DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE ALDOL, MANNICH, FRIEDLAENDER REACTIONS

by

LE LI

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ABSTRACT OF THE DISSERTATION

DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE ALDOL, MANNICH, FRIEDLÄNDER REACTIONS

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In Chapter I, I introduce the explosive development of enantioselective organocatalysis. Selected significant landmarks in this area are reviewed and highlighted in this chapter.

Chapter II focuses on the development of catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes and α-ketoesters.

Chapter III outlines the development of enantioselective Mannich reactions of α-isothiocyanato imides with activated imines and the asymmetric synthesis of α, β-diamino acid derivatives.

In Chapter IV, the first catalytic enantioselective Friedländer condensation is described which provides access to quinolines and tacrines with remote stereogenic centers.

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Finally, I cannot forget giving my sincere gratitude to my family. Their love and continuous support make everything easier.

DEDICATION

I dedicate this thesis to my beloved grandmother, parents and wife. Their love and continuous support always encourage me to move forward.

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Chapter I

Enantioselective Organocatalysis as an Emerging Synthetic Toolbox

Introduction

1.1 Background

The use of small organic molecules as catalysts for organic reactions in the absence of metallic elements has been known for more than one century. However, different from transition-metal catalysis, which took up the central stage of homogeneous catalysis over the past fifty years,[1] organocatalysis did not experience dramatic progress until the last two decades. Today, it has been widely accepted that organocatalysis is one of the most competitive branches of asymmetric catalysis. However, why had people overlooked this area for such a long time? To find out the answer to this question, we have to look back and track the history of organocatalysis.

1.1.1 History

The first report of organocatalysis by Justus von Liebig appeared in 1860.[2] Almost sixty years later, Langenbeck coined the term "organocatalyst" and published a series of papers using small organic molecules as mimics of enzyme catalysts.[3] In 1931, Fischer and Marschall reported amino acid catalyzed aldol reactions.[4] Although these early

reports had initiated two main categories in organocatalysis, “covalent catalysis” and “non-covalent catalysis”, they were not examples of asymmetric catalysis.

The first asymmetric organocatalyzed reaction was reported by Bredig and Fiske in 1912.[5] In their report, the natural alkaloid quinine catalyzed the reaction of HCN and benzaldehyde, although the optical yield was low. In 1960, Pracejus et al. found that O-acetylquinine catalyzed the addition of methanol to phenylmethylketene.[6] Remarkably, 74% ee was obtained with 1 mol% catalyst loading. In the early 1970s, the discovery of the proline–catalyzed intramolecular aldol reaction, namely, the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[7] showcased the tremendous potentials of enamine catalysis. Unfortunately, this type of catalysis was not further explored until 2000 when it was revisited by List, Lerner and Barbas.[8] In the 1980s, some other branches of organocatalysis started to sprout up. Inoue et al. reported that a cyclic peptide catalyzes the addition of HCN to benzaldehyde and high ee’s (up to 90%) were obtained.[9] This remarkable result is considered as one of the pioneering works of peptide catalysis. Later, Juliá and Colona et al. discovered poly-amino acid catalyzed epoxidations of chalcones using alkaline hydrogen peroxide as an oxidant.[10] In this case as well, more than 90% ee was achieved. Almost at the same time, Hiemstra and Wynberg exploited cinchona alkaloid catalyzed Michael additions of thiol to cyclohexenone (up to 75% ee).[11] Meanwhile, asymmetric phase transfer catalytic alkylation of protected glycine was systematically investigated by O’Donnell et al.[12]

1.1.2 Renaissance and Explosive Development

As mentioned above, although a number of reactions can be catalyzed by small organic molecules, most of them were not efficient and economical enough for preparing enantiopure materials in large scale. In sharp contrast, transition metal catalysis and enzymatic catalysis supplied most of the chiral materials in industry at that time and thus the area of organocatalysis before 1990 stagnated in the initial phase. However, this situation started to change at the end of the 20th century. Firstly, the pharmaceutical industry started looking for "greener" processes to avoid the contamination and the toxicity of transition metal. On the other hand, although enzymatic catalysis[13] is very powerful and highly effective in some industrial processes, its highly specific character is not ideal for a wide range of substrates. In addition, for some reactions, no enzymatic approaches were available. As a result, chemists had to look for a third approach to address these issues.

Under these circumstances, organocatalysis launched its renaissance in the 1990s. In 1994, Denmark et al. reported that chiral Lewis bases catalyzed the asymmetric allylation[14] of aldehydes in modest ee. This concept was later expanded to other reactions.[15] Subsequently, Iseki et al. and others realized the same reaction using different organo-catalytic systems.[16] In 1996, Shi and Yang independently utilized chiral ketones to catalyze the enantioselective epoxidations of olefins.[17] In 1997, Corey et al. and Lygo et al. discovered a novel cinchona alkaloid derived phase transfer catalyst, which enabled alkylations of protected glycine with excellent enantioselectivity.[18] Concurrently, Fu's planar-chiral DMAP derivatives catalyzed the kinetic resolution of

secondary alcohols in a highly selective fashion.[19] In 1998, Jacobsen et al. introduced (thio)urea catalysts to catalyze the enantioselective additions of HCN and imines.[20] In the same year, Miller et al. developed synthetic oligo-peptide catalyzed kinetic resolution of alcohols.[21] In 1999, Maruoka et al. developed a new generation of asymmetric phase transfer catalysts based on the binaphthalene backbone[22] and excellent enantioselectivities were achieved in a number of reactions.[23] Also, Corey et al. utilized a chiral guanidine catalyst to catalyze the hydrocyanation of benzaldehydes.[24] In 2000, List et al. revisited enamine catalysis and developed the proline catalyzed intermolecular aldol reactions of ketones and aldehydes.[8] In the same year, MacMillan designed the oxazolidinone catalyst family to enable the enantioselective Diels-Alder reactions of α, β-unsaturated aldehydes,[25] which is regarded as the milestone work of iminium catalysis.

Since 2000, the field of organocatalysis stepped into the age of explosive development,[26] which was also described as a "gold rush" by some chemists.[27] Thousands of publications and more than one hundred types of reactions were discovered by chemists from all over the world. The major branches of organocatalysis will be summarized in the following part of this chapter.

1.2 Major Branches of Organocatalysis

1.2.1 Enamine Catalysis[28]

Since List, Lerner and Barbas' pioneering work[8] on the proline–catalyzed aldol reactions of acetone with aldehydes, enamine catalysis has developed into a powerful synthetic tool in organic synthesis. This activation mode has been widely applied to various substrates and different types of reactions.

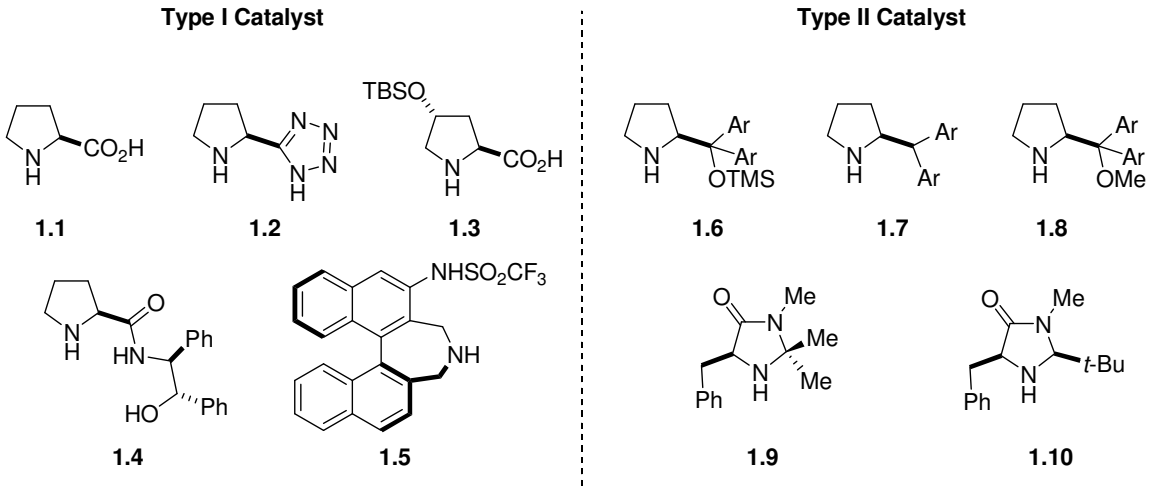
For aldol reactions, the scope of nucleophiles has been greatly extended including cyclic ketones, α-keto acids, α-keto esters, α-keto phosphonates, hydroxyacetone, chloroacetone, ynones, α, α-disubstituted aldehydes and even highly reactive acetaldehyde. For electrophiles, in addition to aliphatic aldehydes and aromatic aldehydes, phenylglyoxalates, α-keto acids, α-keto esters, α-keto phosphonates, protected α-amino aldehydes and isatins are also viable substrates. In addition, Maruoka et al. reported the syn-selective aldol reactions[29] of aliphatic aldehydes with aromatic and activated aliphatic aldehydes using an axially chiral enamine catalyst **1.5**, while anti-selective products are typically obtained in the proline catalyzed reactions.

Extensive studies showed that enamine catalysis has much more applications than aldol reactions. Until now, a number of reaction types have been covered by using enamine catalysis including Mannich reactions, conjugate addition reactions, α-halogenations, α-oxygenations, α-aminations and other α-functionalization processes. Moreover, enamine catalysis has shown impressive potential to catalyze domino reactions and has been greatly developed for the construction of the skeleton of complex molecules.

In addition, a large amount of new catalysts were discovered in the past decade. There are two major categories in these enamine catalysts. The main difference in these two types of catalysts is whether an internal acid or a hydrogen bond donor exists. In other words, type I utilize an acid or a HB donor as a directing group which activates electrophiles while type II usually have a bulky group which only allows the eletrophile to attack from one side. For example, diarylprolinol trimethylsilyl ethers **1.6**, introduced

independently by Jørgensen et al. and Hayashi et al. in 2005, are a class of privileged catalysts of type II.[30] Some representative catalysts are shown in Figure 1.1.

Figure 1.1 **Selected Examples of Enamine Catalysts**



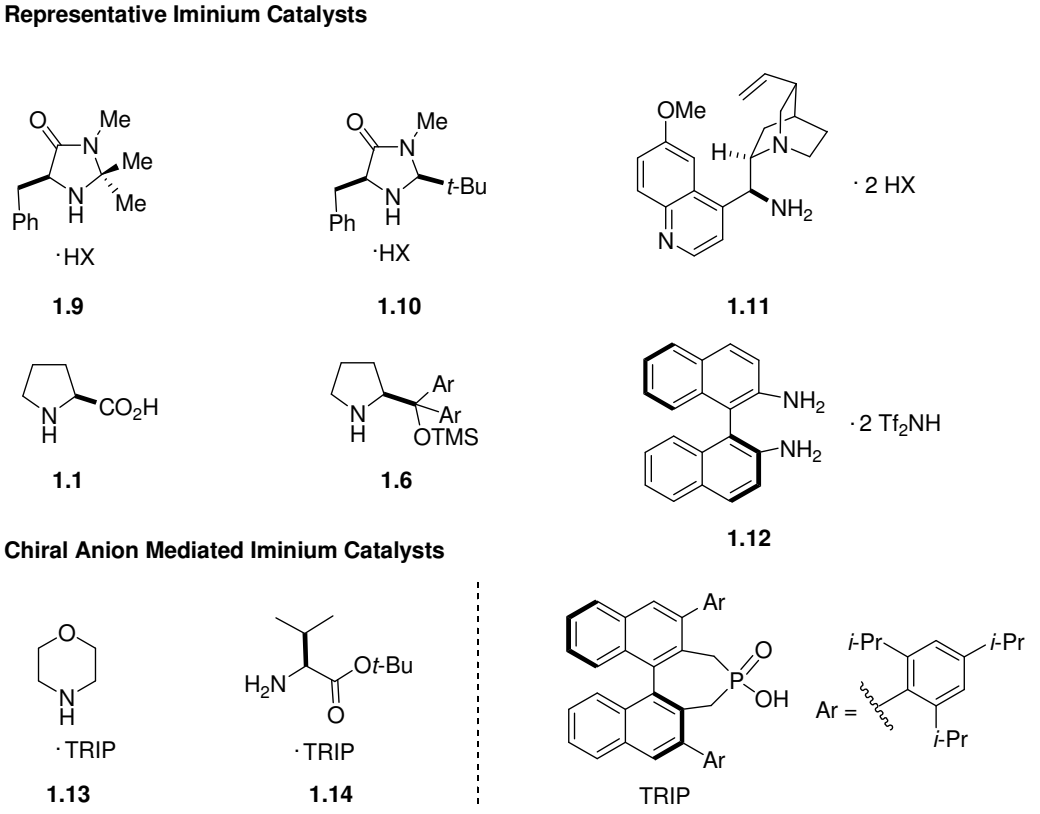
1.2.2 Iminium Catalysis[31]

Similar to enamine catalysis, iminium catalysis was not revived until recently, although early examples of iminium catalysis apparently date back to the early 20th century. In 2000, MacMillan et al. reported the first enantioselective Diels-Alder reactions of α,β-unsaturated aldehydes using an oxazolidinone catalyst **1.9**,[25] which is one of the significant landmarks in iminium catalysis. Subsequently, MacMillan et al. and others discovered a number of applications including [4+2], [3+2], [4+3] cycloadditions, ene reactions, conjugate additions, Friedel-Crafts type alkylations and hydrogenations.

During the past decade, a series of new iminium catalysts were discovered, although MacMillan's oxazolidinone catalyst family continues to play an important role in this type of catalysis. Strikingly, chiral anion mediated iminium catalysis has become

a promising strategy in transfer hydrogenation. Some of these representative catalysts are shown in Figure 1.2.

Figure 1.2 **Selected Examples of Iminium Catalysts**



Recently, combining iminium catalysis with enamine catalysis has become a powerful strategy in the design of new cascade reactions.[32] Several elegant total syntheses utilized this strategy to set up multiple chiral centers in one single step, significantly cutting down steps as compared to previous syntheses.[33]

1.2.3 Hydrogen Bond Catalysis[34]

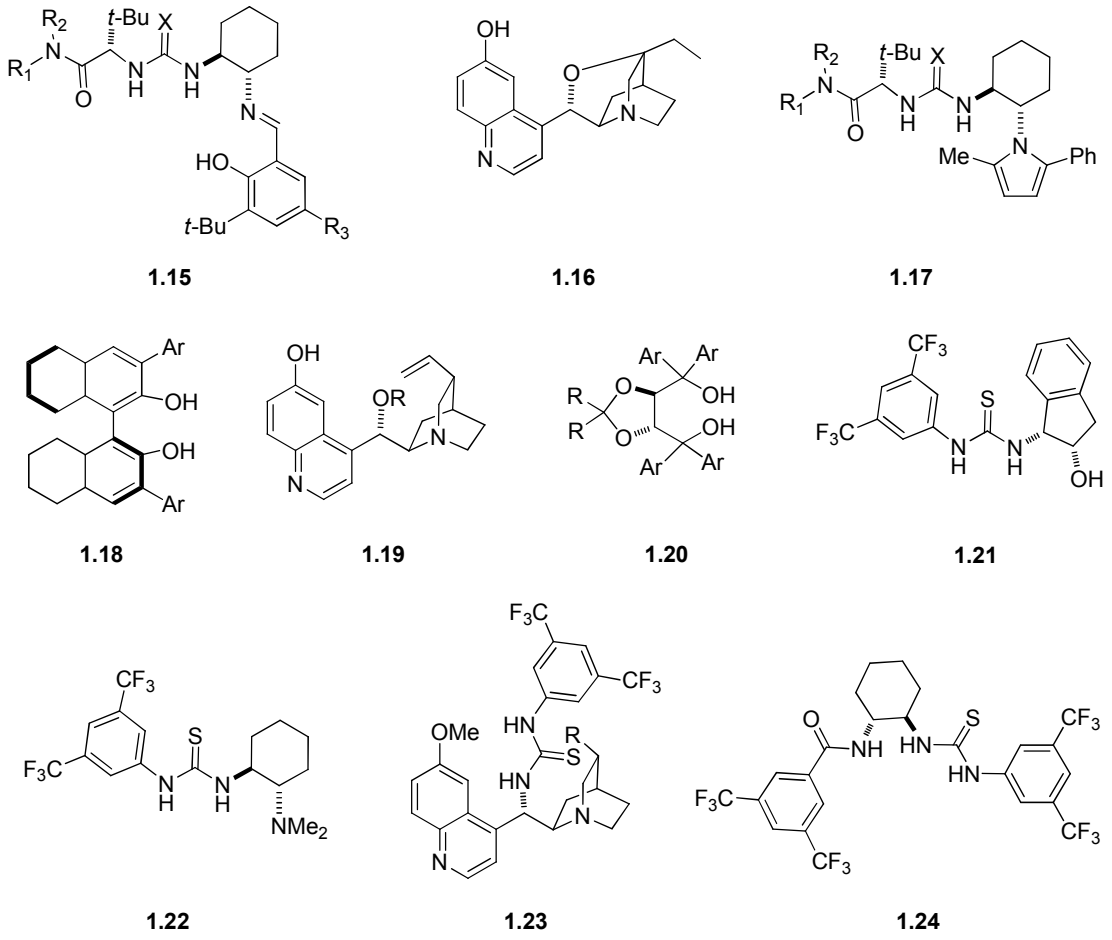
Activation of substrates by hydrogen bond donors in enzymatic catalysis has been recognized for a long time. The extensive investigations of solid-state or solution-state in

molecular recognition and crystallography also showed that hydrogen bond donors could form complexes with themselves or with other molecules containing hydrogen bond acceptors. These facts suggested that hydrogen bonds could be a promising activation force for catalysis. However, hydrogen bond catalysis has not been extensively investigated until recently. This apparent contradiction can be explained by the nature of the hydrogen bond which is a much weaker interaction than covalent bonds.

Hydrogen bond catalysis had not been widely recognized as a key activation mode until the late 20th century. In the early 1980s, the reports from Wynberg et al.,[11] Inoue et al.[9] and Dolling et al.[35] on cinchona alkaloid and oligo-peptide catalyzed reactions disclosed that hydrogen bonding has a beneficial effect on enantioselectivity. In 1998, Sigman and Jacobsen reported that a (thio)urea **1.15** catalyzed Strecker reactions.[20] Later, in proline catalyzed aldol reactions, List and Houk proved that the carboxylic acid of proline activates the incoming aldehyde and accelerates the reaction.[36] In addition to Jacobsen's catalyst family, many other successful catalytic systems were developed in the last decade. Some representative examples are shown in Figure 1.3. In 2003, Takemoto et al. introduced a tertiary amine-(thio)urea type catalyst **1.22** using trans-cyclohexanediamine as backbone.[37] In the same year, the discovery of TADDOL derivatives by Rawal indicated that the chiral diol **1.20** could be a good catalyst for hetero-Diels-Alder reactions.[38] In 1999 and 2004, Hatakeyama et al.[39] and Deng et al.[40] individually discovered their own catalyst family (**1.16** and **1.19**), both of which are derived from cupreine and cupreidine. These systems have been finely tuned and extensively investigated by other researchers.[34] In addition, Miller's intensive research

on synthetic peptide catalysis can be regarded as an extension of hydrogen bond catalysis.[41]

Figure 1.3 **Selected Hydrogen Bond Catalysts**



In 2007, Jacobsen's mechanistic studies[42] on thiourea **1.17**-catalyzed Pictet-Spengler reactions exhibited binding between thiourea and anions, which opened the door to another new branch of hydrogen bond catalysis, anion binding catalysis. Meanwhile, some unprecedented reaction modes were introduced that combine hydrogen bond catalysis with other types of catalysis.[8, 43] In Figure 1.3, some of the classical hydrogen bond catalysts are summarized.

The last decade witnessed the exponential development of hydrogen bond catalysis. It has been expanded into a number of reactions including aldol reactions, Mannich reactions, conjugate additions, Diels-Alder cycloadditions, Baylis-Hillman reactions, aza-Baylis-Hillman reactions, Henry reactions, aza-Henry reactions, Friedel-Crafts additions, Strecker reactions, epoxydations, kinetic resolutions and desymmetrizations, radical cyclizations, photocyclizations, α-hydrazinations, hydrophosphonylation, Claisen rearrangements, Povarov reactions, Pictet-Spengler reactions, alkylations and allylations.

1.2.4 Stronger Brønsted Acid Catalysis[44]

Different from conventional Lewis acid catalysis, Brønsted acid catalysis utilizes protons to catalyze organic transformations. In theory, all hydrogen bond donors, such as (thio)ureas, alcohols, phenols, carboxylic acids and phosphoric acids, can be regarded as Brønsted acids. Also, there is no strict distinction between hydrogen bond catalysis and other Brønsted acid catalysis. The term "stronger Brønsted acid catalysis" introduced by Akiyama[44] was used to describe Brønsted acid catalysis that involves ion pair interactions, not hydrogen bonding interactions.

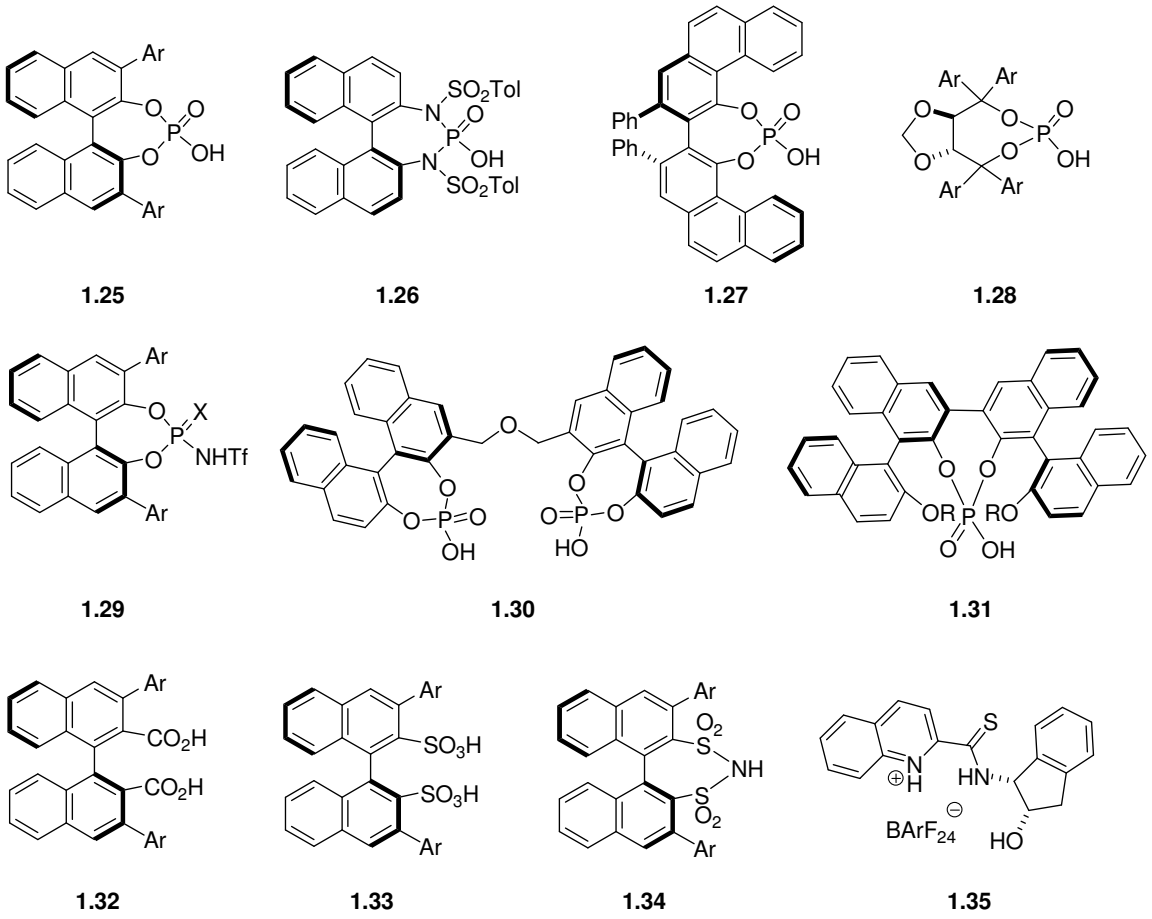
In 2004, Akiyama et al. and Terada et al. independently reported that axially chiral phosphoric acids **1.25** catalyze Mannich reactions in highly enantioselective fashion, a milestone achievement in this area.[45] Afterwards, the concept of chiral stronger Brønsted acid catalysis has been extended into many types of reactions including Mannich reactions, aza-Henry reactions, aza-ene type reactions, hydrophosphonylations of imines, Pictet-Spengler reactions, Friedel-Crafts reactions, alkylations, Strecker reactions, aza-Diels-Alder reactions, 1, 3-dipolar cycloadditions, Biginelli reactions, Nazarov reactions,

transfer hydrogenations, reductive aminations and other types of additions of nucleophiles to imines.

In the last five years, various chiral "stronger Brønsted acid" catalysts were discovered successively (Figure 1.4). Other chiral phosphoric acids were prepared from other chiral scaffolds. In 2005, the Akiyama group reported TADDOL derived phosphoric acids **1.28**.[46] In the same year, Antilla et al. utilized VAPPOL derived phosphoric acids **1.27** to catalyze enantioselective imine amidations.[47] In 2006, BINAM variants **1.26** were developed in the Terada group.[48] In 2008, Gong et al. discovered bisphosphoric acids **1.30** derived from BINOL that successfully catalyze asymmetric 1,3-dipolar cycloadditions.[49] Also, bis-BINOL phosphoric acids **1.31** were used to catalyze the transfer hydrogenation of quinolines by Du et al.[50]

Although chiral phosphoric acids are still the major player in stronger Brønsted acid catalysis, other chiral Brønsted acids have been used as a valuable supplement (Figure 1.4). For instance, more acidic chiral N-triflyl phosphoramides **1.29** provide stronger activation than the corresponding phosphoric acids and are thus good candidates for the activation of less reactive substrates. In 2006, Yamamoto et al. designed this type of catalysts and successfully applied them to asymmetric Diels-Alder reactions of α, β-unsaturated ketones with silyloxydienes.[51] Later, following this line, Yamamoto et al. prepared more acidic chiral N-triflyl thiophosphoramides and their seleno counterparts in 2008. These compounds catalyze the asymmetric protonation of cyclic silyl enol ethers.[52] In addition, chiral carboxylic acids, chiral sulfonic acids and chiral protonated salts were discovered to catalyze asymmetric transformations.[44]

Figure 1.4 **Selected "Strong Brønsted Acid" Catalysts**

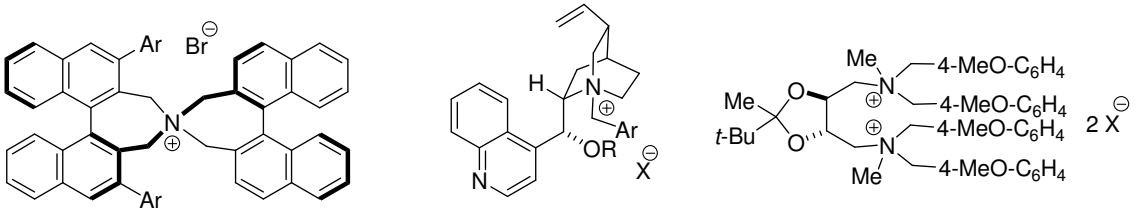


1.2.5 Phase Transfer Catalysis[23, 53]

Since O'Donnell's seminal investigations[12] on alkylations of benzophenone imines of glycine derivatives, this reaction has become one of the most important methods to prepare optically active natural or unnatural α-amino acids. In 1997, Corey and Lygo independently discovered that bulky cinchona alkaloid derived ammonium salts **1.37** catalyze the alkylation of protected glycines with excellent enantioselectivity.[18] In 1999, Maruoka designed a new generation of chiral phase transfer catalysts **1.36** using binaphthalene as chiral backbone.[22] Compared to cinchona alkaloid derived PTC, the

Maruoka catalyst family has several extraordinary advantages such as higher stability (less labile in basic conditions), better modularity and broader reaction scopes, although multi-step synthesis are often required for the preparation of catalysts. These two types of phase transfer catalysts are predominant in this area and most new applications involve them, although other research groups have been trying to design new privileged PTCs based on readily available chiral starting materials[54] (Figure 1.5).

***Figure 1.5* "Privileged" Phase Transfer Catalysts**



1.36 **1.37** **1.38**

After almost 30 years of development, a wide range of reactions are available for asymmetric phase transfer catalysis such as alkylations, fluorinations, aldol reactions, Mannich reactions, Michael additions, Darzens reactions, epoxidations, Neber rearrangements, aziridinations, Strecker reactions and dihydroxylations.

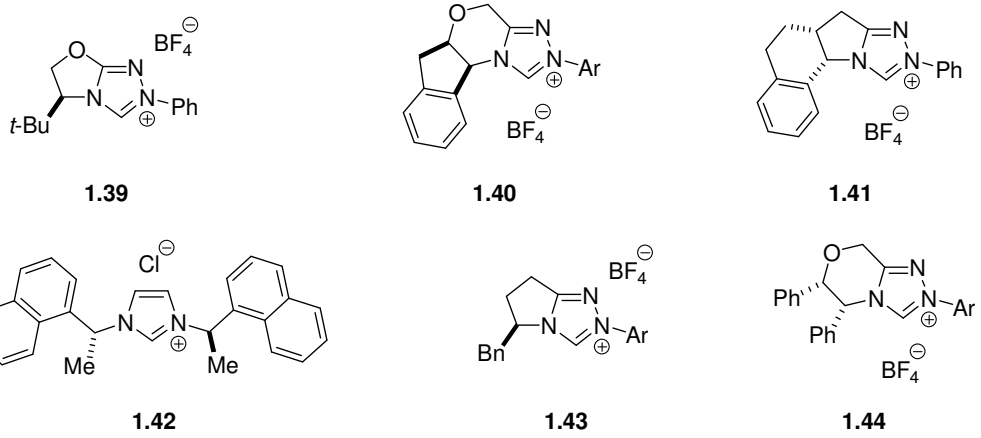
1.2.6 N-heterocyclic Carbenes as Organocatalysts[55]

Carbene catalysts take a significant position in modern synthetic chemistry because of their unique properties. They constitute highly reactive intermediates and facilitate new synthetic pathways. Compared to other carbenes, N-heterocyclic carbenes are more stable and easier to handle.[56] An early example of N-heterocyclic carbenes as organocatalysts was Sheehan and Hunneman's research on asymmetric benzoin

condensations in the 1960s, although the enantioselectivity was low.[57] The breakthrough in this area was achieved by Enders′ group in 2002.[58] A chiral bicyclic triazolium salt **1.39** derived from (*S*)-*tert*-leucine functioned as a carbene precursor to catalyze asymmetric benzoin condensations with good enantioselectivity. This bicyclic structure, first introduced by Leeper and Rawal,[59] was shown to be crucial and many successful applications were discovered using this structure or other variants with similar topology (Figure 1.6). Another interesting application in this area is the asymmetric Stetter reaction. In 2002, Rovis et al. developed another series of triazolium pre-catalysts **1.40** that catalyze intramolecular Stetter reactions with good enantioselectivity.[60]

N-heterocyclic carbenes were also disclosed to catalyze a number of asymmetric redox processes. In 2005, Rovis et al. reported the synthesis of chiral α-chloroesters from α, α-dichloroaldehydes.[61] In 2006, Bode et al. demonstrated that N-heterocyclic carbenes **1.40** catalyze azadiene Diels-Alder reactions with excellent enantioselectivity.[62] The corresponding oxadiene Diels-Alder reactions were also reported by the same group.[63] In 2007, two complementary methods for the synthesis of chiral substituted cyclopentenes were reported by Bode et al.[64] and Scheidt et al.[65] Additionally, N-heterocyclic carbene catalyzed reactions have been applied into the synthesis of FD-838.[66]

Figure 1.6 **Representative Chiral N-Heterocyclic Pre-catalysts**



1.39 **1.40** **1.41**

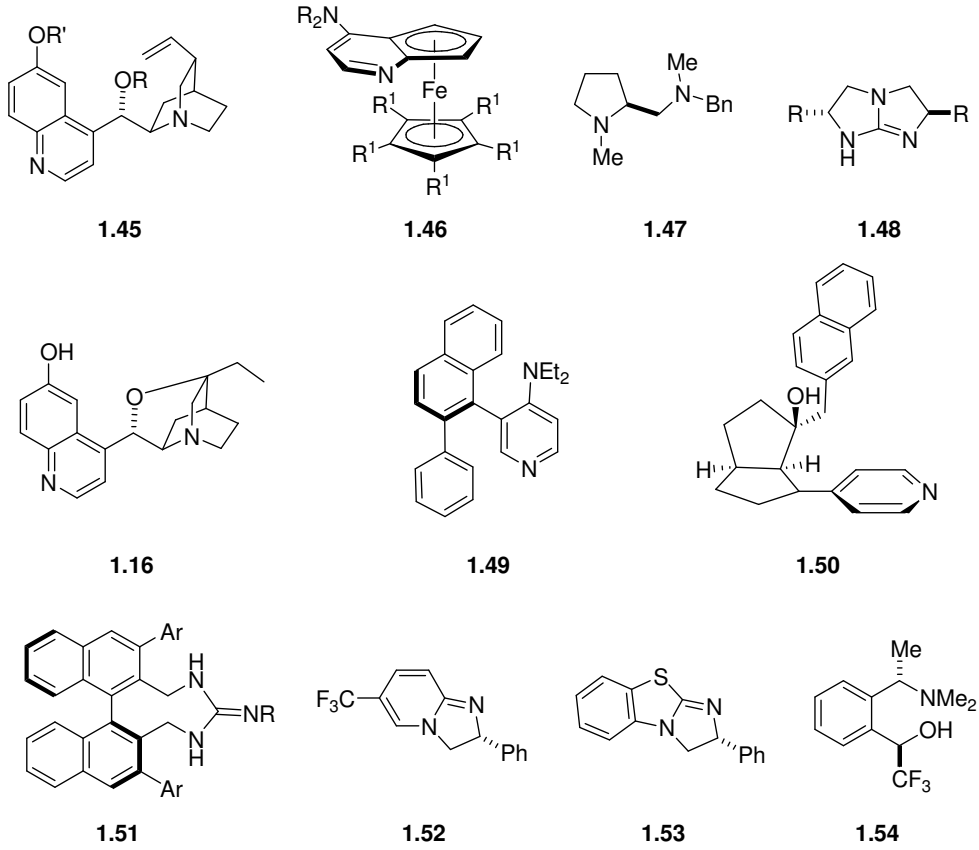
1.42 **1.43** **1.44**

1.2.7 Lewis Base Catalysis[67]

Lewis base catalysis has two major categories: amine catalysis (Figure 1.7) and phosphine catalysis (Figure 1.8). In addition, chiral alcohols, chiral phosphoramides and chiral amine oxides have been also investigated as Lewis base catalysts.

Historically, cinchona alkaloid catalysis[68] played the central role in this area. In 1960, Pracejus et al. first reported the alcoholysis of disubstituted ketenes,[6] which opened up the area of chiral amine nucleophilic catalysis. Recently, Lectka et al. utilized modified cinchona alkaloids **1.45** to catalyze a number of asymmetric reactions involving ketenes.[69] Moreover, cinchona alkaloid derivatives **1.16** and **1.45** were confirmed to be good catalysts for Baylis-Hillman reactions by Hatakeyama et al.[39] and for desymmetrizations of cyclic anhydrides by Deng et al. and others.[40, 70]

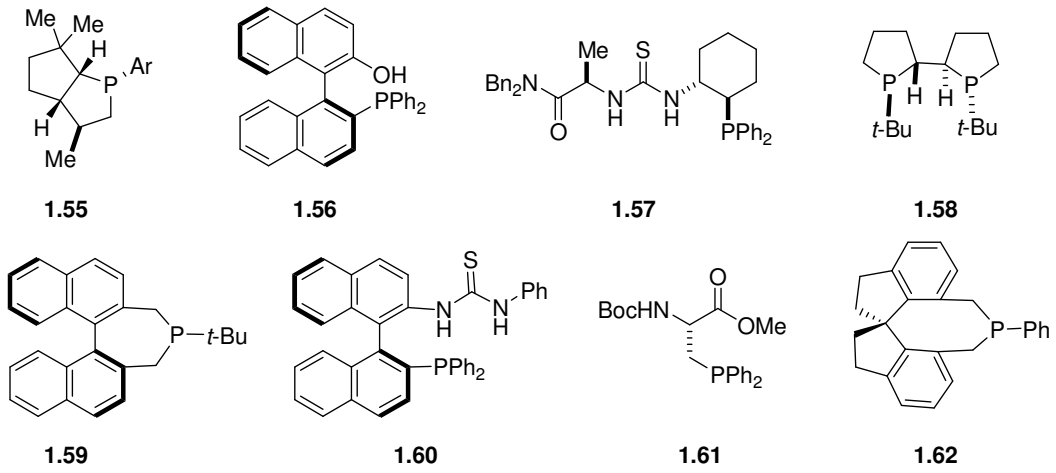
Figure 1.7 **Selected Examples of Chiral Amines as Lewis Base catalysts**



Although there were sporadic reports in the last fifty years, other classes of Lewis base catalysis were not widespread until recently. For example, the common Lewis base catalysts such as imidazole, pyridine and guanidine have been incorporated into chiral scaffolds. In 1996, Fu et al. reported planar-chiral DMAP variants **1.46** catalyzed kinetic resolution of secondary alcohols.[19] In 1998, Oriyama et al. successfully catalyzed the desymmetrizations of meso-diols using a new diamine catalyst **1.47** derived from proline.[71] Concurrently, Spivey et al. and Fuji et al. developed two different chiral PPY catalysts **1.49** and **1.50** to catalyze the same reaction.[72] Also, as mentioned in the previous sections, Miller et al. reported imidazole-containing synthetic peptides and used

them to catalyze a series of reactions.[21, 41] In 1999, Corey et al. utilized a chiral guanidine **1.48** to catalyze the hydrocyanation of benzaldehydes.[24] In 2004, Birman et al. developed a new set of nucleophilic catalysts **1.52** and **1.53** based on dihydroimidazole backbones.[73] Later, these catalysts were applied to a number of kinetic resolution processes and excellent selectivities were obtained. In 2005, Sammakia et al. discovered a new chiral DMAP derivative **1.54** by which the kinetic resolutions of protected α-hydroxyl acid derivatives[74] were achieved.

Figure 1.8 **Selected Examples of Chiral Phosphines as Lewis Base Catalysts**



1.55 **1.56** **1.57** **1.58**

1.59 **1.60** **1.61** **1.62**

Chiral phosphines constitute another important class of asymmetric Lewis base catalysts. In 1996, Vedejs et al. developed the first generation of phosphine **1.55** catalyzed kinetic resolutions of secondary alcohols.[75] In 2002, Shi et al. discovered that axially chiral monophosphine **1.56** catalyzed aza-Baylis-Hillman reactions with excellent enantioselectivity.[76] In 2007, Miller et al. reported that an α-amino acid derived chiral monophosphine **1.61** catalyzes a [3+2] cycloadditions of allenic esters and α, β-unsaturated ketones.[77] In 2008, Jacobsen developed a series of bifunctional phosphine-thiourea catalysts **1.57** to catalyze an asymmetric imine-allene [3+2] cycloaddition.[78]

Recently, Fu et al. disclosed that some well-known chiral phosphine ligands (**1.58**, **1.59** and **1.62**) can function as organocatalysts to catalyze a set of reactions which have never been achieved before.[79]

Until now, a number of reactions have been covered by Lewis base catalysis including aldol reactions, Mannich reactions, Michael additions, Strecker reactions, kinetic resolutions of alcohols and amines, asymmetric protonations of ketenes, cycloadditions of ketenes, halogenations, Baylis-Hillman reactions, desymmetrizations of cyclic anhydrides, Steglich rearrangements, dynamic kinetic resolutions of azlactones, [3+2] annulations, acylations of silyl ketene acetals and silyl ketene imines, allylic substituations and [3+2] cycloadditions of allenic esters.

1.2.8 Miscellaneous Types

As the result of the exploration during the last two decades, organocatalysis has been developed into a highly diversified area. Continuous and intensive investigation in this area has generated some new activation modes.

Besides those organocatalysts mentioned previously, chiral organosulfides,[80] chiral ketones and chiral iminiums[81] have been discovered to accelerate asymmetric reactions. Although the scope of their applications is relatively narrow, some of them are quite useful. For instance, chiral ketone and iminium ion–catalyzed epoxidations are now one of the most significant methods to prepare chiral epoxides from olefins. In addition, chiral organosulfides provide a convenient catalytic approach to access chiral epoxides, aziridines and cyclopropanes.

New activation modes are always of significant interest to chemists. In contrast to organometallic chemistry, most organocatalytic reactions do not involve redox processes except some N-heterocyclic carbene catalyzed reactions, which greatly limited the development of this area. In 2007, MacMillan et al. presented a creative solution to this problem.[82] The new type of catalysis, SOMO activation, involves a reactive cation radical species which inverts the original reactivity of the enamine intermediate. This concept was further used to develop a series of asymmetric reactions,[83] which were unattainable by previous catalytic methods. In 2008, MacMillan et al. reported the direct asymmetric alkylation of aldehydes by merging photoredox catalysis with organocatalysis.[84] This visible light mediated catalysis provides a "green" way to activate substrates by reduction as well as by oxidation, which shows great potential to perform asymmetric catalysis in an environmentally friendly manner.

1.3 Objectives

As mentioned in the last section, enantioselective organocatalysis has emerged as a powerful synthetic tool in organic synthesis, providing a robust platform to construct diversified molecular architectures with chiral centers. During the period of 2000-2010, hundreds of processes have been discovered and some of them have already become classics in modern synthetic chemistry. However, many challenges still remain in this area. For instance, in most of the organo-catalyzed reactions, 5-10 mol% or even higher catalyst loadings are still required. Secondly, the activation provided by organocatalysis is still hard to compare with metal catalyzed reactions, although some breakthroughs addressing this issue were achieved recently.[82-84] In addition, further understanding and

elucidation of mechanisms and topology of privileged structures will be beneficial to the design of "minimized enzymes".

The main objective of this dissertation was to develop new organocatalyzed methodologies addressing the issues mentioned above. Another target was to establish some practical routes to access various chiral building blocks. I hope that these discoveries and achievements will shed some light on further developments in this area. Chapter II focuses on the development of catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes and α-ketoesters.[85, 86] Chapter III outlines the development of enantioselective Mannich reactions of α-isothiocyanato imides with activated imines and the asymmetric synthesis of α, β-diamino acid derivatives.[87] Lastly, in Chapter IV, the first catalytic enantioselective Friedländer condensation is described which provides access to quinolines and tacrines with remote stereogenic centers.

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Chapter II

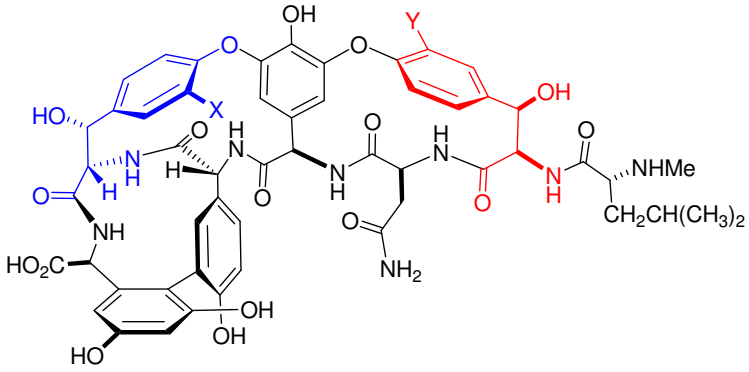
Catalytic Enantioselective Synthesis of β-Hydroxy-α-Amino Acid Derivatives

2.1 Background

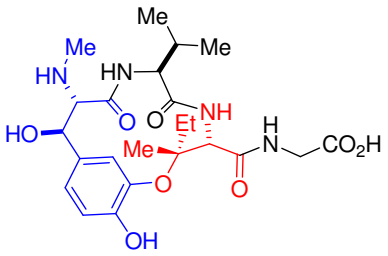
2.1.1 Significance of β-Hydroxy-α-Amino Acid Derivatives

Many biologically active natural products such as biphenomycin A,[1] cyclomarins,[2] exochelins,[3] polyoxins,[4] ustiloxins[5] and vancomycin[6] contain β-hydroxy-α-amino acids within their structural frameworks (Scheme 2.1).

Scheme 2.1 **Selected Natural Products Containing β-Hydroxy-α-Amino Acid Moiety**



2.1 X = Cl, Y = Cl **Vancomycin Aglycon**
2.2 X = H, Y = Cl **Eremomycin Aglycon**
2.3 X = H, Y = H **Orienticin C Aglycon**

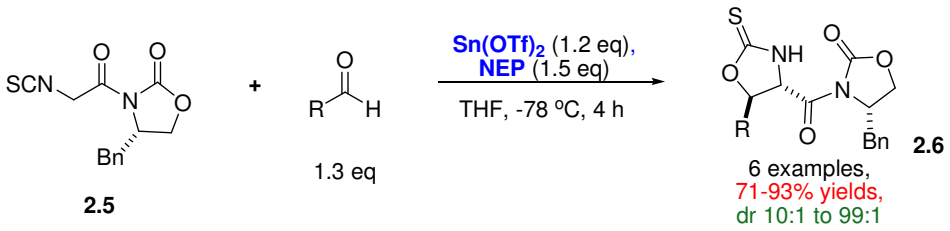


2.4 Ustiloxin D

The majority of methods currently available to synthesize β-hydroxy-α-amino acids rely on diastereoselective approaches, e.g. the use of chiral auxiliaries (Scheme 2.2).[7–9]

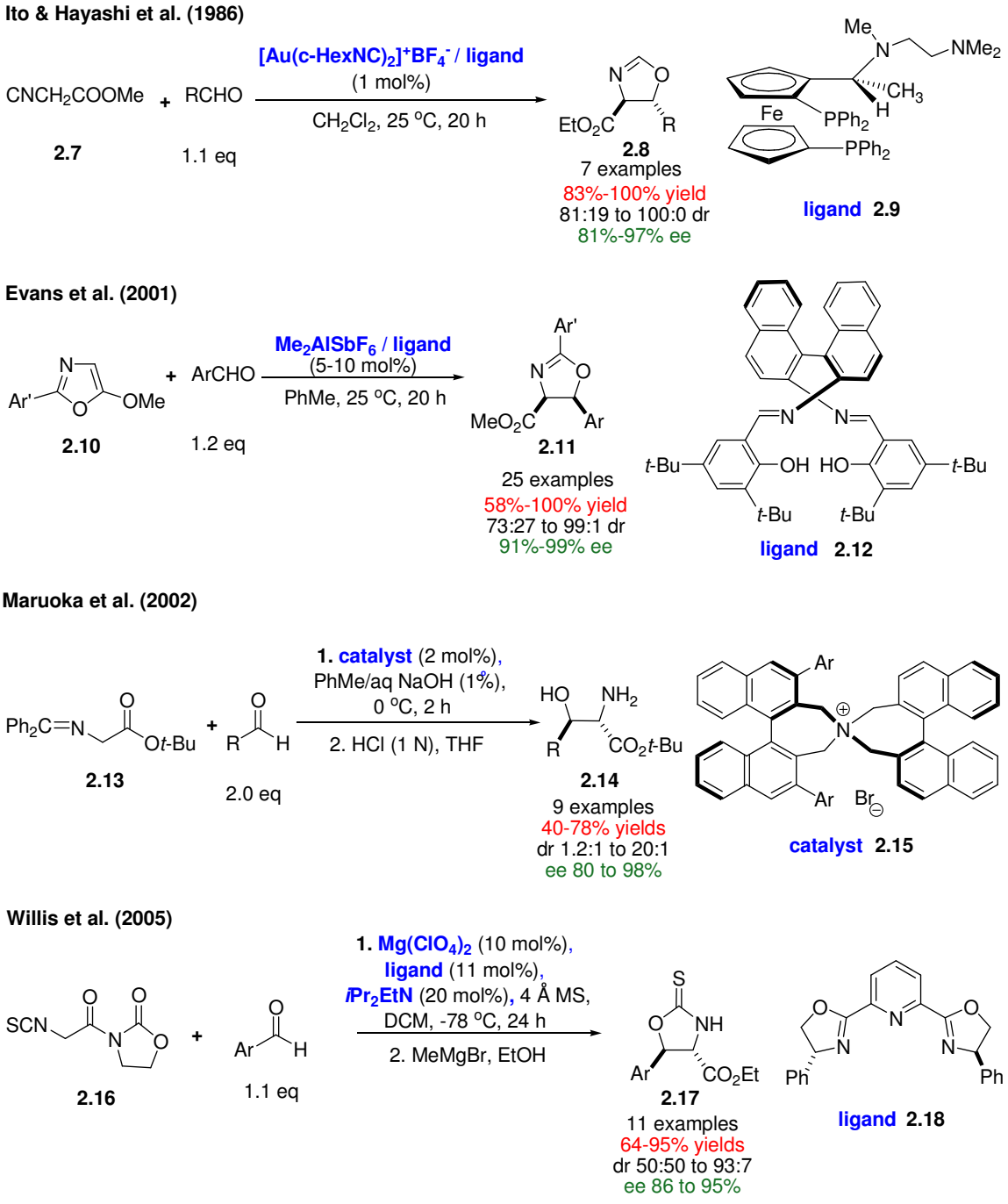
The development of highly efficient catalytic enantioselective variants remains challenging[10–15] with some methods requiring the use of preformed enolate equivalents.[16]

Scheme 2.2 **Diastereoselective Method Using Evans Auxiliary**



Among the methods available to access this building block, direct aldol reactions of glycine equivalents with aldehydes represent a convenient method to obtain β-hydroxy-α-amino acids (Scheme 2.3). In 1986, Ito and Hayashi et al. reported a gold complex-catalyzed asymmetric aldol reaction of α-isocyano acetates **2.7** with aldehydes.[14a] Although excellent ee's were obtained in this elegant example, the use of the costly chiral ferrocene ligand **2.9** and the precious metal limited the application of this methodology. In 1999 and 2001, Suga and Ibata et al. and Evans et al. discovered the enantioselective aldol reactions of 5-alkoxyoxazoles **2.10** with aldehydes.[14b, 14c] Interestingly, *anti* products **2.11** were obtained in this case. In 2002, Maruoka et al. utilized their chiral phase transfer catalysts **2.15** to catalyze the asymmetric aldol reactions of benzophenone imine protected glycine esters **2.13** with aldehydes.[15a] However, the reaction scope was relatively limited. In 2005, Willis et al. developed the asymmetric aldol reaction of α-isothiocyanato imide **2.16** with aldehydes,[10] which is regarded as a catalytic version of the corresponding Evans aldol reaction.[9a]

Scheme 2.3 Direct Aldol Reactions of Glycine Equivalents with Aldehydes



2.2 Proposal and Objective

The last two decades witnessed the explosive development of organocatalyzed enantioselective processes. Compared to metal-catalyzed reactions, organocatalysis provides some unique advantages including relatively mild reaction conditions and less expensive catalysts. Therefore, it is reasonable to hypothesize that the organocatalytic aldol reactions of glycine equivalents and aldehydes may provide a convenient method to access chiral β-hydroxy-α-amino acids. In the following part of this chapter, I will report our efforts towards the asymmetric synthesis of β-hydroxy-α-amino acids.

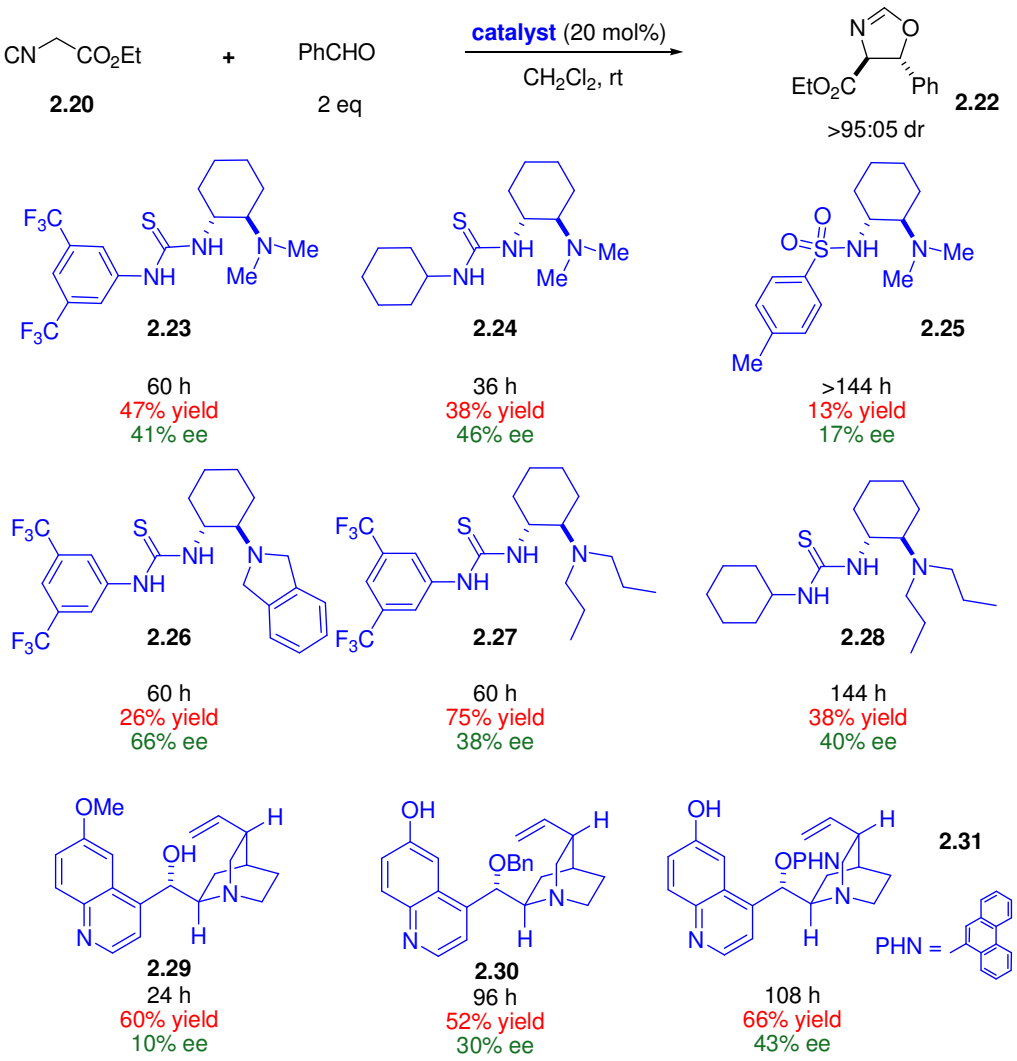
2.3 Results and Discussions

2.3.1 General Considerations

With the goal of developing an organocatalytic approach to β-hydroxy-α-amino acids, we thought that some known glycine equivalents could be the ideal reaction partner including α-isocyano acetates **2.7**, 5-alkoxyoxazoles **2.10**, benzophenone imines of glycine esters **2.13** and α-isothiocyanato esters **2.19**. Finally, commercially available ethyl α-isocyano acetate **2.20** and ethyl α-isothiocyanato ester **2.21** were selected for the evaluation of catalysts. In addition, the corresponding imides were also considered as suitable candidates since they provide different modes of coordination and further modulate the pKa of the substrates.

2.3.2 Preliminary Investigation on Aldol Reactions of α-Isocyano Acetates with Benzaldehydes

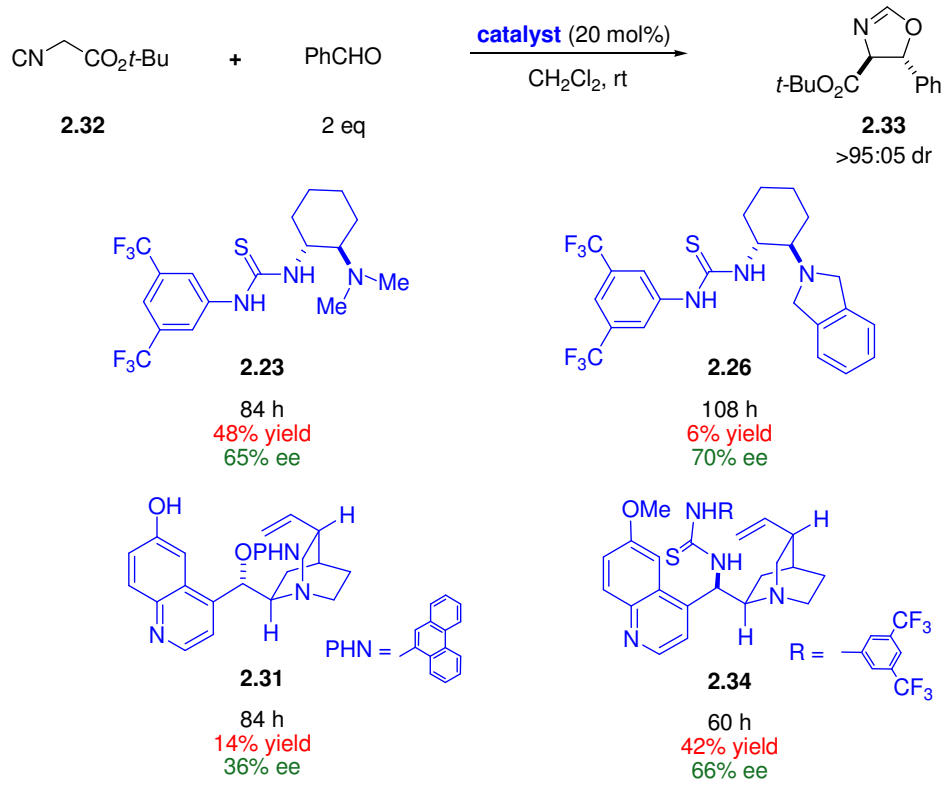
Scheme 2.4 **Aldol Reactions of Ethyl α-Isocyano Acetates with Benzaldehydes**



We initiated our studies by evaluating the reaction between commercially available ethyl α-isocyano acetate and benzaldehyde using readily available organocatalysts. Only modest ee's and yields were obtained with a series of bifunctional organocatalysts under a variety of conditions. Experiments revealed that the bulkier *tert*-butyl ester gave better selectivity than the ethyl ester. However, the reactivity of this substrate is low and long reaction times are required for the completion of reactions. Nevertheless, these

experimental results indicated that bifunctional catalysts derived from *trans*-cyclohexanediamine have a great potential in this type of reaction since they can be modulated in both parts (tertiary amine and thiourea).

Scheme 2.5 **Aldol Reactions of *t*-Butyl α-Isocyano Acetates with Benzaldehydes**



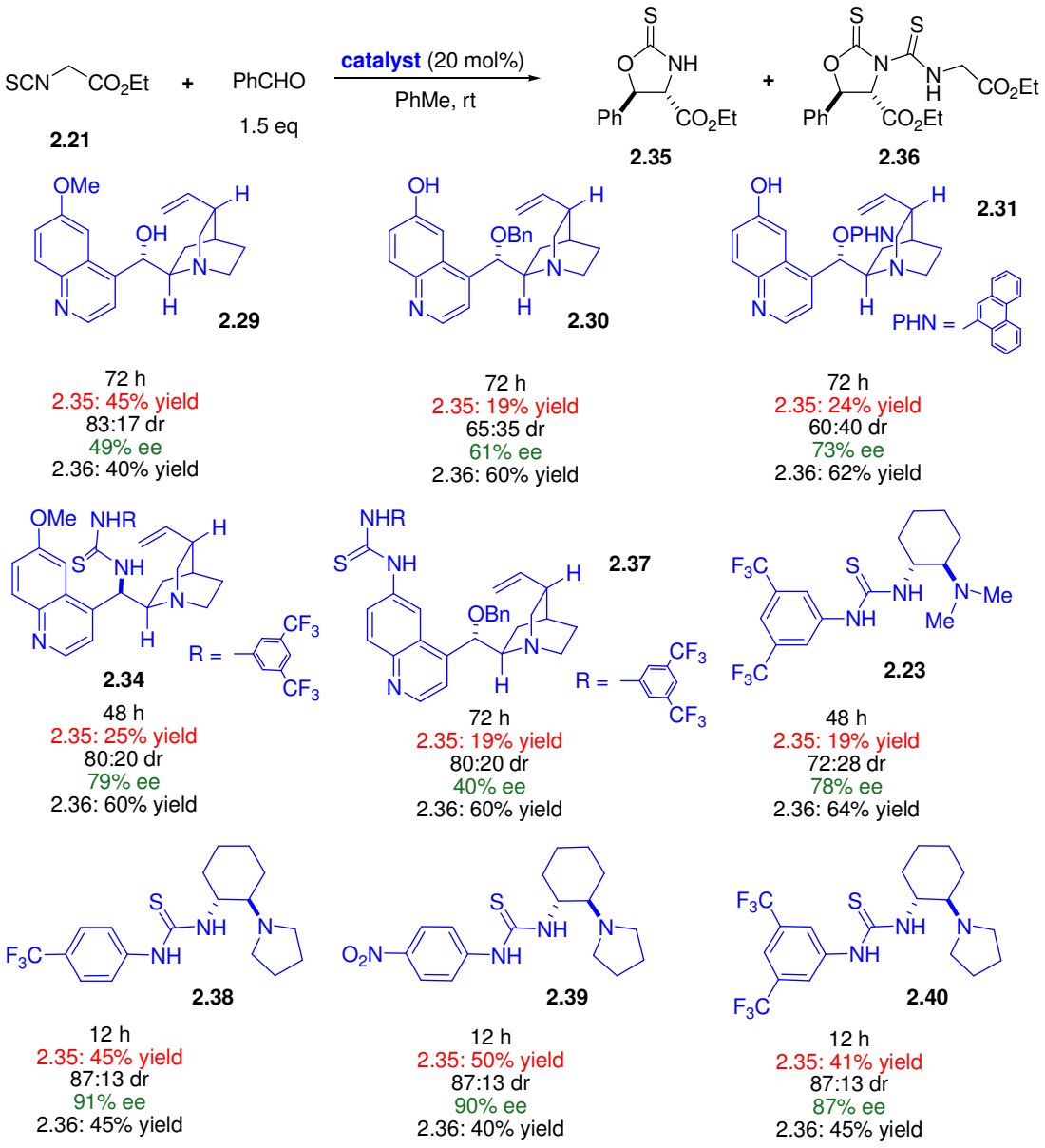
2.3.3 Development of Organocatalyzed Aldol Reactions of α-Isothiocyanato Imides and Esters with Aldehydes

2.3.3.1 Reaction Development

Encouraged with the investigation on aldol reactions of α-isocyano acetates with benzaldehydes, we turned to evaluate more active substrates. α-Isothiocyanato acetate has a lower pKa value and thus could have higher reactivity than the corresponding

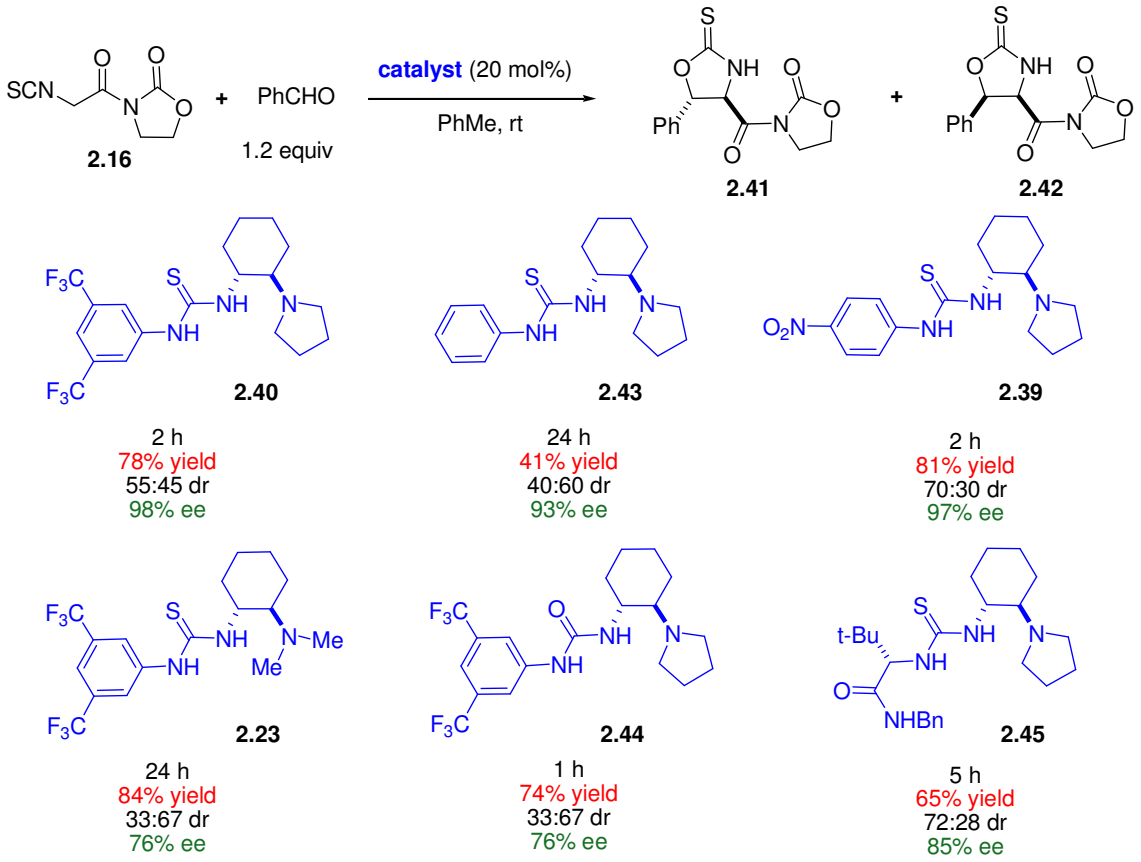
isocyano acetate. The reaction between ethyl α-isothiocyanato acetate **2.21** and benzaldehyde was tested with quinidine **2.29** as the catalyst. In addition to the desired product **2.35**, (obtained in low diastereo-and enantioselectivity), compound **2.36** was obtained as the major product resulting from the addition of primary product **2.35** to

Scheme 2.6 **Aldol Reactions of Ethyl α-Isothiocyanato Acetates with Benzaldehydes**



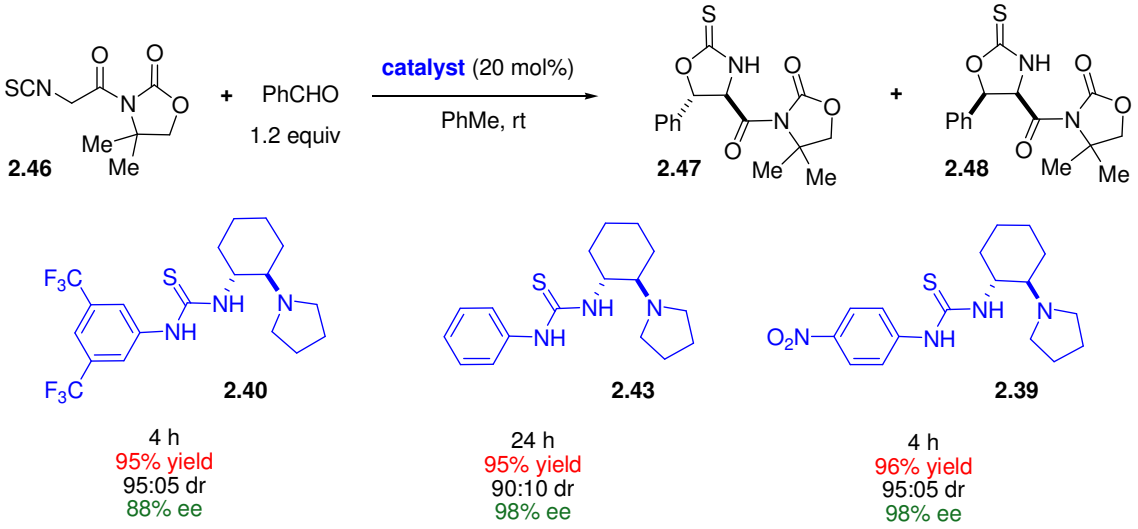
another equivalent of **2.21**. Other readily available organocatalysts[18] were subsequently evaluated (Scheme 2.6). Stereoselectivities were promising in some cases but **2.36** was consistently obtained as the major product. Control experiments revealed that the presence of catalyst is required for the formation of **2.36** from **2.35** and **2.21**. We speculated that the reverse reaction may also be catalyzed by **2.40**. Longer reaction times increase the yield of **2.35** at the expense of **2.36**, but this process was found to be too slow to be practical. When other α-isothiocyanato esters (Me, *i*-Pr, *t*-Bu and Bn) were used, **2.36** was again obtained as the major product.

Scheme 2.7 **Aldol Reactions of α-Isothiocyanato Imides with Benzaldehydes**



The experimental results shown in Scheme 2.6 indicated that the pyrrolidine ring on the catalysts is crucial for both reactivity and selectivity. Therefore, these catalysts were further tested in the reactions of imide **2.16** with benzaldehyde (Scheme 2.7). The yield of products could be dramatically increased with imide **2.16**, the substrate previously used by Willis and coworkers in their enantioselective metal catalyzed approach.[10] Formation of undesired product was almost completely suppressed but the expected product (**2.41** and **2.42**) was obtained in low diastereoselectivity slightly favoring the *cis* isomer **2.42**. A poorly defined enolate geometry might be responsible for the low levels of diastereoselectivity. Greatly enhanced diastereomeric ratios were observed with the dimethyl analogue **2.46**.[19] Evaluation of different catalysts revealed that **2.39** provides product **2.47** in excellent yield and with high levels of selectivity in a relatively short reaction time (Scheme 2.8).

Scheme 2.8 **Aldol Reactions of α-Isothiocyanato Dimethyl Imides with Benzaldehydes**



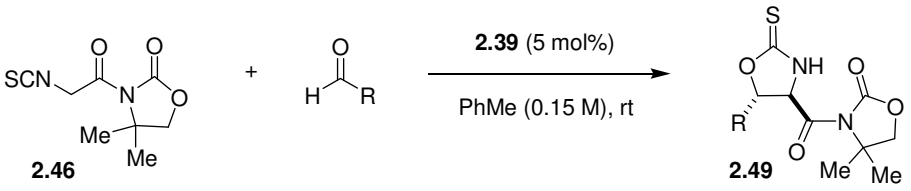
Further optimization allowed for reducing the catalyst loading to 5 mol% and the equivalents of aldehyde to 1.2. Virtually no difference was seen between reactions performed under anhydrous conditions and reactions run simply in capped flasks with HPLC grade toluene and without rigorous exclusion of air or moisture.

2.3.3.2 Scope of the Reaction

The substrate scope was evaluated using these operationally convenient conditions (Table 2.1). Several electron-rich and electron-poor aromatic aldehydes with different substitution patterns gave rise to products that were generally obtained in good yields and with high levels of diastereo- and enantioselectivity. Heteroaromatic systems were also viable substrates as were α,β-unsaturated aldehydes. Aliphatic aldehydes were found to be less reactive and gave rise to products in lower yields and selectivities.

We observed that reaction times are significantly reduced in instances where products (partially) precipitate in the course of the reaction. The minimization of nonproductive product-catalyst interactions could account for this finding which provides an opportunity for practical product recovery. A reaction between benzaldehyde and **2.46** gave rise to analytically pure product **2.47** in 67% yield (dr > 99:01, 98% ee) when worked up through a simple filtration rather than by the usual chromatographic purification. Additional product **2.47** was isolated from the filtrate in 27% yield (dr = 78:22, 77% ee).

Table 2.1 **Scope of the Reaction**



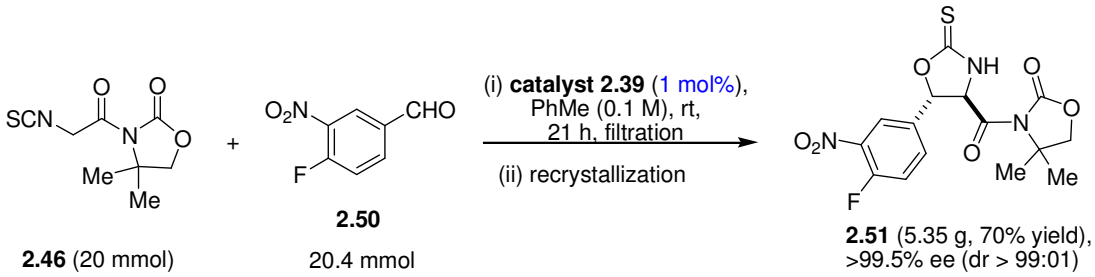
Entry	R	Product	Time [h]	Yield [%][b]	dr[c]	ee [%]
1	Ph	**2.47**[ppt]	4	99	93:07	94
2	4-NO_2-C_6H_4	**2.49a**[ppt]	2	97	95:05	93
3	4-Br-C_6H_4	**2.49b**[ppt]	2	91	95:05	94
4	4-F-C_6H_4	**2.49c**[ppt]	8	97	95:05	94
5	4-MeO-C_6H_4	**2.49d**[ppt]	3	76	97:03	96
6	4-Me-C_6H_4	**2.49e**[ppt]	16	94	94:06	94
7	3-Br-C_6H_4	**2.49f**[ppt]	3	88	88:12	92
8	3-Me-C_6H_4	**2.49g**[ppt]	12	90	94:06	93
9	3-MeO-C_6H_4	**2.49h**[ppt]	6	87	93:07	92
10[d]	2-NO_2-C_6H_4	**2.49i**[ppt]	24	97	98:02	90
11[d,e]	2-Cl-C_6H_4	**2.49j**	48	86	89:11	93
12	2-F-C_6H_3	**2.49k**	20	80	86:14	90
13	2-Me-C_6H_3	**2.49l**	48	80	83:17	90
14	1-naphthyl	**2.49m**	72	60	93:07	94
15	2-naphthyl	**2.49n**[ppt]	2	97	94:06	91
16	2-thiophenyl	**2.49o**[ppt]	12	86	87:13	91
17	C_6F_5	**2.49p**[ppt]	2	83	90:10	90
18	cinnamyl	**2.49q**[ppt]	24	85	85:15	93
19	CH_2CH_2Ph	**2.49r**[ppt]	24	70	90:10	81
20	*n*-Bu	**2.49s**[ppt]	72	55	82:18	82

[a] Reactions were run on a 1 mmol scale using 1.2 equiv of aldehyde. The enantiomeric excess was determined by HPLC analysis. ppt: product partially precipitated in course of the reaction. [b] combined yield of both diastereomers. [c] *trans*:*cis*, determined by ^{1}H-NMR. [d] reaction was performed at 0 °C. [e] performed at 0.1 M concentration.

2.3.3.3 Scale-up Synthesis of Protected β-Hydroxy-α-Amino Acid

To evaluate the applicability of our method, compound **2.51** was prepared on a larger scale (Scheme 2.9). Using only 1 mol% of catalyst **2.39**, product **2.51** was obtained in good yield and with excellent levels of diastereo- and enantioselectivity without the need for chromatographic purification. The protected β-hydroxy-α-amino acid **2.51** is related to intermediates previously used in the synthesis of vancomycin[20] and ristocetin.[21]

Scheme 2.9 **Gram-scale Synthesis of Protected β-Hydroxy-α-Amino Acid**



2.46 (20 mmol) + **2.50** 20.4 mmol → **2.51** (5.35 g, 70% yield), >99.5% ee (dr > 99:01)

2.3.3.4 Summary

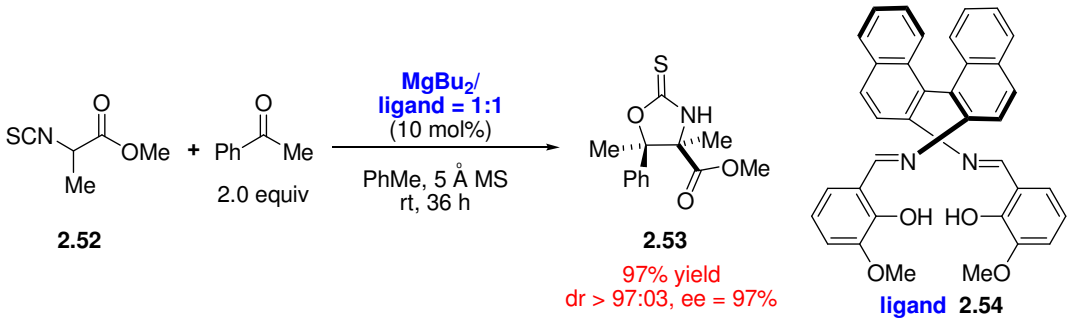
In summary, we have introduced a mild and facile method for catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes. Low catalyst loadings and operationally convenient conditions make this method attractive for the synthesis of various protected *syn* β-hydroxy-α-amino acids.

2.3.4 Development of Organocatalyzed Aldol Reactions of α-Isothiocyanato Imides and Esters with α-Ketoesters

2.3.4.1 Reaction Development

Encouraged with our success on catalytic enantioselective aldol reactions between α-isothiocyanato imide **2.46** and aldehydes[22], we decided to expand this methodology to other substrates. The asymmetric aldol reaction of glycine equivalents and ketones is of significant value since the reaction yields protected β-hydroxy-α-amino acids with a tetra-substituted carbon center. Although a number of catalytic enantioselective methods for the addition of glycine equivalents to aldehydes have been reported,[10–16, 23] the corresponding reaction with ketones as electrophiles has seen much less development.[24] Recently, Shibasaki et al. reported catalytic enantioselective additions of α-isothiocyanato esters **2.52** to aryl alkyl ketones, employing chiral magnesium Schiff base catalysts **2.54**.[24]

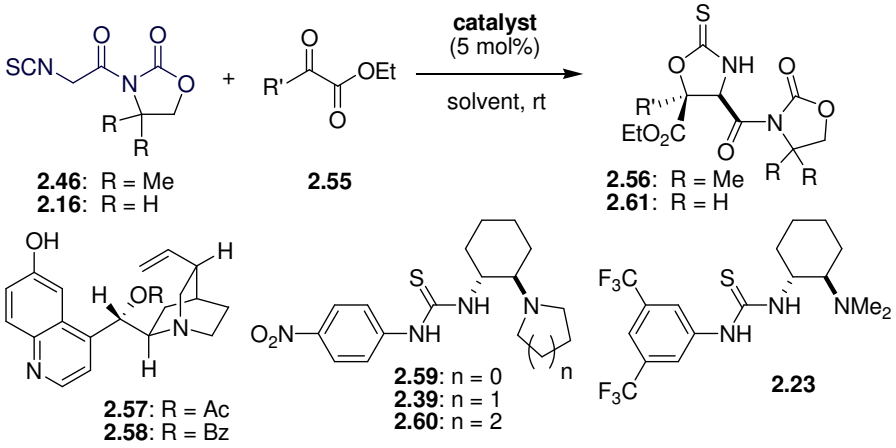
Scheme 2.10 **Aldol Reactions of α-Isothiocyanato Esters with Ketones**



The bifunctional thiourea compound **2.39** proved to be an excellent catalyst for the reaction of imide and aldehydes, providing products **2.49** with high levels of stereoselectivity. However, our attempts using this catalyst for the reaction of imide with simple ketone substrates (acetone, acetophenone and trifluoroacetophenone) were unsuccessful. The lack of reactivity seen for these substrates suggested that more reactive substrates are required. Therefore, we turned to evaluate the reactions between α-isothiocyanato imides **2.16** and **2.46** and highly activated α-ketoesters

2.55. A series of organocatalysts were investigated and the results are summarized in Table 2.2. Different catalysts readily promoted reactions between imides **2.16** and **2.46** and α-ketoesters (ethyl pyruvate **2.55o** or ethyl 2-oxo-2-phenylacetate **2.55a**) in toluene at room temperature. The more sterically encumbered imide **2.46** gave rise to the formation of products with higher levels of diastereo- and enantioselectivity. Amine-thiourea **2.39** was identified as the most efficient and selective catalyst. An evaluation of different solvents revealed methyl *tert*-butyl ether (MTBE) to be superior to toluene with regard to overall efficiency. The best result for the reaction of imide **2.46** and ethyl 2-oxo-2-phenylacetate **2.55a** was obtained in MTBE at 0.15 M concentration, using 5 mol% of catalyst **2.39** (entry 21). In this instance, the reaction went to completion within 3 hours and product **2.56a** was obtained in 93% yield (dr = 80:20; 95% ee). Reactions conducted at lower (entry 22) or higher concentration (entry 23) gave rise to poorer results. Moreover, the use of methyl or *tert*-butyl α-ketoesters yielded inferior results.

Table 2.2 **Optimization of Reaction Parameters**[a]

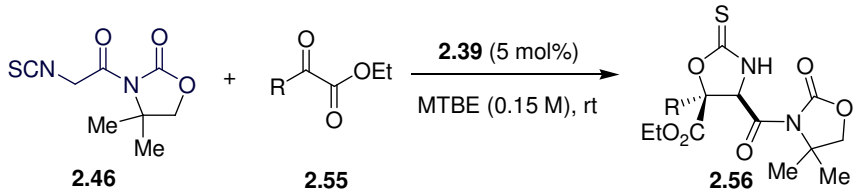


Entry	Catalyst	Sm	R'	Solvent	Time [h]	Yield [%][b]	dr [%][c]	ee [%][d]
1	**2.39**	**2.16**	Me	PhMe	1.5	85	75:25	75
2	**2.23**	**2.16**	Me	PhMe	2	92	75:25	72
3	**2.57**	**2.16**	Me	PhMe	48	81	80:20	74
4	**2.58**	**2.16**	Me	PhMe	48	80	75:25	71
5	**2.59**	**2.16**	Me	PhMe	3	73	75:25	61
6	**2.60**	**2.16**	Me	PhMe	1	76	75:25	72
7	**2.39**	**2.16**	Ph	PhMe	3	85	75:25	86
8	**2.23**	**2.16**	Ph	PhMe	2	98	71:29	74
9	**2.57**	**2.16**	Ph	PhMe	36	81	75:25	72
10	**2.39**	**2.46**	Ph	PhMe	2	93	80:20	90
11	**2.39**	**2.46**	Me	PhMe	4	99	83:17	79
12	**2.39**	**2.16**	Ph	Ether	8	50	67:33	60
13	**2.39**	**2.16**	Ph	xylenes	5	60	67:33	69
14	**2.39**	**2.16**	Ph	$CHCl_3$	12	70	67:33	74
15	**2.39**	**2.16**	Ph	CH_2Cl_2	12	70	67:33	84
16	**2.39**	**2.16**	Ph	THF	7	95	67:33	77
17	**2.39**	**2.16**	Ph	CPME	4	93	67:33	83
18	**2.39**	**2.16**	Me	MTBE	1.5	99	75:25	74
19	**2.39**	**2.16**	Me	MTBE	4.5	95	88:12	70
20	**2.39**	**2.16**	Ph	MTBE	3	99	71:29	92
21	**2.39**	**2.46**	Ph	MTBE	3	93	80:20	95
22[e]	**2.39**	**2.46**	Ph	MTBE	9	71	83:17	90
23[f]	**2.39**	**2.46**	Ph	MTBE	9	71	83:17	81

[a] Reactions were performed at rt on a 0.17 mmol scale in solvent (0.15 M) using 1.1 equiv of ketoester. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis. [b] Combined yield of both diastereomers. [c] Determined by ^{1}H-NMR. [d] ee of major diastereomer shown. [e] Run at 0.1 M concentration. [f] Run at 0.25 M concentration; CPME = cyclopentyl methyl ether; MTBE = methyl *tert*-butyl ether.

2.3.4.2 Substrate Scope

Table 2.3 **Scope of the Reaction**[a]



entry	R	product	time [h]	yield [%][b]	dr[c]	ee [%]
1	Ph	**2.56a**	3	93	80:20	95
2	4-OMe-C_6H_4	**2.5b**	12	80	70:30	94
3	4-Me-C_6H_4	**2.56c**	7	79	75:25	92
4	4-Br-C_6H_4	**2.56d**	2	95	83:17	97
5	4-Cl-C_6H_4	**2.56e**	2.5	99	83:17	98
6	4-CF_3-C_6H_4	**2.56f**	12	95	85:15	97
7	4-*t*-Bu-C_6H_4	**2.56g**	7	90	80:20	96
8	3-OMe-C_6H_4	**2.56h**	48	82	70:30	96
9	3,4-Cl_2-C_6H_3	**2.56i**	1.5	99	83:17	98
10	3,5-F_2-C_6H_3	**2.56j**	2	96	80:20	97
11	2,4-Cl_2-C_6H_3	**2.56k**	8	86	80:20	93
12	2-naphthyl	**2.56l**	5	93	80:20	97
13	2-Cl-C_6H_4	**2.56m**	8	70	75:25	87
14	2-thienyl	**2.56n**	5	95	75:25	92
15[d]	Me	**2.56o**	4	99	83:17	79

[a] Reactions were run at rt on a 0.5 mmol scale using 1.1 equiv of the ketoester. The ee's were determined by HPLC analysis. [b] Combined yield of both diastereomers. [c] Determined by ^{1}H-NMR. [d] Reaction was performed in PhMe.

With the optimized reaction conditions in hand, a series of different α-ketoesters was evaluated (Table 2.3). Electron rich and electron poor aromatic substituents with

different substitution patterns provided products in generally good yields and with high enantioselectivities and moderate diastereoselectivities (entries 1–13). Heteroaromatic α-ketoesters were also viable substrates (entry 14).

As is customary, for all examples reported in Table 2.3, the yields and stereoselectivities correspond to all of the obtained product (solution and solid phase combined). Gratifyingly, in some instances, product precipitation offers the opportunity to directly obtain highly diastereomerically and enantiomerically enriched products by simple filtration. For instance, when a reaction leading to product **2.56e** was worked up by filtration, followed by washing with a small amount of MTBE, this product was obtained in 66% yield as diastereomerically and enantiomerically pure material (within the limits of HPLC detection).

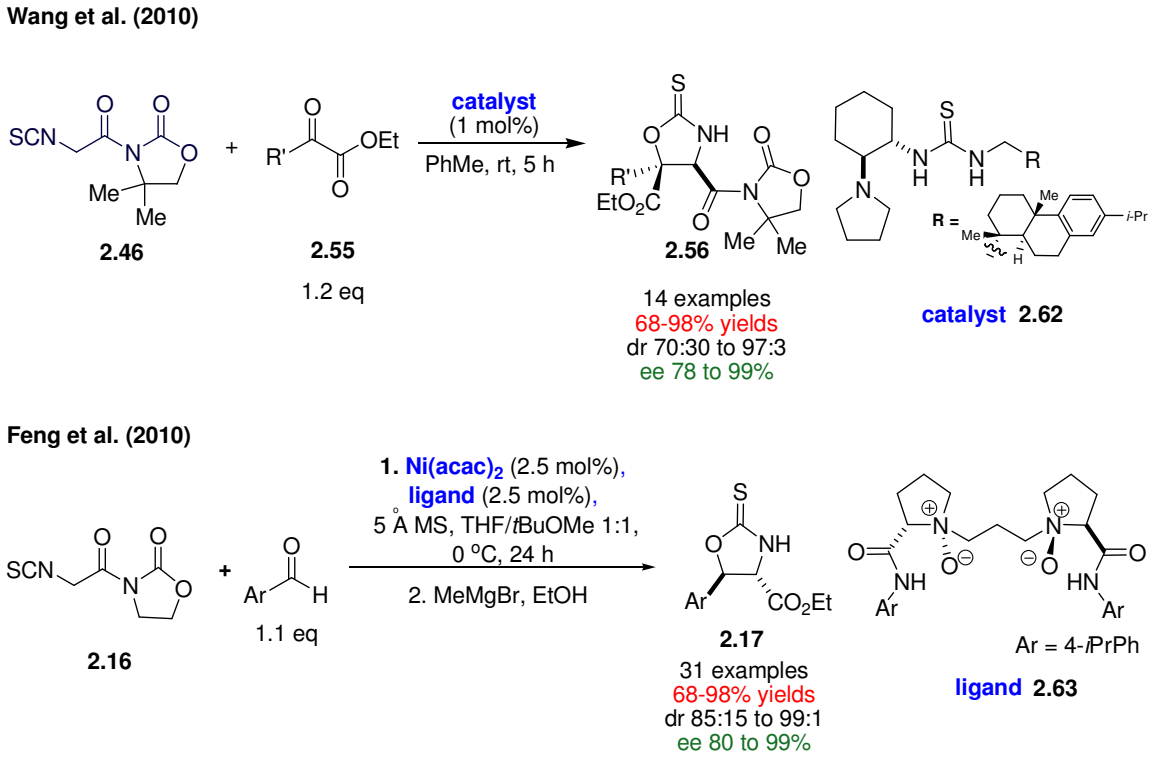
2.3.4.3 Summary

In summary, we have introduced a mild and facile method for catalytic enantioselective aldol additions of α-isothiocyanato imides to α-ketoesters using a readily available bifunctional thiourea catalyst that operates under mild reaction conditions.

2.3.5 Latest Progress in this Area

Recently, Wang and co-workers have reported catalytic enantioselective additions of α-isothiocyanato imides to α-ketoesters, using a rosin-derived amine-thiourea catalyst.[25] Most recently, Feng and co-workers reported catalytic enantioselective additions of α-isothiocyanato imides to aldehydes,[26] using a nickel complex.

Scheme 2.11 **Recent Catalytic Methods for Chiral β-Hydroxy-α-Amino Acids**



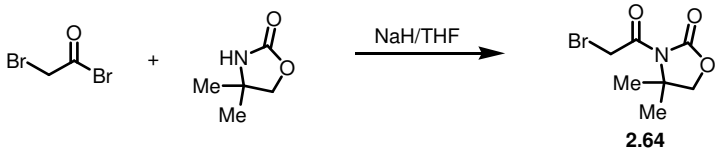
2.4 Experimental Section

2.4.1 Preparation of Substrates and Precursors

Substrate **2.46** was prepared based on the procedures below. Substrate 2**.16** was prepared in a similar manner as **2.46**.

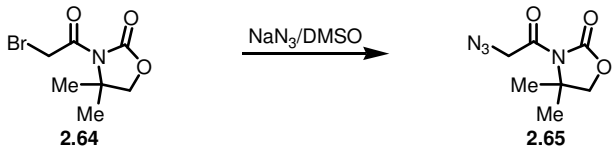
The α-ketoesters **2.55** were prepared according to literatures procedures.[27]

3-(2-bromoacetyl)-4,4-dimethyloxazolidin-2-one (2.64)[28]



4,4-Dimethyloxazolidin-2-one[27] (1.15 g, 10 mmol) was added to a suspension of sodium hydride (0.24 g, 10 mmol) in THF (100 mL) and the mixture was stirred at room temperature for 8 h. After cooling to 0 ^{o}C, bromoacetyl bromide (0.965 mL, 11 mmol) was added to the mixture and the stirring was continued for 1.5 h at the same temperature. The mixture was diluted with saturated aqueous potassium dihydrogen phosphate solution and extracted with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Hexane/EtOAc 4:1 to 2:1 v:v) to give as a pale yellow solid **2.64** (1.77 g, 75% yield). mp 55-57 ^{o}C (EtOAc/Hexane); Rf 0.70 (Hexane/EtOAc 1:1 v/v); IR (KBr) 3007, 2977, 1772, 1718, 1489, 1459, 1397, 1320, 1213, 1171, 1101, 1031, 964, 891, 763, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (s, 2H), 4.08 (s, 2H), 1.58 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 153.8, 75.8, 61.0, 30.4, 24.7; *m/z* (CI-MS) 236(^{79}Br), 238(^{81}Br) $[MH]^{+}$.

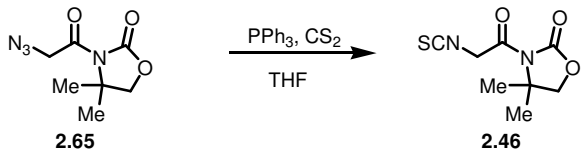
3-(2-azidoacetyl)-4,4-dimethyloxazolidin-2-one (2.65)



Sodium azide(15.60 g, 0.24 mol) was added to a solution of the bromoimide **2.64** (14.16 g, 0.06 mol) in DMSO (100 mL) at room temperature. The reaction mixture was stirred for 1 h and diluted with 250 mL water. The resulting mixture was extracted with

EtOAc (4 x 200 mL). The organic layer was combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Colorless crystals **2.65** (10.94 g, 92% yield) were obtained by flash chromatograghy (Hexane/EtOAc 4:1 to 2:1 v:v). mp 34-35 ^oC (EtOAc/Hexane); Rf 0.64 (Hexane/EtOAc 1:1 v/v); IR (KBr) 3008, 2980, 2947, 2114, 1781, 1709, 1383, 1368, 1312, 1291, 1243, 1179, 1103, 1035, 910, 766, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.35 (s, 2H), 4.03 (s, 2H), 1.54 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 153.8, 75.9, 60.7, 53.4, 24.6; *m/z* (CI-MS) 199 $[MH]^+$.

3-(2-isothiocyanatoacetyl)-4,4-dimethyloxazolidin-2-one (2.46)[9a, 10]

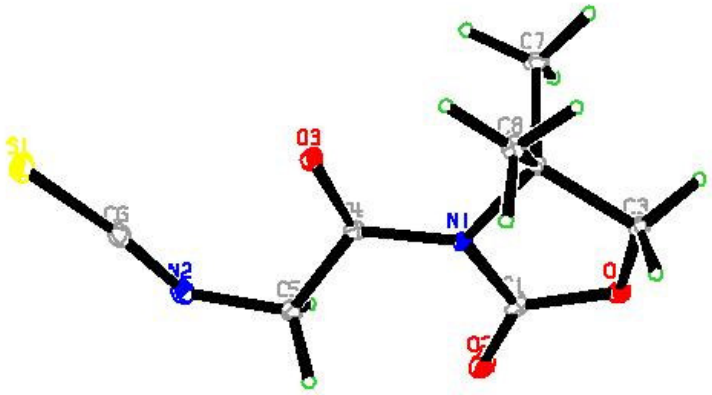


2.65 **2.46**

Triphenylphosphine (18.37 g, 70.0 mmol) was added to a solution of the azidoimide **2.65** (12.62 g, 63.7 mmol) in THF (80 mL) and CS_2 (80 mL) in a 1000 mL round bottom flask fitted with a condenser. After evolution of nitrogen, the solution gently self-refluxed and was left overnight. After concentration under reduced pressure, the residue was purified by flash chromatography (CH_2Cl_2/Hexane 1:1 v:v to CH_2Cl_2) to yield **2.46** as a white solid (10.23 g, 75% yield). mp 106-108 ^oC (CH_2Cl_2/Hexane); Rf 0.57 (Hexane/EtOAc 1:1 v/v); IR (KBr) 2978, 2256, 2048, 1776, 1720, 1397, 1378, 1363, 1311, 1249, 1187, 1091, 1024, 930, 767, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 2H), 4.12 (s, 2H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 153.9, 139.5, 76.4, 61.2, 50.5, 25.0; *m/z* (ESI-MS) 215.0 $[M+H]^+$, 237.1 $[MNa]^+$.

The title compound was further characterized by X-ray crystallography.

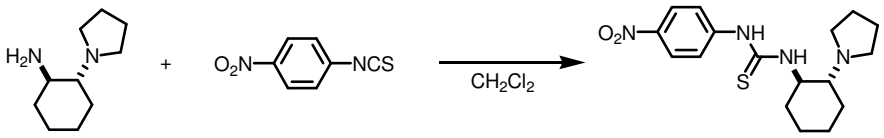
Figure 2.1 **Crystal Structure of Compound 2.46**



2.4.2 Preparation of Catalysts

The catalysts **2.23-2.31**, **2.34**, **2.37**, **2.57** and **2.58** were prepared according to literature methods.[18a, 18b,1 8f, 18g, 29]

1-(4-nitrophenyl)-3-((1R,2R)-2-(pyrrolidin-1-yl)cyclohexyl)thiourea (2.39)



2.39

1-Isothiocyanato-4-nitrobenzene (1.13 g, 6.24 mmol, 1.0 equiv) was added to a solution of (1R,2R)-2-(pyrrolidin-1-yl)cyclohexanamine[30] (1.05 g, 6.24 mmol, 1.0 equiv) in dichloromethane (25 mL) at room temperature. The resulting solution was stirred overnight, then concentrated to ~4 mL in vacuo and loaded onto a silica gel column directly and chromatographed (EtOAc:MeOH:NH_4OH=100:15:1 to 100:20:1) to afford 1-(4-nitrophenyl)-3-((1R,2R)-2-(pyrrolidin-1-yl)cyclohexyl)thiourea (1.84 g, 85% yield) as

an orange solid. mp 80-82 ^{o}C (EtOAc/Hexane); Rf 0.15 (MeOH/EtOAc 1:1 v/v); $[\alpha]_D^{20}$ – 12.0^{o} (c 1.0, CH_2Cl_2); IR (KBr) 3221, 2931, 2856, 1596, 1507, 1330, 1252, 1176, 1110, 850, 748 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.07 (s, 1H), 8.38 (d, *J* = 7.5 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 2H), 7.82 (d, *J* = 9.2 Hz, 2H), 4.18(br, 1H), 2.53-2.86 (comp, 5H), 2.15 (app d, *J* = 8.9 Hz, 1H), 1.81 (app d, *J* = 11.5 Hz, 1H), 1.65-1.78 (comp, 5H), 1.56-1.65 (m, 1H), 1.15-1.46 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 178.5, 146.6, 141.3, 124.6, 119.4, 60.5, 55.8, 47.2, 30.4, 23.9, 23.7, 23.5, 22.4; *m/z* (ESI-MS) 349.2 $[MH]^+$.

The catalysts **2.38**, **2.40**, **2.43-2.45** and **2.59-2.60** were prepared in a similar manner as **2.39**.

2.4.3 General Procedure for the Catalytic Aldol Reaction Between 2.46 and Aldehyde

Catalyst **2.39** (17.5 mg, 0.05 mmol), 3-(2-isothiocyanatoacetyl)-4,4-dimethyloxazolidin-2-one **2.46** (214 mg, 1.00 mmol) and the corresponding aldehyde (1.20 mmol) were dissolved in toluene (6.67 mL) at room temperature. The reaction progress was monitored by TLC analysis. Upon consumption of **2.46**, the crude reaction mixture was applied to silica gel and the mixture of diastereomers were obtained by flash chromatography (CH_2Cl_2/EtOAc 100:2 v/v).

The mixture of diastereomers was dissolved in dry THF (20 mL) and cooled to 0 °C. A solution of methyl magnesium chloride (1.2 eq., 3M in THF) in ethanol (8 mL) at 0 °C was added *via* syringe. After 3 min the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (8 mL). The mixture was concentrated in vacuo, taken up in

aqueous HCl (1M, 16 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic portions were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc 100:2 v/v) to obtain the corresponding ethyl ester as a solid or an oil.

The absolute configuration of the 3-methoxy benzaldehyde adduct **2.66h** was established by X-ray crystallography; the remaining adducts are assigned by analogy or compared with the optical rotations in the literature.[10]

2.4.4 General Procedure for Catalytic Aldol reaction between isothiocyanates and α-ketoesters

α-Keto esters and catalyst were dissolved in anhydrous methyl *t*-butyl ether. The reaction progress was monitored by TLC analysis. Upon consumption of the α-ketoesters the solvent was removed in vacuo and applied to silica gel to separate the diastereomers.

The absolute configuration of **2.56e** was established by X-Ray Crystallography; the remaining adducts were assigned by analogy.

2.4.5 Preparation Procedures for Racemic Samples

Racemic compounds were prepared either by using DABCO/toluene or the literature method.[31]

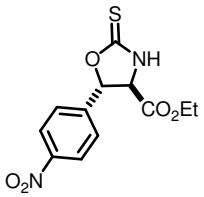
2.4.6 Product Characterization Data

4,4-dimethyl-3-((4R,5S)-5-phenyl-2-thioxooxazolidine-4-carbonyl)oxazolidin-2-one (2.47): Following the general procedure, compound **2.47** was obtained as white crystals in 99% yield (318 mg). mp 154-156 ^{o}C (EtOAc/Hexane); Rf 0.32 (CH_2Cl_2/EtOAc 50:1 v/v); $[\alpha]_D^{20}$ –77.2^{o} (c 1.0, CH_2Cl_2); IR (KBr) 3374, 3017, 2978, 2934, 1779, 1686, 1487, 1376, 1339, 1250, 1178, 1099, 1026, 951 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (br, s, 1H), 7.45-7.35 (comp, 5H), 6.31 (d, *J* = 5.0 Hz, 1H), 5.10 (d, *J* = 5.0 Hz, 1H), 4.17 (d, *J* = 8.5 Hz, 1H), 4.12 (d, *J* = 8.5 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 167.2, 154.5, 137.0, 129.8, 129.3, 126.3, 84.6, 76.4, 66.4, 61.7, 24.8, 24.5; *m/z* (ESI-MS) 321.1 $[MH]^+$.

(4R,5S)-ethyl 5-phenyl-2-thioxooxazolidine-4-carboxylate (2.35): Following the general procedure, compound **2.35** was obtained as a colorless oil in 89% yield (224 mg). Rf 0.33 (CH_2Cl_2/EtOAc 100:2 v/v); (R,S,) $[\alpha]_D^{20}$ –43.5^{o} (c 1.0, CH_2Cl_2, 93% *ee*); (4S,5R) Lit.[3] $[\alpha]_D^{21}$ +44^{o} (c 1.0, CH_2Cl_2, 90% *ee*); IR (neat) 3318, 2982, 2359, 1741, 1497, 1370, 1236, 1172, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ8.15 (br, s, 1H), 7.46-7.33 (comp, 5H), 5.96 (d, *J* = 6.0 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.32 (comp, 2H), 1.34 (app t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 168.2, 137.0, 129.7, 129.4, 125.8, 85.8, 64.8, 63.2, 14.3.; *m/z* (ESI-MS)

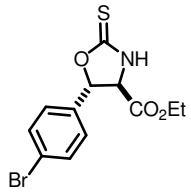
252.0 $[MH]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=28.5 min and t_R=48.0 min (major).

(4R,5S)-ethyl 5-(4-nitrophenyl)-2-thioxooxazolidine-4-carboxylate (2.66a): Following



the general procedure, the title compound was obtained as a pale yellow solid in 80% yield (237 mg). mp 129-130 ^oC (EtOAc/Hexane); Rf 0.19 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ +6.5^o (c 1.0, CH_2Cl_2, 93% *ee*); IR (KBr) 3320, 3183, 2984, 1750, 1724, 1602, 1525, 1506, 1352, 1321, 1241, 1186, 1171, 1104, 1026, 990, 873, 853, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.7 Hz, 2H), 8.13 (br, s, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 6.08 (d, *J* = 6.2 Hz, 1H), 4.47 (d, *J* = 6.2 Hz, 1H), 4.43-4.29 (comp, 2H), 1.37 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 167.7, 148.7, 143.8, 126.7, 124.6, 84.1, 64.6, 63.6, 14.3; *m/z* (ESI-MS) 297.1 $[MH]^+$, 319.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=13.4 min and t_R=21.6 min (major).

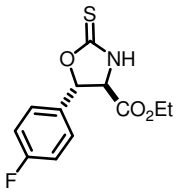
(4R,5S)-ethyl 5-(4-bromophenyl)-2-thioxooxazolidine-4-carboxylate (2.66b):



Following the general procedure, the title compound was obtained as a colorless oil in 74% yield (240 mg). Rf 0.29 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –22.5^o (c 1.0, CH_2Cl_2, 94% *ee*); IR (neat) 3180, 2982, 1736, 1594, 1491, 1370, 1236, 1072, 1011, 923, 823, 736, 576, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (br, s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.92 (d, *J* = 6.2 Hz, 1H), 4.44 (d, *J* = 6.2 Hz, 1H), 4.40-4.23 (comp, 2H), 1.34 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.9, 167.9, 136.0, 132.6, 127.5, 124.0, 85.0, 64.7, 63.3, 14.3; *m/z* (ESI-MS) 329.9(^{79}Br), 332.0(^{81}Br) $[MH]^+$; HPLC: Daicel Chiralpak AS-H, *n*-

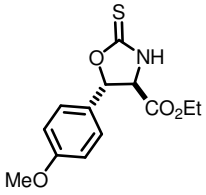
hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=27.1 min and t_R=45.2 min (major).

(4R,5S)-ethyl5-(4-fluorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66c):



Following the general procedure, the title compound was obtained as a colorless oil in 82% yield (221 mg). Rf 0.36 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –21.0° (c 1.0, CH_2Cl_2, 94% *ee*); IR (neat) 3187, 2984, 1743, 1607, 1512, 1370, 1228, 1157, 1100, 1014, 955, 921, 837, 587, 534 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (br, s, 1H), 7.40 (dd, *J* = 5.1, 8.7 Hz, 2H), 7.12 (app t, *J* = 8.7 Hz, 2H), 5.94 (d, *J* = 6.2 Hz, 1H), 4.46 (d, *J* = 6.2 Hz, 1H), 4.41-4.24 (comp, 2H), 1.34 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 168.0, 163.5 (d, J_{C-F} = 249.3 Hz), 132.8 (d, J_{C-F} = 3.3 Hz), 128.0 (d, J_{C-F} = 8.5 Hz), 116.4 (d, J_{C-F} = 21.9 Hz), 85.2, 64.8, 63.3, 14.3; *m/z* (ESI-MS) 270.0 $[MH]^+$, 292.0 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=19.2 min and t_R=31.6 min (major).

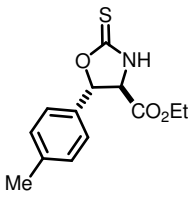
(4R,5S)-ethyl 5-(4-methoxyphenyl)-2-thioxooxazolidine-4-carboxylate (2.66d):



Following the general procedure, the title compound was obtained as a pale yellow oil in 60% yield (168 mg). Rf 0.18 (CH_2Cl_2/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –57.0° (c 1.0, CH_2Cl_2, 96% *ee*); (4S,5R) Lit.[3] $[\alpha]_D^{21}$ +49° (c 1.0, CH_2Cl_2, 86% *ee*); IR (neat) 3188, 2981, 1743, 1613, 1516, 1370, 1233, 1168, 1115, 1028, 949, 918, 832, 591 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (br, s, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.90 (d, *J* = 6.3 Hz, 1H), 4.48 (d, *J* = 6.3 Hz, 1H), 4.39-4.15 (comp, 2H), 3.82 (s, 3H), 1.33 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 168.2, 160.8, 128.8, 127.7, 114.7, 86.0, 64.7, 63.1, 55.6, 14.3; *m/z*

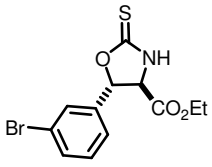
(ESI-MS) 282.1 $[MH]^+$, 304.1 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=28.7 min and t_R=51.3 min (major).

(4R,5S)-ethyl 5-(4-methylphenyl)-2-thioxooxazolidine-4-carboxylate (2.66e):



Following the general procedure, the title compound was obtained as a colorless oil in 80% yield (212mg). Rf 0.32 (CH_2Cl_2/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –38.0° (c 1.0, CH_2Cl_2, 94% *ee*); (4S,5R) Lit.[3] $[\alpha]_D^{21}$ +32° (c 1.0, CH_2Cl_2, 92% *ee*); IR (neat) 3310, 2982, 1742, 1674, 1504, 1371, 1170, 1097, 1020, 956, 816, 590, 513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (br, s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.91 (d, *J* = 6.2 Hz, 1H), 4.48 (d, *J* = 6.2 Hz, 1H), 4.37-4.23 (comp, 2H), 2.36 (s, 3H), 1.33 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 168.2, 139.8, 134.0, 130.0, 126.0, 86.0, 64.8, 63.1, 21.4, 14.3; *m/z* (ESI-MS) 266.0 $[MH]^+$, 288.0 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=17.1 min and t_R=29.0 min (major).

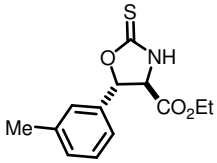
(4R,5S)-ethyl 5-(3-bromophenyl)-2-thioxooxazolidine-4-carboxylate (2.66f):



Following the general procedure, the title compound was obtained as a colorless oil in 70% yield (231mg). Rf 0.31 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –9.5° (c 1.0, CH_2Cl_2, 92% *ee*); IR (neat) 3180, 2982, 1743, 1598, 1573, 1502, 1370, 1235, 1095, 1017, 918, 878, 787, 694, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (br, s, 1H), 7.62-7.50 (comp, 2H), 7.38-7.28 (comp, 2H), 5.93 (d, *J* = 6.2 Hz, 1H), 4.46 (d, *J* = 6.2 Hz, 1H), 4.40-4.27 (comp, 2H), 1.36 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.9, 167.8, 139.2, 132.9, 131.0, 128.9, 124.4, 123.4, 84.7, 64.7, 63.4, 14.3; *m/z* (ESI-MS) 330.0(^{79}Br), 331.9(^{81}Br) $[MH]^+$; HPLC:

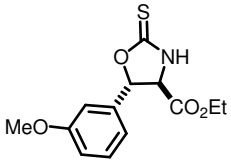
Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=23.9 min and t_R=40.7 min (major).

(4R,5S)-ethyl 5-(3-methylphenyl)-2-thioxooxazolidine-4-carboxylate(2.66g):



Following the general procedure, the title compound was obtained as a colorless oil in 74% yield (196 mg). Rf 0.38 (CH_2Cl_2/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –25.5° (c 1.0, CH_2Cl_2, 93% *ee*); (4S,5R) Lit.[3] $[\alpha]_D^{21}$ +25° (c 1.0, CH_2Cl_2, 86% *ee*); IR (neat) 3319, 2982, 1740, 1610, 1495, 1370, 1232, 1177, 1096, 1020, 924, 790, 701, 574 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (br, s, 1H), 7.34-7.28 (m, 1H), 7.24-7.16 (comp, 3H), 5.93 (d, *J* = 6.1 Hz, 1H), 4.47 (d, *J* = 6.1 Hz, 1H), 4.39-4.26 (comp, 2H), 2.38 (s, 3H), 1.35 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 168.2, 139.3, 137.0, 130.5, 129.2, 126.4, 122.9, 85.9, 64.8, 63.2, 21.6, 14.3; *m/z* (ESI-MS) 266.1 $[MH]^+$, 288.1 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=13.7 min and t_R=23.8 min (major).

(4R,5S)-ethyl 5-(3-methoxyphenyl)-2-thioxooxazolidine-4-carboxylate(2.66h):

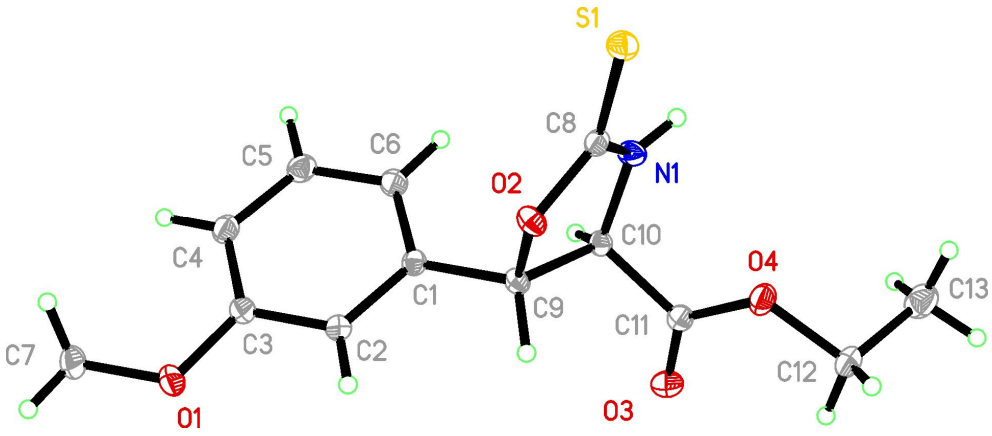


Following the general procedure, the title compound was obtained as colorless crystals in 70% yield (196 mg). mp 78-79 °C (EtOAc:Hexane); Rf 0.25 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –33.0° (c 1.0, CH_2Cl_2, 92% *ee*); IR (KBr) 3300, 2981, 2838, 1743, 1603, 1494, 1370, 1233, 1096, 1038, 923, 859, 787, 734, 696, 559 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (br, s, 1H), 7.33 (app t, *J* = 7.8 Hz, 1H), 6.98 (app d, *J* = 7.8 Hz, 1H), 6.95-6.90 (comp, 2H), 5.93 (d, *J* = 6.0 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 4.39-4.26 (comp, 2H), 3.82 (s, 3H), 1.35 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 168.1, 160.3, 138.5, 130.5, 117.9,

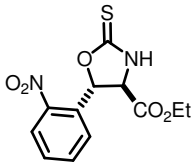
115.2, 111.3, 85.6, 64.8, 63.2, 55.6, 14.3; *m/z* (ESI-MS) 282.1 $[MH]^+$, 304.1 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=20.3 min and t_R=38.4 min (major).

The title compound was further characterized by X-ray crystallography.

Figure 2.2 **Crystal Structure of Compound 2.66h**

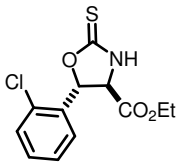


(4R,5S)-ethyl 5-(2-nitrophenyl)-2-thioxooxazolidine-4-carboxylate (2.66i): Following



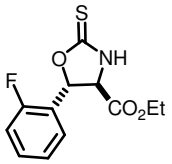
the general procedure, the title compound was obtained as a colorless oil in 81% yield (241 mg). Rf 0.27 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ – 50.1° (c 1.0, $CHCl_3$, 90% *ee*); IR (neat) 3372, 1744, 1612, 1527, 1500, 1347, 1244, 1195, 1169, 1072, 1029, 973, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (br, s, 1H), 8.19 (app d, *J* = 7.7 Hz, 1H), 7.76 (app t, *J* = 7.7 Hz, 1H), 7.67 (app d, *J* = 7.7 Hz, 1H), 7.60 (app t, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 4.43 (d, *J* = 4.0 Hz, 1H), 4.34 (comp, 2H), 1.33 (app t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 167.9, 136.0, 135.2, 129.2, 128.9, 127.2, 123.0, 85.7, 63.1, 62.9, 14.3; *m/z* (ESI-MS) 319.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH=95/5, Flow rate = 1 mL/min, UV = 254 nm, t_R=48.4 min and t_R=51.8 min (major).

(4R,5S)-ethyl 5-(2-chlorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66j):



Following the general procedure, the title compound was obtained as a colorless oil in 68% yield (194 mg). Rf 0.35 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ +17.0° (c 1.0, CH_2Cl_2, 93% *ee*); IR (neat) 3182, 2982, 1746, 1504, 1445, 1371, 1204, 1172, 1036, 973, 758, 613, 572 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (br, s, 1H), 7.50-7.40 (comp, 2H), 7.40-7.32 (comp, 2H), 6.36 (d, *J* = 4.6 Hz, 1H), 4.47 (d, *J* = 4.6 Hz, 1H), 4.40-4.25 (comp, 2H), 1.34 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 167.9, 134.4, 131.9, 130.9, 130.4, 127.8, 127.7, 83.2, 64.0, 63.2, 14.3; *m/z* (ESI-MS) 286.0(^{35}Cl), 288.0(^{37}Cl) $[MH]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.3 min and t_R=28.2 min (major).

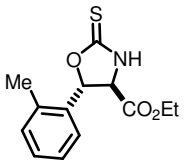
(4R,5S)-ethyl 5-(2-fluorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66k):



Following the general procedure, the title compound was obtained as a white solid in 62% yield (167 mg). mp 58-59 °C (EtOAc/Hexane); Rf 0.28 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –41.0° (c 1.0, CH_2Cl_2, 90% *ee*); IR (KBr) 3313, 2975, 1748, 1614, 1587, 1494, 1365, 1222, 1187, 1168, 1096, 1019, 982, 928, 863, 765, 575 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (br, s, 1H), 7.51-7.33 (comp, 2H), 7.25-7.19 (m, 1H), 7.17-7.09 (m, 1H), 6.19 (d, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 5.8 Hz, 1H), 4.41-4.18 (comp, 2H), 1.33 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 167.9, 160.1 (d, $J_{C\text{-}F}$ = 249.2 Hz), 131.8 (d, $J_{C\text{-}F}$ = 8.4 Hz), 128.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 125.1 (d, $J_{C\text{-}F}$ = 3.7 Hz), 124.1 (d, $J_{C\text{-}F}$ = 12.4 Hz), 116.3 (d, $J_{C\text{-}F}$ = 20.5 Hz), 81.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 63.9 (d, $J_{C\text{-}F}$ = 1.6 Hz), 63.2, 14.2; *m/z* (ESI-MS) 270.0 $[MH]^+$, 292.1 $[MNa]^+$;

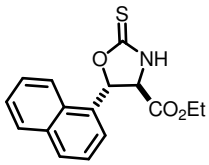
HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.7 min and t_R=25.1 min (major).

(4R,5S)-ethyl 5-(2-methylphenyl)-2-thioxooxazolidine-4-carboxylate (2.66l):



Following the general procedure, the title compound was obtained as a colorless oil in 49% yield (130 mg). Rf 0.26 (CH_2Cl_2/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –24.0° (c 1.0, CH_2Cl_2, 90% *ee*); (4S,5R) Lit.[3] $[\alpha]_D^{21}$ +12.5° (c 1.0, CH_2Cl_2, 89% *ee*); IR (neat) 3310, 2981, 1743, 1495, 1369, 1217, 1181, 1171, 1092, 1023, 968, 760, 617, 576 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (br, s, 1H), 7.51-7.01 (comp, 4H), 6.22 (d, *J* = 5.2 Hz, 1H), 4.44 (d, *J* = 5.2 Hz, 1H), 4.39-4.25 (comp, 2H), 2.41 (s, 3H), 1.34 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 168.3, 135.3, 134.9, 131.3, 129.7, 127.1, 125.9, 83.7, 64.2, 63.2, 19.3, 14.3; *m/z* (ESI-MS) 266.1, $[MH]^+$, 288.1 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.9 min and t_R=27.1 min (major).

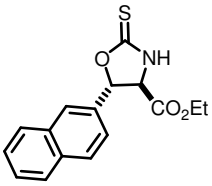
(4R,5S)-ethyl 5-(naphthalen-1-yl)-2-thioxooxazolidine-4-carboxylate (2.66m):



Following the general procedure, the title compound was obtained as a yellow oil in 47% yield (141 mg). Rf 0.31 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –46.5° (c 1.0, CH_2Cl_2, 94% *ee*); IR (neat) 3300, 2982, 1740, 1499, 1371, 1231, 1180, 1089, 1020, 965, 860, 776, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (app d, *J* = 8.3 Hz, 1H), 7.96-7.86 (comp, 2H), 7.76 (br, s, 1H), 7.65-7.45 (comp, 4H), 6.79 (d, *J* = 4.1 Hz, 1H), 4.51 (d, *J* = 4.1 Hz, 1H), 4.46-4.33 (comp, 2H), 1.40 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 168.5, 134.1, 132.0, 130.2, 129.5, 129.4, 127.4, 126.5, 125.6, 123.6, 122.4, 83.9, 64.2, 63.4, 14.3; *m/z* (ESI-

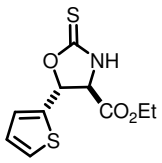
MS) 302.0 $[MH]^+$, 324.1 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=23.1 min and t_R=56.2 min (major).

(4R,5S)-ethyl 5-(naphthalen-2-yl)-2-thioxooxazolidine-4-carboxylate (2.66n):



Following the general procedure, the title compound was obtained as a yellow solid in 83% yield (250 mg). mp 104-106 ^oC (EtOAc:Hexane); Rf 0.28 (CH_2Cl_2/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –40.0^o (c 1.0, CH_2Cl_2, 91% *ee*); (4S,5R) Lit.[3] $[\alpha]_D^{21}$ +46^o (c 1.0, CH_2Cl_2, 87% *ee*); IR (KBr) 3299, 2989, 1746, 1602, 1500, 1340, 1228, 1178, 1194, 1019, 928, 859, 817, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97-7.81 (comp, 5H), 7.59-7.51 (comp, 2H), 7.47 (comp, 2H), 6.14 (d, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 6.0 Hz, 1H), 4.42-4.29 (comp, 2H), 1.37 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 168.2, 134.1, 133.8, 133.2, 129.7, 128.5, 128.0, 127.3, 127.1, 125.6, 122.6, 86.1, 64.7, 63.3, 14.4; *m/z* (ESI-MS) 302.0 $[MH]^+$, 324.1 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=29.7 min and t_R=49.8 min (major).

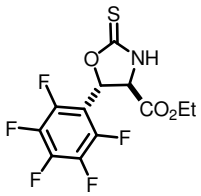
(4R,5R)-ethyl 5-(thiophen-2-yl)-2-thioxooxazolidine-4-carboxylate (2.66o): Following



the general procedure, the title compound was obtained as a colorless oil in 65% yield (167 mg). Rf 0.32 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –102.0^o (c 1.0, CH_2Cl_2, 91% *ee*); IR (neat) 3317, 2982, 1743, 1672, 1501, 1370, 1195, 1097, 1020, 919, 856, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (br, s, 1H), 7.41 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.22 (app d, *J* = 3.5 Hz, 1H), 7.04 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.18 (d, *J* = 6.2 Hz, 1H), 4.65 (d, *J* = 6.2 Hz, 1H), 4.42-4.21 (comp, 2H), 1.32 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4, 167.6, 138.5, 127.8, 127.6, 127.5, 81.9, 64.6, 63.3, 14.3; *m/z* (ESI-MS) 257.9 $[MH]^+$, 280.0 $[MNa]^+$; HPLC: Daicel Chiralpak AS-H, *n*-

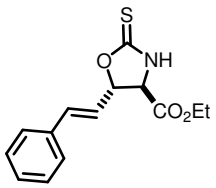
hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=27.8 min and t_R=43.9 min (major).

(4R,5S)-ethyl 5-(perfluorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66p):



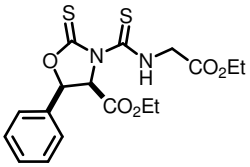
Following the general procedure, the title compound was obtained as a yellow oil in 66% yield (225 mg). Rf 0.39 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –41.8° (c 1.0, $CHCl_3$, 90% *ee*); IR (neat) 3316, 2989, 1747, 1658, 1513, 1372, 1242, 1175, 1136, 946 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ8.72 (br, s, 1H), 6.23 (d, *J* = 7.7 Hz, 1H), 4.74 (d, *J* = 7.7 Hz, 1H), 4.37-4.22 (comp, 2H), 1.30 (app t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 167.2, 146.9-144.5 (m), 144.0-141.6 (m), 139.2-136.7(m), 110.2-109.8 (m), 75.3, 63.5, 62.5, 14.0; *m/z* (ESI-MS) 342.1 $[MH]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.6 min (major) and t_R=25.0 min.

(4R,5S)-ethyl 5-styryl-2-thioxooxazolidine-4-carboxylate (2.66q): Following the general procedure, the title compound was obtained as a yellow solid in 73% yield (202 mg). mp 87-89 °C (EtOAc/Hexane); Rf 0.32 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –97.8° (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 3291, 2977, 1739, 1649, 1491, 1371, 1305, 1262, 1229, 1162, 1022, 983, 914, 749, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (br, s, 1H), 7.43-7.27 (comp, 5H), 6.81 (d, *J* = 15.5 Hz, 1H), 6.28 (m, 1H), 5.55 (app t, *J* = 6.5, 1H) 4.42 (d, *J* = 6.5 Hz, 1H), 4.36-4.25 (comp, 2H), 1.33 (app t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 168.0, 136.2, 135.1, 129.2, 128.9, 127.2, 123.0, 85.7, 63.1, 62.9, 14.3; *m/z* (ESI-MS) 299.9 $[M+Na]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=29.1 min and t_R=48.2 min (major).



(4R,5S)-ethyl 5-phenethyl-2-thioxooxazolidine-4-carboxylate (2.66r): Following the general procedure, the title compound was obtained as a colorless oil in 54% yield (151 mg). Rf 0.30 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ – 100.5° (c 1.0, $CHCl_3$, 81% *ee*); IR (neat) 3316, 3026, 2981, 2934, 1742, 1602, 1499, 1455, 1370, 1216, 1097, 1019, 701, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (br, s, 1H), 7.33-7.27 (comp, 2H), 7.24-7.17 (comp, 3H), 4.93 (ddd, *J* = 11.5, 6.5, 5.0 Hz, 1H), 4.30-4.18 (comp, 3H), 2.94-2.76 (comp, 2H), 2.28-2.12 (comp, 2H), 1.28 (app t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 168.2, 139.9, 128.8, 128.6, 126.6, 84.8, 63.0, 62.3, 36.7, 30.8, 14.2; *m/z* (ESI-MS) 280.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=10.9 min and t_R=17.9 min (major).

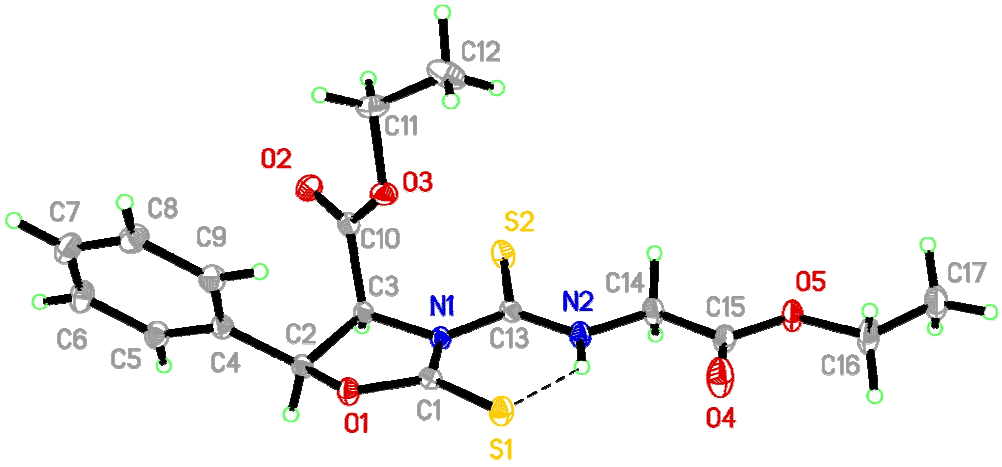
(4R,5S)-ethyl 5-butyl-2-thioxooxazolidine-4-carboxylate (2.66s): Following the general procedure, the title compound was obtained as a colorless oil in 44% yield (102 mg). Rf 0.31 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –38.8° (c 1.0, CH_2Cl_2, 82% *ee*); IR (neat) 3428, 3176, 3053, 2962, 2874, 2305, 1747, 1490, 1371, 1266, 1079, 1024, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (br, s, 1H), 4.93 (m, 1H), 4.32-4.22 (comp, 2H), 4.21 (d, *J* = 6.5 Hz, 1H), 1.94-1.77 (comp, 2H), 1.57-1.34 (comp, 4H), 1.30 (app t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 168.5, 85.7, 62.9, 62.3, 34.7, 26.5, 22.3, 14.2, 14.0; *m/z* (ESI-MS) 232.1 $[MH]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.1 min and t_R=23.8 min (major).

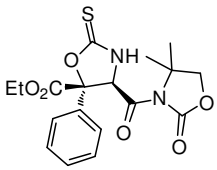
Rac-*cis*-ethyl 3-(2-ethoxy-2-oxoethylcarbamothioyl)-5-phenyl-2-thioxooxazolidine-4-carboxylate (*cis*-2.36): 

The mixture of ***cis*-2.36** and ***trans*-2.36** was prepared from 1a and benzaldehyde using 10 mol% DABCO as catalyst in toluene (0.1 M). The mixture of diastereomers was obtained by flash chromatograpy (EtOAc/Heane 10:90 v:v). ***cis*-2.36** was obtained as colorless crystals from recrystallization(CH_2Cl_2/Hexane). Rf 0.65 (CH_2Cl_2/EtOAc 100:2 v/v); mp 139-140^oC (CH_2Cl_2/Hexane); IR (KBr) 3092, 2995, 2937, 1752, 1743, 1534, 1443, 1422, 1372, 1344, 1317, 1281, 1243, 1205, 1178, 1046, 1019, 933, 895, 753, 699, 677, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.25 (s, 1H), 7.43-7.28 (m, 3H), 7.38-7.32 (m, 2H), 6.00 (d, *J* = 9.1 Hz, 1H), 5.91 (d, *J* = 9.1 Hz, 1H), 4.47 (dd, *J* = 4.5, 18.8 Hz, 1H), 4.37 (dd, *J* = 4.5, 18.8 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.81 (dq, *J* = 7.2, 10.7 Hz, 1H), 3.62 (dq, *J* = 7.2, 10.7 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.80 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 178.0, 168.1, 166.0, 131.5, 130.0, 128.8, 126.8, 81.3, 69.3, 62.13, 62.12, 48.7, 14.4, 13.6; *m/z* (ESI-MS) 396.9 $[MH]^+$, 419.0 $[MNa]^+$.

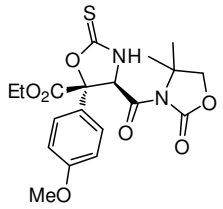
***cis*-2.36** was further characterized by X-ray crystallography.

Figure 2.3 **Crystal Structure of Compound *cis*-2.36**

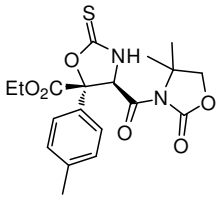




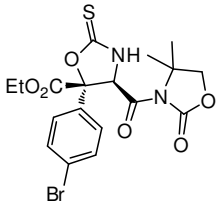
(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-phenyl-2-thioxo-oxazolidine-5-carboxylate (2.56a): mp : 172 –173 °C (EtOAc/CH_2Cl_2); Rf 0.3 (EtOAc/CH_2Cl_2 19:1 v/v); $[\alpha]_D^{20}$ -9.5 (c 1.0, $CHCl_3$, 95% ee); IR (KBr) 3334, 2970, 2932, 1814, 1783, 1740, 1681, 1506, 1473, 1451, 1387, 1339, 1300 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 – 7.69 (d, J = 8.1, 2H), 7.58 (br, s, 1H), 7.38 – 7.44 (comp, 3H), 5.93 (s, 1H), 4.20 – 4.26 (m, 1H), 4.10 – 4.17 (m, 1H), 4.15 (app s, 2H), 1.63 (s, 3H), 1.61 (s, 3H), 1.22 (t, J = 7.3 MHz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.6, 169.1, 167.5, 154.5, 136.1, 129.9, 129.2, 125.2, 92.6, 76.2, 66.0, 64.7, 63.1, 61.6, 25.5, 24.9, 24.0, 14.0; m/z (ESI-MS) 415.1 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 16.48 min (major) and t_R = 22.54 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(4-methoxyphenyl)-2-thioxooxazolidine-5-carboxylate (2.56b): 

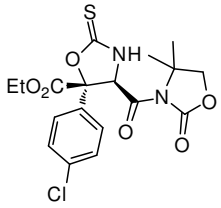
Yellow oil; Rf = 0.25 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ -15.7 (c 1.0, $CHCl_3$, 94% ee). IR (KBr) 3426, 1775, 1736, 1704, 1646, 1610, 1513, 1381, 1306, 1257 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (br, s, 1H), 7.58 – 7.60 (d, J = 8.9 Hz, 2H), 6.91 – 6.93 (d, J = 8.9 Hz, 2H), 5.91 (s, 1H), 4.19 – 4.25 (m, 1H), 4.14 (comp, 3H), 3.81 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.21 (app t, J = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.7, 169.2, 167.7, 160.8, 154.6, 128.0, 126.7, 114.6, 92.6, 76.2, 66.0, 64.7, 63.0, 61.6, 55.6, 25.6, 25.0, 24.0, 14.0; m/z (ES-IMS) 445.0 [MNa]+; HPLC: Daicel (Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 20.91 min (minor), t_R = 23.35 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxo-5-(p-tolyl)oxazolidine-5-carboxylate (2.56c): 

Yellow oil; Rf 0.25 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ -22.0 (c 1.0, $CHCl_3$, 92% ee); IR (KBr) 3441, 1775, 1703, 1646, 1495, 1381, 1303, 1275, 1238, 1201 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 4.1 Hz, 2H), 7.22 (d, J = 7.2 Hz, 2H), 5.9 (s, 1H), 4.19 – 4.26 (m, 1H), 4.10 – 4.17 (comp, 3H), 2.35 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.23 (app t, J = 7.1 Hz, 3H);^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.7, 169.2, 167.6, 154.5, 140, 133.2, 129.9, 125.1, 92.7, 76.2, 66.1, 64.7, 63.1, 61.6, 25.6, 25.0, 24.0, 21.3, 14.1; m/z (ES-IMS) 429.1 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 13.70 min (minor), t_R = 18.31 min.

(4R,5S)-ethyl 5-(4-bromophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56d): 

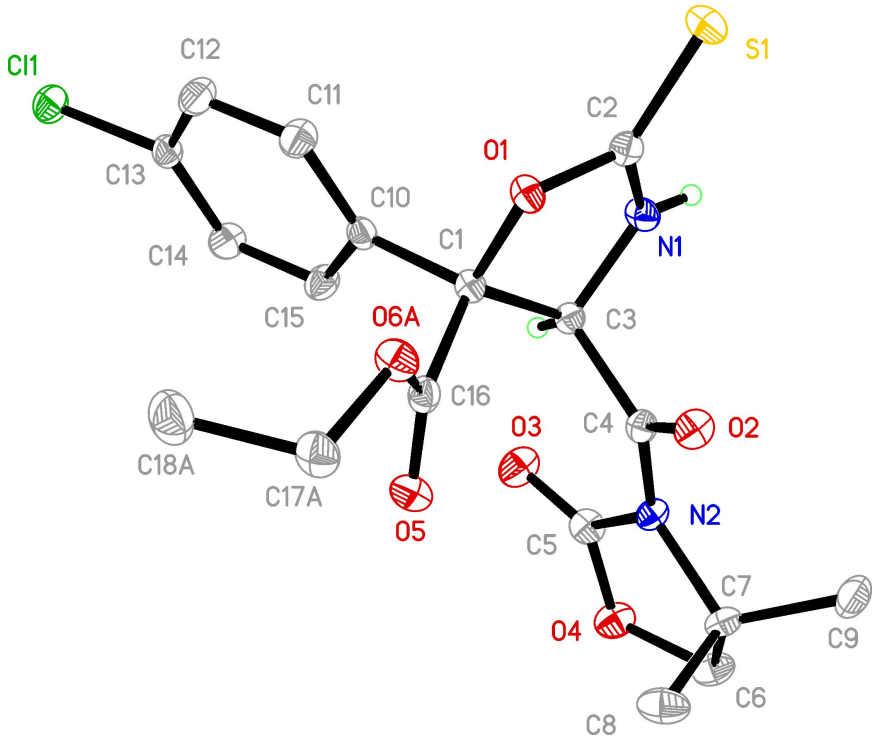
mp : 165-166 °C (EtOAc/ CH_2Cl_2); Rf = 0.25 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ -15.2 (c 1.0, $CHCl_3$, 97% ee); IR (KBr) 3334, 2977, 2932, 1777, 1705, 1490, 1382, 1304 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (app t, J = 9.9Hz, 4H), 7.43 (br, s, 1H), 4.20 – 4.26 (m, 1H), 4.12 – 4.18 (comp, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.23 (app t, J = 7.1 Hz, 3H; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.5, 168.9, 167.0, 154.6, 135.3, 132.4, 127.1, 124.4, 92.2, 76.2, 65.9, 63.4, 61.7, 25.6, 24.9, 24.1, 14.0; m/z (ESI-MS) 494.9 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, F1ow rate = 1 mL/min, UV = 254 nm, t_R = 12.60 min (minor), t_R = 18.23 min.

(4R,5S)-ethyl 5-(4-chlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56e): 

mp : 182 –183 °C(EtOAc/CH_2Cl_2); Rf = 0.25 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ -7.0 (c 1.0, $CHCl_3$, 98% ee); IR (KBr) 3334, 2970, 2932, 1814, 1783, 1740, 1681, 1506, 1473, 1451, 1387, 1339, 1300 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 – 7.64 (d, J = 8.7 Hz, 2H), 7.47 (br, s, 1H), 7.38 – 7.40 (d, J = 8.7 Hz, 2H), 5.86, (s, 1H), 4.10 – 4.27 (comp, 4H), 1.62 (s, 3H), 1.60 (s, 3H), 1.22 (app t, J = 7.1 Hz, 3H);^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.4, 168.9, 167.2, 154.6, 136.2, 134.7, 129.5, 126.8, 92.1, 76.2, 66.1, 63.4, 61.7, 25.0, 24.0, 14.0; m/z (ESI-MS) 449.3 [MNa]+; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 12.05 min (minor), t_R = 17.49 min.

The title compound was further characterized by X-ray crystallography.

Figure 2.4 **Crystal Structure of Compound 2.56e**



(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxo-5-(4-(trifluoromethyl)phenyl)oxazolidine-5-carboxylate (2.56f): mp 157 – 158 °C(EtOAc/CH_2Cl_2);. Rf 0.20 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ -3.1 (c 1.0, $CHCl_3$, 97% ee); IR (KBr) 3231, 2974, 2942, 2915, 2360, 1771, 1753, 1706, 1683, 1618, 1500, 1413, 1382, 1328, 1308; ^{1}H NMR (500 MHz, $CDCl_3$): 7.83 – 7.85 (d, J = 8.1 Hz, 2H, 7.68 – 7.72 (comp, 3H), 5.92 (s, 1H), 4.20 – 4.27 (m, 1H), 4.13 – 4.18 (comp, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.23 (app t, J = 7.0, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.5, 168.8, 166.8, 154.6, 132.1 (q, J_{C-F} = 32.5 Hz), 126.2 (q, J_{C-F} = 3.7 Hz), 125.0, 122.8, 92.1, 77.5, 77.3, 77.0, 76.2, 66.0, 63.6 61.7, 24.8, 24.1, 14.0; m/z (ESI-MS) 483.2 [MNa]+; HPLC: Daicel

(Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 8.63 min (minor), t_R = 11.42 min.

(4R,5S)-ethyl 5-(4-(tert-butyl)phenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56g): mp 182 – 183 °C (EtOAc/CH_2Cl_2); Rf 0.25 (EtOAc/CH_2Cl_2 2:98 v/v); $[\alpha]_D^{20}$ -17.7 (c 1.0, $CHCl_3$, 96% ee); IR (KBr) 3378, 2966, 2870, 1778, 1737, 1708, 1491, 1382, 1304, 1273, 1238, 1175, 1098, 1067, 1033, 927, 762, 711, 671, 564 cm-1; ^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.74 (br, s, 1H), 7.58, (d, J = 4.1 Hz, 2H), 7.42, (d, J = 4.1 Hz, 2H), 5.93 (s, 1H), 4.20 – 4.28 (m, 1H), 4.08 – 4.18 (comp, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.30 (app s, 9H), 1.23 (app t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 169.1, 167.6, 154.5, 153.0133.1, 126.3, 124.9, 92.6, 76.2, 66.1, 63.1, 61.6, 34.9, 31.4, 24.9, 24.1, 14.1; m/z (ESI-MS) 471.2 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 871 min (minor), t_R = 11.51 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(3-methoxyphenyl)-2-thioxooxazolidine-5-carboxylate (2.56h): Yellow oil; Rf 0.25 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ -22 (c 1.0 $CHCl_3$, 96% ee); IR (KBr) 3403, 1775, 1739, 1705, 1602, 1493, 1381, 1303, 1259 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (br, s, 1H), 7.30 (app t, J = 7.3, 1H), 7.23 – 7.26 (comp, 2H), 6.90 – 6.92 (m, 1H), 4.19 – 4.26 (m, 1H), 4.09 – 4.15 (comp, 3H), 3.81 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.21 (app t, J = 7.0 Hz, 3H); ^{13}C-NMR(125 MHz, $CDCl_3$): δ 188.7, 169.1, 167.3, 160.2, 154.5, 137.7, 130.3, 117.2, 116.0, 110.5, 92.6, 76.1, 65.9, 63.2, 61.6, 24.9, 24.1, 14.1 ; m/z (ESI-MS) 445.2 [MNa]+; HPLC: Daicel Chiralpak AD-

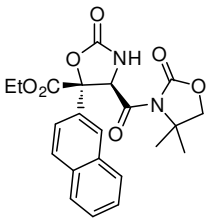
H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 18.78 min (major), t_R = 27.54 min.

(4R,5S)-ethyl 5-(3,4-dichlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56i): mp 161 – 162 °C; (EtOAc/CH_2Cl_2); Rf 0.25 (EtOAc/CH_2Cl_2 2:98 (v/v); $[\alpha]_D^{20}$ –9.2 (c, 1.0, $CHCl_3$, 98% ee); IR (KBr) 3340, 2979, 2936, 1777, 1707, 1574, 1382, 1306, 1240, 1175, 1100, 1071, 1031, 925, 853, 823, 806, 763, 713, 683, 666, 635, 613, 572, 513, 441 cm-1; ^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 4.8 Hz, 1H), 7.51 (d, J = 21.5 Hz, 1H), 5.79 (s, 1H), 4.21 – 4.28 (m, 1H), 4.14 – 4.20 (comp, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 168.6, 166.8, 154.6, 136.4, 134.5, 133.7, 131.2, 127.6, 124.9, 76.3, 66.1, 63.6, 61.7, 24.8, 24.1, 14.0; m/z (ESI-MS) 483.1 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/I-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, t_R = 10.2 min (minor), t_R = 14.3 min.

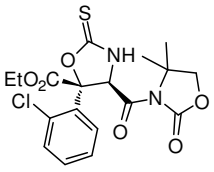
(4R,5S)-ethyl 5-(3,5-difluorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56j): mp 155 – 156°C (EtOAc/CH_2Cl_2); Rf 0.2 (EtOAc/CH_2Cl_2 2:98 v/v); $[\alpha]_D^{20}$ –5.1 (c, 1.0, $CHCl_3$, 97% ee); IR (KBr) 3332, 3103, 2972, 2937, 1770, 1729, 1707, 1627, 1601, 1513, 1477, 1443, 1397, 1382, 1354, 1309, 1274, 1251, 1189, 1158, 1122, 1105, 1079, 1050, 1026, 984, 942, 922, 861, 842, 761, 746, 713, 681, 668, 658, 638, 613, 599, 574, 532, 511 cm-1; ^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.8 (br, s, 1H), 7.26 (m, 1H), 6.84 (tt, J = 8.8 Hz, 1H), 5.85 (s, 1H), 4.21 – 4.28 (m, 1H), 4.10 – 4.20 (comp, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.24 (app t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2,

168.5, 166.6, 164.4 (d, J_{C-F} = 12.6 Hz), 162.4 (d, J_{C-F} = 12.5 Hz) 154.6, 140.1 (t, J_{C-F} = 9.0 Hz), 109.1 (dd, J_{C-F} = 7.3 Hz), 105.5 (t, J_{C-F} = 24.9 Hz), 91.5, 76.3, 66.2, 63.6, 61.7, 24.9, 24.1, 14.0; m/z (ESI-MS) 451.2 [MNa]+; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, t_R = 10.5 min (minor), t_R = 12.5 min.

(4R,5S)-ethyl 5-(2,4-dichlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56k): mp 186 – 187°C (EtOAc/CH_2Cl_2); Rf 0.2 (EtOAc/CH_2Cl_2 2:98 v/v); $[\alpha]_D^{20}$ 18.1 (c 1.0, $CHCl_3$, 93% ee); IR (KBr) 3338, 2980, 1778, 1711, 1587, 1475, 1381, 1308, 1242, 1176, 1099, 1057, 1031, 970, 924, 866, 815, 763, 710, 606, 574, 486 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 4.2 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.41 (br, s, 1H), 7.34 (dd, J =4.2 Hz, 1H), 6.24 (s, 1H), 4.18 – 4.26 (m, 1H), 4.10 – 4.16 (comp, 3H), 1.65 (app s, 3H), 1.60 (app s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0, 167.9, 165.2, 154.3, 136.7, 132.5, 132.3, 131.6, 129.3, 128.0, 91.8, 76.1, 63.6, 63.6, 61.9, 25.0, 23.6, 14.0; m/z (ESI-MS) 483.1 [MNa]+; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, t_R = 11.8 min (minor), t_R = 25.4 min.

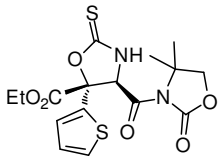
(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(naphthalen-2-yl)-2-oxooxazolidine-5-carboxylate (2.56l): 

Colorless oil; Rf 0.20 (EtOAc/CH_2Cl_2 2:98 v/v); $[\alpha]_D^{20}$ –18.5 (c 1.0, $CHCl_3$, 97% ee); IR (KBr) 3332, 3103, 2972, 2937, 1770, 1729, 1707, 1627, 1601, 1513, 1477, 1443, 1397, 1382, 1354, 1309, 1274, 1251, 1189, 1158, 1122, 1105, 1079, 1050, 1026, 984, 942, 922, 861, 842, 761, 746, 713, 681, 668, 658, 638, 613m, 599, 574, 532, 511 cm-1; ^{1}H NMR (500 MHZ, $CDCl_3$) δ 8.2 (br, s, 1H), 7.89 – 7.93 (comp, 2H), 7.84 – 7.85 (m, 1H), 7.76 (dd, 4.0 Hz, 1H), 7.21 (br, s, 1H), 6.0 (s, 1H), 4.22 – 4.28 (m, 1H), 4.12 – 4.20 (comp, 3H), 1.64 (s, 6H), 1.23 (app t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.8, 169.2, 167.4, 154.6, 133.8, 133.3, 133.0, 129.3, 129.0, 127.8, 127.4, 127.0, 125.1, 122.3, 92.8, 76.2, 65.8, 63.2, 61.7, 24.9, 24.2, 14.1; m/z (ESI-MS) 465.2 [MNa]+; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, t_R = 20.0 min (minor) , t_R = 26.1 min.

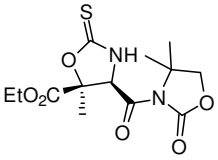
(4R,5S)-ethyl5-(2-chlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56m): 

Colorless oil, Rf 0.30 (EtOAc/CH_2Cl_2 3:97 v/v); $[\alpha]_D^{20}$ 22.1 (c 1.0, $CHCl_3$, 87% ee); IR (KBr) 2980, 1774, 1710, 1506, 1382, 1309, 1248, 1176, 1097, 1030, 913, 743 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.72 (m, 1H), 7.41 – 7.44 (m, 1H), 7.34 – 7.39 (comp, 2H), 6.27 (s, 1H), 4.19 – 4.27 (comp, 2H), 4.10 – 4.15 (comp, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.23 (app t, J = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.2, 168.1, 165.5, 154.3, 133.7, 131.8, 131.6, 131.1, 128.2, 127.8, 76.2, 63.7, 63.4, 61.9, 25.0, 23.6, 14.0; m/z (ESI-MS) 449.3 [Mna]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-

PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 22.91 min (minor), t_R = 31.25 min.

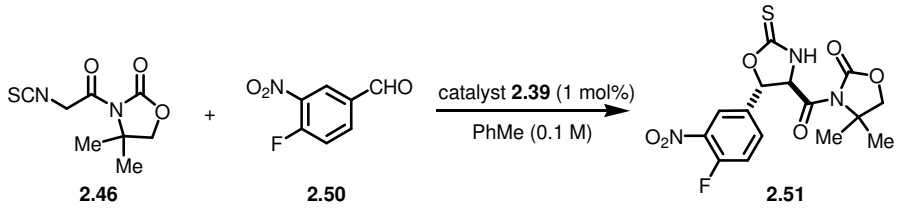
(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(thiophen-2-yl)-2-thioxooxazolidine-5-carboxylate (2.56n): 

Pale Yellow oil; Rf 0.30 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ -44.5 (c 1.0, $CHCl_3$, 92% ee); IR (KBr) 3434, 1773, 1705, 1650, 1496, 1382, 1306, 1275, 1240 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): 7.75 (br, s, 1H), 7.28 – 7.30 (comp, 2H), 7.2 (d, J = 1.2Hz, 1H), 5.80 (s, 1H), 4.12 – 4.25 (comp, 2H), 4.06 (app s, 2H), 1.55 (s, 3H), 1.57 (s, 3H), 1.21 (app t, J = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.1, 168.1, 166.7, 154.6, 138.9, 127.6, 127.6, 126.8, 90.5, 76.3, 67.1, 63.4, 61.6, 24.9, 24.1, 14.1; m/z (ESI-MS) 420.9 [MNa]+; HPLC: (Chiracel AD-H, Hexane/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 28.07 min (major) and t_R = 31.19 min.

(4R,5S)-ethyl4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-methyl-2-thioxo-oxazolidine-5-carboxylate (2.56o): 

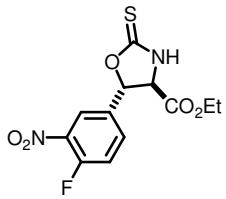
Colorless oil; R_f 0.40 (3% EtOAc/DCM); $[\alpha]_D^{20}$ –17.1 (*c* 1.0, $CHCl_3$, 79% ee); IR (KBr) 3405, 2883, 1773, 1709, 1643, 1505, 1383, 1318, 1248, 1191, 1134, 1088, 1023, 942, 854, 764, 735, 711 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (br, s, 1H), 5.23, (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.11 (app s, 2H), 1.87 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.30 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 168.3, 167.7, 154.8, 90.8, 76.4, 66.4, 63.0, 61.5, 24.9, 24.0, 17.1, 14.1; *m/z* (ESI-MS) 353.6 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R= 8.54 min (minor) and t_R = 10.72 min.

2.4.7 Scale-up Preparation of 3-((4R,5S)-5-(4-fluoro-3-nitrophenyl)-2-thioxooxazolidine-4-carbonyl)-4,4-dimethyloxazolidin-2-one (2.51)



Catalyst **2.39** (70.0 mg, 0.20 mmol), 3-(2-isothiocyanatoacetyl)-4,4-dimethyloxazolidin-2-one **2.46** (4.28 g, 20.00 mmol) and 4-fluoro-3-nitrobenzaldehyde[32] 2.50 (3.45 g, 20.40 mmol) were dissolved in HPLC grade toluene (200 mL) at room temperature. The mixture was stirred at the same temperature for 21 h. Pale yellow solid (7.09 g, 92% yield, 92% *ee*, d.r. ~17:1) was collected by simple filtration. Pure *trans*-product **2.51** (5.35 g, 70% overall yield, >99% *ee*) was obtained as white crystals by recrystallization (THF/Hexane). mp 199-200 ^{o}C (THF/Hexane) ; Rf 0.14 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –32.0^{o} (c 1.0, CH_3CN, 99% *ee*); IR (KBr) 3345, 2980, 1778, 1719, 1621, 1548, 1471, 1394, 1377, 1344, 1311, 1294, 1246, 1208, 1165, 1097, 1031, 844, 763, 598 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.56(s, 1H), 8.20 (app dd, J = 2.4, 7.1 Hz, 1H), 7.80 (ddd, J = 2.4, 4.1, 8.7 Hz, 1H), 7.71(app dd, J = 8.7, 11.2 Hz, 1H), 6.25 (d, J = 2.6 Hz, 1H), 5.44 (d, J = 2.6 Hz, 1H), 4.28-4.12 (comp, 2H), 1.56 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 188.8, 168.5, 154.8 (d, $J_{C\text{-}F}$ = 263.1 Hz), 153.8, 136.6 (d, $J_{C\text{-}F}$ = 7.8 Hz), 135.4 (d, $J_{C\text{-}F}$ = 4.0 Hz), 134.3 (d, $J_{C\text{-}F}$ = 9.5 Hz), 124.6 (d, $J_{C\text{-}F}$ = 2.4 Hz), 119.2 (d, $J_{C\text{-}F}$ = 21.3 Hz), 82.3, 75.4, 64.2, 60.6, 24.0; *m/z* (ESI-MS) 384.1 $[MH]^+$.

(4R,5S)-ethyl 5-(4-fluoro-3-nitrophenyl)-2-thioxooxazolidine-4-carboxylate (2.66t):



Following the general procedure, the title compound was obtained as a pale yellow oil. Rf 0.21 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ +14.5° (c 1.0, CH_2Cl_2, 92% *ee*); IR (neat) 3304, 2986, 1747, 1623, 1596, 1540, 1527, 1351, 1235, 1172, 1087, 1014, 921, 837, 736, 547 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.23-8.10 (comp, 2H), 7.76 (ddd, *J* = 2.4, 4.0, 8.7 Hz, 1H), 7.40 (app dd, *J* = 8.7, 10.1 Hz, 1H), 6.02 (d, *J* = 6.6 Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 4.45-4.28 (comp, 2H), 1.37 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.5, 167.5, 156.0 (d, $J_{C\text{-}F}$ = 268.0 Hz), 137.8 (d, $J_{C\text{-}F}$ = 8.4 Hz), 134.0 (d, $J_{C\text{-}F}$ = 4.2 Hz), 133.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 124.0 (d, $J_{C\text{-}F}$ = 2.4 Hz), 119.8 (d, $J_{C\text{-}F}$ = 21.4 Hz), 83.5, 64.6, 63.7, 14.3; *m/z* (ESI-MS) 315.0 $[MH]^+$, 337.3 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=12.5 min and t_R=14.2 min (major).

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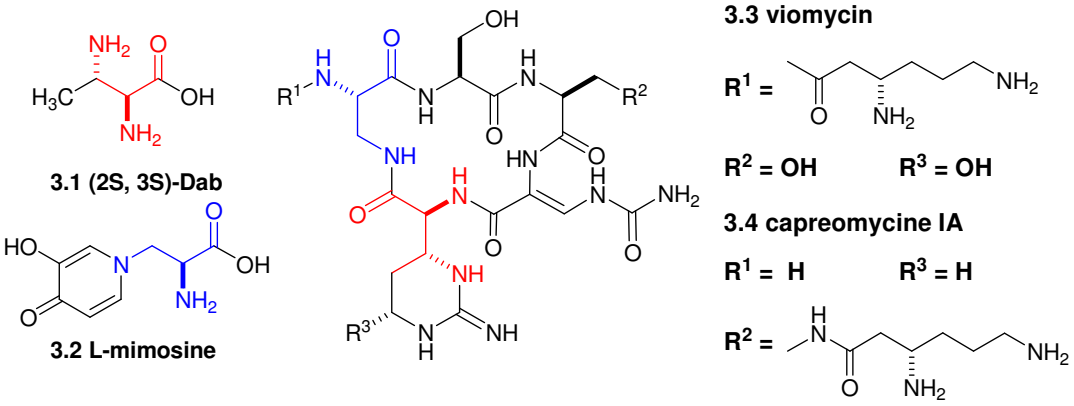
Chapter III

Catalytic Enantioselective Synthesis of α,β-Diamino Acid Derivatives

3.1 Background

3.1.1 Significance of Chiral α,β-Diamino Acid Derivatives

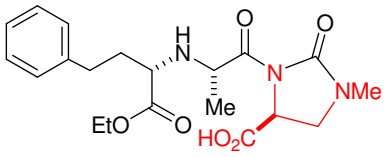
Scheme 3.1 **Selected Natural Products Containing an α,β-Diamino Acid Moiety**



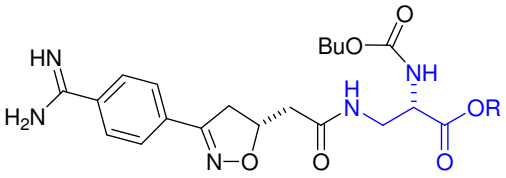
Vicinal diamines are important structural motifs that have been incorporated into chiral auxiliaries, catalysts and ligands.[1] α,β-Diamino acids and their derivatives are part of many biologically active natural products (Scheme 3.1).[2] For example, the polycondensation of Dab **3.1** and some other diamino acids are related to the prebiotic evolution of DNA and RNA genomes. In addition, capreomycins are a class of antibiotics, which have been used in the therapy of tuberculosis. Moreover, some synthetic materials derived from α,β-diamino acids have been used in the treatment of diseases (Scheme 3.2).[2] For instance, imidapril **3.5** is an ACE inhibitor and has been

used clinically for hypertension, chronic congestive heart failure, acute myocardial infarction and diabetic nephropathy. In addition, roxifiban **3.6**, also known as DMP754, is a selective oral antagonist of the platelet glycoprotein IIb/IIIa receptor.

Scheme 3.2 **Selected Synthetic Materials Containing α,β-Diamino Acid Moiety**



3.5 imidapril

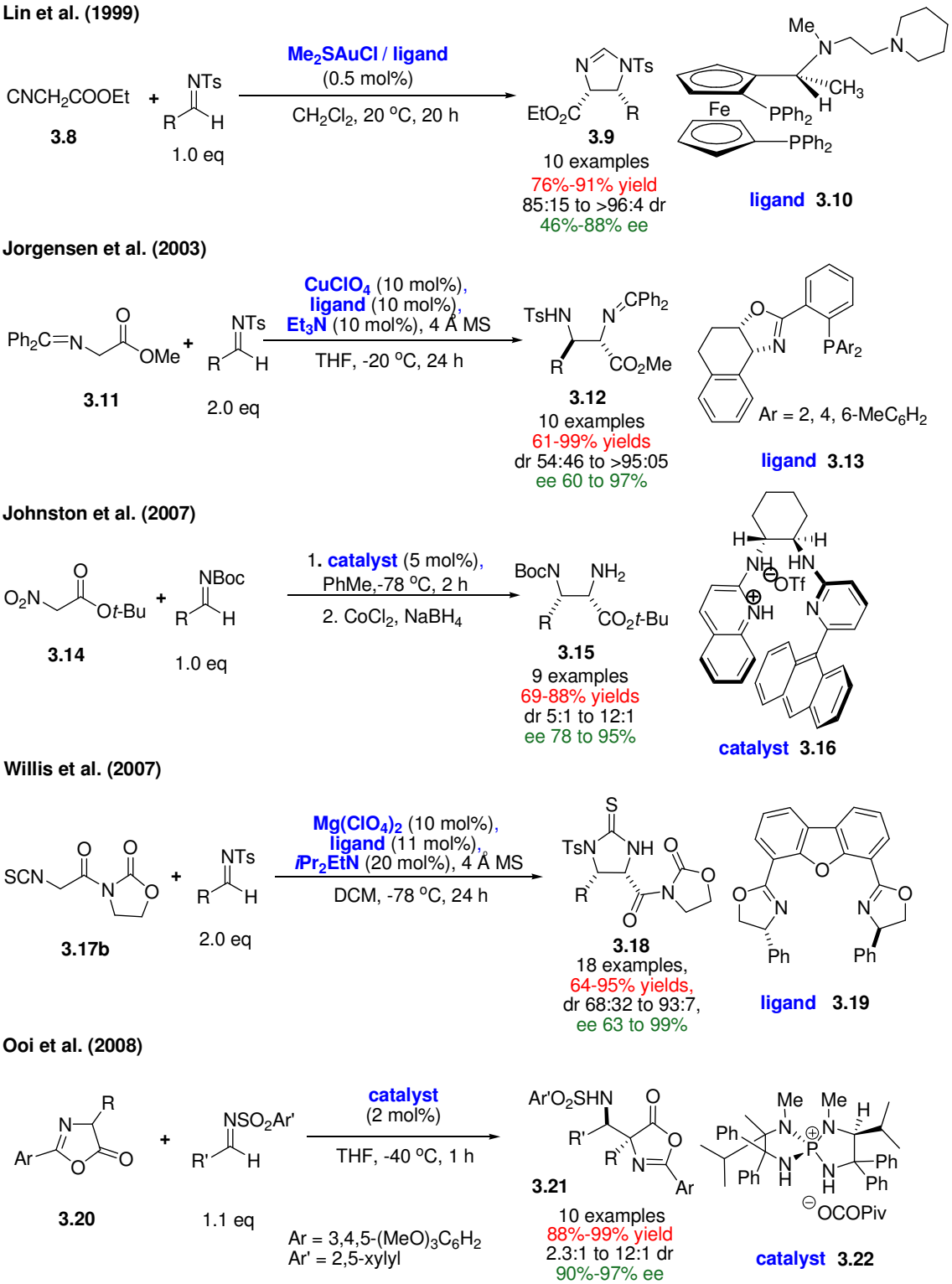


3.6 R = Me, roxifiban (DMP754)
3.7 R = H, XV459

3.1.2 Synthetic Methods for α,β-Diamino Acid Derivatives

Various diastereoselective methods for the synthesis of α,β-diamino acid derivatives have been reported.[3] Catalytic enantioselective approaches have focused on Mannich reactions of glycine imines[4] or nitro esters[5] with various imines. In 2003 Jørgensen et al. reported chiral Copper(I)-**3.13** complex-catalyzed the enantioselective Mannich reactions of imines of glycine alkyl esters with imines.[4a] Five years later, Kobayashi et al. reported the organocatalytic version of this reaction featured with the fluorenone imines of glycine esters as the substrate and a chiral guanidine catalyst.[4e] In 2007, Johnston et al. discovered enantioselective Mannich reactions of nitro esters with imines using a protonated catalyst **3.16**.[5a] In 2008, Hou and Wu et al. realized the highly diastereoselective switchable enantioselective Mannich reaction.[4f] Both *anti* and *syn* products can be obtained in a highly enantioselective fashion. The key of this reaction is

Scheme 3.3 Direct Mannich Reactions for the Synthesis of Chiral α,β-Diamino Acids

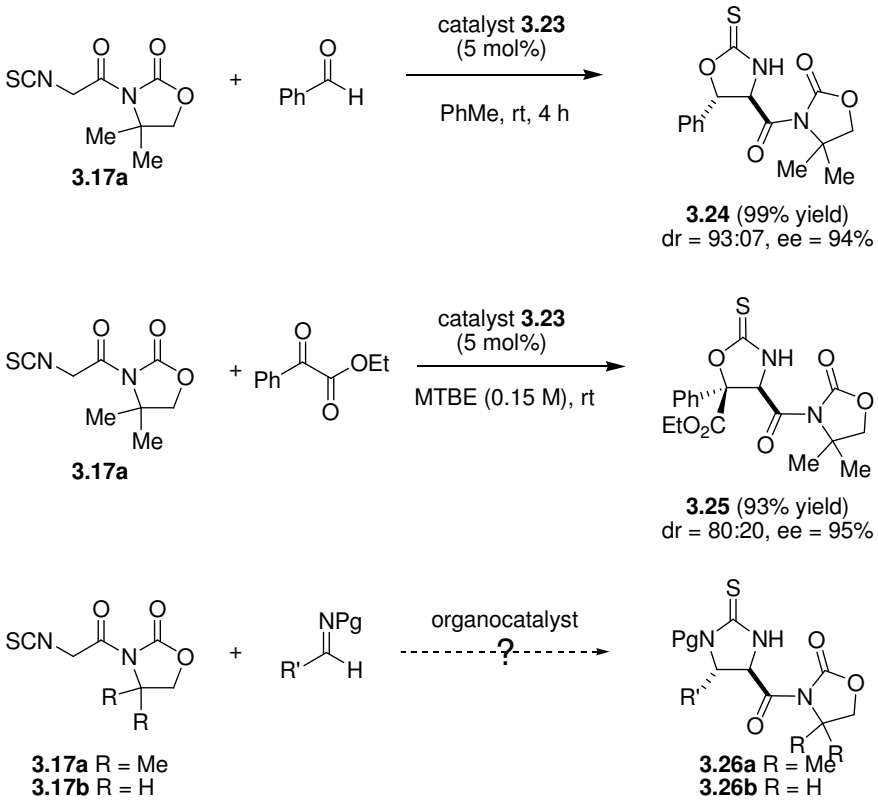


the use of a family of chiral ferrocene ligands. Later, another *anti*-selective Mannich reaction has been reported by Carretero et al.[4g] Furthermore, catalytic enantioselective Mannich reactions of nitroalkanes or silyl nitronates with α-imino esters have also been reported.[6] In addition, α-isocyano esters[7] and azlactones[8] have been employed as glycine equivalents in Mannich reactions. Willis and coworkers have recently used the α-isothiocyanato imide **3.17b** in highly enantioselective aldol and Mannich reactions.[9,10] Using a chiral magnesium complex derived from DBFox **3.19**, products such as **3.18b** were obtained with high levels of enantioselectivity favoring the *anti* product.[9b]

3.2 Proposal and Objective

Although Willis' report has shown that chiral α,β-diamino acid derivatives can be obtained by the metal catalyzed Mannich reaction of α-isothiocyanato imides with imines, no organocatalytic examples of this reaction have been developed. Based on our recent success in using α-isothiocyanato imide **3.17a** in catalytic enantioselective aldol reactions employing catalyst **3.23**,[11] we sought to expand this methodology to the corresponding Mannich reaction (Scheme 3.4). Our approach relies on Mannich reactions between α-isothiocyanato imides and sulfonyl imines (or other activated imines) using readily available organocatalysts.

Scheme 3.4 **Organocatalytic Reactions Using α-Isothiocyanato Imides**



The objective of this project was to develop a convenient method (relatively low catalyst loadings, ambient temperature, scaleable) to access chiral α,β-diamino acid derivatives since few methods currently available are economical for the scale-up synthesis of this building block. In the following part of this chapter, I will report the development of this catalytic enantioselective process.

3.3 Results and Discussions

3.3.1 General Considerations

Since N-alkyl and N-aryl imines are poorer electrophiles than aldehydes, some readily available activated imines could be good candidates for this reaction, such as N-

Boc, N-phosphoryl and N-sulfonyl imines. In addition, it is hard to predict whether the organocatalytic process will be *syn*-selective or *anti*-selective, although Willis' protocol led to *anti* product. The interesting finding that product precipitation can accelerate reactions and lower catalyst loadings in our previously reported aldol reactions could be also applied to this reaction.

3.3.2 Reaction Development

With these considerations in mind, a reaction of **3.17a** with the tosyl imine derived from benzaldehyde was selected as a model reaction. The first trial was incomplete after 3 days when using 5 mol% of catalyst **3.23**. Product **3.18a** was obtained in modest enantioselectivity and yield but with good diastereoselectivity favoring the *syn*-diastereomer (Table 3.1, entry 1). Subsequently, other readily available organocatalysts[12–14] were evaluated. To our delight, the quinidine-derived bifunctional

Scheme 3.5 **Readily Available Organocatalysts for Evaluation**

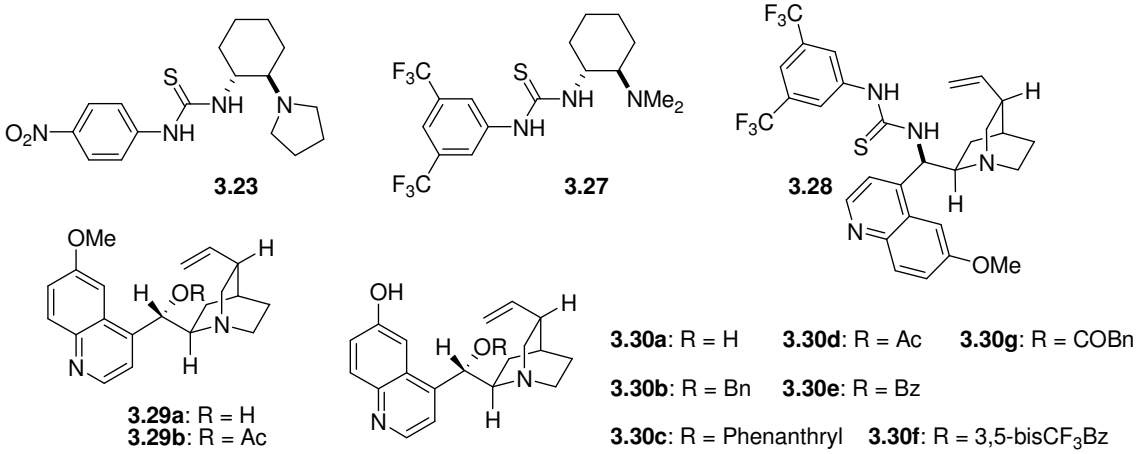
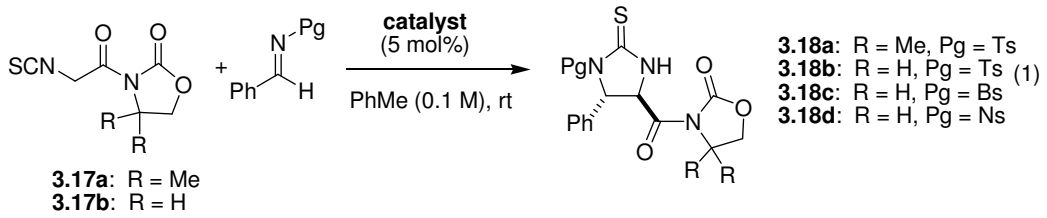


Table 3.1 **Evaluation of Catalysts and Protecting Groups**[a]



Entry	Catalyst	Sm	Pg	Time [h]	Yield [%][b]	dr [%][c]	ee [%][d]
1[e]	**3.23**	**3.17a**	Ts	72	49	94:06	-56
2[e]	**3.27**	**3.17a**	Ts	72	33	90:10	-31
3[e]	**3.28**	**3.17a**	Ts	72	27	87:13	-56
4[e]	**3.30b**	**3.17a**	Ts	72	31	>95:05	60
5[e]	**3.30c**	**3.17a**	Ts	72	22	>95:05	84
6[e]	**3.30d**	**3.17a**	Ts	72	35	>95:05	95
7[e]	**3.30e**	**3.17a**	Ts	72	29	>95:05	96
8	**3.23**	**3.17b**	Ts	48	81	91:09	-61
9	**3.30d**	**3.17b**	Ts	15	94	>95:05	98
10	**3.30e**	**3.17b**	Ts	18	96	>95:05	98
11	**3.30f**	**3.17b**	Ts	42	95	>95:05	95
12	**3.30g**	**3.17b**	Ts	17	94	>95:05	98
13	**3.30d**	**3.17b**	Bs	1.5	95	>95:05	98
14[e]	**3.30d**[f]	**3.17b**	Ts	72	92	>95:05	97
15	**3.30d**[f]	**3.17b**	Bs	10	95	>95:05	97
16	**3.30d**[f]	**3.17b**	Ns	5.5	95	>95:05	97
17[e]	**3.29a**	**3.17b**	Ts	72	80	92:08	55
18[e]	**3.29b**	**3.17b**	Ts	72	62	93:07	50
19[e]	**3.30a**	**3.17b**	Ts	72	79	94:06	52

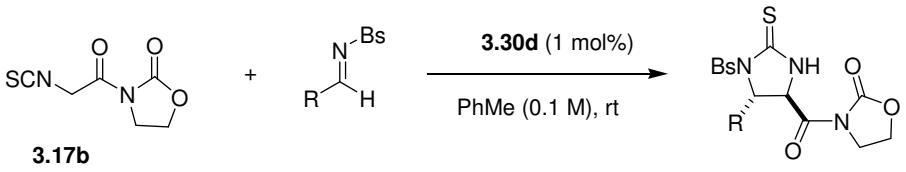
[a] Reactions were performed at rt on a 0.2 mmol scale in anhydrous toluene (0.1 M) using 1.5 equiv of imine. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis of the ester derivatives. [b] Combined yield of both diastereomers. [c] *trans*:*cis*, determined by ^{1}H-NMR. [d] *trans* isomer. [e] The reaction is incomplete. [f] Run with 1 mol% catalyst loading.

catalyst **3.30d**, pioneered by Deng,[14b] provided product **3.18a** in excellent enantio- and diastereoselectivity (entry 6). However, a low reaction rate was observed. Interestingly, significant rate acceleration was achieved by using the unsubstituted α-isothiocyanato imide **3.17b** in place of **3.17a** (entry 9). It was found that product **3.18b** is less soluble in toluene than **3.18a**, limiting the possibility of product inhibition. This should serve at least in part to explain the faster reaction rates observed with this substrate. The nature of the acyl group on catalyst **3.30** was found to have little effect on the ee and dr of the product, with more electron withdrawing groups resulting in lower reaction rates (entries 9–12).

We next focused on the use of other imine protecting groups.[15] Remarkably, replacement of the tosyl group for the simpler benzenesulfonyl (Bs) analogue resulted in a ten-fold rate increase (compare entries 9 and 13). While subtle electronic effects can be invoked to partially rationalize this dramatic rate acceleration, we noted a marked solubility difference in the two products with **3.18c** being less soluble than **3.18b**. This allowed for reduction of the catalyst loading to 1 mol% while maintaining reasonable reaction rates and without adverse effects on the stereoselectivity (entry 15). Employment of the synthetically useful 4-nosyl (Ns) protecting group allowed for complete conversion in only 5.5 hours with 1 mol% of catalyst **3.30d** (entry 16). Control experiments with structurally related quinidine derivatives showed that a free hydroxyl group on the quinoline ring is important for both reactivity and selectivity (entries 17–19). In agreement with Deng's findings,[14b] this suggests a bifunctional role for catalyst **3.30d**.

3.3.3 Substrate Scope

Table 3.2 **Scope of the Reaction**[a]



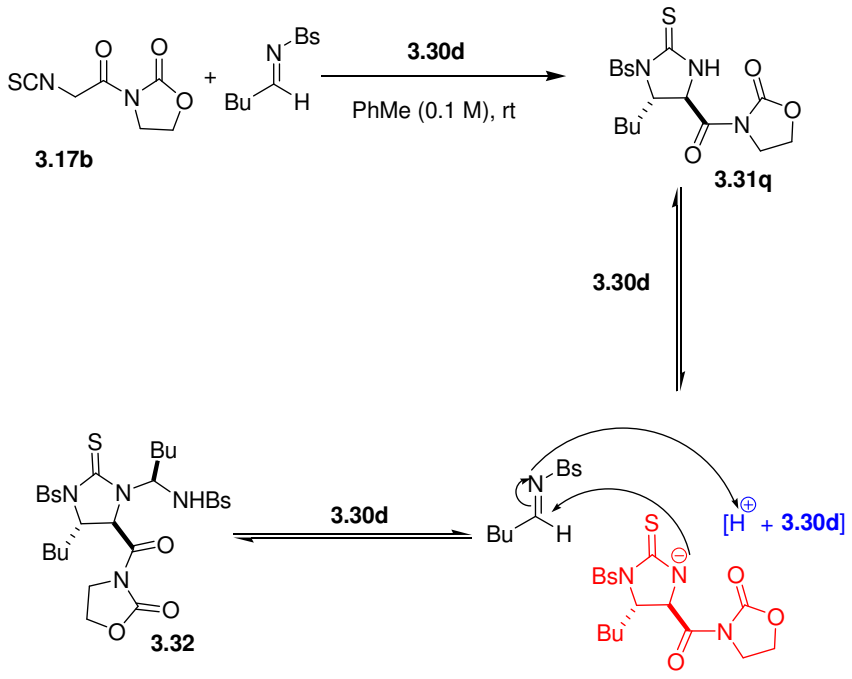
Entry	R	Product	Time [h]	Yield [%][b]	dr[c]	ee [%]
1	Ph	**3.18c**	15	97	>95:05	98
2	4-Me-C_6H_4	**3.31a**	10	96	>95:05	99
3	4-NO_2-C_6H_4	**3.31b**	3	85	92:08	93
4	4-Cl-C_6H_4	**3.31c**	15	92	>95:05	98
5	4-F-C_6H_4	**3.31d**	10	93	>95:05	97
6	4-MeO-C_6H_4	**3.31e**	9	87	>95:05	99
7	3-Me-C_6H_4	**3.31f**	10	95	>95:05	99
8	3-Br-C_6H_4	**3.31g**	7	94	>95:05	97
9	3-MeO-C_6H_4	**3.31h**	15	99	>95:05	97
10[d]	2-Cl-C_6H_4	**3.31i**	48[e]	80	72:28	91
11	2-Me-C_6H_4	**3.31j**	48[e]	90	>95:05	98
12	2-naphthyl	**3.31k**	3	90	>95:05	99
13	1-naphthyl	**3.31l**	48[e]	82	92:08	95
14	2-thienyl	**3.31m**	8	95	>95:05	97
15	2-furyl	**3.31n**	12	97	81:19	92
16	cinnamyl	**3.31o**	44	90	85:15	95
17	CH_2CH_2Ph	**3.31p**	40	90	91:09	89
18	*n*-Bu	**3.31q**	48[e]	53	83:17	91

[a] Reactions were run at rt on a 1 mmol scale using 1.5 equiv of imine. The ee's were determined by HPLC analysis of the ester derivatives. [b] Combined yield of both diastereomers. [c] *trans*:*cis*, determined by ^{1}H-NMR. [d] 1.1 equiv of imine was used. [e] The reaction is incomplete.

