New Synthetic Approaches towards Biologically Important 2-(Het)aryl-4,5-substituted Thiazoles, Thiazolo Fused Quinolines and *β*-Carboline Annulated Heterocycles

A Thesis

Submitted for the Degree of

Doctor of Philosophy

By

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Jakkur, Bengaluru-560064

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April- 2022

Dedicated to

My Wonderful Parents

Declaration

I hereby declare that the entire work embodied in this thesis entitles "***New Synthetic Approaches towards Biologically Important 2-(Het)aryl-4,5-substituted Thiazoles, Thiazolo Fused Quinolines and β-Carboline Annulated Heterocycles"*** is the result of investigations carried out by me in the *New Chemistry unit, Jawaharlal Nehru Center 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 findings of other investigators. Any omissions that might have occurred due to oversight or error in judgment are regretted.

Anusha. S. Avadhani

April, 2022 **Anusha S Avadhani**

Bengaluru (Research Scholar)

Certificate

I hereby certify that the entire work embodied in this thesis entitles "***New Synthetic Approaches towards Biologically Important 2-(Het)aryl-4,5-substituted Thiazoles, Thiazolo fused Quinolines and β-Carboline Annulated Heterocycles"*** has been carried out by Ms. Anusha S Avadhani under my supervision in the *New Chemistry unit, Jawaharlal Nehru Center for advanced Scientific Research (JNCASR), Bengaluru, India* and that no part of it has been submitted elsewhere for any degree or diploma.

April, 2022
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Finally, I would like to thank all my friends, relatives, well-wishers and everybody who was important to the successful realization of the thesis.

Anusha S Avadhani

Synopsis

Title of Thesis: ***"New Synthetic Approaches towards Biologically Important 2-(Het)aryl-4,5-substituted thiazoles, Thiazolo Fused Quinolines and β-Carboline Annulated Heterocycles*****"**

Submitted by: Ms. Anusha Avadhani, New Chemistry Unit, JNCASR, Bangalore, 560064, India

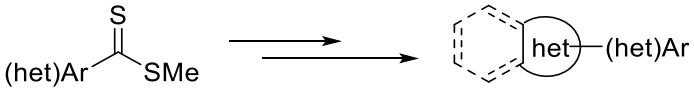
The above-mentioned thesis is divided into five chapters:

Chapter 1: "*Introduction: Organosulfur based synthons in heterocycle synthesis*"

The present chapter gives a brief introduction of synthetic versatility of polarized ketene dithioacetals and its variants, *β*-oxodithioesters and their utilization in organic synthesis, previously reported from our laboratory and other research groups.

Chapter 2: "***Het(aryl) Dithioestrers: Useful Building Blocks for Heterocycle Synthesis": Review***

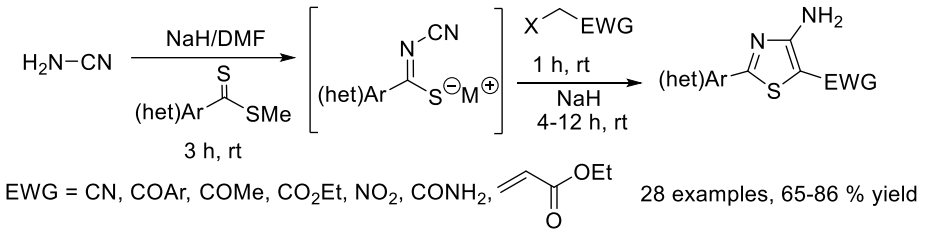
In Chapter 2, we have given a detailed review article of research carried out in last ten years (2012-2021) from our research group at JNCASR, dealing mainly with the synthesis of various substituted and fused five and six membered heterocycles employing (hert)aryl dithioesters which can be considered as thio analogs of estersand have not been previously explored (Scheme 1)



Scheme 1

Chapter 3: "***One-Pot synthesis of 4-Amino-2-(het)aryl-5-substituted thiazoles employing (het)aryl/alkyldithioesters as thiocarbonyl precursors*****"**

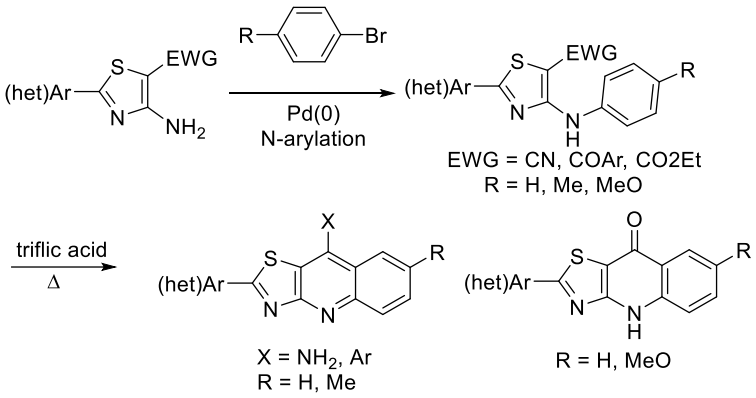
The Chapter 3 of the thesis describes an efficient, straightforward, one-pot, three step protocol for the synthesis of 4-amino-2-(het)aryl-5-substituted thiazoles such as, by employing a broad range of (het)aryl/alkyldithioesters as thiocarbonyl partners and a variety of activated methylene halides (Scheme 2).



Scheme 2

Chapter 4: "***Synthesis of 9-Amino/aryl/oxo-2-(het)arylthiazolo[4,5-b]quinolines via palladium catalyzed N-arylation-cyclization protocol*"**

The Chapter 4 of the thesis deals with a new protocol for the synthesis of thiazolo[4,5-*b*]quinoline, starting from our newly synthesized 2-het(aryl)-4-amino-5-functionalized thiazole precursors**.** We synthesized the corresponding 2-(het)aryl-4-arylamino-functionalized thiazoles precursors from thiazoles via palladium catalyzed *N*-arylation (Buchwald- Hartwig coupling) of 2-(het)aryl-4-amino-5-substituted thiazole, and these *N*-arylated precursors on acid mediated cyclization yielded thiazolo[4,5-*b*]quinoline (Scheme 3).

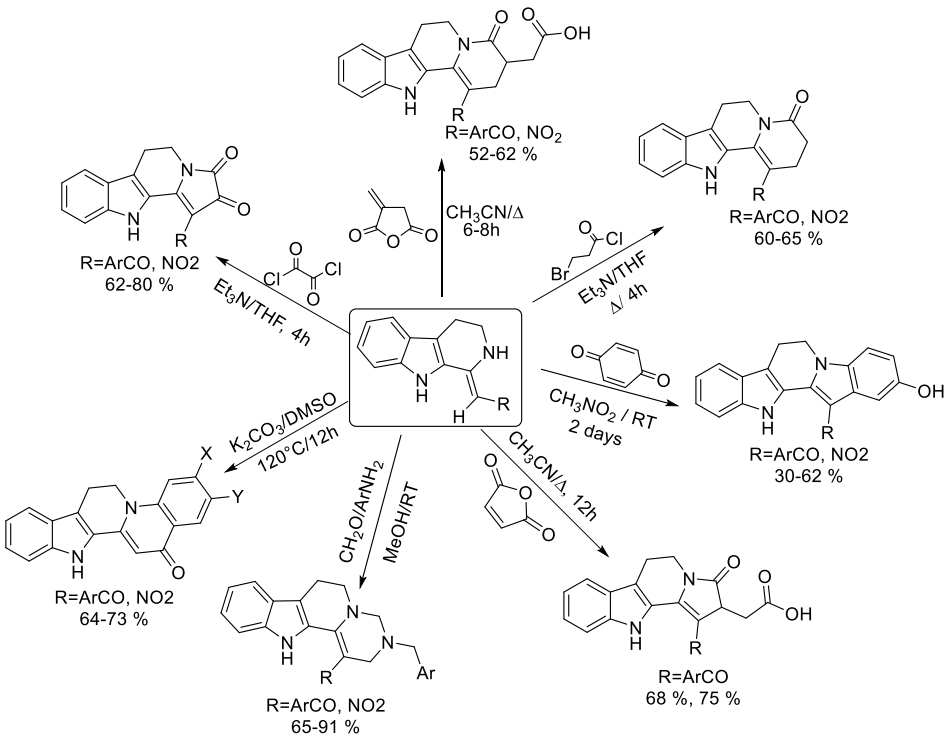


Scheme 3

Chapter 5 : "*Aza-Annulation of 1,2,3,4-Tetrahydro-β-carboline derived enaminones and nitroenamines: synthesis of functionalized Indolizino[8,7-b]indoles, Pyrido[1,2-a:3,4-b']diindoles, Indolo[2,3-a]quinolizidine-4-ones and other Tetrahydro-β-carboline fused heterocycles*"

The Chapter 5 of the thesis deals with Aza-annulation of novel 1,2,3,4-tetrahydro-β-carboline derived enaminones and nitroenamines and the corresponding N,S-acetals with

various 1,2- and 1,3-bis electrophiles, such as oxalyl chloride, maleic anhydride, 1,4-benzoquinone, 3-bromopropionyl chloride, itaconic anhydride, and imines. These methodologies provide simple one-step path- ways for efficient construction of highly functionalized tetrahydro- β-carboline 1,2-fused, five- and six-membered heterocyclic frame-works 51, such as indolizino[8,7-b]indoles, pyrido[1,2-a:3,4-b′]-diindoles, indolo[2,3-a]quinolizidines, and pyrimido[1′,6′:1,2]-pyrido[3,4-b]indoles, which are core structures of many naturally occurring indole alkaloids with diverse bioactivity (Scheme 4).



Scheme 4

Table of Contents

List of Abbreviations

AcOH	:	Acetic acid
DCE	:	Dichloroethane
DMF	:	Dimethylformamide
EtOAc	:	Ethyl acetate
EWG	:	Electron Withdrawing Group
(Het)ar	:	Hetroaryl
IBX	:	Iodoxybenzoic acid
LDA	:	Lithium Di-isopropyl Amide
Ms	:	Mesyl
NBS	:	N-Bromosuccinimide
NMR	:	Nuclear Magnetic Resonance
TFA	:	Trifluroaceticacid
THF	:	Tetrahydrofuran
TLC	:	Thin Layer Chromatography
Ts	:	Tosyl

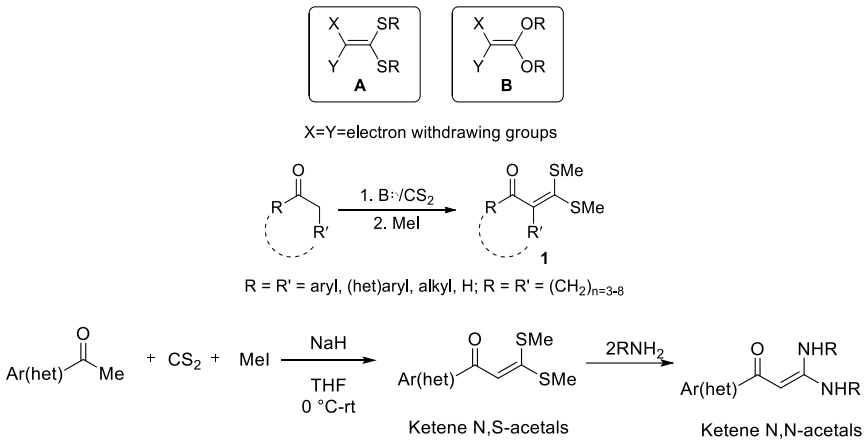
Chapter 1

Introduction: Organosulfur based synthons in heterocycle synthesis

For the past several years, our research group has been involved in design and development of new synthetic methods for five- and six- membered heterocycles and their fused analogs utilizing a series of organosulfur building blocks. A brief account of these intermediates and applications has been given in the present chapter.

1.1 Polarized Ketene Dithioacetals

The family of polarized ketene dithioacetals of the general structure **A** has been proven to be the simplest and useful synthetic building blocks in various organic reactions.[1] Among them, the corresponding *α*- oxoketene dithioacetals **1** have been extensively studied by our research group.[1a-b] These synthons can be easily prepared by one-pot reaction of CS_2 with active methylene ketones in the presence of base, followed by alkylation (Scheme 1). These *S,S*-acetals were prepared easily by sequential treatment of ketones with carbon disulphide and methyl idodide. The methylthio group in *S,S*-acetals were replaced by arylamine groups to obtain the corresponding *N,N*-acetals (Scheme 1).[1c]



Scheme 1

1.2 *α*-Oxoketene dithioacetals: A brief survey

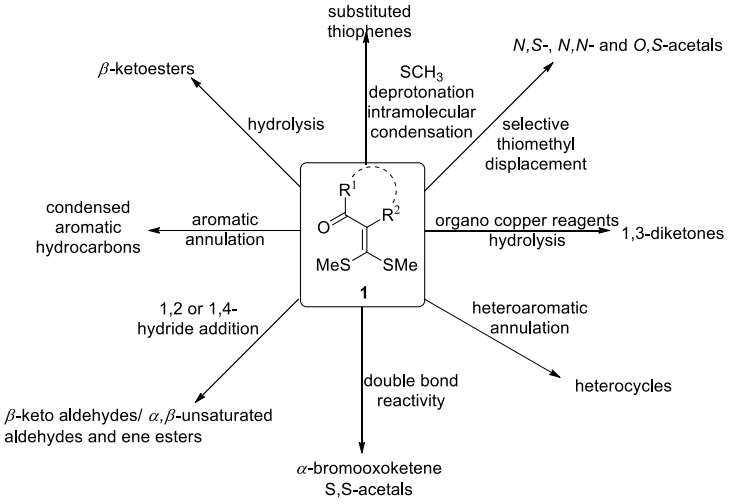
The *α*-oxoketene dithioacetals **1** are stable at room temperature, whereas the corresponding *O,O*-acetals **B** are moisture sensitive and are susceptible for hydrolysis under mild conditions. There are a few reports on *α*-oxoketene dithioacetals in 1910[2] and later on by Thuillier and coworkers.[3] However, it was in 1970's, Junjappa and Ila's group extensively explored the synthetic utility of the compounds and they used these intermediates to develop new general methods for various heterocycles and carbocycles.[1]

1.2.1 Reactivity profile

The reactivity profile of *α*-oxoketene dithioacetals **1** is shown in Scheme 2. The ketene dithioacetal can be readily converted into an ester group, hence, *α*-oxoketene dithioacetals can be seen as masked ketoesters. Alternatively, they may be considered as *α,β*-unsaturated ketones having a highly functionalized *β*-carbon. These intermediates are also 1,3-electrophilic centres exhibiting different electrophilicity. Through 1,2-nucleophilic addition to carbonyl carbon or 1,4-conjugate addition to *β*-carbon of enone, they are useful in the construction of new C-C or C-heteroatom bonds. The hydrides, organomagnesium or organolithium compounds and organocopper reagents give 1,2- or 1,4-addition products characteristic of *α,β*-enone functionality which can be suitably manipulated by the reagents and reaction conditions.[4-6] Using the differential electrophilicity at 1,3-carbon of the *α*-oxoketene dithioacetals, several substituted five- and six- membered heterocycles have been synthesized by reacting **1** with various 1,2- and 1,3-binucleophiles. The enolate anion formed by deprotonation of *α*-oxoketene dithioacetals (R^1 = Me, Et etc.) can undergo condensation with aldehydes to give *α*-enoylketene dithioacetals. (Scheme 2).[7]

The α-oxoketene dithioacetals **1** are shown to undergo facile displacement with primary or secondary amines to give the corresponding *N,S*- and *N,N*-acetals, which can be viewed as

either 1,3-electrophiles with amino functionality or functionalized enaminones or enaminonitriles.[1c,9-10] These intermediates undergo bromination at α-position with *N*-bromosuccinimide.[8] An oxygen nucleophile was displaced on the *S,S*-sulfonium salt of the corresponding α-oxoketene dithioacetals to prepare *O,S*-acetals.[11-12]

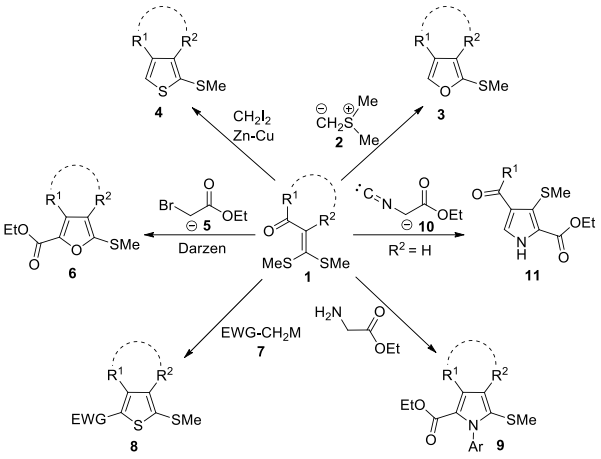


Scheme 2

A brief account of these intermediates highlighting some of the previous work has been mentioned in this chapter.

1.2.2 Synthesis of five membered heterocycles from α-oxoketene dithioacetals

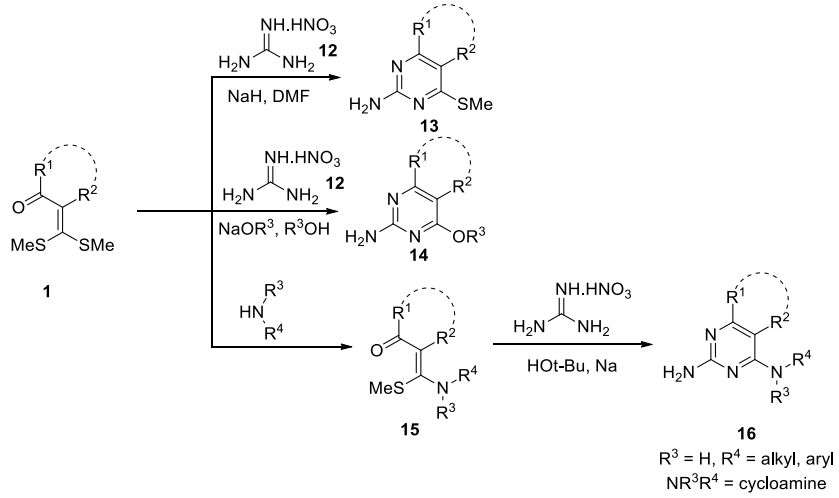
Our research group has developed new general routes for the synthesis of wide range of biologically important five membered heterocycles by utilizing α-oxoketene dithioacetals **1** as three carbon 1,3-bielectrophilic synthons and by reacting them with symmetrical and unsymmetrical bifunctional heteronucleophiles such as hydrazine and hydroxyl amine, to afford various substituted pyrazoles and isoxazoles respectively in a regiocontrolled manner.[13-15] Treating sulfonium ylide **2** with **1** followed by acidic treatment afforded substituted or annulated 2-(methylthio)furans **3** (Scheme 3).[16] Our research group has also reported the synthesis of 3,4-substituted and annulated thiophenes **4** via intramolecular Aldol condensation of in situ generated sulfonium ylide intermediates under Simmon-Smith reaction conditions (Scheme 3).[17]α-Oxoketene dithioacetals **1** have also shown to undergo Darzen's glycidic ester condensation yielding substituted and annulated furan-2-carboxylates **6** in good yields (Scheme 3).[18] In further studies, α-oxoketene dithioacetals **1** were utilized for the synthesis of pyrroles **9** by 1,4-addition followed by intramolecular cyclocondensation with ethyl glycinate.[19a] Furthermore, **1** underwent 1,3-dipolar cycloaddition with carbanions derived from activated methylene isocyanides **10** afford 2,3,4-substituted pyrroles **11**.[19c]



Scheme 3

1.2.3 Synthesis of Six Membered Heterocycles

α-Oxoketene dithioacetals **1** were successfully converted to substituted pyrimidines upon treatment with guanidine nitrate in basic medium (Scheme 4).[20] Thus, **1** was reacted with guanidine nitrate **12** in the presence of NaH to synthesise 2-amino-4-(methylthio)pyrimidines **13**.[20a] Similarly, the reaction of **1** with guanidine nitrate **12** in the presence of sodium alkoxides afforded corresponding 2-amino-4-(alkoxy)pyrimidines **14** (Scheme 4).[20b] Furthermore, 2-amino-5,6-substituted-4-*N*-alkyl/*N*-aryl/*N*-azacyclo-aminopyrimidines **16** were synthesized from the corresponding *N,S*-acetals **15** by treating with guanidine nitrate (Scheme 4).[20d]

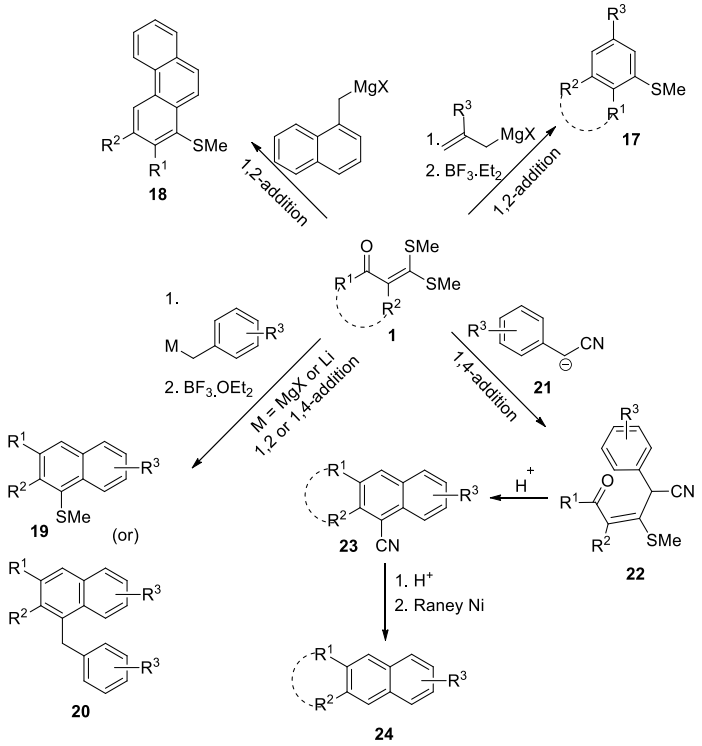


Scheme 4

1.2.4 Aromatic annulations via *α*-oxoketene dithioacetals

Aromatic annulation strategy developed in 1984 is now known as Junjappa-Ila (JI) aromatic and heteroaromatic annulation.[1] This involves an unprecedented protocol for the construction of substituted aromatic ring via [3 + 3] annulation of *α*-oxoketene dithioacetals with a three-carbon 1,3-binucleophilic component. Some examples are shown in Scheme 5.

Thus, when **1** was treated with allyl and methyl Grignard reagents, it furnished methylthio and benzyl substituted aromatics such as **17** and **19-20** *via* 1,2- and 1,4-addition followed by acid induced cyclization. Furthermore, the formation of only methylthio substituted phenanthrenes **18** was observed on treating **1** with naphthyl Grignard reagent, which showed that 1,2-addition is taking place exclusively in the first addition step. Exclusive 1,4-addition-elimination took place when stabilized anions **21** were treated with **1**, affording adducts **22**, which upon acid-induced cyclization yielded the corresponding substituted hydrocarbons **24** (Scheme 5).[21]

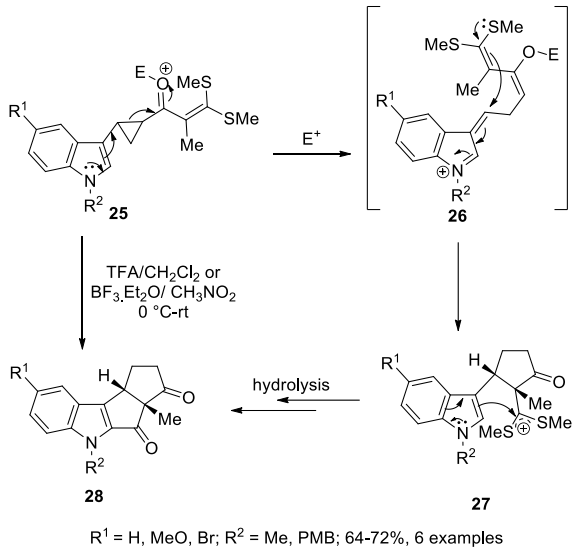


Scheme 5

1.2.5 Ketene dithioacetal functionality as cationic cyclization initiator/terminator in domino carbocationic rearrangements of *α*-[bis(methylthio)methylene]alkyl-2-het(aryl)cyclopropyl ketones

The ketene dithioacetal moiety acts as a potential cationic cyclization initiator or terminator in polyene cyclizations, due to its ability to stabilize a positive charge (because of the two sulfur atoms).[1c] In earlier studies, our group has demonstrated that domino carbocationic rearrangements of newly designed het(aryl)cyclopropyl ketones such as **25** bearing an *α*-bis(methylthio) methylene functionality allow construction of a variety of carbocyclic and heterocyclic scaffolds such as substituted cyclopentanones, cyclopenta[*b*]indanes, diquinanes and other cyclopentano fused heterocycles.[22] In a recent paper, a direct approach to pentaleno fused indolodiketones **28** was demonstrated through

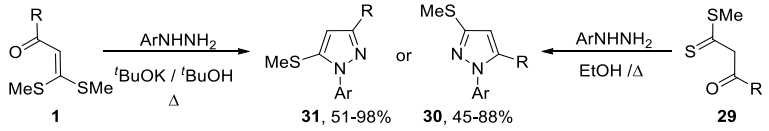
carbocationic rearrangement of α-[bis(methylthio)methylene]alkyl-2-(3/2-indolyl)cyclopropyl ketones such as **25**, involving appendage of two cyclopentanone rings in a cascade process in one pot reaction.[22] The mechanism involves the intermediates **26**-**27**, as shown in Scheme 6.



Scheme 6

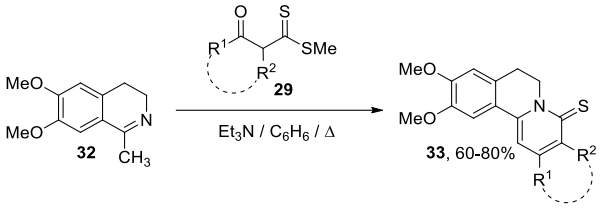
1.3 *β*-Oxodithioesters

Our group has also utilized this *β*-oxodithioesters for the regioselective synthesis of pyrazoles (Scheme 7).[23] Thus, when *β*-oxodithioester **29** was reacted with aryl hydrazines in refluxing ethanol, 1-aryl-3-(methylthio)-4,5-substituted pyrazoles **30** were obtained in excellent yields. The regioisomeric pyrazole, i.e., 1-aryl-5-(methylthio)-3,4-substituted pyrazoles **31** were obtained by the condensation of aryl hydrazines with α-oxoketene dithioacetals **1** (Scheme 7).



Scheme 7

Our group also reported synthesis of fused benzo[*a*]quinolizine-4-thione **33** via base mediated condensation of acyclic/cyclic *β*-oxodithioester **29**, with 3,4-dihydro-1-methylisoquinoline **32** in excellent yields (Scheme 8).[24]

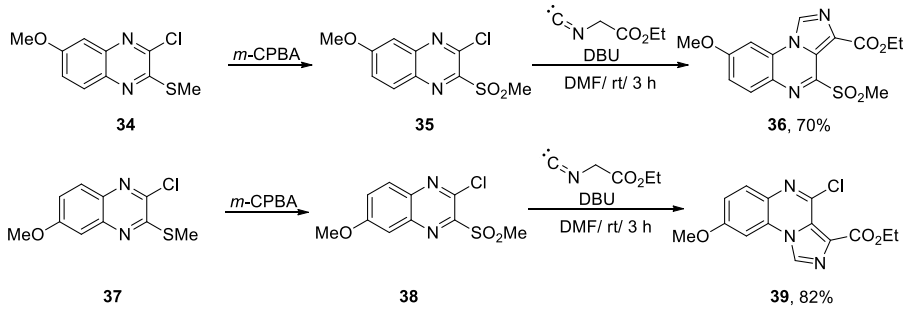


Scheme 8

1.4 Reactivity of polarized ketene *N,S*-acetals: A novel highly regioselective synthesis of unsymmetrical 2,3-substituted quinoxalines and imidazo[1,5-*a*]quinoxaline-3-carboxylates

The polarized ketene *N,S*- and *N,N*-acetals are considered as second generation of reactive intermediates derived from polarized ketene dithioacetals via replacement of one or both methylthio groups by primary or secondary aliphatic or aromatic amines.[1]

We have made use of the diverse reactivity profile of these *N,S*-acetals either as functionalized enaminones or 1,3-electrophilic fragments, for the synthesis of novel five- and six-membered heterocycles. Few years back, our group has reported an efficient regio- and chemoselective synthesis of novel 3-(carbethoxy)imidazole[1,5-*α*]quinoxalines **36** and **39** by treating unsymmetrically substituted methylsulfonylquinoxalines **35** and **38** with ethyl isocyanoacetate on N=C bond in presence of base (Scheme 9).[25]



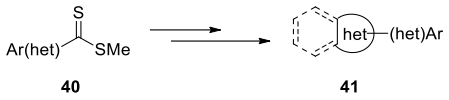
Scheme 9

1.5 Present work

From the foregoing discussion, it is evident that polarized ketene dithioacetals and its variants i.e., *β*-(methylthio)methylene ketones/acrylonitriles are an important class of building blocks for the synthesis of five- and six-membered heterocycles and aromatic compounds. The present thesis is based on further synthetic elaboration of the utility of (het)aryl dithioesters as thiocarbonyl precursors for designing new synthetic methods for five membered heterocycles.

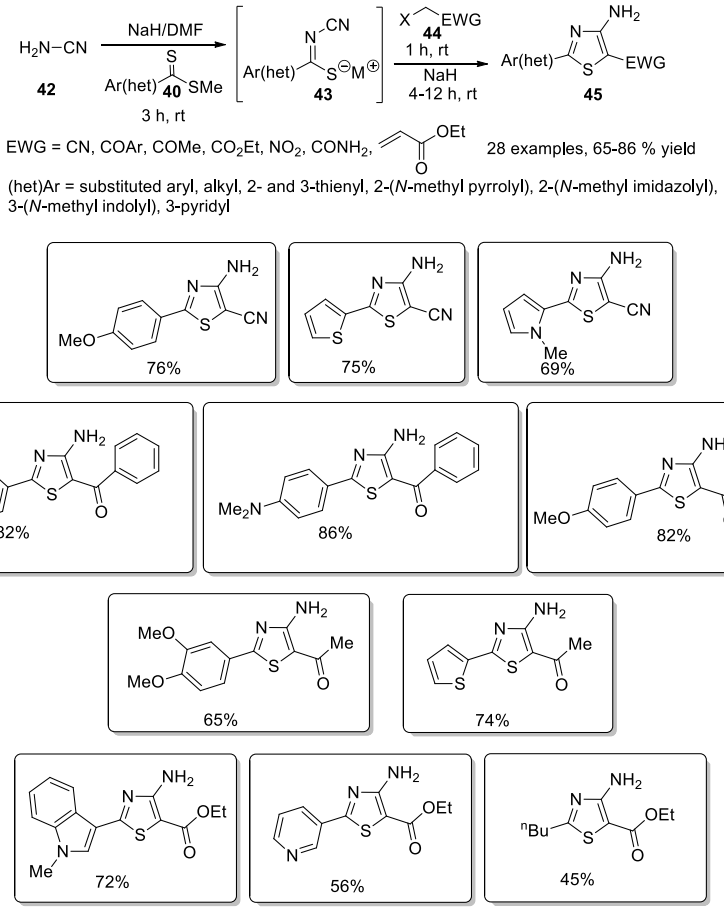
Thus, in **chapter 2**, we have given an account of research carried out in last ten years (2012-2021) from our research group at JNCASR, dealing with the synthesis of various substituted and fused five and six membered heterocycles **41** employing these dithioesters **40**

which can be considered as thio analogs of esters. We have also included few of the synthetic methods which we have been utilizing for their synthesis in our laboratory (Scheme 10).



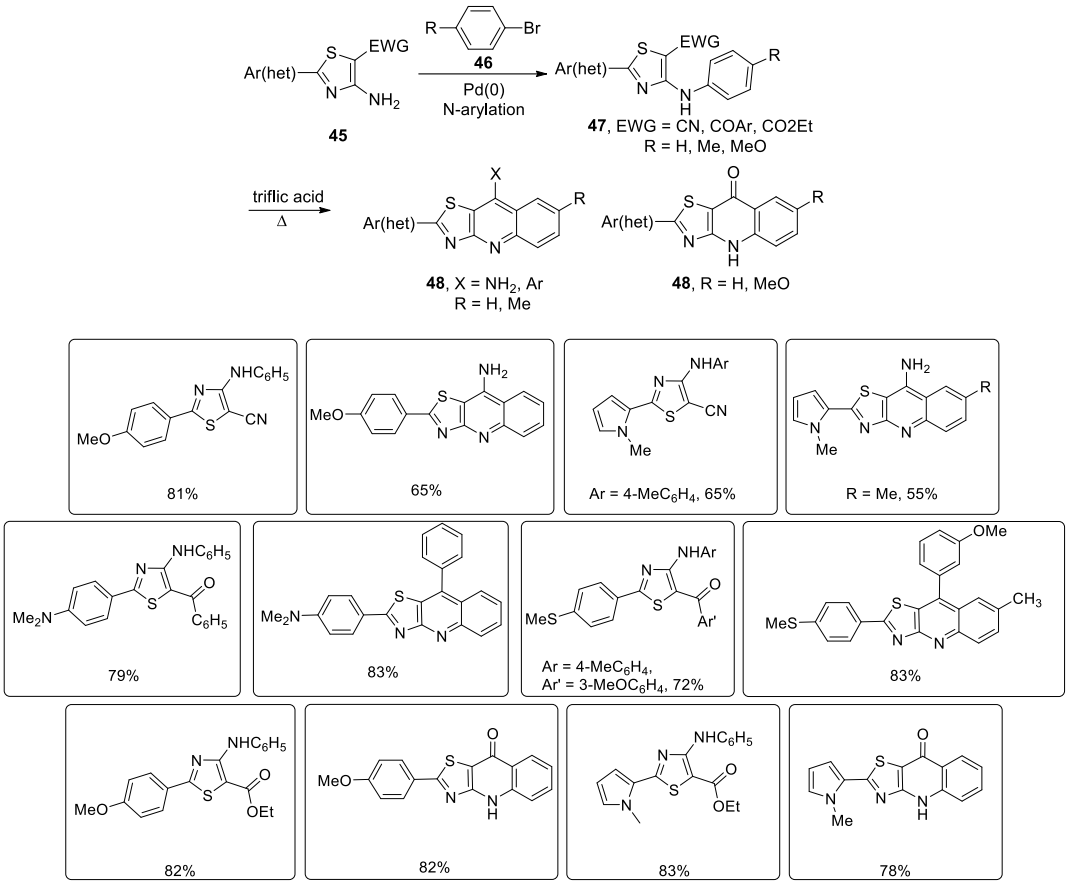
Scheme 10

In **chapter 3** of the thesis, we have described an efficient, straightforward, one-pot, three step protocol for the synthesis of 4-amino-2-(het)aryl-5-substituted thiazoles such as **45**, by employing a broad range of (het)aryl/alkyldithioesters **40** as thiocarbonyl partners and a variety of activated methylene halides **44** (Scheme 11).



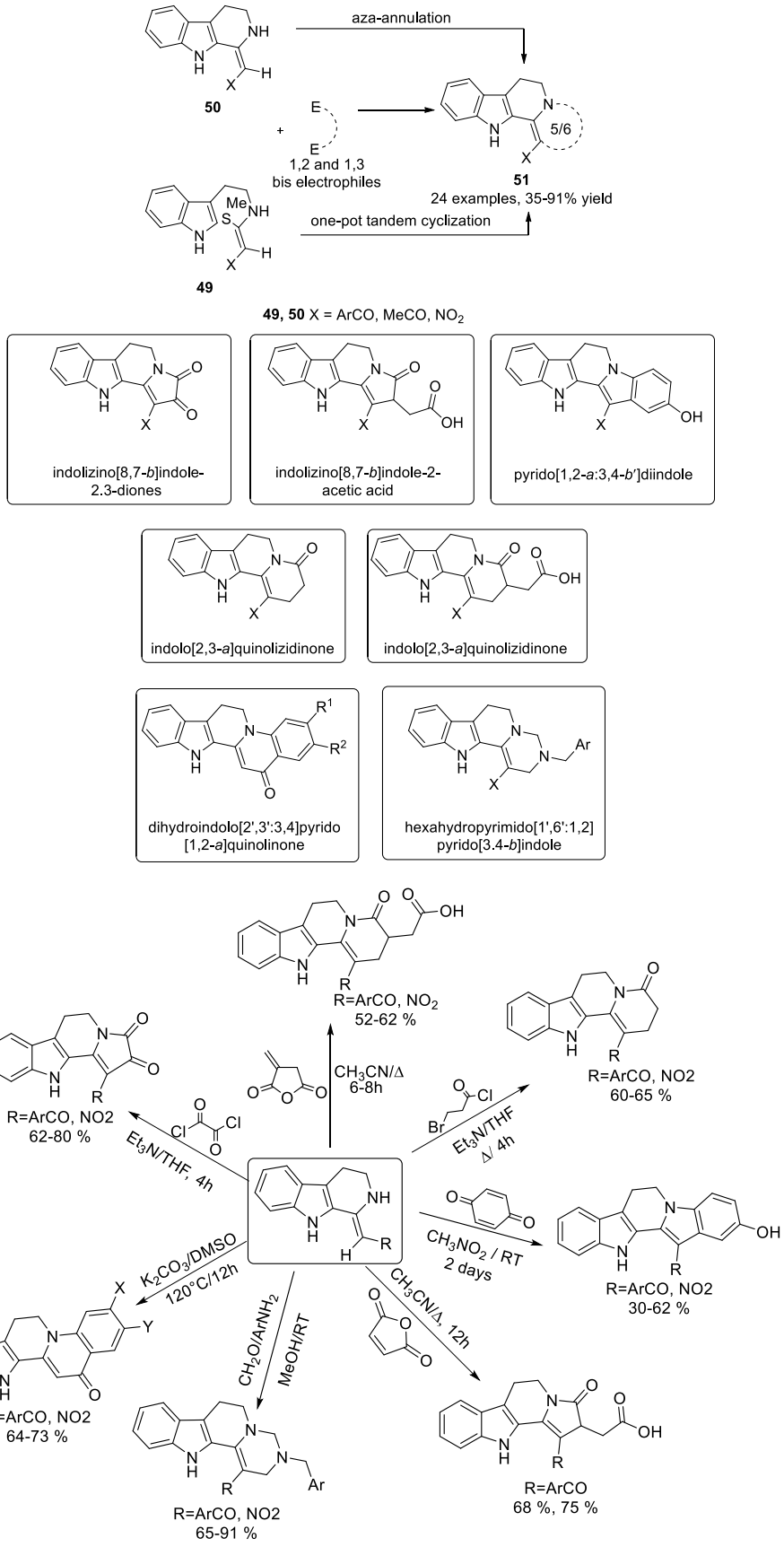
Scheme 11

The **chapter 4** of the thesis, describes a new protocol for the synthesis of thiazolo[4,5-*b*]quinoline **48**, starting from our newly synthesized 2-het(aryl)-4-amino-5-functionalized thiazole precursors **45.** We synthesized the corresponding 2-(het)aryl-4-arylamino—functionalized thiazoles precursors **47** via palladium catalyzed *N*-arylation (Buchwald-Hartwig coupling) of 2-(het)aryl-4-amino-5-substituted thiazole **45**, and these *N*-arylated precursors **47** on acid mediated cyclization yielded thiazolo[4,5-*b*]quinoline **48** (Scheme 12).



Scheme 12

The **chapter 5** of the thesis deals with Aza-annulation of novel 1,2,3,4-tetrahydro-*β*-carboline derived enaminones and nitroenamines **50** and the corresponding *N,S*-acetals **49** with various 1,2- and 1,3-bis electrophiles, such as oxalyl chloride, maleic anhydride, 1,4-benzoquinone, 3-bromopropionyl chloride, itaconic anhydride, and imines. These methodologies provide simple one-step path- ways for efficient construction of highly functionalized tetrahydro-*β*-carboline 1,2-fused, five- and six-membered heterocyclic frame-works **51**, such as indolizino[8,7-*b*]indoles, pyrido[1,2-*a*:3,4-*b′*]-diindoles, indolo[2,3-*a*]quinolizidines, and pyrimido[1′,6′:1,2]-pyrido[3,4-*b*]indoles, which are core structures of many naturally occurring indole alkaloids with diverse bioactivity (Scheme 13).


aza-annulation
50
E
E
1,2 and 1,3
bis electrophiles
5/6
51
24 examples, 35-91% yield
one-pot tandem cyclization
49
49, 50 X = ArCO, MeCO, NO2
indolizino[8,7-b]indole-2.3-diones
indolizino[8,7-b]indole-2-acetic acid
pyrido[1,2-a:3,4-b']diindole
indolo[2,3-a]quinolizidinone
indolo[2,3-a]quinolizidinone
dihydroindolo[2',3':3,4]pyrido [1,2-a]quinolinone
hexahydropyrimido[1',6':1,2] pyrido[3.4-b]indole
R=ArCO, NO2
52-62 %
CH3CN/Δ
6-8h
R=ArCO, NO2
62-80 %
Et3N/THF, 4h
R=ArCO, NO2
60-65 %
Et3N/THF
Δ/ 4h
CH3NO2 / RT
2 days
R=ArCO, NO2
30-62 %
K2CO3/DMSO
120°C/12h
R=ArCO, NO2
64-73 %
CH2O/ArNH2
MeOH/RT
R=ArCO, NO2
65-91 %
CH3CN/Δ, 12h
R=ArCO
68 %, 75 %

Scheme 13

1.6 References

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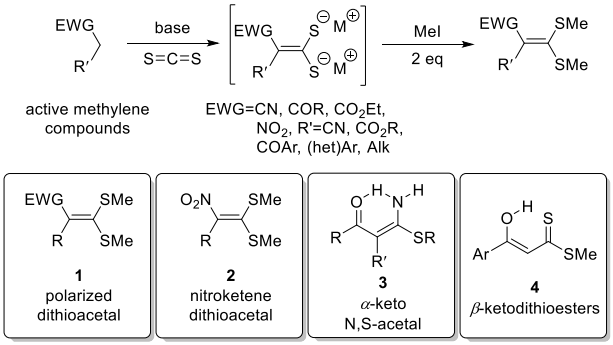
Chapter 2

*Het(aryl)Dithioestrers: Useful Building Blocks for Heterocycle Synthesis: Account**

2.1 Introduction

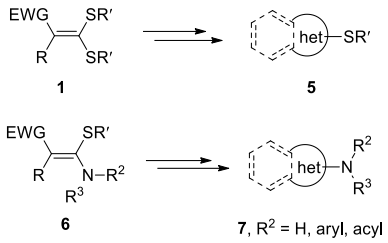
For several years, our research group has been involved in exploring synthetic applications of polarized ketene dithioacetals, derived from various active methylene compounds like ketones or nitromethane and the related *N,S*-acetals derived from them (Scheme 1).[1-2] A large number of new synthetic methods have been developed for five- and six- membered heterocycles and their fused analogs using these intermediates. Since this work has been subject of many reviews by our research group as well as by others,[3-4] we are not covering these intermediates in this account. We have also previously initiated synthetic studies on β-ketodithioesters **4**,[5] which was subsequently taken over by Singh and co-workers[6] (Scheme 1).



Scheme 1

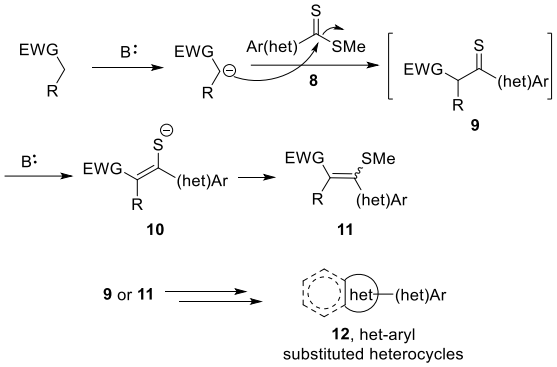
*Invited account to be submitted to *Synlett*

Most of the reactions of polarized ketene dithioacetals especially with bifunctional nucleophiles yields heterocycles bearing a methyl/alkylthio groups, whereas corresponding *N,S*-acetals yield amino substituted heterocycles (Scheme 2).



Scheme 2

During the course of this work, our research group further became interested in the chemistry of (het)aryldithioesters,[7] since the reactions of these intermediates with active methylene compounds in the presence of base will first furnish thiones such as **9**, which might subsequently yield novel heterocycles bearing substituted aryl/hetaryl/alkyl groups, through intermediates **10-11**, depending on the kind of dithioesters used (Scheme 3).



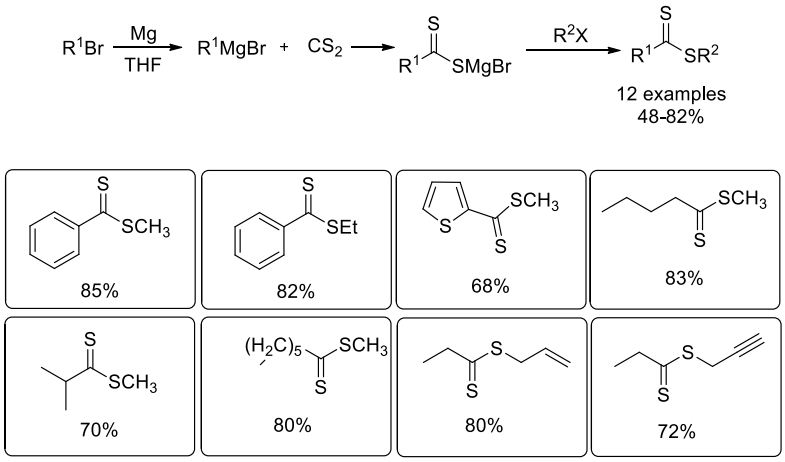
Scheme 3

Our literature survey at this stage revealed, that although there are several reviews on dithioesters[7-9] and their synthesis and several of their reactions have also been studied like thiophilic addition of nucleophiles,[8-9] thioacylation of amines,[10] in radical trapping[11] or reversible addition fragmentation reactions,[12] however systematic studies on synthetic application of dithioesters for preparation of aryl/hetaryl substituted five- and six- membered heterocycles has not been explored. Some of the [4+2] and [3+2] cycloaddition of these phosphonodithioesters as heterodienophiles and/or dipolaraphile have also been reported.[13] They have also been employed in the synthesis of functionalized thiazolines.[14]

In the present account, we have highlighted our own work in last 10-12 years dealing with the synthesis of various substituted and fused five- and six- membered heterocycles employing these dithioesters which can be considered as thio analogs of esters. We have also included few of the synthetic methods which we have been utilizing for their synthesis in our laboratory.

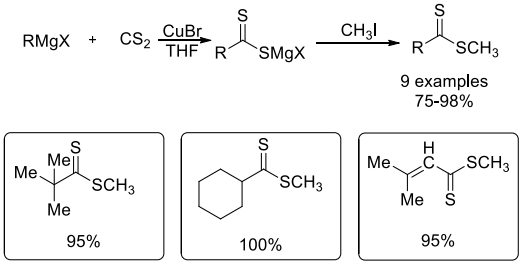
2.2 Synthesis of (het)aryl/alkyl dithioesters

One of the most common oldest methods for the synthesis of alkyl/aryl and heteroaryl dithioester involves reaction of the corresponding Grignard reagents with carbon disulfide, followed by alkylation with various alkyl halides (Scheme 4).[7,15] A variety of dithioesters have been synthesized in good yields using this method, the other halides like benzyl, allyl and propargyl halides can also be used to prepare corresponding dithioesters.



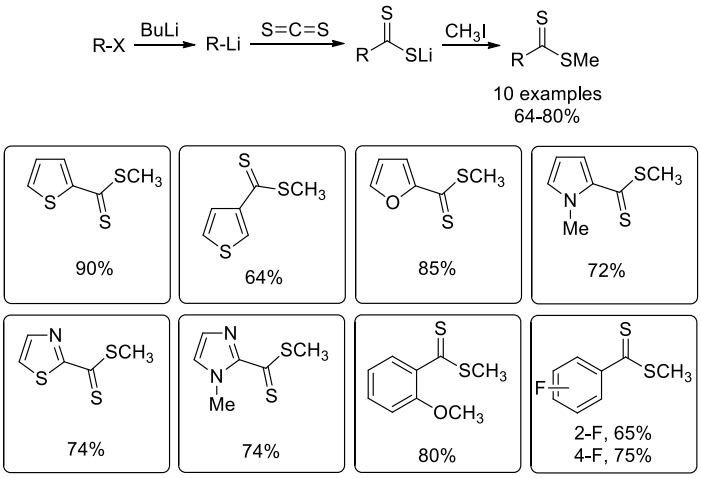
Scheme 4. Synthesis of dithioesters

A few of the dithioesters have also been obtained in high yields by reaction of preformed cuprates (obtained by reaction of corresponding Grignard reagents with cuprous bromide) with carbon disulfide, followed by treatment with alkyl halides (Scheme 5).[7,16]



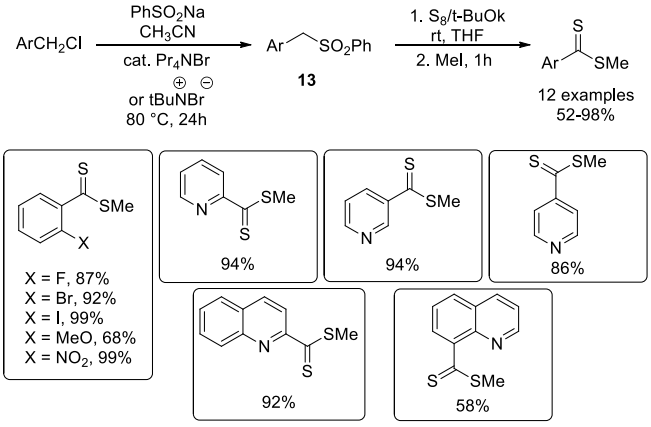
Scheme 5

Since in few cases aryl lithium compounds are obtained most easily than the corresponding Grignard reagents, several of the dithioesters have been synthesized in good yields, using aryl lithium compounds and their subsequent treatment with carbon disulfide and methyl iodide (Scheme 6) .[17]



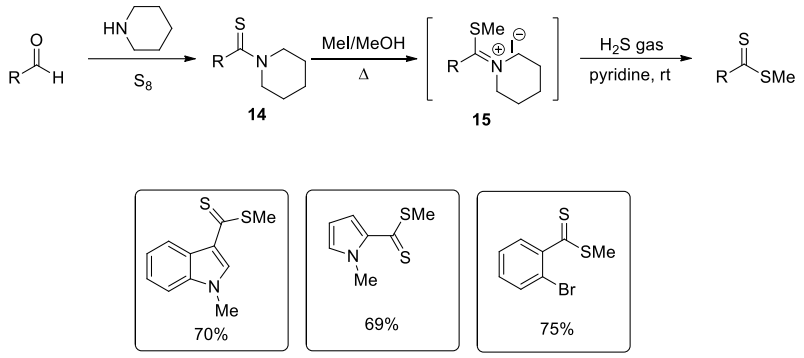
Scheme 6

Masson and coworkers have recently reported[18] a very efficient high yielding procedure for synthesis of *o*-substituted aromatic and electron deficient heteroaromatic dithioesters, involving reaction between phenylsulfonylmethyl heteroaromatic derivatives such as **13** and elemental sulfur in basic medium followed by alkylation (Scheme 7).



Scheme 7

A few of the dithioesters have also been synthesized by thiolysis of the corresponding *S*-alkyl imidium salts **15** (obtained by alkylation of secondary thioamides such as **14**) with hydrogen sulfide (Scheme 8).[19]

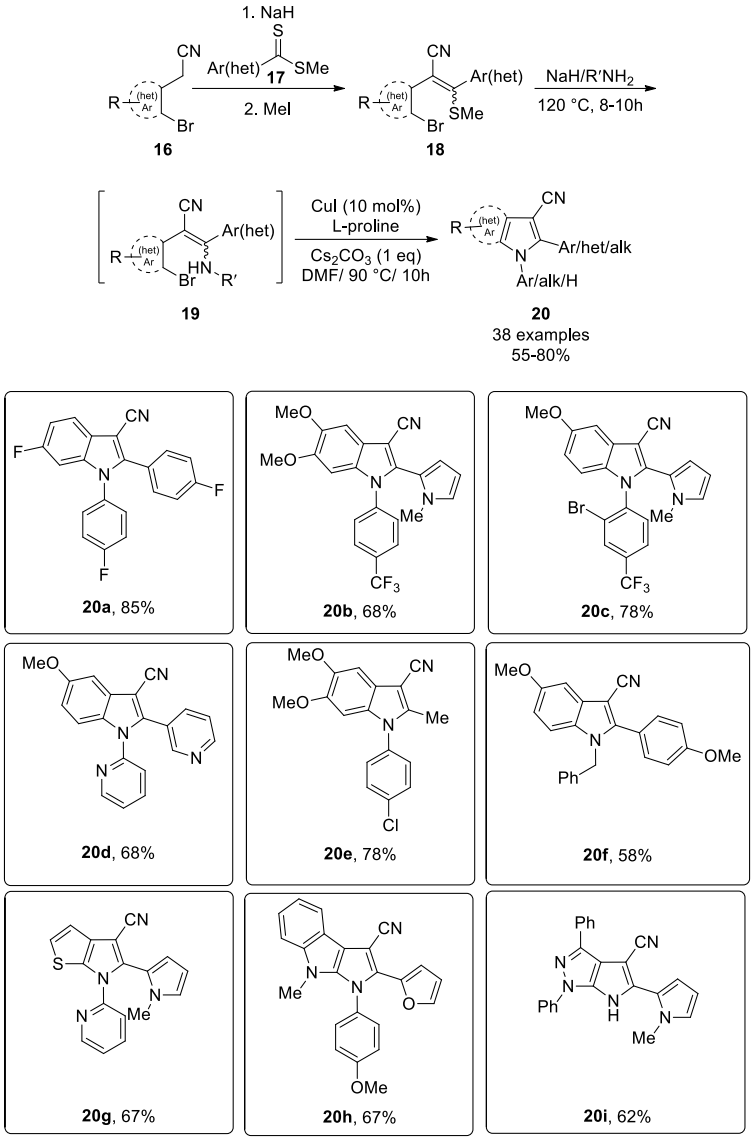


Scheme 8

In the following section, we have described overall research work conducted in our research group, mainly on substrates /building blocks derived from dithioesters leading to various novel heterocycles utilizing different kind of reactions. The research work highlighted here is since 2012-2021 from JNCASR, Bangalore. The previous review on our earlier work was published in 2013.[20]

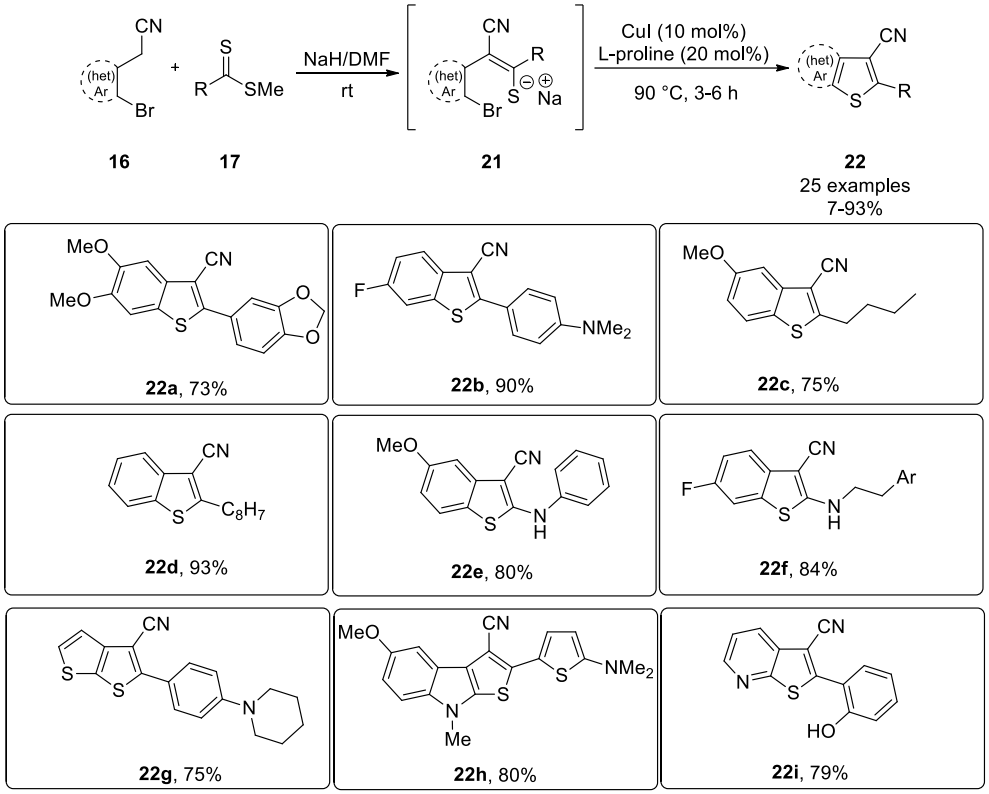
2.3 Synthesis of substituted indoles, benzo[*b*]thiophenes and benzo[*b*]furans *via* copper catalyzed intramolecular C-hetero bond formation

A novel and efficient route to substituted 1-*N*-(het)aryl/*NH*/alkyl-2-(het)aryl-3-cyanoindoles and the related pyrrolo-fused heterocycles has been developed by Vijay Kumar and others from our laboratory.[21] The overall protocol involves initially, the synthesis of a series of 2-[bromo(het)aryl-3-(het)aryl-3-methyl]thioacrylonitrile precursors such as **18** by treatment of the corresponding 2-bromo-(het)arylacetonitriles **16** with various (het)aryl dithioesters **17** in presence of base like sodium hydride followed by *S*-alkylation with methyl iodides (Scheme 9). These 3-(methylthio)acrylonitriles precursors **18** undergo sequential one-pot cycloamination with various aromatic and heteroaromatic amines, few alkyl amines and amides *via* two key *C*-*N* bond forming processes, one base mediated intermolecular and the other copper (1) catalyzed intramolecular amination in presence of proline ligand leading to N(1)-C(2) and N(1)-C(7a) bond formation respectively in two steps (Scheme 9). The synthetic methodology is compatible with a variety of electronically and structurally varied heteroaromatic amines including alkyl amines (**20a-f**). The broad scope of methodology was further illustrated by efficient synthesis of heterofused pyrroles such as thieno[2,3-*b*]pyrroles **20g** , pyrrolo[2,3-*b*]indoles **20h** , pyrrolopyrazoles **20i** structural motifs by subjecting the corresponding 2-[2-bromo(het)arylacrylonitriles to sequential two step, one-pot cycloamination with various primary amines under identical conditions (Scheme 9).



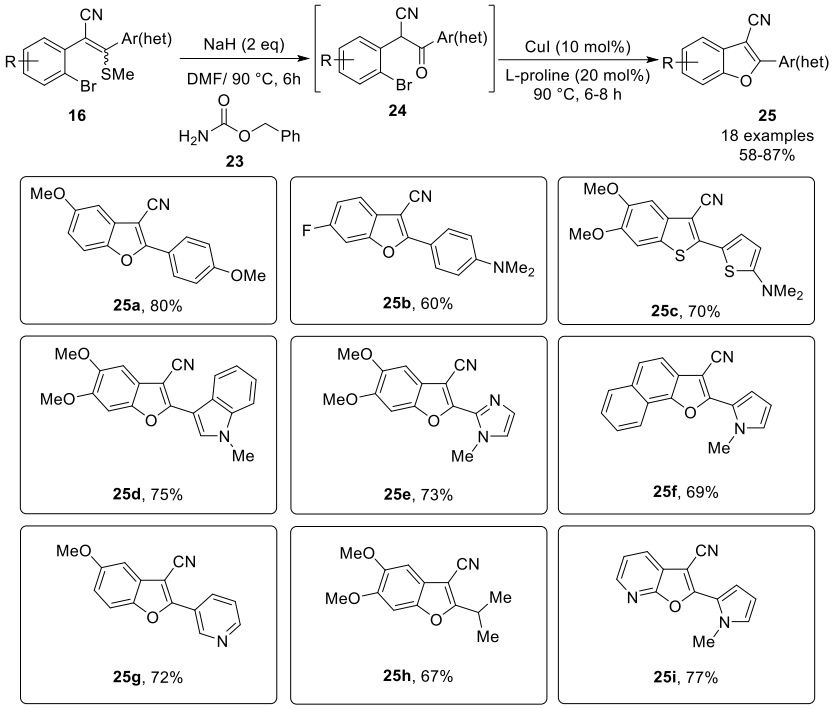
Scheme 9

Subsequently, this Cu catalyzed intramolecular C-heteroatom bond formation was extended for the efficient and practical synthesis of diversely functionalized 2,3-substituted benzo[*b*]thiophenes (**22a-f**) and hetero-fused thiophenes (**22g-i**) from readily available 2-bromo-(het)arylacetonitriles **16** and het(aryl)dithioesters **17** and other thiocarbonyl precursors (Scheme 10).[22] The overall protocol involves a tandem base mediated condensation of 2-bromo(het)aryl acetonitriles **16** and dithioesters **17** (intermolecular C(2)-C(3) bond formation) followed by Cu catalyzed intramolecular arylthioalation of the in situ generated thioenolate intermediate **21** [S(1)-C(7a) bond formation] (Scheme 10). The new methodology allows direct access to a broad range of benzo fused thiophenes (**22a-f**) along with hetero fused thiophenes such as **22g-i**, making it a useful process for structure-activity relationship.[22]



Scheme 10

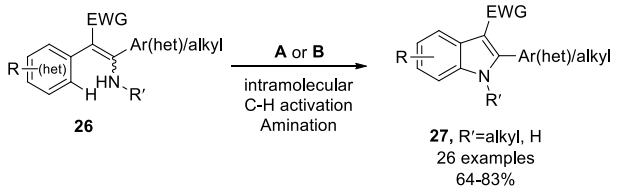
Our research group has also reported a novel one step synthesis of substituted 2-(het)aryl-3-cyanobenzofurans **25**, involving base induced reaction of 2-(2-bromoaryl)-3-(methylthio)-3-(het)arylacrylonitriles **16** with benzyl carbamate **23** and subsequent Cu(1) catalyzed intramolecular C-O bond formation (heterocyclization) of the in situ generated *α*-(2-bromoaryl)acetonitriles **24** (Scheme 11).[23] Although synthesis of substituted benzo[*b*]furans *via* C(7a)-O bond formation by palladium or copper[25] catalyzed intramolecular cyclization of *α*-(2-haloaryl)ketones have been reported in the literature, present method describes a mechanistically interesting high yield approach for 3-cyano-2-(het)arylbenzofurans directly from 2-(2-bromoaryl)-3-methylthio-3-hetarylacrylonitriles. A possible mechanism for base induced cleavage of 2-(2-bromoaryl)-3-(het)aryl-3-(methylthio) acrylonitriles **16** to *α*-(het)aroyl *α*-2-bromoarylacetonitriles **24** in the presence of benzyl carbamate has been proposed.[23]



Scheme 11

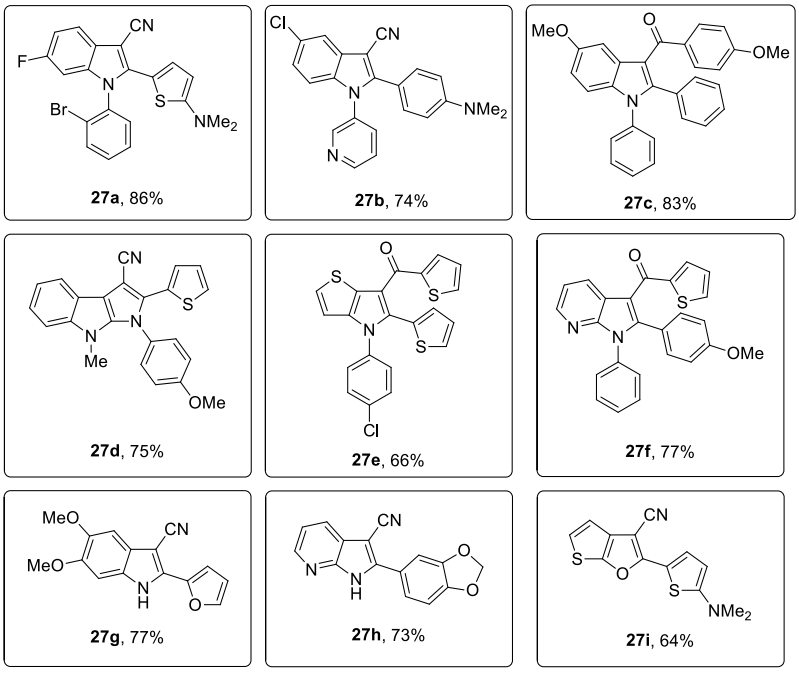
2.4 Synthesis of substituted indoles and benzo[*b*]thiophenes by palladium catalyzed C-H activation-intramolecular C-heteroatom bond formation

Our research group has also synthesized substituted indoles and benzothiophenes by palladium catalyzed intramolecular C-H activation and intramolecular amination or thiolation respectively. Thus Yugandar and others from our group[24] have developed an efficient palladium catalyzed intramolecular oxidative C-H functionalization/C-N bond forming approach for substituted *N*-aryl /*NH* indoles **27** from readily available *N*-arylenaminonitriles and enaminones **26** (EWG = CN or COAr) using palladium acetate/cupric acetate catalytic system under oxygen atmosphere (Scheme 12). This C-H functionalization strategy allows the assembly of indoles with a variety of substitution pattern and functional groups under relatively mild conditions and both electron donating and electron withdrawing groups (such as **27a** and **27c)** are tolerated in the benzene ring. The methodology can be extended to other novel pyrrolo fused heteroaromatics such as thieno[2,3-*b*]pyrroles (**27e**), pyrrolo[2,3-*b*]indoles (**27d**) and pyrrolo[2,3-*b*]pyridines (**27f** and **27h**) in good yields. A probable mechanism for formation of these indoles through palladacycle intermediate has been suggested (Scheme 12).



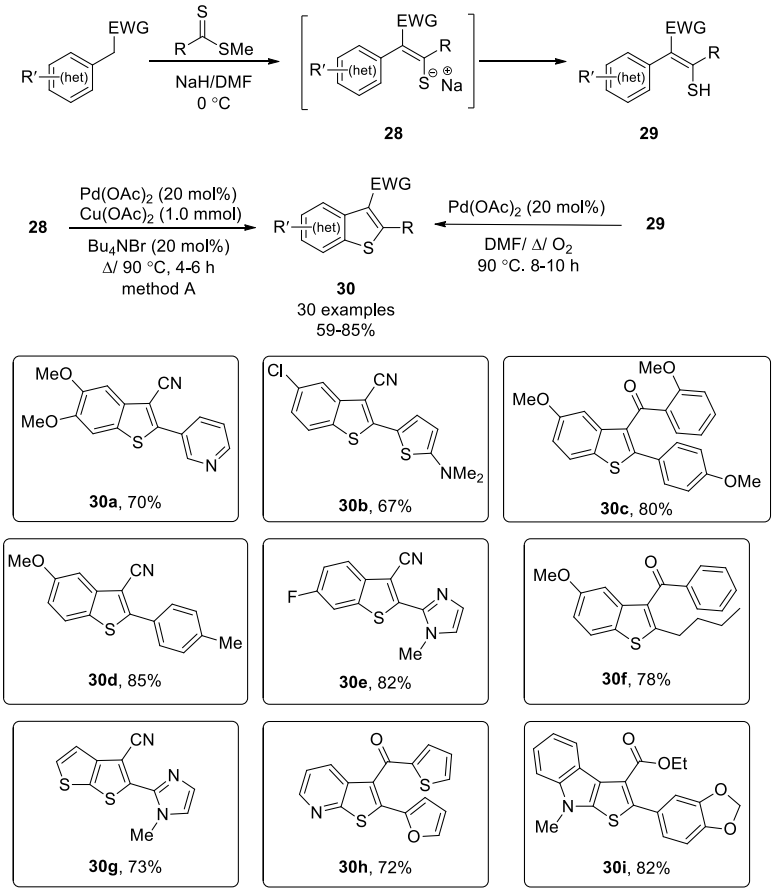
A $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 eq) , O_2, DMSO, 120 °C, 8-10 h

B $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (1.0 eq), PivOH (1.0 eq), O_2, DMSO, 120 °C, 10-12 h



Scheme 12

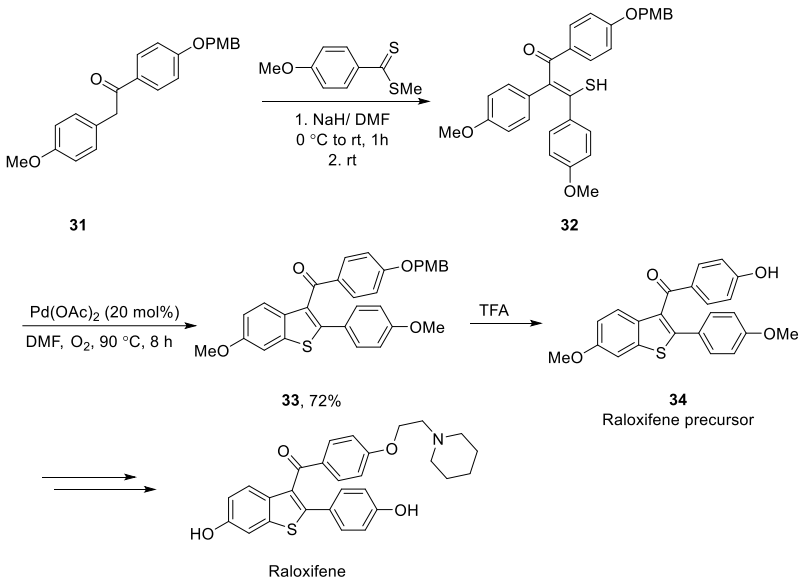
Subsequently, Acharya and others from our group have developed an effective Pd-catalyzed oxidative intramolecular C-H functionalization-arylthiolation approach for the synthesis of substituted benzothiophenes (Scheme 13).[25] Thus overall strategy involves a one-pot, two step process, in which enethioalate salts **28** (generated in situ through base mediated condensation of substituted arylacetonitriles, deoxybenzoins or arylacetates with (het)aryl(or alkyl) dithioesters are subjected to intramolecular C-H functionalization-arylthiolation under the influence of palladium acetate or palladium chloride/ cupric acetate catalytic system. In some cases, the yields of benzothiophenes were better in a two-step process by employing the corresponding enethiols as substrates in presence of Pd(II) acetate catalyst and oxygen instead of cupric acetate as reoxidant, furnishing benzothiophenes in improved yields. The method is compatible with diverse range of substituents on the aryl ring as well as on the 2- and 3-positions of the benzothiophene scaffolds (such as **30a-f**).



Scheme 13

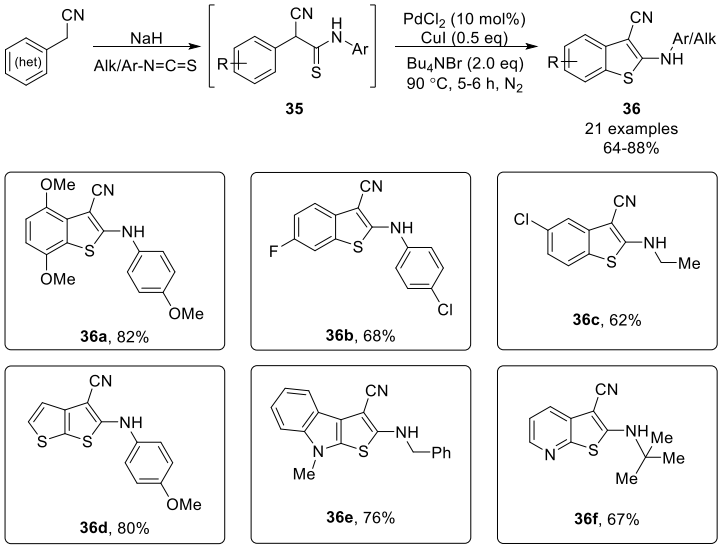
The versatility of this newly developed method was further demonstrated by elaborating it for the synthesis of substituted thieno-fused heterocycles such as thieno[2,3-*b*]thiophenes **30g**, thieno[2,3-*b*]pyridines **30h**, thieno[2,3-*b*]indoles **30i**, thieno[2,3-*c*]pyrazole in high yields. A probable mechanism involving intramolecular electrophilic arylthioalation *via* either Pd-S adduct or palladacycle intermediate has been proposed on the basis of experimental studies.[25]

The protocol could also be extended to the synthesis of raloxifene precursor **34** and tubulin polymerization inhibitor[25] in good yields (Scheme 14).



Scheme 14

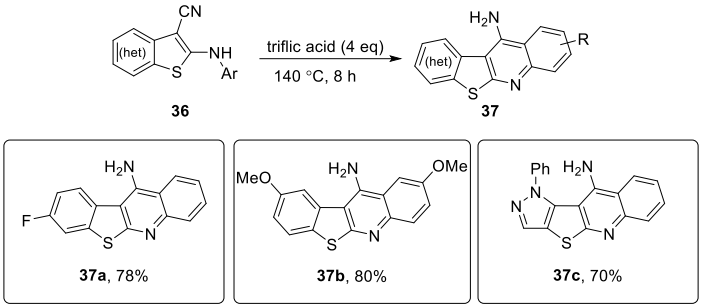
Later on, an efficient highly regioselective one-pot route towards substituted 2-(aryl/alkylamino)-3-cyanobenzo[*b*]thiophenes (such as **36a-c)** and the corresponding hetero fused analogs (such as **36d-f**) have been developed by Saraiah and others from our group by using a palladium catalyzed oxidative intramolecular C-H functionalization-arylthiolation reaction of in situ generated *N*-(aryl/alkyl)thioamides prepared from readily available heteroaryl acetonitriles and aryl/alkyl isothiocyanates in presence of base (Scheme 15).[26]



Scheme 15

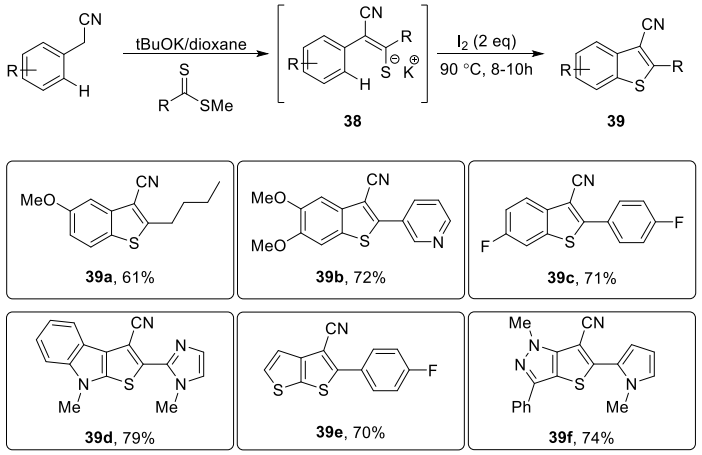
Furthermore, this approach could be further extended towards the synthesis of aryl/alkylamino substituted thieno fused heterocycles (**36d-36f**). In addition a number of 11-amino benzothieno[2,3-*b*]quinolines (such as **37a-c**) could also be synthesized *via* acid

mediated intramolecular cyclocondensation of the corresponding 2-anilino-3-cyanobenzothiophenes (Scheme 16).[26]



Scheme 16

In a further extension of benzothiophenes *via* oxidative intramolecular C-S bond formation, Saraiah and others from our group have developed a metal free one-pot route to substituted 3-cyanobenzothiophenes *via* iodine mediated intramolecular arylthiolation of enethiolates, generated in situ by base mediated condensation of arylacetonitriles and (het)aryldithioesters (Scheme 17).[27] The methodology has been further extended for synthesis of 2-anilinobenzothiophenes as well as hetero-fused benzothiophenes. An electrophilic cyclization mechanism has been proposed based on the experimental observations. [27]



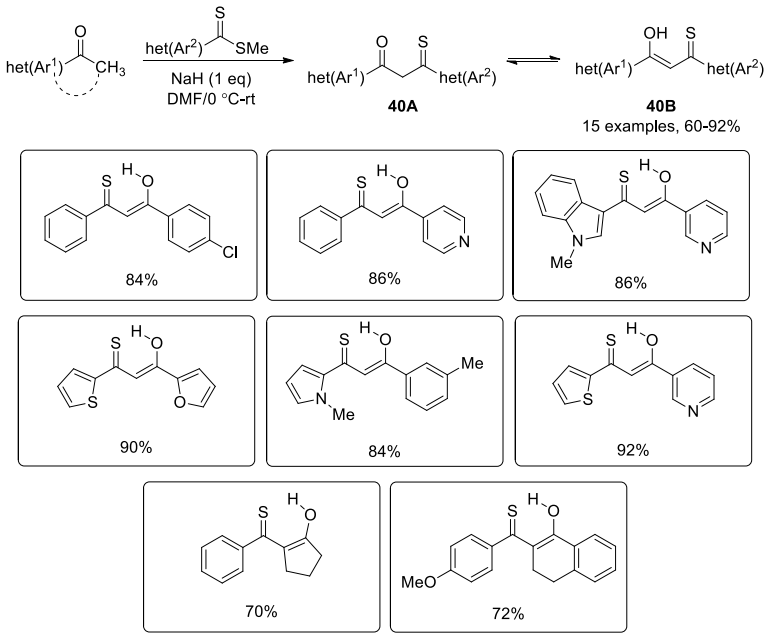
Scheme 17

2.5 Synthesis and applications of 1,3-bis(het)arylmonothio-1,3-diketones in heterocycle synthesis

In the present section, we have described our research group's recent work on 1,3-monothioketones **40** as useful building blocks for regiospecific synthesis of five membered heterocycles. Our literature survey at this stage revealed that monothio-1,3-diketones **40** have been known for a long time,[28] and these intermediates have received considerable attention in

past, as chelating agents, with promising applications, especially in analytical chemistry,[29-31] however, synthetic potential of these compounds as useful precursors for regiospecific synthesis of five- and six- membered heterocycles has been virtually not explored.[31] We therefore undertook a systematic study of these intermediates in last six years for their application in heterocycle synthesis.

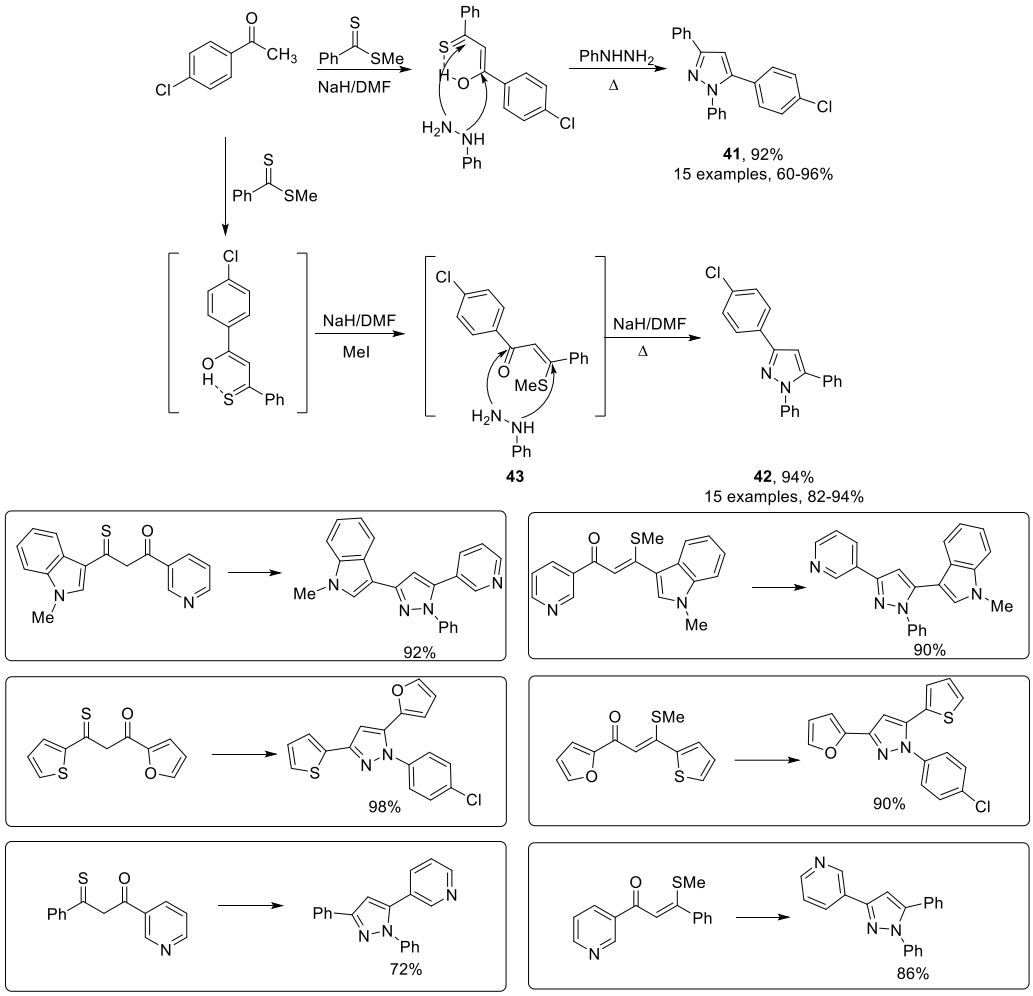
Our research group initially developed general high yield synthesis of acyclic and cyclic monothio-1,3-diketones **40** *via* modification of reported procedure,[31] by base induced thioacylation of various (het)aryl methyl ketones and cyclic ketones with dithioesters in presence of sodium hydride in DMF (Scheme 18).[31] The ^{1}H NMR spectra of **40** show that all these monothioketones exist in enolic tautomeric form **40B**.



Scheme 18

Our research group first developed two highly regioselective routes for the synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles with complementary regioselectivity[31] (Scheme 19, **41** *vs* **42**) by reacting 1,3-monothioketones **40** with phenylhydrazine under neutral conditions furnishing pyrazoles **41** in which (het)aryl moiety attached to thiocarbonyl group of monothioketone **40** is installed at 3-position, by attack of -NH_2 group of arylhydrazine at thiocarbonyl group. In the second method the corresponding 3-(methylthio)-1,3-bis(het)aryl-2-propenones **43** (prepared in situ by base induced alkylation of 1,3-monothioketones **40**) were condensed with arylhydrazine in the presence of sodium hydride in DMF yielding 1-aryl-3,5-bis(hetaryl)pyrazoles **42** with complementary regioselectivity. The efficiency of this protocol was further improved by developing a one-pot

three component procedure for synthesis of pyrazoles **42** directly from active methylene ketones by reacting in situ generated 3-(methylthio)-1,3-bis(hetaryl)-2-propenones **43** with arylhydrazines in presence of sodium hydride (Scheme 19).

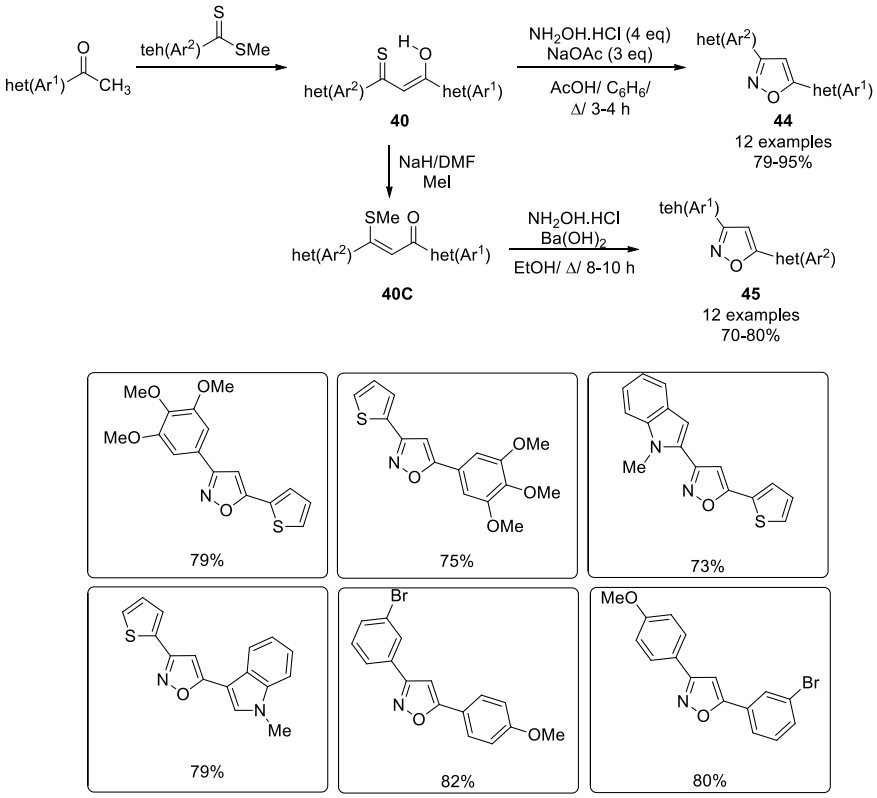


Scheme 19

The regiochemistry of all regioisomeric pyrazoles **41** and **42** were established with the help of X-ray diffraction data.[31]

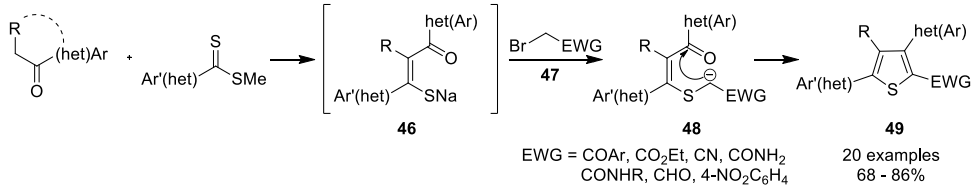
Subsequently, this concept was extended for development of efficient routes for regioselective synthesis of 3,5-bis(het)aryl isoxazoles with complementary regioselectivity (Scheme 20, **44** *vs* **45**).[32] The methods involve cyclocondensation of hydroxylamine hydrochloride with either 1,3-bis(het)arylmonothio-1,3-diketones **40** or 3-(methylthio)-1,3-bis(het)aryl-2-propenones **40C** under various conditions. In the first protocol, monothiodiketones **40** were treated with hydroxylamine hydrochloride in the presence of sodium acetate/acetic acid (pH 2.2) in refluxing ethanol/benzene to give 3,5-bis(het)aryl isoxazoles **44**, in which (het)aryl moiety attached to thiocarbonyl group of monothioketones

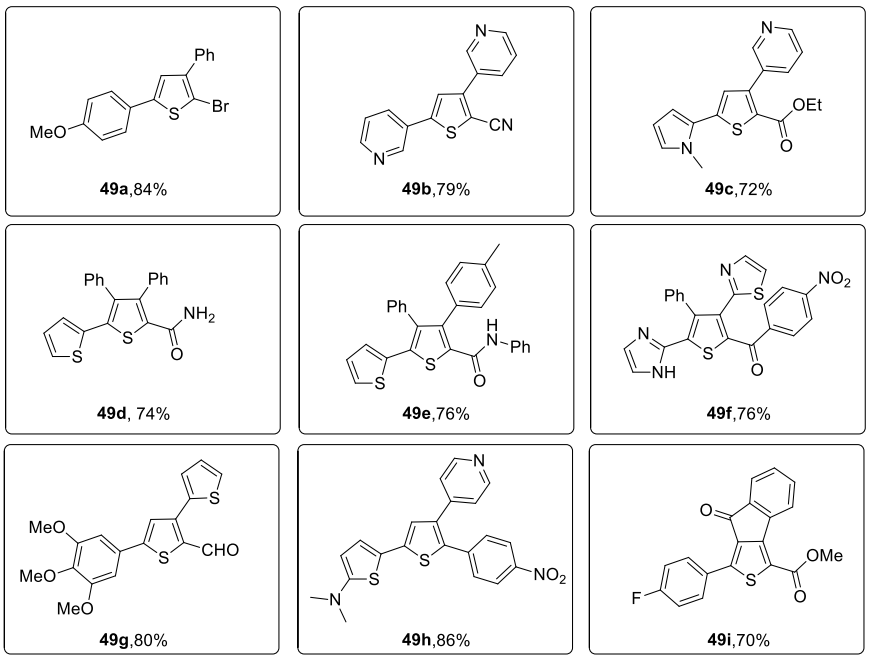
40 is installed at 3-position of isoxazole **44**. On the other hand, the reaction of hydroxylamine hydrochloride with 3-(methylthio)-1,3-bis(het)aryl-2-propenone in presence of barium hydroxide in refluxing ethanol gave 3,5-bis(het)arylisoxazoles**,** with complementary regioselectivity in high yields, exclusively (Scheme 20). A probable mechanism of the formation of regioisomeric isoxazoles **44** and **45** from the respective precursors **40** and **40C** has been suggested.



