New Synthetic Strategies for Sulfur-Containing Benzoheterocycles via Transition Metal-Free/Catalyzed C-S Bond Formation and Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen-Heterocycles

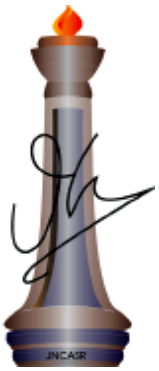
A Thesis

Submitted for the Degree of

Doctor of Philosophy

By

Yogendra Kumar



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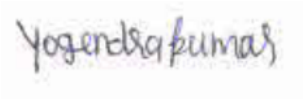
July- 2022

Declaration

I hereby declare that the entire work embodied in this thesis entitled "***New Synthetic Strategies for Sulfur-Containing Benzoheterocycles via Transition Metal-Free/Catalyzed C-S Bond Formation and Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen-Heterocycles***" is the result of investigations carried out by me in the *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, India* under the guidance of **Prof. H. Ila**, and it has not been submitted elsewhere for any degree or diploma.

In keeping with general practice, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omissions that might have occurred due to oversight or error in judgment are regretted.



July, 2022
Bengaluru

Yogendra Kumar
(Research Scholar)

Certificate

I hereby certify that the entire work embodied in this thesis entitled "***New Synthetic Strategies for Sulfur-Containing Benzoheterocycles via Transition Metal-Free/Catalyzed C-S Bond Formation and Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen-Heterocycles***" has been carried out by **Mr. Yogendra Kumar** under my supervision in the *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, India* and that no part of it has been submitted elsewhere for any degree or diploma.

July, 2022
Bengaluru

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Dedicated to

My Loving Parents

Acknowledgement

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Finally, I would like to thank all my friends, relatives, well-wishers, and everybody important to the successful realization of the thesis, as well as expressing my apology that I could not mention personally one by one.

Yogendra Kumar

Synopsis

Title of Thesis: "***New Synthetic Strategies for Sulfur-Containing Benzoheterocycles via Transition Metal-Free/Catalyzed C-S Bond Formation and Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen-Heterocycles***"

Submitted by: Mr. Yogendra Kumar, New Chemistry Unit, JNCASR, Bengaluru-560064, India

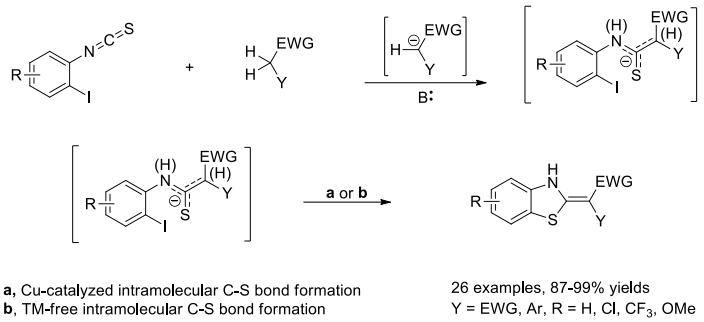
The above thesis is divided into five chapters:

Chapter 1: ''*Introduction*''

The present chapter briefly explains the synthetic versatility of transition metal-free cross-coupling reactions to form C-C or C-heteroatom bonds. We have been utilizing transition metal-catalyzed coupling reactions and domino reactions in our previous research work; however, we have used the first time, the transition metal-free intramolecular C-S coupling for the synthesis of various benzoheterocycles. Besides, transition metal-free base-promoted C-C and C-heteroatom bond coupling reactions are new emerging areas in organic synthesis, we have reported in the following section, a short literature survey of transition metal-free C-C and C-heteroatom coupling reactions leading to the synthesis of useful molecules like biaryls and heterocycles.

Chapter 2: *"Domino Synthesis of 2-Substituted Benzothiazoles by Base-Promoted Intramolecular C-S Bond Formation"*

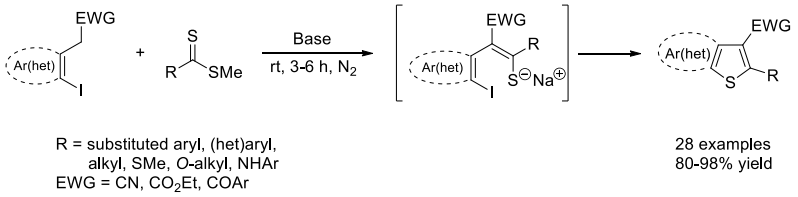
The Chapter 2 of the thesis describes the synthesis of a new, facile transition-metal-free, domino synthesis of 2-substituted benzothiazoles, involving base-mediated one-pot addition of various active methylene compounds to *o*-iodoarylisothioacyanates and subsequent intramolecular C-S bond formation of the resulting thioamidate anion intermediate. The reaction proceeds at room temperature within 1-3 h, affording diversely substituted benzothiazoles in excellent yields. A possible radical intermediate pathway, via an $S_{RN}1$ mechanism, has been proposed for intramolecular C-S bond formation for the synthesis of 2-substituted benzothiazoles (Scheme 1).



Scheme 1. Synthesis of 2-substituted benzothiazoles

Chapter 3: *"Synthesis of Substituted Benzo[b]thiophenes via Base-Promoted Domino Condensation-Intramolecular C-S Bond Formation"*

The Chapter 3 of the thesis deals with a novel one-pot transition metal-free synthesis of 2,3-substituted benzo[*b*]thiophenes and their hetero-fused analogs, involving a tandem base-mediated condensation of *o*-iodoarylacetonitriles/acetates/ketones with (hetero)aryldithioesters or other thiocarbonyl compounds and an intramolecular C-S bond formation at room temperature within 3-6 h. The reaction affords diversely substituted benzothiophenes and hetero-fused thiophenes in excellent yields in metal-free conditions (Scheme 2).

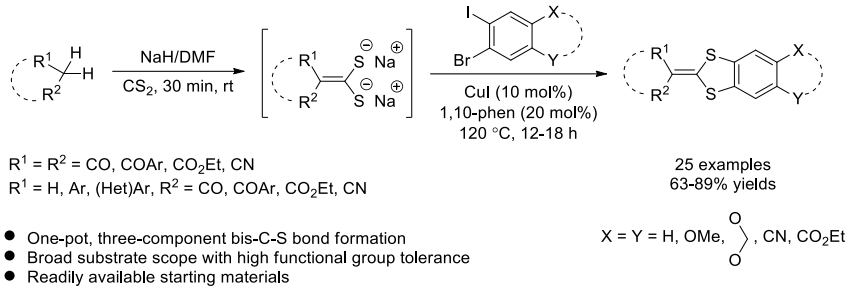


Scheme 2. Synthesis of hetero-fused benzo[*b*]thiophene

Chapter 4: "*An Efficient One-Pot, Three-component Route to Novel Push-Pull 1,3-Benzodithiol-2-ylidenes via Copper-Catalyzed bis-C-S Bond Formation*"

The Chapter 4 of the thesis deals with an efficient one-pot, three-component synthesis of novel push-pull 1,3-benzodithiol-2-ylidene derivatives, involving the reaction of various active methylene compounds with CS_2 in the presence of sodium hydride as the base in DMF solvents, followed by in situ copper-catalyzed bis-C-S coupling of the resulting dithioate salts with 1-bromo-2-iodobenzenes with both electron-donating as well

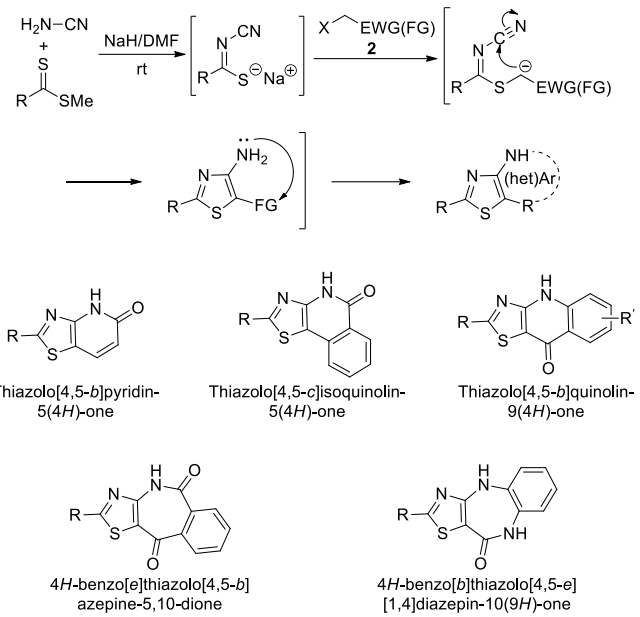
as electron-withdrawing groups containing. The methodology involves readily available starting materials and tolerates a broad range of functional groups (Scheme 3).



Scheme 3. Synthesis of push-Pull 1,3-benzodithiol-2-ylidenes

Chapter 5: "*Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen Heterocycles via Intramolecular Heteroannulation of in situ Generated 2-(Het)aryl-4-amino-5-functionalized Thiazoles*"

The Chapter 5 of the thesis describes the synthesis of novel 2-(het)aryl-substituted thiazolo-fused six- and seven-membered nitrogen-heterocycles, such as thiazolo[4,5-*b*]pyridin-5(4*H*)-ones, thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones, thiazolo[4,5-*b*]quinolin-9(4*H*)-ones, 4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-diones, have been developed in a single-pot operation via intramolecular heteroannulation of in situ generated 2-(het)aryl-4-amino-5-functionalized thiazoles. These 4-amino-5-functionalized thiazoles were readily obtained in a one-pot process by treatment of a range of (het)aryldithioesters with cyanamide in the presence of sodium hydride, followed by in situ *S*-alkylation intramolecular condensations of the resulting thioimidate salts with suitable halo alkylating agents. On the other hand, the corresponding 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones, were synthesized in a two-step process requiring prior isolation of 5-carboethoxy-4-(2-nitrophenyl)aminothiazoles and their subsequent reductive cyclization. The functionalized activated methylene halides employed in these reactions for the synthesis of various thiazolo-fused heterocycles were methyl bromocrotonate, ethyl 2-(bromomethyl)benzoate, 2-fluorophenacyl bromides, ethyl 2-(2-bromoacetyl)benzoate and ethyl bromoacetate. Several of these thiazolo-fused heterocycles display yellow-green to green fluorescence in solution and their absorption and emission spectra have also been examined (Scheme 4).



Scheme 4. Thiazolo-fused six- and seven-membered nitrogen heterocycles

Table of Contents

List of Abbreviations

NMR	:	Nuclear magnetic resonance
ATR	:	Attenuated total reflectance
IR	:	Infrared
HRMS	:	High resolution mess spectroscopy
DCE	:	1,2-Dichloroethane
DMEDA	:	*N*,*N*'-Dimethylethylenediamine
DMF	:	*N*,*N*-Dimethylformamide
DMSO	:	Dimthylsulfoxide
EtOAc	:	Ethyl acetate
EWG	:	Electron withdrawing group
EDG	:	Electron donating group
(Het)ar	:	Heteroaryl
NBS	:	*N*-Bromosuccinimide
NMP	:	*N*-Methylpyrrolidinone
1,10-phen	:	1,10-Phenanthroline
PMB	:	*p*-Methyoxybenzyl
TFA	:	Trifluoroacetic acid
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMEDA	:	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
Ts	:	Tosyl

m.p.	:	Melting point
DCM	:	Dichloromethane
CS_2	:	Carbon disulfide
NaH	:	Sodium hydride
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
B:	:	Base
Nu	:	Nucleophile
Bn	:	Benzyl
equiv	:	Equivalent
rt	:	Room temperature
TM	:	Transition metal
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
SET	:	Single electron transfer
BHAS	:	Base-promoted homolytic aromatic substitution
$S_{NR}1$	:	Unimolecular radical nucleophilic substitution
TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Fe	:	Iron
TTF	:	Tetrathiafulvalene

Chapter 1

Introduction

The present thesis describes the synthesis of several heterocycles employing various strategies like the synthesis of push-pull benzothiazoles and substituted benzothiophenes via transition metal-free intramolecular C-S coupling (Chapters 2 and 3), an efficient one-pot, three-component route to novel push-pull 1,3-benzodithiol-2-ylidenes via copper-catalyzed bis-C-S bond formation (Chapter 4) and domino synthesis of thiazolo-fused six- and seven-membered nitrogen heterocycles via intramolecular heteroannulation of in situ generated 2-(het)aryl-4-amino-5-functionalized thiazoles (Chapter 5). We have been utilizing transition metal-catalyzed coupling reactions and domino reactions in our previous research work; however, we have used the first time, the transition metal-free intramolecular C-S coupling for the synthesis of benzoheterocycles. Besides, transition metal-free C-C and C-heteroatom bond coupling reactions are new emerging areas in organic synthesis, we have reported in the following section, a short literature survey of transition metal-free C-C and C-heteroatom coupling reactions leading to the synthesis of useful molecules like biaryls and heterocycles.

1.1 Transition Metal-Free Coupling Reactions: A Short Literature Survey

Transition metal-catalyzed cross-coupling reactions to form C-C or C-heteroatom bonds constitute a powerful most versatile tool in synthetic organic chemistry including pharmaceutical and medicinal chemistry. They have enriched the toolbox of synthetic organic chemists with a great number of inter-and intramolecular reactions for the step economical synthesis of complex and functionalized molecules. They have revolutionized organic synthesis and incredibly expanded our opportunities to construct complex valuable organic molecules. These greatly efficient synthetic methodologies are currently in high demand in everyday synthetic practice as well as on an industrial scale.[1] These reactions are commonly catalyzed by metals such as Pd, Cu, Fe, and Ni, etc.[1] Many name reactions have been assigned in the textbooks and are well known nowadays (Heck Reaction, Negishi cross-coupling, Stille coupling, Suzuki coupling, etc). This great success and significance of transition metal-catalyzed coupling reactions were highlighted by the Nobel Prize in Chemistry in 2010.[2]

Despite their remarkable advances and pre-eminent status among modern synthetic methods, the transition metal-catalyzed reactions suffer from several drawbacks; such as high cost and toxicity of transition metals along with sophisticated ligands, sometimes high catalytic loading as well as strict demand for the absence of any transition metal impurities in the final product and trace metal contamination, the latter represents a serious practical concern in the pharmaceutical industry and organic electronics and require extra metal removing steps, which are usually time demanding and can render such process cost-intensive and affecting their practicality.[3] Moreover transition metal-catalyzed cross-coupling reactions of polyhalogenated substrates often suffer from partial dehalogenation.[4]

Therefore, the development of alternative approaches toward ‘cross-coupling products’ is highly desirable. Recently, to address the above-mentioned shortcomings; much attention has been paid to the development of transition metal-free cross-coupling reactions, especially those employing the same precursors usually haloarenes, and giving the same product as transition metal-catalyzed reactions.[5] Significant progress has been made in this area and remarkably attractive protocols for the formation of C-C and C-heteroatom bonds in a transition metal-free manner have been developed over the past several years. In general, such protocols are of great synthetic interest, because they allow transition metal impurities to be avoided in the final product.

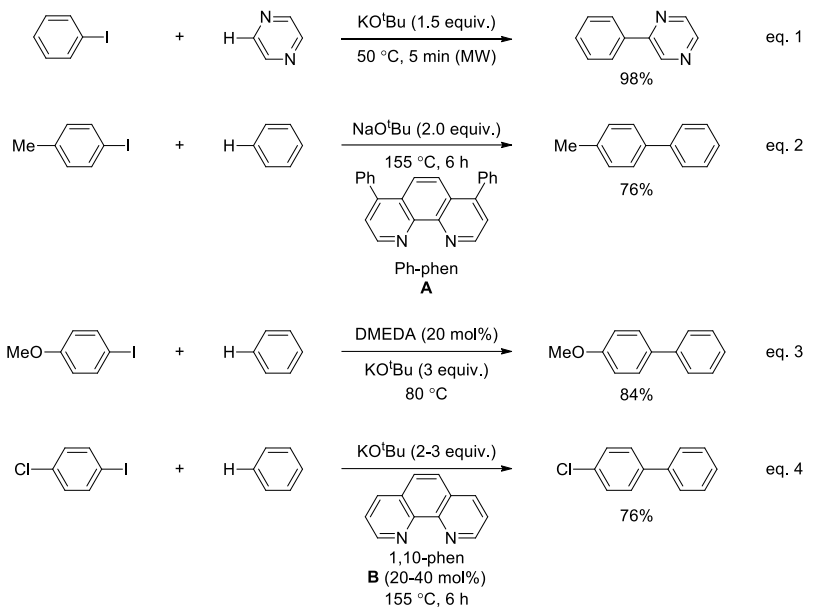
The following section presents a short literature survey on 'transition metal-free C-C and C-heteroatom coupling reactions.

1.1.1 Transition Metal-Free C-C Coupling Reactions

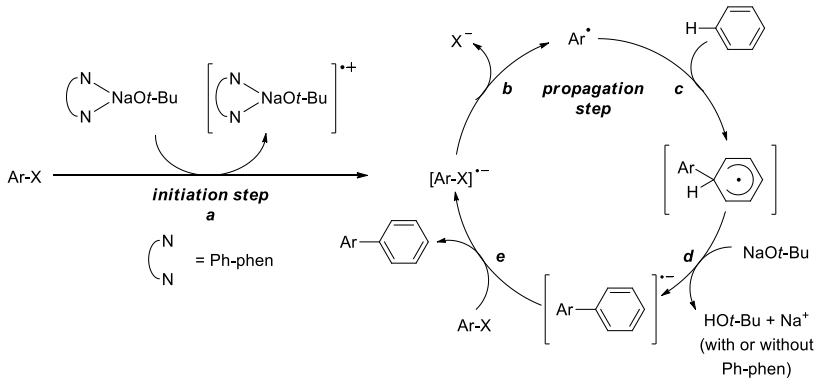
Organic compounds containing aryl-aryl bonds represent important structural motifs, frequently found in several natural products and pharmaceuticals, and functional organic materials. The development of aryl-aryl bond formation has been a subject of great importance in synthetic organic chemistry.[6] The transition metal-catalyzed direct C-H arylation of aromatic compounds has emerged as a useful alternative, to the already existing Pd-catalyzed cross-coupling reactions.[6,7]

In the last few years, several research groups (Itami,[8] Kwong,[5b] Shi,[9] Shirakawa, and Hayashi[10]) have reported C-H bond arylation of aromatic compounds with haloarenes promoted by potassium hydroxide or sodium *tert*-butoxide with or without employing any transition metal catalyst. Thus in 2008, Itami and co-workers reported *tert*-butoxide mediated biaryl coupling of a few nitrogen-based haloarenes (eq. 1). Later on, in 2010, several other groups expanded the scope of this reaction, applicable to unactivated benzene derivatives and catalyzed by certain diamines (eq. 2-4). These reactions represent important advances in synthetic organic chemistry, initially supporting a radical-based mechanism. Most of these workers showed that bases like KO*t*-Bu, NaO*t*-Bu, and LiO*t*-Bu promoted these reactions, either in the presence of an excess of these bases alone or in presence of nitrogen base catalysts. Thus, the reaction of *p*-tolyl-iodide with benzene (120 equiv.) in presence of NaO*t*-Bu (2.0 equiv.) and 4,7-diphenyl phenanthroline (0.1 equiv.) at 155 ºC for 6 h gave 4-methyl biphenyl 76% yield (eq. 2). Phenyl iodide having an electron-donating or withdrawing group, as well as heteroaryl iodide, underwent coupling in high yields. Aryl bromides were found to be less reactive than corresponding iodides. The use of strong bases in combination with phenanthroline ligand was found to be crucial for reaction.

From experimental studies, Shirakawa and Hayashi first proposed a homolytic aromatic substitution mechanism ($S_{RN}1$), suggesting a plausible catalytic cycle (Scheme 2).[10a] They assumed that due to low-lying LUMO, phenanthrolines were acting as SET mediators. Subsequent SET from NaO*t*-Bu-phenanthroline complex to Ar-X gives radical anion $[ArX]^{\cdot-}$, (step ***a*** *initiation*), which is converted to aryl radical $Ar^{\cdot}$ upon elimination of X^- (step ***b***) After the addition of aryl radical to benzene, gives cyclohexadienyl radical

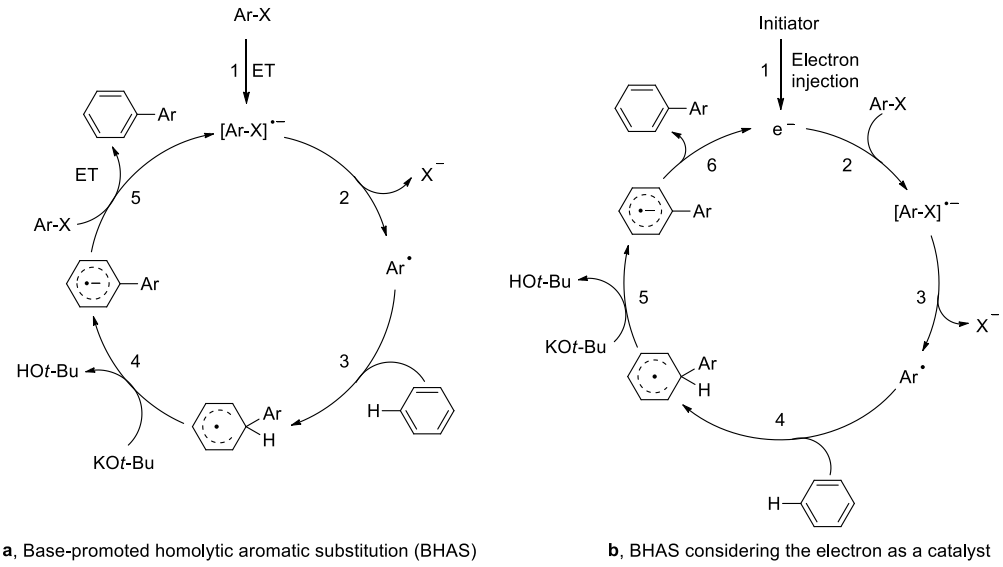


Scheme 1. *Tert*-butoxide mediated C-H bond arylation of aromatic compounds with haloarenes



Scheme 2. The mechanism for the formation of biaryls proposed by Shirakawa and Hayashi

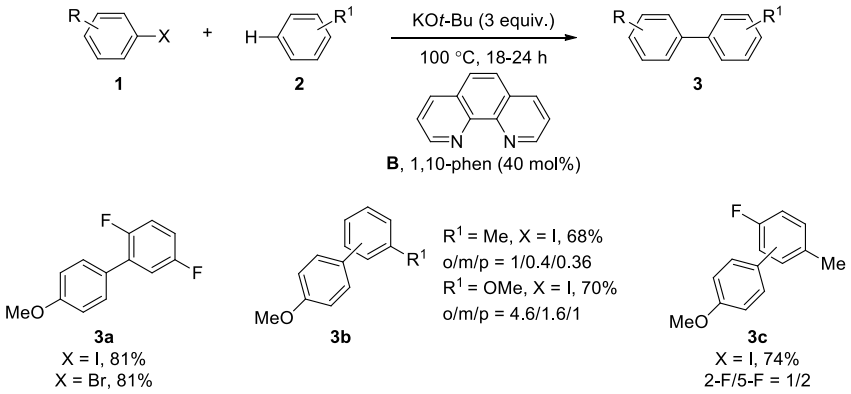
$[Ar\text{-}C_6H_6]^{\bullet-}$ (step ***c***) which on deprotonation gives radical anion $[Ar\text{-}C_6H_5]^{\bullet-}$ (step ***d***). Finally SET from $[Ar\text{-}C_6H_5]^{\bullet-}$ to ArX gives ArC_6H_5 and regenerates $[Ar\text{-}X]^{\bullet-}$ (step ***e***). These reactions were subsequently also called ''*Base promoted homolytic aromatic substitutions*'' (BHAS) by Studer and Curran (Scheme 3a).[11a] In contrast to the $S_{RN}1$ chemistry, the aryl radical in the BHAS reaction, reacts with a neutral arene (step 3) and biaryl radical anion generated (step 4), can formally liberate the electron, providing the product in step 5, the electron then enters as a catalyst in the next catalytic cycle. In their new mechanistic picture, Studer and Curran called '*electron catalyzed reaction*' (Scheme 3b), which can be initiated in different ways with both organic and metal donors (Scheme 3b).[11b]



Scheme 3. New mechanistic picture viewing the electron as a catalyst

1.1.1.1 Intermolecular Base-Promoted Cross-Coupling of Aryl halides with Arenes

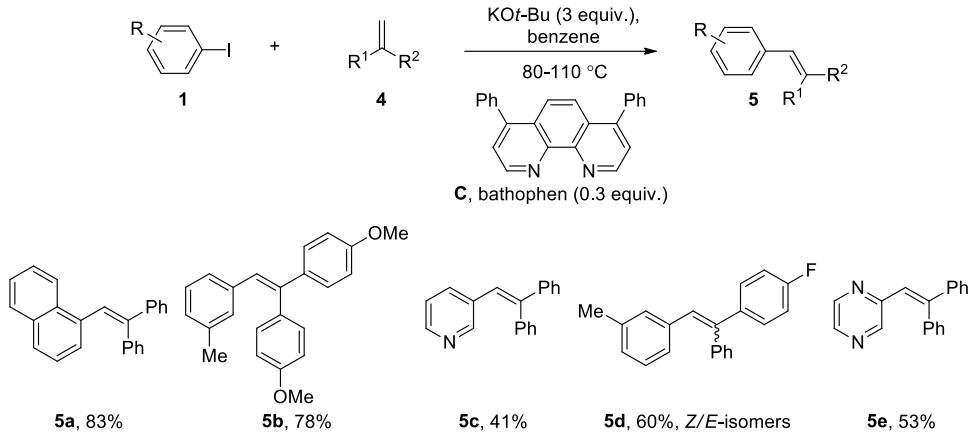
This cross-coupling of aryl iodides/bromides with common arenes indicated good tolerance of functional groups and reactivity of various substrates, but poor regioselectivity (Scheme 4).[5,12-14] The reaction of anisole, toluene, fluorobenzene, and other arenes with different C-H bonds generated a mixture of all regioisomers, suggesting a completely different pathway (Scheme 4). The termination of this reaction by radical scavengers and other experiments, to track the radical intermediates, supported this conclusion and an aryl radical intermediate was considered to be formed in this process.



Scheme 4. BHAS reaction of aryl iodides/bromides with common arenes for biphenyl synthesis

1.1.1.2 Intermolecular Cross-Coupling of Aryl halides with Alkenes: Transition Metal-Free Mizoroki-Heck type Reaction

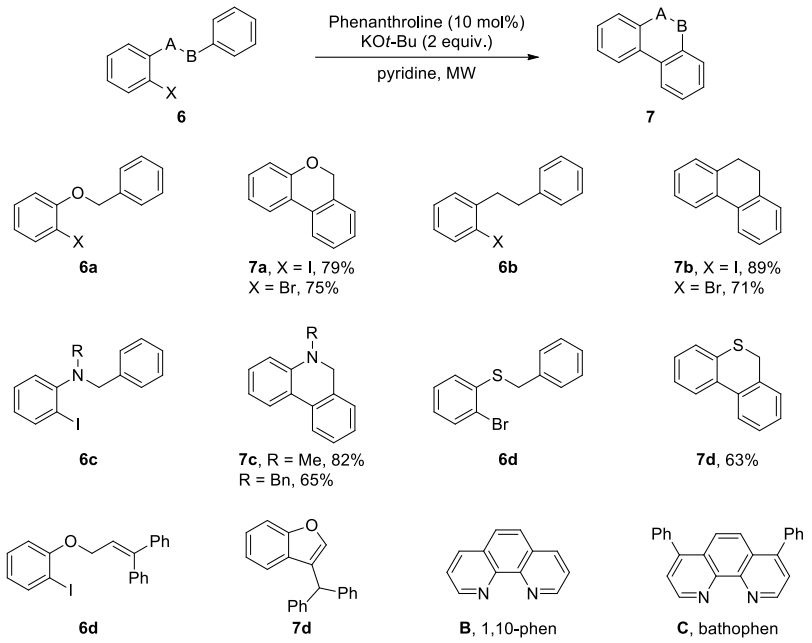
Following their previous work, Shi and co-workers[15-16] developed a KO*t*-Bu-promoted transition metal-free arylation of 1,1-diarylethylene yielding coupling products in high yields which can be considered as a transition metal-free Mizoroki-Heck type reaction (Scheme 5). Although previous studies indicated that the arylation of aryl halides with benzene ran smoothly at 80-110 ºC, benzene was found to be the best solvent in this report, with only a trace amount of biaryl as a byproduct. These results indicated that arylation of olefin was highly preferred over biaryl formation. Further investigation on various substrates showed good tolerance of functional groups (Scheme 5).



Scheme 5. KO*t*-Bu promoted intermolecular arylation of 1,1-diphenylethylenes

1.1.1.3 Transition Metal-Free Intramolecular Cross-Coupling of Aryl halides with Arenes

Several research groups have also reported transition metal-free intramolecular homolytic aromatic substitution (IHAS) with aryl radicals (Scheme 6). After investigation of KO*t*-Bu promoted intermolecular cross-coupling reaction of aryl halides with arenes in the presence of phenanthroline ligands, Shi and co-workers[17] and other groups[18-19] conducted an intensive study of this base promoted intramolecular cross-coupling of aryl halides and a series of 6*H*-benzo[*c*]chromene derivatives and other fused heterocycles were synthesized in good to excellent yields (Scheme 6). Various linkages including ethers, thioethers, amines, and carbon chains provided the desired products with good efficiency and selectivity. These reactions provided a simple efficient transition metal-free approach for the synthesis of fused heterocyclic structures (Scheme 6).



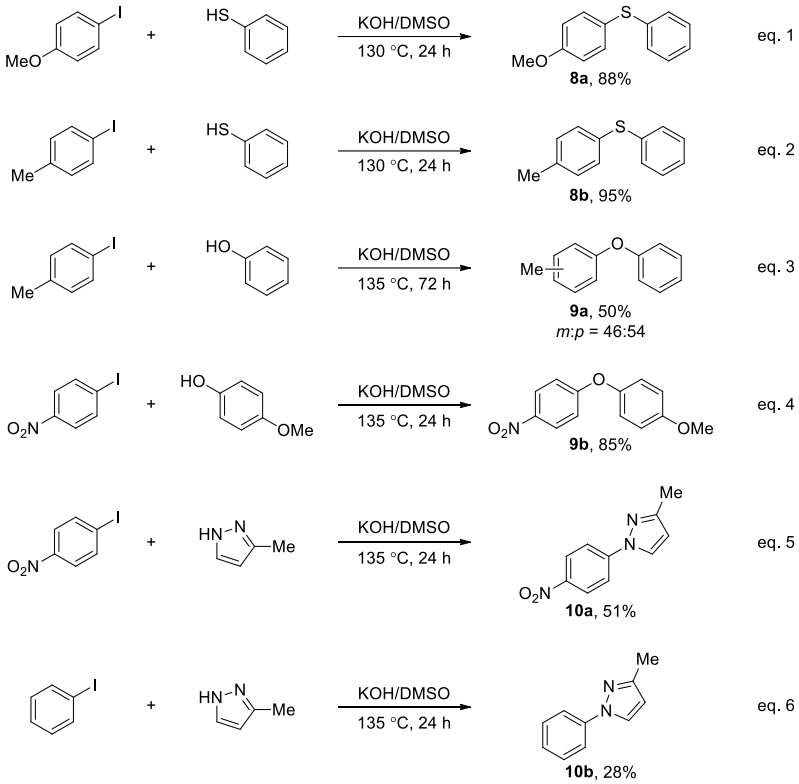
Scheme 6. Examples of intramolecular BHAS reaction

1.1.2. Transition Metal-Free C-heteroatom Coupling: Synthesis of Benzoheterocycles

Transition metal-catalyzed C-heteroatom bond formation (*N*-, *O*- and *S*-arylation) is one of the most important transformations in modern organic synthesis, and most commonly palladium and copper salts are employed as catalysts.[20] In recent years many other metal catalysts *i.e.*, salts of cobalt, nickel, indium, cadmium, and zinc have also been used as catalysts in C-heteroatom bond formation. Recently few examples of *N*-, *O*-, and *S*-arylation in the absence of metal catalysts have also been reported.[20] Most of these reactions proceed either by aromatic nucleophilic substitution (S_NAr), for electron-poor aryl fluoride, chloride, and bromides in presence of dipolar solvents like DMF, NMP, or DMSO. In the case of less activated aryl halides, that do not undergo nucleophilic substitution via the S_NAr mechanism, the nucleophiles appear to react through the benzyne mechanism, in presence of a strong base, via ortho deprotonation of aryl halides, followed by halide elimination.[20]

Bolm and co-workers have recently revealed that in the presence of KOH/DMSO, a 'super base' media (pKa 30-32),[20-21] which is active enough, to allow intermolecular arylation of nucleophiles leading to cross-coupling products, under transition metal-free conditions.[20] They have shown that less activated aryl halides like aryl iodide undergo nucleophilic substitution with thiophenols in presence of KOH/DMSO super base to give

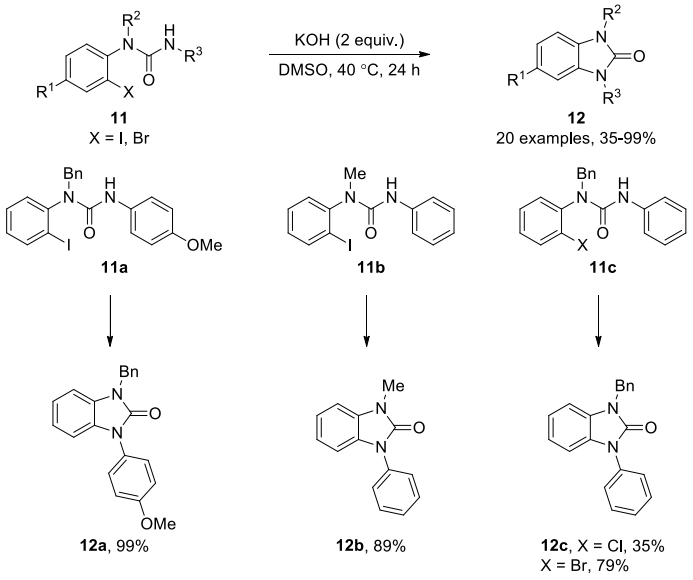
aryl thioethers in good yields (Scheme 7, eq. 1-2).[20] Less acidic and nucleophilic phenols could also be arylated with less activated *p*-iodotoluene to give an *m*/*p* mixture of diaryl ether **9a** which is indicative of an aryne mechanism (Scheme 7, eq 3). With more activated 4-nitroiodobenzene, diaryl ether **9b** was obtained in high yield (Scheme 7, eq 4).[20] The reaction was also attempted with nitrogen nucleophiles. Thus 3-methyl pyrazole reacted with 4-nitroiodobenzene and iodobenzene providing the corresponding products **10a** and **10b** in 51% and 28% yields respectively (Scheme 7, eq 5-6).[20] However mechanism of these reactions was not studied in detail.



Scheme 7. Nucleophilic substitution on aryl halides with sulfur-, oxygen-, and nitrogen-based nucleophiles in the presence of KOH/DMSO

Because of the interest in metal-free routes toward heterocyclic compounds, in pharmaceuticals and agrochemicals, Bolm and co-workers applied these protocols for the formation of heterocycles through intramolecular *N*-arylation. Thus, they have reported a new protocol for the synthesis of substituted benzimidazole-2-ones such as **12** in high yields via intramolecular *N*-arylation of *o*-halo substituted ureas **11** in KOH and DMSO at ambient temperature (Scheme 8).[22] Various aryl halides show satisfying reactivities and a wide range of functionalities are tolerated. The authors ruled out the S_NAr mechanism since aryl

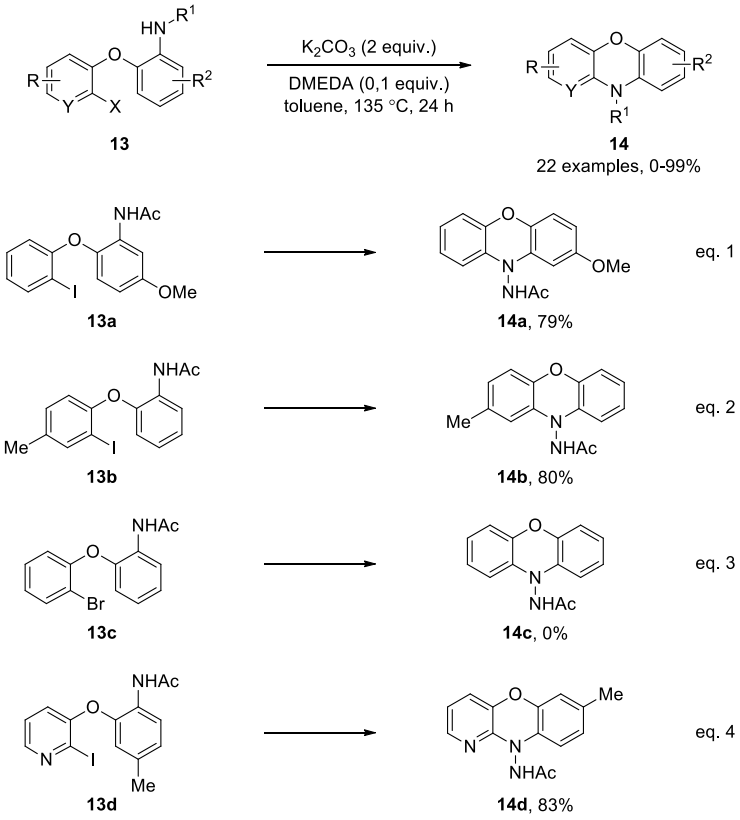
halide reactivity did not follow the expected order (F>Cl>Br). Also, based on experimental studies benzyne mechanism was ruled out. Although a detailed study of the mechanism was not carried out, they proposed the formation of short-lived radical intermediates.[22]



Scheme 8

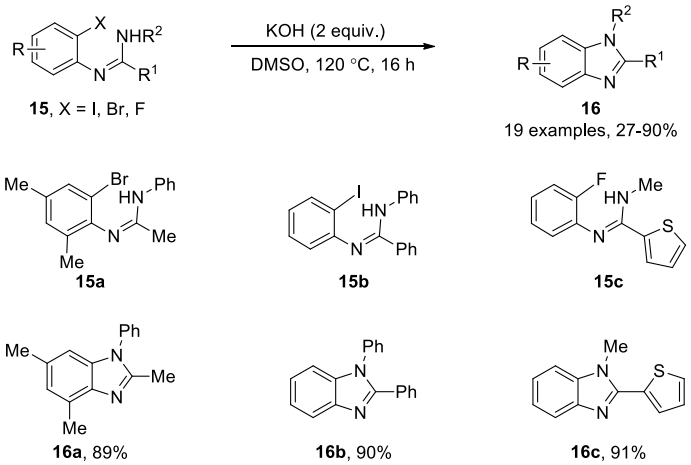
In another study Bolm's group described the synthesis of *N*-substituted phenoxazines and related aza analogs **14** in high yields via transition metal-free, base-mediated cyclization of *N*-acetylated *o*-iodoaryloxy anilides **13** in presence of a mixture of 10 mol% of *N*, *N*-dimethyl ethylenediamine (DMEDA) and 2 equiv of K_2CO_3 in toluene at 135 ºC (Scheme 9).[23] The reaction failed when *o*-bromo precursors were employed (Scheme 9, eq 3). A wide range of electron-donating and withdrawing substituents could be tolerated on the benzene ring. However, the authors did not conduct detailed mechanistic studies although ruling out benzyne or radical intermediate mechanism.

In a subsequent study, Bolm and co-workers have reported the synthesis of *N*-substituted benzimidazoles **16** via intramolecular *N*-arylation of *o*-haloamidines **15** in the presence of KOH and DMSO at 120 ºC (Scheme 10).[24] A broad range of functional groups were tolerated giving access to a wide range of substituted imidazoles in moderate to good yields. The reaction proceeded well with *o*-bromo-, *o*-iodo-, or *o*-fluoroamdines (**15a-c**). A mechanistic probe revealed that the reaction was inconsistent with the S_NAr mechanism (F>Cl>Br>I), iodo- and fluoro-substituted amidines showed the same level of conversion, whereas, with chloro-substituted amidines and sometimes bromo-substituted amidines



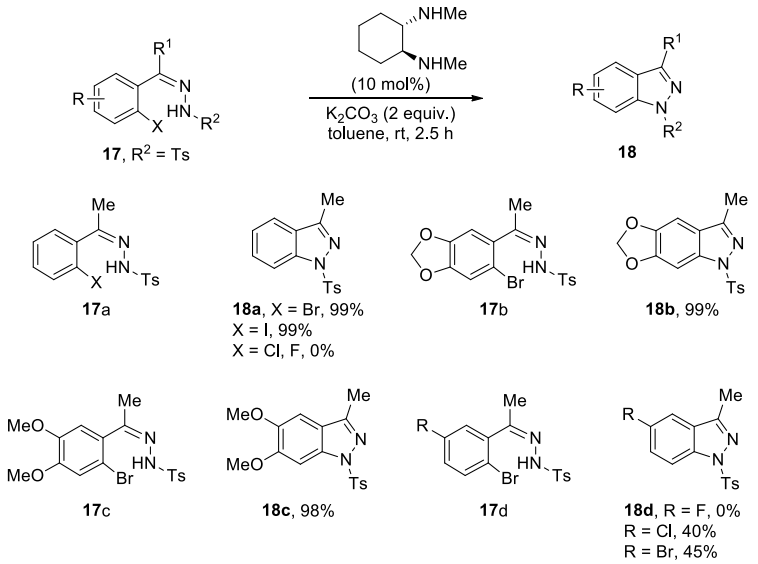
Scheme 9

The conversion was found to be lower. An aryne mechanism was also ruled out based on experimental studies. Taking these results into account the authors suggested the $S_{RN}1$ mechanism and involvement of short-living radicals as most likely for the iodo-containing aryl halides (Scheme 10). In contrast, the fluoro-, bromo-, and chloro-substituted compounds **15** seem to react through a typical S_NAr mechanism.[24]

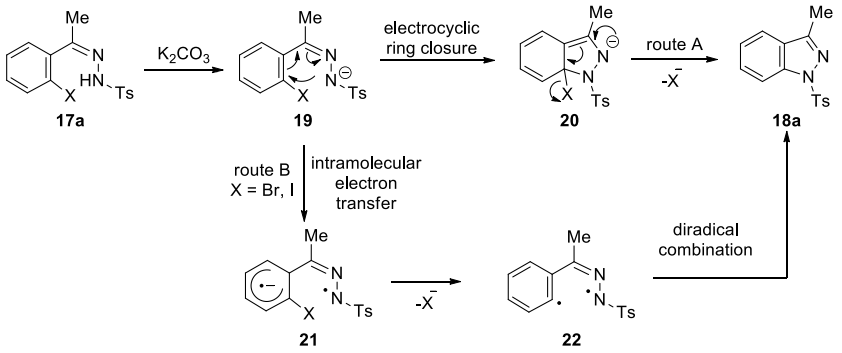


Scheme 10

Bolm and co-workers have recently reported a transition metal-free, the base mediated procedure for the synthesis of 1*H*-indazoles **18** via intramolecular *N*-arylation of *o*-halo tosyl hydrazones **17** in presence of the catalytic amount of trans-*N*,*N'*-dimethyl cyclohexane, and K_2CO_3. The reaction proceeds at room temperature yielding various products **18** in high yields within 2.5 h (Scheme 11).[25] Based on a detailed study, a probable mechanism was suggested as shown in Scheme 12. Thus, deprotonation of hydrazine moiety of starting **17** as the initial step yields allyl diazo anion, which could undergo electrocyclic ring closure to yield intermediate anion **19**, which on the loss of halide anion would give product **18** directly (route A) (Scheme 12). Alternatively, the reaction could proceed through radical intermediate (route B). Thus, intramolecular electron transfer from the allyl diazo anion moiety on to aryl part of **19** could provide intermediate **21**, which



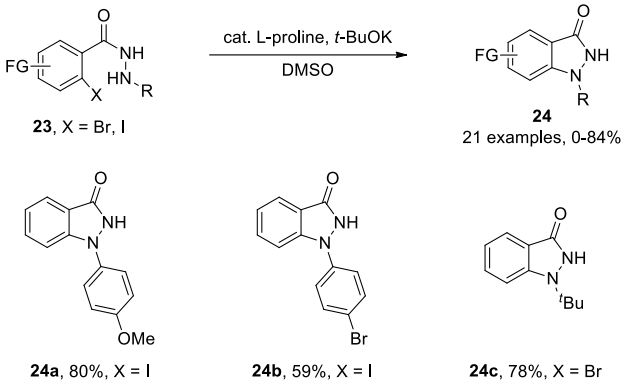
Scheme 11



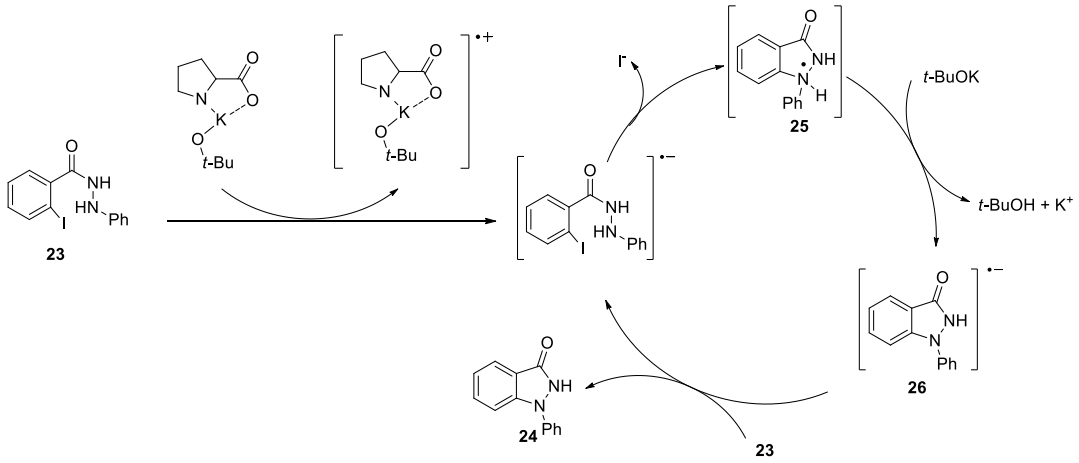
Scheme 12

Would lose a halide anion to give diradical **22** in analogy with well-established $S_{RN}1$ mechanism. Product **18** is formed by the radical combination of diradical **22**. Investigation of the reaction mixture by ESR spectroscopy showed the presence of organic radicals.[25]

Tanimori and co-workers,[26] in a similar study, have reported the formation of indazolones **24**, from 2-halobenzohydrazides **23**, in presence of *tert*-butoxide as a base, catalytic L-proline in DMSO. They have also proposed a similar $S_{RN}1$ mechanism involving radical intermediates **25**-**26** (schemes 13-14).

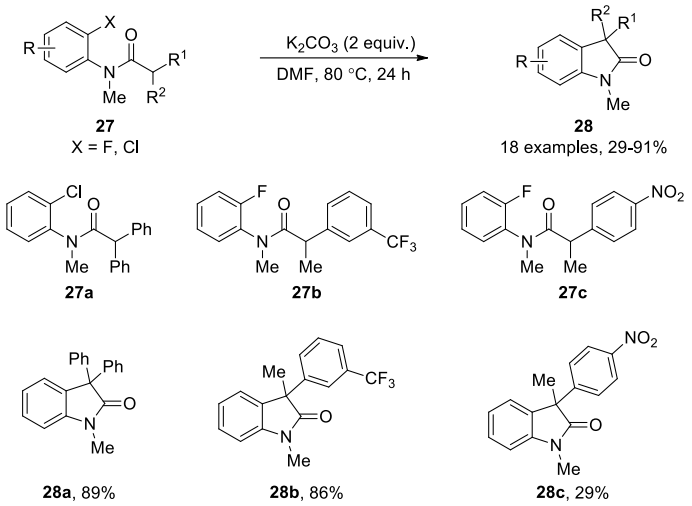


Scheme 13



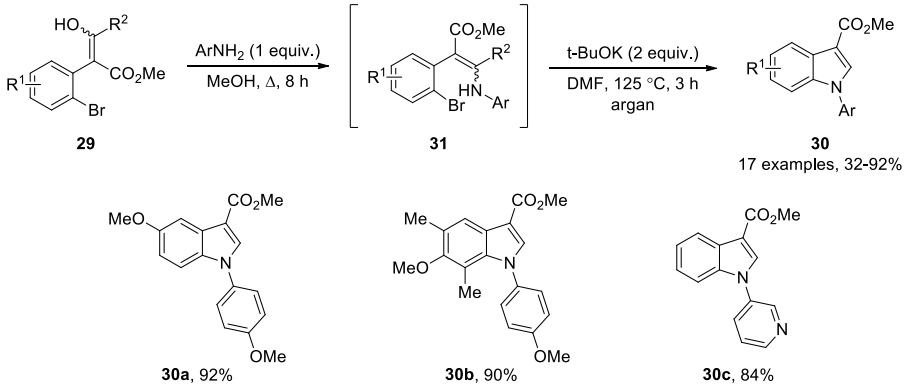
Scheme 14

Bolm and co-workers, in a later study, described *tert*-butoxide mediated intramolecular α- arylation of *o*-fluoro- and chloro- substituted anilides **27** providing oxindoles **28** in high yields (Scheme 15).[27] Based on experimental studies they proposed a probable S_NAr mechanism.



Scheme 15

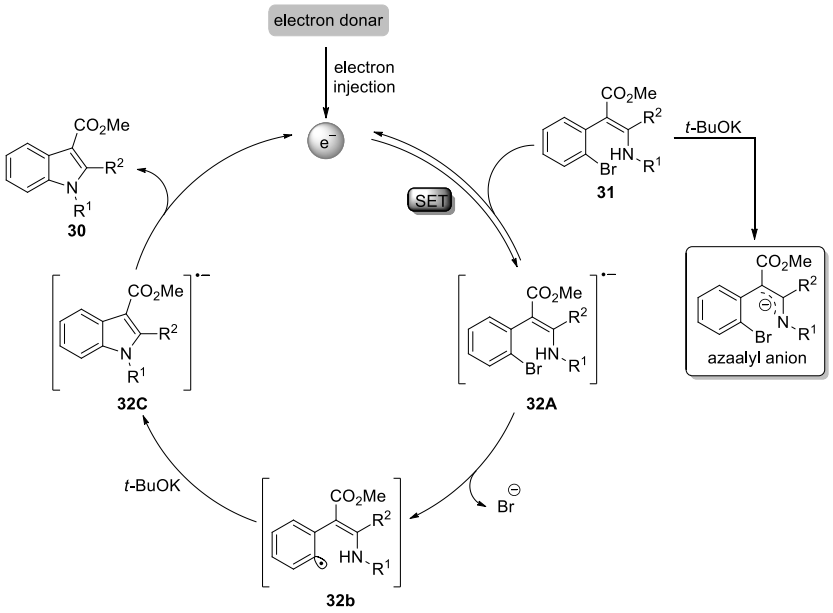
Karchava and co-workers in a recent study, have disclosed a new strategy for *N*-functionalized indole-3-carboxylates **30** under transition metal-free conditions from *o*-bromo eneesters **29** employing t-BuOK/DMF system without any initiator or additives (Scheme 16).[28] These authors have demonstrated high functional group tolerance, the new conditions are particularly useful for large-scale synthesis of halogenated indoles which cannot be made in pure form using TM catalyzed reactions. The authors named it 'electron catalyzed' intramolecular C-N bond formation for this reaction. The proposed mechanism is shown in Scheme 17. According to Studer-Curran's proposal, the reaction begins with the initial injection of an electron providing the actual catalyst the electron. The base BuOk/DMF system or azaallyl anion from **31** can serve as an electron donor to initiate the



Scheme 16

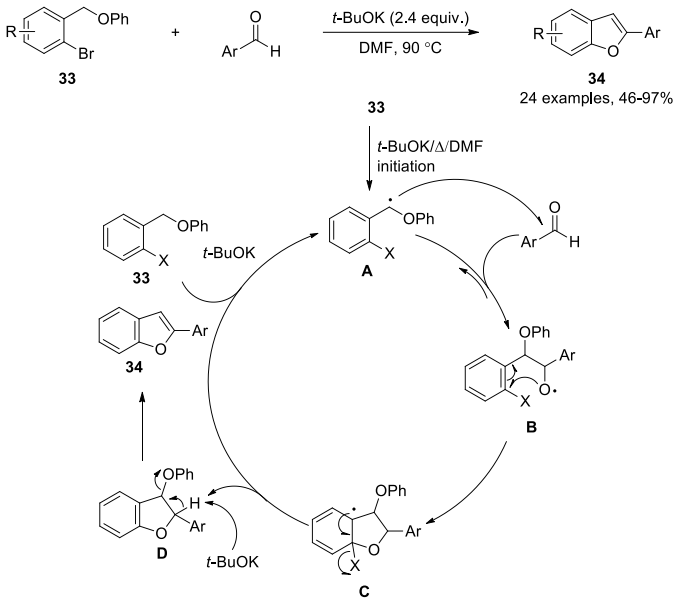
process. Reduction of **31** with a single electron generates the corresponding radical anion **32A** which upon fragmentation of bromide radical provides the radical **32B** followed by

intramolecular trapping of **32B** with *N*-nucleophile generating the radical anion **32C**, which finally acts as an electron donor for the next substrated **31**, thus giving the product **30** and liberating the electron back to catalyst (Scheme 17).



Scheme 17

There are scarce examples of the synthesis of oxygen-containing benzoheterocycles via TM-free intramolecular *O*-arylation Kang and Qu recently reported the synthesis of benzofurans from *o*-halobenzyl ether **33** and aldehydes in presence of potassium *tert*-butoxide as a base (Scheme 18).[29] Reaction involves the first generation of alkyl radical adding to the carbonyl group of aldehyde followed by intramolecular alkoxy radical addition to haloarenes yielding benzofurans **34** in good yields *via* elimination of phenoxy group and radicals (Scheme 18).[29] The author has proposed a radical mechanism based on ESR and other studies (Scheme 18). Thus, radical **A** is generated by the *t*-BuOK-DMF system under heating conditions. Trace alkoxy radical **B** is formed reversibly from the addition of **A** to the carbonyl group of aldehydes. Alkoxy radicals **B** is not thermodynamically favorable and tends to go back to **A** or is trapped by the haloarene via intramolecular radical addition process to form more stable radical **C**, which is converted **D** *via* dehalogenation, yielding the final product benzofuran **34**, *via* elimination of phenoxy radical. The detailed mechanism for the regeneration of **A** is not clear which probably involves a halogen or benzoyl radical.

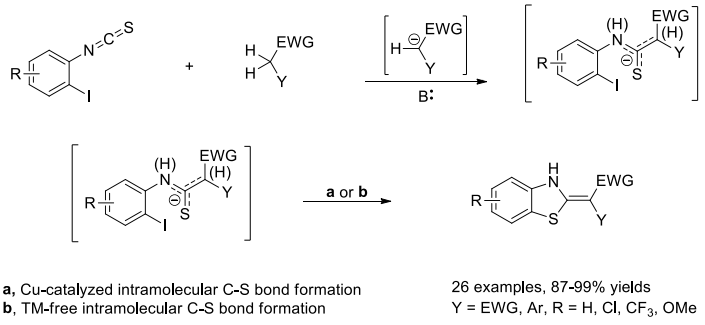


Scheme 18

1.2 Present Work

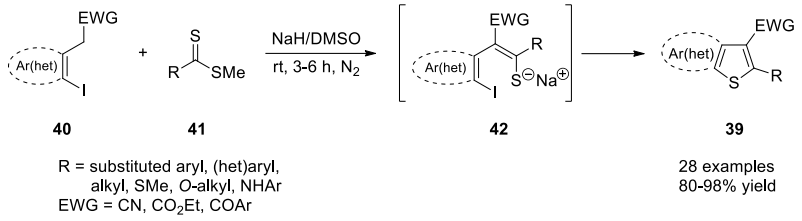
On the basis of the above studies, our research group initiated the synthesis of benzo-fused sulfur-heterocycles, through an intramolecular transition metal-free C-S coupling reaction for which there was no example in the literature.

The Chapter 2 of the thesis, describes a new, facile transition-metal-free, domino synthesis of 2-substituted benzothiazoles **35**, involving base-mediated one-pot addition of active methylene compounds **36**, to *o*-iodoarylisothioacyanates **37** and subsequent intramolecular C-S bond formation of the resulting thioamidate anion **38**. The reaction proceeds at room temperature within 1-3 h, affording diversely substituted benzothiazoles **35** in high yields. A possible radical intermediate pathway, via an $S_{RN}1$ mechanism, has been proposed for intramolecular C-S bond formation (Scheme 19).



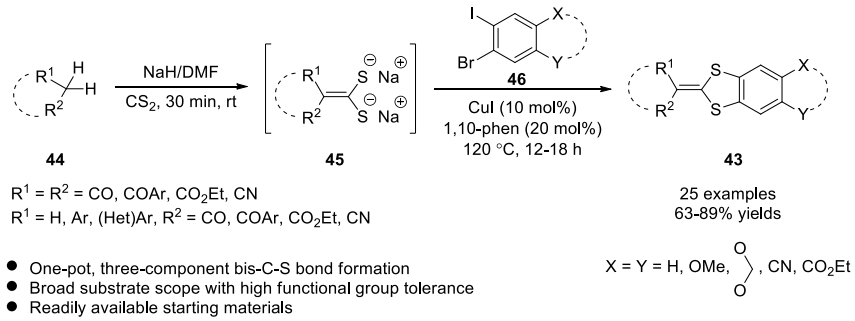
Scheme 19

The Chapter 3 of the thesis deals with a novel transition-metal-free, one-pot synthesis of 2,3-substituted benzo[*b*]thiophenes **39**, involving a tandem base-mediated condensation of *o*-iodoaryl acetonitriles/acetates/ketones **40** with (hetero)aryl dithioesters **41** and an intramolecular C-S bond formation of the resulting enethiolate anion **42**. The reaction affords diversely substituted benzothiophenes and hetero-fused thiophenes in excellent yields (Scheme 20).



Scheme 20

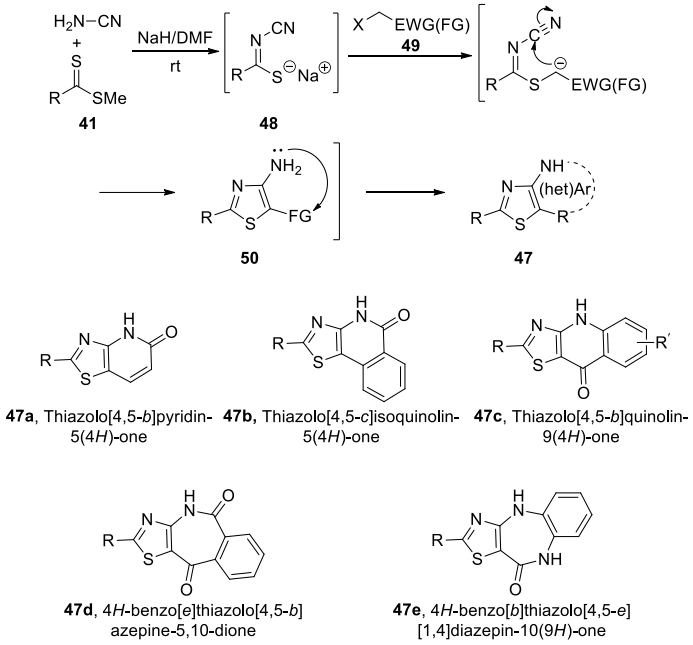
The Chapter 4 of the thesis deals with an efficient one-pot, three-component synthesis of novel push-pull 1,3-benzodithiol-2-ylidenes **43**, involving the reaction of active methylene compounds **44** with CS_2 in the presence of sodium hydride as the base, followed by in situ copper-catalyzed bis-C-S coupling of the resulting dithioate salts **45** with 1-bromo-2-iodobenzenes **46**. The methodology involves readily available starting materials and tolerates a broad range of functional groups (Scheme 21).



Scheme 21

The Chapter 5 of the thesis describes the domino synthesis of novel 2-(het)aryl-substituted thiazolo-fused six- and seven-membered heterocycles, such as thiazolo[4,5-*b*]pyridin-5(4*H*)-ones **47a**, thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones **47b**, thiazolo[4,5-*b*]quinolin-9(4*H*)-ones **47c**, 4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-diones **47d**, have been developed in a single-pot operation via intramolecular heteroannulation of in situ

generated 2-(het)aryl-4-amino-5-functionalized thiazoles **50**. These 4-amino-5-functionalized thiazoles were readily obtained in a one-pot process by treatment of a range of (het)aryldithioesters **41** with cyanamide in the presence of NaH, followed by in situ *S*-alkylation intramolecular condensations of the resulting thioimidate salts **48** with suitable halo alkylating agents **49**. On the other hand, the corresponding 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones **47e**, were synthesized in a two-step process requiring prior isolation of 5-carboethoxy-4-(2-nitrophenyl)aminothiazoles and their subsequent reductive cyclization. The functionalized activated methylene halides employed in these reactions for the synthesis of various thiazolo-fused heterocycles were methyl bromocrotonate, ethyl 2-(bromomethyl)benzoate, 2-fluorophenacyl bromides, ethyl 2-(2-bromoacetyl)benzoate and ethyl bromoacetate. Several of these thiazolo-fused heterocycles display yellow-green to green fluorescence and their absorption and emission spectra have also been examined (Scheme 22).



Scheme 22

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Chapter 2

*Domino Synthesis of 2-Substituted Benzothiazoles by Base-Promoted Intramolecular C-S Bond Formation**

2.1 Introduction

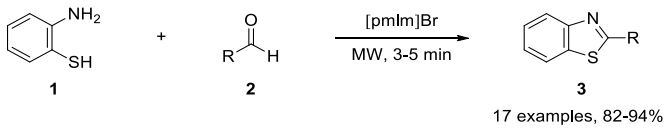
2-Substituted benzothiazoles make up an important class of nitrogen- and sulfur-containing heterocycles, present in several important natural products and synthetic compounds, displaying a broad range of biological activities,[1,2] such as anticancer, anti-Alzheimer's, antibacterial, and antimicrobial activities,[2] and have also found application in material science.[3] Therefore, the development of new, efficient synthetic methods for diversely functionalized benzothiazoles has attracted much attention among synthetic and medicinal chemists.

2.2 Synthesis of 2-Substituted Benzothiazoles: A Short Literature Survey

2.2.1 Synthesis of Benzothiazoles via Oxidative Cyclization

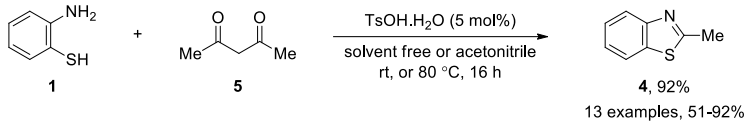
*The overall results of the study described in this chapter have been published in *Org. Lett*. **2019**, *21*, 7863.

One of the approaches for the synthesis of 2-substituted benzothiazoles involves oxidative condensation of 2-aminothiophenols with aldehydes or carboxylic acids. Recently, Ranu and co-workers have reported an efficient method for the synthesis of benzothiazoles **3** via mild oxidative cyclization and condensation of 2-aminothiophenol **1** with aromatic aldehydes **2** in an ionic liquid medium, under microwave irradiation (Scheme 1).[4a]



Scheme 1

Later in 2014, Yamamoto and co-workers have similarly reported the synthesis of benzothiazoles **4** by the Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols **1** with *β*-diketones **5**, which are readily available starting materials and broad substrate scope under mild reaction conditions (Scheme 2).[4b]

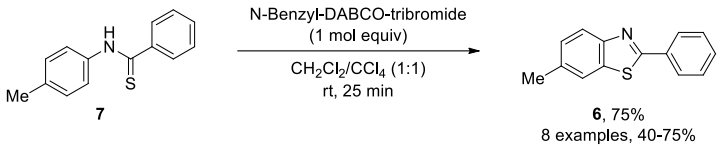


Scheme 2

Another most widely used classical route for the synthesis of 2-substituted benzothiazoles is Jacobson's cyclization or Hugerschoff reaction involving oxidative cyclization of thiobenzanilides. In recent years, several new alternatives for the synthesis of 2-substituted benzothiazoles[5] by Hugerschoff reaction, consisting of the oxidative cyclization of arylthioureas to 2-aminobenzothiazoles with liquid Br_2 in $CHCl_3$ are reported.

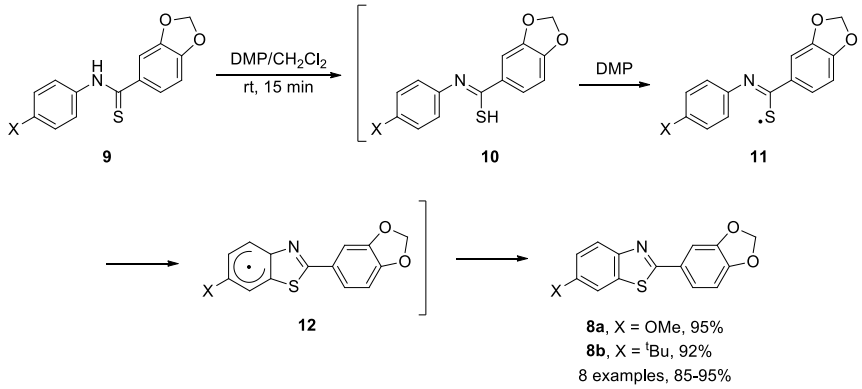
Despite the merits of reaction taking place at room temperature, liquid bromine being a highly toxic and corrosive reagent makes it difficult for handling. Hence, organic ammonium tribromides (OATBs) such as benzyl trimethyl-ammonium tribromide and tetrabutylammonium tribromide, which are stable, crystalline solids, and capable of delivering a stoichiometric amount of bromine are used as effective alternatives.

Benzyl trimethyl-ammonium tribromide has been successfully used for the conversion of substituted aryl thioureas to the respective 2-aminobenzothiazoles. However, this reaction is limited to symmetrical *N*,*N*-dialkylaminothiourea derivatives, as the asymmetric *N*, *N*'-diarylthiourea derivatives could lead to the formation of two different regioisomers. In 2005, Hassan and a co-worker reported an efficient and novel protocol for the synthesis of 2-arylbenzothiazoles **6** exclusively, by treating thiobenzanilide **7** with an equimolar amount of an organic ammonium tribromide (OATB) (Scheme 3).[5a,8b]



Scheme 3

In 2006, Idrees and co-workers have developed a new, mild, and efficient protocol for the synthesis of 2-substituted benzothiazoles **8** via the intramolecular cyclization of thioformanilides by using hypervalent iodine reagents in CH_2Cl_2 at ambient temperature.

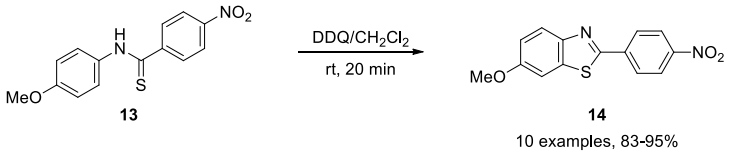


Scheme 4

Among several hypervalent iodine reagents such as IBX, and DAIB were studied for this transformation, DMP (Dess-Martin periodinane) was found to be the most effective in terms of product yields and reaction rates. A plausible mechanism proposed for DMP-promoted cyclization reaction is presented in Scheme 4. Thioiminol **10** form of arylthioformanilide **9**, reacts with DMP to produce thiyl radical **11** while iodine (V) is

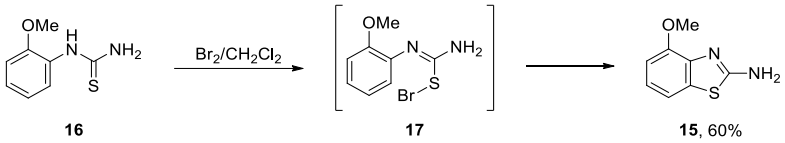
reduced to iodine (IV) at the same time. Subsequently, 1,5-homolytic radical cyclization of **11** followed by aromatization of radical **12** gives 2-arylbenzothiazole **8** (Scheme 4).[5b]

In continuation, Idrees and co-workers have developed an efficient novel and practical approach towards the synthesis of benzothiazoles **14** via the intramolecular cyclization of thioformanilides **13** using DDQ as an oxidizing agent. (Scheme 5).[5c]



Scheme 5

Alternatively, Thiel and co-workers have developed an efficient method to access 2-amino substituted benzothiazoles **15** from 1-(2-methoxyphenyl)thiourea **16** via oxidative cyclization with molecular bromine (Hugerschoff reaction) (Scheme 6).[5d]

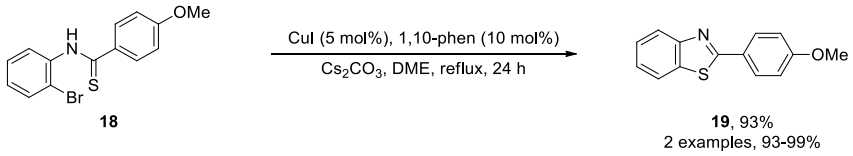


Scheme 6

2.2.2 Synthesis of Substituted Benzothiazoles via Transition Metal-Catalyzed Intramolecular C-S Cross-Coupling Reactions

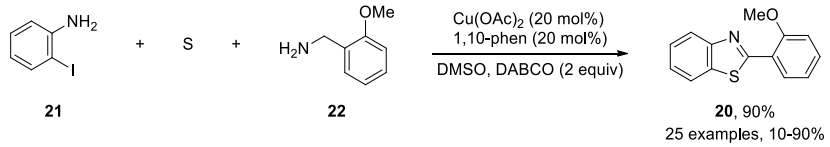
Recent advances in carbon-heteroatom bond formation have led to the development of several new methods for the synthesis of benzothiazoles[4-8] and their analogs, involving transition metal-catalyzed intramolecular C-S bond formation of *o*-halothiobenzanilides.

Batey and co-workers have developed an efficient approach to access benzoxazoles and benzothiazoles **18** using ligand-accelerated copper-catalyzed cyclization of *o*-halobenzanilides **19** through ligand-promoted Ullmann-type coupling reaction (Scheme 7).[6a]



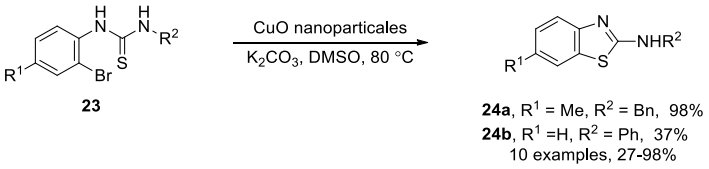
Scheme 7

Wang and co-workers have developed a relatively cheap copper salt-catalyzed, three-component approach providing 2-arylbenzothiazoles **20** in good to excellent yields from commercially available 2-iodoanilines **21**, benzylamines **22**, and sulfur powder (Scheme 8). This methodology allows a general reliable approach for the preparation of various classes of 2-arylbenzothiazoles (Scheme 8).[6b]



Scheme 8

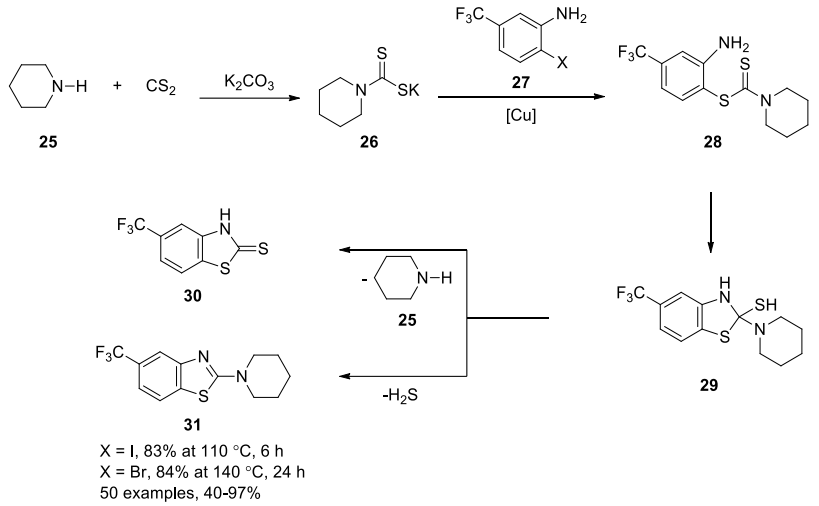
Punniyamurthy and co-workers have recently reported high yield synthesis of 2-aryl/alkylaminobenzothiazoles such as **24**, via copper-catalyzed intramolecular cyclization of *o*-bromoaryl thioureas **23** (Scheme 9).[6c] This methodology gives excellent yields of desired product **24a** when R^2 = alkyl, alicyclic, benzyl and low yields of the products **24b**, when R^2 = aryl (Scheme 9).[6c]



Scheme 9

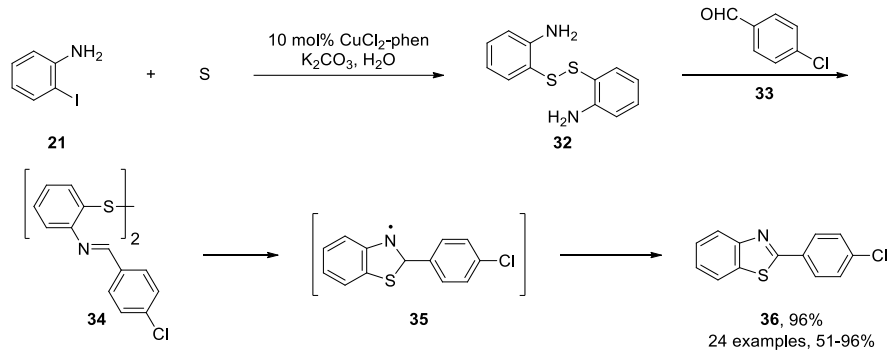
Just a while ago, Ma and co-workers have investigated the reaction of substituted 2-haloarylamine with carbon disulfide and piperidine, under copper catalysis (Scheme 10).[6d] Thus, when commercially available piperidine **25** and CS_2 are reacted in presence of DMF and K_2CO_3, the resulting dithiocarbamate salt **26** undergoes copper-catalyzed C-S coupling with 2-haloaniline **27** providing corresponding dithiocarbamate intermediate **28**

which undergoes intramolecular cyclo-condensation to afford benzothiazole **31** along with minor product **30** (Scheme 10).[6d]



Scheme 10

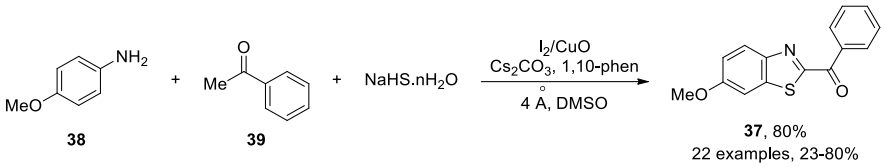
Recently, Zhou and co-workers have reported a three-component synthesis of substituted benzothiazoles in an aqueous medium via Cu-catalyzed coupling of 2-iodoaniline such as **21** with sulfur powder, to provide diaryl disulfide product **32**. Subsequent reaction of **32** with aromatic aldehydes **33** affords benzothiazoles **36** in high yields via imine intermediate **34** (Scheme 11).[6e]



Scheme 11

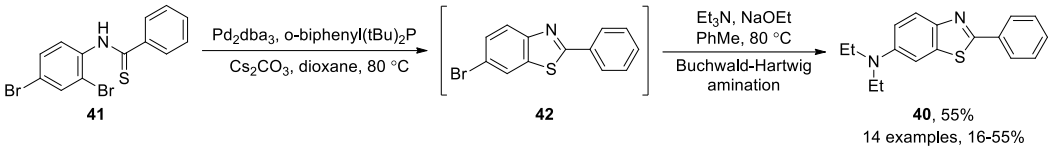
Wu and co-workers have developed a novel and efficient copper-catalyzed protocol to access benzothiazoles **37** from readily available anilines **38**, and aromatic ketones **39** in presence of NaHS $n$$H_2O$ (Scheme 12).[6f] This novel strategy involves the construction of

benzothiazoles **37** via assembling of six sequential reactions in one-pot in a domino fashion (Scheme 12).[6f]



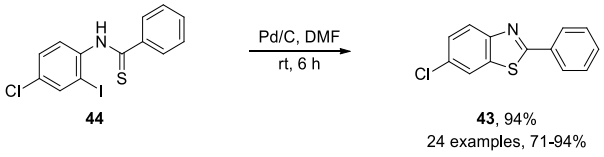
Scheme 12

Vera and coworkers have recently developed the palladium-catalyzed synthesis of 2-aryl-6-dialkylamino benzothiazoles such as **40** from 2,4-bisbromothioamide **41**, involving tandem catalytic *S*-, and *N*-arylation reaction (Scheme 13).[7a]



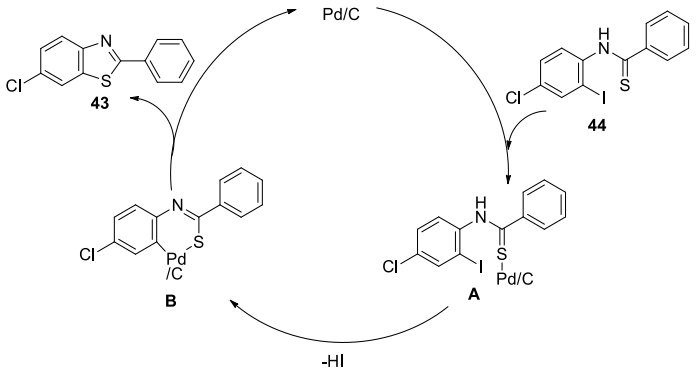
Scheme 13

Recently, Li and co-workers have developed a new highly efficient, and mild protocol for the synthesis of 2-substituted benzothiazole such as **43** by Pd/C-catalyzed intramolecular C-S bond formation *o*-iodothiobenzanilide such as **44** at room temperature without the addition of any ligands and additives (Scheme 14).[7b]



Scheme 14

The plausible reaction pathway suggests that the reaction is likely to be initiated by coordination of the sulfur atom to Pd/C,[7b] leading to the formation of palladacycle intermediate **B** which on reductive elimination affords the 2-substituted benzothiazole **43** and regenerating palladium catalyst (Scheme 15).

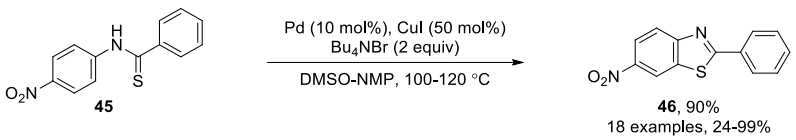


Scheme 15. Proposed mechanism of benzothiazole formation from Pd/C-catalyzed coupling

2.2.3 Transition Metal-Catalyzed Synthesis of 2-Substituted Benzothiazoles via Transition Metal-Catalyzed C-H Functionalization/Intramolecular C-S Bond Formation

Another common protocol for the synthesis of 2-substituted benzothiazoles is transition metal-catalyzed C-H functionalization/intramolecular C-S bond formation.[8] Various catalytic systems based on rhodium, ruthenium, palladium, and copper have been developed to affect C-C and C-heteroatom (nitrogen and oxygen) bond formation.

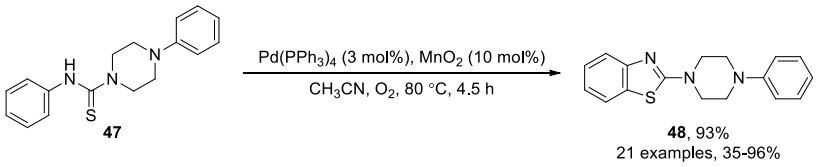
Doi and co-workers have recently developed an efficient protocol for the synthesis of 2-substituted benzothiazoles via palladium-catalyzed intramolecular C-H activation followed by C-S bond formation of thiobenzamide such as *N*-(4-nitrophenyl)benzothioamide **45** using Pd catalyst in presence of CuI as oxidant and Bu_4NBr as an additive, yielding 6-nitro-2-phenylbenzo[*d*]thiazole **46** in 90% yield (Scheme 16).[8a]



Scheme 16

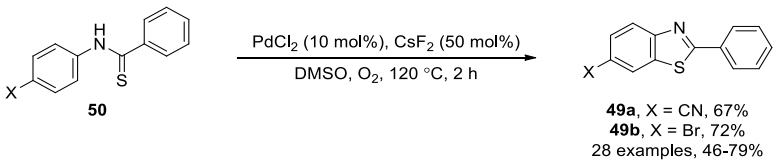
Alternately, Batey and co-workers have reported high yield synthesis of 2-aminobenzothiazoles **48** [6c,6d,8b] from oxidative intramolecular cyclization of *N*-

arylthioureas **47** using an unusual co-catalytic $Pd(PPh_3)_4/MnO_2$ system under oxygen atmosphere at 80 °C (Scheme 17).[8b]



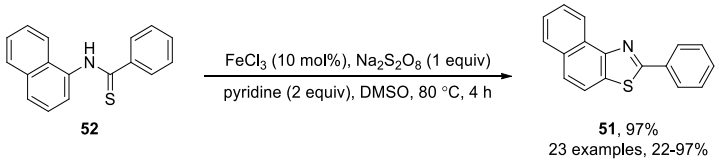
Scheme 17

Similarly, Inamoto, Doi and co-workers explored a facile and efficient protocol for 2-substituted benzothiazoles[4b,5a-b,6a-b,6e,7b] such as **49** via palladium-catalyzed C-H functionalization/intramolecular C-S bond formation under molecular oxygen employed as a re-oxidant in cyclization from thiobenzanilides[5a-c,8a] **50** (Scheme 18).[8c]



Scheme 18

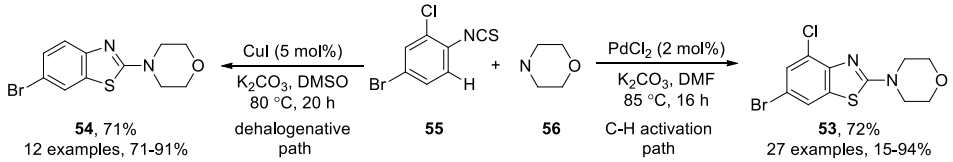
In 2012, Lei and co-workers have reported an efficient approach for the synthesis of 2-substituted benzothiazoles[4b,5a-b,6a-b,6e,7b] derivative such as **51** via Fe-catalyzed direct oxidative C-H functionalization/intramolecular C-S bond formation under mild conditions from thiobenzanilides[5a-c,8a-c] **52**. The mechanistic studies revealed that pyridine played a crucial role in the high yields and selectivity in this transformation (Scheme 19).[8d]



Scheme 19

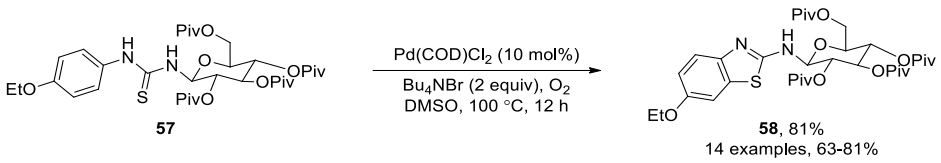
Recently Patel and coworkers have developed, a regioselective intramolecular C-S bond formation during the formation of 2-aminobenzothiazoles **53**, **54** from 2-halothioureas[6c,9d] intermediate generated in situ using either Cu(I) or Pd(II) transition metal catalysts (Scheme 20). These ligand-free regioselective syntheses of 2-amino

benzothiazole[5d,6c-d,8b,9c-d] are advantageous over other reported methods in literature (Scheme 20).[8e]



Scheme 20

Liu and co-workers have recently developed[2f-g] a synthesis of glucose-containing benzothiazoles such as **58** via palladium-catalyzed C-H activation intramolecular-cyclization of sugar-substituted *N*-arylthiourea such as **57** (Scheme 21).[2f]



Scheme 21

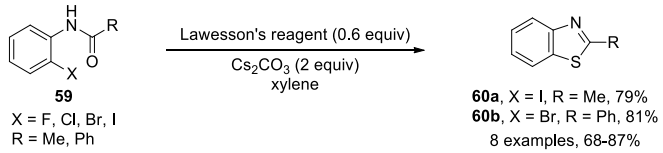
To overcome these shortcomings, the use of toxic and expansive transition metal-catalysts/ligands, prefunctionalization of starting materials, harsh reaction conditions, and somewhat limited substrate scope diminishes the attractiveness of these methods, much attention has been paid recently towards the development of transition metal-free protocols. In recent years, 'transition metal-free cross-coupling processes' for the formation of C-C, C-N, C-O, and C-S bonds, have attracted considerable interest among synthetic organic chemists (Chapter 1).[10] Several research groups have reported significant contributions in this field, in the past several years, including transition metal-free C-H arylations, for the construction of biphenyl frameworks.[11]

Bolm and co-workers, in their pioneering work, first reported a detailed study of intermolecular cross-coupling reactions between aryl halides and various sulfur, oxygen, and nitrogen-based nucleophiles (*N*-, *O*-, *S*- arylation) in the presence of KOH/DMSO as 'superbase' medium[12-13] under transition metal-free conditions (Chapter 1). In particular, these groups and others[14] have also developed base-promoted transition metal-free intramolecular ring closing reactions, involving C-heteroatom bond formation, which

showed great potential for the synthesis of heterocyclic compounds such as 2-oxobenzimidazoles,[15a] phenoxazines,[15b] indazoles,[14a,15a] benzimidazoles,[14d,15d] oxindoles[15e] indoles,[14b] and benzofurans (Chapter 1).[14c] Some of these transition metal-free coupling reactions, are shown to proceed by direct nucleophilic aromatic substitution (S_NAr reaction) or via benzyne mechanism, whereas others were proposed to occur via single electron reduction of aryl halides, involving radical or radical ion species, to induce substitution reaction with heteroatom nucleophiles ($S_{RN}1$ reactions),[10-11] sometimes also termed as 'electron-catalyzed reactions'.[11d, 12f,14b] However, the actual detailed mechanism of some of these reactions has not been fully understood, which may also vary according to the type of substrates and reaction conditions.

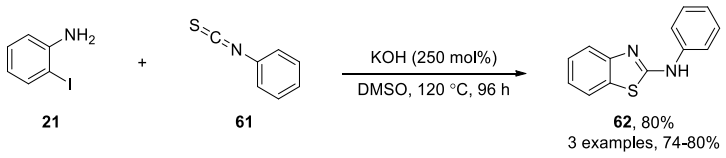
2.2.4 Synthesis of 2-Substituted Benzothiazoles via Base-Promoted Transition Metal-Free Intramolecular C-S Bond Formation

There are few reports in the literature regarding transition metal-free base-promoted synthesis of benzothiazoles via intramolecular cyclization of appropriate precursors. Thus, Kirsch and coworkers have reported the synthesis of benzothiazoles **60**,[5a,9b] by Cs_2CO_3 mediated intramolecular cyclization of in situ generated thiobenzanilides from *o*-halobenzamides **59** on treatment with Lawessons reagent in refluxing xylene (Scheme 22).[9b-c]



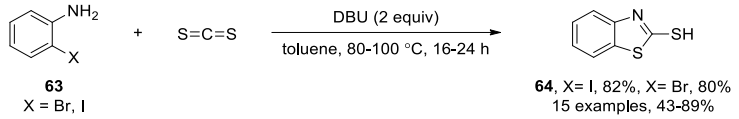
Scheme 22

Yus and co-workers, developed a new protocol for the synthesis of 2-anilinobenzothiazoles such as **62** by heating *o*-iodoaniline **21** with phenyl isothiocyanate **61** in presence of an excess of KOH in DMSO for several days, is described.[9d] They have suggested a possible pathway involving benzyne intermediate (Scheme 23).[9d]



Scheme 23

In 2011, Xi and co-workers have similarly reported an efficient approach for the synthesis of 2-mercaptobenzothiazoles such as **64** by cyclo-condensation of *o*-haloanilines **63** and carbon disulfide in presence of a base like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU (Scheme 24). [9e]



63
X = Br, I

64, X= I, 82%, X= Br, 80%
15 examples, 43-89%

Scheme 24

During the course of our ongoing work on the synthesis of five- and six-membered heterocycles and their benzo-fused analogs,[16] employing organosulfur intermediates, we have developed a facile transition metal-free protocol for the synthesis of substituted benzothiazoles bearing active methylene groups at 2-position [(2-benzothiazol-2(3*H*)-ylidene)esters/ketone/nitriles] via base-promoted tandem addition-intramolecular-cyclization of *o*-iodoarylisothiocyanates with various active methylene compounds in DMSO. The results of these studies have been reported in this chapter. The key features of the synthesis are, that the reaction proceeds at room temperature, within 1-3 h, in high yields, in the absence of any ligands or additives.

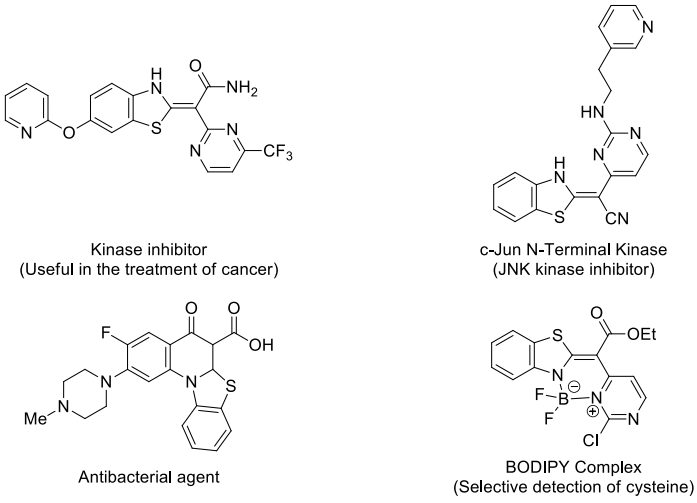
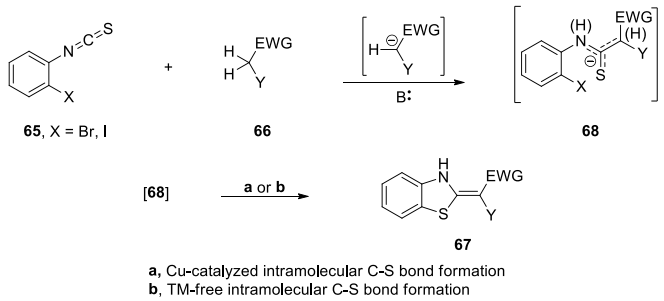


Figure 1. Biologically and material science important 2-substituted benzothiazoles.

A few of the 2-ylidenebenzothiazoles have found applications in medicinal chemistry as well as in material science. Thus, 2-[benzothiazol-2(3*H*)-ylidene]-2-(pyrimidin-2-yl)acetamides and their salts are shown to display "Aurora Kinase, VEGFR2[17a] and C-jun-N-terminal (JNK) kinase[17b] inhibitor" activity and are useful in the treatment of cancer (Figure 1). Similarly, few benzothiazolo-fused 5-oxo-6-carboxyquinoline and naphthyridine scaffolds also exhibit antibacterial properties.[18] Recently, a few of the benzothiazole-pyrimidine bidentate ligand-based boron difluoride[19a] and BODIPY complexes[19b] have been synthesized, which are found to be selective and sensitive fluorescent sensors for cysteine (Figure 1)

2.3 Results and Discussion

Our proposed synthesis of push-pull benzothiazoles **67** is shown in Scheme 25. Thus, it was anticipated, that the carbanion generated by deprotonation of active methylene compound **66**, will add to 2-halophenylisothiocyanate **65** yielding a stabilized thioamide anion **68**, which would undergo copper-catalyzed intramolecular C-S bond formation yielding the desired 2-substituted benzothiazoles **67**. Alternatively, we also envisioned that thioamide anion **68**, generated by base-mediated addition of active methylene compound **66** to *o*-iodophenylisothiocyanate **65** could also, undergo intramolecular C-S bond formation leading to 2-substituted benzothiazoles **67** under transition metal-free conditions either by nucleophilic aromatic substitution (S_NAr) or through radical pathway mechanism (Scheme 25).

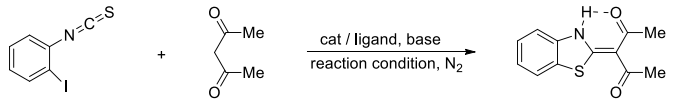


Scheme 25

We, therefore, initiated our studies by reacting *o*-iodophenylisothiocyanate **65a** with acetylacetone **66a** as model substrates for the optimization of reaction conditions, for the synthesis of (2-benzothiazol-2(3*H*)-ylidene)acetylacetone **67a** under copper-catalysis

(Table 1). Thus, when **65a** and **66a** were reacted in the presence of NaH (2 equiv) as a base, CuI (10 mol%) as a catalyst, proline as ligand (20 mole %) in DMF, at rt for 5 h, **67a** was obtained in only 47% yield (Table 1, entry 1). At higher temperature, the yield of **67a** was increased to 75% (Table 1, entry 2). Similarly, changing the ligand from proline to 1,10-phenanthroline resulted in higher yields of **67a** (Table 1, entry 3). However, a dramatic increase in the yield of **67a** was observed, when the reaction was conducted in the presence of CuI, in DMSO as the solvent, even at rt (Table 1, entry 4). The reaction also proceeded smoothly in DMSO, under ligand-free conditions furnishing **67a** in comparable yield (Table 1, entry 5). We, therefore, started wondering, whether copper catalysis was necessary for this cyclization, and indeed, to our delight, when **65a** and **66a** were reacted in the absence of CuI under identical conditions in DMSO, starting materials were consumed within one h, at rt and **67a** was isolated in 95% yield (Table 1, entry 6).

Table 1. Optimization of reaction conditions for the synthesis of benzothiazole **67a**[a]



65a **66a** **67a**

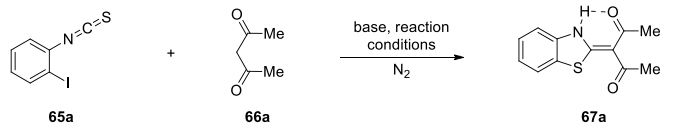
Entry	Catalyst (10 mol%)	Ligand (20 mol%)	Base (2 equiv)	Solvent	Temp (°C)	Time (h)	%Yield (**67a**)[a]
1	CuI	proline	NaH	DMF	rt	5	47
2	CuI	proline	NaH	DMF	60	5	75
3	CuI	1,10-phen	NaH	DMF	60	5	81
4	CuI	proline	NaH	DMSO	rt	5	91
5	CuI	-	NaH	DMSO	rt	4	90
6	**-**	**-**	**NaH**	**DMSO**	**rt**	**1**	**95**

[a]Reaction conditions: **65a** (1 mmol), **66a** (1 mmol), and NaH (2 equiv.) under N_2 atmosphere.Yields of pure isolated product

With these unexpected results in hand, we further examined the effect of various solvents and bases on the yield of **67a** under transition metal-free reaction conditions (Table 2, entries 1-11). Thus, the reaction of **65a** and **66a** was found to be slower at rt, in the presence of bases like *t*-BuOK, KOH, K_2CO_3, and Cs_2CO_3, in DMSO as the solvent, whereas reasonably good yields of **67a** were obtained at a higher temperature after 5-12 h (Table 2, entries 2-6). However, poor yields of **67a** were obtained by employing other solvents (DMF, toluene, THF, CH_3CN) in the presence of NaH as the base even at higher temperature (Table 2, entries 7-10), whereas the use of 1 equiv of NaH resulted in a

diminished yield of **67a** (Table 2, entry 11). We, therefore, employed NaH (2 equiv) as a base in DMSO at rt, as optimal reaction conditions for further studies (Table 2, entry 1).

Table 2. Optimization of reaction conditions for transition metal-free synthesis of **67a**[a]



65a + **66a** → **67a**

Entry	Base (2 equiv)	Solvent	Temp (°C)	Time (h)	% Yield (**67a**)[a]
1	**NaH**	**DMSO**	**rt**	**1**	**95**
2	t-BuOK	DMSO	rt	48	78
3	t-BuOK	DMSO	90	6	80
4	KOH	DMSO	90	12	75
5	K_2CO_3	DMSO	90	6	78
6	Cs_2CO_3	DMSO	90	5	83
7	NaH	DMF	60	12	50
8	NaH	Toluene	90	12	39
9	NaH	THF	65	18	35
10	NaH	CH_3CN	70	18	30
11[b]	NaH	DMSO	rt	10	80

[a]Reaction conditions: **65a** (1 mmol), **66a** (1 mmol), and base (2 equiv) in solvents under N2 atmosphere. [b]Reaction with 1 equiv of NaH. Yields of pure isolated product.

With the optimized reaction conditions in hand, for one-pot domino synthesis of 2-substituted benzothiazoles **67**, we next examined the scope and generality of this protocol and the results are displayed in Schemes 25-29. Various *o*-iodoarylisothiocyanates **65a-d** and other *o*-halo arylisothiocyanates bearing *o*-bromo (**65e**), *o*-chloro (**65f**), *o*-fluoro (**65g**) and *m*-iodo (**65h**) selected for this study are shown in Chart 1. The broad range of active methylene compounds (**66a-r**) selected to study the generality of this reaction are displayed in Chart 2.

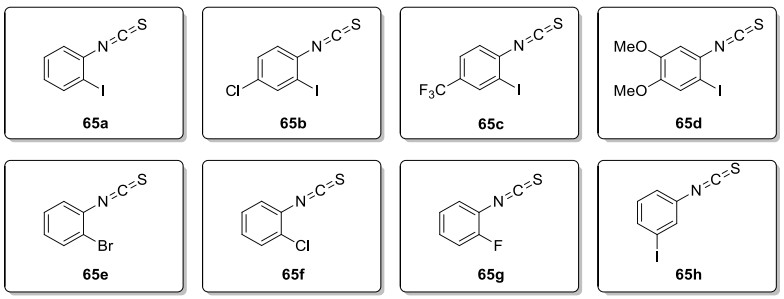


Chart 1. Various *o*-iodoarylisothiocyanates **65** employed for the synthesis of 2-substituted benzothiazoles **67**

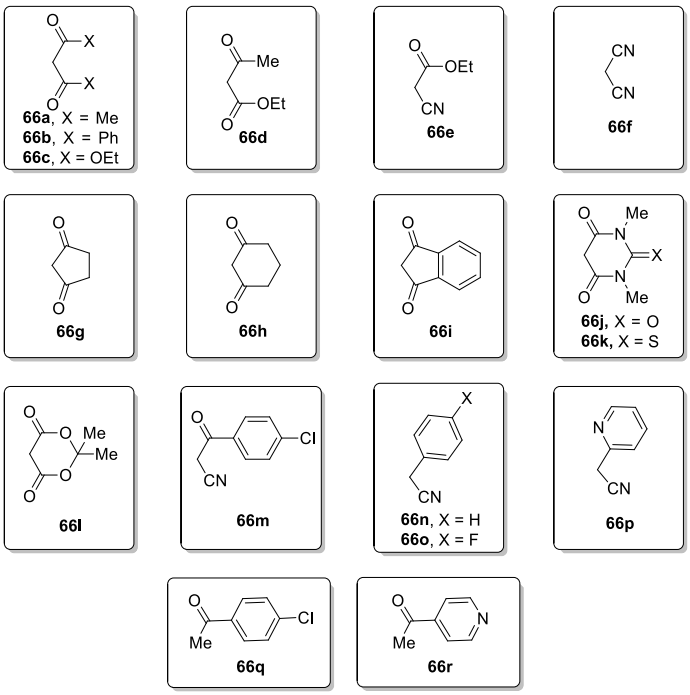
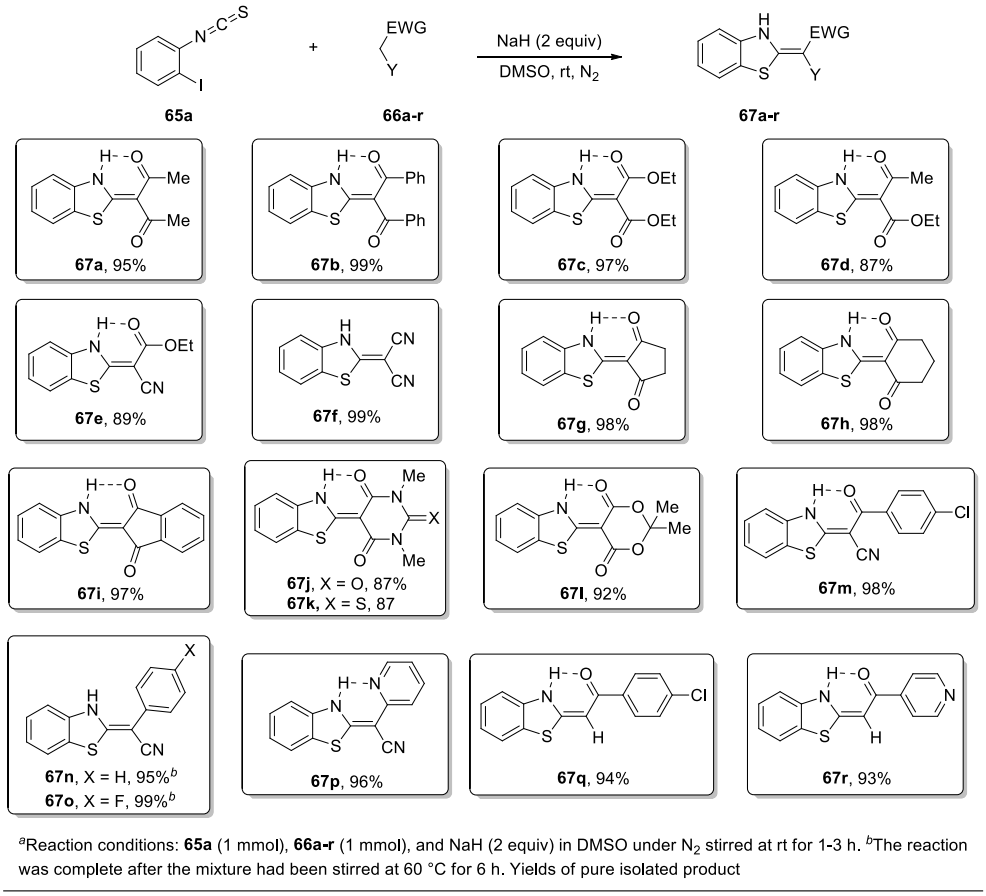


Chart 2. various activated methylene derivatives **66** employed for the synthesis of 2-substituted benzothiazoles **67**

We next explored the scope of this novel transition metal-free synthesis of other 2-substituted benzothiazoles **67**, by reacting the various active methylene compounds **66a-r** with *o*-iodoarylisothiocyanates **65a-d** bearing both electron-withdrawing groups (**65b-c**) and electron donating group (**65d**) in DMSO under optimized reaction conditions (Scheme 26). Thus, acyclic active methylene compounds such as dibenzoyl methane (**66b**), diethyl malonate (**66c**), ethyl acetoacetate (**66d**), ethyl cyanoacetate (**66e**), and malononitrile (**66f**) reacted efficiently with *o*-iodophenylisothiocyanate **65a** under optimal conditions yielding the corresponding 2-substituted benzothiazoles **67b-f** in excellent yields (Scheme 26). The reaction was found to be equally facile with cyclic 1,3-diketones such as cyclopentane-1,3-dione (**66g**), cyclohexane-1,3-dione (**66h**), and indane-1,3-dione (**66i**) furnishing the corresponding sterically crowded (2-benzothiazol-2(3*H*)-ylidene)-1,3-diketones **67g-i** in nearly quantitative yields, when reacted with **65a** under standard reaction conditions (Scheme 26). The structure of these products was further confirmed by X-ray crystallographic data of compound **67h** (CCDC 1952893) (Figure 2).



Scheme 26. Substrate scope for the synthesis of 2-substituted benzothiazoles **67a-r**[a]

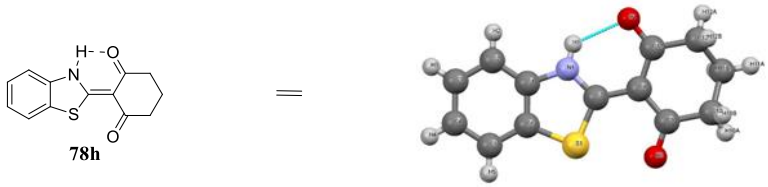
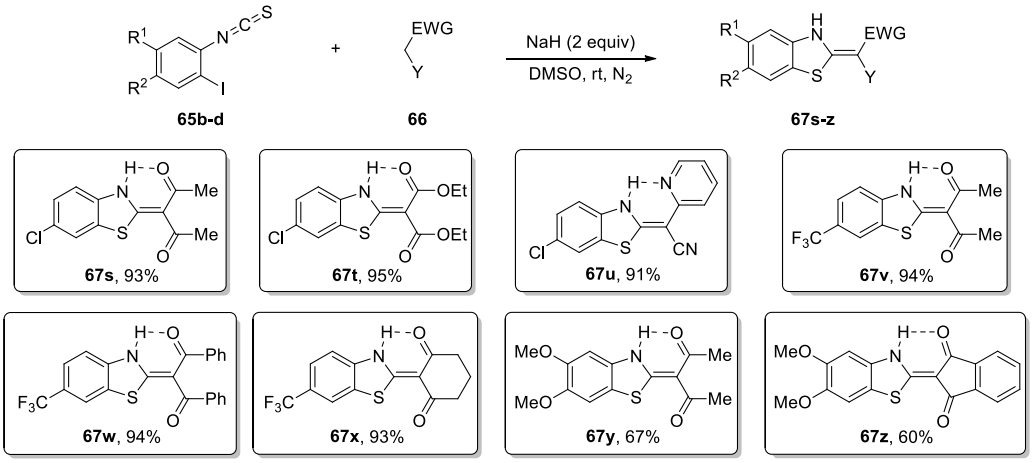


Figure 2. X-ray crystal diagram of **67h**

Further variation in substrate structures by employing sterically incumbent cyclic 1,3-dimethyluracil, thiouracil, and Meldrum's acid **66j-l** also did not affect the yields of benzothiazole products **67j-l** (Scheme 26). The corresponding unsymmetrically substituted active methylene compounds such as 4-chlorobenzoylacetonitrile (**66m**), phenylacetonitriles **66n-o**, 2-pyridylacetonitrile (**66p**) also underwent smooth tandem addition-cyclization with *o*-iodophenyl isothiocyanate **65a** under these optimized reaction conditions affording various functionalized benzothiazoles **67m-p** in very high yields (Scheme 26). The use of less acidic ketones such as 4-chloroacetophenone (**66q**), or 4-

acetylpyridine (**66r**), also did not affect the yields of the corresponding product (2-benzothiazol-2(3*H*)-ylidene) ketones **67q-r**, which were obtained in overall high yields (Scheme 26).

We next investigated the effect of substituents on *o*-iodoarylisothiocyanates **65b-d** bearing both electron withdrawing and electron donating substituents on the aryl ring (Scheme 27). Thus the reaction of isothiocyanates **65b-c** bearing either 4-chloro- or 4-(trifluoromethyl) groups, with acetylacetone (**66a**) or other active methylene compounds such as **66b**, **66c**, **66h**, and **66p**, proceeded smoothly under identical conditions within 1 h, furnishing the corresponding (2-benzothiazol-2(3*H*)-ylidene)carbonyl/nitrile compounds **67s-x** in high yields (Scheme 27). On the other hand, the corresponding 4,5-(dimethoxy)-2-iodophenylisothiocyanate (**65d**) bearing electron-donating groups afforded the cyclized benzothiazoles **67y-z** in decreased yields on reaction with **66a** and **66i** respectively, although the reaction was complete within 3 h (Scheme 27).



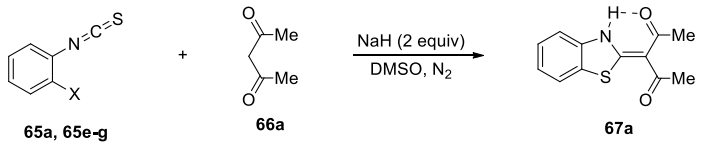
[a]Reaction conditions: **65b-d** (1 mmol), **66** (1 mmol), and NaH (2 equiv.) in DMSO under N_2 stirred at rt for 1-3 h. Yields of pure isolated product.

Scheme 27. Substrate scope for the synthesis of 2-substituted benzothiazoles **67s-z**[a]

The reactivity of a few *o*-halophenylisothiocyanates **65e-g** bearing bromine, chlorine, and fluorine respectively, was also examined towards acetylacetone (**66a**), along with a few additional experiments to provide some insight into the mechanism of this facile transition metal-free coupling reaction (Table 3 and Scheme 28). Thus, whereas, *o*-iodophenylisothiocyanate (**65a**) reacted with acetylacetone (**66a**) under standard

conditions within one hour at rt, yielding the benzothiazole **67a** in nearly quantitative yield (Table 3, entry 1), no trace of benzothiazole **67a** was observed in the reaction mixture, when the corresponding *o*-bromo and *o*-chlorophenylisothiocyanates **65e-f** were reacted with (**66a**) at rt under optimized conditions, even after the prolonged time (Table 3, entries 2 and 4). However, at a higher temperature at 90 ºC, **67a** was obtained in 57% and 60% yields, respectively after prolonged heating (Table 3, entries 3 and 5). On the other hand, the corresponding *o*-fluorophenylisothiocyanate (**65g**), gave only a 30% yield of benzothiazole **67a** at rt along with starting material even after 12 h (Table 3, entry 6), whereas at 60 ºC, **67a** was obtained in higher yield (70%) (Table 3, entry 7).

Table 3. Base-mediated reactions of various *o*-halophenylisothiocyanates **65a**, **65e-g** with Acetylacetone **66a**[a]

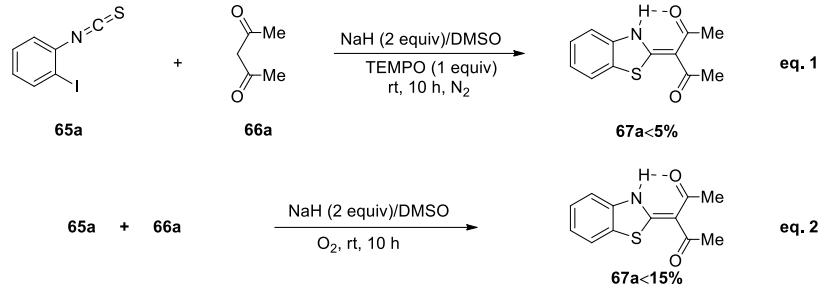


65a, 65e-g **66a** **67a**

Entry	65	X	Temp (°C)	Time (h)	% Yield (**67a**)
1	**65a**	**I**	**rt**	**1**	**92**
2	**65e**	Br	rt	12	-
3	**65e**	Br	90	12	57
4	**65f**	Cl	rt	12	-
5	**65f**	Cl	90	12	60
6	**65g**	F	rt	12	30
7	**65g**	F	60	12	70

[a]Reaction conditions: **65a**, **65e-g** (1 mmol), **66a** (1 mmol), and NaH (2 equiv.) in DMSO under N_2. Yields of pure isolated product.

The addition of TEMPO, a common trapping reagent for free radicals, nearly completely inhibited the cyclization, thus demonstrating the involvement of radical intermediates (Scheme 28, eq. 1). Similarly, when (**65a**) and (**66a**) were reacted under an oxygen atmosphere, the product **67a** was isolated only in 15% yield (Scheme 28, eq. 2). These experiments suggest, that the present transformation involves mainly the radical pathway.

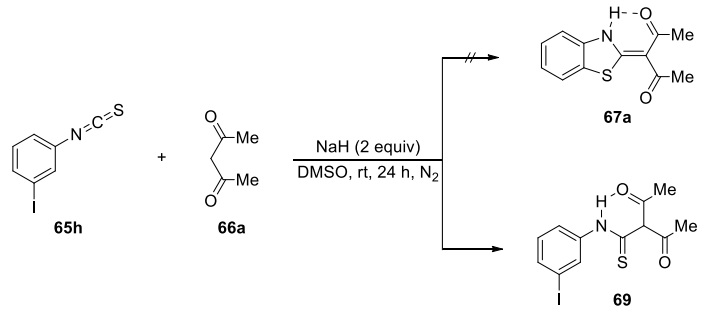


[a]Reaction conditions: (for eq. 1) **65a** (1 mmol), **66a** (1 mmol), and NaH (2 equiv.) in DMSO under N_2. (for eq. 2) **65a** (1 mmol), **66a** (1 mmol), and NaH (2 equiv.) and TEMPO (1 equiv.) in DMSO under O_2

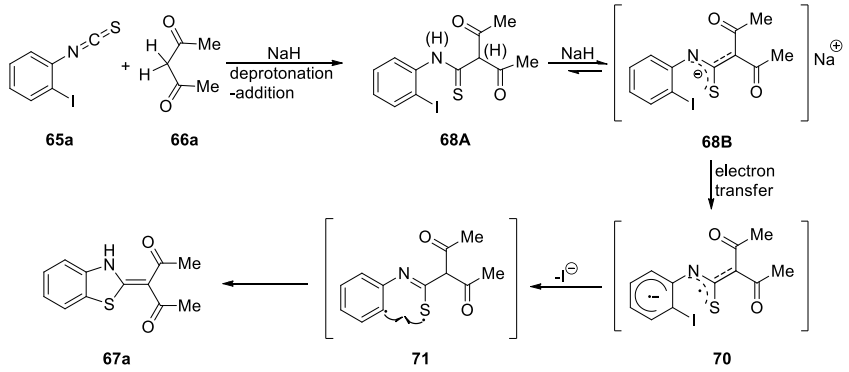
Scheme 28. Reaction of *o*-iodophenylisothiocyanate **65a** with acetylacetone **66a** in the presence of TEMPO and oxygen

Based on the previous reports and our own observations, we propose a possible radical intermediate pathway through $S_{RN}1$ mechanism,[20] as most likely, for this transition metal-free domino synthesis of benzothiazoles **67** from *o*-iodoarylisothiocyanate **65** and active methylene compounds **66**, as shown in the Scheme 29. Thus, the addition of carbanion (generated by deprotonation of (**66a**) to *o*-iodophenylisothiocyanate (**65a**) affords, initially, the thioamide intermediate **68A**, which is transformed into its conjugate base **68B**, under basic conditions. The anionic intermediate **68B** serves as an electron-donor, to initiate the radical process and undergoes intramolecular electron-transfer to aryl part of **68B**, to give the radical anion intermediate **70**. Finally, the loss of iodide ion from the intermediate **70**, in analogy with the well-established $S_{RN}1$ reactions, affords the diradical intermediate **71**, which undergoes intramolecular radical combination to furnish the product **67a** (Scheme 30). Since only *o*-iodoarylisothiocyanate derivatives **65a-d** cyclized efficiently to benzothiazoles **67**, whereas *o*-bromo/chloro/fluoro derivatives **65e-g** were found to be either completely inert or sluggish under identical conditions (Table 3, entries 2,4,6), we consider that an intramolecular nucleophilic substitution pathway (S_NAr) is unlikely, since the reactivity of *o*-halophenylisothiocyanates **65a**, **65e-g** does not follow the expected order of reactivity (F>Cl>Br>I) for a standard S_NAr mechanism. Similarly, failure of *m*-iodophenylisothiocyanate (**65h**) to furnish benzothiazole **67a** (Scheme 29), demonstrates that the benzyne intermediate is not involved in this cyclization reaction. The decreased yields of benzothiazoles **67y-z** obtained from 4,5-dimethoxy-2-iodophenylisothiocyanate (**65d**) (Scheme 27) appears to be due to the destabilization of

radical anion intermediate **70**, because of the presence of two electron-donating methoxy groups.



Scheme 29. Base-mediated reaction of *m*-iodophenylisothiocyanate **65h** with acetylacetone **66a**



Scheme 30. Proposed mechanism for the base-mediated formation of benzothiazole **67a** from **65a** and **66a** (Further we have corrected this mechanism in chapter 3)

2.4 Conclusion

In summary, we have developed a facile transition metal-free domino protocol for the synthesis of 2-substituted benzothiazoles, involving base-mediated tandem addition-intramolecular cyclization of *o*-iodoarylisothiocyanates and active methylene compounds. The cyclization reaction is promoted by NaH in DMSO at rt, proceeding within a few hours, yielding benzothiazoles in excellent yields. A wide range of active methylene compounds, bearing various functional groups are tolerated, giving access to a broad range of 2-substituted benzothiazoles. On the basis of various studies, a reasonable mechanism involving the formation of radical intermediates ($S_{RN}1$) has been proposed. To the best of our knowledge, such a transformation involving intramolecular

C-S bond formation at rt, leading to benzothiazoles, under mild transition metal-free conditions has not been reported in the literature.[15c] It should be noted, that although there are few examples[9] of base-promoted, transition metal-free synthesis of 2-substituted benzothiazoles via intramolecular cyclization of the corresponding *o*-halothiobenzanilides or other thiocarbonyl derivatives (Schemes 22-24),[9b-e] most of them require higher temperature (100-150 ^{0}C), sometimes excess of base and prolonged time.[9d] While potential mechanism for the benzothiazole formation has not been discussed in these reports, it was conceivable that these reactions proceeded via either nucleophilic aromatic substitution (S_NAr) or through a benzyne mechanism.[9e]

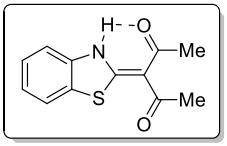
2.5 Experimental Section

2.5.1 General Information. All the reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography (TLC) using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100-200 mesh). Nuclear magnetic resonance spectra were recorded on (400 and 600 MHz) FT-NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts were reported in δ (ppm) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6, in ^{1}H NMR, δ 77.16 for $CDCl_3$, and δ 39.52 for DMSO-d_6 in ^{13}C NMR and ^{19}F NMR spectra were recorded at 564.65 MHz with the Brucker spectrometer). Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), and br (broad). Infrared spectra of neat samples were recorded in attenuated total reflectance (ATR) mode using an FT-IR instrument, and HRMS spectra were recorded using a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in the supporting information of *Org. Lett*. **2019**, *21*, 7863.

All the 2-halophenylisothiocyanates **65a**,[22,23,24] **65e-g**,[21,22,23] substituted 2-iodophenylisothiocyanates **65b-d**[24] and 3-iodophenylisothiocyanate **65h**[21] were prepared

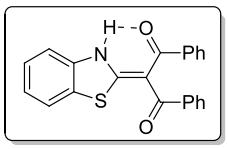
according to the reported procedures. The active methylene compounds **66j-k**,[25,26] **66m**[27] and **66p**[28] were also synthesized according to the reported procedures.

2.5.2 General Procedure for Copper-Catalyzed Synthesis of 3-(Benzo[*d*]thiazol-2(3*H*)-ylidene)pentane-2,4-dione (67a). 

To a stirred suspension of NaH (67 mg, 2.0 mmol) in dry DMSO (3 ml), a solution of acetylacetone **66a** (100 mg, 1.0 mmol) in DMSO (3 ml) was added dropwise, at room temperature under N_2 atmosphere, and the stirring was further continued for 10-20 min, followed by addition of a solution of 2-iodophenylisothiocyanate **65a** (261 mg, 1.0 mmol) in DMSO (4 ml) with CuI (19 mg, 0.1 mmol) and ligand (0.2 mmol). After stirring for 4-5 h (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution (25 ml), extracted with EtOAc (3 X 25 ml), and the combined organic layer was washed with water (3 X 25 ml), and brine (25 mL), dried over Na_2SO_4, and evaporated organic solvent under vacuum to give product **67a**, which was further purified by column chromatography using hexane/ethyl acetate as eluent. Yield 95% (222 mg, 0.95 mmol); white solid; mp 160-161 °C (reported compound)[29]; R_f 0.37 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3255, 3001, 1669, 1596, 1543, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 15.58 (br, 1H), 7.79 (d, J = 8.0 Hz, 1H) 7.56 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 2.65 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 193.0, 169.1, 138.0, 129.5, 127.2, 124.5, 122.1, 114.1, 109.8, 31.6, 31.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}NO_2S$ $[M + H]^+$ 234.0589, found 234.0581.

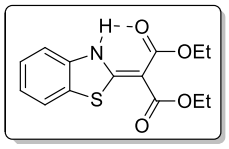
2.5.3 General Procedure for the Synthesis of 2-Substituted 1,3-Benzothiazoles (67a-z, 69). To a stirred suspension of NaH (67 mg, 2.0 mmol) in dry DMSO (3 ml), a solution of appropriate activated methylene compound (**66a-r**) (1.0 mmol) in DMSO (3 ml) was added dropwise, at room temperature under N_2 atmosphere, and the stirring was further continued for 10-20 min, followed by addition of a solution of 2-iodophenylisothiocyanate (**65a-h**) (1.0 mmol) in DMSO (4 ml). After stirring for 1-3 h (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution (25 ml), extracted with EtOAc (3 X 25 ml), the combined organic layer was washed with water (3 X 25 ml), and brine (25 mL), dried over Na_2SO_4, and evaporated under vacuum to give products **67a-z**, which were further purified by column chromatography using hexane/ethyl acetate as eluent.

2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-1,3-diphenylpropane-1,3-dione (67b). Obtained



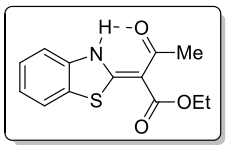
from 2-iodophenylisothiocyanate **65a** and dibenzoylmethane **66b**, yield 99% (353 mg, 0.99 mmol); yellow solid; mp 188-190 °C; R_f 0.37 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3205, 1752, 1594, 1571, 1487, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.64 (br, 1H); 7.83 (d, J = 8.0 Hz, 1H); 7.6 (d, J = 8.0 Hz, 1H); 7.51 (dt, J = 8.0, 0.8 Hz, 1H); 7.43-7.37 (m, 5H); 7.14- 7.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 193.5, 169.6, 141.3, 140.9, 138.4, 130.6, 130.5, 129.24, 129.2, 128.8, 127.7, 127.6, 127.4, 124.6, 122.3, 113.9, 106.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}NO_2S$ $[M + H]^+$ 358.0902, found 358.0892.

Diethyl 2-(benzo[*d*]thiazol-2(3*H*)-ylidene)malonate (67c). Obtained from 2-



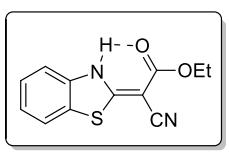
iodophenylisothiocyanate **65a** and diethyl malonate **66c**, yield 97% (284 mg, 0.97 mmol); white solid; mp 138-139 °C (reported compound)[29]; R_f 0.40 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3250, 2986, 1750, 1639, 1581, 1452, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.58 (br, 1H); 7.93-7.90 (m, 2H); 7.41 (dt, J = 8.0, 1.6 Hz, 1H); 7.03 (dt, J = 7.6, 1.6 Hz, 1H); 4.29 (q, J = 7.2 Hz, 4H); 1.35 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.2, 167.7, 138.5, 128.2, 126.8, 123.6, 121.8, 112.7, 103.0, 60.5, 60.4, 14.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}NO_4S$ $[M + H]^+$ 294.0800, found 294.0694.