With the optimized reaction conditions in hand, a series of different Bs protected imines was evaluated (Table 3.2). Electron-rich and electron-poor aromatic imines with

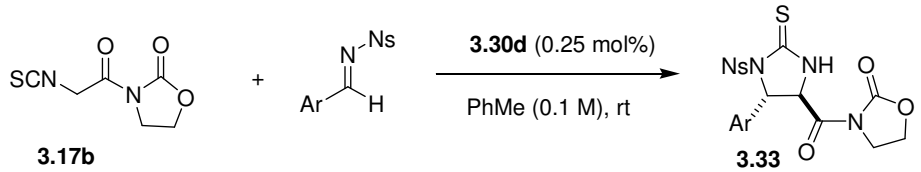
different substitution patterns provide products in generally good yields and with high levels of diastereo- and enantioselectivity (entries 1–13). Heteroaromatic and α,β-unsaturated imines are also viable substrates (entries 14–16).

Scheme 3.6 **Proposed Mechanism of Aminal Product Formation**



In addition, although aliphatic aldimines are typically less stable, these substrates are compatible with the current method. In the reaction yielding product **3.31q**, an aminal byproduct **3.32** was isolated in 27% yield. This byproduct **3.32** results from **3.31q** reacting with an additional equivalent of imine (Scheme 3.6).[16]

Table 3.3 **Reactions with Lower Catalyst Loading**[a]



Entry	Ar	Product	Time [h]	Yield [%][b]	dr[c]	Ee [%]
1	4-Me-C_6H_4	**3.33a**	20	90	95:05	98
2	3-MeO-C_6H_4	**3.33b**	24	92	91:09	97
3	2-naphthyl	**3.33c**	48	87	92:08	94

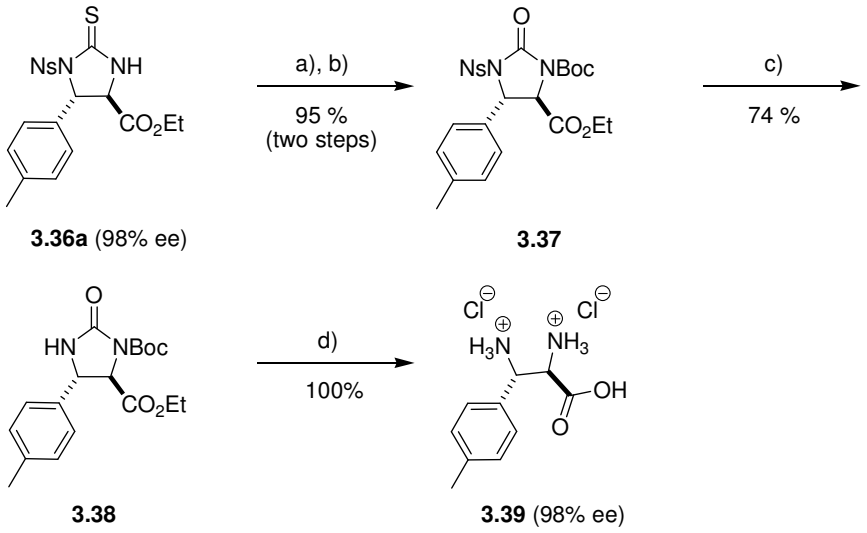
[a] Reactions were run at rt on a 1 mmol scale using 1.5 equiv of imine. The ee's were determined by HPLC analysis of the ester derivatives. [b] Combined yield of both diastereomers. [c] *trans*:*cis*, determined by ^{1}H-NMR.

It was generally observed that reactions yielding more soluble products (e.g., **3.31l**) suffer from lower reaction rates. This is in agreement with our hypothesis that rapid catalyst turnover is linked to product precipitation. In an attempt to lower catalyst loadings further, we evaluated several more reactive and less soluble N-nosyl imines (Table 3.3). Gratifyingly, a catalyst loading of 0.25 mol% can routinely be applied to these substrates. High levels of stereoselectivity are preserved while reaction rates remain reasonable.

3.3.4 Synthesis of a Chiral α,β-Diamino Acid

Starting with product **3.36a**, a facile sequence was developed to access the corresponding α,β-diamino acid. Following the straightforward sequence outlined in Scheme 3.7, the highly enantioenriched α,β-diamino acid **3.39** was obtained in good yield and without loss of ee.

Scheme 3.7 **Conversion of the Product 3.36a into Its Corresponding Diamino Acid**



Reaction Conditions: a) Boc_2O/DMAP, CH_2Cl_2, rt, 4h, 99%; b) $Hg(OAc)_2$, CH_2Cl_2, rt, 24h, 96%; c) PhSH, K_2CO_3, DMF, rt, 3h, 74%; d) 2 M HCl aq., reflux, 5h, 100%.

3.3.5 Conclusion

In summary, we have reported catalytic enantioselective Mannich reactions of α-isothiocyanato imides with sulfonyl protected imines. *Syn*-α,β-diamino acid derivatives can be obtained in highly diastereo- and enantioselective fashion using substrate/catalyst ratios as high as 400:1. Product precipitation based approaches might offer a general solution to achieving lower catalyst loadings in a variety of different processes.

3.3.6 Latest Development in this Area

In 2009, Arrayás and Carretero reviewed the catalytic asymmetric direct Mannich reactions for the synthesis of chiral α,β-diamino acids.[17] Recently, Zhong et al. reported an approach to *syn*-α,β-diamino acid derivatives that is similar to our methodology.[18].

3.4 Experimental Section

3.4.1 Preparation Procedures for Substrates and Catalysts

The substrates **3.17a** and **3.17b** were prepared according to literature methods.[9a,10a,11] The imines were prepared according to literature methods.[19,20,21] The catalysts **3.23, 3.27–3.30** were prepared according to literature methods.[11,14]

3.4.2 General Procedure for the Catalytic Mannich Reaction Between Isothiocyanates and Imines

Catalyst **3.30d** (3.5 mg, 0.01 mmol), 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one (**3.17b**) (186 mg, 1.00 mmol) and the corresponding imine (1.50 mmol) were dissolved in anhydrous toluene (10 mL) at room temperature. The reaction progress was monitored by TLC analysis. Upon consumption of **3.17b,** the crude reaction mixture was applied to silica gel and the mixture of diastereomeric products was obtained by flash chromatography (CH_2Cl_2/EtOAc/hexanes 1:1:1 or CH_2Cl_2/EtOAc 100:10 v/v).

3.4.3 General Procedure for the Conversion of Primary Products into Their Corresponding Ethyl Esters

The mixture of diastereomeric products **3.18**, **3.31** or **3.33** was dissolved in dry THF (20 mL) and cooled to 0 °C. A solution of methyl magnesium iodide (1.2 eq., 3M in THF) in ethanol (8 mL) at 0 °C was added *via* syringe. After 2 min, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (8 mL). The mixture was concentrated in vacuo, taken up in aqueous HCl (1 M, 16 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15

mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc 100:1 or 100:2 v/v) to obtain the corresponding *trans*-ethyl esters as solids or colorless oils. Yields in this step are between 75%-85%.

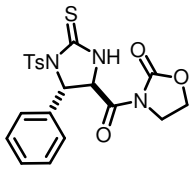
3.4.4 Preparation Procedures for Racemic Samples

Racemic compounds were prepared from ethyl 2-thiocyanatoacetate by using DABCO/toluene or a literature method.[22]

3.4.5 Product Characterization Data

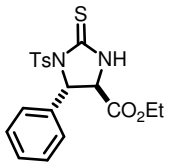
4,4-dimethyl-3-((4R,5S)-5-phenyl-2-thioxo-1-tosylimidazolidine-4-carbonyl) oxazolidin-2-one (3.18a): Following the general procedure, the product (mixture of diastereomers) was obtained as white foam in 98% yield. An analytical sample of the pure *trans*-diastereomer was obtained by flash chromatography. R_f 0.52 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ –14.0 (c 1.0, $CHCl_3$); IR (neat) 3380, 2976, 1777, 1707, 1596, 1470, 1397, 1361, 1310, 1244, 1168, 1094, 1061, 1032, 761, 701, 670, 597, 572, 544 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.41–7.30 (comp, 5H), 7.17 (br s, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.26 (d, *J* = 2.1 Hz, 1H), 4.88 (app t, *J* = 2.1 Hz, 1H), 4.18–4.08 (comp, 2H), 2.36 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 167.4, 154.5, 145.0, 138.6, 135.1, 129.7, 129.4, 129.3, 128.9, 127.2, 76.4, 66.2, 64.9, 61.6, 24.9, 24.7, 21.9; *m/z* (ESI-MS) 474.1 $[MH]^+$, 496.2 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 280 nm, t_R=16.9 min (major) and t_R=23.1 min.

3-((4R,5S)-5-phenyl-2-thioxo-1-tosylimidazolidine-4-carbonyl)oxazolidin-2-one

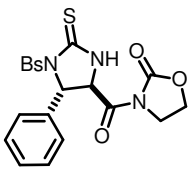


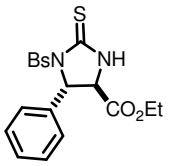
(3.18b): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 98% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 228–229 °C (CH_2Cl_2/hexanes); R_f 0.24 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +18.5 (c 0.5, acetone); IR (KBr) 3365, 3066, 1799, 1778, 1702, 1494, 1396, 1366, 1267, 1216, 1166, 1116, 671 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 9.76 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.43–7.36 (comp, 3H), 7.36–7.30 (comp, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 5.97 (d, *J* = 1.5 Hz, 1H), 5.15 (d, *J* = 1.5 Hz, 1H), 4.53–4.38 (comp, 2H), 4.02–3.85 (comp, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.7, 168.0, 153.7, 144.3, 139.4, 135.3, 128.8, 128.7, 128.5, 128.5, 126.7, 66.7, 63.3, 61.8, 42.7, 21.0; *m/z* (ESI-MS) 446.1 $[MH]^+$, 468.2 $[MNa]^+$.

(4R,5S)-ethyl 5-phenyl-2-thioxo-1-tosylimidazolidine-4-carboxylate (3.34b):



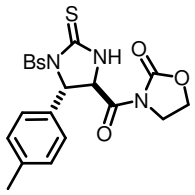
Colorless oil; R_f 0.42 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –20.0 (c 1.0, $CHCl_3$, 98% *ee*); IR (neat) 3349, 2982, 1742, 1596, 1493, 1367, 1216, 1169, 1089, 1064, 1019, 756, 702, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.42–7.32 (comp, 5H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.00 (br, s, 1H), 5.95 (d, *J* = 2.6 Hz, 1H), 4.37–4.23 (comp, 2H), 4.18 (dd, *J* = 2.6, 1.0 Hz, 1H), 2.37 (s, 3H), 1.33 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 168.5, 145.2, 138.9, 135.0, 129.6, 129.4, 129.4, 129.0, 126.8, 67.7, 63.4, 63.1, 21.9, 14.3; *m/z* (ESI-MS) 405.3 $[MH]^+$, 427.2 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.3 min (major) and t_R=12.6 min.

3-((4R,5S)-5-phenyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.18c):  Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 97% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 225–226 °C (CH_2Cl_2/hexanes); R_f 0.21 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +22.5 (c 1.0, acetone); IR (KBr) 3363, 3069, 2996, 1778, 1702, 1495, 1396, 1365, 1268, 1214, 1167, 1114, 725, 692, 605, 570 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 9.83 (s, 1H), 7.70–7.59 (comp, 3H), 7.51–7.43 (m, 2H), 7.43–7.28 (comp, 5H), 6.00 (d, *J* = 1.4 Hz, 1H), 5.17 (d, *J* = 1.4 Hz, 1H), 4.56–4.39 (comp, 2H), 4.05–3.85 (comp, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 179.6, 168.0, 153.7, 139.3, 138.2, 133.7, 128.6, 128.6, 128.6, 128.3, 126.7, 66.7, 63.3, 62.0, 42.7; *m/z* (ESI-MS) 432.2 $[MH]^+$, 454.2 $[MNa]^+$.

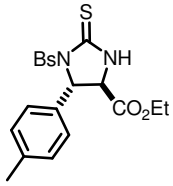
(4R,5S)-ethyl 5-phenyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.34c):  Colorless oil; R_f 0.61 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –10.5 (c 1.0, $CHCl_3$, 98% *ee*); IR (KBr) 3343, 3065, 2981, 1744, 1585, 1482, 1368, 1215, 1171, 1090, 1063, 1026, 857, 757, 726, 686, 600, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.62 (m, 2H), 7.55–7.49 (m, 1H), 7.42–7.28 (comp, 7H), 7.08 (br, s, 1H), 5.96 (d, *J* = 2.6 Hz, 1H), 4.37–4.23 (comp, 2H), 4.19 (d, *J* = 2.6 Hz, 1H), 1.33 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 168.5, 138.7, 138.0, 134.0, 129.5, 129.5, 129.4, 128.4, 126.8, 67.7, 63.4, 63.1, 14.3; *m/z* (ESI-MS) 391.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.9 min (major) and t_R=11.6 min.

3-((4R,5S)-5-phenyl-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.18d): Following the general procedure, the product (mixture of diastereomers) was obtained as a pale yellow solid in 97% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp >250 °C (CH_2Cl_2/hexanes); R_f 0.24 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +41.5 (c 0.5, acetone); IR (KBr) 3363, 3105, 2998, 1796, 1777, 1702, 1531, 1495, 1396, 1378, 1349, 1267, 1213, 1175, 1115, 854, 740, 608, 569 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 10.02 (s, 1H), 8.28 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.45–7.38 (comp, 3H), 7.38–7.29 (comp, 2H), 6.07 (d, *J* = 1.3 Hz, 1H), 5.20 (d, *J* = 1.3 Hz, 1H), 4.54–4.39 (comp, 2H), 4.05–3.85 (comp, 2H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.4, 167.9, 153.5, 150.2, 143.2, 139.0, 130.3, 128.8, 128.7, 126.6, 123.5, 66.9, 63.1, 61.7, 42.3; *m/z* (ESI-MS) 477.4 $[MH]^+$.

(4R,5S)-ethyl 1-(4-nitrophenylsulfonyl)-5-phenyl-2-thioxoimidazolidine-4-carboxylate (3.34d): Pale yellow oil; R_f 0.42 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –47.0 (c 1.0, $CHCl_3$, 98% *ee*); IR (neat) 3385, 3107, 2983, 1743, 1532, 1493, 1371, 1350, 1240, 1214, 1173, 1088, 1065, 1013, 855, 740, 639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16–8.08 (m, 2H), 7.79–7.71 (m, 2H), 7.49–7.42 (m, 1H), 7.42-7.36 (comp, 2H), 7.36-7.30 (comp, 2H), 7.19 (br, s, 1H), 5.97 (d, *J* = 2.4 Hz, 1H), 4.40–4.28 (comp, 2H), 4.26 (d, *J* = 2.4 Hz, 1H), 1.36 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 168.2, 150.7, 143.3, 138.2, 130.9, 130.0, 129.7, 127.1, 123.4, 67.7, 63.4, 63.3, 14.3; *m/z* (ESI-MS) 436.3 $[MH]^+$, 458.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=45.7 min (major) and t_R=26.7 min.

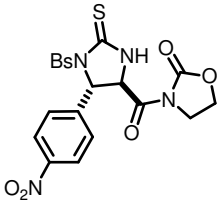
3-((4R,5S)-5-(4-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31a): 

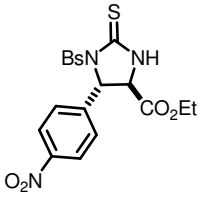
Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 96% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 234–235 °C (CH_2Cl_2/hexanes); R_f 0.21 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +13.0 (c 0.5, acetone); IR (KBr) 3369, 3062, 2995, 2922, 1778, 1702, 1492, 1396, 1366, 1266, 1217, 1168, 1117, 1087, 726, 687, 597, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (app d, *J* = 7.4 Hz, 2H), 7.53 (app t, *J* = 7.4 Hz, 1H), 7.34 (app t, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.13 (br, s, 1H), 6.32 (d, *J* = 1.2 Hz, 1H), 4.85 (app t, *J* = 1.9 Hz, 1H), 4.63–4.48 (comp, 2H), 4.17–4.04 (comp, 2H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 166.6, 154.1, 139.5, 138.1, 135.4, 133.9, 130.0, 129.7, 128.3, 127.0, 66.0, 63.9, 63.7, 42.9, 21.5; *m/z* (ESI-MS) 446.3 $[MH]^+$, 468.2 $[MNa]^+$.

(4R,5S)-ethyl 5-(4-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35a): 

Colorless oil; R_f 0.63 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –19.0 (c 1.0, $CHCl_3$, 99% *ee*); IR (KBr) 3341, 3064, 2985, 2928, 1753, 1496, 1449, 1365, 1216, 1170, 1090, 1066, 1025, 822, 756, 727, 686, 594, 570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.62 (m, 2H), 7.55–7.48 (m, 1H), 7.36–7.28 (m, 2H), 7.25–7.09 (comp, 5H), 5.91 (d, *J* = 2.6 Hz, 1H), 4.36–4.20 (comp, 2H), 4.16 (d, *J* = 2.6 Hz, 1H), 2.37 (s, 3H), 1.31 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 168.5, 139.5, 138.1, 135.8, 133.9, 130.0, 129.5, 128.3, 126.8, 67.6, 63.5, 63.1, 21.4, 14.3; *m/z* (ESI-MS) 405.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H,

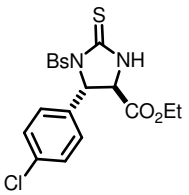
hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.2 min (major) and t_R=10.9 min.

3-((4R,5S)-5-(4-nitrophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31b):  Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 85% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 240–241 °C (CH_2Cl_2/hexanes); R_f 0.13 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +32.0 (c 1.0, acetone); IR (KBr) 3348, 3113, 3046, 1776, 1767, 1707, 1526, 1489, 1458, 1390, 1347, 1260, 1219, 1182, 1169, 1117, 1088, 1057, 621, 587, 567 cm^{-1}; ^{1}H NMR (500 MHz, *d*$_6$-DMSO) δ 9.94 (s, 1H), 8.32–8.27 (m, 2H), 7.77–7.71 (m, 2H), 7.70–7.63 (m, 1H), 7.63–7.56 (m, 2H), 7.54–7.46 (m, 2H), 6.21 (d, *J* = 1.6 Hz, 1H), 5.18 (d, *J* = 1.6 Hz, 1H), 4.55–4.39 (comp, 2H), 4.05–3.84 (comp, 2H);^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.5, 167.6, 153.8, 147.5, 146.4, 138.0, 134.0, 128.6, 128.5, 128.2, 123.9, 65.6, 63.4, 61.4, 42.6; *m/z* (ESI-MS) 477.2 $[MH]^+$, 499.1 $[MNa]^+$.

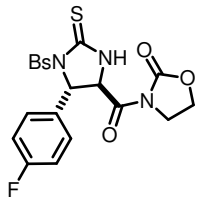
(4R,5S)-ethyl 5-(4-nitrophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35b):  Colorless oil; R_f 0.52 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +20.5 (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 3418, 2981, 2918, 1746, 1627, 1605, 1525, 1483, 1350, 1216, 1174, 1090, 1065, 1024 cm^{-1}; ^{1}H NMR (500 MHz, *d*$_6$-DMSO) δ 10.30 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.76–7.49 (comp, 5H), 6.09 (d, *J* = 2.8 Hz, 1H), 4.36 (d, *J* = 2.8 Hz, 1H), 4.29–4.11 (comp, 2H), 1.21 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 178.3, 168.4, 147.6, 146.8, 137.8, 134.3, 128.7, 128.5, 127.5, 124.3,

65.8, 62.3, 62.1, 13.9; *m/z* (ESI-MS) 436.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=41.6 min (major) and t_R=29.1 min.

3-((4R,5S)-5-(4-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31c): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 92% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2. mp 240–242 °C (CH_2Cl_2); R_f 0.19 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +16.0 (c 1.0, acetone); IR (KBr) 3369, 3063, 2996, 1777, 1702, 1492, 1396, 1368, 1264, 1218, 1168, 1086, 1016, 725, 592, 570 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 9.87 (s, 1H), 7.74–7.69 (m, 2H), 7.69–7.62 (m, 1H), 7.54–7.44 (comp, 4H), 7.39–7.30 (m, 2H), 6.04 (d, *J* = 1.4 Hz, 1H), 5.15 (d, *J* = 1.4 Hz, 1H), 4.55–4.38 (comp, 2H), 4.04–3.84 (comp, 2H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.5, 167.8, 153.8, 138.4, 138.1, 133.9, 133.2, 128.6, 128.6, 128.6, 128.4, 66.0, 63.3, 61.7, 42.6; *m/z* (ESI-MS) 466.0 (^{35}Cl), 468.0 (^{37}Cl) $[MH]^+$, 488.1 (^{35}Cl), 490.1 (^{37}Cl) $[MNa]^+$.

(4R,5S)-ethyl 5-(4-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35c): 

Colorless oil; R_f 0.62 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –19.0 (c 1.0, $CHCl_3$, 98% *ee*); IR (KBr) 3319, 3067, 2982, 1745, 1701, 1594, 1493, 1448, 1371, 1212, 1172, 1089, 1064, 1014, 836, 755, 726, 685, 591, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.59–7.52 (m, 1H), 7.43–7.23 (comp, 7H), 5.91 (d, *J* = 2.7 Hz, 1H), 4.35–4.22 (comp, 2H), 4.14 (dd, *J* = 2.7, 1.0 Hz, 1H), 1.31 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 168.3, 137.9, 137.3, 135.5, 134.2, 129.6, 129.4, 128.5, 128.2, 67.0, 63.3, 63.3, 14.3; *m/z* (ESI-MS) 425.2 (^{35}Cl), 427.2 (^{37}Cl) $[MH]^+$, 447.1 (^{35}Cl), 449.1 (^{37}Cl) $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 280 nm, t_R=17.4 min (major) and t_R=10.5 min.

3-((4R,5S)-5-(4-fluorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31d): 

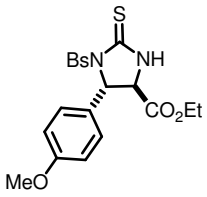
Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 93% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 244–245 °C (CH_2Cl_2/hexanes); R_f 0.19 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +37.0 (c 1.0, acetone); IR (KBr) 3367, 2996, 1799, 1778, 1702, 1512, 1493, 1396, 1368, 1267, 1217, 1168, 1116, 1064, 725, 599, 570 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 9.86 (s, 1H), 7.74–7.60 (comp, 3H), 7.48 (app t, *J* = 7.9 Hz, 2H), 7.43–7.32 (m, 2H), 7.25 (app t, *J* = 8.8 Hz, 2H), 6.03 (d, *J* = 1.2 Hz, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 4.56–4.36 (comp, 2H), 4.03–3.84 (comp, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 179.5, 167.9, 162.0 (d, $^1J_{C\text{-}F}$ = 244.9 Hz), 153.7, 138.2, 135.7 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 133.8, 128.9 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 128.6,

128.3, 115.4 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 66.0, 63.3, 61.9, 42.6; *m/z* (ESI-MS) 450.1 $[MH]^+$, 472.1 $[MNa]^+$.

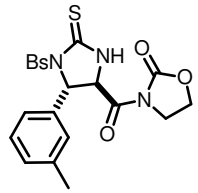
(4R,5S)-ethyl 5-(4-fluorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35d): Colorless oil; R_f 0.60 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –3.0 (c 1.0, $CHCl_3$, 97% *ee*); IR (KBr) 3348, 3067, 2984, 1745, 1606, 1511, 1369, 1227, 1172, 1091, 1064, 841, 756, 728, 686, 595, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.66 (m, 2H), 7.59–7.50 (m, 1H), 7.41–7.30 (comp, 4H), 7.10 (br, s, 1H), 7.08–7.01 (comp, 2H), 5.95 (d, *J* = 2.6 Hz, 1H), 4.36–4.23 (comp, 2H), 4.15 (dd, *J* = 2.6, 0.9 Hz, 1H), 1.33 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 168.4, 163.3 (d, $^1J_{C\text{-}F}$ = 249.2 Hz), 138.0, 134.7 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 134.2, 129.4, 128.8 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 128.5, 116.4 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 67.0, 63.4, 63.3, 14.3; *m/z* (ESI-MS) 409.0 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=17.1 min (major) and t_R=10.3 min.

3-((4R,5S)-5-(4-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31e): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 87% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 239–240 °C (CH_2Cl_2/hexanes); R_f 0.16 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ –5.5 (c 0.5, acetone); IR (KBr) 3347, 1771, 1708, 1514, 1497, 1466, 1391, 1352, 1259, 1224, 1171, 1092, 1062, 1034, 593, 568 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 9.80 (s, 1H), 7.67–7.60 (comp, 3H), 7.49–7.39 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.93 (d, *J* = 1.3 Hz, 1H), 5.14 (d, *J* = 1.3 Hz, 1H), 4.53–4.40 (comp, 2H), 4.03–3.85

(comp, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 179.5, 168.0, 159.4, 153.7, 138.3, 133.7, 131.5, 128.6, 128.2, 128.0, 113.9, 66.5, 63.3, 62.0, 55.2, 42.6; *m/z* (ESI-MS) 462.2 $[MH]^+$, 484.2 $[MNa]^+$.

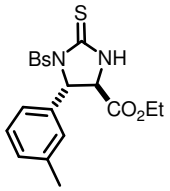


(4R,5S)-ethyl 5-(4-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35e): Pale yellow oil; R_f 0.50 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –31.5 (c 1.0, $CHCl_3$, 99% *ee*); IR (KBr) 3463, 3166, 3062, 2964, 2845, 1739, 1612, 1504, 1358, 1253, 1176, 1095, 1054, 823, 726, 686 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.55–7.48 (m, 1H), 7.36–7.30 (m, 2H), 7.28–7.23 (m, 2H), 7.20–7.12 (br, s, 1H), 6.89–6.82 (m, 2H), 5.90 (d, *J* = 2.6 Hz, 1H), 4.36–4.22 (comp, 2H), 4.17 (d, *J* = 2.6 Hz, 1H), 3.83 (s, 3H), 1.32 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 168.6, 160.4, 138.1, 133.9, 130.8, 129.4, 128.3, 128.3, 114.6, 67.4, 63.5, 63.0, 55.6, 14.3; *m/z* (ESI-MS) 443.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=22.7 min (major) and t_R=15.3 min.

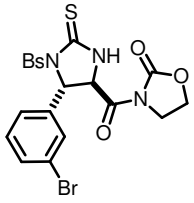


3-((4R,5S)-5-(3-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31f): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 95% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 217–218 °C (CH_2Cl_2/hexanes); R_f 0.21 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +25.0 (c 0.5, $CHCl_3$); IR (KBr) 3353, 1780, 1706, 1494, 1393, 1365, 1268, 1228, 1206, 1168, 1111, 1089, 1065, 726, 688, 606, 571 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.70 (m, 2H), 7.53 (app t, *J* = 7.5 Hz, 1H), 7.35 (app t, *J* = 7.9 Hz, 2H), 7.25–7.12 (comp, 4H), 7.07 (br, s, 1H), 6.34 (d, *J* = 1.9 Hz,

1H), 4.85 (app t, *J* = 1.9 Hz, 1H), 4.62–4.49 (comp, 2H), 4.18–4.04 (comp, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 166.4, 154.1, 139.3, 138.2, 138.0, 134.0, 130.2, 129.7, 129.3, 128.3, 127.4, 124.2, 66.0, 63.9, 63.6, 42.9, 21.6; *m/z* (ESI-MS) 446.1 $[MH]^+$, 468.1 $[MNa]^+$.

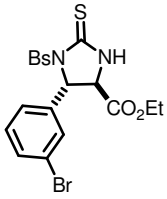


(4R,5S)-ethyl 5-(3-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35f): Colorless oil; R_f 0.64 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +7.5 (c 1.0, $CHCl_3$, 99% *ee*); IR (KBr) 3279, 3192, 2974, 1752, 1733, 1610, 1583, 1495, 1447, 1364, 1228, 1175, 1123, 791, 726, 572 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.62 (m, 2H), 7.58–7.48 (m, 1H), 7.38–7.29 (m, 2H), 7.26–7.04 (comp, 4H), 6.98–6.88 (br, s, 1H), 5.93 (d, *J* = 2.7 Hz, 1H), 4.38–4.23 (comp, 2H), 4.16 (d, *J* = 2.7 Hz, 1H), 2.29 (s, 3H), 1.33 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 168.5, 139.3, 138.5, 138.0, 134.0, 130.2, 129.5, 129.3, 128.3, 127.2, 124.0, 67.8, 63.4, 63.1, 21.5, 14.3; *m/z* (ESI-MS) 405.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=11.6 min (major) and t_R=10.1 min.

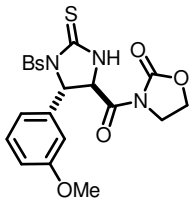


3-((4R,5S)-5-(3-bromophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31g): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 94% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 247–249 °C (CH_2Cl_2/hexanes); R_f 0.22 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +43.0 (c 0.25, $CHCl_3$); IR (KBr) 3357, 3059, 2993, 1794, 1777, 1705, 1489, 1394, 1371, 1264, 1214, 1168, 1114, 1087, 755, 725, 688, 604, 571 cm^{-1}; ^{1}H NMR (500 MHz, *d*$_6$-DMSO) δ 9.89 (s, 1H), 7.75–7.64 (comp, 3H),

7.63–7.57 (m, 1H), 7.55–7.44 (comp, 3H), 7.40 (app t, *J* = 7.8 Hz, 1H), 7.37-7.32 (m, 1H), 6.04 (d, *J* = 1.4 Hz, 1H), 5.17 (d, *J* = 1.4 Hz, 1H), 4.55–4.39 (comp, 2H), 4.03–3.85 (comp, 2H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.5, 167.8, 153.8, 141.8, 138.0, 134.0, 131.5, 130.9, 129.5, 128.6, 128.4, 125.7, 121.6, 65.9, 63.3, 61.7, 42.6; *m/z* (ESI-MS) 510.1 (^{79}Br), 512.0 (^{81}Br) $[MH]^+$, 532.1 (^{79}Br), 534.1 (^{81}Br) $[MNa]^+$.



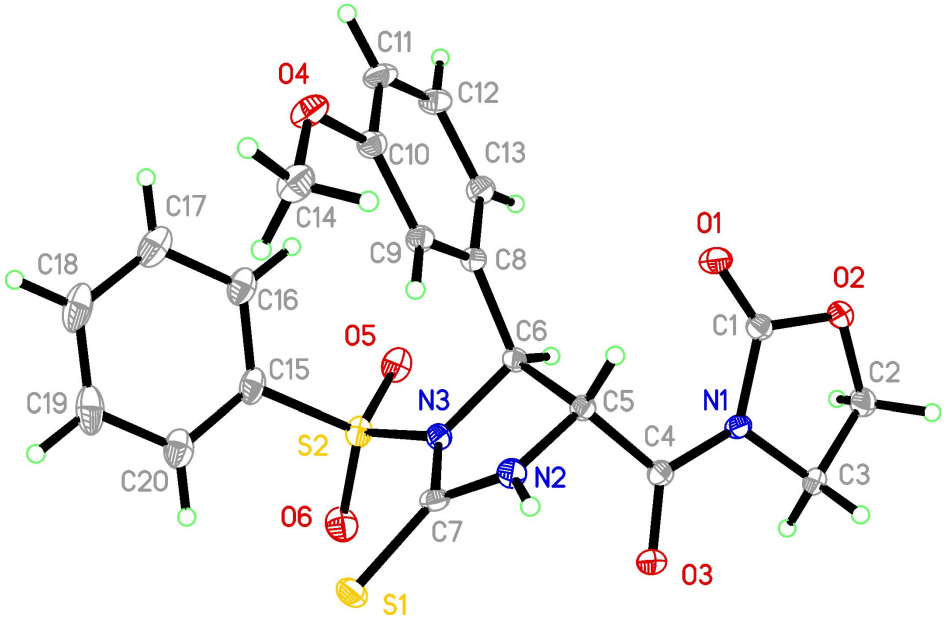
(4R,5S)-ethyl 5-(3-bromophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35g): Colorless oil; R_f 0.68 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +23.5 (c 1.0, $CHCl_3$, 97% *ee*); IR (KBr) 3352, 2984, 2935, 1738, 1576, 1491, 1369, 1265, 1218, 1173, 1091, 1066, 1024, 910, 790, 729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.68 (m, 2H), 7.59–7.53 (m, 1H), 7.53–7.47 (comp, 2H), 7.43–7.33 (comp, 3H), 7.31–7.19 (comp, 2H), 5.89 (d, *J* = 2.8 Hz, 1H), 4.35–4.20 (comp, 2H), 4.13 (dd, *J* = 2.8, 0.9 Hz, 1H), 1.30 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 168.2, 140.8, 137.8, 134.3, 132.6, 131.1, 129.6, 129.3, 128.5, 125.5, 123.4, 66.9, 63.3, 63.2, 14.3; *m/z* (ESI-MS) 469.0 (^{79}Br), 471.0 (^{81}Br) $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=13.2 min (major) and t_R=11.9 min.

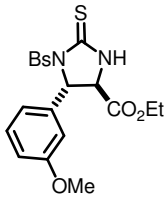
3-((4R,5S)-5-(3-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31h): 

Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 99% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 193–195 °C (CH_2Cl_2/hexanes); R_f 0.18 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +37.5 (c 1.0, acetone); IR (KBr) 3312, 3060, 2992, 2963, 2931, 2839, 1769, 1692, 1601, 1583, 1498, 1397, 1360, 1320, 1262, 1128, 1088, 1051, 798, 756, 727, 686, 632, 609, 575 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78–7.72 (m, 2H), 7.56–7.49 (m, 1H), 7.38–7.32 (m, 2H), 7.29–7.24 (m, 1H), 7.20 (br, s, 1H), 6.94–6.87 (comp, 2H), 6.82–6.78 (m, 1H), 6.32 (d, *J* = 1.9 Hz, 1H), 4.86 (app t, *J* = 1.9 Hz, 1H), 4.63–4.49 (comp, 2H), 4.17–4.04 (comp, 2H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 166.4, 160.3, 154.1, 139.6, 138.0, 134.0, 130.5, 129.7, 128.3, 119.1, 115.3, 112.0, 66.0, 63.8, 63.7, 55.5, 42.9; *m/z* (ESI-MS) 462.1 $[MH]^+$, 484.1 $[MNa]^+$.

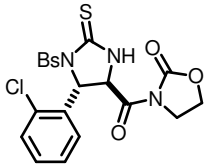
The absolute configuration of the title compound was assigned by X-ray crystallography.

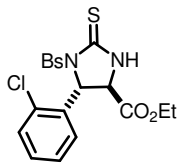
Figure 3.1 **Crystal Structure of Compound 3.31h**

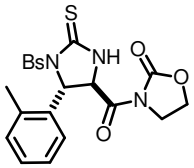


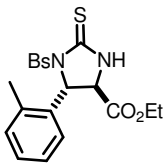


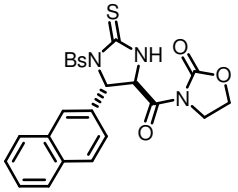
(4R,5S)-ethyl 5-(3-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35h): Colorless oil; R_f 0.52 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +12.0 (c 1.0, $CHCl_3$, 97% *ee*); IR (KBr) 3329, 3063, 2983, 2938, 2838, 1745, 1603, 1492, 1367, 1265, 1213, 1172, 1090, 1064, 1026, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (br, s, 1H), 7.70–7.65 (m, 2H), 7.54–7.48 (m, 1H), 7.36–7.28 (m, 2H), 7.24 (app t, *J* = 7.9 Hz, 1H), 6.92–6.85 (comp, 2H), 6.80–6.76 (m, 1H), 5.88 (d, *J* = 2.6 Hz, 1H), 4.32–4.19 (comp, 2H), 4.15 (dd, *J* = 2.6, 1.2 Hz, 1H), 3.70 (s, 3H), 1.29 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 168.5, 160.2, 140.0, 138.0, 133.9, 130.5, 129.4, 128.2, 118.7, 115.0, 111.9, 67.6, 63.3, 63.0, 55.4, 14.2; *m/z* (ESI-MS) 421.0 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.7 min (major) and t_R=14.4 min.

3-((4R,5S)-5-(2-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31i):  Following the general procedure, the product (mixture of diasteromers) was obtained as white foam in 80% yield. An analytical sample of the pure *trans*-diastereomer was obtained by flash chromatography. R_f 0.39 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +106.0 (c 1.0, $CHCl_3$); IR (KBr) 3427, 1780, 1707, 1476, 1449, 1395, 1366, 1265, 1223, 1172, 757, 598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (app d, *J* = 7.7 Hz, 2H), 7.63–7.55 (m, 1H), 7.50–7.38 (comp, 4H), 7.35–7.27 (comp, 2H), 7.24 (br, s, 1H), 6.94–6.87 (comp, 2H), 6.79 (app s, 1H), 4.80 (app s, 1H), 4.54–4.38 (comp, 2H), 4.13–3.94 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 165.7, 154.1, 137.7, 136.0, 134.3, 131.5, 130.3, 130.2, 129.7, 128.6, 127.9, 127.8, 63.6, 63.3, 62.6, 42.7; *m/z* (ESI-MS) 466.1 (^{35}Cl), 468.1 (^{37}Cl) $[MH]^+$, 488.1 (^{35}Cl), 490.0 (^{37}Cl) $[MNa]^+$.

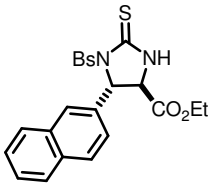
(4R,5S)-ethyl 5-(2-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35i):  Colorless oil; R_f 0.68 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +69.0 (c 1.0, $CHCl_3$, 91% *ee*); IR (KBr) 3315, 3059, 2984, 1742, 1579, 1483, 1370, 1167, 1093, 1063, 911, 757, 728, 686, 600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (app d, *J* = 7.8 Hz, 2H), 7.62–7.50 (comp, 2H), 7.46–7.35 (comp, 4H), 7.34–7.28 (m, 1H), 7.28–7.23 (m, 1H), 6.37 (app s, 1H), 4.32–4.15 (comp, 2H), 4.09 (app s, 1H), 1.27 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 168.1, 137.8, 135.8, 134.2, 132.0, 130.4, 130.4, 129.4, 128.5, 127.8, 65.1, 63.0, 62.6, 14.2; *m/z* (ESI-MS) 425.2 (^{35}Cl), 427.2 (^{37}Cl) $[MH]^+$, 447.1 (^{35}Cl), 449.1 (^{37}Cl) $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=14.1 min (major) and t_R=9.8 min.

3-((4R,5S)-5-(2-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31j):  Following the general procedure, the product (mixture of diasteromers) was obtained as white foam in 90% yield. An analytical sample of the pure *trans*-diastereomer was obtained by flash chromatography. R_f 0.31 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +19.5 (c 1.0, $CHCl_3$); IR (KBr) 3424, 1780, 1704, 1474, 1395, 1365, 1265, 1225, 1172, 1090, 1062, 757, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78–7.70 (m, 2H), 7.57–7.49 (m, 1H), 7.39–7.30 (comp, 3H), 7.27–7.07 (comp, 4H), 6.69 (d, *J* = 2.2 Hz, 1H), 4.78 (app t, *J* = 2.2 Hz, 1H), 4.61–4.46 (comp, 2H), 4.15–4.04 (comp, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 166.4, 154.2, 138.0, 136.7, 135.3, 134.0, 131.3, 129.7, 129.2, 128.4, 127.2, 126.4, 63.7, 63.6, 62.4, 42.9, 19.5; *m/z* (ESI-MS) 446.2 $[MH]^+$, 468.3 $[MNa]^+$.

(4R,5S)-ethyl 5-(2-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35j):  Colorless oil; R_f 0.68 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +15.0 (c 1.0, $CHCl_3$, 98% *ee*); IR (KBr) 3427, 3189, 3057, 2986, 1746, 1478, 1369, 1266, 1223, 1173, 1090, 1066, 1024, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2H), 7.56–7.49 (m, 1H), 7.37–7.30 (m, 2H), 7.26–7.22 (comp, 2H), 7.19 (br, s, 1H), 6.25 (d, *J* = 7.2 Hz, 1H), 4.38–4.22 (comp, 2H), 4.09 (d, *J* = 7.2 Hz, 1H), 2.52 (s, 3H), 1.33 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 168.6, 138.0, 136.8, 135.5, 134.0, 131.2, 129.5, 129.1, 128.3, 127.1, 126.0, 64.1, 63.2, 63.1, 19.3, 14.2; *m/z* (ESI-MS) 405.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=12.2 min (major) and t_R=10.4 min.

3-((4R,5S)-5-(naphthalen-2-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31k): 

Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2. mp >250 °C (CH_2Cl_2); R_f 0.22 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ –19.0 (c 0.5, acetone); IR (KBr) 3366, 3061, 1797, 1776, 1702, 1491, 1396, 1369, 1267, 1218, 1169, 1118, 1088, 726, 591, 570 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 9.90 (s, 1H), 8.00–7.82 (comp, 4H), 7.71–7.63 (m, 2H), 7.63–7.52 (comp, 3H), 7.45 (app dd, *J* = 8.6, 1.7 Hz, 1H), 7.42–7.34 (m, 2H), 6.18 (d, *J* = 1.5 Hz, 1H), 5.29 (d, *J* = 1.5 Hz, 1H), 4.56–4.40 (comp, 2H), 4.07–3.87 (comp, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 179.6, 168.0, 153.7, 138.1, 136.8, 133.7, 132.8, 132.4, 128.6, 128.5, 128.2, 128.0, 127.6, 126.6, 126.6, 126.1, 124.1, 66.9, 63.3, 61.7, 42.7; *m/z* (ESI-MS) 482.2 $[MH]^+$, 504.2 $[MNa]^+$.

(4R,5S)-ethyl 5-(naphthalen-2-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35k): 

Colorless oil; R_f 0.68 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –45.5 (c 1.0, $CHCl_3$, 99% *ee*); IR (KBr) 3307, 3298, 2981, 2935, 1752, 1732, 1601, 1492, 1367, 1219, 1170, 1092, 1069, 1017 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 10.28 (s, 1H), 8.03–7.86 (comp, 4H), 7.79–7.72 (m, 2H), 7.70–7.63 (m, 1H), 7.61–7.55 (comp, 2H), 7.52–7.44 (m, 2H), 7.44–7.37 (m, 1H), 6.06 (d, *J* = 2.7 Hz, 1H), 4.41 (dd, *J* = 2.7, 1.4 Hz, 1H), 4.31–4.16 (comp, 2H), 1.25 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 178.5, 168.8, 138.0, 137.0, 134.0, 132.8, 132.5, 129.1, 128.5, 128.5, 128.0, 127.7, 126.8, 126.7, 125.3, 123.3, 67.0, 62.8, 62.0, 13.9;

m/z (ESI-MS) 463.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=20.0 min (major) and t_R=15.1 min.

3-((4R,5S)-5-(naphthalen-1-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31l): Following the general procedure, the product (mixture of diasteromers) was obtained as white foam in 82% yield. An analytical sample of the pure *trans*-diastereomer was obtained by flash chromatography. R_f 0.34 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +179.0 (c 0.5, $CHCl_3$); IR (KBr) 3376, 3068, 2984, 2924, 1772, 1677, 1475, 1459, 1391, 1377, 1257, 1232, 1177, 1092, 1059, 728, 687, 595, 566 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 9.91 (br, s, 1H), 8.17 (br, s, 1H), 8.06–7.96 (comp, 2H), 7.76–7.38 (comp, 9H), 6.84 (br, s, 1H), 5.28 (br, s, 1H), 4.54–4.36 (comp, 2H), 4.17–4.06 (m, 1H), 4.00–3.88 (m, 1H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.1, 167.8, 153.3, 138.1, 135.8, 133.9, 133.4, 129.4, 129.1, 128.6, 128.4, 126.5, 126.1, 125.5, 123.6, 63.2, 62.3, 61.7, 42.7; *m/z* (ESI-MS) 482.2 $[MH]^+$, 504.1 $[MNa]^+$.

(4R,5S)-ethyl 5-(naphthalen-1-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35l): Colorless oil; R_f 0.70 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +137.0 (c 1.0, $CHCl_3$, 95% *ee*); IR (KBr) 3405, 3053, 2979, 1742, 1602, 1506, 1373, 1236, 1180, 1092, 1055, 1024, 858, 799, 728 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 10.18 (s, 1H), 8.31 (br, s, 1H), 8.12–7.84 (comp, 4H), 7.80–7.50 (comp, 6H), 7.50–7.36 (m, 1H), 6.78 (br, s, 1H), 4.44–4.14 (comp, 3H), 1.28 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 178.6, 168.9, 138.0, 134.8, 134.1, 133.6, 129.1, 129.0, 128.9, 128.7, 128.6, 126.9, 126.3, 125.4, 122.8, 64.1, 62.7, 62.2, 13.9; *m/z* (ESIMS) 441.2 $[MH]^+$, 463.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-

H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.3 min (major) and t_R=13.7 min.

3-((4R,5R)-1-(phenylsulfonyl)-5-(thiophen-2-yl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31m): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 95% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 215–216 °C (CH_2Cl_2/hexanes); R_f 0.24 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +5.0 (c 1.0, acetone); IR (KBr) 3374, 3069, 2987, 1775, 1705, 1484, 1396, 1364, 1261, 1217, 1168, 1119, 1087, 1057, 1034, 726, 757, 705, 604, 586, 570 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 9.91 (s, 1H), 7.70–7.61 (comp, 3H), 7.53 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.49–7.43 (m, 1H), 7.50–7.42 (m, 2H), 7.17 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.30 (app s, 1H), 5.21 (d, *J* = 1.2 Hz, 1H), 4.53–4.40 (comp, 2H), 4.01–3.84 (comp, 2H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 178.9, 167.4, 153.8, 141.4, 138.1, 133.8, 128.7, 128.3, 127.3, 126.5, 126.5, 63.3, 62.8, 62.4, 42.6; *m/z* (ESI-MS) 438.1 $[MH]^+$, 460.1 $[MNa]^+$.

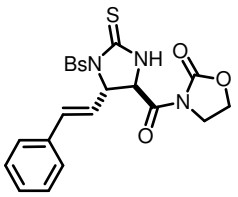
(4R,5R)-ethyl 1-(phenylsulfonyl)-5-(thiophen-2-yl)-2-thioxoimidazolidine-4-carboxylate (3.35m): Yellow oil; R_f 0.65 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ –23.0 (c 1.0, $CHCl_3$, 97% *ee*); IR (KBr) 3447, 2978, 1750, 1636, 1485, 1371, 1206, 1173, 1088, 1059, 1021, 858, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.63 (m, 2H), 7.56–7.49 (m, 1H), 7.38–7.31 (m, 2H), 7.30 (d, *J* = 5.1 Hz, 1H), 7.26 (d, *J* = 3.5 Hz, 1H), 7.03–6.84 (comp, 2H), 6.30 (d, *J* = 2.0 Hz, 1H), 4.36–4.25 (comp, 3H), 1.33 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 168.0, 140.6, 137.9, 134.0, 129.4, 128.5, 128.4, 127.1, 127.1, 63.5, 63.3, 63.3, 14.3; *m/z*

(ESI-MS) 397.0 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=18.3 min (major) and t_R=13.4 min.

3-((4R,5R)-1-(phenylsulfonyl)-5-(furan-2-yl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31n): Following the general procedure, the product (mixture of diasteromers) was obtained as white foam in 97% yield. An analytical sample of the pure *trans*-diastereomer was obtained by flash chromatography. R_f 0.19 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +26.5 (c 1.0, $CHCl_3$); IR (KBr) 3410, 1779, 1708, 1478, 1392, 1365, 1266, 1230, 1171, 1090, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.57–7.50 (m, 1H), 7.42–7.34 (comp, 3H), 7.32 (d, *J* = 1.2 Hz, 1H), 6.60 (d, *J* = 3.2 Hz, 1H), 6.43–6.39 (comp, 2H), 5.11 (t, *J* = 5.0 Hz, 1H), 4.64–4.49 (comp, 2H), 4.15–4.07 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 166.2, 154.2, 149.7, 143.6, 137.9, 134.0, 129.4, 128.5, 111.1, 111.0, 63.8, 60.8, 59.4, 42.9; *m/z* (ESI-MS) 422.1 $[MH]^+$, 444.1 $[MNa]^+$.

(4R,5R)-ethyl 1-(phenylsulfonyl)-5-(furan-2-yl)-2-thioxoimidazolidine-4-carboxylate (3.35n): Pale yellow oil; R_f 0.64 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ +1.5 (c 1.0, $CHCl_3$, 92% *ee*); IR (KBr) 3344, 2983, 1745, 1605, 1484, 1366, 1172, 1090, 1018, 930, 727, 687, 622, 571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2H), 7.57–7.50 (m, 1H), 7.41–7.35 (m, 2H), 7.32 (d, *J* = 1.8, 0.7 Hz, 1H), 7.15 (br, s, 1H), 6.64 (d, *J* = 3.3, 0.7 Hz, 1H), 6.43 (d, *J* = 3.3, 1.8 Hz, 1H), 6.09 (d, *J* = 2.8 Hz, 1H), 4.39 (dd, *J* = 2.8, 1.3 Hz, 1H), 4.36–4.22 (comp, 2H), 1.32 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 168.0, 149.7, 143.6, 137.9, 134.0, 129.3, 128.5, 111.3, 111.1, 63.3, 60.6, 60.0, 14.3; *m/z* (ESIMS) 380.1 $[MH]^+$; HPLC:

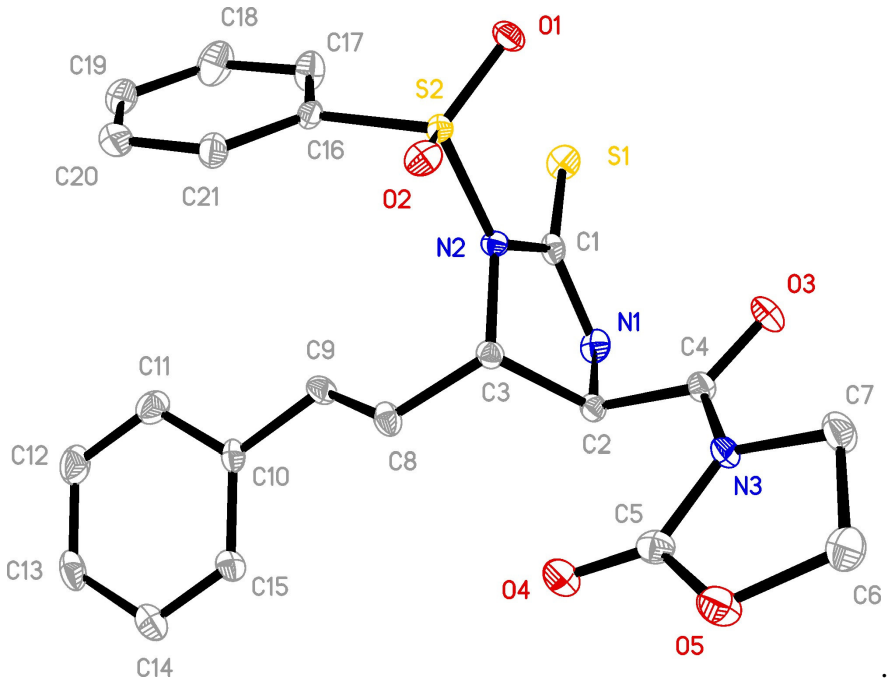
Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.7 min (major) and t_R=13.3 min.

3-((4R,5S)-1-(phenylsulfonyl)-5-styryl-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31o): 

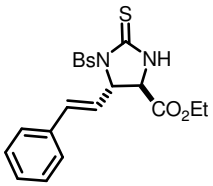
Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 225–226 °C (CH_2Cl_2/hexanes); R_f 0.17 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +12.5 (c 0.25, $CHCl_3$); IR (KBr) 3373, 3060, 3025, 3001, 1776, 1703, 1490, 1395, 1369, 1258, 1220, 1169, 1122, 1088, 1062, 1036, 753, 726, 687, 628, 603, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11–8.05 (m, 2H), 7.59–7.53 (m, 1H), 7.44–7.28 (comp, 7H), 7.19 (br, s, 1H), 6.85 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 15.7, 8.4 Hz, 1H), 5.93 (d, *J* = 8.4 Hz, 1H), 4.86 (t, *J* = 1.7 Hz, 1H), 4.63–4.51 (comp, 2H), 4.16–4.05 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 166.6, 154.2, 138.3, 135.9, 135.3, 134.1, 130.0, 129.0, 129.0, 128.6, 127.2, 123.6, 65.7, 63.7, 61.9, 42.9; *m/z* (ESI-MS) 458.1 $[MH]^+$, 480.1 $[MNa]^+$.

The absolute configuration of the title compound was assigned by X-ray crystallography.

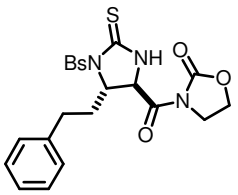
Figure 3.2 **Crystal Structure of Compound 3.31o**

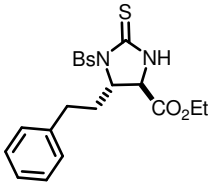


(4R,5S)-ethyl 1-(phenylsulfonyl)-5-styryl-2-thioxoimidazolidine-4-carboxylate



(3.35o): Pale yellow oil; R_f 0.66 (EtOAc/CH_2Cl_2 1:19 v/v); $[\alpha]_D^{20}$ – 10.5 (c 1.0, $CHCl_3$, 95% *ee*); IR (KBr) 3397, 3064, 2983, 2924, 1745, 1629, 1491, 1449, 1367, 1215, 1172, 1090, 1064, 1023, 753, 725, 687, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10–8.02 (m, 2H), 7.60–7.53 (m, 1H), 7.44–7.30 (comp, 7H), 7.15 (br, s, 1H), 6.90 (d, *J* = 15.7 Hz, 1H), 6.18 (dd, *J* = 15.7, 8.7 Hz, 1H), 5.63 (dd, *J* = 8.7, 1.9 Hz, 1H), 4.35–4.21 (comp, 2H), 4.08 (d, *J* = 1.9 Hz, 1H), 1.32 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 168.4, 138.4, 135.9, 135.2, 134.1, 129.8, 129.1, 129.0, 128.6, 127.2, 124.0, 67.1, 63.1, 61.3, 14.3; *m/z* (ESI-MS) 417.1 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.2 min (major) and t_R=13.6 min.

3-((4R,5S)-5-phenethyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31p):  Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2. mp 208-210 °C (CH_2Cl_2); R_f 0.18 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +19.0 (c 1.0, acetone); IR (KBr) 3365, 3064, 3027, 2993, 2956, 2928, 1769, 1708, 1485, 1391, 1357, 1260, 1211, 1165, 1124, 1085, 1065, 1037, 753, 727, 685, 603, 570 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 9.74 (s, 1H), 8.04-7.96 (m, 2H), 7.76-7.68 (m, 1H), 7.63–7.54 (m, 2H), 7.35–7.27 (m, 2H), 7.25–7.14 (comp, 3H), 5.18–5.08 (comp, 2H), 4.55–4.39 (comp, 2H), 3.98–3.82 (comp, 2H), 2.77–2.64 (m, 1H), 2.64–2.52 (m, 1H), 2.32–2.18 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 179.3, 168.5, 154.0, 140.8, 138.4, 133.8, 128.6, 128.6, 128.5, 128.1, 126.0, 64.6, 63.3, 59.0, 42.6, 36.7, 29.0; *m/z* (ESI-MS) 460.2 $[MH]^+$, 482.2 $[MNa]^+$.

(4R,5S)-ethyl 5-phenethyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35p):  Colorless oil; R_f 0.28 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ +11.5 (c 1.0, $CHCl_3$, 89% *ee*); IR (KBr) 3424, 3173, 2927, 1744, 1496, 1370, 1218, 1171, 1089, 725, 570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06–8.00 (m, 2H), 7.66–7.58 (m, 1H), 7.55–7.47 (m, 2H), 7.36–7.27 (m, 2H), 7.26–7.18 (comp, 3H), 6.60 (br, s, 1H), 5.05–4.96 (m, 1H), 4.27–4.09 (comp, 2H), 3.98 (d, *J* = 2.0 Hz, 1H), 2.86–2.70 (comp, 2H), 2.53–2.40 (m, 1H), 2.40–2.26 (m, 1H), 1.25 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 168.9, 139.9, 138.3, 134.2, 129.2, 128.9, 128.8, 128.6, 126.7, 65.6, 62.9, 59.8, 36.8, 30.7, 14.3; *m/z* (ESI-MS) 419.2 $[MH]^+$,

441.2 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=18.8 min (major) and t_R=10.5 min.

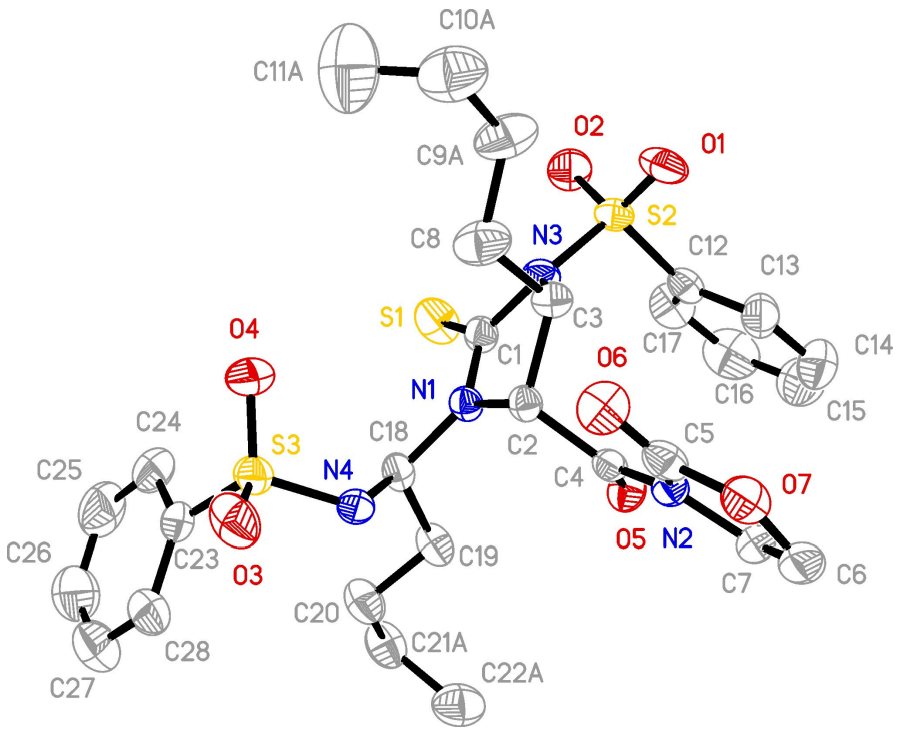
3-((4R,5S)-5-butyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31q): Following the general procedure, the product (mixtures of diastereomers) was obtained as white foam in 53% yield. An analytical sample of the pure *trans*-diastereomer was obtained by flash chromatography. R_f 0.28 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +39.0 (c 1.0, $CHCl_3$, 91% *ee*); IR (KBr) 3425, 2958, 2927, 2861, 1780, 1705, 1475, 1395, 1362, 1223, 1170, 1090, 1064, 1037, 727, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13–8.06 (m, 2H), 7.63–7.56 (m, 1H), 7.54–7.46 (m, 2H), 7.02 (br, s, 1H), 5.40–5.34 (m, 1H), 4.72 (app t, *J* = 1.9 Hz, 1H), 4.58–4.48 (comp, 2H), 4.15–3.94 (comp, 2H), 2.11–1.97 (comp, 2H), 1.46–1.21 (comp, 4H), 0.92 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 167.0, 154.1, 138.3, 134.1, 129.5, 128.6, 64.0, 63.6, 60.2, 42.8, 34.6, 26.2, 22.6, 14.1; *m/z* (ESI-MS) 412.2 $[MH]^+$, 434.2 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=34.4 min (major) and t_R=30.2 min.

N-((R)-1-((4S,5R)-4-butyl-5-(2-oxooxazolidine-3-carbonyl)-3-(phenylsulfonyl)-2-thioxoimidazolidin-1-yl)pentyl)benzenesulfonamide (3.32): The title compound was obtained by flash chromatography. An analytical sample was obtained by recrystallization. mp 162–164 °C ($CHCl_3$); R_f 0.31 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); IR (KBr) 3293, 2960, 2932, 2871, 1788, 1706, 1448, 1414, 1397, 1363, 1337, 1231, 1174, 1091, 1060, 602, 562 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.04 (m, 2H), 7.86–7.79 (m, 2H), 7.66–7.59 (m, 1H), 7.59–7.50 (comp, 3H), 7.50–7.43 (m, 2H), 5.94 (d, *J* = 8.6 Hz, 1H), 5.64 (d, *J* = 1.4

Hz, 1H), 5.48–5.35 (m, 1H), 4.64–4.46 (comp, 3H), 4.16–3.98 (comp, 2H), 2.06–1.78 (comp, 2H), 1.72–1.57 (m, 1H), 1.45–1.22 (comp, 5H), 1.13–0.86 (comp, 7H), 0.68 (app t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 169.6, 154.3, 140.5, 138.6, 133.9, 133.2, 129.5, 129.4, 128.6, 127.3, 67.5, 65.2, 63.2, 60.1, 43.2, 34.8, 33.1, 27.6, 27.0, 22.5, 21.9, 14.1, 14.0; *m/z* (ESI-MS) 658.9[MNa]$^+$.

The absolute configuration of the title compound was assigned by X-ray crystallography.

Figure 3.3 **Crystal Structure of Compound 3.32**



3-((4R,5S)-1-(4-nitrophenylsulfonyl)-2-thioxo-5-p-tolylimidazolidine-4-carbonyl) oxazolidin-2-one (3.33a): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp >250 °C (CH_2Cl_2/hexanes); R_f 0.25 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +22.5 (c 1.0, acetone); IR (KBr) 3365, 3106, 2999, 1798, 1776, 1702, 1533, 1494, 1396, 1377, 1349, 1267, 1213, 1173, 1117, 1087, 740 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 10.01 (s, 1H), 8.32–8.27 (m, 2H), 7.96–7.90 (m, 2H), 7.26–7.18 (comp, 4H), 6.02 (d, *J* = 1.2 Hz, 1H), 5.18 (d, *J* = 1.2 Hz, 1H), 4.55–4.40 (comp, 2H), 4.05–3.97 (m, 1H), 3.95–3.86 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.3, 168.0, 153.7, 150.2, 143.3, 138.2, 136.1, 130.3, 129.2, 126.5, 123.5, 66.7, 63.3, 62.1, 42.7, 20.7; *m/z* (ESI-MS) 491.2 $[MH]^+$, 513.1 $[MNa]^+$.

(4R,5S)-ethyl 1-(4-nitrophenylsulfonyl)-2-thioxo-5-p-tolylimidazolidine-4-carboxylate (3.36a): Pale yellow oil; R_f 0.33 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –59.0 (c 1.0, $CHCl_3$, 98% *ee*); IR (KBr) 3418, 1743, 1609, 1532, 1488, 1402, 1373, 1350, 1240, 1213, 1174, 1089, 741, 599 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.75 (br, s, 1H), 5.94 (d, *J* = 2.5 Hz, 1H), 4.40–4.28 (comp, 2H), 4.20 (d, *J* = 2.5 Hz, 1H), 2.41 (s, 3H), 1.36 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 168.2, 151.0, 143.8, 140.2, 135.6, 131.0, 130.3, 127.0, 123.4, 67.9, 63.6, 63.3, 21.4, 14.3; *m/z* (ESI-MS) 450.1 $[MH]^+$, 472.1 $[MNa]^+$; HPLC:

Daicel Chiralpak AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=41.0 min (major) and t_R=23.0 min.

3-((4R,5S)-5-(3-methoxyphenyl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.33b): Following the general procedure, the product (mixture of diasteromers) was obtained as a pale yellow solid in 92% yield. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp >250 °C (CH_2Cl_2); R_f 0.20 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +49.0 (c 0.25, acetone); IR (KBr) 3364, 3104, 3000, 1797, 1777, 1703, 1526, 1494, 1397, 1375, 1351, 1265, 1210, 1175, 1114, 1085, 854, 740, 582 cm^{-1}; ^1H NMR (400 MHz, *d*$_6$-DMSO) δ 10.02 (s, 1H), 8.34-8.28 (m, 2H), 8.01–7.93 (m, 2H), 7.35 (app t, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.95–6.87 (comp, 2H), 6.06 (d, *J* = 1.2 Hz, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 4.56–4.40 (comp, 2H), 4.06–3.85 (comp, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, *d*$_6$-DMSO) δ 179.4, 167.9, 159.2, 153.7, 150.2, 143.1, 140.3, 130.4, 129.9, 123.5, 118.4, 113.6, 113.0, 66.7, 63.3, 61.9, 55.1, 42.7; *m/z* (ESI-MS) 507.4 $[MH]^+$, 529.3 $[MNa]^+$.

(4R,5S)-ethyl 5-(3-methoxyphenyl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.36b): Pale yellow oil; R_f 0.25 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –31.5 (c 1.0, $CHCl_3$, 97% *ee*); IR (KBr) 3374, 3107, 2981, 1744, 1533, 1493, 1372, 1350, 1238, 1209, 1176, 1088, 1064, 855, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.11 (m, 2H), 7.87–7.78 (m, 2H), 7.33–7.26 (m, 1H), 7.01 (br, s, 1H), 6.98–6.92 (m, 1H), 6.91–6.85 (m, 1H), 6.81–6.77 (m, 1H), 5.93 (d, *J* = 2.5 Hz, 1H), 4.41–4.27 (comp, 2H), 4.22 (d, *J* = 2.5 Hz, 1H), 3.77 (s, 3H), 1.35 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 168.1,

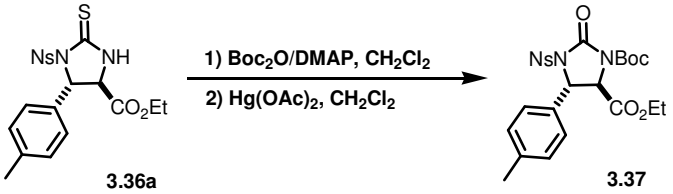
160.5, 150.7, 143.3, 139.5, 131.0, 130.9, 123.4, 118.9, 115.0, 112.9, 67.7, 63.4, 63.3, 55.6, 14.3; *m/z* (ESI-MS) 466.2 $[MH]^+$, 488.2 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=20.9 min (major) and t_R=15.2 min.

3-((4R,5S)-5-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.33c): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 87% yield. The mixture of DCM/EtOAc/THF was used as eluent. An analytical sample of the pure *trans*-diastereomer was obtained by recrystallization from CH_2Cl_2. mp >250 °C (CH_2Cl_2); R_f 0.21 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +65.0 (c 0.5, DMSO); IR (KBr) 3365, 3111, 1798, 1777, 1703, 1531, 1493, 1397, 1372, 1350, 1267, 1215, 1176, 1117, 1085, 740 cm^{-1}; ^1H NMR (500 MHz, *d*$_6$-DMSO) δ 10.11 (s, 1H), 8.25–8.17 (m, 2H), 8.01–7.93 (comp, 4H), 7.92–7.81 (comp, 2H), 7.62–7.53 (comp, 2H), 7.50–7.44 (m, 1H), 6.26 (d, *J* = 1.5 Hz, 1H), 5.32 (d, *J* = 1.5 Hz, 1H), 4.57–4.42 (comp, 2H), 4.09–3.99 (m, 1H), 3.98–3.88 (m, 1H); ^{13}C NMR (125 MHz, *d*$_6$-DMSO) δ 179.4, 168.0, 153.7, 150.1, 143.2, 136.5, 132.8, 132.4, 130.2, 128.6, 128.0, 127.6, 126.7, 126.7, 126.0, 124.0, 123.5, 67.0, 63.4, 61.9, 42.7; *m/z* (ESI-MS) 527.3 $[MH]^+$, 549.3 $[MNa]^+$.

(4R,5S)-ethyl 5-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.36c): Pale yellow oil; R_f 0.33 (CH_2Cl_2/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –86.5 (c 1.0, $CHCl_3$, 94% *ee*); IR (KBr) 3396, 2982, 1743, 1532, 1487, 1372, 1350, 1215, 1177, 1088, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98–7.93 (m, 2H), 7.90–7.85 (m, 1H), 7.84–7.78 (comp, 3H), 7.76–7.70 (m, 2H), 7.63–7.52 (comp, 2H), 7.33–7.28 (m, 1H), 7.23 (br, s, 1H), 6.14 (d, *J* = 2.6 Hz, 1H), 4.43–4.29 (comp, 3H), 1.37 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 168.2, 150.6, 143.3, 135.0, 133.7, 133.1, 130.8, 129.9, 128.4, 128.0, 127.7, 127.5, 127.1, 123.3, 123.3, 68.0, 63.5, 63.2, 14.3; *m/z* (ESI-MS) 486.0 $[MH]^+$, 508.1 $[MNa]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=66.1 min (major) and t_R=33.7 min.

3.4.6 Procedure for the Conversion of Products 3.36a Into Its Corresponding Diamino Acids

(4S,5R)-1-tert-butyl 5-ethyl 3-(4-nitrophenylsulfonyl)-2-oxo-4-p-tolylimidazolidine-1,5-dicarboxylate (3.37)



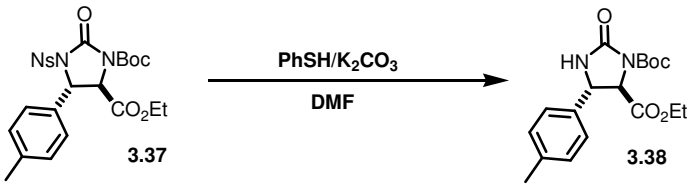
3.36a **3.37**

The mixtures of products **3.36a** (763 mg, 1.697 mmol), DMAP (41.5 mg, 0.2 eq.) and Boc_2O (463 mg, 1.25 eq.) in 35 ml CH_2Cl_2 were stirred at rt until **3.36a** was completely consumed (~4 h). The mixtures were loaded into the flash chromatography

(EtOAc: hexanes = 30:70) directly and the pale yellow foam was obtained in 920 mg (99% yield).

The product from the previous step was dissolved in 50 ml CH_2Cl_2 and then $Hg(OAc)_2$ (800 mg, 1.5 eq) were added in one portion. The reaction mixtures were stirred at rt for 24 h. The product **3.37** was obtained as white foam (856 mg, 96% yield) after the filtration with a short celite column. The product **3.37** is pure enough for the next step. Analytical samples were further purified by flash chromatography. R_f 0.68 (hexanes/EtOAc 60:40 v/v); $[\alpha]_D^{20}$ –21.0 (c 1.0, $CHCl_3$); IR (neat) 3107, 2982, 2931, 1805, 1778, 1752, 1731, 1533, 1370, 1350, 1324, 1256, 1204, 1179, 1096, 1023, 855, 741, 683, 661, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.20 (d, *J* = 1.9 Hz, 1H), 4.46 (d, *J* = 1.9 Hz, 1H), 4.39–4.27 (comp, 2H), 2.38 (s, 3H), 1.48 (s, 9H), 1.34 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 150.8, 148.8, 148.3, 143.5, 140.2, 134.7, 130.2, 130.2, 126.5, 123.9, 85.4, 63.0, 62.3, 59.6, 28.1, 21.4, 14.4; *m/z* (ESI-MS) 533.7 $[MH]^+$, 556.0 $[MNa]^+$.

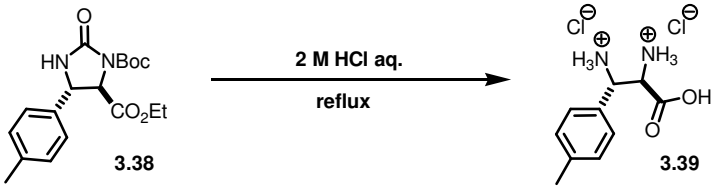
(4S,5R)-1-tert-butyl 5-ethyl 2-oxo-4-p-tolylimidazolidine-1,5-dicarboxylate (3.38)



The mixtures of compound **3.37** (100 mg) and K_2CO_3 (78 mg, 3 eq) were dissolved in 5 ml dry DMF and then PhSH (26.8 mg, 1.3 eq) were added dropwise. The suspension was stirred at rt for 3 h. The solution was diluted with 10 ml water and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layer was dried with Na_2SO_4 and purified by

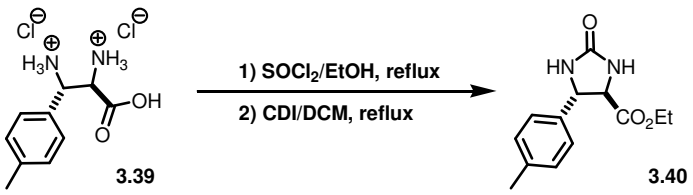
flash chromatography. The product **3.38** was obtained in 74% yield as white foam. R_f 0.24 (hexanes/EtOAc 60:40 v/v); $[\alpha]_D^{20}$ –36.0 (c 1.0, $CHCl_3$); IR (neat) 3294, 2979, 2930, 1784, 1709, 1369, 1331, 1233, 1197, 1160, 1116, 1023, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.43 (br, s, 1H), 4.60 (d, *J* = 3.9 Hz, 1H), 4.41 (d, *J* = 3.9 Hz, 1H), 4.38–4.24 (comp, 2H), 2.36 (s, 3H), 1.44 (s, 9H), 1.36 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 155.5, 149.6, 139.0, 137.5, 130.1 , 125.8, 83.4, 65.0, 62.2, 55.4, 28.1, 21.4, 14.5; *m/z* (ESI-MS) 349.0 $[MH]^+$, 371.1 $[MNa]^+$.

(1R,2S)-1-carboxy-2-p-tolylethane-1,2-diaminium chloride (3.39)



Compound **3.38** (0.273 mmol, 95 mg) in 2 M HCl aqueous solution (12 ml) was heated at reflux for 5 h. The resulting solution was evaporated and the residue was further dried at 40 °C in vacuo overnight. A white solid **3.39** was obtained in quantitative yield. $[\alpha]_D^{20}$ +14.0 (c 0.49, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.40–7.33 (comp, 4H), 4.84 (d, *J* = 4.8 Hz, 1H), 4.50 (d, *J* = 4.8 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 169.4, 141.8, 130.6, 128.0, 126.5, 53.8, 53.3, 20.5; *m/z* (ESI-MS) 195.1 $[MH]^+$.

(4R,5S)-ethyl 2-oxo-5-p-tolylimidazolidine-4-carboxylate (3.40)



Compound **3.39** (73 mg, 0.273 mmol) was dissolved in EtOH (10 ml) and $SOCl_2$ (0.2 ml, 10 eq) was added dropwise at 0 °C. The solution was stirred at 40 °C for 2 h, and reflux for 5 h. The solvent was removed and the residue was extracted with 1 M HCl aq./DCM. Aqueous layer was basified (pH 8-9) with solid Na_2CO_3 and was extracted with 5% MeOH/DCM (3 × 20 ml). The combined organic layer was dried with Na_2SO_4. The solvent was removed after the filtration and the pale yellow oil was obtained in 91% yield without further purification.

The product from the previous step was dissolved in anhydrous CH_2Cl_2 (10 ml) and carbonyldiimidazole (60 mg, 1.5 eq) was added at rt. The solution was heated at reflux for 6 h. The resulting mixture was cooled down to rt and washed by 2 M HCl (5 ml) and water (5 ml). The organic layer was dried with Na_2SO_4. The compound **3.40** was obtained as white solid in 50% yield by flash chromatography. R_f 0.36 (hexanes/EtOAc 20:80 v/v); ^{1}H NMR (500 MHz, CD_3OD) δ 7.28 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 4.82 (d, *J* = 4.8 Hz, 1H), 4.33–4.19 (comp, 2H), 4.06 (d, *J* = 4.8 Hz, 1H), 2.34 (s, 3H), 1.31 (app t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.8, 165.0, 140.1, 139.3, 130.5, 127.0, 64.0, 62.8, 60.5, 21.1, 14.4; *m/z* (ESI-MS) 249.2 $[MH]^+$; HPLC: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 210 nm, t_R=15.5 min (major) and t_R=7.9 min.

C4 and C5 coupling constants (4.8 Hz) of compound **3.40** were consistent with data of syn-diastereomers of similar compounds[23]. Also, ee (98%) of compound **3.40** was otained from chiral HPLC analysis. They proved this reaction sequence did not change the stereo-chemistry of related compounds.

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23. Franklin, A. D.; Deng, J. *Org. Lett.* **2004**, *6*, 2789.

Chapter IV

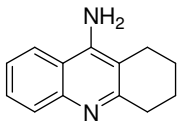
Facile Access to Tetrahydroacridine Derivatives with Remote Stereogenic Centers: Catalytic Enantioselective Friedländer Condensations

4.1 Background

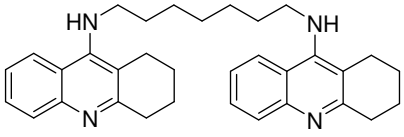
4.1.1 Significance of Tetrahydroacridine Derivatives

Tetrahydroacridines, a class of tricyclic heterocycles, are of increasing interest in medicinal chemistry because of their uses as potent enzyme inhibitors. Without a doubt, tacrine is the most important member of this family since it has been marketed as a commercial drug for Alzheimer's disease.

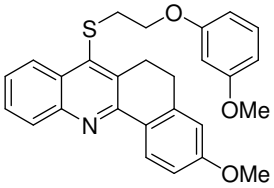
Scheme 4.1 **Selected Examples of Biologically Active Tetrahydroacridines**



4.1 tacrine



4.2 bis(7)-tacrine



4.3 EDT

Tacrine (**4.1**) and its derivatives show efficacy in the treatment of cognitive disorders such as Alzheimer's disease.[1] Tacrine's mode of action is attributed to its potent acetylcholinesterase inhibitor activities,[1b, 1c] and compound **4.1** is also known to inhibit other enzymes including butylcholinesterase[1e] and monoamine oxidase.[1d] In addition, other pharmacological uses of tacrine, such as blockage of potassium channels and inhibition of neuronal monoamine uptake processes, have been reported.[1g] Given their important functions in medicinal chemistry, the synthesis and evaluation of new tacrine analogs continues to be of significant interest. Furthermore, evaluation of tacrine analogs with stereogenic centers may constitute an attractive strategy considering the increasing demand for chiral drugs.[2] Unfortunately, there are no reports focusing on the asymmetric synthesis of chiral non-racemic tacrine analogs.

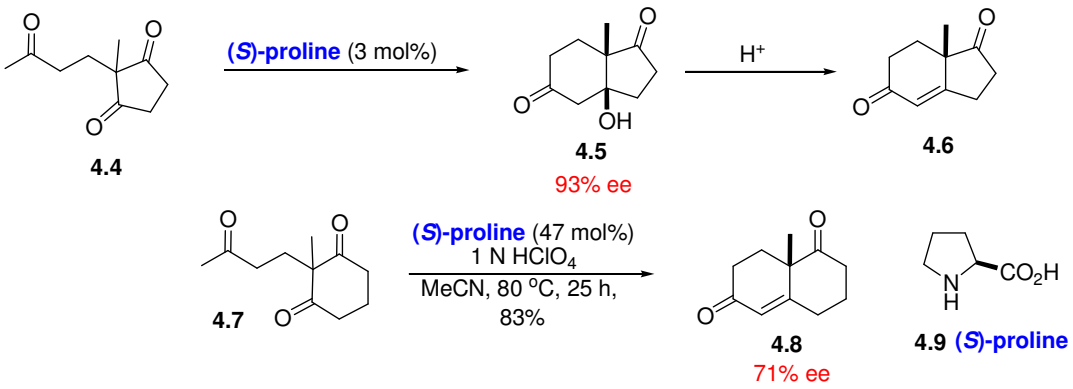
4.1.2 Synthetic Methods for Tacrine and Tetrahydroacridine Derivatives

One of the most convenient methods for the synthesis of tacrine derivatives is the acid- or thermally-promoted condensation of substituted cyclohexanones and *ortho*-amino benzonitriles.[3] Another strategy involves the coupling of the corresponding chloro-tetrahydroacridine and amines. However, these methods usually require strong acidic or thermal conditions, which are typically detrimental to asymmetric catalysis.

For those tetrahydroacridine derivatives without amino group, the condensation of substituted cyclohexanones and *ortho*-amino benzaldehydes, known as the Friedländer condensation,[4] represents the most effective method to construct their tricyclic skeleton. However, relatively harsh reaction conditions are typically required in this type of reaction as well.[5]

4.1.3 Enamine Catalysis as a Powerful Synthetic Tool

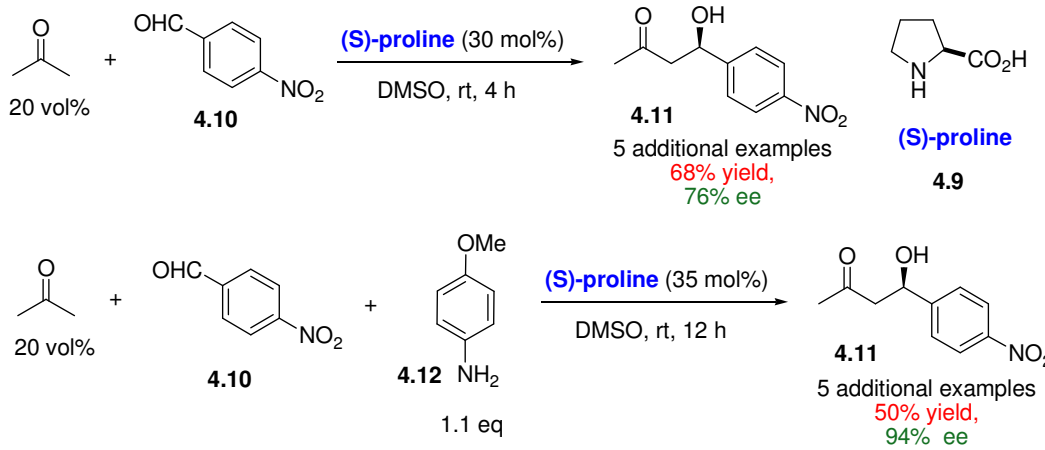
Scheme 4.2 **The Hajos-Parrish-Eder-Sauer-Wiechert Reaction**



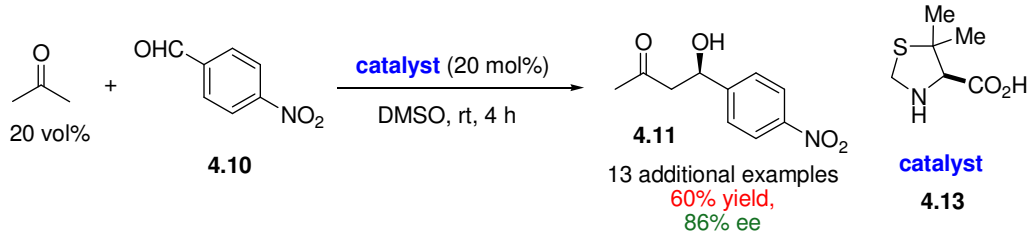
Although the proline-catalyzed intramolecular aldol reaction, namely, the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[7c, 7d] was discovered in the early 1970s (Scheme 4.2), the renaissance of enamine catalysis started in the early 2000's[6-7] (Scheme 4.3). This organocatalytic mode of activation has been developed into a powerful synthetic tool for the preparation of valuable chiral building blocks. Enamine catalysis provides a mild and general solution for the in situ transformation of aldehydes and ketones into their corresponding enolate equivalents. In the past decade, a number of reactions were developed that employ this strategy, including aldol reactions[8], Mannich reactions[9], Michael additions[10] and others.[11] However, relatively few studies have focused on reactions that involve the desymmetrization of prochiral ketones[12] (Scheme 4.4).

Scheme 4.3 Pioneering Works in Enamine Catalysis

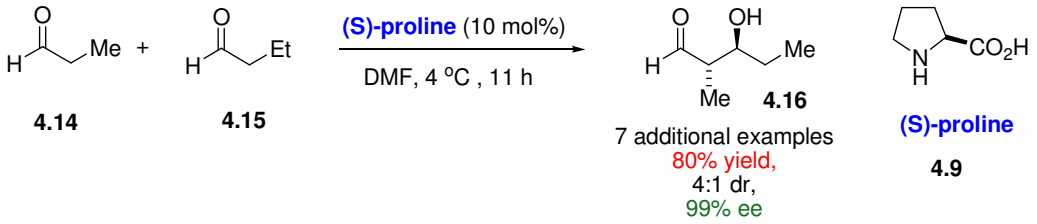
List et al. (2000)



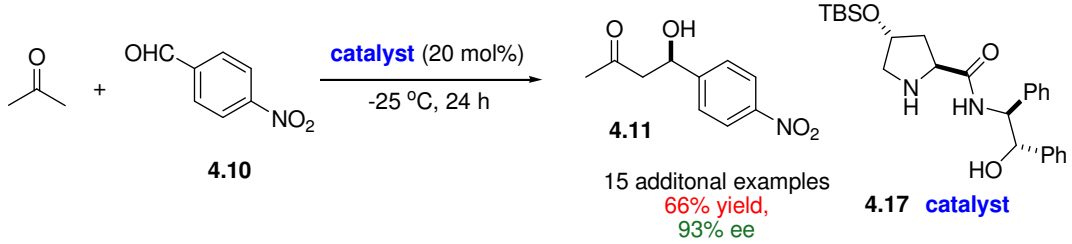
Barbas et al. (2001)



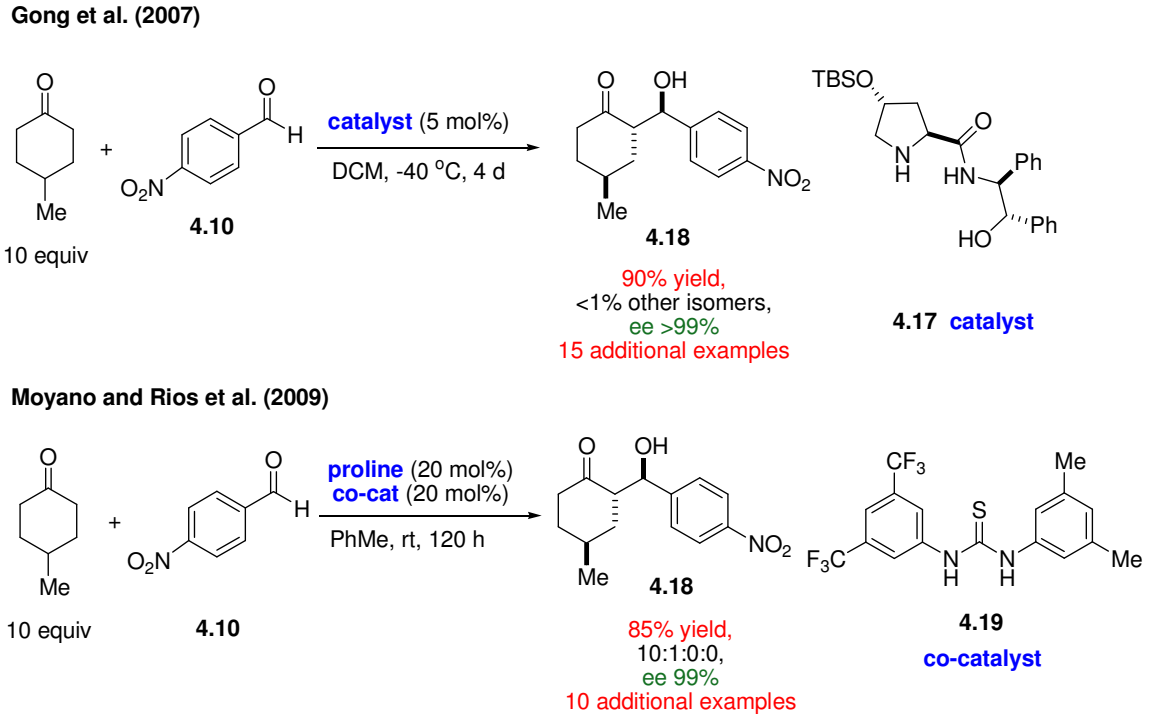
MacMillan et al. (2002)



Gong et al. (2003)

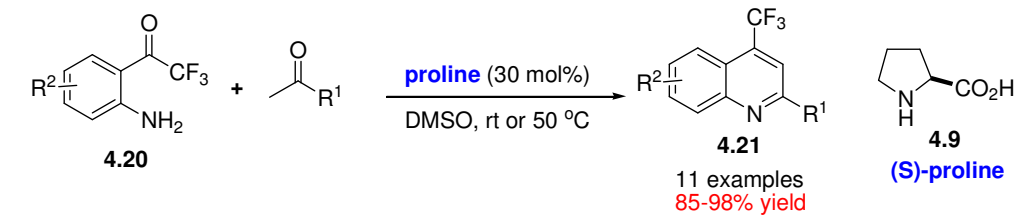


Scheme 4.4 **Desymmetrizations of Prochiral Ketones with Aldol Reactions**



Whereas enamines are considered to be important intermediates in the classical Friedländer process, enamine catalysts such as proline had not been used to catalyze the Friedländer synthesis of achiral quinolines until recently.[13] However, this reaction appears to be limited to the use of highly activated amino-trifluoromethylketones while simultaneously requiring mild heating.

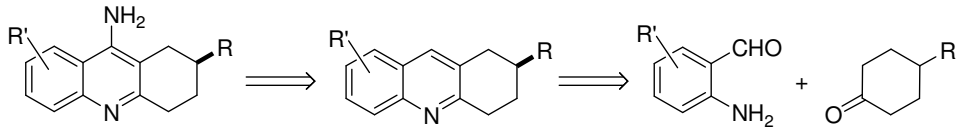
Scheme 4.5 **Proline-Catalyzed Friedländer Condensations**



4.2 Proposal and Objective

Based on the discussions in section 4.1, tacrine derivatives share a common structural unit with tetrahydroacridine. The only difference between them is that tacrine derivatives have an additional amino group on the quinoline ring. Therefore, it is possible for us to envision that chiral nonracemic tacrine derivatives **4.22** may be derived from their corresponding tetrahydroacridines **4.25**. Therefore, the question we raised here is how to develop a convenient method to access these chiral quinolines **4.25** (Scheme 4.6)**.**

Scheme 4.6 **Retrosynthesis of Chiral Tacrine Analogs**



Friedländer condensations[4] are one of the classic methods used to synthesize quinolines. However, no asymmetric version of this reaction had been reported. We proposed that chiral quinolines **4.25** could be prepared via an asymmetric Friedländer condensation of *ortho*-aminobenzaldehydes **4.24** and ketones **4.23**. This catalytic enantioselective process could be realized by asymmetric enamine catalysis.

In addition, the elucidation of the mechanisms of proline-catalyzed desymmetrizations will be beneficial to the design of new small molecule catalysts. Although a number of catalytic systems have successfully catalyzed the desymmetrizations of prochiral cyclic ketones, the process of chirality transfer from

catalyst to products is not clear. This challenging problem is associated with several difficulties. Firstly, some known desymmetrizations including aldol reactions, Mannich reactions and Michael reactions generate multiple chiral centers in the products. It is challenging to analyze all of them experimentally. In other words, the isolations and the characterizations of all diastereomers, especially for those minor products, involve a highly complicated process. Another difficulty is that, compared to the corresponding aldol reactions, an increasing number of parameters should be considered when a theoretical model is established. Accordingly, no theoretical models have been reported to tackle this problem so far, although the models for aldol reactions are well established. The proposed asymmetric Friedländer condensations provide an ideal platform to investigate the origin of enantioselectivity in enamine catalyzed desymmetrization processes. In this reaction, only one chiral center exists in the final product and this simplifies the experimental analysis of products, which means that an experimental standard can be used to evaluate the theoretical model, which is a prerequisite for building up a theoretical model.

In the remaining part of this chapter, I will report the successful realization of this methodology, which was applied to the synthesis of a chiral tacrine analog. Furthermore, a theoretical model was established to explain the origin of enantioselectivity.

4.3 Results and Discussions

4.3.1 General Considerations

From the outset of our study, it was clear that several challenges would have to be addressed. First, compared to the relatively electron-poor benzaldehydes that have been

used predominantly in enamine catalyzed aldol reactions, the corresponding *ortho*-aminobenzaldehydes are appreciably more electron-rich and thus represent less reactive electrophiles. Secondly, it was not clear if it would be possible to conduct the necessary elimination step of the Friedländer sequence under mild enough conditions that would simultaneously allow for a highly enantioselective process. In addition, it is well known that *ortho*-aminobenzaldehydes tend to self-condense, even under mild conditions.[14]

4.3.2 Evaluation of Catalysts

With these considerations in mind, we investigated the reaction of the commercially available and relatively electron poor 3,5-dibromo-aminobenzaldehyde (**4.24a**) with 4-phenyl-cyclohexanone (**4.23a**). Among the readily available organocatalysts tested, only amino acids gave acceptable rates and selectivities[15] (Scheme 4.7 and Table 4.1)

Scheme 4.7 **Selected Chiral Amino Acid Catalysts**

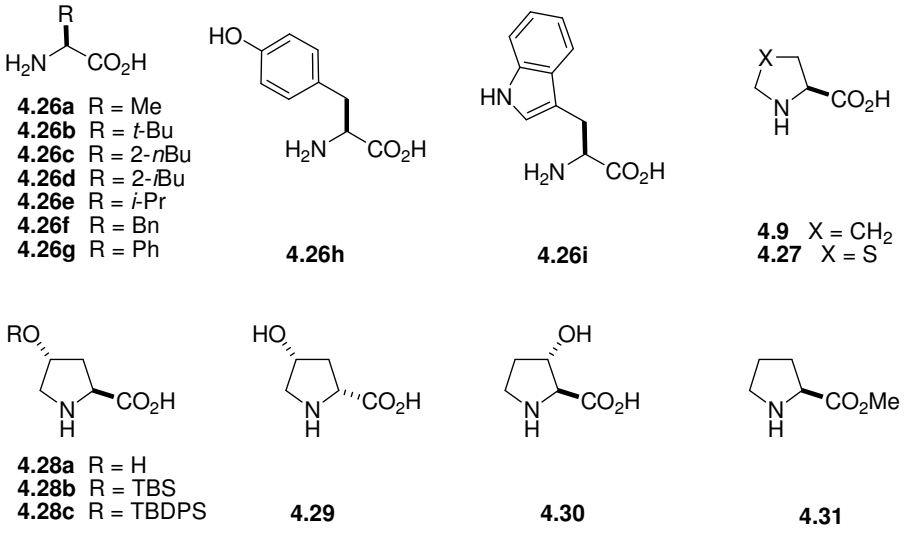
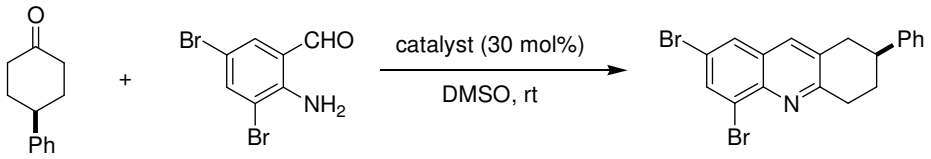


Table 4.1 **Evaluation of Catalysts**[a]



4.23a **4.24a** **4.25a**

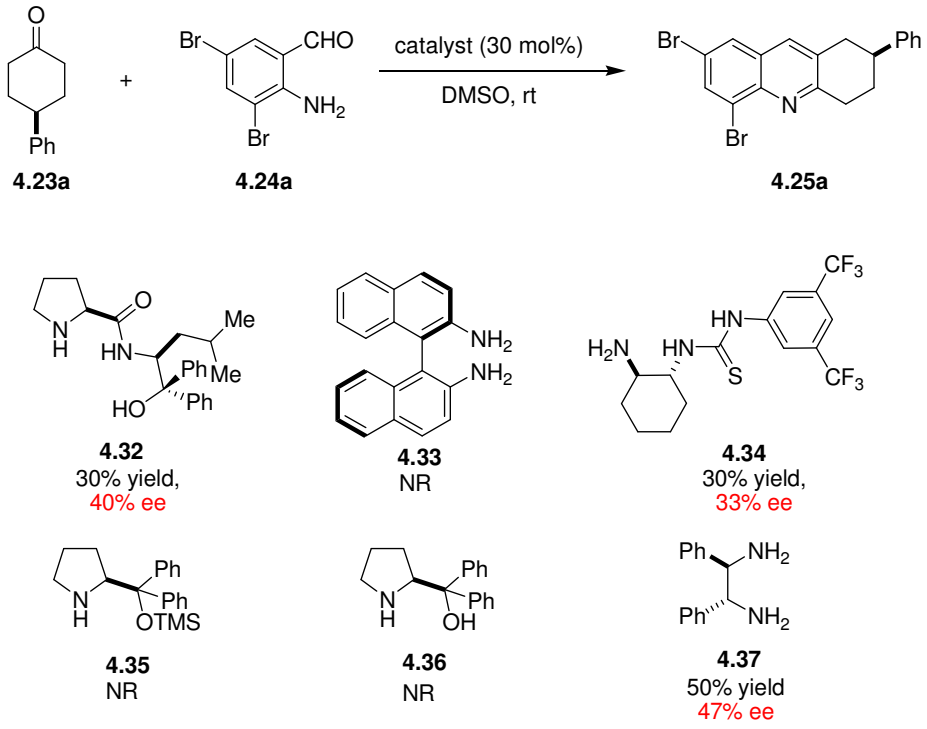
Entry	Catalyst	Time (d)	Yield (%)[b]	ee (%)
1	**4.26a**	3	73	66
2	**4.26b**	3	75	72
3	**4.26c**	3	74	70
4	**4.26d**	3	75	66
5	**4.26e**	3	70	70
6	**4.26f**	3	70	47
7	**4.26g**	3[c]	ND	62
8	**4.26h**	3	65	50
9	**4.26i**	3	65	47
10	**4.9**	1	83	74
11	**4.27**	2	68	67
12	**4.28a**	1	78	79
13	**4.28b**	1	82	78
14	**4.28c**	1	83	76
15	**4.29**	1	75	-67
16	**4.30**	1	80	66
17	**4.31**	3[c]	<5%	ND

[a] Reactions were performed at rt on a 0.2 mmol scale in anhydrous DMSO (0.2 M) using 3.0 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] The reaction was incomplete.

The catalytic results of the amino acid catalysts are summarized in Table 4.1. Proline derivatives provided the best results. *Trans*-4-hydroxy proline (**4.28a**) gave rise

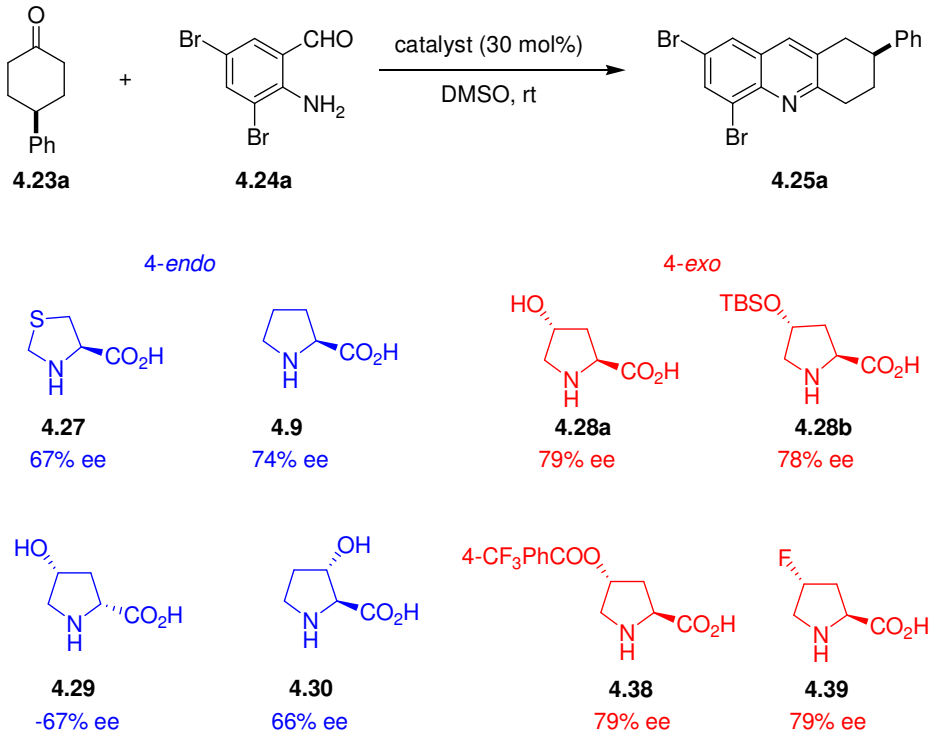
to a slightly higher ee compared to proline itself. Given the poor solubility of proline **4.9** and *trans*-4-hydroxy proline **4.28a** in non-polar solvents, the more soluble silicon protected *trans*-4-hydroxy proline derivatives were prepared.[16] Gratifyingly, the reactivity and selectivity of these catalysts proved to be very similar to that of unmodified *trans*-4-hydroxy proline **4.28a**.

Scheme 4.8 **Evaluation of Non-Amino Acid Catalysts**



Other catalysts such as diarylprolinol **4.36**, diarylprolinol silylether **4.35**, diamine **4.33** and **4.37**, diamine mono-thiourea **4.34** and proline amide **4.32** gave inferior results. Quite surprisingly, proline amides **4.32** incorporating a chiral amino alcohol moiety, which were reported to catalyze the desymmetrization of 4-substituted cyclohexanones with aldehydes, did not give satisfactory results.

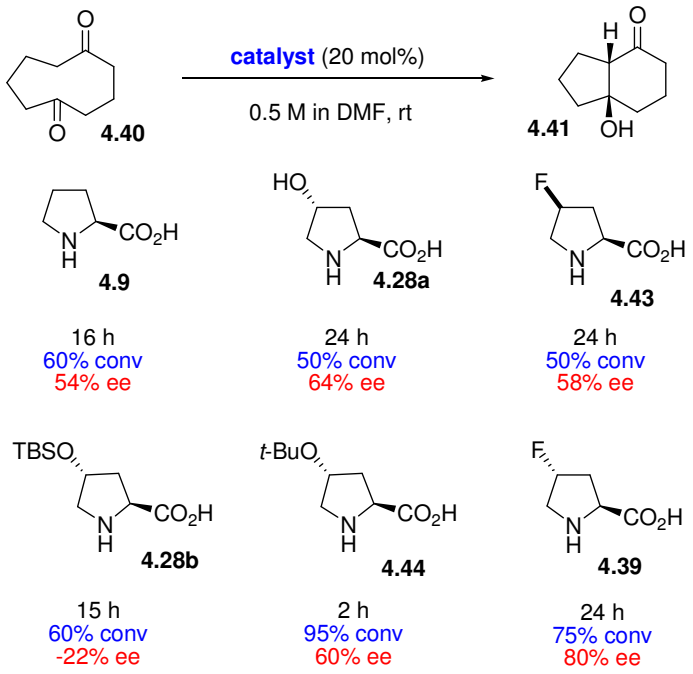
Scheme 4.9 **Conformational Effects in Proline Catalysis**



Another interesting finding is the conformational effect on the proline ring. Proline molecules have two conformers, a 4-*exo*-puckered one and a 4-*endo*-puckered one.[17] Although proline does not have an apparent bias (slightly 4-*endo* favored) for each conformer, substituted prolines can strongly favor one of the conformers, which depends on the substituent itself, the substituted position and the stereochemistry of the compound. In our experiments, the catalysts favoring 4-*exo*-puckered conformation gave better results. Unfortunately, further attempts to increase ee's were not successful. However, this conformational effect could have some valuable applications in other proline-catalyzed reactions. For example, List et al. recently reported catalytic, asymmetric transannular aldolizations for the total synthesis of (+)-hirsutene.[18] In their report, the

enantioselectivity of the product is sensitive to the substitution on the proline ring. *Trans*-4-fluoro-proline **4.39** was found to be the best catalyst but no explanation was provided. We hypothesize that the better enantioselectivity is possibly related to the conformation of *trans*-4-fluoro-proline **4.39**. Further research in this direction will bring new opportunities to proline-catalyzed reactions.

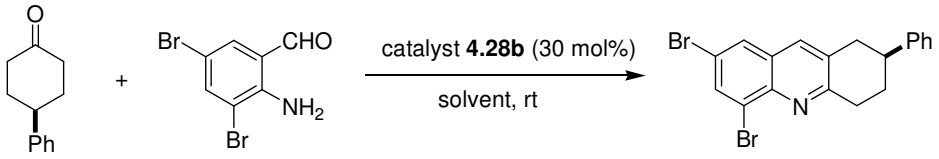
Scheme 4.10 **Substituted Proline-Catalyzed Asymmetric Transannular Aldolizations**



4.3.3 Evaluation of Solvents

In order to improve the rate and selectivity of the reaction, catalyst **4.28b** was tested in a broad range of solvents (Table 4.2).[19] Several interesting observations were made in the course of this study. Apolar solvents containing aromatic rings such as toluene and

Table 4.2 **Evaluation of solvents**[a]



4.23a **4.24a** **4.25a**

Entry	Solvent	Time (h)	Yield (%)[b]	Ee (%)
1	DMSO	16	82	79
2	DMF	24	80	79
3	MeCN	36	83	81
4	EtOAc	48	78	82
5	THF	48	75	82
6	Dioxane	36	78	81
7	$CHCl_3$	72[c]	65	79
8	CH_2Cl_2	72[c]	65	79
9	CCl_4	72[c]	65	83
10	Cyclohexane	72[c]	45	76
11	PhMe	72[c]	67	87
12	Xylenes	72[c]	65	87
13	$PhCF_3$	72[c]	65	82
14	Anisole	72[c]	78	86
15	NMI	10	80	76
16	Pyridine	12	80	83
17[d]	Pyridine	72	75	90
18[e]	Pyridine	96[c]	65	93

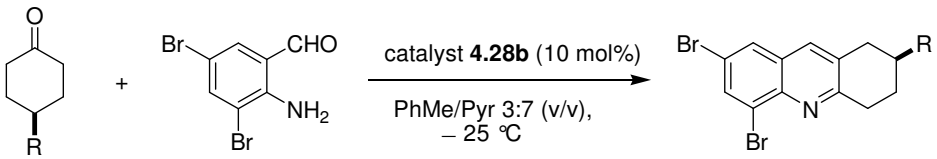
[a] Reactions were performed at rt on a 0.2 mmol scale in anhydrous solvent (0.2 M) using 3 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] The reaction was incomplete. [d] The reaction was run at –20 °C. [e] The reaction was run at –35 °C.

xylenes gave rise to high selectivities but reactions were very slow (incomplete after three days at rt). On the other hand, more polar solvents gave rise to faster reaction rates, albeit at the expense of selectivity. A closer inspection revealed that solvent polarity alone does not directly correlate with reaction rate.[20] Rather, the presence of basic sites on the solvent appeared to be a factor that significantly impacts reaction rate.[21] These collective observations led us to evaluate pyridine as a reaction medium since it combines apparently favorable attributes of other solvents. Indeed, a reaction conducted in pyridine went to completion in only 12 hours while giving rise to product **4.25a** with 83% ee (Table 2, entry 16). This increase in reactivity allowed for the reaction to be performed at lower temperature. At –20 °C, product **4.25a** was recovered with 90% ee (entry 17). Ultimately, a toluene/pyridine solvent mixture was found to provide the best compromise between selectivity and yield. Further optimization also enabled the reduction of catalyst loading to 10 mol %.

4.3.4 Substrate Scope

To illustrate the scope of this methodology, different 4-substituted cyclohexanones were tested under the optimized conditions (Table 4.3). A number of aliphatic and aromatic functional groups with different electronic properties were readily accommodated. Generally, quinoline products were obtained in good yields and with excellent levels of selectivity.

Table 4.3 **Scope of Cyclohexanones**[a]



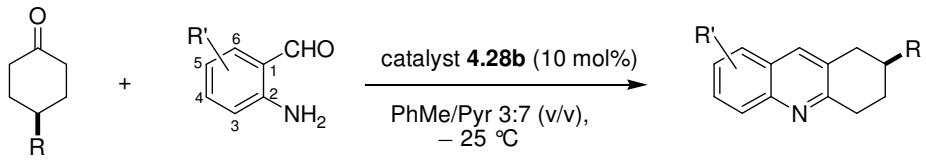
4.23 **4.24a** **4.25**

Entry	R	Product	Method[c]	Yield (%)[b]	ee (%)
1	Ph	**4.25a**	A	76	92
2	4-OH-Ph	**4.25b**	A	60	92
3	4-MeO-Ph	**4.25c**	A	75	93
4	3-MeO-Ph	**4.25d**	A	73	92
5	4-CF_3-Ph	**4.25e**	A	60	90
6	Me	**4.25f**	B[d]	62	91
7	Et	**4.25g**	B[d]	85	94
8	*i*-Pr	**4.25h**	B	80	93
9	*n*-Pr	**4.25i**	B	81	94
10	*t*-Bu	**4.25j**	B	82	91
11	*n*-Pentyl	**4.25k**	B	80	95

[a] Reactions were performed at –25°C on a 0.5 mmol scale in anhydrous solvent for 72 h. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] Method A: 2 equiv of cyclohexanone and solvent (0.5 M); Method B: 2 equiv of cyclohexanone and solvent (0.2 M). [d] 5 equiv of cyclohexanone were used.

As summarized in Table 4.4, a number of *ortho*-amino benzaldehydes were evaluated in combination with 4-*n*Pr- and 4-Ph-substituted cyclohexanones. Due to their attenuated reactivity, more electron-rich *ortho*-aminobenzaldehydes required slightly higher reaction temperatures. Satisfactory yields and ee's were obtained for these substrates. Currently, *ortho*-aminobenzaldehydes with electron-withdrawing substituents do not work well for this protocol due to their low reactivity.

Table 4.4 **Scope of Amino Benzaldehydes**[a]



4.23 **4.24** **4.45**

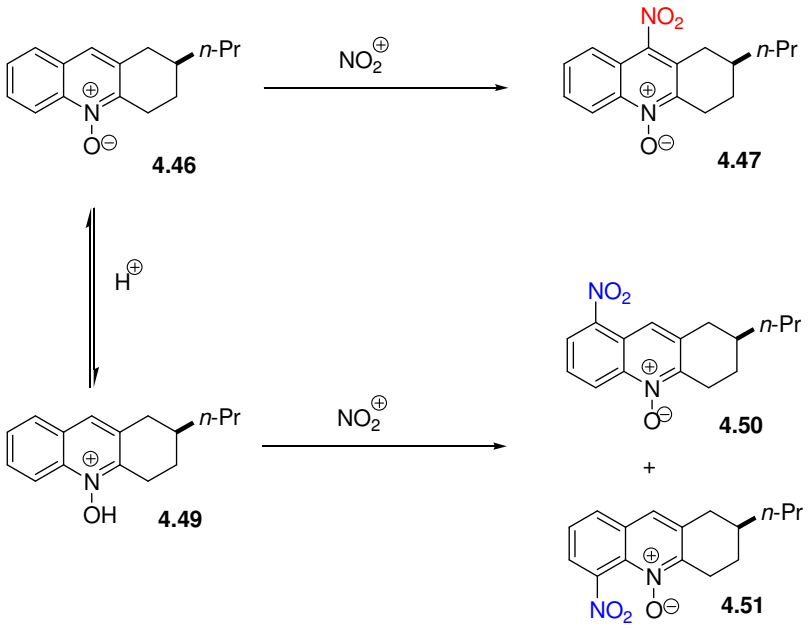
Entry	R	R′	Product	Method[c]	Yield (%)[b]	Ee (%)
1[d]	*n*Pr	H	**4.45a**	A	62	87
2[d]	Ph	H	**4.45b**	B	60	87
3[d]	*n*Pr	4-Cl	**4.45c**	A	73	87
4[d]	Ph	4-Cl	**4.45d**	B	60	87
5	*n*Pr	4-CF_3	**4.45e**	A	70	90
6	Ph	4-CF_3	**4.45f**	B	60	92
7	*n*Pr	4-CO_2Me	**4.45g**	A	88	90
8	Ph	4-CO_2Me	**4.45h**	B	81	90
9	*n*Pr	3,5-Cl_2	**4.45i**	A	77	93
10	Ph	3,5-Cl_2	**4.45j**	B	70	92

[a] Reactions were performed at –25 °C on a 0.5 mmol scale in anhydrous solvent for 72 h. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] Method A: 5 equiv of cyclohexanones and solvent (0.2 M); Method B: 2 equiv of cyclohexanones and solvent (0.5 M). [d] Reactions were performed at –5 °C.

4.3.5 Synthesis of a Chiral Non-Racemic Tacrine Analog

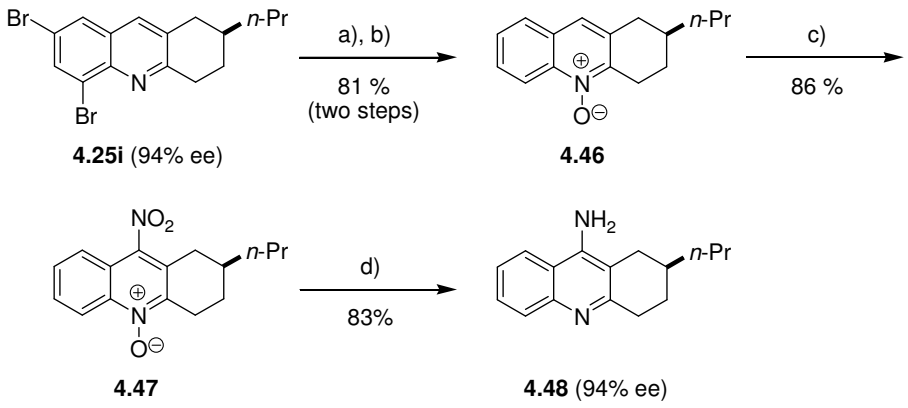
Starting from the chiral quinoline products, a facile sequence was developed to access the corresponding tacrine analogs. Quinoline oxide **4.46** was obtained through hydrogenation followed by *m*-CPBA oxidation. Initially, the nitration of quinoline oxide **4.46** with sulfuric acid and nitric acid gave irreproducible results. The combination of a weaker acid, trifluoroacetic acid, and potassium nitrate was selected based on some reported mechanistic considerations.[22] Compound **4.47** was obtained with a satisfactory

Scheme 4.11 **Mechanistic Considerations of Nitration of Quinoline Oxide**



yield (86%). Then, the reduction with iron power/acetic acid transformed **4.47** into the final product **4.48**.

Scheme 4.12 **Synthesis of an Enantioenriched Tacrine Analog**



Reaction Conditions: a) 10% Pd/C, H_2, Et_3N, MeOH, rt, 8h, 99%; b) *m*-CPBA (2 equiv), CH_2Cl_2, rt, 1h, 82%; c) KNO_3, TFA, 60 ℃, 1h, 86%; d) Fe, AcOH, 110 ℃, 3h, 83%.

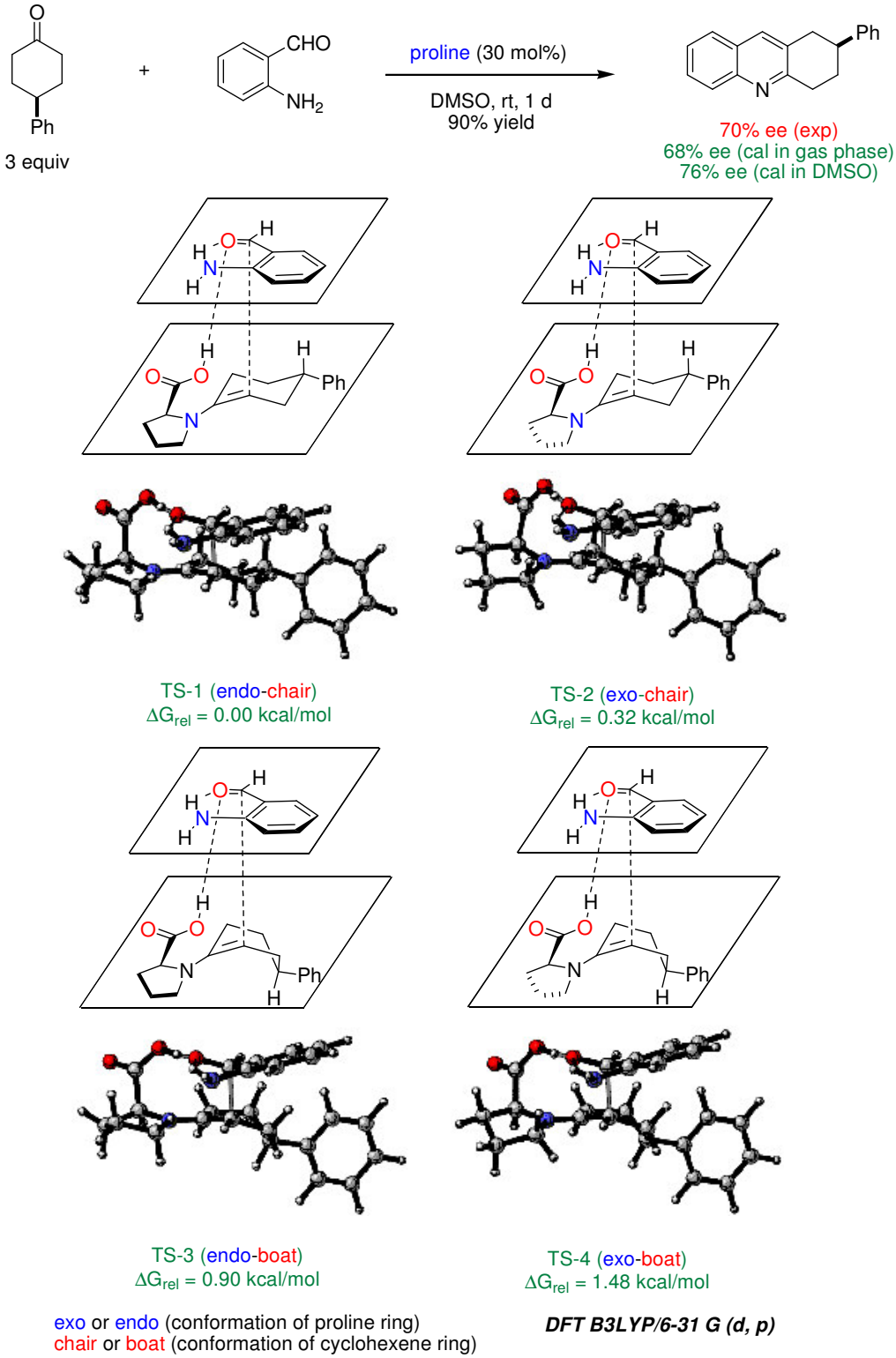
Following the straightforward sequence outlined in Scheme 4.12, the highly enantioenriched tacrine derivative **4.48** was obtained in good yield and without loss of ee.

4.3.6 Computational Study

Given the remoteness of the stereogenic center in the products, the mode of chirality transfer from catalyst to product appeared non-obvious. We thus decided to conduct a computational study to explore the origin of the enantioselectivity for this desymmetrization reaction. As a starting point, we applied the theoretical model first developed by Houk and List.[23] For aldol reactions of aldehydes with cyclohexanones, both experimental and theoretical results have previously indicated that the rate determining step of this reaction corresponds to the enamine attacking the aldehyde, rather than the preceding enamine formation step.[19e, 19k] This trend appears to be reversed in reactions that involve very strong electrophiles.[19j] Given the attenuated electrophilicity of *ortho*-aminobenzaldehydes, we hypothesized that the rate determining step would also be enamine attack. In other words, although the enamine formation step sets the stereogenic center, we assume that equilibration between different enamines is fast compared to the subsequent aldol addition.

DFT calculations[24] were performed to locate 64 possible transition states (TS's) for the C–C bond formation step. These calculations provided several important insights. Firstly, in TS's with lower energy, the cyclohexane ring-substituent is placed in the pseudo equatorial position, rather than the pseudo axial position. Secondly, placement of the enamine double bond *trans* to the proline carboxylic acid fragment is energetically favorable than the corresponding *cis* arrangement. Another interesting feature is the

Scheme 4.13 **Proposed Origin of Enantioselectivity**



presence of an intramolecular hydrogen bond in the *ortho*-aminobenzaldehyde. The four lowest energy TS's are shown in Figure 1.[25] TS 1 and TS 2 both give rise to the observed major enantiomer while TS 3 and TS 4 lead to the minor enantiomer. The calculated ee's[26] for gas phase and DMSO are both consistent with the experimental results.

4.3.7 Conclusion

In conclusion, we have reported the first catalytic enantioselective Friedländer reaction. Enamine catalysis allowed for the efficient desymmetrization of 4-substituted cyclohexanones in the reaction with *ortho*-aminobenzaldehydes. Quinolines with remote stereogenic centers were obtained in generally good yields and with good to excellentlevels of enantioselectivity. Furthermore, a chiral quinoline was converted into a highly enantioenriched tacrine derivative. In addition, a theoretical model was established to explain the origin of product chirality. Our discovery of interesting solvent effects, in particular the rate acceleration observed with pyridine, may have implications for other enamine catalyzed reactions.

4.4 Experimental Section

4.4.1 Preparation Procedures for Catalysts, Cyclohexanones and Amino Aldehydes

Catalysts **4.9**, **4.26a-l**, **4.27**, **4.28a** and **4.29-4.31** were obtained from commercial suppliers and used directly without further purification. Catalysts **4.28b-c** were prepared according to literature methods.[27, 28] 4-Substituted cyclohexanones **4.23a**, **4.23b** and **4.23f-k** were obtained from commercial suppliers and used directly without further purification. Cyclohexanones **4.23c-e** were prepared according to literature methods.[29, 30, 31] Aminobenzaldehyde **4.24a** was obtained from a commercial supplier and used directly

without further purification. Aminobenzaldehydes **4.24b-f** were prepared according to literature methods.[32, 33, 34, 35]

4.4.2 General Procedure for Catalytic Enantioselective Friedländer Condensations

Catalyst **4.28b** (12.0 mg, 0.05 mmol), 4-phenyl cyclohexanone (**4.23a**, 174 mg, 1.00 mmol) and 3,5-dibromo-2-amino-benzaldehyde (**4.24a**, 139 mg, 0.50 mmol) was dissolved in pyridine/toluene (7:3, v/v) (1 mL) at room temperature. The reaction mixture was placed immediately into a –25 °C cooling bath. The reaction progress was monitored by TLC analysis. The crude reaction mixture was loaded directly onto a short silica gel column and eluted with EtOAc. The first 100 mL fraction was collected and dried in vacuo. The residue was purified by flash chromatography (eluent CH_2Cl_2/hexanes 1:3 to 1:1). The product was obtained as pale yellowish oil.

Reaction parameters for specific substrates:

A: 0.5 M in aminobenzaldehyde

B: 0.2 M in aminobenzaldehyde

C: 2.0 equiv. of cyclohexanone

D: 5.0 equiv. of cyclohexanone

E: –25 °C

F: –5 °C

4.25a-e, 4.45f, 4.45h, 4.45j: A+C+E

4.25f-g, 4.45e, 4.45g, 4.45i: B+D+E

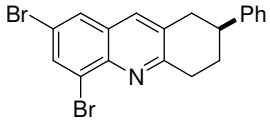
4.25h-k: B+C+E

4.45a, 4.45c: B+D+F

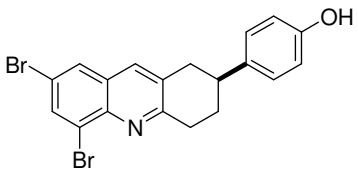
4.45b, 4.45d: A+C+F

4.4.3 Product Characterization Data

(S)-5,7-dibromo-2-phenyl-1,2,3,4-tetrahydroacridine (4.25a): Following the general procedure, compound **4.25a** was obtained as a pale yellowish oil (158 mg, 76% yield). Rf = 0.46 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ – 37.0 (c 1.0, $CHCl_3$, 92% *ee*); IR (KBr) 2922, 1586, 1462, 948, 746, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.72 (s, 1H), 7.40–7.34 (comp, 2H), 7.33–7.29 (comp, 2H), 7.29–7.24 (m, 1H), 3.46–3.37 (m, 1H), 3.33–3.21 (comp, 2H), 3.19–3.09 (comp, 2H), 2.39–2.31 (m, 1H), 2.21–2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 145.5, 142.8, 135.1, 134.6, 132.7, 129.1, 129.1, 128.9, 127.0, 126.9, 125.3, 118.8, 40.4, 37.3, 34.0, 30.5; *m/z* (ESI-MS) 416.2 ($^{79}Br^{79}Br$) $[M+H]^+$, 418.2 ($^{79}Br^{81}Br$) $[M+H]^+$, 420.2 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, t_R = 41.8 min (major) and t_R = 47.2 min.

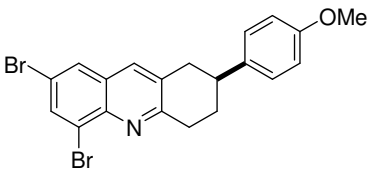


(S)-4-(5,7-dibromo-1,2,3,4-tetrahydroacridin-2-yl)phenol (4.25b): Following the general procedure, compound **4.25b** was obtained as a white solid (130 mg, 60% yield). mp = 238–240 °C (decomposition); Rf = 0.07 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –25.0 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3367, 3067, 2937, 1585, 1515, 1464, 1242, 1205, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.73 (s, 1H), 7.19–7.13 (comp, 2H), 6.85–6.79 (comp, 2H), 4.95 (br s, 1H), 3.44–3.35 (m, 1H), 3.31–3.20 (comp, 2H), 3.14–3.03 (comp, 2H), 2.35–2.26 (m, 1H), 2.15–2.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 154.4, 142.8, 137.7, 135.2, 134.7, 132.8, 129.1, 129.1, 128.1, 125.2, 118.8, 115.7, 39.5, 37.5, 33.9, 30.6; *m/z* (ESI-MS) 432.3 ($^{79}Br^{79}Br$) $[M+H]^+$, 434.3 ($^{79}Br^{81}Br$) $[M+H]^+$, 436.3 ($^{81}Br^{81}Br$) $[M+H]^+$;



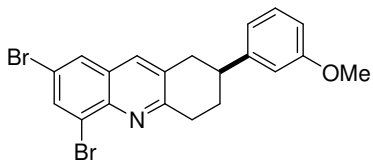
HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 31.0 min (major) and t_R = 36.3 min.

(S)-5,7-dibromo-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroacridine (4.25c): Following



the general procedure, compound **4.25c** was obtained as white foam (167 mg, 75% yield). Rf = 0.24 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –24.5 (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 3062, 2918, 2834, 1608, 1584, 1511, 1460, 1243, 1174, 1030, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.1 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.70 (s, 1H), 7.25–7.19 (comp, 2H), 6.93–6.86 (comp, 2H), 3.82 (s, 3H), 3.45–3.35 (m, 1H), 3.31–3.19 (comp, 2H), 3.15–3.01 (comp, 2H), 2.36–2.26 (m, 1H), 2.17–2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.5, 142.8, 137.6, 135.1, 134.6, 132.7, 129.1, 129.1, 127.9, 125.3, 118.8, 114.3, 55.5, 39.5, 37.5, 34.1, 30.7; *m/z* (ESI-MS) 446.2 ($^{79}Br^{79}Br$) $[M+H]^+$, 448.3 ($^{79}Br^{81}Br$) $[M+H]^+$, 450.3 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 39.5 min (major) and t_R = 46.3 min.

(S)-5,7-dibromo-2-(3-methoxyphenyl)-1,2,3,4-tetrahydroacridine (4.25d): Following

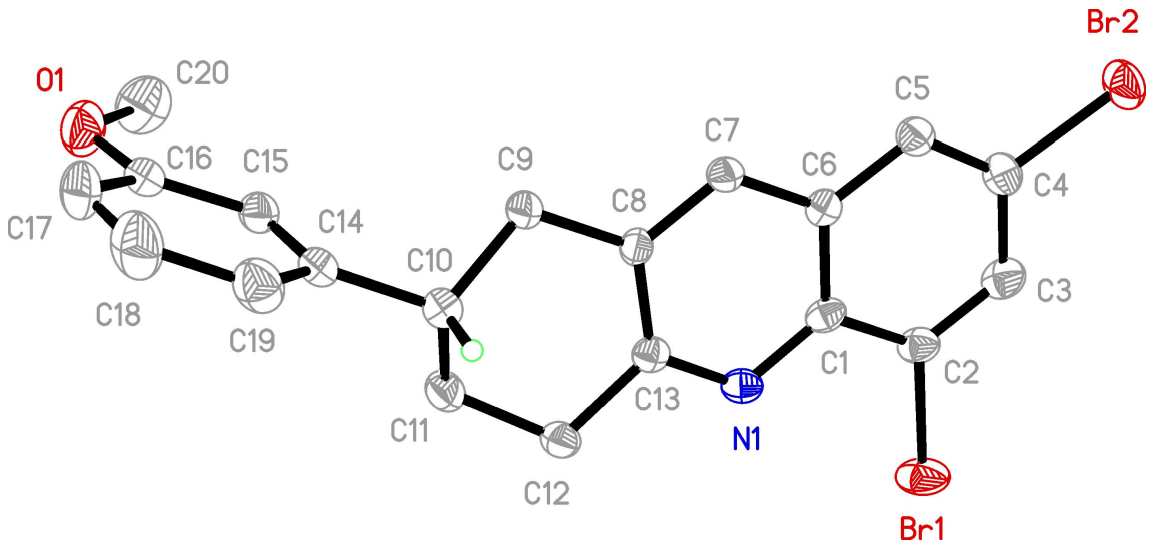


the general procedure, compound **4.25d** was obtained as a pale yellow solid (163 mg, 73% yield). mp = 132–134 °C; Rf = 0.27 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –19.5 (c 1.0, $CHCl_3$, 92% *ee*); IR (KBr) 2932, 1609, 1582, 1486, 1460, 1265, 1049, 925, 780, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.1 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.70 (s, 1H), 7.31–7.24 (m, 1H), 6.89 (app d, *J* = 7.7 Hz, 1H), 6.87–6.83 (m, 1H), 6.83–6.78 (m, 1H), 3.82 (s, 3H), 3.46–3.34 (m, 1H), 3.33–3.18 (comp, 2H), 3.18–3.04 (comp, 2H),

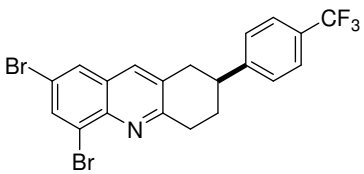
2.38–2.28 (m, 1H), 2.20–2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 160.1, 147.2, 142.8, 135.1, 134.6, 132.6, 130.0, 129.1, 129.1, 125.3, 119.4, 118.8, 113.2, 111.7, 55.5, 40.4, 37.3, 34.0, 30.4; *m/z* (ESI-MS) 446.3 (^{79}Br^{79}Br) $[M+H]^+$, 448.3 (^{79}Br^{81}Br) $[M+H]^+$, 450.3 (^{81}Br^{81}Br) $[M+H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 24.1 min and t_R = 26.5 min (major).

The absolute configuration of the title compound was assigned by X-ray crystallography.

Figure 4.1 **Crystal Structure of Compound 4.25d**



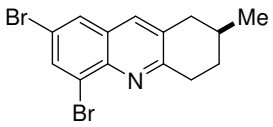
(S)-5,7-dibromo-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroacridine (4.25e):



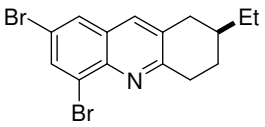
Following the general procedure, compound **4.25e** was obtained as pale yellowish foam (145 mg, 60% yield). Rf = 0.39 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –30.0 (c 1.0, $CHCl_3$, 90% *ee*); IR (KBr) 2927, 1619, 1586, 1463, 1326, 1164, 1124, 1069, 1017, 839, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.73 (s,

1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 3.48–3.36 (m, 1H), 3.35–3.07 (comp, 4H), 2.42–2.30 (m, 1H), 2.24–2.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 149.4 (app d, $J_{C\text{-}F}$ = 1.3 Hz), 142.9, 135.3, 134.7, 132.0, 129.2 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.1, 129.1, 127.4, 125.9 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.3, 124.4 (q, $J_{C\text{-}F}$ = 271.9 Hz), 119.0, 40.3, 37.0, 33.8, 30.2; *m/z* (ESI-MS) 484.2 (^{79}Br^{79}Br) $[M+H]^+$, 486.2 (^{79}Br^{81}Br) $[M+H]^+$, 488.3 (^{81}Br^{81}Br) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, t_R = 23.2 min (major) and t_R = 29.9 min.

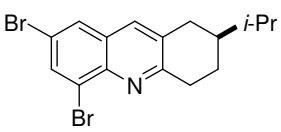
(S)-5,7-dibromo-2-methyl-1,2,3,4-tetrahydroacridine (4.25f): Following the general procedure, compound **4.25f** was obtained as white foam (110 mg, 62% yield). Rf = 0.52 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –46.0 (c 1.0, $CHCl_3$, 91% *ee*); IR (KBr) 2924, 1585, 1463, 1318, 924, 863, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.65 (s, 1H), 3.29 (ddd, *J* = 18.1, 5.5, 3.5 Hz, 1H), 3.12 (ddd, *J* = 18.1, 11.4, 6.2 Hz, 1H), 3.04 (dd, *J* = 16.6, 3.8 Hz, 1H), 2.60 (dd, *J* = 16.6, 10.8 Hz, 1H), 2.14–1.92 (comp, 2H), 1.65–1.55 (m, 1H), 1.13 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 143.8, 136.0, 135.6, 134.1, 130.3, 130.2, 126.4, 119.7, 38.9, 34.7, 32.5, 30.3, 23.0; *m/z* (ESI-MS) 354.3 (^{79}Br^{79}Br) $[M+H]^+$, 356.3 (^{79}Br^{81}Br) $[M+H]^+$, 358.3 (^{81}Br^{81}Br) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.9 min (major) and t_R = 13.6 min.



(S)-5,7-dibromo-2-ethyl-1,2,3,4-tetrahydroacridine (4.25g): Following the general procedure, compound **4.25g** was obtained as a pale yellowish oil (157 mg, 85% yield). Rf = 0.51 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ – 57.5 (c 1.0, $CHCl_3$, 94% *ee*); IR (KBr) 2958, 2922, 2873, 2854, 1586, 1462, 1425, 943, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.67 (s, 1H), 3.30 (ddd, *J* = 18.1, 5.4, 3.7 Hz, 1H), 3.15–3.04 (comp, 2H), 2.60 (dd, *J* = 16.7, 10.7 Hz, 1H), 2.19–2.09 (m, 1H), 1.81–1.70 (m, 1H), 1.64–1.52 (m, 1H), 1.50–1.42 (comp, 2 H), 1.02 (app t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 142.7, 134.8, 134.5, 133.0, 129.1, 129.0, 125.2, 118.6, 35.8, 35.6, 33.5, 29.0, 29.0, 11.7; *m/z* (ESI-MS) 368.4 ($^{79}Br^{79}Br$) $[M+H]^+$, 370.4 ($^{79}Br^{81}Br$) $[M+H]^+$, 372.4 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 254 nm, t_R = 7.0 min (major) and t_R = 12.7 min.



(S)-5,7-dibromo-2-isopropyl-1,2,3,4-tetrahydroacridine (4.25h): Following the general procedure, compound **4.25h** was obtained as a pale yellowish oil (153 mg, 80% yield). Rf = 0.50 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –61.5 (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 2956, 2870, 1586, 1463, 1425, 944, 862, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.68 (s, 1H), 3.35–3.28 (m, 1H), 3.13–2.99 (comp, 2H), 2.71 (dd, *J* = 16.7, 9.7 Hz, 1H), 2.16–2.08 (m, 1H), 1.73–1.54 (comp, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 142.6, 134.8, 134.6, 133.0, 129.1, 129.0, 125.2, 118.5, 40.6, 34.0, 32.9, 32.3, 26.5, 20.0, 20.0; *m/z* (ESI-MS) 382.3 ($^{79}Br^{79}Br$) $[M+H]^+$, 384.3 ($^{79}Br^{81}Br$) $[M+H]^+$, 386.3 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.4



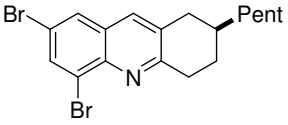
min (major) and t_R = 12.5 min.

(S)-5,7-dibromo-2-propyl-1,2,3,4-tetrahydroacridine (4.25i): Following the general procedure, compound **4.25i** was obtained as a pale yellowish oil (155 mg, 81% yield). Rf = 0.54 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ – 58.0 (c 1.0, $CHCl_3$, 94% *ee*); IR (KBr) 2925, 1586, 1463, 1319, 945, 855, 779, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.68 (s, 1H), 3.29 (ddd, *J* = 18.1, 5.4, 3.9 Hz, 1H), 3.16–3.03 (comp, 2H), 2.61 (dd, *J* = 16.6, 10.6 Hz, 1H), 2.17–2.08 (m, 1H), 1.92–1.80 (m, 1H), 1.64–1.54 (m, 1H), 1.51–1.36 (comp, 4H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 142.7, 134.8, 134.5, 133.0, 129.2, 129.0, 125.2, 118.6, 38.5, 35.9, 33.8, 33.5, 29.3, 20.3, 14.5; *m/z* (ESI-MS) 382.3 ($^{79}Br^{79}Br$) $[M+H]^+$, 384.3 ($^{79}Br^{81}Br$) $[M+H]^+$, 386.3 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.7 min (major) and t_R = 10.8 min.

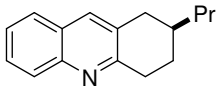
(S)-5,7-dibromo-2-*tert*-butyl-1,2,3,4-tetrahydroacridine (4.25j): Following the general procedure, compound **4.25j** was obtained as a pale yellowish oil (163 mg, 82% yield). Rf = 0.54 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –56.5 (c 1.0, $CHCl_3$, 91% *ee*); IR (KBr) 2959, 1586, 1463, 1394, 1365, 1318, 945, 868, 784, 752, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.69 (s, 1H), 3.33 (ddd, *J* = 17.6, 4.7, 2.6 Hz, 1H), 3.12–2.99 (comp, 2H), 2.72 (dd, *J* = 16.4, 11.9 Hz, 1H), 2.21–2.12 (m, 1H), 1.62–1.47 (comp, 2H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 142.6, 134.8, 134.7, 133.7, 129.2, 129.0, 125.2, 118.5, 44.7, 34.8, 32.8, 30.9, 27.5, 24.6; *m/z* (ESI-MS) 396.2 ($^{79}Br^{79}Br$) $[M+H]^+$, 398.2 ($^{79}Br^{81}Br$) $[M+H]^+$, 400.2 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-

hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.4 min (major) and t_R = 12.2 min.

(S)-5,7-dibromo-2-pentyl-1,2,3,4-tetrahydroacridine (4.25k): Following the general procedure, compound **4.25k** was obtained as pale yellowish foam (165 mg, 80% yield). Rf = 0.53 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –54.5 (c 1.0, $CHCl_3$, 95% *ee*); IR (KBr) 2953, 2928, 2886, 2858, 1584, 1464, 1422, 1317, 924, 869, 851, 777, 734, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 2.1 Hz, 1H), 7.64 (s, 1H), 3.27 (ddd, *J* = 18.1, 5.4, 3.8 Hz, 1H), 3.14–3.00 (comp, 2H), 2.58 (dd, *J* = 16.8, 10.6 Hz, 1H), 2.18–2.04 (m, 1H), 1.90–1.73 (m, 1H), 1.63–1.50 (m, 1H), 1.47–1.22 (comp, 8H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 142.6, 134.7, 134.5, 133.0, 129.1, 129.0, 125.2, 118.5, 36.3, 36.0, 34.0, 33.5, 32.3, 29.3, 26.9, 22.9, 14.3; *m/z* (ESI-MS) 410.4 ($^{79}Br^{79}Br$) $[M+H]^+$, 412.4 ($^{79}Br^{81}Br$) $[M+H]^+$, 414.4 ($^{81}Br^{81}Br$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.5 min (major) and t_R = 11.2 min.

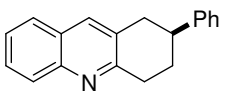


(S)-2-propyl-1,2,3,4-tetrahydroacridine (4.45a): Following the general procedure, compound **4.45a** was obtained as white foam (70 mg, 62% yield). Rf = 0.15 (Hexanes/EtOAc 9 :1 v/v); $[\alpha]_D^{20}$ –77.5 (c 1.0, $CHCl_3$, 87% *ee*); IR (KBr) 2955, 2926, 2870, 1492, 1456, 1415, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (app d, *J* = 8.5 Hz, 1H), 7.78 (s, 1H), 7.68 (app d, *J* = 8.1 Hz, 1H), 7.63–7.55 (m, 1H), 7.46–7.38 (m, 1H), 3.22 (ddd, *J* = 17.6, 5.8, 3.8 Hz, 1H), 3.14–2.99 (comp, 2H), 2.58 (dd, *J* = 16.4, 10.6 Hz, 1H), 2.18–2.05 (m, 1H), 1.92–1.76 (m, 1H), 1.65–1.52 (m, 1H), 1.51–1.34 (comp, 4H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

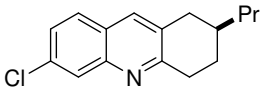


159.6, 146.9, 135.2, 130.9, 128.7, 128.5, 127.4, 127.1, 125.7, 38.6, 36.1, 33.9, 33.3, 29.6, 20.3, 14.6; *m/z* (ESI-MS) 226.4 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.2 min (major) and t_R = 9.5 min.

(S)-2-phenyl-1,2,3,4-tetrahydroacridine (4.45b): Following the general procedure, compound **4.45b** was obtained as pale yellowish foam (78 mg, 60% yield). Rf = 0.17 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –30.0 (c 1.0, $CHCl_3$, 87% *ee*); IR (KBr) 3027, 2929, 1601, 1492, 1415, 751, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (app d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.72 (app d, *J* = 8.1 Hz, 1H), 7.67–7.58 (m, 1H), 7.50–7.42 (m, 1H), 7.41–7.23 (comp, 5H), 3.36 (ddd, *J* = 17.9, 5.6, 3.1 Hz, 1H), 3.31–3.20 (comp, 2H), 3.18–3.06 (comp, 2H), 2.39–2.28 (m, 1H), 2.23–2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 147.0, 145.9, 135.3, 130.6, 129.0, 128.9, 128.6, 127.4, 127.2, 127.1, 126.7, 125.9, 40.7, 37.6, 33.9, 30.7; *m/z* (ESI-MS) 260.3 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.9 min and t_R = 11.9 min (major).

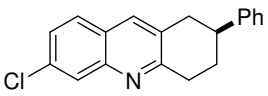


(S)-6-chloro-2-propyl-1,2,3,4-tetrahydroacridine (4.45c): Following the general procedure, compound **4.45c** was obtained as a yellowish solid (75 mg, 73% yield). mp = 70–72 °C; Rf = 0.43 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –58.5 (c 1.0, $CHCl_3$, 87% *ee*); IR (KBr) 2954, 2924, 1485, 1068, 921, 883, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.9 Hz, 1H), 7.74 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 1.9 Hz, 1H), 3.19 (ddd, *J* = 18.0, 5.6, 3.8 Hz, 1H), 3.11–2.97 (comp, 2H), 2.56 (dd, *J* = 16.5, 10.7 Hz, 1H), 2.17–2.05 (m, 1H), 1.90–1.75 (m, 1H), 1.64–1.50 (m, 1H), 1.50–1.33 (comp, 4H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 147.1, 135.0, 134.3, 131.2, 128.3, 127.5, 126.7, 125.7, 38.6, 36.1, 33.8,

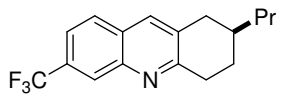


33.3, 29.4, 20.3, 14.5; *m/z* (ESI-MS) 260.4 (^{35}Cl) $[M+H]^+$, 262.4 (^{37}Cl) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.8 min (major) and t_R = 10.2 min.

(S)-6-chloro-2-phenyl-1,2,3,4-tetrahydroacridine (4.45d): Following the general procedure, compound **4.45d** was obtained as a white solid (88 mg, 60% yield). mp = 90–92 °C; Rf = 0.28 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –47.0 (c 1.0, $CHCl_3$, 87% *ee*); IR (KBr) 3028, 2929, 1615, 1484, 1413, 1068, 764, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.9 Hz, 1H), 7.82 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, , *J* = 8.7, 1.9 Hz, 1H), 7.39–7.34 (comp, 2H), 7.34–7.30 (comp, 2H), 7.30–7.24 (m, 1H), 3.33 (ddd, *J* = 18.0, 5.6, 3.1 Hz, 1H), 3.30–3.18 (comp, 2H), 3.17–3.07 (comp, 2H), 2.39–2.29 (m, 1H), 2.23–2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 147.3, 145.7, 135.1, 134.6, 130.9, 128.9, 128.4, 127.6, 127.0, 127.0, 126.8, 125.7, 40.5, 37.5, 33.8, 30.6; *m/z* (ESI-MS) 294.4 (^{35}Cl) $[M+H]^+$, 296.4 (^{37}Cl) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 15.6 min (major) and t_R = 18.1 min.

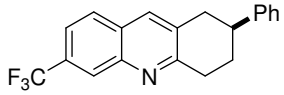


(S)-2-propyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroacridine (4.45e): Following the general procedure, compound **4.45e** was obtained as a white solid (103 mg, 70% yield). mp = 48–49 °C; Rf = 0.45 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –63.5 (c 1.0, $CHCl_3$, 90% *ee*); IR (KBr) 2958, 2929, 2874, 1443, 1418, 1325, 1291, 1222, 1159, 1126, 1058, 904, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.1 Hz, 1H), 7.84 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, , *J* = 8.5, 1.1 Hz, 1H), 3.24 (ddd, *J* = 18.0, 5.6, 3.8 Hz, 1H), 3.15–3.04 (comp, 2H), 2.62 (dd, *J* = 16.6, 10.7 Hz, 1H), 2.18–2.10 (m, 1H), 1.93–1.80 (m, 1H), 1.67–1.55 (m, 1H),

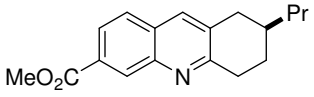


1.50–1.37 (comp, 4H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 145.7, 134.9, 133.2, 130.4 (q, $J_{C\text{-}F}$ = 32.4 Hz), 128.8 (app d, $J_{C\text{-}F}$ = 1.0 Hz), 128.2, 126.5 (q, $J_{C\text{-}F}$ = 4.4 Hz), 124.4 (q, $J_{C\text{-}F}$ = 272.3 Hz), 121.4 (q, $J_{C\text{-}F}$ = 3.2 Hz), 38.5, 36.2, 33.8, 33.3, 29.4, 20.3, 14.5; *m/z* (ESI-MS) 294.4 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, t_R = 4.6 min (major) and t_R = 5.5 min.

(S)-2-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroacridine (4.45f): Following the general procedure, compound **4.45f** was obtained as a white solid (98 mg, 60% yield). mp = 137–138 °C; Rf = 0.35 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –38.0 (c 1.0, $CHCl_3$, 92% *ee*); IR (KBr) 2922, 1606, 1440, 1417, 1333, 1152, 1119, 1058, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (app s, 1H), 7.89 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.63 (dd, , J = 8.5, 1.4 Hz, 1H), 7.42–7.24 (comp, 5H), 3.38 (ddd, J = 18.1, 5.6, 3.2 Hz, 1H), 3.34–3.22 (comp, 2H), 3.22–3.10 (comp, 2H), 2.41–2.32 (m, 1H), 2.25–2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 145.9, 145.5, 135.0, 132.9, 130.7 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.9, 128.8 (app d, $J_{C\text{-}F}$ = 0.8 Hz), 128.3, 127.0, 126.9, 126.6 (q, $J_{C\text{-}F}$ = 4.4 Hz), 124.3 (q, $J_{C\text{-}F}$ = 272.3 Hz), 121.6 (q, $J_{C\text{-}F}$ = 3.1 Hz), 40.5, 37.6, 33.8, 30.5; *m/z* (ESI-MS) 328.4 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, t_R = 20.5 min (major) and t_R = 23.1 min.



(S)-methyl 7-propyl-5,6,7,8-tetrahydroacridine-3-carboxylate (4.45g): Following the general procedure, compound **4.45g** was obtained as an off-white solid (125 mg, 88% yield). mp = 117–118 °C; Rf = 0.10 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –70.0 (c 1.0, $CHCl_3$, 90% *ee*); IR (KBr) 2948, 2931,



2867, 1716, 1446, 1414, 1267, 1218, 1188, 1090, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (app s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.73 (app d, , *J* = 8.5 Hz, 1H), 3.97 (s, 3H), 3.29–3.19 (m, 1H), 3.15–3.02 (comp, 2H), 2.61 (dd, *J* = 16.6, 10.7 Hz, 1H), 2.18–2.07 (m, 1H), 1.92–1.79 (m, 1H), 1.66–1.54 (m, 1H), 1.50–1.36 (comp, 4H), 0.96 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 160.9, 146.1, 134.9, 133.2, 131.3, 130.2, 129.9, 127.3, 125.3, 52.5, 38.6, 36.3, 33.8, 33.3, 29.4, 20.3, 14.5; *m/z* (ESI-MS) 284.4 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 12.7 min (major) and t_R = 17.1 min.

(S)-methyl 7-phenyl-5,6,7,8-tetrahydroacridine-3-carboxylate (4.45h): Following the general procedure, compound **4.45h** was obtained as an off-white solid (128 mg, 81% yield). mp = 143–145 °C; Rf = 0.05 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –45.0 (c 1.0, $CHCl_3$, 90% *ee*); IR (KBr) 2934, 1720, 1441, 1274, 1220, 1091, 759, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.42–7.22 (comp, 5H), 3.98 (s, 3H), 3.41–3.32 (m, 1H), 3.32–3.19 (comp, 2H), 3.19–3.07 (comp, 2H), 2.40–2.29 (m, 1H), 2.23–2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 160.0, 146.2, 145.6, 134.9, 132.8, 131.4, 130.4, 129.8, 128.9, 127.4, 127.0, 126.8, 125.4, 52.6, 40.5, 37.7, 33.8, 30.6; *m/z* (ESI-MS) 318.4 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 74.8 min (major) and t_R = 90.1 min.

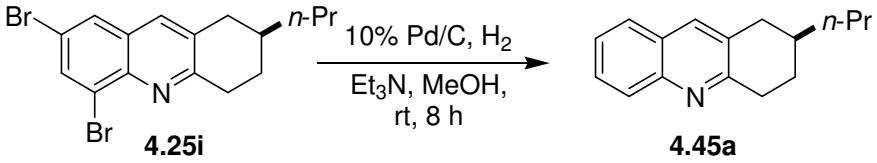
(S)-5,7-dichloro-2-propyl-1,2,3,4-tetrahydroacridine (4.45i): Following the general procedure, compound **4.45i** was obtained as a yellowish solid (113 mg, 77% yield). mp = 62–64 °C; Rf = 0.41 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –70.5 (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 2955, 2926, 2870, 1593, 1464, 1425, 1321, 1237, 1089, 968, 928, 861, 781, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.69 (d, *J* = 2.2 Hz, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 3.30 (ddd, *J* = 18.1, 5.4, 3.9 Hz, 1H), 3.17–3.02 (comp, 2H), 2.60 (dd, *J* = 16.6, 10.6 Hz, 1H), 2.17–2.08 (m, 1H), 1.91–1.80 (m, 1H), 1.62–1.53 (m, 1H), 1.50–1.36 (comp, 4H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 141.7, 134.6, 133.8, 133.1, 130.5, 129.2, 128.7, 125.0, 38.5, 36.0, 33.7, 33.5, 29.3, 20.3, 14.5; *m/z* (ESI-MS) 294.4 ($^{35}Cl^{35}Cl$) $[M+H]^+$, 296.3 ($^{35}Cl^{37}Cl$) $[M+H]^+$, 298.3 ($^{37}Cl^{37}Cl$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.3 min (major) and t_R = 10.7 min.

(S)-5,7-dichloro-2-phenyl-1,2,3,4-tetrahydroacridine (4.45j): Following the general procedure, compound **4.45j** was obtained as a yellowish oil (115 mg, 70% yield). Rf = 0.31 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ –51.0 (c 1.0, $CHCl_3$, 92% *ee*); IR (KBr) 2926, 1593, 1463, 1427, 1321, 1237, 1089, 971, 857, 780, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.40–7.24 (comp, 5H), 3.43 (ddd, *J* = 18.2, 5.4, 3.2 Hz, 1H), 3.34–3.22 (comp, 2H), 3.19–3.08 (comp, 2H), 2.40–2.31 (m, 1H), 2.22–2.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 145.5, 141.8, 134.7, 134.0, 132.7, 130.8, 129.5, 128.9, 128.7, 127.0, 126.9, 125.1, 40.4, 37.4, 34.0, 30.5; *m/z* (ESI-MS) 328.4 ($^{35}Cl^{35}Cl$) $[M+H]^+$, 330.4 ($^{35}Cl^{37}Cl$) $[M+H]^+$, 332.4 ($^{37}Cl^{37}Cl$) $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-

hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 34.4 min (major) and t_R = 38.6 min.

4.4.4 Synthesis of a Chiral Tacrine Analog

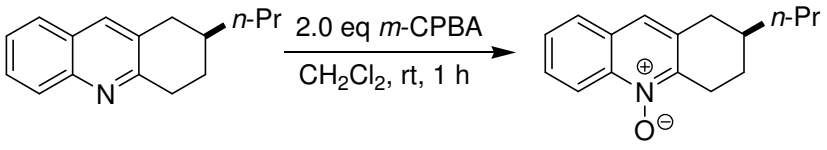
Conversion of 4.25i into 4.45a[36]



4.25i **4.45a**

Compound **4.25i** (766 mg, 2 mmol), triethylamine (0.85 mL, 3.0 equiv.) and Pd/C (10 wt%, 77 mg) was mixed with 10 mL of methanol. The flask was sealed with a septum and charged with a hydrogen gas balloon. After 8 h, the mixture was filtered through a plug of celite and rinsed with EtOAc. The combined filtrate was dried with anhydrous Na_2CO_3. The solvent was removed in vacuo after filtration and compound **4.45a** was obtained (448 mg, 99% yield) and used directly in the next step.

Conversion of 4.45a into (S)-2-propyl-1,2,3,4-tetrahydroacridine 10-oxide (4.46)[37]

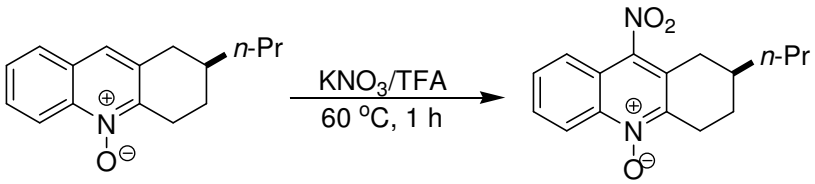


4.45a **4.46**

Compound **4.45a** (245 mg, 1.087 mmol) was dissolved in 4 mL of CH_2Cl_2 and cooled to 0 °C. Subsequently, a solution of *m*-CPBA (500 mg, 2.0 equiv.) in 6 mL of CH_2Cl_2 was added slowly. The reaction was allowed to warm to rt. After completion of the reaction (1 h), the reaction mixture was quenched by dilution with water and extracted with CH_2Cl_2. The organic layer was collected and washed with water. The

solution was dried with anhydrous Na_2SO_4 and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 2:1 to 1:2). Compound **4.46** was obtained as an off-white solid (215 mg, 82% yield). mp = 92–94 °C; Rf = 0.35 (Hexanes/EtOAc 1:1 v/v); $[\alpha]_D^{20}$ –76.5 (c 1.0, CH_2Cl_2, 94% *ee*); IR (KBr) 2954, 2926, 2869, 1569, 1502, 1325, 1234, 1093, 768, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (app d, *J* = 8.8 Hz, 1H), 7.72 (app d, *J* = 8.1 Hz, 1H), 7.68–7.61 (m, 1H), 7.56–7.48 (m, 1H), 7.43 (s, 1H), 3.41 (ddd, *J* = 20.0, 6.1, 3.3 Hz, 1H), 3.10–2.89 (comp, 2H), 2.57 (dd, *J* = 16.2, 10.5 Hz, 1H), 2.20–2.07 (m, 1H), 1.83–1.69 (m, 1H), 1.60–1.30 (comp, 5H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 140.3, 132.2, 129.4, 128.5, 127.8, 127.5, 124.7, 119.6, 37.9, 35.9, 33.0, 28.2, 25.9, 20.3, 14.5; *m/z* (ESI-MS) 242.3 $[M+H]^+$.

Conversion of 4.46 into (S)-9-nitro-2-propyl-1,2,3,4-tetrahydroacridine 10-oxide (4.47)[22]

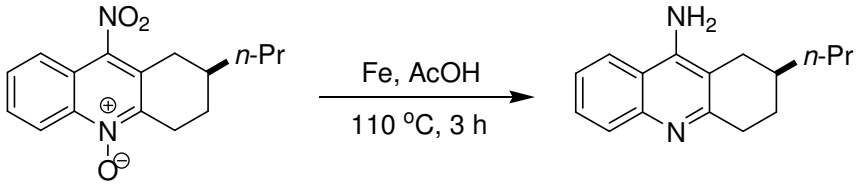


4.46 **4.47**

Compound **4.46** (46 mg, 0.191 mmol) was dissolved in trifluroacetic acid (1.6 mL, 110 equiv.). The resulting solution was warmed to 60 °C and KNO_3 powder (58 mg, 3.0 equiv.) was added in one portion. After maintaining the temperature at 60 °C for one

hour, the reaction mixture was allowed to cool to rt and an excess of water was added. The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, washed with 5% aqueous $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel (Hexanes/EtOAc = 4:1). Compound **4.47** was obtained as a yellowish solid (47 mg, 86% yield). mp = 118–120 °C; Rf = 0.34 (Hexanes/EtOAc 7:3 v/v); $[\alpha]_D^{20}$ – 317.0 (c 1.0, CH_2Cl_{22}, 94% *ee*); IR (KBr) 2953, 1567, 1521, 1102, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (app d, *J* = 8.7 Hz, 1H), 7.81–7.65 (comp, 3H), 3.41 (ddd, *J* = 20.2, 5.3, 2.9 Hz, 1H), 3.05–2.88 (comp, 2H), 2.57 (dd, *J* = 17.3, 10.6 Hz, 1H), 2.23–2.13 (m, 1H), 1.83–1.73 (m, 1H), 1.59–1.49 (m, 1H), 1.48–1.36 (comp, 4H), 0.94 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 142.3, 140.8, 130.9, 130.0, 124.8, 122.3, 120.2, 120.0, 37.7, 32.3, 31.6, 27.3, 26.4, 20.1, 14.4; *m/z* (ESI-MS) 287.2 $[M+H]^+$.

Conversion of 4.13 into (S)-2-propyl-1,2,3,4-tetrahydroacridin-9-amine (4.48)[38]



4.47 **4.48**

Compound **4.47** (47 mg, 0.164 mmol) and iron powder (83 mg, 9.0 equiv.) was mixed with acetic acid (2 mL) at rt. The resulting mixture was heated at 110 °C for 3 h. Subsequently, the mixture was allowed to cool to rt and diluted with ethanol (15 mL). The crude mixture was filtered and the filtrate dried in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/MeOH/NH_4OH = 350:50:2 v/v). Compound **4.48** was obtained as a brownish solid (32.6 mg, 83% yield). mp = 153–155

°C; Rf = 0.11 (MeOH/EtOAc 1:1 v/v); $[\alpha]_D^{20}$ –63.5 (c 1.0, CH_2Cl_2, 94% *ee*); IR (KBr) 3354, 3238, 2954, 2926, 2869, 1644, 1566, 1501, 1427, 1377, 1305, 758, 736 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.01 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.72 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.8, 1.0 Hz, 1H), 7.33 (ddd, *J* = 8.4, 6.8, 1.0 Hz, 1H), 2.99 (ddd, *J* = 17.3, 5.1, 3.3 Hz, 1H), 2.90 (ddd, *J* = 17.3, 11.8, 5.5 Hz, 1H), 2.78 (dd, *J* = 16.1, 5.4 Hz, 1H), 2.15 (dd, *J* = 16.1, 10.5 Hz, 1H), 2.09–1.99 (m, 1H), 1.86–1.74 (m, 1H), 1.57–1.39 (comp, 5H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.7, 150.8, 147.0, 129.9, 127.4, 124.5, 122.4, 118.3, 110.4, 40.2, 35.1, 33.7, 31.5, 30.0, 21.2, 14.7; *m/z* (ESI-MS) 241.4 $[M+H]^+$.

The product **4.48** was benzoylated with BzCl following a reported procedure.[39] The ee of the benzoylated product **4.52** was found to be 94% as determined by HPLC analysis. HPLC conditions: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 20.6 min (major) and t_R = 25.1 min.

4.4.5 Computational Studies

Stationary points of transition state geometries were optimized and characterized by frequency analysis using hybrid density functional theory (B3LYP)[40] and the 6-31G (d, p) basis set as implemented in Gaussian 09.[41] Enthalpies, ΔH_{298}, and free energies, ΔG_{298}, were computed for the gas phase. The solvation energies, $\Delta G_{298(\varepsilon=47)}$, for transition states were computed using a polarizable continuum model[42] with a permittivity of 47, the value for DMSO, the solvent used in the experiments. These calculations involve the solvation model CPCM as implemented in Gaussian 09. Enantiomeric excesses for the

predictions were determined by converting the differences in the calculated gas-phase free energies of activation, $\Delta\Delta G_{298}$, to %ee using absolute rate theory: $\ln(k_1/k_2) = -e^{\Delta\Delta G/RT}$.

A theoretical model was established based on the Houk-List model[23d] for proline catalyzed aldol reactions. The reaction of 4-phenyl cyclohexanone with *ortho*-amino benzaldehyde was selected for this computational study. Six independent parameters (*exo* or *endo* conformation of proline ring, *cis* or *trans* enamine, *ax* or *eq* disposition of the 4-substituent of the cyclohexene ring, *pseudo-boat* or *pseudo-chair* conformation of the cyclohexene ring, *si* or *re* approach of amino benzaldehyde and the conformations of amino benzaldehyde *with* or *without* intramolecular hydrogen bonding) were considered and 64 corresponding TS's were calculated in the gas phase. The four TS's with lowest energy were further calculated in DMSO using CPCM. The stationary point was located in each TS and only one negative frequency was found in each case. For comparison, four TS's from the *cis* enamine were also provided.

Coordinates of TS geometries for the reaction of proline enamine of 4-phenyl cyclohexanone with *ortho*-amino benzaldehyde.

