UNIVERSITY OF KWAZULU-NATAL

SYNTHESIS OF TETRAHYDROISOQUINOLINE (TIQ) LIGANDS AND THEIR APPLICATIONS IN ASYMMETRIC CATALYSIS

2010

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2010

A thesis submitted to the School of Chemistry, Faculty of Science and Agriculture, University of KwaZulu-Natal, Westville, for the degree of Doctor of Philosophy.

This thesis has been prepared according to **Format 4** as outlined in the guidelines from the Faculty of Science and Agriculture which states:

> This is a thesis in which the chapters are written as a set of discrete research papers, with an Overall Introduction and Final Discussion. Where one (or all) of the chapters has already been published. Typically these chapters will have been published in internationally-recognised, peer-reviewed journals.

As the candidate's supervisor, I have approved this thesis for submission.

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ABSTRACT

A series of 88 novel tetrahydroisoquinoline (TIQ) compounds have been synthesised for applications in asymmetric catalysis. Several chiral TIQ ligands, possessing N,O and N,N donor atoms, have been prepared and evaluated for the catalytic asymmetric transfer hydrogenation (ATH) of pro-chiral ketones. The highest selectivity obtained for the asymmetric transfer hydrogenation of acetophenone with the N,O donor atom ligands was >99 % *ee* at low temperatures in *iso*-propanol with $[Ru(p\text{-cymene})Cl_2]_2$ as a pre-catalyst. The observed enantioselectivity was supported by theoretical calculations using the Jaguar interphase program (Paper I). An enantioselectivity of 70 % was obtained with the ligands possessing the N,N donor atoms with the observation that water played a significant role in the enantioselectivity of the ATH reaction of acetophenone (Paper II).

An investigation into the usefulness of the TIQ scaffold with other donor atoms was also undertaken. A series of novel P,N oxazoline ligands were synthesised and coordinated to Iridium BAr_F. These complexes were screened as chiral catalysts for the high pressure asymmetric hydrogenation of unsymmetrical olefins. The reactions proceeded readily at ambient temperature and provided selectivities of up to >91 % *ee* with excellent conversion rates (>99 %) for the benchmark reactions. Based upon these favorable results, the ligands providing the best results were further screened on a variety of functionalized and un-functionalised olefins (Paper III).

The success of the TIQ backbone in ATH reactions prompted an investigation into its applications in carbon-carbon (C-C) bond forming reactions. The Henry (nitroaldol) reaction is an important C-C bond forming reaction with the chiral oxazoline class of ligands being widely utilised. A series of novel, chiral TIQ oxazoline ligands were synthesised and complexed to various metals (Cu, Sc, Co, Zn, Ni and Mn). These complexes were screened as chiral catalysts in the asymmetric Henry reaction. The highest enantioselectivity (>77 %) was obtained when $Cu(OAc)_2$was employed as a pre-catalyst and *iso*-propanol as a solvent (Paper IV).

The final chapter deals with carbon-sulphur bond formations facilitated by the conjugate addition of thioglycolate to various chalcones. A series of novel, chiral TIQ N-oxide ligands were synthesised and complexed to lanthanum. The complexes were screened for activity against the benchmark reaction and an enantioselectivity of 81 % was obtained.

DECLARATIONS

DECLARATION 1 – PLAGIARISM

I, …….……., declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

4. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
   a. Their words have been re-written but the general information attributed to them has been referenced
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5. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References sections.

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DECLARATION 2 – PUBLICATIONS

DETAILS OF CONTRIBUTION TO PUBLICATIONS that form part and/or include research presented in this thesis (include publications in preparation, submitted, *in press* and published and give details of the contributions of each author to the experimental work and writing of each publication)

Publication 1

Sai Kumar Chakka, Pher G. Andersson, Glenn E. M. Maguire, Hendrik G. Kruger* and Thavendran Govender*; *Synthesis and Screening of C^1-Substituted Tetrahydroisoquinoline Derivatives for Asymmetric Transfer Hydrogenation reactions,* European Journal of Organic Chemistry, **2010**, 972–980.

Contributions: I have synthesised all the compounds, carried out all testing and wrote the paper. All other authors are supervisors.

Publication 2

Byron Peters, Sai Kumar Chakka, Tricia Naicker, Pher G. Andersson, Glenn E. M. Maguire, Hendrik G. Kruger* and Thavendran Govender*; *Synthesis of Tetrahydroisoquinoline-diamine ligands and their application in Asymmetric Transfer Hydrogenation*, Tetrahedron Asymmetry **2010**, 21, 679-687.

Contributions: I have contributed to the original idea for the project especially to the synthetic design of the project. I have performed a screening of ligands for table 3 and wrote the experimental section. Byron Peters synthesised all the compounds and screened for the ATH reaction and wrote the introduction and results and discussions for the manuscript. Tricia Naicker confirmed the NMR spectra and edited the manuscript. All other authors are supervisors.

Publication 3

Sai Kumar Chakka, Byron Peters, Pher G. Andersson, Glenn E. M. Maguire, Hendrik G. Kruger* and Thavendran Govender*;*Iridium-catalysed hydrogenation of olefins using TIQ phosphine-oxazoline ligands for olefins*, Tetrahedron Asymmetry **2010,** 21, 2295-2301.

Contributions: I have synthesised all the precursors and metal complexes, characterized the compounds and prepared the manuscript. Byron Peters assisted with the testing of the compounds. All other authors are supervisors.

Publication 4

Rahul B. Kawthekar, Sai Kumar Chakka, Vivian Francis, Pher G. Andersson, Hendrik G. Kruger* Glenn E. M. Maguire, Thavendran Govender*; *Synthesis of tetrahydroisoquinoline (TIQ)-oxazoline ligands and their application in enantioselective Henry reactions*, Tetrahedron Asymmetry **2010**, 21, 846-852.

Contributions: I have contributed to the original idea, synthesised all the compounds, characterised and wrote the results, discussion and experimental for the manuscript. Rahul Kawthekar (PostDoc) wrote the introduction and performed some of the screening of the ligands and edited the manuscript. Vivian Francis repeated the synthesis of the ligands, performed the screening of these ligands and finished table 3 and 4 (Chapter 5). All other authors are supervisors.

Publication 5

Sai Kumar Chakka, Vivian Francis, Pher G. Andersson, Glenn E. M. Maguire, Hendrik G. Kruger and Thavendran Govender*, *Asymmetric conjugate addition of thioglycolate to chalcone using Tetrahydroisoquinoline (TIQ) N,N'-dioxide ligands*, Tetrahedron Asymmetry, submitted.

Contributions: I have contributed for the original idea (design of the synthesis), synthesised three final compounds out of five, carried out the testing and prepared the manuscript. Vivian Francis synthesised two final compounds out of the five, repeated the synthesis of the first three ligands and performed the screening of tables 3,4 (Chapter 6) and wrote their results, discussion and experimental section of the manuscript. All other authors are supervisors.

ACKNOWLEDGEMENTS

First and foremost I offer my sincerest gratitude to my supervisors, Prof. Gert Kruger, Dr. Thavi Govender and Dr. Glenn Maguire, who have accepted me as a student and supported me throughout my research work. In addition, they have assisted me with the thesis write up with patience and have shared their experience whilst allowing me to maintain and develop my own identity. It was pleasure to be part of the GGKM research group.

Special appreciations to Dr. Glenn Maguire for his continued guidance during my research project.

My special thanks to Prof. Pher Andersson for giving me great support and motivation, it was an honour to have collaborated with you.

Acknowledgments to all the technical staff members in the School of Chemistry especially Anita Naidoo, Gregory Moodley (a great South African supporter), Jay Govender, Raj Suchipersadh, Malini Padayachee and rest of the staff members in the department.

I would like to thank Mr. Dilip Jagjivan for assisting me with the NMR experiments.

I would like to thank NRF, Univeristy of KwaZulu-Natal and Aspen Pharma for generous financial support.

I deeply appreciate all of my past and current colleagues especially Byron Peters, Vivian Francis, Tricia Naicker, Kenny - Maya, Jason Paraskaravel, Grant Boyle, Rahul Kawtekhar, Shimoga Sriharsha, Venu Venugopala, Mohamed Altaib, Thashini Chetty and rest of the GGKM research group members for their support. We had great fun during my research work.

I would like to thank my cricket team mates Ziyaad, Leveen, Nivendran, Bayat, Asif, Islam and Pralav for the fun on the weekends at the cricket field.

A special thank to my landlord, Uncle Krishna Thavers, for his friendship and good housing facilities.

Heartily thanks to my friends Rajshekhar Karpoormath (Raj) and Mahidhansha Shaikh (Nizam bhai) for their company (especially on Fridays) and support during my PhD. I am lucky to have such great friends in my life. I would like to continue these relationships.

Special thank to Mrs. Pruthvi Karpoormath for her outstanding company and support during my final year.

My friends in India Azmi Reddy, Raju Cheeralavancha, Prasad P. Dixit, Anil Hajare and Dr. Navnath Karche for their initial motivation in my career. I miss you guys tremendously.

I convey special acknowledgements to my cousin brother Mr. Sreenivas Paluri for his assistance and financial support to support my PhD studies.

I will never forget my brother, Mr. Suresh Chakka, for his motivation and support in chemistry since my undergraduate studies. I would not have joined chemistry if he didn't nurse me into it. I like to say these words to him in my mother tongue, Telugu.

It is a long and great journey in my life and I would not have reached this stage without the motivation of my father and mother. My parents have always given me everything I needed and guided me in a proper way. I am very much thankful to my parents and family members in India. I deeply respect my mother and father for their endless love, sacrifice and support. I miss them alot. Huge hugs to my sister and sweet kisses to my niece for their love and support. Great endless thanks to my grandfather for his financial support and blessings throughout my studies.

Finally, I am very much thankful to Lord Shiridi Sai Baba for giving me the strength, positive attitude and the knowledge.

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LIST OF PUBLICATIONS

1. Sai Kumar Chakka, Pher G. Andersson, Glenn E. M. Maguire, Hendrik G. Kruger* and Thavendran Govender*; *Synthesis and Screening of C^1-Substituted Tetrahydroisoquinoline Derivatives for Asymmetric Transfer Hydrogenation reactions,* European Journal of Organic Chemistry, **2010**, 972–980.

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CHAPTER 1

1.1 HISTORY OF STEREOCHEMISTRY AND CHIRALITY

Stereochemistry describes the orientation in space of atoms in a molecule. Louis Pasteur could rightly be described as the first to discover chirality, a stereochemical property he observed in the salts of tartaric acid collected during wine production.[1] He observed that some of the crystals rotated polarised light in one direction while other crystals rotated the light in the opposite direction. This unique property, in which the two types of tartrate salt stereo isomers differed, is due to optical isomerism.

The term chiral is derived from the greek name kheir meaning "hand" and was coined by Lord Kelvin in 1904.[2] Chirality is a fundamental property of certain three-dimensional objects. It is of prime significance, as biological macromolecules exist exclusively in one enantiomeric form.[2] Enantiomers are defined as non-superimposable mirror images (Figure 1) and they have identical physical and chemical properties except in two important respects:

1. They rotate plane-polarized light in opposite directions, though in equal amounts. The isomer that rotates the plane to the left (counterclockwise) is called the *levo isomer* designated (–), while the one that rotates the plane to the right (clockwise) is called *dextro isomer* and is designated (+).[3]

2. They react at different rates with other chiral compounds.

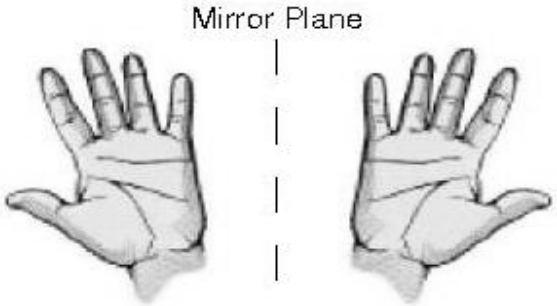


Figure 1. Example of chiral objects[4]

Following Kekule's recognition in 1858 that carbon has a valence of four, Vant' Hoff and Le Bel independently recognized that when four different groups are attached to a carbon atom,

arrayed at the corners of a tetrahedron, then the arrangements can be in two different forms. Cahn, Ingold and Prelog[5] devised a system based on sequence rules of decreasing atomic number (and respective extent of substitution for atoms of the same atomic number) for projection formulas. This method allows for the assignment of a nomenclature based on the *absolute configuration* assignments of *R* (for rectus, Latin for right) and *S* (for sinister, Latin for left).

1.2 IMPORTANCE OF CHIRALITY IN DRUGS

Understanding the phenomenon of chirality is extremely significant in the preparation of therapeutic drugs. For example, one enantiomer of penicillamine is a potent anti-arthritic agent[6] whereas the other enantiomer is highly toxic.[7] Perhaps the most amazing example of the difference in activity between enantiomers is that of Thalidomide. This drug was seen as a panacea for the treatment of morning sickness in pregnant women. However, the drug was marketed as a racemic mixture with only one enantiomer, the (*R*)- having the desired therapeutic effect. The (*S*)- enantiomer unfortunately, has been associated with well-characterized birth defects that arose from use of the drug.[8]

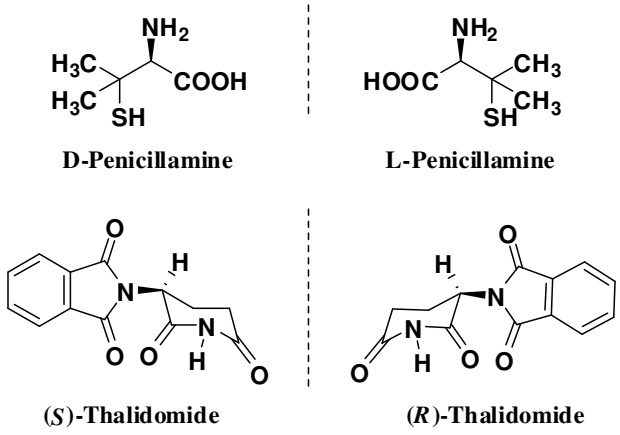


Figure 2. The mirror image relationship between chiral molecules

1.3 ROUTES TO ENATIOMERICALLY PURE COMPOUNDS

It is important to have sources of enantiomerically pure compounds, especially for the use of pharmaceutical drug production. In general, there are three routes for obtaining enantiopure compounds. They can be obtained from a chiral pool, from prochiral substrates or from a racemic mixture. Figure 3 shows the various routes to obtain enaniomerically pure molecules.

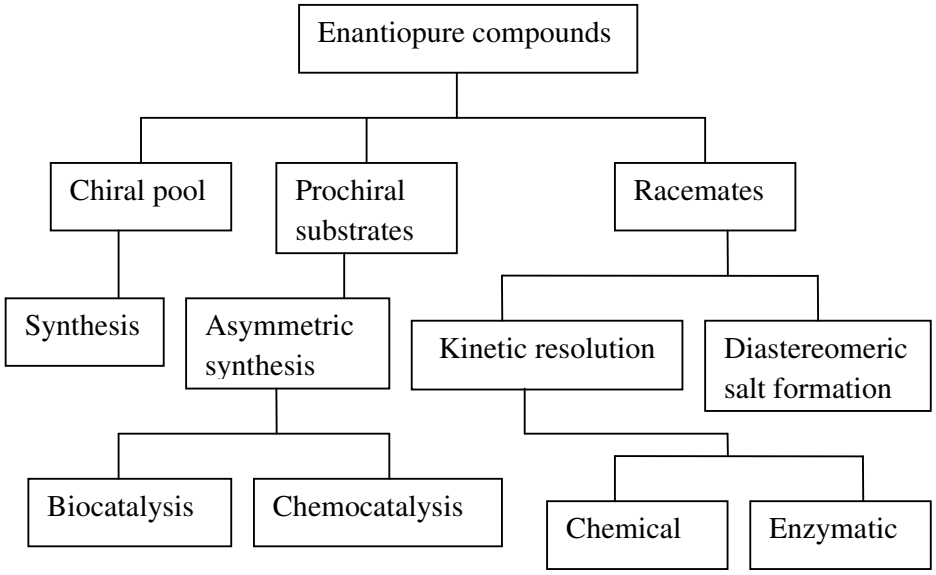


Figure 3. Schematic diagram of methods to obtain enantiomerically pure derivatives

1.3.1 CHIRAL POOL STRATEGY

The utilization of naturally occurring chiral starting materials, also called the chiral pool approach,[9] plays an important role in the synthesis of enantiomerically enriched compounds. Nature provides good chiral species in several varieties of compound classes of which amino acids, carbohydrates, terpenes, carboxylic acids and alkaloids play important roles (Figure 4).

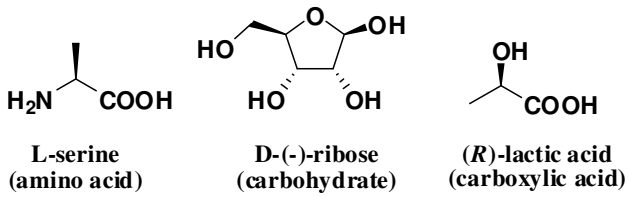
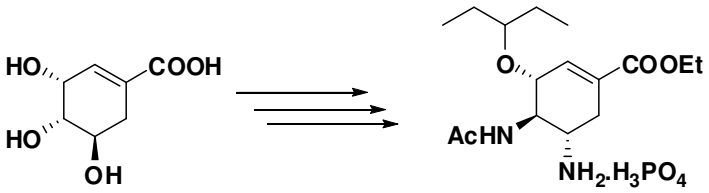


Figure 4. Several examples of naturally occurring chiral compounds.

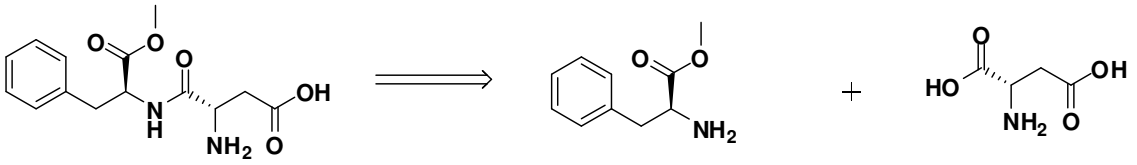
Many chiral compounds have been synthesised using the chiral pool strategy. Synthesis of oseltamivir phosphate, Tamiflu®, is an example of the chiral pool approach. This drug is a potent antiviral agent and is synthesized from the naturally occurring chiral compound (-)-shikimic acid (Scheme 1).[10] The main disadvantage of this strategy is that it suffers from a limited number of starting materials and often the availability of only one enantiomer.



(-)-Shikimic acid **Tamiflu®**

Scheme 1. Synthesis of Tamiflu® starting from (-)-shikimic acid

Another example for this synthetic approach would be the preparation of aspartame, an artificial sweetener which is a simple dipeptide. From retro-synthetic methodology, it was observed that the two natural amino acids (*S*)-phenyl alanine methyl ester and (*S*)-aspartic acid can be condensed to form the desired aspartame.[11]



(*S*)-phenyl alanine methyl ester **(*S*)-aspartic acid**

Scheme 2. Retro-synthetic approach for the aspartame

1.3.2 RESOLUTION OF RACEMATES

The separation of a racemate into its two optically pure compounds is called resolution.[12] It is a classic approach to obtain enantiopure compounds from racemates which were temporarily converted into diastereomers. The reagents used to form the diastereomers are often from a natural source, eg. tartaric acid, brucine, quinidine and lactic acid. The main drawback of this strategy is efficiency and low yields of the enantiomerically pure compounds (the maximum theoretical yield is 50 %). On further development of this technique, researchers developed kinetic resolution and dynamic kinetic resolution.

1. In kinetic resolution two enantiomers show different reaction rates in a chemical reaction thereby creating an excess of the less reactive enantiomer. The excess goes through a maximum and disappears on full completion of the reaction.

2. Dynamic kinetic resolution (DKR) is an extension of kinetic resolution. By using this technique, the less reactive isomer is racemized *in situ* and then transformed again

into the desired enantiomer *via* resolution.[13] Due to the increase of entropy, it is a completely thermodynamically favoured process.[14] From the appropriate combination of metal catalysts, enzymes, acyl donors and reaction conditions, a broad range of secondary alcohols as chiral substrates have been implemented for DKR process. Figure 5 shows the different varieties of secondary carbinols which were accessed through this method. From the approach of dynamic kinetic resolution, a large scale chemoenzymatic process for secondary alcohols has been setup in 2002.[14]

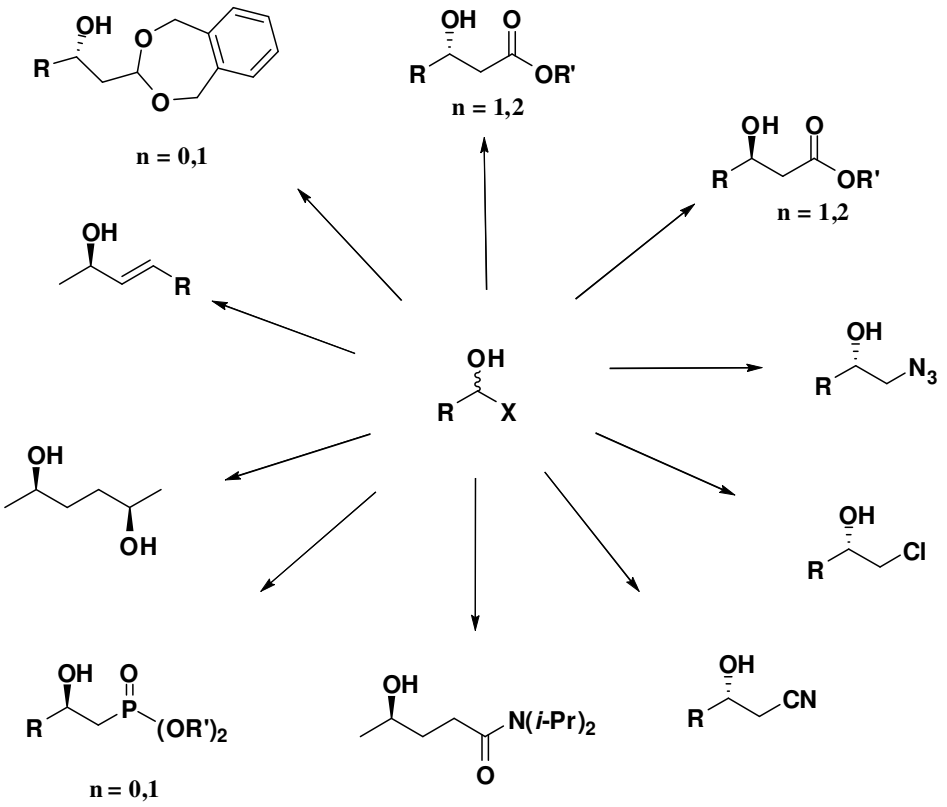


Figure 5. Few varieties of secondary carbinols accessed through dynamic kinetic resolution.

1.3.3 ASYMMETRIC SYNTHESIS

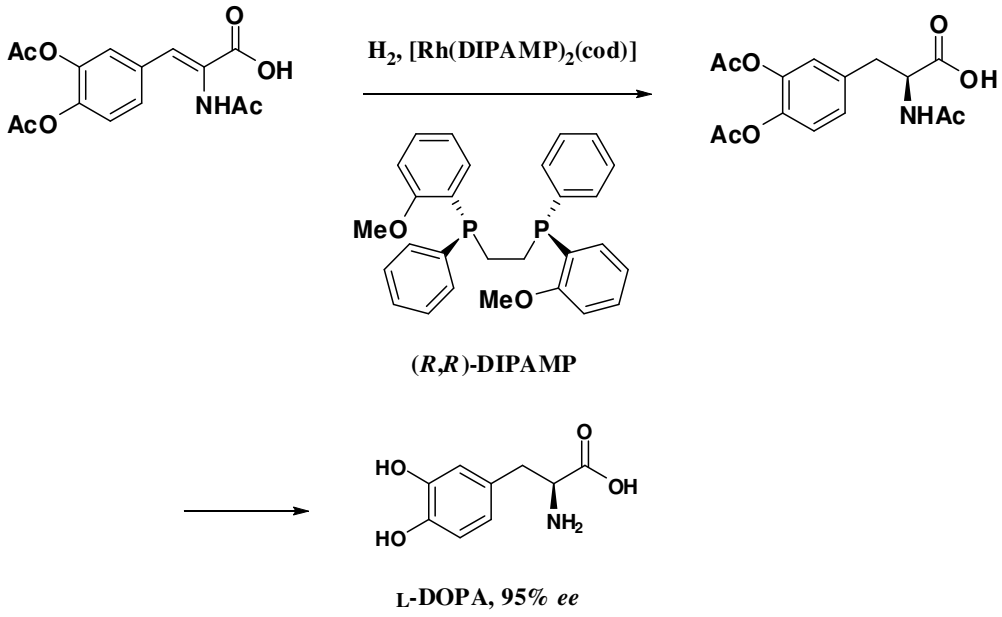
The development of new methodologies for the preparation of stereoisomers is amongst the most important topics in modern organic synthesis.[15] There are several methods to obtain enantiomerically pure isomers like enzymatic resolution, chromatographic separation and resolution of racemates. Due to the high atom economy of these methods,[16] asymmetric catalysis is the most desirable method for producing enantiomerically pure compounds. This method allows large quantities of the chiral materials to be produced using a small amount of a chiral catalyst.[17] An interest in our research group is the development of novel metal

complexes as catalysts for stereoselective transformations such as: asymmetric transfer hydrogenation of unsymmetrical ketones, high pressure hydrogenation of functionalized, non-functionalized olefins and enantioselective C–C bond formation reactions.

1.3.4 ASYMMETRIC CATALYSIS BY CHIRAL METAL COMPLEXES

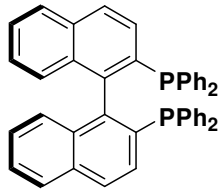
A catalyst is defined as a species that increases the rate of a chemical reaction without itself being consumed or changed in the overall reaction. The first synthetically useful asymmetric catalysis was reported in the late 1950s. During the last few decades, transition-metal-catalyzed reactions have been extremely useful in organic synthesis.[18-19] Izumi *et al*. first applied and reported the asymmetric hydrogenation of methyl acetoacetate into methyl β-hydroxybutyrate with enantioselectivities of up to 80 % using Raney nickel modified with tartaric acid.[20]

The first industrial application employing asymmetric catalysis was Monsanto's production of L-DOPA, an important anti-Parkinson's drug.[21] The process involved the asymmetric hydrogenation of an acyl enamine with a modified Wilkinson catalyst, developed by William Knowles (Scheme 3).[22-23]



Scheme 3. Monsanto's L-DOPA process

Later, Ryoji Noyori introduced the binapthalene based ligands that coordinated to ruthenium and rhodium metal species for the asymmetric hydrogenation of olefins and ketones (Figure 6).[24]



(*S*)-BINAP

Figure 6. Noyori's BINAP ligand

1.3.5 IMPORTANCE OF ASYMMETRIC CATALYSIS

In recent years, there has been considerable effort directed towards the use of chiral metal complexes as catalysts for a wide variety of asymmetric transformations.[25-27] For example, it is often possible to transform a pro-chiral substrate into an enantiomerically pure chiral product.[28] These types of conversions are extremely important for the synthesis of drugs and natural products, which usually contain at least one chiral center.[29-31] Currently, one of the main focuses of organic synthetic research groups is the development of new chiral metal catalysts for stereoselective synthesis. Some of the most important industrially applied asymmetric catalysis include C-C bond formation and reduction reactions.[32-34]

Enantioselective C-C bond formation reactions are one of the greatest challenges in modern synthetic organic chemistry.[35] Considering the recent survey on the use of C-C bond formations in pharmaceutical industry,[36] Figure 7 shows that the palladium catalysed reactions are the amongst the most popular.

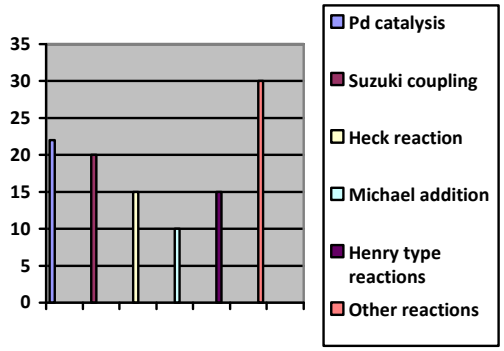
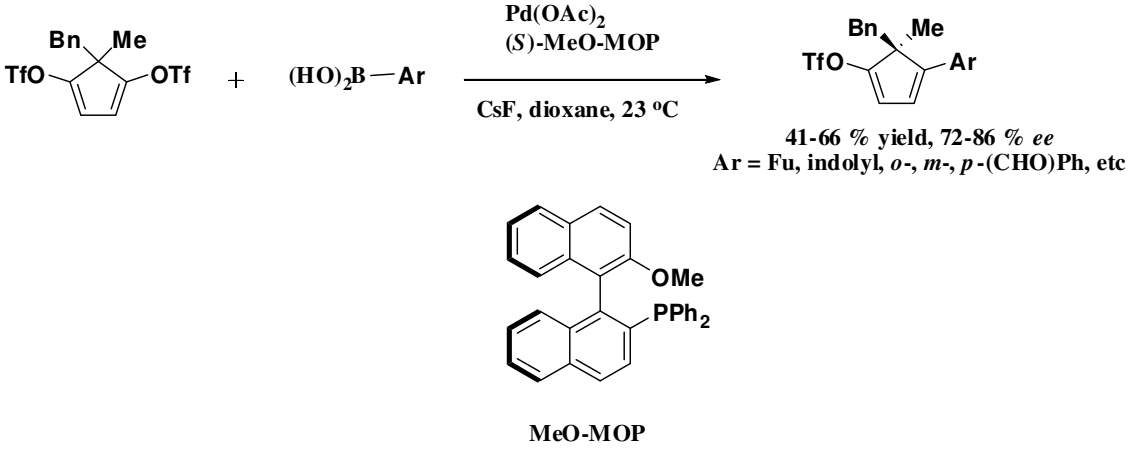


Figure 7. Chart for the usage of C-C bond formation reactions (this graph was adapted from the literature[36])

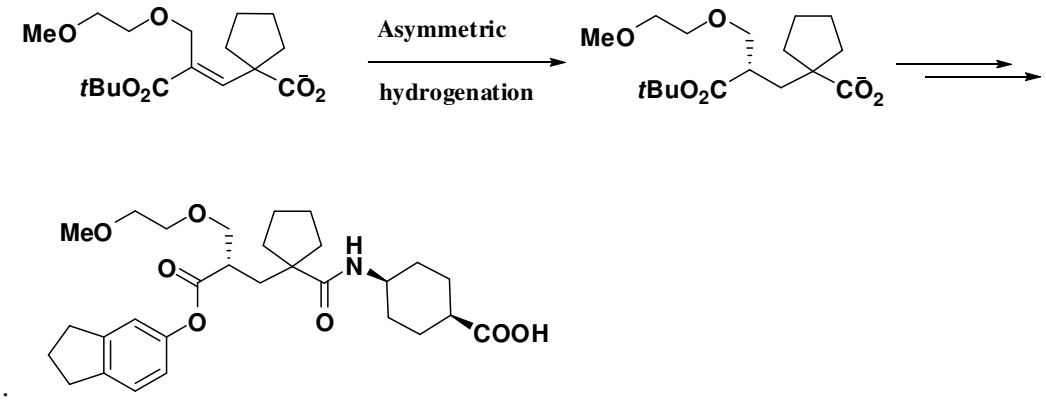
From the recent approaches in the applications of C-C bond reactions, researchers have achieved excellent enantioselectivities (>99 %) in Suzuki coupling,[37-38] Heck reaction[39-40] and other palladium catalysed couplings[41-42] with good turnover rates. Scheme 4 shows the important C-C bond formations using MOP chiral metal catalysts.[37]



Scheme 4. Example for Suzuki coupling[37]

Beginning with Wilkinson's catalyst for the synthesis of L-DOPA, researchers considered the importance of asymmetric hydrogenation reactions by utilizing transition metal complexes.[21] Asymmetric reduction reactions involved the hydrogenation of C=C, C=O and C=N to CH-CH, CH-OH and CH-NH respectively.[43-44] In many instances, the use of transition metal catalysts was found to be the optimum choice for this transformation.[45-46] A large array of new chiral catalysts has been used for the bulk production of drugs in the pharmaceutical

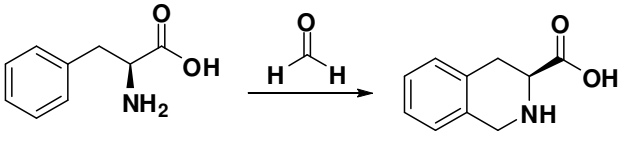
industry.[47-48] In this respect, asymmetric hydrogenations have progressed significantly over the past few decades. It is now a conventional method by which the manufacture of a wide range of chiral compounds in the agrochemical, pharmaceutical, fragrance and fine chemical industries is achieved. Enantiomerically enriched amines, amino acids, esters, alcohols and acids are commercially synthesized utilizing chiral catalysts.[49] Ruthenium, rhodium and iridium based metal catalysts have played an important role in the synthesis of bulk scale drugs in pharmaceutical industries (Scheme 5).[50]



Scheme 5. Approach for the asymmetric hydrogenation of candoxatril.[50]

1.4 HISTORY OF TETRAHYDROISOQUINOLINE (TIQ) BACKBONE AND APPLICATIONS IN ASYMMETRIC CATALYSIS

The 1,2,3,4-tetrahydroisoquinoline (TIQ) moiety is commonly found in biologically important molecules of either natural or synthetic origin.[51-58] Several well established synthetic routes like the Pictet-Spengler (Scheme **6**),[59] Bischler- Napieralsky[60] and Pomeranz-Fritschto[61] reactions have been used to obtain the backbone of TIQ compounds. These traditional methods involve an electrophilic aromatic substitution as a key step.



Scheme 6. Pictet-Spengler reaction of phenylalanine

To date, very little research has been applied to the TIQ backbone as a chiral ligand in asymmetric catalysis. TIQ derivatives as catalytic ligands have yielded limited success with poor to moderate enantioselectivities in allylic alkylation[62] and borane mediated hydrogenation reactions.[63-64] In the alkylation reactions, TIQ oxazoline ligands were synthesised and coordinated with palladium and iridium metals and tested for a variety of C-C bond formation reactions (Figure 8). Our focus is the design and synthesis of novel TIQ derivatives as ligands for application in asymmetric reactions.

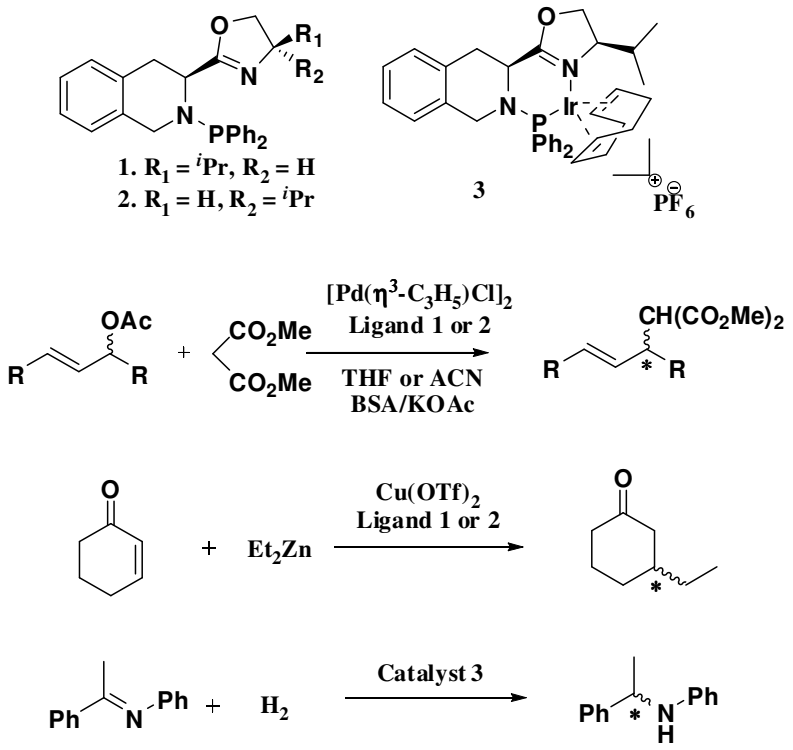


Figure 8. Previously reported TIQ oxazoline ligands and their applications.

From the previous literature reports various five membered, bicyclic and heterocyclic backbones were introduced as ligands for the applications of asymmetric catalysis (Figure 9).[65]

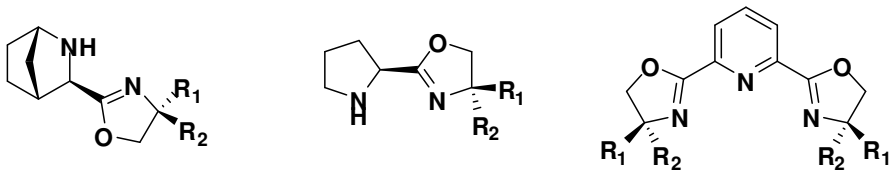


Figure 9. Some of the examples of chiral ligands with difference backbones

Andersson *et al.* were the first to introduce the bicyclic amino alcohol system in asymmetric catalysis. The bicyclic backbone was modified and introduced as amino alcohol ligands for Asymmetric Transfer Hydrogenation (ATH) reactions.[66] The results obtained from this system were excellent and further confirmed by computational studies. Keeping this concept in mind we decided to design a six-membered backbone (TIQ backbone), for designing various ligands which structurally resembles the bicyclic amino alcohol ligands (Figure 10).