Scheme 20

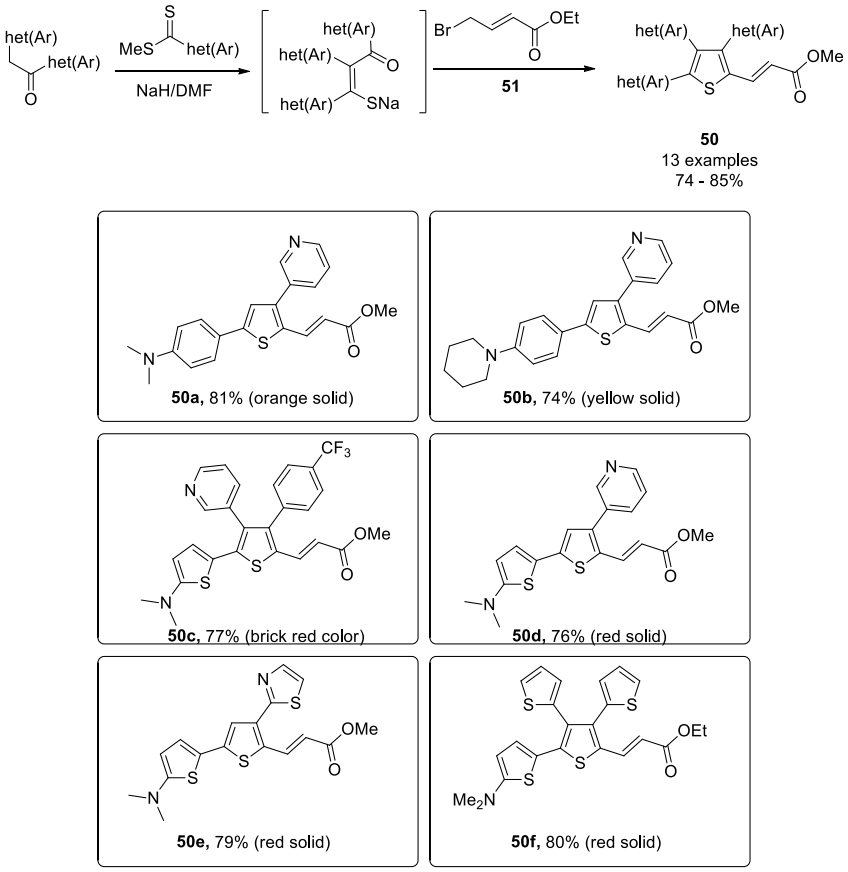
Later on Acharya and others from our group reported one-pot three component synthesis of highly functionalized tri- and tetra- substituted thiophenes involving (het)aryldithioesters as thiocarbonyl precursors (Scheme 21).[33] The overall process involves sequential base mediated condensation of readily available (het)aryl active methylene ketones with (het)aryl dithioesters followed by *S*-alkylation of the resulting enethioalate salts **46** (of 1,3-monothioketones) with activated halomethylene compounds **47** and concurrent intramolecular Aldol type condensation of *S*-alkylated compounds **48** affording substituted thiophenes **49** in excellent yields with high level of diversity at various position of thiophene scaffold. (Scheme 21).





Scheme 21

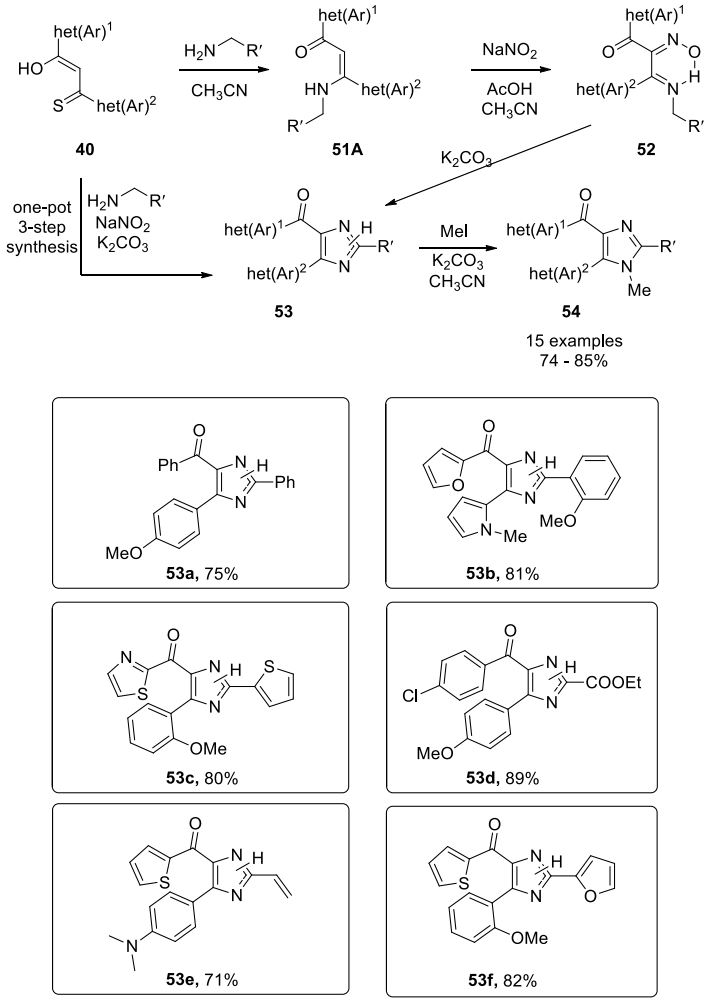
Also, the methodology could be extended for the synthesis of several push-pull thiophenes such as **50**, with extended π-conjugation, displaying yellow-red fluorescence with large Stokes shift, using (het)aryldithioesters with electron donating groups and bromocrotonate **51** as active methylene alkylating agent (Scheme 22).[33]



Scheme 22

Yugandar and others from our group have developed an efficient highly regiocontrolled one-pot three step protocol,[34] involving [2+2+1]annulation, for the synthesis of a series of diversly functionalized trisubstituted 4(5)-het(aroyl)-2,5(4)-het(aryl)/alkyl imidazoles **53** from readily available 1,3-bishet(aryl)monothiol-1,3-diketones, **40** α-substituted methylamines and sodium nitrite (as precursor for ring nitrogen) and their subsequent *N*-alkylation to the corresponding *N*-methyl derivatives (Scheme 23). This novel sequential one-pot three step protocol, wherein three new carbon-nitrogen bonds are formed in continuous fashion, involves in situ generation of enaminones **51A** by reaction of monothiol-1,3-diketones **40**, with α-substituted methylamines, followed by their nitrosation with sodium nitrite and subsequent base mediated intramolecular heterocyclization of the resulting α-hydroxyiminoamines **52** to tri-substituted imidazoles **53** in high yields under mild conditions (Scheme 23). These newly prepared imidazoles **53** are shown to exist as tautomeric mixture, however, their subsequent alkylation with methyl iodide in the presence of potassium carbonate affords the corresponding 1-*N*-methyl-2,5-bis(het)aryl-4-(het)aroylimidazoles **54** in highly regioselective fashion in most of the cases (Scheme 23).[34] A variety of substituents including aryl-, hetaryl-, carboethoxy-

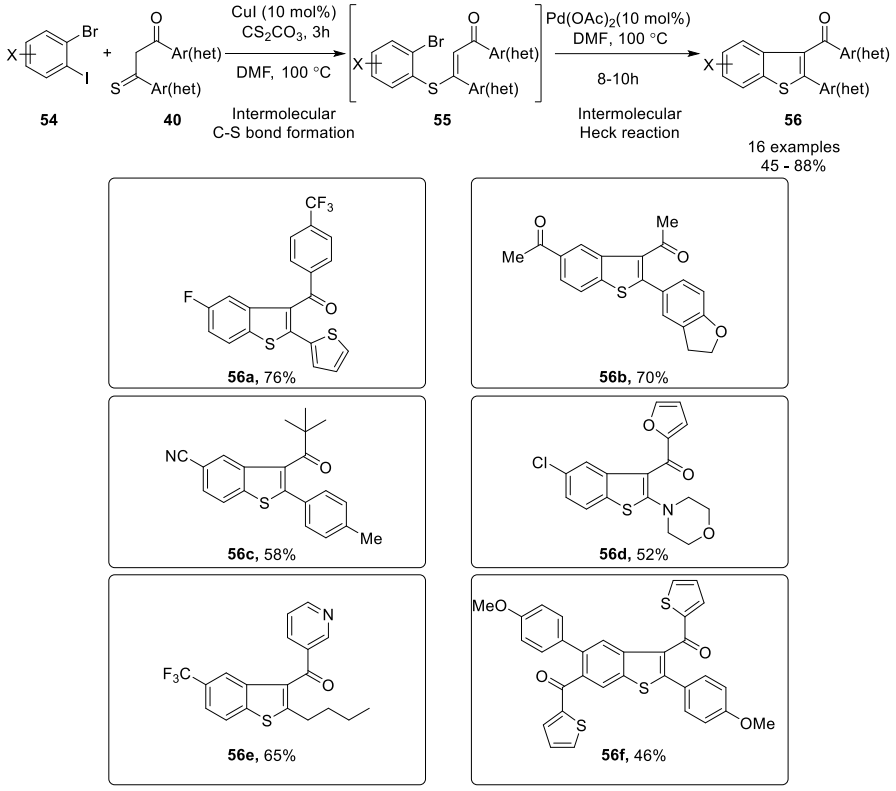
(**53d**), vinyl (**53e**)groups could be introduced depending on the choice of α-substituted methylamines



Scheme 23

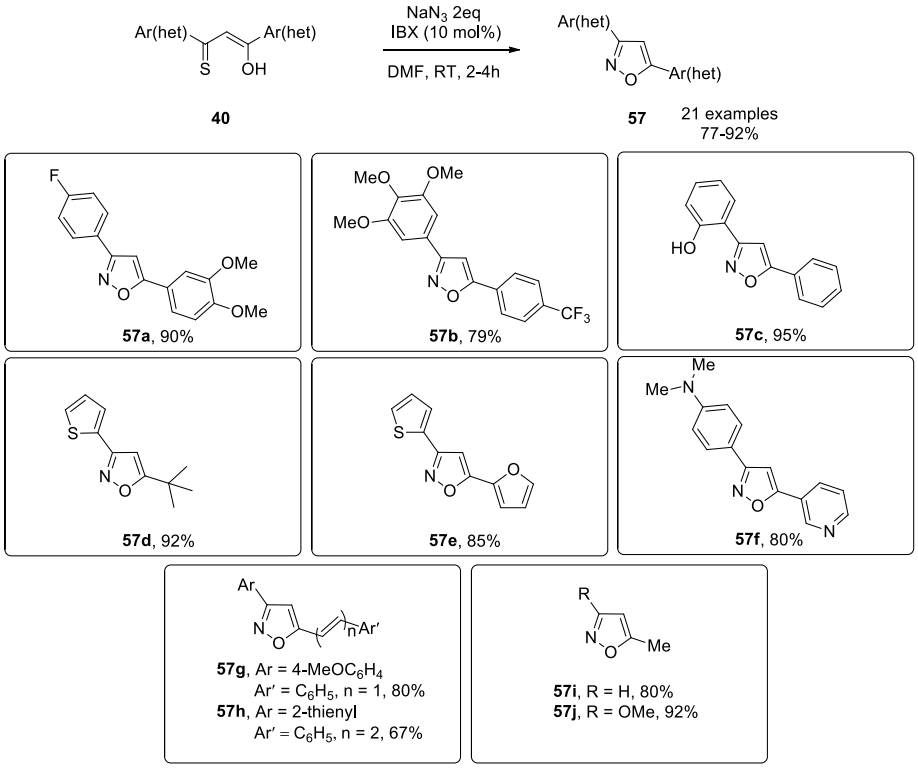
The method provides rapid access especially to imidazoles with sterically demanding (het)aromatic groups on 2-, 4-, and 5- positions (such as **53b** and **53f**), as well as to 4(5)-(2-hydroxyphenyl)imidazoles (such as **53c**)which are known to be good coordinating agents.

Yugandar and others from our research group have developed an efficient, convergent, one-pot synthesis of 2-(het)aryl/alkyl-3-acylbenzo[*b*]thiophenes **56** from readily available 1,3-bis(het)aryl-1,3-monothioketones **40** and *o*-bromoiodoarenes **54** involving a sequential copper catalyzed Ullman type intermolecular C-S coupling followed by an in situ palladium catalyzed intramolecular Heck-reaction of the resulting β-(arylthio)vinyl ketones **55** (Scheme 24).[35] It should be noted that such kind of disconnection approach for the construction of a benzo[*b*]thiophene ring has not been reported in the literature. The new methodology provides access to a broad range of substituted thiophenes displaying functional group diversity at various positions including benzene ring (Scheme 24).[35]



Scheme 24

In a further exploration of synthetic application of newly synthesized 1,3-monothioketones Mary and others from our laboratory have recently reported[36] an efficient new approach for the synthesis of 3,5-bis(het)arylisoxazoles **57** involving the reaction of 1,3-bis(het)arylmonothio-1,3-diketones **40** with sodium azide in the presence of IBX as catalyst (Scheme 25). The reaction proceeds at room temperature in high yields and is applicable to a broad range of substrates including the synthesis of 5-methyl-3-arylisoxazoles (such as **57i-j**), a key subunit present in several *β*-lactamase resistant antibiotics. The methodology has also been extended for the synthesis of 5-styryl/arylbutadienyl-3-(het)aryl isoxazoles (such as **57g-h**) from the appropriate precursors (Scheme 25).



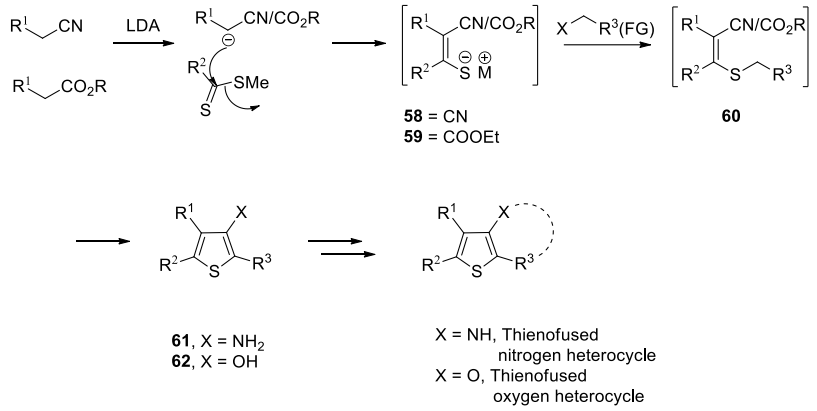
Scheme 25

A probable mechanism for the formation of isoxazoles from monothioketones and sodium azide has been suggested. Unlike previously known widely applicable synthetic approaches to isoxazoles, the present synthesis provides a new set of disconnection involving tandem intermolecular C-N and intramolecular N-O bond formation. The examples of such kind of synthetic sequences for isoxazole synthesis are very few in the literature.[36]

2.6 Synthesis of thieno-fused five- and six- membered nitrogen and oxygen heterocycles *via* intramolecular heteroannulation of 4,5-substituted-3-amino or 3-hydroxy -2-functionalized thiophenes

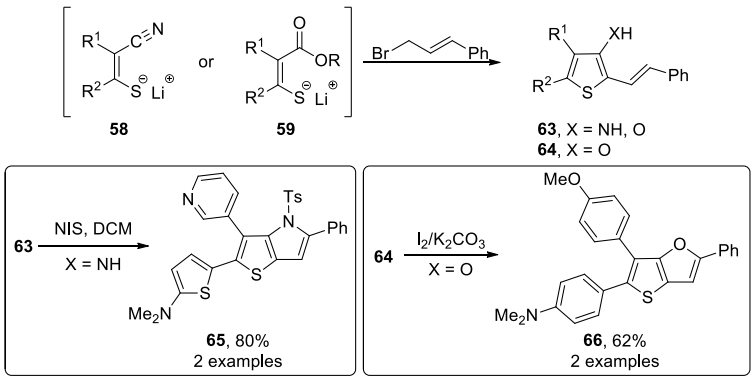
Acharya and others from our laboratory, in a recent elaborate publication,[37] have reported simple general protocols, to access a series of diverse range of novel thieno-fused five- and six- membered nitrogen and oxygen heterocycles involving either in situ or stepwise intramolecular heterocyclization of newly generated 4,5-substituted-3-amino or 3-hydroxy-2-functionalized thiophenes **61** or **62**. These 3-amino or 3-hydroxy thiophenes **61-62** are readily assembled in high yields from easily accessible precursors such as (het)aryl substituted acetonitriles or acetates with (het)aryl dithioesters in the presence of LDA in a sequential one-pot process followed by alkylation-intramolecular condensation of the resulting enethioalte salts **58** or **59** with functionalized activated methylene halides (Scheme 26). Further in situ or

step-wise intramolecular cyclization of these 2-functionalized-3-amino/hydroxy thiophenes **61** or **62** depends on the choice of activated methylene halides employed, such as cinnamoyl bromide, 2-bromobenzyl chloride, bromocrotonate, 2(bromomethyl)benzoate or 2-chlorophenacyl bromide.



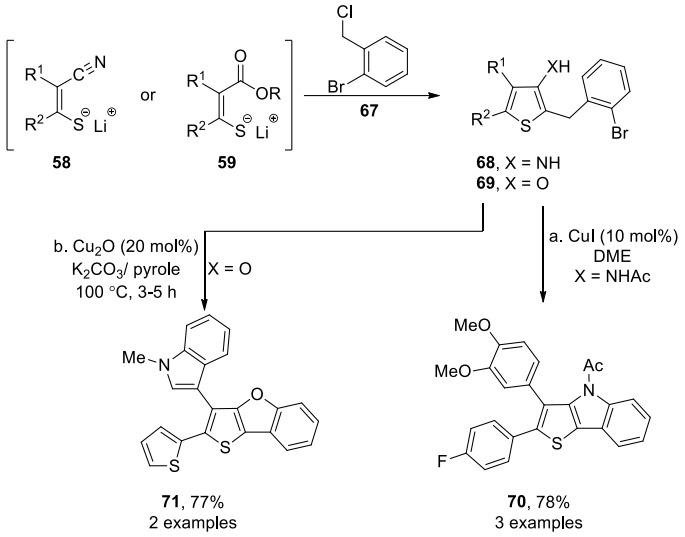
Scheme 26

Thus in one example, thieno fused five membered heterocycles such as thieno[3,2-*b*]pyrroles **65**, thieno[3, 2-*b*] furans **66** were synthesized *via* initial synthesis of 3-amino or 3-hydroxy-2-styrylthiophenes such as **63** and **64**, by reacting salts **58** or **59** with cinnamyl bromide. These 3-amino and 3-hydroxy-2-styryl thiophenes **63**-**64** were then subjected to intramolecular C-N or C-O bond formation in presence of either NIS or iodine to afford the corresponding thieno-fused pyrroles or **65** or furans **66** in good yields (Scheme 27).[37]



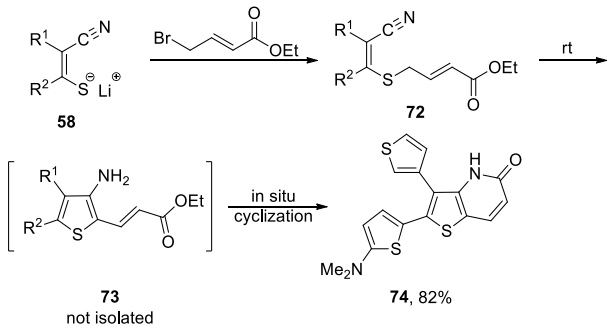
Scheme 27

Similarly, when salts **58** or **59** were reacted with *o*-bromobenzyl chloride **67**, the corresponding 2-(2-bromobenzyl)-3-amino or 3-hydroxy thiophenes **68** and **69** were obtained in good yields (Scheme 28). Both thiophenes **68**-**69** underwent intramolecular copper catalyzed C-N or C-O coupling to afford the corresponding thieno[3,2-*b*]indoles **70** or thieno[3,2-*b*]furans **71** in good yields (Scheme 28).[37]



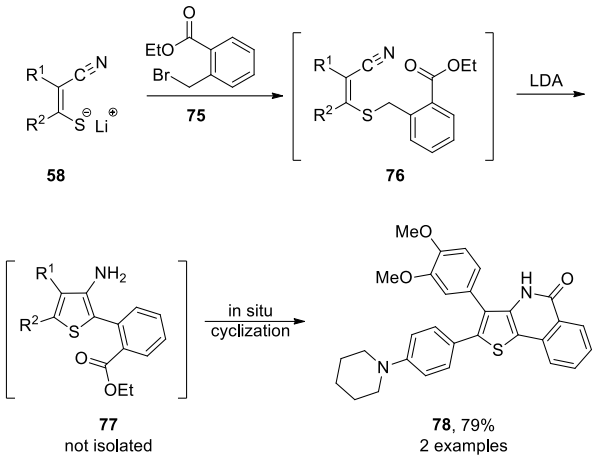
Scheme 28

Interestingly, when the salt **58** from arylacetonitrile was reacted with bromocrotonate, work up of the reaction mixture afforded directly thieno[3,2-*b*]pyridones **74** in good yield, (without isolation of acyclic intermediates **72** or **73**) *via* in situ intramolecular cyclization of thiophene-3-aminoacrylate **73 (**Scheme 29).



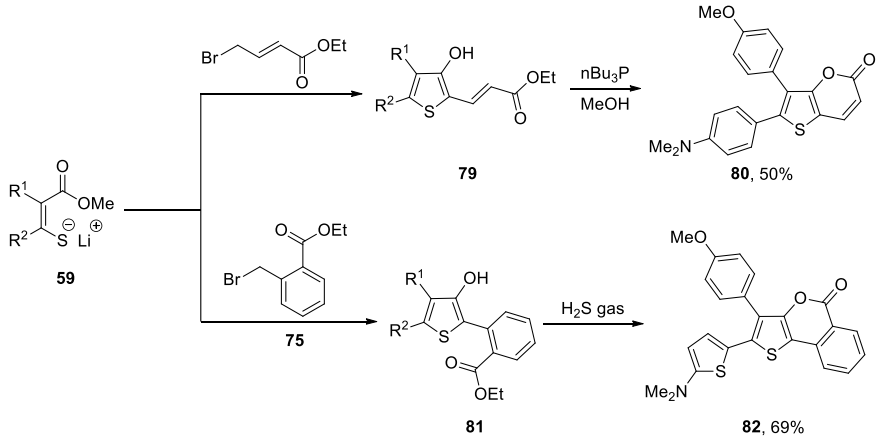
Scheme 29

Similarly, in situ alkylation of the salt **58** with *o*-(bromobenzyl)benzoate **75**, afforded directly the corresponding thieno[3,2-*b*]isoquinolone **78** in a domino fashion involving formation of four bonds and two rings in a one pot reaction (Scheme 30).[37]



Scheme 30

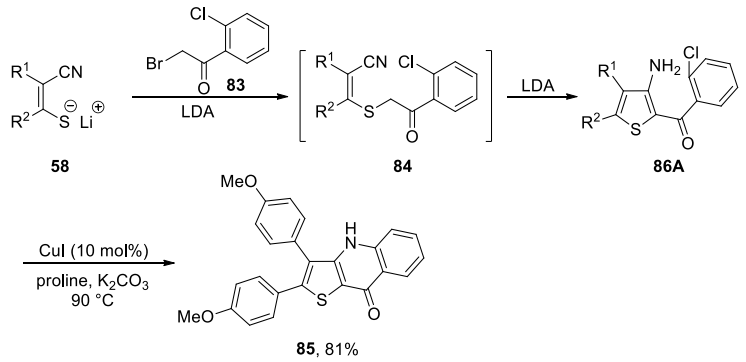
On the other hand treatment of salt **59** from aryl acetate and dithioester with either bromocrotanate or *o*-(bromo benzyl)benzoate **75** did not proceed in domino fashion, yielding only either 3-hydroxythiophene acrylate **79** or thiophene 3-hydroxy-2-(2-carboethoxyphenyl)thiophene **81** which could be subsequently cyclized to the desired thieno[3,2-*b*]pyrone **80** or the corresponding thieno[3,2-*b*]chromanone **82** in presence of tributylphosphine or sulphuric acid respectively (Scheme 31).[37]



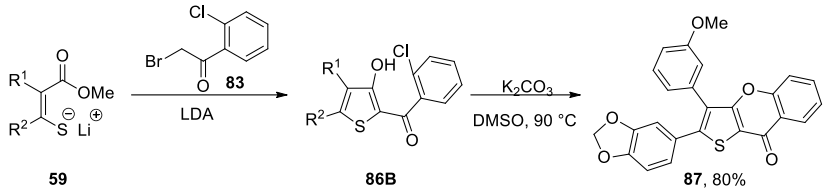
Scheme 31

Finally, the synthesis of the corresponding thieno[3,2-*b*]-9-quinolone **85** and thieno[3,2-*b*]chroman-9-one **87** was also achieved in two step protocol by reaction of salt **58** or **59** with *o*-chlorophenacyl bromide **83** and subsequent intramolecular cyclization of the corresponding 3-amino-2-(2-chlorobenzoyl)thiophene **86A** or 3-hydroxy-2-(2-chlorobenzoyl)thiophene **86B** either *via* Cu catalyzed intramolecular C-N bond formation (for **85**) or in presence of K_2CO_3 in DMSO yielding the desired thieno[3,2-*b*] 9-quinolone **85** or 9-chromanone **87** in good yields. Thus, following simple procedures from easily available

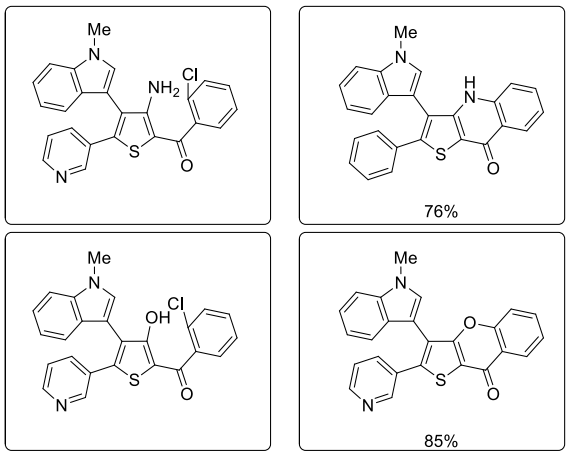
starting materials, it was possible to construct ten new thieno fused nitrogen or oxygen heterocycles scaffolds as shown in the Schemes 32-33 and 33A.[37]



Scheme 32



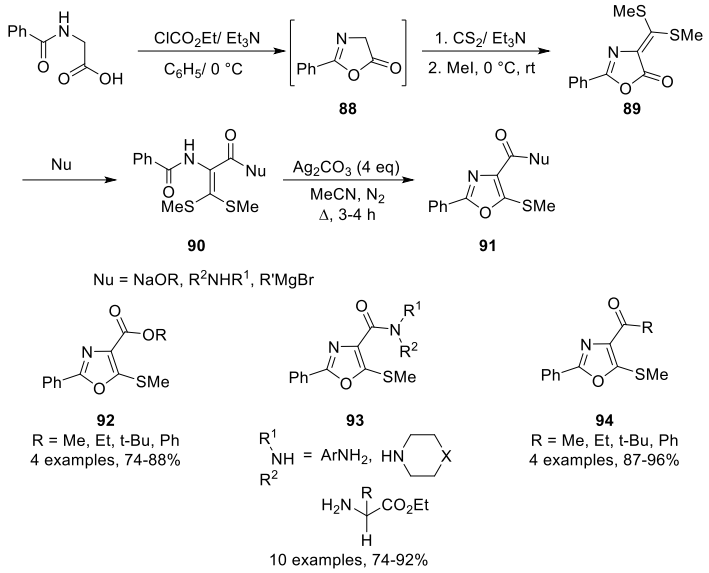
Scheme 33



Scheme 33A

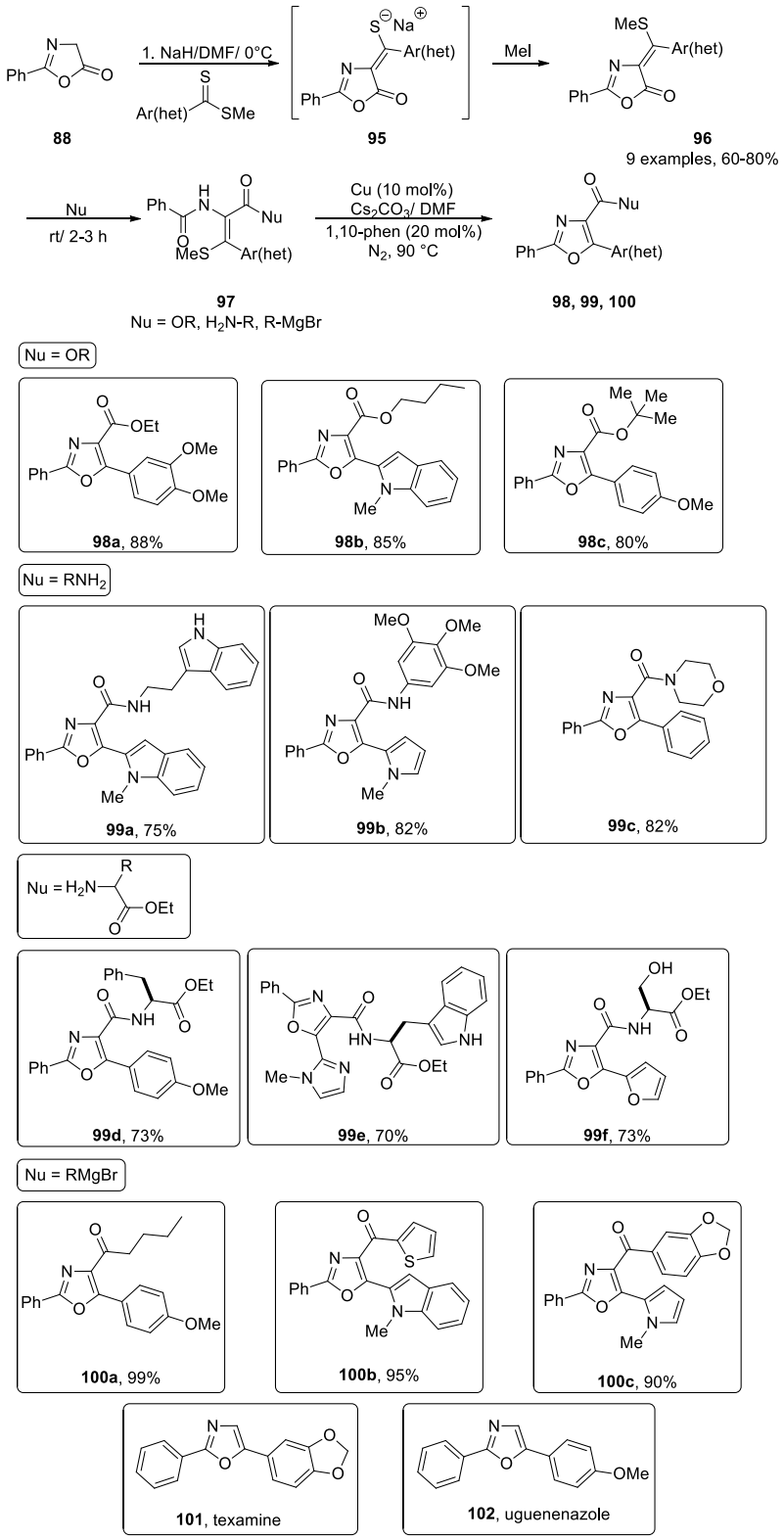
2.7 Synthetic transformations of 4-(methylthio)hetero(aryl)methylene-2-(het)aryl-5-oxazolones

We have previously reported synthesis and nucleophilic ring opening of 4-bis(methylthio)methylene-2-phenyloxazoloe-5-ones **89** by various oxygen, nitrogen and carbon nucleophiles generating highly functionalized *N*-benzoyl-*β*-bis(methylthio)enamides of general structure **90** (Scheme 34). These enamides intermediates were subsequently transformed into 2-phenyl-5-(methylthio)-4-alkoxycarbonyl, amido and acyloxazoles **92-94** in good yields by silver carbonate induced *5-endo* cyclization (Scheme 34).[38]



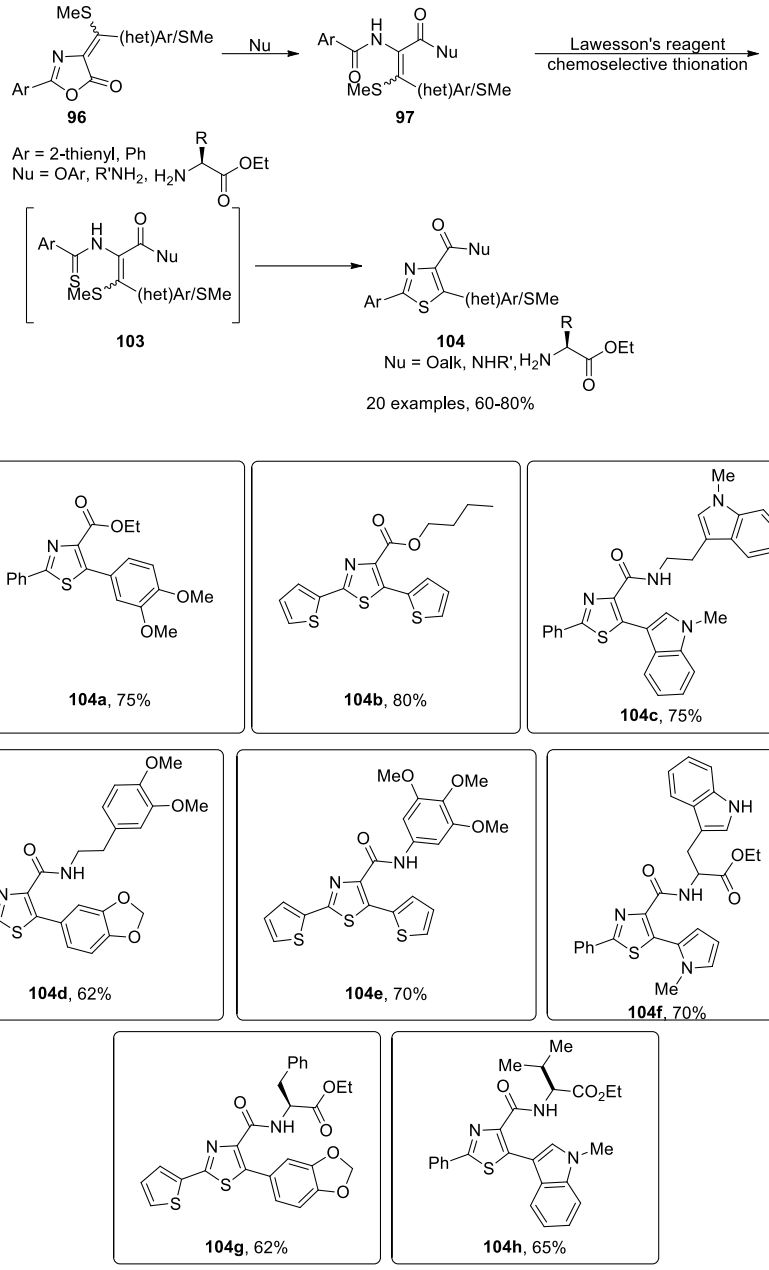
Scheme 34

In further elaboration of this work, Vijay Kumar and others from our research group have reported an efficient two step synthesis of 2-phenyl-4,5-(het)aryl-substituted oxazoles from readily available novel 4-(methylthio)(aryl/heteroaryl)methylene-2-phenyl-5-oxazolone precursors **96**, obtained by base catalyzed condensation of oxazolone **88** with (het)aryldithioesters and subsequent *S*-alkylation of the resulting thiolate anion **95 .**[39] The overall strategy involves highly regioselective nucleophilic ring opening of **96** by alkoxides, amines and Grignard reagents and subsequent copper catalyzed intramolecular cyclization of the resulting functionalized *β*-(methylthio)heteroarylenamides **97** leading to introduction of an ester, amide or acyl functionalities at 4-position of product oxazoles **98-100** (Scheme 35). Additionally, the aminoacid derived enamides provide access to a range peptidomimetic oxazoles (such as **99d-f**). The methodology is further applied for the synthesis of two naturally occurring oxazoles i.e., texamine **101** and uguenenazole **102** (Scheme 35).[39]



Scheme 35

In a further extension of this work, Vijay Kumar and others from our laboratory developed an efficient chemoselective high yield route to 2-phenyl/2-thienyl-5-(het)aryl/(methylthio)-4-functionalized thiazoles **104** *via* one step chemoselective thionation cyclization of highly functionalized enamides **97** mediated by Lawesson's reagent (Scheme 36).[40]

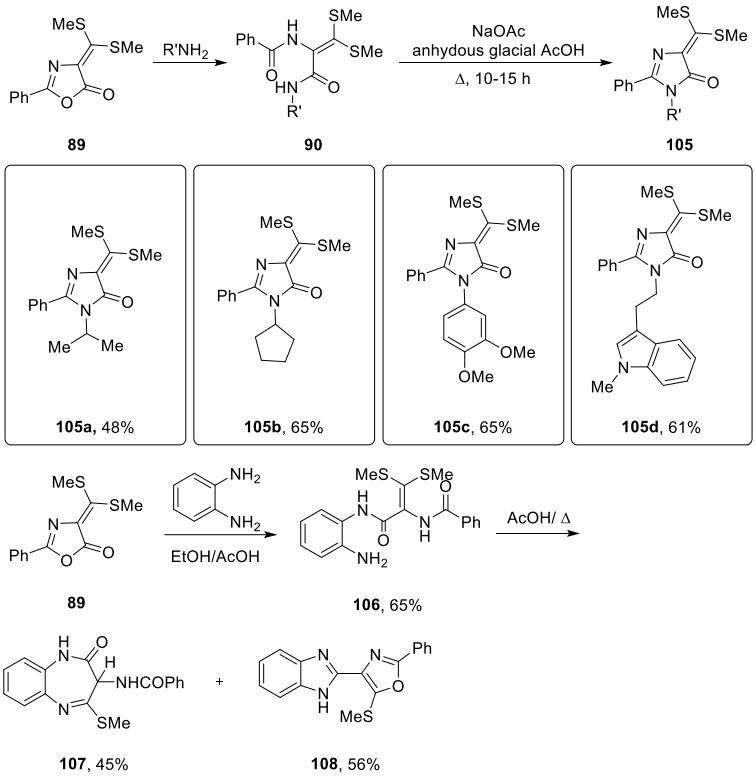


Scheme 36

These enamides precursors are obtained by nucleophilic ring opening of 2-phenyl/(2-thienyl)-4-(methylthio)-het(aryl)methylene-5-oxazolones **96** with alkoxides, primary amines and amino acid esters as previously shown in Scheme 35, leading to introduction of an ester (such as **104a-b**), *N*-substituted carboxamide (**104c-e**) or peptide functionality (**104f-h**) in the 4- position of product thiazoles **104** (Scheme 36).[40]

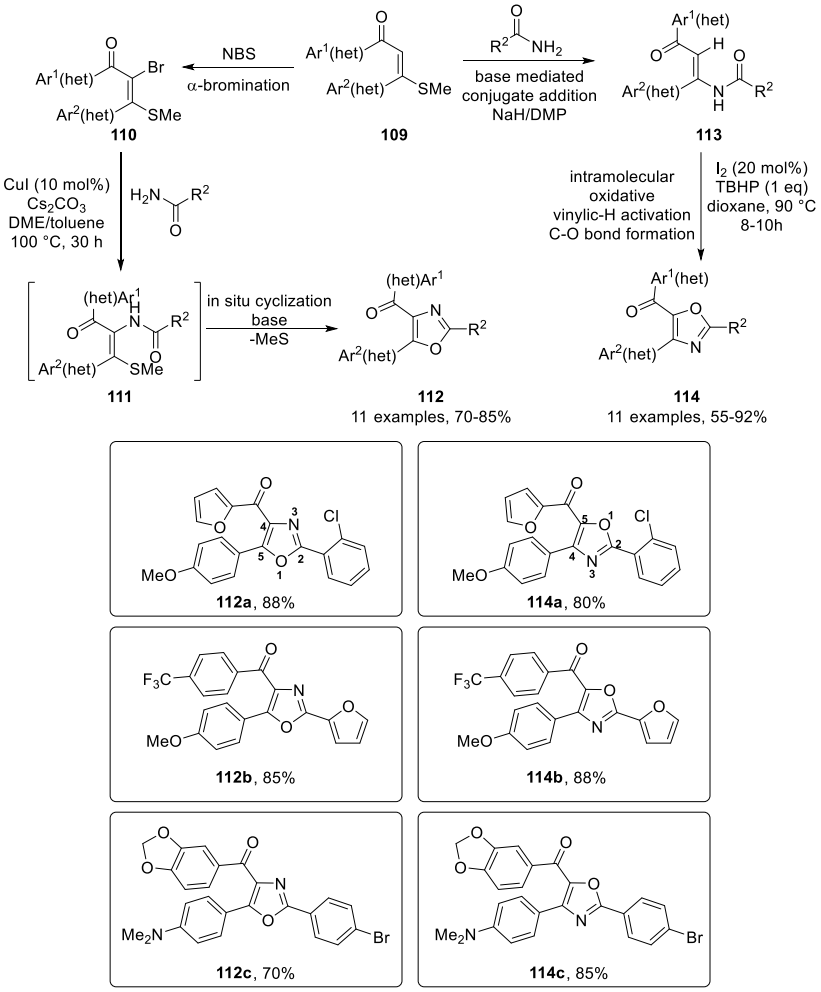
In a previous study from our research group, the enamides **90** obtained by nucleophilic ring opening of 2-phenyl-4-bis(methylthio)methylene oxazol-5-one **89** were transformed into 4-bis(methylthio)methylene-2-phenyl-1-alkyl/arylimidazol-5(4*H*)ones **105** in good yields in the presence of anhydrous sodium acetate and acetic acid (Scheme 37).[41] Similarly, the amide

adduct **106** from *o*-phenylenediamine and **89**, affords substituted 3*H*-1,5-benzodiazepinone **107** and 2-(5-methylthio-2-phenyl-4-oxazolyl-1*H*-benzimidazole **108** in presence of Ag_2CO_3 in refluxing acetic acid (Scheme 37).[41]



Scheme 37

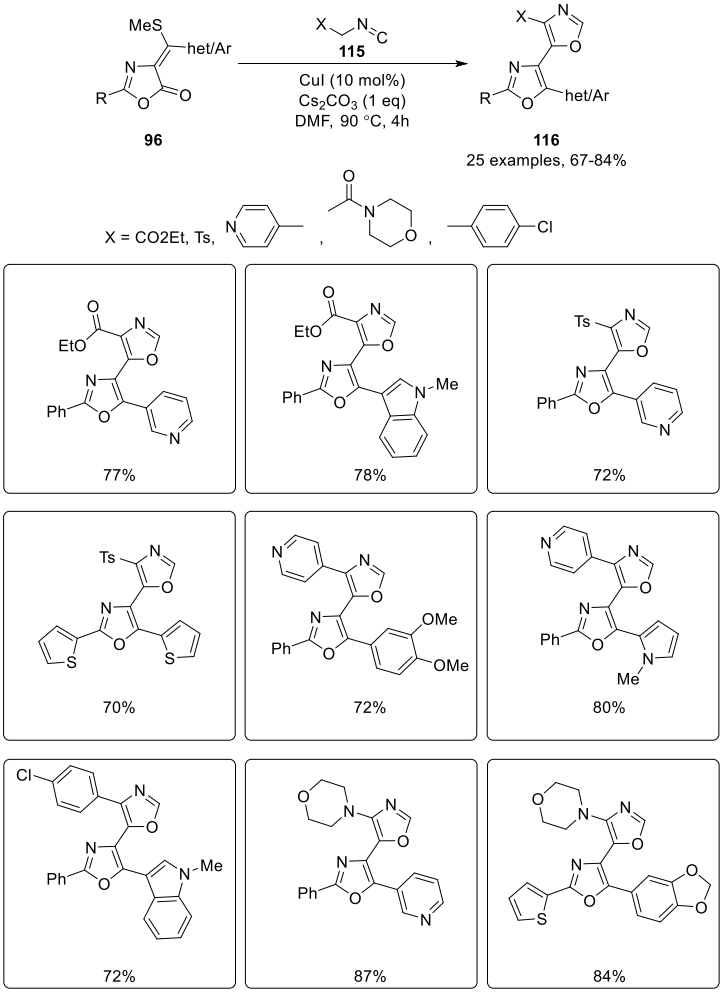
An efficient protocol for the synthesis of 2,5-substituted 4-acyloxazoles (**112**) and 2,4-substituted-5-acyloxazoles (**114**) with complementary regioselectivity, from the corresponding *β*-(het)aryl-(methylthio)enone precursors **109** has been recently reported from our laboratory (Scheme 38).[42] In the first protocol, the intermediates **109** were converted to the corresponding *α*-bromo-*β*-(methylthio)enones **110**, by treatment with NBS, followed by copper catalyzed inter/intramolecular annulation of these intermediates with various primary amides affording 2,5-substituted-4-acyloxazoles **112** *via* concomitant formation of the C4-N and C5-O bonds *via* enamide intermediates **111** (Scheme 38). In the second approach, the starting *β*-(methylthio)enones **109** were subjected to base induced conjugate addition-elimination with various primary amides to furnish *β*-aroylenamides **113,** which on subsequent iodine catalyzed intramolecular oxidative C-H functionalization /C-O bond formation, afforded the corresponding regioisomeric 2-(het)aryl/alkyl-4-(het)aryl-5-(het)aroyloxazoles **114** with complementary regioselectivity in excellent yields (Scheme 38).



Scheme 38

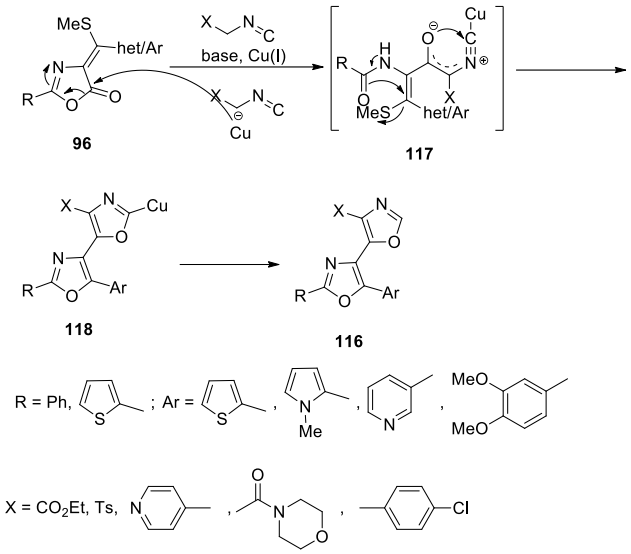
2.8 Domino reactions

Yugandar and others from our laboratory have previously demonstrated,[43] a novel, mild and efficient Cu(I) catalyzed domino process from readily available previously synthesized oxazolones **96** and activated methylene isocyanides **115**, providing a straightforward direct route for diversity oriented synthesis of hitherto unreported 2,5,4'-trisubstituted 4,5'-bisoxazoles **116** (Scheme39).[43] The reaction displays broad substrate scope and excellent functional group compatibility by employing a wide range of substituted oxazolones **96** with diverse het(aryl) groups and activated methylene isocyanides **115** (X= CO_2Et, Ts, 4-pyridyl, 4- ClC_6H_4, morphilinoamide).



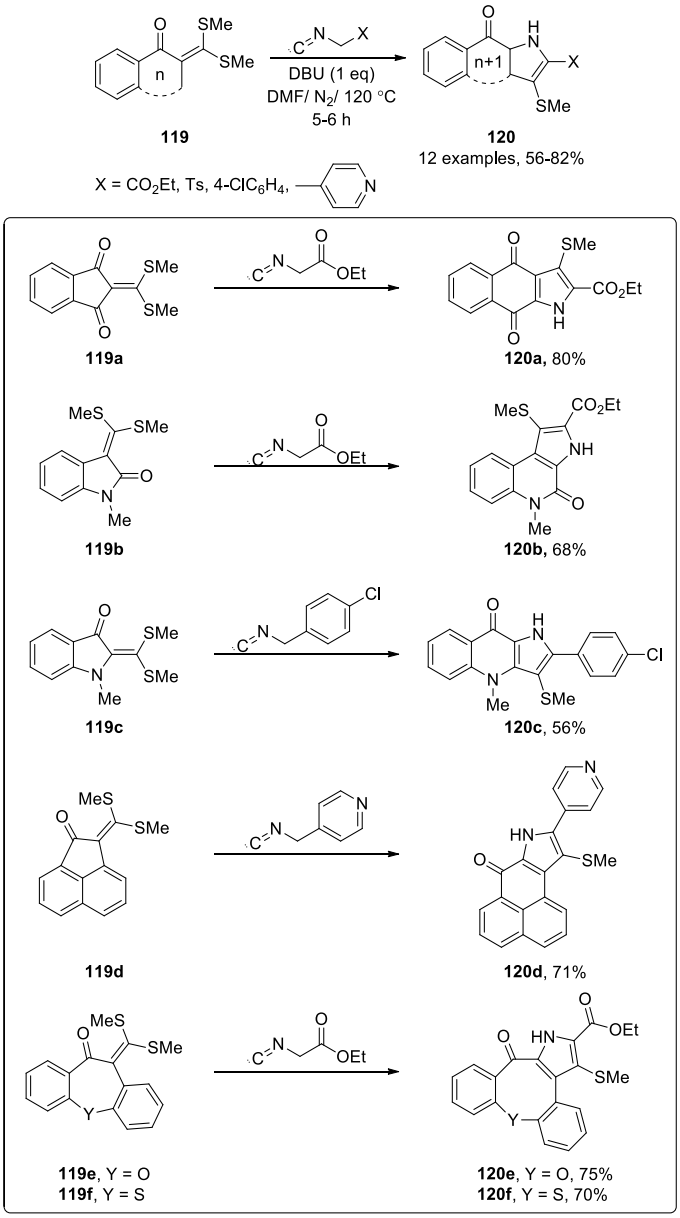
Scheme 39

The overall domino process comprised of the formation of one C-C and two C-O along with two oxazole rings from acyclic intermediate **117 (**Scheme 40). The probable mechanism is shown in the Scheme 40, Thus initial nucleophilic ring opening of **96** by copper complexed isocyanide anion yields the acyclic intermediate **117**, followed by sequential construction of two oxazole ring in presence of copper catalyst through intermediate **118** , affords bisoxazoles **116** in good yields (Scheme 40).[43]



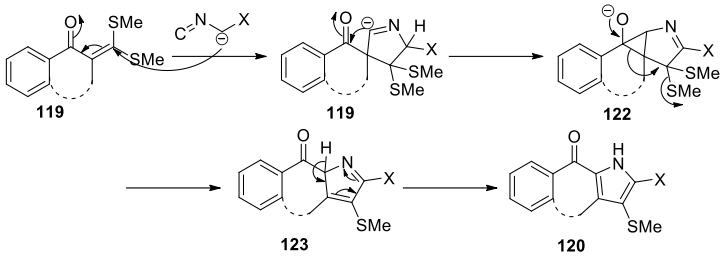
Scheme 40

A highly interesting novel pyrrole annulation ring-expansion domino process, demonstrated in our laboratory, was observed when cyclic ketene *S,S*-acetals of the general structure **119** were reacted with activated methylene isocyanides in presence of DBU as base in DMF at higher temperature, leading to formation of diverse range of annulated pyrroles along with a unexpected unique highly regioselective one carbon ring expansion of cyclic ketones as the key step (Scheme 41).[44] Thus in one example, when 2-(bis)methylthio methylene-1,3-indanedione **119a** was reacted with ethyl isocyanoacetate in presence of DBU as base in DMF at 120 ^{0}C , work up of the reaction mixture furnished only one product characterized as 2-carboethoxy-3-(methylthio)pyrrolo[2,3-*b*]naphthoquinone **120a** (80%), in which five membered ring of 1,3-indanedione has undergone one carbon ring expansion to give pyrroleannulated naphthoquinone(Scheme 41). The method provides facile access to biologically important, fused pyrroles with structures ranging from pyrrolonaphthoquinones (**120a**), angular and linear pyrroloquinolones(**120b-c**)tetracyclic fused indole (**120d**) and pyrrole annulated dibenzooxocinones and dibenzothiocinones **120e-f** (Scheme 41).[44]



Scheme 41

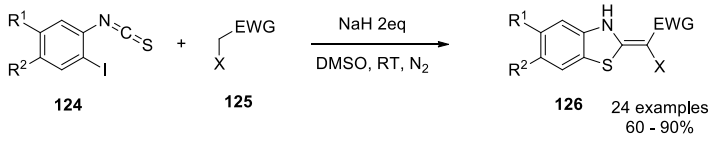
The probable mechanism for the formation of various annulated pyrroles **120** from cyclic ketenedithioacetals **119** is shown in the Scheme 42.Thus initial 1,4-conjugate addition of methylene isocyanide carbanion to **119**, followed by intramolecular cyclization of the adduct initially furnishes the unstable spiropyrrolenine anion **121**,which attacks the carbonyl group of **121** intramoleculary affording highly strained tetracycliuc intermediate **122**, which on subsequent ring expansion along with elimination of methylthioalate anion and isomerization of the resulting intermediate **123**, affords the observed pyrrole annulatred products **120** in good yields(Scheme 42).[44]



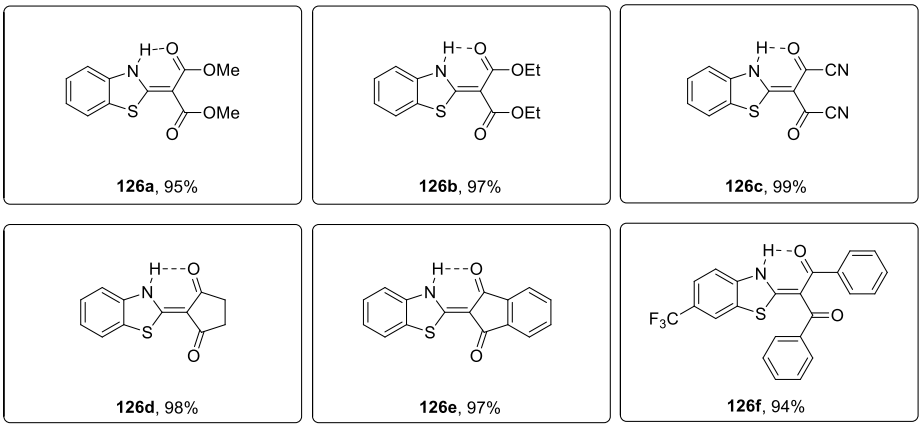
Scheme 42

2.9 Transition metal- free base- promoted C-heteroatom bond formation reactions

Recently Kumar from our laboratory has developed a novel and facile transition metal free domino protocol for the synthesis of 2-substituted benzothiazoles **126** involving tandem base promoted addition-intramolecular cyclization of *o*-iodoarylisothiocyanates **124** and active methylene compounds **125** and subsequent intramolecular C-S bond formation of the resulting thioimidate anion **127**(Scheme 43).[45] The key feature of the synthesis is that the reaction proceeds at room temperature within 1-3 h, in high yields in the absence of any ligands or additives. A possible radical intermediate pathway through an $S_{RN}1$ mechanism has been proposed for the formation of benzothiazoles **126** from **124** and **125** (Scheme 43). Thus, addition of a carbanion from active methylene compound to *o*-iodoarylisothiocyanate **124** affords initially anionic intermediate **127** which undergoes intramolecular electron transfer to the aryl part of **127**, to give radical anion intermediate **128**. Finally the elimination of iodide from **128** affords diradical intermediate **129,** which undergoes intramolecular radical combination to furnish benzothiazoles **126** in excellent yields (Scheme 43).

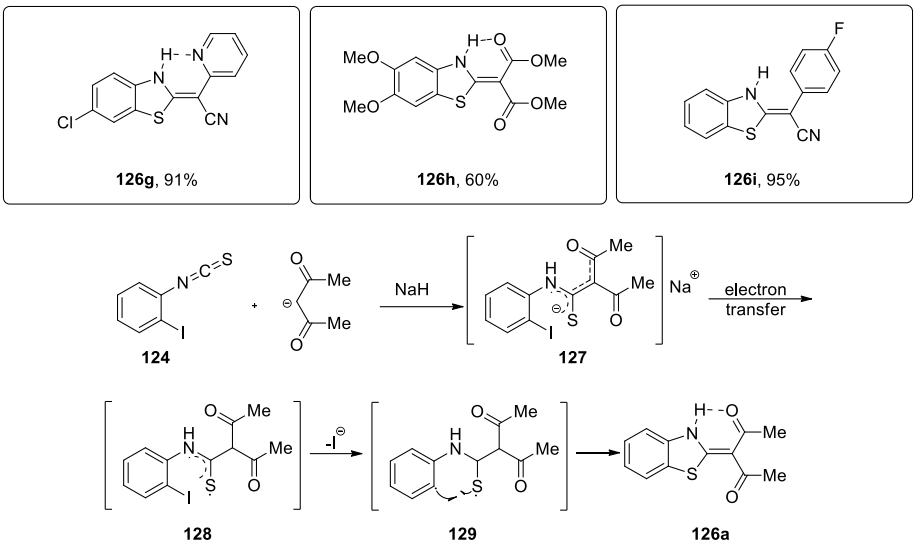


124 **125** **126** 24 examples 60 - 90%



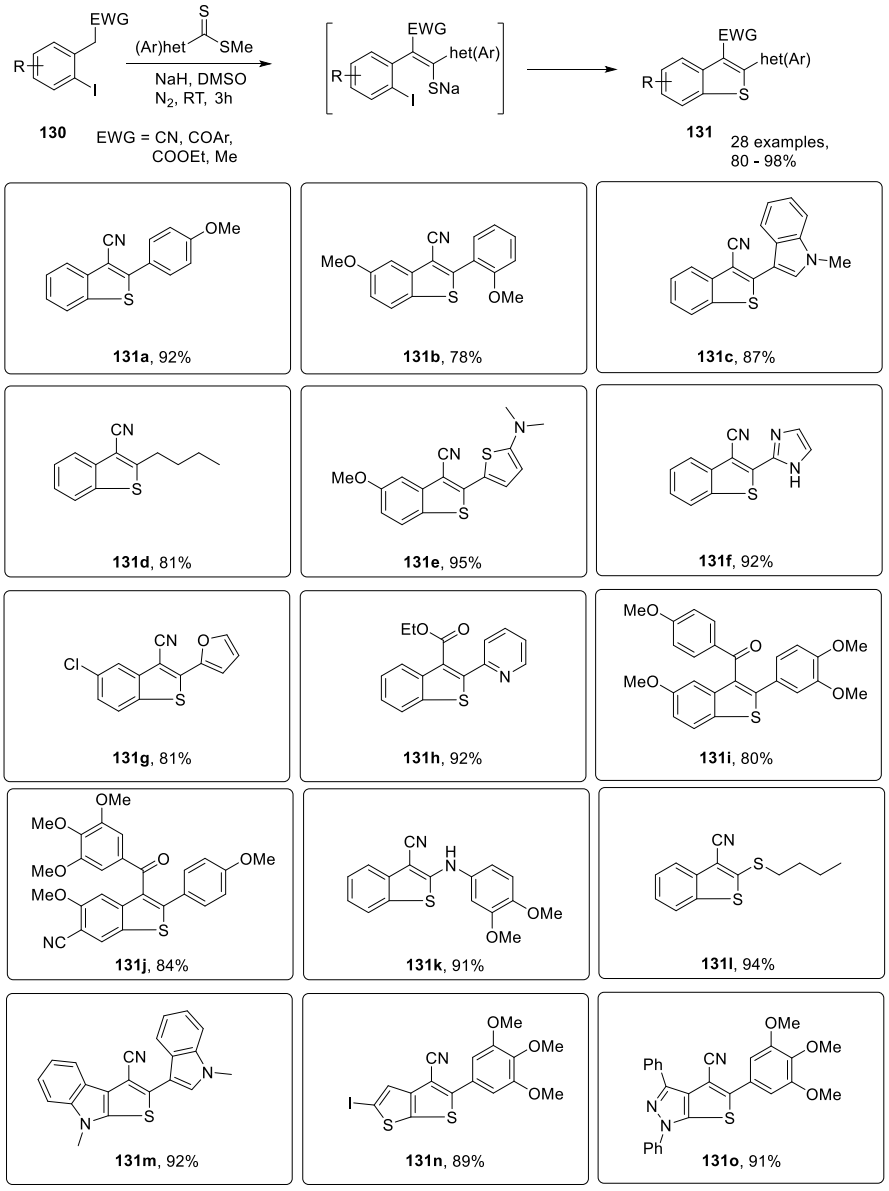
126a, 95% **126b**, 97% **126c**, 99%

126d, 98% **126e**, 97% **126f**, 94%



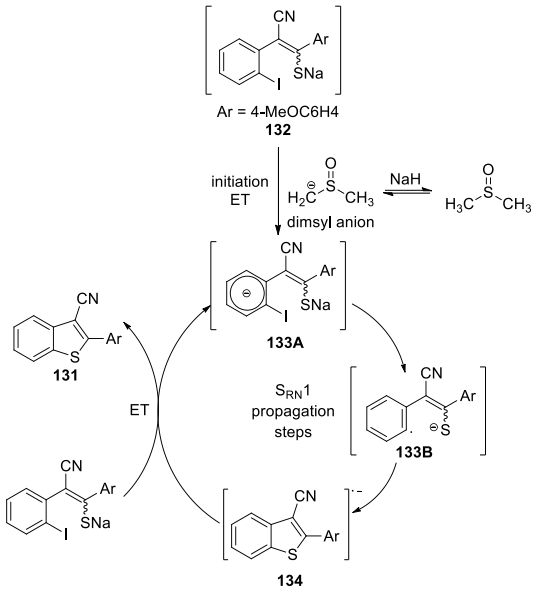
Scheme 43

Kumar from our laboratory has also recently reported another novel TM free protocol for the synthesis of 2,3-substituted benzothiophenes **131** and their hetero analogs (Scheme 44).[46] The reaction involves base mediated tandem addition-cyclization of *o*-iodoarylacetonitriles/acetates /ketones **130** with hetaryl dithioesters through intramolecular C-S bond formation. The new protocol has broad substrate scope and is also applicable for the synthesis of heterosubstituted thiophenes such as **131g-i** (Scheme 44).[46]



Scheme 44

A probable SET mechanism pathway for the formation of benzothiophenes from **130** and dithioesters is shown in the Scheme 45. It is proposed that the radical process is initiated by single electron transfer (SET) from dimsyl anion to thioenolate anion intermediate **132** to afford radical anion species **133A** which undergoes fragmentation to deliver the corresponding aryl radical intermediate **133B** along with iodide ion. Intramolecular trapping of aryl radical by thioenolate anion in the intermediate **133B** furnishes the benzothiophene radical anion **134** which acts as electron donor to starting **132** furnishing the final product **131** and radical anion **133A** (Scheme 45).[46]



Scheme 45

2.10 Conclusion

In the present account, we have highlighted our last ten years research work (2012-2021) based on new building blocks derived either in situ or isolated by base mediated condensation of active methylene compounds with (het)aryldithioesters. It should be noted that this is the first report of synthetic applications of these dithioesters in heterocycle synthesis, which were earlier used only in analytical chemistry. Further work to explore the synthetic application of these intermediates is in progress in our laboratory and will be published.

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Chapter 3

*Single-Pot Preparation of 4-Amino-2-(het)aryl-5-Substituted Thiazoles Employing Functionalized Dithioesters as Thiocarbonyl Precursors**

3.1 Introduction

The thiazole heterocyclic core is present in several biologically active microbial and marine natural products, and also in synthetic compounds[1,2] displaying broad range of biological activity.[3] Thus, several substituted thiazoles exhibit biological activities such as anti-inflammatory, antibacterial, antiviral, antifungal, anticancer, tubulin polymerization inhibitor, CDK inhibitor, and Src/AB1 inhibitor such as Dasatinibs,[3] besides acting as peptidomimetics and enzyme inhibitors (Figure 1).[4] Due to the presence of synthetic thiazoles in various marketed drugs, this heterocyclic core occupies an important place in the drug discovery process.[3,5] Thiazole derivatives have also found applications in material science,[6a] as liquid crystals for ferroelectric displays,[6b] and as cosmetic sunscreens.[6c] As a consequence, considering the structural heterogeneity of complex naturally occurring thiazoles, as well as the biological activity of synthetic analogues, new versatile protocols continue to appear in the literature for the synthesis of multifunctionalized thiazoles.[1,2,7-8]

*****The overall results of study described in this chapter have been published in *J. Org. Chem.* **2021**, *86*, 8508.

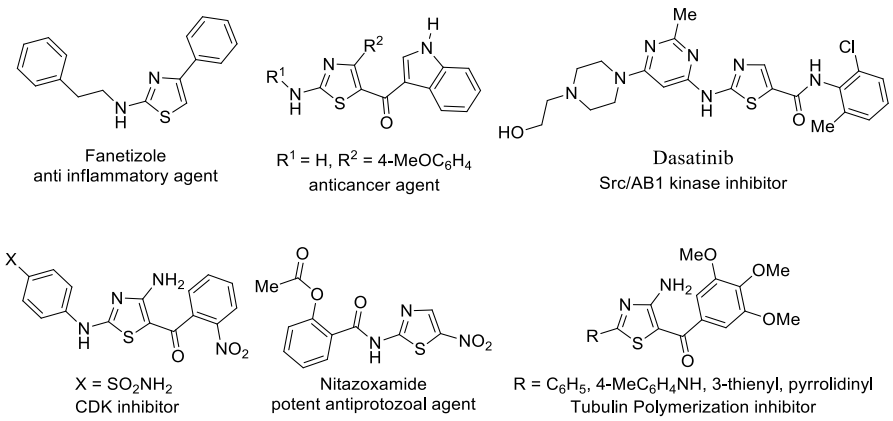


Figure 1. Biologically important multifunctional thiazoles

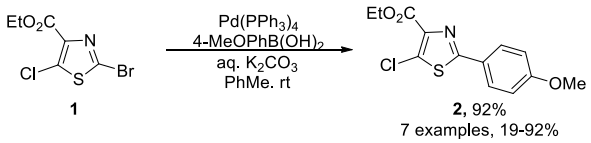
In the present chapter, we have described a novel one-pot synthesis of 4-amino-2-(het)aryl-5-functionalized thiazoles employing (het)aryl dithioesters as thiocarbonyl precursors in modified Thorpe-Ziegler synthesis (Scheme 23). Before coming to our results, a short survey of recent synthesis of substituted thiazoles have been described.

3.2 Synthesis of substituted thiazoles: A short literature survey

There are many methods reported in the literature, for the synthesis of substituted thiazoles. The synthetic approaches are classified into two main groups: derivatization of the heterocyclic core[1,2,8] and constructing the thiazole ring from acyclic precursors.[1,2] The latter route is found to be more versatile in terms of efficiency and diversity generation in functionalized thiazoles.

3.2.1 Synthesis of thiazoles by derivatization of heterocyclic core

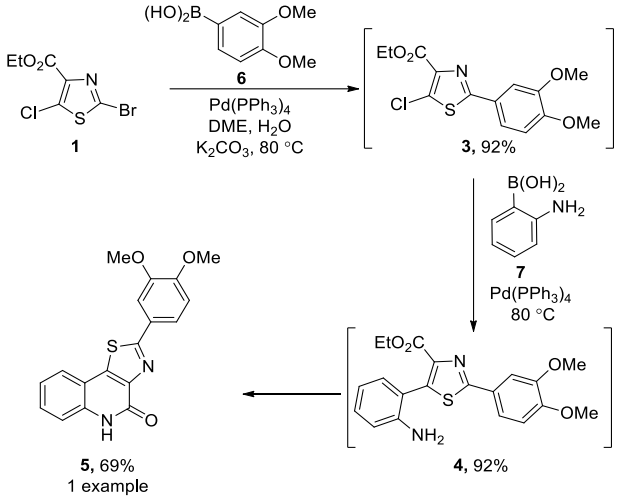
Functionalization of the already existing thiazole core is one of the most common methods for the synthesis of thiazoles. Thus Hodgetts and co-workers have reported regiocontrolled synthesis of 2-aryl-5-chloro-thiazole-4-carboxylates such as **2** via palladium catalyzed Suzuki coupling of 2-bromo-5-chlorothiazole-5-carboxylate **1** (Scheme 1).[8a]



Scheme 1

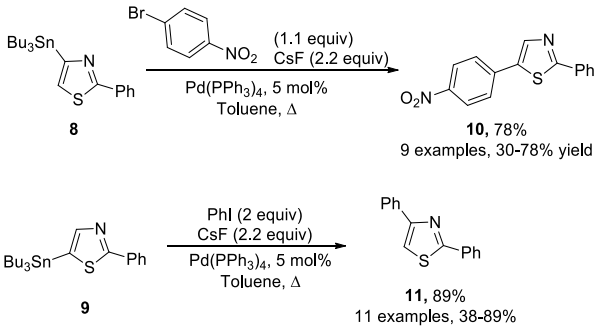
These workers have subsequently extended this strategy for the synthesis of 2-aryl-thiazolo[4,5-*c*]quinoline-4(5*H*)ones **5** by one-pot sequential Suzuki coupling of **1** with

arylboronic acids **6** and **7** followed by in situ intramolecular cyclocondensation of the resulting 2,5-(2-aminophenyl) thiazole carboxylate **4** (Scheme 2).[8b]



Scheme 2

Later in 2008, Stanetty and group have reported regioselective synthesis of 2,5- and 2,4-bis-arylthiazoles **10-11** involving Stille cross-coupling of the corresponding 4- and 5-substituted organotin substituted (stannyl) thiazoles **8-9** (Scheme 3).[8c]

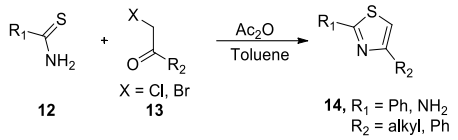


Scheme 3

3.2.2 Synthesis of thiazoles from acyclic precursors

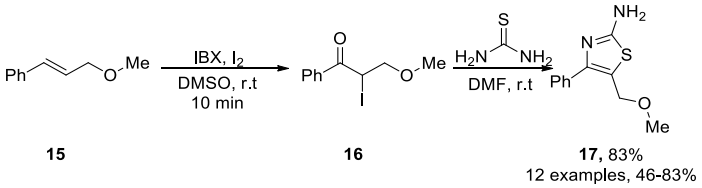
3.2.2.1 Hantzsch synthesis

Hantzsch synthesis is one of the most widely used, reliable and prominent methods for the construction of 2,4,5-trisubstituted thiazoles involving condensation of α-haloketones **12** or its variants with thioamides **13** (Scheme 4).[1,9-10]



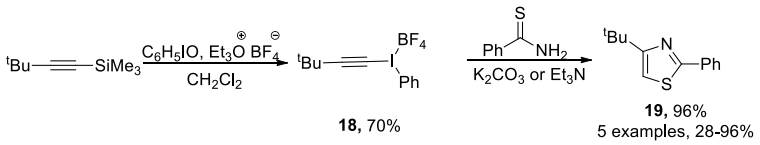
Scheme 4

In recent years, several new variations of Hantzsch synthesis have appeared in the literature.[10a-f] Thus, Smith and co-workers reported a direct preparation of thiazoles and other heterocycles like imidazoles from readily accessible alkenes **15** via two-step ketoiodination with IBX and iodine, to obtain the intermediate iodoketone **16**, followed by its cyclization with thiourea to give 2-amino-4,5-substituted thiazole **17** (Scheme 5). This method displays broad functional group tolerance in alkenes, besides being applicable to *N*-substituted thioureas, alkyl/aryl thioamides as nucleophiles to obtain various thiazoles in good yields (Scheme 5).[10b]



Scheme 5

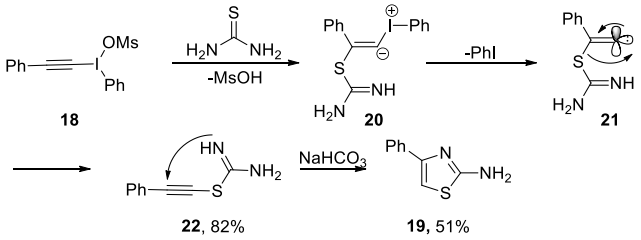
In 2005, Ochiai and co-workers reported an efficient method for the synthesis of substituted thiazoles such as **19** by utilizing 1-alkynyl(phenyl)-λ^3-iodanes salts **18**[10a] instead of α-haloketones as coupling partners with thioamides or thioureas under mild conditions (Scheme 6).[10c] 1-alkynyl(phenyl)-λ^3-iodanes salts **18** were prepared by treating t-butynyltrimethylsilane with iodosylbenzene and triethyloxonium tetrafluoroborate.[10g]



Scheme 6

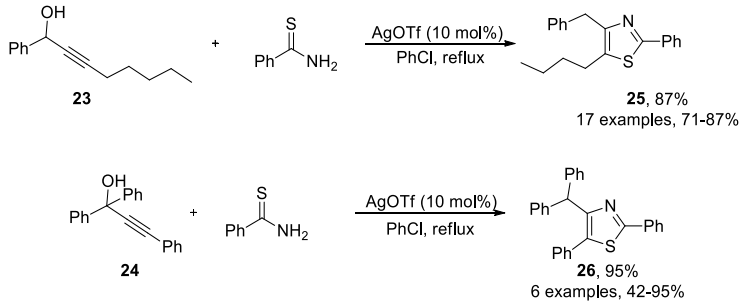
These workers proposed a different mechanism for the reaction, in contrary to the previous mechanism suggested by Wipf and co-workers (Scheme 7).[10a] The reaction proceeds through Michael addition of thiourea to **18**, to give the adduct **20**, followed by α-elimination of iodobenzene to generate alkylidene carbene intermediate **21**, which undergoes 1,2-rearrangement affording the stable 1-(alkynyl)isothiouronium intermediate **22** in excellent

yield. The intermediate **22** could be isolated and transformed into thiazole **19** in moderate yield in the presence of sodium bicarbonate thus further confirming the mechanism (Scheme 7). [10c]



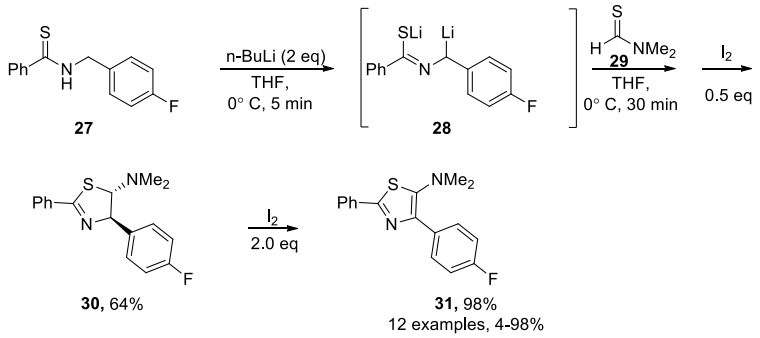
Scheme 7

Zhan and co-workers have developed a novel synthesis of trisubstituted thiazoles such as **25** and **26** in excellent yields via silver triflate catalyzed cyclocondensation of thioamides with secondary and tertiary propargyl alcohols such as **23** or **24** as three carbon electrophilic fragments (Scheme 8).[10d]



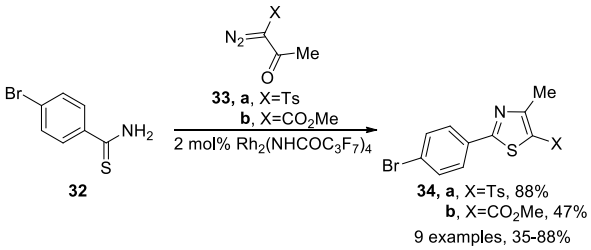
Scheme 8

Maruyama and co-workers have recently reported a new synthesis of 5-(dimethyl)amino-2,4-diarylthiazolines **30** and the corresponding thiazoles **31** through sequence of reaction shown in Scheme 9.[10e] Thus the thioamide dianions **28** derived by treatment of secondary *N*-arylmethyl thioamides **27** with butyl lithium, were reacted with thioformamide **29**, followed by addition of 0.5 equiv of iodine, afforded the thiazoline **30** in 64% yield. Dehydrogenation of 5-amino-2-thiazoline **30** with 2 equiv, of iodine, furnished the corresponding thiazoles **31** in 98% yield (Scheme 9). The thiazoles **31** were found to be highly florescent.[10e]



Scheme 9

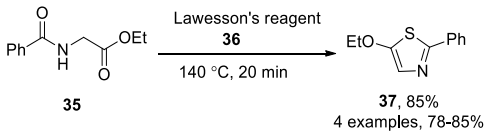
Moody and co-workers have described dirhodium tetraacetate catalyzed reaction of arene thiocarboxamides **32** with α-diazo-β-keto-carboxylates, phosphonates or sulfones such as **33a-b** to afford 2-arylthiazole-4-sulfones **34a** in excellent yields, however yield of thiazole 5- carboxylate by reaction of thioamide with *α*–diazo-*β*-ketocarboxylates **33b** were found to be moderate(Scheme 10).[10f]



Scheme 10

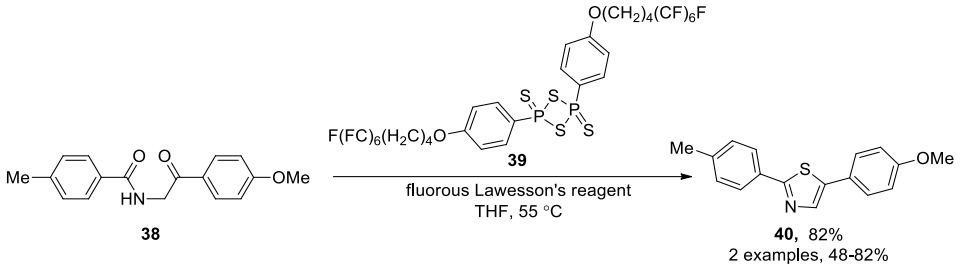
3.2.2.2 Gabriel Synthesis: Synthesis of thiazoles via intramolecular cyclization of α-thioacylaminocarbonyl compounds

Although Hantzsch synthesis is the most commonly used method for thiazole synthesis, it involves several steps to prepare the starting materials *α*-haloketones and thioamides from commercially available compounds. Another promising method for thiazole synthesis is 'Gabriel Synthesis,' which involves intramolecular cyclization of *α*-acylaminoketones **35,** and precursors, in presence of various thionating agents , such as P_2S_5,[11a] Lawesson's[11b-c,12] or Belleau's reagent, to give 2,4,5-trisubstituted thiazoles **37**(Scheme 11).[11c]



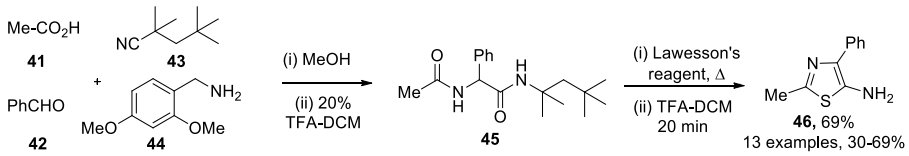
Scheme 11

Lawesson's reagent is widely used in Gabriel synthesis of thiazoles. Dembinski and co-workers have described a synthesis of 2,5-diaryl substituted 1,3-thiazole **40** by thionation of 1,4-diketones **38** using a fluorous analogue of Lawesson's reagent **39**(Scheme 12).[11b]



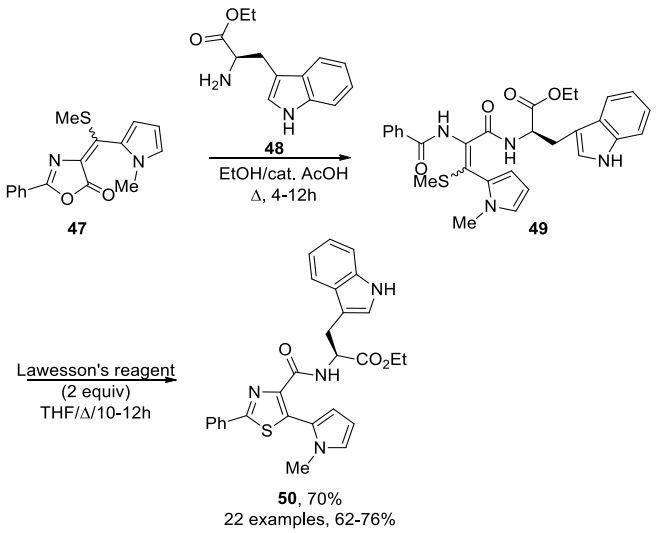
Scheme 12

A versatile assembly of 5-aminothiazoles were prepared by Chen and co-workers in 2008 through Ugi-four-component coupling reaction between **41**-**44** gave diamide adducts **45**, which on cyclization in presence of Lawesson's reagent, followed by deprotection provided 5-aminothiazole **46** (Scheme 13).[12a]



Scheme 13

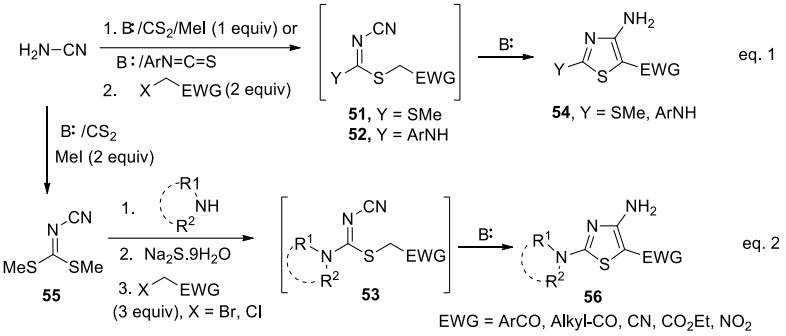
Our research group has recently reported an efficient route to 2-aryl-5-(het)aryl-4-functionalized thiazoles such as **50** *via* one step chemoselective-thionation-cyclization of highly functionalized enamides such as **49,** mediated by Lawesson's reagent (Scheme 14).[2a] These enamide precursors are obtained by nucleophilic ring opening of 2-aryl-4-substituted methylene-5-oxazolones such as **47** with various nucleophile such as alkoxides, amines and aminoacid esters (tryptophan ester **48** in the present case)(Scheme 14).