For *trans*-enamine TS's:

TS1 (endo-chair in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.690005	1.107330	0.778955
2	1	0	0.837083	-3.151743	0.159196
3	1	0	0.483725	-1.964944	1.391889
4	1	0	-1.642322	-0.379379	-1.846220
5	6	0	0.142333	0.076954	-0.742962
6	1	0	0.531390	0.724304	-1.524858
7	7	0	2.211733	-1.142108	-0.783794

8	6	0	0.310491	-2.210580	0.334329
9	6	0	0.916559	-1.101414	-0.495608
10	8	0	2.004072	1.045775	0.895140
11	6	0	-1.965684	-1.078587	0.175280
12	1	0	2.794693	-3.130251	-0.305678
13	6	0	3.171866	-2.110879	-0.203742
14	6	0	2.900701	-0.208445	-1.718582
15	6	0	3.443815	-1.924857	1.327981
16	1	0	-1.334113	-2.834604	-0.927360
17	1	0	-1.803236	-0.686662	1.188312
18	8	0	4.166796	-2.767791	1.832064
19	8	0	2.879069	-0.938348	1.964334
20	1	0	2.467126	-0.044796	1.420680
21	1	0	2.643749	-0.509298	-2.742884
22	1	0	2.584662	0.819410	-1.561788
23	1	0	-1.838735	0.913181	-0.686482
24	6	0	-1.374855	-0.067303	-0.827387
25	1	0	-1.585816	-3.134054	0.785590
26	6	0	-1.190441	-2.404120	0.071786
27	1	0	0.120845	0.567886	1.552785
28	6	0	0.084212	2.452909	0.510545
29	6	0	-1.184970	2.750614	1.024660
30	6	0	0.765560	3.446691	-0.240163
31	6	0	-1.807043	3.975931	0.796320
32	1	0	-1.686443	2.000938	1.632076
33	6	0	0.128466	4.677645	-0.472524
34	6	0	-1.140851	4.937496	0.033620
35	1	0	-2.788922	4.179335	1.210906
36	1	0	0.650519	5.436973	-1.050264
37	1	0	-1.604276	5.901361	-0.156947
38	6	0	4.448890	-1.912822	-1.037888
39	1	0	4.415326	-2.544353	-1.932879
40	1	0	5.329171	-2.190542	-0.457260
41	6	0	4.385645	-0.431219	-1.428411
42	1	0	5.010902	-0.181420	-2.289023
43	1	0	4.694899	0.197324	-0.586814
44	6	0	-3.464579	-1.264329	0.002319
45	6	0	-4.340209	-0.971631	1.055584
46	6	0	-4.011683	-1.739158	-1.199329
47	6	0	-5.718554	-1.143297	0.917720
48	1	0	-3.936997	-0.605221	1.996662
49	6	0	-5.387952	-1.912919	-1.342116
50	1	0	-3.359112	-1.976354	-2.035532
51	6	0	-6.247723	-1.614908	-0.283278
52	1	0	-6.376816	-0.908217	1.749209
53	1	0	-5.789491	-2.281330	-2.281887
54	1	0	-7.319590	-1.749425	-0.394442
55	7	0	2.028707	3.184330	-0.766809
56	1	0	2.549148	4.011276	-1.029017
57	1	0	2.546060	2.533346	-0.178704

HF=-1266.6267378
Sum of electronic and zero-point Energies= -1266.146447
Sum of electronic and thermal Energies= -1266.121821
Sum of electronic and thermal Enthalpies= -1266.120876

Sum of electronic and thermal Free Energies= -1266.201430

TS1' (endo-chair in DMSO)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.109742	-0.043650	0.097387
2	1	0	-0.320266	0.127015	4.516670
3	1	0	0.886120	0.055588	3.251065
4	1	0	-1.660017	3.190567	1.894376
5	6	0	-1.316537	1.125643	1.456281
6	1	0	-2.169952	0.946158	0.812129
7	7	0	-1.735054	-0.946178	2.580845
8	6	0	-0.042945	0.557870	3.551810
9	6	0	-1.105897	0.245645	2.519046
10	8	0	-0.263360	-1.290634	0.198735
11	6	0	0.409241	2.768635	2.376943
12	1	0	-1.262830	-1.634631	4.531662
13	6	0	-1.392455	-2.026168	3.520485
14	6	0	-2.934477	-1.284092	1.777324
15	6	0	-0.074368	-2.772831	3.192945
16	1	0	-0.652149	2.509588	4.248347
17	1	0	1.252382	2.276064	1.875984
18	8	0	0.303590	-3.609615	4.030251
19	8	0	0.569232	-2.508046	2.108437
20	1	0	0.078737	-1.805520	1.137393
21	1	0	-3.781272	-0.686608	2.138570
22	1	0	-2.783926	-1.059889	0.722440
23	1	0	-0.654805	2.919271	0.488580
24	6	0	-0.845974	2.559957	1.506438
25	1	0	1.077971	2.206673	4.370698
26	6	0	0.203304	2.062457	3.727584
27	1	0	0.963633	0.273406	0.695282
28	6	0	-0.099891	0.689165	-1.147882
29	6	0	0.737486	1.794820	-1.405247
30	6	0	-1.083864	0.328590	-2.116586
31	6	0	0.630759	2.541704	-2.571297
32	1	0	1.495026	2.047647	-0.669171
33	6	0	-1.181821	1.100097	-3.292909
34	6	0	-0.342194	2.184587	-3.515586
35	1	0	1.293352	3.382024	-2.749198
36	1	0	-1.929150	0.827669	-4.032950
37	1	0	-0.440871	2.752208	-4.436298
38	6	0	-2.618084	-2.962590	3.464250
39	1	0	-3.364853	-2.625674	4.190245
40	1	0	-2.346652	-3.991188	3.706677
41	6	0	-3.142511	-2.776920	2.036254
42	1	0	-4.188789	-3.068778	1.920587
43	1	0	-2.543306	-3.364443	1.332805
44	6	0	0.768481	4.238671	2.515312
45	6	0	-0.066737	5.142606	3.193072
46	6	0	1.953155	4.733529	1.950523
47	6	0	0.273103	6.492642	3.302298

48	1	0	-0.992791	4.792309	3.640214
49	6	0	2.296987	6.084241	2.054755
50	1	0	2.614621	4.051398	1.422191
51	6	0	1.457047	6.970220	2.732540
52	1	0	-0.388143	7.172497	3.832097
53	1	0	3.220098	6.441346	1.607037
54	1	0	1.720430	8.020398	2.816361
55	7	0	-1.966971	-0.711971	-1.897814
56	1	0	-2.437225	-1.064115	-2.721523
57	1	0	-1.631342	-1.432620	-1.271914

HF=-1266.6682576
Sum of electronic and zero-point Energies= -1266.189769
Sum of electronic and thermal Energies= -1266.164672
Sum of electronic and thermal Enthalpies= -1266.163728
Sum of electronic and thermal Free Energies= -1266.245061

TS2 (exo-chair in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.727859	1.119600	-0.794997
2	1	0	-4.022501	-1.817901	2.818100
3	1	0	-0.855685	-3.106584	-0.273917
4	1	0	-4.926312	-0.332591	2.486295
5	6	0	-4.539909	-1.593521	0.718574
6	1	0	-4.958915	-0.809768	0.078214
7	1	0	-5.257355	-2.414303	0.759581
8	1	0	-0.448951	-1.885812	-1.457414
9	1	0	1.603429	-0.322453	1.825807
10	6	0	-0.172029	0.112280	0.701896
11	1	0	-0.581896	0.748908	1.483504
12	7	0	-2.207690	-1.146573	0.772114
13	6	0	-0.313559	-2.166251	-0.403806
14	6	0	-0.924963	-1.082081	0.449479
15	8	0	-2.045791	1.035019	-0.921831
16	6	0	1.955287	-1.035775	-0.186767
17	1	0	-2.983918	-3.093319	0.434515
18	6	0	-3.190288	-2.061138	0.135980
19	6	0	-2.846212	-0.296156	1.812059
20	6	0	-3.216411	-2.040160	-1.419945
21	1	0	1.300186	-2.797470	0.899243
22	1	0	1.813872	-0.645228	-1.203516
23	8	0	-3.678070	-3.034348	-1.956774
24	8	0	-2.794400	-0.972644	-2.034110
25	1	0	-2.456096	-0.037423	-1.464058
26	1	0	-2.189927	-0.242546	2.684545
27	6	0	-4.170039	-1.013796	2.088398
28	1	0	-2.993232	0.714873	1.430471
29	1	0	1.806594	0.962476	0.658605
30	6	0	1.346431	-0.019347	0.801814
31	1	0	1.594070	-3.091218	-0.808364
32	6	0	1.180403	-2.364455	-0.101953

33	6	0	3.450632	-1.219545	0.017441
34	6	0	4.347895	-0.923366	-1.016417
35	6	0	3.972772	-1.696142	1.229457
36	6	0	5.723242	-1.093714	-0.849752
37	1	0	3.964165	-0.555375	-1.964978
38	6	0	5.345888	-1.868682	1.400936
39	1	0	3.302986	-1.936058	2.051177
40	6	0	6.227445	-1.567378	0.361119
41	1	0	6.398635	-0.856079	-1.666633
42	1	0	5.727925	-2.238837	2.348124
43	1	0	7.296872	-1.701003	0.494610
44	6	0	-0.157739	2.482105	-0.525537
45	6	0	-0.869461	3.462494	0.215329
46	6	0	1.109950	2.807228	-1.026991
47	6	0	-0.260583	4.707635	0.451371
48	6	0	1.702968	4.046132	-0.795385
49	1	0	1.633668	2.067993	-1.628497
50	6	0	1.007846	4.994238	-0.041499
51	1	0	-0.805281	5.456646	1.021682
52	1	0	2.684167	4.270167	-1.200817
53	1	0	1.447898	5.968463	0.151939
54	1	0	-0.149641	0.604677	-1.578701
55	7	0	-2.133367	3.178295	0.726318
56	1	0	-2.676666	3.996828	0.967371
57	1	0	-2.624851	2.505432	0.140995

HF=-1266.6259906
Sum of electronic and zero-point Energies= -1266.146035
Sum of electronic and thermal Energies= -1266.121326
Sum of electronic and thermal Enthalpies= -1266.120382
Sum of electronic and thermal Free Energies= -1266.200916

TS2' (exo-chair in DMSO)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.001933	-0.001685	-0.002673
2	1	0	-0.003864	0.003589	5.830007
3	1	0	3.373388	0.000623	2.865349
4	1	0	-1.573384	-0.699298	5.397380
5	6	0	0.174191	-1.828523	4.680076
6	1	0	-0.502796	-2.493173	4.132510
7	1	0	0.567889	-2.374306	5.539018
8	1	0	2.962697	-0.451360	1.221357
9	1	0	1.538545	3.550583	1.318811
10	6	0	0.736592	1.574423	1.457993
11	1	0	-0.277144	1.824447	1.753076
12	7	0	0.773507	-0.129873	3.131423
13	6	0	2.886396	0.361417	1.955216
14	6	0	1.422098	0.631597	2.226814
15	8	0	-0.470759	-0.968542	0.738019
16	6	0	2.883702	2.236603	0.242073
17	1	0	2.206868	-1.128176	4.332234

18	6	0	1.313006	-1.359071	3.743579
19	6	0	-0.516323	0.266365	3.742786
20	6	0	1.696457	-2.489681	2.766639
21	1	0	3.721009	2.335243	2.240733
22	1	0	2.778779	1.461860	-0.528493
23	8	0	2.456119	-3.367671	3.207441
24	8	0	1.187047	-2.510091	1.582099
25	1	0	0.319458	-1.637346	1.179206
26	1	0	-0.528061	1.347632	3.900232
27	6	0	-0.552149	-0.531392	5.047472
28	1	0	-1.353912	0.009664	3.087936
29	1	0	0.875711	2.948604	-0.184006
30	6	0	1.467491	2.651033	0.689476
31	1	0	4.639728	1.314107	1.137704
32	6	0	3.624525	1.600979	1.431649
33	6	0	3.648983	3.389657	-0.386025
34	6	0	4.004976	3.346950	-1.742005
35	6	0	4.021282	4.521867	0.358303
36	6	0	4.708891	4.395957	-2.340080
37	1	0	3.728493	2.479569	-2.336222
38	6	0	4.726066	5.571933	-0.233799
39	1	0	3.761009	4.586377	1.411191
40	6	0	5.073045	5.513991	-1.586880
41	1	0	4.972639	4.337504	-3.392245
42	1	0	5.004777	6.436466	0.361981
43	1	0	5.621055	6.330821	-2.047048
44	6	0	-0.906413	0.825995	-0.793177
45	6	0	-2.288789	0.991193	-0.478824
46	6	0	-0.382498	1.477341	-1.929379
47	6	0	-3.074502	1.807658	-1.318166
48	6	0	-1.171842	2.274585	-2.748062
49	1	0	0.666945	1.330837	-2.168367
50	6	0	-2.527378	2.437277	-2.429295
51	1	0	-4.127464	1.935222	-1.082885
52	1	0	-0.746665	2.758043	-3.621173
53	1	0	-3.163817	3.053686	-3.057468
54	1	0	1.006183	-0.126739	-0.407018
55	7	0	-2.848149	0.420808	0.649707
56	1	0	-3.858091	0.360009	0.650755
57	1	0	-2.382263	-0.414176	0.980636

HF=-1266.6683266
Sum of electronic and zero-point Energies= -1266.189771
Sum of electronic and thermal Energies= -1266.164666
Sum of electronic and thermal Enthalpies= -1266.163722
Sum of electronic and thermal Free Energies= -1266.245088

TS3 (endo-boat in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.715874	1.171449	0.784668
2	1	0	0.472432	-3.122890	0.008777

3	6	0	-1.178046	-1.969064	0.806759
4	6	0	4.330700	-2.099863	-1.076835
5	1	0	0.893447	-2.187570	1.433366
6	1	0	-1.595006	-2.922745	1.144693
7	6	0	0.129049	0.081992	-0.704393
8	1	0	0.540549	0.698932	-1.497700
9	7	0	2.178148	-1.168337	-0.722238
10	6	0	0.315810	-2.154280	0.502833
11	6	0	0.895418	-1.081876	-0.393064
12	8	0	2.035424	1.133220	0.843173
13	6	0	-1.395105	-0.043288	-0.776861
14	1	0	2.683447	-3.121296	-0.066785
15	6	0	3.130603	-2.126063	-0.120210
16	6	0	2.848883	-0.326367	-1.751283
17	6	0	3.553327	-1.777236	1.354003
18	1	0	-1.671901	-2.121936	-1.267997
19	8	0	4.378729	-2.531242	1.845332
20	8	0	2.977480	-0.780005	1.952950
21	1	0	2.508388	0.117554	1.372932
22	1	0	2.479100	-0.639916	-2.736263
23	6	0	4.335939	-0.650157	-1.579638
24	1	0	2.620266	0.727204	-1.612015
25	6	0	-1.926439	-1.452051	-0.433908
26	1	0	-1.729870	0.233248	-1.782842
27	1	0	-1.861868	0.688103	-0.108576
28	1	0	-1.309352	-1.263408	1.635580
29	6	0	0.083806	2.496813	0.495239
30	6	0	-1.137351	2.825855	1.099000
31	6	0	0.694865	3.443729	-0.368369
32	6	0	-1.784693	4.033198	0.846647
33	1	0	-1.575565	2.119535	1.799993
34	6	0	0.030262	4.654261	-0.626605
35	6	0	-1.194486	4.942804	-0.032982
36	1	0	-2.727487	4.263003	1.332008
37	1	0	0.496007	5.376425	-1.293173
38	1	0	-1.680299	5.890749	-0.246053
39	1	0	0.186429	0.642677	1.591306
40	1	0	4.168172	-2.792882	-1.910217
41	1	0	5.237917	-2.397544	-0.550557
42	1	0	4.774290	0.009751	-0.823643
43	1	0	4.891190	-0.514077	-2.510818
44	6	0	-3.437230	-1.481321	-0.278879
45	6	0	-4.226003	-2.225612	-1.165123
46	6	0	-4.083150	-0.776942	0.748505
47	6	0	-5.615059	-2.268463	-1.034351
48	1	0	-3.745347	-2.779397	-1.968162
49	6	0	-5.470220	-0.817731	0.884730
50	1	0	-3.499337	-0.189668	1.452215
51	6	0	-6.242587	-1.564117	-0.007237
52	1	0	-6.204808	-2.852832	-1.734878
53	1	0	-5.948608	-0.265758	1.688792
54	1	0	-7.322943	-1.595664	0.098432
55	7	0	1.914917	3.152813	-0.975837
56	1	0	2.398825	3.961857	-1.342851
57	1	0	2.492401	2.557398	-0.386550

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 HF=-1266.6242472
 Sum of electronic and zero-point Energies=          -1266.144610
 Sum of electronic and thermal Energies=             -1266.119816
 Sum of electronic and thermal Enthalpies=           -1266.118871
 Sum of electronic and thermal Free Energies=        -1266.199998
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TS3' (endo-boat in DMSO)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.005704	-0.000603	0.000283
2	1	0	-0.009497	0.034357	4.500477
3	6	0	1.796786	0.008532	3.306322
4	6	0	-4.025362	0.000998	3.432215
5	1	0	0.037146	-1.248139	3.306132
6	1	0	2.305759	-0.424309	4.173545
7	6	0	0.069691	1.558449	1.661790
8	1	0	-0.567440	2.234266	1.103623
9	7	0	-1.885432	0.509127	2.558771
10	6	0	0.284471	-0.194110	3.467282
11	6	0	-0.549068	0.675368	2.550143
12	8	0	-1.250357	-0.368907	-0.063929
13	6	0	1.491594	2.035613	1.870319
14	1	0	-2.141206	-0.681848	4.292674
15	6	0	-2.590370	-0.545345	3.306106
16	6	0	-2.835494	1.466803	1.941984
17	6	0	-2.555468	-1.942121	2.626272
18	1	0	1.675699	2.022968	4.013382
19	8	0	-3.132068	-2.860792	3.236678
20	8	0	-1.934092	-2.096408	1.512727
21	1	0	-1.538292	-1.084230	0.704608
22	1	0	-2.757722	2.425743	2.469354
23	6	0	-4.205578	0.814284	2.144886
24	1	0	-2.605049	1.637086	0.891139
25	6	0	2.139183	1.501313	3.165458
26	1	0	1.498982	3.132887	1.887471
27	1	0	2.115149	1.754483	1.011564
28	1	0	2.157411	-0.534070	2.424593
29	6	0	0.589924	0.784643	-1.080680
30	6	0	1.982711	0.685765	-1.283663
31	6	0	-0.175097	1.630255	-1.938708
32	6	0	2.629866	1.391696	-2.289953
33	1	0	2.549485	0.017246	-0.642081
34	6	0	0.498327	2.341882	-2.951828
35	6	0	1.872983	2.227346	-3.122297
36	1	0	3.700641	1.291197	-2.430850
37	1	0	-0.081031	2.984485	-3.608736
38	1	0	2.357111	2.786365	-3.917686
39	1	0	0.690634	-0.657816	0.533706
40	1	0	-4.091837	0.653682	4.308805
41	1	0	-4.748864	-0.806718	3.550777
42	1	0	-4.430010	0.147755	1.305650

43	1	0	-5.002792	1.557948	2.211740
44	6	0	3.631413	1.778578	3.225894
45	6	0	4.523520	1.221108	2.294226
46	6	0	4.158991	2.601535	4.231426
47	6	0	5.894072	1.477067	2.368374
48	1	0	4.146184	0.580501	1.501823
49	6	0	5.530041	2.862044	4.309507
50	1	0	3.486580	3.043666	4.962486
51	6	0	6.404283	2.299413	3.377302
52	1	0	6.564326	1.033566	1.637445
53	1	0	5.912694	3.503432	5.098317
54	1	0	7.470249	2.498571	3.435005
55	7	0	-1.533822	1.807533	-1.755527
56	1	0	-2.028724	2.210150	-2.540829
57	1	0	-2.013526	1.030058	-1.321258

HF=-1266.6669817
Sum of electronic and zero-point Energies= -1266.187813
Sum of electronic and thermal Energies= -1266.162661
Sum of electronic and thermal Enthalpies= -1266.161716
Sum of electronic and thermal Free Energies= -1266.243801

TS4 (exo-boat in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.754370	1.206492	-0.785845
2	1	0	-3.797722	-2.013873	2.840175
3	1	0	-0.571139	-3.086505	-0.082768
4	6	0	1.128718	-1.956109	-0.826113
5	1	0	-4.825369	-0.581271	2.682483
6	6	0	-4.525001	-1.709669	0.811393
7	1	0	-5.079698	-0.931575	0.276091
8	1	0	-5.163214	-2.592469	0.865860
9	1	0	-0.930892	-2.117503	-1.497025
10	1	0	1.534962	-2.918778	-1.151012
11	6	0	-0.170339	0.114781	0.672301
12	1	0	-0.586995	0.733094	1.463347
13	7	0	-2.216904	-1.128412	0.711369
14	6	0	-0.375759	-2.113152	-0.552928
15	6	0	-0.941142	-1.047515	0.356527
16	8	0	-2.079656	1.197202	-0.817429
17	6	0	1.352597	-0.024045	0.750418
18	1	0	-2.918536	-3.059386	0.195023
19	6	0	-3.211116	-2.013891	0.058456
20	6	0	-2.822970	-0.362253	1.829378
21	6	0	-3.397087	-1.797798	-1.476129
22	1	0	1.587797	-2.104031	1.258325
23	8	0	-3.981004	-2.700059	-2.058238
24	8	0	-2.962229	-0.697211	-2.006604
25	1	0	-2.542807	0.215285	-1.373986
26	1	0	-2.105407	-0.287851	2.649708
27	6	0	-4.066639	-1.184014	2.176851

28	1	0	-3.073146	0.647282	1.499778
29	6	0	1.865490	-1.443683	0.423908
30	1	0	1.688036	0.259989	1.753994
31	1	0	1.828763	0.693870	0.074420
32	1	0	1.288631	-1.257570	-1.655998
33	6	0	3.377904	-1.497479	0.292150
34	6	0	4.140419	-2.256079	1.189198
35	6	0	4.051113	-0.801490	-0.723324
36	6	0	5.530538	-2.320571	1.080660
37	1	0	3.638201	-2.803729	1.983197
38	6	0	5.439429	-0.863614	-0.837065
39	1	0	3.487882	-0.204022	-1.435155
40	6	0	6.185495	-1.623787	0.065585
41	1	0	6.099693	-2.915627	1.789177
42	1	0	5.939355	-0.317512	-1.631969
43	1	0	7.266816	-1.671849	-0.022593
44	6	0	-0.092201	2.520347	-0.505692
45	6	0	1.113576	2.834981	-1.146480
46	6	0	-0.658372	3.467081	0.388224
47	6	0	1.788078	4.029779	-0.905636
48	1	0	1.517247	2.127333	-1.866765
49	6	0	0.033675	4.665199	0.633831
50	6	0	1.241671	4.940256	0.001140
51	1	0	2.717739	4.249409	-1.420131
52	1	0	-0.397237	5.387704	1.323078
53	1	0	1.749267	5.878617	0.205863
54	1	0	-0.259903	0.679599	-1.615379
55	7	0	-1.858567	3.187399	1.036531
56	1	0	-2.322010	4.000052	1.421183
57	1	0	-2.461142	2.596346	0.469095

HF=-1266.6222908
Sum of electronic and zero-point Energies= -1266.143046
Sum of electronic and thermal Energies= -1266.118019
Sum of electronic and thermal Enthalpies= -1266.117075
Sum of electronic and thermal Free Energies= -1266.199064

TS4' (exo-boat in DMSO)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.002327	-0.000401	0.000717
2	1	0	-0.020731	-0.016331	5.850244
3	1	0	3.366004	0.008007	3.003672
4	6	0	3.583996	0.706926	0.963086
5	1	0	-1.684354	-0.509672	5.484174
6	6	0	-0.130056	-1.880766	4.742324
7	1	0	-0.913036	-2.462941	4.244313
8	1	0	0.222725	-2.451871	5.602510
9	1	0	2.860775	-1.151430	1.792326
10	1	0	4.657654	0.517191	1.062125
11	6	0	0.888187	1.426410	1.509457
12	1	0	-0.102343	1.779865	1.774253

13	7	0	0.653839	-0.298844	3.147374
14	6	0	2.839340	-0.087326	2.044154
15	6	0	1.415182	0.373941	2.262805
16	8	0	-0.706286	-0.841763	0.714310
17	6	0	1.780307	2.437965	0.820227
18	1	0	1.970513	-1.509463	4.282355
19	6	0	1.020163	-1.596378	3.746206
20	6	0	-0.562104	0.269144	3.774795
21	6	0	1.161068	-2.771256	2.754349
22	1	0	3.491022	2.501304	2.121600
23	8	0	1.760548	-3.776233	3.176880
24	8	0	0.624355	-2.686652	1.589285
25	1	0	-0.095450	-1.626256	1.167006
26	1	0	-0.436381	1.346578	3.903541
27	6	0	-0.662053	-0.489333	5.099161
28	1	0	-1.441157	0.099877	3.146272
29	6	0	3.284896	2.210829	1.082797
30	1	0	1.501470	3.445188	1.154844
31	1	0	1.594847	2.428999	-0.261687
32	1	0	3.290377	0.353242	-0.032311
33	6	0	4.164089	3.071643	0.191898
34	6	0	4.993956	4.052981	0.753421
35	6	0	4.178590	2.916103	-1.204795
36	6	0	5.811590	4.855661	-0.047137
37	1	0	4.998719	4.190023	1.831926
38	6	0	4.994017	3.714807	-2.009017
39	1	0	3.546973	2.165101	-1.671006
40	6	0	5.814761	4.689306	-1.433556
41	1	0	6.444623	5.609009	0.412988
42	1	0	4.988793	3.575894	-3.086438
43	1	0	6.448507	5.310480	-2.059459
44	6	0	-0.668807	0.967357	-0.862003
45	6	0	0.023215	1.420859	-2.004244
46	6	0	-1.982457	1.462591	-0.607195
47	6	0	-0.537765	2.335971	-2.886407
48	1	0	1.012789	1.018671	-2.201273
49	6	0	-2.534228	2.394510	-1.509361
50	6	0	-1.825568	2.823525	-2.625418
51	1	0	0.010684	2.661229	-3.763870
52	1	0	-3.534135	2.774196	-1.318239
53	1	0	-2.284360	3.537607	-3.303019
54	1	0	0.981026	-0.339684	-0.336525
55	7	0	-2.684424	1.097724	0.526365
56	1	0	-3.679023	1.280573	0.496995
57	1	0	-2.443687	0.191966	0.907087

HF=-1266.6662798
Sum of electronic and zero-point Energies= -1266.186765
Sum of electronic and thermal Energies= -1266.161666
Sum of electronic and thermal Enthalpies= -1266.160722
Sum of electronic and thermal Free Energies= -1266.242172

For *cis*-enamine TSs:

TS5 (endo-chair in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.874068	1.222444	-0.883888
2	1	0	-2.898114	1.463790	-0.216177
3	8	0	-4.826804	-0.206223	-2.328844
4	6	0	-0.899784	1.554890	-0.577713
5	1	0	1.322429	-0.111234	-1.719664
6	1	0	-3.166224	-0.376857	2.393634
7	6	0	0.854160	-0.798734	-1.008741
8	8	0	-1.875436	1.767082	0.294815
9	1	0	-5.487256	-2.008412	-0.728661
10	1	0	-2.931584	-2.131614	2.245279
11	6	0	-3.309588	-1.237920	1.737147
12	6	0	2.050097	3.358894	1.066489
13	6	0	-3.465390	-1.217722	-0.704893
14	1	0	-5.276015	-0.483577	1.213413
15	6	0	-4.099111	0.053179	-1.378817
16	6	0	2.471266	3.119546	-1.303251
17	6	0	-1.245512	-0.869962	0.405256
18	6	0	-0.601132	-0.394587	-0.780181
19	6	0	-4.598021	-2.067295	-0.101944
20	7	0	-2.560045	-1.033152	0.467358
21	1	0	3.818006	4.075722	0.087518
22	1	0	-1.197015	-0.520228	-1.681999
23	1	0	-2.920818	-1.752201	-1.485086
24	1	0	-5.312656	-2.075518	1.992572
25	6	0	-4.761078	-1.445858	1.290307
26	1	0	-4.290780	-3.116909	-0.021129
27	6	0	0.408457	2.227642	-0.329692
28	1	0	0.909494	2.154317	-2.413271
29	1	0	0.869951	-1.785507	-1.493319
30	1	0	-1.202997	1.653015	-1.627312
31	1	0	2.357696	3.720173	2.044986
32	6	0	-0.420111	-1.003602	1.660662
33	1	0	3.094737	3.291812	-2.174123
34	6	0	1.708863	-0.856894	0.274453
35	6	0	2.870960	3.558526	-0.038256
36	6	0	1.246558	2.471391	-1.429335
37	6	0	0.810711	2.702550	0.949178
38	1	0	-0.286162	0.003371	2.079894
39	6	0	0.955230	-1.631189	1.369331
40	1	0	-0.943307	-1.595098	2.414534
41	1	0	1.833594	0.169610	0.633562
42	1	0	0.819489	-2.677568	1.067839
43	1	0	1.543316	-1.645794	2.292798
44	6	0	3.097840	-1.413792	0.004052
45	6	0	4.220179	-0.580437	0.097867
46	6	0	3.298005	-2.756482	-0.350662

47	6	0	5.503424	-1.070812	-0.149598
48	1	0	4.083348	0.464797	0.363062
49	6	0	4.578513	-3.250957	-0.597551
50	1	0	2.446791	-3.427280	-0.436108
51	6	0	5.687665	-2.409150	-0.496744
52	1	0	6.358799	-0.405737	-0.070241
53	1	0	4.710185	-4.294659	-0.869022
54	1	0	6.685195	-2.793609	-0.688365
55	7	0	0.024479	2.489114	2.076553
56	1	0	0.206168	3.125453	2.841120
57	1	0	-0.960051	2.374239	1.846043

HF=-1266.6171773
Sum of electronic and zero-point Energies= -1266.137376
Sum of electronic and thermal Energies= -1266.112561
Sum of electronic and thermal Enthalpies= -1266.111617
Sum of electronic and thermal Free Energies= -1266.193363

TS6 (exo-chair in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.710204	0.888110	-1.591337
2	1	0	-2.918181	1.361793	-0.816622
3	8	0	-4.130988	-1.027163	-2.693005
4	6	0	-0.889986	1.469247	-0.833686
5	1	0	1.257791	-0.295659	-1.751810
6	1	0	-3.704835	0.237794	2.025320
7	6	0	0.817541	-0.882507	-0.939501
8	8	0	-2.009251	1.802811	-0.198378
9	1	0	-2.695992	-1.002202	2.780944
10	6	0	-3.322370	-0.783963	1.918637
11	6	0	1.724343	3.509185	1.089804
12	6	0	-3.457183	-1.294091	-0.470546
13	6	0	-3.754312	-0.396043	-1.713434
14	6	0	2.539261	3.060543	-1.141850
15	6	0	-1.236496	-0.731758	0.552548
16	6	0	-0.627529	-0.443730	-0.713338
17	6	0	-4.807314	-1.571032	0.232996
18	7	0	-2.555074	-0.845477	0.652629
19	1	0	3.625439	4.175945	0.354526
20	1	0	-1.255410	-0.709449	-1.561486
21	1	0	-3.023897	-2.218225	-0.859981
22	6	0	-4.457983	-1.781971	1.708747
23	6	0	0.354743	2.202681	-0.440887
24	1	0	1.194908	1.958990	-2.398922
25	1	0	0.811425	-1.921827	-1.295987
26	1	0	-0.985181	1.430049	-1.926804
27	1	0	1.858214	3.970542	2.065478
28	6	0	-0.360401	-0.734852	1.783985
29	1	0	3.295224	3.171458	-1.912079
30	6	0	1.718697	-0.786033	0.308489
31	6	0	2.718110	3.624869	0.123694
32	6	0	1.359538	2.370136	-1.406308
33	6	0	0.529260	2.814211	0.830492

34	1	0	-0.211764	0.305950	2.102305
35	6	0	0.996059	-1.412469	1.512483
36	1	0	-0.852722	-1.250788	2.610933
37	1	0	1.861507	0.275180	0.534455
38	1	0	0.836320	-2.484560	1.339839
39	1	0	1.617531	-1.330298	2.410257
40	1	0	-4.097797	-2.801460	1.888044
41	1	0	-5.299140	-1.595814	2.381411
42	1	0	-5.451765	-0.691940	0.126615
43	1	0	-5.317569	-2.415782	-0.231198
44	6	0	3.094411	-1.385020	0.060588
45	6	0	4.225923	-0.559109	0.035151
46	6	0	3.272769	-2.759220	-0.159484
47	6	0	5.497044	-1.086530	-0.198507
48	1	0	4.105093	0.509480	0.193405
49	6	0	4.541108	-3.290519	-0.392231
50	1	0	2.414296	-3.425957	-0.151867
51	6	0	5.659585	-2.455300	-0.411921
52	1	0	6.359704	-0.426323	-0.214212
53	1	0	4.655855	-4.357838	-0.559486
54	1	0	6.647427	-2.868469	-0.593729
55	7	0	-0.439922	2.695457	1.824363
56	1	0	-0.398455	3.416555	2.532413
57	1	0	-1.368432	2.542578	1.435532

HF=-1266.6130553
Sum of electronic and zero-point Energies= -1266.133234
Sum of electronic and thermal Energies= -1266.108357
Sum of electronic and thermal Enthalpies= -1266.107413
Sum of electronic and thermal Free Energies= -1266.189093

TS7 (endo-boat in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.886442	1.301506	-0.572028
2	1	0	-2.815561	1.492333	0.089318
3	8	0	-4.915483	0.112559	-2.181252
4	6	0	-0.903491	1.598100	-0.441483
5	1	0	1.477488	0.162281	-1.193147
6	1	0	-3.167729	-0.649832	2.365066
7	6	0	0.858953	-0.732896	-1.076014
8	8	0	-1.804613	1.730506	0.531815
9	1	0	-5.483113	-1.953762	-0.891477
10	1	0	-2.859046	-2.365892	2.039891
11	6	0	-3.284435	-1.445270	1.624634
12	1	0	-0.727515	-2.141423	1.972801
13	6	0	-3.481699	-1.125467	-0.788789
14	1	0	-5.291458	-0.720236	1.237355
15	6	0	-4.145817	0.231555	-1.233790
16	6	0	-0.455346	-1.148546	1.591518
17	6	0	-1.246563	-0.901429	0.330251
18	6	0	-0.597565	-0.334165	-0.812593
19	6	0	-4.581070	-2.079121	-0.293238

20	7	0	-2.557983	-1.085316	0.379291
21	6	0	1.066596	-1.062273	1.401720
22	1	0	-1.201921	-0.371080	-1.715294
23	1	0	-2.945611	-1.526245	-1.650685
24	1	0	-5.244107	-2.402385	1.793464
25	6	0	-4.735145	-1.659835	1.174257
26	1	0	-4.249250	-3.122004	-0.364064
27	6	0	0.407274	2.275230	-0.260715
28	1	0	-0.782360	-0.426316	2.349727
29	1	0	0.915450	-1.264457	-2.033010
30	1	0	-1.310178	1.768976	-1.443356
31	1	0	1.032448	-2.624761	-0.061369
32	1	0	1.557540	-1.620131	2.205490
33	1	0	1.390144	-0.022711	1.496376
34	6	0	1.475157	-1.621552	0.028093
35	6	0	2.867053	3.630598	-0.095807
36	6	0	1.134250	2.621375	-1.412050
37	6	0	0.928311	2.644108	1.009378
38	6	0	2.164663	3.316890	1.061763
39	6	0	2.353174	3.287853	-1.349933
40	1	0	0.713228	2.364934	-2.381413
41	1	0	2.562522	3.600461	2.033262
42	1	0	2.887873	3.543313	-2.258513
43	1	0	3.813987	4.157287	-0.018278
44	6	0	2.978241	-1.777103	-0.129403
45	6	0	3.535749	-3.033789	-0.396320
46	6	0	3.843862	-0.678539	-0.010505
47	6	0	4.914736	-3.196032	-0.540622
48	1	0	2.880931	-3.896705	-0.493064
49	6	0	5.222037	-0.837141	-0.152579
50	1	0	3.442101	0.310073	0.193957
51	6	0	5.763628	-2.096465	-0.418221
52	1	0	5.323377	-4.180931	-0.748403
53	1	0	5.874479	0.026129	-0.056141
54	1	0	6.837143	-2.218237	-0.529288
55	7	0	0.264235	2.314413	2.183298
56	1	0	0.518103	2.874686	2.985445
57	1	0	-0.735732	2.189853	2.051625

HF=-1266.6146207
Sum of electronic and zero-point Energies= -1266.134323
Sum of electronic and thermal Energies= -1266.109517
Sum of electronic and thermal Enthalpies= -1266.108573
Sum of electronic and thermal Free Energies= -1266.190560

TS8 (exo-boat in gas phase)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.253857	-0.677798	-2.250423
2	1	0	-2.813318	0.267280	-1.738716
3	8	0	-3.597260	-2.867971	-1.919208
4	6	0	-0.895210	1.012132	-1.363854

5	1	0	1.555994	-0.203847	-1.392815
6	1	0	-2.787992	0.685119	2.212161
7	6	0	1.038124	-1.017879	-0.876409
8	8	0	-2.204212	1.195877	-1.206477
9	1	0	-2.396911	-0.868471	2.965064
10	6	0	-2.914903	-0.399000	2.124162
11	1	0	-0.294262	-1.014628	2.567110
12	6	0	-3.309880	-1.609656	0.040510
13	6	0	-3.347259	-1.741403	-1.515477
14	6	0	-0.126953	-0.261451	1.784380
15	6	0	-1.001623	-0.647887	0.609781
16	6	0	-0.448978	-0.674469	-0.715112
17	6	0	-4.635575	-1.030406	0.547831
18	7	0	-2.298429	-0.816854	0.832238
19	6	0	1.374300	-0.194326	1.462252
20	1	0	-1.059513	-1.226268	-1.421172
21	1	0	-3.201040	-2.642035	0.389593
22	6	0	-4.387351	-0.827132	2.045228
23	6	0	-0.012076	2.096883	-0.808656
24	1	0	-0.475538	0.692690	2.193753
25	1	0	1.132254	-1.895623	-1.524459
26	1	0	-0.582712	0.760449	-2.390104
27	1	0	1.399641	-2.248158	0.851621
28	1	0	1.939287	-0.304538	2.393450
29	1	0	1.625927	0.787913	1.053699
30	6	0	1.767959	-1.289663	0.457400
31	6	0	1.708872	4.123300	0.126348
32	6	0	1.205966	2.377622	-1.444924
33	6	0	-0.395236	2.903220	0.296746
34	6	0	0.487916	3.898009	0.752868
35	6	0	2.074374	3.368505	-0.990297
36	1	0	1.464157	1.815497	-2.338691
37	1	0	0.193712	4.506520	1.605065
38	1	0	3.007135	3.561550	-1.510214
39	1	0	2.365069	4.904800	0.498657
40	1	0	-4.537460	-1.769610	2.581603
41	1	0	-5.047449	-0.081498	2.495434
42	1	0	-4.823800	-0.078225	0.041070
43	1	0	-5.464624	-1.706218	0.329552
44	6	0	3.269544	-1.426157	0.272070
45	6	0	3.896148	-2.663731	0.465546
46	6	0	4.064433	-0.330746	-0.099634
47	6	0	5.273869	-2.809631	0.295313
48	1	0	3.296582	-3.524452	0.752510
49	6	0	5.441488	-0.472426	-0.269040
50	1	0	3.606561	0.642072	-0.257203
51	6	0	6.052291	-1.712467	-0.072335
52	1	0	5.736721	-3.780046	0.450742
53	1	0	6.039303	0.388459	-0.555118
54	1	0	7.124716	-1.821452	-0.204798
55	7	0	-1.614322	2.693758	0.948965
56	1	0	-1.958805	3.514684	1.430733
57	1	0	-2.293165	2.271371	0.313747

HF=-1266.6118924

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Sum of electronic and zero-point Energies=          -1266.131631
Sum of electronic and thermal Energies=             -1266.106905
Sum of electronic and thermal Enthalpies=           -1266.105961
Sum of electronic and thermal Free Energies=        -1266.186322
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References

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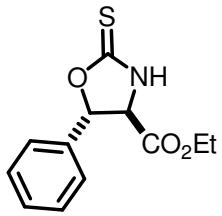
APPENDIX

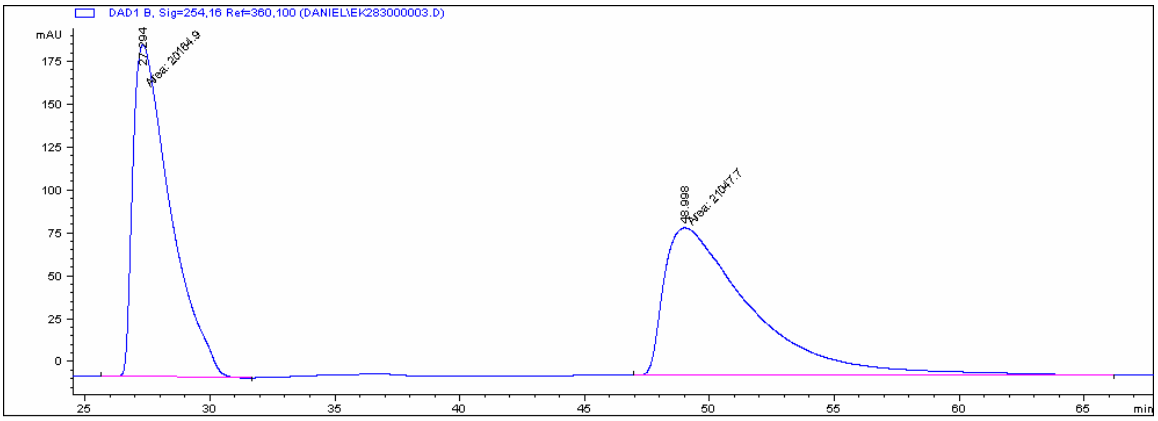
Selected HPLC Profiles and NMR Spectra

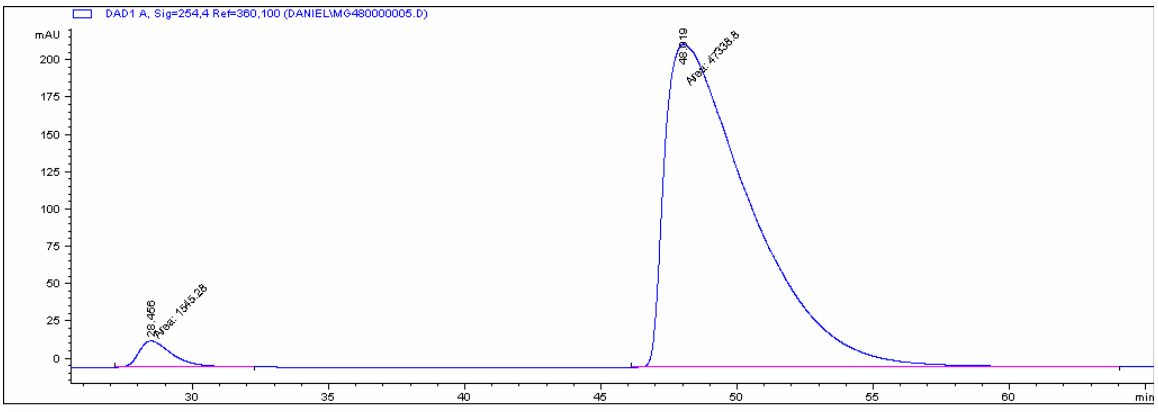
General Information

Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument or a 400 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm and d_6-DMSO at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex; br = broad; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument or a Varian VNMRS-400 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.2 ppm, CD_3OD at 49.0 ppm and d_6-DMSO at 39.5 ppm). HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors.

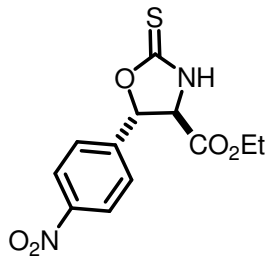
HPLC profiles of 2.35

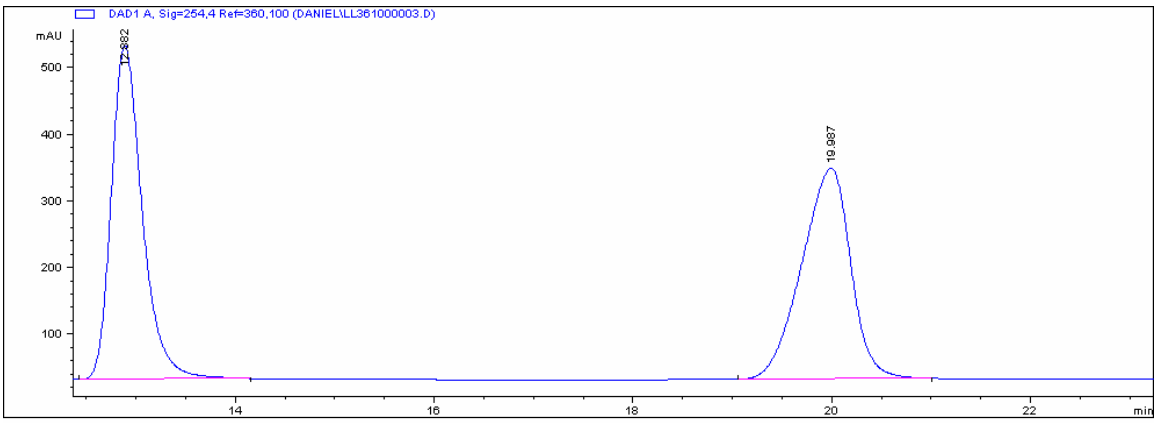


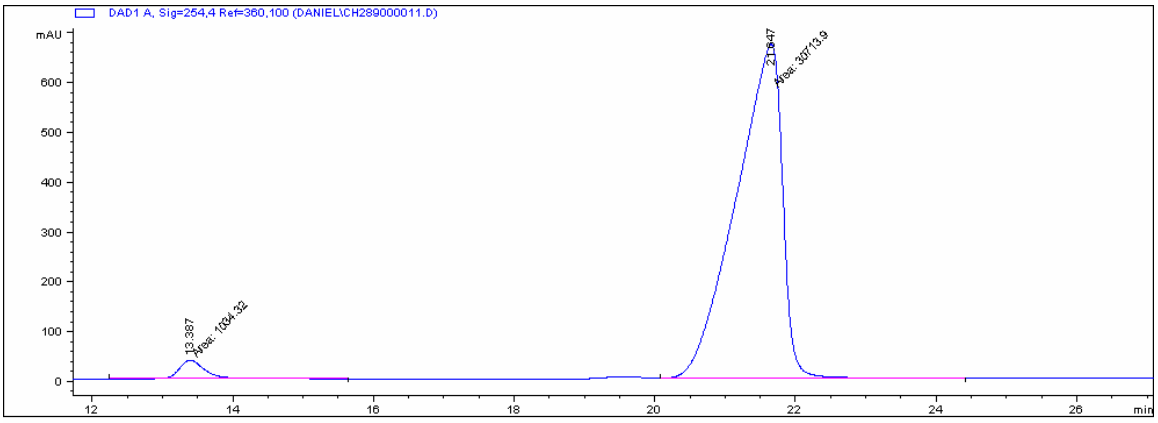




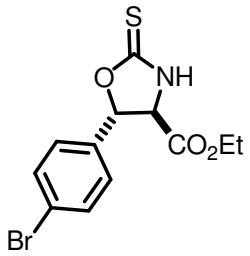
HPLC profiles of 2.66a

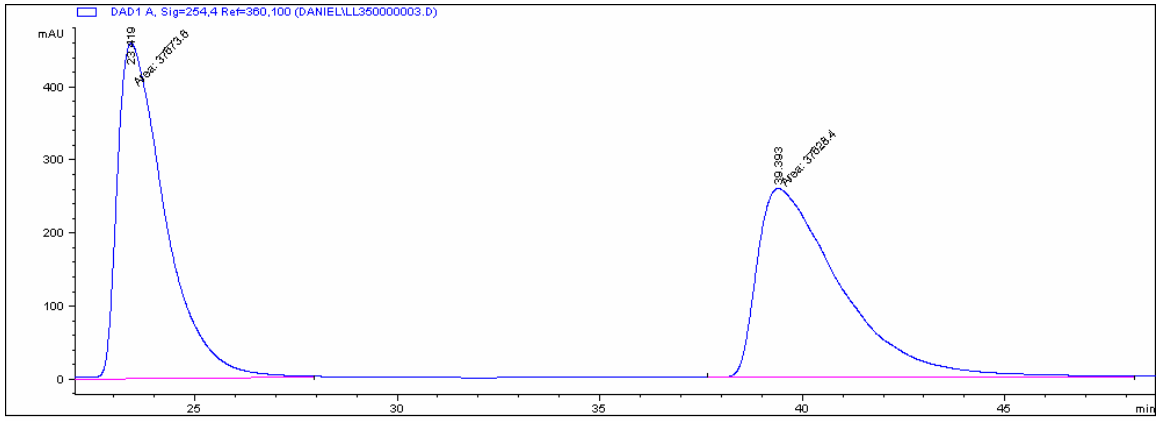


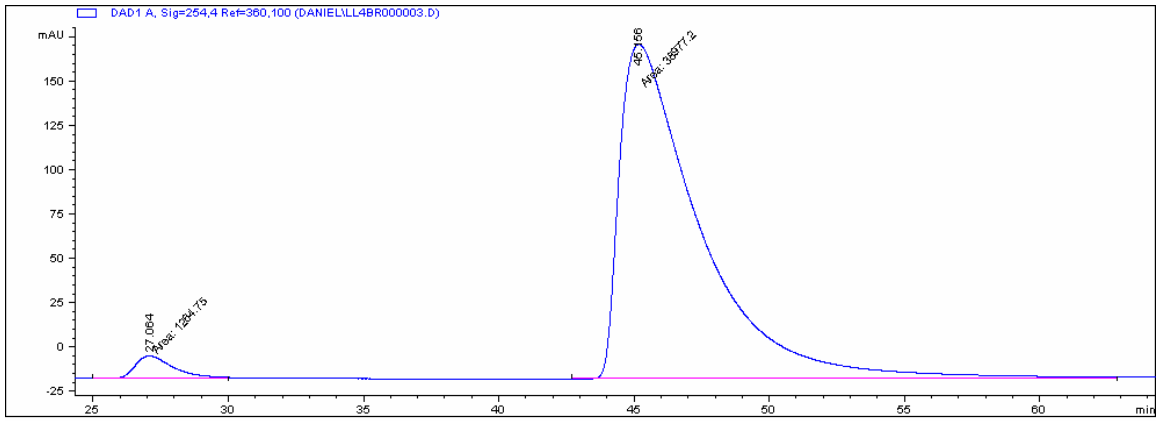




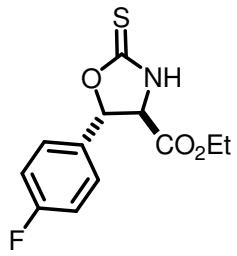
HPLC profiles of 2.66b

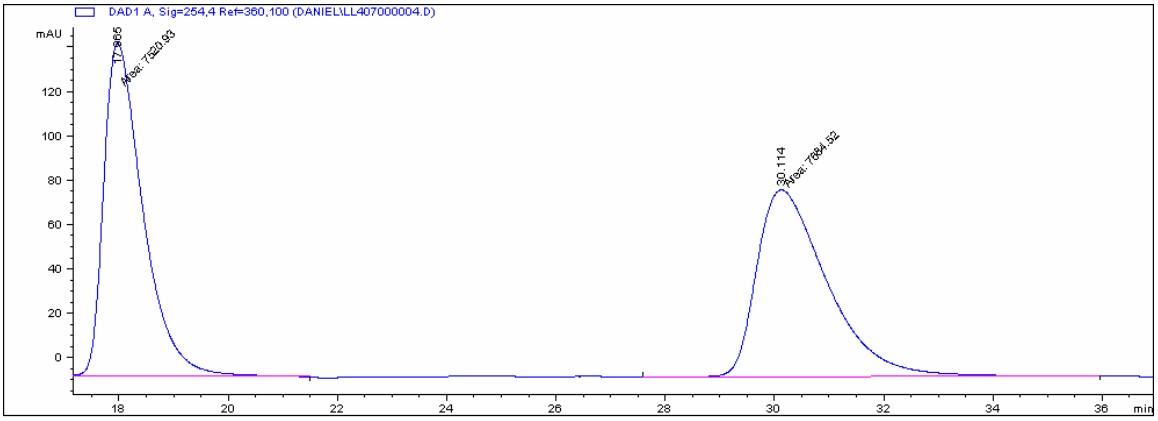


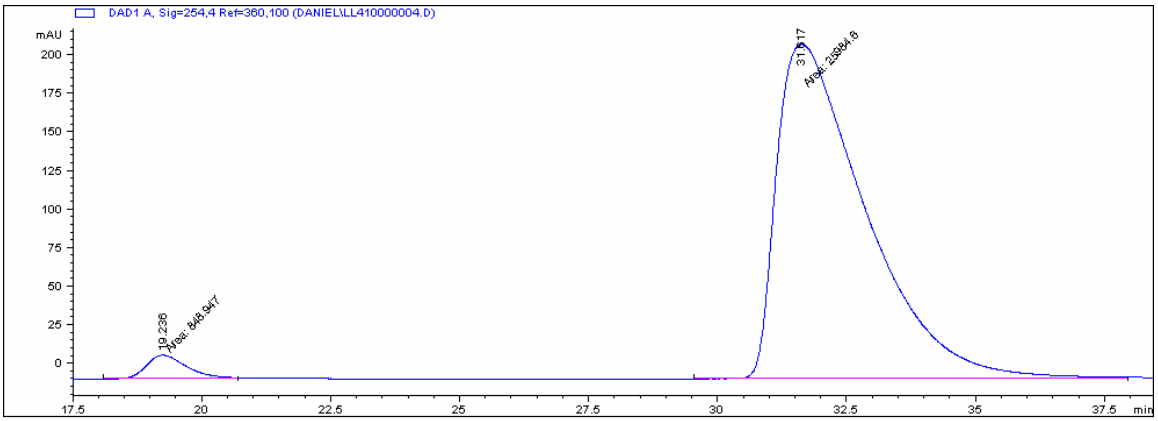




HPLC profiles of 2.66c







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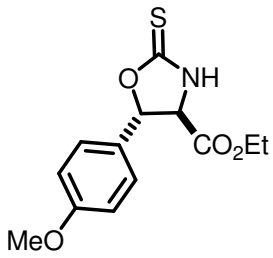

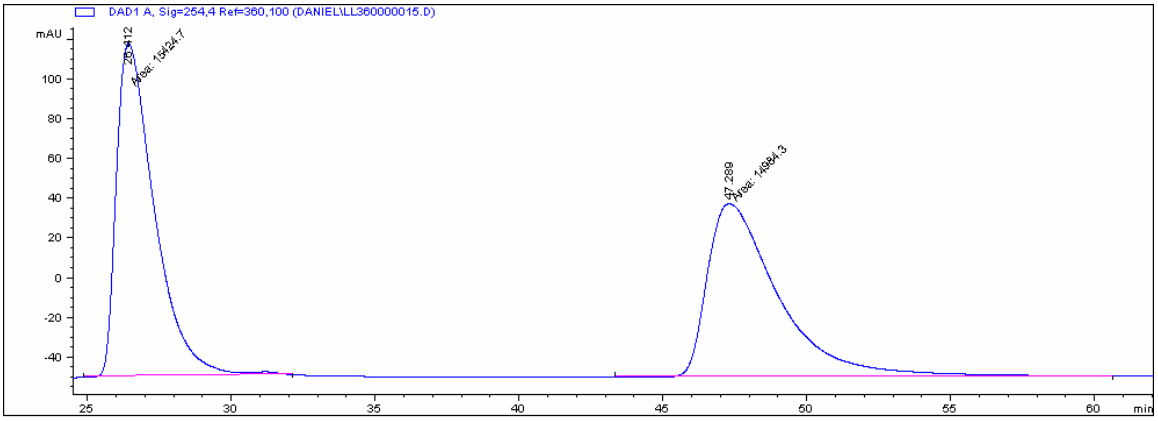

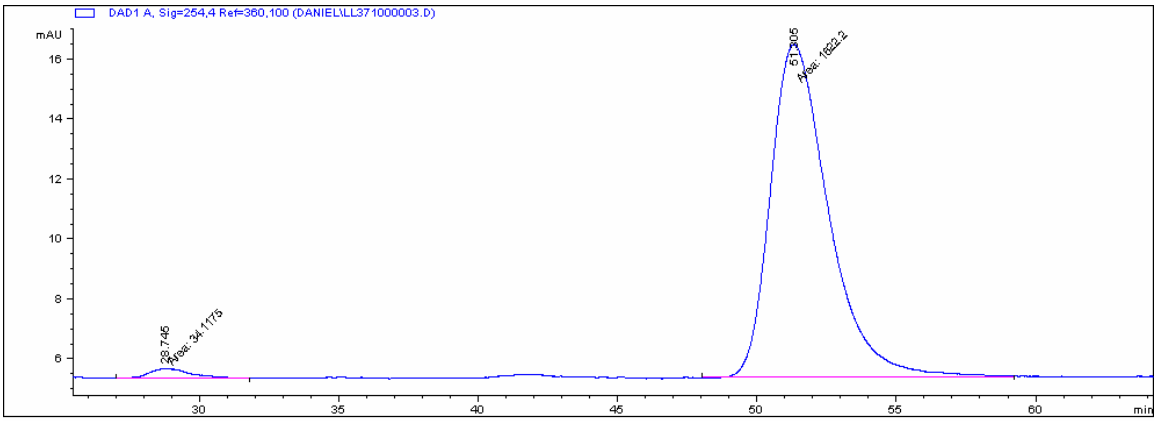

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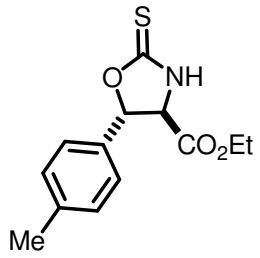
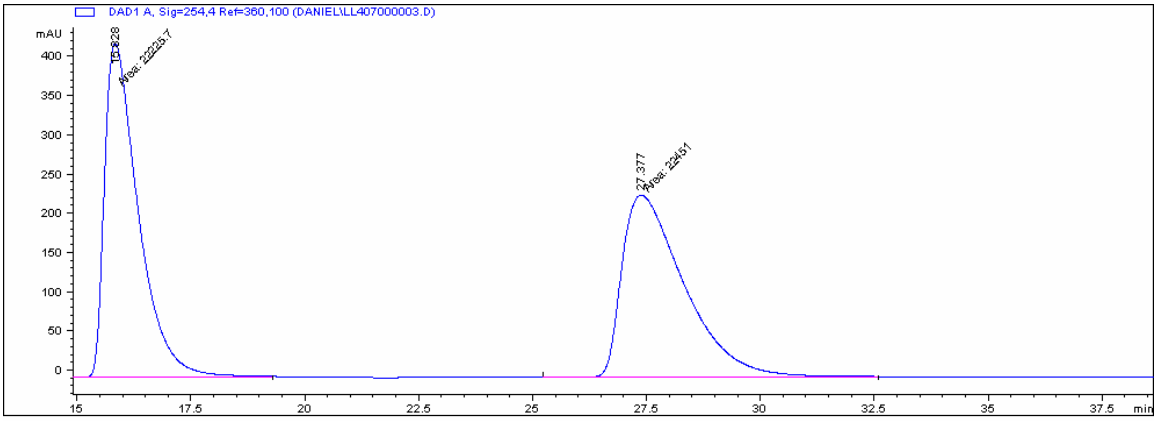
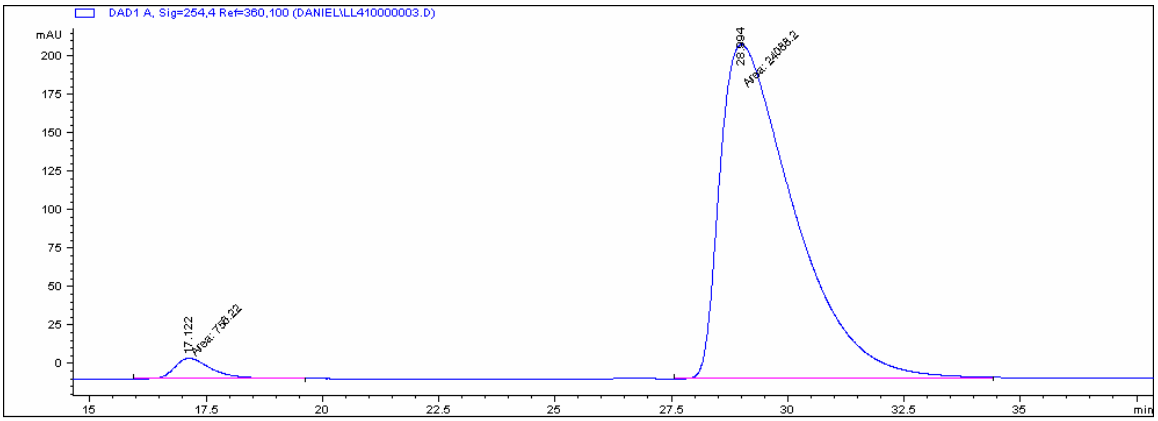
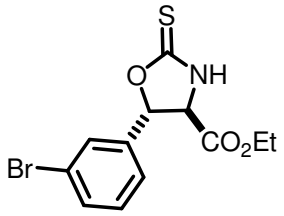
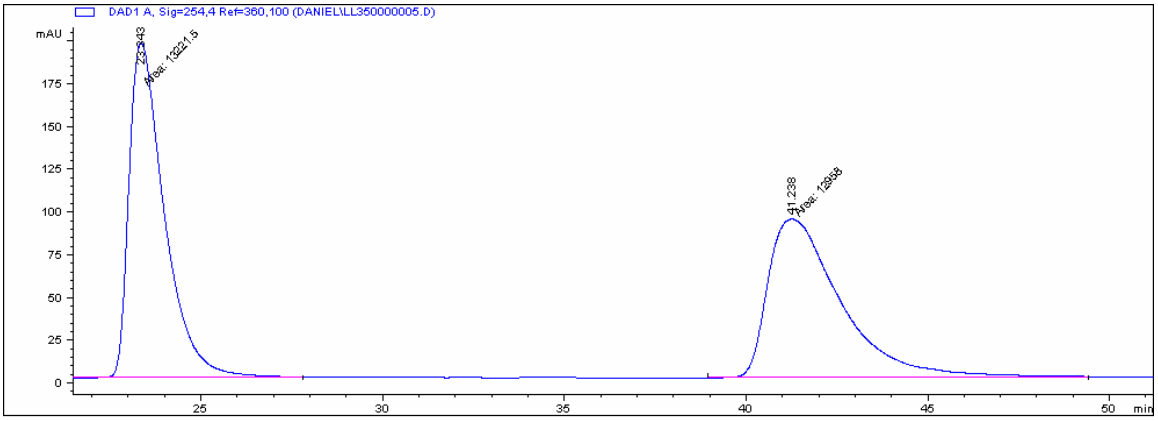


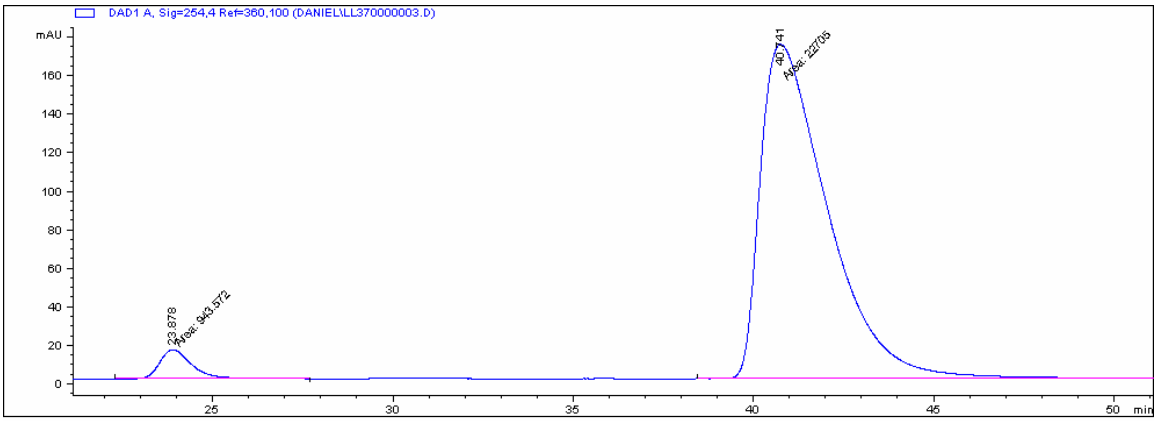




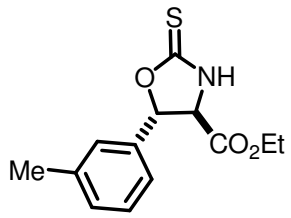
HPLC profiles of 2.66f

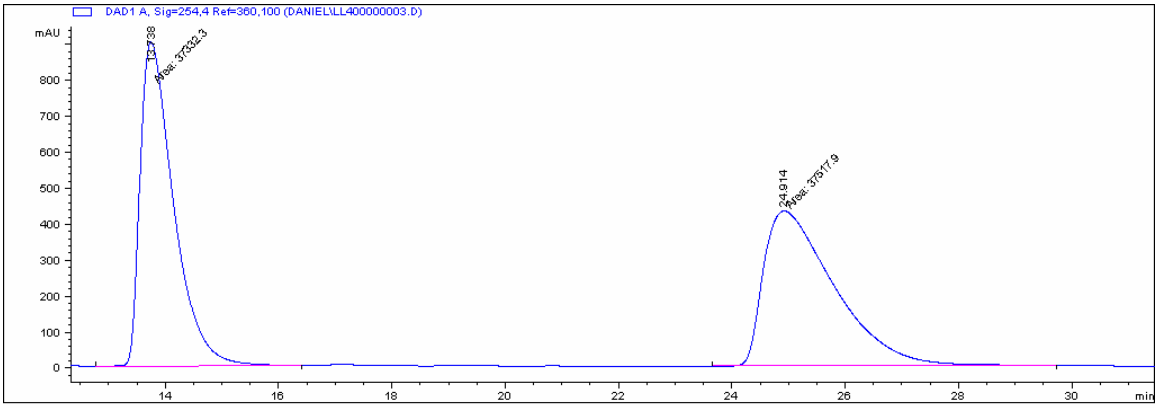


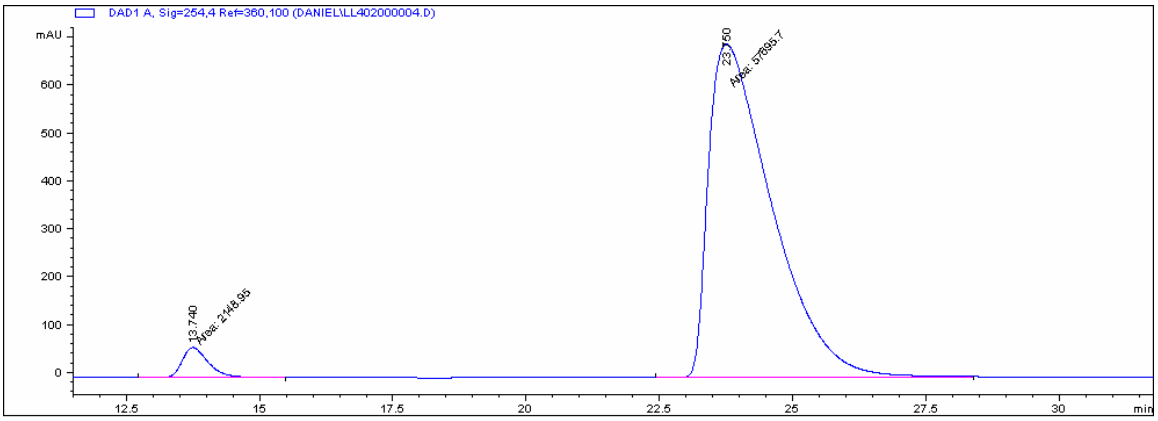




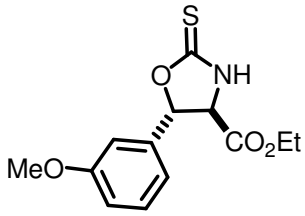
HPLC profiles of 2.66g

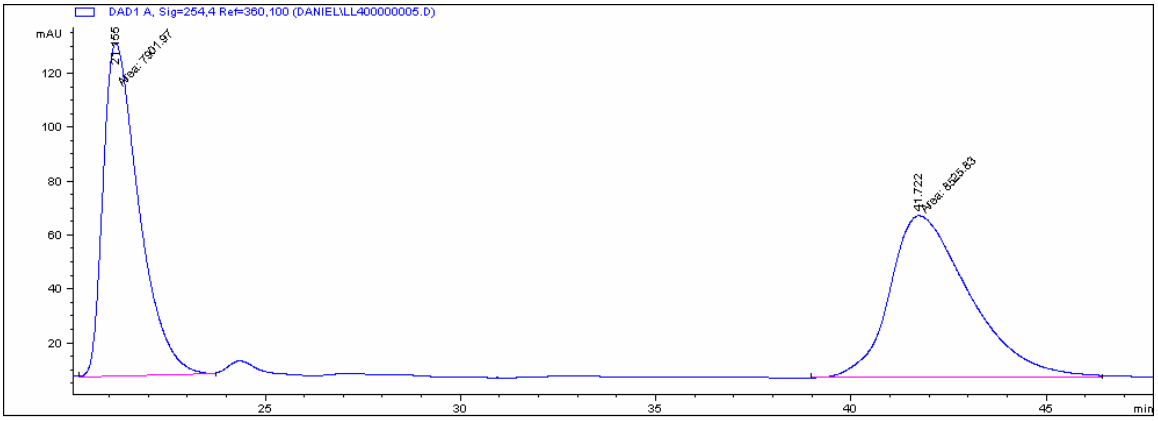


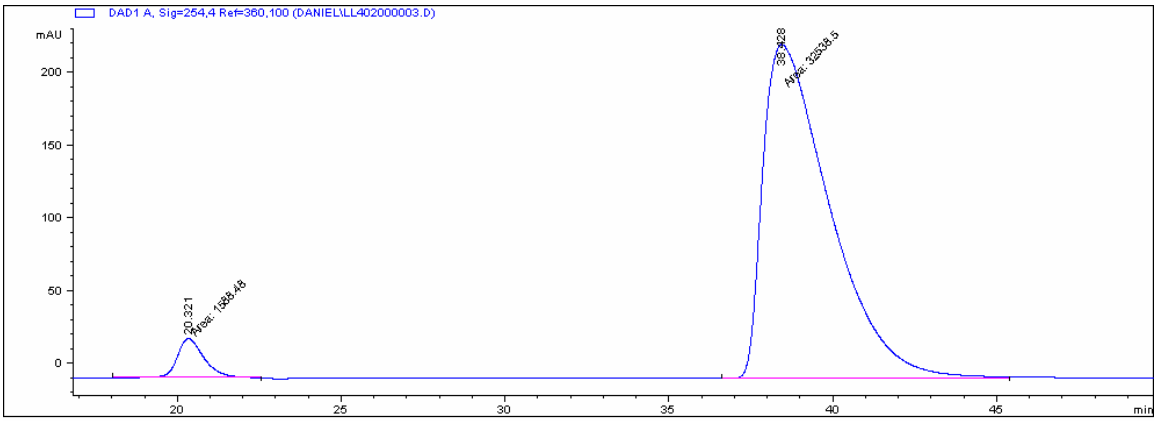




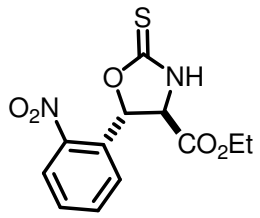
HPLC profiles of 2.66h

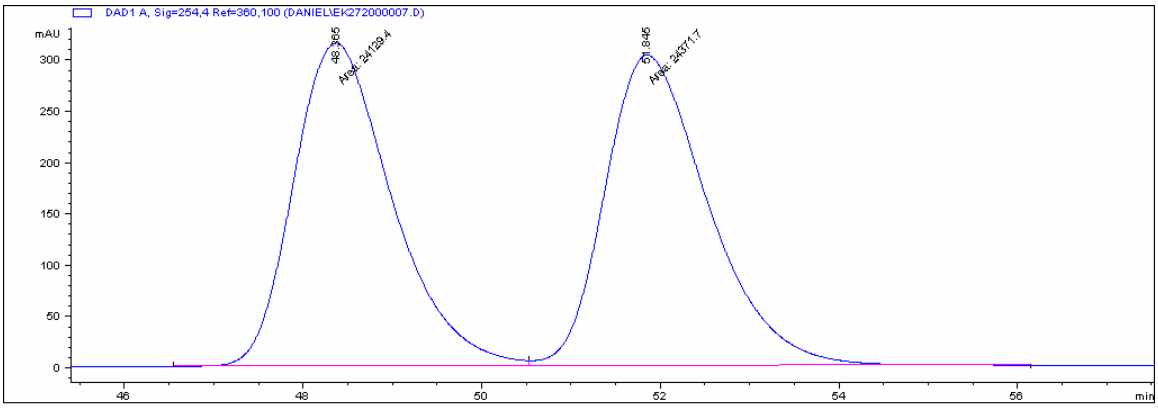


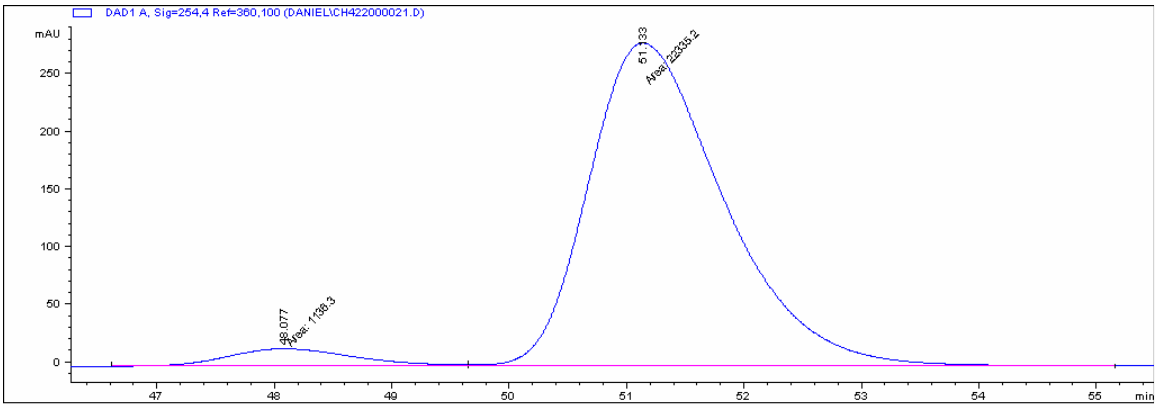




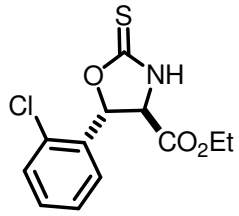
HPLC profiles of 2.66i

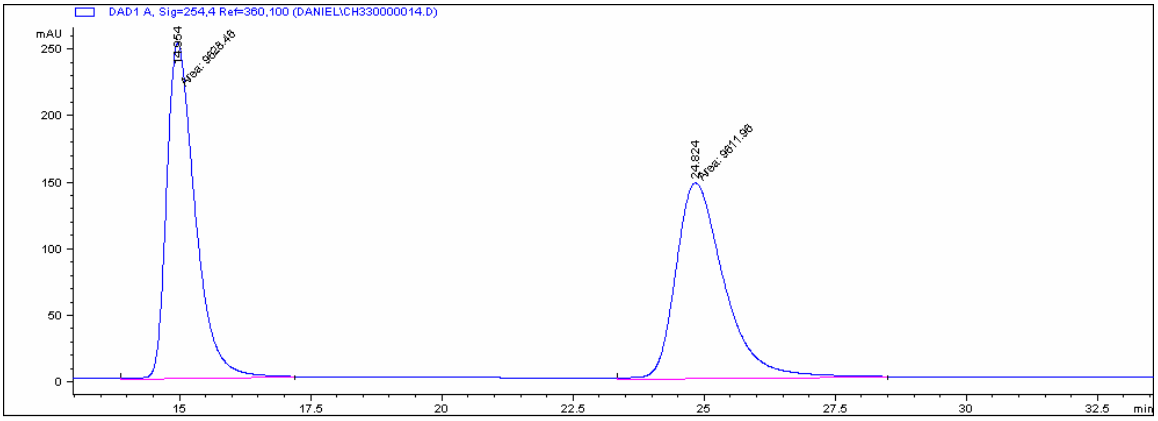


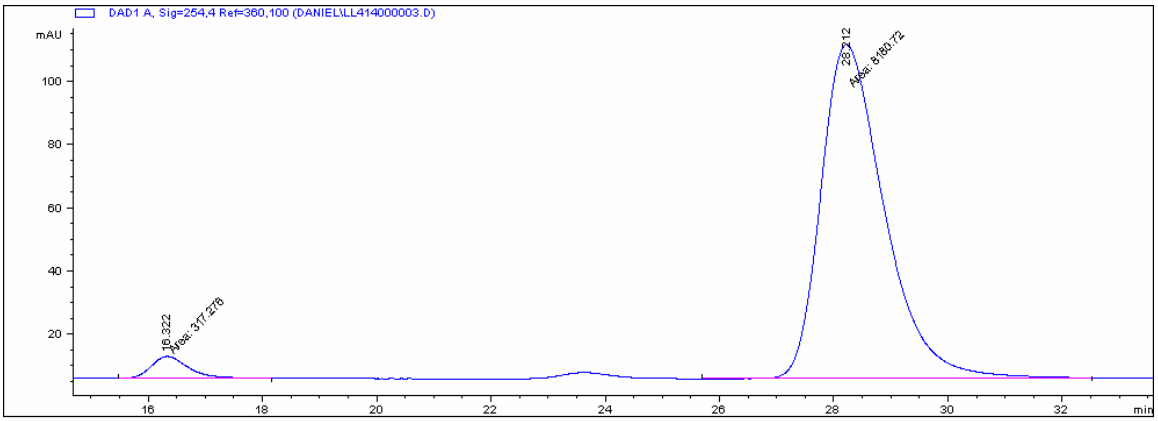




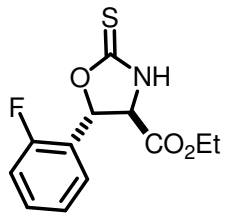
HPLC profiles of 2.66j

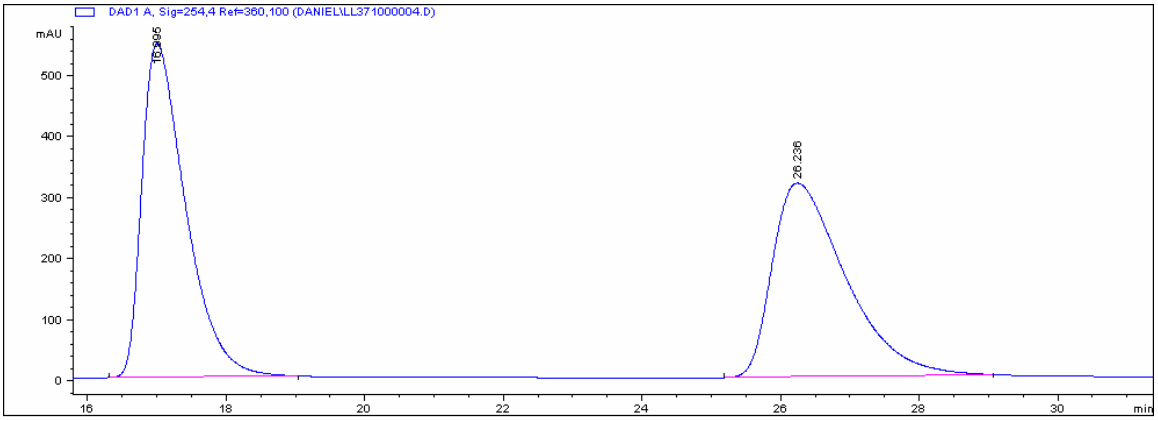


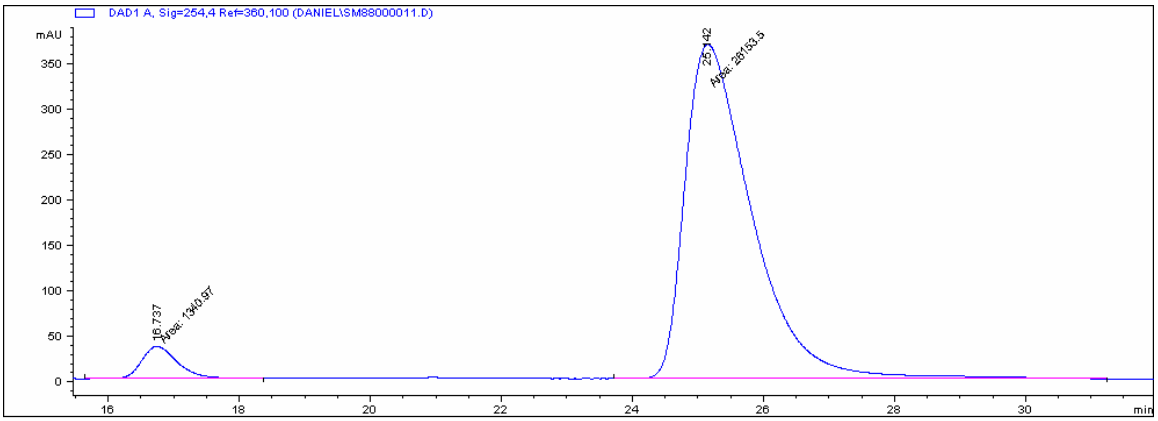




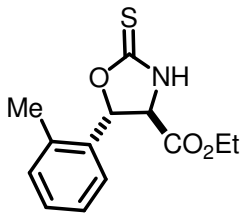
HPLC profiles of 2.66k

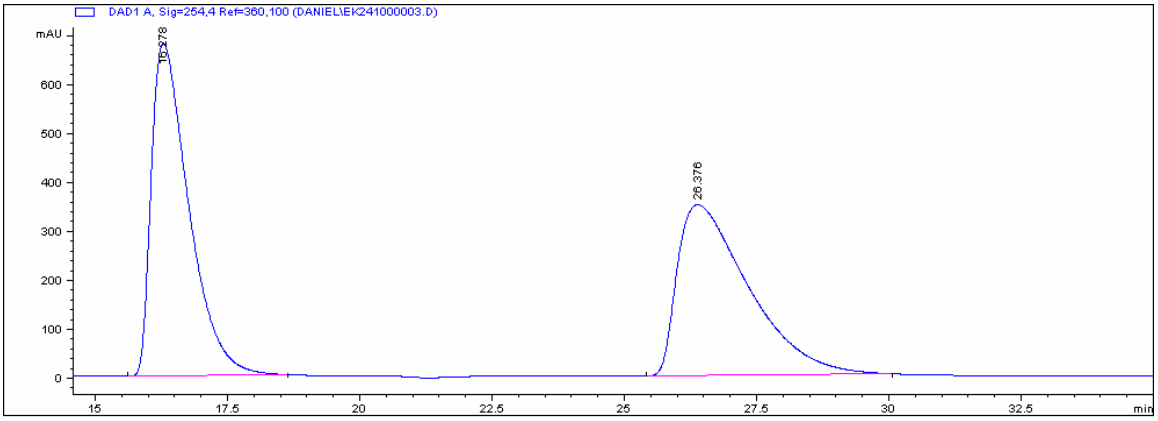


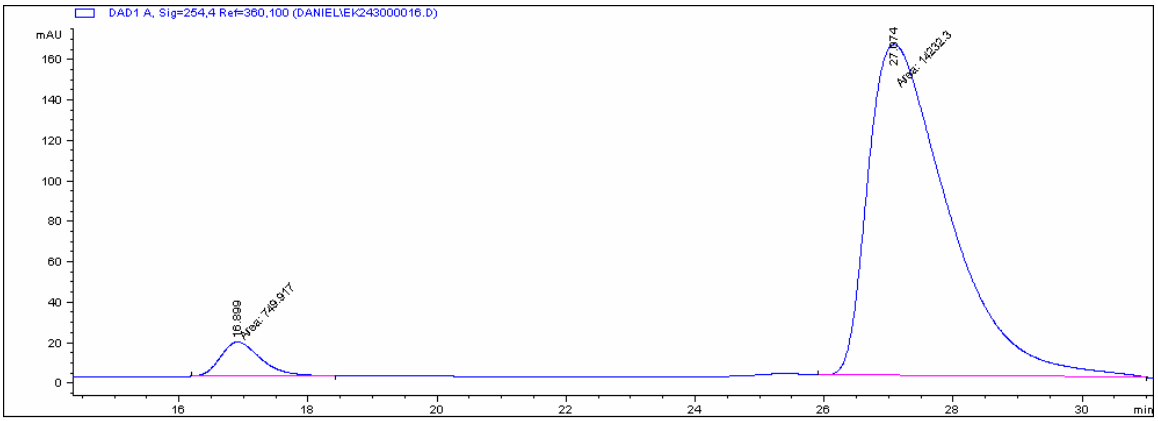




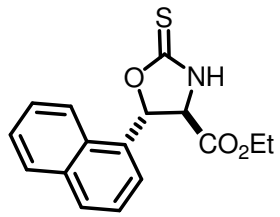
HPLC profiles of 2.66l

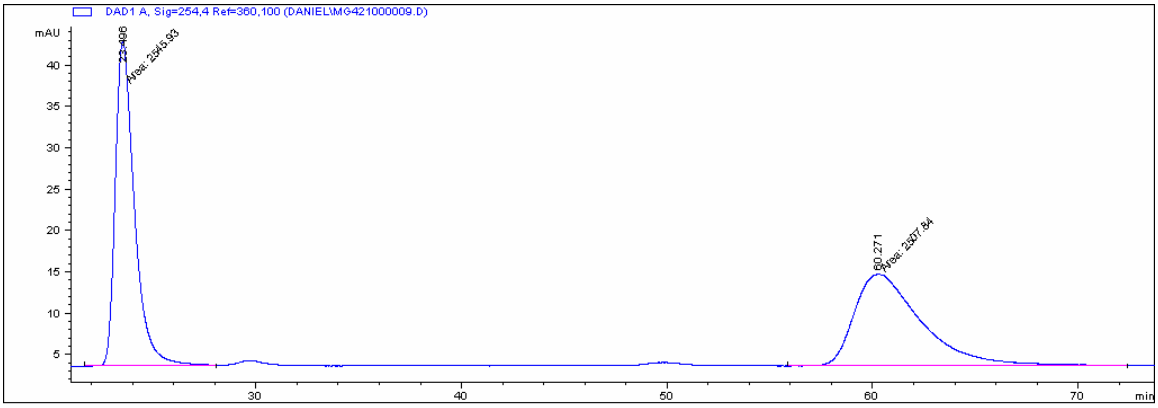


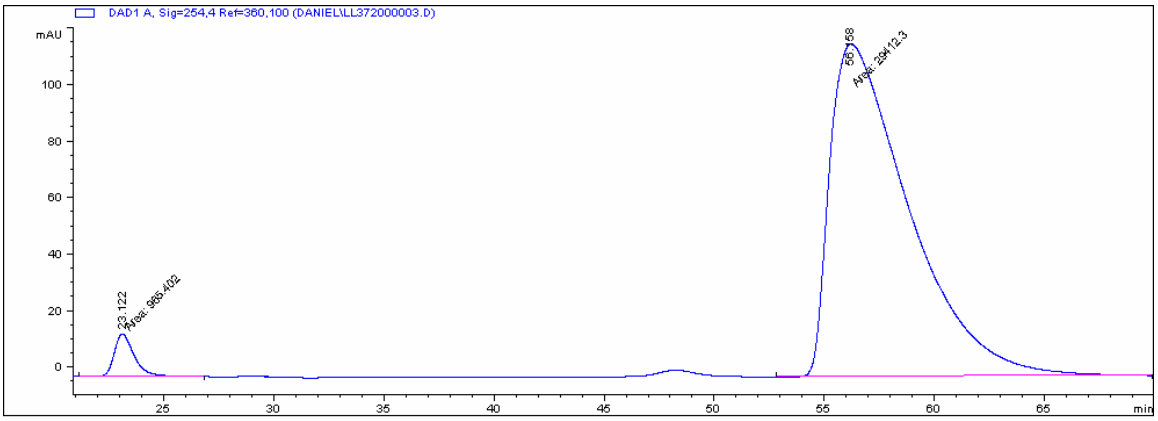




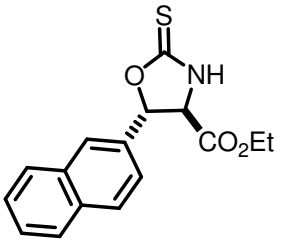
HPLC profiles of 2.66m

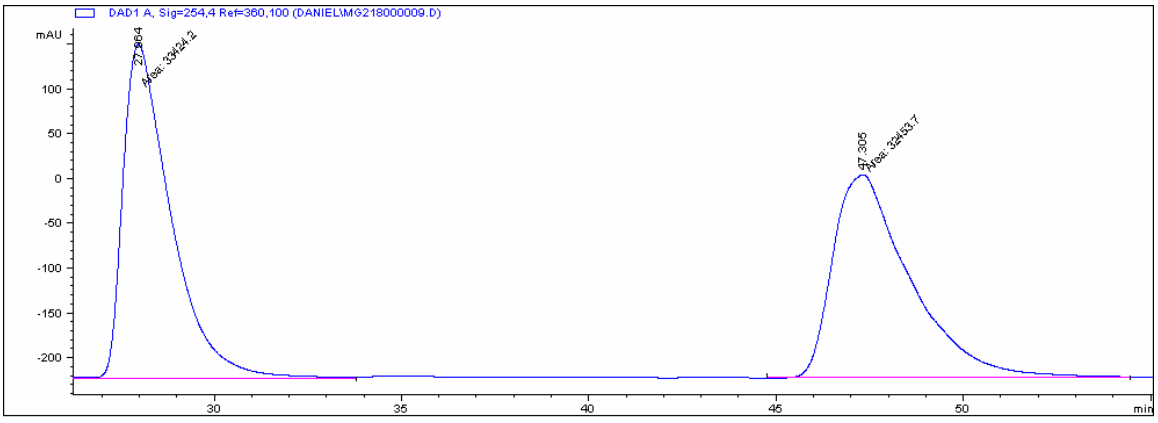


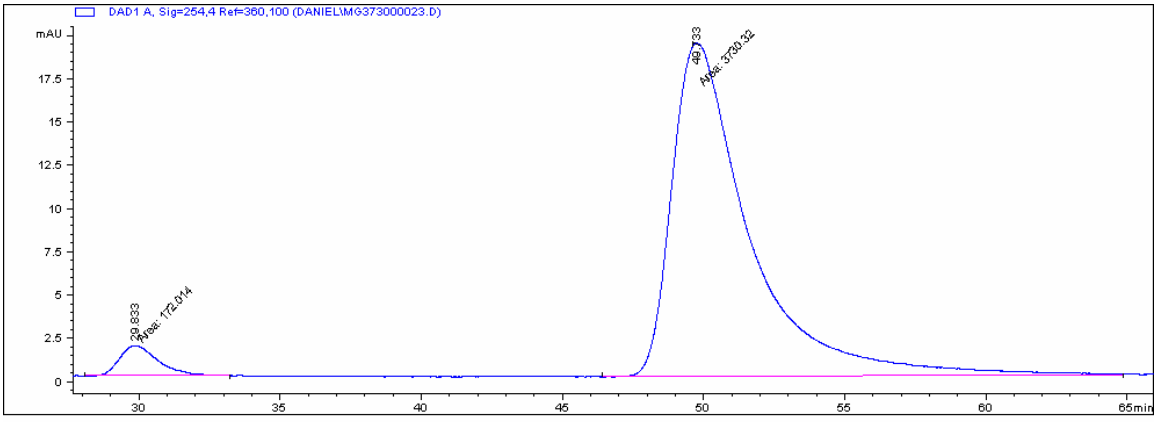




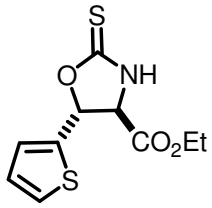
HPLC profiles of 2.66n

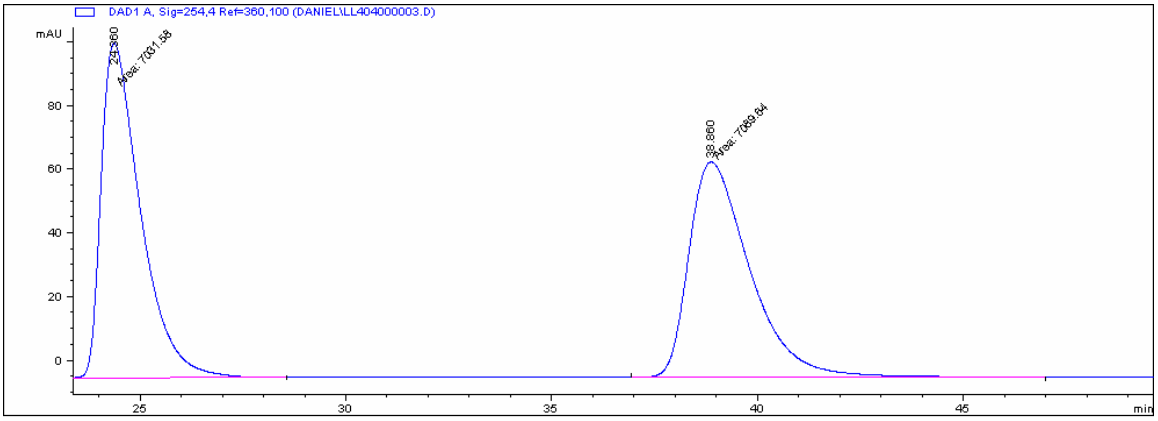


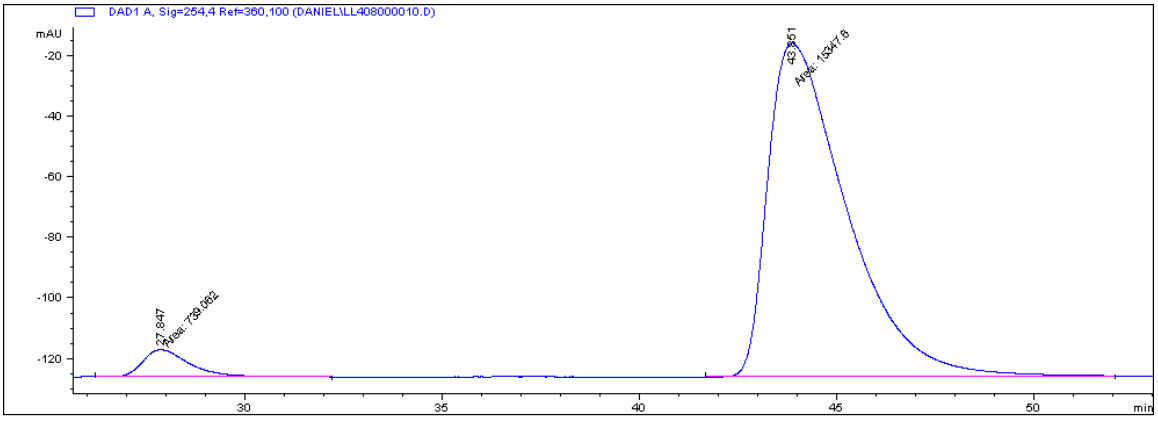




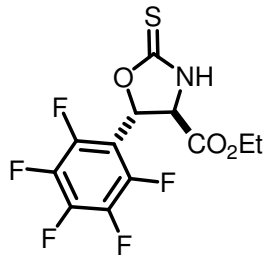
HPLC profiles of 2.66o

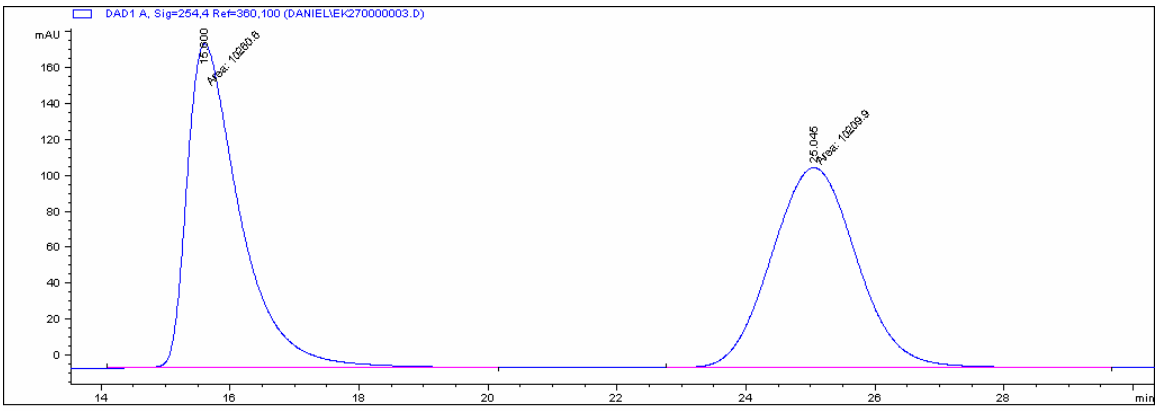


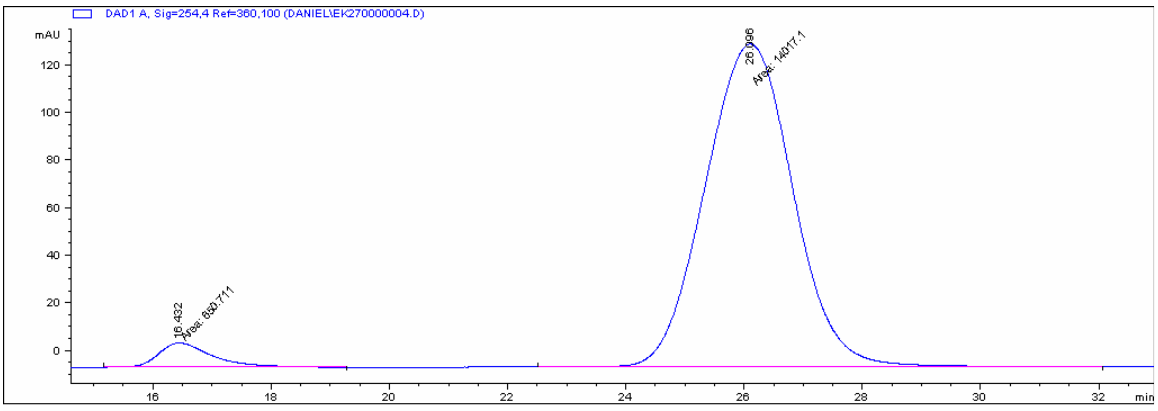




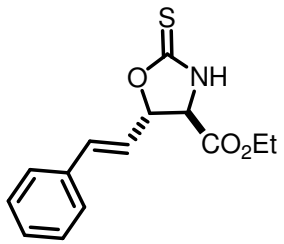
HPLC profiles of 2.66p

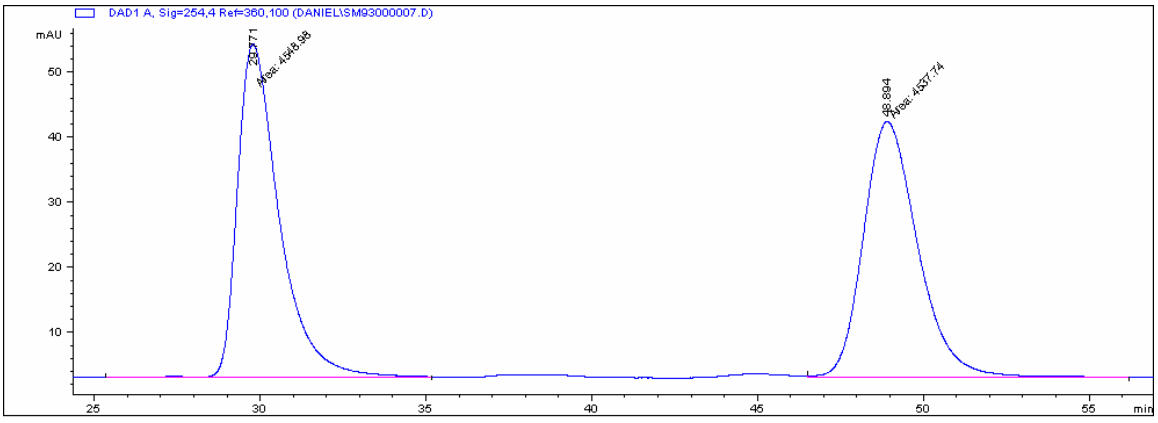


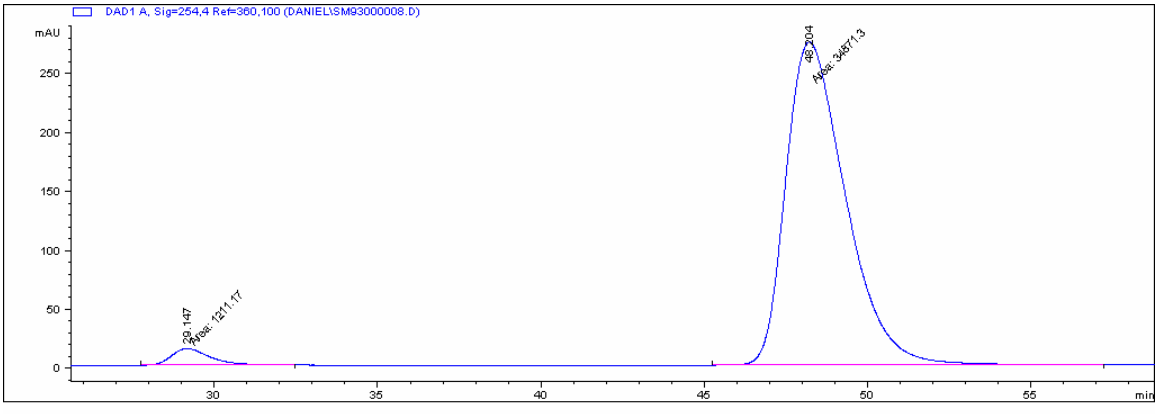




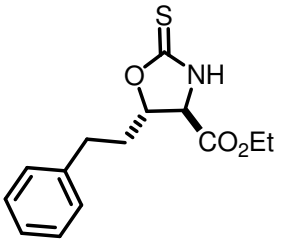
HPLC profiles of 2.66q

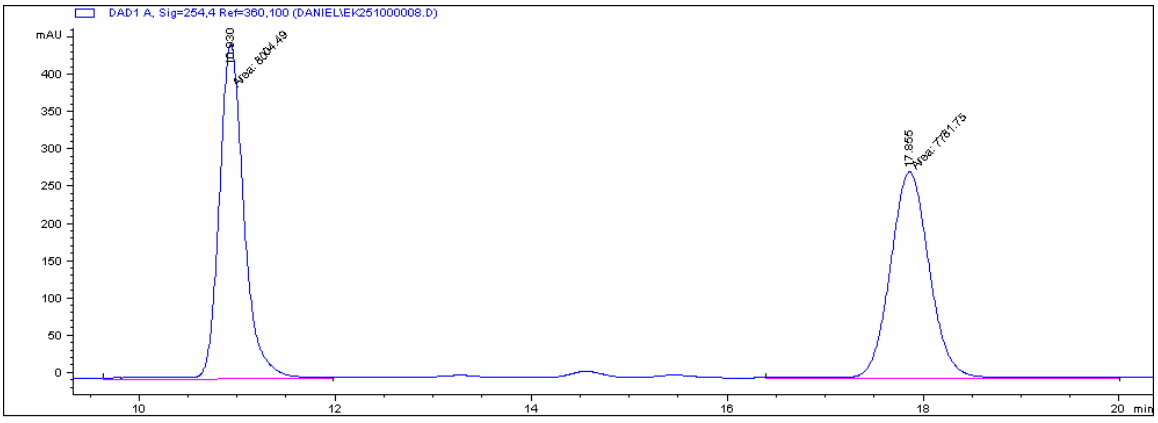


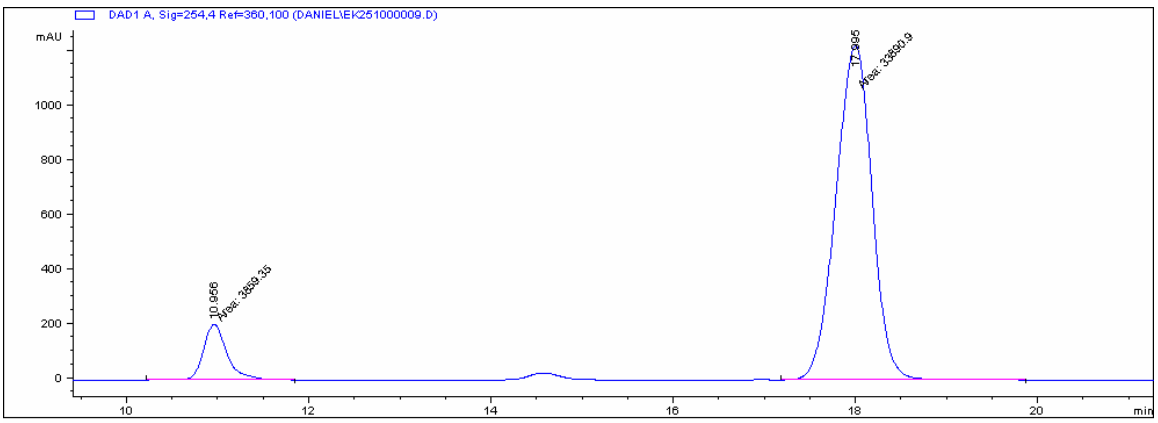




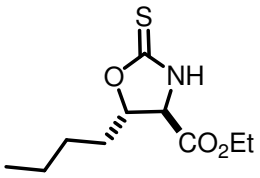
HPLC profiles of 2.66r

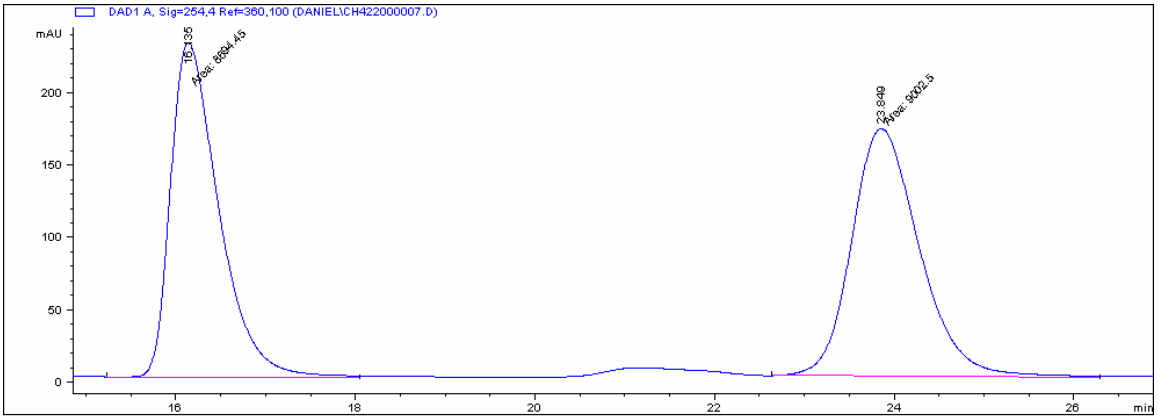


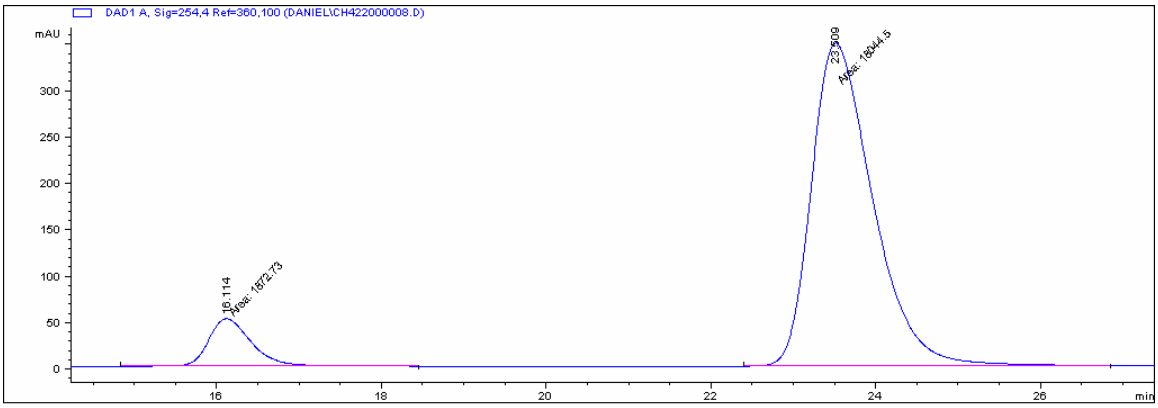




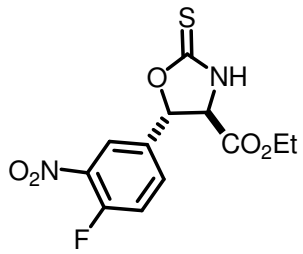
HPLC profiles of 2.66s

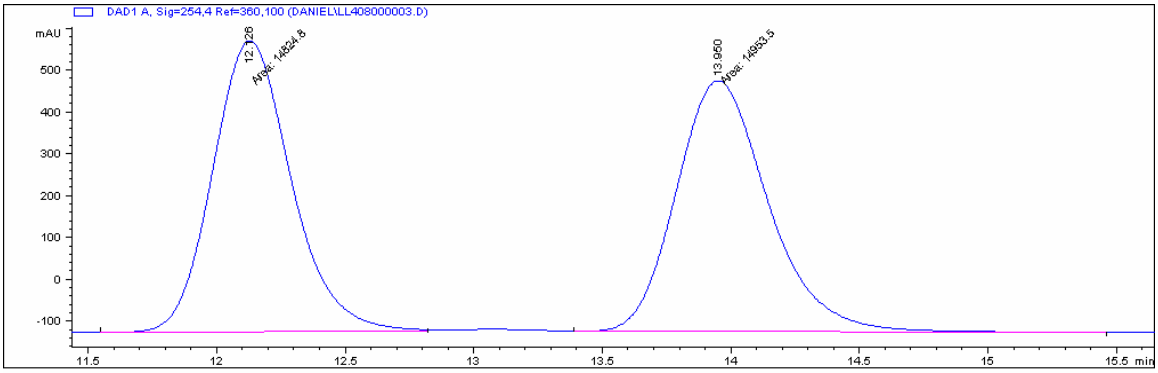


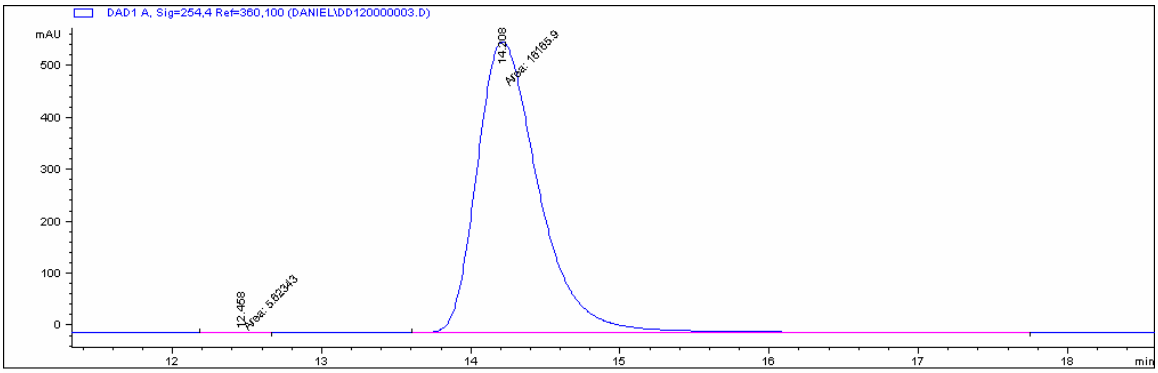




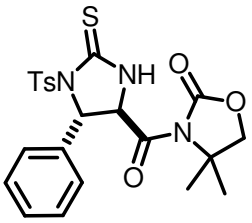
HPLC profiles of 2.66t

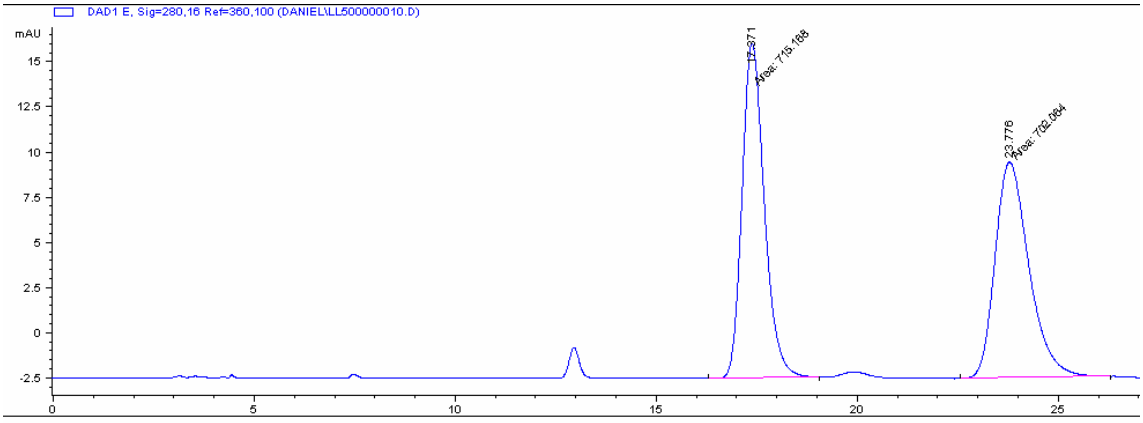


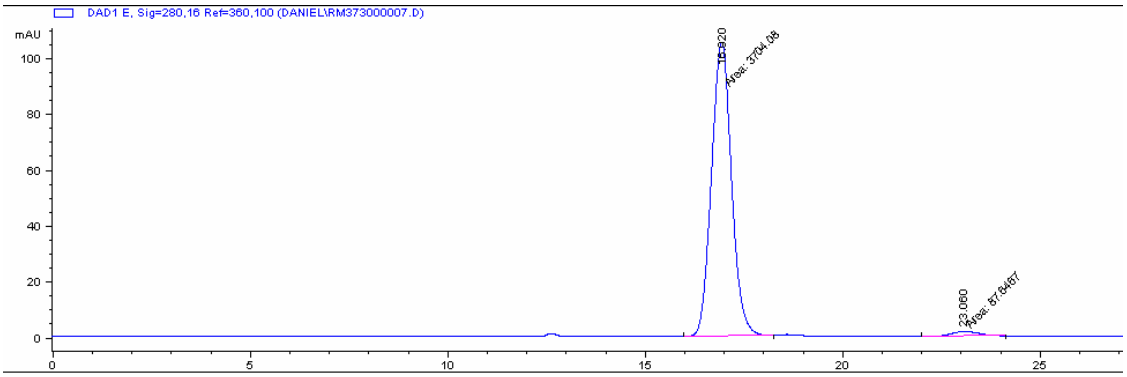




HPLC profiles of 3.18a







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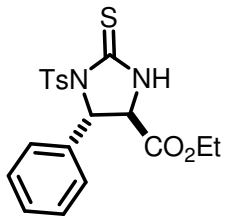
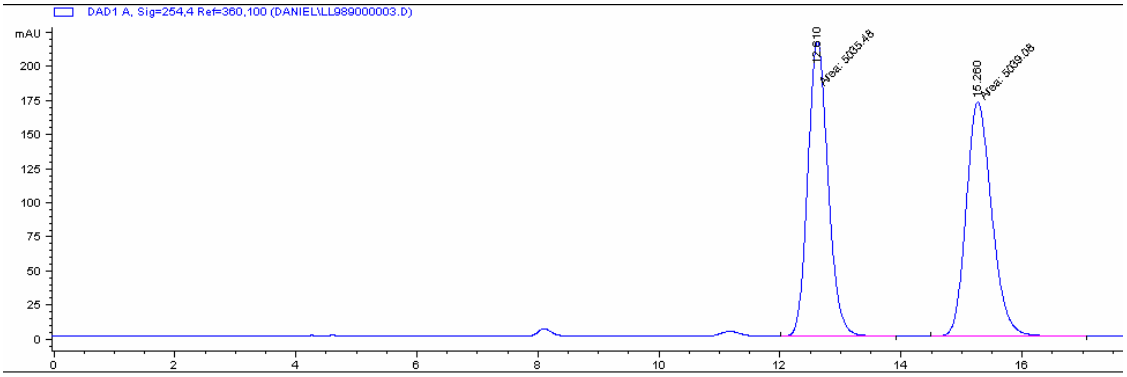
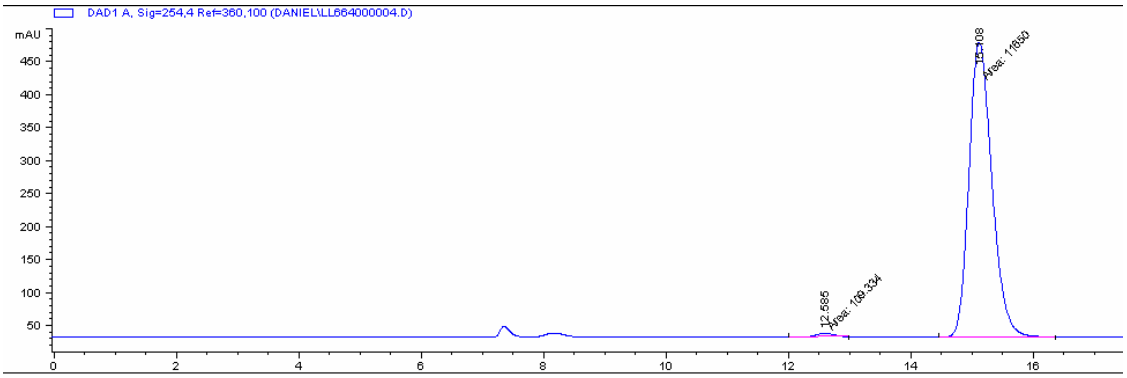
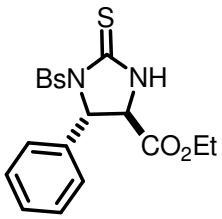
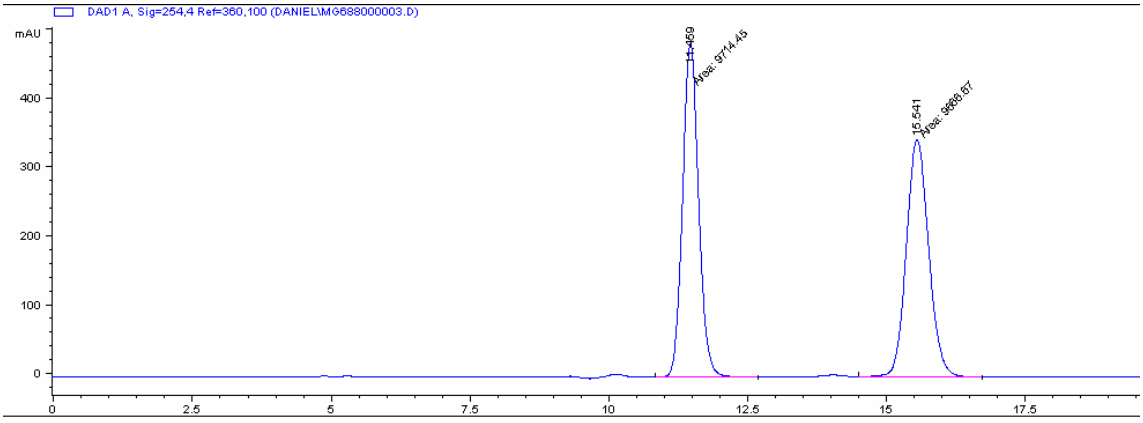