(*Z*)-Ethyl 2-(benzo[*d*]thiazol-2(3*H*)-ylidene)-3-oxobutanoate (67d). Obtained from 2-



iodophenylisothiocyanate **65a** and ethyl acetoacetate **66d**, yield 87% (229 mg, 0.87 mmol); off-white solid; mp 127-128 °C (reported compound)[29]; R_f 0.36 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3280, 2986, 1750, 1639, 1581, 746; ^{1}H NMR (600 MHz, $CDCl_3$) δ 15.79 (br, 1H); 7.73 (d, J = 7.8 Hz, 1H); 7.52 (d, J = 8.4 Hz, 1H); 7.43 (t, J = 7.8 Hz, 1H); 7.31 (t, J = 7.8 Hz, 1H); 4.38 (q, J = 7.2 Hz, 2H); 2.61 (s, 3H); 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.9, 170.1, 167.9, 139.5, 137.4, 126.9, 124.2, 121.7, 114.3, 104.7, 60.6, 30.9, 14.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}NO_3S$ $[M + H]^+$ 264.0694, found 264.0669.

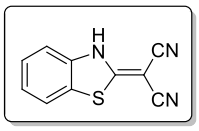
(*E*)-Ethyl 2-(benzo[*d*]thiazol-2(3*H*)-ylidene)-2-cyanoacetate (67e). Obtained from 2-



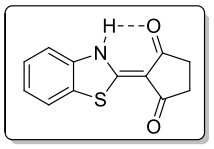
iodophenylisothiocyanate **65a** and ethyl cyanoacetate **66e**, yield 89% (219 mg, 0.89 mmol); white solid; mp 220-221 °C (reported compound)[29]; R_f 0.56 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3400, 3025, 2202, 1750, 1663, 1526, 744; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.16 (br, 1H);

7.89 (d, *J* = 7.8 Hz, 1H); 7.57 (d, *J* = 7.8 Hz, 1H); 7.44 (t, *J* = 7.8 Hz, 1H); 7.28 (t, *J* = 7.8 Hz, 1H); 4.19 (q, *J* = 7.2 Hz, 2H); 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.2, 165.9, 139.3, 127.2, 126.8, 123.6, 122.4, 117.0, 113.6, 112.8, 60.1, 14.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}N_2O_2S$ $[M + H]^+$ 247.0541, found 247.0509.

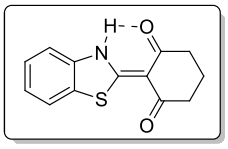
2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)malononitrile (67f). Obtained from 2-iodophenylisothiocyanate **65a** and malononitrile **66f**, yield 99% (196 mg, 0.99 mmol); off-white solid; mp 290-292 °C (reported compound)[29]; R_f 0.25 (1:3 EtOAc/hexane); IR (neat, cm^{-1}) 3066, 2201, 1604, 1567, 742; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, *J* = 7.6 Hz, 1H); 7.51-7.43 (m, 3H); 7.29 (dt, *J* = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.9, 147.3, 136.5, 130.0, 128.4, 127.7, 114.1, 113.9, 113.2, 69.8; HRMS (ESI) *m/z* calcd for $C_{10}H_6N_3S$ $[M + H]^+$ 200.0282, found 200.0267.



2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)cyclopentane-1,3-dione (67g). Obtained from 2-iodophenylisothiocyanate **65a** and cyclopentane-1,3-dione **66g**, yield 98% (226 mg, 0.98 mmol); white solid; mp 176-178 °C; R_f 0.53 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3239, 3010, 1734, 1664, 1566, 1441, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.32 (br, 1H); 7.94 (d, *J* = 8.0 Hz, 1H); 7.70 (d, *J* = 8.0 Hz, 1H); 7.42 (t, *J* = 7.6 Hz, 1H); 7.06 (t, *J* = 7.6 Hz, 1H); 2.86 (t, *J* = 5.6 Hz, 2H); 2.59 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 199.7, 187.7, 139.7, 138.9, 129.3, 128.5, 128.1, 110.5, 95.7, 31.6, 28.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{10}NO_2S$ $[M + H]^+$ 232.0432, found 232.0421.



2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)cyclohexane-1,3-dione (67h). Obtained from 2-iodophenylisothiocyanate **65a** and cyclohexane-1,3-dione **66h**, yield 98% (240 mg, 0.98 mmol); white solid; mp 190-192 °C; R_f 0.53 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3278, 3001, 1739, 1630, 1563, 1441, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.92 (br, 1H); 7.82 (d, *J* = 7.6 Hz, 1H); 7.60 (d, *J* = 8.0 Hz, 1H); 7.50 (dt, *J* = 7.2, 1.2 Hz, 1H); 7.38 (dt, *J* = 8.0, 1.2 Hz, 1H); 2.67 (t, *J* = 6.4 Hz, 2H); 2.64 (t, *J* = 6.4 Hz, 2H); 2.07 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 194.6, 166.6, 137.8, 128.7, 127.5, 124.8, 122.5, 114.2, 106.1, 37.2, 36.6, 20.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}NO_2S$ $[M + H]^+$ 246.0589, found 246.0577.



2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-1*H*-indene-1,3(2*H*)-dione (67i). Obtained from 2-iodophenylisothiocyanate **65a** and 1,3-indandione **66i**, yield 97% (271 mg, 0.97 mmol); greenish yellow solid; mp 354-356 °C; R_f 0.45 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3450, 3158, 1678, 1631, 1576, 751; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (br, 1H); 8.03 (d, J = 7.6 Hz, 1H); 7.97 (d, J = 8.0 Hz, 1H); 7.68 (br, 4H); 7.52 (t, J = 7.8 Hz, 1H); 7.38 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.0, 192.4, 168.7, 159.9, 139.1, 133.2, 127.5, 125.6, 124.5, 122.9, 121.5, 121.0, 115.2, 100.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{10}NO_2S$ $[M + H]^+$ 280.0432, found 280.0420.

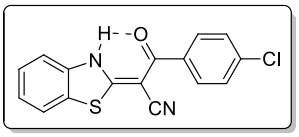
5-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (67j). Obtained from 2-iodophenylisothiocyanate **65a** and 1,3-dimethylbarbituric acid **66j**, yield 87% (252 mg, 0.87 mmol); brown solid; mp 302-303 °C; R_f 0.17 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3287, 3172, 2963, 1702, 1605, 1504, 787; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.81 (br, 1H); 7.81 (d, J = 8.0 Hz, 1H); 7.57 (d, J = 8.0 Hz, 1H); 7.51 (t, J = 8.2 Hz, 1H); 7.39 (t, J = 8.4 Hz, 1H); 3.434 (s, 3H); 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.6, 163.6, 162.2, 137.7, 128.1, 127.7, 124.9, 122.5, 113.8, 99.7, 27.9, 27.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}N_3O_3S$ $[M + H]^+$ 290.0599, found 290.0587.

5-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-1,3-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (67k). Obtained from 2-iodophenylisothiocyanate **65a** and 1,3-dimethyl-2-thiobarbituric acid **66k**, yield 87% (266 mg, 0.87 mmol); brown solid; mp 253-254 °C; R_f 0.21 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3293, 2983, 2857, 1745, 1645, 1625, 1527, 750; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.96 (br, 1H); 7.89 (d, J = 6.6 Hz, 1H); 7.85 (d, J = 7.2 Hz, 1H); 7.56 (t, J = 8.4 Hz, 1H); 7.04 (t, J = 7.8 Hz, 1H); 3.85 (s, 3H); 3.84 (s,3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.8, 167.7, 163.9, 160.9, 139.8, 129.3, 128.1, 125.3, 122.5, 114.2, 98.8, 35.2, 34.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}N_3O_2S_2$ $[M + H]^+$ 306.0371, found 306.0358.

5-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (67l). Obtained from 2-iodophenylisothiocyanate **65a** and meldrum's acid **66l**, yield 92% (256 mg, 0.92 mmol); off-white solid; mp (decomposed at 206 °C); R_f 0.36 (3:7 EtOAc/hexane); IR (neat, cm^{-}

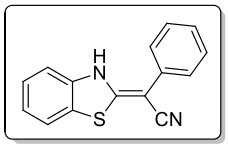
[1]) 3403, 3100, 1750, 1663, 1519, 1459, 750; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.83 (br, 1H); 7.78 (d, J = 7.8 Hz, 1H); 7.60 (d, J = 8.4 Hz, 1H); 7.51 (t, J = 8.4 Hz, 1H); 7.39 (t, J = 7.8 Hz, 1H); 1.78 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 165.1, 163.4, 137.9, 127.9, 127.8, 125.1, 122.5, 114.0, 113.9, 104.9, 26.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}NO_4S$ $[M + H]^+$ 278.0487, found 278.0473.

(*E*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-3-(4-chlorophenyl)-3-oxopropanenitrile



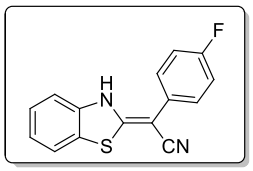
(67m). Obtained from 2-iodophenylisothiocyanate **65a** and 3-(4-chlorophenyl)-3-oxopropanenitrile **66m**, yield 98% (306 mg, 0.98 mmol); white solid; mp 279-281 °C; R_f 0.25 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 3165, 3020, 2198, 1745, 1615, 1598, 746; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.75 (br, 1H); 8.02 (d, J = 7.8 Hz, 1H); 7.84 (d, J = 7.8 Hz, 2H); 7.75 (d, J = 7.8 Hz, 1H); 7.59 (d, J = 7.8 Hz, 2H); 7.54 (t, J = 7.8 Hz, 1H); 7.39 (t, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 184.3, 168.2, 140.4, 137.3, 135.8, 129.6, 128.3, 127.6, 127.2, 124.4, 122.8, 119.1, 114.4, 75.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{10}ClN_2OS$ $[M + H]^+$, $[M + H + 2]^+$ 313.0202, 315.0202 found 313.0193, 315.0172.

(*Z*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-2-phenylacetonitrile (67n). Obtained from 2-



iodophenylisothiocyanate **65a** and phenylacetonitrile **66n**, yield 95% (237 mg, 0.95 mmol); off-white solid; mp 108-109 °C (reported compound)[29]; R_f 0.61 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 2929, 2861, 2150, 1634, 1480, 763; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, J = 7.8 Hz, 2H); 8.25 (d, J = 8.4 Hz, 1H); 8.02 (d, J = 7.8 Hz, 1H); 7.67 (t, J = 7.2 Hz, 1H); 7.60- 7.54 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 154.1, 137.2, 135.1, 134.1, 131.4, 128.7, 127.8, 127.1, 125.9, 122.3, 82.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}N_2S$ $[M + H]^+$ 251.0643, found 251.0539.

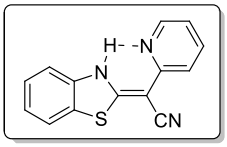
(*Z*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-2-(4-fluorophenyl)acetonitrile (67o). Obtained



from 2-iodophenylisothiocyanate **65a** and 4-fluorophenylacetonitrile **66o**, yield 99% (265 mg, 0.99 mmol); yellow solid; mp 94-95 °C; R_f 0.56 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3083, 2922, 2199, 1620, 1590, 757; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (dd, J = 7.2, 1.8 Hz, 2H); 8.21 (dd, J = 8.4, 1.2 Hz, 1H); 8.00 (dd, J = 8.1, 1.5 Hz, 1H); 7.55 (dt, J = 7.8, 1.2 Hz, 1H); 7.50 (dt, J = 7.8, 1.2 Hz, 1H); 6.75 (dd, J = 7.2, 1.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 165.7, 137.2, 134.4, 134.3, 131.4,

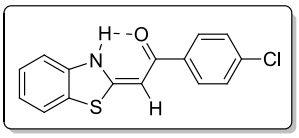
127.9, 127.2, 125.9, 122.3, 115.9, 115.8, 85.3; $^{19}F\{^{1}H\}$ NMR (564.65 MHz, $CDCl_3$) δ -103.01; HRMS (ESI) *m/z* calcd for $C_{15}H_{10}FN_2S$ $[M + H]^+$ 269.0549, found 269.0493.

(*Z*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-2-(pyridin-2-yl)acetonitrile (67p). Obtained



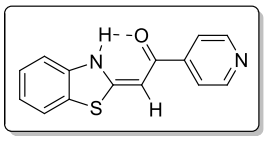
from 2-iodophenylisothiocyanate **65a** and 2-pyridylacetonitrile **66p**, yield 96% (241 mg, 0.96 mmol); yellow solid; mp 149-150 °C; R_f 0.51 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3401, 3025, 2183, 1640, 1580746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1521 (br, 1H); 7.83 (d, *J* = 6.0 Hz, 1H); 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H); 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H); 7.57-7.52 (m, 1H); 7.39-7.33 (m, 2H); 7.21 (dt, *J* = 7.6, 1.2 Hz, 1H); 6.68 (dt, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.3, 150.9, 138.1, 135.7, 130.7, 126.1, 123.1, 121.3, 120.6, 120.2, 118.3, 112.9, 68.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{10}N_3S$ $[M + H]^+$ 252.0595, found 252.0584.

(*E*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-1-(4-chlorophenyl)ethanone (67q). Obtained



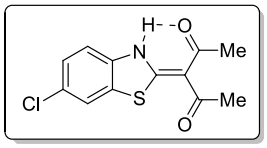
from 2-iodophenylisothiocyanate **65a** and 4-chloroacetophenone **66q**, yield 94% (270 mg, 0.94 mmol); pale yellow solid; mp 142-144 °C (reported compound)[29]; R_f 0.60 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3296, 3055, 3015, 1754, 1615, 1596, 724; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.41 (br, 1H); 8.06 (d, *J* = 9.0 Hz, 1H); 7.94 (d, *J* = 8.4 Hz, 2H); 7.50 (d, *J* = 8.4 Hz, 1H); 7.44 (t, *J* = 7.8 Hz, 1H); 7.37 (d, *J* = 8.4 Hz, 2H); 7.07 (t, *J* = 7.5 Hz, 1H); 6.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.7, 168.2, 142.1, 140.4, 139.7, 133.7, 130.5, 129.5, 129.1, 127.9, 127.8, 109.3, 91.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}ClNOS$ $[M + H]^+$, $[M + H + 2]^+$ 288.0250, 290.0250 found 288.0237, 290.0203.

(*E*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-1-(pyridin-4-yl)ethanone (67r). Obtained from



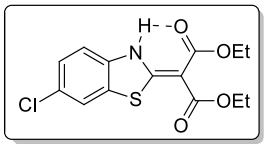
2-iodophenylisothiocyanate **65a** and 4-acetylpyridine **66r**, yield 93% (236 mg, 0.93 mmol); red solid; mp 124-126 °C; R_f 0.31 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3335, 3035, 2941, 1737, 1620, 1593, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (br, 1H); 8.79 (d, *J* = 5.2 Hz, 2H); 7.98 (d, *J* = 7.6 Hz, 1H); 7.74 (d, *J* = 4.8 Hz, 2H); 7.50 (t, *J* = 7.6 Hz, 1H); 7.39 (d, *J* = 7.6 Hz, 1H); 7.16 (t, *J* = 7.6 Hz, 1H); 6.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 167.4, 162.3, 150.2, 142.3, 131.8, 126.9, 124.8, 121.6, 120.5, 119.8, 92.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}N_2OS$ $[M + H]^+$ 255.0592, found 255.0586.

3-(6-Chlorobenzo[*d*]thiazol-2(3*H*)-ylidene)pentane-2,4-dione (67s). Obtained from 4-



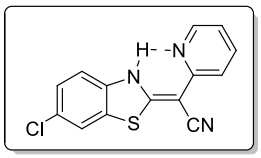
chloro-2-iodophenylisothiocyanate **65b** and acetylacetone **66a**, yield 93% (249 mg, 0.93 mmol); white solid; mp 189-191 °C; R_f 0.36 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3390, 3099, 1670, 1610, 1591, 808; ^1H NMR (400 MHz, $CDCl_3$) δ 15.72 (br, 1H); 7.76 (d, J = 2.4 Hz, 1H); 7.46 (s, 1H); 7.42 (d, J = 2.0 Hz, 1H); 2.65 (s, 3H); 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 193.1, 169.3, 136.9, 131.3, 130.2, 127.7, 121.8, 115.0, 109.9, 31.4, 31.1; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}ClNO_2S$ $[M + H]^+$, $[M + H + 2]^+$ 268.0199, 270.0199 found 268.0186, 270.0157.

Diethyl 2-(6-chlorobenzo[d]thiazol-2(3H)-ylidene)malonate (67t). Obtained from 4-



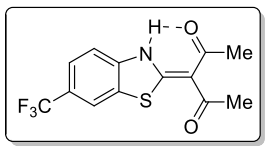
chloro-2-iodophenylisothiocyanate **65b** and diethyl malonate **66c**, yield 95% (310 mg, 0.95 mmol); white solid; mp 194-195 °C; R_f 0.48 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3310, 3012, 1750, 1639, 1581, 806; ^1H NMR (400 MHz, $CDCl_3$) δ 13.22 (br, 1H); 7.62 (d, J = 2.0 Hz, 1H); 7.32 (d, J = 1.6 Hz, 1H); 7.28 (s, 1H); 4.34 (q, J = 7.1 Hz, 4H); 1.38 (q, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.2, 167.8, 137.3, 130.0, 129.3, 127.4, 121.7, 113.5, 86.7, 60.7, 60.1, 14.5, 14.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}ClNO_4S$ $[M + H]^+$, $[M + H + 2]^+$ 328.0410, 330.0410 found 328.0380, 330.0315.

(*Z*)-2-(6-Chlorobenzo[*d*]thiazol-2(3*H*)-ylidene)-2-(pyridin-2-yl)acetonitrile (67u).



Obtained from 4-chloro-2-iodophenylisothiocyanate **65b** and 2-pyridylacetonitrile **66p**, yield 91% (260 mg, 0.91 mmol); brown solid; mp 218-220 °C; R_f 0.48 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3350, 3005, 2173, 1627, 1578, 810; ^1H NMR (400 MHz, $CDCl_3$) δ 15.15 (br, 1H); 7.79 (t, J = 6.4 Hz, 1H); 7.71 (d, J = 2.0 Hz, 1H); 7.61-7.56 (m, 2H); 7.37 (d, J = 8.8 Hz, 1H); 7.33 (dd, J = 8.6, 2.2 Hz, 1H); 6.69 (dt, J = 6.7, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 152.1, 150.8, 138.6, 134.7, 132.7, 128.6, 126.7, 121.0, 120.6, 120.4, 119.6, 112.8, 68.2; HRMS (ESI) *m/z* calcd for $C_{14}H_9ClN_3S$ [M + H]+, $[M + H + 2]^+$ 286.0206, 288.0206 found 286.0196, 288.0178.

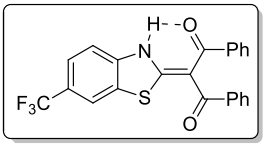
3-(6-(Trifluoromethyl)benzo[*d*]thiazol-2(3*H*)-ylidene)pentane-2,4-dione (67v).



Obtained from 4-(trifluoromethyl)-2-iodophenylisothiocyanate **65c** and acetylacetone **66a**, yield 94% (283 mg, 0.94 mmol); yellow solid; mp 187-189 °C; R_f 0.35 (1:4 EtOAc/hexane); IR

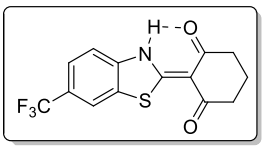
(neat, cm^{-1}) 3280, 3020, 1738, 1600, 1540, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.80 (br, 1H); 8.07 (s, 1H); 7.72 (d, J = 8.4 Hz, 1H); 7.64 (d, J = 8.8 Hz, 1H); 2.67 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 193.2, 170.3, 140.7, 130.2, 127.1, 126.8, 124.4, 124.3, 119.8, 119.79, 119.75, 114.4, 110.3, 31.4, 31.1; $^{19}F\{^{1}H\}$ NMR (564.65 MHz, $CDCl_3$) δ -61.32; HRMS (ESI) *m/z* calcd for $C_{13}H_{11}F_3NO_2S$ $[M + H]^+$, 302.0463, found 302.0450.

1,3-Diphenyl-2-(6-(trifluoromethyl)benzo[*d*]thiazol-2(3*H*)-ylidene)propane-1,3-



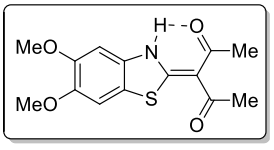
dione (67w). Obtained from 4-(trifluoromethyl)-2-iodophenylisothiocyanate **65c** and dibenzoylmethane **66b**, yield 94% (400 mg, 0.94 mmol), white solid; mp 295-296 °C; R_f 0.30 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3338, 3037, 1739, 1637, 1655, 715; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.66 (br, 1H); 8.12 (s, 1H); 7.84 (d, J = 8.0 Hz, 1H); 7.61 (d, J = 8.0 Hz, 1H); 7.45- 7.38 (m, 5H); 7.15-7.03 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 194.4, 170.5, 143.5, 142.2, 141.8, 139.3, 131.5, 131.4, 130.2, 130.1, 129.7, 128.6, 128.5, 128.3, 125.6, 125.2, 124.9, 123.2, 121.7, 114.8, 107.1; $^{19}F\{^{1}H\}$ NMR (564.65 MHz, $CDCl_3$) δ -62.61; HRMS (ESI) *m/z* calcd for $C_{23}H_{15}F_3NO_2S$ $[M + H]^+$, 426.0776, found 426.0767.

2-(6-(Trifluoromethyl)benzo[*d*]thiazol-2(3*H*)-ylidene)cyclohexane-1,3-dione (67x).



Obtained from 4-(trifluoromethyl)-2-iodophenylisothiocyanate **65c** and cyclohexane-1,3-dione **66h**, yield 93% (291 mg, 0.93 mmol); white solid; mp 278-280 °C; R_f 0.47 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3358, 3092, 2962, 1735, 1605, 1560, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.09 (br, 1H); 8.09 (s, 1H); 7.75 (d, J = 8.4 Hz, 1H); 7.69 (d, J = 8.4 Hz, 1H); 2.69 (t, J = 6.4 Hz, 2H); 2.65 (t, J = 6.4 Hz, 2H); 2.09 (quin, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 194.8, 167.7, 140.5, 129.4, 127.4, 127.1, 124.7, 124.6, 124.3, 120.1, 120.0, 114.6, 106.6, 36.8, 36.5; $^{19}F\{^{1}H\}$ NMR (564.65 MHz, $CDCl_3$) δ -61.38; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}F_3NO_2S$ $[M + H]^+$, 314.0463, found 314.0369.

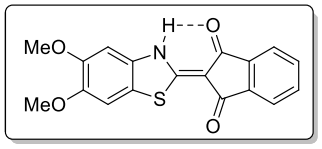
3-(5,6-Dimethoxybenzo[*d*]thiazol-2(3*H*)-ylidene)pentane-2,4-dione (67y). Obtained



from 4,5-dimethoxy-2-iodophenylisothiocyanate **65d** and acetylacetone **66a**, yield 67% (197 mg, 0.67 mmol); off-white solid; mp 120-121 °C; R_f 0.47 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3309, 3025, 2982, 1745, 1615, 1541, 1075, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.72 (br, 1H); 7.20 (s, 1H); 7.06 (s, 1H); 3.96 (s, 6H); 2.63 (s, 3H); 2.61 (s, 3H); ^{13}C NMR

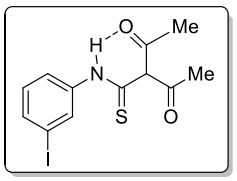
(100 MHz, $CDCl_3$) δ 193.6, 192.6, 168.4, 150.1, 148.0, 132.3, 121.6, 109.9, 103.6, 97.4, 56.6, 56.5, 31.5, 31.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}NO_4S$ $[M + H]^+$, 294.0800, found 294.0730.

2-(5,6-Dimethoxybenzo[*d*]thiazol-2(3*H*)-ylidene)-1*H*-indene-1,3(2*H*)-dione (67z).



Obtained from 4,5-dimethoxy-2-iodophenylisothiocyanate **65d** and 1,3-indandione **66i**, yield 60% (204 mg, 0.60 mmol); pale yellow solid; mp 178-180 °C; R_f 0.43 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3310, 3006, 2945, 1745, 1628, 1586, 1028, 766; ^1H NMR (400 MHz, $CDCl_3$) δ 10.83 (br, 1H); 7.66 (dd, J = 5.4, 3.0 Hz, 1H); 7.55 (dd, J = 5.2, 3.2 Hz, 1H); 6.56 (s, 1H); 6.55 (s, 1H); 6.53 (d, J = 2.4 Hz, 1H); 6.45 (d, J = 2.4 Hz, 1H); 3.76 (s, 3H); 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 192.1, 168.7, 155.4, 148.9, 147.4, 139.1, 132.7, 132.0, 129.6, 120.9, 120.4, 116.2, 110.9, 108.2, 94.5, 56.2, 55.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}NO_4S$ $[M + H]^+$, 340.0644, found 340.0629.

2-Acetyl-*N*-(3-iodophenyl)-3-oxobutanethioamide (69). Obtained from 3-iodophenyl isothiocyanate **65h** and acetylacetone **66a**, yield 94% (340 mg, 0.94 mmol); yellow solid; mp 82-84 °C; R_f 0.46 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3201, 2986, 1750, 1598, 1570, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 16.32 (br, 1H); 8.21 (d, J = 2.0 Hz, 1H); 7.79 (dd, J = 8.2, 2.2 Hz, 1H); 7.65 (dd, J = 7.8, 1.4 Hz, 1H); 7.18 (t, J = 8.0 Hz, 1H); 2.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 189.4, 189.2, 139.5, 136.3, 131.5, 130.6, 122.1, 93.9, 82.0, 23.9, 23.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}INO_2S$ $[M + H]^+$, 361.9712, found 361.9685.



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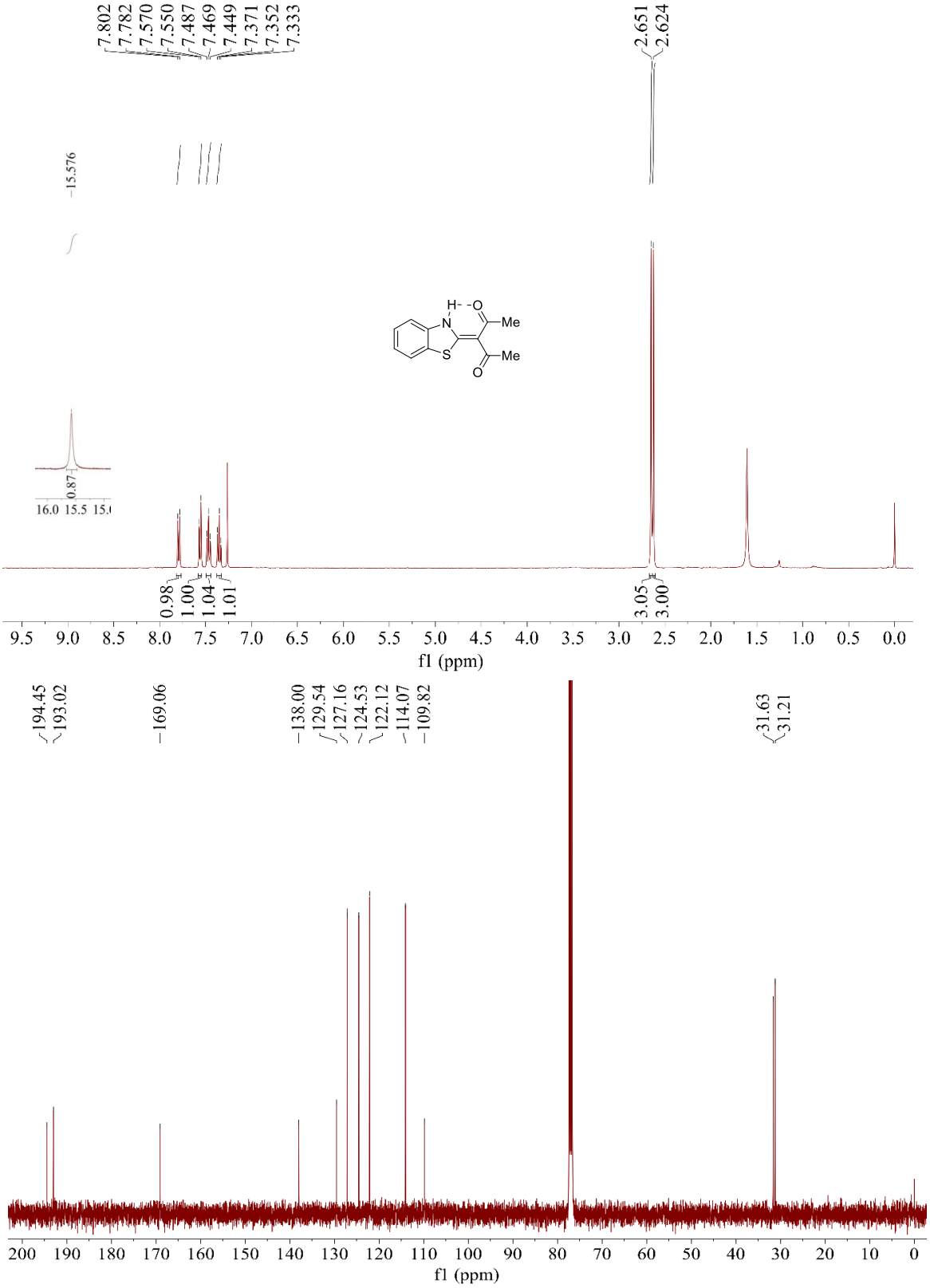
2.7 Representative Spectra



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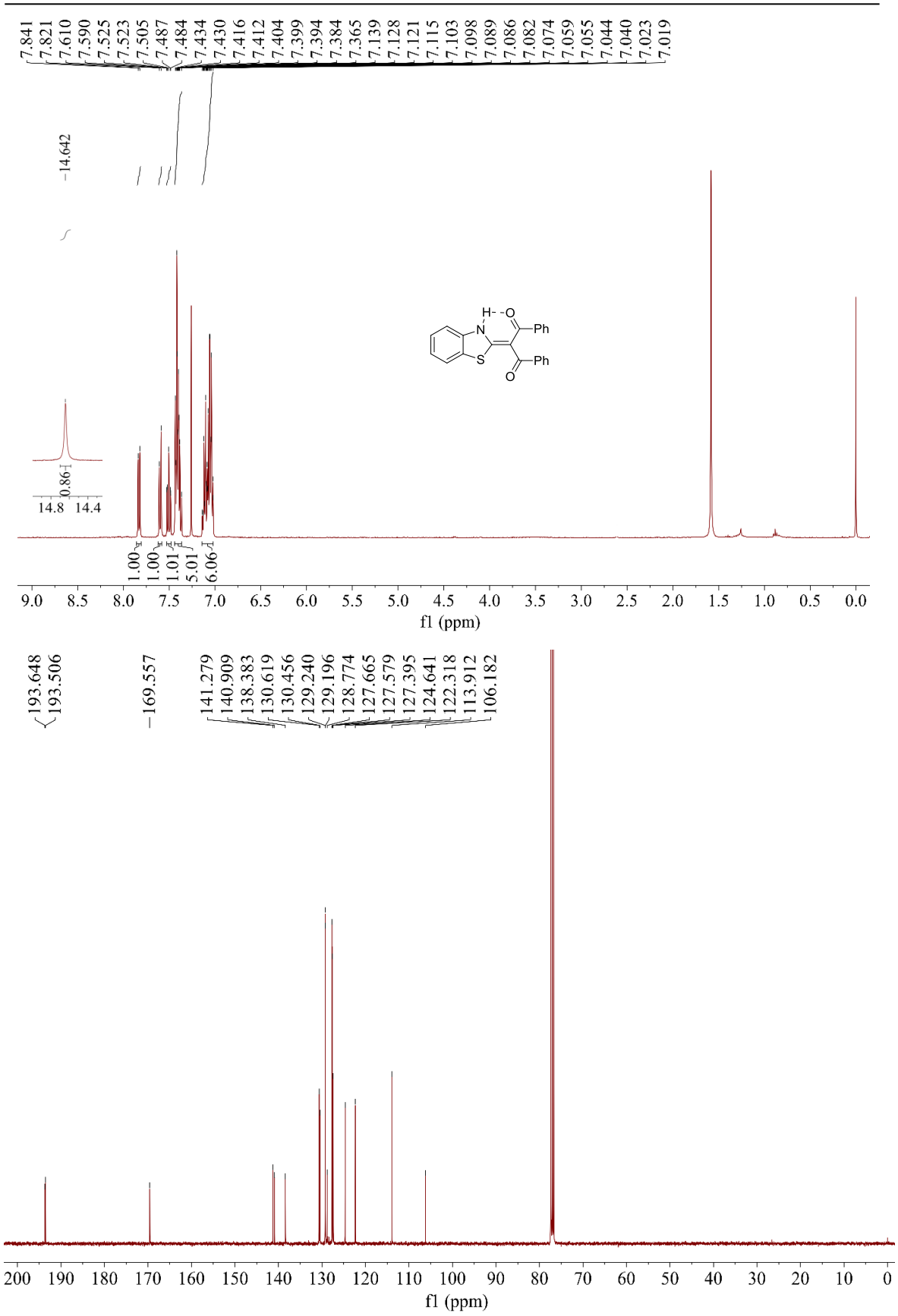

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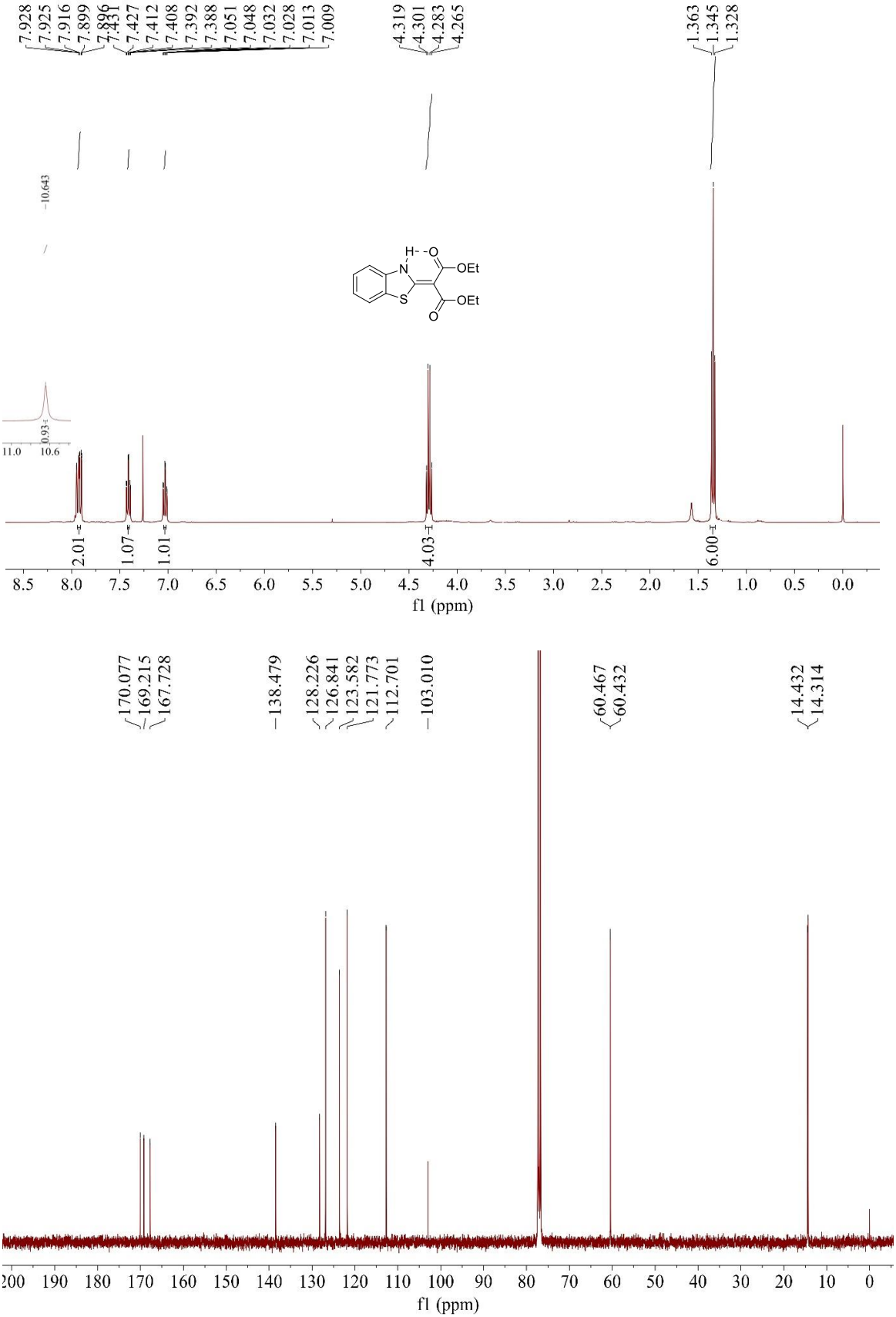

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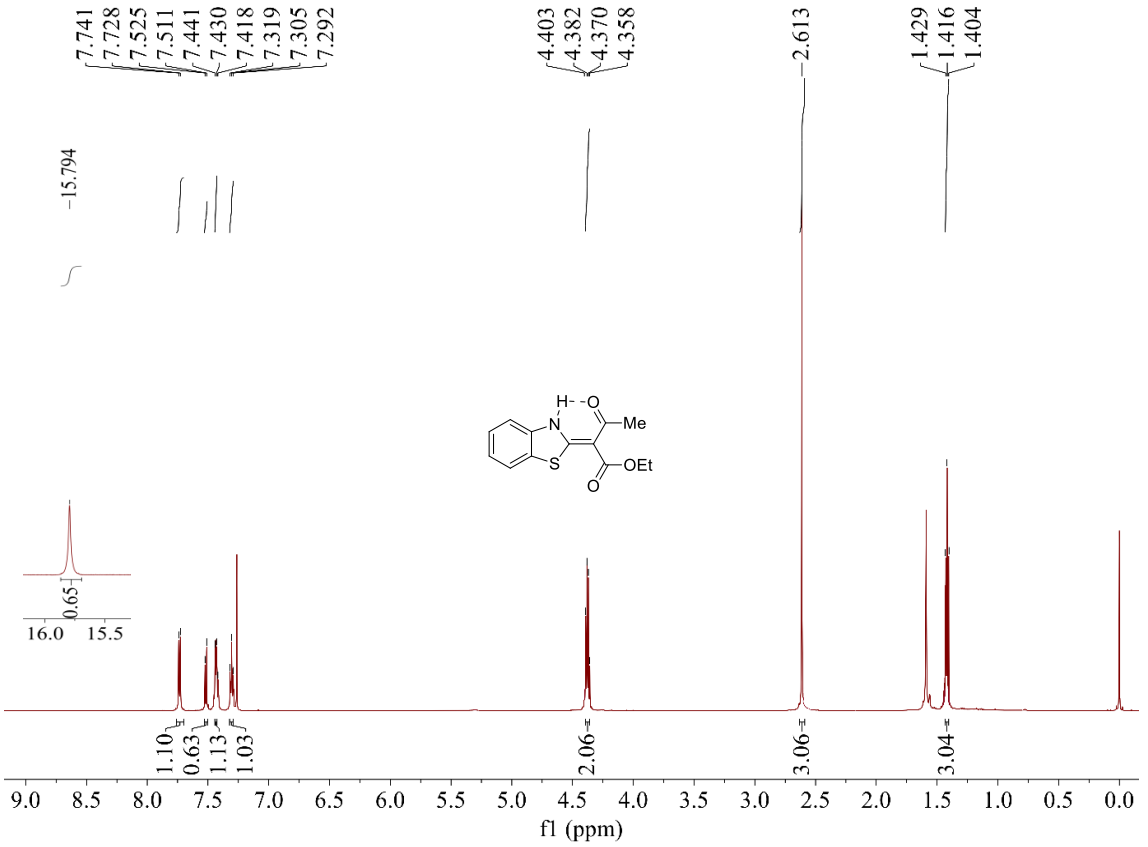

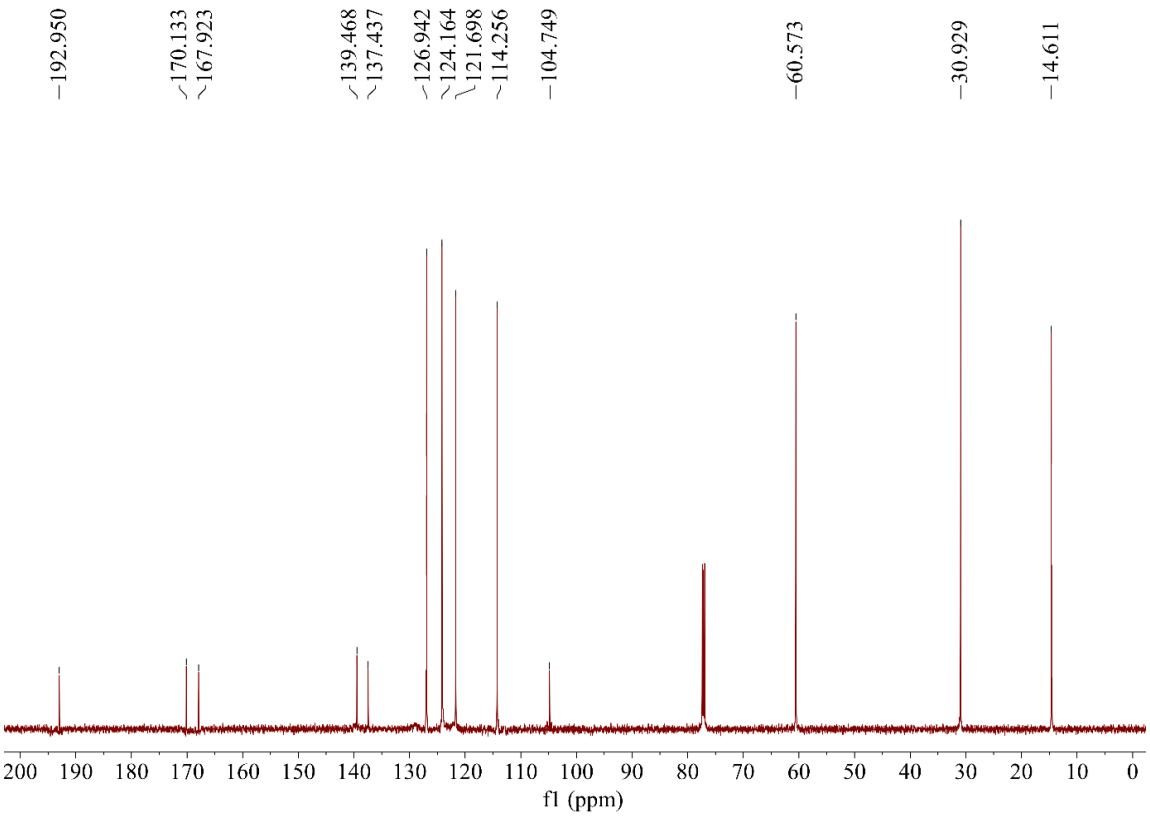

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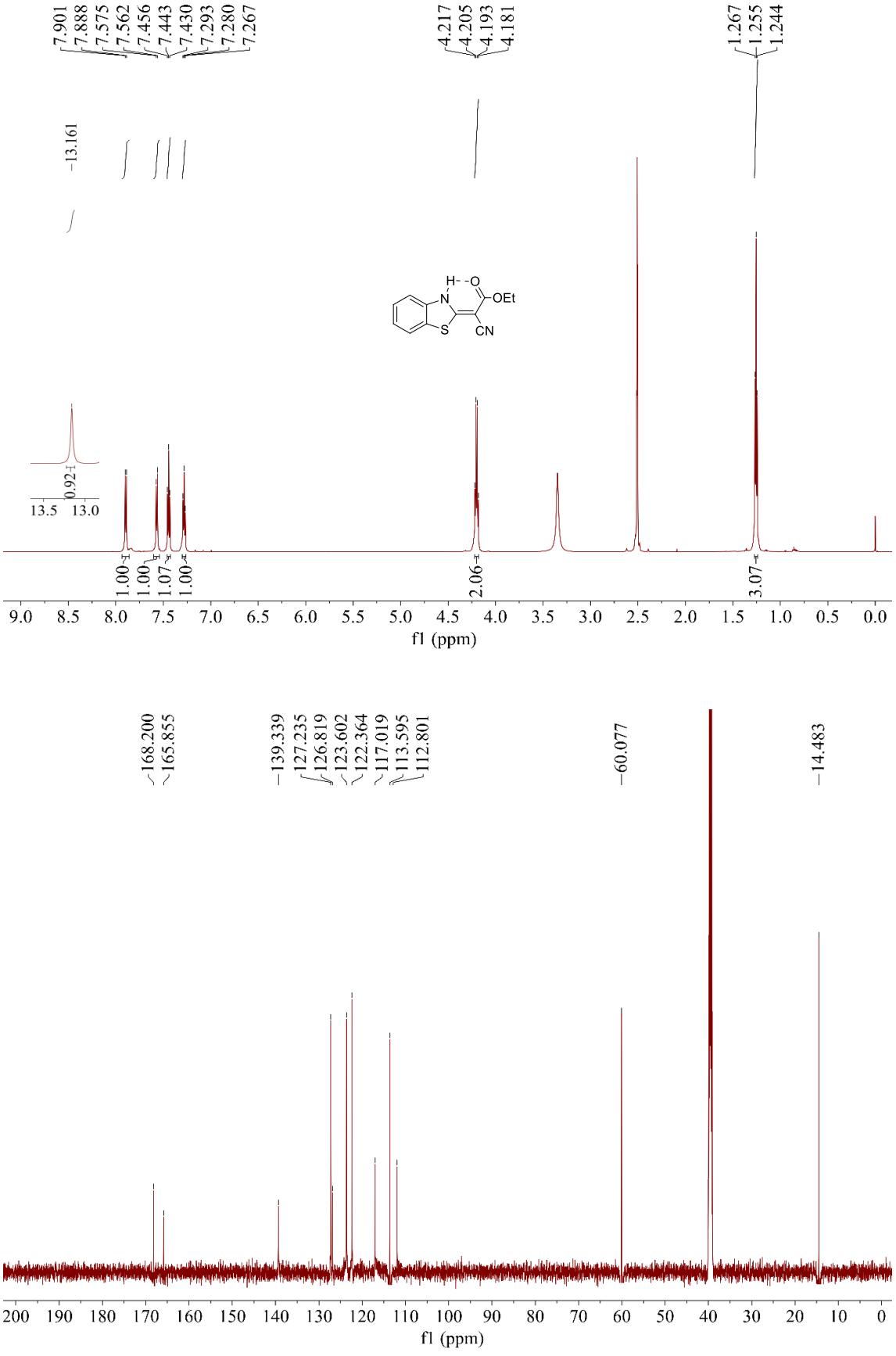

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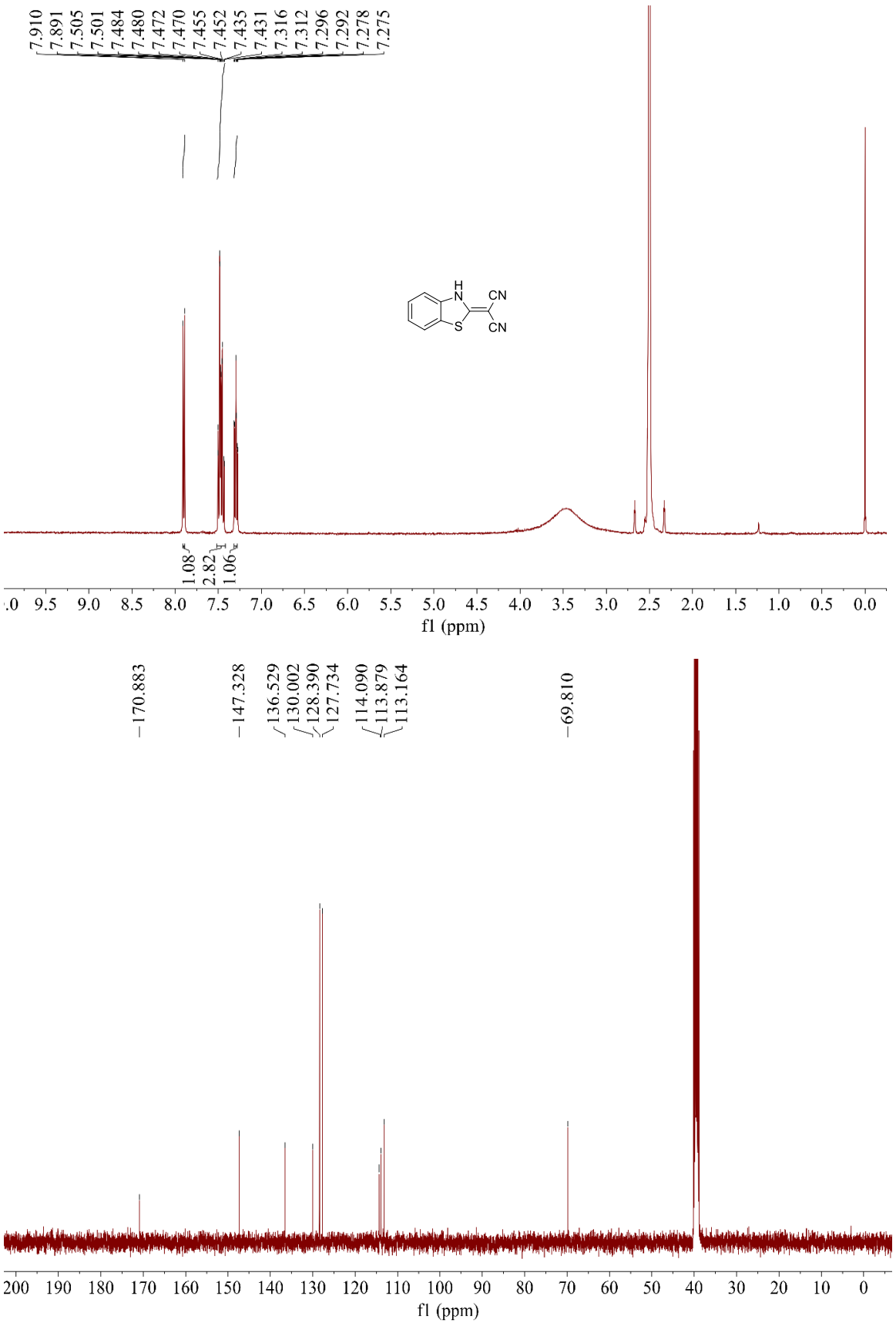

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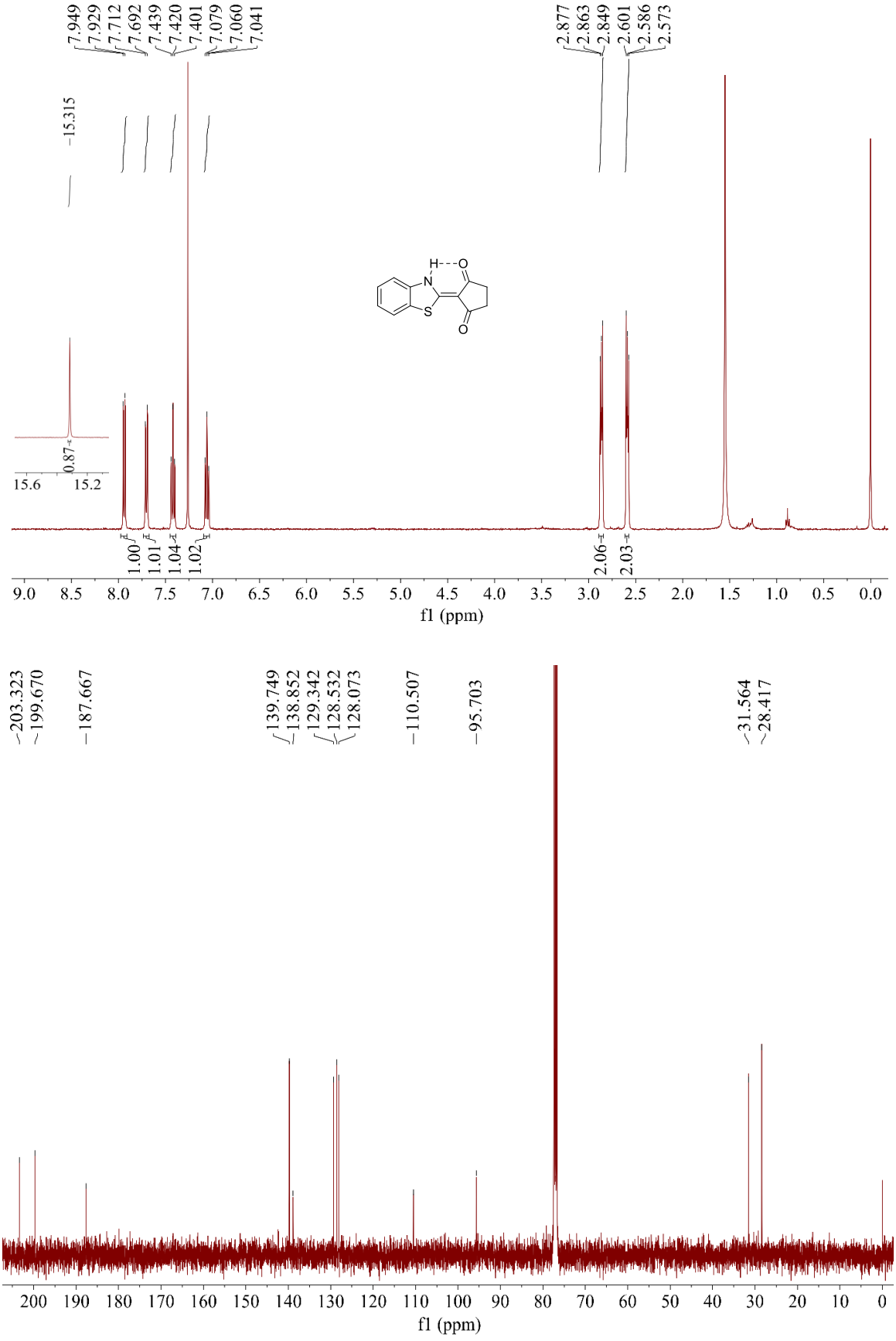

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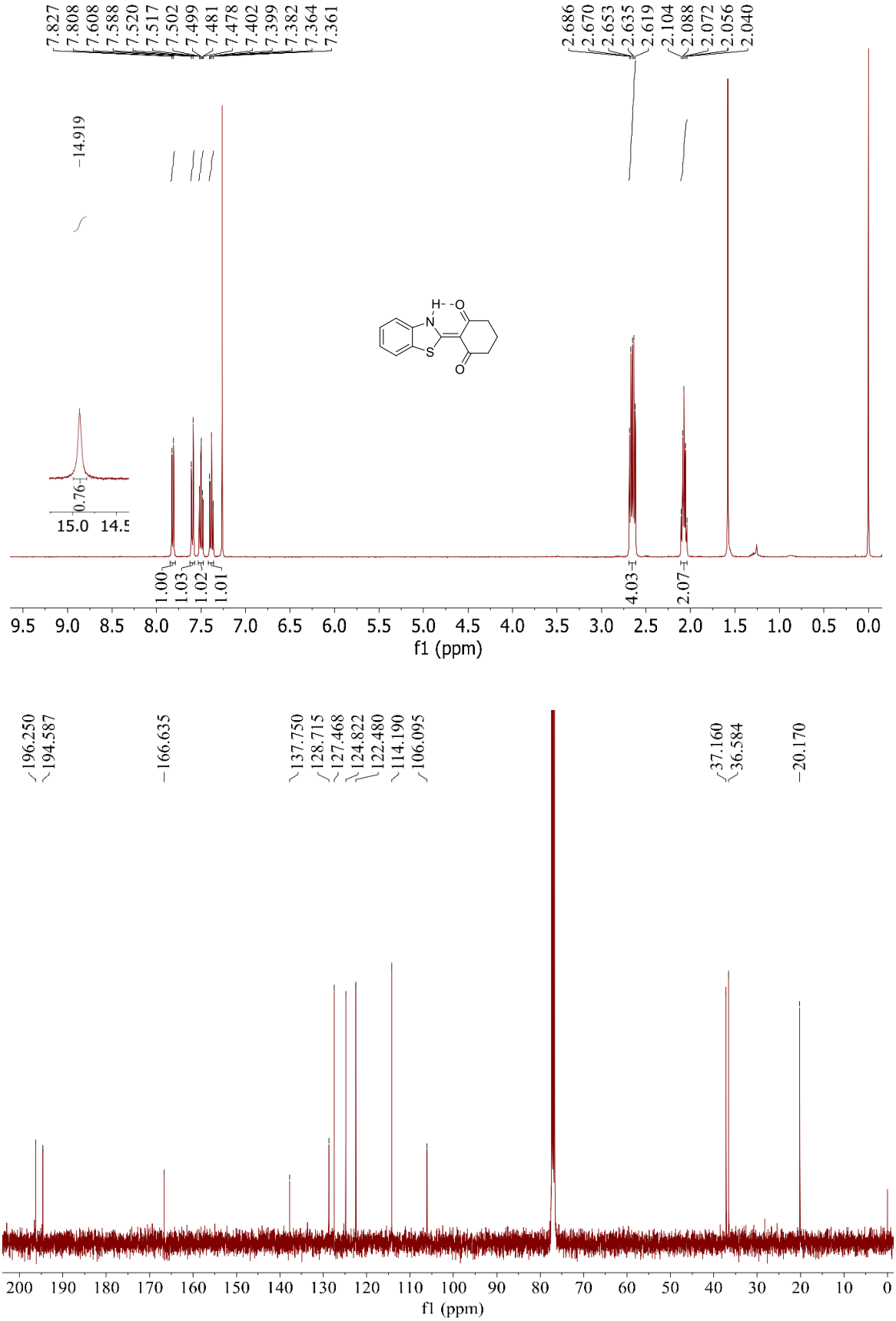

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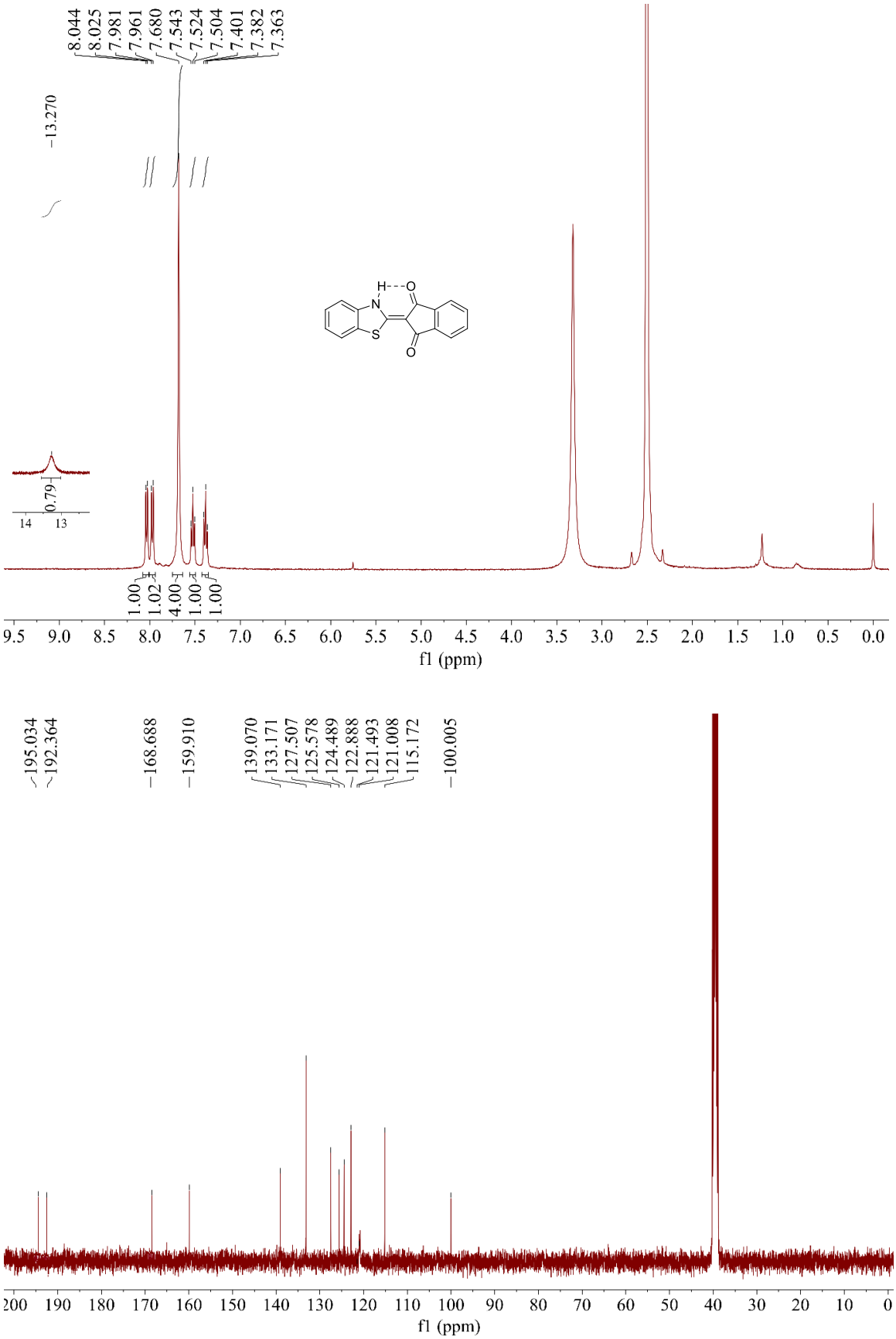

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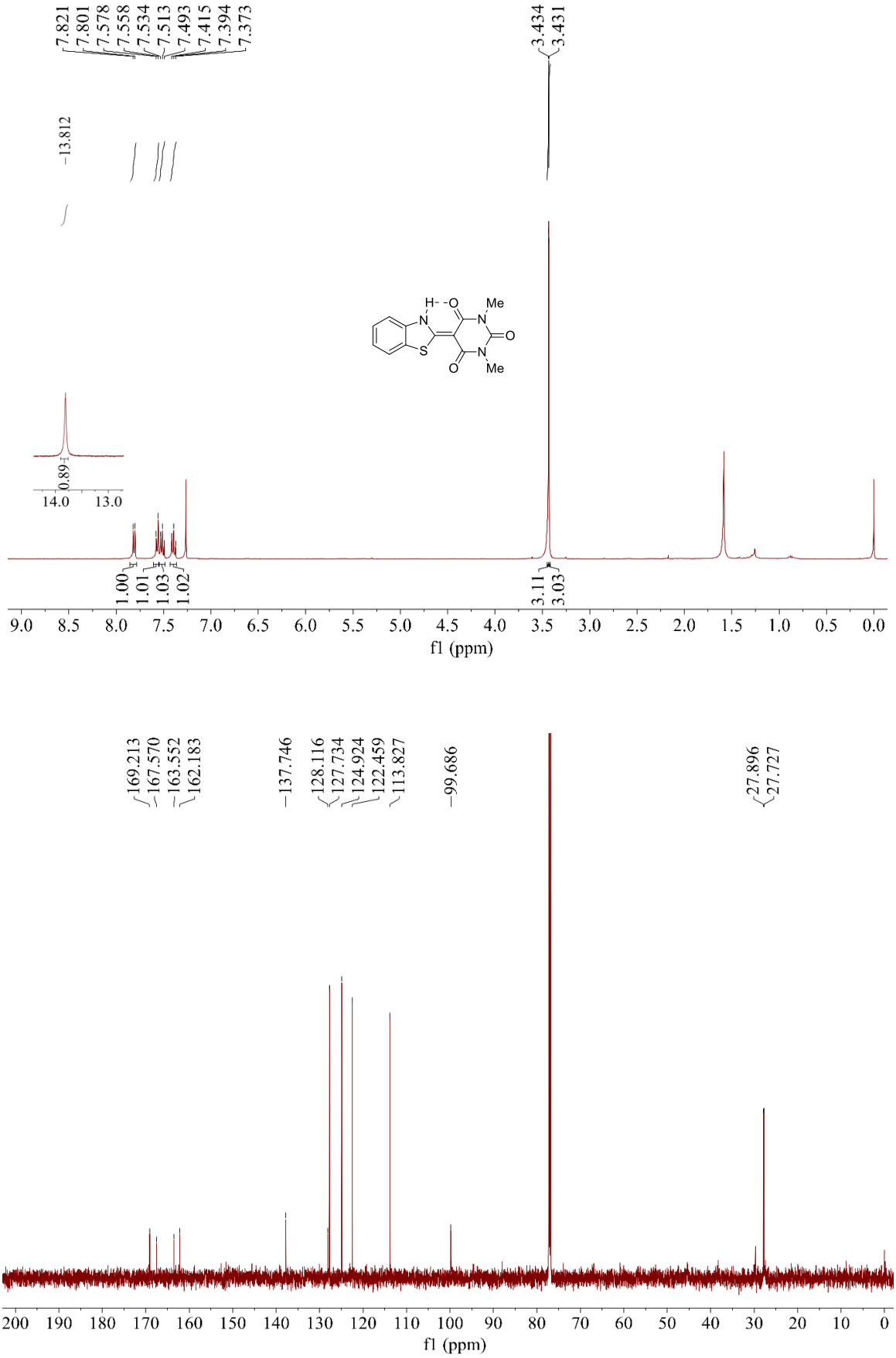

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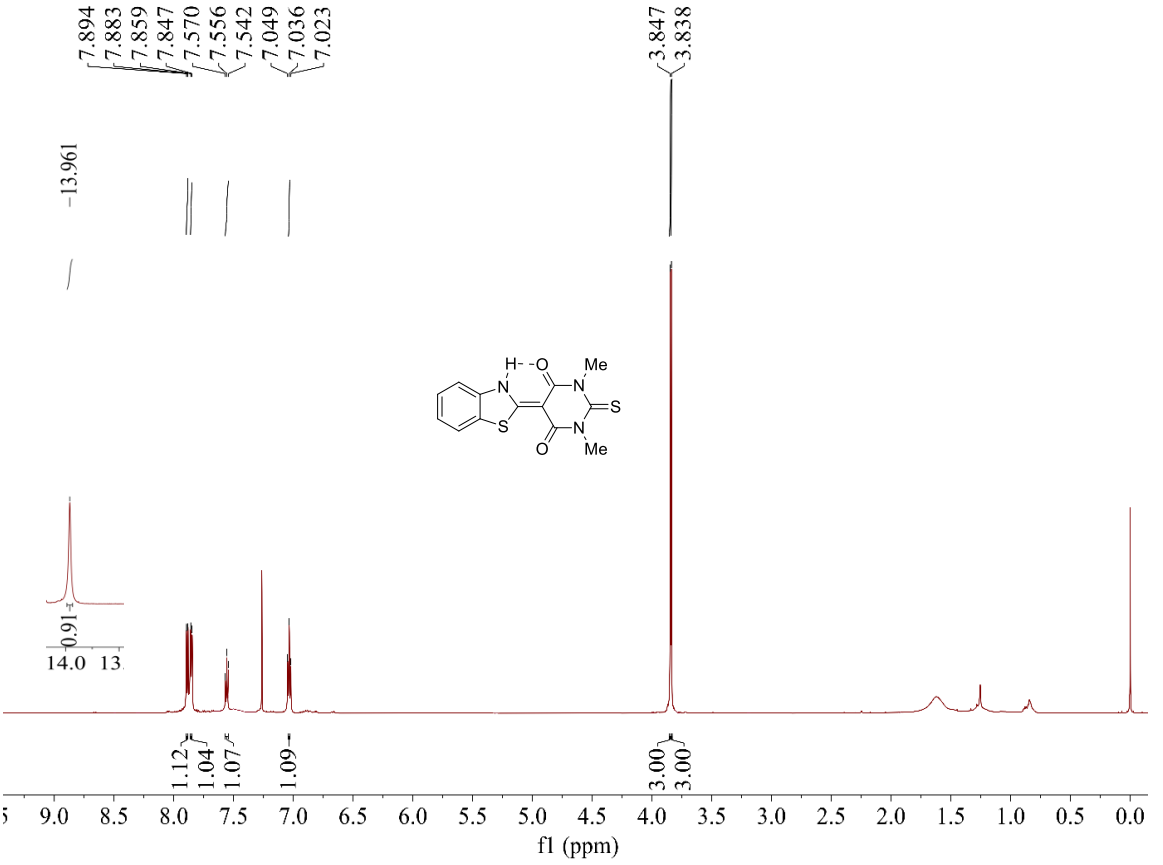

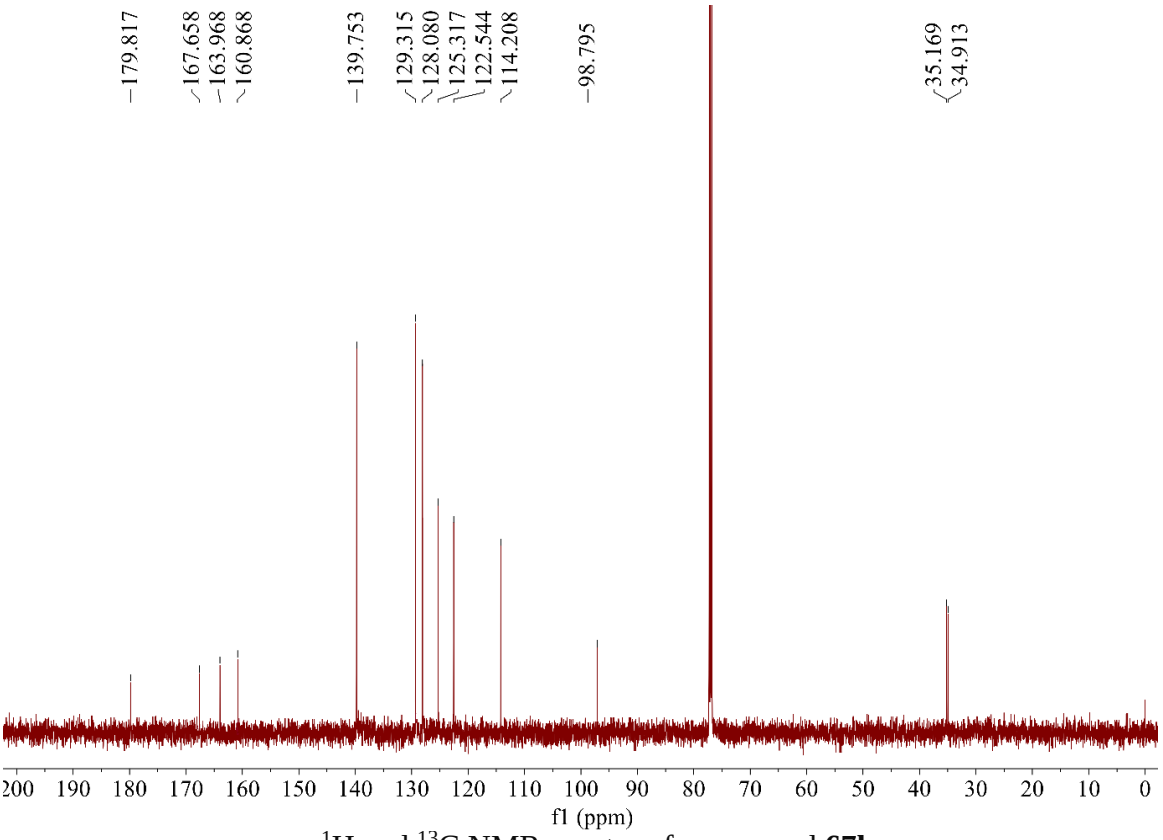

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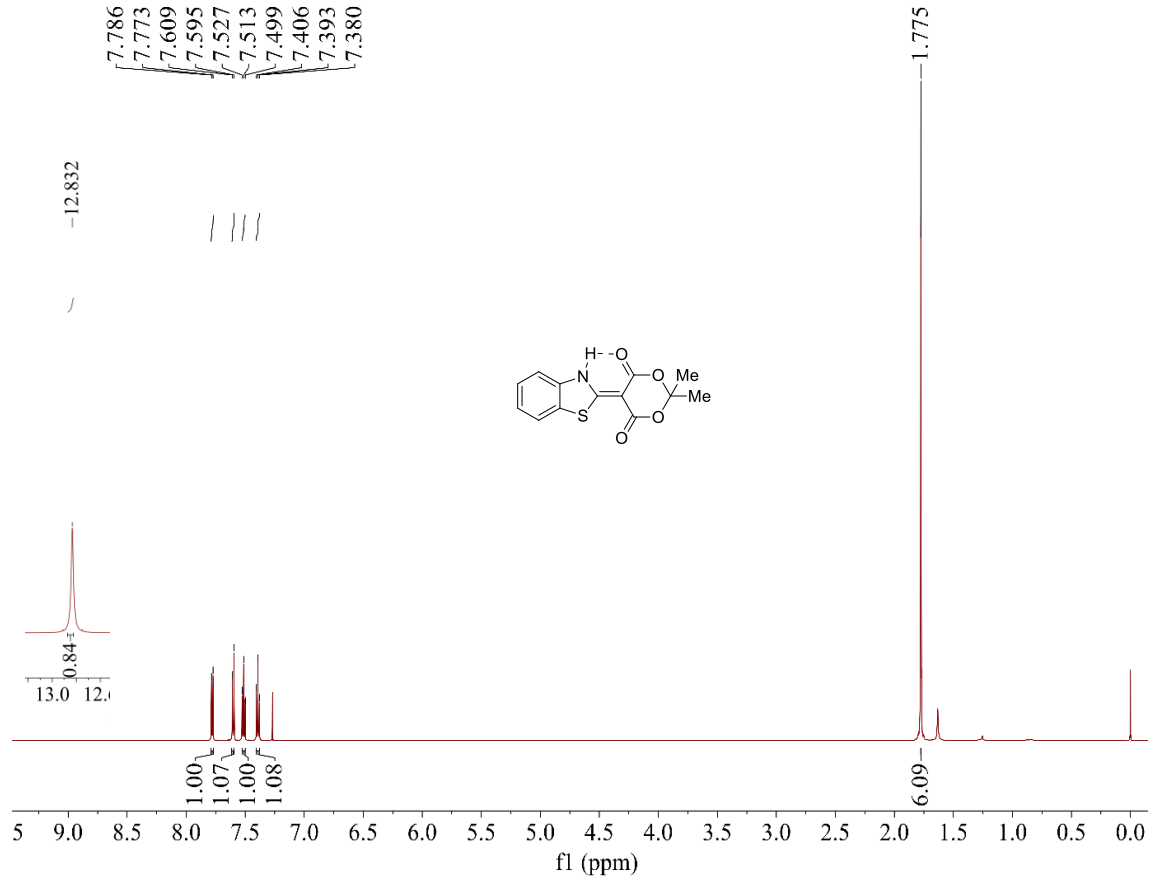

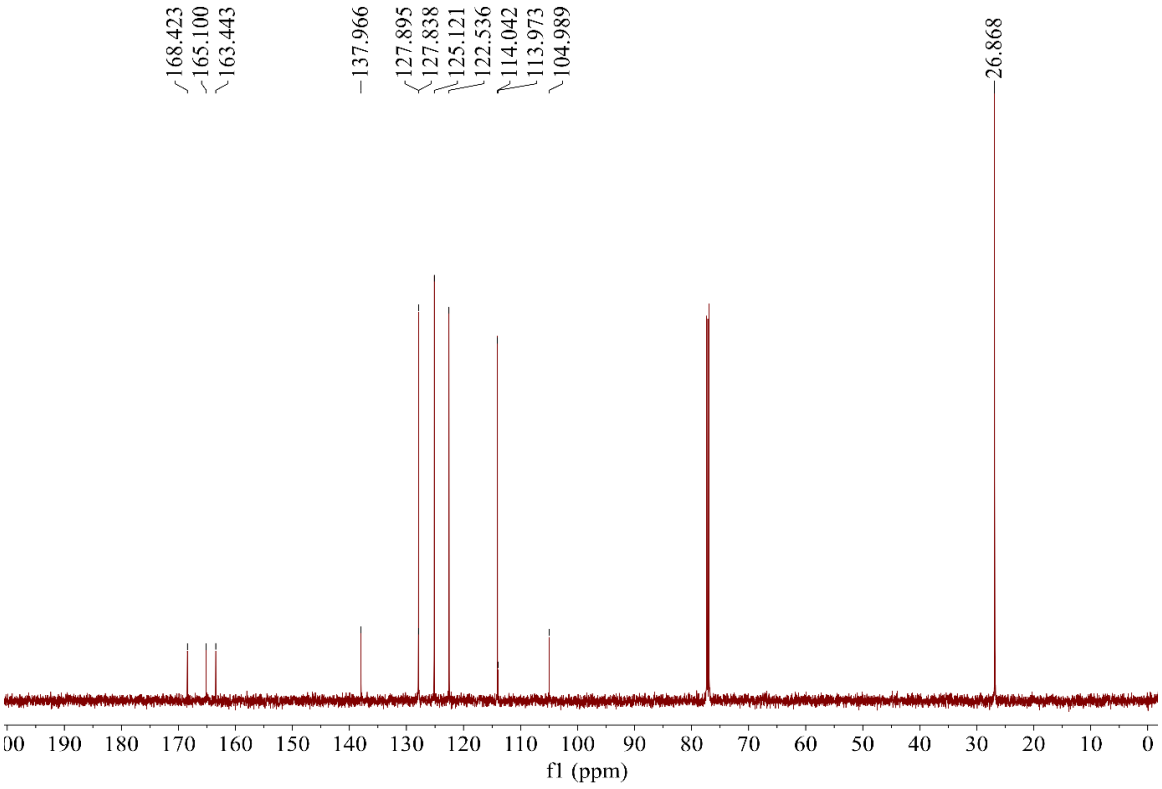

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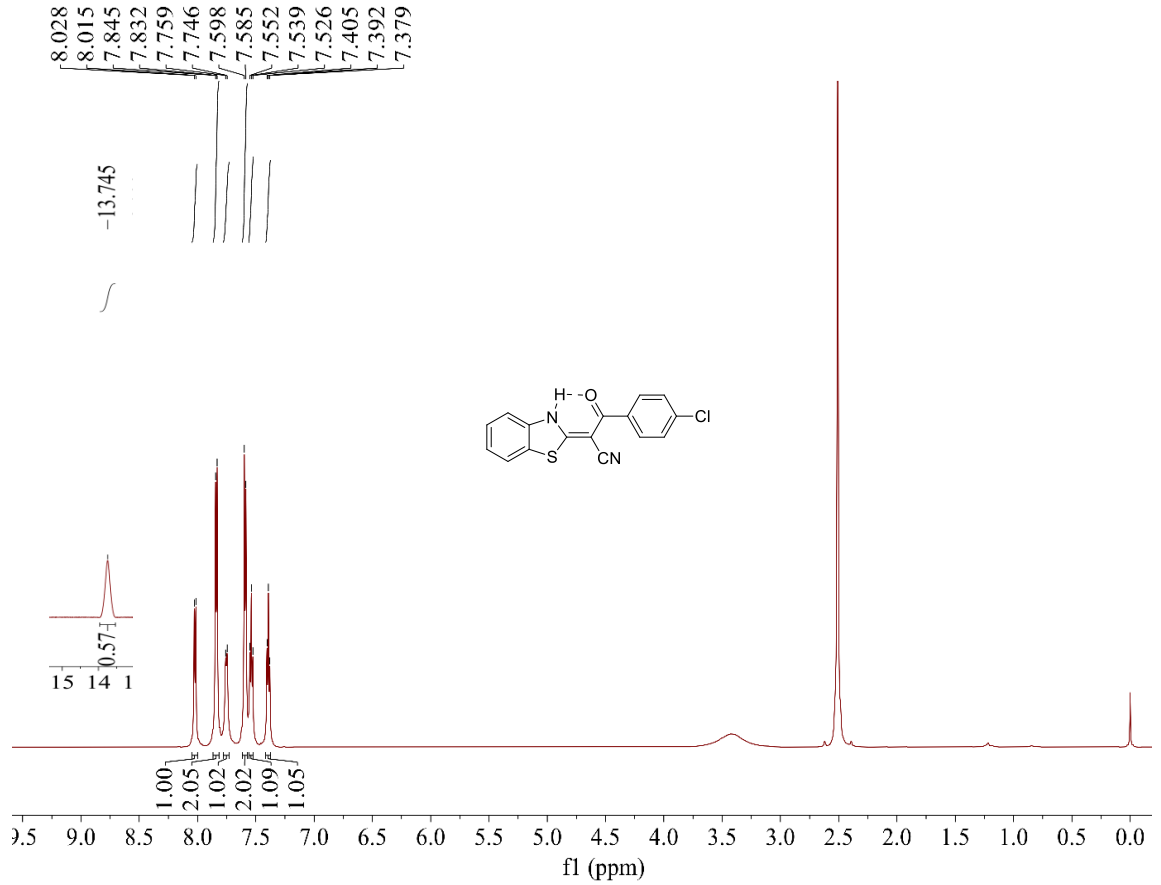

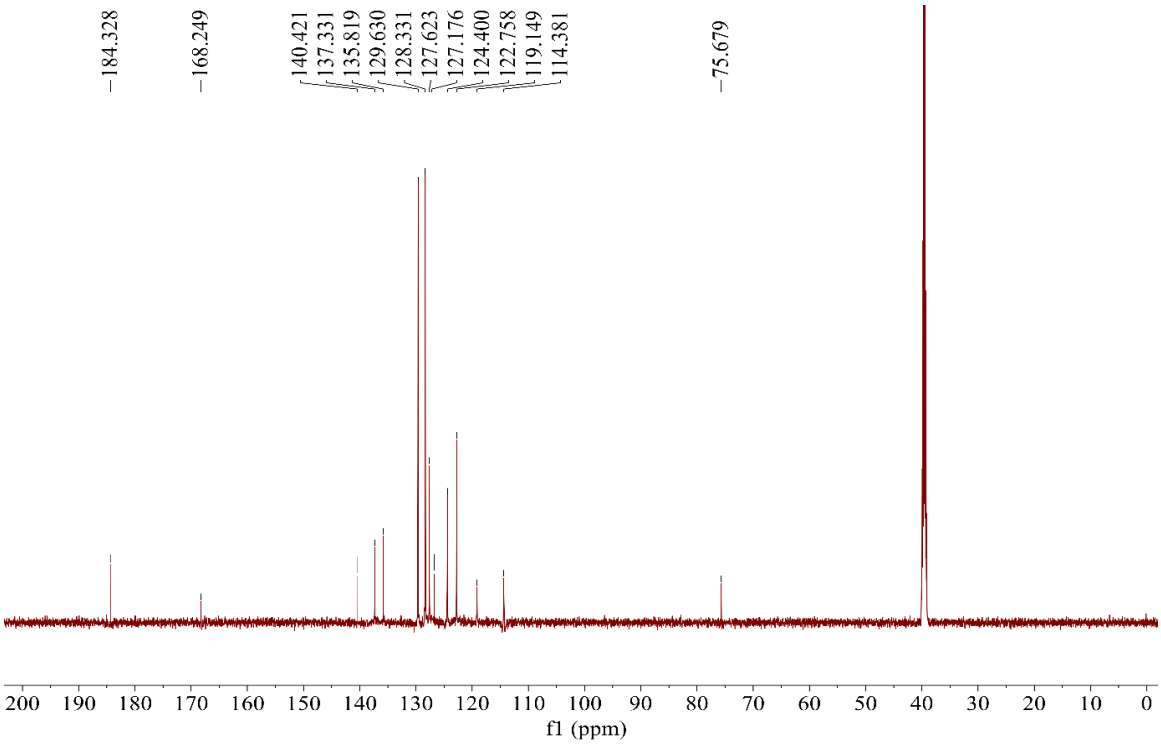

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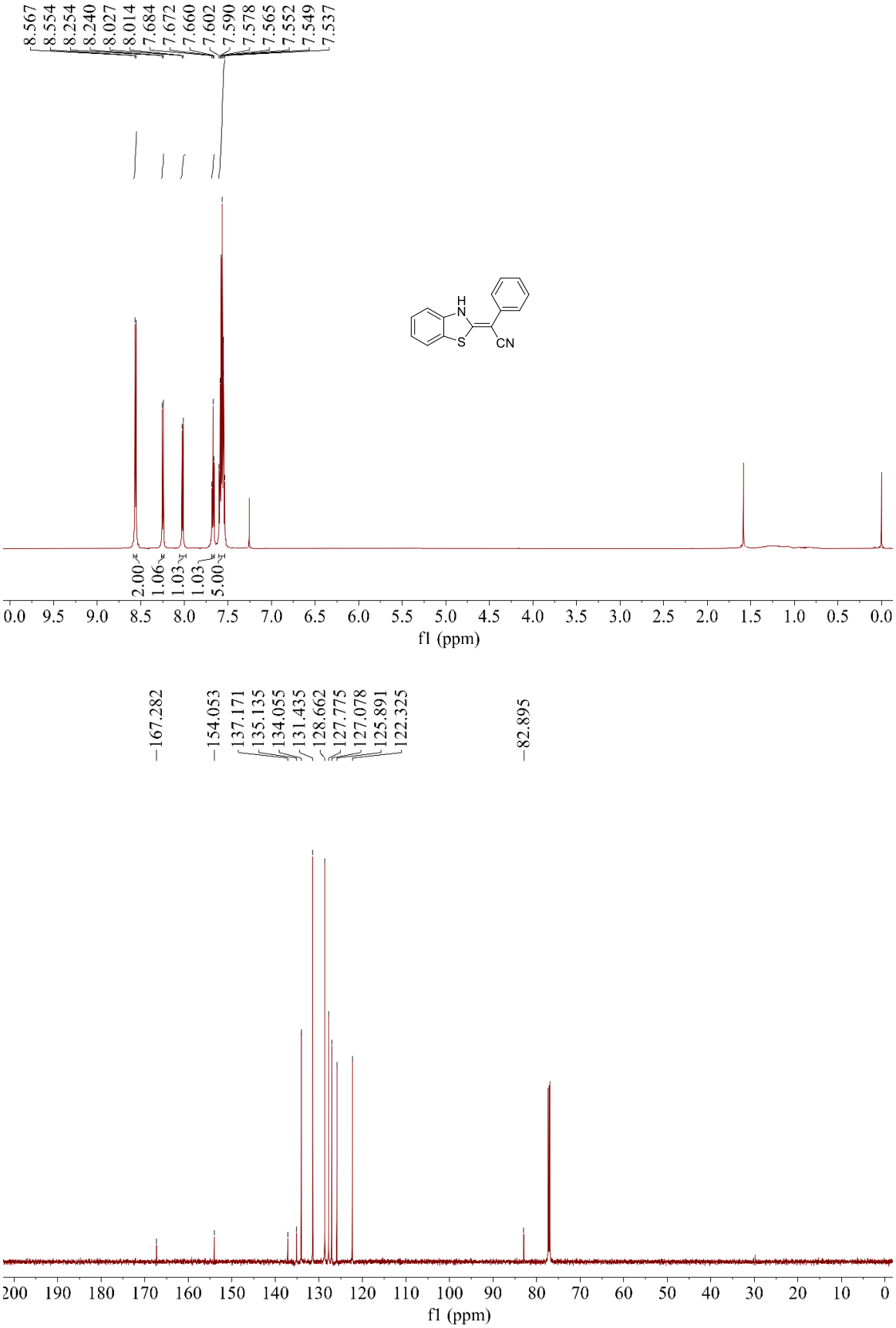

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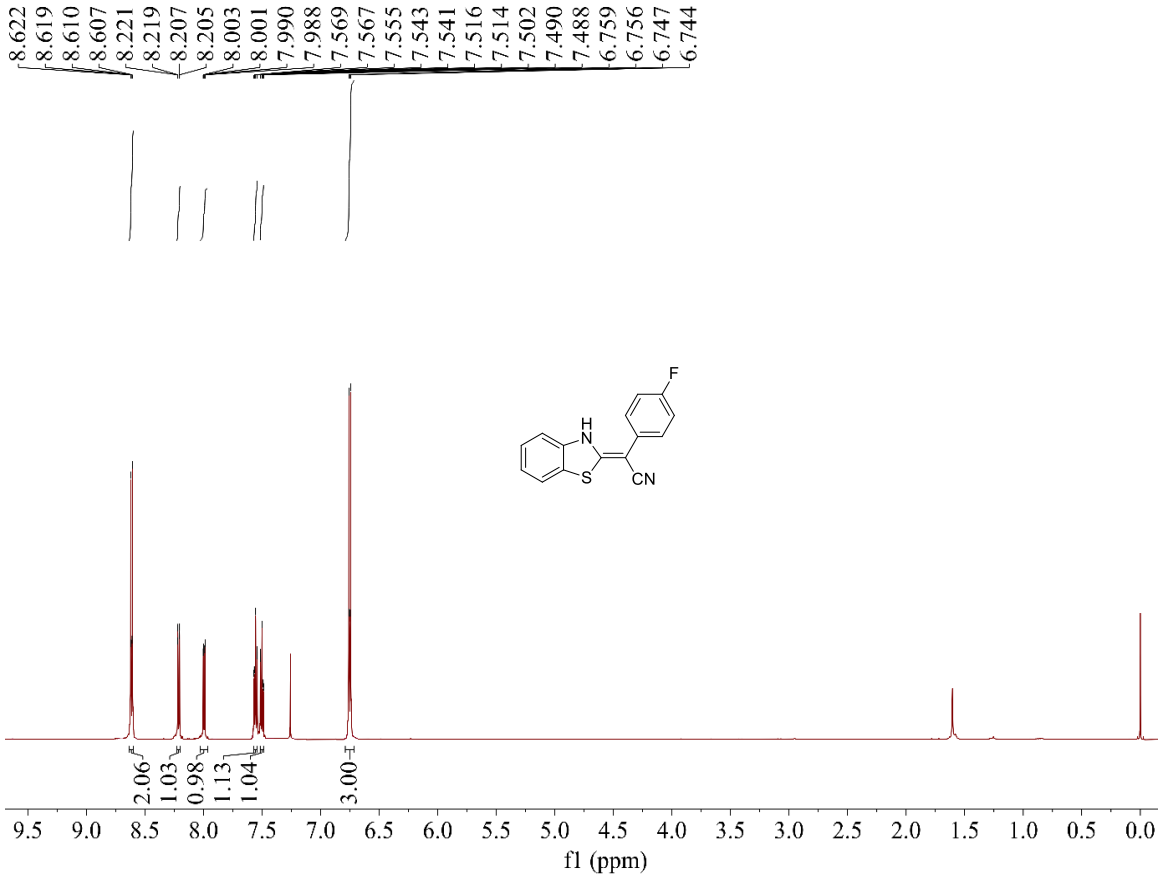

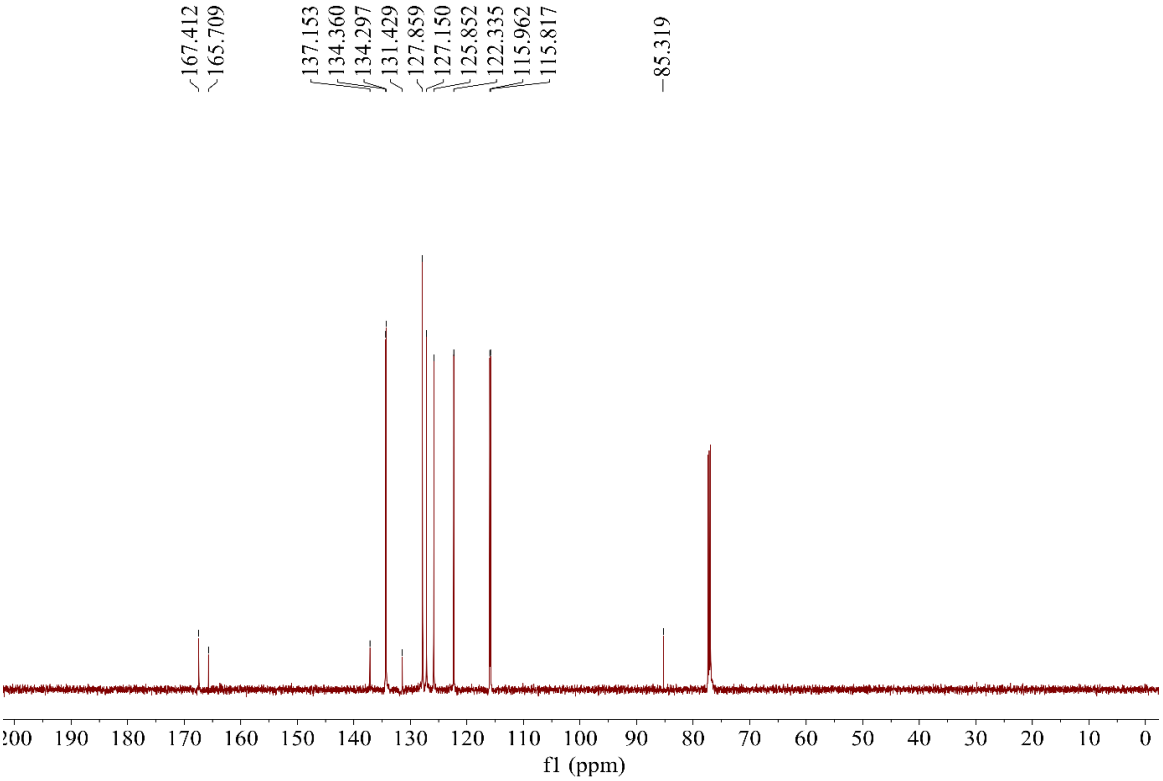

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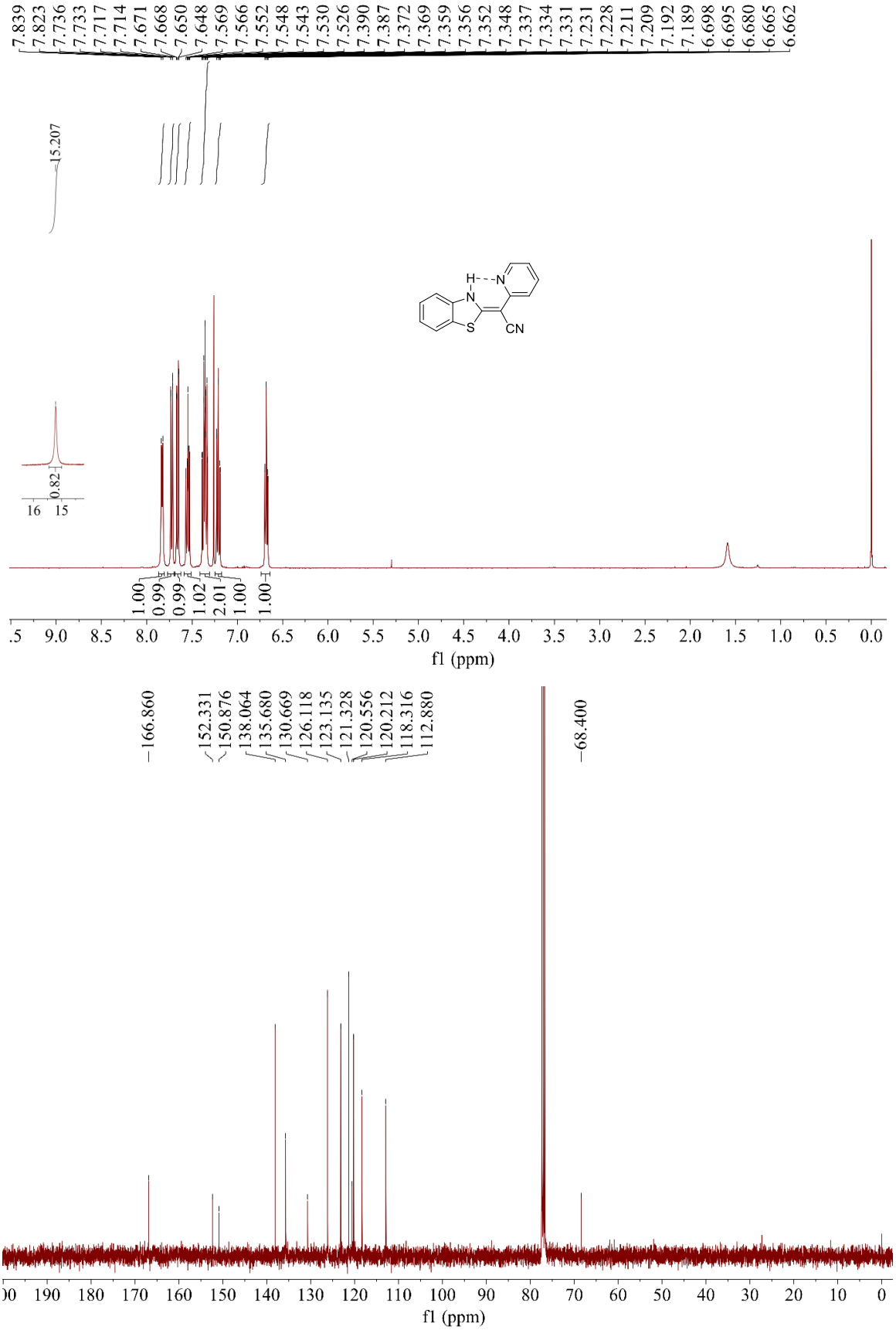

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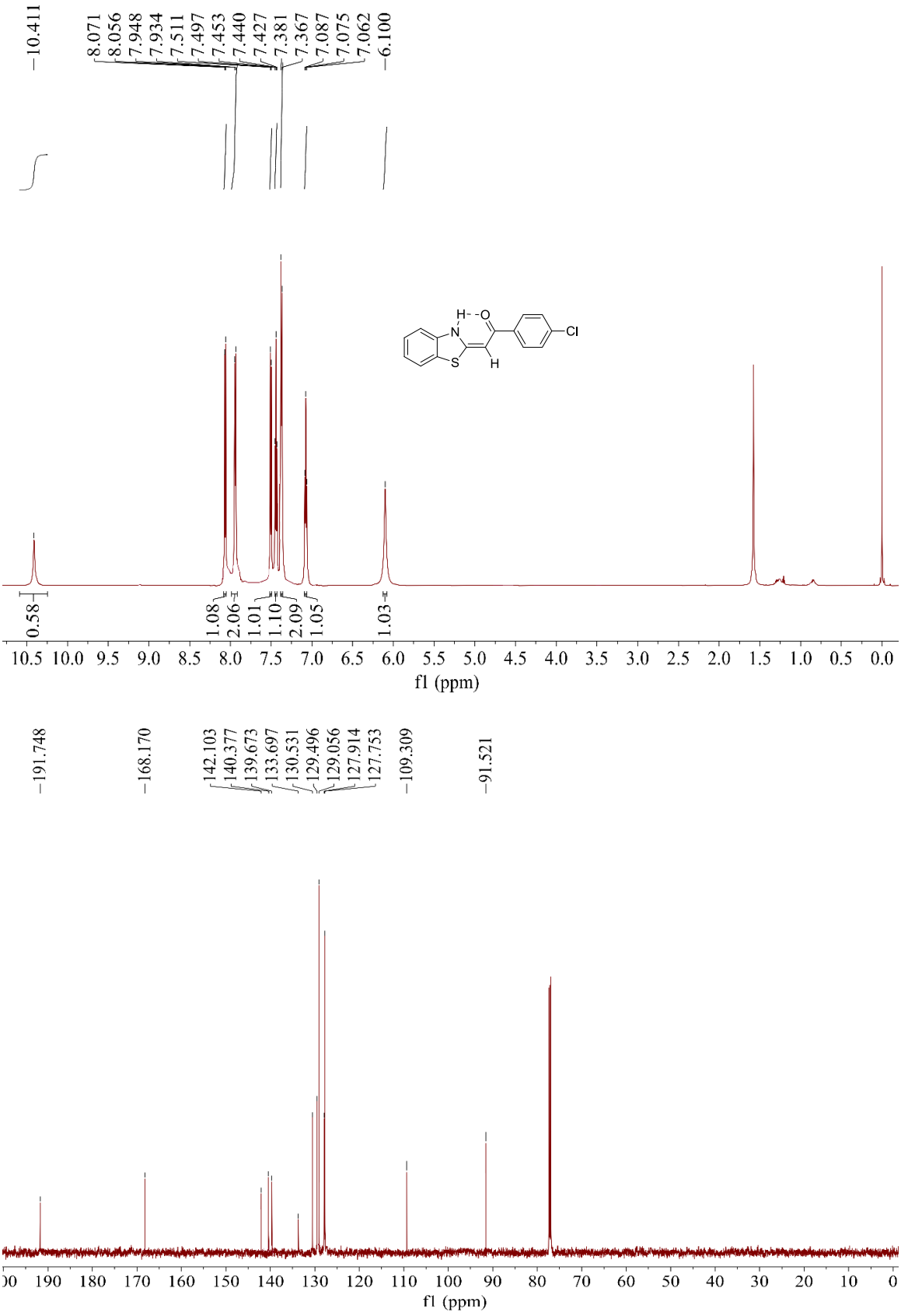

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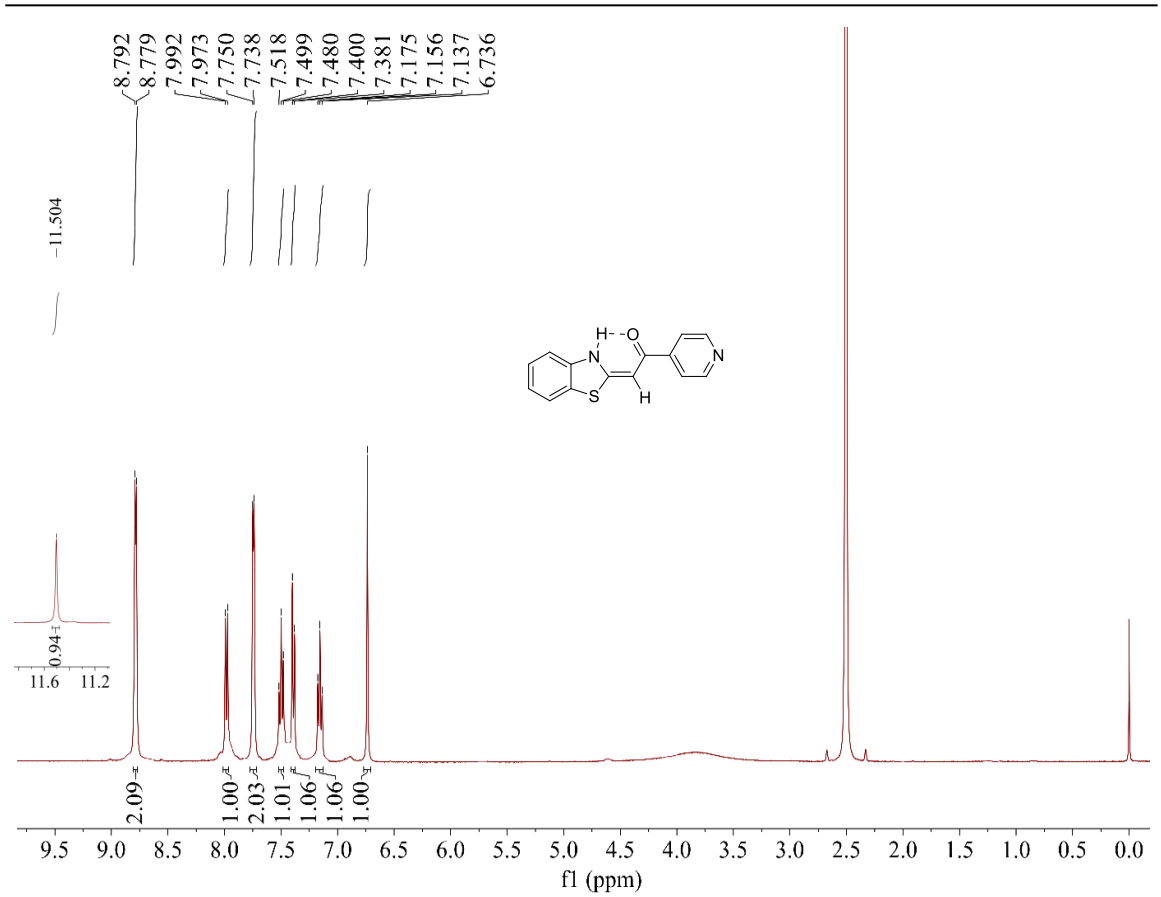

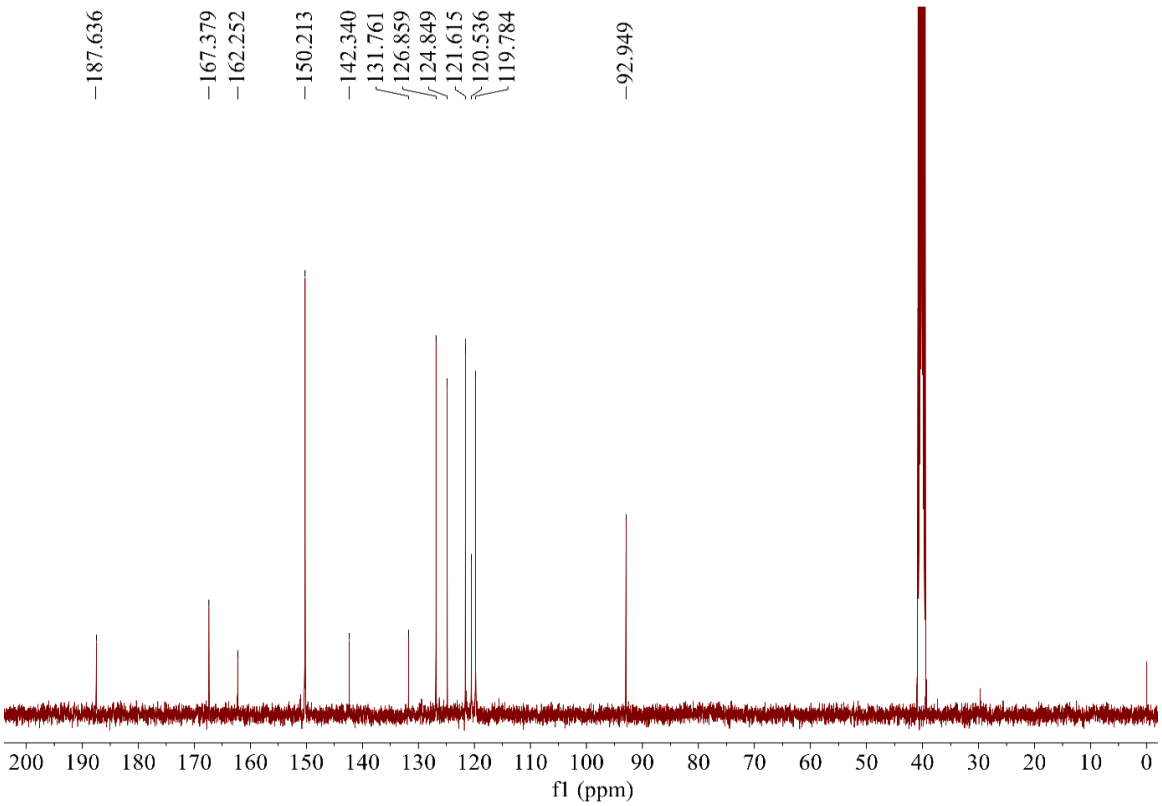

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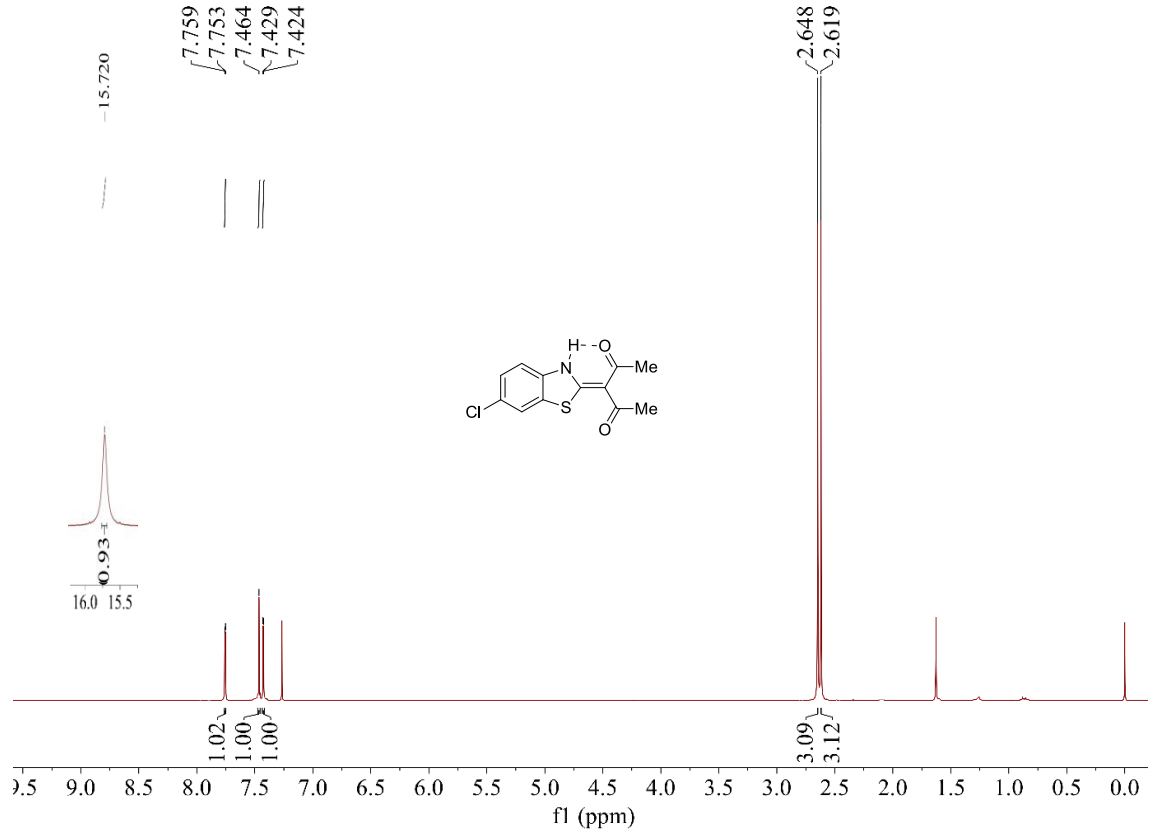

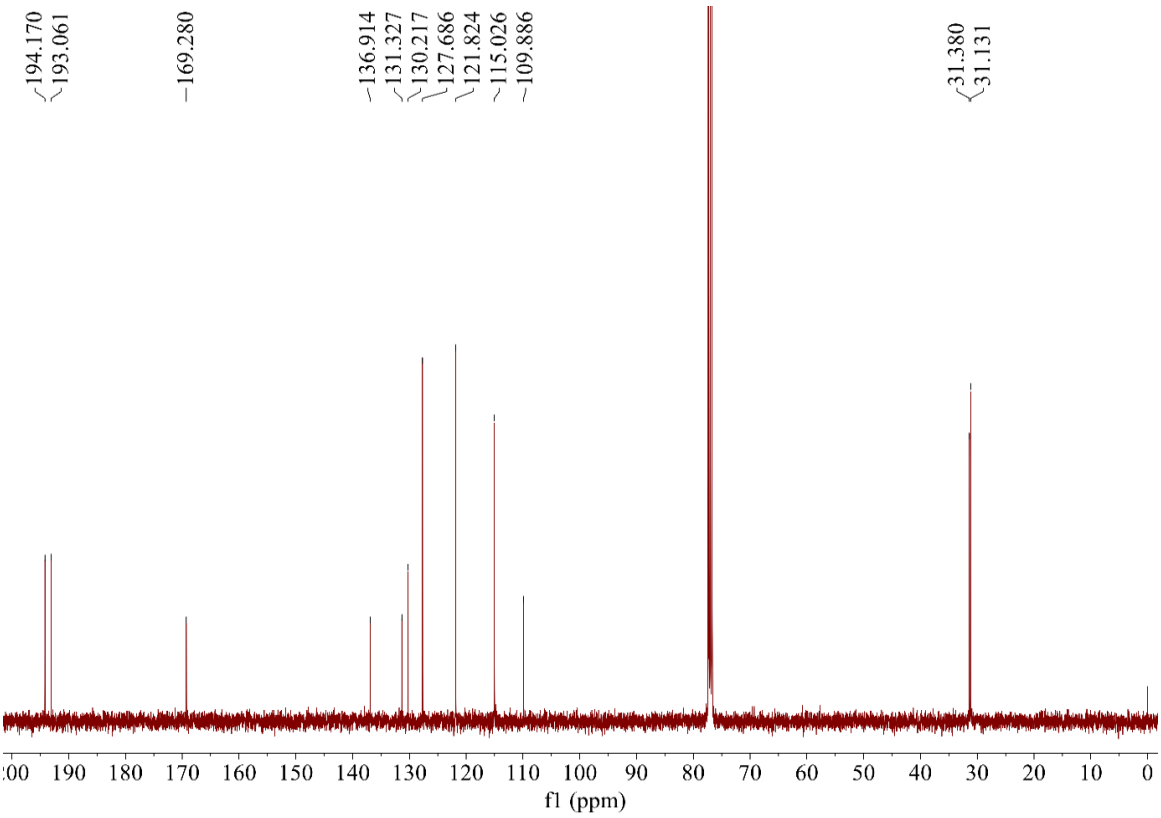

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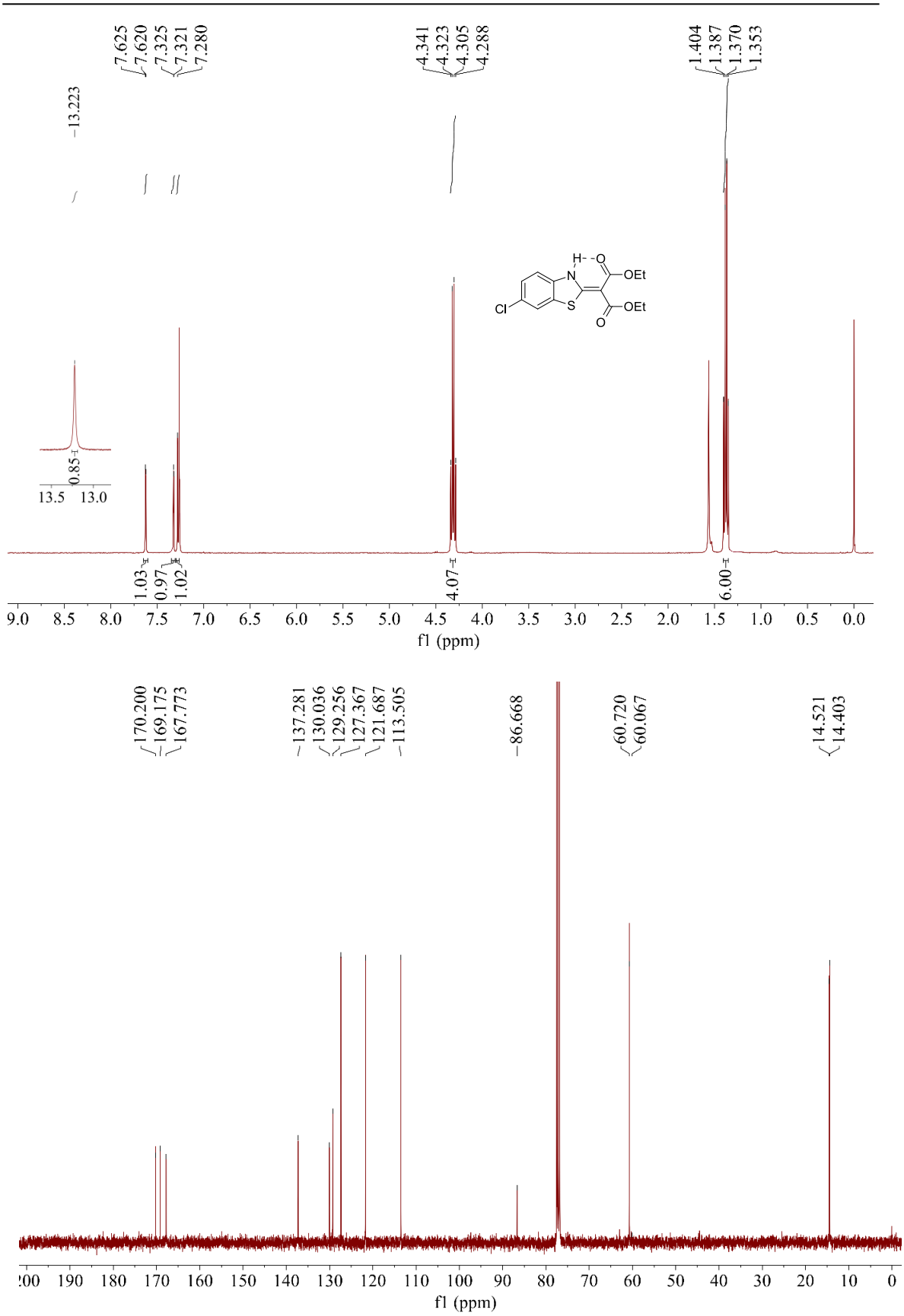

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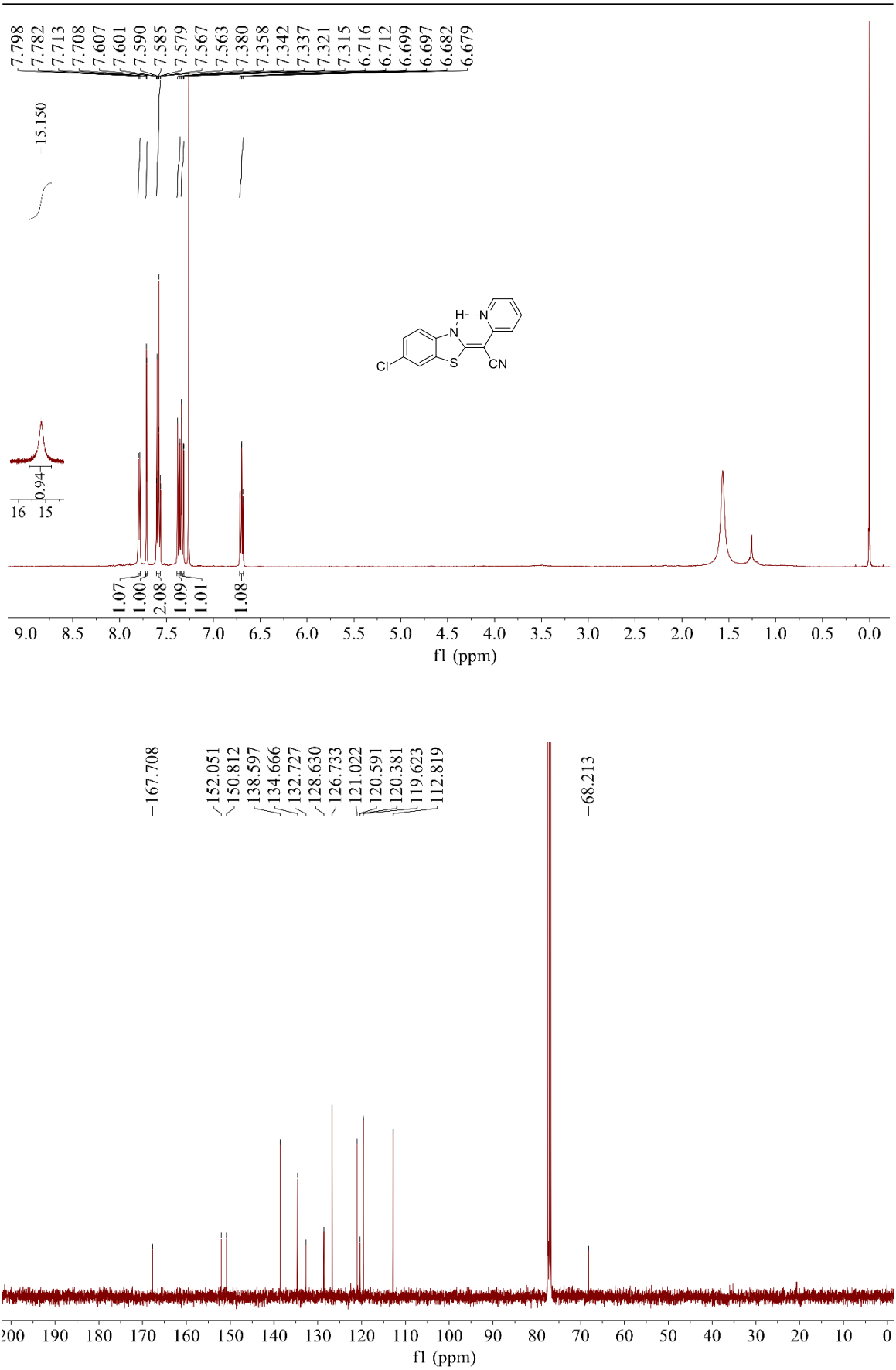