Scheme 14

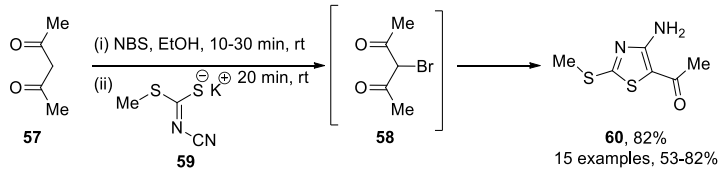
3.2.2.3 Synthesis of thiazoles through Thorpe-Zeigler cyclization

Another attractive method of synthesizing substituted thiazoles includes base mediated intramolecular Thorpe−Zeigler type cyclization of *N*-cyanodi/thioimidate intermediates such as **51**-**53**, which provides a useful synthesis of 4-amino-2,5-substitutedthiazoles (Scheme 15). [13-16]. The intermediates **51** and **52** are generated in situ *via* reaction of cyanamide with either carbon disulfide or arylthiocyanates[13a,16b] respectively in presence of base, followed by successive alkylation with one equivalent of MeI (for **51**) and activated methylene halides furnishing directly the 2-(methylthio/arylamino)-4-amino-5-substituted thiazoles **54** (Scheme 15, eq, 1).[13-16] Kirsch and co-workers have developed an alternate one-pot three component sequential procedure for 2-(*N*-secondaryamino)-4-amino-5-substituted thiazoles **56** *via* stable dimethyl-*N*-cyanodithioimidothioimido carbonates precursor **55**,[14a,b] *via* displacement of one of the -methylthio groups by secondary amine followed by sequential in situ treatment with sodium sulfide and excess of activated methylene halides(Scheme 15, eq. 2). These methods appear to be useful for the synthesis of 4-amino-2,5-substituted thiazoles with various functionalities at 5-position such as ester, nitrile and carbonyl substituents, however substituent diversity at 2-posit ion is limited only to 2-(methylthio) or arylamino functionalities.[13-16]



Scheme 15

Recently Li and co-workers have reported an NBS mediated one pot synthesis of multifunctionalized thiazoles such as **60** from 1,3-dicarbonyl compounds **57** and mercaptonitrile salts **59** under mild conditions (Scheme 16).[15a] This transformation involves sequential bromination/S_N2 alkylation /Thorpe Ziegler cyclization/ regioselective elimination of COR group, affording desired thiazoles in moderate to good yields (Scheme 16).[15a]

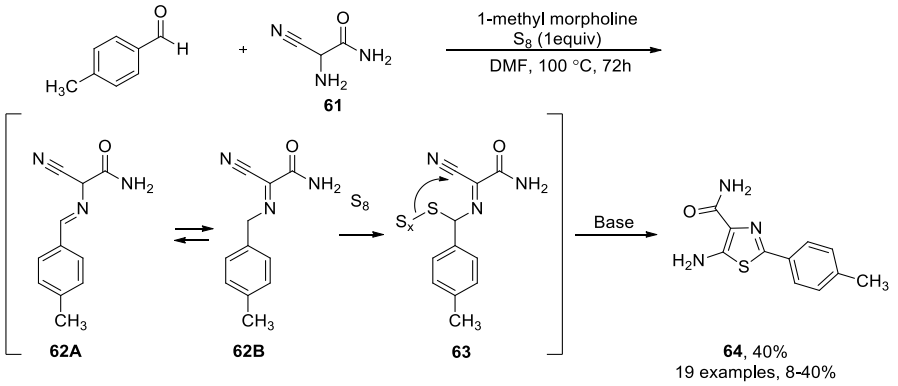


Scheme 16

3.2.2.4 Recent miscellaneous approaches for the synthesis of substituted thiazoles

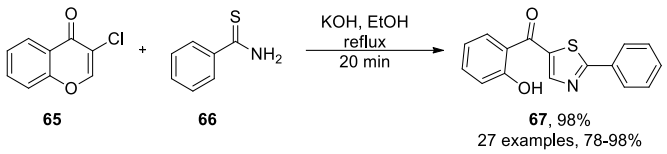
Other than established synthesis of substituted thiazoles as described in above section, several new innovative syntheses of thiazoles have been described in recent years, some of them are shown in the following section.[17a-g]

Childers and co-workers reported a novel one-step, multicomponent reaction to prepare 5-amino-4-carboxamidthiazoles such as **64** although in low yields, based on Gewald reaction (Scheme 17).[17a] Thus when *p*-tolualdehyde and commercially available 2-amino-2-cyanoacetamide **61** are heated in presence of 1-methyl morpholine and sulfur in DMF at higher temperature for prolonged time, the 5-amino-4carboximidothiazole **64** was obtained in 40% yield. The reaction proceeds initially via intermediates **62-63** which undergoes intramolecular cyclization to provide thiazoles in low yields (Scheme 17).[17a]



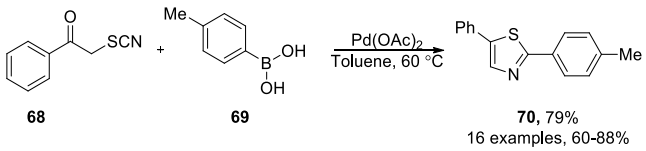
Scheme 17

Yang and co-workers explored a facile and efficient strategy for 2-aryl-5-(2-hydroxybenzoylthiazoles such as **67** via ring opening and cyclization of 3-chlorochromone derivative **65** with thioamide **66** in presence of ethanolic KOH under mild conditions(Scheme 18).[17c]



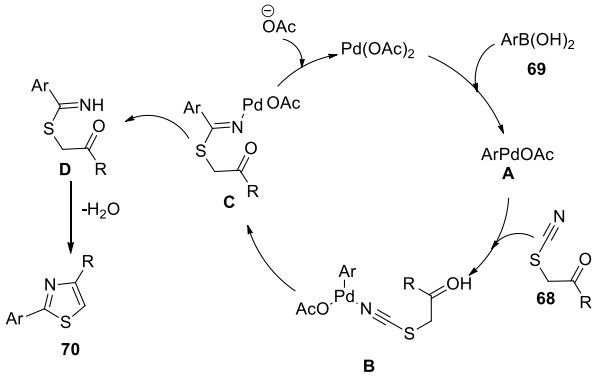
Scheme 18

Yu and co-workers have developed an efficient method to access 2,4-disubstituted thiazoles such as **70** *via* Pd(II) catalyzed C(sp)-C(sp^2) coupling of phenacyl isothiocyanate **68** and aryl boronic acid **69**, followed by intramolecular C-N bond formation, under ligand free conditions (Scheme 19).[17d]



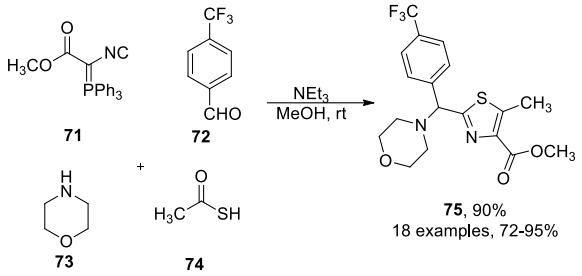
Scheme 19

The mechanism of thiazole formation involves transmetalation of palladium acetate and arylboronic acid to give arylpalladium intermediate **A**, which on coordination with the N-atom of cyano group of **68** yields N-coordinated palladium intermediate **B**. Insertion of aryl group into the nitrile group, generates Pd(II) ketimine complex **C**, which on cleavage with acetate ion yields ketimine derivative **D**, which on intramolecular condensation affords the product thiazole **70** (Scheme 20).[17d]



Scheme 20. Mechanism of thiazole formation from Pd(II) catalyzed coupling of **68** and **69**

Ding and co-workers have developed a new four component synthesis of polysubstituted thiazoles such as **75** *via* cascade Ugi/Wittig cyclization (Scheme 21).[17e] Thus four component reaction of the odorless isocyano(triphenylphosphoranylidene)acetate **71** , aldehyde **72**, amine **73** and thiocarboxylic acid **74** produces 2,4,5-trisubstituted [17e] thiazoles **75** in moderate to good yields(Scheme 21).

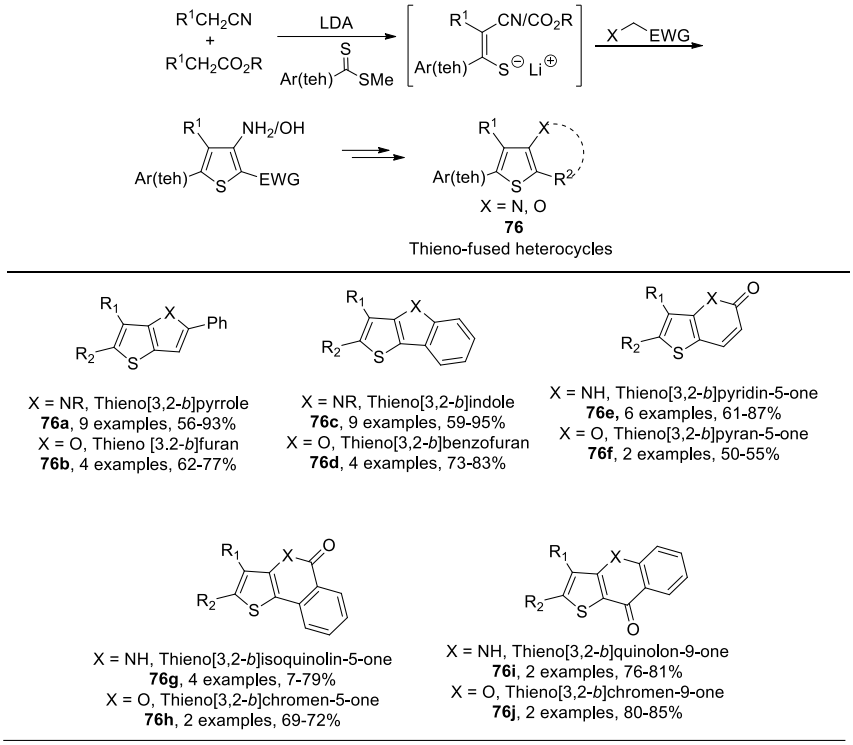


Scheme 21

Since the past few years, we have been exploring newly designed organosulfur intermediates[18–21] which are readily obtained by the condensation of the appropriate active methylene derivatives with functionalized dithioesters in the presence of base, followed by alkylation of the generated enethiolate intermediates (discussed in detail in Chapter 1). By utilizing these precursors, we have developed new synthetic routes for a variety of (het)aryl/ alkylsubstituted, sulfur containing, as well as sulfur-free five membered heterocycles,[20,20a] such as pyrazoles, isoxazoles, oxazoles, imidazoles, thiophenes,[20a] thiazoles,[2] and the corresponding benzo/heterofused analogues, i.e., indoles,[19c], benzothiophenes,[19b,e,21] and benzofurans.[19f] These methods (discussed in detail in Chapter 1) provide alternate way for regiospecific introduction of (het)aryl groups in various heterocycles from built-in precursors by utilizing (het)aryl/alkyldithioesters, instead of transition metal catalyzed coupling reactions.[8] Although the synthesis of various (het)aryl/alkyldithioesters has been previously described in the

literature,[22] their potential synthetic applications as thiocarbonyl coupling partners for the synthesis of various (het)aryl/alkyl substituted heterocycles had not been explored until we undertook their systemic investigation.

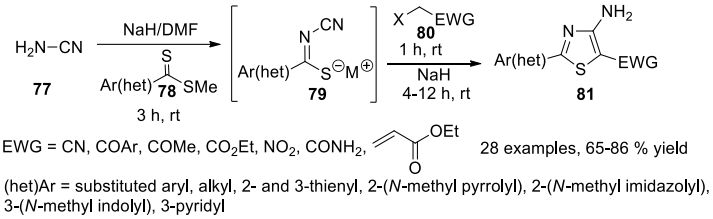
During the course of above studies, we have recently reported an efficient one-pot Thorpe−Ziegler type construction of 2-(het)aryl-3-substituted-4-amino/hydroxythiophenes with several reactive functionalities at 5 positions, by condensation of various arylacetonitriles (or arylacetates) with broad range of (het)aryldithioesters as thiocarbonyl precursors and activated methylene halides in the presence of a base. These 4-amino(hydroxy)-5-functionalized thiophenes were subsequently transformed into thieno-fused 5- or 6- membered nitrogen/oxygen heterocycles either in a one-pot protocol or in a two-step procedure (Scheme 22).[21]



Scheme 22

As a continuation of these research works, we additionally thought of employing these (het)aryl/alkyldithioesters **78** as thiocarbonyl coupling partners in a modified Thorpe−Ziegler synthesis for developing an effective one-pot construction of 4-amino-2-(het)aryl/alkyl-5-functionalized thiazoles, which could be subsequently elaborated into thiazolo-fused nitrogen heterocycles.[23] We have successfully realized this target and presented in this chapter a concise

one-pot, three step, diversity oriented construction of a series of 2-substituted-4-amino-5-functionalized thiazoles **81** (Scheme 23).

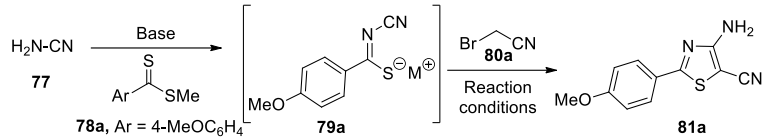


Scheme 23

3.3 Results and Discussion

The dithioester **78a** and bromoacetonitrile **80a** were selected as model substrates, to study their reaction with cyanamide, in the presence of various bases/solvents, with a view to optimize reaction conditions, to develop one-pot procedure for the synthesis of thiazole **81a**, without isolation of *N*-cyanothioimidate salt **79a** (Table 1). Thus, the reaction of cyanamide with dithioester **78a** using excess of NaH (4 equiv), followed by addition of bromoacetonitrile **80a** afforded the thiazole **81a** in only 53% yield along with other side products (entry 1). However, dramatic increase in the yield of **81a** was observed when NaH was added sequentially, i.e., cyanamide was initially reacted with dithioester **78a** in the presence of 2 equivalents of NaH, followed by addition of bromoacetonitrile **80a**, and subsequent addition of 2 equivalents of NaH (entry 2). Reducing the amount of NaH resulted in decreased yield of thiazole **81a** (entry 3). Similarly, at higher temperature, lower yield of **81a** was obtained (entry 4).

Table 1. Optimization of the Reaction Conditions for One-Pot Synthesis of Thiazole 81a[a]



entry	base	solvent	temperature (°C)	time (h)	%yield, **3a**[a]
1[b]	NaH	DMF	rt	3	53
2[c]	NaH	DMF	rt	**3**	**76**
3[d]	NaH	DMF	rt	6	55
4[e]	NaH	DMF	90	2	62
5[f]	K_2CO_3	DMF	rt	24	0
6[f]	K_2CO_3	DMF	70	12	68
7[f]	Et_3N	EtOH	rt	12	0
8[f]	Et_3N	EtOH	60	12	52
9[f]	KOH	EtOH	80	12	20
10[f]	MeONa	MeOH	rt	12	0
11[f]	MeONa	MeOH	65	12	30
12*f*	^{t}BuOK	DMF	rt	24	45
13[f]	^{t}BuOK	DMF	90	12	70

[a]Reaction conditions: **78a** (1 mmol), cyanamide (1 mmol) and **80a** (1.2 mmol). [b]Reaction was conducted with 4 equiv. of NaH in the first step. [c]NaH (2 equiv) and cyanamide (1 equiv) were stirred in DMF for 10 minutes, followed by addition of **78a** (1 mmol) and further stirring for 3 h, and subsequent addition of **80a** (1.2 mmol), after further stirring for 1 h, NaH (2 equiv) was added. [d]2 equivalents of NaH was used. [e]Reaction was conducted by sequentially adding 2 equivalents of NaH, and heating at 90 °C (oil bath). [f]All reactions were conducted by sequentially adding 2 equivalents of base.

On the other hand, no reaction was observed, when weaker bases like K_2CO_3 or Et_3N were employed at rt (entries 5, 7), whereas at higher temperature, moderate yields of **81a** were obtained (entries 6, 8). Similar behavior was also observed with bases like KOH or NaOMe in solvents like EtOH or MeOH, respectively, yielding thiazole **81a** in low yields at higher temperature (Table 1 entries 9-11). However, good yield of **81a** was obtained with ^{t}BuOK as base, although at higher temperature after prolonged heating (oil bath) (entries 12-13). We therefore employed NaH as base for optimal reaction conditions, by its sequential addition in two lots at rt in DMF as solvent for our further studies (Table 1, entry 2).

With the optimized reaction conditions in hand, for one-pot synthesis of thiazole **81a**, we next examined the scope and generality of this protocol and the results are displayed in Scheme 24-26. Various (het)aryl/alkyldithioesters **78** and activated methylene halides **80**, selected for this study are shown in Chart 1 and Chart 2.

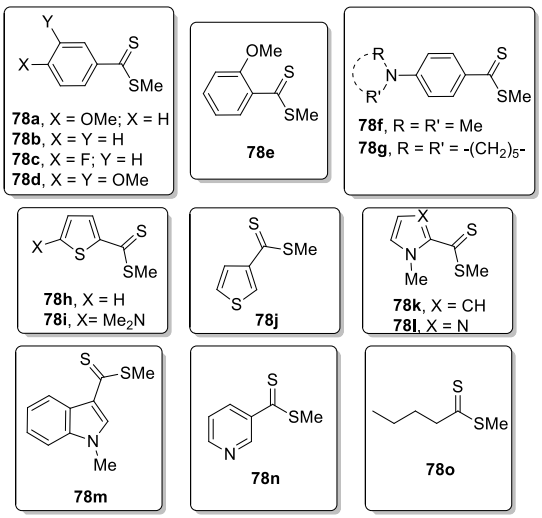


Chart 1. (Het)aryl/alkyldithioesters **78** employed for the synthesis of functionalized thiazoles **81**, **82**

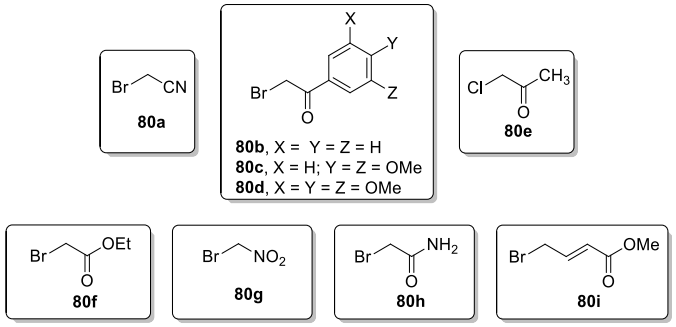
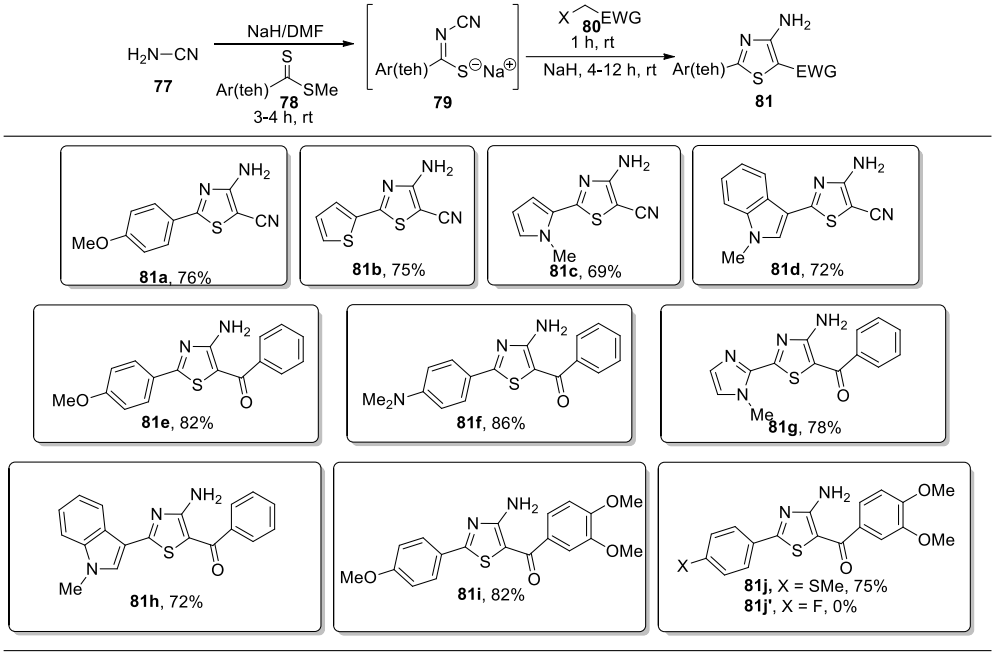


Chart 2. Activated methylene halides **80** employed for the synthesis of functionalized thiazoles **81, 82**

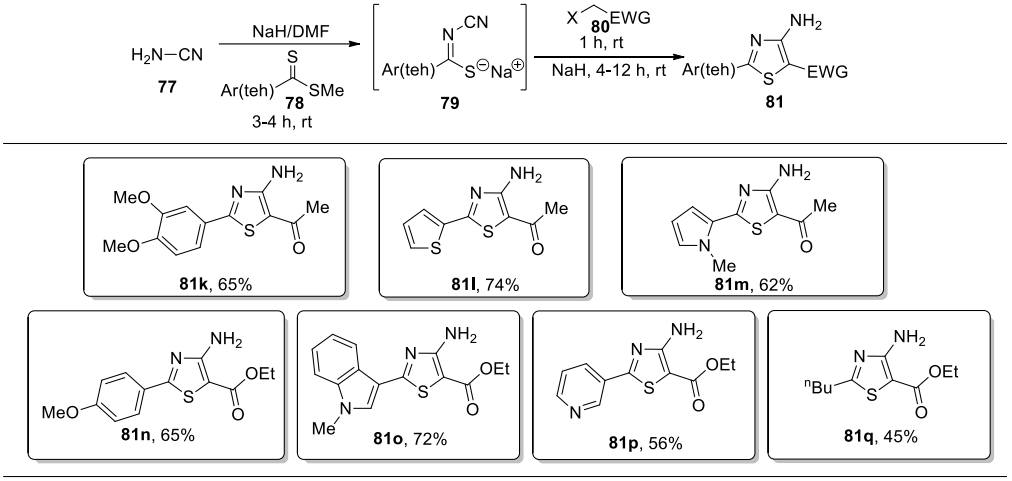
Thus both aryl- (**78a**) and (het)aryldithioesters with 2-thienyl(**78h**)-,2-(*N*-methylpyrrolyl) (**78k**) and 3-(1-*N*-methyl)indolyl-(**78m**) moieties reacted smoothly with cyanamide **77** and bromoacetonitrile **80a** in sequential manner, to afford the corresponding 2-(het)aryl-4-amino-5-cyanothiazoles **81a-d** in excellent yields (Scheme 24). The reaction was next extended to phenacyl bromide **80b** and its dimethoxy-variant **80c** for the synthesis of 2-(het)aryl-4-amino-5-aroylthiazoles **81e-j** (Scheme 24). Thus, the thioimidate salts obtained from cyanamide and aryldithioesters **78a**,**78f** and (het)aryldithioesters **78l-m**, reacted smoothly with phenacyl bromides **80b-c** affording the related thiazole **81e-i** in high yields. Interestingly, when the 4-fluorophenyl dithioester **78c** was employed in the reaction with phenacyl bromide **80c**, product thiazole was characterized as 2-[(4-methylthio)phenyl]-4-amino-3-arylthiazoles **81j**, in which the 4-fluoro group was replaced by methylthio group (eliminated during the reaction) via S_NAr process (Scheme 24) and no trace of the corresponding 2-(4-fluoro)phenylthiazole **81j'** could be isolated from the reaction mixture.



Scheme 24. Synthesis of 2-(het)aryl-4-amino-5-cyanothiazoles **81a-d** and 2-(het)aryl-4-amino-5-aroylthiazoles **81e-j**[a]

[a]Reaction conditions. H_2N-CN (1 mmol), NaH (2 mmol), **78** (1 mmol) in DMF (2-3 mL) stirred at rt for 3 h, followed by addition of **80** (1.2 mmol) in DMF (1 mL) and addition of NaH (2 mmol) and further stirring for 4 h.

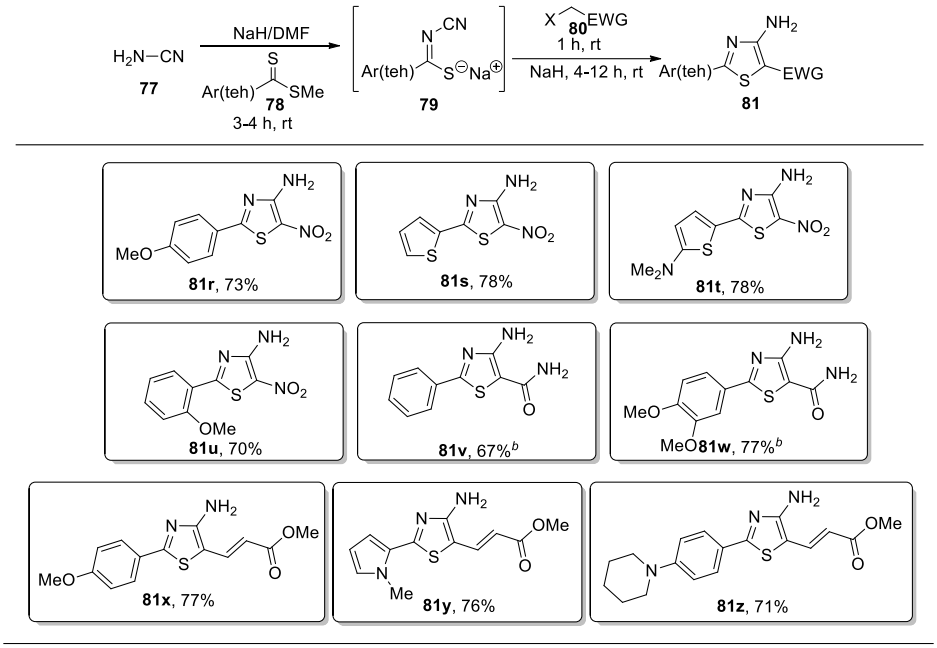
Further diversity in terms of various functionalities at 2 and 5-position of thiazoles **81** was achieved by using activated methylene halides like chloroacetone **80e** and ethyl bromoacetate **80f**, which on reaction with cyanamide and the corresponding dithioesters furnished the respective 4-amino-5-acetyl-thiazoles(**81k-m**) and 4-amino thiazole-5-carboxylates **81n-p** in high yields. The scope of reaction was further widened by the synthesis of 2-(*n*-butyl)-thiazole **81s**, 4-carboxylates **81q** with a 2-alkyl side chain in moderate yield(Scheme 25).



Scheme 25. Synthesis of 4-amino-5-acetyl-thiazoles **81k-m** and 4-amino thiazole-5-carboxylates **81n-q**[a]

[a]Reaction conditions. H_2N-CN (1 mmol), NaH (2 mmol), **78** (1 mmol) in DMF (2-3 mL) stirred at rt for 3 h, followed by addition of **80** (1.2 mmol) in DMF (1 mL) and addition of NaH (2 mmol) and further stirring for 4 h.

Similarly, by utilizing bromonitromethane **80g** as active methylene halide coupling partners and (het)aryldithioesters **78a**, **78e**, **78h-i**, as thiocarbonyl components, it was possible to synthesize novel 2-(het)aryl-5-nitro 4-aminothiazoles **81r-u** in excellent yields, thus adding further diversity at 5-position of thiazoles **81** (Scheme 26). The thiazole **81t** was found to be highly fluorescent. We further extended the reaction for the synthesis of 2-(het)aryl-4-aminothiazole-5-carboxamides **81v-w** by reacting the corresponding thioimidate salts **79** with bromoacetamide **80h**, however the reaction require longer time (24 h) for completion yielding the products **81v-w** in good yields(Scheme 26). Finally, we could also synthesize 2-substituted 4-aminothiazole-5-acrylates **81x-z**, with extended conjugation, in good yields, by reaction of few dithioesters **78a**, **78g**, **78k** with ethyl bromocrotonate **80i** under identical conditions (Scheme 26).

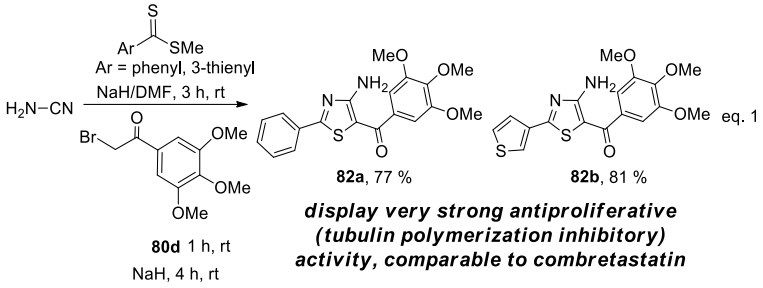


Scheme 26. Synthesis of 2-(het)aryl-5-nitro 4-aminothiazoles **81r-u**, 2-(het)aryl-4-aminothiazole-5-carboxamides **81v-w**, and 2-substituted 4-aminothiazole-5-acrylates **81x-z**[a]

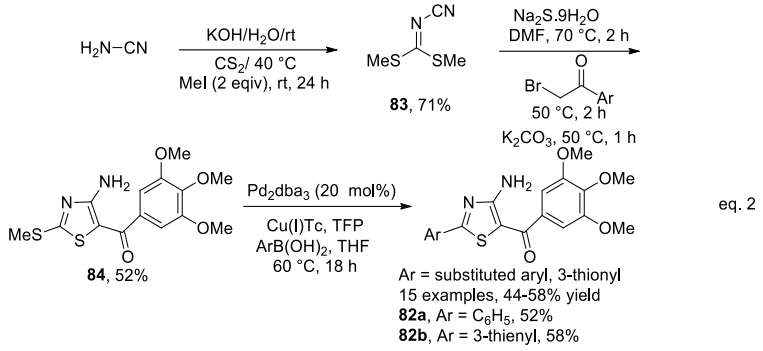
[a]Reaction conditions. H_2N-CN (1 mmol), NaH (2 mmol), **78** (1 mmol) in DMF (2-3 mL) stirred at rt for 3 h, followed by addition of **80** (1.2 mmol) in DMF (1 mL) and addition of NaH (2 mmol) and further stirring for 4 h [b]stirred for 12 h. Yield of isolated products.

To further demonstrate the versatility of this newly developed methodology, we also synthesized 4-amino-2-phenyl- and 2-(thiophen-3-yl)-5-(2,3,4-trimethoxybenzoyl) thiazoles **82a-b** in high yields, which are shown to display very strong antiproliferative (tubulin polymerization inhibitory) activity, comparable to combretastatin,[24] through this one pot protocol, by employing (trimethoxy)phenacyl bromide **80d** and phenyl-, 3-thienyl- dithioesters **78b** and **78j** respectively under optimized conditions. On the other hand, previously, these compounds have been obtained in moderate yields in three steps from cyanamide by first converting it to *N*-cyanoimidodithiocarbonate **83**,[15a,15c] and then successively reacting it with sodium sulfide, trimethoxyphenacyl bromide in presence of K_2CO_3, furnishing the corresponding 2-(methylthio)-4-amino-5-(trimethoxybenzoyl)thiazole **84** in 52% yield (Scheme 27). Subsequent palladium catalyzed, Cu(I)Tc mediated Liebeskind-Srogl coupling of 2-methylthio- group in **84** with respective arylboronic acids in the presence of TFP, provided 2-phenyl- and 2-(thiophen-3-yl)-4-amino-5-(trimethoxy)benzoyl thiazoles **82a-b** in moderate yields of 52% and 58% respectively (Scheme 27, eq 2).[24]

Present Synthesis



Previous synthesis from cyanamide



Scheme 27. Synthesis of Antiproliferative Tubulin Polymerization Inhibitors **82a-b**

In summary, an efficient, straightforward, one-pot protocol for the synthesis of 4-amino-2-(het)aryl-5-substituted thiazoles, by employing a broad range of (het)aryl/alkyldithioesters as thiocarbonyl partners and a variety of activated methylene halides, has been developed. Since some of these thiazoles display significant biological activity, the present methodology enables preparation of thiazoles having two points of diversity and is highly flexible and amenable for the high through-put chemical synthesis of thiazole based libraries. Further, these 4-aminothiazoles **81** bearing a range of functionalities at 5-position serve as potentially useful building blocks for the synthesis of thiazolo-fused nitrogen heterocycles,[23] through subsequent derivatization of these functionalities, which is presently under progress, in our laboratory and will be published later.

3.4 EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All reactions were monitored by thin layer chromatography (TLC) using standard thin-layer chromatography 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 Brucker (400 MHz) ultrashield plus FT-NMR spectrometer with $CDCl_3$, DMSO-d_6 as solvents. Chemical shifts were reported in δ ppm using either residual solvent protons as internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-$d_6$in ^{1}H NMR, δ 77.16 for $CDCl_3$, δ 39.52 for DMSO-d_6 in ^{13}C NMR) or TMS as internal standard. Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sextet (sextet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), m (multiplet), and br (broad). Infrared spectra of neat samples were recorded in attenuated total reflectance mode using Fourier transform infrared instrument (Agilent technologies) and HRMS on a 6538 UHD accurate mass Q-TOF LC/MS spectrometer through electron spray ionization (ESI) mode. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. The precursors **80a**, **80b**, **80e-i** were purchased from commercial suppliers, whereas **80c**,[25] **80d**[26] were prepared according to the reported procedures. The methyl (het)/aryl/alkyldithioester compounds **78a-o** were prepared according to the reported procedures.[20a,22]

General procedure for the synthesis of thiazoles 81a-z, 82a-b.

To a stirred and ice-cooled suspension of NaH(60% suspension in mineral oil) (67 mg, 2.0 mmol, 2.0 equivalents)and appropriate dithioester **78** (1.0 mmol, 1.0 equivalent) in DMF (2 mL), solution of cyanamide (42 mg, 1.0 mmol, 1.0 equivalent) in DMF (1 mL) was added, under N_2 atmosphere. After further stirring at room temperature for 3 h, a solution of activated methylene halides **80**(1.2 mmol, 1.2 equivalents) in DMF (1 mL) was added to the reaction mixture at 0 °C, along with addition of another lot of NaH(60% suspension in mineral oil)(67 mg, 2.0 mmol, 2.0 equivalents) after 1 hr. The stirring was continued at room temperature for 4 h (monitored by TLC), and the reaction mixture was then quenched with saturated NH_4Cl solution (25 mL) and extracted with EtOAc (2×25mL). The combined organic layer was washed with water (3×25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the crude residue was purified by silica gel chromatography.

4-amino-2-(4-methoxyphenyl)thiazole-5-carbonitrile (81a). Yield 176 mg (76%) from 200 mg (1 mmol) of **78a**, 144 mg (1.2 mmol) of **80a**; yellow solid; mp 202−204 °C; R_f 0.2 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 3213, 2195, 1023; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.25 (brs, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.6, 166.2, 162.1, 128.1, 124.4, 114.8, 114.7, 67.7, 55.5; HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{11}H_{10}N_3OS$ 232.0545, found 232.0537.

4-amino-2-(thiophen-2-yl)thiazole-5-carbonitrile (81b). Yield 155 mg (75%) from 175 mg (1 mmol) of **78h**, 144 mg (1.2 mmol) of **80a**; yellow solid; mp 200−202 °C; R_f 0.2 (6:4

EtOAc/hexane); IR (neat, cm^{-1}) 3213, 3172, 2925, 2194, 704; ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 3.6 Hz, 1H), 7.30 (brs, 2H), 7.19 (t, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.8, 163.4, 135.2, 131.3, 129.2, 128.9, 114.6, 67.9; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_6N_3S_2$ 208.0003, found 207.9983.

4-amino-2-(1-methyl-1*H*-pyrrol-2-yl)thiazole-5-carbonitrile (81c).Yield 140 mg (69%) from 170 mg (1 mmol) of **78k**, 144 mg (1.2 mmol) of **80a**; yellow solid; mp 210−212 °C; R_f 0.21 (7:3 EtOAc/hexane); IR (neat, cm^{-1}) 3390, 3351, 2194;^1H NMR (400 MHz, $CDCl_3$) δ6.78 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 4.0, 1.6 Hz, 1H), 6.15 (dd, J = 4.0, 2.4 Hz, 1H), 5.01 (brs, 2H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ 164.6, 163.8, 128.9, 125.5, 115.0, 114.7, 109.3, 70.7, 37.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_9H_9N_4S$ 205.0548, found 205.0556.

4-amino-2-(1-methyl-1*H*-indol-3-yl)thiazole-5-carbonitrile (81d). Yield 182 mg (72%) from 220 mg (1 mmol) of **78m**, 144 mg (1.2 mmol) of **80a**; yellow solid; mp 208−210 °C; R_f 0.2 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3412, 3356, 2197, 1251;^1H NMR (400 MHz, DMSO-d_6) δ8.21 (s, 1H), 8.13 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.33-7.25 (m, 2H), 7.13 (brs, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.9, 165.3, 137.1, 132.4, 124.4, 122.9, 121.6, 120.3, 115.5, 110.9, 108.6, 64.5, 33.1; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{13}H_{11}N_4S$ 255.0704, Found 255.0681.

4-amino-2-(4-methoxyphenyl)thiazol-5-yl)(phenyl)methanone(81e). Yield 255 mg (82%) from 200 mg (1 mmol) of **78a**, 239 mg (1.2 mmol) of **80b**; yellow solid; mp 208−210 °C; R_f 0.25 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3412, 3375, 1594;^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 6.8 Hz, 2H), 7.55-7.47 (m, 3H), 6.95 (d, J = 8.8 Hz, 4H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.3, 172.5, 165.5, 162.7, 141.2, 131.4, 128.7, 128.6, 127.7, 125.6, 114.5, 102.4, 55.6; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_2S$ 311.0854, found 311.0851.

(4-amino-2-(4-(dimethylamino)phenyl)thiazol-5-yl)(phenyl)methanone (81f). Yield 277 mg (86%) from 210 mg (1 mmol) of **78f**, 239 mg (1.2 mmol) of **80b**; yellow solid; mp 215−217 °C; R_f 0.26 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3362, 2920, 1604;^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.52-7.46 (m, 3H), 6.97 (brs, 2H), 6.68 (d, J = 8.8 Hz, 2H), 3.06 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.9, 173.7, 165.8, 152.9, 141.5, 131.2, 128.6, 128.5, 127.7, 120.5, 111.6, 101.6, 40.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{18}H_{18}N_3OS$ 324.1171, found 324.1150.

(4-amino-2-(1-methyl-1*H*-imidazol-2-yl)thiazol-5-yl)(phenyl)methanone (81g).Yield 221 mg (78%) from 172 mg (1 mmol) of **78l**, 239 mg (1.2 mmol) of **80b**;yellow solid; mp 205−207

°C; R_f 0.23 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3241, 3193, 1611, 1324; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.14 (s, 1H), 7.04 (s, 1H), 6.87 (brs, 2H), 4.13 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ187.8, 165.1, 163.3, 140.8, 139.9, 131.7, 130.2, 128.6, 127.9, 125.6, 102.7, 35.9; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{14}H_{13}N_4OS$ 285.0810, found 285.0782.

(4-amino-2-(1-methyl-1*H*-indol-3yl)thiazol-5-yl)(phenyl)methanone(81h).Yield 239 mg (72%) from 220 mg (1 mmol) of **78m**, 239 mg (1.2 mmol) of **80b**;yellow solid; mp 220−222 °C; R_f 0.22 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3387, 3160, 1718;^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.6 Hz, 1H), 7.84 (d,J = 9.6 Hz, 3H), 7.51-7.45 (m, 3H), 7.33-7.29 (m, 3H), 7.06 (brs, 2H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ186.7, 168.1,165.5, 141.6, 137.7, 131.6, 131.1, 128.5, 127.7, 125.2, 123.3, 122.1, 121.1, 110.6, 110.3, 100.7, 33.6; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{19}H_{16}N_3OS$ 334.1014, found 334.1012.

(4-amino-2-(4-methoxyphenyl)thiazol-5-yl)(3,4-dimethoxyphenyl)methanone (81i). Yield 303 mg (82%) from 200 mg (1 mmol) of **78a**, 311 mg (1.2 mmol) of **80c**;yellow solid; mp 251−253 °C; R_f 0.21 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 3213, 2195, 1023; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 9.0, 3.8 Hz, 2H), 7.55 (ddd, J = 8.0, 3.8, 2.0 Hz, 1H), 7.44 (dd, J = 3.6, 2.0 Hz, 1H), 6.99 (brs, 2H), 6.96-6.91 (m, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.0, 171.9, 165.4, 162.5, 151.8, 148.9, 133.7, 128.5, 125.5, 121.4, 114.4, 110.9, 110.2, 101.9, 56.0, 55.5; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{19}H_{19}N_2O_4S$ 371.1066, found 371.1062.

(4-amino-2-(4-methylthiophenyl))thiazol-5-yl)(3,4-dimethoxyphenyl)methanone (81j). Yield 289 mg (75%) from 185 mg (1 mmol) of **78c**, 311 mg (1.2 mmol) of **80c**; yellow solid; mp 212−214 °C; R_f0.2 (5:5 EtOAc/hexane); IR (neat, cm^{-1}) 3377, 3262, 1618, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 7.8, 1.8 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.25 (s, 1H), 6.93 (d, J = 8.4 Hz, 3H), 3.96 (s, 6H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.2, 171.5, 165.3, 151.9, 149.0, 143.9, 133.6, 129.1, 127.0, 125.8, 121.4, 110.9, 110.1, 102.2, 56.2, 56.0, 15.0; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{19}H_{19}N_2O_3S_2$387.0837, found 387.0843.

1-(4-amino-2-(3,4-dimethoxyphenyl)thiazol-5-yl)ethanone (81k). Yield 180 mg (65%) from 230 mg (1 mmol) of **78d**,139 mg (1.5 mmol) of **80e**; yellow solid; mp 202−204 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3247, 3309, 1634;^1H NMR (400 MHz, DMSO-d_6) δ 7.63 (brs, 2H), 7.54 (dd, J= 8.4, 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 3.84 (s, 6H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 188.4, 169.3, 163.4, 151.9, 148.9,

124.9, 120.0, 111.9, 108.9, 101.9, 55.7, 55.6, 29.4; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{13}H_{15}N_2O_3S$ 279.0803, found 279.0796.

1-(4-amino-2-(thiophen-2-yl)thiazol-5-yl)ethanone (81l). Yield 165 mg (74%) from 175 mg (1 mmol) of **78h**, 139 mg (1.5 mmol) of **80e**; yellow solid; mp 203−205 °C; R_f 0.31 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3411, 3300, 2924, 1742; ^1H NMR (400 MHz, $CDCl_3$) δ7.59 (s, 1H), 7.49 (s, 1H), 7.10 (s, 1H), 6.67 (brs, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ189.7, 163.9, 162.9, 136.8, 130.1, 128.5, 128.4, 103.5, 29.5; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_9N_2OS_2$225.0156, found 225.0147.

1-(4-amino-2-(1-methyl-1*H*-pyrrol-2-yl)thiazol-5-yl)ethanone (81m).Yield 137 mg (62%) from 170 mg (1 mmol) of **78k**, 139 mg (1.5 mmol) of **80e**; yellow solid; mp 220−222 °C; R_f 0.2 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3121, 3072, 1609, 1357; ^1H NMR (400 MHz, $CDCl_3$) δ6.83 (dd, J = 4.0, 1.6 Hz, 1H), 6.79 (t, J = 2.2 Hz, 1H), 6.56 (brs, 2H), 6.17 (dd, J = 4.0, 2.8 Hz, 1H), 3.99 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.5, 163.2, 163.1, 128.9, 126.2, 115.1, 109.2, 101.9, 37.3, 29.7; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{10}H_{12}N_3OS$ 222.0701, found 222.0688.

Ethyl-4-amino-2-(4-methoxyphenyl)thiazole-5-carboxylate (81n). Yield 181 mg (65%) from 200 mg (1 mmol) of **78a**, 334 mg (2.0 mmol) of **80f**; yellow solid; mp 225−227 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3437, 3307, 1669; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 5.87 (brs, 2H), 4.32 (q, J = 14.4, 7.2 Hz, 2H), 3.87 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ172.6, 170.6, 164.5, 162.3, 128.4, 125.9, 123.6, 114.5, 60.6, 55.6, 14.7; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{13}H_{15}N_2O_3S$ 279.0803, found 279.0794.

Ethyl-4-amino-2-(1-methyl-1*H*-indol-2-yl)thiazole-5-carboxylate (81o).Yield 217 mg (72%) from 220 mg (1 mmol) of **78m**, 334 mg (2.0 mmol) of **80f**; brown solid; mp 223−225 °C; R_f 0.2 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3413, 3323, 1652, 1225;^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 6.8 Hz, 1H), 7.81 (s, 1H), 7.37 (t, J = 6.0 Hz, 1H), 7.34-7.30 (m, 2H), 5.96 (s, 2H), 4.33 (q, J = 14.2, 7.0 Hz, 2H), 3.85 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 164.7, 163.1, 137.6, 130.8, 125.3, 123.2, 121.9, 120.9, 110.7, 110.2, 60.3, 33.5, 14.8; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{15}H_{16}N_3O_2S$ 302.0963, found 302.0959.

Ethyl-4-amino-2-(pyridine-3-yl)thiazole-5-carboxylate (81p). Yield 139 mg (56%) from 170 mg (1 mmol) of **78n**, 334 mg (2.0 mmol) of **80f**; yellow solid; mp 219−221 °C; R_f 0.2 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2955, 2924, 1726, 1604; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 2.4 Hz, 1H), 8.68 (dd, J = 4.8, 1.6 Hz, 1H), 8.18 (dt, J = 8.0, 2.0 Hz, 1H), 7.38 (dd, J =

8.0, 4.8 Hz, 1H), 6.01 (s, 2H), 4.32 (q, *J* = 14.2, 7.0 Hz, 2H), 1. 37 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 164.2, 163.3, 151.8, 147.9, 133.8, 129.1, 123.8, 94.8, 60.8, 14.6; HRMS (ESI-Q-TOF*) m/z*: $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_2S$ 250.0650, found 250.0647.

Ethyl-4-amino-2-butylthiazole-5-carboxylate (81q). Yield 102 mg (45%) from 150 mg (1 mmol) of **78o**, 334 mg (2.0 mmol) of **80f**; white solid; mp 207−209 °C; R_f 0.2 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 3498, 3212, 1662, 1296;^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (brs, 2H), 4.26 (q, *J* = 14.2, 7.0 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 1.72 (quint, *J* = 7.6 Hz, 2H), 1.41 (sextet, *J* = 7.4 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.9, 164.3, 162.6, 128.9, 60.4, 33.7, 31.6, 22.2, 14.6, 13.8; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{10}H_{17}N_2O_2S$ 229.1011, found 229.1008.

2-(4-Methoxyphenyl)-5-nitrothiazol-4-amine (81r). Yield 183 mg (73%) from 200 mg (1 mmol) of **78a**, 154 mg (1.1 mmol) of **80g**; orange solid; mp 202−204 °C; R_f 0.32 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3356, 3212, 1610, 1018;^{1}H NMR (400 MHz, DMSO-d_6) δ9.13 (brs, 1H), 8.29 (brs, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.2, 163.4, 158.8, 129.1, 123.9, 116.1, 114.9, 55.7; HRMS (ESI-Q-TOF) *m/z*: $[M + Na]^+$calcd for $C_{10}H_9N_3NaO_3S$ 274.0262, found 274.0262.

5-Nitro-2-(thiophen-2-yl)thiazol-4-amine (81s). Yield 177 mg (78%) from 175 mg (1 mmol) of **78h**, 154 mg (1.1 mmol) of **80g**; orange solid; mp 243−245 °C; R_f0.2 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2916, 2721, 1530;^{1}H NMR (400 MHz, DMSO-d_6) δ9.19 (brs, 1H), 8.26 (brs, 1H), 8.01 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 3.6 Hz, 1H), 7.27 (t, *J* = 4.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ164.9, 158.4, 135.1, 134.1, 131.9, 129.4, 115.8; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_6N_3O_2S_2$ 227.9901, found 227.9889.

2-(5-(Dimethylamino)thiophen-2-yl)-5-nitrothiazol-4-amine (81t). Yield 210 mg (78%) from 215 mg (1 mmol) of **78i**, 154 mg (1.1 mmol) of **80g**; dark brown solid; mp 202−204 °C; R_f 0.3 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 2922.2, 2853.3, 1576.1;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (brs, 1H), 8.13 (brs, 1H), 7.78 (d, *J* = 4.8 Hz, 1H), 6.21 (d, *J* = 4.4 Hz, 1H), 3.10 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ167.0, 164.3, 159.6, 136.5, 115.6, 105.4, 41.9; HRMS (ESI-Q-TOF) *m/z*: $[M + Na]^+$calcd for $C_9H_{10}N_4NaO_2S_2$ 293.0143, found 293.0143.

2-(2-Methoxyphenyl)-5-nitrothiazol-4-amine (81u). Yield 210 mg (70%) from 200 mg (1 mmol) of **78e**, 154 mg (1.1 mmol) of **80g**; yellow solid; mp 230-232 °C; R_f 0.32 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 2922.2, 2853.3, 1576.1;^{1}H NMR (400 MHz, DMSO-d_6) δ8.64 (brs, 2H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ165.1, 158.1, 157.3, 134.3,

128.1, 121.1, 119.5, 118.0, 112.6, 56.3; HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$calcd for $C_{10}H_{10}N_3O_3S$ 252.0443, found 252.0427.

4-Amino-2-phenylthiazole-5-carboxamide (81v). Yield 147 mg (67%) from 170 mg (1 mmol) of **78b**, 166 mg (1.2 mmol) of **80h**; yellow solid; mp 255-257 °C; R_f 0.32 (8:2 EtOAc/hexane); IR (Neat, cm^{-1}) 2922.2, 2853.3, 1576.1;^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ*8.03 (d, *J* = 7.6 Hz, 2H), 7.69 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.50 (brs, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$) *δ*180.9, 155.7, 136.6, 134.0, 131.8, 129.4, 128.3, 127.4; HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$calcd for $C_{10}H_{10}N_3OS$ 220.0545, found 220.0540.

4-Amino-2-(3,4-dimethoxyphenyl)thiazole-5-carboxamide (81w). Yield 175 mg (77%) from 228 mg (1 mmol) of **78d**, 166 mg (1.2 mmol) of **80h**; yellow solid; mp 265-267 °C; R_f 0.32 (9:2 EtOAc/hexane); because of insolubility in most of the solvents^{1}H and ^{13}C{^{1}H} could not be recorded; HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$calcd for $C_{12}H_{14}N_3O_3S$280.0756, found 280.0737.

(*E*)-Ethyl-3-(4-amino-2-(4-methoxyphenyl)thiazol-5-yl)acrylate (81x).Yield 234 mg (77%) from 200 mg (1 mmol) of **70a**, 215 mg (1.2 mmol) of **80i**; red solid; mp 234−236 °C; R_f 0.25 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2999.5, 2951, 1718.9;^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 7.99 (d, *J* = 15.2 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.89 (brs, 2H), 5.57 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.66 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$) *δ* 167.3, 167.2, 161.9, 161.4, 135.5, 128.2, 125.4, 114.9, 108.9, 100.7, 55.7, 51.2; HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$calcd for $C_{14}H_{15}N_2O_3S$ 291.0803, found 291.0785.

(*E*)-Ethyl-3-(4-amino-2-(1-methyl-1*H*-pyrrol-2-yl)thiazol-5-yl)acrylate (81y).Yield 210 mg (76%) from 170 mg (1 mmol) of **78k**, 215 mg (1.2 mmol) of **80i**; yellow solid; mp 230−232 °C; R_f 0.31 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3445, 3146, 1365, 1121;^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.68 (d, *J* = 14.8 Hz, 1H), 6.76-6.74 (m, 2H), 6.16 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.73 (d, *J* = 15.2 Hz, 1H), 4.66 (brs, 2H), 3.98 (s, 3H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ* 168.1, 160.8, 158.2, 133.4, 128.4, 126.4, 114.5, 111.4, 109.1, 102.5, 51.6, 37.2; HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$calcd for $C_{12}H_{14}N_3O_2S$ 264.0807, found 264.0805.

(*E*)-Ethyl-3-(4-amino-2-(4-(piperidin-1-yl)phenyl)thiazol-5-yl)acrylate (81z).Yield 253 mg (71%) from 250 mg (1 mmol) of **78g**, 215 mg (1.2 mmol) of **80i**; yellow solid; mp 234−236 °C; R_f 0.2 (6:4 EtOAc/hexane); IR (neat, cm^{-1}) 3412, 3392, 1705, 1589; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 7.99 (d, *J* = 14.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.84 (brs, 2H), 5.49 (d, *J* = 14.8 Hz, 1H), 3.65 (s, 3H), 2.50 (s, 4H), 1.58 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$) *δ* 167.6, 167.1, 161.4, 152.8, 135.4, 127.6, 121.3, 114.2, 107.4, 99.4,

50.8, 48.0, 24.9, 23.9; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{18}H_{22}N_3O_2S$ 344.1433, found 344.1413.

(4-Amino-2-phenylthiazol-5-yl)(3,4,5-trimethoxyphenyl)methanone(82a). Yield 285 mg (77%) from 168 mg (1 mmol) of **78b**, 347 mg (1.2 mmol) of **80d**; yellow solid; mp 157−159 °C (reported 156-158 °C)[24a]; R_f 0.2 (6:4 EtOAc/hexane); IR (neat, cm^{-1}) 3482, 3401, 2922, 1616;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.2, 1.0 Hz, 2H), 7.53-7.44 (m, 3H), 7.13 (s, 2H), 6.99 (brs, 2H), 3.94 (s, 6H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 172.5, 165.5, 153.2, 141.1, 136.2, 132.7, 131.9, 129.2, 126.9, 105.4, 102.7, 61.1, 56.5; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{19}H_{19}N_2O_4S$ 371.1066, found 371.1064.

(4-Amino-2-(thiophen-3-yl)thiazol-5-yl)(3,4,5-trimethoxyphenyl)methanone (82b). Yield 304 mg (81%) from 175 mg (1 mmol) of **78j**, 347 mg (1.2 mmol) of **80d**; yellow solid; mp 200−202 °C (reported 198-200 °C)[24a]; R_f 0.27 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 3313.1, 3270.8, 1620.9, 1132.0;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 3.2, 1.2 Hz, 1H), 7.52 (dd, J = 5.2, 1.2 Hz, 1H), 7.40 (dd, J = 5.0, 3.0 Hz, 1H), 7.10 (d, J = 4.0 Hz, 2H), 6.97 (brs, 2H), 3.93 (s, 6H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 167.0, 165.3, 153.1, 140.9, 136.1, 134.9, 127.2, 126.6, 126.0, 105.3, 105.2, 101.8, 60.9, 56.3; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$calcd for $C_{17}H_{17}N_2O_4S_2$ 377.0630, found 377.0622.

3.5 References

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3.6 ^{1}H and ^{13}C NMR Spectra of Representative Compounds

