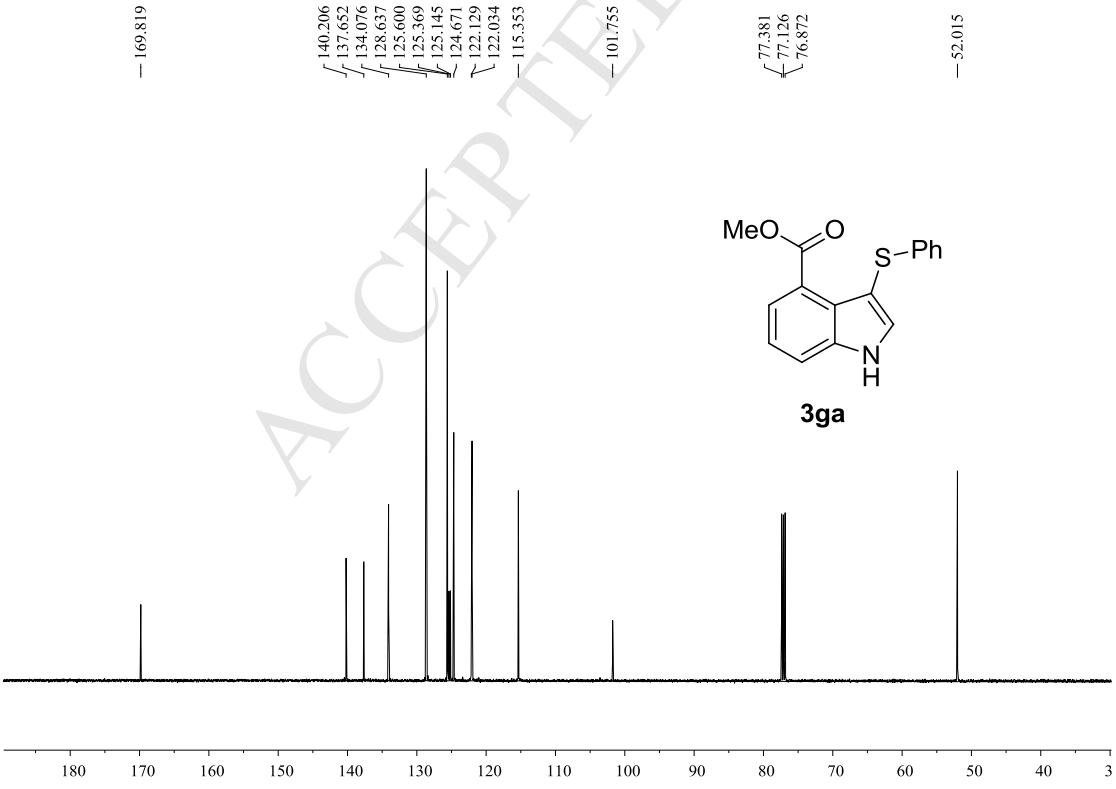
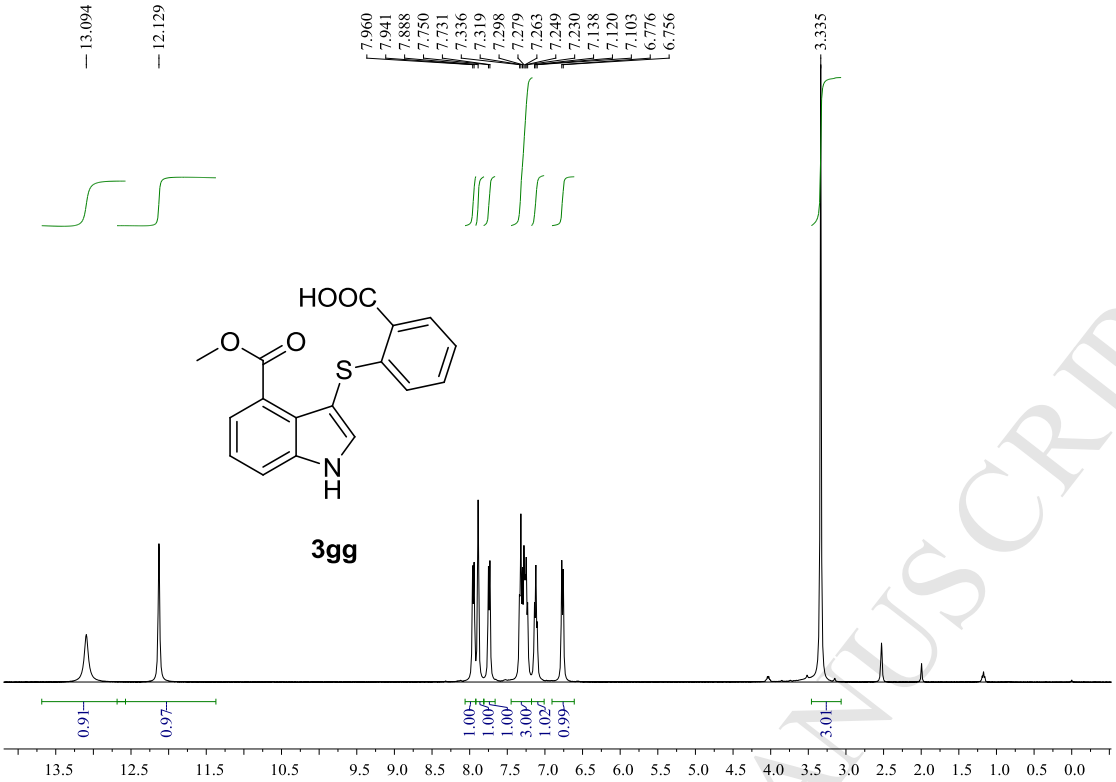
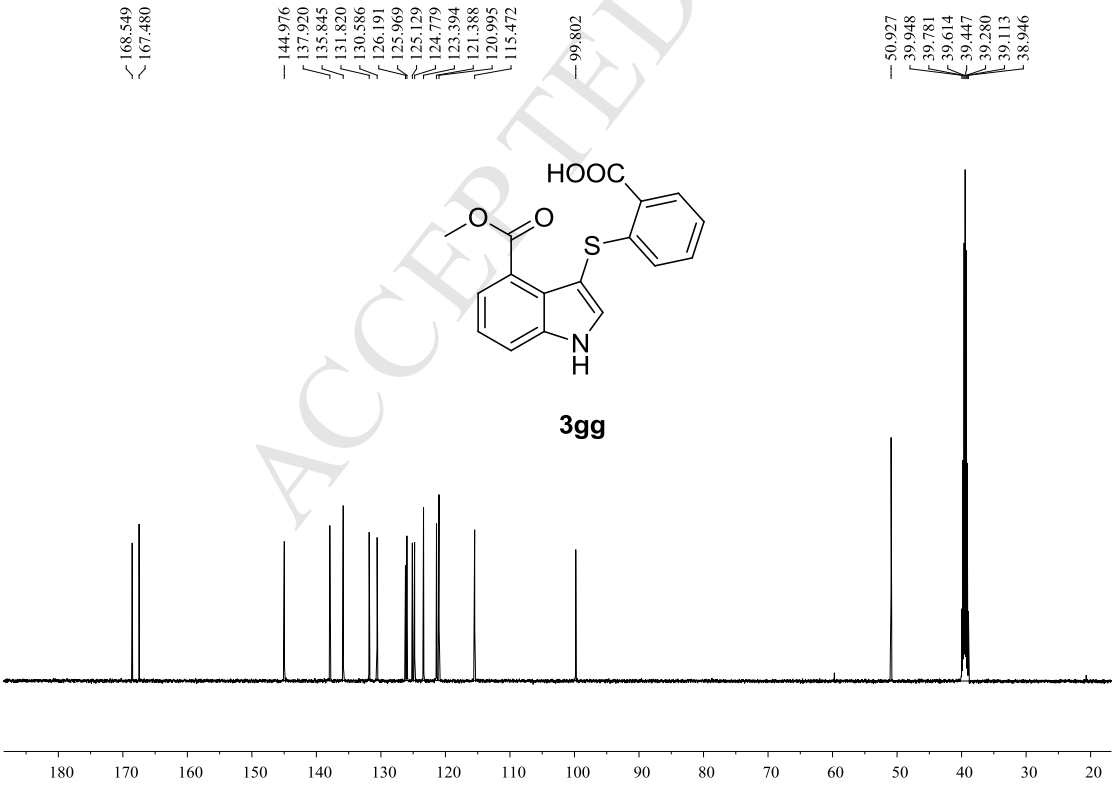