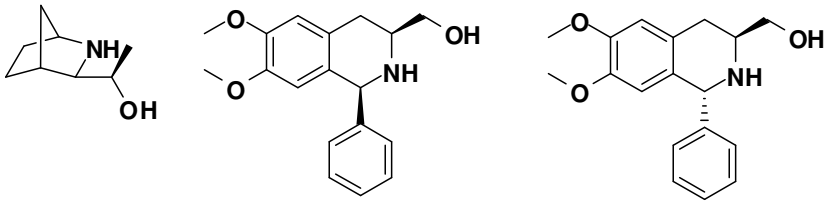


Figure 10. Comparison of Bicyclic ligands with TIQ ligands

Furthermore, they have developed chiral oxazoline ligands for a wide range of substrates. In particular, the bicyclic oxazolines are among the most successful and have produced excellent results in the hydrogenation of N-aryl amines,[67] enol phosphinates[68] and olefins.[69] Since asymmetric hydrogenation of unfunctionalized olefins remains a challenge due to substrate dependence, we have decided to synthesise TIQ oxazoline ligands for applications in asymmetric hydrogenation of olefins and C-C bond formation reactions (Figure 11).

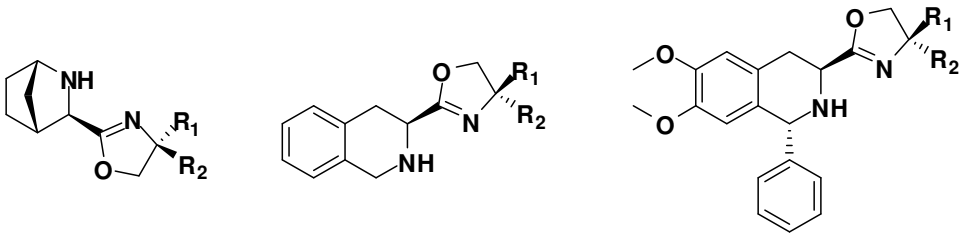


Figure 11. Design of TIQ oxazoline ligands from bicyclic oxazoline ligands

In recent years, the contribution of proline derived ligands to the field of asymmetric catalysis was outstanding. The N-oxide type ligands were introduced by Feng *et al* for the enantioselective Strecker reaction,[70] C-C bond formation reaction,[71] and conjugate addition to chalcones.[72] The success of these ligands prompted us to synthesise TIQ N-oxide ligands for various applications. Intial study focused on the conjugate addition of thioglycolate to chalcones using Novel TIQ *N,N*'-dioxide ligands (Figure 12).

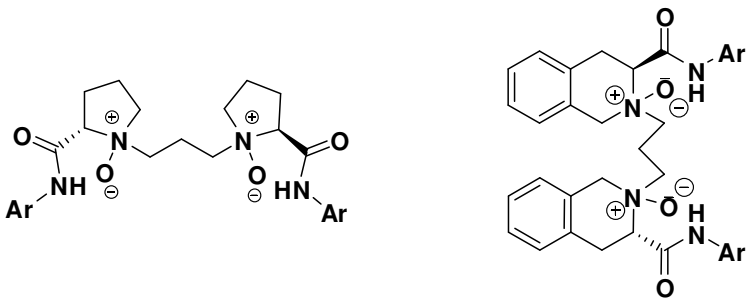


Figure 12. Examples for Proline N-oxide and TIQ N-oxide ligands

1.5 RESEARCH PERFORMED IN THIS THESIS

This thesis contains five papers describing the application catalysts developed from the TIQ backbone in asymmetric reductions, C-C bond formation and asymmetric conjugate addition of sulphur to chalcones. The asymmetric reactions involve the reduction of pro-chiral ketones into chiral alcohols and olefins into chiral alkanes. In papers I and II novel tetrahydroisoquinoline amino alcohols and TIQ diamine ligands were reported. These ligands have been evaluated in the asymmetric transfer hydrogenation of acetophenone by coordination with ruthenium-, rhodium- and iridium metals. As part of the work, the minimum energy transition states of TIQ amino alcohol coordinating with ruthenium and acetophenone were calculated (Paper I). The results obtained thus far prompted a change in donor atoms and a series of TIQ P,N oxazoline ligands were synthesised. These ligands were screened in the asymmetric hydrogenation of olefins by complexation with Iridium tetrakis[(3,5-trifluoromethyl)phenyl]borate (Ir-BAr_F) (Paper III). In paper IV novel C^1 substituted TIQ oxazoline ligands were designed and synthesised for the copper catalysed Henry reaction. Paper V describes the design and evaluation of novel TIQ N-oxide ligands for carbon-sulfur bond formation.

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CHAPTER 2

SYNTHESIS AND SCREENING OF C^1-SUBSTITUTED TETRAHYDROISOQUINOLINE DERIVATIVES FOR ASYMMETRIC TRANSFER HYDROGENATION REACTIONS

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ABSTRACT

Tetrahydroisoquinoline (TIQ) derivatives exhibit good biological activity. However, utilization of TIQ compounds in asymmetric catalysis is limited. This paper presents a series of TIQ derivatives in asymmetric transfer hydrogenation (ATH) reactions. Chiral TIQ amino alcohol ligands were synthesized and screened for the ATH reaction of aromatic ketones. The effect of a cis- and trans-phenyl substitution at the C^1 position on the ligand backbone was investigated both experimentally and computationally. The results showed that the trans orientation on the TIQ scaffold yields higher turnover rates with a selectivity of up to 94 % ee obtained at room temperature with an Ru complex. The cis isomer results in a high turnover rate with no selectivity. The trans isomer gave 99 % ee at lower temperatures. Furthermore, it was observed that substitution at the C^3-α position results in a drop of the enantioselectivity and the reactivity of the catalyst.

Keywords: Tetrahydroisoquinoline; Amino alcohols; Ruthenium; Hydrogenation; Asymmetric catalysis

INTRODUCTION

Chiral amino alcohol containing ligands (Figure 1) are among the more successful classes of compounds in asymmetric transfer hydrogenation reactions (ATH).[1-3] In these reactions transfer hydrogenation has been applied to ketones and imines.[4-5] In particular it has been very successful for the reduction of a range of unsymmetrical ketones. Nevertheless, there is still significant interest in the development of new chiral scaffolds as potential ligands in asymmetric catalysis.

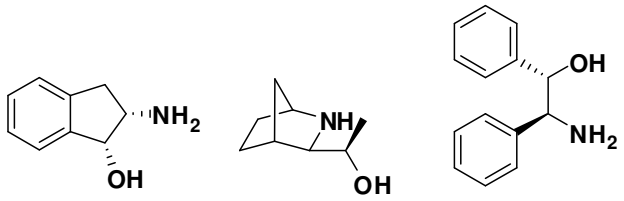

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Figure 1. Examples of chiral amino alcohol ligands reported with high selectivity in ATH reactions

Since the isolation of naphthyridinomycin in 1974, the biological activity of tetrahydroisoquinoline (TIQ) carboxylic acid derivatives have been widely investigated.[6-8] Our interest in the development of novel chiral backbones prompted us to investigate the application of the TIQ scaffold as a source of chirality in ATH reactions. Previous reports on the use of TIQ derivatives as catalytic ligands have indicated limited success, with poor to moderate enantioselectivities in asymmetric reactions such as allylic alkylation[9] and borane-mediated hydrogenation reactions.[10-11] Recently, a related study of different TIQ ligands on the addition of diethylzinc to benzaldehyde was reported with promising results.[12]

Given the reports in the literature thus far, we aimed to couple the catalytic success of the chiral amino alcohol containing class of ligands, with the innovation of the TIQ scaffold towards the development of a novel series of efficient C^1-phenyl and C^3-α-phenyl substitutions. The ligands were coordinated to (arene) ruthenium, -rhodium, and -iridium precursors, and their efficiency was investigated as ATH catalysts for the reduction of prochiral ketones.[13-15] To the best of our knowledge, this is the first successful application of a TIQ ligand to effect high enantioselective transfer hydrogenations yielding high turnover rates at reasonable catalyst loading.

RESULTS AND DISCUSSION

Mechanistic studies on non-TIQ-related ligands[1,3] developed by Noyori have demonstrated that typically two stereogenic centers, a cyclic secondary amine and a secondary alcohol are required for optimal chiral activity.[16-18] For maximum activity these two metal coordination sites are typically within three bonds of each other. In this paper, we introduce the tetrahydroisoquinoline (TIQ) ligands, which have initially a single chiral center, a secondary amine in a six-membered ring with a primary alcohol as a side chain. Our first choice was ligand **4**, which represents a simple TIQ backbone (Figure 2) from the literature.[19] The ATH reduction of acetophenone proved to be inefficient with this ligand after coordination with a $[Ru(p\text{-cymene})Cl_2]_2$ complex and with isopropyl alcohol as the hydride source (Table 1, Entry 1).

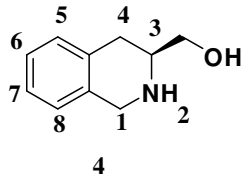

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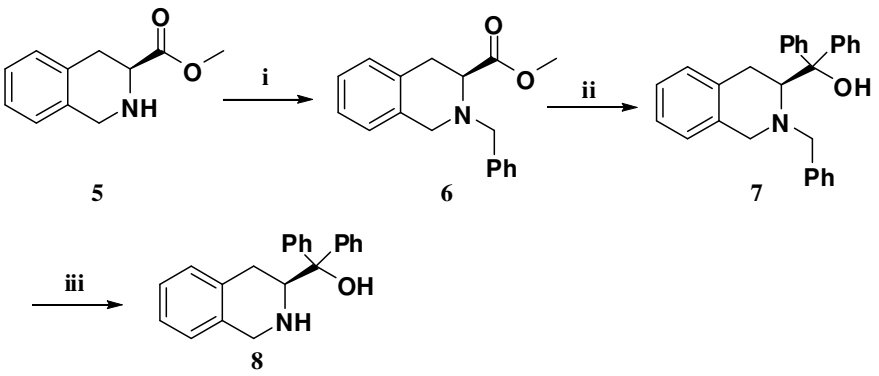
Figure 2. Unsubstituted TIQ ligand for ATH reactions

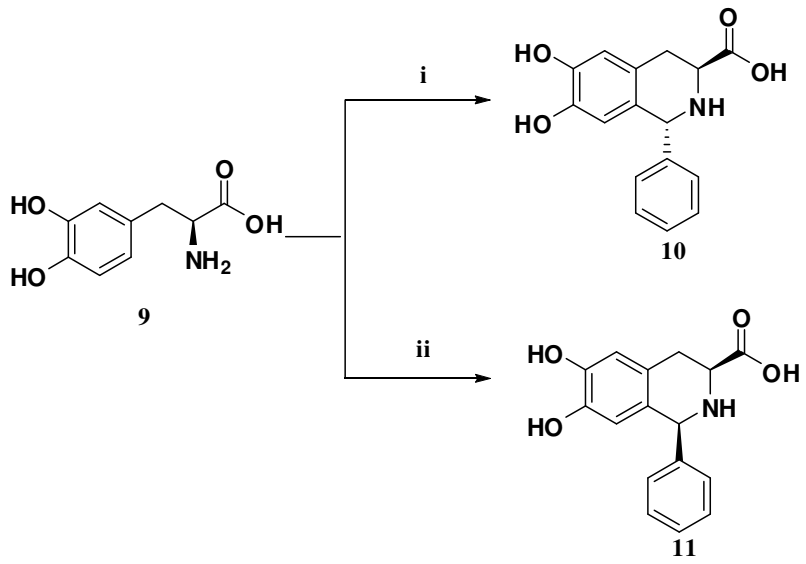
From our lead molecule we thought conversion of the primary alcohol **4** to a secondary alcohol could potentially improve the ligand activity. However, due to the difficulty in the synthesis as will be demonstrated later, we designed and synthesized the amino tertiary alcohol **8**, introducing phenyl moieties as bulky groups at the C^3 position. Ligand **8** was synthesized from the TIQ amino ester **5**,[19] and the benzyl protection of the secondary amine was carried out with benzyl bromide and K_2CO_3 in acetonitrile. Subsequently, a Grignard reaction on **6** afforded **7** in less than 20 % yields. Ultimately, deprotection of **7** resulted in the formation of ligand **8** as shown in Scheme 1.



Scheme 1. Reagents for the synthesis of ligand **8**: (i) Benzyl bromide, K_2CO_3, CH_3CN, reflux, 3hrs; (ii) PhMgBr, dry THF, reflux, 6 hrs; (iii) 10 wt.- % Pd/C, H_2 (1 atm), MeOH.

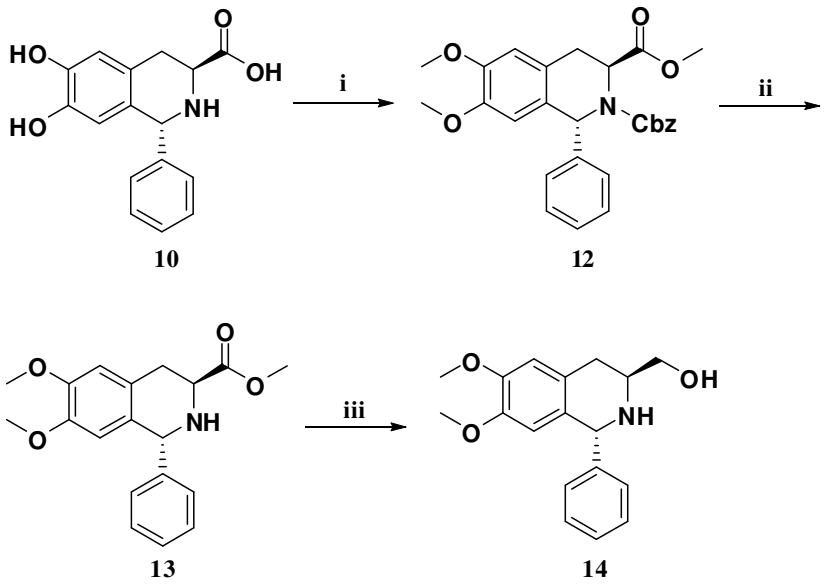
Disappointingly, phenyl substitution at the C^3-α position did not improve the catalytic activity, in fact, no reactivity was observed with this ligand (Table 1, Entry 2). To further investigate the factors affecting the efficiency of our TIQ backbone, we returned to the primary alcohol system and substituted a phenyl group creating a stereogenic center at the C^1 position while increasing the pK_a of the secondary nitrogen atom and the steric bulk of the ligand. All attempts to achieve substitution at the C^1 position through a Pictet–Spengler reaction between phenylalanine and benzaldehyde were met with limited success. It was essential to employ the activated aromatic group of L-DOPA (**9**) to facilitate product formation.

Aubry *et al* reported on the effect of solvent on the stereocontrol of Pictet–Spengler reactions.[20] For ligand **14**, L-DOPA (**9**) was treated with benzaldehyde in the presence of K_2CO_3 and aqueous EtOH to afford the trans-substituted TIQ compound **10** in 20 % yield (Scheme 2).[20] The cis-substituted TIQ compound **11** was obtained from benzaldehyde and K_2CO_3 in water giving a 20 % yield.



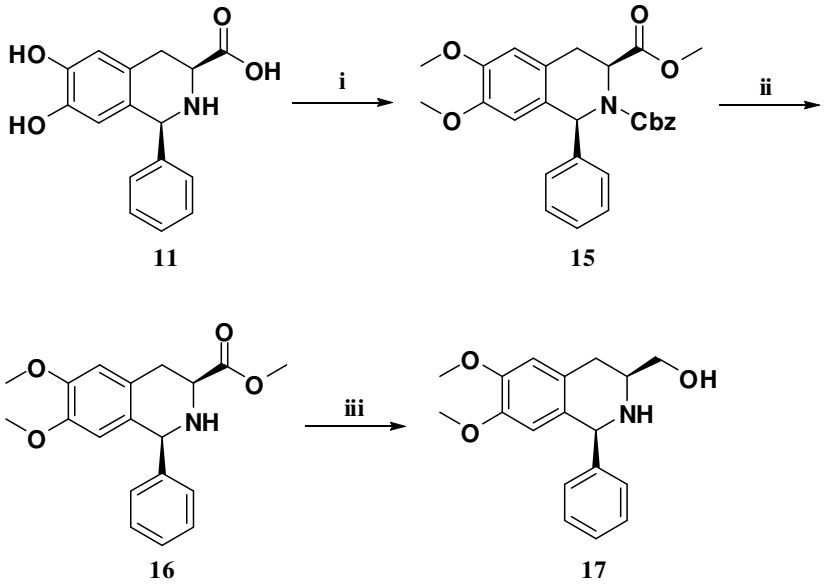
Scheme 2. Reagents for the synthesis of TIQ acids **10** and **11**: (i) PhCHO, K_2CO_3, EtOH/H_2O, 0 ^oC – r.t.; (ii) PhCHO, K_2CO_3, H_2O, 0 ^oC – r.t.

To obtain compound **12**, C^1-substituted *N*-Cbz protected methyl ester, an *in situ* reaction was performed on **10** with benzyl chloroformate (Cbz) and monitored with LCMS. After completion of the reaction, the solvent was evaporated under vacuum and the crude product was used directly and methylated at the phenolic and carboxylic acid positions. This was achieved by refluxing the compound in acetone in the presence of Me_2SO_4 and $KHCO_3$.[21] The crude product was purified by column chromatography to obtain the desired compound **12** in 80 % yield. Deprotection of the Cbz group gave **13**, which was reduced to the amino alcohol **14** (Scheme 3). It was observed that partial racemization had occurred during the reduction of the ester at elevated temperatures (diastereomers were observed by HPLC and TLC). To afford maximum optical purity, the reduction of **13** was subsequently repeated at 0 °C yielding the pure ligand **14** (Scheme 3).



Scheme 3. Reagents for the synthesis of ligand **14**: (i) $KHCO_3$, Cbz-Cl, dioxane/water *in situ* solvent evaporation $KHCO_3$, Me_2SO_4, acetone, reflux, overnight; (ii) 10 wt.- % Pd/C, H_2 (1 atm), MeOH, r.t.; (iii) $LiAlH_4$, dry THF, 0 ^oC, 2 hrs.

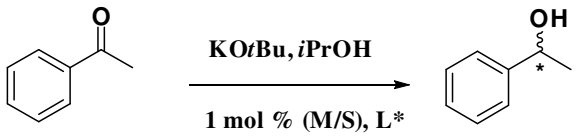
A similar synthetic route was applied to produce the *cis* TIQ amino alcohol **17** starting from **11** (Scheme 4).



Scheme 4. Reagents for the synthesis of ligand **17**: (i) $KHCO_3$, Cbz-Cl, dioxane/water *in situ* solvent evaporation $KHCO_3$, Me_2SO_4, acetone, reflux, overnight; (ii) 10 wt.- % Pd/C, H_2 (1 atm), MeOH, r.t.; (iii) $LiAlH_4$, dry THF, 0 ^oC, 2 hrs.

Interesting results were observed for the ATH reaction of acetophenone utilizing ligands **14** and **17**. Ligand **14** showed good catalytic activity with 94 % conversion and 94 % *ee* (*R*) in 45 min. In the case of **17**, a racemic mixture was observed with an 80 % conversion (Table 1, Entries 3 and 4).

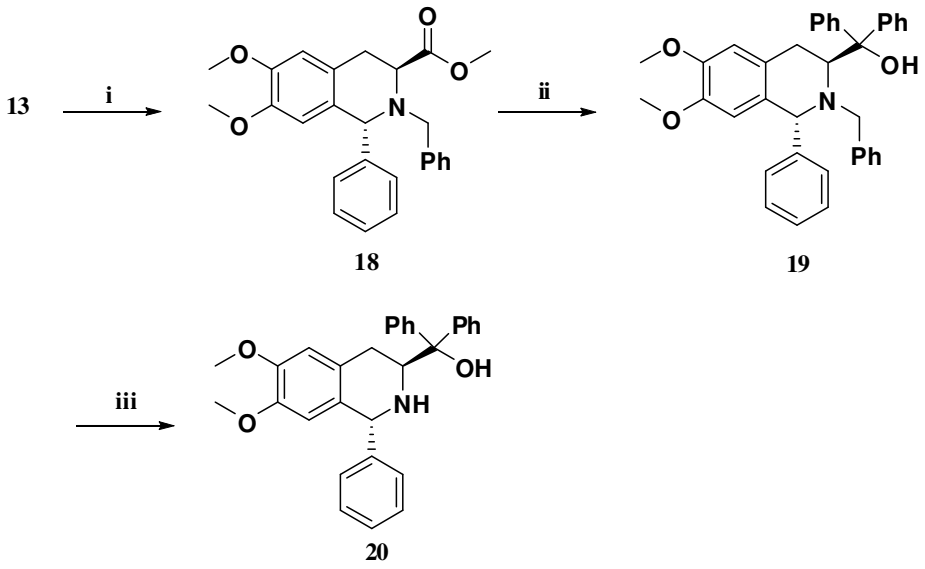
Table 1. Asymmetric transfer hydrogenation of acetophenone using different ligands complexed with $[Ru(p\text{-cymene})Cl_2]_2$.



Entry	Ligand	Time (h)	Conv. (%)[a]	*ee* (%)(R/S)[b]
1	**4**	24.0	28	35 (S)
2	**8**	24.0	NR[c]	NR[c]
3	**14**	0.75	94	94 (R)
4	**17**	0.75	80	Racemic

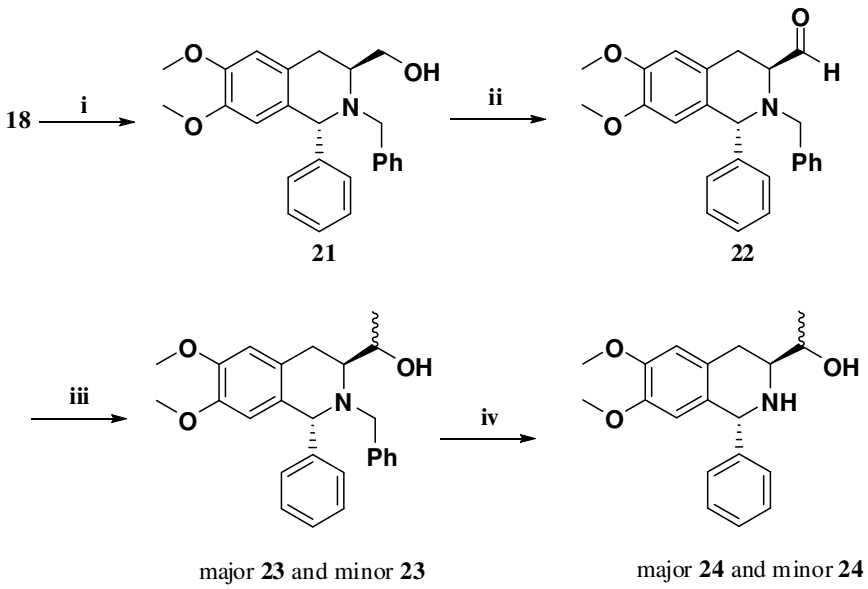
[a]Determined by chiral GC analysis.
[b]Absolute configuration determined by comparison with reported retention times values reported are the average of three runs.
[c]No reaction observed.

The reason for this difference in catalytic activity is not readily understood. With the encouraging results from ligand **14**, however, we decided to modify the ligand by introducing phenyl groups at the C^3-α position to re-investigate the effect of steric bulk. To obtain this ligand, intermediate **13** could be converted into the N-benzyl methyl ester **18**. In order to introduce the phenyl groups, the secondary amine was first benzyl-protected, after which a Grignard reaction with phenylmagnesium bromide afforded **19**. Deprotection of **19** (Scheme 5) resulted in the formation of ligand **20**. It was comparable to ligand **8** (Table 2, Entry 1) and thus confirmed that bulky groups present on the C^3-α position hinder the catalytic activity.



Scheme 5. Reagents for the synthesis of ligand **20**: (i) Benzyl Bromide, K_2CO_3, CH_3CN, reflux, 3 hrs; (ii) PhMgBr, dry THF, reflux, 6 hrs; (iii) 10 wt.- % Pd/C H_2 (1 atm), MeOH.

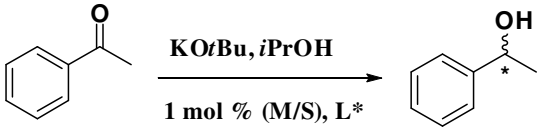
From the results of ligand **14** and **20**, it was decided to investigate the effect of less bulky substitution at the C^3-α position. There were two reasons for this: (i) it is known from the literature that amino alcohols with a secondary alcohol exhibit excellent reactivity and selectivity;[22-23] (ii) this allows us to introduce another chiral center into our catalytic ligand design. The reduction of ester **18** with $LiAlH_4$ followed by a Swern oxidation afforded the aldehyde **22** in 82 % yield. Subsequently, a Grignard reaction with methylmagnesium iodide under reflux conditions afforded two diastereomeric alcohols in a 1:1 mixture. To improve the selectivity, the Grignard reaction was repeated at 0 °C giving the diastereomers in a 9:1 ratio and in good yields. These diastereomers were named major **23** and minor **23**. Separation of the isomers followed by deprotection afforded ligands major **24** and minor **24** in 60 % yield (Scheme 6).



Scheme 6. Reagents for the synthesis of major **24** and minor **24** ligands: (i) $LiAlH_4$, dry THF, r.t.; (ii) DMSO, oxalyl chloride, TEA, CH_2Cl_2, –78 °C; (iii) CH_3MgI, dry THF, 0 °C; (iv) 10 wt.- % Pd/C, H_2 (1 atm), MeOH, r.t. (All experimental details are available in supporting information).

Ligands major **24** and minor **24** were tested for transfer hydrogenation activity under identical conditions. Ligand major **24** gave a 94 % *ee* (*R*), and minor **24** gave 70 % *ee* (*S*), albeit both with low conversions (Table 2, Entries 2, 3).

Table 2. Asymmetric transfer hydrogenation of acetophenone using different ligands with $[Ru(p\text{-cymene})Cl_2]_2$.



Entry	Ligand	Time (h)	Conv. (%)[a]	*ee* (%)(*R*/*S*)[b]
1	20	1.0	NR[c]	NR[c]
2	Major **24**	0.5	33	94 (*R*)
3	Minor **24**	0.5	30	70 (*S*)

[a]Determined by chiral GC analysis.
[b]Absolute configuration determined by comparison with reported retention times. Values reported are the average of three runs.
[c]No reaction observed.

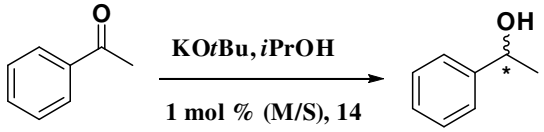
To summarize, a total of seven ligands were prepared and evaluated in the ruthenium-catalyzed ATH of acetophenone; the results are found in Tables 1 and 2. Unsubstituted amino alcohol **4** reduced acetophenone with low conversion rates and enantiomeric excess (Table 1, Entry 1). Phenyl substitution at the C^3-α position of ligands **8** (Table 1, Entry 2) and **20** (Table 2, Entry 1) deactivated the catalyst. Similar phenyl substitution at the C^1 position gave *cis* and *trans* configurations, which enhanced the turnover rates in ATH reactions. In this system, ligand **14** (*trans*) provided better selectivity than ligand **17** (*cis*) (Table 2, Entry 3, 4). The TIQ amino alcohols with smaller substituents at the C^3-α position (ligands major **24** and minor **24**) showed a decrease in activity compared to ligand **14**.

Having identified an efficient and selective ligand for catalytic purposes, the system was varied with the introduction of different metal complexes. Half-sandwich π complexes such as ruthenium, rhodium or iridium complexes are the most important metal sources associated with amino alcohol ligands in ATH reactions.[1,3,24] In this study, we measured the reactivity of **14** with various organometallic complexes i.e. $[Ru(p\text{-cymene})Cl_2]_2$, $[RhCl_2Cp^*]_2$ and $[IrCl_2Cp^*]_2$.

All of the new complexes, catalytic conversions and selectivities are shown in Table 3. Also the reactions at lower temperatures provided improved selectivities. We repeated the hydrogenation of acetophenone at 0 °C using $[Ru(p\text{-cymene})Cl_2]_2$, and an excellent

selectivity was observed with upto 99 % *ee* but with a low conversion of 35 %. $[RhCl_2Cp^*]_2$ gave a higher reactivity (94 % conversion) than $[Ru(p\text{-cymene})Cl_2]_2$, but with a diminished enantioselectivity of 90 % *ee* (Table 3, Entry 4). The reaction was repeated at different temperatures affording respectable selectivities with moderate conversions (Table 3, Entries 5, 6). Due to the higher rates when rhodium was used, we attempted the same reaction with a low catalyst loading of 0.5 mol- % (metal/substrate). The reaction rate was reduced providing good selectivity and conversion rates (Table 3, Entry 7). Replacing rhodium with iridium gave poorer selectivity and conversion results.

Table 3. ATH of acetophenone using different metal precursors with chiral ligand **14**.



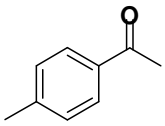
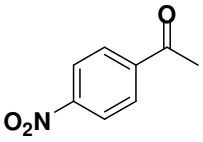
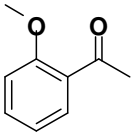
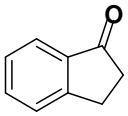
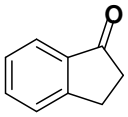
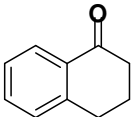
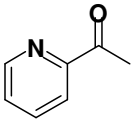
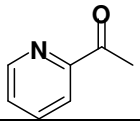
Entry	Metal	Temp.	Time (h)	Conv.(%)[a]	*ee* (%)(*R*/*S*)[b]
1	$[Ru(p\text{-cymene})Cl_2]_2$	RT	0.75	94	94 (*R*)
2	$[Ru(p\text{-cymene})Cl_2]_2$	0 °C	1.0	35	99 (*R*)
3[c]	$[Ru(p\text{-cymene})Cl_2]_2$	RT	1.25	85	94 (*R*)
4	$[RhCl_2Cp^*]_2$	RT	0.25	94	90 (*R*)
5	$[RhCl_2Cp^*]_2$	0 °C	0.5	86	94 (*R*)
6	$[RhCl_2Cp^*]_2$	−15 °C	0.5	42	99 (*R*)
7[c]	$[RhCl_2Cp^*]_2$	RT	0.5	94	91 (*R*)
8	$[IrCl_2Cp^*]_2$	RT	0.5	35	75 (*R*)

[a]Determined by chiral GC analysis.
[b]Absolute configuration determined by comparison with reported optical rotation. Values reported are the average of three runs.
[c]Reaction was performed using 0.5 mol- % of metal/substrate.

Having identified the most efficient metal complex in our system we then undertook studies on different substrates. The results are summarized in Table 4. In general, when compared to the reduction of acetophenone, all of the other substrates tested led to decreased

conversions. The substrates can be grouped based on their electronic and steric properties. Electron-donating (4-methylacetophenone) or electron-withdrawing (4-nitroacetophenone) groups decreased the rate of conversion. Replacing the phenyl ring with a pyridyl species completely arrests any reactivity. This could be due to transient coordination of the sp^2 nitrogen atom to the metal center thereby disrupting the active transition state. An increase in steric bulk (indanone and tetralone) renders a loss in selectivity and conversion rate.

Table 4. ATH of various aryl-alkyl ketones with [Ru(*p*-cymene)Cl_2]$_2$ and **14** as chiral ligand at ambient temperature.

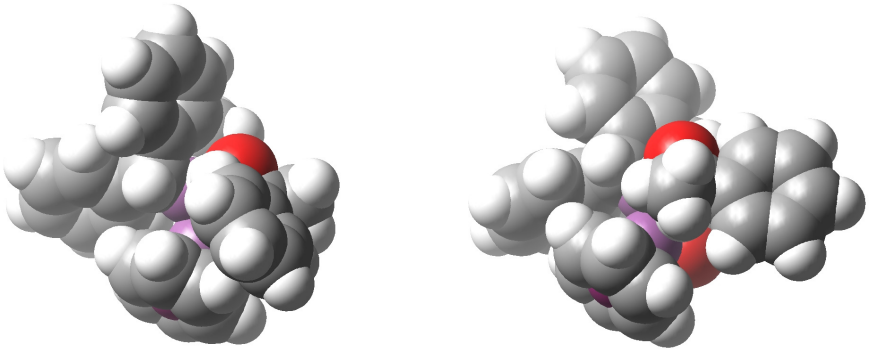
Entry	Substrate	Time(h)	Conv. (%)[a]	*ee* (*R/S*)[b]
1		1.0	80	92 (*R*)
2		1.0	98	68 (*R*)
3		1.0	94	82 (*S*)
4		1.0	31	65 (*S*)
5		24.0	40	69 (*S*)
6		1.0	40	*racemic*
7		1.0	NR[c]	NR[c]
8		24.0	NR[c]	NR[c]

[a]Determined by chiral GC analysis.
[b]Absolute configuration determined by comparison with reported optical rotation. Values reported are the average of two runs.
[c]No reaction observed.

The observed enantioselectivity could be explained by the mechanism proposed for Ru-catalyzed transfer hydrogenations using amino alcohol ligands.[16,25] According to this mechanism, a ruthenium hydride and a proton from the ligand are simultaneously transferred from the catalyst to the prochiral carbonyl group. The structures of the two possible

diastereomeric transition states were calculated using the Jaguar program.[26] The transition-state structures were located using the quadratic synchronous transit (QST) method and the B3LYP functional together with the LACVP ECP basis set. Normal mode analysis revealed one imaginary frequency for each structure (Figure 3). LACVP in Jaguar defines a combination of the LANL2DZ basis set for ruthenium[27] and the 6-31G basis set for other atoms. LACVP implies the use of an effective core potential for 28 core electrons of ruthenium and a (5s,6p,4d) primitive basis contracted to [3s,3p,2d]. Final energies were retrieved from single-point calculations at B3LYP/LACV3p+**.

LACV3p+** differs from LACVP by using the 6-311+G** basis set in place of 6-31G.



3.2 Kcal/mol 0.0 Kcal/mol

Figure 2. The calculated (*S*) (left) and (*R*) (right) transition states for the reduction of acetophenone using ligand **14**. The (*S*)-transition state showing a close-contact between the phenyl of the substrate and the arene ligand, making it less favorable. The Cartesian coordinates of the optimized structures are available as supplementary material.

The energy of the transition state leading to the (*S*)-alcohol product is significantly higher in energy than that of the (*R*)-alcohol product. This theoretical result supports the observed experimental result for ligand **14** reported in Tables 1, 2, 3, and 4.

CONCLUSIONS

We have synthesized and evaluated seven ligands of a new class of N,O TIQ compounds. These ligands were coordinated with ruthenium, and they were evaluated in the asymmetric transfer hydrogenation of acetophenone. C^1-substituted TIQ amino primary alcohol **14** gave

rise to a catalyst that induced good enantioselectivity, upto 94 % *ee*. The reaction was repeated under various conditions, affording 99 % *ee* at lower temperature as the best result. The rhodium complex with amino alcohol ligand **14** showed the fastest rate of all complexes evaluated in this study, 94 % conversion in 0.5 h using a 0.5 mol- % ratio of metal/substrate with a lower selectivity of 91 % *ee*. Considering the good selectivity at ambient temperature, we screened different alkyl aryl ketone substrates, rendering moderate to reasonable results. Acetophenone as substrate gave the best results.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments. Chemical shifts are expressed in ppm relative to TMS, and coupling constants are reported in Hz. NMR Spectra were obtained at room temperature, except if stated different. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified by column chromatography using Silica gel (60–200 mesh except if stated different). All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin Elmer Polarimeter (Model 341). All melting points are uncorrected. All testing reactions were carried out under dry UHP Argon gas. The results of all testing reactions that were analyzed using GC analysis were obtained on an Agilent capillary gas chromatograph with a CP-Chirasil-β-Dex column (25 m with 0.25 mm inner diameter), nitrogen as carrier gas, and a flame ionization detector. LC traces were recorded on an Agilent 1100 HPLC with reverse phase using 0.1 % formic acid in acetonitrile and Millipore water. High resolution mass spectrometric data was obtained using a Bruker microTOF-Q II instrument operating at ambient temperatures, using a sample concentration of approximately 1 ppm.

General procedure for transfer hydrogenation of aromatic ketones

To an oven-dried Schlenk tube was added $[Ru(p\text{-cymene})Cl_2]_2$ (3.0 mg, 4.8 μmol), ligand (4 equiv.) and the system was evacuated for 10 minutes. Thereafter, freshly distilled isopropyl alcohol (6 mL) was added under a dry argon atmosphere. The mixture was stirred for 15 minutes and freshly prepared 0.1 M t-BuOK solution was added to the complex, followed by the substrate. An aliquot of the reaction mixture was tested at different intervals by quenching with 5 % acetic acid in isopropyl alcohol and passing through a pad of silica-gel

and monitoring by GC with a chiral β-dex column. The percentage *ee* values were calculated from the integration values of the GC peaks for each enantiomer. The experiment was repeated two or three times and the average values are reported in the tables.