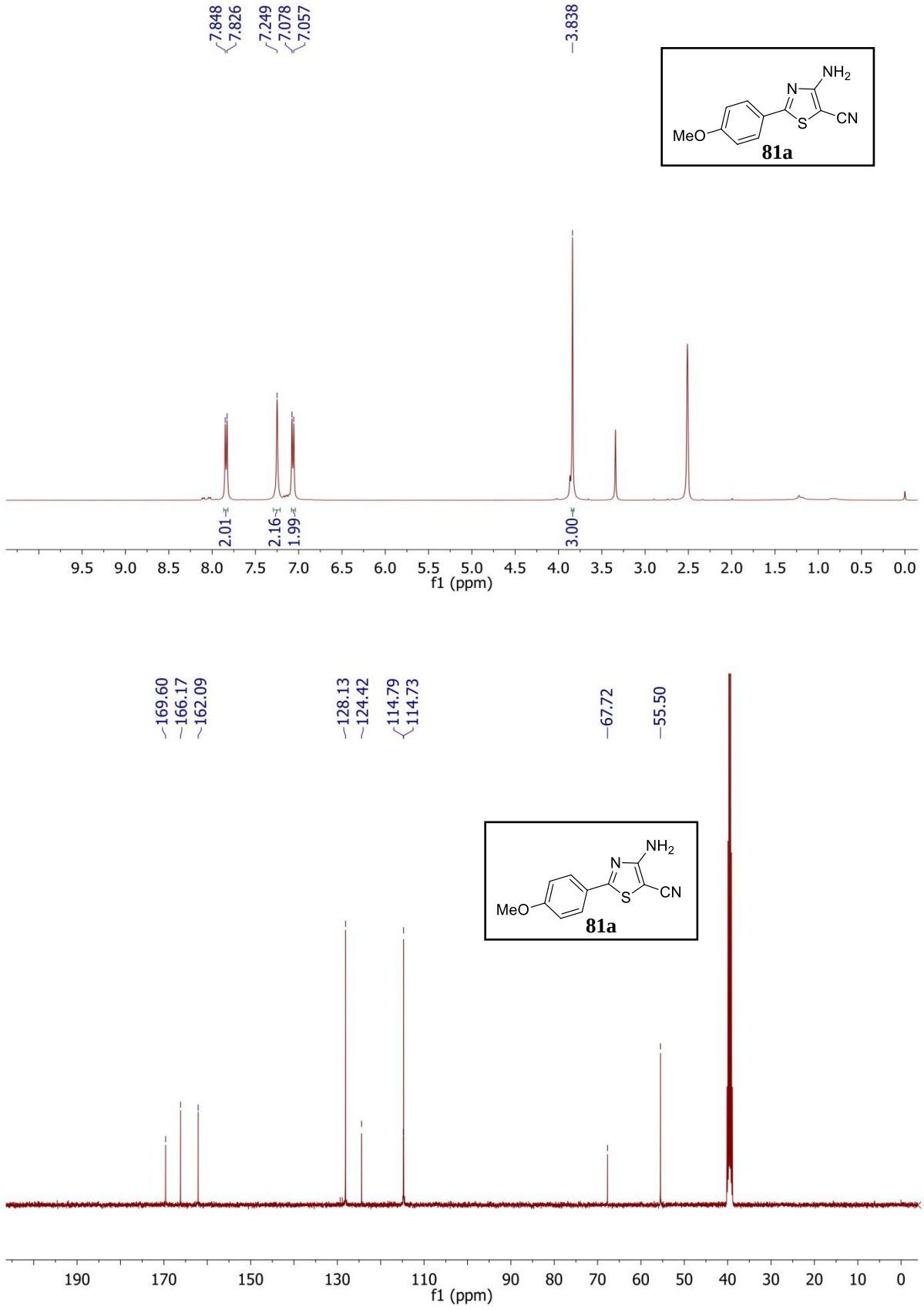


Figure 1. ^{1}H and ^{13}C NMR of compound 81a

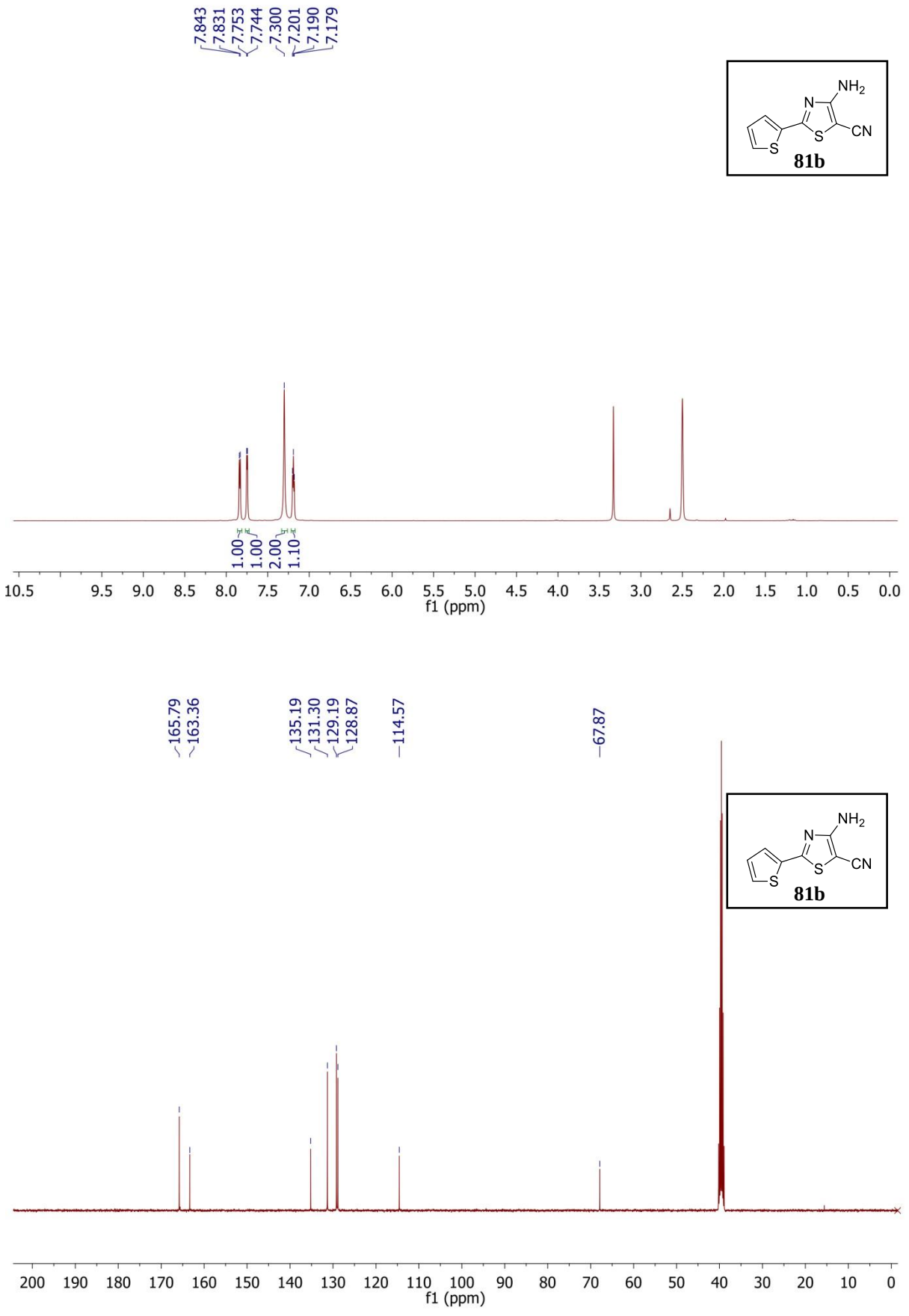


Figure 2. ^{1}H and ^{13}C NMR of compound 81b

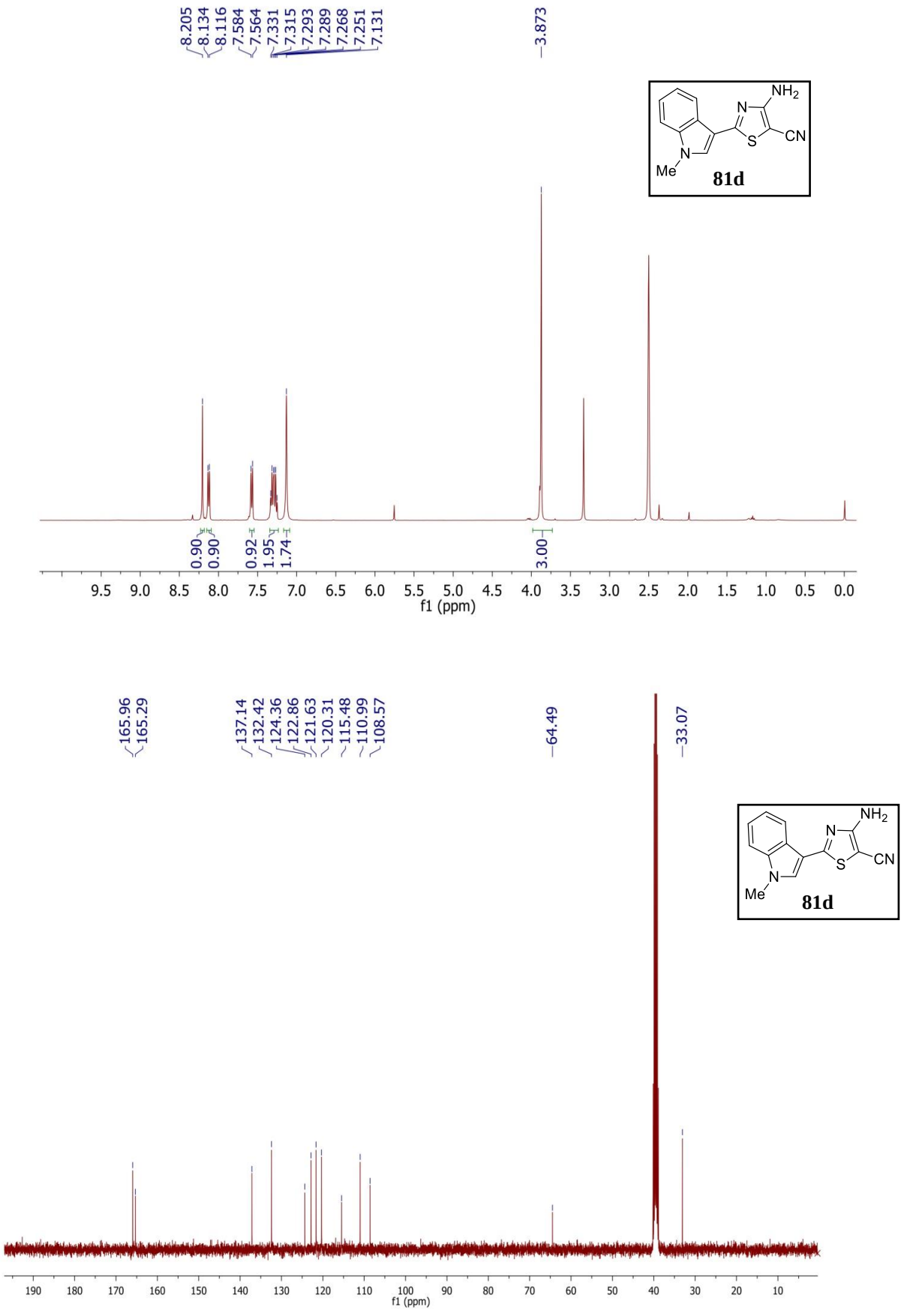


Figure 3. ^{1}H and ^{13}C NMR of compound 81d

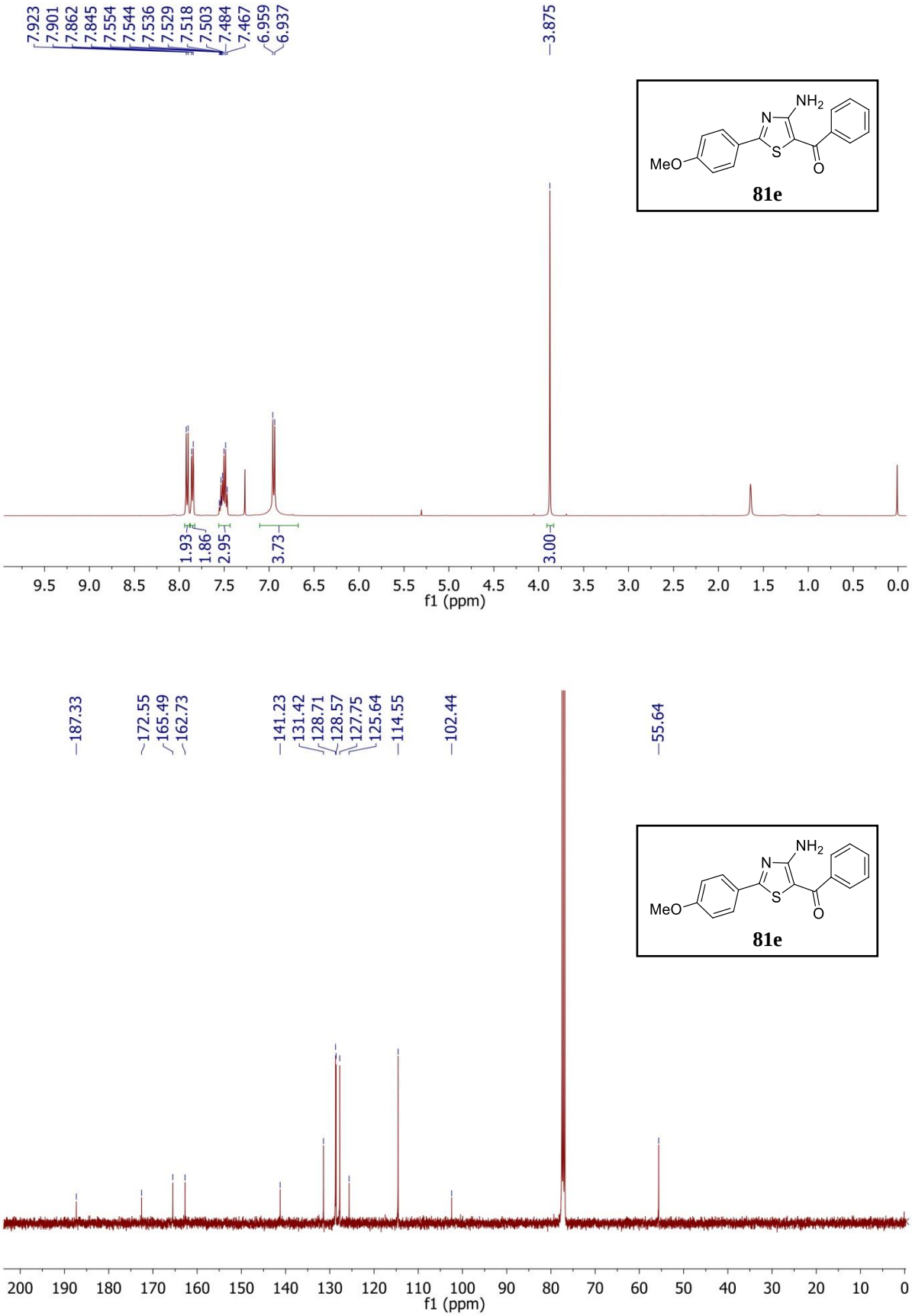


Figure 4. ^{1}H and ^{13}C NMR of compound 81e

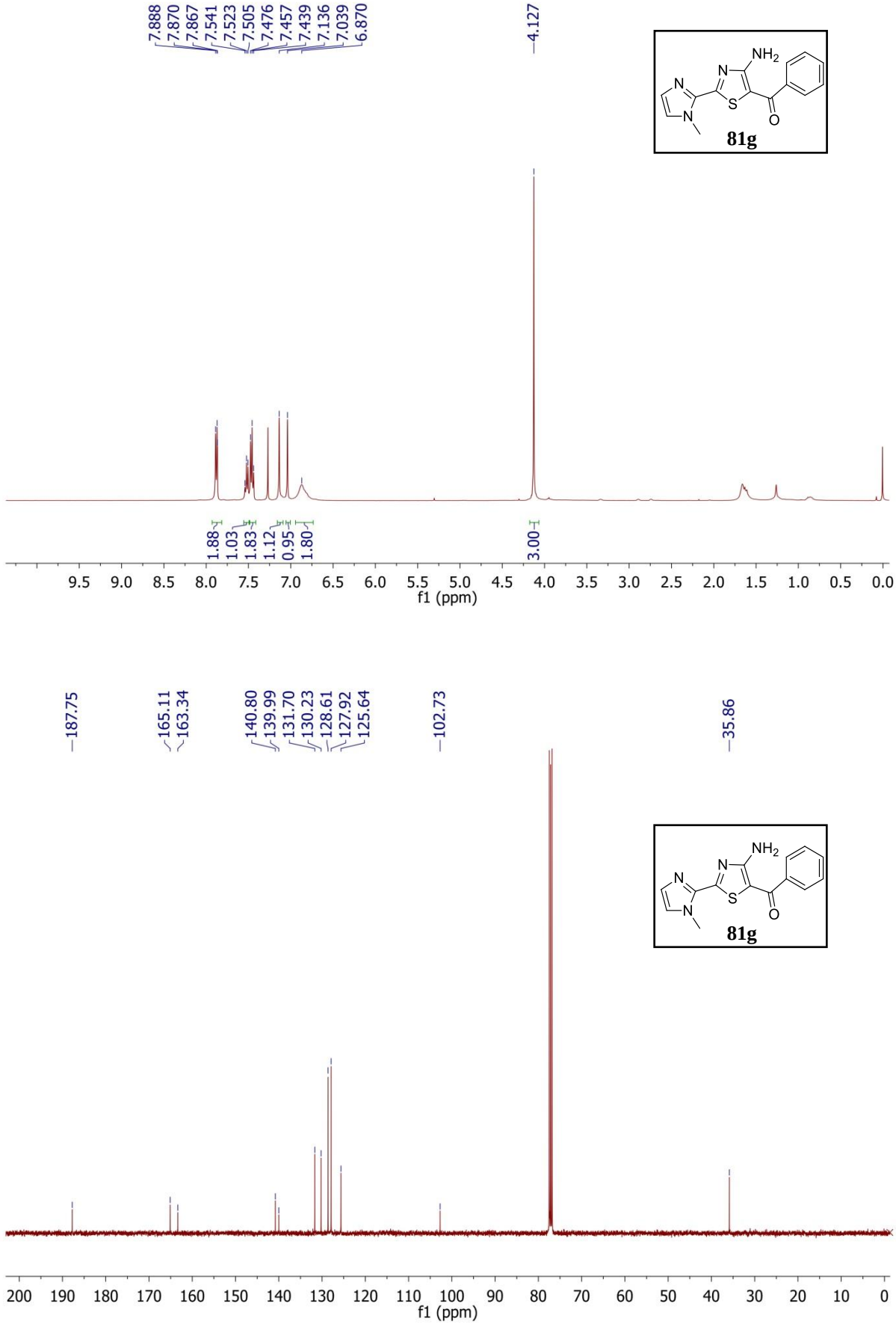


Figure 5. ^{1}H and ^{13}C NMR of compound 81g

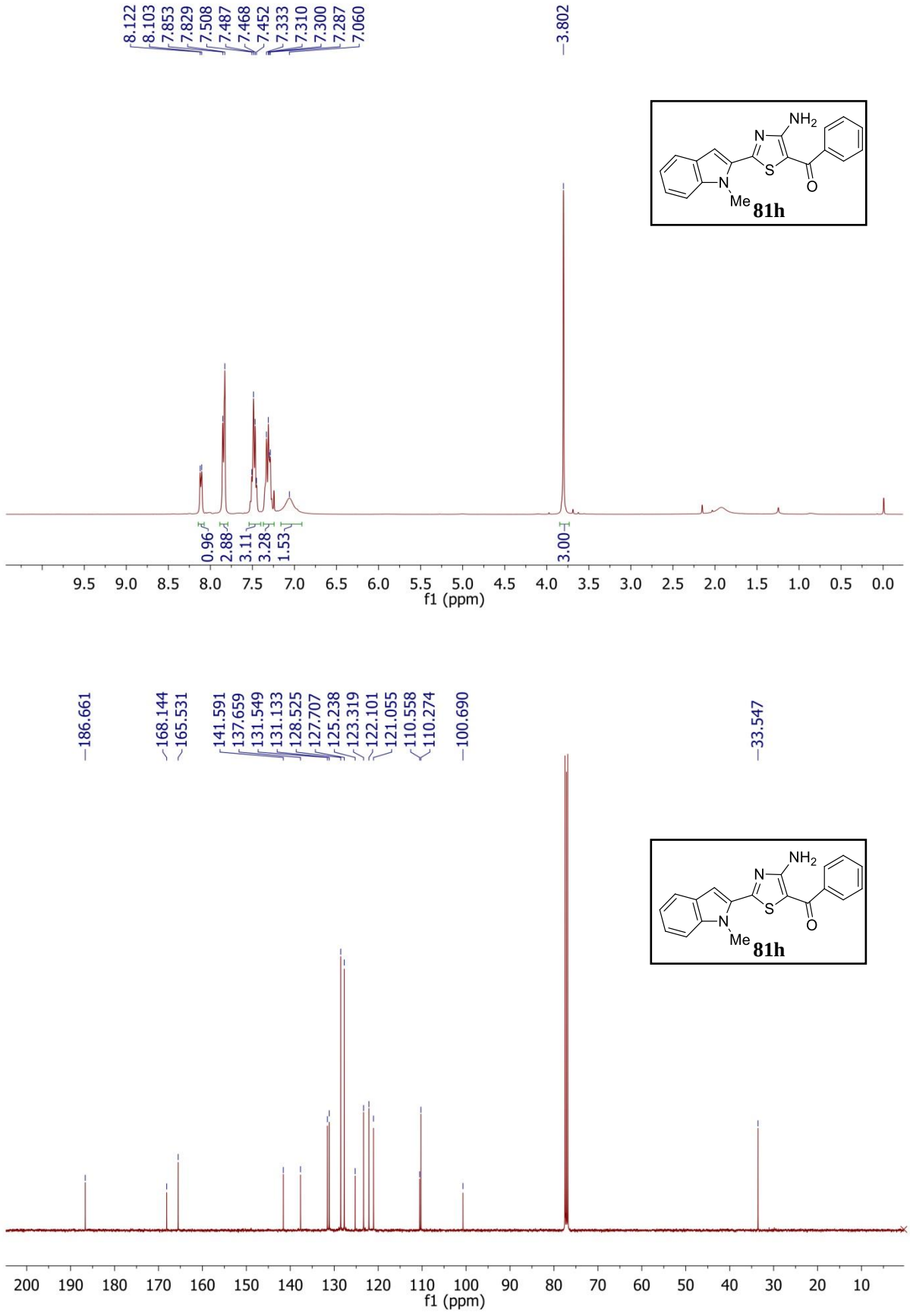


Figure 6. ^{1}H and ^{13}C NMR of compound 81h

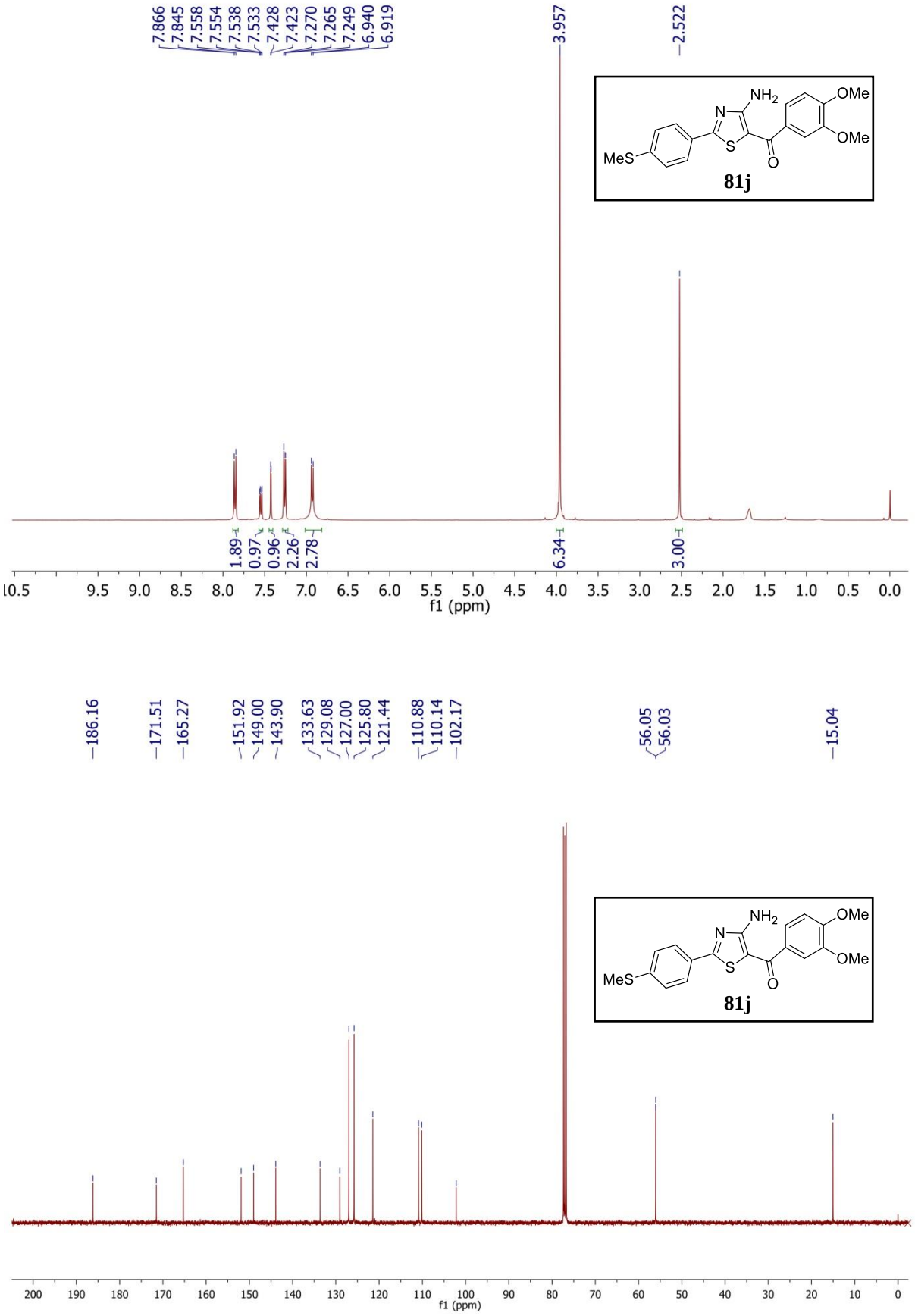


Figure 7. ^{1}H and ^{13}C NMR of compound 81j

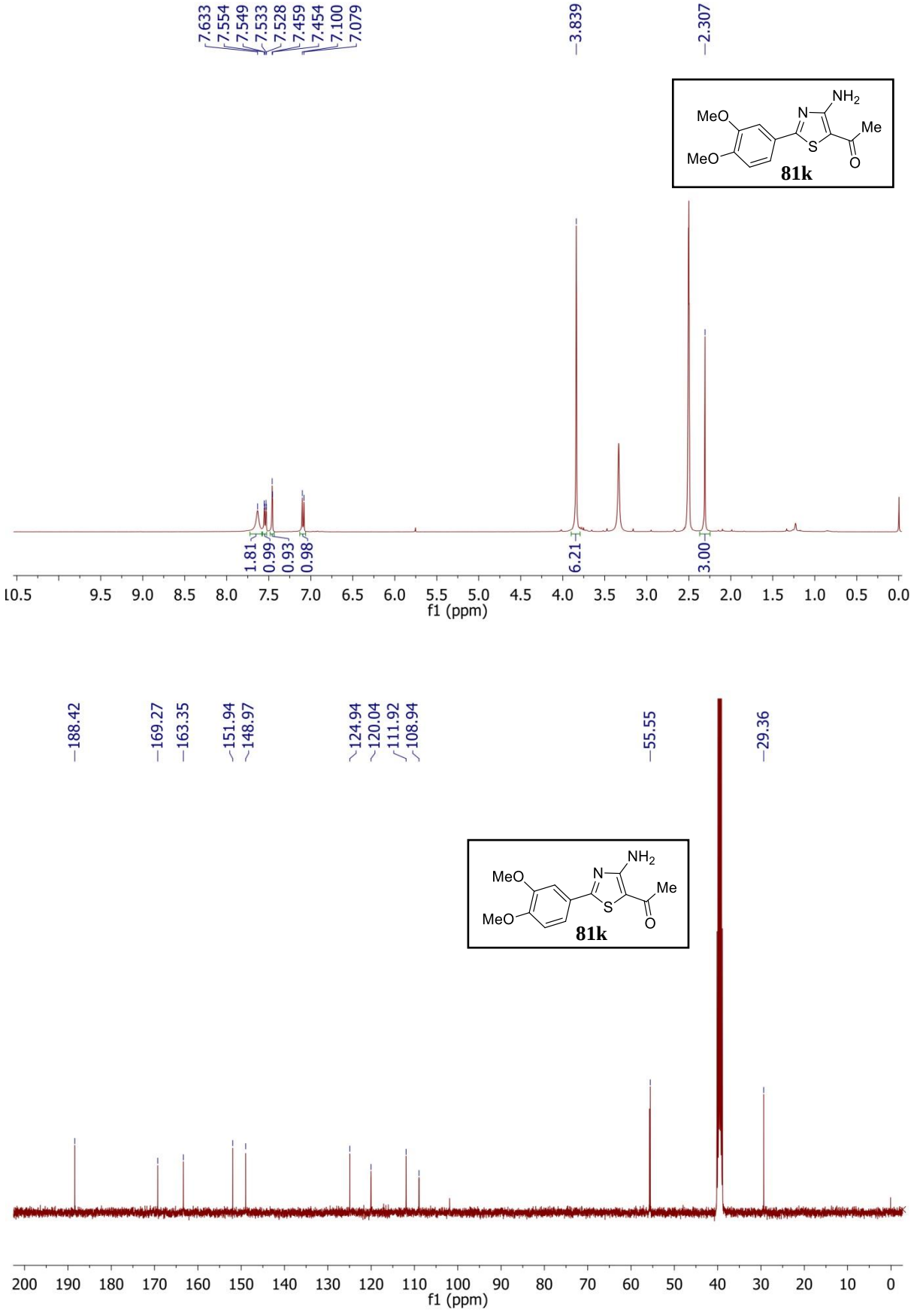


Figure 8. ^{1}H and ^{13}C NMR of compound 81k

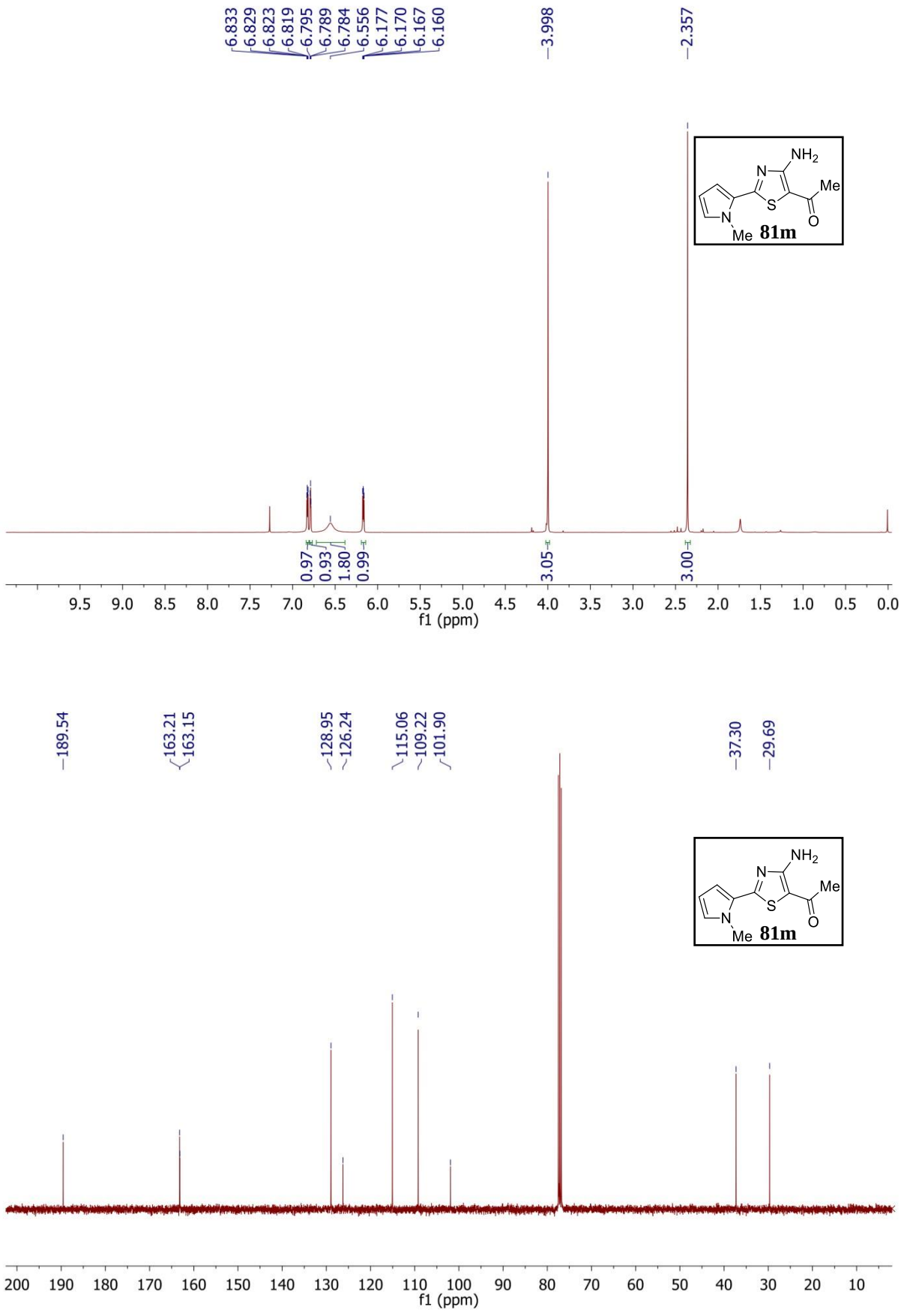


Figure 9. ^{1}H and ^{13}C NMR of compound 81m

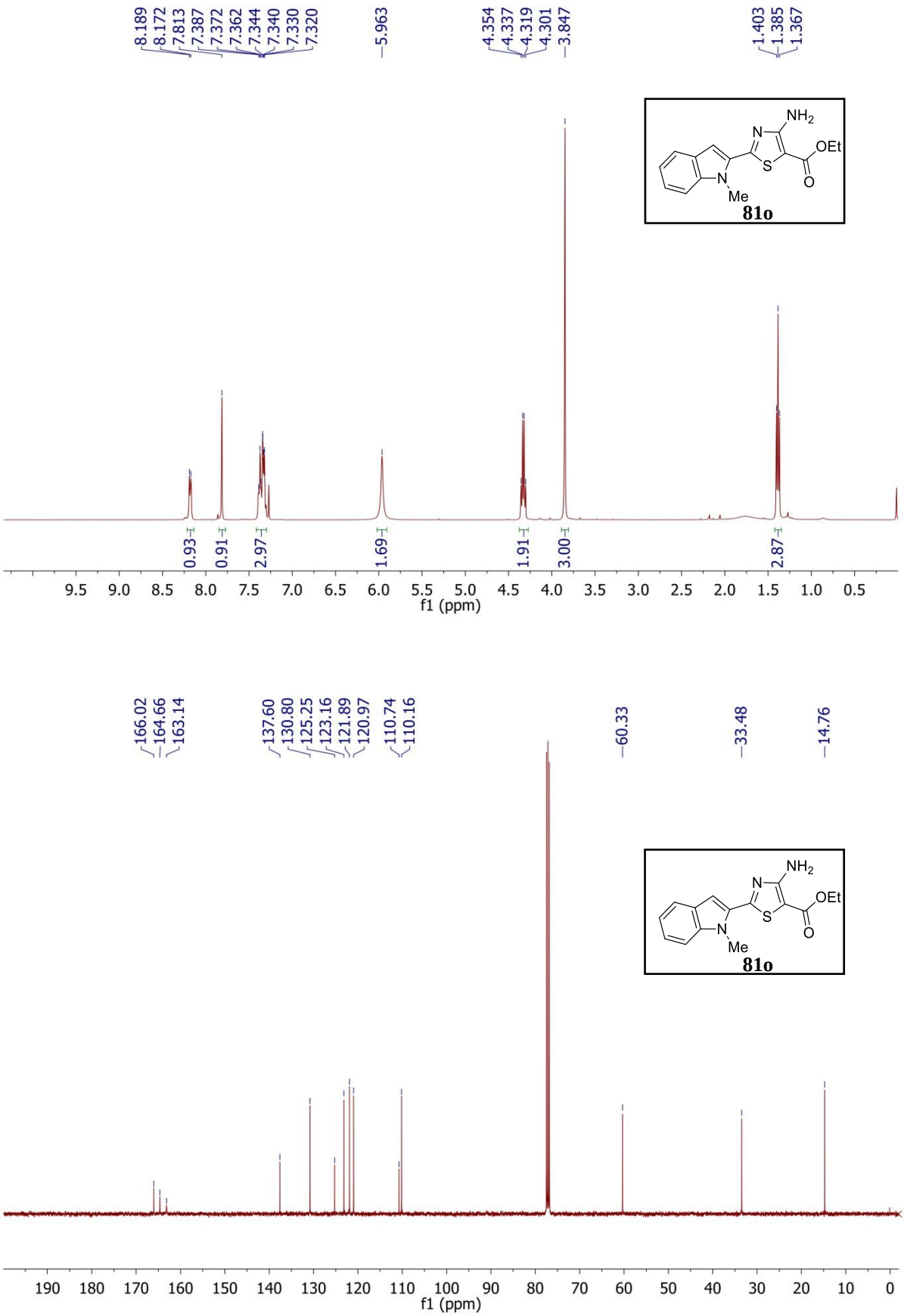


Figure 10. ^{1}H and ^{13}C NMR of compound 81o

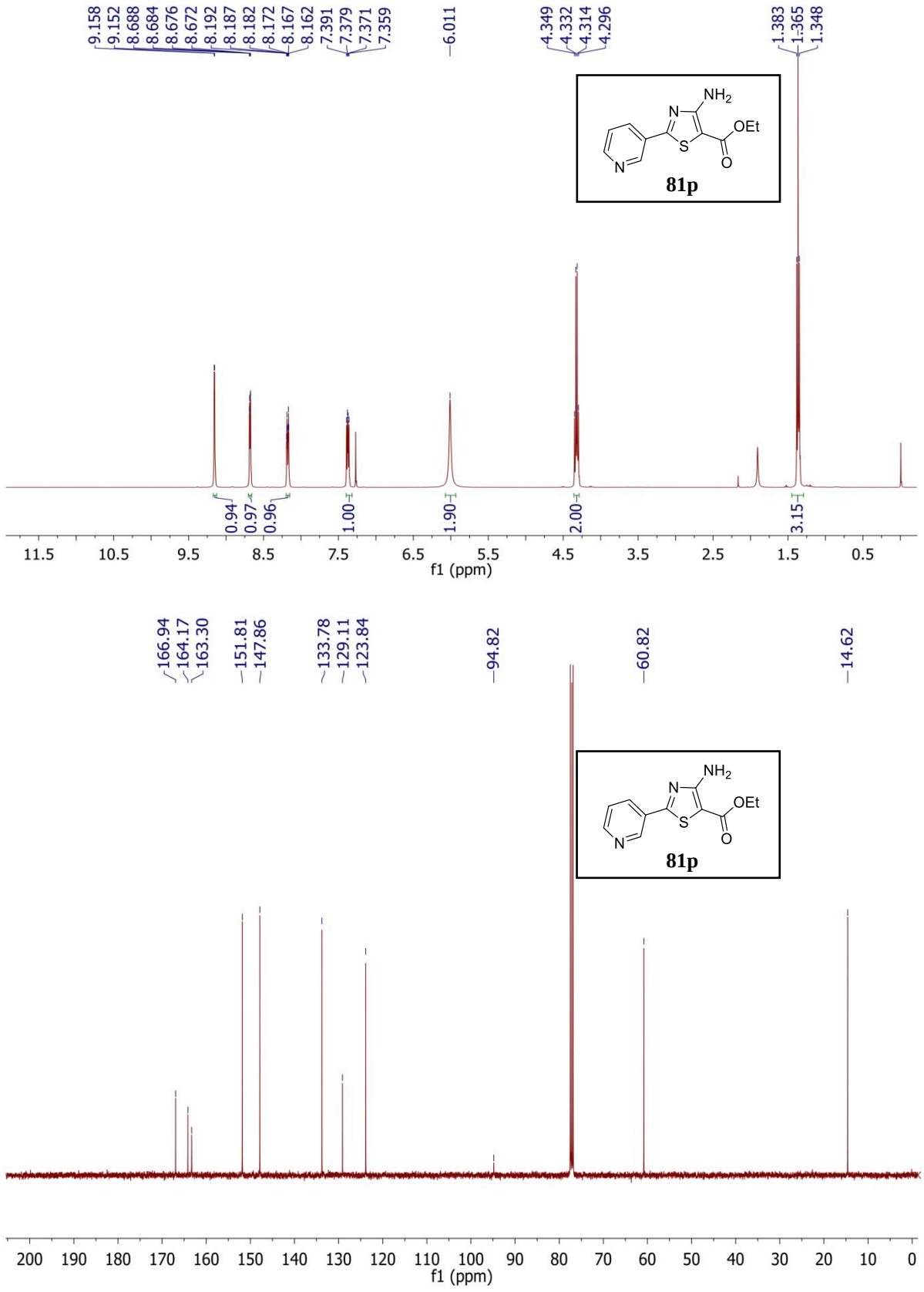


Figure 11. ^{1}H and ^{13}C NMR of compound 81p

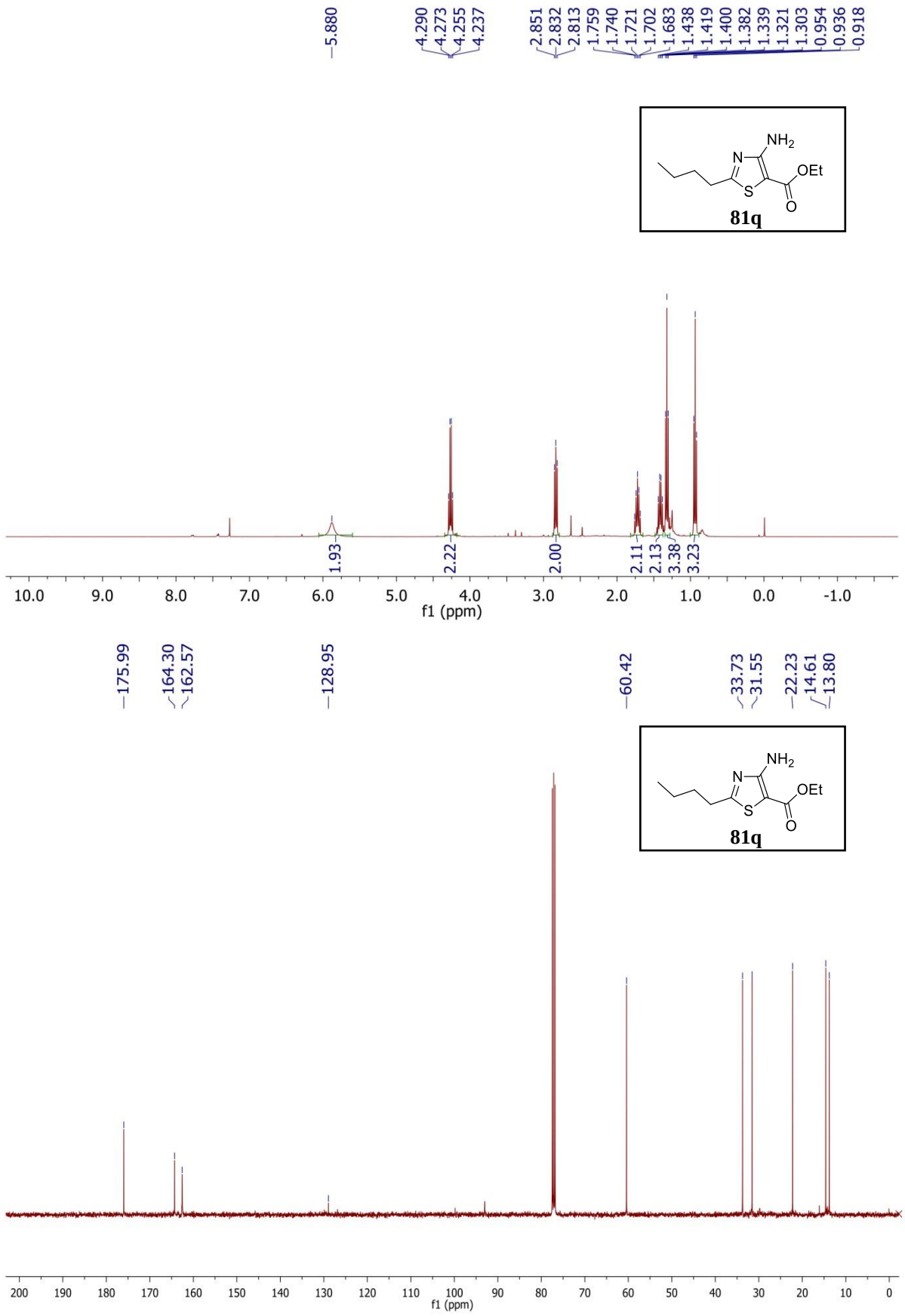


Figure 12. ^{1}H and ^{13}C NMR of compound 81q

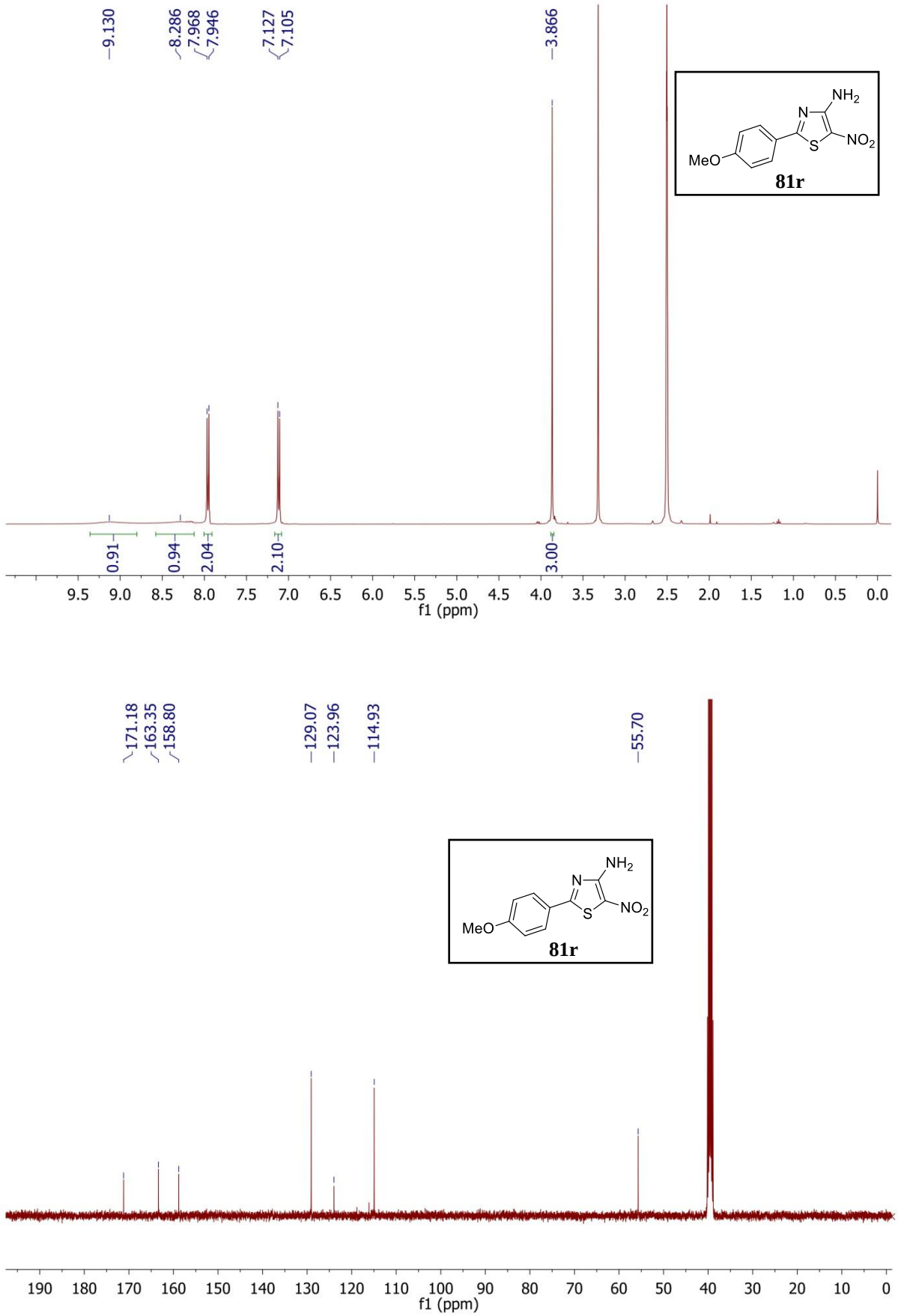


Figure 13. ^{1}H and ^{13}C NMR of compound 81r

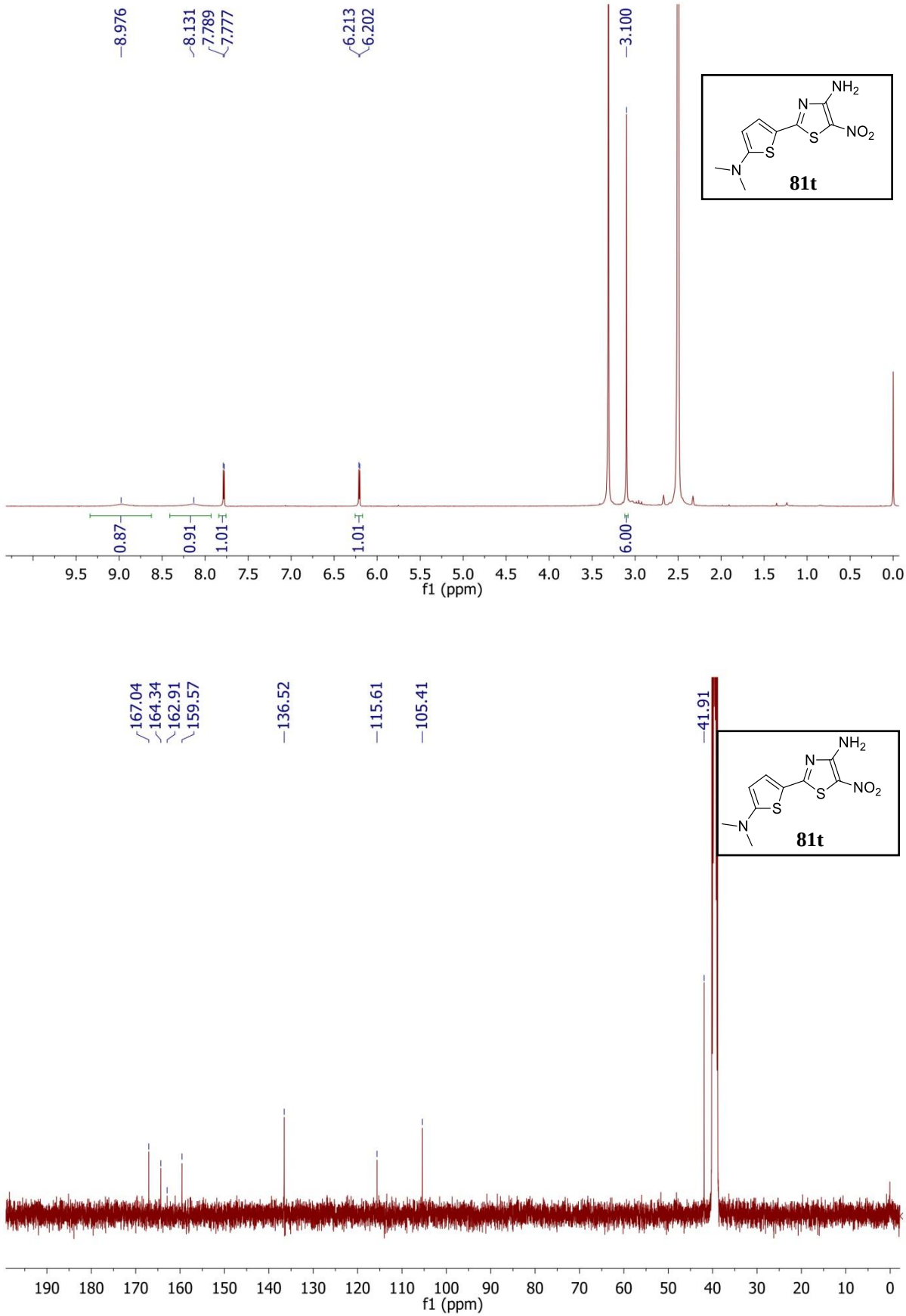


Figure 14. ^{1}H and ^{13}C NMR of compound 81t

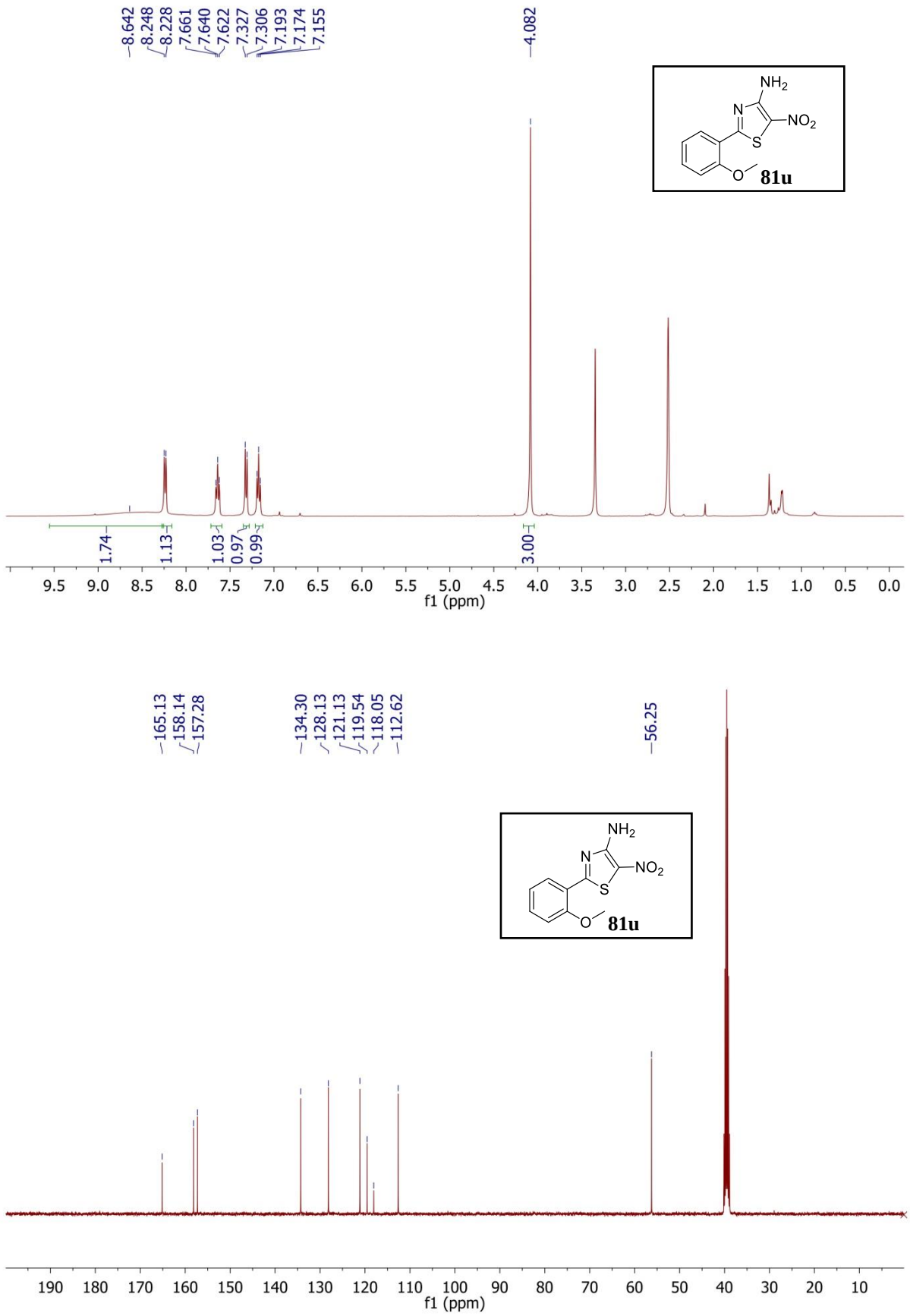


Figure 15. ^{1}H and ^{13}C NMR of compound 81u

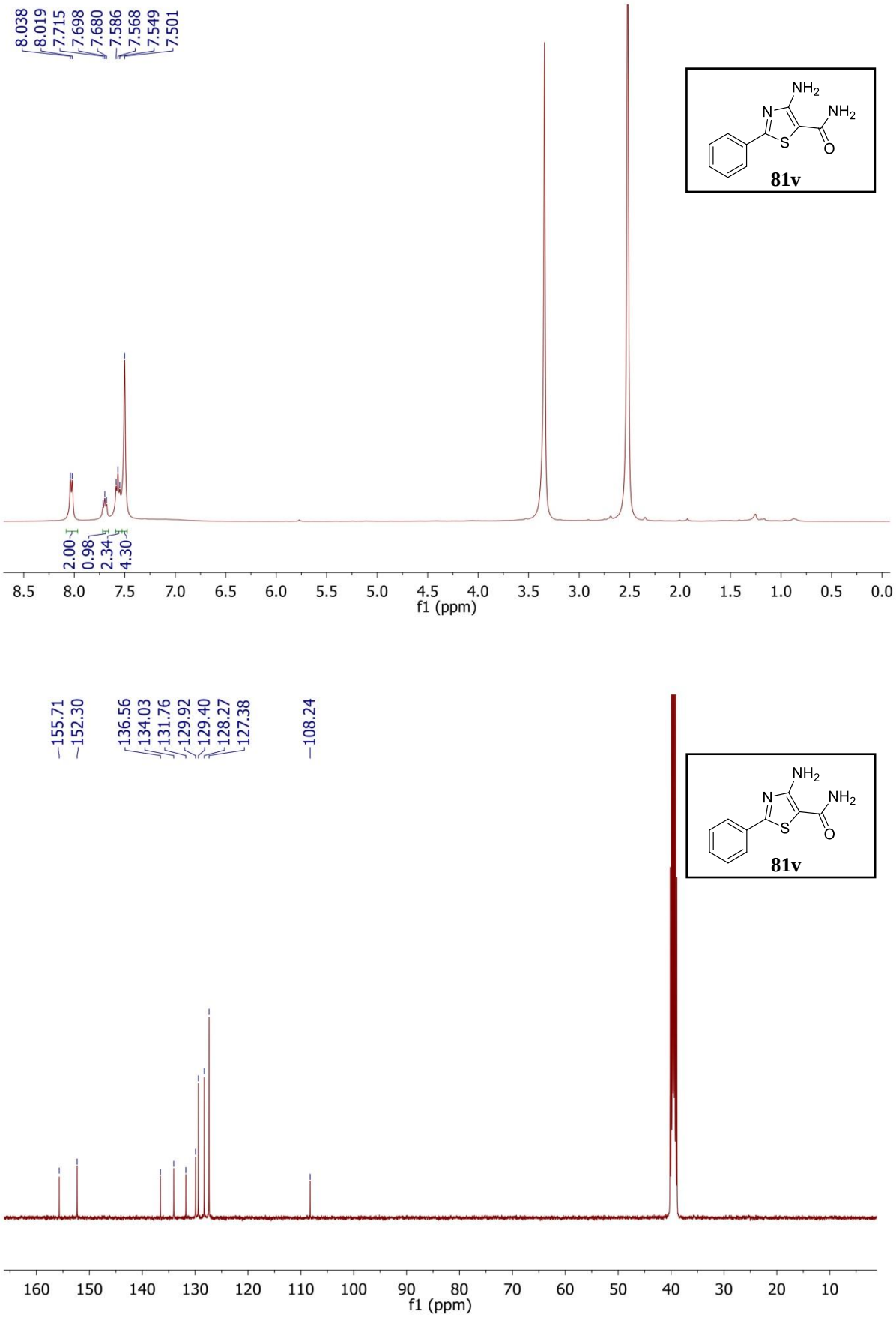


Figure 16. ^{1}H and ^{13}C NMR of compound 81v

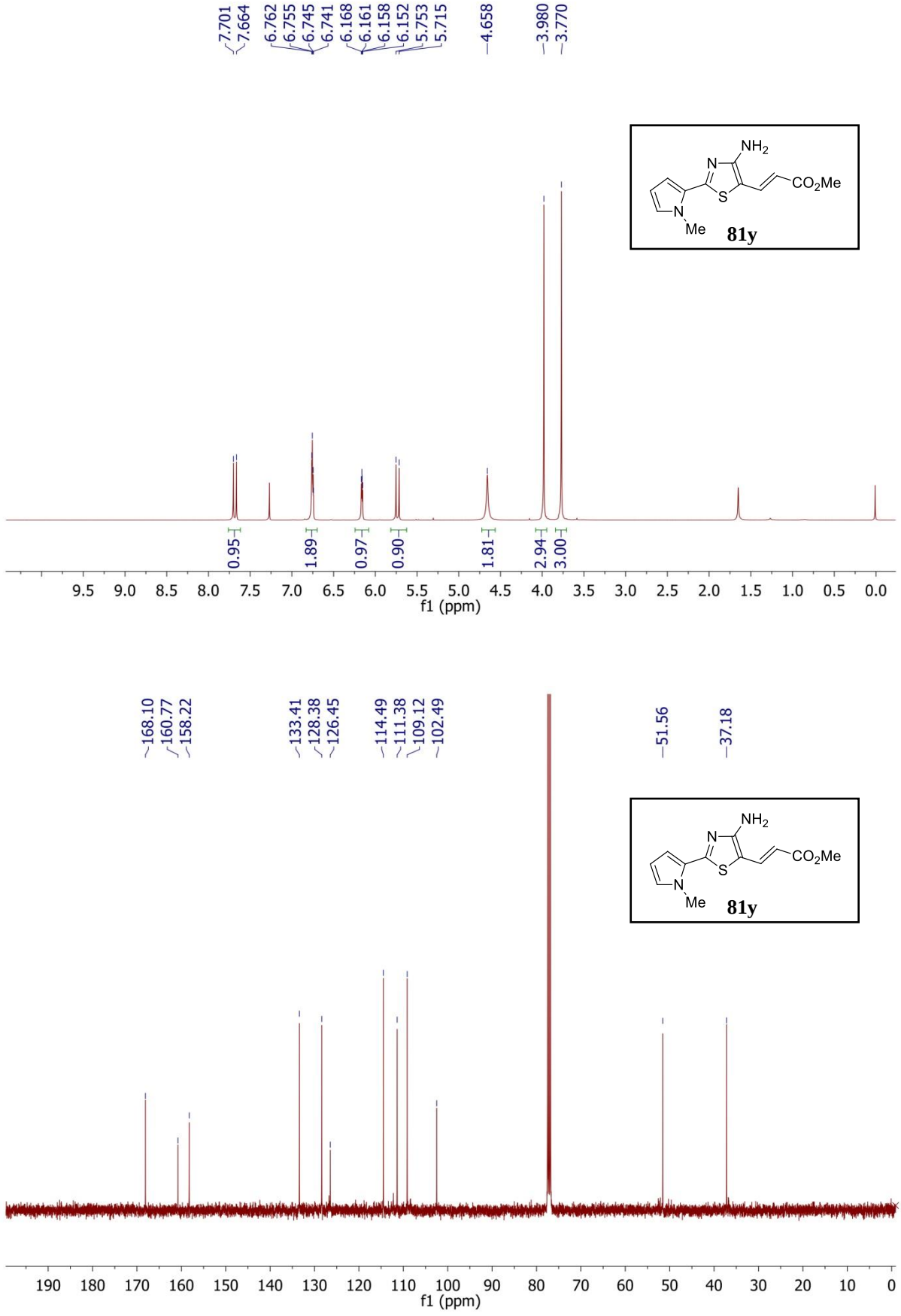


Figure 17. ^{1}H and ^{13}C NMR of compound 81y

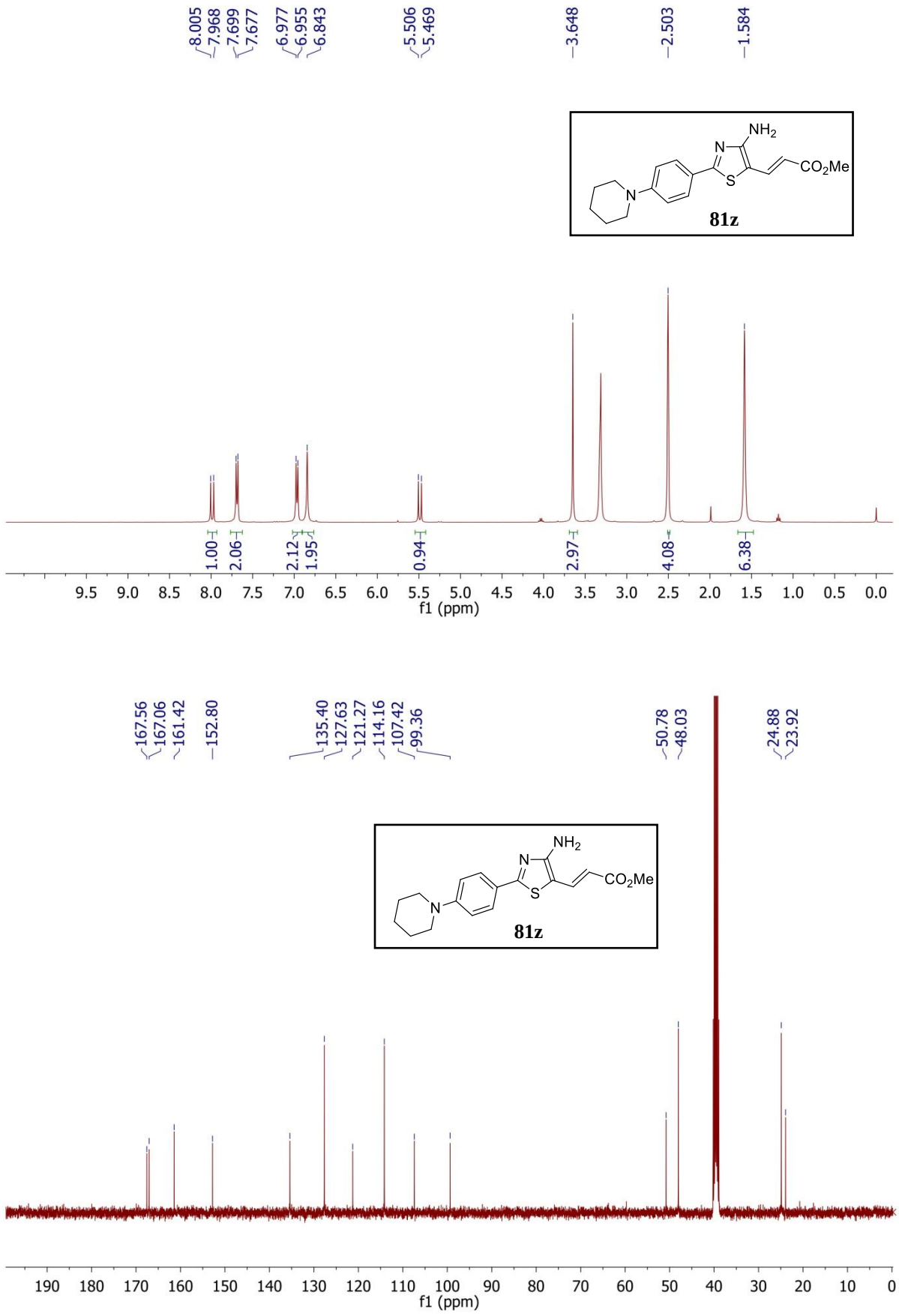


Figure 18. ^{1}H and ^{13}C NMR of compound 81z

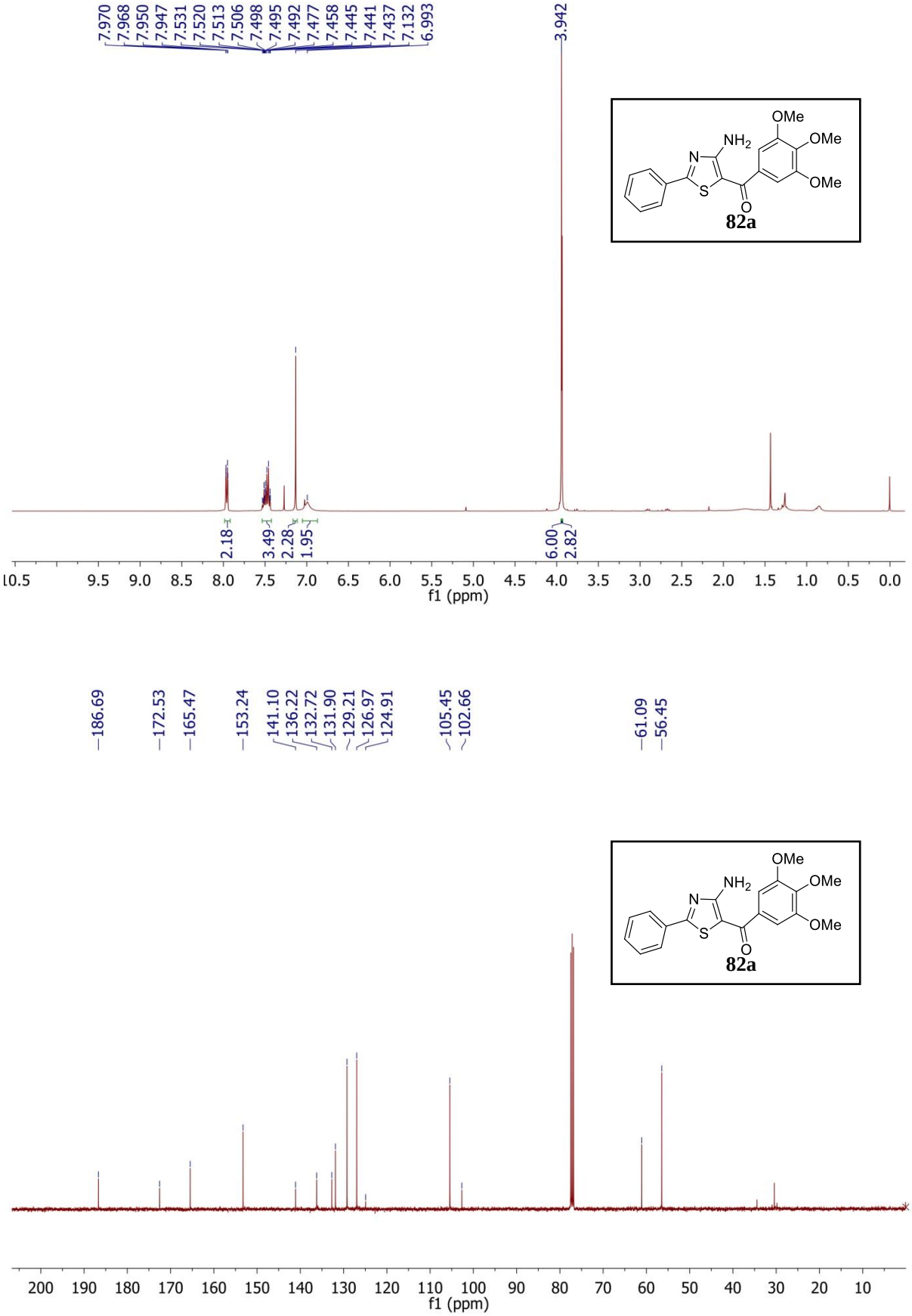


Figure 19. ^{1}H and ^{13}C NMR of compound 82a

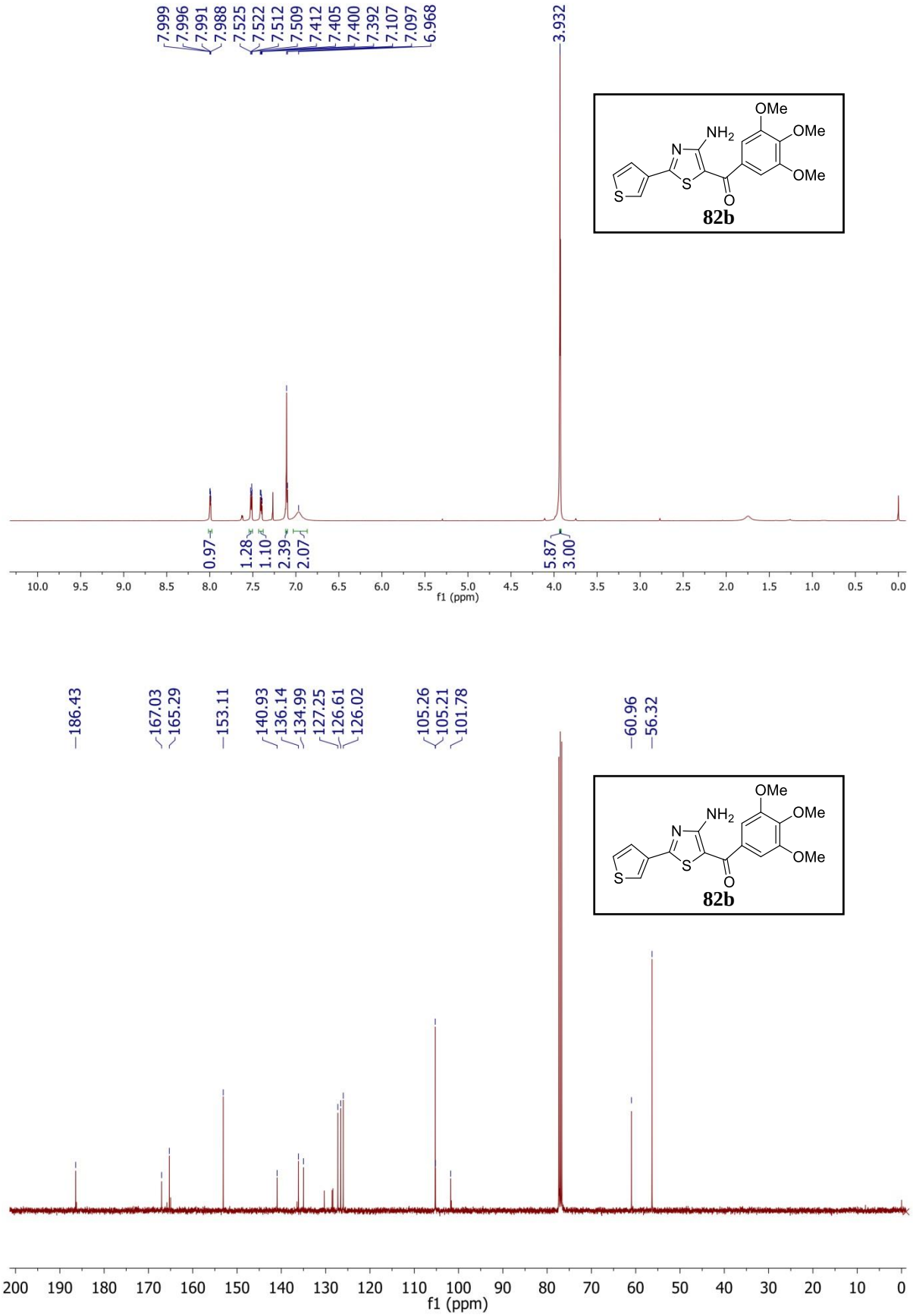


Figure 20. ^{1}H and ^{13}C NMR of compound 82b

Chapter 4

*Synthesis of 9-Amino/aryl/oxo-2-(het)arylthiazolo[4,5-b]quinolines via Palladium Catalyzed N-Arylation-cyclization Protocol**

4.1 Introduction

Substituted acridine analogs constitute an important class of heteroaromatic framework and have been widely explored, because of the broad range of biological activity displayed by these class of compounds.[1] Thus several acridine derivatives have been shown to be potent antibacterial, antimalarial, anticancer, anti-inflammatory, fungicidal, antileukemic, and antiviral agents,[1-3] whereas , several 9-aminoacridines have been found to exhibit potential antitumor activity, *via* intercalation with DNA and inhibition of the DNA topoisomerase II enzyme.[2] This privileged structure is core motif of several approved and marketed drugs such as proflavine, aminoacridine, ethacridine, mepacrine, amsacrine (*m*-AMSA) and acrisorcin etc (Figure 1).[3]

*Communicated to Synthesis

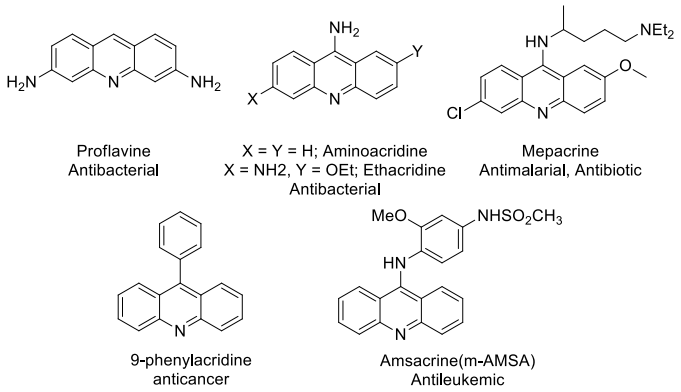


Figure 1. Selected examples of biologically important acridines

Isosteric replacement of one of the benzene rings in the acridine template by five membered heterocyclic ring leads to several condensed quinoline frameworks, many of which have been synthesized and their biological activity have been evaluated (Figure 2).

Thus SAR studies on 4-amino/pyrazolo[3,4-*b*]quinolines **1**,[4] thieno- and benzothieno[2,3-*b*] /[3,2-*b*]quinolines **2**,[5] has shown them to be effective cytotoxic,[4b,5a] antimycobacterial,[4d] antifungal agents,[5b] as well as potent and selective PDE10A inhibitor for treatment of schizophrenia.[4c] On the other hand, synthetic 4-anilino/phenoxyfuro[2,3-*b*]quinolines **3**,[6] and indolo[2,3-*b*]quinolines **4**,[7] along with their naturally occurring analogs (dictamnine, robustine and cryptotackieine) are known to be established cytotoxic agents, by intercalation with DNA, inhibiting DNA topoisomerase II enzyme , [6b-c,7a-b] some of them also displaying anti-inflammatory[6a] as well as antimycobacterial activity.[7d] Recently, Alavarez-Ibarra and other workers have synthesized several 2-(methylthio)/alkylamino-9-aryl/alkylaminothiazolo[5,4-*b*]quinoline analogs **5**, which were shown to display good cytotoxic activity, as a new class of potential antitumor agents.[8a-c] On the other hand, the related thiazolo[4,5-*b*]quinoline derivatives **6** have rarely been reported in the literature (Figure 2).

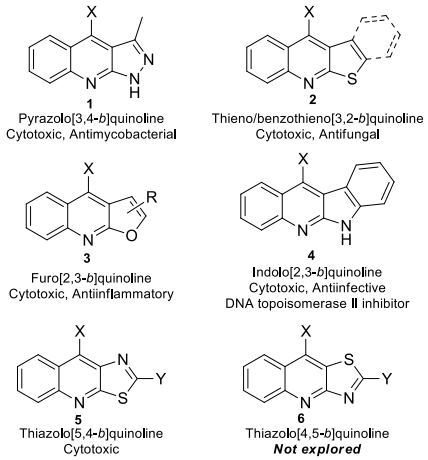
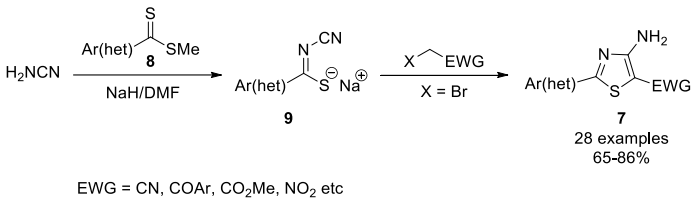


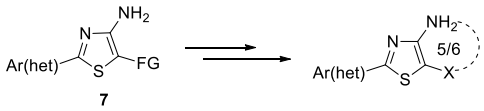
Figure 2. Selected examples of isosteric hetero fused quinolines.

Our own interest in hetero-fused quinolines is derived from our recent report on a novel one step synthesis of substituted 2-(het)aryl-4-amino-5-functionalized thiazoles **7**, involving condensation of cyanamide with functionalized dithioesters **8** in the presence of base and subsequent concurrent *S*-alkylation-Thorpe Ziegler type intramolecular cyclization of the resulting *N*-cyano-(het)arylthioimidate salts **9** with activated methylene halides (Scheme 1).[9]



Scheme 1

We have also recently reported synthesis of thieno-fused five- and six- membered heterocycles following similar strategy (Chapter 2. Scheme 22). During the course of these studies, we further became interested in elaboration of these newly synthesized 2-(het)arylthiazoles **7**, incorporating a 4-amino and adjacent 5-functionalities, to thiazolo-fused condensed nitrogen heterocycles (Scheme 2).



Scheme 2

In the present chapter, we have developed a general strategy for elaborating these thiazoles **7** into previously unexplored 2-(het)aryl-9-amino/aryl/oxo-thiazolo[4,5-*b*]quinolines **68** that combine general substitution of acridine derivatives with thiazolo[4.5-*b*]quinoline template (Scheme 14). However, before presenting our results, we describe in the following section, our recent literature search, relevant to our work, mainly focused on the synthesis of thiazolo fused six membered nitrogen heterocycles starting from 2-substituted-4-amino-5-functionalized thiazole precursors. The literature is not exhaustive.

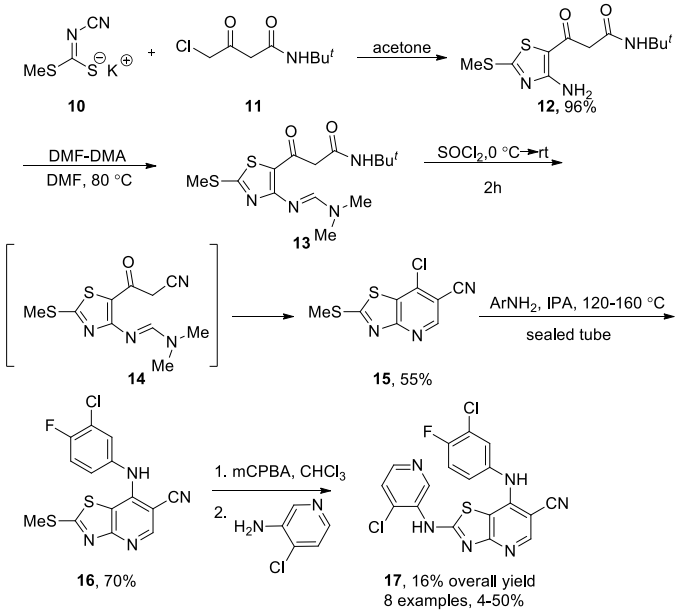
4.2 Synthesis of Thiazolo-fused six membered heterocycles: A short literature survey

Our literature search at this stage, revealed that a few research groups have reported synthetic transformation of 2-(methylthio)-/(*sec*-amino)-4-amino-5-functionalized thiazoles to substituted thiazolo[4,5-*b*]pyridine derivatives either in step-wise manner or in a single–pot

operation (Schemes 3-6).[10-11] Similarly, some of these 4-amino-5-functionalized thiazole derivatives have also been converted into biologically important 2,7-diaminothiazolo[4,5-*d*]pyrimidine analogs or thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives, through a series of transformations (Schemes 7-9).[12] A few of the selected recent synthesis of thiazolo[4,5-*d*]pyridine and thiazolo[5,4-*d*]pyrimidine analogs is described in the following section.

4.2.1 Synthesis of Thiazolo[4,5-*b*]pyridines

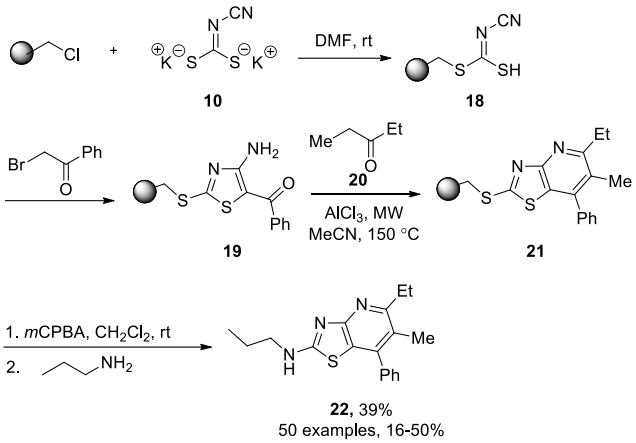
Johnson and co-workers have recently reported a concise synthesis of 7-chloro-2-methylsulfanyl-thiazolo[4,5-*b*]pyridine-6-carbonitriles **15** in a sequence of reaction as shown in Scheme 3.[10a]. Thus, cyanoimidodithiocarbonate salt **10** was condensed with 4-chloro-*β*-keto-*t*-butylamide **11** in acetone to furnish 4-amino-2-methythiothiazole-5-*t*-butylamide **12** in 96% yield. The thiazole amide **12** was transformed directly into the corresponding 6-cyano-5-chlorothiazolo[4,5-*b*] pyridine **15** by sequential treatment with DMF dimethylacetal to give amidine **13** and then with thionyl chloride at rt through intermediate **14**. The 7-chloro- moiety and 2-(methythio)-substituent (*via* conversion to 2-methylsulfanyl group by MCPBA oxidation) in thiazolopyridines **15** were subsequently replaced by various anilines to provide corresponding 7-anilino-6-cyanothiazolopyridines **16** and 2,7-anilino analog **17** as potential kinase inhibitors in varying yields (Scheme 3).[10a]



Scheme 3

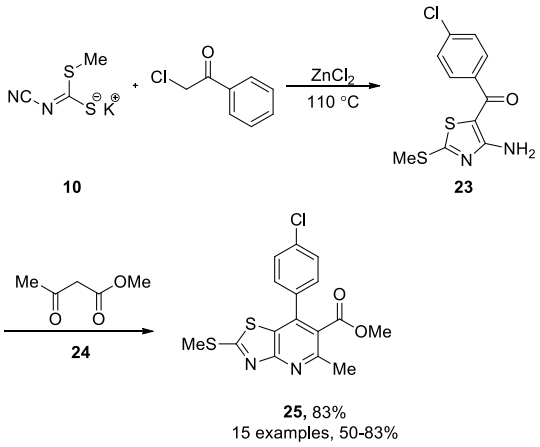
Lee and co-workers have described traceless solid-phase synthesis of 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridine derivatives such as **22**, *via* Thorpe-Ziegler type

cyclization of solid supported *N*-cyanocarboimidodithioate salt **18** with *α*-haloketones, affording 4-amino-5-benzoylthiazole resin **19**, which were converted to the desired thiazolopyridine resin **21** by Friedlander protocol under microwave irradiation(Scheme 4).[10b-c] After oxidation of sulfides **21** to sulfones, and nucleophilic desulfonative substitution with amines in **21**, the target thiazolo[4,5-*b*]pyridine derivatives such as **22** were obtained in overall good yields (Scheme 4).



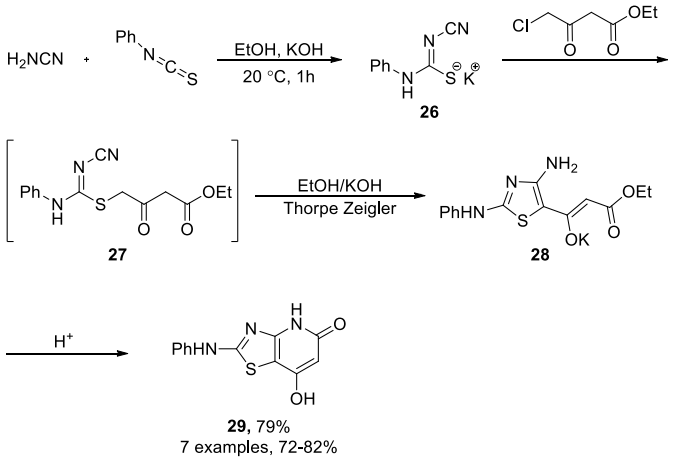
Scheme 4

A $ZnCl_2$-promoted one-pot tandem synthesis of multisubstituted thiazolo[4,5-*b*]pyridines from mercaptonitrile salts, *α*-chloro active methylene ketones, has been recently developed by Li and co-workers (Scheme 5).[11a] This approach involves a tandem S_N2 alkylation-Thorpe Ziegler cyclization -Friedlander reaction, which allows the creation of two heterocyclic rings and four new bonds in a single operation (Scheme 5). The reaction proceeds smoothly under solvent free conditions to afford thiazolo- fused pyridines such as **25** in moderate to good yields (Scheme 5).



Scheme 5

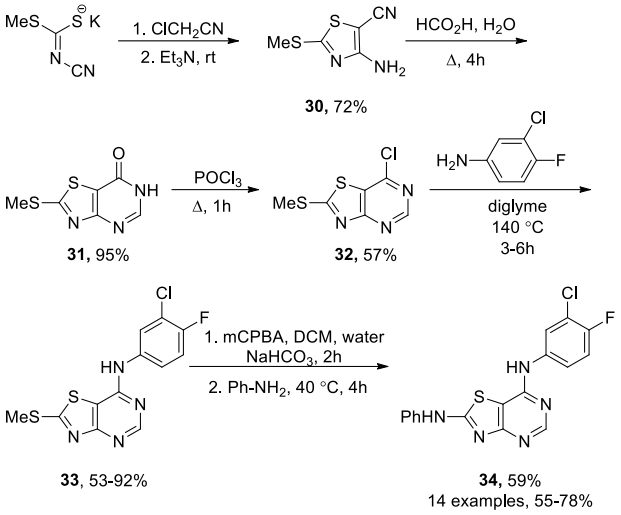
Shestapalov and co-workers have reported a direct one step synthesis of 7-hydroxy-2-anilino/methylthio[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones, such as **29** by treatment of *N*-cyanothioimidate salts, such as **26** (derived from cyanamide and phenyl isothiocyanate) with ethyl-4-chloroacetoacetate in ethanolic KOH, with the initial formation of 2-substituted-4-amino-5-functionalized thiazoles **28,** through intermediate **27**, which undergo concurrent in situ intramolecular cyclocondensation, leading to construction of pyridone ring of **29** (Scheme 6).[11b]The *N*-cyanothioimidate salts are derived from reaction of cyanamide, either with CS_2 or aryl isothiocyanates, thus limiting the substituent pattern at 2- position to either 2-methylthio or 2-anilino groups.



Scheme 6

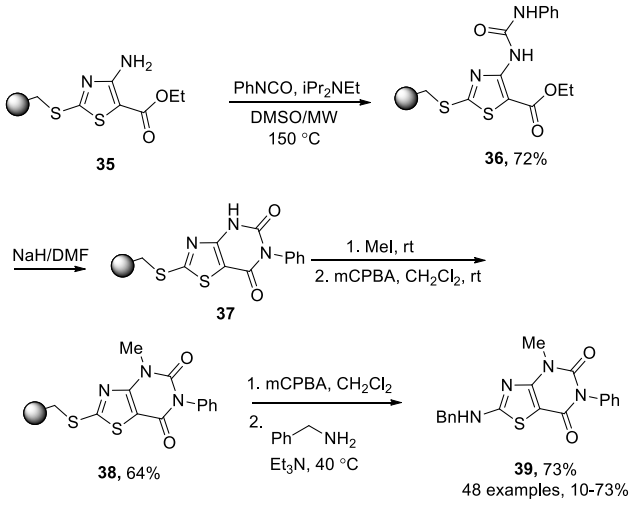
4.2.2 Synthesis of Thiazolo[4,5-*d*]pyrimidines

Lin and co-workers have reported synthesis of 2,7-diamino-thiazolo[4,5-*d*]pyrimidine analogs such as **33** and **34** as potential antitumor epidermal growth factor receptor (EFGR) tyrosine kinase inhibitors,[12a] starting from 2-methylsulfanyl-thiazole-5-carbonitrile **30,** which on refluxing in formic acid afforded corresponding 2-methylsulfanyl-6*H*-thiazolo[4,5-*d*]pyrimidine-7-one **31** in high yield (Scheme 7). Subsequent treatment of **31** with $POCl_3$ provided the corresponding 7-chloro-2-methylsulfanyllthiazolo[4,5-*d*]pyrimidin-7-one **32**, which on substitution with aromatic amines in diglyme at 140 °C yielded the 2-(methylsulfanylthiazolo[4,5-*d*]pyrimidine-7-yl) amines such as **33** in in 53-92% overall yields. The pyrimidines **33** were transformed into 2, 7-anilino thiazolopyrimidines **34** by subsequent oxidation of methylthio group with *m*CPBA and replacement of methylsulfonyl group with various aromatic amines (Scheme 7).[12a]



Scheme 7

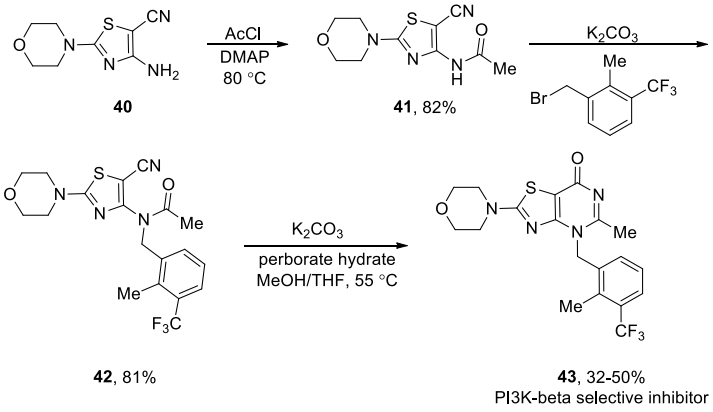
Lee and co-workers have developed an expedient traceless, solid-phase synthesis of 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidin-5,7-dione derivatives such as **39**,[12b] *via* initial, urea formation (**36**) by reaction of resin bound 4-aminothiazole-5-carboxylate **35** with phenyl isocyanate followed by base mediated cyclization of urea derivative **36** to thiazolopyrimidindiones **37**, which were in situ alkylated to give *N*-4, *N*-6 disubstituted thiazolo[4,5-*d*]pyrimidines **38** bearing two points of diversity. The thiazolopyrimidines **38**, were subjected to oxidation with mCPBA to form sulfone followed by its nucleophilic C-2 substitution with amines, to afford the target 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidines 5,7-diones derivatives **39**, having three points of diversity (Scheme 8).[12b]



Scheme 8

Recently, a novel thiazolopyrimidinone series as potential PI3K-beta selective inhibitors such as **43** has been identified and synthesized (Scheme 9).[12c] Thus the 4-amino-5-

cyanothiazole **40** was subjected to acylation with acetyl chloride to give *N*-acetylthiazole derivative **41**, which on subsequent *N*-alkylation with 2-methyl-3-trifluoromethylbenzyl bromide afforded the *N*,*N*-disubstituted thiazole **42** in good yield, which was cyclized in the presence of potassium carbonate and perborate hydrate to give desired 2-morpholino-5-methyl-4-*N*-(2-methyl-3-trifluotobenzyl)pyrimidin-7-one **43** in good yield (Scheme 9). This compound showed potent growth inhibition in the PTEN deficient breast cancer cell line MDA-MB-468 and also demonstrated pharmacodynamic effect and efficacy in a PTEN deficient prostate cancer PC-3 xenograft mouse model .[12c]



Scheme 9

4.2.3 Synthesis of Thiazolo[5,4-*b*] and Thiazolo[4,5-*b*]quinolines

Synthetic and biological profile of various regioisomeric thiazoloquinolines has been recently reviewed by Abdel-Wahab.[13a] A few of the biologically important thiazoloquinolines are displayed in Figure 3, among them , thiazolo[4,5-*f*]and thiazolo[5,4-*h*]quinolines **45-46** display strong antibacterial activity comparable to nalidixic acid.[13a] However, the present discussion is limited only to thiazolo[5,4-*b*] and thiazolo[4,5-*b*]quinolines, which are relevant to our work.

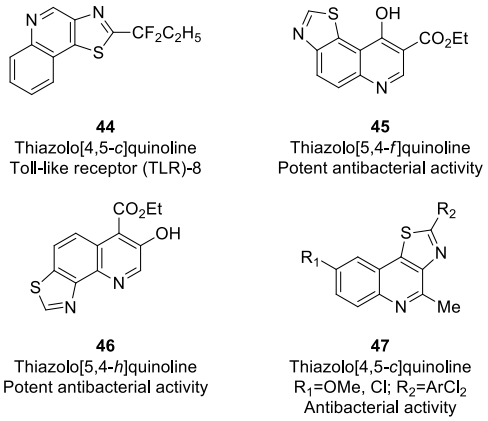
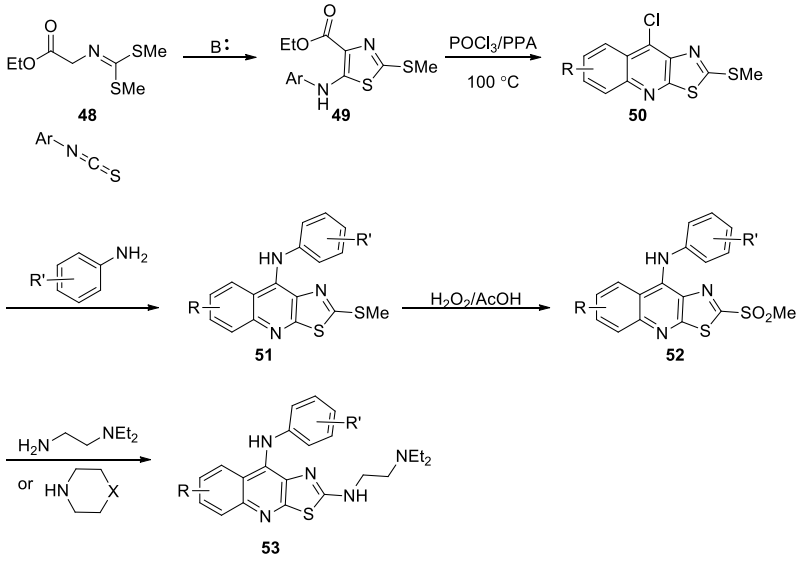


Figure 3

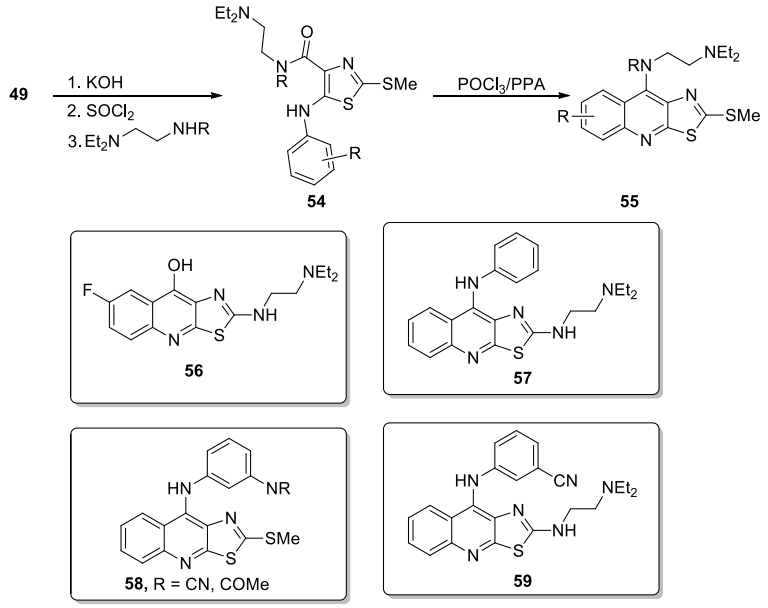
Alvarez-Ibarra[8a] and others[8b-d] have extensively examined the synthesis and biological activity of a series of 2-(methylthio)/amino-9-hydroxy/ary/alkyllamino-thiazolo[5,4-*b*]quinoline derivatives such as **53** and **55** (Figure 2, Scheme 10 and 11), which are shown to be cytotoxic on several cancer cell lines as well as being DNA intercalators and inhibitor of human topoisomerase II *in vitro*. These thiazolo[5,4-*b*]quinolines have been synthesized from the corresponding 2-(methylthio)-5-anilino-thiazolo-4-carboxylates **49**, involving their intramolecular cyclocondensation with $POCl_3$/PPA to give **50** and subsequent replacement of 9-chloro and 2-(methylthio) derivative in **50** with various amines affording 9-anilino- and 2-alkylamino-9-anilino derivatives such as **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 **48** and aryl isothiocyanates (Scheme 10).[16]



Scheme 10

Alternatively, a few of the 9-amino-2-(methylthio) thiazolo[5,4-*b*]quinolines such as **55** were prepared by $POCl_3$/PPA mediated cyclocondensation of the corresponding amide derivatives **54**, obtained by base mediated hydrolysis of the ester **49** and subsequent amidation with various amines in the presence of thionyl chloride (Scheme 11).

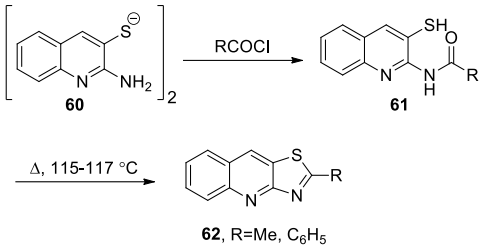
A structure activity relationship of various thiazolo[5,4-*b*]quinolines synthesized, showed that 7-fluoro-2-[(*N*,*N*-diethylamino)ethylamino]thiazolo[5,4-*b*]quinoline **56** exhibited significant cytotoxicity against mouse leukemic P-388, human lung carcinoma A-549, and human colon tumour HT-29cell growth *in vitro*.[8a] Similarly the corresponding 9-anilino-2-[(*N*,*N*-diethylamino)ethylaminothiazolo[5,4-*b*]quinoline **57** showed the best cytotoxicity among series, in several cancer cell lines.[8b] In a further study, Lira-Rocha and co-workers evaluated *in vitro* cytotoxicity of few newly prepared 9-anilino 2-alkylamino thiazolo[5,4-*b*]quinolines such as **58** and **59** and showed that inclusion of electron withdrawing/acceptor hydrogen bond groups at position 3' of anilino ring and the presences of an alkylamino chain on the tricyclic framework, regardless of position, seem to be the structural feature relevant to cytotoxicity and inhibition over human topoisomerase II of these compounds (Schemes 10-11).[8c-d]



Scheme 11

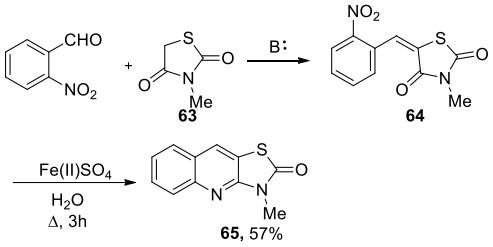
Despite extensive synthetic and biological studies on various substituted thiazolo[5,4-*b*]quinolines, our literature survey revealed that the synthesis of the related regioisomeric thiazolo[4,5-*b*]quinolines **6** have been scarcely investigated, [13] whereas the biological profile of these structural frame-works 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 .[14-15] Thus, in one isolated example, 2-methyl/phenylthiazolo[4.5-*b*]quinolines **62** have been synthesized in unreported yields via acylation of 2-amino-3-mercapto disulfide **60** followed by thermal cyclization of *N*-acyl derivatives **61** at higher temperature (Scheme 12).[14a]



Scheme 12

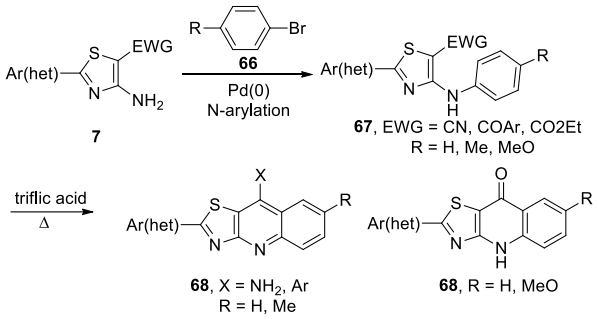
Similarly in an another example, the corresponding *N*-methyl-2-oxo-thiazolo[4,5-*b*]quinoline **65** was obtained in unreported yield by reductive cyclization of *N*-methyl- 5-(*o*-nitrobenzylidine)2,4-dioxoathiazolidine **64**, obtained by base mediated Aldol condensation of 2,4-dioxathiazolidine **63** with *o*-nitronbenzaldehyde (Scheme 13).[15a] Except these two literature examples, synthesis of thiazolo[4,5-*b*]quinolines completely remains unexplored.



Scheme 13

We therefore intended to develop new protocol for the synthesis of thiazolo[4,5-*b*]quinoline **6**, starting from our newly synthesized 2-het(aryl)-4-amino-5-functionalized thiazole precursors **7**, following a similar strategy as reported for regioisomeric thiazolo[5,4-*b*]quinolines **50** and **55** via acid mediated intramolecular cyclocondensation of 2-methyl-5-anilinothiazole-4-carboxylates precursors **49** (Scheme 10-11). However, for this purpose, we required to synthesize the corresponding 2-(het)aryl-4-arylamino—functionalized thiazoles precursors **67** from thiazoles **7** for which, we could not find any suitable, general methods for their synthesis in the literature. We have therefore developed successfully, a new two-step strategy for the synthesis of a series of hitherto unexplored 9-amino/aryl/oxothiazolo[4,5-*b*]quinolines **6** via palladium catalyzed *N*-arylation (Buchwald-Hartwig coupling) of 2-(het)aryl-4-amino-5-substituted thiazole **7**, to the corresponding 4-arylamino-2,5-

functionalized thiazole precursors **67** and followed by their acid mediated cyclocondensation to target thiazolo[4,5-*b*]quinolines **68** (Scheme 14). The results of these studies are described in the present chapter.



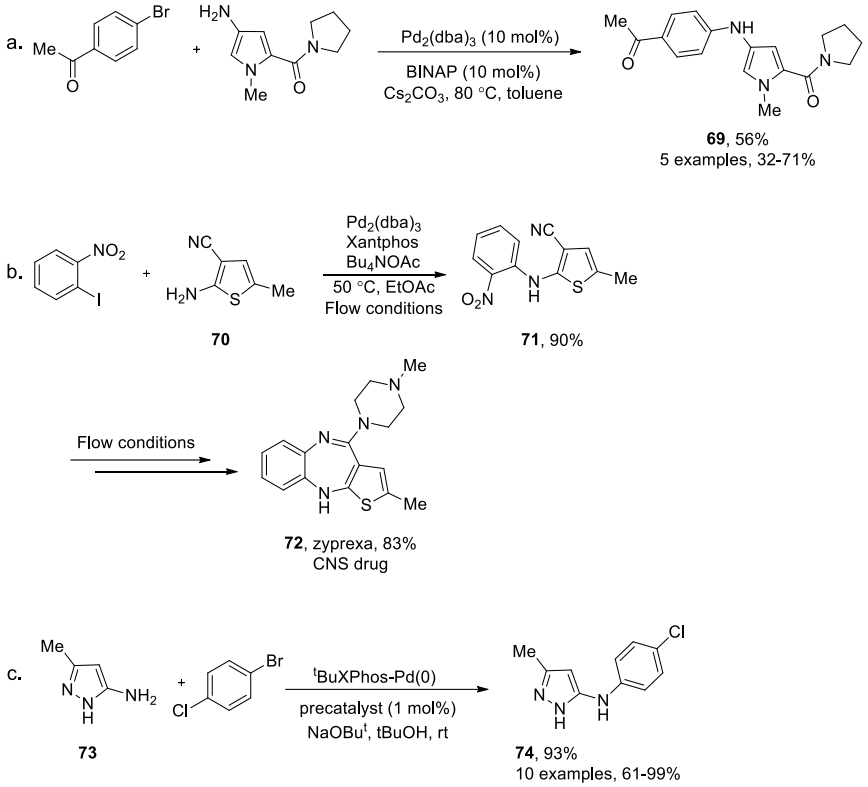
Scheme 14

However before reporting our research work, we first describe in the following section, a short recent literature survey of palladium catalyzed *N*-arylation of amino substituted 5- and 6-membered heterocycles relevant to our work.

4.2.4. Palladium catalyzed *N*-arylation of aminoheterocycles (Buchwald-Hartwig Coupling): A short literature survey

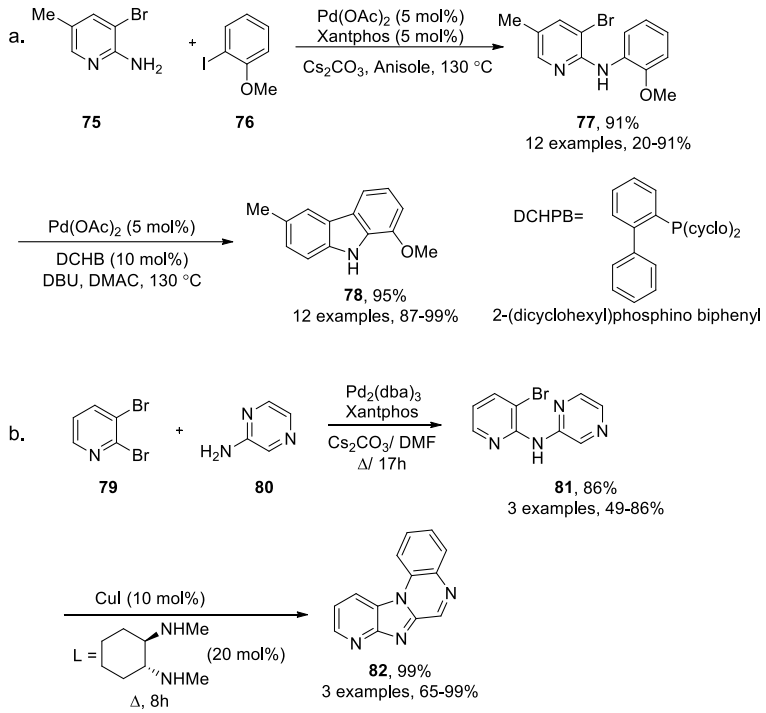
Palladium catalyzed cross coupling of aryl halides and NH containing derivatives (Buchwald Hartwig coupling) has been recognized as versatile method for construction of C-N bonds in organic synthesis and is widely practiced for the synthesis of pharmaceutical compounds, natural products and organic materials both in pharmaceutical and fine chemical industries as well as in academic setting.[17] A wide range of aryl halides can be coupled with primary and secondary aromatic or aliphatic amines under mild conditions with excellent functional group compatibility. Our literature search at this stage showed, however, that despite the wide application of this C-N coupling reaction, only a limited examples of Pd catalyzed *N*-arylation of heteroarylamines with aryl halides are known in the literature,[17] which is mainly limited to few five- and six- membered amino substituted heterocycles such as aminopyridines and aminoazines analogs.[17] A few reports of Pd catalyzed *N*-arylation of aminoazoles have been described,[17a] which are found to be more challenging substrates because of low *p*Ka value and corresponding decreased nucleophilicity of the amino group,[17a] which varies to some degree with the position of the NH_2 on the heteroaryl ring, often, resulting in low yields of *N*-arylated products, deactivation of catalyst and substrate decomposition and requiring high catalyst loading, longer reaction time and in most cases requiring an activated electrophile.[17a]

However, despite the sensitivity of five-membered aminoheterocycles to strongly basic conditions, the palladium catalyzed *N*-arylation of these compounds has been frequently exploited by medicinal chemists using ligands such as BINAP, Xantphos and others.[17a] Temperatures ranging from 60 to 150 °C are typically required to achieve satisfactory yields. A few selected examples of palladium catalyzed *N*-arylation of five- and six- membered aminoheterocycles are shown in the Schemes 15 -18. Thus, among one heteroatom five-membered heterocycles, *N*-protected 3-aminopyrroles were successfully arylated by Tanatani and coworkers to access tumour cell antagonists precursors **69** (Scheme 15a).[18] Scheme 15b depicts the continuous flow synthesis of the antipsychotic olanzapine (Zyprexa) **72**,a drug prescribed for the treatment of bipolar disorders and schizophrenia, which was achieved in overall 83% yield.[19] Thus, Kirschning and colleagues replaced the originally reported nucleophilic aromatic substitution step between 2-fluoronitrobenzene and aminothiophene **70** with a Pd-catalyzed cross coupling reaction with *o*-iodonitrobenzene derivative in either THF or EtOAc, leading to the desired arylaminothiophene intermediate **71** in high yield (90%). The reaction was conducted in a flow reactor filled with steel beads and using high-frequency inductive heating at 50 °C, higher temperatures led to decomposition and lower ones to reduced yields. The presence of base-sensitive *ortho*-substituents in both coupling partners was not problematic under these reaction conditions (Scheme 15b).[19] Example of methods for the *N*-arylation of unprotected amino-substituted pyrazole in a chemoselective fashion is displayed in Scheme 15c.[20] Moss and co-workers showed that using Pd-catalyzed cross-coupling conditions, 5-amino -1*H* pyrazole **73** is arylated exclusively at amino group in chemoselective manner, at room temperature in the presence of *t*-BuXPhos Pd-precatalyst and NaO*t*Bu to give 5-*N*-arylated pyrazoles **74** in high yields, with various aryl and hetaryl halides (Scheme 15c).[20]



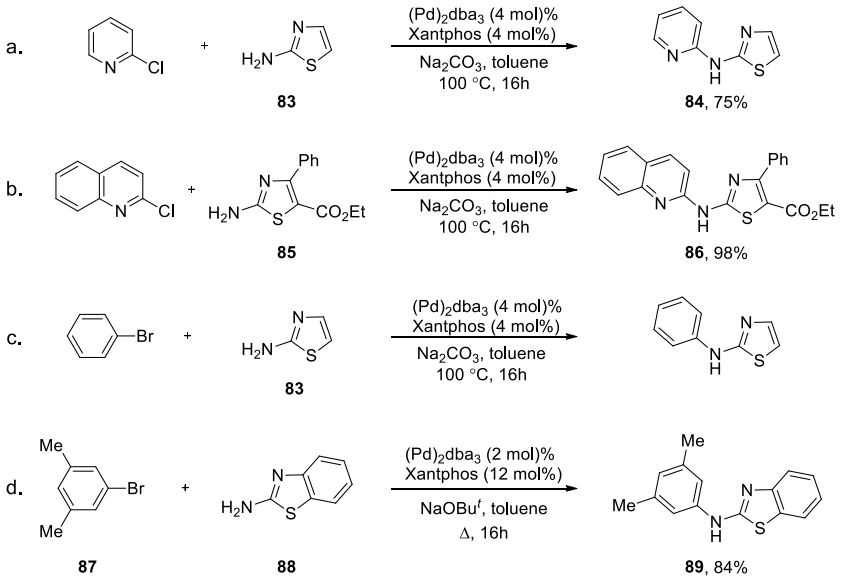
Scheme 15

Scheme 16a shows palladium catalyzed coupling of 2-amino-3-bromopyridine with aryl halides for accessing *α*-carbolines as shown by Sakamoto and co-workers[21a] previously, and recently by Mineno and Mizufune.[21b] Both *α*-carboline syntheses required different catalysts for each coupling step. Thus, selective *N*-arylation of 2-amino-3-bromopyridine **75** with a variety of aryl iodides led to arylated intermediates of type **77,** which were isolated in 20−91% yields. Next, intramolecular arylation was carried out to yield the *α*-carbolines **78** in 87-99% yield using DCHB ligand (Scheme 16a). Maes and co-workers have reported the preparation of tetracyclic heteroaromatic compound such as **82** by Pd catalyzed cross-coupling of aminobenzodiazines such as **80** and 2,3-dihalopyridines **79**.[22] In few cases, two consecutive C−N bond-formation events occur in auto tandem fashion or in sequential operations using Pd and Cu catalysts (Scheme 16b). In all reactions, a Pd catalyst and Xantphos ligand facilitated the first step in the presence of weak base and at high temperatures. The ring closing second step of **81** to **82** was achieved in presence of Cu catalyst and *trans* cyclohexane 1,2-diamine ligand (Scheme 16b).[22]



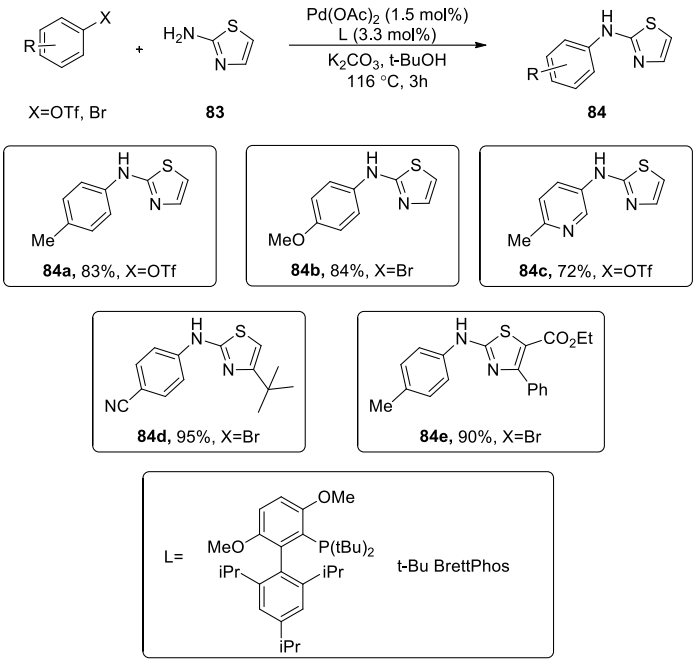
Scheme 16

Yin and co-workers have recently demonstrated palladium catalyzed *N*-arylation of mostly unfunctionalized 2-aminothiazoles such as **83** with electrophiles like 2-chloropyridine, 2-chloropyrimidines, 2-chloroquinoline or 4-nitrochlorobenzene, using Xantphos as ligand (Schemes 17a-17b), however reaction failed to proceed when 2-aminothiazole **83** was reacted with electron neutral bromoarenes under varying conditions (Scheme 17c).[23] On the other hand, 2-aminobenzothiazole **88** was found to react with aryl bromide **87** using sodium t-butoxide as base yielding 2-*N*-arylated benzothiazole **89** in 84% yield (Scheme 17d).[23]



Scheme 17

Buchwald and co-workers have also reported recently, palladium catalyzed *N*-arylation of 2-aminothiazole **83** and successfully achieved *N*-arylation of 2-aminothiazoles with electron neutral aryl bromide to furnish *N*-arylated compounds **84a-e** in high yields, using combination of $Pd(OAc)_2$, *t*-BuBrettPhos as ligand and potassium carbonate as base in *t*-butanol as solvent (Scheme 18).[24]



Scheme 18

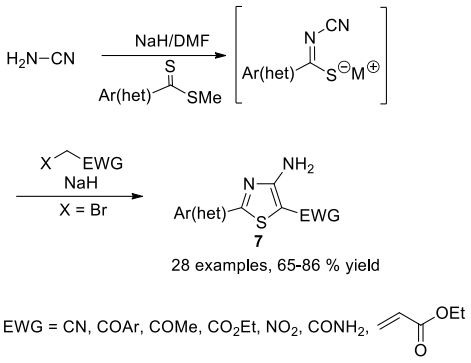
On the other hand, to the best of our knowledge, there are no examples in the literature for the intermolecular C-N bond formation between 4/5-amino thiazoles and their functionalized analogs with aryl halides, despite their pharmacological importance.