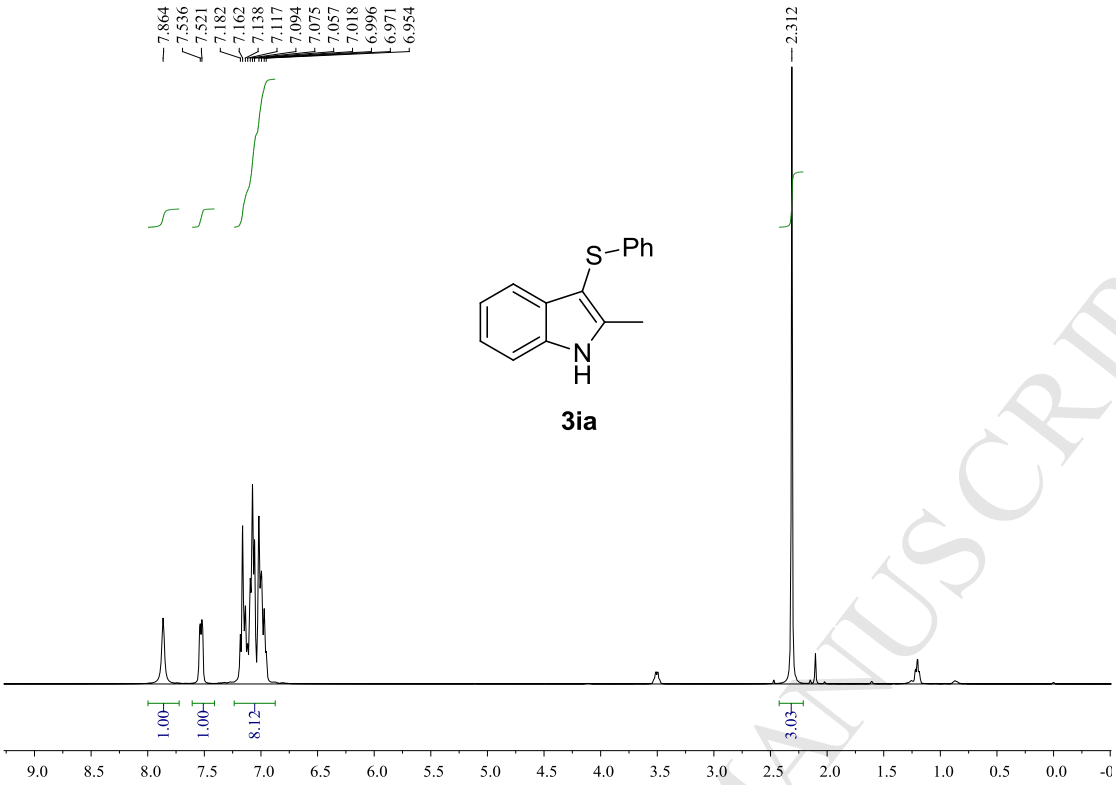
^{1}H NMR of 3gg



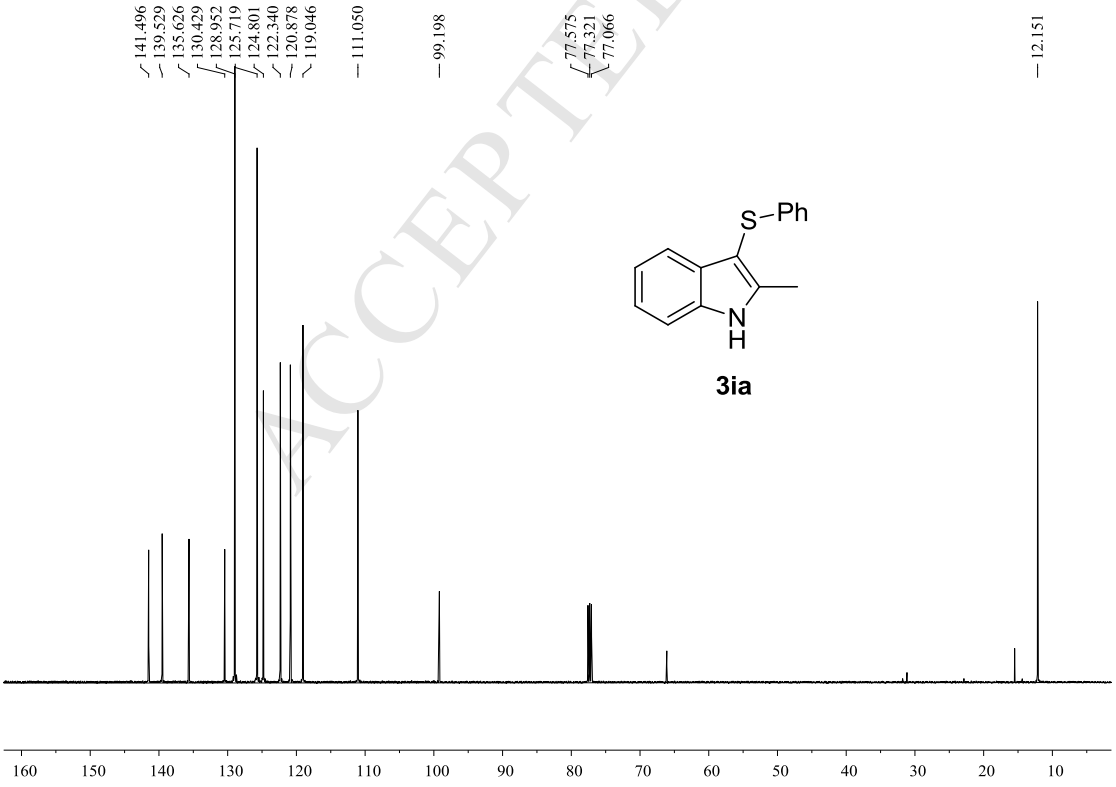
^{13}C NMR of 3gg



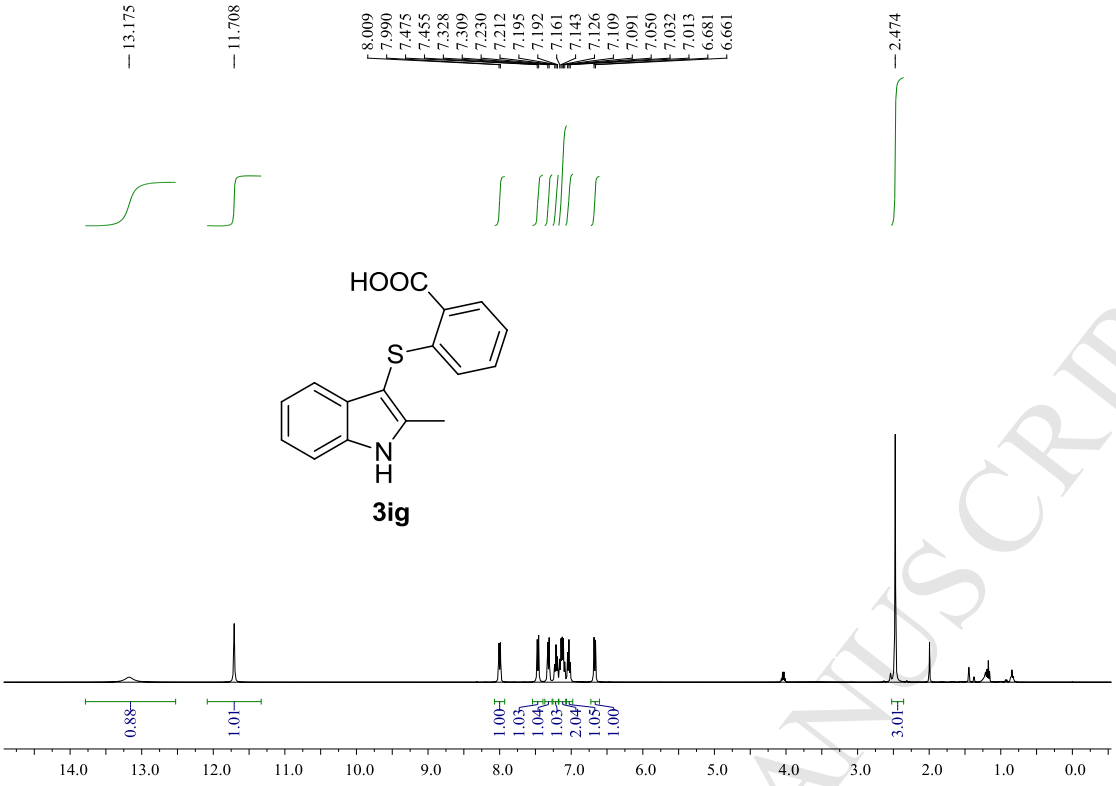
^{1}H NMR of 3ia



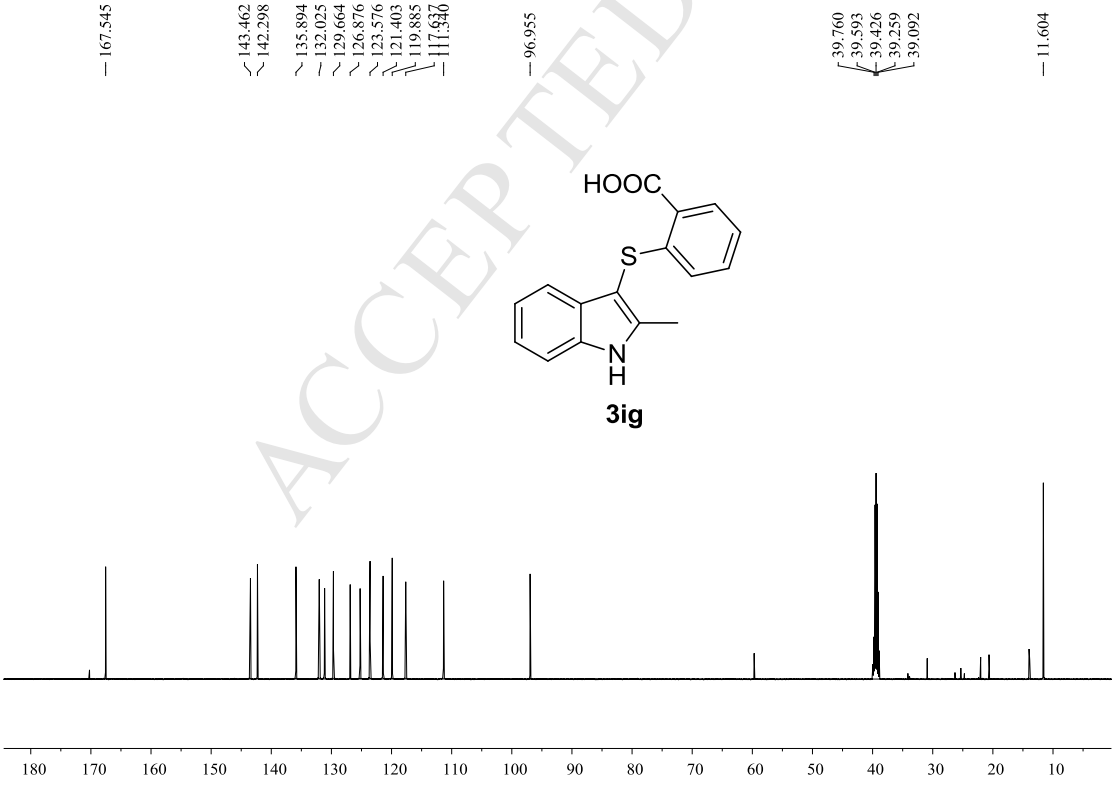
^{13}C NMR of 3ia



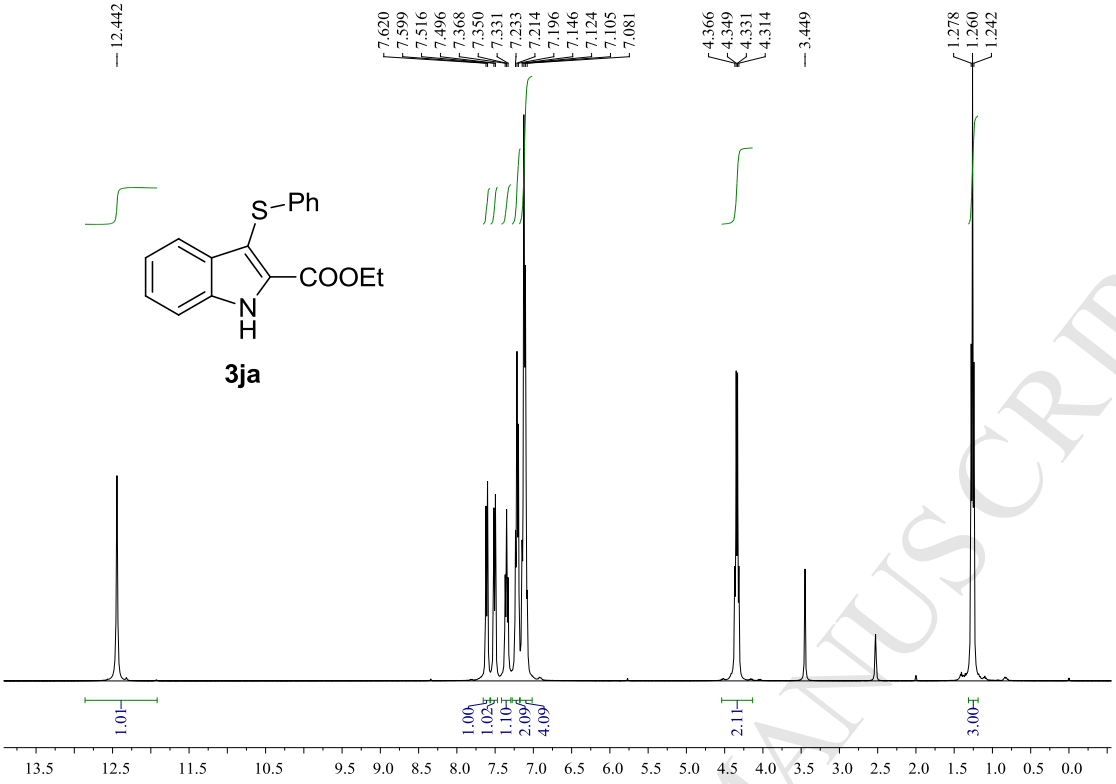
^{1}H NMR of 3ig



^{13}C NMR of 3ig



^{1}H NMR of 3ja



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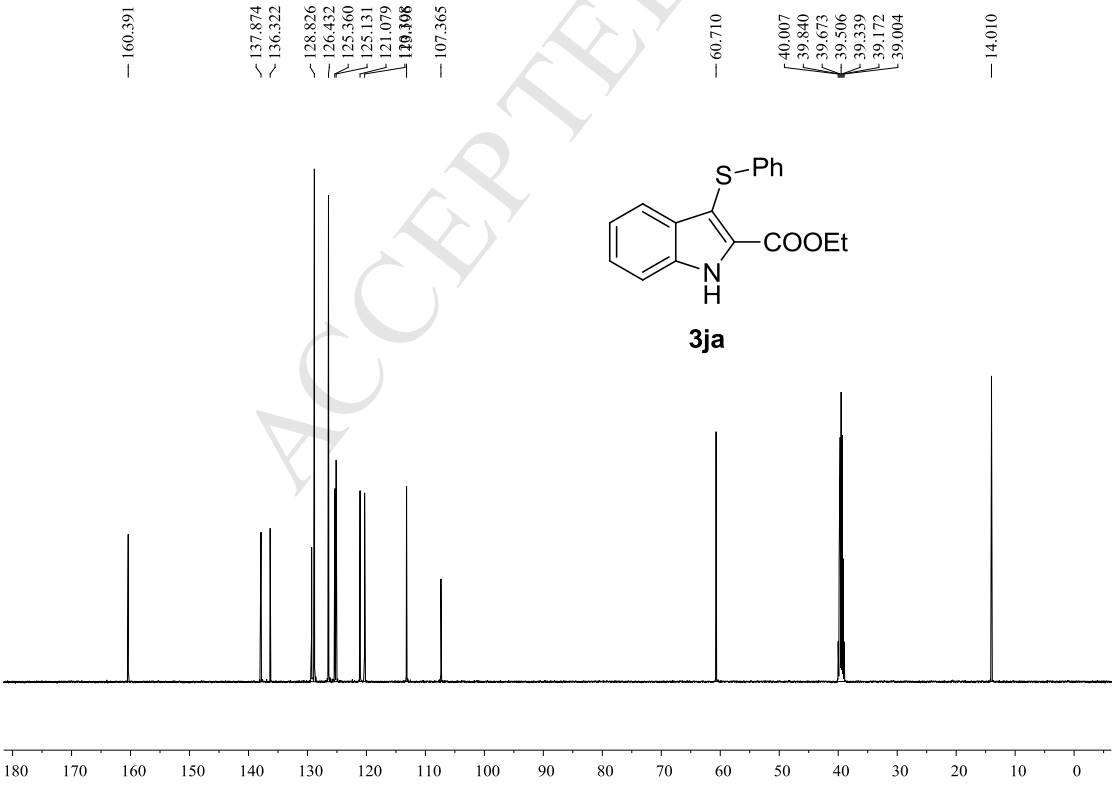
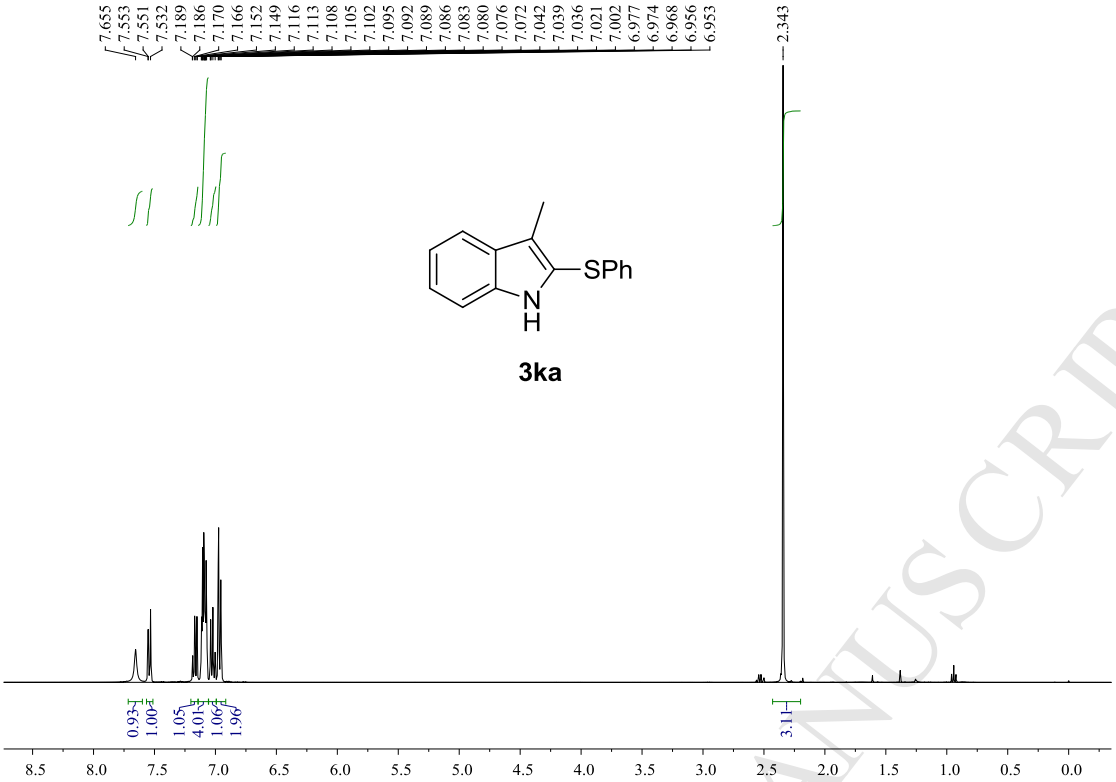
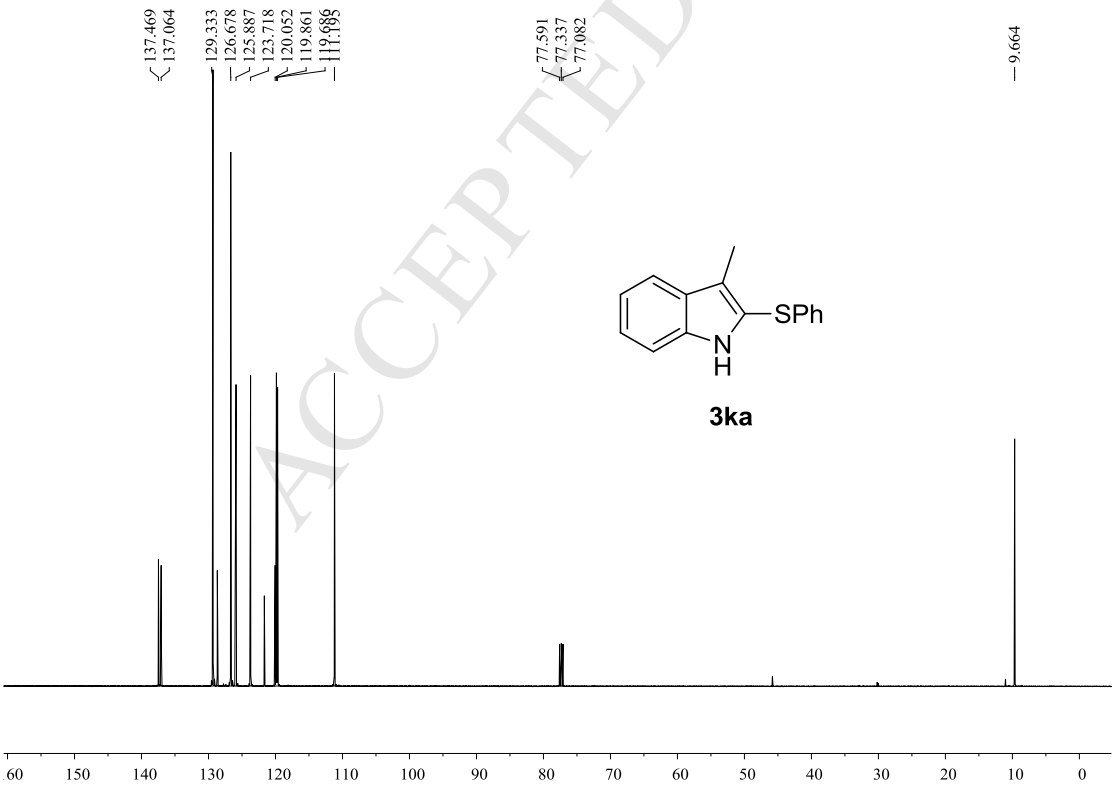