General procedure for compounds 12 and 15

To a solution of C^1 substituted TIQ carboxylic acid (1.0 g, 3.5 mmol) in dioxane (20 mL) and water (10 mL) at 0 °C a solution of potassium hydrogen carbonate (2.1 g, 21.1 mmol) in water (10 mL) was added dropwise over 15 minutes followed by addition of Cbz-Cl (0.65 g, 3.8 mmol). The solution was stirred for 1.5 hours at 0 °C and then at ambient temperature for a further 1.5 hours. The reaction was monitored with LC-MS (by neutralizing the reaction mixture with 10 % HCl and extracting with ethyl acetate). The solvent was evaporated under reduced pressure and the residue dried under high vacuum. The crude residue obtained was dissolved in acetone (40 mL) and potassium hydrogen carbonate (7.0 g, 70.1 mmol) was added followed by dimethyl sulfate (4.4 g, 35.2 mmol) and stirred for 16 hours (overnight) at reflux. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (60/40, R_f 0.6). The reaction solvent was evaporated under reduced pressure, and ethyl acetate (60 mL) was added and the resulting mixture was washed with 20 mL (2 × 10) of water followed by 10 mL of brine. The organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to afford crude Cbz-ester, which was purified by column chromatography using 0–40 % ethyl acetate in hexane as the eluent to yield approximately 1.3 g (80 % yield) of pure compounds **12** and **15**.

General deprotection procedure for preparation of amino esters 13 and 16

A solution of the Cbz protected TIQ ester (1.0 g, 2.1 mmol) in THF (20 mL) was added to a suspension of activated 10 wt.- % Pd/C (500 mg) in dry MeOH (20 mL). The mixture was supplied with H_2 under atmospheric pressure and stirred at room temperature for 1 hour. The reaction was monitored with TLC using hexane/ethyl acetate (40/50, R_f 0.4). The Pd/C was filtered off through a celite pad and washed with methanol (20 mL). The filtrate was evaporated under reduced pressure affording the crude amino ester, which was purified by column chromatography using 0–50 % ethyl acetate in hexane as the eluent to yield approximately 0.65 g (95 % yield) of the pure compounds **12** and **16**.

General procedure for 14 and 17

A solution of amino ester (0.5 g, 1.5 mmol) in dry THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.18, 4.5 mmol) in dry THF (20 mL) under N_2 atmosphere at 0 °C. The mixture was stirred at 0 °C for 2 hours, and the reaction was monitored with TLC using hexane/ethyl acetate (50/50, R_f 0.5). Excess lithium aluminium hydride was quenched with saturated sodium sulphate solution at 0 °C. The reaction mixture was filtered and the solid was washed with THF (20 mL). The organic solution was evaporated to dryness, ethyl acetate (20 mL) was added to the residue and the resulting solution was washed with water (2 × 5 mL), the organic layer was separated and dried over anhydrous $MgSO_4$ to afford the crude amino alcohol. This was purified by gradient column chromatography; Solvent A: 10:90 saturated ammonia in DCM:DCM and solvent B: 2:98 MeOH:DCM to yield approximately 0.33 g (70 % yield) of pure amino alcohols **14** and **17**.

(*S*)-Diphenyl(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (8)

White solid: m.p. 104–106 °C (MeOH); Spectroscopic data identical to literature values.[28]; $[\alpha]^{20}_D$ − 130 (*c* 0.26 in $CHCl_3$); HRESIMS *m/z* 316.1774 $[M + 1H]^{1+}$ (calc. for $C_{22}H_{22}NO$, 316.1701).

Spectroscopic data of novel compounds

(1*R*,3*S*)-2-Benzyl 3-methyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (12)

R_f 0.6 (hexane/EtOAc 6:4); White solid: m.p. 127–129 °C (hexane–ethyl acetate); $[\alpha]^{20}_D$ =+9.54 (*c* 0.26 in $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d6, 100 °C): δ 7.36–7.15 (m, 9H), 7.09 (s, 1H), 6.76 (s, 1H), 5.16–5.05 (m, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H), 3.21 (dd, *J* = 15.69, 5.97 Hz, 1H), 3.13–3.04 (m, 2H); ^{13}C NMR (150 MHz, DMSO, 100 °C): δ 172.1, 155.9, 149.0, 148.9, 137.0, 130.3, 128.6, 128.1, 127.7, 126.9, 126.4, 124.2, 113.4, 113.2, 67.2, 59.6, 56.8, 56.6, 55.9, 55.8, 52.1, 30.9; IR (neat): 2942, 1744, 1714, 1204, 735, 698 cm^{-1}; HRESIMS *m/z* 462.1896 $[M + 1H]^{1+}$ (calc. for $C_{27}H_{28}NO_6$, 462.1916) and 484.1720 $[M + Na]^{23+}$(calc. for $C_{27}H_{27}NNaO_6$, 484.1736).

(1*R*,3*S*)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13)

R_f 0.5 (hexane/EtOAc 6:4); Colorless oil; $[\alpha]^{20}_D$ =+15.38 (*c* 0.26 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (m, 3H), 7.23–7.16 (m, 2H), 6.65 (s, 1H), 6.34 (s, 1H), 5.25 (s,

1H), 3.88 (s, 3H), 3.80 (q, *J* = 8.58, 5.06 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.15 (dd, *J* = 16.02, 5.08 Hz, 1H) 3.01 (dd, *J* = 16.02, 8.68Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 147.9, 147.4, 144.5, 128.6, 128.4, 127.9, 127.3, 125.6, 111.1, 110.8, 58.8, 55.8, 52.0, 51.3, 31.0; IR (neat): 2928, 2600, 1746, 1516, 1250, 1123, 727 cm^{-1}; HRESIMS *m/z* 328.1547 $[M + 1H]^{1+}$ (calcd for $C_{19}H_{22}NO_4$, 328.1548).

[(1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl]-methanol (14)

R_f 0.4 (CH_2Cl_2/MeOH/sat.NH_3 in $CHCl_3$ 9.5:0.5:1); Pale yellow solid; m.p. 115–117 °C (CH_2Cl_2); $[\alpha]^{20}_D$ =+3.7 (*c* 0.27 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 3H), 7.18–7.13 (m, 2H), 6.64 (s, 1H), 6.42 (s, 1H), 5.19 (s, 1H), 3.88 (s, 3H), 3.72 (s, 3H), 3.66–3.60 (dd, *J* = 10.76, 2.96 Hz, 1H), 3.49–3.41 (dd, *J* = 10.64, 7.81 Hz, 1H), 3.12–3.02 (m, 1H), 2.70 (dd, *J* = 16.38, 4.56 Hz, 1H), 2.57 (dd, *J* = 16.38, 10.28 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.2, 144.6, 128.7, 128.2, 127.1, 126.7, 111.5, 110.9, 65.7, 58.9, 55.9, 55.8, 48.8, 30.5; IR (neat): 3264, 2832, 1515, 1222, 1066, 981, 726, 694 cm^{-1}; HRESIMS *m/z* 300.1622 $[M + 1H]^{1+}$ (calcd for $C_{18}H_{22}NO_3$, 300.1600).

(1*S*,3*S*)-2-Benzyl 3-methyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoqui-noline-2,3(1H)-dicarboxylate (15)

Colorless oil; $[\alpha]^{20}_D$ =–38.27 (*c* 0.39 in $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d6, 100 °C): δ 7.40–7.15 (m, 10H), 7.02 (s, 1H), 6.93 (s, 1H), 5.16 (s, 1H), 4.43 (q, *J* = 10.81, 5.71 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.49 (s, 3H), 3.02 (dd, *J* = 15.09, 5.67 Hz, 1H), 2.70 (dd, *J* = 14.73, 11.13 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d6, 100 °C): δ 172.1, 156.1, 149.4, 148.8, 142.0, 136.9, 129.6, 128.7, 128.2, 128.2, 127.9, 127.5, 127.1, 126.2, 113.5, 67.6, 67.6, 58.8, 56.9, 56.8, 56.7, 56.7, 56.5, 51.9, 30.2, 30.1; IR (neat): 1752, 1693, 1514, 1404, 1295, 1216, 1102, 697, 596 cm^{-1}; HRESIMS *m/z* 462.1906 $[M + 1H]^{1+}$ (calcd for $C_{27}H_{28}NO_6$, 462.1916) and 484.1730 $[M + Na]^{23+}$(calcd for $C_{27}H_{27}NO_6Na$, 484.1736).

(1*S*,3*S*)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (16)

R_f 0.6 (hexane/EtOAc 6:4); Colorless oil; $[\alpha]^{20}_D$ =–42.0 (*c* 0.24 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 6.64 (s, 1H), 6.17 (s, 1H), 5.09 (s, 1H), 3.91–3.86 (m, 4H), 3.85–3.74 (m, 4H), 3.56–3.61 (s, 3H), 3.41–3.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 147.7, 147.3, 143.8, 130.2, 129.0, 128.5, 127.8, 126.0, 111.2, 110.5, 62.8,

56.5, 55.8, 55.8, 52.1, 32.2; IR (neat): 3020, 1737, 1514, 1244, 1213, 749, 665 cm^{-1}; HRESIMS *m/z* 328.1548 $[M + 1H]^{1+}$ (calcd for $C_{19}H_{22}NO_4$, 328.1548).

((1*S*,3*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (17)

R_f 0.4 (CH_2Cl_2/MeOH/sat.NH_3 in $CHCl_3$ 9.5/0.5/1); Off white solid: m.p. 175–177 °C (CH_2Cl_2); $[\alpha]^{20}_D$ =–24.0 (*c* 0.25 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 6.62 (s, 1H), 6.14 (s, 1H), 5.04 (s, 1H), 3.85 (s, 1H), 3.79–3.72 (m, 1H), 3.62–3.53 (m, 4H), 3.26–3.10 (m, 1H), 3.00–2.52 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.0, 143.7, 130.2, 128.9, 128.5, 127.7, 126.8, 111.4, 110.7, 65.5, 66.5, 62.8, 55.8, 55.7, 55.7, 31.2; IR (neat): 3256, 2919, 1511, 1453, 1258, 1215, 1100, 1073, 822, 737, 700, 561 cm^{-1}; HRESIMS *m/z* 300.1594 $[M + 1H]^{1+}$ (calcd for $C_{18}H_{22}NO_3$, 300.1600).

(1*R*,3*S*)-Methyl 2-benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroiso-quin-oline-3-carboxylate (18)

To a solution of compound **13** (0.5 g, 1.5 mmol) in acetonitrile (20 mL), solid K_2CO_3 (635 mg, 4.5 mmol) was added followed by benzyl bromide (286 mg, 1.6 mmol) at ambient temperature. Thereafter the reaction mixture was refluxed for 3 hours. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (60/40, R_f 0.5). The solvent was evaporated, 30 mL of ethyl acetate was added and the mixture washed with 2 × 10 mL of water, the organic layer was separated, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford crude product, which was purified by column chromatography using 0–20 % ethyl acetate/hexane as the eluent to yield 0.44 g (90 % yield) pure benzyl ester (**18**): R_f 0.7 (hexane/EtOAc 6/4); White solid; m.p. 146–148 °C (hexane/EtOAc); $[\alpha]^{20}_D$ =–164.3 (*c* 0.28 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J*=7.26 Hz, 2H), 7.32–7.16 (m, 9H), 6.54 (s, 1H), 6.26 (s, 1H), 5.19 (s, 1H), 3.85–3.72 (m, 6H), 3.61 (s, 6H), 3.23 (dd, *J*=5.10, 15.66 Hz, 1H), 2.98 (dd, *J*=3.00, 15.72, Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.5, 147.4, 147.3, 145.4, 139.3, 129.7, 128.7, 128.3, 128.2, 127.1, 127.0, 123.8, 111.5, 110.9, 64.7, 55.7, 55.7, 55.3, 54.6, 51.2, 31.5; IR (neat): 2944, 1729, 1511, 1152, 753, 699 cm^{-1}; HRESIMS *m/z* 418.2012 $[M + 1H]^{1+}$ (calcd for $C_{26}H_{28}NO_4$, 418.2018).

[(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquin-olin-3-yl]diphenylmet-hanol (19)

A solution of compound **18** (500 mg, 1.1 mmol) in THF (10 mL) was added to freshly prepared Grignard reagent of phenyl magnesium bromide (2.17 g, 11.9 mmol) under dry inert atmosphere at ambient temperature for 15 minutes. Completion of the reaction was monitored with TLC, and the reaction mixture was quenched with saturated ammonium chloride solution at 0 °C. The reaction mixture was filtered off and washed with 20 mL of ethyl acetate. The filtrate was evaporated under reduced pressure to yield 0.52 g (80 % yield) of the crude C_3-α diphenyl tert alcohol: R_f 0.5 (hexane/EtOAc 6/4); White solid: m.p. 205–207 °C (hexane/EtOAc); $[\alpha]^{20}_D$ =+20.37 (*c* 0.27 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ7.44 (d, *J*=1.16 Hz, 2H), 7.32–7.10 (m, 14H), 7.0–6.88 (m, 6H), 6.69 (s, 1H), 6.38 (s, 1H), 4.74 (s, 1H), 4.21 (d, *J*=13.60 Hz, 1H), 4.14 (q, *J*=3.70, 12.74 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.57 (s, 1H), 3.30–3.18 (m, 2H), 2.60 (dd, *J*=3.60, 16.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 147.5, 146.1, 145.5, 143.4, 140.2, 129.8, 129.1, 128.2, 128.1, 127.7, 127.6, 127.0, 126.7, 126.3, 126.1, 125.5, 112.1, 111.6, 79.4, 64.6, 56.8, 55.8, 55.8, 51.8, 23.4); IR (neat): 3589, 1509, 1240, 1093, 694 cm^{-1}; HRESIMS *m/z* 542.2698 $[M + 1H]^{1+}$ (calcd for $C_{37}H_{36}NO_3$, 542.2695).

[(1*R*,3*S*)-6,7-Dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]diphe-nylmethanol (20)

A solution of compound **19** (400 mg, 0.7 mmol) in methanol (10 mL/mmol) was added to a suspension of activated Pd/C (200 mg, 10 wt.- %) in dry MeOH under inert atmosphere. The reaction mixture was connected to H_2 source at 1 atmosphere and stirred for 6 hours at room temperature. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (40/60, R_f 0.5). The Pd/C was filtered off through a celite pad and washed with methanol (10 mL). The filtrate was evaporated under reduced pressure affording the crude amino ester, which was purified by column chromatography using 0–2 % methanol in dichloromethane as the eluent to yield 0.30 g (92 % yield) of pure compound **20**. R_f 0.3 (hexane/EtOAc 5/5); Pale yellow solid: mp 77–79 °C (CH_2Cl_2); $[\alpha]^{20}_D$ –119.5 (*c* 0.26 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ7.42–7.34 (m, 5H), 7.29–7.24 (t, *J*=15.20 Hz, 1H), 7.05–7.21 (m, 6H), 7.02–6.96 (m, 2H), 6.56 (s, 1H), 6.43 (s, 1H), 5.23 (s, 1H), 3.89–3.85 (q, *J*=10.94, 3.86 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.03–2.92 (dd, *J*=16.42, 10.94 Hz, 1H), 2.24–2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ148.0, 147.2, 145.1, 144.6, 144.0, 128.4, 128.0, 127.7, 127.4, 126.9, 126.5, 126.2, 126.0, 125.4, 111.4, 110.6, 78.3, 60.0, 55.9, 55.8, 51.9, 28.5; IR (neat): 2926, 1512,

1447, 1243, 1063, 698 cm^{-1}; HRESIMS *m/z* 452.2220 $[M + 1H]^{1+}$ (calcd for $C_{30}H_{30}NO_3$, 452.2226).

[(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (21)

A solution of compound **18** (1.30 g, 3.1 mmol) in dry THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.35 g, 9.3 mmol) in 30 mL of dry THF under N_2 atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (80/20, R_f: 0.6). Excess lithium aluminium hydride was quenched with saturated sodium sulphate solution at 0 °C. The reaction mixture was filtered and the solid washed with 20 mL of THF. The solvent was evaporated to dryness under reduced pressure. Ethyl acetate (20 mL) was added and the resulting solution washed with water (2 × 5 mL). The organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated to give crude amino alcohol. The crude product was purified with column chromatography using 0–40 % ethyl acetate in hexane as a mobile phase and silica gel as a stationary phase to yield 0.85 g (70 % yield) of pure amino alcohol. R_f 0.3 (hexane/EtOAc 5/5); Yellow solid: m.p. 108−110 °C; $[\alpha]^{20}_D$ =+66.0 (*c* 0.25 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.28 (m, 5H), 7.24–7.12 (m, 3H), 6.98 (d, *J*=6.88 Hz, 2H), 6.70 (s, 1H), 6.41 (s, 1H), 4.85 (s, 1H), 3.98–3.89 (m, 4H), 3.77−3.69 (m, 4H), 3.58−3.49 (m, 1H), 3.41−3.29 (m, 2H), 2.69 (dd, *J*=11.60, 11.56 Hz, 1H), 2.53 (dd, *J*=4.68, 4.68 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.5, 143.7, 139.2, 129.2, 129.0, 128.5, 127.9, 127.2, 126.9, 125.9, 112.3, 111.6, 62.6, 61.2, 55.8, 52.2, 49.0, 25.5; IR (neat): 3511, 2919, 1609, 1514, 1292, 1127, 1029, 697 cm^{-1}; HRESIMS *m/z* 390.2060 $[M + 1H]^{1+}$ (calcd for $C_{25}H_{28}NO_3$, 390.2069).

(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carbaldehyde (22)

To a solution of oxalyl chloride (0.34 g, 2.6 mmol) in dry CH_2Cl_2 (12 mL) at −78 °C was added a solution of DMSO (0.45 g, 5.8 mmol) in CH_2Cl_2 (1.2 mL) over 5 minutes, and the reaction mixture was stirred for 10 minutes at −78 °C. Compound **21** (0.95 g, 2.4 mmol) was added as a solution in CH_2Cl_2 (1 mL) over 5 minutes. The reaction mixture was stirred for 15 minutes, and an excess of Et_3N (0.86 g, 8.5 mmol) was added over 5 minutes. The cooling bath was removed for the temperature to rise to room temperature. Water (30 mL) was added

and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded a residue that was purified by column chromatography using 0–30 % ethyl acetate in hexane as a mobile phase and silica gel as a stationary phase to yield approximately 0.80 g (85 % yield) of the aldehyde 22 as an yellow oil: R_f 0.8 (hexane/ethyl acetate 7/3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.40–7.16 (m, 10H), 6.68 (s, 1H), 6.33 (s, 1H), 5.0 (s, 1H), 3.87 (s, 3H), 3.77–3.63 (m, 6H), 3.01–2.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 147.9, 147.6, 144.1, 138.8, 129.1, 129.0, 127.4, 127.3, 127.2, 124.7, 111.9, 111.3, 63.8, 60.9, 55.8, 55.8, 54.1, 25.2; IR (neat): 2931, 2832, 1726, 1511, 1238, 1220, 697 cm^{-1}.

1-[(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]ethanol (23)

A solution of compound **22** (0.65 g, 1.6 mmol) in dry THF (10 mL) was added to freshly prepared methyl magnesium iodide (1.4 g, 8.4 mmol) under inert atmosphere at 0 °C for 15 minutes. The reaction was stirred at 0 °C for 3 hours and monitored with TLC by quenching the aliquote of reaction mixture with a saturated ammonium chloride solution at 0 °C for 15 minutes using 30/70 ethyl acetate/hexane. The reaction mixture was filtered and the solid washed with ethyl acetate (20 mL). Evaporation of the filtrate gave 0.54 g of the crude C_3-α methyl secondary alcohol (80 % yield) obtained as a 9:1 mixture of diastereomers, which were separated with column chromatography using 0–40 % ethyl acetate/hexane and silica gel (230–400 mesh) as a stationary phase.

Major 23

R_f 0.6 (hexane/EtOAc 7/3); Yellow oil; $[\alpha]^{20}_D$ =+64.15 (*c* 0.26 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.05 (m, 12H), 6.74 (s, 1H), 6.39 (s, 1H), 4.74 (s, 1H), 3.92–3.98 (m, 1H), 3.91 (s, 3H), 3.84 (d, 1H), 3.73 (s, 3H), 3.48 (d, 1H), 2.95–2.76 (m, 3H), 2.34–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 147.2, 144.1, 139.9, 129.0, 128.9, 128.4, 127.7, 127.0, 126.6, 125.9, 112.3, 111.7, 69.7, 63.1, 57.2, 55.8, 55.8, 50.7, 31.9, 29.6, 29.3, 25.7, 21.6; IR (neat): 2924, 2853, 1510, 1449, 1243, 1219, 1099, 1028, 749, 698 cm^{-1}; HRESIMS *m/z* 404.2225 $[M + 1H]^{1+}$ (calcd for $C_{26}H_{30}NO_3$, 404.2226).

Minor 23

R_f 0.65 (hexane/EtOAc 7/3); Yellow oil; $[\alpha]^{20}_D$ =+57.69 (*c* 0.28 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.37 (m, 4H), 7.21–7.14 (s, 3H), 6.92 (d, 2H), 6.73 (s, 1H), 6.42 (s, 1H), 4.86 (s, 1H), 4.0 (d, *J*=12.92 Hz, 1H), 3.92 (s, 3H), 3.91–3.82 (m, 2H), 3.75 (s, 3H), 3.33 (d, *J*=12.88 Hz, 1H), 2.89–2.54 (m, 3H), 2.37–2.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.6, 143.3, 139.0, 129.4, 128.6, 127.3, 126.9, 125.2, 112.3, 111.6, 65.7, 62.3, 57.9, 55.9, 55.8, 49.3, 24.5, 19.3; IR (neat): 2931, 2850, 1510, 1493, 1450, 1222, 1102, 751, 699 cm^{-1}; HRESIMS *m/z* 404.2220 $[M + 1H]^{1+}$ (calcd for $C_{26}H_{30}NO_3$, 404.2226).

(*S*)-1-((1*R*,3*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)ethanol (24)

A solution of benzyl protected TIQ *sec* alcohol **23** (300 mg, 0.7 mmol) in methanol (10 mL) was added to a suspension of 10 wt.- % Pd/C (0.2 g) in methanol (10 mL). The reaction mixture was connected to a H_2 source at atmospheric pressure and stirred at room temperature for 6 hours. The Pd/C was filtered off on a celite pad and the filtrate was concentrated under reduced pressure to afford crude amino ester. The products were purified with column chromatography using hexane/ethyl acetate as an eluent to yield a combined mass of 0.14 g (60 % yield) for major **24** and minor **24**.

Major 24

R_f 0.3 (hexane/EtOAc 4/6); Brown oil; $[\alpha]^{20}_D$ =–11.11 (*c* 0.27 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.19 (m, 3H), 7.13–7.03 (m, 2H), 6.66 (s, 1H), 6.39 (s, 1H), 5.19 (s, 1H), 3.86 (s, 3H), 3.73–3.65 (m, 4H), 2.83–2.74 (m, 1H), 2.92–2.85 (m, 1H), 2.67–2.59 (dd, *J*=4.20, 4.21 Hz, 1H), 1.12 (d, *J*=6.40 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.1, 145.0, 128.5, 128.2, 127.7, 127.2, 127.1, 111.5, 110.8, 69.5, 59.6, 55.8, 51.5, 27.7, 18.2; IR (neat): 2930, 1589, 1520, 1454, 1346, 1226, 1124, 755, 702 cm^{-1}; HRESIMS *m/z* 314.1761 $[M + 1H]^{1+}$ (calcd for $C_{19}H_{24}NO_3$, 314.1756).

Minor 24

R_f 0.3 (hexane/EtOAc 4/6); Colorless oil; $[\alpha]^{20}_D$ =–10.71 (*c* 0.28 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ=7.40–7.15 (m, 5H), 6.66 (s, 1H), 6.40 (s, 1H), 5.50 (s, 1H), 3.88 (s, 3H), 3.81–3.67 (m, 4H), 2.97–2.69 (m, 3H), 1.16 (d, *J*=5.72 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 147.9, 139.7, 129.3, 128.5, 125.0, 111.2, 110.5, 68.0, 57.9, 55.9, 55.8, 54.3, 29.4, 19.5; IR (neat): 2933, 1694, 1513, 1451, 1243, 1089, 751 cm^{-1}; HRESIMS *m/z* 314.1756 $[M + 1H]^{1+}$ (calcd for $C_{19}H_{24}NO_3$, 314.1756).

ACKNOWLEDGEMENT

This work was supported by National Research Foundation (South Africa, GUN nr 2073251), SA/Swedish Research Links Programme grant and Aspen Pharmacare, SA. The technical staff at UKZN chemistry department, Westville campus is thanked for their assistance. The rest of the group members are thanked for their help and support.

SUPPORTING INFORMATION

NMR, LC traces, HRMS and Cartesian coordinates for DFT calculations.

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CHAPTER 3

SYNTHESIS OF TETRAHYDROISOQUINOLINE (TIQ)-DIAMINE LIGANDS AND THEIR APPLICATION IN ASYMMETRIC TRANSFER HYDROGENATION

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ABSTRACT

The use of the tetrahydroisoquinoline scaffold is well documented in biologically active compounds. However, reports of the utilisation of tetrahydroisoquinoline compounds in asymmetric catalysis are limited. The synthesis of novel diamine ligands possessing the tetrahydroisoquinoline (TIQ) backbone and evaluation of their activity in the asymmetric transfer hydrogenation of acetophenone are presented. The diamine ligands in conjunction with i-PrOH as the hydrogen source and $[RhCl_2(Cp^*)]_2$ as the metal precursor proved to be the most effective of the tetrahydroisoquinoline derivatives for this catalytic system. Water was found to have a profound influence on the enantioselectivity of the reaction. Optimisation of the amount water, i-PrOH and catalytic loading rendered the best result of 70% enantioselectivity for the (S)-1-phenylethanol isomer product.

INTRODUCTION

Since the isolation of naphthyridinomycin in 1974, the biological activity of tetrahydroisoquinoline carboxylic acid derivatives has been widely investigated.[1-3] Previous reports on the use of tetrahydroisoquinoline derivatives as catalytic ligands have yielded limited success, with poor to moderate enantioselectivities in asymmetric catalysis such as allylic alkylation[4] and borane-mediated hydrogenation reactions.[5-6] However, in a related study the use

of different tetrahydroisoquinoline ligands for the addition of diethylzinc to benzaldehyde gave promising results.[7] We have recently reported the use of tetrahydroisoquinoline amino alcohol derivatives to catalyse the asymmetric transfer hydrogenation of prochiral ketones with high reaction rates and moderate to good selectivities.[8]

It has been shown in the literature that amine and diamine based ligands can be used for various asymmetric catalytic reactions.[9-13] Noyori *et al*. reported a variety of simple amino alcohols and diamines with a ruthenium precursor, an *i*-PrOH source and KOH as a co-catalyst for the reduction of acetophenone (see Fig. 1).[14-15] It was noted that a two carbon bridge between the donors formed the ideal chelater, and that unlike the amino alcohols, the diamines required one of the amines to be functionalised with an electron-withdrawing group. Inherently the *p*-toluene sulfonyl (tosyl) group proved effective, which in turn spawned the (1*S*,2*S*)-*N*-(*p*-toluenesulfony1)-1,2-diphenylethylenediamin (Ts-DPEN) **1**.[15]

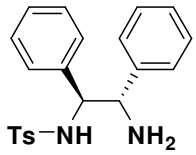

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Figure 1. Noyori's diamine ligand

Since this discovery there has been a surge of interest into asymmetric transfer hydrogenation, with the development of many successful catalysts.[16-20] Other studies have attempted to optimise the performance of these catalysts, by varying steric, electronic and solubility properties.[21-22] Development of the triethylamine: formic acid azeotrope (TEAF) and more recently formate salts in aqueous media have also broadened the scope for activity and selectivity.[20,23] The aqueous systems show promise and in many cases enhanced overall performance has been observed in the presence of water. A rigorous screening of these variables is necessary to discover the potential of any new ligand.

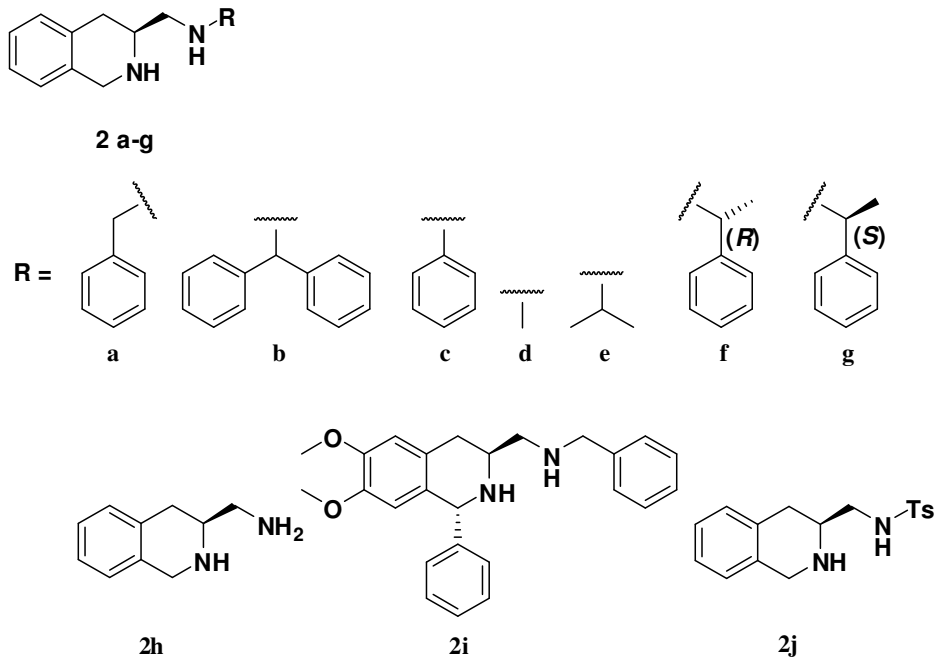


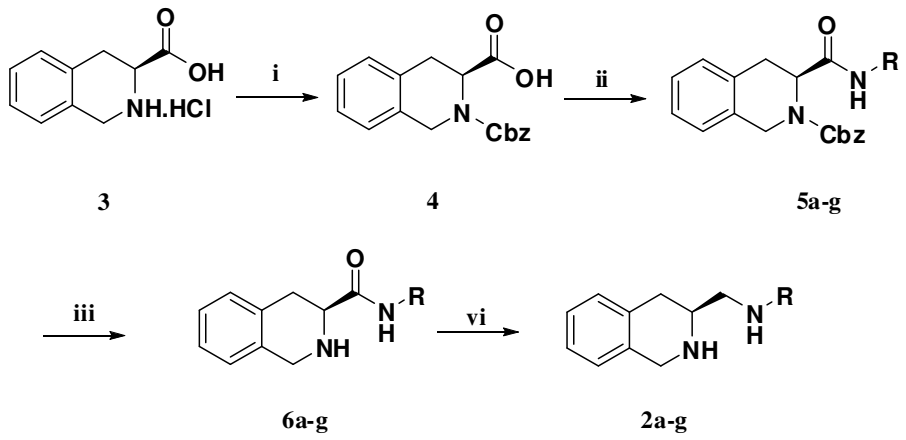
Figure 2. Diamine ligands studied for activity in asymmetric transfer hydrogenation

Herein we report a systematic study of novel diamine ligands possessing tetrahydroisoquinoline as a rigid and tuneable chiral backbone in pre-catalysts for the asymmetric reduction of acetophenone.

RESULTS AND DISCUSSION

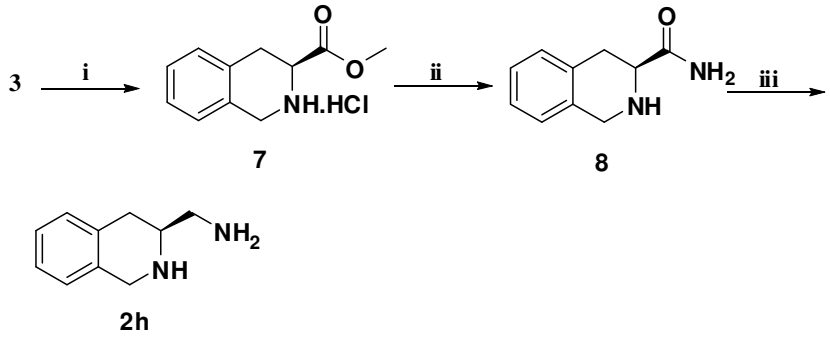
SYNTHESIS

Ligands **2a–g** (Scheme 1) were synthesised from commercially available tetrahydroisoquinoline amino acid **3**. Benzyl carbamate (Cbz) protection of **3** allowed for subsequent coupling of the respective amines to yield **5a–g**. Thereafter, removal of the Cbz group with palladium on carbon (Pd/C) and one atmosphere of hydrogen (H_2) gas afforded the amides **6a–g**. The desired diamine products were obtained by lithium aluminium hydride ($LiAlH_4$) reduction of **6a–g**.



Scheme 1. Synthetic route used to prepare **2a-g**. Reagents and conditions: (i) $KHCO_3$, dioxane, water, Cbz-Cl; (ii) EDC.HCl, HOBt, R-NH_2, DMAP, DMF; (iii) 10 % wt. Pd/C, H_2, MeOH, THF; (iv) $LiAlH_4$, THF.

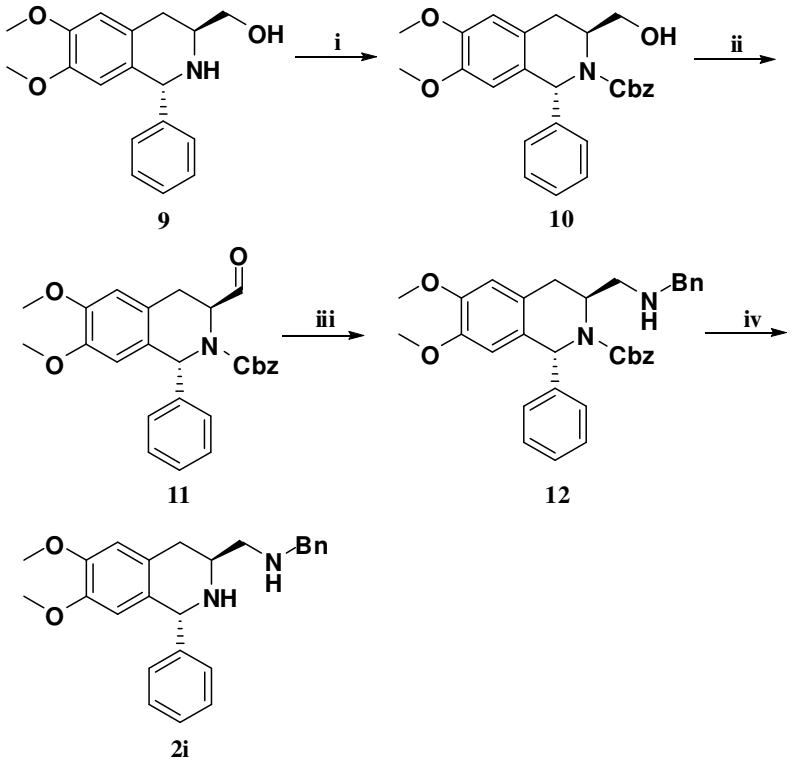
Ligand **2i** (Scheme 2) was prepared as previously reported.[24-25] Esterification of **3** via an *in situ* reaction to form the acyl chloride with thionyl chloride followed by condensation with methanol gave the methyl ester hydrochloride salt **7**. Conversion to the amide **8** was achieved by the treatment of this salt with a large excess of 25 % ammonium hydroxide with stirring for several hours and reduction of the amide with $LiAlH_4$ in refluxing THF then afforded the desired ligand **2h**.



Scheme 2. Synthetic route used to prepare **2h**. Reagents and conditions: (i) $SOCl_2$, MeOH (ii) 25 % NH_4OH; (iii) $LiAlH_4$, THF.

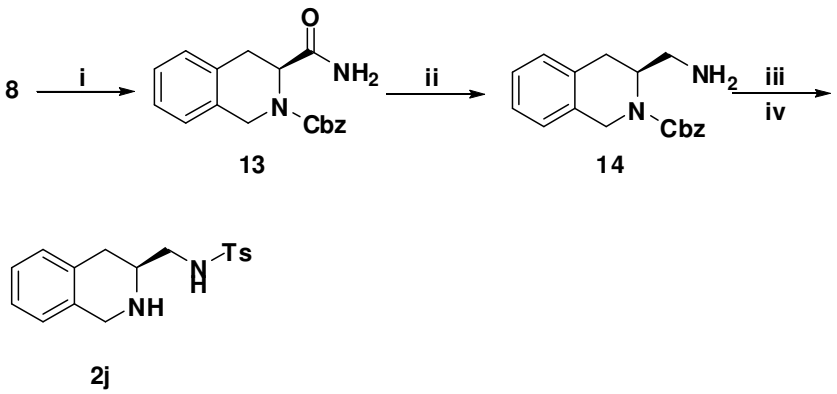
Ligand **2i** (Scheme 3) could not be prepared following the same approach as for **2a–g**, due to racemisation, which was observed under $LiAlH_4$ reduction conditions. Therefore an alternate procedure employing a milder reduction condition was sought. Cbz protection of the amino alcohol **9**[8] yielded **10** which was subsequently oxidised with pyridinium chlorochromate to

obtain compound **11**. Reductive amination on **11** using benzylamine and sodium cyanoborohydride afforded the desired product **12**. Selective deprotection of the *N*-Cbz group of **12** with Pd/C at one atm H_2 furnished **2i**.