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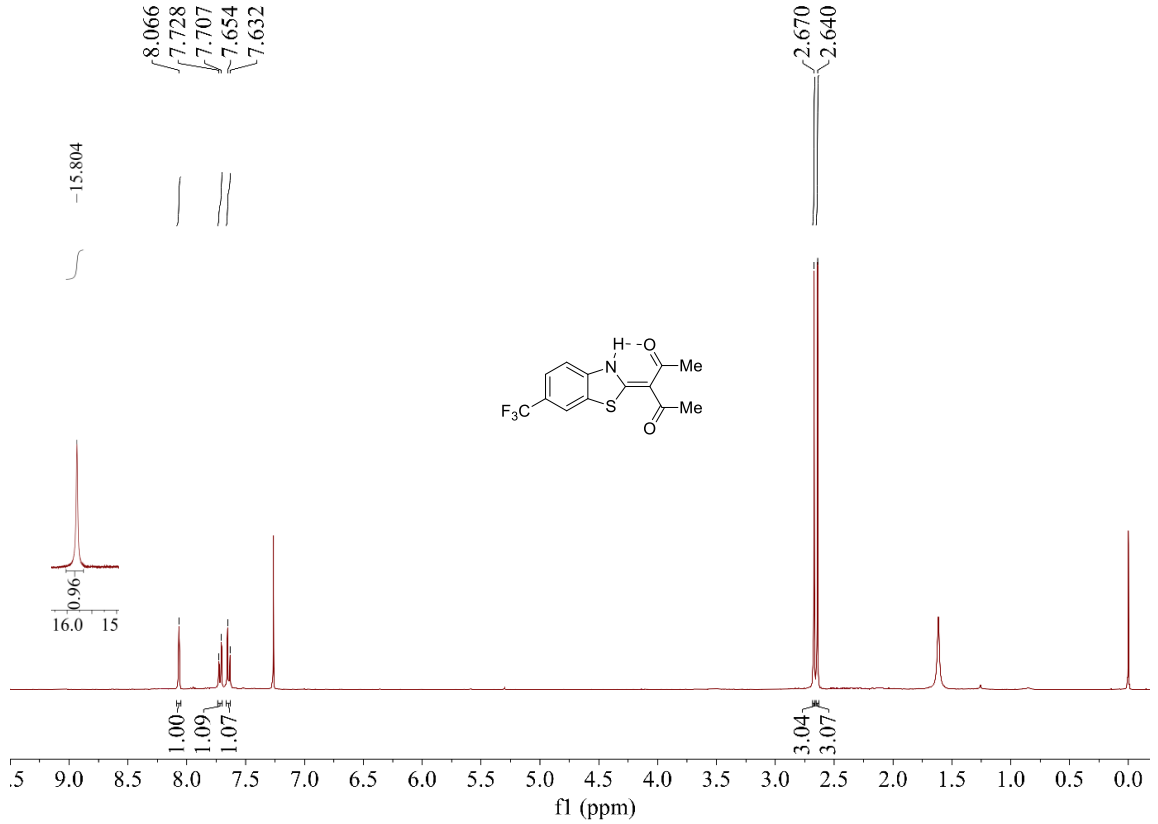

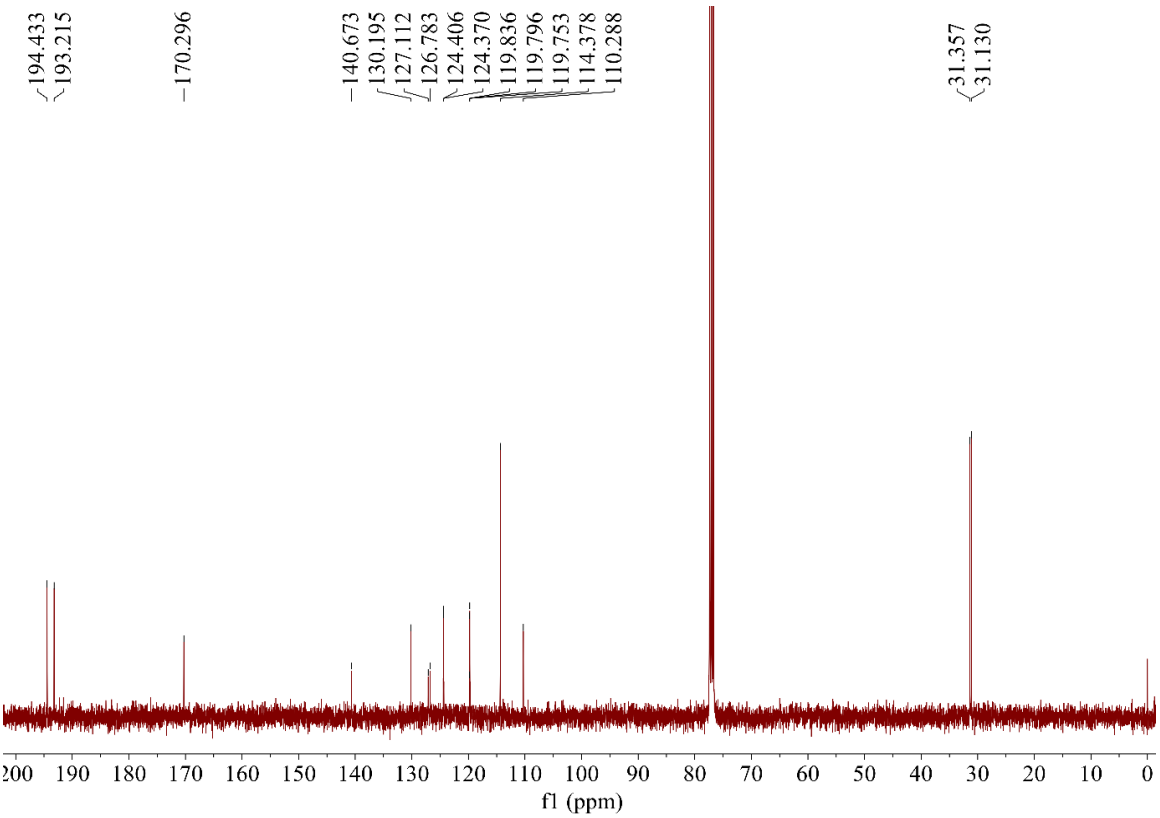

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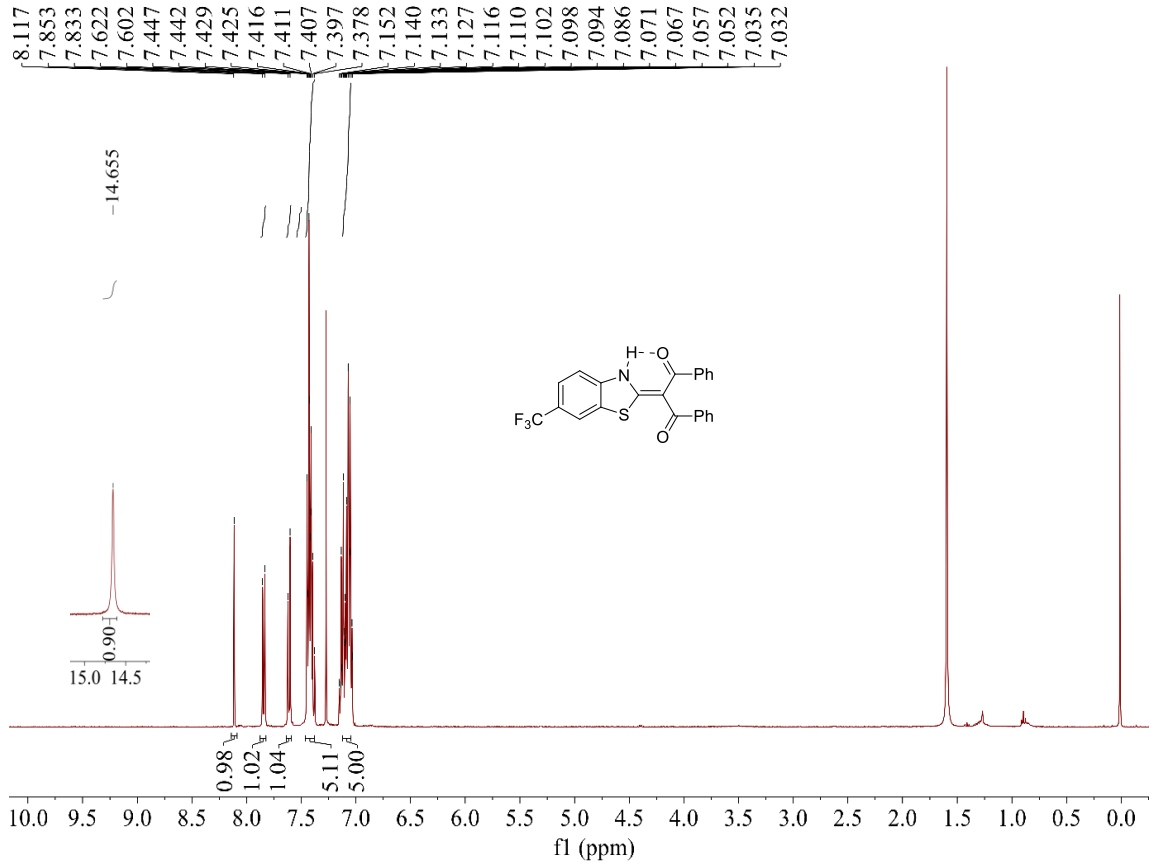

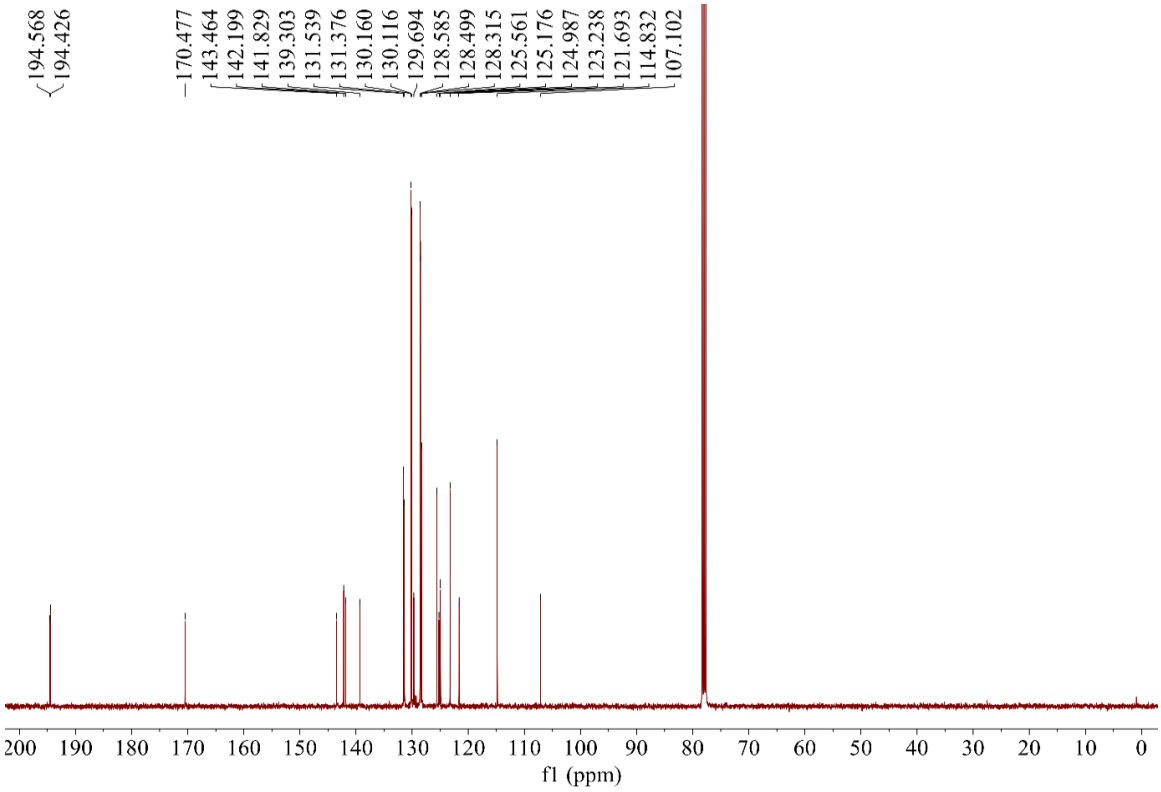

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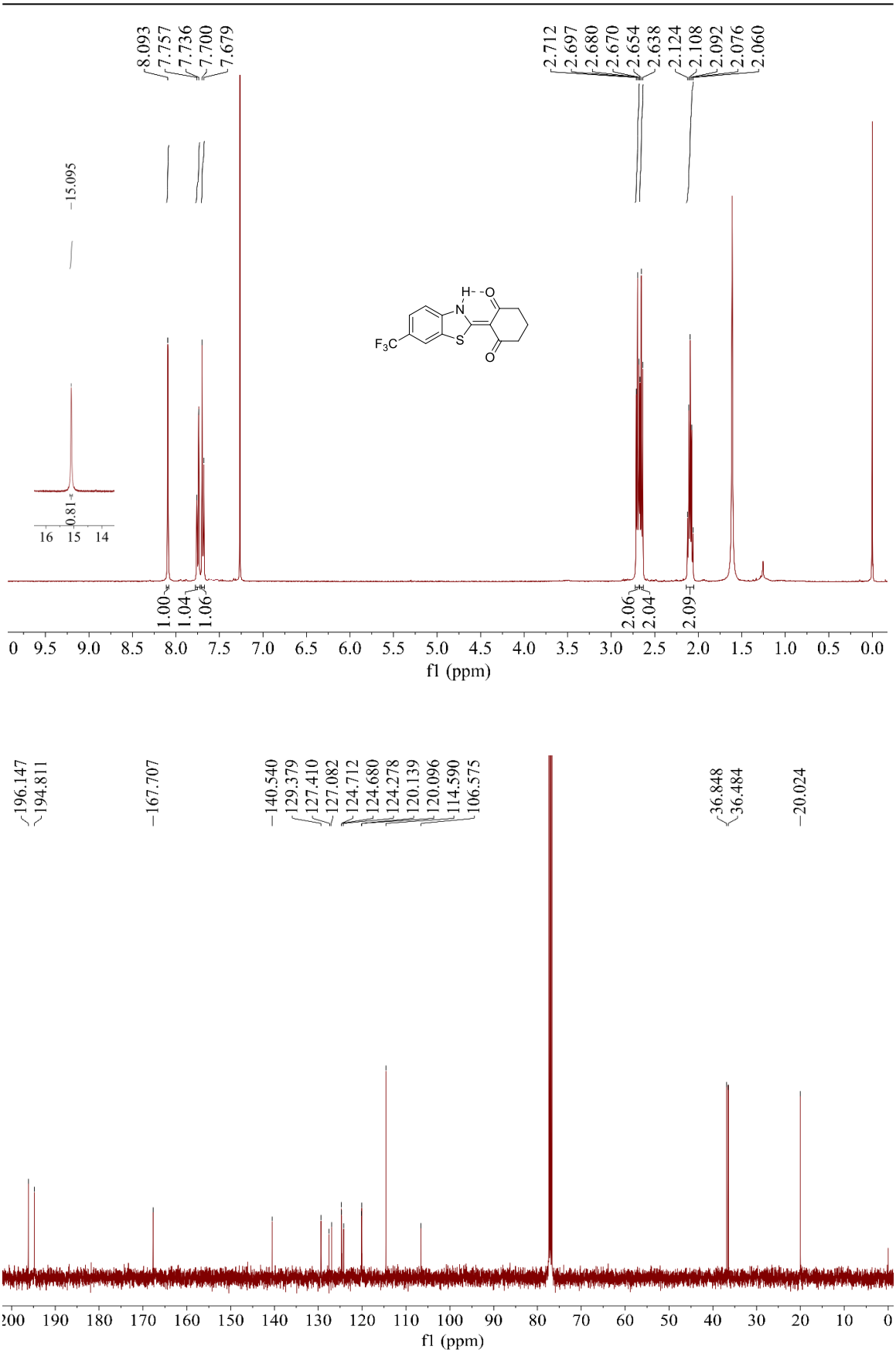

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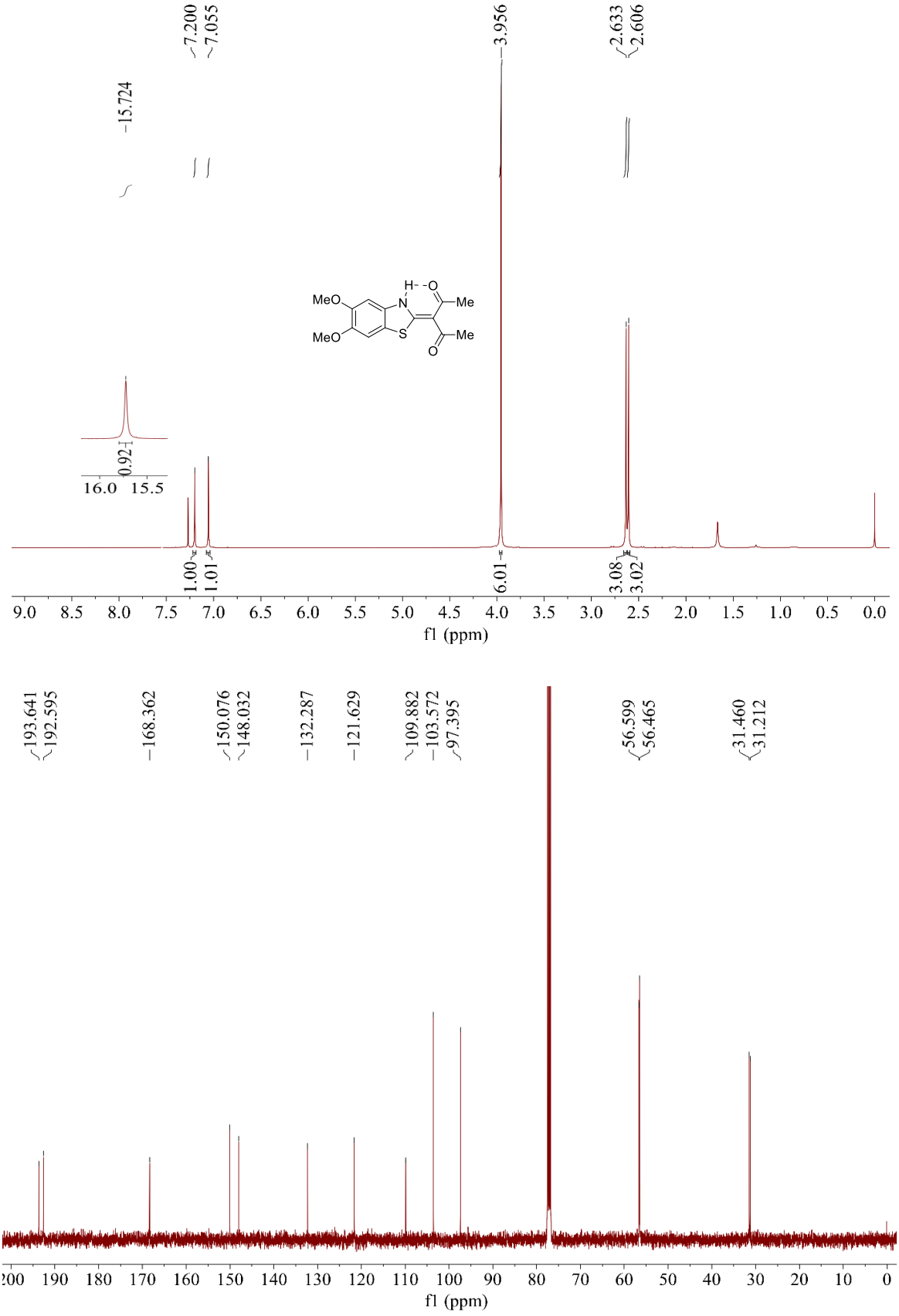

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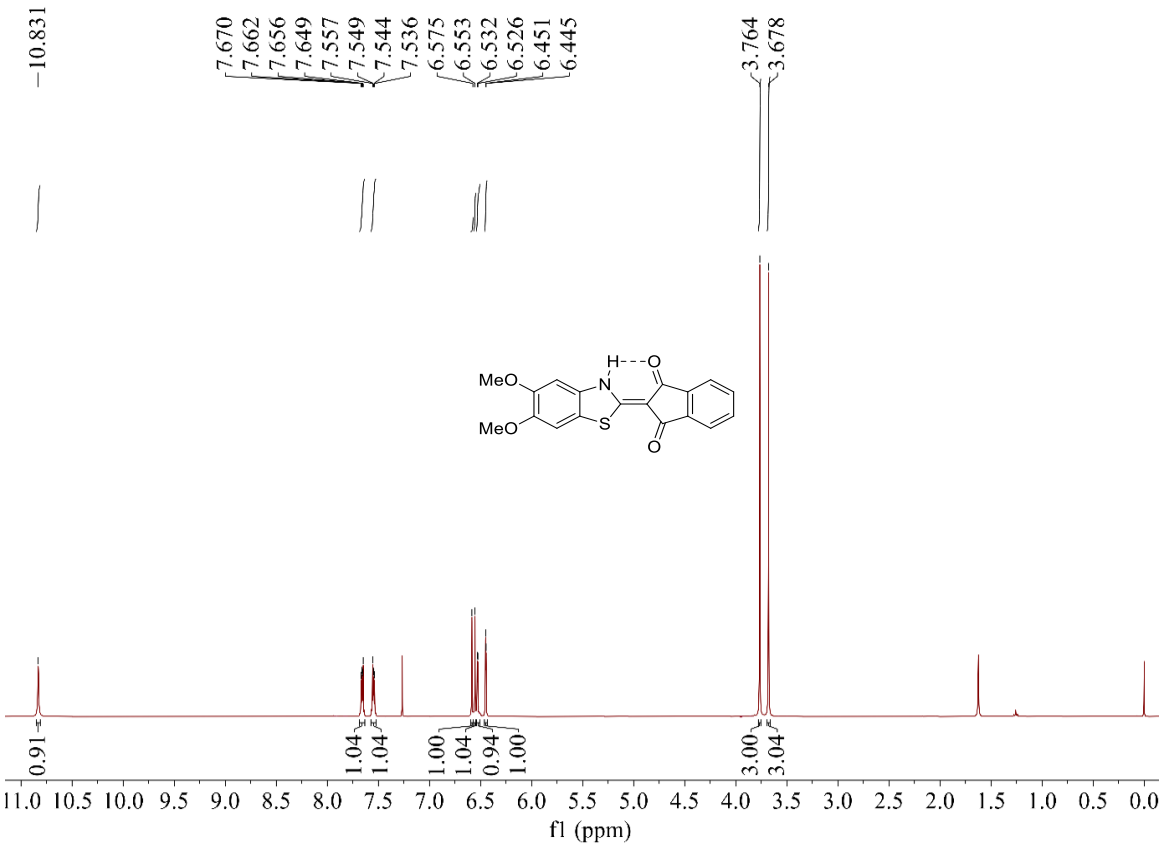

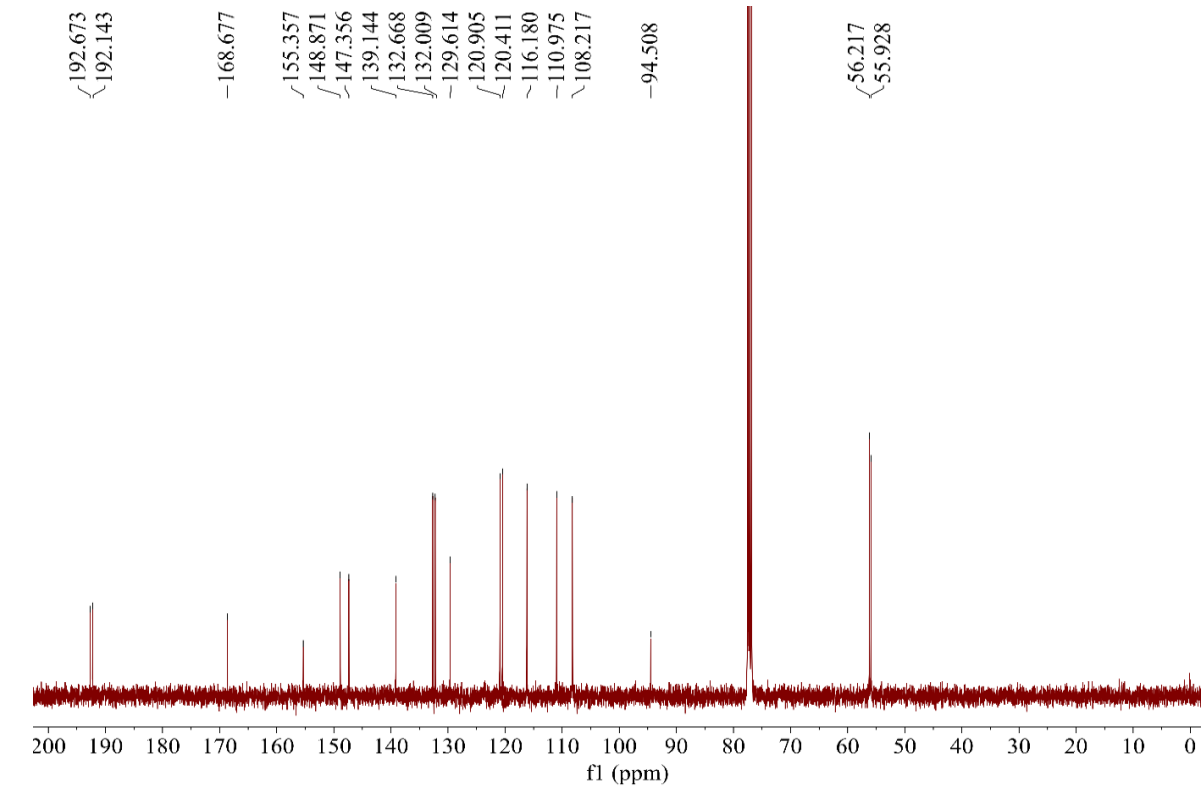

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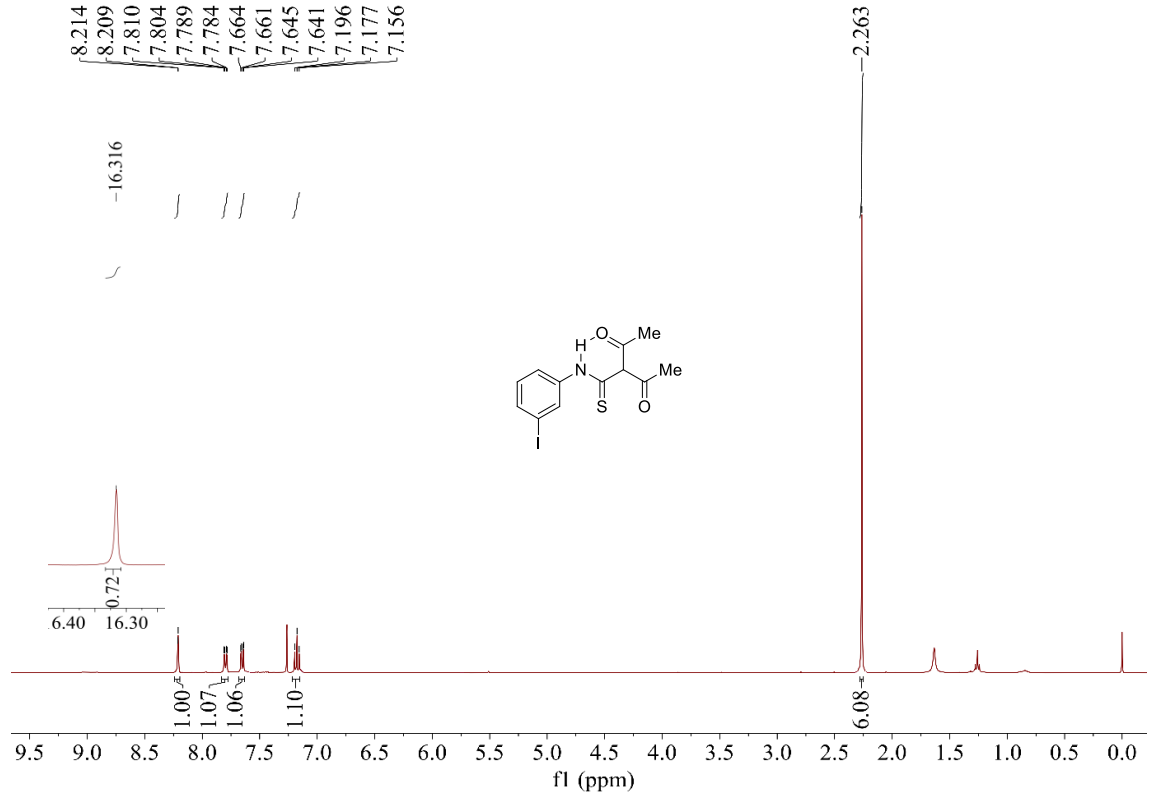
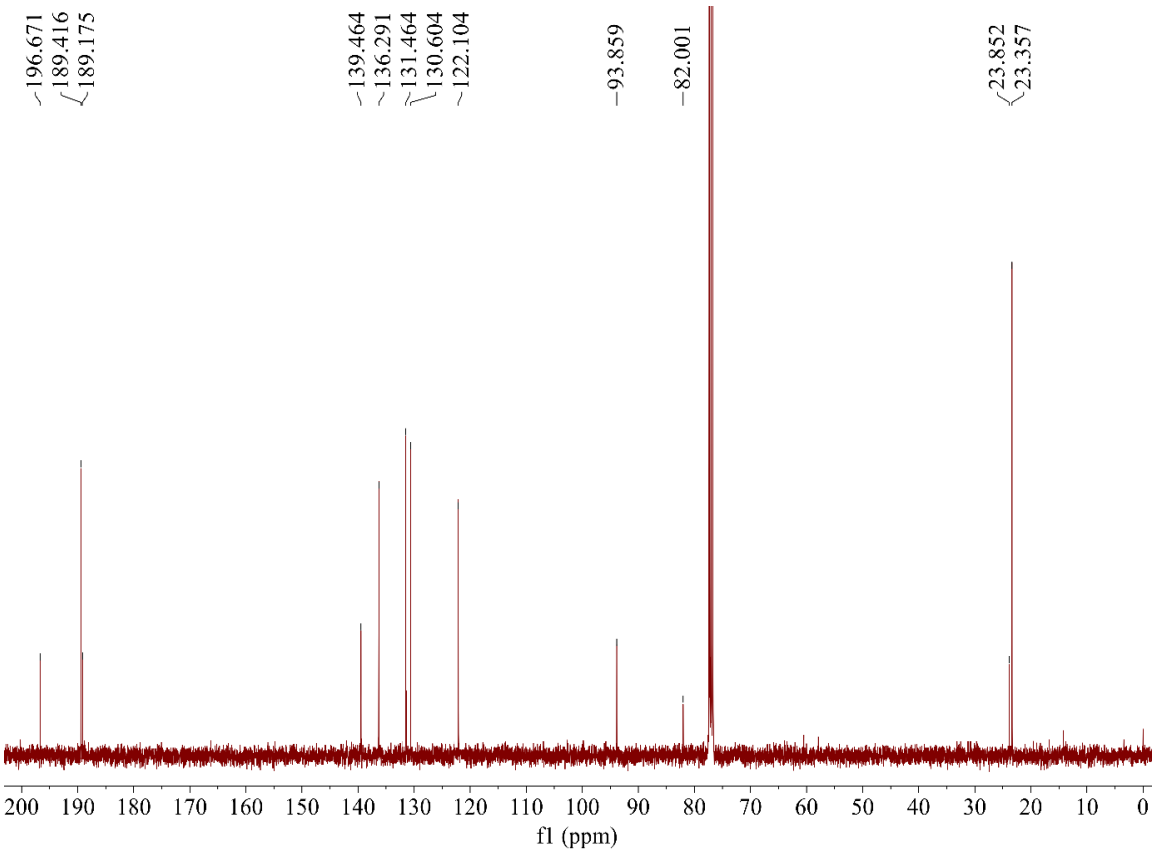




^{1}H and ^{13}C NMR spectra of compound **69**

Chapter 3

*Synthesis of Substituted Benzo[b]thiophenes via Base-Promoted Domino Condensation-Intramolecular C-S Bond Formation**

3.1 Introduction

Substituted benzo[*b*]thiophenes and its derivatives are heterocycles of pivotal significance, which were proven for their activity which include their use as presence in both synthetic and naturally occurring compounds, displaying a broad range of biological activities, such as acetyl-CoA carboxylase inhibitors, HIV-1 reverse transcriptase inhibitors, antidepressants, and selective estrogen receptor modulators (SERMs) for the treatment of postmenopausal disorders, such as Raloxifene **A** (Figure 1),[1] a commercial drug (marketed as Evista, by Eli-Lily) has been utilized for blockage and medicaments of osteoporosis in postmenopausal women, whereas some of its analogs like Arzoxifene **B**,[1a,c,2] are also under examination for breast cancer therapy as well as for administering and medicaments of uterine cancer and Alzheimer's disease.[3] A few of the marketed drugs having the capacity for the benzothiophene core, such as zileuton **C**,[4] a potent and selective inhibitor of 5-lipoxygenase. Just a while ago, not too many of the 2-aryl-3-

*The overall results of the study described in this chapter have been published in *Org. Lett.* **2021**, *23*, 1698.

trimethoxyaroylbenzo[*b*]thiophene derivatives such as **D**, derivatives of Combretastatin A4, have been accepted as tubulin polymerization inhibitors (Figure 1).[5] Also, benzo[*b*]thiophene and its condensed derivatives were also commenced to be fruitful application in the advancement of optoelectronic materials,[6] field-effect transistors (FET),[6] and including organic photovoltaics.[6]

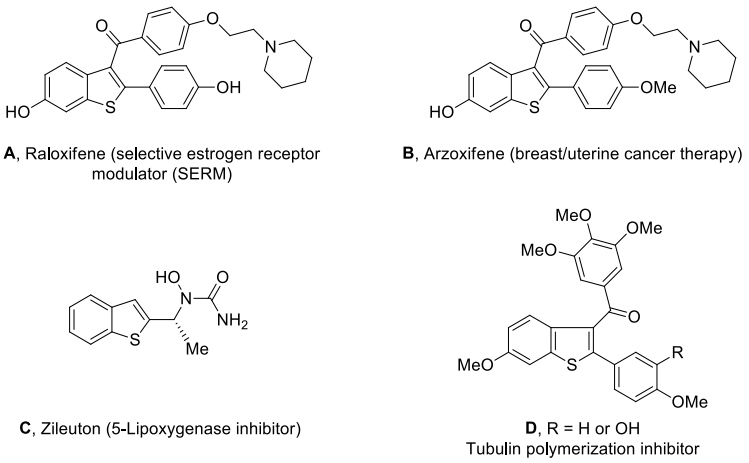


Figure 1. Biologically important substituted benzo[*b*]thiophenes.

Consequently, the synthesis of these privileged compounds has attracted much attention in recent years and many efficient methods have been developed.[7-12]

In the present chapter, the synthesis of substituted benzo[*b*]thiophenes via base-promoted domino condensation-intramolecular C-S bond formation has been described (Scheme 22-23). Before presenting our results, a short literature survey of recent syntheses of benzo[*b*]thiophenes has been presented.

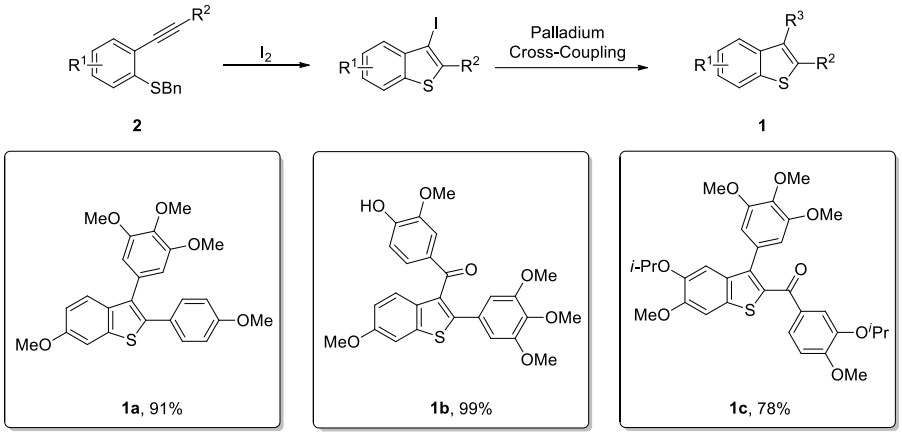
3.2 Synthesis of substituted benzo[*b*]thiophenes: A short literature survey

Among recent syntheses, the most common approach for the benzo[*b*]thiophenes suggests intramolecular electrophilic *5-endo*-cyclization of *o*-alkynyl arylthioetherss or their substitute agents, accommodating electrophilic reagents.[1b,6] Recently, several syntheses involving transition metal (mainly Pd, Cu, or Au) catalyzed intramolecular C-S bond formation in these precursors have been developed, which provide more efficient, practical, and straightforward approaches for the construction of benzothiophenes.[1,3-4,7-10] The crucial bond-forming event in these reactions is the intramolecular attack of nucleophilic sulfur atom on the activated C-C multiple bonds leading to the formation of

S(1)-C(2) bond of the benzothiophene framework. These reactions although selective and efficient, however, require prior synthesis of difficult-to-access prefunctionalized thiophenol precursors.

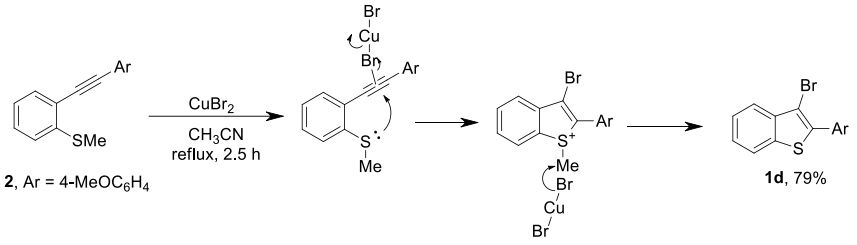
As a result of its extensive utilization in medicinal and material chemistry, research on the way to the new combination of multisubstituted benzo- and hetero-fused thiophenes has been constructively tracked over the last few years and numerous methodical procedures have been succeeded.[7]

Flynn and co-workers have developed the synthesis of benzo[*b*]thiophenes **1** via electrophilic cyclization of *o*-alkynylbenzyl sulfides **2** in the attendance of diatomic iodine (Scheme 1).[13a] Afterwards these authors elongated the procedure and practiced it for the synthesis of several tubulin-binding inhibiting agents **1a-c** in excellent yield via palladium-mediated cross-coupling of resulting 3-iodo-2-substituted benzothiophenes with various substituted aromatic aldehydes (Scheme 1).[13b-c]

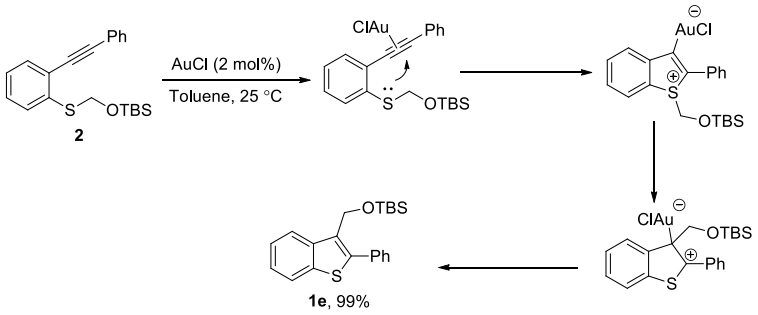


Scheme 1. Synthesis of benzo[*b*]thiophenes **1** with tubulin binding inhibitor activity

This approach has also been continued via transition metal-catalyzed electrophilic cyclization of these *o*-alkynylbenzyl sulfides **2** analogs, where Pd,[9] Cu,[14a] or Au[14b-c] have been used for the cyclization of these *o*-alkynyl thioethers **2** to syntheses of various 2,3-disubstituted benzo[*b*]thiophenes such as **1** (Scheme 2 and 3).

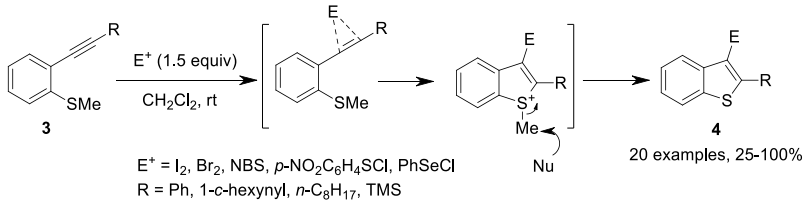


Scheme 2. Cu-mediated electrocyclic synthesis of benzo[*b*]thiophenes



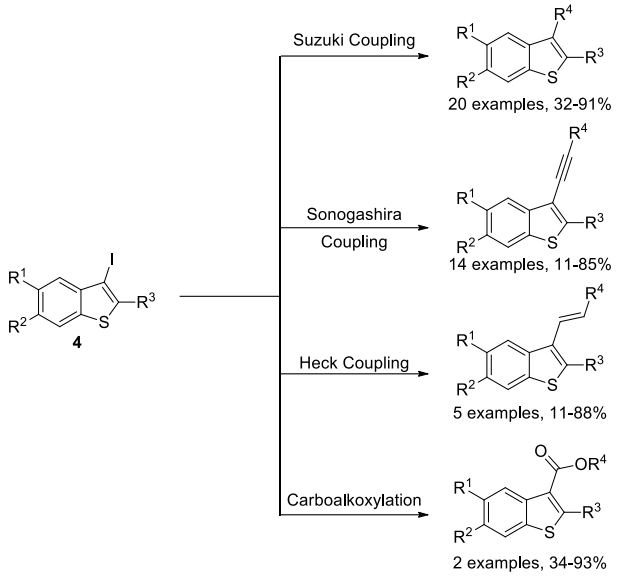
Scheme 3. Au-catalyzed electrocyclic synthesis of benzo[*b*]thiophenes

In the recent past, Larock and co-workers have described electrophilic cyclization of *o*-(1-alkynyl)thioanisole **3** leading to 2,3-substituted benzo[*b*]thiophenes **4** using diatomic iodine, diatomic bromine, *N*-bromosuccinimide, 4-$NO_2C_6H_4SCl$ and PhSeCl as electrophiles.[13d] They have demonstrated that the nature of electrophile plays a predominant role in such types of reactions, thus while diatomic iodine and *N*-bromosuccinimide cyclization gave a high yield of 3-iodo or 3-bromo benzothiophenes, the use of diatomic bromine as electrophile gave a poor yield of 3-bromobenzo[*b*]thiophenes **4** (Scheme 4).[13d]



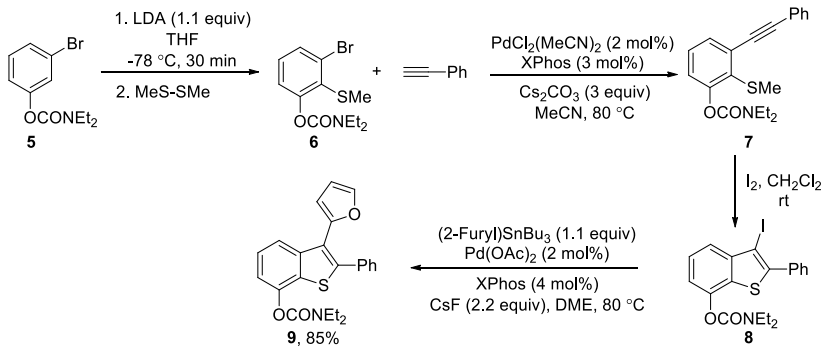
Scheme 4. Synthesis of benzo[*b*]thiophenes **4** via electrocyclization

The carbon-halogen bond of 2-substituted-3-iodobenzo[*b*]thiophenes **4** was then efficiently used to bring about a library of 2,3-substituted benzo[*b*]thiophenes **1** by Pd-catalyzed Suzuki-Miyaura, Sonogashira, Heck coupling and carboalkoxylation (Scheme 5).[13h]



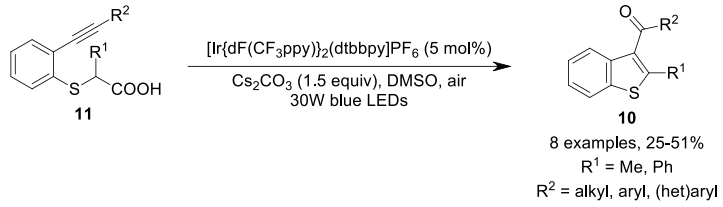
Scheme 5

Sanz and co-workers have developed an efficient protocol for the synthesis of 3-halo-7-substituted functionalized benzo[*b*]thiophenes **8** beginning from *N*, *N*-diethyl-*O*-3-*S*-halophenylcarbamates **6** (Scheme 6).[13e] The synthesis requires *o*-lithiation of **5**, bringing about 3-halo-2-(methylthio)phenol derivatives **6**, subsequently Sonogashira coupling with various aromatic acetylenic substrates and subsequent electrophilic cyclization of the successive acetylenic derivative **7** in the presence of diatomic iodine. The subsequent functionalization of these 3-halobenzo[*b*]thiophenes products **8** permitting access to a variety of 2,3,7-substituted benzo[*b*]thiophenes **9** has also been carried out via palladium-catalyzed Stille reaction with aryl/(het)aryl organostannanes (Scheme 6).



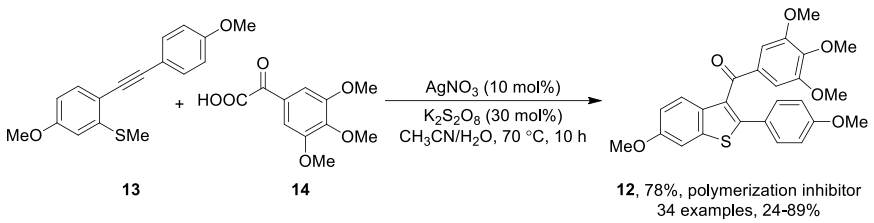
Scheme 6

Just a while ago, Xia and co-worker have developed a skillful strategy for easy access to 3-carbonylated benzo[*b*]thiophene heteroaromatic compounds **10** via a visible-light-promoted (using blue LEDs as the light source) intramolecular decarboxylative cyclization reaction of (phenylthio)- acetic acid derivatives such as **11** via using $[Ir\{dF(CF_3ppy)\}_2(dtbbpy)]PF_6$ as the photocatalyst in the presence of Cs_2CO_3 as a base (Scheme 7).[13f]



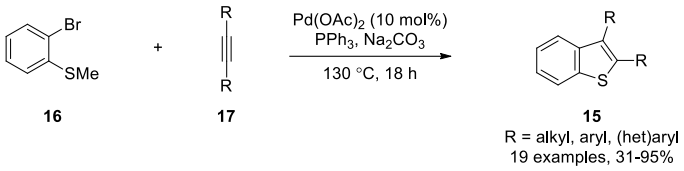
Scheme 7

Wu and co-worker have developed a novel and direct protocol to access 3-acylbenzothiophene such as **12** from 2-alkynylthioanisole **13** and α-oxocarboxylic acid such as **14** in the presence of $AgNO_3$ via a radical cascade cyclization (Scheme 8).[13g] This approach features easy handling and good functional-group compatibility. In particular, the utility of this novel methodology was demonstrated in the synthesis of a polymerization inhibitor[5,13f] and a raloxifene precursor (Scheme 8).[1,13g]



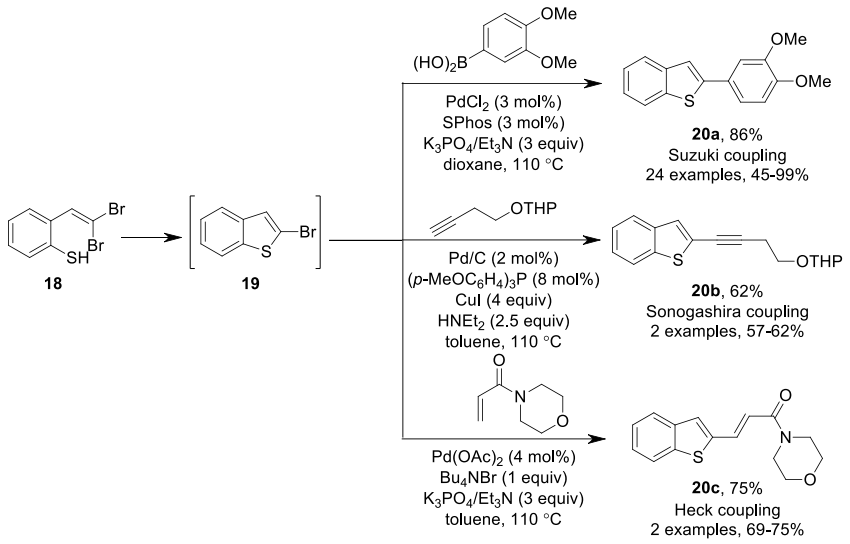
Scheme 8

Recently, Chatani and co-workers have developed a new methodology for the synthesis of 2,3-disubstituted benzothiophenes **15** involving the palladium-catalyzed annulation of aryl sulfides **16** with substituted alkynes **17**. This convergent approach exhibited good functional group tolerance, providing rapid access to a diverse array of derivatives from simple, readily available starting materials (Scheme 9).[14d]



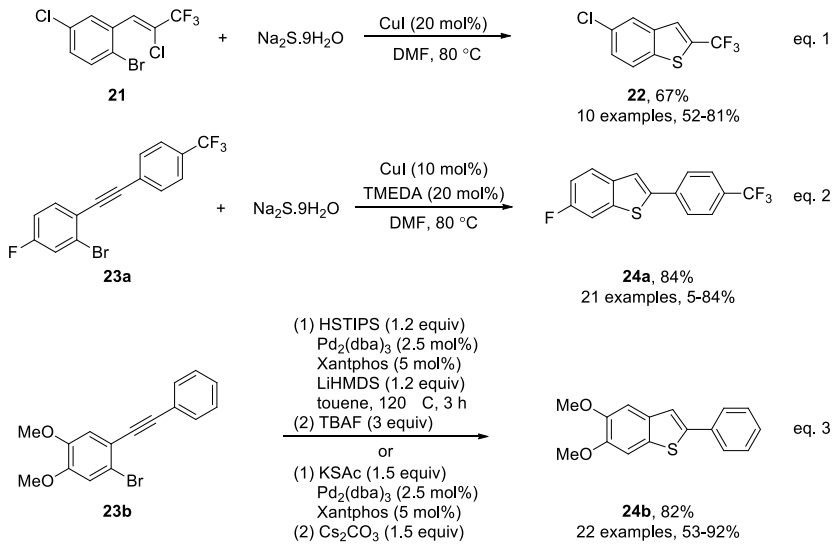
Scheme 9

Lauten and co-workers have described the synthesis of 2-halo substituted benzo[*b*]thiophenes **19** via Pd or Cu-catalyzed tandem intramolecular *S*-vinylation and intermolecular cross-coupling reactions of *o*-(*gem*-dibromovinyl) thiophenols such as **18** (Scheme 10).[14e] The 2-bromo functionality in these thiophenes **19** is another comprehensive to various 2-substituted thiophenes **20a-c** via Suzuki, Sonogashira, and Heck coupling respectively (Scheme 10).[14e-f]



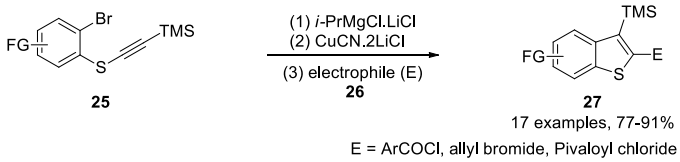
Scheme 10

In all the above detailed reactions leads to the construction of S(1)-C(2) bond of benzothiophenes. These reactions in spite of being selective and valuable, on the other hand, depend upon the prior synthesis of prefunctionalized thiophenol precursors, which are challenging to access. Just a while ago, Cu-catalyzed (or palladium-catalyzed) double thiolation of *o*-(2-halovinyl)halobenzenes **21** (Li and co-workers, eq. 1),[15a] or 2-bromo alkynyl benzenes **23a** (Zhang and co-workers, eq. 2),[15b] with metal sulfides or its representatives such as **23b** (Sanz and co-workers, eq. 3),[15c] well-known to 2-substituted benzo[*b*]thiophenes **22**, **24a-b** (Scheme 11).[15]



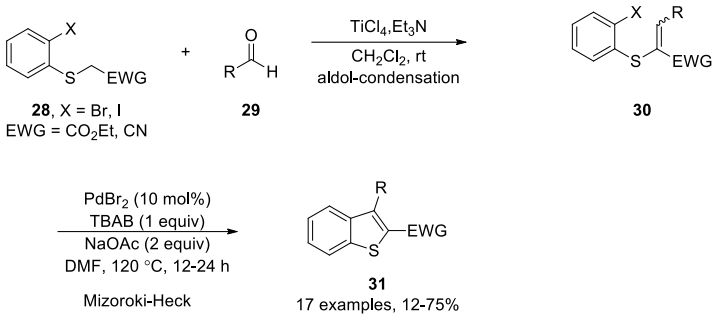
Scheme 11

Knochel and co-workers have reported a new intramolecular copper-catalyzed carbomagnesiation procedure for the preparation of magnesiated benzothiophenes starting from alkynyl(aryl)thioethers **25**. Further reactions with various electrophiles **26** gave access to highly functionalized benzo[2,3-*b*]thiophenes and benzo[*b*]thieno[2,3-*d*]thiophenes **27**[13d,14d,16a] in excellent yields (Scheme 12).[16a]



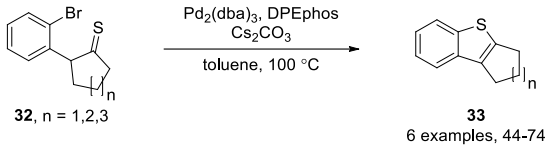
Scheme 12

Recently, Gong and co-workers have developed a productive methodology for the synthesis of 3-substituted benzo[*b*]thiophene-2-carboxylates/nitriles via intramolecular Mizoroki-Heck reaction of 2-thiosubstituted acrylates. When, aryl, heteroaryl, and alkyl aldehydes **29** bearing various functional groups were reacted in the titanium-mediated aldol condensation with the acetate/nitrile **28**, which readily gave acrylates **30**. Further Heck reaction with the acrylate **30** in the presence of palladium (II) bromide as catalyst and TBAB (tetrabutylammonium bromide) additive and NaOAc as base give 3-substituted benzo[*b*]thiophene-2-carboxylates **31** (Scheme 13).[16b]



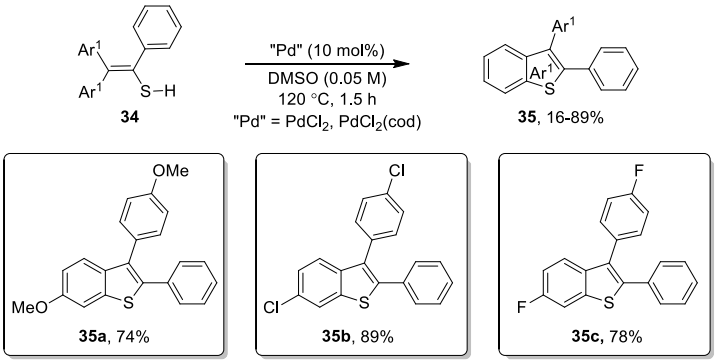
Scheme 13

Just a while ago, Gillmore and co-workers have reported the synthesis of 2,3-annulated benzo[*b*]thiophenes such as **33** in moderate to good yields via palladium-catalyzed intramolecular cyclization of *S*-(halo)aryl-substituted cyclic thioketones **32** (Scheme 14).[17a]



Scheme 14

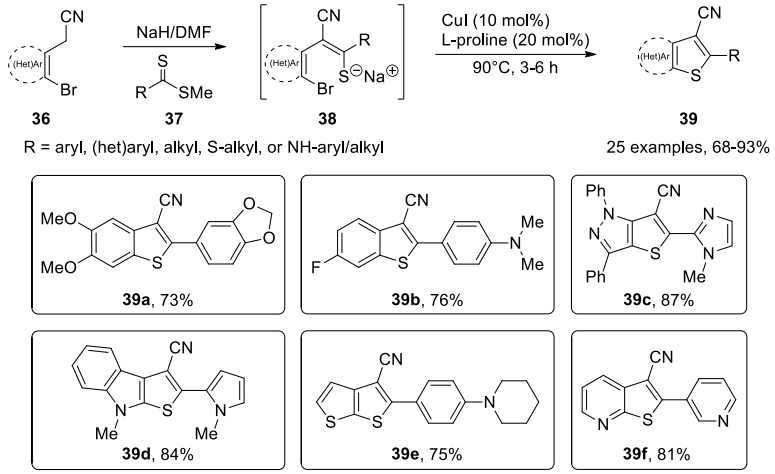
Inamoto and co-workers have recently reported one-pot direct conversions of thioenols such as **34** to multisubstituted benzo[*b*]thiophenes **35** in the presence of palladium catalyst such as $PdCl_2$ or $PdCl_2$(COD) without any redox-active reagents in the presence of DMSO as solvent (Scheme 15).[17b]



Scheme 15

Our research group, and others have also recently reported the synthesis of 2,3-substituted benzo[*b*]thiophenes and their hetero-fused analogs involving intramolecular S(1)-C(7a) bond formation via Cu-catalyzed intramolecular C-S cross-coupling[7a-b,17] and C-H activation reactions.[18]

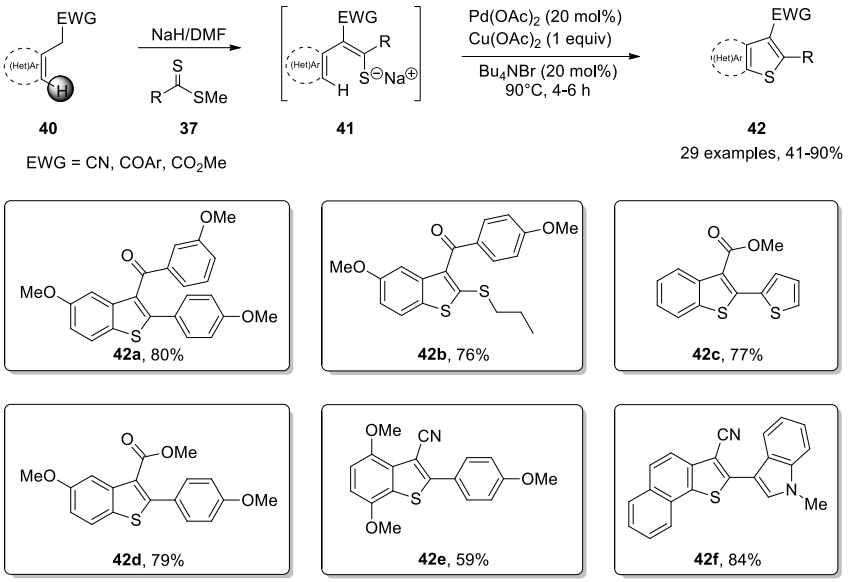
Thus Acharya and others from our research group, have developed a valuable one-pot synthesis of diversely functionalized multisubstituted benzo[*b*]thiophenes and hetero-fused thiophenes **39** (Scheme 16).[7a,17] The overall procedure involves sequential base-mediated tandem condensation of readily available 2-bromohet(aryl)acetonitrile precursors **36** with (het)aryl/alkyl dithioesters **37** or other thiocarbonyl species, followed by Cu-catalyzed intramolecular cross-coupling arylthiolation of the in situ generated enethioenolate intermediate **38** yielding multisubstituted benzo[*b*]thiophenes **39** (Scheme 16).



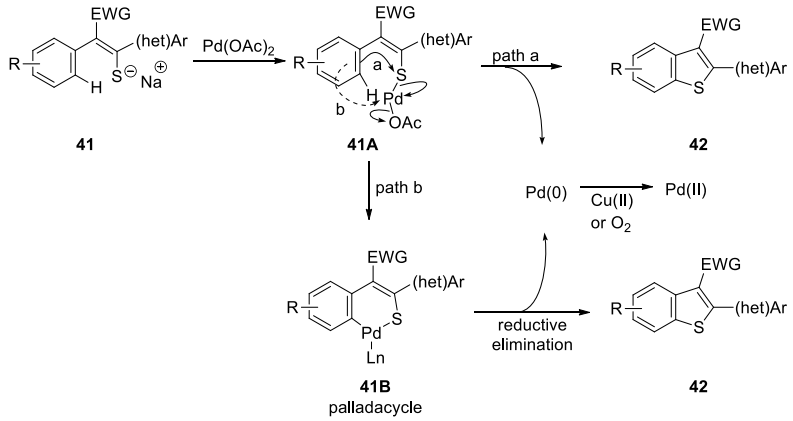
Scheme 16

In another report from our research group, Acharya and others have reported a valuable high yielding route to a variety of diversly substituted benzo[*b*]thiophenes and their hetero-fused analogs **42** through palladium-catalyzed intramolecular oxidative C-H functionalization/arylthiolation of enethiolate intermediates **41** generated via base-mediated tandem condensation of substituted arylacetonitriles, deoxybenzoins, or aryl acetates **40** with (het)aryl/alkyl dithioesters **37** (Scheme 17).[7b,17] The overall strategy involves a one-pot, two-step procedure in which in situ generated enethiolate **41** is reacted with palladium acetate catalyst in presence of cupric acetate (as an oxidant) and tetrabutylammonium bromide (Bu_4NBr) as an additive to afford a variety of substituted and

hetero-annulated benzothiophenes **42**. A probable mechanism involving intramolecular arylthiolation via either a Pd-S adduct **41A** or palladacycle intermediate **41B** has been proposed for this transformation based on experimental studies (Scheme 18).

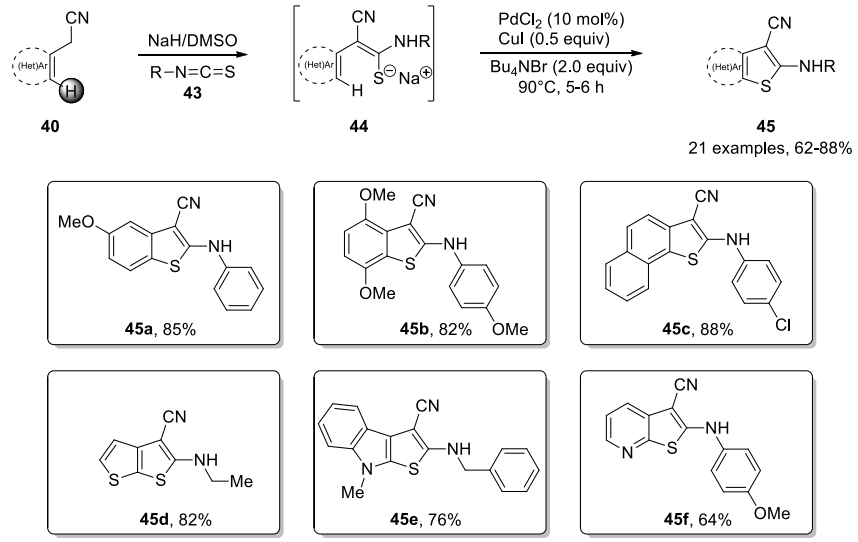


Scheme 17



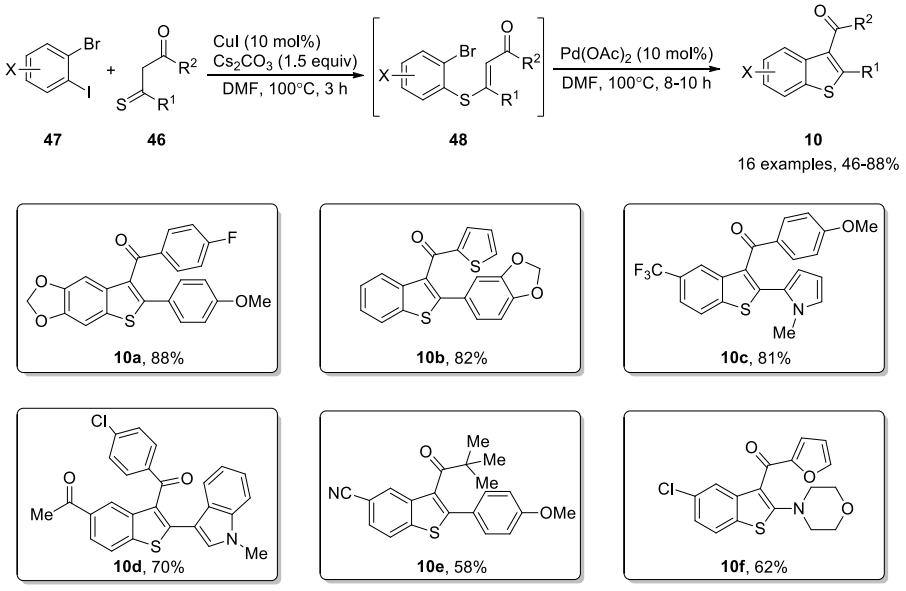
Scheme 18

Saraiah and others from our research group have also developed an efficient, highly regioselective one-pot high-yielding synthesis of multi-substituted 2-(aryl/alkyl)amino-3-cyanobenzo[*b*]thiophenes and their hetero-fused analogs **45**, via palladium-catalyzed intramolecular oxidative C-H functionalization/arylthiolation reaction of in situ generated *N*-(alkyl/aryl)thioamides salts **44**, obtained from readily available (hetero)arylacetonitriles **40** and alkyl/aryl isothiocyanates **43** (Scheme 19).[18a]



Scheme 19

Recently, Yugandar and others from our research group have described an efficient one-pot protocol for the synthesis of 2-het(aryl)-3-acyl/benzoylbenzothiophenes **10** from readily available 1,3-bishet(aryl)-1,3-monothiodiketones **46** and *o*-bromoiodoarenes **47**, involving a consecutive Cu-catalyzed intermolecular C-S bond formation, followed by Pd-catalyzed intramolecular Heck reaction of the resulting *β*-arylthiovinyl ketones **48** (Scheme 20).[10]



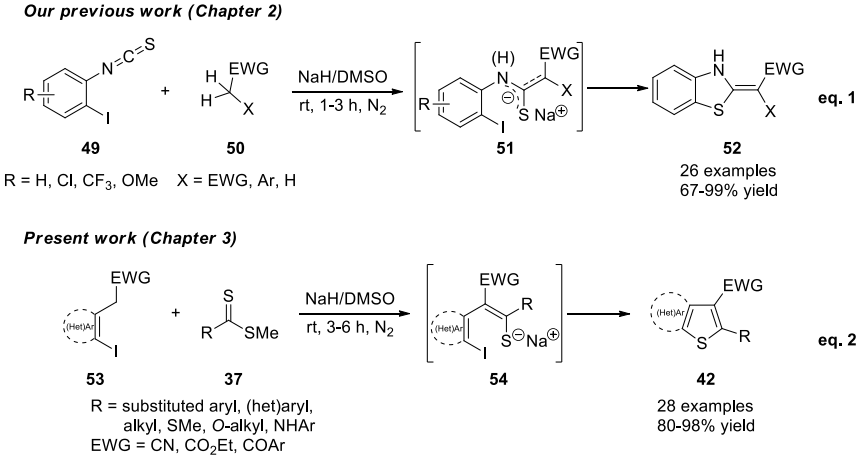
Scheme 20

Some of the other common useful approaches for the syntheses of benzo[*b*]thiophenes and fused thiophene analogs have been discussed in Anand Acharya's thesis (Chapters 2 and 3) from our research group.

However, the above-mentioned syntheses of benzo[*b*]thiophenes, although, efficient, employ toxic and costly transition metal-catalysts/ligands and usually harsh reaction conditions, thus reducing the attractiveness of these methods. In recent years, much attention has been paid towards, the development of transition metal-free protocols, and transition metal-free cross-coupling reactions for the construction of C-C, C-N, C-O, and C-S bonds have attracted much interest among synthetic organic chemists (Chapters 1-2).[19-21] Considerable progress has been made in this field by several research groups for the development of TM-free C-C cross-coupling reactions leading to the synthesis of biaryl derivatives. Bolm and co-workers[23], on the other hand, first reported a detailed study of intermolecular C-heteroatom bond formation[22-23] by reactions between aryl halides and various sulfur, oxygen, and nitrogen-based nucleophiles, in the presence of KOH/DMSO as 'superbase' medium under TM-free conditions.[22] Subsequently, these workers and others have also developed base-promoted transition metal-free intramolecular C-heteroatom bond formation reactions, leading to the construction of several five- and six-membered benzoheterocycles in high yields (Chapters 1-2).[19,22-24]

During the course of our studies on the synthesis of five- and six-membered heterocycles and their benzo-fused analogs via transition metal-catalyzed intramolecular carbon-heteroatom bond formation, employing organosulfur intermediates.[7,10,18,25] we became interested in developing base-mediated transition metal-free synthesis of heterocycles. Thus, in Chapter 2, we have recently reported a facile transition metal-free domino protocol, for the synthesis of 2-substituted benzothiazoles via base-promoted tandem addition-intramolecular cyclization of *o*-iodoarylisothiocyanates with various active methylene compounds in DMSO at room temperature (Scheme 21, eq. 1).[19] In continuation of these studies in the present chapter, we now report a facile transition metal-free protocol for the synthesis of 2,3-substituted benzo[*b*]thiophenes and their hetero-fused analogs via base-promoted tandem condensation of *o*-iodoarylacetonitriles, and other *o*-iodo-(het)aryl active methylene compounds with het(aryl)dithioesters and subsequent intramolecular C-S bond formation of the in situ generated thioenolates, in DMSO at room

temperature (Scheme 21, eq.2). The results of these studies are described in the following section.



Scheme 21

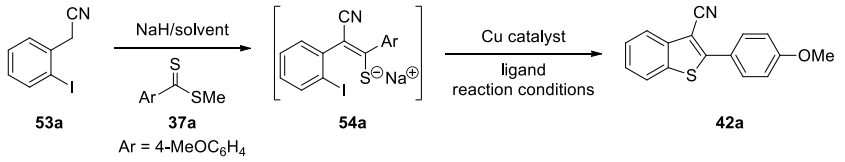
3.3 Results and Discussion

3.3.1 Synthesis of Substituted Benzo[*b*]thiophenes and their Hetero-Fused Analogs

In our previous studies for the synthesis of 3-cyano-2-substituted benzo[*b*]thiophenes **39**[7a] from in situ generated enethiolate intermediate **38** under copper-catalyzed conditions, we had reacted *o*-bromoarylacetonitriles **36** with dithioesters **37** in the presence of NaH in DMF (Scheme 16). However, in the present study, on the basis of our previous experience with base-mediated synthesis of benzothiazoles,[19] we selected *o*-iodophenylacetonitrile **53a** and (4-methoxyphenyl)dithioester as **37a** as model substrates for the optimization of reaction conditions leading to the synthesis of benzo[*b*]thiophene **42a**, for comparative study under both copper-catalyzed and base-mediated reaction conditions (Table 1). Thus, when **53a** was reacted with **37a** in the presence of NaH in DMF, followed by CuI (10 mol%) catalyzed cyclization of resulting thioenolate **54a**, in the presence of ligands like L-proline or 1,10-phenanthroline, at room temperature, the corresponding benzothiophene **42a** was obtained in low yield (Table 1, entries 1-2). However, increasing the temperature (90 ^{0}C), furnished the benzothiophene **42a** with a higher yield (entry 3). A good yield of **42a** was also obtained with 1,10-phenanthroline as a ligand at a higher temperature under Cu-catalysis (entry 4). However, the use of DMSO as the solvent instead of DMF, in the presence or absence of ligand, resulted in a dramatic

increase in the yield of **42a** even at room temperature under Cu catalysis (Table 1, entries 5-6). With these results in hand, we next performed the reaction under identical conditions at room temperature, in the absence of CuI catalyst in DMSO, and to our delight, the reaction was complete within 3 h, yielding benzothiophene **42a** in 92% yield. (Table 1, entry 7). However, no trace of **42a** was obtained when the reaction was conducted in solvents such as DMF or toluene under identical conditions (Table 1, entries 8 and 9).

Table 1. Optimization of reaction conditions for the synthesis of benzothiophene **42a**[a]



53a **37a** Ar = 4-MeOC$_6$H$_4$ **54a** **42a**

entry	catalyst (10 mol%)	solvent	ligand (20 mol%)	temp (°C)	time (h)	% yield, **42a**[b]
1	CuI	DMF	L-proline	rt	12	41
2	CuI	DMF	1, 10-phen	rt	12	45
3	CuI	DMF	L-proline	90°C	12	72
4	CuI	DMF	1, 10-phen	90°C	12	80
5	CuI	DMSO	L-proline	rt	12	89
6	CuI	DMSO	-	rt	6	90
7	**-**	**DMSO**	**-**	**rt**	**3**	**92**
8	-	DMF	-	rt	12	-
9	-	Toluene	-	rt	12	-

[a]Reaction conditions: **53a** (1 mmol), **37a** (1 mmol), and NaH (2 equiv) in 8 mL solvent under N_2, stirred at rt for 30 min and then CuI (10 mol%), ligand (20 mol%). [b]Yield of pure isolated product

With the optimized reaction conditions in hand, for one-pot domino synthesis of substituted benzo[*b*]thiophene **42**, we next examined the scope and generality of this protocol and the results are displayed in Schemes 22-25. Various 2-halo substituted activated methylene compounds **53a-h**, **55a-c**, **56-59,** and **60a-b** selected for this study for the synthesis of benzo[*b*]thiophene are shown in Chart 1. The broad range of het(aryl)dithioesters **37a-q** and other thiocarbonyl precursors **61-63**, selected for the present study to examine the generality of this reaction are displayed in Chart 2.

For comparison purposes, we further examined the reactivity and efficacy of other *o*-halophenylacetonitriles **55a** and **56-57**, bearing bromine, chlorine, and fluorine respectively, towards dithioester **37a** under base-promoted transition metal-free conditions

for the synthesis of benzothiophene **42a**, and the results are shown in Table 2. Thus, no trace of **42a** could be isolated from the reaction mixture, when *o*-bromo or *o*-chlorophenylacetonitriles **55a**, **56** were reacted with **37a** at room temperature in the presence of NaH in DMSO as solvent under optimal conditions (Table 2, entries 2 and 5)

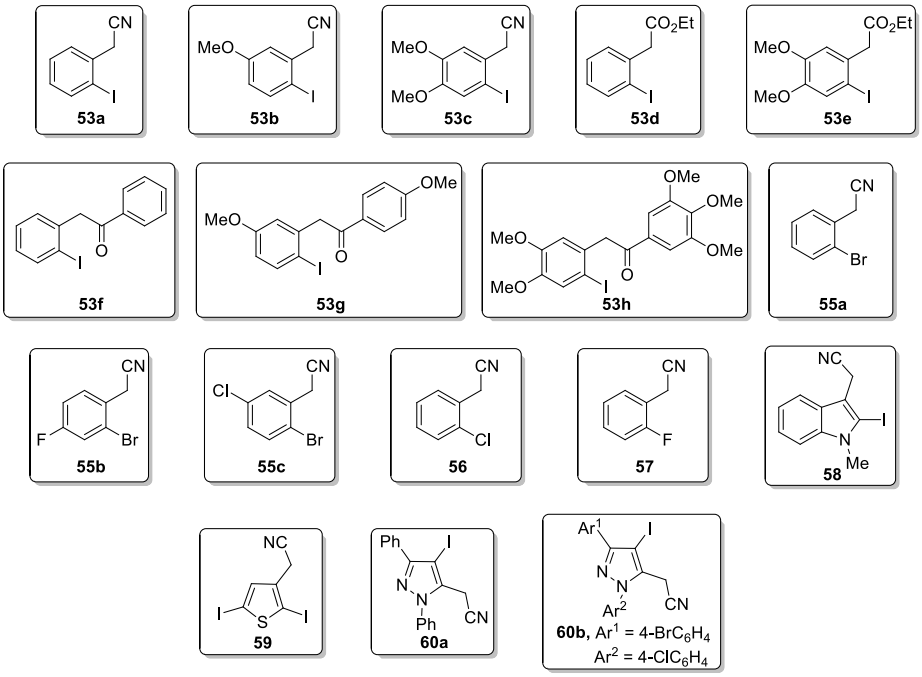


Chart 1. Various 2-halo substituted activated methylene compounds are employed for the synthesis of benzo[*b*]thiophene **42**.

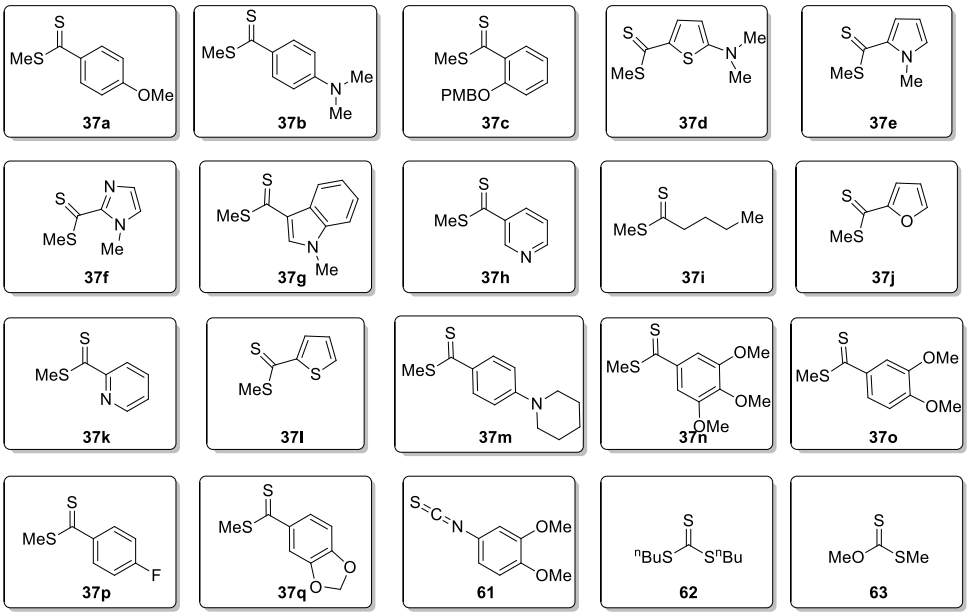
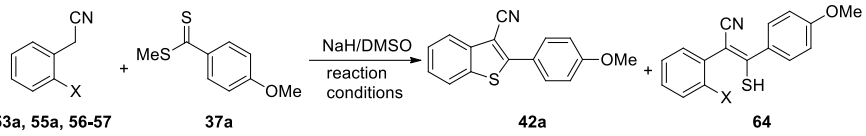


Chart 2. Various het(aryl)dithioesters employed for the synthesis of benzo[*b*]thiophene **42**.

even after a prolonged time, the only product isolated in good yields was found to be thioenol adducts **64b** or **64c** (Table 2, entries 2 and 5). At higher temperatures, however, benzothiophene **42a** was obtained in moderate yields along with reduced yields of **64b** and

Table 2. Base-mediated cyclo-condensation of various *o*-halophenylacetonitrile **53a**, **55a**, **56**-**57** with **37a**[a]



53a, 55a, 56-57 **37a** **42a** **64**

entry	**53a, 55a, 56-57**	X	temp (°C)	time (h)	% yield **42a**[b]	**64**	% yield **64**[c]
1	**53a**	I	**rt**	**3**	**92**	**64a**	0
2	**55a**	Br	rt	24	-	**64b**	93
3	**55a**	Br	60	18	40	**64b**	43
4	**55a**	Br	90	12	45	**64b**	42
5	**56**	Cl	rt	24	-	**64c**	85
6	**56**	Cl	90	12	43	**64c**	50
7	**57**	F	rt	24	5	**64d**	83
8	**57**	F	90	12	49	**64d**	42

[a]Reaction conditions: **53a, 55a, 56-57** (1 mmol), **37a** (1 mmol), NaH (2 equiv) in 8 mL of DMSO under N_2.
[b,c]Yields of pure isolated products

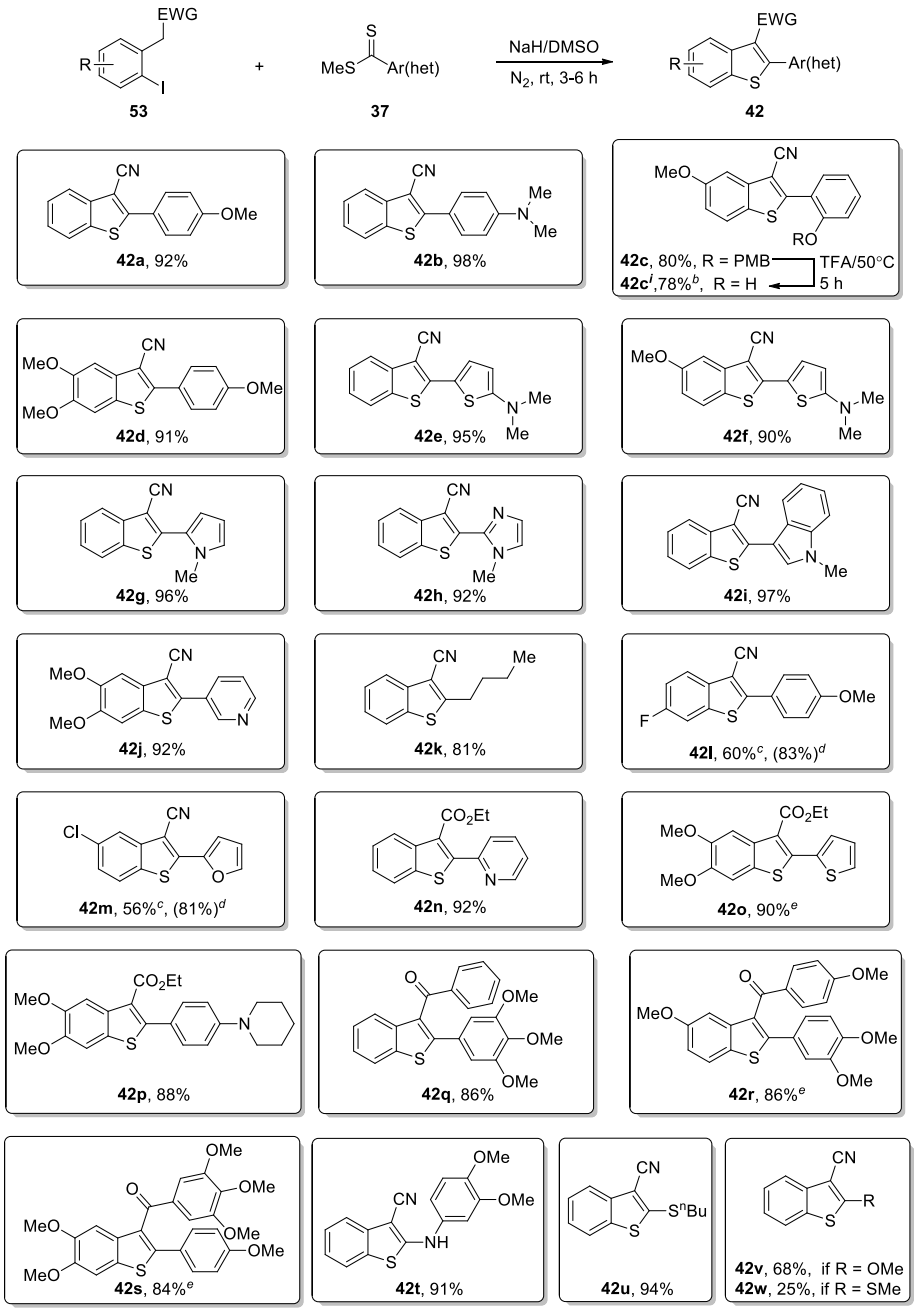
64c (Table 2, entries 3-4 and 6). Similar results were also obtained with *o*-fluorophenyl acetonitrile **57**, when reacted with dithioester **37a** under optimal conditions, yielding benzothiophene **42a** in 49% yield at a higher temperature, along with thioenol adduct **64d** (Table 2, entries 7-8). Thus, similar to our previous synthesis of 2-substituted benzothiazoles from *o*-iodophenyl isothiocyanate,[19] apparently, the *o*-iodophenylacetonitrile **53a** is found to be most efficient for base-promoted synthesis of benzothiophene **37a** under transition metal-free condition (Table 2, entry 1). We, therefore, employed various *o*-iodo(het)arylacetonitriles and other *o*-iodo(het)aryl-substituted active methylene compounds and reacted them with a broad range of (het)aryldithioesters in presence of NaH (2 equiv.) in DMSO at room temperature, as optimal reaction conditions for the synthesis of various substituted benzothiophenes **42** and their hetero-fused analogs in our subsequent studies (Scheme 22 and 23), with two exceptions (Scheme 22, **42l**-**m**).

With optimized reaction conditions in hand, we next explored the scope and generality of this new base-mediated, transition metal-free protocol for the synthesis of

other substituted benzo[*b*]thiophenes by reacting several *o*-iodo(het)arylacetonitriles **53** and various dithioesters **37** under these conditions and the results are displayed in the Scheme 22. Thus *o*-iodophenylacetonitriles **53a** and **53b-c** bearing elecelectron-donatinghoxy groups, reacted efficiently with aryldithioesters **37a** and **37b-c** with 4-(dimethylamino) and 2-(4-methoxybenzyloxy) substituents respectively, under optimized reaction conditions, yielding the corresponding benzothiophenes **42b-d** in excellent yields (Scheme 22). The 5-Methoxy-2-(2-((4-methoxybenzyl)oxy)phenyl)benzo[*b*]thiophene-3-carbonitrile **42c** was subsequently transformed into 2-(2-Hydroxyphenyl)-5-methoxybenzo[*b*]thiophene-3-carbonitrile **42c*i*** in high yield on treatment with TFA. Further diversity at 2-position of benzothiophenes **42** was introduced by reacting various (het)aryldithioesters with (5-dimethylamino)-2-thienyl- (**37d**), 2-(*N*-methyl)pyrrolyl- (**37e**), 2-(*N*-methylimidazolyl)- (**37f**), 3-(*N*-methylindolyl)- (**37g**), and 3-(pyridyl)- (**37h**) substituents, with *o*-iodophenylacetonitriles **53a-c** under identical conditions, furnishing the corresponding 2-(het)aryl-3-cyanobenzothiophenes **42e-j** in excellent yields (Scheme 22). Similarly, the corresponding 2-(*n*-butyl)-3-cyanobenzothiophene **42k**, with an alkyl-side chain, was also obtained in high yield, employing an alkyldithioester **37i**. However, our attempted syntheses of *o*-iodoarylacetonitriles bearing electron-withdrawing substituents were not successful.[26] We, therefore, reacted the corresponding 2-bromophenylacetonitriles bearing 4-fluoro- (**55b**) and 5-chloro- (**55c**) substituents with dithioesters **37a** and **37j** respectively, under standard reaction conditions, affording the 6-fluoro- and 5-chlorobenzothiophenes **42l-m** only in moderate yields, however excellent yields of **42l-m** were obtained, when the reactions were conducted at higher temperature (Scheme 22).

We next extended our studies to other 2-iodo substituted active methylene compounds such as 2-iodophenyacetates **53d-e,** which also reacted efficiently with various dithioesters **37k-m** under optimized reaction conditions, furnishing the corresponding 2-(het)arylbenzothiophene-3-carboxylates **42n-p** in high yields (Scheme 22). Similarly, the corresponding 3-aroyl-2-substituted benzothiophenes **42q-s** could also be synthesized in high yields, when *o*-iododeoxybenzoins **53f-h** were reacted with various substituted dithioesters **37n-o** and **37a** respectively, under identical conditions (Scheme 22). The benzothiophene **42s** is a methoxy analog of bioactive tubulin inhibitor.[27] The other thiocarbonyl components like aryl isothiocyanate **61**, di(*n*-butyl)trithiocarbonate **62,** and

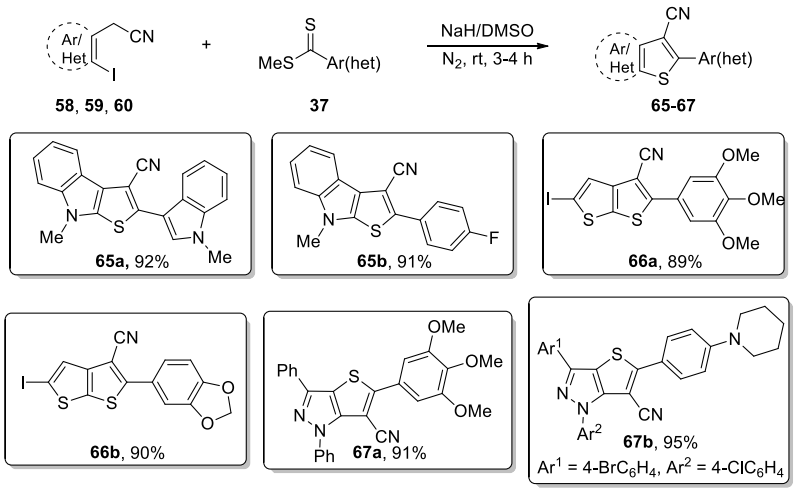
methyl xanthate (*O*, *S*-dimethyl carbonodithioate) **63** also participated smoothly, reacting with *o*-iodophenylacetonitrile **53a**, under similar conditions, yielding the 3-cyanobenzothiophenes **42t-w** with 2-(arylamino), 2-alkylthio and 2-alkoxy side chains respectively in good to excellent yields (Scheme 22).



[a]Reaction conditions: **53a-h**, **55b-c** (1 mmol), **37a-o**, **61-63** (1 mmol), NaH (2 equiv) in 8 mL DMSO under N_2, stirred at rt for 3-4 h, Isolated yields. [b]**42c** (0.5 mmol) in 4 mL TFA, stirred at 50 °C (oil bath) for 5 h. [c]Stirred at rt for 12 h. [d]Stirred at 90 °C (oil bath) for 6 h. [e]Stirred at rt for 5-6 h.

Scheme 22. Substrate scope for the synthesis of hetero-fused benzo[*b*]thiophene **42**[a]

With the successful implementation of the present base-mediated transition metal-free methodology for the synthesis of various substituted benzothiophenes (Scheme 22), we next extended this novel protocol for the synthesis of hetero-fused thiophenes, by react ing few 2-iodo-(het)arylacetonitriles with various dithioesters under optimized conditions. Thus the reaction of 2-iodo-3-indolylacetonitrile **58** with dithioesters **37g** and **37p** afforded the 2,3-substituted indolo[2,3-*b*]thiophenes **65a-b** in excellent yields (Scheme 23). Similarly, the corresponding 2,5-bis(iodo)thiophene-3-acetonitriles **59** also reacted with dithioesters **37n** and **37q** in highly regioselective manner, yielding the 5-iodo-substituted thieno[2,3-*b*]thiophene-3-carbonitriles **66a-b** in 89-90% yields (Scheme 23). The corresponding thieno-fused pyrazoles **67a-b** could also be accessed smoothly in high yield by annulation of 1,3-diaryl-4-iodopyrazole-5-acetonitrile precursors **60a-b** with dithioesters **37n** and **37m** respectively under similar conditions (Scheme 23).



[a]Reaction conditions: **58**, **59**, **60** (1 mmol), **37** (1 mmol), and NaH (2 equiv) in 8 mL DMSO under N_2 stirred at rt for 3-6 h. [b]Yields of pure isolated product.

Scheme 23. Substrate scope for the synthesis of hetero-fused benzothiophene **65-67**[a]

3.3.2 UV-Vis Absorption and Emission Studies

During the course of our studies, we observed that few of the newly synthesized 2-(het)aryl-3-cyano benzothiophenes with extended conjugation are found to display pronounced yellow-green, yellow to orange fluorescence, which was visible even on TLC during reaction monitoring. We, therefore, studied the absorption and emission spectra (photophysical properties) of these benzothiophenes, which are depicted in Table 3 and figure 2.

Table 3. UV−vis absorption and emission properties of compounds **42a-b**, **42d-f**, **42h-j**, **42l**, **42o-p**, and **66a-b**, **67a-b**

compound	absorption $\lambda_{max,abs}$ (nm) (ε L mol^{-1} cm^{-1})[a]	emission $\lambda_{max,em}$ (nm)[b]	Stokes shift Δ (cm^{-1})
42a	322 (22450)	404	6303
42b	386 (24050)	471	4675
42d	344 (26650)	451	6897
42e	443 (35700)	502	2653
42f	445 (18250)	505	2670
42h	324 (18450)	410	6474
42j	339 (25700)	451	7326
42l	323 (18200)	404	6207
42o	347 (17800)	465	7313
42p	365 (26000)	486	6821
66a	331 (15400)	424	6627
66b	335 (15900)	418	5927
67a	331 (27100)	453	8136
67b	395 (20100)	498	5236
	335 (14800)		

[a]Recorded in DMSO, T = 293 K, c (**42**, **66**, **67**) = 20 × 10^{-6} M. [b]Recorded in DMSO, T = 293 K, c (**42**, **66**, **67**) = 2 × 10^{-6} M.

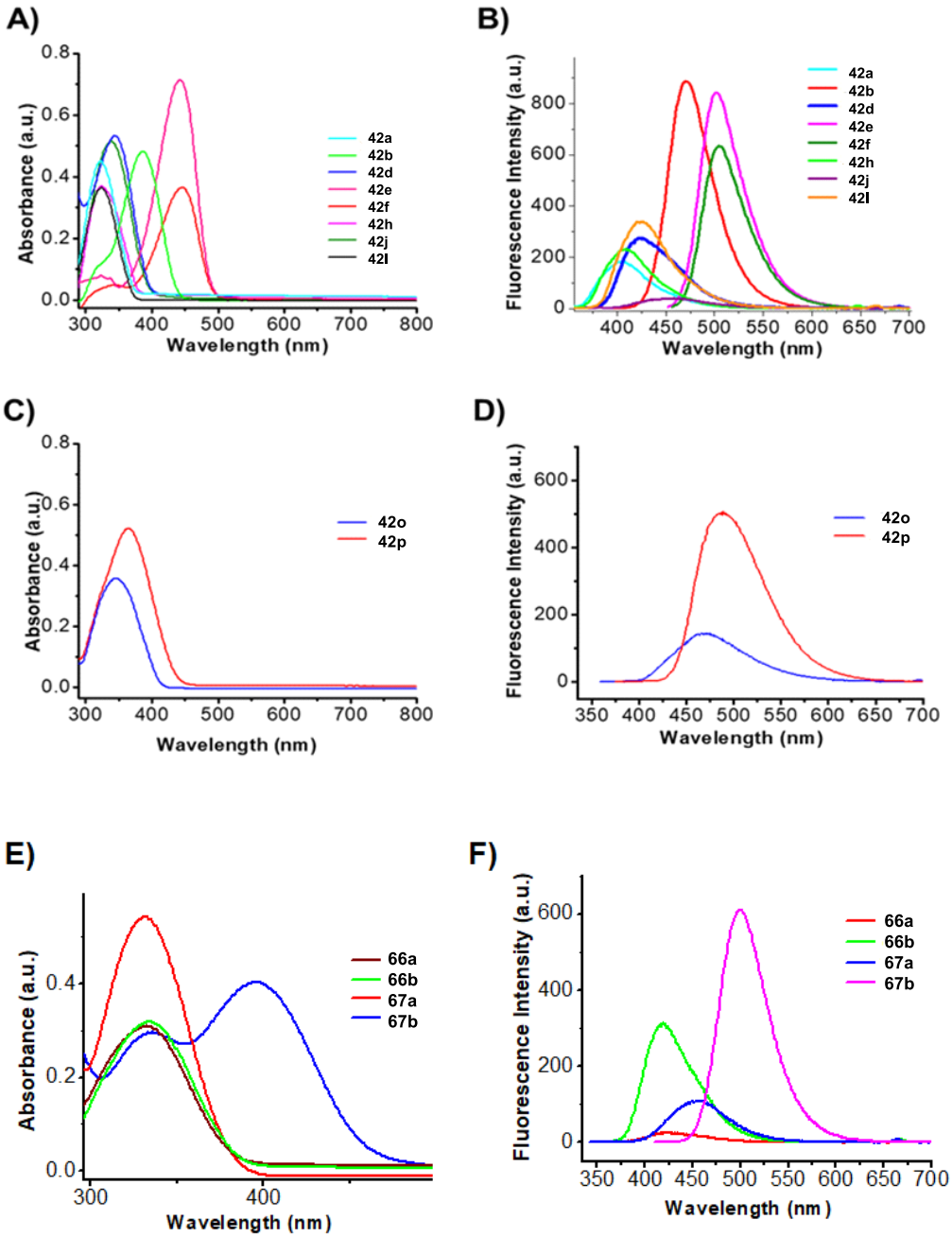
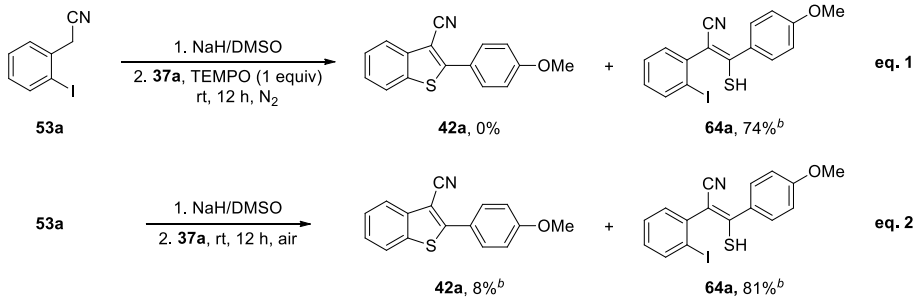


Figure 2. UV-vis absorption and fluorescence intensity spectra of compounds **42a-b**, **42d-f**, **42h**, **42j**, **42l**, **42o-p**, **66a-b** and **67a-b**: **(A)** UV-vis absorption spectra of **42a-b**, **42d-f**, **42h**, **42j** and **42l**; **(B)** fluorescence intensity spectra of **42a-b**, **42d-f**, **42h**, **42j** and **42l**; **(C)** UV-vis absorption spectra of **42o-p**; **(D)** fluorescence intensity spectra of **42o-p**; **(E)** UV-vis absorption spectra of **66a-b**, **67a-b**; **(F)** fluorescence intensity spectra of **66a-b**, **67a-b**. Recorded in DMSO, T = 293 K. Excitation at longest absorption wavelength of all compounds.

The electronic absorption spectra of 3-cyano-4-(het)arylbenzothiophenes **42a-b**, **42d-f**, **42h**, **42j**, **42l**, and the corresponding 3-(het)arylbenzothiophene-3-carboxylates **42o-p** display longest wavelength absorption band between 322-445 nm with molar extinction coefficient ranging between 17800-35700 L $mol^{-1}cm^{-1}$ (Table 3, Figures **A**, **C**). All these benzothiophenes exhibit pale yellow to yellow-green fluorescence in solution with emission maxima varying between 404-505 nm along with pronounced Stokes shift ranging from 2653-7326 cm^{-1} (Figures **B**, **D**). A study of substituent effect in a consanguineous series of 2-(het)aryl-3-cyano/carboethoxy benzothiophenes **42a-b**, **42d-f**, **42h**, **42j**, **42l**, and **42o-p** reveals that 3-cyanobenzothiophenes **42b**, **42e-f** bearing an electron-donating [4-(*N*,*N*-dimethylamino)phenyl] (**42b**), [4-(*N*-piperidine)pheny] (**42p**) or 4[4-(dimethylamino)thiophene-2-yl] groups (**42e-f**) groups at 2-position exhibit maximum wavelength absorption because of push-pull effect. A similar trend is observed for the emission band in this series. The corresponding 3-(4-methoxyphenyl) 3-cyanobenzothiophenes **42a**, **42d**, and **42l** on the other hand, absorb at a lower wavelength at 322, 344, and 323 nm respectively with a similar trend in their emission spectra. The corresponding 2-(het)aryl-3-cyanobenzothiophene **42h**, **42j** and **42o** display absorbance wavelength at 324, 339 and 347 nm respectively with emission ranging from 410-465 nm, with largest Stokes shift of 7326 and 7313 L $mol^{-1}cm^{-1}$ for the corresponding 3-(3-pyridyl)-(**42j**) and 3-(thiophen-2-yl)benzothiophene-4-carboxylate (**42o**).

The effect of substituent on the aromatic ring of benzothiophene is not much apparent. The presence of an electron-donating methoxy group at 4- (**42f**) or two methoxy groups at 4-, 5- positions (**42d**, **42j**, **42o**, **42p**) of the benzothiophene ring does not appear to have any significant effect on absorption and emission wavelength of these compounds, with a bathochromic shift of 22 nm (**42a** vs **42d**). Similarly, an electron-withdrawing 6-fluoro substituent also does not affect the wavelength of absorption although with reduced absorbance (**42a** vs **42l**). Among hetero-fused thiophenes, the thieno[2,3-*b*]thiophenes **66a-b** do not display any significant fluorescence, on the other hand, the corresponding thienopyrazole **67b**, exhibits yellow-orange fluorescence, with higher wavelength absorbance maxima at 395 nm along with emission wavelength of 498 nm (Table 3, Figure **E**, **F**). In view of the limited examples of fluorescent benzothiophenes available in the present work, a detailed study of the photophysical properties of these compounds will be published later, combining the previous examples in our earlier papers.[7a-b,18a]

The mechanism of benzothiophene formation from thioenolate anions **54** derived from the base-mediated reaction of *o*-iodoaryl acetonitriles **53a** and aryldithioesters such as **37a**, appear to be similar to that of benzothiazole **52** synthesis from *o*-iodophenylisothiocyanates **49** and active methylene compounds such as **50** in the presence of NaH in DMSO at rt (Scheme 21, eq.1), via a radical pathway through $S_{RN}1$ mechanism.[19] However we carry out a few experiments to substantiate the viability of this mechanism. As shown previously in Table 2, the other *o*-haloarylacetonitriles **55a**, **56**-**57** (X = Br, Cl, F) were found to be much less reactive in comparison to *o*-iodophenylacetonitrile **53a**, yielding either no trace of benzothiophene **42a** at rt (Table 2, entries 2, 5, 7) or in moderate yields at a higher temperature after prolonged reaction time under identical conditions (entries 3, 4, 6, 8). These observations rule out the S_NAr mechanism, as the reaction does not follow the expected order of reactivity (F>Cl>Br>I) for nucleophilic aromatic substitution.[13] Also, as we had observed in our benzothiazole synthesis, the cyclization of thioenolate salt intermediate **54** was nearly completely inhibited, when the reaction was conducted in presence of TEMPO, a common trapping agent for free radicals (Scheme 24, eq. 1). Similarly, when **53a** and **37a** were reacted in the absence of nitrogen atmosphere in the air, benzothiophene **42a** was obtained in a decreased yield of only 8% (Scheme 24, eq. 2), These experiments suggest the involvement of radical intermediates and/or a SET process in this transformation.

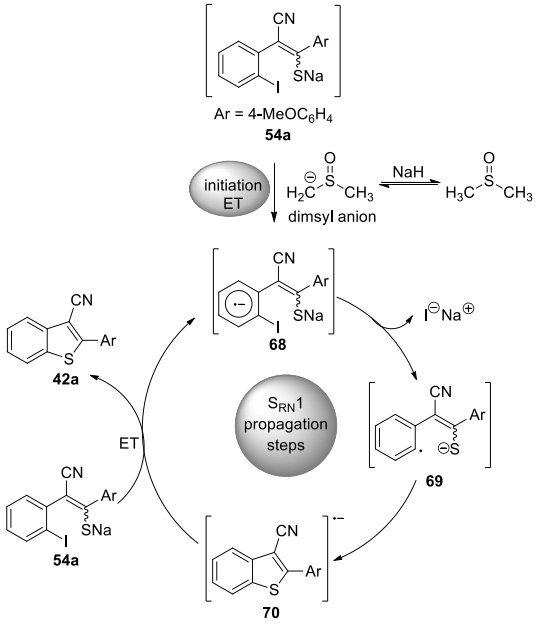


[a]Reaction conditions: **53a** (1 mmol), **37a** (1 mmol), NaH (2 equiv), TEMPO (1 mmol) in 8 mL DMSO. [b]Yields of pure isolated product.

Scheme 24. The reaction of 2-iodophenylacetonitrile **53a** with **37a** in presence of TEMPO[a]

Based on our previous studies,[20,21] and the present experimental observations, we suggest a possible mechanistic pathway for the formation of **42a** from **53a** and **37a**, involving the $S_{RN}1$ mechanism, as shown in Scheme 25. Since no trace of benzothiophene **42a** was obtained when the reaction was conducted in solvents like DMF or toluene (Table

1, entries 8 and 9), we believe that the radical process is initiated by single electron transfer (SET) from dimsyl anion[28] to thioenolate salt intermediate **54a** to afford the radical anion species **68**, which undergoes fragmentation to deliver the corresponding aryl radical intermediate **69** along with iodide ion. Intramolecular trapping of the aryl radical by thioenolate anion in the intermediate **69**, furnishes the benzothiophene radical anion intermediate **70**, which acts as an electron donor to the starting thioenolate **54a**, furnishing the final product **42a** and radical anion **68**, thus completing the radical chain cycle (Scheme 25).



Scheme 25. Proposed mechanism for base-mediated synthesis of benzothiophene **42a** from **53a** and **37a**

3.4 Conclusion

In summary, we have developed a facile, transition metal-free protocol for the synthesis of 2,3-substituted benzothiophenes and their hetero-analogs. The reaction involves base-mediated tandem addition-cyclization of *o*-iodoarylacetonitriles and other *o*-iodoaryl active methylene compounds with (het)aryl dithioesters through intramolecular C-S bond formation. This new protocol has broad substrate scope and is also applicable for the synthesis of hetero-fused thiophenes. A probable mechanistic pathway involving the formation of radical intermediates ($S_{RN}1$) has been proposed for this process. To the best of our knowledge, such a high yield synthesis of benzothiophenes, via intramolecular C-S

bond formation at rt under transition metal-free conditions, has not been reported in the literature.[29]

3.5 Experimental section

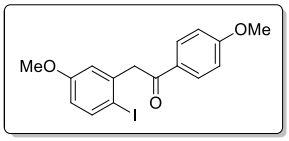
3.5.1 General Information. All reagents were obtained from commercial suppliers and used without further purification. Yields for all compounds were determined by column chromatography which was generally performed on silica gel (60-120 mesh) using petroleum ether/EtOAc as eluent, and reactions were monitored by thin-layer chromatography (TLC) on a glass plate coated with silica gel using UV light. Nuclear magnetic resonance (NMR) spectra were recorded on (400 and 600 MHz) FT-NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts were reported in δ (ppm) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6, in ^{1}H-NMR, δ 77.16 for $CDCl_3$, and δ 39.52 for DMSO-d_6 in ^{13}C-NMR). Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), and br (broad). Infrared spectra of neat samples were recorded in attenuated total reflectance (ATR) mode using an FT-IR instrument, and HRMS spectra were recorded using a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. Electronic absorption spectra were recorded on a UV-vis-NIR spectrometer. Emission spectra were recorded on a luminescence spectrometer.

The ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in the supporting information of *Org. Lett.* **2021**, *23*, 1698.

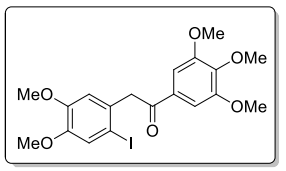
All the 2-(2-halophenyl)acetonitrile **53a**, **55a**, **56**, and **57** reagents were purchased from commercial suppliers, **53b-f**[30-34] and **59**[35] and also **55b**,[36] **55c**[37] were prepared according to their reported procedures respectively. The other new unreported halo substituted (het)aryl active methylene compounds such as **53g-h**, **58,** and **60a-b** have been described in their preparation in detail in supporting information in Org. Lett. 2021, 23, 1698. The spectral and analytical data of new halo substituted active methylene compounds such as **53g-h**, **58,** and **60a-b** is given below. The methyl (het)/aryl dithioester compounds **37a-c**,[38] **37d-e**,[38,39] **37f**,[40] **37g**,[39] **37h**,[41] **37i**,[38] **37j**[40] **37k**[41] and **37l-q**[38] were prepared

according to the reported procedures. The compounds **61**,[42] **62**[43] and **63**[44] were also synthesized according to the reported procedures.

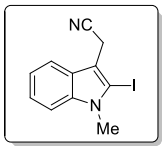
2-(2-Iodo-5-methoxyphenyl)-1-(4-methoxyphenyl)ethanone (53g). Yellow solid; (6.11 g, 94% yield); mp 90-92 °C; R_f 0.34 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3050, 2955, 1672, 1454, 746, 569; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.74 (s, 1H), 6.93 (d, J = 8.0 Hz, 2H), 3.88 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 163.7, 158.2, 139.4, 136.8, 132.4, 130.9, 123.7, 113.9, 112.2, 84.1, 56.3, 55.5, 45.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}IO_3$ 383.0144; found 383.0128.



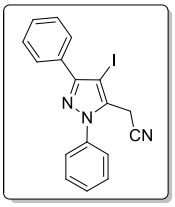
2-(2-Iodo-4,5-dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethanone (53h). White solid; (7.71 g, 96% yield); mp 147-150 °C; R_f 0.49 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3056, 2949, 1684, 1451, 751, 564; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.26 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 4.38 (s, 2H), 4.05 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 157.5, 154.0, 149.3, 148.4, 142.1, 131.7, 125.8, 125.7, 121.6, 113.7, 107.2, 89.5, 61.6, 60.9, 56.2, 56.1, 55.9, 54.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}IO_6$ 473.0461; found 473.0448.



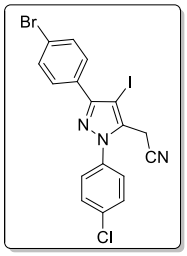
2-(2-Iodo-1-methyl-1*H*-indol-3-yl)acetonitrile (58). Brown solid; (4.48 g, 89% yield); mp 93-95 °C; R_f 0.41 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3022, 2930, 2235, 746, 572; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.33-7.23 (m, 2H), 7.16 (t, J = 7.4 Hz, 1H), 3.79 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 127.4, 126.5, 122.4, 119.8, 118.3, 118.2, 109.7, 92.5, 32.8, 14.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{10}IN_2$ 296.9889; found 296.9875.



2-(4-Iodo-1,3-diphenyl-1*H*-pyrazol-5-yl)acetonitrile (60a). Light yellow solid; (2.78 g, 85% yield); mp 98-100 °C; R_f 0.52 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3021, 2922, 2242, 746, 572; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 6.8 Hz, 2H), 7.59-7.52 (m, 5H), 7.49-7.42 (m, 3H), 3.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 138.6, 134.5, 131.9, 129.8, 129.5, 128.8, 128.4, 128.2, 125.4, 114.5, 63.9, 17.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}IN_3$ 386.0154; found 386.0145.

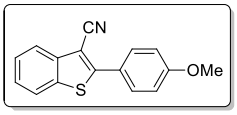


2-(3-(4-Bromophenyl)-1-(4-chlorophenyl)-4-iodo-1*H*-pyrazol-5-yl)acetonitrile (60b).



Off-white solid; (3.42 g, 81% yield); mp 140-142 °C; R_f 0.29 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3010, 2878, 2238, 828, 650, 548; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.47(d, J = 8.8 Hz, 2H) 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 136.9, 135.7, 134.8, 131.7, 130.7, 130.1, 129.7, 126.5, 123.3, 114.3, 64.3, 17.0; HRMS (ESI) *m/z*: $[M + H]^+$, $[M + H + 2]^+$, $[M+H+4]^+$ calcd for $C_{17}H_{11}BrClIN_3$ 497.8870, 499.8870, 501.8870; found 497.8851, 499.8826, 501.8798.

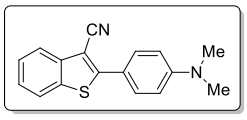
3.5.2 Procedure for Copper-Catalyzed Synthesis of 2-(4-Methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (42a) (table-1, entry 1). To a stirred suspension of NaH (60% suspension in mineral oil) (67 mg, 2.0 mmol) in dry DMF (2 mL), a solution of 2-(2-iodophenyl)acetonitrile **53a** (243 mg, 1.0 mmol) in DMF (2 mL) was added dropwise, at room temperature under N_2 atmosphere, and the stirring was further continued for 20 min, followed by addition of a solution of methyl 4-methoxybenzodithioate **37a** (198 mg, 1.0 mmol) in DMF (2 mL). The resulting mixture was further stirred for 30 min at rt, followed by the addition of CuI (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol), and after further stirring for 12 h (monitored by TLC). It was then quenched with saturated aqueous NH_4Cl solution (25 mL), extracted with EtOAc (3 X 25 mL). The combined organic layer was washed with water (3 X 25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, and evaporated under vacuum to give benzothiophene **42a**, which was further purified by column chromatography using hexane/ethyl acetate as eluent, white solid; yield 92% (244 mg, 0.92 mmol); mp 160-162 °C; R_f 0.60 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3095, 2220, 1609, 1528,1457, 1320, 1208, 1129, 1064, 937, 857, 782, 702, 627; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 6.6, 2.2 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.50 (td, J = 7.6, 1.2 Hz, 1H), 7.42 (td, J = 7.6, 1.2 Hz, 1H), 7.03 (dd, J = 6.8, 2.0 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 155.1, 139.3, 136.9, 129.7, 125.9, 125.8, 124.0, 122.3, 122.2, 115.5, 114.7, 100.7, 55.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}NOS$ 266.0640; found 266.0645.



3.5.3 General Procedure for Transition Metal-Free Synthesis of 2,3-Disubstituted benzo[*b*]thiophene 42, 65, 66, 67 and Thioenol 64. To a stirred suspension of NaH (60%

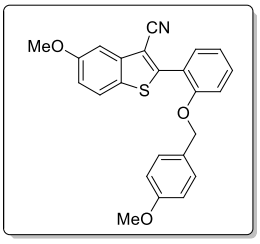
suspension in mineral oil) (67mg, 2.0 mmol) in dry DMSO (2 mL), a solution of 2-iodo (het)aryl acetonitrile **53a-h**, **55a-c**, **56**, **57** and **58**, **59**, **60a-b** (1.0 mmol) in DMSO (2-3 mL) was added dropwise over 5 min, at room temperature under N_2 atmosphere, and the stirring was further continued for 20-25 min, followed by addition of a solution of appropriate (het)aryl dithioate compound (**37a-q**) or **61-63** (1.0 mmol) in DMSO (2-3 mL). After stirring for 3-6 h (monitored by TLC), the reaction mixture was quenched with saturated aqueous NH_4Cl solution (25 mL), extracted with EtOAc (3 X 25 mL), the combined organic layer was washed with water (3 X 25 mL), and brine (25 mL), dried over anhydrous Na_2SO_4, and evaporated under vacuum to give the corresponding 2,3-disubstituted benzo[*b*]thiophene **42**, **65**, **66**, **67** and thioenol **64** products, which were further purified by column chromatography using hexane/ethyl acetate as eluent.

2-(4-(Dimethylamino)phenyl)benzo[*b*]thiophene-3-carbonitrile (42b). Obtained from



2-(2-iodophenyl)acetonitrile **53a** and methyl 4-(dimethylamino)benzodithioate **37b**, yellow solid; yield 98% (272 mg, 0.98 mmol); mp 175-177 °C; R_f 0.56 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3092, 2212, 1601, 1494, 1368, 811, 752, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.84 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.46 (td, *J* = 7.6, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 6.77 (dd, *J* = 6.8, 2.0 Hz, 2H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 151.7, 139.7, 136.4, 129.2, 125.8, 125.3, 122.1, 121.9, 118.9, 116.2, 111.9, 98.5, 40.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{15}N_2S$ 279.0956; found 279.0975.

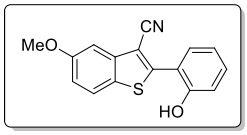
5-Methoxy-2-(2-((4-methoxybenzyl)oxy)phenyl)benzo[*b*]thiophene-3-carbonitrile



(42c). Obtained from 2-(2-iodo-5-methoxyphenyl)acetonitrile **53b** and methyl 2-((4-methoxybenzyl)oxy)benzodithioate **37c**, yellow solid; yield 80% (321 mg, 0.80 mmol); mp 81-83 °C; R_f 0.57 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3050, 2232, 1597, 1450, 1240, 817, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.65 (d, *J* = 8.8, Hz, 1H), 7.41 (td, *J* = 7.8, 1.7 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 7.34 (d, *J* = 8.8, Hz, 2H), 7.09 (d, *J* = 6.4 Hz, 2H), 7.05 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.12 (s, 2H), 3.90 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.6, 155.8, 152.4, 139.6, 131.7, 131.3, 130.9, 129.2, 128.3, 122.9, 121.3, 121.0, 116.7, 115.5, 114.0, 113.4, 104.3, 103.8, 70.7, 55.7, 55.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for

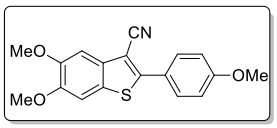
$C_{24}H_{20}NO_3S$, $[M + Na]^+$ calcd for $C_{24}H_{19}NNaO_3S$ 402.1164, 424.0983; found 402.1151, 424.0973.

2-(2-Hydroxyphenyl)-5-methoxybenzo[*b*]thiophene-3-carbonitrile (42c'). Obtained



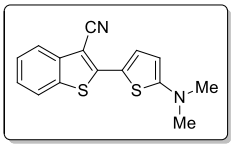
from 5-methoxy-2-(2-((4-methoxybenzyl)oxy)phenyl)benzo[*b*]thiophene-3-carbonitrile **42c**, off-white solid; yield 78% (219 mg, 0.78 mmol); mp 197-199 °C; R_f 0.80 (1:3 EtOAc/hexane); IR (neat, cm^{-1}) 3410, 3009, 2201, 1723, 1449, 1217, 848, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.55 (td, J = 7.8, 1.2 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.35 (td, J = 7.6, 1.2 Hz, 1H), 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 156.9, 151.8, 151.5, 137.7, 131.2, 129.8, 124.6, 124.1, 122.9, 118.5, 117.4, 117.3, 117.2, 106.7, 55.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}NO_2S$ 282.0589; found 282.0576.

5,6-Dimethoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (42d). Obtained



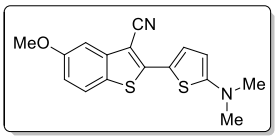
from 2-(2-iodo-4,5-dimethoxyphenyl)acetonitrile **53c** and methyl 4-methoxybenzodithioate **37a**, white solid; yield 91% (296 mg, 0.91 mmol); mp 159-161 °C; R_f 0.35 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3082, 2215, 1615, 1483, 1254, 822, 796; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 6.6, 2.2 Hz, 2H), 7.29 (s, 1H), 7.23 (s, 1H), 7.02 (dd, J = 6.8, 2.0 Hz, 2H), 4.00 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 152.9, 149.6, 149.3, 133.1, 129.7, 129.4, 124.4, 115.9, 114.7, 103.7, 103.3, 100.4, 56.3, 56.27, 55.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}NO_3S$ 326.0851; found 326.0833.

2-(5-(Dimethylamino)thiophen-2-yl)benzo[*b*]thiophene-3-carbonitrile (42e). Obtained



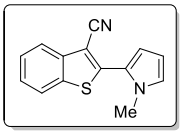
from 2-(2-iodophenyl)acetonitrile **53a** and methyl 5-(dimethylamino)thiophene-2-carbodithioate **37d**, brown solid; yield 95% (270 mg, 0.95 mmol); mp 138-140 °C; R_f 0.38 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3050, 2199, 1558, 1500, 1408, 886, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 4.4 Hz, 1H), 7.41 (td, J = 7.6, 1.2 Hz, 1H), 7.29 (td, J = 7.6, 1.2 Hz, 1H), 5.87 (d, J = 4.4 Hz, 1H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 149.6, 139.5, 135.1, 130.8, 125.9, 124.9, 121.8, 121.3, 116.6, 116.3, 102.7, 95.2, 42.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}N_2S_2$ 285.0520; found 285.0528.

2-(5-(Dimethylamino)thiophen-2-yl)-5-methoxybenzo[*b*]thiophene-3-carbonitrile



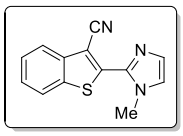
(42f). Obtained from 2-(2-iodo-5-methoxyphenyl)acetonitrile **53b** and methyl 5-(dimethylamino)thiophene-2-carbodithioate **37d**, yellow solid; yield 90 % (283 mg, 0.90 mmol); mp 124-126 °C; R_f 0.45 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3034, 2198, 1596, 1497, 1283, 827, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 6.0 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 8.8, 2.4 Hz, 1H), 5.87 (d, J = 4.4 Hz, 1H), 3.89 (s, 3H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 158.8, 150.6, 140.7, 130.5, 127.1, 122.5, 116.8, 116.5, 115.2, 103.5, 102.7, 95.1, 55.7, 42.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{15}N_2OS_2$ 315.0626; found 315.0629.

2-(1-Methyl-1*H*-pyrrol-2-yl)benzo[*b*]thiophene-3-carbonitrile (42g). Obtained from 2-



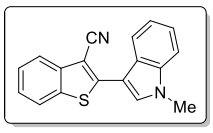
(2-iodophenyl)acetonitrile **53a** and methyl 1-methyl-1*H*-pyrrole-2-carbodithioate **37e**, gray solid; yield 96% (228 mg, 0.96 mmol); mp 92-94 °C; R_f 0.56 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3075, 2225, 1434, 733; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.52 (td, J = 7.6, 1.2 Hz, 1H), 7.43 (td, J = 7.8, 1.2 Hz, 1H), 6.87 (t, J = 2.2 Hz, 1H), 6.81 (dd, J = 3.8, 1.8 Hz, 1H), 6.29 (dd, J = 4.0, 2.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 138.4, 137.4, 127.5, 126.1, 125.8, 123.9, 122.3, 122.1, 115.3, 114.5, 109.4, 102.7, 35.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2S$ 239.0643; found 239.0621.

2-(1-Methyl-1*H*-imidazol-2-yl)benzo[*b*]thiophene-3-carbonitrile (42h). Obtained from



2-(2-iodophenyl)acetonitrile **53a** and methyl 1-methyl-1*H*-imidazole-2-carbodithioate **37f**, off-white solid; yield 92 % (220 mg, 0.92 mmol); mp 146-148 °C; R_f 0.42 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3081, 2228, 1565, 1288, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.57 (td, J = 7.6, 1.2 Hz, 1H), 7.52 (td, J = 7.6, 1.3 Hz, 1H), 7.29 (d, J = 1.2 Hz, 1H), 7.14 (d, J = 1.2 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 139.0, 138.3, 138.1, 130.7, 126.8, 126.4, 124.6, 122.9, 122.5, 114.5, 105.3, 35.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}N_3S$ 240.0595; found 240.0576.

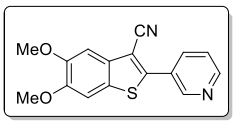
2-(1-Methyl-1*H*-indol-3-yl)benzo[*b*]thiophene-3-carbonitrile (42i). Obtained from 2-(2-



iodophenyl)acetonitrile **53a** and methyl 1-methyl-1*H*-indole-3-carbodithioate **37g**, yellow solid; yield 97% (279 mg, 0.97 mmol); mp 162-164 °C; R_f 0.48 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3045, 2209,

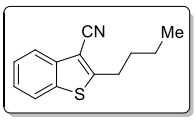
1520, 1232, 927, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 8.4 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 6.8 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 138.6, 137.2, 136.4, 130.0, 125.9, 125.8, 124.9, 123.2, 122.1, 121.6, 121.5, 120.3, 116.7, 110.1, 107.6, 97.9, 33.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{13}N_2S$ 289.0799; found 289.0771.