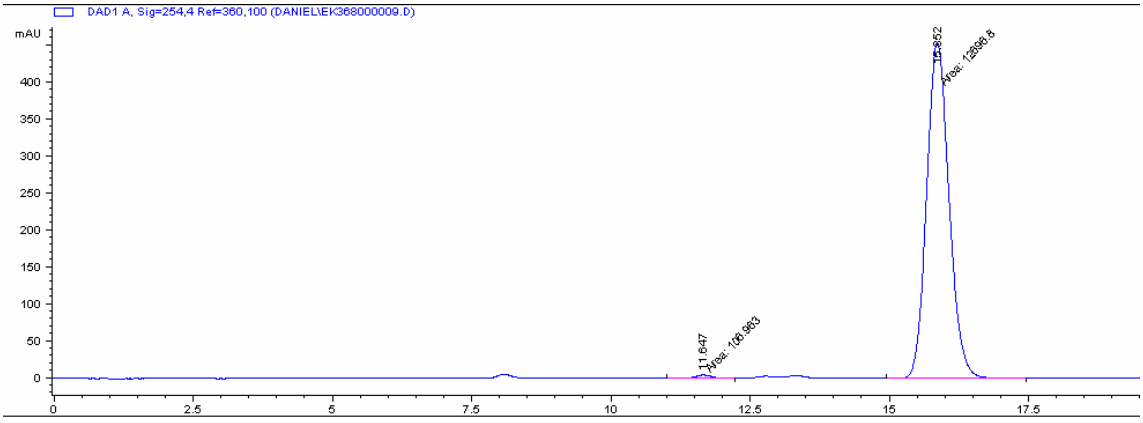




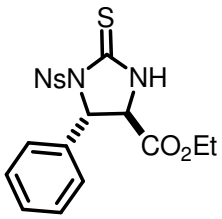
HPLC profiles of 3.34c



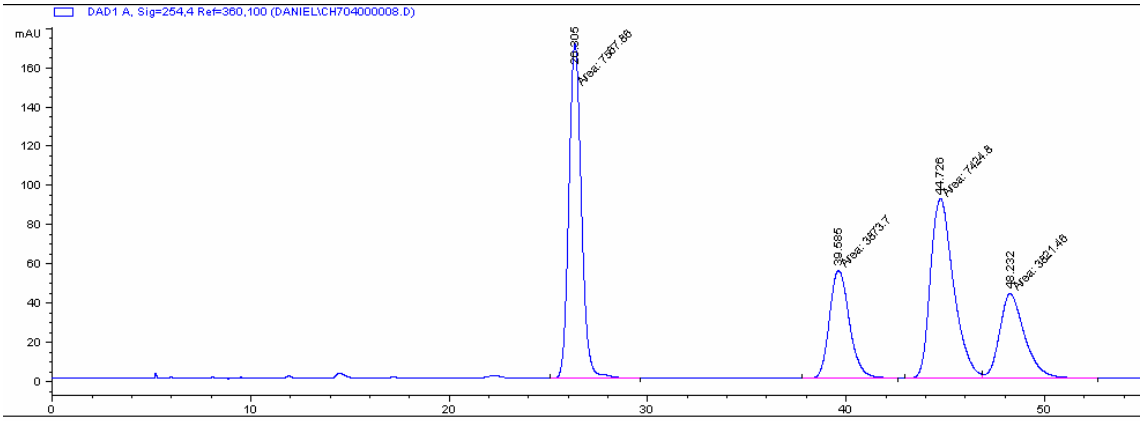


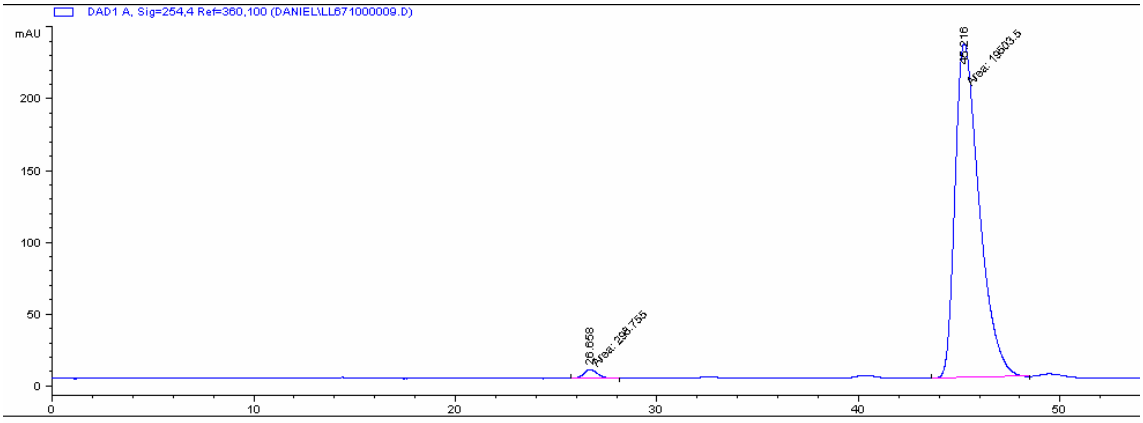


HPLC profiles of 3.34d

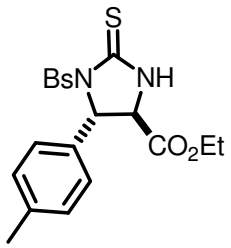


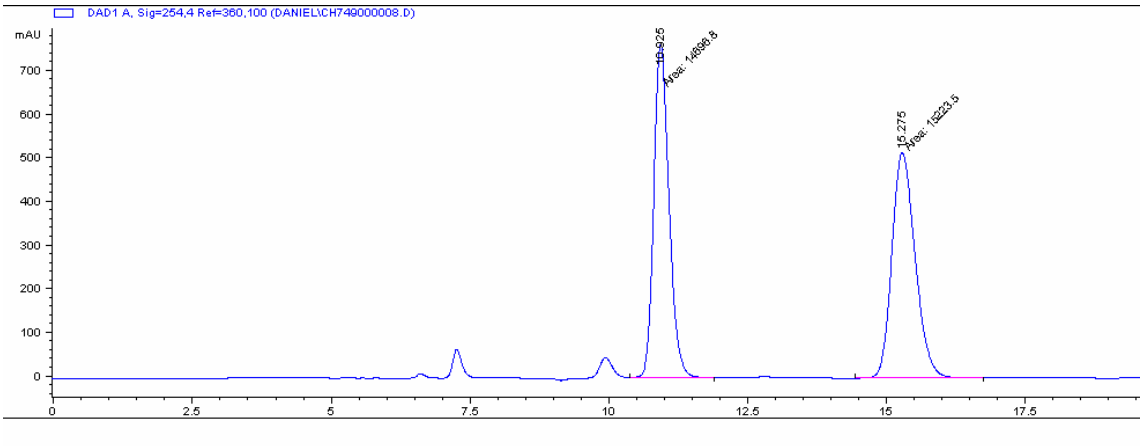
trans+cis enantiomers

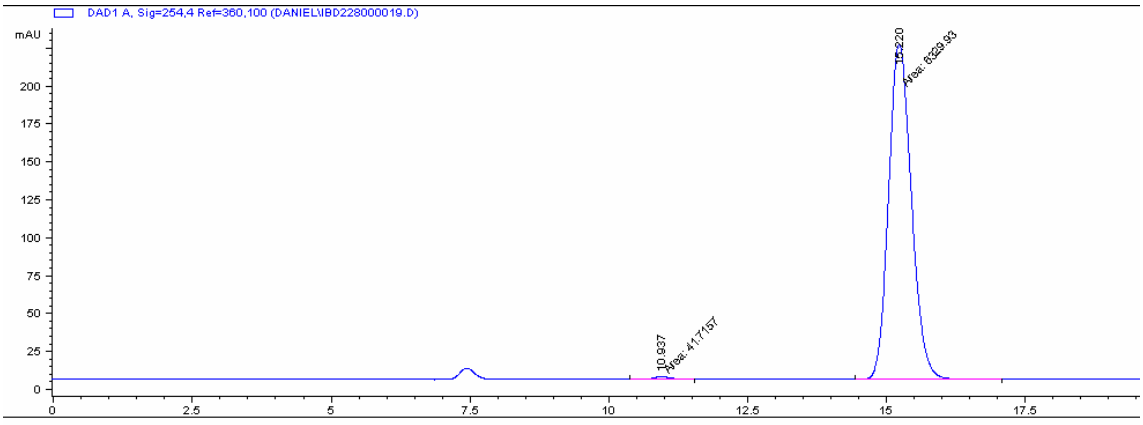




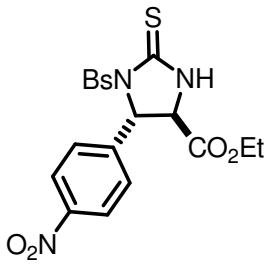
HPLC profiles of 3.35a

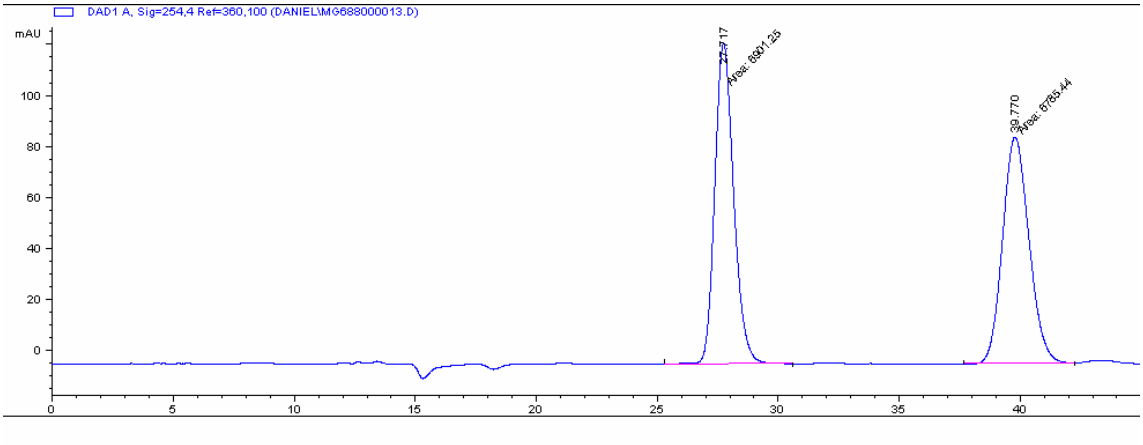


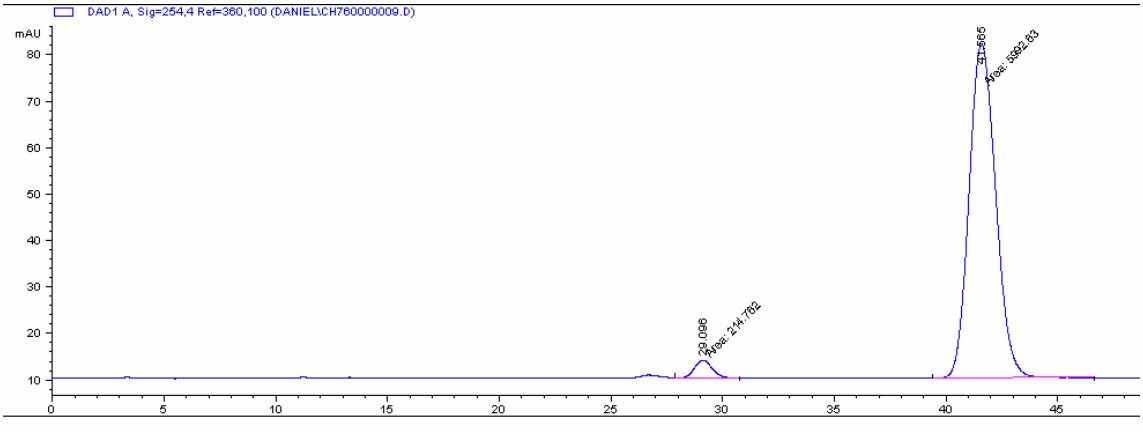




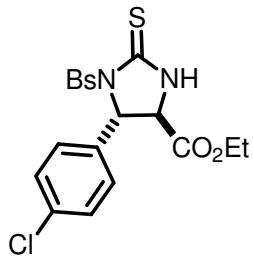
HPLC profiles of 3.35b

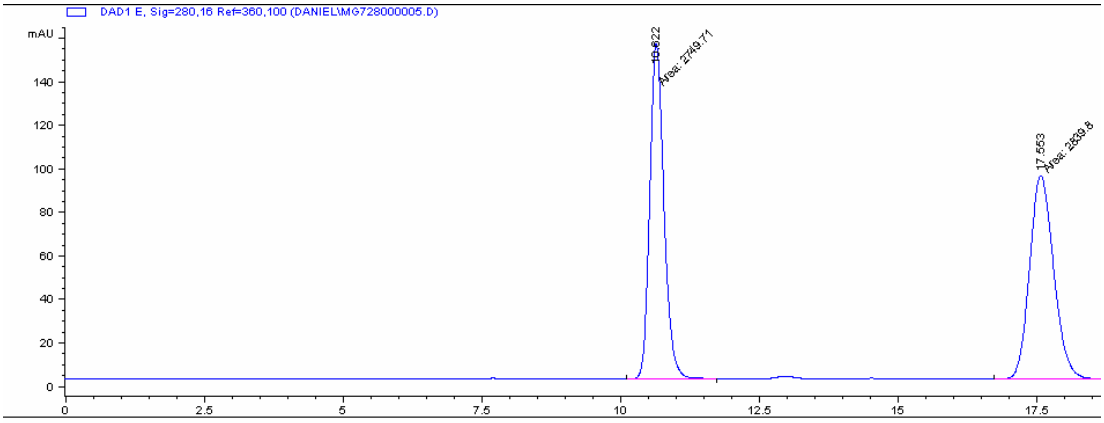


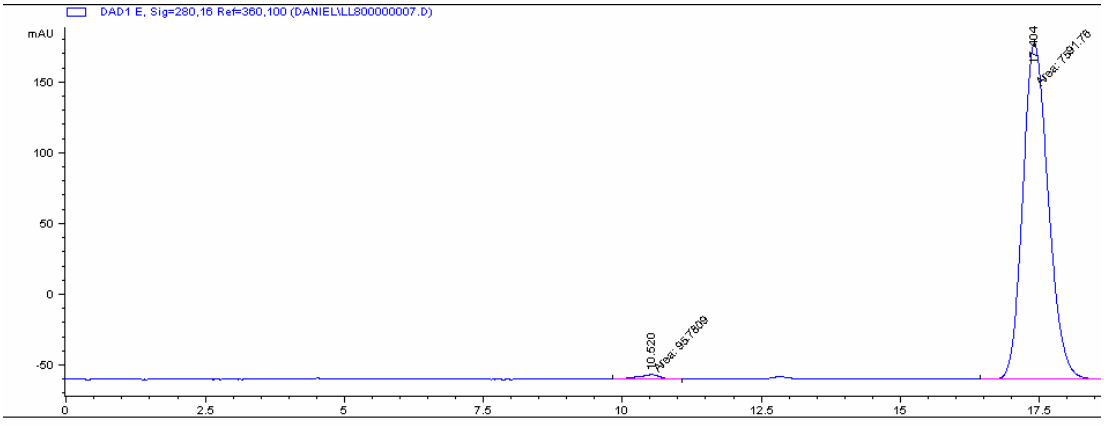




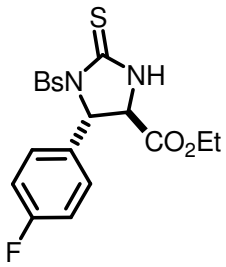
HPLC profiles of 3.35c

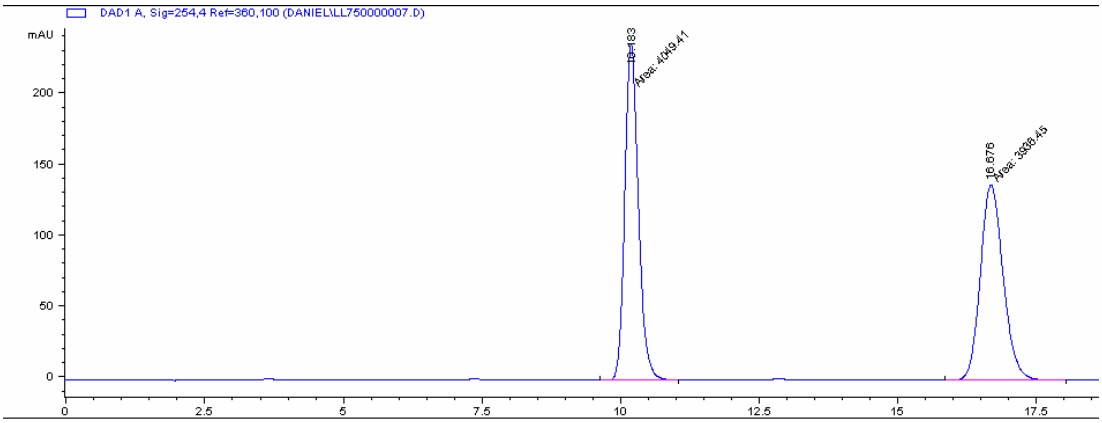


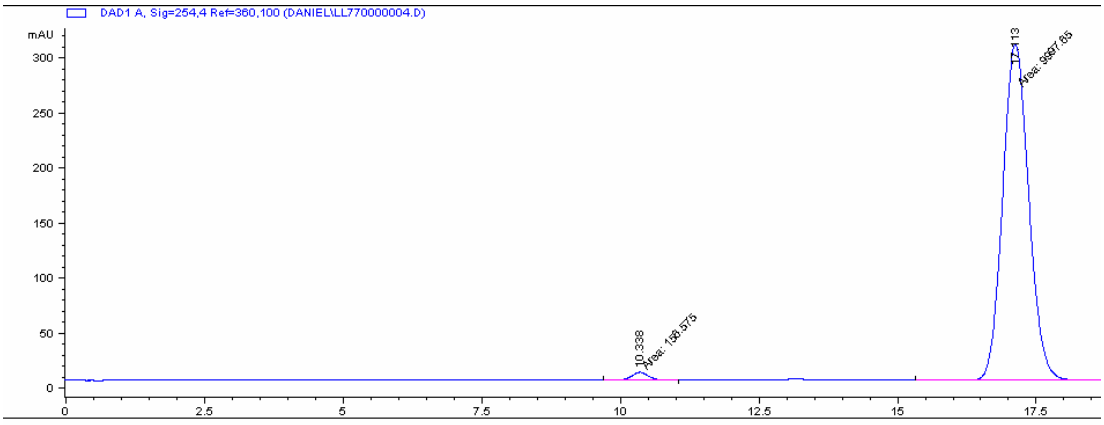




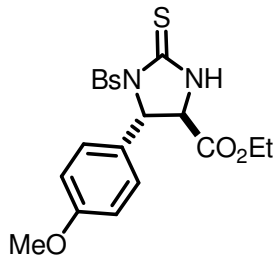
HPLC profiles of 3.35d

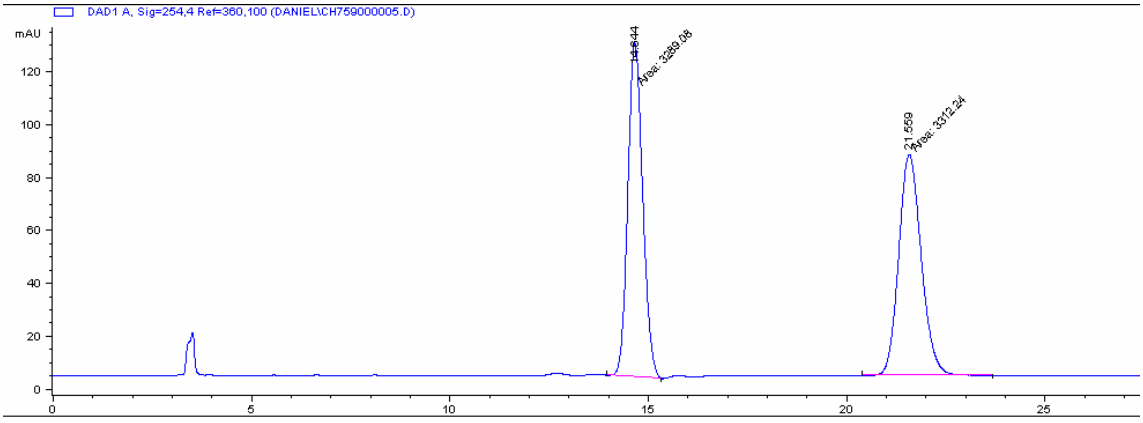


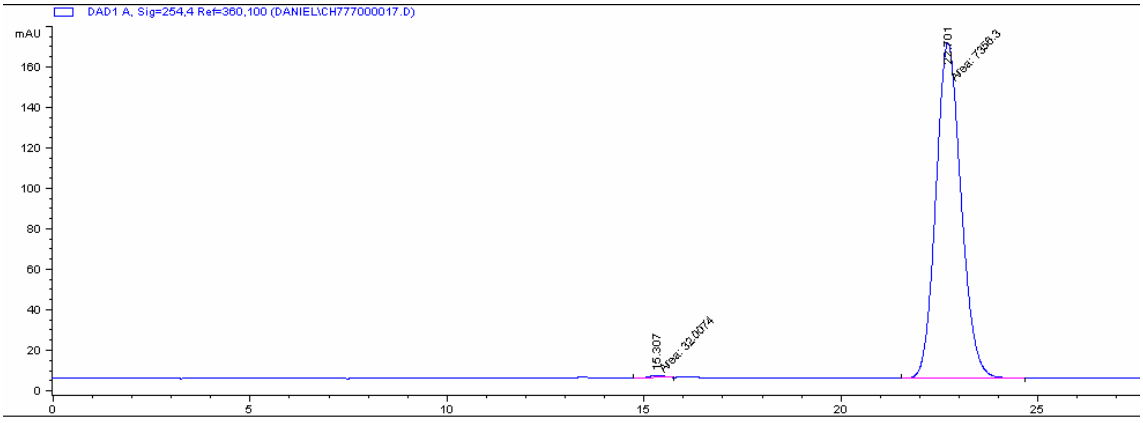




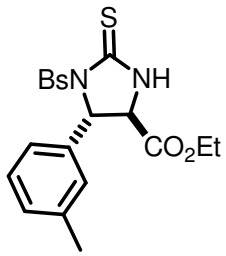
HPLC profiles of 3.35e

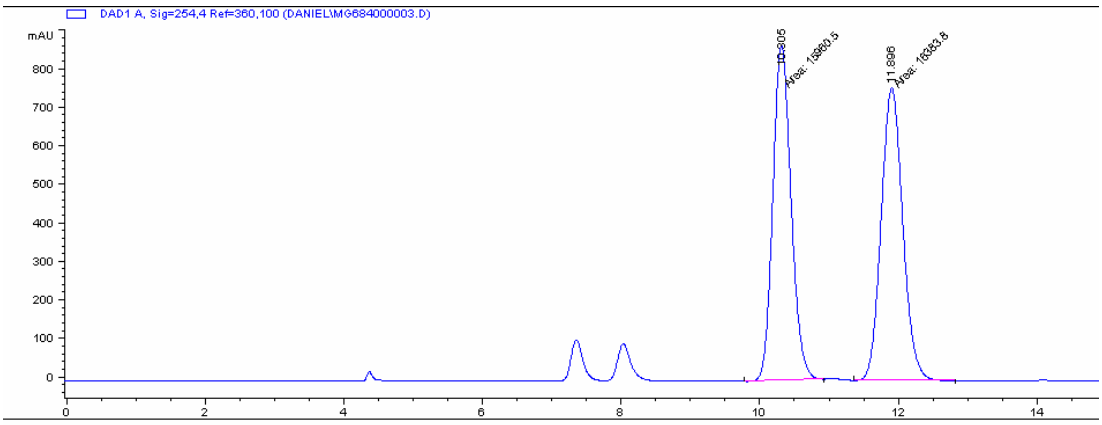


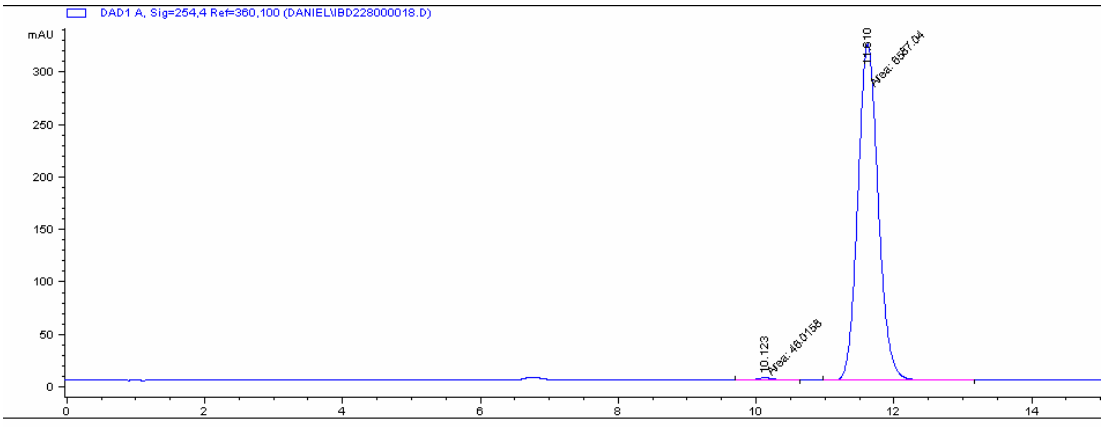




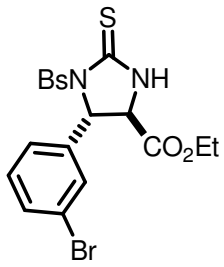
HPLC profiles of 3.35f

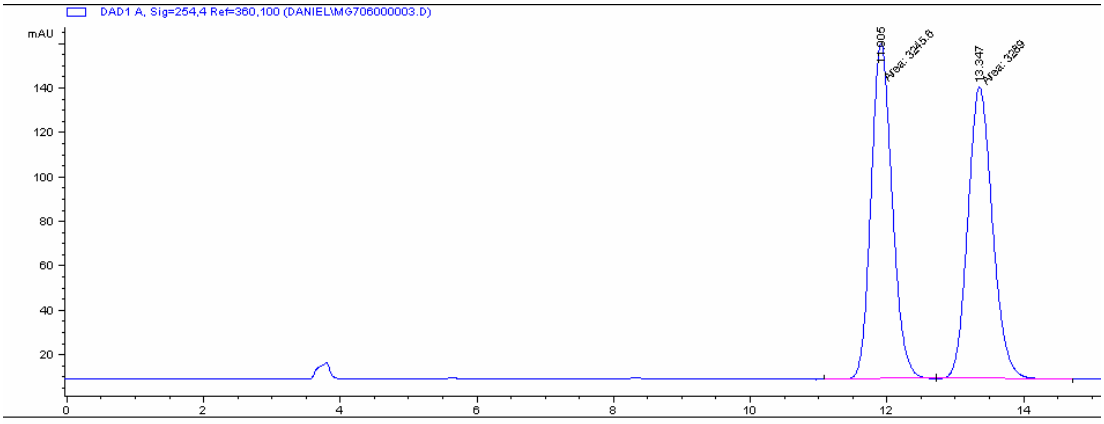


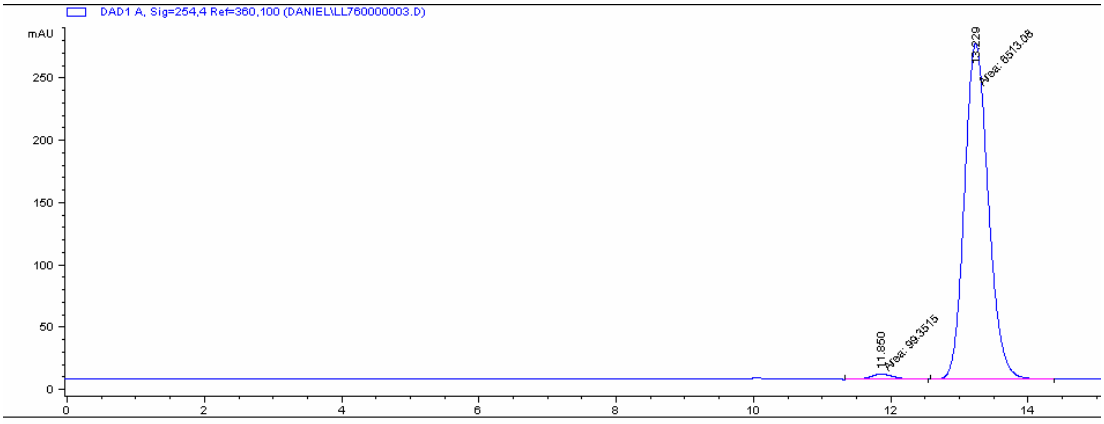




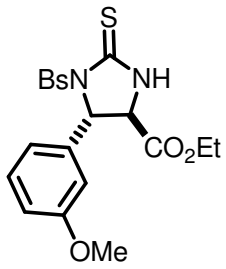
HPLC profiles of 3.35g

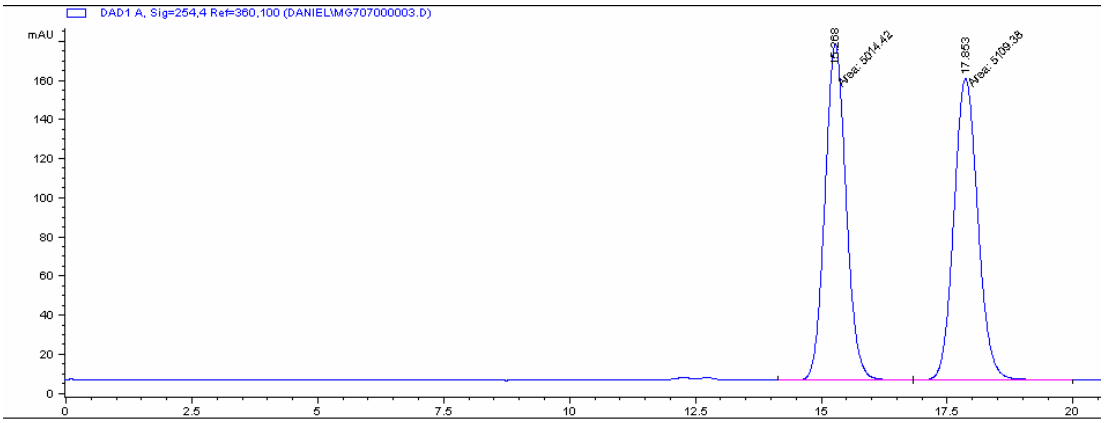


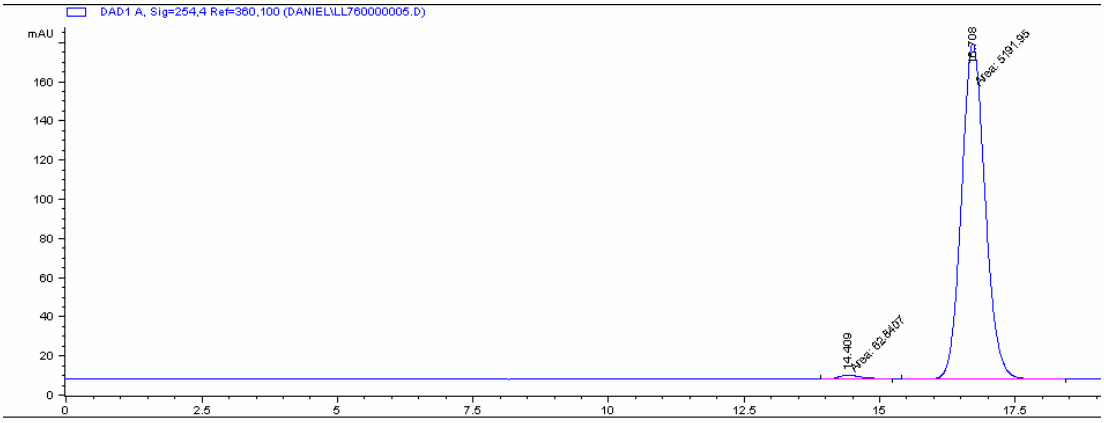




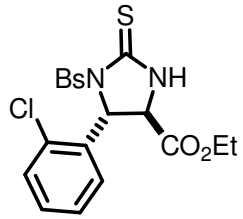
HPLC profiles of 3.35h

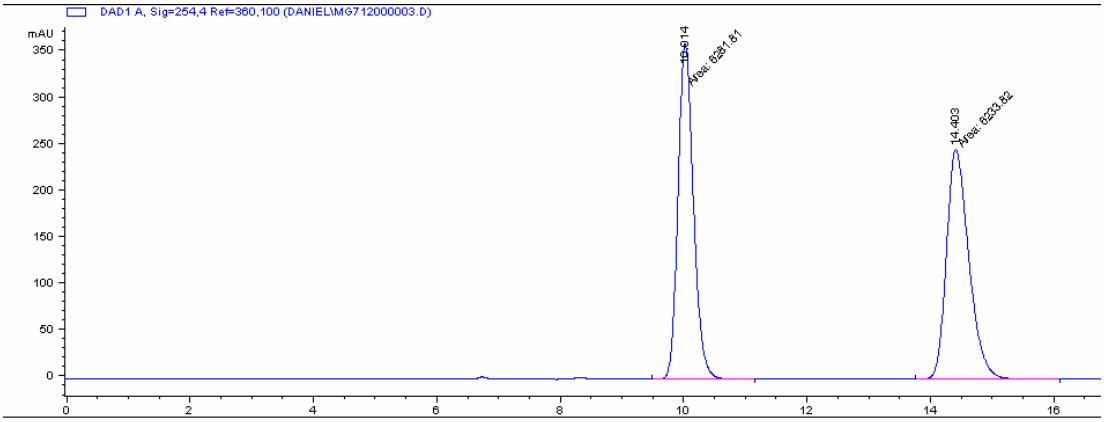


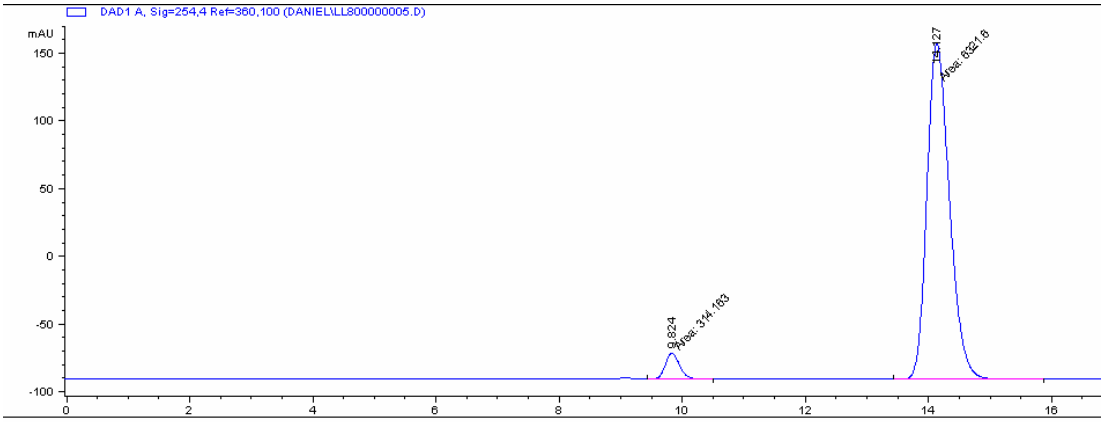




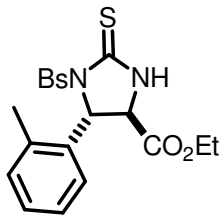
HPLC profiles of 3.35i

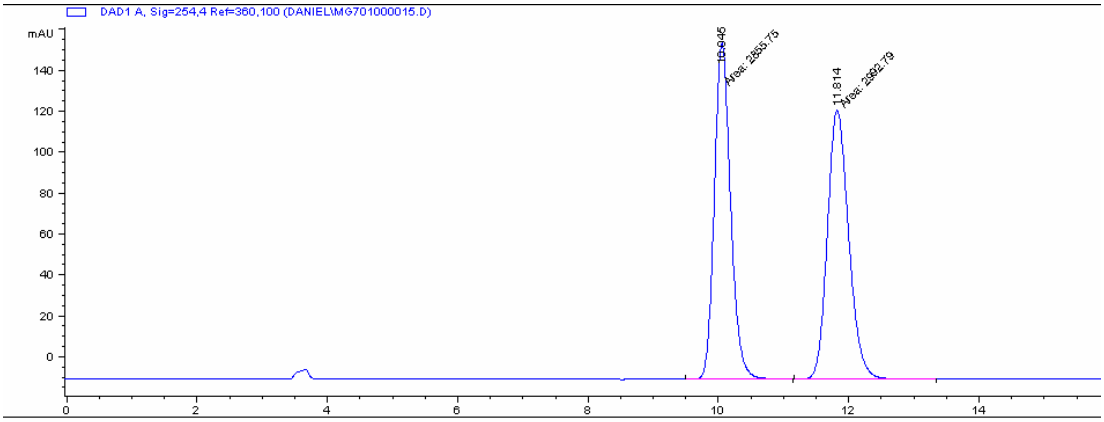


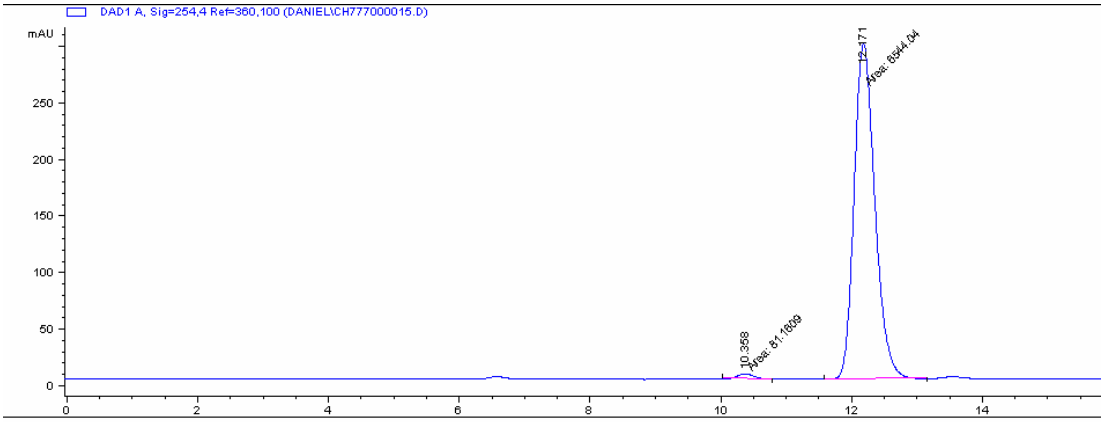




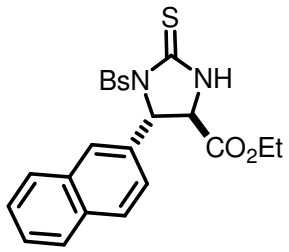
HPLC profiles of 3.35j

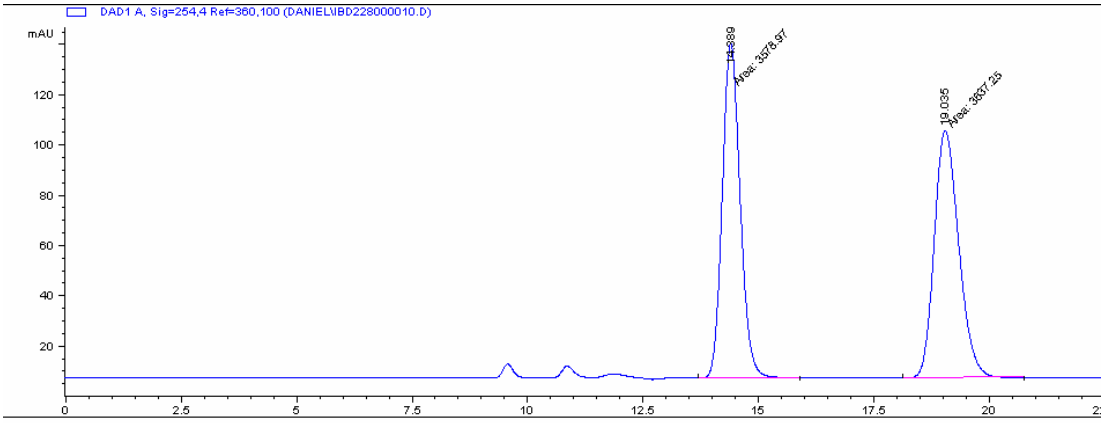


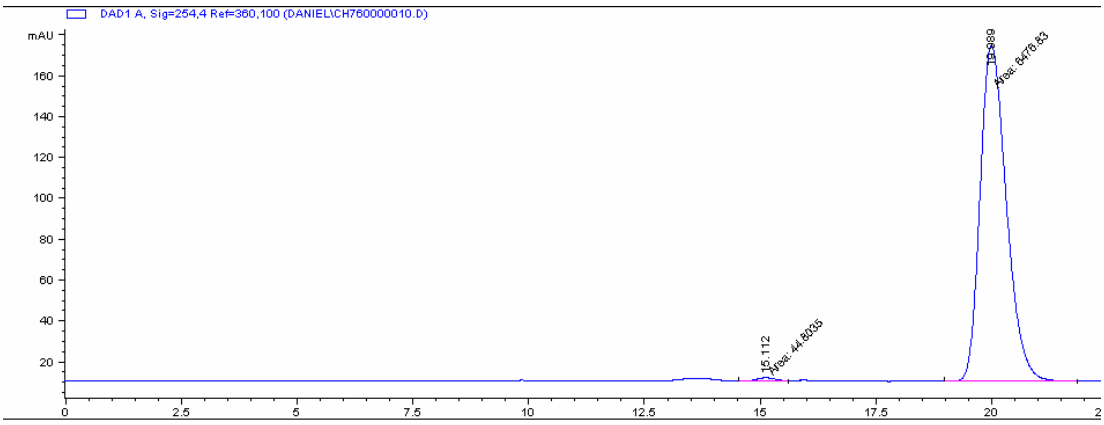




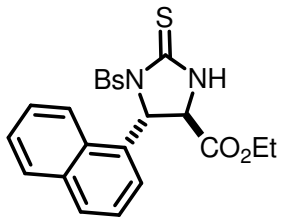
HPLC profiles of 3.35k

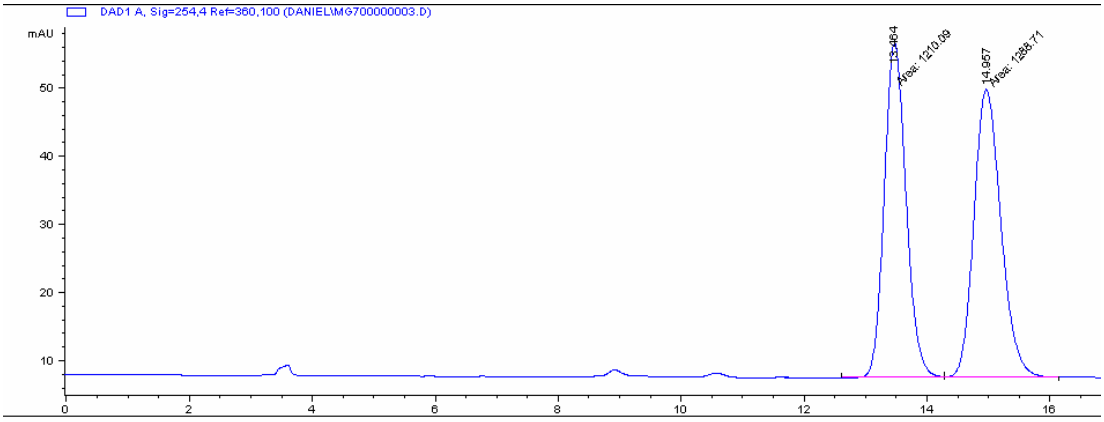


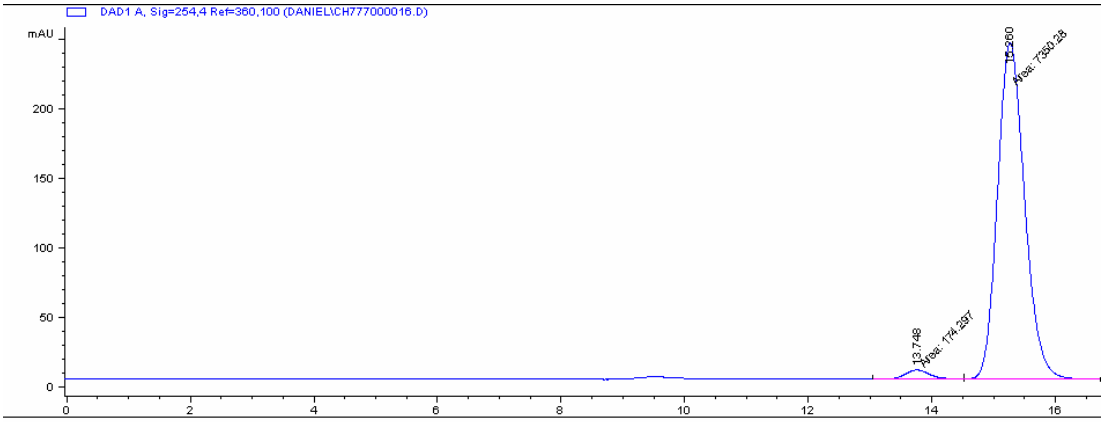




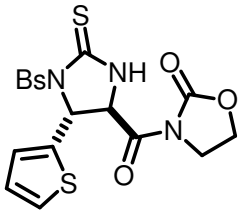
HPLC profiles of 3.35l

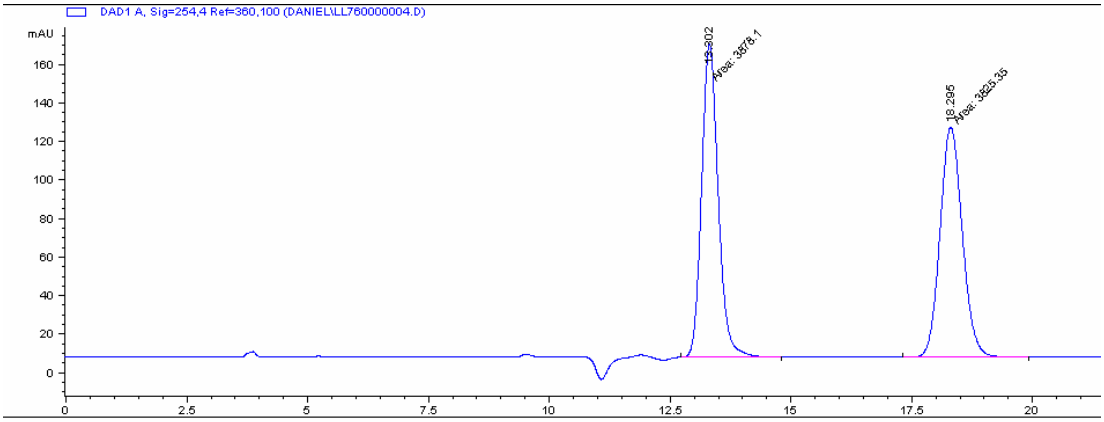


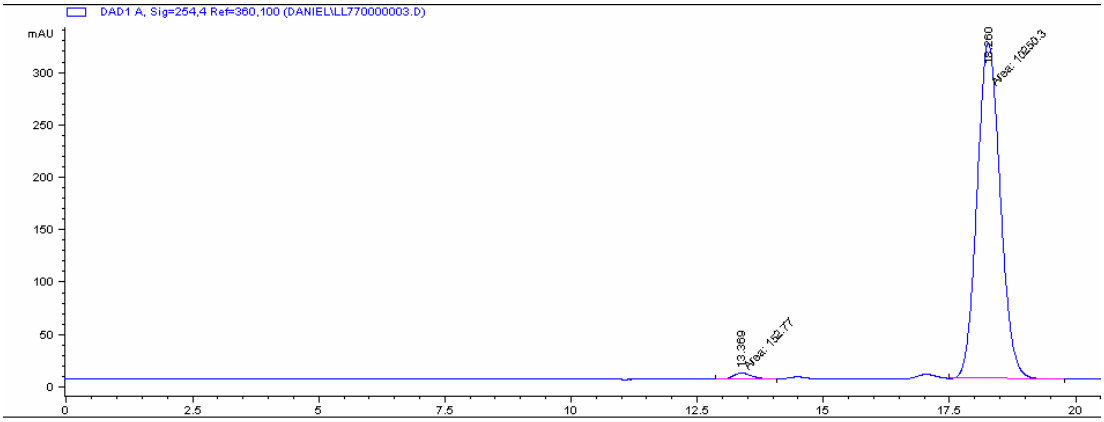




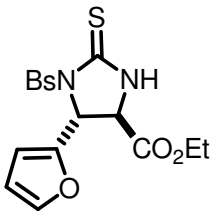
HPLC profiles of 3.35m

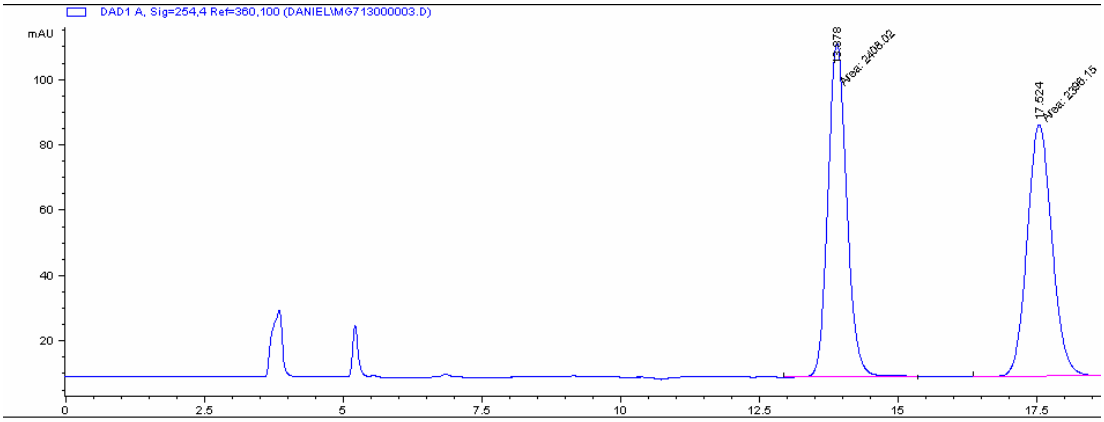


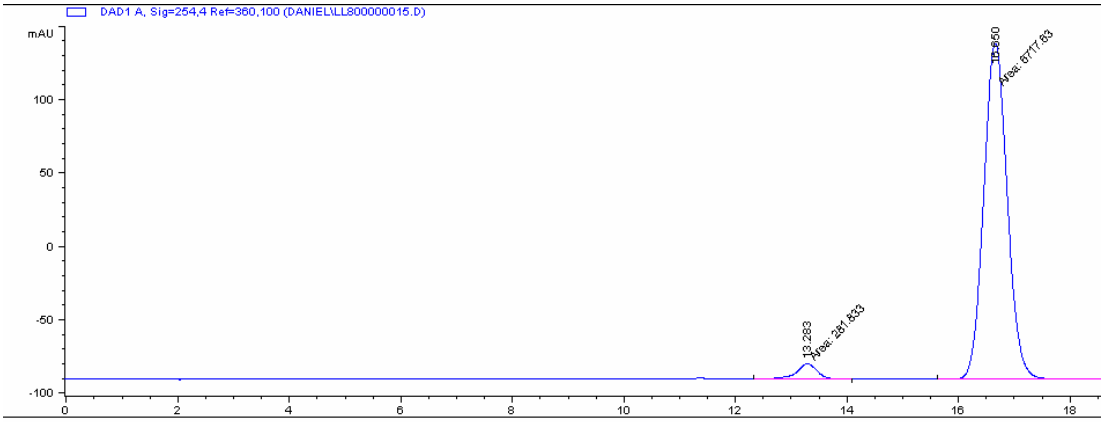




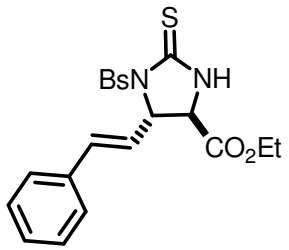
HPLC profiles of 3.35n

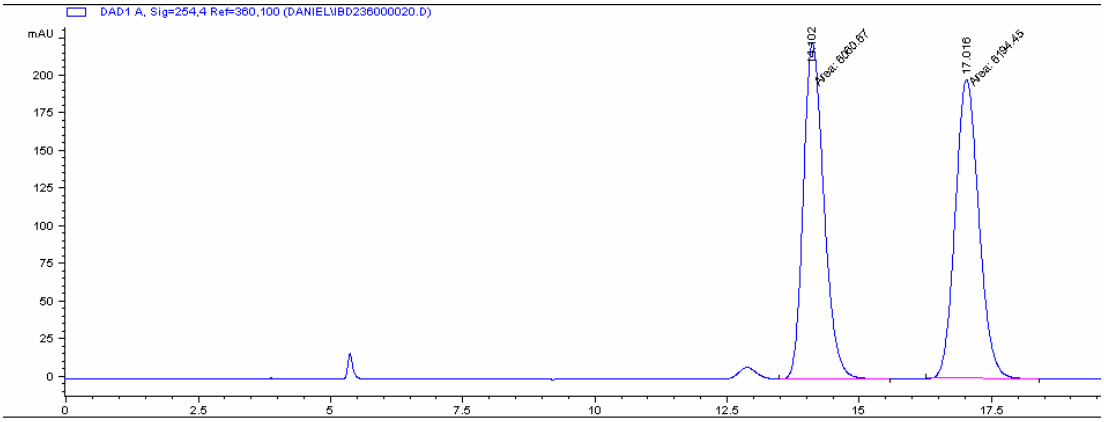


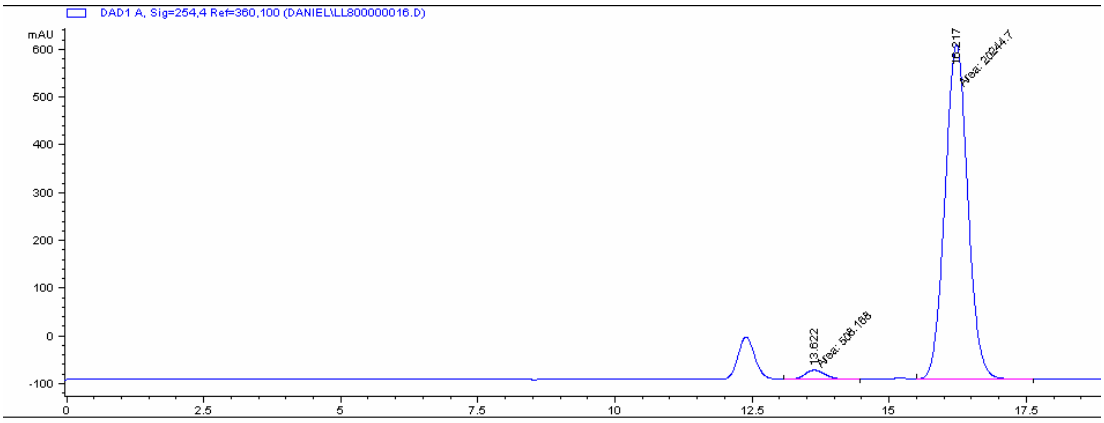




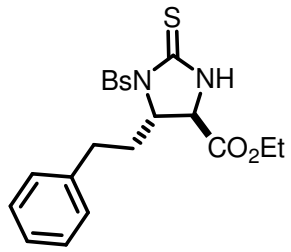
HPLC profiles of 3.35o

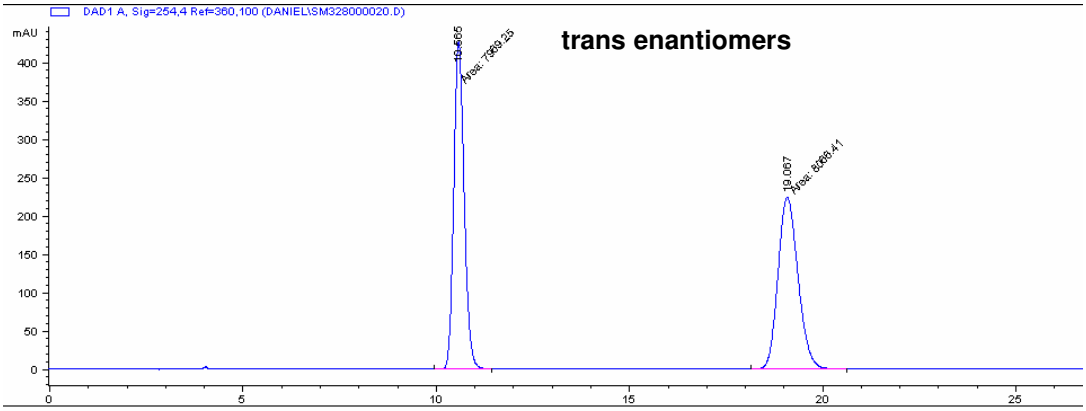


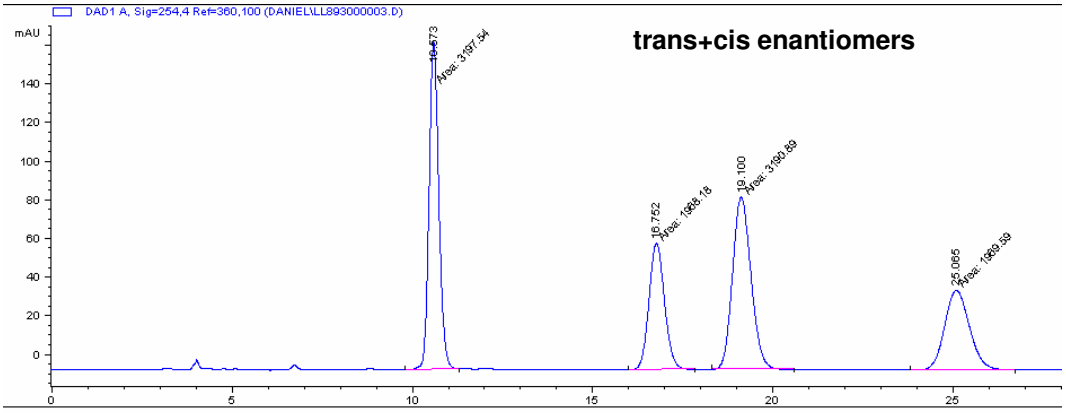


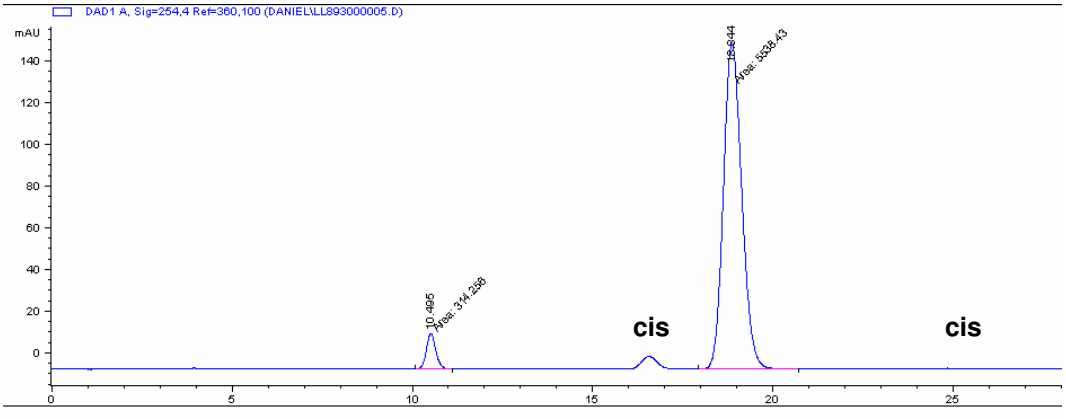


HPLC profiles of 3.35p

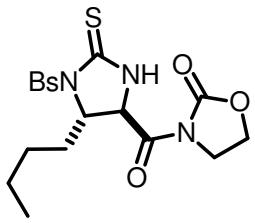


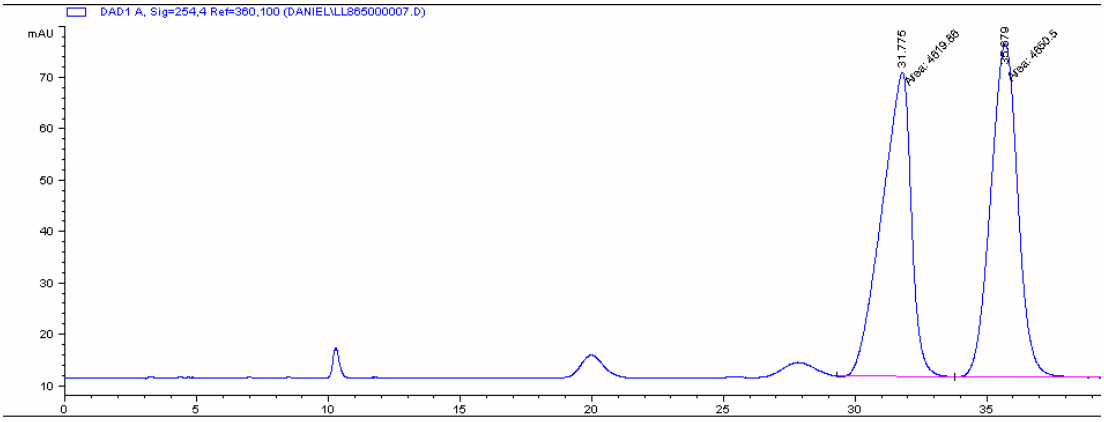


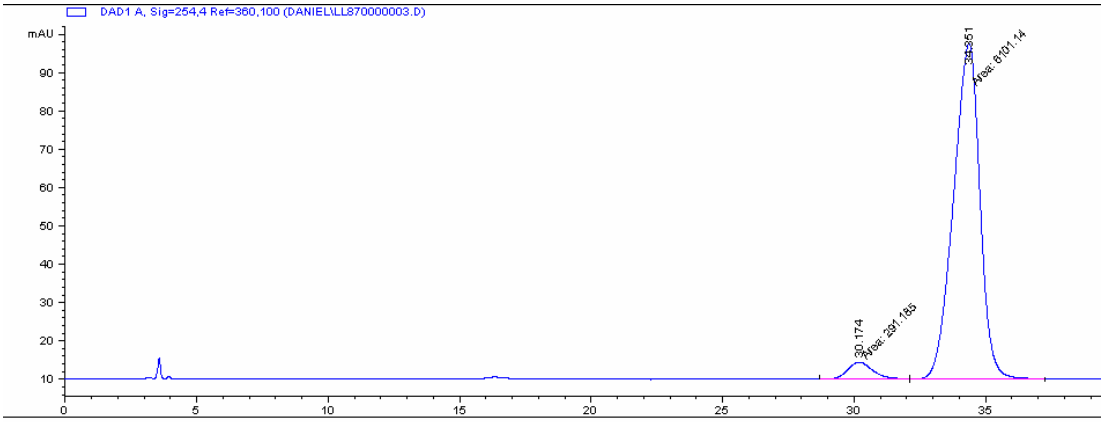




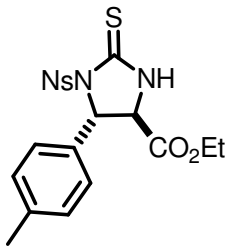
HPLC profiles of 3.31q

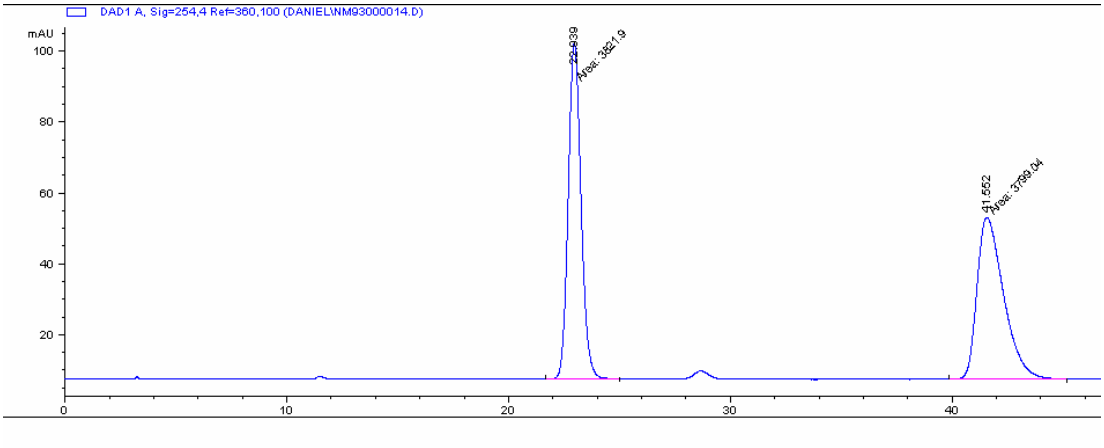


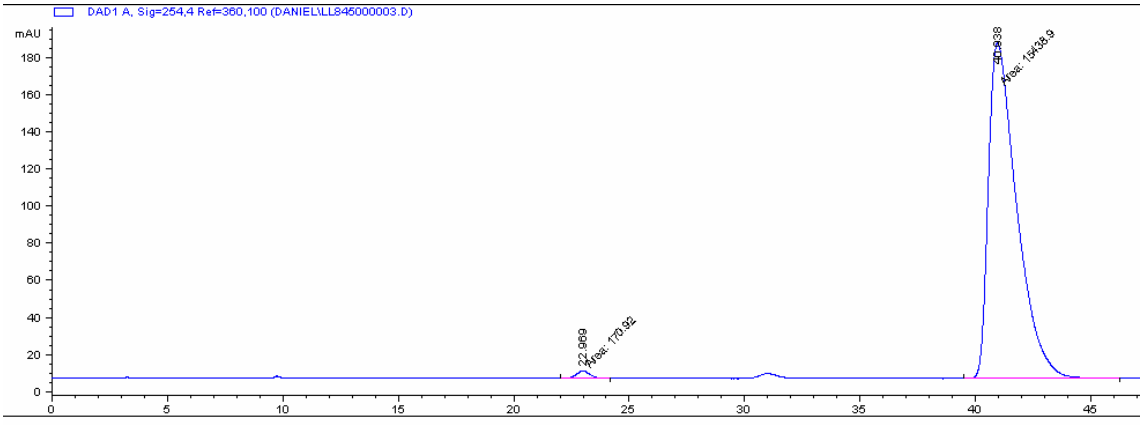




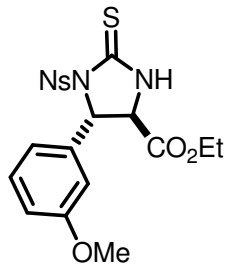
HPLC profiles of 3.36a

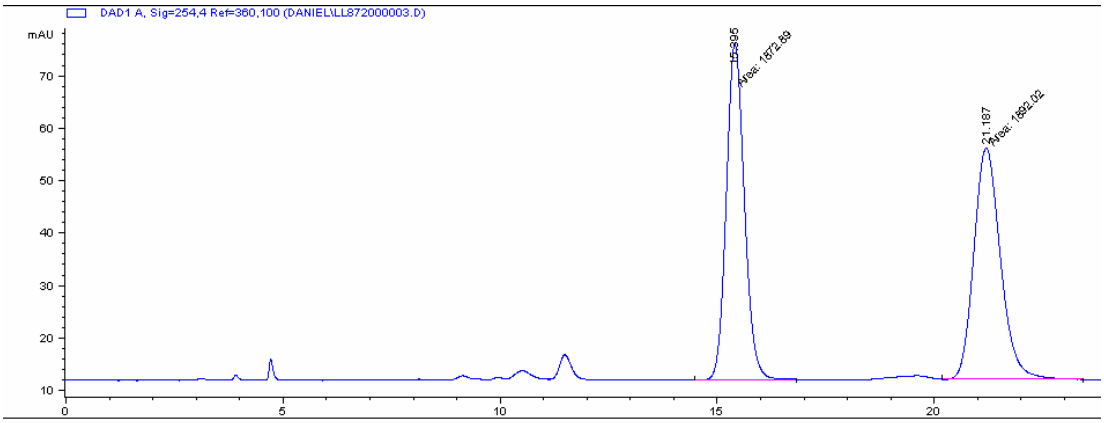


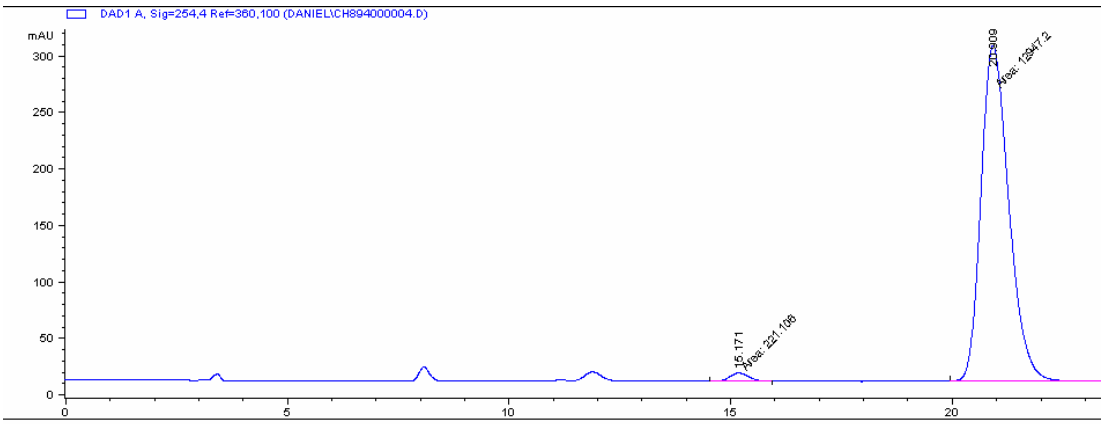




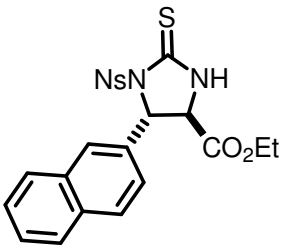
HPLC profiles of 3.36b

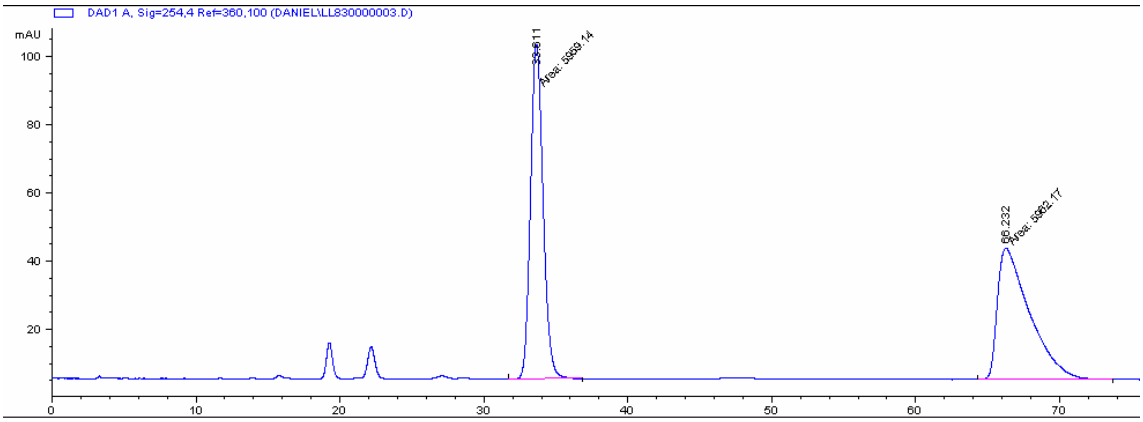


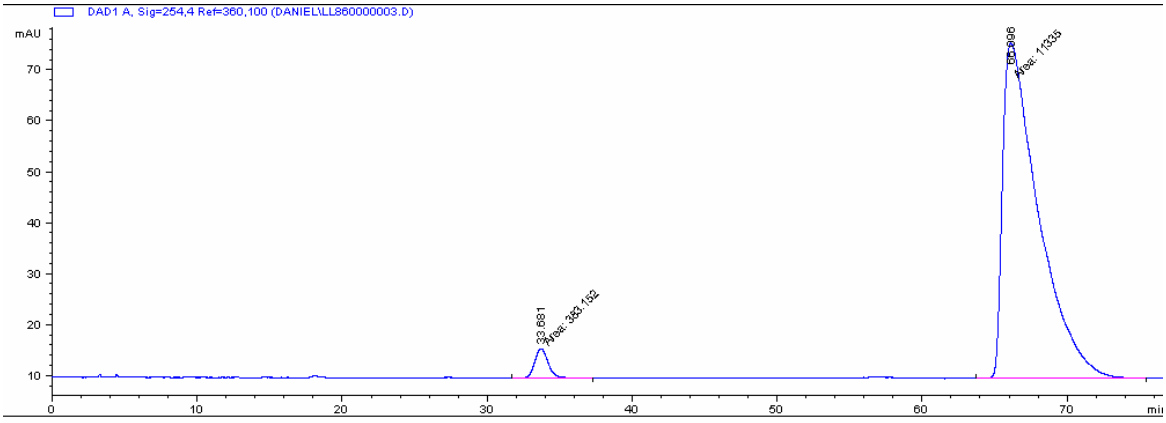




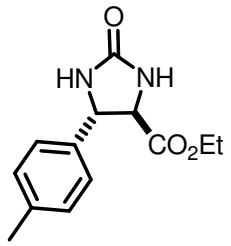
HPLC profiles of 3.36c

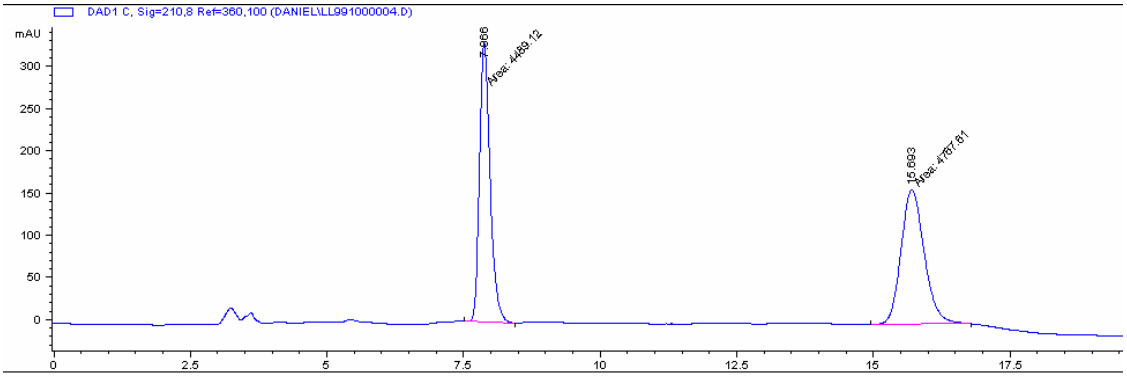


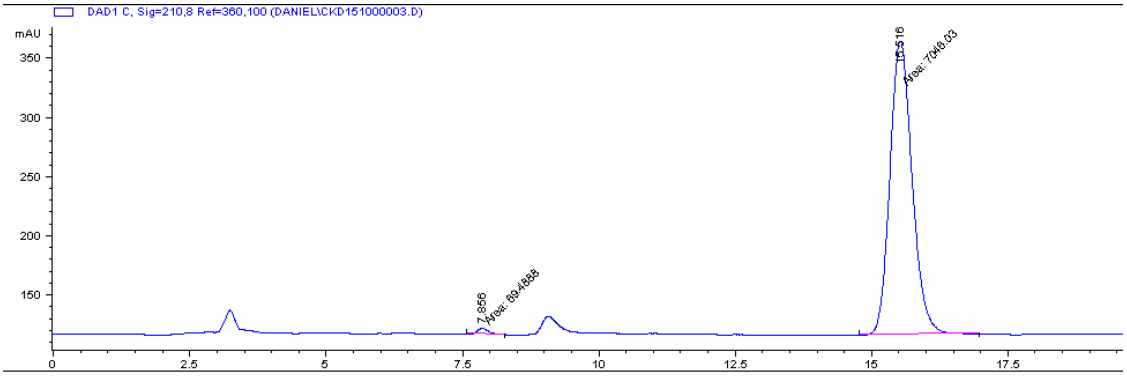




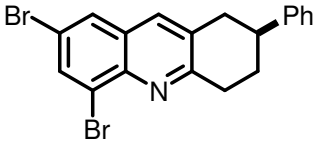
HPLC profiles of 3.40

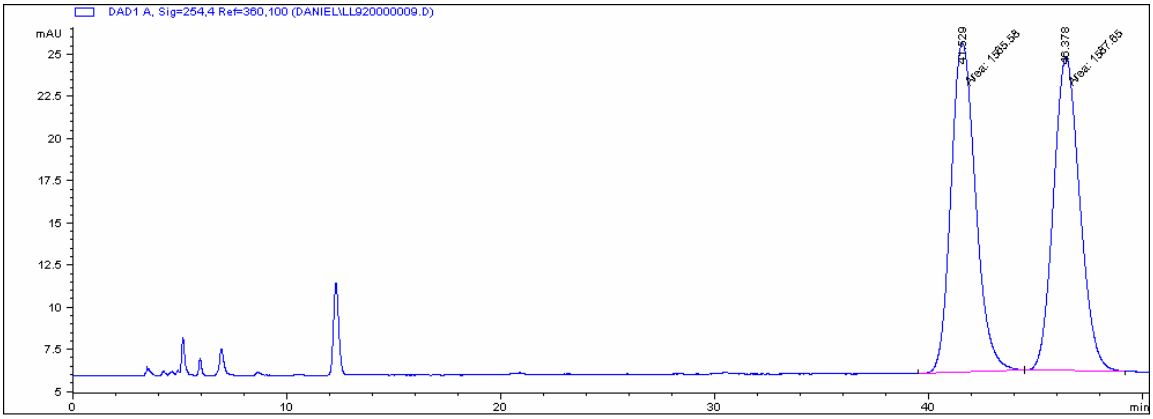


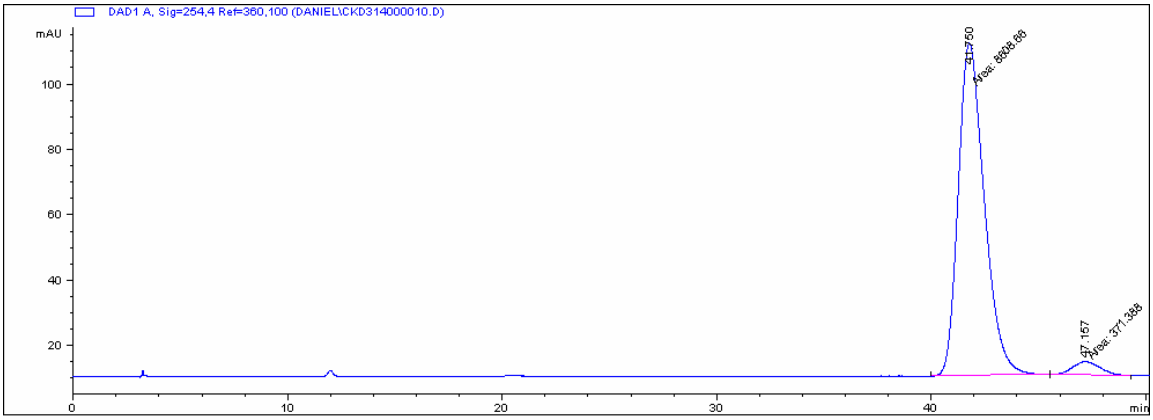




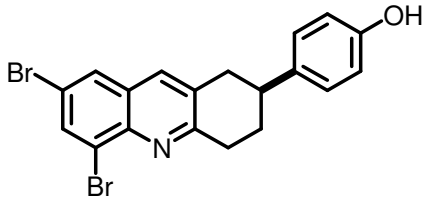
HPLC profile of 4.25a

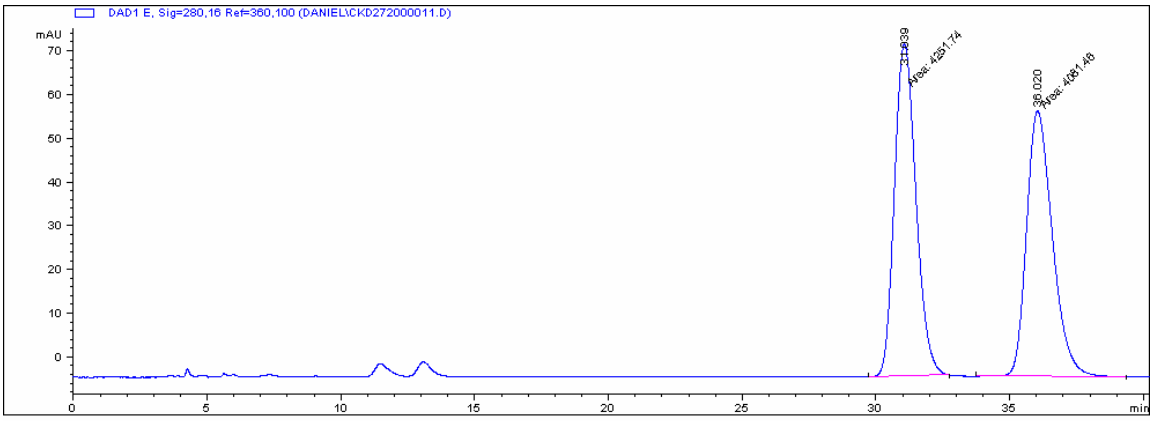


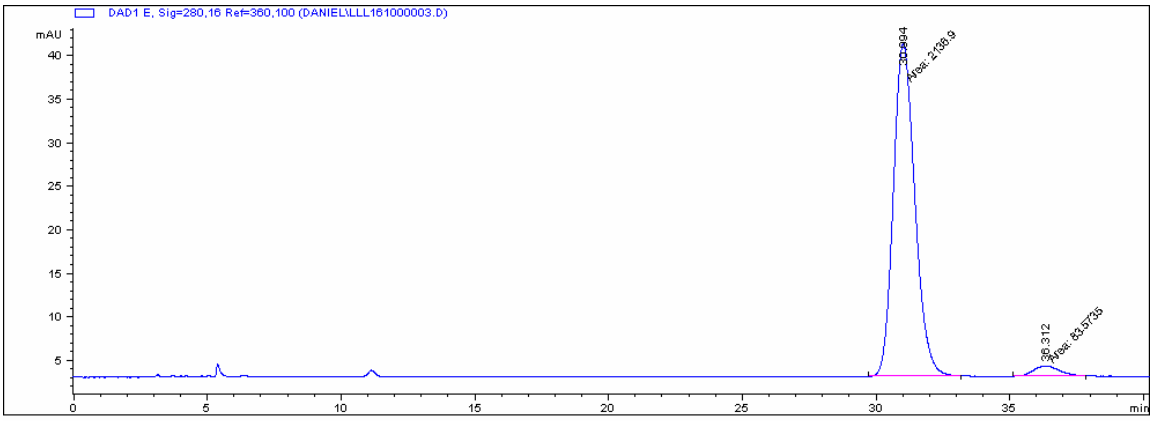




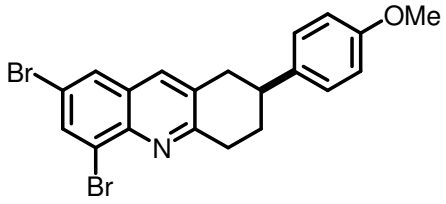
HPLC profile of 4.25b

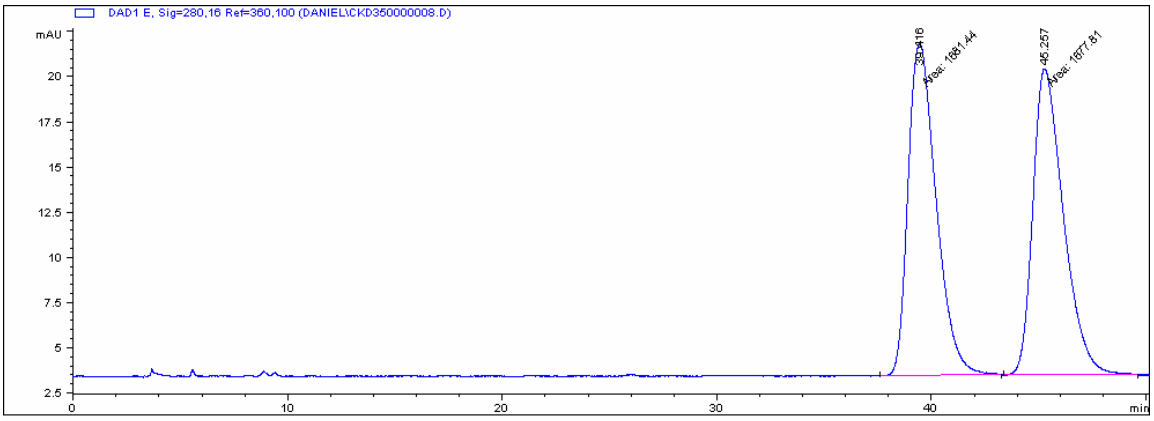


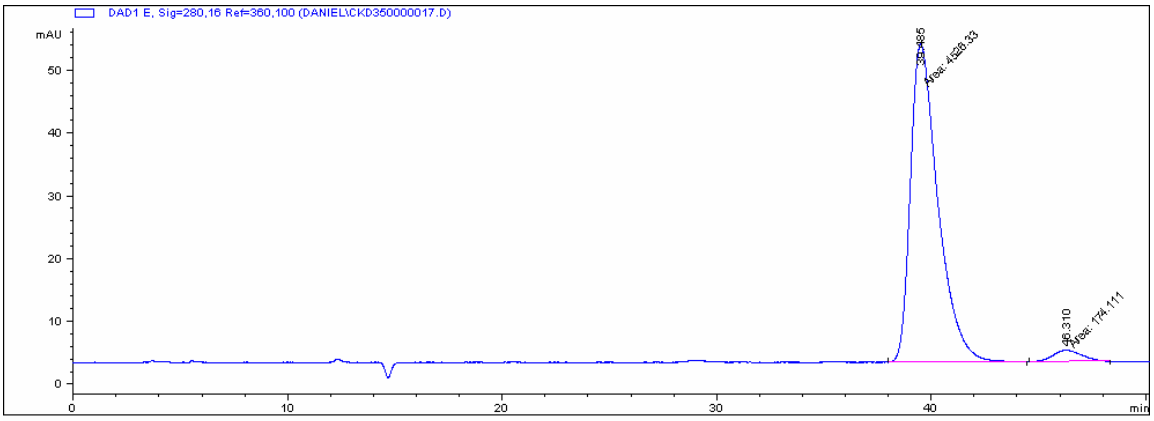




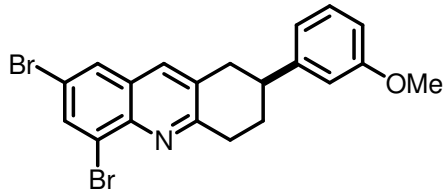
HPLC profile of 4.25c

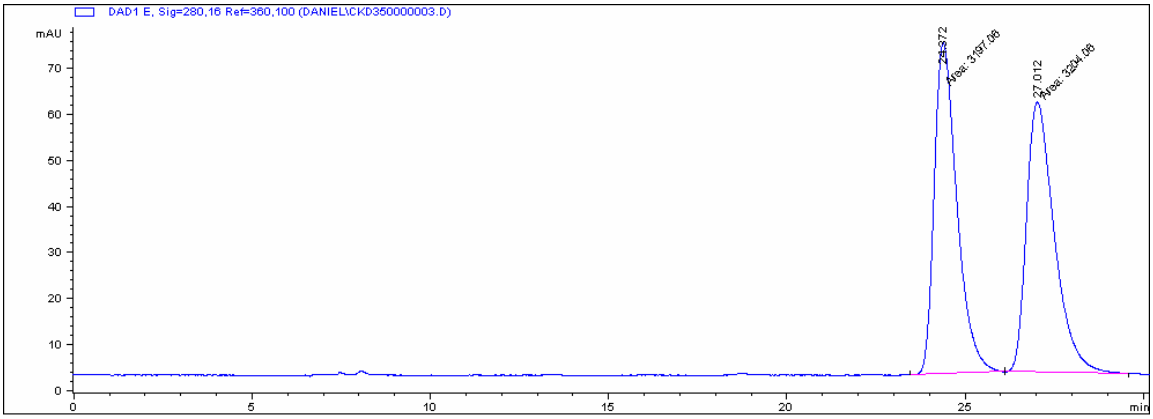


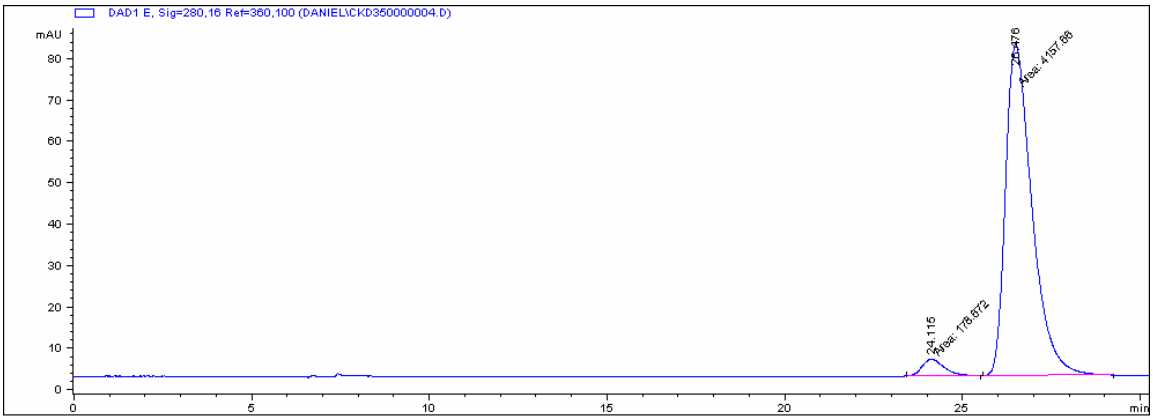




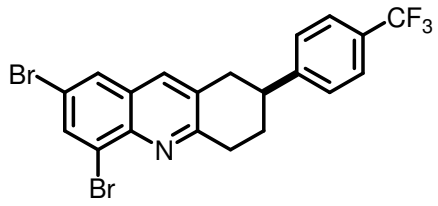
HPLC profile of 4.25d

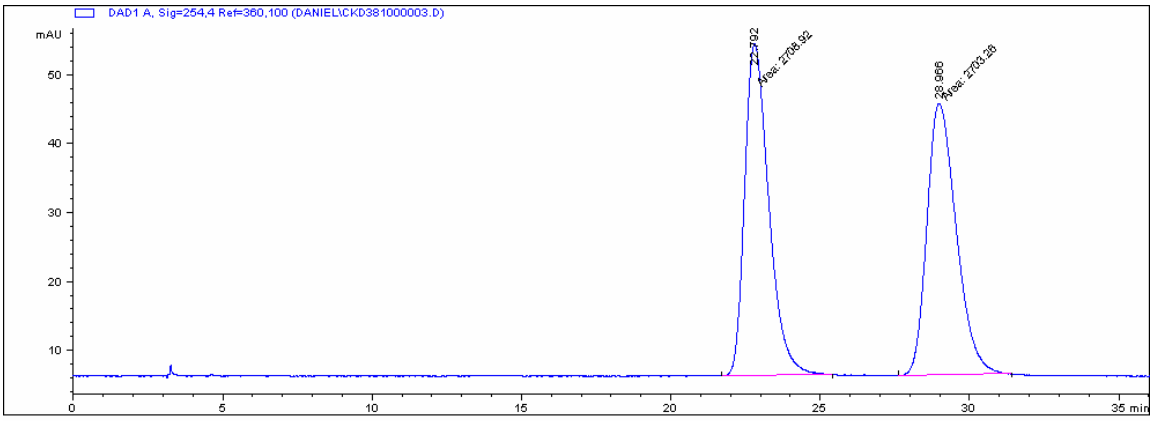


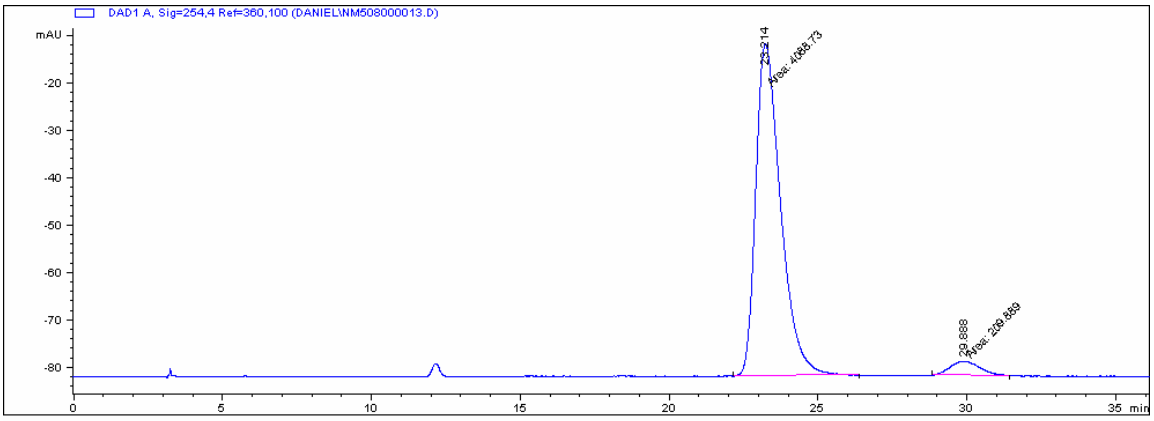




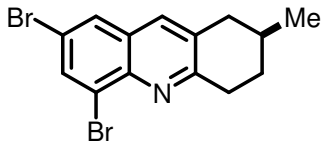
HPLC profile of 4.25e

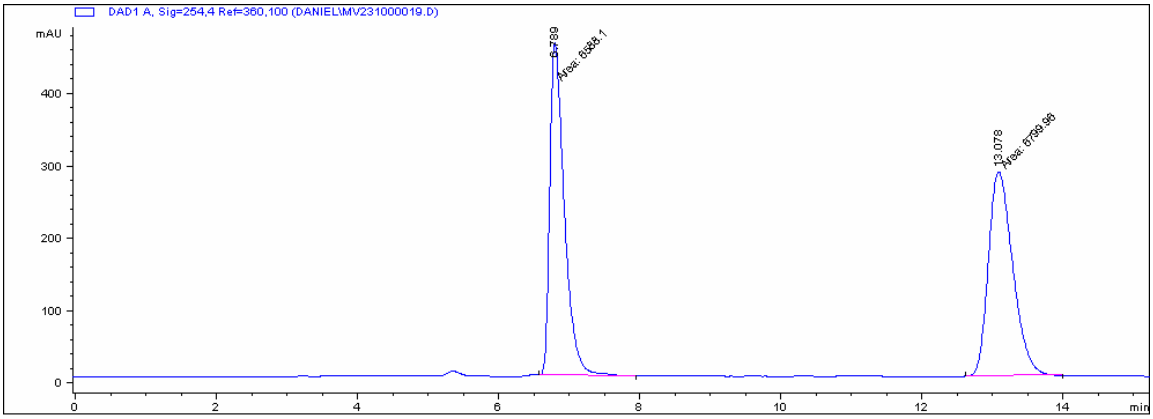


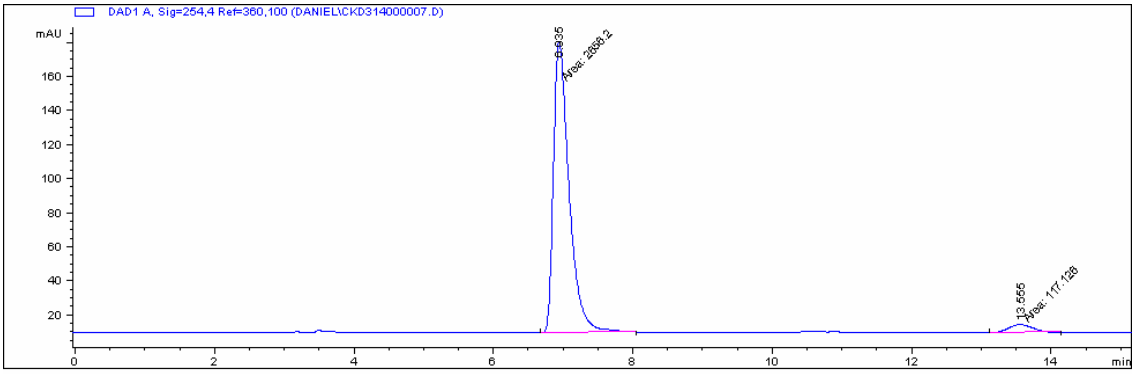




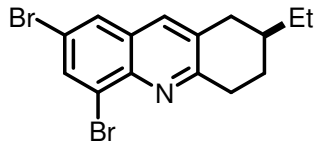
HPLC profile of 4.25f

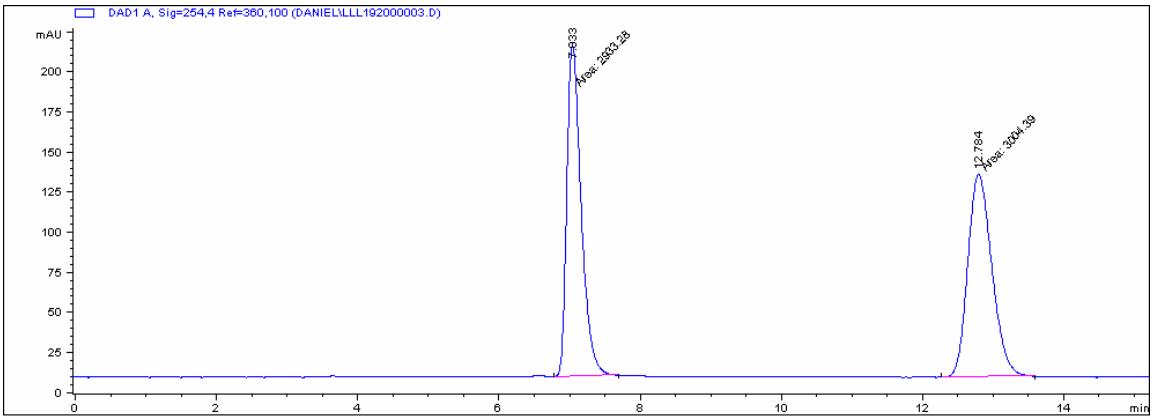


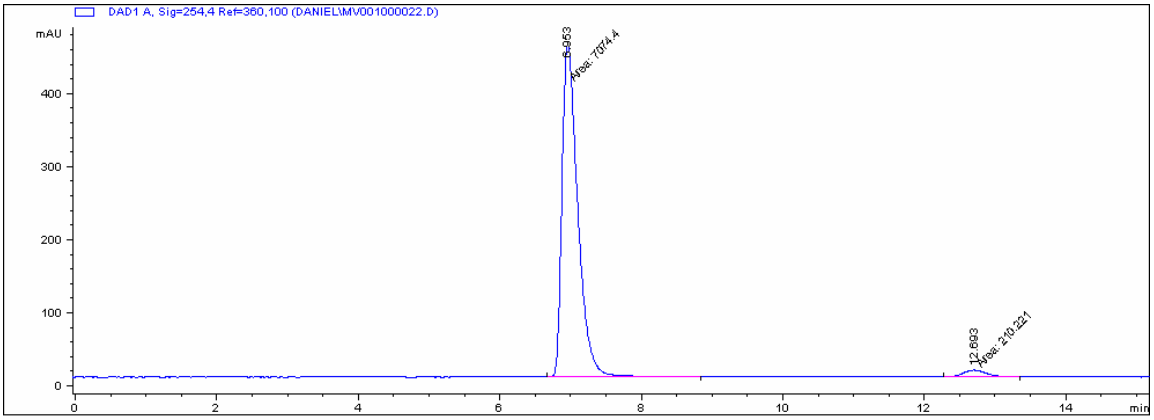




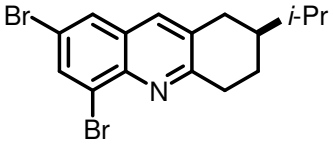
HPLC profile of 4.25g

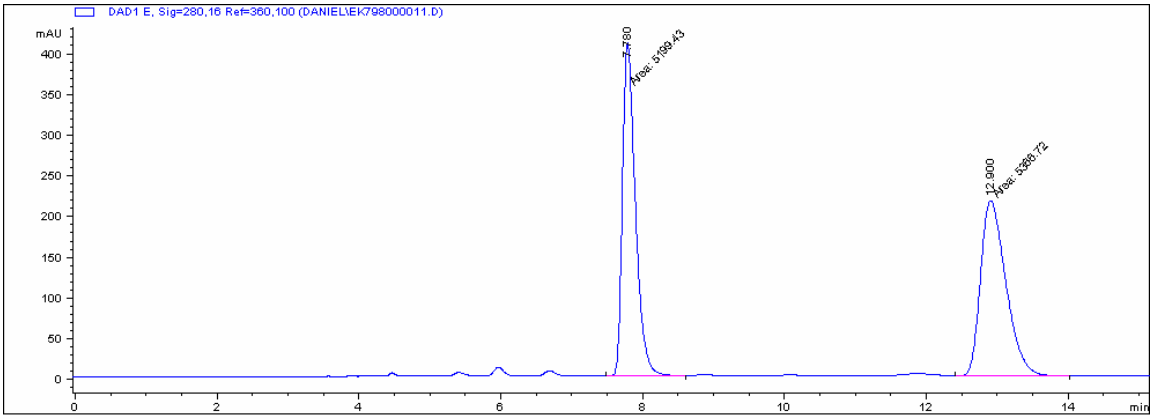


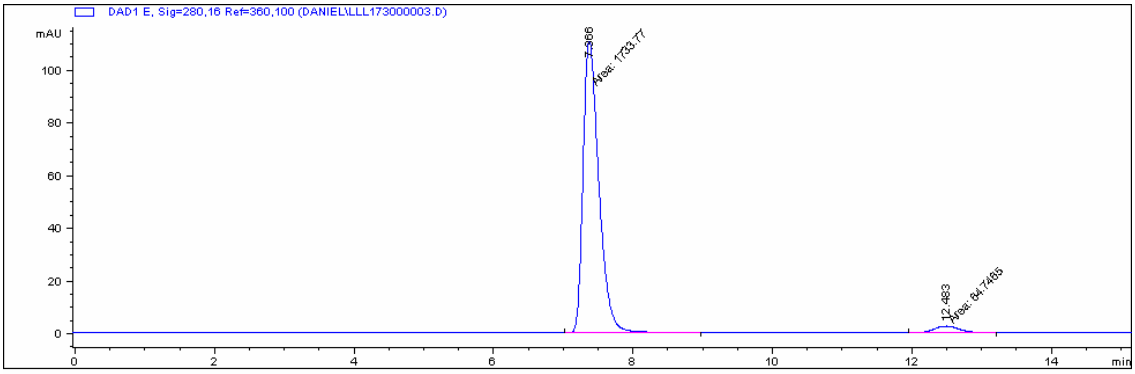




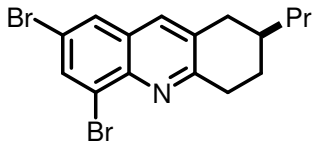
HPLC profile of 4.25h

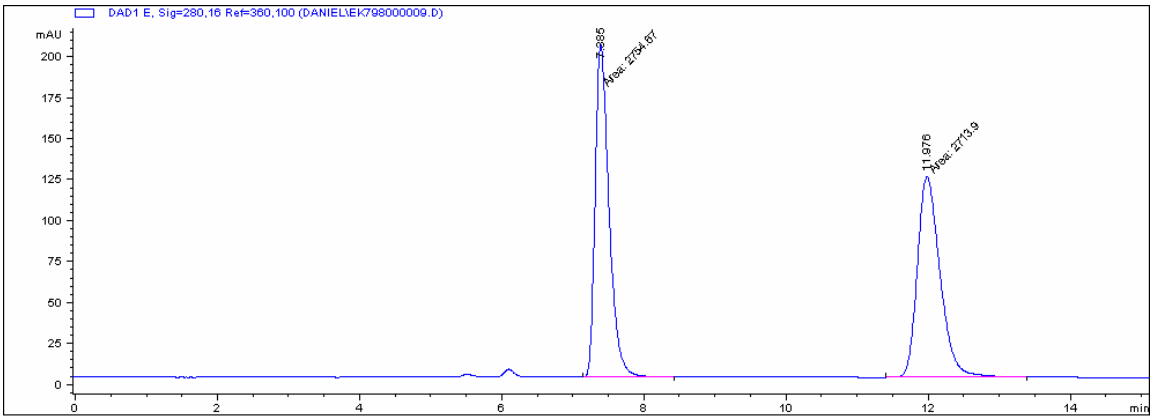


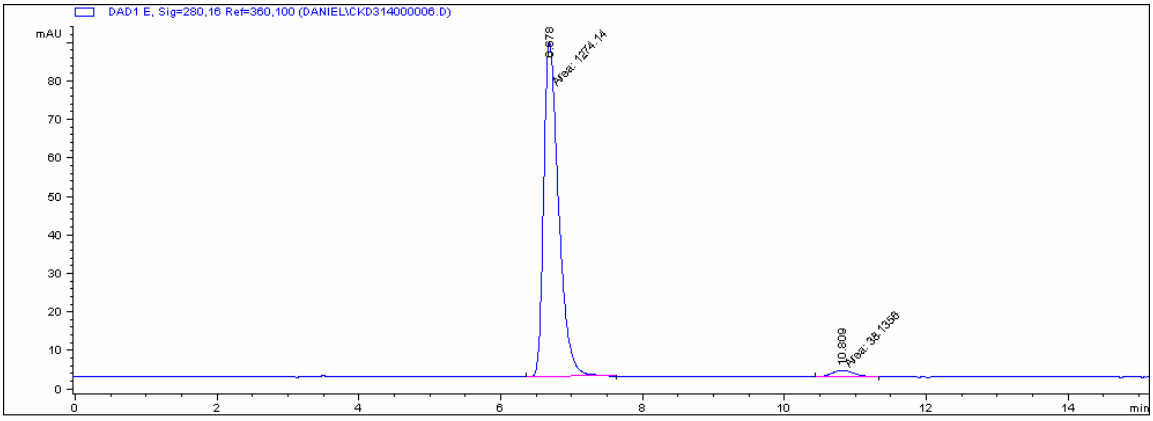




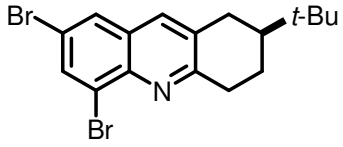
HPLC profile of 4.25i

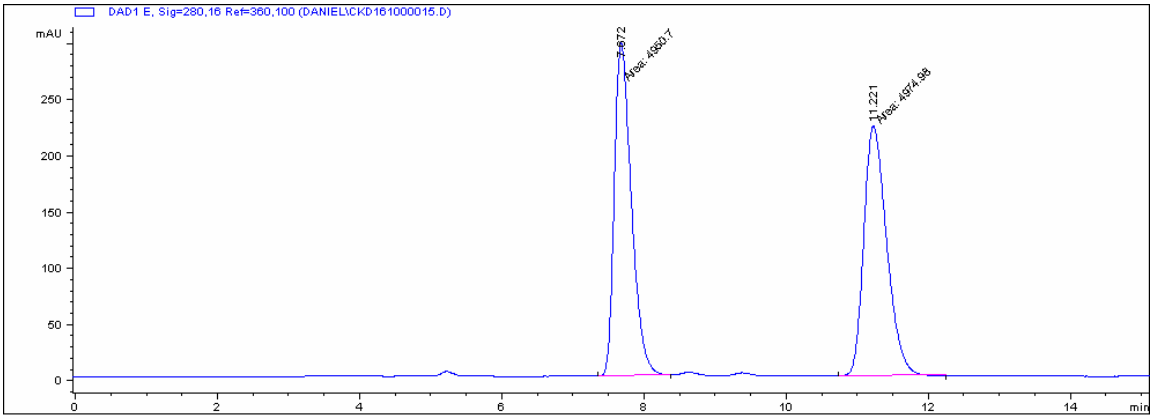


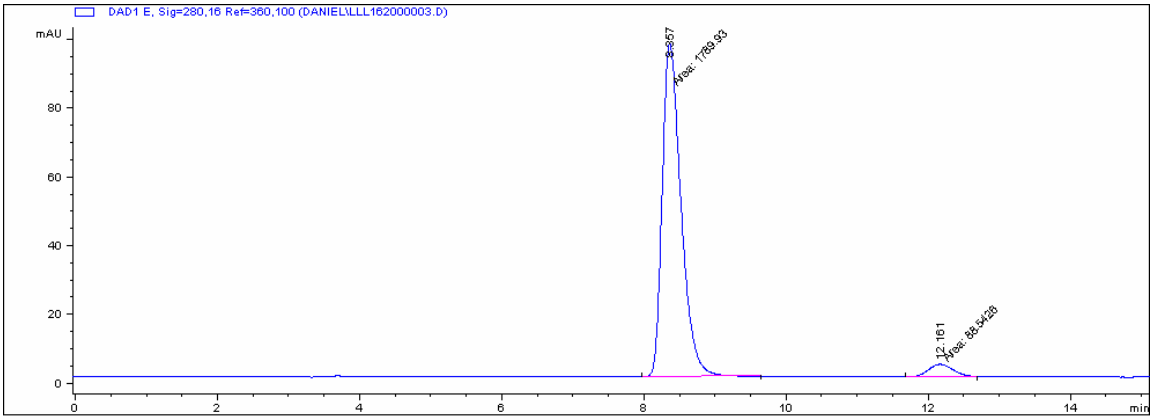




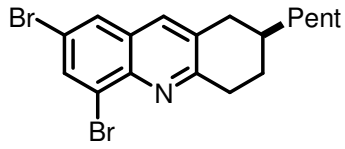
HPLC profile of 4.25j

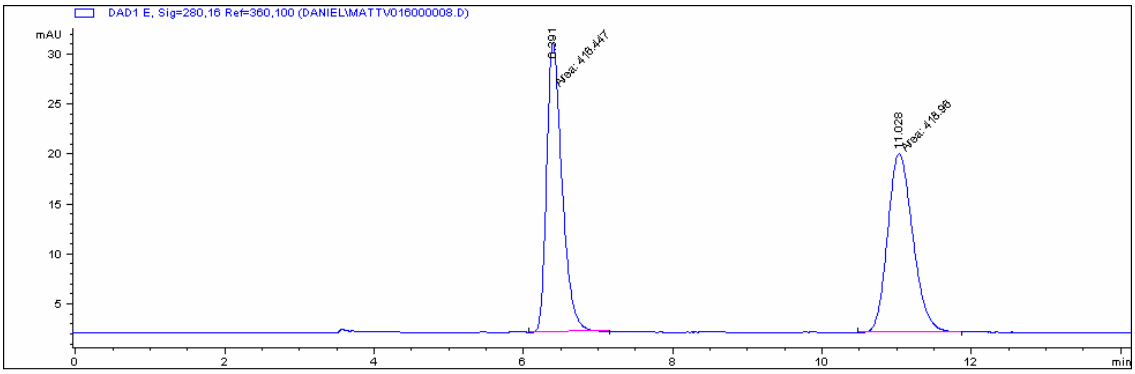


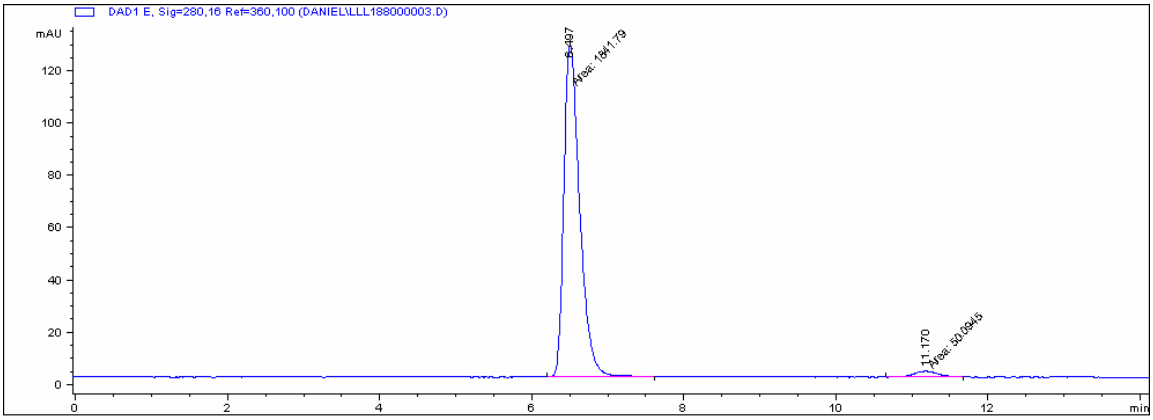




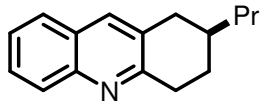
HPLC profile of 4.25k

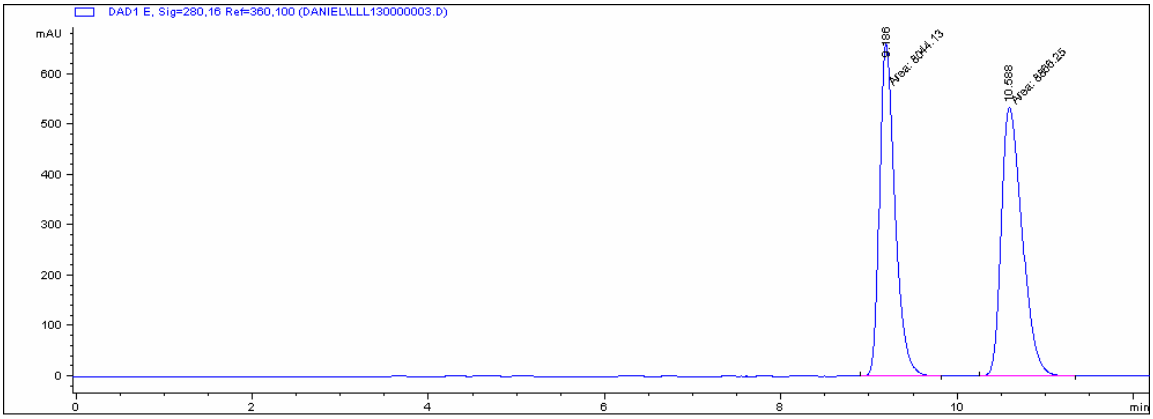


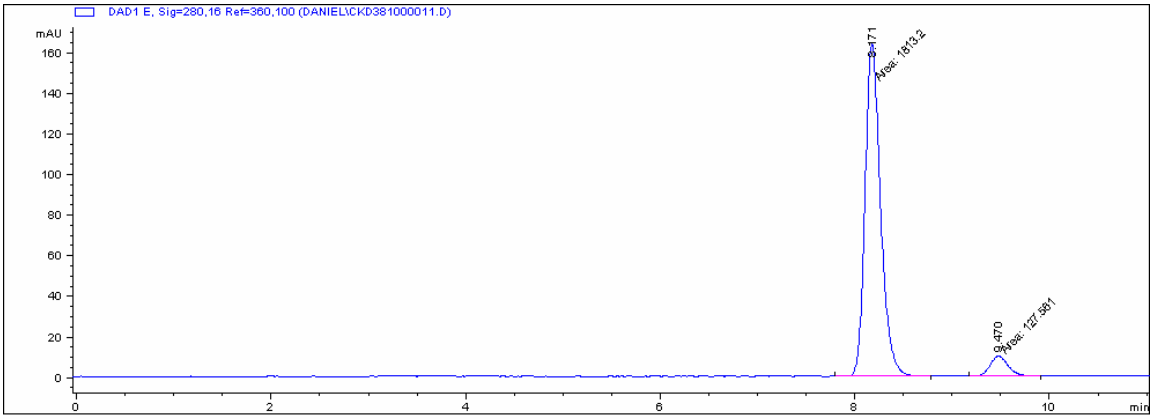




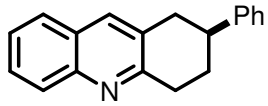
HPLC profile of 4.45a

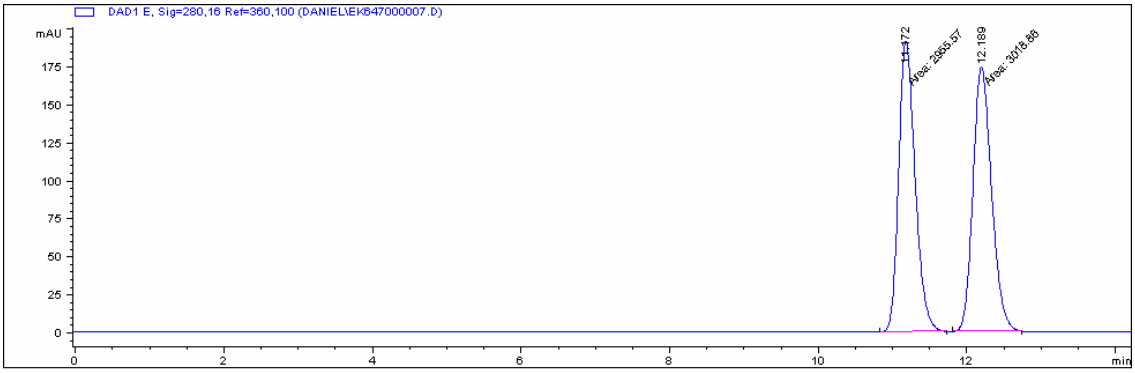


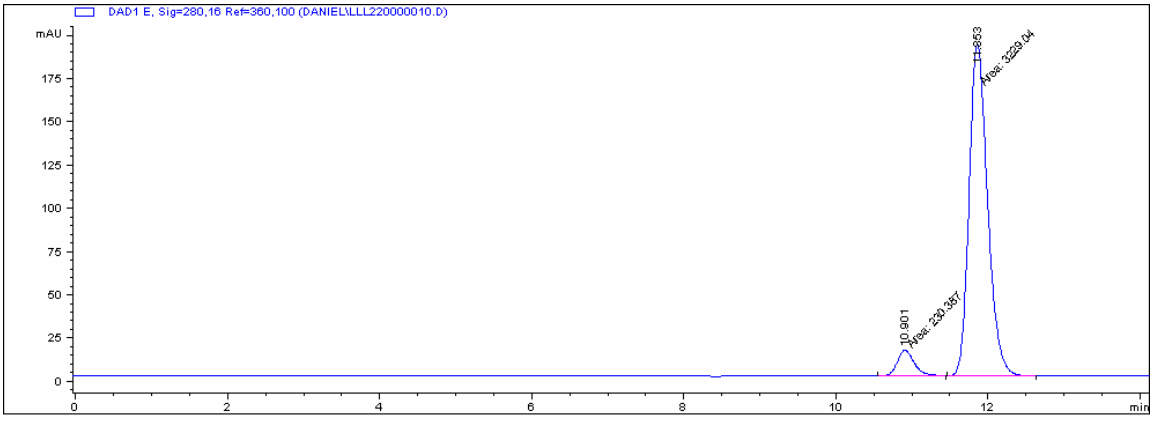




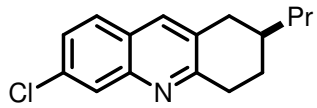
HPLC profile of 4.45b

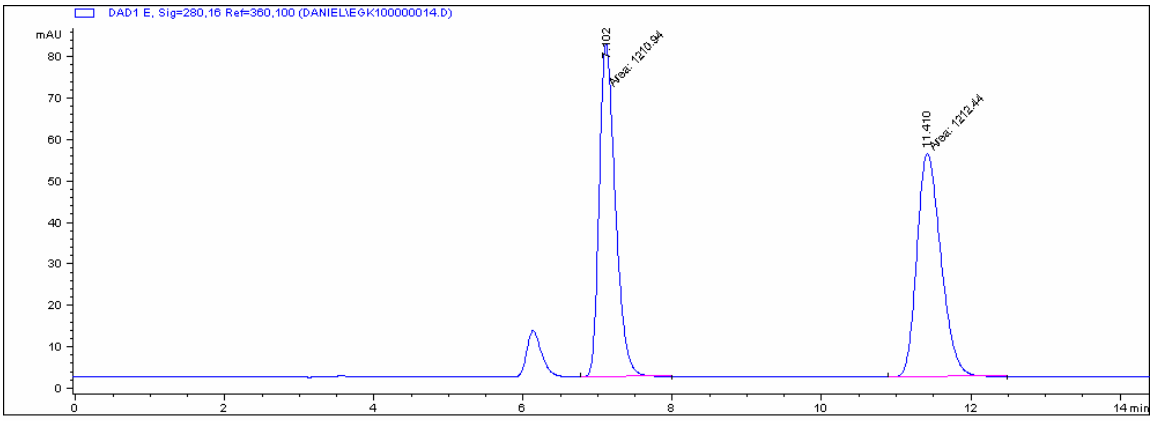


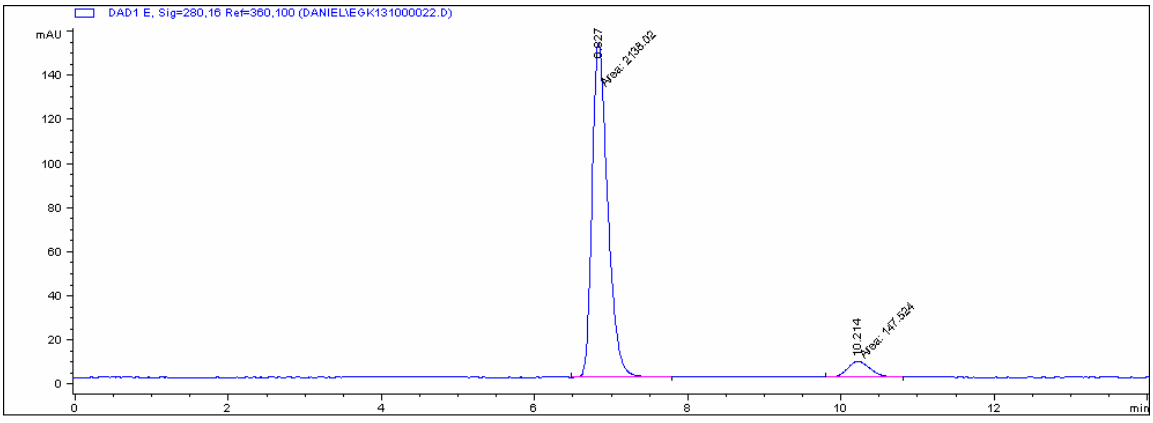




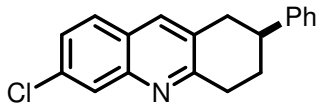
HPLC profile of 4.45c

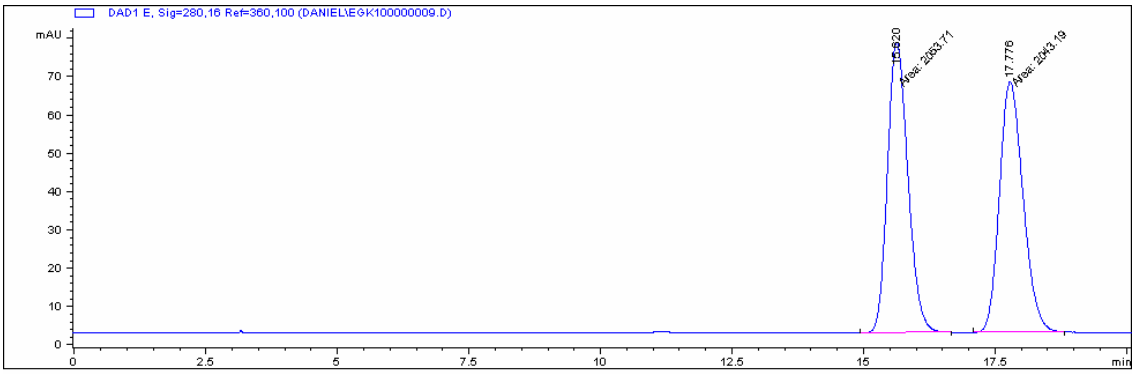


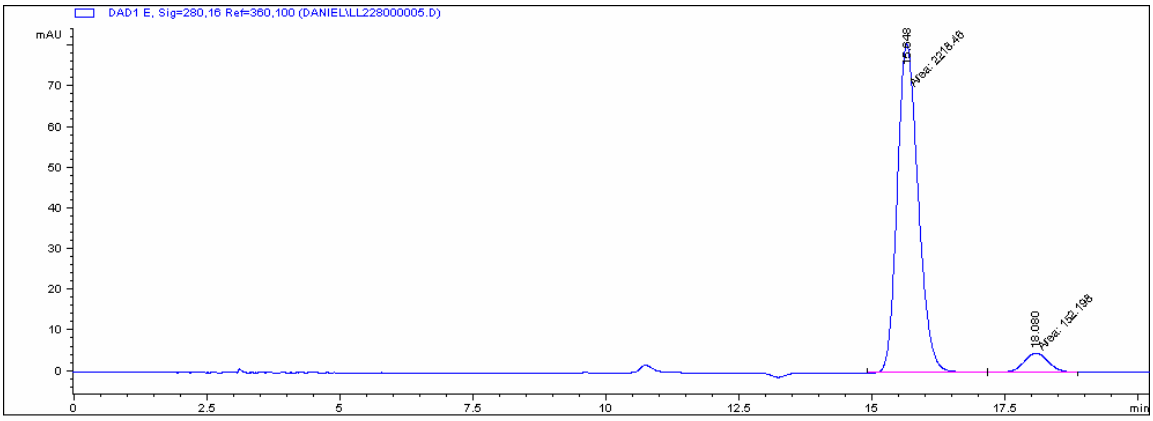




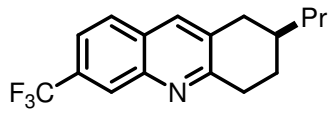
HPLC profile of 4.45d

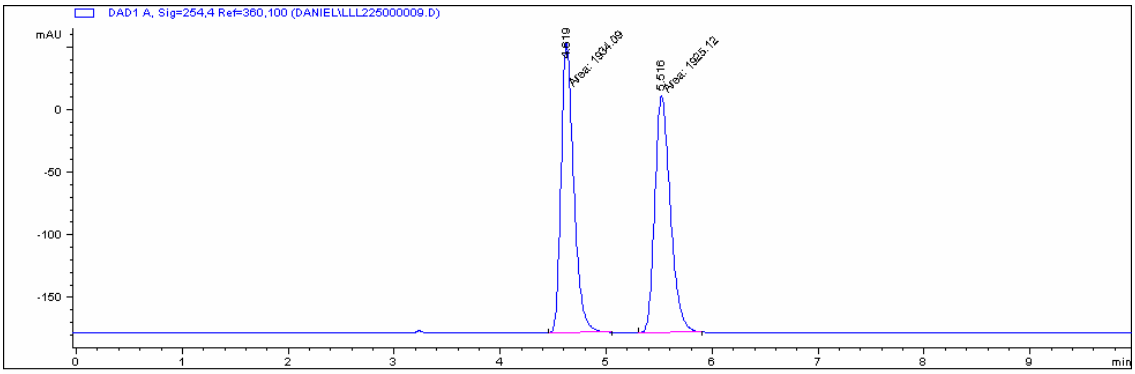


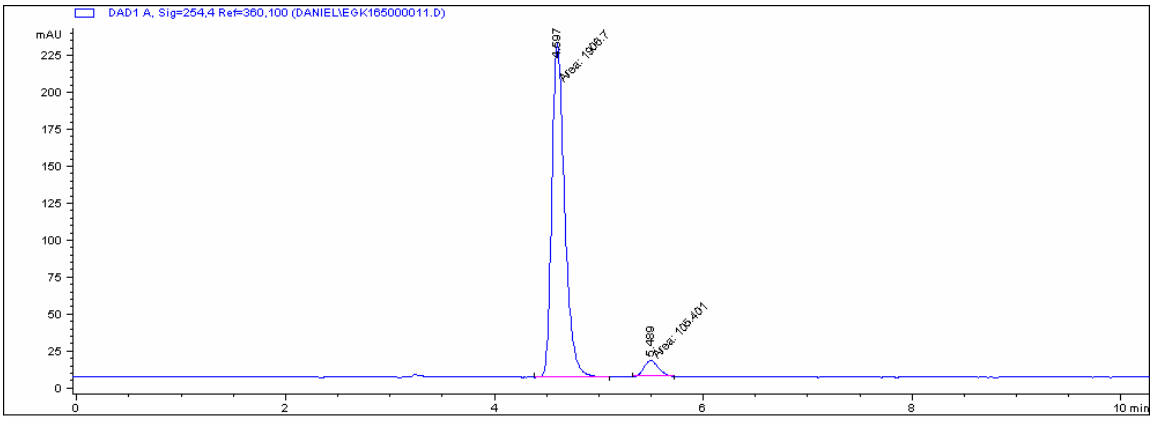




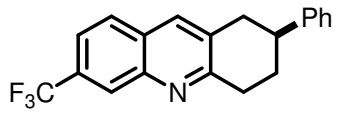
HPLC profile of 4.45e

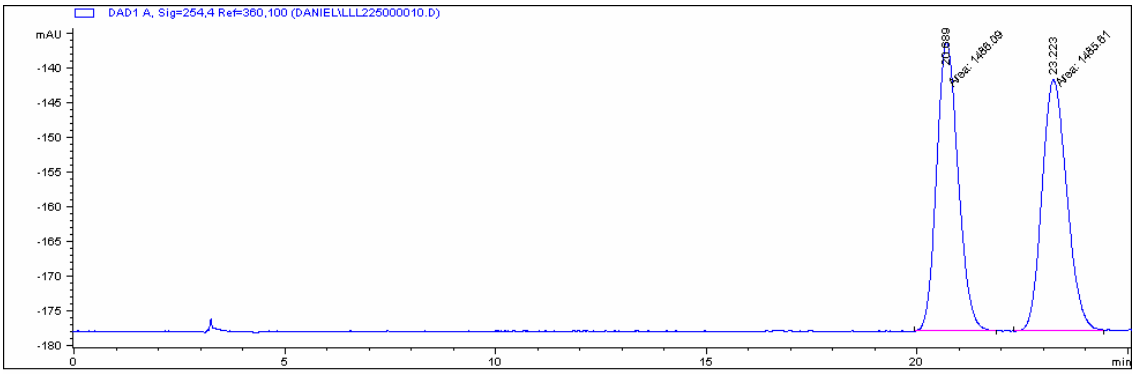


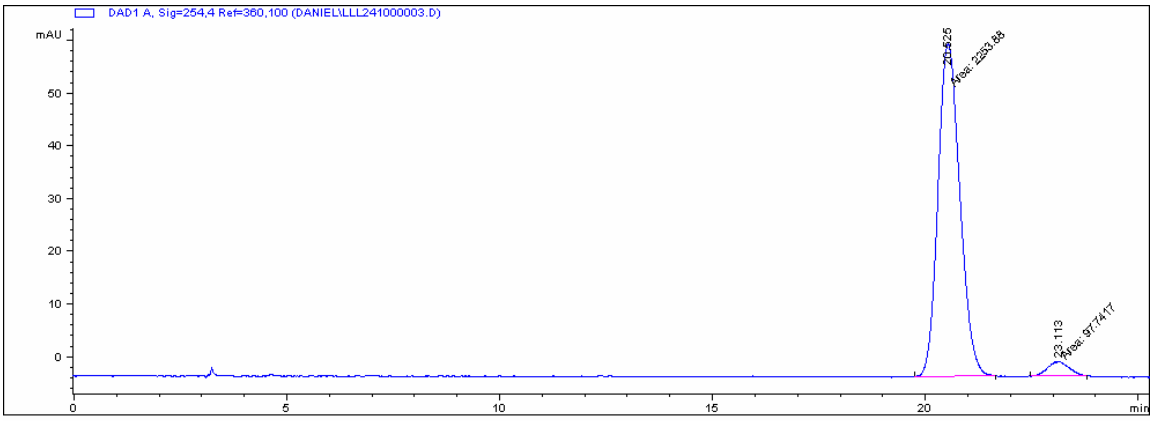




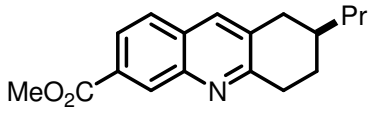
HPLC profile of 4.45f

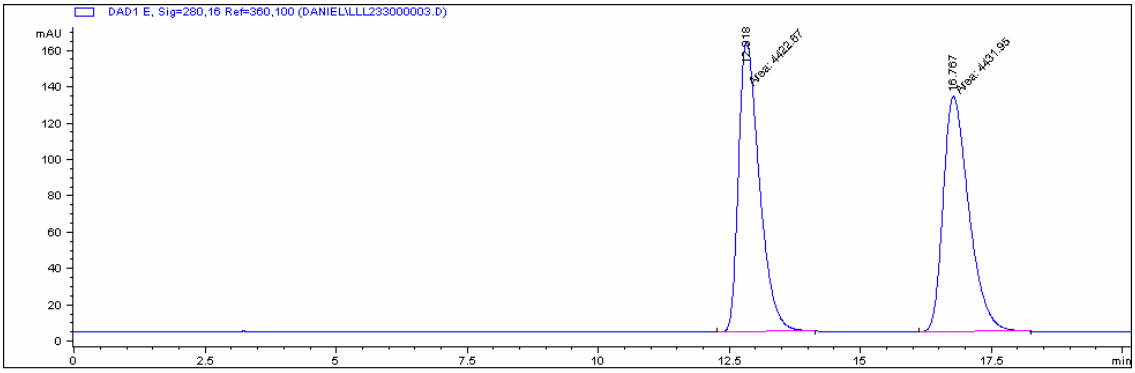


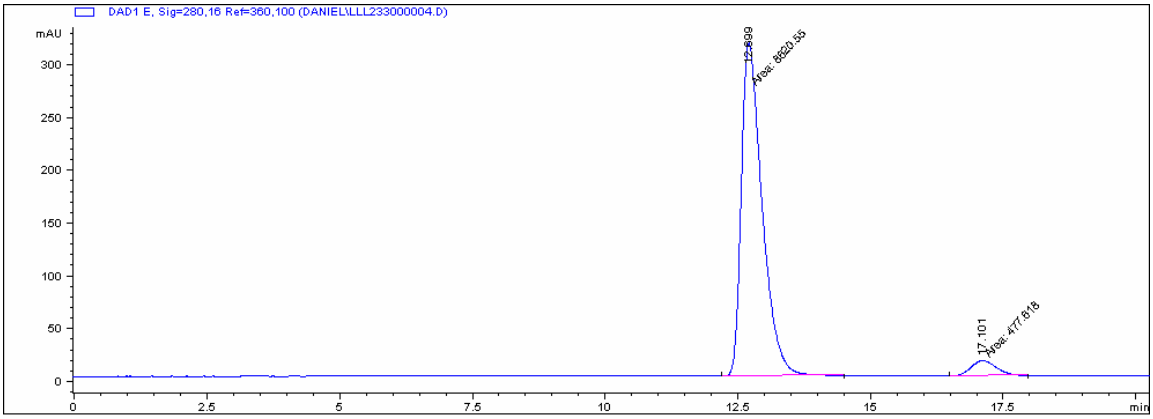




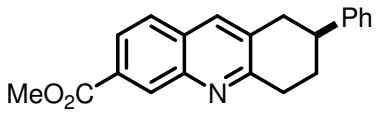
HPLC profile of 4.45g

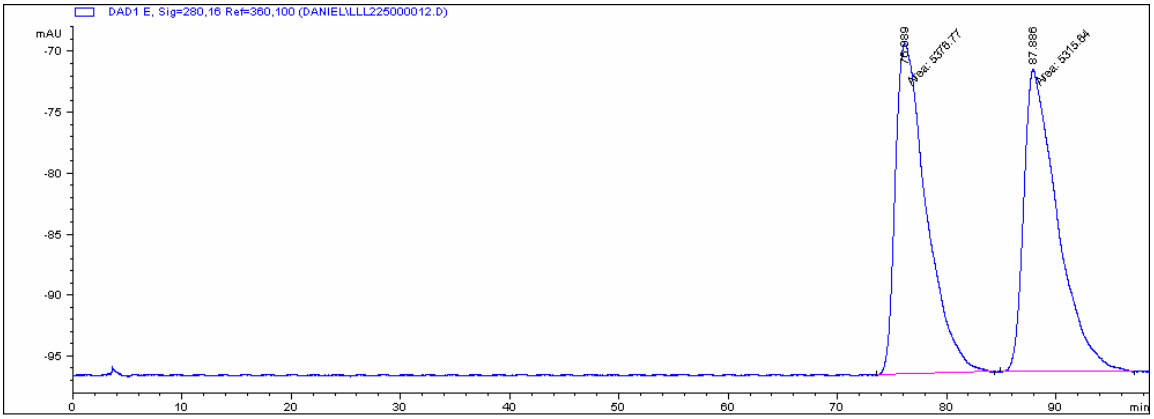


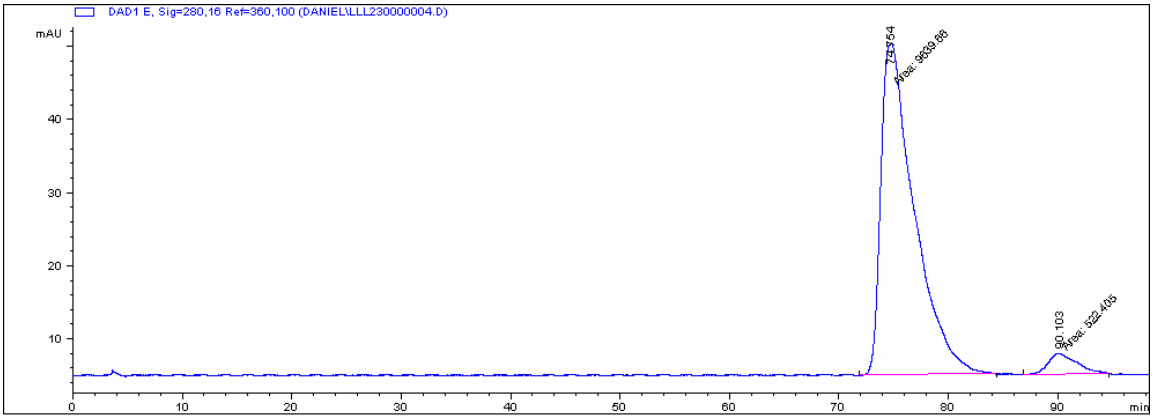




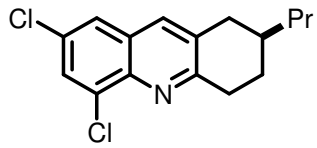
HPLC profile of 4.45h

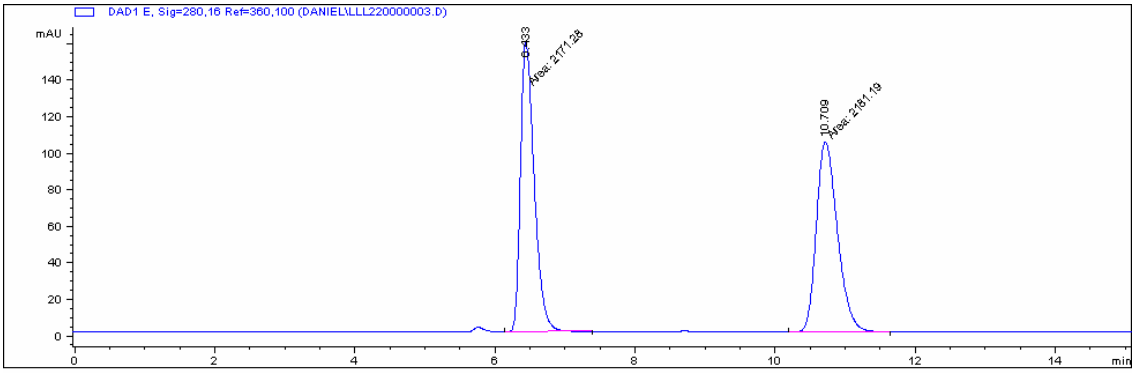


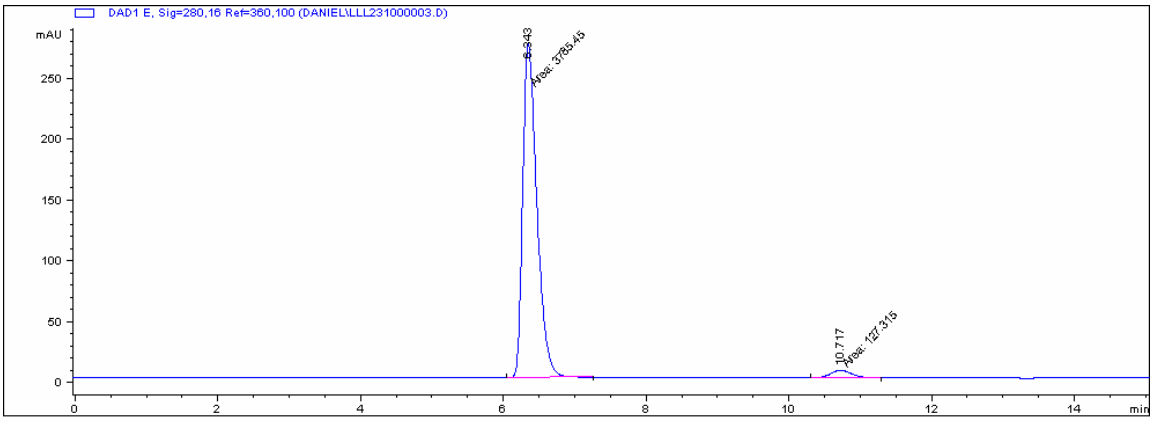




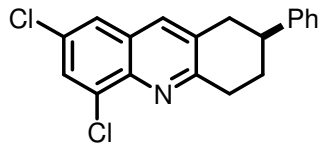
HPLC profile of 4.45i

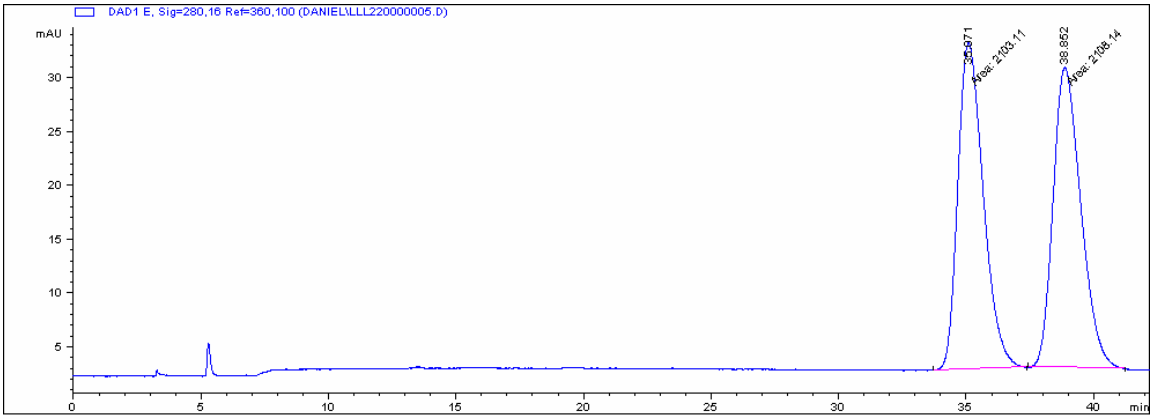


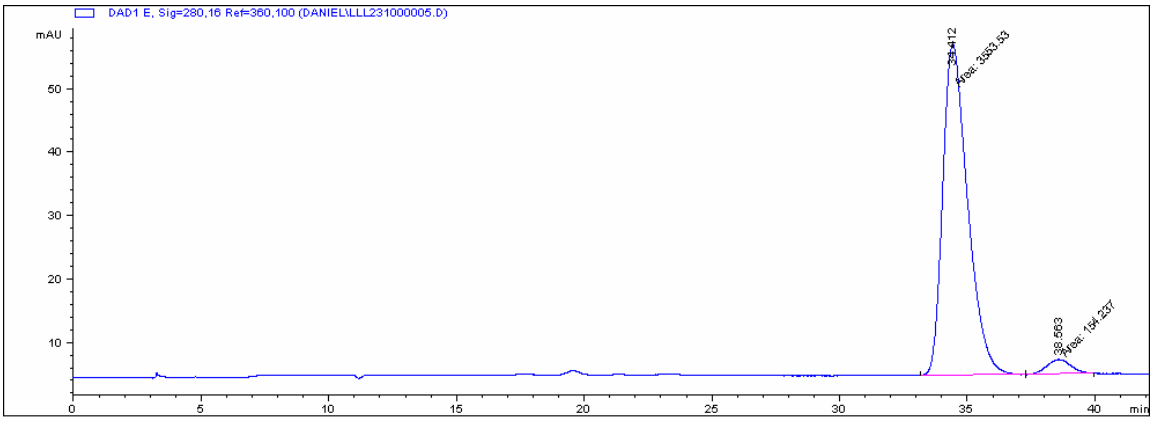




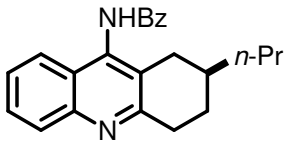
HPLC profile of 4.45j

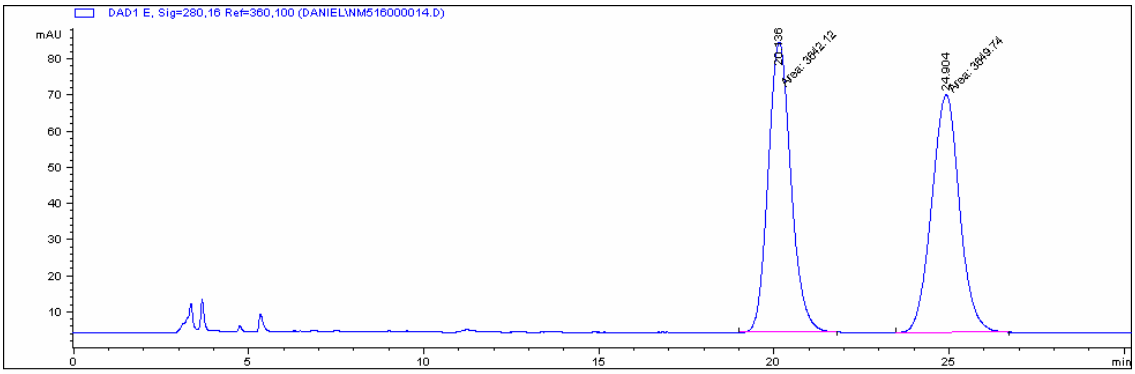


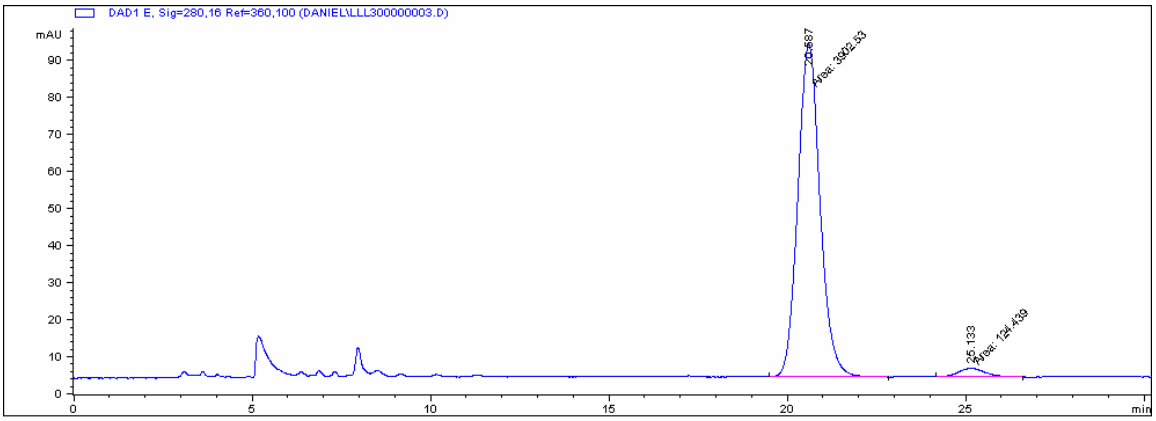


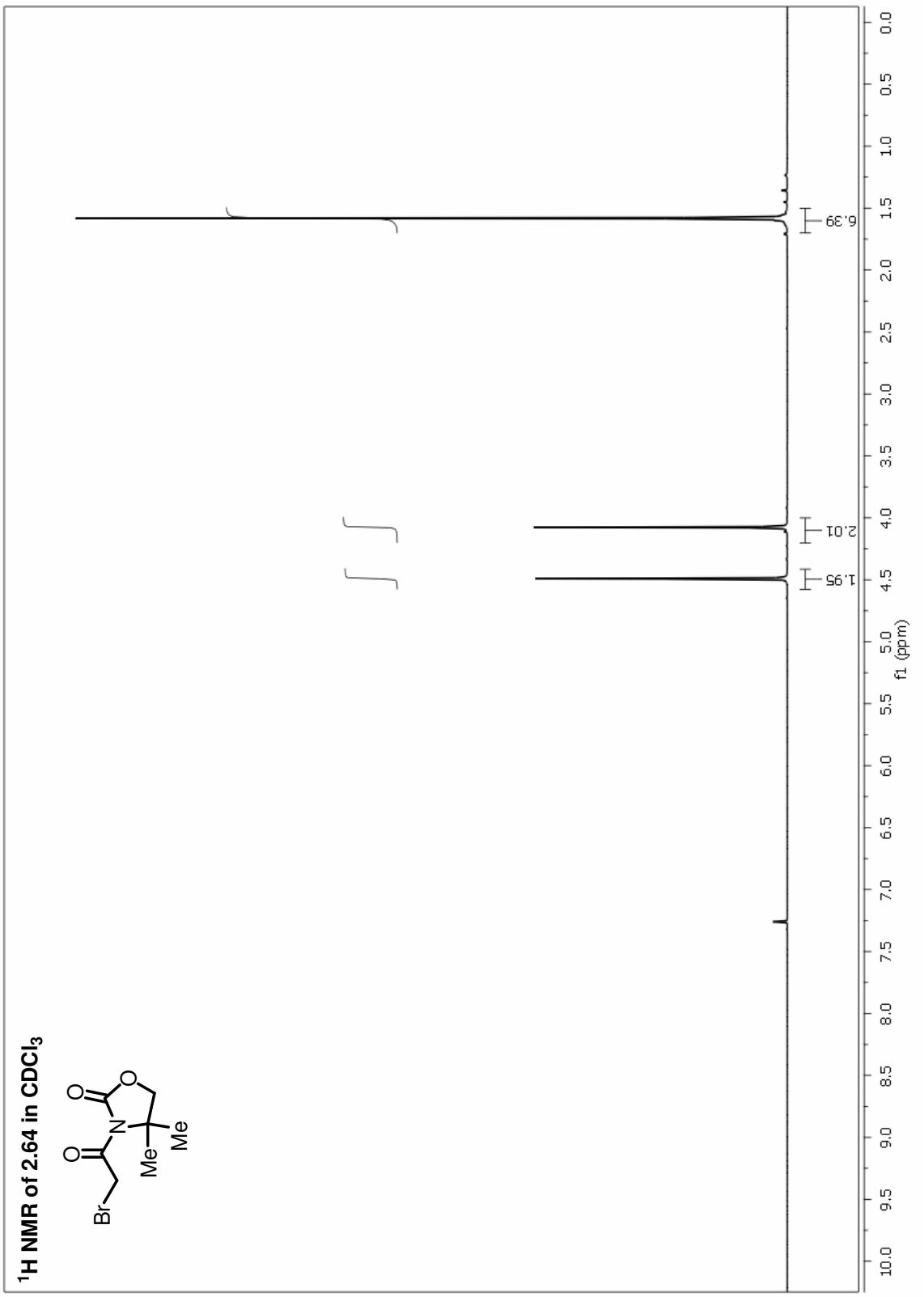


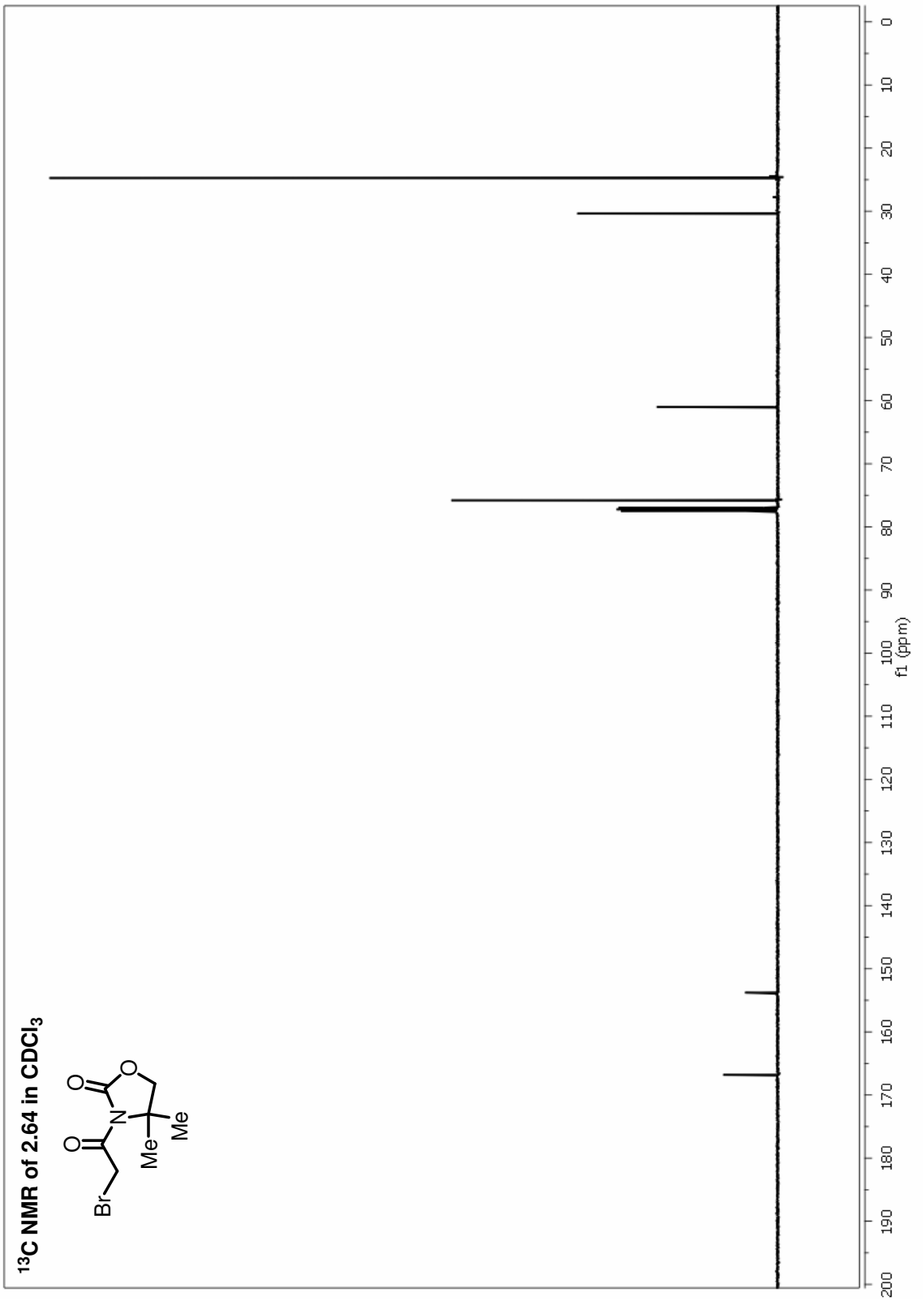
HPLC profile of 4.52

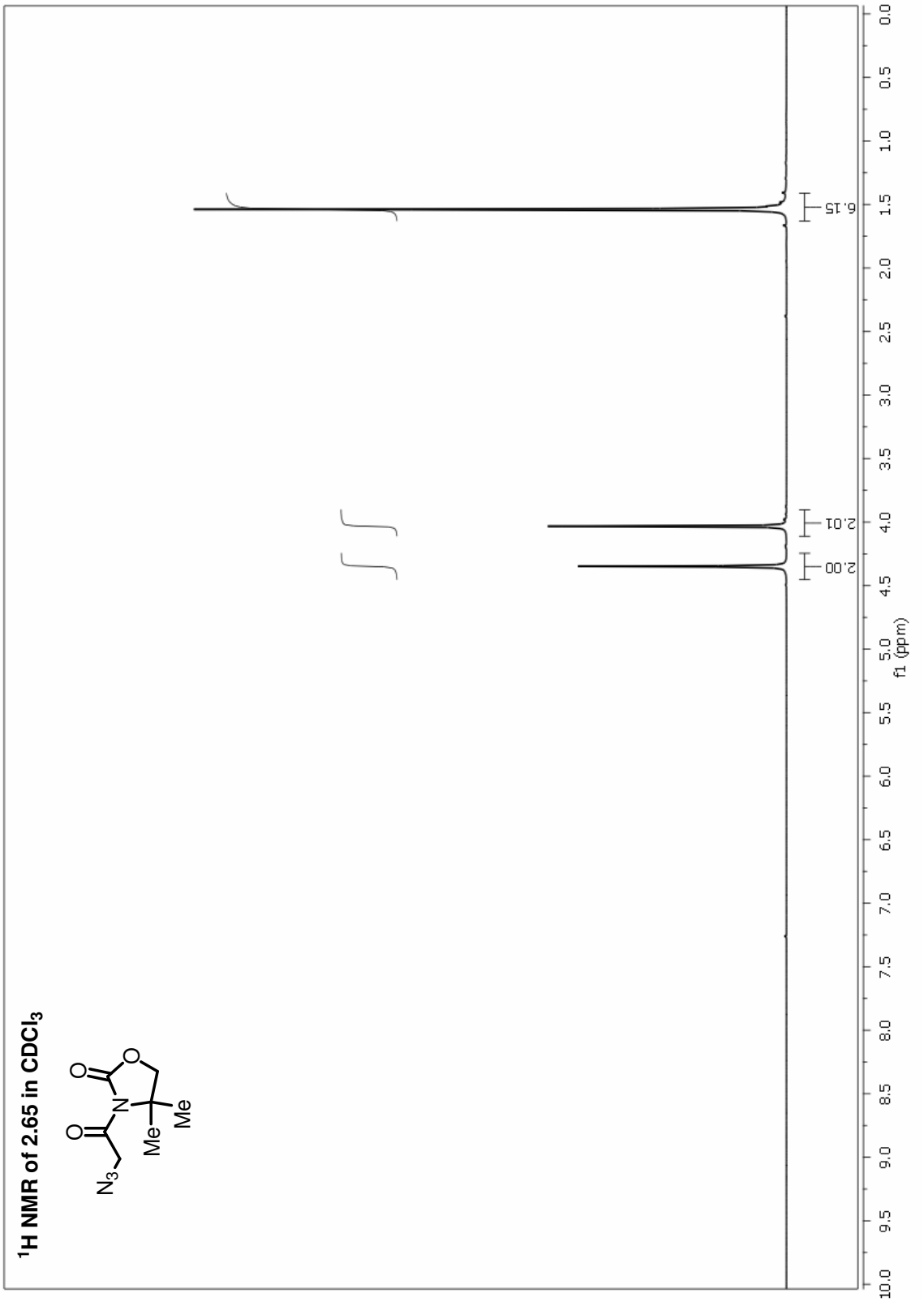


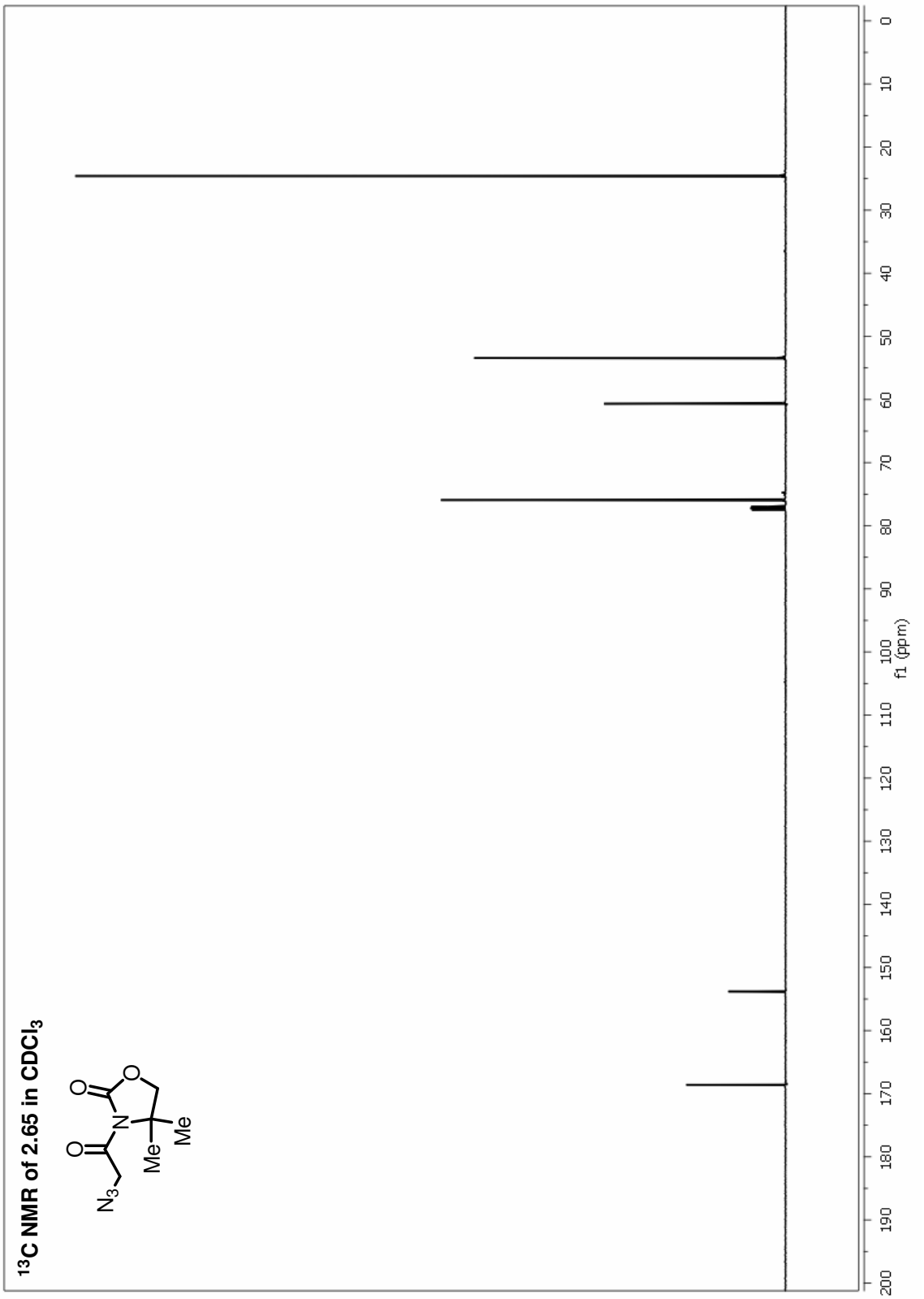


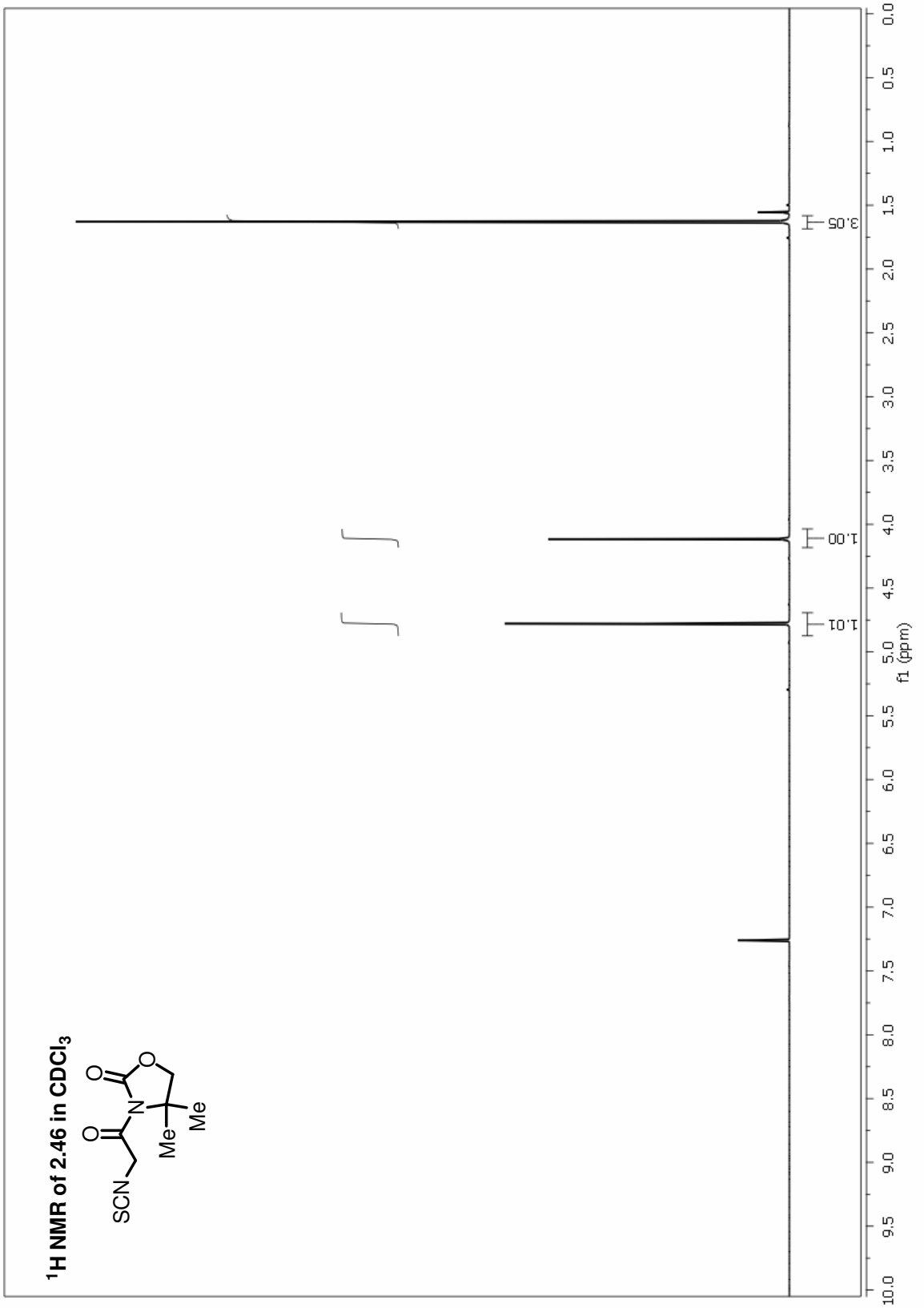


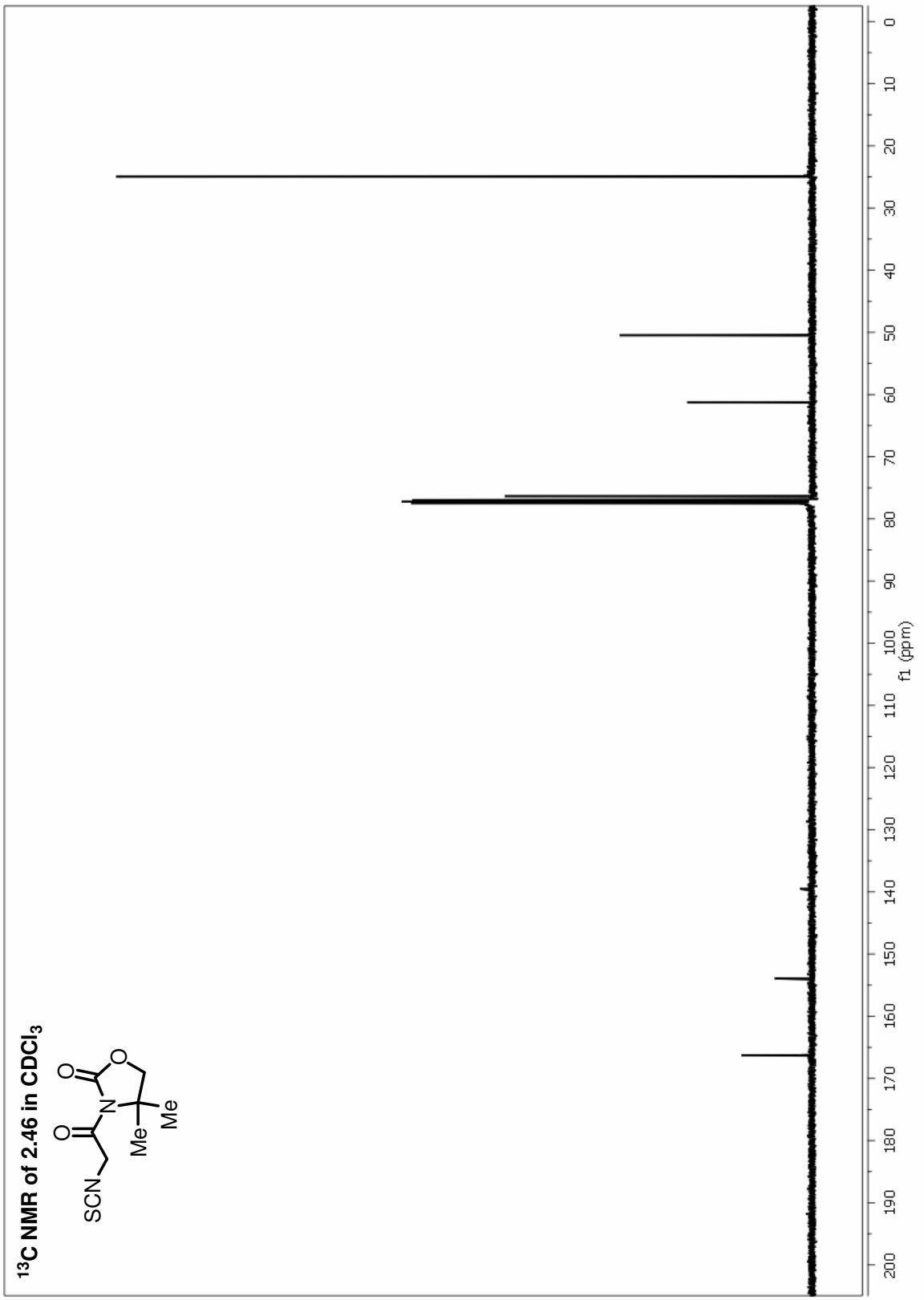

^{1}H NMR of 2.64 in $CDCl_3$
Br
O
O
N
O
Me
Me
6.39
2.01
1.95
f1 (ppm)

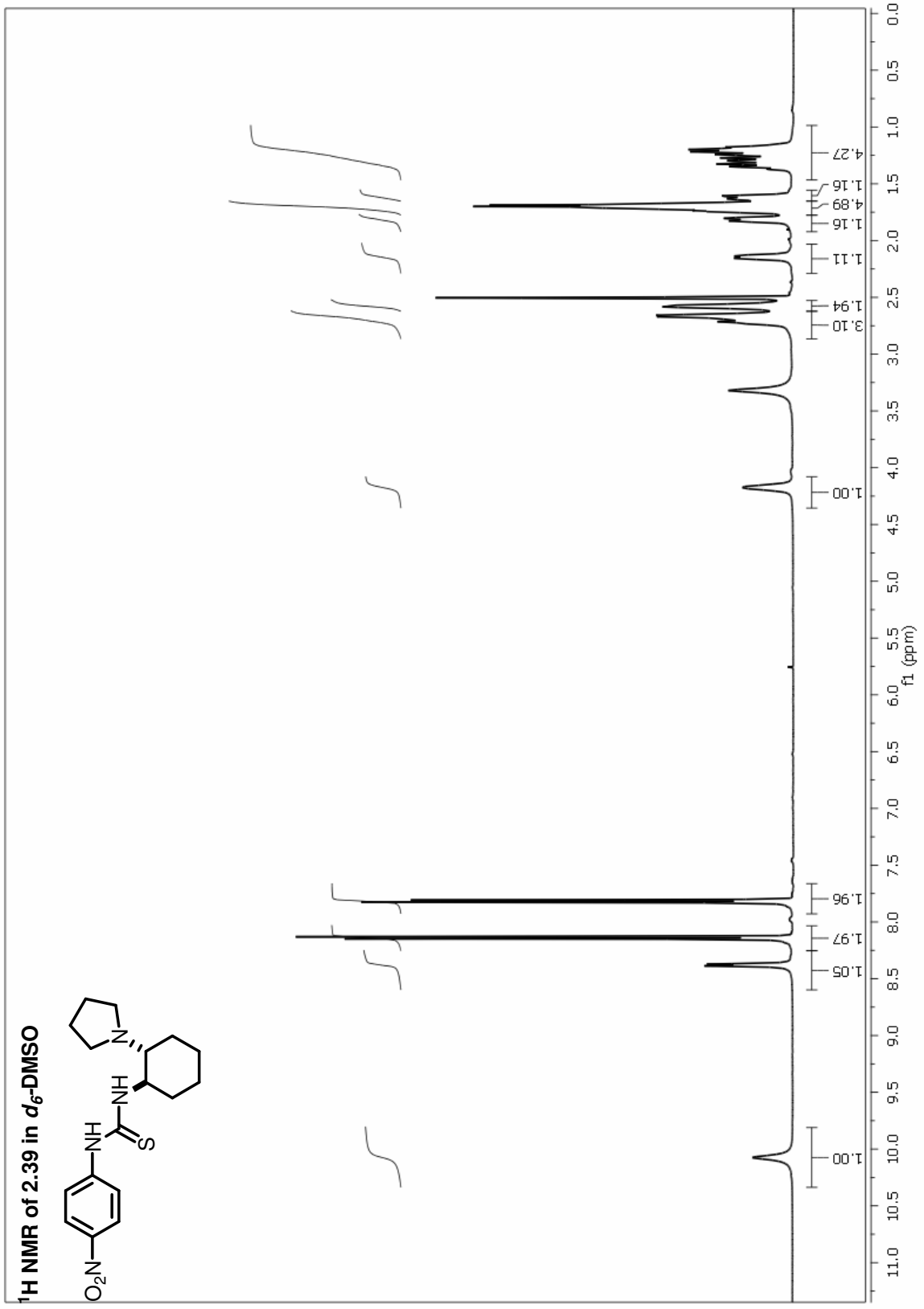

^{13}C NMR of 2.64 in $CDCl_3$
O
O
N
O
Br
Me
Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

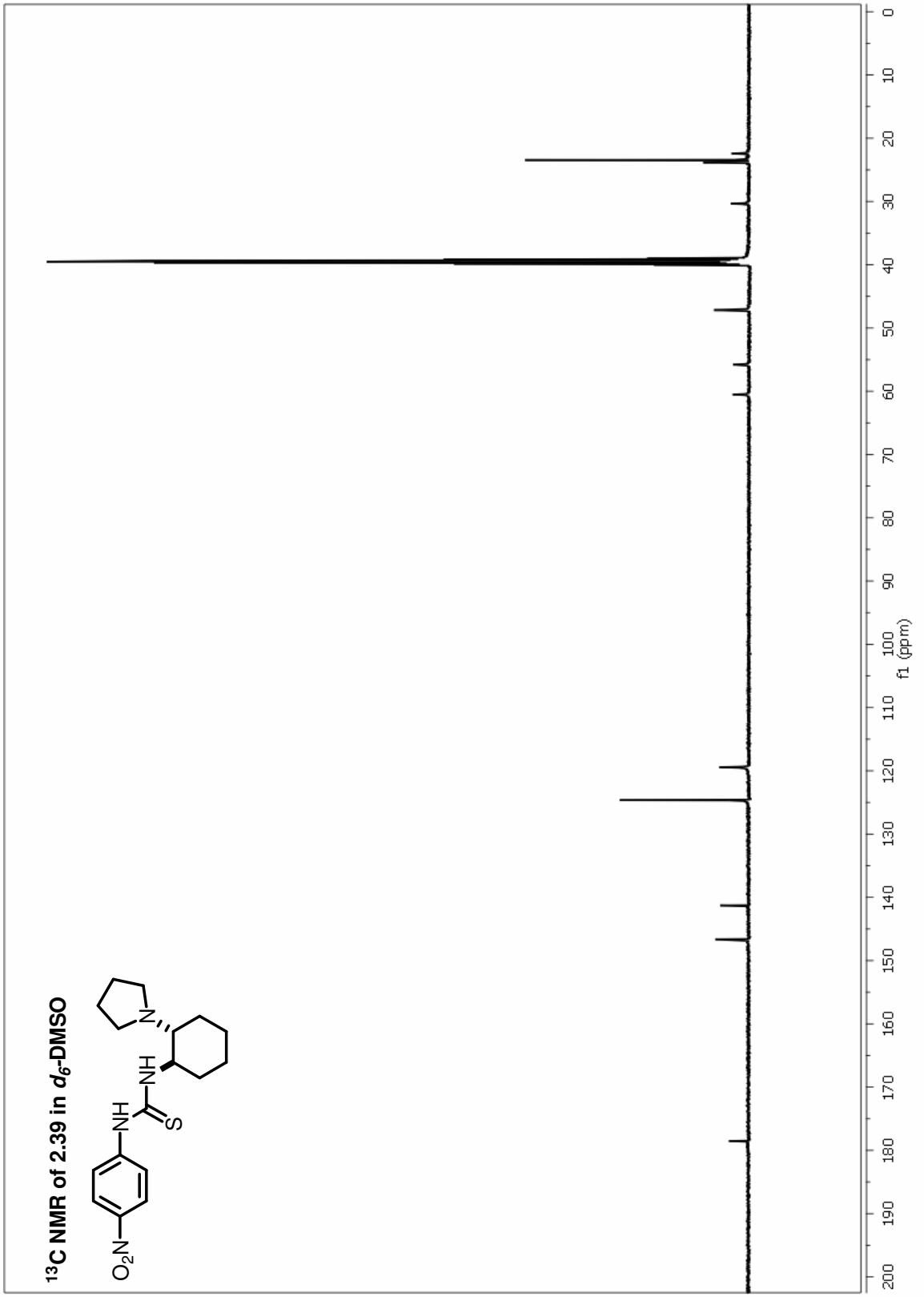

^{1}H NMR of 2.65 in $CDCl_3$
6.15
2.01
2.00
f1 (ppm)
Me
Me
N
O
O
O
N_3

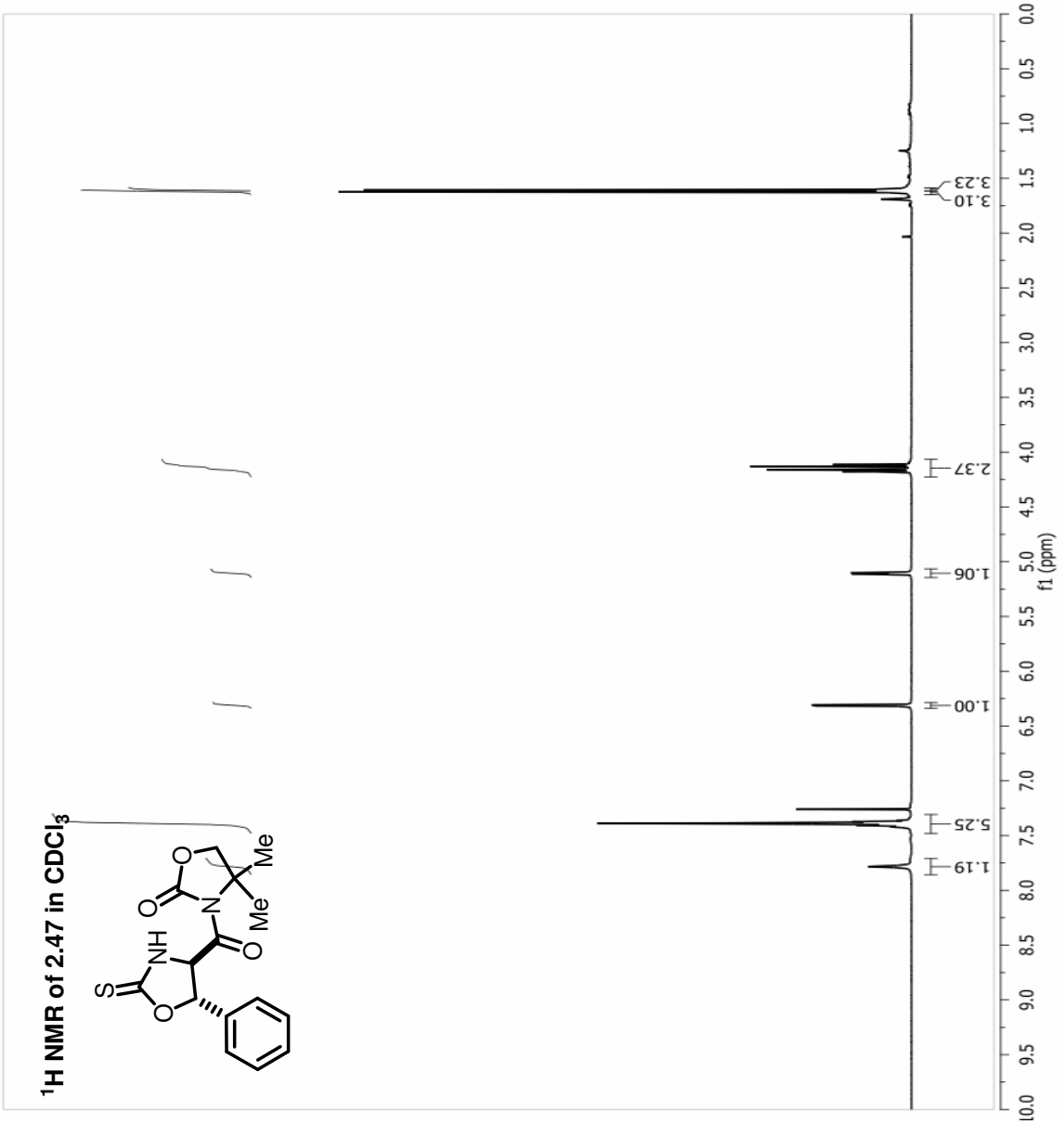

^{13}C NMR of 2.65 in $CDCl_3$
O
O
N
O
Me
Me
N_3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

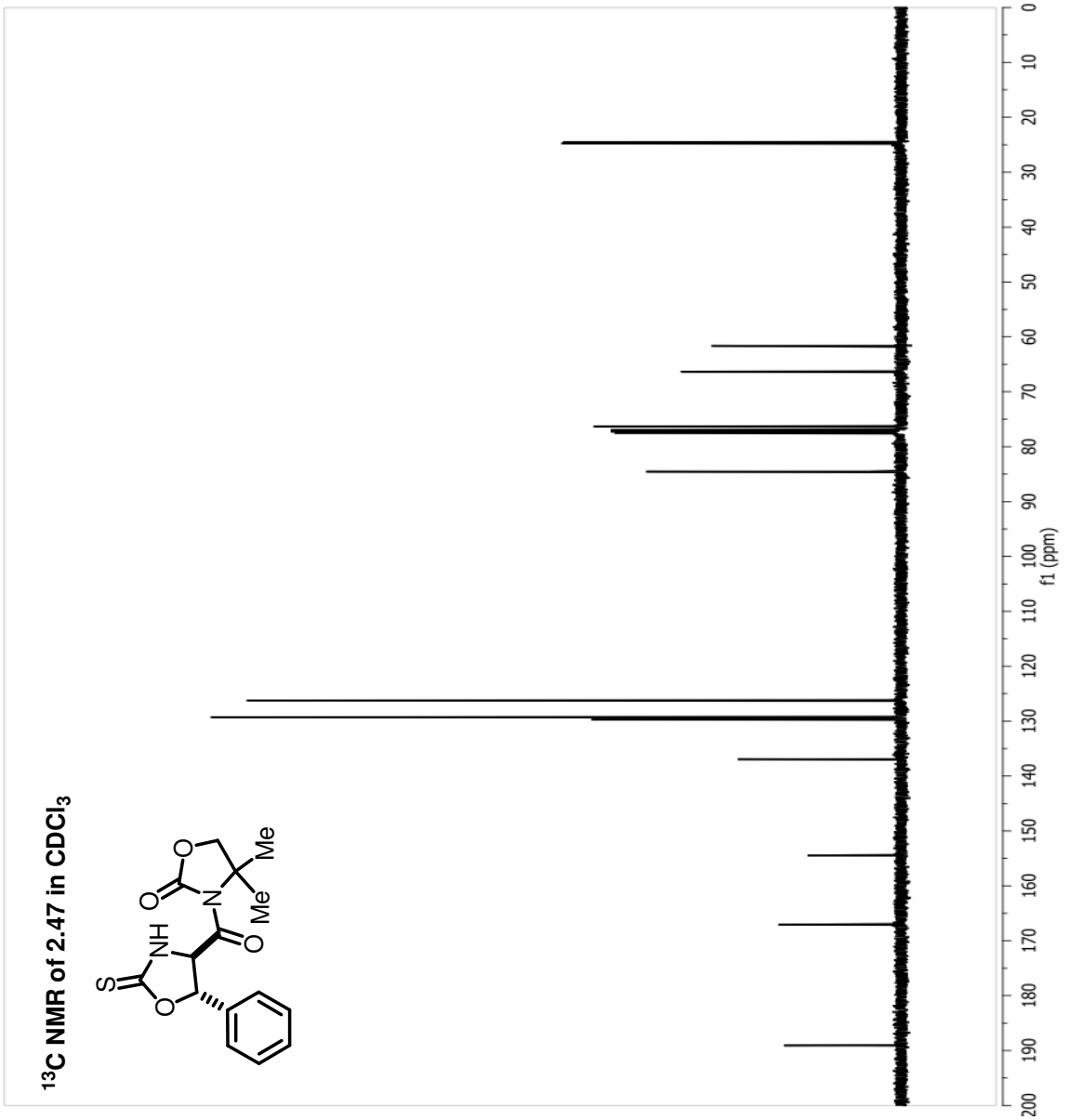

^{1}H NMR of 2.46 in $CDCl_3$
SCN
O
O
N
O
Me
Me
3.05
1.00
1.01
f1 (ppm)

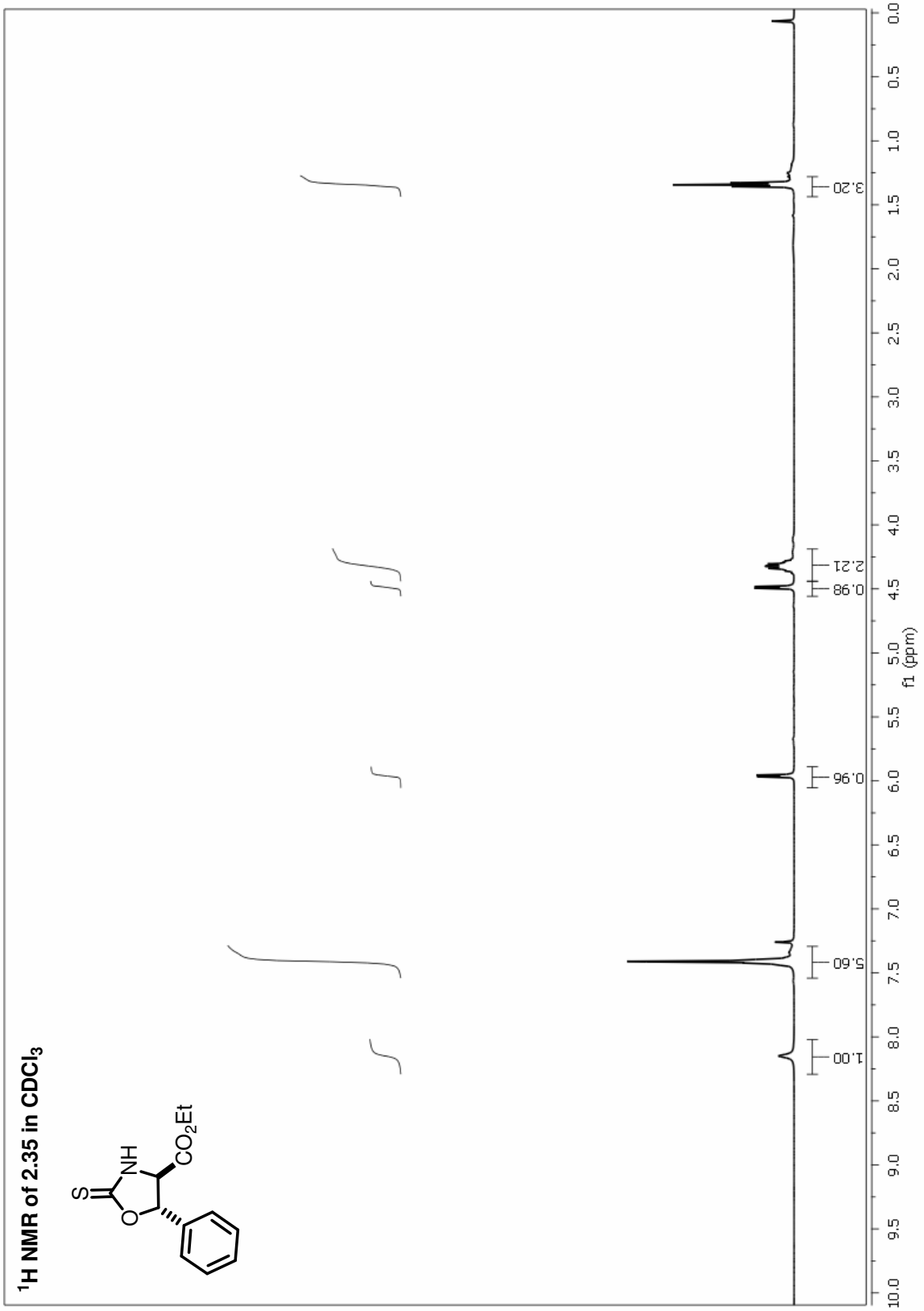

^{13}C NMR of 2.46 in $CDCl_3$
SCN
O
O
N
O
O
Me
Me
f1 (ppm)

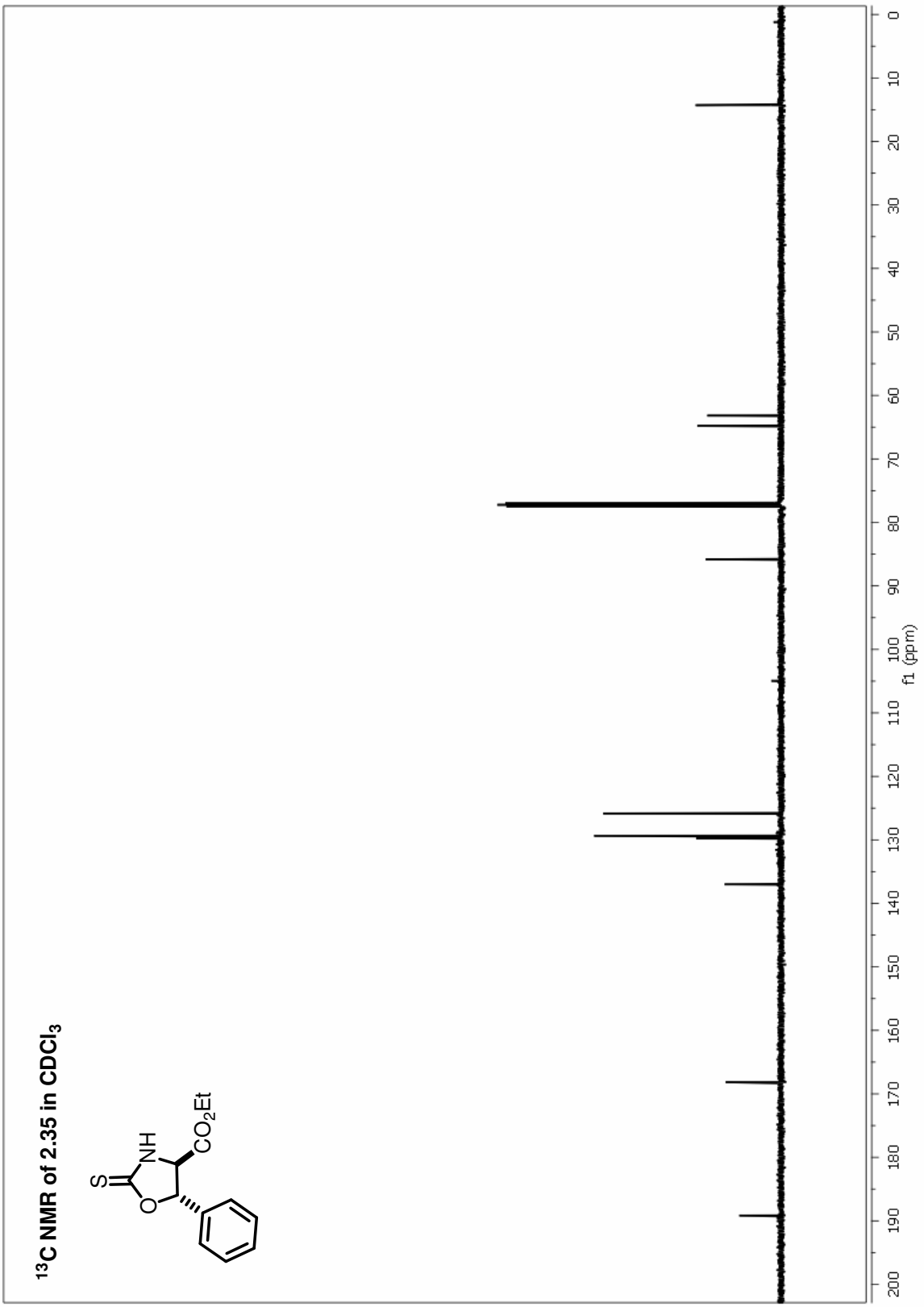

^{1}H NMR of 2.39 in d_6-DMSO
O_2N
NH
HN
S
N
1.00
1.05
1.97
1.96
1.00
3.10
1.94
1.11
1.16
4.89
1.16
4.27
f1 (ppm)

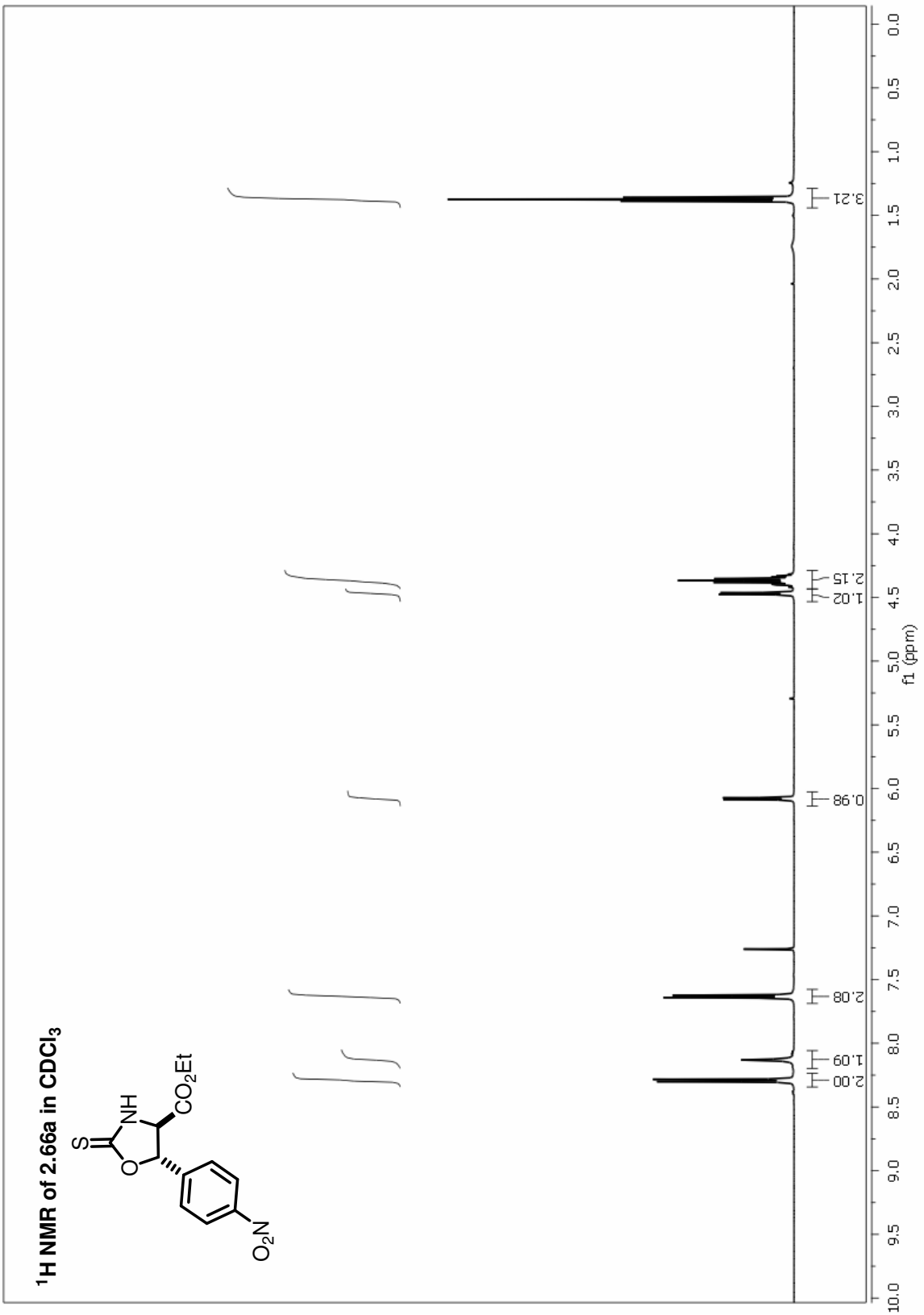

^{13}C NMR of 2.39 in d_6-DMSO
O_2N
NH
NH
S
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

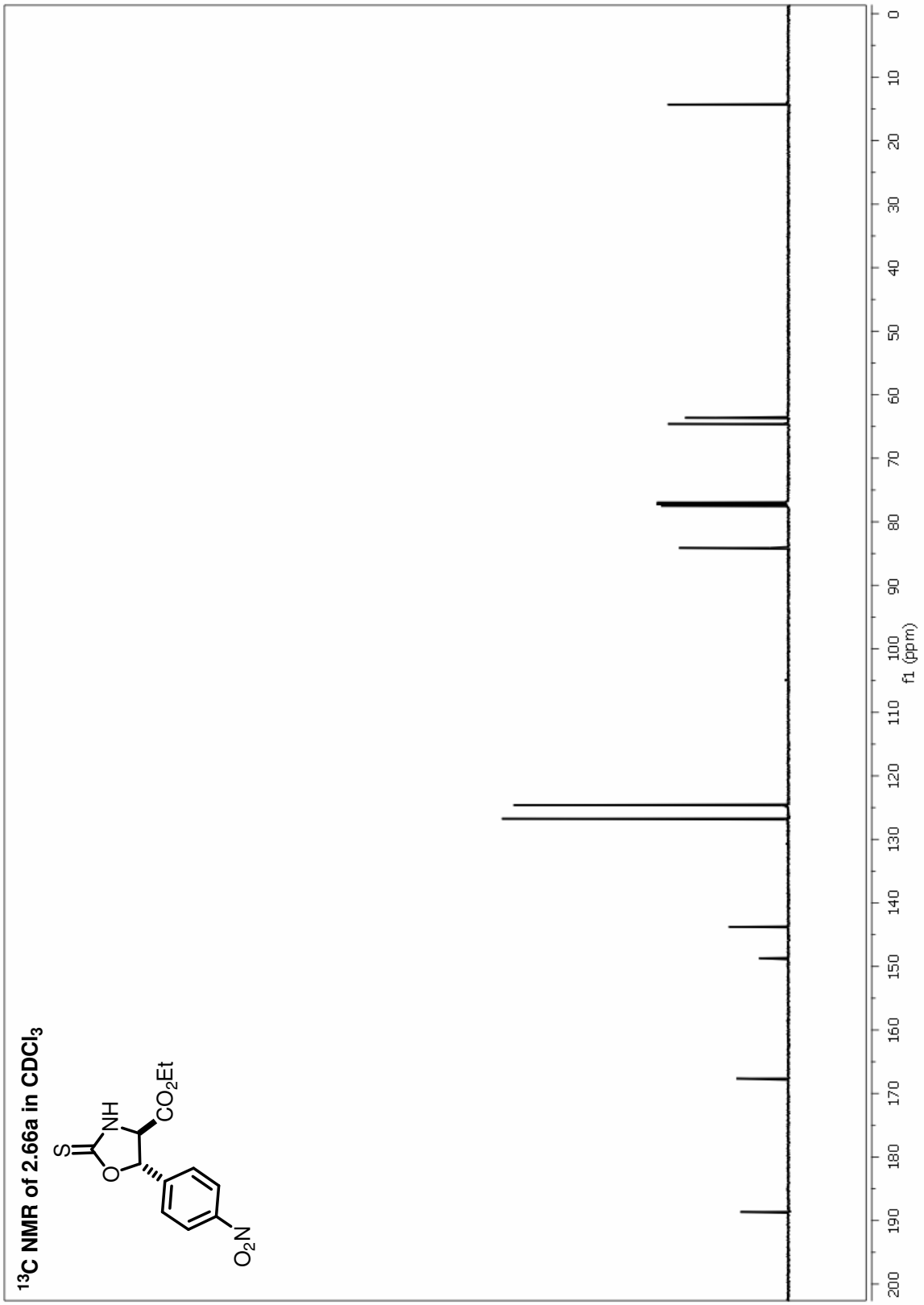

^{1}H NMR of 2.47 in $CDCl_3$
Me
Me
O
O
N
O
NH
S
O
3.10
3.23
2.37
1.06
1.00
5.25
1.19
f1 (ppm)

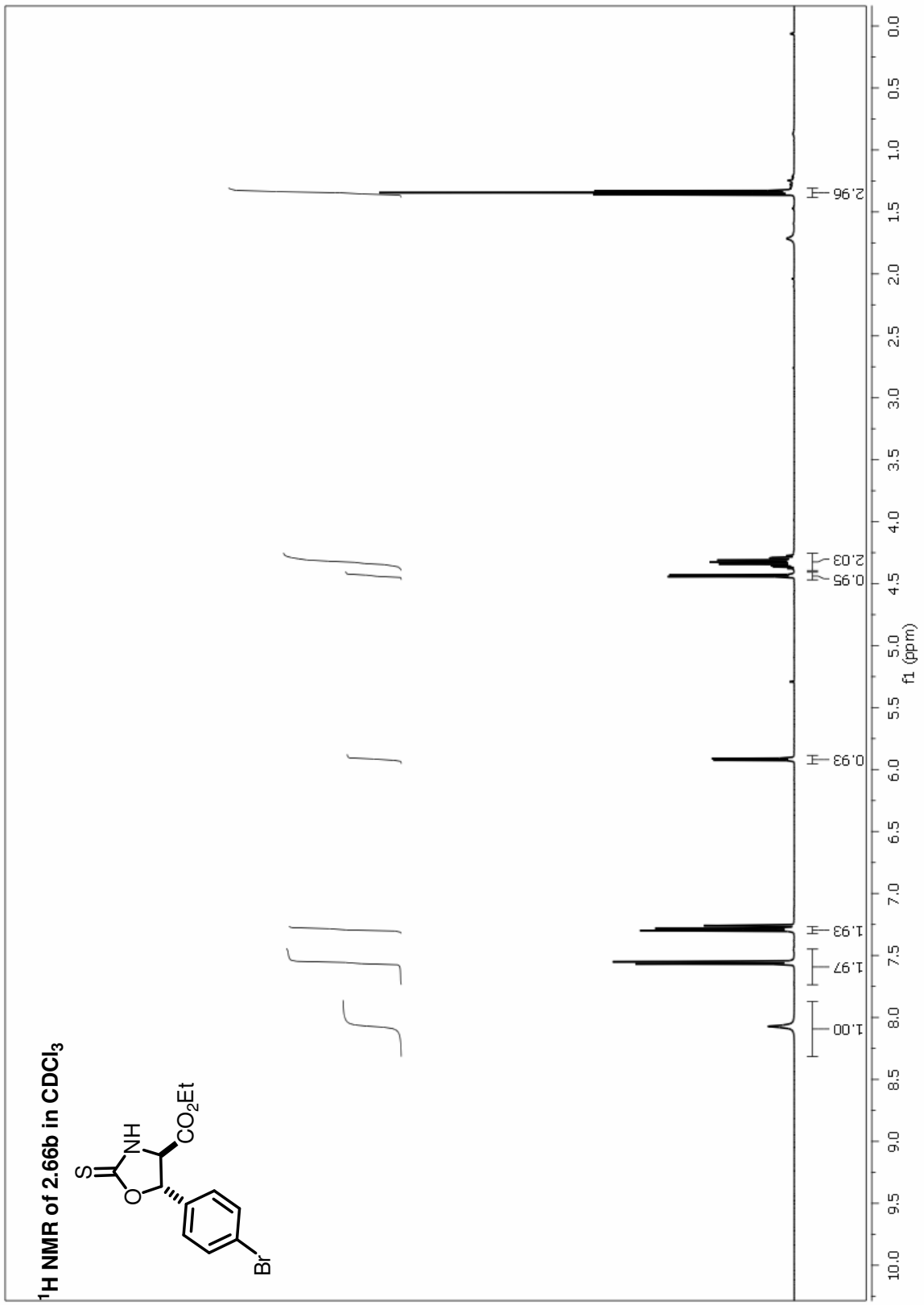

^{13}C NMR of 2.47 in $CDCl_3$
f1 (ppm)

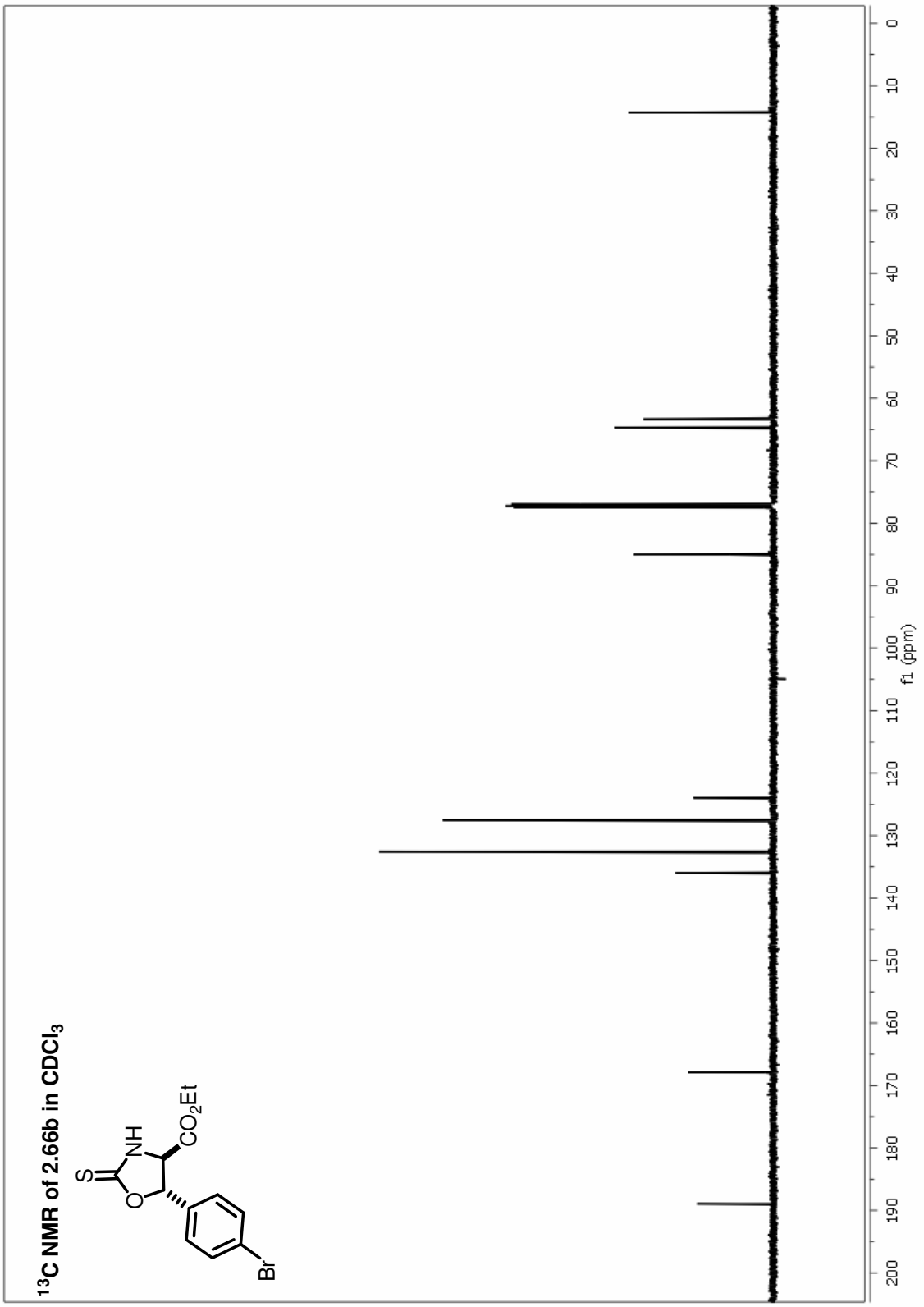

^{1}H NMR of 2.35 in $CDCl_3$
S
NH
O
CO_2Et
1.00
5.60
0.96
0.98
2.21
3.20
f1 (ppm)

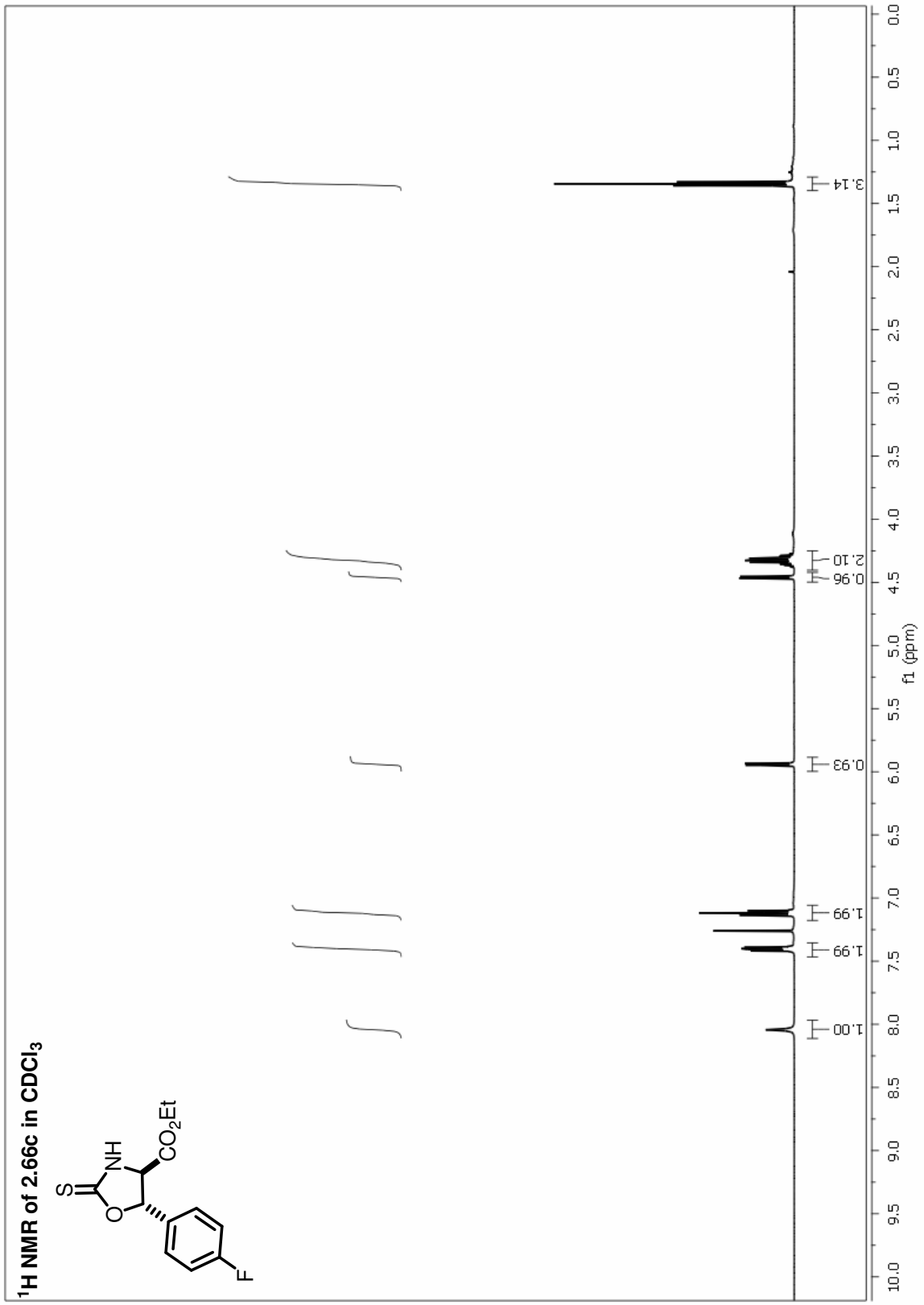

^{13}C NMR of 2.35 in $CDCl_3$
NH
S
O
CO_2Et
f1 (ppm)

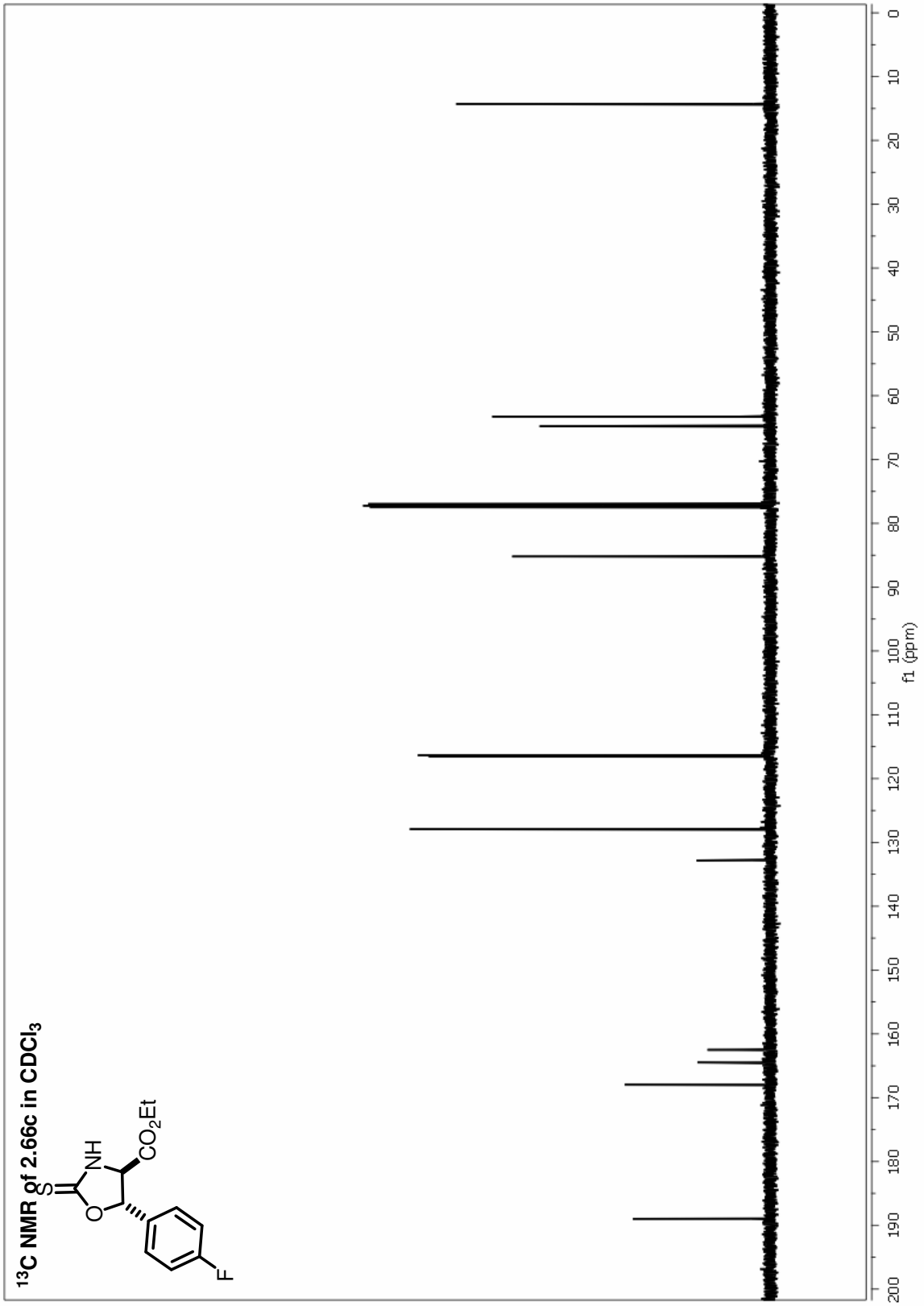

^{1}H NMR of 2.66a in $CDCl_3$
S
NH
O
CO_2Et
O_2N
3.21
1.02
2.15
0.98
2.08
1.09
2.00
f1 (ppm)

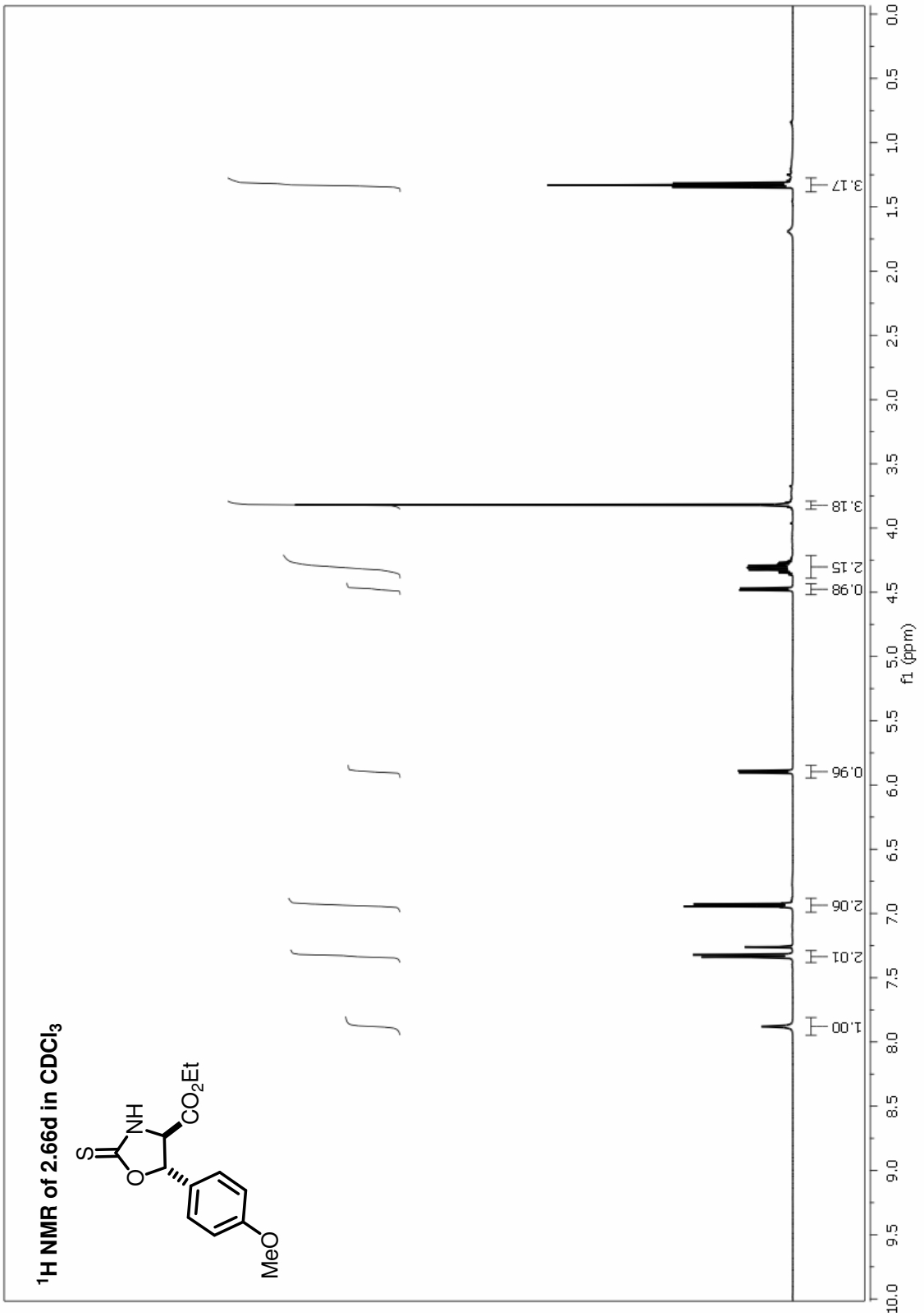

^{13}C NMR of 2.66a in $CDCl_3$
S
NH
O
CO_2Et
O_2N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

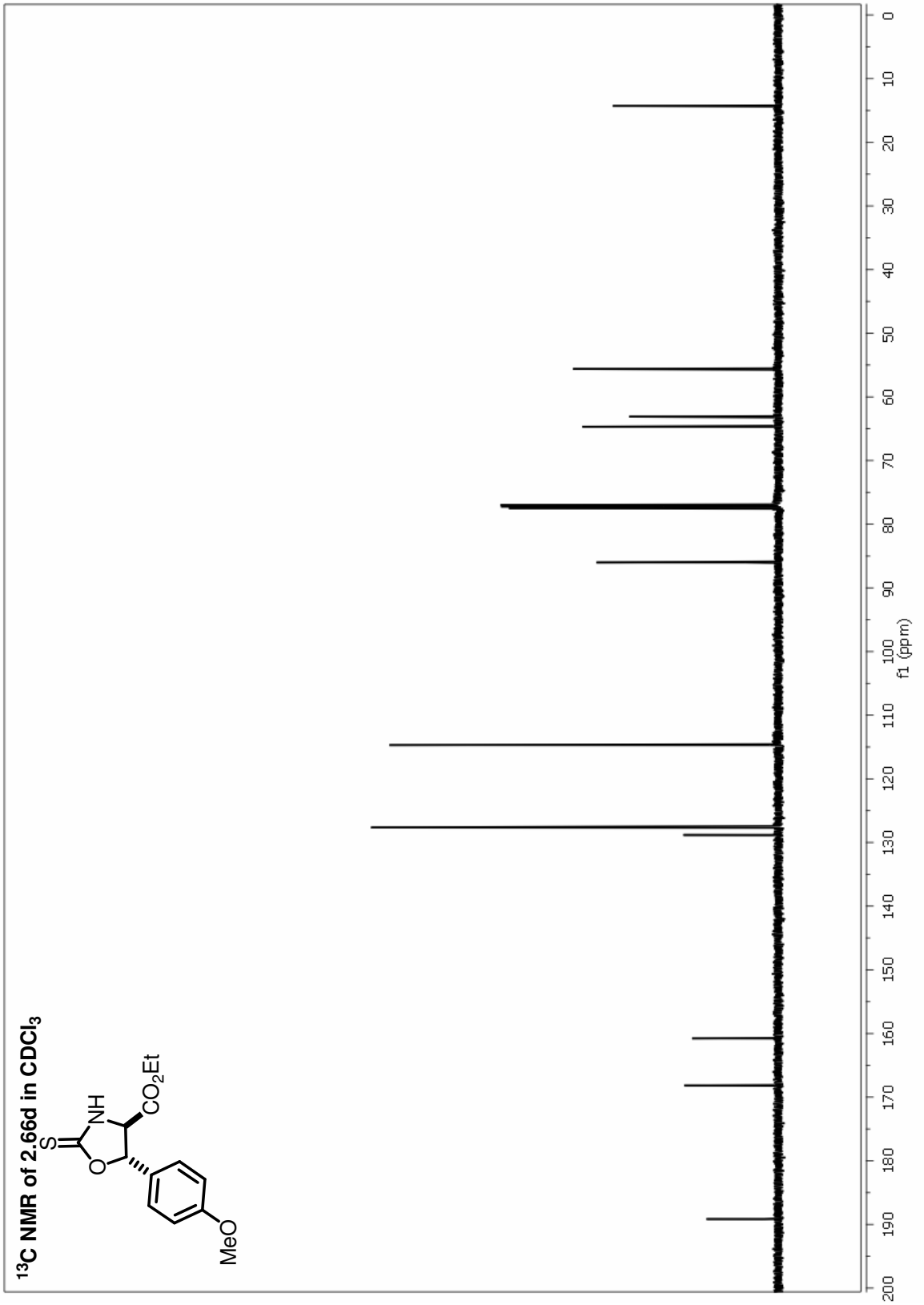

^{1}H NMR of 2.66b in $CDCl_3$
S
NH
O
CO_2Et
Br
2.96
0.95
2.03
0.93
1.93
1.97
1.00
f1 (ppm)

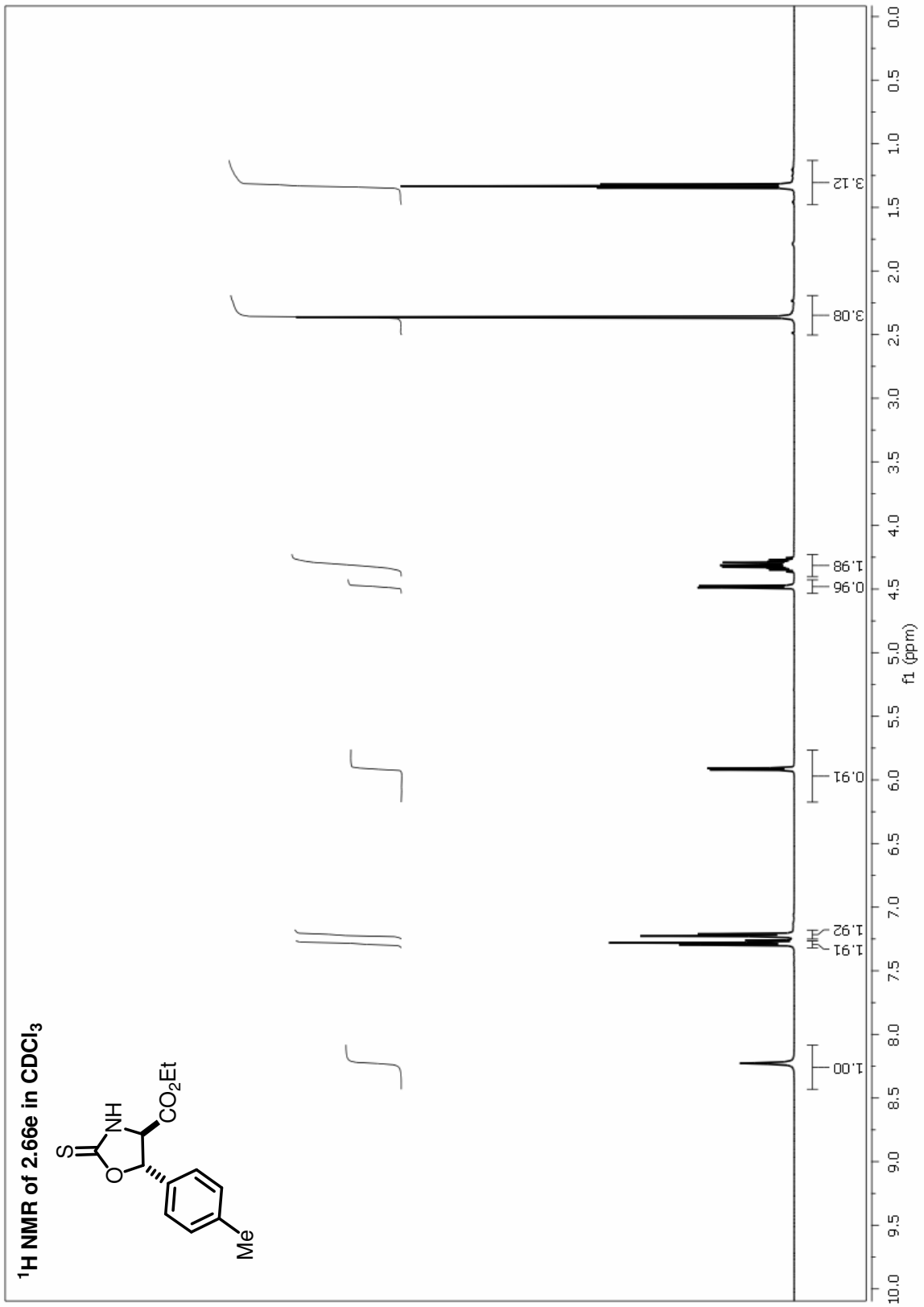

^{13}C NMR of 2.66b in $CDCl_3$
NH
S
O
CO_2Et
Br
f1 (ppm)

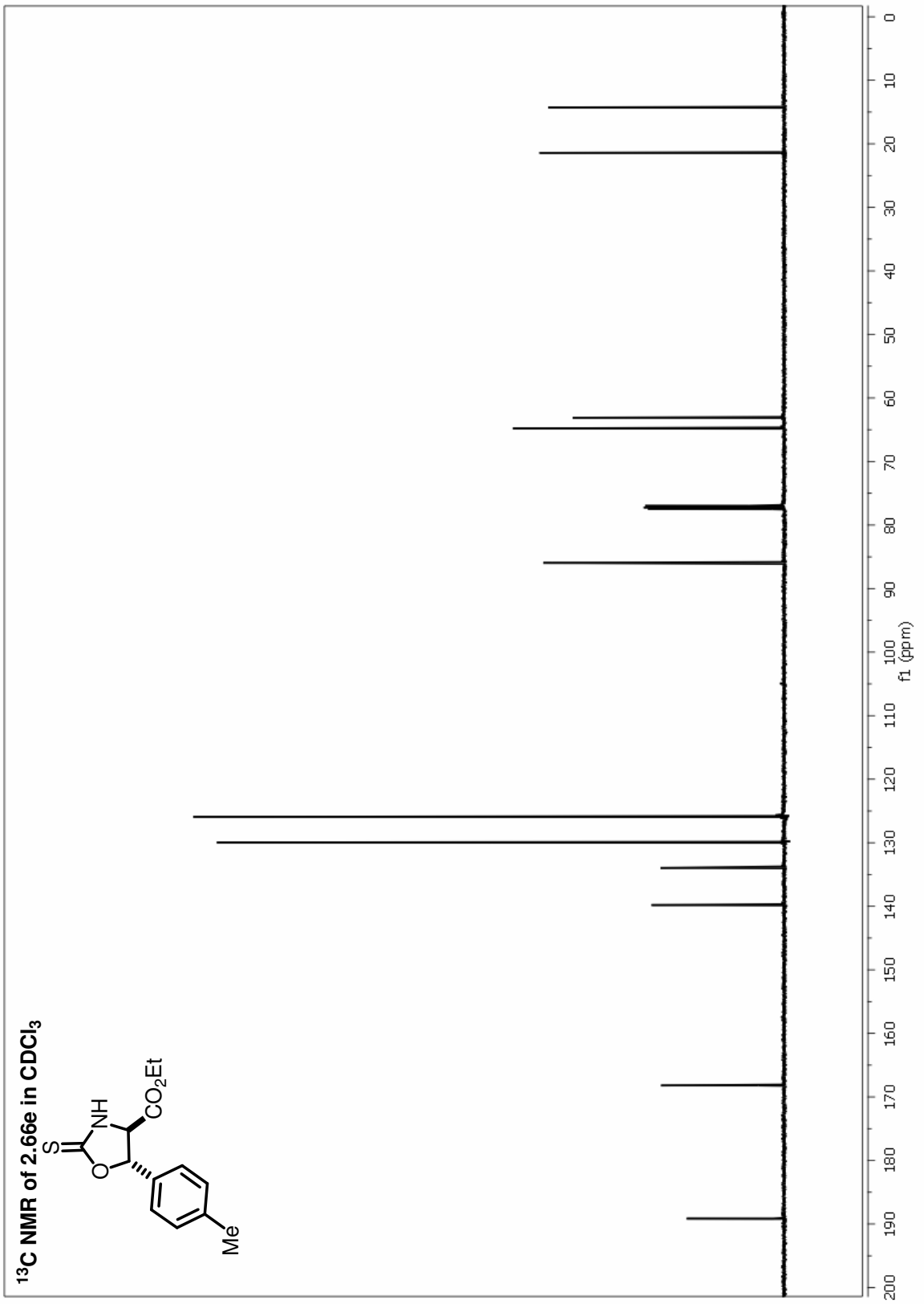

^{1}H NMR of 2.66c in $CDCl_3$
S
NH
O
CO_2Et
F
1.00
1.99
1.99
0.93
2.10
0.96
3.14
f1 (ppm)

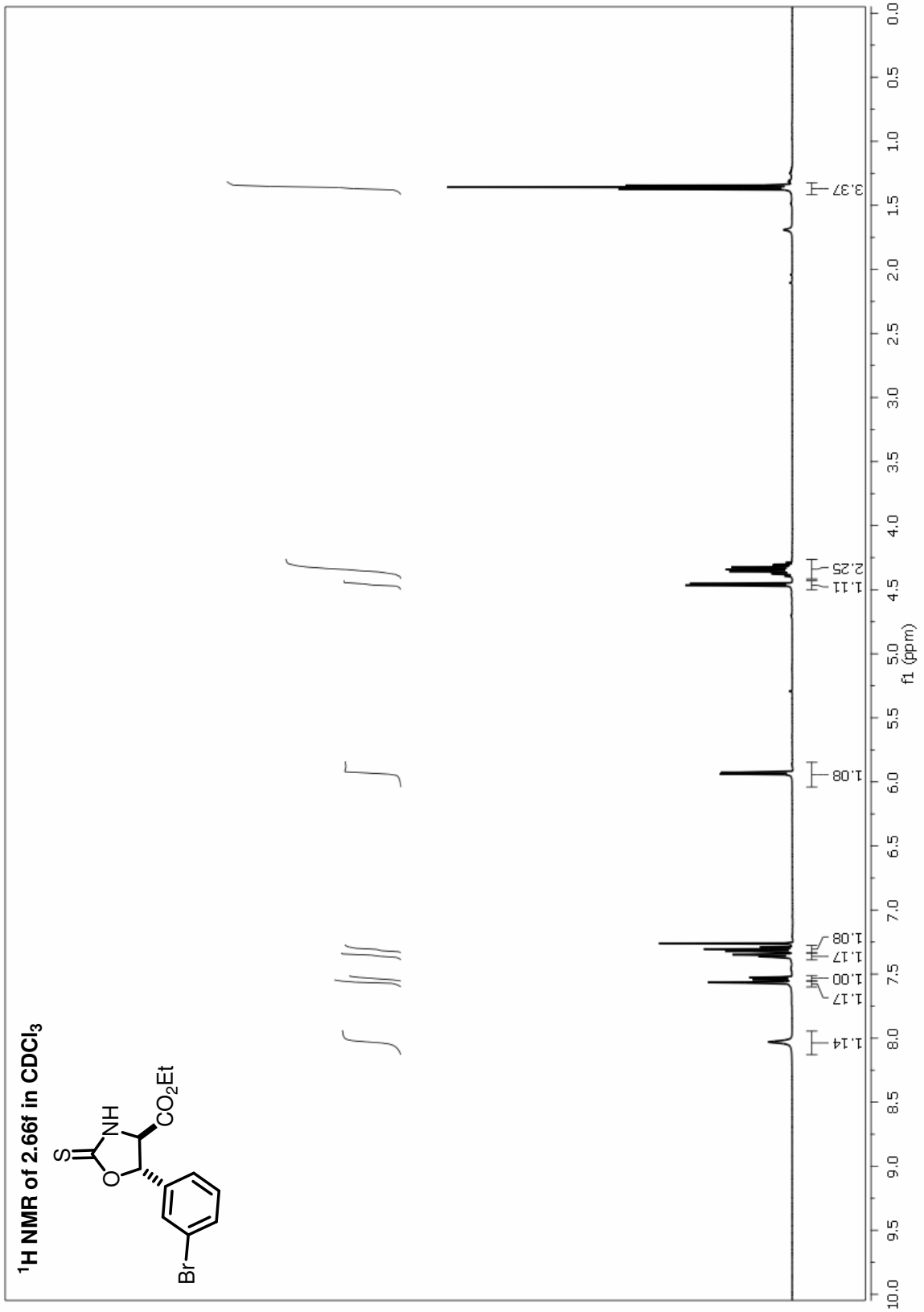

^{13}C NMR of 2.66c in $CDCl_3$
NH
CO_2Et
O
S
F
f1 (ppm)

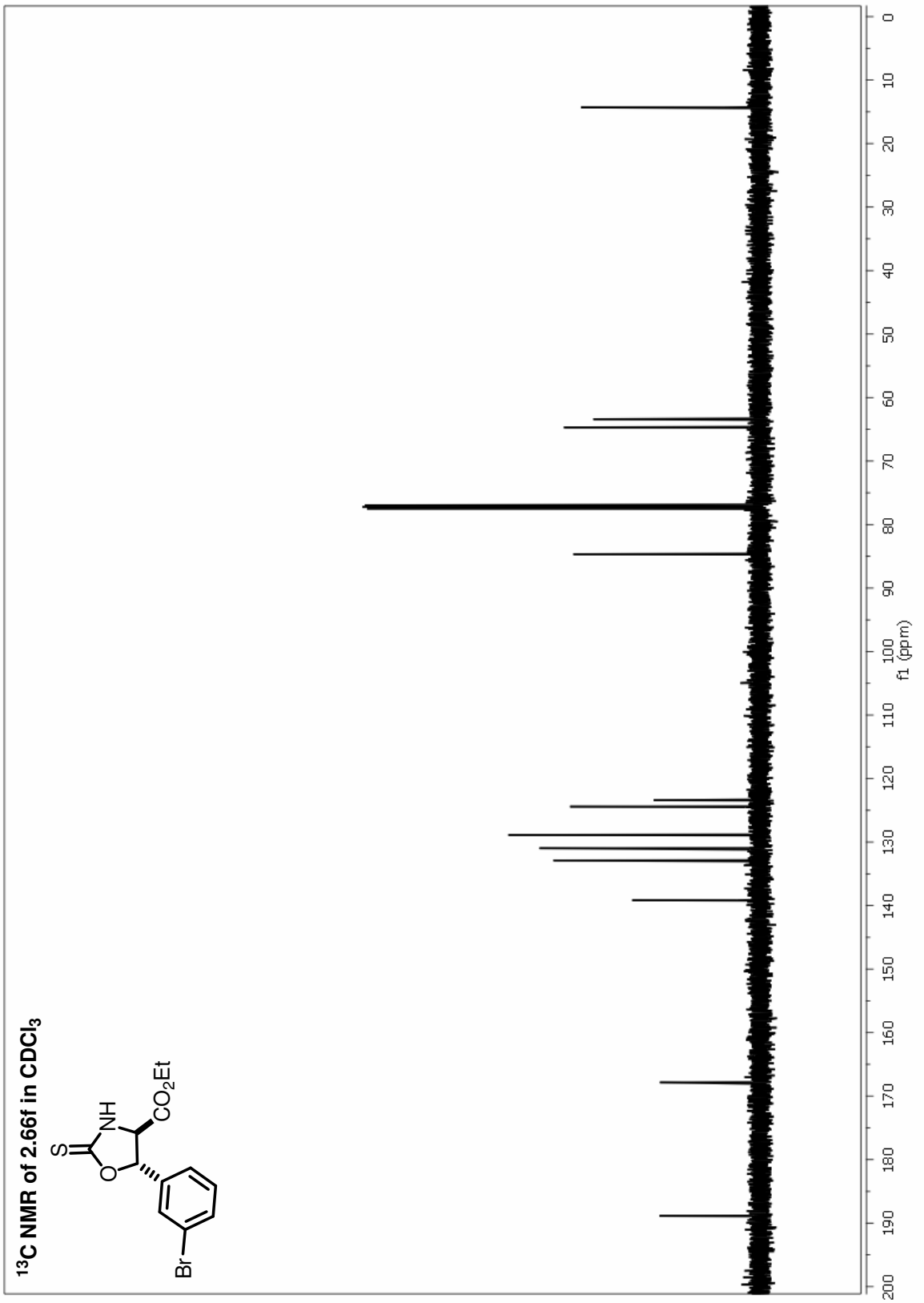

^{1}H NMR of 2.66d in $CDCl_3$
NH
CO_2Et
S
O
MeO
3.17
3.18
2.15
0.98
0.96
2.06
2.01
1.00
f1 (ppm)

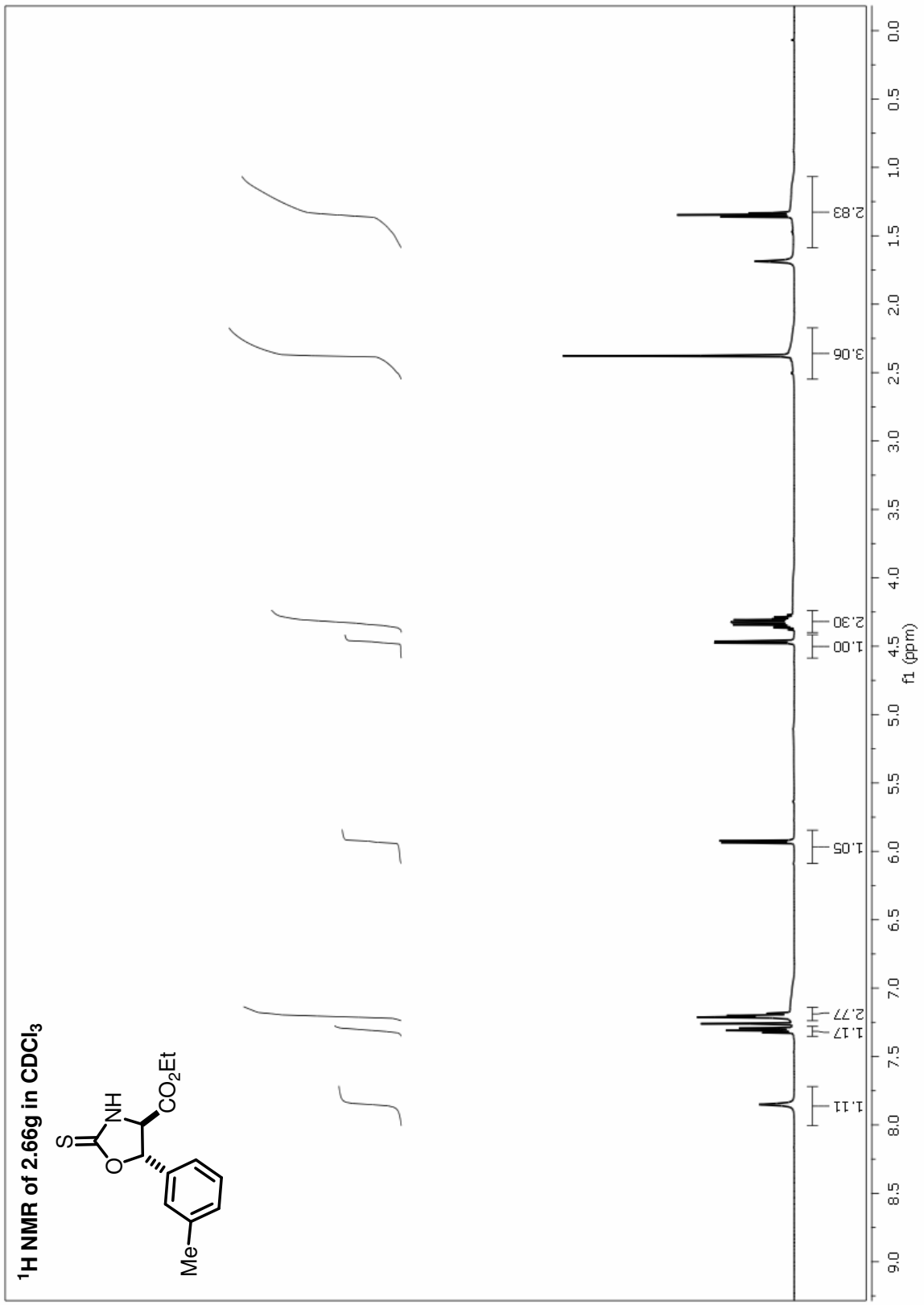

^{13}C NMR of 2.66d in $CDCl_3$
NH
CO_2Et
S
O
MeO
f1 (ppm)