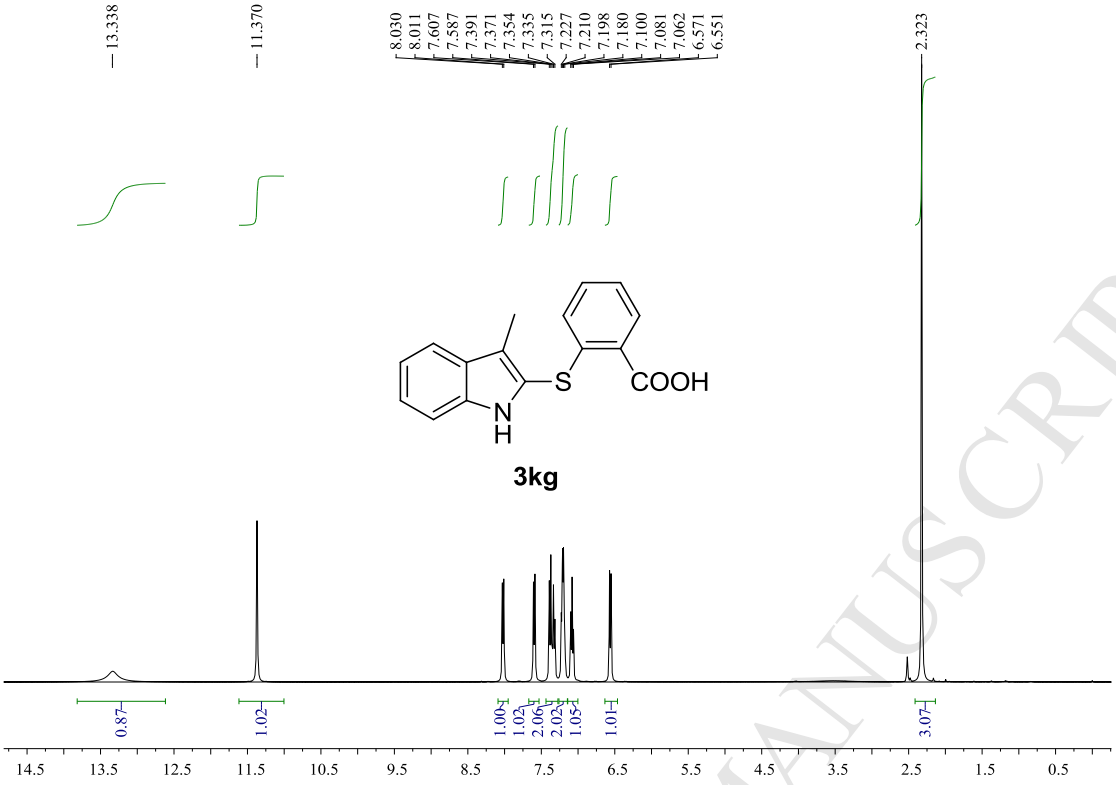
^{1}H NMR of 3ka



^{13}C NMR of 3ka



^{1}H NMR of 3kg



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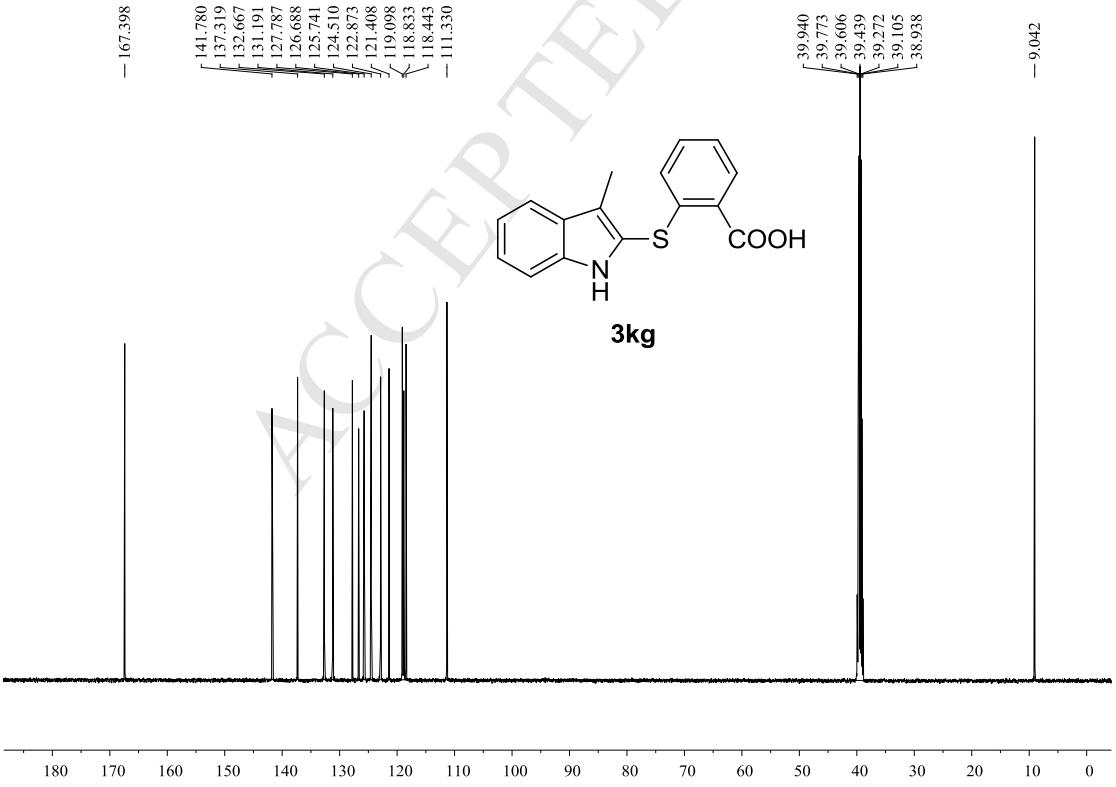
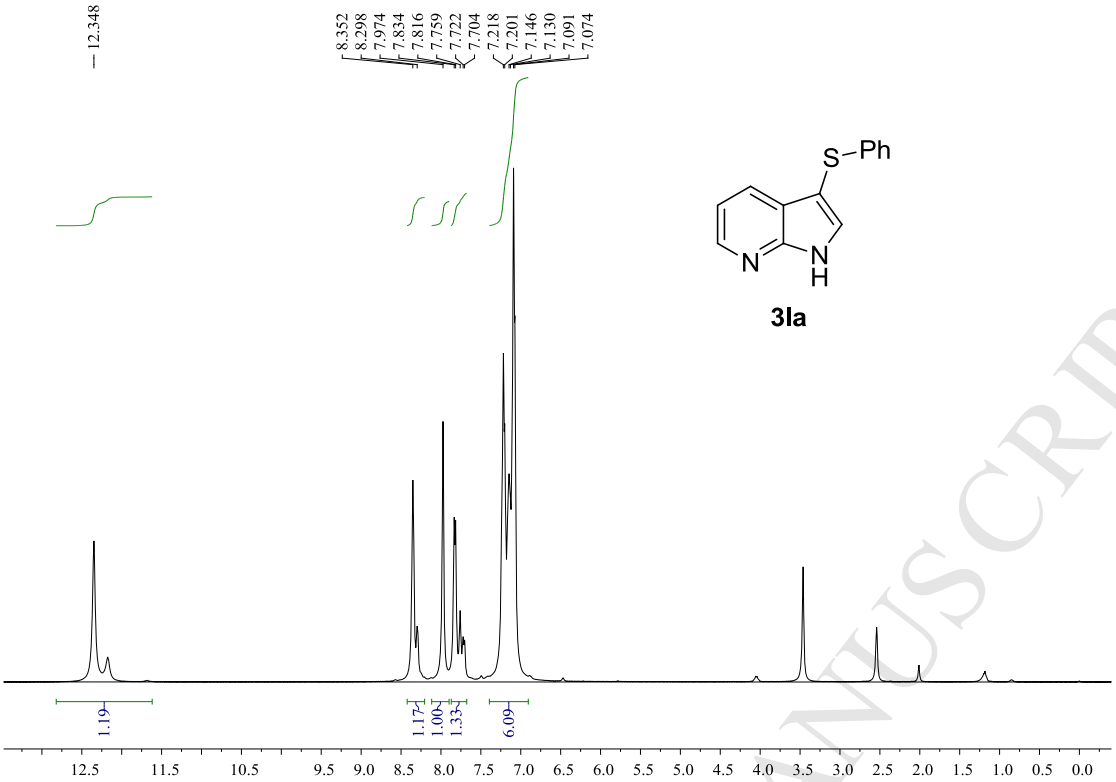