We therefore described in the following section, palladium catalyzed *N*-arylation of our newly synthesized 2-substituted-4-amino 5-functionalized thiazoles **7** with aryl halides with a view to develop effective reaction conditions for the synthesis of *N*-arylated aminothiazoles **67** for our further studies to develop a new synthetic route for a series of 9-amino/aryl/oxothiazolo[4,5-*b*]quinolines.

4.3 Results and Discussion

4.3.1 Palladium catalyzed *N*-arylation of 2-(het)aryl-4-amino-5-functionalized thiazoles

The desired 4-amino-2-(het)aryl-5-substituted thiazoles **7a-o** selected for the present study, were synthesized according to our previously reported procedure from cyanamide, (het)aryldithioesters and various activated methylene halides (Scheme 19, Chart 1).[9a]



Scheme 19

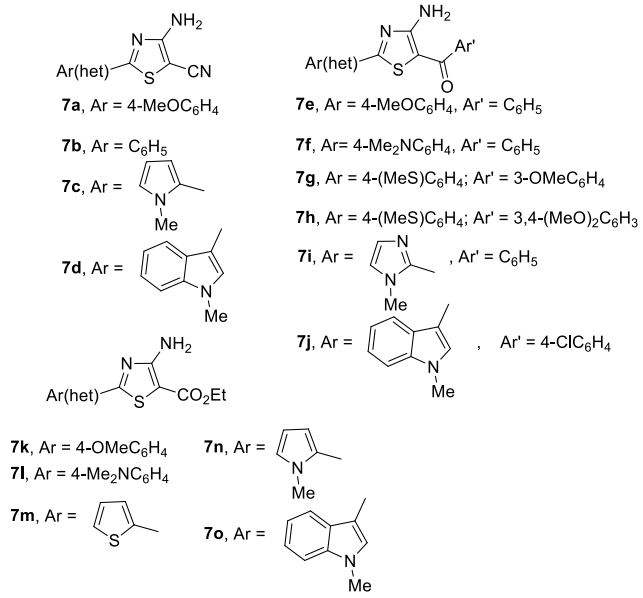


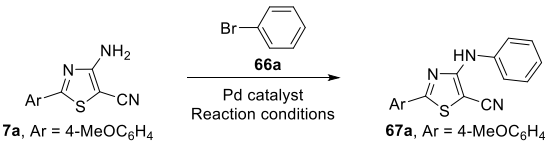
Chart 1. Various 2,5-substituted-4-aminothiazoles employed for the present study.

The reaction between 2-phenyl-4-amino-5-cyanothiazole **7a** and bromobenzene was first investigated to obtain optimal conditions for formation of **67a** via palladium catalyzed C-N cross- coupling (Table 1). Among various palladium sources tested as precatalysts, palladium acetate $Pd(OAc)_2$ yielded best results. Ligands such as racemic BINAP, DPPF and Xantphos, tBuBrettPhos have been previously employed for C-N cross coupling of various heterocyclic substrates.[17-18] Similarly sodium *t*-butoxide, Cs_2CO_3, K_2CO_3 and K_3PO_4 are quite often used as preferred bases in such kind of *N*-arylation reactions. We therefore focused our preliminary studies using these ligands and bases and the results are summarized in Table 1.

Thus, by heating a solution of thiazole **7a** and bromobenzene using 5 mol% of palladium acetate, BINAP (10 mol%) as ligand in the presence of sodium *t*-butoxide (2 equiv) as base for 15 hr at 100 ^{0}C, showed only low conversion to **67a** (entry 1). Similar results were also obtained by applying DPPF as ligand (entry 2). However, improved, but moderate yield of **67a** was obtained using Xantphos as ligand (entry 3). Increasing the catalytic loading from 5 mol% to 10 mol % resulted in full conversion and yielding **67a** in improved yield (entry 4) (to improve

the reaction efficiency). Further enhancement in the yield of **67a** was observed by replacing sodium *t*-butoxide by weaker base like Cs_2CO_3 under identical conditions (entry 5).Better results were obtained when reaction was conducted in dioxane as solvent instead of toluene, producing **67a** in 81 % yield within 12 hr (entry 6). Use of other weaker bases such as K_3PO_4 or K_2CO_3 also yielded **67a** in decreased yields (Table 1, entries 7-8). Reducing the catalytic loading to 8 mol % from 10 mol% resulted in lower yield of **67a** (entry 9). Reaction with $Pd(dba)_3$ as palladium source instead of $Pd(OAc)_2$ also did not show any marked effect in reaction yield (entry 10). Unfortunately, these general reaction conditions were found to be incompatible with chlorobenzene as electrophile with **7a** succumbing to very low product conversion (entry 11). We therefore proceeded with further *N*-arylation studies by applying optimal reaction conditions shown in entry 6 requiring higher catalytic loading.

Table 1 Optimization of reaction conditions for Pd catalyzed *N*-arylation of 4-Amino-5-cyanothiazole **7a** to **67a**



7a, Ar = 4-MeOC$_6$H$_4$ — **67a**, Ar = 4-MeOC$_6$H$_4$

Entry	Pd catalyst	Ligand	Base	Solvent	temperature (°C)	time (h)	% yield, 68a[a]
1[a]	$Pd(OAc)_2$	BINAP	tBuONa	Toluene	100	15	10
2[a]	$Pd(OAc)_2$	DPPF	tBuONa	Toluene	100	15	23
3[a]	$Pd(OAc)_2$	Xantphos	tBuONa	Toluene	100	15	62
4[b]	$Pd(OAc)_2$	Xantphos	tBuONa	Toluene	100	15	70
5[b]	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Toluene	100	15	78
6[b]	**$Pd(OAc)_2$**	**Xantphos**	**Cs_2CO_3**	**Dioxane**	**100**	**12**	**81**
7[b]	$Pd(OAc)_2$	Xantphos	K_3PO_4	Dioxane	100	12	62
8[b]	$Pd(OAc)_2$	Xantphos	K_2CO_3	Dioxane	100	12	58
9[c]	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Dioxane	100	12	68
10[b]	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	Dioxane	100	12	69
11[d]	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Dioxane	100	12	15

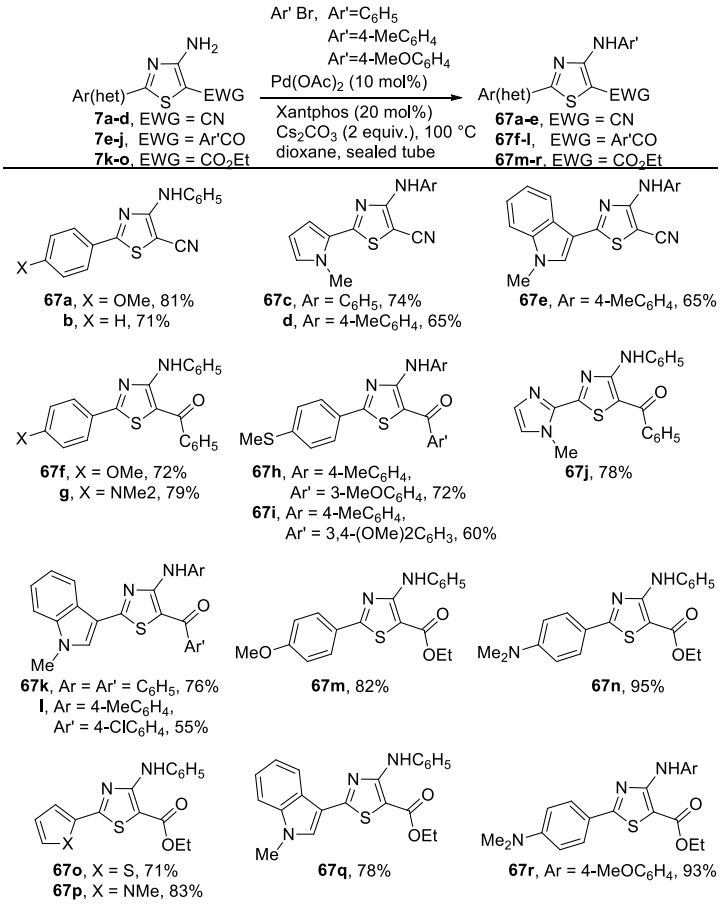
[a]Reaction conditions: 1.0 mmol **7a**; 1.05 mmol BrC_6H_5; [a]5 mol% $Pd(OAc)_2$; 10 mol% ligand; [b]10 mol% $Pd(OAc)_2$; 20 mol% ligand; [c]8 mol% $Pd(OAc)_2$; 10 mol% ligand; [d]chlorobenzene as electrophile.

After optimization conditions were established, we explored (evaluated) the generality and scope of the reaction for Pd catalyzed N-arylation of various (few selected) 4-aminothiazoles **7** with different functionalities at 2 and 5 positions (Scheme 20). Thus 2-substituted aryl- and 2-(2-*N*-methylpyrrolyl)- and 2-(*N*-methyl-3-indolyl)-5-cyanothiazoles **7b-d** also underwent smooth N-arylation with bromobenzene **66a**, yielding products **67b-d** in good yields. When 4-methylbromobenzene **66b** was used as an electrophilic coupling partner and reacted with thiazole **7c**, the corresponding *N*-arylthiazole **67e** was obtained in accepted (reasonable) yield of 65% (Scheme 20). On the other hand, the corresponding 4-

methoxybromobenzene **66c** was found to be ineffective under these conditions, when reacted with thiazole **7a,** furnishing only complex mixture of products.

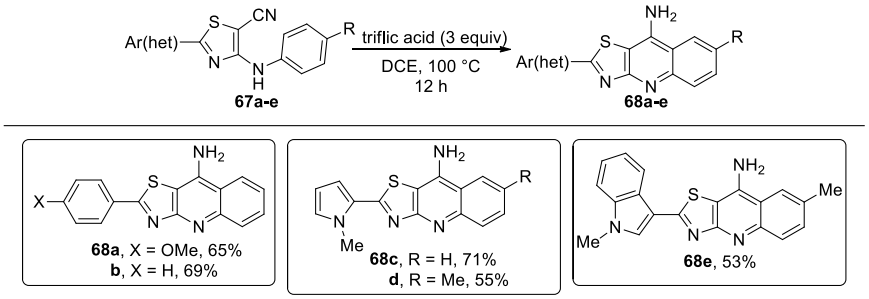
With successful results with various 4-amino-5-cyanothiazoles , we next extended these studies for N-arylation of 5-aroylthiazoles **7e-j** (Chart 1, Scheme 20). Thus the present reaction conditions were found to be equally effective (viable) for these substrates and bromobenzene as electrophilic partner, affording the corresponding 2-substituted-4-anilino-5-benzoylthiazoles **67f-i** in high yields (Scheme 20). Similarly, the related 4-methylanilino-5-aroyl thiazoles **67j-l** could also be prepared in moderate to good yields by employing 4-bromotoluene as electrophilic coupling partner under identical conditions.

These optimized Pd catalyzed N-arylation reaction conditions were found to be equally effective for the N-arylation of 4-aminothiazole 5-carboxylates **7k-o** yielding the corresponding 4-*N*-arylaminothiazole carboxylates 10m-q in overall reasonable good yields (Scheme 20).



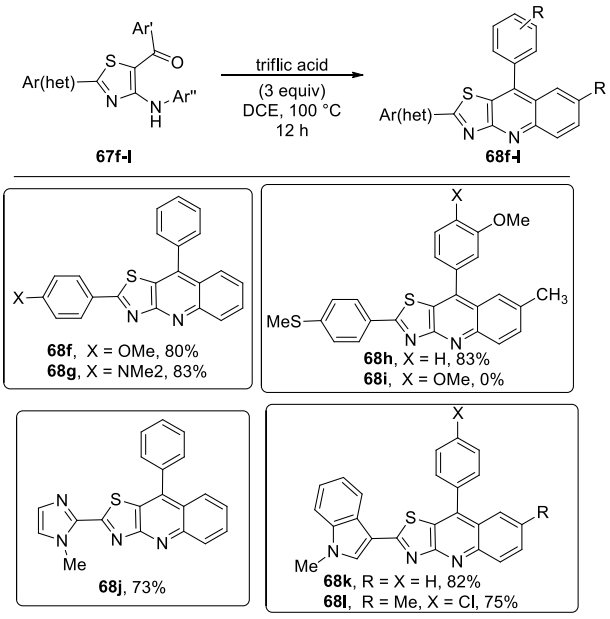
Scheme 20

Cyclocondensation of the 4-(*N*-arylated)-5- cyano-/5-aroylthiazoles **67a-e** and **67f-l** to the corresponding 9-amino-/aryl-thiazolo[4,5-*b*]quinolines **68a-e** and **68f-l** was next examined in the presence of various protic and Lewis acids (dilute H_2SO_4) TsOH, MsOH, PPA, TFA, triflic acid $AlCl_3$ etc). However, present cycloisimerization of **67a** to **68a** required drastic conditions and best yield of 9-aminothiazolo[4,5-*b*]quinoline **68a** was obtained, when the **67a** was reacted with 3 equiv of triflic acid in dichloroethane at 100 ^{0}C for 12-15 hr (Scheme 21). These reaction conditions were followed for cyclization of other 5-cyano-4-anilino-thiazoles **67b-e** also, furnishing the corresponding 2-(het)aryl-9-aminothiazolo[4,5-*b*]quinolines **68b-e** in moderate to good yields (Scheme 21).



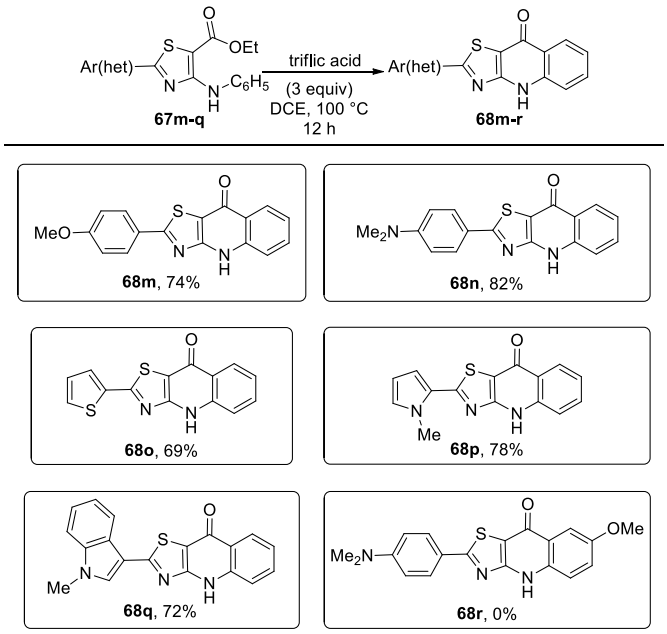
Scheme 21

On the other hand, cycization of the corresponding 5-aroyl-4-*N*-arylated thiazoles **67f-l** was found to be very facile under these reaction conditions, affording the respective 9-aryl-2-(het)aryl-thiazolo[4,5-*b*]quinolines **68f-l** in excellent yields (73-83%) (Scheme 22). The 4-(4-methylanilino)-5-(3,4-dimethoxy)benzoylthiazole **67l** however, yielded complex mixture of products , because of concurrent demethylation of 4-methoxy group under these conditions (Scheme 22).



Scheme 22

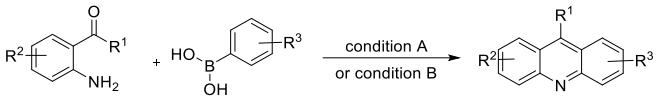
Intramolecular cyclization of the corresponding 4-anilinothiazole-5-carboxylates **67m-q** also proceeded smoothly under these conditions using triflic acid yielding thiazolo[4,5-*b*]quinolones **68m**-q in good yields (Scheme 23).



Scheme 23

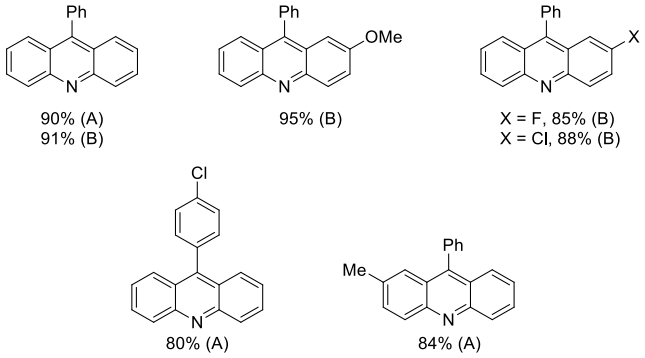
4.3.2 Attempted Synthesis of 9-arylthiazolo[4,5-*b*]quinolines via Tandem *N*-Arylation-Cyclization Protocol

We also attempted tandem *N*-arylation-cyclization of 4-amino 5-benzoylthiazole **67f** with a view to obtain the thiazolo[4,5-*b*]quinoline **68f** directly in one pot reaction, as described for the synthesis of 9-aryl/amino acridines by several research groups in recent papers. This transformation is usually achieved in acridine series, either by intermolecular copper catalyzed Chan-Lam coupling of *o*-aminophenones/ benzaldehydes with arylboronic acids and subsequent in situ intramolecular Friedel-Crafts type cyclization of the resulting *o*-*N*-aryl ketones, or sometimes in the presence of added reagents like *t*-butyl bromide/TFE (Scheme 24) .[25a-b]



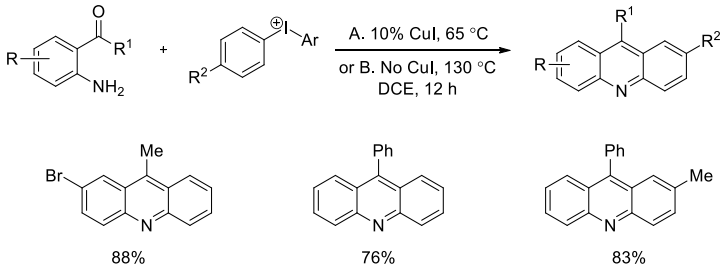
Condition A: $Cu(OTf)_2$. TFE, 100 °C.

Condition B: 1. $Cu(OAc)_2$ (10 mol%), CF_3CH_2OH (TFF) 1 mL, rt, 12 h; 2. t-butyl bromide, (2 equiv), rt, 24 h.



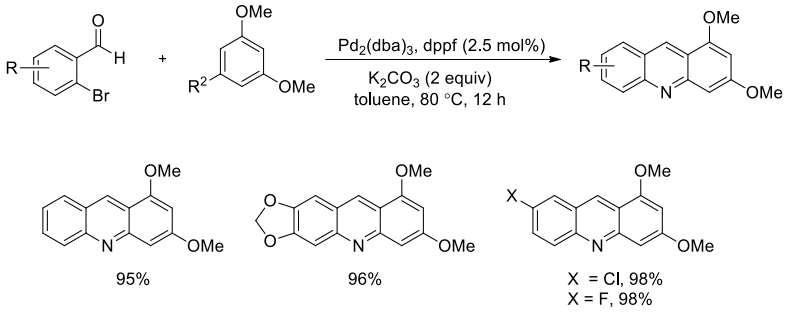
Scheme 24

Alternatively, the 2-acylanilines have also been shown to couple with diarylaiodinium salts in presence of copper catalyst, which acts as promoter for in situ intramolecular cyclization to 9-substituted acridines (Scheme 25).[25c-d]



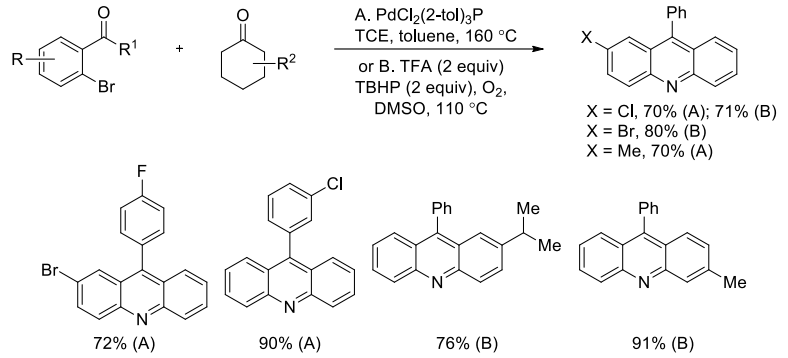
Scheme 25

9-Substituted acridines have also been synthesized by Pd catalyzed tandem N-arylation-intramolecular cyclization of *o*-aminoaldehydes with either aromatic halides/triflates (Scheme 26) [26a-b]



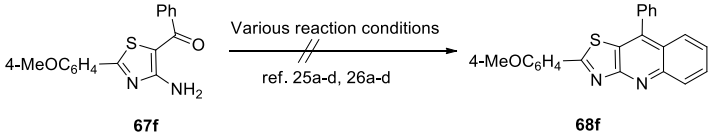
Scheme 26

or by Pd catalyzed condensation-cyclization and aromatization sequence of *o*-aminobenzophenone with cyclohexanone in presence of tri(*o*-tolyl) phosphine ligand,[20c] or by oxidative cyclization in the presence of TFA, *t*-butyl hydroperoxide (TBHP) under O_2 atmosphere in DMSO at higher temperature (Scheme 27).[26d]



Scheme 27

However, our attempted concomitant *N*-arylation -intramolecular cyclization of thiazole **67f** to **68f** under various reaction conditions and catalyst did not meet with much success, yielding either N-arylation products or intractable reaction mixture (Scheme 28). Further work in this direction is under progress in our laboratory.



Scheme 28

4.4 Conclusion

In summary, we have developed(demonstrated) an efficient approach for the facile synthesis of novel 9-aryl/aminothiazolo[4,5-*b*]quinoline scaffolds from 2-substituted-4-amino-5-aroyl/cyano thiazoles involving palladium catalyzed N-arylation-cyclization sequence. Further, the reaction could be successfully extended to prepare thiazolo[4,5-*b*]quinolones from 4-aminothiazole-5-carboxylate as starting material following similar strategy. Because of the promising activity of the reported thiazolo[5,4-*b*]quinoline derivatives as potent antiproliferative and cytotoxic agents,[8] further elaboration of these newly synthesized thiazolo[4,5-*b*]quinolines is currently underway in our laboratory for biological screening. Since Pd catalyzed *N*-arylation of five membered amino substituted heterocycles is found to be challenging and not much explored, the present method offers an alternative approach to access new heterocyclic scaffolds, especially bioisosteres of acridine (heterofused quinolines) with potential biological activity. This work along with to develop tandem one-pot *N*-arylation-cyclization protocol are in progress in our laboratory and will be published later.

4.5 Experimental section

4.5.1 General Information.

All reagents were purchased from commercial suppliers and used without further purification. All reactions were monitored by thin layer chromatography (TLC) and silica gel plates were visualized with UV light. Column chromatography was performed using silica gel (60−120 mesh). Nuclear magnetic resonance spectra were recorded on Brucker (400 MHz) ultrashield plus FT-NMR spectrometer with $CDCl_3$, DMSO-d_6 as solvents. Chemical shifts were reported in δ ppm using either residual solvent protons as internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6 in ^{1}H NMR, δ 77.16 for $CDCl_3$, δ 39.52 for DMSO-d_6 in ^{13}C NMR) or TMS as internal standard. Coupling constants were reported as *J* values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), m (multiplet), and br (broad). Infrared spectra of neat samples were recorded in attenuated total reflectance mode using Fourier transform infrared instrument (Agilent technologies) and HRMS on a 6538 UHD accurate mass Q-TOF LC/MS spectrometer through electron spray ionization (ESI) mode. Melting points were recorded using an electrothermal capillary melting point

apparatus and are uncorrected. All thiazoles **7a-o** were prepared according to the reported procedure.[9a] The data of unreported thiazoles **7b, 7g, 7j, 7l-n** are given below.

4.5.2 Spectral data of compounds 7b, 7g, 7j, 7l-n

4-Amino-2-phenylthiazole-5-carbonitrile (7b): After column chromatography (EtOAc/hexane 3:7) 146 mg (73%) of brown solid was obtained; mp 210-211 °C. R_f = 0.3 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 3450, 2245. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.2 Hz, 2H), 7.57-7.50 (m, 3H), 7.29 (brs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.0, 171.4, 137.1, 136.9, 134.6, 131.6, 119.8, 74.2. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{10}H_8N_3S$ 202.0439, found 202.0469.

(4-Amino-2-(4-(methylthio)phenyl)thiazol-5-yl)(3-methoxyphenyl)methanone (7g): After column chromatography (EtOAc/hexane 2:8) 249 mg (70%) of yellow solid was obtained; mp 149-150 °C. R_f 0.2 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3143, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.45-7.36 (m, 3H), 7.25 (d, J = 8.4 Hz, 2H), 7.07 (ddd, J = 8.0, 2.6, 1.0 Hz, 1H), 6.99 (brs, 2H), 3.88 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 172.2, 165.4, 159.8, 144.1, 142.4, 129.6, 129.1, 127.1, 125.9, 120.1, 117.7, 112.6, 102.6, 55.6, 15.1. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_2S_2$ 357.0731, found 357.0714.

(2-Amino-2-(1-methyl-1*H*-indol-3-yl)thiazol-5-yl)(4-chlorophenyl)methanone (7j): After column chromatography (EtOAc/hexane 2:8) 260 mg (71%) of brown solid was obtained; mp 130-131 °C; R_f 0.3 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3211, 1725. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.19 (s, 1H), 8.17 (brs, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 7.32 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 6.6 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.3, 167.7, 166.3, 140.1, 137.3, 135.6, 133.3, 129.1, 128.6, 124.6, 122.9, 121.8, 120.6, 111.1, 108.9, 97.6, 33.2. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{19}H_{15}ClN_3OS$ 368.0624, found 368.0614.

Ethyl-4-amino-2-(4-(dimethylamino)phenyl)thiazole-5-carboxylate (7l): After column chromatography (EtOAc/hexane 4:6) 276 mg (95%) of orange solid was obtained.Orange solid; mp 152-153. °C. R_f 0.3 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3325, 1720. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 9.2 Hz, 2H), 6.67 (d, J = 9.2 Hz, 2H), 5.86 (brs, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.04 (s, 6H), 1.35 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 171.5, 164.5, 163.3, 152.4, 128.1, 120.8, 111.5, 60.2,

40.1, 14.6. HRMS (ESI-QTOF) *m/z* $[M]^+$ calcd for $C_{14}H_{17}N_3O_2S$ 291.1041, found 291.1036.

Ethyl-4-amino-2-(thiophen-2-yl)thiazole-5-carboxylate (7m): After column chromatography (EtOAc/hexane 1:9) 190 mg (75%) of yellow solid was obtained; mp 119-120°C; R_f 0.2 (1:9 EtOAc/hexane). IR (neat, cm^{-1}) 3257, 1715. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 3.2 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.09 (t, J = 4.4 Hz, 1H), 5.97 (brs, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 163.9, 162.8, 136.8, 129.4, 128.2, 127.9, 126.5, 60.5, 14.5. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_2S_2$ 255.0262, found 255.0259.

Ethyl-4-amino-2-(1-methyl-1*H*-pyrrol-2-yl)thiazole-5-carboxylate (7n): After column chromatography (EtOAc/hexane 3:7) 200 mg (80%) of yellow solid was obtained; mp 125-126 °C. R_f 0.3 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 3150, 1726. ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, J = 4.0, 1.6 Hz, 1H), 6.76 (t, J = 2.0 Hz, 1H), 6.15 (dd, J = 3.8, 2.6 Hz, 1H), 5.84 (brs, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 163.1, 162.9, 128.3, 126.3, 114.3, 108.9, 60.3, 37.0, 14.6. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{11}H_{14}N_3O_2S$ 252.0807, found 252.0799.

4.5.3 General procedure for the synthesis of 2-(het)aryl-4-*N*-arylamino-5 functionalized thiazoles 67a-r

A solution of commercially available Cs_2CO_3 (650 mg, 2 equiv), $Pd(OAc)_2$ (23 mg, 10 mol%), Xantphos (116 mg, 20 mol%), corresponding bromoarenes **13a-c** and the thiazole **7** in dioxane (6 mL) was heated at 100 °C in a sealed tube for 12 hours (monitored by TLC), and the reaction mixture was then quenched with satd. NH_4Cl solution (25 mL) and extracted with EtOAc (2×25 mL). The combined organic layer was washed with water (3×25 mL) and brine (1×25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the crude residue was purified by column chromatography.

2-(4-Methoxyphenyl)-4-(phenylamino)thiazole-5-carbonitrile (67a): After column chromatography (EtOAc/hexane 1:9) 248 mg (81%) of yellow solid was obtained; mp 162-163 °C. R_f 0.3 (1:9 EtOAc/hexane). IR (neat, cm^{-1}) 3322, 2199. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 8.0 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.91 (brs, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 162.9, 161.6, 139.7, 129.3, 128.7, 125.2, 123.4, 119.3,

114.7, 114.2, 75.1, 55.7. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}N_3OS$ 308.0858, found 308.0848.

2-Phenyl-4-(phenylamino)thiazole-5-carbonitrile (67b): After column chromatography (EtOAc/hexane 1:9) 197 mg (71%) of yellow solid was obtained; mp 153-154 °C. R_f 0.2 (1:9 EtOAc/hexane). IR (neat, cm^{-1}) 3312, 2199. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.8 Hz, 2H), 7.54-7.52 (m, 3H), 7.48 (td, J = 8.4, 1.6 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.92 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 162.2, 129.5, 124.9, 117.2, 115.0, 114.6, 114.5, 110.3, 108.9, 65.5. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}N_3S$ 278.0752, found 278.0743.

2-(1-Methyl-1*H*-pyrrol-2-yl)-4-(phenylamino)thiazole-5-carbonitrile (67c): After column chromatography (EtOAc/hexane 3:7) 207 mg (74%) of yellow solid was obtained; mp 178-179 °C. R_f 0.2 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 3327, 2194. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.08 (t, J = 7.4 Hz, 1H), 6.92 (brs, 1H), 6.84 (dd, J = 4.0, 1.6 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.19 (dd, J = 4.0, 2.4 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.2, 139.7, 129.1, 129.0, 125.6, 123.1, 119.2, 115.1, 114.3, 109.4, 72.8, 37.3. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_{12}N_4S$ 281.0861, found 281.0846.

2-(1-Methyl-1*H*-pyrrol-2-yl)-4-(*p*-tolylamino)thiazole-5-carbonitrile (67d): After column chromatography (EtOAc/hexane 2:8) 191 mg (65%) of yellow solid was obtained; mp 180-181 °C. R_f 0.2 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3485, 2250. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.96 (brs, 1H), 6.82 (t, J = 3.4 Hz, 2H), 6.19 (t, J = 3.2 Hz, 1H), 3.99 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.5, 137.2, 132.8, 129.5, 129.0, 125.6, 119.5, 115.0, 114.6, 109.3, 71.9, 37.3, 20.8. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}N_4S$ 295.1017, found 295.0988.

2-**(1-Methyl-1*H*-indol-3-yl)-4-(*p*-tolylamino)thiazole-5-carbonitrile (67e):** After column chromatography (EtOAc/hexane 4:6) 224 mg (65%) of yellow solid was obtained; mp 160-161 °C. R_f 0.25 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3500, 2237. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.2 Hz, 1H), 7.83 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.40-7.36 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.80 (brs, 1H), 3.89 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 160.7, 136.7, 136.4, 132.0, 130.3, 128.8, 124.2, 122.5, 121.4, 120.0, 118.9, 113.9, 109.5, 109.3, 70.8, 32.6, 19.9. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_4S$ 345.1174, found 345.1149.

(2-(4-Methoxyphenyl)-4-(phenylamino)thiazol-5-yl) (phenyl)methanone (67f): After column chromatography (EtOAc/hexane 2:8) 278 mg (72%) of yellow solid was obtained; mp 120-121 °C. R_f 0.2 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3004, 1738. ^1H NMR (400 MHz, $CDCl_3$) δ 11.14 (brs, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.54-7.47 (m, 3H), 7.38 (t, J = 8.0 Hz, 2H), 7.08 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 172.7, 162.8, 161.8, 141.2, 139.9, 131.4, 129.0, 128.8, 128.5, 127.7, 125.7, 122.8, 119.7, 114.4, 104.5, 55.5. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2S$ 387.1167, found 387.1221.

(2-(4-(Dimethylamino)phenyl)-4-(phenylamino)thiazol-5-yl)(phenyl)methanone (67g): After column chromatography (EtOAc/hexane 3:7) 315 mg (79%) of yellow solid was obtained; mp 141-142 °C. R_f 0.2 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 3009, 1737. ^1H NMR (400 MHz, $CDCl_3$) δ 11.27 (brs, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.89 (dd, J = 7.8, 1.4 Hz, 2H), 7.85 (d, J = 7.6 Hz, 2H), 7.54-7.50 (m, 3H), 7.39 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 3.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 173.9, 162.2, 152.9, 141.7, 140.3, 131.2, 129.1, 128.8, 128.6, 127.8, 127.7, 120.7, 119.8, 111.6, 103.8, 40.2. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}N_3OS$ 400.1484, found 400.1462.

(3-Methoxyphenyl)(2-(4-(methylthio)phenyl)-4-(*p*-tolylamino)thiazol-5-yl)methanone (67h): After column chromatography (EtOAc/hexane 2:8) 321 mg (72%) of yellow solid was obtained; mp 123-124 °C. R_f 0.3 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3092, 1720. ^1H NMR (400 MHz, $CDCl_3$) δ 11.06 (brs, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.46 (dd, J = 6.4, 1.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.08 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 3.89 (s, 3H), 2.53 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 172.4, 161.9, 159.7, 144.2, 142.5, 137.3, 132.5, 129.59, 129.58, 129.2, 127.2, 125.7, 120.0, 119.8, 117.7, 112.6, 104.3, 55.5, 20.9, 15.0. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_2S$ 447.1201, found 447.1206.

(3,4-Dimethoxyphenyl)(2-(4-(methylthio)phenyl)-4-(*p*-tolylamino)thiazol-5-yl)methanone (67i): After column chromatography (EtOAc/hexane 3:7) 285 mg (60%) of yellow solid was obtained; mp 152-153 °C. R_f 0.2 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 2921, 1737. ^1H NMR (400 MHz, $CDCl_3$) δ 11.09 (brs, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 8.4, 2.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 3.97 (s, 3H), 3.96

(s, 3H), 2.53 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 171.8, 161.9, 151.9, 149.1, 144.1, 137.5, 133.8, 132.4, 129.6, 129.3, 127.2, 125.8, 121.5, 119.7, 110.9, 110.2, 103.9, 56.1, 20.9, 15.0. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_3S_2$ 477.1307, found 477.1275.

(2-(1-Methyl-1*H*-imidazol-2-yl)-4-(phenylamino)thiazol-5-yl)(phenyl)methanone (67j): After column chromatography (EtOAc/hexane 5:5) 280 mg (78%) of yellow solid was obtained; mp 153-154 °C. R_f 0.2 (5:5 EtOAc/hexane). IR (neat, cm^{-1}) 2921, 1737. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (brs, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.58-7.53 (m, 1H), 7.51-7.47 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.17 (s, 1H), 7.12-7.08 (m, 2H), 4.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 163.3, 161.4, 140.8, 140.1, 139.8, 131.7, 130.3, 128.9, 128.6, 127.8, 125.7, 123.0, 119.9, 104.7, 35.9. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_4OS$ 361.1123, found 361.1166.

(2-(1-Methyl-1*H*-indol-3-yl)-4-(phenylamino)thiazol-5-yl)(phenyl)methanone (67k): After column chromatography (EtOAc/hexane 5:5) 310 mg (76%) of yellow solid was obtained; mp 140-141 °C. R_f 0.2 (5:5 EtOAc/hexane). IR (neat, cm^{-1}) 2997, 1738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (brs, 1H), 8.19 (t, *J* = 4.4 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.85 (t, *J* = 8.0 Hz, 3H), 7.54-7.48 (m, 3H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.37-7.32 (m, 3H), 7.09 (t, *J* = 7.4 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 168.4, 162.0, 141.7, 140.3, 137.7, 131.9, 131.2, 129.1, 128.6, 127.8, 125.3, 123.4, 122.8, 122.3, 121.2, 120.0, 111.0, 110.3, 102.8, 33.6. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}N_3OS$ 410.1327, found 410.1336.

(4-Chlorophenyl)(2-(1-methyl-1*H*-indol-3-yl)-4-(*p*-tolylamino)thiazol-5-yl)methanone (67l): After column chromatography (EtOAc/hexane 5:5) 251 mg (55%) of yellow solid was obtained; mp 135-136 °C. R_f 0.2 (5:5 EtOAc/hexane). IR (neat, cm^{-1}) 2997, 1738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (brs, 1H), 8.19 (dd, *J* = 6.6, 2.8 Hz, 1H), 7.92 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.41-7.34 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 168.5, 162.4, 140.0, 137.6, 137.5, 137.1, 132.5, 131.9, 129.5, 129.1, 128.7, 125.2, 123.3, 122.2, 121.1, 120.1, 110.9, 110.2, 101.9, 33.5, 20.9. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}ClN_3OS$ 458.1094, found 458.1093.

Ethyl-2-(4-methoxyphenyl)-4-(phenylamino)thiazole-5-carboxylate (67m): After column chromatography (EtOAc/hexane 2:8) 290 mg (82%) of yellow solid was obtained; mp 300-302 °C. R_f 0.2 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3298, 1657. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (brs, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz,

2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6. 98 (d, *J* = 8.8 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.5, 164.8, 162.4, 160.0, 140.6, 129.1, 128.6, 126.2, 122.1, 118.8, 114.5, 94.9, 60.8, 55.6, 14.7. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_3S$ 355.1116, found 355.1109.

Ethyl-2-(4-(dimethylamino)phenyl)-4-(phenylamino)thiazole-5-carboxylate (67n): After column chromatography (EtOAc/hexane 3:7) 348 mg (95%) of orange solid was obtained; mp 320-322 °C. R_f 0.2 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 3286, 1651. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.21 (brs, 1H), 7.89 (d, *J* = 9.2 Hz, 2H), 7.71 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.00 (td, *J* = 7.8, 1.2 Hz, 1H), 6.69 (d, *J* = 9.2 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.04 (s, 6H), 1.38 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.4, 164.8, 160.0, 152.5, 140.6, 128.9, 128.3, 121.8, 121.0, 118.5, 111.5, 93.4, 60.4, 40.1, 14.6. HRMS (ESI-QTOF) *m/z* $[M]^+$ calcd for $C_{20}H_{21}N_3O_2S$ 367.1354, found 367.1330

Ethyl-4-(phenylamino)-2-(thiophen-2-yl)thiazole-5-carboxylate (67o): After column chromatography (EtOAc/hexane 2:8) 234 mg (71%) of yellow solid was obtained; mp 295-297 °C. R_f 0.2 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3298, 1658. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.19 (brs, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.64 (s, 1H), 7.49 (d, *J* = 4.0 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 3.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 4.36 (q, *J* = 6.8 Hz, 2H), 1.40 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.5, 163.8, 159.4, 140.2, 137.2, 129.7, 129.0, 128.2, 127.9, 122.1, 118.5, 94.7, 60.8, 14.5. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2S_2$ 331.0575, found 331.0564.

Ethyl-2-(1-methyl-1*H*-pyrrol-3-yl)-4-(phenylamino)thiazole-5-carboxylate (67p): After column chromatography (EtOAc/hexane 4:6) 271 mg (83%) of yellow solid was obtained; mp 305-307 °C. R_f 0.2 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3390, 1654. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.21 (brs, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.81 (s, 1H), 6.19 (t, *J* = 3.2 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.9, 163.2, 159.7, 140.6, 129.0, 128.7, 126.6, 122.1, 118.9, 114.8, 109.2, 92.7, 60.7, 37.5, 14.7. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2S$ 328.1120, found 328.1108.

Ethyl-2-(1-methyl-1*H*-indol-3-yl)-4-(phenylamino)thiazole-5-carboxylate (67q): After column chromatography (EtOAc/hexane 4:6) 294 mg (78%) of yellow solid was

obtained; mp 310-312 °C. R_f 0.2 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3095, 1738. ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (brs, 1H), 8.25 (dd, J = 5.8, 2.2 Hz, 1H), 7.85 (s, 1H), 7.75 (dd, *J* = 8.0, 0.8 Hz, 2H), 7.39 (d, J = 7.2 Hz, 2H), 7.37-7.34 (m, 3H), 7.05 (t, *J* = 7.4 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 164.9, 159.8, 140.7, 137.5, 131.0, 128.9, 125.2, 123.1, 121.9, 121.7, 120.9, 118.8, 111.0, 110.1, 92.3, 60.4, 33.4, 14.6. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3O_2S$ 378.1276, found 378.1267.

Ethyl-2-(4-(dimethylamino)phenyl)-4-((4-methoxyphenyl)amino)thiazole-5-carboxylate (67r): After column chromatography (EtOAc/hexane 4:6) 369 mg (93%) of yellow solid was obtained; mp 298-300 °C. R_f 0.2 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3060, 1651. ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (brs, 1H), 7.88 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.62 (dd, *J* = 6.8, 2.0 Hz, 2H), 6.92 (dd, *J* = 6.8, 2.0 Hz, 2H), 6.69 (dd, *J* = 7.2, 2.0 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.05 (s, 6H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.9, 160.5, 154.9, 152.4, 134.2, 128.3, 121.0, 120.3, 114.2, 111.5, 92.3, 60.3, 55.6, 40.1, 14.6. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}N_3O_3S$ 398.1538, found 398.1542.

4.5.4 General procedure for the synthesis of 2-(het)aryl-9-amino/aryl/oxothiazolo[4,5-*b*]quinolines 68a-q

To a solution of 2-(het)aryl-4-*N*-(arylamino)-5-functionalized thiazoles **67a-r** (1.0 mmol) in DCE (5 mL), triflic acid (0.26 mL, 3.0 mmol) was added and the reaction mixture was heated at 100 °C for 12 h. It was then cooled, neutralized with satd. solution of $NaHCO_3$ (30 mL), and the resulting mixture was extracted with DCM (3 × 25 mL). The combined organic layers were washed with water (3 × 25 mL), brine (1 × 25 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to give pure **68a-q**.

2-(4-Methoxyphenyl)thiazolo[4,5-*b*]quinolin-9-amine (68a): After column chromatography (EtOAc/hexane 9:1) 199 mg (65%) of yellow solid was obtained; mp 60-61 °C. R_f 0.2 (9:1 EtOAc/hexane). IR (neat, cm^{-1}) 3051, 1216. ^1H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.44 (brs, 2H), 7.43 (t, *J* = 6.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H) 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2, 162.5, 147.6, 130.1, 129.6, 129.0, 127.9, 125.4, 123.1, 122.0, 115.2, 114.9, 114.4, 105.9, 55.6. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}N_3OS$ 308.0858, found 308.0875.

2-Phenylthiazolo[4,5-*b*]quinolin-9-amine (68b): After column chromatography (EtOAc/hexane 9:1) 190 mg (69%) of yellow solid was obtained; mp 78-79°C. R_f 0.3 (9:1 EtOAc/hexane). IR (neat, cm^{-1}) 3442, 1005. ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 8.4 Hz, 1H), 8.16 (dd, J = 7.0, 2.2 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.65 (dd, J = 5.2, 1.6 Hz, 3H), 7.54 (brs, 2H), 7.45 (t, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 157.4, 142.9, 142.1, 139.9, 135.9, 134.6, 132.8, 132.6, 131.4, 131.1, 129.2, 128.2, 127.3. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}N_3S$ 278.0752, found 278.0741.

2-(1-Methyl-1*H*-pyrrol-2-yl)thiazolo[4,5-*b*]quinolin-9-amine (68c): After column chromatography (EtOAc/hexane 9:1) 199 mg (71%) of yellow solid was obtained; mp 80-81 °C; R_f 0.3 (9:1 EtOAc/hexane). IR (neat, cm^{-1}) 3019, 1217. ^1H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.33 (brs, 2H), 7.22 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 4.0, 1.6 Hz, 1H), 6.25 (dd, J = 3.8, 2.6 Hz, 1H), 4.13 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 163.3, 147.8, 146.6, 130.4, 129.2, 128.4, 125.7, 122.8, 121.8, 115.8, 114.8, 109.2, 104.7, 37.1. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}N_4S$ 281.0861, found 281.0643.

7-Methyl-2-(1-methyl-1*H*-pyrrol-2-yl)thiazolo[4,5-*b*]quinolin-9-amine (68d): After column chromatography (EtOAc/hexane 8:2) 162 mg (55%) of yellow solid was obtained; mp 252-253 °C. R_f 0.3 (8:2 EtOAc/hexane). IR (neat, cm^{-1}) 3501, 1164. ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.20 (brs, 2H), 7.09 (s, 1H), 6.82 (s, 1H), 4.08 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 162.8, 146.0, 145.9, 134.9, 132.1, 131.3, 127.9, 127.0, 125.1, 120.6, 114.6, 113.5, 104.7, 36.9, 33.1. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}N_4S$ 295.1017, found 295.1011.

7-Methyl-2-(1-methyl-1*H*-indol-3-yl)thiazolo[4,5-*b*]quinolin-9-amine (68e): After column chromatography (EtOAc/hexane 9:1) 182 mg (53%) of yellow solid was obtained; mp 65-66 °C. R_f 0.2 (9:1 EtOAc/hexane). IR (neat, cm^{-1}) 3478, 1217. ^1H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 4.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.49 (brs, 2H), 7.37 (t, J = 3.8 Hz, 2H), 3.96 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 137.5, 135.4, 133.5, 132.0, 131.4, 129.2, 127.3, 124.9, 123.0, 121.8, 120.9, 120.7, 117.5, 114.5, 110.9, 109.7, 104.7, 33.2, 21.2. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_4S$ 345.1174, found 345.1162.

2-(4-Methoxyphenyl)-9-phenylthiazolo[4,5-*b*]quinoline (68f): After column chromatography (EtOAc/hexane 6:4) 294 mg (80%) of yellow solid was obtained; mp 205-206 °C. R_f 0.2 (6:4 EtOAc/hexane). IR (neat, cm^{-1}) 3026, 1483. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.63-7.58 (m, 5H), 7.49 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 164.8, 163.4, 148.3, 142.7, 137.5, 130.0, 129.9, 129.4, 129.3, 129.2, 128.4, 126.1, 126.0, 125.1, 124.4, 114.6, 55.7. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2OS$ 369.1062, found 369.1061.

***N,N*-Dimethyl-4-(9-phenylthiazolo[4,5-*b*]quinolin-2-yl)aniline (68g):** After column chromatography (EtOAc/hexane 7:3) 316 mg (83%) of yellow solid was obtained; mp 233-234°C. R_f 0.2 (7:3 EtOAc/hexane). IR (neat, cm^{-1}) 2926, 1437. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.81 (t, J = 7.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.68-7.62 (m, 5H), 7.56 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 3.06 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.0, 164.5, 153.3, 153.1, 147.4, 141.5, 136.8, 136.6, 129.40, 129.34, 129.29, 129.02, 127.8, 125.9, 124.6, 123.4, 119.1, 111.7, 38.9. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}N_3S$ 382.1378, found 382.1349.

9-(3-Methoxyphenyl)-7-methyl-2-(4-(methylthio)phenyl)thiazolo[4,5-*b*]quinoline (68h): After column chromatography (EtOAc/hexane 7:3) 355 mg (83%) of yellow solid was obtained; mp 206-207 °C. R_f 0.2 (7:3 EtOAc/hexane). IR (neat, cm^{-1}) 3009, 1228. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.58 (dd, J = 8.6, 1.8 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 7.6 Hz, 1H), 7.14-7.10 (m, 2H), 3.89 (s, 3H), 2.53 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 163.8, 160.0, 146.8, 144.9, 141.7, 138.7, 136.1, 131.8, 130.3, 129.6, 129.5, 128.7, 128.1, 125.7, 124.3, 123.5, 121.5, 114.7, 114.6, 55.5, 21.9, 14.9. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2OS_2$ 429.1095, found 429.1093.

2-(1-Methyl-1*H*-imidazol-2-yl)-9-phenylthiazolo[4,5-*b*]quinoline (68j): After column chromatography (EtOAc/hexane 8:2) 250 mg (73%) of yellow solid was obtained; mp 88-89 °C. R_f 0.2 (8:2 EtOAc/hexane). IR (neat, cm^{-1}) 3018, 1217. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.69-7.60 (m, 5H), 7.57 (t, J = 7.6 Hz, 1H), 7.31 (s, 1H), 7.19 (s, 1H), 4.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.6, 148.3, 143.2, 140.3, 137.1, 130.9,

129.9, 129.6, 129.4, 129.3, 129.2, 128.2, 126.7, 126.4, 125.2, 124.6, 36.4. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}N_4S$ 343.1017, found 343.1003.

2-(1-Methyl-1*H*-indol-3-yl)-9-phenylthiazolo[4,5-*b*]quinoline (68k): After column chromatography (EtOAc/hexane 8:2) 320 mg (82%) of yellow solid was obtained; mp 230-231 °C. R_f 0.2 (8:2 EtOAc/hexane). IR (neat, cm^{-1}) 2970, 1216. ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 7.6 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.63-7.57 (m, 5H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 164.9, 148.0, 141.9, 137.8, 137.7, 132.9, 129.7, 129.3, 129.2, 127.6, 125.7, 125.5, 124.9, 124.2, 123.6, 122.4, 122.2, 111.3, 110.1, 33.7. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{25}H_{18}N_3S$ 392.1221, found 392.1322.

9-(4-Chlorophenyl)-7-methyl-2-(1-methyl-1*H*-indol-3-yl)thiazolo[4,5-*b*]quinoline (68l): After column chromatography (EtOAc/hexane 6:4) 330 mg (75%) of yellow solid was obtained; mp 210-211 °C. R_f 0.2 (6:4 EtOAc/hexane). IR (neat, cm^{-1}) 3450, 734. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.94 (s, 1H), 7.60 (t, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.0 Hz, 3H), 7.49 (s, 1H), 7.38-7.34 (m, 3H), 3.88 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 139.7, 137.9, 136.3, 135.8, 135.2, 132.9, 131.7, 130.8, 129.5, 127.7, 127.6, 125.9, 125.7, 123.9, 123.7, 123.2, 122.5, 122.2, 111.4, 110.1, 109.6, 33.8, 22.0. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{26}H_{19}ClN_3S$ 440.0988, found 440.0936.

2-(4-Methoxyphenyl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (68m): After column chromatography (EtOAc/hexane 4:6) 228 mg (74%) of yellow solid was obtained; mp 201-202 °C. R_f 0.2 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3450, 1709. ^1H NMR (400 MHz, DMSO-d_6) δ 13.18 (brs, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 171.7, 162.6, 155.5, 139.5, 132.3, 128.9, 128.7, 124.9, 122.5, 121.9, 118.1, 114.9, 112.4, 55.6. HRMS (ESI-QTOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_2S$ 309.0698, found 309.0717.

2-(4-(Dimethylamino)phenyl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (68n): After column chromatography (EtOAc/hexane 3:7) 263 mg (82%) of yellow solid was obtained; mp 202-203 °C. R_f 0.2 (3:7 EtOAc/hexane). IR (neat, cm^{-1}) 3400, 1706. ^1H NMR (400 MHz, DMSO-d_6) δ 13.10 (brs, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.35 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 2H), 3.05 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 171.3, 155.8, 152.9, 139.4, 132.0, 128.6,

124.8, 122.3, 121.9, 119.3, 118.0, 111.7, 111.2, 40.2. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3OS$ 322.1014, found 322.1000.

2-(Thiophen-2-yl)thiazolo[4,5-*b*]quinolin-9-(4*H*)-one (68o): After column chromatography (EtOAc/hexane 2:8) 195 mg (69%) of yellow solid was obtained; mp 240-241 °C. R_f 0.2 (2:8 EtOAc/hexane). IR (neat, cm^{-1}) 3020, 1602. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (brs, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 3.2 Hz, 1H), 7.99 (d, J = 4.8 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.30 (t, J = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 166.7, 154.9, 139.4, 135.7, 132.5, 132.4, 130.8, 129.2, 124.8, 122.6, 121.9, 118.1, 112.3. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{14}H_9N_2OS_2$ 285.0156, found 285.0138.

2-(1-Methyl-1*H*-pyrrol-2-yl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (68p): After column chromatography (EtOAc/hexane 4:6) 220 mg (78%) of yellow solid was obtained; mp 184-185 °C. R_f 0.2 (4:6 EtOAc/hexane). IR (neat, cm^{-1}) 3018, 1602. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (brs, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 6.8 Hz, 2H), 7.23 (s, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.25 (s, 1H), 4.10 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 165.4, 155.4, 139.4, 132.1, 130.7, 125.4, 124.7, 122.5, 119.0, 118.1, 116.4, 110.5, 109.4, 36.9. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{14}H_9N_2OS_2$ 282.0701, found 282.0689.

2-(1-Methyl-1*H*-indol-3-yl)thiazolo[4,5-*b*]quinolin-9(4*H*)-one (68q): After column chromatography (EtOAc/hexane 5:5) 238 mg (72%) of yellow solid was obtained; mp 228-229 °C. R_f 0.2 (5:5 EtOAc/hexane). IR (neat, cm^{-1}) 3009, 1709. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (brs, 1H), 8.44 (s, 1H), 8.37 (t, J = 4.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.75-7.69 (m, 2H), 7.63 (t, J = 4.6 Hz, 1H), 7.38-7.35 (m, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2, 168.7, 155.7, 139.3, 137.4, 133.8, 131.9, 124.7, 124.6, 123.1, 122.3, 122.1, 121.9, 120.6, 118.0, 111.1, 109.9, 109.3, 33.2. HRMS (ESI-QTOF) *m/z* [M + H]$^+$ calcd for $C_{19}H_{14}N_3OS$ 332.0858, found 332.0844.

4.6 References

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4.7 ^{1}H and ^{13}C NMR Spectra of Representative Compounds