Scheme 3. Synthetic route used to prepare **2i**. Reagents and conditions: (i) $KHCO_3$, dioxane/water, Cbz-Cl; (ii) PCC, dry DCM; (iii) Benzylamine, $NaBH_3CN$, MeOH/THF; (iv) 10 % wt. Pd/C H_2 1 atm, MeOH/THF.

Ligand **2j** (Scheme 4) was prepared from the amide **8**, which was Cbz protected to form **13**. Using $NaBH_4$ with acetic acid in dioxane,[26] the amide was reduced without cleavage of the Cbz group to yield **14**. Reaction of **14** with toluenesulfonyl chloride with base followed by removal of Cbz with Pd/C and H_2 rendered **2j**.



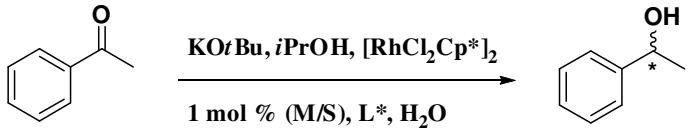
Scheme 4 Synthetic route used to prepare 2j. Reagents and conditions: (i) $KHCO_3$, dioxane/water, Cbz-Cl; (ii) $NaBH_4$, AcOH, dioxane, reflux; (iii) TsCl, DCM, TEA; (iv) 10 % wt. Pd/C H_2 1 atm, MeOH/THF.

STRUCTURAL MODIFICATIONS

Given that the amines were designed to incorporate broad structural diversity to investigate the scope of tetrahydroisoquinoline-diamine ligands in asymmetric transfer hydrogenation, we proceeded to modify the backbone by changing the structural features of the substituent on the amine (see Fig. 1) and tested them for activity in asymmetric transfer hydrogenation of acetophenone (see Table 1). The groups were chosen to cover both steric and electronic character. Ligand **2a** was the first of the diamine derivatives to be prepared and tested for its catalytic activity in asymmetric transfer hydrogenation, producing reasonable results (81% conv., 70% *ee*, entry 1). Derivatives **2b** and **2c** (entries 2 and 3) possessing diphenyl or aniline groups, respectively, inherently make the amine more acidic. Unfortunately **2b** demonstrated very poor reactivity and little selectivity (22% conv., 11% *ee*, entry 2) while **2c** showed no activity at all (entry 3). When the pKa of the nitrogen was increased using derivatives **2d** (methyl) and **2e** (iso-propyl), **2d** also showed no activity (entry 4). However, **2e** was found to possess moderate reactivity with fair selectivity (67% conv., 71% *ee*, entry 5). It seemed apparent that the electronic effects of the substituents on the nitrogen were not the issue, but rather a steric effect dictating the selectivity. To examine further, chiral amines possessing a benzyl and methyl group were employed. These would have similar effects on the pKa as that of the benzyl group on **2a** and offer less steric crowding than the diphenyl group on **2b**. Promising results were obtained with the (*R*)-methylbenzylamine derivative **2f** (24% conv., 77% *ee*, entry 6) yielding the (*R*)-1-phenylethanol enantiomers, which then led us to try the (*S*) isomer. The (*S*)-methylbenzyamine derivative **2g** showed lower reactivity and selectivity than the (*R*) enatiomer (5.5% conv., 51% *ee*, entry 7), but had preference for the expected (*S*)-1-

phenylethanol enantiomer. Compound **2h** was prepared to determine whether the primary amine could also be used as a ligand in asymmetric transfer hydrogenation reaction, but it was found to have no activity in this reaction (entry 8). Out of curiosity, and given our recent success with the amino alcohol derivative of the C^1-substituted tetrahydroisoquinoline ligand, **2i** was prepared (Scheme 3). Disappointingly, this auxiliary showed no activity (entry 9). Based on the significant increase in rate, an often selectivity observed, upon tosylation of one of the amine donors we investigated **2j** for activity in asymmetric transfer hydrogenation of acetophenone. However the ligand was found to have no activity at all (entry 10).

Table 1. Asymmetric transfer hydrogenation of acetophenone by ligand **2a-j** rhodium complexes



Entry	Ligand	Conv. (%)	*ee* (%)	Isomer
1	**2a**	81	70	*S*
2	**2b**	22	11	*S*
3	**2c**	-	-	-
4	**2d**	-	-	-
5	**2e**	67	71	*S*
6	**2f**	24	77	*R*
7	**2g**	5.5	51	*S*
8	**2h**	-	-	-
9	**2i**	-	-	-
10	**2j**	-	-	-

All reactions were carried out at 25 °C. In the case where the hydrogen source is KCO_2H the solvent used was water.

i-PrOH was used as the solvent when employed as the HS along with *t*-BuOK as the base. Testing was carried out using a S/C of 100.

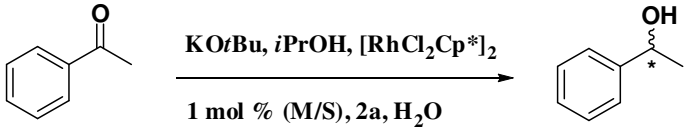
[a] Measured by GC with chiral capillary column *β*-DEX™ 120.

EFFECT OF WATER

As stated earlier it has been demonstrated in the literature that water has the potential to influence performance of a catalyst in asymmetric transfer hydrogenation reactions.[20-21,27-32] This prompted us to investigate how much water was necessary to obtain the highest enantiomeric excess using ligand **2a** (Table 2). Adding 1 equiv of water to the metal complex was found to increase activity (27 % *ee*, entry 1). Progressively increasing the amount of water

from 2 to 400 equiv showed the selectivity to improve even more (entries 2–6). Thereafter raising the amount of water to a 1000 and then further to 3000 equiv a maximum of 94 % conversion was reached with an optimum of 70% enantioselectivity (entries 7–9). Extending the amount to 50:50 i-PrOH/water (many times excess) destroyed the reactivity completely (entry 10). Since reactivity dropped significantly at 3000, 1500 equiv was taken as the best compromise between reactivity and selectivity for subsequent testing.

Table 2. Results of the effect in varying the water content on the reaction of acetophenone by rhodium complexes of ligand **2a**



Entry	Molar equiv H_2O to Rhodium	Conv. (%)[a]	*ee* (%)[a]
1	1	64	27
2	2	81	43
3	10	88	45
4	100	92	54
5	200	88	62
6	400	92	66
7	1000	94	68
8	1500	81	70
9	3000	61	70
10[b]	50:50	-	-

All reactions were carried out at 25 °C. In the case where the hydrogen source is KCO_2H the solvent used was water.

i-PrOH was used as the solvent when employed as the hydrogen source along with *t*-BuOK as the base. Testing was carried out using a S/C of 100.

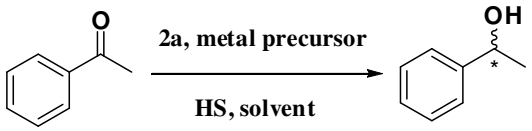
[a] Measured by GC with chiral capillary column *β*-DEX™ 120.

[b] A 50/50 mixture of water and *i*-PrOH was used.

METAL AND DONOR STUDY

Compound **2a** was chosen as a representative of the di-secondary amine ligands for this study, the results of which are shown in Table 3. Entries 1 and 4 show that very little activity is observed when the asymmetric transfer hydrogenation reaction is carried out in water using potassium formate as the hydrogen source (2 %, entry 1), and no activity with *i*-PrOH (entry 4) when [Ru(*p*-cymeme)Cl_2]$_2$ is employed as the metal precursor. The same held for the formate hydrogen source with [$IrCl_2$(*Cp**)]$_2$ (10 %, entry 2). However a marked increase in activity was observed when the hydrogen source was changed to *i*-PrOH (40 %, entry 5). Implementing a [$RhCl_2$(*Cp**)]$_2$ precursor rendered significant activity with the formate (43 %, entry 3), but the greatest catalytic activity was seen when the *i*-PrOH was used instead (90 %, entry 6). The results for the [$RhCl_2$(*Cp**)]$_2$ prompted us to investigate whether using the TEAF hydrogen source could increase activity. Unfortunately this proved unsuccessful (entry 7). Changing from the [$RhCl_2$(*Cp**)]$_2$ (arene) to the $RhPPh_3COH$ (hydride) did not improve on the [$RhCl_2$(*Cp**)]$_2$ system (10 %, entry 8). Therefore optimised conditions were found to be with the use of [$RhCl_2$(*Cp**)]$_2$ precursor and *i*-PrOH.

Table 3. Asymmetric transfer hydrogenation of acetophenone by different hydrogen sources and ligand **2a** metal complexes



Entry	Metal Complex	Hydrogen Source	Conv. (%)[a]	*ee* (%)[a]	Isomer
1	$[Ru(p\text{-cymene})Cl_2]_2$	HCO_2K	2	10	*R*
2	$[IrCl_2(Cp^*)]_2$	HCO_2K	10	25	*R*
3	$[RhCl_2(Cp^*)]_2$	HCO_2K	43	50	*R*
4	$[Ru(p\text{-cymene})Cl_2]_2$	*i*-PrOH	-	-	-
5	$[IrCl_2(Cp^*)]_2$	*i*-PrOH	40	-	-
6	$[RhCl_2(Cp^*)]_2$	*i*-PrOH	90	-	*S*
7	$[RhCl_2(Cp^*)]_2$	TEAF	-	-	-
8	$RhPPh_3COH$	*i*-PrOH	10	48	*R*

All reactions were carried out at 25 °C. In the case where the hydrogen source is KCO_2H the solvent used was water.

i-PrOH was used as the solvent when employed as the hydrogen source along with *t*-BuOK as the base. Testing was carried out using a S/C of 100.

[a] Measured by GC with chiral capillary column *β*-DEX™ 120.

CONCLUSIONS

We have prepared a series of diamine ligands possessing the tetrahydroisoquinoline backbone and tested them for activity in the asymmetric transfer hydrogenation of acetophenone. The amine donors were all secondary ligands **2a–g** and **i**, but **2h** possessed both a primary and secondary amine. It was found that when using $[RhCl_2(Cp^*)]_2$ in conjunction with an *i*-PrOH, the best conversion achieved was 92 % in 1 h. Furthermore, it was determined that no selectivity was obtained under anhydrous conditions, and that an optimum of 1500 equiv of water to rhodium gave the best selectivity of 77 % *ee* for ligand **2f**. However with regards to the best overall catalytic performance, ligands **2a** and **2d** bearing the benzyl and isopropyl

substituents, respectively, shared both good reactivity and selectivity for the asymmetric reduction of acetophenone. We believe that these ligands could be successfully employed as catalysts for other asymmetric transformations.

EXPERIMENTAL

GENERAL

All reagents and solvents were purchased from Aldrich, Merck and Fluka unless stated otherwise. All NMR analysis was carried out on either a Bruker AVANCE III 400 or 600 MHz instrument. Chemical shifts are expressed in parts per million (ppm) downfield from a TMS signal, and coupling constants are reported in Hertz. NMR spectra were obtained at room temperature, except if stated differently. Thin layer chromatography (TLC) was performed using Merck Kiesel gel 60 F254. Crude compounds were purified via column chromatography using Silica Gel (60–200 mesh except if stated otherwise). All solvents were dried using standard procedures, for example, Vogel.[26] All IR spectra were recorded on a Perkin Elmer Spectrum 100 instrument with a universal ATR attachment. Optical rotations were measured on a Perkin Elmer Polarimeter. All melting points are uncorrected. High resolution mass spectrometric data were obtained using a Bruker micrOTOF-Q II instrument, using a sample concentration of approximately 1 ppm. All gas chromatography was carried out on an Agilent 6820 instrument.

General procedure for transfer hydrogenation of acetophenone

i-PrOH hydrogen source

To an oven-dried Schlenk tube was added metal precursor (3.0 mg) followed by the ligand (4 mol equiv) and freshly distilled *i*-PrOH (5 mL) under a dry argon atmosphere. The mixture was heated to 60 °C and stirred for 20 min, after which the solution was allowed to cool to ambient temperature. The desired amount of acetophenone was then added (substrate/catalyst, S/C = 100) followed by freshly prepared 0.1 M *t*-BuOK (2 equiv to metal) in *i*-PrOH. To monitor the reactions, small aliquots were drawn, diluted with *i*-PrOH and then run through a small plug of silica to remove any catalyst. The eluted sample was then injected into the GC.

_i_-PrOH hydrogen source in water

The reaction was carried out as reported above with the exception that the water was added after complexation and just before the addition of acetophenone. Monitoring of the progress of the reaction remained the same.

Formate hydrogen source

The metal precursor and ligand were complexed as describe above. Water was then added (2 mL), and the reaction mixture heated to 40 °C and stirred for 30 min. The mixture was then cooled and the acetophenone (S/C = 100) was added followed by the potassium formate. To monitor the reactions, small aliquots were drawn and extracted with hexane; the hexane extracts were then used for GC analysis.

TEAF hydrogen source

The TEAF was prepared as reported in the literature.[23] The metal precursor and ligand were stirred in DCM for 30 min, followed by the addition of acetophenone (S/C = 100) and TEAF (0.9ml). The reaction was monitored using a method similar to that used with the *i*-PrOH hydrogen source.

(*S*)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid 4

To a suspension of **3** (5 g, 19.4 mmol) in dioxane (80 mL) and water (40 mL) was added $NaHCO_3$ (77.8 mmol) at 0 °C following Schotten–Baumann conditions. After addition of the base, Cbz-Cl was added and the reaction mixture was allowed to stir at 0 °C for 1.5 h and then at room temperature for a further 1.5 h. The product was extracted twice with ethyl acetate, the organic layer dried with anhydrous magnesium sulfate and concentrated to dryness affording **4** (5.56 g, 92% yield) that was carried forward without any purification.

General procedure for the preparation of 5a–g

(*S*)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **4** (1.5 g, 4.8 mmol) was dissolved in DMF (15 mL) followed by addition of EDC.HCl (1.1 g, 5.8 mmol), HOBt (0.81 g, 5.3 mmol), a catalytic amount of DMAP and the appropriate amine (5.3 mmol). The reaction mixture was then stirred at room temperature until no more starting material could be detected by

TLC analysis (approximately 1 h). The reaction mixture was poured into 30 volumes of chilled water; the mixture was then extracted twice with ethyl acetate. The extracts were combined, washed with 10% HCl (aq) to remove latent EDC urea, dried over anhydrous magnesium sulfate and then concentrated to dryness affording the crude product which was purified by column chromatography.

General procedure for the preparation of 6a–g

The precursors **5a–g** in 50/50 MeOH/THF with 0.5 eq. of 10 % palladium on carbon (Pd/C) was stirred under hydrogen (approximately 1 atm) for 2 h. The reaction was limited for this period as side products were observed. The crude product was obtained by filtering off the Pd/C through a plug of Celite, the filtrate was then concentrated to dryness and the residue purified by column chromatography.

General procedure for the preparation of 2a–g

The amino amides **6a–g** were reduced with 4 equiv of $LiAlH_4$ in refluxing dry THF under a nitrogen atmosphere for 3–4 days or alternatively the reductions could be carried out at 85 °C in a microwave reactor for 4–5 h. The reactions were quenched by slow addition of saturated sodium sulfate solution and the white aluminium sulfate precipitate was then filtered off. The filtrate was washed with water, dried over anhydrous magnesium sulfate and concentrated to dryness affording the crude product which was purified by column chromatography.

(*S*)-benzyl 3-(benzylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5a

The resultant product from reaction with benzylamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.45) to afford the benzyl substituted TIQ derivative **5a** (1.44 g, 75 %) as a white powder. $[\alpha]^{20}_D$ = – 8.333 (c = 0.12, CH_2Cl_2); IR ν_{max}: 695, 729, 1118, 1216, 1302, 1322, 1400, 1650, 1680, 3029 and 3331. Melting point: 105 – 107 °C. HRMS calculated for $C_{25}H_{24}N_2O_3$ (M + H^+) = 401.1867 *m/z*, Found 401.1860 *m/z*. (NMR spectra are reported for a mixture of two rotamers).[33] ^{1}H NMR (400 MHz, DMSO): δ 8.42 (m, 1H), 7.51 – 7.07 (m, 12H), 6.91-6.76 (m, 2H), 5.27 – 5.07 (m, 2H), 4.87 – 4.42 (m, 3H), 4.28-4.05 (m, 2H), 3.26-3.06 (m, 2H); ^{13}C NMR (101 MHz, DMSO): δ 170.6, 139.2 – 126.1, 66.4, 54.5, 44.7, 41.8 and 31.8.

(*S*)-*N*-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6a

Removal of Cbz and purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~ 0.4) gave the benzyl amide TIQ **6a** (85%) as a white solid. $[\alpha]^{20}_D$ = – 54.76 (c =

0.42, CH_2Cl_2). IR ν_{max}: 435, 467, 613, 694, 736, 797, 1029, 1222, 1453, 1546, 1643, 2925, 3033, 3057, 3279 and 3330. Melting point: 83 – 85 °C. HRMS calculated for $C_{17}H_{18}N_2O$ (M + H^+) = 267.1492 *m/z*, Found 267.1504 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.42 – 7.12 (m, 9H), 4.48 (d, *J* = 5.6, 2H), 4.05 – 3.91 (d, *J* = 6.52 Hz, 2H), 3.61 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.28 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.88 (dd, *J* = 16.4, 10.3 Hz, 1H), The NH proton was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 138.3, 135.9, 134.4, 129.2, 128.7, 127.7, 127.4, 126.6, 126.2, 125.5, 56.5, 47.5, 43.1 and 31.0.

(*S*)-*N*-benzyl-1-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 2a

After reduction of **6a**, the crude compound was purified by column chromatography (DCM/MeOH/Et_2O/10% NH_3 in $CHCl_3$ = 66:4:20:10, R_f ~ 0.4) to afford the *N*-benzyl amine derivative **2a** (31 %) as an off white/yellow solid. $[\alpha]^{20}_D$ = – 70.93 (c = 0.43, CH_2Cl_2). IR ν_{max}: 695, 729, 1118, 1216, 1302, 1322, 1400, 1650, 1680, 3029 and 3331 cm^{-1}. Melting point: 85 – 87 °C. HRMS calculated for $C_{17}H_{20}N_2$ (M + H^+) = 253.1699 *m/z*, found 253.1708 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 3H), 7.28 – 7.23 (m, 2H), 7.16 – 6.99 (m, 4H), 4.04 (s, 2H), 3.84 (d, *J* = 2.8 Hz, 2H), 3.05 – 2.96 (m, 1H), 2.86 (dd, *J* = 11.9 and 3.8 Hz, 1H), 2.73 (dd, *J* = 16.3 and 4.0 Hz, 1H), 2.64 (dd, *J* = 11.9 and 8.9 Hz, 1H), 2.59 – 2.51 (m, 1H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.3, 135.8, 134.4, 129.2, 128.4, 128.1, 127.0, 126.1, 126.0, 125.7, 54.4, 54.1, 53.4, 48.2 and 33.3.

(*S*)-benzyl 3-(benzhydrylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5b

The resultant product from the reaction with diphenylmethanime was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.4) to afford the diphenyl substituted TIQ derivative **5b** (1.62 g, 71 %) light yellow oil. $[\alpha]^{20}_D$ = – 11.43 (c = 0.36, CH_2Cl_2). IR ν_{max}: 528, 546, 604, 616, 639, 695, 738, 909, 1001, 1028, 1094, 1120, 1215, 1303, 1346, 1403, 1453, 1494, 1658, 1696, 2851, 2925, 3029 and 3300 cm^{-1}. HRMS calculated for $C_{31}H_{28}N_2O_3$ (M + H^+) = 477.2137 *m/z*, found 477.2155 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, DMSO) δ = 8.95 – 8.69 (m, 1H), 7.64 – 6.88 (m, 19H), 6.11 – 5.85 (m, 1H), 5.30 – 4.37 (m, 5H), 3.02 – 3.27 (m, 2H). ^{13}C NMR (101 MHz, DMSO): δ 170.2, 155.3 – 125.9, 86.6, 66.4, 54.8, 44.8 and 32.1.

(*S*)-N-benzhydryl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6b

Removal of Cbz and purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f =0.4) gave the diphenylmethamide tetrahydroisoquinoline **6b** (80 %) as a light

brown solid. $[\alpha]^{20}_D$ = – 105.7 (c = 0.35, CH_2Cl_2). IR ν_{max}: 402, 406, 619, 683, 734, 1159, 1219, 1365, 1451, 1493, 1544, 1640, 2929, 2973 and 3292 cm^{-1}. HRMS calculated for $C_{23}H_{22}N_2O$ ($M+H^+$) = 343.1795 m/z, found 343.1805 m/z. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 – 8.10 (m, 1H), 7.42 – 6.95 (m, 14H), 7.09 – 7.02 (m, 1H), 4.08 – 3.95 (m, 2H), 3.58 – 3.40 (m, 1H), 3.31 – 3.19 (m, 1H), 2.99 – 2.87 (m, 1H), the NH proton of the amine was not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 141.6, 141.5, 129.1–125.3, 56.4, 56.2, 47.1 and 30.3.

(*S*)-1,1-diphenyl-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)methanamine 2b

After the reduction of **6b**, the crude compound was purified by column chromatography (MeOH/Et_2O = 5:95, R_f ~ 0.6) to afford the *N*-diphenylmethanamine amine derivative **2b** (21 %) as a yellow solid. $[\alpha]^{20}_D$ = – 55.77 (c = 0.52, CH_2Cl_2). IR ν_{max}: 430, 696, 706, 743, 800, 1027, 1429, 1447, 1490, 1580, 1595, 2780, 2911, 3289 and 3324 cm^{-1}. Melting point: 89 – 91 °C. HRMS calculated for $C_{23}H_{24}N_2$ ($M + H^+$) = 329.2012 *m/z*, found 329.2004 *m/z*. ^1H NMR (600 MHz, $CDCl_3$): δ 7.43 – 6.98 (m, 14H), 4.87 (s, 1H), 4.06 (s, 2H), 3.00 (m, 1H), 2.83 (dd, *J* = 11.8 and 3.8 Hz, 1H), 2.73 (dd, *J* = 16.2 and 3.9 Hz, 1H), 2.64 (dd, *J* = 11.8 and 8.7 Hz, 1H), 2.56 (dd, *J* = 16.2 and 10.8 Hz, 1H), the two NH protons were not observed. ^{13}C NMR (151 MHz, $CDCl_3$): δ 144.2, 143.9, 135.9, 134.5, 129.2, 128.5, 127.3, 127.3, 127.04, 127.02, 126.1, 126.0, 125.7, 67.7, 53.7, 53.6, 48.3 and 33.4.

(*S*)-benzyl 3-(phenylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5c

The resultant product from reaction with aniline was purified by column chromatography purified (EtOAc/Hex = 40:60, R_f ~ 0.5) to afford the aniline substituted TIQ derivative **5c** (1.54 g, 83 %) light yellow oil. $[\alpha]^{20}_D$ = – 38.10 (c = 0.42, CH_2Cl_2). IR ν_{max}: 487, 693, 736, 749, 960, 1099, 1127, 1184, 1413, 1546, 1665, 1701, 3027 and 3301 cm^{-1}. Melting point: 137 – 139 °C. HRMS calculated for $C_{24}H_{22}N_2O_3$ ($M + H^+$) = 387.1703 *m/z*, found 387.1689 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^1H NMR (400 MHz, DMSO): δ 10.04 (d, *J* = 5.1 Hz, 1H), 7.62 – 6.85 (m, 14H), 5.22 – 5.02 (m, 3H), 4.90 – 4.51 (m, 2H), 3.33 – 3.02 (m, 2H). ^{13}C NMR (101 MHz, DMSO): δ 169.9, 155.3 – 119.2, 66.5, 54.9, 44.8 and 31.8.

(*S*)-*N*-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6c

Removal of Cbz group the aniline amide TIQ **6c** (88%) formed as a white solid, which required no further purification. $[\alpha]^{20}_D$ = – 144.7 (c = 0.38 , CH_2Cl_2). IR ν_{max}: 440, 551, 695, 736, 1060, 1190, 1258, 1364, 1408, 1496, 1597, 1697, 2891, 2927, 2968, 3045 and 3299 cm^{-1}. Melting

point: 183 – 185 °C. HRMS calculated for $C_{16}H_{16}N_2O$ (M + H^+) = 253.1317 *m/z*, found 253.1335 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7,8 Hz, 2H), 7.01 – 7.25 (m, 5H), 4.05 (d, *J* = 5.4 Hz, 2H), 3.73 (dd, *J* = 10.3 and 5.3 Hz, 1H), 3.37 (dd, *J* = 16.4 and 5.2 Hz, 1H), 2.95 (dd, *J* = 16.3 and 10.3 Hz, 1H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 137.7, 135.8, 134.3, 129.2, 129.1, 126.9, 126.4, 125.5, 124.1, 119.4, 56.7, 47.3 and 30.5.

(*S*)-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)aniline 2c

After reduction of **6c**, the crude compound was purified by column chromatography (100 % diethyl ether, R_f ~ 0.5), yielding a white solid **2c** (57 %). $[\alpha]^{20}_D$ = – 64.29 (c = 0.14, CH_2Cl_2). IR ν_{max}: 435, 488, 513, 585, 690, 743, 805, 1258, 1346, 1494, 1600, 2792, 2929, 3218 and 3301 cm^{-1}. Melting point: 90 – 92 °C. HRMS calculated for $C_{16}H_{18}N_2$ (M + H^+) = 239.1543 *m/z*, found 239.1543 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 6.99 (m, 6H), 6.76 – 6.62 (m, 3H), 4.07 (br s, 2H), 3.36 (d, *J* = 12.1 Hz, 1H), 3.26 – 3.17 (m, 1H), 3.14 – 3.06 (m, 1H), 2.85 (dd, *J* = 16.3 and 4.1 Hz, 1H), 2.66 (dd, *J* = 16.3 and 10.5 Hz, 1H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.4, 135.7, 134.0, 129.3, 129.3, 126.2, 126.0, 125.9, 117.5, 113.0, 53.0, 49.2, 48.1 and 33.1.

(*S*)-benzyl 3-(methylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5d

The resultant product from the reaction with methylamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.4) to afford the methyl substituted TIQ derivative **5d** (1.06 g, 68 %) light yellow oil. $[\alpha]^{20}_D$ = – 6.45 (c = 0.62, CH_2Cl_2). IR ν_{max}: 495, 616, 696, 742, 908, 1011, 1120, 1215, 1302, 1323, 1406, 1536, 1655, 1695, 2939, 3031, 3065 and 3314 cm^{-1}. HRMS calculated for $C_{19}H_{20}N_2O_3$ (M + H^+) = 325.1547 *m/z*, found 325.1546 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, DMSO): δ 7.85 (m, 1H), 7.58 – 7.08 (m, 9H), 5.36 – 4.98 (m, 2H), 4.86 – 4.28 (m, 2H), 3.22 – 2.89 (m, 2H), 2.60 – 2.52 (m, 1H), 2.47 (d, 4.66 Hz, 3H). ^{13}C NMR (101 MHz, DMSO): δ 170.8, 136.7 - 125.9, 66.4, 54.1, 44.4, 31.3 and 25.6.

(*S*)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6d

Removal of Cbz and purification by column chromatography (DCM/MeOH/10 % NH_3 in $CHCl_3$ = 87:3:10, R_f ~ 0.4) afforded methyl amide TIQ **6d** (77 %) as a white solid. $[\alpha]^{20}_D$ = – 222.5 (c = 0.20 , CH_2Cl_2). IR ν_{max}: 399, 435, 515, 609, 674, 738, 797, 963, 1129, 1225, 1413, 1562, 1643, 2835, 2877, 2940 and 3302 cm^{-1}. Melting point: 84 – 86 °C. HRMS calculated for

$C_{11}H_{14}N_2O$ (M + H^+) = 191.1179 *m/z*, found 191.1183 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (br s, 1H), 7.19 – 7.11 (m, 3H), 7.03 (m, 1H), 3.99 (d, *J* = 3.6 Hz, 2H), 3.52 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.24 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.85 (d, *J* = 5.0 Hz, 3H), 2.80 (dd, *J* = 16.5 and 10.8 Hz, 1H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 135.9, 134.4, 129.2, 126.6, 126.2, 125.5, 56.6, 47.6, 31.0 and 25.8.

Synthesis of (*S*)-*N*-methyl-1-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 2d

After reduction the crude product **2d** was purified by column chromatography (DCM/MeOH/10 % NH_3 in $CHCl_3$ = 87:3:10, R_f ~ 0.4). However this purification was not sufficient, therefore further refinement was achieved by precipitating the compound out as the dihydrochloride salt using a solution of HCl gas bubbled in ether, which generated a precipitate when added to the compound in DCM. The precipitated salt was filtered and washed with a 90:10 mixture of ether:DCM affording **2d** (15 %) a light brown solid. $[\alpha]^{20}_D$ = – 1.30 (c = 0.1, MeOH). IR ν_{max}: 428, 448, 763, 1025, 1451, 2598, 2717, 2941 and 3395 cm^{-1}. HRMS calculated for $C_{11}H_{16}N_2$ (M + H^+) = 177.1386 *m/z*, found 177.1389 *m/z*. ^{1}H NMR (400 MHz, MeOD): δ 7.13 – 7.26 (m, 4H), 4.42 (s, 2H), 3.98 – 3.89 (m, 1H), 3.46 (dd, *J* = 13.6, 6.5 Hz, 1H), 3.37 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.24 (d, *J* = 4.7 Hz, 1H), 3.03 (dd, *J* = 17.1, 11.0 Hz, 1H) and 2.76 (s, 3H), the two NH protons were not observed in the spectra. ^{13}C NMR (101 MHz, MeOD): δ 130.9, 130.2, 129.5, 128.7, 128.4, 127.7, 51.8, 51.2, 46.0, 34.4, 30.4.

(*S*)-benzyl 3-(isopropylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5e

The resultant product from the reaction with isopropyl amine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.45) to afford the **5e** (1.43 g, 85 %) as a beige powder. $[\alpha]^{20}_D$ = – 3.44 (c = 0.58, THF). IR ν_{max}: 695, 733, 749, 1124, 1212, 1311, 1408, 1546, 1644, 1701, 2970 and 3299 cm^{-1}. Melting point: 95 – 97 °C. HRMS calculated for $C_{21}H_{24}N_2O_3$ (M + H^+) = 353.1860 *m/z*, found 353.1860 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, DMSO): δ 7.69 (m, 1H), 7.53 – 7.01 (m, 9H), 5.33 – 4.84 (m, 2H), 4.78 – 4.35 (m, 3 H), 3.72 (m, 1 H), 3.21 – 2.81 (m, 2 H), 0.99 – 0.82 (m, 6 H). ^{13}C NMR (101 MHz, DMSO): δ 169.6, 155.2 – 125.8, 67.0, 55.2, 44.6, 40.5, 31.8 and 22.1.

(*S*)-*N*-isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6e

Removal of Cbz and purification by column chromatography (DCM/MeOH/10 % NH_3 in $CHCl_3$ = 87:3:10, R_f ~ 0.5) afforded the isopropyl amide TIQ **6e** (92 %) as a white solid. $[\alpha]^{20}_D$ = – 105.7 (c = 0.35, CH_2Cl_2). IR ν_{max}: 402, 406, 619, 683, 734, 1159, 1219, 1365, 1451, 1493, 1544,

1640, 2929, 2973 and 3292 cm^{-1}. Melting point: 87 – 89 °C. HRMS calculated for $C_{13}H_{18}N_2O$ ($M + H^+$) = 219.1492 *m/z*, found 219.1501 *m/z*. ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 – 7.19 (m, 3H), 7.08 – 6.93 (m, 2H), 4.10 (m, 1H), 4.00 (d, *J* = 4.1 Hz, 2H), 3.50 (dd, *J* = 10.7 and 5.0 Hz, 1H), 3.24 (dd, *J* = 16.5 and 5.0 Hz, 1H), 2.80 (dd, *J* = 16.5 and 10.7 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 135.8, 134.4, 129.2, 126.6, 126.1, 125.5, 56.6, 47.7, 40.8, 31.1, 22.8, 22.7.

(*S*)-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)propan-2-amine 2e

After reduction of **6e**, the crude compound was purified by column chromatography (EtOAc:MeOH = 95:5, R_f ~ 0.5), yielding an off white solid **2e** (46 %). $[\alpha]^{20}_D$ = – 8.33 (c = 0.12, CH_2Cl_2). IR ν_{max}: 695, 729, 1118, 1216, 1302, 1322, 1400, 1650, 1680, 3029 and 3331 cm^{-1}. Melting point: 39 – 41 °C. HRMS calculated for $C_{13}H_{20}N_2$ ($M + H^+$) = 205.1699 *m/z*, found 205.1708 *m/z*. ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 – 6.99 (m, 4H), 4.05 (s, 2H), 3.02 – 2.90 (m, 1H), 2.71 – 2.87 (m, 3H), 2.60 – 2.52 (m, 2H), 1.09 (overlapping-d, *J* = 6.5 Hz, 6H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.0, 134.5, 129.2, 126.0, 126.0, 25.7, 53.9, 52.9, 49.0, 48.3, 33.5, 23.1 and 23.0.

(*S*)-benzyl 3-((*R*)-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5f

The resultant product from the reaction with (*R*)-1-phenylethanamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.4) to afford the (*R*)-1-phenylethanamine substituted TIQ derivative **5f** (1.55 g, 78%) as a light yellow oil. $[\alpha]^{20}_D$ = + 10.68 (c = 1.03, CH_2Cl_2). IR ν_{max}: 491, 599, 696, 740, 905, 1001, 1093, 1119, 1214, 1302, 1322, 1347, 1400, 1448, 1522, 1638, 1697, 2932, 3029, 3062 and 3315 cm^{-1}. HRMS calculated for $C_{26}H_{26}N_2O_3$ ($M + H^+$) = 415.2016 *m/z*, found 415.1998 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^1H NMR = (400 MHz, DMSO): δ 8.24 (m, 1H), 7.53 – 6.91 (m, 14H), 5.32 – 4.96 (m, 2H), 4.93 – 4.41 (m, 4H), 3.20 – 3.02 (m, 2H), 1.25 (d, *J* = 7.07 Hz, 3H). ^{13}C NMR (101 MHz, DMSO): δ 170.1, 144.1 – 125.6, 66.4, 54.4, 47.5, 44.7, 32.0 and 22.0.

(*S*)-*N*-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6f

Removal of Cbz and purification by column chromatography (Et_2O:Acetone = 80:20, R_f ~ 0.5) gave the (*R*)-1-phenylethanamide TIQ **6f** (72 %) as a white solid. $[\alpha]^{20}_D$ = – 33.82 (c = 0.34, CH_2Cl_2). IR ν_{max}: 430, 583, 617, 695, 733, 748, 790, 803, 1180, 1221, 1446, 1492, 1544, 1643, 2838, 2926 and 3284 cm^{-1}. Melting point: 119 – 121 °C. HRMS calculated for $C_{18}H_{20}N_2O$ (M

+ H^+) = 281.1648 *m/z*, found 281.1645 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 7.20 – 7.12 (m, 3H), 7.04 (m, 1H), 5.14 (m, 1H), 3.99 (d, *J* = 11.82 Hz, 2H), 3.59 (dd, *J* = 10.2 and 5.2 Hz, 1H), 3.23 (dd, *J* = 16.4 and 5.2 Hz, 1H), 2.82 (dd, *J* = 16.4 and 10.2 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 143.3, 135.9, 134.4, 129.2, 128.6, 127.2, 126.6, 126.2, 126.0, 125.5, 56.4, 48.1, 47.6, 31.0 and 22.0.

(*R*)-1-phenyl-*N*-(((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine 2f

After reduction of **6f**, the crude compound was purified by column chromatography (DCM/MeOH/10 % NH_3 in $CHCl_3$ = 87:4:10, R_f ~ 0.5) to yield **2f** (30%), a light yellow oil. $[\alpha]^{20}_D$ = – 43.55 (c = 0.93, CH_2Cl_2). IR ν_{max}: 431, 543, 695, 783, 1118, 1451, 1492, 2789, 2918, 2960, 3026 and 3240. HRMS calculated for $C_{18}H_{22}N_2$ (M + H^+) = 267.1856 *m/z*, found 267.1846 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.29 (m, 4H), 7.21 (m, 1H), 7.10 – 7.05 (m, 2H), 7.03 – 6.96 (m, 2H), 3.96 (d, *J* = 16.78 Hz, 2H), 3.74 (m, 1H), 2.82 (m, 1H), 2.66 – 2.61 (m, 2H), 2.51 – 2.42 (m, 2H), 1.37 (d, *J* = 6.7, 3H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.6, 135.9, 134.5, 129.2, 128.4, 126.9, 126.5, 126.0, 126.0, 125.6, 58.2, 53.7, 52.8, 48.3, 33.3 and 24.6.