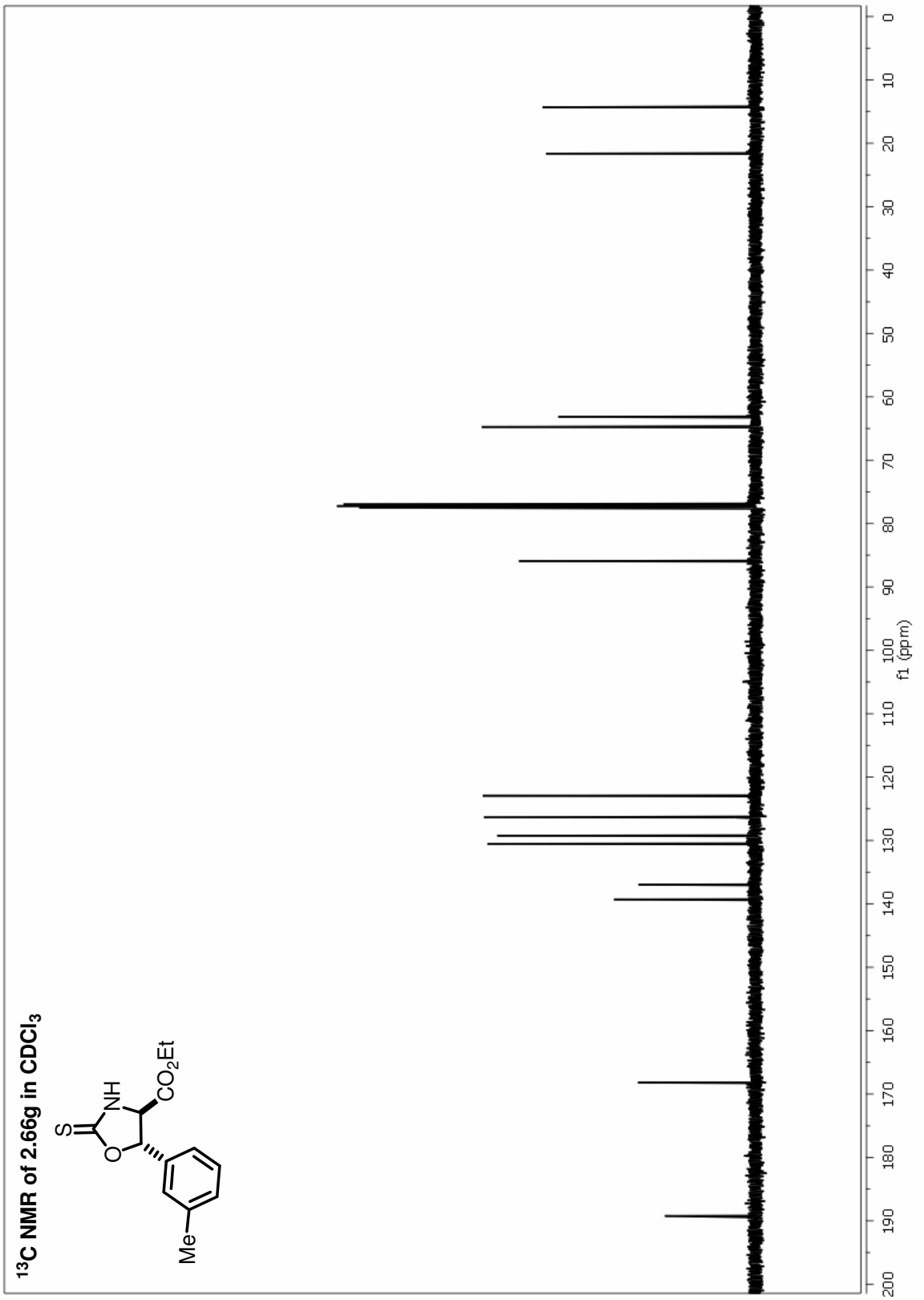

^{1}H NMR of 2.66e in $CDCl_3$
S
NH
O
CO_2Et
Me
1.00
1.91
1.92
0.91
1.98
0.96
3.08
3.12
f1 (ppm)

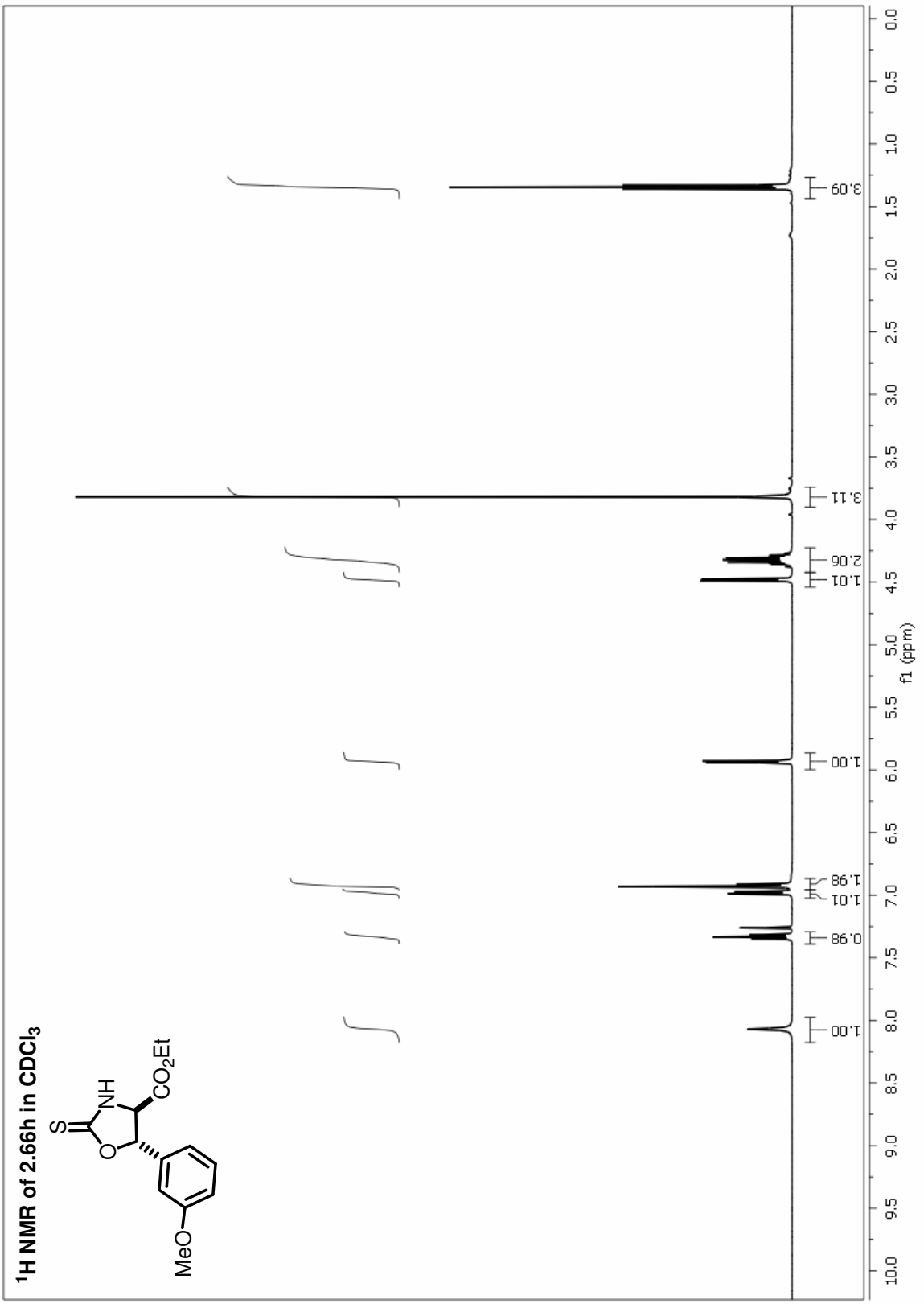

^{13}C NMR of 2.66e in $CDCl_3$
S
NH
O
CO_2Et
Me
f1 (ppm)

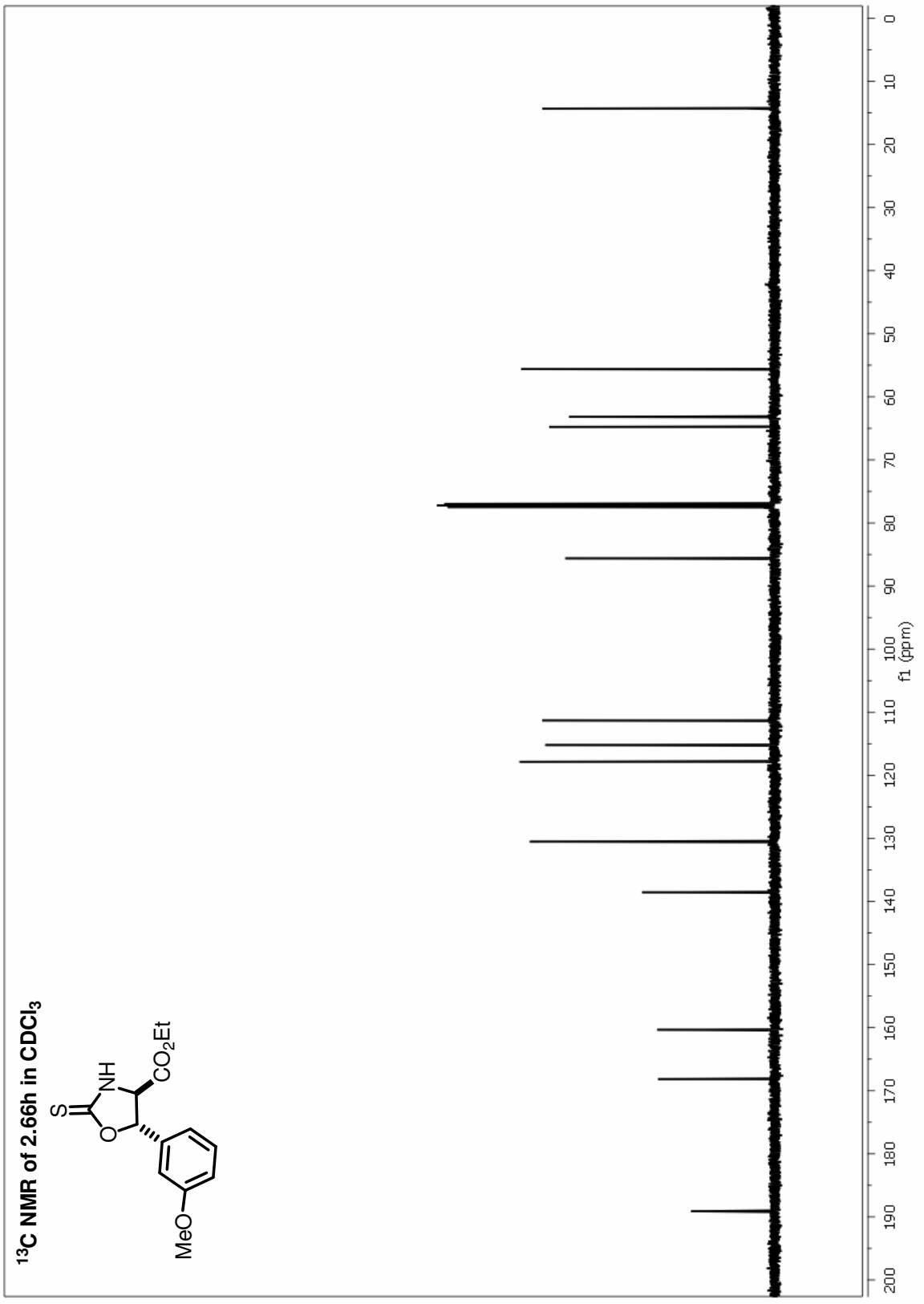

^{1}H NMR of 2.66f in $CDCl_3$
NH
CO_2Et
S
O
Br
3.37
2.25
1.11
1.08
1.17
1.00
1.17
1.08
1.14
f1 (ppm)

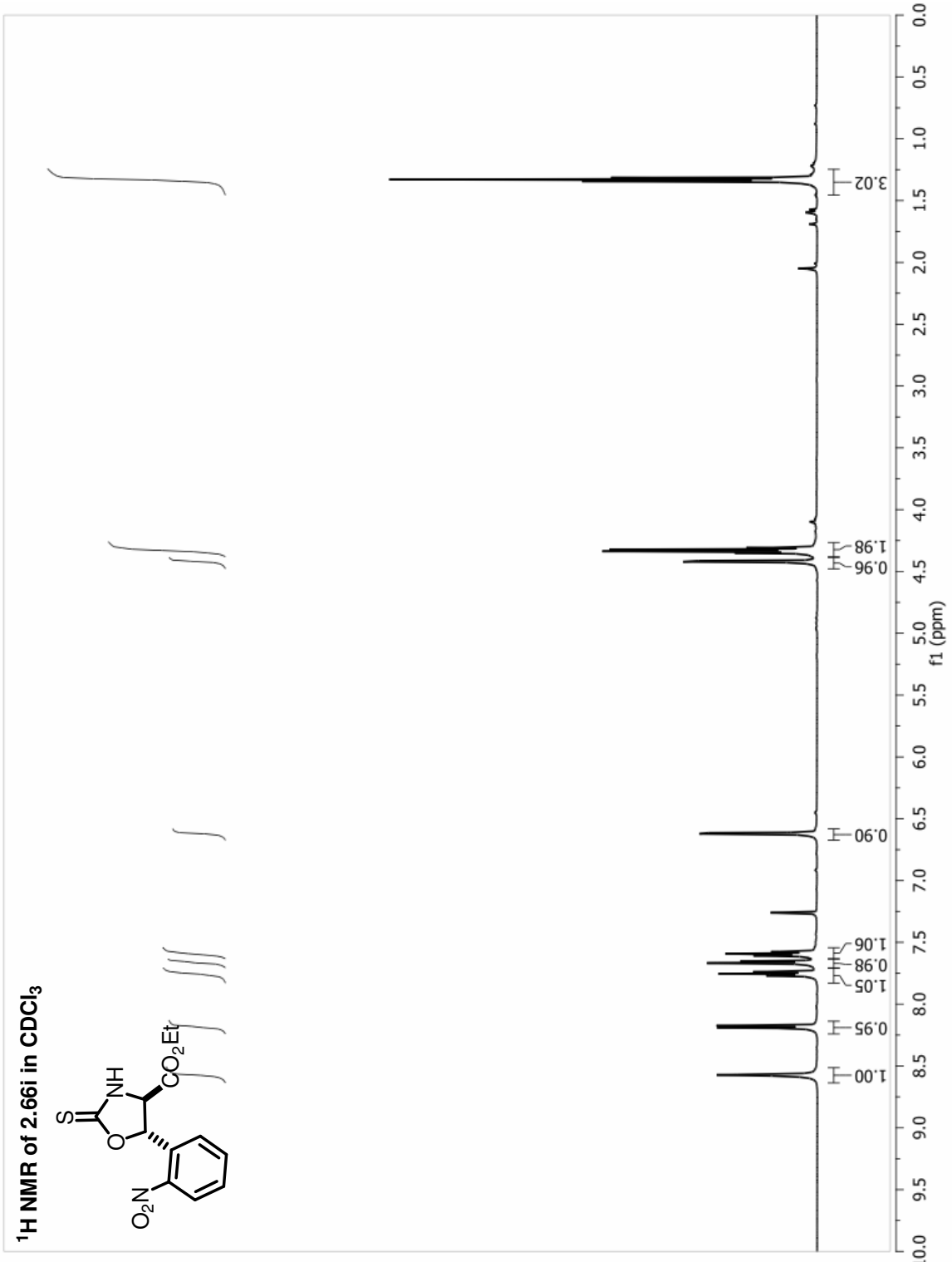

^{13}C NMR of 2.66f in $CDCl_3$
S
NH
O
CO_2Et
Br
f1 (ppm)

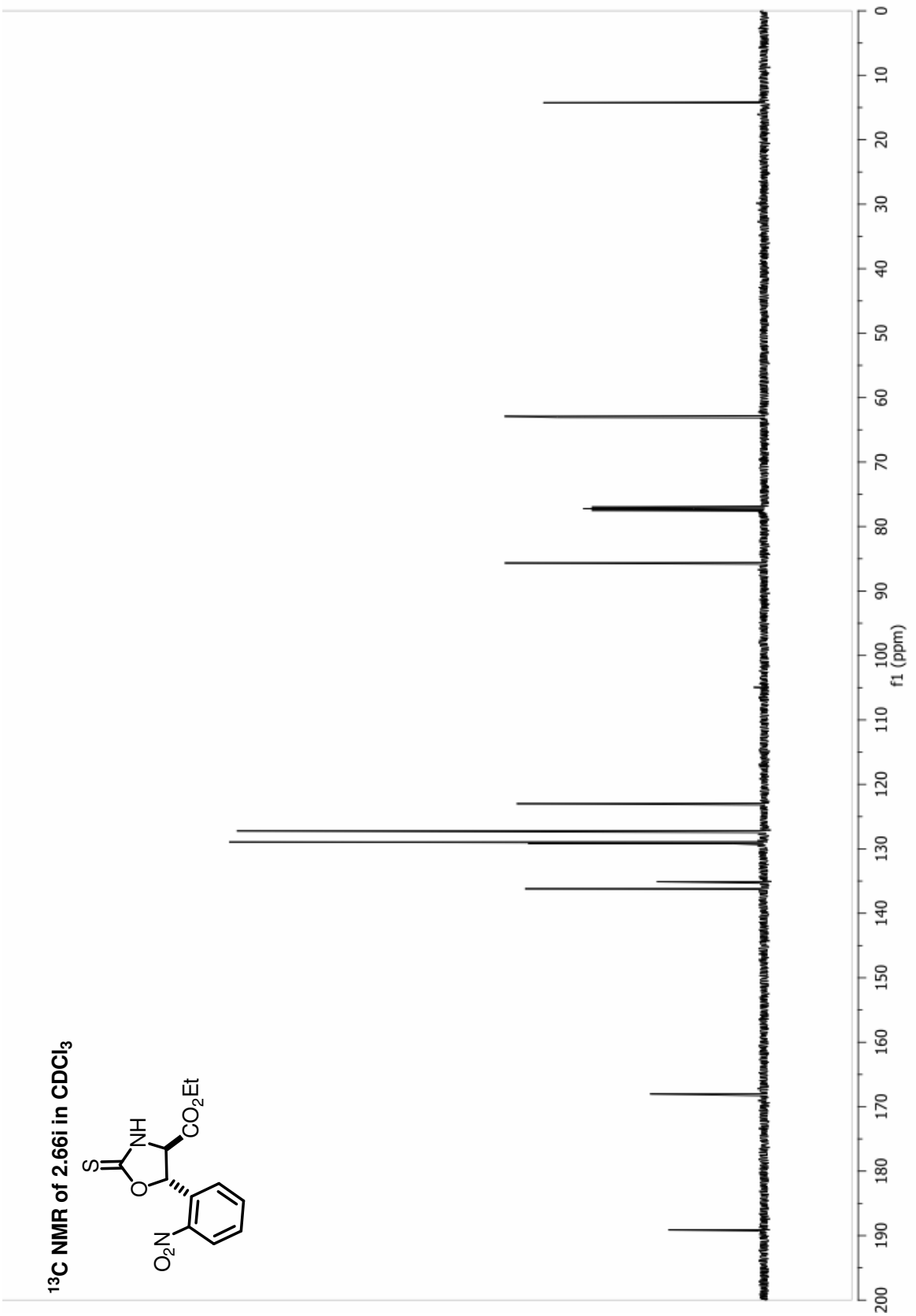

^{1}H NMR of 2.66g in $CDCl_3$
NH
S
O
CO_2Et
Me
1.11
1.17
2.77
1.05
1.00
2.30
3.06
2.83
f1 (ppm)

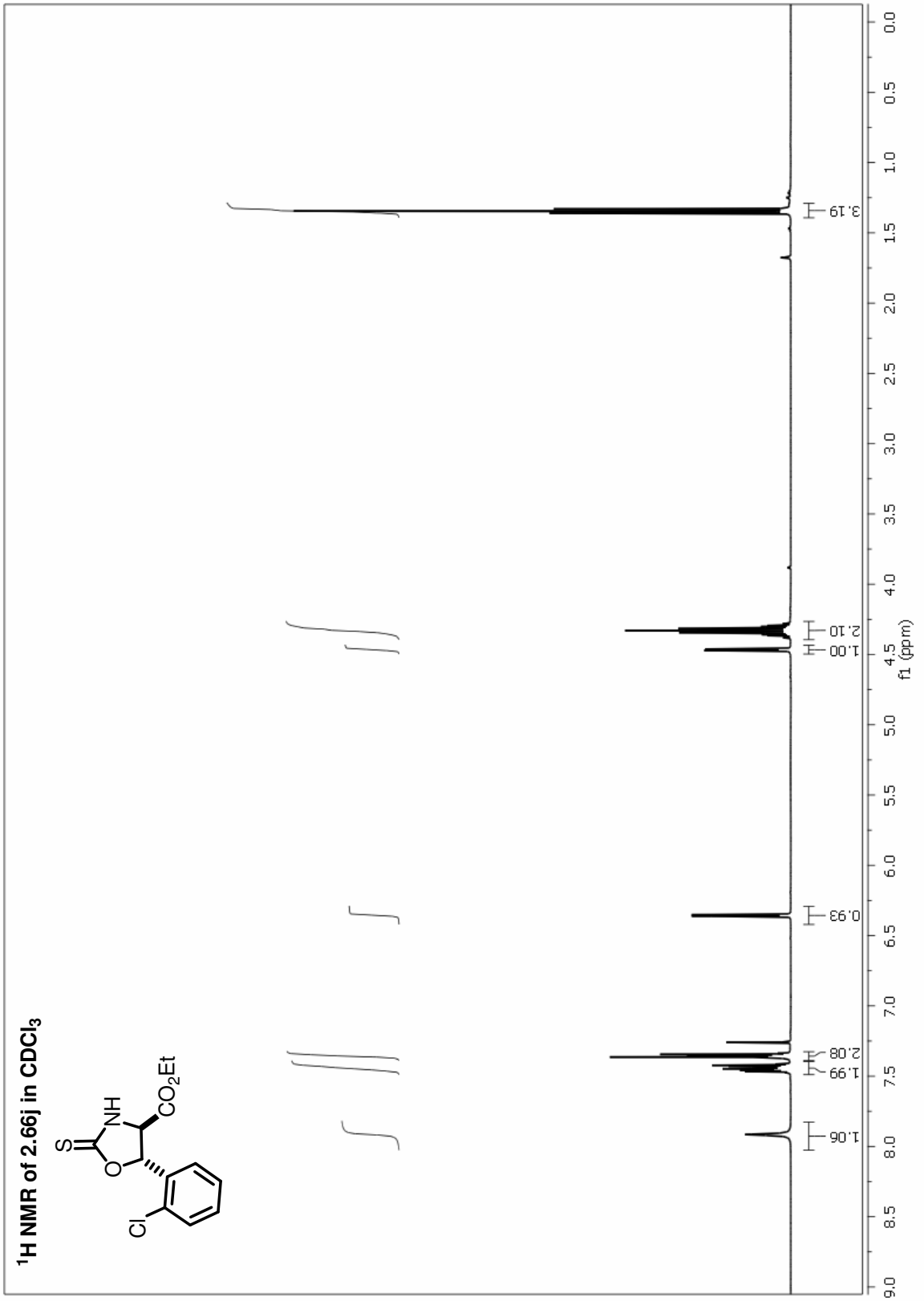

^{13}C NMR of 2.66g in $CDCl_3$
S
NH
O
CO_2Et
Me
f1 (ppm)

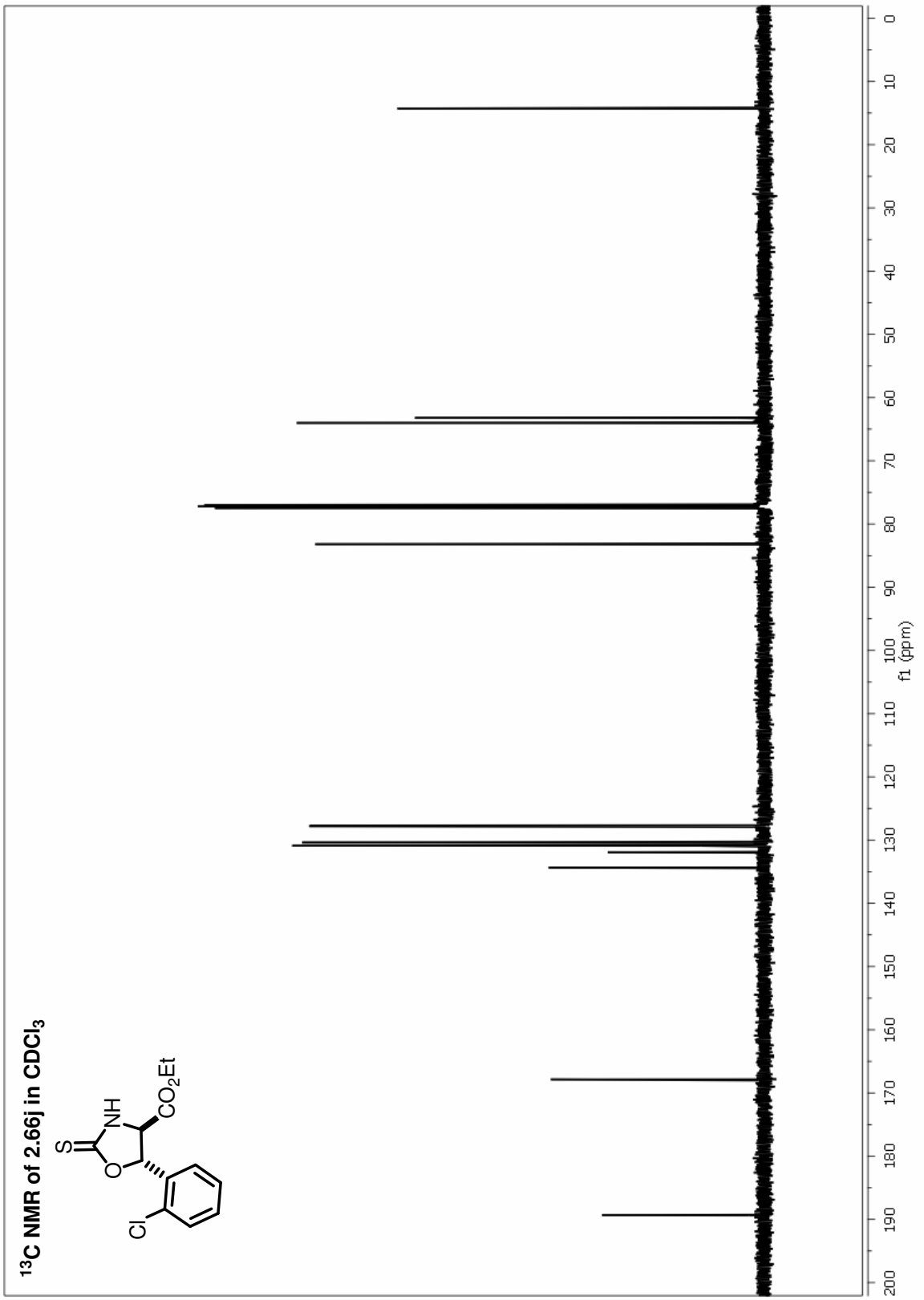

^{1}H NMR of 2.66h in $CDCl_3$
S
NH
O
CO_2Et
MeO
3.09
3.11
2.06
1.01
1.00
1.98
1.01
0.98
1.00
f1 (ppm)

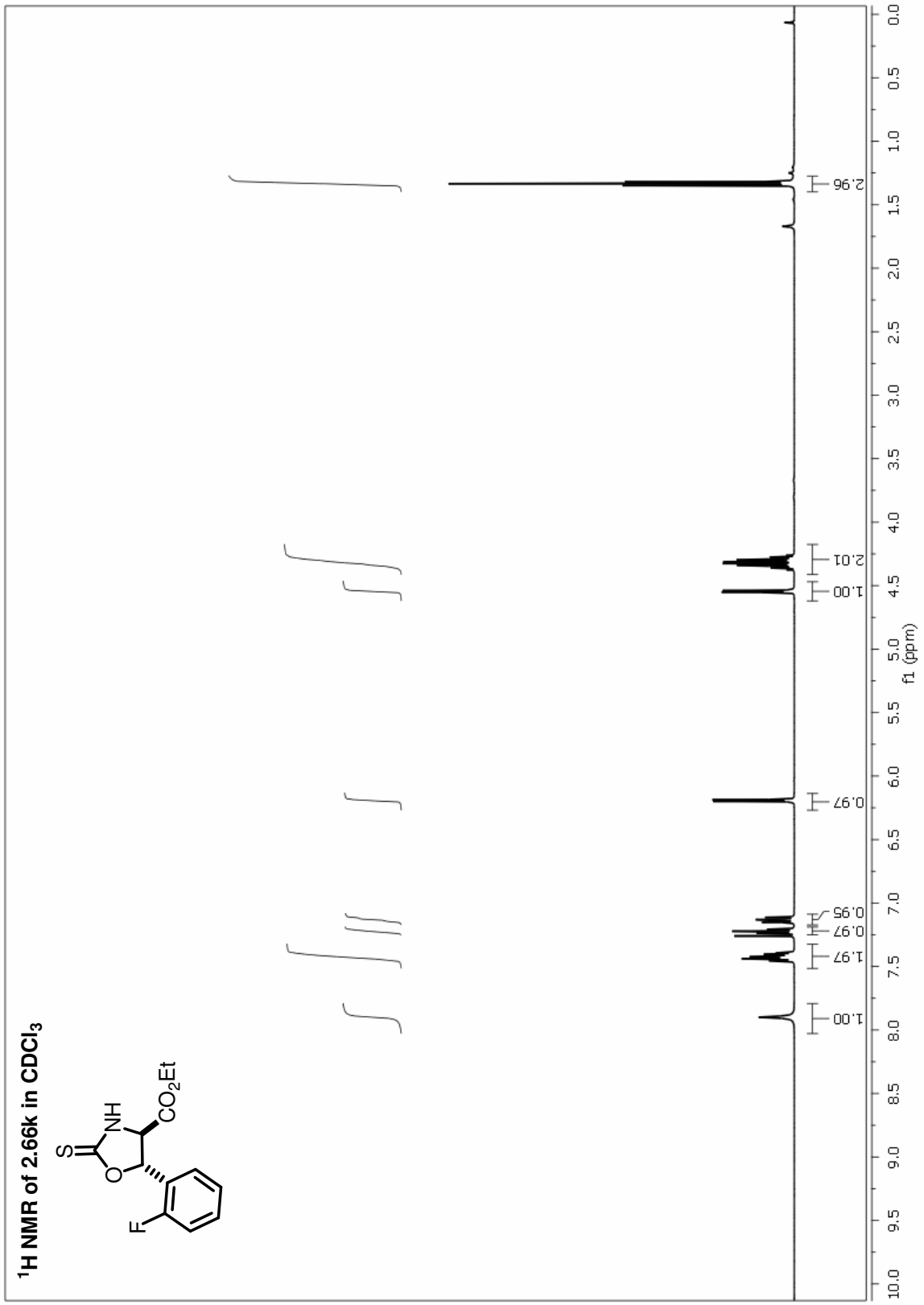

^{13}C NMR of 2.66h in $CDCl_3$
S
NH
O
CO_2Et
MeO
f1 (ppm)

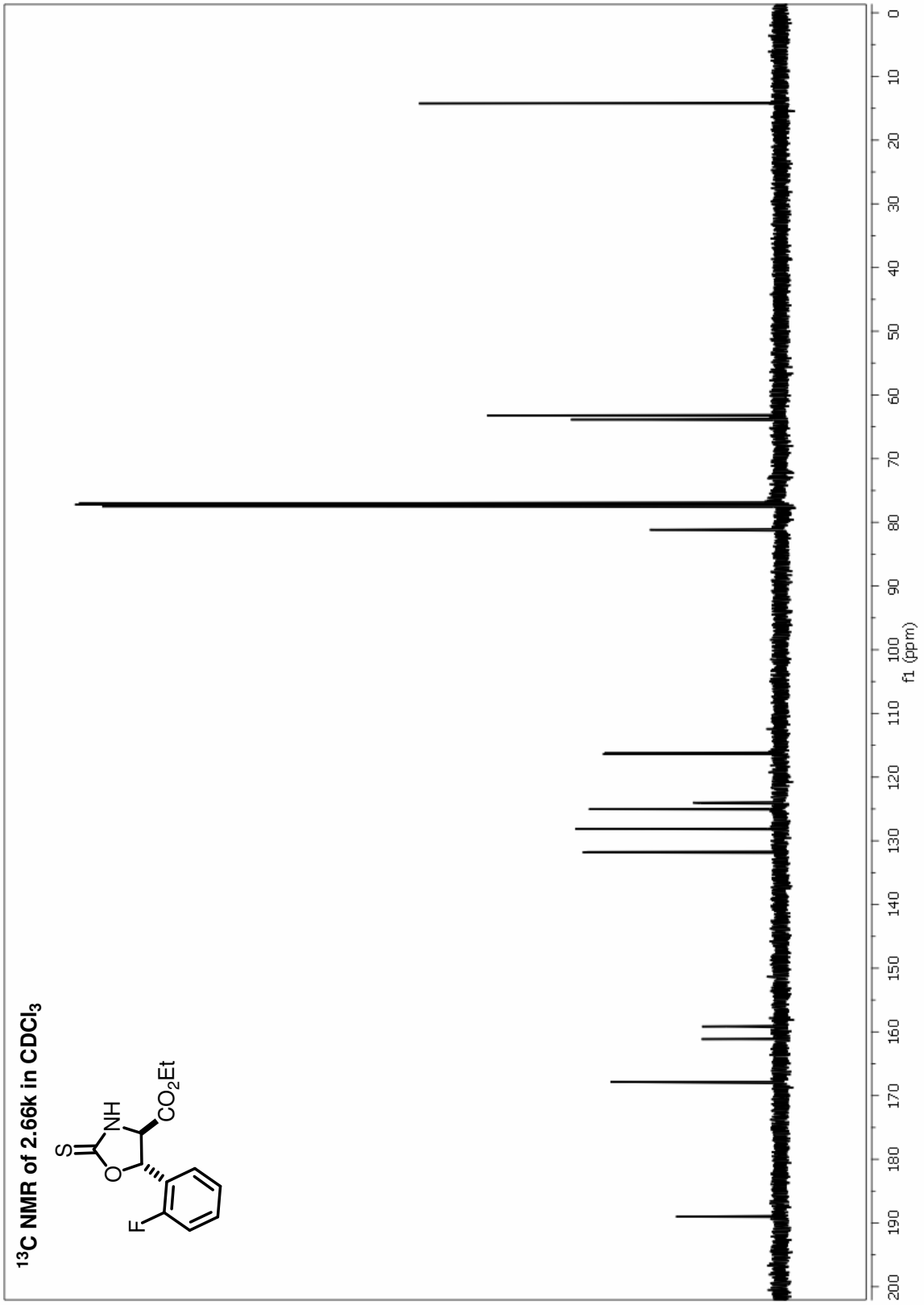

^{1}H NMR of 2.66i in $CDCl_3$
NH
S
O
CO_2Et
O_2N
1.00
0.95
1.05
0.98
1.06
0.90
1.98
0.96
3.02
f1 (ppm)

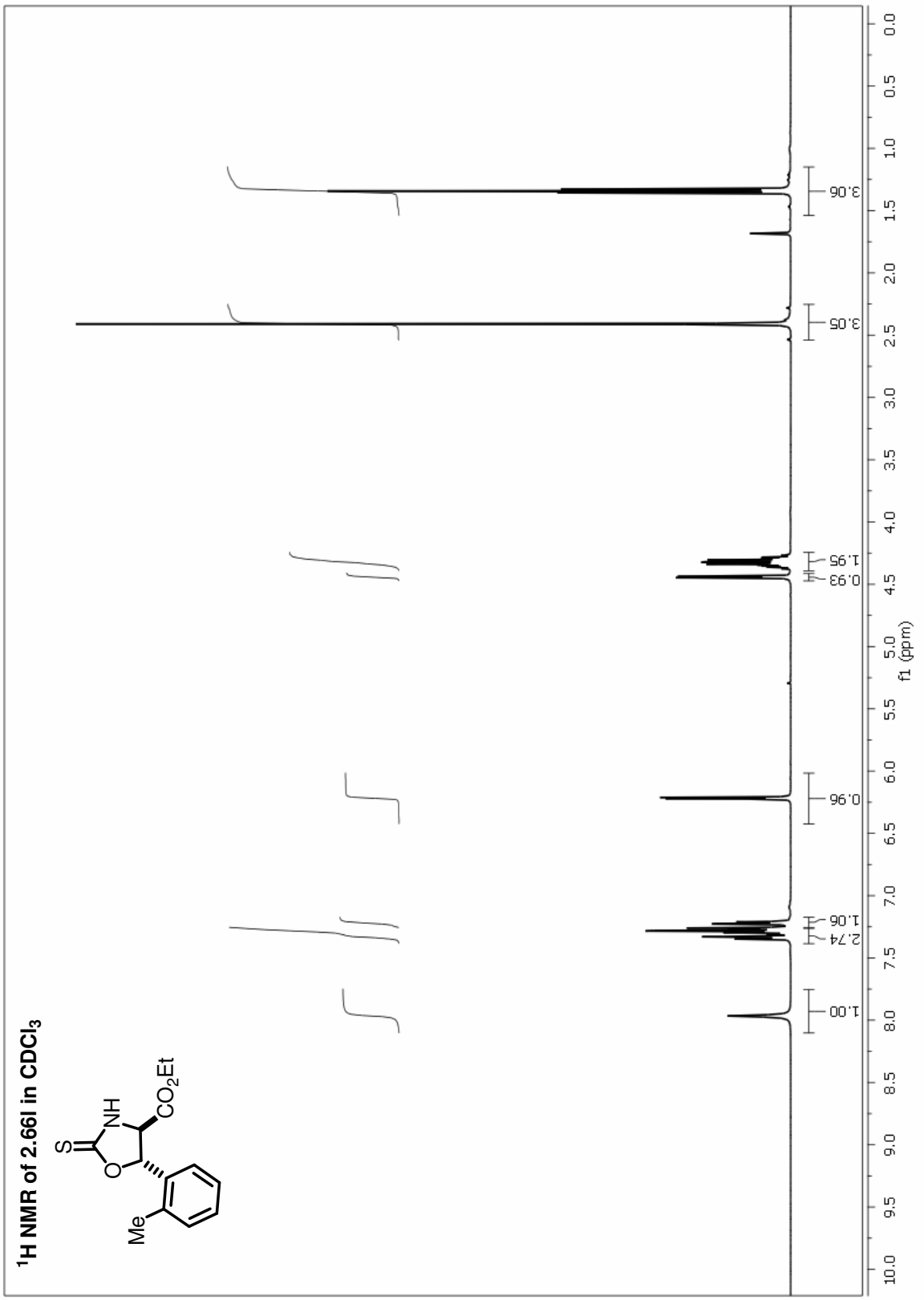

^{13}C NMR of 2.66i in $CDCl_3$
S
NH
O
CO_2Et
O_2N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

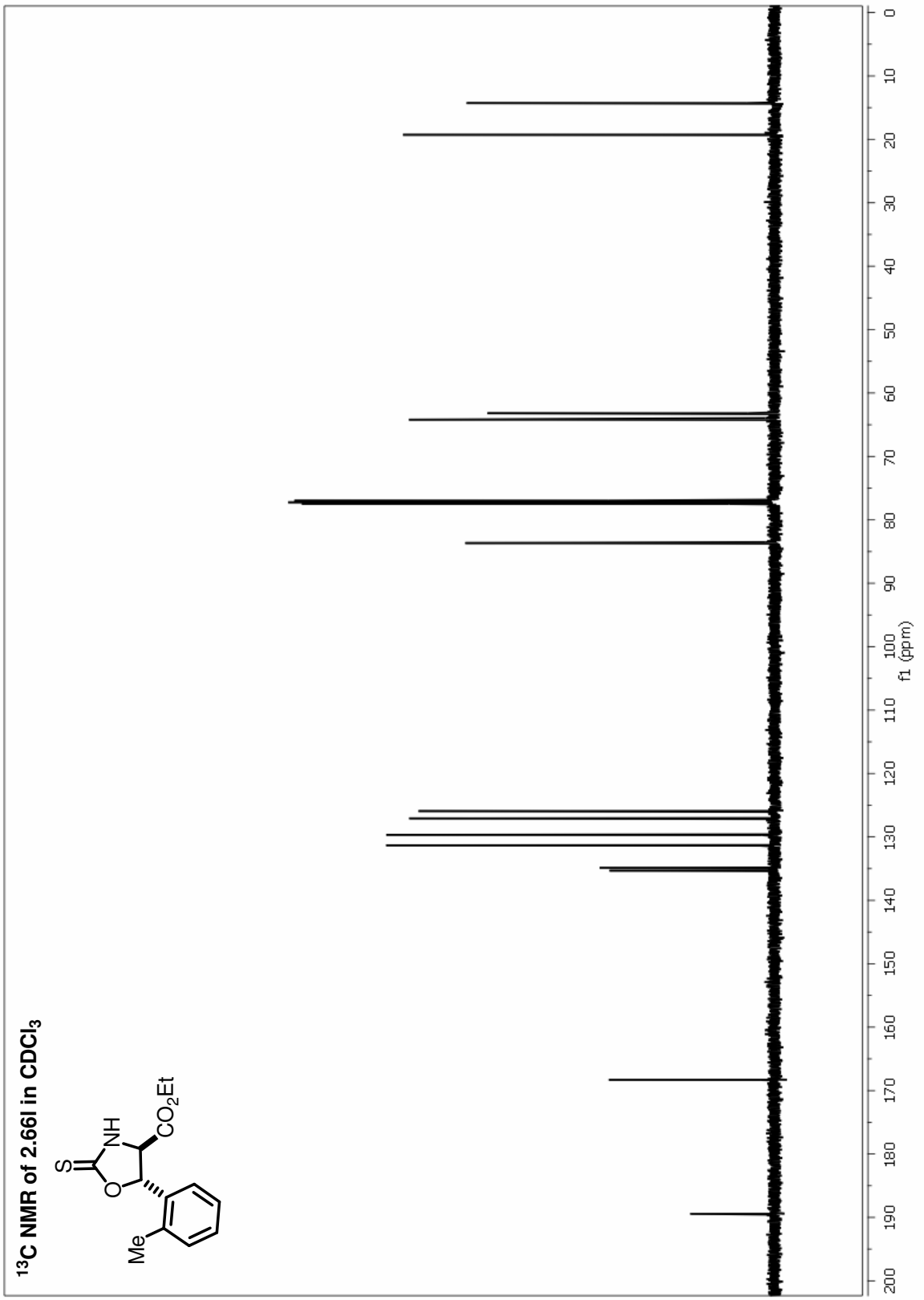

^{1}H NMR of 2.66j in $CDCl_3$
NH
CO_2Et
S
O
Cl
3.19
1.00
2.10
0.93
1.06
1.99
2.08
f1 (ppm)

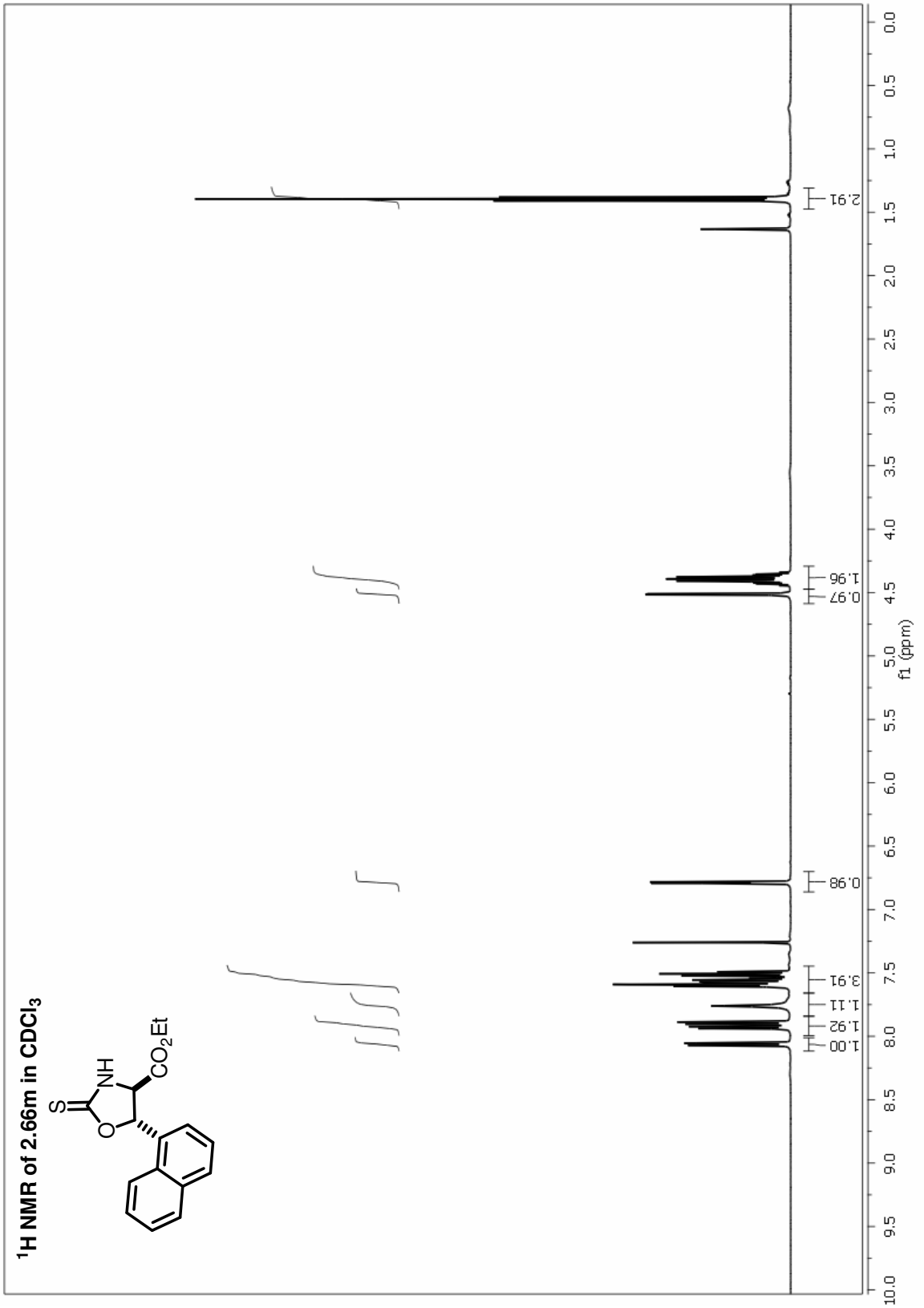

^{13}C NMR of 2.66j in $CDCl_3$
S
NH
O
CO_2Et
Cl
f1 (ppm)

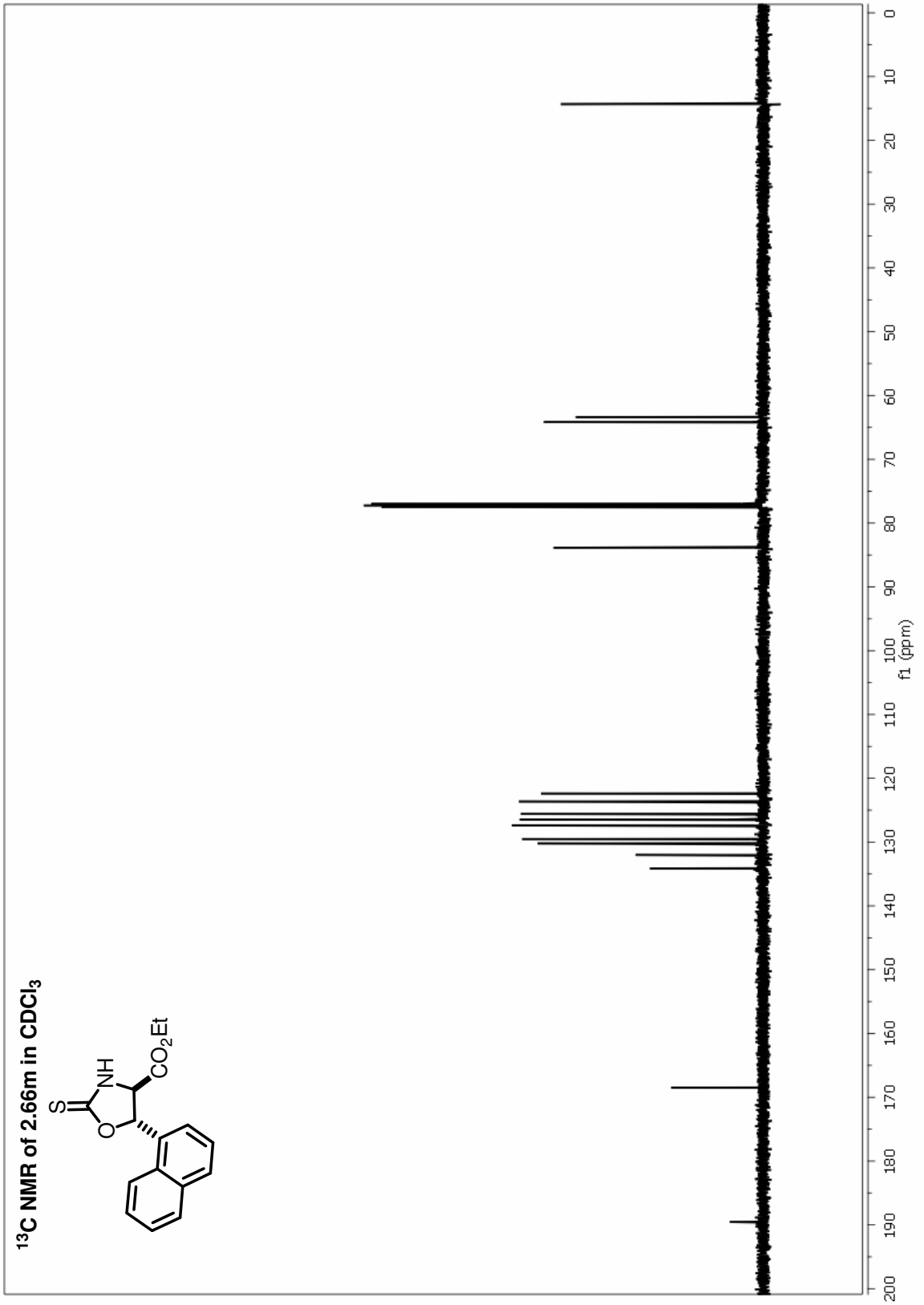

^{1}H NMR of 2.66k in $CDCl_3$
NH
CO_2Et
S
O
F
2.96
2.01
1.00
0.97
0.95
0.97
1.97
1.00
f1 (ppm)

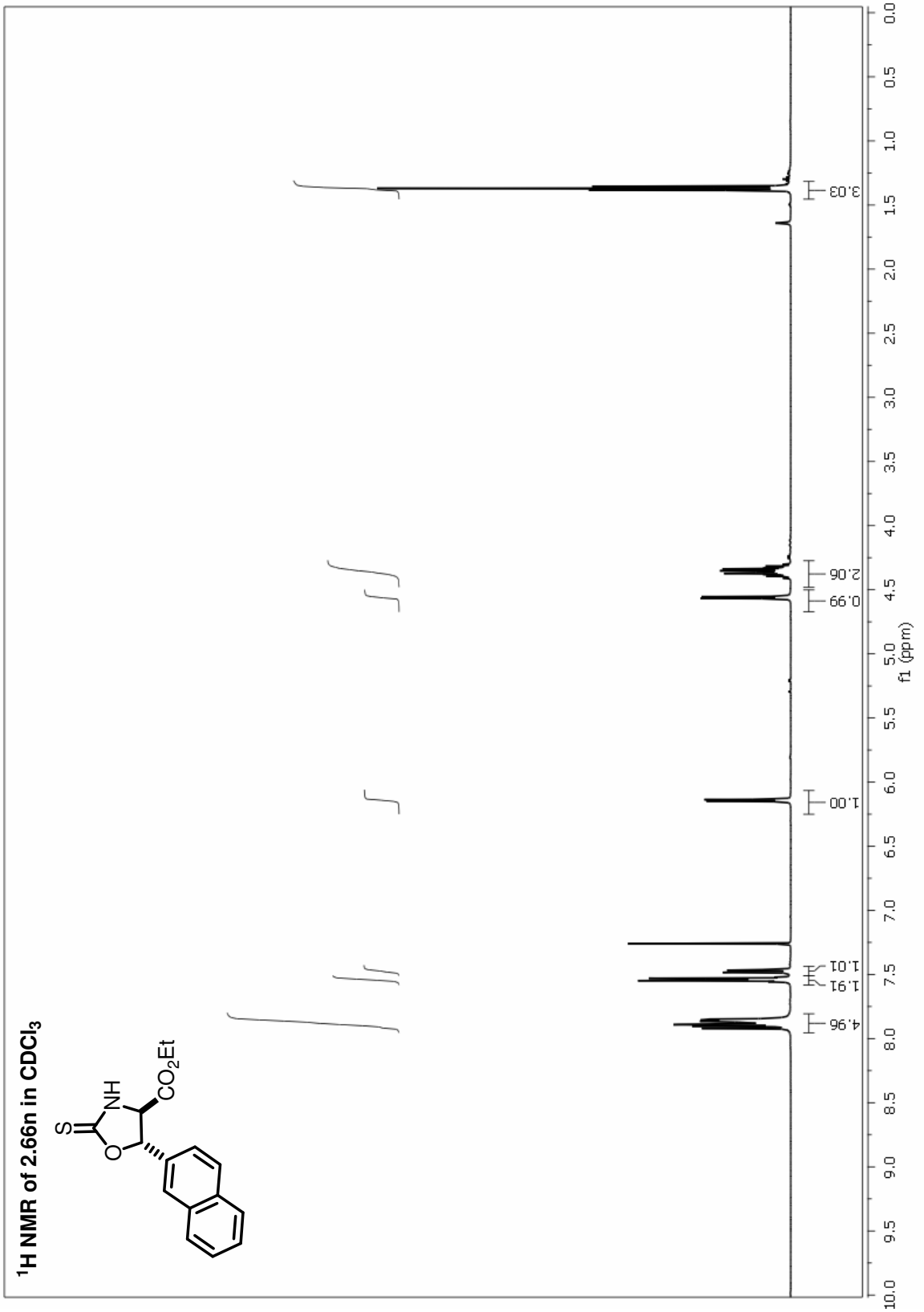

^{13}C NMR of 2.66k in $CDCl_3$
S
NH
O
CO_2Et
F
f1 (ppm)

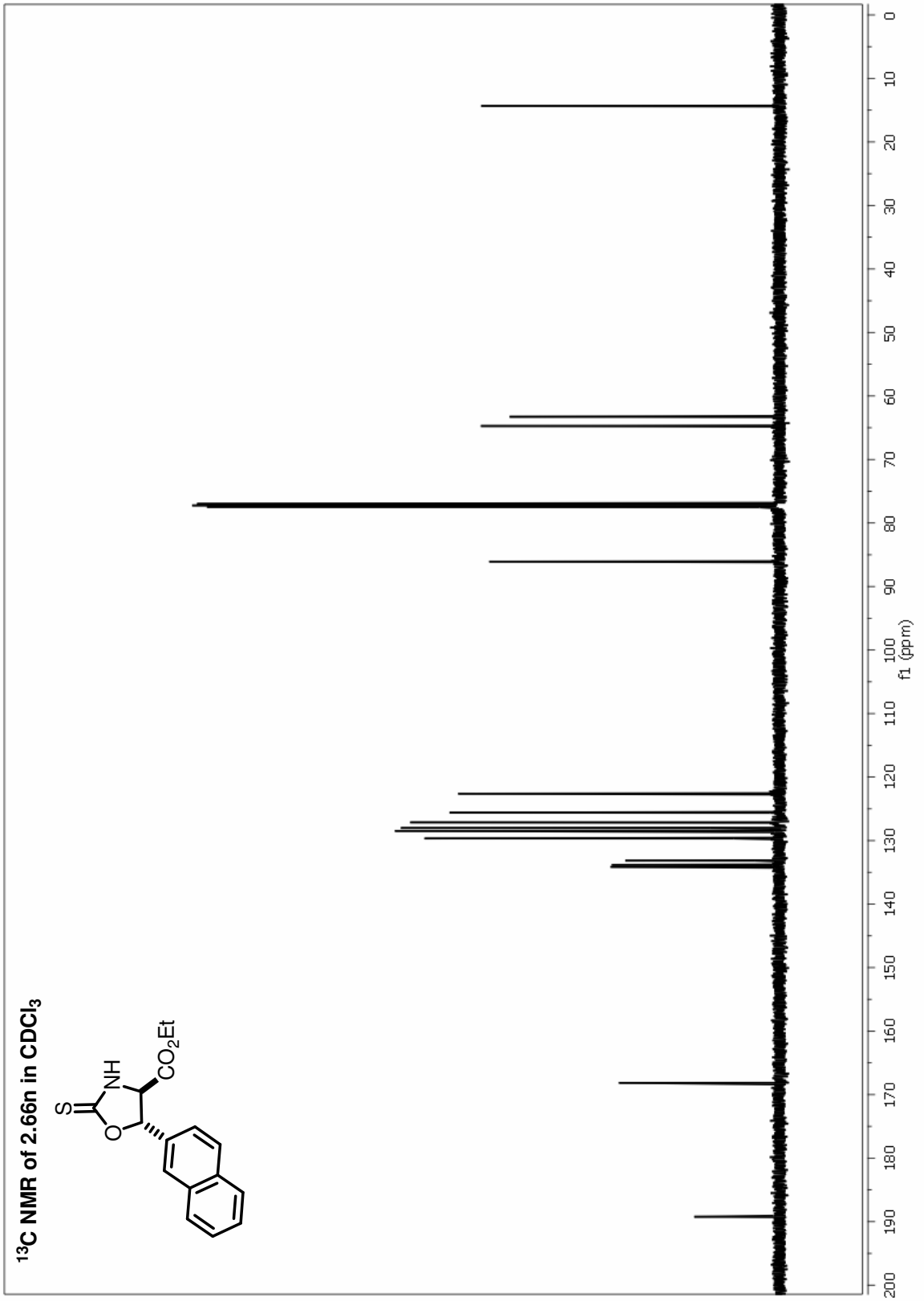

^{1}H NMR of 2.66l in $CDCl_3$
S
NH
O
CO_2Et
Me
1.00
2.74
1.06
0.96
1.95
0.93
3.05
3.06
f1 (ppm)

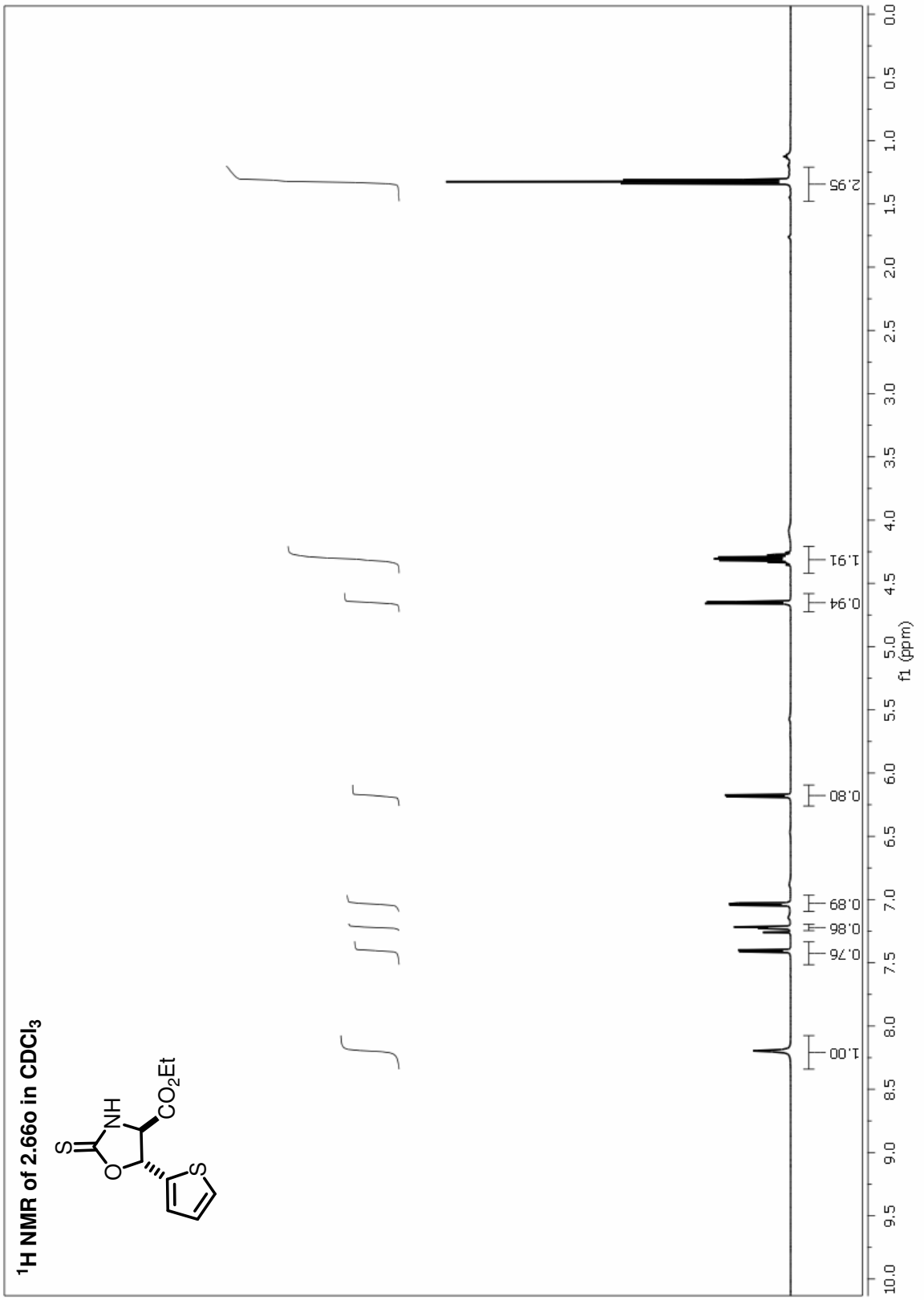

^{13}C NMR of 2.66l in $CDCl_3$
S
NH
O
CO_2Et
Me
f1 (ppm)

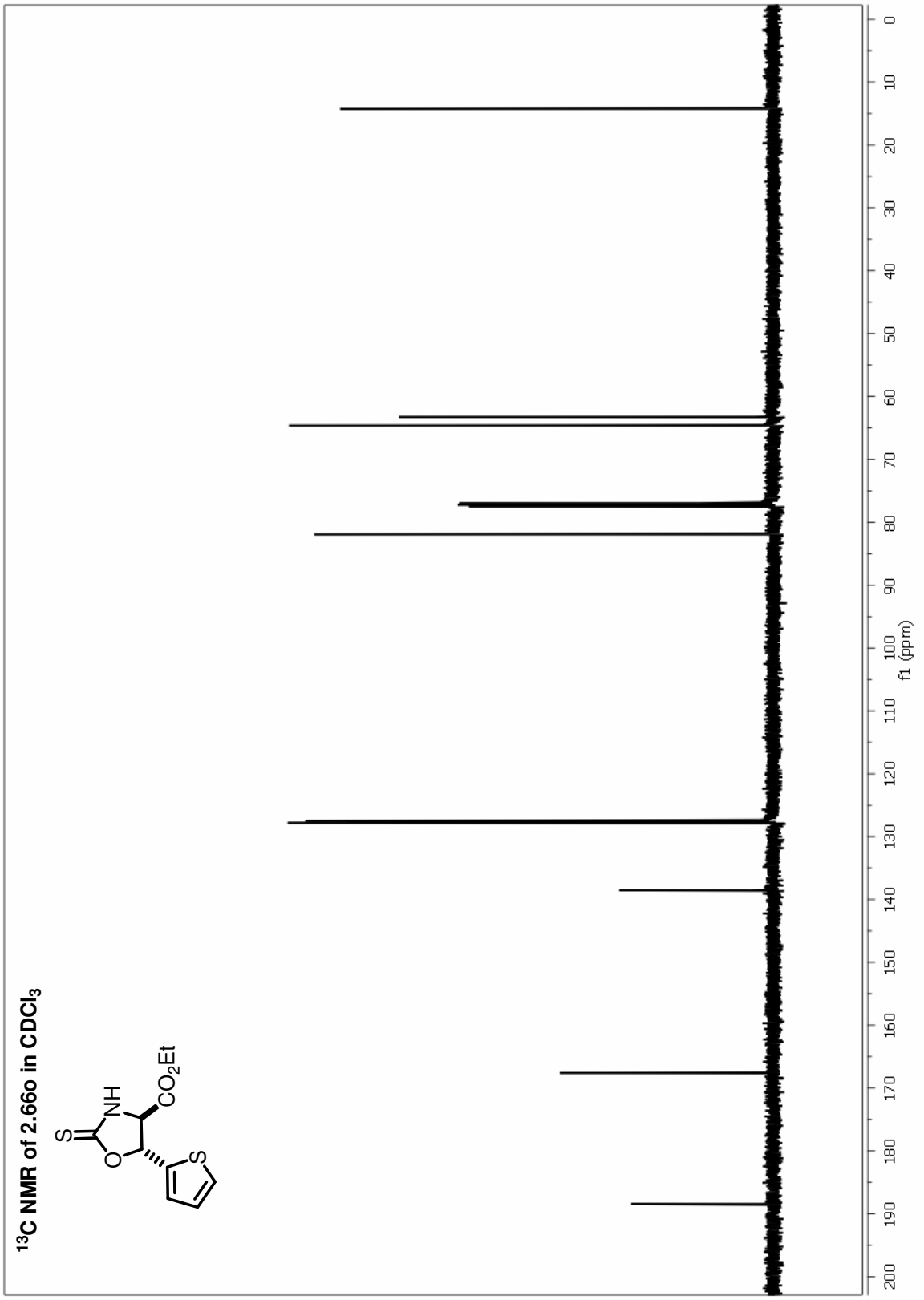

^{1}H NMR of 2.66m in $CDCl_3$
NH
S
O
CO_2Et
2.91
1.96
0.97
0.98
3.91
1.11
1.92
1.00
f1 (ppm)

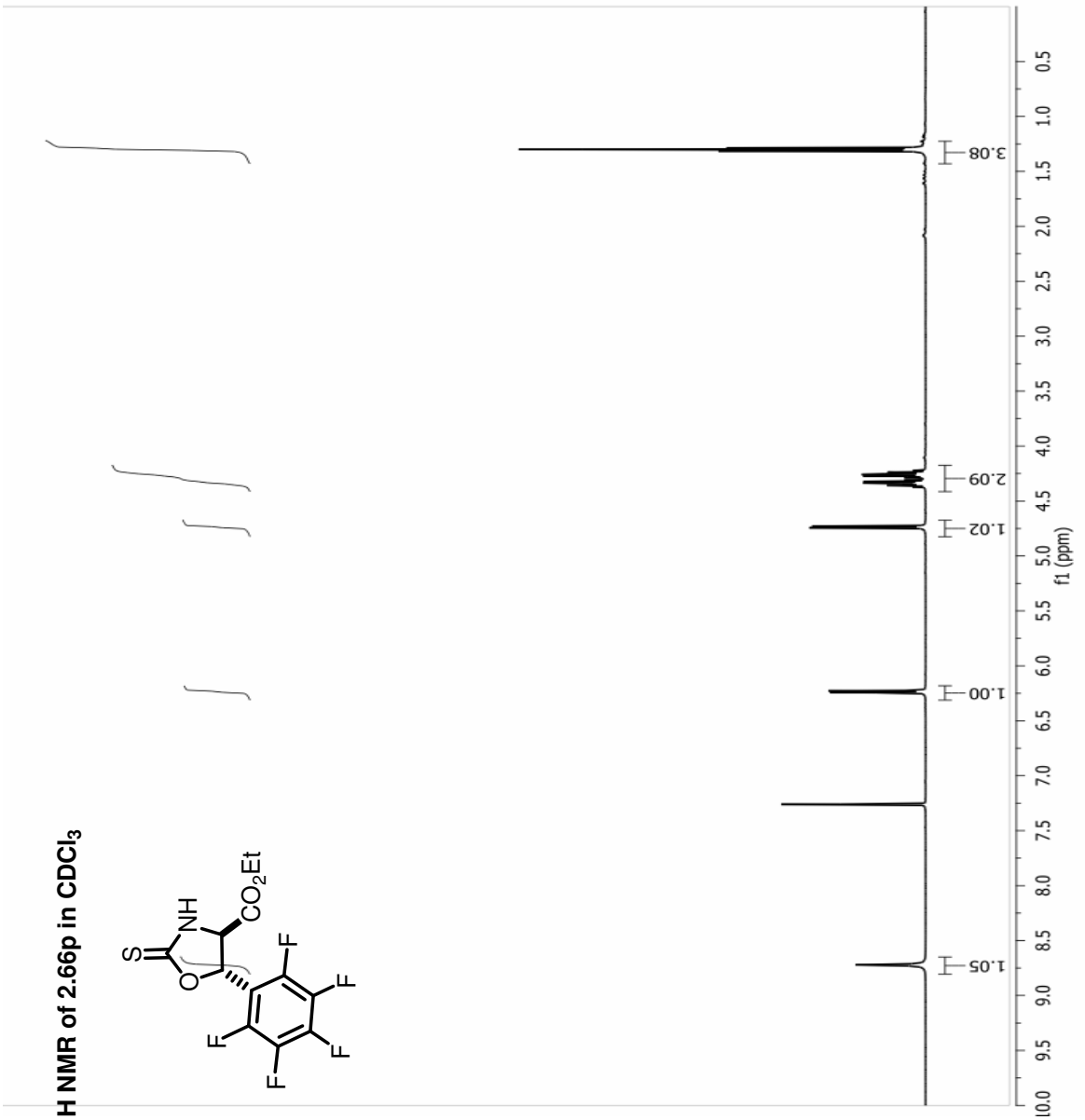

^{13}C NMR of 2.66m in $CDCl_3$
S
NH
O
CO_2Et
f1 (ppm)


^{1}H NMR of 2.66n in $CDCl_3$
NH
S
O
CO_2Et
4.96
1.91
1.01
1.00
0.99
2.06
3.03
f1 (ppm)

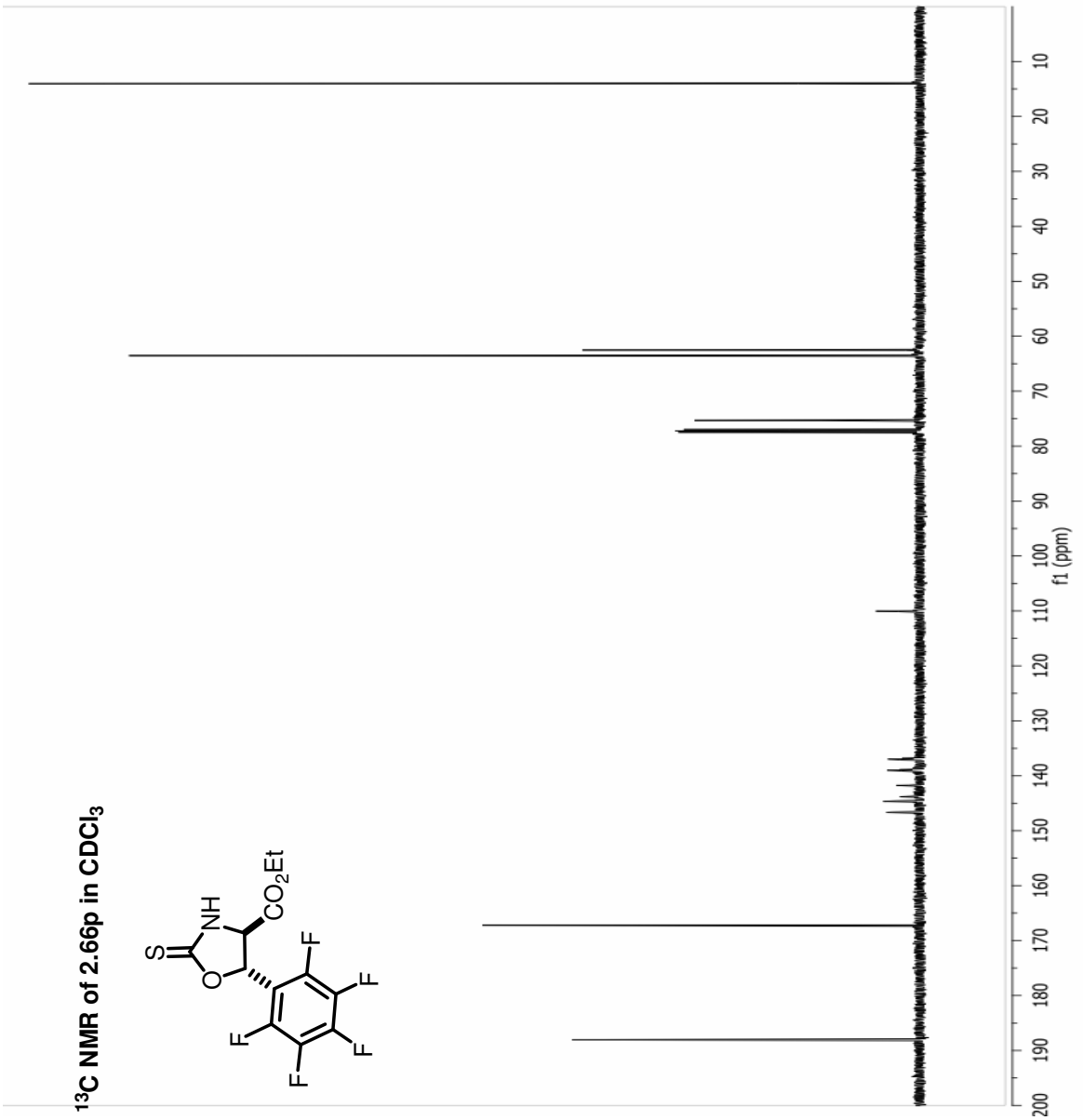

^{13}C NMR of 2.66n in $CDCl_3$
S
NH
O
CO_2Et
f1 (ppm)

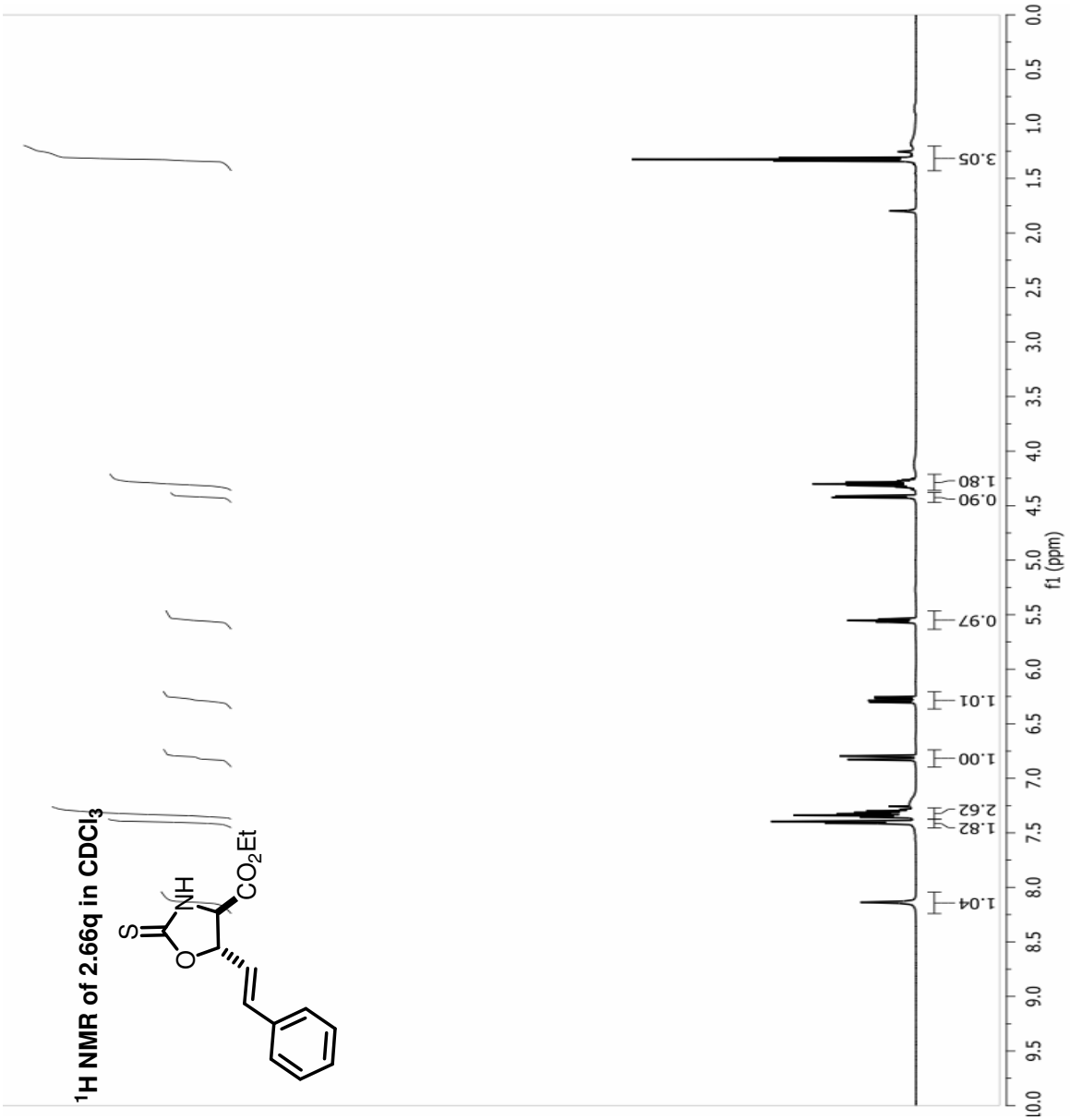

^{1}H NMR of 2.66o in $CDCl_3$
NH
CO_2Et
S
O
S
1.00
0.76
0.86
0.89
0.80
0.94
1.91
2.95
f1 (ppm)

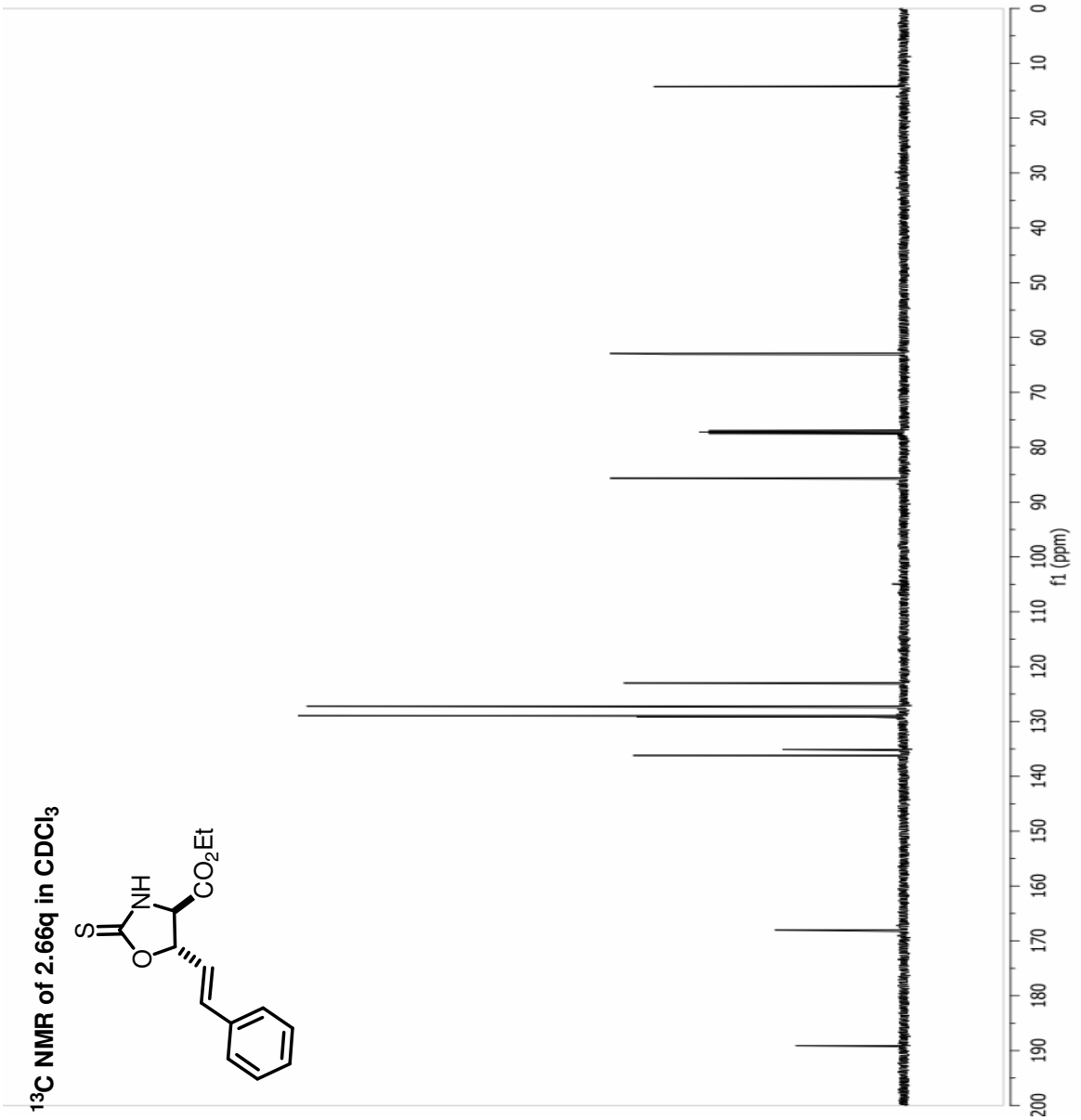

^{13}C NMR of 2.66o in $CDCl_3$
NH
CO_2Et
S
O
S
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

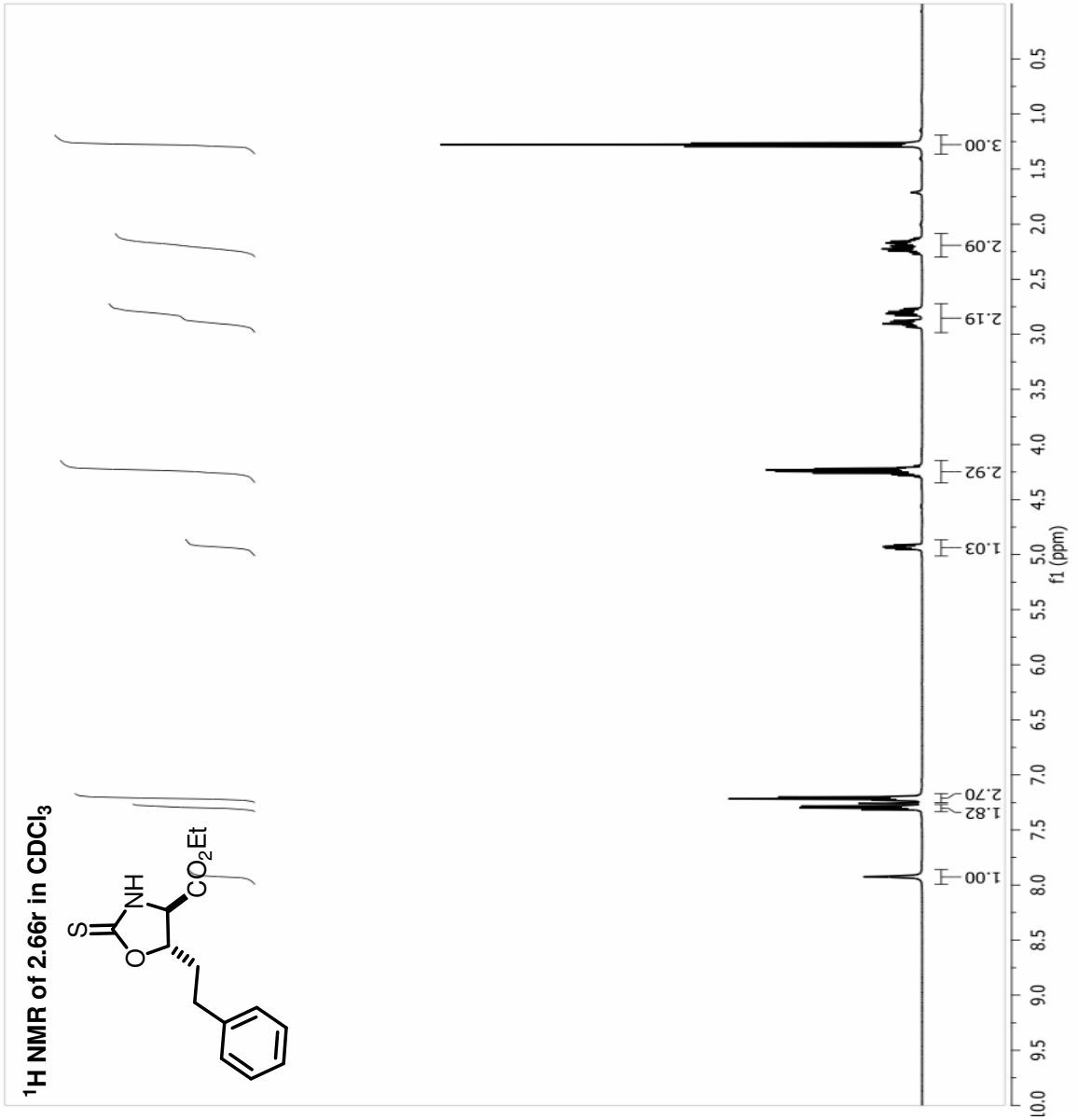


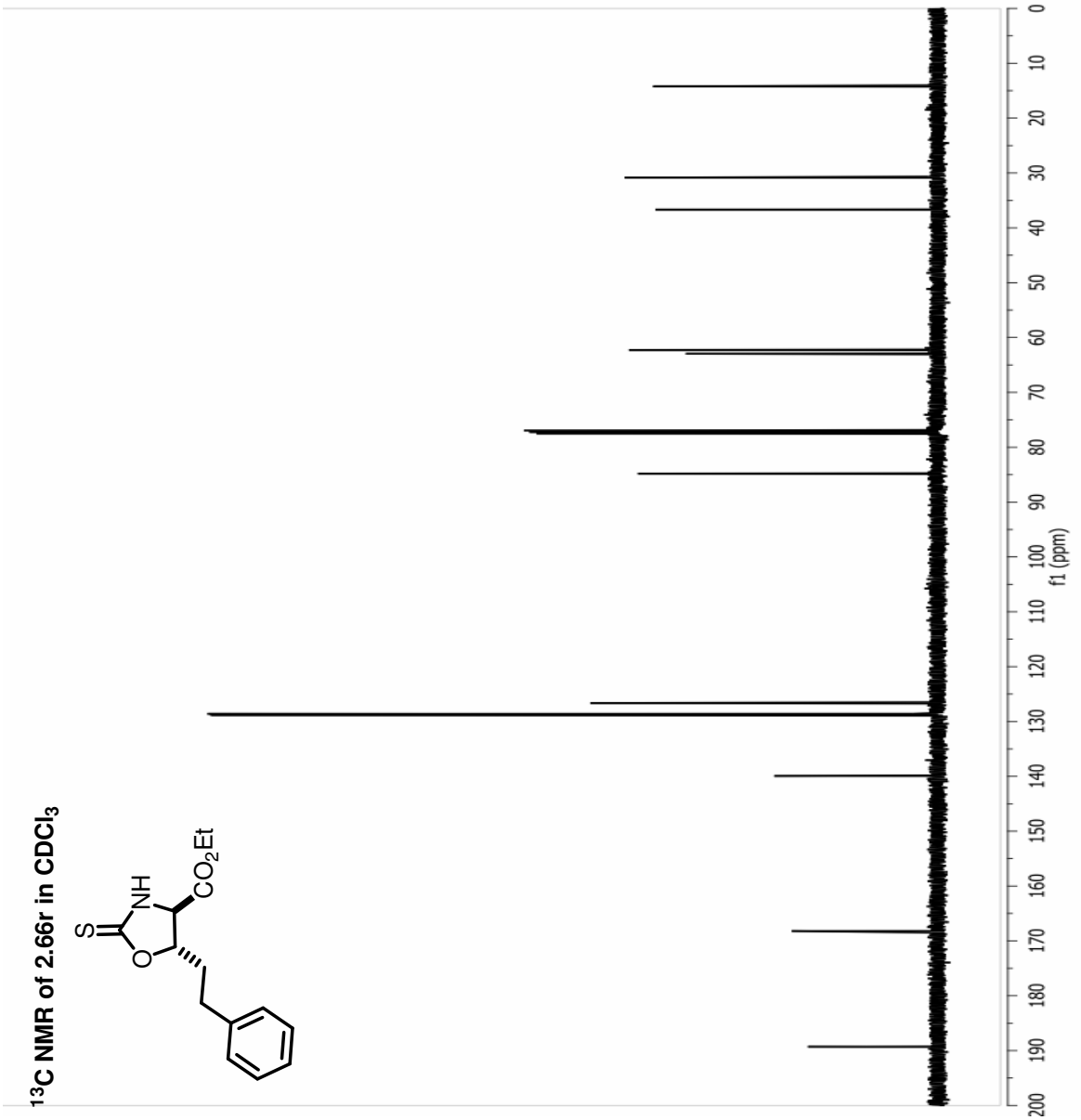
^{1}H NMR of 2.66p in $CDCl_3$

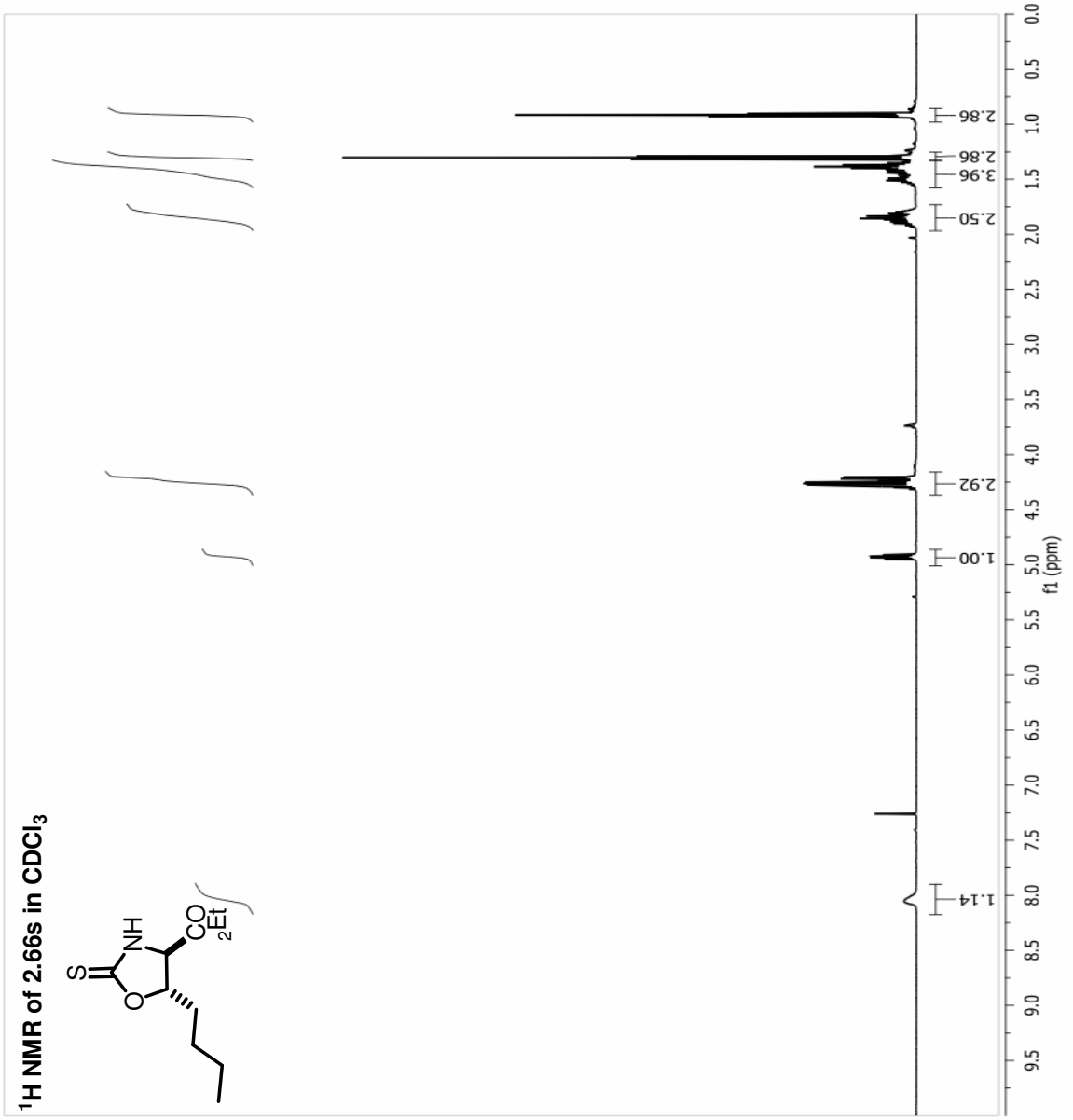

^{13}C NMR of 2.66p in $CDCl_3$
NH
CO_2Et
S
O
F
F
F
F
f1 (ppm)

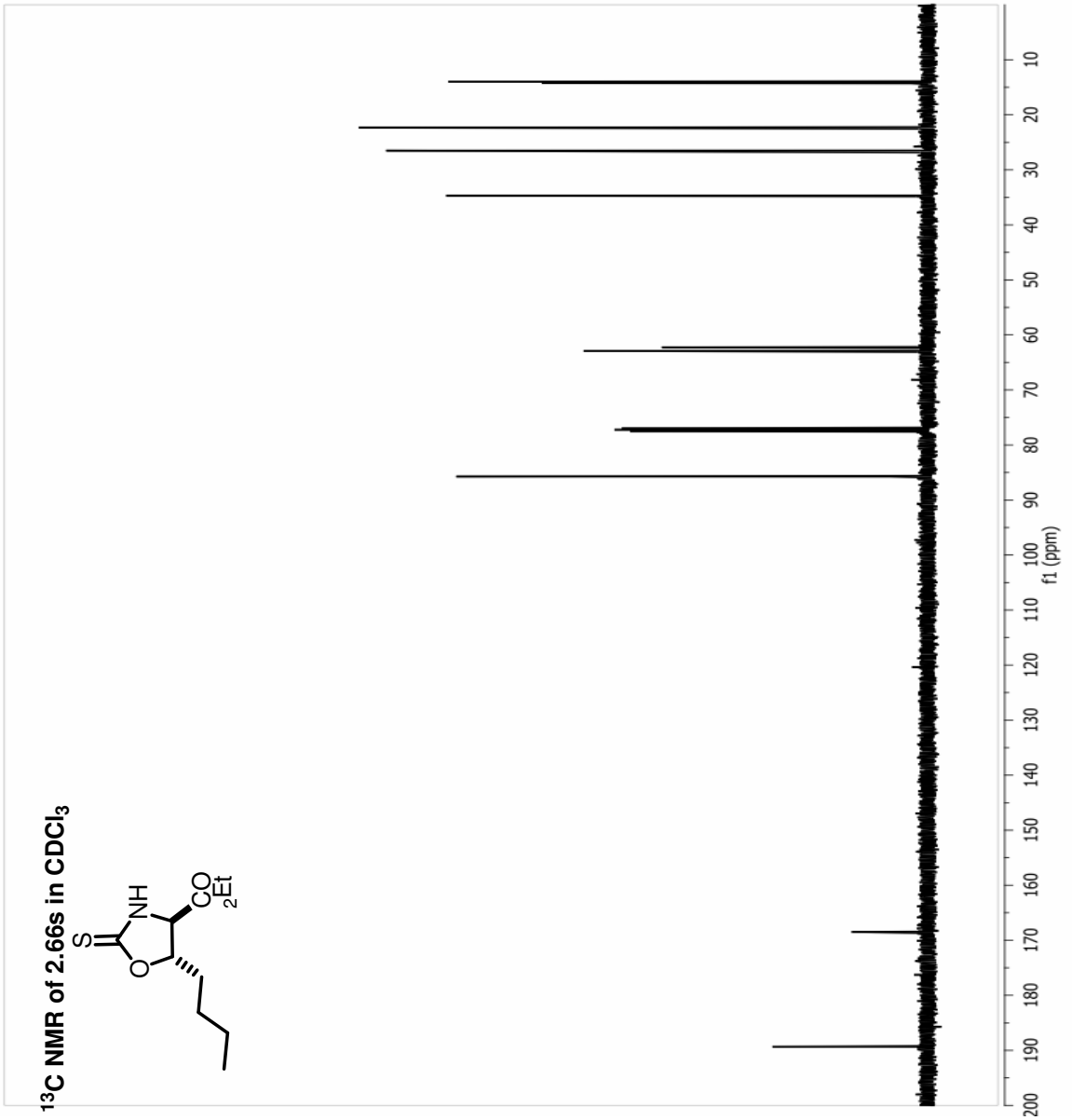

^{1}H NMR of 2.66q in $CDCl_3$
NH
S
O
CO_2Et
3.05
1.80
0.90
0.97
1.01
1.00
1.82
2.62
1.04
f1 (ppm)

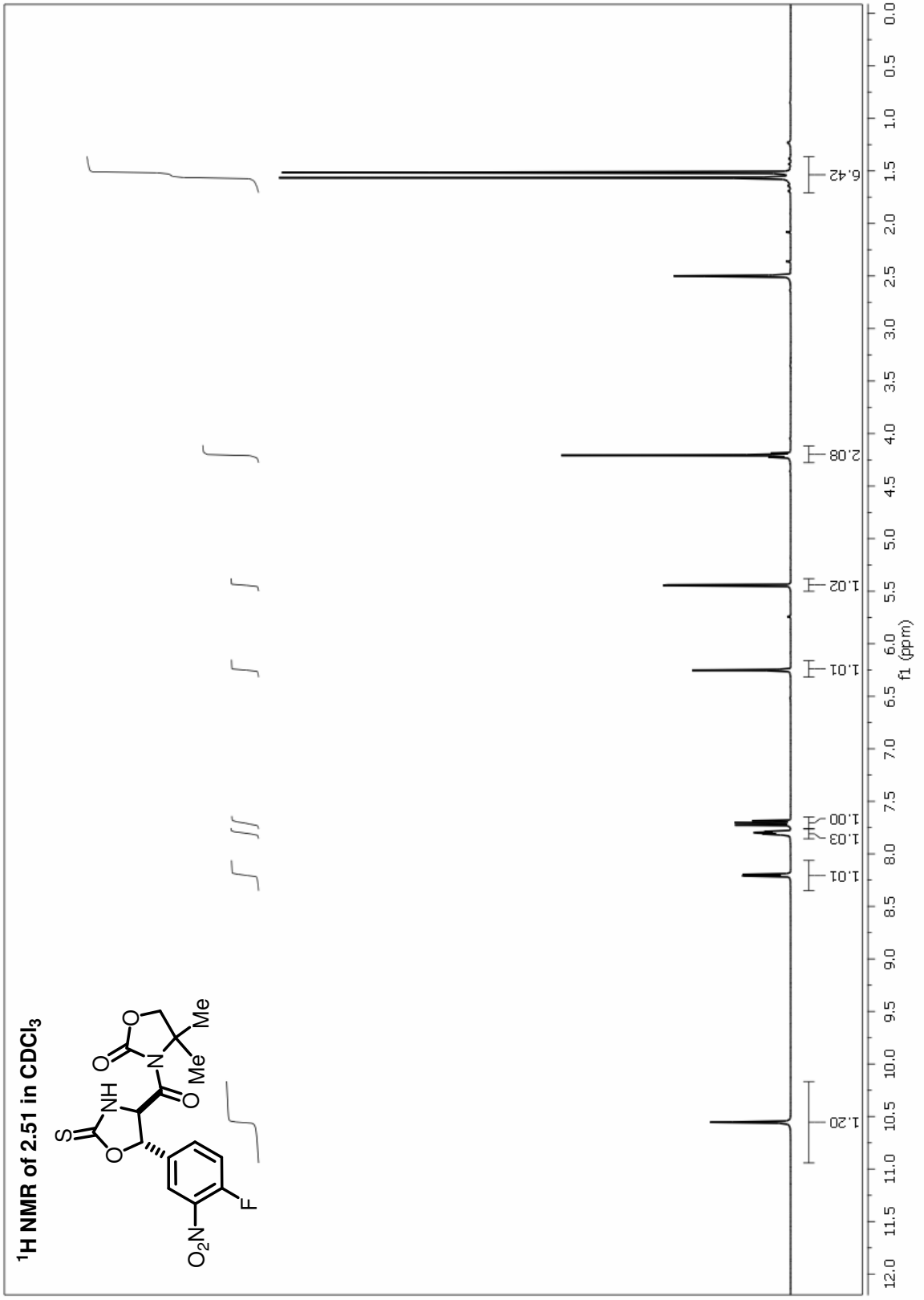

^{13}C NMR of 2.66q in $CDCl_3$
S
NH
O
CO_2Et
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

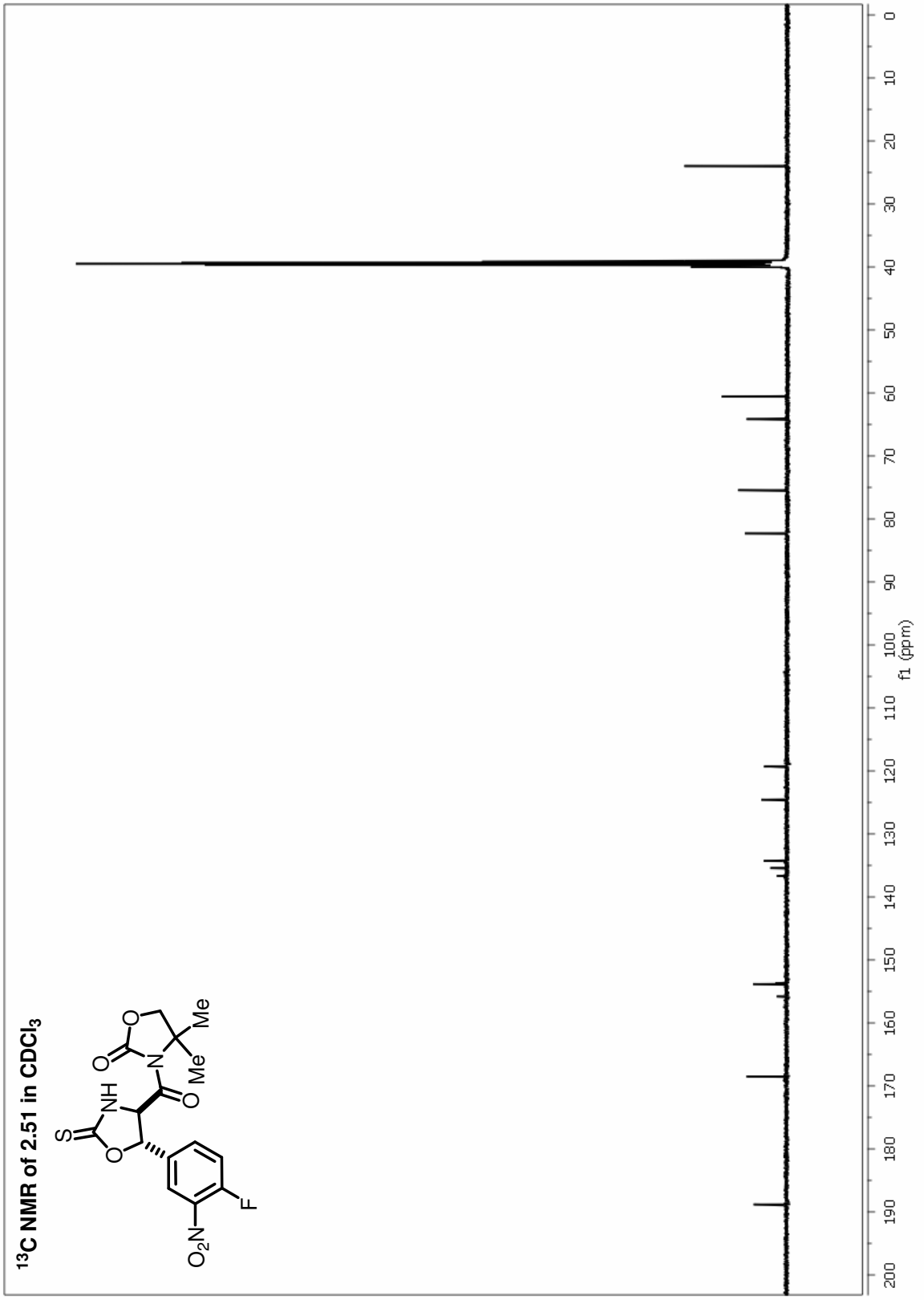

^{1}H NMR of 2.66r in $CDCl_3$
S
NH
O
CO_2Et
3.00
2.09
2.19
2.92
1.03
1.82
2.70
1.00
f1 (ppm)

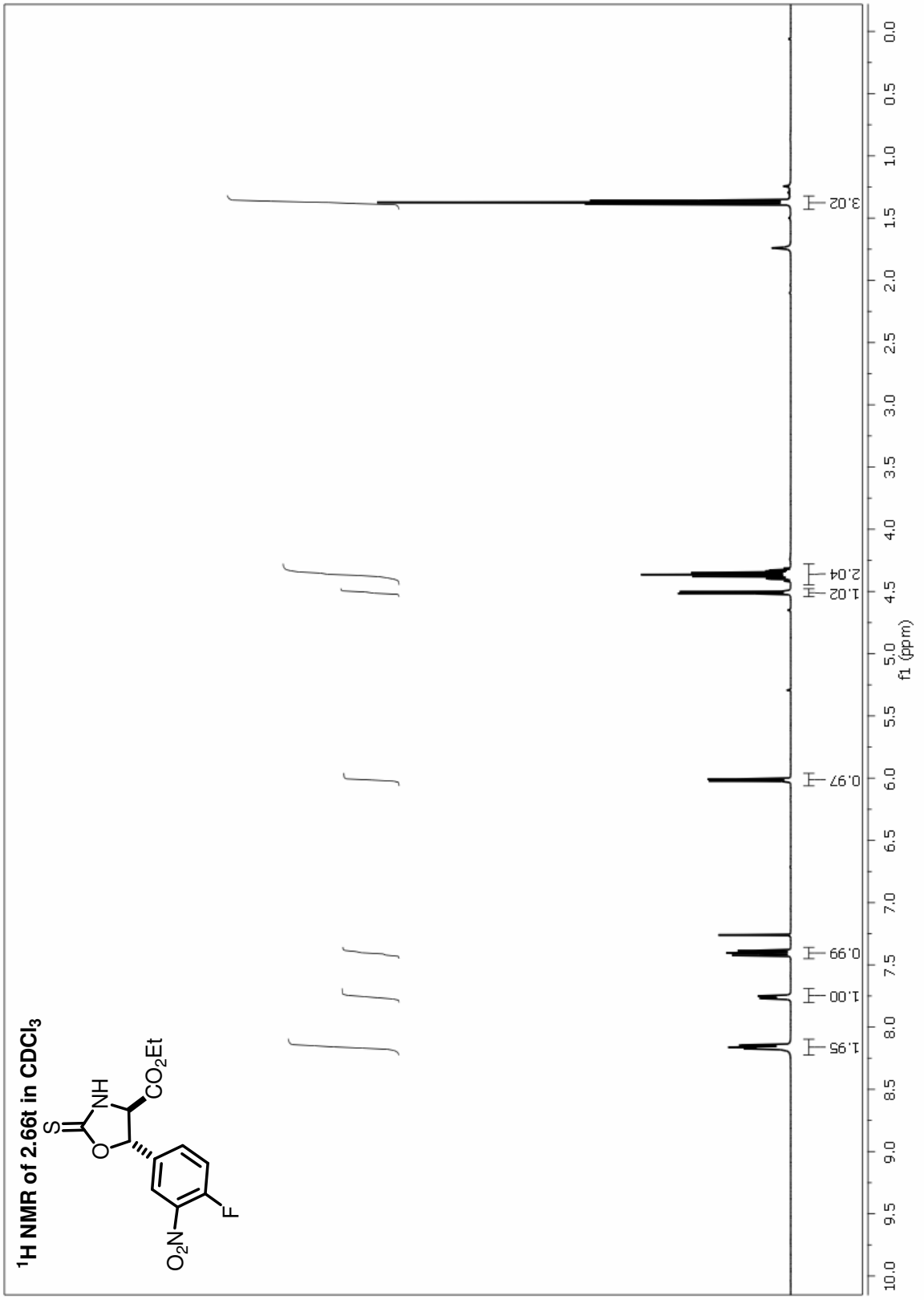

^{13}C NMR of 2.66r in $CDCl_3$
S
NH
O
CO_2Et
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

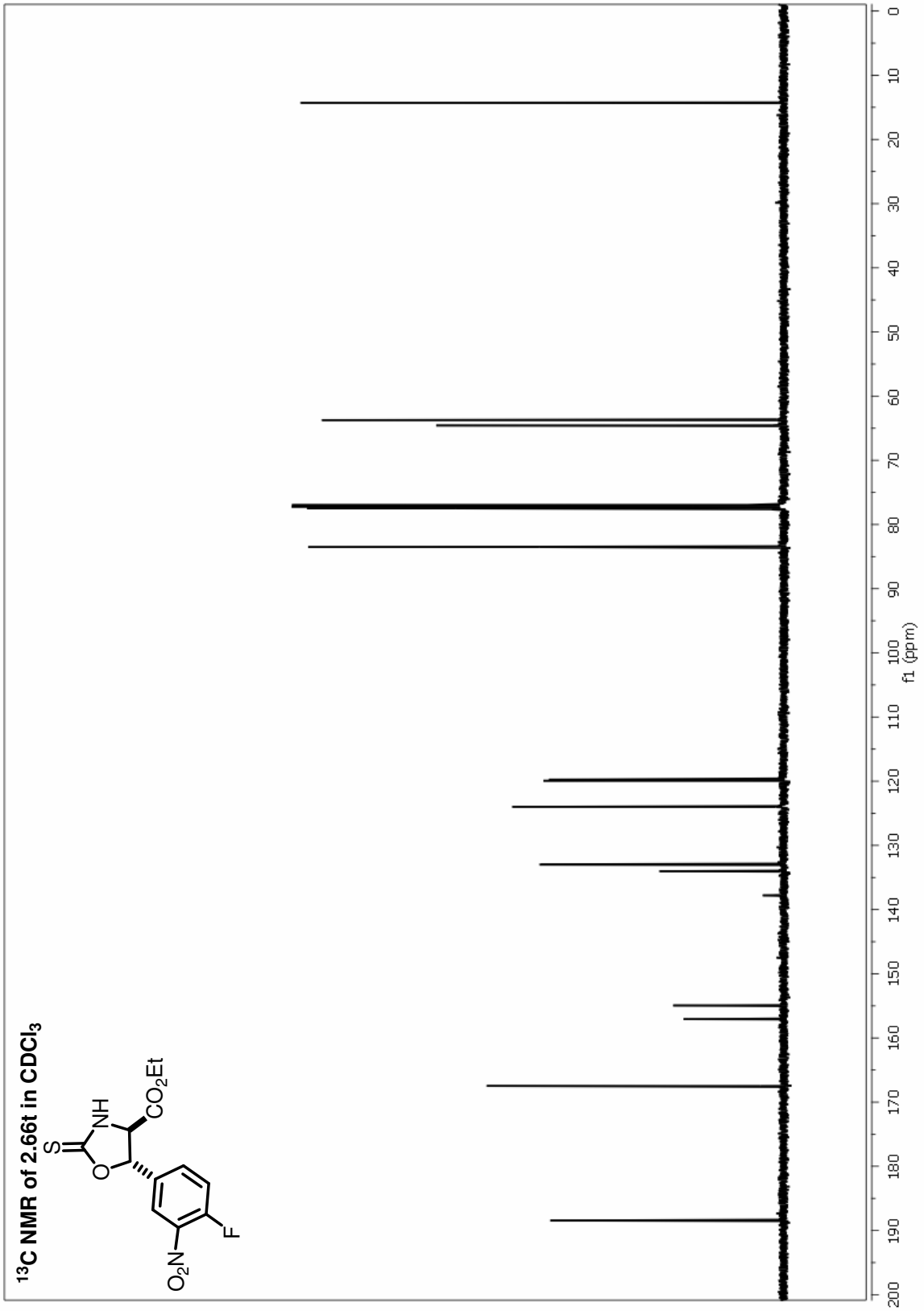

^{1}H NMR of 2.66s in $CDCl_3$
NH
S
O
CO2Et
2.86
2.86
3.96
2.50
2.92
1.00
1.14
f1 (ppm)

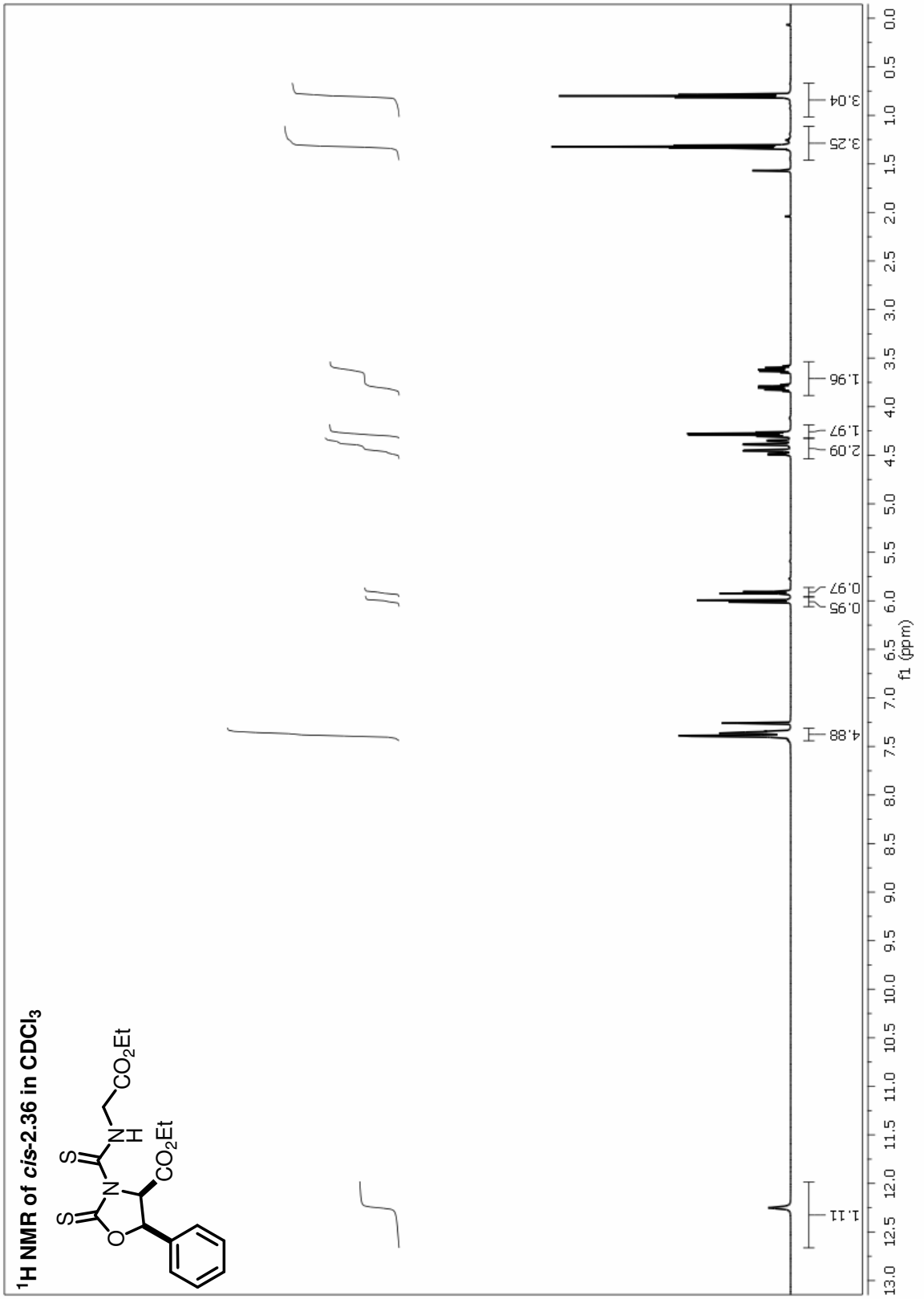

^{13}C NMR of 2.66s in $CDCl_3$
S
NH
O
CO
2Et
f1 (ppm)

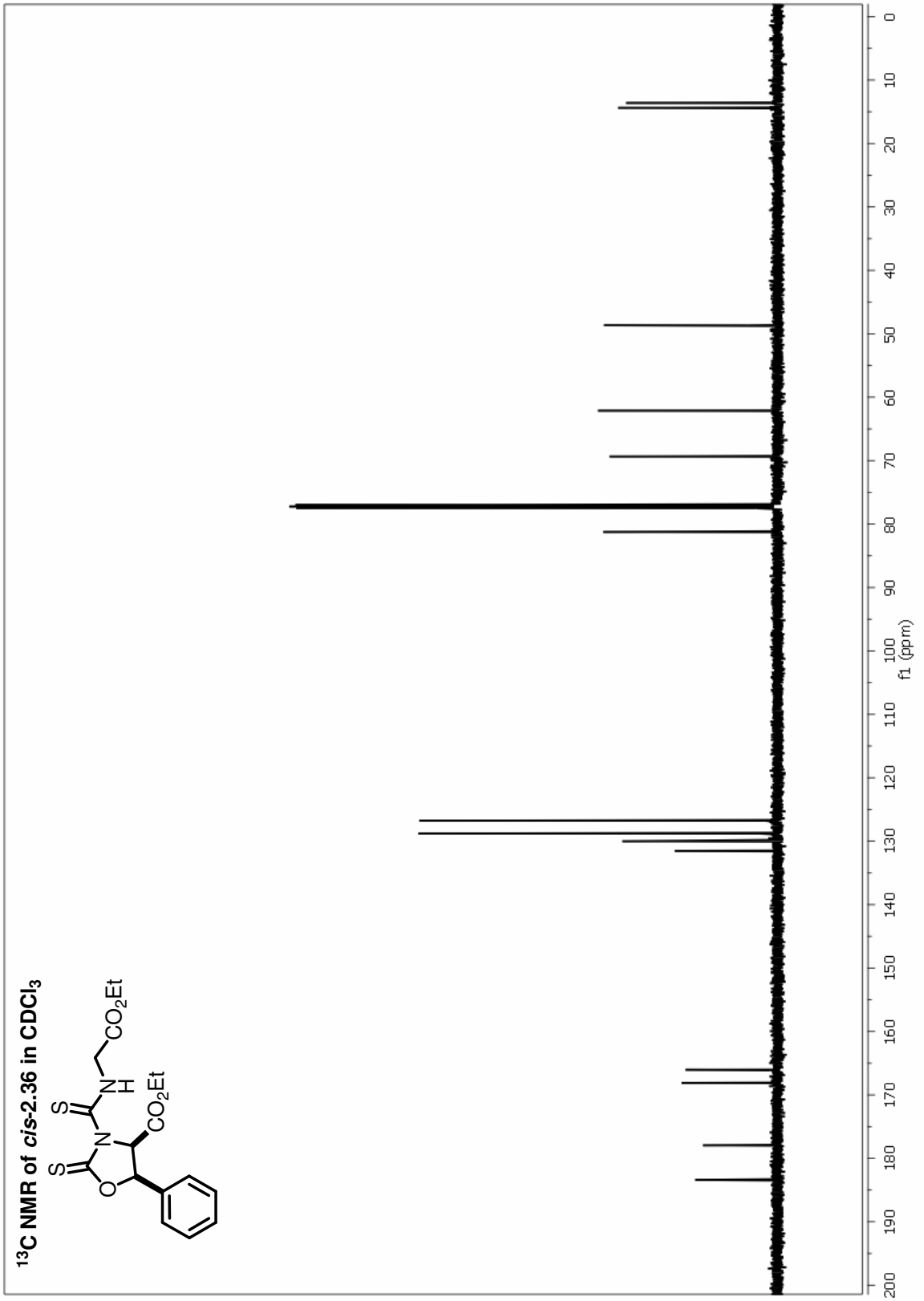

^{1}H NMR of 2.51 in $CDCl_3$
1.20
1.01
1.03
1.00
1.01
1.02
2.08
6.42
f1 (ppm)

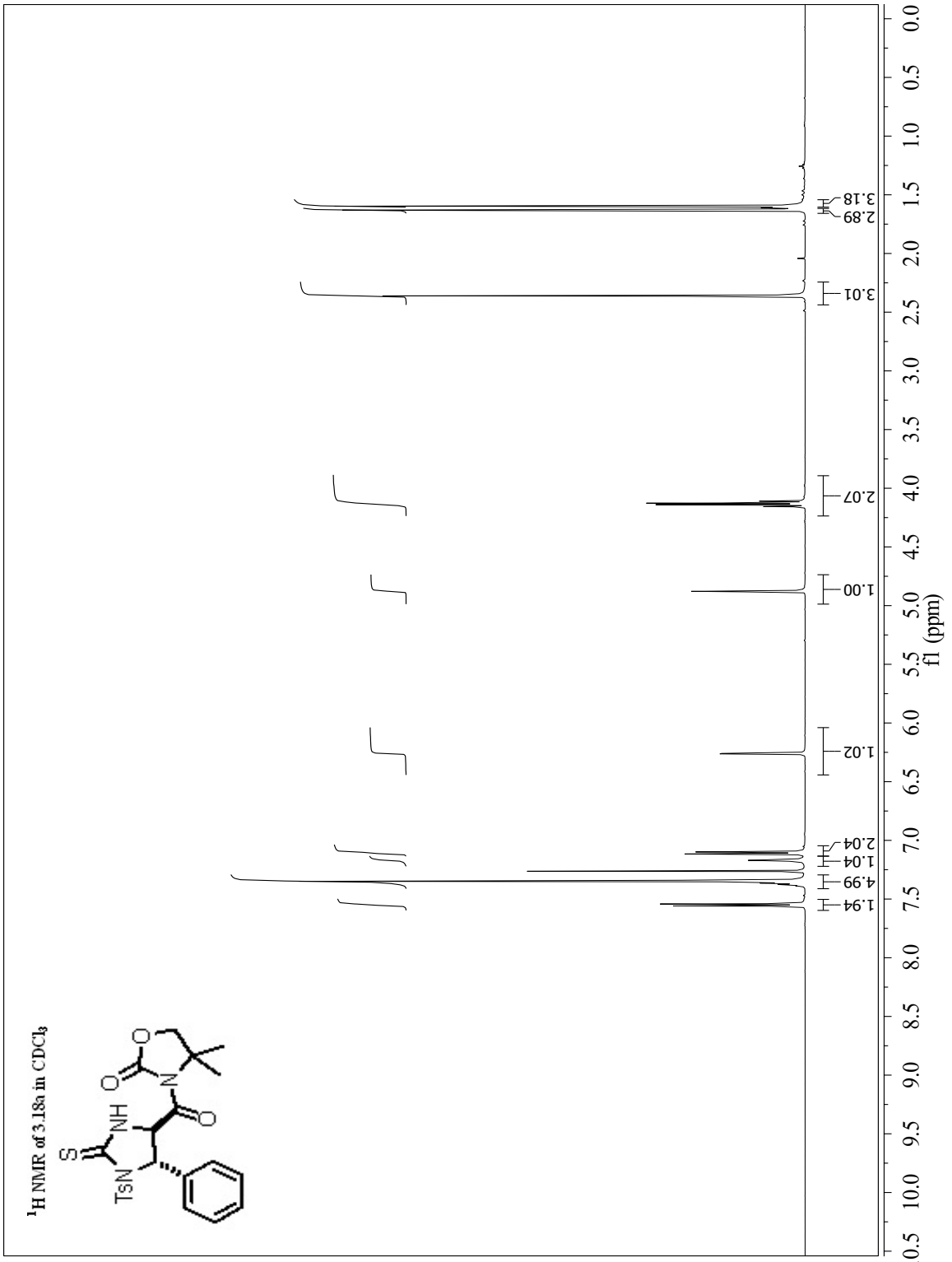

^{13}C NMR of 2.51 in $CDCl_3$
f1 (ppm)

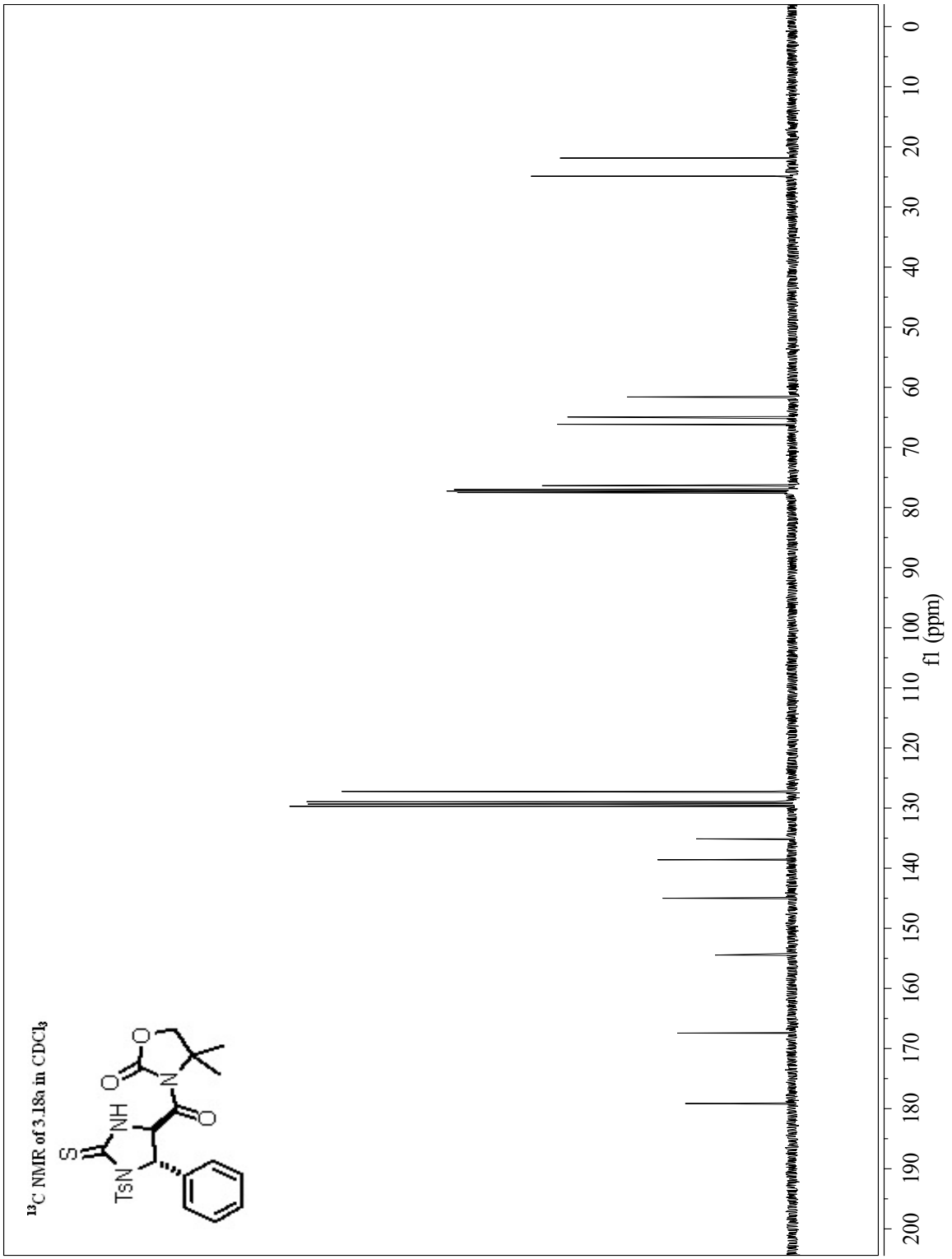

^{1}H NMR of 2.66t in $CDCl_3$
S
NH
O
CO_2Et
O_2N
F
3.02
2.04
1.02
0.97
0.99
1.00
1.95
f1 (ppm)

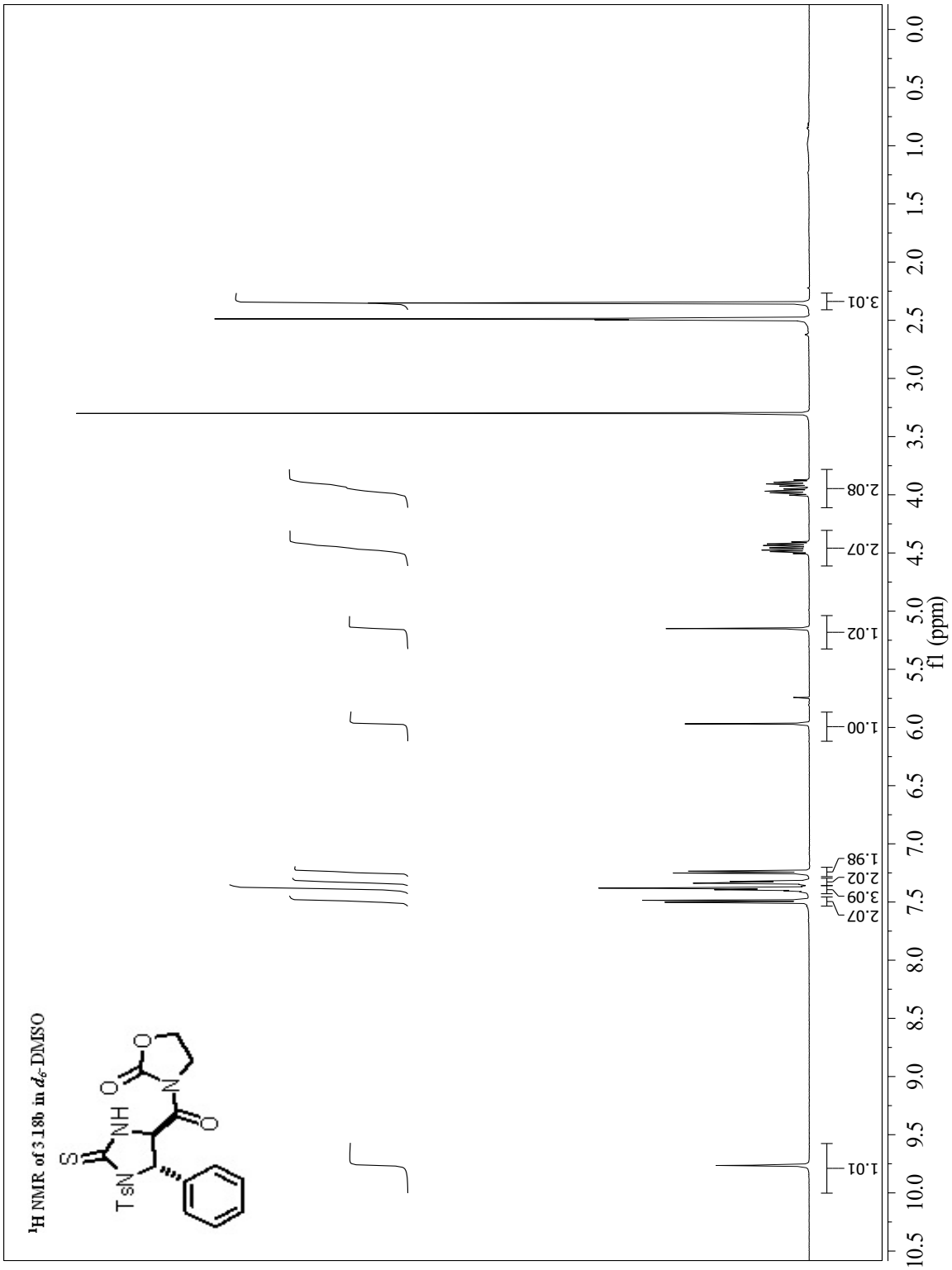

^{13}C NMR of 2.66t in $CDCl_3$
S
NH
O
CO_2Et
O_2N
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

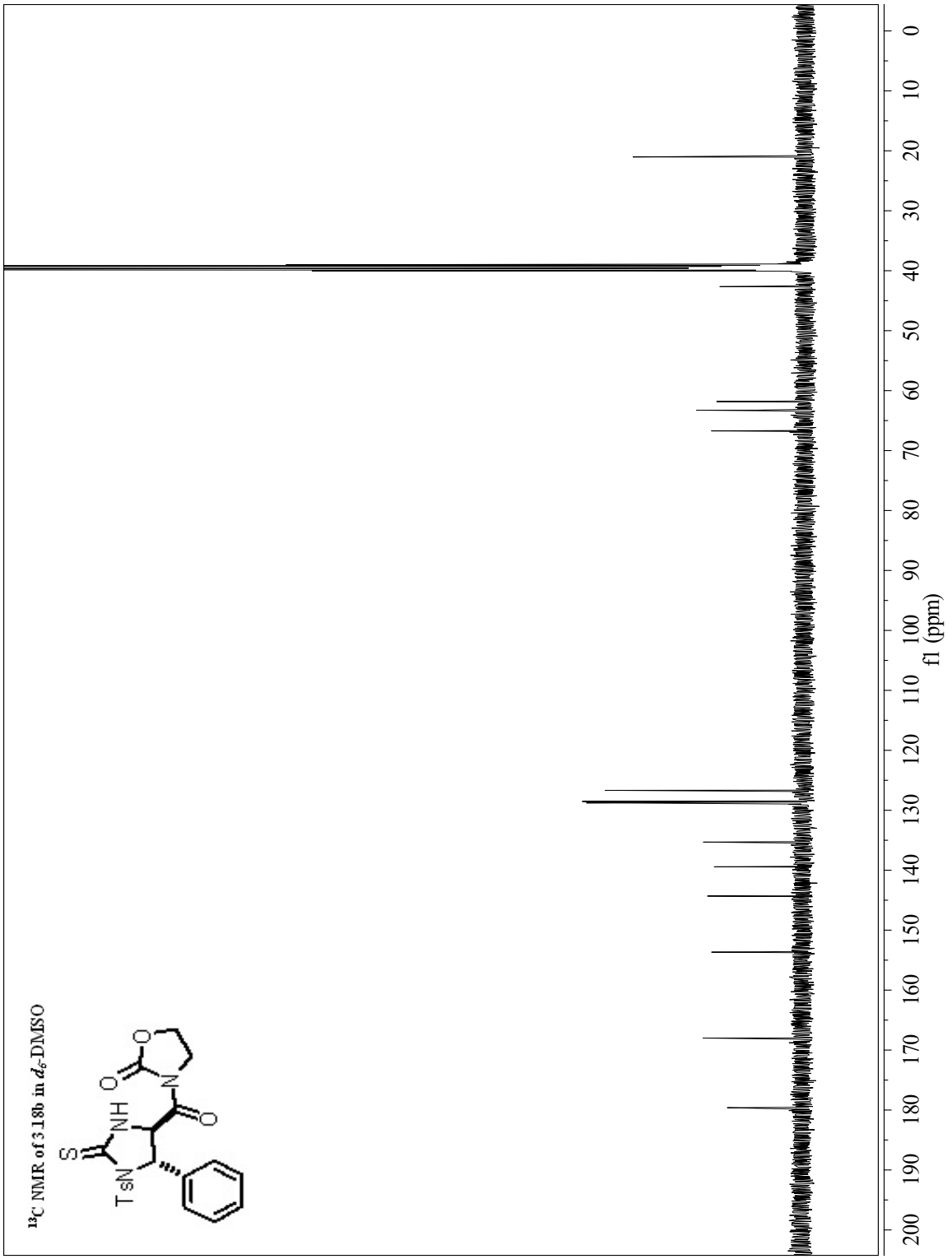

^{1}H NMR of *cis*-2.36 in $CDCl_3$
S
N
H
CO_2Et
S
N
O
CO_2Et
1.11
4.88
0.95
0.97
2.09
1.97
1.96
3.25
3.04
f1 (ppm)

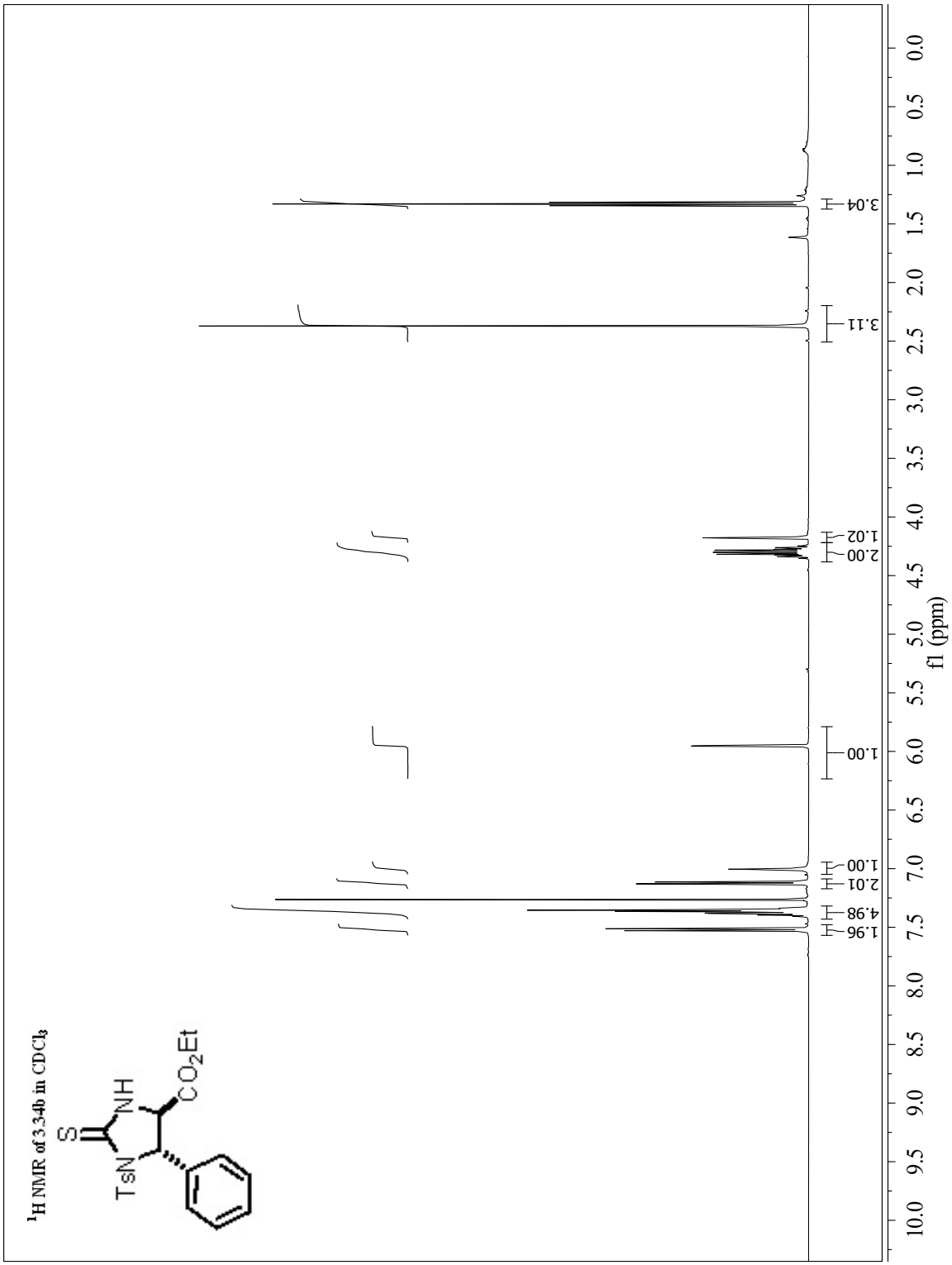

^{13}C NMR of *cis*-2.36 in $CDCl_3$
S
N
H
CO_2Et
S
N
O
CO_2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

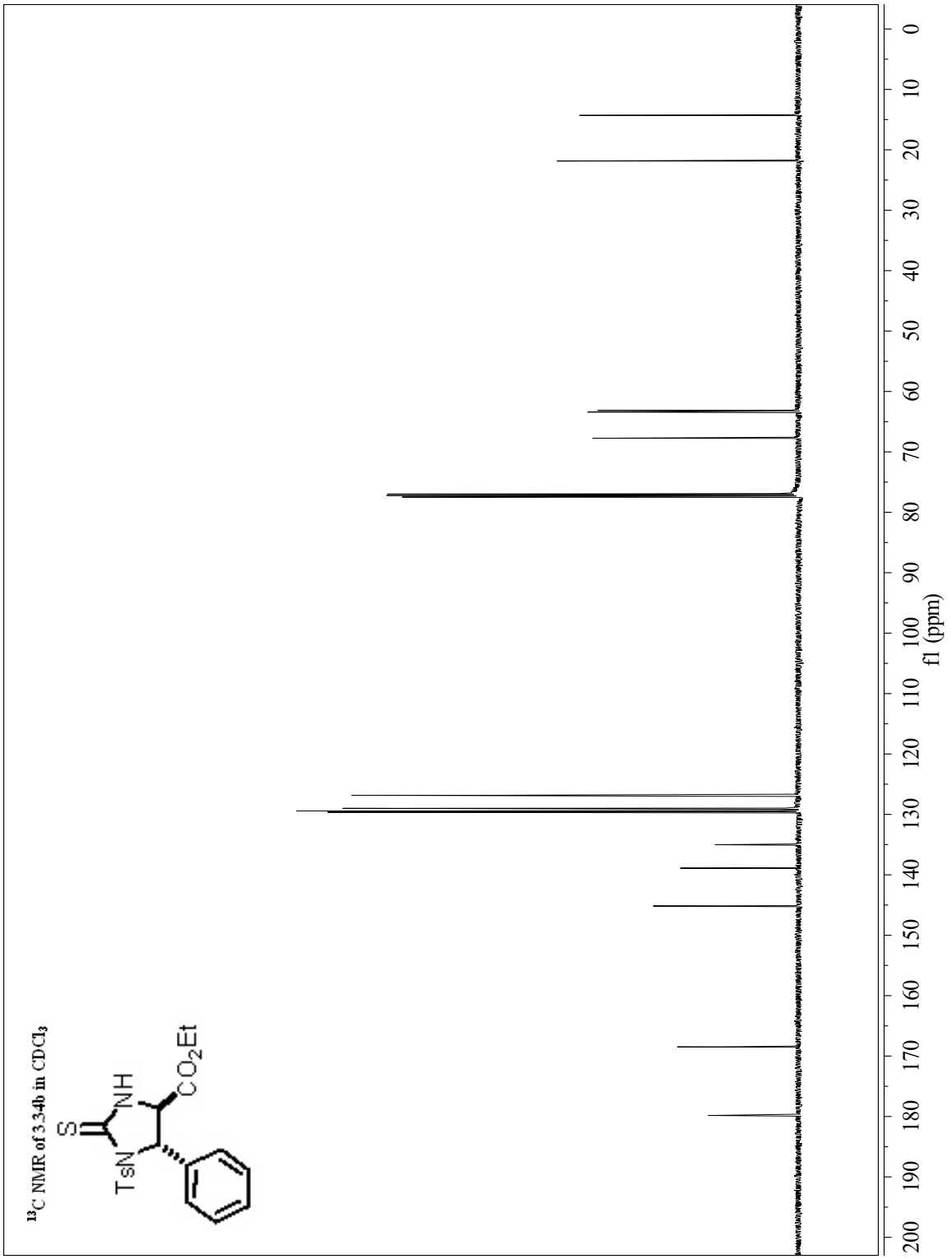

^{1}H NMR of 3.18a in $CDCl_3$
TsN
NH
S
O
O
O
O
N
1.94
4.99
1.04
2.04
1.02
1.00
2.07
3.01
2.89
3.18
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

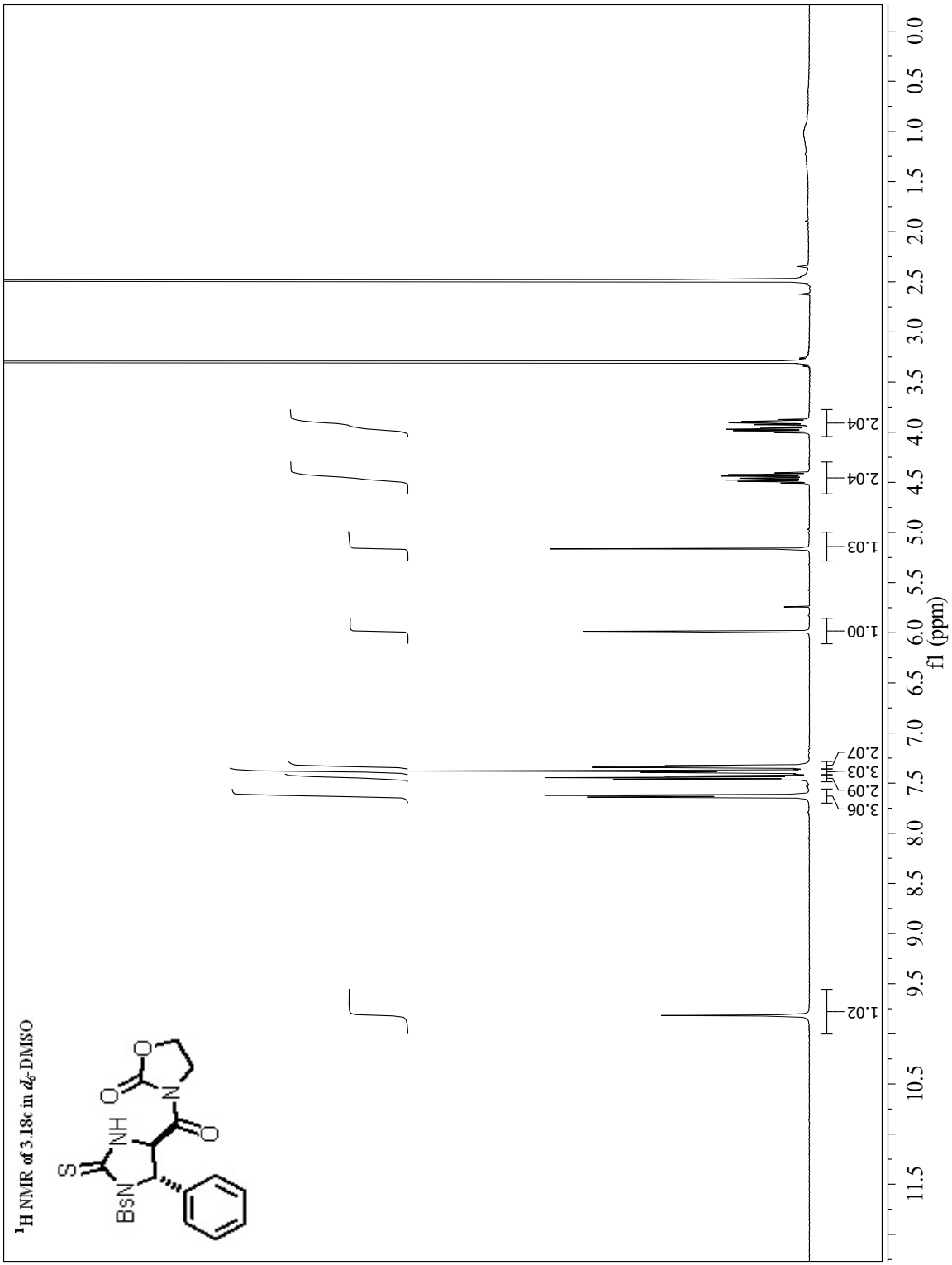

^{13}C NMR of 3.18a in $CDCl_3$
TsN
NH
S
O
O
O
O
N
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

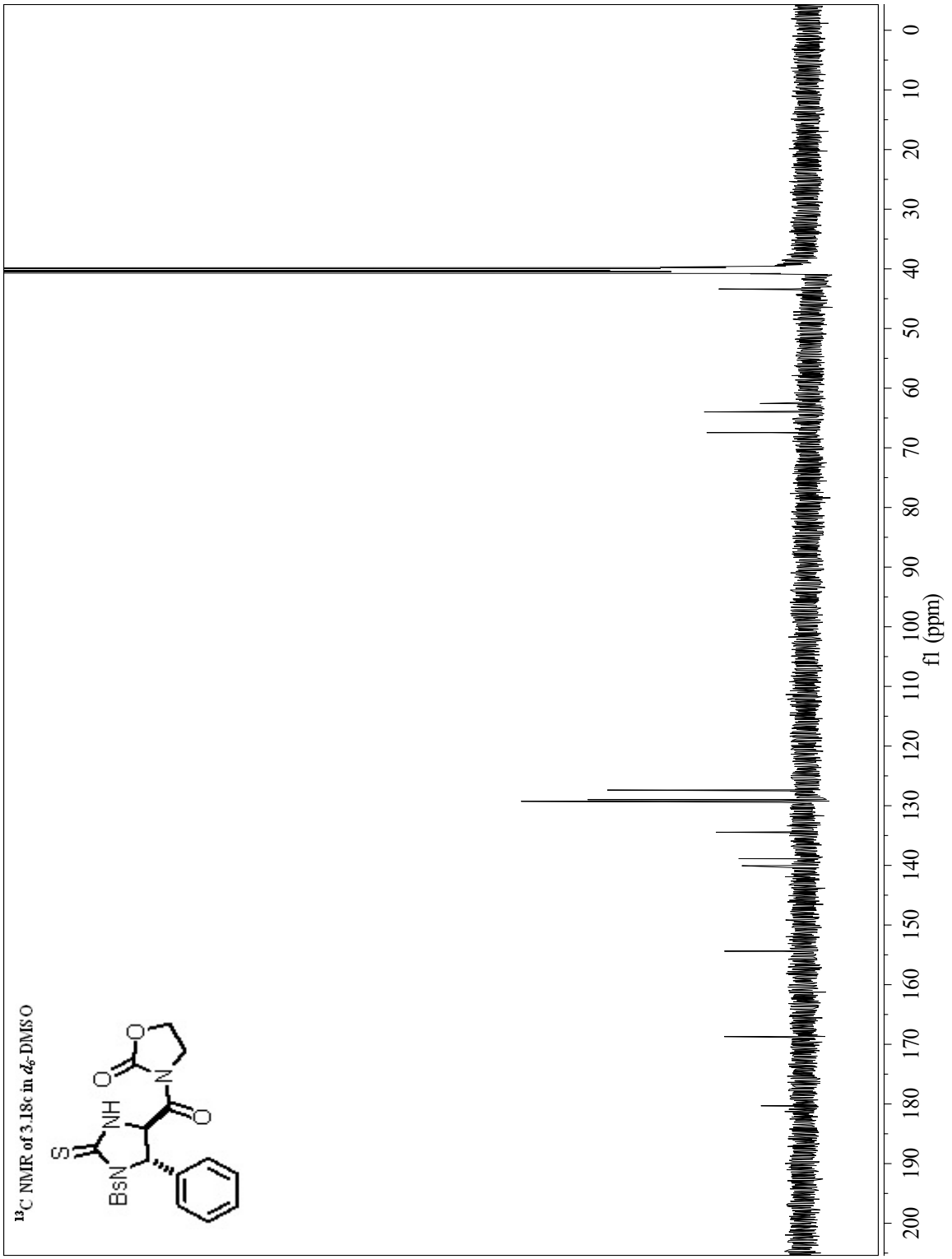

^{1}H NMR of 3 18b in d_6-DMSO
Ts
N
NH
S
O
O
O
O
N
1.01
2.07
3.09
2.02
1.98
1.00
1.02
2.07
2.08
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

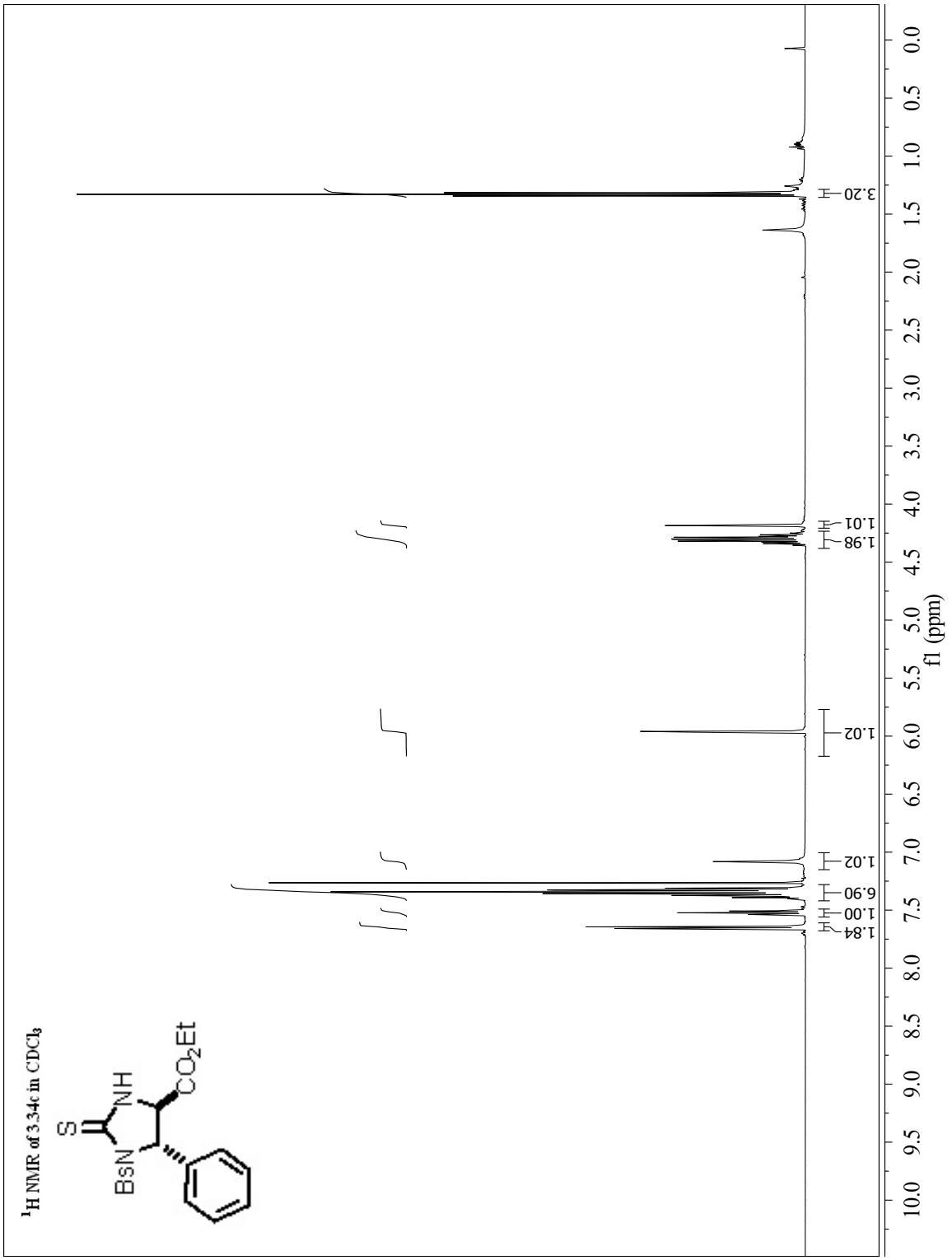

^{13}C NMR of 3 18b in d_6-DMSO
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

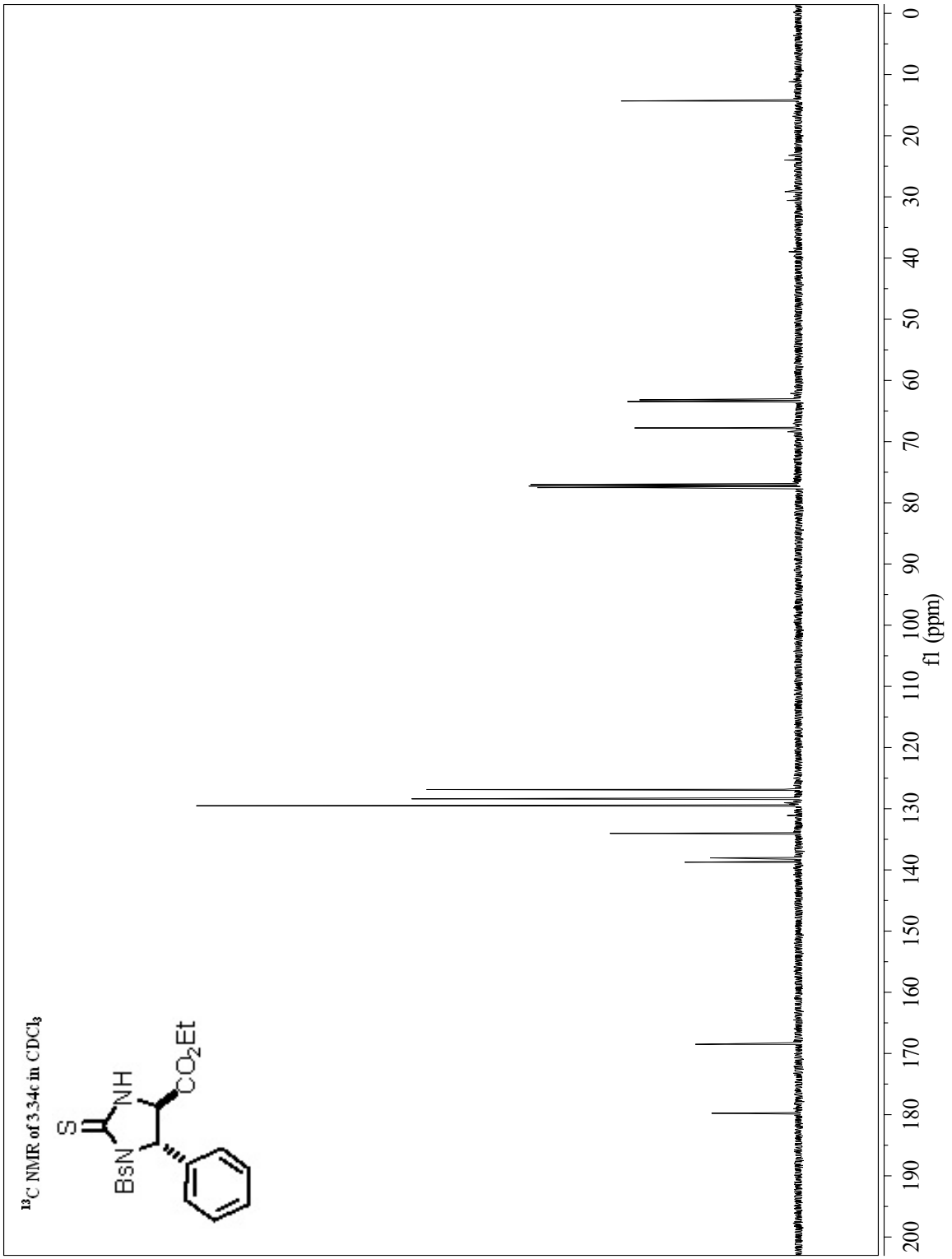

^{1}H NMR of 3.34b in $CDCl_3$
TsN
NH
S
CO_2Et
1.96
4.98
2.01
1.00
1.00
2.00
1.02
3.11
3.04
f1 (ppm)

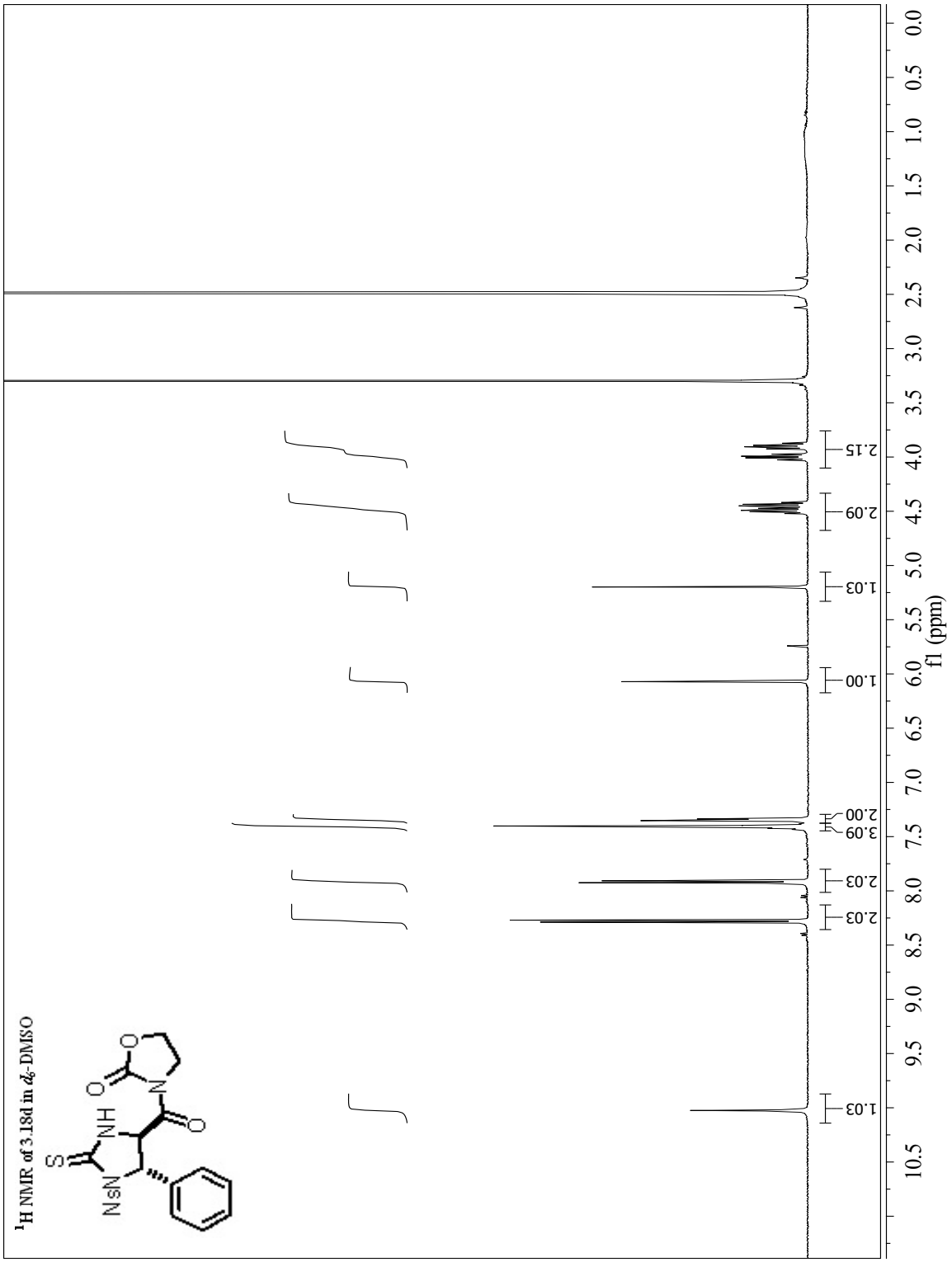

^{13}C NMR of 3.34b in $CDCl_3$
S
NH
TsN
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

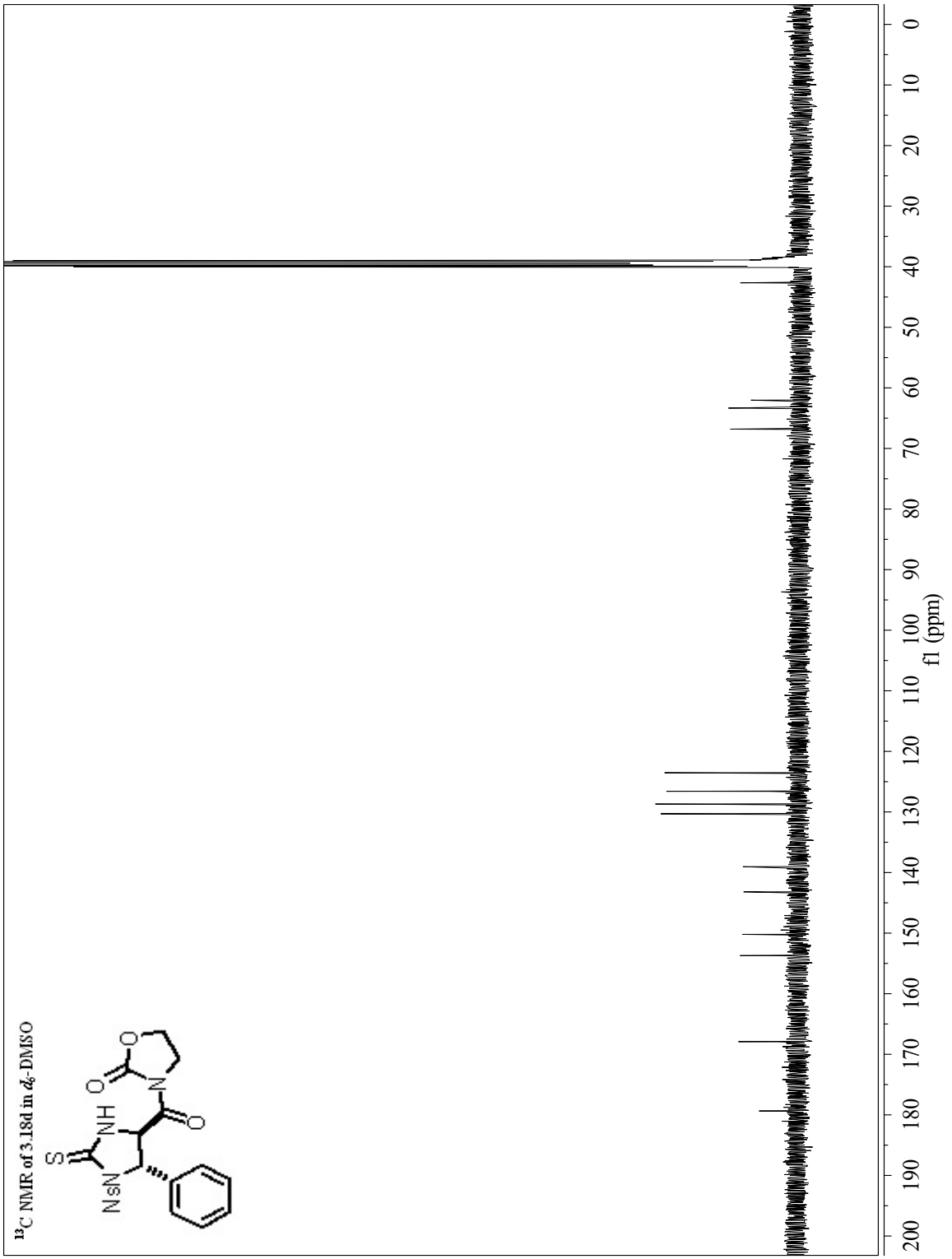

^{1}H NMR of 3.18c in d_6-DMSO
f1 (ppm)
1.02
3.06
2.09
3.03
2.07
1.00
1.03
2.04
2.04

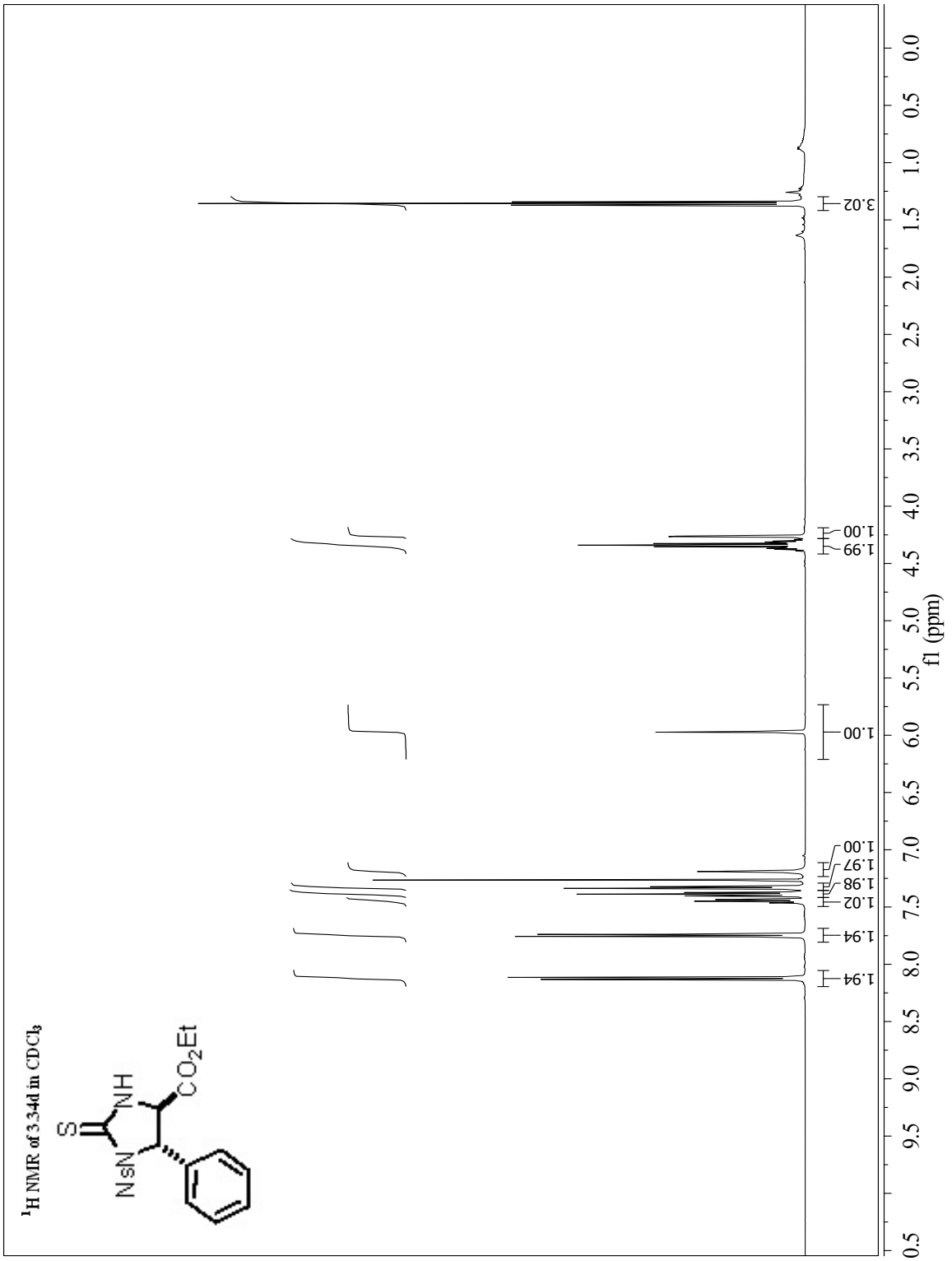

^{13}C NMR of 3.18c in d_6-DMSO
S
NH
BsN
O
O
N
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

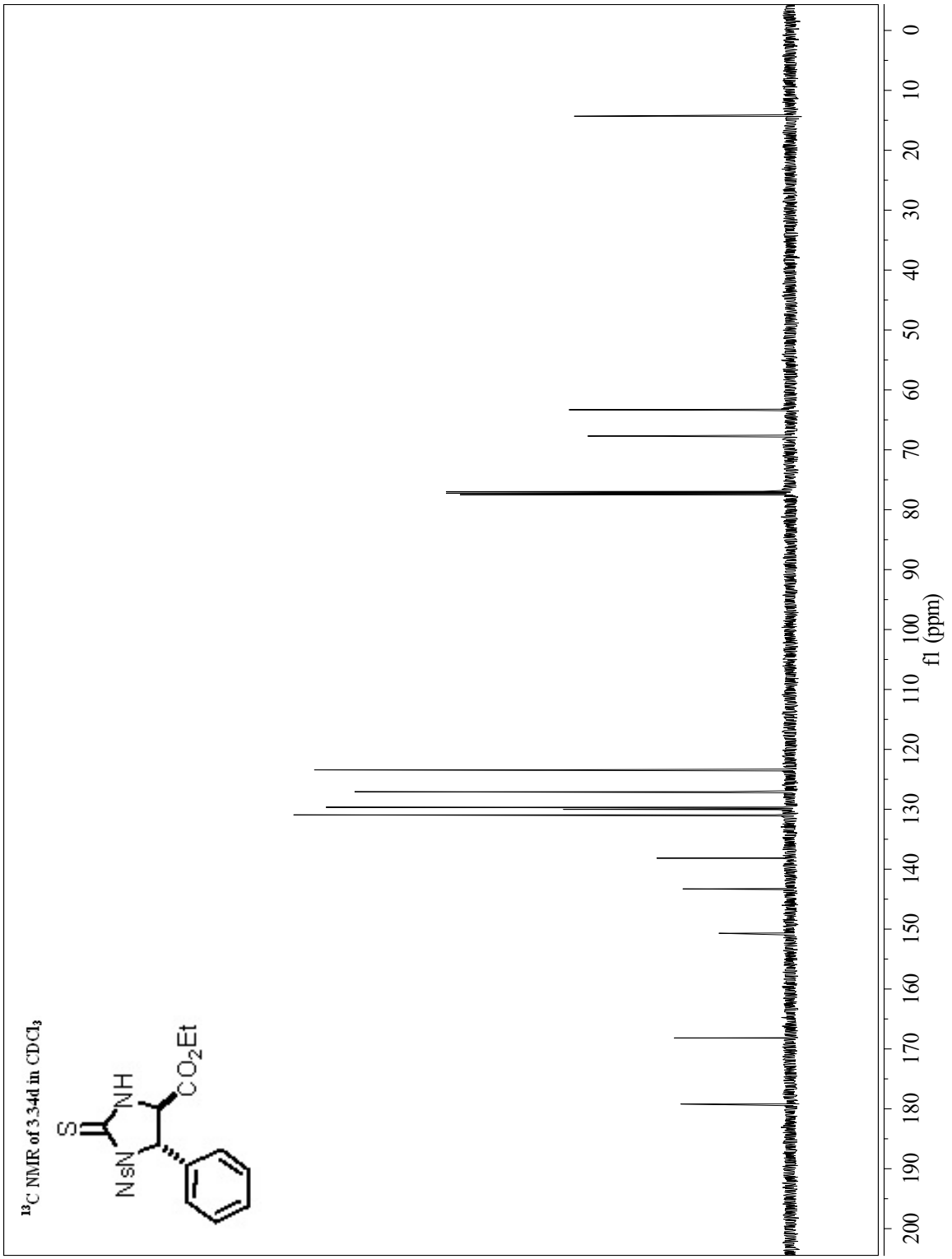

^{1}H NMR of 3.34c in $CDCl_3$
S
NH
CO_2Et
BsN
3.20
1.98
1.01
1.02
1.02
6.90
1.00
1.84
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