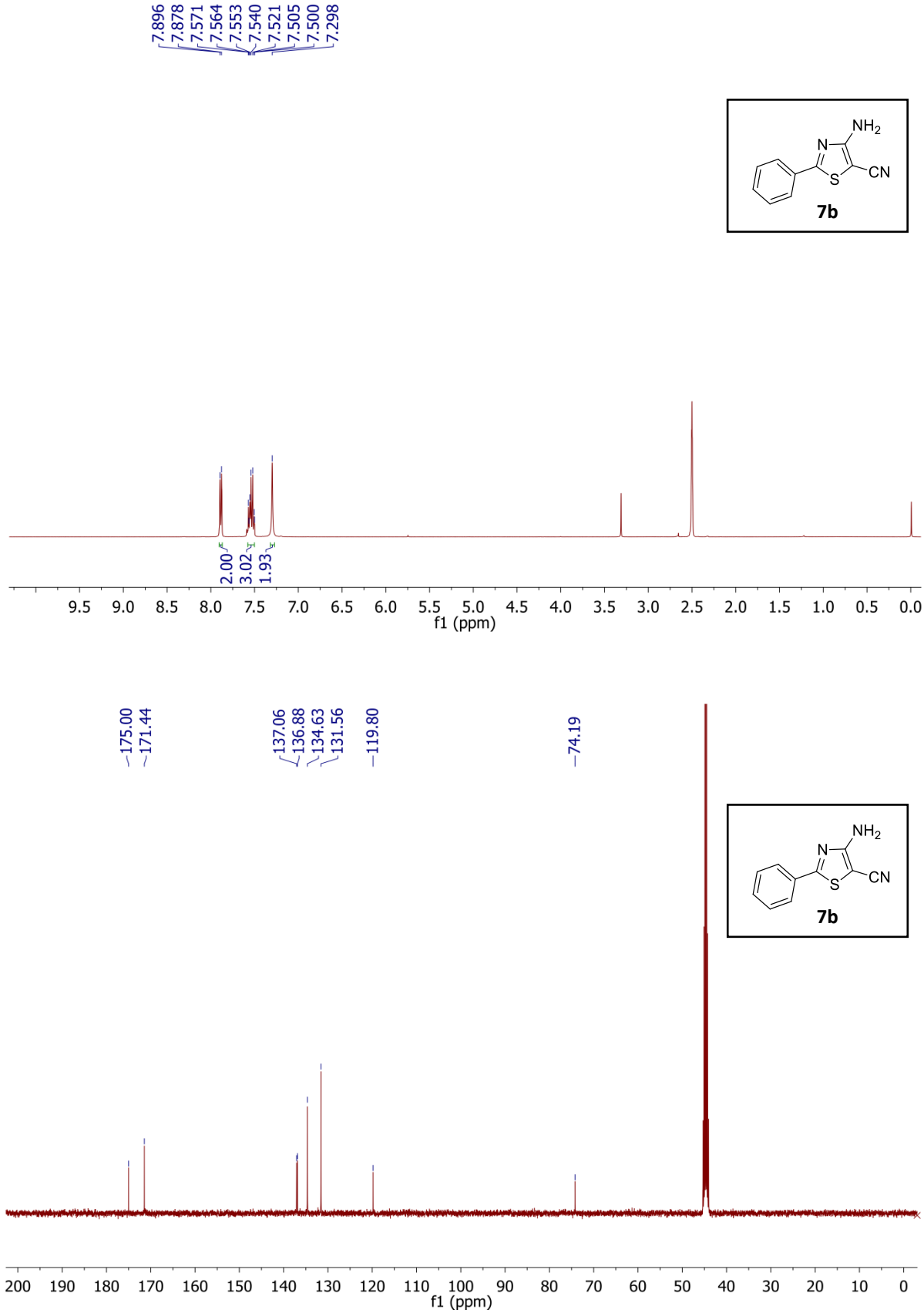


Figure 1. ^{1}H and ^{13}C NMR of compound 7b

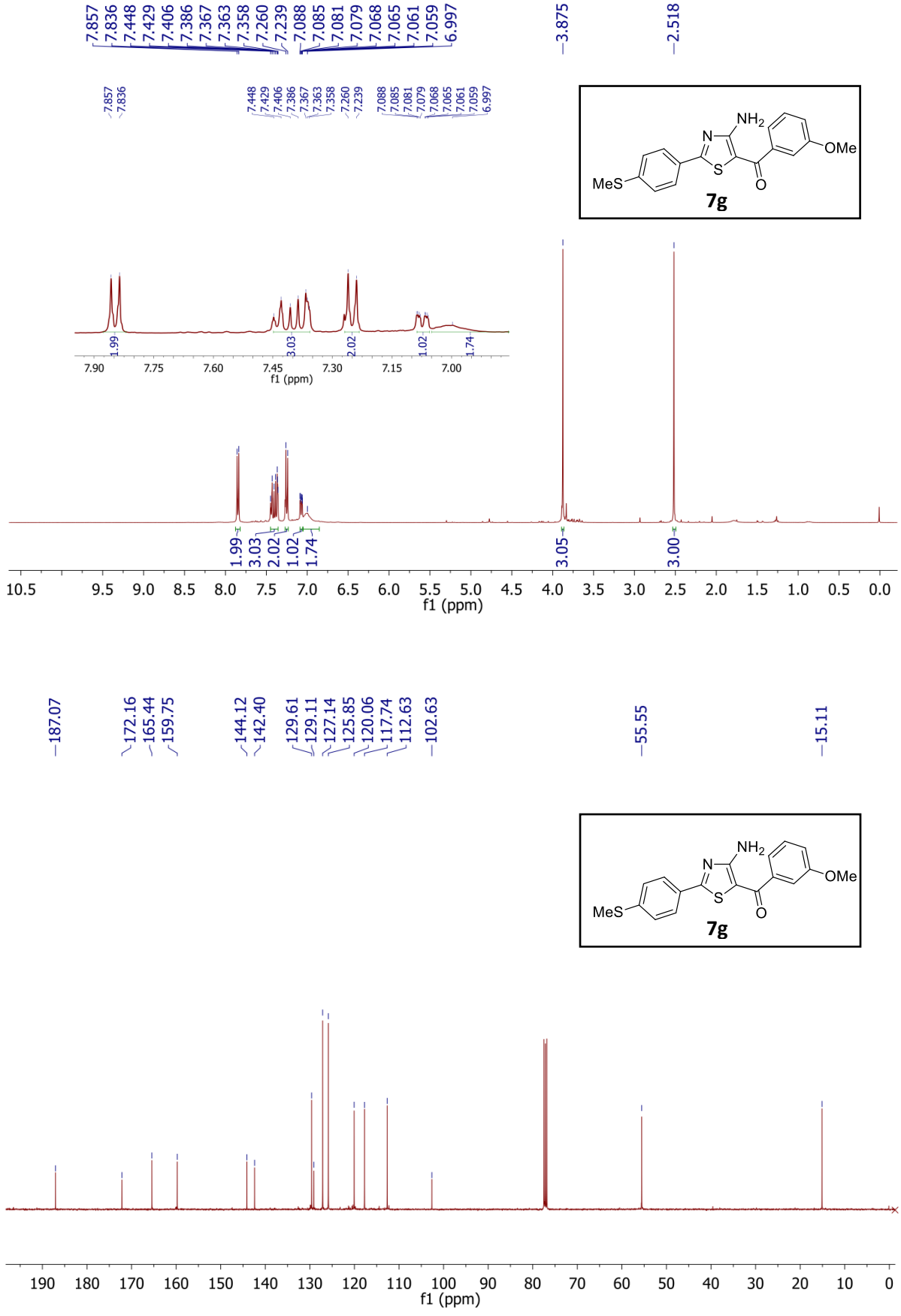


Figure 2. ^{1}H and ^{13}C NMR of compound 7g

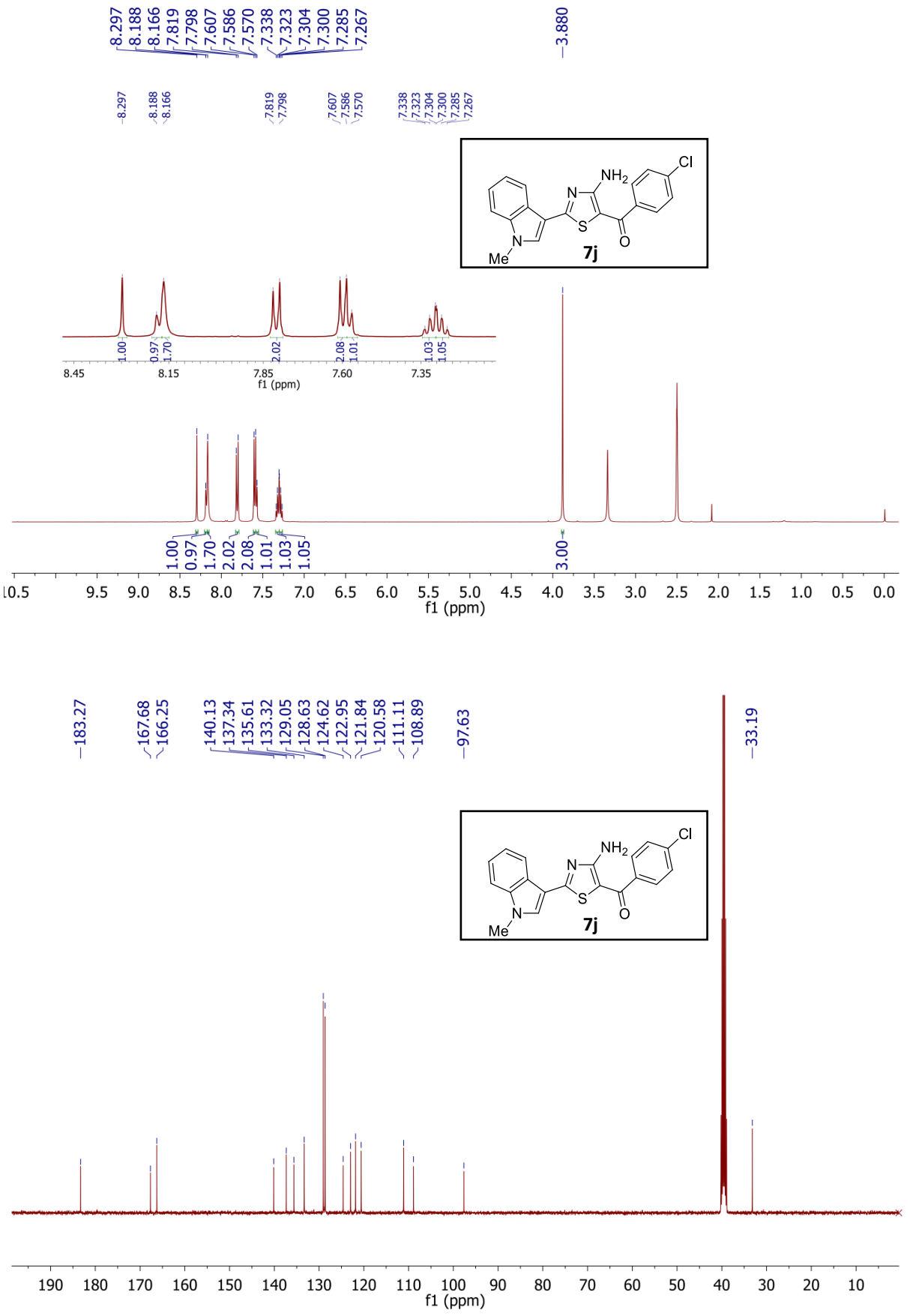


Figure 3. ^{1}H and ^{13}C NMR of compound 7j

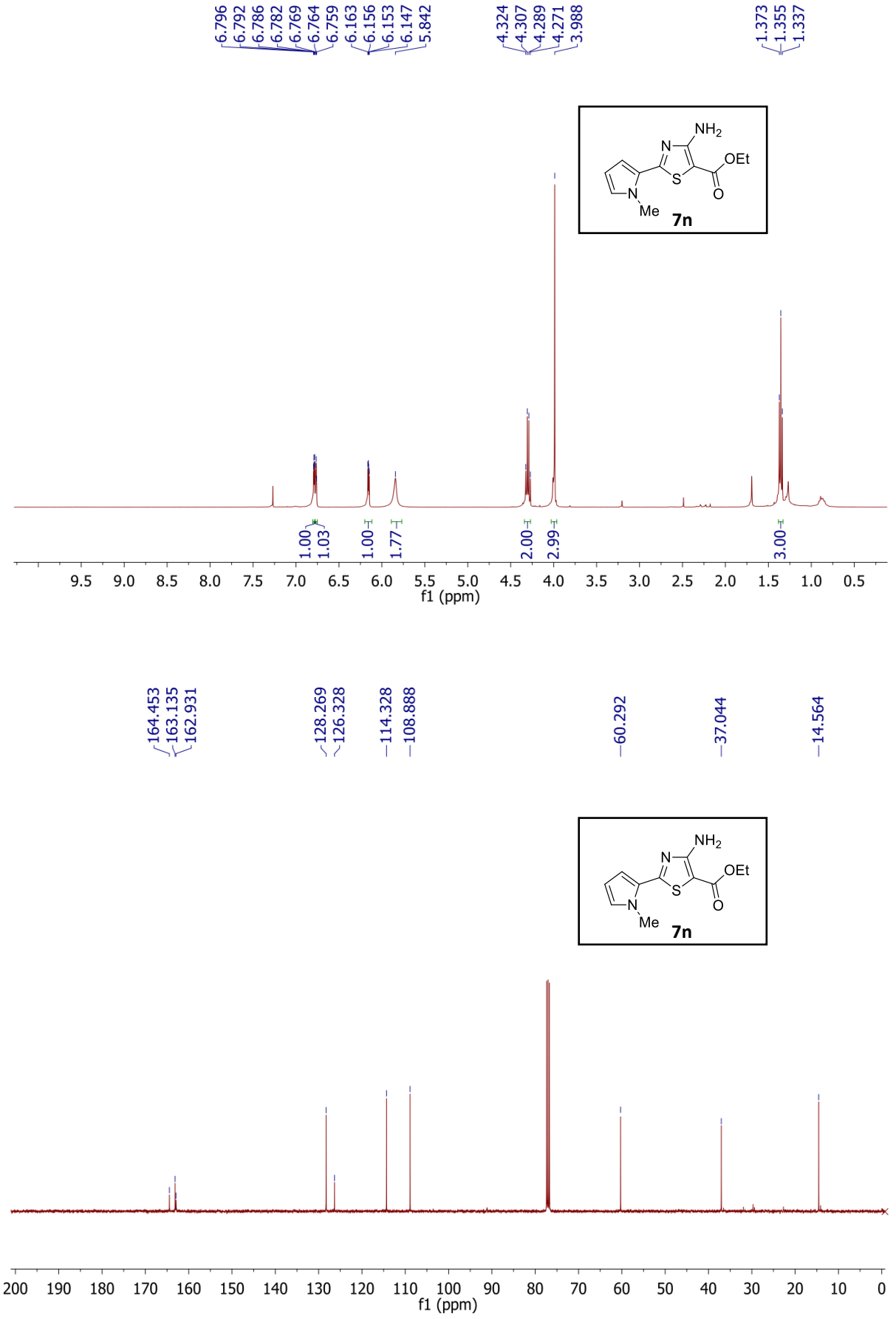


Figure 4. ^{1}H and ^{13}C NMR of compound 7n

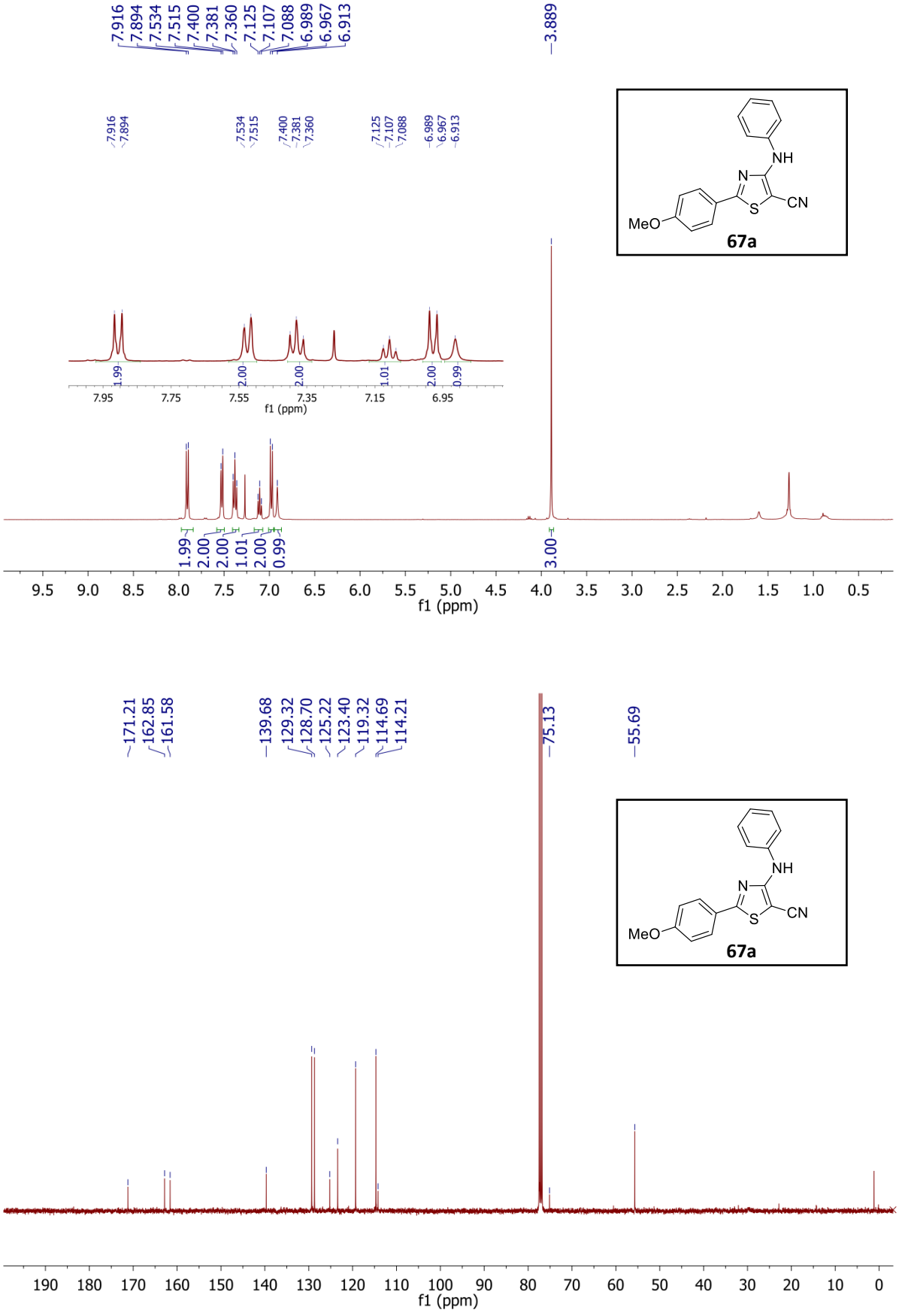


Figure 5. ^{1}H and ^{13}C NMR of compound 67a

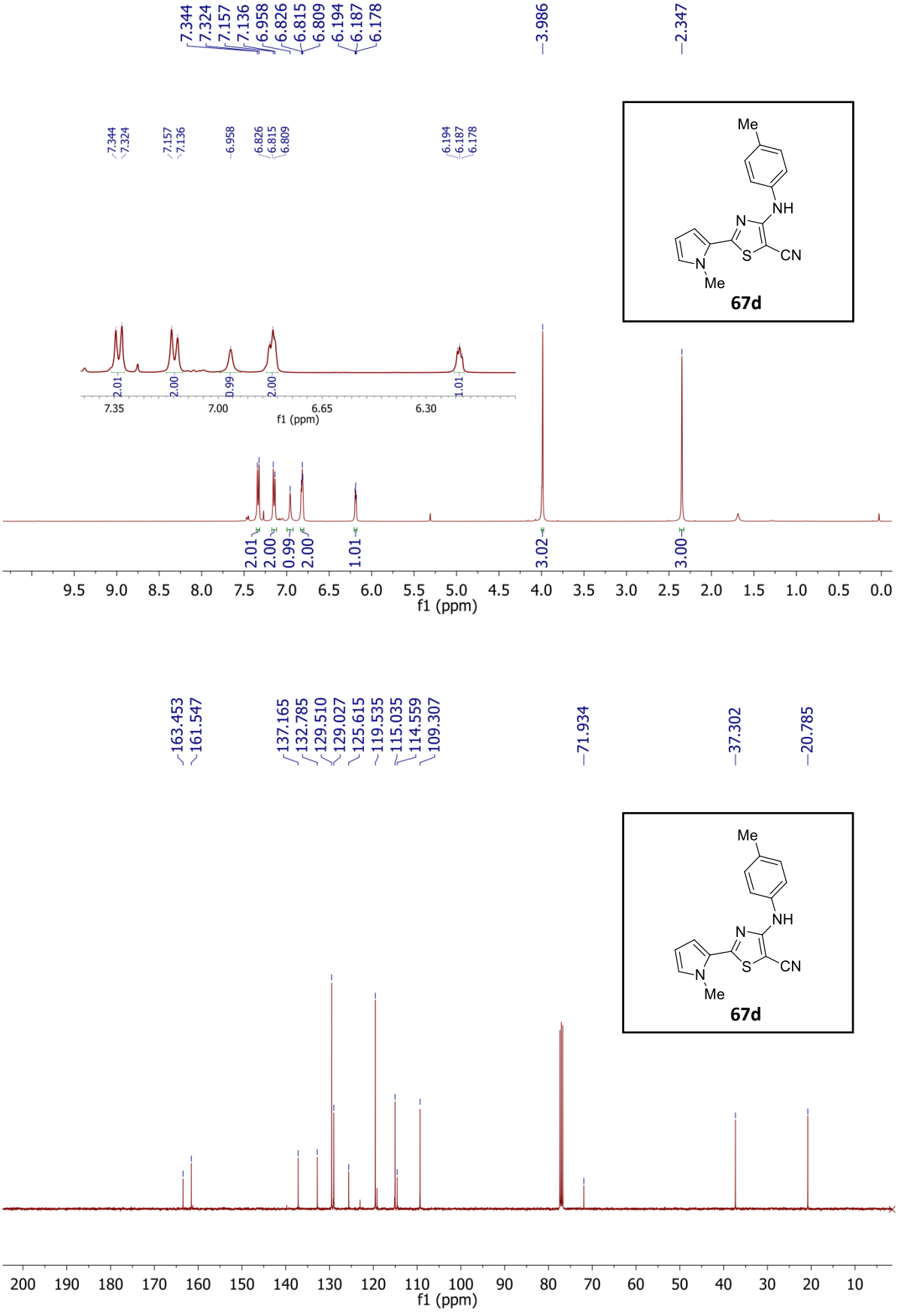


Figure 6. ^{1}H and ^{13}C NMR of compound 67d

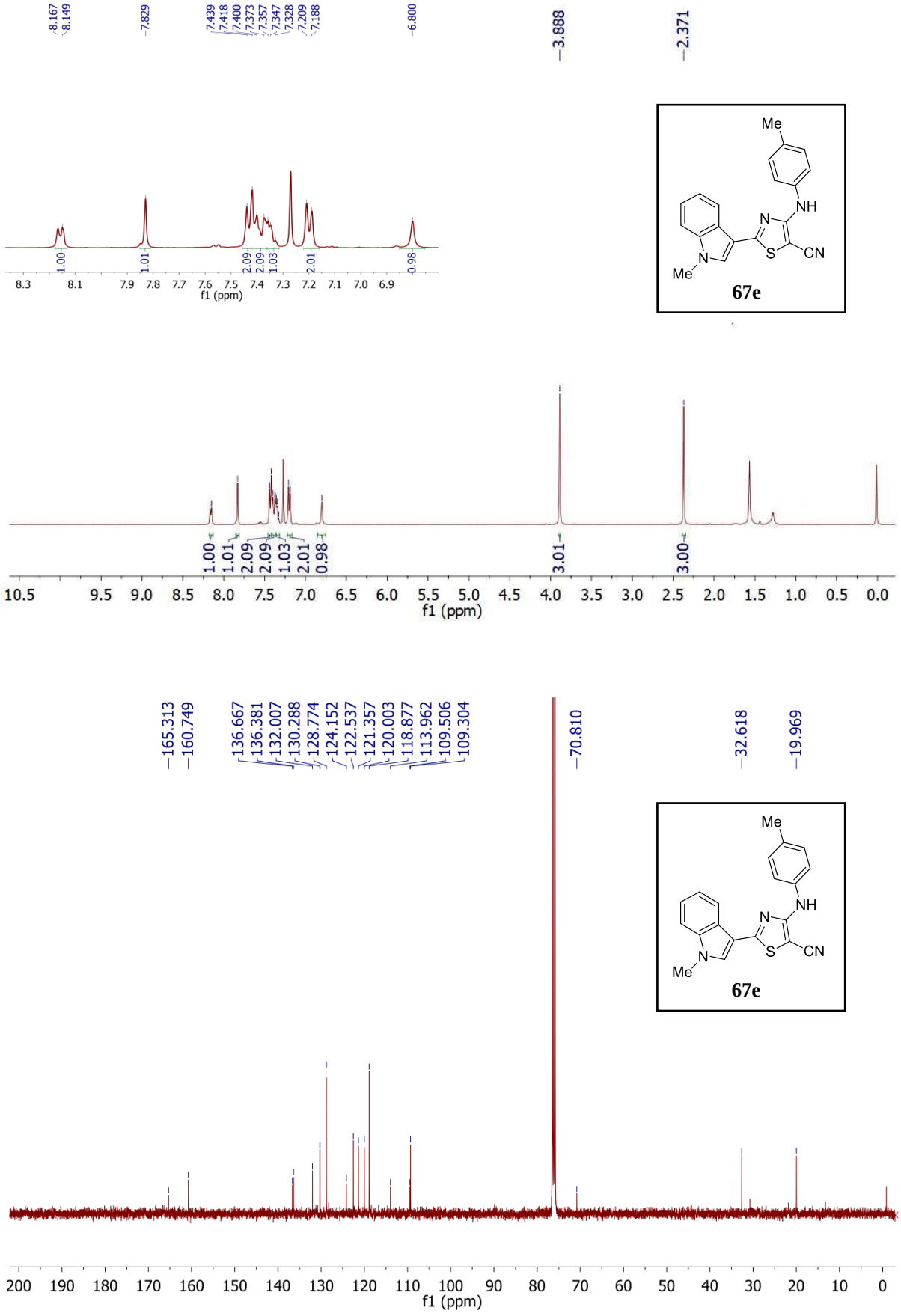


Figure 7. ^{1}H and ^{13}C NMR of compound 67e

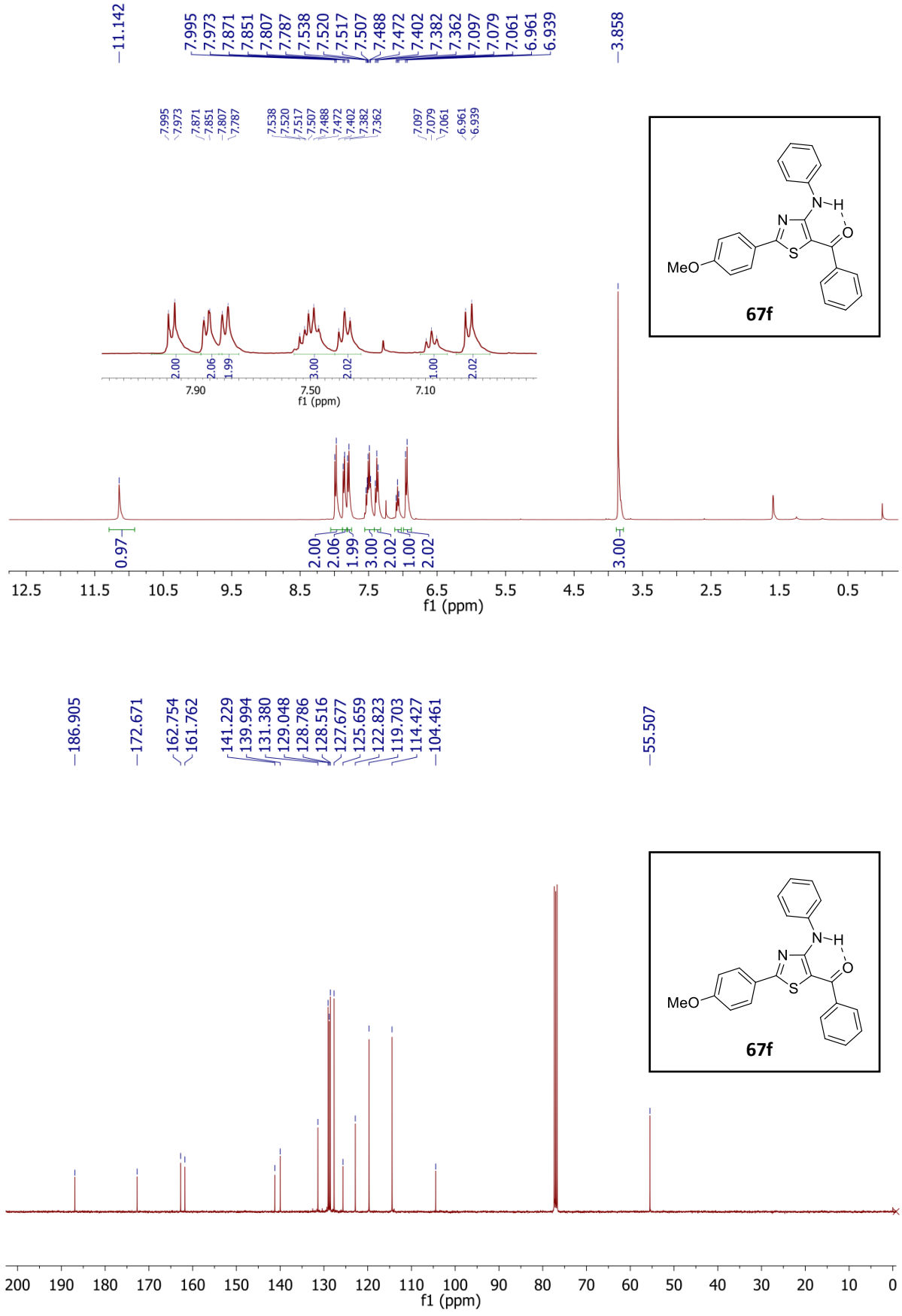


Figure 8. ^{1}H and ^{13}C NMR of compound 67f

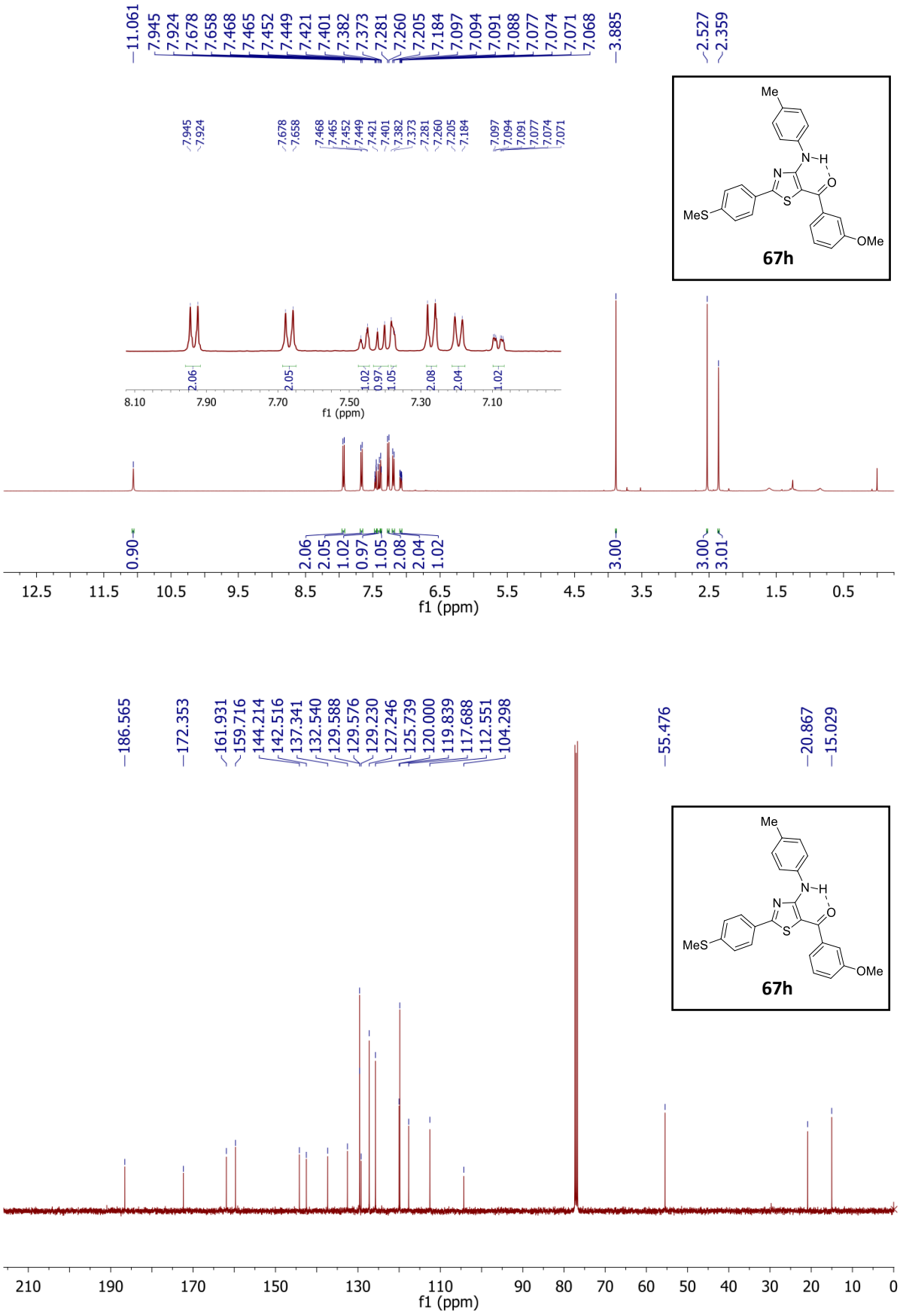


Figure 9. ^{1}H and ^{13}C NMR of compound 67h

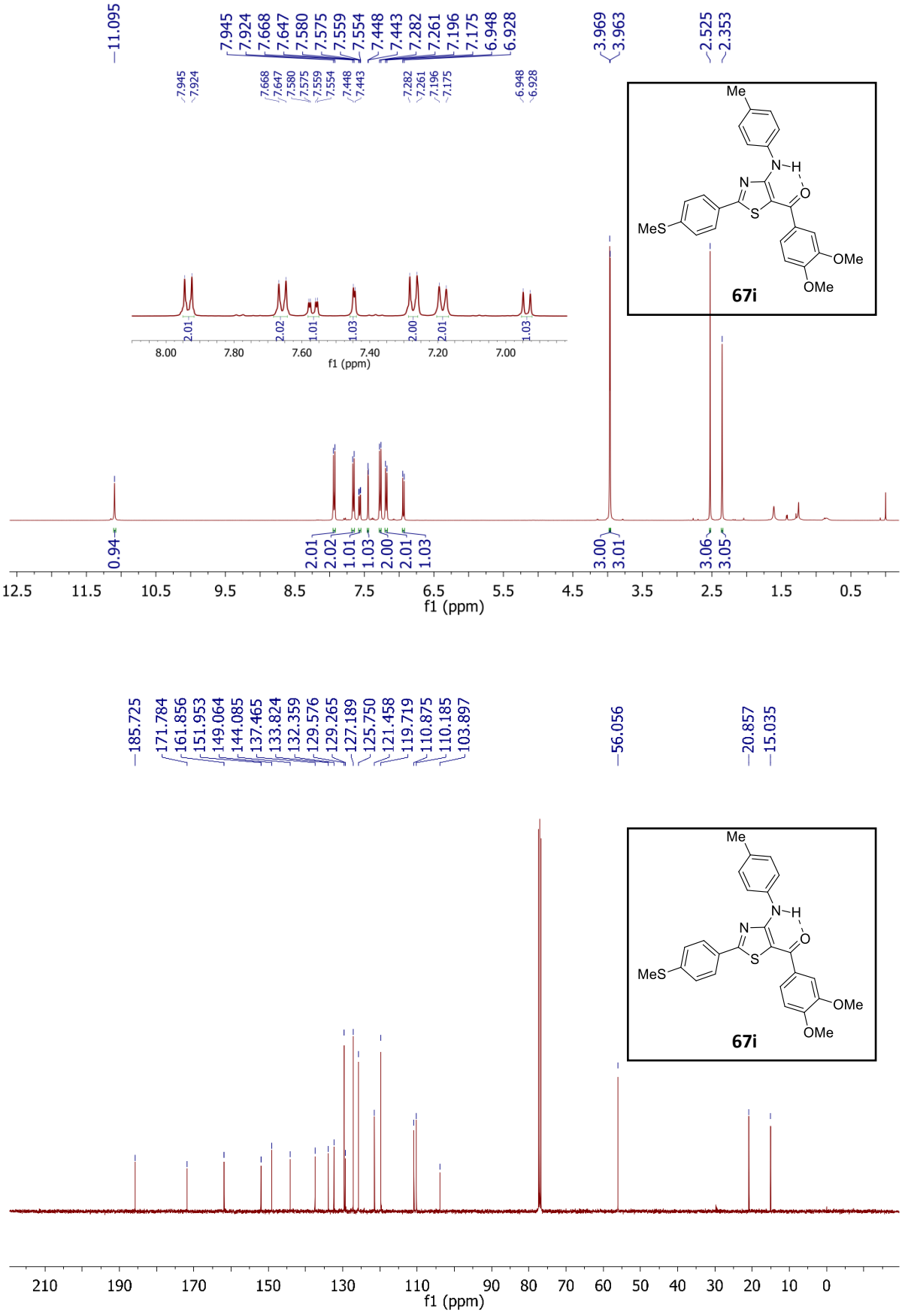


Figure 10. ^{1}H and ^{13}C NMR of compound 67i

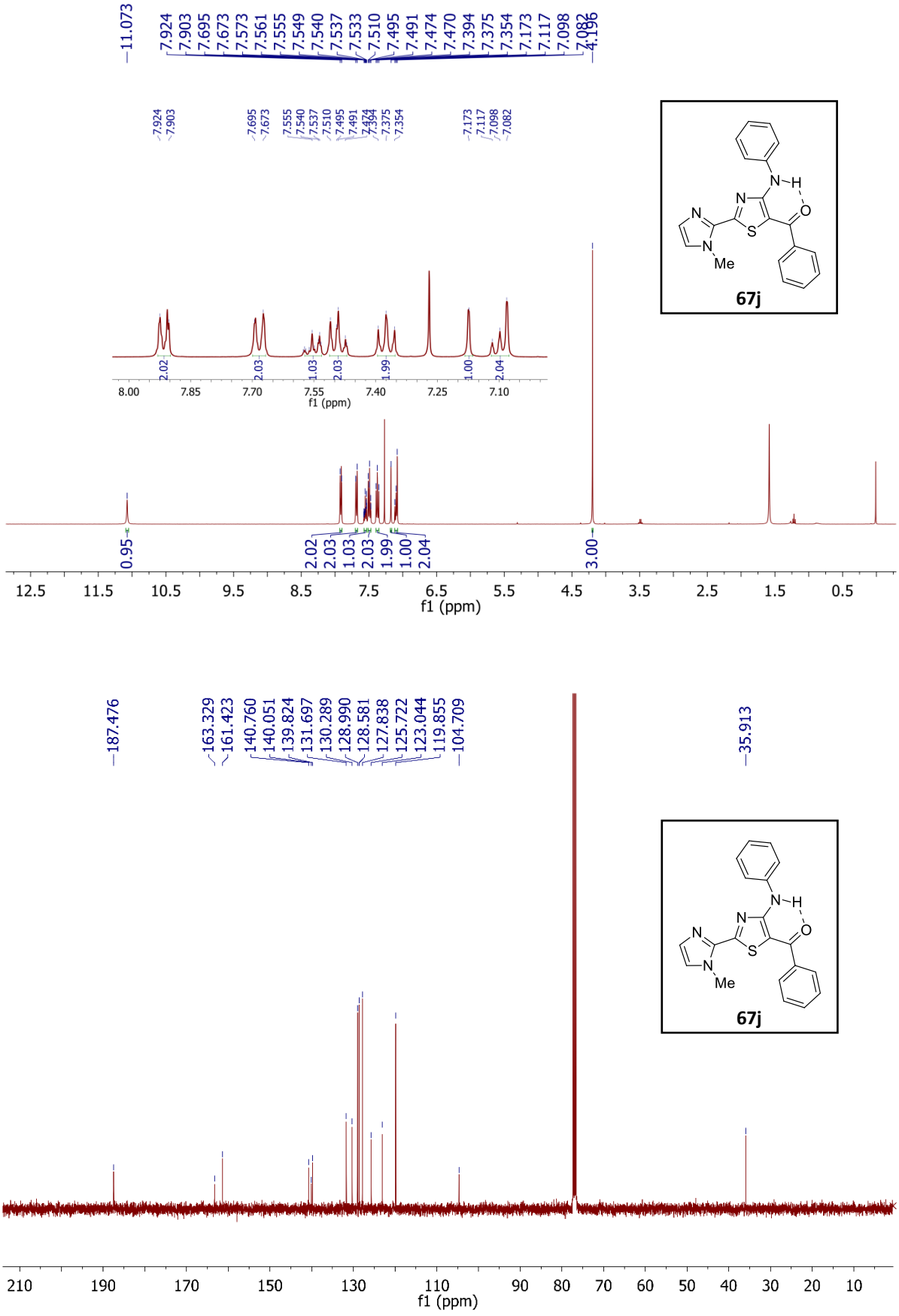


Figure 11. ^{1}H and ^{13}C NMR of compound 67j

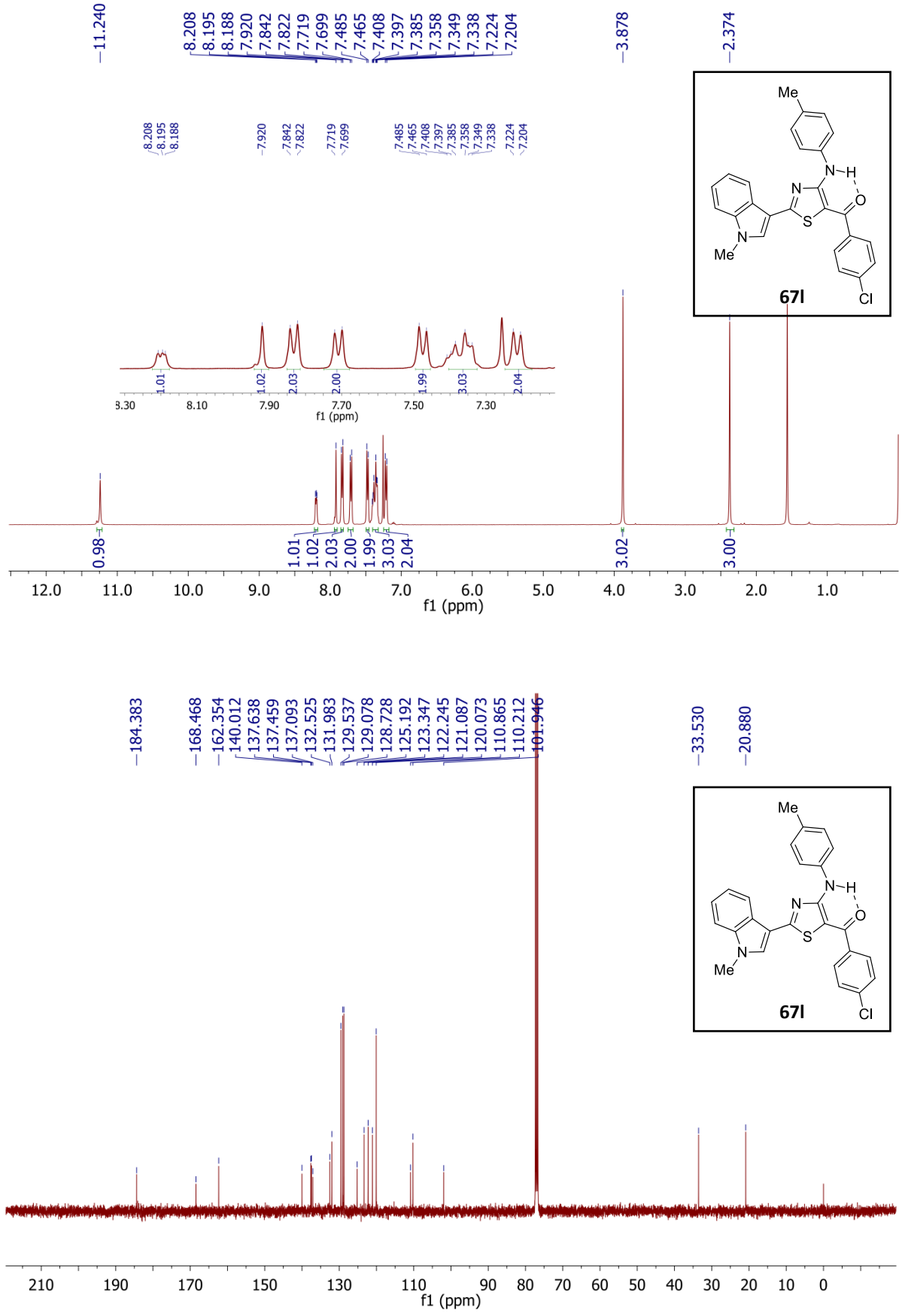


Figure 12. ^{1}H and ^{13}C NMR of compound 67l

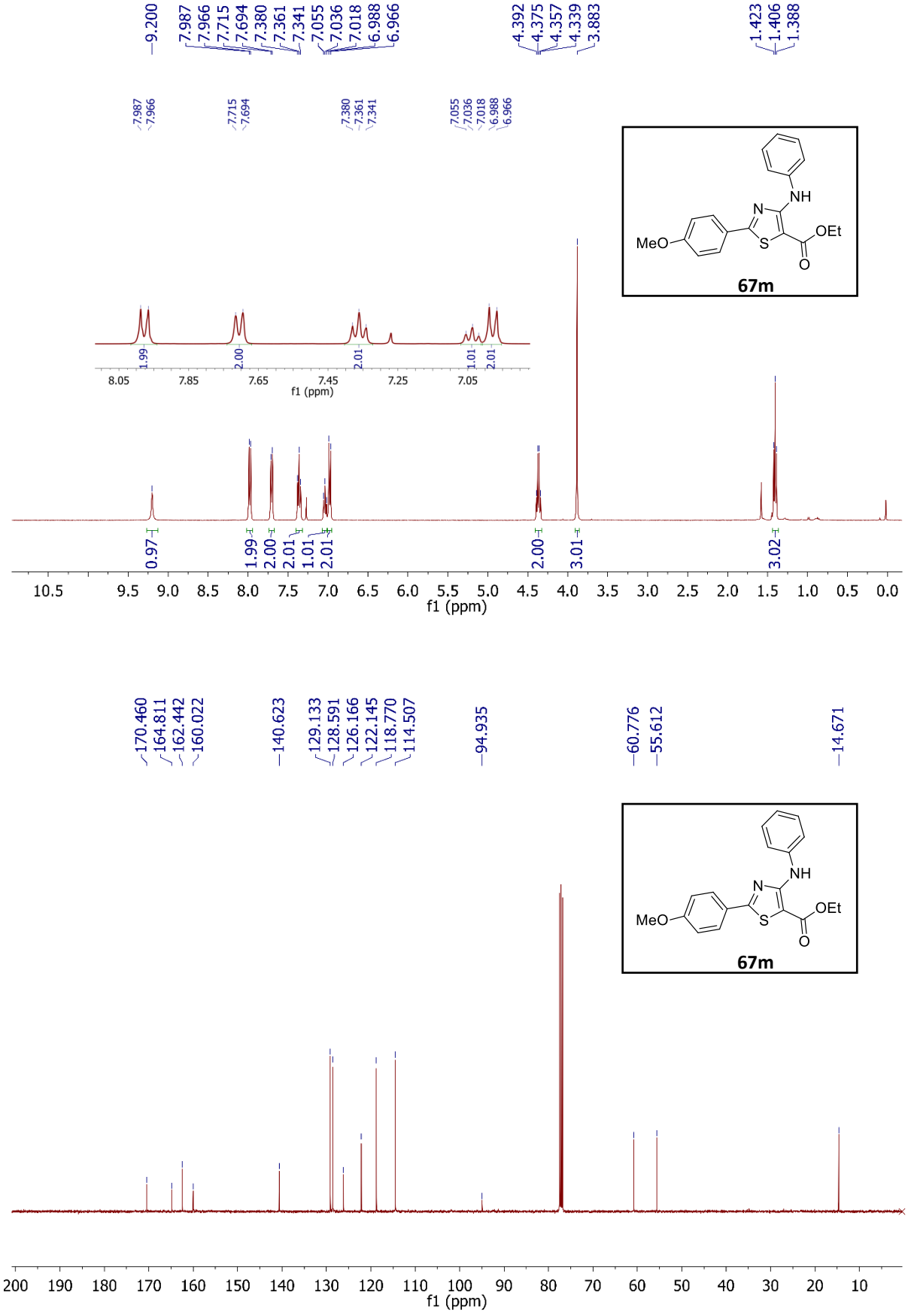


Figure 13. ^{1}H and ^{13}C NMR of compound 67m

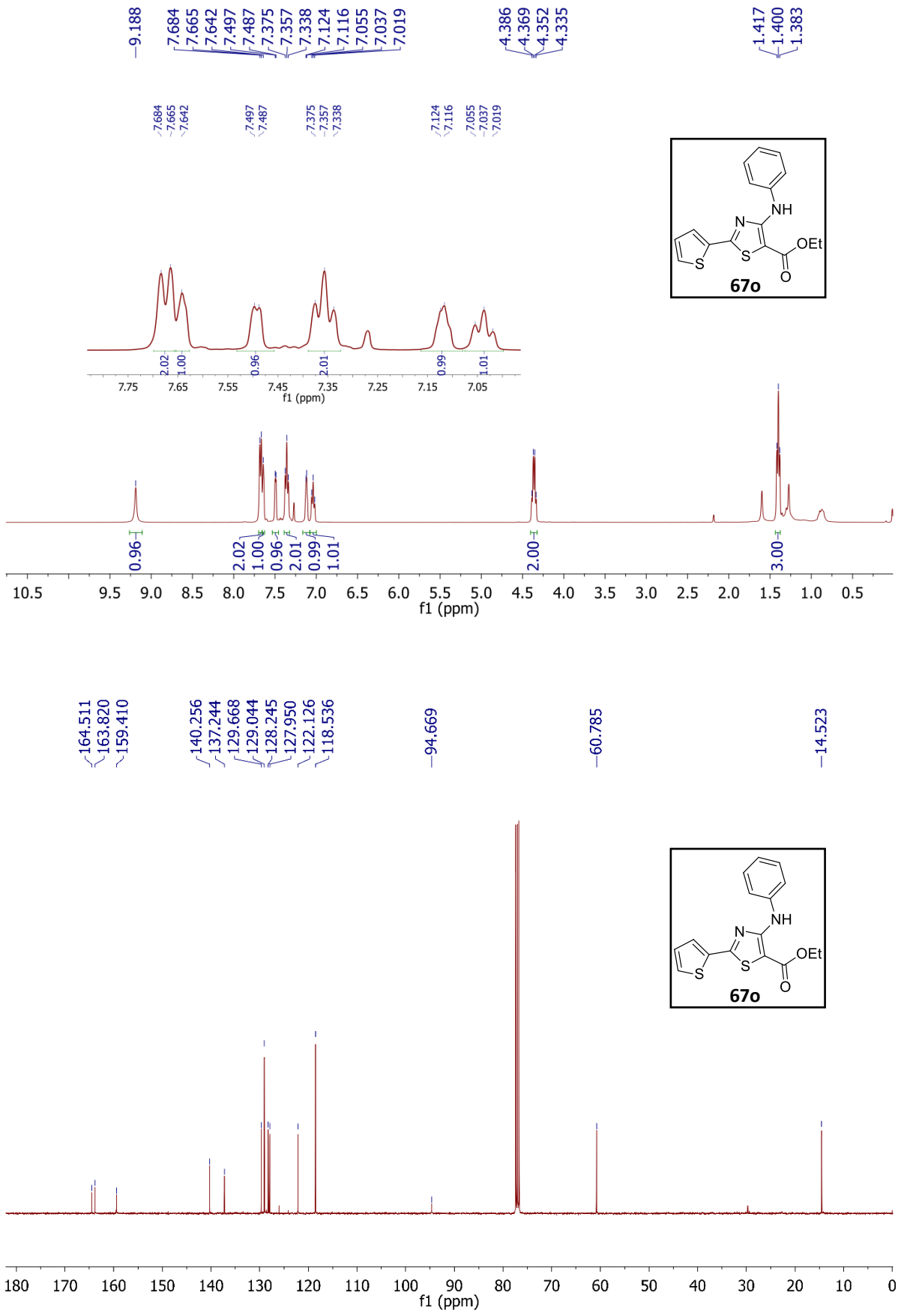


Figure 14. ^{1}H and ^{13}C NMR of compound 67o

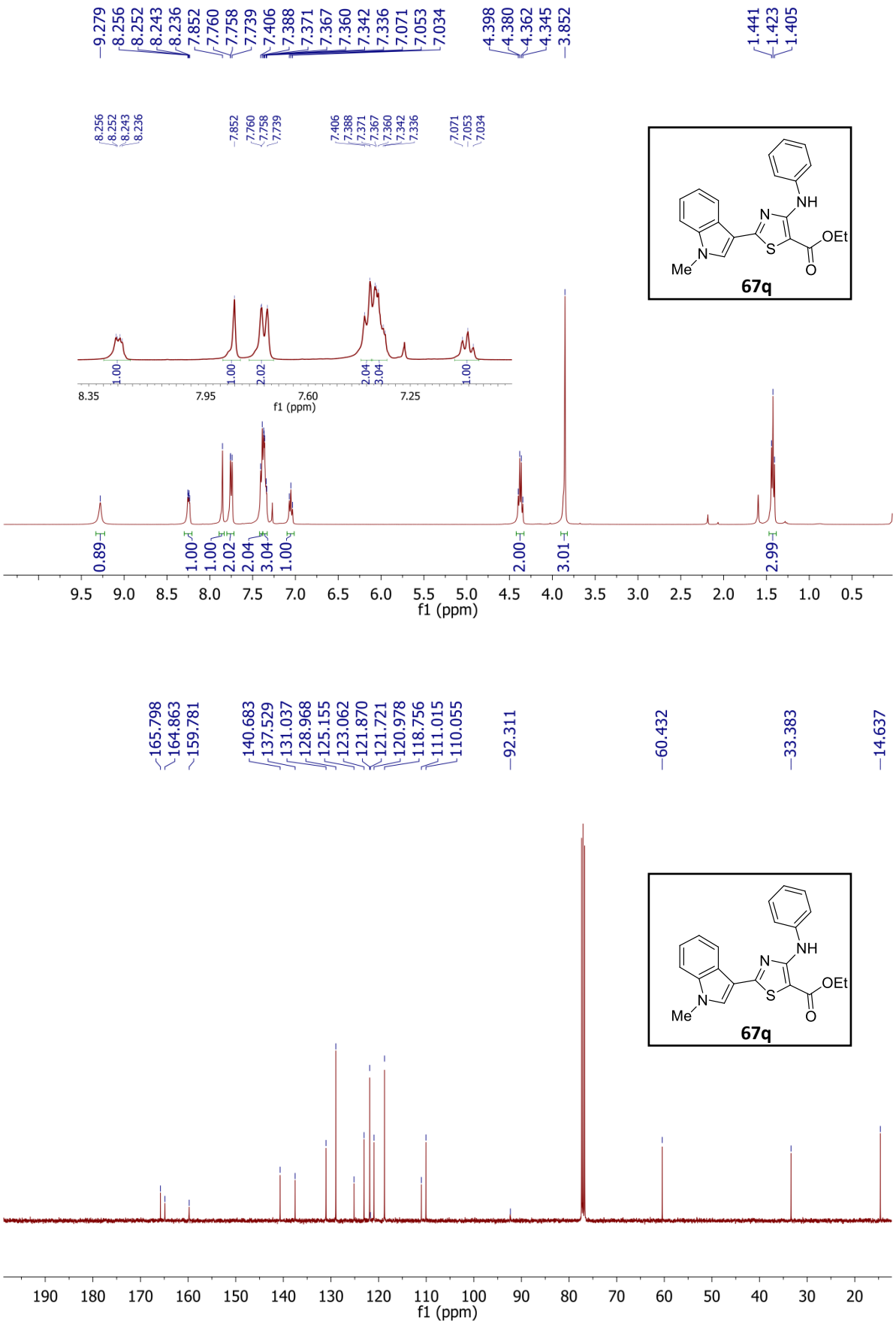


Figure 15. ^{1}H and ^{13}C NMR of compound 67q

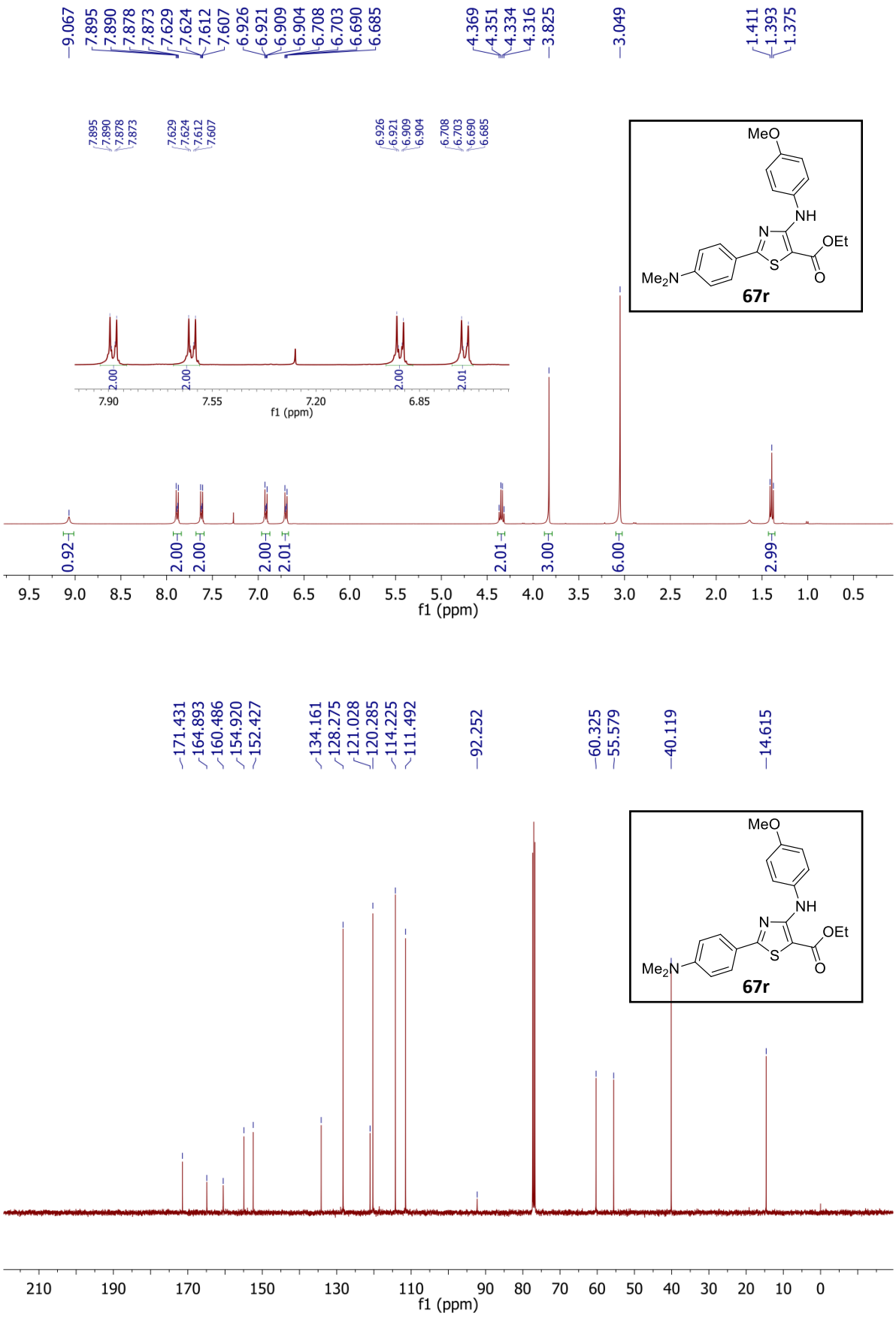


Figure 16. ^{1}H and ^{13}C NMR of compound 67r

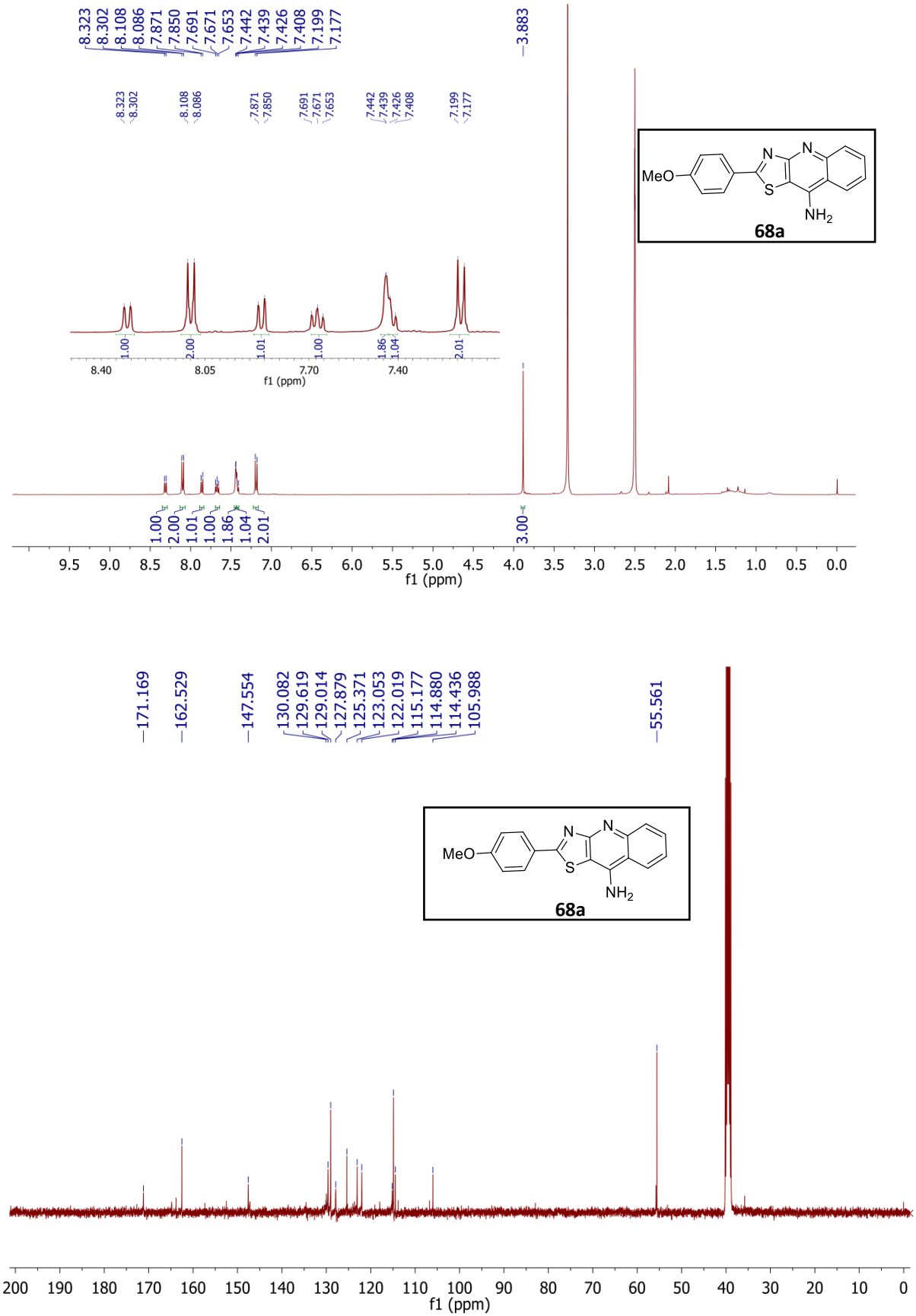


Figure 17. ^{1}H and ^{13}C NMR of compound 68a

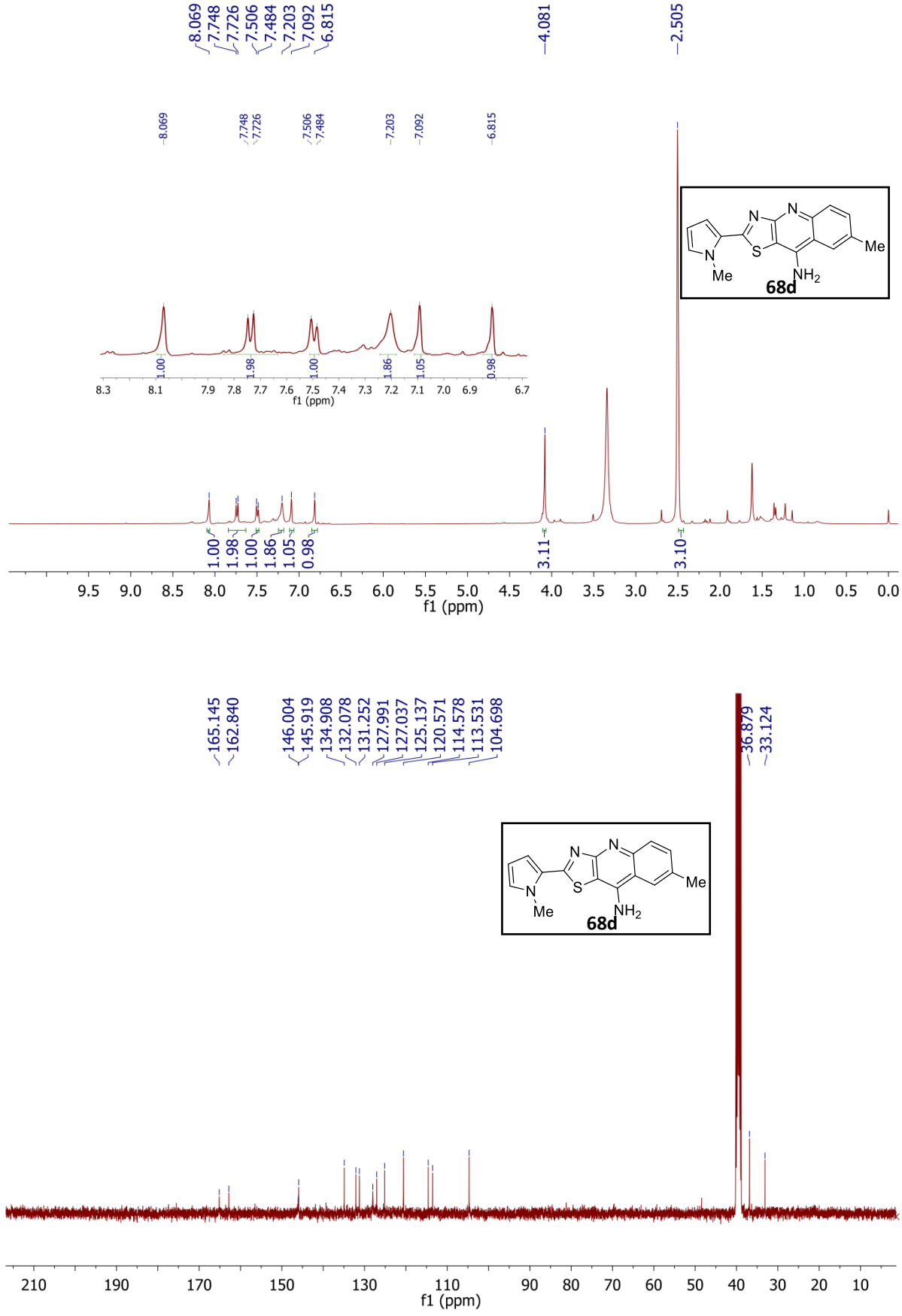


Figure 18. ^{1}H and ^{13}C NMR of compound 68d

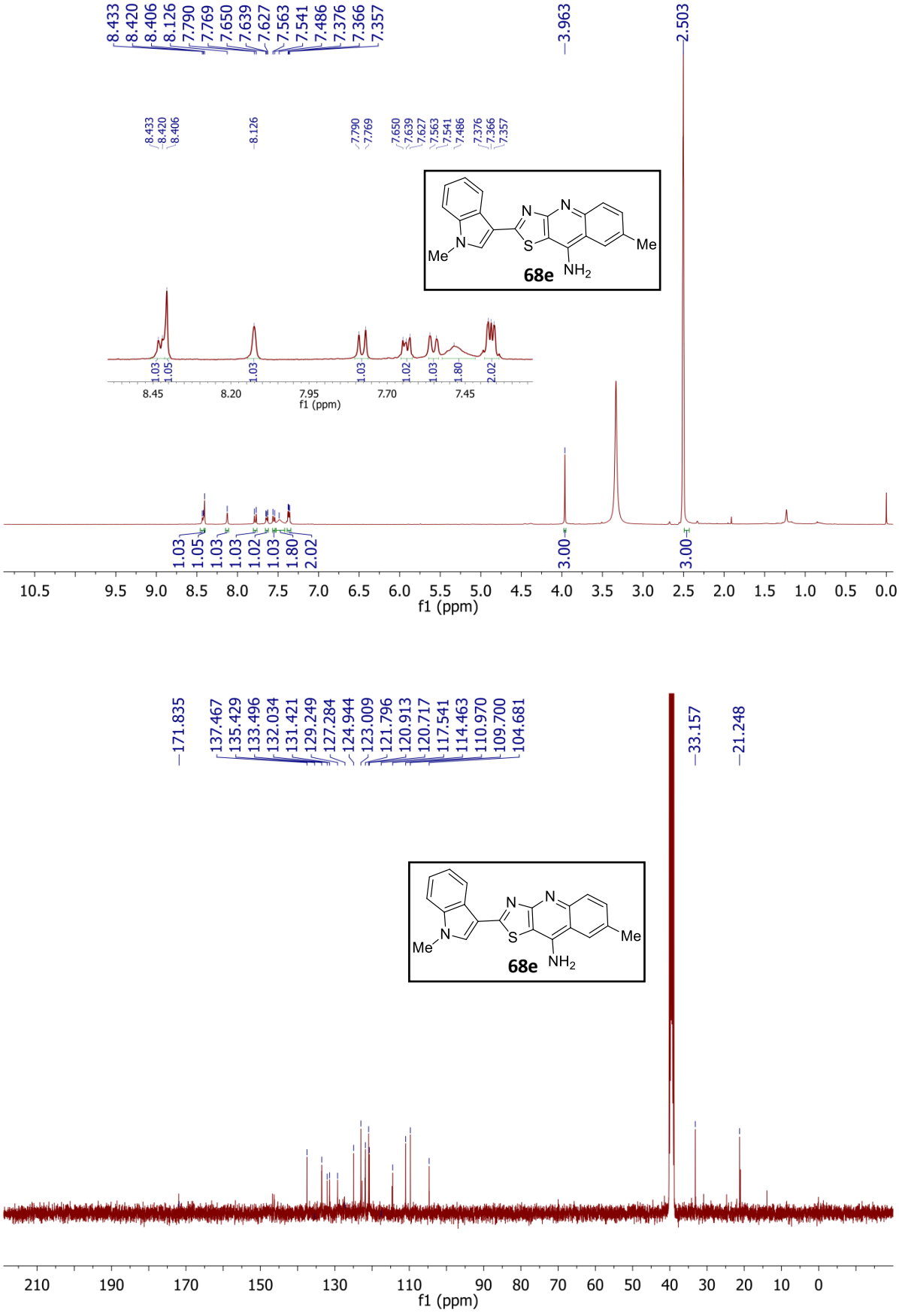


Figure 19. ^{1}H and ^{13}C NMR of compound 68e

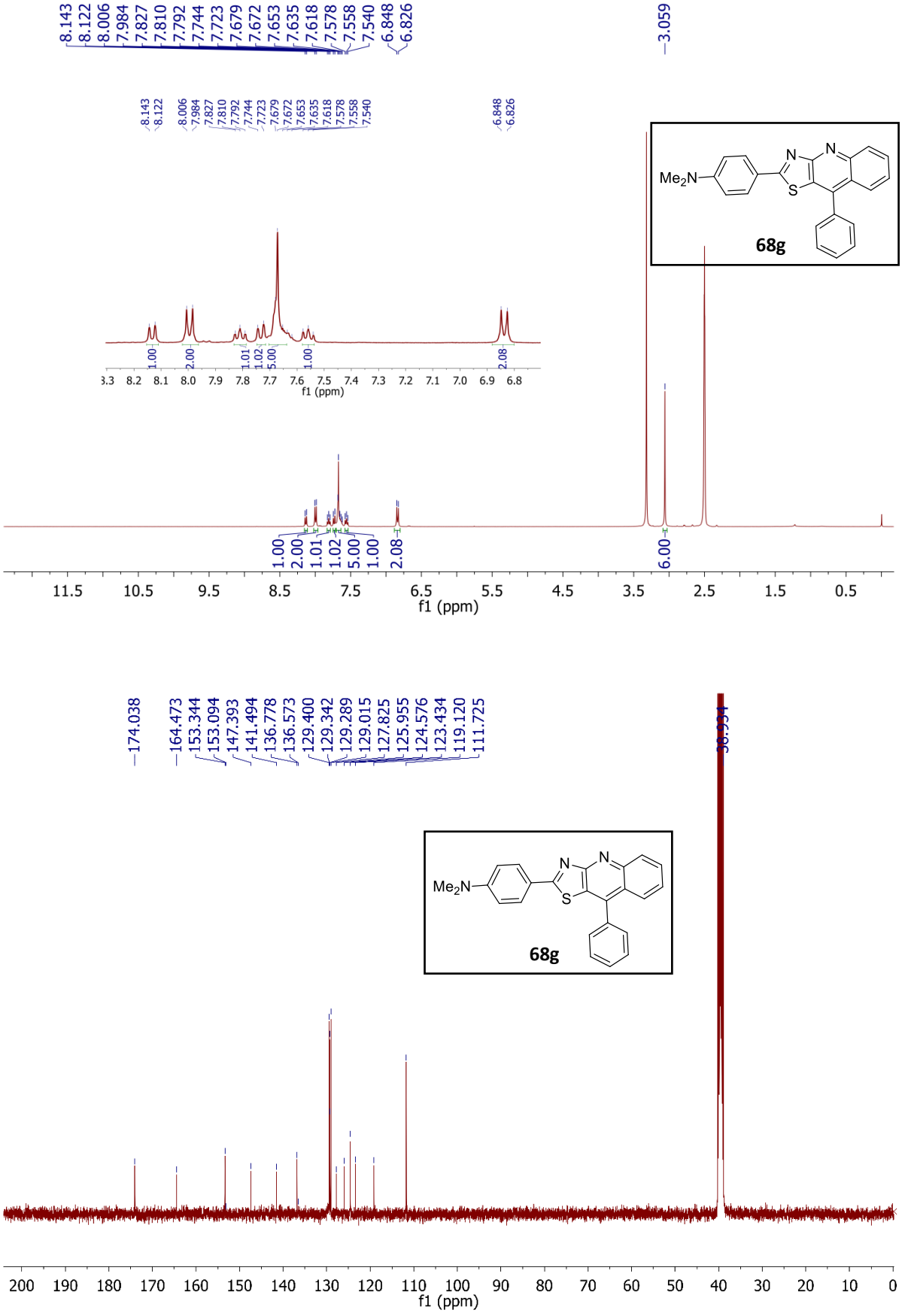


Figure 20. ^{1}H and ^{13}C NMR of compound 68g

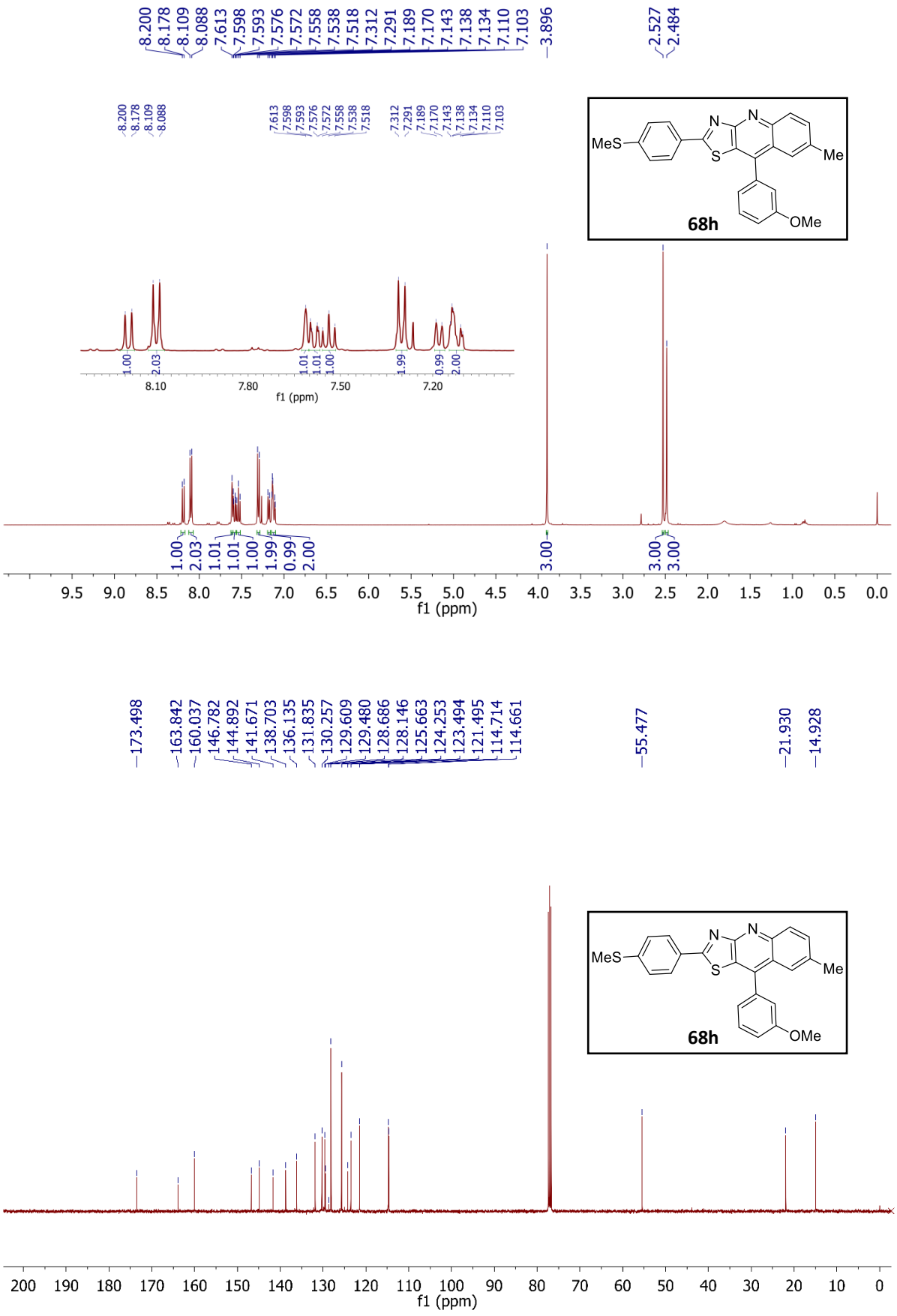


Figure 21. ^{1}H and ^{13}C NMR of compound 68h

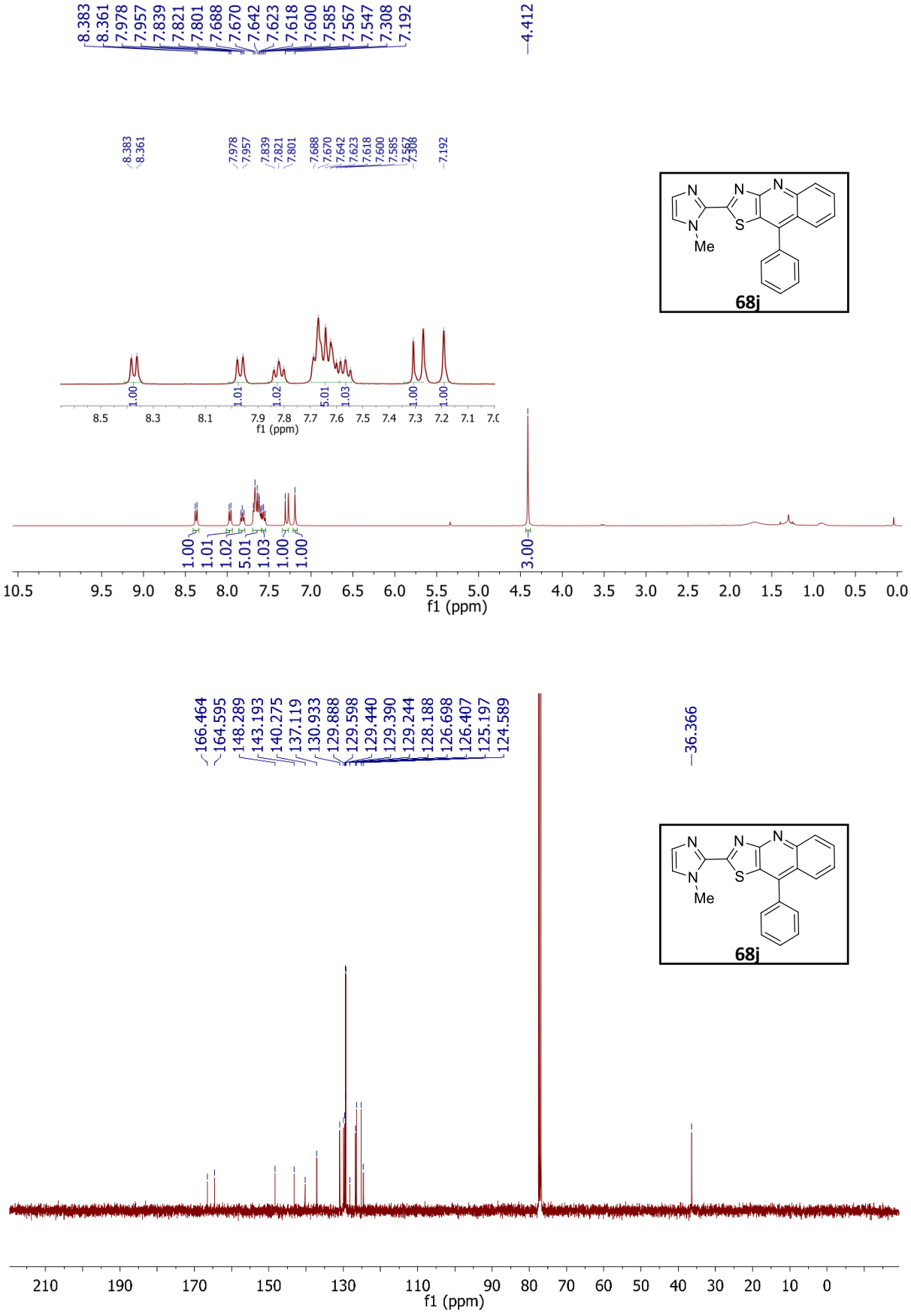


Figure 22. ^{1}H and ^{13}C NMR of compound 68j

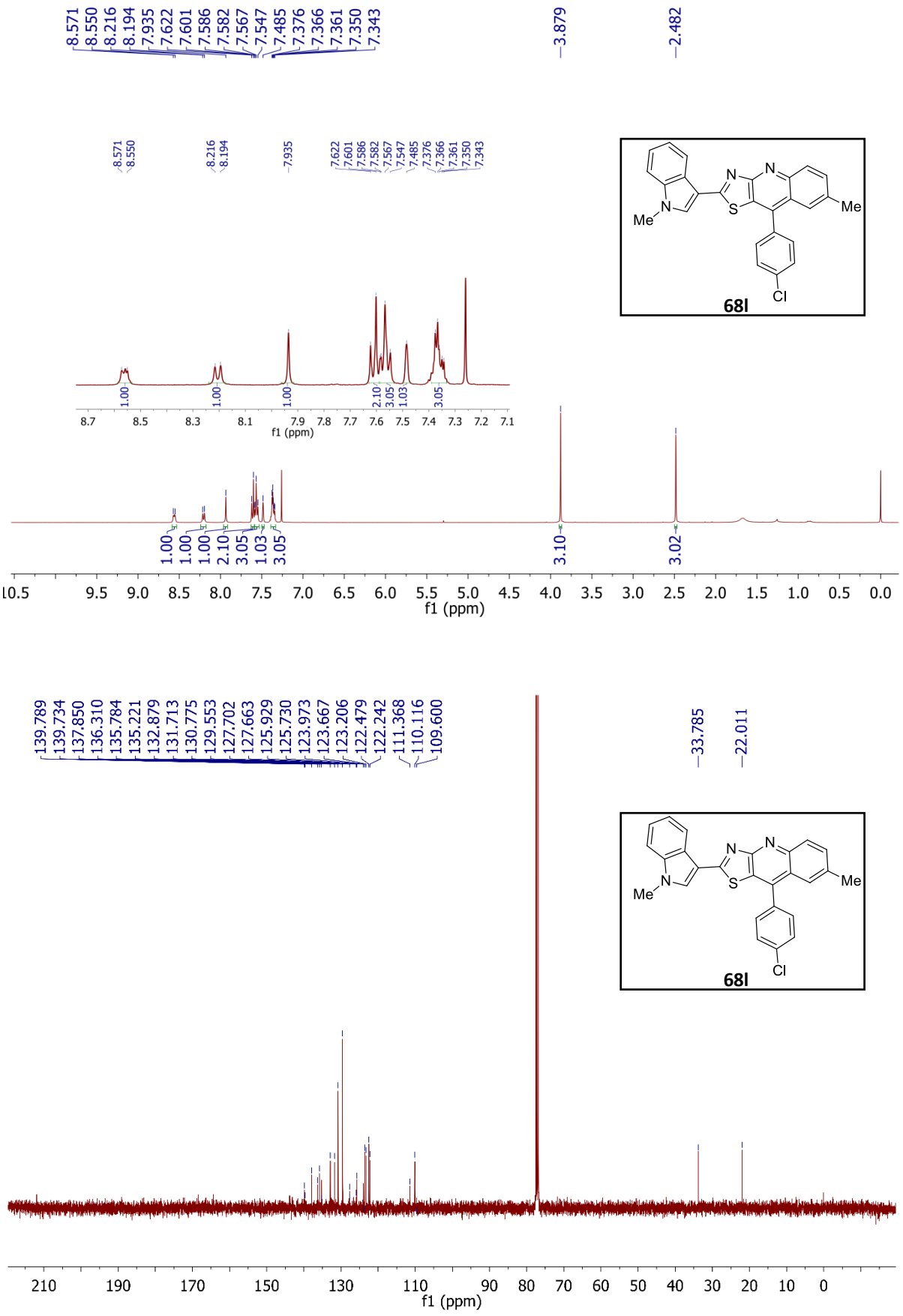


Figure 23. ^{1}H and ^{13}C NMR of compound 68l

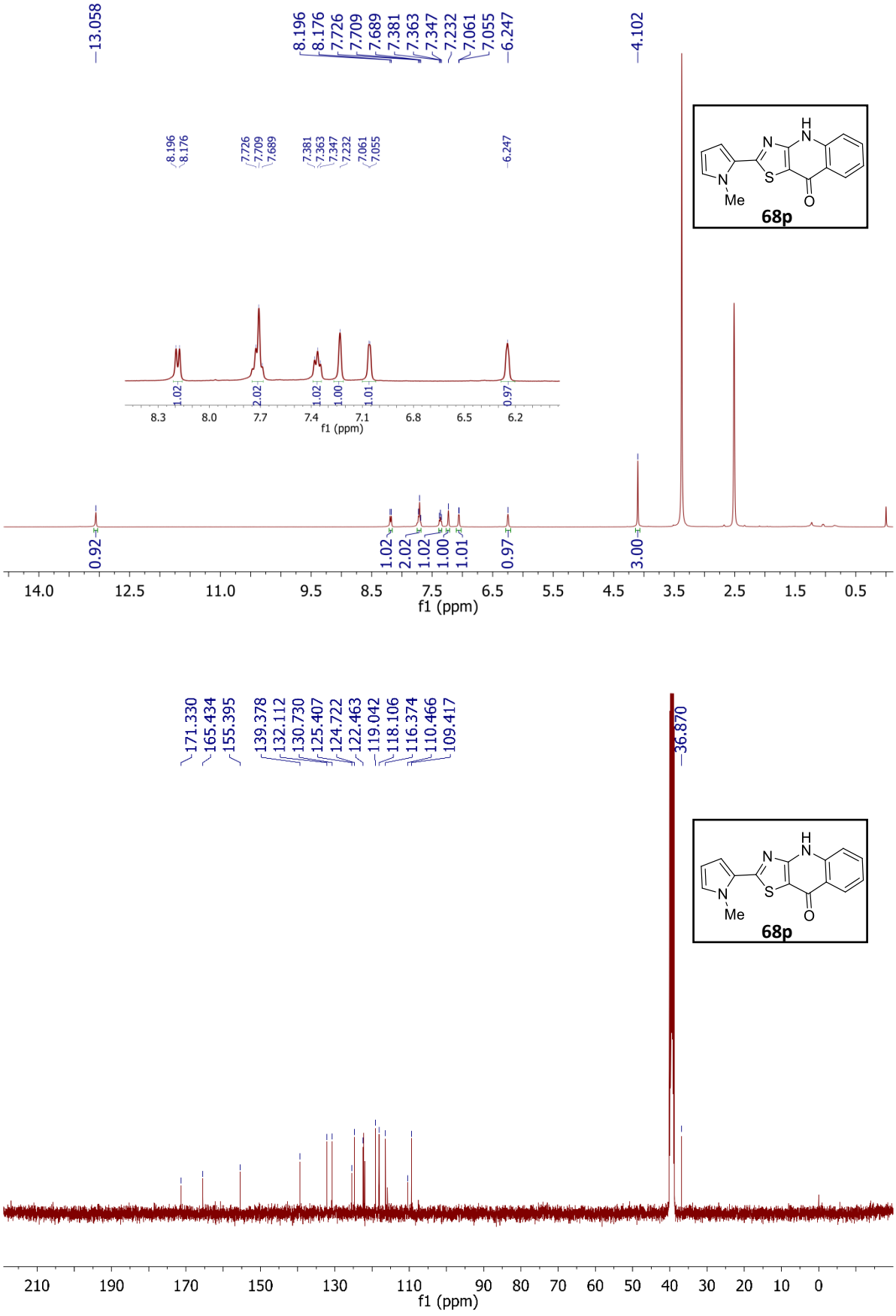


Figure 24. ^{1}H and ^{13}C NMR of compound 68p

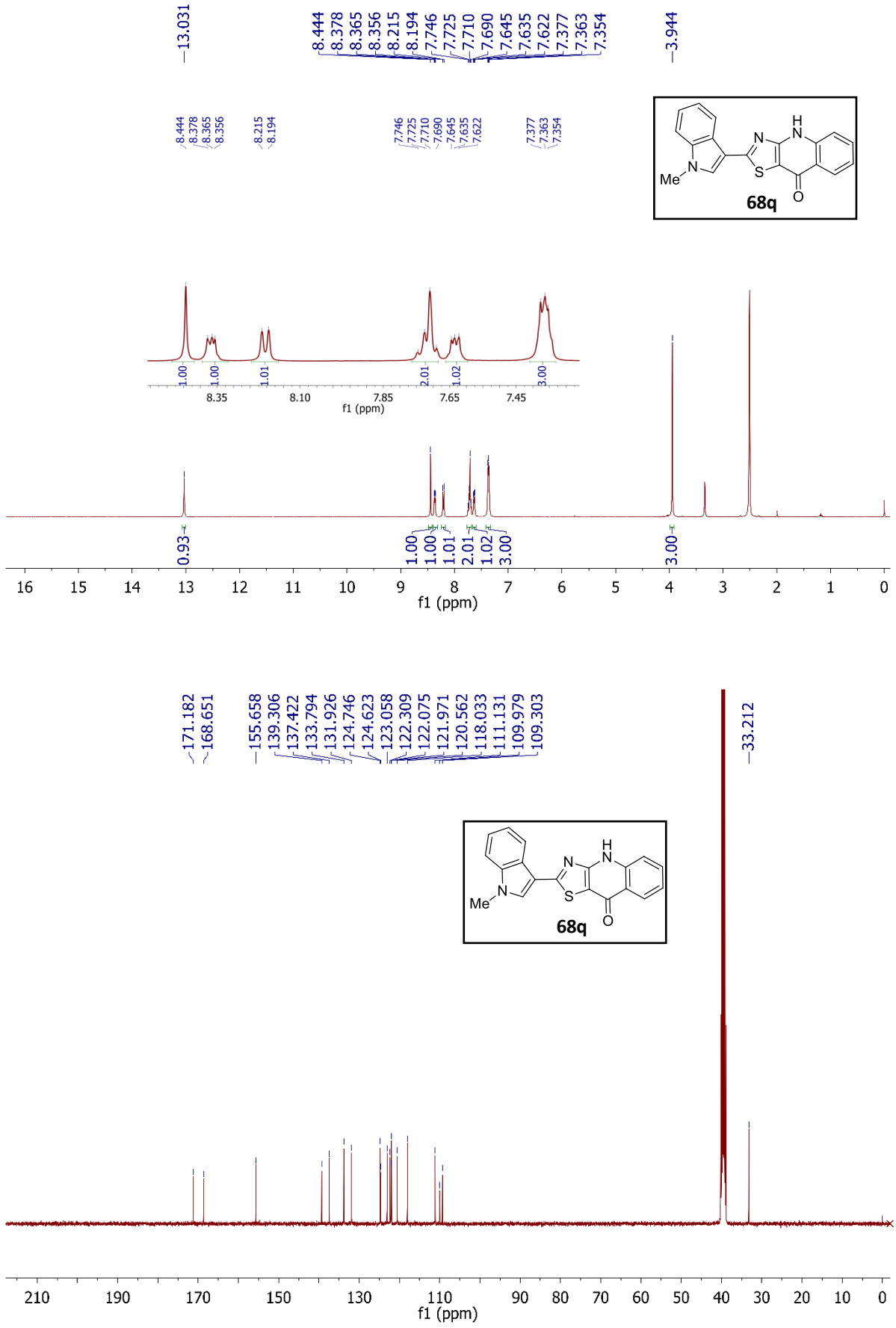


Figure 25. ^{1}H and ^{13}C NMR of compound 68q

Chapter 5

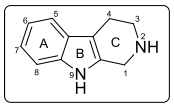
*Aza-Annulation of 1,2,3,4-Tetrahydro-β-carboline Derived Enaminones and Nitroenamines: Synthesis of Functionalized Indolizino[8,7-b]indoles, Pyrido[1,2-a:3,4-b']diindoles, Indolo[2,3-a]quinolizidine-4-ones and Other Tetrahydro-β-carboline Fused Heterocycles**

5.1 Introduction

Indole structure motif represents one of the most privileged classes of heterocycles present in structural core of many natural and non-natural compounds with a broad range of biological activities.[1] The indole alkaloids have been subject of intense structural, pharmacological, biosynthetic and synthetic studies, because of the structural diversity and complexity of many of its members, along with the important physiological and medicinal properties displayed by this class of compounds.[2] Similarly, natural product inspired compounds based on polycyclic indole alkaloids, also exhibit interesting biological activities.[3] Therefore, the development of new synthetic methods, that allow rapid and efficient access to these natural and non-natural indole containing scaffolds has attracted much attention for several decades among organic as well as medicinal chemists.[3]

Tetrahydro-*β*-carboline (Figure 1) constitutes recurring subunit in numerous indole alkaloids,[4] besides, they are also templates for drug discovery and have been used as scaffolds for combinatorial libraries.[4a-e] A search of the World Drug Index reveals 222 citations of these compounds in several therapeutic areas.[4e]

*****The overall results of study described in this chapter have been published in *ACS Omega* **2019**, *4*, 17910.



1

Figure 1

Some of the tetrahydro-*β*-carboline derivatives have been shown to efficiently inhibit monoamine oxidase A10 and display pronounced antitumor and antiviral activities. [4f] Some of these compounds also bind to serotonin receptors with nanomolar affinity[4] or to the $GABA_A$ receptor ion channel thus modulating molecular mechanisms controlling anxiety, convulsions, and sleep.[4] A few of the biologically active *β*-carboline containing alkaloids are shown in Chart 1. Thus the naturally occurring *β*-carbolines such as harman **2** and harmine **3** are shown to possess potent antitumor and anti-HIV activity (Chart 1),[3c] whereas the alkaloid flavopereirine (**4**) is isolated from *Geissospermum* and has been investigated for the treatment of Malaria.[3d] The alkaloid demethoxyfumitremorgin (**5**) has been reported to be useful template for drug discovery.[3e] Also, compounds containing *β*-carboline framework such as eudistomine K (**6**),[3f] azatoxin (**7**),[3g] picrasidine L (**8**),[3h] and javacarboline (**9**)[3i] are shown to display cytotoxic activities in various cancer cell lines (Chart 1).

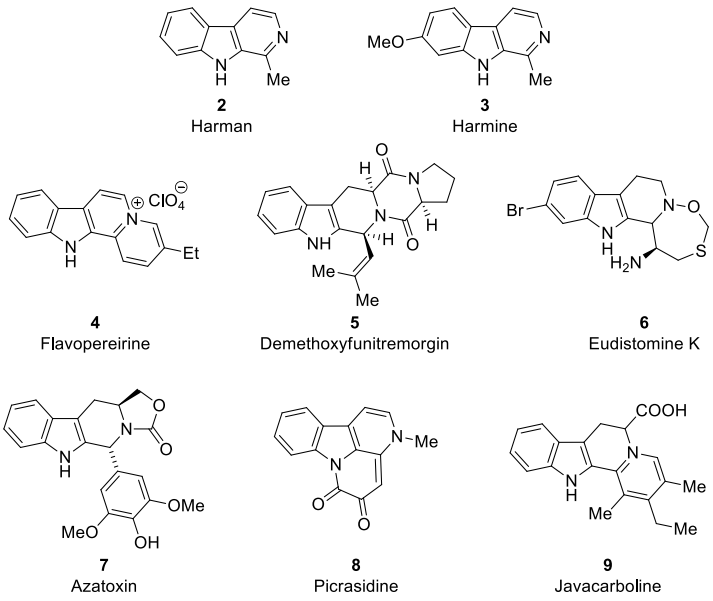
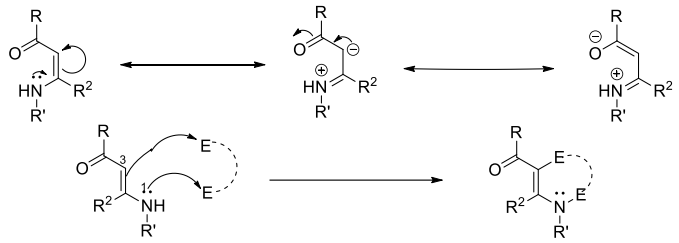


Chart 1. Biologically important natural products containing b-carboline framework

In view of the wide range of biological activity displayed by *β*-carboline containing alkaloids, several research groups have been engaged in synthesis of these naturally occurring alkaloids, as well as for the construction of structurally novel, non-natural alkaloid-type

polycyclic heterocyclic scaffolds, containing this subunit, which is highly challenging and rewarding endeavour in the fast-emerging area of organic synthesis.

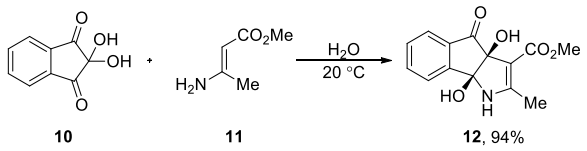
Enaminoketones, esters and nitriles, including nitroenamines have been shown to be versatile building blocks for the synthesis of various five- and six- membered heterocycles and are frequently used in domino and multicomponent reactions, because of the rich reactive sites present in these intermediates (Scheme 1).[5] Because of partial negative charge localized on both nitrogen and *β*-carbon atom, these enaminoketones and their other functional analogs undergo cycloannulation with a variety of biselectrophilic species, yielding novel five- and six- membered substituted and condensed heterocycles (Scheme 1).



Scheme 1

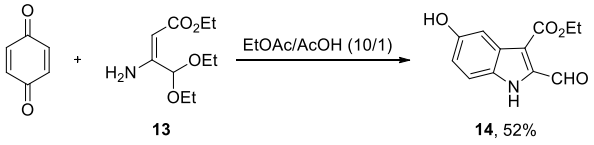
Some of the cycloannulation reactions of enaminoketones yielding fused heterocycles are shown in Schemes 2-4.[5e-g]

Huffmann has reported the synthesis of indeno[1,2-*b*]pyrrole **12** with 94% yield, by treating ninhydrin with the enaminoeser **11** in water. The vinyl carbon of **11** underwent 1,2-addition across the central carbonyl group of ninhydrin and the amino group has attacked the adjacent carbonyl group from the same face (Scheme 2).[5e]



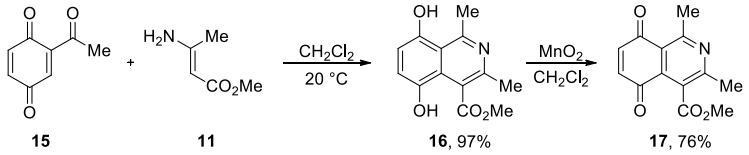
Scheme 2

Similarly, Troschutz and co-workers have described synthesis of 2-formylindole-3-carboxylate **14** in moderate yield by reacting 1,4-benzoquinone with enaminone **13** through Nenitzescu indole synthesis using EtOAc/AcOH (10/1) as solvent (Scheme 3).[5f]



Scheme 3

Hirschmann's grorup has evaluated the reaction of 2-acetyl-1,4-benzoquinone **15** with methyl-3-aminocrotonate **11** at room temperature, to yield dihydroisoquinoline **16**, which on oxidation with MnO_2 gave isoquinoline containing quinone **17** in high yield (Scheme 4).[5g]



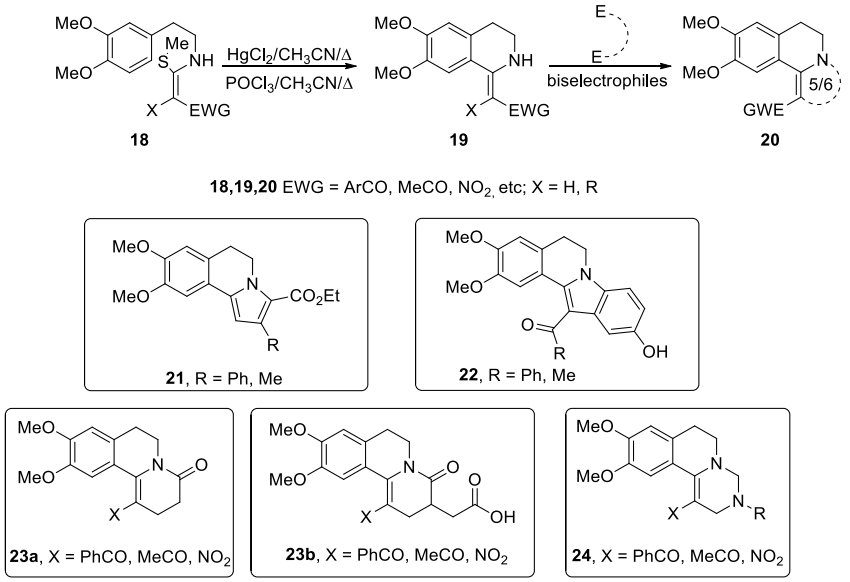
15 **11** **16**, 97% **17**, 76%

Scheme 4

Our literature survey at this stage revealed however that the corresponding heterocyclic enaminones/esters derived from tetrahydro-*β*-carboline framework have not been much explored for the construction of indole annulated heterocycles, despite their considerable synthetic potential.[4a,6] This may be due to the lack of general synthetic methods for this class enaminone intermediates. However, acyclic *β*-enaminoesters generated from reaction of tryptamine and alkyl propiolates have been frequently employed as useful building blocks for construction of indole annulated heterocycles via sequential Pictet-Spengler reaction (Scheme 11)[7a-b]

We have previously reported an efficient general approach for the synthesis of 6,7-dimethoxytetrahydroisoquinoline-derived push-pull enaminones/esters/nitriles of the general structure **19** and their subsequent synthetic elaboration to tetrahydroisoquinoline-fused five- and six-membered heterocycles **20** (Scheme 5).[8] The overall process involves the Bischler−Napieralski type cyclization of newly synthesized ketene *N*,*S*-acetals **18** derived from 3,4-dimethoxyphenylethylamine and polarized ketene dithioacetals[8a] and subsequent aza-annulation of the resulting enaminones/nitroenamines **19** with two or three carbon 1,2- and 1,3-electrophilic species, affording highly functionalized isoquinoline-fused five- and six-membered heterocycles, such as pyrrolo[2,1-*a*]isoquinolines **21**,[8b,d] indolo[2,1-*a*]isoquiolines **22**,[8b] and substituted benzo[*a*]-quinolizidin-4-one **23a**, **23b** and pyrimido[6,1-*a*]isoquinoline **24** structural motifs[8d] present in several naturally occurring alkaloids and physiologically active drugs (Scheme 5).[8]

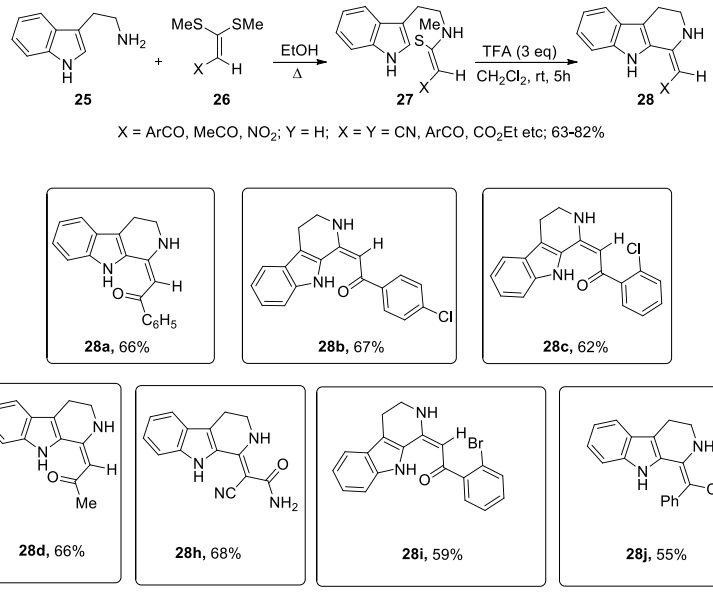
Previous work



Scheme 5

Our fascination with this class of molecules prompted us to extend these studies for the synthesis of tetrahydro-*β*-carboline derived functionalized push-pull enamines, as potentially useful building blocks for the synthesis of 1,2-heteroannulated tetrahydro-*β*-carbolines derived 5- and 6- membered heterocycles and related natural products. Thus, we had previously reported the synthesis of a series of functionalized 1,2,3,4-tetrahydro-*β*-carboline derived enaminones/esters/nitriles **28** via trifluoroacetic acid induced Bischler-Napieralski type cyclization of newly prepared polarized ketene *N*,*S*-acetals **27** from tryptamine **25** and polarized ketene *S*,*S*-acetals **26** (Scheme 6).[4a]

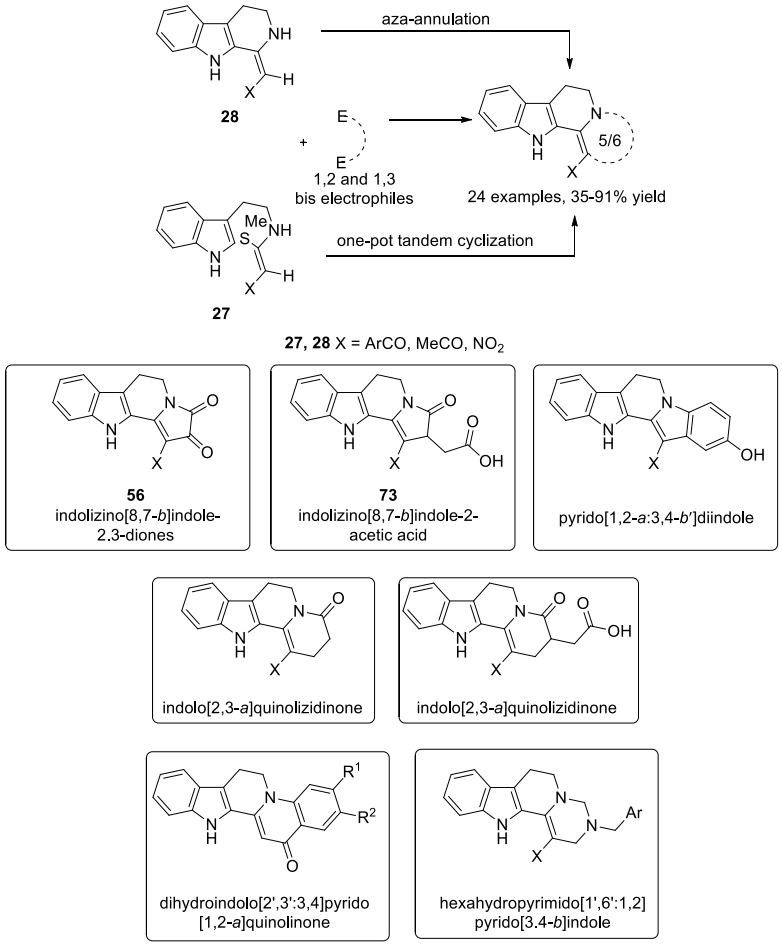
Previous work



Scheme 6

On the basis of our previous studies, with tetrahydroisoquinoline-based enaminones (Scheme 5),[8b,c] we anticipated that tetrahydro-*β*-carboline-derived enaminones and nitroenamines such as **28** could also be employed in efficient aza-annulation reactions with various 1,2- and 1,3-biselectrophiles, leading to a variety of tetrahydro-*β*-carboline 1,2-annulated five- and six-membered heterocycles (Scheme 7). Also, because of our previous experience in exploring the reactivity and synthetic potential of polarized ketene *N*,*S*-acetals as functionalized enaminones,[9] we also envisioned the possibility of synthesizing the target tetrahydro-*β*-carboline-fused heterocycles, directly from acyclic *N*,*S*-acetals **27**, with concurrent formation of both tetrahydropyridine and 5/6 membered rings in a tandem one-pot operation (Scheme 7). The results of these studies have been presented in the present chapter, and we also report one-step synthetic elaboration of a few of these enaminones/nitroenamine **28** to 1,2-tetrahydro-*β*-carboline-annulated heterocycles, such as substituted dihydroindolizino[8,7-*b*]indoles, pyrido[1,2-*a*:3,4-*b′*]diindole, indolo[2,3-*a*]quinolizidines, their benzo-fused analogues, and other novel heterocyclic scaffolds (Scheme 7).

Present work



Scheme 7

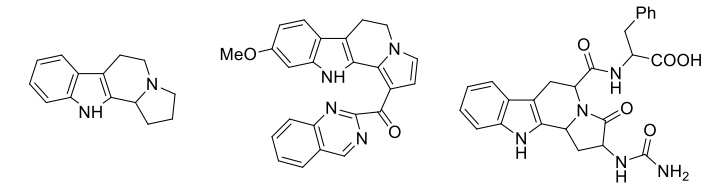
In the foregoing section, we describe the results of our studies on cycloannulation of these novel beta-carboline derived enamines with various biselectrophiles yielding a variety of beta-carboline fused heterocycles.

5.2 Azaannulation of *β*-carboline derived enaminones with oxalyl chloride and maleic anhydride

In the present section, we describe the results of our studies on azannulation of β-carboline derived enaminones and nitroenamines with oxalyl chloride and maleic anhydride yielding dihydroindolizino[8,7-b]indoles derivatives. Before describing our results, we have given a short and recent literature survey on synthesis of this heterocyclic framework.

5.2.1 Synthesis of dihydroindolizino[8,7-*b*]indoles: A short literature survey

Indolizino[8,7-*b*]indole represents an important class of indole containing heterocyclic core present in several naturally occurring bioactive alkaloids, such as harmicine (**29**), pegaharmalines B (**30**), and also in synthetic pharmacologically active compounds such as human CCK_1 receptor antagonists (**31**) (Figure 2).[7a-c,10] Therefore , there has been considerable attention towards development of new synthetic approaches for these class of heterocyclic scaffolds.