(*S*)-benzyl 3-((*S*)-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 5g

The resultant product from reaction with (*S*)-1-phenylethanamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.4) to afford the (*S*)-1-phenylethanamine substituted TIQ derivative **5g** (1.77 g, 89 %) light yellow oil. $[\alpha]^{20}_D$ = – 21.43 (c = 0.70, CH_2Cl_2). IR ν_{max}: 696, 738, 1059, 1119, 1213, 1303, 1329, 1407, 1449, 1495, 1534, 1656, 1697, 2972, 3029, 3062 and 3299 cm^{-1}. HRMS calculated for $C_{26}H_{26}N_2O_3$ (M + H^+) = 415.2016 *m/z*, found 415.2009 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, DMSO): δ 8.29 (m, 1H), 7.49 – 6.91 (m, 14H), 5.22 – 4.99 (m, 2H), 4.86 – 4.41 (m, 4H), 3.23 – 2.97 (m, 2H), 1.30 – 1.13 (m, 3H). ^{13}C NMR (101 MHz, DMSO): δ 169.9, 154.9 – 125.5, 66.3, 54.1, 47.5, 44.7, 31.8, 22.1.

Synthesis of (*S*)-*N*-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6g

Removal of Cbz and purification by column chromatography (Et_2O:Acetone = 80:20, R_f ~ 0.5) afforded the (*S*)-1-phenylethanamide TIQ **6g** (76%) as a cream/beige solid. $[\alpha]^{20}_D$ = – 100.7 (c = 0.36, CH_2Cl_2). IR ν_{max}: 428, 449, 525, 551, 609, 643, 697, 734, 750, 780, 1077, 1137, 1225, 1248, 1493, 1533, 1646, 2926, 2966 and 3333 cm^{-1}. Melting point: 119 – 121 °C. HRMS

calculated for $C_{18}H_{20}N_2O$ (M + H^+) = 281.1648 *m/z*, found 281.1644 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 1H), 7.38 – 7.11 (m, 8H), 7.04 (m, 1H), 5.13(m, 1H), 3.99 (s, 2H), 3.53 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.23 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.85 (dd, *J* = 16.4, 10.5 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 143.3, 135.7, 134.3, 129.2, 128.7, 128.5, 127.3, 126.6, 126.2, 125.5, 56.5, 48.3, 47.5, 31.0 and 22.0.

(*S*)-1-phenyl-*N*-(((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine 2g

After reduction of **6g**, the crude compound was purified by column chromatography (DCM/MeOH/10 % NH_3 in $CHCl_3$ = 87:4:10, R_f ~ 0.5) to yield **2g** (35 %), a light yellow oil, which was then also stored as the dihydrochloride salt. $[\alpha]^{20}_D$ = – 43.55 (c = 0.93, CH_2Cl_2). IR ν_{max}: 431, 543, 695, 783, 1118, 1451, 1492, 2789, 2918, 2960, 3026 and 3240 cm^{-1}. HRMS calculated for $C_{18}H_{22}N_2$ (M + H^+) = 267.1856 *m/z*, found 267.1846 *m/z*. ^{1}H NMR (400 MHz, MeOD): δ 7.58 – 7.10 (m, 9H), 4.52 – 4.31 (m, 3H), 3.87 (m, 1H), 3.49 (m, 1H), 3.19 – 3.01 (m, 3H), 1.71 (d, *J* = 6.7, 3H). ^{13}C NMR (101 MHz, MeOD): δ 137.1, 131.0, 130.6, 130.1, 129.4, 129.0, 128.7, 128.6, 128.3, 127.7, 61.3, 52.5, 48.5, 46.0, 30.6 and 19.5.

(1*R*,3*S*)-benzyl 3-(hydroxymethyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 10

Compound **9** (1 g, 3.3 mmol) was protected with a Cbz group, under the conditions described in the general procedure to afford **10** (1.31 g, 91 %), a light yellow oil after column chromatography (EtOAc/Hex = 60:40, R_f ~ 0.5). $[\alpha]^{20}_D$ = + 40.38 (c = 0.26, CH_2Cl_2). IR ν_{max}: 697, 1088, 1220, 1285, 1337, 1404, 1516, 1638, 1688, 2247, 3301 and 3553 cm^{-1}. HRMS calculated for $C_{26}H_{27}NO_5$ (M + H^+) = 434.1928 *m/z*, found 434.1962 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 6.92 (m, 10H), 6.78 (s, 1H), 6.66 (s, 1H), 6.01 (s, 1H), 5.38 – 4.87 (m, 2H), 4.47 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.63 (m, 1H), 3.34 (m, 1H), 3.02 – 2.89 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.4 – 125.3, 112.0, 110.7, 67.5, 64.4, 59.8, 56.1, 55.9, 54.7 and 29.4.

(1*R*,3*S*)-benzyl 3-formyl-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 11

Oxidation of **10** (0.8 g, 1.8 mmol) with PCC (3 equiv.) and anhydrous $MgSO_4$ (3 equiv.) in dry DCM[34] gave **11** (0.45 g, 57 %) as a yellow oil after treatment with wet diethylether and filtration through a small plug of silica gel to remove excess PCC and other metal species. $[\alpha]^{20}_D$ = +

41.46 (c = 0.41, CH_2Cl_2). IR ν_{max}: 594, 697, 737, 994, 1028, 1092, 1221, 1264, 1339, 1397, 1513, 1692, 2838 and 2924 cm^{-1}. HRMS calculated for $C_{26}H_{25}NO_5$ (M + Na^+) = 454.1625 *m/z*, found 454.1606 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (m, 1H), 7.65 – 7.02 (m, 10H), 6.96 – 5.90 (m, 3H), 5.38 – 4.84 (m, 2H), 4.59 (m, 1H), 3.95 – 3.75 (m, 6H), 3.24 – 2.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5 – 126.0, 110.7, 67.5, 60.6, 56.0, 55.9 and 29.7.

(1*R*,3*S*)-benzyl 3-((benzylamino)methyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 12

To a 50 % mixture of dry THF in MeOH (6 mL) was added compound **11** (0.3 g, 0.6 mmol), followed by benzyl amine (0.23 g, 2.0 mmol) and the mixture was allowed to stir at room temperature for 3 h. The reaction mixture was then cooled to 0 °C with an ice bath, followed by slow addition of $NaCNBH_3$ (~ 0.3 g) and stirred for 30 minutes at 0 °C, and a further 30 minutes at RT. Water was added to the reaction and the resultant mixture was extracted three times with DCM. The crude product was purified by column chromatography (EtOAc/Hex = 70:30, R_f ~ 0.7) to afford **12** (0.21 g, 60%) yellow oil. $[\alpha]^{20}_D$ = + 27.27 (c = 0.44, CH_2Cl_2). IR ν_{max}: 593, 697, 736, 999, 1028, 1092, 1219, 1338, 1397, 1452, 1514, 1689, 2931 and 3028 cm^{-1}. HRMS calculated for $C_{33}H_{34}N_2O_4$ (M + H^+) = 523.2591 *m/z*, found 523.2579 *m/z*. NMR spectra are reported for a mixture of two rotamers. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.10 (m, 15H), 6.78 (s, 1H), 6.59 (s, 1H), 5.99 (s, 1H), 5.26 – 4.91 (m, 2H), 4.46 (m, 1H), 3.97 – 3.56 (m, 9H), 3.08 – 2.68 (m, 3H), NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 128.3 – 126.0, 112.2, 110.8, 77.3 – 77.0, 76.6, 67.5, 60.3, 56.1 – 55.9, 53.5, 30.1 and 29.6.

N-benzyl-1-((1R,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 2i

Compound **12** (0.1 g, 0.19 mmol) was treated with palladium on carbon as mentioned in the general procedure, to remove the Cbz group. The reaction was monitored carefully to avoid removal of the benzyl group. Purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~ 0.5) yielded **2i** (0.038 g, 52%) as a white oil. $[\alpha]^{20}_D$ = – 26.83 (c = 0.41, CH_2Cl_2). IR ν_{max}: 573, 699, 753, 819, 1057, 1127, 1224, 1293, 1449, 1519, 1609, 2832, 2920, 2994 and 3060 cm^{-1}. HRMS calculated for $C_{25}H_{28}N_2O_2$ (M + H^+) = 389.2224 *m/z*, found 389.2224 *m/z*. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.13 (m, 10H), 6.63 (s, 1H), 6.41 (s, 1H), 5.10 (s, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.50 (s, 2H), 3.02 (m, 1H), 2.74 – 2.67 (m, 2H), 2.59 – 2.47 (m, 2H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8,

147.1, 145.3, 140.3, 128.5, 128.34, 128.33, 128.32, 128.1, 128.10, 126.9, 126.8, 111.4, 111.0, 59.3, 55.89, 55.83, 53.8, 53.4, 46.2 and 33.1.

(*S*)-benzyl 3-carbamoyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 13

Compound **8** (0.4 g, 2.2 mmol) was protected with a Cbz group, under the conditions described in the general procedure to afford **13** (0.63 g, 89%), a colourless oil after column chromatography (EtOAc/Hex = 20:80, R_f ~ 0.5). $[\alpha]^{20}_D$ = – 2.26 (c = 0.59, CH_2Cl_2). IR ν_{max}: 427, 593, 675, 697, 740, 908, 983, 1027, 1038, 1091, 1119, 1216, 1348, 1403, 1496, 1605, 1661, 2158, 2586, 2882 and 3179 cm^{-1}. HRMS calculated for $C_{18}H_{18}N_2O_3$ ($M + Na^+$) = 333.1210 *m/z*, found 333.1211 *m/z*. (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.00 (m, 9H), 5.29 – 4.86 (m, 3H), 4.84 – 4.50 (m, 2H), 3.37 – 3.02 (m, 2H), the amide protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 136.6, 132.5, 129.0, 128.5, 128.5, 128.0, 127.9, 126.7, 126.3, 126.0, 67.3, 52.5, 43.3, 43.1 and 30.7.

(*S*)-benzyl 3-(aminomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 14

To a solution of **13** (0.5 g, 1.5 mmol) in dioxane (3 mL) was added $NaBH_4$ (0.17 g, 4.5 mmol). The mixture was then cooled to 0 °C and acetic acid (0.18 g, 4.5 mmol) was added dropwise, after addition the reaction was set to reflux for 48 hours to yield **14** as yellow oil.[35] Due to problems with stability problems, the crude product **14** (0.07 g, 15 % in ~ 90 % purity) was carried forward without further purification. $[\alpha]^{20}_D$ = – 15.0 (c = 0.16, CH_2Cl_2). IR ν_{max}: 426, 495, 548, 565, 658, 705, 746, 810, 850, 880, 1071, 1093, 1154, 1314, 1450, 1494, 1598, 1722, 2853, 2922, 3031 and 3288 cm^{-1}. HRMS calculated for $C_{18}H_{20}N_2O_2$ ($M + H^+$) = 297.1595 *m/z*, found 297.1598 *m/z*. (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.24 (m, 5H), 7.23 – 6.98 (m, 4H), 5.26 – 5.10 (m, 2H), 4.89 (m, 1H), 4.59 – 4.25 (m, 2H), 3.06 (m, 1H), 2.77 (m, 1H), 2.70 (dd, *J* = 13.24, 7.94 Hz, 1H), 2.59 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 136.6, 132.5, 129.0, 128.5, 128.5, 128.0, 127.9, 126.7, 126.3, 126.0, 67.3, 52.5, 43.3, 43.1 and 30.7.

(*S*)-4-methyl-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzenesulfonamide 2j

Compound **14** (0.06 g, 0.2 mmol) was first treated with TsCl (0.042 g, 0.2 mmol) and TEA (0.045 g, 0.45 mmol) in CH_2Cl_2 (1.5 mL) for 12 hours at room temperature. Water was then added, and the organic layer washed with diluted HCl and then saturated sodium carbonate. The resulting oil was dried and the deprotection of the Cbz group was carried out as described in the

general procedure. The crude oil was purified by column chromatography (EtOH:Toluene, 20:80 R_f ~ 0.7) to yield **2j** (0.038 g, 60%) as a pale yellow oil: $[\alpha]^{20}_D$ = – 13.82 (c = 0.17, CH_2Cl_2). HRMS calculated for $C_{17}H_{20}N_2O_2S$ (M + H^+) = 317.1339 *m/z*, found 317.1318 *m/z*. IR ν_{max}: 430, 457, 594, 696, 735, 808, 912, 1020, 1095, 1117, 1217, 1249, 1320, 1418, 1495, 1678, 2927, 3030 and 3315 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.13 Hz, 2H), 7.30 (d, *J* = 8.75 Hz, 2H), 7.14 – 6.96 (m, 4H), 3.94 (d, *J* = 4.66 Hz, 2H), 3.19 (dd, *J* = 3.86, 12.66 Hz, 1H), 3.00 (m, 1H), 2.84 (dd, *J* = 8.99, 12.65 Hz, 1H), 2.71 (dd, *J* = 4.43, 16.27 Hz, 1H), 2.49 (dd, *J* = 10.86, 16.83 Hz, 1H), 2.41 (s, 3H), The NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.4, 136.8, 135.1, 133.3, 129.8, 129.2, 127.2, 126.4, 126.1, 125.1, 68.3, 52.7, 47.4, 32.2 and 21.5.

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CHAPTER 4

IRIDIUM CATALYZED ASYMMETRIC HYDROGENATION OF OLEFINS USING TIQ PHOSPHINE-OXAZOLINE LIGANDS

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ABSTRACT

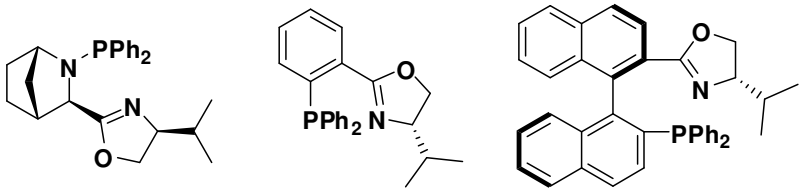
A novel family of tetrahydroisoquinoline (TIQ) phosphine-oxazoline ligands and four corresponding iridium complexes have been developed and applied to the asymmetric hydrogenation of unfunctionalised olefins. The results showed that the best conversion rates were observed up to 99 % with an enantioselectivity of 91 %.

INTRODUCTION

The enantioselective hydrogenation of olefins represents an important process for obtaining optically pure biologically active compounds.[1-3] The discovery of the Wilkinson catalyst ($RhCl[P(C_6H_5)_3]_3$) possessing chiral phosphine ligands for the hydrogenation of olefins sparked the development of other chiral ligands in this field.[4-6] Early ligands were coordinated with ruthenium- and rhodium metals and applied to the asymmetric hydrogenation of olefins.[6] There have been many reports more recently describing the use of chiral N,P ligands and Ir-catalyzed hydrogenations of olefins.[7-8] The first chiral mimic of the Crabtree complex[9] was reported by Pfaltz and co-workers,[10] and was successfully used in asymmetric hydrogenation of olefins. Amongst the nitrogen donor ligands, oxazoline has become one of the most popular moieties in asymmetric catalysis (Figure 1).[7,11-14] Andersson *et al*. have developed chiral iridium catalysts for a wide range of substrates.[15-16] In particular, derivatives of the bicyclic phosphene-oxazoline **1** are among the most successful and have produced excellent results in the

hydrogenation of acyclic aromatic *N*-arylamines,[17] enol phosphinates[18] and vinyl boronates.[19] The asymmetric hydrogenation of unfunctionalised olefins remains a challenge due to substrate dependence, and the development of new catalysts targeting this class of substrate is imperative.[20]

Recently, we have reported on the synthesis and evaluation of several novel classes of chiral tetrahydroisoquinoline (TIQ) ligands.[21-23] Their metal complexes have been employed for asymmetric transfer hydrogenation[21-22] and Henry type reactions. Previous reports described the application of N,P derived TIQ oxazoline ligands for asymmetric C–C bond forming reactions.[24-26] In this paper, we report a new class of iridium phosphine-oxazoline catalysts for the asymmetric hydrogenation of olefins.



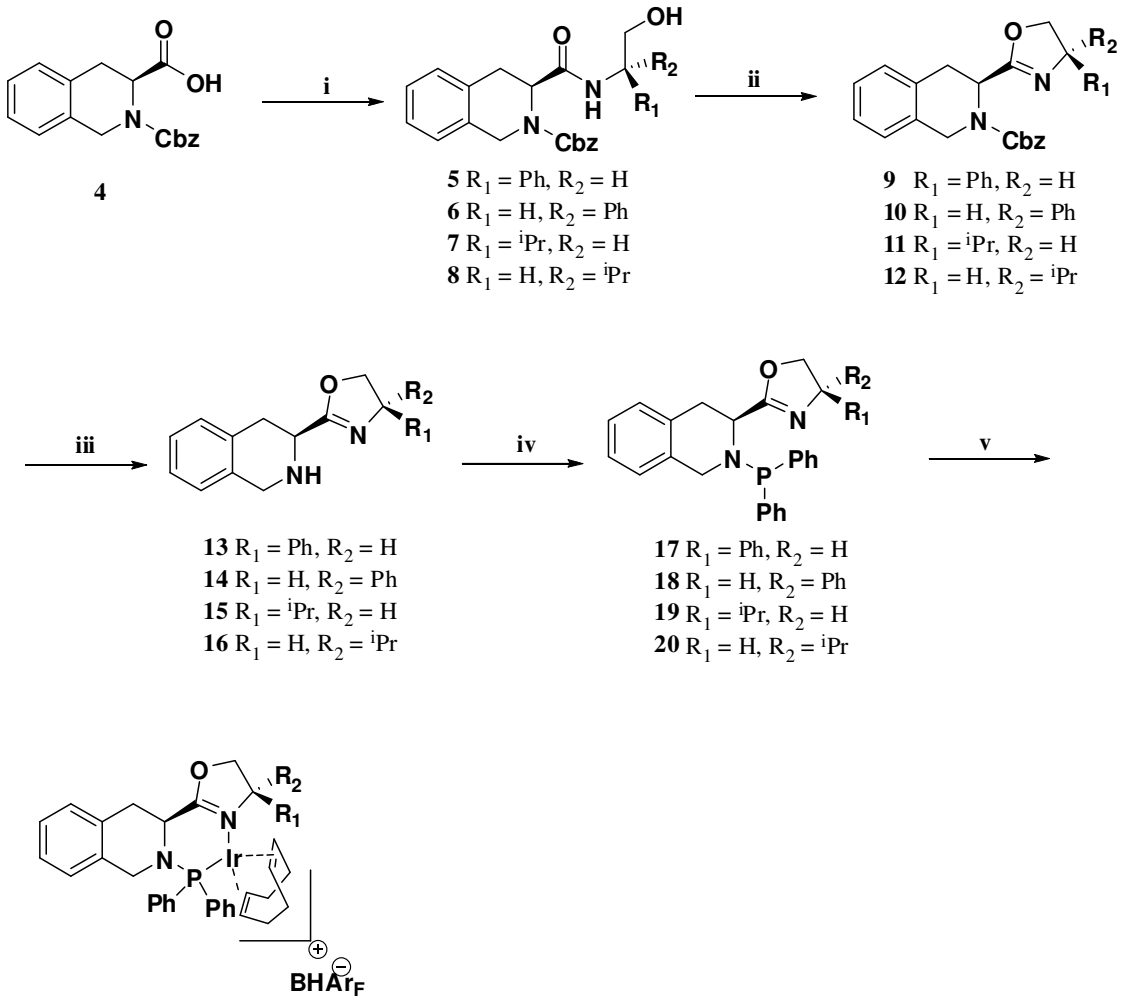
1 **2** **3**

Figure 1. Previously reported P,N oxazoline ligands

RESULTS AND DISCUSSIONS

The first alternate route to that employed by Blanc *et al*. for the synthesis of the TIQ phosphine-oxazoline ligands is described in this report, whereby the diphenyl phosphine is introduced after the formation of the oxazoline (Scheme 1). The TIQ carboxylic acid is easily available from a Pictet-Spengler reaction of L-phenyl alanine.[27] The amine was protected with benzyl chloroformate (Cbz) to give TIQ-Cbz acid **4**[27] followed by amide coupling with the appropriate L- and D-amino alcohols leading to hydroxylamides **5-8**.[17] The compounds were subsequently converted into five membered oxazoline rings **9-12** with triphenyl phosphine and diethyl azodicarboxylate (DEAD) by the Mitsunobu reaction in good yields.[28] The cleavage of the Cbz group was accomplished by hydrogenolysis using palladium on carbon as a catalyst to yield the amines **13-16**. The ligands **17-20** were obtained by treating these amines with diphenylphosphine chloride in the presence of diisopropylethylamine.[17] Due to compound instability upon addition of the phosphine onto the sp^3 nitrogen of the TIQ oxazolines, the structures of these ligands were only confirmed by ^{31}P, ^{1}H NMR spectroscopy. Iridium

complexes **21-24** were prepared by refluxing the appropriate phosphine-oxazoline ligands and $[Ir(COD)Cl]_2$ in CH_2Cl_2 followed by counter-ion exchange with sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaBAr_F$) in a CH_2Cl_2/H_2O mixture with vigorous stirring. The crude complexes were purified by column chromatography on silica gel deactivated by triethylamine to afford the desired Ir-complexes **21-24** as crystalline compounds.



4

5 R_1 = Ph, R_2 = H
6 R_1 = H, R_2 = Ph
7 R_1 = ^{i}Pr, R_2 = H
8 R_1 = H, R_2 = ^{i}Pr

9 R_1 = Ph, R_2 = H
10 R_1 = H, R_2 = Ph
11 R_1 = ^{i}Pr, R_2 = H
12 R_1 = H, R_2 = ^{i}Pr

13 R_1 = Ph, R_2 = H
14 R_1 = H, R_2 = Ph
15 R_1 = ^{i}Pr, R_2 = H
16 R_1 = H, R_2 = ^{i}Pr

17 R_1 = Ph, R_2 = H
18 R_1 = H, R_2 = Ph
19 R_1 = ^{i}Pr, R_2 = H
20 R_1 = H, R_2 = ^{i}Pr

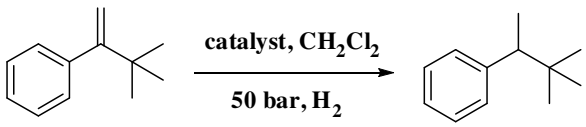
21 R_1 = Ph, R_2 = H
22 R_1 = H, R_2 = Ph
23 R_1 = ^{i}Pr, R_2 = H
24 R_1 = H, R_2 = ^{i}Pr

Scheme 1. Reagents for the synthesis of iridium complexes **21**-**24** (i) EDC.HCl, HOBt, Triethylamine, amino alcohol, THF, H_2O, rt, 16 hrs; (ii) PPh_3, DEAD, dichloromethane, 0 °C-rt, 3 hrs; (iii) 10 % Pd/C wt. H_2 (1 atm), MeOH, rt, 1 hr; (iv) PPh_2Cl, DIPEA, dichloromethane, rt, 16 hrs; (v) $[Ir(COD)Cl]_2$, dichloromethane, reflux 1 hr then H_2O, $NaBAr_F.3H_2O$, rt, 2 hrs;

LIGAND ACTIVITY

In the first set of experiments, we used the Ir-catalyzed hydrogenation of (3,3-dimethylbut-1-en-2-yl) benzene **25** as the benchmark reaction for the catalysts **21-24**. The reaction was performed in dichloromethane with a catalyst loading of 0.5 mol % under a pressure of 50 bar of hydrogen gas. Good conversion rates were observed up to >99 % using the catalysts **21**-**24** for the benchmark reaction with variable enantioselectivities (table 1). The best enantioselectivity was obtained for catalysts **22** and **23** with 88 % for the (*S*) isomer and 91 % for the (*R*) isomer respectively (entries 2 and 3, table 1). The enantioselectivity of the reaction was observed to be dependent on the chirality of the oxazoline ring.

Table 1: Asymmetric hydrogenation of (3,3-dimethylbut-1-en-2-yl) benzene **25** using catalysts **21**-**24**[a]



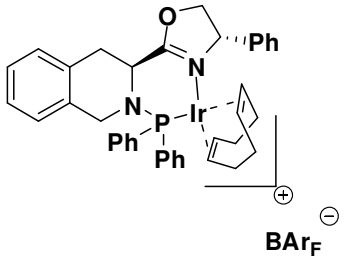
25

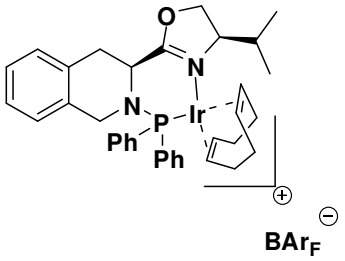
Entry	Catalyst	Conv. (%)[b]	*ee* (%)[c]
1	**21**	99	79 (*R*)
2	**22**	99	88 (*S*)
3	**23**	99	91 (*R*)
4	**24**	99	72 (*S*)

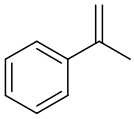
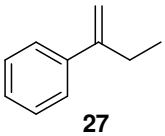
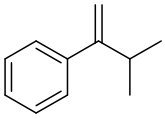
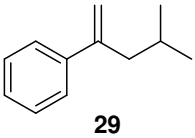
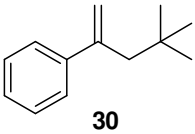
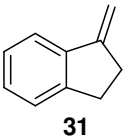
[a]All reactions were carried out at 50 bar H_2 in DCM at RT for 2 hours with 0.5 mol % S/C loading. [b]Conversions were determined by ^{1}H NMR. [c]Enantiomeric excess was determined using HPLC with a chiral column and by GC using a β-dex chiral capillary column.

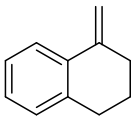
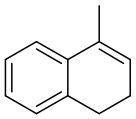
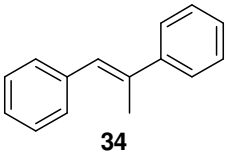
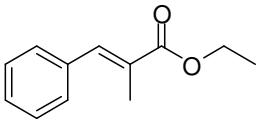
The results obtained from the Ir-complexes **22** and **23**, encouraged us to screen a wider range of olefins. Most substrates were hydrogenated with high conversions and moderate selectivities (Table 2).

Table 2: Asymmetric hydrogenation of olefins using **22** and **23** as catalysts[a]





Entry	Substrate	Conv. (%)[b]	*ee* (%)[c]	Conv. (%)[b]	*ee* (%)[c]
1	 **26**	0	-	0	-
2	 **27**	99	40 (*S*)	99	67 (*R*)
3	 **28**	99	63 (*S*)	99	48 (*R*)
4	 **29**	99	41 (*S*)	99	71 (*R*)
5	 **30**	99	46 (*S*)	99	73 (*R*)
6	 **31**	99	13 (*S*)	99	racemic

7	 **32**	99	6 (*S*)	99	48 (*R*)
8	 **33**	99	16 (*S*)	99	51 (*R*)
9	 **34**	57	60 (*R*)	99	28 (*R*)
10	 **35**	27	47 (*S*)	41	racemic

[a]All reactions were carried out at 50 bar H_2 in DCM at RT for 2 hours with 0.5 mol % S/C loading. [b]Conversions were determined by ^{1}H NMR. [c]Enantiomeric excess was determined using HPLC with a chiral column and by GC using a β-dex chiral capillary column.

Considerable differences were observed for hydrogenations of the cyclic and acyclic olefins. No activity was observed for the propene substrate (table 2, entry 1) but >99 % conversion for the butene and pentene analogs was achieved (table 2, entries 2-5). An increase in bulk did not result in a difference in conversion but did give higher enantioselectivities. This effect was more profound for the butene derivatives and presumably this can be attributed to the increased steric crowding closer to the pro-chiral center. The exocyclic olefins (table 2, entries 6 and 7) and an internal cyclic olefin (table 2, entry 8) gave quantitative conversions but essentially racemic mixtures. Poor conversions and selectivities were observed for activated branched olefins (table 2, entries 9 and 10).

CONCLUSION

We have developed TIQ phosphine-oxazoline iridium complexes for asymmetric hydrogenation of olefins. The best results obtained in this study were with 99 % conversions and enantioselectivities of up to 91 % in 2 hours with 0.5 mol % catalyst loading. The variation in

results clearly supports other reports of the substrate dependence for this important class of olefins and encourages further investigations.

EXPERIMENTAL

GENERAL

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments at room temperature. Chemical shifts are expressed in ppm downfield from TMS as an internal standard, and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel (60–200 mesh except if stated differently). All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin-Elmer Polarimeter (Model 341). All melting points are uncorrected. High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, and a sample concentration of approximately 1 ppm.

General procedure for preparation hydroxylamides 5, 6, 7 and 8

This method was adapted from literature.[14] To a round bottom flask was added Cbz-protected TIQ acid **4** (2.0 g, 0.04 mol), the amino alcohol (1.1 equiv.) and HOBt (2.0 equiv.) in THF (60 mL). The mixture was cooled to 0 ºC followed by the addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.0 equiv.) and triethylamine (3.0 equiv.) and allowed to react at ambient temperature for 16 hours. Completion of the reaction was monitored by TLC using dichloromethane/methanol (98:2, R_f = 0.4). The solvent was evaporated, and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with 10 % HCl (10 mL) followed by saturated $NaHCO_3$ (10 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated to give crude hydroxylamide, which was purified by column chromatography using 0-2% MeOH/CH_2Cl_2 as the eluent to yield pure compounds **5**, **6**, **7** and **8**.

General procedure for preparation of protected oxazolines 9, 10, 11 and 12

This method was adapted from literature.[28] To a stirred solution of Cbz-protected TIQ-hydroxylamide (1.0 g) in dry dichloromethane (60 mL) was added triphenylphosphine (2.0 equiv.) at room temperature under N_2 atm. The reaction mixture was cooled to 0 °C and to this

was added a solution of diethyl azodicarboxylate (2.2 equiv.) in dry dichloromethane (20 mL) drop-wise over a period of 20 min and the resulting mixture was stirred for 4 h under a N_2 atmosphere. After completion of the reaction, the mixture was diluted with dichloromethane (10 mL), washed with water (2 × 10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using (EtOAc/hexane, 50:50) as the eluent to yield pure compounds **9**, **10**, **11** and **12**.

General deprotection procedure for preparation of TIQ-oxazolines 13, 14, 15 and 16

This method was adapted from literature.[14] A solution of Cbz-protected TIQ–oxazoline (1.0 g) in methanol (30 mL) was added to a suspension of 10 wt.-% Pd/C (0.5 g) in methanol (10 mL). The reaction mixture was connected to a hydrogen source at one atm. and stirred at room temperature for 2 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate (50:50, R_f = 0.5). The Pd/C was filtered off on a Celite pad, and the filtrate was concentrated under reduced pressure to afford the crude TIQ-oxazoline ligand. The crude compounds were purified on a deactivated silica gel column. The deactivation was done as follows: the column was packed with a suspension of silica gel in 20 % Et_3N/CH_2Cl_2 and the silica was washed with 1 % Et_3N/CH_2Cl_2. The chromatography was performed using 0–2 % MeOH : 1 % Et_3N : 99–97 % CH_2Cl_2 as the eluent to afford pure oxazoline compounds **13**, **14**, **15** and **16**.

General procedures for preparation of ligands 17, 18, 19 and **20**

This method was adapted from literature.[20] The TIQ-oxazoline was co-evaporated with dry toluene (3 × 20 mL) and dissolved in dry THF (6 mL) under a N_2 atmosphere. Freshly distilled di-isopropylethylamine was added and the solution was cooled to 0 ºC in an ice-bath. Freshly distilled chlorodiphenylphosphene was added dropwise and the reaction was kept at 4 ºC (fridge) overnight. The reaction was quenched with saturated $NaHCO_3$ (20 mL) under a N_2 atmosphere at room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and the crude product was purified by column chromatography using deactivated silica gel with Et_3N: CH_2Cl_2: pentane as the eluent to afford ligands **17**, **18**, **19** and **20**.

General procedure for preparation of iridium complexes 21-24

The ligand and $[Ir(COD)Cl]_2$ (0.5 equiv.) was dissolved in CH_2Cl_2 (2 mL) under a N_2 atmosphere and the mixture was refluxed for 1 h. After the solution was allowed to cool to room temperature, distilled water was added and whilst vigorously stirring, $NaBAr_F.3H_2O$ was added to the reaction mixture in one portion and reacted for 1 h at ambient temperature. The complex was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. Evaporation of the solvent produced the crude complex and purification by column chromatography on silica gel with CH_2Cl_2: pentane (1:1) as the eluent afforded the metal complexes **21-24**.

General procedure for iridium-catalyzed asymmetric hydrogenation of olefins

A vial was charged with substrate and the iridium complex in dry CH_2Cl_2 (2 mL). The reaction vessel was placed in a high-pressure hydrogenation apparatus and flushed with hydrogen gas three times before the pressure was adjusted to 50 bar. The mixture was stirred for 2 h, the pressure released and the solvent removed under vacuum. Conversion was determined by ^1H NMR analysis of the crude product. The residue was filtered through a short pad of silica gel with pentane: diethyl ether (1:1) as the eluent. After the solvent was removed, the enantiomeric excess was determined by chiral HPLC or GC.

Literature preparations

Substrates **25**,[29] **27**,[30] **28**,[30] **29**,[31] **30**,[32] **32**,[33] **33**,[34] and **35**[34] were prepared according to the literature procedures.

(*S*)-benzyl 3-((*R*)-2-hydroxy-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (5)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2); Off white solid (2.2 g, yield 80 %); m.p: 133−135 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ = –26.19 (*c* 0.42 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 − 6.89 (m, 13H), 6.40 (m, 1H), 5.31 − 5.08 (m, 2H), 4.99 − 4.50 (m, 4H), 3.72 − 3.27 (m, 3H), 3.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.7, 128.6, 128.3, 128.0, 127.7, 127.2, 126.4, 126.0, 67.9, 65.9, 55.6, 45.2; IR ν_{max}/cm^{-1} (neat): 3230, 3063, 1702, 1647, 1336, 1308, 1231, 740, 691, 534; HR ESI MS: *m*/*z* = 431.1940 $[M+H]^+$ (calcd. for $C_{26}H_{27}N_2O_4$ 431.1965).

(*S*)-benzyl 3-((*S*)-2-hydroxy-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2); Off white solid (2.0 g, yield 74 %); m.p: 120–122 ºC; $[\alpha]_D^{20}$ = +10.71 (*c* 0.70 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.02 (m, 11H), 6.85 – 6.32 (m, 3H), 5.40 – 5.06 (m, 2H), 5.04 – 4.43 (m, 4H), 3.89 – 3.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 133.6, 133.3, 128.6, 128.5, 128.4, 128.2, 127.3, 126.0, 67.9, 65.5, 56.5, 55.9, 54.7, 45.3, 31.5; IR ν_{max}/cm^{-1} (neat): 3438, 3309, 2912, 1656, 1672, 1412, 1354, 1205, 1132, 749, 730, 691; HR ESI MS: *m*/*z* = 431.1985[M+ H] $^+$ (calcd. for $C_{26}H_{27}N_2O_4$ 431.1965).

(*S*)-benzyl 3-((*R*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-3,4-dihydroisoquino-line-2(1H)-carboxylate (7)

R_f = 0.5 (CH_2Cl_2/MeOH, 9.8:0.2); Off white solid (2.2 g, yield 86 %); m.p: 110–112 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ = +4.37 (*c* 0.80 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.05 (m, 9H), 5.29 – 5.13 (m, 2H), 4.84 – 4.44 (m, 3H), 3.61 – 3.02 (m, 5H), 1.76 (m, 1H), 0.96 – 0.47 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 128.8, 128.6, 128.3, 128.2, 128.0, 128.0, 126.9, 67.9, 63.3, 57.0, 56.6, 45.3, 32.6, 31.3, 28.5, 19.2, 18.5; IR ν_{max}/cm^{-1} (neat): 3479, 3306, 2946, 1678, 1647, 1554, 1421, 1346, 1225, 1136, 1047, 756, 728, 692; HR ESI MS: *m*/*z* = 419.1941[M+ Na] $^+$ (calcd. for $C_{23}H_{28}N_2NaO_4$ 419.1941).

(*S*)-benzyl 3-((*S*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-3,4-dihydroisoquino-line-2(1H)-carboxylate (8)

R_f = 0.5 (CH_2Cl_2/MeOH, 9.8:0.2); White solid (2.2 g, yield 86 %); m.p: 110–112 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ = – 23.08 (*c* 1.17 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.07 (m, 9H), 5.86 (m, 1H), 5.41 – 4.99 (m, 2H), 4.89 – 4.40 (m, 3H), 3.64 – 2.99 (m, 5H), 0.79 – 0.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 128.6, 128.4, 127.9, 126.9, 126.1, 125.9, 67.9, 63.5, 56.7, 45.4, 28.6, 19.3, 17.8; IR ν_{max}/cm^{-1} (neat): 3407, 3333, 2955, 1678, 1662, 1538, 1411, 1347, 1228, 1124, 1094, 736; HR ESI MS: *m*/*z* = 419.1941[M+ Na] $^+$ (calcd. for $C_{23}H_{28}N_2NaO_4$ 419.1941).