5,6-Dimethoxy-2-(pyridin-3-yl)benzo[*b*]thiophene-3-carbonitrile (42j). Obtained from



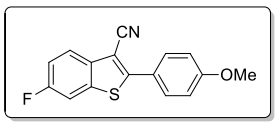
2-(2-iodo-4,5-dimethoxyphenyl)acetonitrile **53c** and methyl pyridine-3-carbodithioate **37h**, pale yellow solid; yield 92% (272 mg, 0.92 mmol); mp 222-224 °C; R_f 0.32 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2214, 1512, 1278, 1028, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.23 (dd, J = 8.4, 2.0 Hz, 1H), 7.47 (dd, J = 8.0, 4.8 Hz, 1H), 7.34 (s, 1H), 7.28 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 150.1, 149.9, 148.6, 148.0, 134.9, 132.9, 130.7, 128.2, 123.9, 115.0, 103.6, 103.4, 102.9, 56.4, 56.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{13}N_2O_2S$ 297.0698; found 297.0698.

2-Butylbenzo[*b*]thiophene-3-carbonitrile (42k). Obtained from 2-(2-



iodophenyl)acetonitrile **53a** and methyl pentanedithioate **37i**, red oily liquid; yield 81% (175 mg, 0.81 mmol); R_f 0.65 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2957, 2930, 2220, 1527, 1436, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.2 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 3.13 (t, J = 7.6 Hz, 2H), 1.79 (quintet, J = 7.6 Hz, 2H), 1.46 (sextet, J = 7.4 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 137.8, 137.3, 125.8, 125.5, 122.4, 121.9, 114.3, 104.5, 33.2, 30.1, 22.2, 13.7; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{14}NS$ 216.0847; found 216.0829.

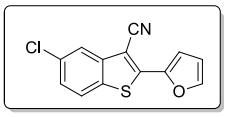
6-Fluoro-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (42l). Obtained from



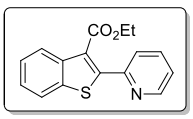
2-(2-bromo-4-fluorophenyl)acetonitrile **55b** and methyl 4-methoxybenzodithioate **37a**, white solid; (170 mg, 0.60 mmol, 60% yield, at room temperature reaction for 12 h) and (235 mg, 0.83 mmol, 83% yield, at 90 °C reaction for 6 h); mp 158-159 °C; R_f 0.49 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2924, 2218, 1471, 1244, 1179, 1034, 809; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 9.0, 4.6 Hz, 1H), 7.83 (dd, J = 6.8, 2.0 Hz, 2H), 7.52 (dd, J = 8.4, 2.4 Hz, 1H), 7.25 (td, J = 8.9, 2.0 Hz, 1H), 7.04 (dd, J =6.8, 2.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 161.5, 161.1 (C-F, d, $^1J_{C\text{-}F}$ = 245.8 Hz), 154.95, 154.91, 137.9 (C-F, d, $^3J_{C\text{-}F}$ = 10.2 Hz), 135.7, 129.6, 123.7 (C-F, d, $^3J_{C\text{-}F}$ = 16.7 Hz), 123.5, 115.1 (C-F, d, $^2J_{C\text{-}F}$ = 24.9 Hz), 114.8, 108.7 (C-F, d, $^2J_{C\text{-}F}$ = 26.1 Hz), 100.3, 55.5; $^{19}F\{^1H\}$ NMR (564.65 MHz, CDCl3) δ -114.3; HRMS (APCI) *m*/*z*: $[M]^+$ calcd for $C_{16}H_{10}FNOS$ 283.0467; found 283.0449.

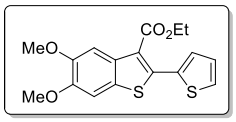
5-Chloro-2-(furan-2-yl)benzo[*b*]thiophene-3-carbonitrile (42m). Obtained from 2-(2-bromo-5-chlorophenyl)acetonitrile **55c** and methyl furan-2-carbodithioate **37j**, off-white solid; (145 mg, 0.56 mmol, 56% yield, at room temperature reaction for 12 h) and (210 mg, 0.81 mmol, 81% yield, at 90 °C reaction for 6 h); R_f 0.60 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3009, 2215, 1578, 1478, 801, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.35 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 144.9, 144.8, 139.8, 134.7, 133.0, 126.8, 123.6, 122.1, 114.5, 113.2, 112.6, 98.2; HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{13}H_6ClNOS$ 258.9859; found 258.9848.



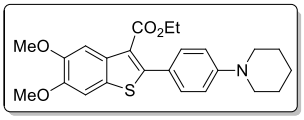
Ethyl 2-(pyridin-2-yl)benzo[*b*]thiophene-3-carboxylate (42n). Obtained from ethyl 2-(2-iodophenyl)acetate **53d** and methyl pyridine-2-carbodithioate **37k**, yellow oily liquid; yield 92% (261 mg, 0.92 mmol); R_f 0.44 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2922, 1709, 1585, 1459, 1203, 1094, 726; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 4.8, 1.2 Hz, 1H), 8.22 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.86 (d, *J* = 7.6, Hz, 1H), 7.75 (td, *J* = 7.6, 1.9 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 152.2, 149.4, 148.8, 139.2, 138.5, 136.1, 125.5, 125.3, 124.9, 124.4, 124.0, 123.2, 122.1, 61.1, 13.9; HRMS (ESI) *m*/*z*: [M + H]+ calcd for $C_{16}H_{14}NO_2S$ 284.0745; $[M + H]^+$ found 284.0795.



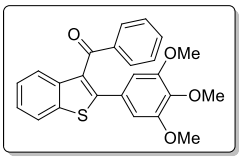
Ethyl 5,6-dimethoxy-2-(thiophen-2-yl)benzo[*b*]thiophene-3-carboxylate (42o). Obtained from ethyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate **53e** and methyl thiophene-2-carbodithioate **37l**, yellow solid; yield 90% (313 mg, 0.90 mmol); mp 78-80 °C; R_f 0.45 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3065, 1724, 1416, 1204, 825, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.43 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.34 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.19 (s, 1H), 7.08 (td, *J* = 5.2, 1.6 Hz, 1H), 4.35 (q, *J* = 7.07 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 1.29(t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 148.9, 141.3, 134.8, 132.5, 131.2, 129.0, 127.7, 127.0, 122.9, 105.9,



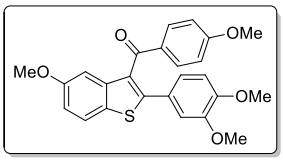
103.6, 102.8, 60.8, 56.1, 56.0, 14.0; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{17}O_4S_2$ 349.0568; found 349.0553.

Ethyl 5,6-dimethoxy-2-(4-(piperidin-1-yl)phenyl)benzo[*b*]thiophene-3-carboxylate (42p). 

Obtained from ethyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate **53e** and methyl 4-(piperidin-1-yl)benzodithioate **37m**, yellow solid; yield 88% (374 mg, 0.88 mmol); mp 92-94 °C; R_f 0.54 (1:3 EtOAc/hexane); IR (neat, cm^{-1}) 2995, 1696, 1477, 1271, 817, 721; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.38 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.21 (s, 1H), 6.93 (dd, *J* = 6.6, 2.2 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.25 (t, *J* = 5.6 Hz, 4H), 1.75 -1.69 (m, 4H), 1.64-1.59 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 152.1, 150.9, 148.6, 148.2, 132.8, 130.9, 130.5, 124.1, 121.3, 114.9, 105.8, 103.1, 60.4, 56.1, 56.0, 49.9, 25.6, 24.4, 14.0; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{28}NO_4S$ 426.1739; found 426.1755.

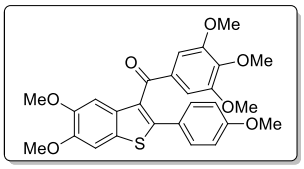
Phenyl(2-(3,4,5-trimethoxyphenyl)benzo[*b*]thiophen-3-yl)methanone (42q). 

Obtained from 2-(2-iodophenyl)-1-phenylethanone **53f** and methyl 3,4,5-trimethoxybenzodithioate **37n**, red semi solid; yield 86% (348 mg, 0.86 mmol); R_f 0.56 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3048, 1645, 1579, 1495, 1225, 826, 728; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.86 (m, 1H), 7.79-7.76 (m, 3H), 7.43 (td, *J* = 7.4, 1.6 Hz, 1H), 7.39 (t, *J* = 2.0 Hz, 1H), 7.38 (t, *J* = 2.0 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 6.63 (s, 2H), 3.76 (s, 3H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 153.2, 146.3, 139.8, 138.82, 138.79, 137.7, 133.5, 131.5, 129.8, 128.8, 128.6, 125.4, 125.3, 123.7, 122.1, 106.9, 60.9, 56.2; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{21}O_4S$ 405.1161; found 405.1153.

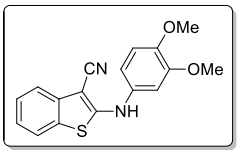
(2-(3,4-Dimethoxyphenyl)-5-methoxybenzo[*b*]thiophen-3-yl)(4-methoxyphenyl)methanone (42r). 

Obtained from 2-(2-iodo-5-methoxyphenyl)-1-(4-methoxyphenyl)ethanone **53g** and methyl 3,4-dimethoxybenzodithioate **37o**, yellow semi solid; yield 86 % (373 mg, 0.86 mmol); R_f 0.51 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3022, 1652, 1594, 1460, 1239, 910, 844, 727; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.05-6.99 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 6H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 163.8, 158.1, 149.5, 148.7, 146.5, 140.9, 132.2, 131.0, 130.7,

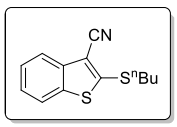
130.5, 126.3, 122.6, 121.8, 115.5, 113.7, 112.3, 111.1, 105.2, 55.9, 55.8, 55.6, 55.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{23}O_5S$ 435.1266, found 435.1254.

(5,6-Dimethoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (42s). 

Obtained from 2-(2-iodo-4,5-dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethanone **53h** and methyl 4-methoxybenzodithioate **37a**, yellow semi solid; yield 84% (415 mg, 0.84 mmol); R_f 0.28 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3018, 1648, 1587, 1461, 1244, 830, 727; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.28 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.26 (s, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 6.4, 2.4 Hz, 2H), 6.44 (d, *J* = 8.8 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 159.8, 156.9, 153.7, 148.9, 148.6, 147.1, 142.1, 133.4, 132.1, 131.1, 130.9, 130.2, 127.9, 126.7, 126.2, 114.4, 113.7, 106.5, 105.1, 103.3, 61.9, 60.8, 56.3, 56.2, 56.1, 55.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{27}O_7S$ 495.1477; found 495.1471.

2-((3,4-Dimethoxyphenyl)amino)benzo[*b*]thiophene-3-carbonitrile (42t). 

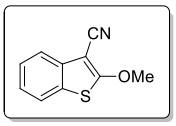
Obtained from 2-(2-iodophenyl)acetonitrile **53a** and 4-isothiocyanato-1,2-dimethoxybenzene **61**, white solid; yield 91% (282 mg, 0.91 mmol); mp 140-142 °C; R_f 0.43 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3348, 3008, 2204, 1509, 1463, 1239, 845, 742; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.15 (br s, 1H), 6.93 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.89 (d, *J* = 4.0 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 149.8, 147.4, 136.9, 133.2, 128.9, 126.1, 123.4, 121.9, 119.6, 115.4, 114.1, 111.8, 106.4, 82.0, 56.2, 56.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_2S$ 311.0854; found 311.0843.

2-(Butylthio)benzo[*b*]thiophene-3-carbonitrile (42u). 

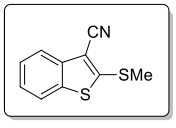
Obtained from 2-(2-iodophenyl)acetonitrile **53a** and *n*-dibutyl carbonotrithioate **62**, orange oily liquid; yield 94% (232 mg, 0.94 mmol); R_f 0.57 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2957, 2928, 2871, 2216, 1460, 1259, 751; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H), 3.15 (t, *J* = 7.4 Hz, 2H), 1.75 (quintet, *J* = 7.4 Hz, 2H), 1.49 (sextet, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 152.7, 138.4, 138.2, 126.1, 125.6, 121.9, 121.7, 113.8, 107.2, 36.7, 31.5, 21.7, 13.5; HRMS (APPI) *m*/*z*: $[M]^+$ calcd for $C_{13}H_{13}NS_2$ 247.0489; found 247.0457.

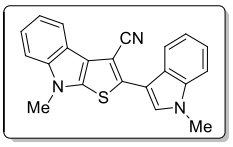
2-Methoxybenzo[*b*]thiophene-3-carbonitrile (42v). Obtained from 2-(2-iodophenyl)acetonitrile **53a** and *O*,*S*-dimethyl carbonodithioate **63**, yellow semi solid; yield 68% (129 mg, 0.68 mmol); R_f 0.38 (3:97 EtOAc/hexane); IR (neat, cm^{-1}) 3050, 2997, 2213, 1684, 1464, 1285, 747; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 4.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 140.3, 135.7, 126.4, 124.5, 122.4, 121.1, 113.4, 85.9, 62.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_8NOS$ 190.0327; found 190.0311.



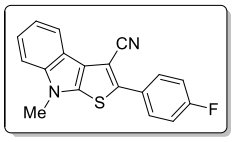
2-(Methylthio)benzo[*b*]thiophene-3-carbonitrile (42w). Obtained from 2-(2-iodophenyl)acetonitrile **53a** and *O*,*S*-dimethyl carbonodithioate **63**, white solid; yield 25% (51 mg, 0.25 mmol); mp 79-80 °C; R_f 0.42 (3:97 EtOAc/hexane); IR (neat, cm^{-1}) 3042, 2923, 2207, 1456, 1419, 747, 719; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38 (td, *J* = 7.6, 1.2 Hz, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.3, 137.7, 126.2, 125.4, 121.9, 121.5, 113.7, 105.1, 18.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_8NS_2$ 206.0098; found 206.0087.



8-Methyl-2-(1-methyl-1*H*-indol-3-yl)-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (65a). Obtained from 2-(2-iodo-1-methyl-1*H*-indol-3-yl)acetonitrile **58** and methyl 1-methyl-1*H*-indole-3-carbodithioate **37g**, yellow solid; yield 92% (314 mg, 0.92 mmol); mp 187-189 °C; R_f 0.44 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2987, 2202, 1478, 1330, 1135, 736; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.81 (s, 1H), 7.40-7.37 (m, 2H), 7.34 (td, *J* = 7.4, 1.2 Hz, 2H), 7.29-7.24 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 140.7, 140.6, 137.0, 128.8, 125.8, 123.0, 122.9, 121.0, 120.86, 120.76, 120.13, 119.9, 119.2, 117.1, 109.9, 109.3, 108.0, 95.1, 33.3, 32.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{16}N_3S$ 342.1065; found 342.1050.

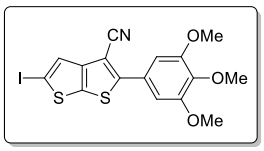


2-(4-Fluorophenyl)-8-methyl-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (65b). Obtained



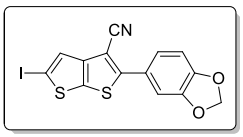
from 2-(2-iodo-1-methyl-1*H*-indol-3-yl)acetonitrile **58** and methyl 4-fluorobenzodithioate **37p**, dark red brown solid; yield 91% (279 mg, 0.91 mmol); mp 195-197 °C; R_f 0.52 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2993, 2217, 1521, 1487, 1414, 1328, 1221, 1157, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 1H), 7.77 (td, J = 5.8, 2.9 Hz, 2H), 7.38 (d, J = 4.8 Hz, 2H), 7.29 (dd, J = 8.0, 4.0 Hz, 1H), 7.18 (td, J = 7.5, 2.3 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (C-F, d, $^1J_{C\text{-}F}$ = 248.8 Hz), 143.8, 141.9, 141.3, 129.4 (C-F, d, $^3J_{C\text{-}F}$ = 8.5 Hz), 128.8 (C-F, d, $^4J_{C\text{-}F}$ = 3.0 Hz), 123.6, 122.4, 120.8, 120.5, 119.3, 116.4 (C-F, d, $^2J_{C\text{-}F}$ = 21.8 Hz), 115.8, 109.4, 97.7, 32.4; $^{19}F\{^1H\}$ NMR (564.65 MHz, CDCl3) δ -111.29; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{12}FN_2S$ 307.0705; found 307.0697.

5-Iodo-2-(3,4,5-trimethoxyphenyl)thieno[2,3-*b*]thiophene-3-carbonitrile (66a).



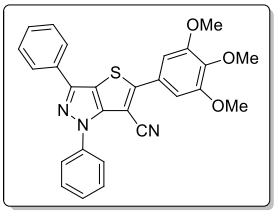
Obtained from 2-(2,5-diiodothiophen-3-yl)acetonitrile **59** and methyl 3,4,5-trimethoxybenzodithioate **37n**, white solid; yield 89% (407 mg, 0.89 mmol); mp 220-222 °C; R_f 0.44 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3009, 2219, 1741, 1581, 1242, 1132, 996, 815, 623; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.98 (s, 2H), 3.94 (s, 6H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.8, 147.1, 139.9, 138.3, 131.5, 128.6, 126.7, 115.0, 105.1, 97.5, 61.0, 56.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{13}INO_3S_2$ 457.9382; found 457.9380.

2-(Benzo[*d*][1,3]dioxol-5-yl)-5-iodothieno[2,3-*b*]thiophene-3-carbonitrile (66b).



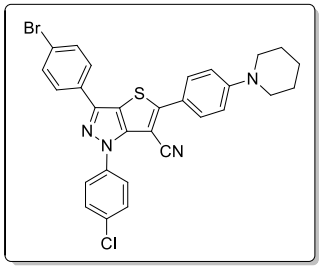
Obtained from 2-(2,5-diiodothiophen-3-yl)acetonitrile **59** and methyl benzo[*d*][1,3]dioxole-5-carbodithioate **37q**, off-white solid; yield 90% (370 mg, 0.90 mmol); mp 170-172 °C; R_f 0.46 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3011, 2217, 1739, 1477, 1252, 1036, 934, 856, 718, 617; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.28 (dd, J = 8.0, 2.0 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 149.3, 148.5, 146.4, 134.7, 129.7, 125.8, 122.4, 119.1, 115.3, 109.1, 108.1, 101.8, 98.5; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_7INO_2S_2$ 411.8963; found 411.8951.

1,3-Diphenyl-5-(3,4,5-trimethoxyphenyl)-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile



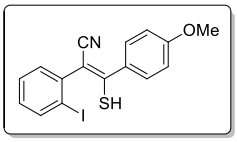
(67a). Obtained from 2-(4-iodo-1,3-diphenyl-1*H*-pyrazol-5-yl)acetonitrile **60a** and methyl 3,4,5-trimethoxybenzodithioate **37n**, white solid; yield 91% (425 mg, 0.91 mmol); mp 222-224 °C; R_f 0.39 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2992, 2220, 1742, 1584, 1497, 1244, 1005, 910, 816, 756, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.2, 1.6 Hz, 2H), 7.78 (dd, J = 7.4, 1.4 Hz, 2H), 7.58 (td, J = 7.0, 1.8 Hz, 2H), 7.51 (td, J = 6.7, 1.5 Hz, 2H), 7.49-7.40 (m, 2H), 7.07 (s, 2H), 3.96 (s, 6H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 153.7, 144.9, 143.7, 140.3, 138.6, 131.2, 129.3, 129.0, 128.8, 128.5, 127.2, 125.9, 124.2, 118.2, 114.2, 105.5, 90.6, 61.1, 56.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{22}N_3O_3S$ 468.1382; found 468.1464

3-(4-Bromophenyl)-1-(4-chlorophenyl)-5-(4-(piperidin-1-yl)phenyl)-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (67b).



Obtained from 2-(3-(4-bromophenyl)-1-(4-chlorophenyl)-4-iodo-1*H*-pyrazol-5-yl)acetonitrile **60b** and methyl 4-(piperidin-1-yl)benzodithioate **37m**, orange solid; yield 95% (543 mg, 0.95 mmol); mp 138-140 °C; R_f 0.81 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2985, 2219, 1742, 1600, 1492, 1237, 1071, 915, 821, 717, 632; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 6.8, 2.0 Hz, 2H), 7.74 (dd, J = 7.0, 2.2 Hz, 2H), 7.69 (dd, J = 6.4, 2.0 Hz, 2H), 7.62 (dd, J = 6.8, 2.0 Hz, 2H), 7.53 (dd, J = 6.6, 2.2 Hz, 2H), 6.96 (dd, J = 6.8, 2.0 Hz, 2H), 3.35 (t, J = 5.2 Hz, 4H), 1.74-1.65 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 153.1, 145.2, 142.9, 137.1, 134.0, 132.2, 130.2, 129.7, 129.4, 129.1, 129.0, 127.5, 125.2, 122.8, 120.7, 117.3, 114.9, 114.5, 88.2, 48.9, 25.4, 24.3; HRMS (ESI) *m*/*z*: $[M + H]^+$, $[M + H + 2]^+$, $[M + H + 4]^+$ calcd for $C_{29}H_{23}BrClN_4S$ 573.0515, 575.0515, 577.0515; found 573.0559, 575.0543, 577.0533.

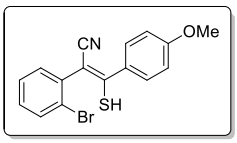
(*E*)-2-(2-Iodophenyl)-3-mercapto-3-(4-methoxyphenyl)acrylonitrile (64a).



Obtained from 2-(2-iodophenyl)acetonitrile **53a** and methyl 4-methoxybenzodithioate **37a**, off-white solid; (yields are described in the Scheme 23); mp 106-108 °C; R_f 0.16 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3348, 2224, 1605, 1435, 1251, 1185, 822, 749, 573; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100

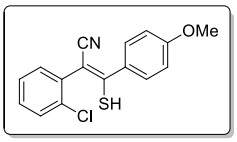
MHz, $CDCl_3$) δ 161.4, 155.2, 139.4, 136.9, 129.7, 126.0, 125.8, 124.1, 122.4, 122.3, 115.5, 114.8, 100.8, 55.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{13}INOS$ 393.9763; found 393.9748.

(*E*)-2-(2-Bromophenyl)-3-mercapto-3-(4-methoxyphenyl)acrylonitrile (64b). Obtained



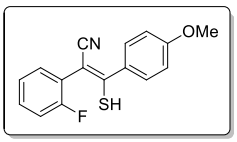
from 2-(2-bromophenyl)acetonitrile **55a** and methyl 4-methoxybenzodithioate **37a**, light orange solid; (yields are described in the Table 2); mp 196-198 °C; R_f 0.14 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3356, 2228, 1608, 1430, 1248, 1188, 822, 749, 680; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (brs, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 155.5, 138.5, 136.2, 129.6, 126.4, 125.9, 123.0, 121.5, 121.4, 116.3, 115.1, 99.0, 55.5; HRMS (ESI) *m/z*: $[M + H]^+$, $[M + H + 2]^+$ calcd for $C_{16}H_{13}BrNOS$ 345.9901, 347.9901; found 345.9883, 347.9867.

(*E*)-2-(2-Chlorophenyl)-3-mercapto-3-(4-methoxyphenyl)acrylonitrile (64c). Obtained



from 2-(2-chlorophenyl)acetonitrile **56** and methyl 4-methoxybenzodithioate **37a**, white solid; (yields are described in the Table 2); mp 180-182 °C; R_f 0.13 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3357, 2223, 1610, 1428, 1254, 1184, 820, 753, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.75 (br s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 160.6, 142.9, 133.9, 131.6, 131.4, 130.7, 130.0, 126.9, 125.9, 116.7, 114.2, 108.0, 55.5; HRMS (ESI) *m/z*: $[M + H]^+$, $[M + H + 2]^+$ calcd for $C_{16}H_{13}ClNOS$ 302.0406, 304.0406; found 302.0398, 304.0372.

(*E*)-2-(2-Fluorophenyl)-3-mercapto-3-(4-methoxyphenyl)acrylonitrile (64d). Obtained



from 2-(2-fluorophenyl)acetonitrile **57** and methyl 4-methoxybenzodithioate **37a**, off-white solid; (yields are described in the Table 2); mp 220-222 °C; R_f 0.12 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3352, 2227, 1612, 1429, 1287, 1170, 823, 750, 654; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 155.6, 138.5, 136.3, 129.6, 126.5, 126.0, 123.1,

121.6, 121.5, 116.4, 115.2, 99.1, 55.5; $^{19}F\{^{1}H\}$ NMR (564.65 MHz, DMSO-d_6) δ -115.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{13}FNOS$ 286.0702; found 286.0684.

3.6 References

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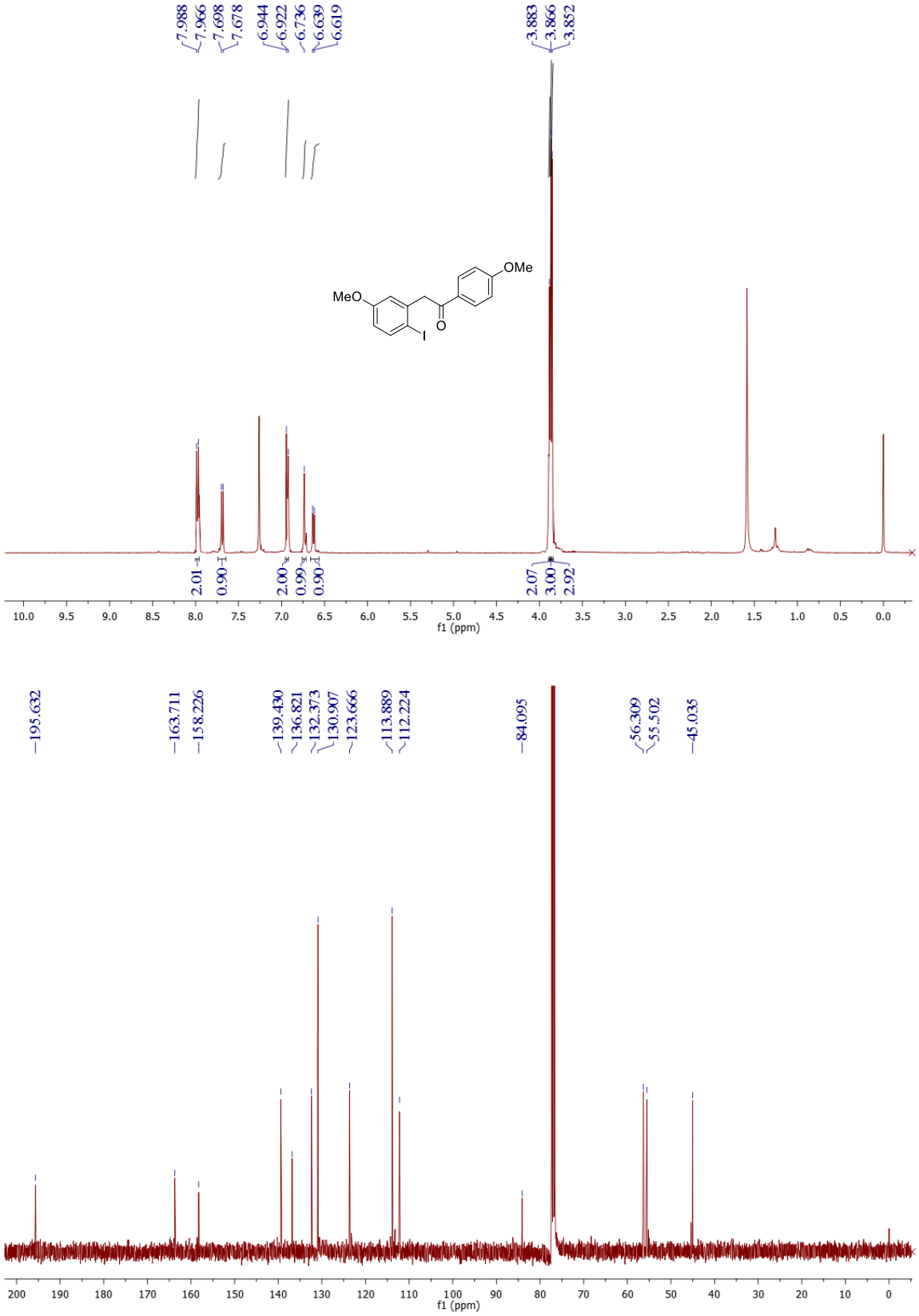
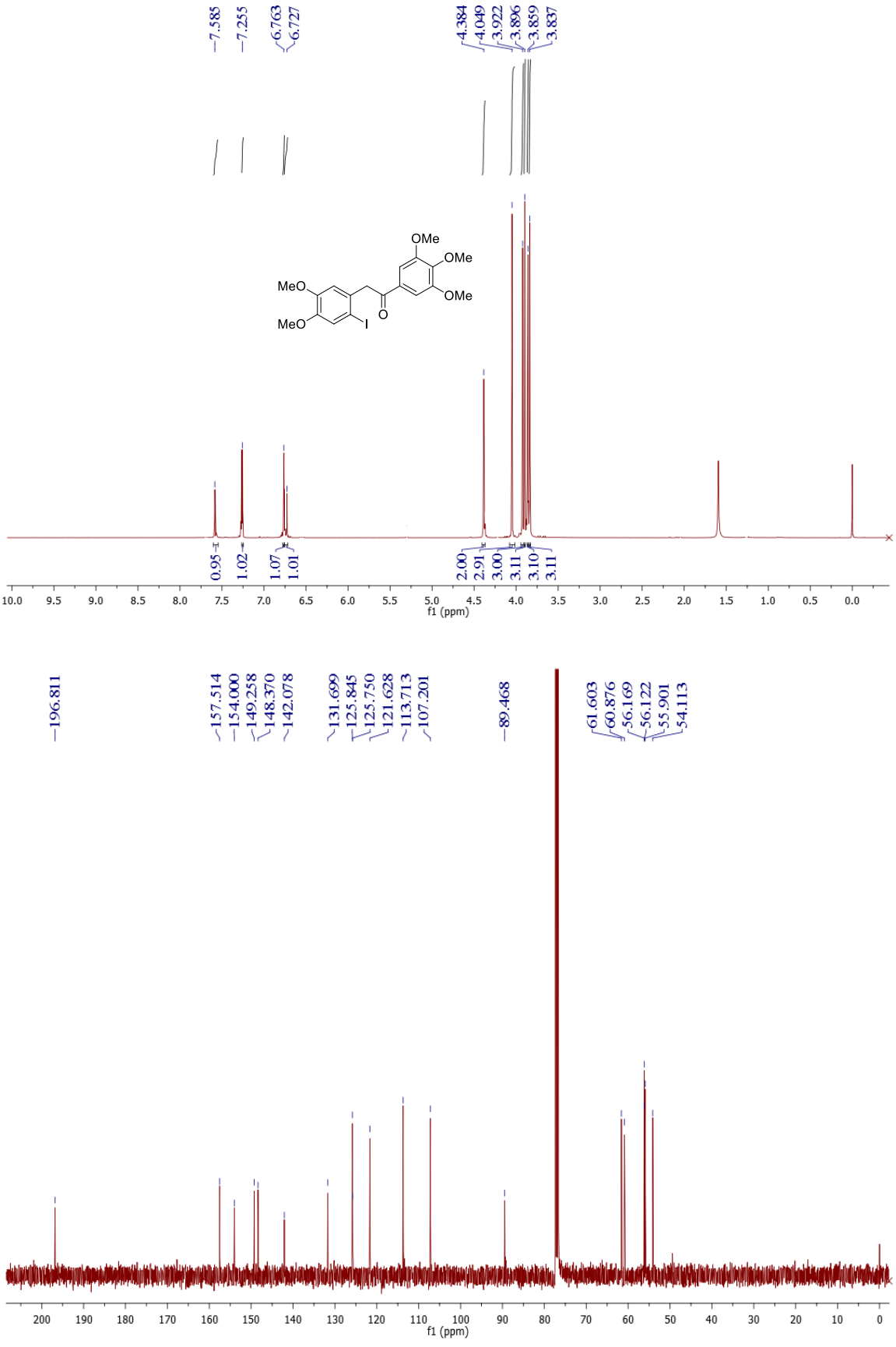
3.7 Representative Spectra



^{1}H and ^{13}C NMR spectra of compound **53g**



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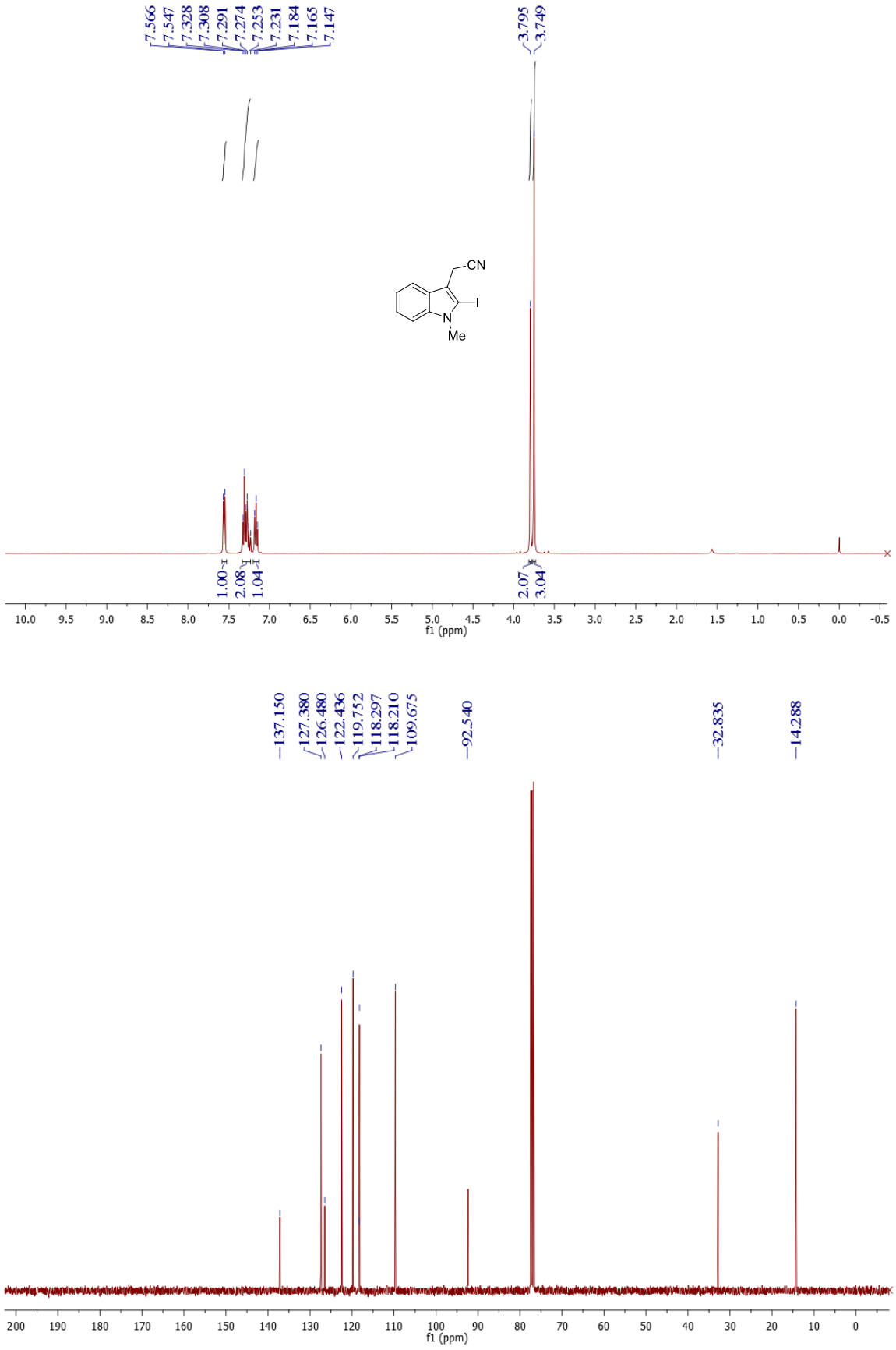

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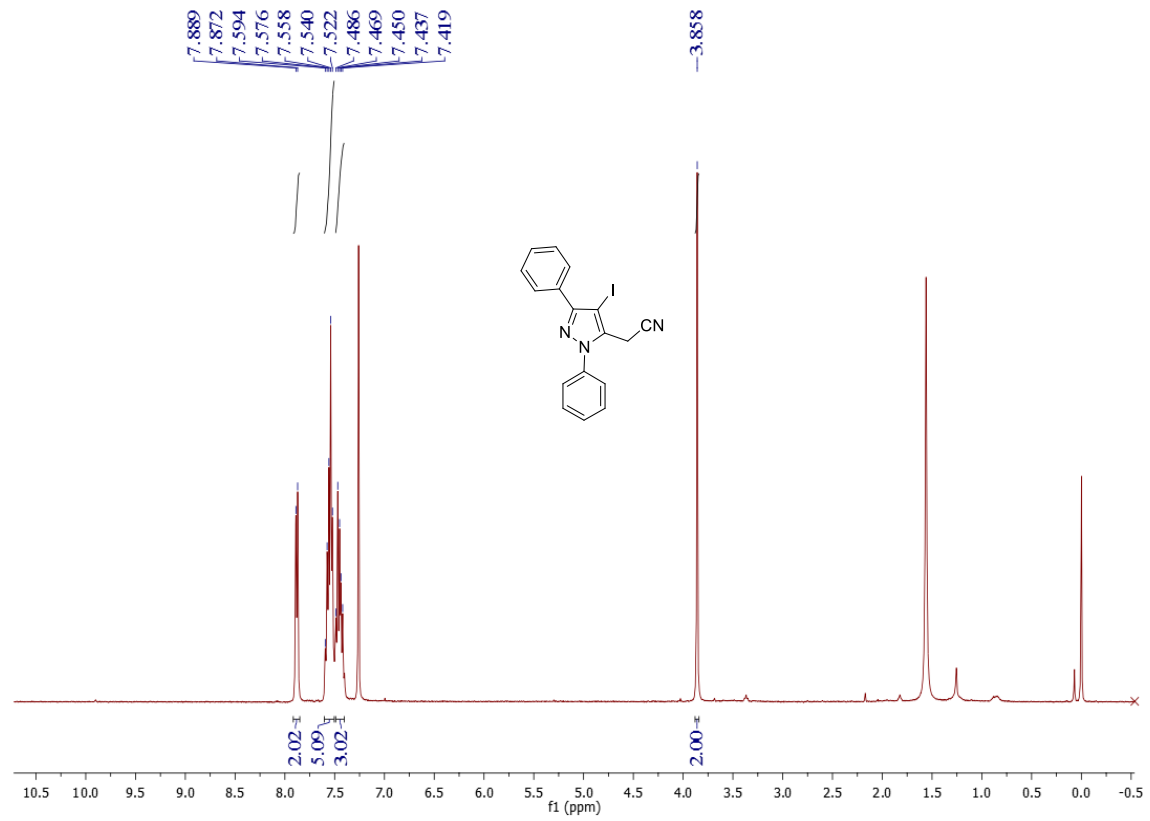

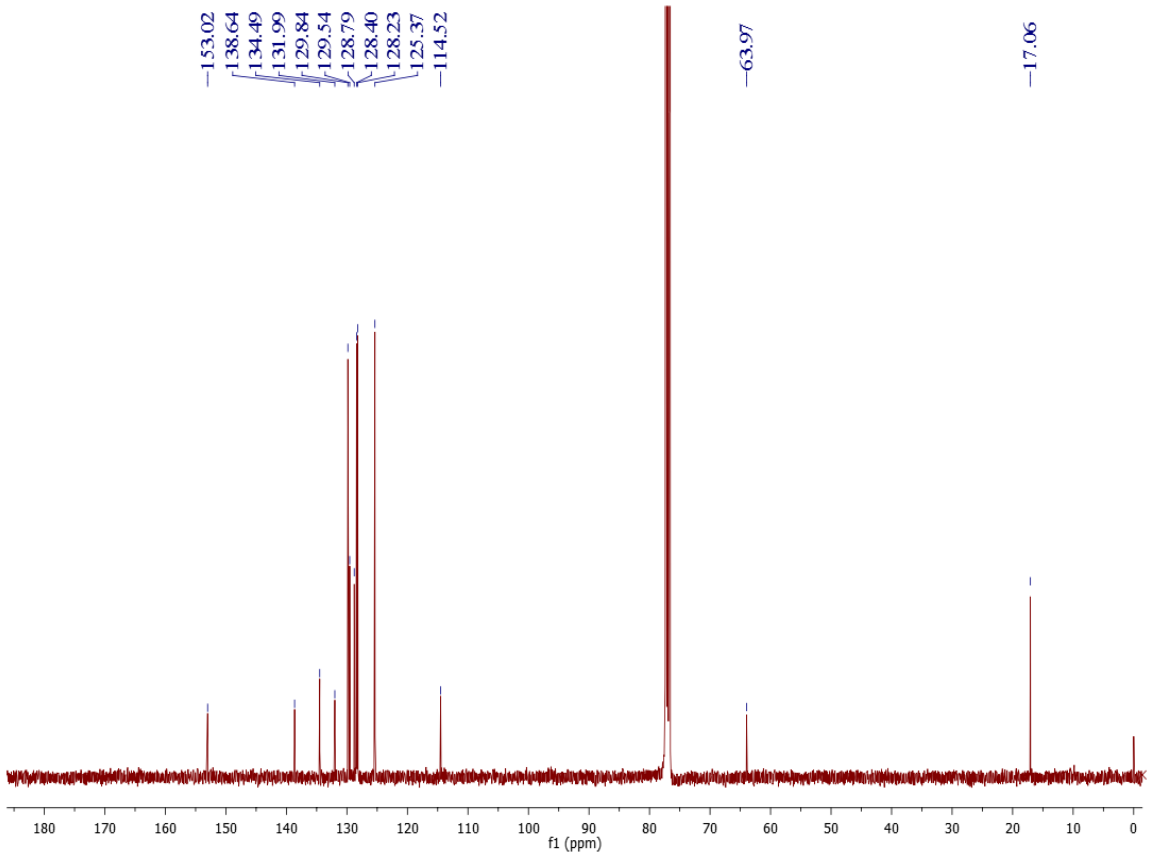

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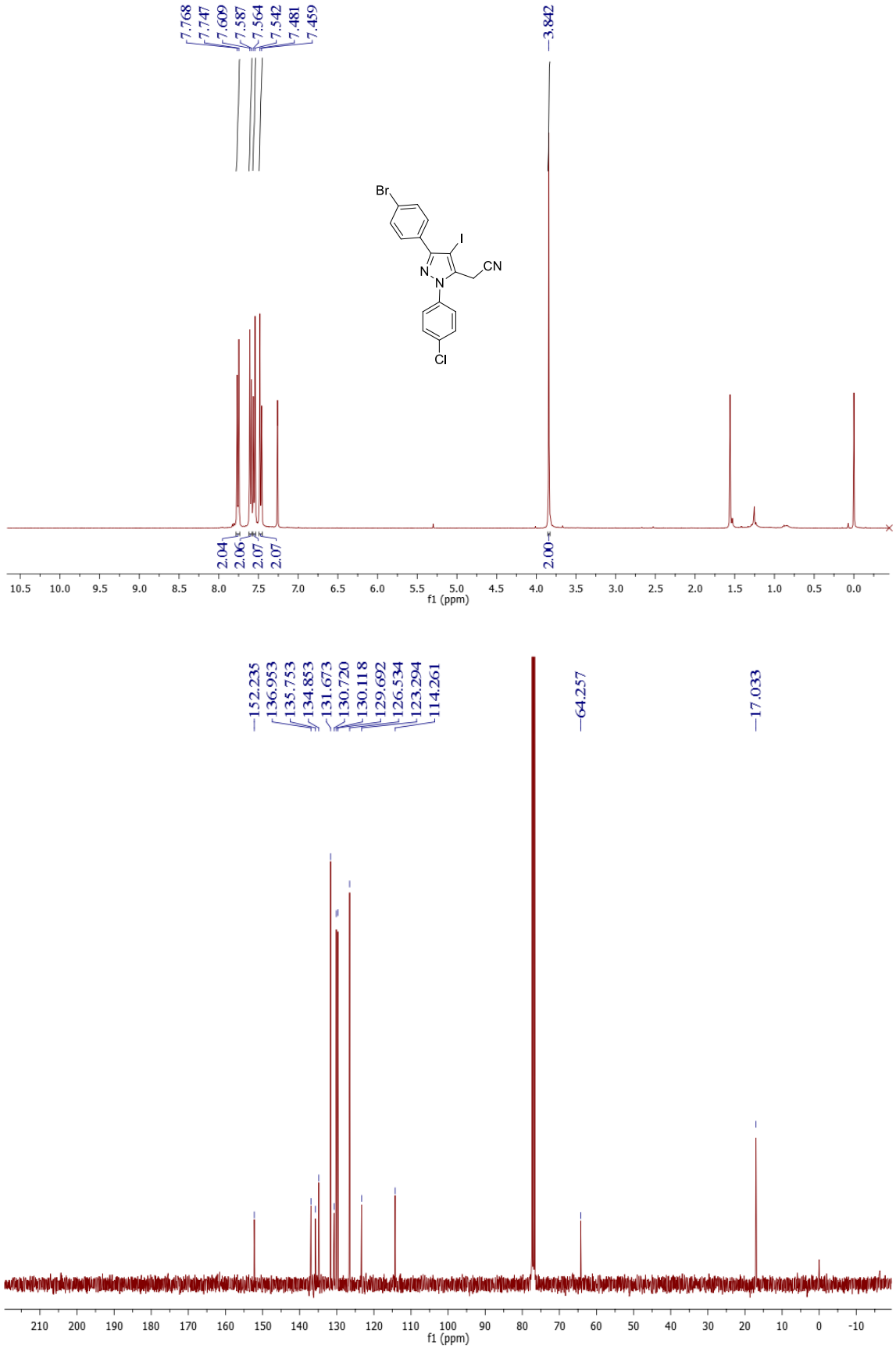

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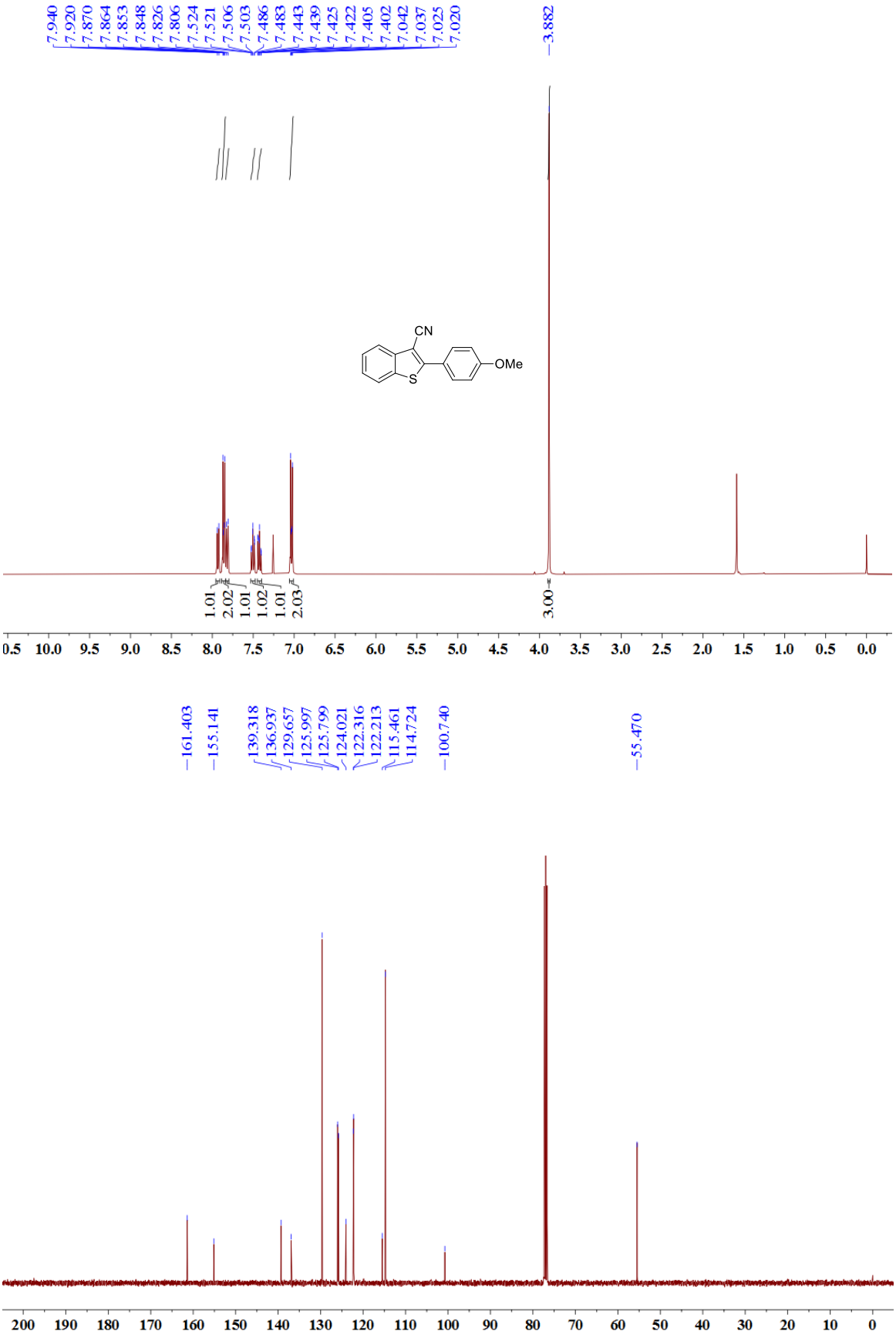
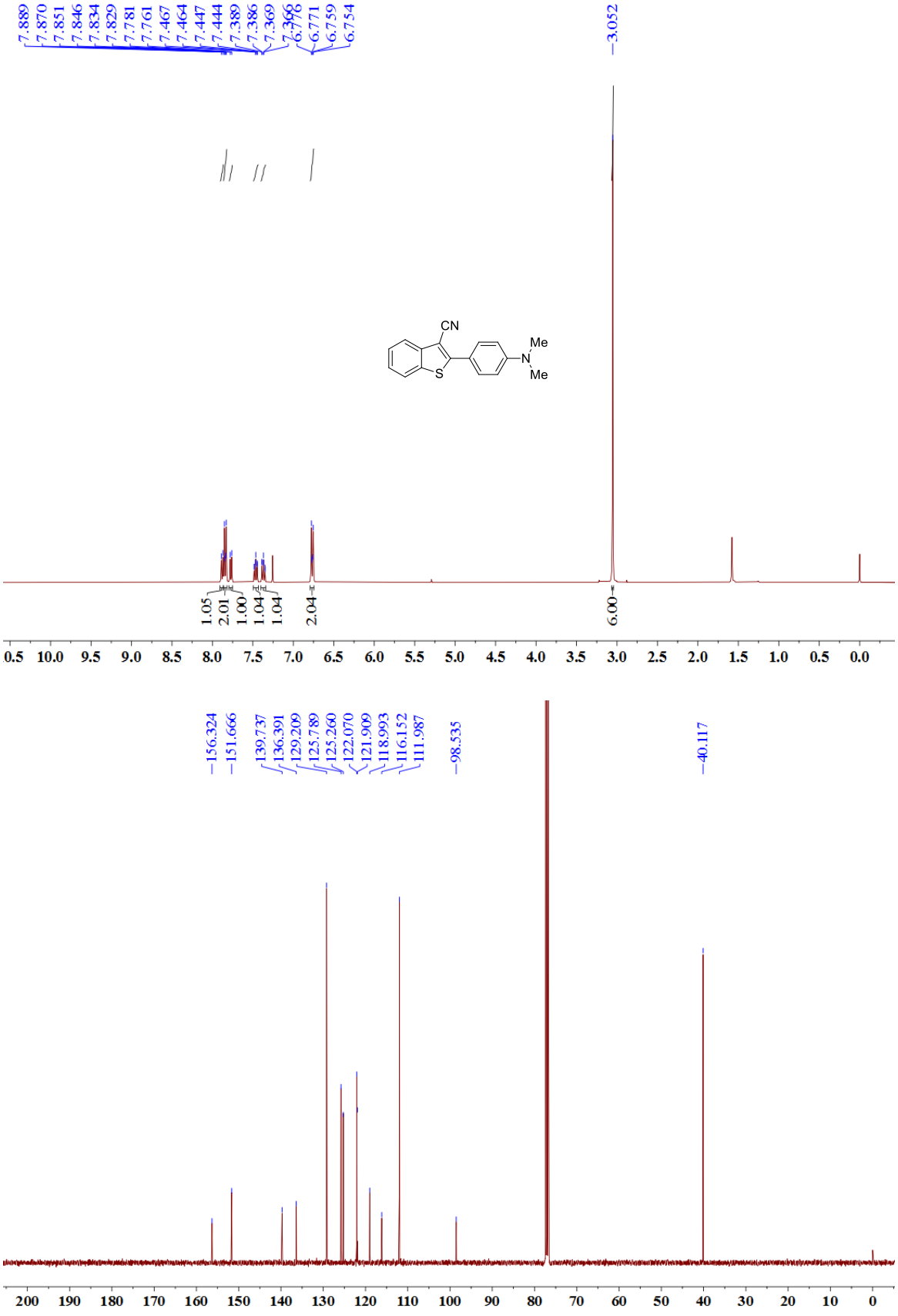


^{1}H and ^{13}C NMR spectra of compound **42a**



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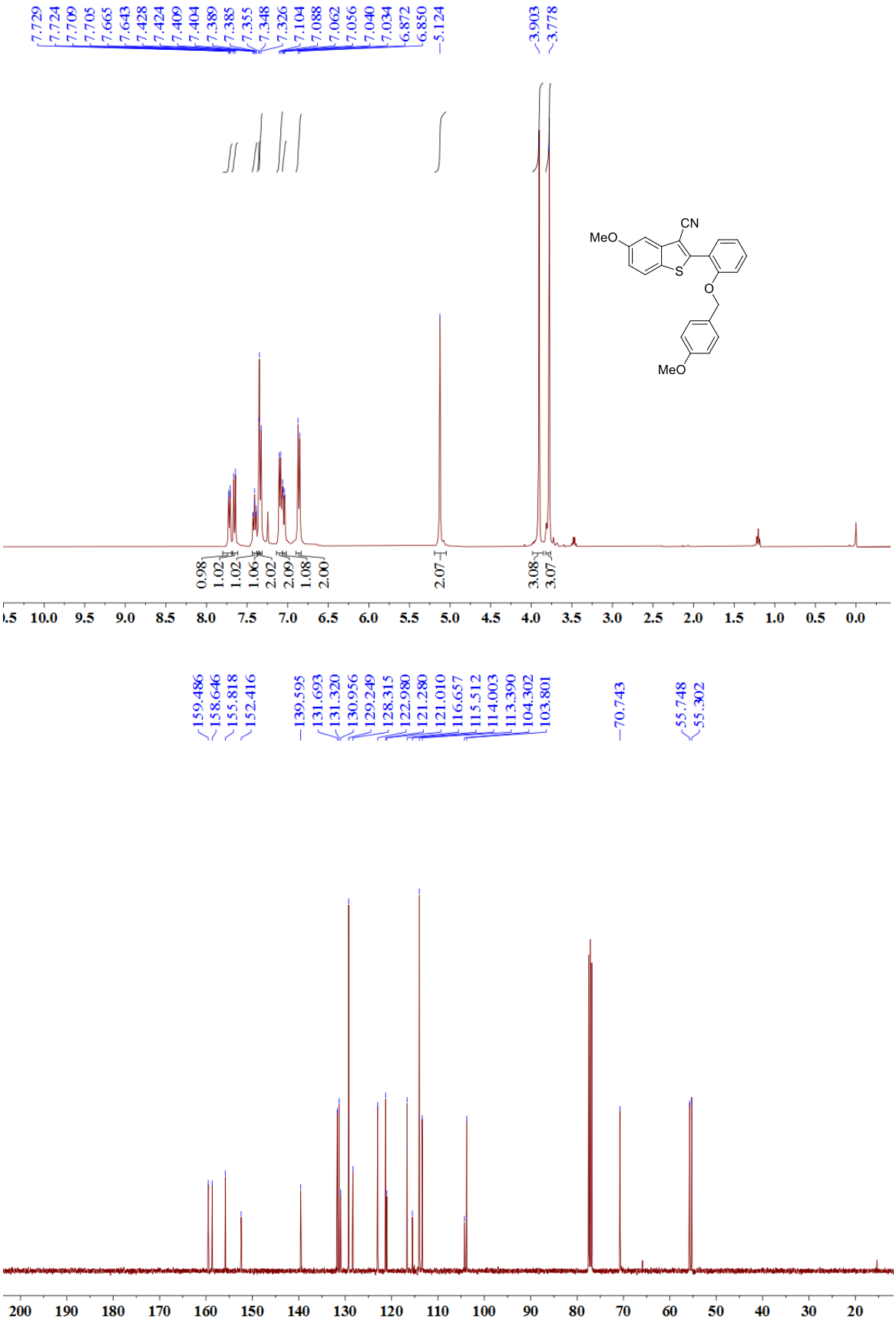
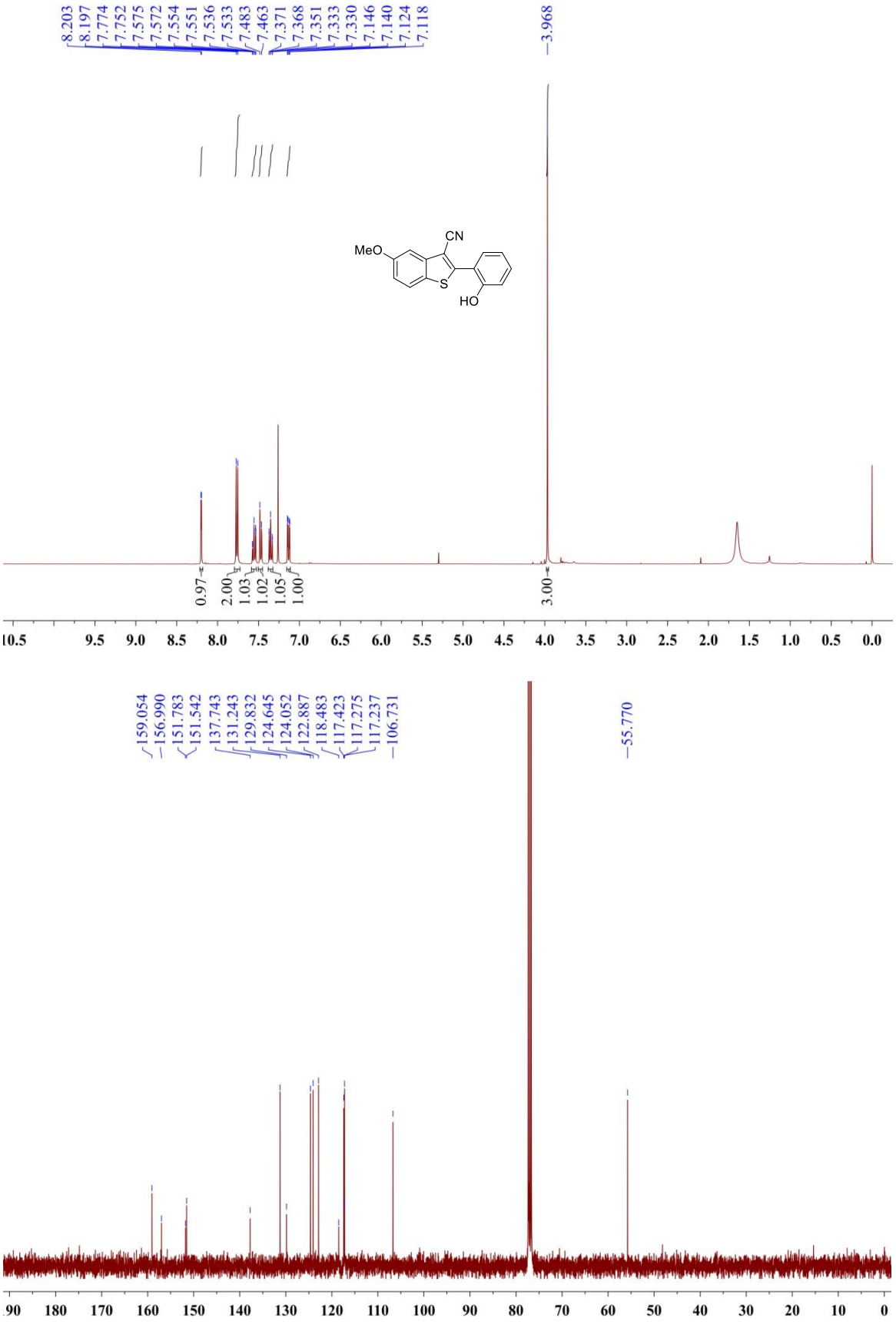
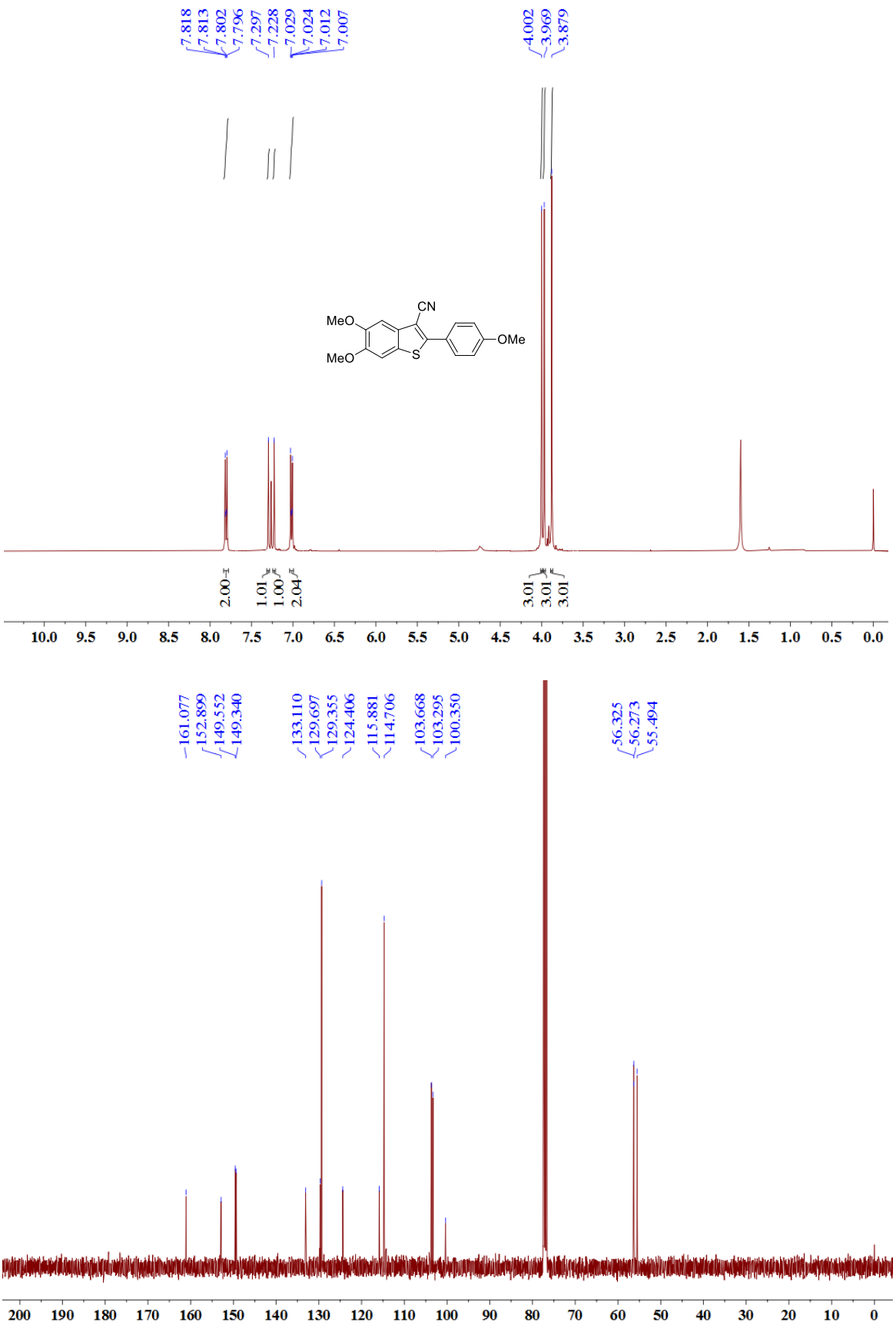


^{1}H and ^{13}C NMR spectra of compound **42c**



^{1}H and ^{13}C NMR spectra of compound **42c'**



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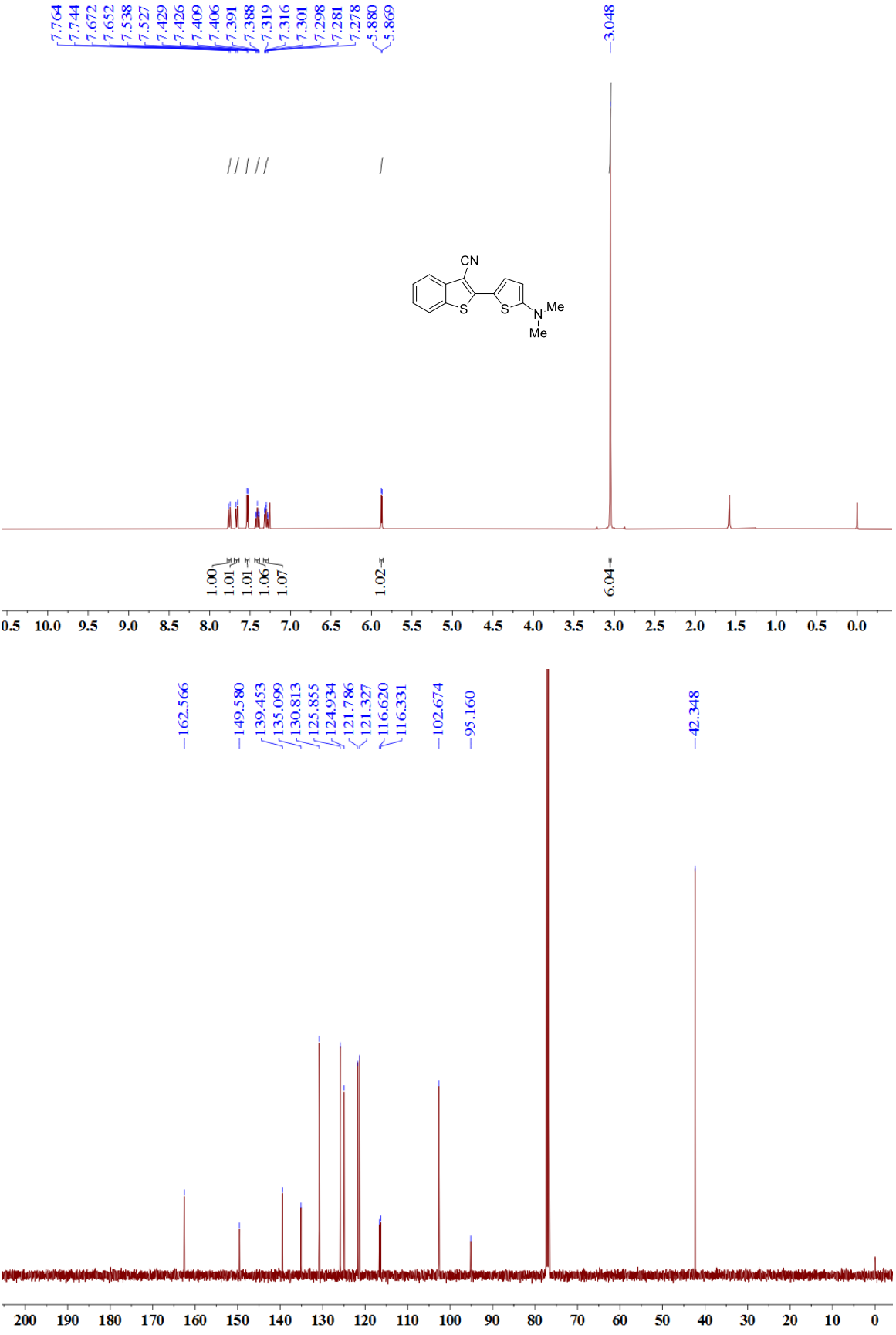
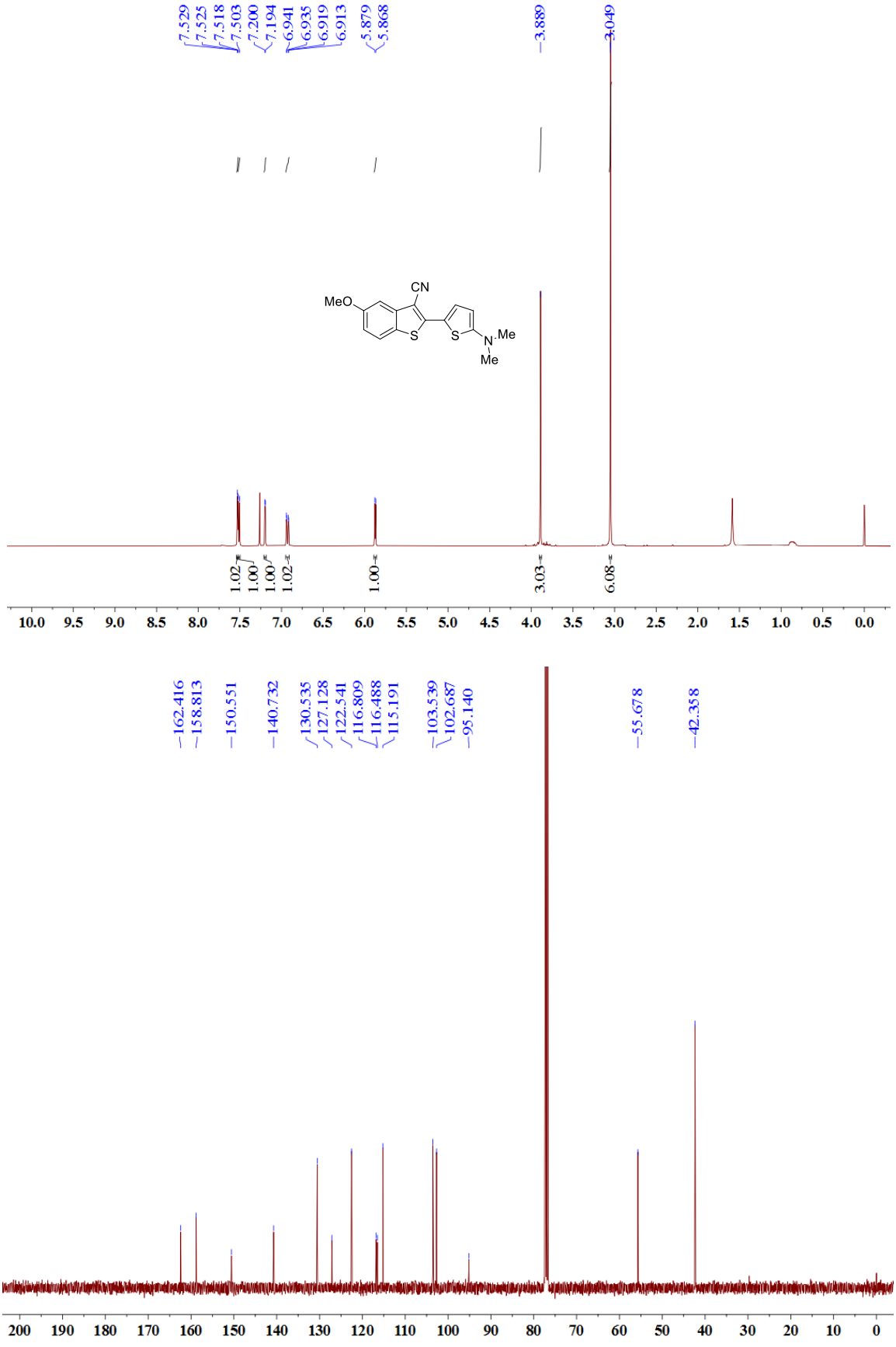


^{1}H and ^{13}C NMR spectra of compound **42e**



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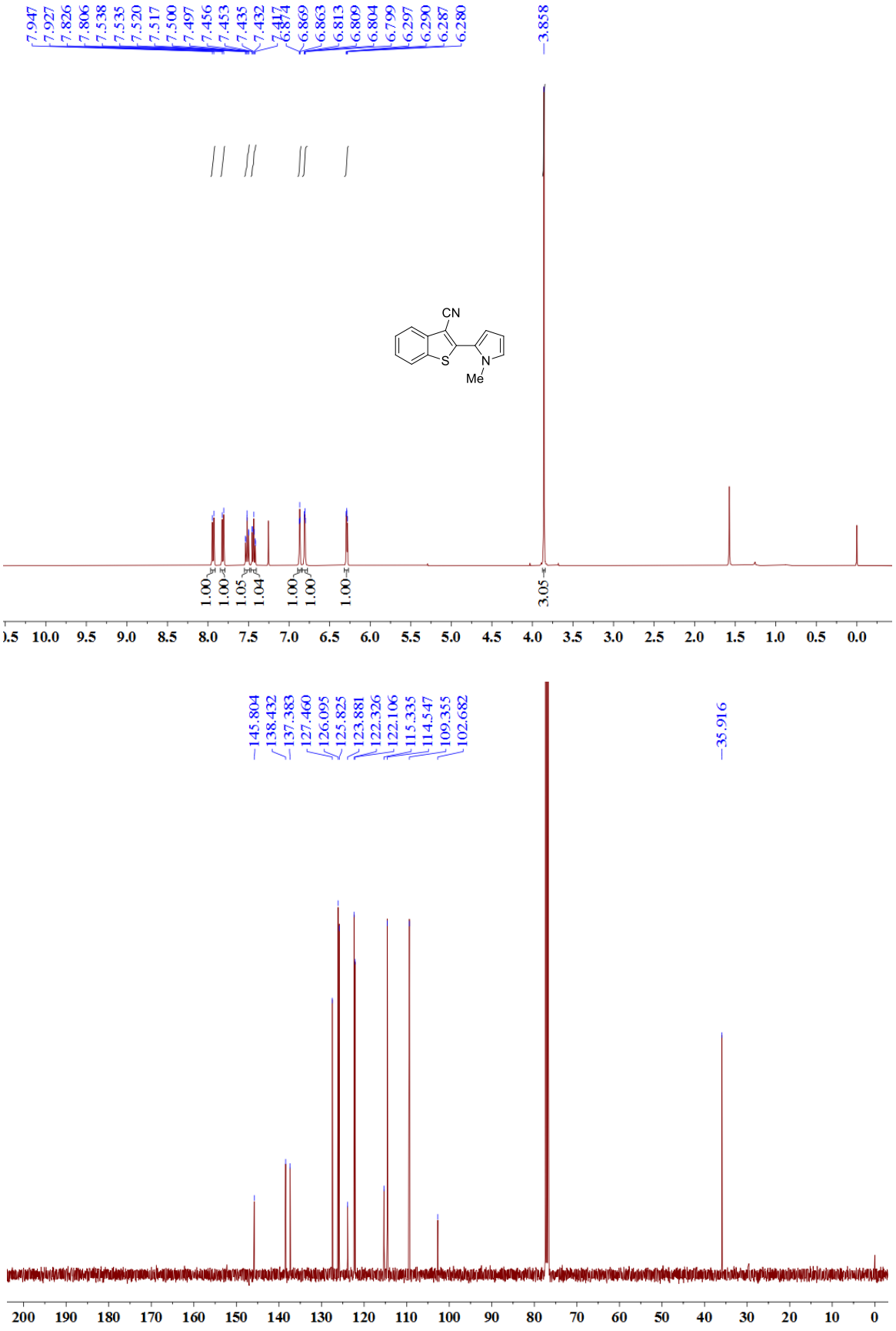

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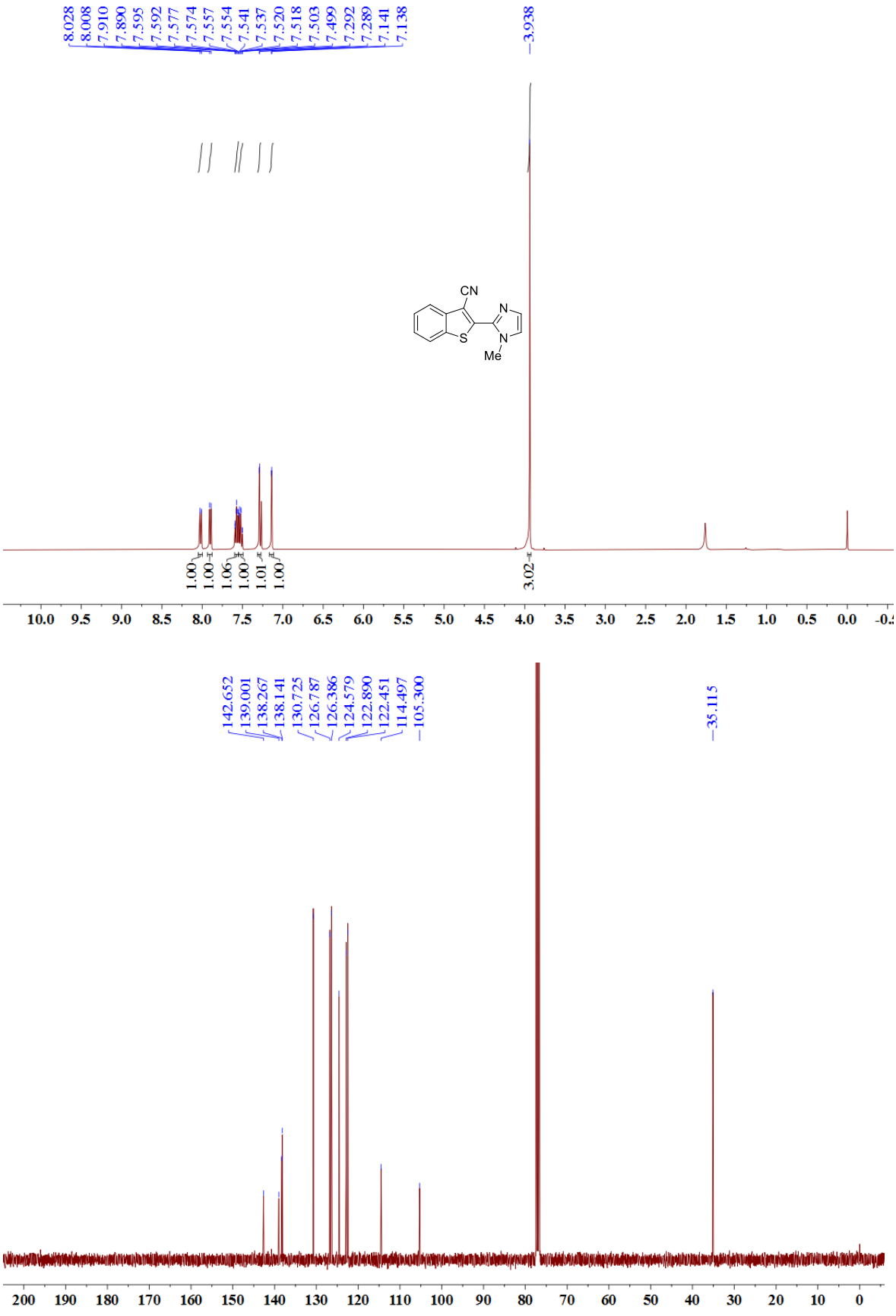
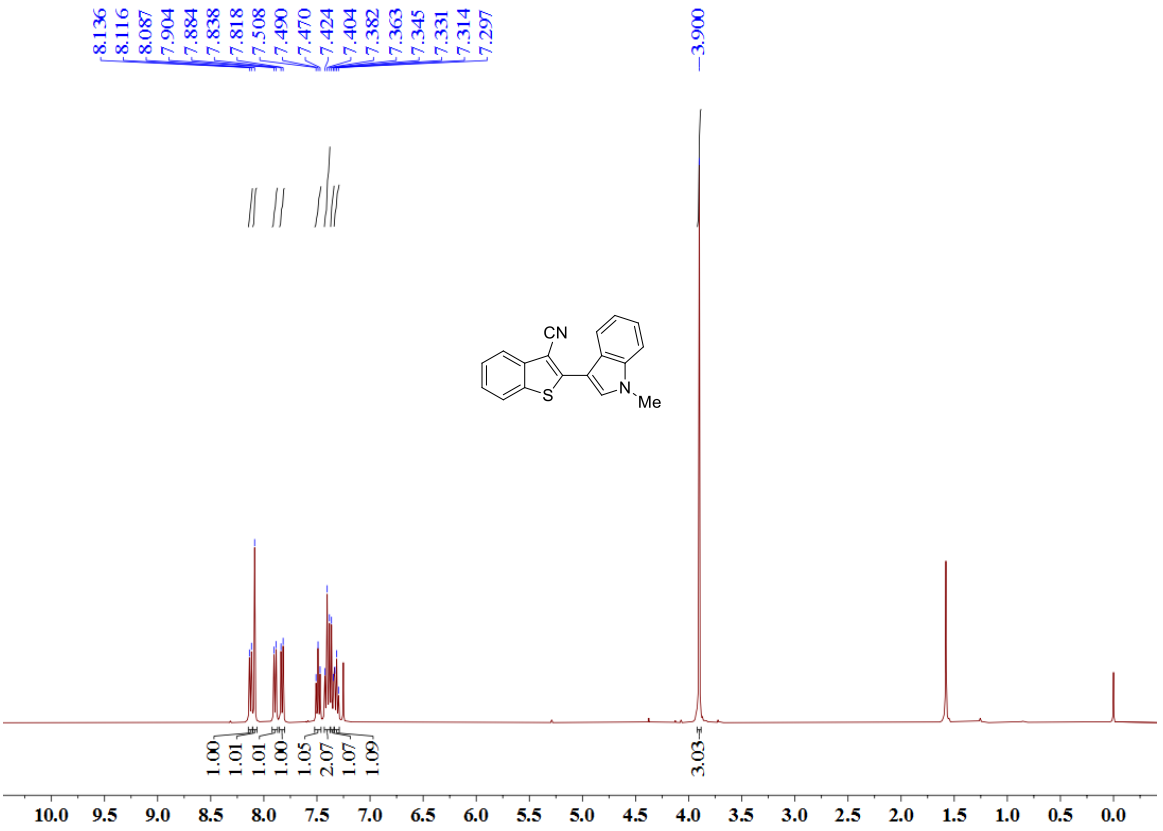
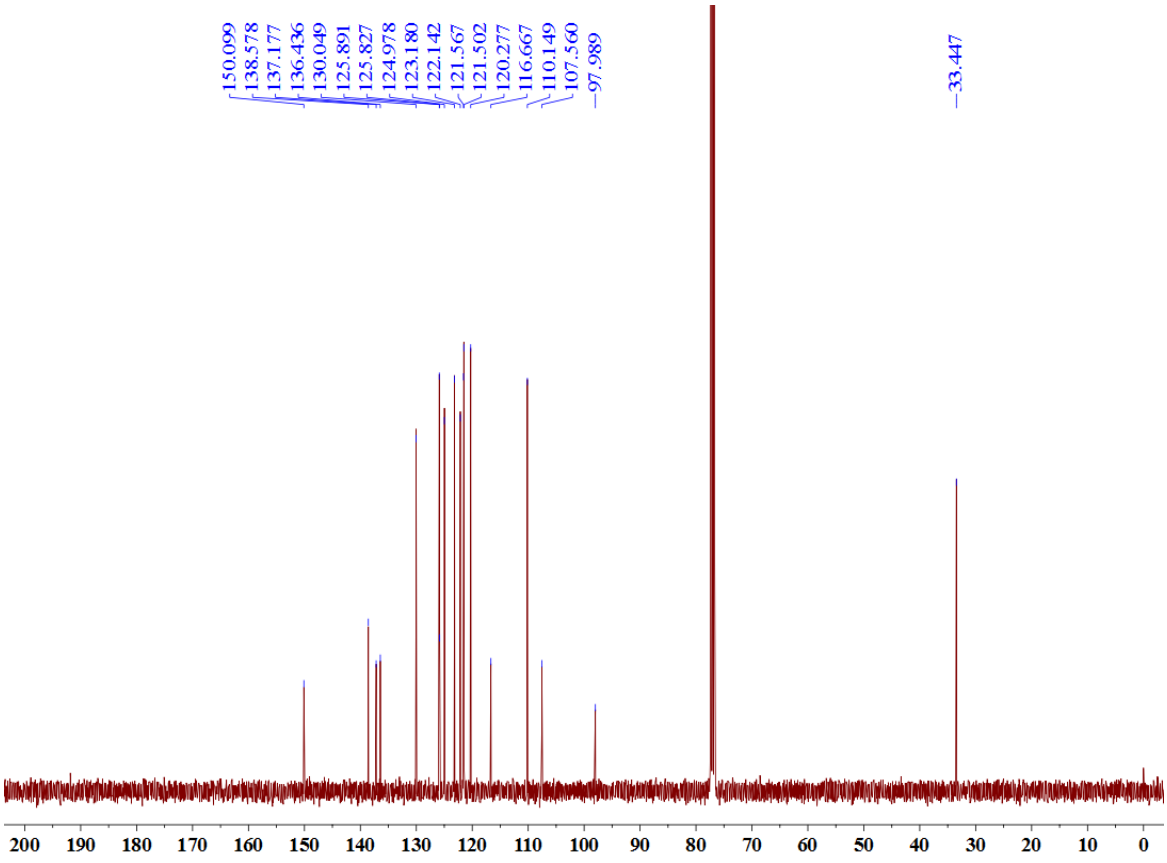


^{1}H and ^{13}C NMR spectra of compound **42h**





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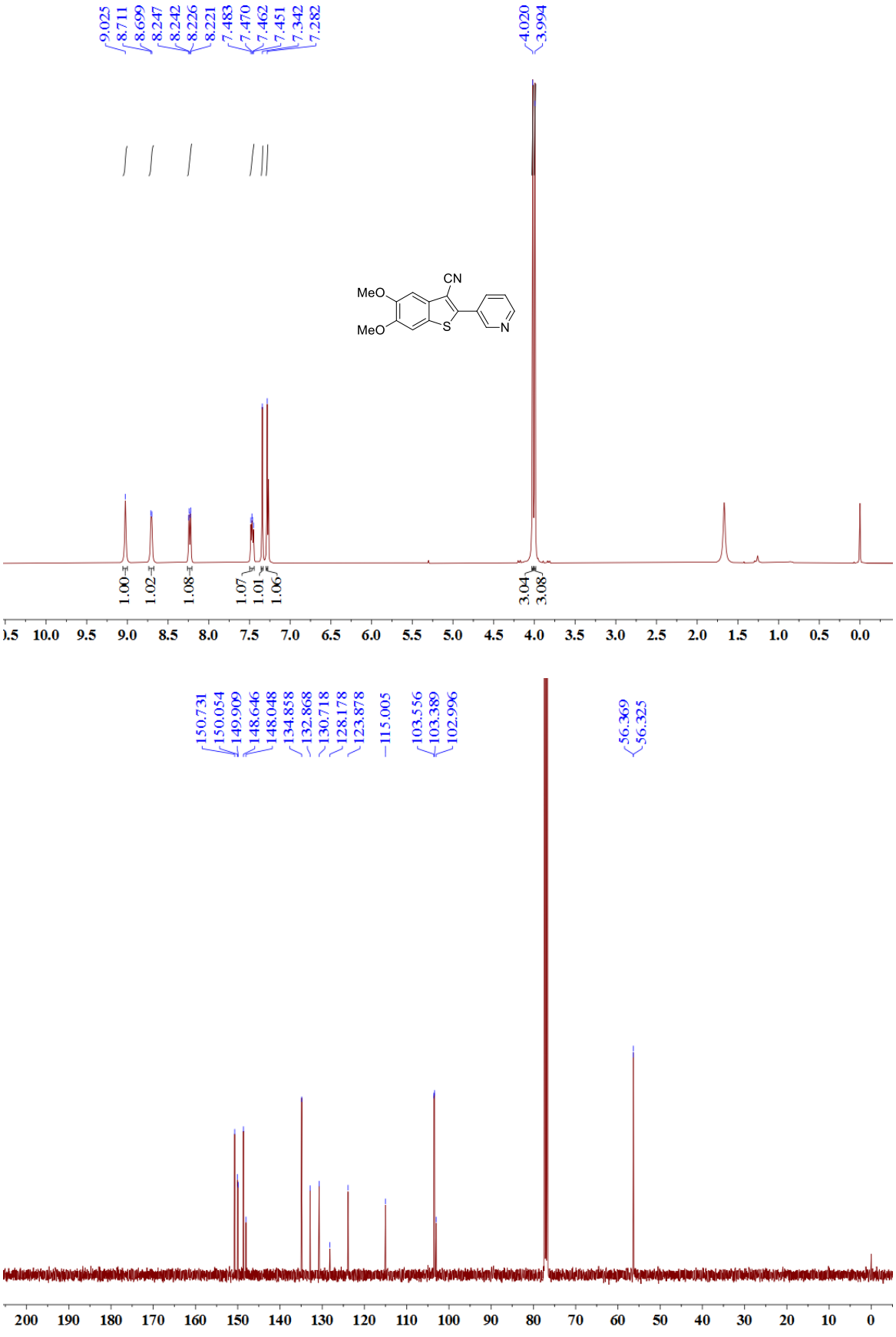

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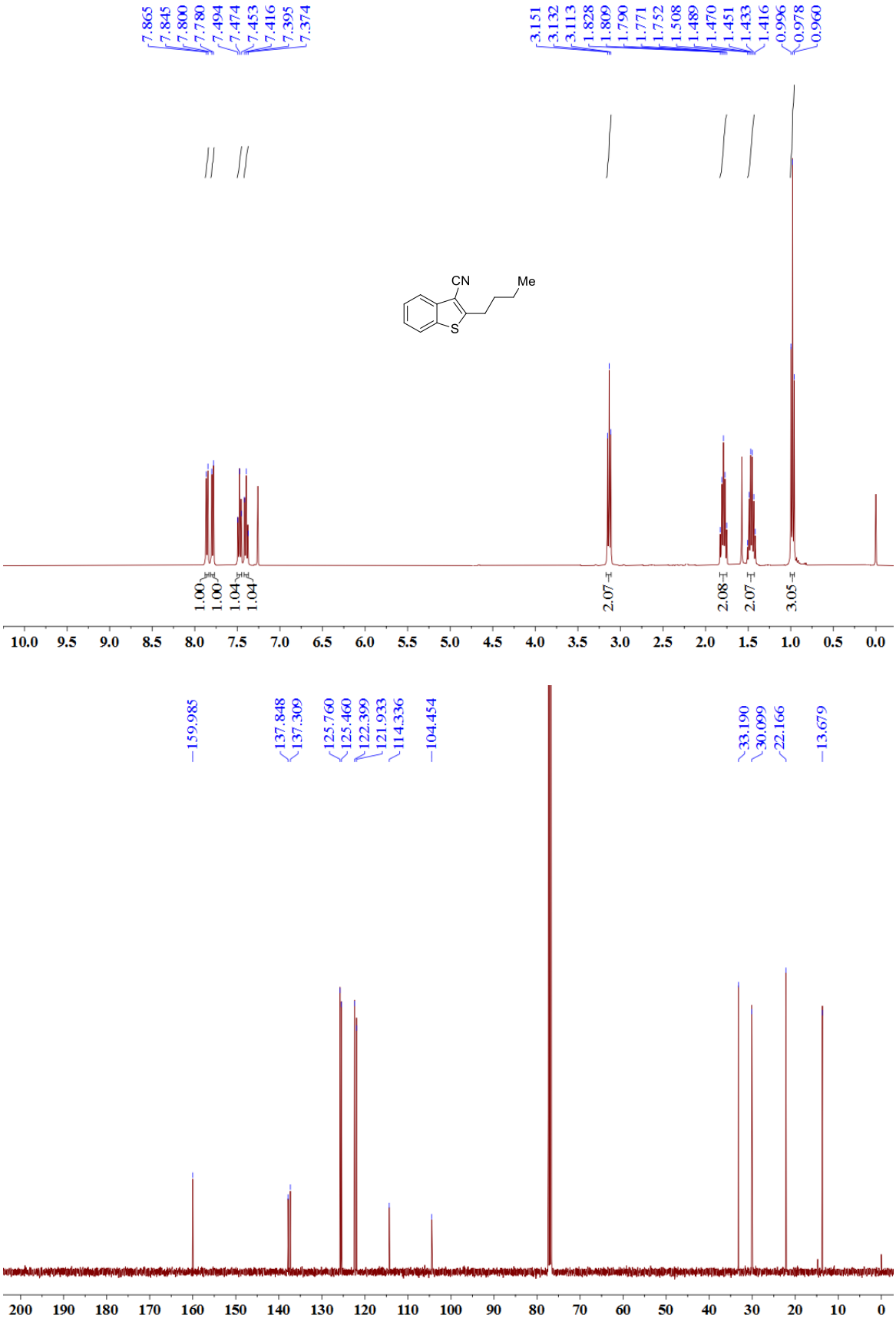

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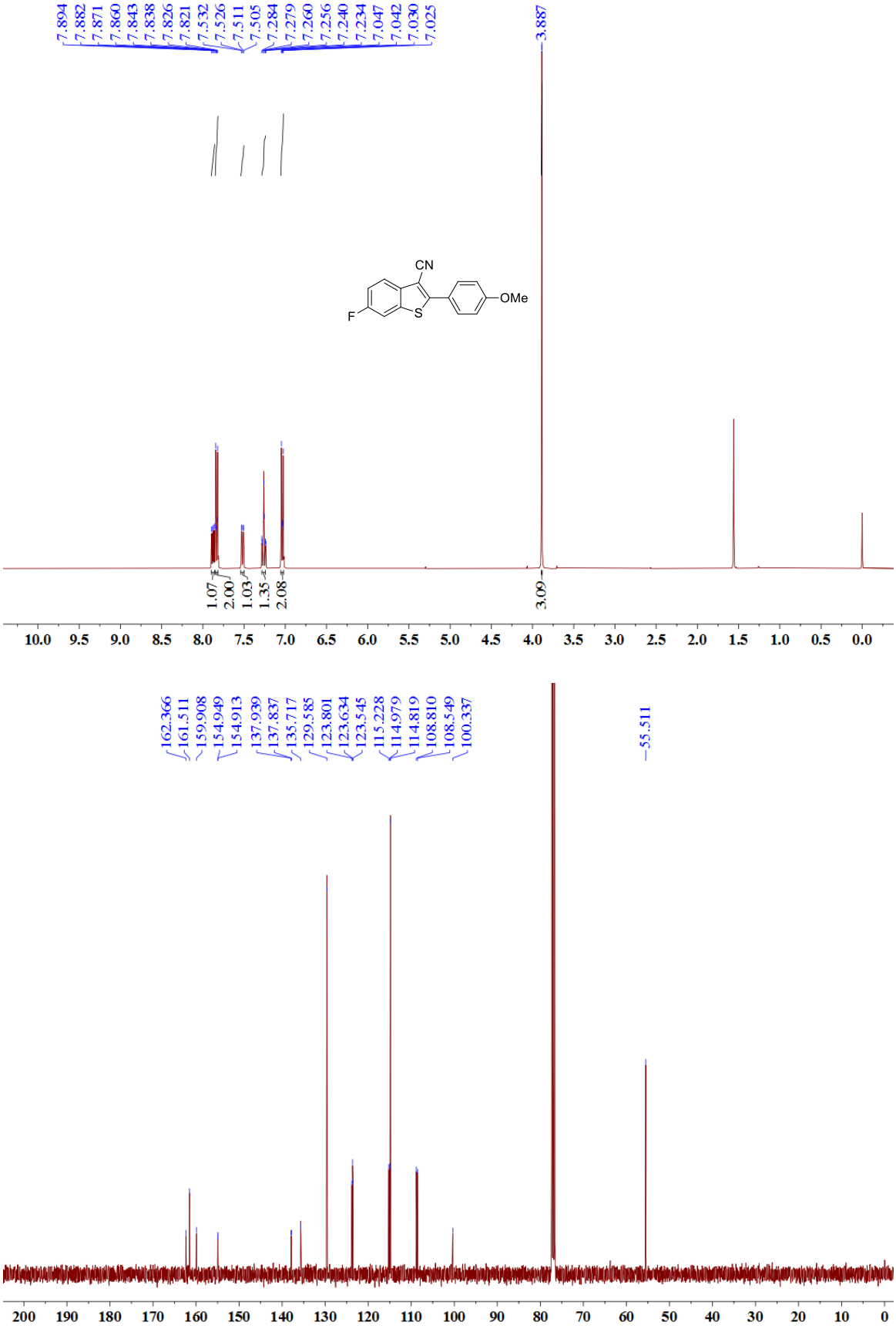

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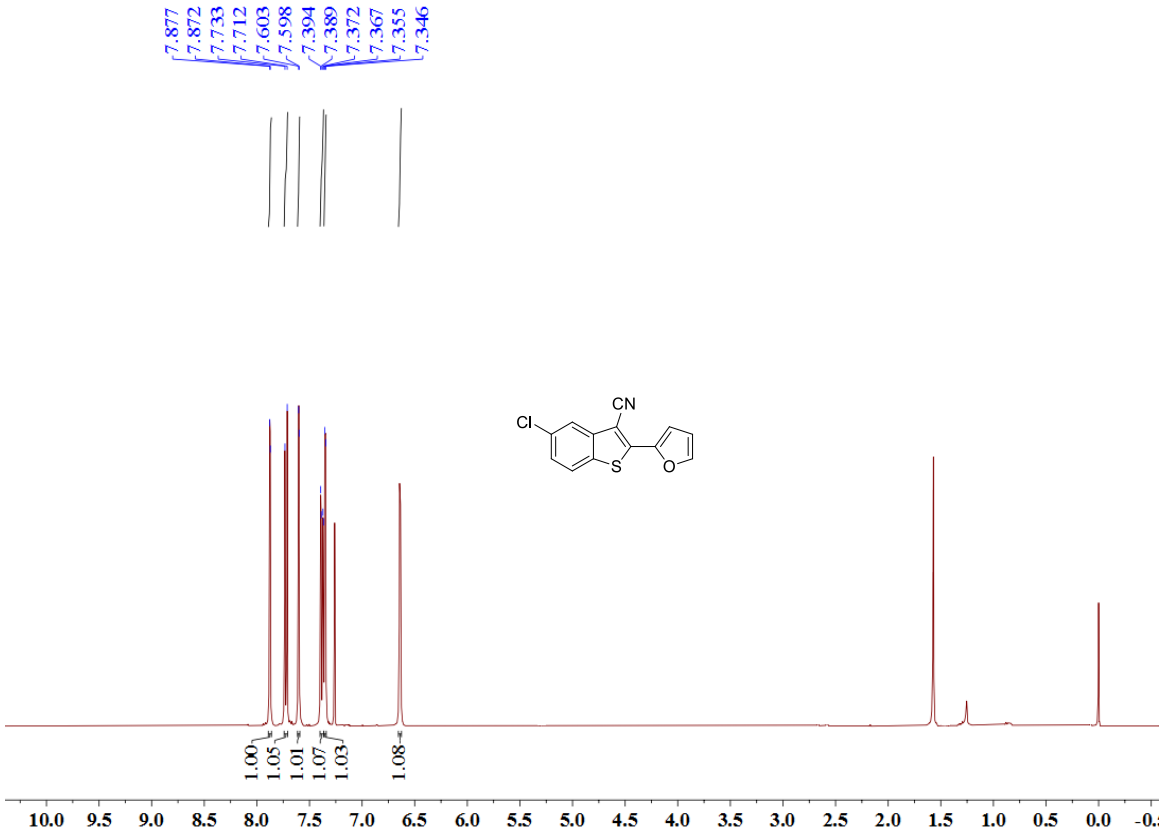

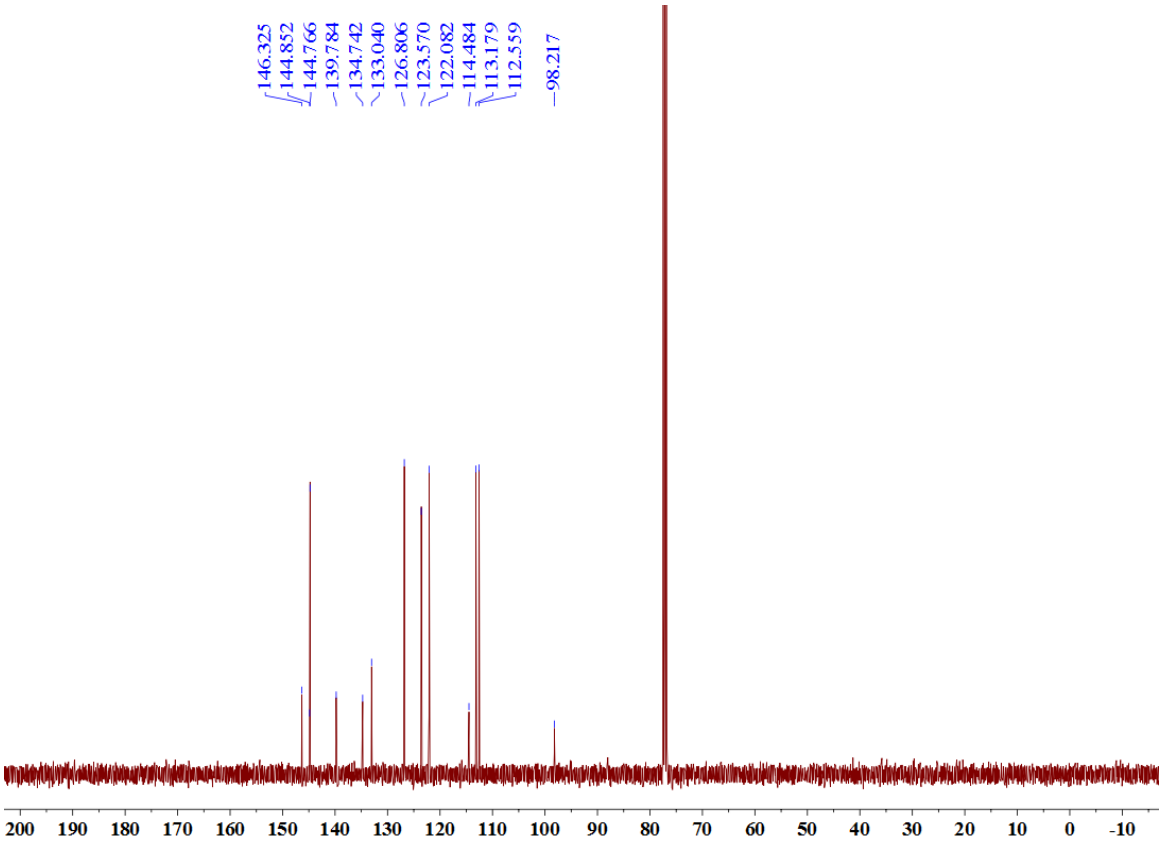

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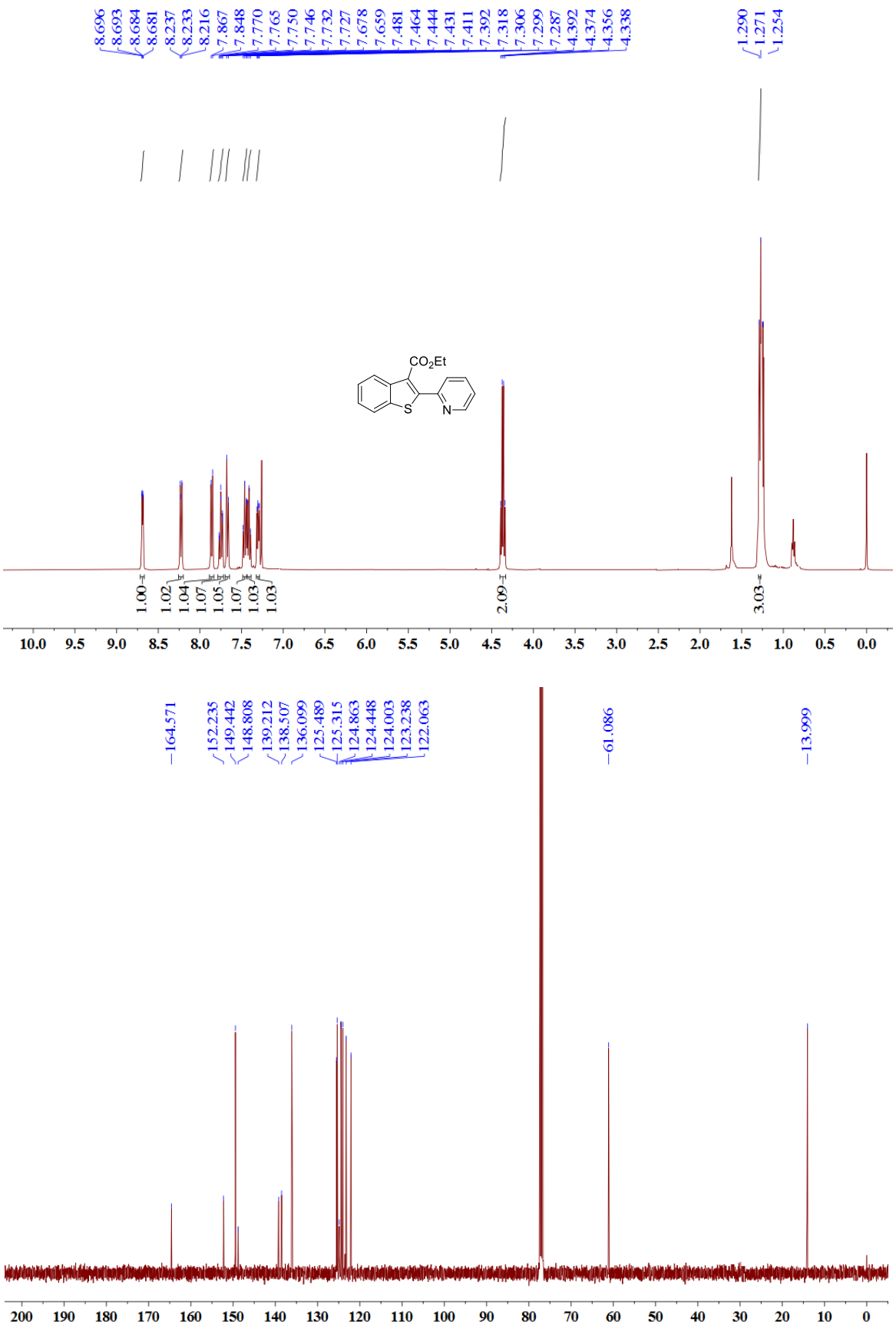

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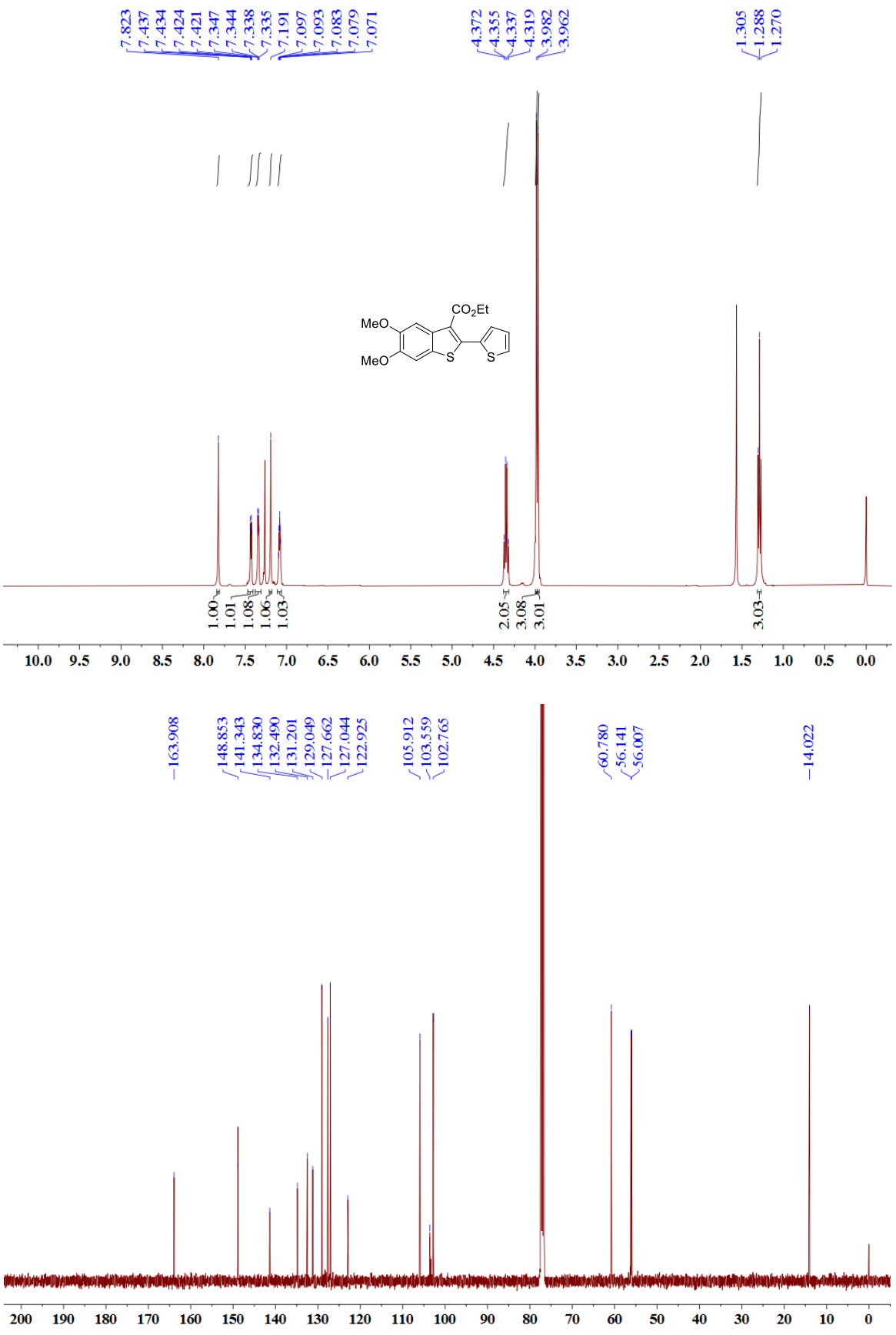

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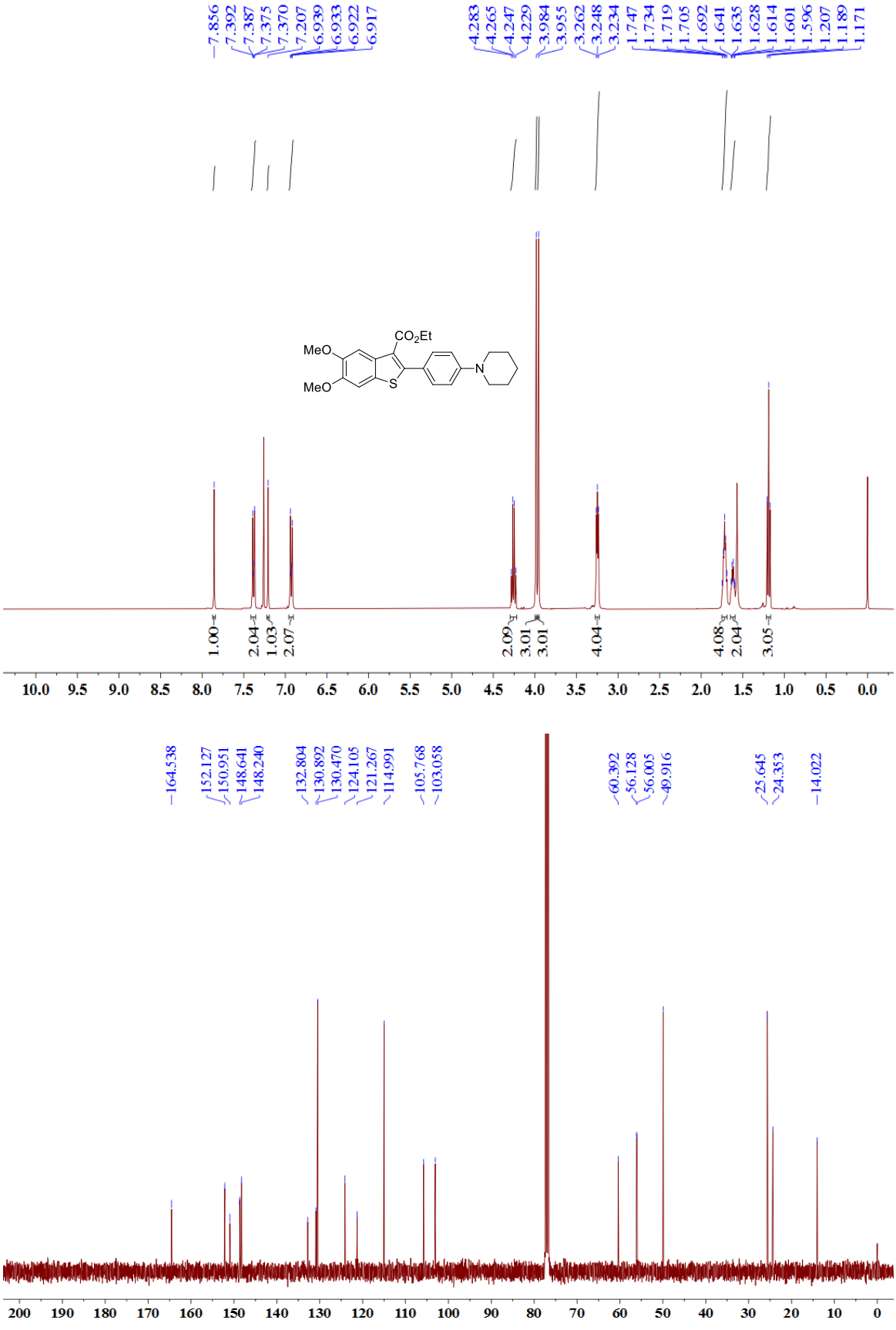

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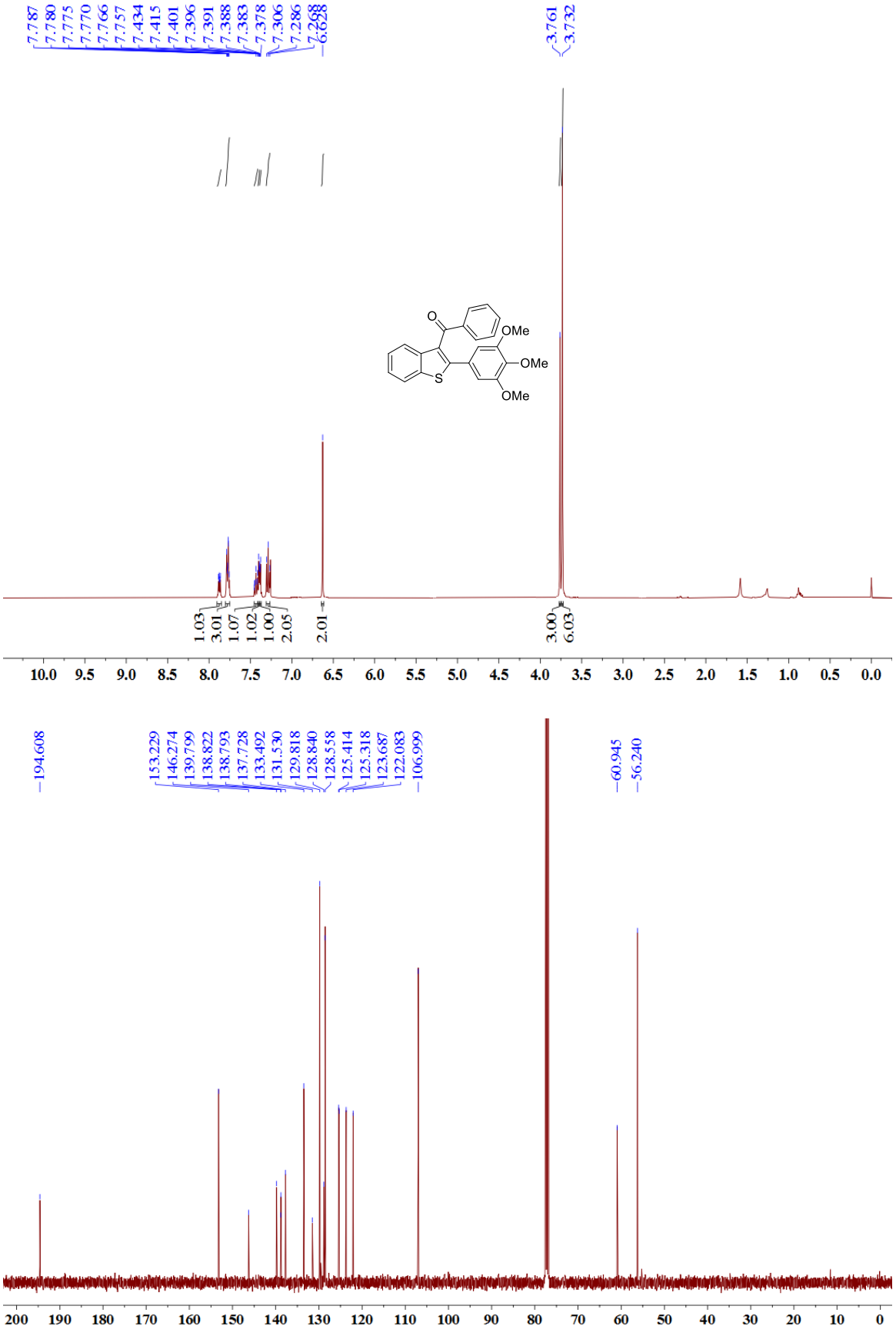