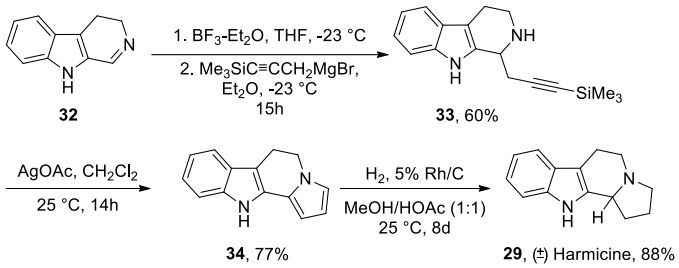
29, Harmicine antispasmodic, anticaner

30, Pegaharmaline B cytotoxic activity

31, CCK_1 receptor antagonist

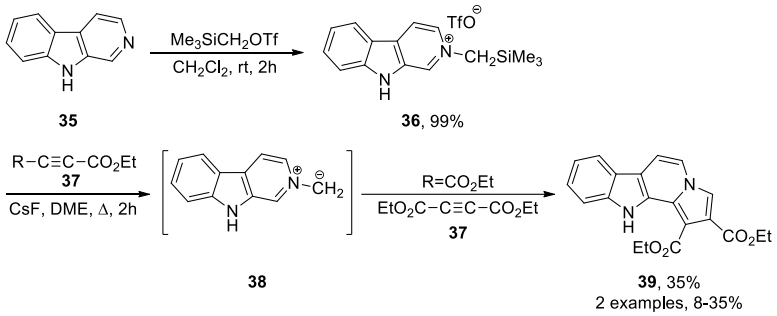
Figure 2. natural products and pharmaceutical compounds with dihydroindolizino [8,7-*b*]indole moiety

Several synthetic approaches for the construction of this heterocyclic core have been reported in recent years.[7-14] In most of these protocols, the pyrrole ring of indolizino[8,7-*b*]indole framework has been constructed in various ways. Thus, Knolker and co-workers have reported a two-step procedure for the construction of the pyrrole ring by addition of a propargyl Grignard reagent to 3,4-dehydro-*β*-carboline **32** and subsequent silver(I)-promoted oxidative cyclization of the resulting adduct, yielding the corresponding indolizino[8,7-*b*]indole **34** in 77% yield (Scheme 8).[12a] which is a synthetic precursor for the indolizidino[8,7-*b*]indole alkaloid harmicine **29**. Thus, chemoselective hydrogenation of the pyrrole ring of **34** using 5% rhodium on activated charcoal as catalyst provided directly (±)-harmicine **29** in good yield (Scheme 8).[12b]



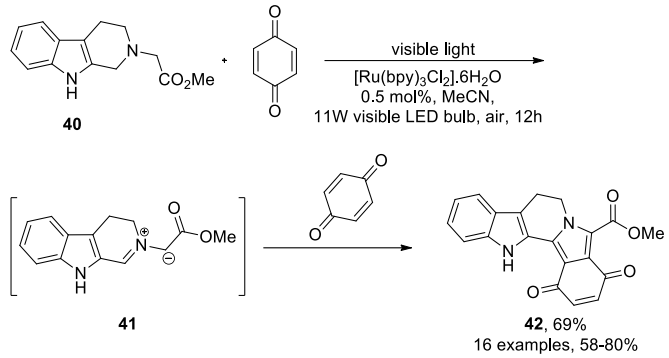
Scheme 8

The pyrrole ring has also been constructed by several research groups via 1,3-dipolar cyclo-addition of tetrahydro-*β*-carboline-derived azomethine ylides[13a] (or munchnones)[13b] with various dipolarophiles, including a photoredox-catalyzed oxidation/1,3-dipolar cycloaddition reported by Maurya and co-workers.[13c] Thus Dodd and co-workers have demonstrated the synthesis of indolizino[8,7-*b*]indole derivative **39**, via 1,3-dipolar cycloaddition of diethyl acetyledene dicarboxylate (DEAD) **37** with in situ generated azomethine ylide **38** from 2-*N*-[(trimethylsilyl)methyl]triflate salt **36** on treatment with cesium fluoride (Scheme 9).[13a]



Scheme 9

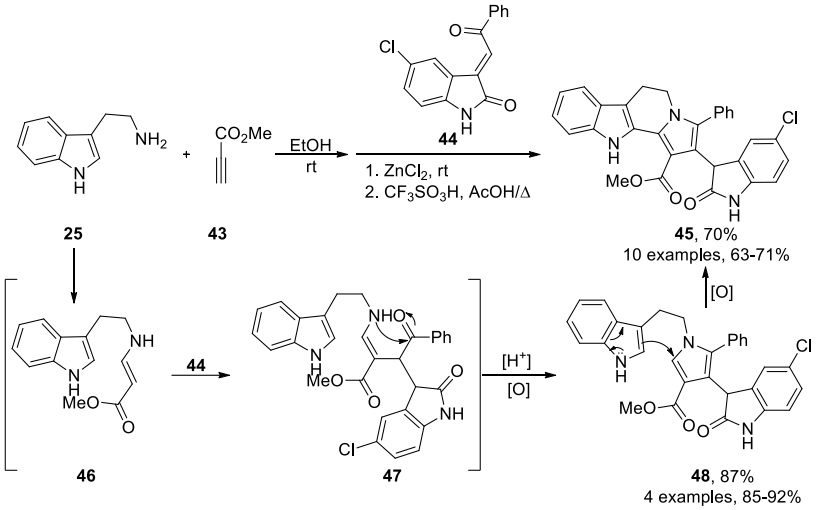
Recently, fused *β*-carboline derivatives such as **42** were synthesized by Maurya and group *via* a one-pot visible light photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade in flow microreactors. Thus, methyl 2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]-indol-2-yl)acetate **40** was coupled with 1,4-benzoquinone in visible light, in the presence of catalytic amount of photoredox catalyst $[Ru(bpy)_3Cl_2].6H_2O$ to obtain the aromatized cycloadduct **42**. The reaction proceeded *via* photoredox generation of azomethine ylide **41** and subsequent [3+2] dipolar cycloaddition reaction (Scheme 10).[13c]



Scheme 10

Functionalized tetrahydroindolizino[8,7-*b*]indoles have also been obtained *via* a one-pot or stepwise reaction of tryptamine, alkyl propiolates, and *β*-nitroalkenes/*α*,*β*-unsaturated ketones *via* intermediacy of acyclic *β*-enaminoesters, with concomitant formation of both tetrahydropyridine and pyrrole ring in a domino fashion.[7a,b]

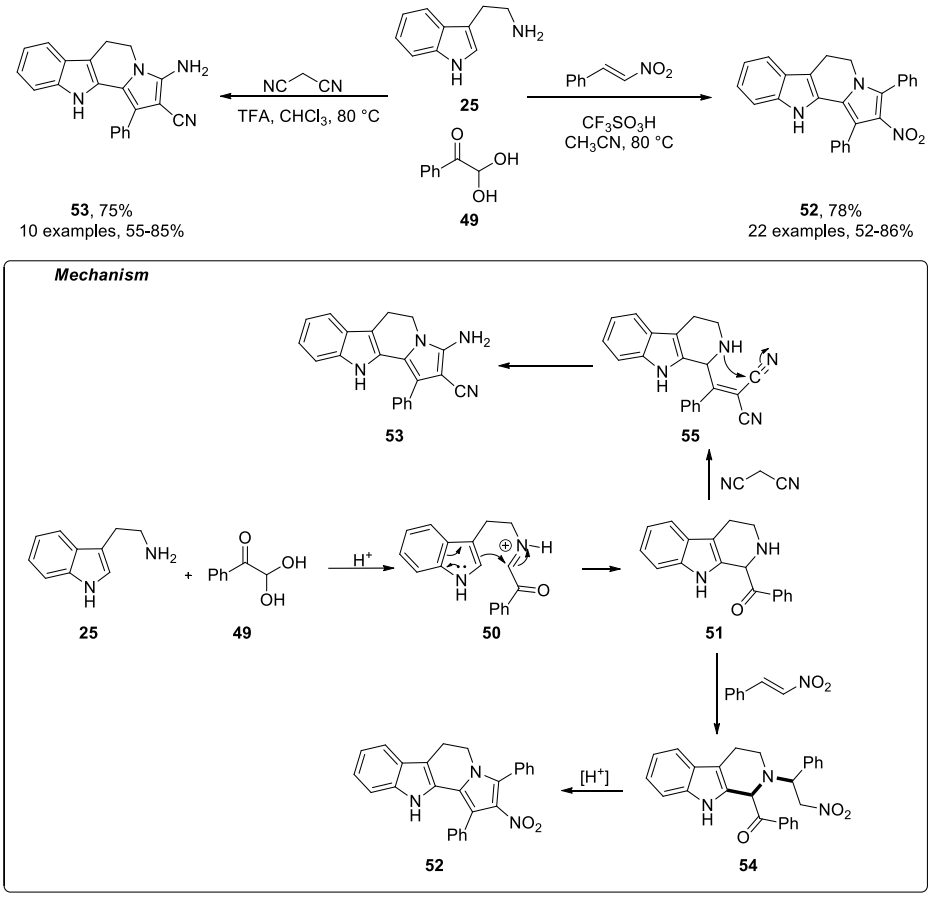
Yan and co-workers have recently reported a convenient procedure for synthesis of polysubstituted 6,11-dihydro-5*H*-indolizino[8,7-*b*]indole **45** via one- pot sequential reaction of tryptamine **25**, alkyl propiolate **43** and 3-phenylideneoxindole **44.** Thus Michael addition of in situ generated *β*-enaminoester **46 (**from tryptamine and methyl propiolate **43)**, with the exocyclic carbon of **44**, gave the intermediate adduct **47**, which under the catalysis of anhydrous zinc chloride and triflic acid yields final product **45** *via* intramolecular cyclocondensation (**47** to **48**) of the intermediate **48** followed by its ring closure (Scheme 11).[7b]



Scheme 11

Wu and co-workers have developed an acid-catalyzed multicomponent tandem cyclization protocol for the synthesis of dihydroindolizino[8,7-*b*]indoles **52** and **53**, under metal-free conditions by reaction of tryptamine **25** with phenylglyoxal monohydrate **49** and *β*-nitrostyrene or malononitrile (Scheme 12).[10] Thus, Pictet-Spengler cyclization of the

intermediate **50** obtained by condensation of tryptamine and phenylglyoxal dihydrate affords the tetrahydroisoquinoline intermediate **51**, which on Michael addition with *β*-nitrostyrene and subsequent intramolecular oxidative cyclization of the Michael adduct **54** affords the product **52** in good yields (Scheme 12). Similarly, for the formation of product **53**, from **25, 49** and malononitrile, intermediate **51** undergoes a Knoevenagel condensation with malanonitrile to furnish the intermediate **55** which on subsequent intramolecular cyclocondensation affords product **53**(Scheme 12).[10]



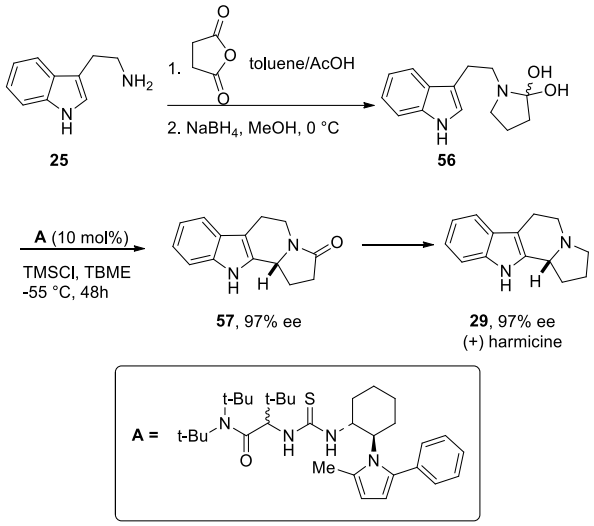
Scheme 12

5.2.2 Synthesis of Indolizino[8,7-*b*]indoles and related analogs via cycloannulatiuon of acyclic and cyclic enaminones with maleic anhydride: A short literature survey

Aza-annulation of a few acyclic and cyclic enaminones/esters/nitriles with maleic anhydride/maleimide has been reported in the literature affording substituted monocyclic and bicyclic pyrrolidinones.[8b,11,15]

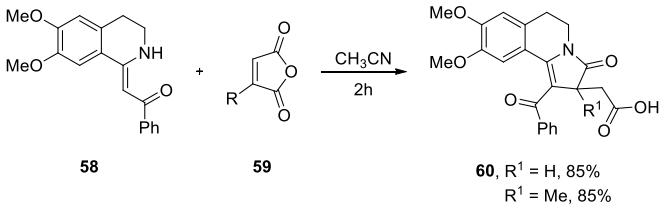
Jacobsen and group have described the synthesis of (+) harmicine **29** by enantioselective Pictet-Spengler type cyclization of hydrolactam **56**. When tryptamine was treated with succinic anhydride, followed by reduction with $NaBH_4$, it yielded the hydrolactam

56 which in the presence of chiral thiourea derived catalyst **A** gave (*R*)indolizino[8,7-*b*]indole-3-one **57**, which on $LiAlH_4$ reduction furnished (+) harmicine (Scheme 13).[11]



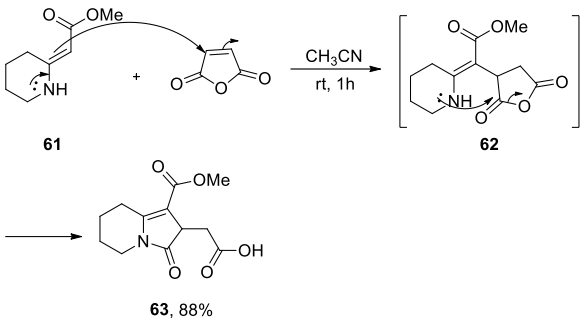
Scheme 13

Earlier, our research group has studied the annulation reactions of dimethoxytetrahydroisoquinoline-derived push-pull enamine **58** with substituted maleic anhydrides **59** in acetonitrile furnishing functionalized pyrrolo[2,1-*a*]isoquinoline **60** in excellent yield (Scheme14).[8b]



Scheme 14

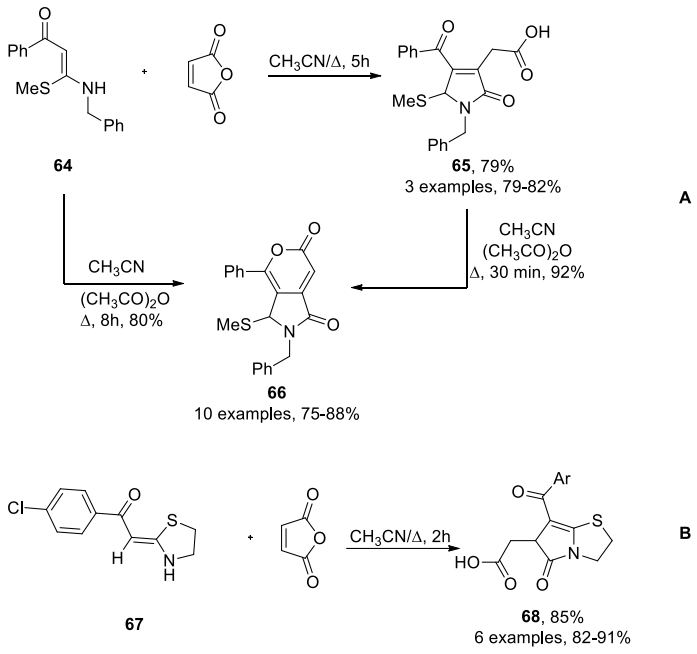
Recently Sabino and coworkers have investigated domino aza-annulation of cyclic enaminones such as **61** with maleic anhydride to develop the synthesis of alkaloid-like indolizidinone frameworks like **63** *via* [3+3] cycloaddition reactions. A concerted aza-ene reaction between enaminone **61** and maleic anhydride gave the intermediate **62**, which on intramolecular N-acylation affords the product **63** (Scheme 15).[15a]



Scheme 15

Earlier, our research group has described a convenient one-step method for synthesis of pyrano[3,4-*c*]pyrroles and other condensed pyrrole derivatives via cycloannulation of polarized ketene *N,S*- and *N,N*-acetals with maleic anhydride in good yields (Scheme 16).[15b] Thus when the *N,S*-acetal **64** was refluxed with maleic anhydride in acetonitrile, the product pyrrolinone-3-acetic acid **65** was obtained in good yields. The compound **65** was then cyclized in presence of acetic anhydride to get 2-benzyl-3-(methylthio)-4-phenyl-2,3-dihydropyrano[3,4-*c*]pyrrole-1,6-dione **66** in 92% yield, which could also be obtained directly in comparable yields (85%) by refluxing **64** with acetic anhydride in acetonitrile solvent (Scheme 16A).[15b]

The reaction was then extended to cyclic *N,S*-acetal **67** which on treatment with maleic anhydride gave the corresponding pyrrolo[2,1-*b*]thiazole derivative **68** in excellent yield (Scheme 16B).[15b]



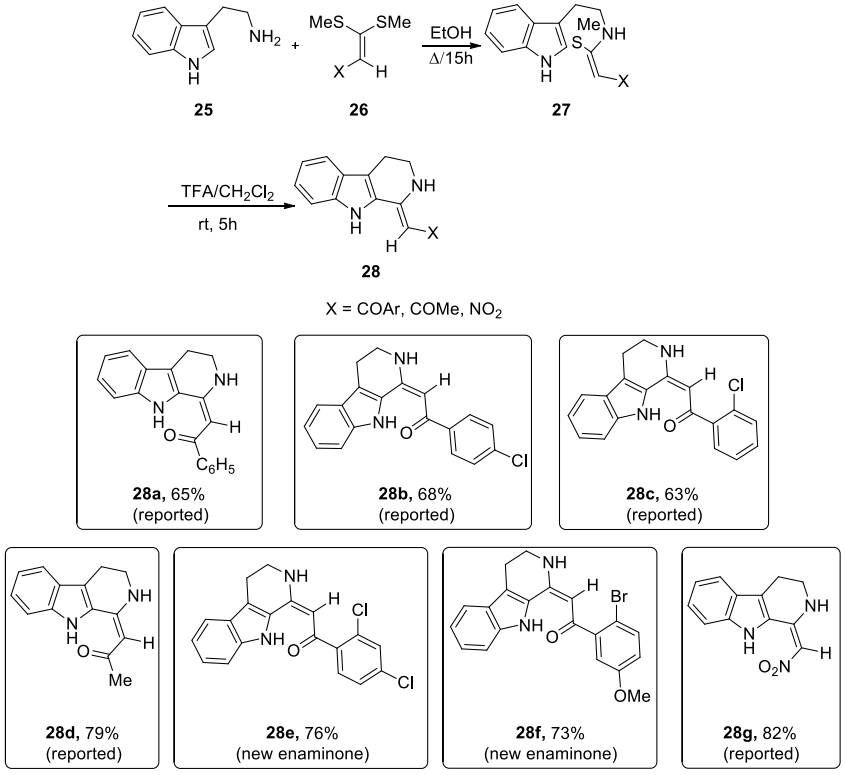
Scheme 16

In the following section ,we present results of our study on the cycloannulation of *β*-carboline derived enaminones and nitroenamines with oxalyl chloride and maleic anhydride yielding indolizino[8,7-*b*]indole derivatives .

5.2.3 Results and discussion

5.2.3.1 Azaannulation of *β*-carboline derived enaminones with oxalyl chloride: Synthesis of indolizino[8,7-b]indole derivatives

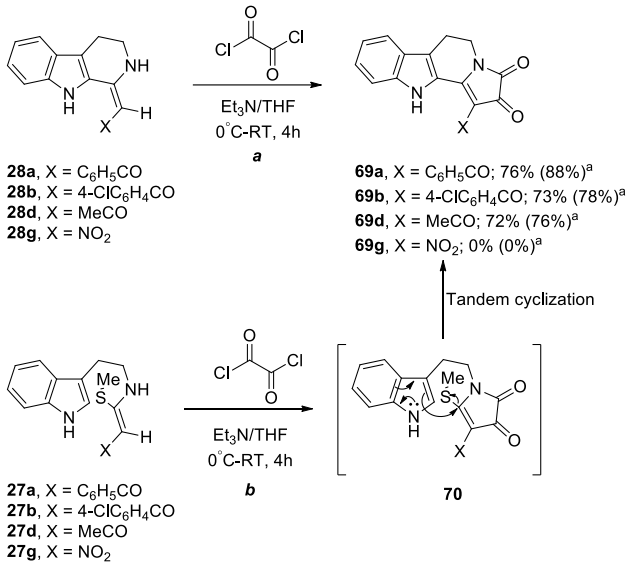
For our study, the desired enaminones **28a-f** and nitroenamine**28g** were synthesized according to our earlier reported procedure[4a] as shown in the Scheme 17. The corresponding *N,S*-acetals **27** were prepared in high yields *via* direct displacement of the appropriate polarized ketene dithioacetals **26** with tryptamine in refluxing ethanol, which on cyclization with TFA in dichloromethane yielded the *β*-carboline derived enaminones **28** (Scheme 17).



Scheme 17

We first examined the reactions of enaminone **28a** with oxalyl chloride, with a view to synthesize indolizino[8,7-*b*]indole-2,3-dione **69a** (Scheme 18). Thus, **28a** was reacted with oxalyl chloride in the presence of triethylamine in tetrahydrofuran (THF) at room temperature, work-up and purification of the crude reaction mixture afforded a red crystalline solid, in 76% yield, which was characterized as the expected 1-benzoyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-2,3-dione **69a** on the basis of its spectral and analytical data (Scheme 18). Similarly, the corresponding 4-chlorobenzoyl and acetyl-substituted enaminones **28b** and **28d** also

reacted with oxalyl chloride under identical conditions, yielding the corresponding indolizino[8,7-*b*]indole-2,3-diones **69b** and **69d** in high yields (Scheme 18). Alternatively, we also reacted the corresponding tryptamine-derived acyclic *N*,*S*-acetals **27a**, **b**, **27d** with oxalyl chloride under similar conditions, expecting the formation of the desired indolizino[8,7-*b*]indole-2,3-diones **69** in a domino fashion, with concomitant formation of both the rings *via* intramolecular cyclization of the initially formed *N*-substituted 4-benzoyl-5-methylthiopyrrolidin-2,3-diones **70** (Scheme 18). Indeed, the reactions proceeded as expected, yielding the desired tetracyclic indolizino[8,7-*b*]indole-2,3-diones **69a**,**b**,**d** in comparatively better yields (route b, Scheme 18). However, the corresponding cyclic nitroenamine **28g** or the acyclic nitroketene *N*,*S*-acetal **27g** failed to furnish the desired 1-nitro-indolizino[8,7-*b*]indole-2,3-dione **69g** under above described conditions, yielding only an intractable reaction mixture (Scheme 18).

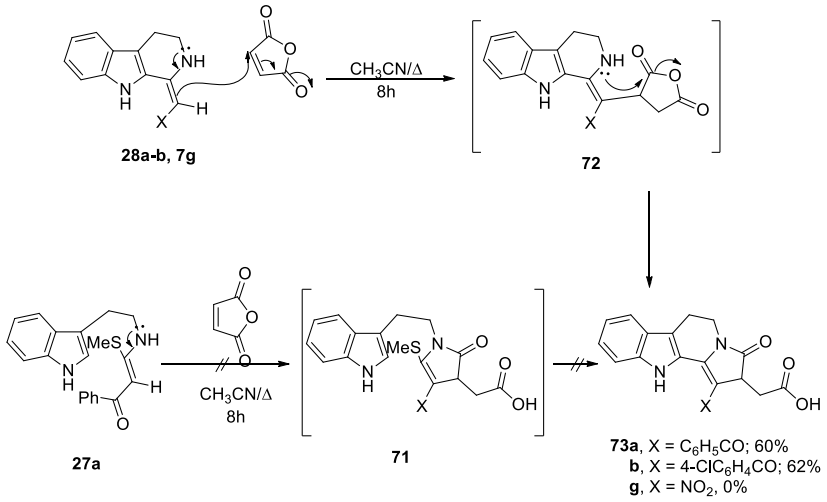


Scheme 18

5.2.3.2 Azaannulation of *β*-carboline derived enaminones with maleic anhydride:Synthesis of indolizino[8,7-b]indolyl-2-yl-acetic acid analogs

With the successful isolation of indolizino[8,7-*b*]indole-2,3-diones **69** from the reactions of enaminones **28** with oxalyl chloride, we next investigated aza-annulation of enaminones **28** with maleic anhydride, with a view to synthesize functionalized indolizino[8,7-*b*]indoles such as **73** with an acetic acid side chain (Scheme 19). Thus when the enaminone **28a** was reacted with equimolar quantity of maleic anhydride in solvents such as benzene, toluene, and acetonitrile under reflux conditions, the product isolated after work-up, was characterized as expected 2-(1-benzoyl-3-oxo-3,5,6,11-tetrahydro-2*H*-indolizino[8,7-

b]indol-2-yl)acetic acid **73a**, with the help of spectral and analytical data (Scheme 19). However, the best yield (60%) of **73a** were obtained in refluxing acetonitrile, whereas in other solvents, formation of side products was observed along with **73a**. Similarly the 4-chlorobenzoyl substituted enaminone **28b** also afforded the substituted indolizino[8,7-*b*]indole-2-acetic acid **73b** in good yield (Scheme 19). However, the corresponding nitroenamine **28g**, although reacted completely with maleic anhydride under identical conditions, however the products could not be isolated in pure form, even after repeated column chromatography. Similarly, attempted domino cyclization of *N*,*S*-acetal **27a** with maleic anhydride was not successful and neither the tetracyclic product **72** nor the pyrrolidinone intermediate **71** could be isolated from the reaction mixture (Scheme 19).



Scheme 19

5.3 Nenitzescu reaction of *β*-carboline derived enamonones with benzoquinone: Synthesis of pyrido[1,2-*a*:3,4-*b*']diindoles

The pentacyclic pyrido[1,2-*a*:3,4-*b'*]diindole framework constitutes core structure of several marine alkaloids including red pigment fascaplysin, homofascaplysins B-C and their bromo-analogues (Figure 3).[16] Fascaplysin displays broad range of biological activities, such as antibacterial, antifungal, antiviral, antimalarial, HIV-1-RT, and especially inhibition of cyclin dependent kinase 4, which regulates the G_0-G_1/S checkpoint of cell cycle.[16-17] Therefore, there is considerable interest in development of synthesis of fascaplysin and its analogues, as lead compounds for potential anticancer drugs and for other therapeutic applications.[16-17] Similarly, naturally occurring alkaloids cladoniamide G possessing an unprecedented indolotryptoline skeleton have also shown to display significant toxicity against human colon and breast cancer (Figure 3).[18]

In the present section, we describe the results of our study on Nenitzescu reaction of *β*-carboline derived enaminones with 1,4-benzoquinone yielding pentacyclic pyrido[1,2-*a*:3,4-*b*']diindole analogs in one step (Scheme 22).Before presenting our work , we have given a short recent literature survey on the synthesis of this ring system.

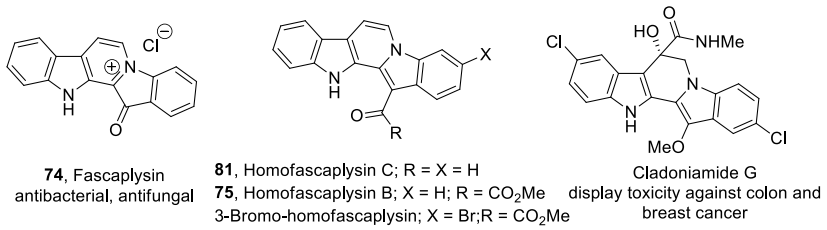
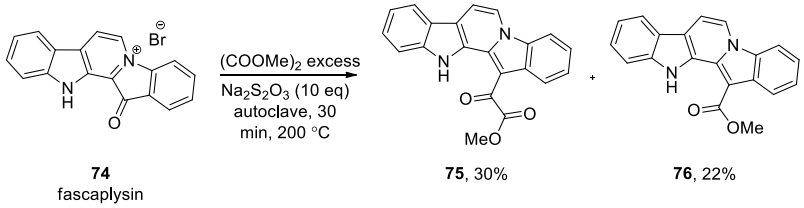


Figure 3. Natural products containing 12H-pyrido[1,2-a:3,4-b']diindole skeleton

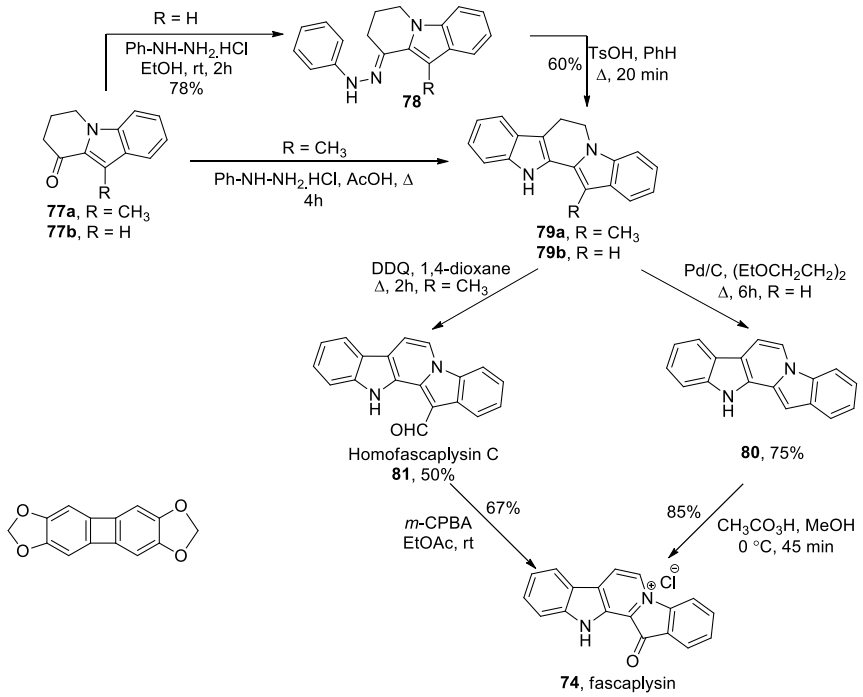
5.3.1 Synthesis of pyrido[1,2-*a*:3,4-*b*']diiondoles analogs : A short literature survey

Lyakhova and coworkers have described one-step conversion of marine alkaloid fascaplysin **74** into homofascaplysin B **75** by reductive acylation in the presence of excess of diethyl oxalate and sodium thiosulphate, yielding **75** in 30% yield along with the decarbonylated side product **76** (22%) (Scheme 20).[16a]



Scheme 20

Zhidkov and co-workers have reported a practical approach for the synthesis of fascaplysin **74** starting from indoloketone **77a-b** (Scheme 21). Thus the indoloketones **77a-b** were subjected to Fischer indole-cyclization by treatment with phenyl hydrazine and subsequent acid mediated cyclization of intermediate phenylhydrazones **78** furnishing pyridodiindole derivatives **79a-b** in good yields**.** The product **79a** (R=CH_3) was transformed in to fascaplysin in two steps vis oxidation of methyl group with benzoquinone to give homofascaplysin C **81** in 50% yield. Subsequent Baeyer-Villiger rearrangement of **81** with *m*-CPBA affords fascaplysin (**74**) with an overall yield of 18% (Scheme 21).On the other hand the unsubstituted pyridodiindole analog **79b** was converted to fascaplysin **74** in high yield by oxidative dehydrogenation with Pd/C, followed by peracetic acid oxidation of the intermediate **80** (Scheme 21).[16b]

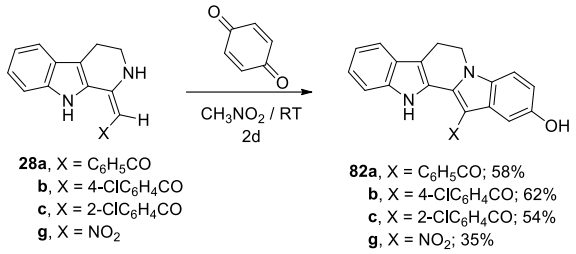


Scheme 21

5.3.2 Results and discussion: Synthesis of 2-hydroxy-13-acyl/nitro-12*H*-pyrido[1,2-*a*:3,4-*b*']diindole by cycloannulation of *β*-carboline derived enaminones and nitroenamines with 1,4-benzoquinone

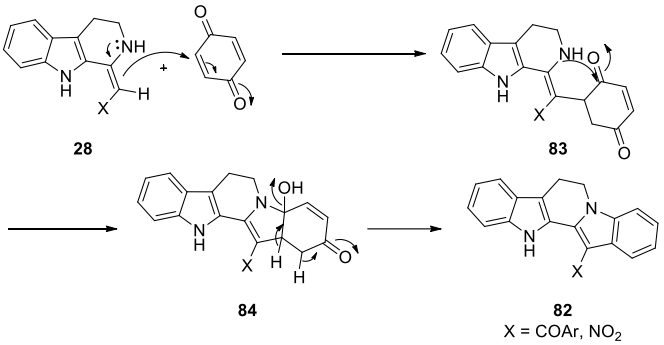
Although, Nenitzescu reaction for the synthesis of 5-hydroxyindole has been widely studied and various acyclic and cyclic enaminoesters/enaminones have been employed as enamine components in this reaction,[5a] the corresponding heterocyclic enaminones such as **28a-d** or nitroenamine **28g** derived from *β*-carboline have not been explored for the construction of pyridodiindole framework. Based on our previous studies with tetrahydroisoquinoline derived enaminones **25** (Scheme 5),[8b] we have developed a new one step procedure for the synthesis of novel pentacyclic pyrido[1,2-*a*:3,4-*b'*]diindole framework through Nenitzescu reaction of enaminones **28** with 1,4-benzoquinone (Scheme 22). Thus, the reaction of **28a** with 1,4-benzoquinone in either refluxing acetic acid or in presence of $ZnCl_2$ catalyst(20 mol%)[5a] in dichloromethane yielded only complex mixture of products, however when the enaminone **28a** was stirred with 1,4-benzoquinone in nitromethane for 2 days under our earlier described conditions,[8b,8e] the reaction mixture after usual work-up and purification yielded a yellow solid (58%) characterized as 6,7-dihydro-2-hydroxy-13-bezoyl-12*H*-pyrido[1,2-*a*:3,4-*b*']diindole **82a** (Scheme 22). Similarly, the other substituted enaminones **28b-c** also underwent cycloannulation with 1,4-benzoquinone under identical conditions furnishing the corresponding 2-hydroxy-13-aroyldihydropyridodiindoles **82b-c** in moderate to

good yields (Scheme 22). Interestingly, the nitroenamine **28g** could also be reacted with benzoquinone yielding the corresponding hitherto unreported 2-hydroxy-13-nitropyridodiindole analogue **82g**, although in low yield (35%) (Scheme 22).



Scheme 22

The probable mechanism of the formation of products pyridodiindoles **82** from enaminones and benzoquinone is shown in the Scheme 23. The *β*-carbon of enaminones undergo Michael addition with benzoquinone to give intermediate **83** which on intramolecular cyclocondensation with carbonyl group, on nitrogen atom affords the product **82** through intermediate **84** *via* dehydration and tautomerization (Scheme 23).



Scheme 23

5.4 Cycloannulation of *β*-carboline derived enaminones with 2-bromopropionyl chloride and itaconic anhydride: Synthesis of indolo[2,3-*a*]quinolizidin-4-one framework

In the present section, we describe the results of our studies on azannulation of *β*-carboline derived enaminones and nitroenamines with 2-bromopropionyl chloride and itaconic anhydride yielding indolo[2,3-*a*]quinolizidin-4-one derivatives (Schemes 32-33). Before describing our results, we have given a short and recent literature survey on synthesis of this heterocyclic framework.

5.4.1 Synthesis of indolo[2,3-*a*]quinolizidin-4-ones: A short literature survey

The indolo[2,3-*a*]quinolizidine structural motif is of significant importance, since this privileged structure is present in plethora of numerous naturally occurring, bioactive indole

alkaloids[1d,6b,19] such as deplancheine, geissoschizine, dihydrocorynantheine, including ajmalicine and yohimbane, a potent modulator of tubulin cytoskeleton, and important anticancer drugs (Figure 4).[3] (check spellings of all alkaloids)

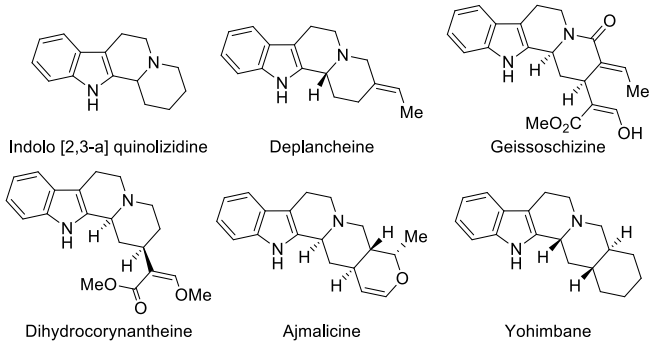
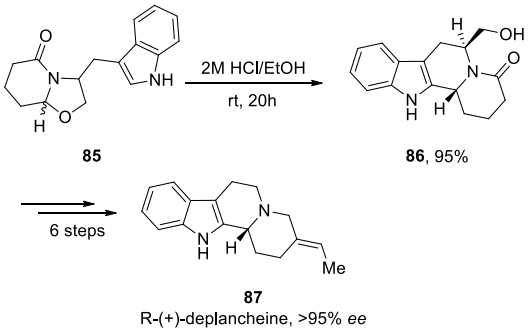


Figure 4. Naturally occurring indole alkaloids with indolo[2,3-*a*]quinolizidine framework.

Because of their complex structures and pharmacological properties, new synthetic routes for the construction of this tetracyclic indolo[2,3-*a*]quinolizines and the corresponding quinalozin-4-ones with diverse functionalities, have attracted much attention, among synthetic as well as medicinal chemists.[20] Some of the recent approaches for the construction of this challenging heterocyclic targets, involve cyclization of *N*-acyliminium ion on pendant indole ring,[20a-b] Bischler-Napieralski reaction,[21a] and Fischer Indole synthesis.[21b]

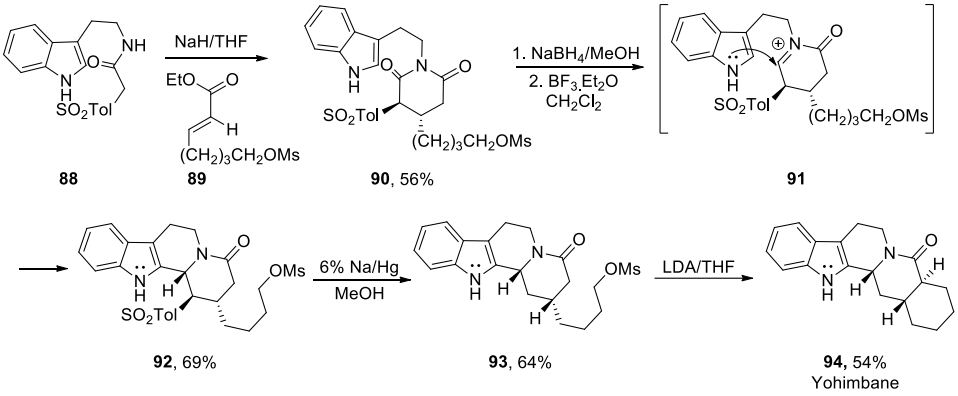
Elsegood and co-workers have reported a highly stereoselective approach for the construction of indolo[2,3-*a*]quinolizidine ring from a readily available non-racemic chiral template. Thus, treatment of diastereomeric **85** with 2M HCl in ethanol at room temperature gave the cyclized indolo[2,3-*a*]quinolizidine **86** in 95% yield, as a single diasteroisomer. The method was further extended to synthesise the alkaloid R-(+)-deplancheine **87** with >95% *ee* (Scheme 24).[20b]



Scheme 24

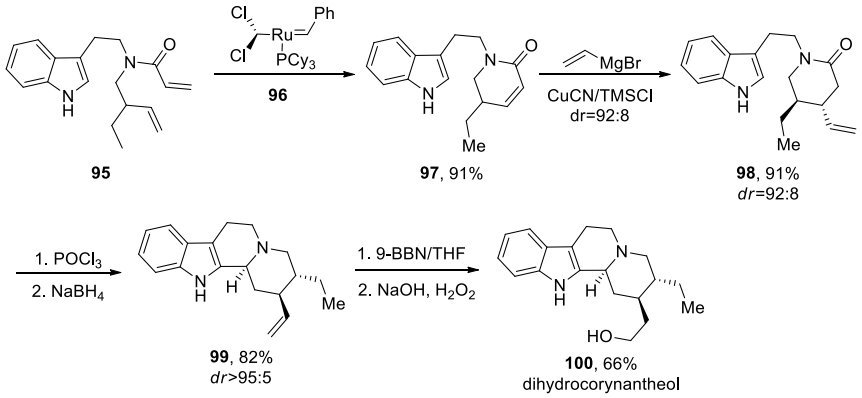
Chang and co-workers have described an efficient synthesis of indolo[2,3-*a*]quinolizidin-4-one derivatives **92**, which serves as a useful building block for the synthesis of alkaloid yohimbane (**94**). Thus, the initial *α*-sulfonyl tryptaminylacetamide precursor **88**

was subjected to cycloannulation with *α,β*-unsaturated ester **89** in the presence of sodium hydride, yielding directly the glutarimide derivative **90**, which on subsequent reduction followed by dehydration undergoes intramolecular cyclization via iminium ion intermediate **91** furnishing the tetracyclic indolo[2,3-*a*]quinolizidin-4-one **92** in moderate yields. The compound **92** was transformed into yohmbane **94** in two steps via desulfonylation with sodium amalgum followed by base mediated intramolecular cyclization. (Scheme 25).[20a]



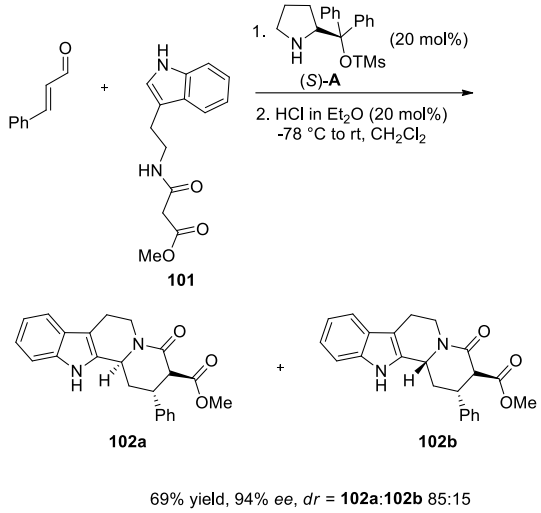
Scheme 25

Martin and Dieters have developed a stereoselective synthesis of indole alkaloid dihydrocorynantheol **100** from the intermediate amide **95** (structure of **95** is not correct the double bond adjascent to nitrogen should be C=O), obtained in three steps starting from indole-3-acetic acid. The amide **95**, was subjected to olefinic metathesis with catalyst **96**, yielding the cyclic amide **97** in high yield. Michael addition of vinylmagnesium iodide on **97** in the presence of copper salt and TMSCl afforded **98** in 91% yield as diastereomeric mixture. The intermediate amide **98** underwent Bischler Napieralski cyclization ($POCl_3$) followed by reduction ($NaBH_4$) to afford pentacyclic indoloquinolizidine derivative **99** in 82% yield.. Regioselctive hydroboration of vinyl group of **99** with 9-BBN furnished dihydrocorynantheol **100** in 66% yield (Scheme 26).[21a]



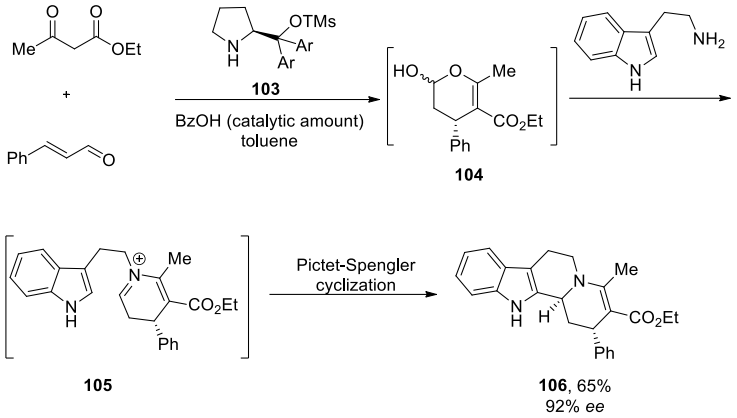
Scheme 26

Franzeń[22] and Wu's[23] groups have recently developed facile organocatalytic enantioselective one-pot, three- component, cascade approaches for highly substituted indoloquinolizidines, involving a Michael addition-Pictet–Spengler sequence on tryptamine derived *β*-ketoester amide such as **101** (or alkyl propiolates),and *α,β*-unsaturated aldehydes, (Scheme 27 and 28).[22,23] Thus, the organocatalytic conjugate addition of cinnamic aldehyde with indole substituted amide **101** using proline derived (*S)* **A** as organocatalyst followed by acid catalyzed Pictet- Spengler cyclization, afforded indoloquinolizidinones **102a** and **102b** with excellent enantioselectivity (94% *ee*)) with a diastereoselectivity of 85:15 (Scheme 27).[22a]



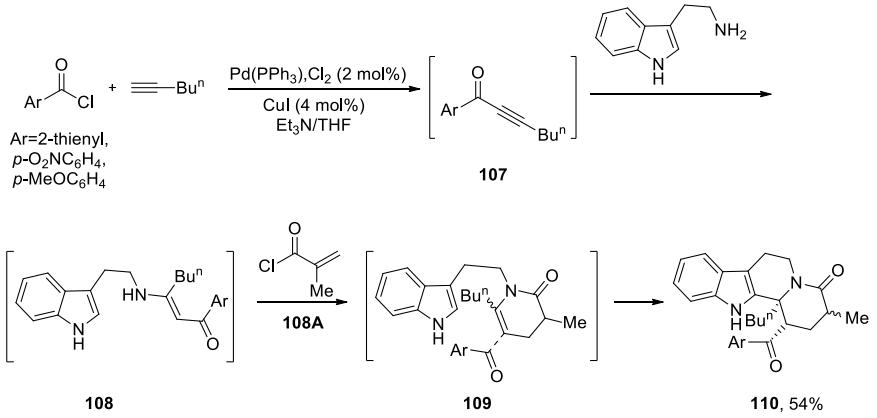
Scheme 27

Wu and co-workers have developed an enantioselective organocatalytic three component approach for the synthesis of highly substituted indoloquinolizidines **106** as shown in the Scheme 28. Thus, organocatalytic Michael addition of acetoacetic ester and cinnamic aldehyde using the proline derived organocatalyst **103,** affords intermediate hemiacetal **104** which without isolation, was reacted with tryptamine and subsequent Pictet-Spengler cyclization of the resulting iminium ion **105**, in one-pot operation, afforded the product **106** in 65% yield and 92% *ee* (Scheme 28).[23a]



Scheme 28

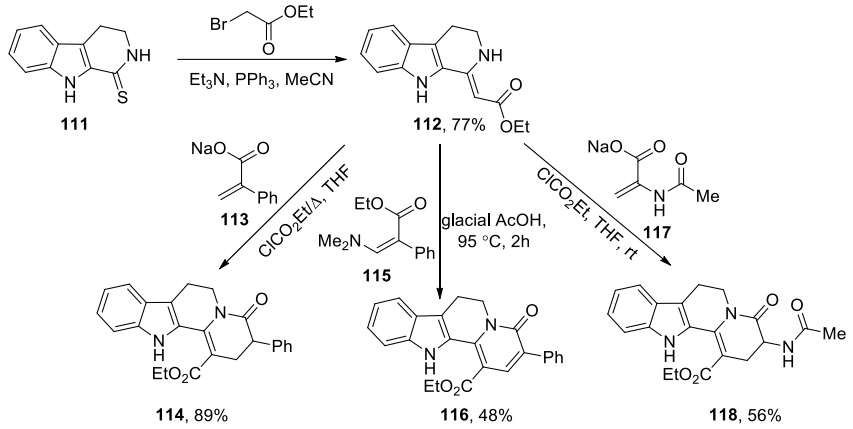
Muller and co-workers[4b] have recently reported a sequential, four-component, one-pot synthesis of highly substituted indolo[2,3-*a*]quinolizidin-4-ones such as **110**, involving Sonogashira coupling of acid chlorides and terminal alkynes, followed by amination with a tryptamine, aza-annulation-Pictet−Spengler sequence. Thus, in one example, the acid chloride was treated with 1-hexyne in the presence of 2 mol% palladium catalyst and copper iodide, yielding the *β* – (*n*-butyl) propynone **107**, which on in situ Michael addition with tryptamine gave the enaminone intermediate **108.** The enaminone **108** without isolation, was subjected to azaannulation with *α*-*β*-unsaturated acid chloride **108A** to give cyclic amide intermediate **109**, which underwent in situ intramolecular cyclization through acyliminium ion intermediate yielding quinolizidinone **110** in 54 % yield (Scheme 29).[4b]



Scheme 29

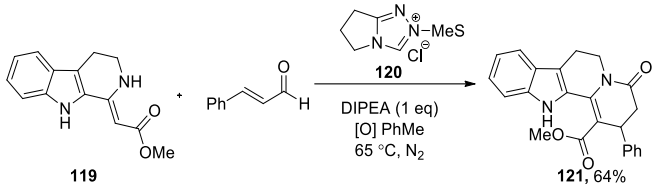
A few of the indoloquinolizidin-4-ones have also been synthesized by aza-annulation of *β*-carboline derived enaminoester **112** with acrylate derivatives (Scheme 30).[6a] Thus Benovsky and Stille have demonstrated the aza-annulation of enamino ester **112**,as an effective alternative to the syntheses of non-benzidiazepine scaffolds for treatment of sleep and anxiety disorders. The enaminoester **112** was obtained by treatment of thiolactam **111** with ethyl bromoaetate. Aza-annulation of **112** with acrylate intermediates **113**, **115**, **117** under varying

conditions afforded indoloquinolizidone derivatives **114**, **116**, **118** respectively in moderate to good yields (Scheme 30).[6a]



Scheme 30

Du and co-workers have developed a novel synthetic approach for functionalized indolo[2,3-*a*]quinolizidin-4-ones such as **121** via *N*-heterocyclic carbene-catalyzed annulation of *β*-enaminoester **119** with enealdehydes like cinnamaldehyde using the N-heterocyclic carbene catalyst **120** in presence of DIPEA to afford quinolizidinone derivative **121** in 64% yield.(Scheme 31).[6b]



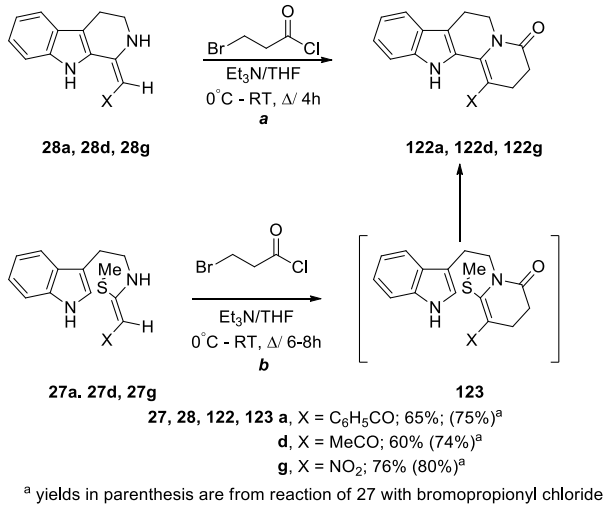
Scheme 31

5.4.2 Results and discussion

5.4.2.1 Azaannulation of *β*-carboline derived enaminones 28 with bromopropionyl chloride: Synthesis of indolo[2,3-*a*]quinolizidin-4-one derivatives

In our study, we first examined aza-annulation of enaminones **28a, 28d** and nitroenamine **28g** with 3-bromopropionoyl chloride with a view to synthesize 1-aroyl/nitro-tetrahydroindolo[2,3-*a*]quinolizidin-4-ones **122** (Scheme 32). Thus, under optimized reactions conditions, when **28a** was reacted with 3-bromopropionoyl chloride in refluxing THF and triethylamine, the reaction proceeded smoothly, yielding the desired indoloquinolizidin-4-one **122a** in 65% yield. Alternatively, we also attempted one-pot tandem cyclization of open-chain *N,S*-acetal **27a** with 3-bromopropionoyl chloride, under identical conditions, and to our delight, the indoloquinolizidinone **122a** was obtained in increased yield of 75%, without isolation of the corresponding tetrahydro-2-pyridone intermediate **123a** (Scheme 32). The corresponding

1-acetyl and hitherto unreported 1-nitroindoloquinolizidinone **122d** and **122g** were similarly obtained in good yields from respective cyclic enaminone **28d, 28g** or the corresponding *N,S*-acetals **27d** and **27g** under identical conditions (Scheme 32).

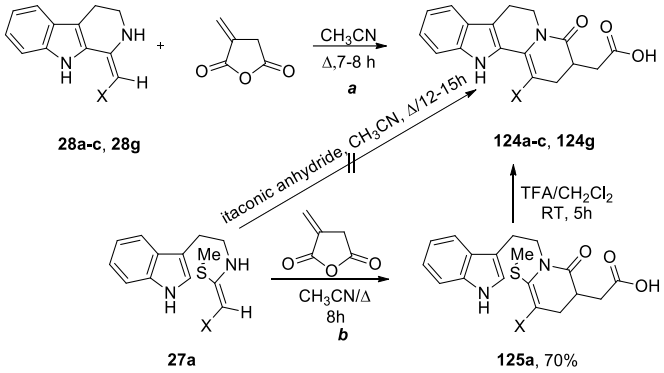


Scheme 32

5.4.2.2 Aza-annulation of *β*-carboline derived enaminones with itaconic anhydride: Synthesis of indolo[2,3-*a*]quinolizidin-4-one-2-acetic acid analogs

With the successful synthesis of 1-substituted tetrahydroindolo[2,3-*a*]quinolizidinones **122** by cycloannulation of enaminones **28** with 3-bromopropionyl chloride, we next examined the aza-annulation of enaminones **28a-c** and nitroenamine **28g** with itaconic anhydride, with anticipation to synthesize functionalized indoloquinolizidin-4-ones **124**, bearing an acetic acid side chain (Scheme 33). There are very few reports of aza-annulation of enamine substrates with exocyclic anhydrides, like itaconic anhydride **124**.[4a,9a] Thus when the enaminone **28a** was reacted with itaconic anhydride in refluxing acetonitrile, under our previously described conditions,[4a,9a] work-up and purification of the reaction mixture yielded a single product, which was found to be the expected 1-benzoyl-indolo[2,3-*a*]quinolizidin-4-one-3-acetic acid **124a** (62%) on the basis of its spectral and analytical data (Scheme 33). Similarly the enaminones **28b-c**, and the nitroenamine **28g** also reacted with itaconic anhydride under identical conditions furnishing the corresponding 1-aroyl- and 1-nitroindolo[2.3-*a*]quinolizidin-4-one-3-acetic acids **124b-c, 124g** in good yields (Scheme 33). In an alternative procedure, the acyclic *N,S*-acetal **27a** was reacted with itaconic anhydride with a view to obtain the target functionalized indolo[2,3-*a*]quinolizidinone **124a** in a tandem one-pot operation. However, when **27a** was reacted with itaconic anhydride in refluxing acetotonitrile, the product isolated was found to be only acyclic substituted dihydropyridone **125a** (70%), which did not cyclize to indoloquinolizidone **124a** even on prolonged heating of the reaction mixture (Scheme 33).

However, treatment of the pure isolated dihydropyridone **125a** with trifluoroacetic acid at room temperature furnished the quinolizidinone **124a** in good yield (64%, Scheme 33). In fact, it was not necessary to purify the pyridone **125a** and the crude reaction mixture after evaporation of acetonitrile (from the reaction of **27a** and itaconic anhydride), afforded **124a** in comparable yield, on treatment with TFA.



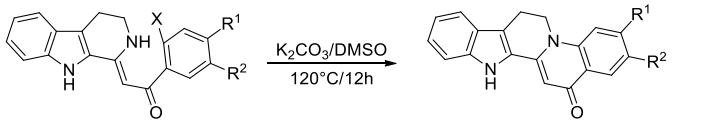
124a, X = C_6H_5CO; 62% (64%)[a]
b, X = 4-ClC_6H_4CO; 58%
c, X = 2-ClC_6H_4CO; 54%
g, X = NO_2; 59%

[a]Yield in the parenthesis is from reaction **125a** with TFA

Scheme 33

5.5 Synthesis of pentacyclic dihydroindolo[2', 3':3,4]pyrido[1,2-*a*]quinolin-2-ones

We also subjected 2-chloro/bromobenzoylenaminones such as **28c**, **28e-f** to intramolecular nucleophilic aromatic substitution (S_NAr), with a view to synthesize heitherto unreported pentacyclic dihydroindolo[2',3':3,4]pyrido[1,2-*a*]quinolin-2-ones **126** (Scheme 34).[25] Thus when *o*-chlorobenzoylenaminone **28c** was heated in either DMF or DMSO in the presence of bases like K_2CO_3, Cs_2CO_3 or sodium *t*-butoxide at higher temperature for prolonged time, the desired product **126c** was formed in varying yields, however best yield (71%) of **126c** was obtained when *N*,*S*-acetal **28c** was heated in DMSO in presence of K_2CO_3 for 12h at 120ºC (Scheme 34). Similarly, the other substituted *o*-halobenzoyl enaminones **28e-f** also underwent intramolecular nucleophilic substitution to give the corresponding indolo-fused dihydroindolopyridoquinolin-2-ones **126e-f** in high yields. However, the products **126e-f** were found to be highly insoluble, and **126e** could be characterized by ^{1}H NMR/HRMS data, whereas **126f** only by HRMS.It should be noted that pentacyclic indolopyridoquinolin-2-one ring system is not reported in literature



28c, X = Cl; $R^1 = R^2$ = H
28e, X = R^1 = Cl; R^2 = H
28f, X = Br; R^1 = H, R^2 = OMe

126c, $R^1 = R^2$ = H; 71%
126e, R^1 = Cl, R^2 = H; 73%
126f, R^1 = H, R^2 = OMe; 64%[a]

[a]Heated in NMP at 140°C for 36h

Scheme 34

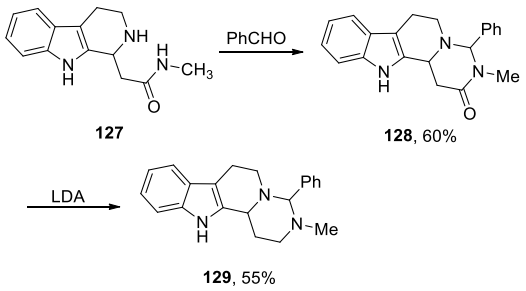
5.6 Synthesis of hexahydropyrimido [1',6':1,2]pyrido[3,4-*b*]indoles

Finally, we also synthesized a few of the 2,3,4,6,7,12-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indoles **133a-c** via cycloannulation of enaminones and nitroenamines **28a**, **28g** via double Mannich reaction with formaldehyde and primary amines (Scheme 37). Some of these compounds are shown to be potent inhibitor of lipid peroxidation.[26]

Before describing our results, we have given a short and recent literature survey on synthesis of this heterocyclic framework.

5.6.1 Synthesis of hexahydropyrimido [1',6':1,2]pyrido[3,4-*b*]indoles: A short literature survey

Balter and co-workers developed a procedure for the synthesis of tetracyclic and pentacyclic indolo[2,3-*a*]quinolizine containing heteroatoms in D and E ring. Thus, condensation of pyrido[3,4-*b*]indol-acetamide **127** with benzaldehyde yielded the compound **128**, which on reduction with LDA gave the tetracyclic indolo[2,3-*a*]quinolizine **129** (Scheme 35).[26b]



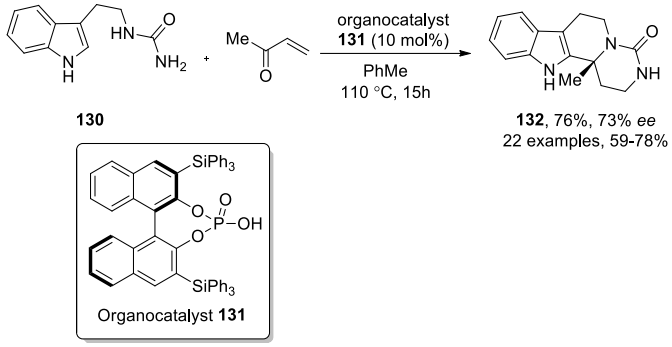
127

128, 60%

129, 55%

Scheme 35

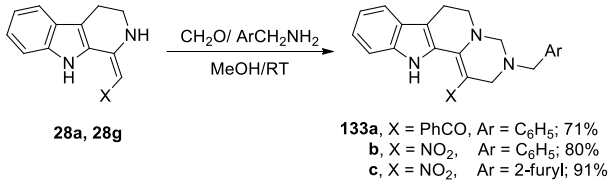
Dixon and co-workers have reported an enantioselective Michael addition/iminium ion cyclization of tryptamine derived urea **130** using BINOL phosphoric acid (BPA) catalyst **131** to get the polycyclic product **132** in high enantiomeric excess (Scheme 36).[26c]



Scheme 36

5.6.2 Results and discussion: Synthesis of hexahydropyrimido [1',6':1,2]pyrido[3,4-*b*]indoles

Thus when the enaminone **28a** was stirred with formaldehyde and benzylamine at room temperature in solvents like THF, CH_2Cl_2, acetonitrile, benzene, starting materials remained unchanged whereas in methanol as solvent, the corresponding 1-benzoyl-3-*N*-benzylhexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole **133a** was obtained in 65% yield. On the other hand, annulation of nitroenamine **28e** with formaldehyde and benzyl or furfuryl amines was found to be very facile providing the corresponding, 1-nitro-3-benzyl/furfuryl-hexahydrpyrimido[1',6':1,2]pyrido[3,4-*b*]indoles **133b-c** in 80% and 91% yields respectively (Scheme 37).

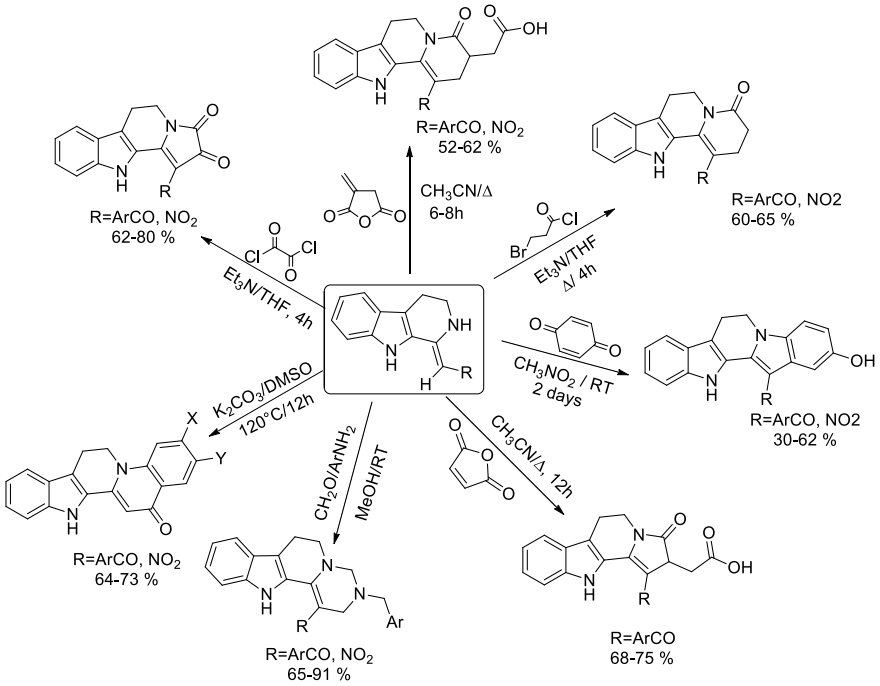


Scheme 37

5.7 Conclusion

In summary, we have carried out a detailed study of aza-annulation of newly synthesized *β*-carboline derived enaminones and nitroenamines with various 1,2- or 1,3-biselectrophilic species like oxalyl chloride, maleic anhydride, 1,4-benzoquinone, 3-bromopropionyl chloride, itaconic anhydride etc. and successfully developed convenient one-pot protocols for the construction of a variety of novel *β*-carboline 1,2- fused highly functionalized five and six membered tetra- and pentacyclic heterocyclic motifs, in reasonable yields. It should be noted that, while there are few reports of aza-annulation of *β*-carboline derived enaminoesters (or in situ generated acyclic enaminoester from tryptamine and ethyl propiolate) furnishing tetrahydroindolizino[8,7-*b*]indoles or indolo[2,3-*a*]quinolizidines

derivatives, the synthesis and reactivity of the corresponding *β*-carboline derived enaminones and especially nitroenamines have not been explored. Also, the aza-annulations of these *β*-carboline derived enamines with maleic anhydride, itaconic anhydride and 1,4-bezoquinone have not been reported in the literature. This novel protocols provide a rapid and efficient access to biologically important non-natural indole alkaloids in a highly concise fashion. The overall study reveals possibility of construction of a range of novel substituted *β*-carboline fused heterocyclic scaffolds with potential biological activity employing this protocol.



5.8 Experimental section

5.8.1 General Information

All 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 using standard TLC Silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100-200 mesh) or neutral alumina wherever mentioned. Nuclear magnetic resonance spectra were recorded on Brucker (400 MHz) ultrashield plus and Jeol (600 MHz) ECZ 600R FT-NMR spectrometer with $CDCl_3$, DMSO-d_6, or CD_3OD as solvent. Chemical shifts were reported in δ ppm using residual solvent protons as 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 (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra of neat samples

were recorded in ATR (attenuated total reflectance) mode using FT-IR instrument (Agilent technologies) and HRMS on 6538 UHD accurate mass Q-TOF LC/MS spectrometer through ESI mode). Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. All the tetrahydro-*β*-carboline derived enaminones **28a-f** and nitroenamine **28g** were prepared according our earlier reported procedure from the respective *N*,*S*-acetals **27a-g**.[4a] The spectral data of the known enaminones **28a-d** and **28g** has been reported earlier,[4a] whereas spectral and analytical data of unknown enaminones **28e-f** is given below.

1-(2,4-dichlorobenzoyl)methylene-1,2,3,4-tetrahydro-β-carboline (28e). Obtained from **27e**; yellow solid (542 mg, 76%); mp 192-194°C; R_f 0.26 (2:8 EtOAc/hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.64 (s, 1H,N*H*), 10.34 (s, 1H, indole N*H*), 7.67 (brs, 1H,Ar*H*), 7.61 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.55 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.50 (dd, *J* = 8.4, 1.2 Hz, 1H, Ar*H*), 7.40 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.25 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.08 (t, *J* = 7.6 Hz, 1H, Ar*H*), 5.90 (s, 1H, =C*H*), 3.67-3.65 (m, 2H, NCH_2), 3.00 (t, *J* = 7.0 Hz, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.7, 152.2, 140.5, 137.8, 133.8, 130.9, 130.2, 129.3, 127.2, 127.0, 125.2, 124.6, 119.8, 119.75, 116.4, 112.1, 89.3, 39.0, 19.7; IR (neat, cm^{-1}) 3020, 1725, 740; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}Cl_2N_2O$ $[M+H]^+$ 357.0561, found 357.0551

1-(2-bromo-5-methoxybenzoyl)methylene-1,2,3,4-tetrahydro-β-carboline (28f). Obtained from **27f**; yellow solid (416 mg, 70%); mp 198-200°C; R_f 0.26 (4:6 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H,N*H*), 9.35 (s, 1H, indole N*H*), 7.71 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 7.29-7.25 (m, 1H, Ar*H*), 7.15 (d, *J* = 2.8 Hz, 1H, Ar*H*), 7.79 (dd, *J* = 8.8, 3.2 Hz, 1H, Ar*H*), 5.89 (s, 1H, =C*H*), 3.89 (s, 3H, OCH_3), 3.73 (dt, *J* = 7.2, 2.8 Hz, 1H, NCH_2), 3.15 (t, *J* = 7.2 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 158.7, 152.8, 144.3, 137.9, 133.9, 127.2, 125.9, 125.2, 120.5, 119.7, 117.5, 116.4, 114.2, 112.1, 109.9, 89.7, 55.5, 40.2, 20.3; IR (neat, cm^{-1}) 3059, 1722, 642; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}BrN_2O_2$ $[M+H]^+$ 397.0552, found 397.0531.

5.8.2 General procedure for reaction of enaminones 28a-b, 28d or *N*,*S*-acetals 27a-b, 27d with oxalyl chloride. Synthesis of 1-aroyl/nitro-5,6-dihydro-2*H*-indolizino[8,7-*b*]indole-2,3(11*H*)-diones 69.To a stirred solution of the appropriate enaminones **28** (1.09 mmol) or the *N*,*S*-acetal **27** and triethylamine (0.38 mL, 2.7 mmol) in dry THF (15 mL) under nitrogen atmosphere, oxalyl chloride (0.95 mL, 1.1 mmol) was added at 0ºC. After stirring the reaction mixture for 4h (monitored by TLC), the solvent was evaporated under reduced pressure, the residue dissolved in CH_2Cl_2 and washed three times with water (3 × 10 mL). The organic layer

was dried over anhydrous Na_2SO_4, evaporated under reduced pressure and the crude residue was purified by silica gel chromatography using (2:8) EtOAc/hexane as eluent to give pure **69**.

1-benzoyl-5,6-dihydro-2H-indolizino[8,7-b]indole-2,3(11H)-dione (69a). Obtained from **27a** or **28a**; red solid (328 mg, 88% from **27a;** 283 mg,76 % from **28a**); mp 202-204°C; R_f 0.2 (3:7 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.96 (s, 1H, N*H*), 7.73-7.71 (m, 3H, Ar*H*), 7.59-7.56 (m, 1H, Ar*H*), 7.53-7.51 (m, 2H, Ar*H*), 7.48-7.44 (m, 2H, Ar*H*), 7.24-7.22 (m, 1H, Ar*H*), 4.16 (t, *J* = 7.8 Hz, 2H, NCH_2), 3.42 (t, *J* = 7.8 Hz, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.4, 177.7, 159.9, 158.6, 141.1, 138.6, 132.6, 130.4, 129.3, 127.1, 125.6, 123.2, 122.1, 121.5, 113.5, 105.2, 37.8, 20.4; IR (neat, cm^{-1}) 3040, 1746, 1688, 1608; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}N_2O_3$ $[M+H]^+$ 343.1083, found 343.1063.

1-(4-chlorobenzoyl)-5,6-dihydro-2H-indolizino[8,7-b]indole-2,3(11H)-dione (69b). Obtained from **27b** or **28b**; orange solid (294 mg, 78% from **27b**; 299 mg 73% from **28b**); mp 197-198 °C; R_f 0.2 (2:8 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.94 (s, 1H, N*H*), 7.73 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.67 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.55-7.51 (m, 2H, Ar*H*), 7.45 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.24-7.23 (m, 1H, Ar*H*), 4.16 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.42 (t, *J* = 7.0 Hz, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.5, 178.1, 159.6, 158.8, 141.0, 137.6, 136.9, 131.1, 129.5, 127.9, 124.8, 122.6, 121.6, 121.4, 114.2, 104.7, 37.3, 19.7; IR (neat, cm^{-1}) 2921, 1749, 1688, 1611, 742; HRMS (ESI) *m/z* calcd for $C_{21}H_{14}ClN_2O_3$ $[M+H]^+$ 377.0637, found 377.0616.

1-acetyl-5,6-dihydro-2H-indolizino[8,7-b]indole-2,3(11H)-dione (69d). Obtained from **27d** or **28d**; red flaky solid (238 mg, 76% from **27d**; 220 mg, 72% from **28d**); mp195-197 °C; R_f 0.3 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H, N*H*), 7.71 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.57-7.50 (m, 2H, Ar*H*), 7.24-7.22 (m, 1H, Ar*H*), 4.14 (t, *J* = 6.8 Hz, 2H, NCH_2), 3.40 (t, *J* = 6.8 Hz, 2H, CH_2), 2.69 (s, 3H, COCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.2, 190.3, 179.8, 159.3, 158.9, 141.5, 130.8, 127.4, 125.9, 123.5, 122.4, 121.8, 114.0, 38.1, 30.4, 20.7; IR (neat, cm^{-1}) 3100, 1742, 1704, 1611; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}N_2O_3$ $[M+H]^+$ 281.0926, found 281.0906.

5.8.3 General procedure for the reaction of enaminones 28a-b with maleic anhydride: **Synthesis of 2-(1-aroyl-3-oxo-3,5,6,11-tetrahydro-2*H*-indolizino[8,7-*b*]indol-2-yl)acetic acids 73**. A Solution of **28** (1.09 mmol) and maleic anhydride (107 mg, 1.1 mmol) in dry acetonitrile (15 mL) was refluxed for 8h (monitored by TLC). The reaction mixture was then brought to room temperature, evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with water, dried (anhydrous Na_2SO_4) and evaporated

to afford the crude product, which was purified by column chromatography over neutral-alumina column using (9:1) EtOAc/ hexane as eluent.

2-(1-benzoyl-3-oxo-3,5,6,11-tetrahydro-2H-indolizino[8,7-b]indol-2-yl)acetic acid (73a). Obtained from **28a**; yellow solid (230 mg, 60%); mp 185-187ºC; R_f 0.13 (4:6 EtOAc/hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.92 (s, 1H, CO_2H), 7.74-7.70 (m, 4H, Ar*H*), 7.57 (t, *J* = 7.6 Hz,1H, Ar*H*), 7.50 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.32 (t, *J* = 7.6 Hz, 1H, Ar*H*) 7.14 (t, *J* = 7.8 Hz, 1H, Ar*H*), 4.20-4.18 (m, 2H, NCH_2), 3.58-3.53 (m, 1H, ArC*H*H-6), 3.26 (dt, *J* = 16.8, 4.2 Hz, 1H, ArCH*H*-6), 3.13-3.08 (m, 1H, =CC*H*-2), 2.60 (dd, *J* = 16.8, 3.0 Hz, 1H, CH*H*CO_2H), 1.87 (dd, *J* = 16.8, 6.0 Hz, 1H, C*H*HCO_2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.9, 177.5, 171.7, 146.5, 141.6, 137.5, 131.6, 129.1, 127.7, 126.2, 125.5, 124.2, 120.8, 120.5, 119.1, 113.8, 110.6, 44.7, 38.4, 34.2, 19.8; IR (neat, cm^{-1}) 3100 (br), 1725, 1610, HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_2O_4$ $[M+H]^+$ 387.1308, found 387.1338.

2-(1-(4-chlorobenzoyl)-3-oxo-3,5,6,11-tetrahydro-2H-indolizino[8,7-b]indol-2-yl)acetic acid (73b). Obtained from **28b**; yellow solid (233 mg, 62%); mp 188-190 ºC; R_f 0.13 (4:6 EtOAc/hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.25 (brs,1H, N*H*),11.83 (s, 1H, CO_2H), 7.72 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.69-7.66 (m, 2H, Ar*H*), 7.53 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.31 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.12 (t, *J* = 7.8 Hz, 1H, Ar*H*), 4.15-4.12 (m, 2H, NCH_2), 3.60-3.50 (m, 1H, ArCH*H*-6), 3.23 (dt, *J* = 16.2, 4.8 Hz, 1H,ArC*H*H-6), 3.10-3.08 (m, 1H, =CC*H*-*2*)), 2.62 (dd, *J* = 16.8, 3.6 Hz,1H, CH*H*CO_2H), 1.94 (dd, *J* = 16.8, 5.4 Hz, 1H, C*H*HCO_2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.9, 176.8, 171.1, 146.3, 139.7, 137.0, 135.8, 129.2, 128.6, 125.8, 124.9, 123.5, 120.2, 120.0, 118.8, 113.3, 109.7, 44.0, 37.9, 33.8, 19.2; IR (neat, cm^{-1}) 2995 (br), 1720, 1650, 746; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}ClN_2O_4$ $[M+H]^+$ 421.0955, found 421.0956.

5.8.4 General procedure for reaction of enaminones 28a-c and nitroenamine 27g with 1,4-benzoquinone. Synthesis of 2-Hydroxy-7,12-dihydro-6*H*-indolo[2,1-*a*]*β*-carbolin-13-yl-aryl/nitro methanones 82. To a stirred solution of the appropriate enaminones **28a-c**, **28g** (1.6 mmol) in nitromethane, *p*-benzoquinone (237 mg, 2.2 mmol) was added under nitrogen atmosphere and the reaction was stirred at 25 ºC for 1.5-2 days (monitored by TLC). The reaction mixture was concentrated under reduced pressure, residue dissolved in EtOAc and the organic layer was washed with water (3 × 10 mL) and dried (anhydrous Na_2SO_4). The solvent was evaporated under reduced pressure to afford the crude products, which were purified by silica-gel column chromatography using (2:8) EtOAc/hexane as eluent.

2-Hydroxy-7,12-dihydro-6H-indolo[2,1-a]β-carbolin-13-yl-phenylmethanone (82a). Obtained from **28a**; yellow solid (180 mg, 58%); mp 230-231 ºC; R_f 0.40 (3:7 EtOAc/hexane);

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H, N*H*), 8.93 (s, 1H, O*H*), 7.73-7.65 (m, 5H, Ar*H*), 7.59 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.47 (d, *J* = 8.8 Hz, 1H, *ArH-4*), 7.21 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.12 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.74 (dd, *J* = 8.8, 2.4 Hz , 1H, Ar*H-3*), 6.11 (d, *J* = 2.4 Hz, 1H, Ar*H-1*), 4.47 (t, *J* = 7.6 Hz, 2H, NCH_2), 3.33 (t, *J* = 7.6 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.1, 152.6, 140.9, 136.5, 136.2, 131.5, 131.1, 128.4, 128.3, 127.7, 125.5, 125.4, 123.4, 119.7, 118.8, 112.7, 111.6, 110.9, 109.1, 105.2, 41.4, 19.6; IR (neat, cm^{-1}) 3289, 2921, 1700; HRMS (ESI) *m/z* calcd for $C_{25}H_{19}N_2O_2$ [M+H]$^+$379.1447; found 379.1540.

(4-Chlorophenyl)(2-hydroxy-7,12-dihydro-6H-pyrido[1,2-a:3,4-b']diindol-13-yl)methanone (82b). Obtained from **28b**; yellow solid (380 mg, 62 %); mp 230-231 ºC; R_f 0.34 (3:7 EtOAc /hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.28 (s, 1H, N*H*), 8.99 (s, 1H, O*H*), 7.70 (d, *J* = 5.6 Hz, 2H, Ar*H*), 7.65-7.59 (m, 4H, Ar*H*), 7.45 (d, *J* = 8.4 Hz, 1H, Ar*H-4*), 7.19 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.08 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H-3*), 6.13 (d, *J* = 2.4 Hz, 1H, Ar*H-1*), 4.43 (t, *J* = 7.2 Hz, 2H, NCH_2), 3.26 (t, 2H, *J*= 7.2 Hz, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.4, 153.3, 140.2, 137.2, 136.8, 131.7, 130.9, 129.2, 128.1, 126.1, 126.0, 124.0, 120.3, 119.4, 113.3, 112.5, 111.7, 109.5, 105.5, 41.9, 20.1; IR (neat, cm^{-1}) 3274, 2922, 1606, 760; HRMS (ESI) *m/z* calcd for $C_{25}H_{18}ClN_2O_2$ [M+H]$^+$ 413.0934; found 413.0908.

(2-Chlorophenyl)(2-hydroxy-7,12-dihydro-6H-pyrido[1,2-a:3,4-b']diindol-13-yl)methanone (82c). Obtained from **28c**; yellow solid **(**173 mg, 54%); mp 197-198ºC; R_f 0.36 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H, N*H*), 9.01 (s, 1H, O*H*), 7.76 (d,*J* = 8.4 Hz, 1H, Ar*H-4*), 7.70-7.67 (m, 2H, Ar*H*), 7.63 (t, *J* = 8.4 Hz, 1H, Ar*H*), 7.55 (t, *J* = 7.6 Hz, 1H,Ar*H*), 7.47 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.26 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.13 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.75 (brd, *J* = 8.4 Hz, 1H, Ar*H-3*), 5.56 (brs, 1H, Ar*H-1*), 4.47 (t, *J* = 7.4 Hz, 2H, NCH_2), 3.38 (t, *J* = 7.4 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 153.2, 141.6, 137.3, 136.0, 131.3, 131.0, 129.9, 129.0, 127.8, 127.6, 125.4, 125.3, 123.8, 119.9, 119.0, 112.9, 112.8, 112.4, 111.2, 109.4, 104.3, 41.5, 19.5; IR (neat, cm^{-1}) 3387, 2923, 1698, 760; HRMS (ESI) *m/z* calcd for $C_{25}H_{18}ClN_2O_2$ [M+H]$^+$ 413.0939; found 413.0910.

13-Nitro-7,12-dihydro-6H-pyrido[1,2-a:3,4-b']diindol-2-ol (82g). Obtained from **28g;** yellow solid (180mg, 35 %); mp 215-217 ºC; R_f 0.40 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H, N*H*), 9.56 (s, 1H, O*H*), 7.76 (d, *J* = 8 Hz, 1H, Ar*H*), 7.68 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.63 (d, *J* = 2.4 Hz, 1H, Ar*H-1*), 7.57 (d, *J* = 8.8 Hz, 1H, Ar*H-4*), 7.27 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.13 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar*H-3*), 4.46 (t, *J* = 7.6 Hz, 2H, NCH_2), 3.36 (t, *J* = 7.6 Hz, 2H,CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ

155.2, 137.2, 132.5, 129.3, 124.7, 124.5, 123.1, 122.2, 121.8, 120.1, 119.3, 115.1, 114.3, 113.3, 112.0, 104.7, 41.6, 19.4; IR (neat, cm^{-1}) 3395, 2922, 1454; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}N_3O_3$ $[M+H]^+$ 320.1035; found 320. 1011.

5.8.5 General procedure for reaction of enaminones 28a, 28d and nitroenamine 28g, or *N,S*-acetals 27a, 27d, 27g with 3-bromopropionyl chloride. Synthesis of 1-acyl/nitro-2,3,6,7-tetrahydroindolo[2,3-*a*]quinolizin-4(12*H*)-ones 122. To a stirred solution of the appropriate enaminones **28** (1.46 mmol) or *N,S*-acetal **27** and triethylamine (0.5 mL, 3.64 mmol) in dry THF (15 mL) under nitrogen atmosphere, 3-bromopropionyl chloride (0.17 mL, 1.75 mmol) was added at 0ºC. The mixture was allowed to stir for 3h (monitored by TLC). The solvent was evaporated under reduced pressure, the residue dissolved in CH_2Cl_2 (15 mL), washed with water (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography using (3:7) EtOAc/hexane as eluent.

1-Benzoyl-2,3,6,7-tetrahydroindolo[2,3-a]quinolizin-4(12H)-one (122a). yellow solid (375 mg, 75% from **27a**, 327 mg, 65% from **28a**); mp124-126 °C; R_f 0.3 (3:7 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H, N*H*), 7.79-7.76 (m, 2H, Ar*H*), 7.58-7.55 (m, 2H, Ar*H*), 7.52-7.48 (m, 2H, Ar*H*), 7.35 (brd, *J* = 8.0 Hz, 1H, Ar*H*), 7.29-7.25 (m, 1H, Ar*H*), 7.14-7.11 (m, 1H, Ar*H*), 4.32 (t, *J* = 6.0 Hz, 2H, NCH_2), 3.06 (t, *J* = 6.0 Hz, 2H, ArCH_2), 2.71-2.63 (m, 4H, COCH_2, =CCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 170.5, 139.4, 139.0, 137.0, 132.6, 128.6, 128.5, 126.7, 125.3, 120.2, 119.3, 118.3, 113.8, 112.1, 40.7, 31.9, 26.0, 20.8; IR (neat, cm^{-1}) 2916, 1672, 1356, HRMS (ESI) *m/z* calcd for $C_{22}H_{19}N_2O_2$ $[M+H]^+$ 343.1447, found 343.1437.

1-Acetyl-2,3,6,7-tetrahydroindolo[2,3-a]quinolizin-4(12H)-one (122d). yellow solid (301 mg, 74% from **27d**, 247 mg, 60% from **28d**); mp 138-139 °C; R_f 0.32 (3:7 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 12.19 (s, 1H, N*H*), 7.58 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.46 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.31 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.13 (t, *J* = 7.2 Hz, 1H, Ar*H*), 4.28 (t, *J* = 6.0 Hz, 2H, NCH_2), 3.02 (t, *J* = 6.0 Hz, 2H, ArCH_2), 2.83-2.80 (m, 2H, COCH_2), 2.65-2.62 (m, 2H, =CCH_2), 2.47 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 170.5, 140.0, 136.4, 126.8, 125.4, 125.0, 120.1, 119.4, 118.5, 114.4, 112.4, 41.2, 31.5, 30.7, 24.1, 21.0; IR (neat, cm^{-1}) 3200, 1697, 1626, HRMS (ESI) *m/z* calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1290, found 281.1277.

1-Nitro-2,3,6,7-tetrahydroindolo[2,3-a]quinolizin-4(12H)-one (122g). red solid (384 mg, 80% from **27g**; 316 mg, 76% from **28g**); mp 165-166 °C; R_f 0.45 (2:8 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H, N*H*), 7.61 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.44-7.37 (m,

2H, Ar*H*), 7.18 (brt, *J* = 7.6 Hz, 1H, Ar*H*), 4.31 (t, *J* = 6.4 Hz, 2H, NCH_2), 3.20 (t, *J* = 7.6 Hz, 2H, =CCH_2), 3.06 (t, *J* = 6.4 Hz, 2H, ArCH_2), 2.76 (t, *J* = 7.6 Hz, 2H, COCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 138.6, 137.8, 128.6, 127.4, 124.7, 123.5, 121.0, 120.1, 112.4, 42.1, 30.2, 23.4, 20.9; IR (neat, cm^{-1}) 2922, 1686, 1560, 1257; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}N_3O_3$ $[M+H]^+$ 284.1028, found 284.0999.

5.8.6 General procedure for the reaction of enaminones 28a-c and nitroenamine 27g with itaconic anhydride. Synthesis of 2-(1-aroyl/nitro-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizin-3-yl)acetic acids 124. A Solution of the appropriate enaminone **28** (1.5 mmol) and itaconic anhydride (180 mg, 1.6 mmol) in dry acetonitrile (15 mL) was refluxed for 10 h (monitored by TLC). The reaction mixture was then brought to room temperature, evaporated under reduced pressure and the residue was dissolved in EtOAc (15 mL). The organic layer was washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford the crude product, which was purified by column chromatography over neutral alumina column using (8:2) EtOAc/hexane as eluent.

2-(1-benzoyl-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)acetic acid (124a). Obtained from **28a**; yellow solid **(**200 mg, 64%); mp 170-172 ºC; R_f 0.18 (8:2 EtOAc /hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (brs, 1H, N*H*), 10.33 (s, 1H, CO_2H) , 7.84 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.59-7.46 (m, 4H, Ar*H*), 7.39 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.16 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.03 (t, *J* = 7.6 Hz, 1H, Ar*H*), 4.78 (dt, *J* = 12.8, 4.8 Hz, 1H, NCH*H*-6), 3.43-3.36 (m, 1H, NCH*H*-6), 3.01 (dt, *J* = 16.4, 4.0 Hz, 1H, ArCH*H*-7), 2.93-2.88 (m, 2H, ArCH*H*-7, *H*-3), 2.77-2.68 (m, 2H,=CH_2), 2.53-2.52 (m, merged with DMSO signal , 1H, C*H*HCO$_2$H), 2.34 (dd, *J* = 16.4, 6.4 Hz, 1H, CH*H*CO$_2$H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 172.8, 170.9, 138.3, 137.2, 136.1, 132.5, 128.9, 128.4, 126.1, 124.7, 124.1, 119.5, 119.0, 116.7, 112.9, 112.3, 40.3, 37.0, 34.0, 30.0, 20.3; IR (neat, cm^{-1}) 3400, 2923, 1708, HRMS (ESI) *m/z* calcd for $C_{24}H_{21}N_2O_5$ $[M+H]^+$ 401.1628; found 401.1607.

2-(1-(4-chlorobenzoyl)-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)acetic acid (124b). Obtained from **28b**; yellow solid (617 mg, 58%); mp 217-218 ºC; R_f 0.18 (8:2 EtOAc/hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.36 (s, 1H, N*H*), 7.80 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.50-7.47 (m, 3H, Ar*H*), 7.32 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.10 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.97 (t, *J* = 7.8 Hz, 1H Ar*H*), 4.71 (dt, *J* = 12.0, 4.0 Hz, 1H, NCH*H*-6) 3.36 (td, *J* = 12.0, 4.1 Hz, 1H, NCH*H*-6), 2.96 (dt, *J* = 16.2, 3.8 Hz,1H,ArCH*H*-7), 2.92-2.85 (m, 2H, ArCH*H*-7, *H*-3), 2.70-2.65 (m, 2H,=CH_2), 2.51-2.48 (dd, , *J* = 16.8, 5.4 Hz, 1H, C*H*HCO$_2$H), 2.34 (dd, *J*=16.8, 7.2 Hz, 1H, CH*H*CO$_2$H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 195.1, 173.5, 171.6,

137.9, 137.7, 137.7 137.2, 131.3, 129.0, 126.6, 125.2, 124.8, 120.1, 119.7, 117.5, 112.8, 112.7, 40.8, 37.6, 34.7, 31.8, 30.3, 20.9; IR (neat, cm^{-1}) 3445, 2921, 1701, 1678, 746; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}ClN_2O_4$ $[M+H]^+$ 435.1112; found 435.1121.

2-(1-(2-chlorobenzoyl)-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)aceticacid (124c). Obtained from **28c**; yellow solid (392 mg, 54%); mp 217-218 ºC; R_f 0.18 (8:2 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (brs, 1H, N*H*), 11.67 (s, 1H, CO_2H), 7.62 (d, *J* = 8 Hz, 1H, Ar*H*), 7.58-7.44 (m, 5H, Ar*H*), 7.28 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.10 (t, *J* = 7.6 Hz, 1H, Ar*H*), 4.83 (dt, *J* = 12.8, 4.0 Hz, 1H, NCH*H*-6), 3.52 (td, *J* = 12.8, 4.0 Hz, 1H, NC*H*H-6), 3.05 (dt, *J* = 16.8, 6.0 Hz, 1H, ArC*H*H-7), 2.96-2.86 (m, 2H, ArCH*H*-7, *H*-3), 2.65 (dd, *J* = 16.8, 6.0 Hz, 1H, =C*H*H-2), 2.55 (d, *J* = 16.8 Hz, 1H, =CH*H*-2), 2.45 (dd, *J* = 16.8, 6.8 Hz, 1H, CH*H*CO_2H), 2.34 (dd, *J* = 16.4, 6.8 Hz, 1H, C*H*HCO_2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.6, 172.7, 171.1, 140.7, 140.1, 136.6, 131.3, 129.7, 129.4, 128.9, 127.4, 126.2, 125.2, 124.5, 119.9, 119.5, 118.9, 112.6, 112.3, 41.0, 36.8, 33.8, 28.8, 20.2; IR (neat, cm^{-1}) 3200, 2922, 1687, 745; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}ClN_2O_4$ $[M+H]^+$ 435.0994; found 435.0966.

2-(1-nitro-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)acetic acid (124g). Obtained from **28g**; red solid (326 mg, 59%); mp 206-207 ºC; R_f 0.16 (8:2 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (brs, 1H, N*H*, 11.05 (s, 1H,CO_2H), 7.63 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.52 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.30 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.09 (t, *J* = 7.2 Hz, 1H, Ar*H*), 4.58 (brd, *J* = 12.4 Hz, 1H, NCH*H*-6), 3.48-3.40 (m,1H,NCH*H*), 3.28 (dd, *J* = 13.6, 5.6 Hz, 1H, =C*H*H-2), 3.87-2.85 (m,4H, =CH*H*-2, ArCH_2-7, *H*-3), 2.77 (dd, *J* = 16.8, 5.6 Hz, 1H, C*H*HCO_2H), 2.60-2.45 (m, merged with DMSO signal, 1H, CH*H*CO_2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 170.7, 138.1, 136.9, 125.9, 125.9, 123.8, 123.5, 121.7, 119.9, 119.8, 112.6, 40.7, 36.4, 34.0, 27.7, 20.0; IR (neat, cm^{-1}) 3383, 2920, 1690, 1330, 747; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}N_3O_5$ $[M+H]^+$ 342.1090; found 342.1083.