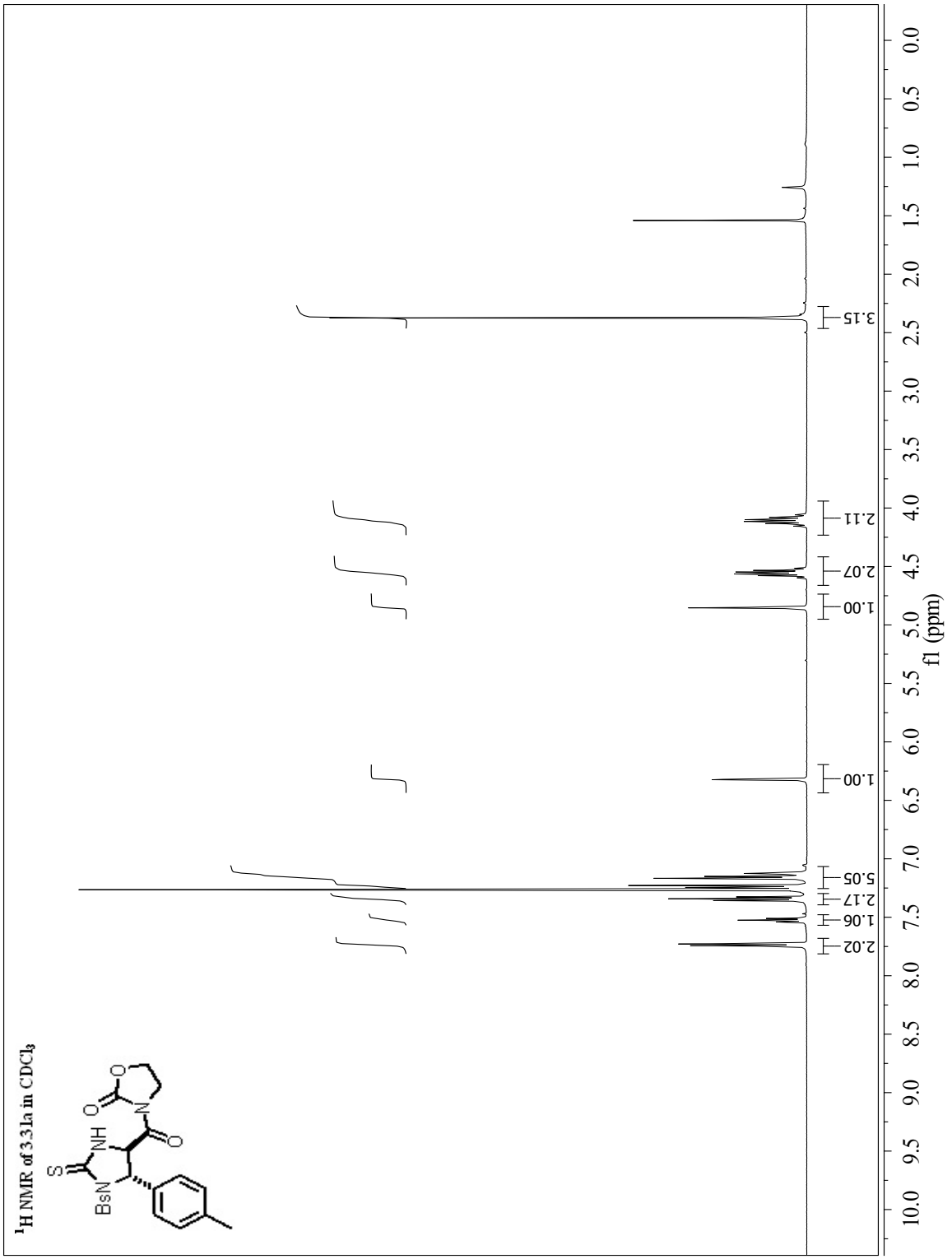

^{13}C NMR of 3.34c in $CDCl_3$
S
NH
BsN
CO_2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

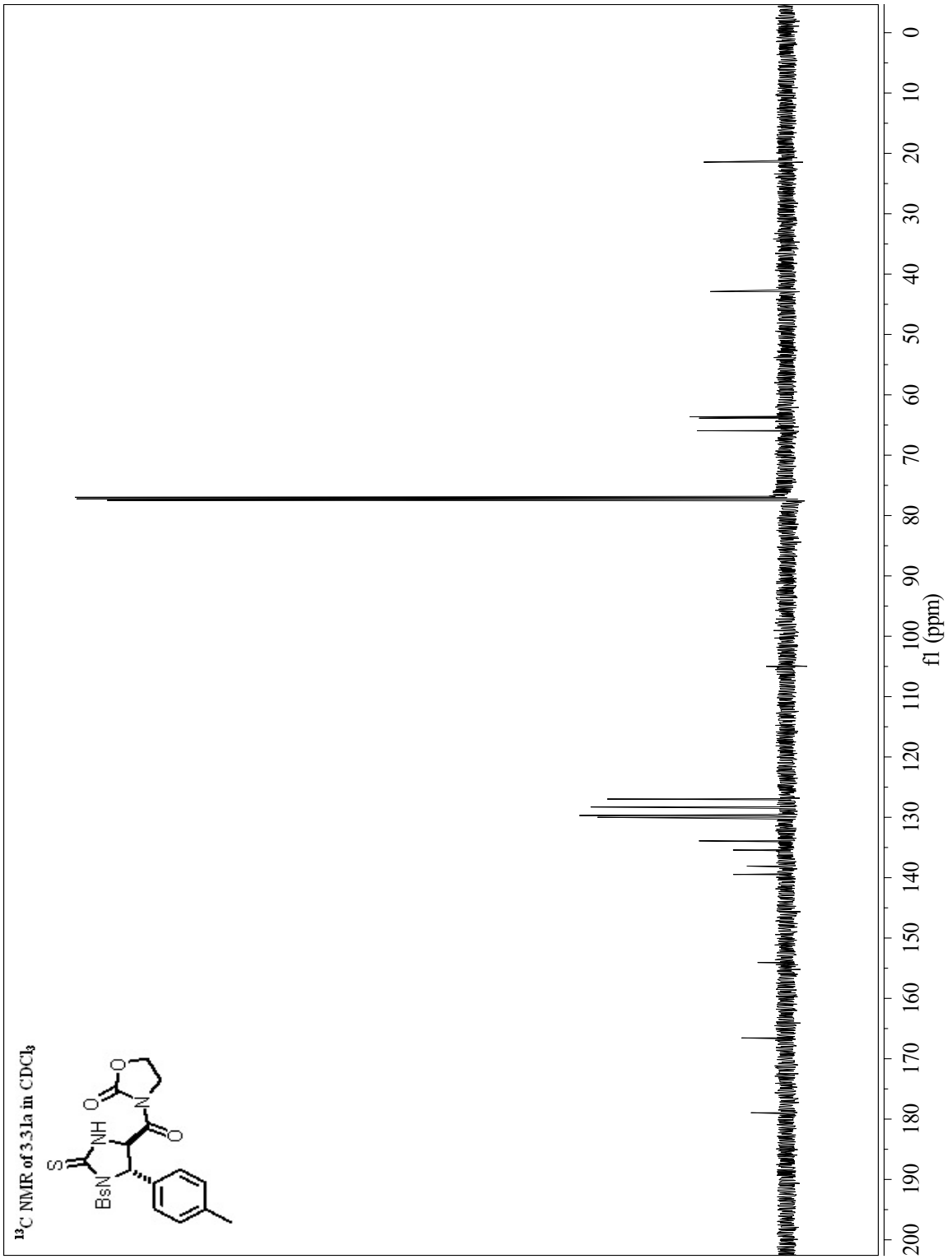

^{1}H NMR of 3.18d in d_6-DMSO
NH
S
O
O
N
O
NsN
1.03
2.03
2.03
3.09
2.00
1.00
1.03
2.09
2.15
f1 (ppm)

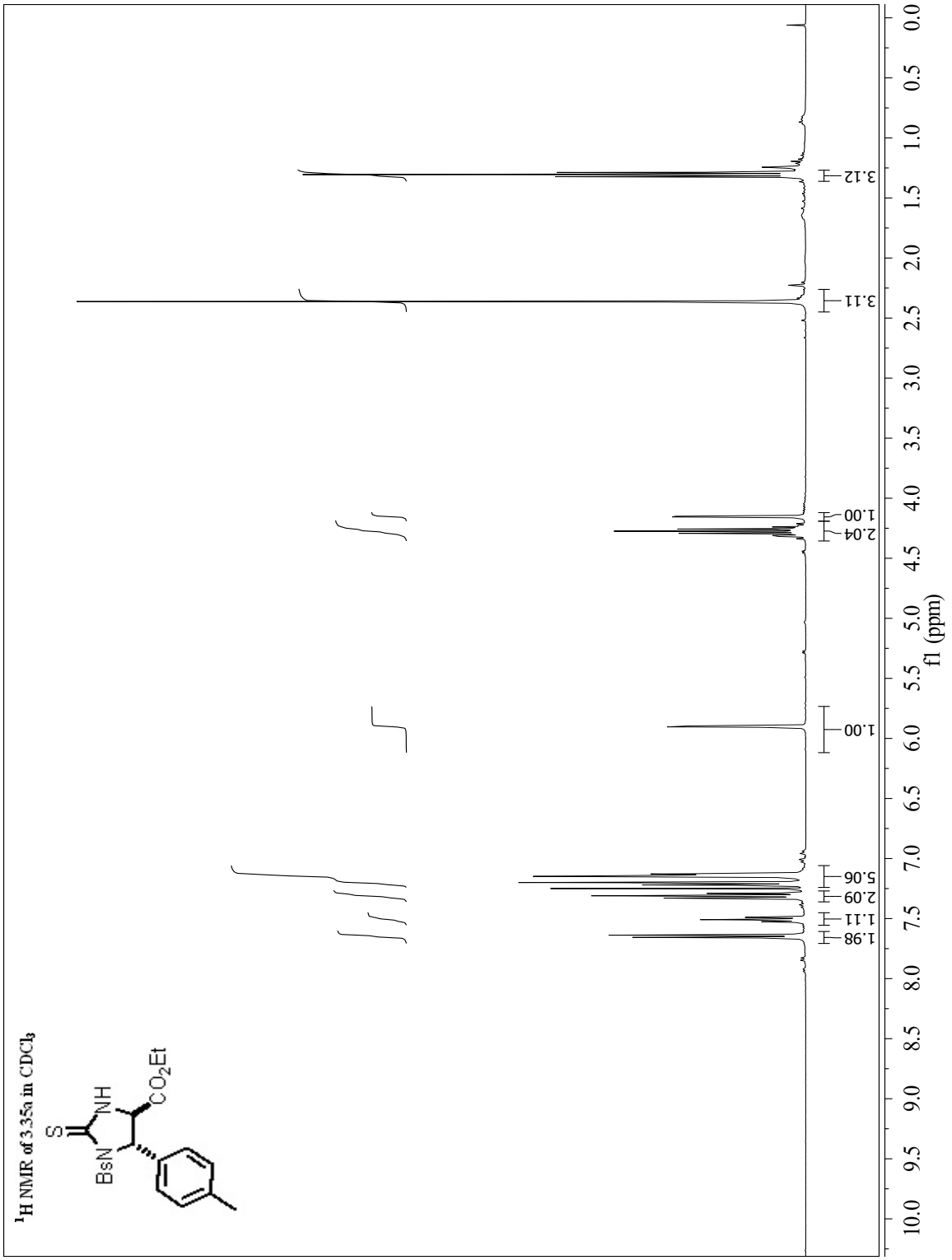

^{13}C NMR of 3.18d in d_6-DMSO
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

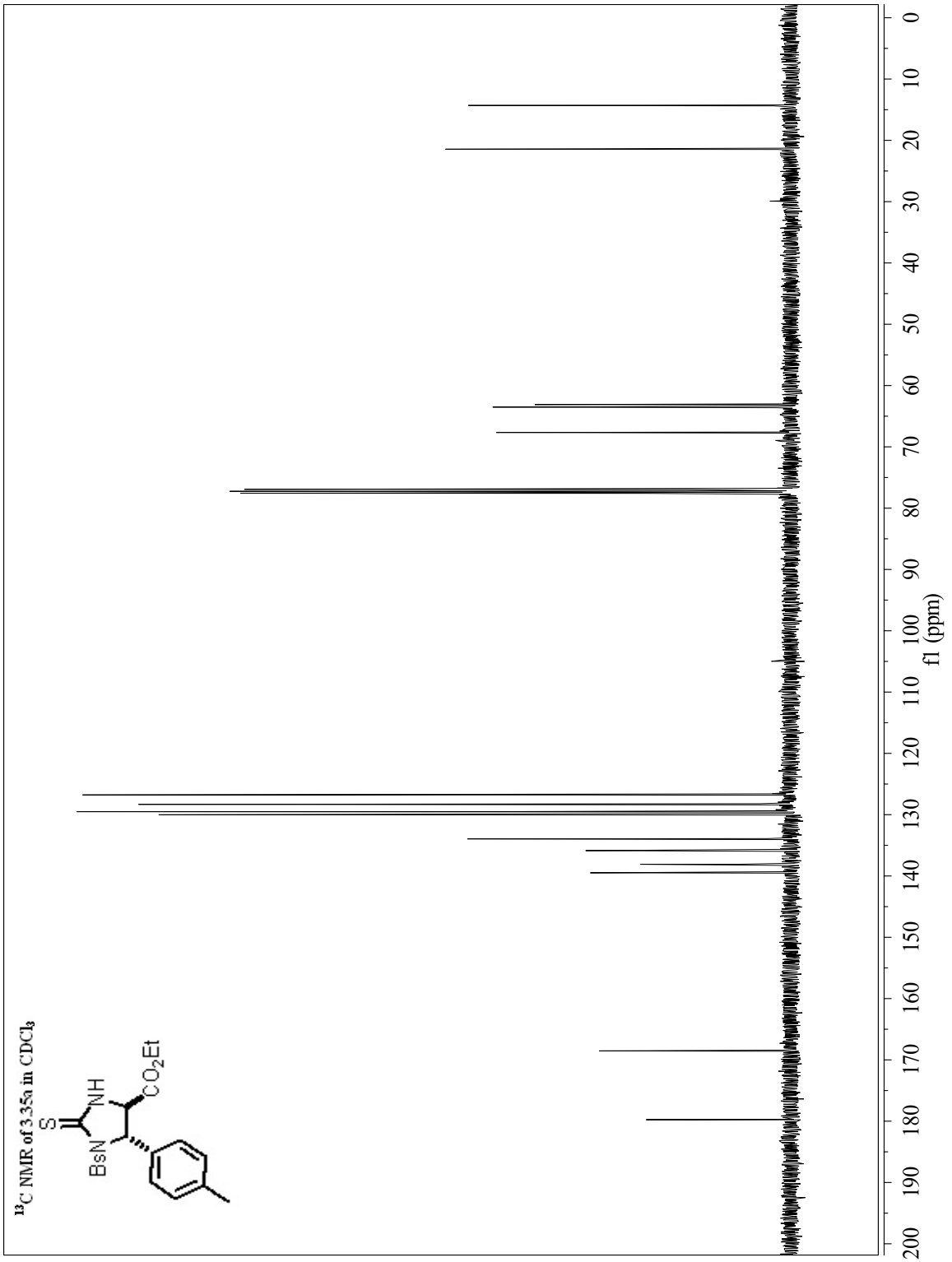

^{1}H NMR of 3.344 in $CDCl_3$
S
NH
NsN
CO_2Et
3.02
1.99
1.00
1.00
1.97
1.98
1.02
1.94
1.94
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

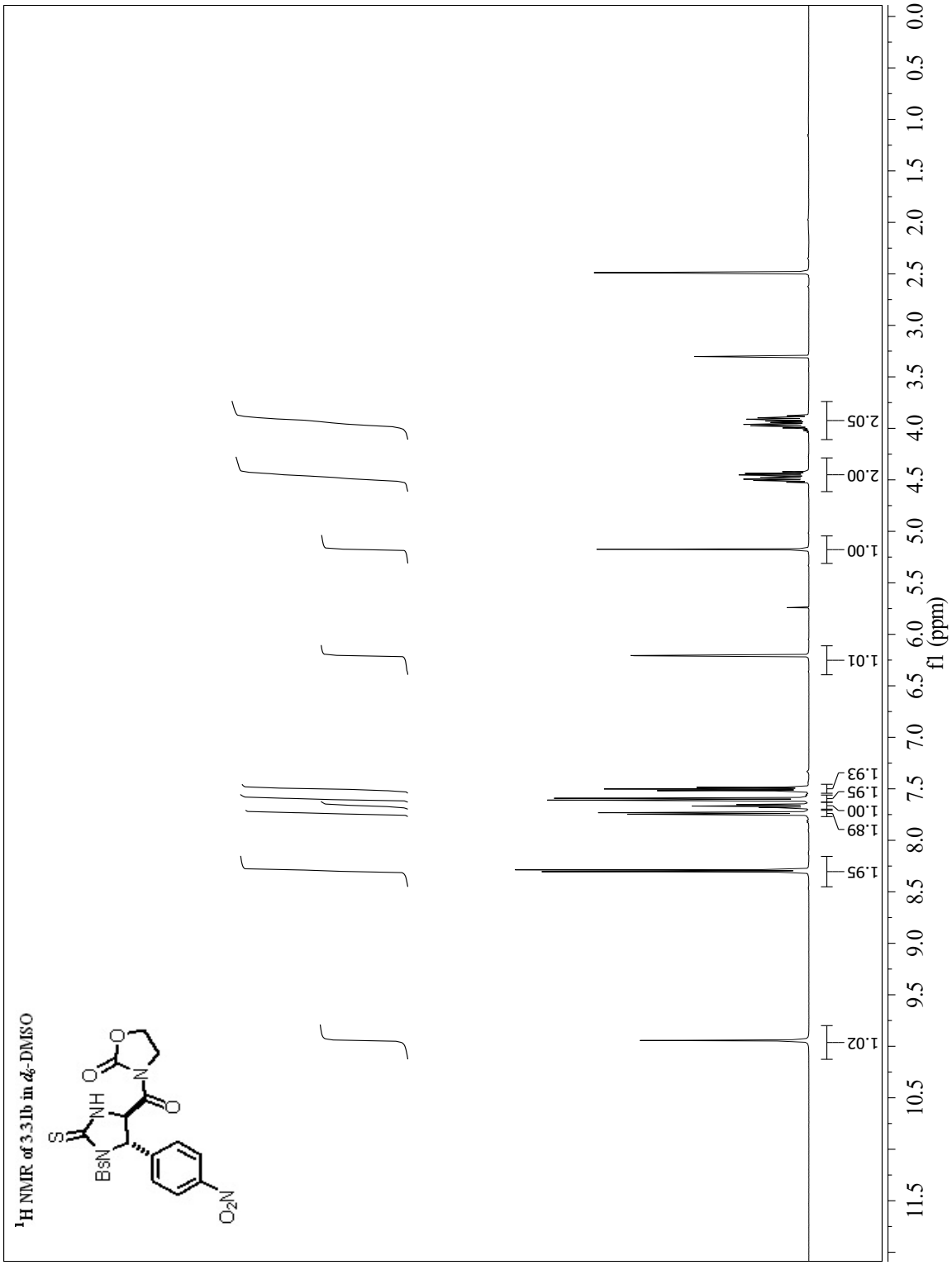

^{13}C NMR of 3.34d in $CDCl_3$
S
NH
NsN
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

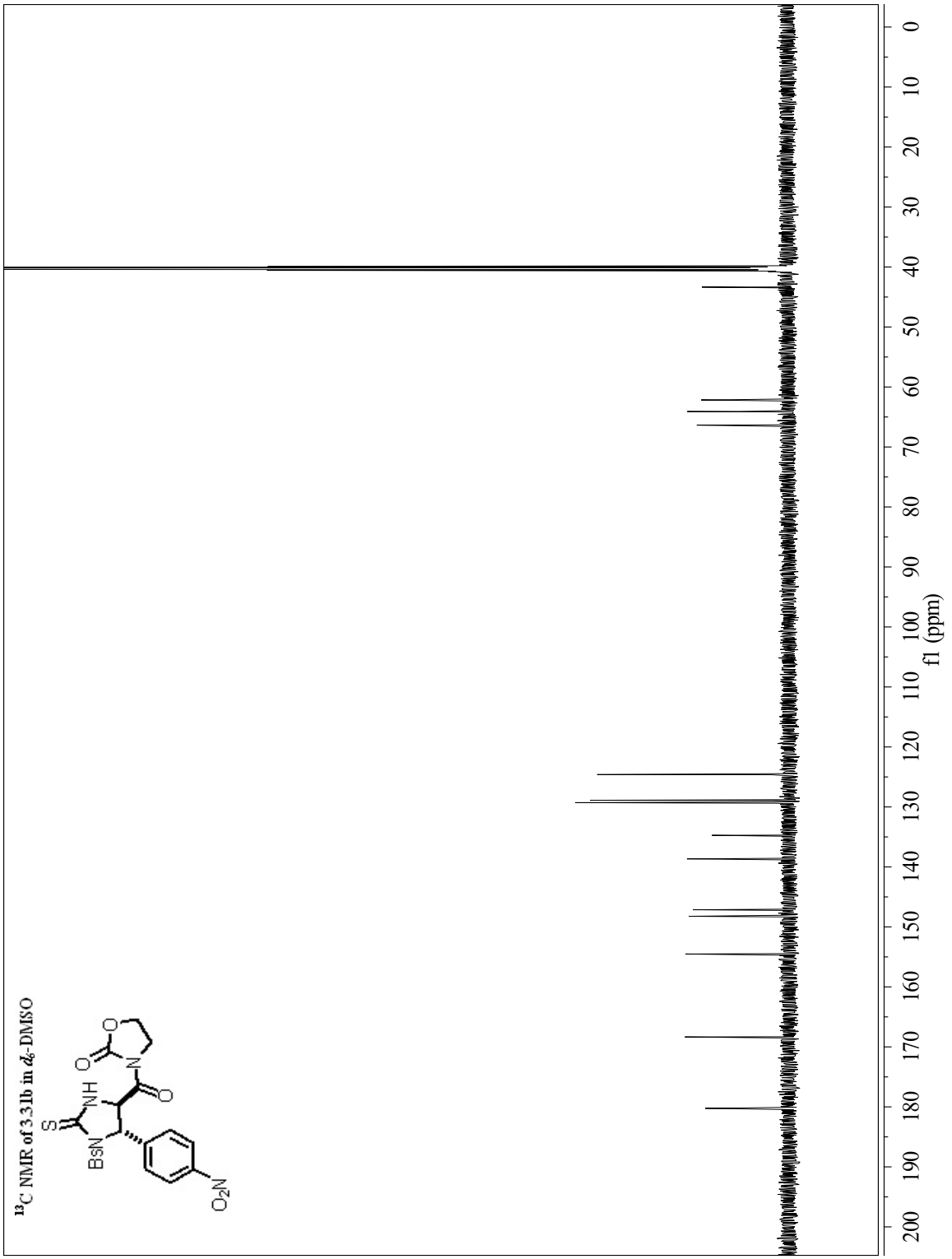

^{1}H NMR of 3.3.1a in $CDCl_3$
S
NH
O
O
N
O
BsN
2.02
1.06
2.17
5.05
1.00
1.00
2.07
2.11
3.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

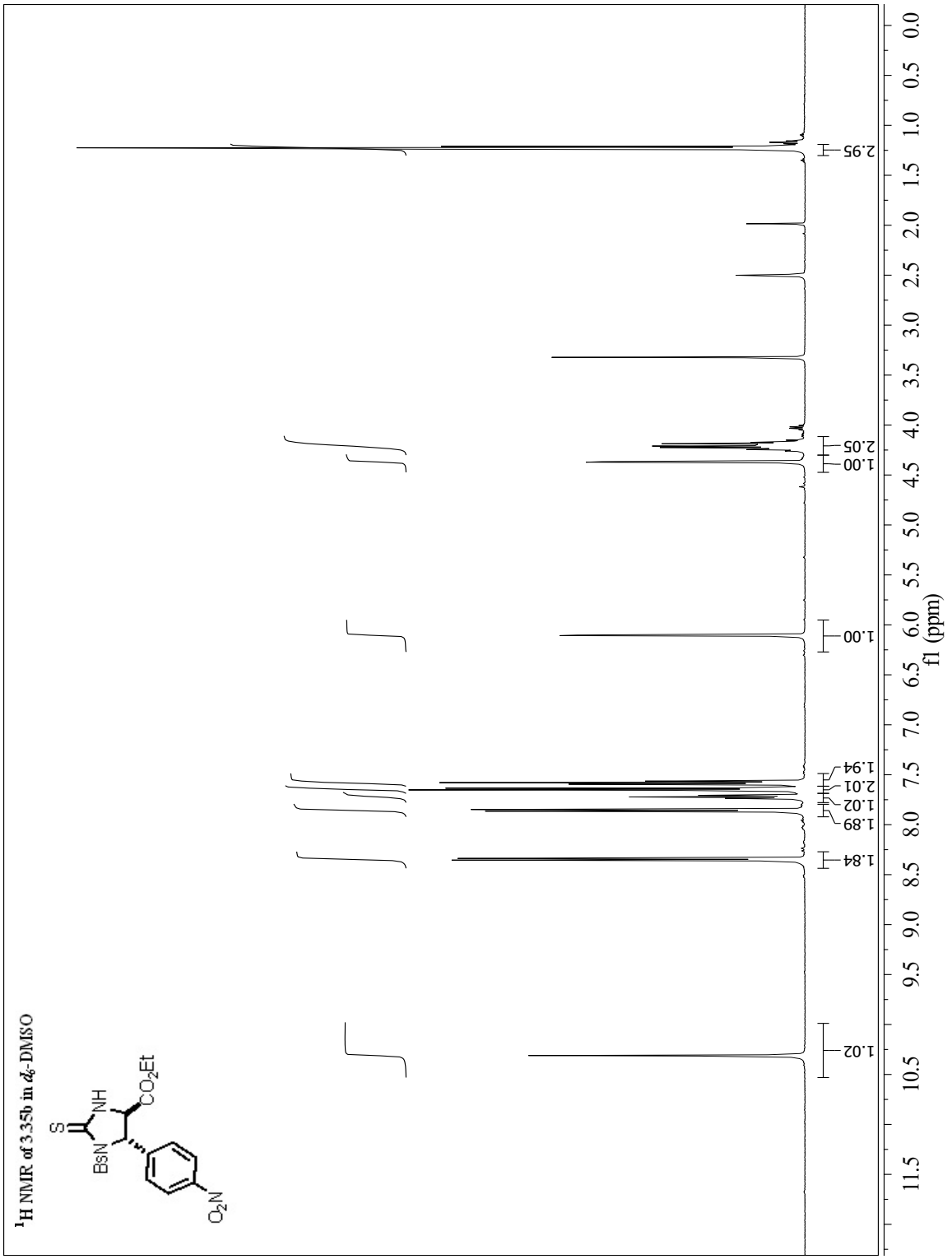

^{13}C NMR of 3.3Ia in $CDCl_3$
Bs
N
NH
O
O
O
O
S
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

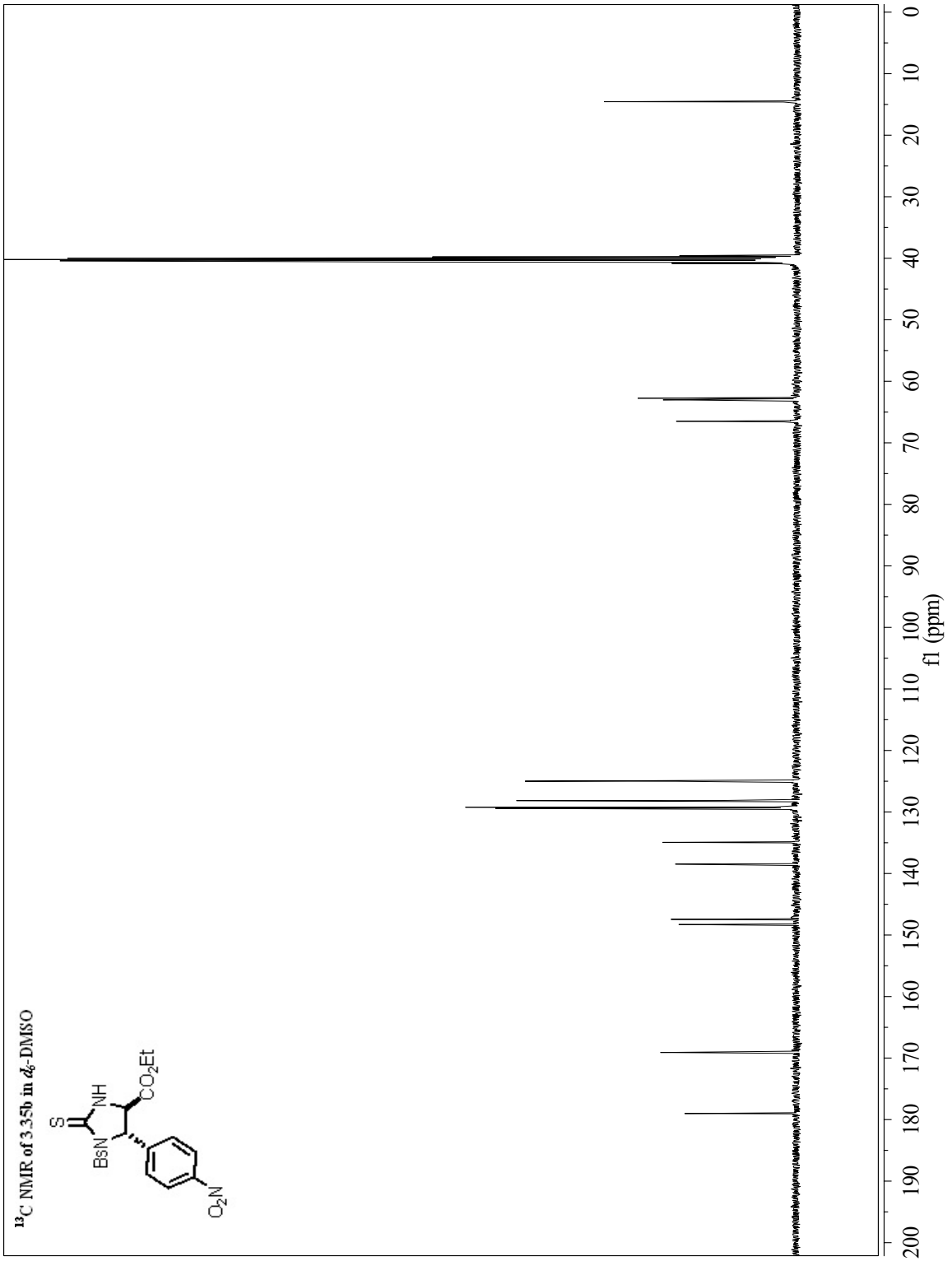

^{1}H NMR of 3.35a in $CDCl_3$
S
NH
BsN
CO_2Et
1.98
1.11
2.09
5.06
1.00
2.04
1.00
3.11
3.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

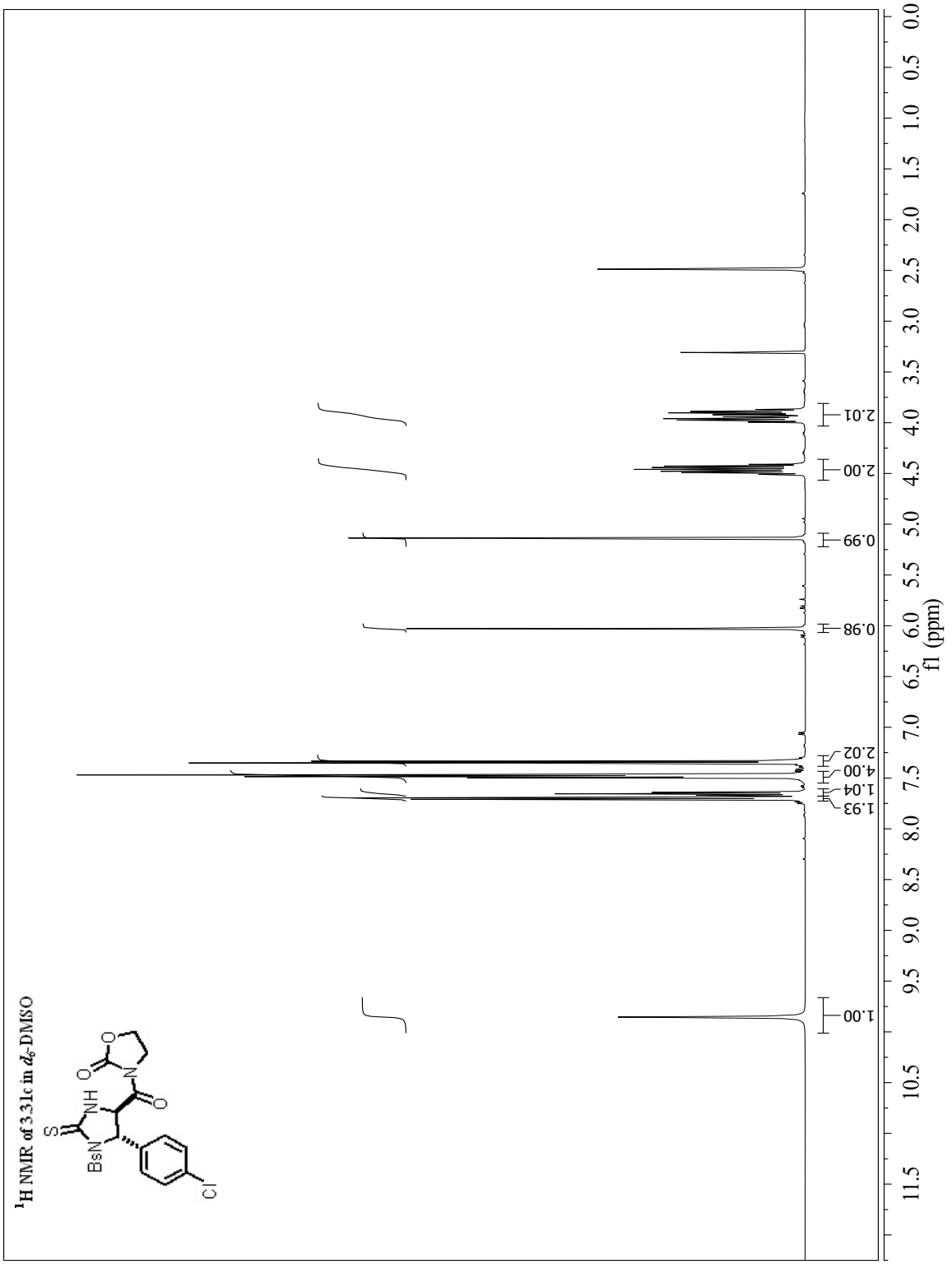

^{13}C NMR of 3.35a in $CDCl_3$
S
NH
BsN
CO_2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

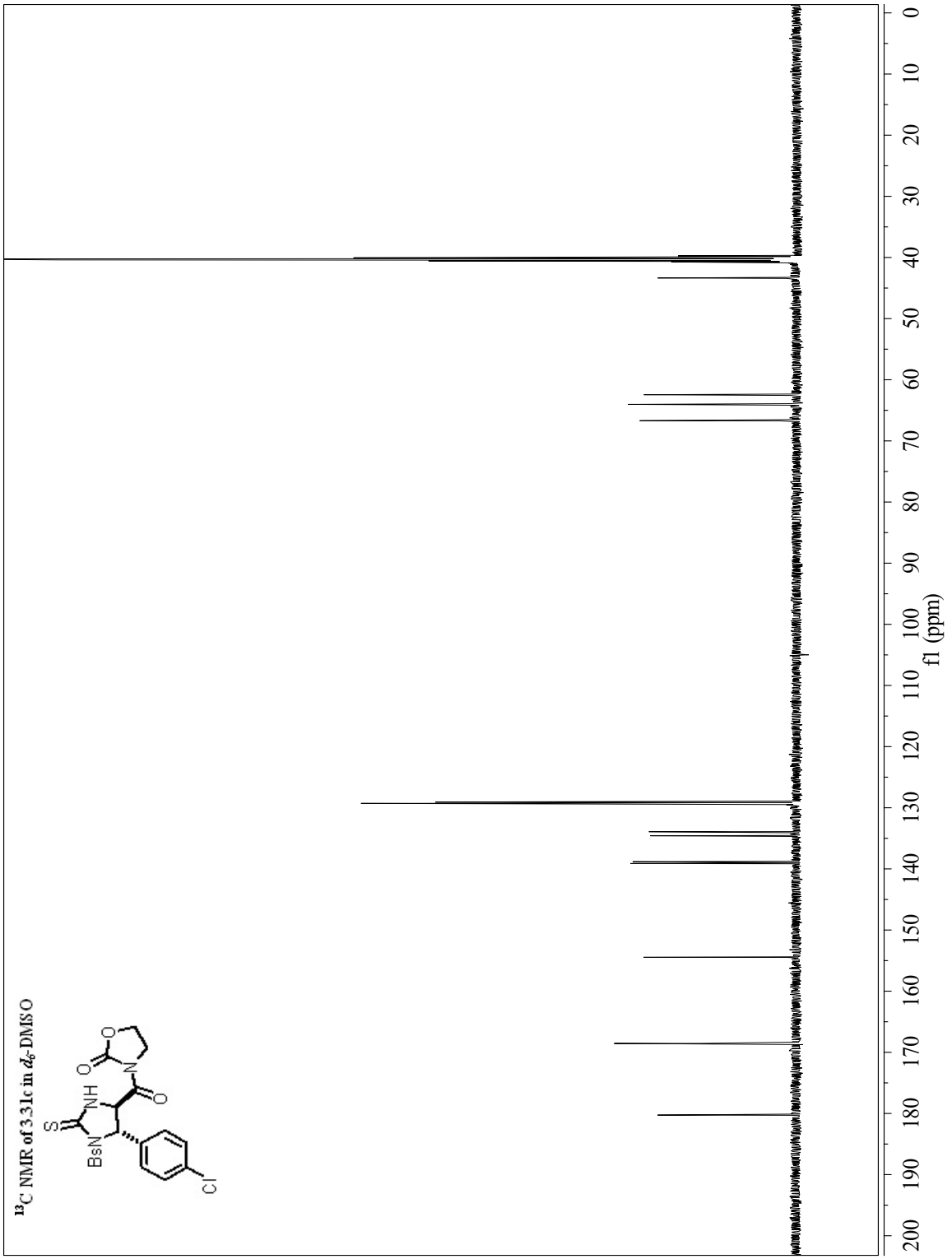

^{1}H NMR of 3.31b in d_6-DMSO
Bsl
NH
S
O
O
O
N
O_2N
1.02
1.95
1.89
1.00
1.95
1.93
1.01
1.00
2.00
2.05
f1 (ppm)

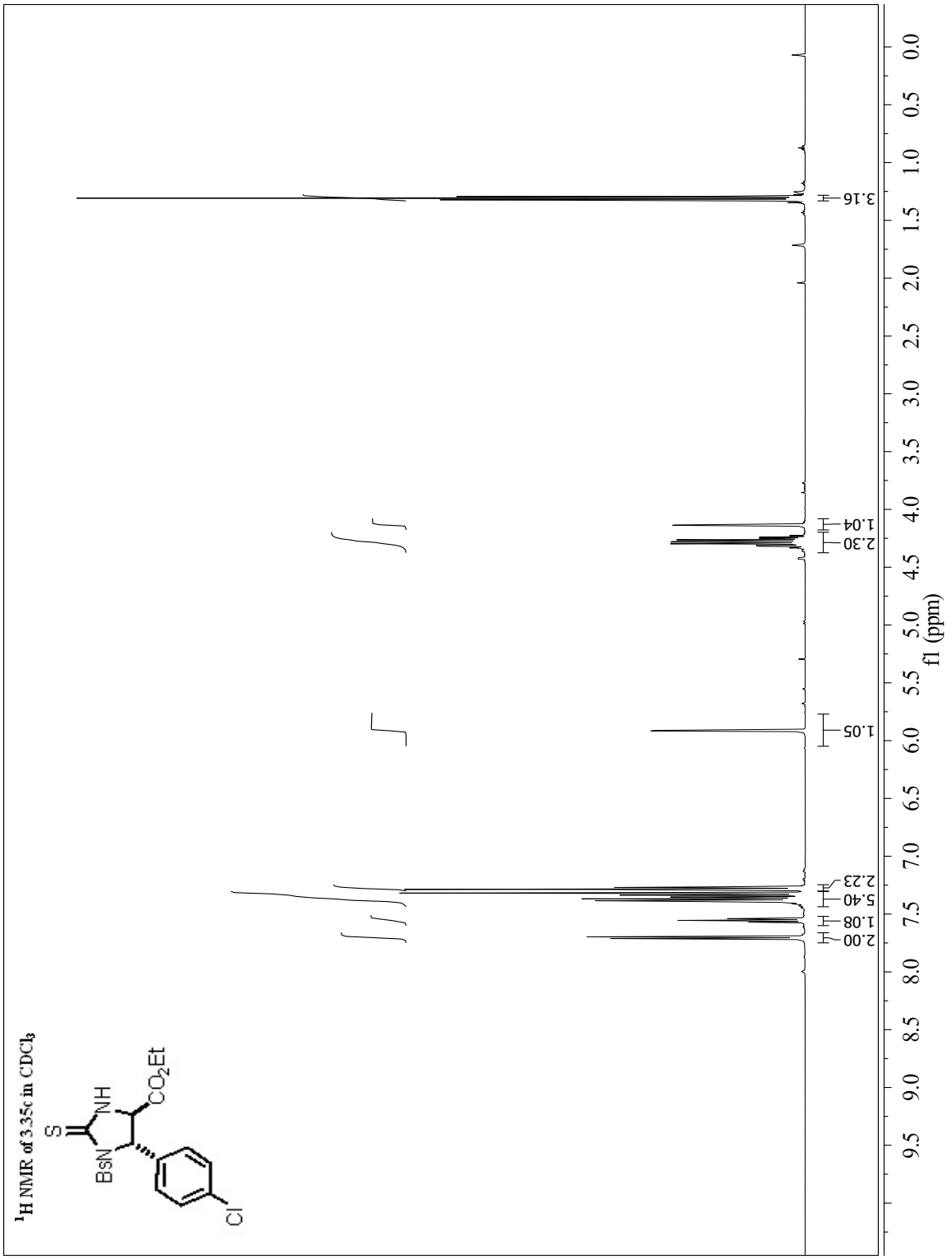

^{13}C NMR of 3.3.1b in d_6-DMSO
f1 (ppm)

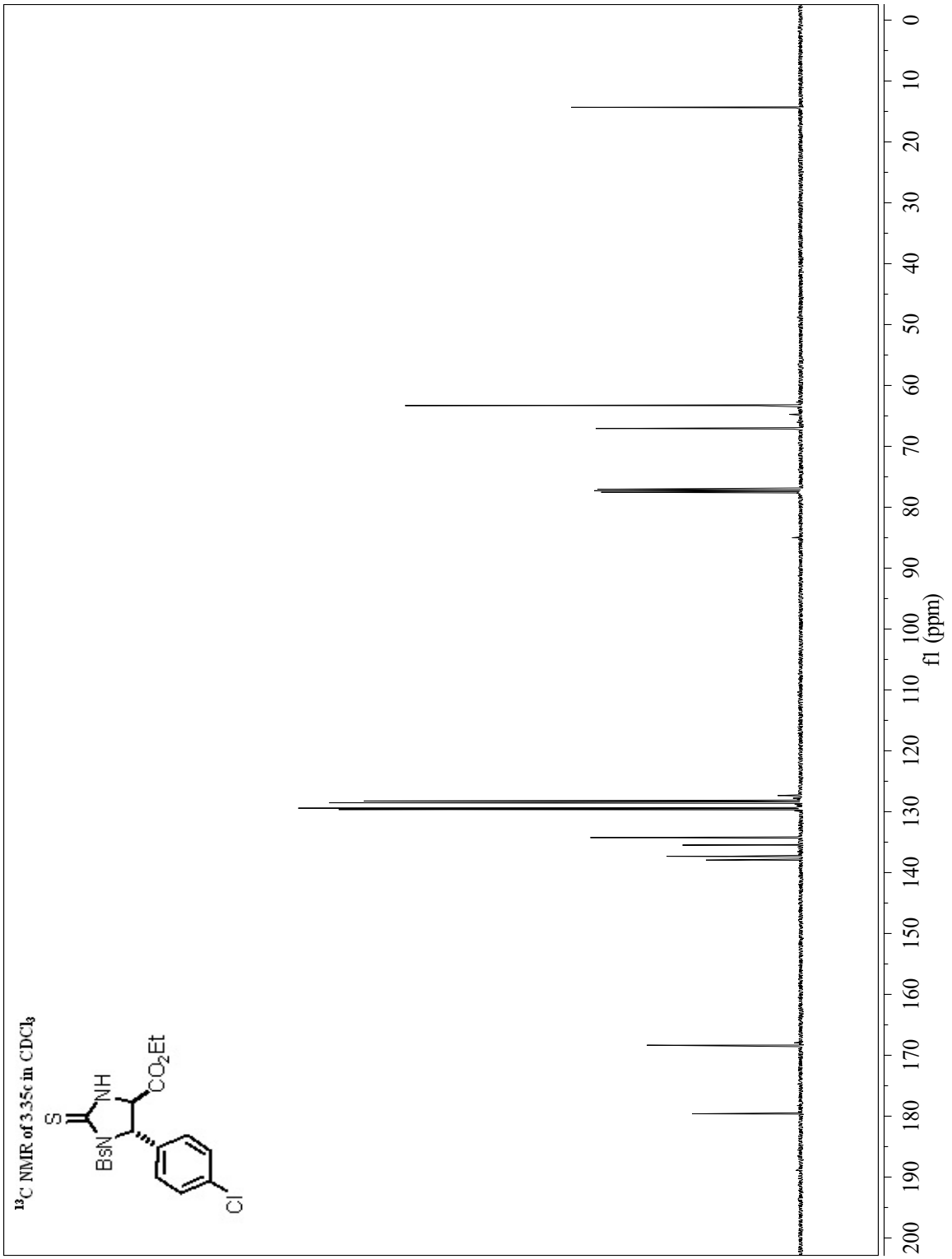

^{1}H NMR of 3.35b in d_6-DMSO
S
NH
CO_2Et
BsN
O_2N
2.95
1.00
2.05
1.00
1.94
2.01
1.02
1.89
1.84
1.02
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

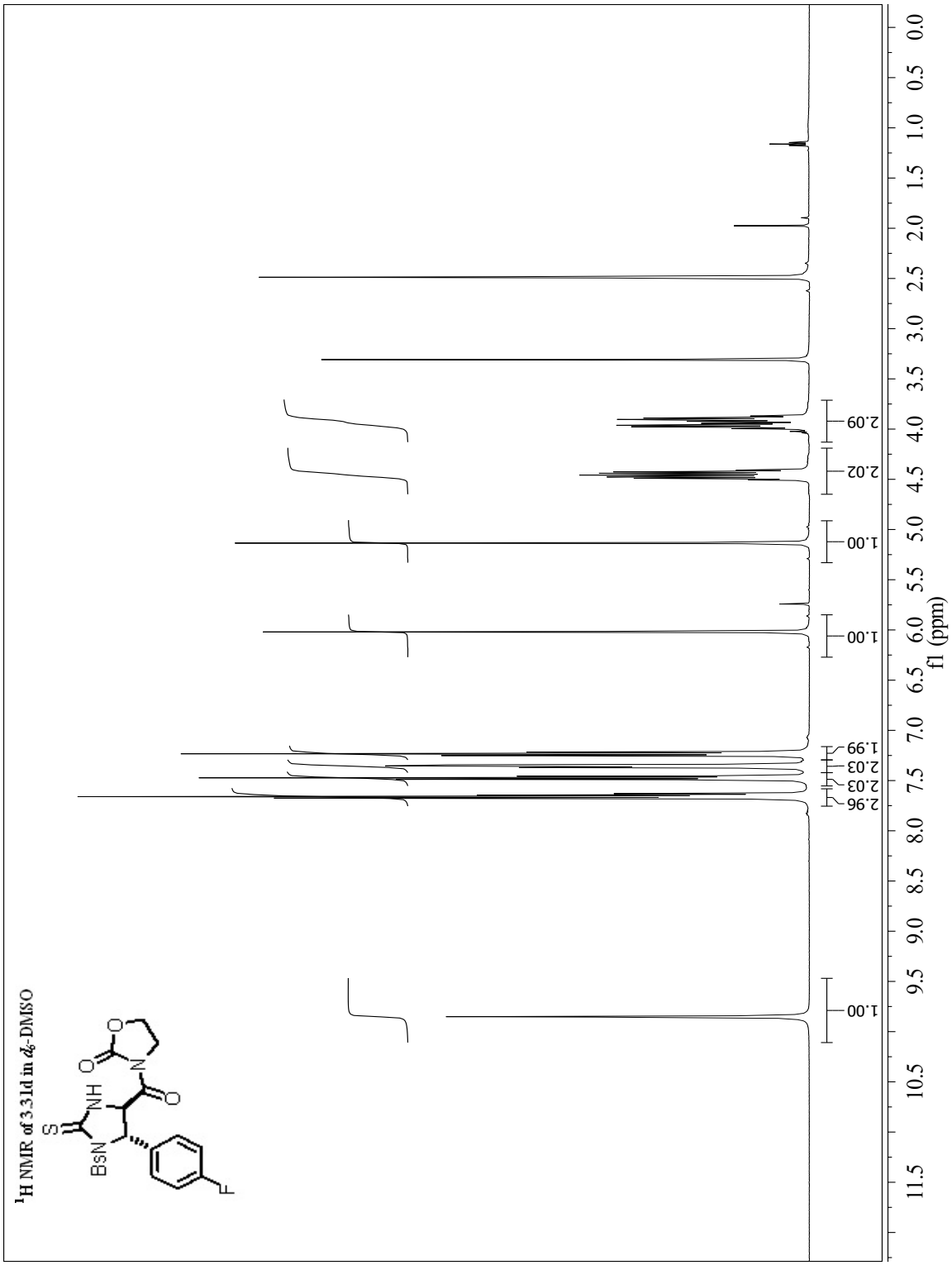

^{13}C NMR of 3.35b in d_6-DMSO
Bsn
NH
S
CO_2Et
O_2N
f1 (ppm)

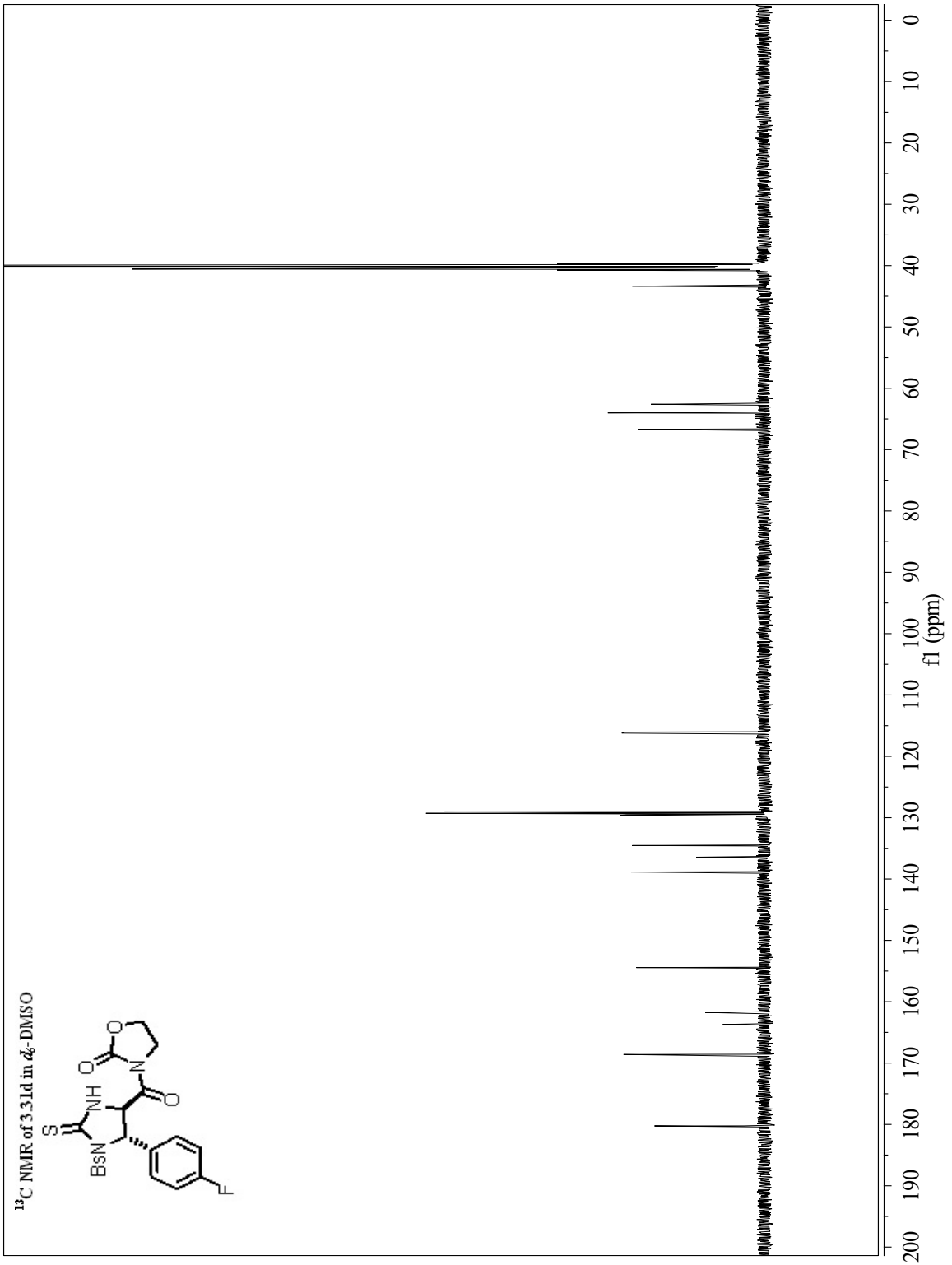

^{1}H NMR of 3.31c in d_6-DMSO
1.00
2.01
2.00
0.99
0.98
2.02
4.00
1.04
1.93
f1 (ppm)

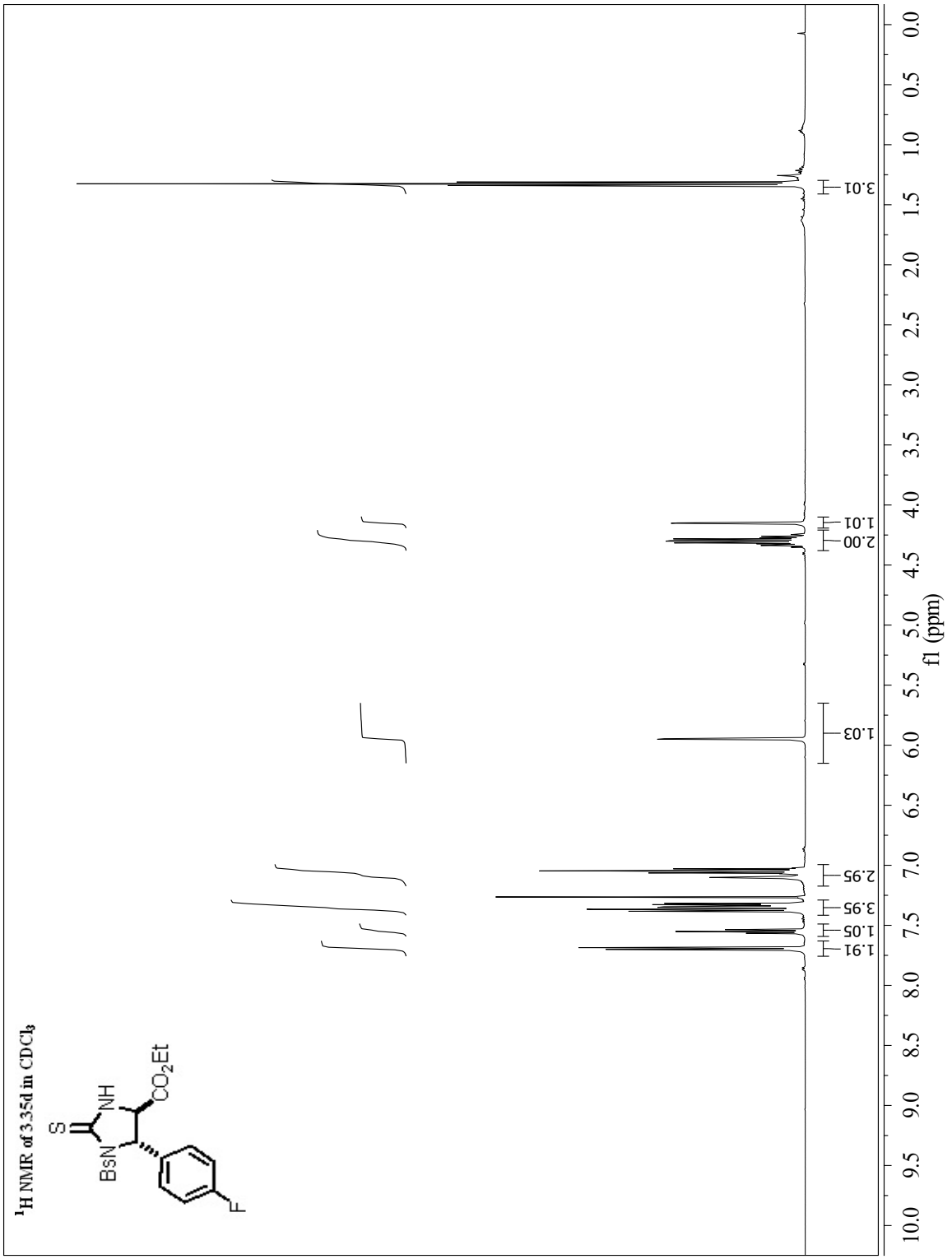

^{13}C NMR of 3.31c in d_6-DMSO
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

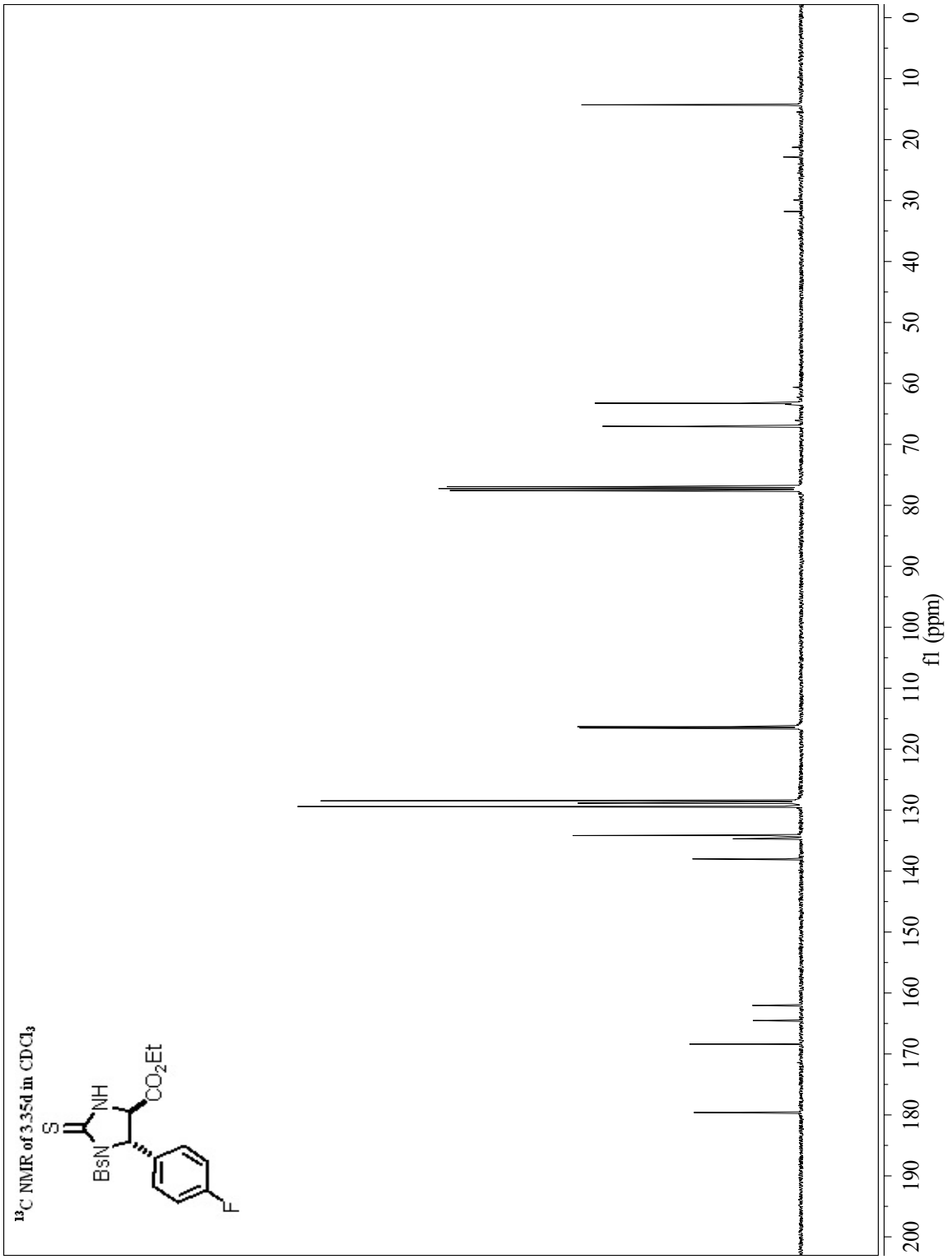

^{1}H NMR of 3.35c in $CDCl_3$
S
NH
CO_2Et
Bsn
Cl
2.00
1.08
5.40
2.23
1.05
1.04
2.30
3.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

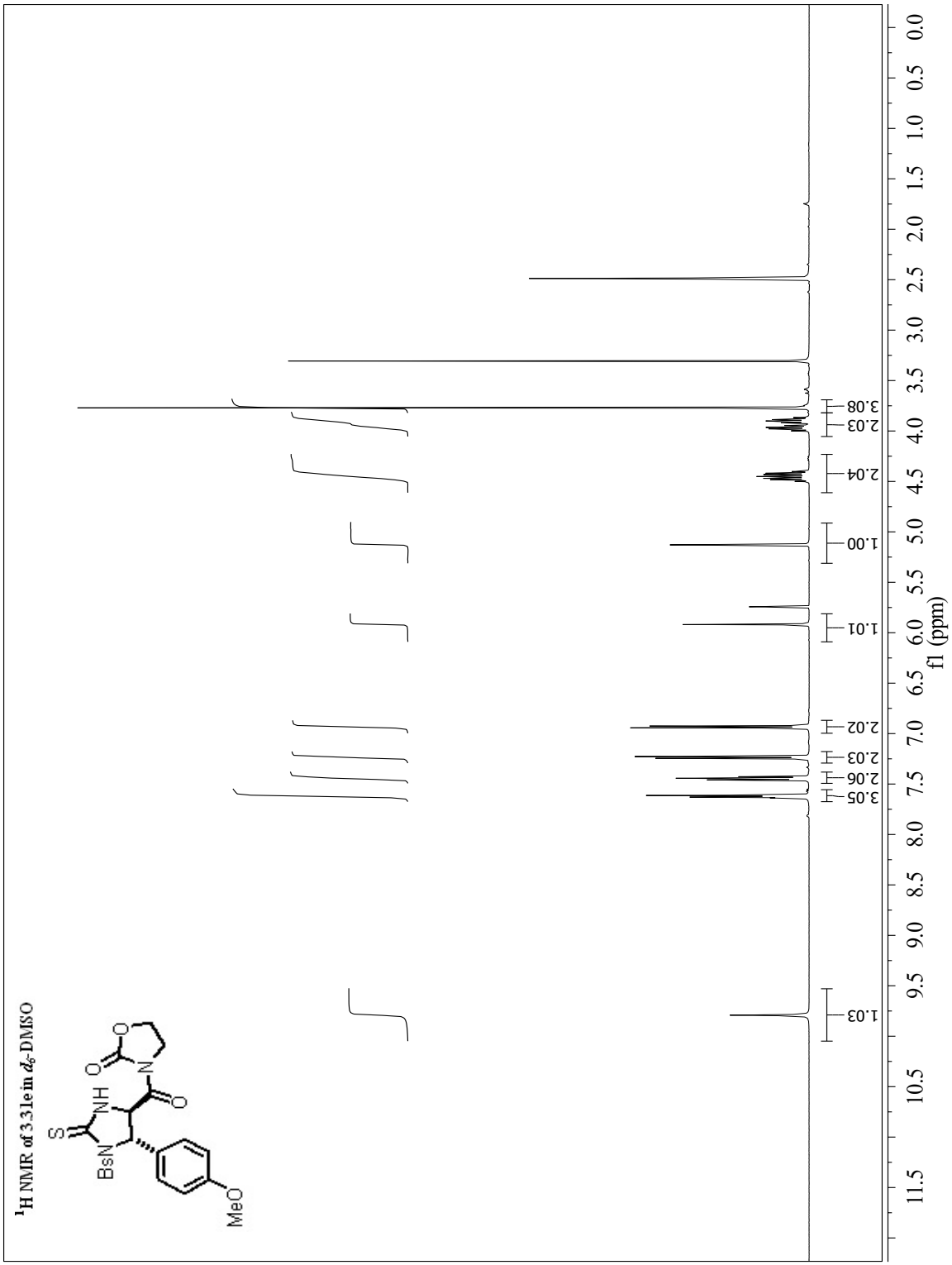

^{13}C NMR of 3.35c in $CDCl_3$
S
NH
BsN
CO_2Et
Cl
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

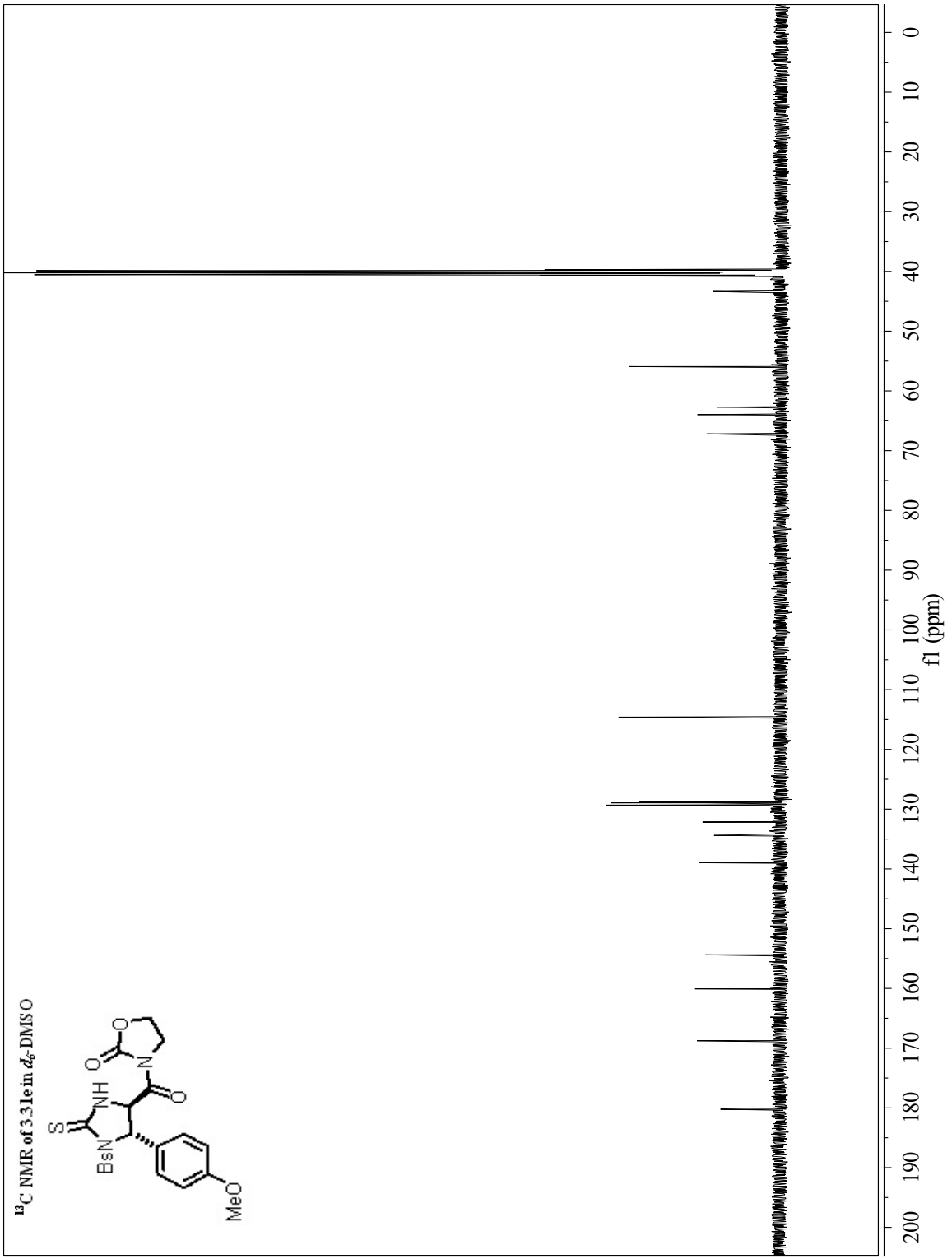

^{1}H NMR of 3.31d in d_6-DMSO
f1 (ppm)
1.00
2.96
2.03
2.03
1.99
1.00
1.00
2.02
2.09

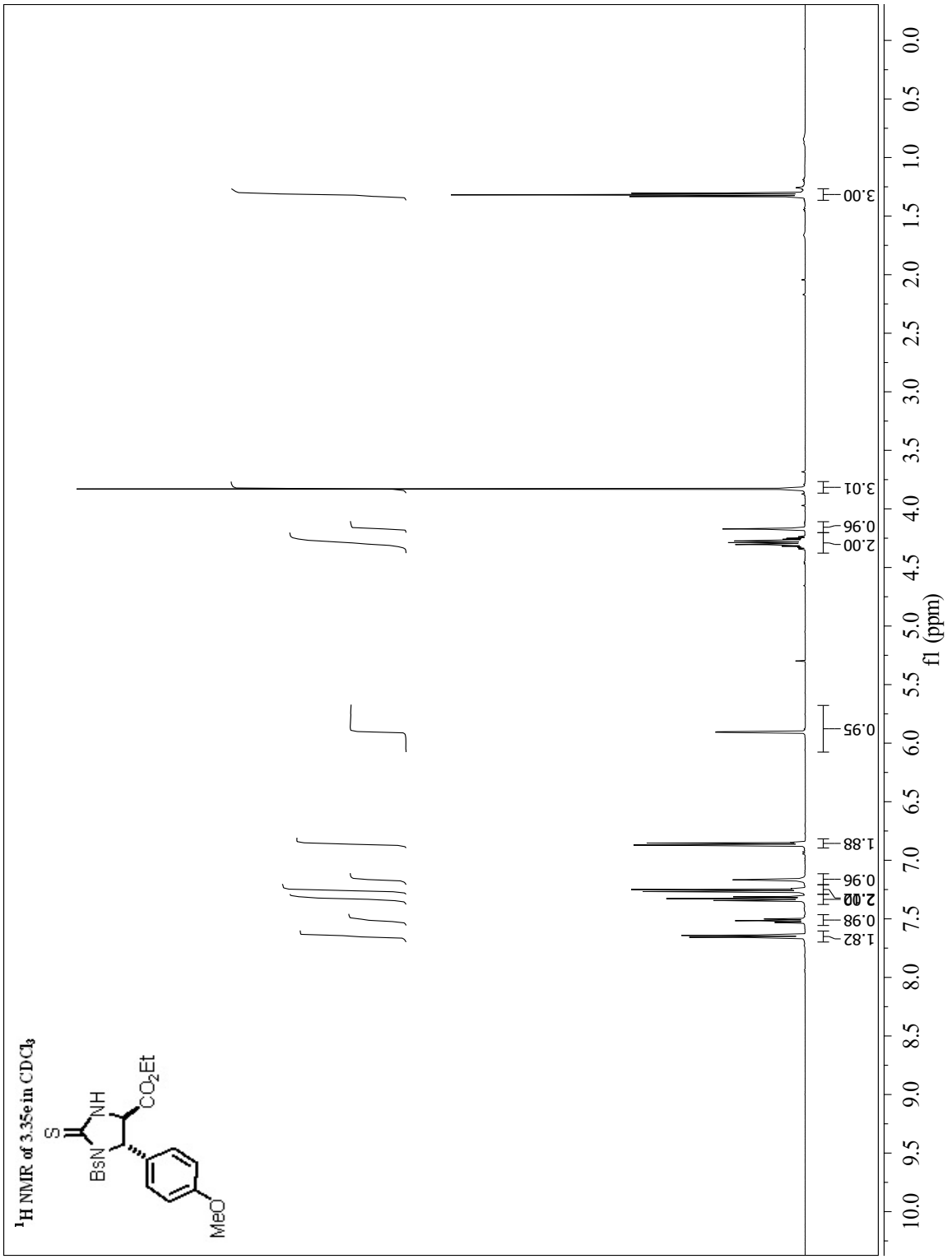

^{13}C NMR of 3.31d in d_6-DMSO
S
NH
O
N
O
O
BsN
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

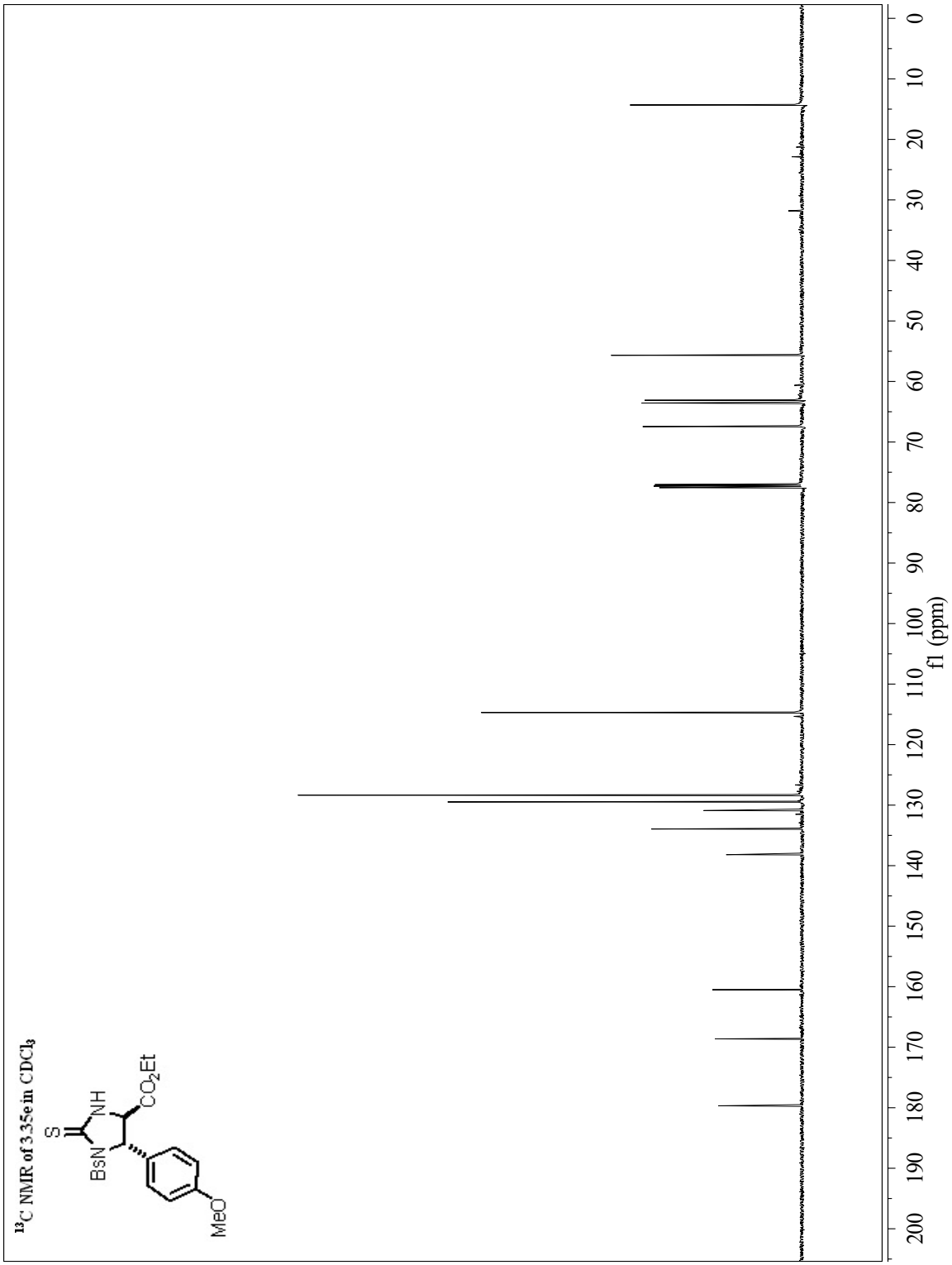

^{1}H NMR of 3.35d in $CDCl_3$
S
NH
CO_2Et
BsN
F
3.01
1.01
2.00
1.03
2.95
3.95
1.05
1.91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

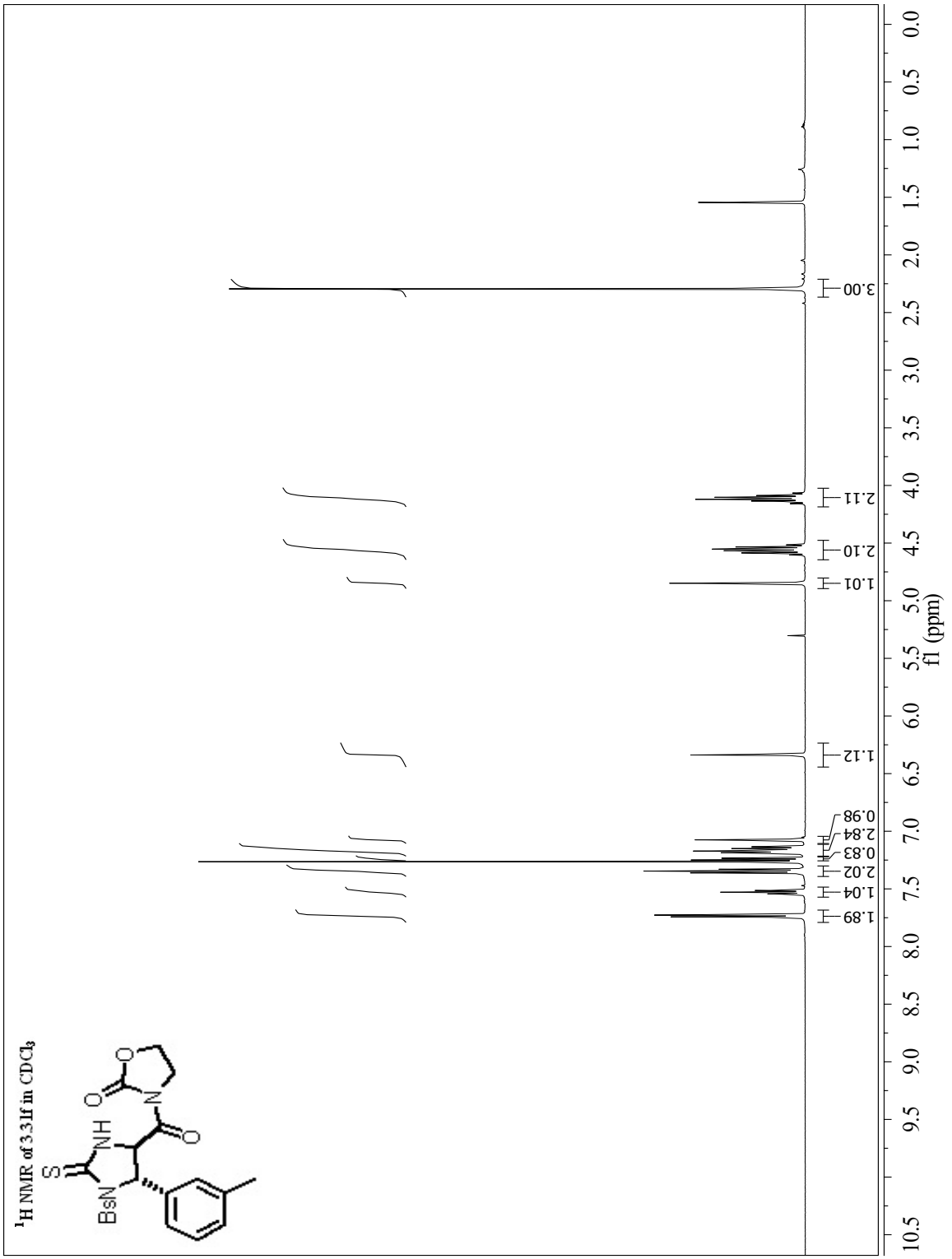

^{13}C NMR of 3.35d in $CDCl_3$
S
NH
CO_2Et
BsN
F
f1 (ppm)

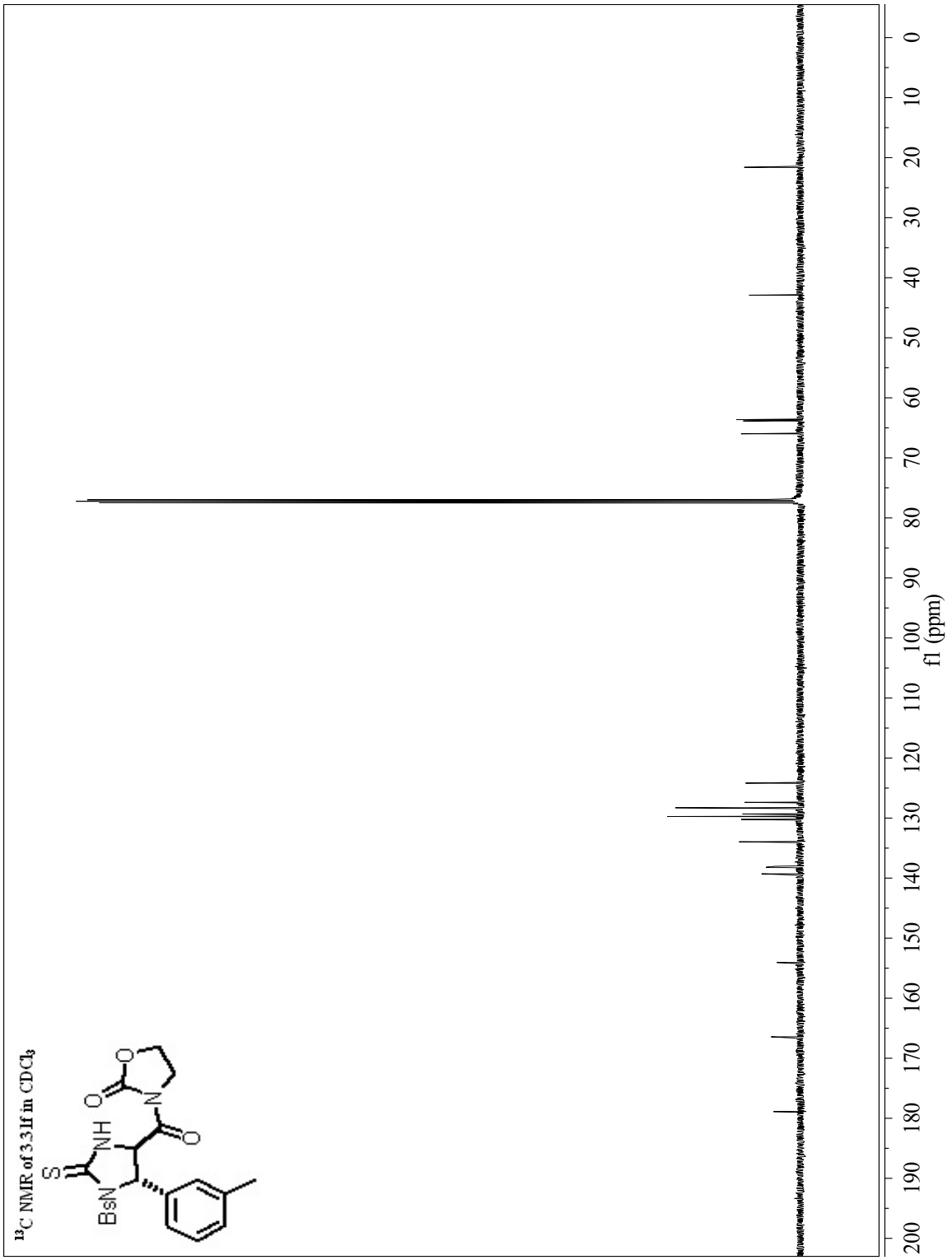

^{1}H NMR of 3.31e in d_6-DMSO
MeO
BsN
NH
S
O
O
O
N
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1.03
3.05
2.06
2.03
2.02
1.01
1.00
2.04
2.03
3.08

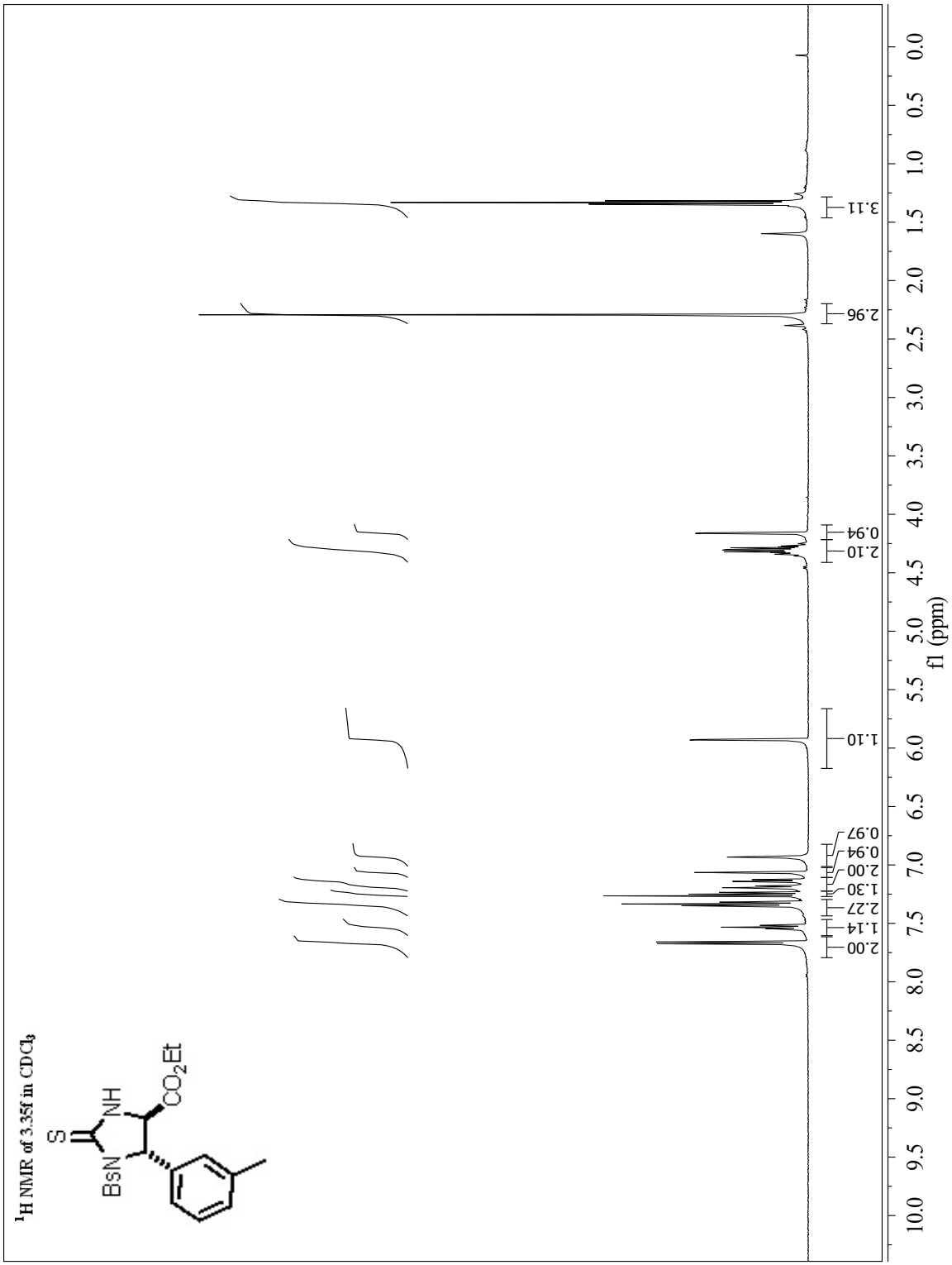

^{13}C NMR of 3.31e in d_6-DMSO
MeO
BsN
NH
S
O
O
O
O
N
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

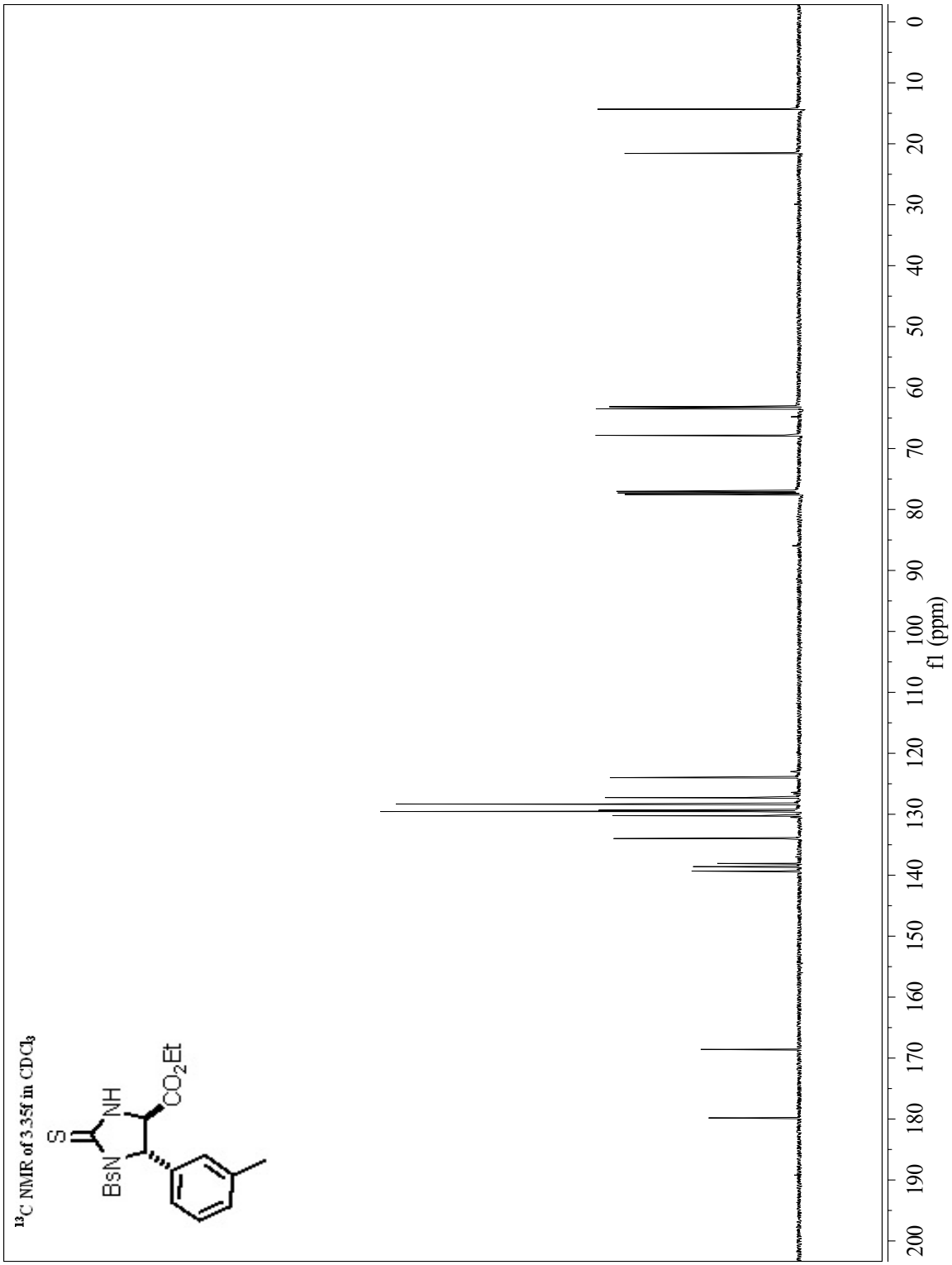

^{1}H NMR of 3.35e in $CDCl_3$
S
NH
CO_2Et
BsN
MeO
3.00
3.01
0.96
2.00
0.95
1.88
0.96
2.00
0.98
1.82
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

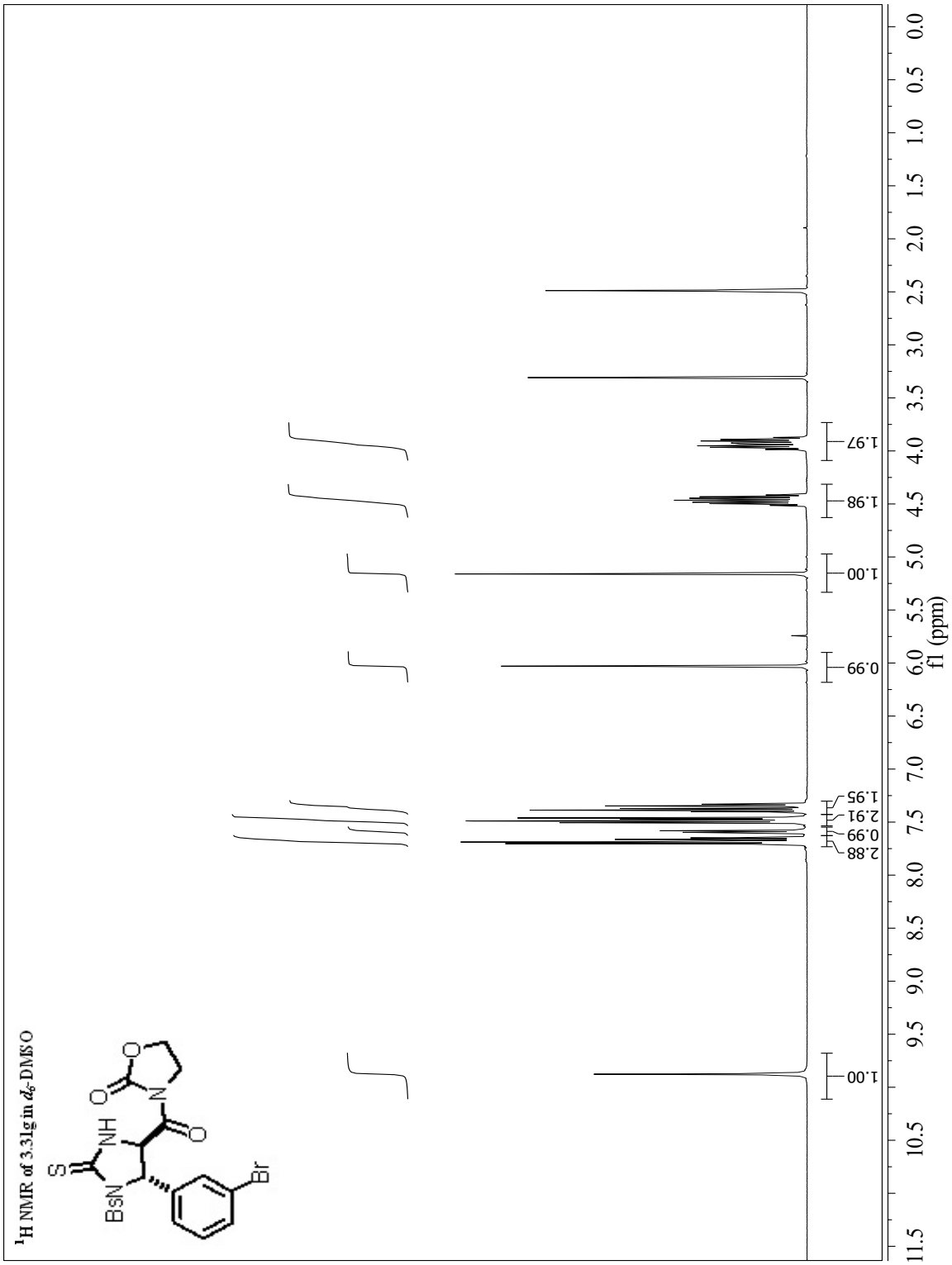

^{13}C NMR of 3.35e in $CDCl_3$
S
NH
CO_2Et
BsN
MeO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

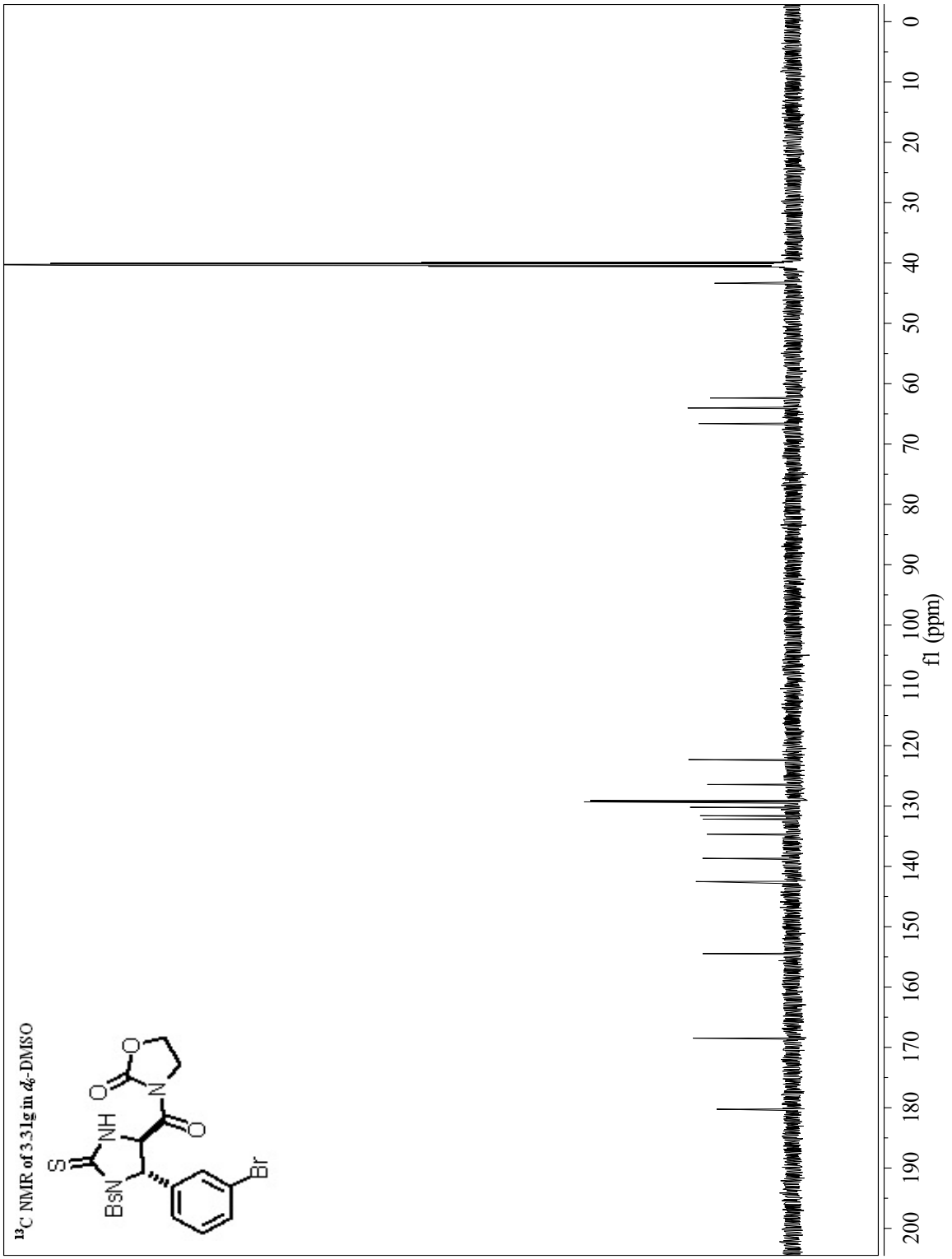

^{1}H NMR of 3.3.1f in $CDCl_3$
3.00
2.11
2.10
1.01
1.12
0.98
2.84
0.83
2.02
1.04
1.89
f1 (ppm)

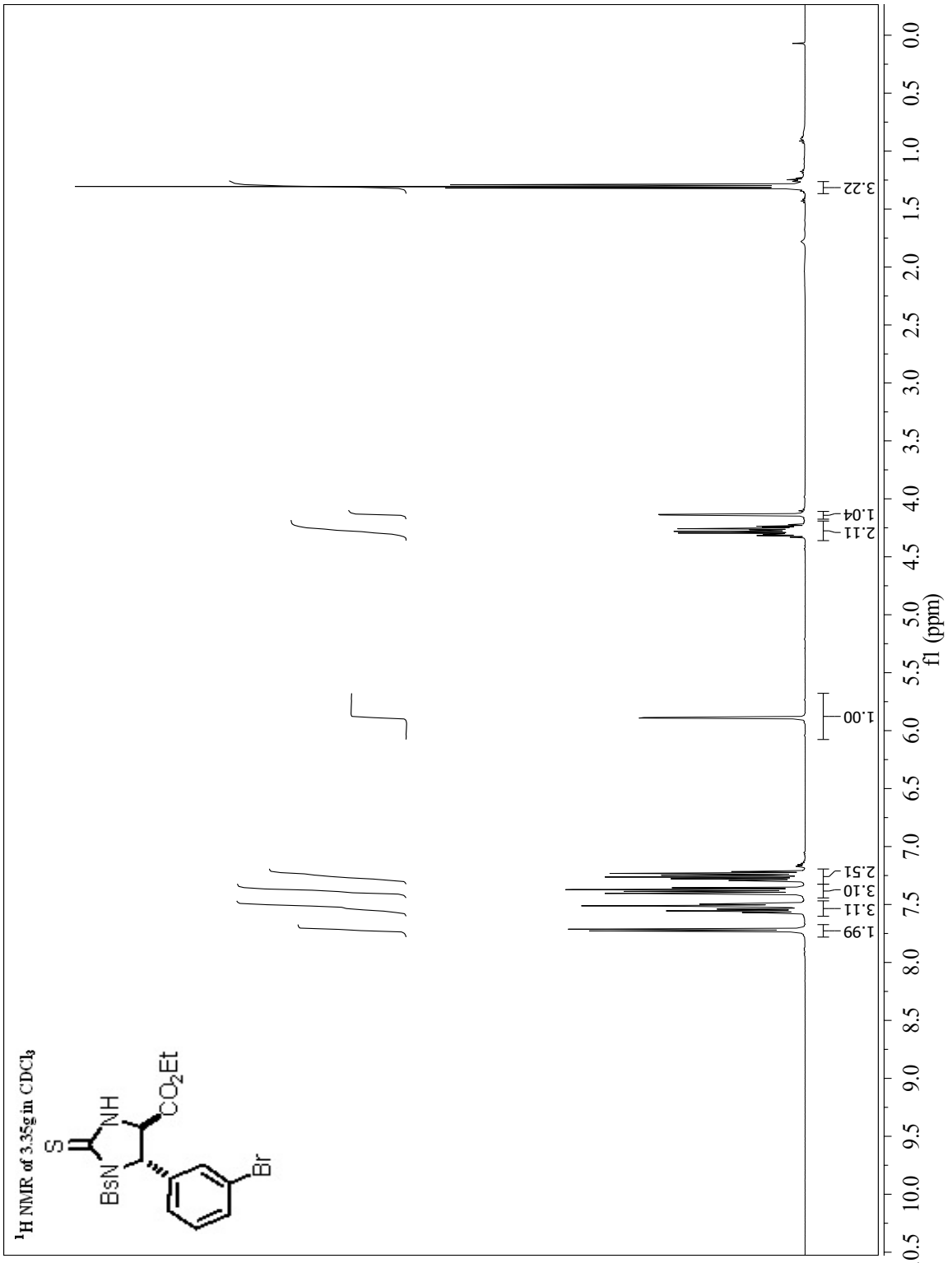

^{13}C NMR of 3.3If in $CDCl_3$
S
NH
O
O
N
O
O
BsN
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

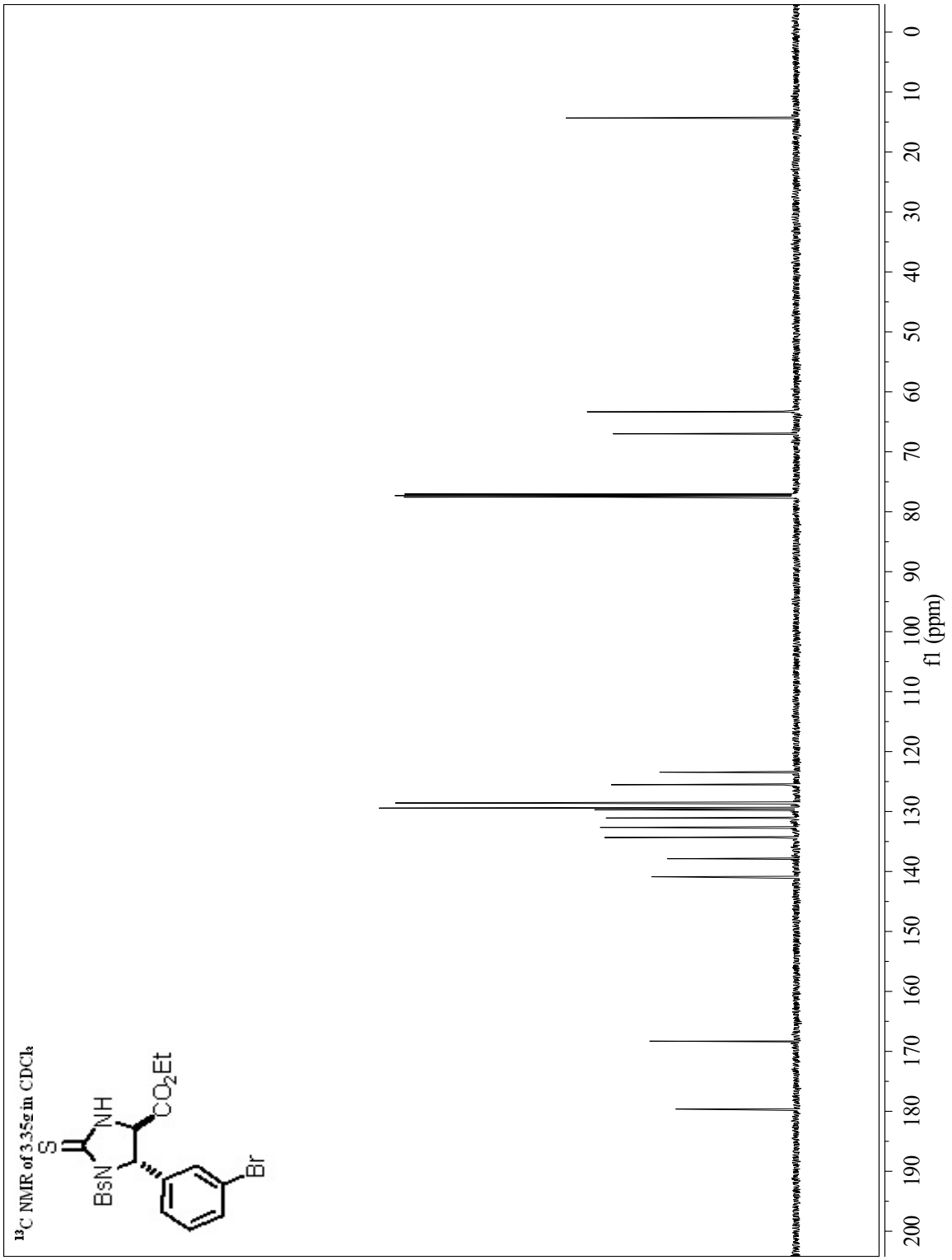

^{1}H NMR of 3.35f in $CDCl_3$
S
NH
CO_2Et
BsN
2.00
1.14
2.27
1.30
2.00
0.94
0.97
1.10
0.94
2.10
2.96
3.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

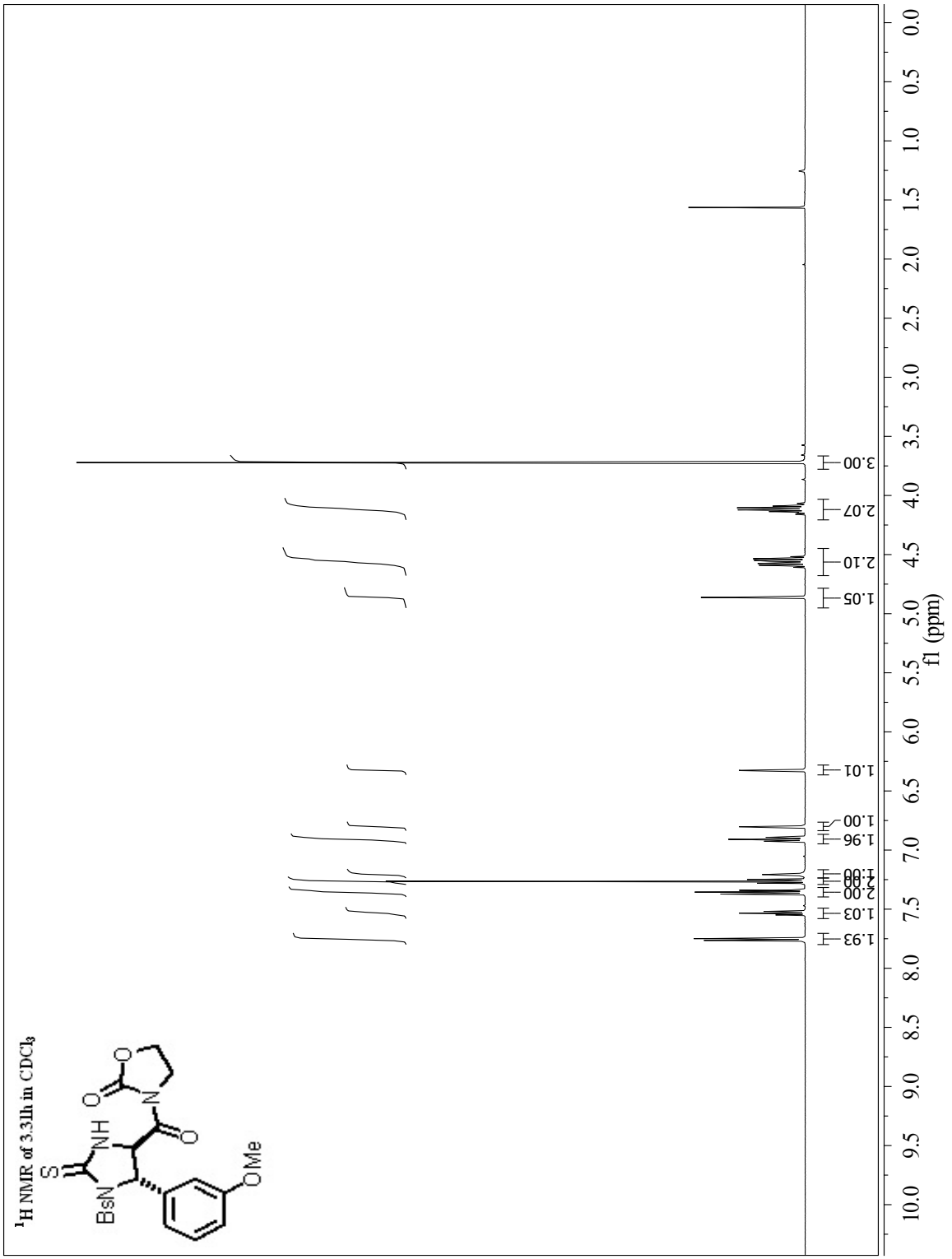

^{13}C NMR of 3.35f in $CDCl_3$
S
NH
CO_2Et
BsN
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

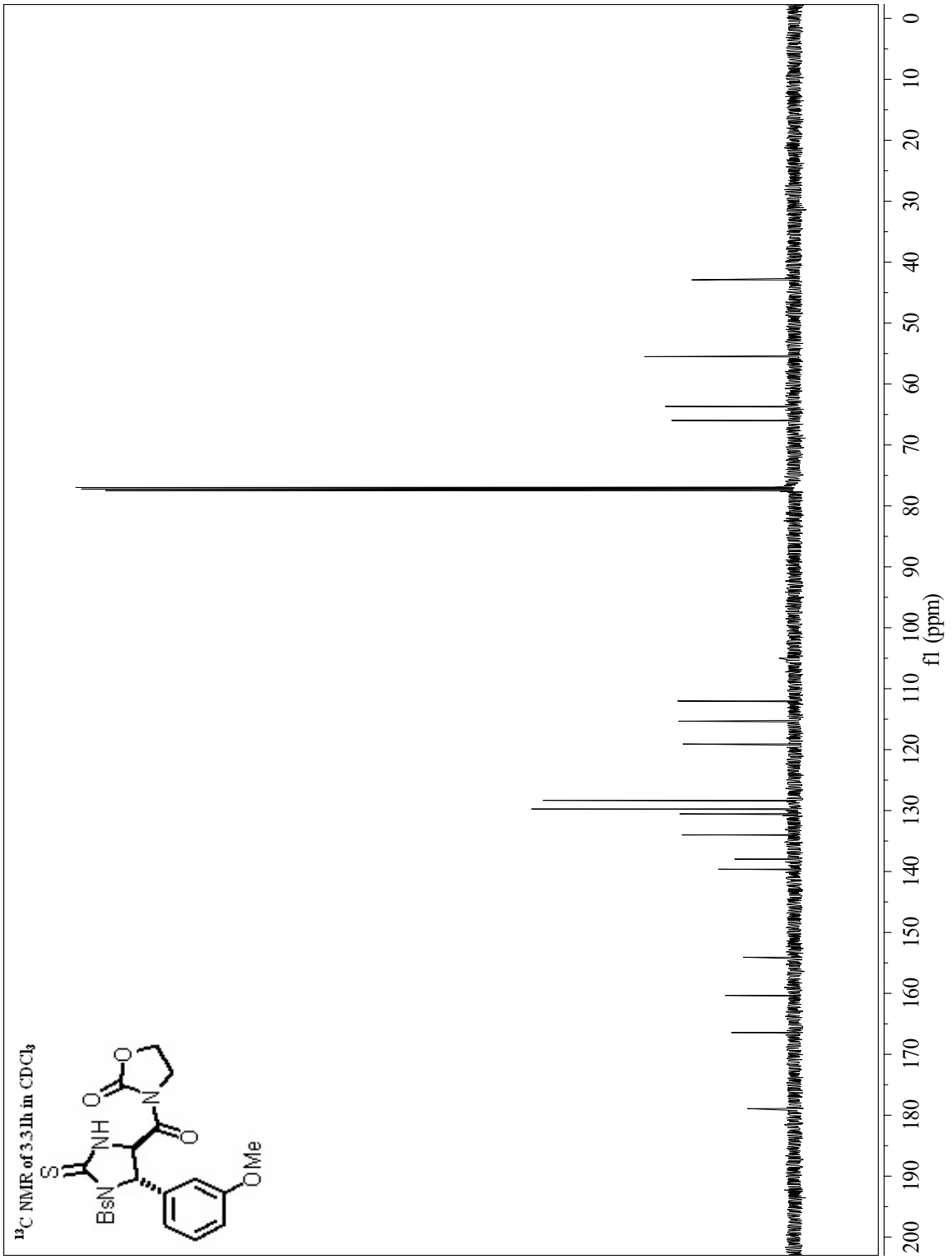

^{1}H NMR of 3.31g in d_6-DMSO
O
N
O
NH
S
BsN
Br
1.00
2.88
0.99
2.91
1.95
0.99
1.00
1.98
1.97
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

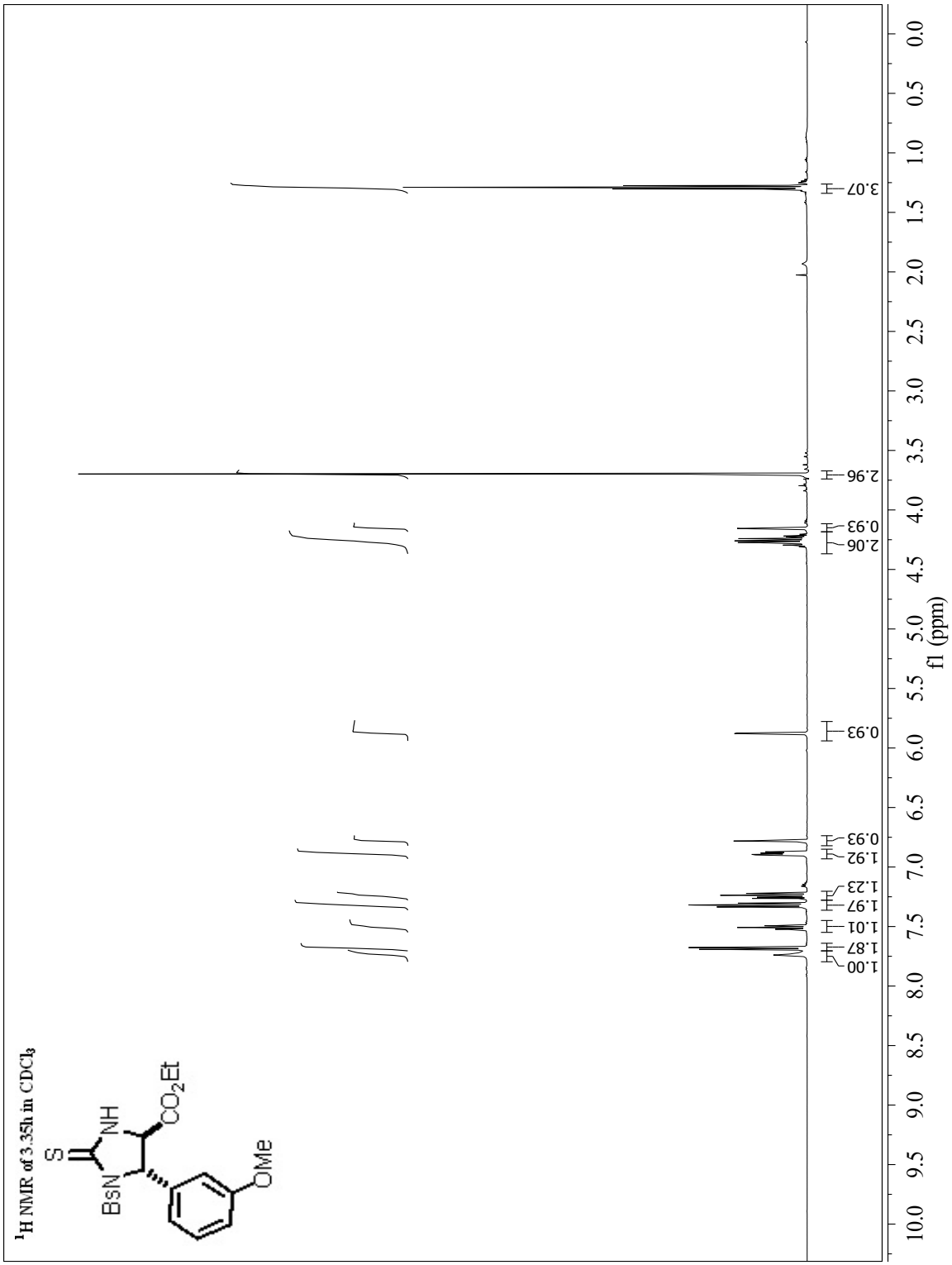

^{13}C NMR of 3.31g in d_6-DMSO
O
O
N
O
NH
S
BsN
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

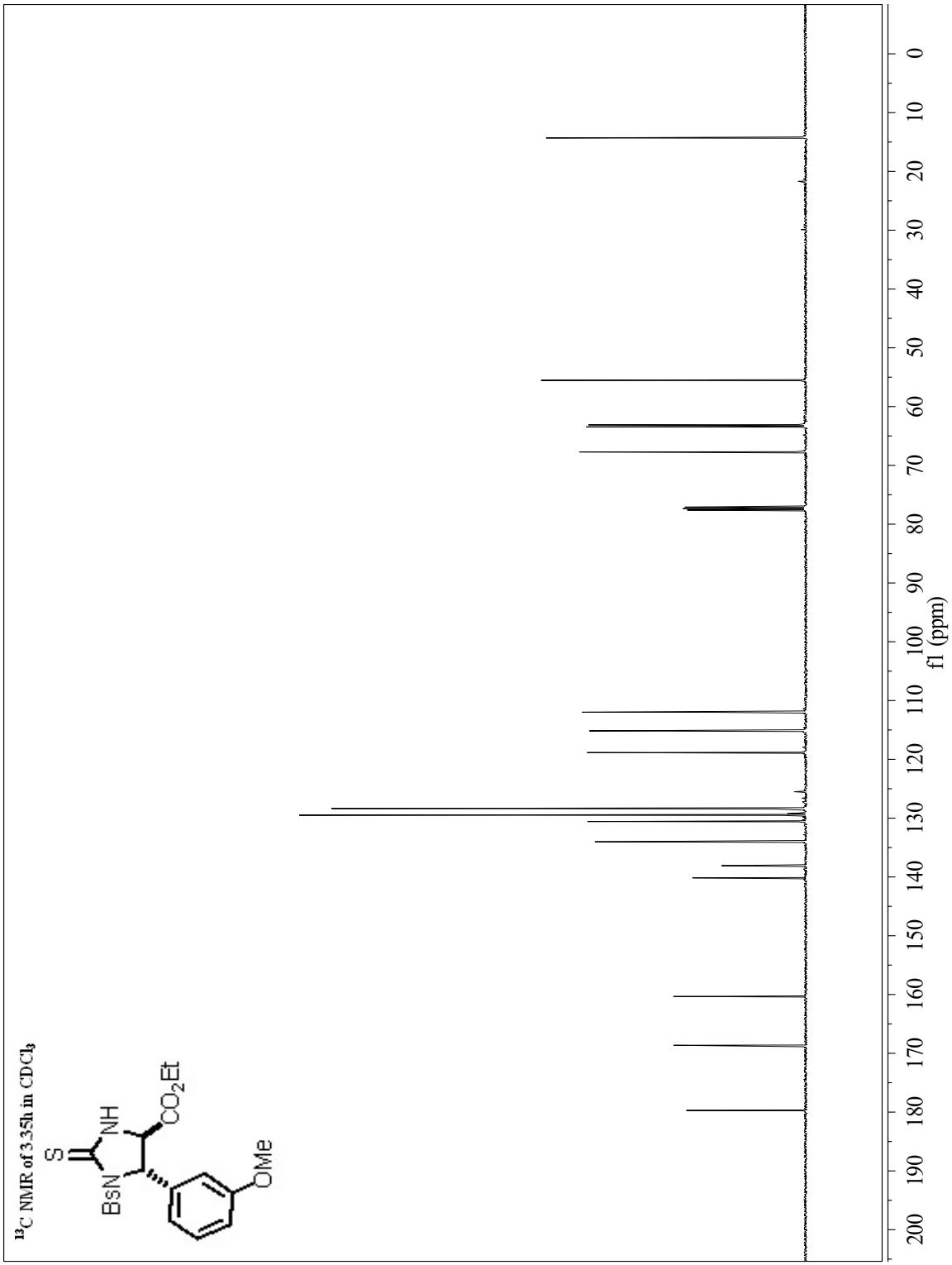

^{1}H NMR of 3.35g in $CDCl_3$
S
NH
CO_2Et
BsN
Br
3.22
1.04
2.11
1.00
2.51
3.10
3.11
1.99
f1 (ppm)

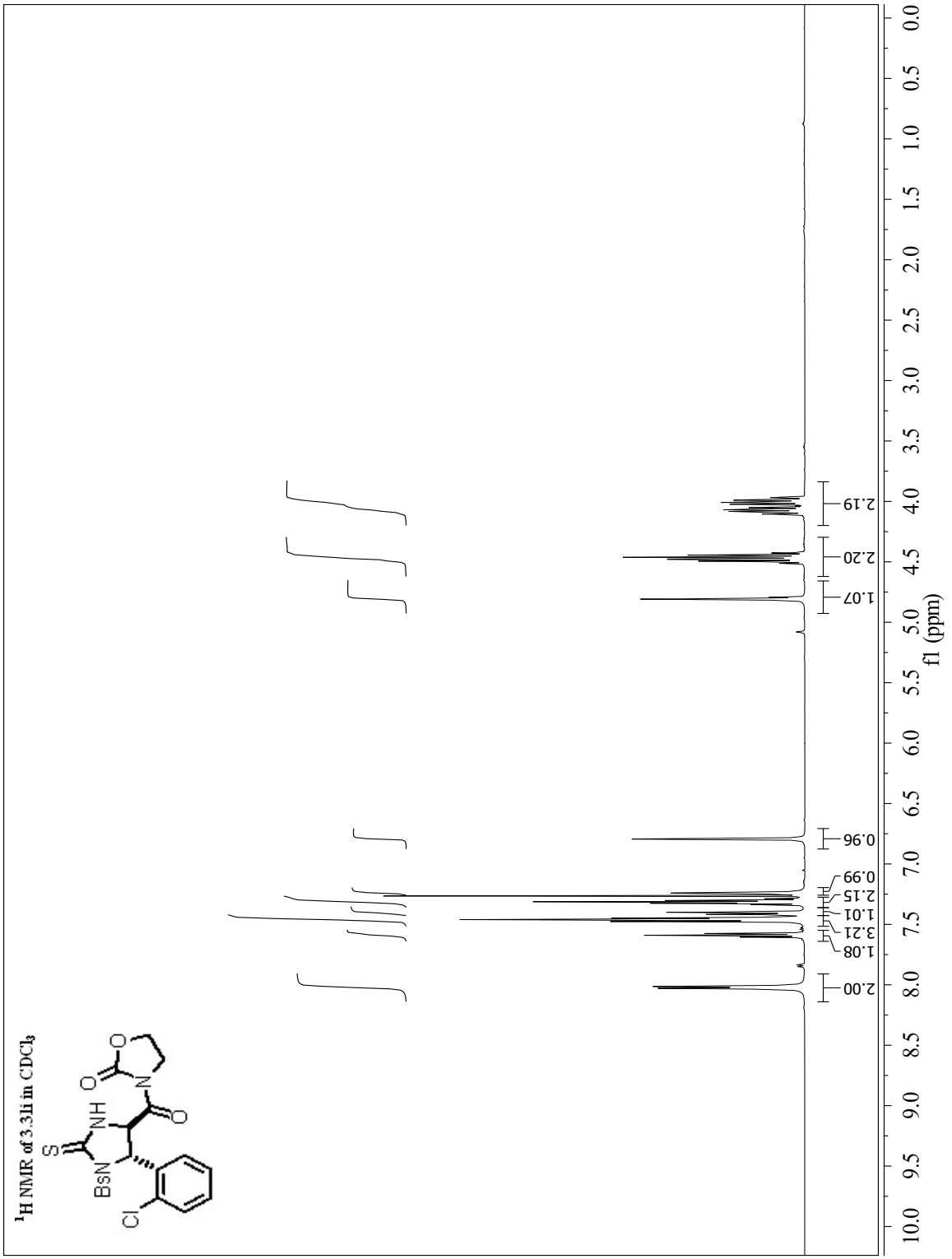

^{13}C NMR of 3.35g in CDCl$_3$
S
NH
CO$_2$Et
BsN
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

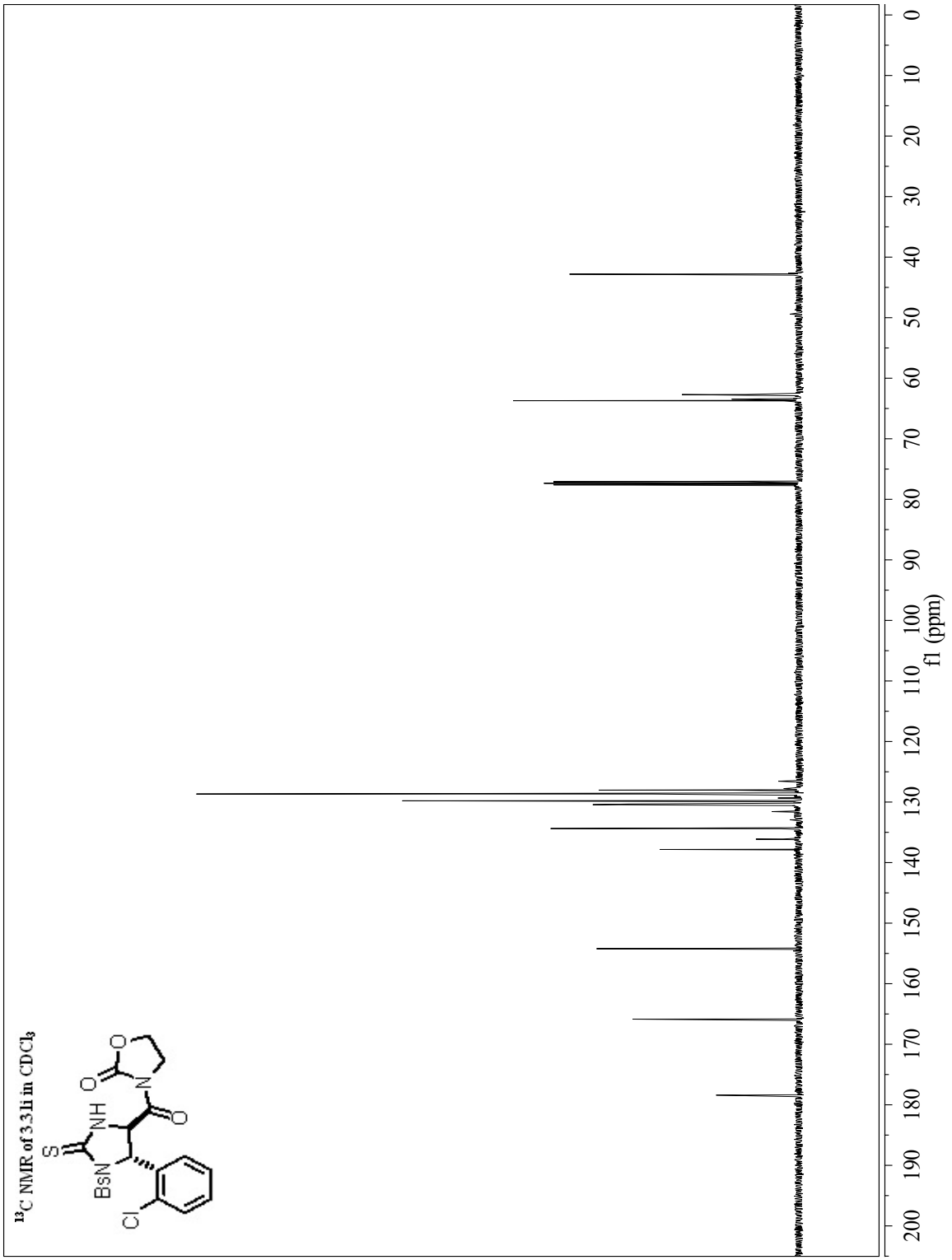

^{1}H NMR of 3.3lh in $CDCl_3$
BsN
NH
OMe
f1 (ppm)

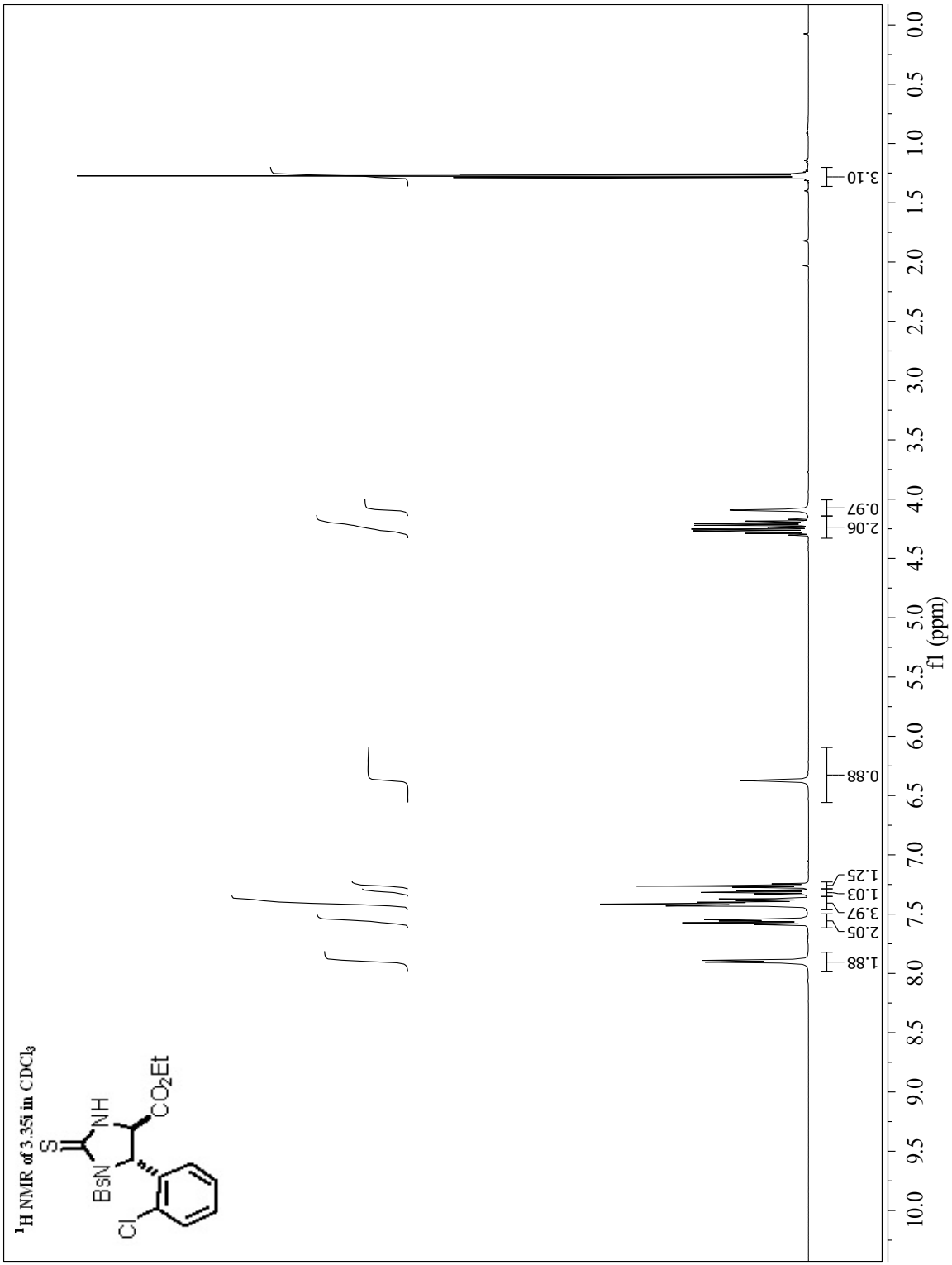

^{13}C NMR of 3.3Ih in $CDCl_3$
S
NH
O
O
N
O
BsN
OMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

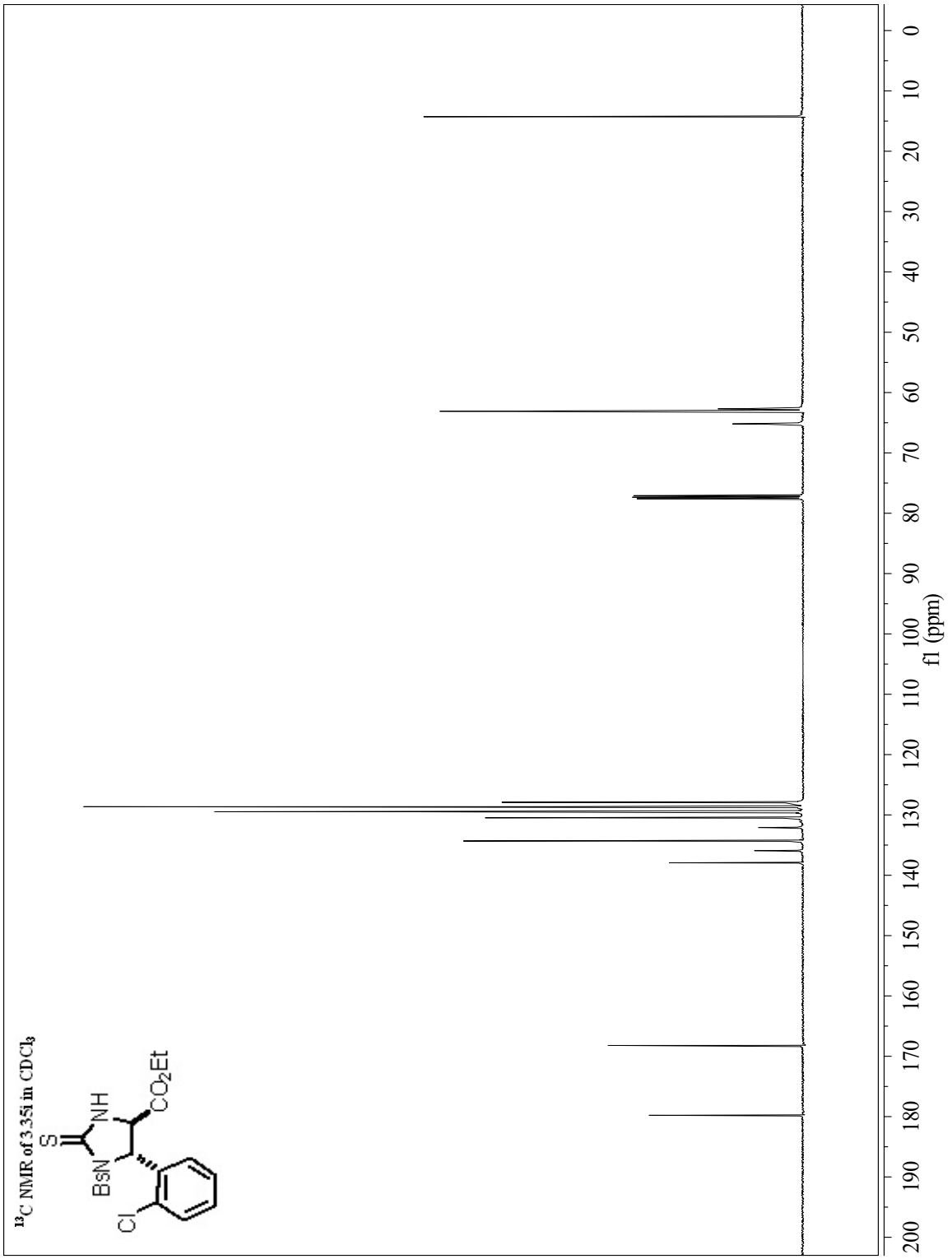

^{1}H NMR of 3.35h in $CDCl_3$
S
NH
CO_2Et
BsN
OMe
3.07
2.96
2.06
0.93
0.93
1.92
0.93
1.23
1.97
1.01
1.87
1.00
f1 (ppm)

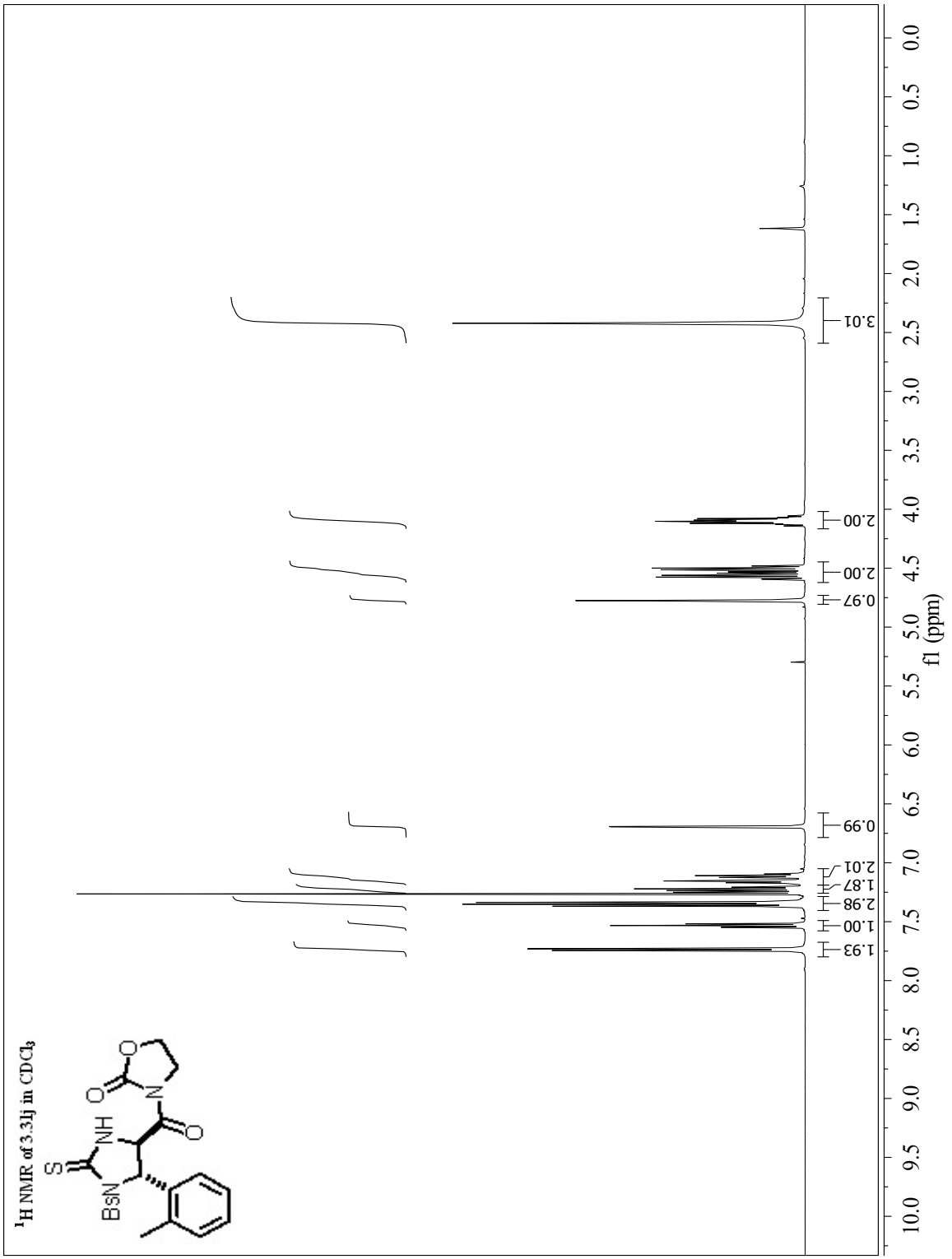

^{13}C NMR of 3.35h in $CDCl_3$
S
NH
CO_2Et
BsN
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

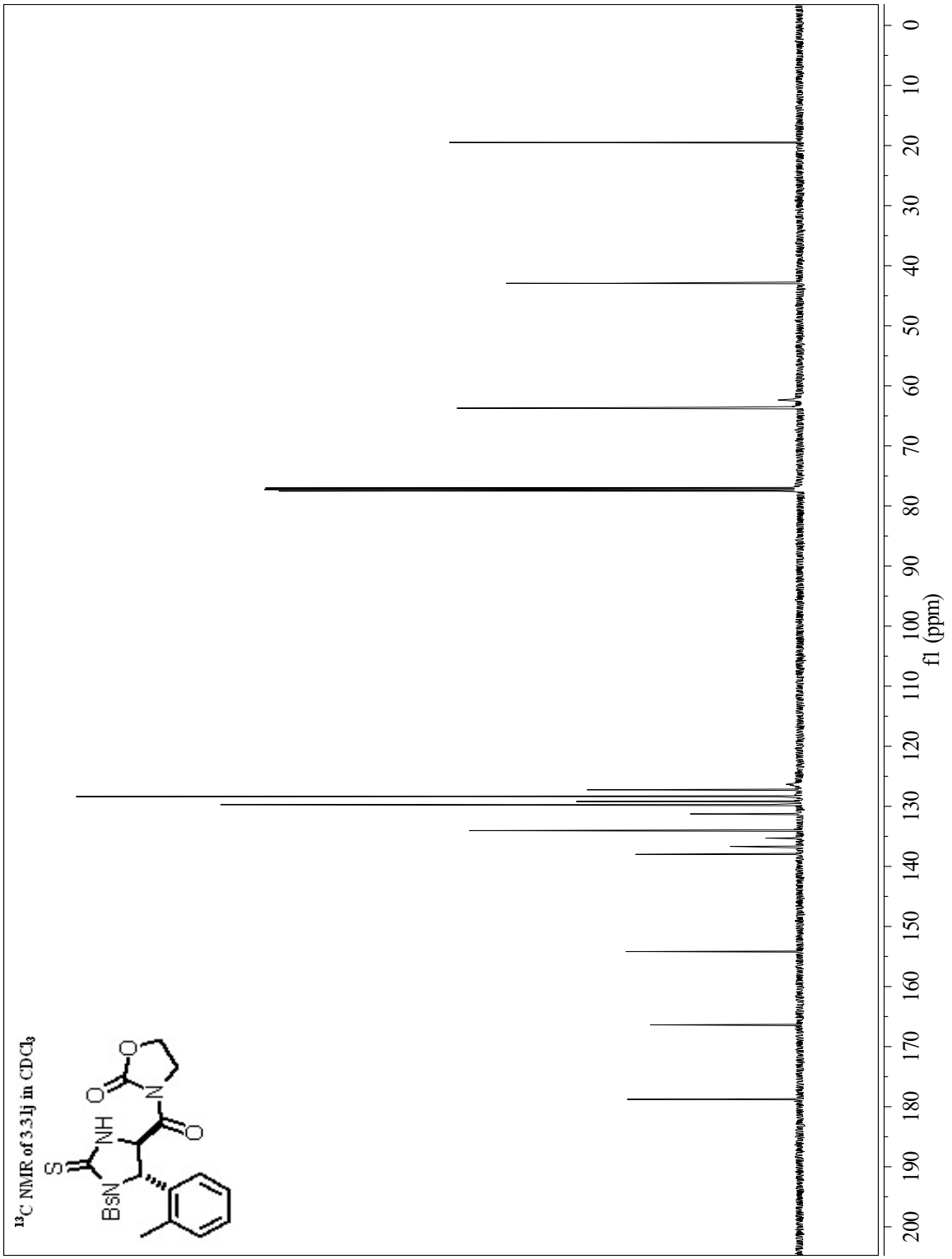

^{1}H NMR of 3.3li in CDCl$_3$
O
O
N
O
NH
S
BsN
Cl
2.00
1.08
3.21
1.01
2.15
0.99
0.96
1.07
2.20
2.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

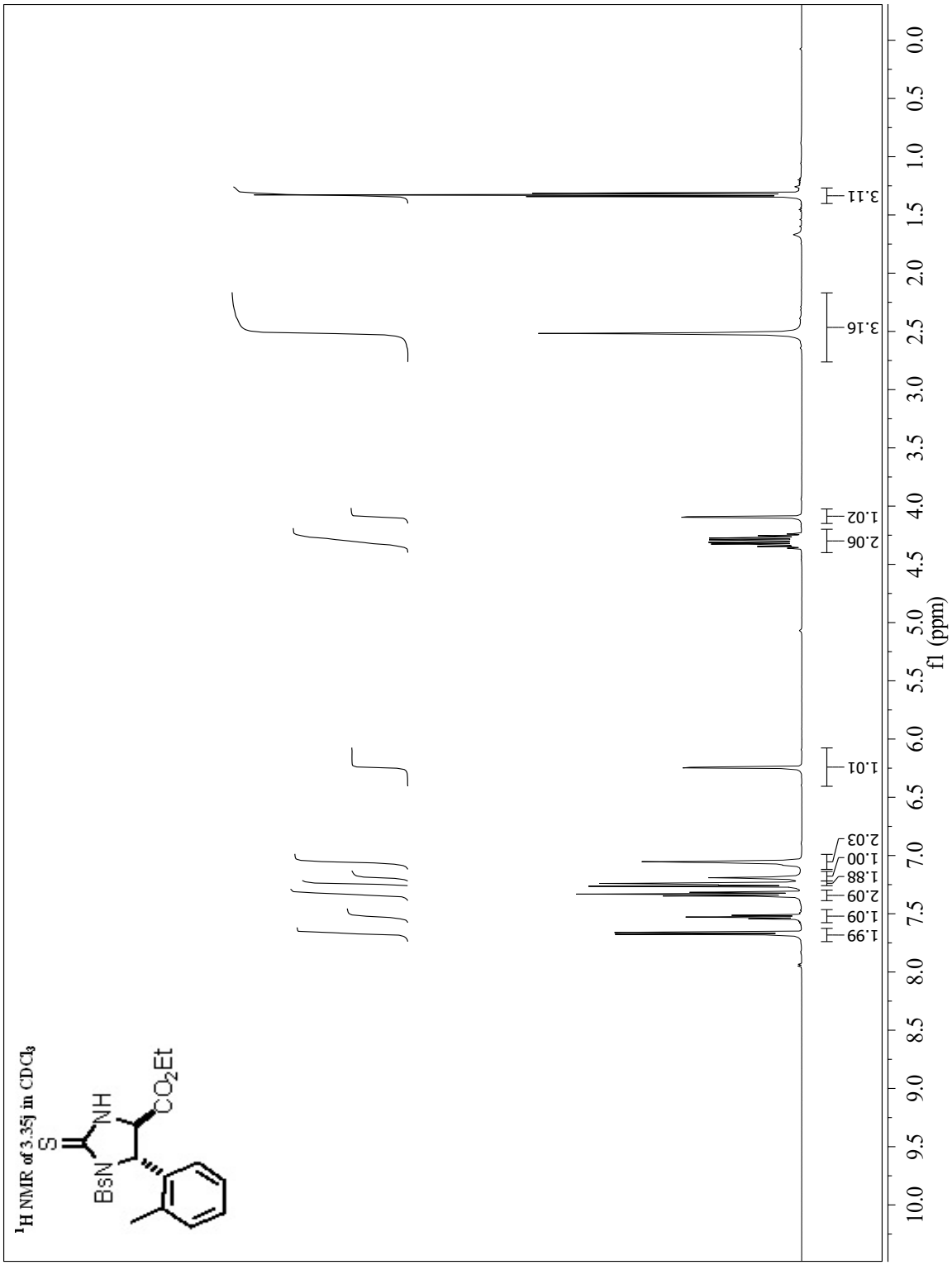

^{13}C NMR of 3.3li in $CDCl_3$
S
NH
O
O
N
O
BsN
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

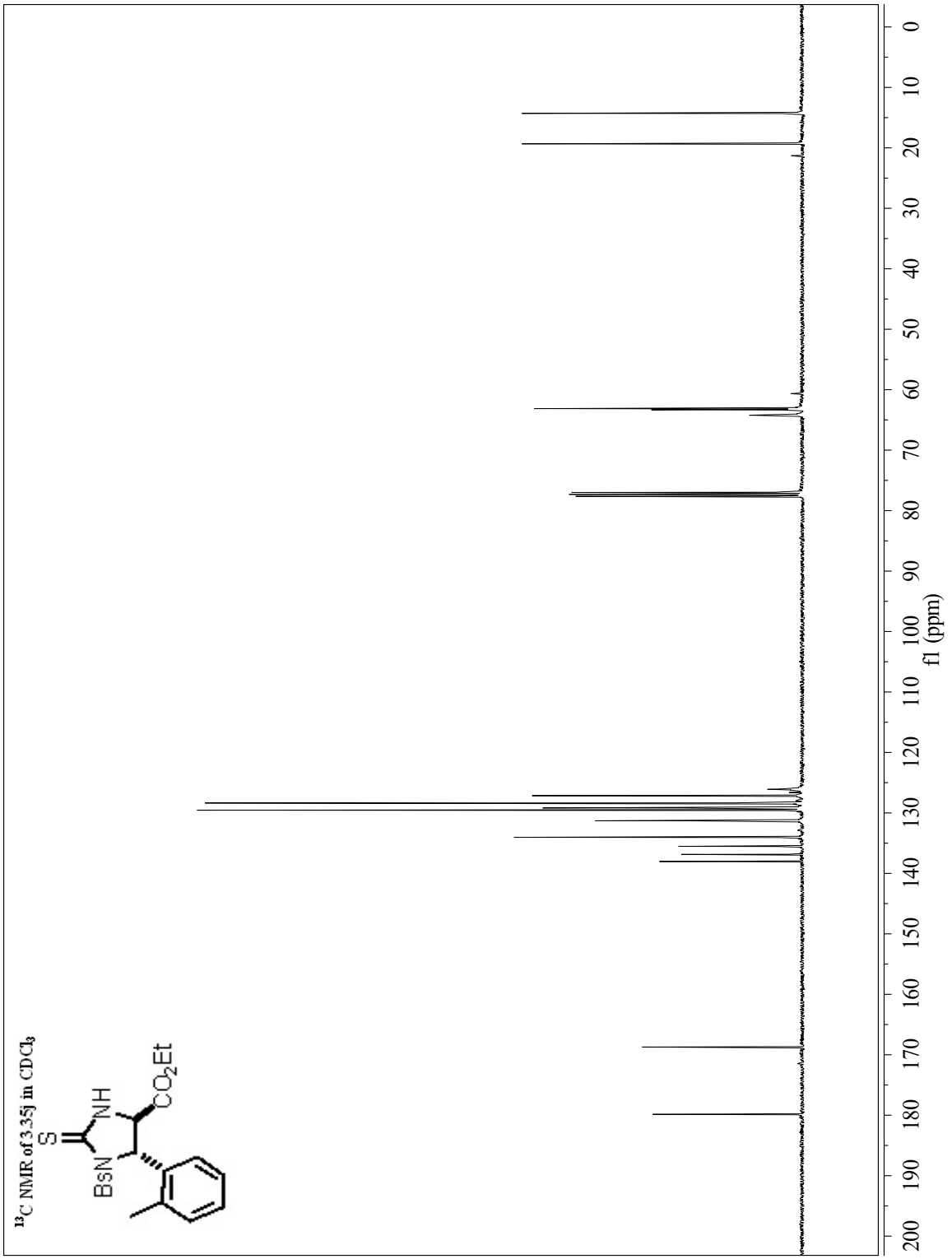

^{1}H NMR of 3.35l in $CDCl_3$
S
NH
CO_2Et
Bsn
Cl
3.10
2.06
0.97
0.88
1.25
1.03
3.97
2.05
1.88
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

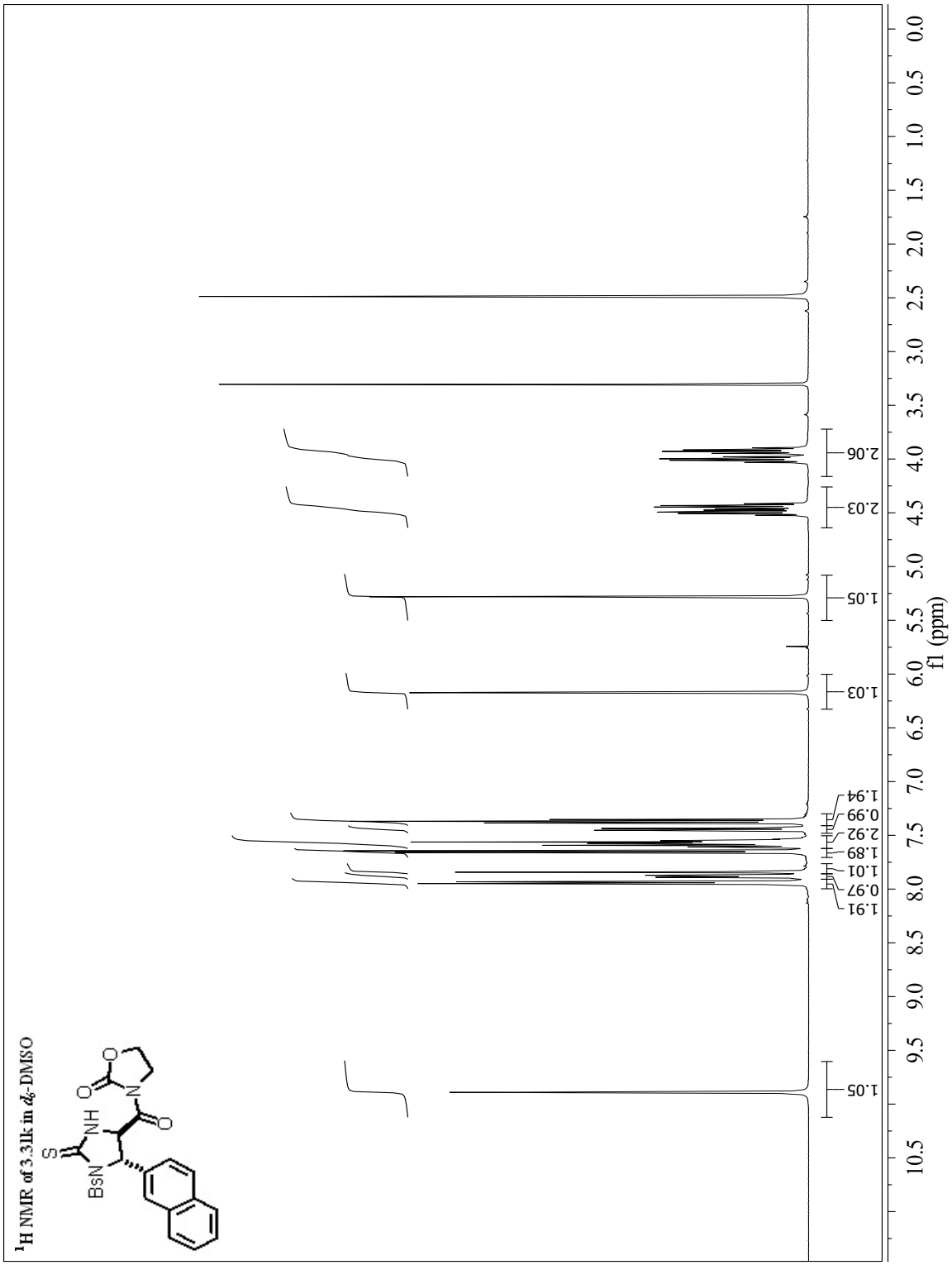

^{13}C NMR of 3.35i in $CDCl_3$
S
NH
CO_2Et
BsN
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

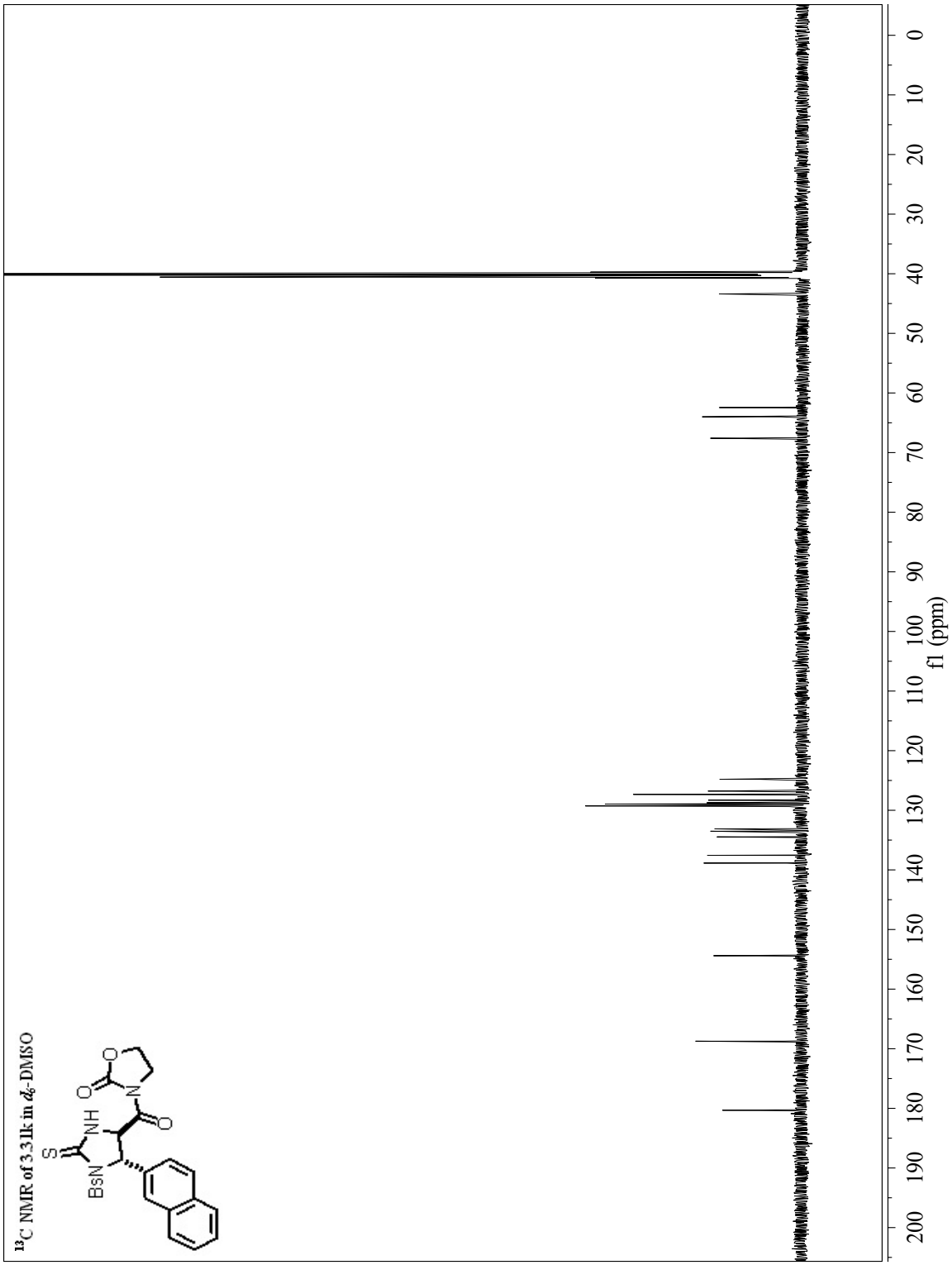

^{1}H NMR of 3.3Ij in $CDCl_3$
BsN
NH
S
O
O
O
N
3.01
2.00
2.00
0.97
0.99
2.01
1.87
2.98
1.00
1.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

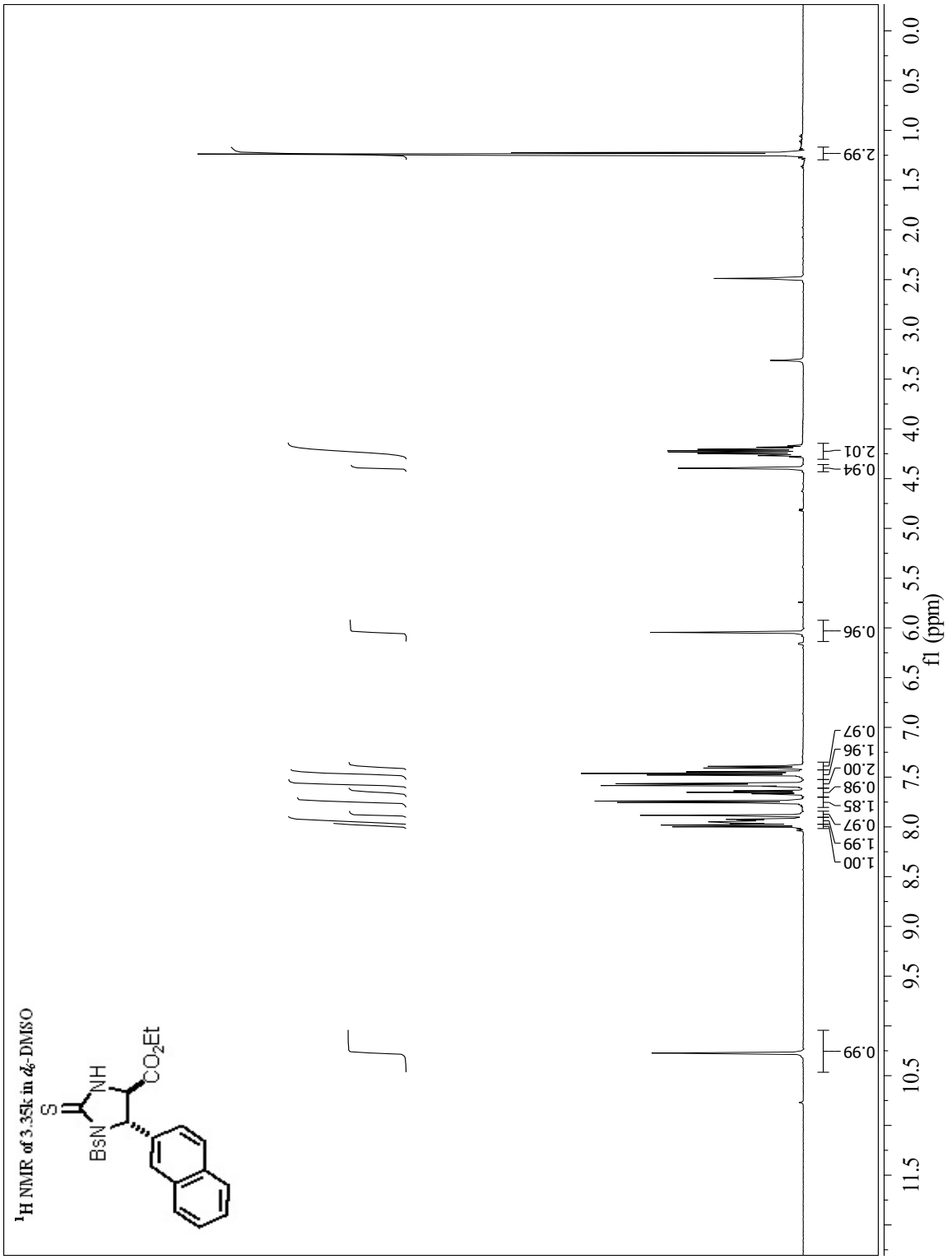

^{13}C NMR of 3.3Ij in $CDCl_3$
O
O
N
O
NH
S
BsN
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

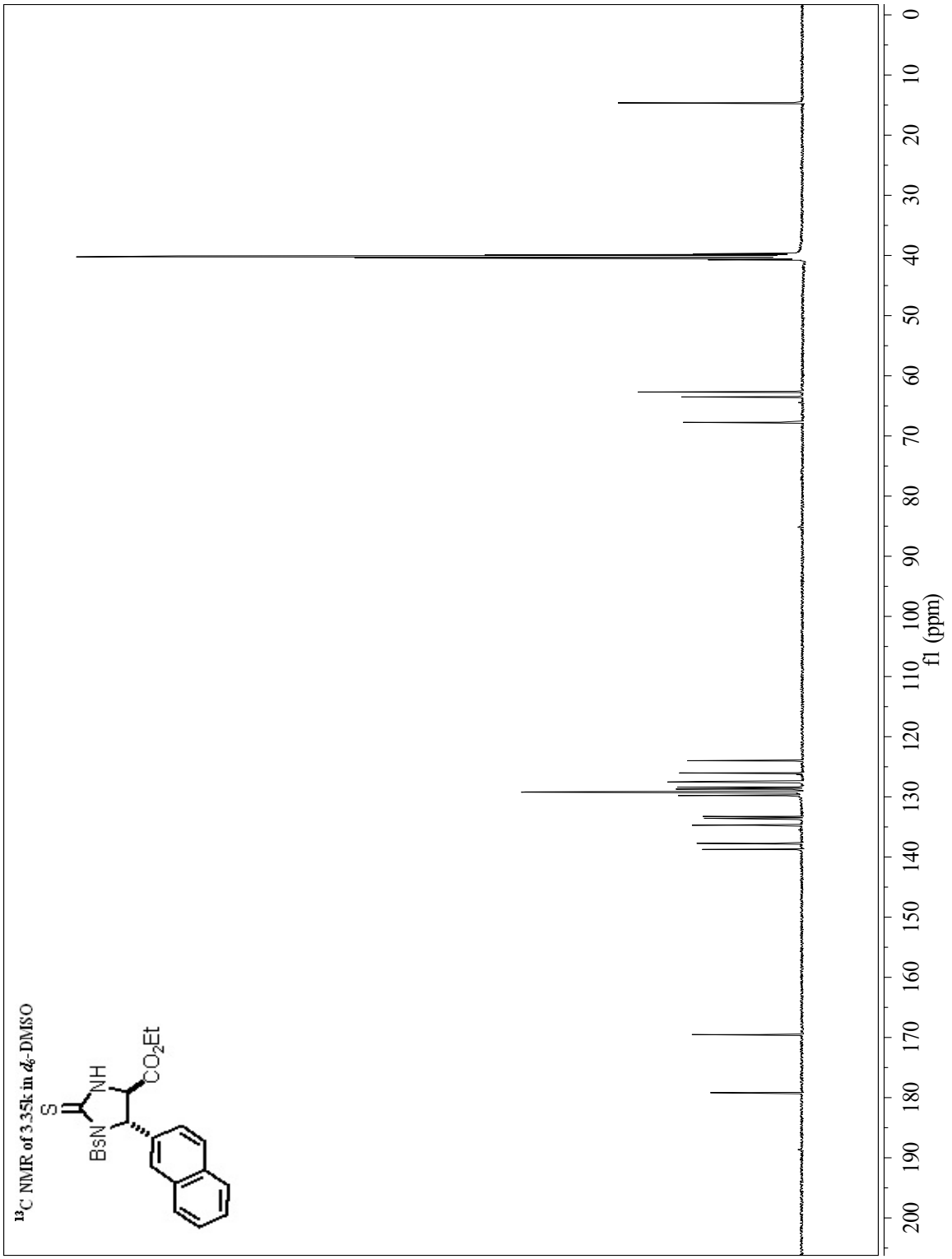

^{1}H NMR of 3.35j in $CDCl_3$
Bs
N
NH
S
CO_2Et
1.99
1.09
2.09
1.88
1.00
2.03
1.01
1.02
2.06
3.16
3.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

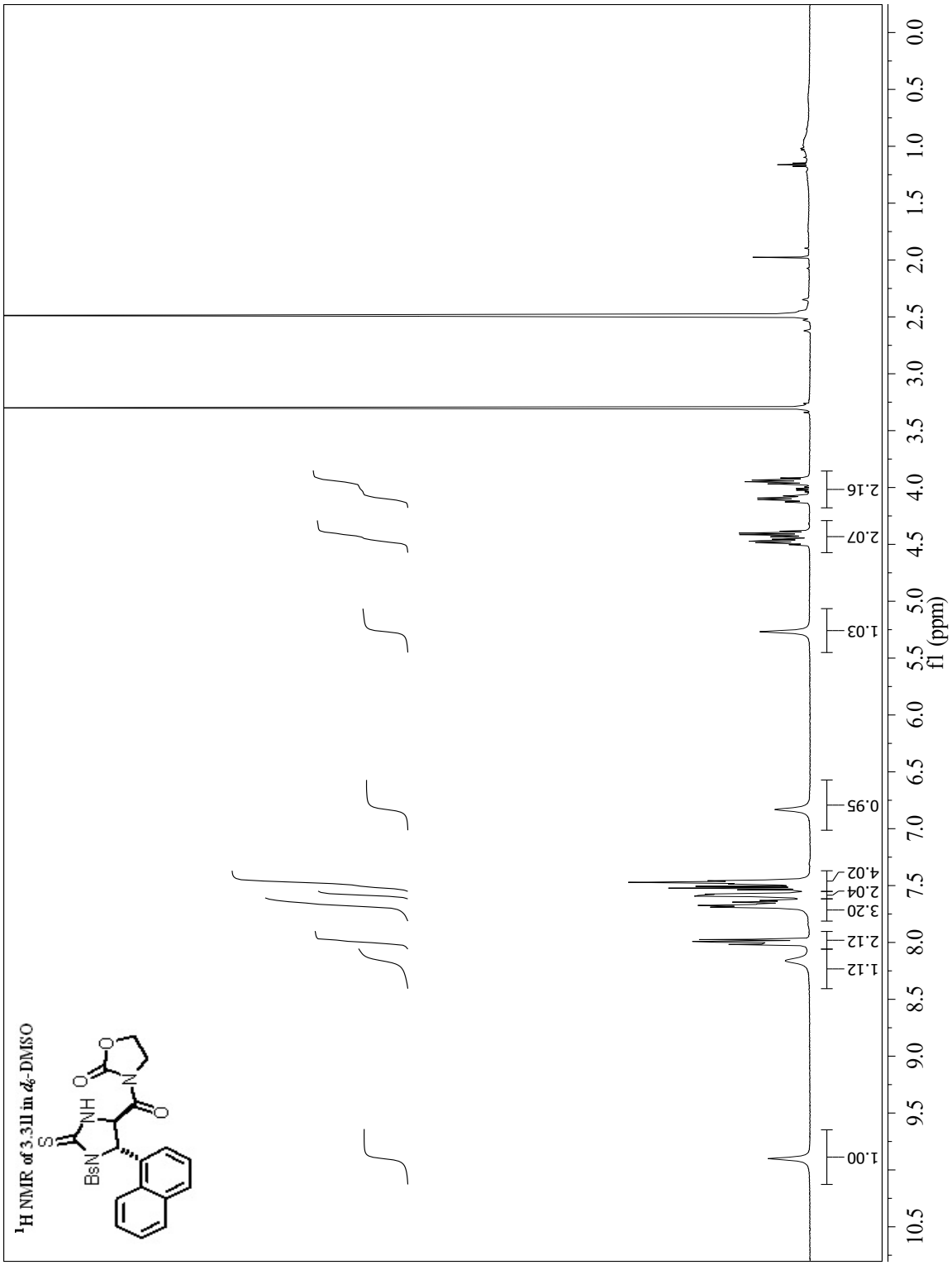

^{13}C NMR of 3.35j in $CDCl_3$
Bs
N
NH
S
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

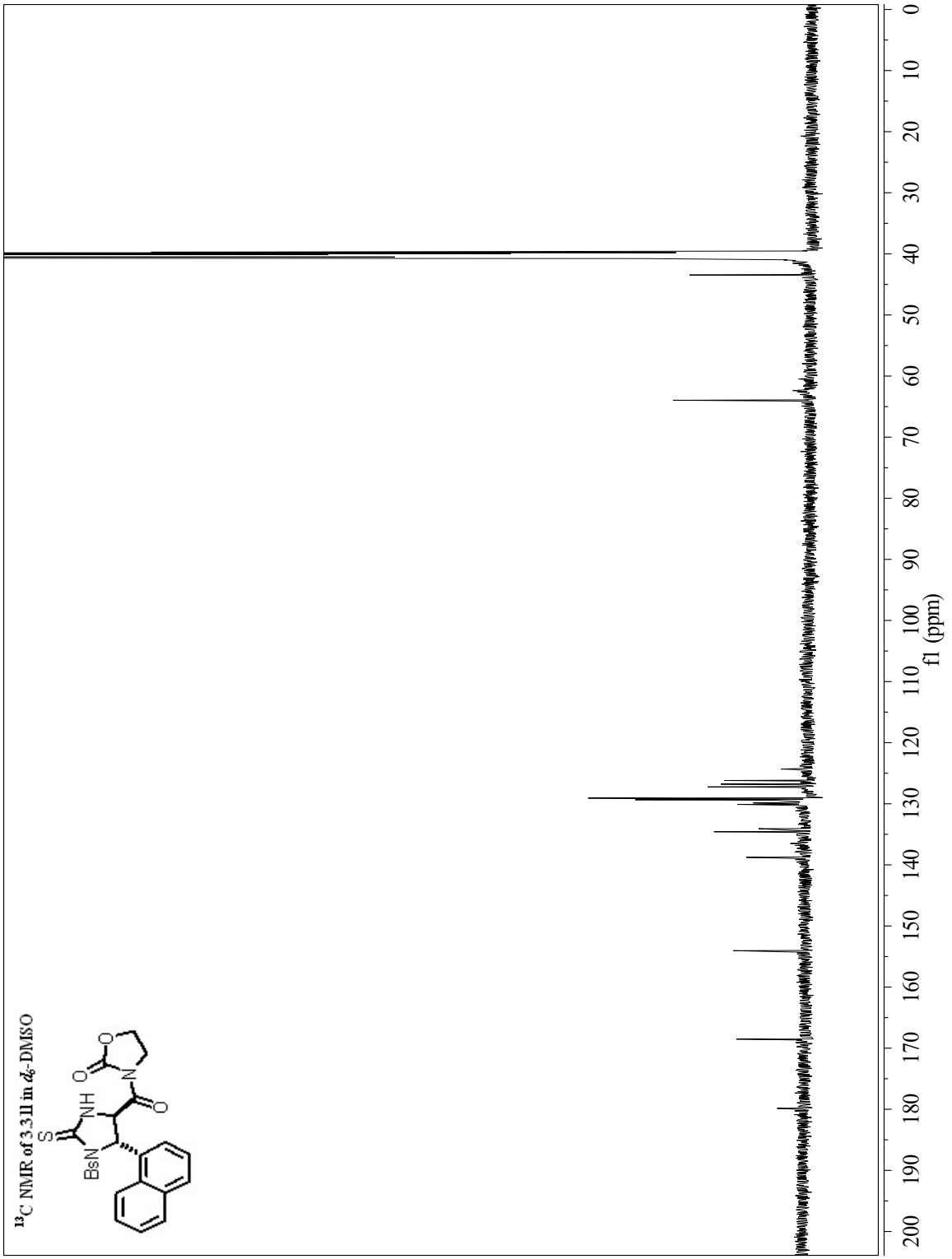

^{1}H NMR of 3.3Ik in d_6-DMSO
Bsn
NH
O
N
S
1.05
1.91
0.97
1.01
1.89
2.92
0.99
1.94
1.03
1.05
2.03
2.06
f1 (ppm)