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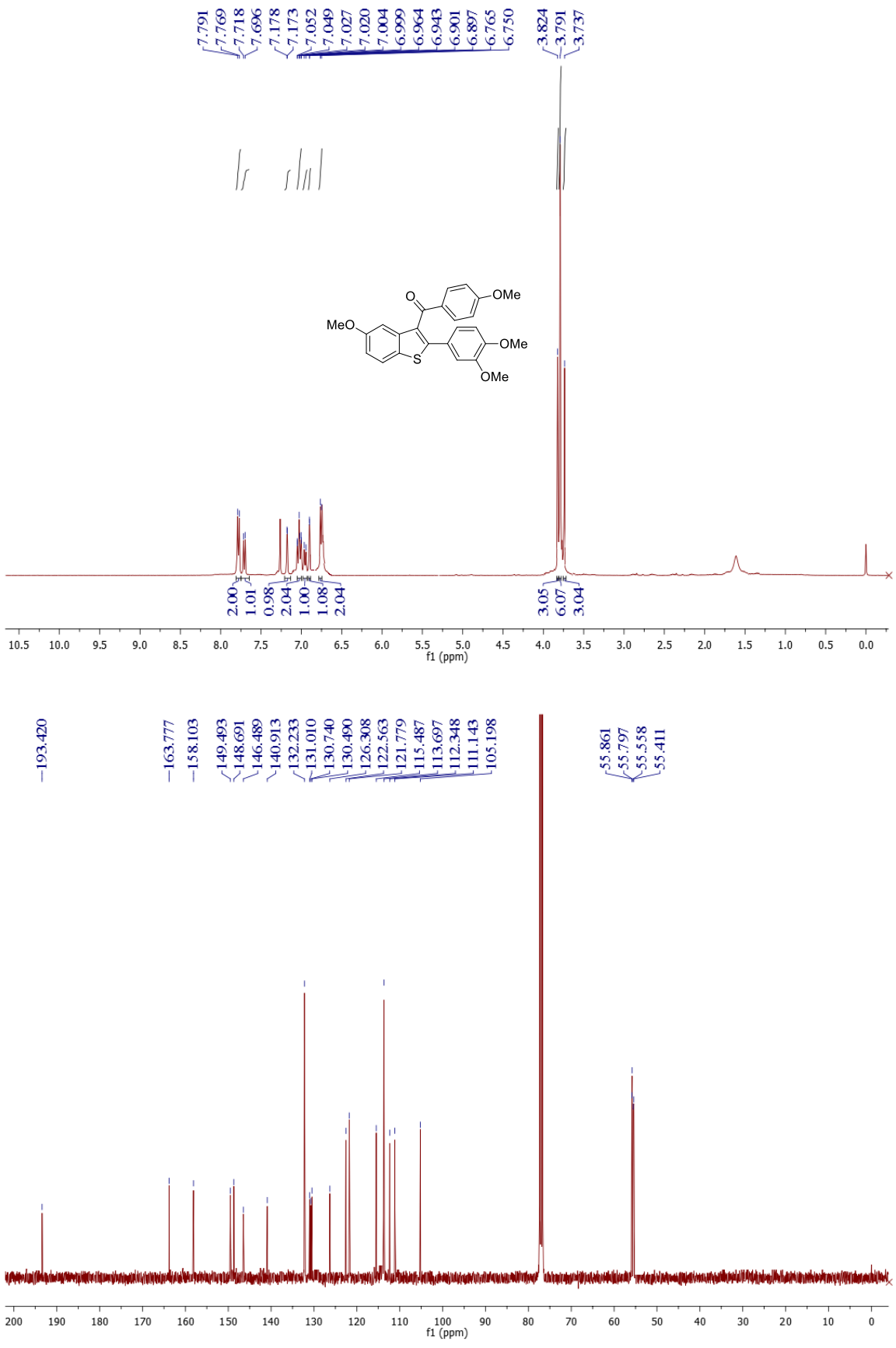
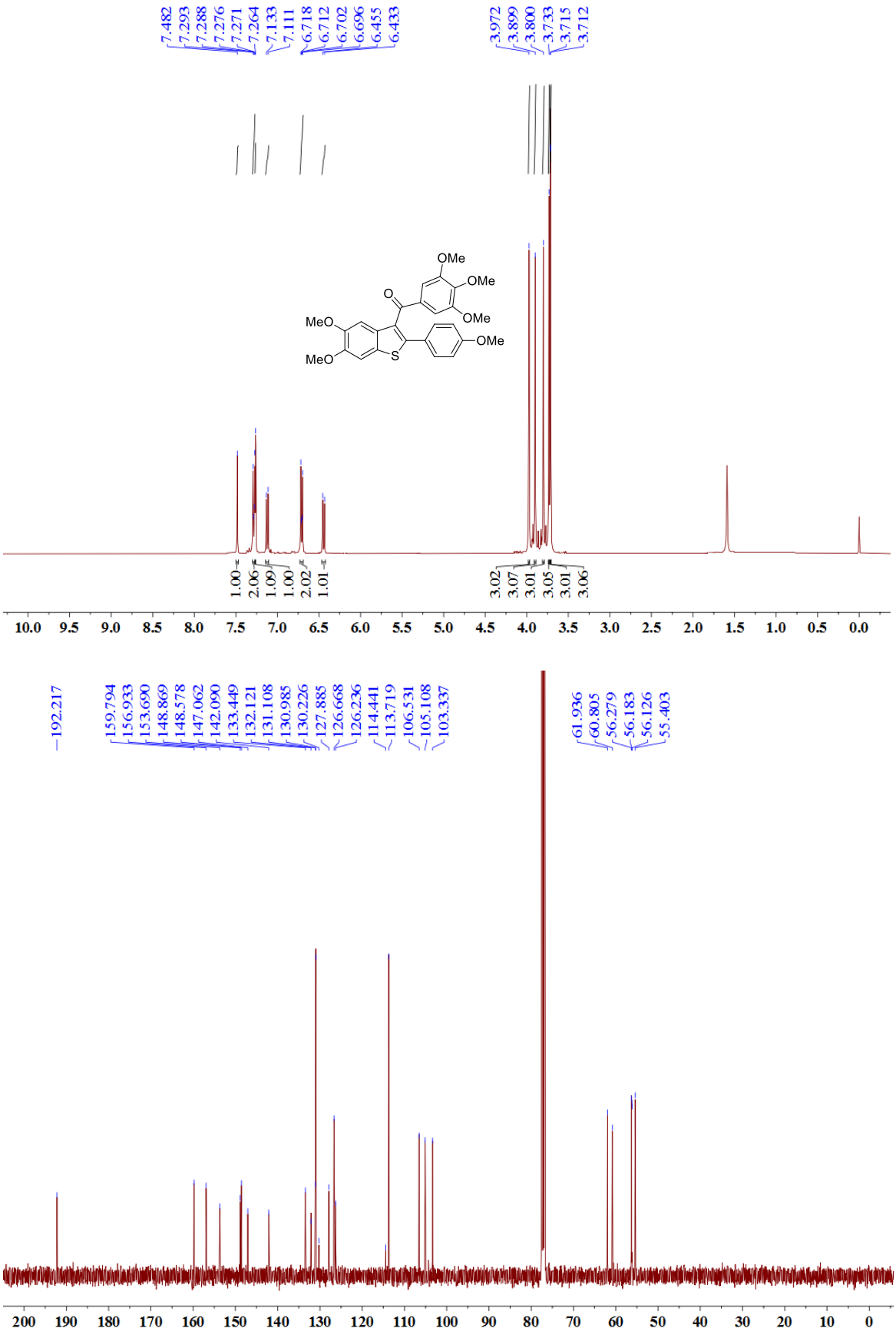
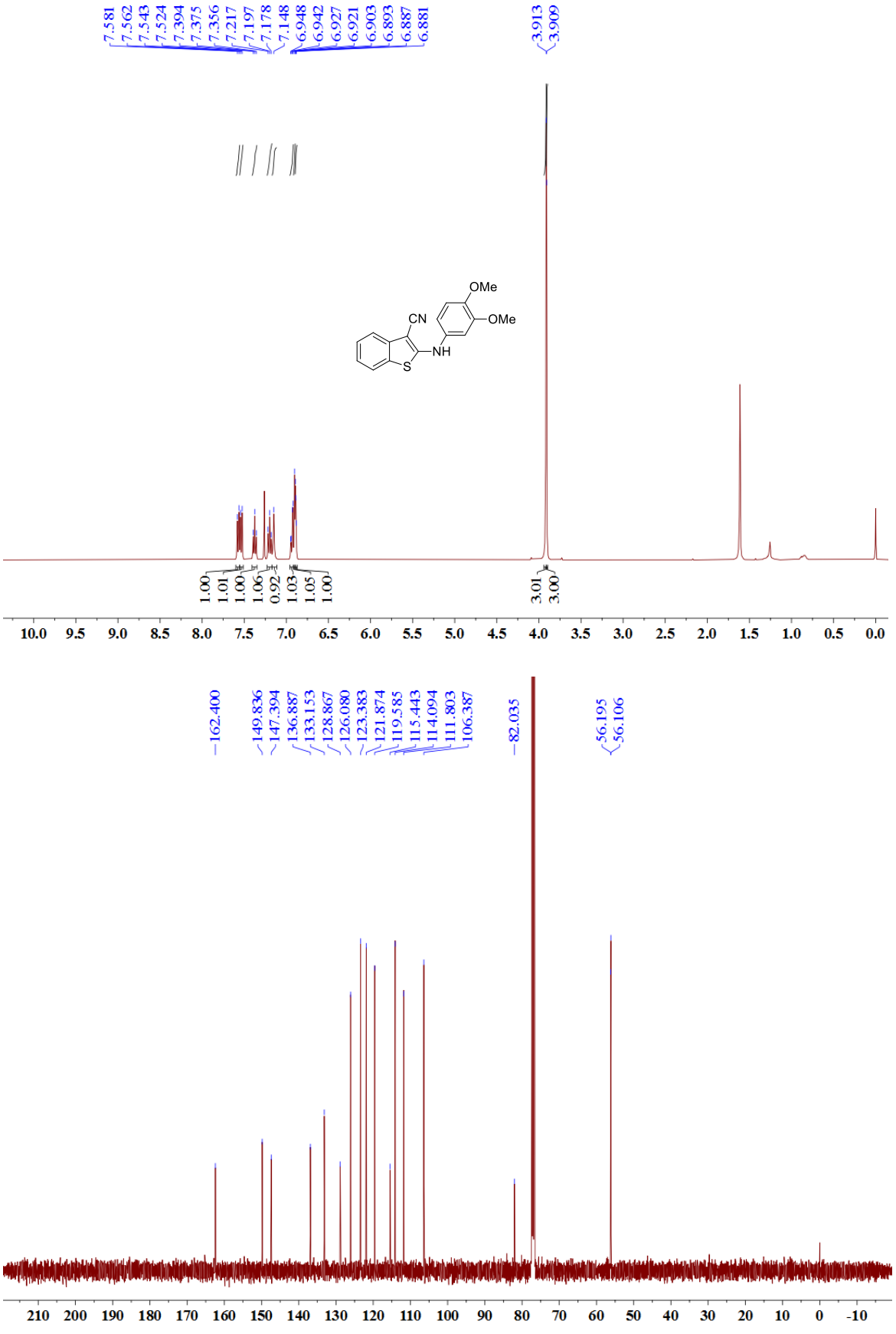


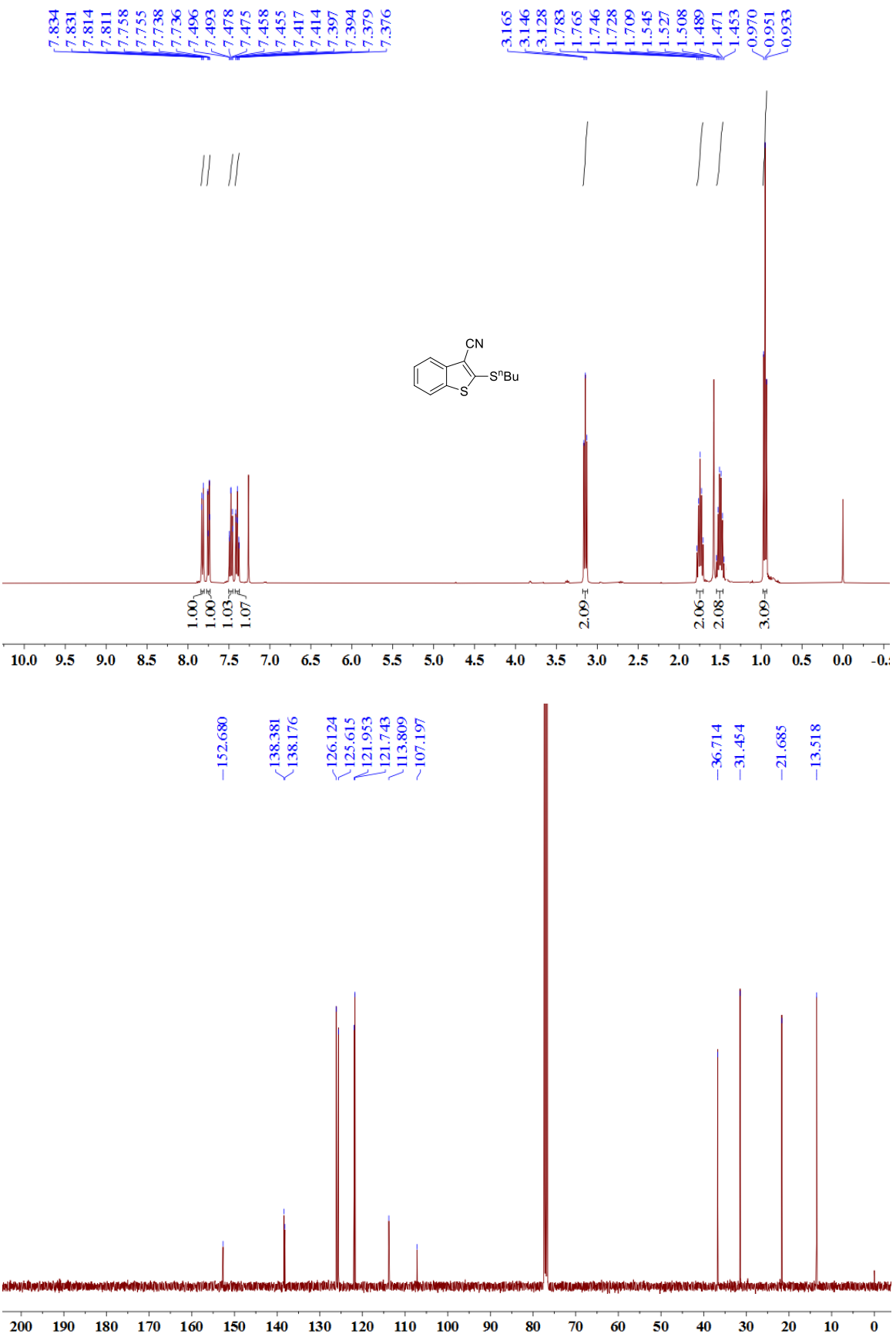
^{1}H and ^{13}C NMR spectra of compound **42r**



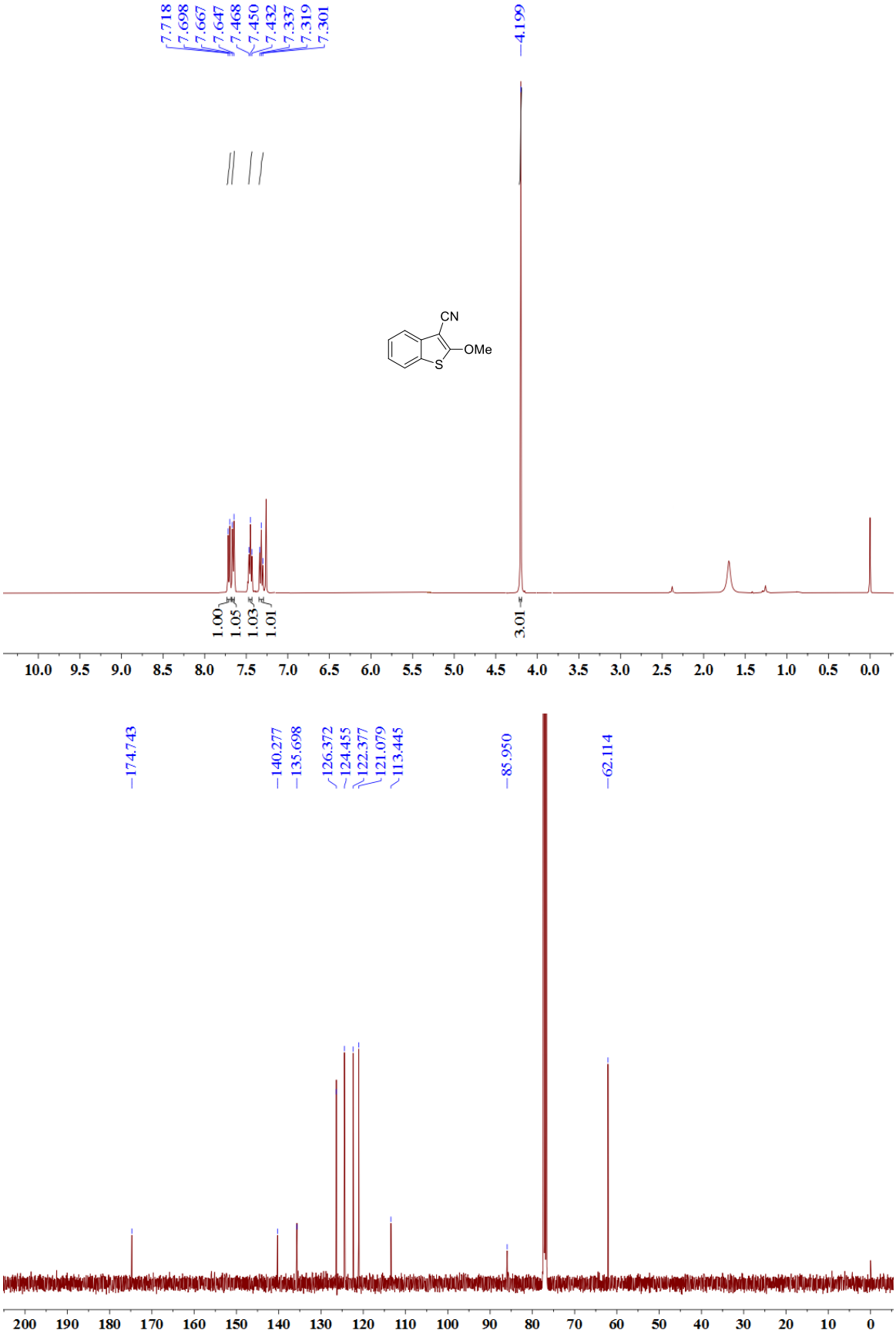
^{1}H and ^{13}C NMR spectra of compound **42s**



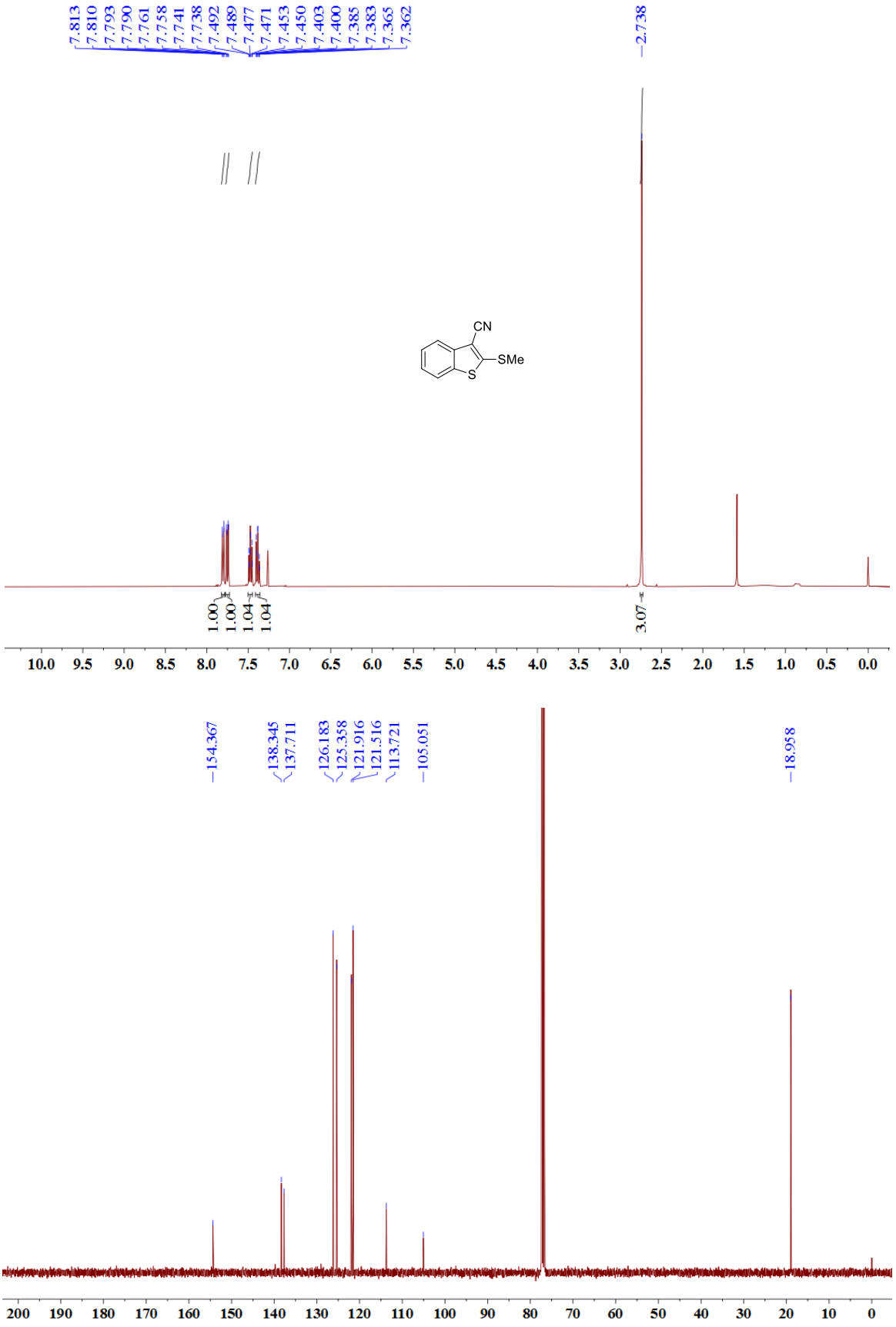
^{1}H and ^{13}C NMR spectra of compound **42t**



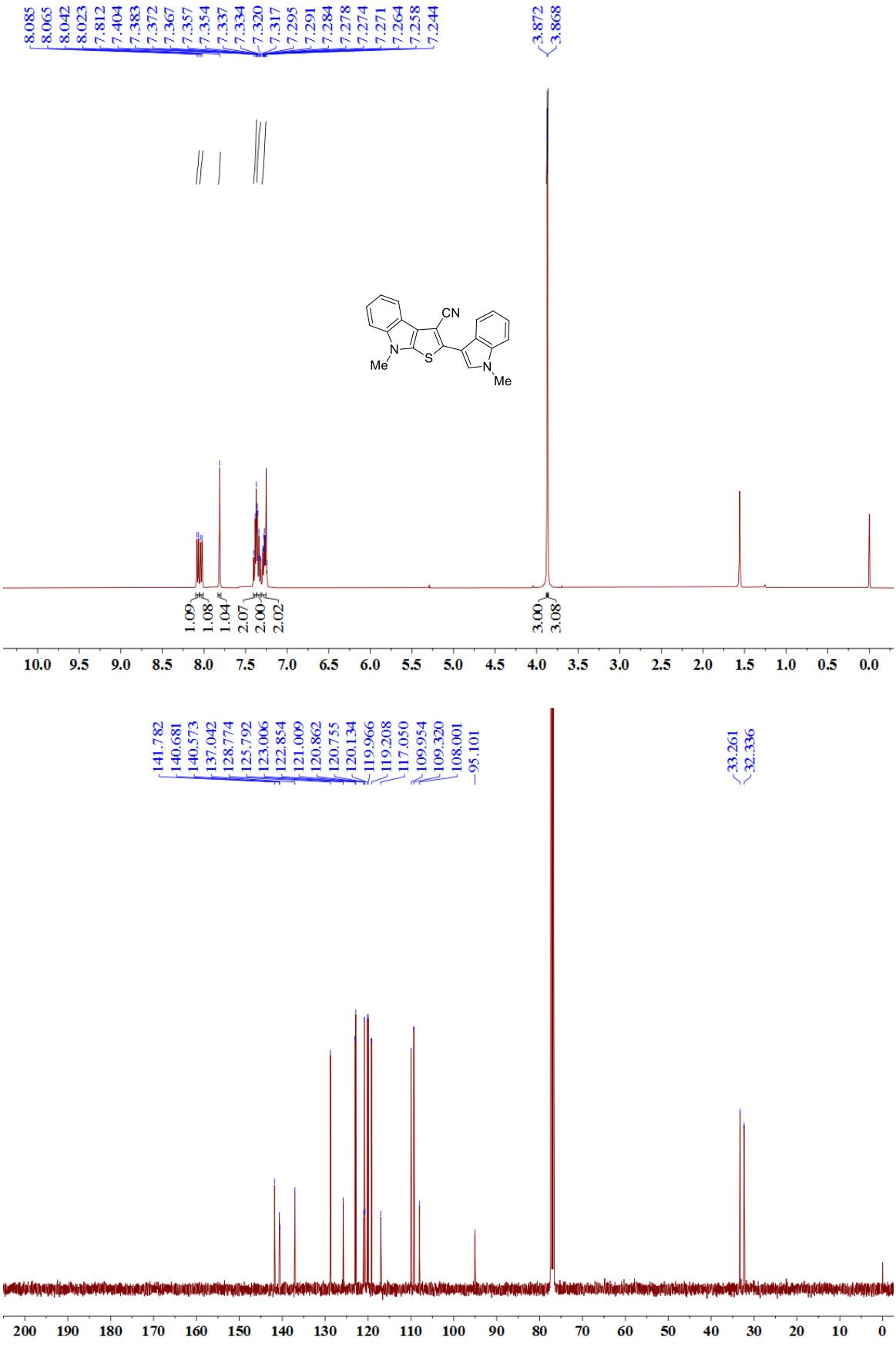
^{1}H and ^{13}C NMR spectra of compound **42u**



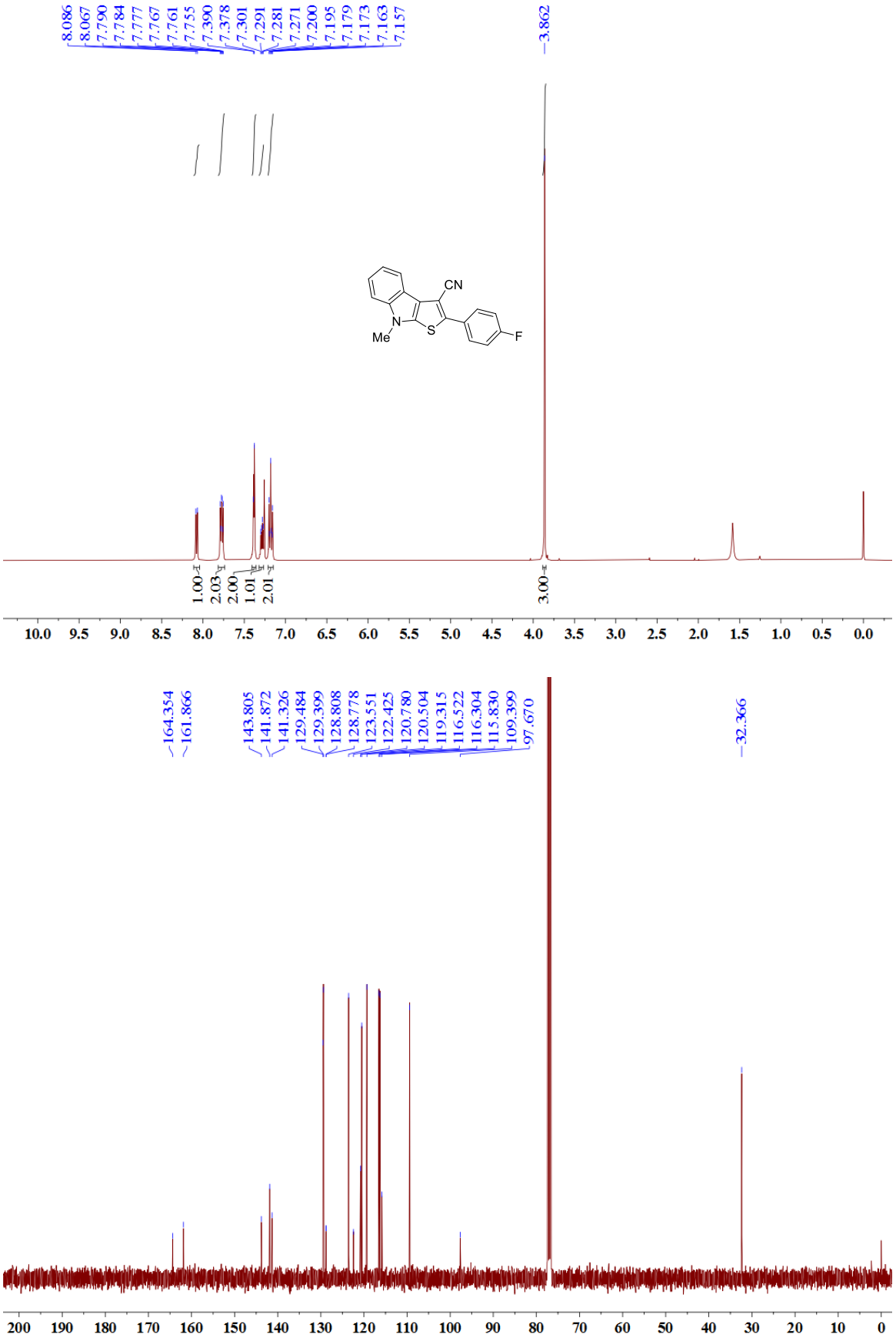
^{1}H and ^{13}C NMR spectra of compound **42v**



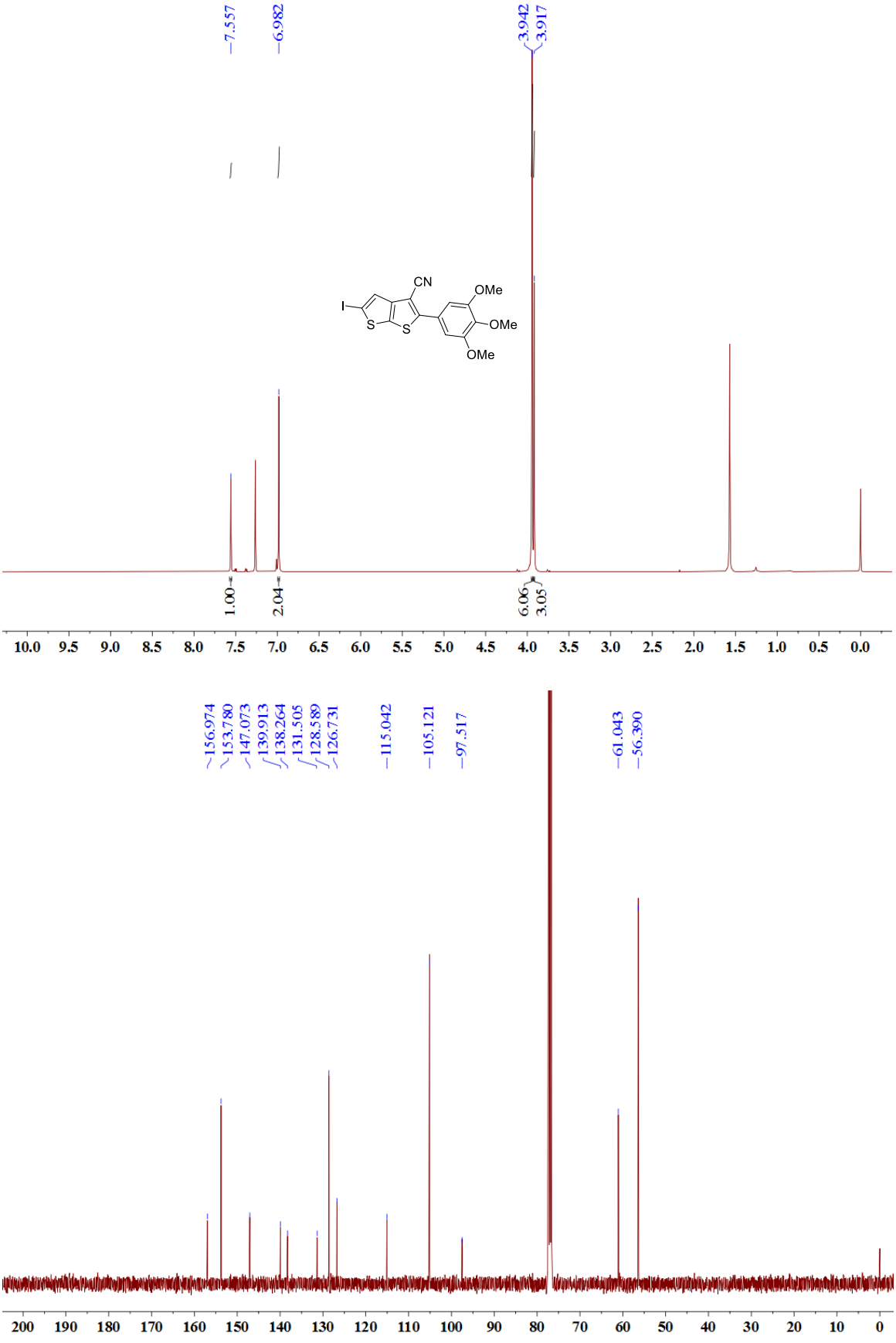
^{1}H and ^{13}C NMR spectra of compound **42w**



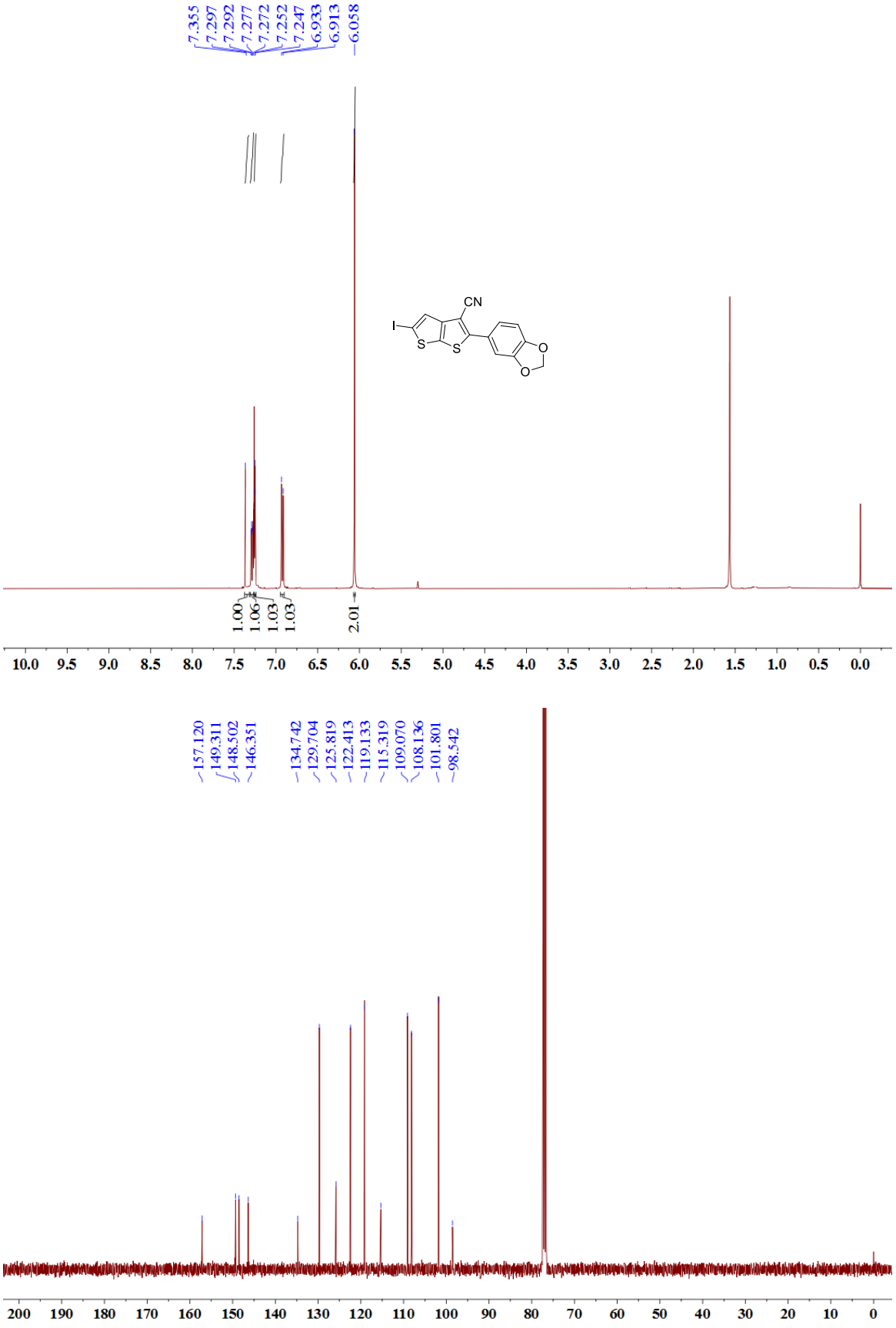
^{1}H and ^{13}C NMR spectra of compound **65a**



^{1}H and ^{13}C NMR spectra of compound **65b**



^{1}H and ^{13}C NMR spectra of compound **66a**



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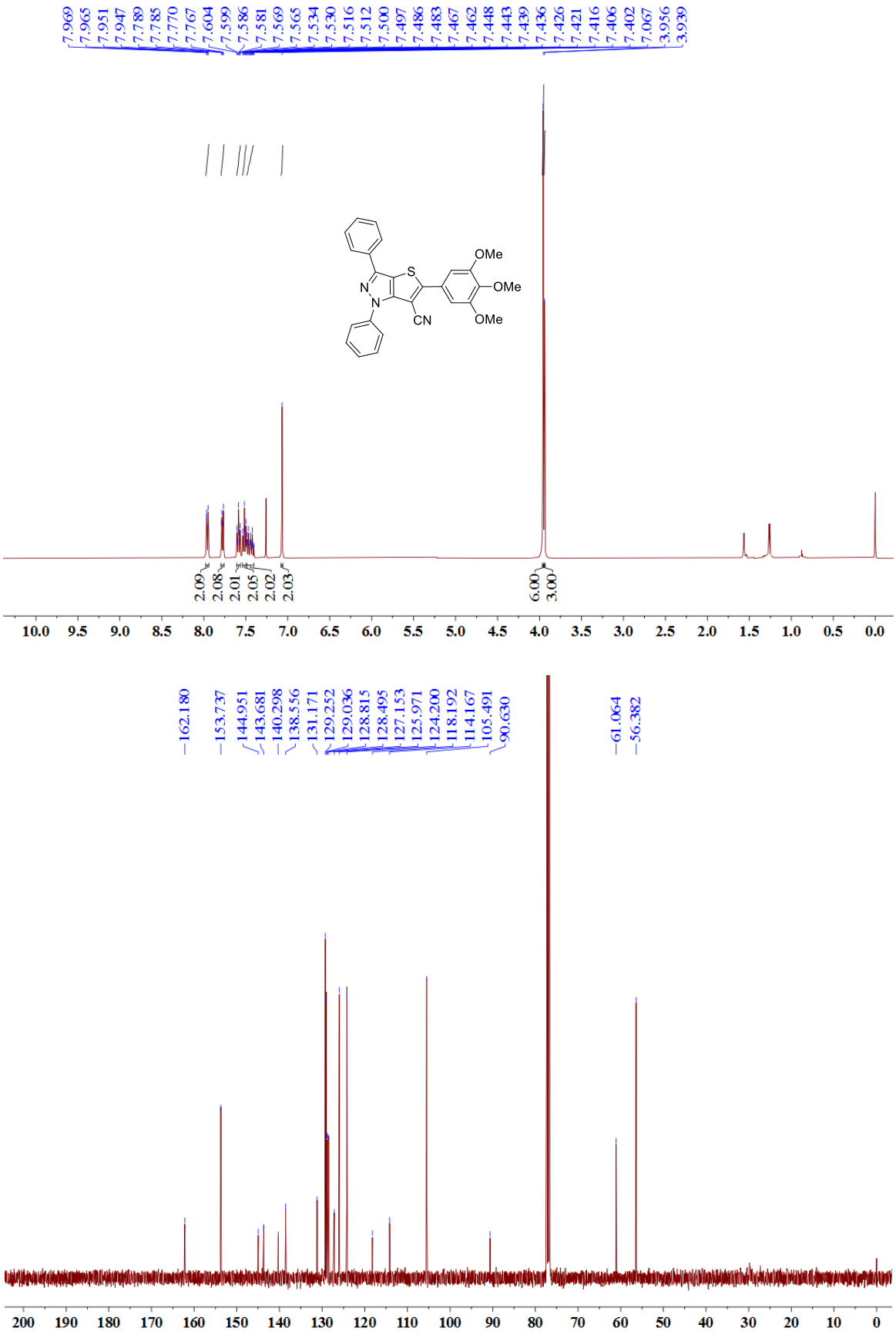
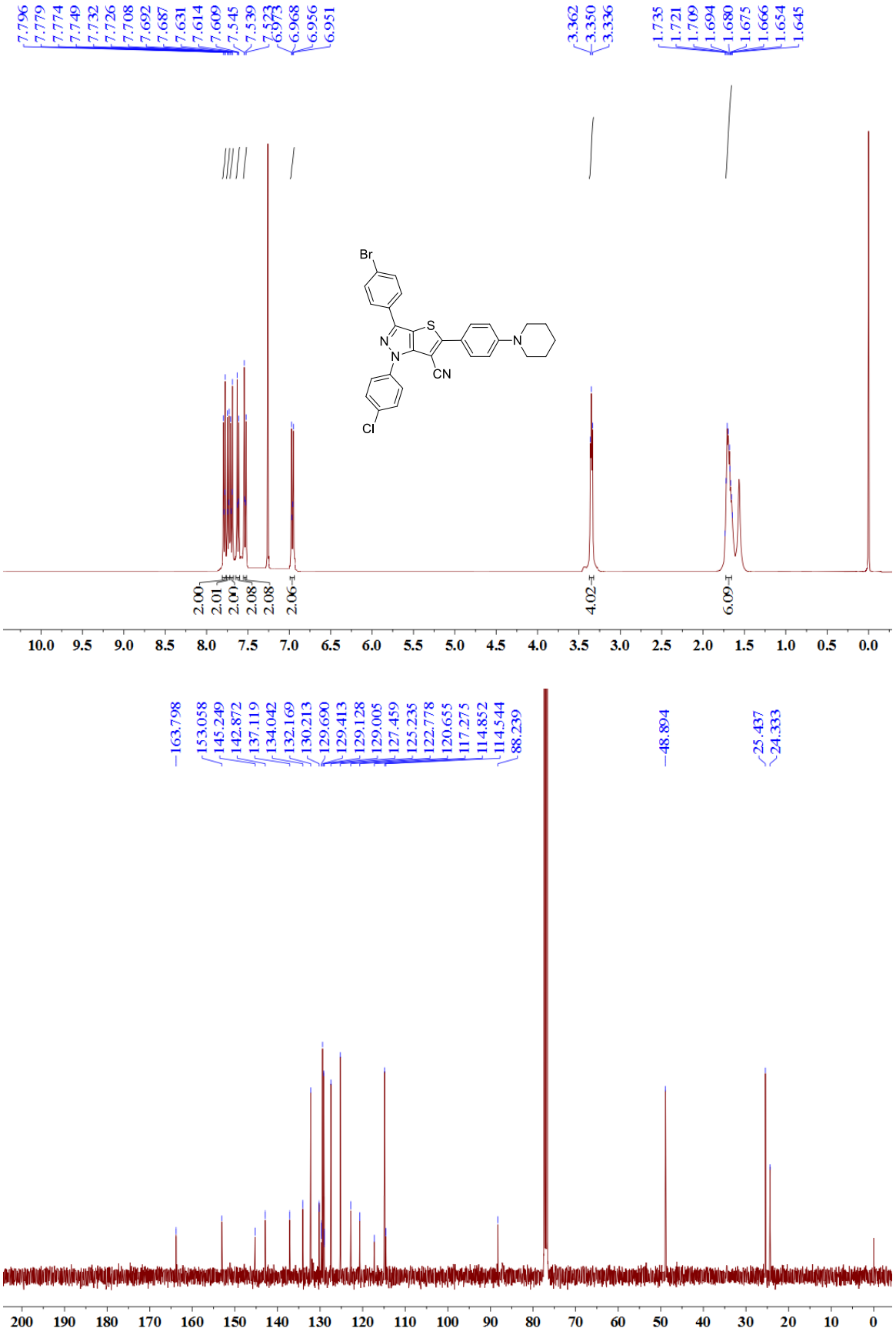
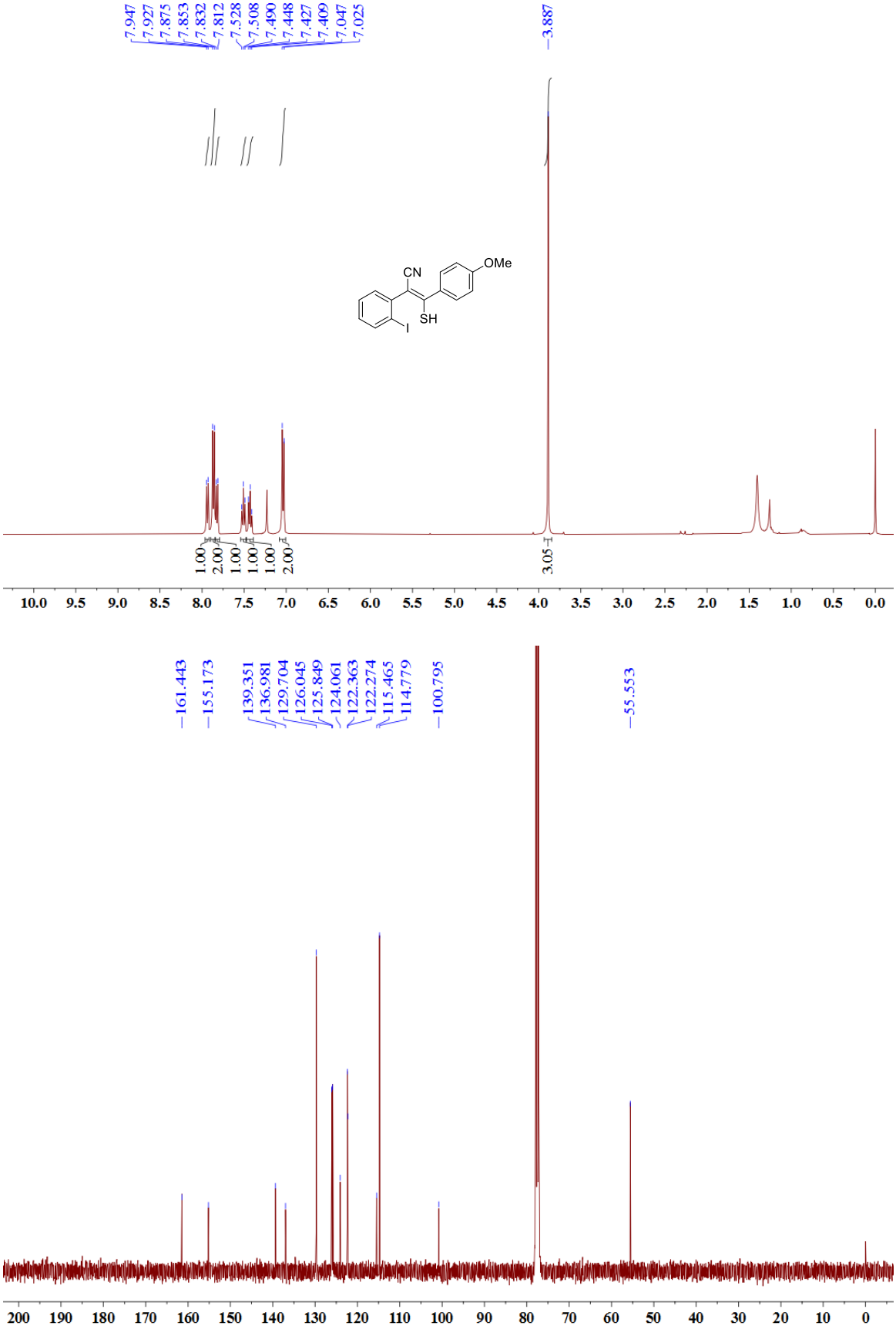


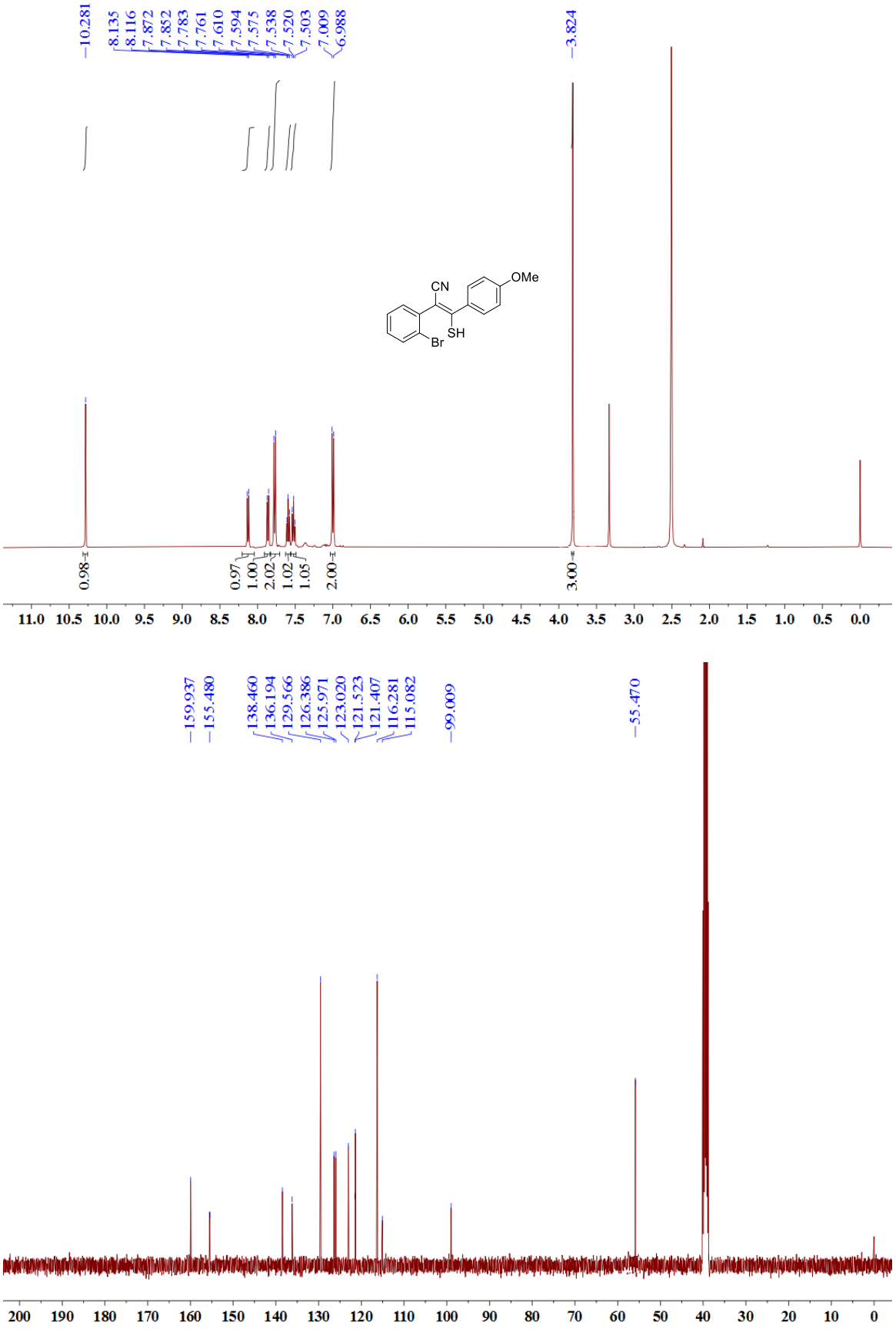
^{1}H and ^{13}C NMR spectra of compound **67a**



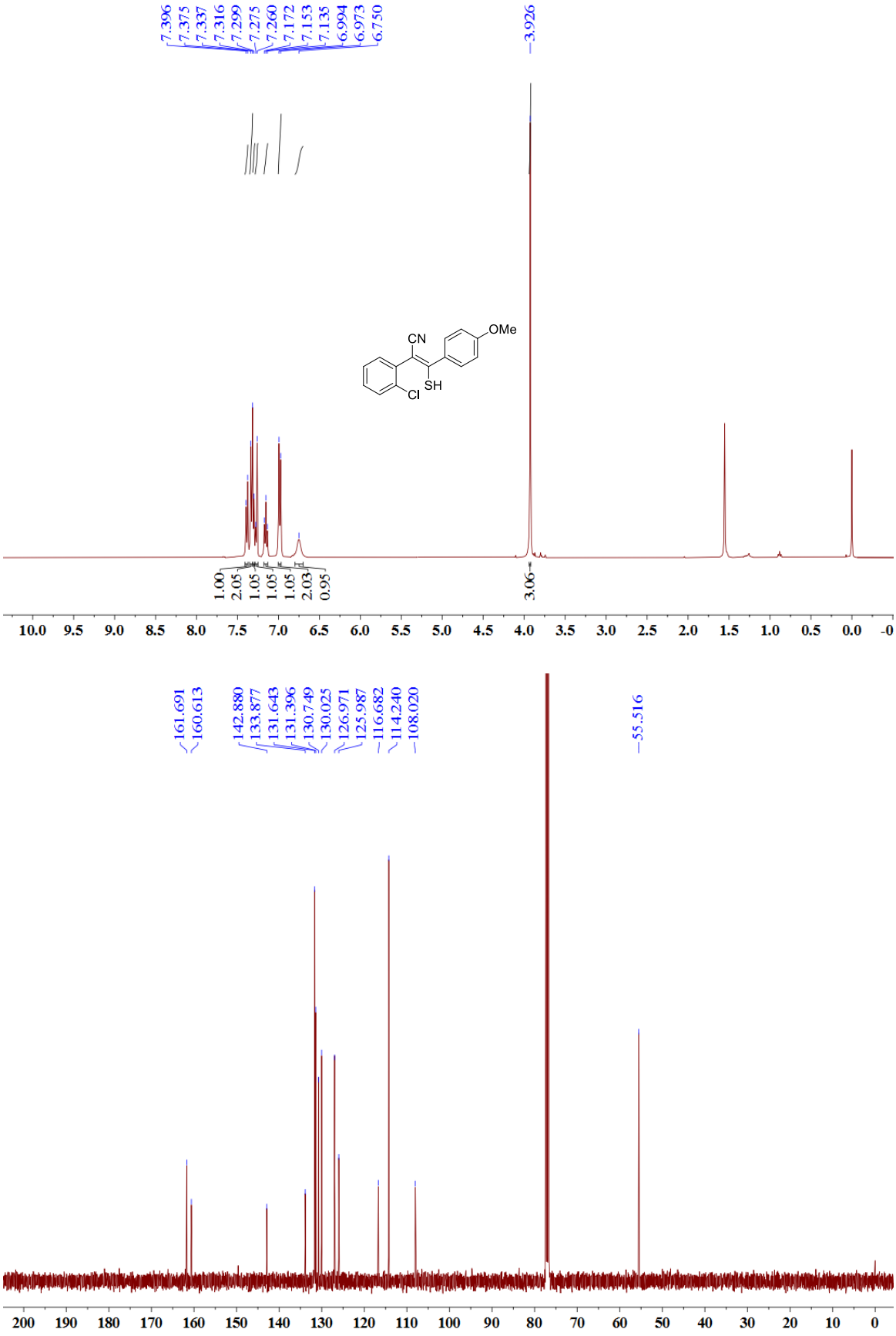
^{1}H and ^{13}C NMR spectra of compound **67b**



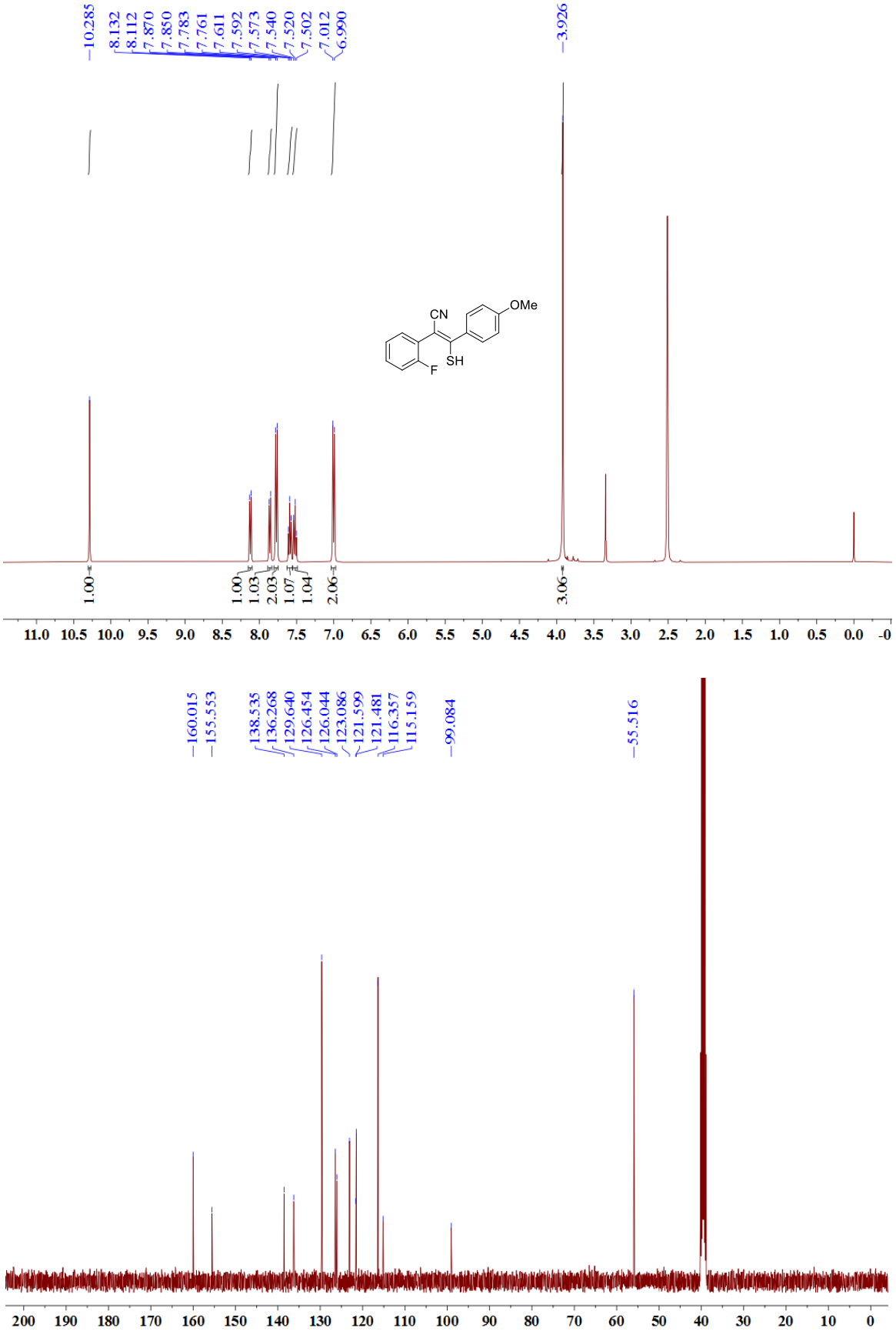
^{1}H and ^{13}C NMR spectra of compound **64a**



^{1}H and ^{13}C NMR spectra of compound **64b**



^{1}H and ^{13}C NMR spectra of compound **64c**



^{1}H and ^{13}C NMR spectra of compound **64d**

Chapter 4

An Efficient One-Pot, Three-Component Route to Novel Push-Pull 1,3-Benzodithiol-2-ylidenes via Copper-Catalyzed Bis-C-S Bond Formation

4.1 Introduction

Since the discovery of conducting properties of tetrathiafulvalene and its derivatives, these molecules have been the subject of extensive studies for their electrochemical properties.[1] Synthesis of a new class of π-extended donors, based on chemical modification of the TTFs framework has been the subject of elaborate study in recent years, to modify their electrochemical properties.[2-3] In this regard, several π-extended dithiafulvalenes such as **B** have also been synthesized and several novel 1,1'-bis(1,3-benzo-dithiol-2-ylidene)heteroaryl/aryl ferrocenes derivatives **C** have also emerged as a new class of electron donor compounds (Schemes 5-6).

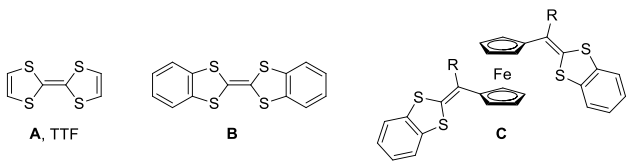


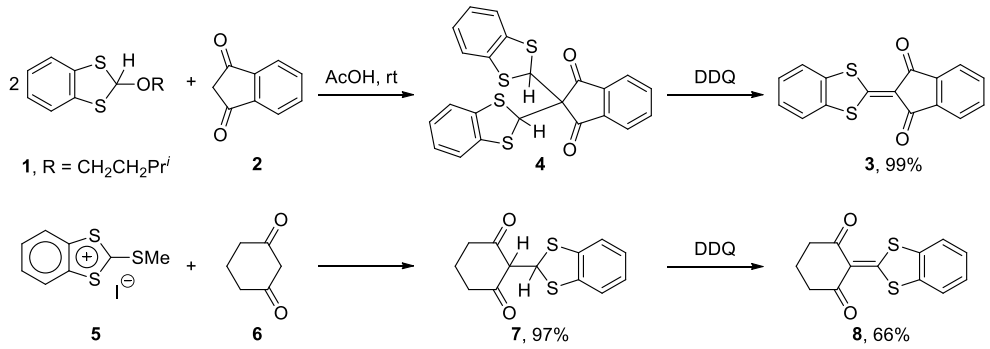
Figure 1. Chemical modification of tetrathiafulvalene

*The overall results of the study described in this chapter have been published in *Tetrahedron. Letters.* **2022**, *102,* 153951.

Our own interest in the synthesis of these classes of compounds is derived from our longstanding contribution toward exploring synthetic applications of α-oxoketene dithioacetals and related polarized ketene dithioacetals for developing novel routes for five- and six-membered heterocycles and their benzo-fused analogs.[4] These intermediates have proved to be versatile building blocks and have been the subject of several reviews.[5] The most general method for synthesis of these intermediates, involves the reaction of active methylene ketones and other compounds with carbon disulfide in presence of base followed by bis-*S*-alkylation of resulting thioate salts. During the course of these studies, we became interested in developing new general routes for the related push-pull α-(1,3-benzothiol)-2-ylidene such as **30**, which have been scarcely explored in terms of their reactivity and physiochemical properties (Scheme 9-12). Before presenting our work, we have given a short literature survey of previous syntheses of these classes of compounds.

4.2 Synthesis of 1,3-Benzodithiol-2-ylidene Derivatives: A Short Literature Survey

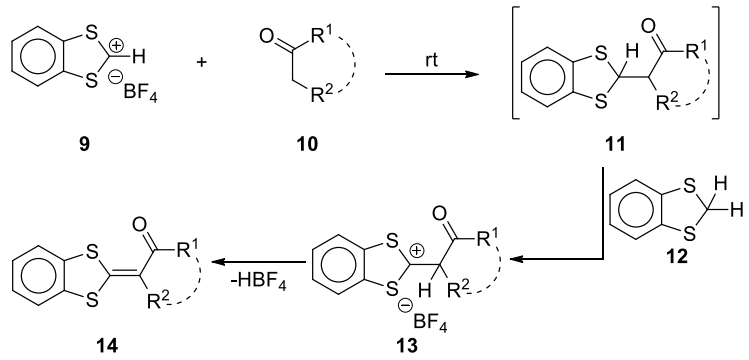
In an isolated study, α-(1,3-benzodithiol-2-yidene) ketone **3** derived from indanone has been reported, to be synthesized by reacting 1,3-indanedione **2** with 2-alkoxy-1,3-benzodithiole **1**, in acetic acid at room temperature to give 2,2-bis(1,3-benzodithiol-2-yl)1,3-indanedione **4**, which on oxidation with DDQ gave 2,3-benzo-6,7-benzodithiafulavene 1,4-quinone **3** in nearly quantitative yields (Scheme 1).[6a] The corresponding 2-(1,3-benzodithiol-2-ylidene cyclohexane 1,3-dione **8** was also prepared by reaction of 2-methylthio-1,3-benzodithiolanylium methyl-sulfate salt **5** with 1,3-cyclohexanedione **6** and subsequent oxidation of dihydro derivative **7** with DDQ was yielded 66% (Scheme 1).[6]



Scheme-1

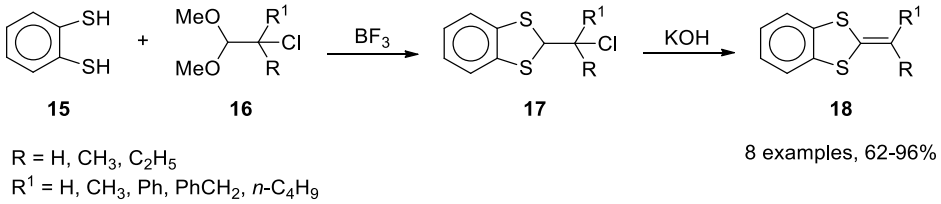
In an improved procedure, α-(1,3-benzodithiol-2-yidene) ketones **14** have been prepared by reacting a series of cyclic and acyclic active methylene ketones with two

equivalents of 1,3-benzothiolylium tetrafluoroborate salt **9** at room temperature (Scheme 2).[7] The hydride abstraction by **9** from initial product **11** occurs to produce 2-(2-oxocyclopentyl)-1,3-benzodithiolylium salt **13** and 1,3-benzodithiole **12**. Deprotonation of the newly formed dithiolylium salt **13**, during workup, gives the above dithioacetals **14**. Yields were good for cyclic ketones but moderate for acyclic ketones, besides the reaction was limited only to a few active methylene ketones (Scheme 2).[7]



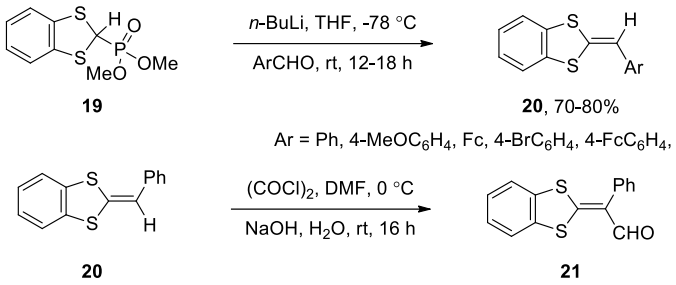
Scheme-2

2-Akylidene-1,3-benzodithioles **18** have also been obtained by boron trifluoride promoted transdithioacetalization of *α*-chloroacetals **16** with 1,2-benzodithioles **15** to afford 2-(1-chloroalkyl)-1,3-benzodithioles **17** in good yields, which on-base mediated dehydrochlorination afford **18** in satisfactory yields (Scheme 3).[8]



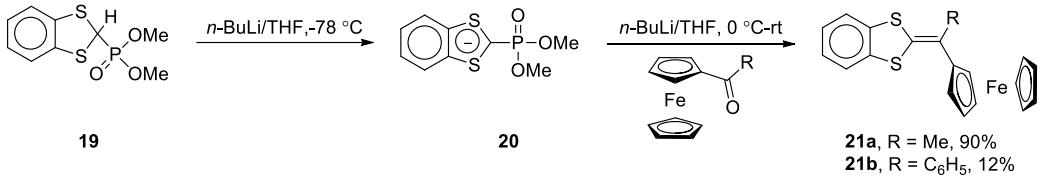
Scheme-3

2-Alkyl/arylidene-1,3-benzodithioles, (1,4-dithiafulavenes) **20** have also been obtained by Wittig-Horner reaction with dimethyl 1,3-benzodithiol-2-ylphosphonate **19** by deprotonation with butyl lithium under anhydrous conditions and subsequent reaction of the resulting anion with various aldehydes (Scheme 4).[9-10] Vilsmeier reaction on **20** affords benzodithioles **21** with aldehyde functionality (Scheme 4).[10]

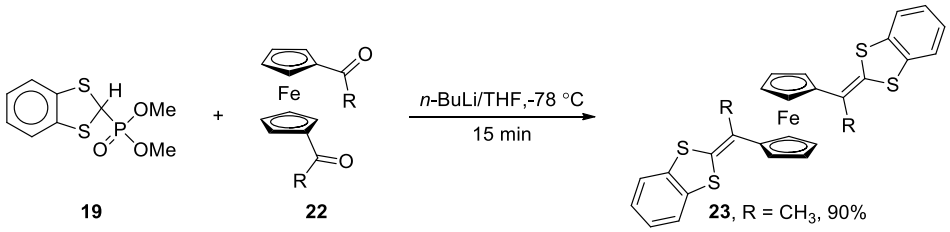


Scheme-4

This Wittig Horner method has been recently extended for the synthesis of a few of the 1,3-benzodithilydene containing ferrocene moieties such as **21**, **23** by reaction between 2-dimethoxyphosphinyl 1,3-benzodithiole **19** and ferrocenyl ketones in presence of butyllithium (Schemes 5 and 6).[11-12] The 2-dimethoxyphosphinyl-1,3-benzodithiole**19** was prepared in several steps starting from anthranilic acid in four steps via diazotization .[11a]

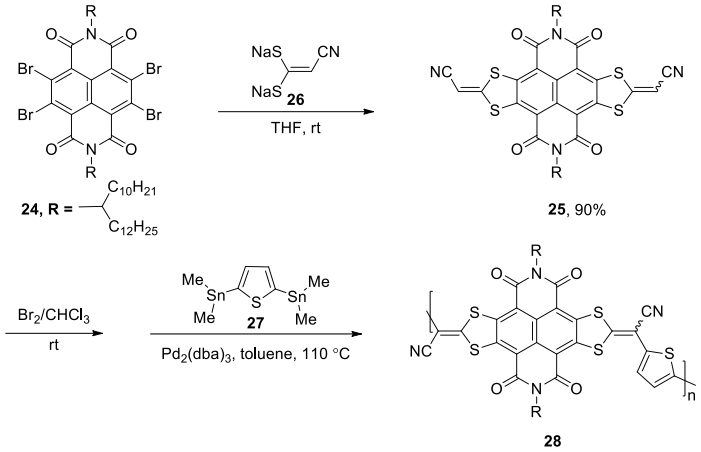


Scheme-5



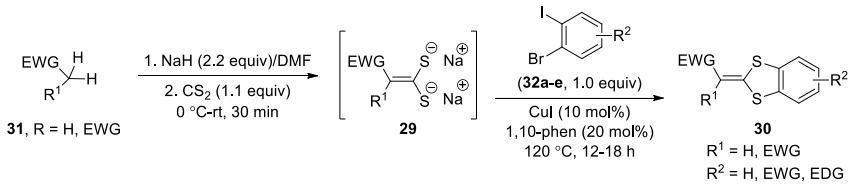
Scheme-6

In a recent paper, naphthalenediimide fused with 2-(1,3-dithiol-2-ylidene) acetonitrile such as **28** have been synthesized as strong electron-deficient building blocks for high-performance n-type polymeric semiconductors *via* aromatic nucleophilic substitution of *α*-cyanobismethylthio acetal **26** with tetrabromobisnaphthalenediimides **24**, followed by bromination and Stille coupling with various aryl tin monomeric units (Scheme 7).[13]



Scheme-7

We have developed a one-pot three-component synthesis of these compounds by reaction of active methylene compounds with carbon disulfide in presence of sodium hydride followed by copper-catalyzed bis-C-S bond formation with 1-bromo-2-iodobenzenes (Scheme 8).



Scheme-8

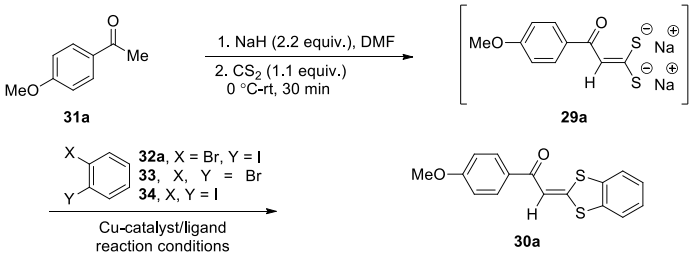
4.3 Result and Discussion

We planned to synthesize push-pull 1,3-benzothiazol-2-ylidenes of the general structure **30** via three-component one-pot coupling of dithioate salts of the general structure **29** generated by the reaction of active methylene compounds **31** in presence of a base, followed by the copper-catalyzed bis-C-S bond formation of the resulting dithioate salts with 1-bromo-2-iodobenzenes **32** (Scheme 8).

The synthesis of 2-(4-methoxy)benzoylidene-1,3-benzodithiole **30a** was chosen for optimization studies starting from 4-methoxyacetophenone **31a** as active methylene compounds, carbon disulfide and 1-bromo-2-iodobenzene **32**a coupling agent (Table 1). Optimization studies were performed with cuprous iodide as a catalyst, as it gave the best yields in comparison to other copper salts (Table 1, entries 11-12). Thus when 4-methoxyacetophenone **31a** and carbon disulfide were reacted with sodium hydride in DMF

at room temperature, the resulting dithiaote salt **29a** was subjected to intermolecular bis-C-S coupling in the presence of 5 mol% of cuprous iodide at 90 ^{0}C, and L-proline as a ligand (20 mol%) yielding the 1,3-benzothiazol-2-ylidene **30a** in moderate yield (entry 1). When catalyst loading was increased to 10 mol%, **30a** was obtained in an improved yield of 61% (entry 2). However, a dramatic increase in yield of **30a** was observed when 1,10-phenanthroline (20 mol%) was employed as a ligand instead of L-proline (entry 3). The yield of **30a** was further increased when the reaction was carried out at a higher temperature (120 ^{0}C). The use of other ligands such as DMEDA or *trans*-1,2-diaminocyclohexane afforded the 1,3-benzothiazol-2-ylidenes **30a** in decreased yields under identical conditions (entries 5-6). We, therefore, selected 1,10-phenanthroline (20 mol%) as ligand, with CuI (10 mol%) as a catalyst at 120 ^{0}C for optimized conditions (entry 4). Use of other bases

Table 1. Optimization of reaction conditions for the synthesis of **30a**[a]



entry	Cu-catalyst (mol%)	ligand (20 mol%)	base	temp (°C)	time (h)	% yield, **30a**[a]
1	CuI (5 mol%)	L-proline	NaH	90	24	50
2	CuI (10 mol%)	L-proline	NaH	90	24	61
3	CuI (10 mol%)	1,10-phen	NaH	90	24	73
4	**CuI (10 mol%)**	**1,10-phen**	**NaH**	**120**	**12**	**82**
5	CuI (10 mol%)	DMEDA	NaH	120	18	74
6	CuI (10 mol%)		NaH	120	18	72
7	CuI (10 mol%)	1,10-phen	K_2CO_3	120	18	68
8	CuI (10 mol%)	1,10-phen	Cs_2CO_3	120	18	75
9	CuI (10 mol%)	1,10-phen	K_3PO_4	120	18	65
10	CuI (20 mol%)	1,10-phen	NaH	120	12	80
11	CuCl (10 mol%)	1,10-phen	NaH	120	18	70
12	CuBr (10 mol%)	1,10-phen	NaH	120	15	73
13[b]	CuI (10 mol%)	1,10-phen	NaH	120	18	74
14[c]	CuI (10 mol%)	1,10-phen	NaH	120	8	80

[a]Reaction conditions. **31a** (1 mmol), **32a**, **33-34** (1 mmol) in DMF under N_2 atmosphere. [b]with 1,2-dibromobenzene **33**, [c]with 1,2-diiodobenzene **34**. Yields of pure isolated product.

such as K_2CO_3, Cs_2CO_3, or K_3PO_4 yielded 1,3-benzothiazol-2-ylidene **30a** only in reduced yield in comparison to entry 4. Similarly, cuprous iodide (10 mol%) was found to be the best catalyst in comparison to other copper catalysts such as CuCl and CuBr (entries 11-12). When 1,2-dibromobenzene **33** was employed as a dihalo-coupling partner, the 1,3-benzodithiol-2-ylidene **30a** was obtained in decreased yield under similar conditions (entry 13). On the other hand, the use of 1,2-diiodobenzene **34** as a dihalo-coupling agent, gave **30a** in parallel yield, with a shorter reaction time within 8 hr (entry 14). However, because of the higher cost of 1,2-diiodobenzene **34** and ease of preparation of substituted 1-bromo-2-iodobenzenes (**32b-e**), we continued our study with 1-bromo-2-iodobenzenes **32**, as 1,2-dihalo-precursors.

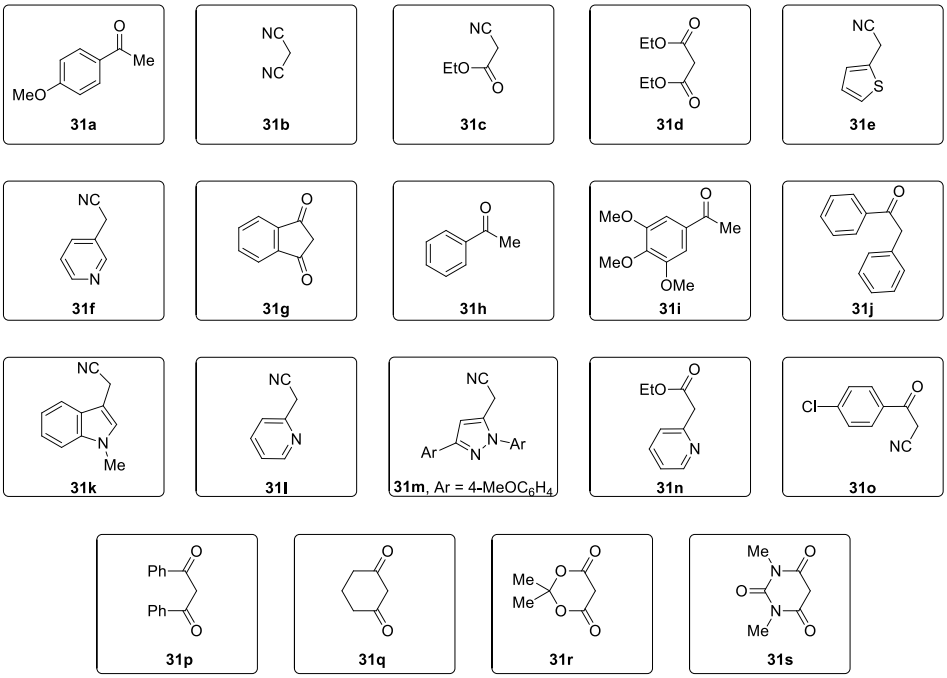


Chart 1. Various active methylene compounds employed for the synthesis of **30**

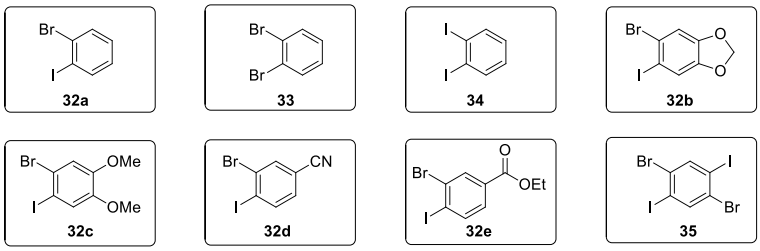
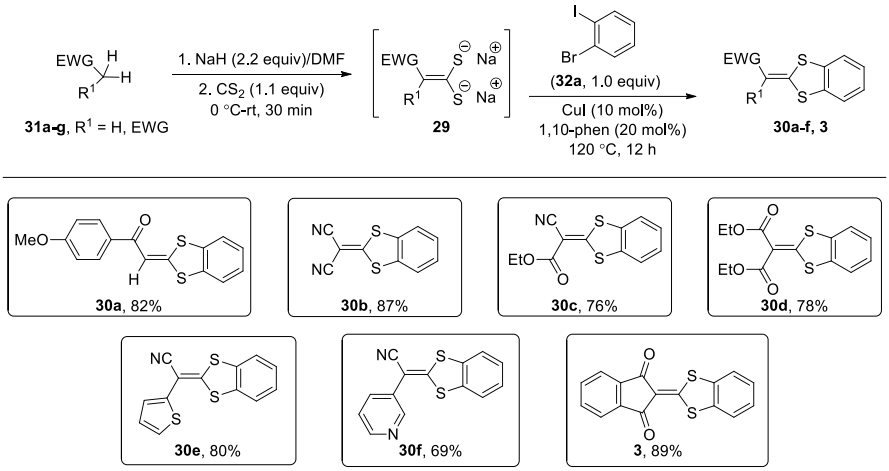


Chart 2. Various halo-compounds employed for the synthesis of **30**

After having established optimized conditions for the synthesis of 2-(4-methoxy)benzoylidene-1,3-benzodithiole **30a**, we next explored the generality of the methodology for the synthesis of a wide range of push-pull 1,3-benzodithio-2-ylidenes **30**, from a variety of active methylene, compounds **31** (Chart 1) and substituted 1-bromo-2-iodo benzenes **32a-e** with both electron-donating, as well as electron-withdrawing groups (Chart 2) and the results are shown in Scheme 9-12. Thus, doubly activated active methylene compounds such as malononitrile (**31b**), ethyl cyanoacetate (**31c**), diethyl malonate (**31d**), thiophene-2-acetonitrile (**31e**), 3-pyridylacetonitrile (**31f**) and 1,3-indanedione (**31g**) reacted smoothly with carbon disulfide in the presence of sodium hydride and the resulting dithioate salts **29** underwent smooth CuI catalyzed bis-C-S bond formation with 1-bromo-2-iodobenzene **32a,** yielding the corresponding push-pull 1,3-benzodithiol-2-ylidenes **30b-f**, and **3** respectively in high yields (Scheme 9)

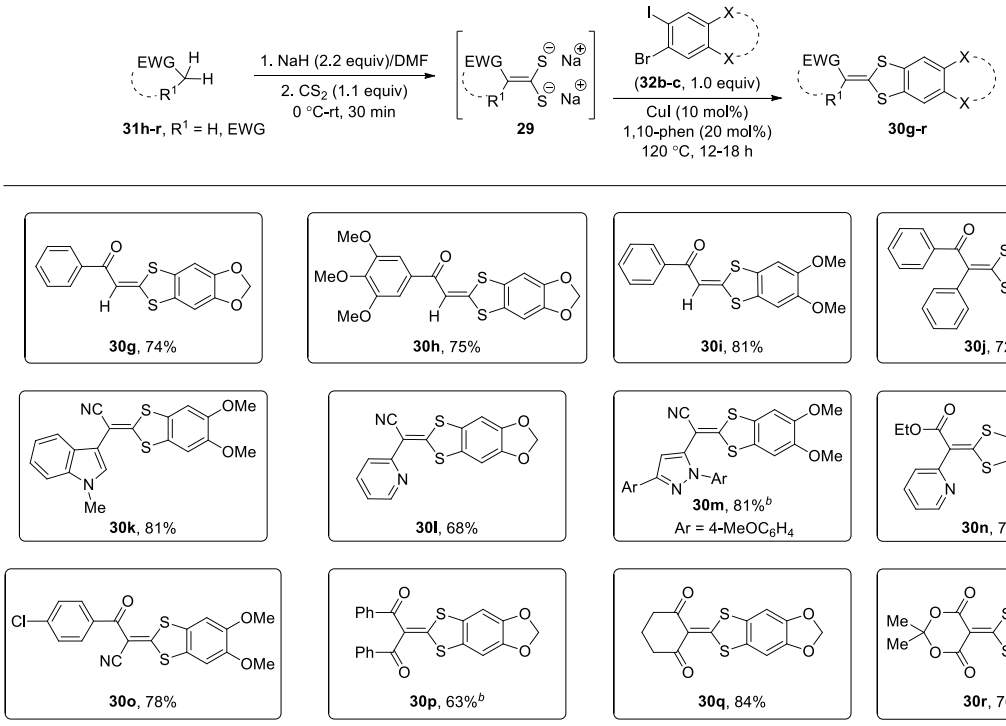


[a]Reaction conditions. **31a-g** (1 mmol), NaH (2.2 equiv.), CS_2 (1.1 equiv.), **32a** (1 mmol), CuI (10 mol%) and 1,10-phen (20 mol%) in DMF under N_2 atmosphere for 12 h at 120 ºC. Yields of pure isolated product

Scheme-9

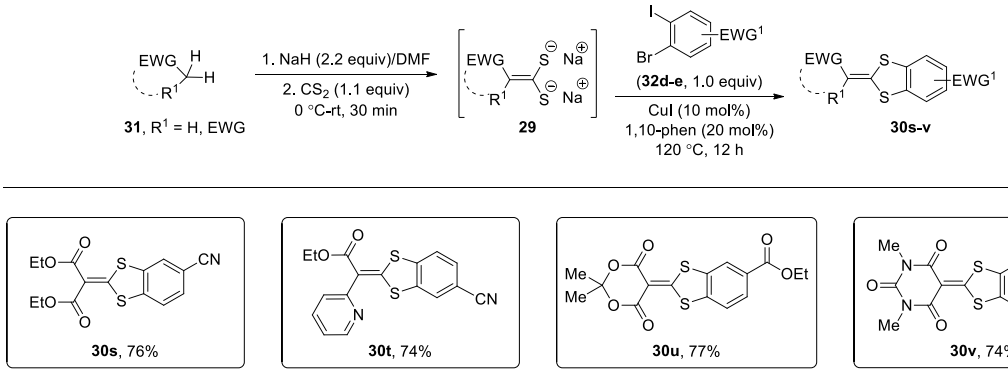
We next explored copper-catalyzed C-S bond formation of a few dithioate salts **29** derived from various active methylene compounds **31h-r** with 1-bromo-2-iodobenzenes **32b-c**, bearing electron-donating substituents (Chart 2). Thus the dithioate salts derived from various acyclic active methylene ketones like acetophenone (**31h**), trimethoxy acetophenone (**31i**), deoxybenzoin (**31j**), indole-3-acetonitrile (**31k**), 2-pyridylacetonitrile (**31l**), pyrazole-4-acetonitrile (**31m**), 2-pyridylacetate (**31n**), 4-chlorobenzoylacetonitrile (**31o**), and dibenzoyl methane (**31p**) underwent copper-catalyzed C-S bond formation with these electron-rich 1,2-dihalobenzenes **32b-c** yielding the desired 2-alkylidene-1,3-benzodithioles **30g-30p** in high yields, except in case of dibenzoyl methane, some amount

of debenzoylated product **30g** was isolated in 12% yield (Scheme 10). The cyclic 1,3-cyclohexanedione **31q** and Meldrum's acid **31r** also reacted smoothly with respective **32b** under identical conditions furnishing the products **30q-r** in high yields (Scheme 10).



[a]Reaction conditions. **31h-r** (1 mmol), NaH (2.2 equiv.), CS_2 (1.1 equiv.), **32b-c** (1 mmol), CuI (10 mol%) and 1,10-phen (20 mol%) in DMF under N_2 atmosphere for 12 h at 120 ºC. [b]15-18 h at 120 ºC. Yields of pure isolated product

Scheme-10



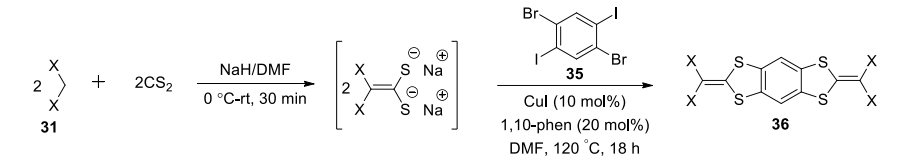
[a]Reaction conditions. **31** (1 mmol), NaH (2.2 equiv.), CS_2 (1.1 equiv.), **32d-e** (1 mmol), CuI (10 mol%) and 1,10-phen (20 mol%) in DMF under N_2 atmosphere for 12 h at 120 ºC. Yields of pure isolated product

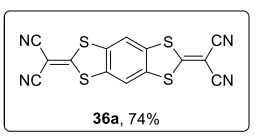
Scheme-11

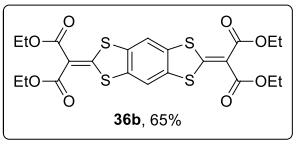
Similarly, when 1-bromo-2-iodobenzenes **32d-e** bearing electron-withdrawing groups (CN, CO_2Et), were subjected to Cu-catalyzed cross-coupling with few dithioate

salts **29**, derived from both acyclic and cyclic active methylene compounds, *i.e.* diethyl malonate (**31d**), 2-pyridylacetate (**31n**), Meldrum's acid **31r** and 1,3-dimethyl barbituric acid **31s**, the corresponding substituted 1,3-benzodithiol-2-ylidenes **30s-v** were obtained in good yields (Scheme 11).

We also attempted copper-catalyzed cross-coupling of 1,4-dibromo-2,5-diiodobenzene such as **35** with few dithioate salts derived from malononitrile **31b** and dimethyl malonate **31d**, which successfully afforded the corresponding 2,2'-(benzobis([1,3]dithiole)-2,6-diylidene) derivatives **36a-b** in good yields. However, this reaction was not successful with few active methane like dibenzoyl methane or 1,3-indanediones yielding a complex mixture of products (Scheme 12).







[a]Reaction conditions. **31** (1 mmol), NaH (2.2 equiv.), CS_2 (1.1 equiv.), **35** (0.5 mmol), CuI (10 mol%) and 1,10-phen (20 mol%) in DMF under N_2 atmosphere for 18 h at 120 °C. Yields of pure isolated product

Scheme-12

4.4 Conclusion

In summary, we have developed a high yield, facile, one-pot, three-components route, for the synthesis of novel push-pull 1,3-benzodithiol-2-ylidenes via Cu-catalyzed bis-C-S bond formation of the in situ generated dithioate salts, derived from a variety of active methylene compounds, with 1-bromo-2-iodobenzenes. The new methodology is highly efficient, and versatile, utilizing a large variety of readily available active methylene compounds, showing broad diversity and high yields. The ready availability of a large number of these push-pull 1,3-benzodithiolylidenes gives an opportunity for the study of their reactivity and physicochemical properties, which have not been explored.

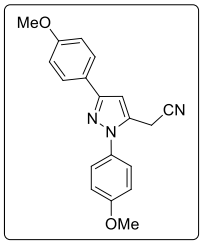
4.5 Experimental Section

4.5.1 General Information. All the reagents were purchased from commercial suppliers and used without further purification. All the reactions were monitored by thin-layer

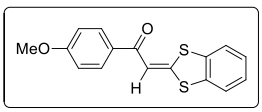
chromatography (TLC) using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100-200 mesh). Nuclear magnetic resonance spectra were recorded on (400 and 600 MHz) FT-NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts were reported in δ (ppm) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6, in ^{1}H NMR, δ 77.16 for $CDCl_3$, and δ 39.52 for DMSO-d_6 in ^{13}C NMR spectra were recorded with the Brucker spectrometer). Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), ddd (double double doublet) dt (doublet of triplet), td (triplet of doublet) and m (multiplet). Infrared spectra of neat samples were recorded in attenuated total reflectance (ATR) mode using an FT-IR instrument, and HRMS spectra were recorded using a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. The active methylene compounds **31a-j**, **31l**, **31n**, and **31p-s** and 1,2-dihalophenyl compounds such as **32a** and **33** were purchased from commercial suppliers, and **31k**,[14] **31m,**[15] **31o**[16] were synthesized according to the reported procedures. All the 1,2-dihalophenyl compounds **32b**,[17] **32c**,[18] **32d-e**[19] and **34**[20] and 1,4-dibromo-2,5-diiodobenzene **35**[21] were prepared according to the reported procedures.

The ^{1}H NMR and ^{13}C NMR spectra of all the compounds are available in supporting information of *Tetrahedron. Letters.* **2022**, *102*, 153951.

2-(1,3-Bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl)acetonitrile (31m).[15] Yield 70% (1.64 g, 0.007 mol); light-brown solid; mp 103-105 °C; R_f 0.44 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3033, 2887, 2238; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 6.6, 2.2 Hz, 2H), 7.37 (dd, *J* = 6.6, 2.2 Hz, 2H) 7.01 (dd, *J* = 6.6, 2.2 Hz, 2H), 6.94 (dd, *J* = 6.6, 2.2 Hz, 2H), 6.73 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.9, 151.9, 132.9, 131.6, 127.2, 127.1, 125.4, 115.9, 114.9,114.2, 104.4, 55.8, 55.4, 16.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_3O_2$ $[M + H]^+$ 320.1399, found 320.1396.



4.5.2 Procedure for the Synthesis of 2-(Benzo[*d*][1,3]dithiol-2-ylidene)-1-(4-methoxyphenyl)methanone (30a). To an ice-cooled stirred suspension of NaH, (60% in mineral oil) (74 mg, 2.2 mmol) in dry DMF (2 mL), a solution of 4-methoxyacetophenone **31a** (150 mg, 1.0 mmol) in DMF (2 mL) was added dropwise over 5 minutes, under N_2 atmosphere, and the stirring was



continued for 10 minutes. Carbon disulfide (84 mg, 67 μL, 1.1 mmol) in DMF (1 mL) was added to the ice-cold reaction mixture and further stirred for 30 minutes at room temperature. After complete consumption of 4-methoxyacetophenone **31a** (monitored by TLC), 1-bromo-2-iodobenzene **32a** (283 mg, 1.0 mmol), CuI (19 mg, 10 mol%) and 1,10-phenanthroline (36 mg, 20 mol%) were added and the reaction mixture stirred for 12 h at 120 ºC (monitored by TLC). It was then cooled to room temperature, and filtered by using a Buchner funnel, on the celite-545 under vacuum. The filtrate was then quenched with saturated NH_4Cl solution (25 mL), extracted with EtOAc (3 X 25 mL) and the combined organic layer was washed with water (2 X 25 mL), brine (25 mL), dried over Na_2SO_4. The organic solvent was evaporated under vacuum, which was further purified by column chromatography, using hexane/ethyl acetate as eluent to give product **30a**. Yield 82% (246 mg, 0.82 mmol); Off-white solid; mp 92-94 °C; R_f 0.35 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3058, 2917, 1716, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 6.8, 2.0 Hz, 2H), 7.57 (dd, J = 6.8, 2.4 Hz, 1H) 7.48 (dd, J = 6.8, 2.0 Hz, 1H), 7.41 (s, 1H), 7.29 (td, J = 4.6, 2.4 Hz, 2H), 6.96 (dd, J = 6.8, 2.0 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 162.9, 161.2, 138.6, 132.6, 131.1, 130.0, 126.6, 126.5, 123.0, 121.7, 113.9, 104.9, 55.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_2S_2$ $[M + H]^+$ 301.0357, found 301.0355.

4.5.3 General Procedure for the Synthesis of 2-Alkyl/arylidene-1,3-benzodithioles 30 and 36. To an ice-cooled stirred suspension of NaH, (60% in mineral oil) (74 mg, 2.2 mmol) in dry DMF (2 mL), a solution of appropriate active methylene compound **31a-s** (1.0 mmol) in DMF (2 mL) was added dropwise over 5 minutes, under N_2 atmosphere, and the stirring was continued for 10-15 minutes. Carbon disulfide (84 mg, 67 μL, 1.1 mmol) in DMF (1 mL) was added to the ice-cold reaction mixture and further stirred for 20-30 minutes at room temperature. After complete consumption of appropriate active methylene compound **31a-s** (monitored by TLC), 1-bromo-2-iodobenzenes **32a-e** (1.0 mmol, for **30**) or 1,4-dibromo-2,5-diiodobenzene **35** (0.5 mmol, for **36**), CuI (19 mg, 10 mol%) and 1,10-phenanthroline (36 mg, 20 mol%) were added and the reaction was stirred for 12-18 h at 120 ºC (monitored by TLC). It was then cooled to room temperature, and filtered by using a Buchner funnel on the celite-545 under vacuum. The filtrate was quenched with saturated NH_4Cl solution (25 mL), extracted with EtOAc (3 X 25 mL) and the combined organic layer was washed with water (2 X 25 mL), brine (25 mL), and dried over Na_2SO_4. The organic solvent was evaporated under vacuum, which was further purified by column

chromatography using hexane/ethyl acetate as eluent to give corresponding product **30** or **36**.

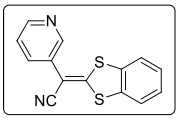
2-(Benzo[*d*][1,3]dithiol-2-ylidene)malononitrile (30b). Obtained from malononitrile **31b** and 1-bromo-2-iodobenzene **32a**, yield 87% (188 mg, 0.87 mmol); light-yellow solid; mp 238-240 °C; R_f 0.45 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3062, 2207, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (m, 2H), 7.49-7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 134.9, 128.0, 124.2, 113.4, 61.7; HRMS (ESI) *m/z* calcd for $C_{10}H_4N_2S_2$ $[M]^+$ 215.9816, found 215.9803.

Ethyl 2-(benzo[*d*][1,3]dithiol-2-ylidene)-2-cyanoacetate (30c). Obtained from ethyl 2-cyanoacetate **31c** and 1-bromo-2-iodobenzene **32a**, yield 76% (200 mg, 0.76 mmol); pale-yellow solid; mp 135-137 °C; R_f 0.61 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3048, 2930, 2204, 1739, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H), 7.43-7.40 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 163.8, 138.3, 133,2, 127.4, 127.2, 122.9, 122.5, 115.6, 85.2, 61.9, 14.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{10}NO_2S_2$ $[M + H]^+$ 264.0153, found 264.0128.

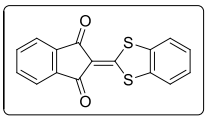
Diethyl 2-(benzo[*d*][1,3]dithiol-2-ylidene)malonate (30d). Obtained from diethyl malonate **31d** and 1-bromo-2-iodobenzene **32a**, yield 78% (242 mg, 0.78 mmol); white solid; mp 89-91 °C; R_f 0.29 (hexane); IR (neat, cm^{-1}) 3052, 2980, 1660, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 6.0, 3.2 Hz, 2H), 7.34 (dd, J = 6.0, 3.2 Hz, 2H), 4.34 (q, J = 7.1 Hz, 4H), 1.37 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 165.9, 137.1, 126.5, 121.9, 104.8, 61.2, 14.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}O_4S_2$ $[M + H]^+$ 311.0412, found 311.0388.

2-(Benzo[*d*][1,3]dithiol-2-ylidene)-2-(thiophen-2-yl)acetonitrile (30e). Obtained from 2-(thiophen-2-yl)acetonitrile **31e** and 1-bromo-2-iodobenzene **32a**, yield 80% (218 mg, 0.80 mmol); brown solid; mp 85-87 °C; R_f 0.41 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3035, 2208, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (td, J = 8.0, 1.8 Hz, 2H), 7.39 (dd, J = 5.2, 1.2 Hz, 1H), 7.29 (dd, J = 4.4, 2.0 Hz, 1H), 7.28-7.26 (m, 2H), 7.11 (dd, J = 5.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 136.9, 135.7, 134.7, 127.5, 127.1, 126.6, 125.8, 125.6, 122.4, 122.1, 117.3, 90.5; HRMS (ESI) *m/z* calcd for $C_{13}H_8NS_3$ $[M + H]^+$ 273.9819, found 273.9807.

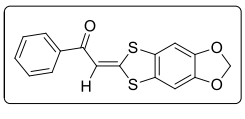
2-(Benzo[*d*][1,3]dithiol-2-ylidene)-2-(pyridin-3-yl)acetonitrile (30f). Obtained from 2-(pyridin-3-yl)acetonitrile **31f** and 1-bromo-2-iodobenzene **32a**, yield 69% (185 mg, 0.69 mmol); off-white solid; mp 120-122 °C; R_f 0.35 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3025, 2195, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.57 (d, J = 6.4 Hz, 1H), 7.86 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.47 (dd, J = 7.2, 2.0 Hz, 1H), 7.38 (td, J = 7.3, 1.6 Hz, 2H), 7.30 (td, J = 6.8, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 148.9, 147.9, 134.8, 134.6, 134.1, 130.5, 127.2, 126.9, 123.7, 122.3, 122.2, 117.7, 91.4; HRMS (ESI) *m/z* calcd for $C_{14}H_9N_2S_2$ $[M + H]^+$ 269.0207, found 269.0207.



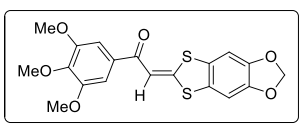
2-(Benzo[*d*][1,3]dithiol-2-ylidene)-1*H*-indene-1,3(2*H*)-dione (3). Obtained from 1*H*-indene-1,3(2*H*)-dione **31g** and 1-bromo-2-iodobenzene **32a**, yield 89% (263 mg, 0.89 mmol); yellow solid; mp 129-131 °C; R_f 0.32 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3041, 1654, 746; ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (dd, J = 5.8, 3.4 Hz, 2H), 7.85-7.79 (m, 4H), 7.58 (dd, J = 6.0, 3.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 184.0, 169.6, 139.7, 135.1, 134.6, 127.8, 123.9, 122.3, 112.2; HRMS (ESI) *m/z* calcd for $C_{16}H_9O_2S_2$ $[M + H]^+$ 297.0072, found 297.0088.



2-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)-1-phenylethanone (30g). Obtained from acetophenone **31h** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 74% (232 mg, 0.74 mmol); orange solid; mp 188-190 °C; R_f 0.31 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3038, 1742, 753; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.0, 1.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.39 (s, 1H), 7.02 (s, 1H), 6.92 (s, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 164.1, 148.0, 147.9, 138.2, 131.9, 130.5, 128.7, 127.8, 124.4, 104.5, 103.3, 102.3, 102.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}O_3S_2$ $[M + H]^+$ 315.0150, found 315.0140.

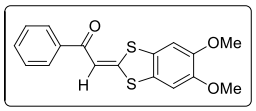


2-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)-1-(3,4,5-trimethoxyphenyl)ethanone (30h). Obtained from 1-(3,4,5-trimethoxyphenyl)ethanone **31i** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 75% (303 mg, 0.75 mmol); brown solid; mp 117-119 °C; R_f 0.25 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3039, 2903, 1732, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.25 (s, 2H), 7.04 (s, 1H), 6.95 (s, 1H), 6.05 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 164.1, 153.3, 148.0, 147.9, 141.7, 133.6, 130.5, 124.3, 105.2, 104.2, 103.3, 102.3,



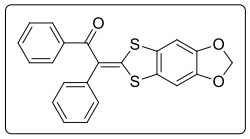
102.0, 61.0, 56.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}O_6S_2$ $[M + H]^+$ 405.0467, found 405.0460.

2-(5,6-Dimethoxybenzo[*d*][1,3]dithiol-2-ylidene)-1-phenylethanone (30i). Obtained



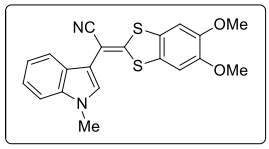
from acetophenone **31h** and 1-bromo-2-iodo-4,5-dimethoxybenzene **32c**, yield 81% (267 mg, 0.81 mmol); yellow solid; mp 109-111 °C; R_f 0.28 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3042, 2912, 1721, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.0, 1.6 Hz, 2H), 7.52-7.43 (m, 3H), 7.41 (s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 164.0, 149.1, 149.0, 138.3, 131.9, 129.7, 128.6, 127.7, 123.7, 105.6, 104.5, 104.4, 56.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_3S_2$ $[M + H]^+$ 331.0450, found 331.0463.

2-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)-1,2-diphenylethanone

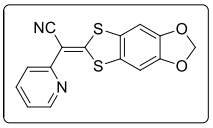


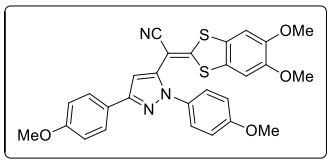
(30j). Obtained from deoxybenzoin **31j** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 72% (281 mg, 0.72 mmol); yellow solid; mp 155-157 °C; R_f 0.31 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3032, 1738, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 3H), 7.31 (dd, J = 8.4, 1.6 Hz, 2H), 7.28-7.22 (m, 3H), 7.14 (td, J = 6.8, 1.6 Hz, 2H), 7.05 (s, 1H), 6.81 (s, 1H), 6.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 164.9, 147.7, 147.6, 139.3, 139.2, 131.8, 130.5, 129.9, 129.3, 129.0, 128.2, 127.5, 125.4, 122.1, 102.9, 102.1, 101.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{15}O_3S_2$ $[M + H]^+$ 391.0463, found 391.0466.

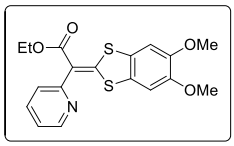
2-(5,6-Dimethoxybenzo[*d*][1,3]dithiol-2-ylidene)-2-(1-methyl-1*H*-indol-3-

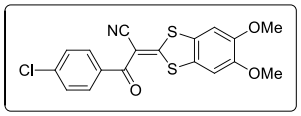


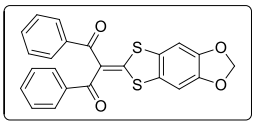
yl)acetonitrile (30k). Obtained from 2-(1-methyl-1*H*-indol-3-yl)acetonitrile **31k** and 1-bromo-2-iodo-4,5-dimethoxybenzene **32c**, yield 81% (308 mg, 0.81 mmol); red-brown solid; mp 158-160 °C; R_f 0.31 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3033, 2928, 2191, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 2.0 Hz, 1H), 7.34 (dt, J = 8.0, 1.2 Hz, 1H), 7.31 (dd, J = 6.6, 1.4 Hz, 1H), 7.28 (s, 1H), 7.20 (td, J = 7.4, 1.6 Hz, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 3.88 (s, 3H), 3.824 (s, 3H), 3.815 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.5, 148.9, 148.6, 136.6, 128.0, 126.1, 125.9, 125.1, 122.7, 120.2, 118.5, 109.6, 109.1, 105.29, 105.17, 88.1, 56.4, 56.3, 33.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_2O_2S_2$ $[M + H]^+$ 381.0731, found 381.0722.

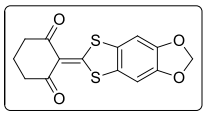
2-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)-2-(pyridin-2-yl)acetonitrile (30l).  Obtained from 2-(pyridin-2-yl)acetonitrile **31l** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 68% (212 mg, 0.68 mmol); yellow solid; mp 192-194 °C; R_f 0.32 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3035, 2193, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 6.4, 1.2 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.59 (dd, J = 6.8, 1.2 Hz, 1H), 7.09 (td, J = 7.5, 1.3 Hz, 1H), 6.97 (s, 1H), 6.95 (s, 1H), 6.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 151.4, 148.1, 147.9, 147.4, 136.9, 131.8, 124.7, 119.8, 119.7, 117.9, 102.9, 102.4, 102.2, 91.9; HRMS (ESI) *m/z* calcd for $C_{15}H_9N_2O_2S_2$ $[M + H]^+$ 313.0105, found 313.0094.

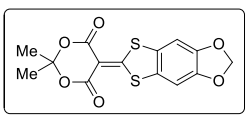
2-(1,3-Bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl)-2-(5,6-dimethoxybenzo[*d*][1,3]dithiol-2-ylidene)acetonitrile (30m).  Obtained from 2-(1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl)acetonitrile **31m** and 1-bromo-2-iodo-4,5-dimethoxybenzene **32c**, yield 81% (429 mg, 0.81 mmol); pale-yellow solid; mp 179-181 °C; R_f 0.41 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3037, 2918, 2188, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 6.6, 2.2 Hz, 2H), 7.45 (dd, J = 6.8, 2.0 Hz, 2H), 6.98-6.95 (m, 4H), 6.88 (s, 1H), 6.86 (s, 1H), 6.81 (s, 1H), 3.88 (s, 3H), 3.85 (s, 6H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 159.9, 159.6, 151.9, 149.4, 149.2, 136.1, 132.6, 127.1, 126.2, 125.9, 125.6, 116.3, 114.6, 114.2, 105.4, 105.3, 104.7, 83.2, 56.5, 56.4, 55.6, 55.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{24}N_3O_4S_2$ $[M + H]^+$ 530.1208, found 530.1190.

Ethyl 2-(5,6-dimethoxybenzo[*d*][1,3]dithiol-2-ylidene)-2-(pyridin-2-yl)acetate (30n).  Obtained from ethyl 2-(pyridin-2-yl)acetate **31n** and 1-bromo-2-iodo-4,5-dimethoxybenzene **32c**, yield 70% (263 mg, 0.70 mmol); yellow-green solid; mp 121-123 °C; R_f 0.30 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3028, 2903, 1738, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 6.0, 2.0 Hz, 1H), 7.71 (td, J = 7.8, 1.8 Hz, 1H), 7.55 (dd, J = 8.0, 1.2 Hz, 1H), 7.18 (ddd, J = 7.4, 4.1, 1.0 Hz, 1H), 6.98 (s, 1H), 6.87 (s, 1H), 4.31 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 163.3, 155.4, 148.5, 147.8, 136.1, 129.2, 126.6, 124.9, 121.4, 112.6, 104.6, 104.3, 60.8, 56.3, 56.2, 14.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}NO_4S_2$ $[M + H]^+$ 376.0677, found 376.0677.

3-(4-Chlorophenyl)-2-(5,6-dimethoxybenzo[*d*][1,3]dithiol-2-ylidene)-3-oxopropanenitrile (30o).  Obtained from 3-(4-chlorophenyl)-3-oxopropanenitrile **31o** and 1-bromo-2-iodo-4,5-dimethoxybenzene **32c**, yield 78% (303 mg, 0.78 mmol); yellow solid; mp 256-258 °C; R_f 0.46 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3021, 2950, 2197, 1742, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 6.4, 2.0 Hz, 2H), 7.46 (dd, J = 6,4, 2.0 Hz, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 179.7, 150.2, 150.0, 138.5, 135.5, 131.0, 129.9, 128.8, 124.7, 118.2, 105.3, 104.4, 90.7, 56.51, 56.48; HRMS (ESI) *m/z* calcd for $C_{18}H_{13}ClNO_3S_2$ $[M + H]^+$, $[M + H + 2]^+$ 390.0025, 392.0025, found 390.0002, 392.0002.

2-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)-1,3-diphenylpropane-1,3-dione (30p).  Obtained from dibenzoyl methane **31p** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 63% (263 mg, 0.63 mmol); yellow solid; mp 210-212 °C; R_f 0.37 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3019, 1720, 726; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.0, 1.8 Hz, 4H), 7.19 (s, 2H), 7.18-7.14 (m, 2H), 7.09 (td, J = 8.1, 1.7 Hz, 4H), 6.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 176.5, 148.6, 140.5, 131.3, 130.2, 129.1, 127.9, 119.7, 102.6, 102.4; HRMS (ESI) *m/z* calcd for $C_{23}H_{15}O_4S_2$ $[M + H]^+$ 419.0412, found 419.0400.

2-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)cyclohexane-1,3-dione (30q).  Obtained from cyclohexane-1,3-dione **31q** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 84% (257 mg, 0.84 mmol); yellow solid; mp decomposed at 160 °C (turned black); R_f 0.32 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3012, 2907, 1738, 742; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 2H), 6.11 (s, 2H), 2.71 (t, J = 6.6 Hz, 4H), 2.06 (quin, J = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 175.5, 148.9, 130.9, 118.9, 102.6, 102.4, 37.3, 19.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}O_4S_2$ $[M + H]^+$ 307.0099, found 307.0084.

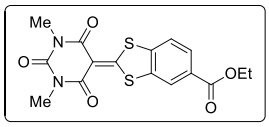
5-([1,3]Dithiolo[4',5':4,5]benzo[1,2-*d*][1,3]dioxol-6-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (30r).  Obtained from 2,2-dimethyl-1,3-dioxane-4,6-dione **31r** and 5-bromo-6-iodobenzo[*d*][1,3]dioxole **32b**, yield 76% (257 mg, 0.76 mmol); orange-brown solid; mp 219-221 °C; R_f 0.52 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3015, 2901, 1655, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2H), 6.12 (s, 2H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9,

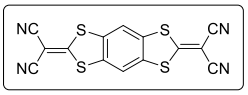
161.8, 148.9, 130.4, 104.5, 102.7, 102.4, 95.1, 27.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{10}O_6S_2$ $[M]^+$ 337.9919, found 337.9906.

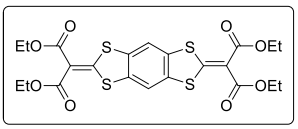
Diethyl 2-(5-cyanobenzo[*d*][1,3]dithiol-2-ylidene)malonate (30s). Obtained from diethyl malonate **31d** and 3-bromo-4-iodobenzonitrile **32d**, yield 76% (255 mg, 0.76 mmol); white solid; mp 143-145 °C; R_f 0.31 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3048, 2916, 2228, 1742, 735; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 6.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 4.35 (q, J = 7.2 Hz, 4H), 1.38 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 165.6, 138.6, 131.9, 131.6, 129.6, 129.3, 122.6, 110.5, 106.8, 61.6, 14.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NO_4S_2Na$ $[M + Na]^+$ 358.0184, found 358.0171.

(*E*/*Z*)-Ethyl 2-(5-cyanobenzo[*d*][1,3]dithiol-2-ylidene)-2-(pyridin-2-yl)acetate (30t). Obtained from ethyl 2-(pyridin-2-yl)acetate **31n** and 3-bromo-4-iodobenzonitrile **32d**, yield 74% (252 mg, 0.74 mmol); light-yellow solid; mp 102-104 °C; R_f 0.48 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3064, 2923, 2229, 1741, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69-8.67 (m, 1H), 7.75-7.58 (m, 3H), 7.57-7.56 (m, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.26-7.23 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 159.1, 154.3, 154.2, 147.71, 147.67, 143.7, 141.7, 139.4, 137.5, 136.3, 131.8, 131.7, 131.5, 129.29, 129.25, 129.23, 129.19, 124.8, 124.7, 124.6, 124.4, 122.1, 121.97, 121.93, 121.7, 118.13, 118.10, 109.80, 109.77, 61.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}N_2O_2S_2$ $[M + H]^+$ 341.0418, found 341.0413.

Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)benzo[*d*][1,3]dithiole-5-carboxylate (30u). Obtained from 2,2-dimethyl-1,3-dioxane-4,6-dione **31r** and ethyl 3-bromo-4-iodobenzoate **32e**, yield 77% (282 mg, 0.77 mmol); orange-red solid; mp 214-216 °C; R_f 0.27 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3048, 2990, 1704, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.2 Hz, 1H), 8.15 (dd, J = 8.4, 1.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.78 (s, 6H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 165.1, 161.8, 141.9, 137.7, 130.3, 128.5, 124.2, 122.9, 104.9, 97.2, 61.9, 27.3, 14.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}O_6S_2Na$ $[M + Na]^+$ 389.0129, found 389.0109.

Ethyl 2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)benzo[*d*][1,3]dithiole-5-carboxylate (30v).  Obtained from 1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione **31s** and ethyl 3-bromo-4-iodobenzoate **32e**, yield 74% (280 mg, 0.74 mmol); white solid; mp 251-253 °C; R_f 0.25 (3:17 EtOAc/hexane); IR (neat, cm^{-1}) 3018, 2922, 1714, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 1.2 Hz, 1H), 8.14 (dd, J = 8.4, 1.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 3.45 (s, 6H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 165.2, 161.0, 150.9, 142.1, 137.9, 130.1, 128.3, 124.1, 122.7, 103.2, 61.9, 28.4, 14.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_2O_5S_2$ $[M + H]^+$ 379.0422, found 379.0398.

2,2'-(Benzo[1,2-d:4,5-*d*']bis([1,3]dithiole)-2,6-diylidene)dimalononitrile (36a).  Obtained from malononitrile **31b** and 1,4-dibromo-2,5-diiodobenzene **35**, yield 74% (262 mg, 0.74 mmol); brown solid; mp 211-213 °C; R_f 0.53 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3068, 2201, 740; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.5, 137.3, 132.8, 110.3, 81.0; HRMS (APPI) *m/z* calcd for $C_{14}H_2N_4S_4$ $[M]^+$ 353.9162, found 353.9160.

Tetraethyl 2,2'-(benzo[1,2-d:4,5-*d*']bis([1,3]dithiole)-2,6-diylidene)dimalonate (36b).  Obtained from diethyl malonate **31d** and 1,4-dibromo-2,5-diiodobenzene **35**, yield 65% (352 mg, 0.65 mmol); white solid; mp 138-140 °C; R_f 0.27 (1:3 EtOAc/hexane); IR (neat, cm^{-1}) 3022, 2928, 1738, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 4.34 (q, J = 7.2 Hz, 8H), 1,37 (t, J = 7.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 165.7, 138.3, 126.2, 106.2, 61.6, 14.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_8S_4$ $[M + H]^+$ 543.0276, found 543.0267.