(*S*)-benzyl 3-((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxy-late (9)

R_f = 0.6 (hexane/EtOAc, 65:35); Off white solid (0.86 g, yield 90 %); m.p: 96–98 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ = +2.70 (*c* 0.37 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.03 (m, 12H), 6.65 – 6.43 (m, 2H), 5.54 – 5.13 (m, 3H), 5.04 (m, 1H), 4.89 – 4.67 (m, 2H), 4.52 (m, 1H), 3.89 (m, 1H), 3.39 – 3.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 156.0, 142.1, 133.4, 132.9, 131.6, 128.9, 128.4, 128.0, 127.9, 127.2, 126.8, 126.6, 126.2, 69.5, 67.6, 67.4, 49.1, 48.9, 44.7, 32.1; IR ν_{max}/cm^{-1} (neat): 3324, 1702, 1665, 1411, 1326, 1304, 1184, 1114, 997, 744, 697; HR ESI MS: *m*/*z* = 413.1895 [M+ H]$^+$ (calcd. for $C_{26}H_{25}N_2O_3$ 413.1860).

(*S*)-benzyl 3-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (10)

R_f = 0.6 (hexane/EtOAc, 65:35); Off white solid (0.85 g, yield 89 %); m.p: 60–62 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ = +12.20 (*c* 0.41 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.04 (m, 12H), 6.77 (m, 2H), 5.55 – 4.99 (m, 4H), 4.97 – 4.38 (m, 3H), 3.94 (m, 1H), 3.44 – 3.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 156.3, 142.3, 136.4, 133.8, 132.2, 129.4, 129.0, 127.3, 127.0, 75.8, 68.0, 48.8, 44.8, 31.5; IR ν_{max}/cm^{-1} (neat): 3313, 3031, 2925, 1662, 1407, 1216, 1119, 744, 696; HR ESI MS: *m*/*z* = 413.1861[M+ H]$^+$ (calcd. for $C_{26}H_{25}N_2O_3$ 413.1860).

(*S*)-benzyl 3-((*R*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (11)

R_f = 0.6 (hexane/EtOAc, 60:40); Colorless oil (0.85 g, yield 89 %); $[\alpha]_D^{20}$ = +3.37 (*c* 0.89 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 6.94 (m, 9H), 5.42 – 5.10 (m, 3H), 4.90 – 4.55 (m, 2H), 4.36 – 3.96 (m, 4H), 3.93 – 3.74 (m, 2H), 3.25 – 3.03 (m, 2H), 1.47 (m, 1H), 0.67 – 0.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 155.8, 136.5, 132.6, 128.3, 127.8, 127.6, 127.0, 126.7, 126.2, 71.6, 70.0, 67.4, 64.1, 62.5, 62.2, 48.5, 44.4, 31.8, 17.9, 17.1, 14.3; IR ν_{max}/cm^{-1} (neat): 3301, 2958, 1679, 1647, 1256, 1225, 1049, 756, 729; HR ESI MS: *m*/*z* = 379.2016[M+ H]$^+$ (calcd. for $C_{23}H_{27}N_2O_3$ 379.2016).

(*S*)-benzyl 3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (12)

R_f = 0.6 (hexane/EtOAc, 60:40); Colorless oil (0.85 g, yield 89 %); $[\alpha]_D^{20}$ = –9.72 (*c* 0.72 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.07 (m, 9H), 6.65 (m, 1H), 5.39 – 5.07 (m, 2H), 4.91 – 4.44 (m, 3H), 3.64 –

3.01 (m, 4H), 1.90 (m, 1H), 0.91 – 0.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 132.1, 131.9, 128.6, 128.5, 128.3, 127.1, 126.5, 126.0, 67.7, 63.4, 62.2, 45.2, 28.4, 19.3, 17.9; IR ν_{max}/cm^{-1} (neat): 3334, 2956, 1662, 1679, 1412, 1220, 1121, 1095, 737, 694; HR ESI MS: *m*/*z* = 379.2016[M+ H] $^+$ (calcd. for $C_{23}H_{27}N_2O_3$ 379.2016).

(*R*)-4-phenyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole (13)

R_f = 0.3 (CH_2Cl_2/MeOH, 98:2); White solid (0.41 g, yield 59 %); m.p: 129–131 ºC (CH_2Cl_2); $[\alpha]_D^{20}$ = +46.15 (*c* 0.26 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.23 (m, 3H), 7.23 – 7.10 (m, 5H), 7.08 – 7.02 (m, 1H), 5.23 (t, *J* = 18.21 Hz, 1H), 4.68 (q, *J* = 10.10, 3.46 Hz, 1H), 4.16 (m, 3H), 3.92 (m, 1H), 3.19 – 3.06 (m, 2H), 1.93 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 142.0, 135.0, 133.3, 129.2, 128.7, 127.6, 126.5, 126.2, 126.1, 126.0, 75.0, 69.4, 51.5, 47.6, 32.4. IR ν_{max}/cm^{-1} (neat): 3225, 1663, 1493, 1454, 1366, 957, 916, 740, 697; HR ESI MS: *m*/*z* = 279.1500 [M+ H] $^+$ (calcd. for $C_{18}H_{19}N_2O$ 279.1492).

(*S*)-4-phenyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole (14)

R_f = 0.3 (CH_2Cl_2/MeOH, 98:2); Yellow oil (0.45, yield 65 %); $[\alpha]_D^{20}$ = −7.40 (*c* 1.85 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.01 (m, 9H), 5.23 (t, *J* = 18.33 Hz, 1H), 4.68 (q, *J* = 10.04, 8.56 Hz, 1H), 4.20 – 4.13 (m, 3H), 3.92 (t, *J* = 5.84 Hz, 1H), 3.13 (d, *J* = 9.08 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 142.1, 135.0, 133.4, 129.4, 129.0, 127.8, 126.8, 126.4, 126.2, 75.2, 69.5, 51.6, 47.7, 32.5; IR ν_{max}/cm^{-1} (neat): 3227, 1663, 1493, 1109, 957, 916, 907, 749, 697; HR ESI MS: *m*/*z* = 279.1492[M+ H] $^+$ (calcd. for $C_{18}H_{19}N_2O$ 279.1492).

(*R*)-4-isopropyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole (15)

R_f = 0.3 (CH_2Cl_2/MeOH, 9.8:0.2); Pale yellow oil (0.35 g, 54 %); $[\alpha]_D^{20}$ = −12.73 (*c* 0.55 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.07 (m, 3H), 7.03 (m, 1H), 4.28 (q, *J* = 9.32, 8.12 Hz, 1H), 4.12 (s, 2H), 4.05 – 3.92 (m, 2H), 3.81 – 3.75 (m, 1H), 3.09 – 2.94 (m, 2H), 1.78 (m, 1H), 1.27 (t, *J* = 7.18 Hz, 1H), 0.96 (d, *J* = 6.88 Hz, 3H), 0.87 (t, *J* = 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 135.2, 133.6, 129.1, 126.2, 126.06, 126.04, 72.1, 70.4, 51.8, 48.0, 32.6, 18.9, 18.1; IR ν_{max}/cm^{-1} (neat): 3298, 2960, 1717, 1642, 1525, 1222, 1065, 741, 615; HR ESI MS: *m*/*z* = 245.1468[M+ H] $^+$ (calcd. for $C_{15}H_{21}N_2O$ 245.1462).

(*S*)-4-isopropyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole (16)

R_f = 0.3 (CH_2Cl_2/MeOH, 9.8:0.2); Pale yellow oil (0.38 g, yield 59 %); $[\alpha]_D^{20}$ = −10.87 (*c* 0.69 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 − 7.08 (m, 3H), 7.02 (m, 1H), 4.33 − 4.14 (m, 2H), 4.11 (s, 2H), 4.05 − 3.91 (m, 2H), 3.79 (m, 1H), 3.02 (d, *J* = 7.58 Hz, 2H), 1.77 (m, 1H), 1.25 (t, *J* = 14.3 Hz, 1H), 0.96 (d, *J* = 6.79 Hz, 3H), 0.87 (d, *J* = 6.79 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 135.1, 133.6, 129.4, 126.4, 126.2, 72.1, 70.4, 51.7, 47.8, 32.6, 32.5, 18.9, 18.1; IR ν_{max}/cm^{-1} (neat): 3279, 2957, 1744, 1644, 1559, 1225, 1069, 880, 736; HR ESI MS: *m*/*z* = 245.1468[M+ H] $^+$ (calcd. for $C_{15}H_{21}N_2O$ 245.1462).

(*R*)-2-((*S*)-2-(diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl-4,5-dihydrooxazole (17)

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.85 (t, 2H), 7.54 (t, 2H), 7.21 − 6.84 (m, 13H), 6.71 − 6.61 (m, 2H), 4.82 − 4.56 (m, 3H), 4.20 (dd, *J* = 9.34, 2.99 Hz, 1H), 3.84 (m, 1H), 3.56 (m, 1H), 3.31 (m, 1H), 3.18 (m, 1H); ^{31}P NMR (162 MHz, C_6D_6): δ 65.81;

(*S*)-2-((*S*)-2-(diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl-4,5-dihydrooxazole (18)

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.83 − 7.45 (m, 4H), 7.23 − 6.90 (m, 13H), 6.78 − 6.58 (m, 3H), 4.82 − 4.58 (m, 3H), 4.20 (d, *J* = 8.64 Hz, 1H), 3.88 (m, 1H), 3.56 (m, 1H), 3.31 (m, 1H), 3.08 (m, 1H); ^{31}P NMR (162 MHz, C_6D_6): δ 65.38;

(*R*)-2-((*S*)-2-(diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-isopropyl-4,5-dihydrooxazole (19)

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.78 (m, 2H), 7.45 (m, 2H), 7.25 − 6.76 (m, 9H), 6.56 (m, 1H), 4.68 − 3.80 (m, 5H), 3.66 − 2.89 (m, 3H), 1.23 (m, 1H), 0.57 (d, *J* = 6.7 Hz, 3H), 0.50 (d, *J* = 6.7 Hz, 3H); ^{31}P NMR (162 MHz, C_6D_6): δ 67.99;

(*S*)-2-((*S*)-2-(diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-isopropyl-4,5-dihydrooxazole (20)

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.76 (m, 2H), 7.44 (m, 2H), 7.21 − 6.79 (m, 9H), 6.57 (m, 1H), 4.63 (m, 1H), 4.41 (d, 16.4 Hz, 1H), 4.10 (d, 16.1 Hz, 1H), 3.64 − 3.01 (m, 6H), 1.27 (m, 1H), 0.64 (d, *J* = 6.8 Hz, 3H), 0.54 (d, *J* = 6.8 Hz, 3H); ^{31}P NMR (162 MHz, C_6D_6): δ 68.39;

Complex 21:

Yield: 64 %; $[\alpha]_D^{20}$ = –3.12 (*c* 0.32 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.58 (m, 10H), 7.56 – 7.41 (m, 7H), 7.40 – 7.11 (m, 11H), 6.82 (m, 2H), 6.71 (m, 1H), 5.21 – 4.72 (m, 2H), 4.38 (m, 1H), 4.11 (m, 2H), 3.76 (m, 2H), 3.36 – 3.18 (m, 3H), 2.76 (m, 1H), 2.31 – 2.06 (m, 2H), 1.98 – 1.78 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 163.1 – 160.7, 138.9, 135.0, 133.0 – 131.4 (m), 130.5 – 127.4 (m), 126.31, 125.6, 125.2, 123.8, 122.0, 117.6 (d, *J* = 3.89 Hz), 42.4, 36.2, 29.2, 20.1, 8.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 66.13; IR ν_{max}/cm^{-1} (neat): 2928, 2034, 1610, 1353, 1273, 1115, 885, 838, 744, 711; HR ESI MS: *m*/*z* = 763.2418 $[M - BAr_F]^+$ (calcd. for $C_{38}H_{39}IrN_2OP$ 763.2424).

Complex 22:

Yield: 62 %; $[\alpha]_D^{20}$ = +40.87 (*c* 1.15 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 – 6.82 (m, 30H), 6.67 (m, 1H), 5.16 – 4.77 (m, 2H), 4.62 (m, 1H), 4.55 – 4.28 (m, 4H), 3.66 (m, 1H), 3.44 – 3.28 (m, 2H), 3.10 – 2.88 (m, 2H), 2.51 – 1.85 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 162.2 (q), 138.3, 135.2, 133.6 – 131.9 (m), 130.6 – 127.6 (m), 126.5, 126.4, 123.6, 120.9, 117.9 (t), 94.7, 69.1, 65.9, 63.9, 57.6, 53.9, 52.3, 36.5, 34.6, 30.1, 27.5, 22.8, 14.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.83; IR ν_{max}/cm^{-1} (neat): 2924, 2024, 1610, 1353, 1272, 1114, 885, 734, 711, 681; HR ESI MS: *m*/*z* = 763.2424 $[M - BAr_F]^+$ (calcd. for $C_{38}H_{39}IrN_2OP$ 763.2424).

Complex 23:

Yield: 68 %; $[\alpha]_D^{20}$ = +1.56 (*c* 0.64 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.83 (m, 3H), 7.78 – 7.45 (m, 15H), 7.43 – 7.07 (m, 7H), 6.63 (d, 1H), 5.02 – 4.66 (m, 5H), 3.48 – 3.01 (m, 4H), 2.74 (m, 1H), 2.44 – 1.16 (m, 8H), 0.94 – 0.73 (m, 6H), 0.32 (d, *J* = 6.79 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 162.1 (q, *J* = 96.43, 44.72 Hz), 135.0 – 131.9 (m), 129.9 – 129.0 (m), 127.7 – 125.7 (m), 123.4, 120.7, 117.6, 94.7 (d), 92.8 (d), 73.3, 65.6 (t), 57.2, 53.6, 51.8, 42.4, 36.1, 35.4, 32.5, 29.1, 26.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.5;IR ν_{max}/cm^{-1} (neat): 2924, 2036, 1610, 1353, 1272, 1114, 885, 744; HR ESI MS: *m*/*z* = 729.2580 $[M - BAr_F]^+$ (calcd. for $C_{35}H_{41}IrN_2OP$ 729.2580).

Complex 24:

Yield: 65 %; $[\alpha]_D^{20}$ = +30.23 (*c* 0.86 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.64 (m, 5H), 7.64 – 7.47 (m, 9H), 7.40 – 7.09 (m, 9H), 6.87 – 6.77 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H),

5.04 – 4.62 (m, 5H), 3.46 – 3.19 (m, 4H), 2.80 (m, 1H), 2.01 – 1.62 (m, 8H), 1.61 – 1.41 (m, 3H), 0.78 (d, J = 6.7 Hz, 3H), 0.17 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (m), 162.1 (q, J = 99.58, 49.81 Hz), 135.3, 133.0 – 132.6 (m, 132.3 (m), 130.3 – 127.6 (m), 126.0 (m), 125.4, 124.1, 122.3, 117.9, 95.4, 70.1, 65.8, 64.1, 57.1, 52.4, 36.7, 36.0, 32.7, 32.4, 30.2, 29.2, 26.8, 18.8, 14.6, 13.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.94; IR ν_{max}/cm^{-1} (neat): 2990, 2791, 2029, 1641, 1353, 1272, 1114, 885, 744; HR ESI MS: m/z = 729.2580 $[M - BAr_F]^+$ (calcd. for $C_{35}H_{41}IrN_2OP$ 729.2580).

ACKNOWLEDGEMENTS

This work is supported by the UKZN productivity research grant, a SA/Swedish research links programme grant (GUN no. 65387) and Aspen pharmacare, SA. The NRF is thanked for their support.

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CHAPTER 5

SYNTHESIS OF TETRAHYDROISOQUINOLINE (TIQ)-OXAZOLINE LIGANDS AND THEIR APPLICATION IN ENANTIOSELECTIVE HENRY REACTIONS

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ABSTRACT

A novel family of eleven new tetrahydroisoquinoline (TIQ)-oxazoline intermediates and five corresponding copper(II) catalysts has been developed and applied to the catalytic asymmetric Henry reaction of various aldehydes with nitromethane to provide β-hydroxy nitroalkanes in high conversion (>99 %). This paper describes the synthesis of the TIQ compounds from L-dihydroxyphenylalanine (L-DOPA) as the starting material. The chiral ligands were complexed in situ with various transition metals such as Cu, Sc, Co, Zn, Ni, Mn and tested as a chiral catalysts for the Henry reaction. The reaction was optimized in terms of the metal, counter ion, solvent, temperature and over a range of substrates. The corresponding catalyst with copper(II) acetate and 2-propanol as the solvent provide the best enantioselectivities (up to 77 % ee) for the formation of the corresponding nitroalcohol from 4-chlorobenzaldehyde.

INTRODUCTION

Chiral ligands containing nitrogen donor atoms are widely used as catalysts for asymmetric carbon-carbon bond formation reactions.[1] In particular, the Henry reaction is one of the classic methods for carbon-carbon bond formation in organic synthesis[2] and has received much attention after the pioneering work of Shibasaki and co-workers.[3-25] Moreover, compounds containing a chiral-oxazoline ring are amongst the most frequently used ligands in asymmetric

catalysis. Specific structural features of oxazoline rings have been used with great success in asymmetric reactions due to their modular nature and applicability to a wide range of metal-catalyzed transformations.[26] The majority of these ligands are synthesized from readily available chiral amino alcohols through amidation, followed by chlorination and base-induced cyclisation to obtain the oxazoline.[27] Evans *et al.* reported a novel Cu-bis(oxazoline) catalyst which could efficiently catalyse the asymmetric nitroaldol reaction with a variety of aldehydes in excellent yield and 96 % *ee*.[28]

To the best of our knowledge, only a few syntheses of oxazoline ligands with sp^2 and sp^3 nitrogen systems have been reported.[11-12] It has been reported that the TIQ class of molecules exhibits a wide array of biological effects including stimulation of the β_3-adrenergic receptor[29], δ opioid receptor[30], and $5HT_{1A}$ receptor antagonism.[31] It is also a common key intermediate in many biosynthetic pathways[32] contributing further to the level of interest conferred upon it. Previous reports on the use of TIQ derivatives as ligands have yielded limited success, with poor to moderate enantioselectivities in asymmetric catalysis of allylic alkylation[33], borane-mediated hydrogenation[34-35] and the addition of diethylzinc to benzaldehyde.[36] We are investigating the use this class of scaffold as chiral ligands and have recently reported the use of TIQ amino alcohols for the asymmetric transfer hydrogenation of prochiral ketones.[37] Herein we report the synthesis of a new class of oxazoline ligands built on the TIQ scaffold and a preliminary investigation of their efficiency for the asymmetric Henry reaction of aldehydes with nitromethane (Figure 1).

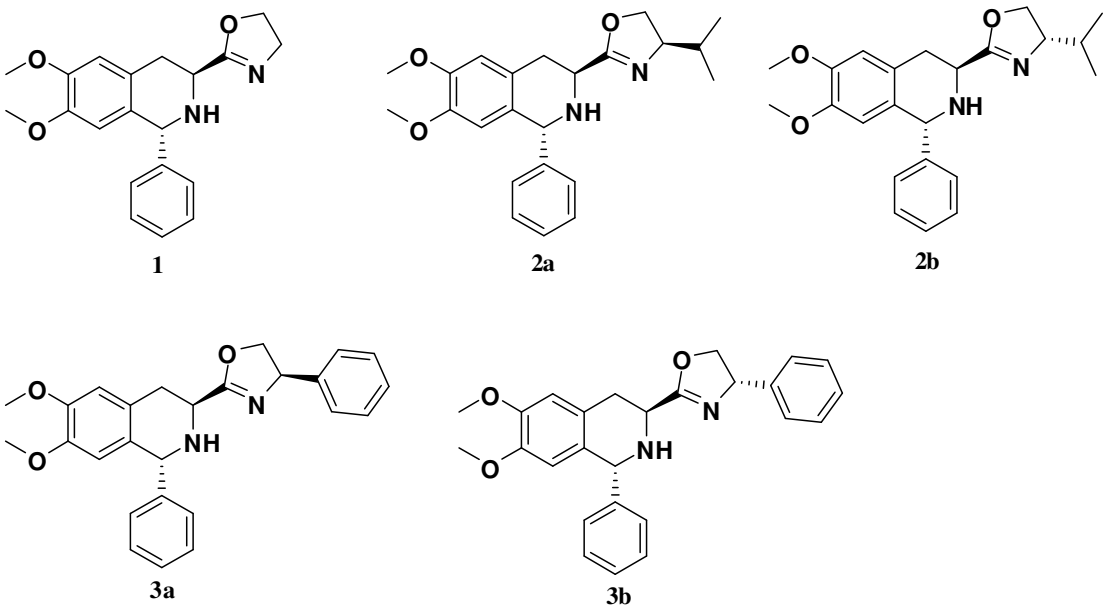
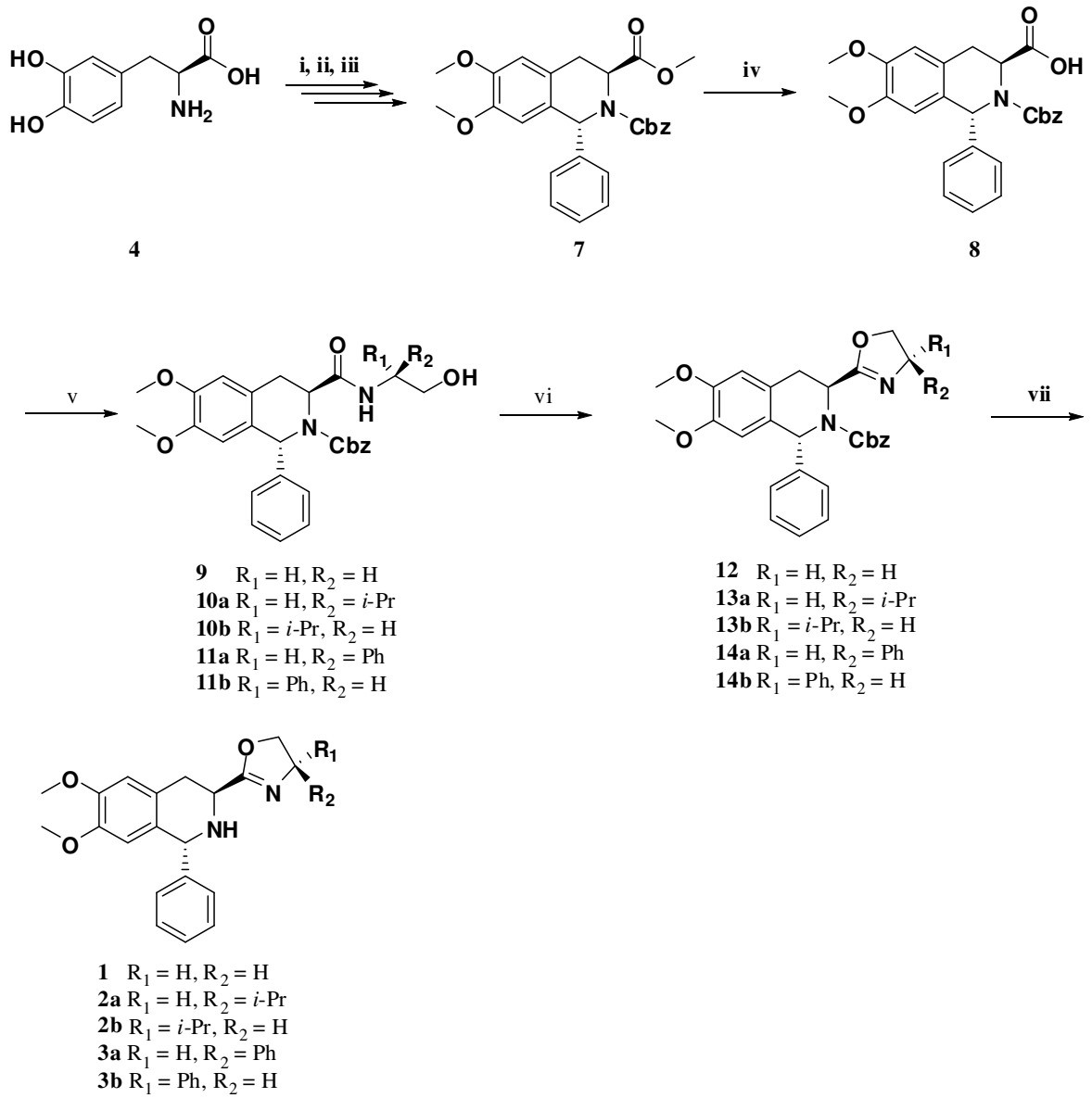


Figure 1. Novel chiral TIQ-oxazoline ligands used in this study

RESULTS AND DISCUSSION

SYNTHESIS OF THE TIQ-OXAZOLINE LIGANDS

The synthesis of the each ligand was achieved from commercially available L-3,4-dihydroxyphenylalanine (L-DOPA) **4** as the starting material. Compound **7** was synthesized as reported previously[37] and upon hydrolysis with lithium hydroxide, yielded the *N*-Cbz protected amino acid **8**. This molecule served as the key intermediate for the synthesis of all the ligands. The amide bond coupling to the appropriate amino alcohols was facilitated by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) to yield the hydroxyl amides **9**–**11b**. Attempts to form the oxazoline ring *via* chlorination and base mediated cyclisation[27] were inefficient with our system and low yields of product were obtained. This was possibly due to harsh reaction conditions such as high temperatures and the use of $SOCl_2$ as the chlorination agent. However, the Mitsunobu reaction[38-42] for the preparation of oxazoline derivatives, under mild and neutral conditions, was found to be successful for our ligand synthesis. The Mitsunobu protocol was used to convert the hydroxyl amides **9**–**11b** to the corresponding oxazolines **12**–**14b**. Removal of the Cbz protecting group was facilitated with Pd/C under a hydrogen atmosphere to yield ligands **1**–**3b**. The sequence of reactions is presented in Scheme 1. Intermediates **8–14b** are all new compounds.



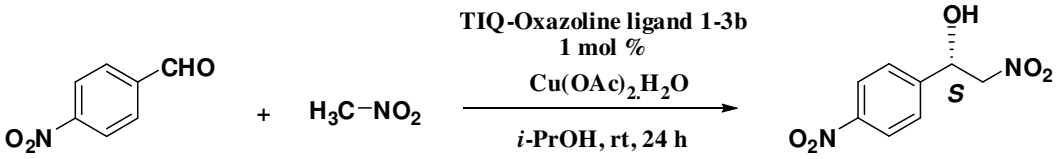
Scheme 1. Reagents for the synthesis of ligands **1**-**3b** (i) Benzaldehyde, K_2CO_3, EtOH/H_2O, 1.5 hrs; (ii) CbzCl, $KHCO_3$, dioxane/H_2O, 0 ºC-rt, 3 hrs; (iii) Me_2SO_4, $KHCO_3$, acetone, reflux, 24 hrs; (iv) LiOH, THF, MeOH, H_2O, rt, 22 hrs; (v) EDC, HOBt, NMM, DMF, rt, 18 hrs; (vi) DEAD, PPh_3, DCM, 0 ºC-rt, 2 hrs; (vii) Pd/C, H_2 (1atm), MeOH, rt, 1.5 hrs

METAL SCREENING AND REACTION OPTIMIZATION

The metal catalyzed Henry reaction between *p*-nitrobenzaldehyde and nitromethane was used as a benchmark reaction to evaluate the enantioselectivity of the TIQ-oxazoline ligands **1**–**3b** (Table 1). All the reactions were complete in 24 hours with just 1 mol % of the ligands **1**–**3b** using $Cu(OAc)_2.H_2O$ as the metal source in the presence of 2-propanol at room temperature.

The procedure used to execute the reaction was similar to those reported before.[25,28] Ligand **1** gave 28 % *ee* with the model reaction (Table 1), which is comparable to the selectivity obtained with ligand **2a**, derived from (*R*)-valinol. Whereas ligand **2b**, derived from (*S*)-valinol, gave 52 % *ee* for the same reaction. The (*S*)-phenylglycinol-derived TIQ-oxazoline ligand **3a** was found to be the most selective with 62 % *ee*. From these results, it is deduced that the presence and orientation of the substituent on the oxazoline ring is crucial for enantioselectivity. Furthermore, ligand **3a** was identified as the most effective among the chiral catalytic series, and it was selected for further optimization.

Table 1 The enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane in the presence of different ligands[a]



Entry	Ligand	Conv. (%)[b]	*ee* (%)[c]
1	**1**	99	28
2	**2a**	95	27
3	**2b**	97	52
4	**3a**	99	62
5	**3b**	99	42

[a]All the reactions were carried out with 0.33 mmol of 4-nitrobenzaldehyde, 3.3 mmol of nitromethane and 0.05 mmol of catalyst in 2 mL of 2-propanol. [b]Determined by HPLC. [c]The enantiomeric excess was determined by HPLC using a Chiralcel IB-H column. Reported values are the average of two runs.

The benchmark reaction was investigated using ligand **3a** and $Cu(OAc)_2.H_2O$ at different substrate/catalyst molar ratios as well as at different temperatures, and the results are summarized (Table 2). Loading of the ligands and the reaction temperature had a significant influence on the efficiency of the reaction with regards to selectivity and reactivity. The reaction with ligand **1** was repeated with 1 mol % of the ligand, the reaction was completed in 24 hours at room temperature and the nitroaldol adduct was obtained in 62 % *ee* with 99 % conversion (Table 2). A lower loading (0.5 mol %) resulted in a reduction in enantioselectivity

to 49 % *ee* (Table 2, entry 2). No significant advantage was realized with an increased amount of the ligand (2 mol % and 5.0 mol %). Decreased reaction temperatures led to slightly higher enantioselectivities but with significant declines in the reactivity. On the basis of these observations, it became clear that 1 mol % of ligand is the optimal quantity for the reaction at room temperature as well as at lower temperatures.

Table 2 The effect of the loading of ligand **3a**–$Cu(OAc)_2 \cdot H_2O$ and temperature on the enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane[a]

Entry	Mol %	Temperature	Time (h)	Conv. (%)[b]	*ee* (%)[c]
1	1	rt	24	99	62
2	0.5	rt	24	95	49
3	2	rt	24	99	59
4	5	rt	24	99	46
5	1	0	90	83	70
6	2	0	90	89	69
7	1	-15	90	45	68

[a]All the reactions were carried out with 0.33 mmol of 4-nitrobenzaldehyde, 3.3 mmol of nitromethane and 0.05 mmol of catalyst in 2 mL of 2-propanol. [b]Determined by HPLC. [c] The enantiomeric excess was determined by HPLC using a Chiralcel IB-H column. Reported values are the average of two runs.

It was found that the type of solvent had a significant effect on both the conversion and enantioselectivity of the Henry products with the best catalyst system [**3a**–$Cu(OAc)_2 \cdot H_2O$, see Table 3]. 2-propanol was found to be the best solvent for this catalytic system (Table 3, entry 5). The use of different protic and aprotic solvents such as THF, ethanol, methanol, *n*-butanol, acetonitrile and dichloromethane led to a decrease in enantioselectivities.

Table 3 Effect of various solvents on the enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane at room temperature using ligand **3a**–$Cu(OAc)_2 \cdot H_2O$[a]

Entry	Solvent	Conv. (%)[b]	*ee* (%)[c]
1	THF	97	33
2	ethanol	89	47
3	methanol	89	36
4	2-propanol	99	62
5	acetonitrile	4	16
6	dichloromethane	75	39

[a]All the reactions were carried out with 0.33 mmol of 4-nitrobenzaldehyde, 3.3 mmol of nitromethane and 0.05 mmol of catalyst in 2 mL of appropriate solvent. [b]Determined by HPLC. [c] The enantiomeric excess was determined by HPLC using a Chiralcel IB-H column. Reported values are the average of two runs.

The effect of other transition metals as Lewis acids was investigated by forming catalytic complexes with the TIQ-oxazoline ligand **3a** (Table 4). Different counter ions were also investigated for the best catalytic system. The acetate counter ion was found to be crucial for the best reactivity of ligand **3a** with the copper(II) ion giving the best selectivity.

Table 4 Effect of Lewis acid on the enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane using ligand **3a**[a]

Entry	Lewis acid	Conv. (%)[c]	*ee* (%)[d]
1[b]	—	10	*rac*
2	$CuCl_2$	3	*rac*
3	$Cu(OTf)_2$	5	10
4	$Cu(OAc)_2.H_2O$	99	62
5	$Co(ClO)_4$	12	*rac*
6	$Sc(OTf)_2$	2	*rac*
7	Zn(II) $(OAc)_2.H_2O$	97	12
8	Ni(II) $(OAc)_2.2H_2O$	99	25
9	Mn(II) $(OAc)_2.2H_2O$	99	*rac*

[a]All the reactions were carried out with 0.33 mmol of 4-nitrobenzaldehyde, 3.3 mmol of nitromethane and 0.05 mmol of catalyst in 2 mL of 2-propanol. [b]Reaction was performed in absence of metal. [c]Determined by HPLC. [d]The enantiomeric excess was determined by HPLC using a Chiralcel IB-H column. Reported values are the average of two runs.

As shown in Table 5, the scope of the catalytic enantioselective Henry reaction was demonstrated by treatment of various aromatic aldehydes with nitromethane in the presence of 1 mol % TIQ-oxazoline **3a**-$Cu(OAc)_2.H_2O$ complex in 2-propanol. In all cases, the reactions proceeded with moderate to good enantioselectivities. In general, the reactions performed at room temperature exhibit moderate enantioselectivity (40–64 % *ee*, Table 5, entries 1, 4, 7 and 10–12). Higher enantiomeric excesses (72–77 % *ee*, Table 5, entries 2, 3, 5 and 8) are observed at 0 °C for aromatic aldehydes bearing either electron-withdrawing (4-fluorobenzaldehyde, 4-chlorobenzaldehyde) or electron-donating (4-methylbenzaldehyde) groups. It became clear that the electronic nature and steric hindrance of the substituent at the aromatic rings does not have much of an effect on the enantioselectivity for our system. (Table 5, entries 3, 5 and 8).

Table 5 Enantioselective Henry reaction of nitromethane with different aldehydes using ligand **3a**–$Cu(OAc)_2 \cdot H_2O$[a]

Entry	Aldehyde	Ligand **3a**-mol%	Temp °C	Time (hrs)	Conv. (%)[b]	*ee*(%)[c] (*R*/*S*)[d]
1	4-chlorobenzaldehyde	**1**	r.t.	24	97	62(*S*)
2	4-chlorobenzaldehyde	**1**	0	90	22	76(*S*)
3	4-chlorobenzaldehyde	**2**	0	90	50	77(*S*)
4	4-fluorobenzaldehyde	**1**	r.t.	24	25	52(*S*)
5	4-fluorobenzaldehyde	**1**	0	90	3	72(*S*)
6	4-fluorobenzaldehyde	**2**	0	90	10	67(*S*)
7	4-methylbenzaldehyde	**1**	r.t.	24	84	60(*S*)
8	4-methylbenzaldehyde	**1**	0	90	16	72(*S*)
9	4-methylbenzaldehyde	**2**	0	90	24	63(*S*)
10	3, 5-dimethoxybenzaldehyde	**1**	r.t.	24	76	40(*S*)
11	Piperonal	**1**	r.t.	24	87	53(*S*)
12	Naphthaldehyde	**1**	r.t.	24	96	64(*S*)

[a]All the reactions were carried out with 0.33 mmol of corresponding benzaldehyde, 3.3 mmol of nitromethane and 0.05 mmol in 2 mL of 2-propanol. [b]Determined by HPLC. [c]The enantiomeric excess was determined by HPLC using a Chiralcel IB-H column. Reported values are the average of two runs. [d]The absolute configurations were established by comparison with literature data.[25]

Despite high enantioselectivities obtained by other groups for this reaction, some limitations are still encountered such as high catalyst loading, a low required temperature and the use of additives for optimal enantioselectivity. In most instances, a high catalyst loading is the essential parameter to obtain high enantioselectivities. Christensen *et al*. used 20 mol % of the Cu^{II}–BOX (BOX= bis-oxazoline) system for the addition of silyl nitronates to aldehydes with

moderate enantioselectivities.[10-12] Maheswaran *et al*. also used 20 mol % of dichloro[(–)-sparteine-*N*,*N*']copper(II) complex for the Henry reaction with nitromethane and obtained a 97 % *ee*.[14] You and Ma have reported the use of 10 mol% for a series of new chiral bis-imidazoline ligands and their application to the copper(II)-catalyzed Henry reaction with a best enantioselectivity of 98 % *ee*.[43] Recently the groups of Sasai[3-5] and Bandini[16-17] described highly enantioselective Henry reactions (99 % *ee*) catalyzed by copper(II) complexes with diamino ligands using 5 mol % and 12 mol % of ligand, respectively. Feng and co-workers have described the use of 10 mol % of copper(I) complexes with *N*,*N*'-dioxide[16] and tetrahydrosalen ligands with 96 % *ee*.[18] Finally, Evans *et al*. reported the 1 mol % copper acetate/bisoxazoline catalyzed addition of nitromethane to aldehydes on large-scale reactions with an excellent 94 % enantiomeric excess after 56 h.[28] The low catalyst loading required by our TIQ based compounds could make them a promising new catalyst. A computational chemistry investigation of chiral steric hindrance induced by the Ligand may be required to improve the enantioselectivity of the reaction.