^{1}H NMR of 3la



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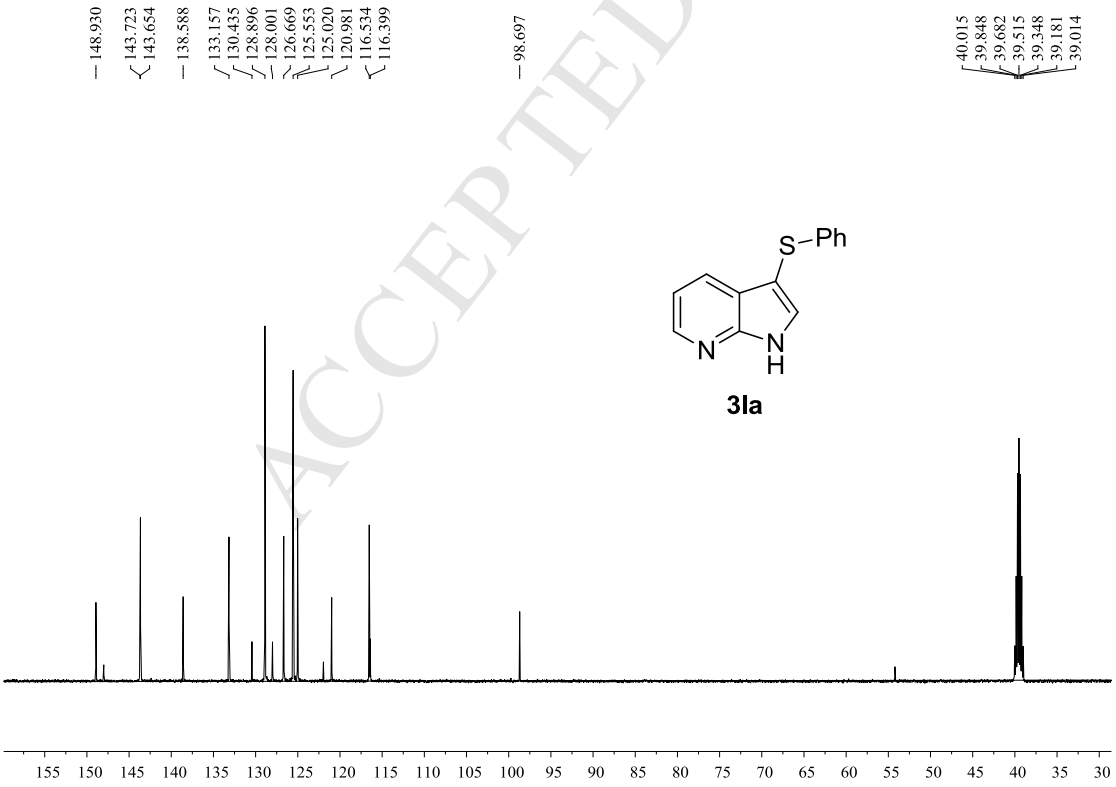
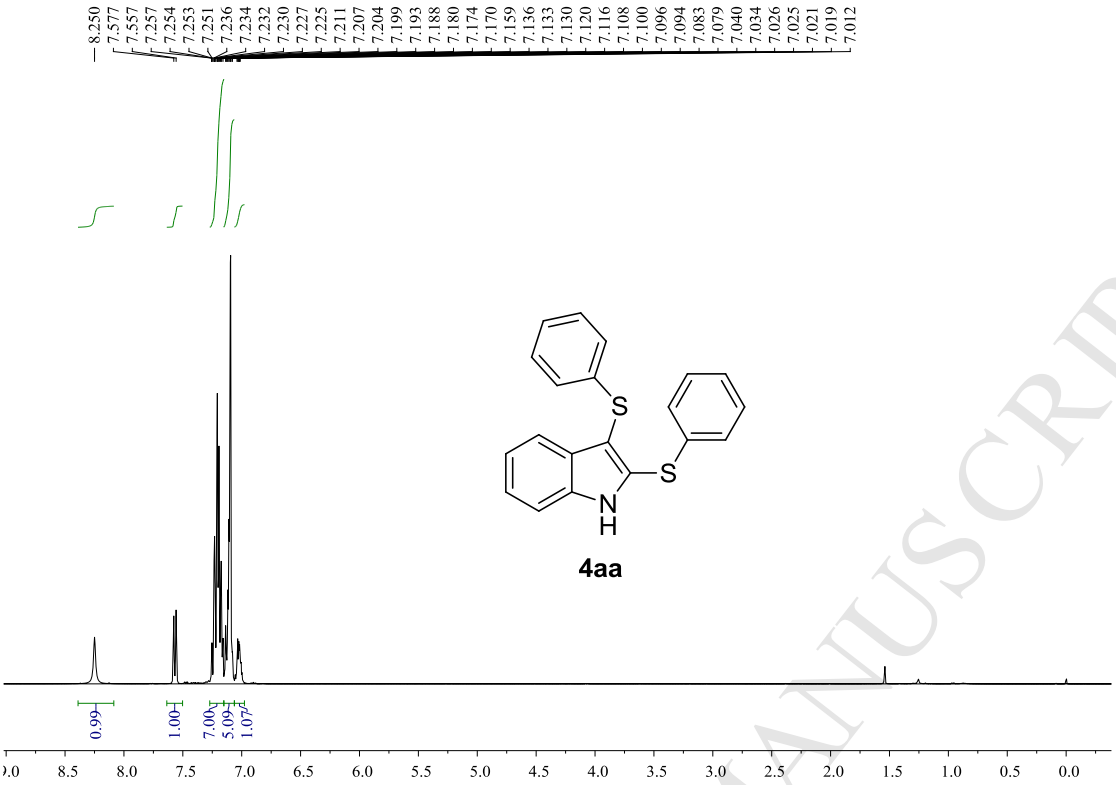
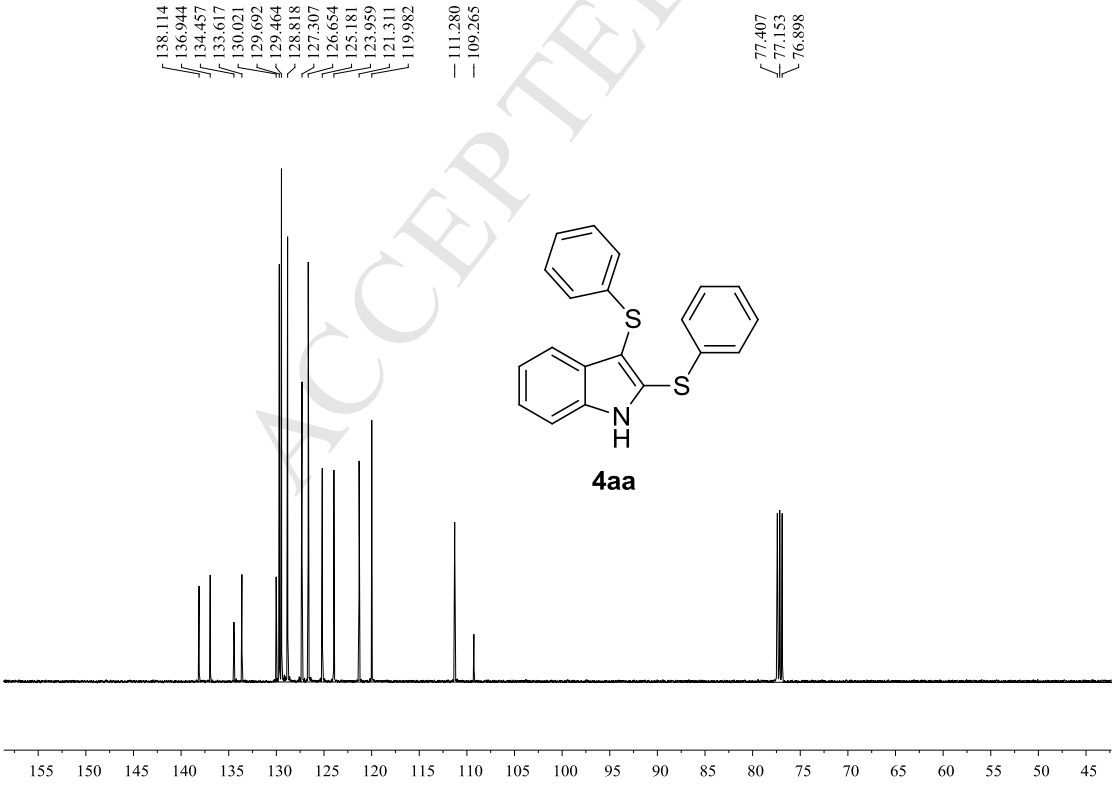