4.6 References

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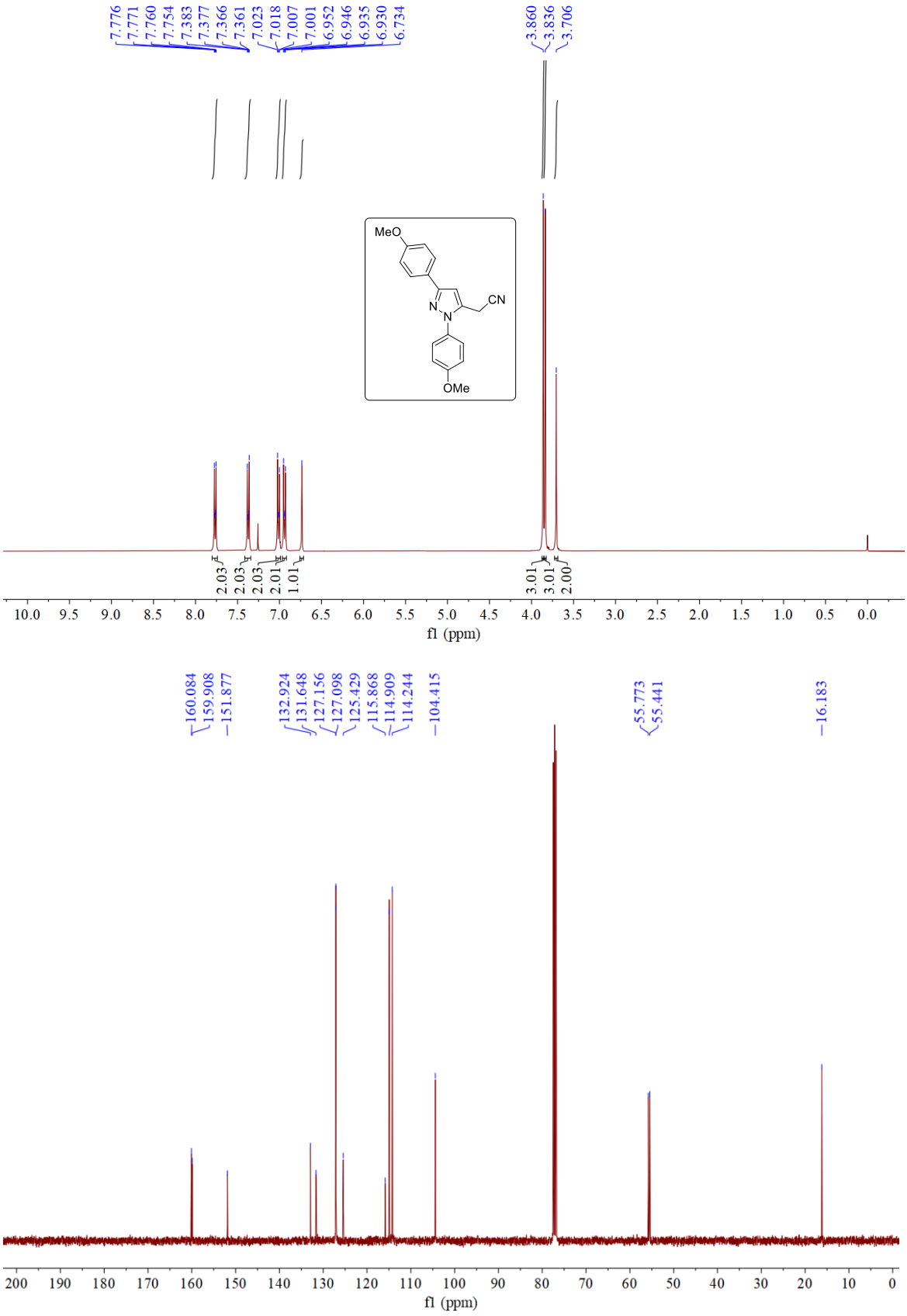
4.7 Representative Spectra



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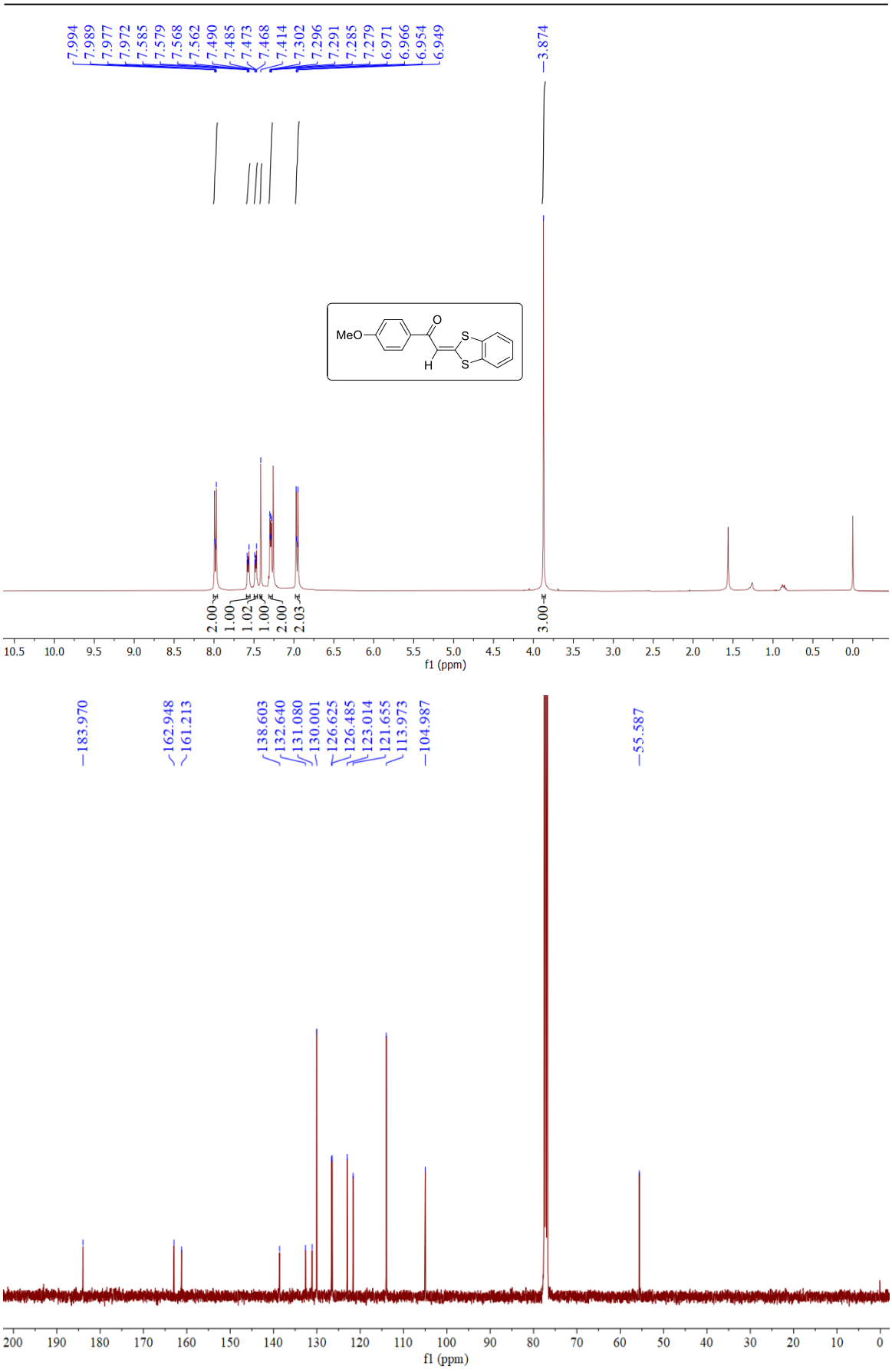

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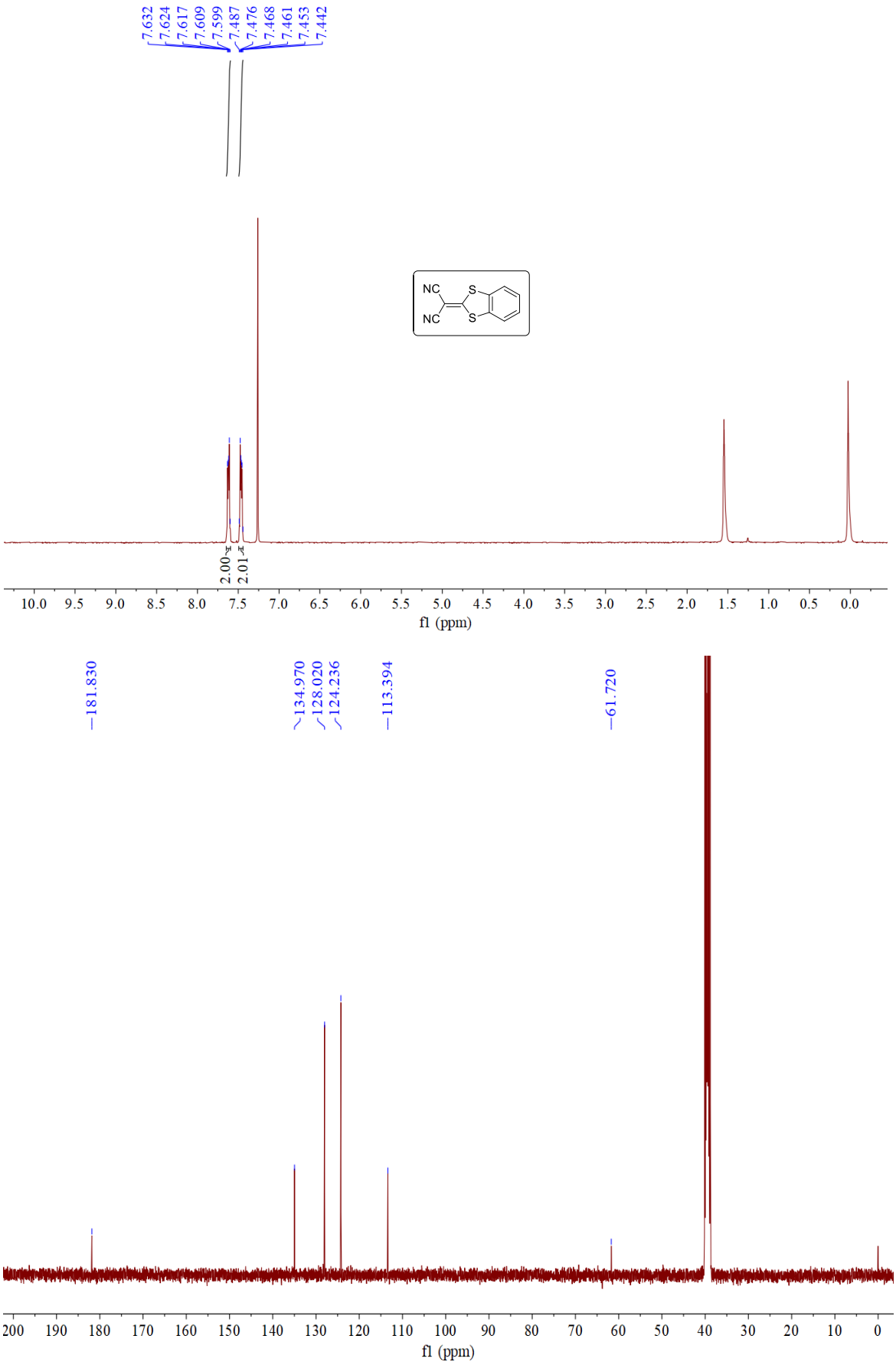

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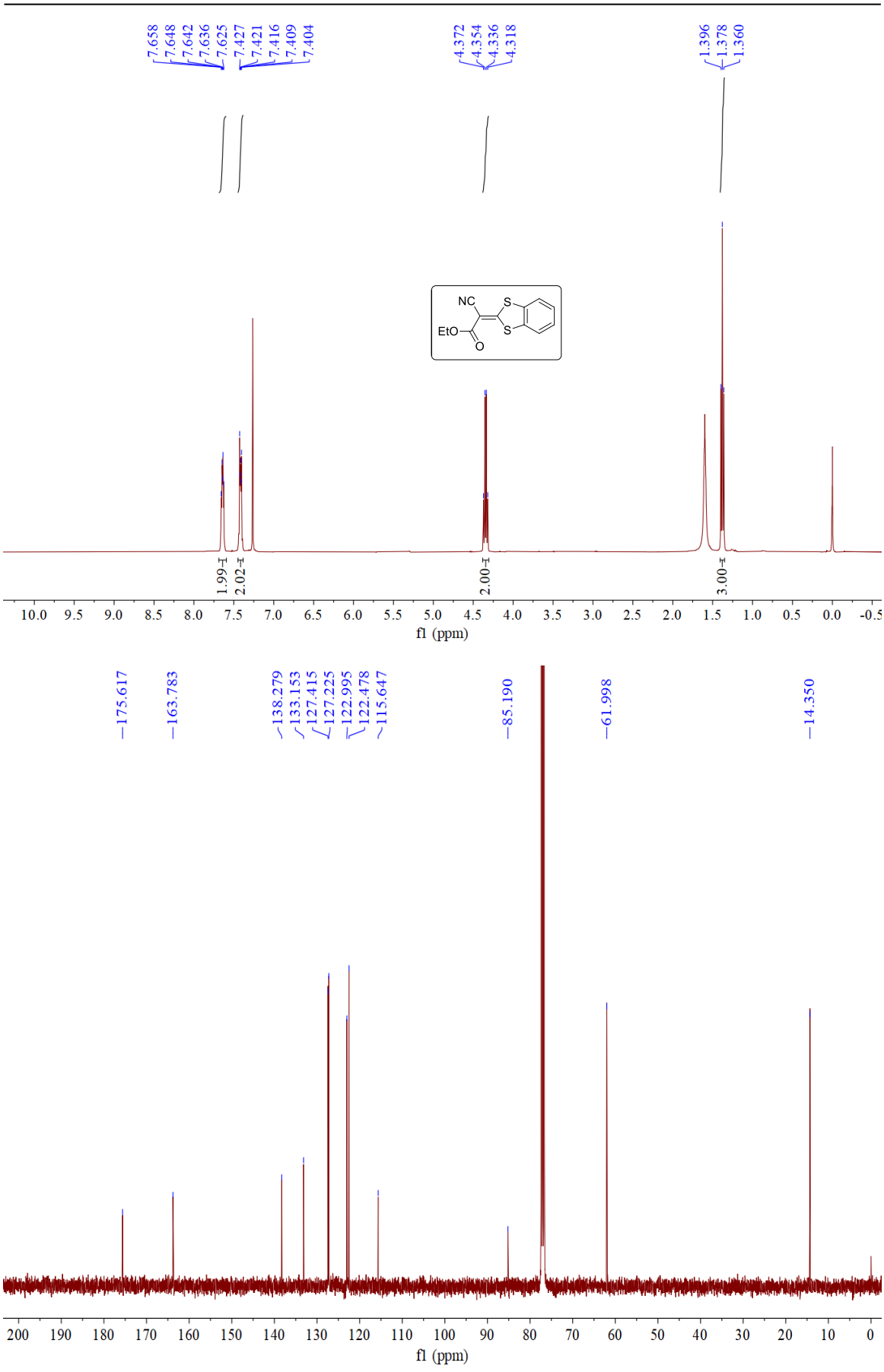

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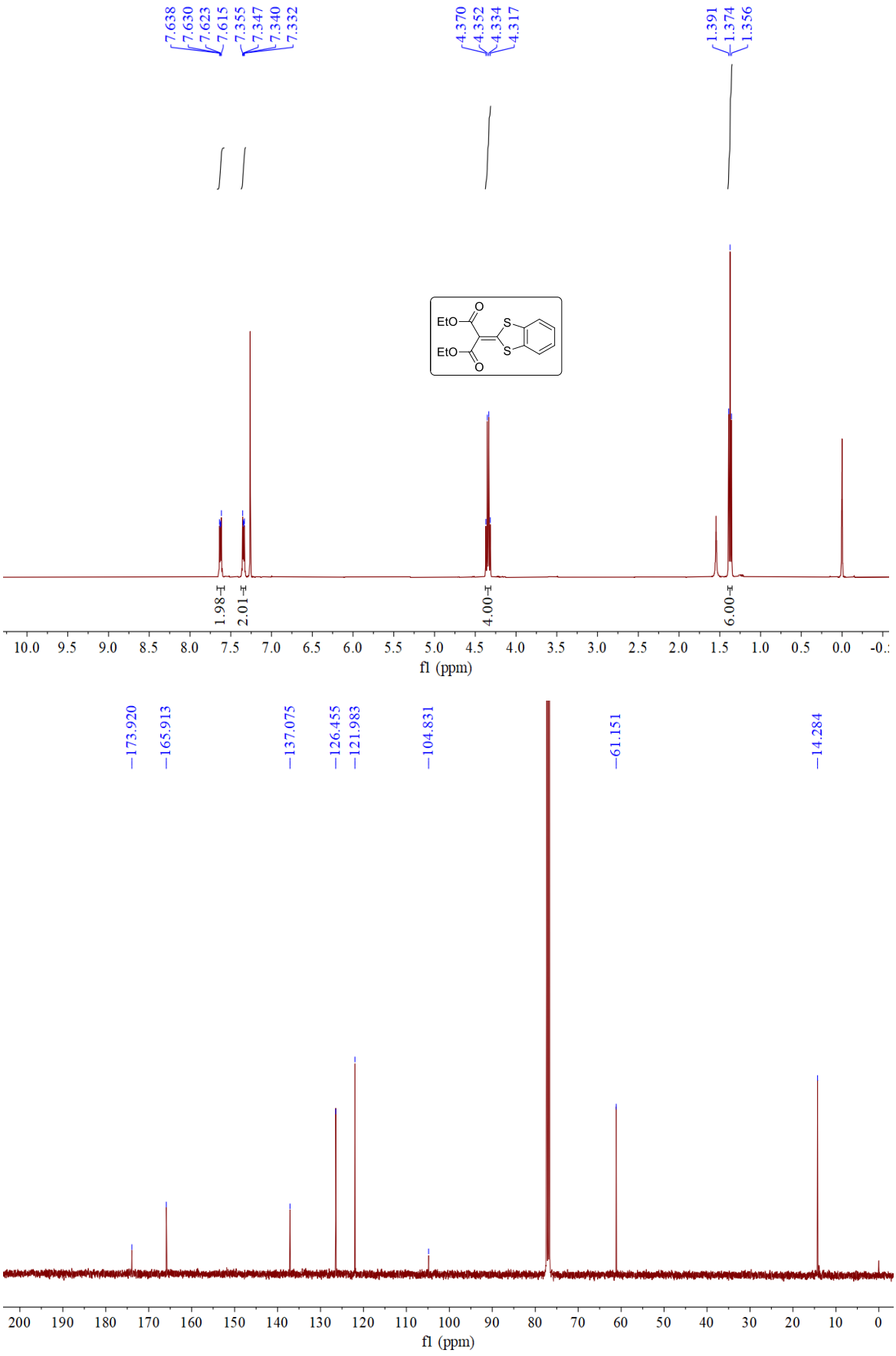

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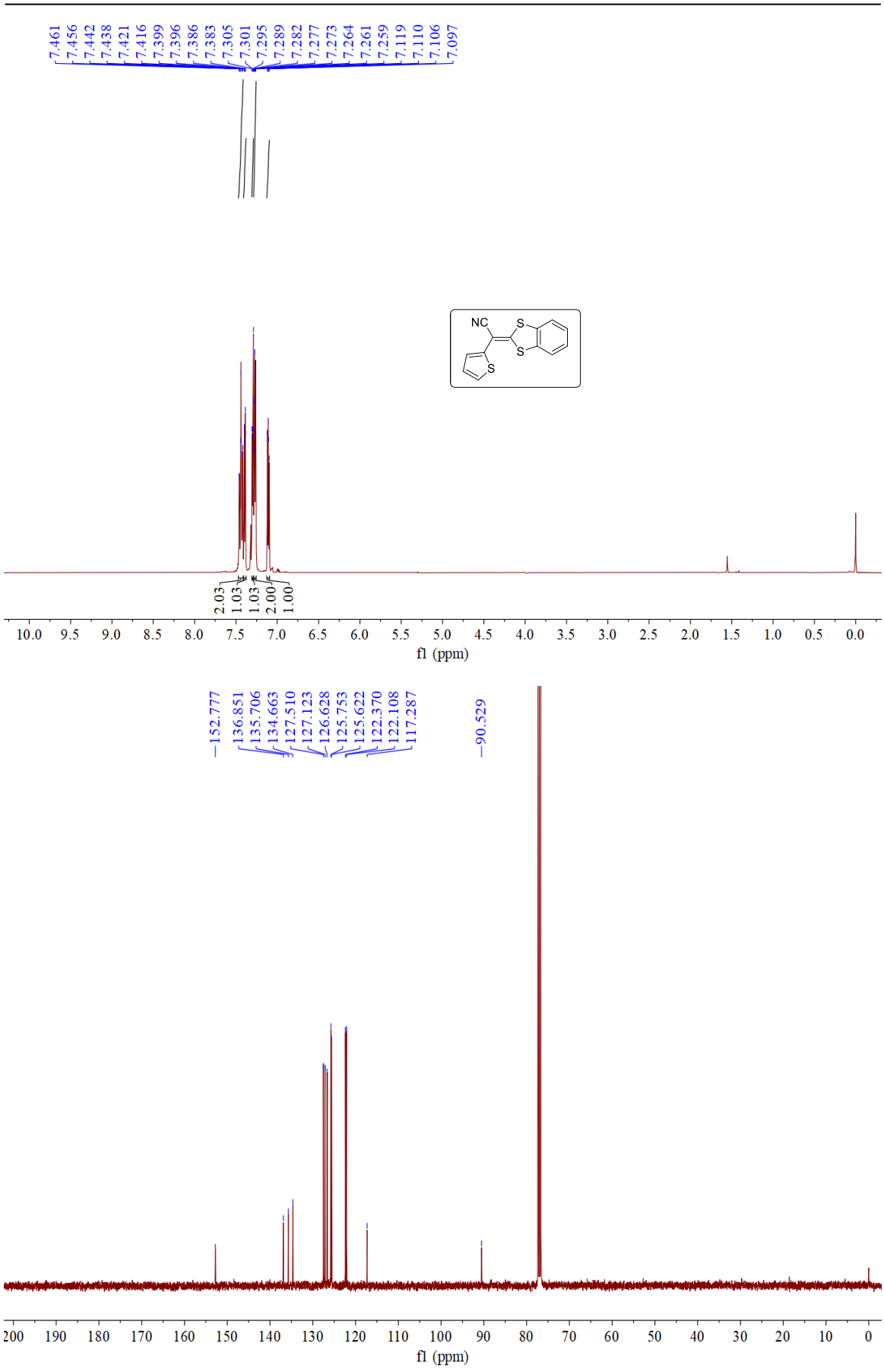

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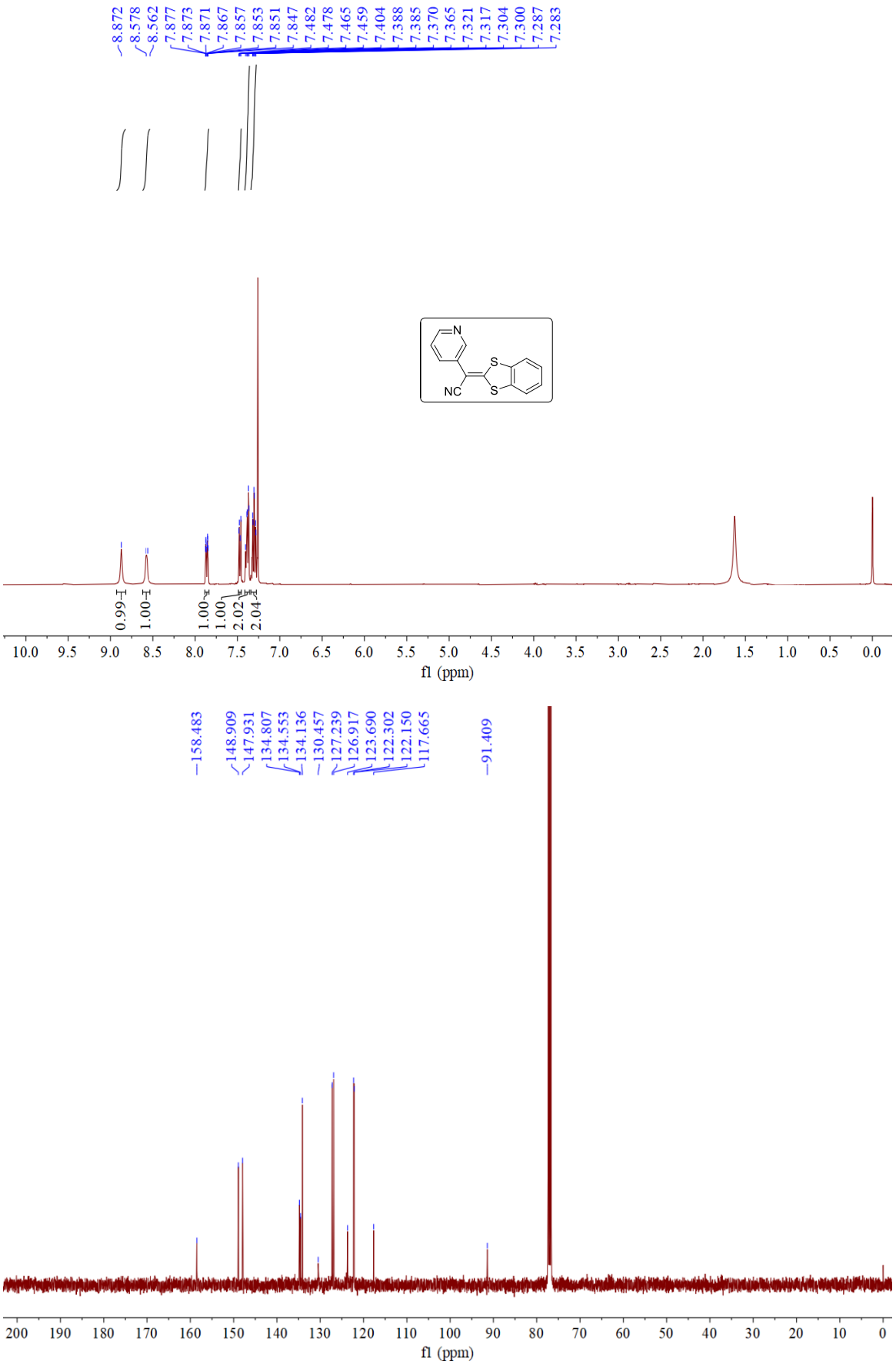
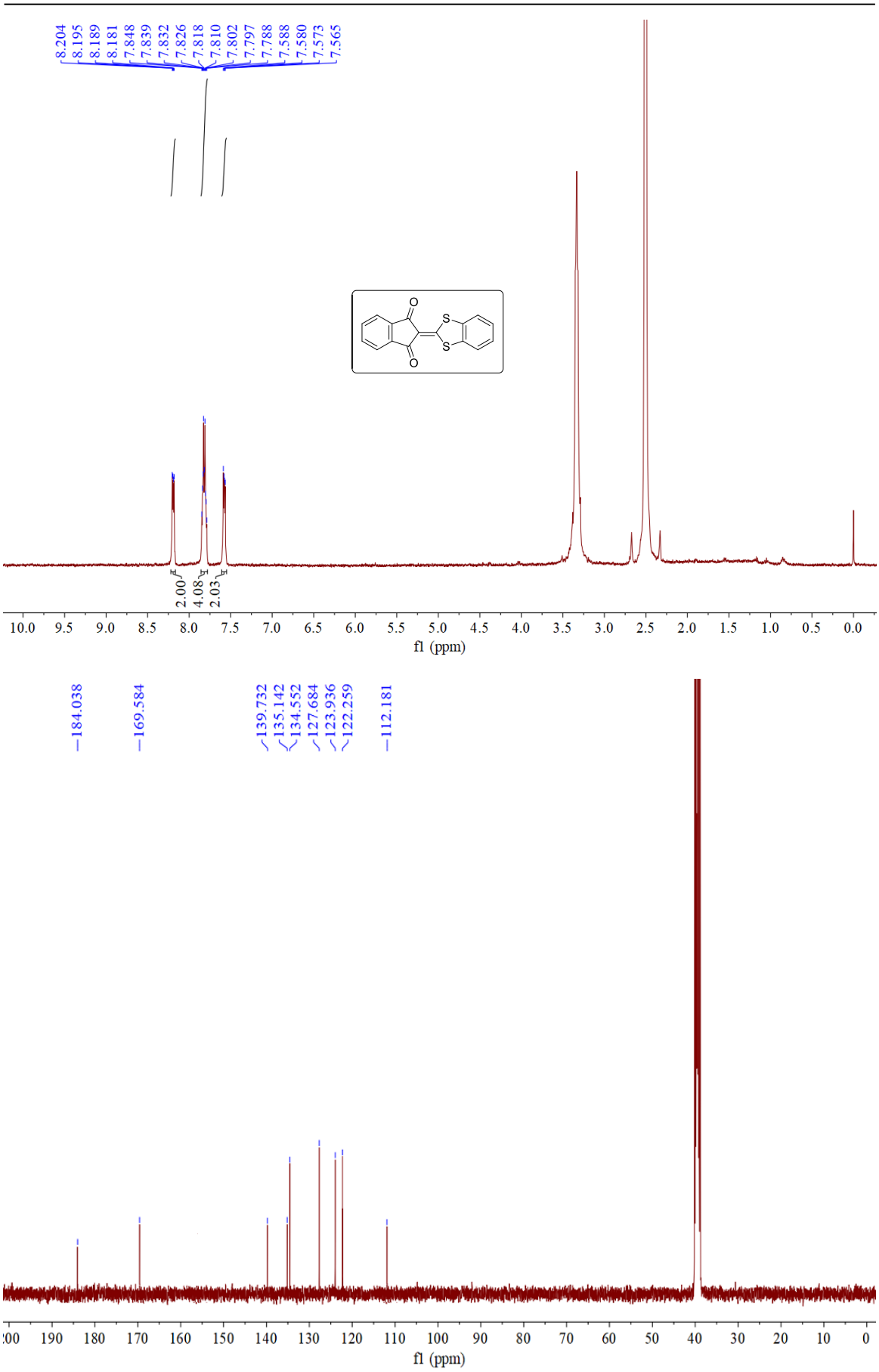


^{1}H and ^{13}C NMR spectra of compound **30f**



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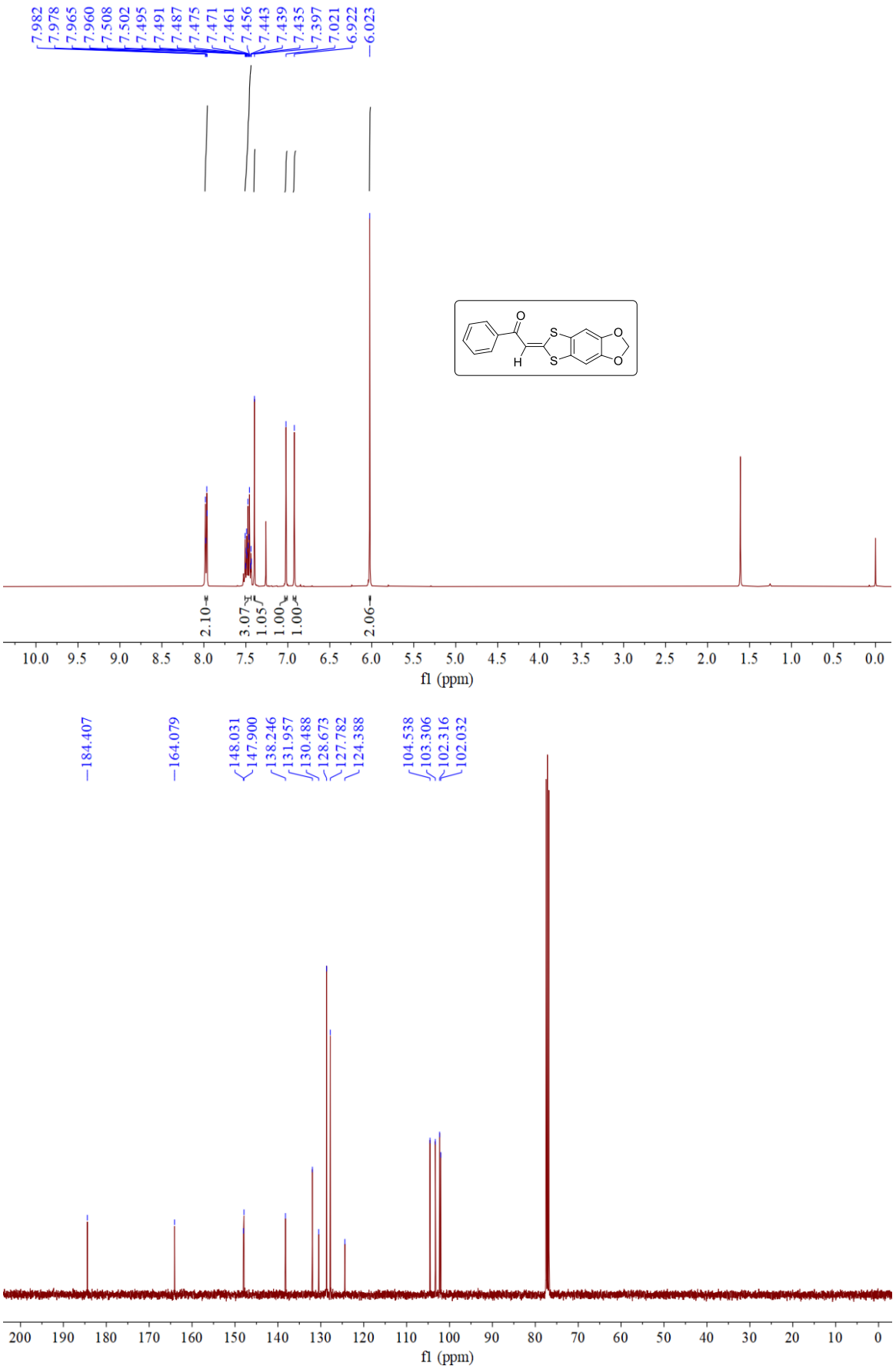

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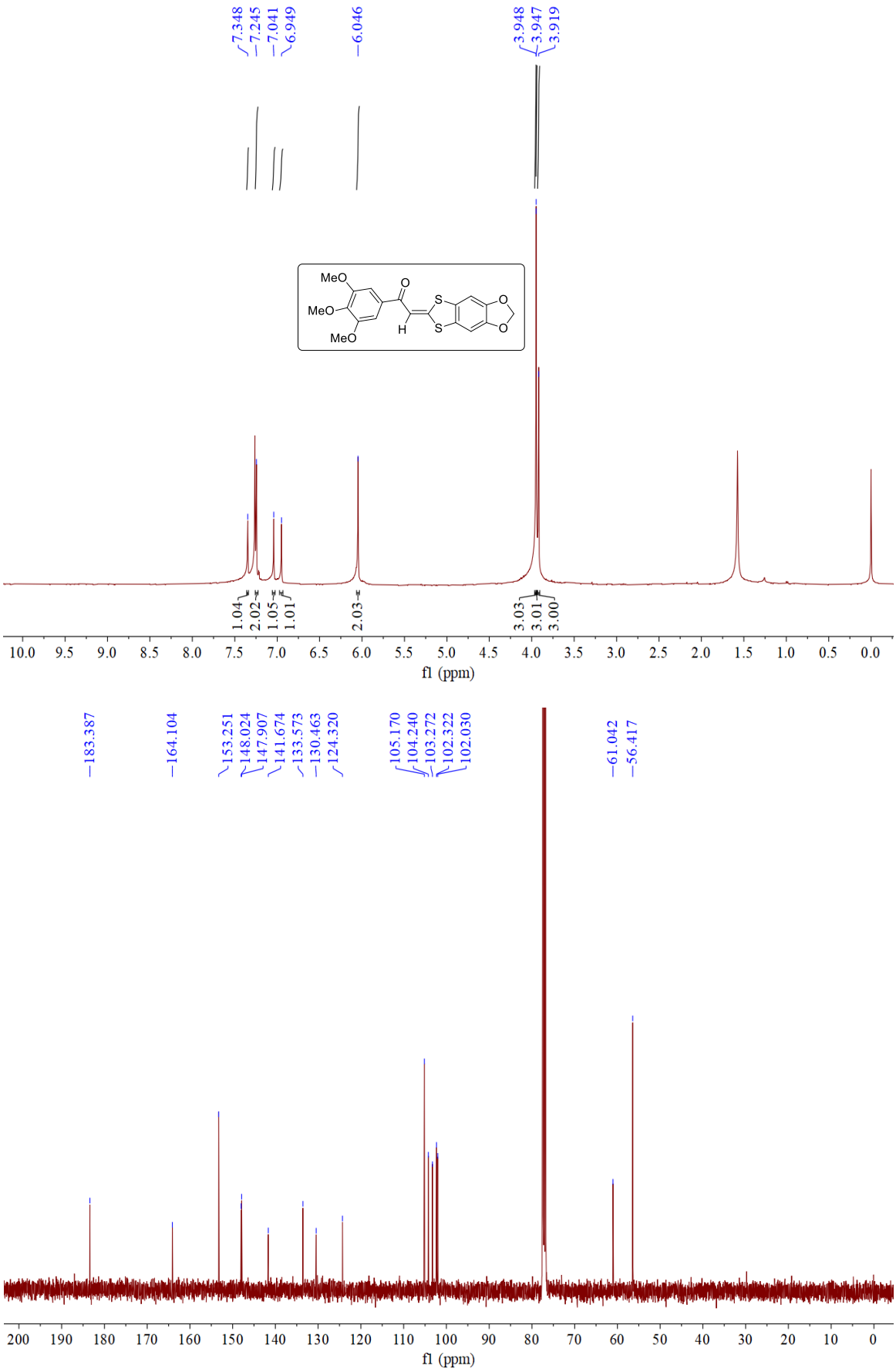

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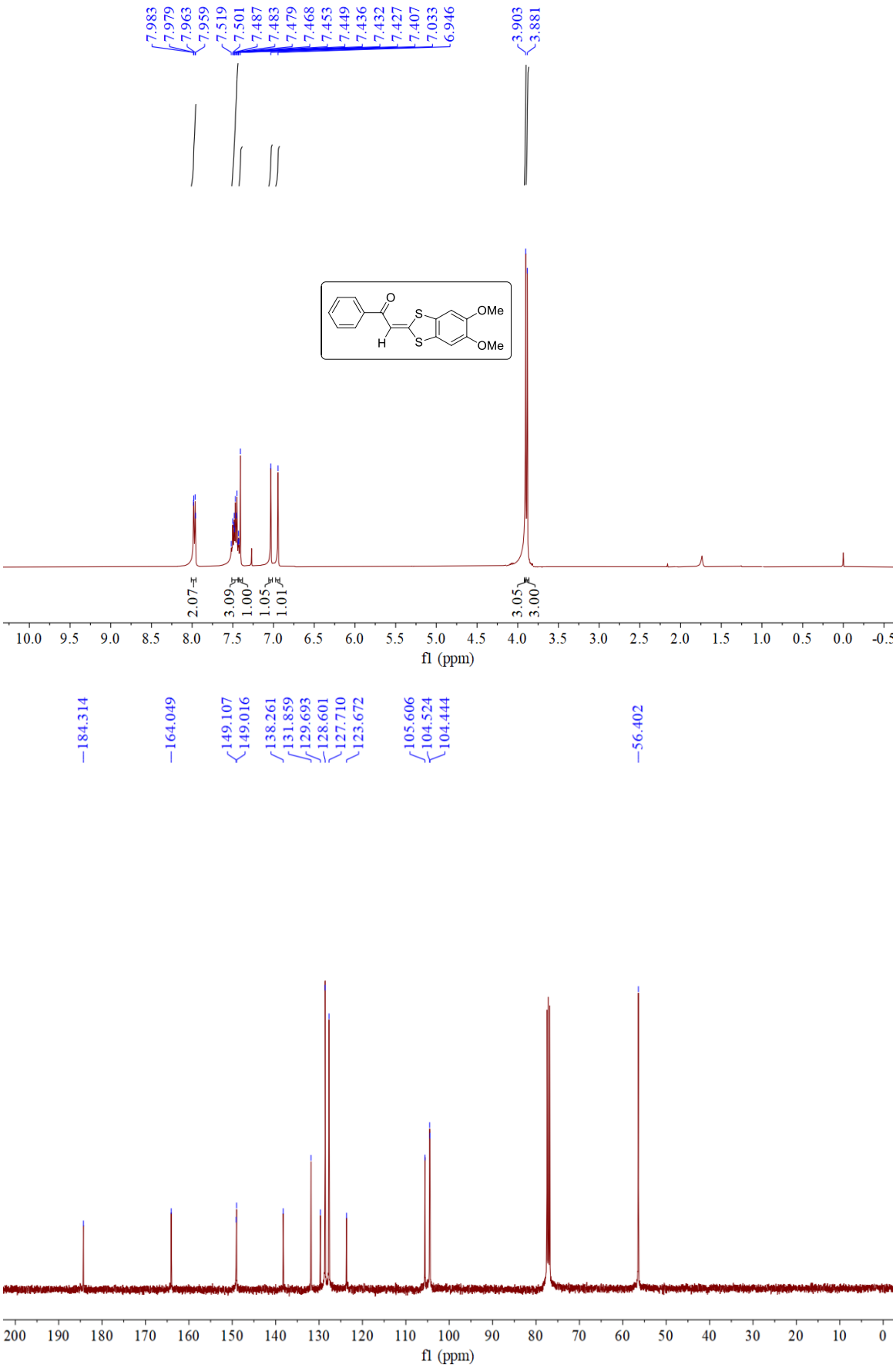

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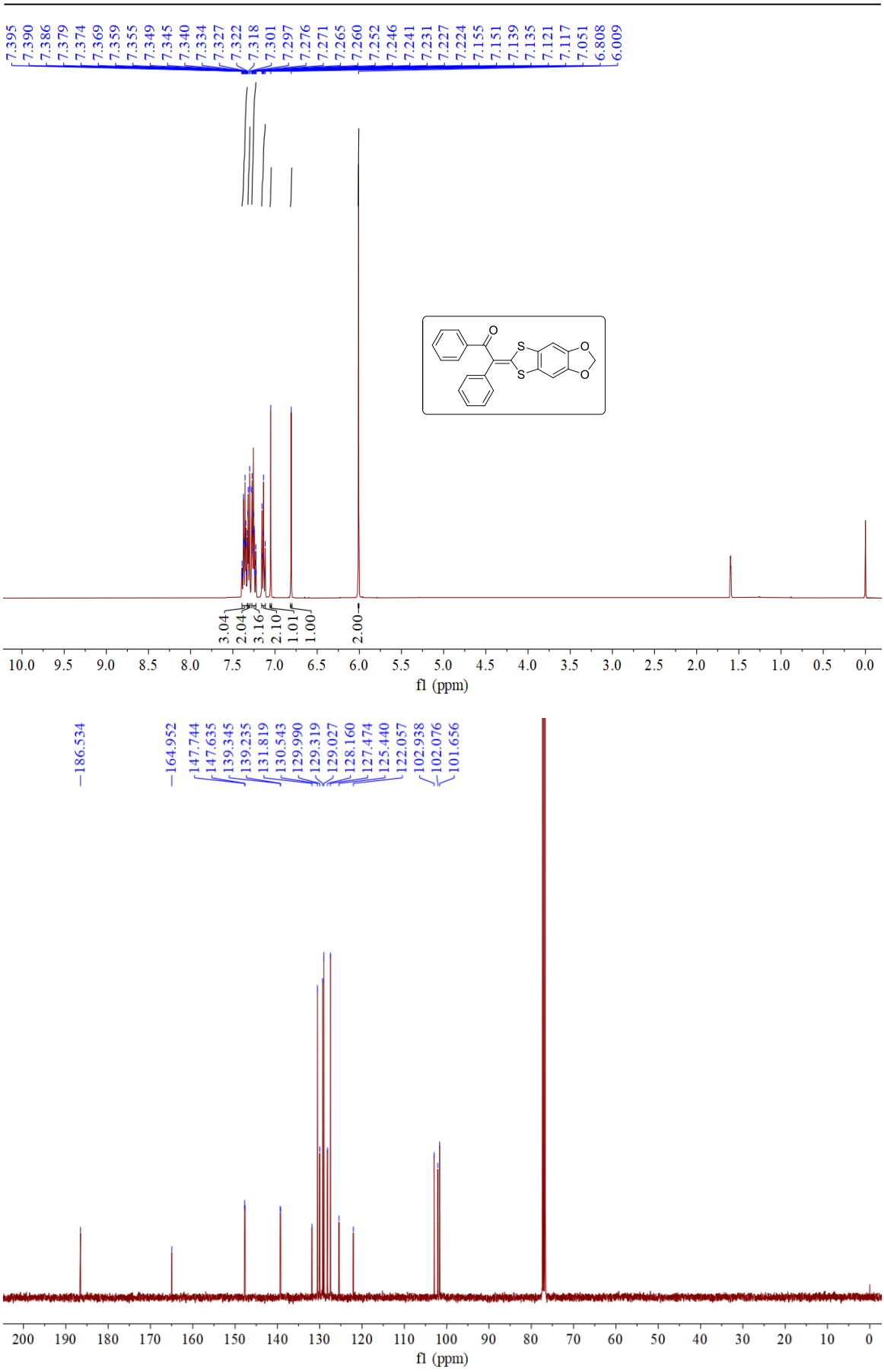

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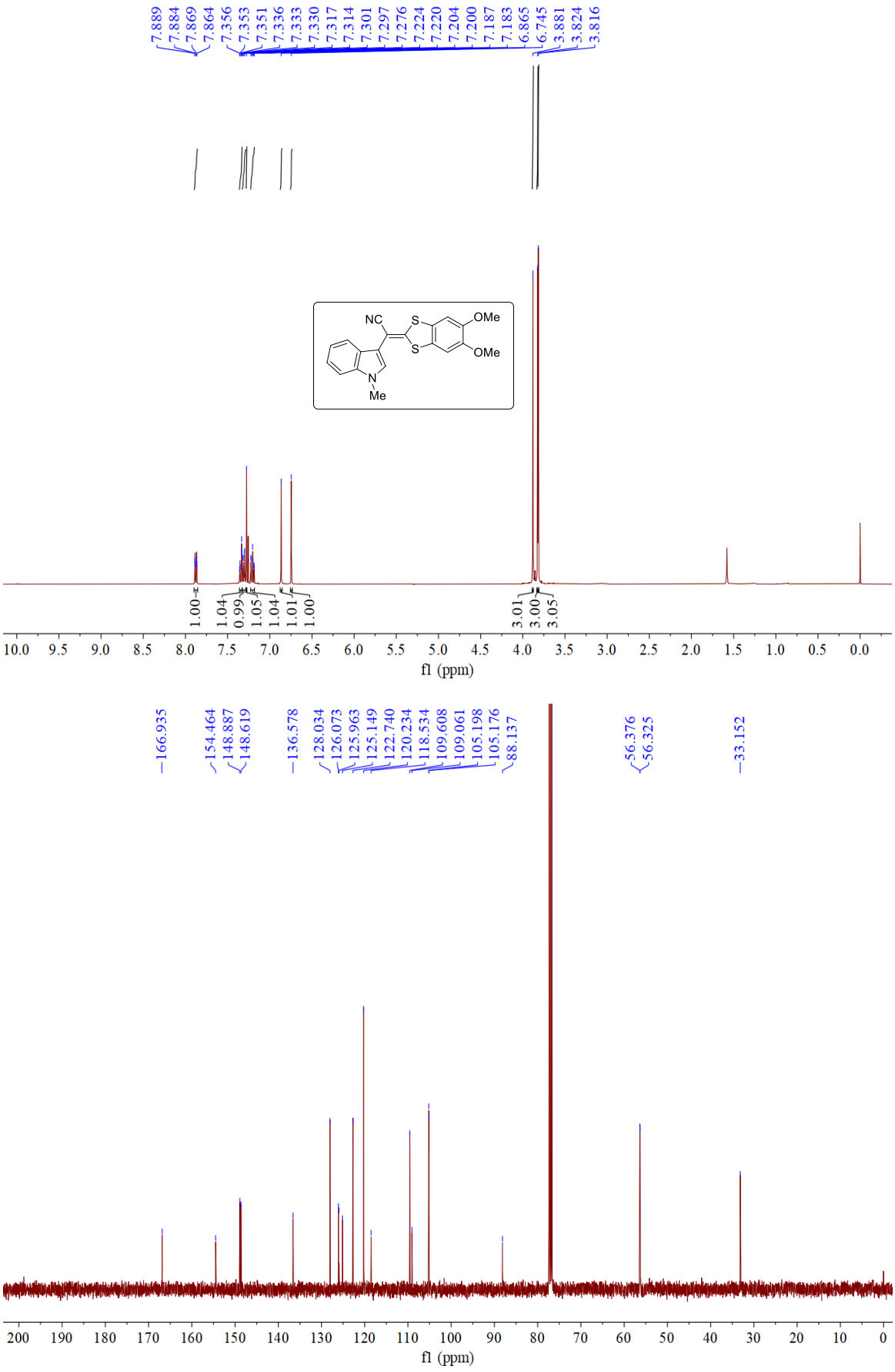

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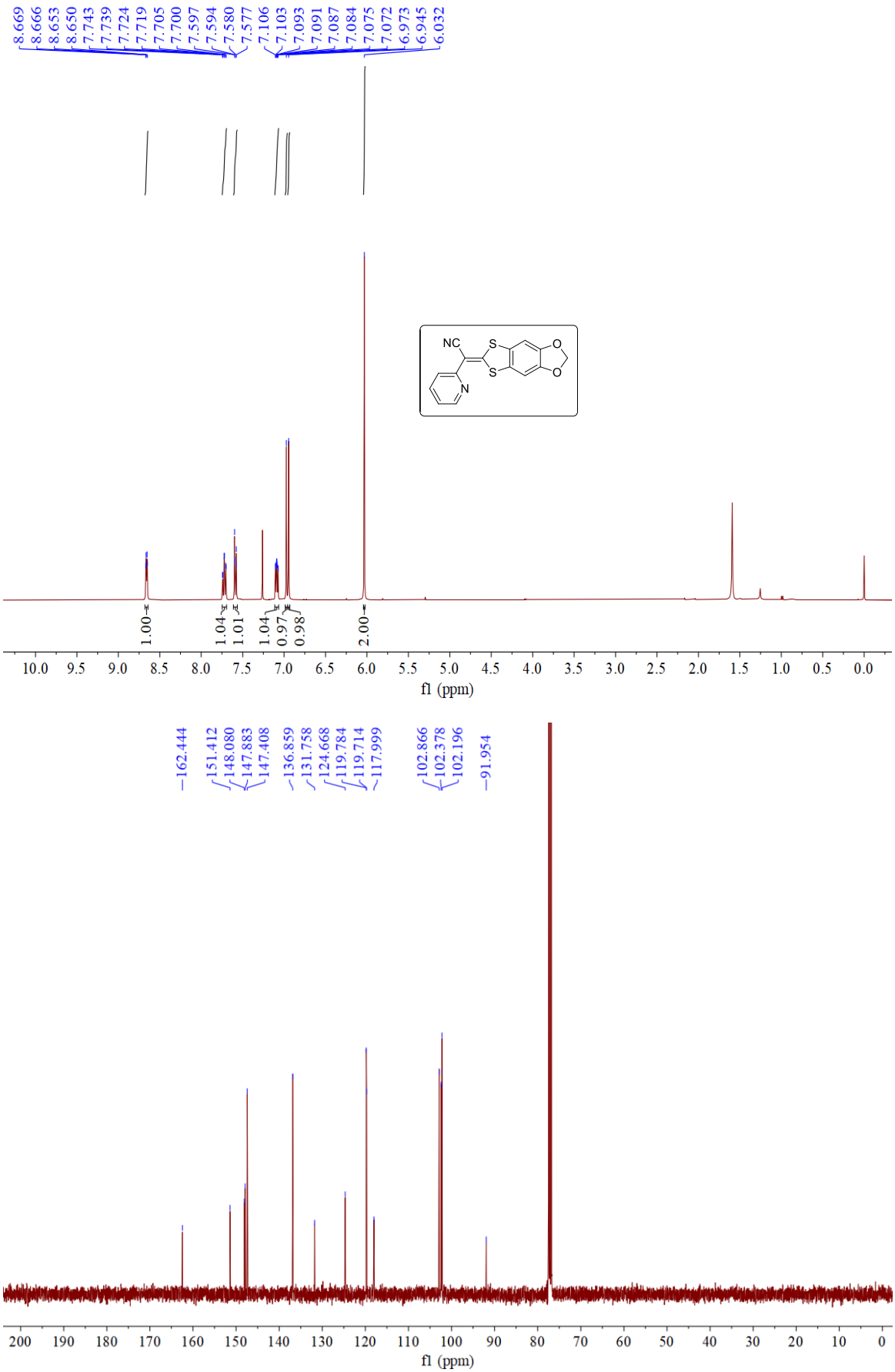

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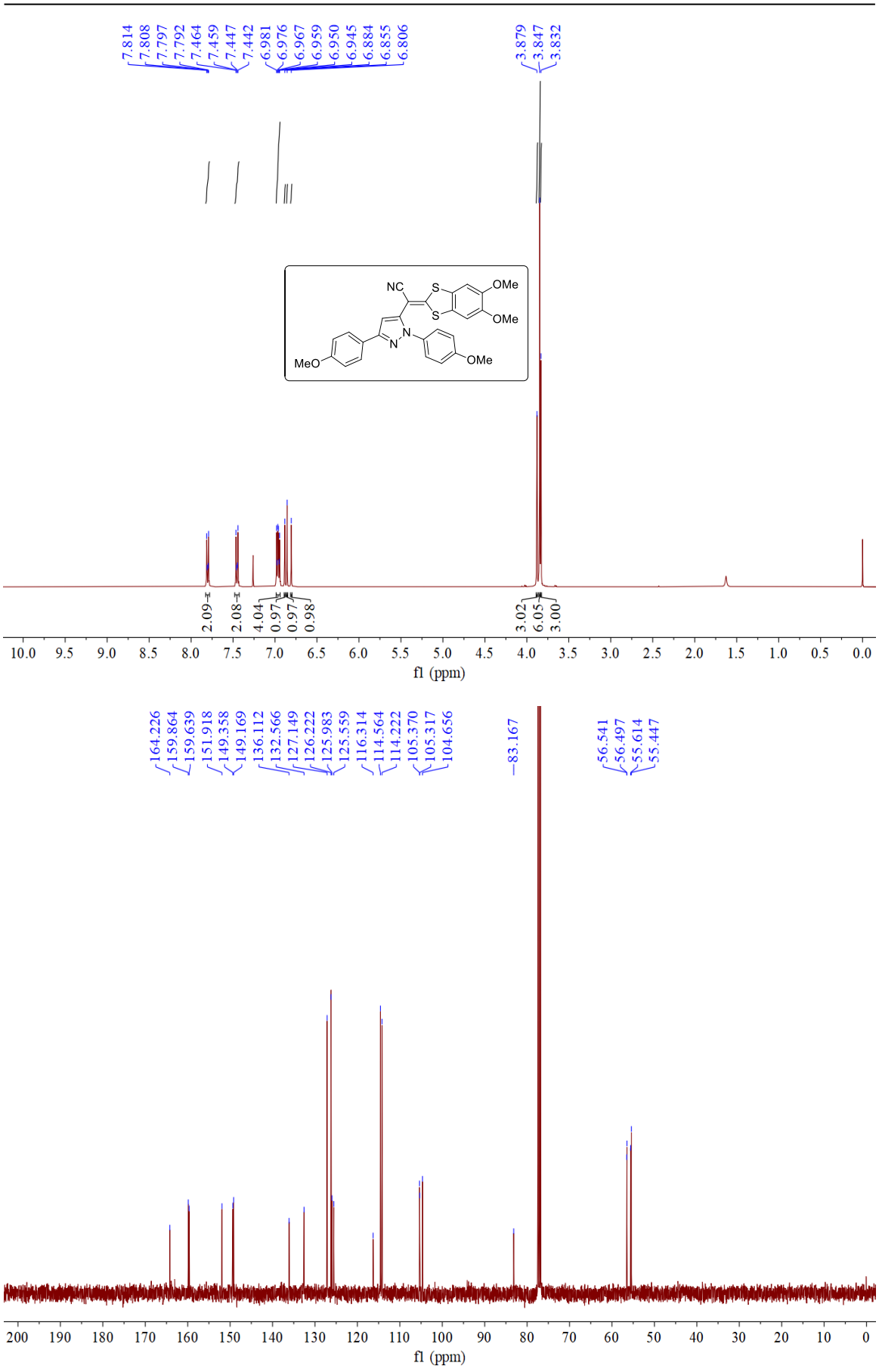

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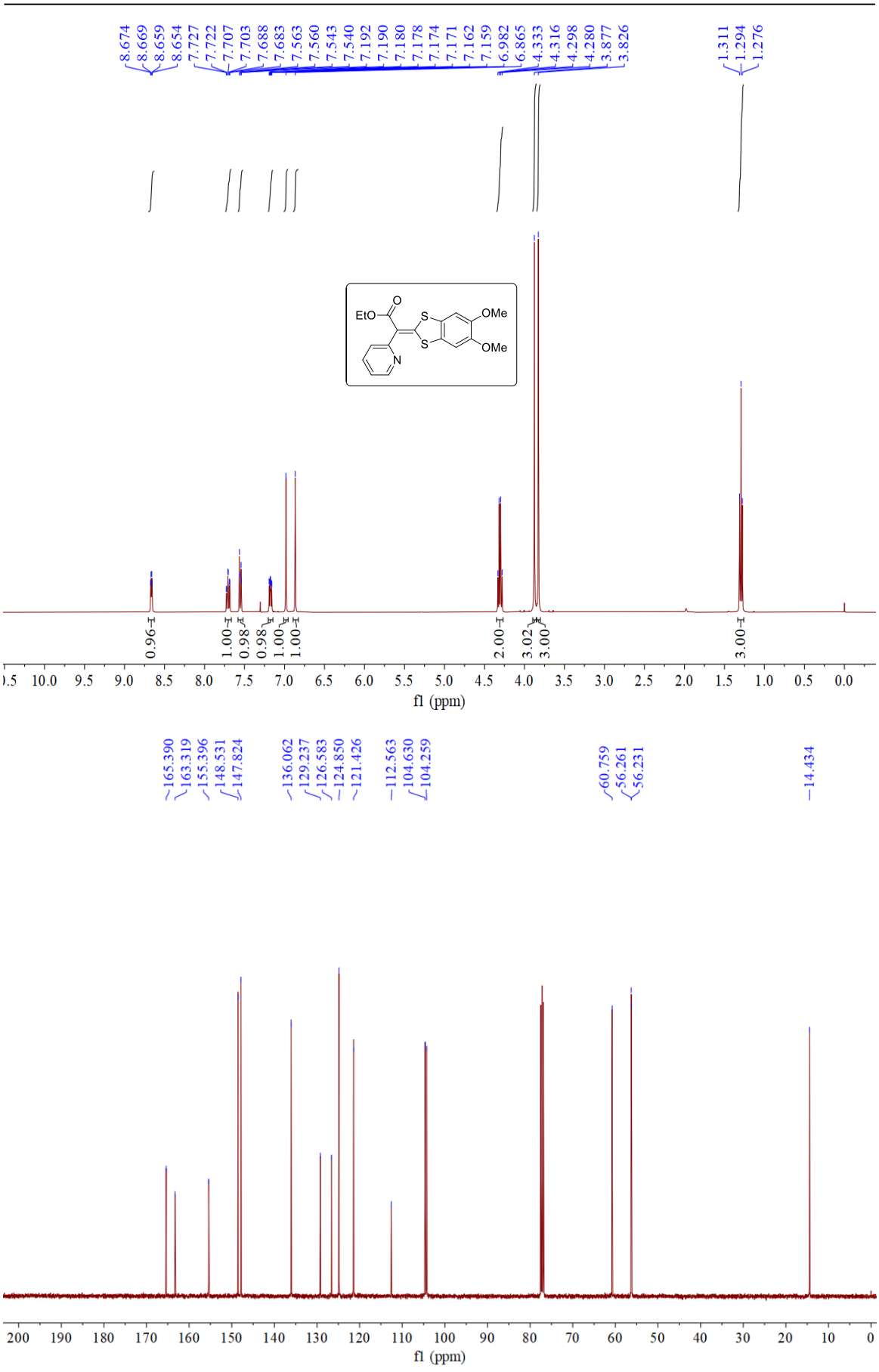

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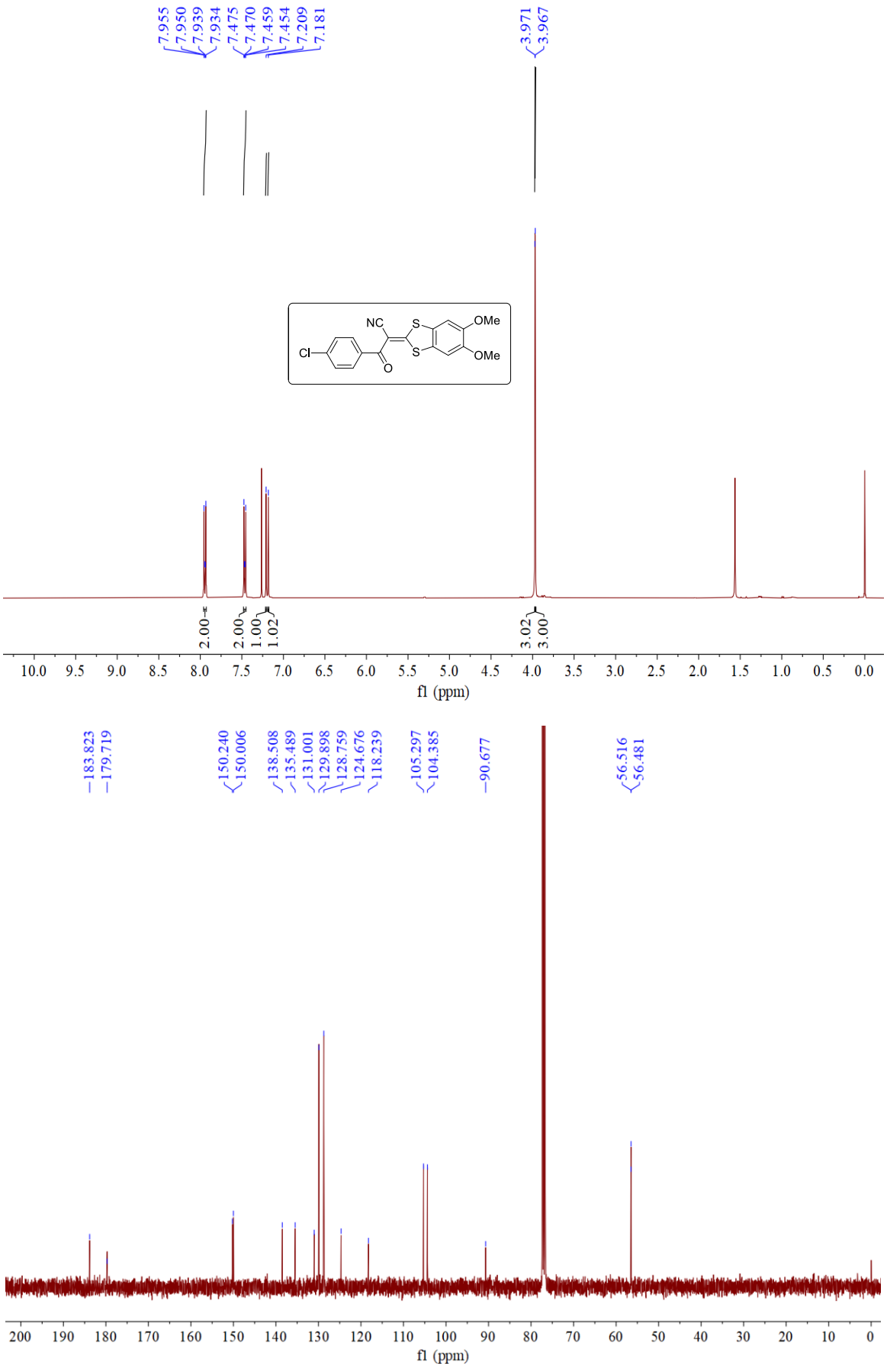

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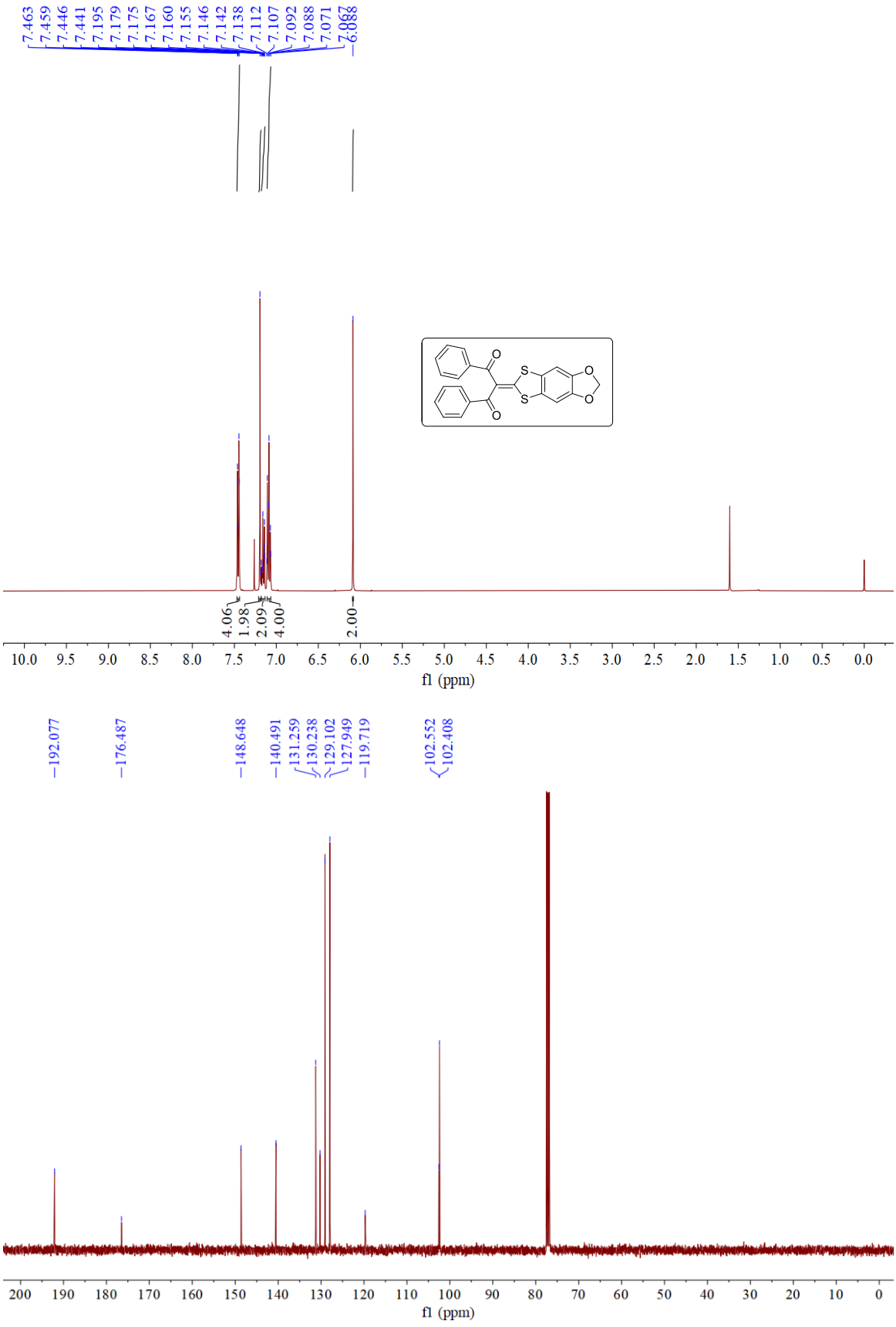

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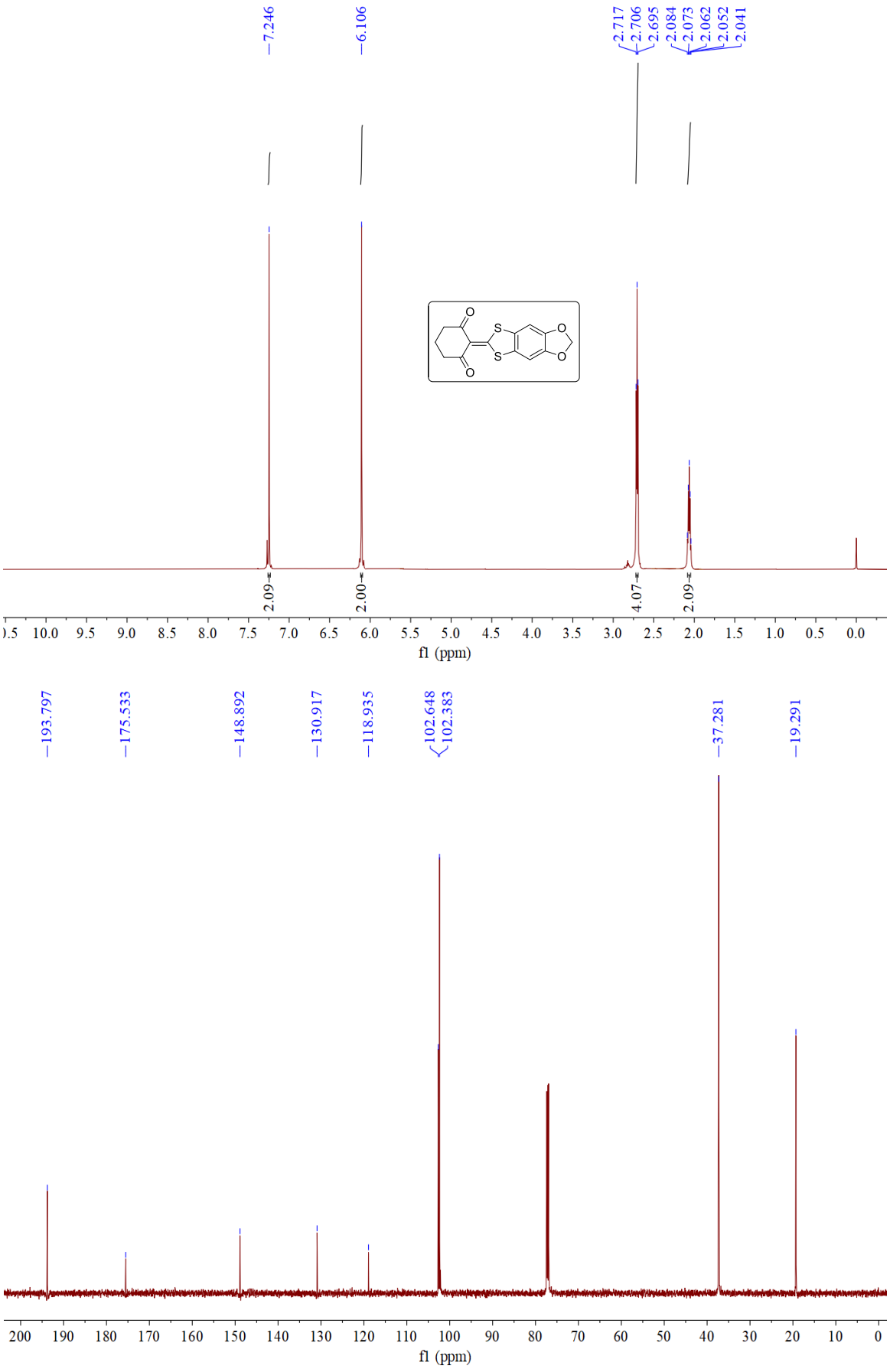

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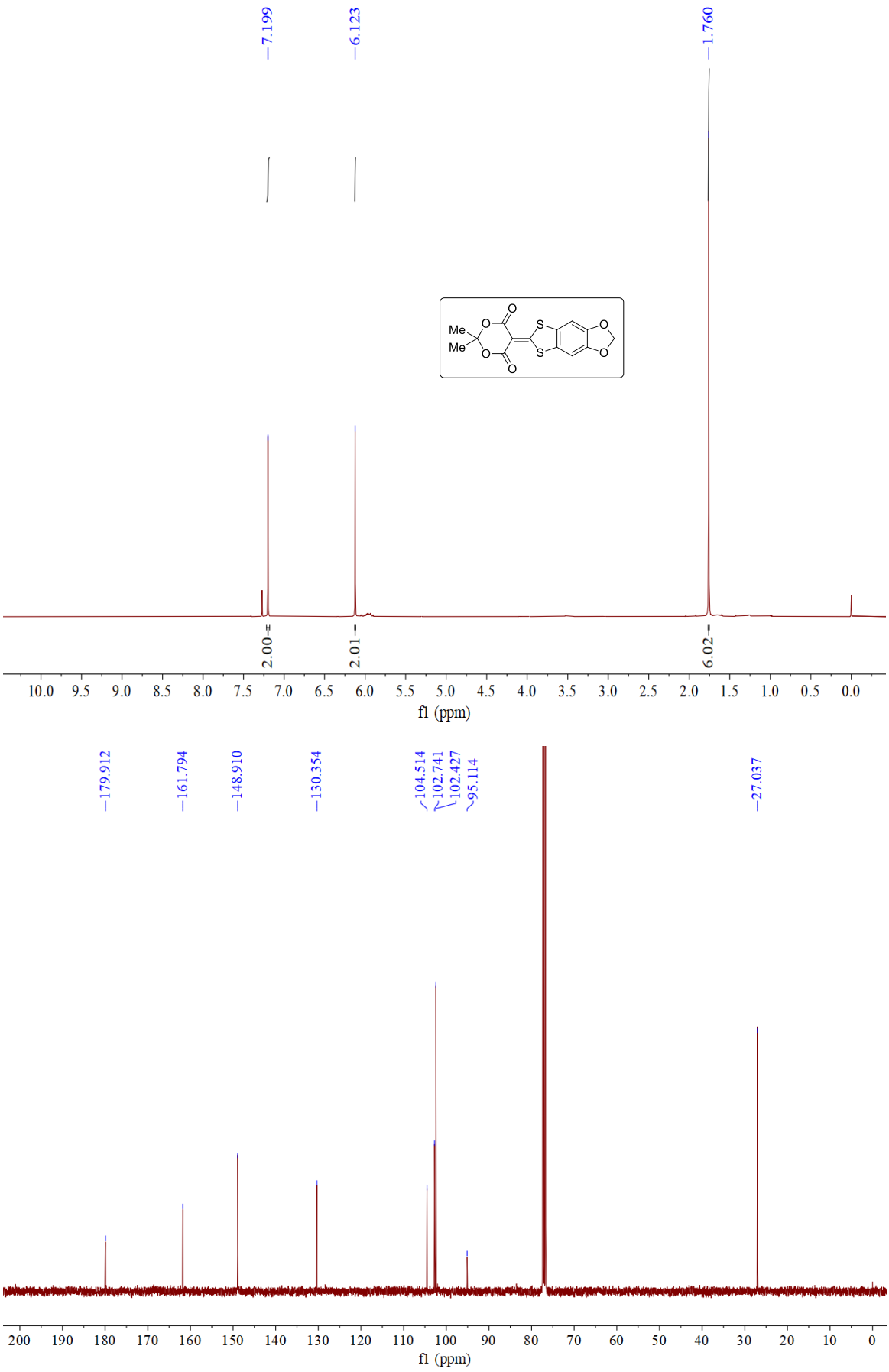

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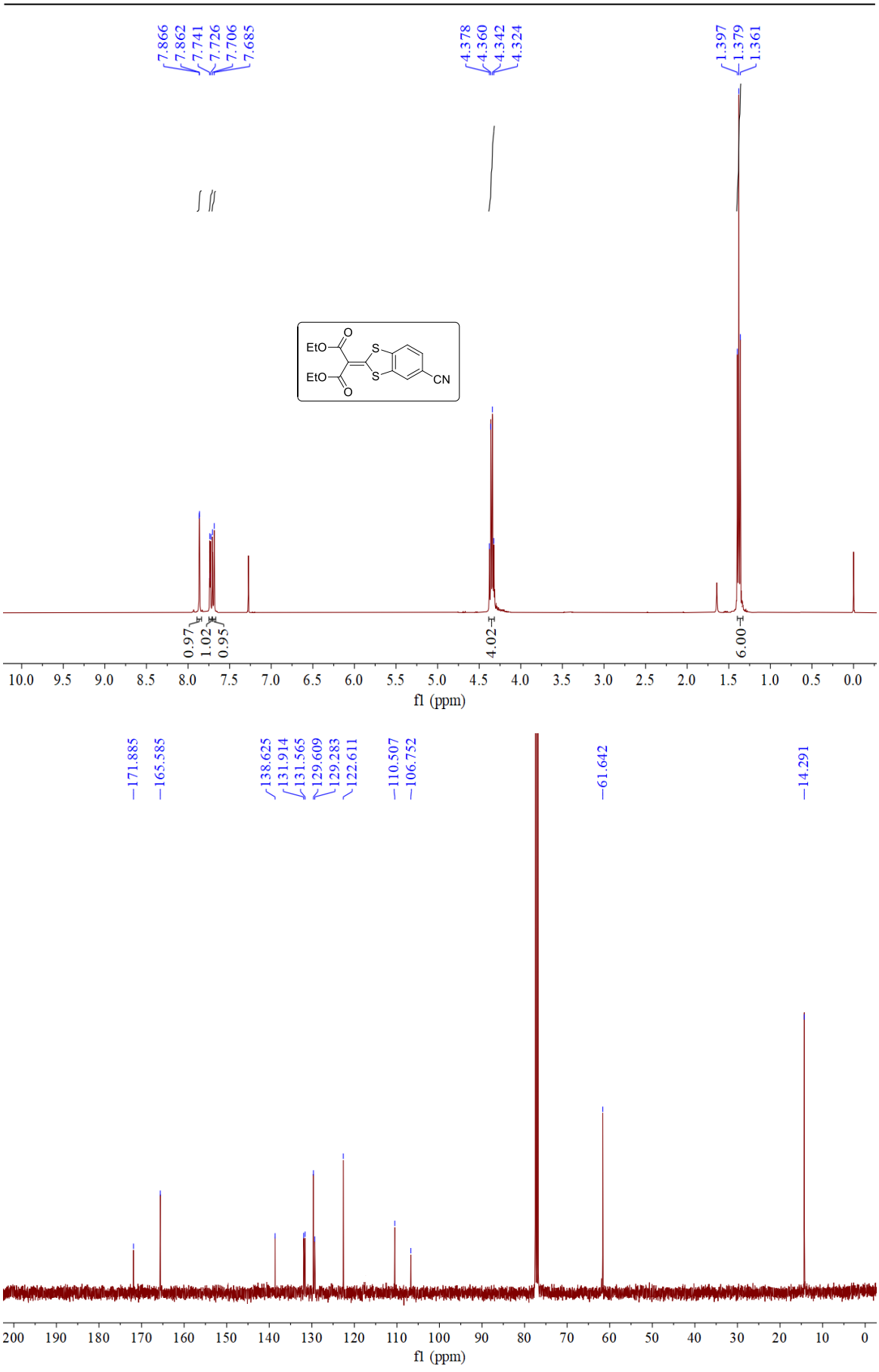

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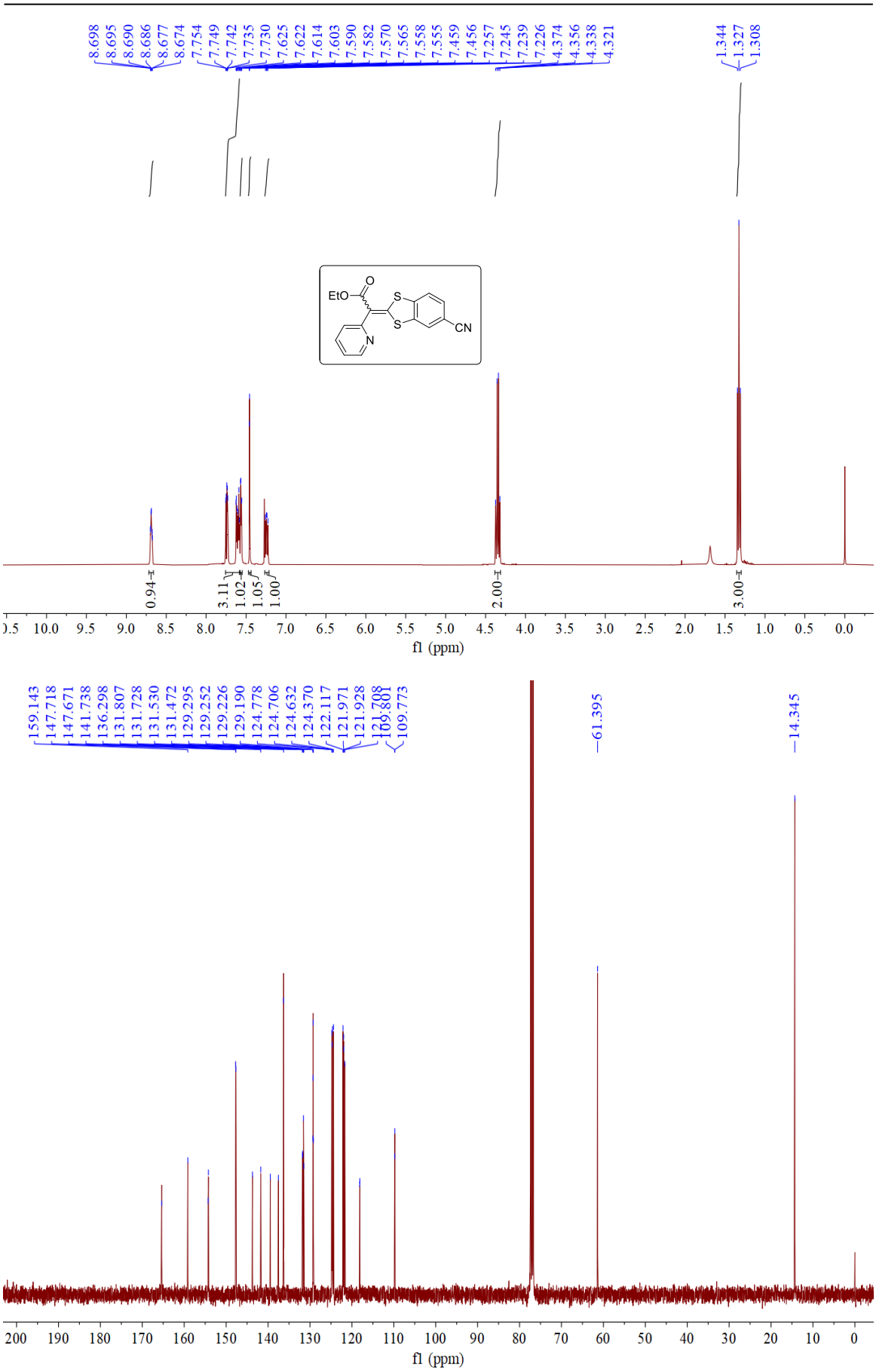
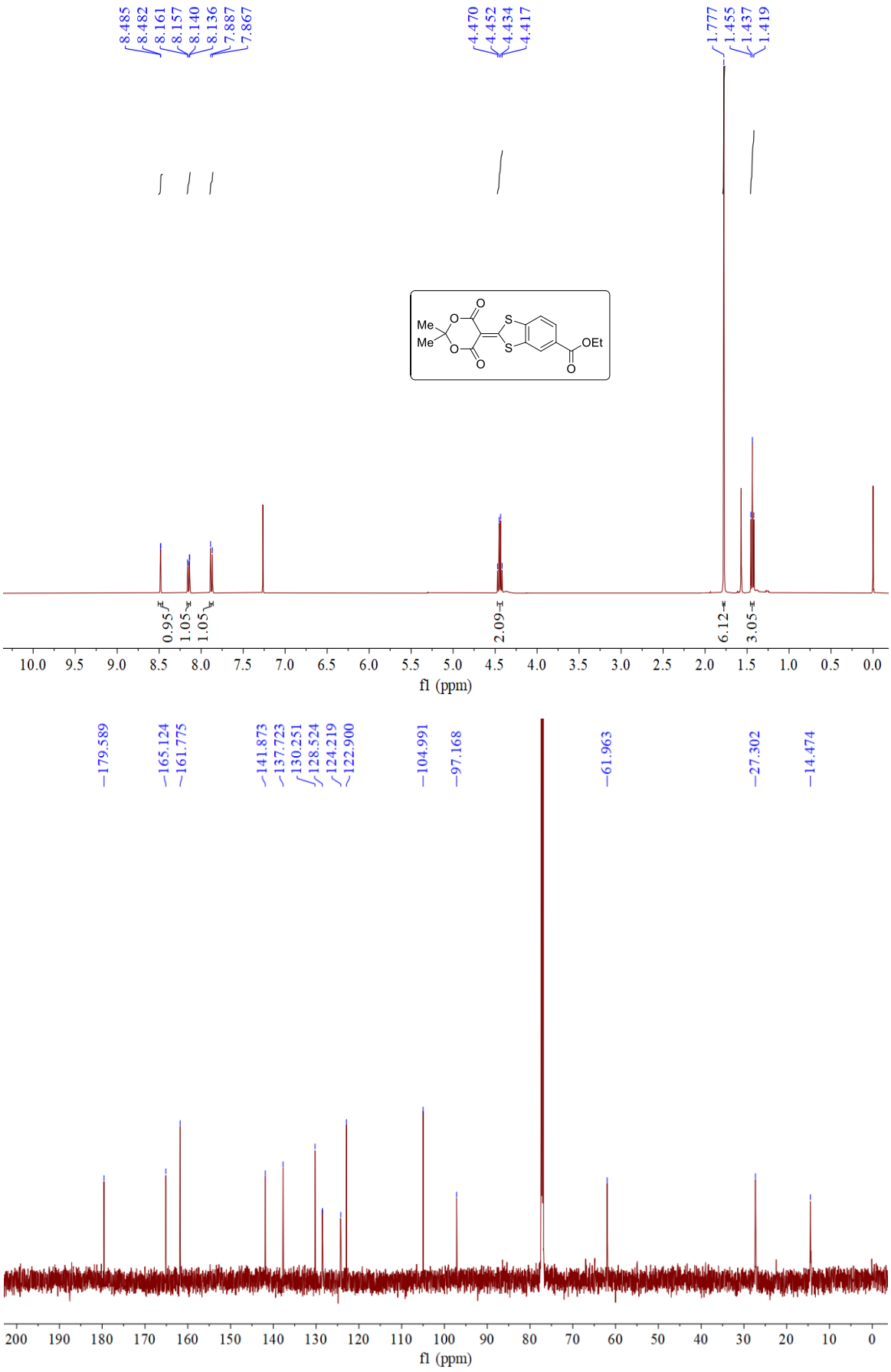


^{1}H and ^{13}C NMR spectra of compound **30t**



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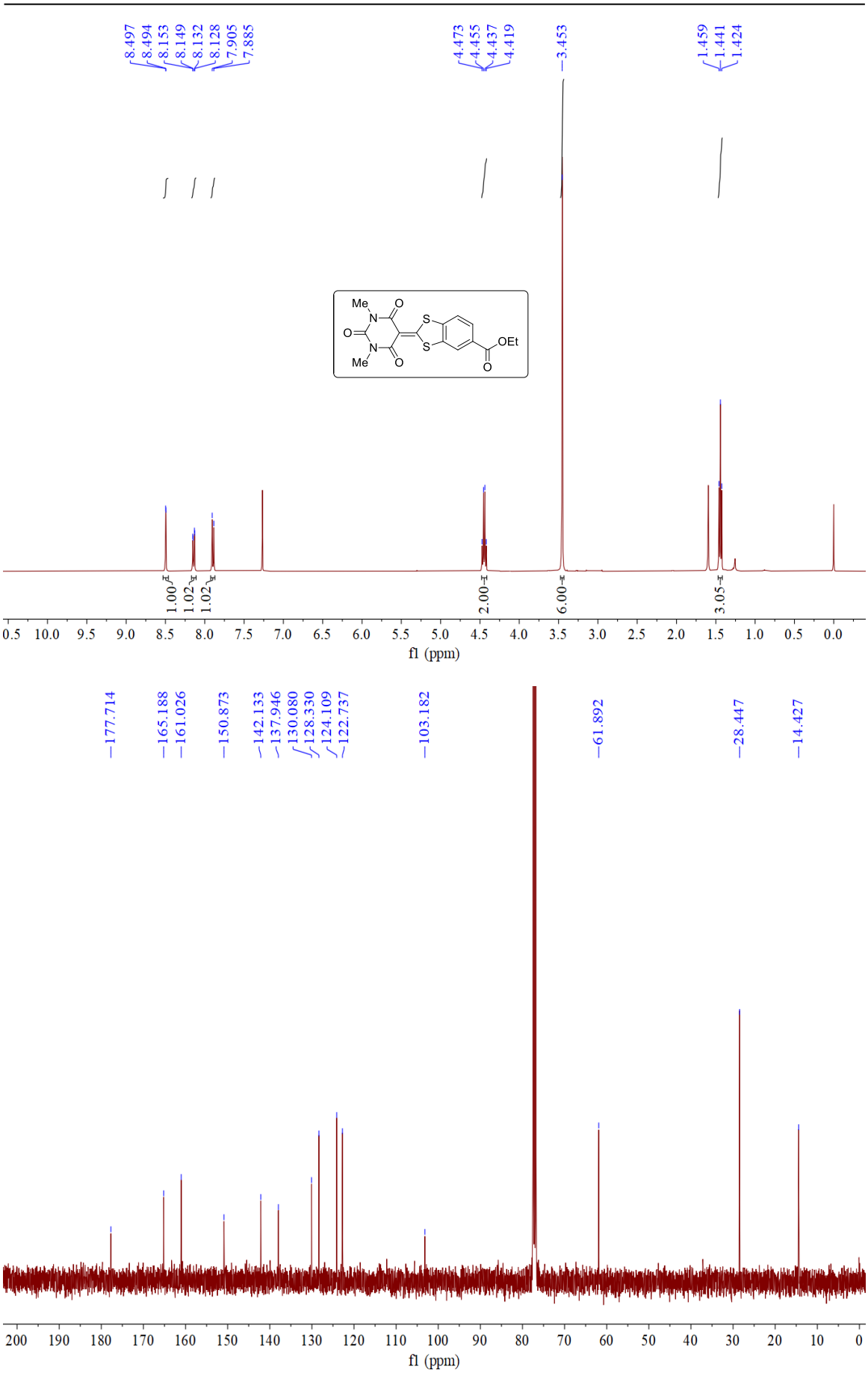

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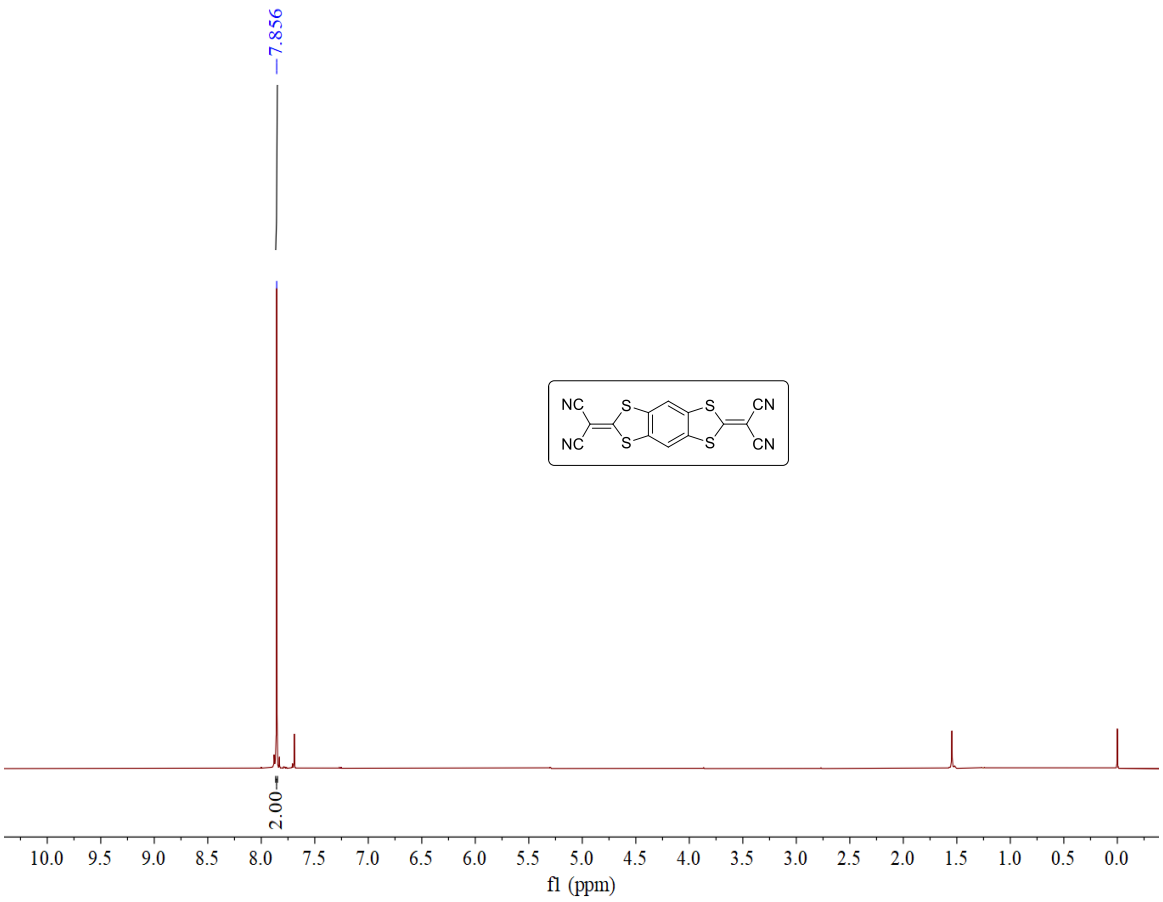
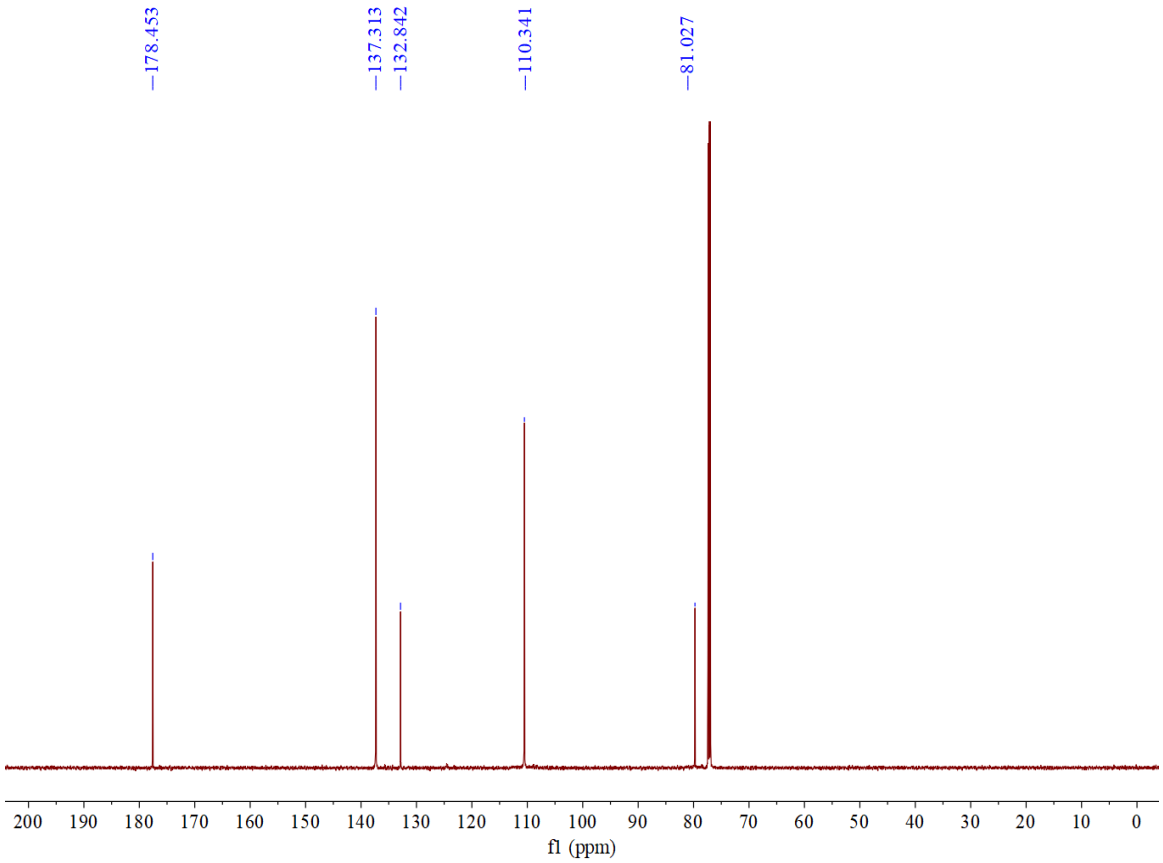
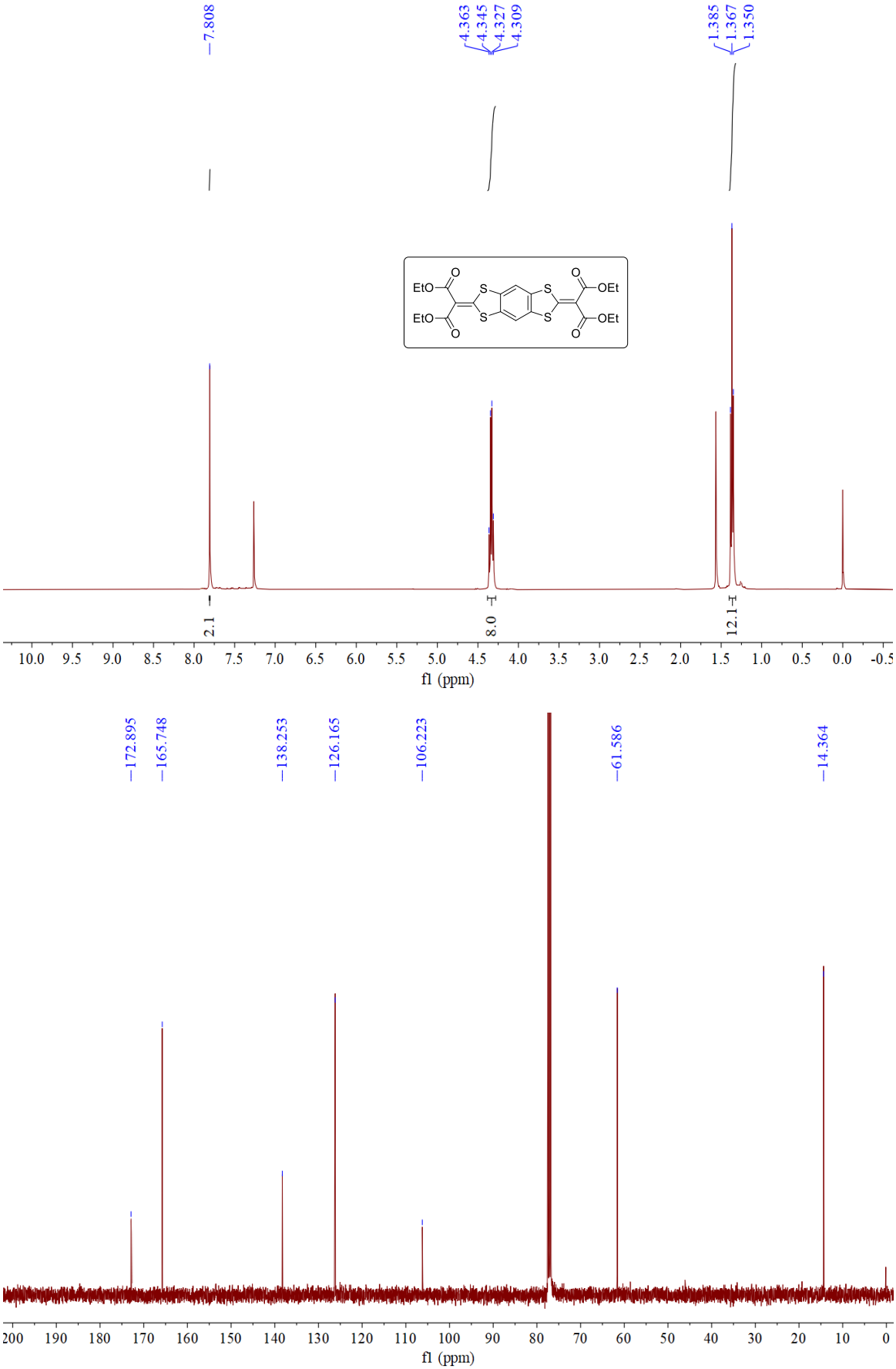




^{1}H and ^{13}C NMR spectra of compound **36a**



^{1}H and ^{13}C NMR spectra of compound **36b**

Chapter 5

*Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen-Heterocycles via Intramolecular Heteroannulation of in situ Generated 2-(Het)aryl-4-amino-5-functionalized Thiazoles**

5.1 Introduction

Thiazole heterocycles constitute an important class of structural motif, because of their presence in natural products, besides their broad application in medicinal chemistry, as well as functional organic materials.[1] Thiazole framework is shown to be an important pharmacophore for biological activity and thiazole-containing compounds show a broad range of physiological activity, such as anticancer, antiviral, antifungal, anti-inflammatory, antimicrobial, tubulin-polymerization and CDK inhibitors.[2] It is one of the most frequent nitrogen heterocycles present in several FDA-approved drugs, such as dasatinib (anticancer), abafungin (antifungal), nizatidine (antiulcer), cefixime (antibiotic), meloxicam (anti-inflammatory), fanetizole (immunoregulating activity), nitazoxanide (antiprotozoal), *etc*.[1-2] Similarly, the fusion of thiazole ring with other five-, six- and seven-membered heterocycles[3] such as thiazolo-fused pyrroles,[4-5] pyridines,[6]

*The overall results of the study described in this chapter have been communicated to *J. Org. Chem.*

pyrimidines,[7] quinolines,[8,9] benzoazepines[10] and benzodiazepines[11] generates a new class of lead structures, displaying diverse kind of biological activities (Figure 1).

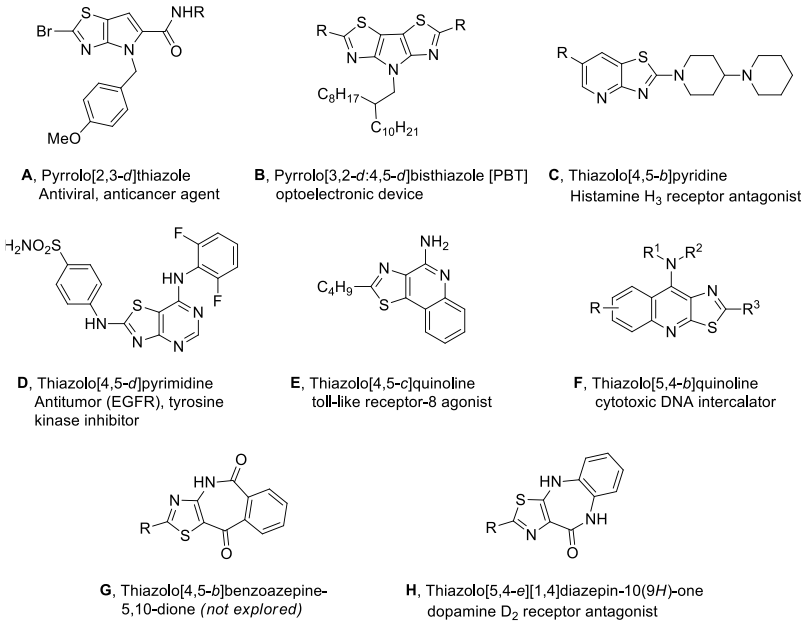


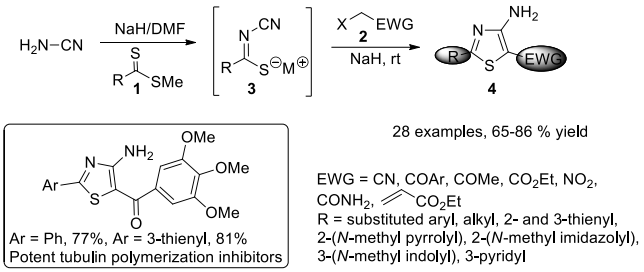
Figure 1. Biologically important multifunctional thiazoles from literature

Also, some of the bisthiazolo-fused heterocycles such as pyrrolobisthiazoles (PBT) have been synthesized and used as building blocks in the π-conjugated polymeric backbone, which have found applications in photovoltaic cells (OPV) and field-effect transistors (FETs), some of them, displaying high ionization potential, low bandgap and good solubility in optoelectronic devices (Figure 1).[5a-b] A few of the bisaryldithiazolopyridines are shown to be useful and selective chemosensors for metal ions.[5c] Therefore, in view of the importance of thiazolo-fused heterocycles in pharmaceuticals as well as in material science, the design and development of new efficient, synthetic routes for these class of structural frameworks is a useful and desirable endeavor.

Our interest in the synthesis of thiazolo-fused heterocycles results from our recent report, describing an efficient three-step, one-pot synthesis of 2-(het)aryl-4-amino-5-functionalized thiazoles **4** via a modified Thorpe-Ziegler type cyclization, involving a variety of aryl/alkyl dithioesters **1** as thiocarbonyl precursors, along with a broad range of activated methylene halides **2** as coupling partners (Scheme 1).[2] This methodology has

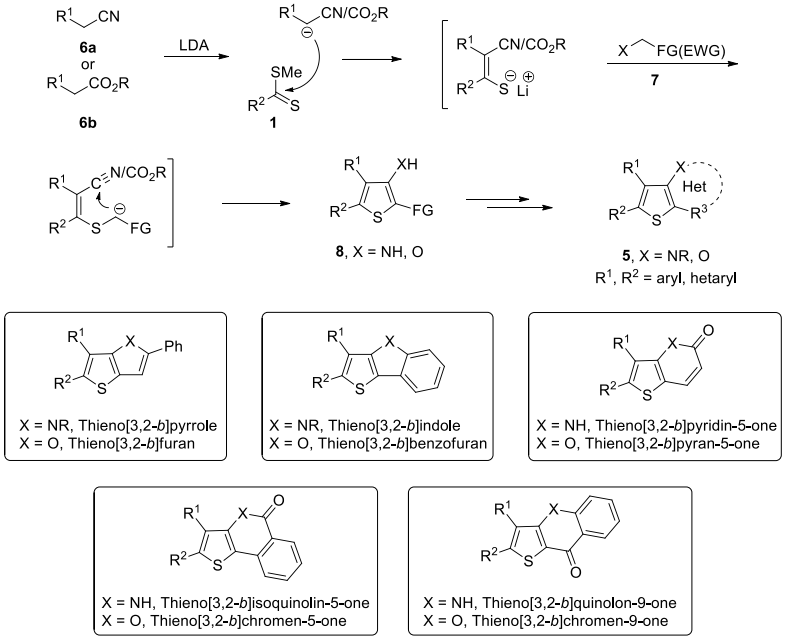
been further applied for the facile synthesis of two highly potent tubulin polymerization inhibitors.[2]

Our Previous work



Scheme 1. Synthesis of 4-amino-2,5-substituted thiazoles

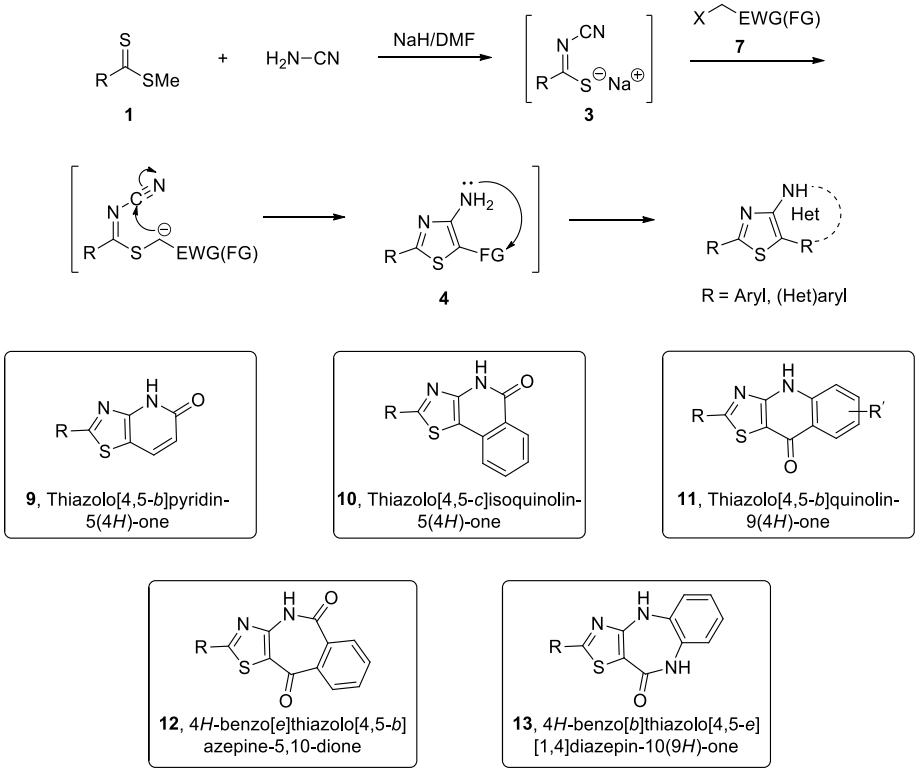
Also, Acharya and others from our laboratory have recently demonstrated new efficient protocols for assembling a range of novel thieno-fused five- and six-membered nitrogen and oxygen heterocycles **5**.[12] The overall strategy involves stepwise or in situ intramolecular cyclization of 3-hydroxy/amino-4,5-substituted-2-functionalized thiophenes **8**, which are obtained in one-pot operation, via base-mediated cyclo-condensation of aryl acetonitriles or aryl acetates **6a**-**6b** with aryl dithioesters **1** and a series of activated methylene halides **7** possessing appropriate functionalities for subsequent transformations (Scheme 2).[12]



Scheme 2. Synthesis of thieno-fused five- and six-membered *N*- and *O*-heterocycles

On the basis of these previous studies,[12] and our continued interest in heterocycle synthesis,[13-14] we further became interested in designing efficient methodologies for the synthesis of thiazolo-fused nitrogen heterocycles by elaboration of these newly synthesized 2-(het)arylthiazoles **4**, with a 4-amino and adjacent 5-functionalities. We, therefore, conceived of constructing new thiazolo-fused six- and seven-membered nitrogen heterocycle frameworks with potential biological activity and fluorescence properties, in a one-pot fashion, through sequential domino cyclization of in situ generated 4-amino 5-functionalized thiazoles **4**, instead of in stepwise manner (Scheme 3). We have successively achieved this goal and present in this paper a sequential one-step, domino synthesis of a few thiazolo-fused six- and seven-membered nitrogen heterocycles such as thiazolo[4,5-*b*]pyridin-5(4*H*)-one (**9**), thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (**10**), thiazolo[4,5-*b*]quinolin-9(4*H*)-one (**11**), 4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione (**12**), from easily available starting materials, except two-step synthesis of and 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one (**13**) (Scheme 3).

Present Work

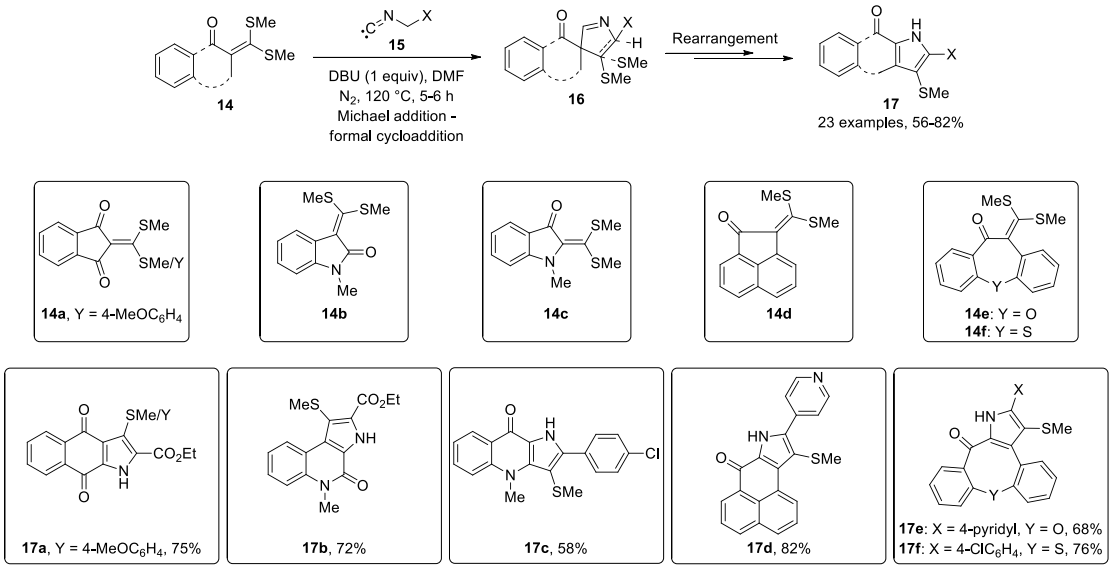


Scheme 3. Synthesis of thiazolo-fused six- and seven-membered nitrogen-heterocycles

5.2 Domino Reactions from our Research Group: Recent Examples

In recent years, domino reactions have emerged as useful, viable, and reliable alternatives for performing multistep sequences in a single operation, for the synthesis of target compounds with the desired level of complexity and diversity, besides being environmentally friendly and economically beneficial.[15] Our research group has also been involved in designing new domino reactions,[15i] and a few of the recent ones are shown in Schemes 4-7.

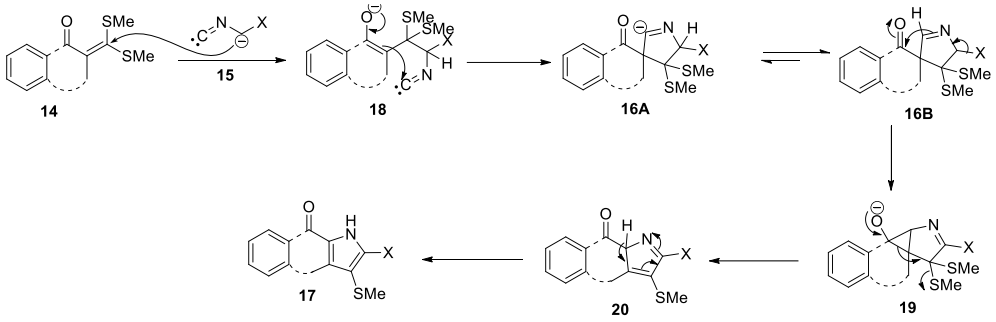
Yugandar and others from our research group have developed an efficient domino process involving a base-mediated (DBU) reaction of cyclic *α*-oxoketene dithioacetals **14** with activated methylene isocyanides **15**, which yields first the strained spiro heterocycles such as **16** via Michael addition-formal cycloaddition, which undergoes further reaction/rearrangement including cleavage of cyclic ketones **16** leading to the formation of a diverse range of annulated pyrroles **17**[15g] along with a highly regioselective one-carbon ring expansion of cyclic ketones as the key step (Scheme 4).[15g]



Scheme 4

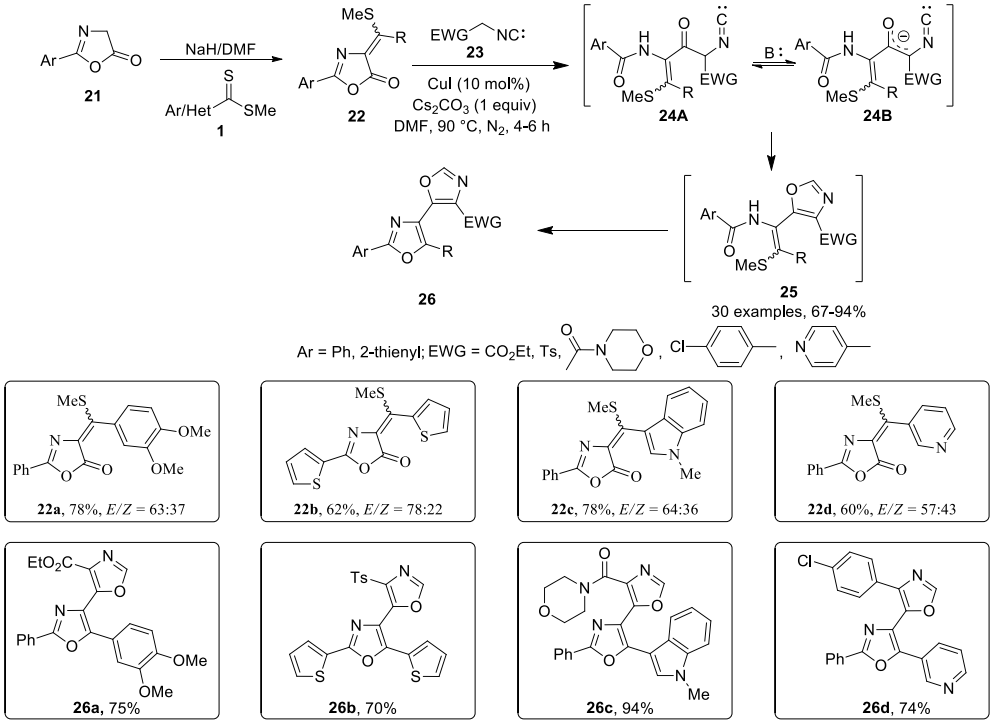
The probable mechanism for the formation of various annulated pyrroles such as **17** from the corresponding cyclic *α*-oxoketene dithioacetals **14** is shown in Scheme 5. Thus 1,4-addition -cyclization of activated methylene isocyanide anion with **14** produces initially spiropyrrolenine anion **16A**, which equilibrates to stable azaallyl anion **16B**.

Subsequent ring expansion of **16B** via strained tricyclic intermediate **19** followed by elimination of methylthio anion via intermediate **20** yields annulated pyrroles **17**.



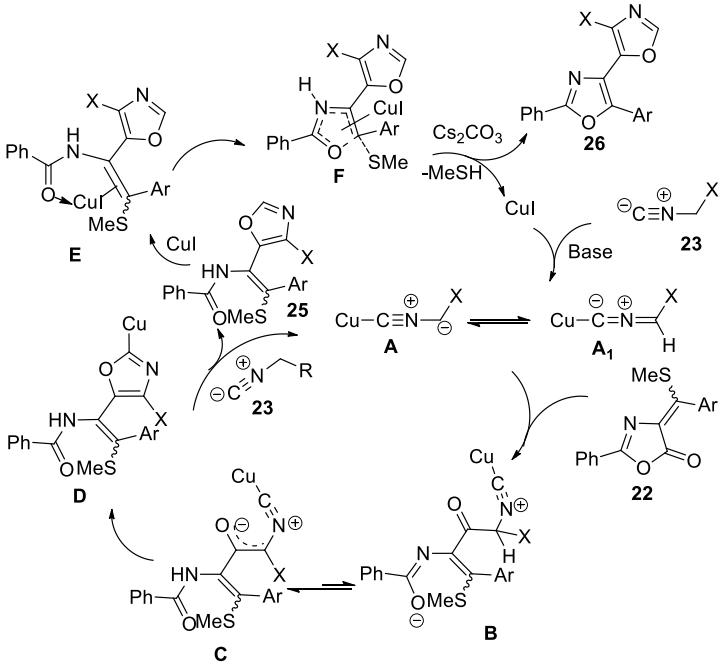
Scheme 5. Proposed mechanism for the formation of annulated pyrroles **17**

Yugandar and others from our research group have also developed an efficient, copper-catalyzed, and base-mediated nucleophilic ring-opening-cyclization of 2-phenyl/thienyl-4-[(heteroaryl)-(methylthio)methylene]-5-oxazolones **22**, [obtained via base-mediated cyclo-condensation of aryl(heteroaryl) dithioesters **1** with 2-phenyloxazolone **21**] with various activated methylene isocyanides **23** in domino fashion, providing a straightforward direct synthesis of a wide range of 2,5,4′-substituted-4,5′-bisoxazoles **26** in excellent yields (Scheme 6).[15h]



Scheme 6

The proposed detailed mechanism for the formation of a wide range of 2,5,4′-substituted-4,5′-bisoxazoles **26** from various 2-phenyl/thienyl-4-[(hetaryl)-(methylthio)methylene]-5-oxazolones **22** and activated methylene isocyanides **23** is shown in Scheme 7.



Scheme 7. A probable mechanism for Cu-catalyzed formation of bisoxazoles **26**

5.3 Results and Discussion

In view of our previous experience in designing new domino reactions from our research group, we, therefore, aimed to synthesize a few selected thiazolo-fused nitrogen heterocyclic motifs such as **9-13**, in a single-step from cyanamide, (het)aryl dithioesters **1** and activated methylene halides **7** with appropriate functionalities involving sequential domino and multicomponent reactions (Scheme 3).

Various (het)aryl dithioesters **1**, chosen as thioacyl precursors, along with a few polyfunctional activated methylene halides as coupling partners **7**, were selected to construct various thiazolo-fused heterocyclic scaffolds are shown in Charts 1 and 2 respectively. Few of the dithioesters (**1a**, **1c-f**, **1h-j**) with electron-donating groups in aromatic/heteroaromatic rings were chosen to create extended π-conjugation in the thiazolo-fused heterocycles, possessing electron attracting carbonyl groups in the

appropriate positions, which may impart fluorescent properties in the resulting donor-acceptor molecules.

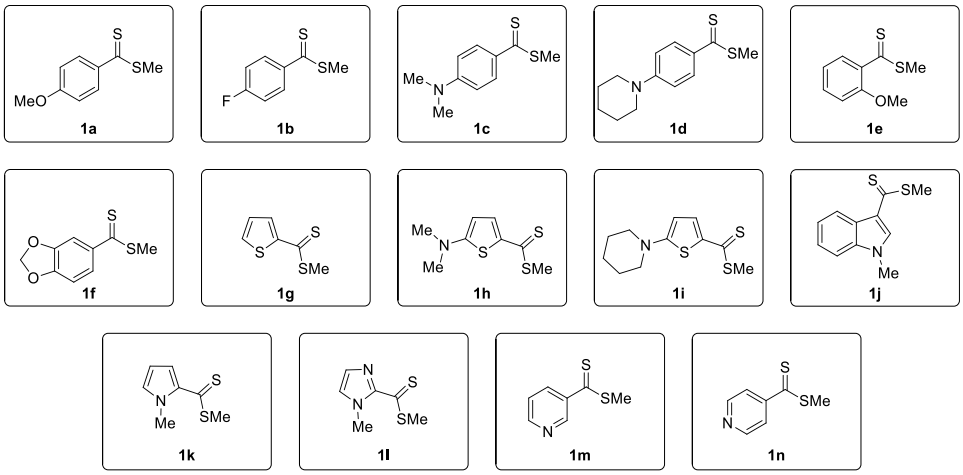


Chart 1. Various substituted aryl/(heteroaryl) dithioesters are used for the synthesis of thiazolo-fused heterocycles

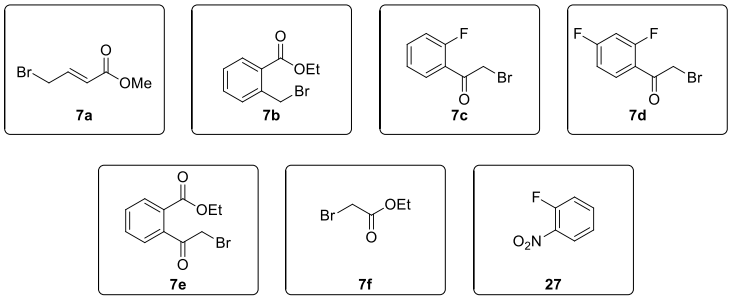


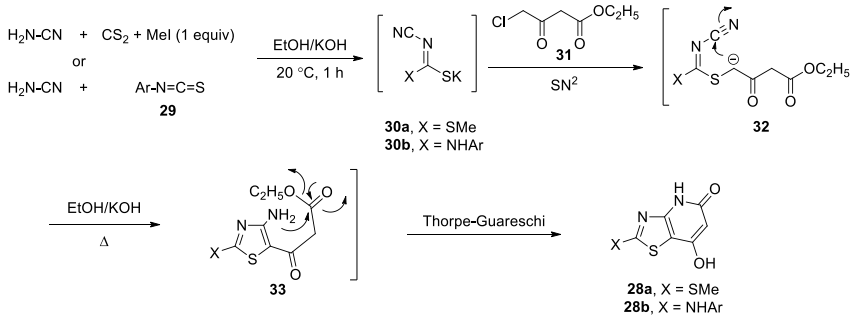
Chart 2. Various activated methylene halides or activated aromatic halides are used for the synthesis of thiazolo-fused heterocycles

5.3.1 Domino Synthesis of 2-(Het)aryl thiazolo[4,5-*b*]pyridin-5(4*H*)-one

We commenced our investigation, by undertaking domino synthesis of 2-(het)aryl-thiazolo[4,5-*b*]pyridin-5(4*H*)-ones **9** as displayed in Scheme 9. Thiazolo[4,5-*b*]pyridine derivatives are shown to display a variety of biological activity and clinical applications,[6a] such as non-histamine H_3 receptor antagonists,[6e] anti-inflammatory[15a], tyrosine kinase (EGFR) inhibitors,[15b] leukotriene A_4 hydrolase inhibitors,[15c] G-protein-coupled receptor ($mGluR_5$) antagonists[15d] and as 3',5'-cyclic adenosine monophosphate phosphodiesterase (PDE) III inhibitors,[15e] as well as antibacterial[15f] and anticancer[15f]

activities. There is considerable interest in developing new synthetic routes for this class of target molecules with the result.

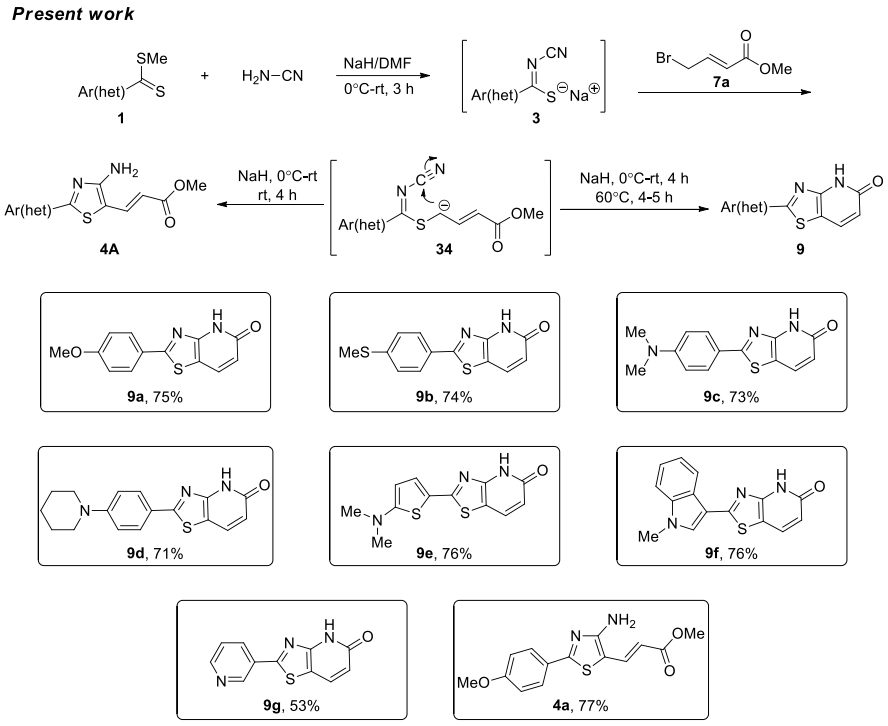
Most of the syntheses of thiazolo[4,5-*b*]pyridines, reported in the literature, involve two-stage protocols, either via annulation of thiazole ring to pyridine precursors[6e,16,17] or in a reverse way, starting from preconstructed thiazole derivatives.[18] There are only two isolated examples of direct one-step synthesis of 7-hydroxy[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones **28**, involving treatment of *N*-cyanothioimidate salts **30**,[19a-b] with ethyl 4-chloroacetoacetate **31** in ethanolic KOH, with the initial formation of ethyl 3-(4-amino-2-substituted thiazol-5-yl)-3-oxopropanoate **33**, which undergo concurrent intramolecular cyclo-condensation, leading to the construction of pyridinone ring of **28**. The *N*-cyanothioimidate salts **30** are derived from the reaction of cyanamide, either with CS_2 or aryl isothiocyanates **29**, thus limiting the substituent pattern at 2-position to either 2-methylthio or 2-anilino groups (Scheme 8).



Scheme 8

In line with our previous study on the synthesis of thieno[3,2-*b*]pyridinones,[12] we selected few (het)aryl dithioesters **1** bearing electron-donating aryl groups or heterocyclic substituents, as thioacyl precursors, along with methyl bromocrotonate **7a** as halogenated methylene partner, and conceived of constructing a new class of push-pull thiazolopyridin-2-ones with potential fluorescent properties. Thus when cyanamide was reacted with 4-methoxyphenyldithioester **1a** in presence of NaH and DMF, followed by the addition of methyl bromocrotonate **7a** and subsequent addition of another equivalent (2.2 equiv.) of NaH and stirring for 4 h at room temperature, the corresponding 4-aminothiazole-5-acrylate **4a** was isolated as the sole product in good yield (Scheme 9).[2] However when the reaction mixture was heated at 60 ºC, for 5 h, after addition of the second lot of NaH, the product isolated was found to be 2-(4-

methoxyphenyl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one **9a**, formed exclusively in 75% yield, apparently by in situ intramolecular cyclization of open-chain acrylate **4A** (Scheme 9). The other 2-(4-substituted aryl) thiazolopyridinones **9b-d** along with 2-[(5-dimethylamino)-2-thienyl] **1h**, 2-(*N*-methyl-3-indolyl) **1j** and 2-(3-pyridyl) **1m** analogs **9e-g** were similarly obtained in overall good yields under identical conditions, displaying yellow-green fluorescence (Scheme 9).



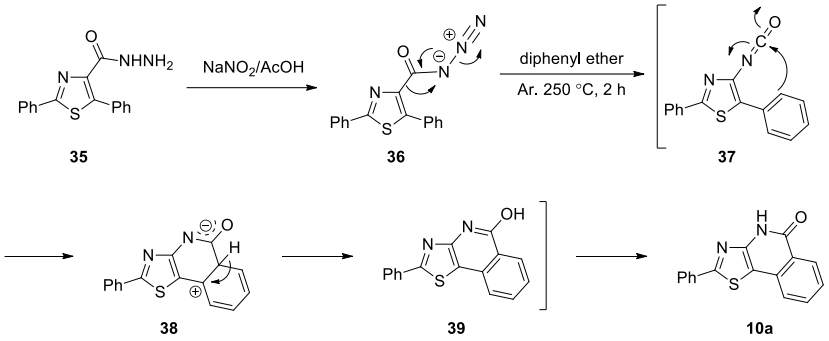
[a]Reaction conditions: **1** (1 mmol), H_2N-CN (1 mmol), NaH (2.2 mmol), in DMF (4 mL) stirring for 3 h at rt, followed by addition of solution of **7a** (1 mmol) in DMF (2 mL) stirring for 3 h at rt, and addition of another lot of NaH (2.2 mmol) and further stirring for 4-5 h at 60 ºC. Yield of isolated products.