5.8.7 Procedure for reaction of *N,S*-acetal 27a with itaconic anhydride: Synthesis of 2-(1-(2-(1*H*-indol-3-yl)ethyl)-5-benzoyl-6-(methylyhio)-2-oxo-1,2,3,4-tetrahydropyridin-3-yl)acetic acid (125a). A Solution of the *N,S*-acetal 27**a** (509 mg, 1.5 mmol) and itaconic anhydride (180 mg, 1.6 mmol) in dry acetonitrile (15mL) was refluxed for 8h (monitored by TLC). The reaction mixture was then brought to room temperature, solvent evaporated under reduced pressure and the residue was dissolved in EtOAc (15 mL). The organic layer was washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford the crude **125a**, which

was purified by column chromatography over neutral-alumina column using (9:1) EtOAc/hexane as eluent.

2-(1-(2-(1H-indol-3-yl)ethyl)-5-benzoyl-6-(methylthio)-2-oxo-1,2,3,4-tetrahydropyridin-3-yl)acetic acid (125a). Obtained from **27a**; yellow solid (474 mg, 70 %); mp 140-142 ºC; R_f 0.15 (9:1 EtOAc/hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.21 (s, 1H,N*H*), 10.86 (s, 1H, CO_2*H*), 7.59-7.56 (m, 4H, Ar*H*), 7.47 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.34 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.17 (d, *J* = 2.4 Hz, 1H, indole *H*-2), 7.05 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.97 (t, *J* = 7.2 Hz, 1H, Ar*H*), 4.23-4.22 (m, 1H, NCH*H*), 3.94-3.91 (m, 1H, NCH*H*), 2.99-2.89 (m, 3H,ArCH_2, *H*-3), 2.67 (dd, *J* = 17.4, 6.6 Hz, 1H,=C*H*H-4), 2.39-2.33 (m, 3H, CH_2CO_2H, =CH*H*-4), 1.98 (s, 3H, SCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 195.5, 173.5, 171.7, 137.7, 137.2, 136.7, 133.6, 129.3, 127.9, 126.9, 123.7, 121.5, 118.9, 118.8, 111.9, 111.3, 44.1, 37.3, 34.4, 28.9, 24.8, 18.4; IR (neat, cm^{-1}) 3104 (br), 3450, 1707, 1661, 742; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_4S$ $[M+1]^+$ 449.1540; found 449.1565.

Conversion of 125a to 124a. To a solution of **125a** (450 mg, 1 mmol) in dichloromethane (10 mL), TFA (0.23 mL, 3 mmol) was added and the reaction mixture was stirred at room temperature for 5h (monitored by TLC). After evaporation of solvent, it was neutralized with sat.$NaHCO_3$ (15 mL), extracted with EtOAc (3 x 10 mL).The organic layer was washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford the crude product, which was purified by column chromatography over neutral-alumina column using (8:2) EtOAc/hexane as eluent to give pure **124a**; (yield, 256 mg), 64%; spectral and analytical data as mentioned above.

5.8.8 General procedure for base mediated intramolecular nucleophilic substitution of 28c, 28e and 28f: Synthesis of dihydroindolo[2',3':3,4]pyrido[1,2-*a*]quinolin-2-ones 126. To a stirring solution of enaminones **28** (1.0 mmol) in DMSO (10 mL) in a sealed tube, K_2CO_3 (414 mg, 3.0 mmol) was added and the reaction mixture was heated to 120 ºC for 12 h (monitored by TLC). For the product **126f**, the enaminone **28f** was heated in *N*-methylpyrrolidine (NMP), at 140 ºC for 36 h in a sealed tube. The reaction mixture was cooled to room temperature and was diluted with sat. NH_4Cl solution (15 mL). The precipitated product was filtered, washed with water and hexane. The crude product was purified by column chromatography using (6:4) EtOAc/hexane as eluent.

8,9-Dihydroindolo [2',3':3,4]pyrido [1,2-a]quinolin-2(14H)-one (126c). Obtained from **28c**; yellow solid (203 mg, 71%); mp 345-347 ºC; R_f 0.2 (6:4 EtOAc/hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.73 (s, 1H, N*H*), 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar*H*), 7.98 (d, *J* = 8.4 Hz, 1H,

Ar*H*), 7.72 (dt, *J* = 7.8, 1.8 Hz, 1H, Ar*H*), 7.64 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.42 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.32 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.24 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.07 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.69 (s,1H, =C*H*), 4.51 (t, *J* = 6.6 Hz, 2H, NCH_2), 3.23 (t, *J* = 6.6 Hz, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.1, 142.3, 142.1, 138.8, 132.8, 128.1, 126.9, 126.1, 125.7, 124.9, 123.3, 120.3, 120.2, 117.0, 114.4, 112.5, 103.8, 44.3, 20.2; IR (neat, cm^{-1}) 3215, 1592, 1293; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}N_2O$ $[M+H]^+$ 287.1157; found 287.1128.

5-Chloro-8,9-dihydroindolo [2',3':3,4]pyrido [1,2-a]quinolin-2(14H)-one (126e). Obtained from **28e**; yellow solid (200 mg, 73%); mp 350-352 ºC; R_f 0.2 (4:6 EtOAc/hexane); ^{1}H NMR (600 MHz, CD_3OD) δ 11.75 (s, 1H, N*H*), 8.15 (d, *J* = 8.4 Hz, 1H, Ar*H-3*), 8.09 (d, *J* = 1.8 Hz, 1H, Ar*H-6*), 7.65 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.41 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.37 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar*H-4*), 7.24 (dt, *J* = 7.8, 1.2 Hz, 1H, Ar*H*), 7.08 (dt, *J* = 7.8, 1.2 Hz,, 1H, Ar*H*), 6.65 (s, 1H, =C*H*), 4.50 (t, *J* = 7.2 Hz, 2H, NCH_2), 3.22 (t, *J* = 7.2 Hz, 2H, CH_2); IR (neat, cm^{-1}) 3200, 1612, 743; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}ClN_2O$ $[M+H]^+$ 321.0795; found 321.0778.

4-Methoxy-8,9-dihydroindolo [2',3':3,4]pyrido [1,2-a]quinolin-2(14H)-one (126f). Obtained from **28f**; (202 mg, 64%); brown solid; mp 300-302 ºC; R_f 0.2 (3:7 EtOAc/hexane); insoluble in most of the solvents; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$ 317.1290; found 317.1274.

5.8.9 General procedure for the synthesis of 1-Benzoyl/nitro-2,3,4,6,7,12-hexahydropyrimido[1'6':1,2]pyrido[3,4-b]indoles 133. A solution of the enaminone **28a** (288 mg, 1 mmol),or nitroenamine **28g** (230 mg,1 mmol), formaldehyde (37-41% w/v aq. solution) (0.3 mL, 8 mmol), and appropriate amine (1.5 mmol) in methanol(15mL), was stirred at room temperature for 4 h (monitored by TLC). The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (20 mL), the organic layer was washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford the crude product, which was purified by column chromatography over silica gel using (1:9) EtOAc/hexane as eluent.

3-benzyl-1-benzoyl-2,3,4,6,7,12-hexahydropyrimido[1'6':1,2]pyrido[3,4-b]indole (133a). Obtained from **28a** and benzylamine; yellow solid (297 mg, 71%); mp 128-130 ºC; R_f 0.35 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.93 (s, 1H, N*H*), 7.57 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.43 (d, *J* = 7.2 Hz, 4H, Ar*H*), 7.34-7.26 (m, 8H, Ar*H*), 7.11 (t, *J* = 7.2 Hz, 1H, Ar*H*), 4.24 (s, 2H, NCH_2N), 3.78 (s, 2H, =CCH_2N), 3.68 (s, 2H, CH_2Ph), 3.49 (t, *J* = 6.4 Hz, 2H, NCH_2-6), 3.09 (t, *J* = 6.4 Hz, 2H, ArCH_2-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 149.2, 143.2, 137.7, 136.1, 129.0, 129.0, 128.2, 128.1, 127.7, 127.4, 127.1, 125.0, 124.6, 119.8, 119.0,

114.9, 112.8, 97.6, 70.4, 56.3, 54.1, 49.0, 20.3; IR (neat, cm^{-1}) 3051, 1558, 1271; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}N_3O$ $[M+H]^+$ 420.2076; found 420.2081.

3-benzyl-1-nitro-2,3,4,6,7,12-hexahydropyrimido[1'6':1,2]pyrido[3,4-b]indole (133b). Obtained from nitroenamine **28g** and benzyl amine; yellow solid (288 mg, 80%); mp 175-177 ºC; R_f 0.35 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H, N*H*), 7.72 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.42 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.34-7.15 (m, 7H, Ar*H*), 5.25 (s, 2H, NCH_2N), 4.16 (s, 2H, =CCH_2N), 3.74 (brt, *J* =7.2 Hz 2H, NCH_2-6), 3.67 (s, 2H, CH_2Ph), 3.08 (t, *J* = 7.2 Hz, 2H, ArCH_2-7); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.9, 138.2, 137.8, 128.4, 128.2, 127.2, 126.4, 125.6, 124.0, 120.5, 120.3, 120.2, 115.7, 110.8, 64.8, 54.4, 52.1, 40.5, 19.5; IR (neat, cm^{-1}) 3058, 1446, 1365; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}N_4O_2$ $[M+H]^+$ 361.1665; found 361.1657.

3-(furan-2-ylmethyl)-1-nitro-2,3,4,6,7,12-hexahydropyrimido[1'6':1,2]pyrido[3,4-b]indole (133c). Obtained from **28g** and 2-furfurylamine; yellow solid (318 mg, 91%); mp 63-65 ºC; R_f 0.35 (1:9 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H, N*H*), 7.56 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.39-7.14 (m, 4H, Ar*H*, furyl*H*), 6.30 (d, *J* = 2.8 Hz, 2H, furyl*H*), 4.22 (s, 2H, NCH_2N), 4.07 (s, 2H, =CCH_2N), 3.76 (s, 2H, CH_2furyl), 3.67 (brs, 2H, NCH_2-6), 3.11 (brs, 2H, ArCH_2-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 147.6, 142.8, 137.4, 126.6, 124.8, 124.5, 120.7, 119.9, 119.8, 116.4, 112.7, 110.4, 109.4, 70.0, 52.3, 50.3, 49.2, 20.2; IR (neat, cm^{-1}) 3304, 1490, 1330, 1081; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_4O_3$ $[M+H]^+$ 351.1457; found 351.1443.

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5.10 ^{1}H and ^{13}C Spectra of Representative Compounds

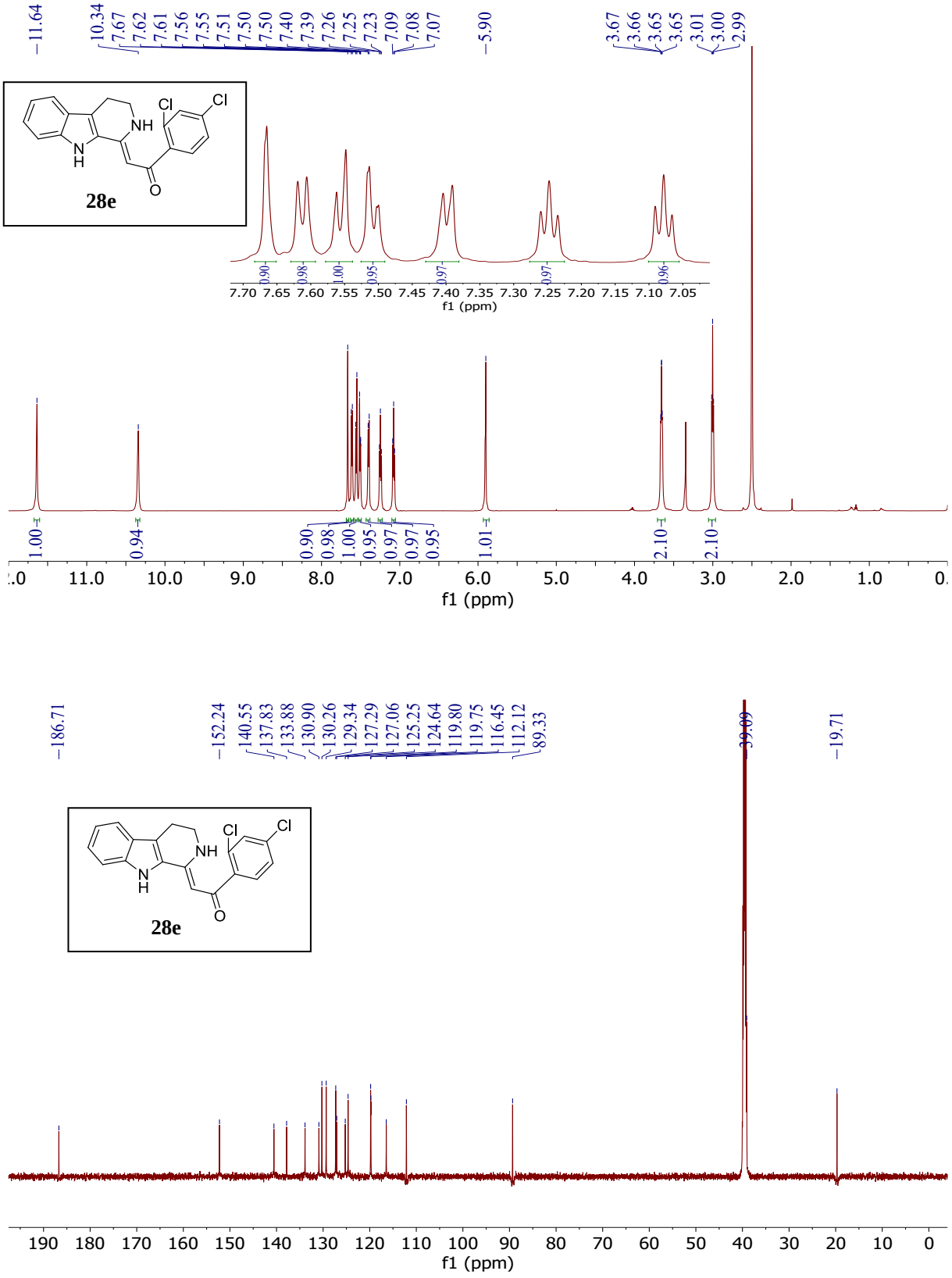

Figure 1. ^{1}H and ^{13}C NMR of compound 28e

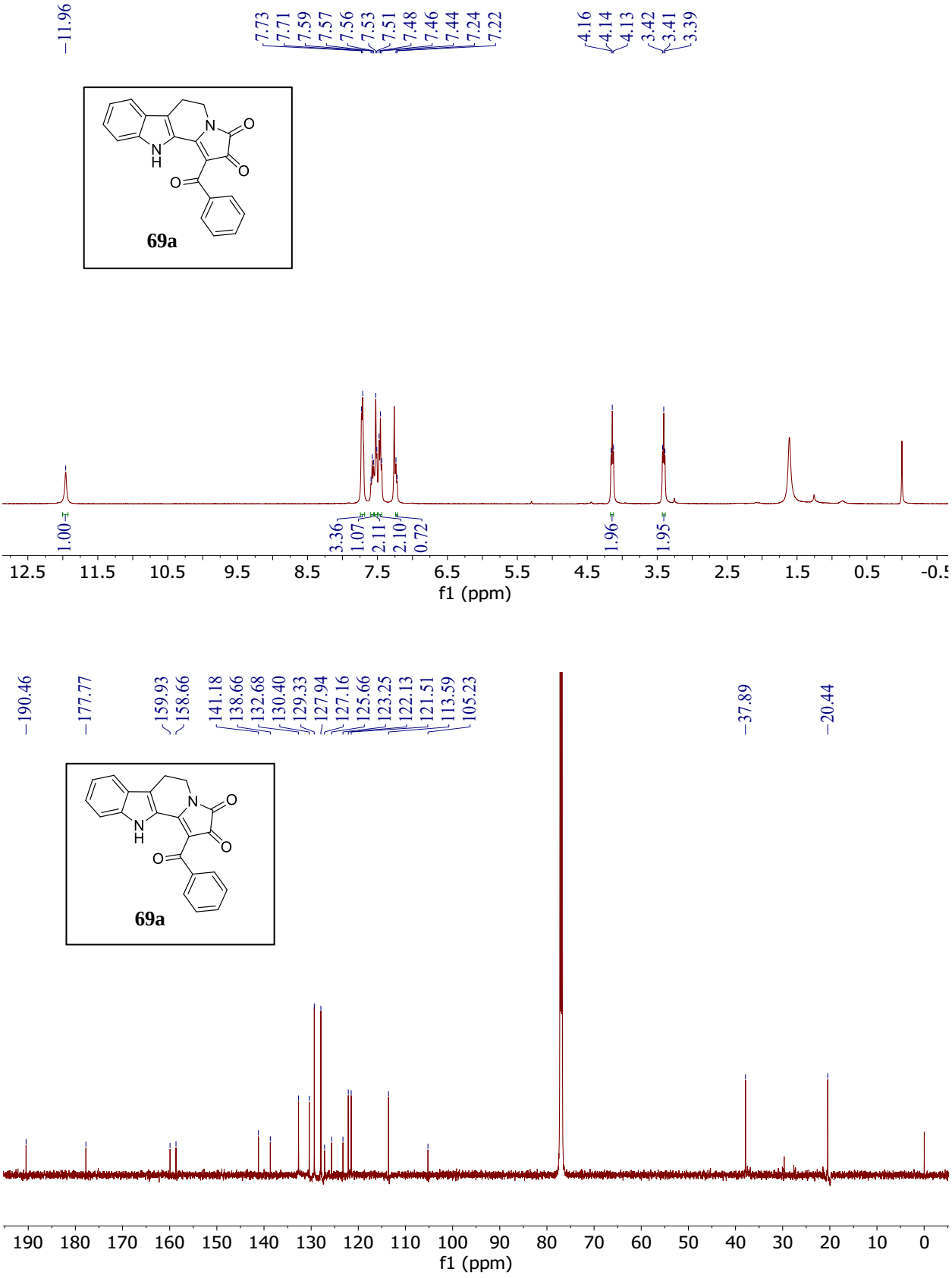

Figure 2. ^{1}H and ^{13}C NMR of compound 69a

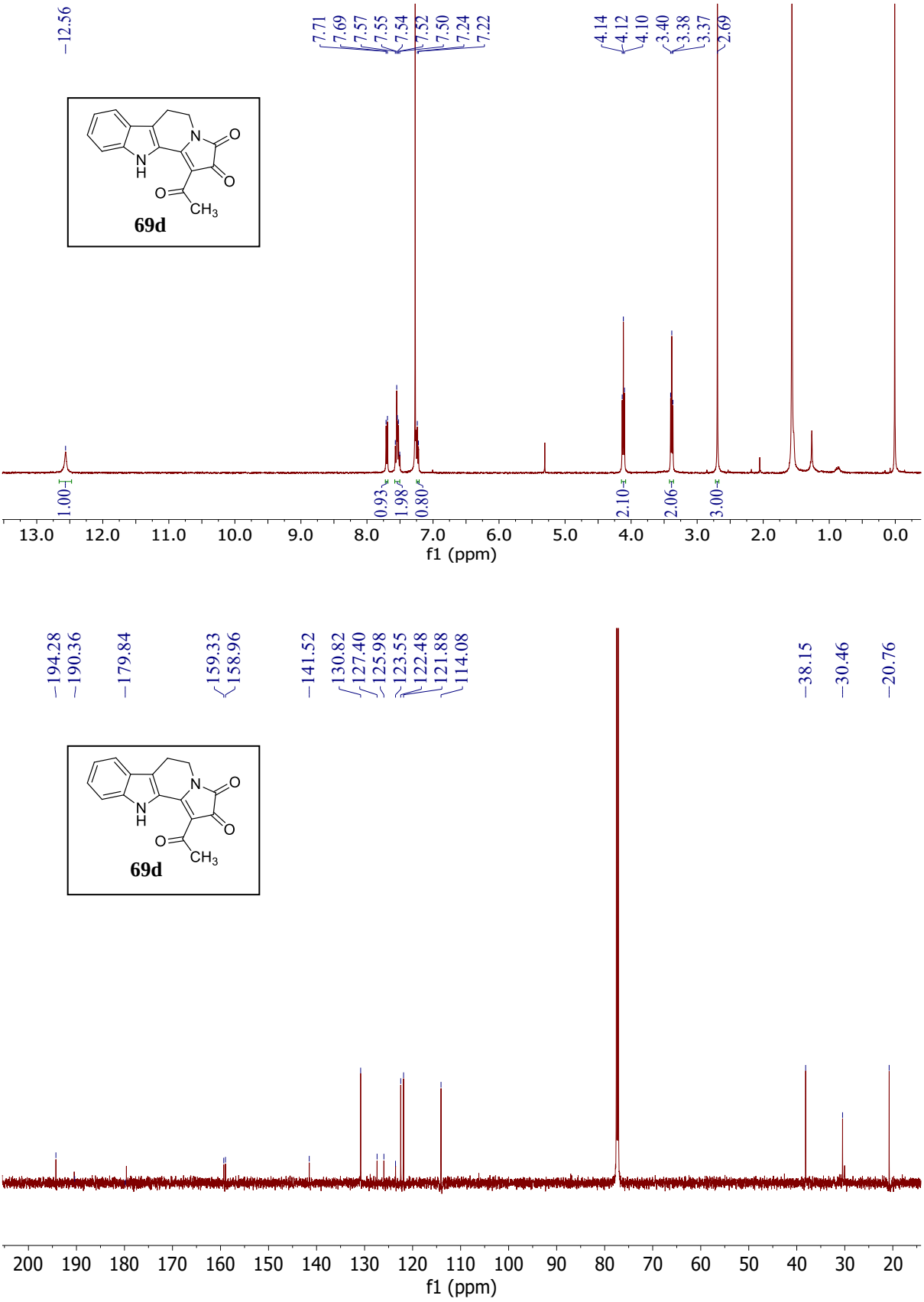

Figure 3. ^{1}H and ^{13}C NMR of compound 69d

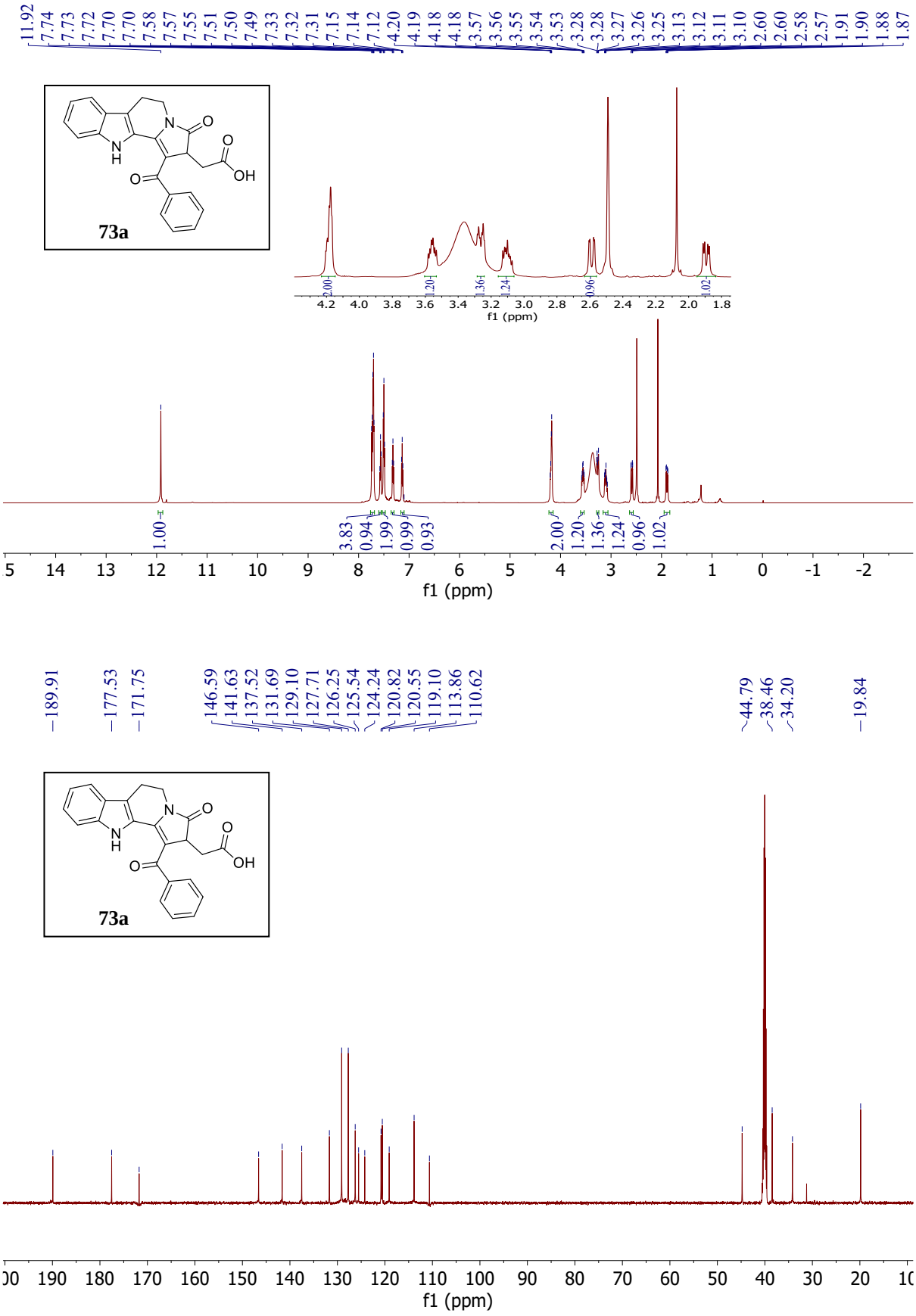

Figure 4. ^{1}H and ^{13}C NMR of compound 73a

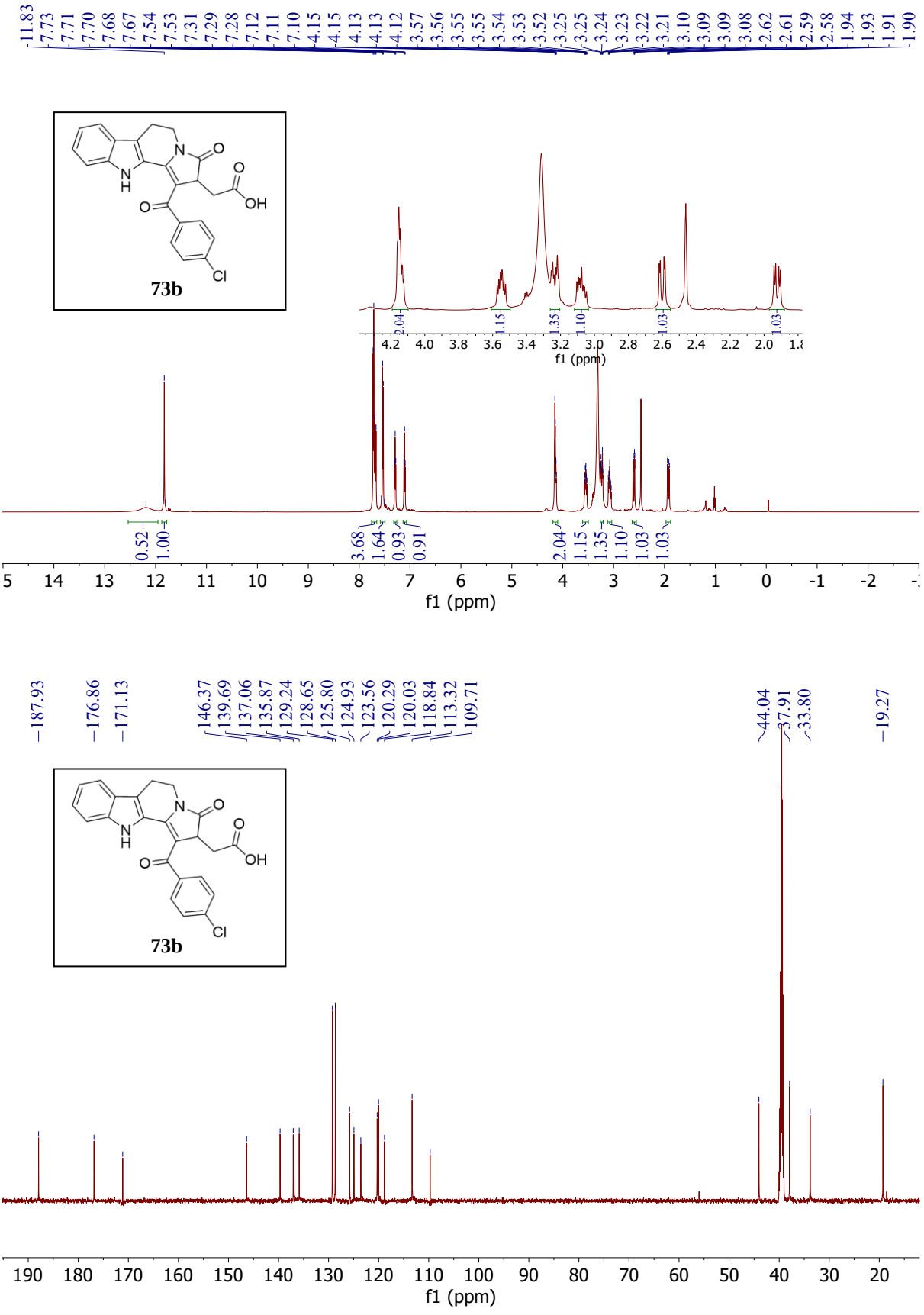

Figure 5. ^{1}H and ^{13}C NMR of compound 73b

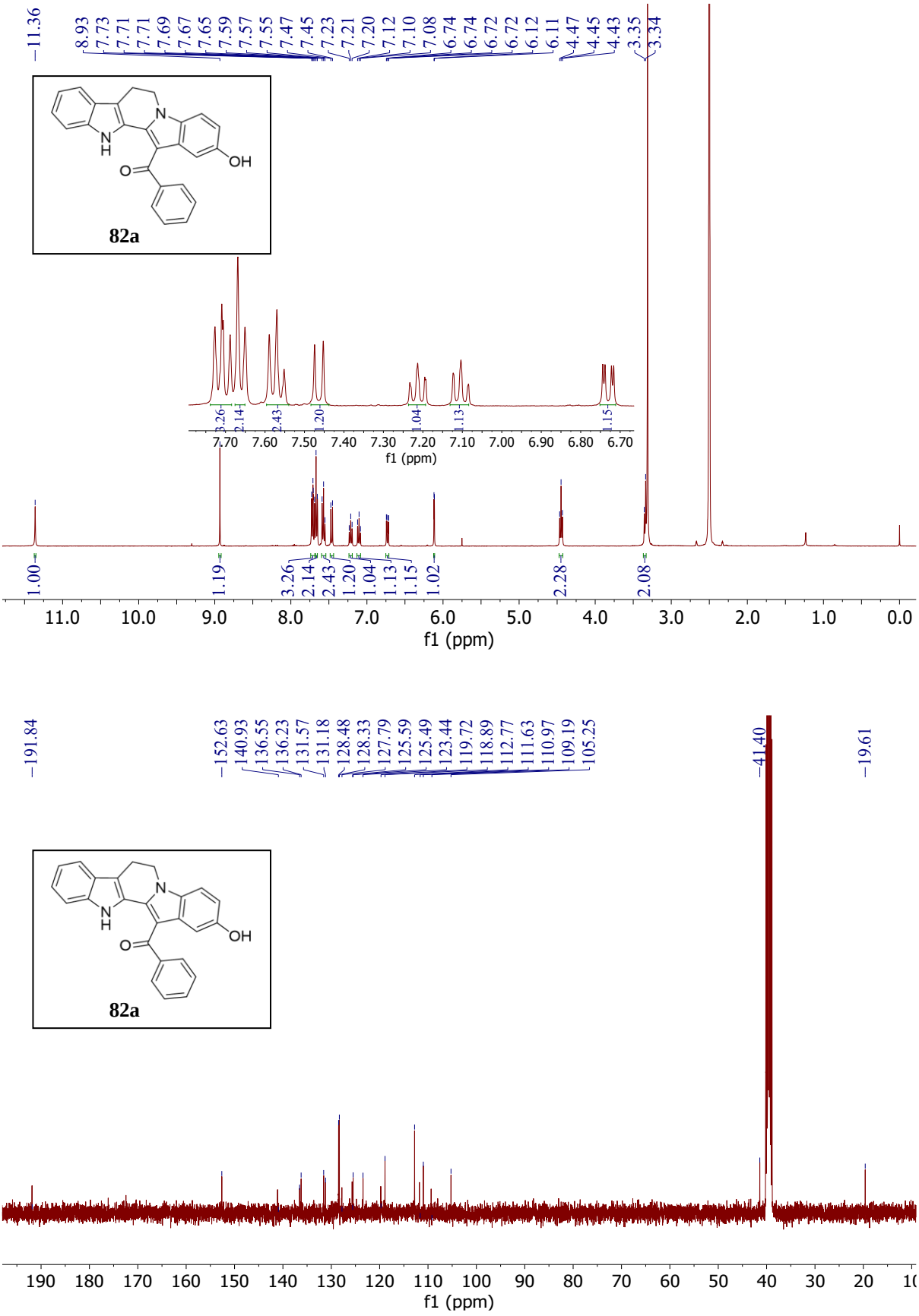

Figure 6. ^{1}H and ^{13}C NMR of compound 82a

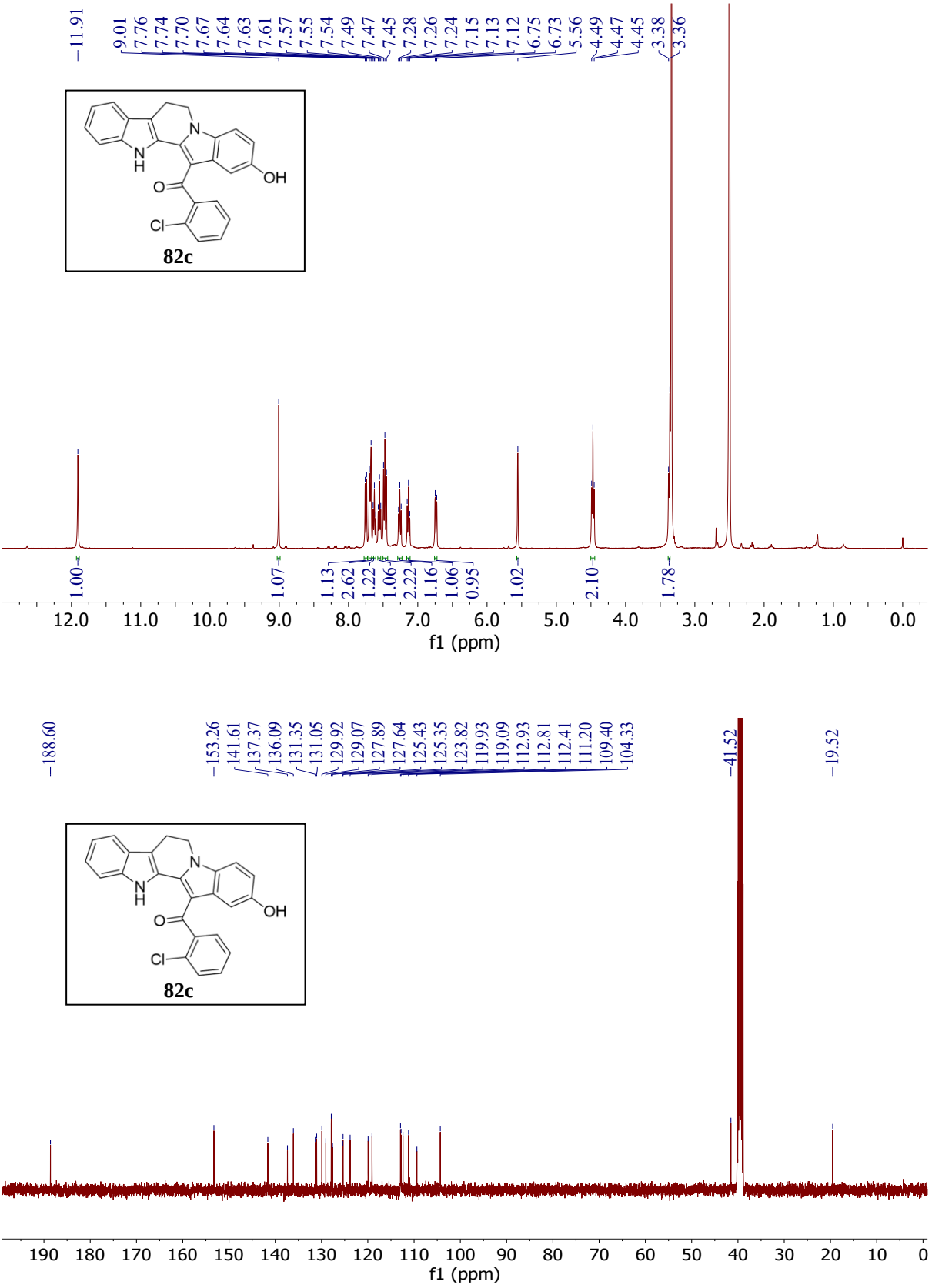

Figure 7. ^{1}H and ^{13}C NMR of compound 82c

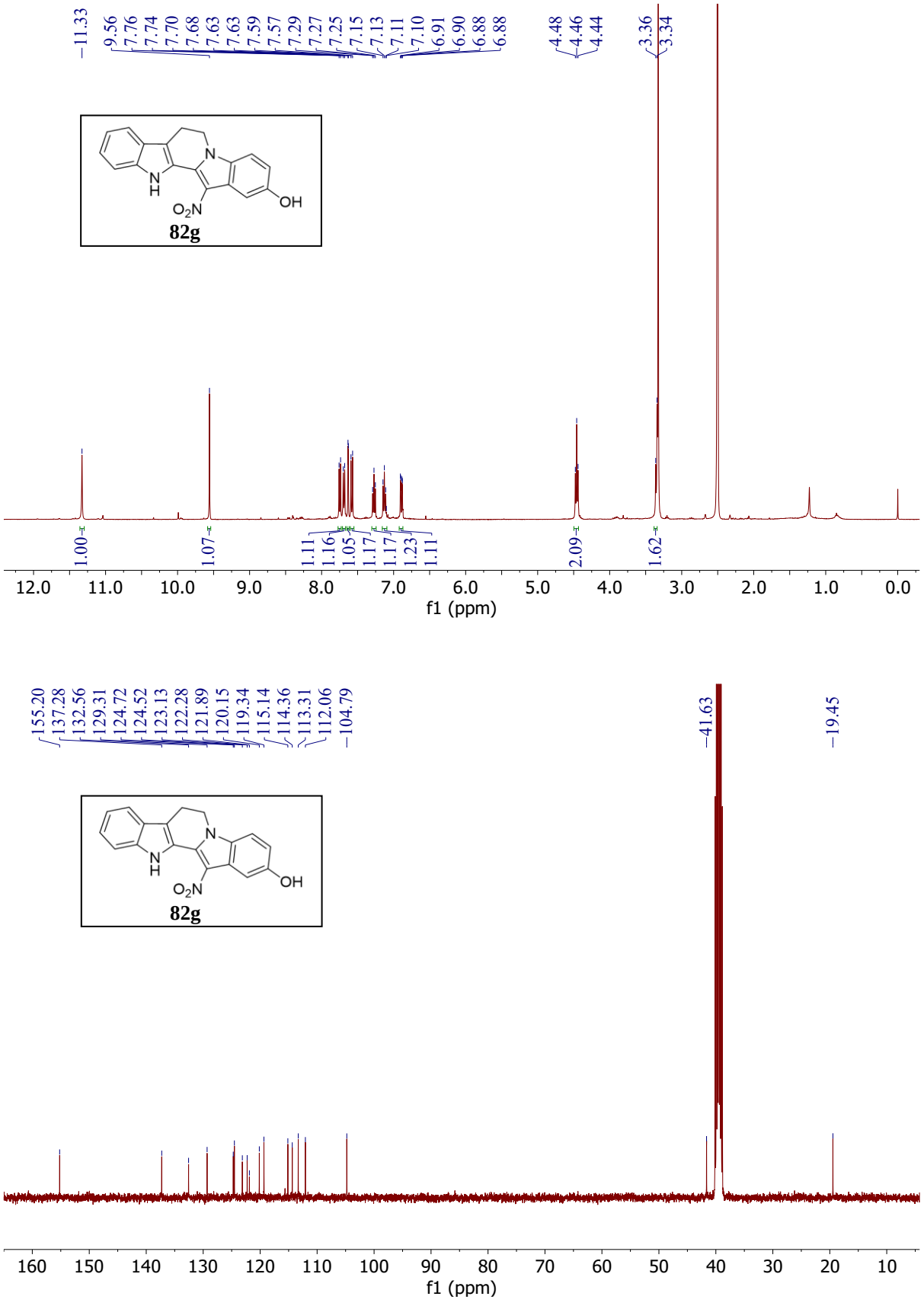

Figure 8. ^{1}H and ^{13}C NMR of compound 82g

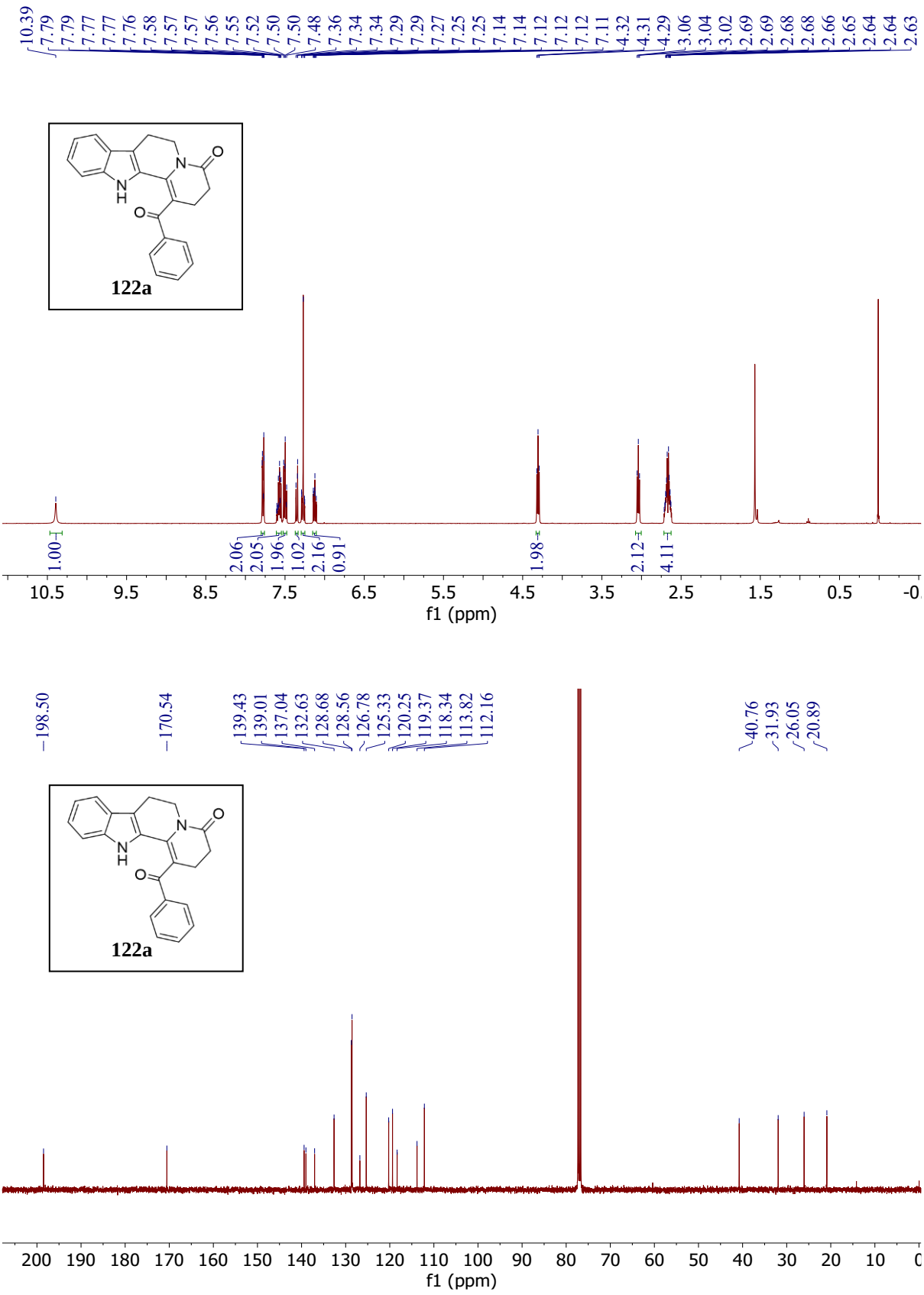

Figure 9. ^{1}H and ^{13}C NMR of compound 122a

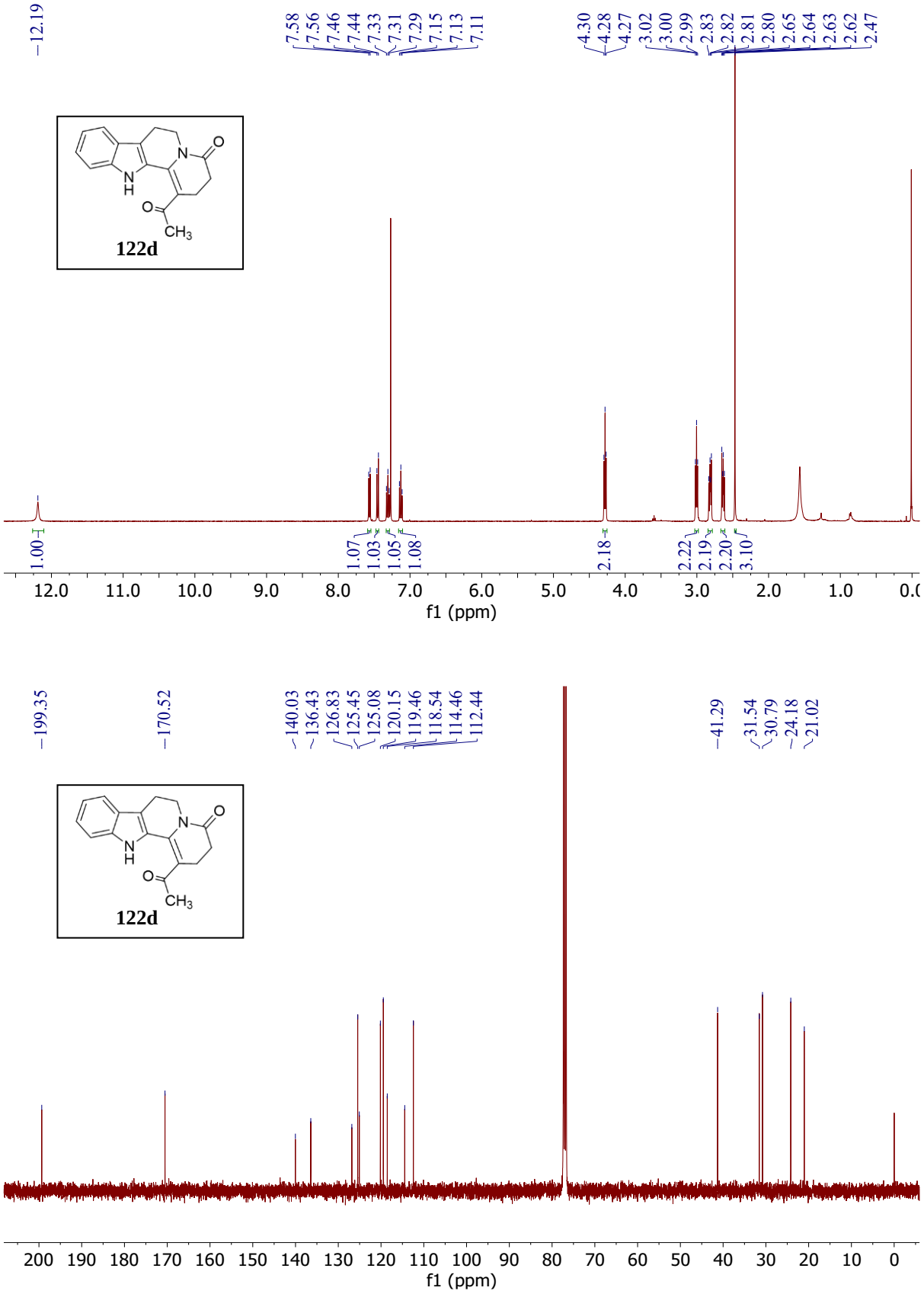

Figure 10. ^{1}H and ^{13}C NMR of compound 122d

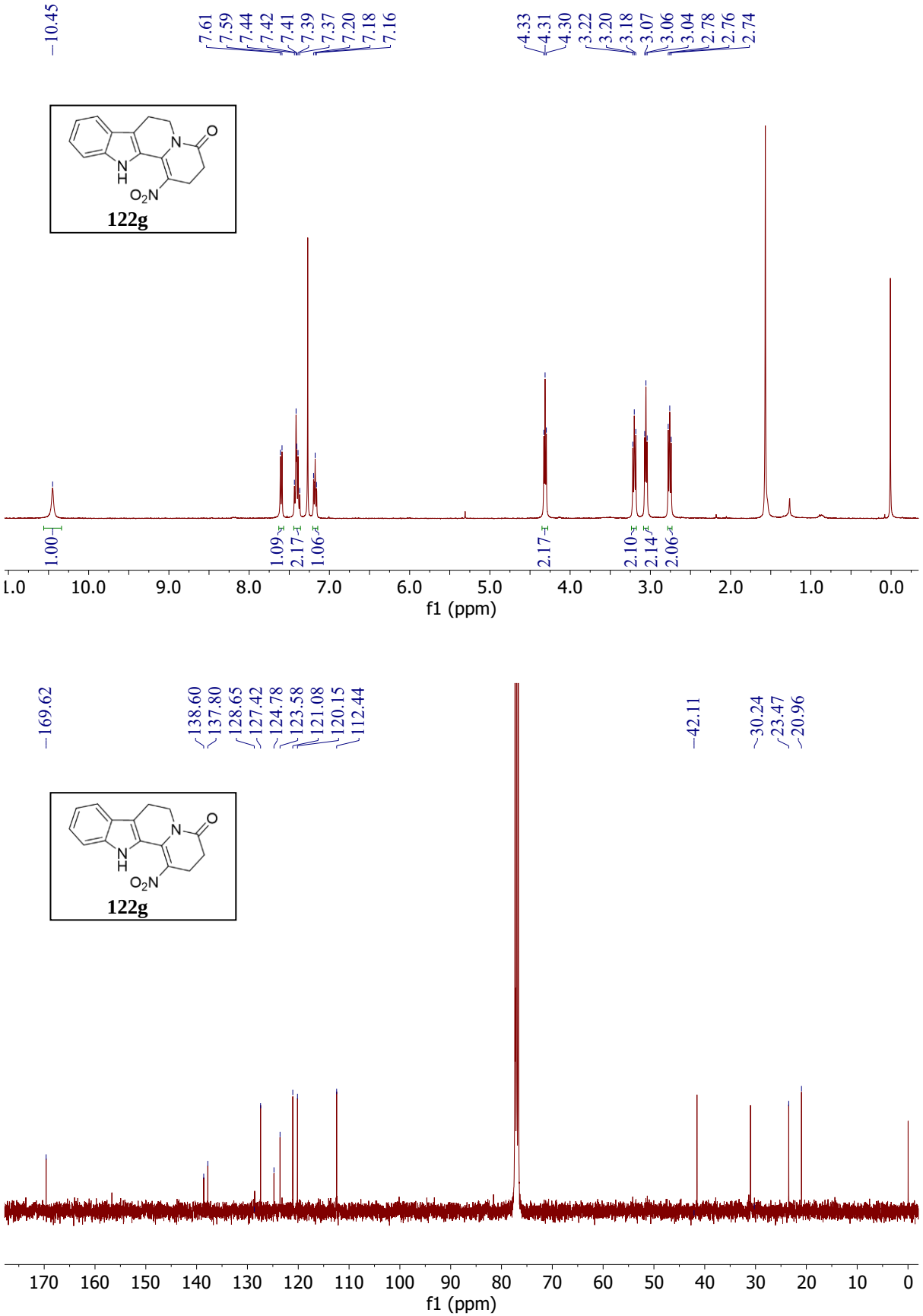

Figure 11. ^{1}H and ^{13}C NMR of compound 122g

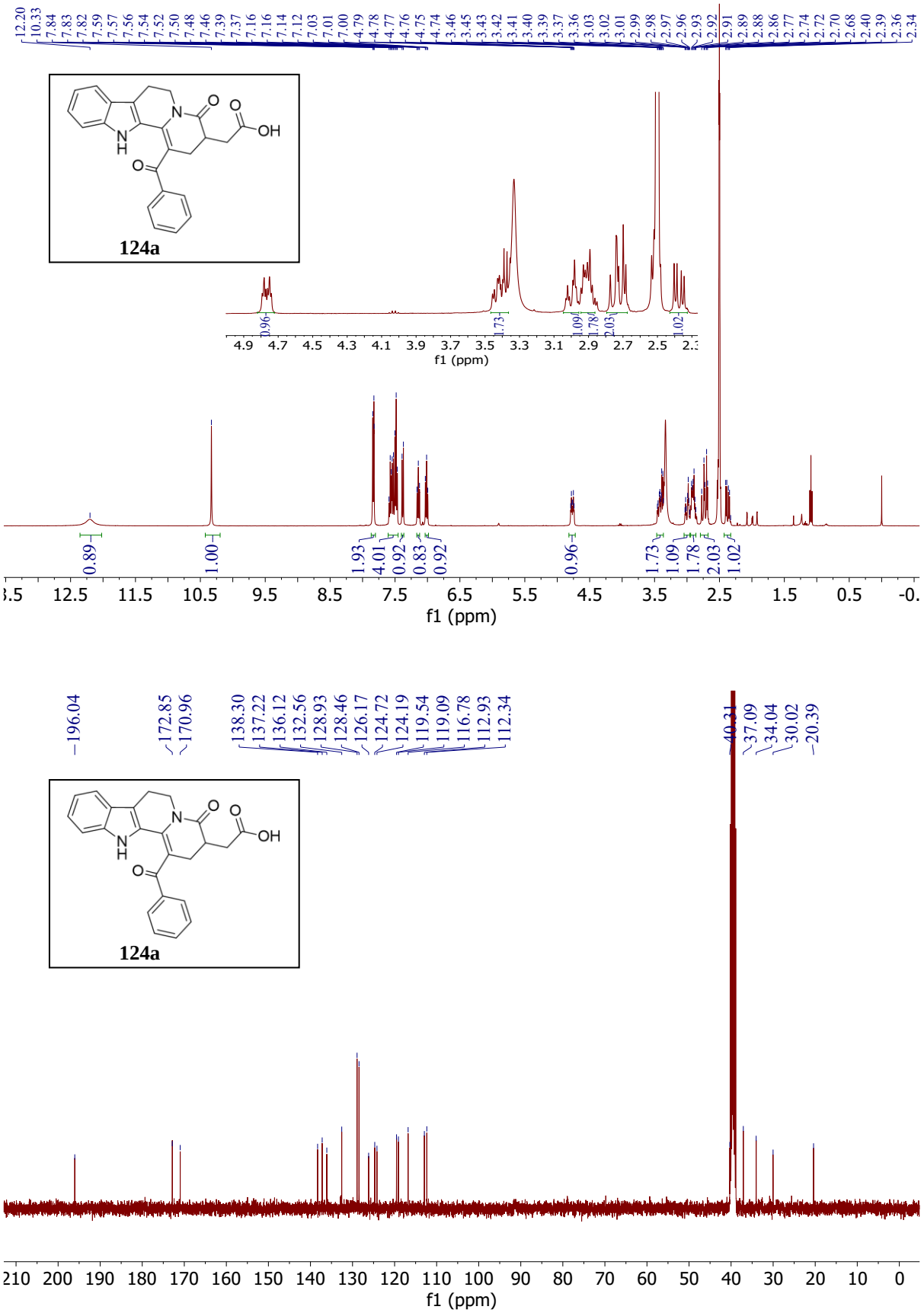

Figure 12. ^{1}H and ^{13}C NMR of compound 124a

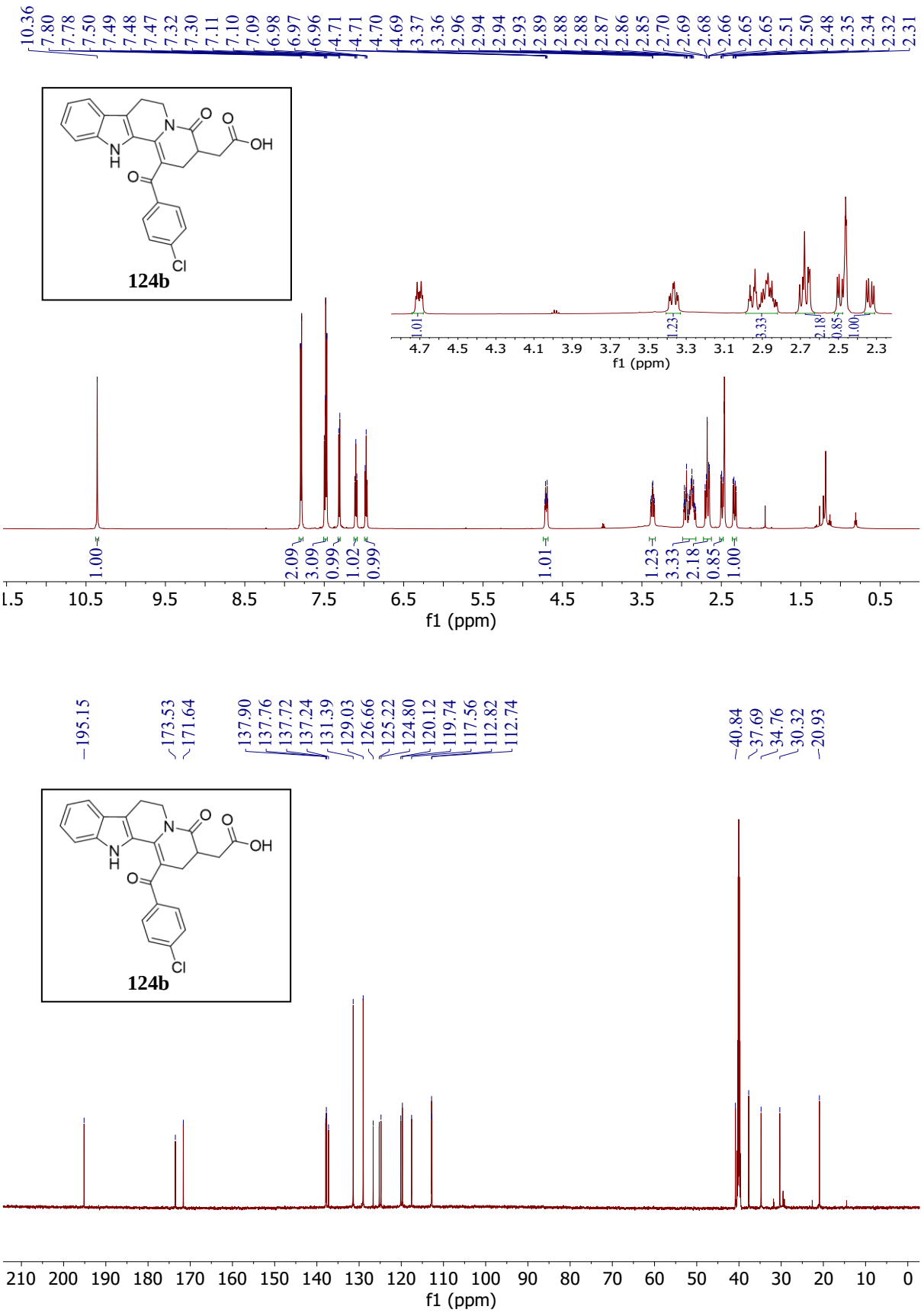

Figure 13. ^{1}H and ^{13}C NMR of compound 124b

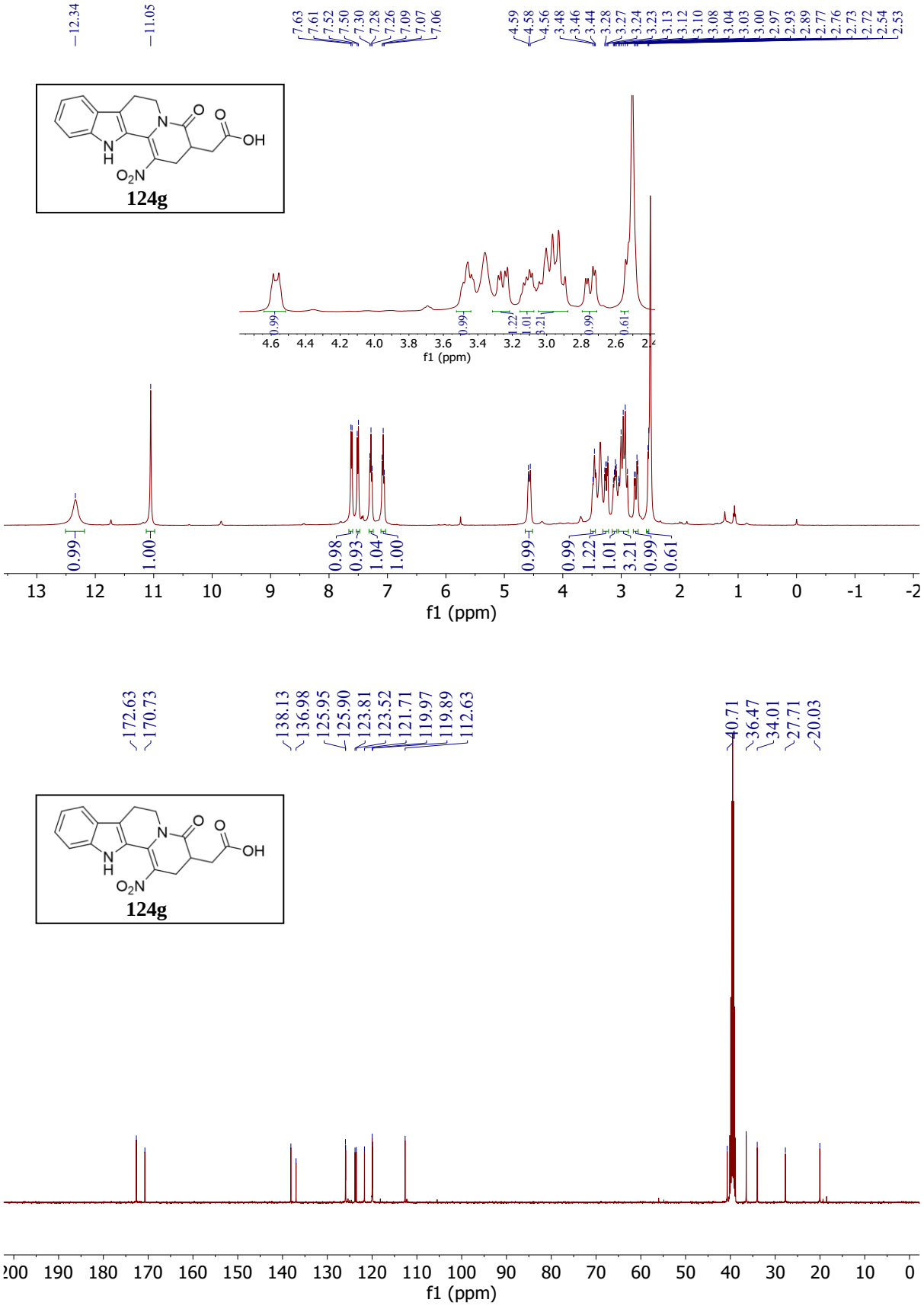

Figure 14. ^{1}H and ^{13}C NMR of compound 124g

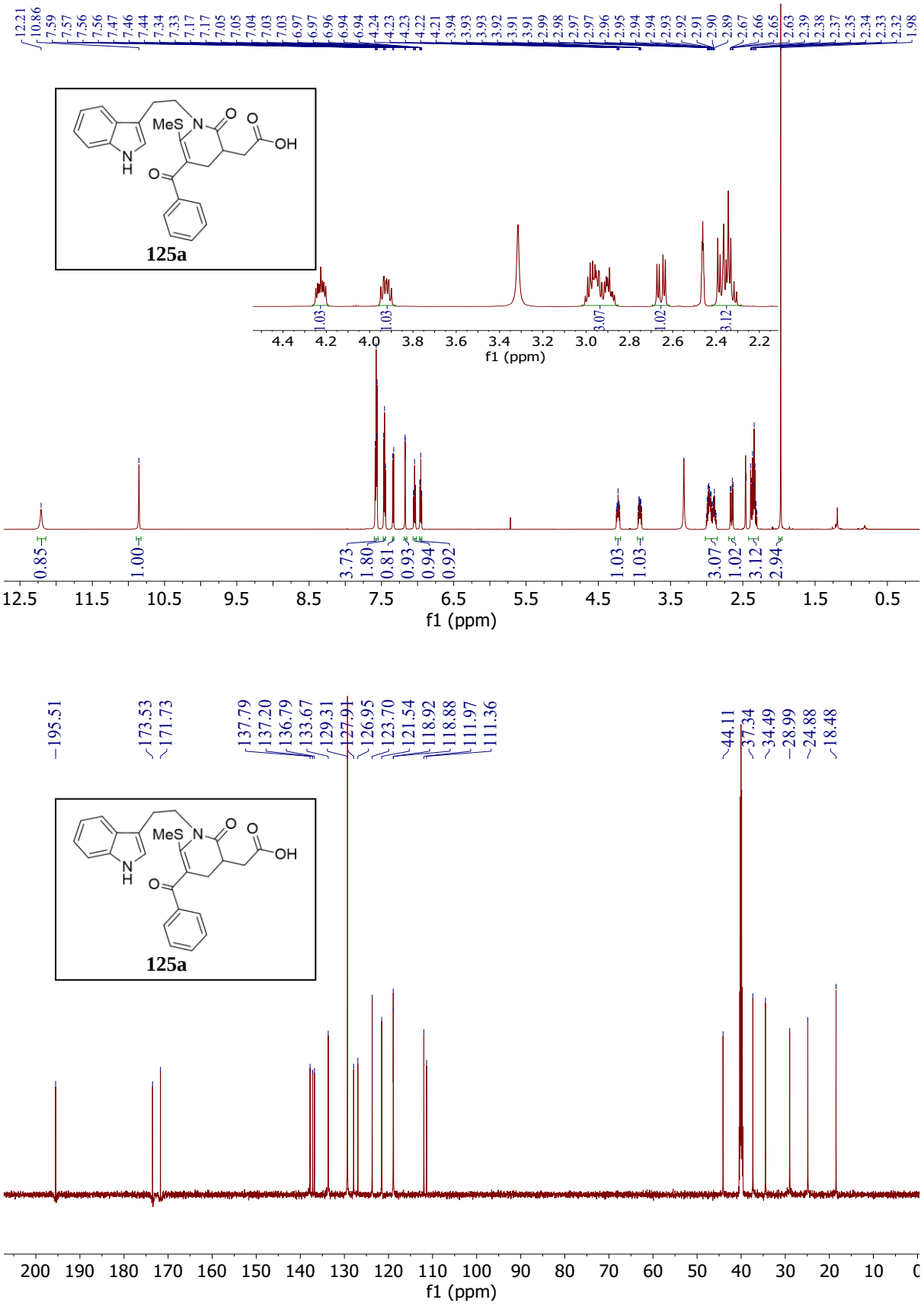

Figure 15. ^{1}H and ^{13}C NMR of compound 125a

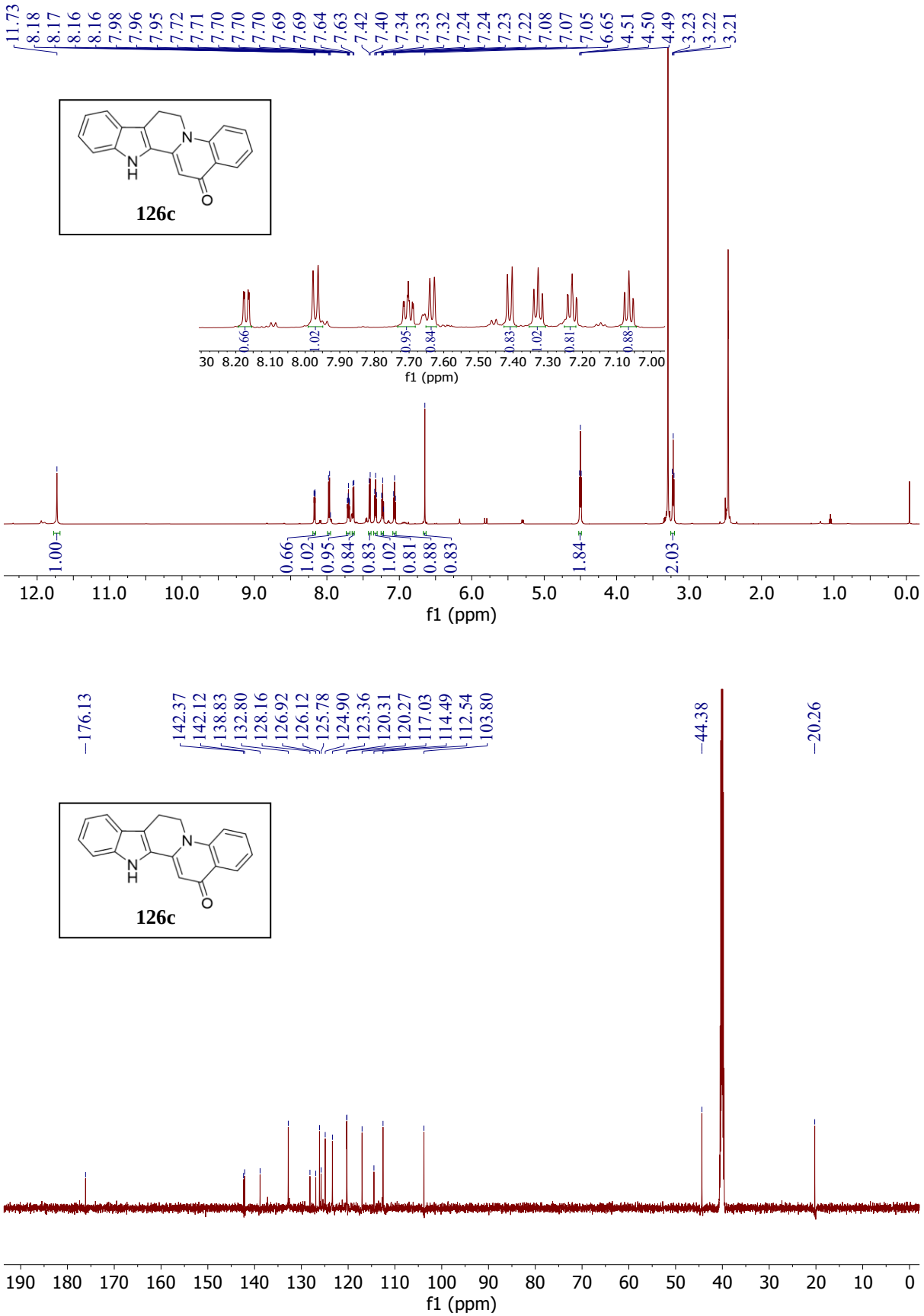

Figure 16. ^{1}H and ^{13}C NMR of compound 126c

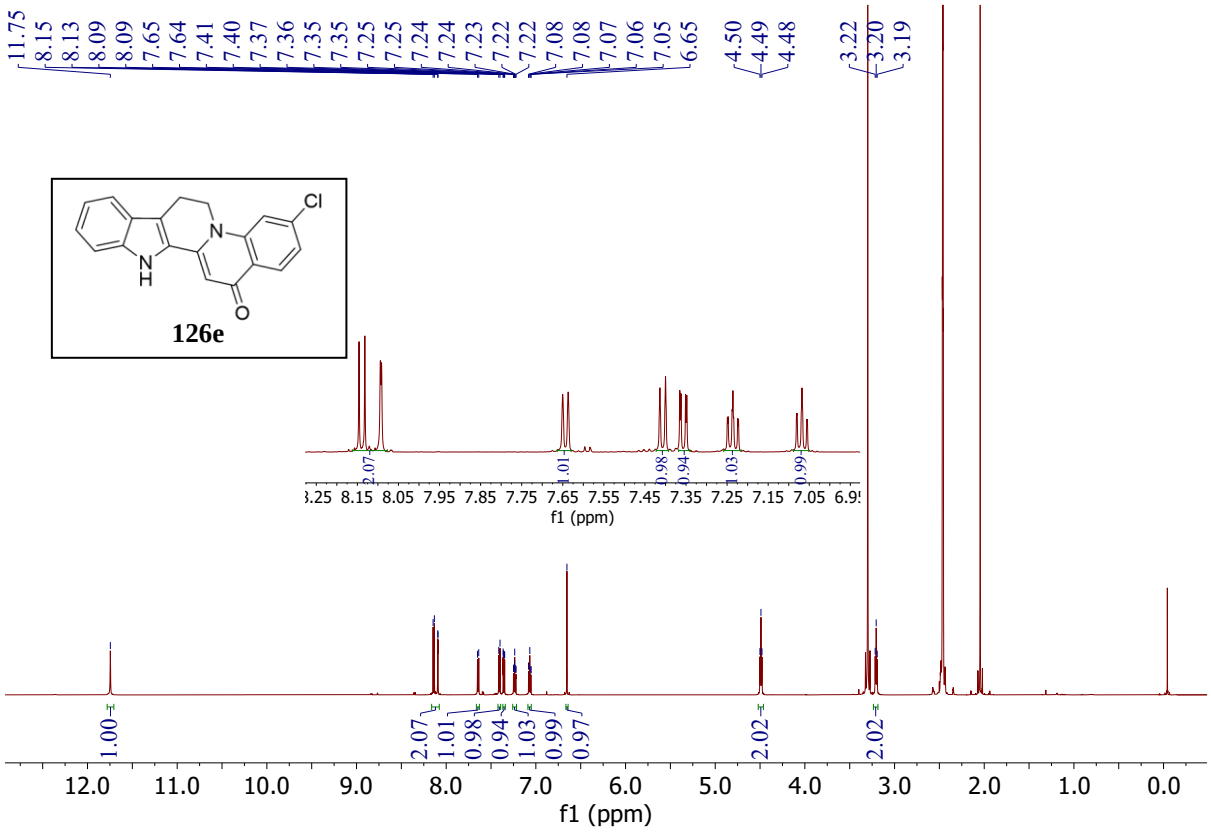

Figure 17. ^{1}H NMR of compound 126e

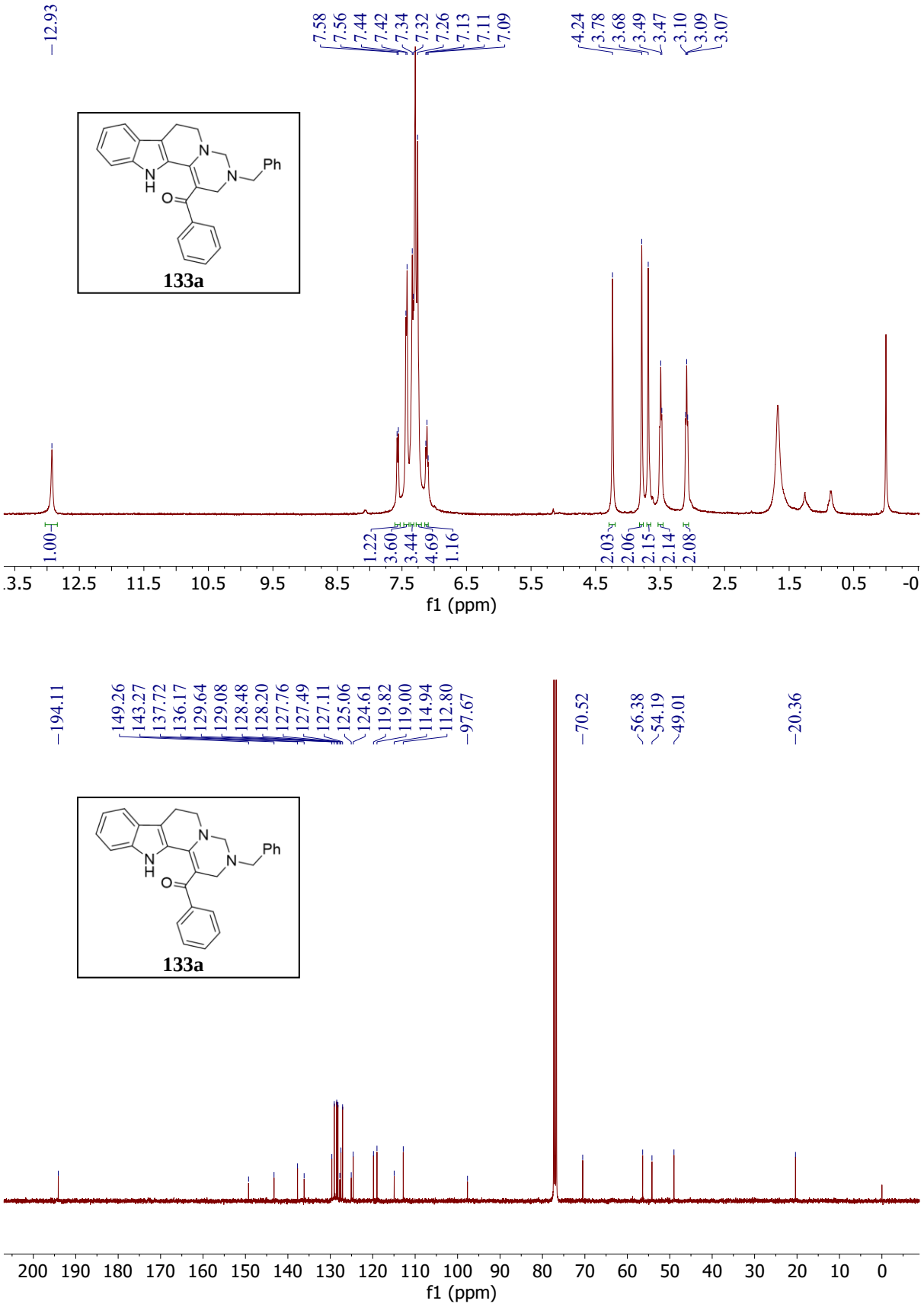

Figure 18. ^{1}H and ^{13}C NMR of compound 133a

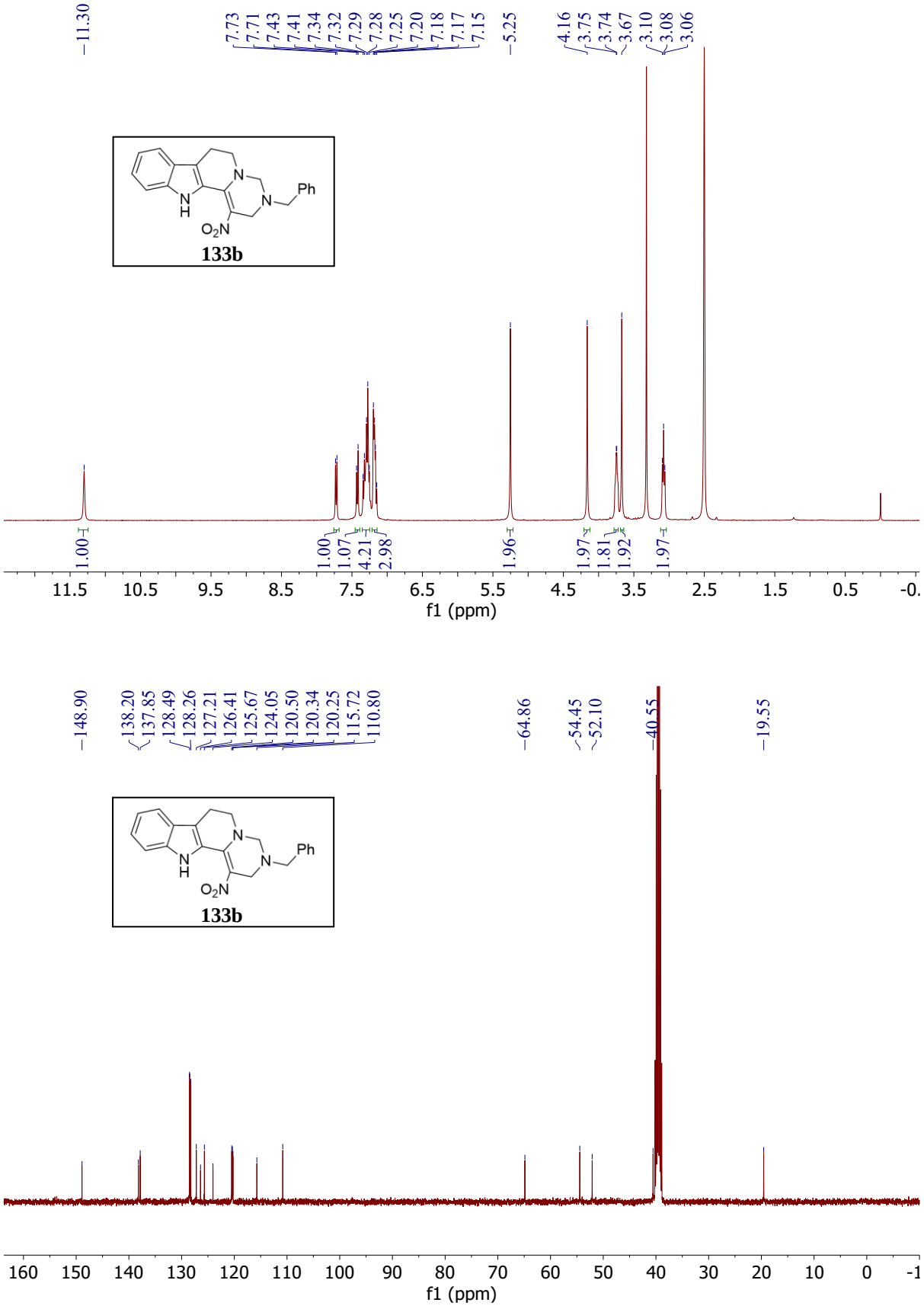

Figure 19. ^{1}H and ^{13}C NMR of compound 133b

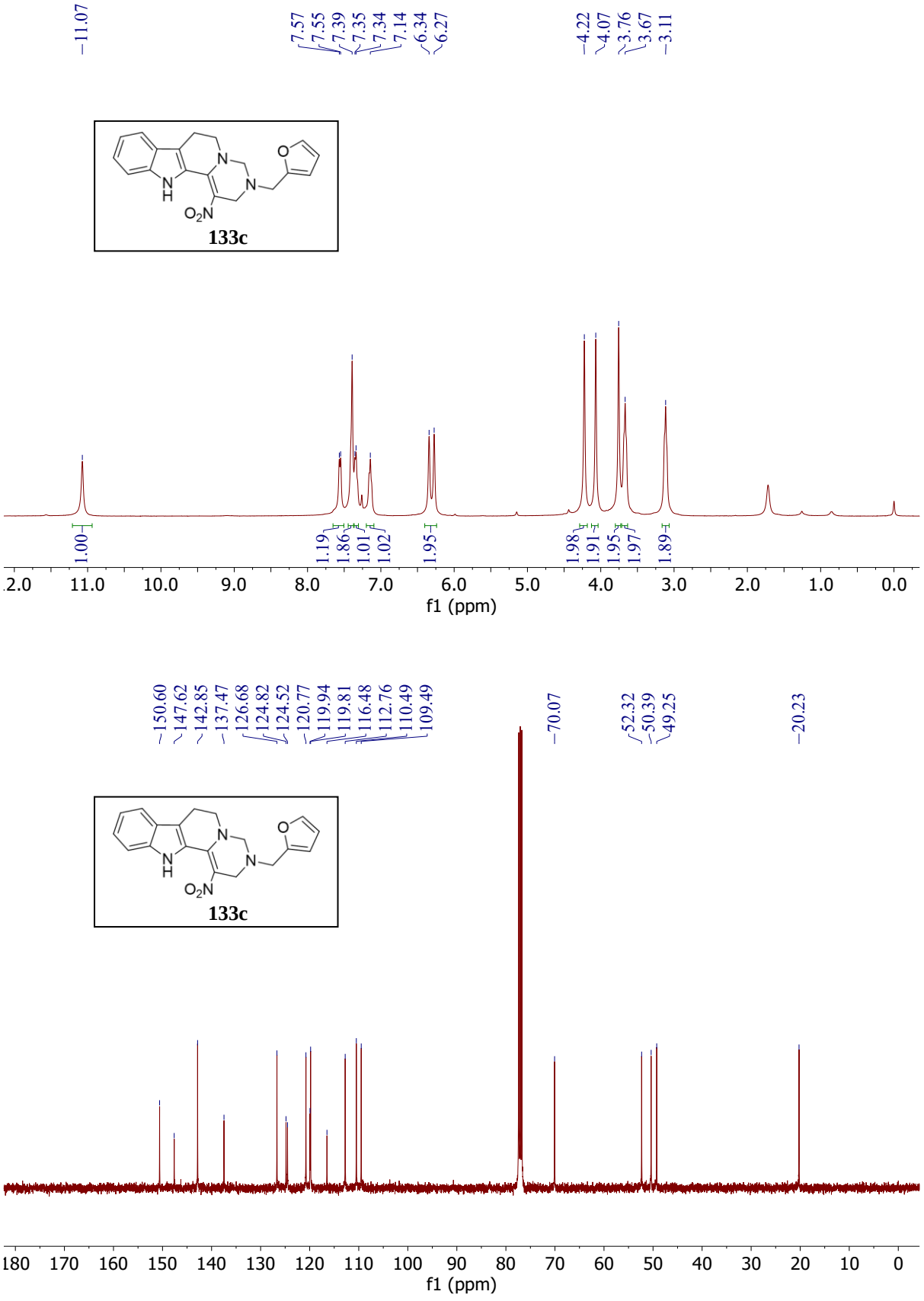

Figure 20. ^{1}H and ^{13}C NMR of compound 133c