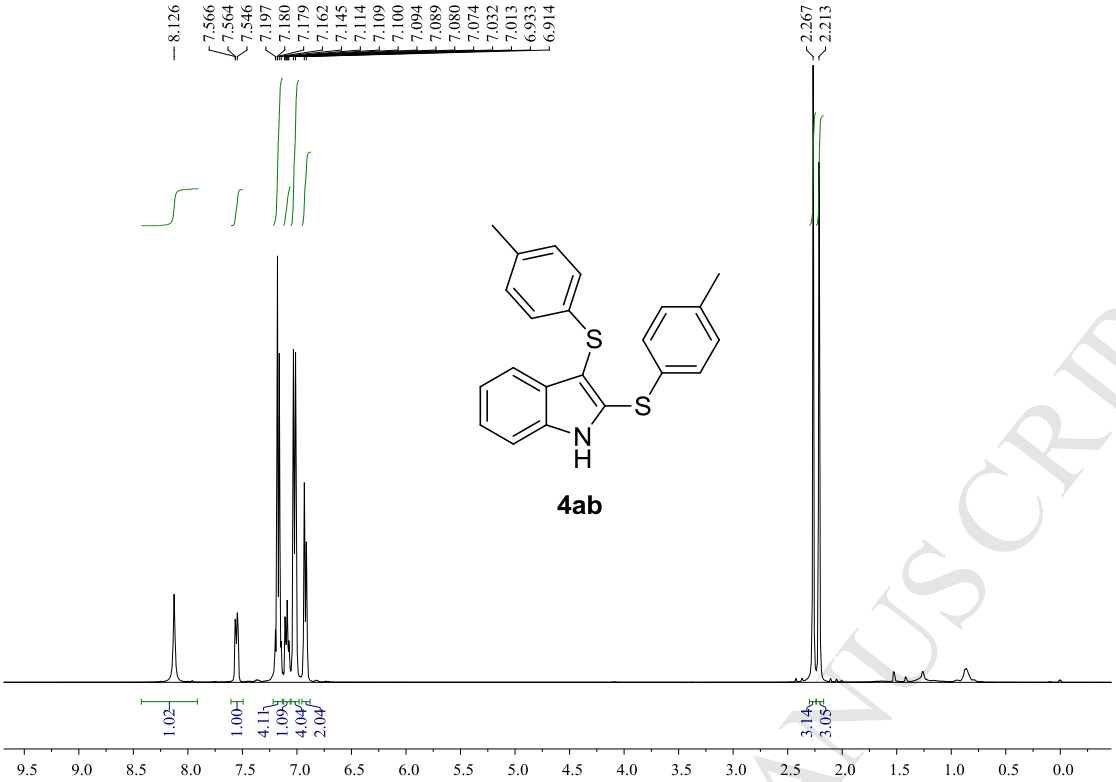
^{1}H NMR of 4aa



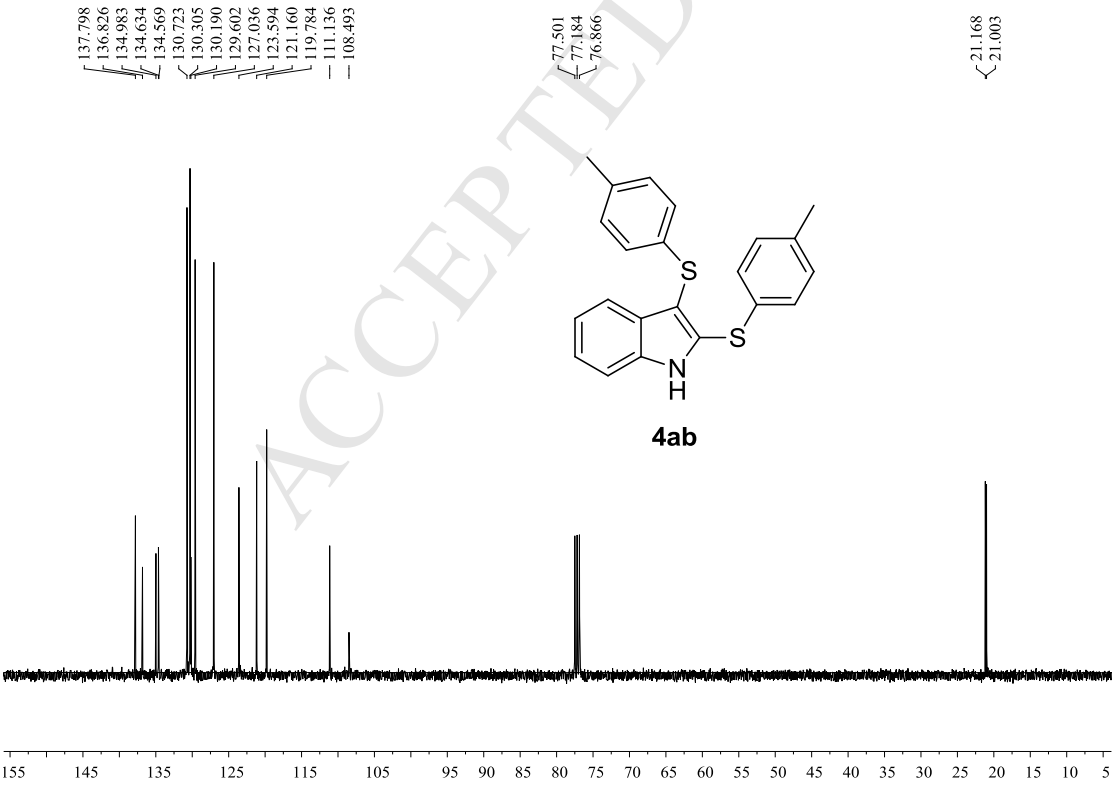
^{13}C NMR of 4aa



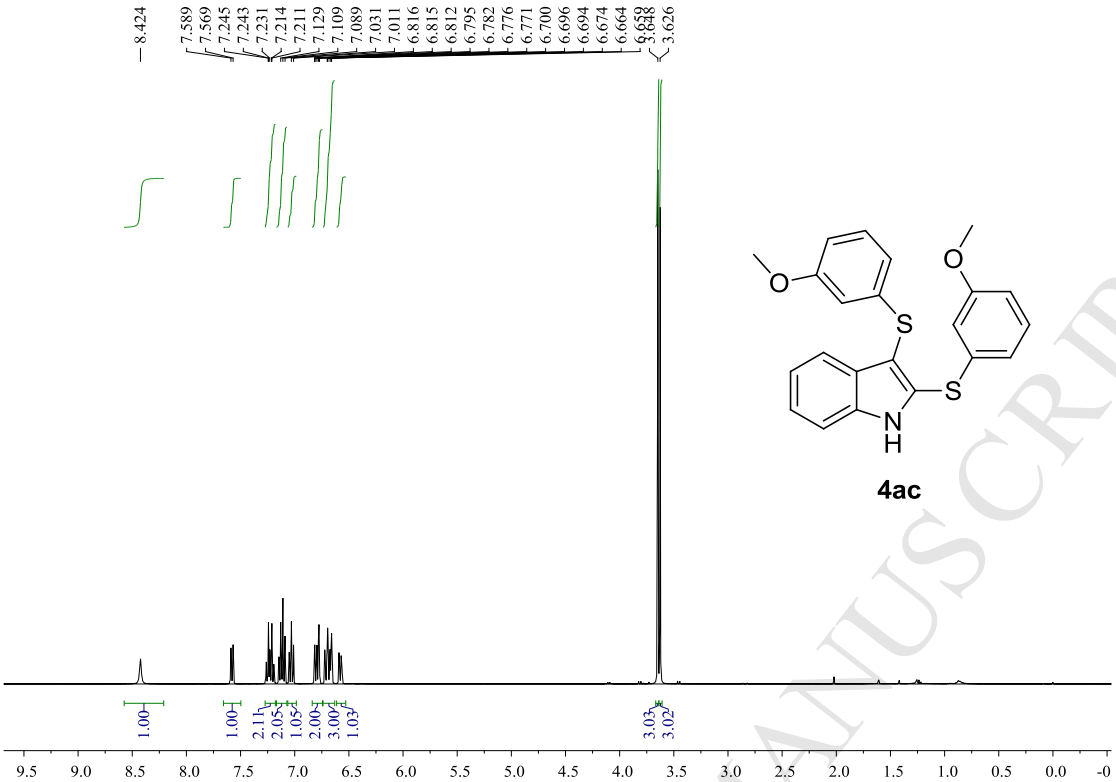
^{1}H NMR of 4ab



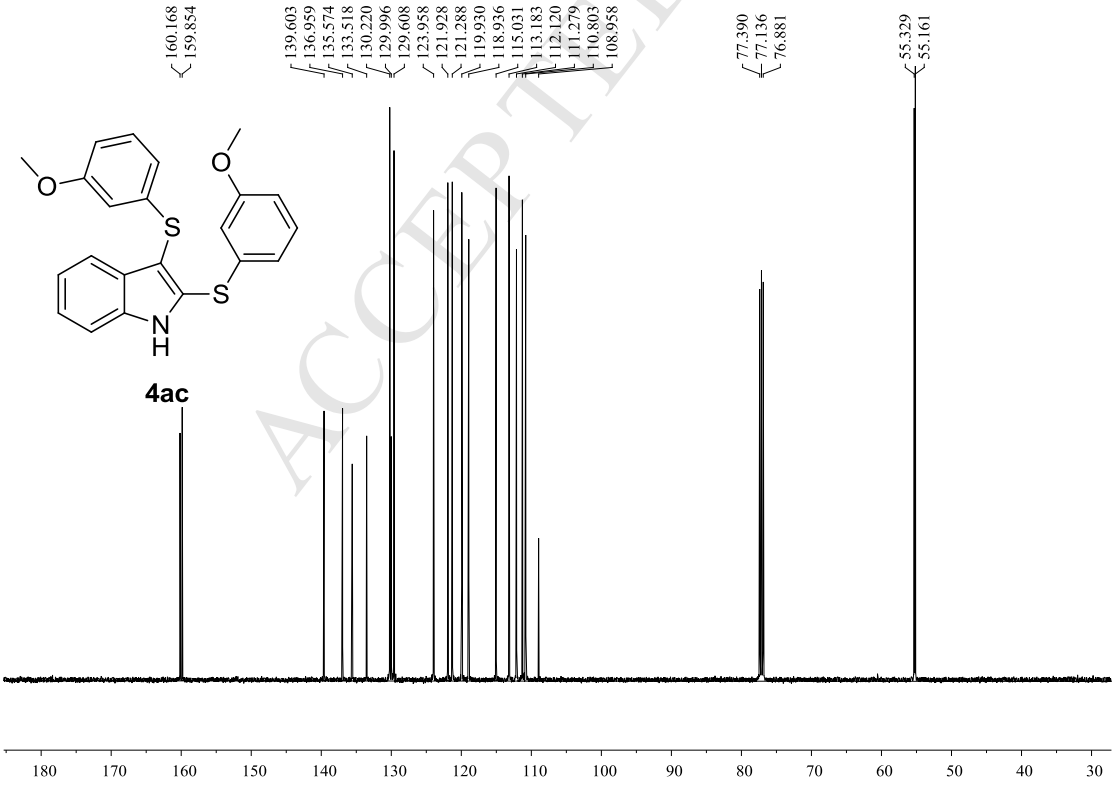
^{13}C NMR of 4ab



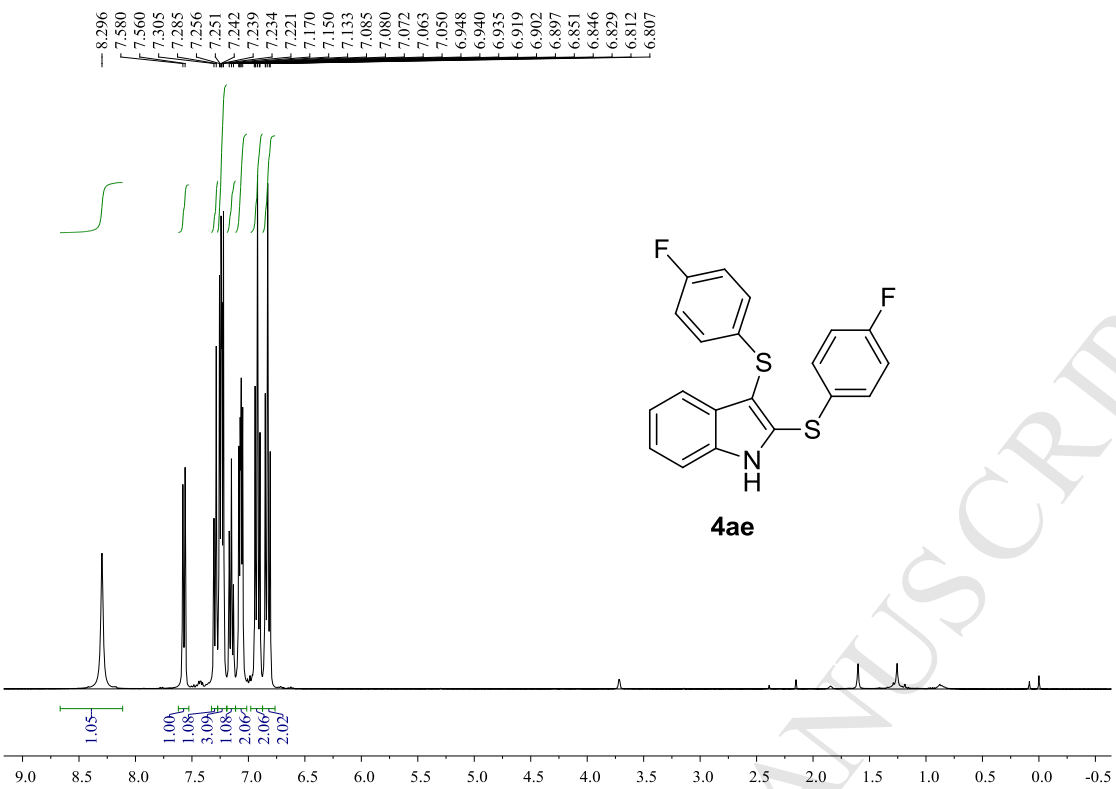
^{1}H NMR of 4ac



^{13}C NMR of 4ac



^{1}H NMR of 4ae



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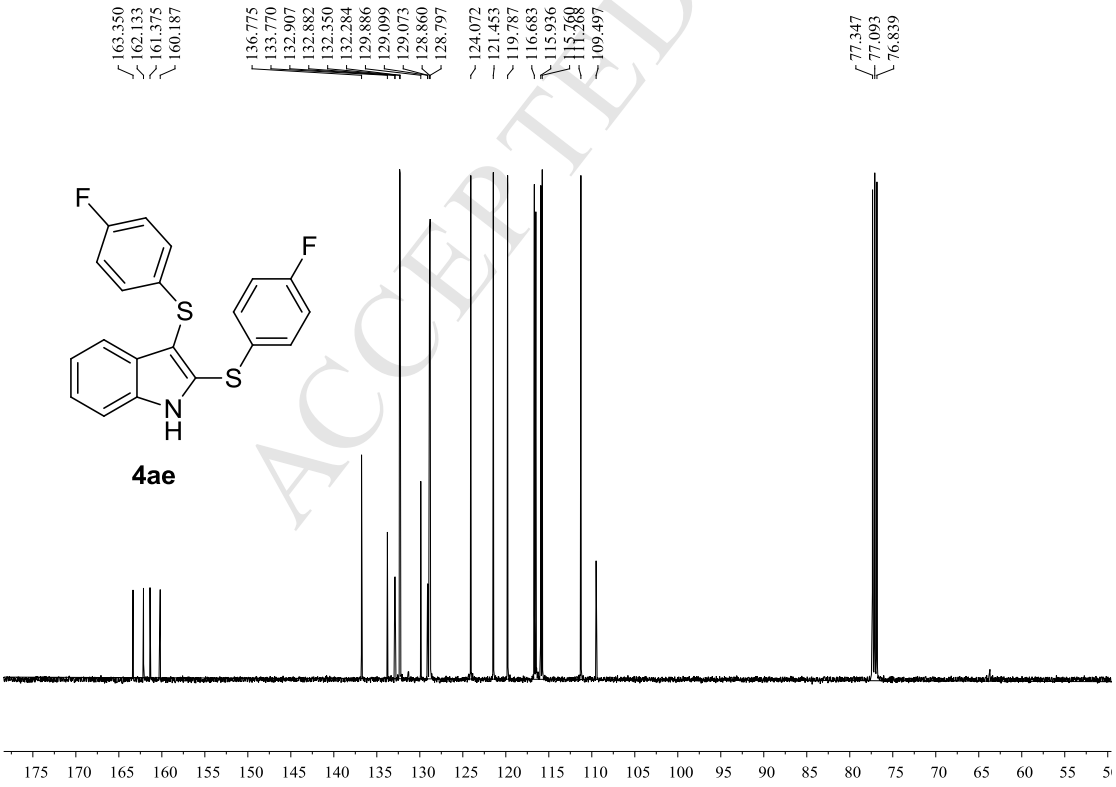

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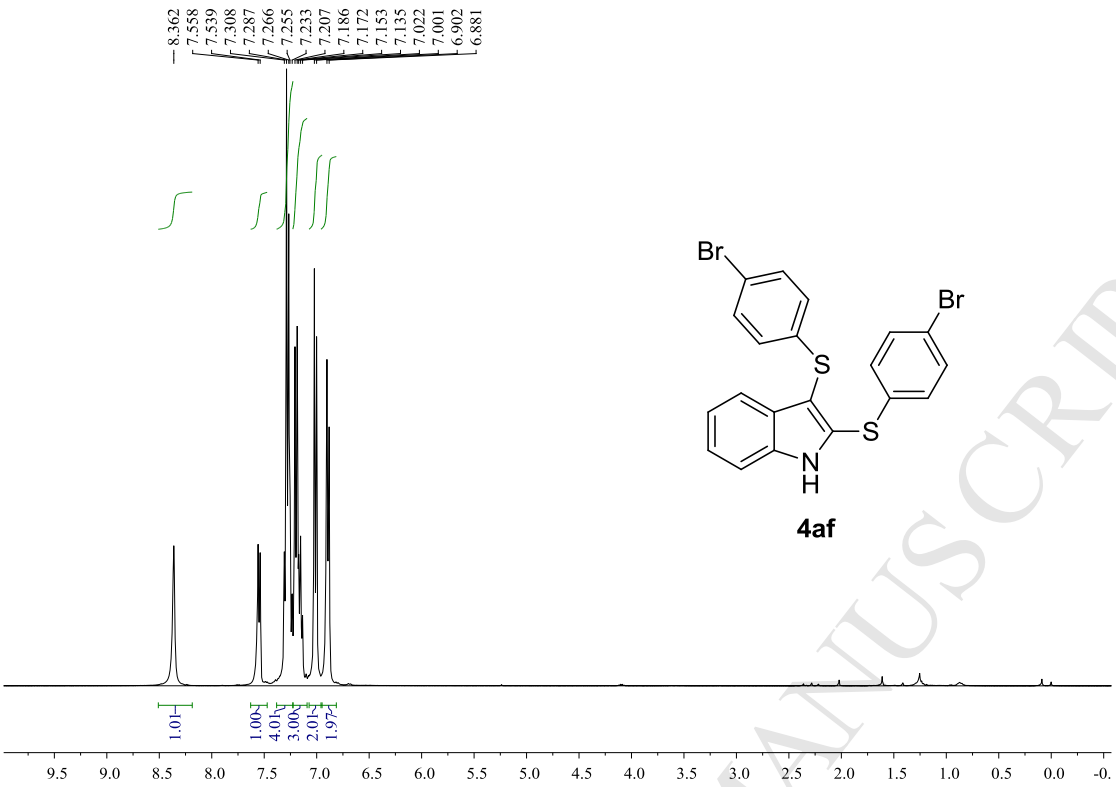