CONCLUSION

In conclusion, we have explored a new class of chiral TIQ-oxazoline-$Cu(OAc)_2.H_2O$ catalysts for the asymmetric Henry reaction. To the best of our knowledge, this is the first report of the use of the TIQ-backbone in combination with an oxazoline ring with sp^2 and of sp^3 nitrogen systems for the asymmetric Henry reaction. This effective TIQ ligand is readily prepared by using the Mitsunobu protocol to form the external oxazoline ring under mild conditions. More importantly, the catalysts **3a**-$Cu(OAc)_2.H_2O$ gave 62 % *ee* at minimal catalyst loading (1 mol %) at room temperature and affording 77 % *ee* at lower temperature. Efforts are underway to elucidate the mechanistic details and other significant applications of this catalytic system.

EXPERIMENTAL

GENERAL

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments at room temperature. Chemical shifts are expressed in ppm downfield from $CDCl_3$ as an internal standard, and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using

Silica gel (60–200 mesh except if stated different). All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin-Elmer Polarimeter (Model 341). All melting points are uncorrected. All testing reactions were carried out under dry UHP Argon (99.999 % purity). High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, and a sample concentration of approximately 1 ppm.

General procedure for the enantioselective Henry reaction

After a study of the methods used in literature for this reaction, it was decided to use a modification of the method reported by Ginotra *et al.*[25]

A solution of ligand **3a** (1.3 mg, 0.031 mmol) and Cu(OAc)·H_2O (0.7 mg, 0.03 mmol, 10 mol %) in anhydrous 2-propanol (2 mL) was stirred for 4 hrs at room temperature under Ar. To the resulting green solution, nitromethane (0.18 ml, 3.3 mmol), and *p*-nitrobenzaldehyde (50 mg, 0.33 mmol) were added at room temperature. The reaction mixture was stirred for the appropriate time and the progress of the reaction monitored by TLC (EtOAc:hexane, 15:85, R_f = 0.12). After completion of the reaction, the volatile components were removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 15:85 and increased to 20:80) to afford the nitro aldol product. It was obtained in a maximum of 62 % *ee*. Enantiomeric excess was determined by HPLC with a Chiralcel IB-H column (hexane/2-propanol 85:15, λ = 254 nm); flow rate 0.8 mL/min; t_R = 16.5 min (*R*), 18.8 min (*S*); $[\alpha]_D^{20}$ = +21 (*c* 1, CH_2Cl_2). The reaction was repeated three times and the average value is reported.

Synthesis of the precursors

(1*R*,3*S*)-2-benzyl 3-methyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (7)[37]

(1*R*,3*S*)-2-(benzyloxycarbonyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (8)

The experimental procedure used for this reaction was taken from literature.[44] To a round bottom flask was added **7** (6.0 g, 0.01 mmol), LiOH.H_2O (4.6 g, 0.19 mmol), THF (142 mL), MeOH (9.5 mL) and H_2O (4.7 mL). The reaction mixture was stirred for three days until TLC

indicated that all starting material had been consumed (R_f = 0.4, EtOAc/hexane, 30:70). The organic solvents were removed under reduced pressure; the aqueous layer was acidified to pH 1 using 10% HCl and filtered off white solid, washed with 10 mL of water and dried under vacuum to yield **8** as white solid (5.6 g, 96 %); m.p: 86–88 °C; $[\alpha]_D^{20}$ = 23.08 (*c* 0.13 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers.)[45] ^{1}H NMR (400 MHz, DMSO-d6): δ 7.45–7.11 (m, 10H), 6.91 (d, *J* = 6.96 Hz, 1H), 6.75 (d, *J* = 6.84 Hz, 1H), 6.09 (d, *J* = 10.68 Hz, 1H), 5.14–4.94 (m, 3H), 3.79–3.64 (m, 6H), 3.18–3.01 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 172.9, 172.6, 155.4, 147.6, 145.0, 143.9, 136.5, 129.4, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 127.0, 126.8, 126.3, 125.8, 125.6, 123.3, 123.0, 111.5, 111.2, 66.4, 66.2, 59.0, 58.7, 55.6, 55.4, 55.0, 54.9; IR ν_{max}/cm^{-1} (neat): 3603, 3498, 2938, 1686, 1606, 1515, 1404, 1224, 1090, 990, 696. HR ESI MS: *m*/*z* = 470.1574 [M+ Na] + (calcd. for $C_{26}H_{25}NNaO_6$ 470.1556).

General procedure for the formation of amino alcohols (9-11b)

This method was adapted from literature.[45] To a round bottom flask was added acid **8** (2.0 g, 0.04 mol) together with the amino alcohol (1.1 equiv.), HOBt (1.3 equiv.) and DMF (40 mL). The mixture was allowed to stir in an ice bath until its temperature reached 0 ºC. To the stirred mixture was added EDC.HCl (1.2 equiv.) and *N*-methylmorpholine (3.0 equiv.) and the reaction was allowed to proceed for 16 hours at ambient temperature. The mixture was acidified with 10% HCl until a milky precipitate formed. Ethyl acetate (20 mL) was added to the reaction flask and allowed to stir for 15 minutes. The organic layer was separated and washed with H_2O (2 x 20 mL) and a saturated solution of $NaHCO_3$ (2 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure affording the crude amino alcohol, which was purified by column chromatography using (MeOH:DCM 2.5:97.5) as the eluent to yield pure compounds **9-11b**.

General procedure for oxazoline formation (12-14b)

This method was adapted from literature.[42] To a stirred solution of Cbz-protected TIQ-oxazoline amino alcohol (1.0 g) in dry dichloromethane (80 mL) triphenyl phosphine (2.0 equiv.) was added at room temperature and under N_2 atmosphere. The reaction mixture was cooled to 0 °C and to this was added a solution of diethylazodicarboxylate (2.2 equiv.) in dry dichloromethane (20 mL) in a dropwise manner over period of 20 min. The resulting reaction mixture was stirred at the same temperature for 4 h under N_2 atmosphere. After completion of the reaction, the reaction mixture was diluted with dichloromethane (10 mL), washed with water

(2 × 10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield crude product, which was purified by column chromatography using (EtOAc/hexane, 35:65) as the eluent to yield pure compounds **12-14b**.

General procedure for nitrogen deprotection (1-3b)

This method was adapted from literature.[45] A solution of Cbz-protected TIQ–oxazoline (0.8 g) in methanol (30 mL) was added to a suspension of 10 wt.-% Pd/C (0.4 g) in methanol (10 mL). The reaction mixture was connected to a hydrogen source at atmospheric pressure and stirred at room temperature for 6 h. The Pd/C was filtered off on a Celite pad, and the filtrate was concentrated under reduced pressure to afford the crude TIQ-oxazoline ligand. The crude compounds were purified on a deactivated silica gel column. The deactivation was done as follows: the column was packed with a suspension of silica gel in 20 % Et_3N/CH_2Cl_2 and the silica was washed with 1 % Et_3N/CH_2Cl_2. The chromatography was performed using 0–2 %MeOH/1% Et_3N/CH_2Cl_2 as the eluent to afford pure oxazoline compounds **1-3b**.

(1*R*,3*S*)-benzyl 3-(2-hydroxyethylcarbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (9)

R_f = 0.3 (EtOAc/hexane, 6:4). Pale yellow solid (1.8 g, yield 82 %); m.p: 154–156 °C (CH_2Cl_2); $[\alpha]_D^{20}$= 44.00 (*c* 0.5 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.40–6.98 (m, 10H), 6.88 (m, 1H), 6.62 (s, 1H), 6.22 (m, 1H), 5.37–5.00 (m, 2H), 4.83 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.51–2.98 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 162.5, 148.8, 148.0, 128.5, 128.2, 127.4, 127.4, 125.8, 125.6, 125.3, 111.7, 110.9, 110.7, 67.9, 61.9, 61.4, 57.6, 56.2, 56.0, 41.9; IR ν_{max}/cm^{-1} (neat): 3312, 2933, 1705, 1665, 1514, 1398, 1239, 1219, 1126, 700.48; HR ESI MS: *m*/*z* = 513.1996 [M+ Na] + (calcd. for $C_{28}H_{30}N_2NaO_6$ 513.1984).

(1*R*,3*S*)-benzyl 3-((*R*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (10a)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (2.0 g, yield 84 %); m.p: 185–187 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = 36.36 (*c* 0.11 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.01 (m, 10H), 6.90–6.60 (m, 3H), 6.61–6.31 (m, 4H), 6.30–6.07 (m, 1H), 5.51–5.14 (m, 2H), 5.13–4.81 (m, 2H), 4.62–4.26 (m, 1H), 3.98–3.76 (m, 7H), 3.46–3.03 (m, 2H), 1.78–1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5,

156.3, 148.1, 140.5, 135.9, 128.6, 128.5, 128.4, 128.3, 127.1, 125.7, 125.5, 112.0, 111.0, 68.1, 63.3, 59.5, 58.9, 58.2, 57.9, 56.5, 56.4, 55.9, 31.3, 28.4, 19.2, 17.5 ; IR ν_{max}/cm^{-1} (neat): 3549, 2958, 1697, 1662, 1515, 1405, 1238, 1220, 1127, 1090, 697; HR ESI MS: *m*/*z* = 533.2646 [M+ H] + (calcd. for $C_{31}H_{37}N_2O_6$ 533.2642).

(1*R*,3*S*)-benzyl 3-((*S*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-6,7-dimethox-y-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (10b)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Pale yellow solid (2.1 g, yield 88 %); m.p: 136–138 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = 31.82 (*c* 0.11 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.05 (m, 10H), 6.98–6.86 (m, 1H), 6.37–6.12 (m, 1H), 5.57–5.35 (m, 1H), 5.31–5.06 (m, 2H), 4.92–4.81 (m, 1H), 3.95–3.74 (m, 6H), 3.62–2.88 (m, 5H), 1.52–1.37 (m, 1H), 0.67–0.48 (m, 3H), 0.41–0.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 156.3, 148.1, 140.5, 135.9, 128.6, 128.5, 128.4, 128.3, 127.1, 125.7, 125.5, 112.0, 111.0, 68.1, 63.3, 59.5, 58.9, 58.2, 57.9, 56.5, 56.4, 55.9, 31.3, 28.4, 19.2, 17.5; IR ν_{max}/cm^{-1} (neat): 3549, 2958, 1697, 1662, 1515, 1405, 1238, 1220, 1127, 1090, 697. HR ESI MS: *m*/*z* = 533.2646 [M+ H] + (calcd. for $C_{31}H_{37}N_2O_6$ 533.2627).

(1*R*,3*S*)-benzyl 3-((*R*)-2-hydroxy-1-phenylethylcarbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (11a)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (2.1 g, yield 83 %); m.p: 86–88 °C; $[\alpha]_D^{20}$ = 23.08 (*c* 0.13 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, DMSO): δ 7.42-6.61 (m, 15H), 6.39–5.76 (m, 2H), 5.31–5.04 (m, 2H), 5.0–4.52 (m, 2H), 3.98–3.77 (m, 6H), 3.70–3.25 (m, 2H), 3.16–2.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 156.1, 149.1, 148.2, 140.5,138.3, 135.8, 128.7, 128.5, 128.2, 127.9, 127.6, 127.2, 126.3, 125.8, 125.5, 125.1, 111.8, 111.2, 110.8, 68.1, 66.4, 66.0, 58.8, 58.0, 57.5, 56.4, 56.4, 56.2, 56.1, 55.8; IR ν_{max}/cm^{-1} (neat): 3313, 2936, 1662, 1513, 1401, 1339, 1238, 1221, 1092, 697. HR ESI MS: *m*/*z* = 567.2474 [M+ H] + (calcd. for $C_{34}H_{35}N_2O_6$ 567.2474).

(1*R*,3*S*)-benzyl 3-((*S*)-2-hydroxy-1-phenylethylcarbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (11b)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Yellow oil (2.05, yield 81 %); $[\alpha]_D^{20}$ = + 39.13 (*c* 0.23 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.04 (m, 12H), 6.94 (s, 1H), 6.63–6.16 (m, 4H), 5.40–5.12 (m, 2H), 5.03–4.72 (m, 2H), 3.98–3.66 (m, 7H), 3.63–3.27 (m, 2H), 3.11–2.80 (m, 4H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 172.0, 162.5, 156.2, 149.0, 141.2, 128.6, 128.3, 128.1, 127.4, 127.1, 126.0, 125.4, 111.9, 110.7, 68.0, 65.64, 59.6, 58.9, 58.1, 57.9, 56.1, 55.8, 54.3, 54.1, 36.4, 31.4, 30.9; IR ν_{max}/cm^{-1} (neat): 3323, 2933, 1696, 1661, 1514, 1402, 1222, 1128, 1092, 696. HR ESI MS: *m*/*z* = 567.2490 [M+ H] + (calcd. for $C_{34}H_{35}N_2O_6$ 567.2479).

(1*R*,3*S*)-benzyl 3-(4,5-dihydrooxazol-2-yl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (12)

R_f = 0.3 (EtOAc/hexane, 7:3). Off white solid (0.72 g, yield 73 %); m.p: 68–70 °C (hexane/ EtOAc); $[\alpha]_D^{20}$ = –3.22 (*c* 0.62 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–6.40 (m, 12H), 6.11 (m, 1H), 5.39–4.77 (m, 2H), 4.24–3.44 (m, 9H), 3.34–2.89 (m, 2H), 1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 148.1, 132.2, 129.5, 128.7, 128.6, 128.2, 127.9, 127.1, 126.9, 126.1, 111.7, 110.9, 68.3, 68.2, 67.6, 60.2, 59.6, 56.4, 56.2, 54.5, 51.2, 31.3; IR ν_{max}/cm^{-1} (neat): 2934, 1698, 1513, 1398, 1338, 1266, 1223, 1093, 993, 740, 698; HR ESI MS: *m*/*z* = 473.2071 [M+ H] + (calcd. for $C_{28}H_{29}N_2O_5$ 473.2049).

(1*R*,3*S*)-benzyl 3-((*R*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (13a)

R_f = 0.6 (EtOAc/hexane, 5:5). Pale yellow solid (0.81 g, yield 83 %); m.p: 128–130 °C (hexane/ethylacetate); $[\alpha]_D^{20}$ = 3.22 (*c* 0.31 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–6.84 (m, 10H), 6.76 (m, 1H), 6.55 (m, 1H), 6.11 (m, 1H), 5.35–4.92 (m, 3H), 4.18–3.57 (m, 9H), 3.34–2.90 (m, 2H), 1.67 (m, 2H), 1.42 (m, 1H), 0.66–0.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 148.0, 129.8, 128.4, 128.1, 127.8, 127.6, 126.7, 126.9, 123.7, 123.3, 111.8, 111.0, 71.4, 69.9, 67.3, 60.1, 59.6, 56.0, 51.0, 18.2, 17.8; IR ν_{max}/cm^{-1} (neat): 3337, 2961, 1695, 1684, 1513, 1399, 1222, 1126, 1093, 1028, 737, 698. HR ESI MS: *m*/*z* = 537.2360 [M+ Na] + (calcd. for $C_{31}H_{34}N_2NaO_5$ 537.2365).

(1*R*,3*S*)-benzyl 3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-6,7-dimethoxy-1-phenyl-3,4-dihy-droisoquinoline-2(1*H*)-carboxylate (13b)

R_f = 0.6 (EtOAc/hexane, 5:5). Off white solid (0.71 g, yield 73 %); m.p: 80–82 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = 17.65 (*c* 0.17 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–6.85 (m, 11H), 6.41–6.12 (m, 1H), 5.68–5.08 (m, 3H), 4.84 (d, *J* = 8.36 Hz), 3.96–3.75 (m, 7H), 3.48–2.89 (m, 6H), 1.89–1.44 (m, 6H), 0.87–0.51 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 148.4, 130.0, 128.3, 128.0, 127.8, 126.8, 126.7, 126.1, 111.9, 111.1, 71.8, 70.1, 60.1, 56.2, 51.2, 18.4, 17.1; IR ν_{max}/cm^{-1} (neat): 3337, 2961, 1695, 1684, 1513, 1399, 1222, 1126, 1093, 1028, 737, 698. HR ESI MS: *m*/*z* = 537.2360 [M+ Na] + (calcd. for $C_{31}H_{34}N_2NaO_5$ 537.2365).

(1*R*,3*S*)-benzyl 6,7-dimethoxy-1-phenyl-3-((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (14a)

R_f = 0.6 (EtOAc/hexane, 5:5). Colorless oil (0.85 g, yield 88 %); $[\alpha]_D^{20}$ = –14.29 (*c* 0.28 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.02 (m, 10H), 6.95–6.64 (m, 3H), 6.58–6.33 (m, 3H), 6.31–6.06 (m, 1H), 5.53–5.15 (m, 2H), 5.14–4.81 (m, 2H), 4.63–4.26 (m, 1H), 3.98–3.76 (m, 7H), 3.45–3.05 (m, 2H), 1.78–1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.7, 156.3, 156.1, 148.3, 144.6, 143.2, 142.2, 136.0, 130.1, 128.4, 127.9, 127.3, 126.9, 126.7, 126.5, 126.2, 125.9, 123.1, 111.7, 111.4, 111.0, 110.6, 76.0, 75.7, 69.2, 67.5, 67.4, 62.2, 60.1, 59.6, 56.0, 55.0, 51.2; IR (neat): 3028, 2935, 1697, 1514, 1397, 1224, 1093, 993, 698; HR ESI MS: *m*/*z* = 549.2384 [M+ H] + (calcd. for $C_{34}H_{33}N_2O_5$ 549.2379).

(1*R*,3*S*)-benzyl 6,7-dimethoxy-1-phenyl-3-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-3,4-dihydr-oisoquinoline-2(1*H*)-carboxylate (14b)

R_f = 0.6 (EtOAc/hexane, 5:5). Yellow oil (0.81 g, yield 84 %); $[\alpha]_D^{20}$ = –39.29 (*c* 0.28 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.09 (m, 11H), 6.98–6.58 (m, 5H), 6.19–5.97 (m, 1H), 5.56–5.31 (m, 1H), 5.30–4.83 (m, 3H), 4.45–4.05 (m, 2H), 3.96–3.69 (m, 8H), 3.41–3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.7, 156.3, 156.1, 148.3, 144.6, 143.2, 142.2, 136.0, 130.1, 128.4, 128.3, 128.1, 127.9, 127.6, 126.9, 126.5, 126.2, 125.9, 123.1, 111.7, 111.4, 110.6, 76.0, 75.7, 69.2, 67.5, 67.4, 62.2, 60.1, 59.6, 56.0, 55.0, 51.2; IR ν_{max}/cm^{-1} (neat): 3028, 2935, 1697, 1514, 1397, 1224, 1093, 993, 698. HR ESI MS: *m*/*z* = 549.2384 [M+ H] + (calcd. for $C_{34}H_{33}N_2O_5$ 549.2385).

2-((1R,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole (1)

R_f = 0.3 (CH_2Cl_2/MeOH, 8:2). Pale yellow oil (0.21 g, yield 40 %); $[\alpha]_D^{20}$ = – 39.47 (*c* 0.19 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.15 (m, 5H), 6.68 (s, 1H), 6.34 (s, 1H), 5.34 (s, 1H), 3.95–3.75 (m, 6H), 3.65 (m, 3H), 3.02–2.75 (m, 2H), 1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 148.9, 148.0, 140.6, 136.2, 130.0, 128.7, 126.2, 125.9, 117.1, 114.9, 111.0,

55.7, 36.6, 31.6; IR ν_{max}/cm^{-1} (neat): 2946, 1685, 1610, 1542, 1232, 1112, 1058, 672; HR ESI MS: *m*/*z* = 339.1703 [M+ H] + (calcd. for $C_{20}H_{23}N_2O_3$ 339.1708).

(*R*)-2-((1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-isopropyl-4,5-dihydrooxazole (2a)

R_f = 0.3 (EtOAc/hexane, 5:5). Off white solid (0.35 g, yield 59 %); m.p: 126–128 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = –63.64 (*c* 0.22 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.18 (m, 3H), 7.19–7.18 (m, 2H), 6.62 (s, 1H), 6.32 (s, 1H), 5.26 (s, 1H), 3.96–3.76 (m, 6H), 3.65 (s, 3H), 3.06 (dd, *J* = 4.88 Hz, 1H), 2.95 (dd, *J* = 9.08 Hz, 1H), 2.50 (q, *J* = 7.48, 14.29 Hz, 1H), 1.70 (m, 1H), 0.87 (d, *J* = 6.68 Hz, 3H), 0.79 (d, *J* = 6.80 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 147.8, 147.3, 144.7, 128.7, 128.3, 128.0, 127.2, 126.0, 111.1, 110.8, 71.7, 69.9, 62.2, 58.9, 55.88, 55.82, 46.4, 46.1, 32.3, 31.9, 18.6, 17.7, 14.4; IR ν_{max}/cm^{-1} (neat): 3243, 2951, 1646, 1623, 1516, 1240, 1224, 1112, 1062, 696, 539. HR ESI MS: *m*/*z* = 381.2173 [M+ H] + (calcd. for $C_{23}H_{29}N_2O_3$ 381.2192)**.**

(*S*)-2-((1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-isopropyl-4,5-dihydrooxazole (2b)

R_f = 0.3 (EtOAc/hexane, 5:5). Pale Yellow solid (0.3 g, yield 50 %); m.p: 106–108 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = –42.11 (*c* 0.38 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.19 (m, 3H), 7.18–7.13 (m, 2H), 6.63 (s, 1H), 6.31 (s, 1H), 5.19 (s, 1H), 3.96–3.82 (m, 6H), 3.65 (s, 3H), 3.06–3.0 (m, 2H), 1.73–1.63 (m, 1H), 0.87 (d, *J* = 6.80 Hz, 3H), 0.78 (d, *J* = 6.76 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 147.8, 147.2, 144.6, 132.1, 132.0, 131.96, 131.94, 128.7, 128.5, 128.4, 128.3, 127.9, 127.2, 126.1, 111.1, 110.8, 71.9, 70.1, 62.2, 59.0, 55.85, 55.81, 46.6, 46.1, 32.3, 31.8, 18.6, 17.8, 14.4; IR ν_{max}/cm^{-1} (neat): 3243, 2951, 1646, 1623, 1516, 1240, 1224, 1112, 1062, 696, 539. HR ESI MS: *m*/*z* = 381.2173 [M+ H] + (calcd. for $C_{23}H_{29}N_2O_3$ 381.2189)**.**

(*R*)-2-((1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl-4,5-dihydrooxazole (3a)

R_f = 0.3 (EtOAc/hexane, 5:5). White solid (0.38 g, yield 63 %); m.p: 70–72 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = –46.43 (*c* 0.14 in CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.18 (m, 8H), 7.13–7.08 (m, 2H), 6.68 (s, 1H), 6.37 (s, 1H), 5.33 (s, 1H), 5.16 (t, *J* = 17.9 Hz,1H), 4.59 (q, *J* = 10.08, 8.48 Hz, 1H), 4.08 (t, *J* = 16.08, 1H), 4.01–3.95 (m, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.21 (dd, *J* = 5.00, 5.00 Hz, 1H), 3.11 (dd, *J*

= 8.28 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 147.9, 147.4, 144.8, 142.1, 129.2, 128.7, 128.6, 128.3, 128.2, 127.5, 127.2, 126.5, 125.8, 111.2, 110.9, 74.9, 69.4, 58.9, 55.8, 46.9, 46.2, 32.0; IR ν_{max}/cm^{-1} (neat): 2931, 1652, 1511, 1450, 1246, 1220, 1113, 1027, 838, 756, 698. HR ESI MS: *m*/*z* = 415.2016 [M+ H] + (calcd. for $C_{26}H_{27}N_2O_3$ 415.1979).

(*S*)-2-((1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl-4,5-dihydrooxazole (3b)

R_f = 0.3 (EtOAc/hexane, 5:5). Off white solid (0.32 g, yield 53 %); m.p: 70–72 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = –57.14 (*c* 0.28 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.16 (m, 8H), 7.11–7.06 (m, 2H), 6.67 (s, 1H), 6.34 (s, 1H), 5.24 (s, 1H), 5.17 (t, 1H), 4.59 (q, *J* = 10.08, 8.48 Hz, 1H), 4.07(t, *J* = 8.12 Hz, 1H), 4.04–3.98 (t, *J* = 6.46 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.16 (d, *J* = 6.48 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 147.9, 147.3, 144.6, 142.1, 128.7, 128.6, 128.4, 128.1, 127.5, 127.3, 126.5, 126.0, 111.2, 110.8, 74.9, 69.4, 59.0, 55.89, 55.82, 47.1, 31.8; IR ν_{max}/cm^{-1} (neat): 2907, 1738, 1658, 1511, 1451, 1351, 1244, 1220, 1115, 1027, 757, 699. HR ESI MS: *m*/*z* = 415.2016 [M+ H] + (calcd. for $C_{26}H_{27}N_2O_3$ 415.1996).

ACKNOWLEDGEMENTS

This work was supported by the UKZN productivity research grant, a SA/Swedish Research Links Programme grant and Aspen Pharmacare, SA. The NRF (South Africa) is thanked for the support.

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CHAPTER 6

ASYMMETRIC CONJUGATE ADDITION OF THIOGLYCOLATE TO CHALCONE USING TETRAHYDROISOQUINOLINE (TIQ) *N,N'*-DIOXIDE LIGANDS

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ABSTRACT

A series of novel TIQ based N,N'-dioxide ligands were synthesised and screened for their catalytic activity in the enantioselective conjugate addition of a sulphur-containing nucleophile on a range of α,β-unsaturated ketones. Bulkier groups on the side chain of the TIQ backbone provided the highest enantioselectivity up to 81 % with a 10 mol % catalytic loading. It was also observed that these reactions proceeded optimally in the presence of dichloromethane as a solvent. Screening of various metals revealed La(OTf)$_3$ as the ideal pre-catalyst for this particular reaction. Further catalytic testing on α,β-unsaturated substrates yielded novel sulphur-containing molecules. To the best of our knowledge, this is the second report for the conjugate addition of thioglycolates to chalcones.

INTRODUCTION

The drive to synthesise optically pure compounds accounts for the huge interest in the field of asymmetric catalysis.[1-3] Reactions involving C-C bond formations provide methods by which larger molecules can be synthesised.[4-7] In this methodology, some of the important reactions

like Suzuki couplings,[8-9] Heck reactions[10-11] and Michael additions[12-13] play a significant role in organic chemistry as well as in asymmetric catalysis.

The Michael addition is ubiquitous in organic chemistry and has been utilized to produce a diverse array of compounds for applications in various fields.[12-15] Furthermore, the use of the Michael reaction for applications other than C-C bond formation opens up avenues by which molecules that possess unique properties can be realized. One such deviation is the addition of sulphur as a nucleophile to α,β-unsaturated ketones. These types of conjugate addition have been widely reported[16-19] and applications in total synthesis have already been realized.[20-21]

The use of *N*-oxide containing ligands in asymmetric catalysis are well documented with numerous examples of catalytic systems possessing this chemical moiety.[22] Some examples of these molecules are shown in Figure 1. Applications of *N*-oxide ligands include allylation of aldehydes,[23-24] asymmetric aldol reactions,[25-26] asymmetric opening of *meso*-epoxides,[27] cyanosilylation of ketones[28-29] and Michael additions.[30]

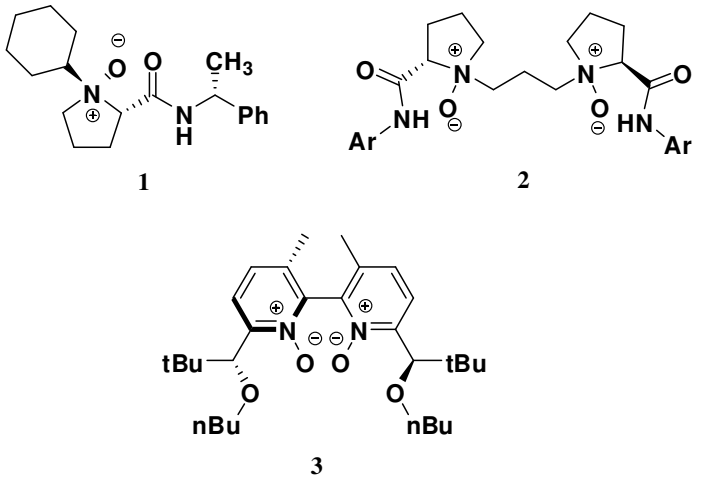


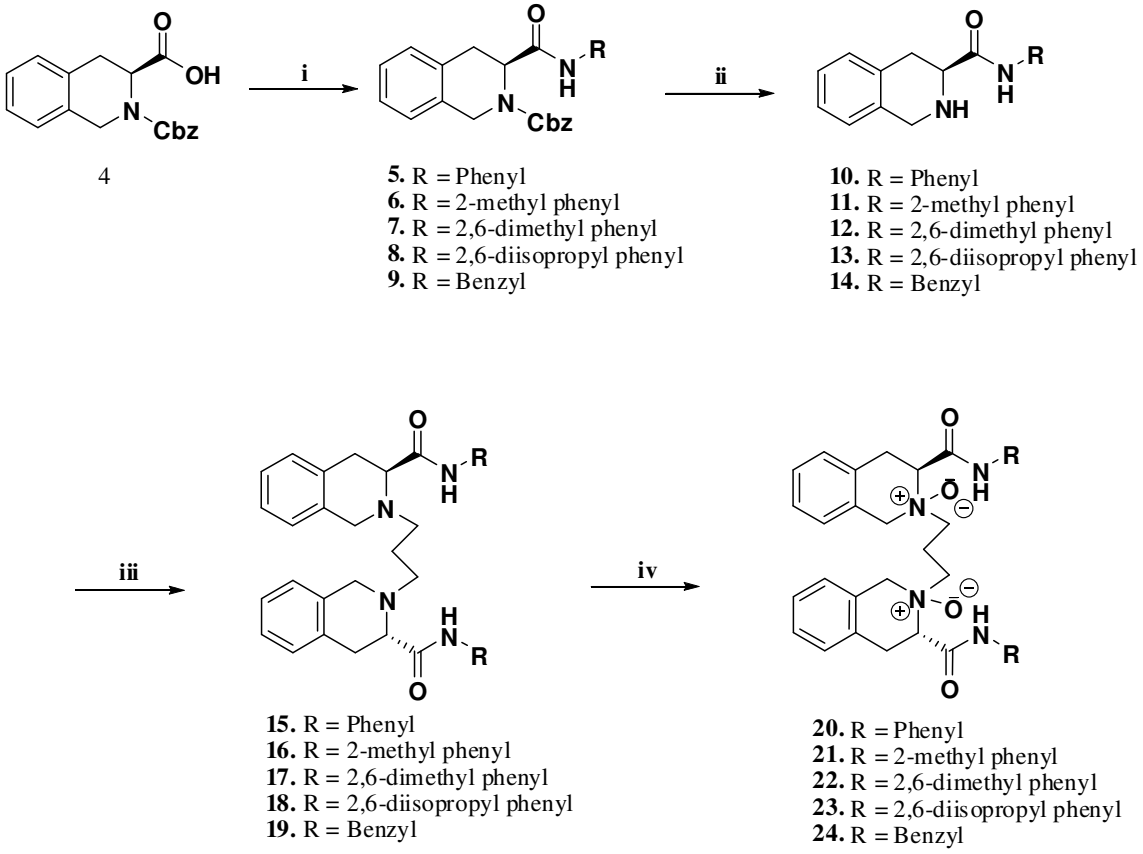
Figure 1. Examples of N-oxide ligands utilized in asymmetric catalysis.

The use of the TIQ scaffold in asymmetric catalysis is an ongoing interest in our research group. Applications include catalytic asymmetric transfer hydrogen (ATH),[31-32] high pressure hydrogenation of unsymmetrical olefins,[33] Henry type C-C bond formations[34] and as an organocatalyst in the Diels-Alder reaction.[35] In this paper, we extended the utilization of the TIQ backbone in the construction of a catalyst for carbon-sulphur bond formation *via* conjugate addition. The backbone was modified to include the *N,N'*-dioxide moiety. Furthermore, the use

of uncommon molecules in the analysis of the substrate scope afforded novel sulphur-containing compounds.

RESULTS AND DISCUSSIONS

The ligands were synthesized as illustrated in Scheme 1. The benzyl chloroformate (Cbz) protected TIQ acid[36] underwent amide coupling, facilitated by active ester formation with ethyl chloroformate, with various substituted amines to afford the intermediates **5-9**.[37] The cleavage of the Cbz group was accomplished with 10 % wt. Pd/C under a hydrogen atmosphere (1 atm) to afford the free amines **10-14**. Bridging of these free secondary amines **10-14** was accomplished with K_2CO_3 and 1,3-dibromopropane in acetonitrile to yield the products **15-19**. Finally, intermediates **15-19** were oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) and K_2CO_3 in dichloromethane at –78 °C – rt afforded the final ligands **20-24** in moderate yields.



4

5. R = Phenyl
6. R = 2-methyl phenyl
7. R = 2,6-dimethyl phenyl
8. R = 2,6-diisopropyl phenyl
9. R = Benzyl

10. R = Phenyl
11. R = 2-methyl phenyl
12. R = 2,6-dimethyl phenyl
13. R = 2,6-diisopropyl phenyl
14. R = Benzyl

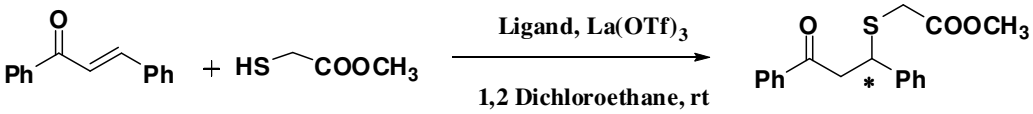
15. R = Phenyl
16. R = 2-methyl phenyl
17. R = 2,6-dimethyl phenyl
18. R = 2,6-diisopropyl phenyl
19. R = Benzyl

20. R = Phenyl
21. R = 2-methyl phenyl
22. R = 2,6-dimethyl phenyl
23. R = 2,6-diisopropyl phenyl
24. R = Benzyl

Scheme 1. Reagents for the synthesis of TIQ *N*-oxide ligands 20-24: (i) Ethyl chloroformate, triethyl amine, amines, DCM, 0 °C – rt, 18 h; (ii) 10 % wt. Pd/C, H_2 (1 atm), MeOH/THF, rt, 3 h; (iii) 1,3-dibromopropane, anhydrous K_2CO_3, ACN, microwave, 90 °C, 12 h; (iv) *m*-CPBA (70 %), anhydrous K_2CO_3, DCM, –78 °C – rt 8 h;

The activities of the synthesized ligands **20**-**24** were determined with the conjugate addition of methyl thioglycolate to chalcone (Table 1). The reaction conditions chosen were adopted from literature.[37,30,38] Ligand **20**, possessing the phenyl substitution, provided poor selectivity across a range of catalytic loading (Table 1, entries 1-3). Replacement of the phenyl group with groups possessing substitution on aromatic side chain resulted in a marked increase in the selectivity of the ligands. Substitution of a 2-methyl phenyl group on the side chain of the TIQ backbone resulted in a selectivity of 50 % (Table 1, entry 6) whilst substitution with 2,6-dimethyl phenyl group afforded a selectivity of 71 % (Table 1, entry 9). Replacing the 2-methylphenyl group with 2,6-diisopropyl phenyl groups resulted in the highest enantioselectivity of 81 % (Table 1, entry 12). Reactions at lower temperatures did not affect the enantioselectivity (Table 1, entry 13). The use of the benzyl amide **24** group resulted in a complete loss of selectivity (Table 1, entries 14-16).

Table 1 Asymmetric conjugate addition of thioglycolate to chalcone catalysed by various ligands with $La(OTf)_3$



Entry	Ligand	Mol %	Yield (%)[b]	*ee* (%)[c]
1	20	1	75	*rac*
2	20	5	82	2
3	20	10	90	6
4	21	1	65	11
5	21	5	85	33
6	21	10	92	50
7	22	1	69	28
8	22	5	85	43
9	22	10	93	71

10	23	1	78	32
11	23	5	89	53
12	23	10	95	81
13[d]	23	10	45	80
14	24	1	69	*rac*
15	24	5	78	*rac*
16	24	10	93	*rac*

[a]All reactions were performed at 0 °C to room temperature. [b]Crude products were purified through column chromatography. [c]Determined by Chiral HPLC column (IB-H). [d]Performed the reaction at 0 °C for 18 h.

Ligand **23**, showing the best activity at a loading of 10 mol % was then used to screen a range of solvents under these specific reaction conditions (Table 2). DCM provided the best selectivity whilst other chlorinated solvents such as DCE and $CHCl_3$ provided moderate to low selectivities (Table 2, entries 1-3). Non-chlorinated solvents such as THF and acetonitrile showed poor selectivity and provided racemic mixtures respectively (Table 2, entries 4-5).