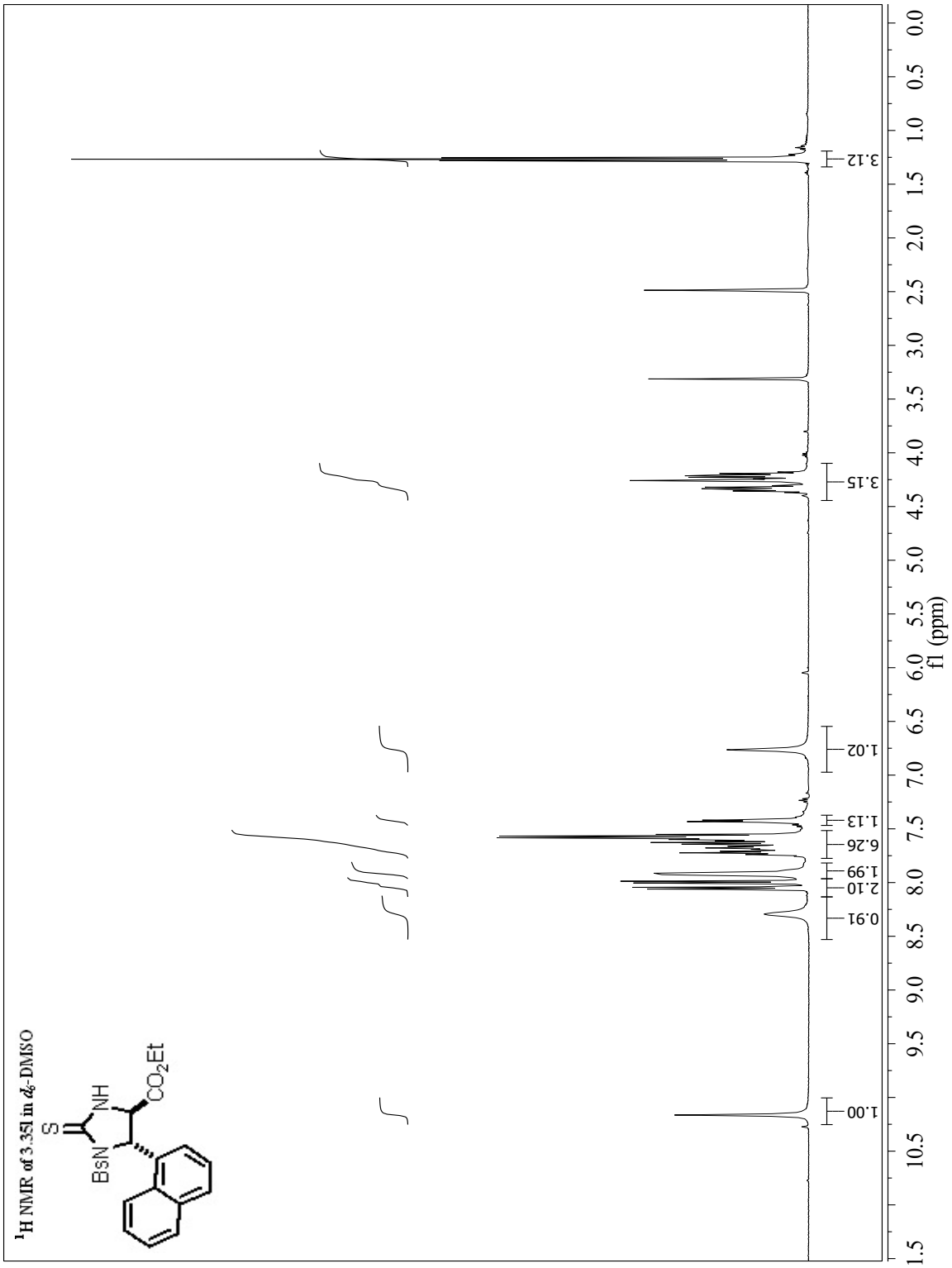

^{13}C NMR of 3.3 Ik in d_6-DMSO
BsN
NH
S
O
O
O
N
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

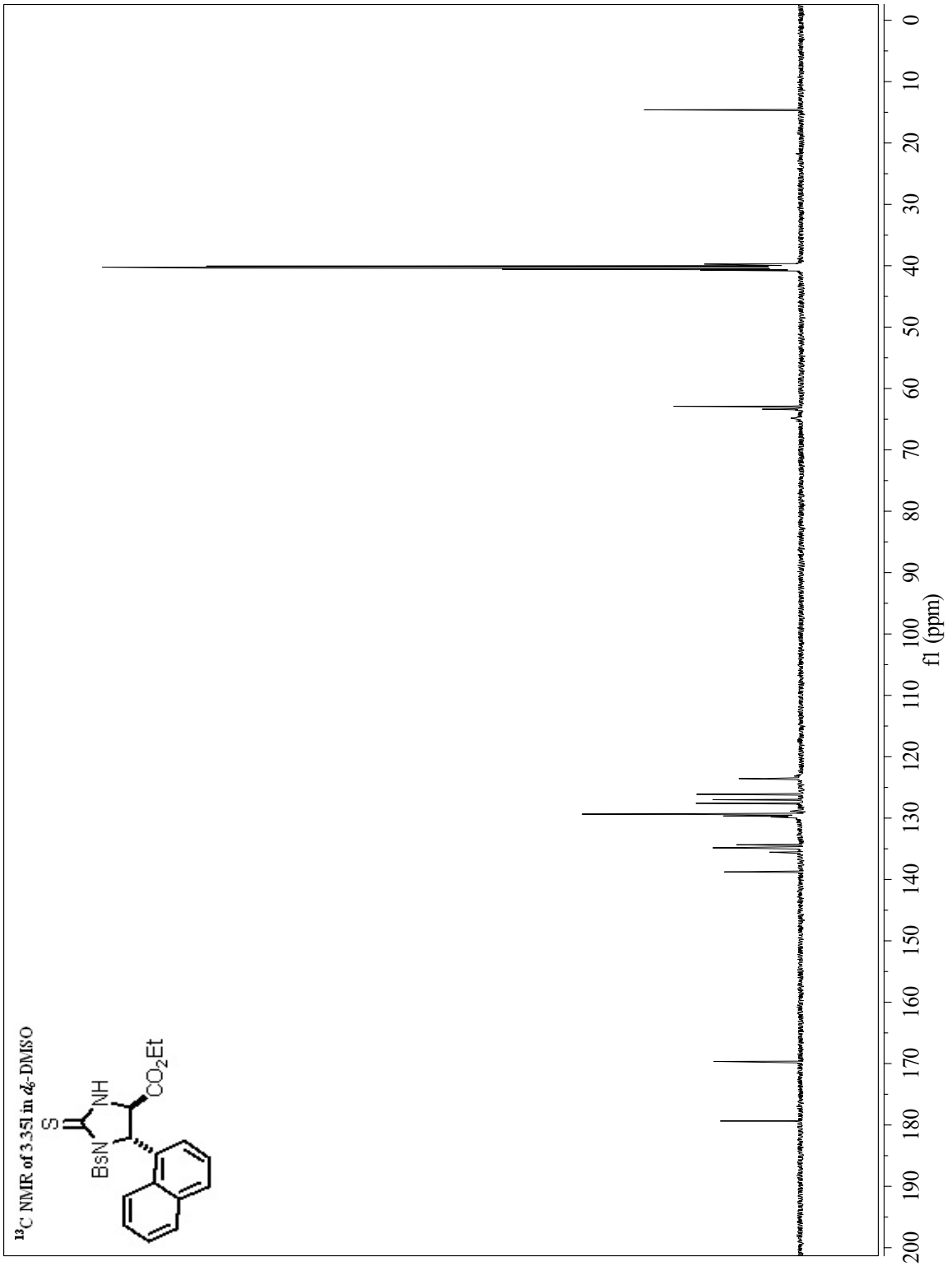

^{1}H NMR of 3.35k in d_6-DMSO
S
NH
BsN
CO_2Et
2.99
2.01
0.94
0.96
1.00
1.99
0.97
1.85
0.98
2.00
1.96
0.97
0.99
f1 (ppm)

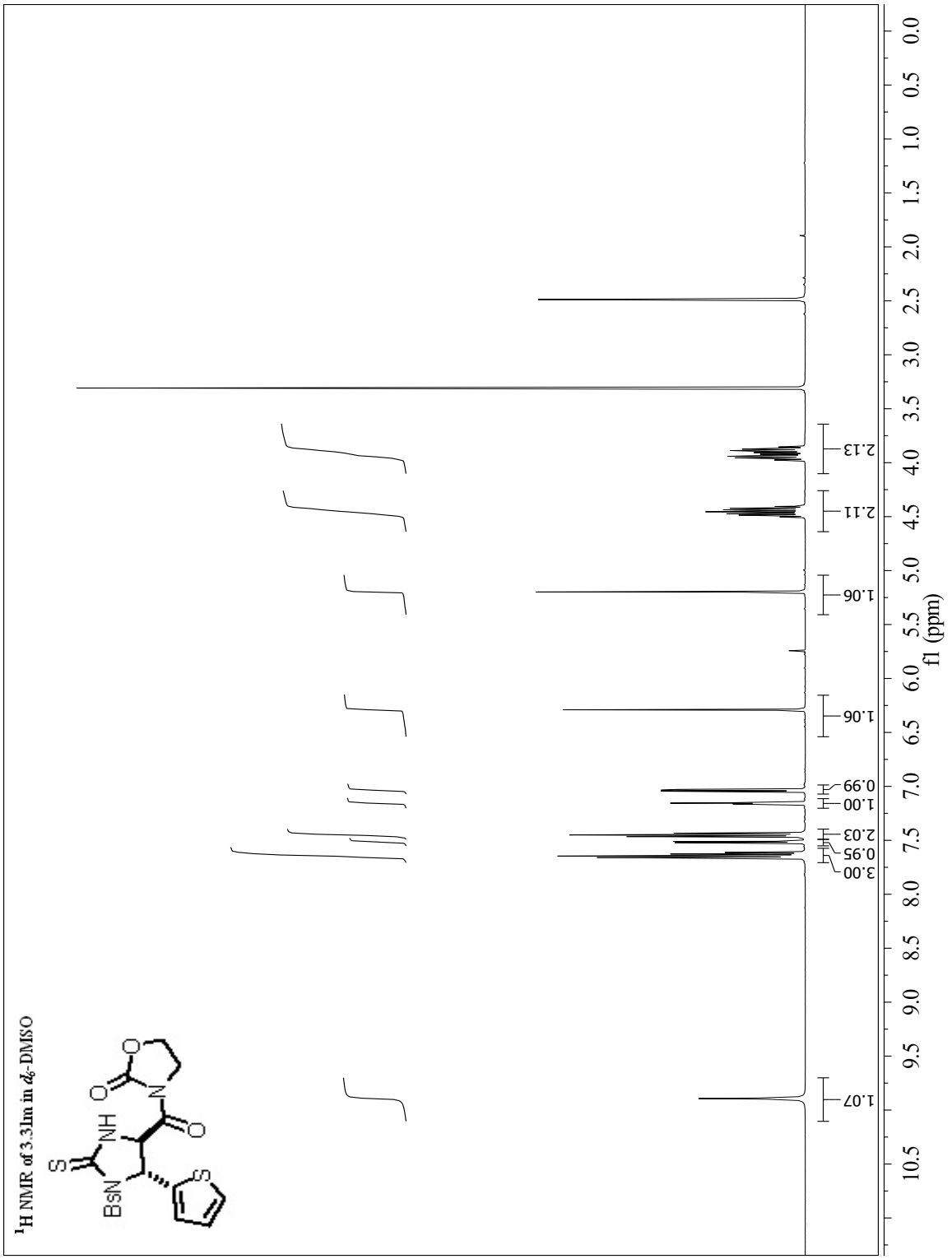

^{13}C NMR of 3.35k in d_6-DMSO
S
NH
BsN
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

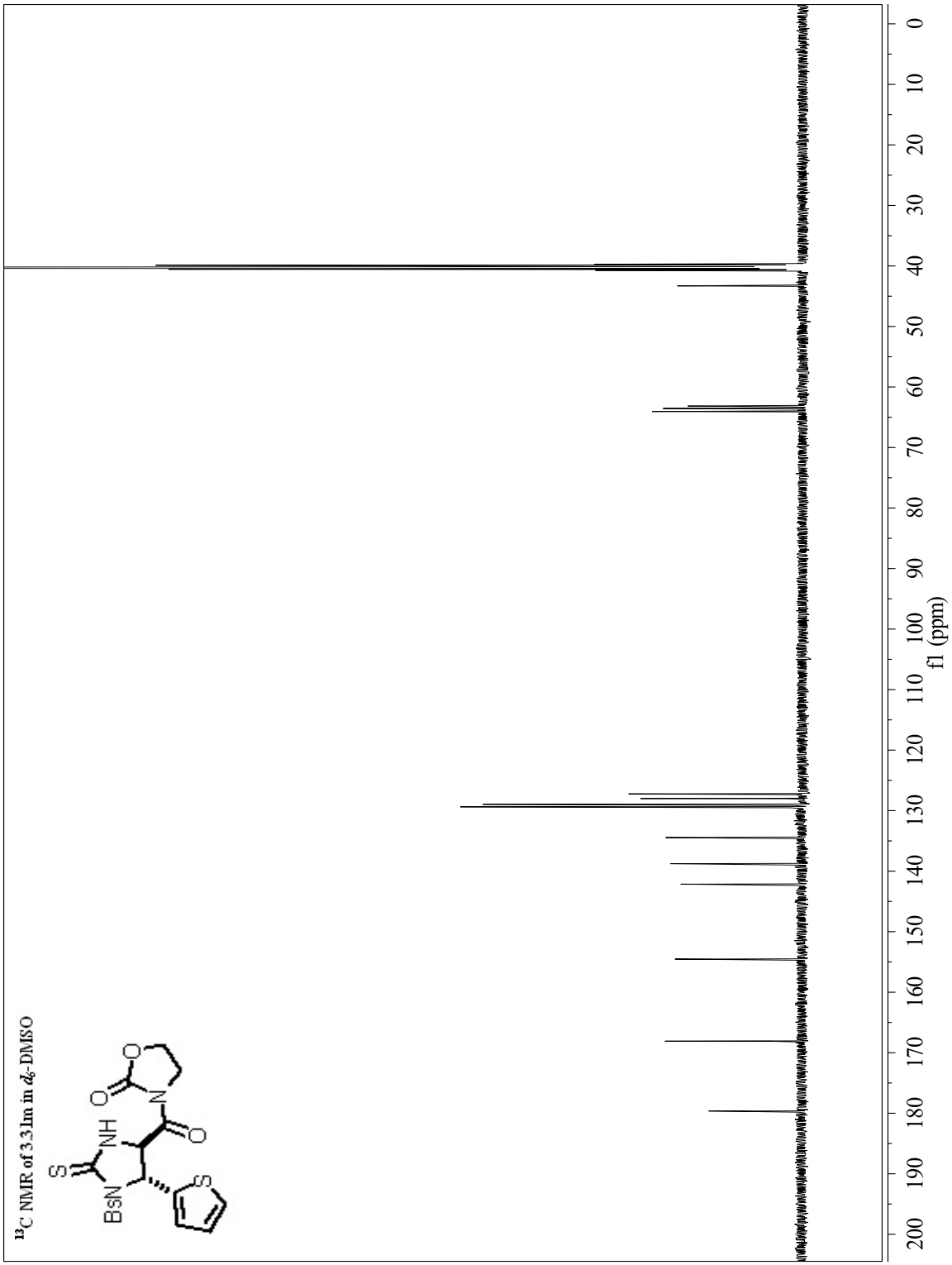

^{1}H NMR of 3.3II in d_6-DMSO
BsN
NH
S
O
O
O
N
1.00
1.12
2.12
3.20
2.04
4.02
0.95
1.03
2.07
2.16
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

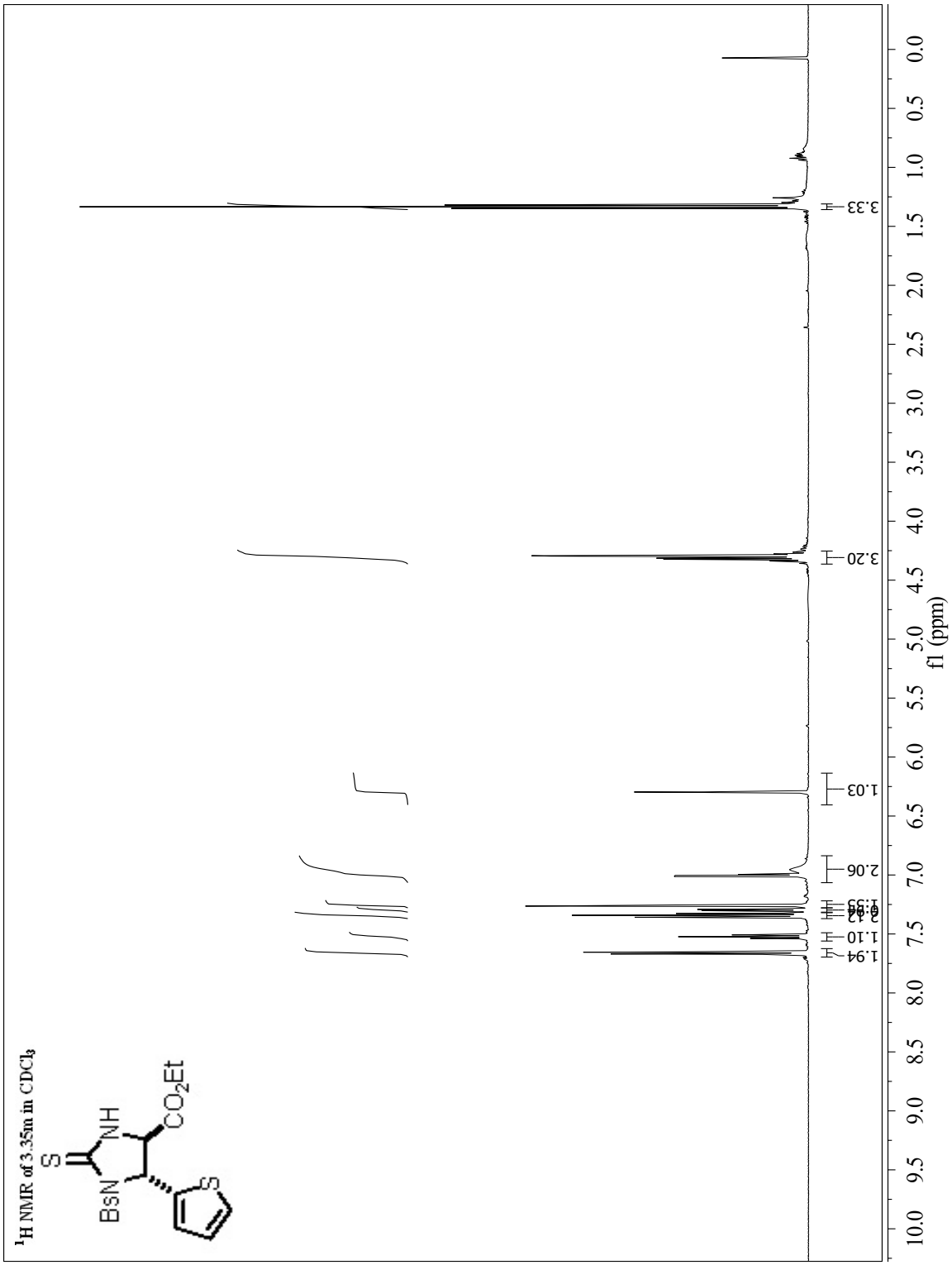

^{13}C NMR of 3.3ll in d_6-DMSO
Bsn
NH
S
O
O
O
O
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

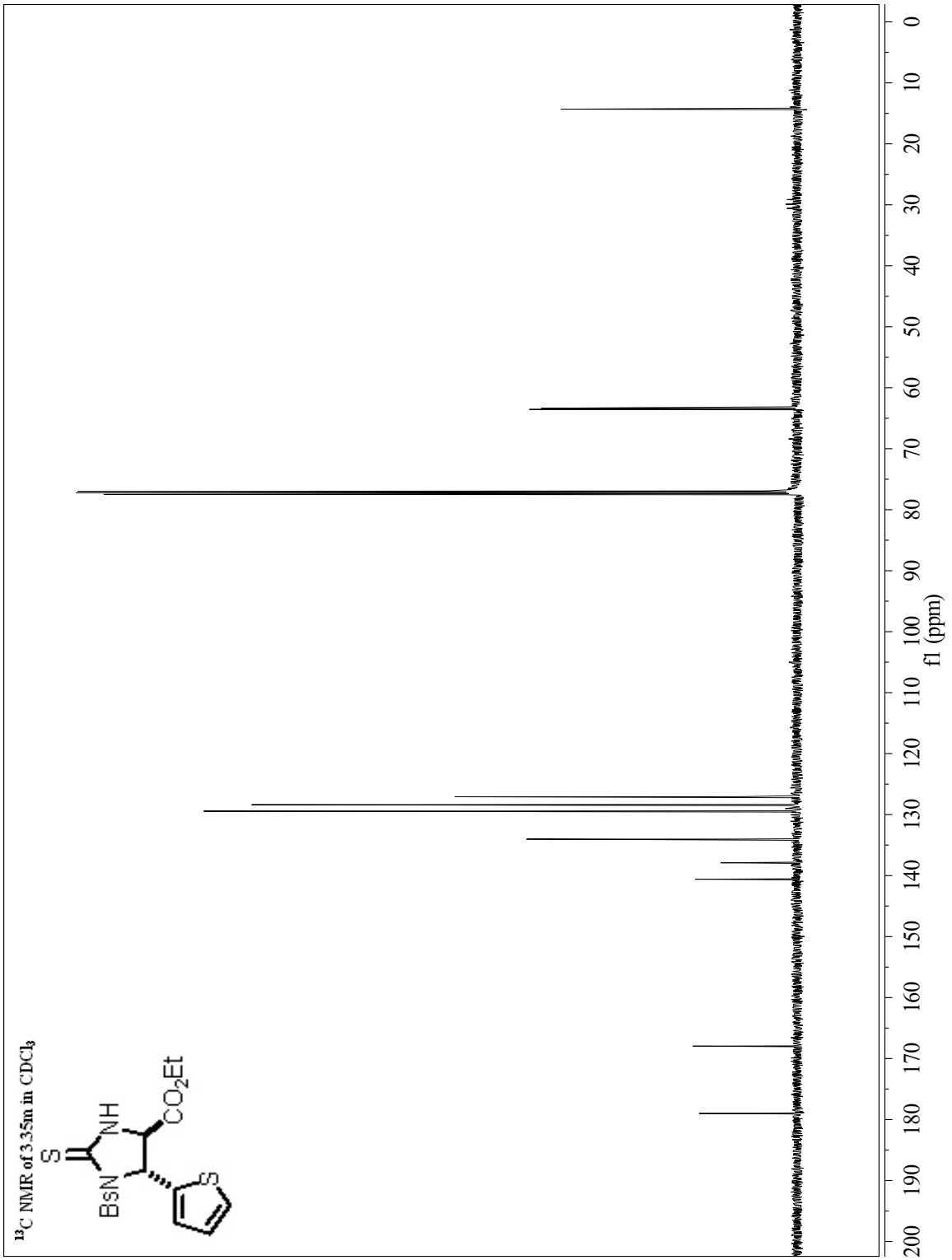

^{1}H NMR of 3.35l in d_6-DMSO
S
NH
CO_2Et
BsN
1.00
0.91
2.10
1.99
6.26
1.13
1.02
3.15
3.12
f1 (ppm)

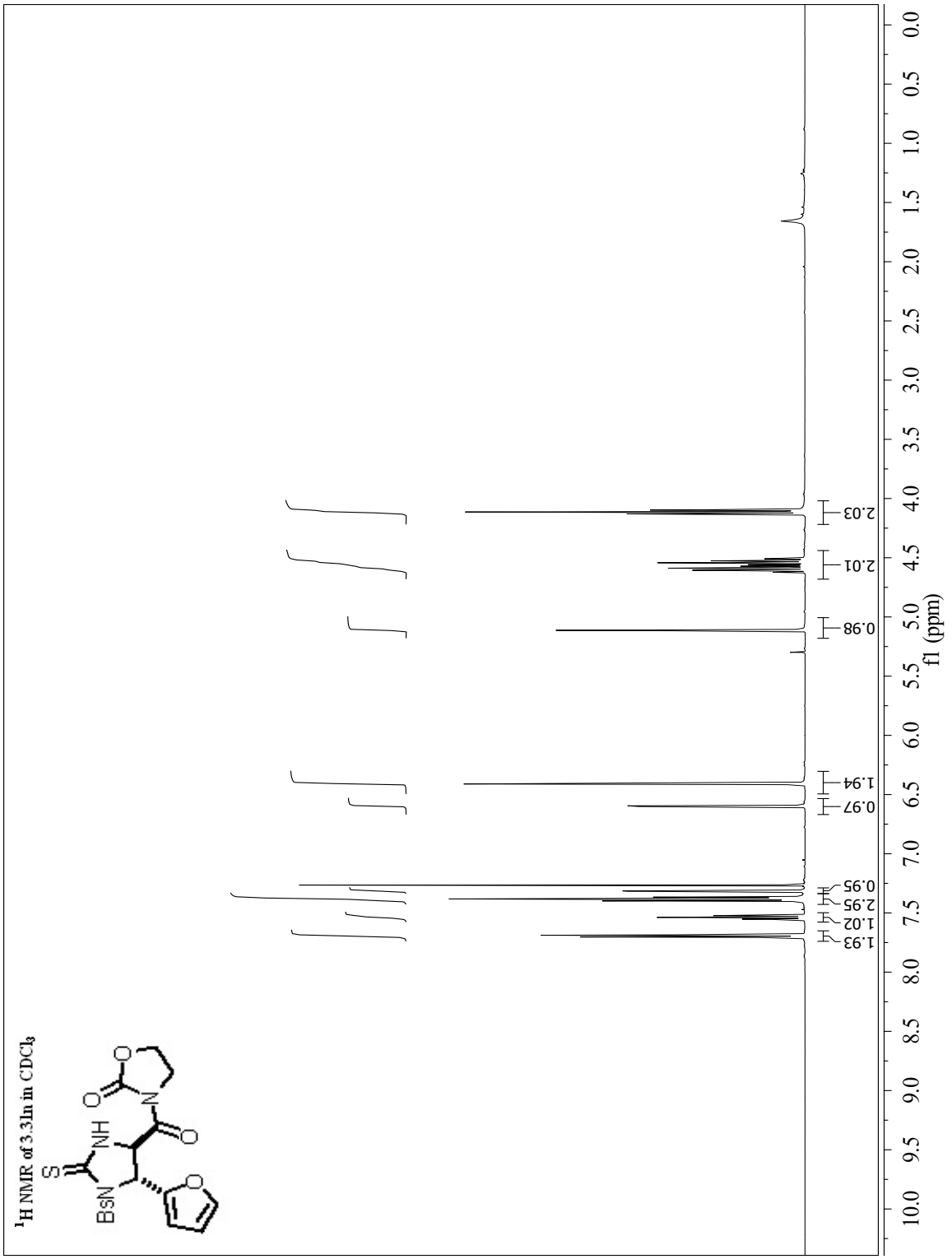

^{13}C NMR of 3.35l in d_6-DMSO
S
NH
BsN
CO_2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

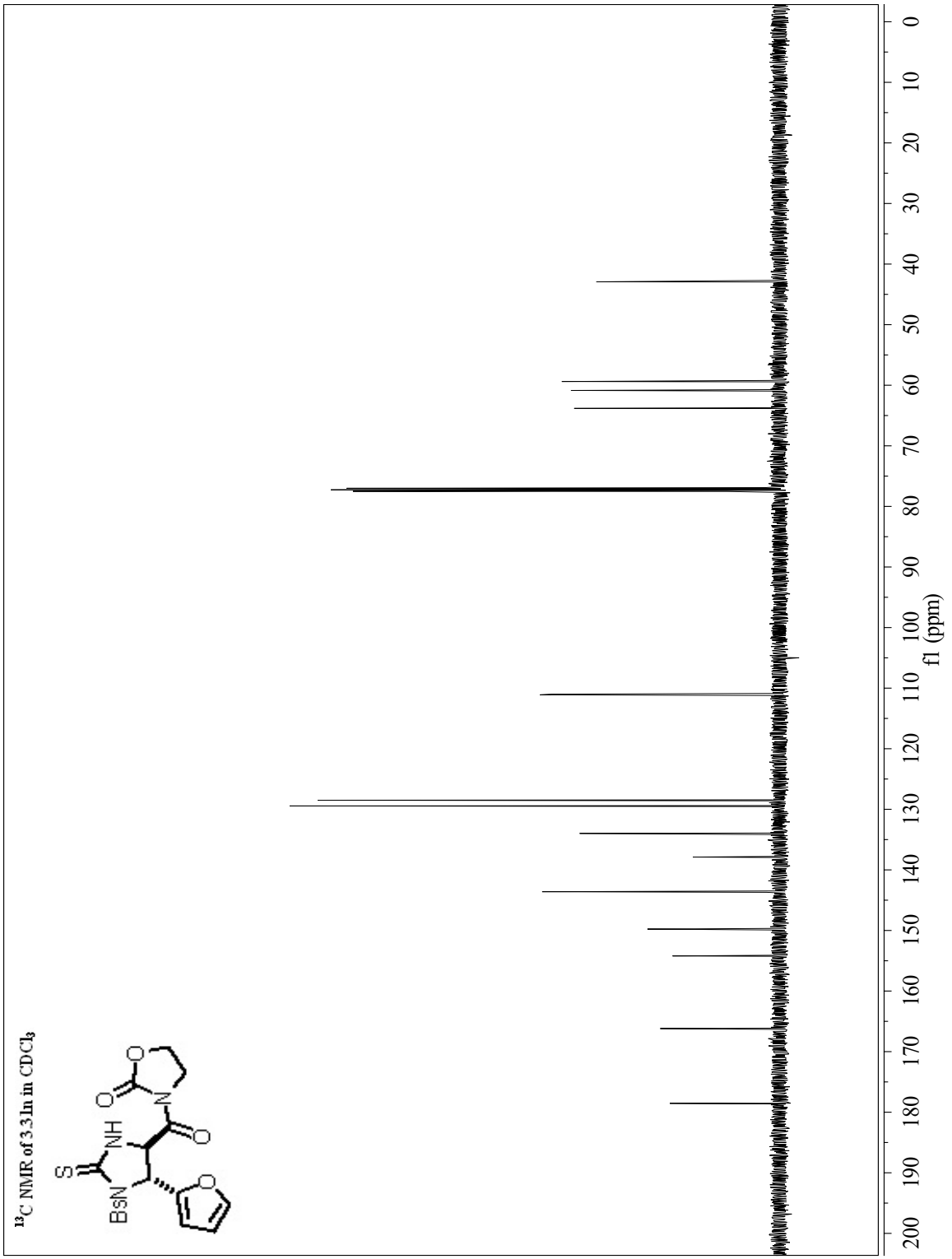

^{1}H NMR of 3.3lm in d_6-DMSO
BsN
NH
O
S
f1 (ppm)
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.07
3.00
0.95
2.03
1.00
0.99
1.06
1.06
2.11
2.13

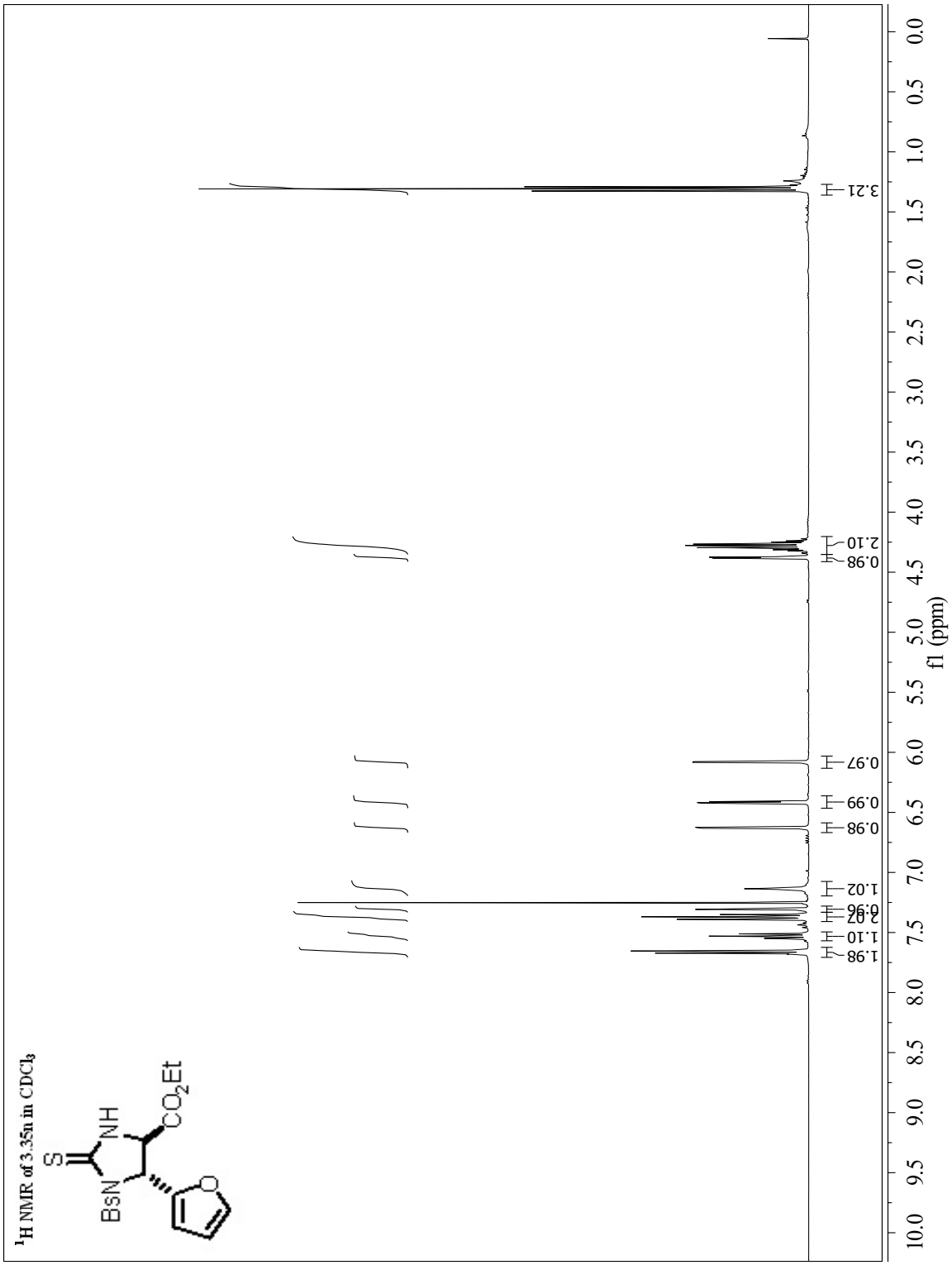

^{13}C NMR of 3.3 lm in d_6-DMSO
BsN
NH
S
O
O
O
N
S
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

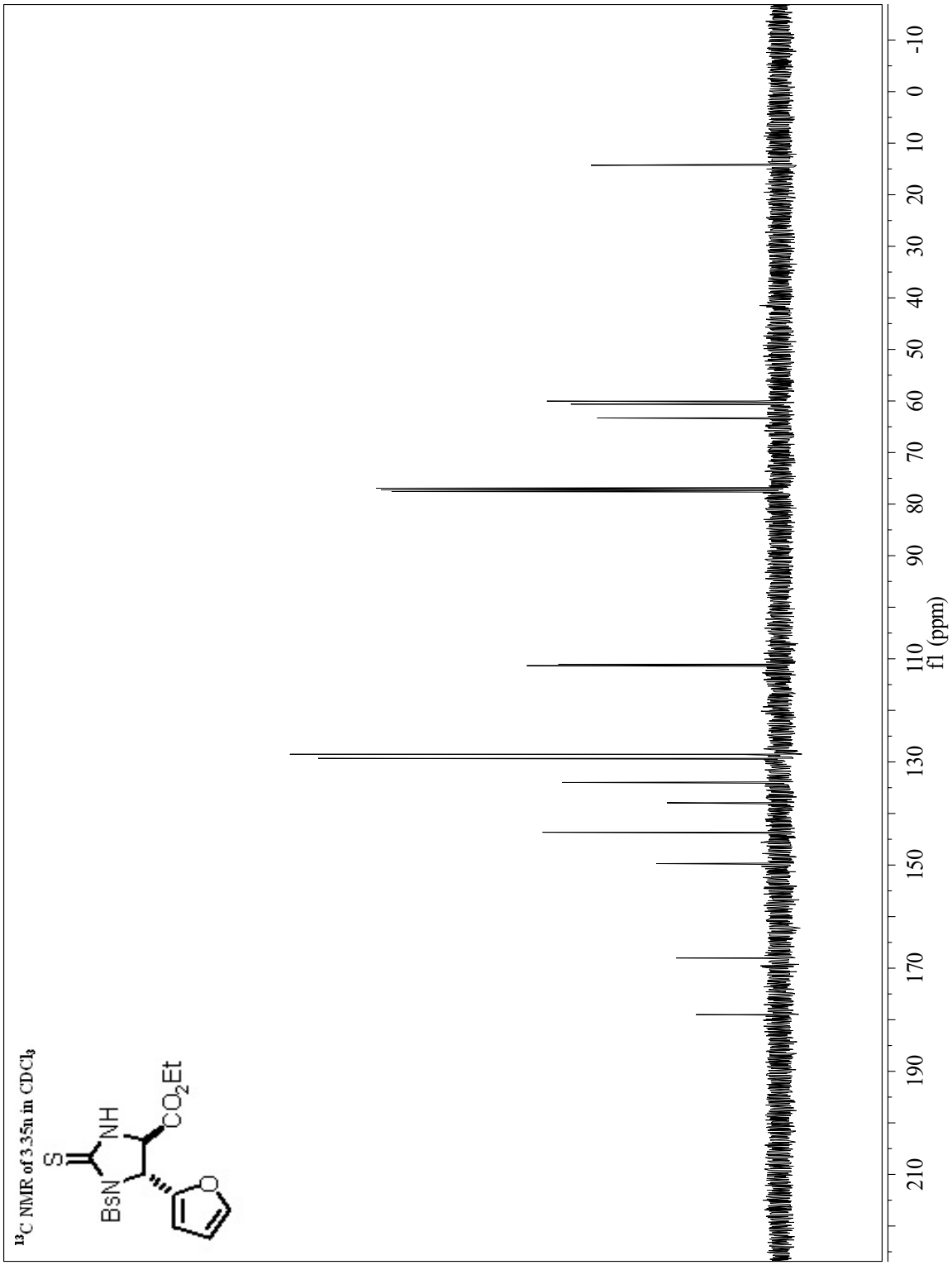

^{1}H NMR of 3.35m in $CDCl_3$
S
NH
CO_2Et
BsN
S
3.33
3.20
1.03
2.06
2.13
1.10
1.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

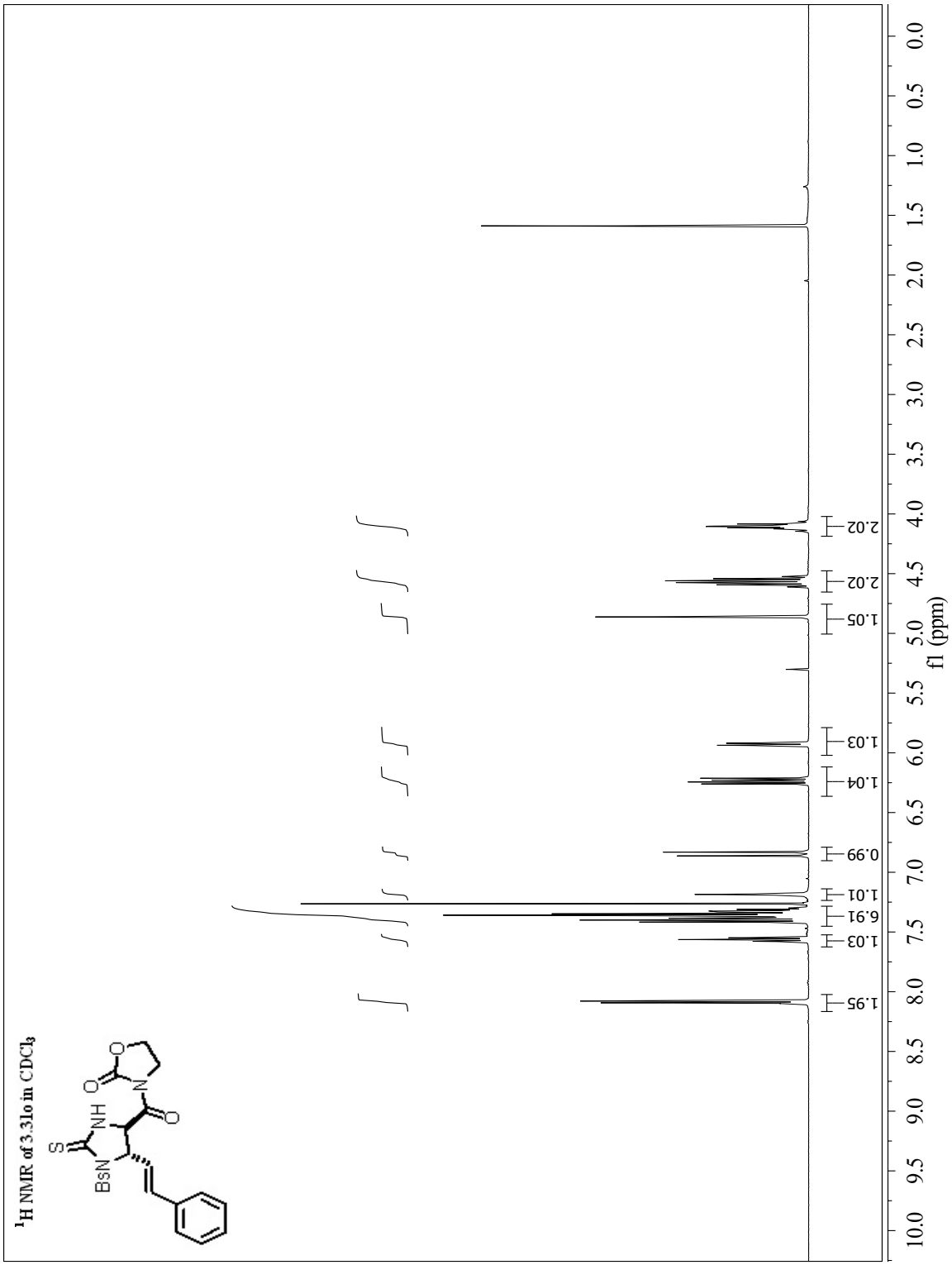

^{13}C NMR of 3.35m in $CDCl_3$
S
NH
CO_2Et
BsN
S
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

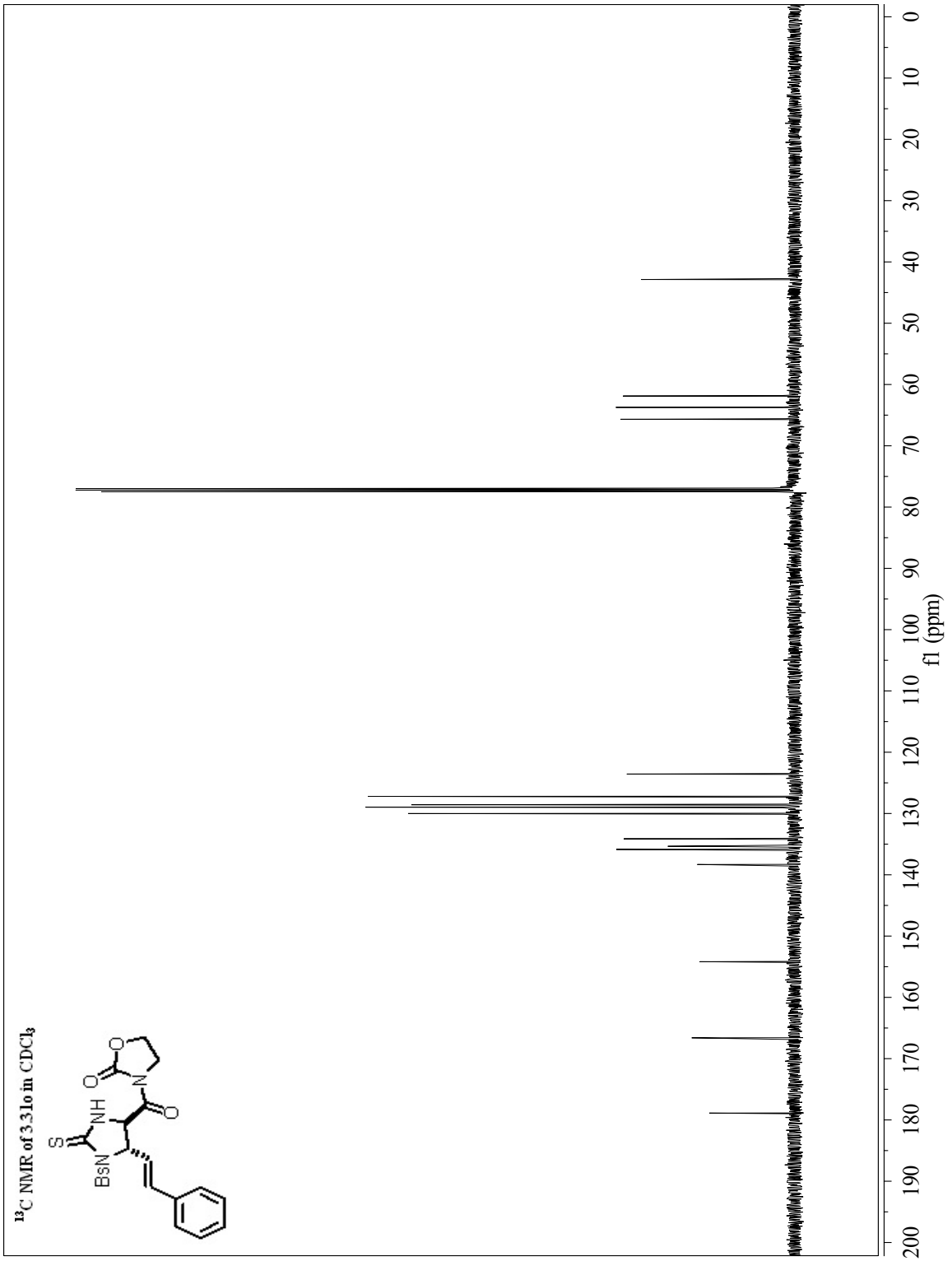

^{1}H NMR of 3.3ln in $CDCl_3$
NH
S
BsN
O
N
1.93
1.02
2.95
0.95
0.97
1.94
0.98
2.01
2.03
f1 (ppm)

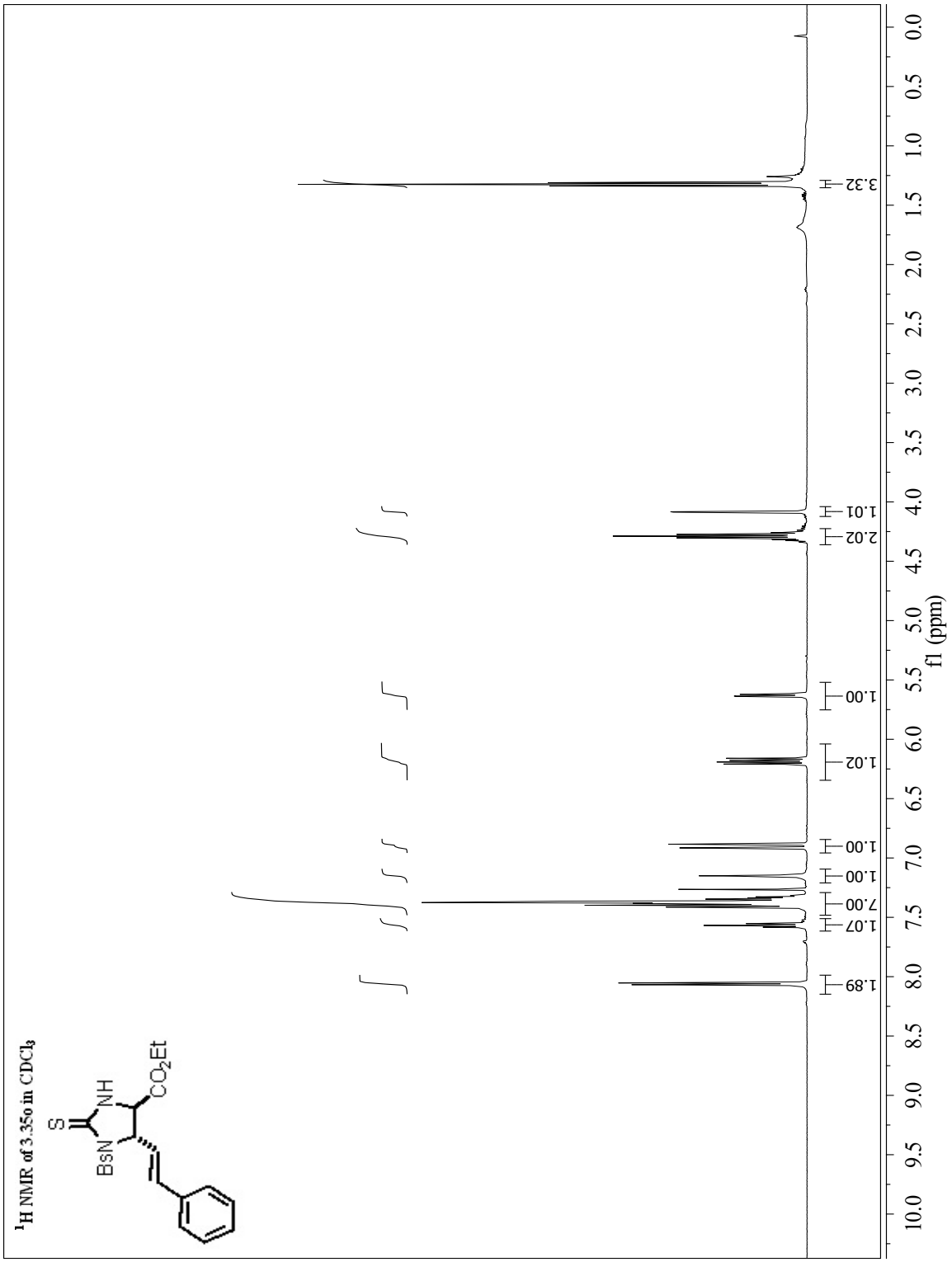

^{13}C NMR of 3.3.In in $CDCl_3$
S
NH
O
O
N
O
BsN
O
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

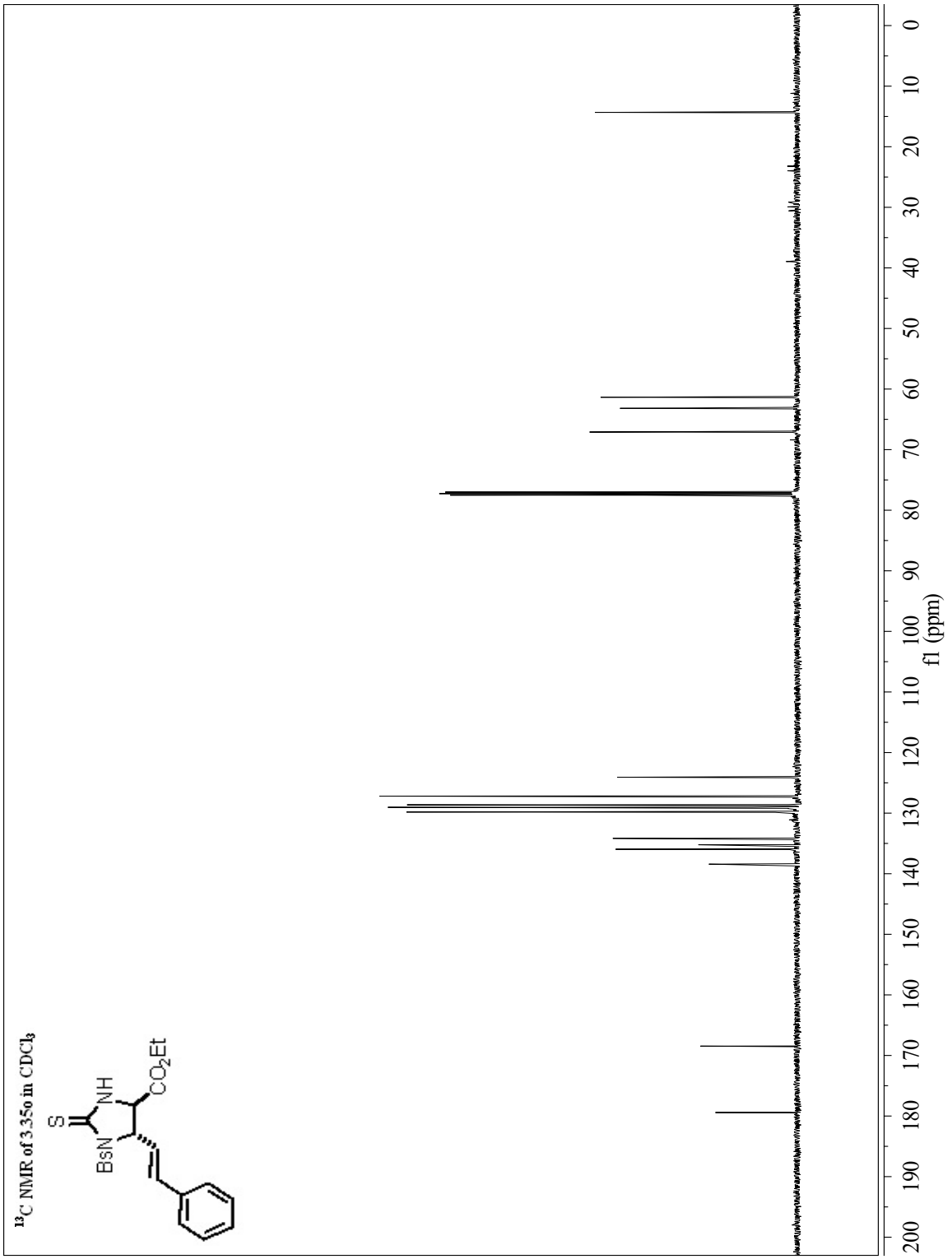

^{1}H NMR of 3.35n in $CDCl_3$
S
NH
CO_2Et
BsN
O
3.21
2.10
0.98
0.97
0.99
0.98
1.02
0.96
2.02
1.10
1.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

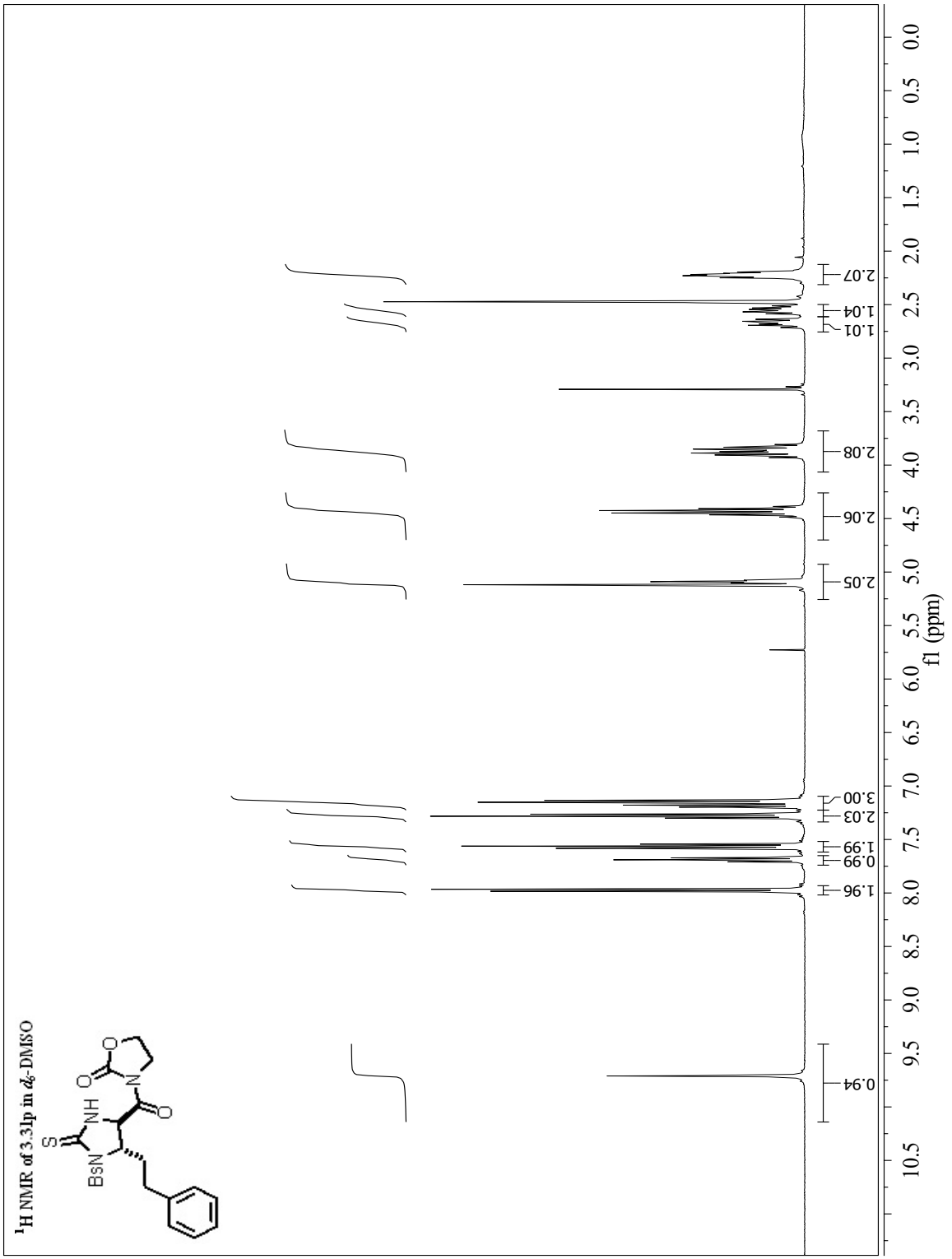

^{13}C NMR of 3.35n in $CDCl_3$
S
NH
CO_2Et
BsN
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

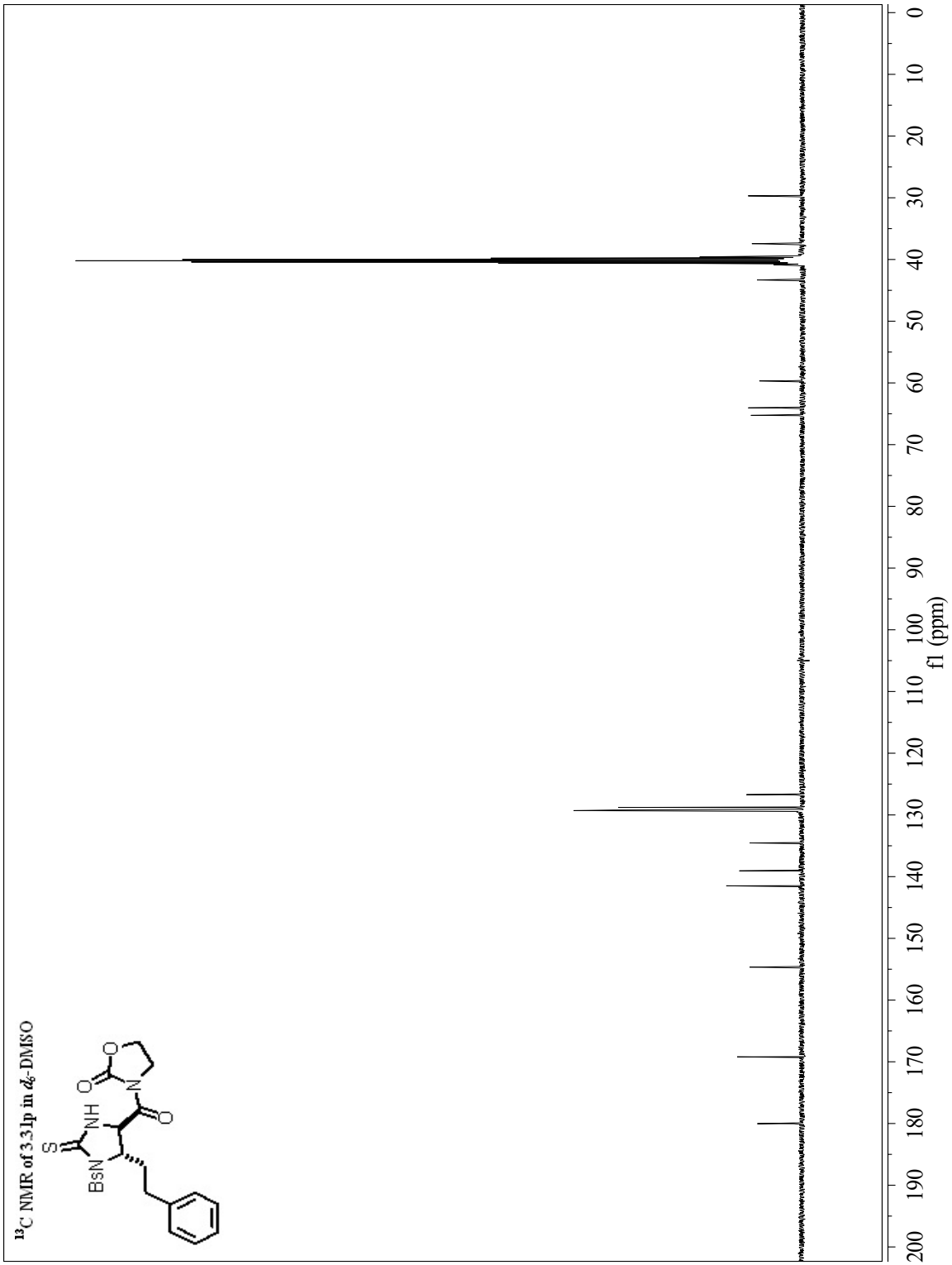

^{1}H NMR of 3.31o in $CDCl_3$
Bsn
NH
S
O
O
O
N
1.95
1.03
6.91
1.01
0.99
1.04
1.03
1.05
2.02
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

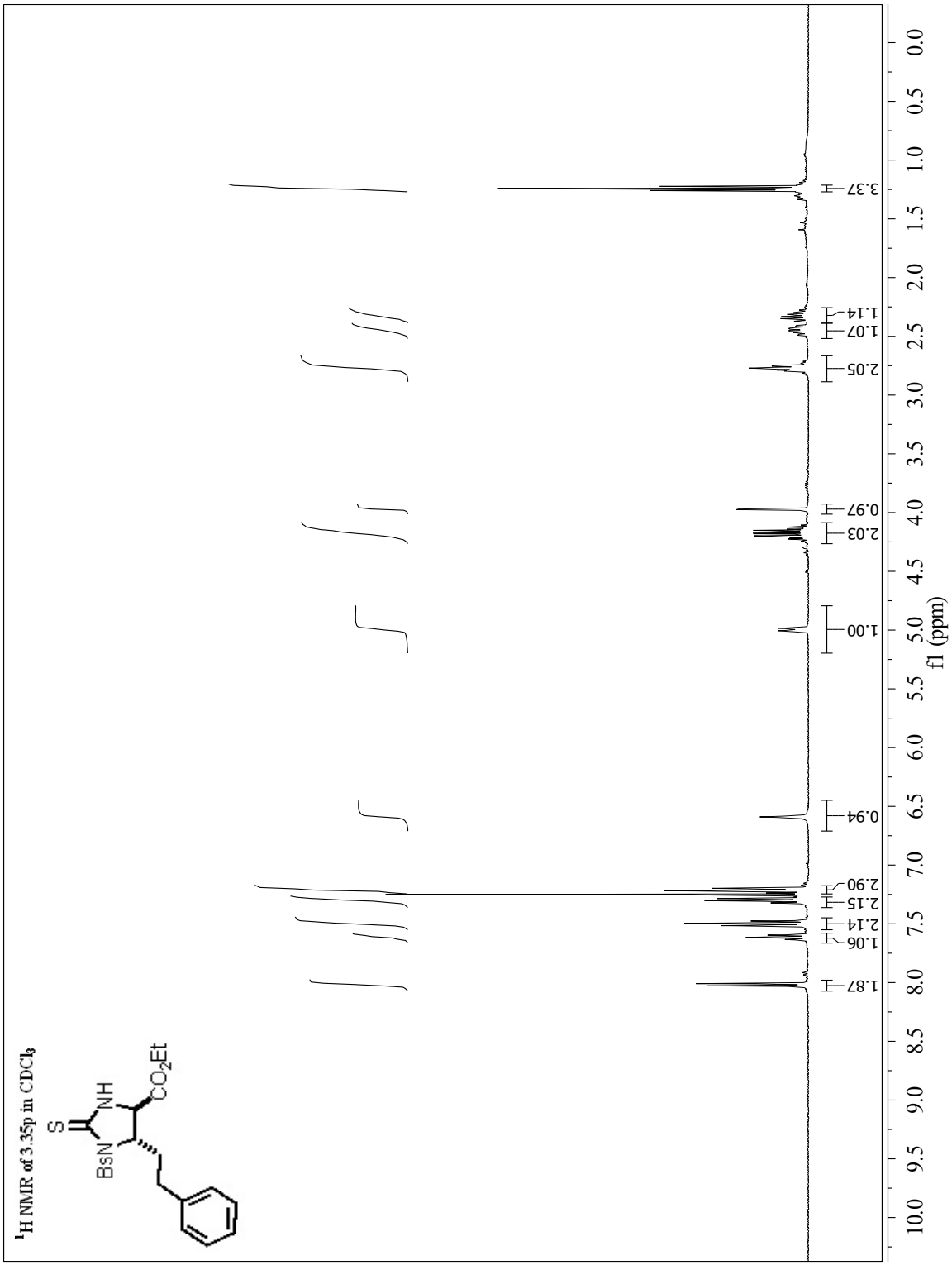

^{13}C NMR of 3.31o in $CDCl_3$
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

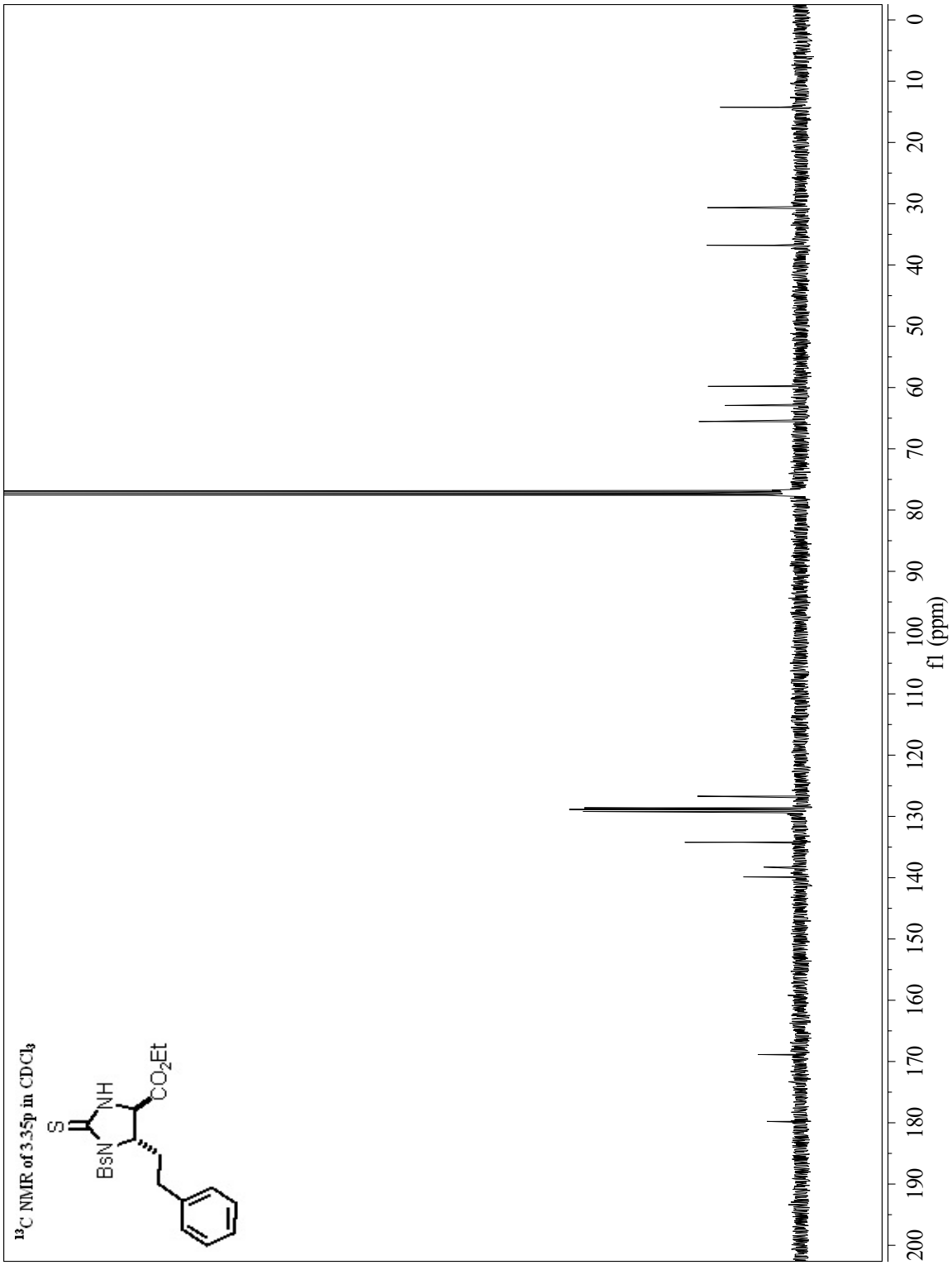

^{1}H NMR of 3.35o in $CDCl_3$
S
NH
BsN
CO_2Et
3.32
1.01
2.02
1.00
1.02
1.00
1.00
7.00
1.07
1.89
f1 (ppm)

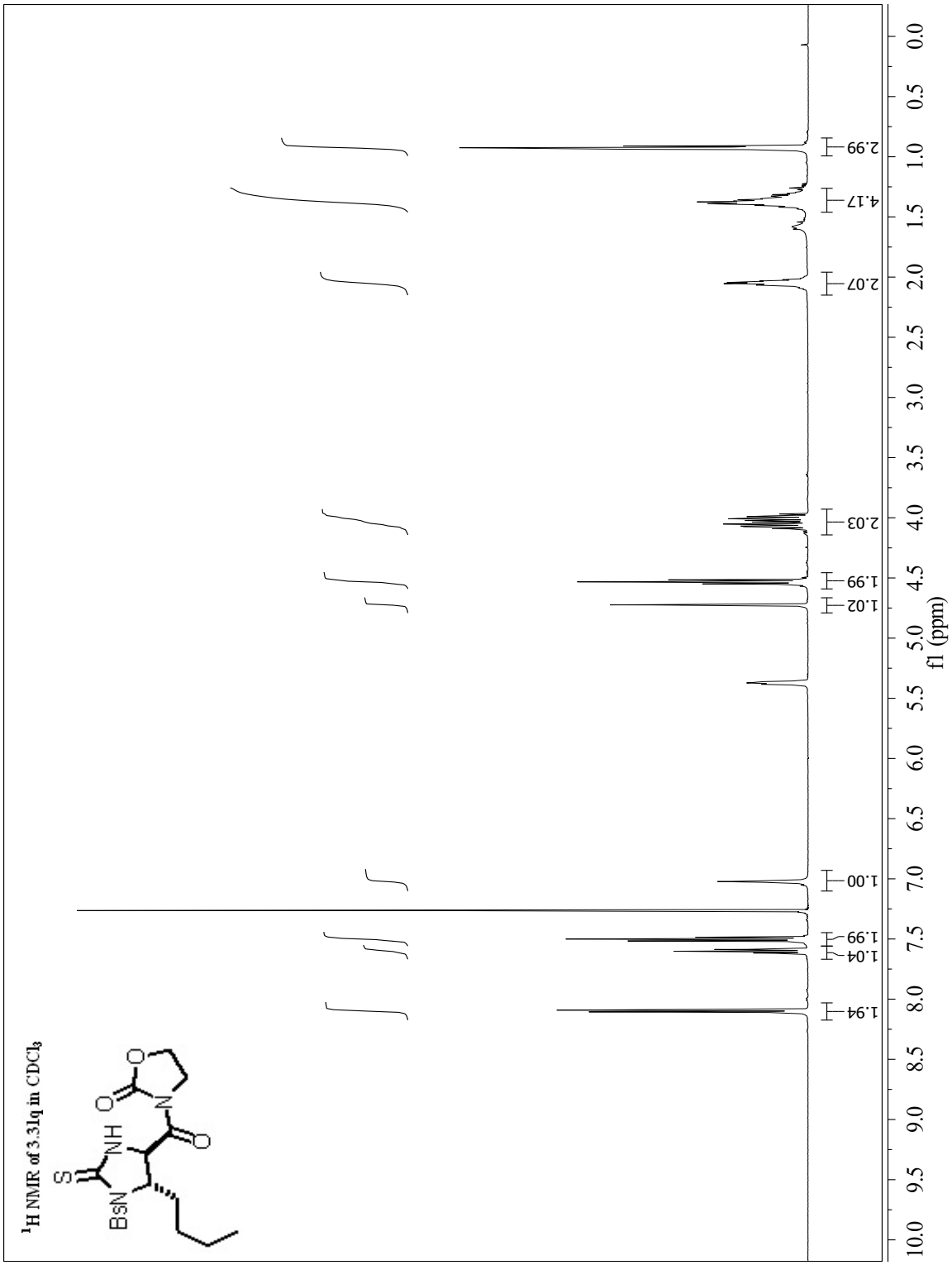

^{13}C NMR of 3.35o in $CDCl_3$
S
NH
BsN
CO_2Et
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

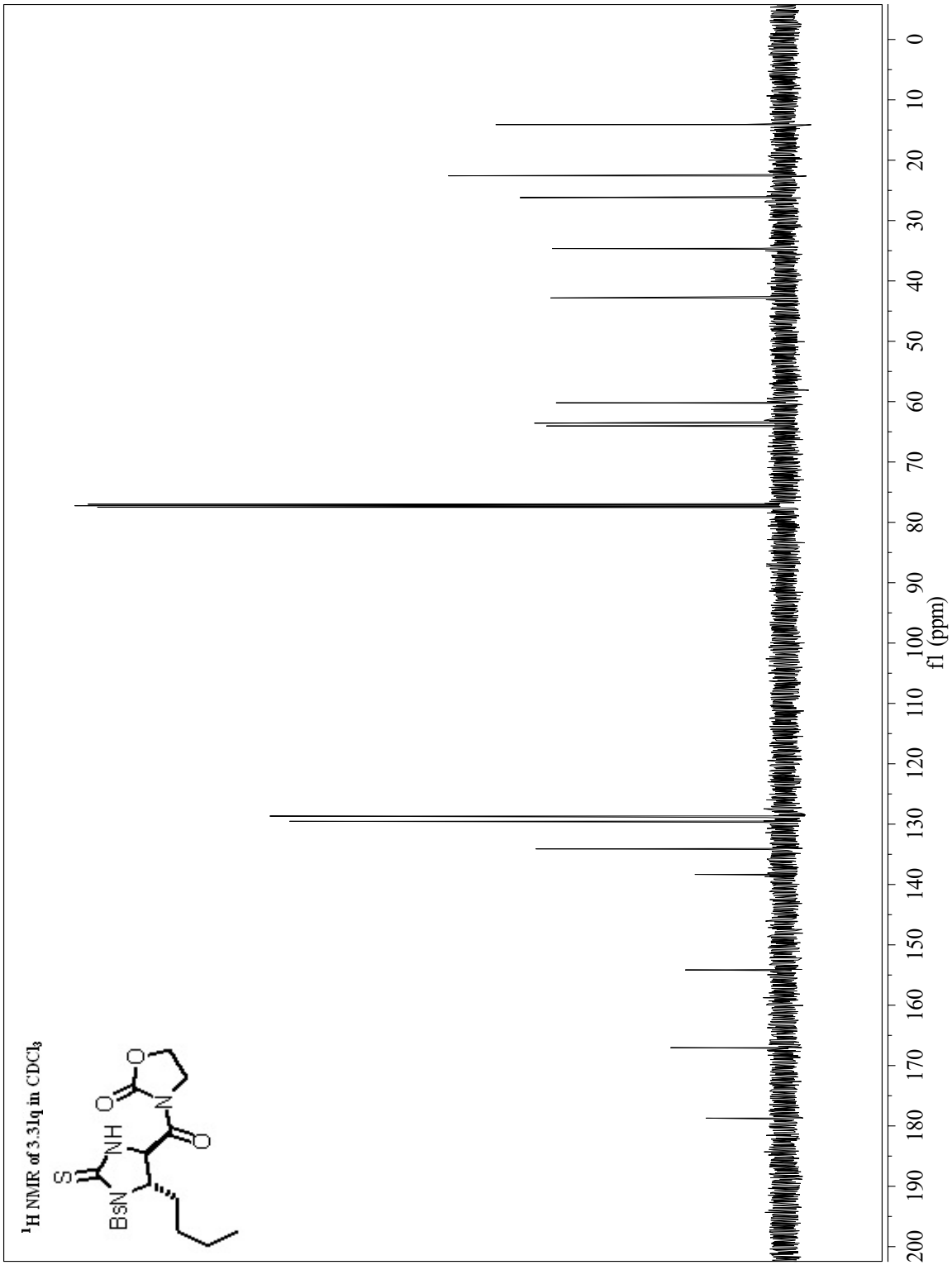

^{1}H NMR of 3.31p in d_6-DMSO
Bsn
NH
S
O
O
O
N
0.94
1.96
0.99
1.99
2.03
3.00
2.05
2.06
2.08
1.01
1.04
2.07
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

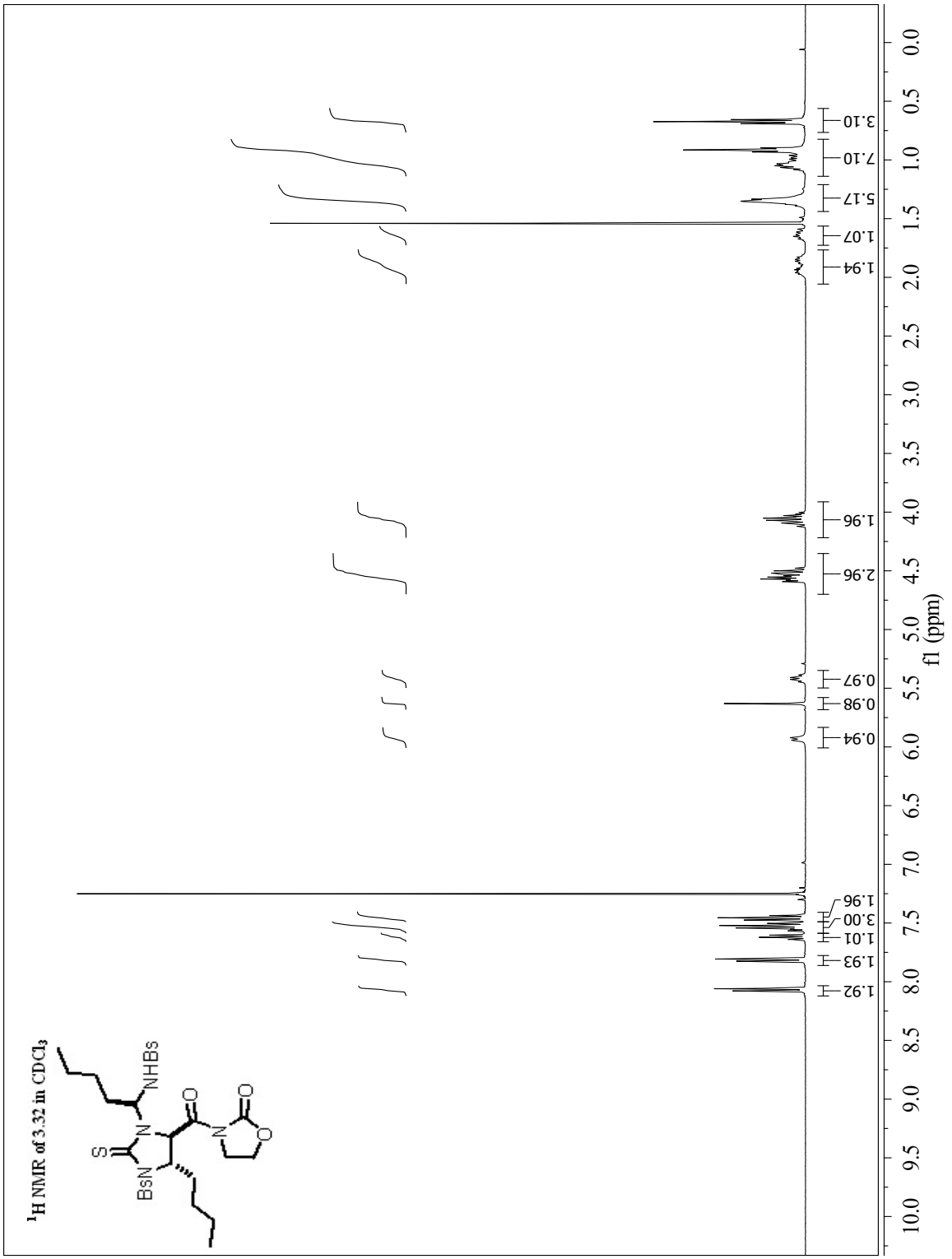

^{13}C NMR of 3.3.1p in d_6-DMSO
BsN
NH
S
O
O
O
N
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

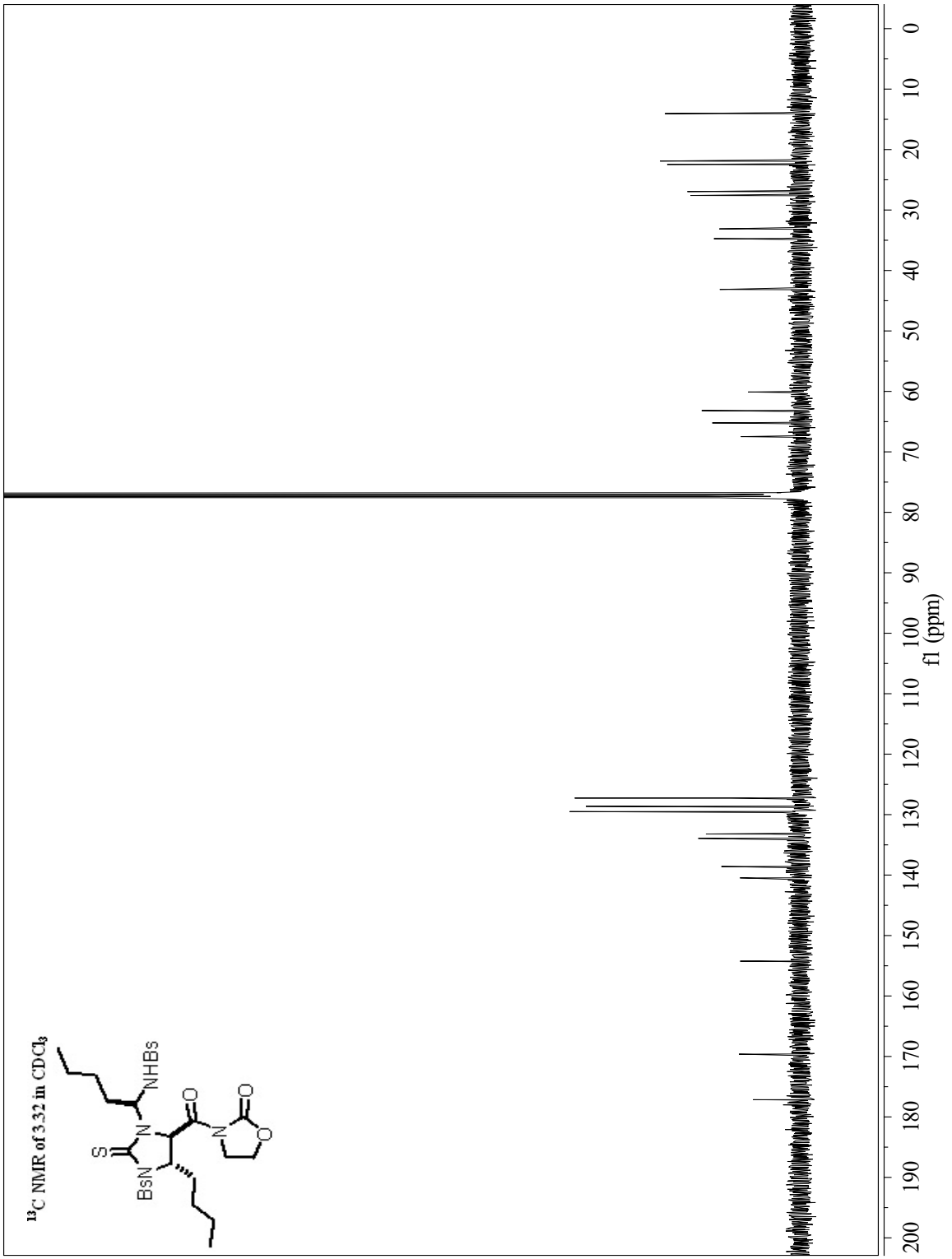

^{1}H NMR of 3.35p in $CDCl_3$
S
NH
BsN
CO_2Et
1.87
1.06
2.14
2.15
2.90
0.94
1.00
2.03
0.97
2.05
1.07
1.14
3.37
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

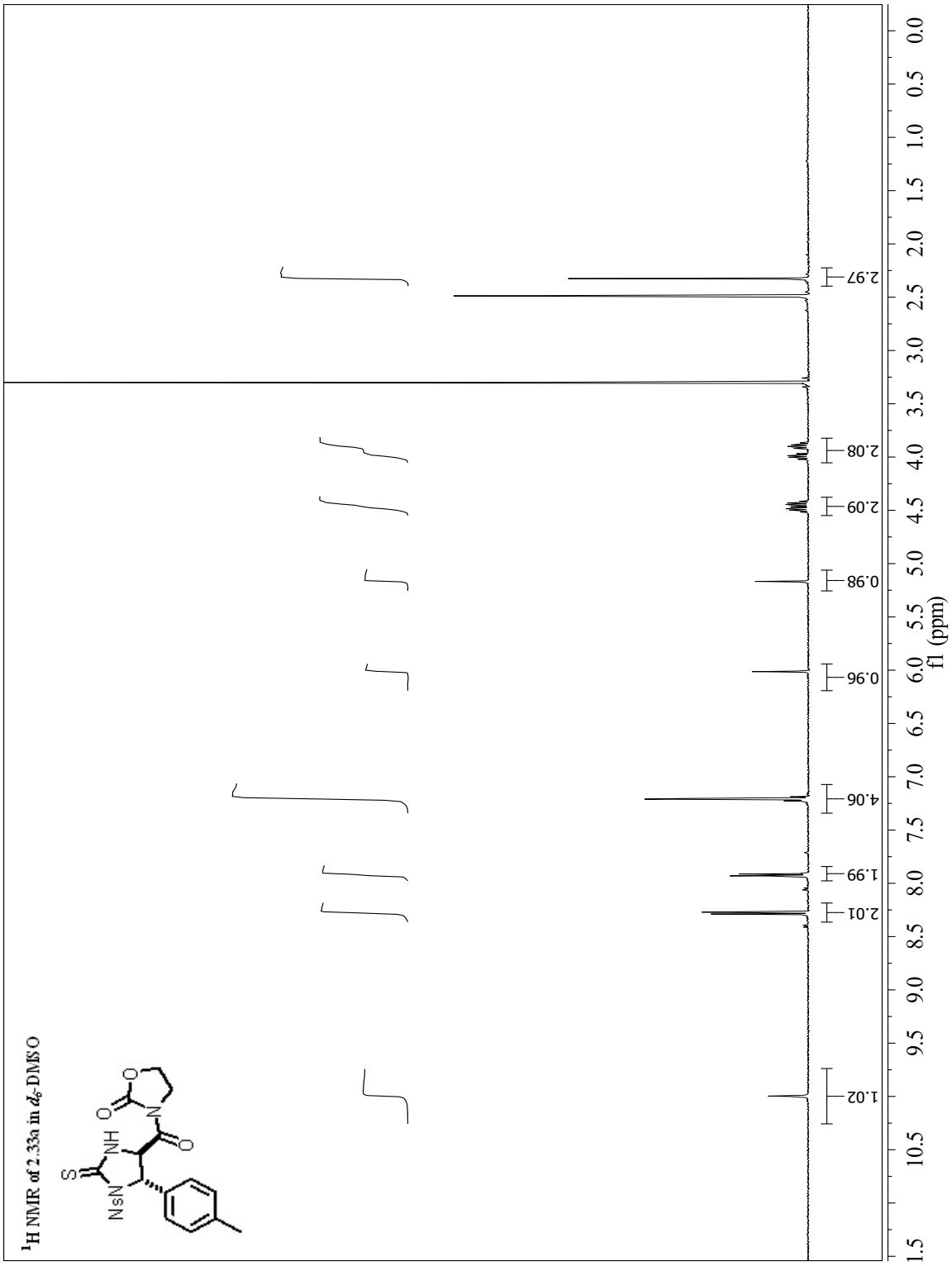

^{13}C NMR of 3.35p in $CDCl_3$
S
NH
BsN
CO_2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

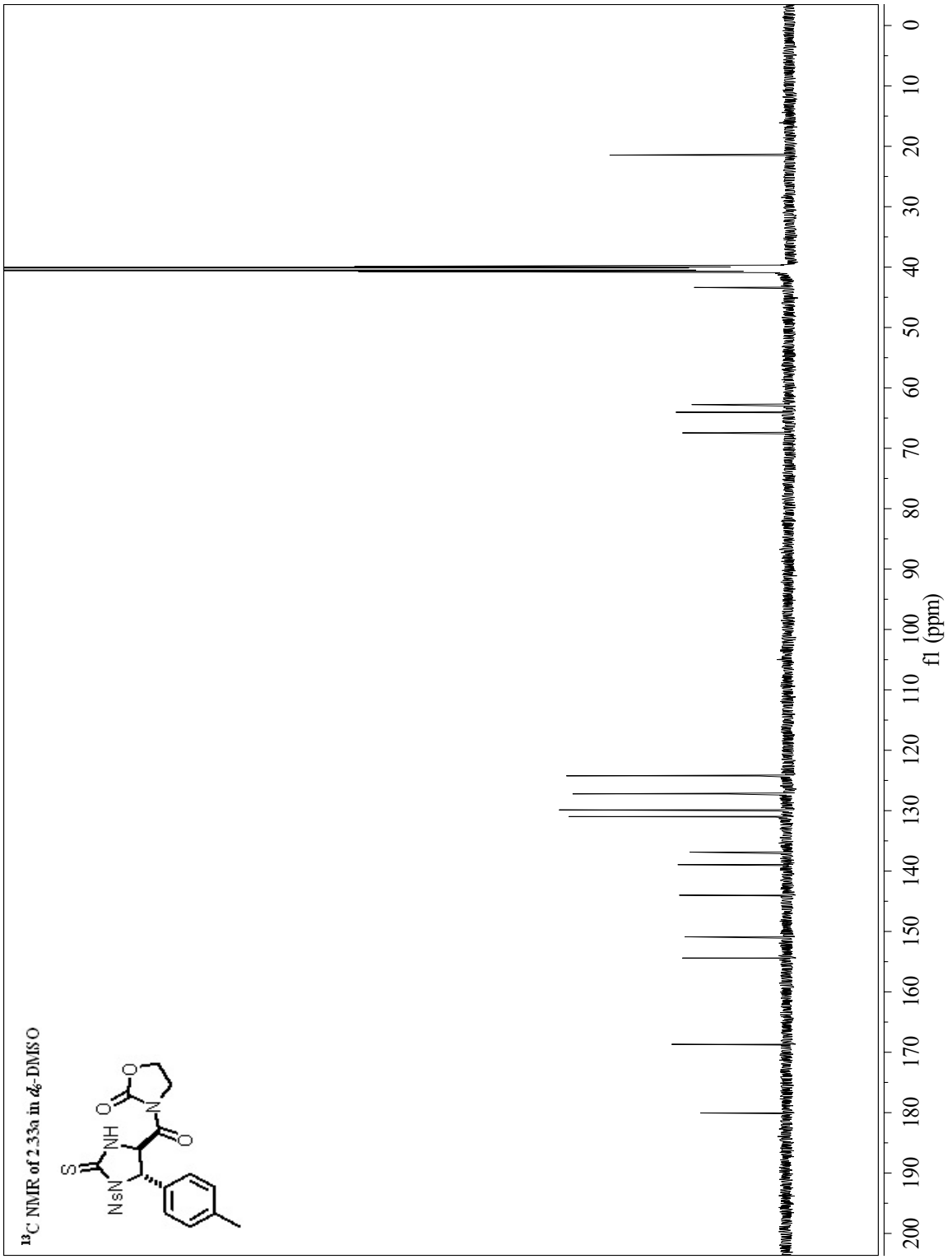

^{1}H NMR of 3.31q in CDCl$_3$
Bsn
NH
S
O
O
O
N
1.94
1.04
1.99
1.00
2.03
1.99
1.02
2.07
4.17
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

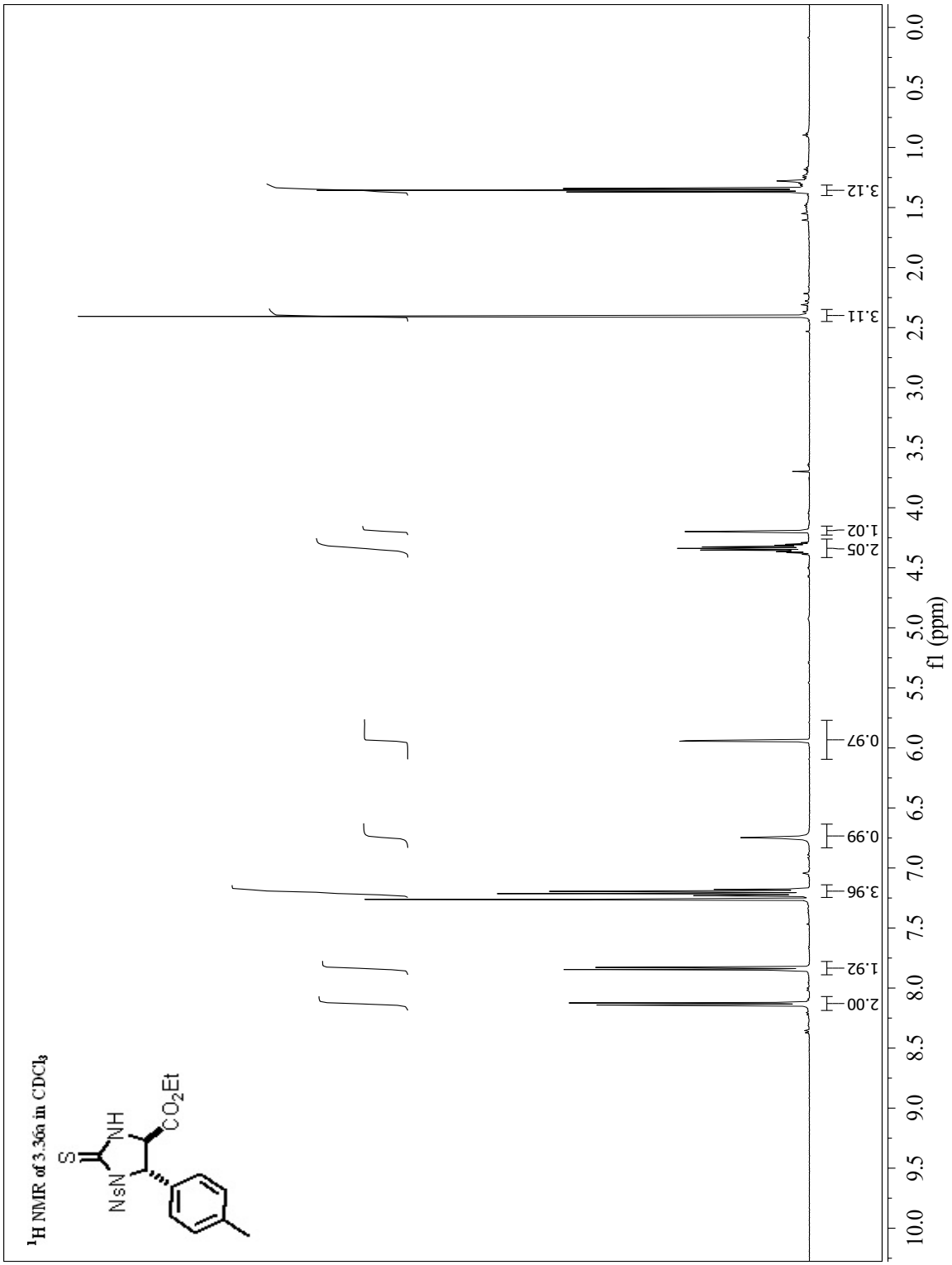

^{1}H NMR of 3.31q in CDCl$_3$
S
NH
O
O
O
N
O
BsN
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

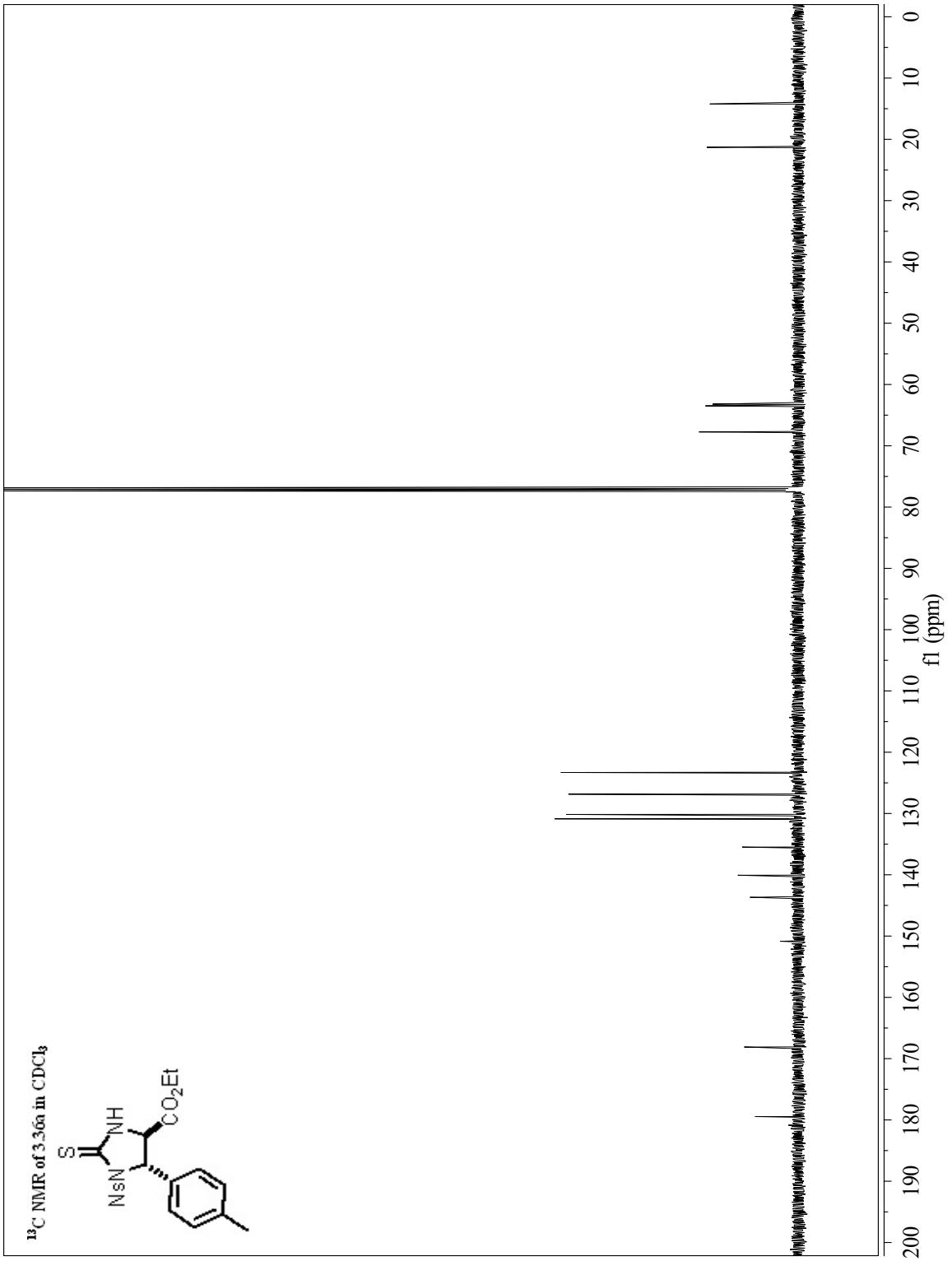

^{1}H NMR of 3.32 in $CDCl_3$
NHBs
BsN
S
O
O
N
N
O
1.92
1.93
1.01
3.00
1.96
0.94
0.98
0.97
1.96
2.96
1.96
3.10
7.10
5.17
1.07
1.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

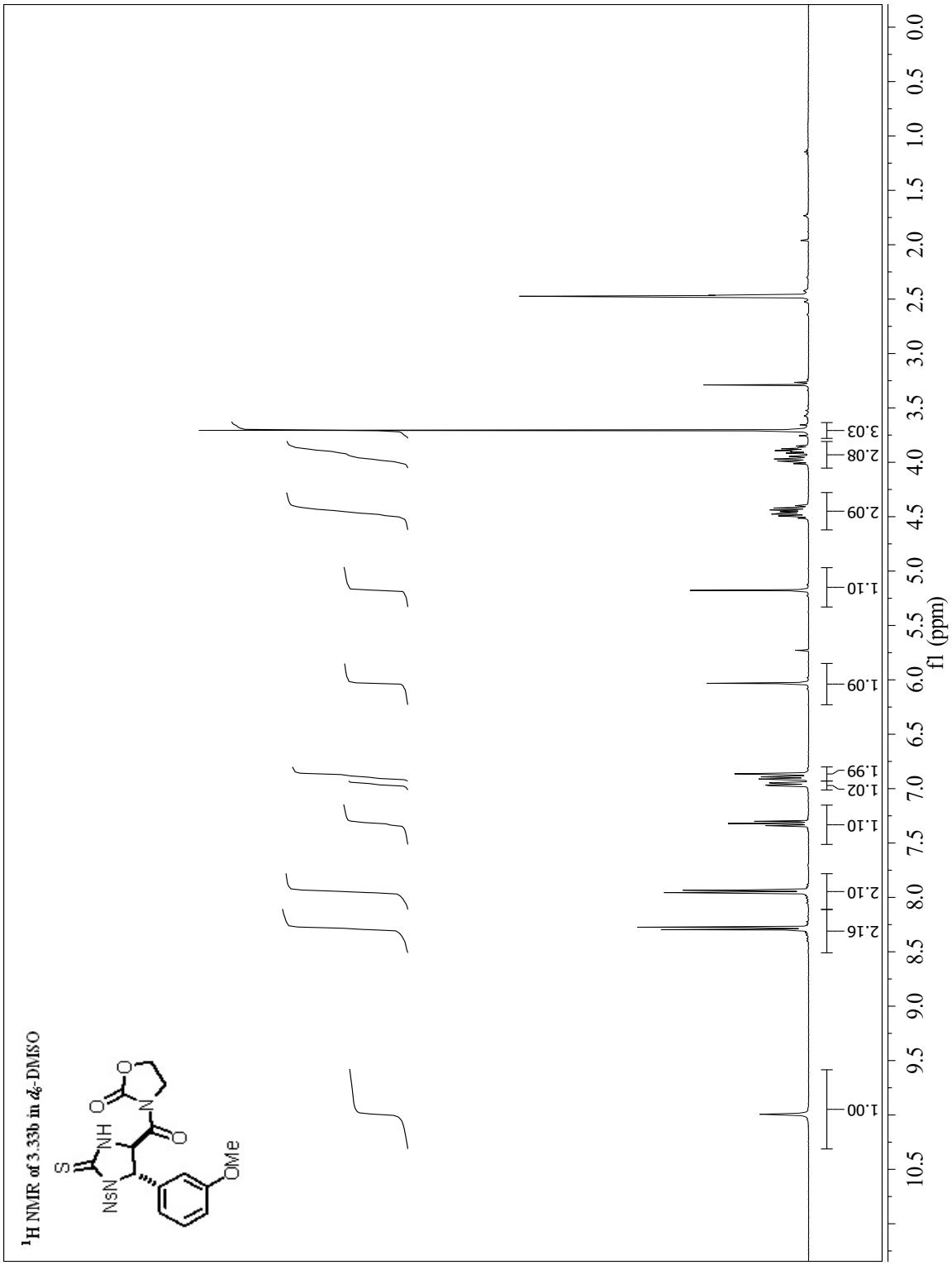

^{13}C NMR of 3.32 in $CDCl_3$
NHBs
BsN
S
O
N
O
O
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

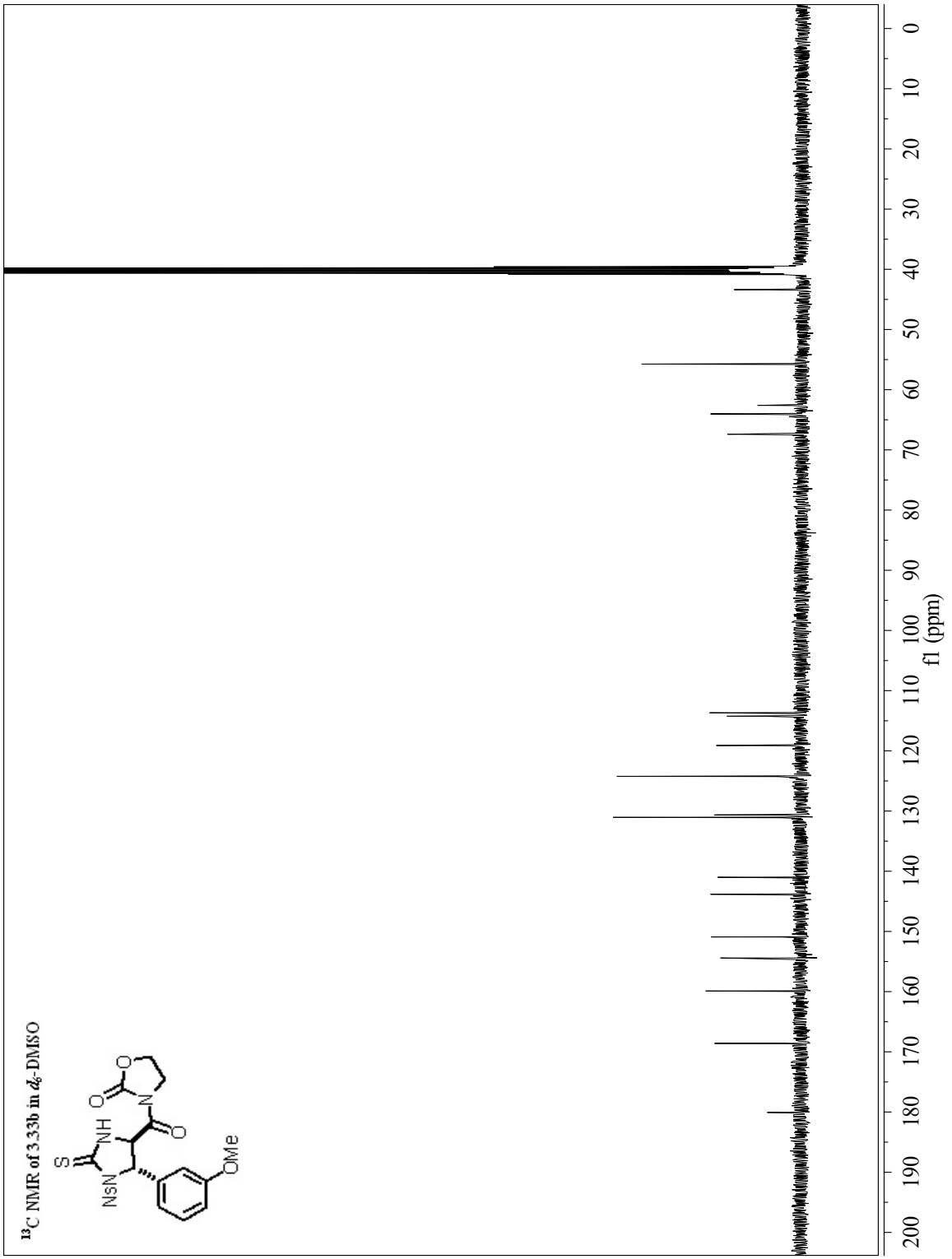

^{1}H NMR of 2.33a in d_6-DMSO
NH
NsN
S
O
O
O
O
N
1.02
2.01
1.99
4.06
0.96
0.98
2.09
2.08
2.97
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

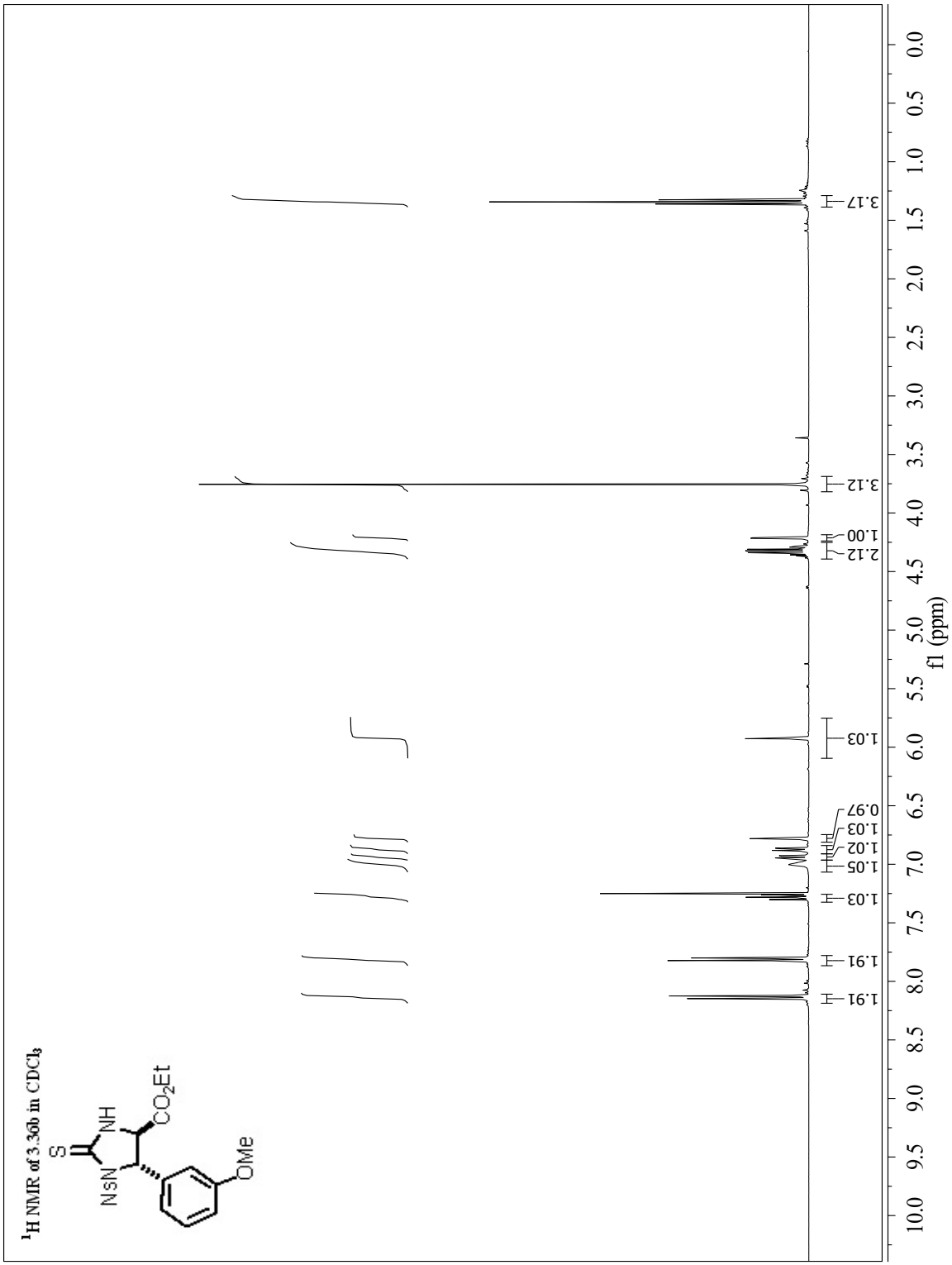

^{13}C NMR of 2.33a in d_6-DMSO
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

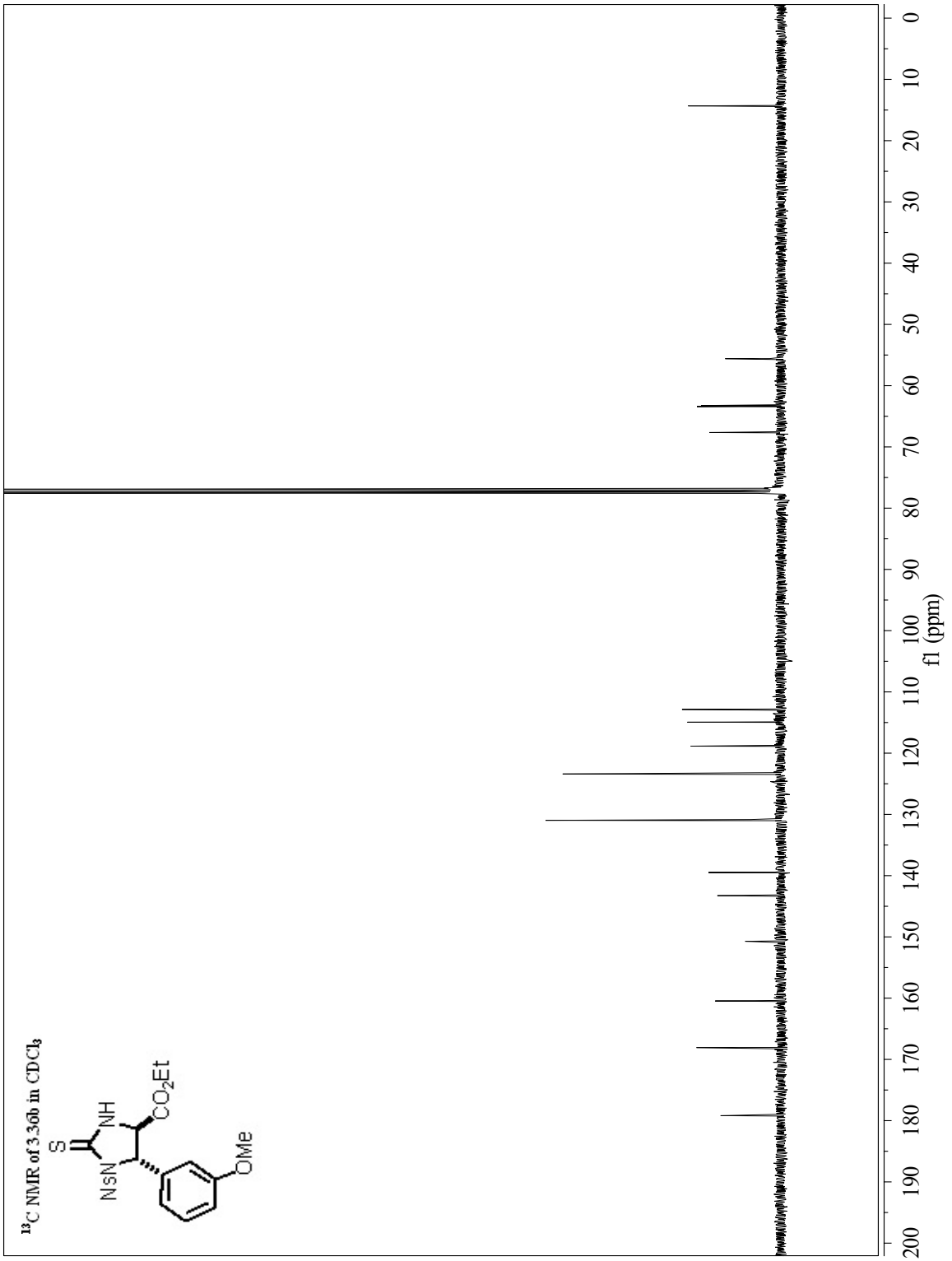

^{1}H NMR of 3.36a in $CDCl_3$
S
NH
NsN
CO_2Et
3.12
3.11
1.02
2.05
0.97
0.99
3.96
1.92
2.00
f1 (ppm)

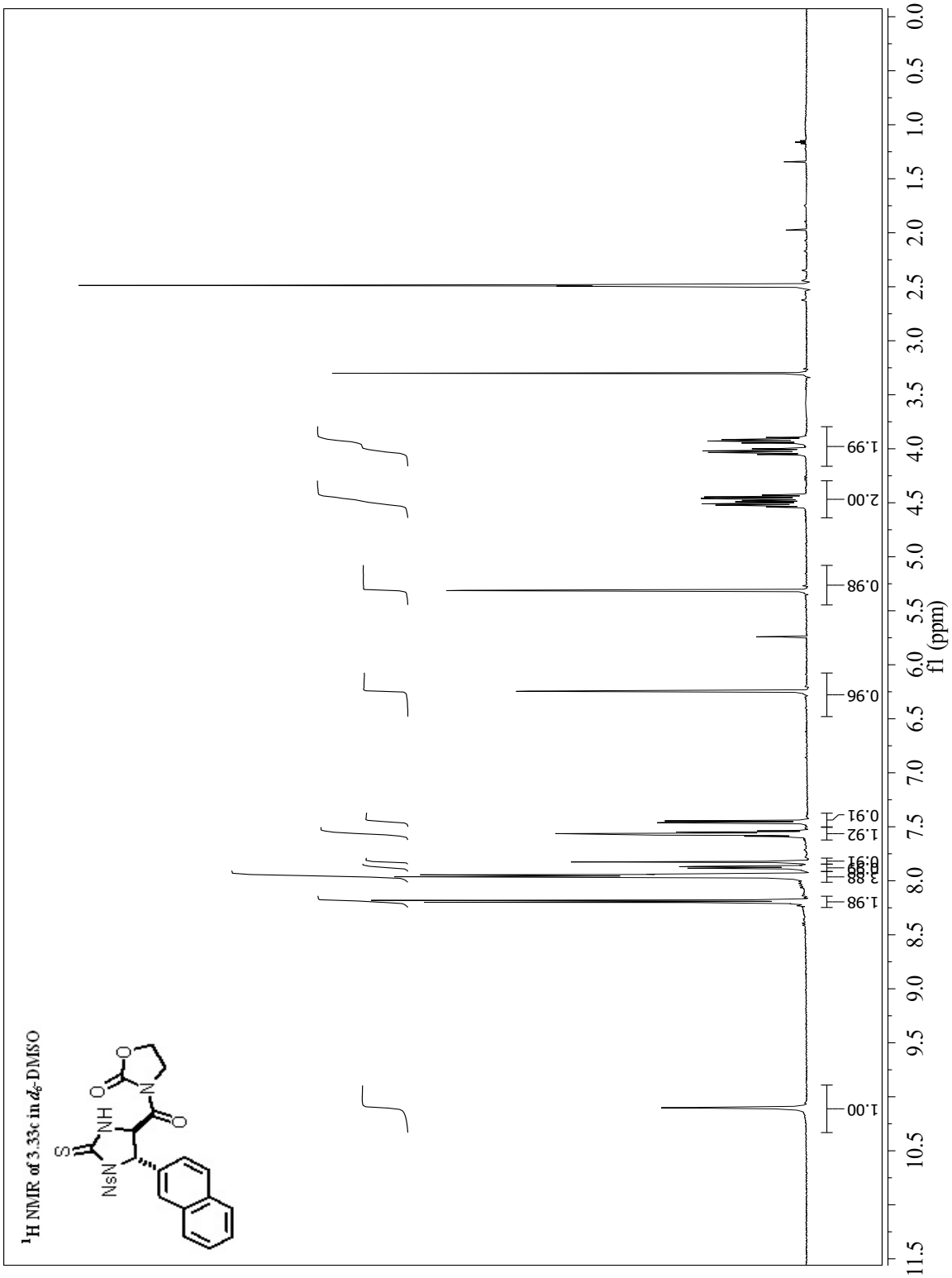

^{13}C NMR of 3.36a in $CDCl_3$
S
NH
NsN
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

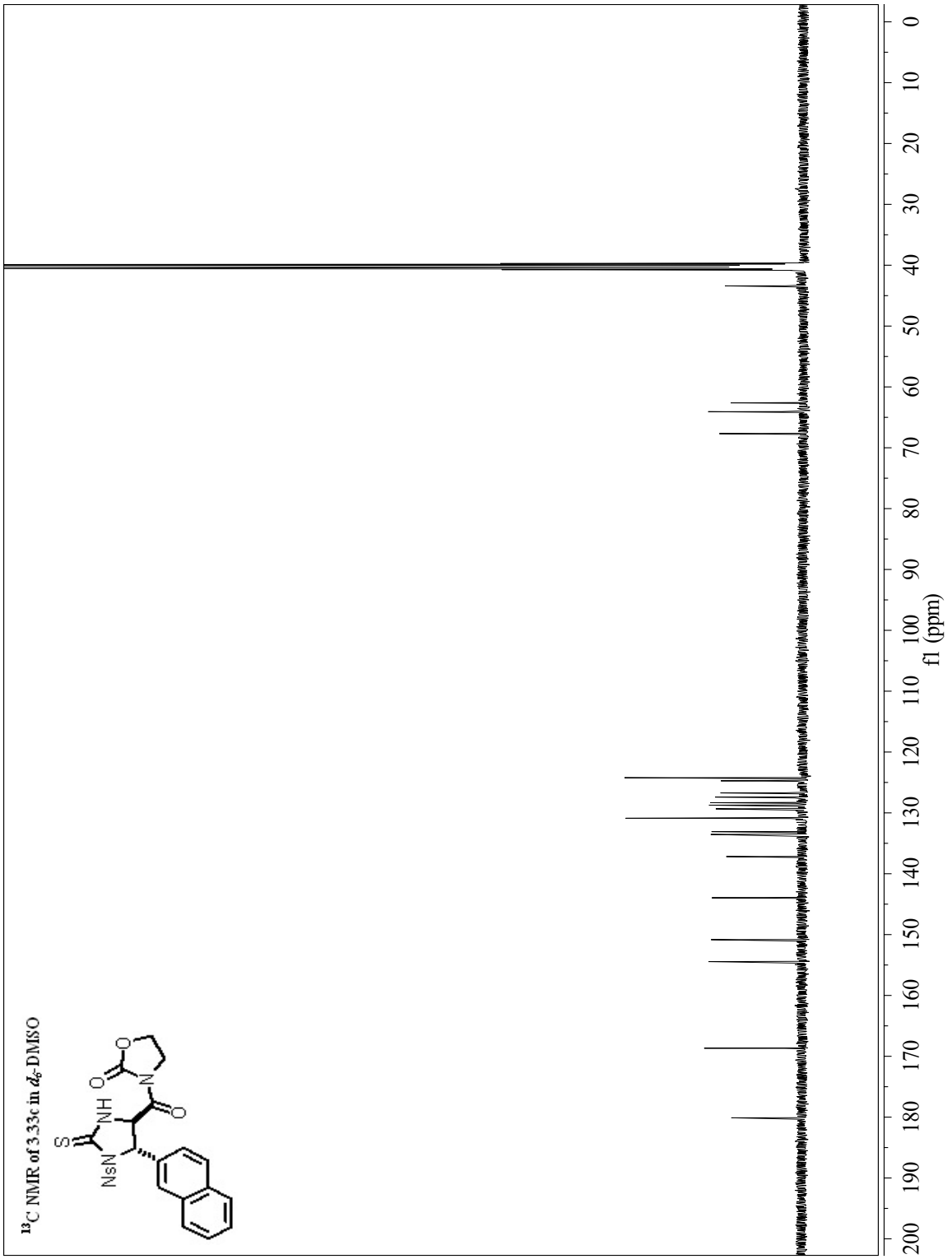

^{1}H NMR of 3.33b in d_6-DMSO
S
NH
O
O
N
O
NsN
OMe
1.00
2.16
2.10
1.10
1.02
1.99
1.09
1.10
2.09
2.08
3.03
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

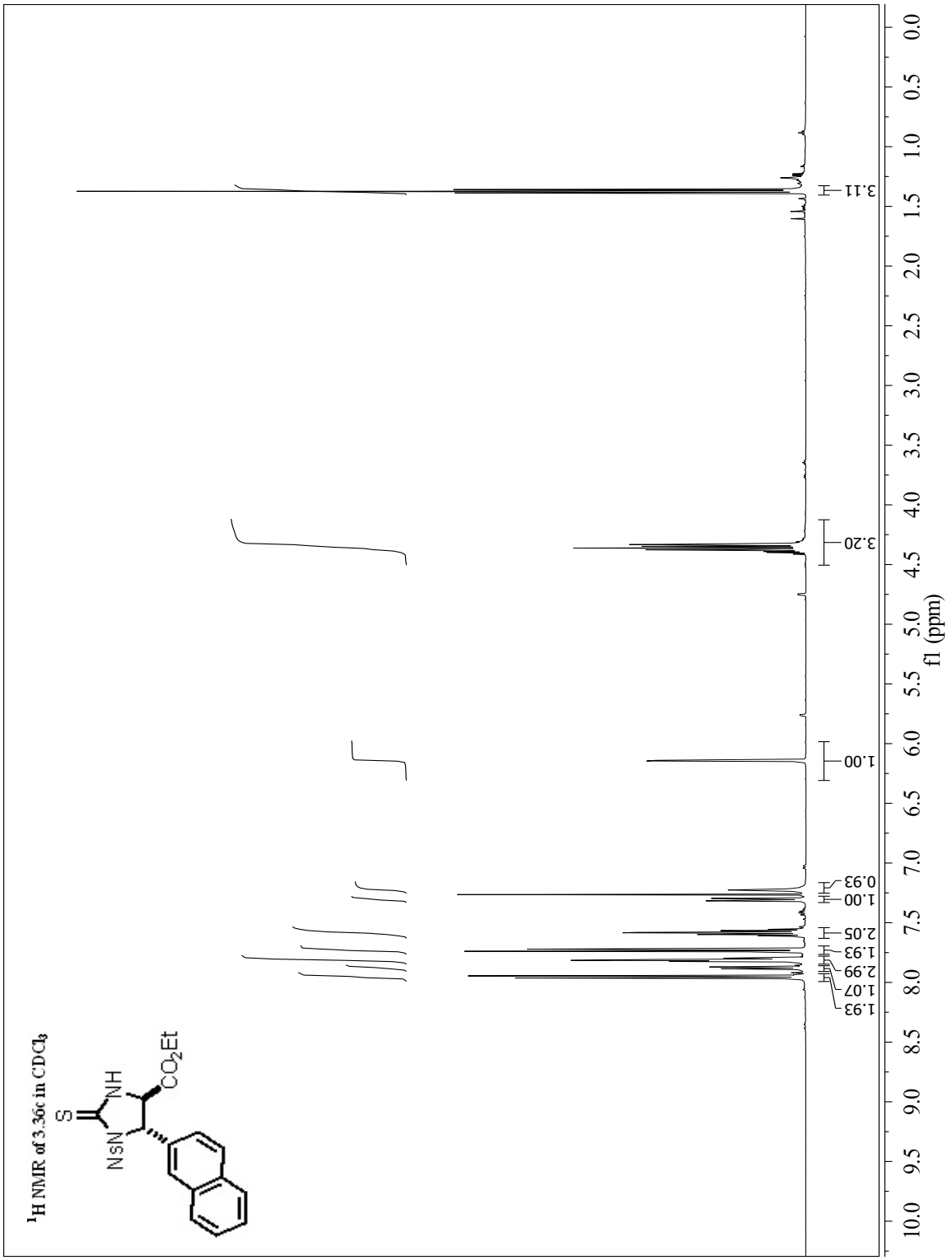

^{13}C NMR of 3.33b in d_6-DMSO
S
NH
O
O
O
N
NSN
OMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

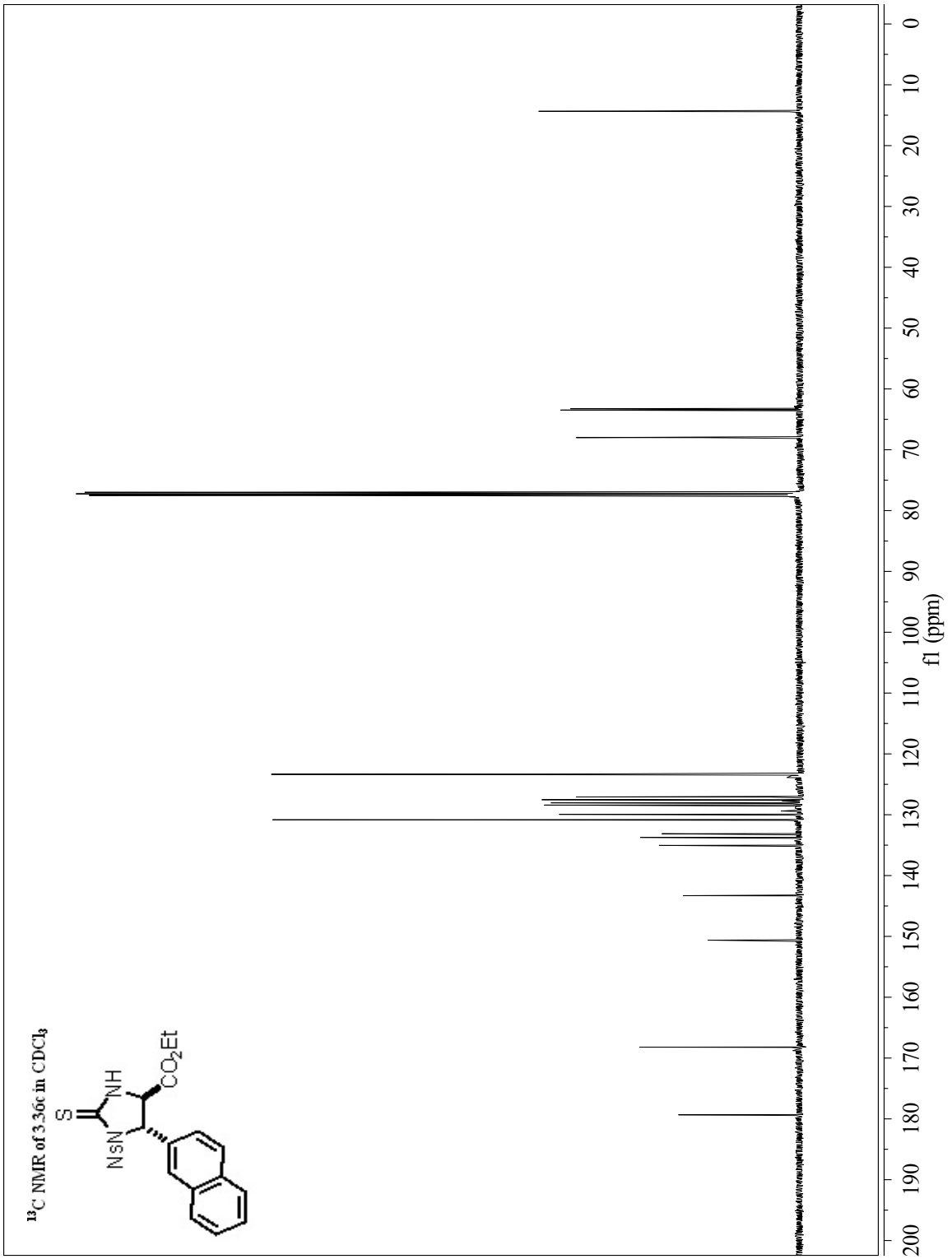

^{1}H NMR of 3.36b in $CDCl_3$
S
NH
CO_2Et
NsN
OMe
1.91
1.91
1.03
1.03
1.05
1.02
1.03
0.97
1.03
2.12
1.00
3.12
3.17
f1 (ppm)

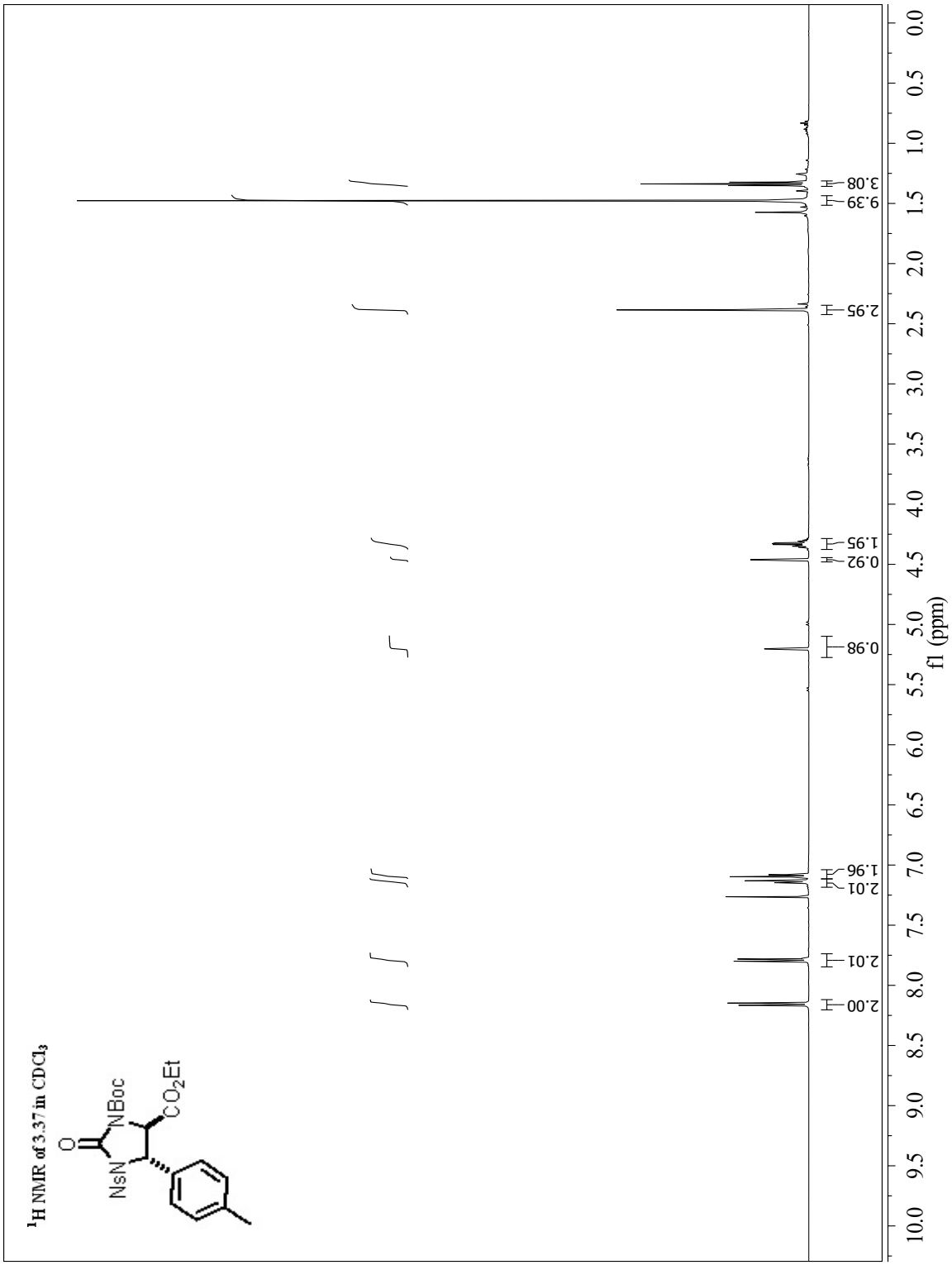

^{13}C NMR of 3.36b in $CDCl_3$
S
NH
NsN
CO_2Et
OMe
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

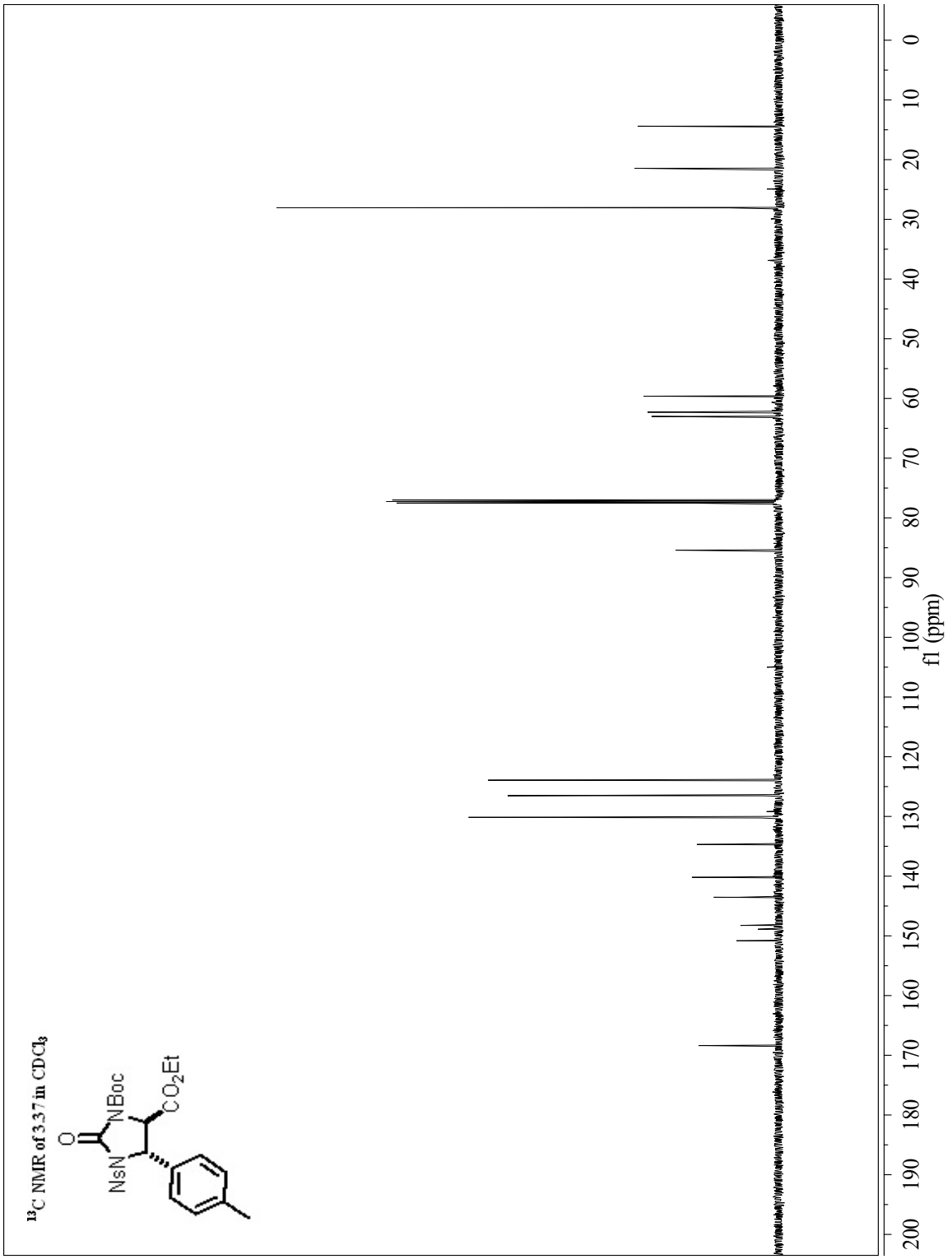

^{1}H NMR of 3.33c in d_6-DMSO
f1 (ppm)
1.00
1.98
3.88
0.91
1.92
0.96
0.98
2.00
1.99

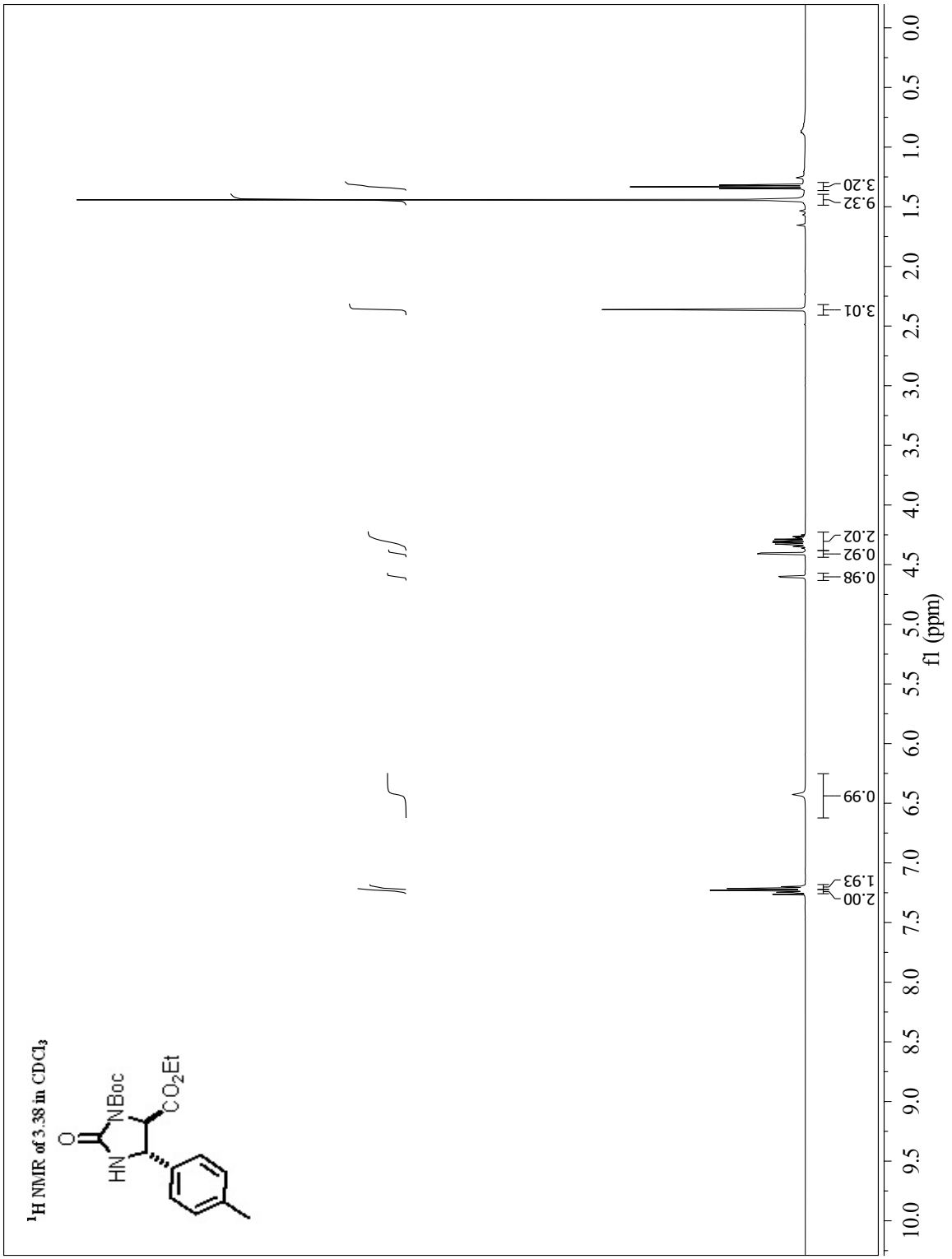

^{13}C NMR of 3.33c in d_6-DMSO
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

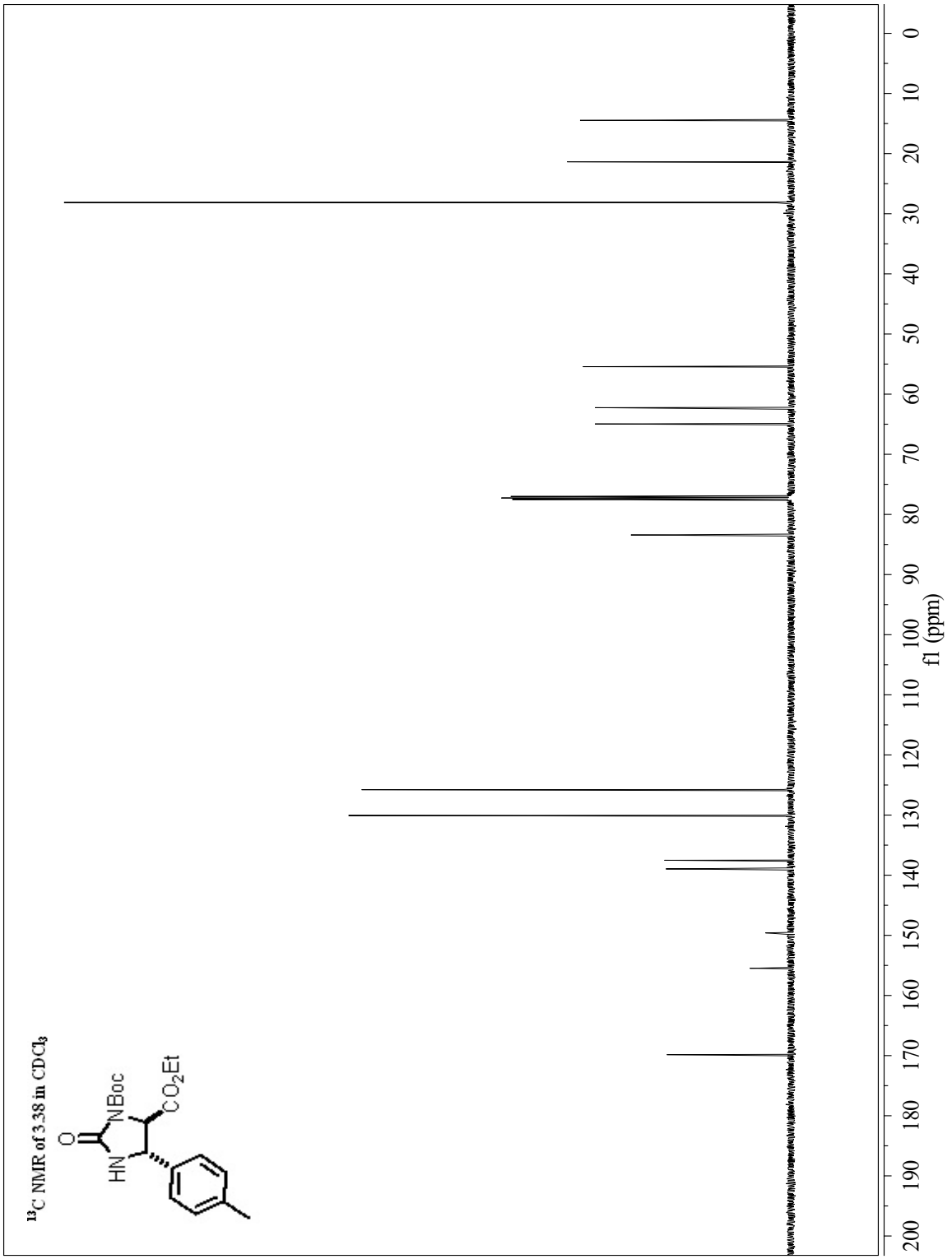

^{1}H NMR of 3.36c in $CDCl_3$
S
NH
NsN
CO_2Et
3.11
3.20
1.00
0.93
1.00
2.05
1.93
2.99
1.07
1.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

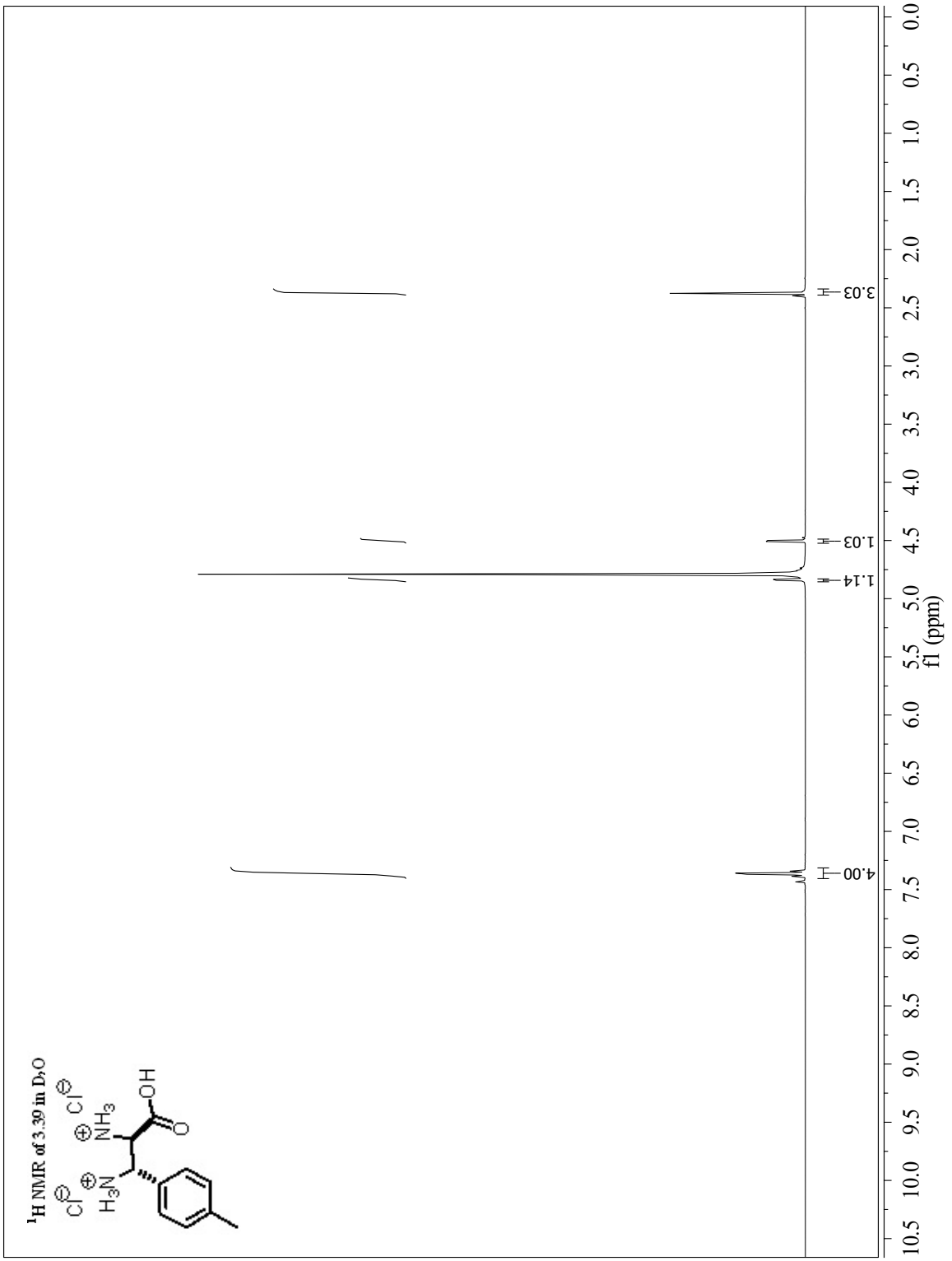

^{13}C NMR of 3.36c in $CDCl_3$
S
NH
NsN
CO_2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

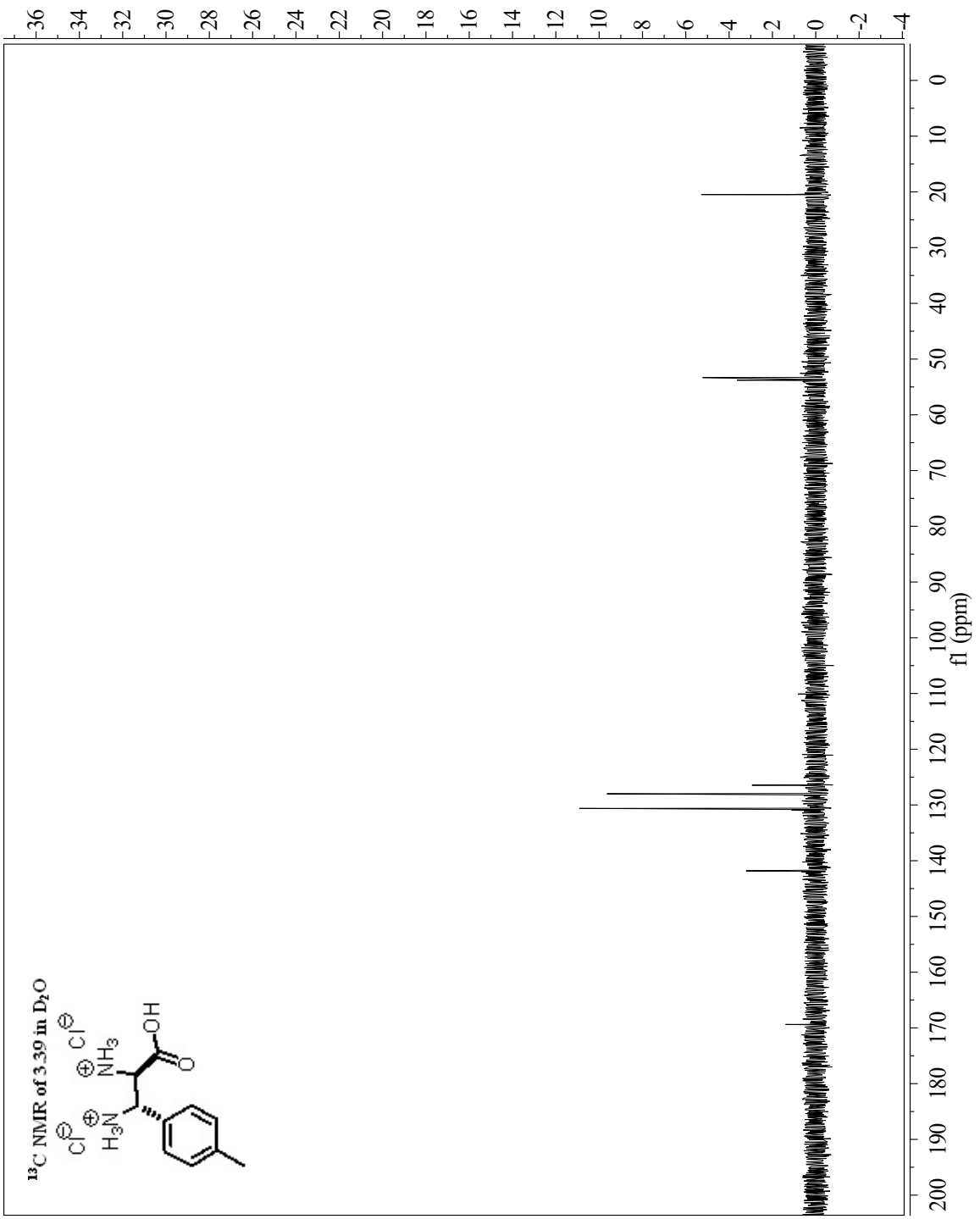

^{1}H NMR of 3.37 in $CDCl_3$
NBoc
NsN
O
CO_2Et
2.00
2.01
2.01
1.96
0.98
0.92
1.95
2.95
9.39
3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

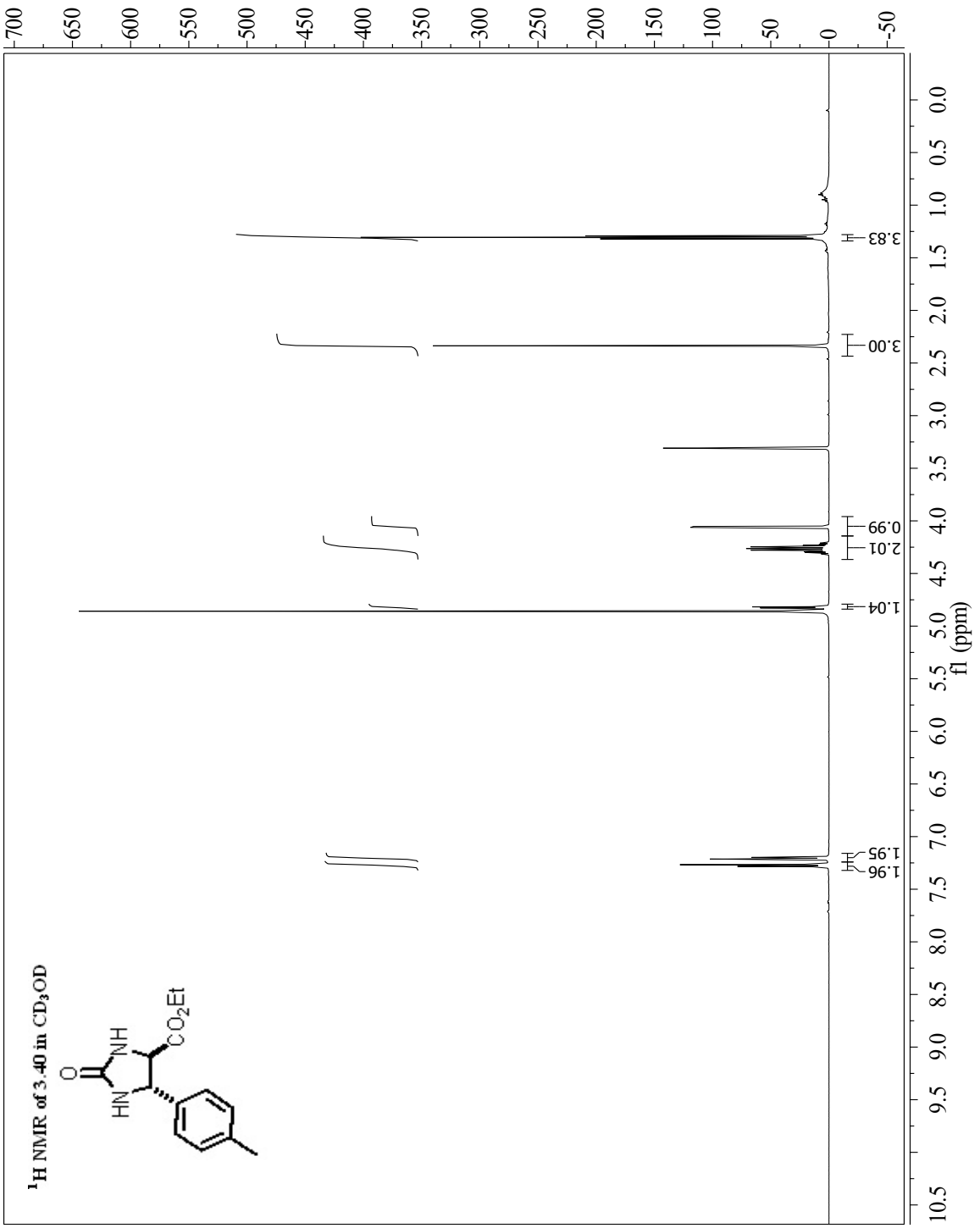

^{13}C NMR of 3.37 in $CDCl_3$
O
NBoc
NsN
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

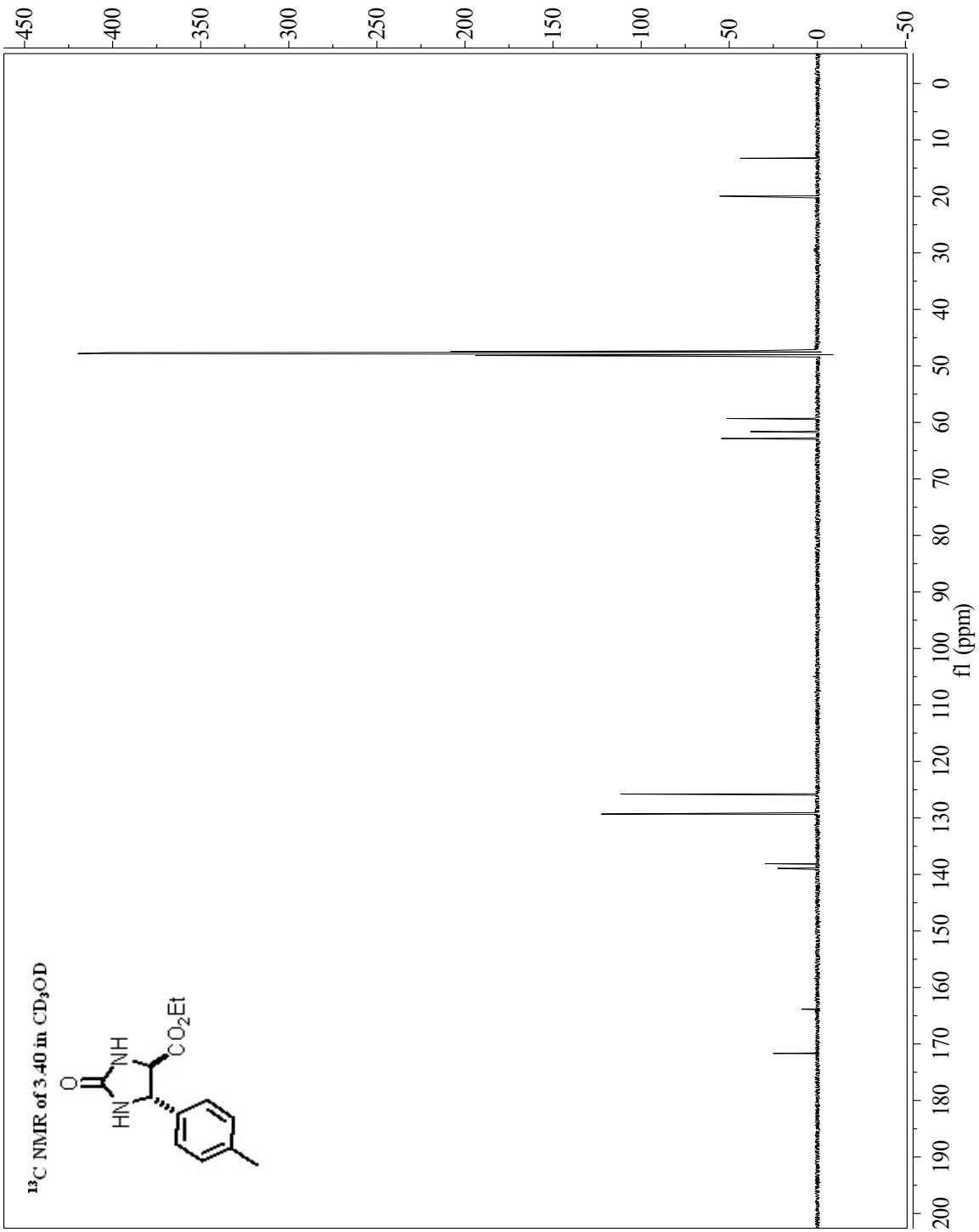

^{1}H NMR of 3.38 in $CDCl_3$
NBoc
CO_2Et
HN
O
2.00
1.93
0.99
0.98
0.92
2.02
3.01
9.32
3.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

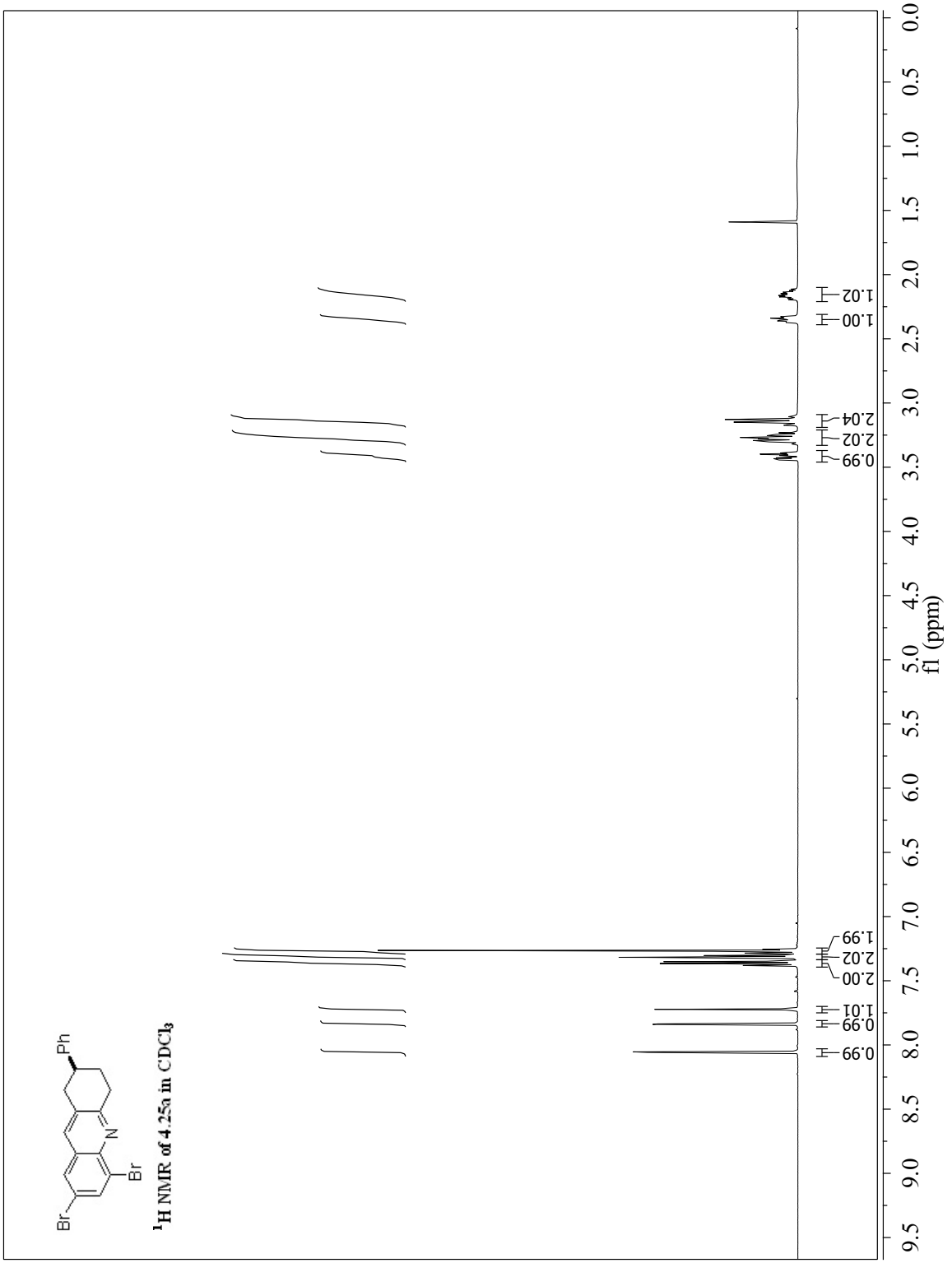

^{13}C NMR of 3.38 in $CDCl_3$
O
NBoc
HN
CO_2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


^{1}H NMR of 3.39 in D$_2$O
3.03
1.03
1.14
4.00
f1 (ppm)

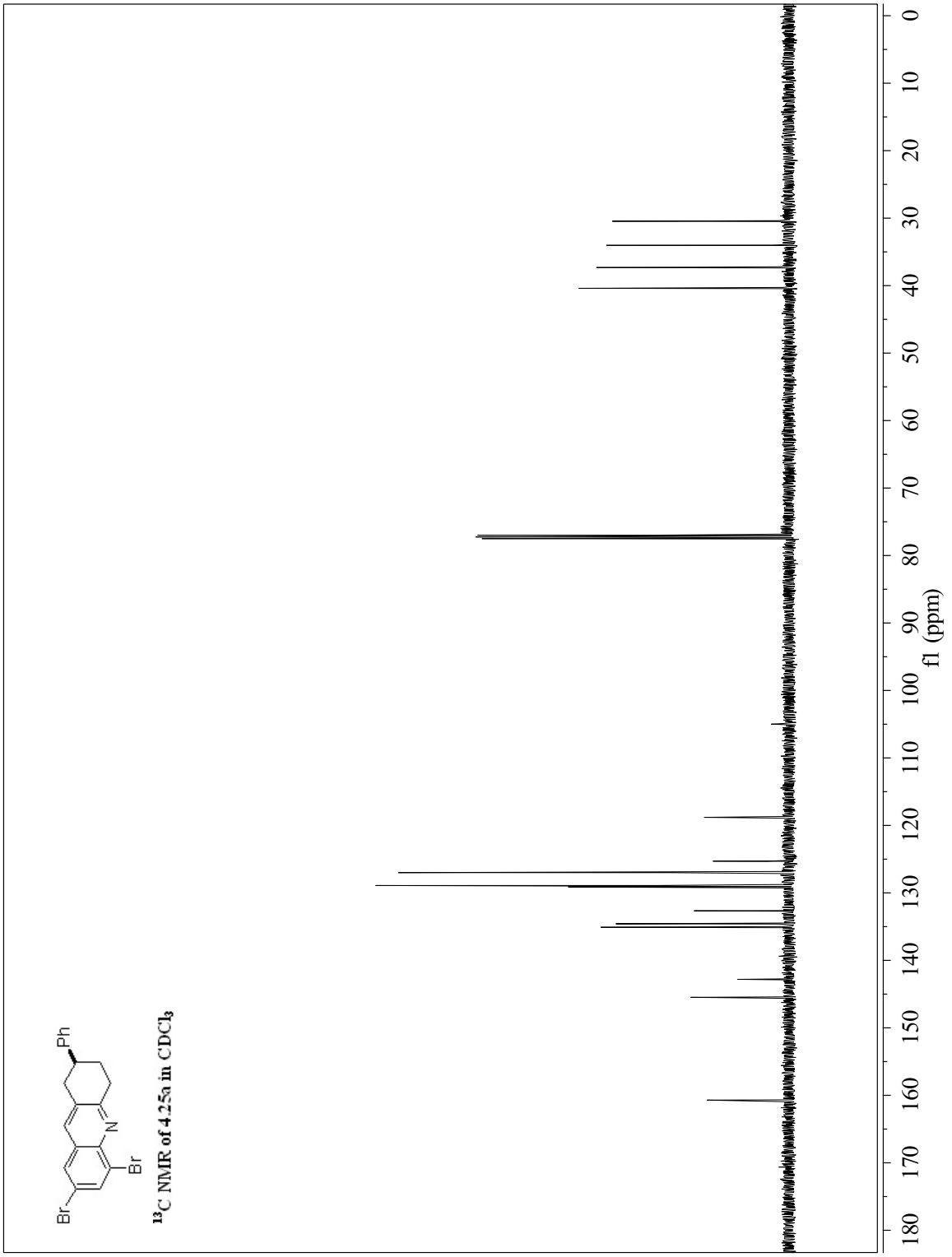

^{13}C NMR of 3.39 in D_2O
fl (ppm)


^{1}H NMR of 3.40 in CD_3OD
O
NH
HN
CO_2Et
3.83
3.00
0.99
2.01
1.04
1.96
1.95
f1 (ppm)

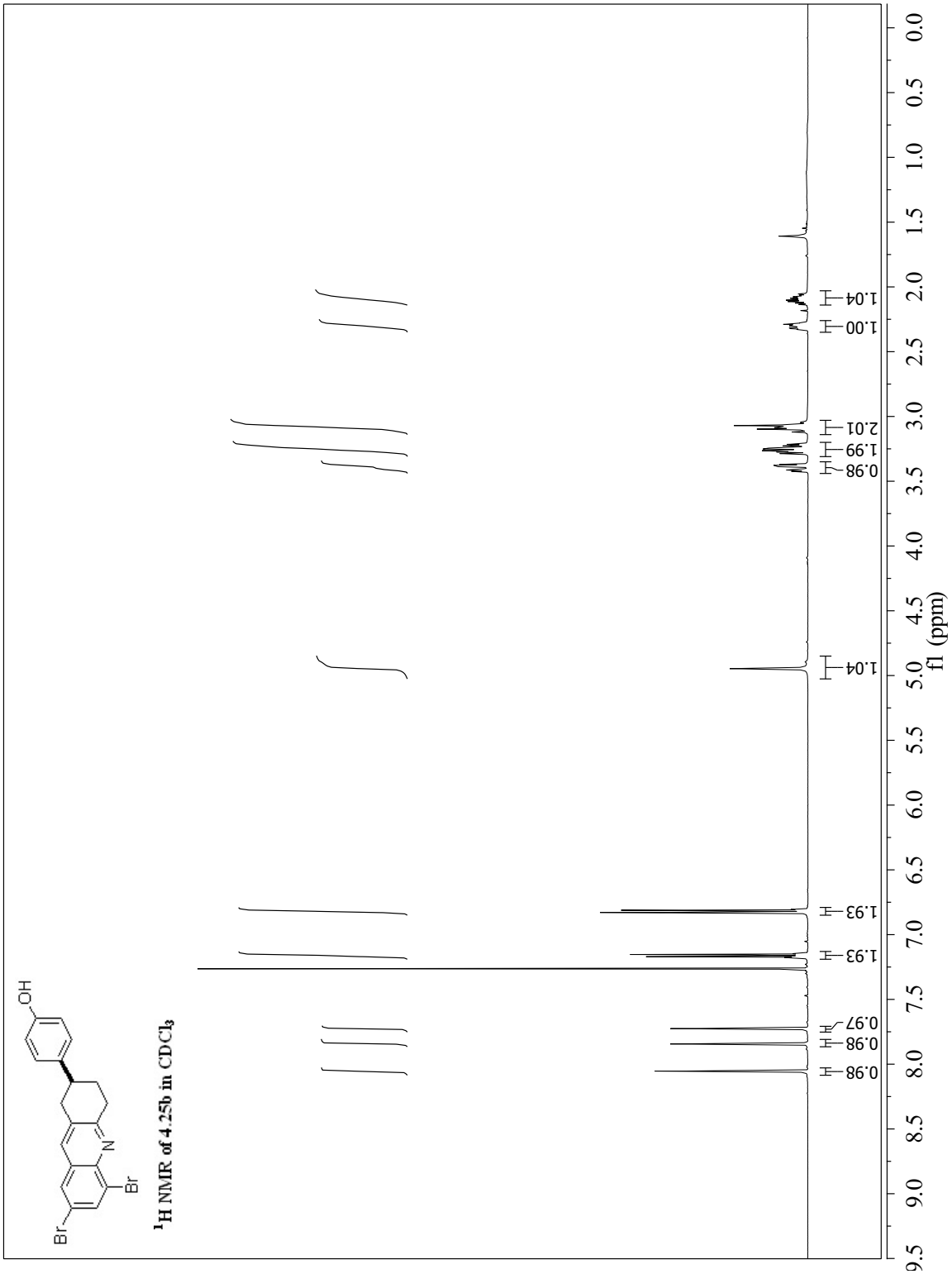

^{13}C NMR of 3.40 in CD_3OD
O
NH
HN
CO_2Et
f1 (ppm)