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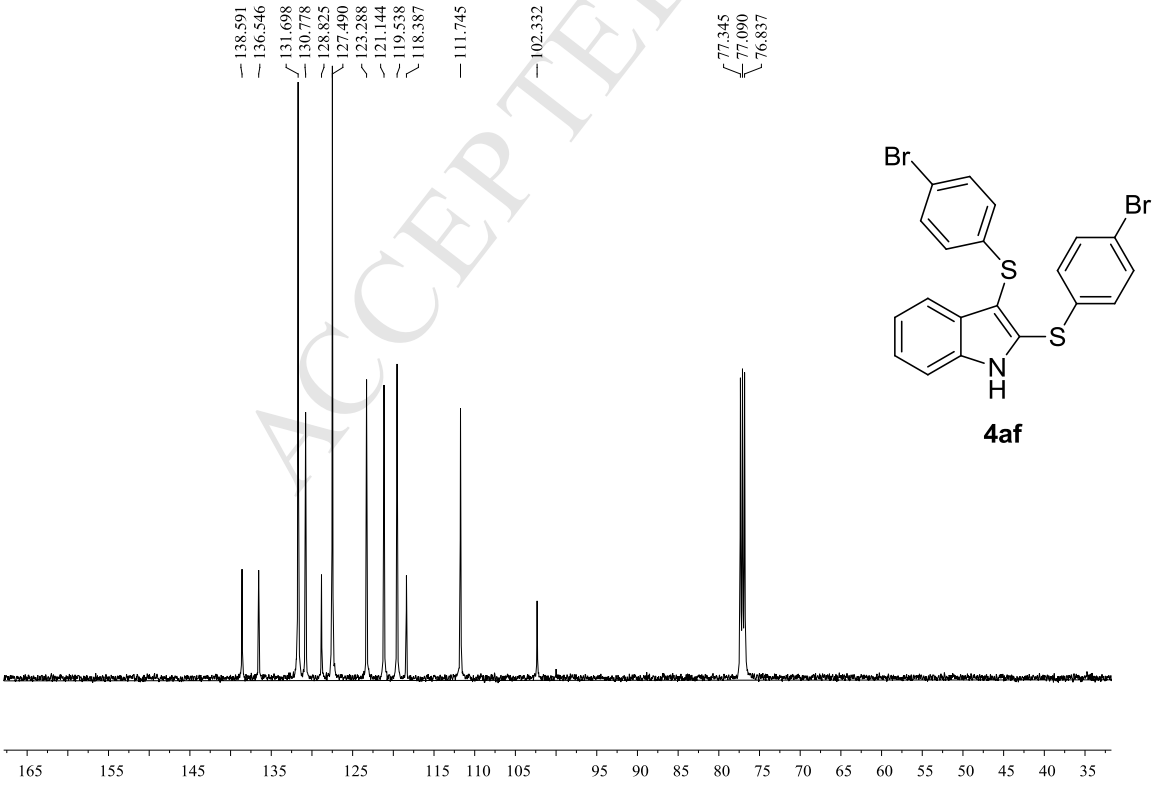
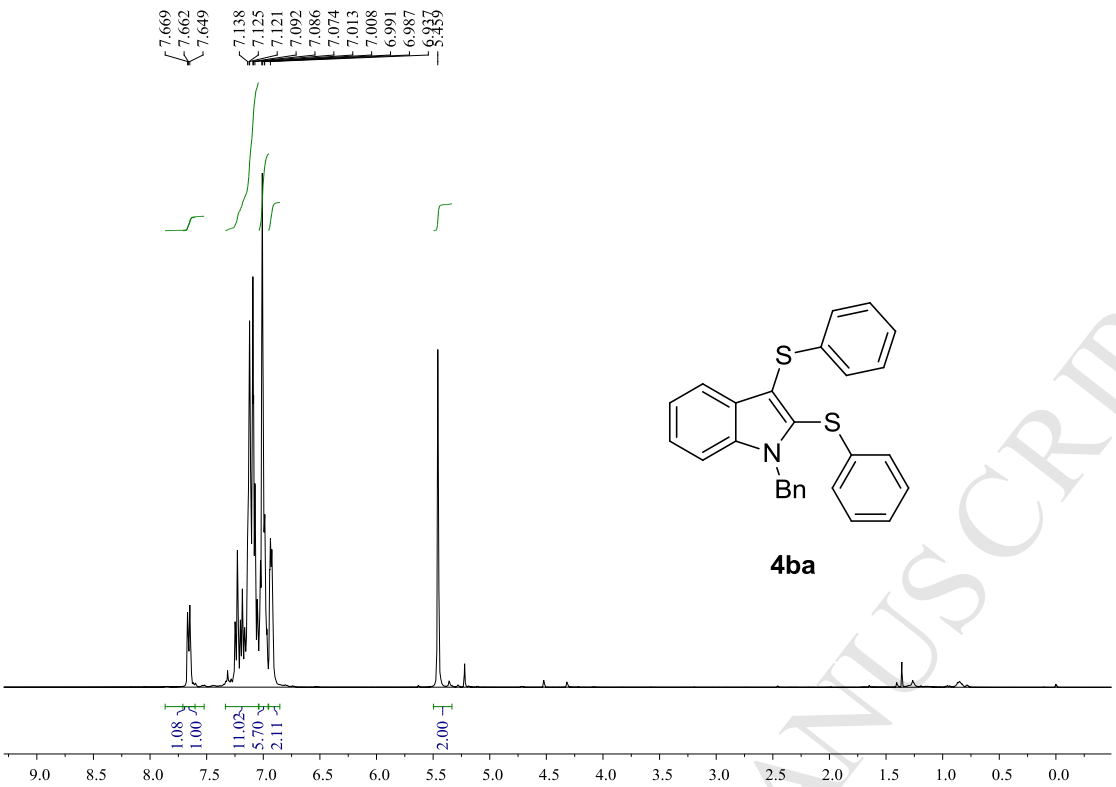
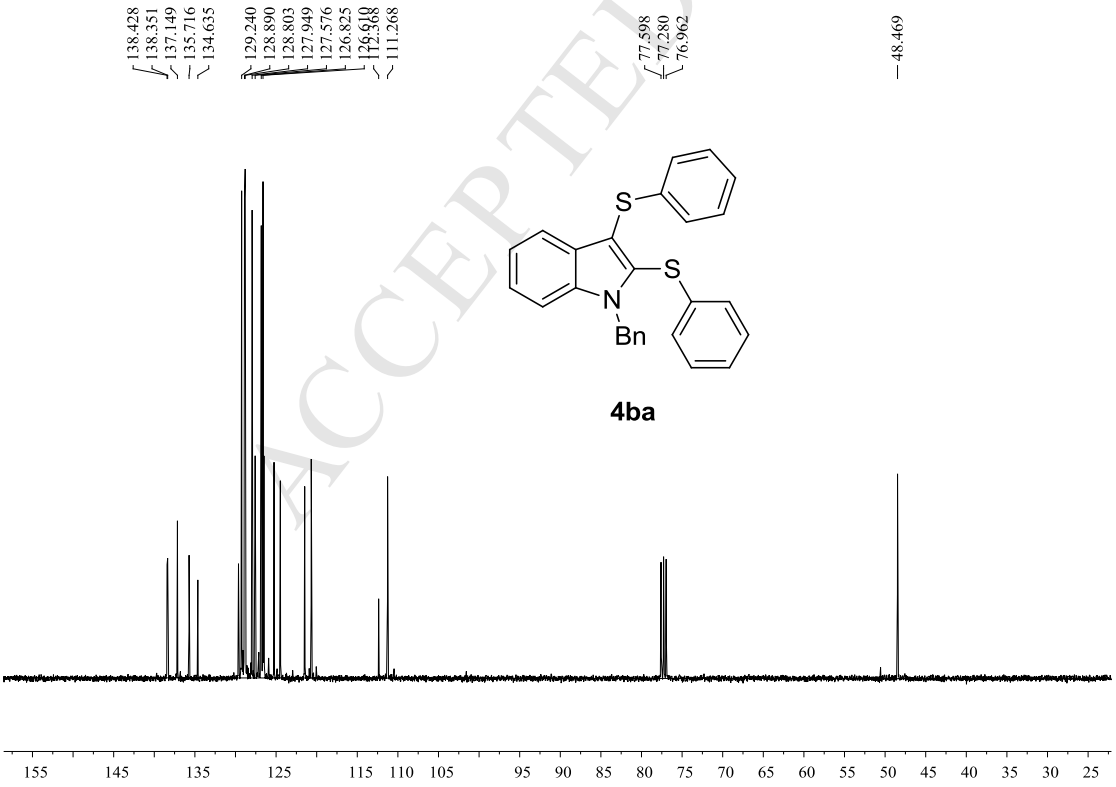


^{1}H NMR of 4ba



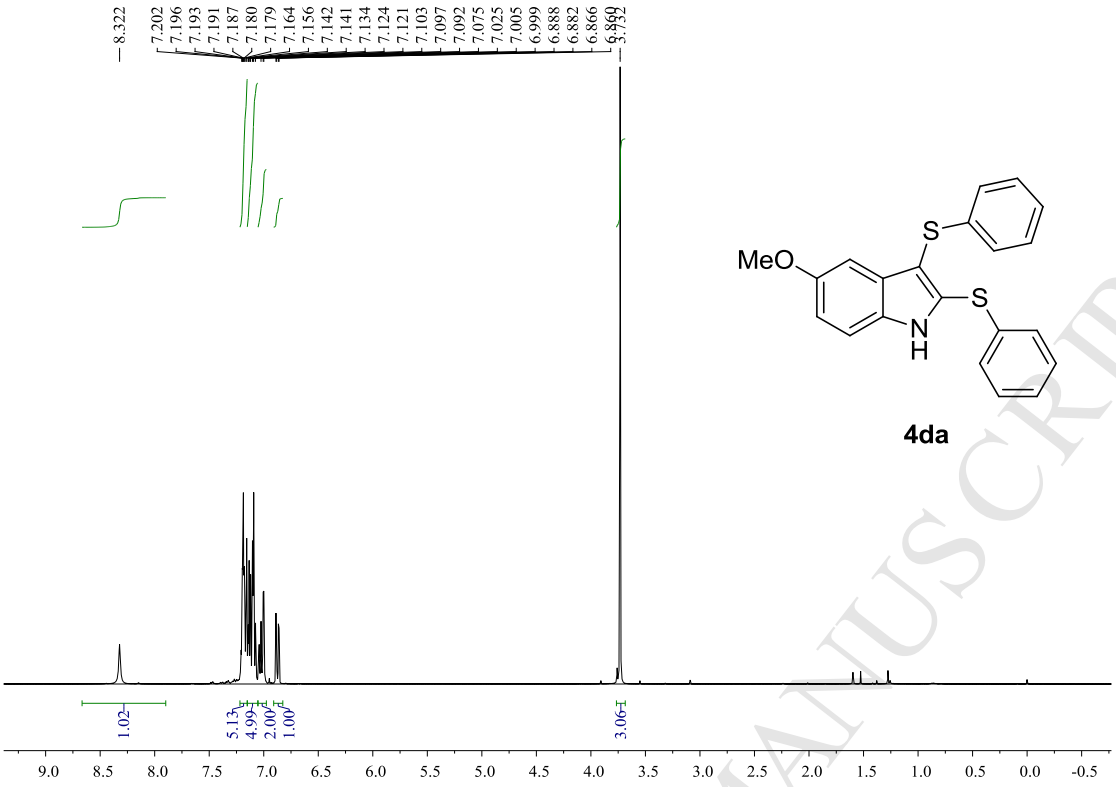
4ba

^{13}C NMR of 4ba



4ba

^{1}H NMR of 4da



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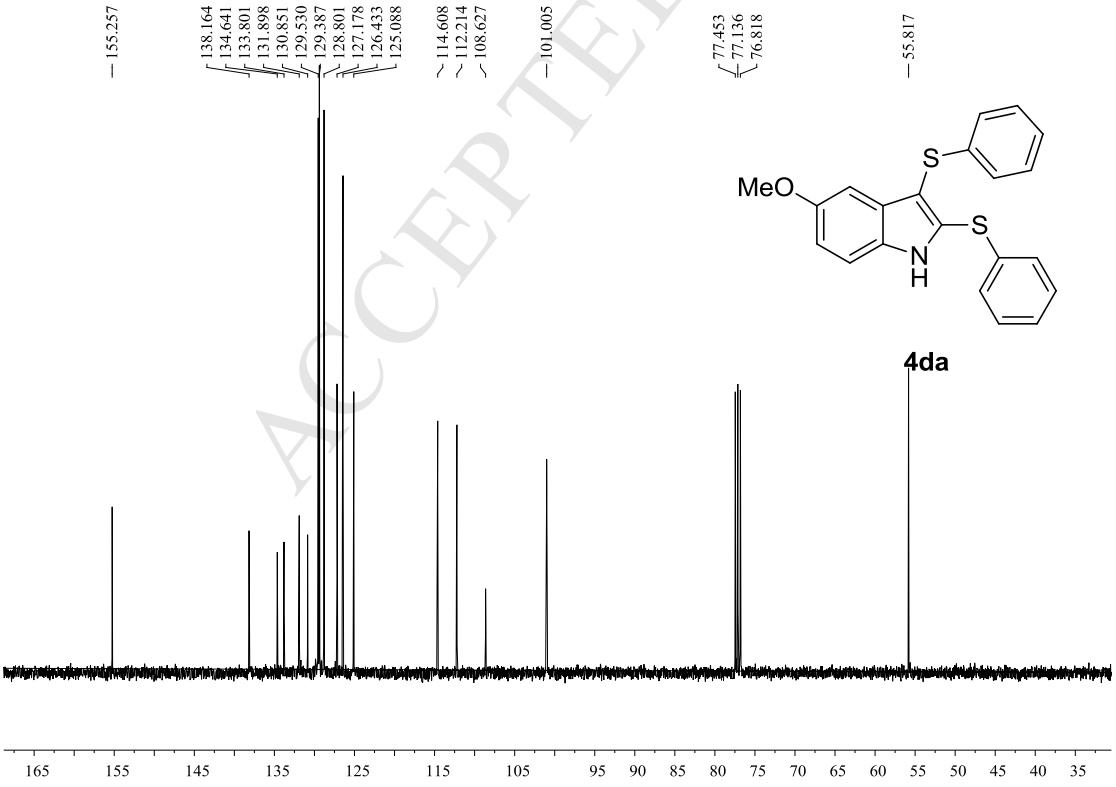