Scheme 9. Synthesis of 2-(het)aryl substituted thiazolo[4,5-*b*]pyridin-5(4*H*)-ones **9**[a]

5.3.2 Domino Synthesis of 2-(Het)aryl thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones

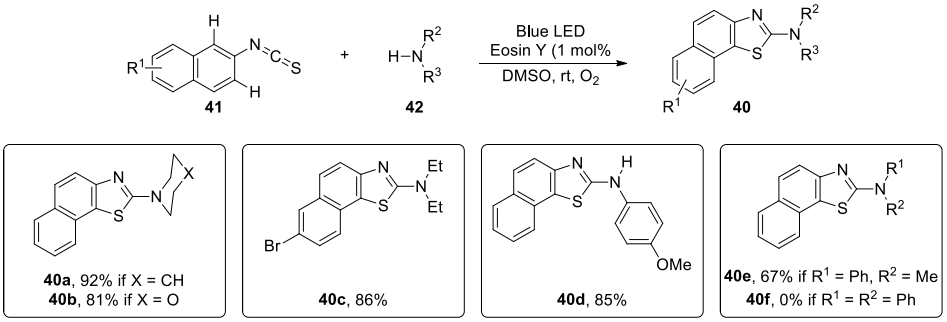
After successful synthesis of a series of 2-substituted thiazolo[4,5-*b*]pyridinones **9** (Scheme 9), we next investigated the construction of 2-substituted thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones **10** in domino fashion, by employing ethyl 2-bromomethyl benzoate **7b** as halo substituted active methylene component, as shown in the Scheme 12. Very few examples of thiazolo[4,5-*c*]isoquinoline framework along with their synthesis are documented in the literature,[20] whereas there is no report on the biological activity of this heterocyclic scaffold. Thus in an isolated case, Mamedov and co-workers observed the formation of 2-phenyl-4*H*-thiazolo[4,5-*c*]isoquinolin-5-one **10a** in 65% yield, during

thermolysis of 2,5-diphenylthiazole-4-carboxylic acid azide **36** via intramolecular cyclization of 2,5-diphenylthiazol-4-yl isocyanate **37** intermediate generated in the reaction (Scheme 10).[20a]



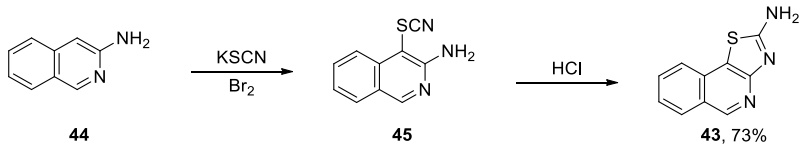
Scheme 10

Yang and co-workers in a recent paper, have described the synthesis of 2-dialkylamino substituted naphtho[2,1-*d*]thiazol-2-amines **40** in good yields, via visible-light-induced cross-dehydrogenative coupling of 2-isothiocyanatonaphthalenes **41** with various secondary amines **42** in the presence of oxygen (Scheme 11).[20b]



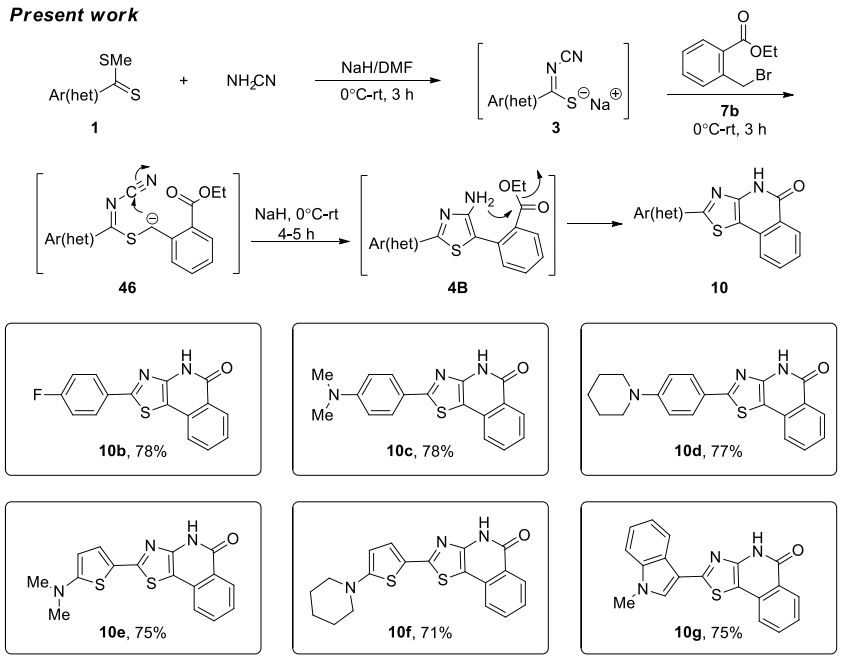
Scheme 11

Previously, 2-aminothiazolo[4,5-*c*]isoquinoline **43** has also been obtained in multistep synthesis from 3-aminoisoquinoline **44** by intramolecular cyclization of 3-amino-4-thiacyanoquinoline **45** under acidic conditions (Scheme 12).[20c]



Scheme 12

In the present study, we, therefore, proceeded with the synthesis of 2-(4-fluorophenyl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one **10b** by reacting in situ generated *N*-cyanothioimidate salt **3** from 4-fluorophenyl dithioester **1b** and cyanamide, with one equiv of ethyl 2-bromomethyl benzoate **7b** under standard conditions at room temperature (Scheme 13). The reaction was complete within 4 h, with the formation of a single product (78%), which was characterized as 2-(4-fluorophenyl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one **10b** on the basis of its spectral and analytical data. Unlike our previous studies on the synthesis of 2,3-substituted thieno[3,2-*c*]isoquinolin-5-ones,[12] no trace of the open-chain 4-amino-5-(2-carboethoxyphenyl)thiazole intermediate **4B** was isolated from the reaction mixture. The other 2-substituted thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones **10c-g** were also obtained in overall high yields from the using dithioesters **1c-d**, **1h-i** and **1j**, cyanamide, and **7b** and under identical conditions (Scheme 13). All these newly synthesized thiazoloisoquinolones were found to exhibit green fluorescence except 4-fluoro **10b** and 2-(*N*-methyl-3-indolyl) **10g** substituted derivatives.



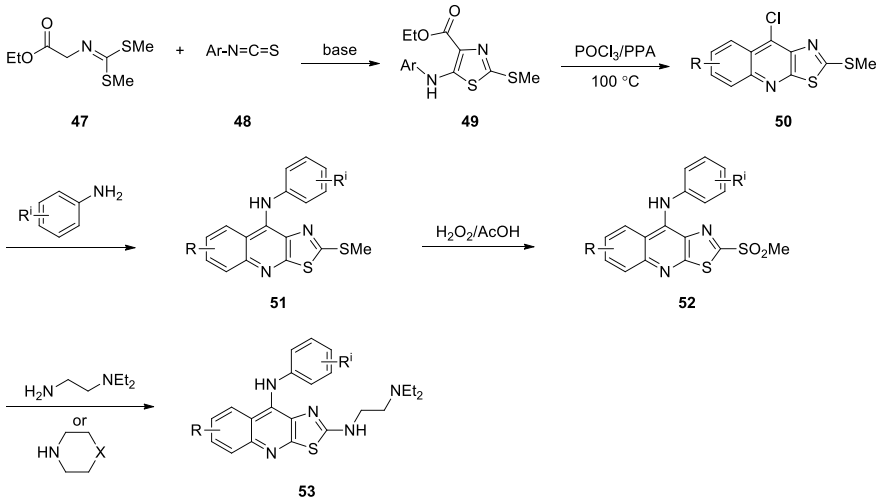
[a]Reaction conditions: **1** (1 mmol), H_2N-CN (1 mmol), NaH (2.2 mmol), in DMF (4 mL) stirring for 3 h at rt, followed by addition of a solution of **7b** (1 mmol) in DMF (2 mL) stirring for 3 h at rt, and addition of another lot of NaH (2.2 mmol) and further stirring for 4-5 h at rt. Yield of isolated products.

Scheme 13. Synthesis of 2-(het)aryl thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones **10**[a]

5.3.3 Domino Synthesis of 2-(Het)aryl Thiazolo[4,5-*b*]quinolin-9(4*H*)-ones

We next ventured into developing a one-pot domino synthesis of thiazolo[4,5-*b*]quinolin-9(4*H*)-ones **11** according to the synthetic design as depicted in Scheme 14. Our literature search at this stage revealed, that several 2-(methylthio/alkylamino)-9-aryl/alkylamino-thiazolo[5,4-*b*]quinolines have been synthesized and are shown to display strong cytotoxicity against several cancer lines, also inhibiting human topoisomerase II enzyme, *in vitro* (Figure 1).[9,21] On the other hand, the related thiazolo[4,5-*b*]quinolines have been scarcely investigated[8a,22] and only a few isolated and old syntheses of thiazolo[4,5-*b*]quinolines have been reported in the literature,[23] whereas, their biological profile is completely unexplored. This may be possible, due to the lack of general synthetic methods for this class of regioisomeric heterocyclic framework.

Alvarez-Ibarra[21a] and others[21b-d] have widely studied the synthesis and biological activity of a series of 2-(methylthio)/amino-9-hydroxy/ary/alkyllamino-thiazolo[5,4-*b*]quinoline derivatives such as **53** (Scheme 14) and **F** (Figure 1), which are shown to be cytotoxic on several cancer cell lines as well as being DNA intercalators and inhibitor of human topoisomerase II *in vitro*. These thiazolo[5,4-*b*]quinolines **53** have been synthesized from the corresponding 2-(methylthio)-5-anilino-thiazolo-4-carboxylates **49**, involving their intramolecular cyclo-condensation with $POCl_3$/PPA to give **50** and subsequent replacement of 9-chloro and 2-(methylthio) derivative in **50** with various

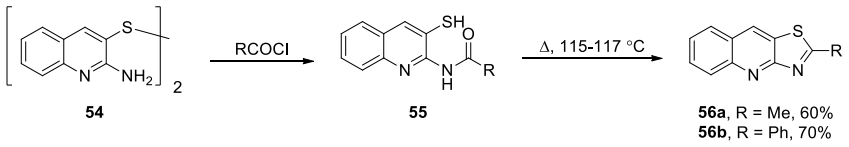


Scheme 14

amines affording 9-anilino- or 2-alkylamino-9-anilino derivatives **51** and **53** in good yields (Scheme 10).[8b] The corresponding 2-(methylthio)-4-(ethoxycarbonyl)-5-

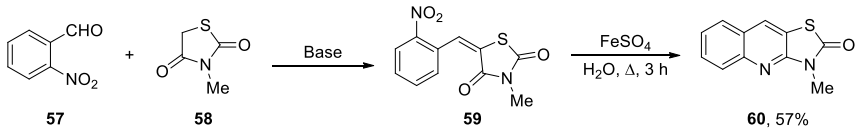
(arylamino)thiazole precursors **49** were synthesized in high yields via base-mediated cyclization of ethyl *N*-[bis(methylthio)methylene]glycinate **47** and aryl isothiocyanates **48** (Scheme 14).[22]

Despite the overall synthetic and biological studies on various substituted thiazolo[5,4-*b*]quinolines, our literature survey showed the synthesis of the corresponding regioisomeric thiazolo[4,5-*b*]quinolines has been scarcely examined,[8a,22] whereas the biological profile of these compounds completely remained unexplored. Only two isolated, old syntheses of thiazolo[4,5-*b*]quinolines have been reported in the literature by Tanasescu and co-workers.[23] Thus, in one example, 2-methyl/phenylthiazolo[4,5-*b*]quinolines **56a-b** have been synthesized via acylation of 2-amino-3-mercapto disulfide **54** followed by thermal cyclization of *N*-acyl derivatives **55** at higher temperature (Scheme 15).[23a]



Scheme 15

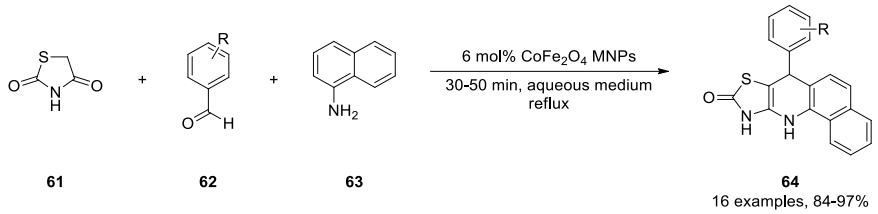
Also, in an another example, the corresponding *N*-methyl-2-oxo-thiazolo[4,5-*b*]quinoline **60** was obtained in 57% yield by reductive cyclization of *N*-methyl-5-(*o*-nitrobenzylidine)-2,4-dioxoathiazolidine **59**, obtained by base-mediated aldol condensation of *o*-nitronbenzaldehyde **57** with 2,4-dioxathiazolidine **58** (Scheme 16).[23c]



Scheme 16

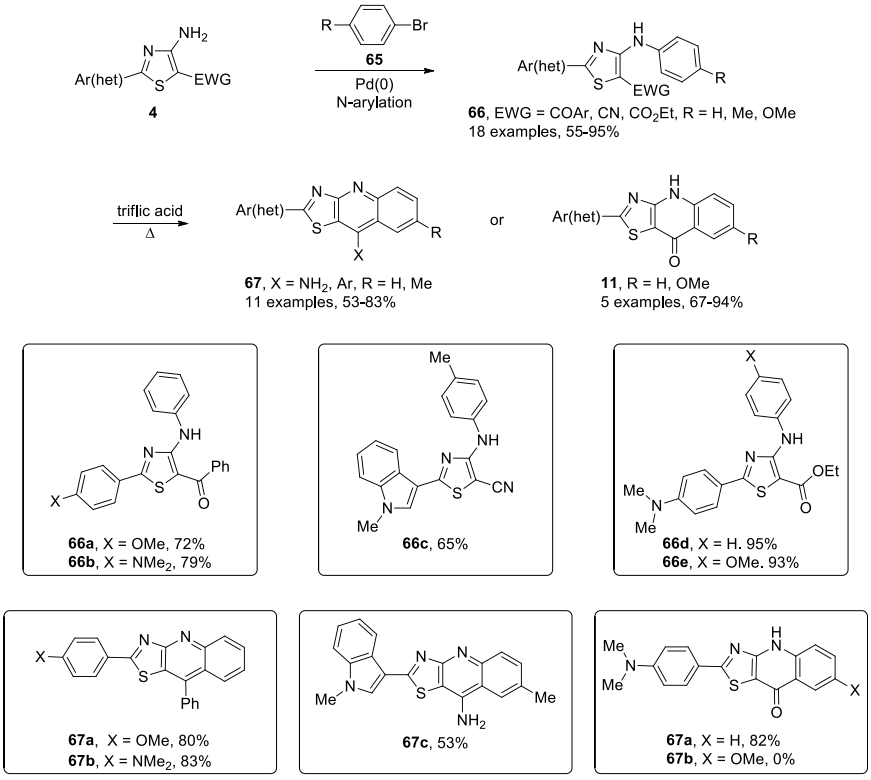
Recently, Hamad and co-workers have developed a simple three-component procedure for the green synthesis of 7-phenyl-10,11-dihydrobenzo[*h*]thiazolo[4,5-*b*]quinolin-9(7*H*)-one derivatives **74**,[23d] via magnetically recyclable $CoFe_2O_4$

nanoparticles-catalyzed cyclization of thiazolidine-2,4-dione **71**, substituted aromatic aldehyde **72** and naphthalen-1-amine **73** in aqueous media, under reflux conditions (Scheme 17).



Scheme 17

We have recently developed an efficient methodology for the synthesis of novel hitherto unexplored, 2-(het)aryl-9-amino/arylthiazolo[4,5-*b*]quinolines **67** and the corresponding thiazolo[4,5-*b*]quinolin-9(4*H*)-ones **11** via two-step synthetic elaboration of 2-substituted-4-amino-5-cyano/aroyl/carboethoxy thiazoles **4** (Scheme 18).[2,13e] The

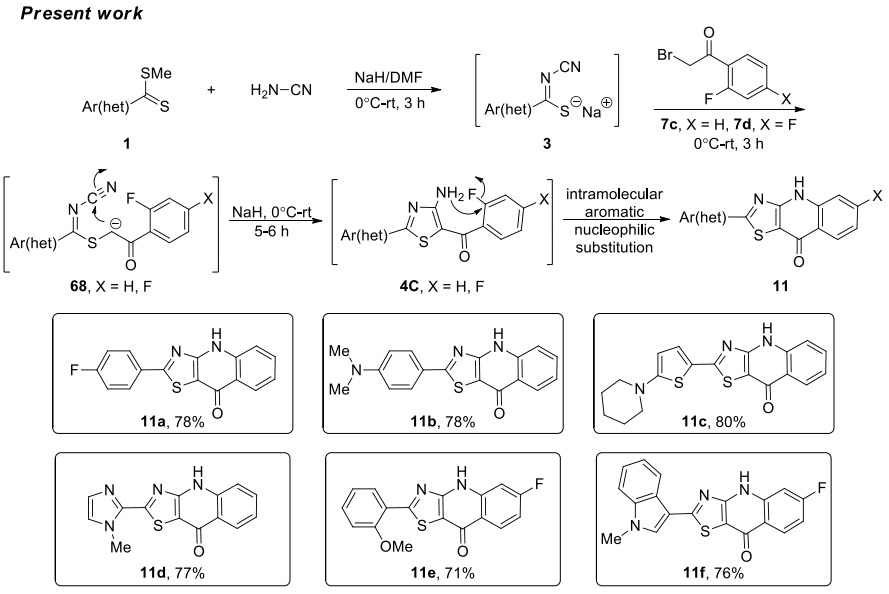


Scheme 18

the overall approach involves Pd-catalyzed *N*-arylation of these 2-(het)aryl-4-amino-5-functionalized thiazoles **4** with bromoarenes **65** to the corresponding 2-(het)aryl-4-*N*-

arylamino-5-functionalized thiazoles **66**, by Buckwald-Hartwig coupling and successive triflic acid-mediated intramolecular cyclo-condensation of **66** to the target compounds **76** or **11** (Scheme 18).[13e]

In the present study, we planned to develop an alternate straightforward domino synthesis of 2-substituted thiazolo[4,5-*b*]-quinolin-9(4*H*)-ones **11** by using *o*-fluorophenacyl bromides such as **7c-d** as halomethylene precursors, and it was contemplated that the intermediate 4-amino-5-(2-fluorobenzoyl)thiazole **4C** formed, by concurrent *S*-alkylation of thioimidate salt **3** with **7** and subsequent Thorpe-Ziegler cyclization of the resulting intermediate **68**, should afford the 4-amino-5-(*o*-fluoroaroyl) thiazole **4C** (Scheme 19). We further anticipated that the 4-amino group of the thiazole **4C**, might undergo in situ spontaneous intramolecular aromatic nucleophilic substitution on *o*-fluorobenzoyl moiety, yielding directly 2-(het)aryl-thiazolo[4,5-*b*]-quinolin-9-ones such as **11** in one-pot reaction (Scheme 19). Indeed, to our delight, the reaction proceeded as expected, when *N*-cyanothioimdate salt **3a** from cyanamide and 4-fluorophenyl dithioester **1b**, was reacted with *o*-fluorophenacyl bromide **7c** at room temperature, under



[a]Reaction conditions: **1** (1 mmol), H_2N-CN (1 mmol), NaH (2.2 mmol), in DMF (4 mL) stirring for 3 h at rt, followed by addition of a solution of **7c**/**7d** (1 mmol) in DMF (2 mL) stirring for 3 h at rt, and addition of another lot of NaH (2.2 mmol) and further stirring for 5-6 h at rt. Yield of isolated products.

Scheme 19. Synthesis of 2-(het)aryl thiazolo[4,5-*b*]quinolin-9(4*H*)-ones **11**[*a*]

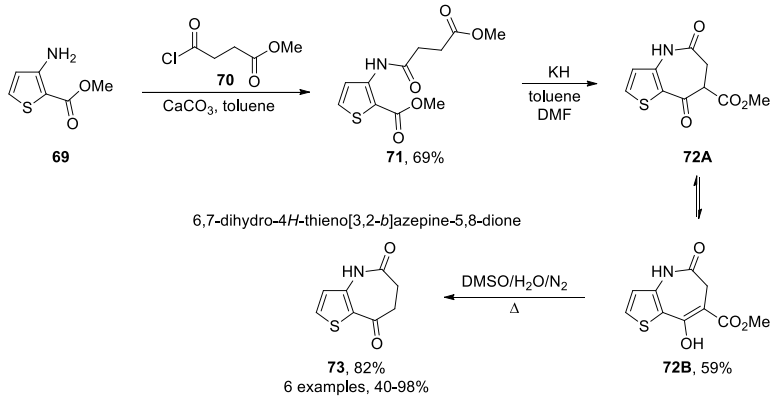
standard reaction conditions, yielding 2-(4-fluorophenyl)thiazolo[4,5-*b*]-quinolin-9(4*H*)-one **11a** in 78% yield. The generality of the reaction was further established by synthesis

of various 2-substituted thiazolo[4,5-*b*]quinolin-9(4*H*)-one analog, bearing 2-[4-(dimethylamino)phenyl] (**11b**), 2-[5-(*N*-piperidinyl)-2-thienyl] (**11c**), and 2-(2-imidazolyl) (**11d**) in high yields from the appropriate dithioesters and *o*-fluorophenacylbromide **7c** (Scheme 19). Similarly, the corresponding 6-fluoro-2-(hetaryl)-thiazolo[4,5-*b*]quinolin-9(4*H*)-ones **11d-e** were also obtained in good yields, when 2,4-difluorophenacyl bromide **7d** was employed as activated methylene coupling partner, thus adding further diversity to the basic skeleton of **11** (Scheme 19).

5.3.4 Domino Synthesis of 2-(Het)aryl-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione

After successful elaboration of thiazolo-annulated six-membered heterocycles such as thiazolopyridones **9**, thiazoloisoquinolones **10**, and thiazoloquinolones **11** via one-pot construction of both the rings in domino fashion (Schemes 9, 13, 19), we further ventured of designing parallel strategies for the construction of thiazolo-fused seven-membered nitrogen heterocycles (Schemes 23 and 25). Benzo-fused seven-membered nitrogen heterocycles such as benzoazepinediones and benzodiazepinones have drawn considerable attention, because of their diverse biological activities, especially as CNS agents.[24] Therefore, much effort has been directed towards the development of efficient methods for the construction of these fused heterocyclic cores.[24] On the other hand, heterocyclo-fused benzoazepinediones and benzodiazepinones have not been much investigated in terms of their synthesis and biological activity, probably because of difficulty in the synthesis of these structural motifs.[25]

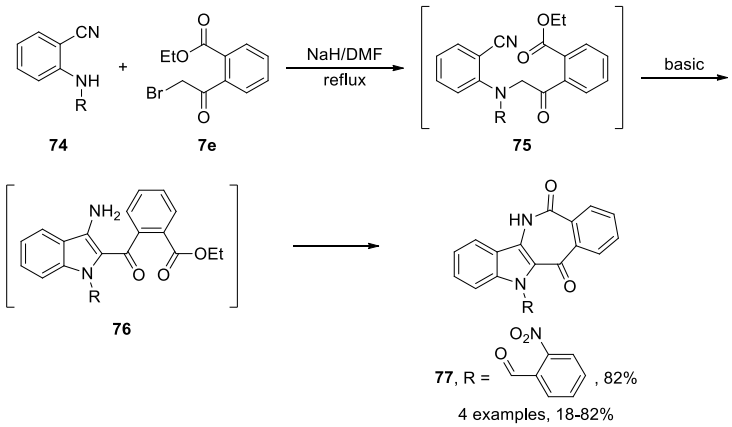
Our literature search revealed that the syntheses of a few heterocyclo-fused azepinediones have been reported. Thus thieno-fused azepindione **73**, has been



Scheme 20

synthesized starting from 3-aminothiophene-2-carboxylate **69**, via its *N*-acetylation to give amide **71**. Subsequent intramolecular Dieckmann cyclization of **71** in presence of potassium hydride followed by dealkoxycarbonylation of the resulting product **72B** under neutral conditions, affords the corresponding 6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione **73** in 82% (Scheme 20).[25a-b]

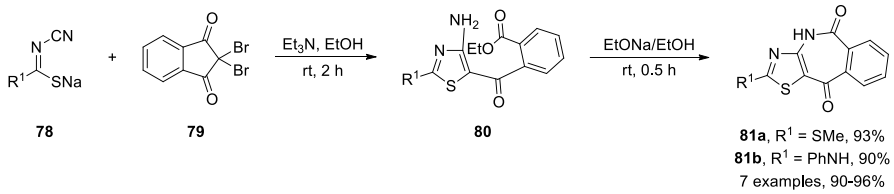
Similarly, the corresponding indolobenzoazapin-6,11-diones **77**, has been synthesized in a single-pot operation, involving *N*-alkylation of 2-*N*-substituted aminobenzonitrile **74** with 2-ethyloxycarbonylphenacyl bromide **7e** in the presence of NaH in DMF and subsequent in situ base-mediated intramolecular cyclocondensation of the resulting 3-aminoindole intermediate **76**, to afford the product **77** in 82% yield (Scheme 21).[26b] They have also synthesized benzofuro[3,2-*c*]benzoazepin-6,11-diones[26d] in good yields by using 2-hydroxybenzonitrile as a nucleophile partner via the same methodology.



Scheme 21

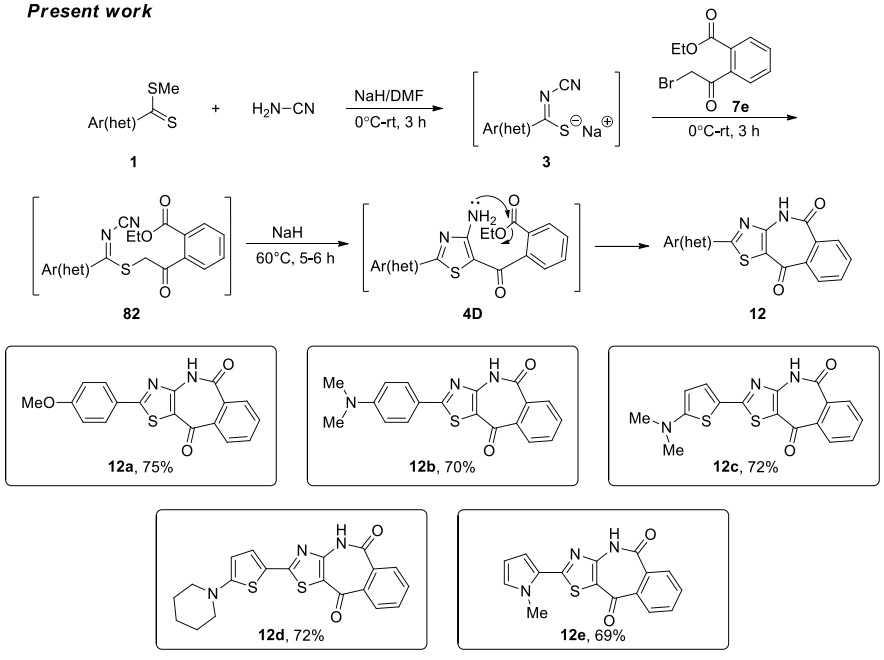
We, therefore, started our investigation, to develop a one-step protocol for the synthesis of thiazolo-fused benzazepinediones **12** as depicted in Scheme 23. This skeleton was unknown in the literature and only recently, Li and co-workers have described[26a] a step-wise synthesis of 2-(methylthio)/anilino-benzothiazoloazepin-5,8-diones involving ring opening-cyclization of 2,2-dibromo-1,3-indandione **79** with cyanothioimidate salts **78** (from cyanamide and carbon disulfide or phenyl isothiocyanate) to yield first open-chain 2-substituted 4-amino-5-(2-carboethoxybenzoyl) thiazoles **80** in moderate yields via an unspeculative mechanism. The intermediate **80** was subsequently subjected to

intramolecular *N*-acylation in the presence of ethanolic sodium ethoxide to give 2-methylthio/anilinothiazolobenzodiazepinones **81** in good yields (Scheme 22).[26a]



Scheme 22

We envisaged, that by employing a suitably functionalized halomethylene precursor such as 2-carboethoxyphenacyl bromide **7e**, it should be possible to develop a direct synthesis of **12** in a domino fashion, involving initial *S*-alkylation of the thioimidate salt **3** with **7e** and subsequent Thorpe Ziegler cyclization of the intermediate **82** to afford 4-amino-5-(2-carboethoxybenzoyl)thiazole **4D**. It was further anticipated that the thiazole intermediate **4D** should undergo, in situ intramolecular *N*-acylation under the basic conditions, furnishing the desired thiazolo-fused benzoazepinedione **12** in one pot sequence (Scheme 23). This strategy worked out well to our delight, and when in situ-



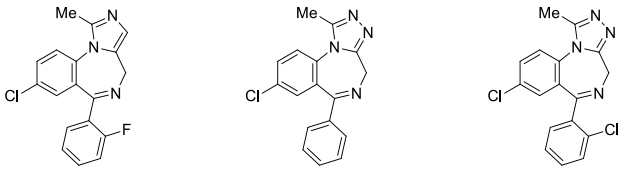
[a]Reaction conditions: **1** (1 mmol), H_2N-CN (1 mmol) and NaH (2.2 mmol), in DMF (4 mL) stirring for 3 h at rt, followed by addition of a solution of **7e** (1 mmol) in DMF (2 mL) stirring for 3 h at rt, and addition of another lot of NaH (2.2 mmol) and further stirring for 5-6 h at 60 °C. Yield of isolated products.

Scheme 23. Synthesis of 2-(het)aryl 4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione **12**[a]

generated thioimidate salt **3** from dithioester **1a** and cyanamide, was reacted with *o*-carboethoxyphenacyl bromide **7e** in the presence of sodium hydride in DMF, at room temperature and further heating at 60 ^{0}C for 5-6 h after addition of the second lot of sodium hydride, under optimized reaction conditions, the corresponding 2-(4-methoxyphenyl)-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione **12a** was obtained as the only product in 75% yield, without isolation of any open-chain precursor such as **82a** or 4-aminothiazole **4D** (Scheme 23). The other 2-aryl- and (het)aryl-substituted thiazolobenzoazepinediones **12b-e** were similarly obtained in 69-72% overall yields, by using various substituted (het)aryl dithioesters with *o*-carboethoxy phenacyl bromide **7e** as an alkylating agent under identical conditions (Scheme 23). All newly synthesized thiazolobenzoazepinediones derivatives **12** were found to display yellow-green fluorescence.

5.3.5 Domino Synthesis of 2-(Het)aryl 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones

Among the wide varieties of heterocyclic compounds, the 1,4-benzodiazepine ring system is a privileged scaffold, that constitutes the core structure of many marketed psychotropic drugs, therapeutic leads, and bioactive natural products.[27a-c] Besides, the fusion of this seven-membered ring with various heterocycles led to the development of new scaffolds with a broader spectrum of biological activities. For example, the imidazolo- and triazolo-fused 1,4-benzodiazepines such as midazolam (imidazole fused) **I**, alprazolam **J**, and triazolam (1,2,4-triazolo fused) **K** are already established psychotropic drugs used in the treatment of anxiety disorder and insomnia.[27d]

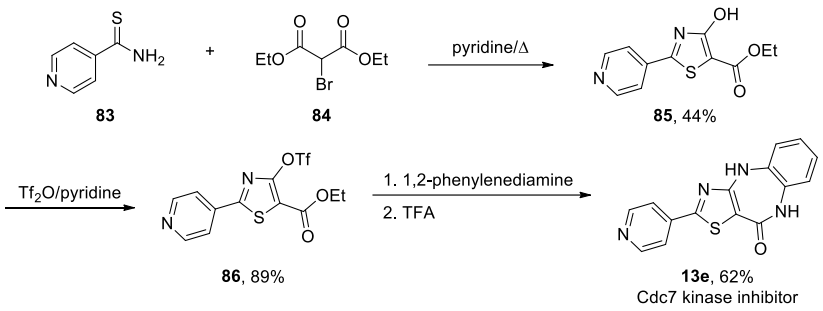


I, Midazolam **J**, Alprazolam **K**, Triazolam

Figure 2

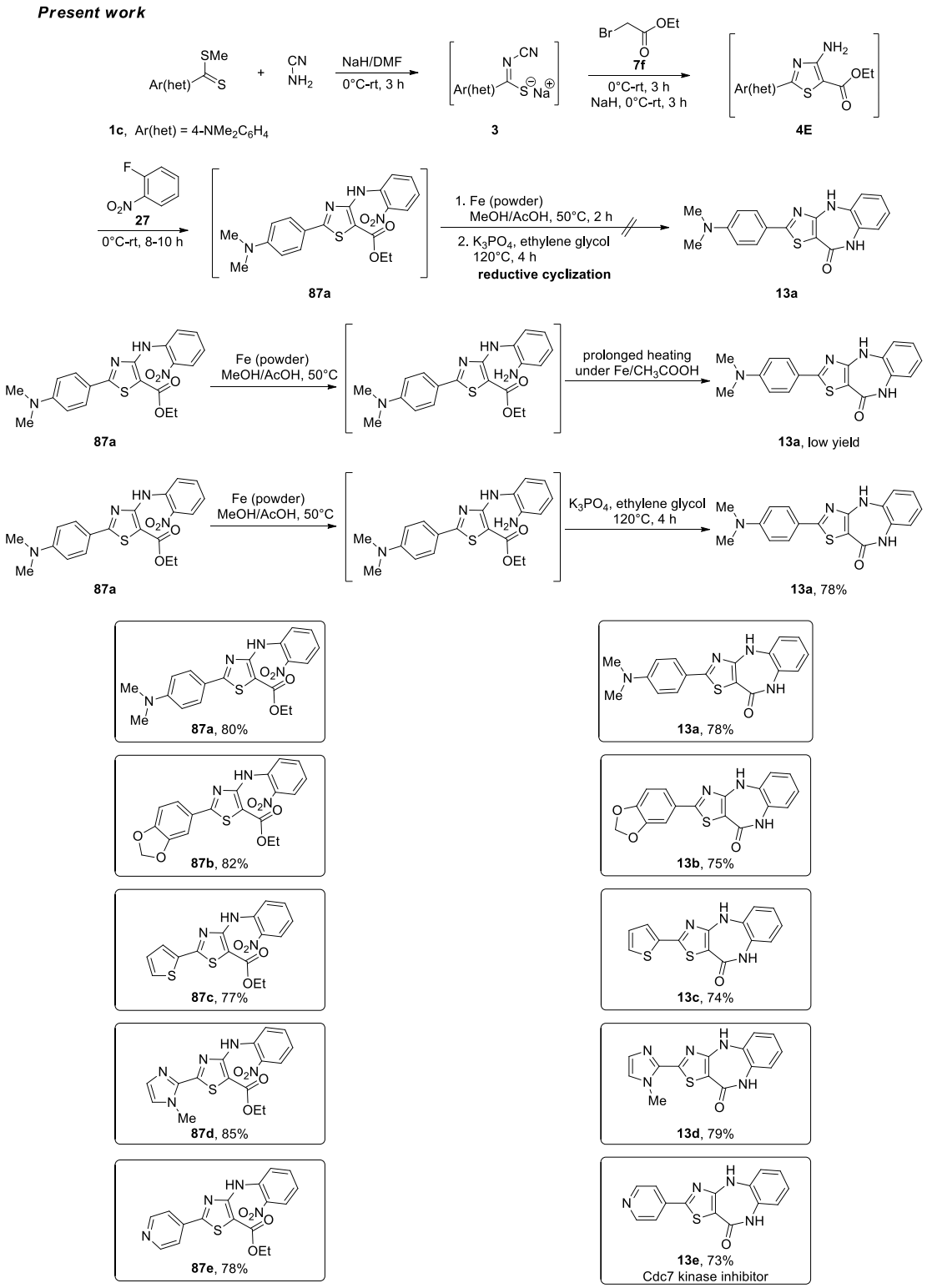
Therefore, the development of new routes for the synthesis of heterocyclo-fused 1,4-benzodiazepines is of considerable interest among synthetic and medicinal chemists. In view of their biological significance, we also targeted the synthesis of thiazolo-fused

benzodiazepinone derivatives such as **13**, (Figure 1), with a speculation to design a sequential one-pot domino process (Scheme 25). Two recent patents from literature [11a,28a] have highlighted the synthesis and biological activity of several substituted thiazolo-fused benzodiazepine i.e., 4*H*-benzo[*b*]thiazolo[5,4-*e*][1,4]diazepin-10(9*H*)-one **H** (Figure 1), starting from 2-substituted-5-amino-thiazole-4-carboxylate. On the other hand, its regioisomeric structural framework, i.e., 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones **13** has been scarcely investigated and there is only one example of 2-(4-pyridyl)analog **13e**, which is shown to exhibit Cdc7 kinase inhibitor activity.[28b] The compound has been prepared via displacement-cyclization of 2-(4-pyridyl)-5-carboethoxythiazolyl-4-triflate **86** with an *o*-phenylene diamine in 62% yield.[28b] The thiazole **86** has been synthesized via reaction of 4-pyridylthioamide **83** with bromomalonate **84** and subsequent treatment of the resulting 4-hydroxythiazole-5-carboxylate with triflic anhydride (Scheme 24).



Scheme 24

In our present study, the synthetic design for assembling 2-(het)aryl-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one **13** has been displayed in Scheme 25. Thus, the reaction of in situ generated thioimidate salts **3** from various dithioesters **1**, and cyanamide in the presence of sodium hydride, with bromoacetate **7f** furnishes the respective 2-het(aryl)-4-aminothiazole-4-carboxylates **4E** which, without isolation, were subjected to aromatic nucleophilic substitution with *o*-fluoronitrobenzene **27** at room temperature for 8-10 h, affording the acyclic 4-(2-nitrophenylamino)thiazole-5-carboxylates **87a-e** in good yields. However, our attempts to subject these 4-(2-nitrophenylamino)thiazole-5-carboxylates **87a** to in situ reductive cyclization to the corresponding thiazolobenzodiazepinones **13a** was not successful under one-pot conditions, yielding an only intractable mixture of products. Therefore, the intermediate



[a]Reaction conditions for **87**: **1** (1 mmol), H_2N-CN (1 mmol), NaH (2.2 mmol), in DMF (4 mL) stirring for 3 h at rt, followed by addition of a solution of **7f** (1 mmol) in DMF (2 mL) stirring for 3 h at rt, and addition of another lot of NaH (2.2 mmol) and stirring for 3 h at rt, and followed by the addition of DMF (2 mL) solution of **27** (1.2 mmol) stirring for 8-10 h at rt. [b]Reaction conditions for **13**: **87** (0.5 mmol), Fe (2.5 mmol) in AcOH/MeOH (3/3 mL) stirring for 2 h at 50 ºC, followed by addition of K_3PO_4 (1.5 mmol) with ethylene glycol (5 mL) stirring for 4 h at 120 ºC. Yield of isolated products.

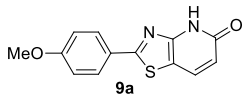
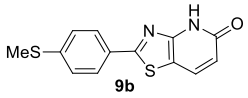
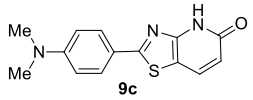
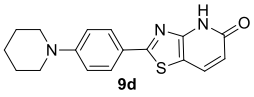
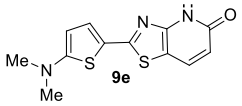
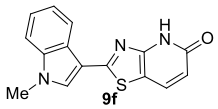
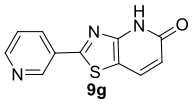
Scheme 25. Synthesis of 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones **13**[*b*]

87a, after purification, were subjected to reductive cyclization in the presence of iron powder in acetic acid. Prolonged heating of this reaction mixture afforded the thiazolobenzodiazepinone **13a** in low yield, along with the formation of side products. However, when the reaction mixture was heated in ethylene glycol in the presence of tripotassium phosphate at 120 ^{0}C for 4 h, the work-up of the reaction yielded the thiazolobenzodiazepinone **13a** in 78% yield. Similarly, the other 2-substituted thiazolobenzodiazepinones **13b-d** were also synthesized in high yields, following the above general procedure from acyclic 4-(2-nitrophenylamino)-thiazole-5-carboxylates **87b-d** in high yields. We could also synthesize the 2-(4-pyridyl)thiazolobenzodiazepinone **13e** exhibiting Cdc7 kinase inhibiting activity in good yield by the above procedure (Scheme 25).[28b]

5.4 UV-Vis Absorption and Emission Studies

As several of these thiazolo-fused heterocycles display fluorescent properties, especially those bearing (het)aryl groups with the electron-donating group and displaying extended conjugation with the electron-withdrawing carbonyl group present in all these compounds. We have therefore examined the absorption and emission spectra of a few selected compounds from each series which are displayed in Tables 1-5 and figures 3-7. Thus electronic spectra of thiazolo[4,5-*b*]pyridinones **9** (Table 1, Figure 3) display the longest wavelength band between 444-358 nm with molar extinction coefficient varying between 58000-306000 Lmol^{-1}cm^{-1} All these compounds display yellow, green to dark green fluorescence in solution with emission spectra varying between 448-483 nm along with pronounced Stokes shift ranging from 2992-5955 cm^{-1}. A study of substituent effect in this series reveals that aryl groups at 2-position of thiazolopyridinones **9**, bearing an electron-donating secondary 4-*N*-dimethylamino/*N*-piperidino group (**9c** and **9d**) at (2-aryl) substituent and [2-(5'-dimethylamino)-2-thienyl] group **(9e**) show bathochromic shift at highest wavelengths (Table 1). On the other hand, thiazolopyridinones **9a**, **9b**, **9f,** and **9g** (Scheme 9) with less electron-donating 4-methoxyphenyl and 4-(methylthio)phenyl, 3-indolyl and electron-withdrawing 3-pyridyl substituent respectively are blue shift at a lower wavelength in their absorption spectra (Figure 3).

Table 1. UV-vis absorption and emission data of compounds **9a-g**

Compound	absorption $\lambda_{max,abs}$ (nm) ε (L mol^{-1} cm^{-1})[a]	emission $\lambda_{max,em}$ (nm)[b]	Stokes shift Δ (cm^{-1})
 **9a**	366 (146000)	448	5001
 **9b**	376 (190000)	457	4714
 **9c**	404 (306000)	480	3919
 **9d**	400 (162000)	483	4296
 **9e**	444 (198000)	512	2992
 **9f**	380 (214000)	458	4482
 **9g**	358 (58000)	455	5955

[a]Recorded in DMSO, T = 293 K, c (**9**) = 5.0 × 10^{-6} M. [b]Recorded in DMSO, T = 293 K, c (**9**) = 2.5 × 10^{-8} M. (Yellow, light green-green-dark green)

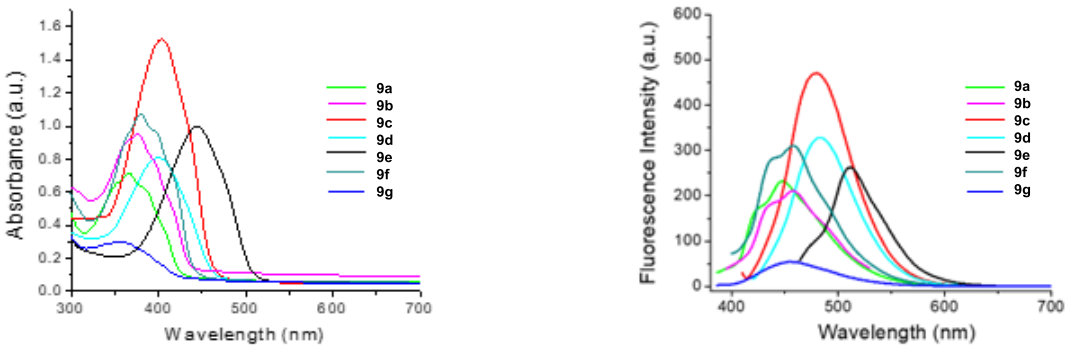
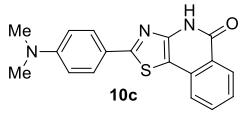
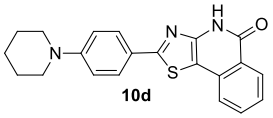
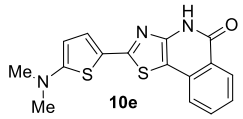
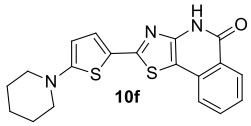


Figure 3. UV-vis absorption and fluorescence intensity spectra of compounds **9a-g**

A similar trend was also observed in the thiazolo[4,5-*c*]isoquinolinone series (**10b-g**) (Table 2, Figure 4), thus all compounds bearing either a 4-dialkylamino group at 2-aryl group (**10c-d**) and [5′-dimethylamino/(*N*-piperidinyl)]-2-thienyl moiety (**10e-f**) show absorption maxima at a highest wavelength between 448 and 451 nm with extinction coefficient varying between 64000-256000 $Lmol^{-1}cm^{-1}$) with pronounced Stokes effect. The 2-thienyl compounds **10e** and **10f** display absorption spectra at a highest wavelength at 451 and 448 nm respectively. The emission spectra of these compounds also show a similar trend and compounds **10e-f** appear at higher wavelengths at 513 and 518 nm respectively. All, these compounds show green fluorescence in solution, whereas the product **10b** with 2-(4-fluorophenyl substituent and **10g** with 2-(3-indoly)l moiety did not show any fluorescence or absorption in the visible region (Scheme 13).

Table 2. UV-vis absorption and emission data of compounds **10c-f**

Compound	absorption $\lambda_{max,abs}$ (nm) ε ($L\ mol^{-1}\ cm^{-1}$)[a]	Emission $\lambda_{max,em}$ (nm)[b]	Stokes shift Δ (cm^{-1})
 **10c**	409 (256000)	479	3573
 **10d**	407 (230000)	484	3909
 **10e**	451 (176000)	513	2680
 **10f**	448 (64000)	518	3016

[a]Recorded in DMSO, T = 293 K, c (**10**) = 5.0×10^{-6} M. [b]Recorded in DMSO, T = 293 K, c (**10**) = 2.5×10^{-8} M. (green)

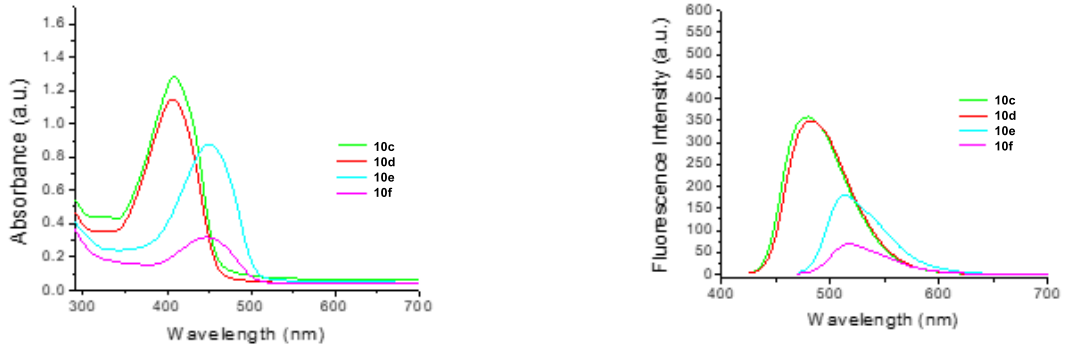
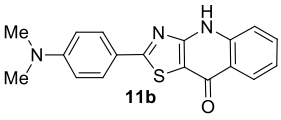
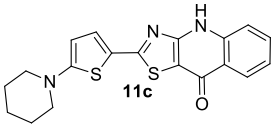


Figure 4. UV-vis absorption and fluorescence intensity spectra of compounds **10c-f**

Among 2-functionalized thiazolo[4,5-*b*]quinolin-9(4*H*)-ones **11**, only two compounds with 2-(4-dimethylaminophenyl)-(**11b**) and 2[-(5-*N*-piperidino-2-thienyl] substituents) (**11c**) displayed light to dark green fluorescence with highest absorption spectra peak appearing at 416 and 458 nm respectively (Table 3) (Figure 5) along with higher wavelength emission spectra at 482 and 510 nm respectively (Figure 5). The other compounds in this series **11a** and **7d-f** did not show any fluorescence or absorption in the visible region mainly due to the presence of electron-withdrawing 4-fluoro group or less electron-donating methoxy group or neutral substituents like 2-imidazolyl and 3-indolyl groups (Scheme 19).

Table 3. UV-Vis absorption and emission data of compounds **11b-c**

Compound	absorption $\lambda_{max,abs}$ (nm), ε (L mol^{-1} cm^{-1})[a]	Emission $\lambda_{max,em}$ (nm)[b]	Stokes shift Δ (cm^{-1})
 **11b**	416 (94000) 367 (66000)	482	3291
 **11c**	458 (290000) 375 (92000)	510	2226

[a]Recorded in DMSO, T = 293 K, c (**11**) = 5.0 × 10^{-6} M. [b]Recorded in DMSO, T = 293 K, c (**11**) = 2.5 × 10^{-8} M. (green)

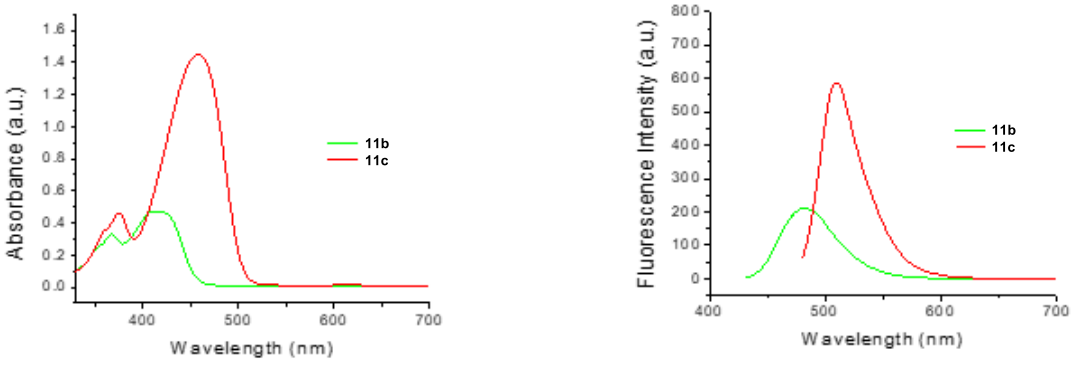
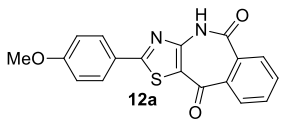
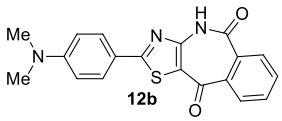
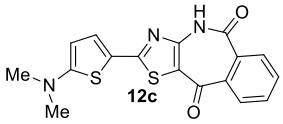
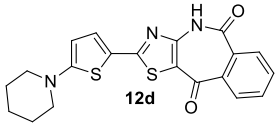
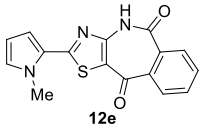


Figure 5. UV-vis absorption and fluorescence intensity spectra of compounds **11b-c**

Among seven-membered 2-functionalized 4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione series **12** (Scheme 23), (Table 4), most of these compounds possessing electron-donating 2-[4-dialkylaminophenyl] (**12b**) or [5-dialkylamino/*N*-piperidino-2-thienyl] substituents (**12c-d**), displayed highest wavelength absorption at 445, 495 and 501 nm respectively because of longer conjugation. Similarly, compound **12e** bearing the 2-(2-*N*-methylpyrrolyl) group also displayed higher absorption at 415 nm because of the electron-donating effect of the 2-pyrrolyl group, whereas compound **12a** with a 2-(4-methoxyphenyl) substituent showed absorption only 388 nm. All compounds of this series were displaying yellow, green to red fluorescence with pronounced absorption maxima varying between 450-566 nm along with a prominent Stokes effect (Table 4) (Figure 6).

Table 4. UV-vis absorption and emission data of compounds **12a-e**

Compound	absorption $\lambda_{max,abs}$ (nm), ε (L mol^{-1} cm^{-1})[a]	emission $\lambda_{max,em}$ (nm)[b]	Stokes shift Δ (cm^{-1})
 **12a**	388 (30000) 299 (28000)	450	3551
 **12b**	445 (220000) 319 (74000)	557	4518

 **12c**	495 (358000) 337 (68000)	566	2534
 **12d**	501 (250000) 370 (134000)	517	618
 **12e**	414 (178000) 308 (98000)	484	3493

[a]Recorded in DMSO, T = 293 K, c (**12**) = 5.0 × 10^{-6} M. [b]Recorded in DMSO, T = 293 K, c (**12**) = 2.5 × 10^{-7} M. (light yellow-yellow, red, green)

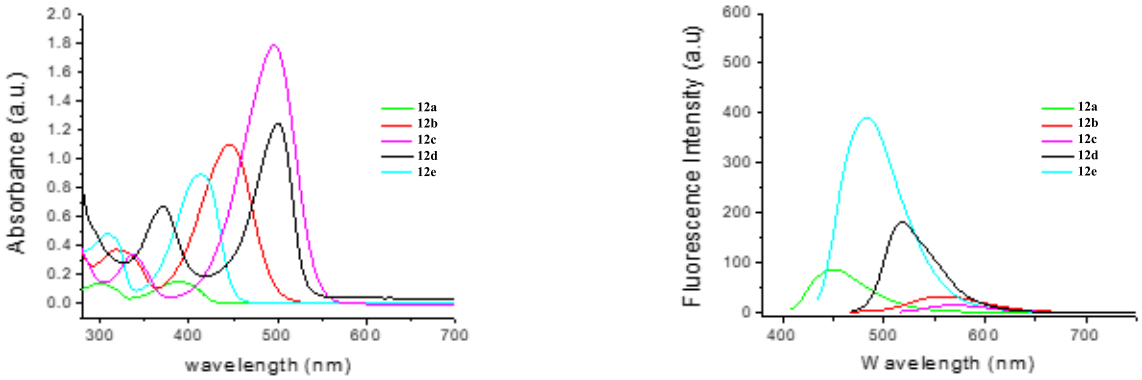
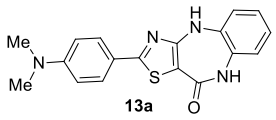
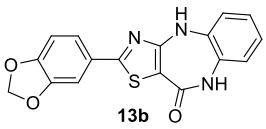
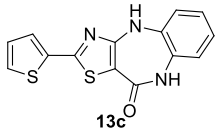
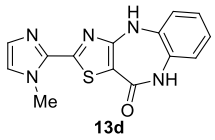


Figure 6. UV-vis absorption and fluorescence intensity spectra of compounds **12a-e**

Similarly in the last, 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10-ones series **13a-d**, most of the compounds show yellow to light green fluorescence (Scheme 27), with absorption wavelength varying between 331-362 nm (Table 5) (Figure 7). The compound **13a** with a 2-(4-dimethylamino)phenyl group displayed an absorption band at 362 nm, whereas those bearing weakly conjugated methylenedioxyphenyl substituent (**13b**) 2-(2-thienyl) **(13c**), and 2-(2-imidazolyl) group (**13d**) are blue-shifted in the range of 331-340 nm with emission spectra varying between 401-426 nm (Figure 7) (Scheme 25).

Table 5. UV-vis absorption and emission data of compounds **13a-d**

Compound	absorption $\lambda_{max,abs}$ (nm), ε (L mol^{-1} cm^{-1})[a]	emission $\lambda_{max,em}$ (nm)[b]	Stokes shift Δ (cm^{-1})
 **13a**	362 (182000) 289 (78000)	426	4150
 **13b**	335 (114000) 286 (88000)	407	5281
 **13c**	340 (78000) 284 (82000)	423	5771
 **13d**	331 (92000) 286 (84000)	401	5274

[a]Recorded in DMSO, T = 293 K, c (**13**) = 5.0 × 10^{-6} M. [b]Recorded in DMSO, T = 293 K, c (**13**) = 2.5 × 10^{-8} M. (yellow, light green-green)

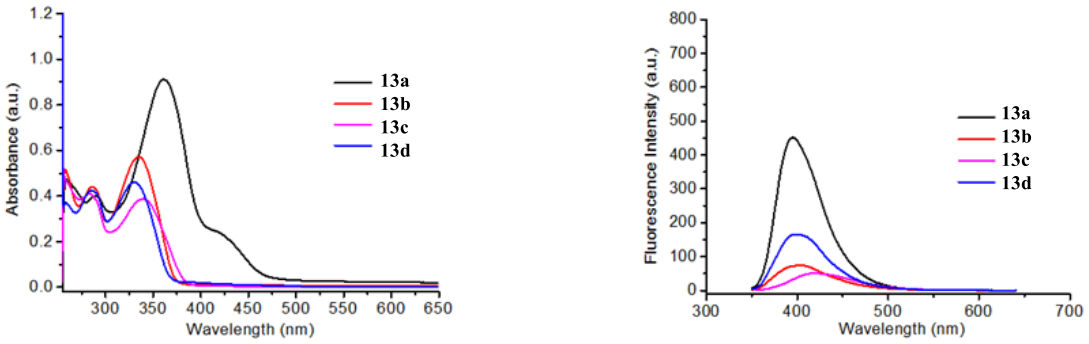


Figure 7. UV-vis absorption and fluorescence intensity spectra of compounds **13a-d**

5.5 Conclusion

In summary, we have successfully demonstrated efficient general protocols for assembling of five thiazolo-fused heterocyclic cores *i.e.*, 2-substituted thiazolo[4,5-

b]pyridin-5(4*H*)-ones **9**, thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones **10**, thiazolo[4,5-*b*]quinolin-9(4*H*)-one **11**, 4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione **12** and 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones **13** from readily accessible starting materials under very mild conditions in high yields (Schemes 9, 13, 19, 23 and 25). Whereas thiazolo-heterocycles **9**-**12** were obtained in a single operation in one pot process via a sequential domino process (Schemes 9, 13, 19, and 23), the synthesis of 4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-ones **13**, necessitated isolation of final adducts **87** and their subsequent reductive cyclization to thiazolo-1,4-benzodiazepinones **13** in a separate experiment (Scheme 25). Several diversely substituted aryl and heteroaryl substituents could be introduced at 2-positions of these heterocycles, through the choice of various (het)aryl dithioesters **1** as thiocarbonyl precursors, especially those bearing electron-donating groups at 4-positions, imparting extended π conjugation in some of these compounds, thus resulting in their fluorescent properties. We have also studied the absorbance and emission spectra of a few of these novel heterocycles. These simple protocols developed herein could be utilized to access several thiazolo-fused heterocycles which would find applications in medicinal chemistry for library synthesis, as well as in material science. Further work to extend these protocols for the synthesis of another novel thiazolo-fused heterocycle is in progress in our laboratory.

5.6 Experimental Section

5.6.1 General Information. Reagents and anhydrous solvents were purchased from commercial sources and used without further purification. Yields for compounds were determined by column chromatography which was generally performed on silica gel (60-120 mesh) using petroleum ether/EtOAc as eluent, and reactions were monitored by thin-layer chromatography (TLC) on a glass plate coated with silica gel using UV light. Nuclear magnetic resonance (NMR) spectra were recorded on a (400 and 600 MHz) FT-NMR spectrometer with $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts were reported in δ (ppm) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6, in ^{1}H NMR, δ 77.16 for $CDCl_3$, and δ 39.52 for DMSO-d_6 in ^{13}C NMR). Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet), and brs (broad singlet). Infrared spectra of neat samples were recorded in

attenuated total reflectance (ATR) mode using an FT-IR instrument, and HRMS spectra were recorded using a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and were uncorrected. Electronic absorption spectra were recorded on a PerkinElmer UV-vis-NIR spectrometer lambda 750. Emission spectra were recorded on a PerkinElmer LS55 fluorescence spectrometer.

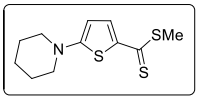
All the methyl (het)/aryl dithioester compounds **1a**[29], **1b**[29,31], **1c-d**[29], **1e**[31], **1f-g**[29], **1h**[29,30], **1j**[30], **1k**[29,30], **1l**[31] and also **1m-n**[32] were prepared according to their reported procedures respectively. The halo alkylating agent such as methyl 4-bromocrotonate **7a**, ethyl bromoacetate **7f**, and 1-fluoro-2-nitrobenzene **27** were obtained from commercial suppliers, **7b**[33], **7c**[34], **7d**[35,] and **7e**[36] were prepared according to the literature procedure

5.6.2 Procedure for the Preparation of Methyl 5-(Piperidin-1-yl)thiophene-2-carbodithioate (1i) from 5-Bromothiophene-2-carbaldehyde.

Procedure for the Preparation of 5-(Piperidin-1-yl)thiophene-2-carbaldehyde from 5-Bromothiophene-2-carbaldehyde[37]. To a solution of 5-bromothiophene-2-carbaldehyde (25 g, 0.13 mol) in 60 mL DMSO in a single neck round bottom flask (250 mL) was added piperidine (15.5 mL, 0.16 mol). The resulting reaction mixture was reflux at 90 ºC for 8 h (monitored by TLC). The reaction flask was allowed to cool down to room temperature. It was then quenched with saturated aqueous NH_4Cl solution (100 mL), extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with H_2O (3 X 50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated under a vacuum. The crude product was purified by chromatography on silica gel 60-120 mesh size (EtOAc/hexane 2:3) to furnish 5-(piperidin-1-yl)thiophene-2-carbaldehyde[37] as grey solid; (22.4 g, 88%); mp 86-88 ºC; R_f 0.32 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3055, 2936, 2835, 2740, 1738, 1442; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.47 (d, J = 4.4 Hz, 1H), 6.06 (d, J = 4.4 Hz, 1H), 3.35 (t, J = 5.4 Hz, 4H), 1.73-1.63 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 168.4, 140.1, 126.8, 103.9, 50.9, 24.9, 23.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{14}NOS$ 196.0796; found 196.0792.

Procedure for the Preparation of Piperidin-1-yl(5-(piperidin-1-yl)thiophen-2-yl)methanethione from 5-(Piperidin-1-yl)thiophene-2-carbaldehyde[30]. To a solution of 5-(piperidin-1-yl)thiophene-2-

carbaldehyde (20 g, 0.10 mol) sulfur (3.3 g, 0.10 mol), and piperidine (15.2 mL, 0.15 mol), in a single neck round bottom flask (250 mL) were refluxed for 9 h (monitored by TLC). The reaction flask was allowed to cool down to room temperature and the reaction mixture was then poured into an ice-cold 20% aq. HCl, and it was extracted with DCM (3 x 50 mL). The combined organic layer was washed with water (2 x 100 mL), brine (1 x 100 mL), and dried over anhy. Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel 60-120 mesh size (EtOAc/hexane 1:4) to furnish piperidin-1-yl(5-(piperidin-1-yl)thiophen-2-yl)methanethione[30] as yellow solid; (23.8 g, 80%); mp 93-95 ºC; R_f 0.60 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3063, 2921, 1428, 1231; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, J = 3.6 Hz, 1H), 5.92 (d, J = 3.6 Hz, 1H), 4.09 (brs, 4H), 3.23 (t, J = 5.0 Hz, 4H), 1.74-1.59 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 165.2, 129.3, 128.1, 102.9, 53.5, 50.9, 26.4, 25.0, 24.6, 23.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{23}N_2S_2$ 295.1303; found 295.1300.

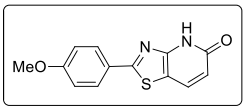
Procedure for the Preparation of Methyl 5-(Piperidin-1-yl)thiophene-2-carbodithioate (1i) from Piperidin-1-yl(5-(piperidin-1-yl)thiophen-2-yl)methanethione[30]. 

The Thioamide intermediate (22 g, 0.075 mol) and MeI (9.3 mL, 0.15 mol) were added to methanol (80 mL) in a single neck round bottom flask (250 mL) was refluxed for 3 h. Removal of methanol from the reaction mixture gave the corresponding salt in quantitative yield which was used as such for further transformation. To a stirred suspension of the above thioamide salt (0.075 mol) in pyridine (30 mL), H_2S gas was passed for 1 h at 0 ºC (monitored by TLC). The reaction mixture was poured into cold 10% aq. HCl (50 mL) and the aqueous layer was extracted with DCM (3 x 40 mL). The combined organic extracts were washed with water (3 x 50 mL), brine (1 x 50 mL), and dried over anhy. Na_2SO_4. The solvent was evaporated under reduced pressure to give red viscous oil which was purified by chromatography on silica gel 60-120 mesh size (EtOAc/hexane 1:9) to furnish methyl 5-(piperidin-1-yl)thiophene-2-carbodithioate[30] as Shiny red solid; (15 g, 78%); mp 116-118 ºC; R_f 0.65 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3071, 2935, 1442, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 4.4 Hz, 1H), 6.09 (d, J = 4.8 Hz, 1H), 3.37 (t, J = 5.6 Hz, 4H), 2.72 (s, 3H), 1.69-1.67 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 170.4, 135.3, 131.1, 105.7,

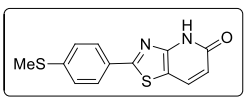
50.9, 24.9, 23.6, 18.3; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{16}NS_3$ 258.0445; found 258.0437.

5.6.3 General Procedure for the Synthesis of 2-(Het)aryl Thiazolo[4,5-*b*]pyridin-5(4*H*)-ones 9a-g. To an ice-cooled stirred suspension of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) and appropriate dithioester, **1** (1.0 mmol, 1.0 equiv.) in DMF (2 mL), a solution of cyanamide (42 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise over 5 minutes, under N_2 atmosphere. After further stirring at room temperature for 3 h (at 90 ºC for 3 h, for **1h** dithioester), a solution of methyl 4-bromocrotonate **7a** (179 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise to the ice-cold reaction mixture and stirred for 3 h at room temperature. Followed by the addition of another lot of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) to the ice-cold reaction mixture, stirring was further continued for 4-5 h at 60 ºC (monitored by TLC). The reaction mixture, after cooling, and the quenching with saturated NH_4Cl solution (50 mL). The reaction mixture was extracted with DCM (3 × 25 mL) and the collected organic layer was further water (3 × 25 mL) washed and brine (25 mL) washed, and then dried over anhydrous Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by column chromatography over silica gel using EtOAc as eluent.

2-(4-Methoxyphenyl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9a). Obtained from methyl 4-methoxybenzodithioate **1a** and methyl 4-bromocrotonate **7a**, yellow solid (194 mg, 75%); mp 242-244 ºC; R_f 0.30 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3350, 2926, 2833, 1641, 680; ^1H NMR (400 MHz, DMSO-d_6): δ 12.35 (brs, 1H), 8.15 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 169.5, 162.7, 161.9, 133.9, 130.3, 128.3, 125.2, 114.8, 113.9, 111.9, 55.5; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{11}N_2O_2S$ $[M + H]^+$ 259.0541, found 259.0534.

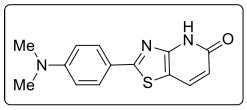


2-(4-(Methylthio)phenyl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9b). Obtained from methyl 4-fluorobenzodithioate **1b** and methyl 4-bromocrotonate **7a**, yellow solid (203 mg, 74%); mp 264-266 ºC; R_f 0.30 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3347, 2915, 1633, 700, 650; ^1H NMR (400 MHz, DMSO-d_6): δ 12.38 (brs, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 6.49 (d, J



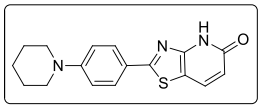
= 9.2 Hz, 1H), 2.56 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 169.1, 162.7, 149.6, 147.6, 143.2, 133.9, 128.8, 127.0, 126.8, 125.9, 14.1; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{11}N_2OS_2$ $[M + H]^+$ 275.0313, found 275.0300.

2-(4-(Dimethylamino)phenyl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9c). Obtained from



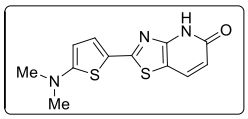
methyl 4-(dimethylamino)benzodithioate **1c** and methyl 4-bromocrotonate **7a**, dark green solid (198 mg, 73%); mp decomposed at 335 ºC (turned black); R_f 0.30 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3365, 2922, 2853, 1629, 1458, 677; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.35 (brs, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 9.2 Hz, 1H), 3.03 (s, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 170.6, 165.3, 162.7, 152.4, 143.1, 136.9, 133.9, 127.9, 119.8, 111.9, 40.3; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{14}N_3OS$ $[M + H]^+$ 272.0858, found 272.0851.

2-(4-(Piperidin-1-yl)phenyl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9d). Obtained from



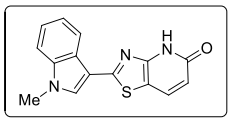
methyl 4-(piperidin-1-yl)benzodithioate **1d** and methyl 4-bromocrotonate **7a**, dark green solid (221 mg, 71%); mp 248-250 ºC; R_f 0.28 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3290, 2932, 2830, 1639, 1443, 700; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.31 (brs, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 9.2 Hz, 1H), 3.33 (brs, 4H), 1.59 (brs, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 170.2, 162.6, 153.0, 149.8, 148.4, 146.9, 133.8, 127.9, 121.1, 114.2, 47.9, 24.8, 23.9; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{18}N_3OS$ $[M + H]^+$ 312.1171, found 312.1157.

2-(5-(Dimethylamino)thiophen-2-yl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9e). Obtained



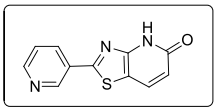
from methyl 5-(dimethylamino)thiophene-2-carbodithioate **1h** and methyl 4-bromocrotonate **7a**, black solid (211 mg, 76%); mp 245-247 ºC; R_f 0.28 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3290, 2985, 1625, 1502, 694; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (brs, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.55 (d, *J* = 4.4 Hz, 1H), 6.29 (d, *J* = 9.2 Hz, 1H), 6.03 (d, *J* = 4.4 Hz, 1H), 3.03 (s, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 164.1, 163.3, 162.6, 135.0, 133.6, 131.6, 117.4, 103.1, 41.8; HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{12}N_3OS_2$ $[M + H]^+$ 278.0422, found 278.0415.

2-(1-Methyl-1*H*-indol-3-yl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9f). Obtained from



methyl 1-methyl-1*H*-indole-3-carbodithioate **1j** and methyl 4-bromocrotonate **7a**, yellow solid (214 mg, 76%); mp 179-181 ºC; R_f 0.25 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3336, 3060, 2920, 1628, 1529, 701; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (brs, 1H), 8.30 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.36-7.28 (m, 2H), 6.39 (d, J = 9.2 Hz, 1H), 3.91 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 165.3, 162.7, 137.3, 133.7, 133.6, 132.3, 124.5, 124.4, 122.9, 122.7, 121.6, 120.5, 110.9, 109.2, 33.1; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{12}N_3OS$ $[M + H]^+$ 282.0701, found 282.0686.

2-(Pyridin-3-yl)thiazolo[4,5-*b*]pyridin-5(4*H*)-one (9g). Obtained from methyl pyridine-



3-carbodithioate **1m** and methyl 4-bromocrotonate **7a**, coffee colour solid (122 mg, 53%); mp 120-122 ºC; R_f 0.26 (EtOAc); IR (neat, cm^{-1}) 3360, 2961, 1637, 1470, 704; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (brs, 1H), 9.19 (d, J = 1.6 Hz, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 7.60 (dd, J = 8.0, 4.8 Hz, 1H), 6.56 (d, J = 9.2 Hz, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 166.5, 162.8, 151.9, 149.4, 147.1, 146.3, 134.1, 134.0, 128.6, 124.4; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_8N_3OS$ $[M + H]^+$ 230.0388, found 230.0379.

5.6.4 General Procedure for the Synthesis of 2-(Het)aryl thiazolo[4,5-*c*]isoquinolin-5(4*H*)-ones 10b-g. To an ice-cooled stirred suspension of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) and appropriate dithioester, **1** (1.0 mmol, 1.0 equiv.) in DMF (2 mL), a solution of cyanamide (42 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise over 5 minutes, under N_2 atmosphere. After further stirring at room temperature for 3 h (at 90 ºC for 3 h, for **1h** and **1i** dithioester), a solution of ethyl 2-(bromomethyl)benzoate **7b** (243 mg, 1.0 mmol, 1.0 equiv.) in DMF (2 mL) was added dropwise to the ice-cold reaction mixture and stirred for 3 h at room temperature. Followed by the addition of another lot of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) to the ice-cold reaction mixture, stirring was further continued for 4-5 h at room temperature (monitored by TLC). The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with DCM (3 × 25 mL) and the collected organic layer was further water (3 × 25 mL) washed and brine (25 mL) washed, and then dried over anhydrous Na_2SO_4 and concentrated under a vacuum, and the crude residue

was purified by column chromatography over silica gel using EtOAc/petroleum ether (50:50) as eluent.

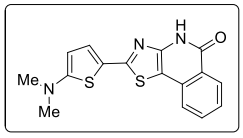
2-(4-Fluorophenyl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (10b). Obtained from methyl 4-fluorobenzodithioate **1b** and ethyl 2-(bromomethyl)benzoate **7b**, yellow solid (232 mg, 78%); mp 203-205 ºC; R_f 0.49 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3355, 3025, 2978, 1647; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.21 (brs, 1H), 8.18-8.13 (m, 2H), 7.99 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.65 (dd, J = 8.0, 4.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 171.9, 164.5 (C-F, d, $^1J_{C\text{-}F}$ = 249.7 Hz), 160.2, 147.9, 139.6 (C-F, d, $^4J_{C\text{-}F}$ = 3.7 Hz), 133.9, 132.6, 132.5, 129.7 (C-F, d, $^3J_{C\text{-}F}$ = 9.2 Hz), 128.9, 128.4, 127.4, 125.9, 116.8 (C-F, d, $^2J_{C\text{-}F}$ = 22.1 Hz); HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{10}FN_2OS$ $[M + H]^+$ 297.0498, found 297.0486.

2-(4-(Dimethylamino)phenyl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (10c). Obtained from methyl 4-(dimethylamino)benzodithioate **1c** and ethyl 2-(bromomethyl)benzoate **7b**, red solid (251 mg, 78%); mp 257-259 ºC; R_f 0.28 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3370, 3010, 2970, 1640, 1366; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (brs, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.78 (t, J = 8.0 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H) 3.03 (s, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 167.4, 161.7, 152.0, 149.5, 133.2, 131.9, 130.4, 128.2, 127.5, 125.9, 123.6, 123.4, 119.7, 111.8, 40.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{16}N_3OS$ $[M + H]^+$ 322.1014, found 322.1009.

2-(4-(Piperidin-1-yl)phenyl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (10d). Obtained from methyl 4-(piperidin-1-yl)benzodithioate **1d** and ethyl 2-(bromomethyl)benzoate **7b**, light-Green solid (278 mg, 77%); mp 204-206 ºC; R_f 0.31 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3370, 3040, 2971, 1645, 1523; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (brs, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 3.33 (t, J = 5.2 Hz, 4H) , 1.71-1.65 (m, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 168.3, 162.6, 153.5, 148.5, 133.3, 132.7, 129.3,

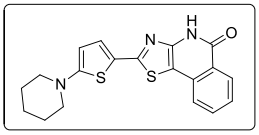
128.0, 126.1, 123.9, 123.4, 122.4, 114.7, 108.2, 49.1, 25.5, 24.3; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{20}N_3OS$ $[M + H]^+$ 362.1327, found 362.1324.

2-(5-(Dimethylamino)thiophen-2-yl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (10e).



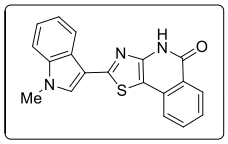
Obtained from methyl 5-(dimethylamino)thiophene-2-carbodithioate **1h** and ethyl 2-(bromomethyl)benzoate **7b**, red-brown solid (246 mg, 75%); mp 268-270 ºC; R_f 0.42 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3293, 3045, 2921, 1632, 1490; ^1H NMR (400 MHz, DMSO-d_6): δ 12.49 (brs, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.4 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 4.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 6.02 (d, J = 4.4 Hz, 1H), 3.02 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 162.7, 161.6, 161.2, 148.9, 133.2, 131.9, 130.8, 128.2, 125.5, 123.3, 123.1, 117.5, 104.3, 102.9, 41.7; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{14}N_3OS_2$ $[M + H]^+$ 328.0578, found 328.0566.

2-(5-(Piperidin-1-yl)thiophen-2-yl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (10f).



Obtained from methyl 5-(piperidin-1-yl)thiophene-2-carbodithioate **1i** and ethyl 2-(bromomethyl)benzoate **7b**, red-orange solid (261 mg, 71%); mp 195-197 ºC; R_f 0.48 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3320, 3045, 2928, 2852, 1664, 1575; ^1H NMR (400 MHz, DMSO-d_6): δ 12.53 (brs, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.6 Hz, 2H), 7.75 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 4.0 Hz, 1H), 6.23 (d, J = 4.4 Hz, 1H), 4.06 (brs, 4H), 1.92 (brs, 6H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 168.4, 162.9, 148.9, 139.8, 133.2, 132.7, 131.3, 130.9, 130.6, 130.4, 130.2, 128.2, 128.1, 126.9, 57.8, 24.4, 22.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{18}N_3OS_2$ $[M + H]^+$ 368.0891, found 368.0872.

2-(1-Methyl-1*H*-indol-3-yl)thiazolo[4,5-*c*]isoquinolin-5(4*H*)-one (10g). Obtained from

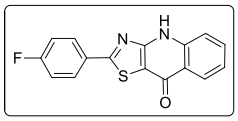


methyl 1-methyl-1*H*-indole-3-carbodithioate **1j** and ethyl 2-(bromomethyl)benzoate **7b**, yellow solid (249 mg, 75%); mp 208-210 ºC; R_f 0.20 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3325, 3040, 2971, 1646, 1533; ^1H NMR (400 MHz, DMSO-d_6): δ 12.62 (brs, 1H), 8.30 (s, 1H), 8.28 (s, 2H), 7.79 (t, J = 7.4 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.62-7.59 (m, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.37-7.30 (m, 2H), 3.92 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 162.2, 161.8, 149.2, 137.1, 133.2, 132.0, 131.7, 128.2, 125.7, 124.4, 123.5, 123.4, 122.8, 121.4,

120.3, 110.9, 109.1, 104.5, 32.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{14}N_3OS$ $[M + H]^+$ 332.0858, found 332.0854.

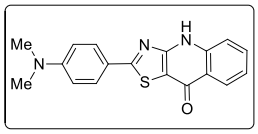
5.6.5 General Procedure for the Synthesis of 2-(Het)aryl thiazolo[4,5-*b*]quinolin-9(4*H*)-ones 11a-f. To an ice-cooled stirred suspension of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) and appropriate dithioester, **1** (1.0 mmol, 1.0 equiv.) in DMF (2 mL), a solution of cyanamide (42 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise over 5 minutes, under N_2 atmosphere. After further stirring at room temperature for 3 h (at 90 ºC for 3 h, for **1i** dithioester), a solution of 2-fluorophenacyl bromide **7c**/2,5-difluorophenacyl bromide **7d** (217 mg for **7c** and 235 mg for **7d**, 1.0 mmol, 1.0 equiv.) in DMF (2 mL) was added dropwise to the ice-cold reaction mixture and stirred for 3 h at room temperature. Followed by the addition of another lot of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) to the ice-cold reaction mixture, stirring was further continued for 5-6 h at room temperature (monitored by TLC). The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with DCM (3 × 25 mL) and the collected organic layer was further water (3 × 25 mL) washed and brine (25 mL) washed, and then dried over anhydrous Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by column chromatography over silica gel using EtOAc as eluent.

2-(4-Fluorophenyl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (11a). Obtained from methyl 4-



fluorobenzodithioate **1b** and 2-fluoro phenacyl bromide **7c**, pale yellow solid (231 mg, 78%); mp 301-303 ºC; R_f 0.72 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3320, 3064, 2950, 1625, 1577, 1235; ^1H NMR (400 MHz, DMSO-d_6): δ 13.25 (brs, 1H), 8.22-8.17 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.4 Hz, 1H), 7.69 (dd, J = 8.0, 4.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 172.7, 171.8, 164.3 (C-F, d, $^1J_{C\text{-}F}$ = 249.7 Hz), 155.2, 144.4, 139.5 (C-F, d, $^4J_{C\text{-}F}$ = 3.7 Hz), 132.4, 129.5 (C-F, d, $^3J_{C\text{-}F}$ = 9.2 Hz), 127.2, 125.7, 124.8, 122.6, 116.6 (C-F, d, $^2J_{C\text{-}F}$ = 22.1 Hz), 113.1; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{10}FN_2OS$ $[M + H]^+$ 297.0498, found 297.0485.

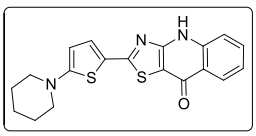
2-(4-(Dimethylamino)phenyl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (11b). Obtained from



methyl 4-(dimethylamino)benzodithioate **1c** and 2-fluoro phenacyl bromide **7c**, yellow solid (251 mg, 78%); mp 330-332 ºC; R_f 0.55

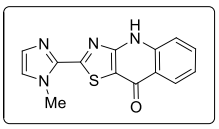
(4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3375, 3050, 1660, 1570; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (brs, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.73-7.67 (m, 2H), 7.35 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 3.05 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 173.9, 171.2, 155.7, 152.8, 139.3, 131.9, 128.5, 124.7, 122.3, 121.9, 119.2, 117.9, 111.7, 111.1, 40.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{16}N_3OS$ $[M + H]^+$ 322.1014, found 322.1000.

2-(5-(Piperidin-1-yl)thiophen-2-yl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (11c). Obtained



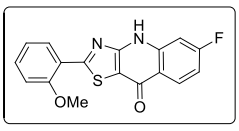
from methyl 5-(piperidin-1-yl)thiophene-2-carbodithioate **1i** and 2-fluoro phenacyl bromide **7c**, red-brown solid (294 mg, 80%); mp 312-314 ºC; R_f 0.56 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3345, 3042, 2935, 1619, 1540; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.97 (brs, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 4.4 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 6.30 (d, J = 4.4 Hz, 1H), 3.33 (brs, 4H), 1.65-1.59 (m, 6H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 170.6, 166.9, 164.8, 155.4, 139.1, 133.4, 131.7, 124.6, 122.2, 122.1, 117.8, 117.4, 110.1, 104.9, 50.5, 24.4, 22.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{18}N_3OS_2$ $[M + H]^+$ 368.0891, found 368.0880.

2-(1-Methyl-1*H*-imidazol-2-yl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (11d). Obtained from



methyl 1-methyl-1*H*-imidazole-2-carbodithioate **1l** and 2-fluoro phenacyl bromide **7c**, yellow solid (209 mg, 74%); mp 353-355 ºC; R_f 0.65 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3290, 3096, 2919, 1626, 1575; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (brs, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.77-7.71 (m, 2H), 7.59 (d, J = 4.8 Hz, 1H), 7.38 (t, J = 7.0 Hz, 1H), 7.20 (d, J = 4.8 Hz, 1H), 4.19 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 171.9, 164.6, 155.2, 139.6, 138.9, 132.4, 130.0, 127.5, 124.8, 122.6, 121.9, 118.2, 112.3, 35.4; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{11}N_4OS$ $[M + H]^+$ 283.0654, found 283.0643.

6-Fluoro-2-(2-methoxyphenyl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (11e). Obtained from



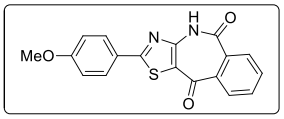
methyl 2-methoxybenzodithioate **1e** and 2,5-difluoro phenacyl bromide **7d**, yellow solid (232 mg, 71%); mp 326-328 ºC; R_f 0.69 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3215, 3056, 2918, 1636, 1520; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (brs, 1H), 8.37 (d, J = 7.6 Hz, 1H), 8.24 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 8.6 Hz, 2H), 7.21 (d, J = 6.4 Hz, 1H),

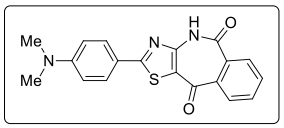
7.18 (d, J = 6.8 Hz, 1H), 4.11 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 171.6, 167.4, 164.2 (C-F, d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 157.5, 154.4, 141.1 (C-F, d, $^{3}J_{C\text{-}F}$ = 12.9 Hz), 133.4, 128.2 (C-F, d, $^{3}J_{C\text{-}F}$ = 10.8 Hz), 128.1, 121.1, 120.2, 118.9, 113.9, 112.6, 110.9 (C-F, d, $^{2}J_{C\text{-}F}$ = 23.5 Hz), 103.0 (C-F, d, $^{2}J_{C\text{-}F}$ = 25.1 Hz), 56.1; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{12}FN_2O_2S$ $[M + H]^+$ 327.0604, found 327.0597.

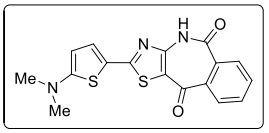
6-Fluoro-2-(1-methyl-1*H*-indol-3-yl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (11f). Obtained from methyl 1-methyl-1*H*-indole-3-carbodithioate **1j** and 2,5-difluoro phenacyl bromide **7d**, yellow solid (266 mg, 76%); mp 301-303 ºC; R_f 0.50 (4:1 EtOAc/hexane); IR (neat, cm^{-1}) 3335, 3066, 2970, 1640, 1542; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.09 (brs, 1H), 8.43 (s, 1H), 8.33 (td, J = 5.2, 1.6 Hz, 1H), 8.25-8.21 (m, 1H), 7.64-7.61 (m, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.37-7.35 m, 2H), 7.21 (td, J = 8.7, 2.1 Hz, 1H), 3.93 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 170.5, 168.9, 164.0 (C-F, d, $^{1}J_{C\text{-}F}$ = 246.2 Hz), 156.0, 140.8 (C-F, d, $^{3}J_{C\text{-}F}$ = 12.8 Hz), 137.4, 133.9, 128.0 (C-F, d, $^{3}J_{C\text{-}F}$ = 10.8 Hz), 124.63, 124.60, 123.1, 122.0, 120.5, 119.2, 111.1 (C-F, d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 110.1, 109.2, 103.1 (C-F, d, $^{2}J_{C\text{-}F}$ = 25.0 Hz), 33.2; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{13}FN_3OS$ $[M + H]^+$ 350.0763, found 350.0787.

5.6.6 General Procedure for the Synthesis of 2-(Het)aryl-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione 12a-e. To an ice-cooled stirred suspension of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) and appropriate dithioester, **1** (1.0 mmol, 1.0 equiv.) in DMF (2 mL), a solution of cyanamide (42 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise over 5 minutes, under N_2 atmosphere. After further stirring at room temperature for 3 h (at 90 ºC for 3 h, for **1h** and **1i** dithioester), a solution of *o*-carboethoxy phenacyl bromide **7e** (271 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise to the ice-cold reaction mixture and stirred for 3 h at room temperature. Followed by the addition of another lot of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) to the ice-cold reaction mixture, stirring was further continued for 5-6 h at 60 ºC (monitored by TLC). The reaction mixture, after cooling, and the quenching with saturated NH_4Cl solution (50 mL). The reaction mixture was extracted with DCM (3 × 25 mL) and the collected organic layer was further water (3 × 25 mL) washed and brine (25 mL) washed, and then dried over anhydrous Na_2SO_4 and

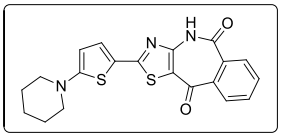
concentrated under a vacuum, and the crude residue was purified by column chromatography over silica gel using EtOAc as eluent.

2-(4-Methoxyphenyl)-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione (12a).  Obtained from methyl 4-methoxybenzodithioate **1a** and *o*-carboethoxy phenacyl bromide **7e**, pale-yellow solid (252 mg, 75%); mp 272-274 ºC; R_f 0.59 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3370, 2980, 1674, 1605, 1561; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (brs, 1H), 8.55 (t, J = 4.6 Hz, 1H), 8.39 (t, J = 4.6 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.93 (t, J = 4.6 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 177.9, 172.8, 164.1, 162.7, 149.9, 133.7, 133.5, 133.2, 131.1, 129.7, 128.8, 124.4, 118.5, 114.9, 55.6; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{13}N_2O_3S$ $[M + H]^+$ 337.0647, found 337.0630.

2-(4-(Dimethylamino)phenyl)-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione (12b).  Obtained from methyl 4-(dimethylamino)benzodithioate **1c** and *o*-carboethoxy phenacyl bromide **7e**, orange-yellow solid (245 mg, 70%); mp 288-290 ºC; R_f 0.49 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3350, 3058, 2916, 1641, 1600, 1543; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.29 (brs, 1H), 8.55 (d, J = 8.8 Hz, 1H), 8.39 (d, J = 9.2 Hz, 1H), 7.90 (dd, J = 7.2, 3.6 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 3.05 (s, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 177.1, 173.6, 164.0, 152.9, 150.1, 133.8, 133.4, 133.2, 133.1, 130.9, 129.6, 128.4, 118.8, 111.6, 39.9; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{16}N_3O_2S$ $[M + H]^+$ 350.0963, found 350.0960.

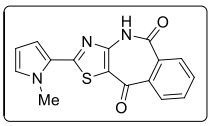
2-(5-(Dimethylamino)thiophen-2-yl)-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione (12c).  Obtained from methyl 5-(dimethylamino)thiophene-2-carbodithioate **1h** and *o*-carboethoxy phenacyl bromide **7e**, red solid (256 mg, 72%); mp 262-264 ºC; R_f 0.44 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 3080, 2922, 1650, 1601, 1494; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (brs, 1H), 8.52 (d, J = 7.2 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.90-7.84 (m, 2H), 7.69 (d, J = 4.4 Hz, 1H), 6.09 (d, J = 4.4 Hz, 1H), 3.05 (s, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 175.8, 166.8, 165.1, 163.9, 149.9, 134.3, 133.7, 133.3, 133.1, 132.9, 130.7, 129.4, 116.3, 115.4, 104.1, 41.7; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{14}N_3O_2S_2$ $[M + H]^+$ 356.0527, found 356.0515.

2-(5-(Piperidin-1-yl)thiophen-2-yl)-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione



(12d). Obtained from methyl 5-(piperidin-1-yl)thiophene-2-carbodithioate **1i** and *o*-carboethoxy phenacyl bromide **7e**, brown solid (284 mg, 72%); mp 202-204 ºC; R_f 0.68 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3345, 3065, 2922, 2852, 1655, 1605, 1457; ^1H NMR (400 MHz, DMSO-d_6): δ 12.81 (brs, 1H), 7.78 (d, J = 4.4 Hz, 1H), 7.65 (brs, 2H), 7.62 (brs, 2H), 6.61 (d, J = 4.8 Hz, 1H), 3.51 (brs, 4H), 1.64 (brs, 6H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 179.4, 171.7, 164.1, 156.1, 146.9, 145.4, 140.3, 138.3, 133.1, 131.5, 128.8, 126.3, 123.4, 120.7, 107.7, 50.7, 24.7, 22.8; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{18}N_3O_2S_2$ $[M + H]^+$ 396.0840, found 396.0833.

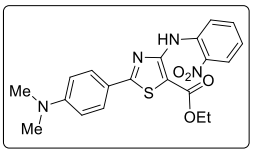
2-(1-Methyl-1*H*-pyrrol-2-yl)-4*H*-benzo[*e*]thiazolo[4,5-*b*]azepine-5,10-dione (12e).



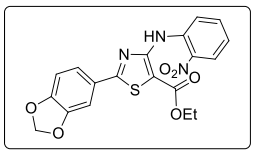
Obtained from methyl 1-methyl-1*H*-pyrrole-2-carbodithioate **1k** and *o*-carboethoxy phenacyl bromide **7e**, yellow solid (214 mg, 69%); mp 317-319 ºC; R_f 0.58 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3365, 3075, 2954, 1662, 1604, 1492; ^1H NMR (600 MHz, DMSO-d_6): δ 12.31 (brs, 1H), 8.56 (dd, J = 7.2, 2.4 Hz, 1H), 8.39 (dd, J = 7.5, 2.1 Hz, 1H), 7.92-7.90 (m, 2H), 7.19 (s, 1H), 7.03 (dd, J = 3.9, 1.5 Hz, 1H), 6.22 (dd, J = 3.9, 2.7 Hz, 1H), 4.04 (s, 3H); $^{13}C\{H\}$ NMR (150 MHz, DMSO-d_6): δ 177.1, 165.1, 164.0, 149.6, 133.7, 133.4, 133.2, 133.1, 130.8, 129.5, 125.0, 116.3, 116.1, 109.4, 36.8; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{12}N_3O_2S$ $[M + H]^+$ 310.0650, found 310.0639.

5.6.7 General procedure for the synthesis of 2-(het)aryl-4-((2-nitrophenyl)amino)thiazole-5-carboxylate 87a-e. To an ice-cooled stirred suspension of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) and appropriate dithioester, **1** (1.0 mmol, 1.0 equiv.) in DMF (2 mL), a solution of cyanamide (42 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise over 5 minutes, under N_2 atmosphere. After further stirring at room temperature for 3 h, a solution of ethyl 2-bromoacetate **7f** (167 mg, 1.0 mmol, 1.0 equiv.) in DMF (1 mL) was added dropwise to the ice-cold reaction mixture and stirred for 3 h at room temperature. Followed by the addition of another lot of NaH (60% suspension in mineral oil) (74 mg, 2.2 mmol, 2.2 equiv.) to the ice-cold reaction mixture, stirring was further continued for 3 h at room temperature. The reaction is monitored by thin-layer chromatography (TLC), after consumption of **7f**, a solution of 1-fluoro-2-nitrobenzene **27** (141 mg, 1.0 mmol, 1.0

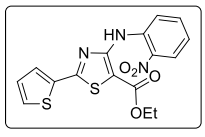
equiv.) in DMF (1 mL) was added dropwise to the ice-cold reaction mixture and stirred for 3 h at room temperature. The reaction mixture, after cooling, and the quenching with saturated NH_4Cl solution (50 mL). The reaction mixture was extracted with DCM (3 × 25 mL) and the collected organic layer was further water (3 × 25 mL) washed and brine (25 mL) washed, and then dried over anhydrous Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by column chromatography over silica gel using EtOAc/petroleum ether as eluent.

Ethyl 2-(4-(dimethylamino)phenyl)-4-((2-nitrophenyl)amino)thiazole-5-carboxylate (87a). 

Obtained from methyl 4-(dimethylamino)benzodithioate **1c**, ethyl 2-bromoacetate **7f** and 1-fluoro-2-nitrobenzene **27**, deep-red solid (330 mg, 80%); mp 139-141 ºC; R_f 0.53 (1:3 EtOAc/hexane); IR (neat, cm^{-1}) 3327, 3055, 2971, 1738, 1599, 1530, 1366; ^1H NMR (400 MHz, $CDCl_3$): δ 11.79 (brs, 1H), 8.99 (dd, J = 8.8, 1.2 Hz, 1H), 8.24 (dd, J = 8.4, 1.6 Hz, 1H), 7.87 (dd, J = 6.8, 2.0 Hz, 2H), 7.61 (td, J = 8.0, 2.1 Hz, 1H), 7.01 (td, J = 7.8, 1.6 Hz, 1H), 6.72 (dd, J = 7.2, 2.0 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.07 (s, 6H), 1.41 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 170.9, 163.3, 156.3, 152.6, 137.7, 135.3, 135.1, 128.2, 126.1, 120.9, 120.6, 120.2, 111.6, 61.1, 40.1, 14.6; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{21}N_4O_4S$ $[M + H]^+$ 413.1284, found 413.1274.

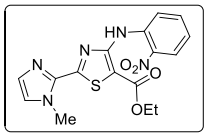
Ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-((2-nitrophenyl)amino)thiazole-5-carboxylate (87b). 

Obtained from methyl benzo[*d*][1,3]dioxole-5-carbodithioate **1f**, ethyl 2-bromoacetate **7f** and 1-fluoro-2-nitrobenzene **27**, red-brown solid (338 mg, 82%); mp 208-210 ºC; R_f 0.57 (1:19 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 2970, 1738, 1495, 1336; ^1H NMR (400 MHz, $CDCl_3$): δ 11.78 (brs, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.07 (s, 2H), 4.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 169.5, 163.1, 156.1, 150.6, 148.4, 137.4, 135.4, 135.2, 127.2, 126.1, 124.4, 121.7, 120.8, 120.4, 108.8, 106.7, 101.9, 61.4, 14.6; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{16}N_3O_6S$ $[M + H]^+$ 414.0760, found 414.0753.

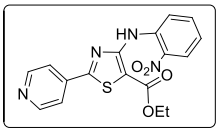
Ethyl 4-((2-nitrophenyl)amino)-2-(thiophen-2-yl)thiazole-5-carboxylate (87c). 

Obtained from methyl thiophene-2-carbodithioate **1g**, ethyl 2-

bromoacetate **7f** and 1-fluoro-2-nitrobenzene **27**, deep-orange solid (289 mg, 77%); mp 205-207 ºC; R_f 0.53 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3335, 3056, 2970, 1738, 1531, 1366; ^1H NMR (400 MHz, $CDCl_3$): δ 11.81 (brs, 1H), 8.88 (d, J = 8.8 Hz, 1H), 8.25 (dd, J = 8.4, 1.6 Hz, 1H), 7.64 (t, J = 4.0 Hz, 2H), 7.52 (d, J = 5.2 Hz, 1H), 7.14 (t, J = 4.4 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 163.4, 162.9, 155.9, 137.3, 136.8, 135.4, 135.3, 129.9, 128.5, 128.2, 126.1, 120.8, 120.6, 101.3, 61.5, 14.6; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{14}N_3O_4S_2$ $[M + H]^+$ 376.0426, found 376.0408.

Ethyl 2-(1-methyl-1*H*-imidazol-2-yl)-4-((2-nitrophenyl)amino)thiazole-5-carboxylate (87d). 

Obtained from methyl 1-methyl-1*H*-pyrrole-2-carbodithioate **1l**, ethyl 2-bromoacetate **7f** and 1-fluoro-2-nitrobenzene **27**, orange solid (317 mg, 85%); mp 196-198 ºC; R_f 0.50 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3293, 3056, 2971, 1738, 1475, 1354; ^1H NMR (400 MHz, DMSO-d_6): δ 11.39 (brs, 1H), 8.62 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.16 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.08 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ 162.5, 155.6, 135.9, 135.7, 135.6, 134.8, 129.8, 127.2, 127.1, 125.9, 121.6, 121.0, 118.4, 61.2, 35.5, 14.2; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{16}N_5O_4S$ $[M + H]^+$ 374.0923, found 374.0919.

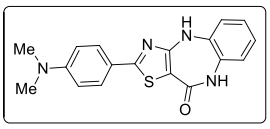
Ethyl 4-((2-nitrophenyl)amino)-2-(pyridin-4-yl)thiazole-5-carboxylate (87e). 

Obtained from methyl pyridine-4-carbodithioate **1n**, ethyl 2-bromoacetate **7f** and 1-fluoro-2-nitrobenzene **27**, yellow solid (289 mg, 78%); mp 194-196 ºC; R_f 0.56 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 3056, 2970, 1736, 1506, 1379; ^1H NMR (400 MHz, $CDCl_3$): δ 11.81 (brs, 1H), 8.85 (dd, J = 8.8, 1.2 Hz, 1H), 8.79 (d, J = 6.0 Hz, 2H), 8.27 (dd, J = 8.4, 1.6 Hz, 1H), 7.84 (dd, J = 4.4, 1.6 Hz, 2H), 7.64 (td, J = 7.9, 2.0 Hz, 1H), 7.08 (td, J = 7.8, 2.0 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 166.6, 162.7, 156.5, 150.9, 139.3, 136.9, 135.7, 135.3, 126.2, 120.9, 120.6, 120.1, 104.0, 61.8, 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{15}N_4O_4S$ $[M + H]^+$ 371.0814, found 371.0821.

5.6.7 General Procedure for the Synthesis of 2-(Het)aryl-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one 13a-e from 2-(Het)aryl-4-((2-nitrophenyl)amino)thiazole-

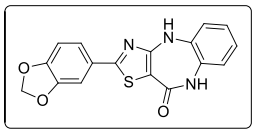
5-carboxylate 87a-e. A solution of 2-(het)aryl-4-((2-nitrophenyl)amino)thiazole-5-carboxylate **87** (0.5 mmol, 1.0 equiv.) and Fe powder (140 mg, 2.5 mmol, 5.0 equiv.) in acetic acid (2 mL)/methanol (2 mL) (V/V) was heated at 50 ºC for 2 h. After reduction of **87**, tripotassium phosphate (318 mg, 1.5 mmol) and ethylene glycol (3 mL) were added and heated to the reaction mixture at 120 ºC for 4 h. The reaction is monitored by thin-layer chromatography (TLC), the reaction mixture, after cooling, and the quenching with saturated NH_4Cl solution (50 mL). The reaction mixture was extracted with DCM (3 × 25 mL) and the collected organic layer was further water (3 × 25 mL) washed and brine (25 mL) washed, and then dried over anhydrous Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by column chromatography over silica gel using EtOAc/petroleum ether as eluent.

2-(4-(Dimethylamino)phenyl)-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one



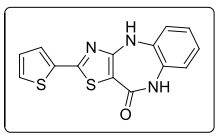
(13a). Obtained from **87a**, gray solid (131 mg, 78%); mp 183-185 ºC; R_f 0.36 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 3320, 3055, 2971, 1625, 1480 ; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (brs, 1H), 7.97-7.95 (m, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.14-7.08 (m, 3H), 6.82 (d, J = 8.8 Hz, 2H), 3.01 (s, 6H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 166.0, 152.6, 151.7, 145.1, 128.5, 128.1, 126.9, 122.2, 121.1, 120.4, 112.1, 111.9, 109.1, 103.9, 40.2; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{17}N_4OS$ $[M + H]^+$ 337.1123, found 337.1119.

2-(Benzo[*d*][1,3]dioxol-5-yl)-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one



(13b). Obtained from **87b**, off-white solid (127 mg, 75%); mp 257-259 ºC; R_f 0.29 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3369, 3342, 3056, 3007, 1622; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (brs, 1H), 7.97 (d, J = 3.2 Hz, 1H), 7.88 (s, 1H), 7.58 (brs, 1H), 7.56 (s, 1H), 7.15-7.13 (m, 2H), 7.09 (t, J = 7.4 Hz, 2H), 6.15 (s, 2H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 164.8, 152.5, 149.3, 148.2, 145.3, 128.3, 128.1, 126.9, 122.4, 121.2, 120.6, 112.1, 109.1, 108.9, 105.9, 105.8, 101.8; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{12}N_3O_3S$ $[M + H]^+$ 338.0599, found 338.0592.

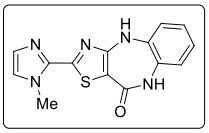
2-(Thiophen-2-yl)-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one (13c).



Obtained from **87c**, off-white solid (111 mg, 74%); mp 197-199 ºC; R_f 0.33 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3350, 3292, 3040, 2971,

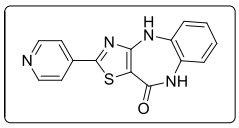
1671; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (brs, 1H), 7.89-7.88 (m, 2H), 7.79 (brs, 2H), 7.22 (t, J = 4.2 Hz, 1H), 7.13-7.12 (m, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 158.9, 152.4, 144.8, 136.1, 129.2, 128.6, 128.2, 128.1, 127.3, 122.4, 121.1, 111.8, 109.1, 106.1; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{10}N_3OS_2$ $[M + H]^+$ 300.0265, found 300.0257.

2-(1-Methyl-1*H*-imidazol-2-yl)-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one



(13d). Obtained from **87d**, green solid (117 mg, 79%); mp 251-253 ºC; R_f 0.28 (7:3 EtOAc/hexane); IR (neat, cm^{-1}) 3350, 3310, 3056, 2971, 1645; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (brs, 1H), 7.89 (brs, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.46 (s, 1H), 7.12-7.09 (m, 4H), 4.13 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 157.4, 152,5 144.8, 139.5, 128.8, 128.4, 128.1, 125.6, 122.3, 121.2, 111.4, 109.2, 107.6, 35.2; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{12}N_5OS$ $[M + H]^+$ 298.0763, found 298. 0759.

2-(Pyridin-4-yl)-4*H*-benzo[*b*]thiazolo[4,5-*e*][1,4]diazepin-10(9*H*)-one (13e). Obtained



from **87e**, rust color solid (107 mg, 73%); mp 257-259 ºC; R_f 0.27 (7:3 EtOAc/hexane); IR (neat, cm^{-1}) 3353, 3307, 3037, 2986, 1637; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.53 (brs, 1H), 9.39 (brs, 1H), 8.76 (dd, J = 6.8, 2.0 Hz, 2H), 7.82 (dd, J = 4.8, 1.6 Hz, 2H), 6.98-6.86 (m, 4H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ 164.0, 154.1, 150.0, 148.9, 148.1, 147.1, 144.8, 139.5, 128.1, 125.6, 122.3, 121.2, 119.2; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{11}N_4OS$ $[M + H]^+$ 295.0654, found 295.0643.

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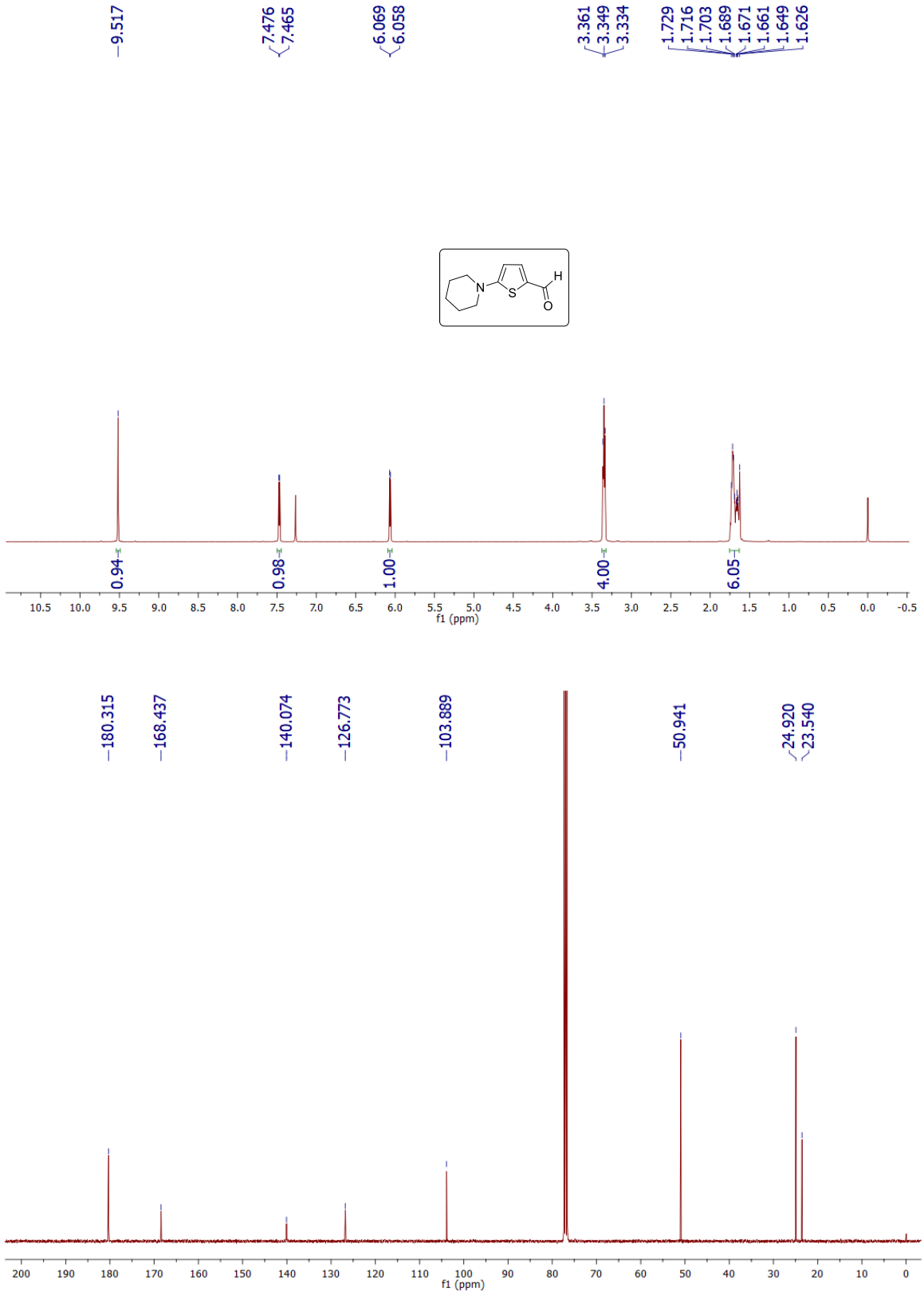
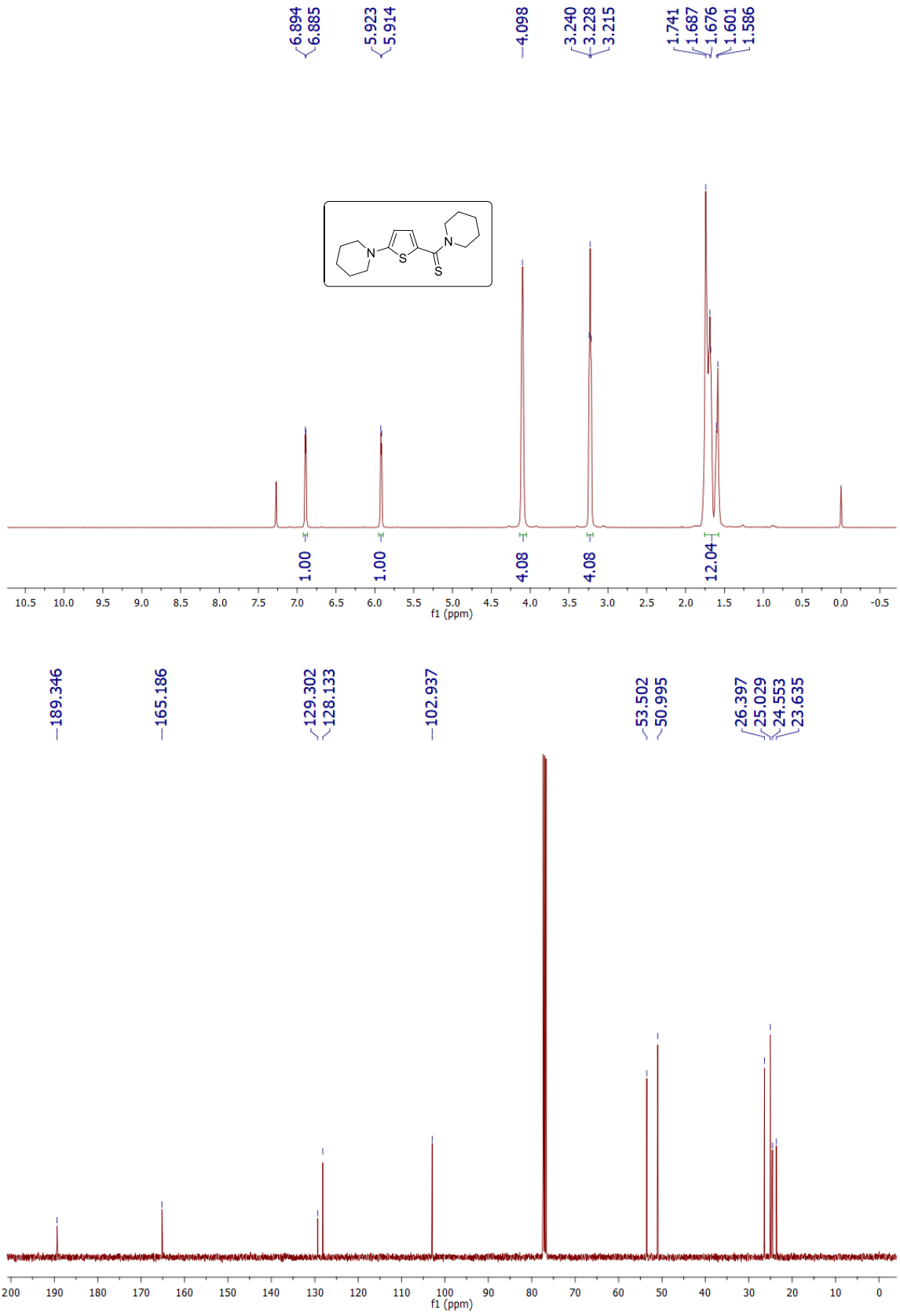
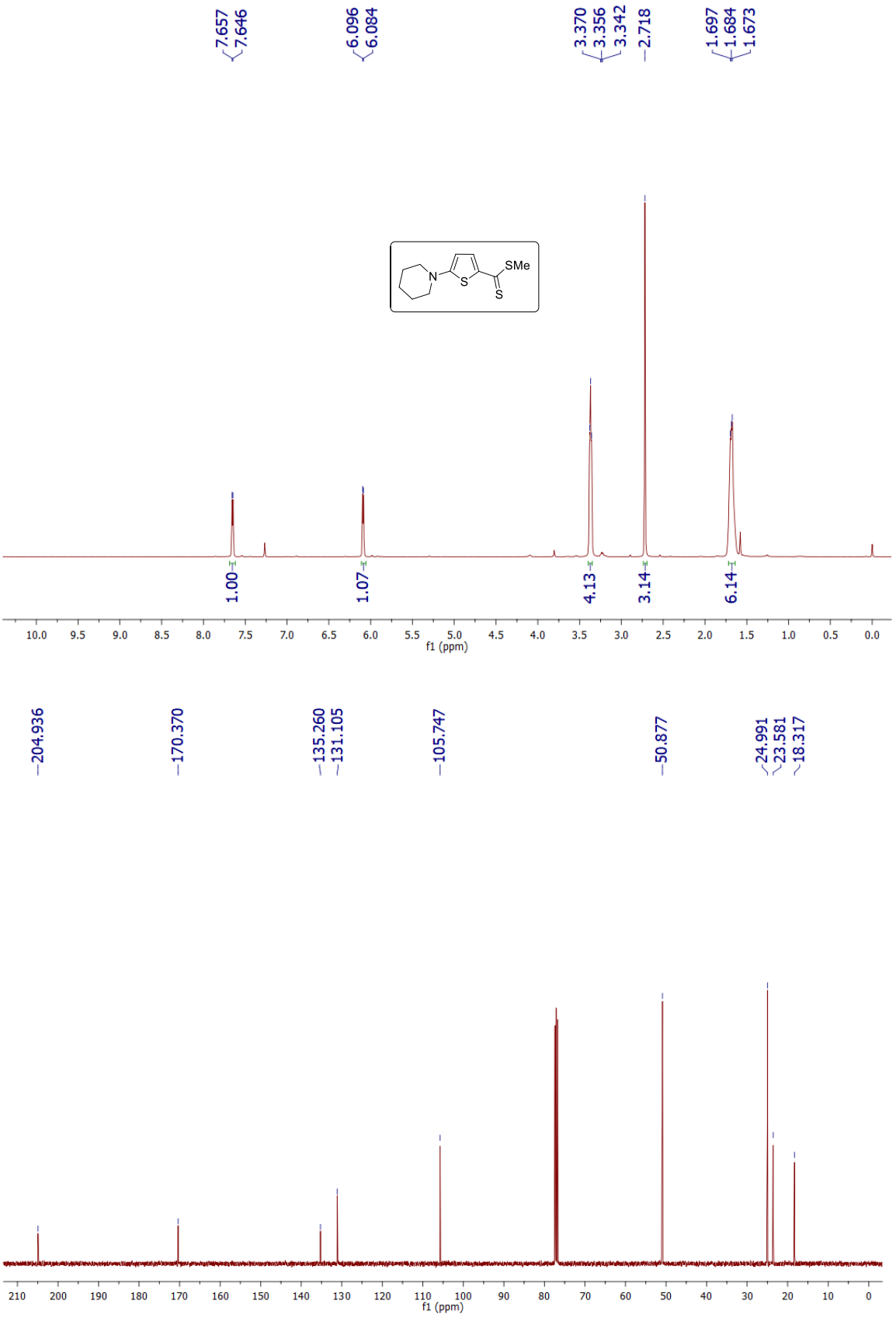
5.8 Representative Spectra



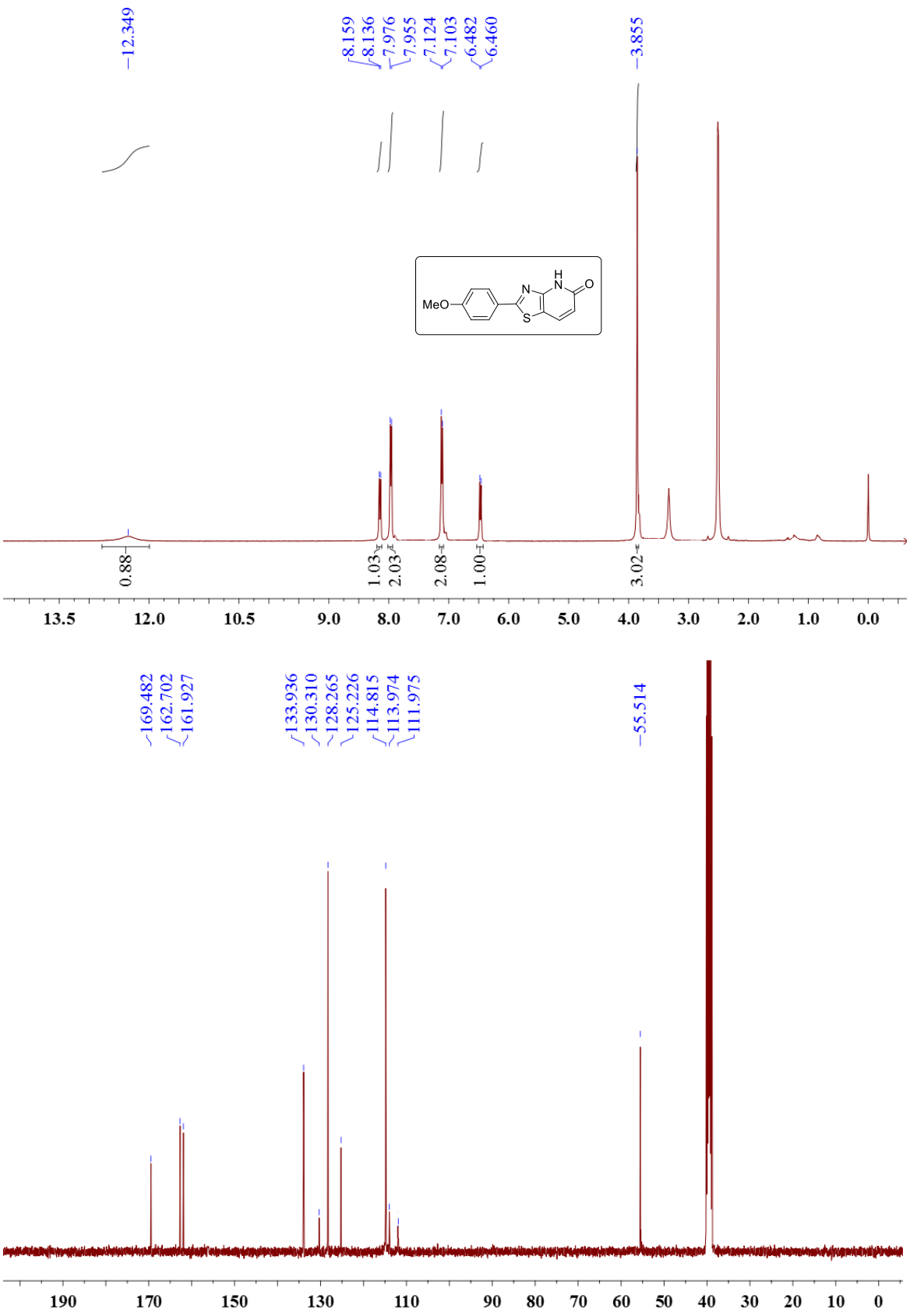
^{1}H and ^{13}C NMR spectra



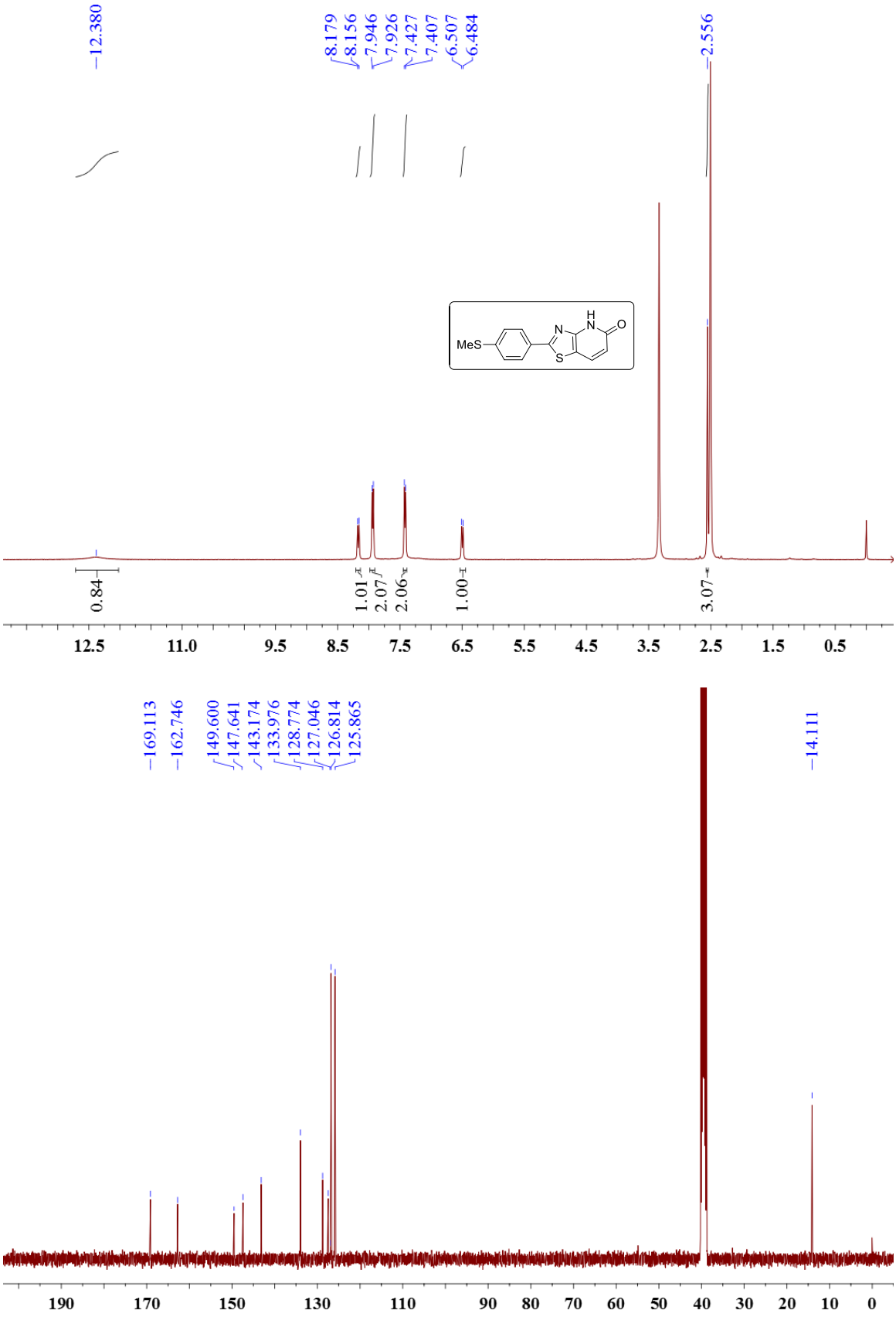
^{1}H and ^{13}C NMR spectra



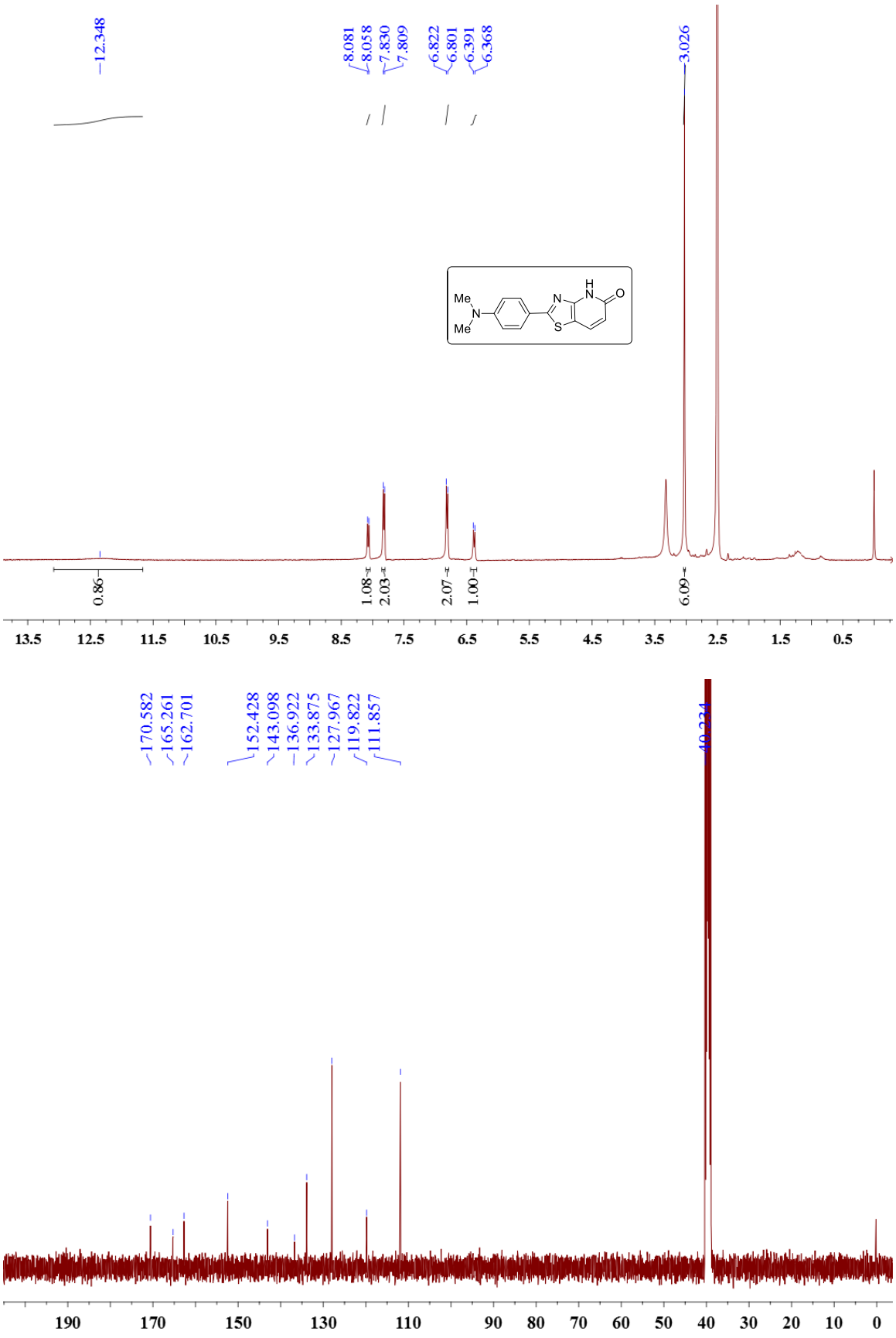
^{1}H and ^{13}C NMR spectra of compound **1i**