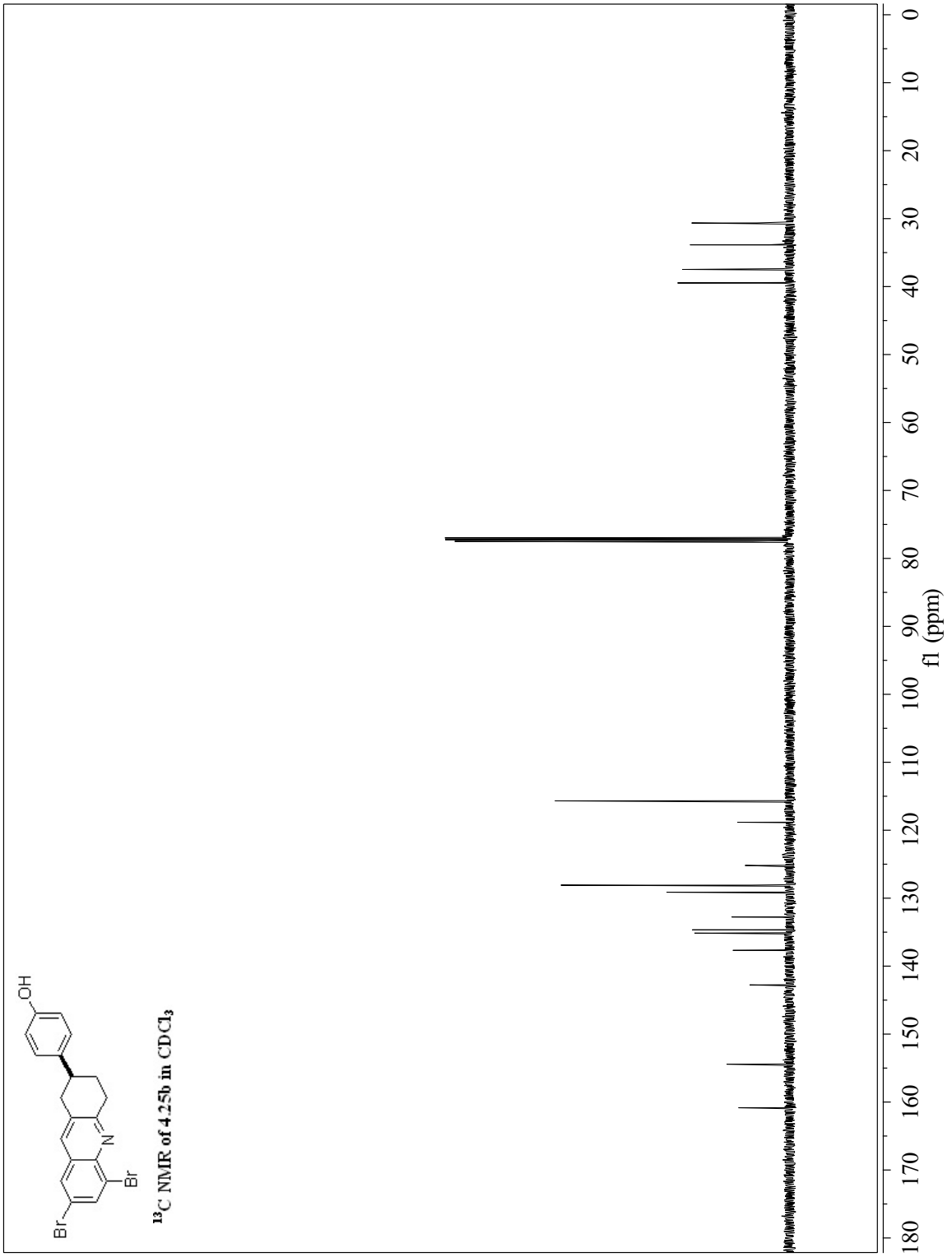


^{1}H NMR of 4.25a in $CDCl_3$

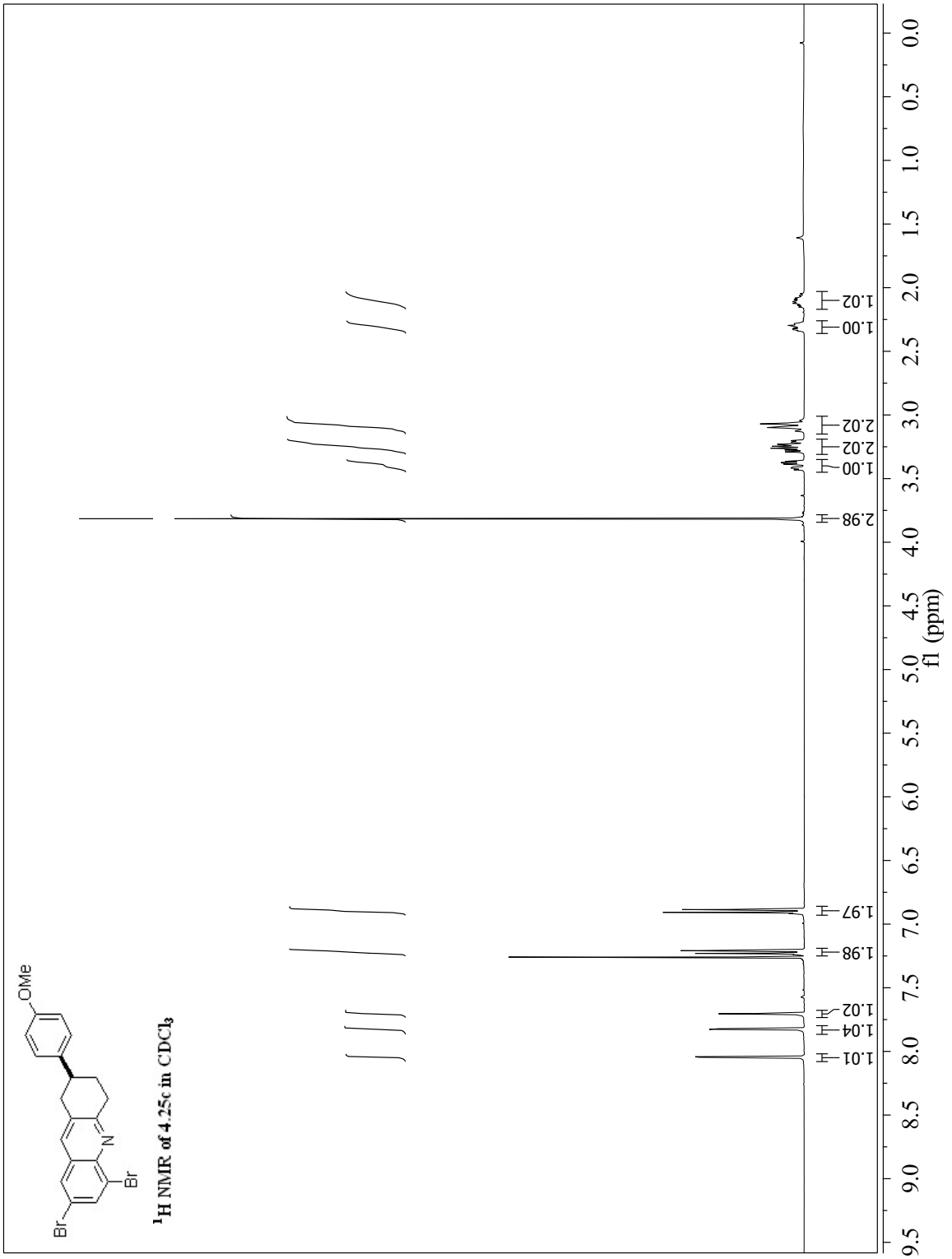


^{13}C NMR of 4.25a in $CDCl_3$

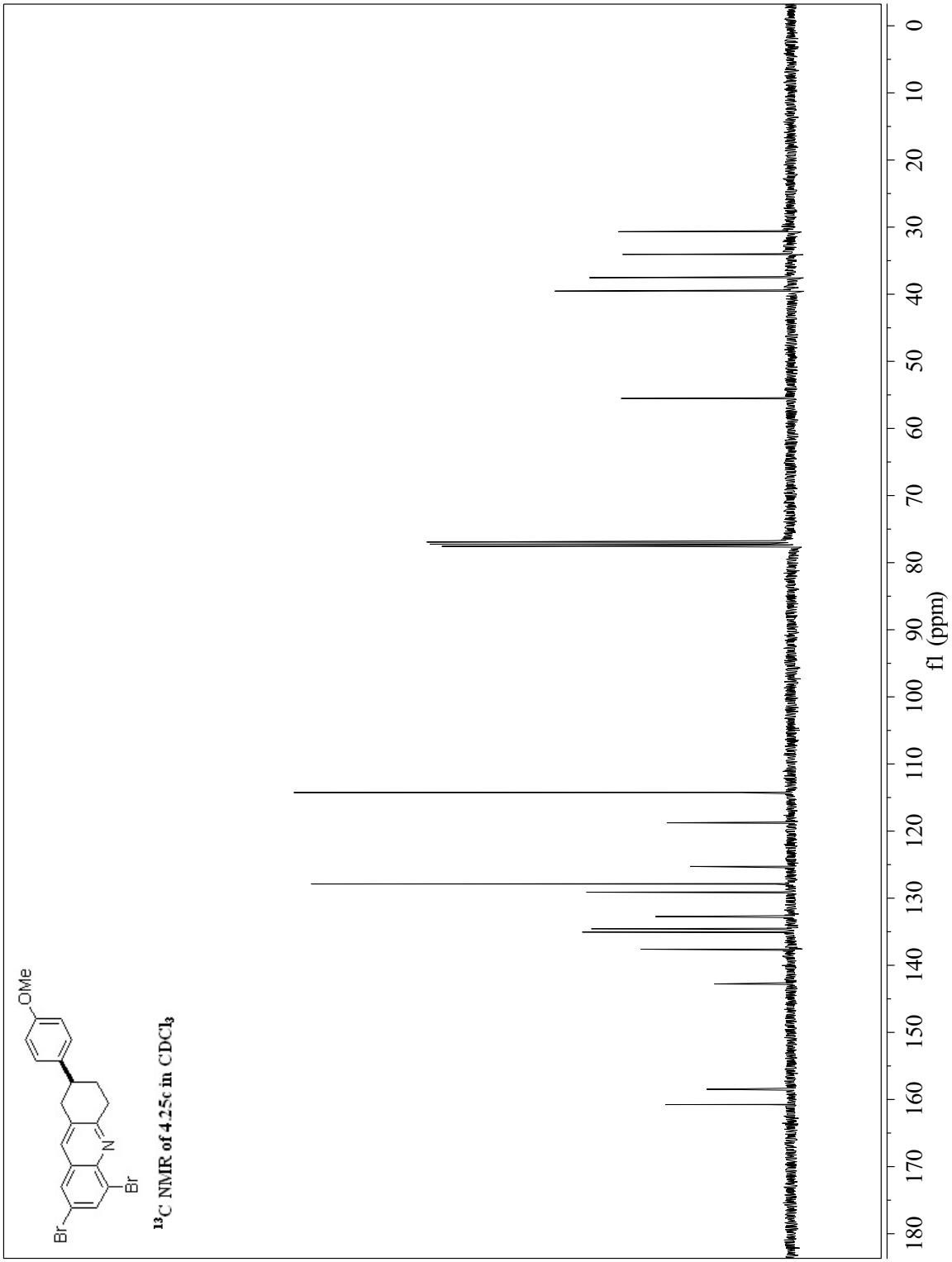

OH
Br
N
Br
^{1}H NMR of 4.25b in $CDCl_3$
0.98
0.98
0.97
1.93
1.93
1.04
0.98
1.99
2.01
1.00
1.04
f1 (ppm)



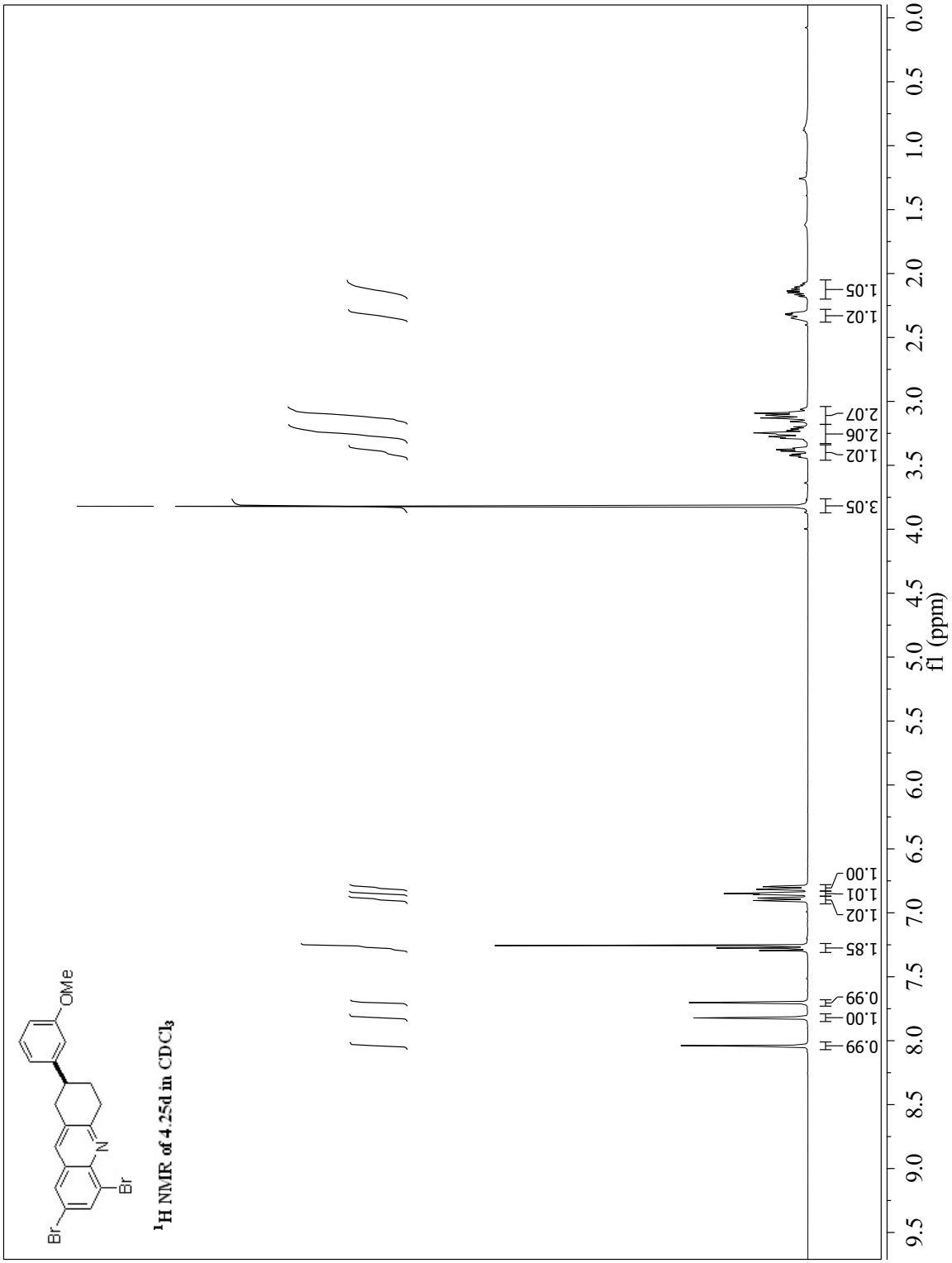
^{13}C NMR of 4.25b in $CDCl_3$

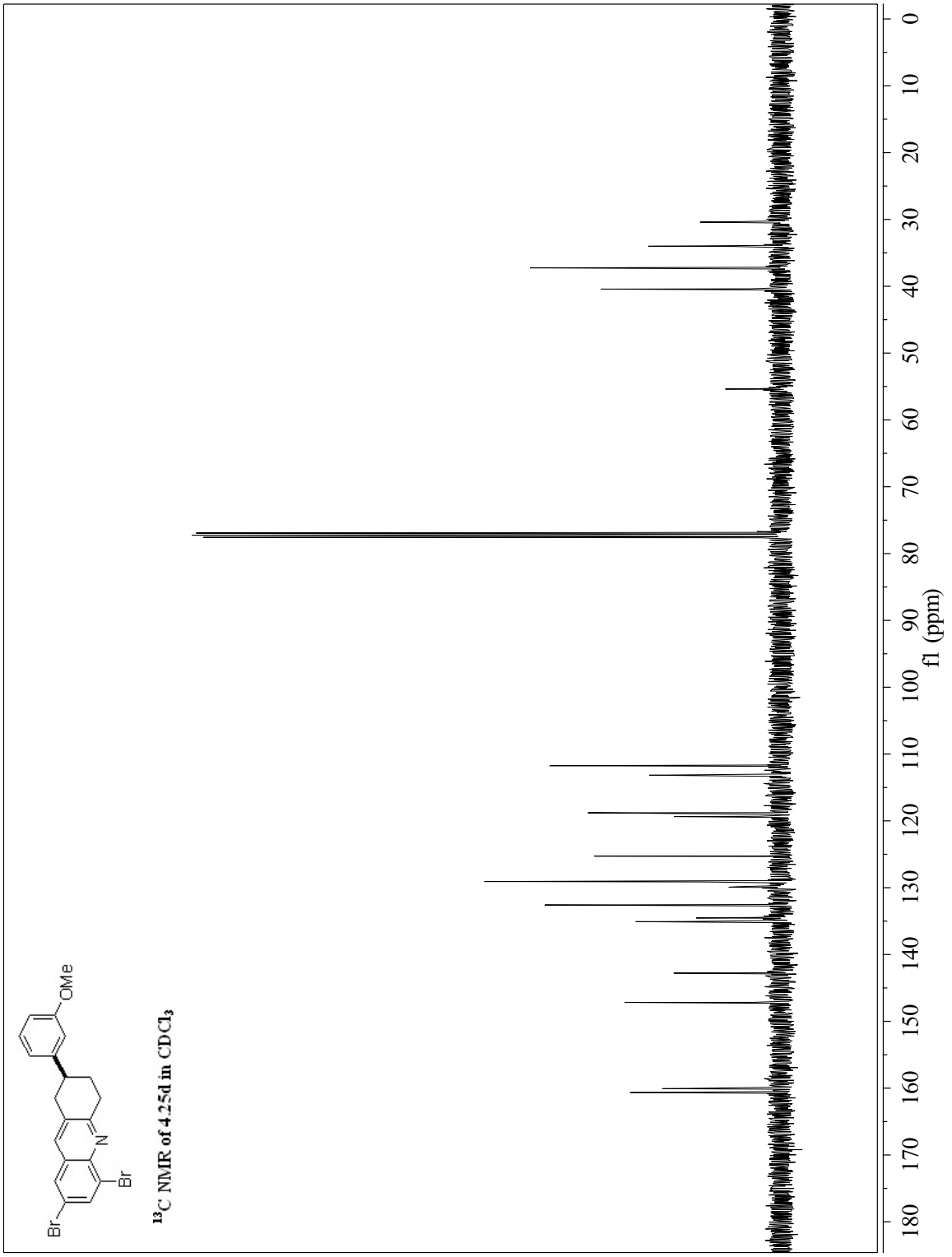


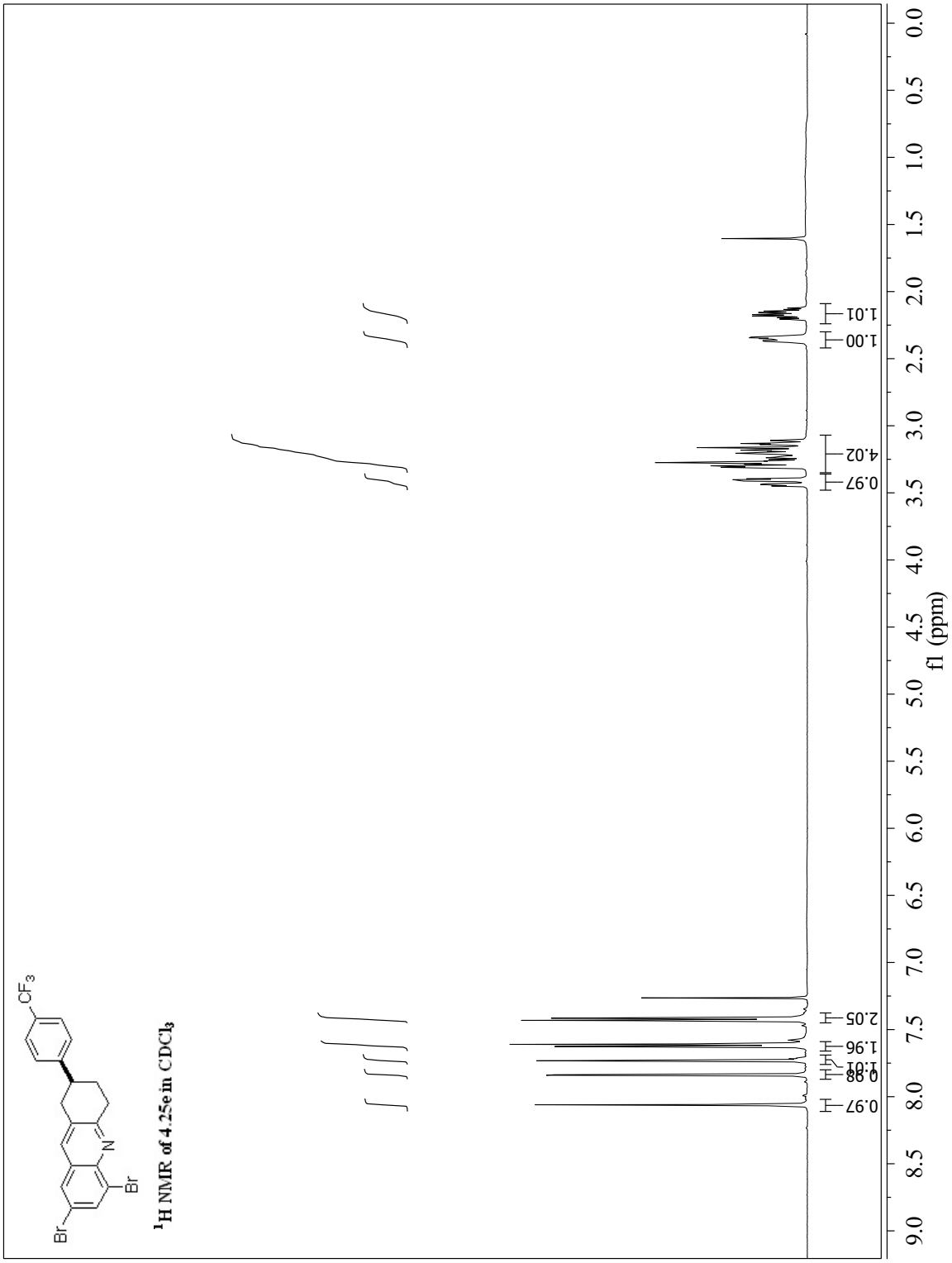
^{1}H NMR of 4.25c in $CDCl_3$

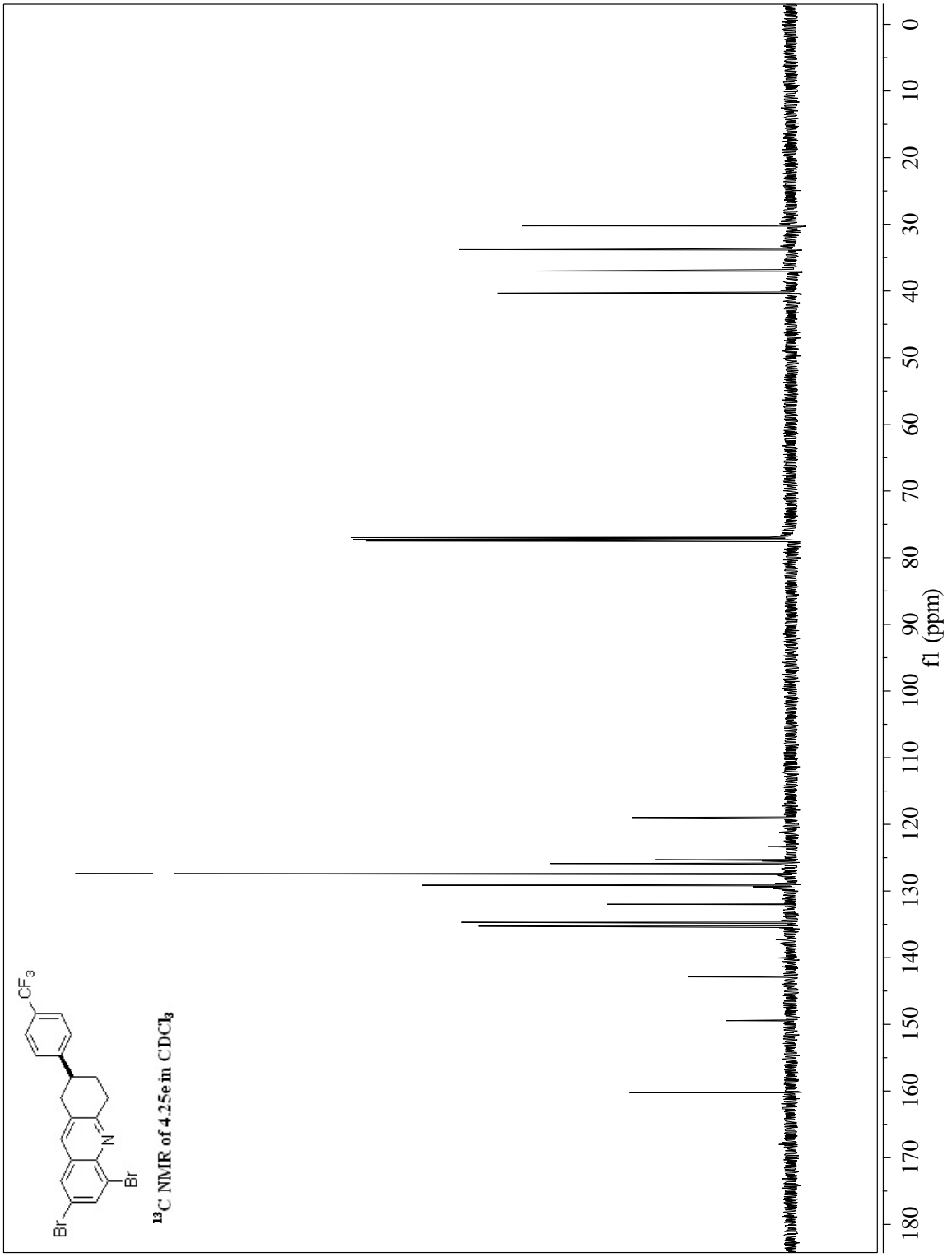


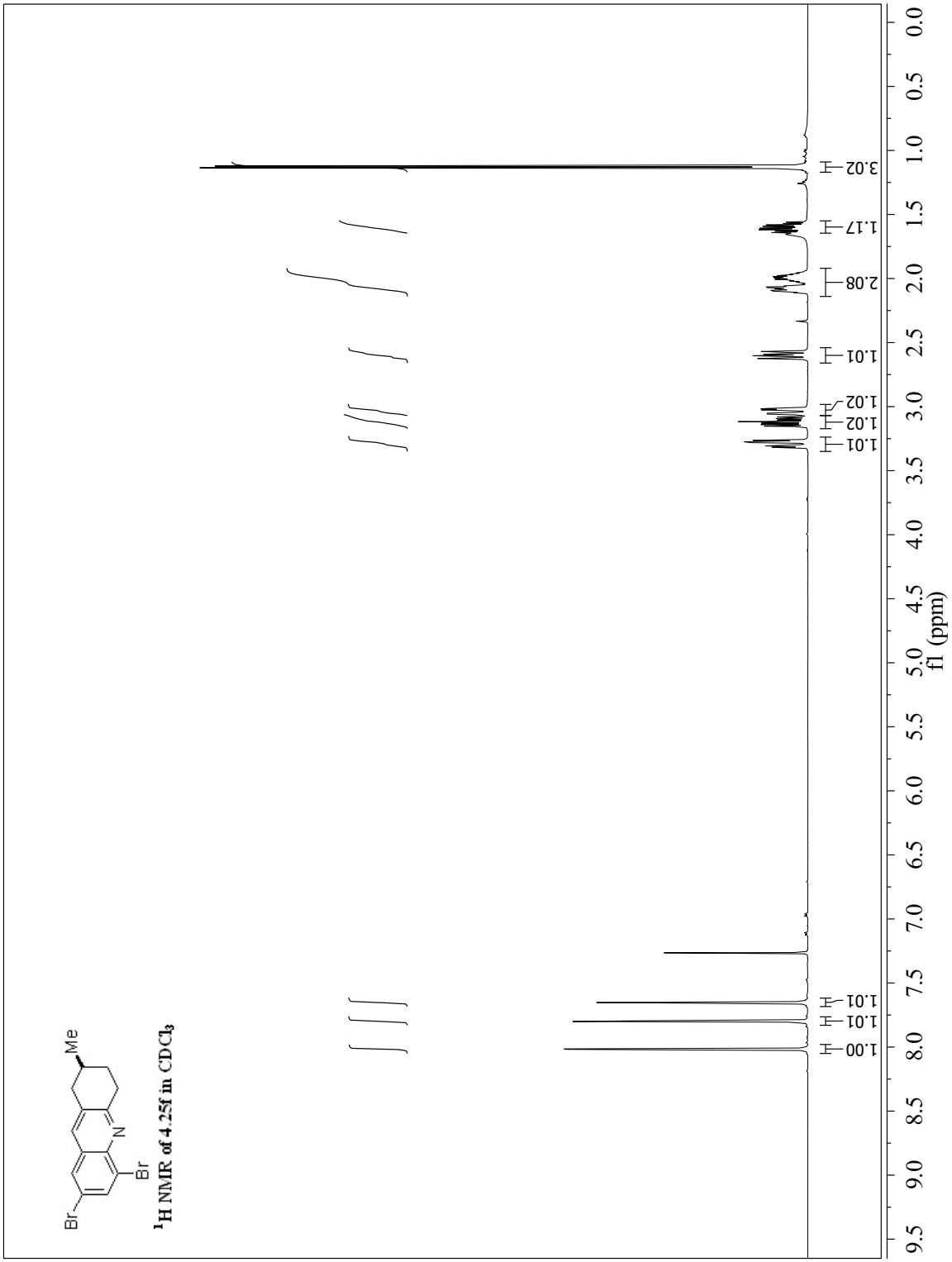
^{13}C NMR of 4.25c in $CDCl_3$


OMe
N
Br
Br
^{1}H NMR of 4.25d in $CDCl_3$
0.99
1.00
0.99
1.85
1.02
1.01
1.00
3.05
1.02
2.06
2.07
1.02
1.05
f1 (ppm)

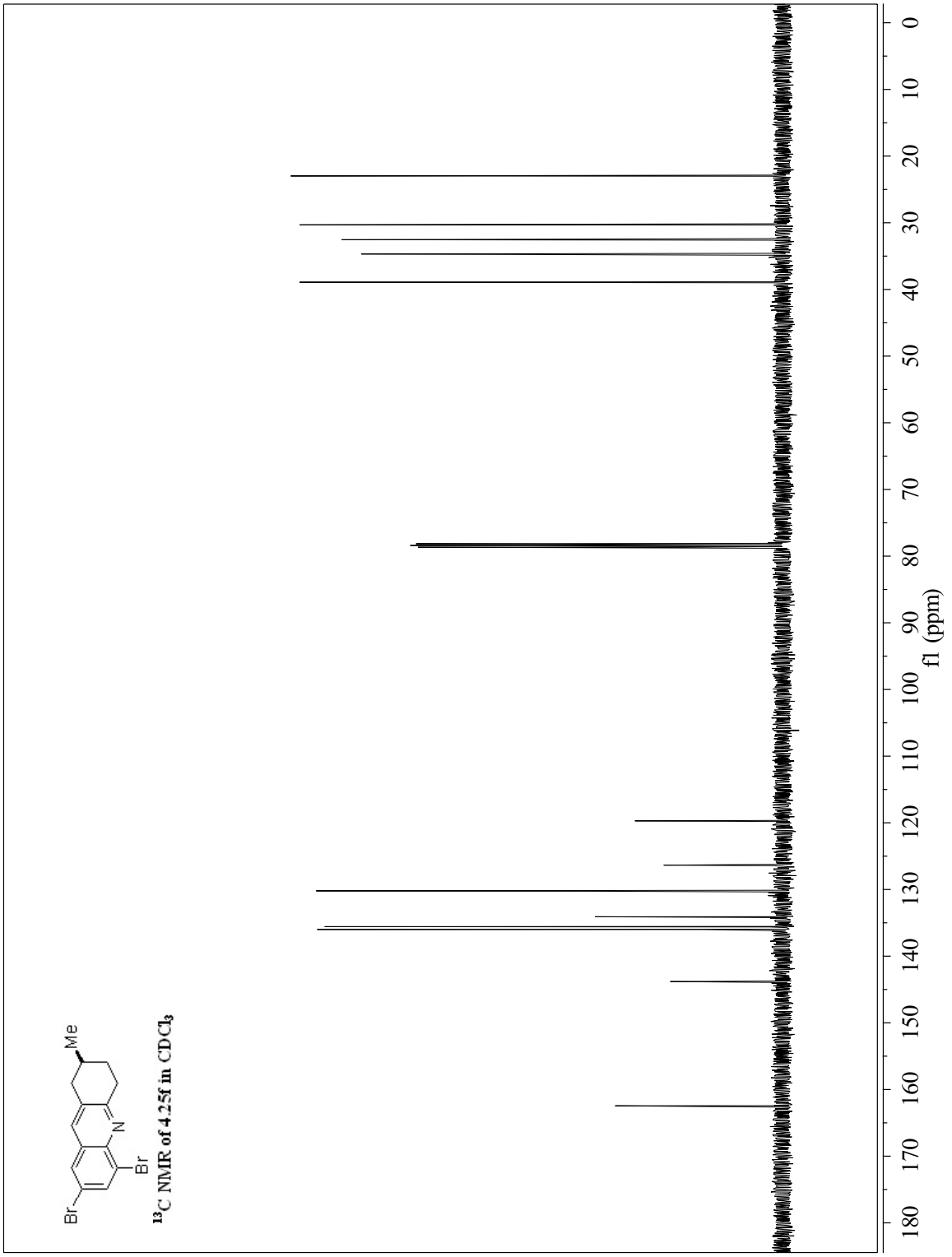

OMe
N
Br
Br
^{13}C NMR of 4.25d in $CDCl_3$
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180


CF3
N
Br
Br
1H NMR of 4.25e in CDCl3
0.97
0.88
1.01
1.96
2.05
0.97
4.02
1.00
1.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

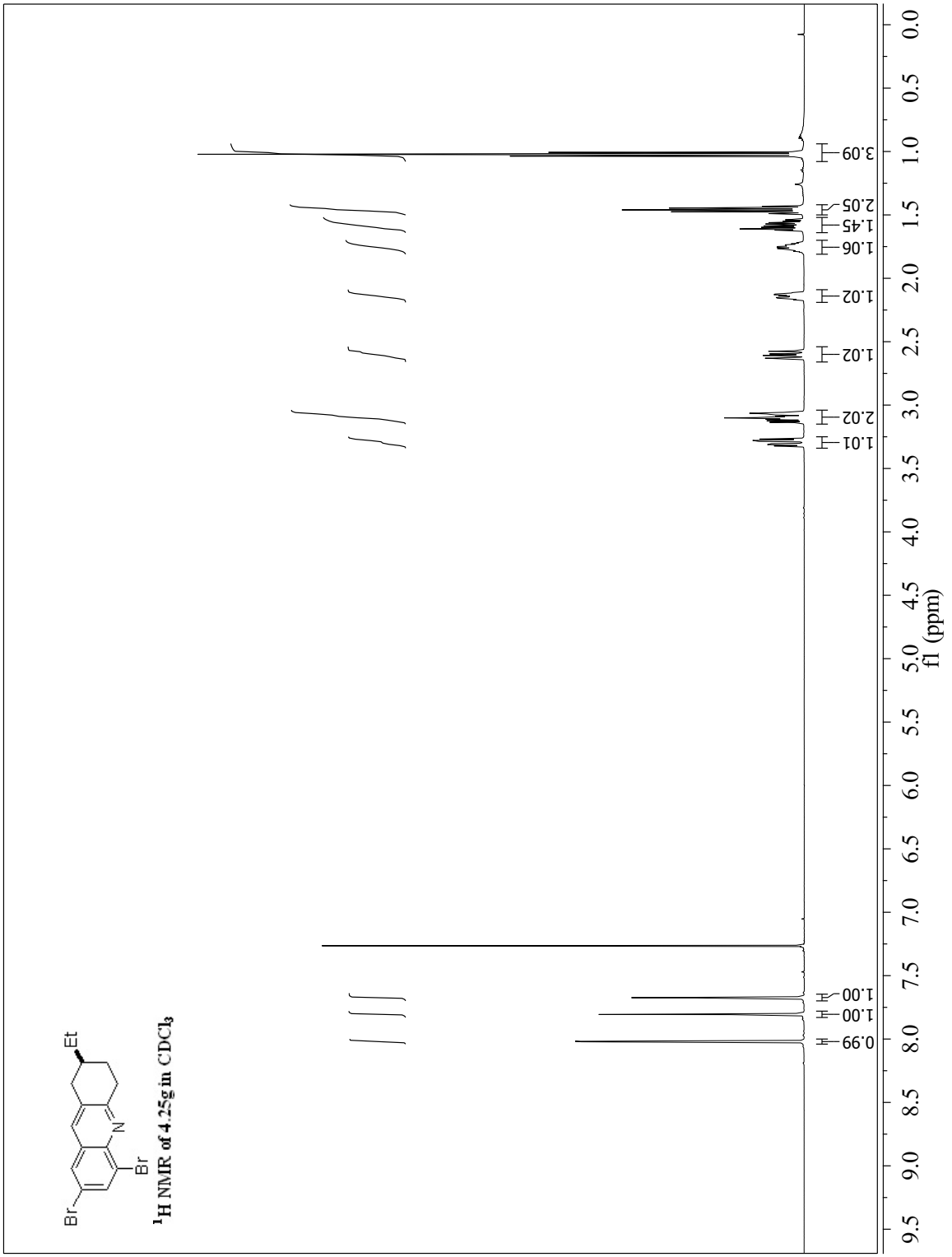

CF3
N
Br
Br
13C NMR of 4.25e in CDCl3
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

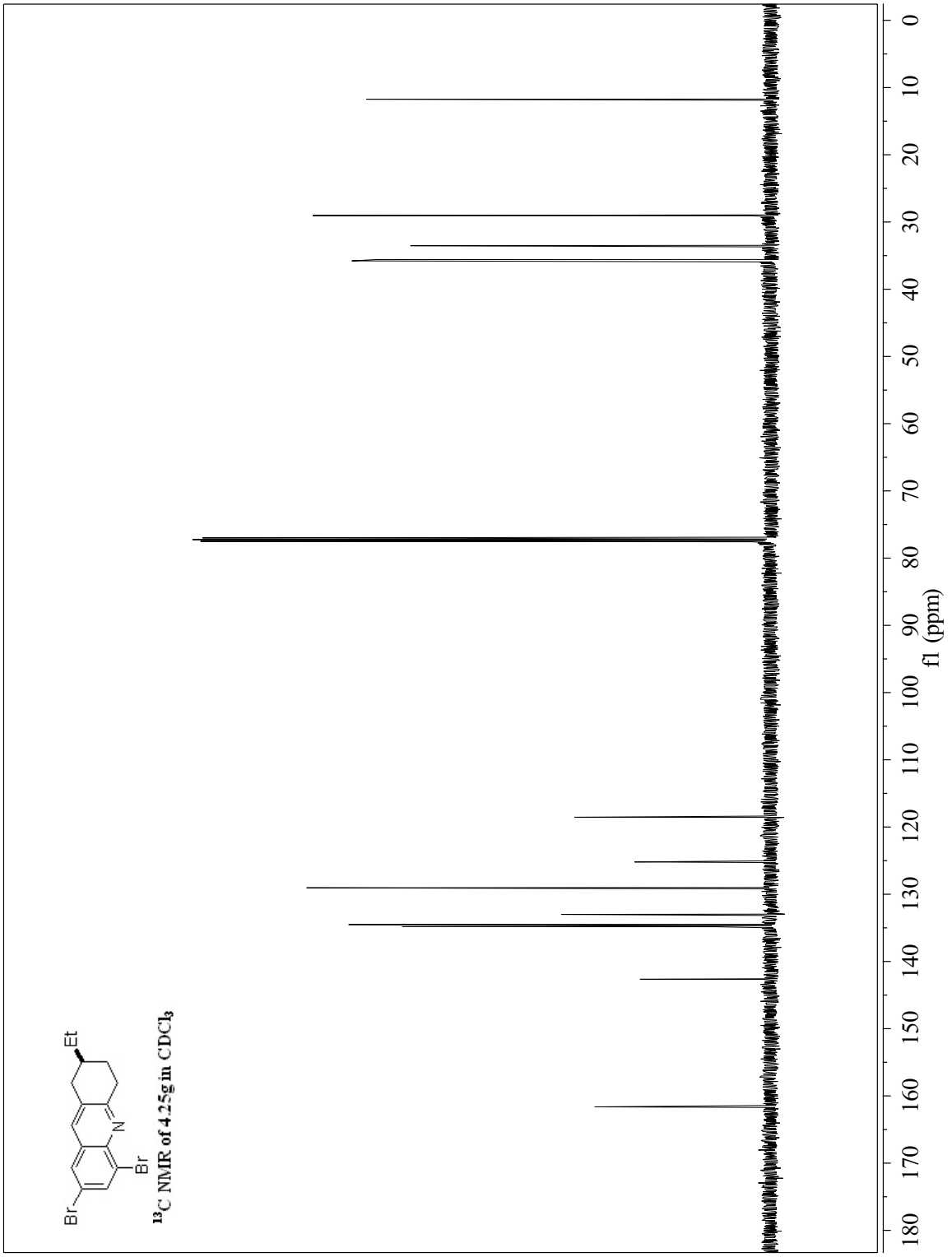


^{1}H NMR of 4.25f in $CDCl_3$

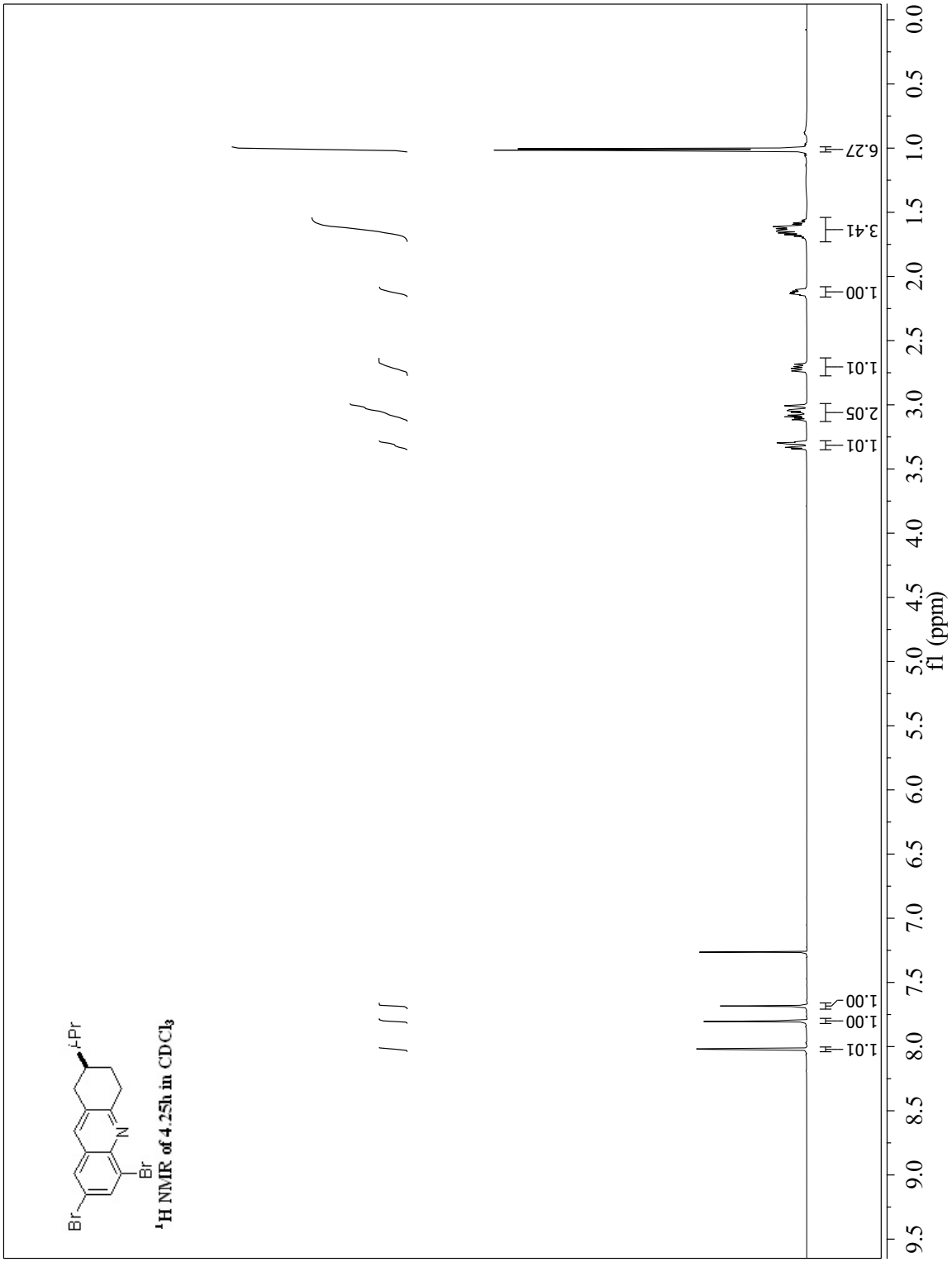


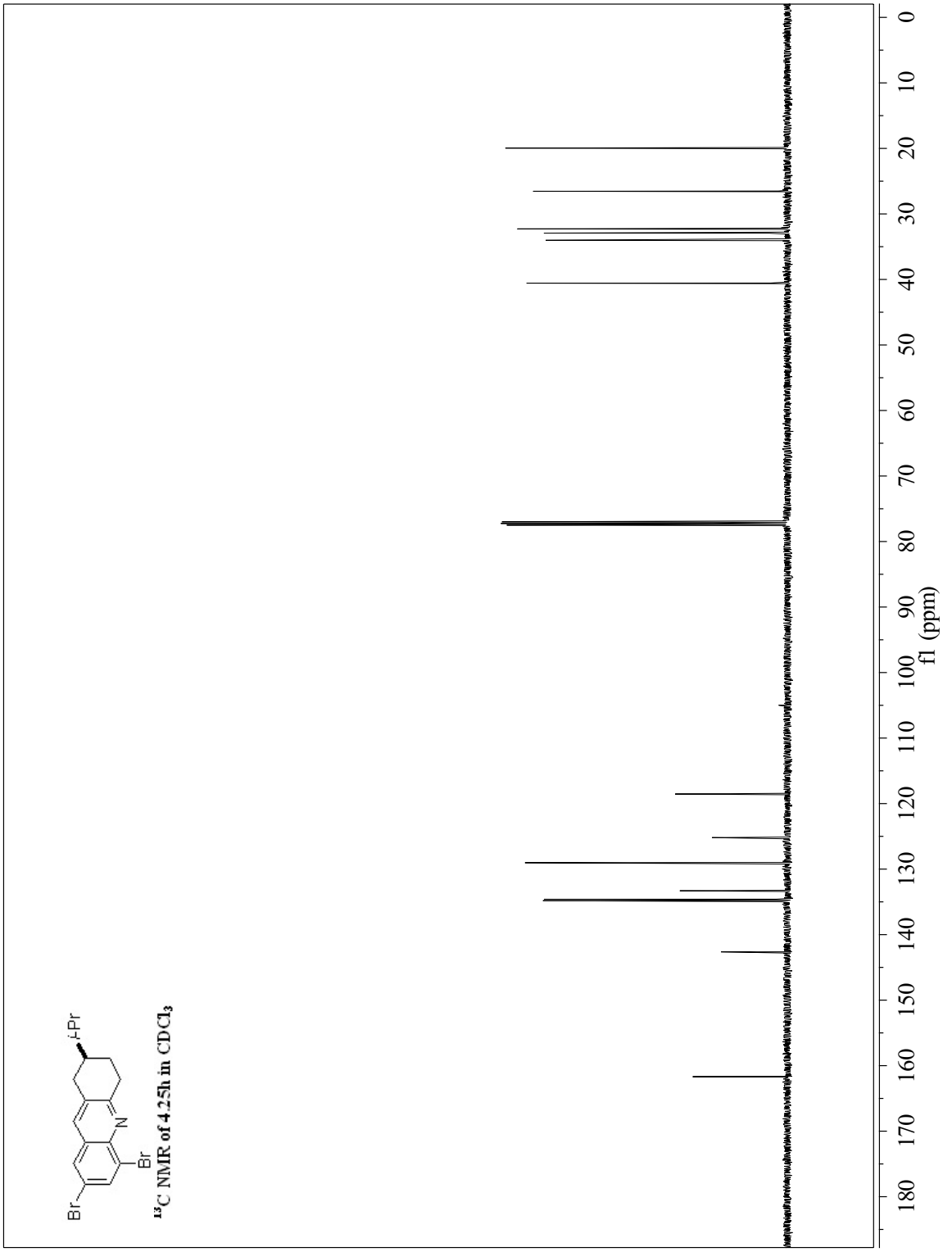
^{13}C NMR of 4.25f in $CDCl_3$


Et
N
Br
Br
^{1}H NMR of 4.25g in $CDCl_3$
3.09
2.05
1.45
1.06
1.02
1.02
2.02
1.01
1.00
1.00
0.99
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
f1 (ppm)

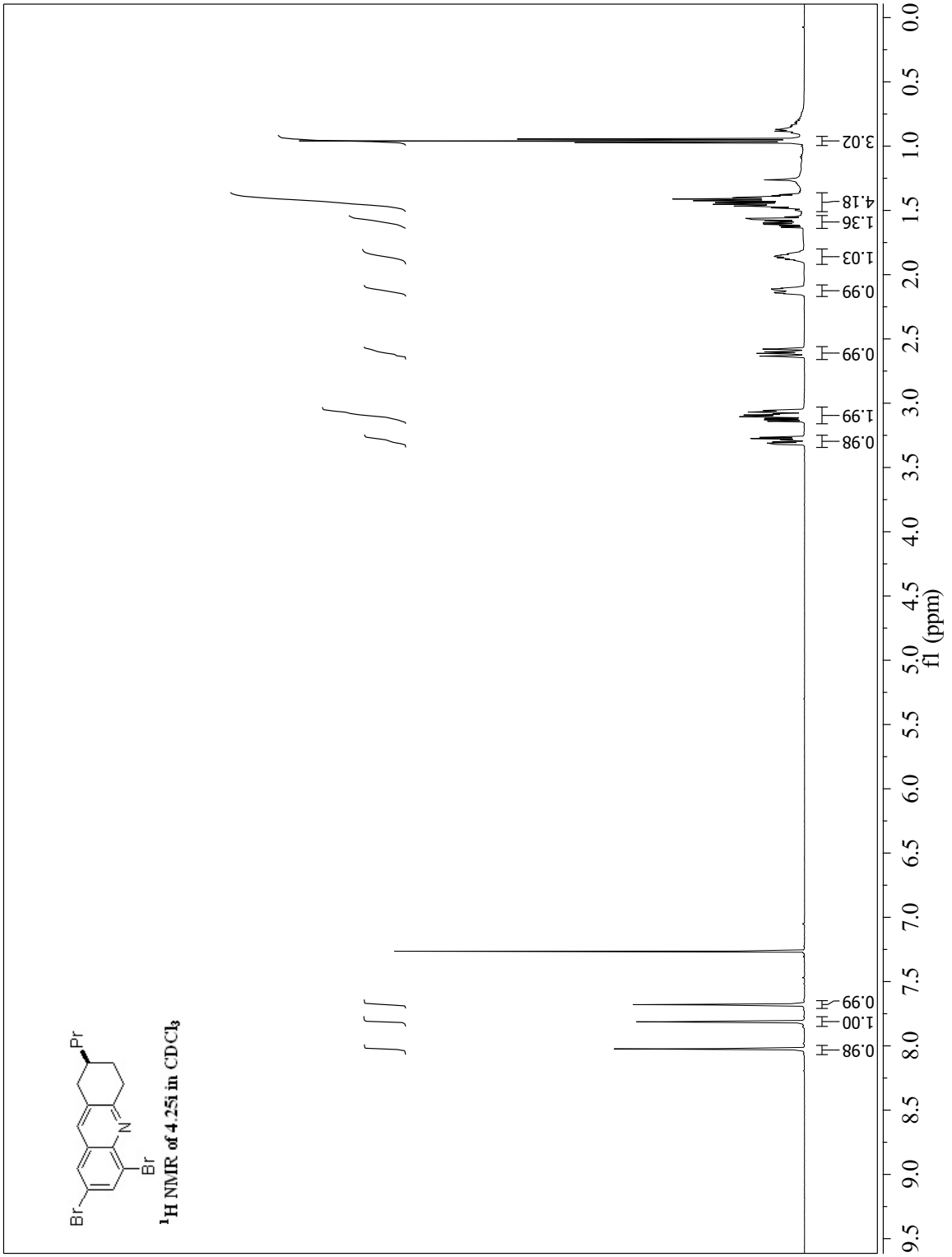


^{13}C NMR of 4.25g in $CDCl_3$

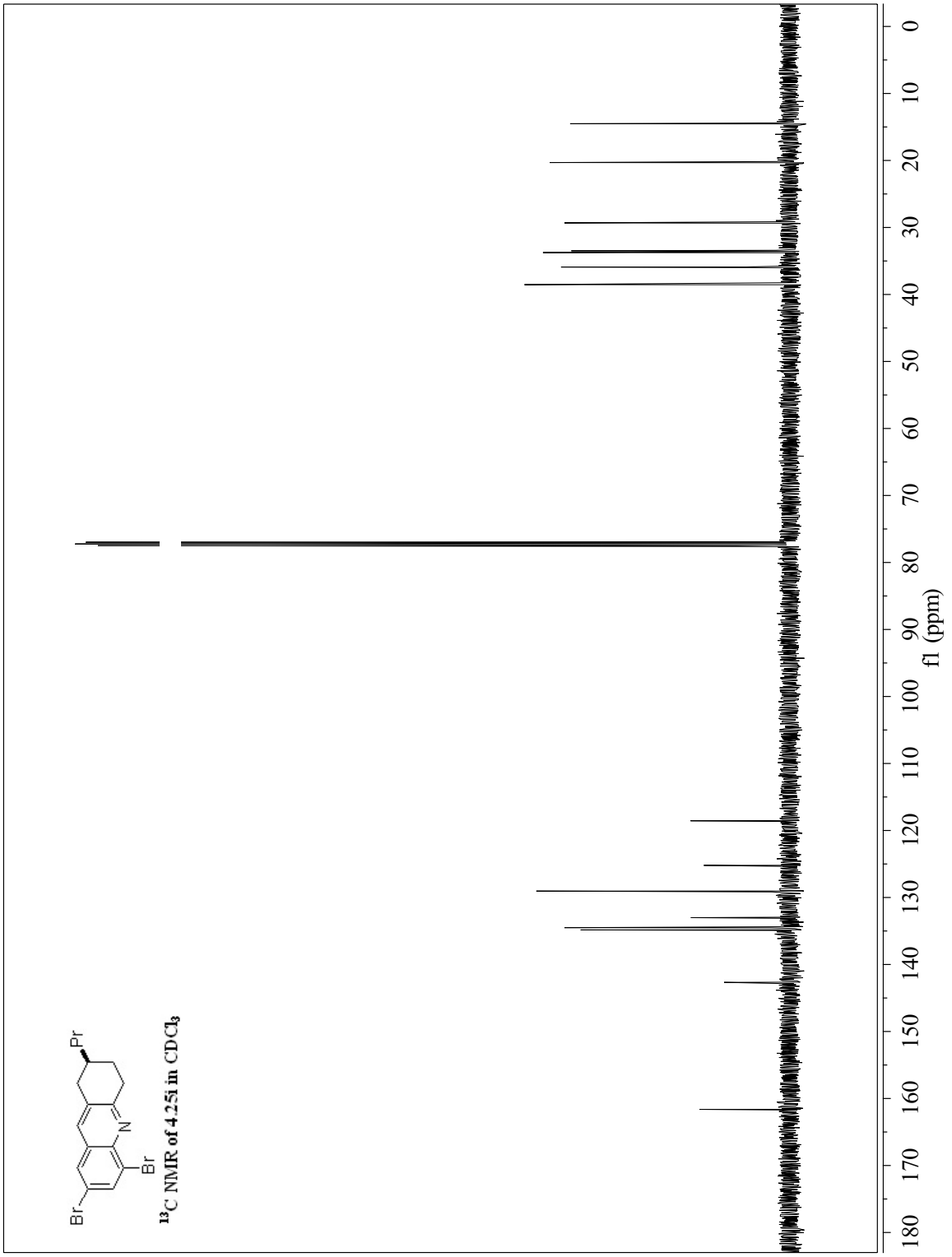

i-Pr
N
Br
Br
^{1}H NMR of 4.25h in $CDCl_3$
1.01
1.00
1.00
6.27
3.41
1.00
1.01
2.05
1.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

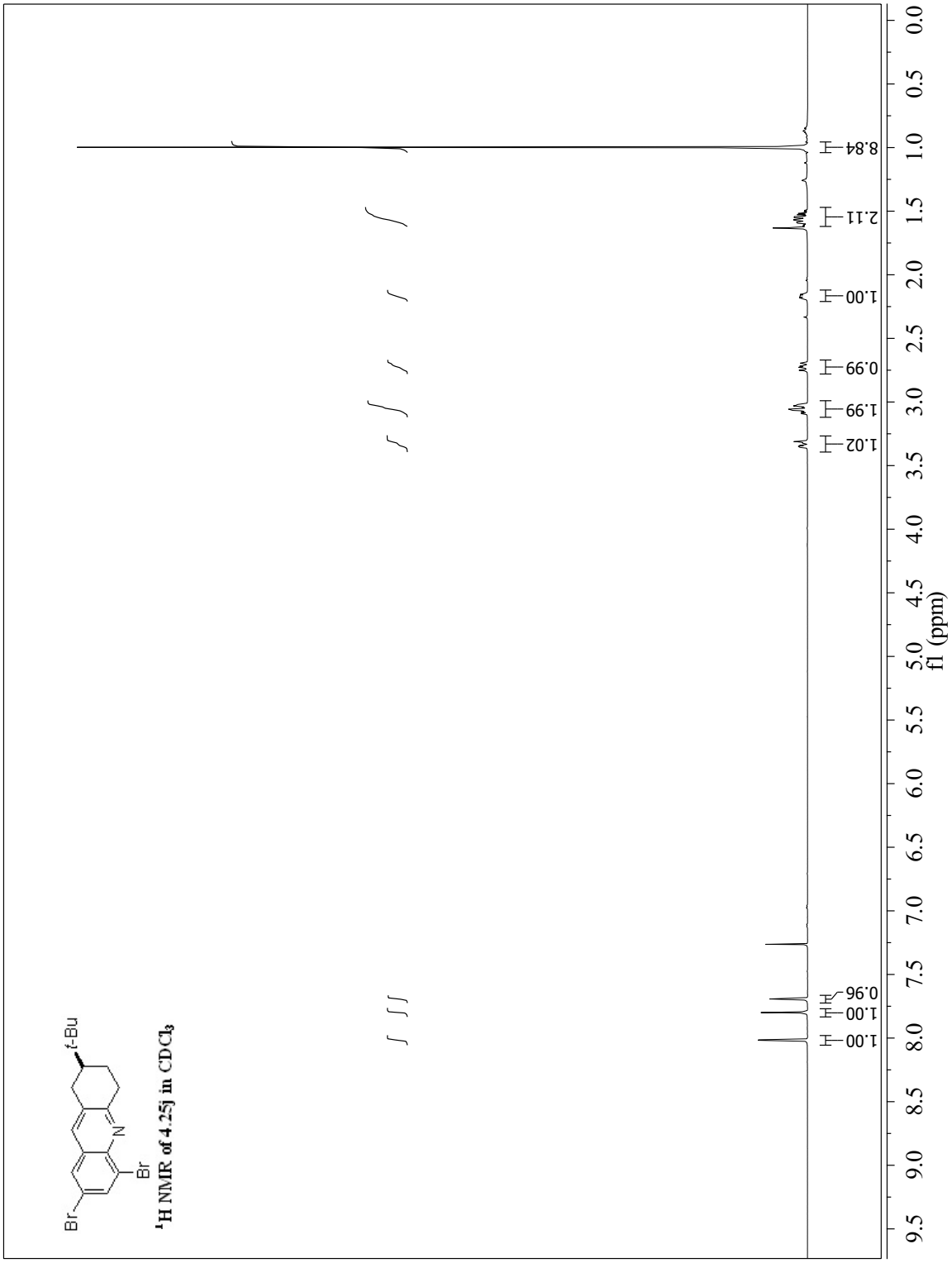


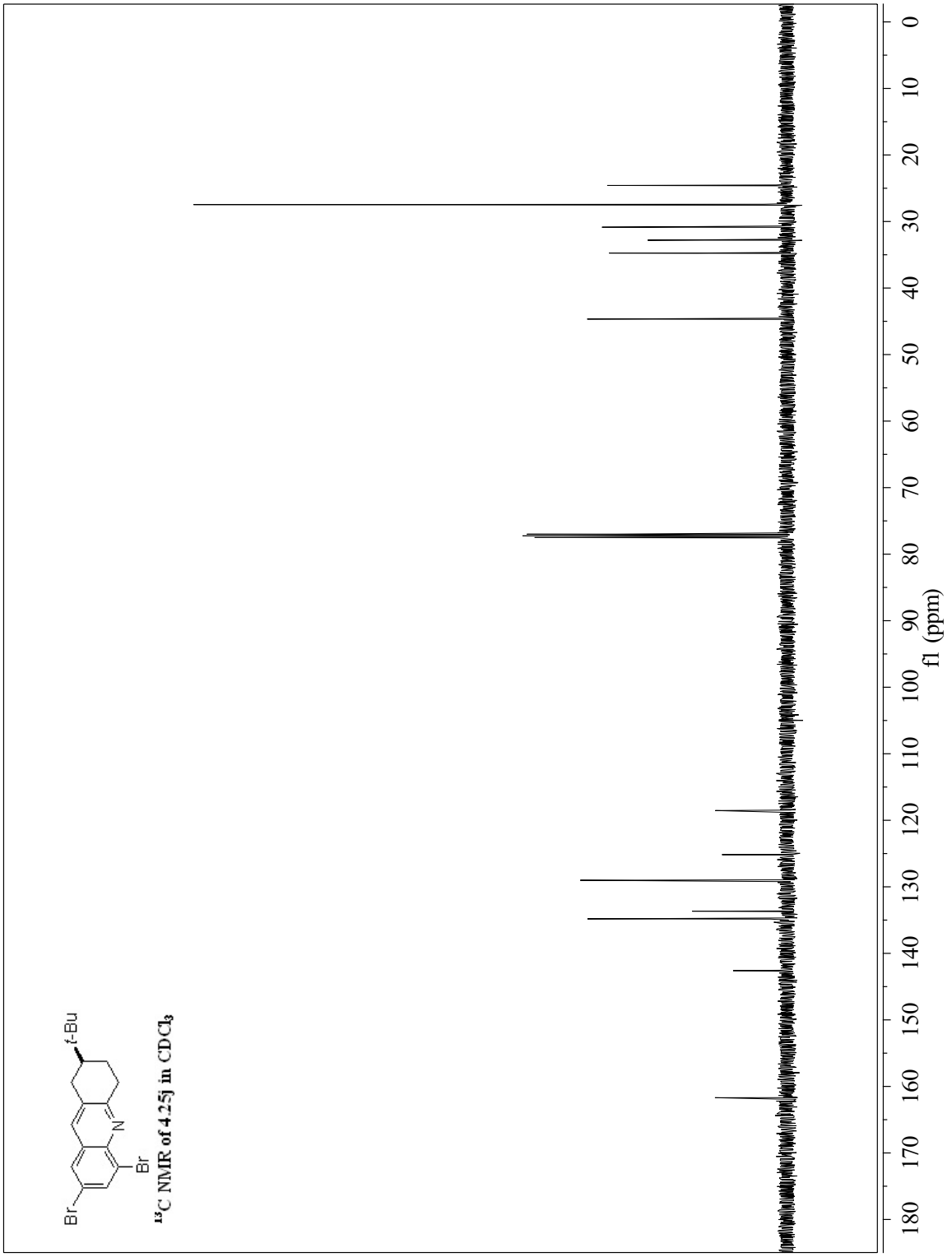
^{13}C NMR of 4.25h in $CDCl_3$

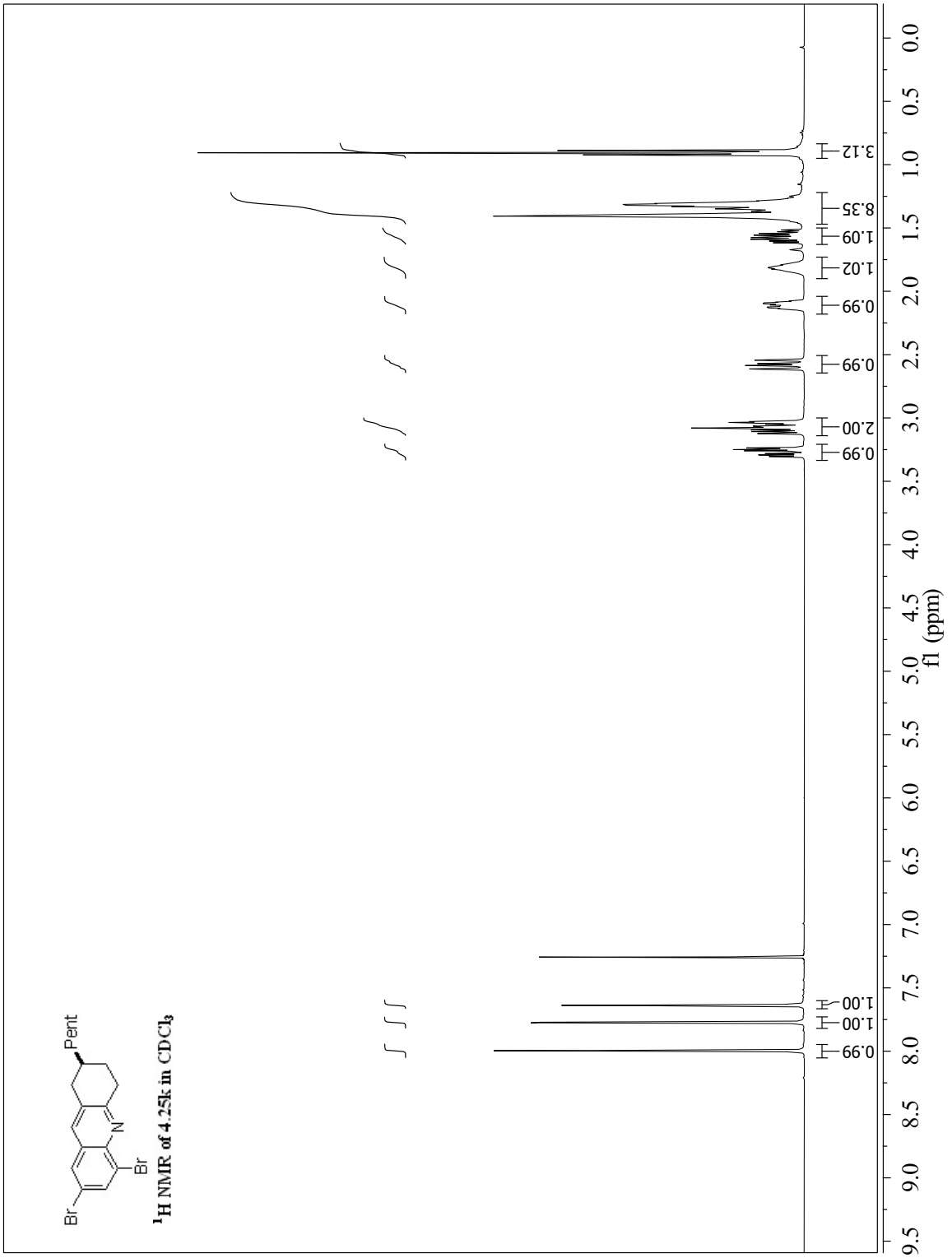


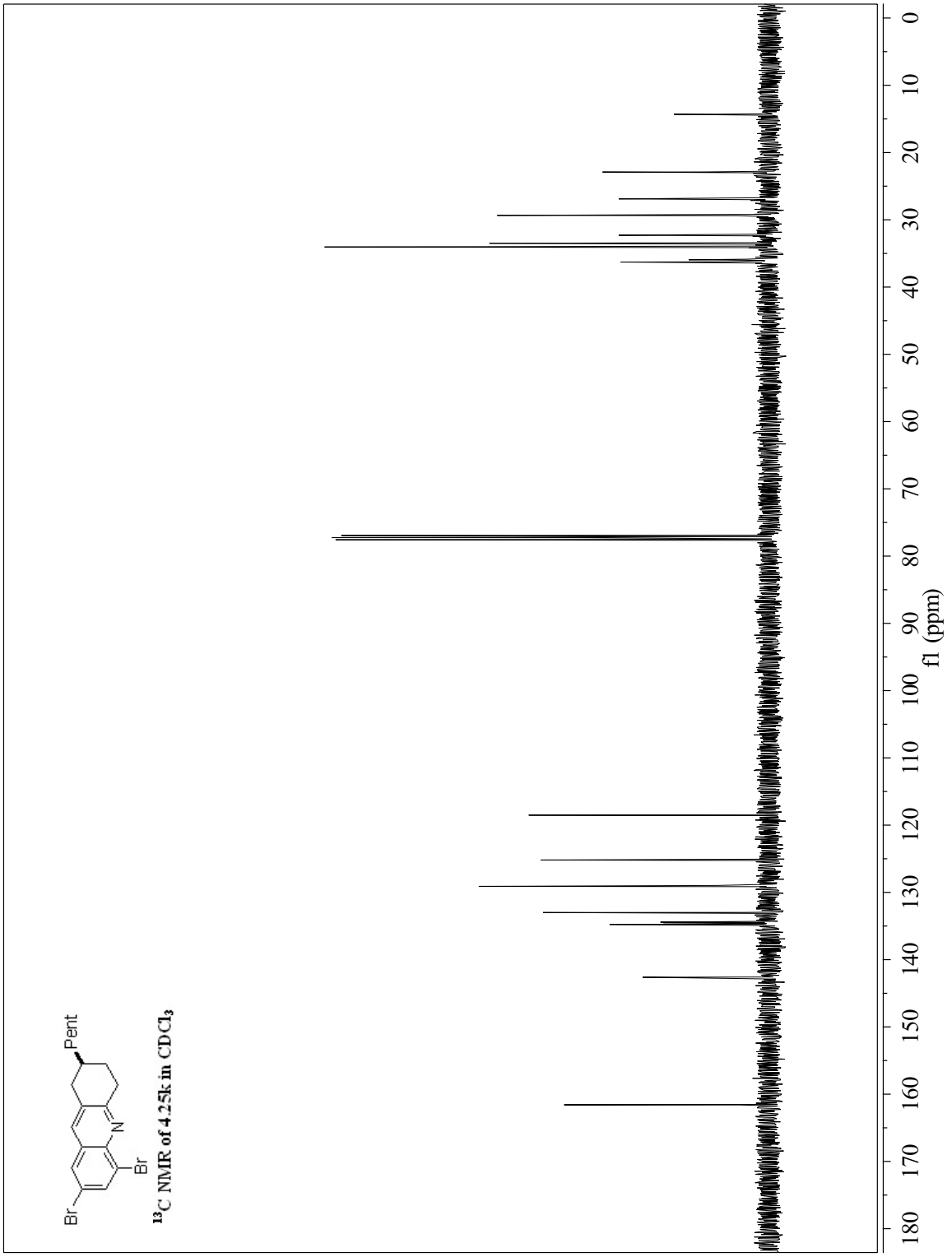
^{1}H NMR of 4.25i in $CDCl_3$

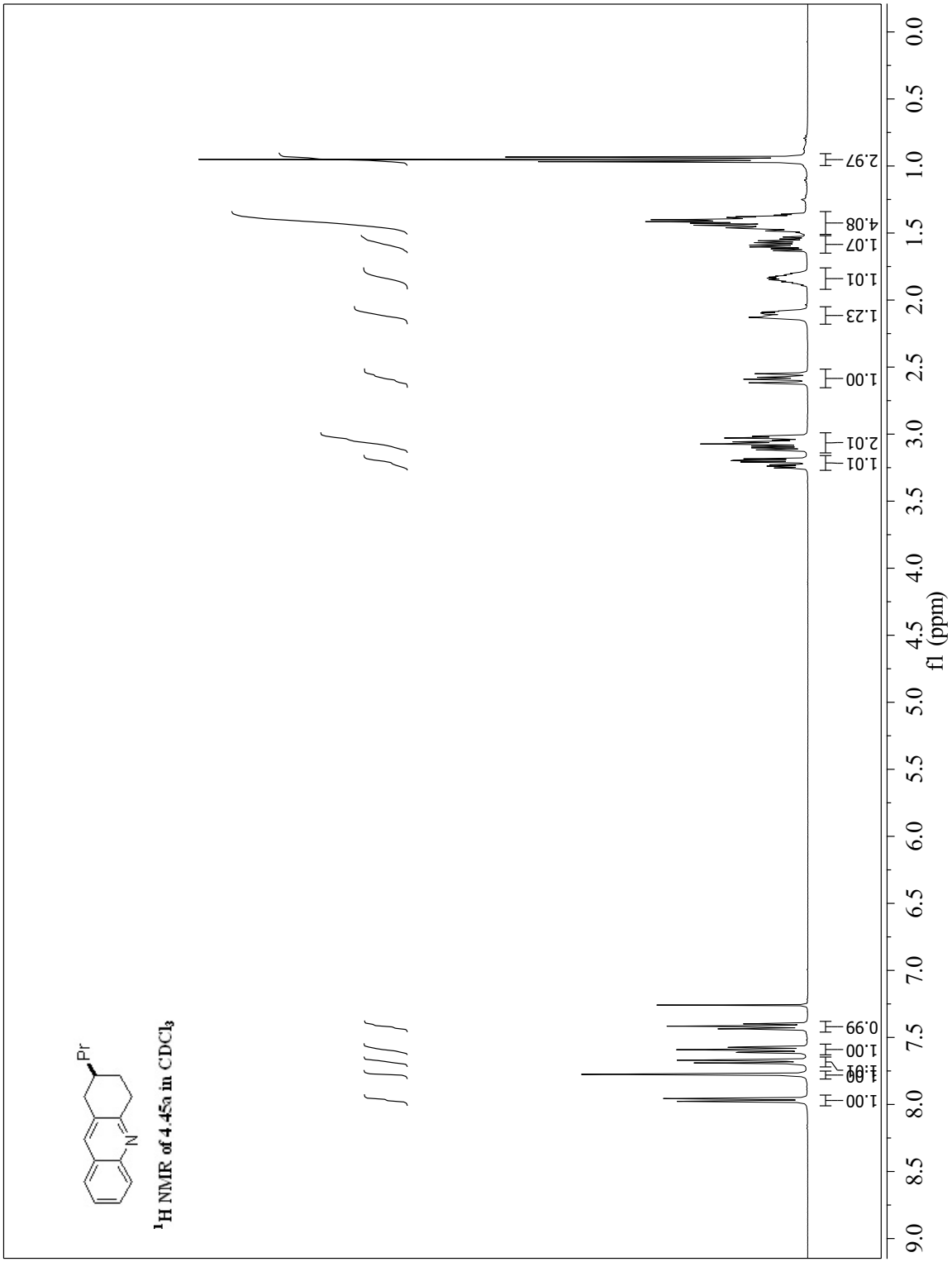

Pr
N
Br
Br
^{13}C NMR of 4.25i in $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

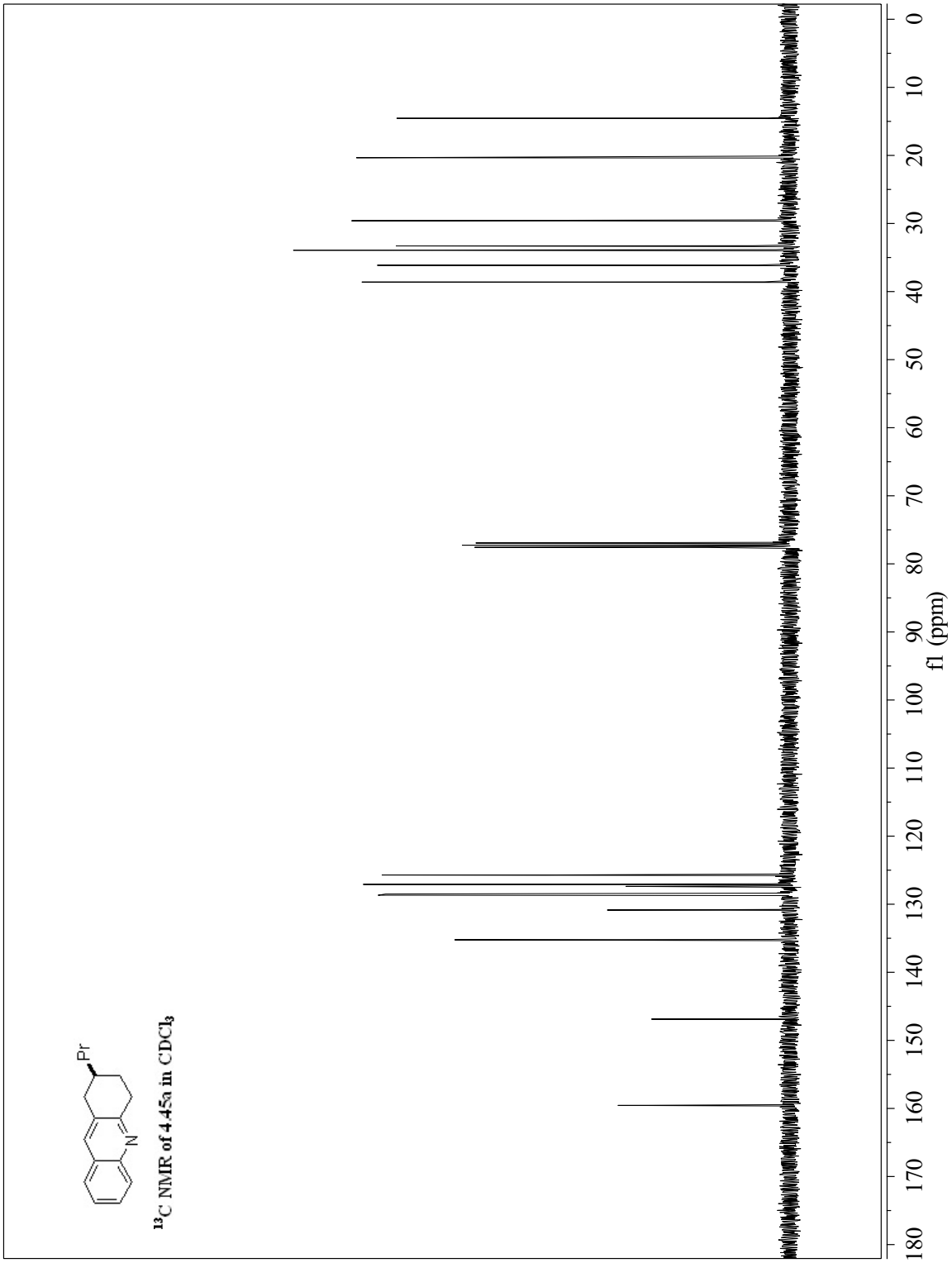

t-Bu
Br
N
Br
1H NMR of 4.25j in CDCl3
8.84
2.11
1.00
0.99
1.99
1.02
1.00
1.00
0.96
f1 (ppm)


t-Bu
Br
Br
N
^{13}C NMR of 4.25j in $CDCl_3$
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

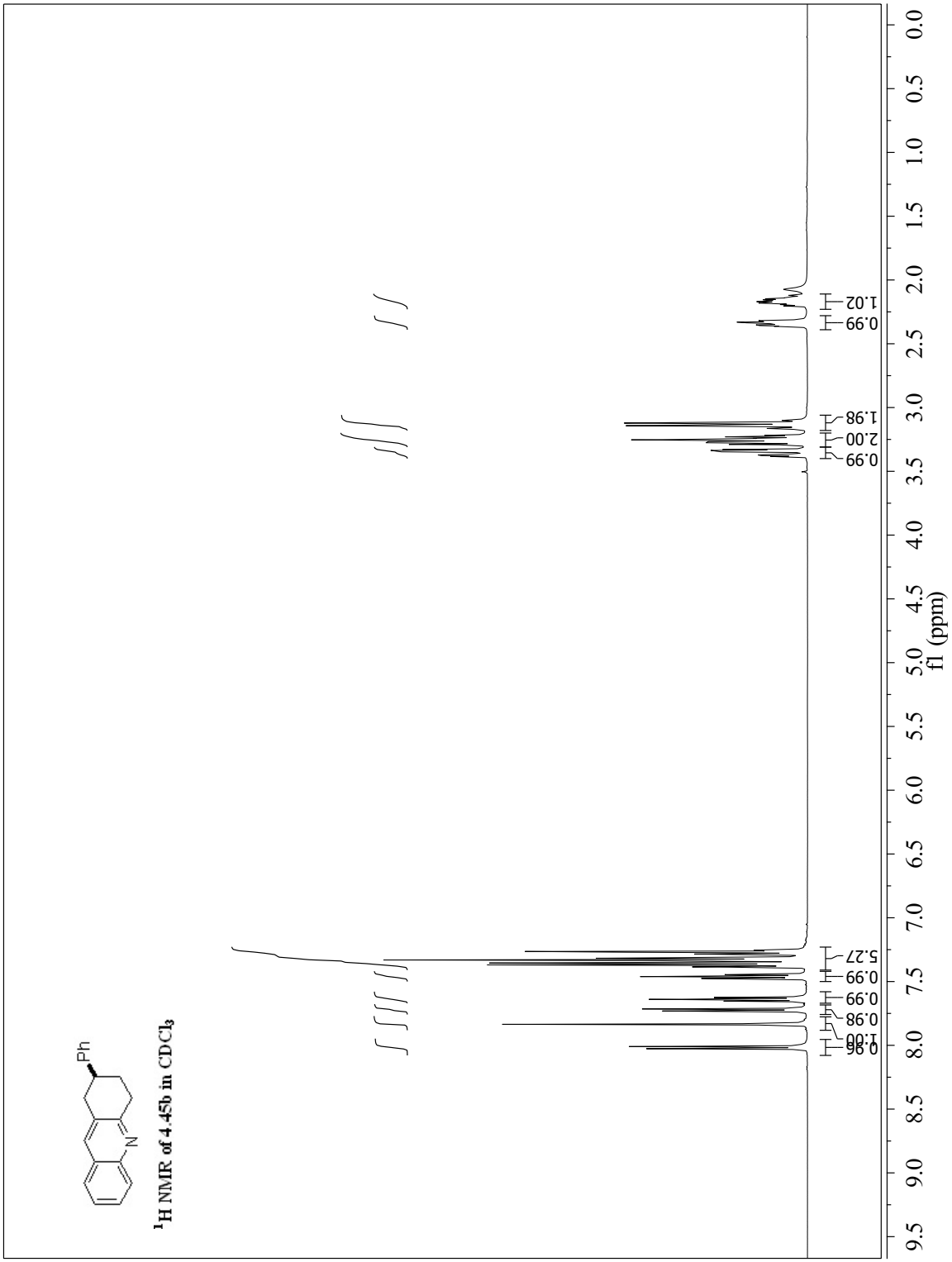

Pent
N
Br
Br
^{1}H NMR of 4.25k in $CDCl_3$
0.99
1.00
1.00
0.99
2.00
0.99
0.99
1.02
1.09
8.35
3.12
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
f1 (ppm)

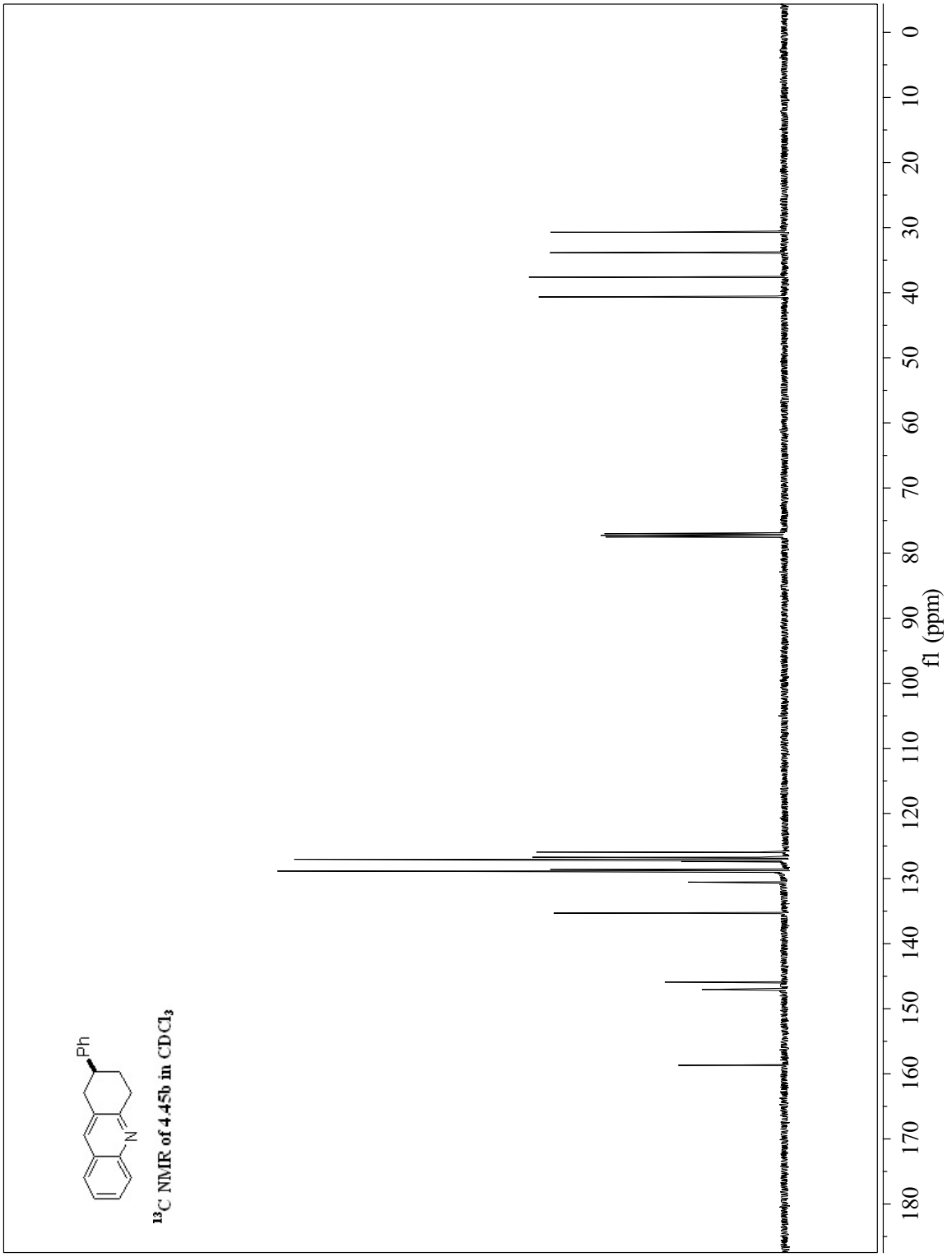

Pent
N
Br
Br
^{13}C NMR of 4.25k in $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

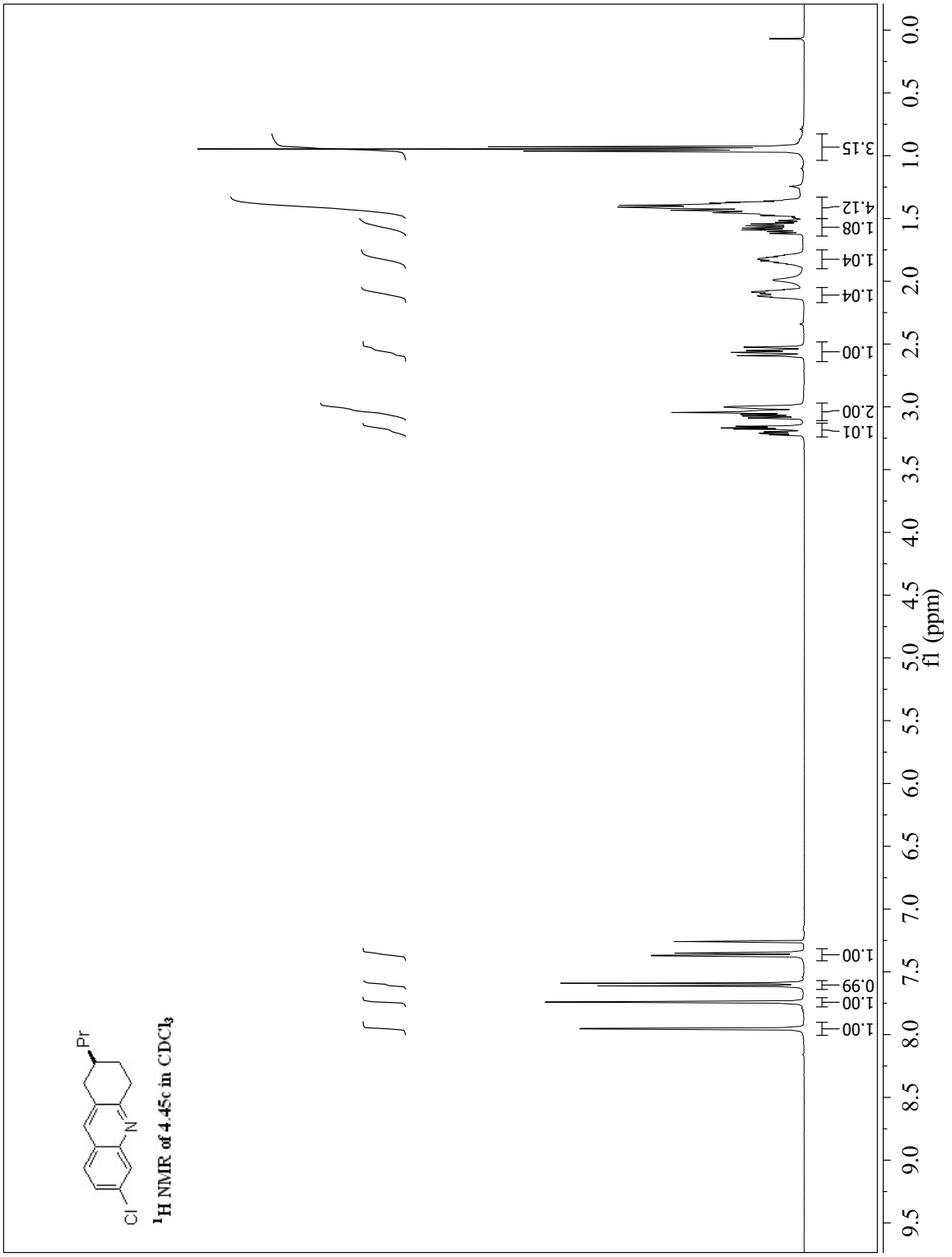

Pr
N
^{1}H NMR of 4.45a in $CDCl_3$
1.00
1.00
1.00
0.99
1.00
1.01
2.01
1.00
1.23
1.01
1.07
4.08
2.97
f1 (ppm)

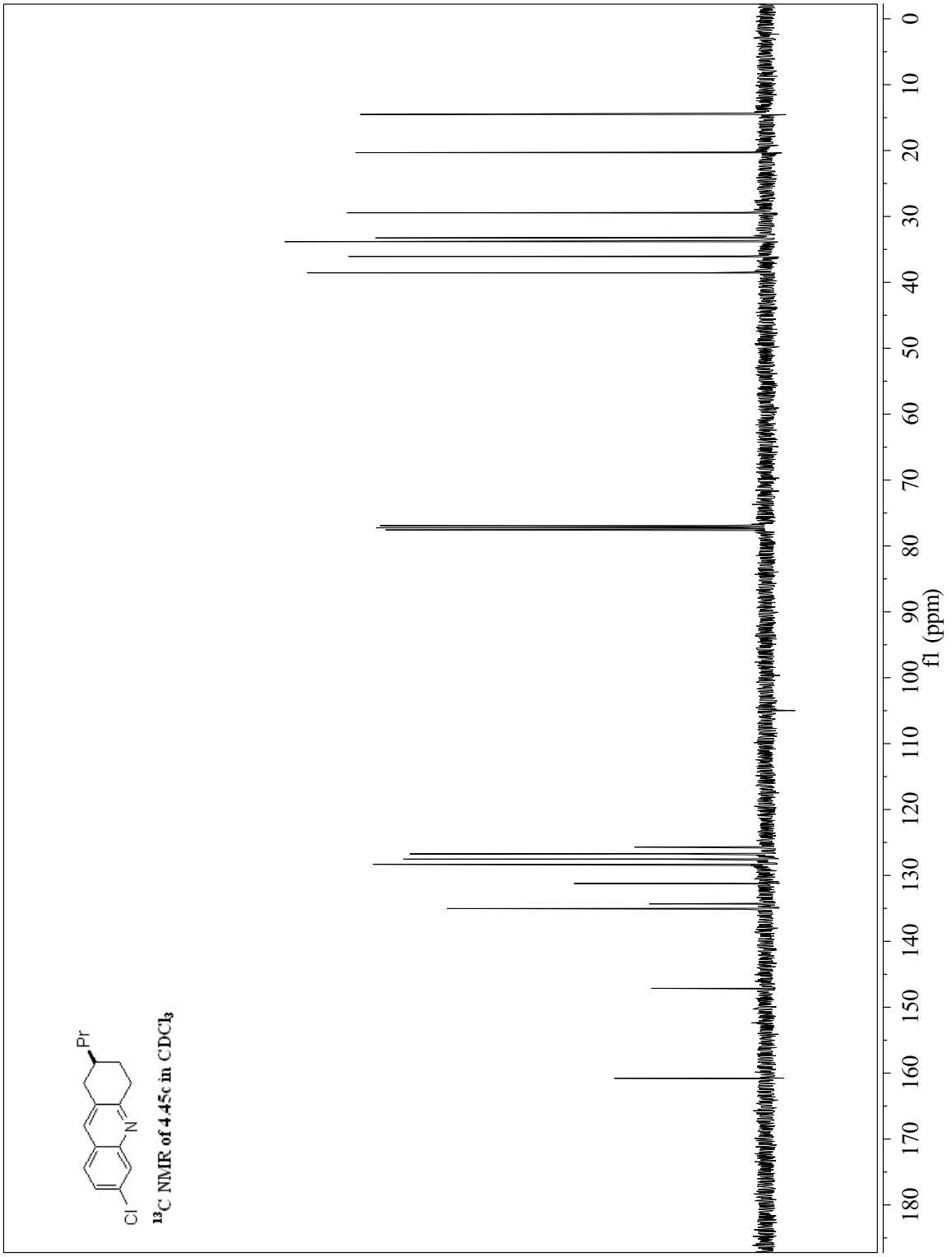


^{13}C NMR of 4.45a in $CDCl_3$

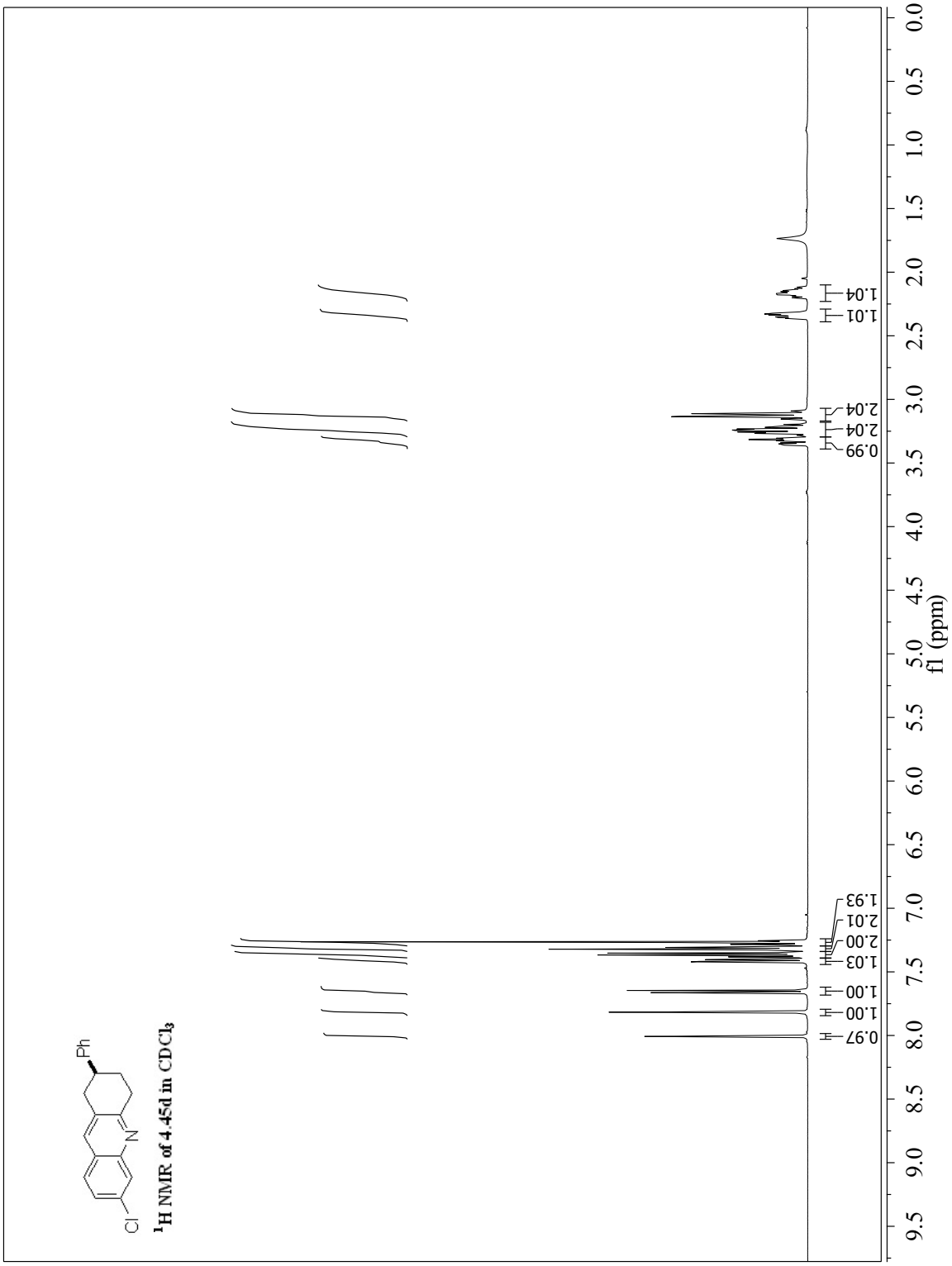

Ph
N
^{1}H NMR of 4.45b in $CDCl_3$
0.96
1.00
0.98
0.99
0.99
5.27
0.99
2.00
1.98
0.99
1.02
f1 (ppm)

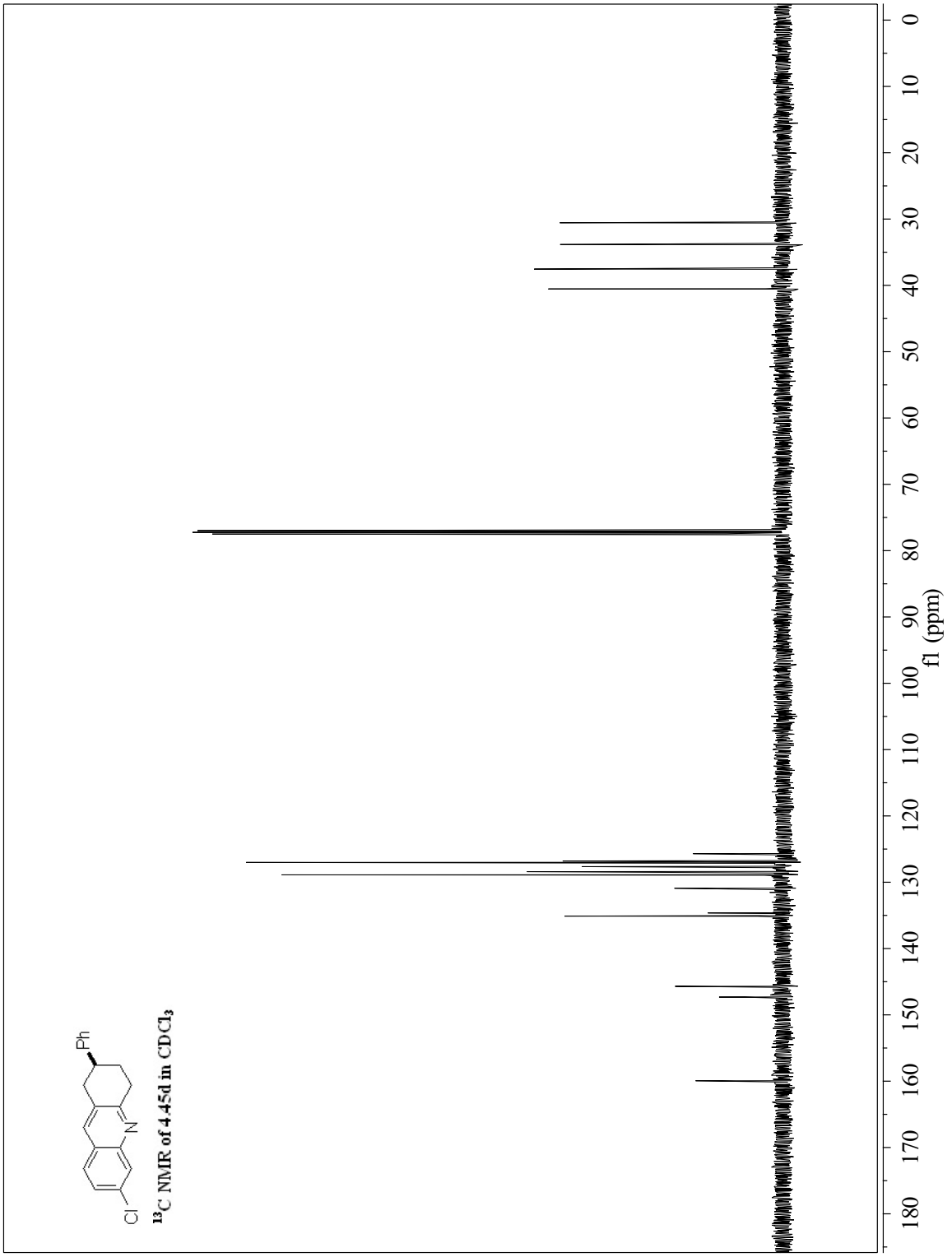

Ph
N
^{13}C NMR of 4.45b in $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)


Pr
N
Cl
^{1}H NMR of 4.45c in $CDCl_3$
1.00
0.99
1.00
1.00
1.00
2.00
1.01
1.04
1.04
1.08
4.12
3.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

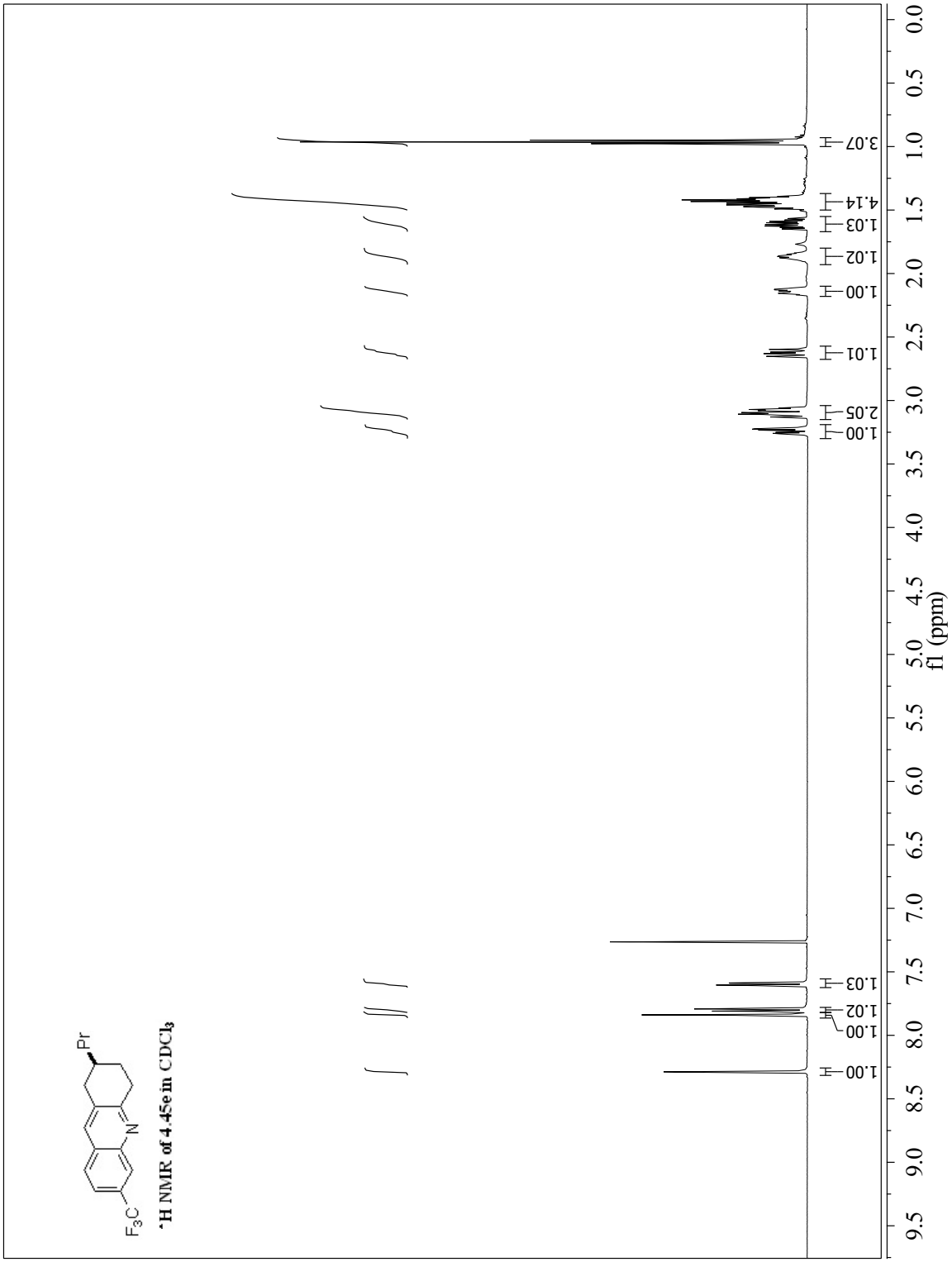


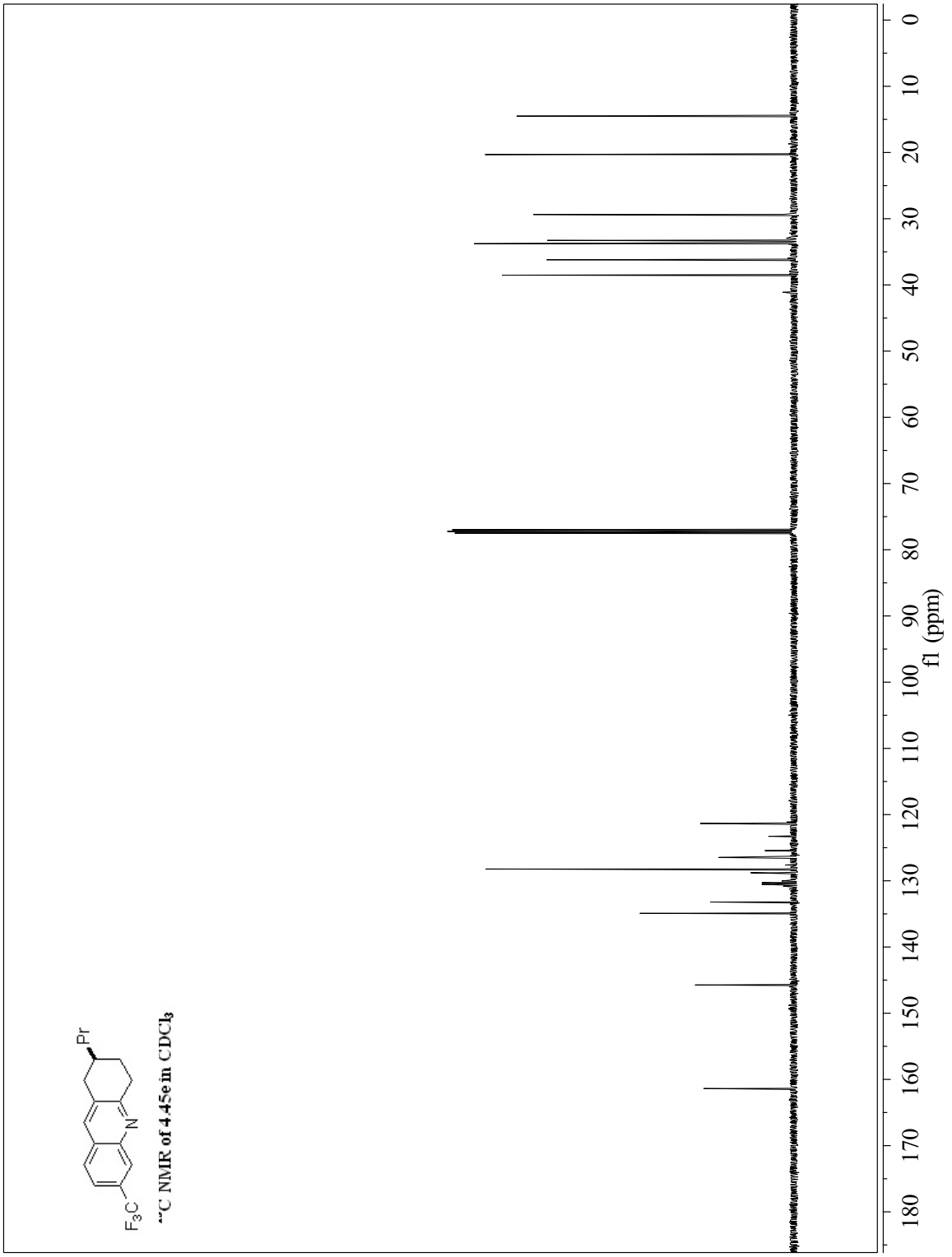
^{13}C NMR of 4.45c in $CDCl_3$

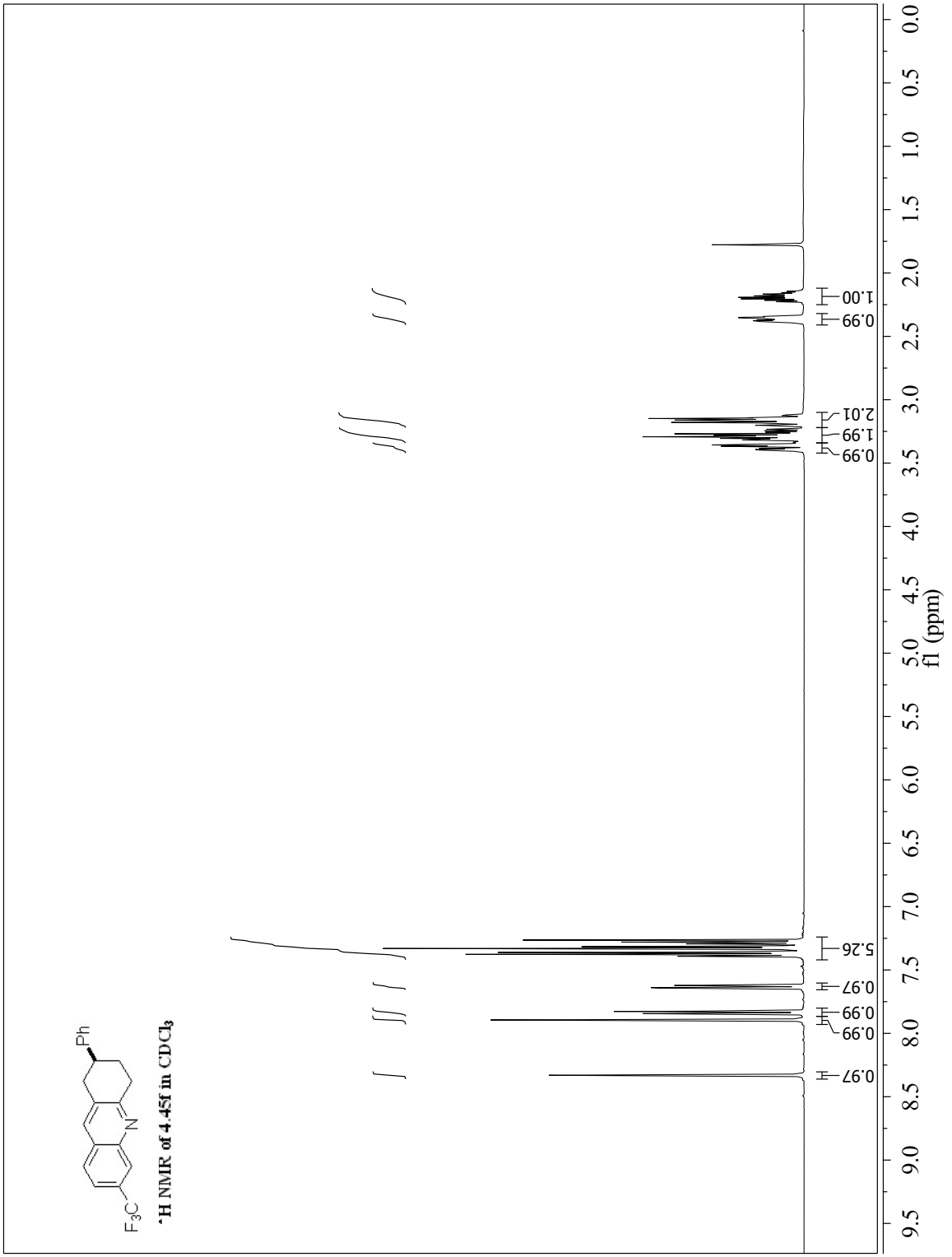

Ph
N
Cl
^{1}H NMR of 4.45d in $CDCl_3$
0.97
1.00
1.00
1.03
2.00
2.01
1.93
0.99
2.04
2.04
1.01
1.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



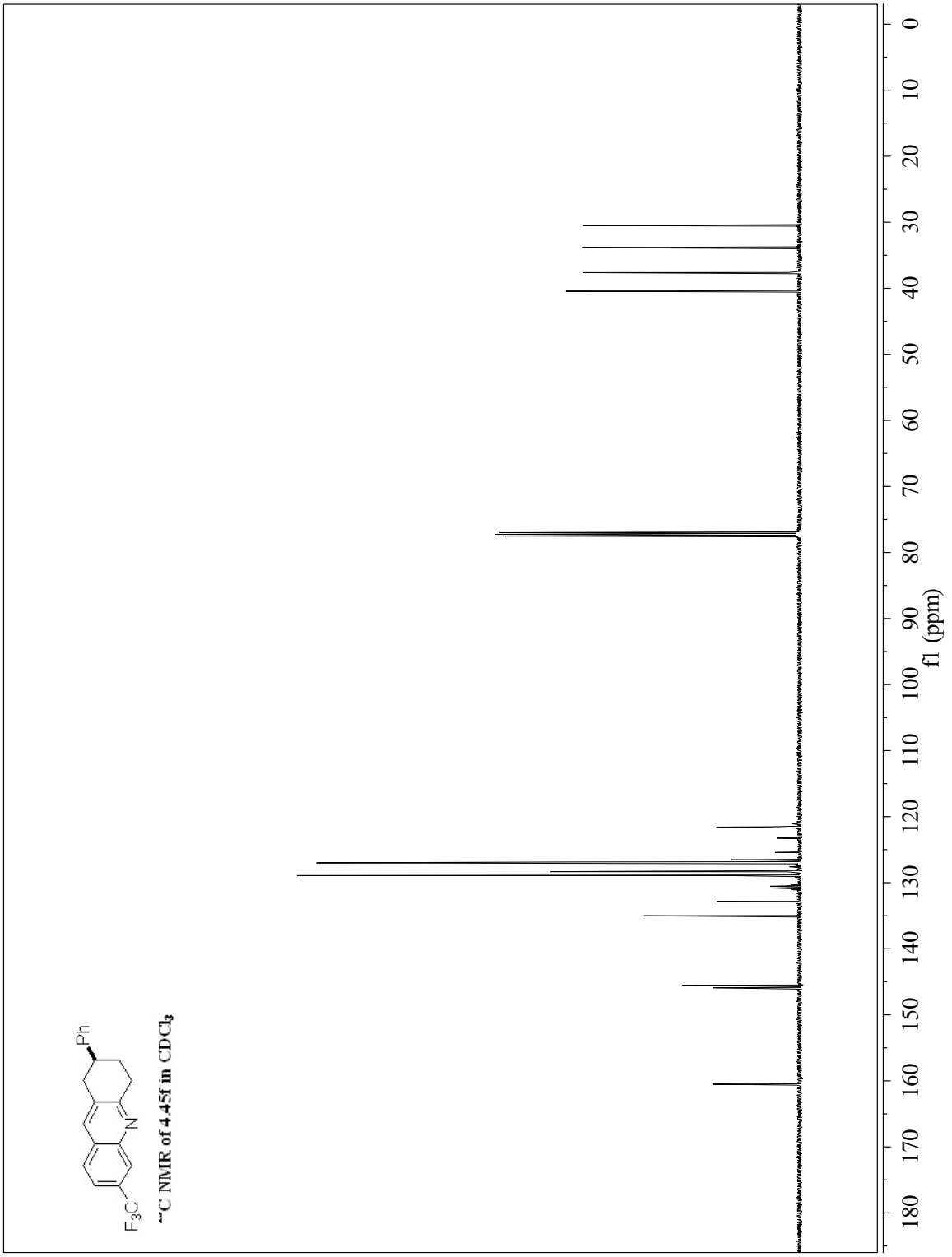
^{13}C NMR of 4.45d in $CDCl_3$

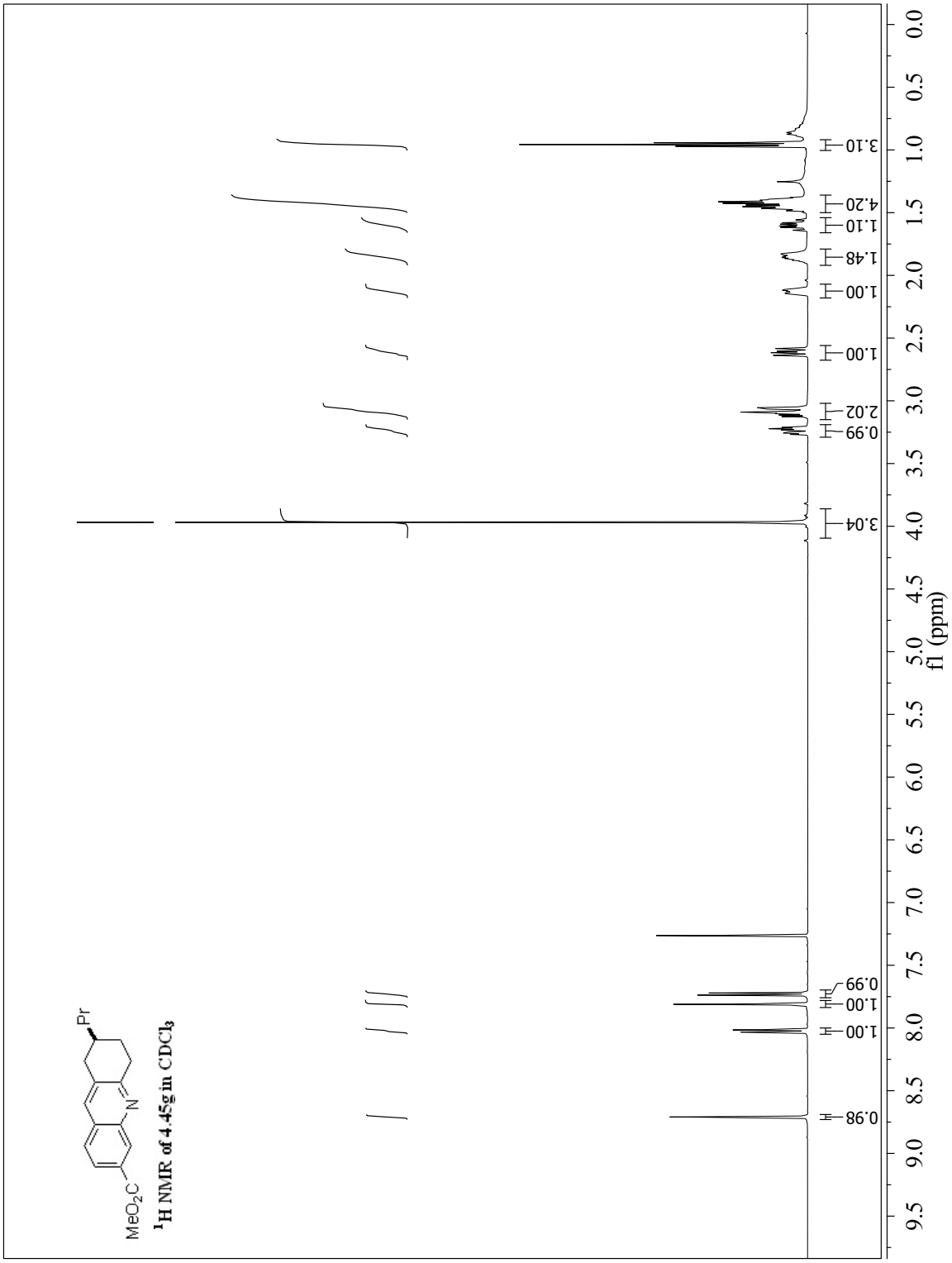

Pr
F3C
N
^{1}H NMR of 4.45e in $CDCl_3$
1.00
1.00
1.02
1.03
3.07
4.14
1.03
1.02
1.00
1.01
2.05
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

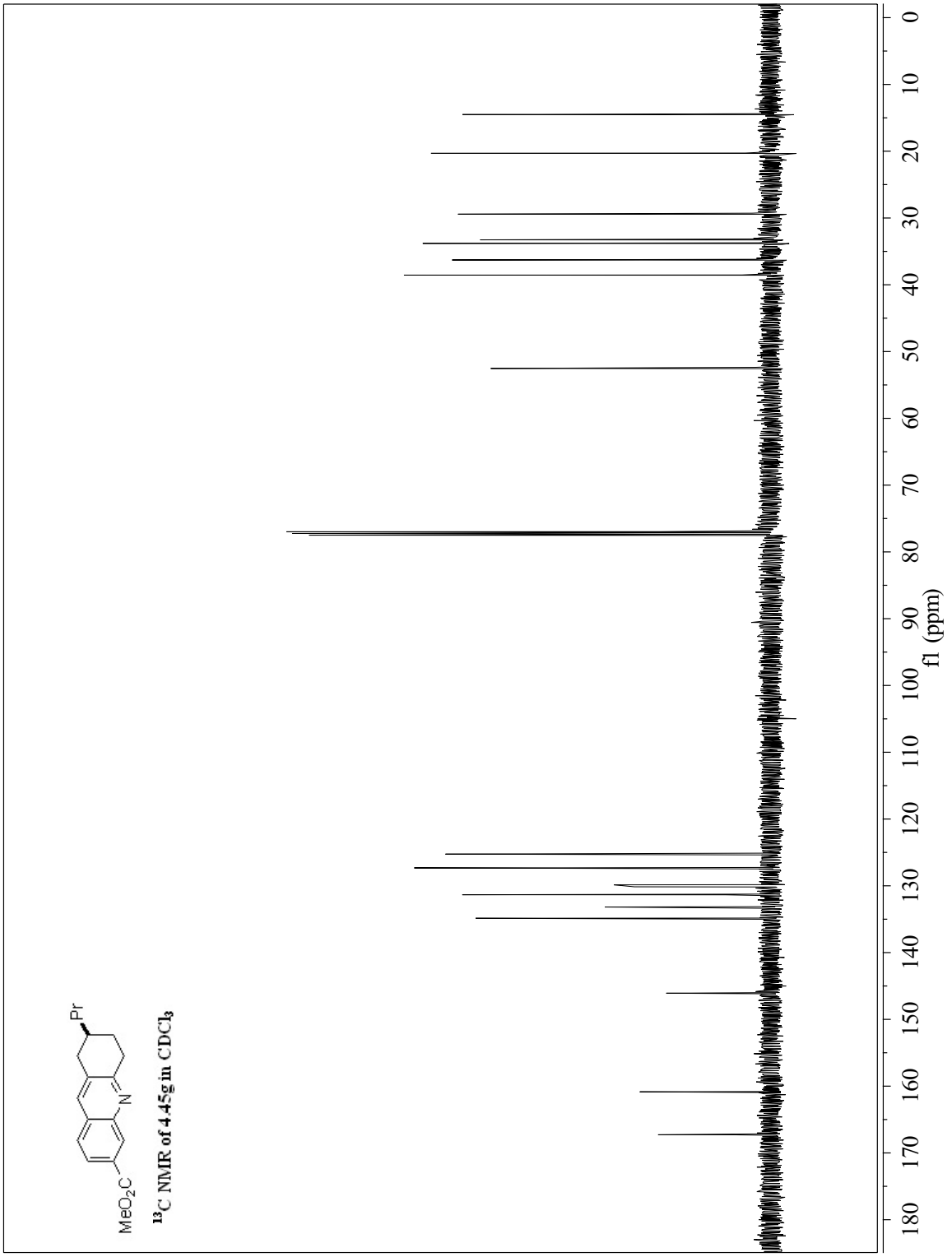

Pr
F3C
N
13C NMR of 4.45e in CDCl3
f1 (ppm)

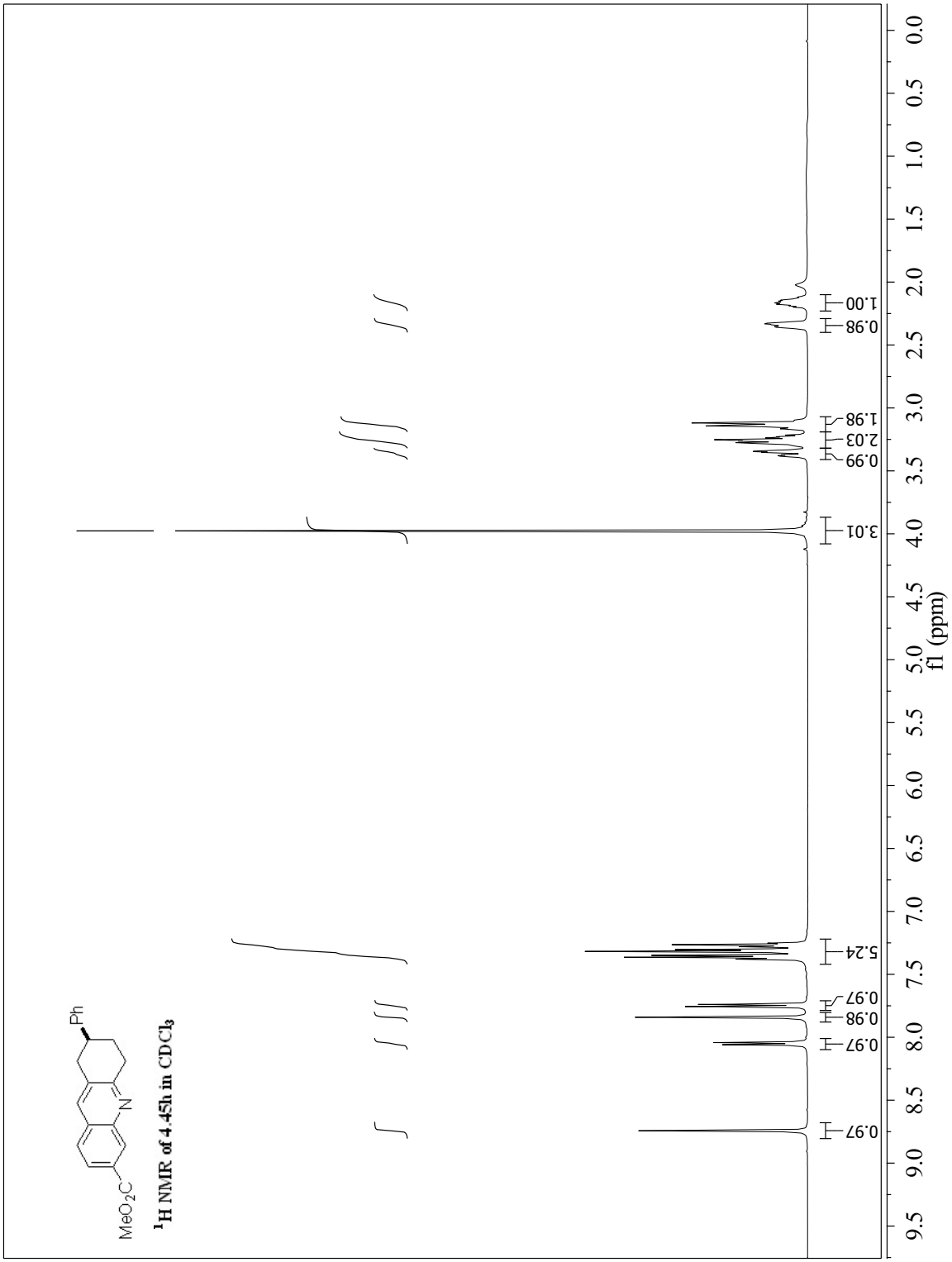


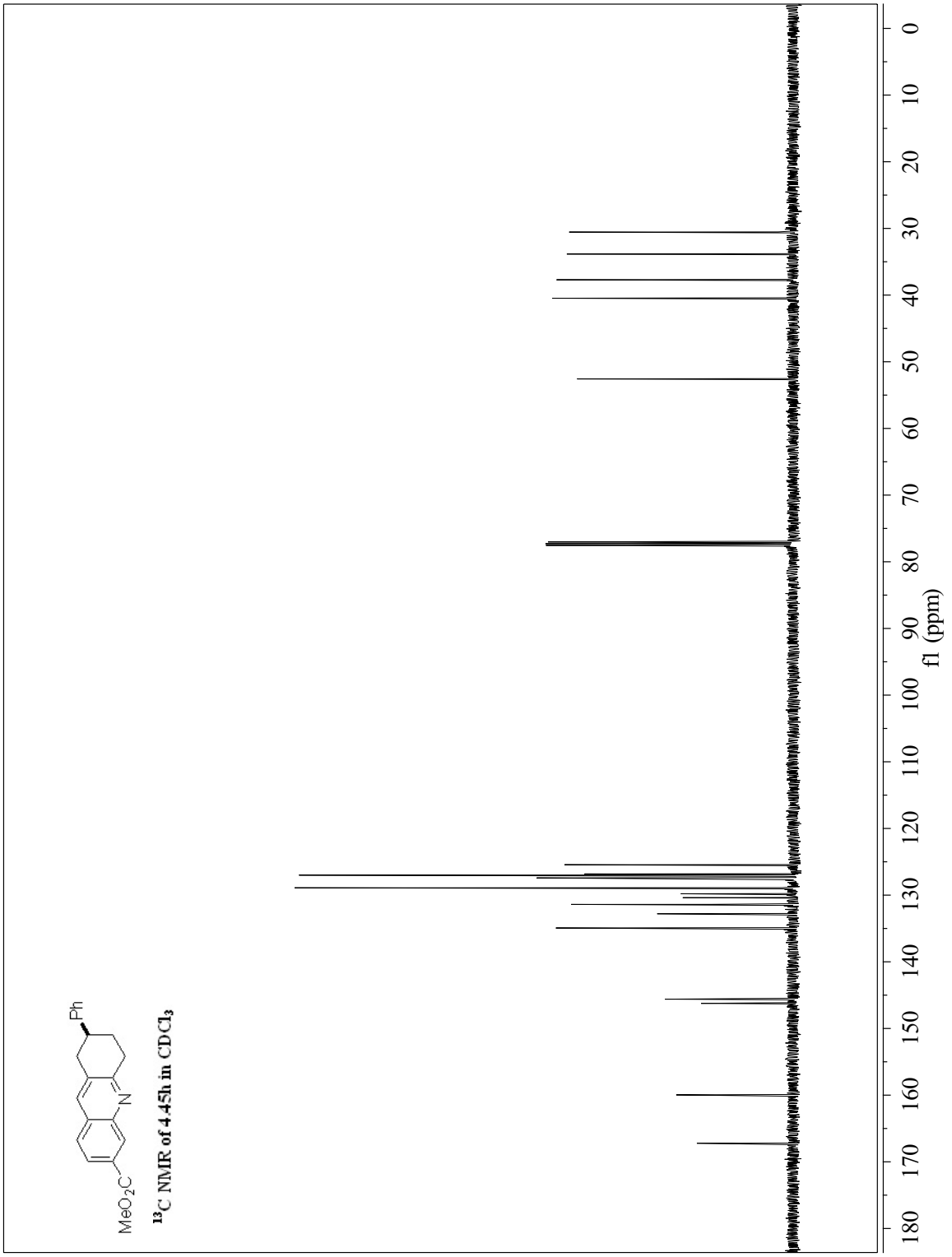
^{1}H NMR of 4.45f in $CDCl_3$

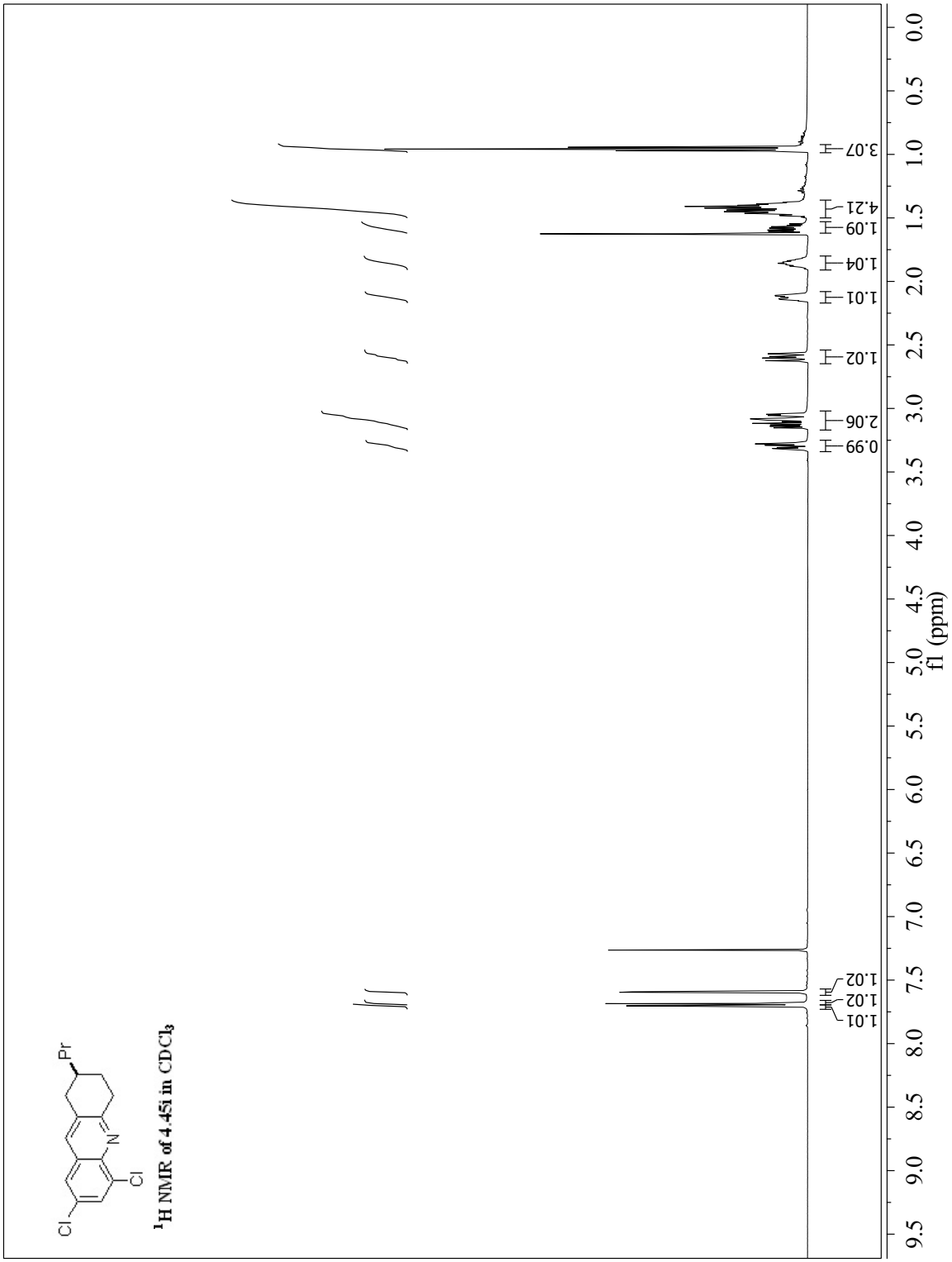

Ph
F3C
N
13C NMR of 4.45f in CDCl3
f1 (ppm)

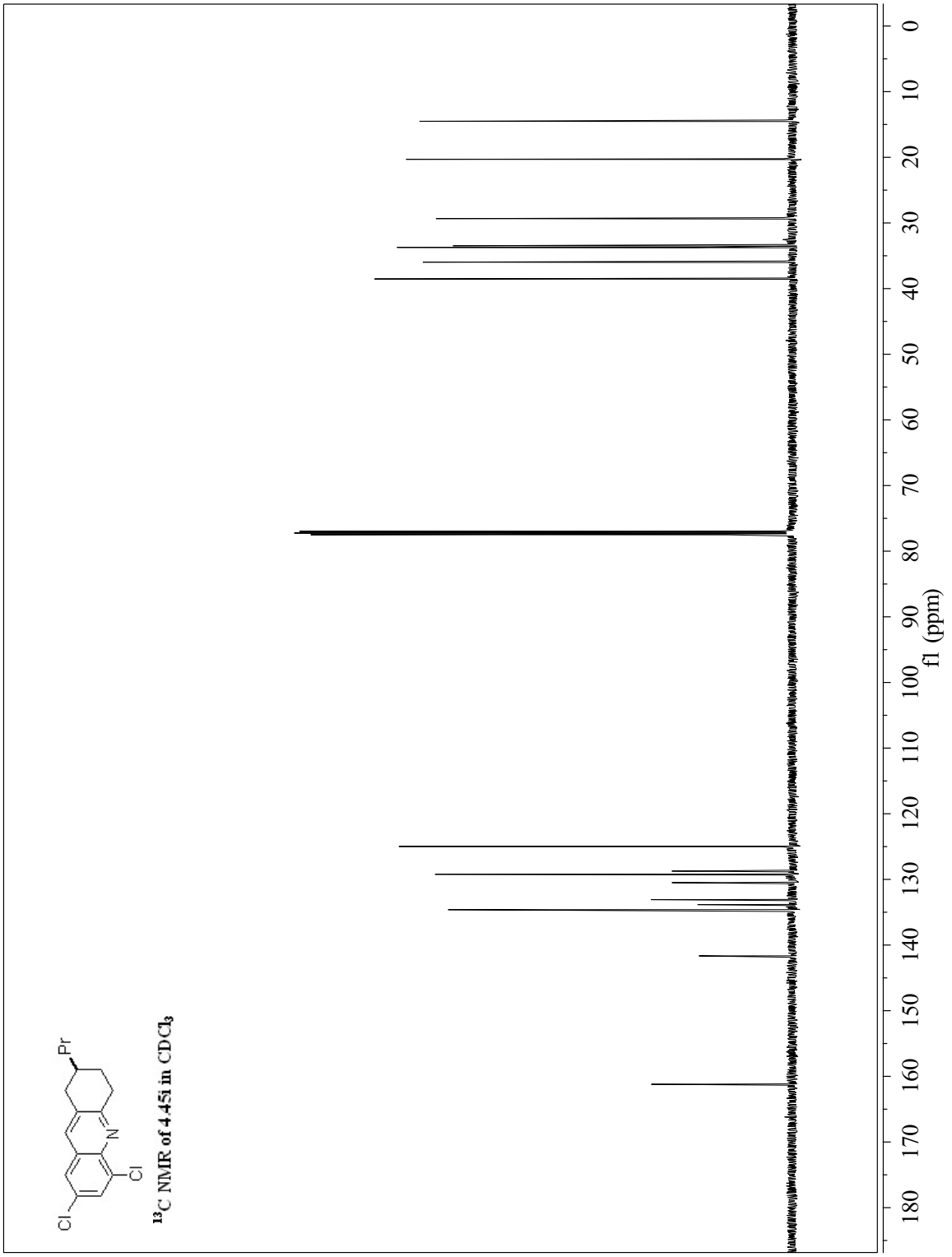

Pr
MeO2C
N
1H NMR of 4.45g in CDCl3
0.98
1.00
1.00
0.99
3.04
0.99
2.02
1.00
1.00
1.48
1.10
4.20
3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

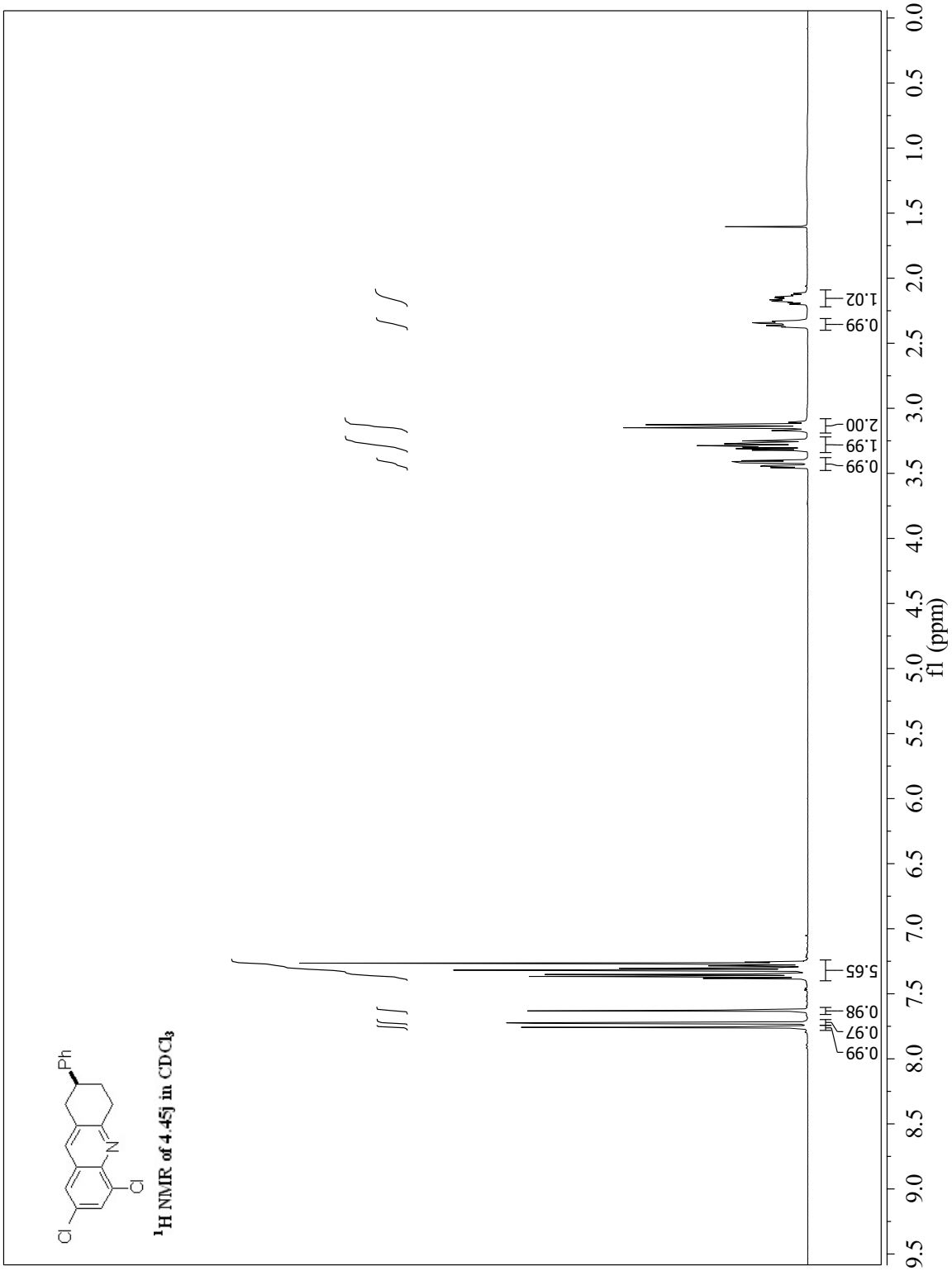

Pr
N
MeO2C
13C NMR of 4.45g in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)


Ph
N
MeO2C
1H NMR of 4.45h in CDCl3
0.97
0.98
0.97
0.97
5.24
3.01
0.99
2.03
1.98
0.98
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

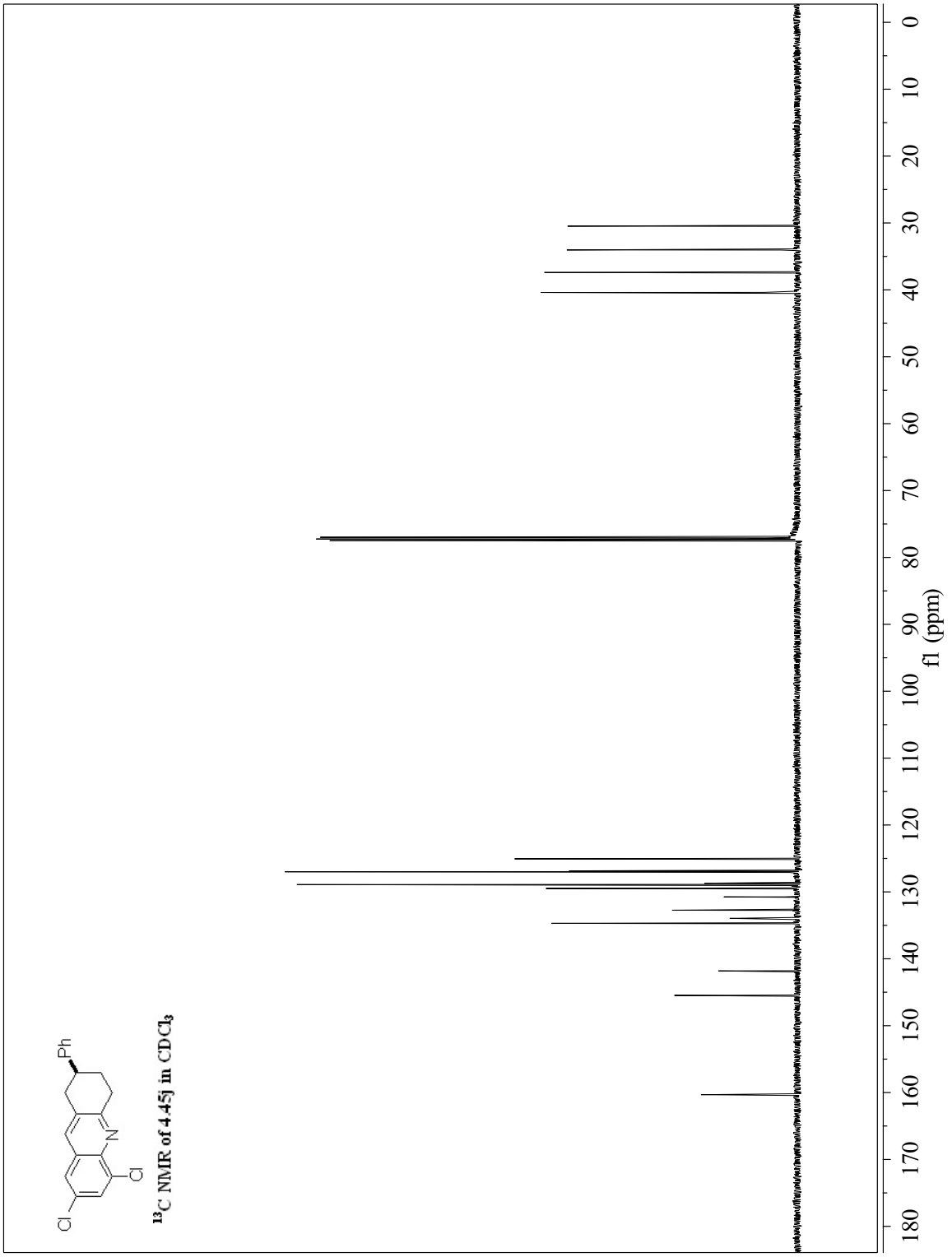

Ph
N
MeO2C
13C NMR of 4.45h in CDCl3
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Pr
N
Cl
Cl
^{1}H NMR of 4.45i in $CDCl_3$
3.07
4.21
1.09
1.04
1.01
1.02
2.06
0.99
1.01
1.02
1.02
f1 (ppm)

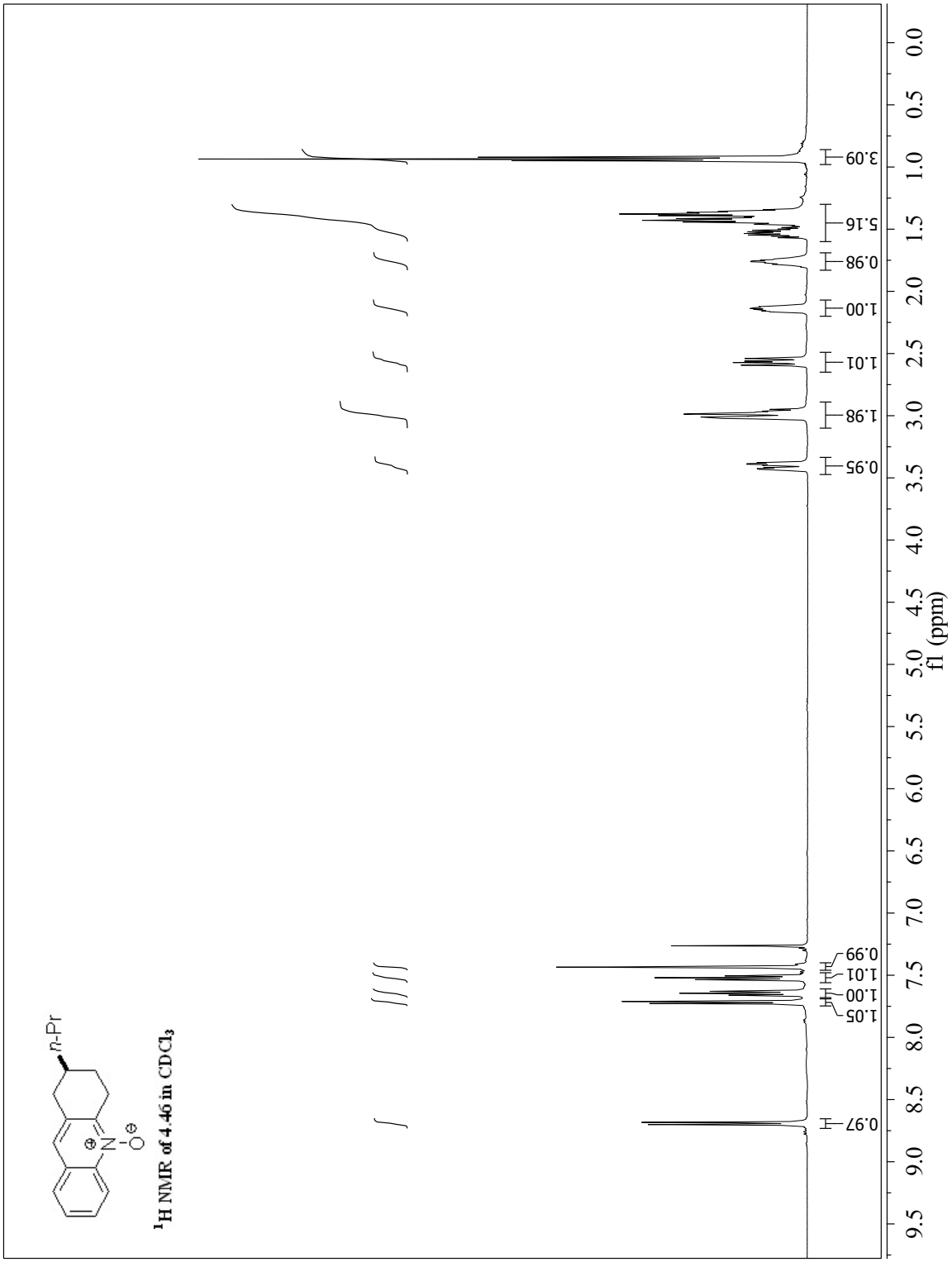

Pr
N
Cl
Cl
^{13}C NMR of 4.45i in $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

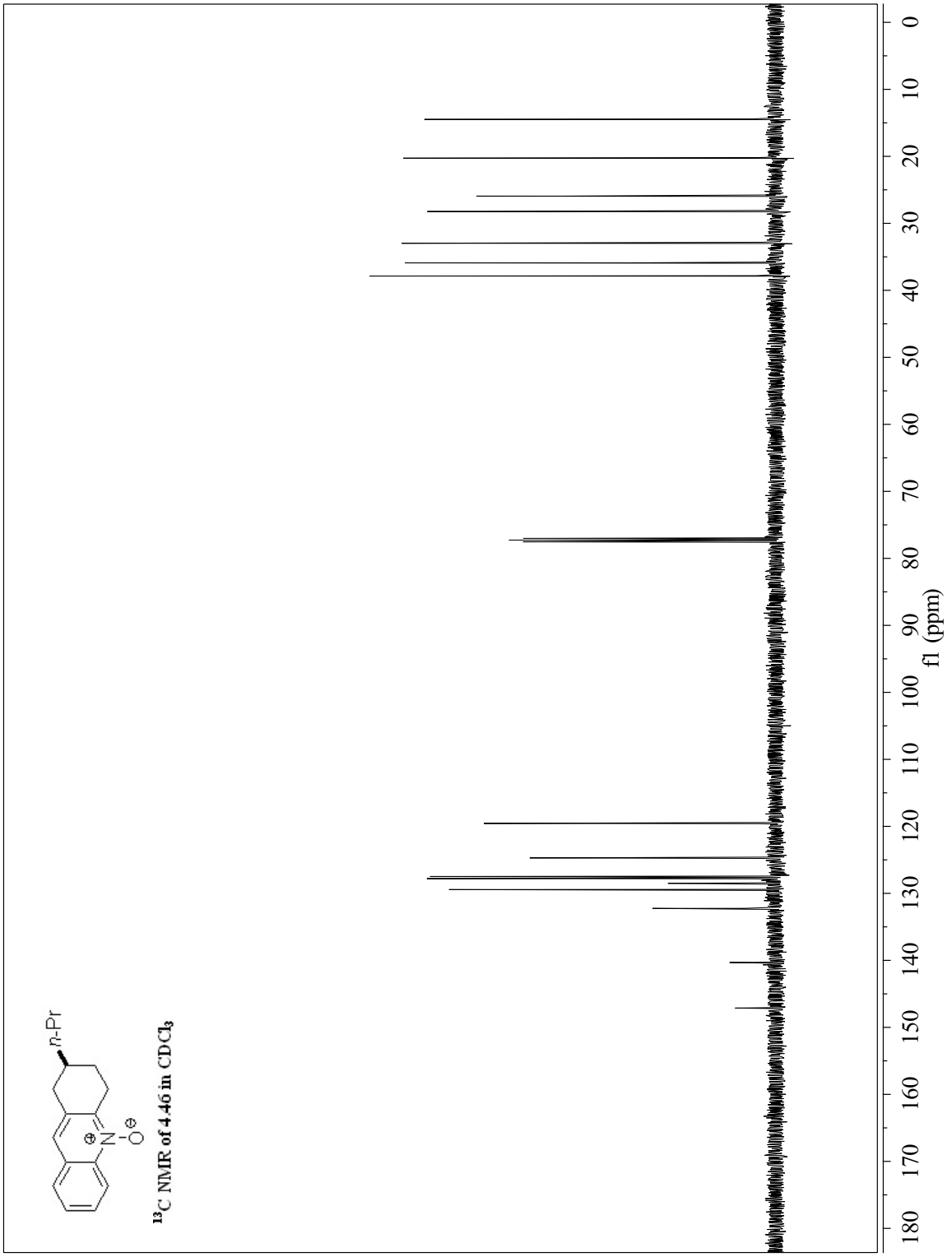


^{1}H NMR of 4.45j in $CDCl_3$

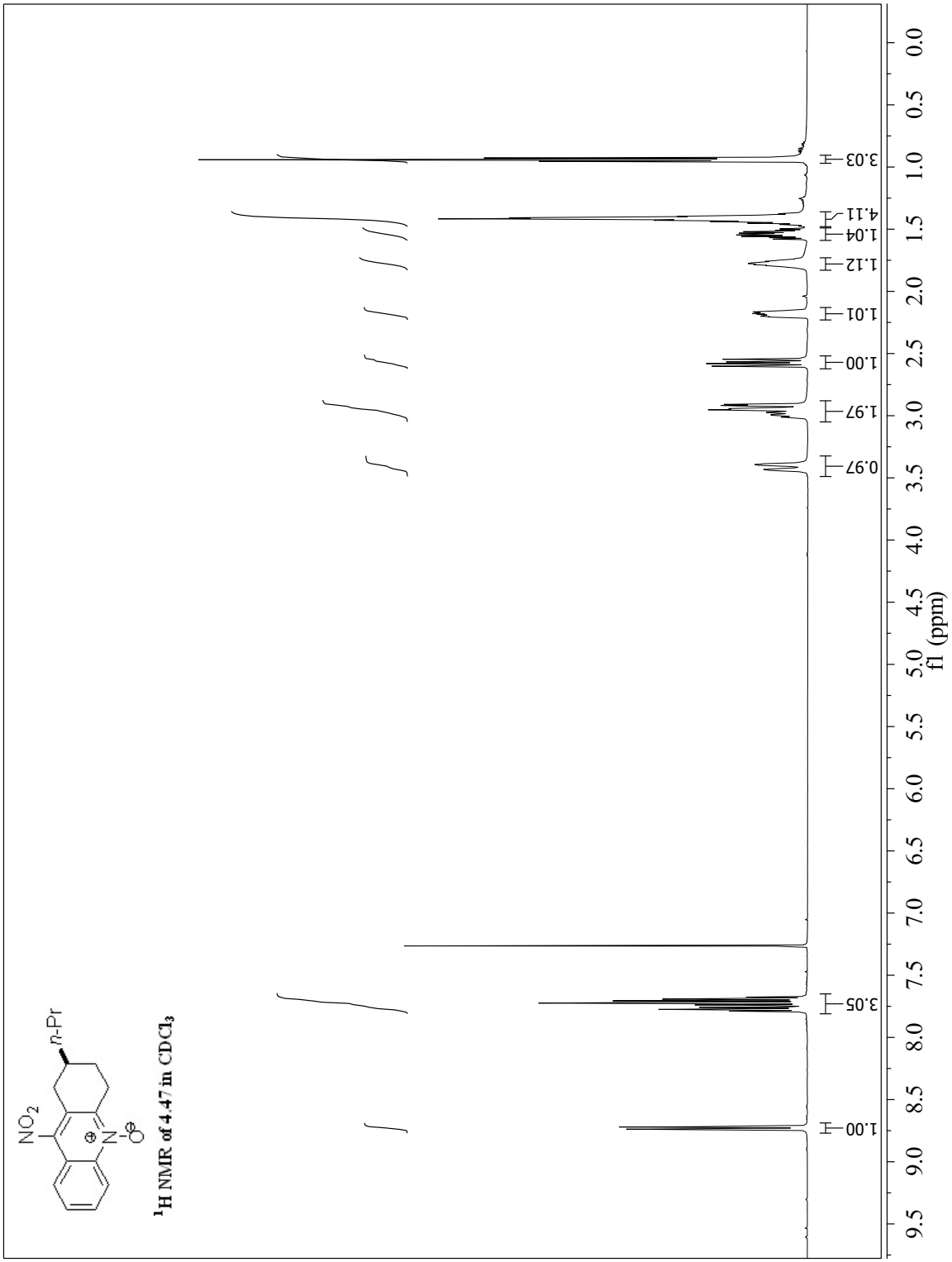


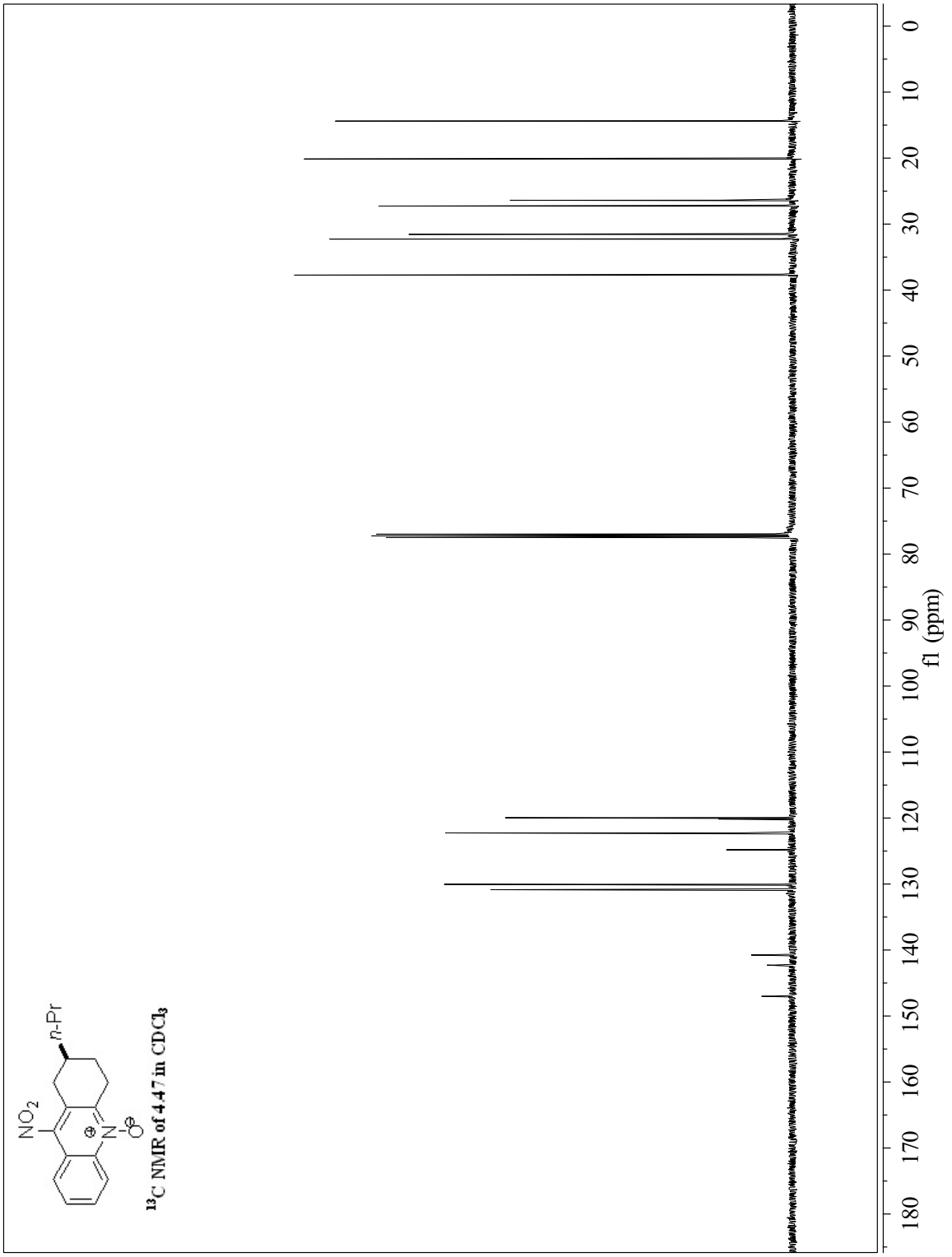
^{13}C NMR of 4.45j in $CDCl_3$


n-Pr
⊕
N
O
⊖
¹H NMR of 4.46 in CDCl₃
0.97
1.05
1.00
1.01
0.99
3.09
5.16
0.98
1.00
1.01
1.98
0.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

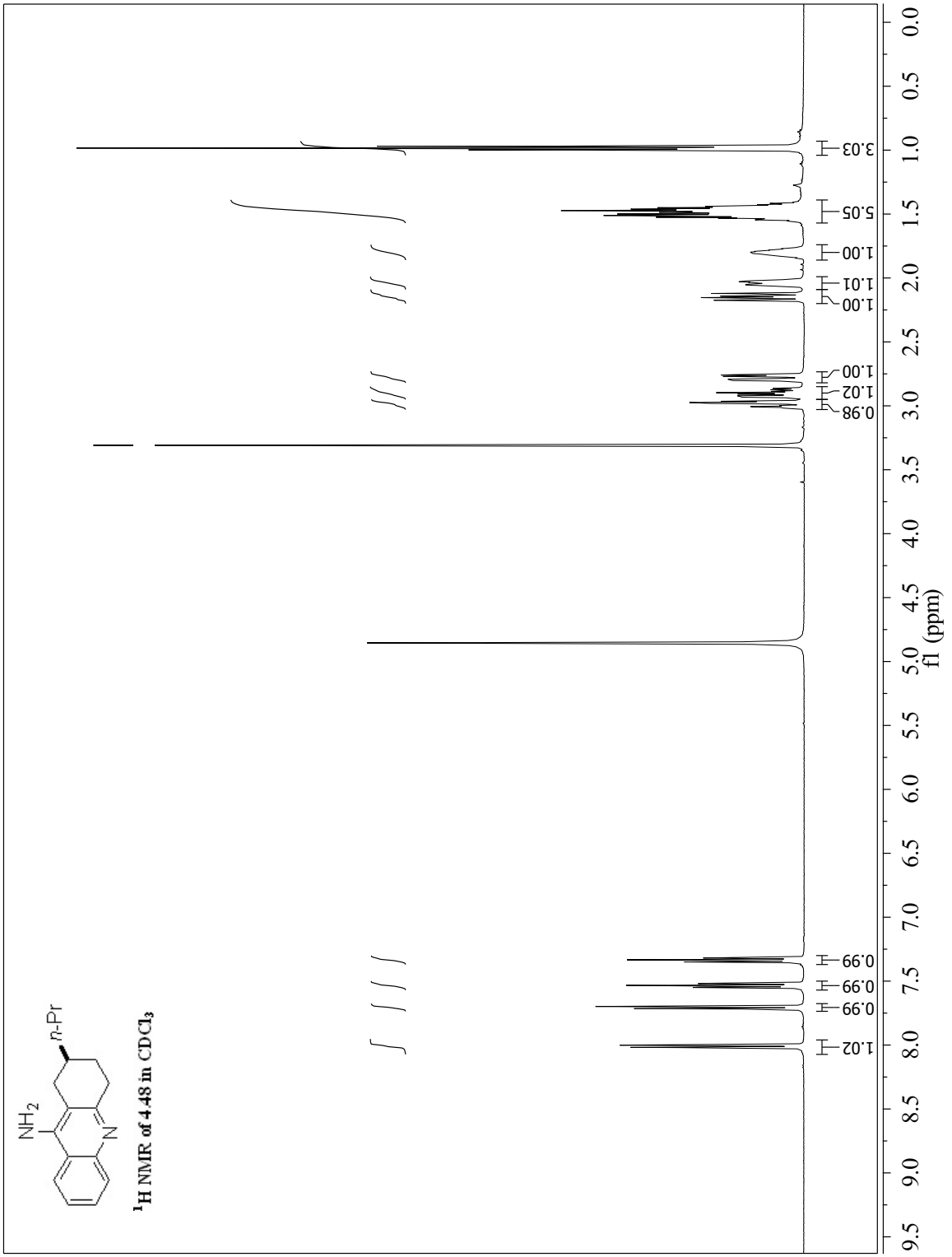


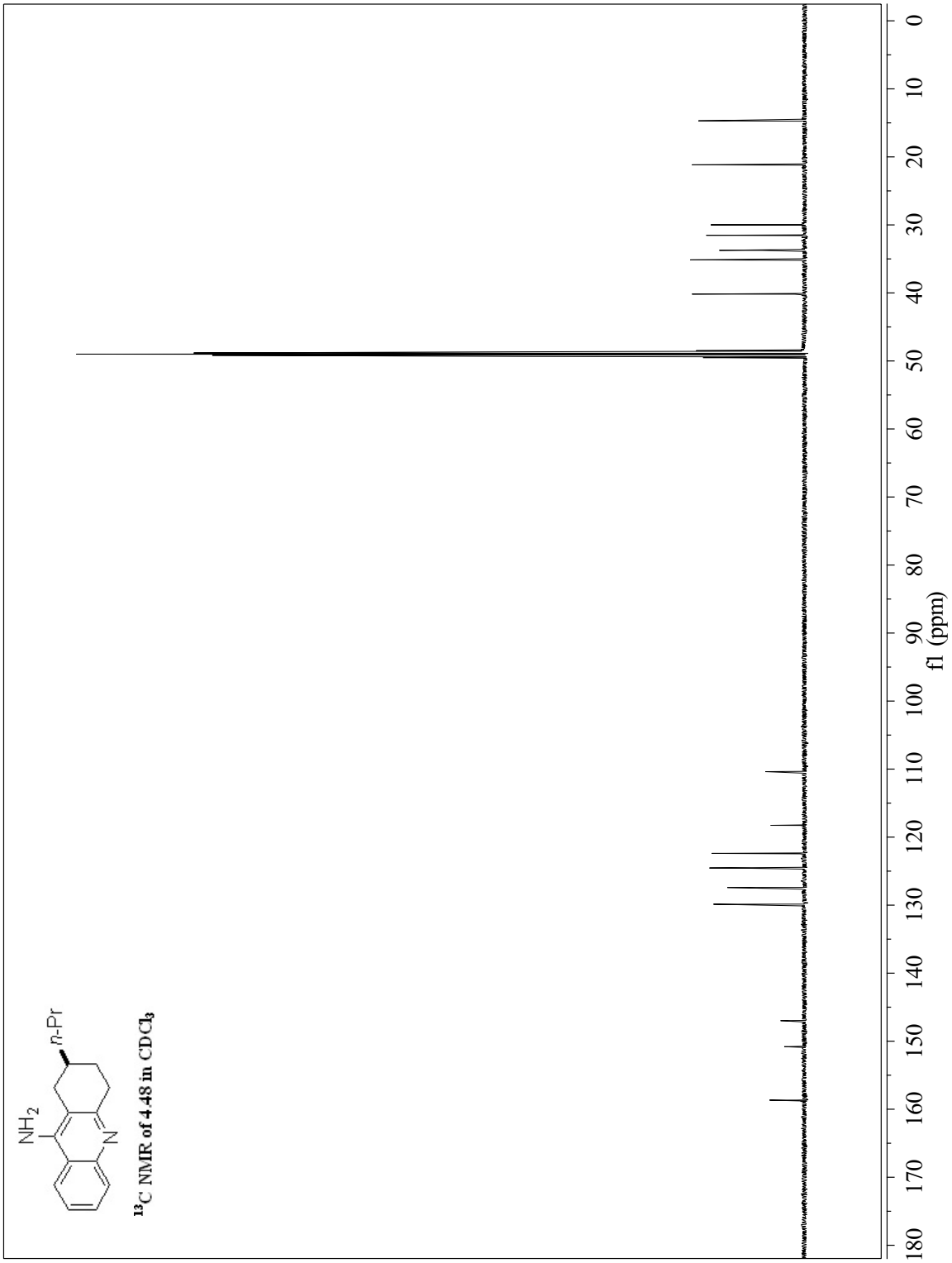
^{13}C NMR of 4.46 in $CDCl_3$


n-Pr
NO2
N
O
1H NMR of 4.47 in CDCl3
1.00
3.05
0.97
1.97
1.00
1.01
1.12
1.04
4.11
3.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



^{13}C NMR of 4.47 in $CDCl_3$


NH2
n-Pr
N
1H NMR of 4.48 in CDCl3
3.03
5.05
1.00
1.01
1.00
1.00
1.02
0.98
0.99
0.99
0.99
1.02
f1 (ppm)


NH2
n-Pr
N
13C NMR of 4.48 in CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

Curriculum Vitae

Le Li

Education Background

2005-present	Ph.D. in Organic Chemistry, Department of Chemistry and Chemical Biology, Rutgers University, New Brunswick, NJ, USA; Research Advisor: Prof. **Daniel Seidel**
2002-2005	M.S. in Polymer Chemistry, Institute of Polymer Chemistry, Nankai University, Tianjin, China; Research Advisors: Prof. **Xiaoxia Zhu** (Université de Montréal, Canada) Prof. **Zhengpu Zhang** (Nankai University, China)
1998-2002	B.S. in Chemistry, Department of Chemistry, Nankai University, Tianjin, China; Research Advisor: Prof. **Tianying Guo**

Publications

1) **Le Li**, Daniel Seidel. "Catalytic Enantioselective Friedländer Condensations: Facile Access to Quinolines with Remote Stereogenic Centers." *Submitted*.
2) Matthew K. Vecchione, **Le Li** and Daniel Seidel. "Catalytic Enantioselective Aldol Reactions of α-Isothiocyanato Imides to α-Ketoesters." *Chem. Commun.* **2010**, 4604–4606.
3) **Le Li**, Madhu Ganesh, and Daniel Seidel. "Catalytic Enantioselective Synthesis of α,β-Diamino Acid Derivatives." *J. Am. Chem. Soc.* **2009**, *131*, 11648–11649.

   Highlighted in "SYNFACT", October 2009; also, highlighted in "JACS Select #7", 2009.

4) **Le Li**, Eric G. Klauber, and Daniel Seidel. "Catalytic Enantioselective Aldol Additions of α-Isothiocyanato Imides to Aldehydes." *J. Am. Chem. Soc.* **2008**, *130*, 12248–12249.

   Highlighted as "SYNFACT of the month," November 2008.

5) Qian Li, **Le Li**, Wenbo Pei, Shanwei Wang, and Zhengpu Zhang. "Synthesis of the novel chiral catalysts by click chemistry and their application." *Syn. Comm.* **2008,** *38(9),* 1470–1477.
6) **Le Li**, Zhengpu Zhang, Xiaoxia Zhu, A. Popa, and Shanwei Wang. "Asymmetric alkylation of a tert-butyl benzophenone Schiff base derivative in water." *Synlett* **2005,** 1873–1876.