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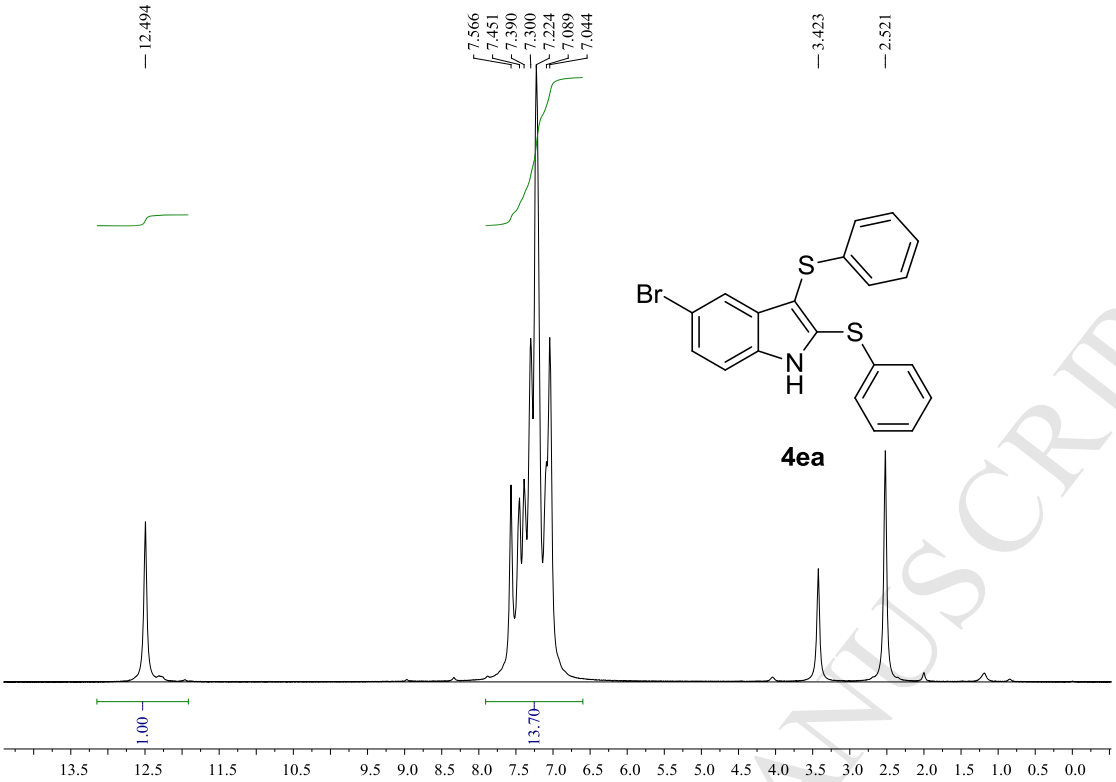

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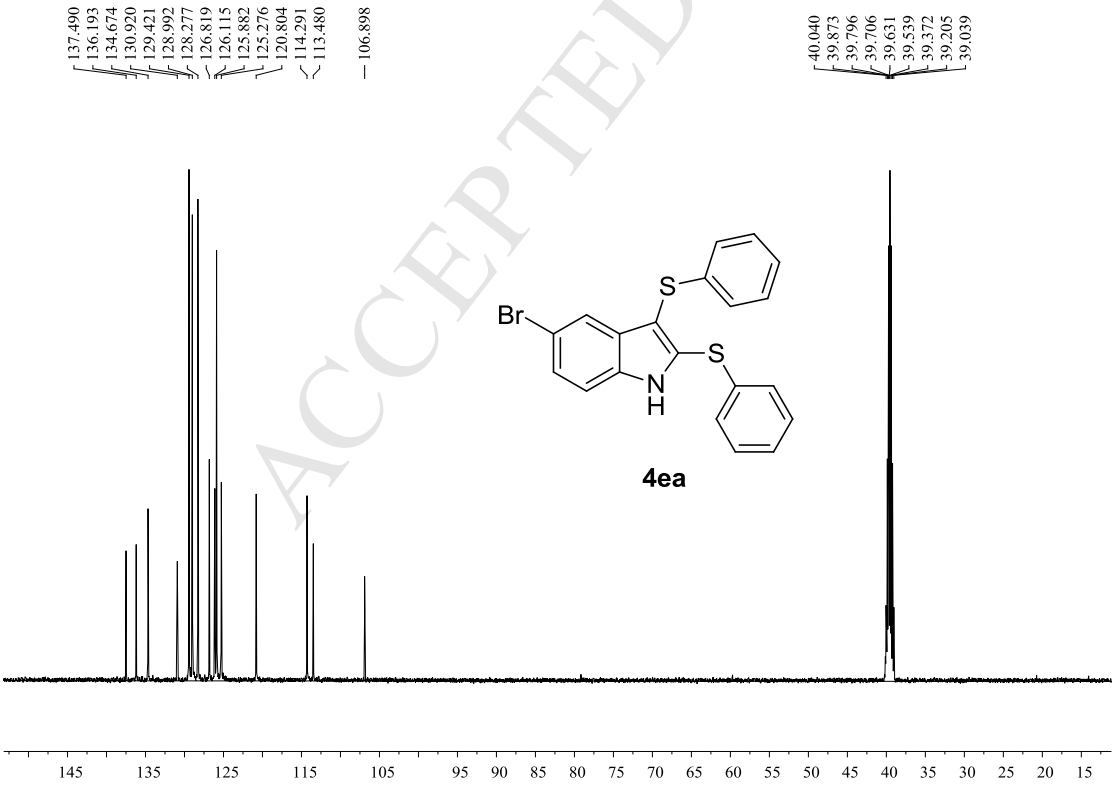
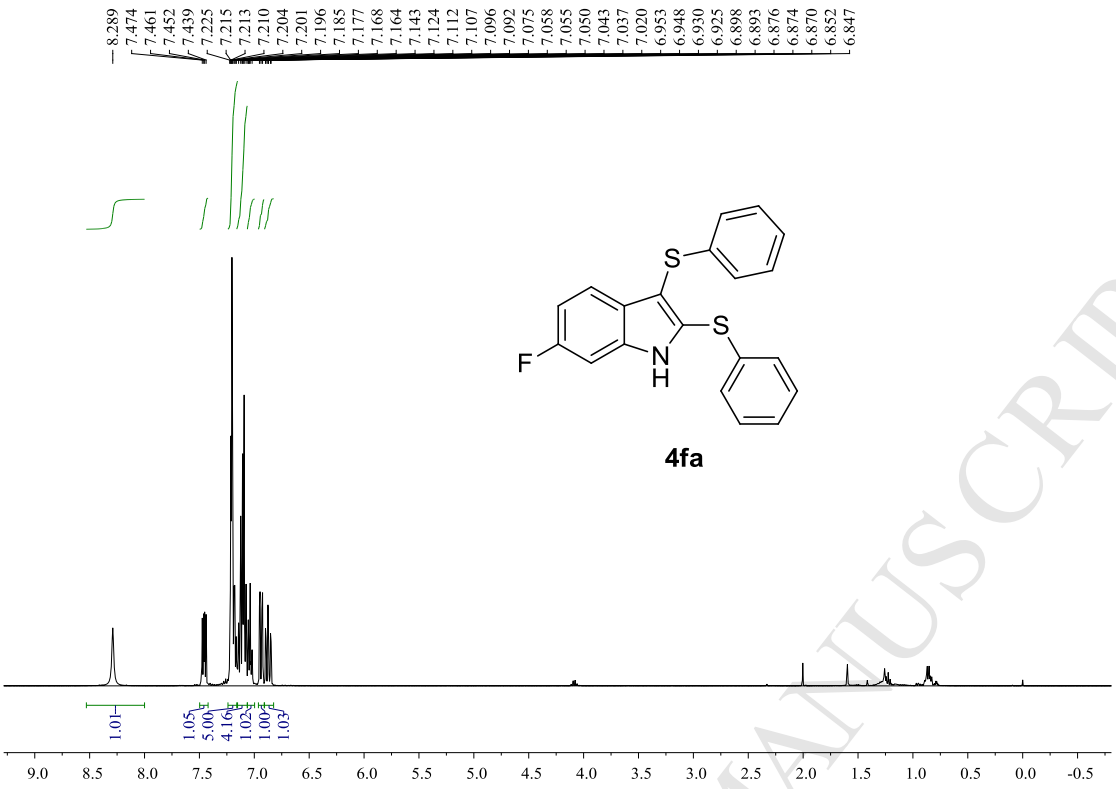
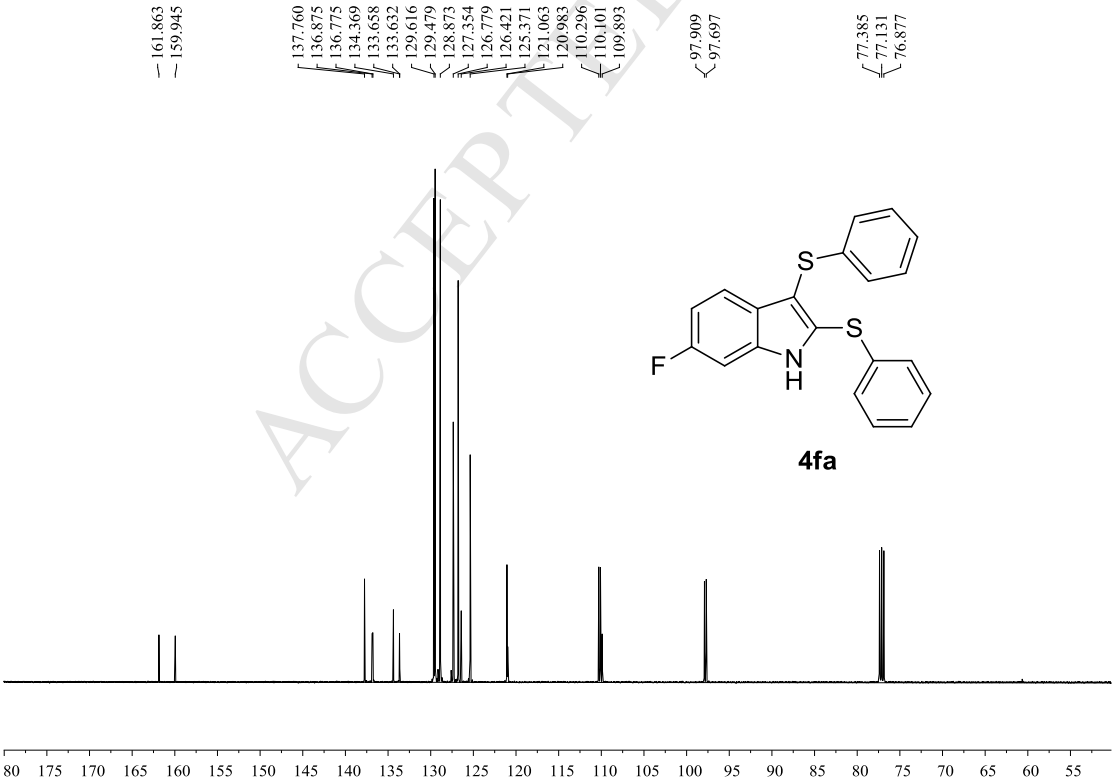