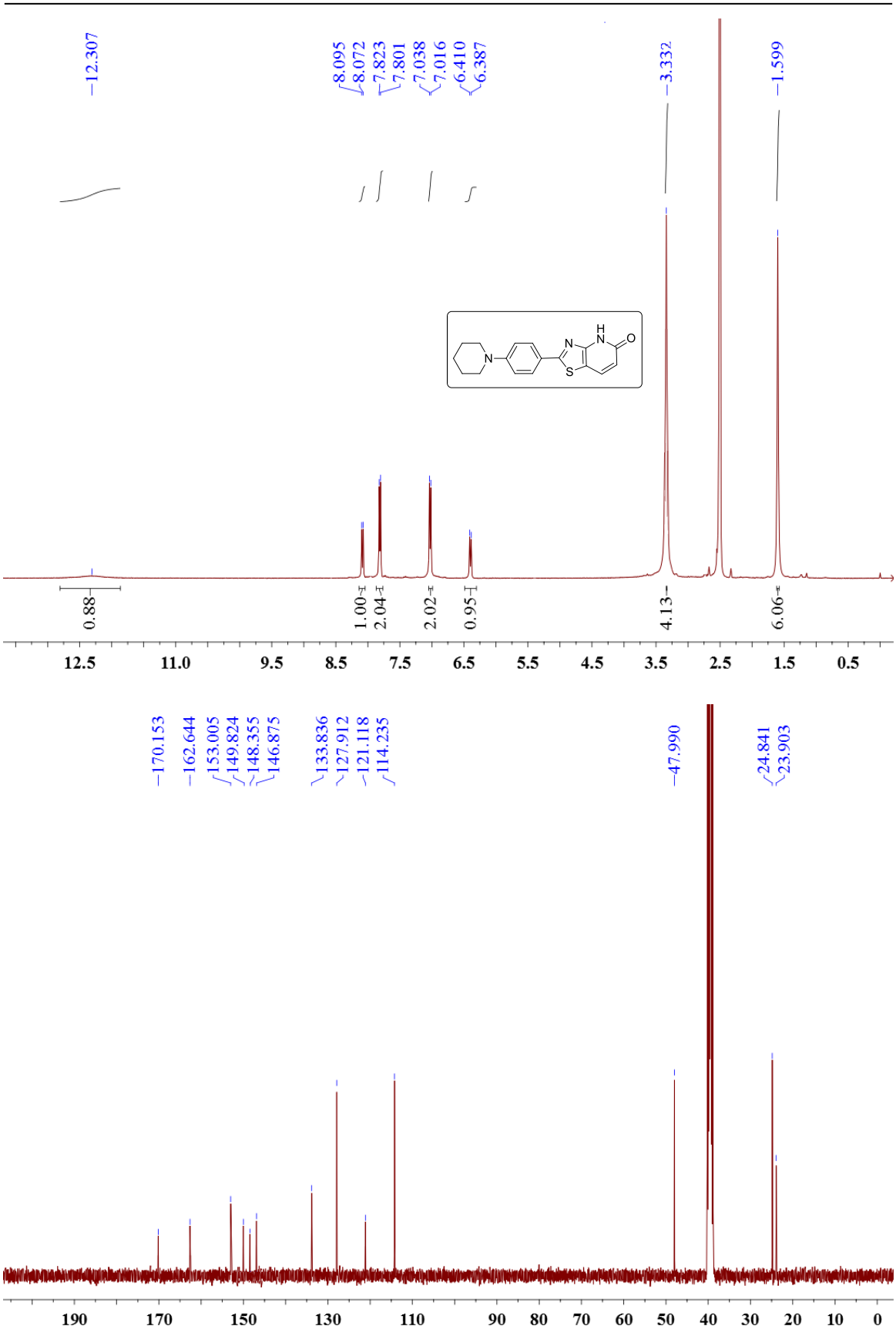
^{1}H and ^{13}C NMR spectra of compound **9a**



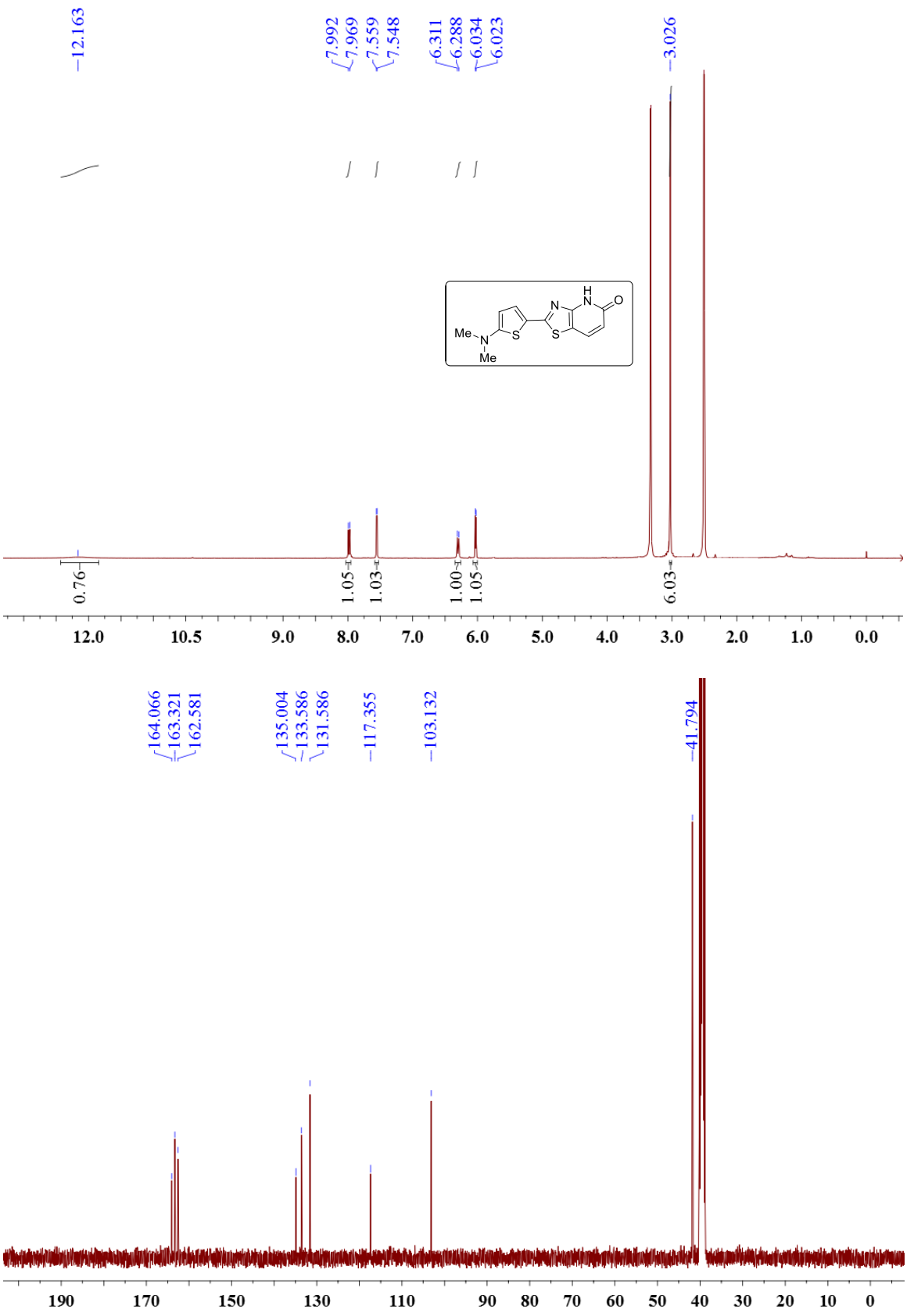
^{1}H and ^{13}C NMR spectra of compound **9b**



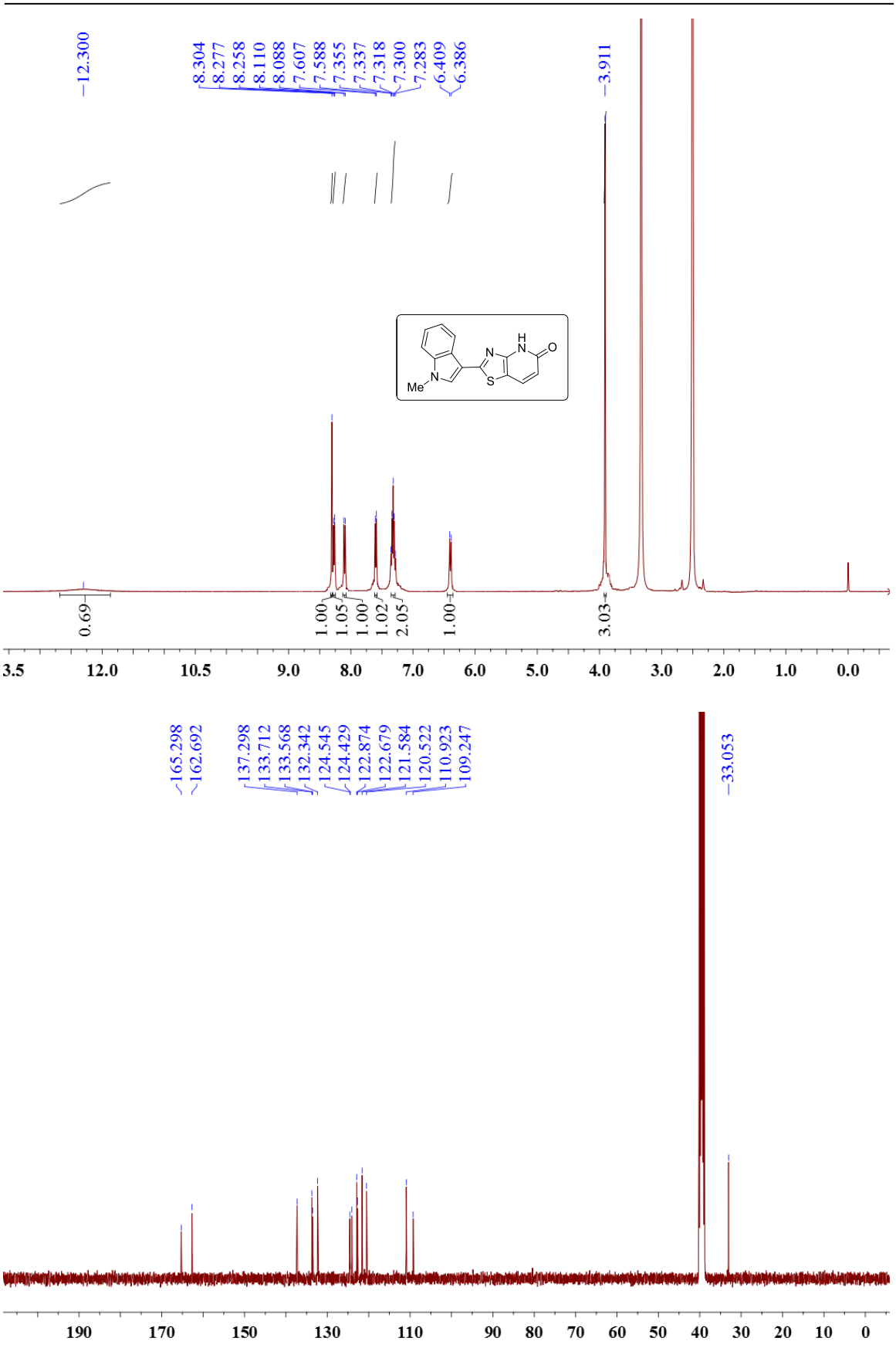
^{1}H and ^{13}C NMR spectra of compound **9c**



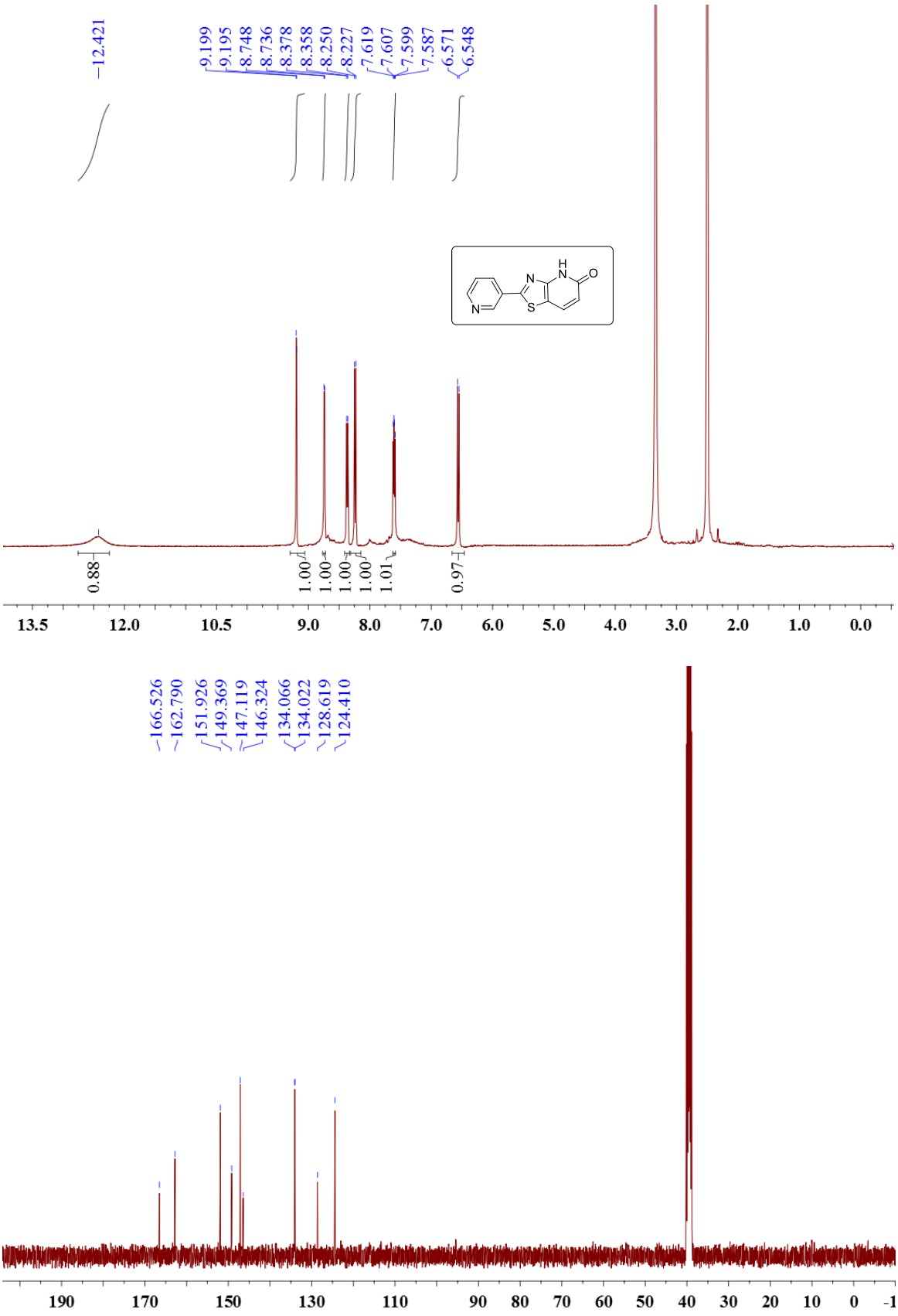
^{1}H and ^{13}C NMR spectra of compound **9d**



^{1}H and ^{13}C NMR spectra of compound **9e**



^{1}H and ^{13}C NMR spectra of compound **9f**



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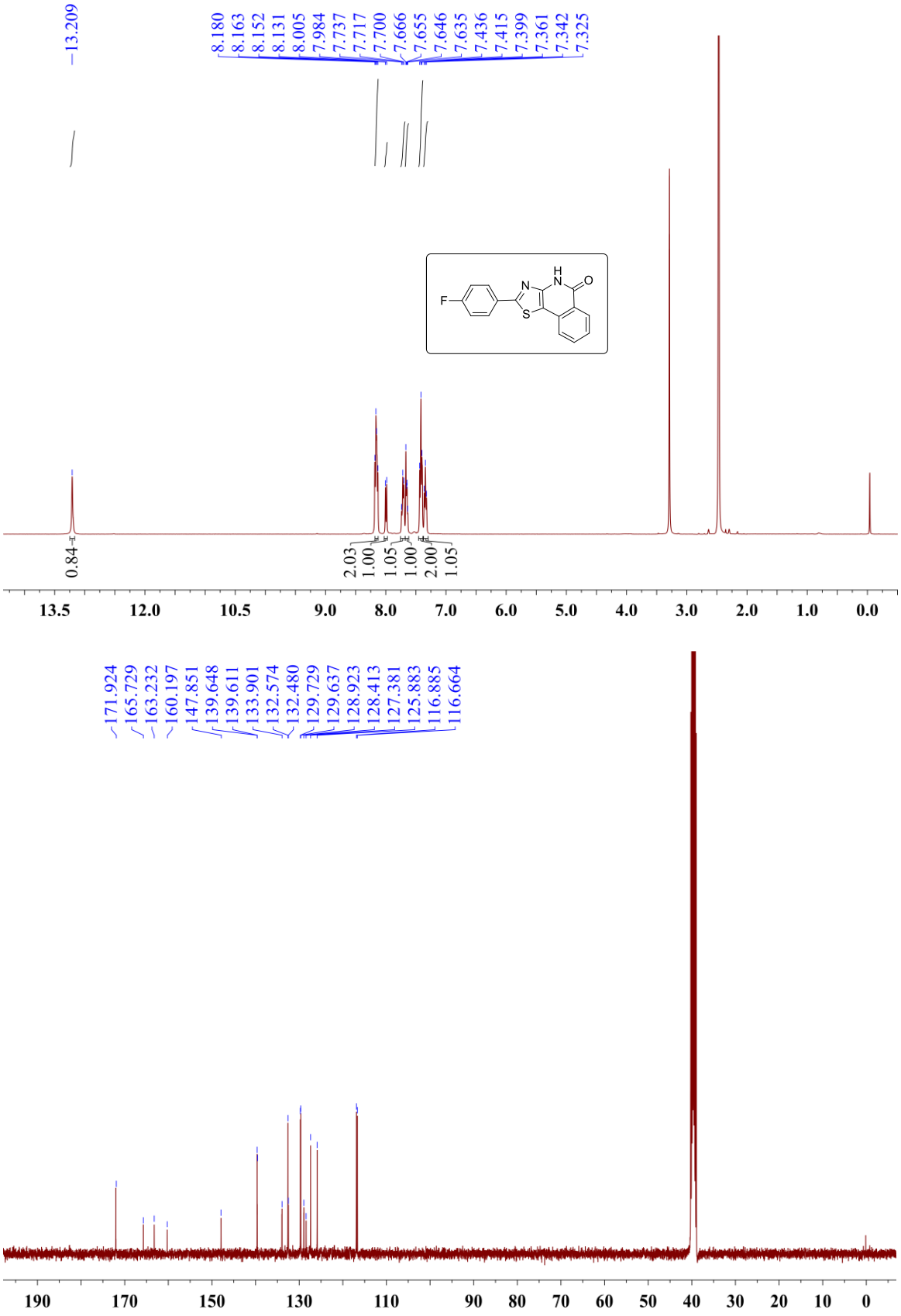
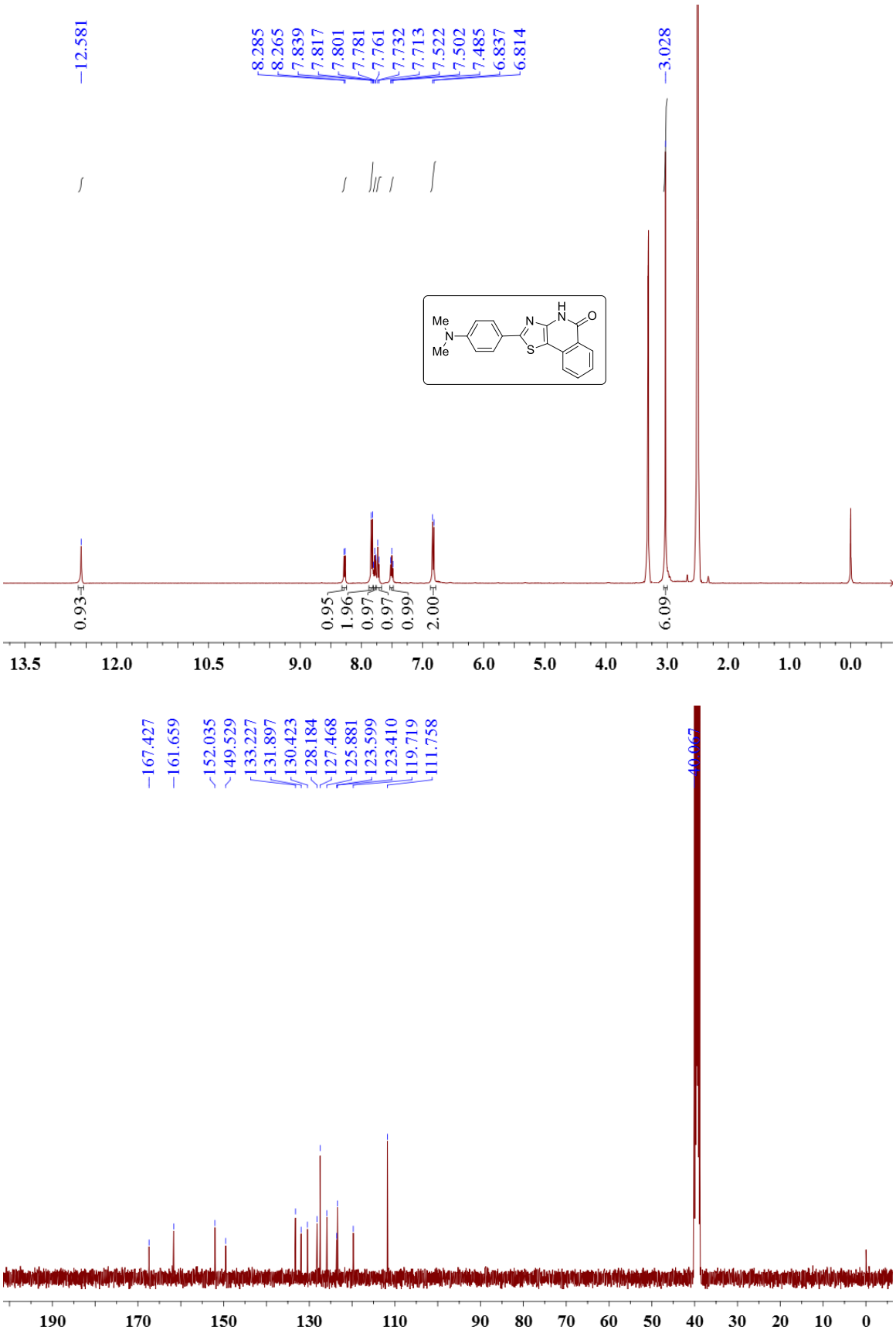
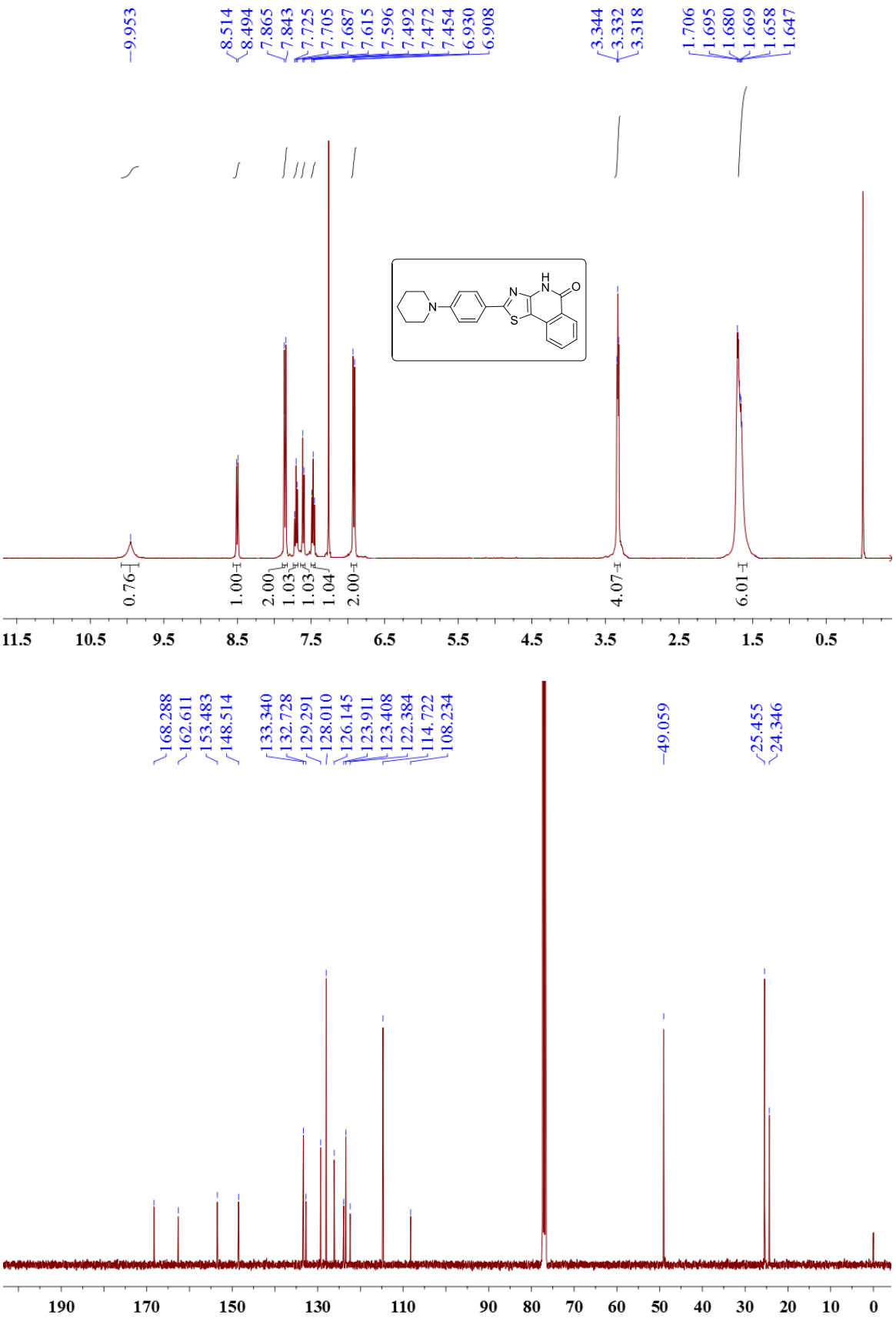


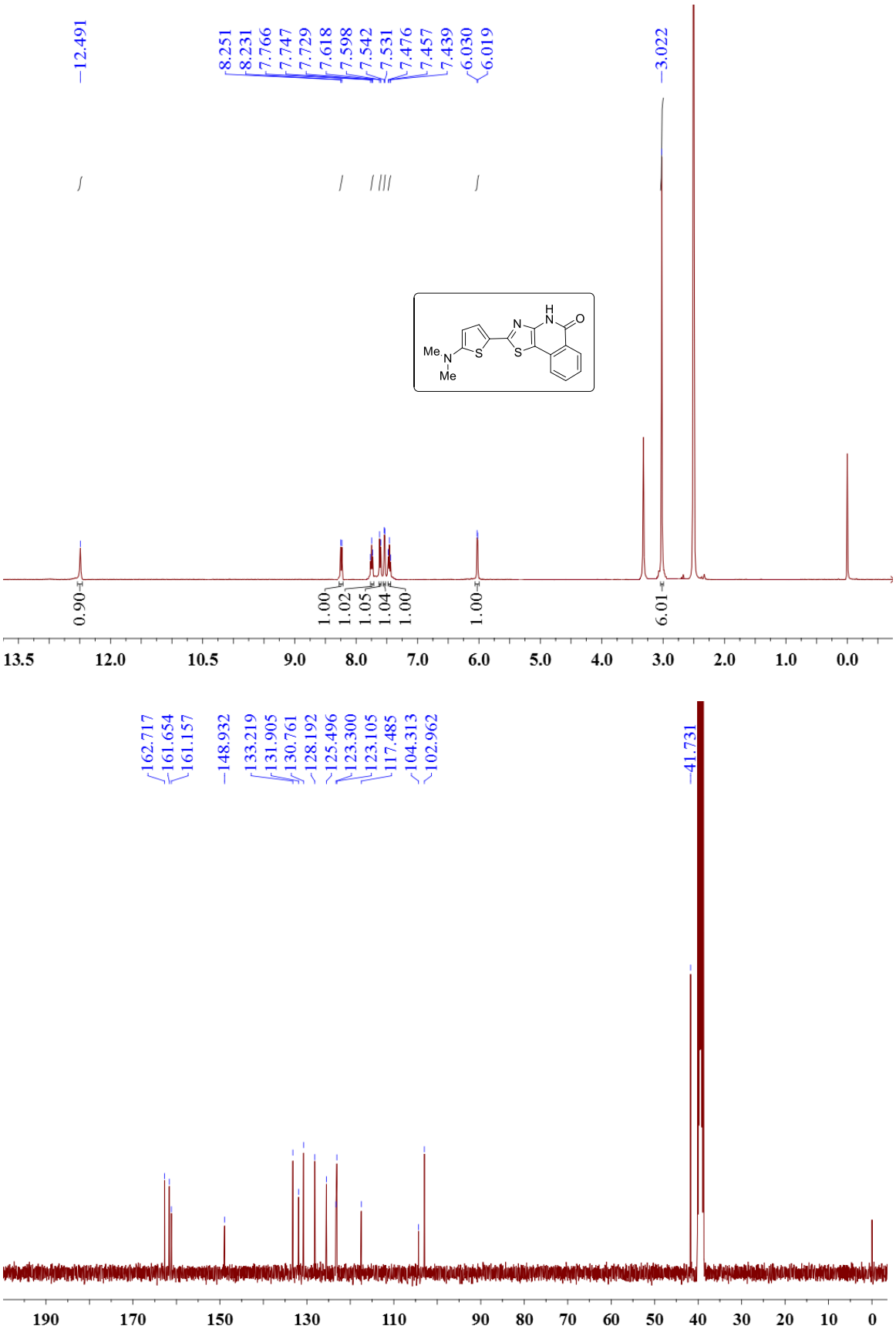
^{1}H and ^{13}C NMR spectra of compound **10b**



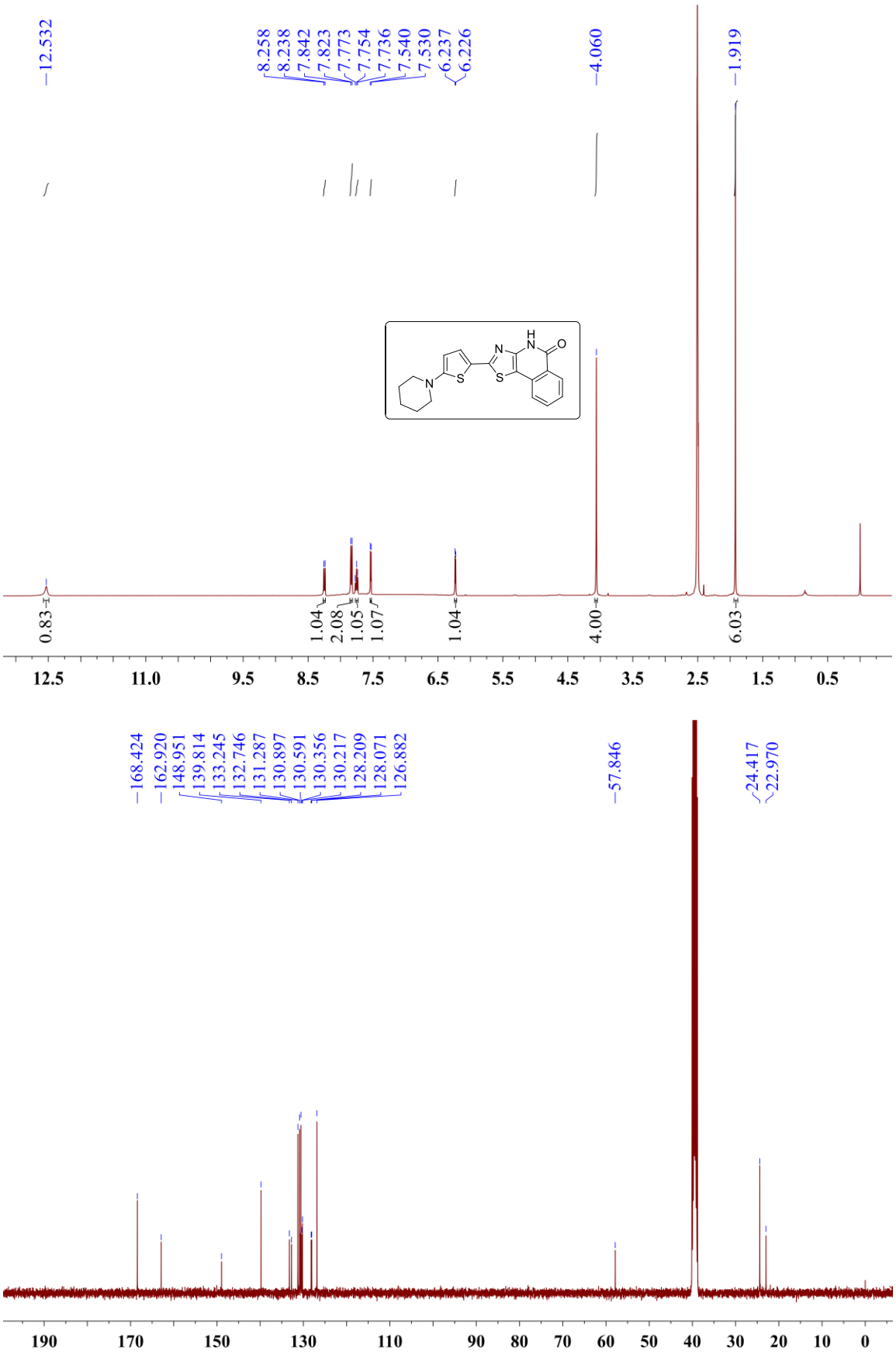
^{1}H and ^{13}C NMR spectra of compound **10c**



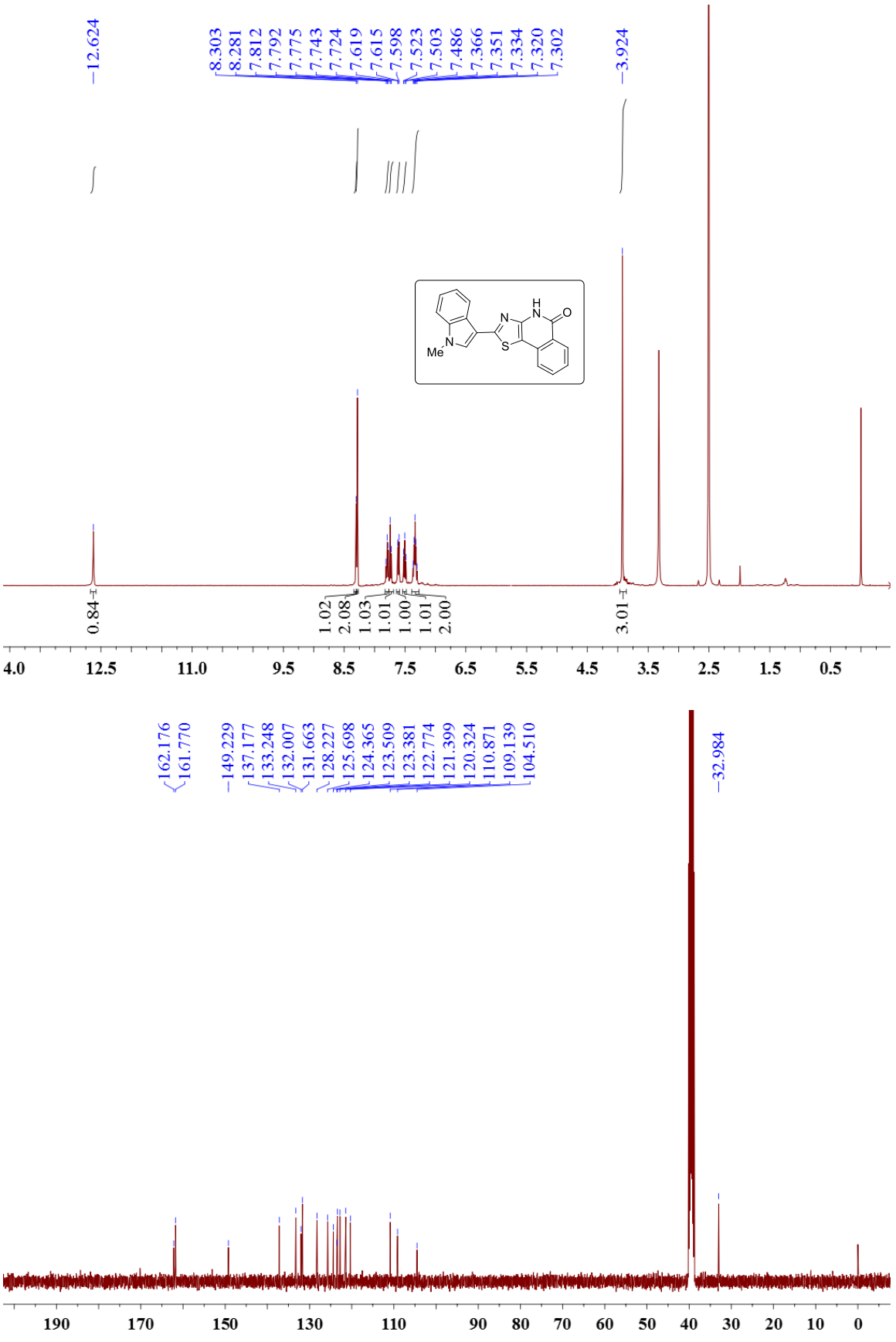
^{1}H and ^{13}C NMR spectra of compound **10d**



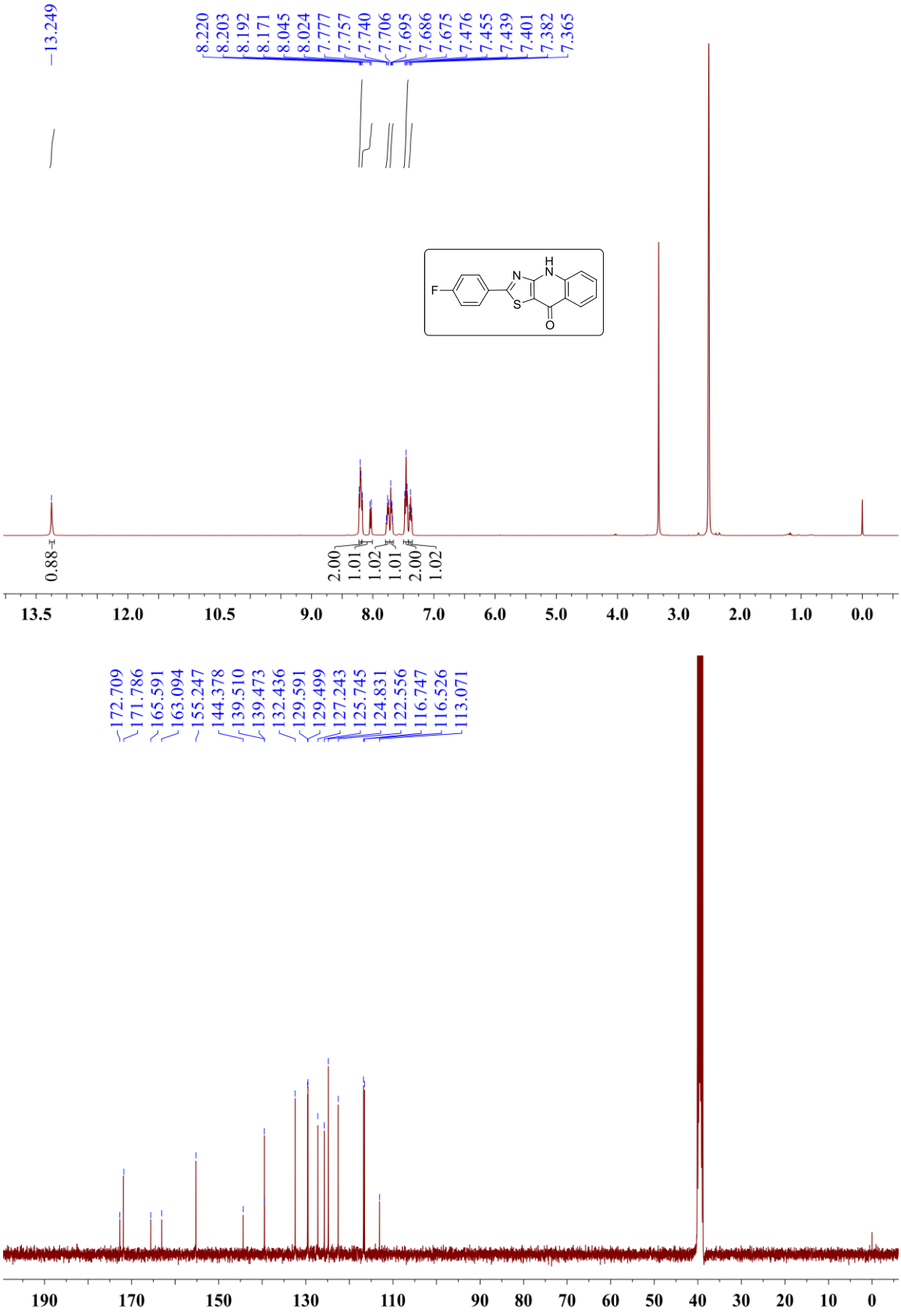
^{1}H and ^{13}C NMR spectra of compound **10e**



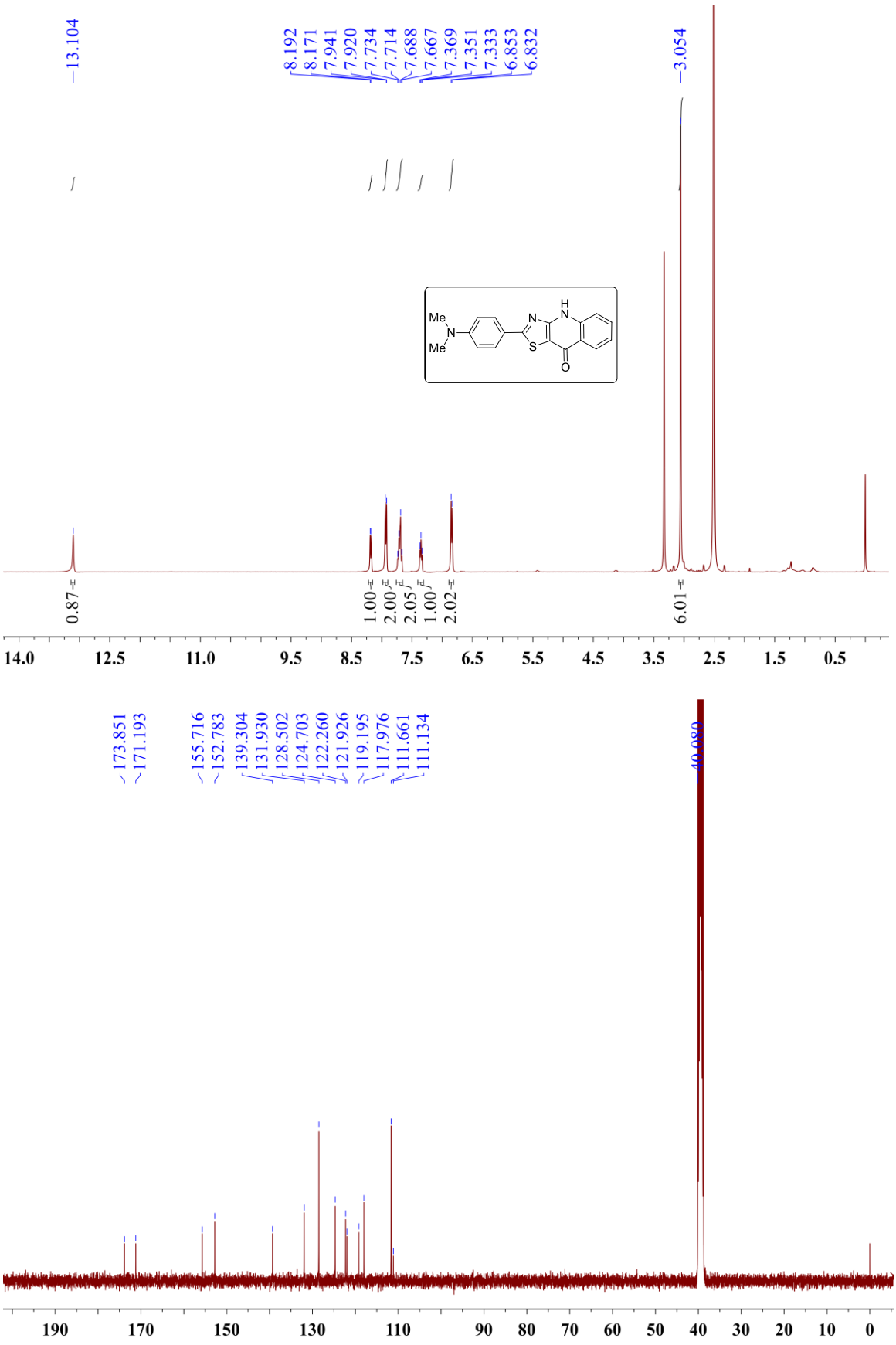
^{1}H and ^{13}C NMR spectra of compound **10f**



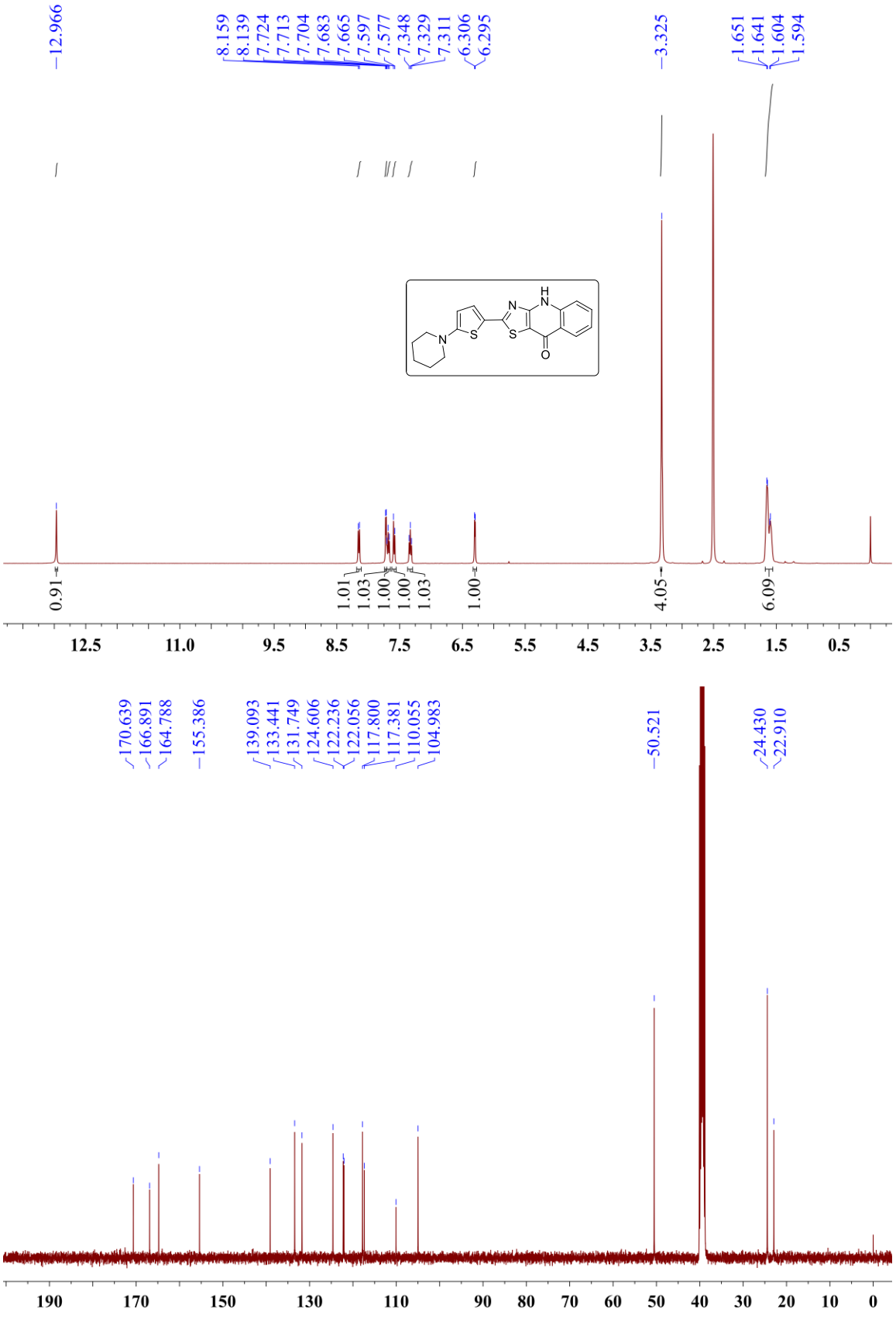
^{1}H and ^{13}C NMR spectra of compound **10g**



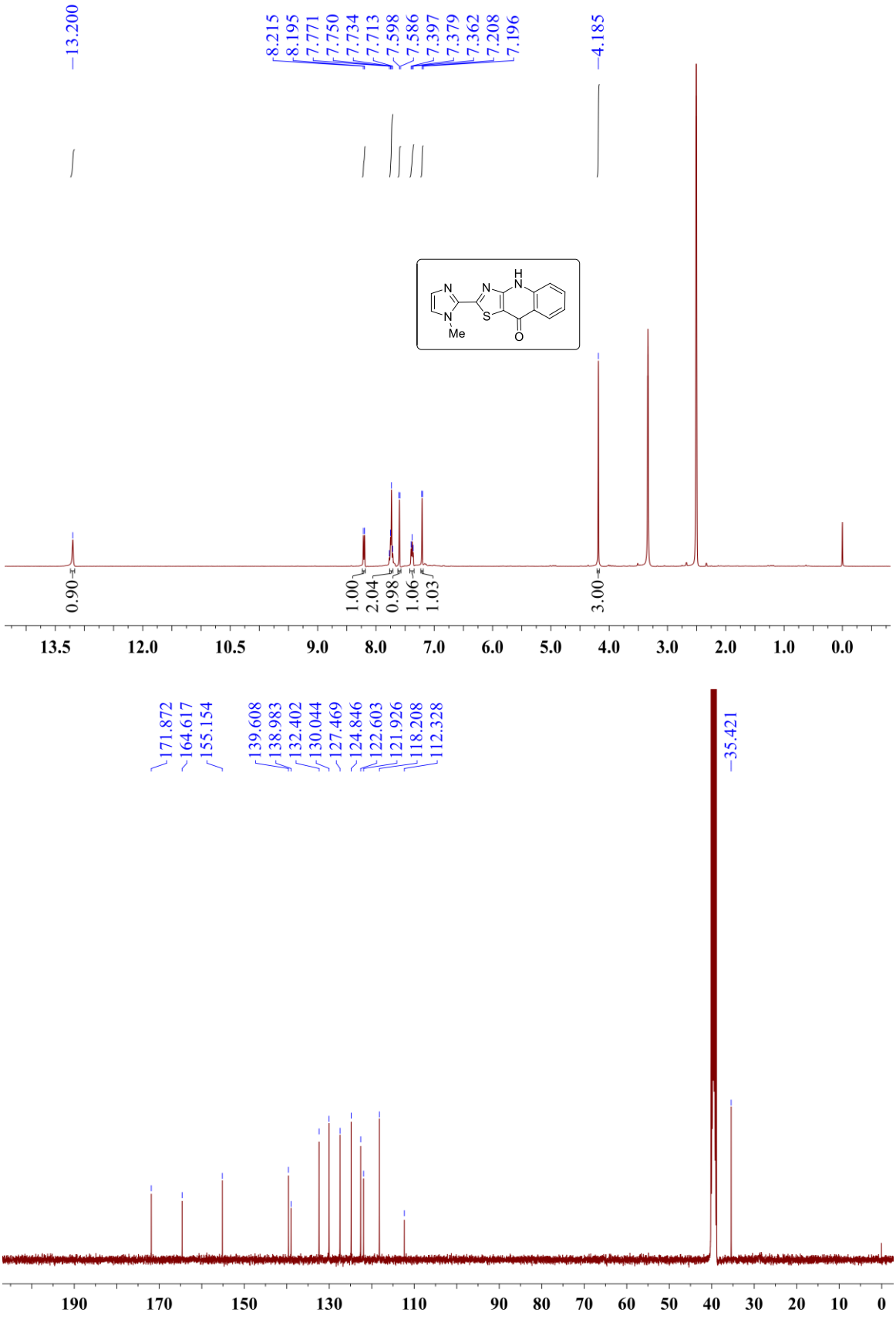
^{1}H and ^{13}C NMR spectra of compound **11a**



^{1}H and ^{13}C NMR spectra of compound **11b**



^{1}H and ^{13}C NMR spectra of compound **11c**



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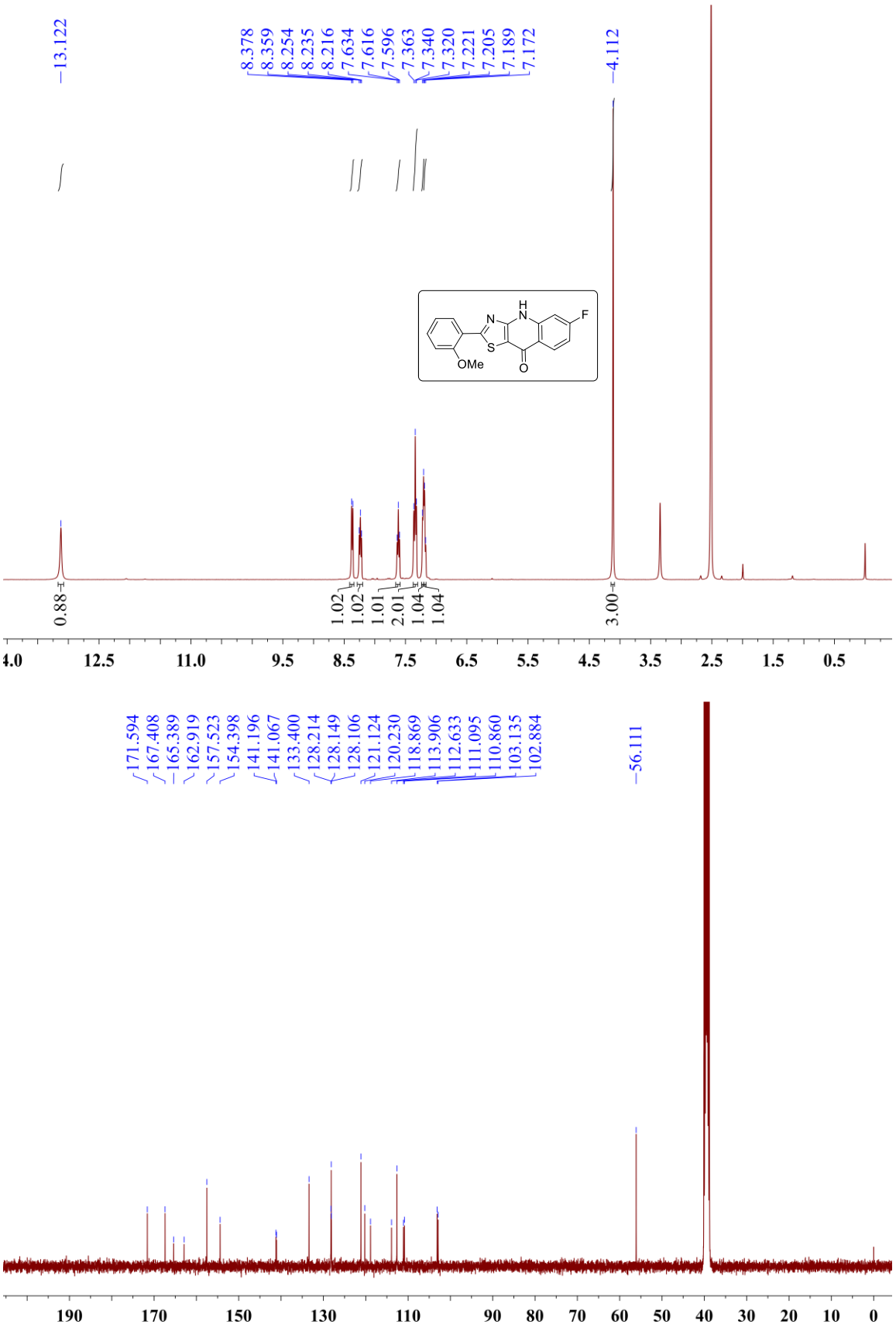
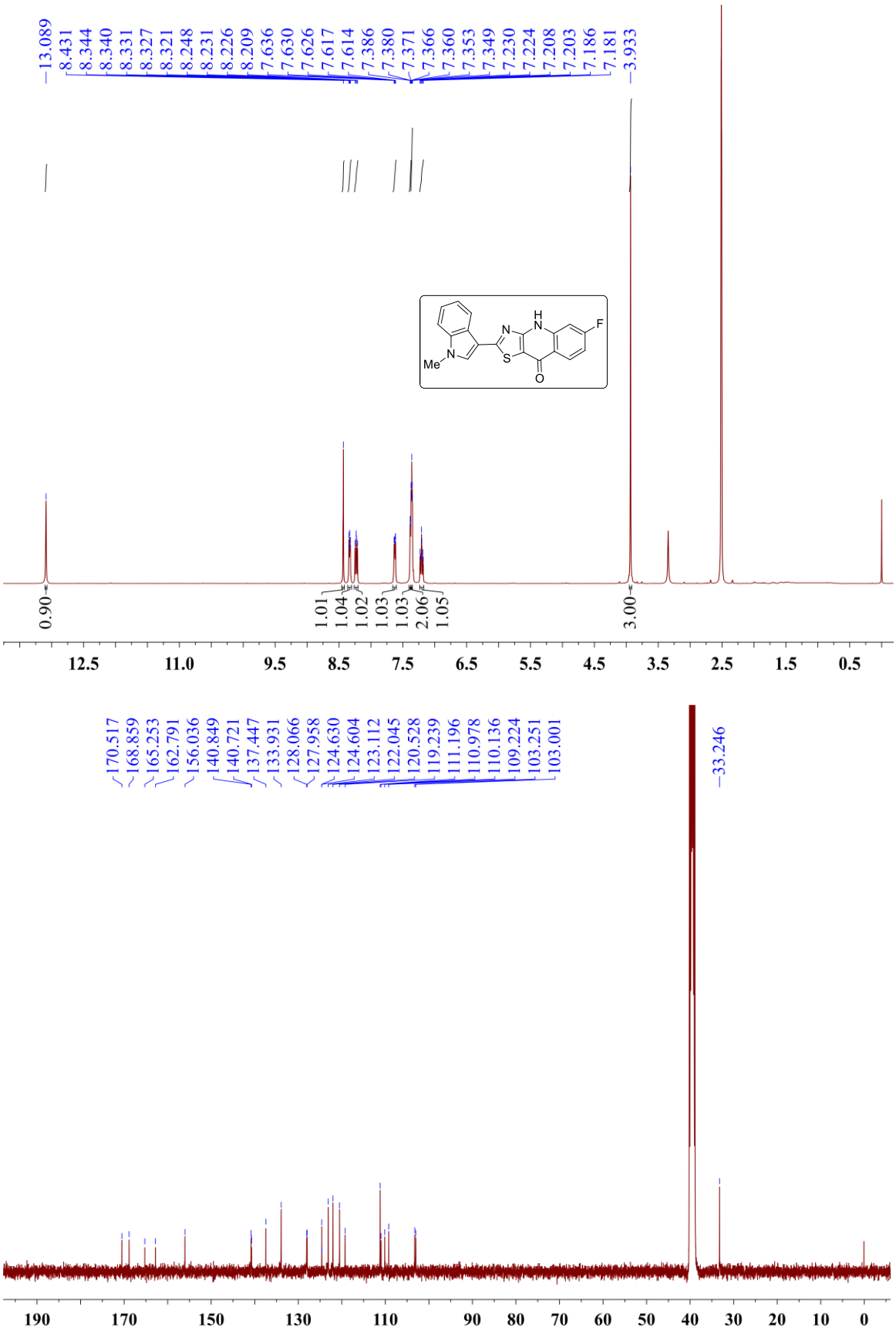
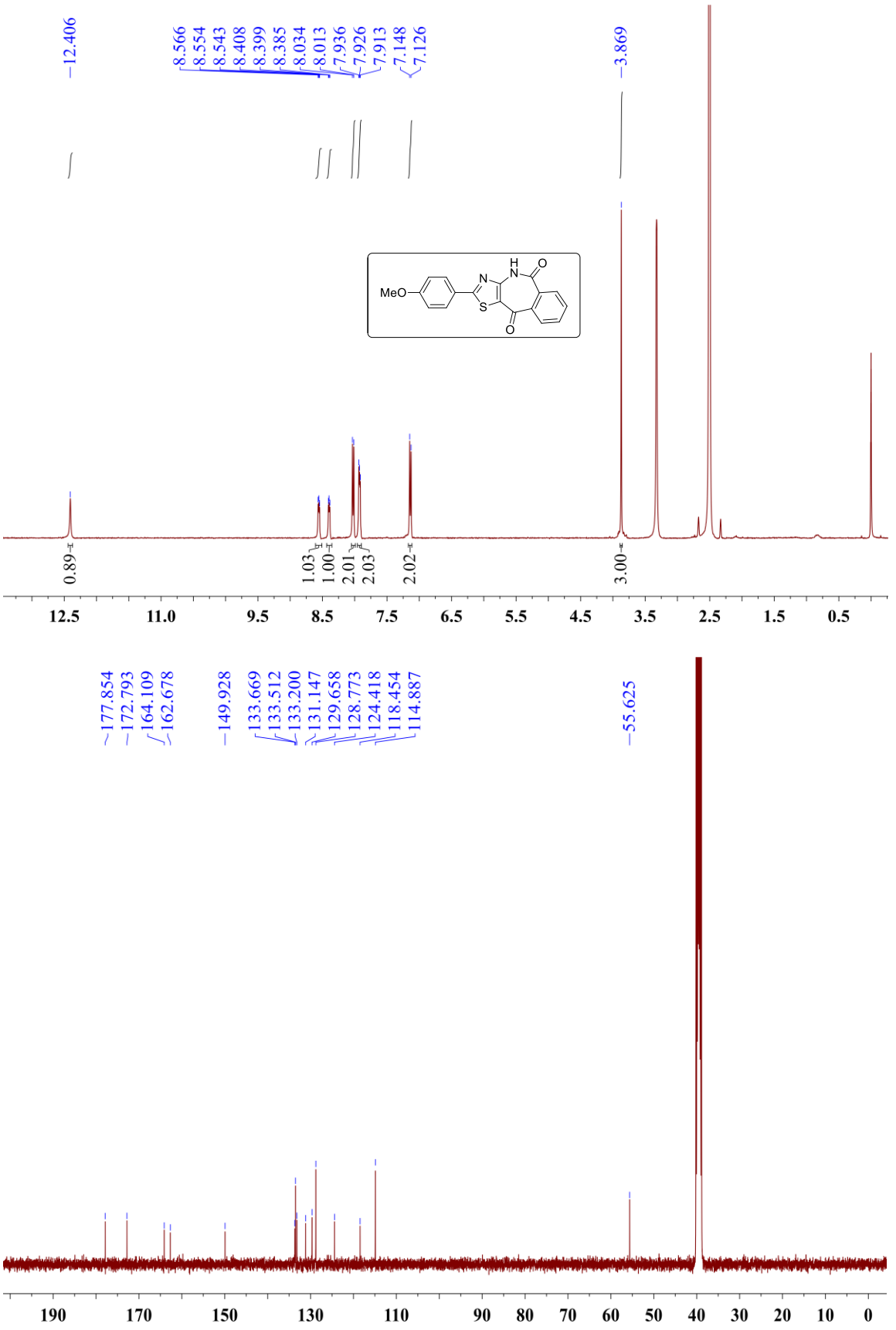


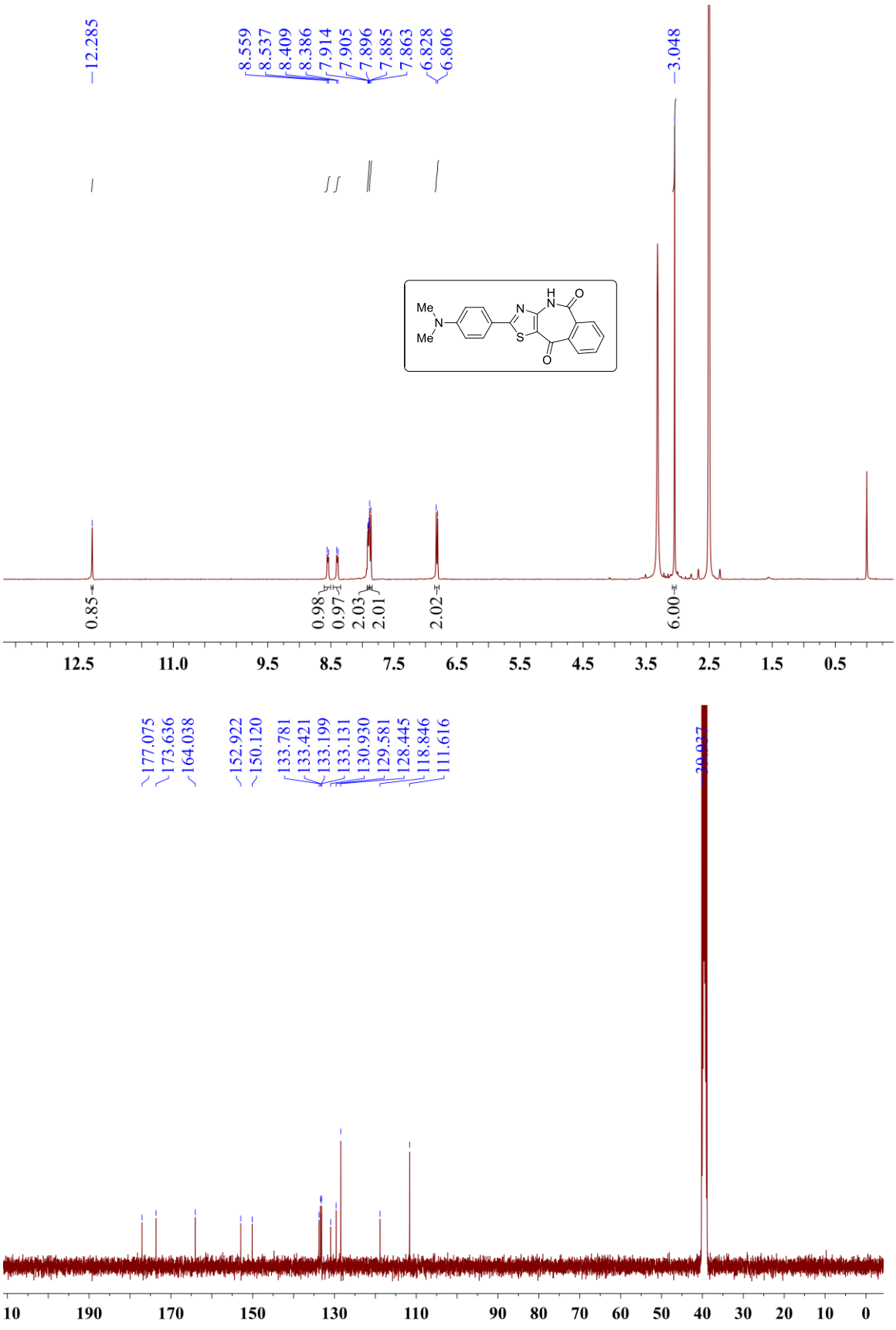
^{1}H and ^{13}C NMR spectra of compound **11e**



^{1}H and ^{13}C NMR spectra of compound **11f**



^{1}H and ^{13}C NMR spectra of compound **12a**



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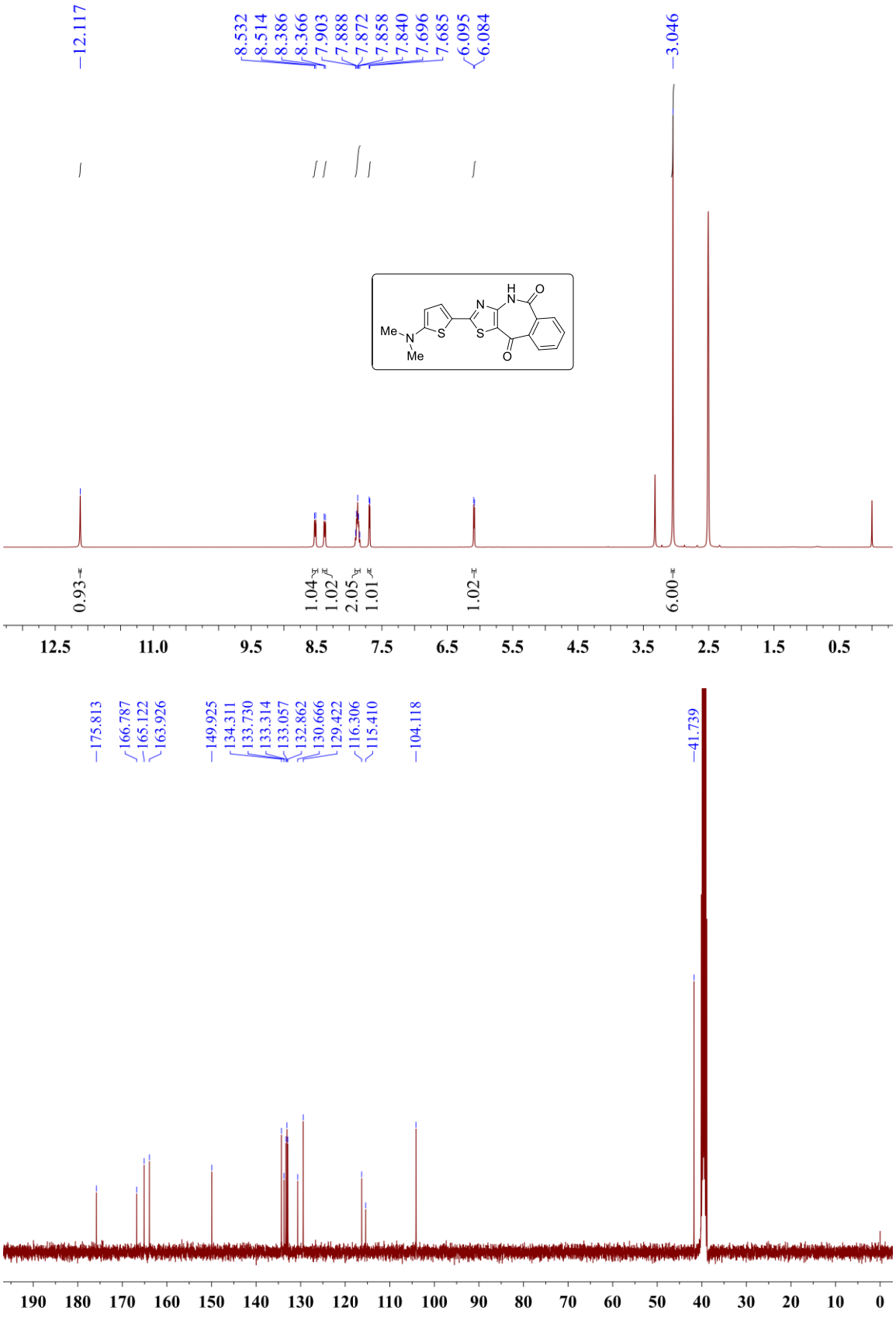
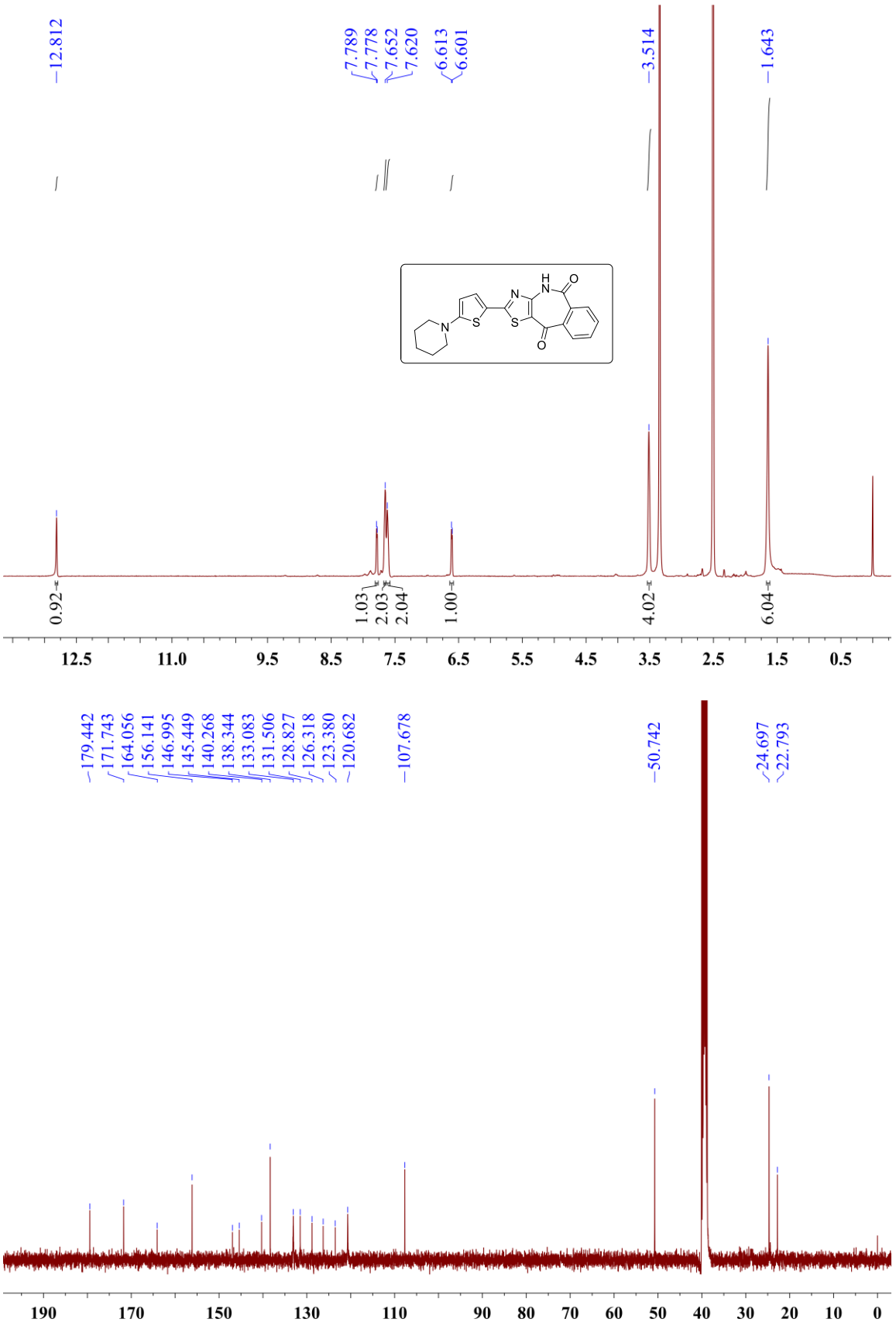


^{1}H and ^{13}C NMR spectra of compound **12c**



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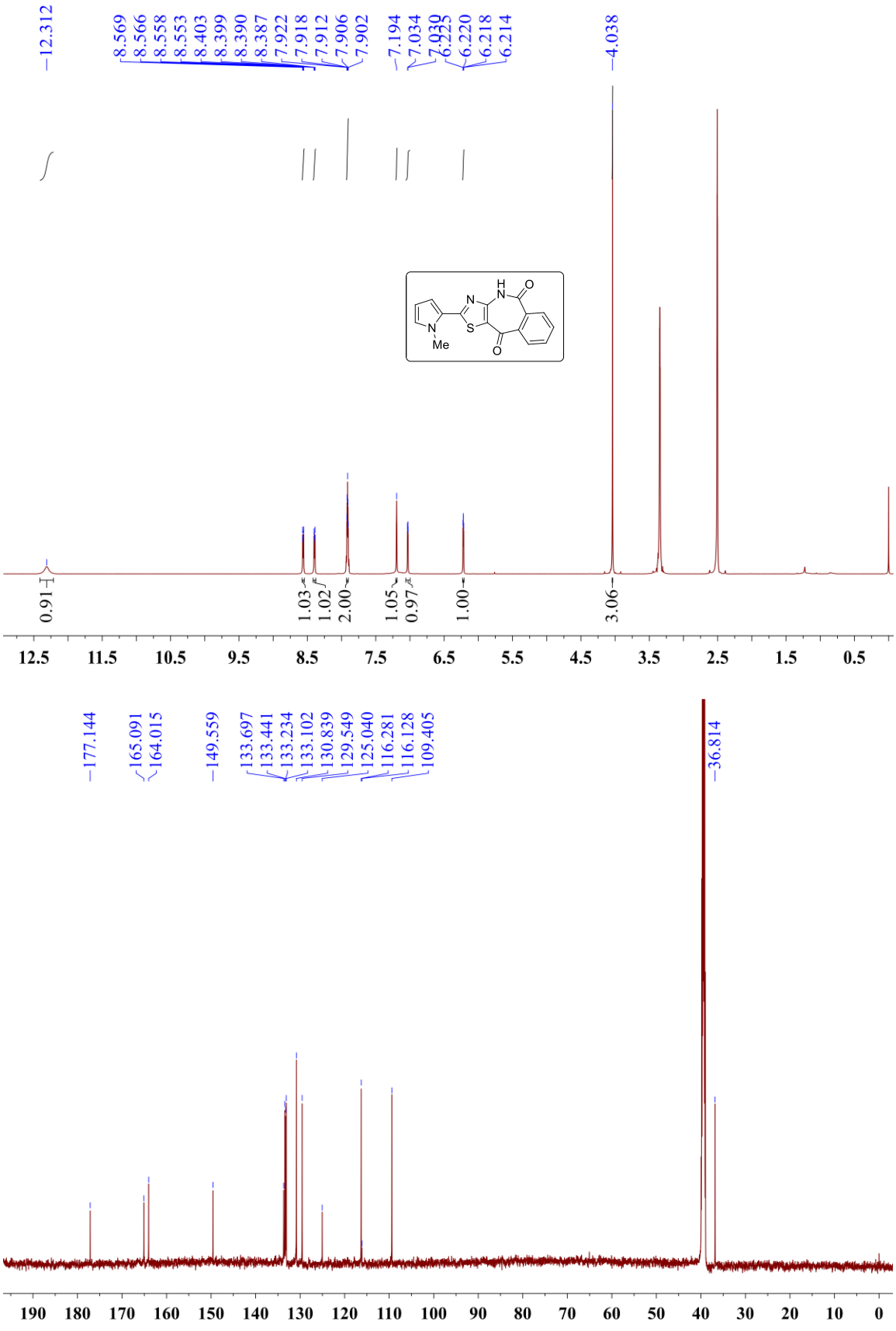

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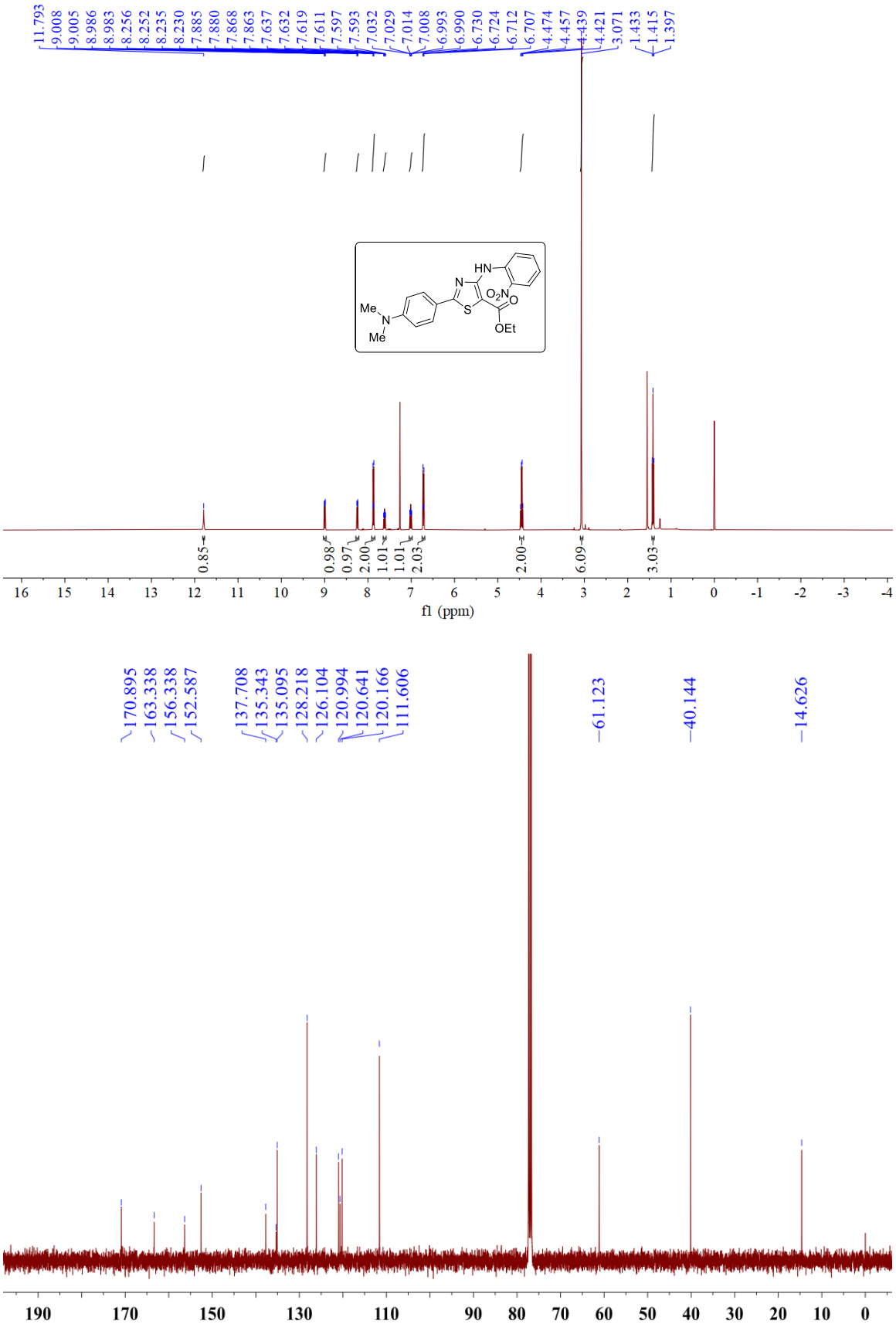

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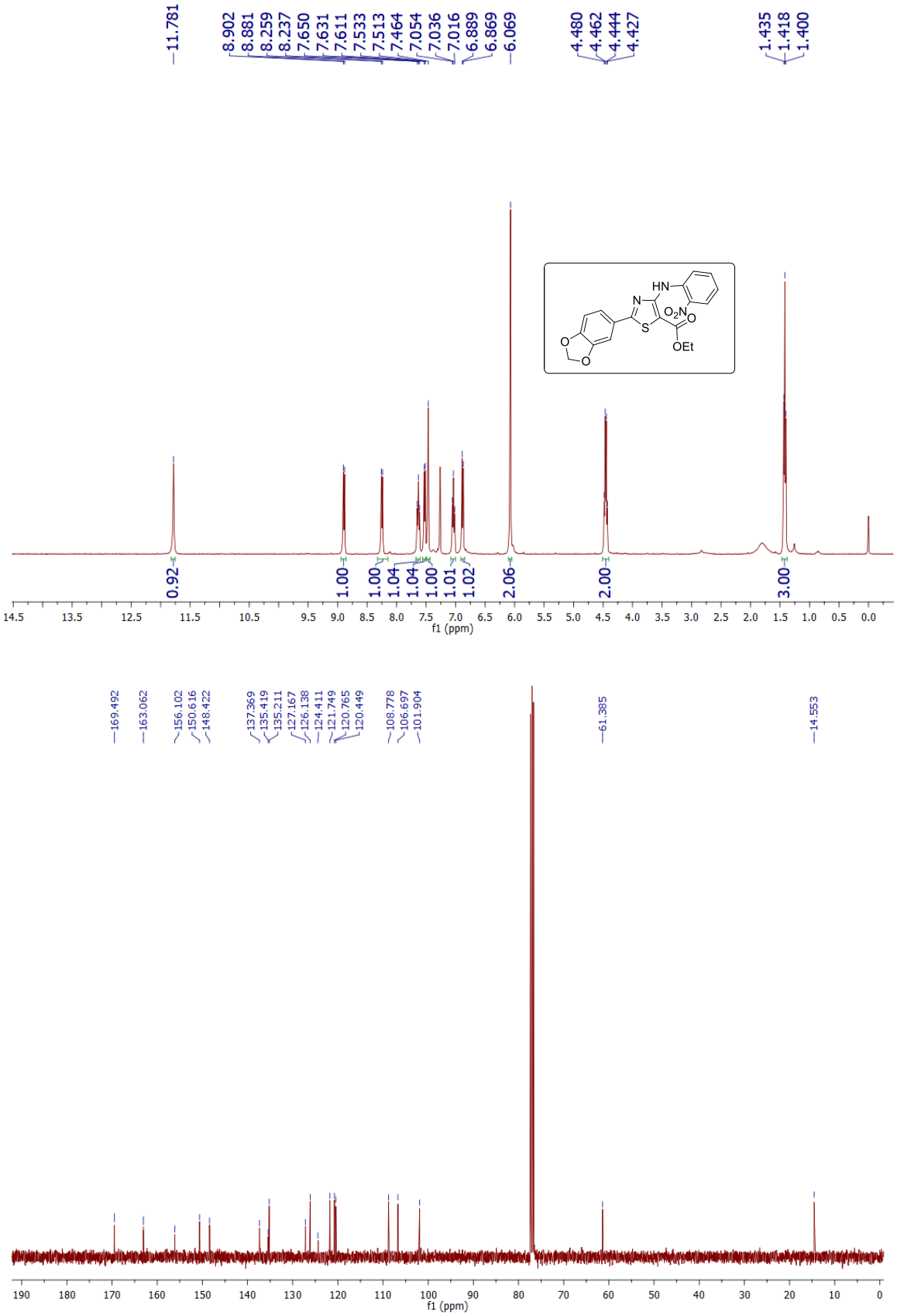
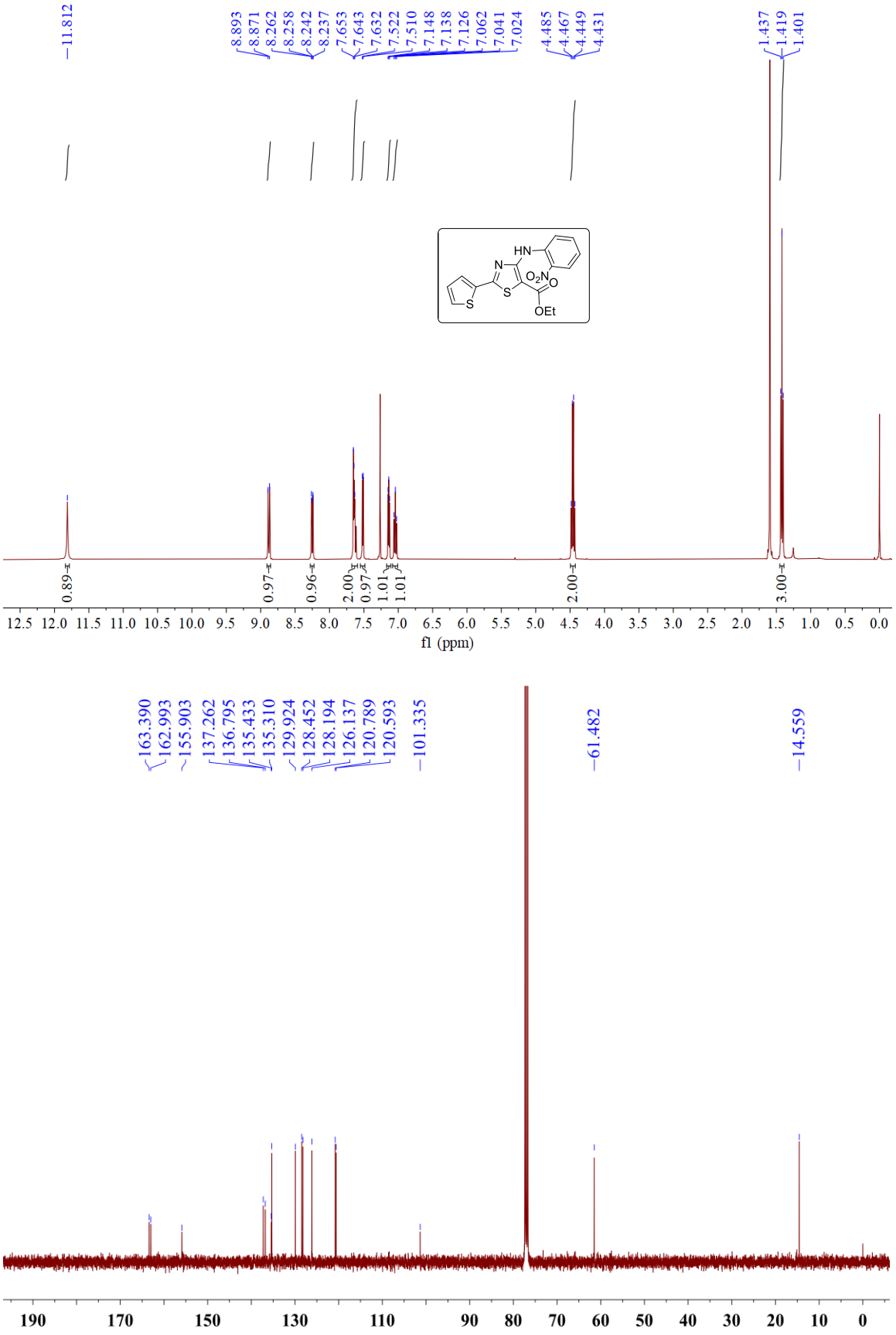


^{1}H and ^{13}C NMR spectra of compound **87b**



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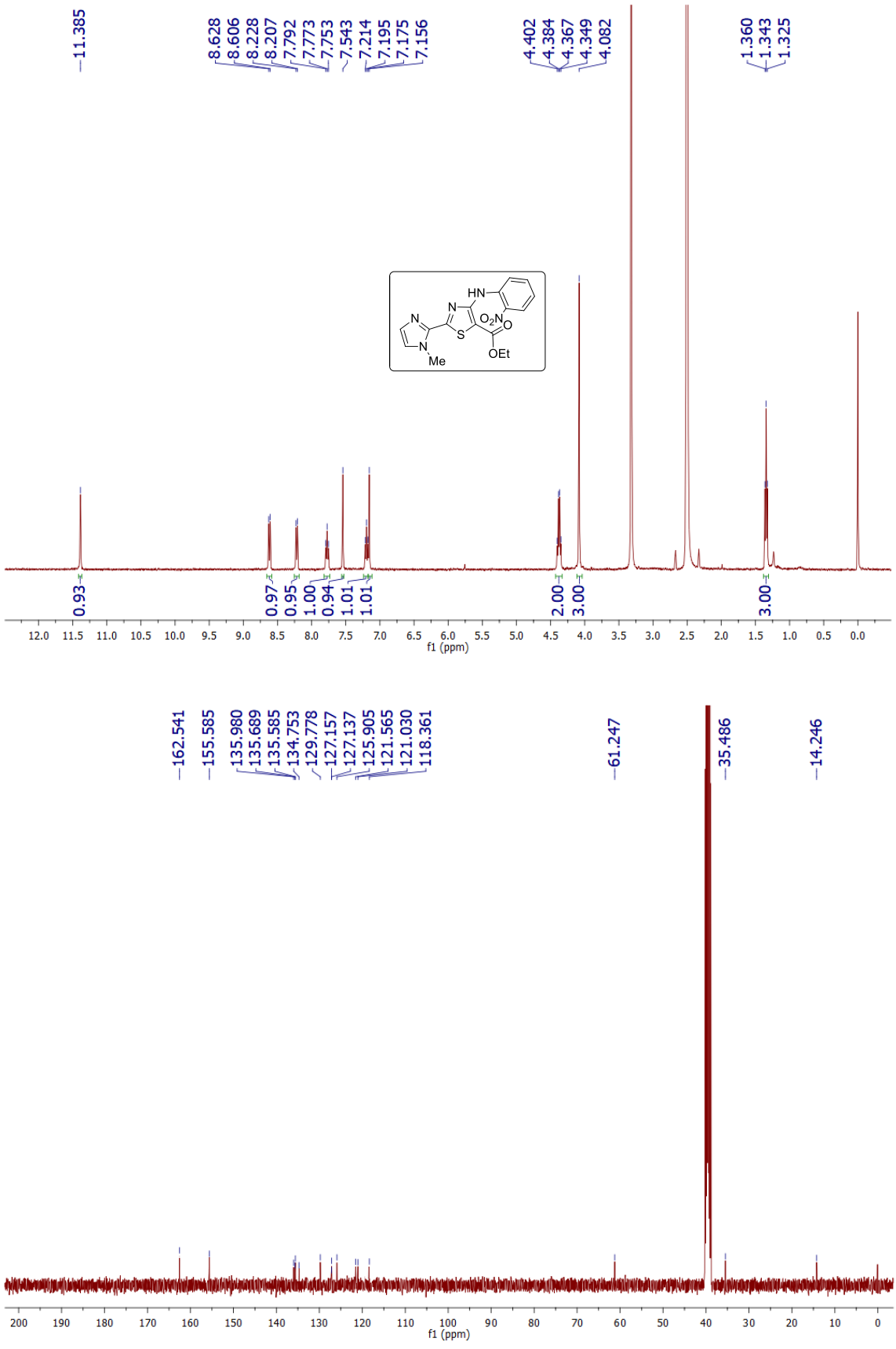
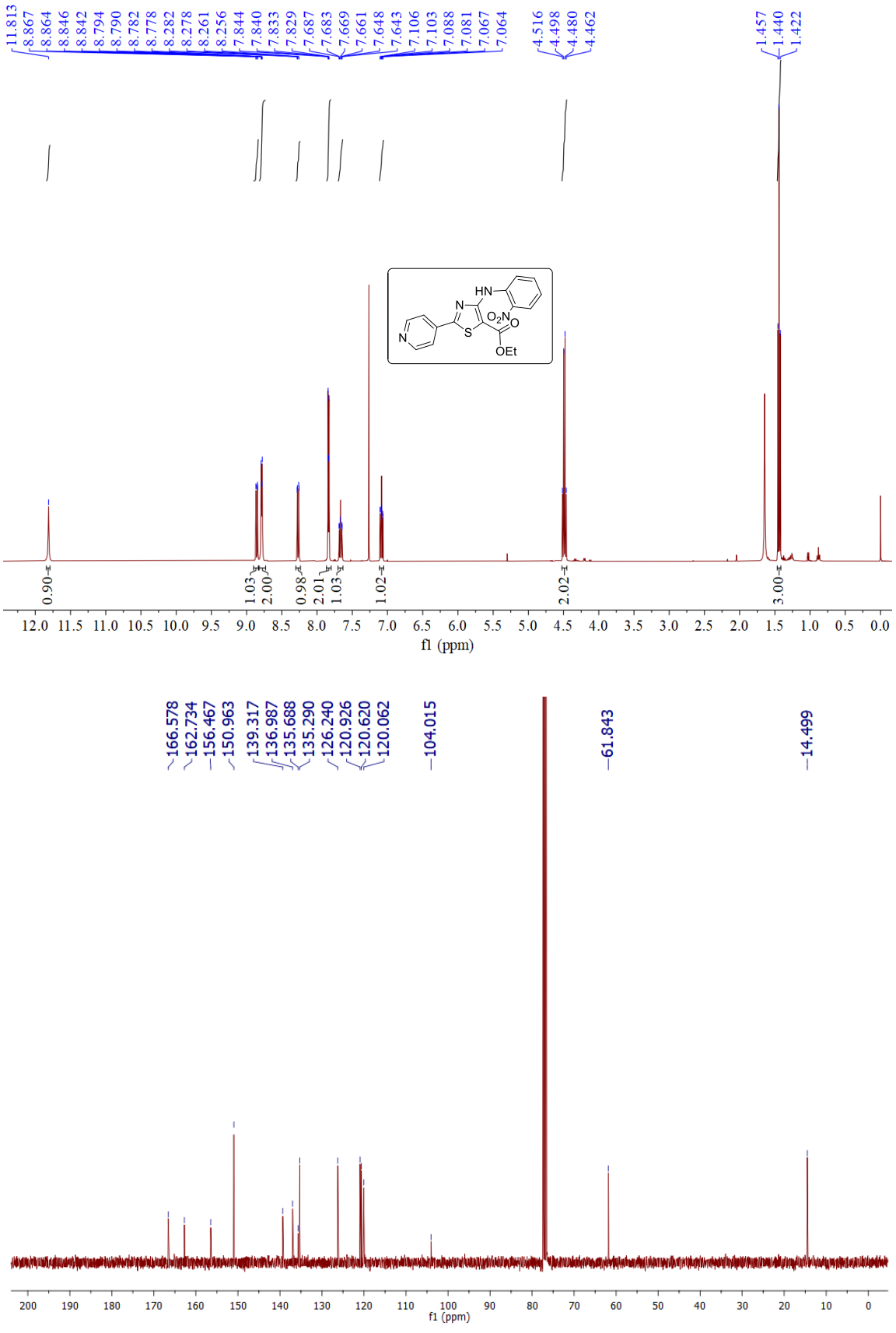
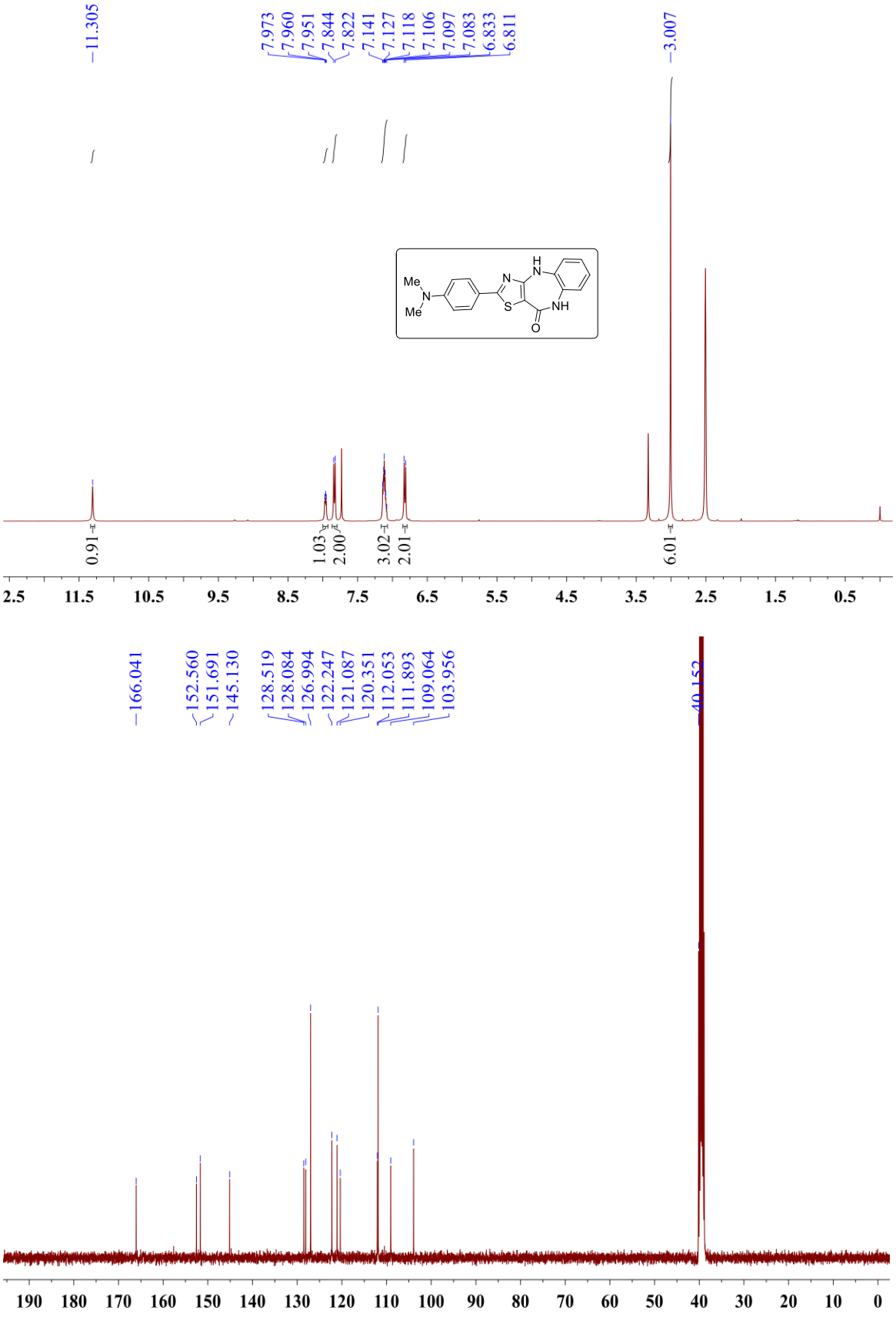


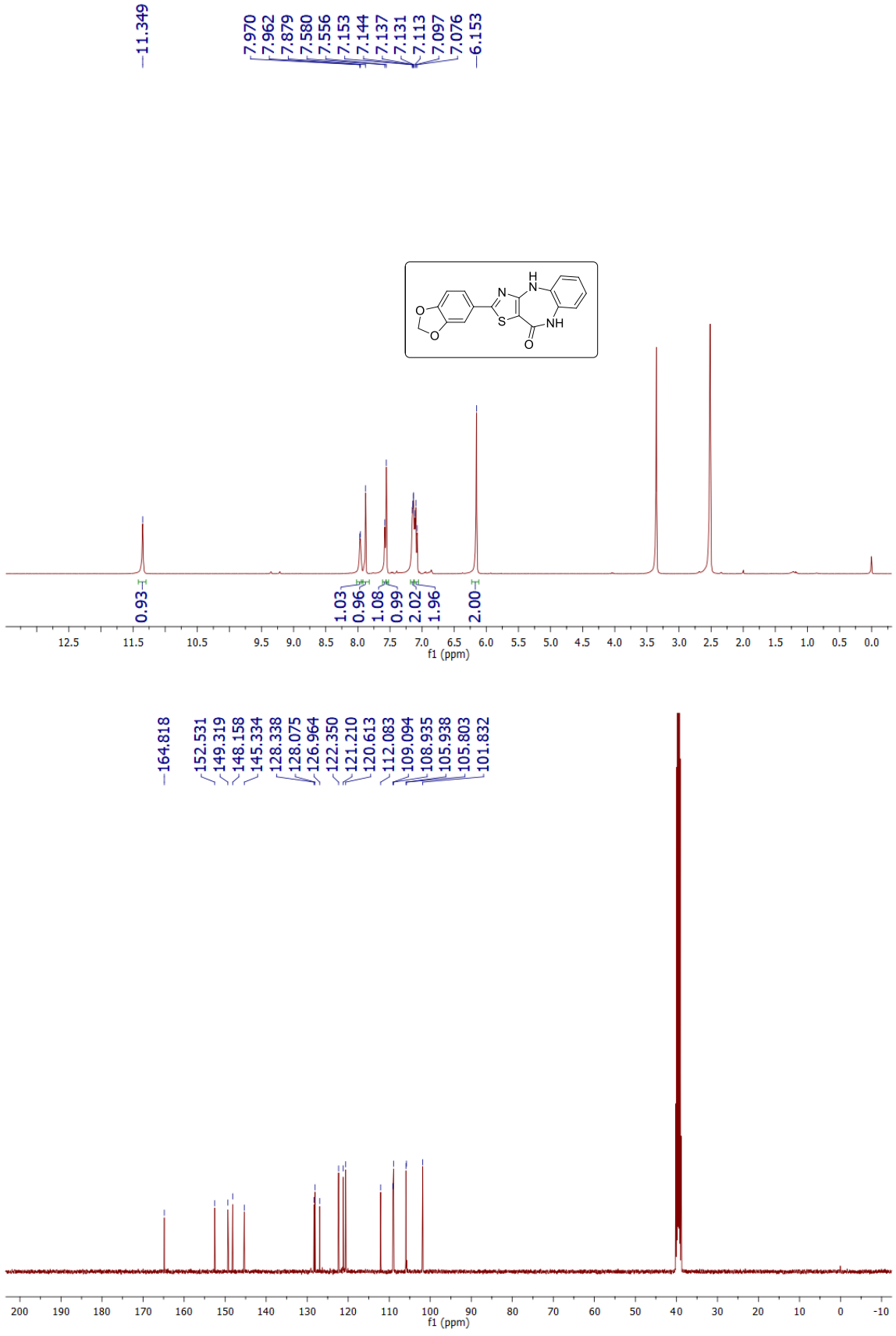
^{1}H and ^{13}C NMR spectra of compound **87d**



^{1}H and ^{13}C NMR spectra of compound **87e**



^{1}H and ^{13}C NMR spectra of compound **13a**



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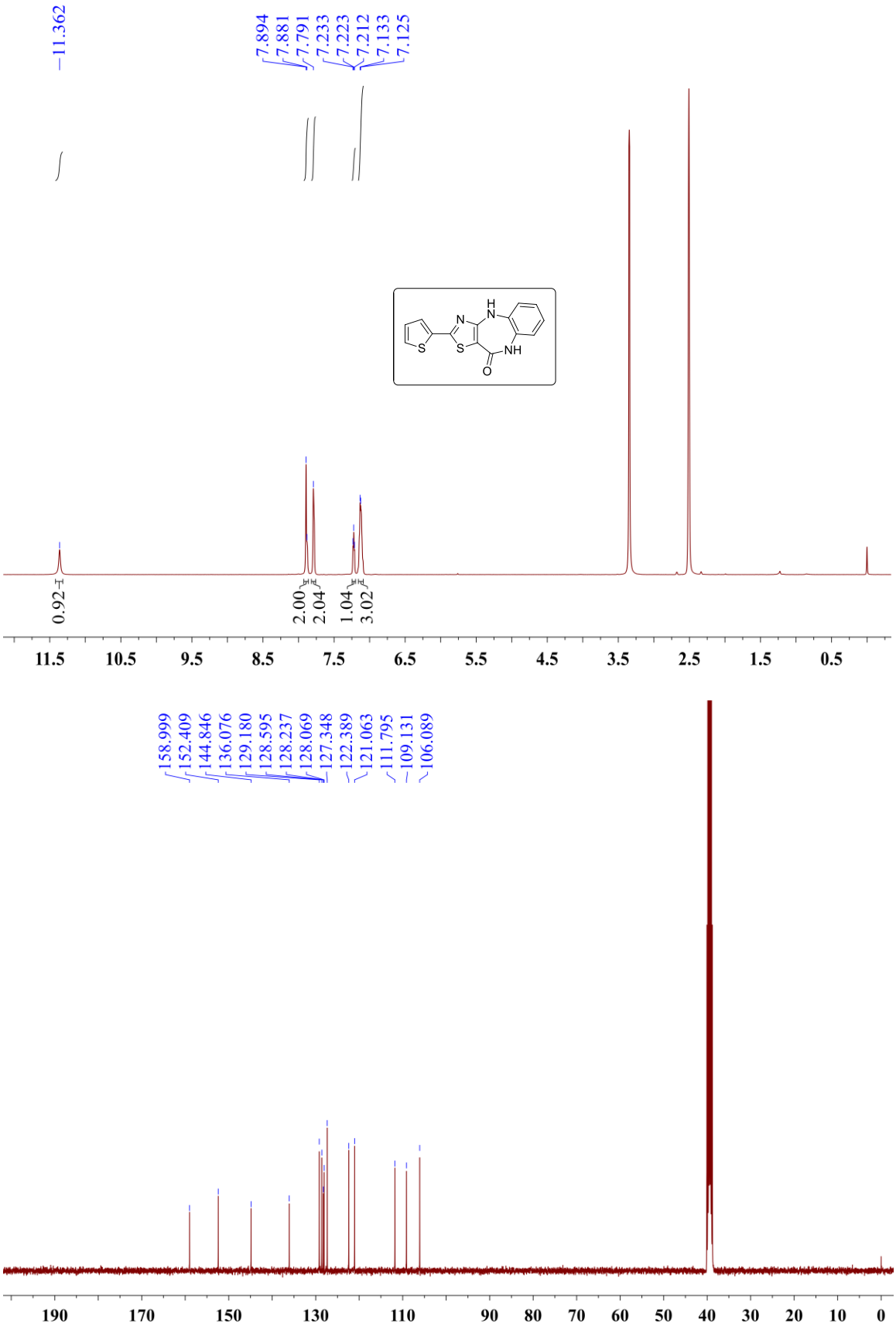

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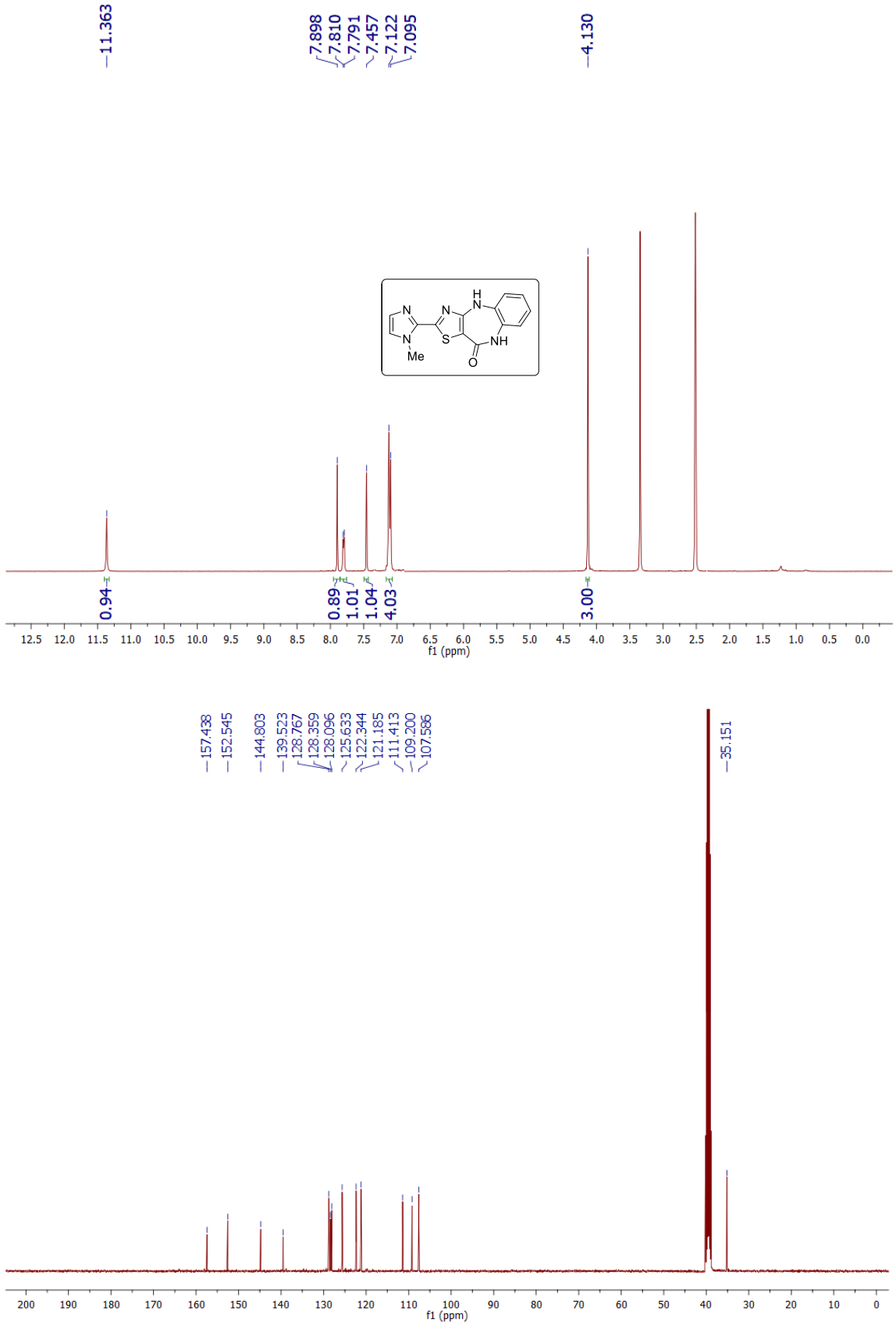
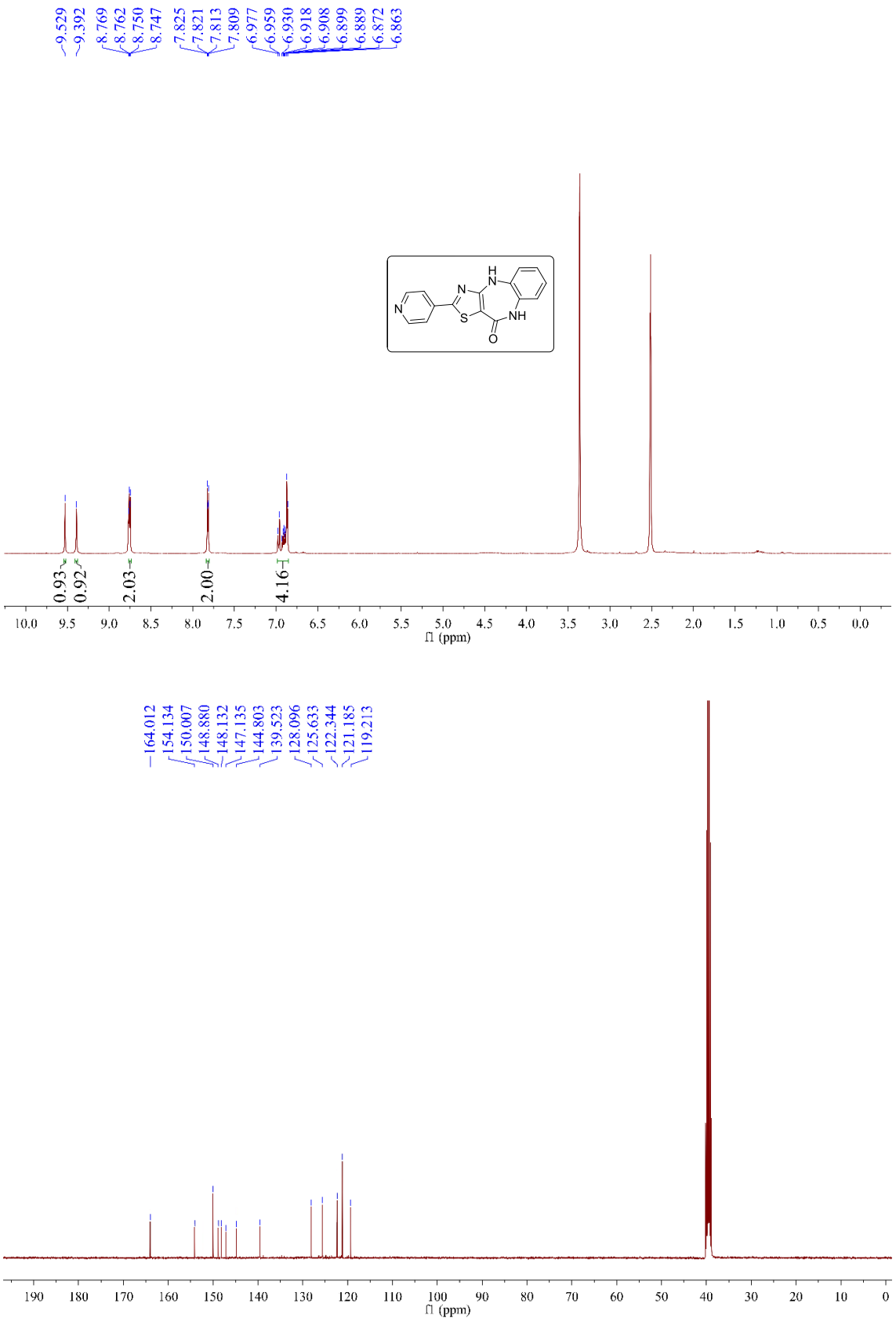


^{1}H and ^{13}C NMR spectra of compound **13d**



^{1}H and ^{13}C NMR spectra of compound **13e**

List of Publications:

1) ‘‘Domino Synthesis of 2-Substituted Benzothiazoles by Base-Promoted Intramolecular C−S Bond Formation’’
Kumar, Y.; Ila, H. *Org. Lett.* **2019**, *21*, 7863.

2) ‘‘Synthesis of Substituted Benzo[*b*]thiophenes via Base-Promoted Domino Condensation-Intramolecular C−S Bond Formation’’
Kumar, Y.; Ila, H. *Org. Lett.* **2021**, *23*, 1698.

3) ‘‘An Efficient One-Pot, Three-Component Route to Novel Push-Pull 1,3-Benzodithiol-2-ylidenes via Copper-Catalyzed Bis-C−S Bond Formation’’
Kumar, Y.; Antony, M. P.; Iniyavan, P.; Ila, H. *Tetrahedron Letters* **2022**, *102*, 153951.

4) ‘‘Domino Synthesis of Thiazolo-Fused Six- and Seven-Membered Nitrogen-Heterocycles via Intramolecular Heteroannulation of in situ Generated 2-(Het)aryl-4-amino-5-functionalized Thiazolos’’
Kumar, Y.; Ila, H. Communicated to *J. Org. Chem.*

5) ‘‘Single-Pot Preparation of 4-Amino-2-(het)aryl-5-Substituted Thiazoles Employing Functionalized Dithioesters as Thiocarbonyl Precursors’’
Avadhani, A.; Iniyavan, P.; **Kumar, Y.**; Ila, H. *J. Org. Chem.* **2021**, *86*, 8508.

6) ‘‘Synthesis of Novel 9-Amino/aryl/oxo-2-(het)arylthiazolo[4,5-*b*]quinolines via Palladium Catalyzed *N*-Arylation-cyclization Protocol’’
Iniyavan, P.; Avadhani, A.; **Kumar, Y.**; Chakravarthy, A. S. J.; Antony, M. P.; Ila, H. *J. Heterocycl. Chem.*, Accepted for publication.