^{1}H NMR of 4fa



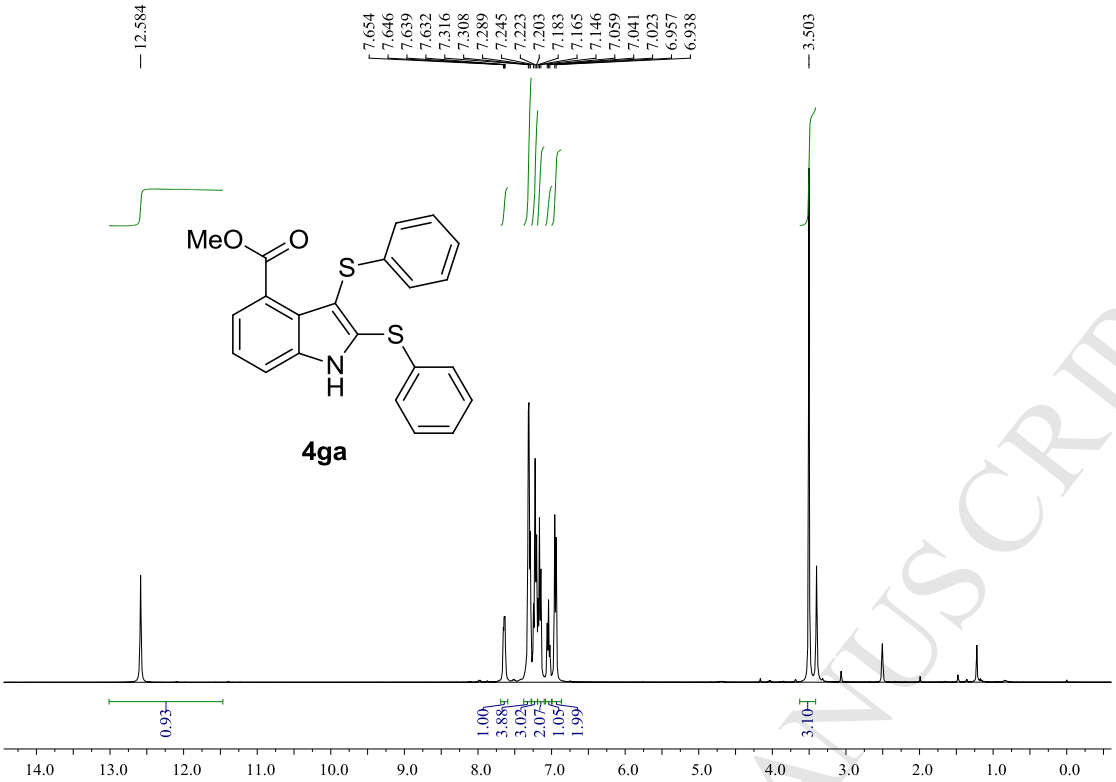
4fa

^{13}C NMR of 4fa



4fa

^{1}H NMR of 4ga



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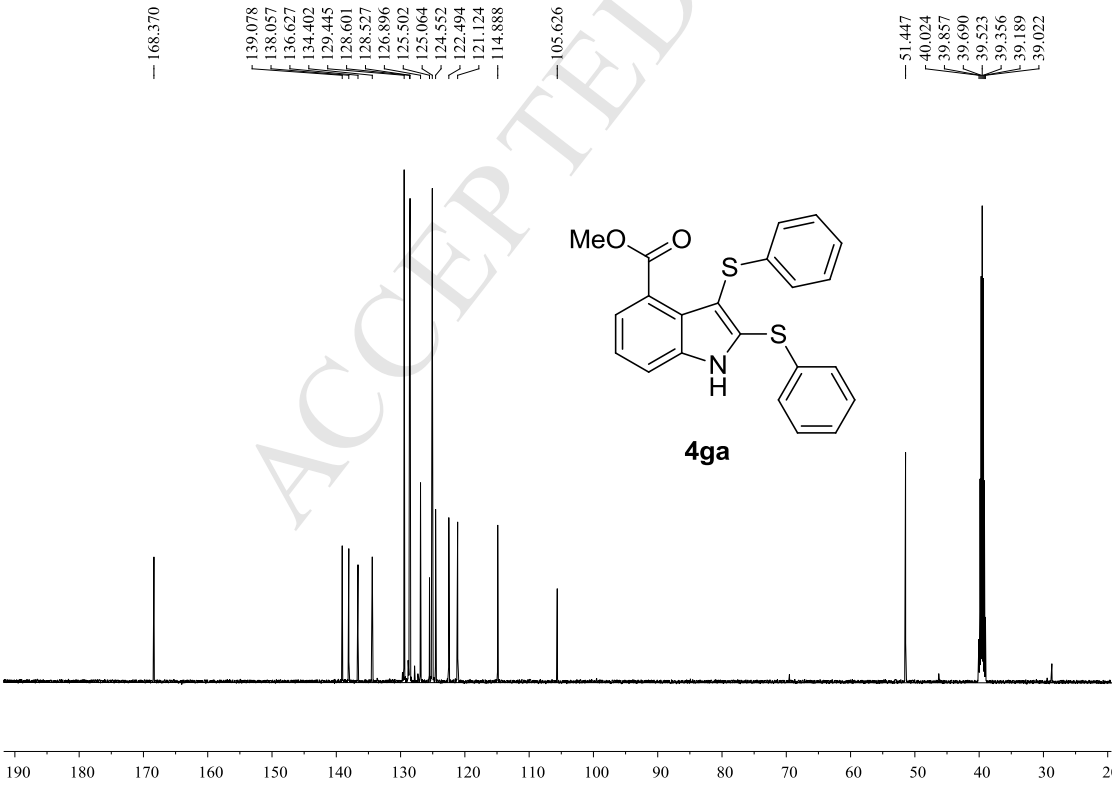
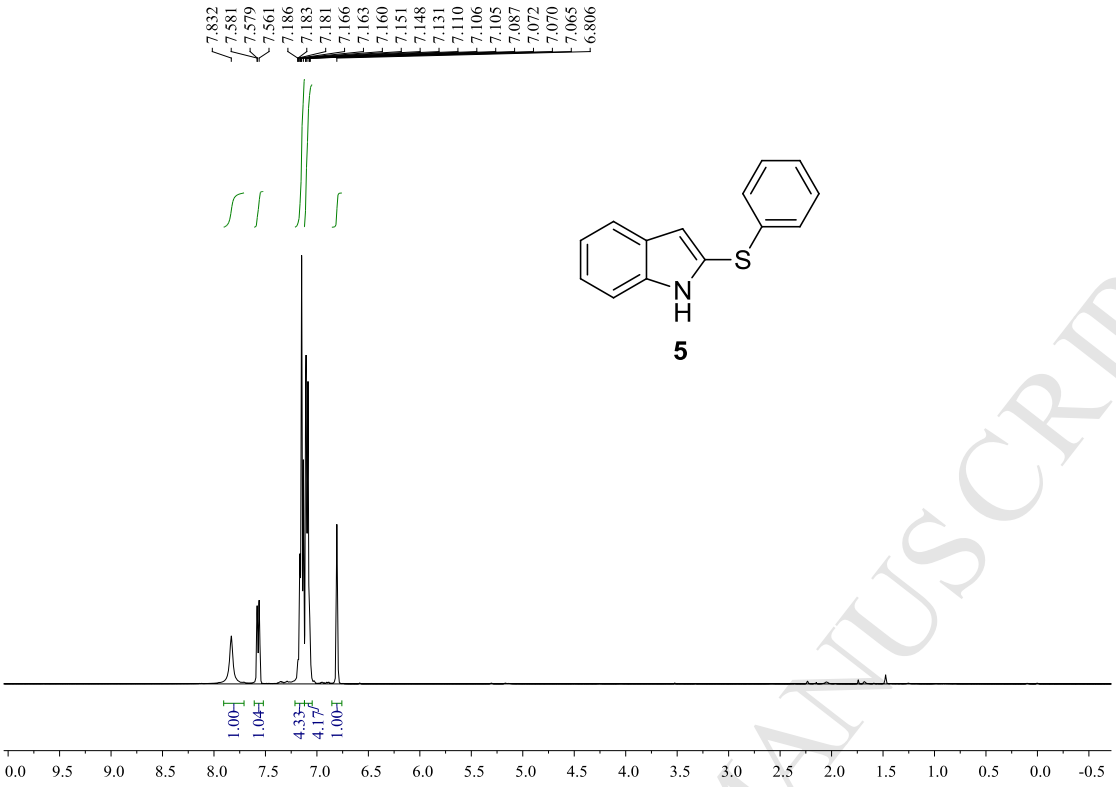


^{1}H NMR of 5



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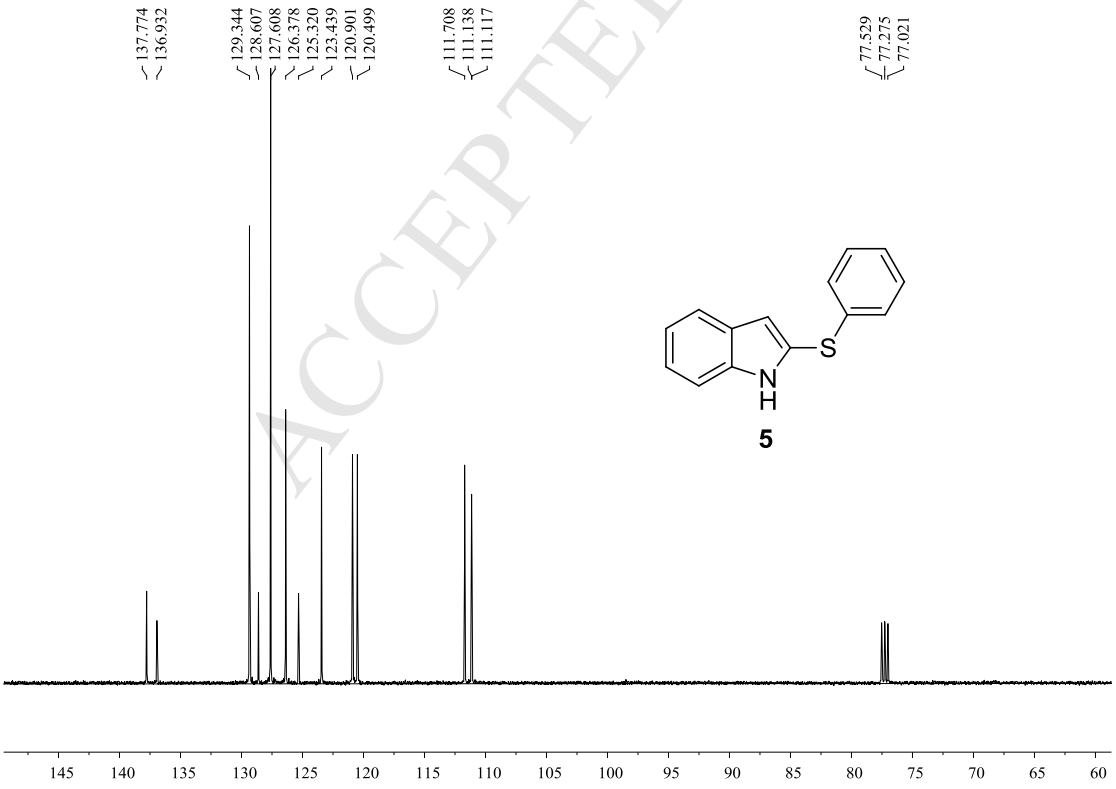
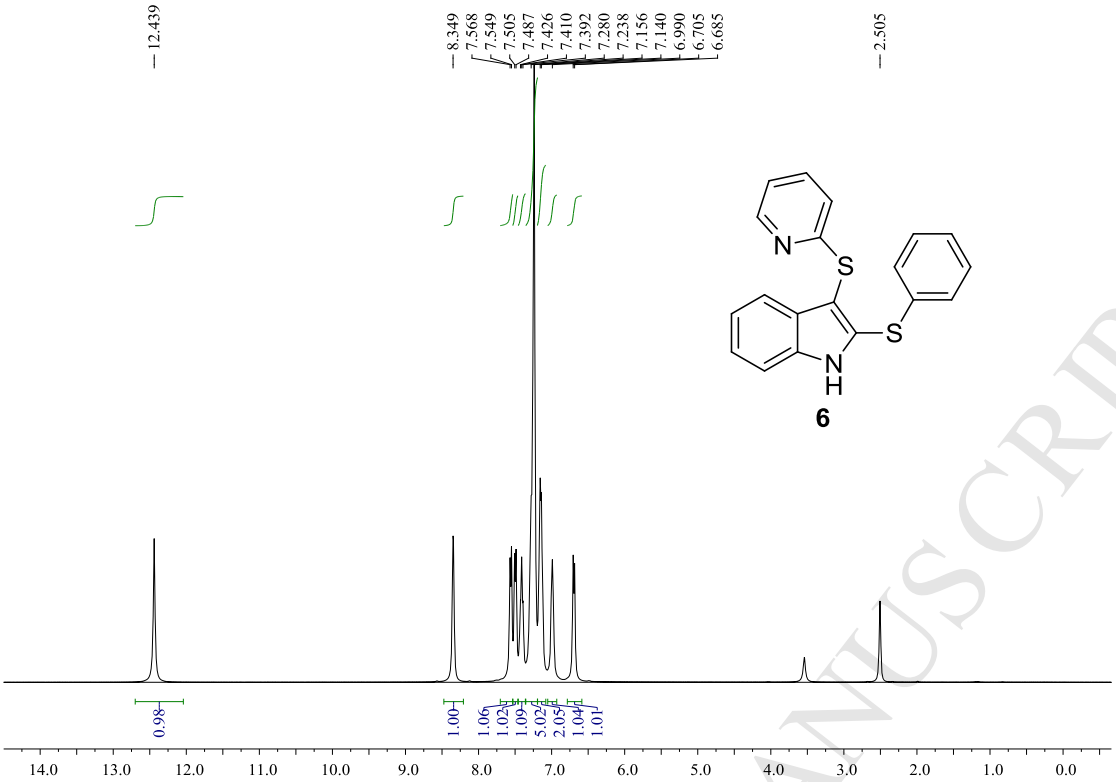


^{1}H NMR of 6



^{13}C NMR of 6