Table 2 Asymmetric conjugate addition of thioglycolate to chalcone using $La(OTf)_3$ with ligand **23** in different solvents

Entry	**Solvent**	**Yield (%)[b]**	***ee* (%)[c]**
1	$ClCH_2CH_2Cl$	92	76
2	CH_2Cl_2	95	81
3	$CHCl_3$	65	17
4	THF	45	9
5	CH_3CN	35	*rac*

[a]All reactions were performed at 0 °C to room temperature. [b]Crude products were purified through column chromatography. [c]Determined by Chiral HPLC column (IB-H)

After the identification of appropriate solvent, various other lanthanide group metals were screened to determine the best pre-catalyst for this system (Table 3). The metal chosen earlier in the study was seen to be the best choice as all other metals showed lower selectivity with good yields (Table 3, entries 2-5). This observation is in agreement with that made by Feng *et. al.*[37]

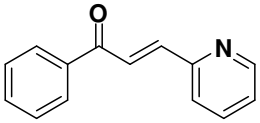
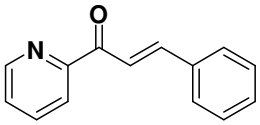
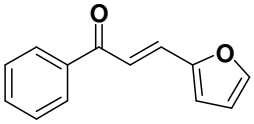
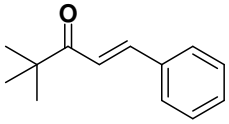
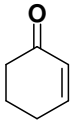
Table 3 Asymmetric conjugate addition of thioglycolate to chalcone catalysed by different metals with ligand **23**

Entry	Metal	Mol%	Yield (%)[b]	*ee* (%)[c]
1	$La(OTf)_3$	10	95	81
2	$Yb(OTf)_3$	10	56	2
3	$Y(OTf)_3$	10	35	4
4	$In(OTf)_3$	10	43	1
5	$Sc(OTf)_3$	10	65	6

[a]All reactions were performed at 0 °C to room temperature. [b]Crude products were purified through column chromatography. [c]Determined by Chiral HPLC column (IB-H)

To study the scope of applications of these *N,N'*-dioxide ligands, it was decided to screen the activity and selectivity of the catalytic system on a unique range of substrates using the optimized conditions (Table 4). Considering the importance of hetero aromatic and aliphatic groups in medicinal chemistry, we selected a variety of aromatic and non-aromatic substituted chalcones for asymmetric conjugate addition. An enormous fall in selectivity was observed for the substrates having a pyridyl group (Table 4, entries 1-2). Replacement of the pyridyl with a five membered furfuryl group on the chalcone increased the rate of reaction with lower selectivity (Table 4, entry 3). This effect was more profound when substituting an aliphatic side chain on the chalcone which resulted in racemic product poor conversion rates (Table 4, entry 4). From the literature we found that cyclohexenone, a well known substrate for Michael type additions and diethyl zinc reactions, afforded poor conversion rates with racemic product for this thioglycolate conversion (Table 4, entry 5).

Table 4 Asymmetric conjugative addition of thioglycolate to various chalcones catalysed by metal $La(OTf)_3$ with Ligand **23** in DCM

Entry	Substrate	Yield (%)	*ee* (%)
1		60	18
2		62	3
3		72	9
4		45	*rac*
5		25	*rac*

[a]All reactions were performed at 0 °C to room temperature. [b]Crude products were purified through column chromatography. [c]Determined by Chiral HPLC column (IB-H)

CONCLUSION

A series of novel TIQ based *N*-oxide ligands have been synthesised and evaluated in the conjugate addition of thioglycolate to a diverse array of α,β-unsaturated carbonyl substrates. Complexation of these novel ligands with various metals highlighted lanthanum as the optimum choice for this particular reaction. These results show that bulkier amide substituents afforded the higher enantioselectivity. The choice of solvent played an important role in the selectivity of the reaction with chlorinated solvents, particularly dichloromethane, being realised as the optimum solvent for the reaction. This conjugate addition is heavily dependent upon catalytic loading as high enantioselectivities were only achieved with loadings of 10 mol %. Further investigation into this new class of ligands is ongoing.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments. Chemical shifts are expressed in ppm downfield from TMS as an internal standard, and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel (60–200 mesh except if stated different). All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin-Elmer Polarimeter (Model 341). All melting points are uncorrected. High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, and a sample concentration of approximately 1 ppm.

Typical procedure for enantioselective conjugate addition of thioglycolate to chalcones

A solution of ligand **23** (7.44 mg, 0.001 mmol), $La(OTf)_3$ (5.86 mg, 0.001 mmol) and chalcone (20.8 mg, 0.1 mmol) in anhydrous dichloromethane (2 mL) was stirred under microwave irradiation at 35 °C for 30 min. The reaction mixture was cooled to 0 °C and the thioglycolate (15.92 mg, 0.15 mmol) was added, the reaction mixture was stirred at 0 °C for 2 h followed by 16 h at room temperature. Solvents were evaporated under reduced pressure and the residue was purified through column chromatography using (hexane/ethyl acetate, 80:20) to afford pure addition product. The enantioselectivity was determined by chiral HPLC using the IB-H column (hexane/2-propanol 90:10, λ = 254 nm); flow rate 0.8 mL/min.

General procedure for synthesis of amides 2-6

This method was adapted from the literature.[37] To a stirred solution of TIQ Cbz acid **4** (2.0 g, 6.3 mmol) in dichloromethane (20 mL), triethylamine (0.71 g, 7.0 mmol) and ethyl chloroformate (0.76 g, 7.0 mmol) was added at 0 ^{o}C. After 1 h, the amine (1.1 eq) was added and the mixture stirred at ambient temperature for 18 h. Completion of the reaction was monitored by thin layer chromatography. The reaction mixture was washed with saturated sodium hydrogen carbonate (20 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and purified through column chromatography using hexane/ethyl acetate as the mobile phase and silica gel as the stationary phase.

General procedure for removal of Cbz group 7-11

A solution of the Cbz-amide (1.0 g) in THF (20 mL) was added to a suspension of activated Pd/C (500 mg, 10 wt.-%) in methanol under an inert atmosphere. The reaction mixture was connected to a H_2 source at 1 atm and stirred at room temperature for 3 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate (7:3). The Pd/C was filtered off on a pad of celite and washed with ethyl acetate (10 mL) followed by dichloromethane (5 mL). The filtrate was concentrated under reduced pressure affording the crude amide, which was purified by column chromatography using hexane/ethyl acetate as the mobile phase and silica gel as the stationary phase.

General Procedure to form bridged compounds 12-16

This method was adapted from the literature.[37] To a solution of deprotected amine (0.20 g) in acetonitrile (10 mL), anhydrous K_2CO_3 (5.0 eq) followed by 1,3-dibromopropane (1.1 eq) was added and the mixture stirred in the microwave reactor at 100 °C for 12 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate. The solvent was evaporated and the crude product taken up in ethyl acetate (20 mL), washed with water (2 x 10 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated under reduced pressure affording the crude bridged compound, which was purified by column chromatography using hexane/ethyl acetate as the eluent to get the pure bridged amide.

General procedure to form the *N*-oxide 17-21

To a solution of the bridge amide (0.2 g) in dichloromethane (10 mL) was added anhydrous K_2CO_3 (5.0 eq) and the reaction mixture was cooled to –78 °C. *m*-CPBA (2.2 eq) was added in one portion and the temperature maintained for 3 h. The reaction mixture was allowed to warm to room temperature and stirred for 2 h whilst the completion of the reaction was monitored by TLC. The reaction mixture was diluted with dichloromethane (5 mL), filtered through a pad of celite and concentrated under reduced pressure to afford the crude *N,N′*-dioxide. The pure *N,N′*-dioxide was obtained after column chromatography using dichloromethane/methanol as the eluent.

(*S*)-benzyl3-(phenylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (5)[32]

(*S*)-benzyl 3-(o-tolylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6)

R_f = 0.4 (Hexane/ethyl acetate, 7:3). Off white solid (1.7 g, yield 68 %); m.p: 108 – 110 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$ = –19.23 (*c* 0.78 in $CHCl_3$); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 6.86 (m, 13H), 5.41 – 4.40 (m, 5H), 3.55 – 2.99 (m, 2H), 2.05 – 1.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 133.5, 130.3, 128.6, 128.4, 128.1, 127.7, 127.3, 126.8, 126.5, 126.3, 125.4, 123.4, 68.1, 57.1, 49.5, 45.2, 32.1, 16.8; IR ν_{max}/cm^{-1} (neat): 3259, 1701, 1661, 1533, 1412, 1202, 760, 698; HR ESI MS: *m*/*z* = 401.1864 [M+ H]$^+$ (calcd. for $C_{25}H_{25}N_2O_3$ 401.1860).

(*S*)-benzyl 3-(2,6-dimethylphenylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (7)

R_f = 0.5 (Hexane/ethyl acetate, 7:3). Off white solid (1.6 g, yield 48 %); m.p: 143 – 145 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$ = –32.00 (*c* 0.50 in $CHCl_3$); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 6.82 (m, 12H), 5.43 – 4.91 (m, 3H), 4.91 – 4.41 (m, 2H), 3.49 (m, 1H), 3.16 (m, 1H), 1.93 – 1.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 135.4, 133.8, 133.0, 128.8, 128.6, 128.1, 127.4, 126.6, 126.4, 68.3, 56.7, 45.9, 32.5, 17.8; IR ν_{max}/cm^{-1} (neat): 3275, 1697, 1650, 1526, 1417, 1207, 1123, 1093, 739; HR ESI MS: *m*/*z* = 415.2016 [M+ H]$^+$ (calcd. for $C_{26}H_{27}N_2O_3$ 415.2016).

(*S*)-benzyl 3-(2,6-diisopropylphenylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (8)

R_f = 0.4 (Hexane/ethyl acetate, 70:30). Off white solid (1.5 g, yield 51 %); m.p: 60 – 62 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$ = –11.32 (*c* 0.53 in $CHCl_3$); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 6.93 (m, 12H), 5.58 – 5.00 (m, 3H), 4.93 – 4.52 (m, 2H), 3.53 (m, 1H), 3.12 (m, 1H), 1.22 (m, 2H), 0.88 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 146.1, 132.6, 128.7, 128.4, 127.9, 123.2, 68.2, 56.6, 45.9, 32.2, 28.2, 23.6; IR ν_{max}/cm^{-1} (neat): 3280, 1643, 1547, 1453, 1222, 1029, 963, 755, 694; HR ESI MS: *m*/*z* = 471.2639 [M+ H]$^+$ (calcd. for $C_{30}H_{35}N_2O_3$ 471.2642).

(*S*)-benzyl 3-(benzylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (9)[32]

(*S*)-N-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10)[32]

(*S*)-N-o-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (11)

R_f = 0.3 (Hexane/ethyl acetate, 7:3). Off white solid (0.6 g, yield 90 %); m.p: 124 – 126 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$ = –60.00 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40

(s, 1H), 8.08 (d, *J* = 7.96 Hz, 2H), 7.25 – 7.15 (m, 3H), 7.09 (m, 1H), 7.04 (m, 1H), 4.06 (d, *J* = 9.96 Hz, 2H), 3.74 (q, *J* = 9.98, 5.58 Hz, 1H), 3.35 (dd, *J* = 16.28, 5.56 Hz, 1H), 2.94 (dd, *J* = 16.28, 10.22 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 136.4, 135.9, 134.6, 130.4, 129.2, 127.8, 127.0, 126.9, 126.5, 125.6, 124.5, 121.4, 57.0, 47.4, 30.8, 17.8; IR ν_{max}/cm^{-1} (neat): 3280, 2905, 1659, 1587, 1531, 1455, 1125, 1042, 807, 724, 715; HR ESI MS: *m*/*z* = 267.1491 $[M+ H]^+$ (calcd. for $C_{17}H_{19}N_2O$ 267.1492).

(*S*)-N-(2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (12)

R_f = 0.4 (Hexane/ethyl acetate, 7:3). Off white solid (0.61 g, yield 91 %); m.p: 195 – 197 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$ = –78.79 (*c* 0.33 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.24 – 7.16 (m, 3H), 7.13 – 7.03 (m, 4H), 4.09 (d, *J* = 10.48 Hz, 2H), 3.80 (q, *J* = 9.38, 5.62 Hz, 1H), 3.33 (dd, *J* = 16.14, 5.58 Hz, 1H), 3.01 (dd, *J* = 16.08, 9.40 Hz, 1H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 136.3, 135.1, 134.6, 133.9, 129.1, 128.2, 127.1, 127.0, 126.5, 125.7, 56.5, 47.3, 31.3, 18.5; IR ν_{max}/cm^{-1} (neat): 3250, 2928, 1670, 1594, 1525, 1466, 1220, 761, 742, 713; HR ESI MS: *m*/*z* = 281.1648 $[M+ H]^+$ (calcd. for $C_{18}H_{21}N_2O$ 281.1649).

(*S*)-N-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (13)

R_f = 0.4 (Hexane/ethyl acetate, 7:3). Off white solid (0.66 g, yield 93 %); m.p: 142 – 144 °C (hexane/ethyl acetate); $[\alpha]_D^{20}$ = –58.33 (*c* 0.48 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.29 – 7.06 (m, 7H), 4.09 (d, *J* = 15.72 Hz, 2H), 3.85 (q, *J* = 8.84, 5.76 Hz, 1H), 3.31 (dd, *J* = 16.0, 5.72 Hz, 1H), 3.05 (dd, *J* = 15.98, 8.90 Hz, 1H), 2.88 (m, 2H), 1.15 (d, *J* = 6.88 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 145.9, 136.4, 134.8, 131.3, 129.0, 128.1, 127.0, 126.5, 125.7, 123.4, 56.3, 47.2, 31.2, 28.9, 23.7; IR ν_{max}/cm^{-1} (neat): 3234, 2958, 1671, 1494, 1454, 1471, 799, 742; HR ESI MS: *m*/*z* = 337.2274 $[M+ H]^+$ (calcd. for $C_{22}H_{29}N_2O$ 337.2273).

(*S*)-N-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (14)[32]

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(N-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) (15)

R_f = 0.5 (Hexane/ethyl acetate, 1:1). Colourless oil (0.16 g, yield 68 %); $[\alpha]_D^{20}$ = –28.57 (*c* 0.35 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 2H), 7.43 (d, *J* = 7.84 Hz, 4H), 7.26 (t, *J* = 7.44 Hz, 4H), 7.22 – 7.12 (m, 6H), 7.11 – 7.01 (m, 4H), 3.92 (d, *J* = 15.00 Hz, 2H), 3.72 (d, *J* = 14.84 Hz, 2H), 3.47 (t, *J* = 6.78 Hz, 2H), 3.17 – 3.04 (m, 4H), 2.71 – 2.57 (m, 4H), 1.85 (m,

2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 137.6, 134.5, 134.2, 129.1, 128.2, 127.4, 126.6, 126.4, 124.2, 119.3, 63.3, 52.0, 28.3, 26.5; IR ν_{max}/cm^{-1} (neat): 3281, 2955, 2926, 1684, 1599, 1517, 1440, 1287, 1123, 1075, 743, 692; HR ESI MS: *m*/*z* = 545.2917 [M+ H]$^+$ (calcd. for $C_{35}H_{37}N_4O_2$ 545.2911).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(N-o-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) (16)

R_f = 0.4 (Hexane/ethyl acetate, 1:1). Yellow oil (0.16 g, yield 69 %); $[\alpha]_D^{20}$ = –15.15 (*c* 0.33 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (s, 2H), 7.92 (d, *J* = 7.96 Hz, 2H), 7.22 – 7.12 (m, 8H), 7.11 – 7.04 (m, 4H), 7.03 – 6.96 (m, 2H), 3.92 (d, *J* = 14.12 Hz, 2H), 3.71 (d, *J* = 14.12 Hz, 2H), 3.53 (t, *J* = 6.12 Hz, 2H), 3.13 (d, *J* = 6.12 Hz, 4H), 2.80 – 2.62 (m, 4H), 1.95 – 1.85 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 135.8, 135.2, 134.4, 130.4, 128.1, 127.6, 126.9, 126.7, 126.2, 124.5, 121.3, 63.5, 54.0, 51.9, 29.4, 26.7, 17.5; IR ν_{max}/cm^{-1} (neat): 3287, 2955, 2926, 1724, 1686, 1586, 1518, 1454, 1289, 1120, 745; HR ESI MS: *m*/*z* = 573.3228 [M+ H]$^+$ (calcd. for $C_{37}H_{41}N_4O_2$ 573.3224).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(N-(2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) (17)

R_f = 0.4 (Hexane/ethyl acetate, 1:1). Pale yellow oil (.15 g, yield 65 %); $[\alpha]_D^{20}$ = –35.71 (*c* 0.14 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.7 (s, 2H), 7.24 – 7.11 (m, 8H), 7.08 – 6.89 (m, 6H), 3.98 (d, *J* = 13.12 Hz, 2H), 3.71 (d, *J* = 13.08 Hz, 2H), 3.60 (q, *J* = 7.16, 3.44 Hz, 2H), 3.26 (dd, *J* = 15.28, 3.44 Hz, 2H), 3.13 (dd, *J* = 15.16, 7.24 Hz, 2H), 2.91 – 2.75 (m, 4H), 2.04 (m, 2H), 1.90 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 135.6, 134.7, 133.7, 128.2, 128.0, 127.7, 127.1, 126.8, 126.1, 63.1, 54.7, 52.1, 30.4, 26.5, 18.4 ; IR ν_{max}/cm^{-1} (neat): 3205, 2955, 1725, 1646, 1520, 1263, 1135, 764, 728; HR ESI MS: *m*/*z* = 601.3538 [M+ H]$^+$ (calcd. for $C_{39}H_{45}N_4O_2$ 601.3537).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(N-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinolin-e-3-carboxamide) (18)

R_f = 0.4 (Hexane/ethyl acetate, 7:3); Colourless oil (0.17 g, yield 75 %); $[\alpha]_D^{20}$ = –12.50 (*c* 0.16 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 2H), 7.31 – 7.14 (m, 9H), 7.11 – 6.98 (m, 5H), 4.00 (d, *J* = 13.12 Hz, 2H), 3.69 (d, *J* = 13.12 Hz, 2H), 3.62 (q, *J* = 7.14, 2.42 Hz, 2H), 3.31 (dd, *J* = 15.05, 3.10 Hz, 2H), 3.1 (dd, *J* = 15.14, 7.22 Hz, 2H), 2.99 – 2.77 (m, 4H), 2.14 – 2.04 (m, 2H), 1.64 (m, 4H), 1.03 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 145.7, 136.0,

135.0, 131.2, 128.1, 127.87, 127.80, 126.8, 126.1, 123.4, 63.3, 55.4, 51.9, 30.6, 28.6, 26.8, 23.8, 23.7; IR ν_{max}/cm^{-1} (neat): 3269, 2958, 2925, 1664, 1486, 1472, 1256, 1129, 1098, 797, 738, 510; HR ESI MS: m/z = 713.4794 $[M+ H]^+$ (calcd. for $C_{47}H_{61}N_4O_2$ 713.4789).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(N-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) (19)

R_f = 0.4 (Hexane/ethyl acetate, 3:2). Yellow oil (0.16 g, yield 69 %); $[\alpha]_D^{20}$ = –5.88 (*c* 0.17 in CH_2Cl_3); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.25 – 7.15 (m, 13H), 7.05 (d, *J* = 6.52 Hz, 2H), 6.92 (m, 3H), 4.45 (dd, *J* = 15.04, 6.88 Hz, 2H), 4.18 (dd, *J* = 15.04, 5.28 Hz, 2H), 3.77 (d, *J* = 14.32 Hz, 2H), 3.54 (d, *J* = 14.53 Hz, 2H), 3.38 (t, *J* = 6.33 Hz, 2H), 3.11 (dd, *J* = 15.99, 6.08 Hz, 2H), 3.03 (dd, *J* = 15.82, 6.60 Hz, 2H), 2.48 (t, *J* = 7.26 Hz, 4H), 1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 138.3, 135.1, 134.4, 128.5, 128.0, 127.2, 126.4, 126.2, 62.6, 53.1, 52.0, 42.8, 29.3, 26.1; IR ν_{max}/cm^{-1} (neat): 3298, 2928, 1650, 1517, 1496, 1453, 1257, 1029, 742, 698; HR ESI MS: m/z = 573.3227 $[M+ H]^+$ (calcd. for $C_{37}H_{41}N_4O_2$ 573.3224).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(3-(phenylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) (20)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). White solid (0.15 g, yield 71 %); m.p: 100 – 102 °C (DCM/MeOH); $[\alpha]_D^{20}$ = –27.27 (*c* 0.11 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 12.62 (s, 2H), 7.67 – 7.46 (m, 4H), 7.36 – 6.92 (m, 14H), 4.82 – 4.37 (m, 4H), 4.35 – 4.01 (m, 2H), 3.99 – 3.47 (m, 4H), 3.48 – 3.11 (m, 4H), 2.78 – 2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 137.9, 129.9, 129.7, 129.0, 128.9, 128.5, 128.4, 128.2, 127.8, 127.6, 127.3, 126.7, 126.3, 124.5, 120.1, 73.0, 68.0, 66.1, 29.6, 29.3, 29.0, 25.7, 17.3; IR ν_{max}/cm^{-1} (neat): 2958, 1726, 1683, 1597, 1552, 1497, 1290, 1077, 906, 753, 692; HR ESI MS: m/z = 577.2808 $[M+ H]^+$ (calcd. for $C_{35}H_{37}N_4O_4$ 577.2809).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(3-(o-tolylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) (21)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). White solid (0.14 g, yield 66 %); m.p: 112 – 114 °C (DCM/MeOH); $[\alpha]_D^{20}$ = – 20.0 (*c* 0.1 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 12.63 (s, 2H), 8.05 (d, *J* = 8.04 Hz, 2H), 7.34 – 6.93 (m, 14H), 4.67 (d, *J* = 15.16 Hz, 2H), 4.48 (d, *J* = 15.16 Hz, 2H), 3.95 (dd, *J* = 17.16, 8.56 Hz, 2H), 3.78 – 3.62 (m, 4H), 3.24 (dd, *J* = 16.90, 4.58 Hz, 2H), 2.99 – 2.86 (m, 2H), 2.28 – 2.15 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 136.1, 130.4, 129.9, 128.9, 128.4, 128.3, 128.2, 128.0, 127.5, 127.4, 127.2, 126.7, 126.5, 124.4,

120.9, 72.7, 66.2, 66.0, 50.6, 29.7, 29.4, 29.0, 18.3, 17.3; IR ν_{max}/cm^{-1} (neat): 2918, 1677, 1588, 1547, 1458, 1290, 753; HR ESI MS: *m*/*z* = 605.3118 $[M+ H]^+$ (calcd. for $C_{37}H_{41}N_4O_4$ 605.3122).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(3-(2,6-dimethylphenylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) (22)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (0.13 g, yield 62 %); m.p: 106 – 108 °C (DCM/MeOH); $[\alpha]_D^{20}$ = –26.67 (*c* 0.15 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 2H), 7.34 – 7.19 (m, 5H), 7.14 – 6.95 (m, 9H), 4.82 (d, *J* = 15.20 Hz, 2H), 4.54 (d, *J* = 15.24 Hz, 2H), 4.03 (dd, *J* = 17.10, 8.30 Hz, 2H), 3.95 – 3.68 (m, 4H), 3.31 (dd, *J* = 17.08, 4.88 Hz, 2H), 3.00 (m, 2H), 2.21 (s, 12H), 2.30 – 2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ165.1, 134.1, 133.5, 130.9, 129.8, 128.8, 128.3, 128.2, 128.1, 127.4, 127.2, 27.1, 126.9, 126.6, 72.9, 66.0, 65.6, 29.9, 19.0, 18.4; IR ν_{max}/cm^{-1} (neat): 2958, 2926, 1728, 1682, 1522, 1470, 1377, 1285, 1123, 1073, 767, 741; HR ESI MS: *m*/*z* = 633.3435 $[M+ H]^+$ (calcd. for $C_{39}H_{45}N_4O_4$ 633.3435).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(3-(2,6-diisopropylphenylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) (23)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (0.16 g, yield 77 %); m.p: 78 – 80 °C (DCM/MeOH); $[\alpha]_D^{20}$ = – 38.46 (*c* 0.13 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.96 (s, 2H), 7.33 – 7.13 (m, 9H), 7.04 (m, 5H), 4.81 (d, *J* = 15.40 Hz, 2H), 4.56 (d, *J* = 15.40 Hz, 2H), 4.18 – 4.02 (m, 2H), 3.90 (m, 2H), 3.65 (m, 2H), 3.46 (m, 2H), 3.31 (dd, *J* = 17.06, 4.74 Hz, 2H), 3.19 – 3.02 (m, 4H), 2.31 (m, 2H), 1.31 – 1.11 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.5, 164.7, 145.9, 145.2, 136.0, 133.0, 131.0, 129.9, 128.9, 128.3, 128.0, 127.4, 126.5, 123.5, 72.6, 66.5, 60.7, 45.3, 31.8, 29.8, 29.1, 23.8, 23.6, 22.5; IR ν_{max}/cm^{-1} (neat): 3248, 2960, 2927, 2868, 1724, 1681, 1500, 1458, 1383, 1272, 1122, 797, 740; HR ESI MS: *m*/*z* = 745.4686 $[M+ H]^+$ (calcd. for $C_{47}H_{61}N_4O_4$ 745.4686).

(3*S*,3'*S*)-2,2'-(propane-1,3-diyl)bis(3-(benzylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) (24)

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (0.17 g, yield 81 %); m.p: 72 – 74 °C (DCM/MeOH); $[\alpha]_D^{20}$ = – 22.22 (*c* 0.18 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 2H), 7.83 – 6.68 (m, 18H), 4.80 – 4.14 (m, 8H), 3.68 – 2.84 (m, 6H), 2.80 – 1.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 138.2, 130.9, 130.1, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.6, 127.4, 127.1, 126.5, 72.8, 66.1, 65.2, 43.0, 29.6, 16.5; IR ν_{max}/cm^{-1} (neat): 3230, 2927,

1727, 1670, 1542, 1497, 1454, 1271, 1120, 1029, 919, 740, 699; HR ESI MS: *m/z* = 605.3129 $[M+ H]^+$ (calcd. for $C_{37}H_{41}N_4O_4$ 605.3122).

ACKNOWLEDGEMENTS

This work is supported by the UKZN productivity research grant and Aspen Pharmacare, SA. NRF is thanked for their support.

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CHAPTER 7

SUMMARY

The research outlined in this thesis involves the development of novel tetrahydroisoquinoline (TIQ) ligands for enantioselective reactions with the research carried out having relevance in both the academic and pharmaceutical fields. The newly synthesized TIQ amino alcohols exhibited remarkable reactivity with significantly higher than enantioselectivities for the asymmetric transfer hydrogenation (ATH) reactions. With results obtained from these experiments, and with the support of computations from the Jaguar interphase program, it was observed that it is critical to have a phenyl group at the C^1 position, in the *trans* form, for greater enantioselectivity. The highest selectivity obtained in the ATH reaction, with acetophenone as a substrate, was >99 % with higher conversion rates observed at lower temperatures (Paper I). In addition to the amino alcohols, a series of novel *N,N* TIQ ligands were synthesized and evaluated for their activities in the ATH reaction. Water played an important role in enhancing the selectivity in the ATH reaction when using $[RhCp^*Cl_2]_2$ as a pre-catalyst. An enantioselectivity of 70 % was obtained with higher conversion rates at ambient temperature (Paper II).

Novel derivatives of *P,N* TIQ oxazoline ligands were synthesised and coordinated to iridium BAr_F. These iridium catalysts were stable at room temperature and screened for the asymmetric high-pressure hydrogenation of terminal, functionalized and non-functionalized alkenes. The best enantioselectivity obtained was >92 % *ee*. All reactions were carried out at room temperature using dichloromethane (DCM) as a solvent (Paper III).

In the literature thus far, very few TIQ ligands have been designed and tested for C-C bond formation reactions. We extended the scope of the TIQ backbone in the field of asymmetric catalysis by designing a series of TIQ ligands for use in this particular application. A novel class of C^1 substituted TIQ oxazoline ligands were synthesized, coordinated with various metals (Cu, Sc, Co, Zn, Ni and Mn) and screened in the Henry (nitroaldol) reaction. The best enantioselectivity obtained was >77 % *ee* when $Cu(OAc)_2$ was employed as a pre-catalyst and iso-propanol as a solvent at ambient temperature (Paper IV).

In the final chapter, the scope of the TIQ backbone in the construction of *N*-oxide ligands was investigated. Utilization of C-hetero bond forming reactions is essential in the pharmaceutical industry. Novel *N*-oxide ligands were synthesised with the TIQ backbone and screened for the conjugate addition of thioglycolate to alpha-beta unsaturated carbonyl substrates. The highest enantioselectivity (>81 % *ee*) obtained was only possible with a loading of 10 mol % and with bulky groups on the terminal chain. This is only the second report describing the conjugate addition of thioglycolate conjugation to an alpha-beta unsaturated carbonyl system (Paper V).

The catalysts designed and synthesised in this thesis have great potential in the field of asymmetric catalysis. With the array of synthetic approaches outlined, a novel class of promising TIQ ligands has been realised. However, there is still unlimited scope for these ligands in other applications. All ligands were characterized using analytical techniques including infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR), polarimetry and high-resolution mass spectrometry (HRMS).

APPENDIX 1

SUPPLAMENTARY INFORMATION FOR CHAPTER 2

Synthesis and Screening of C^1-Substituted Tetrahydroisoquinoline Derivatives for Asymmetric Transfer Hydrogenation Reactions

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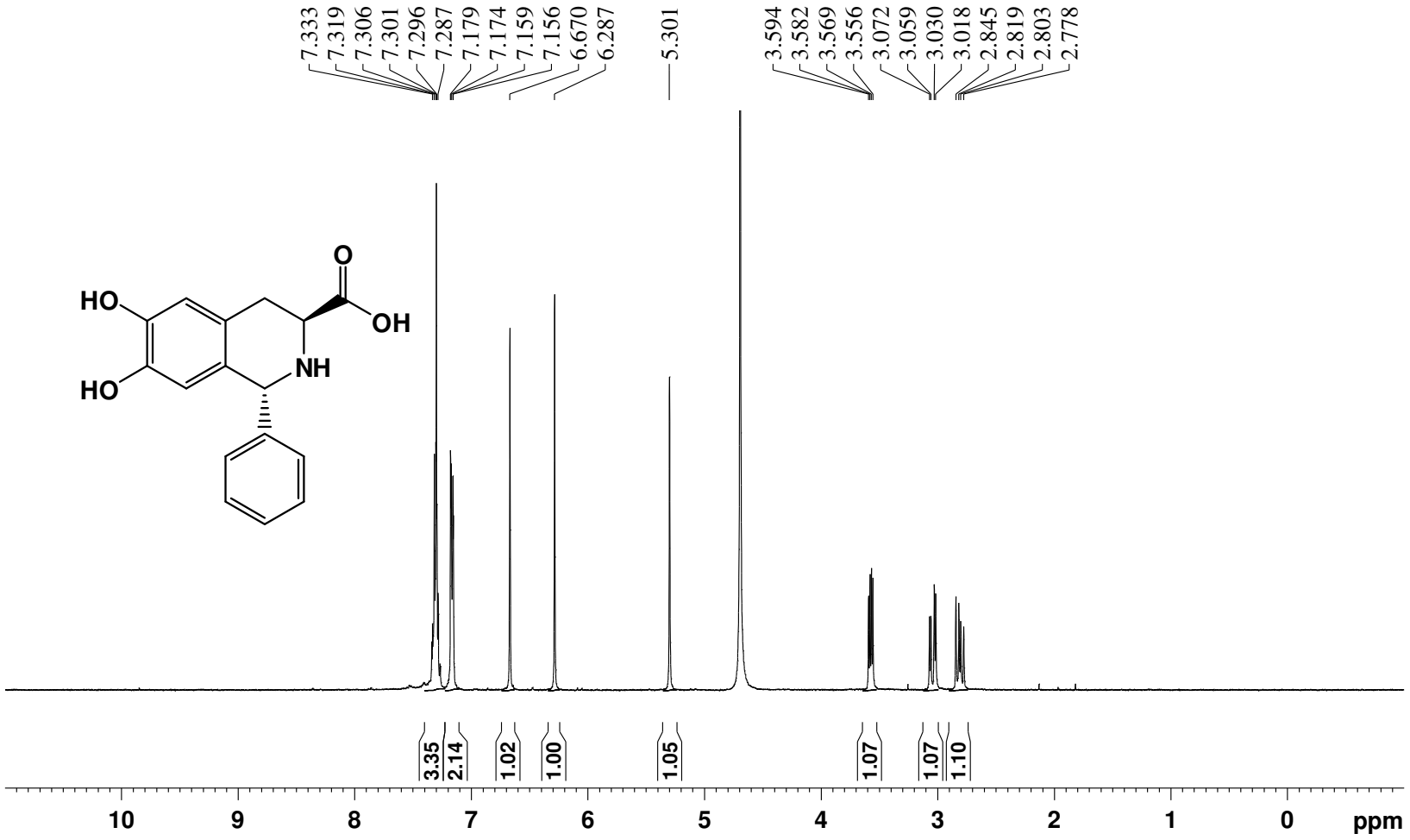
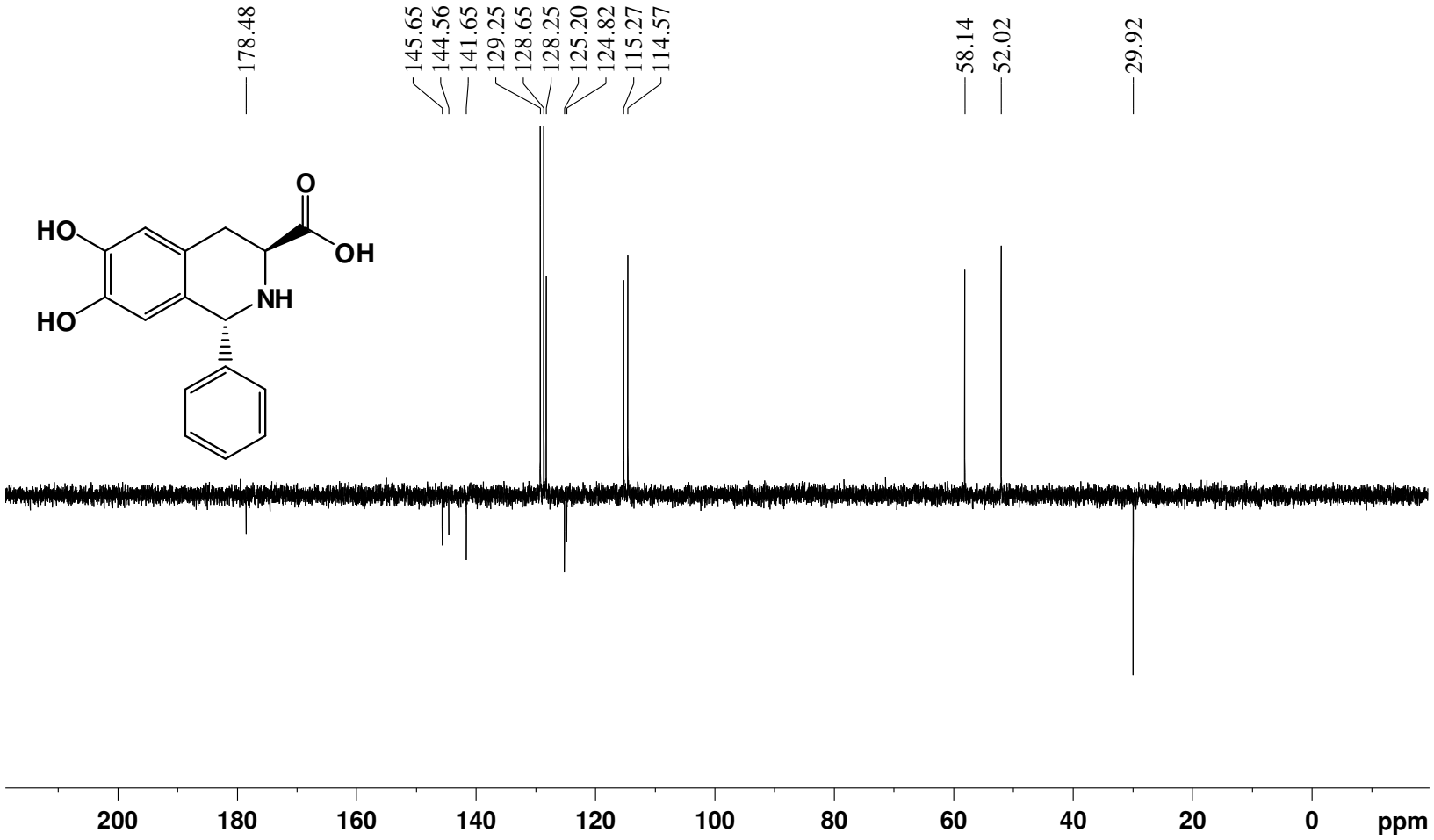
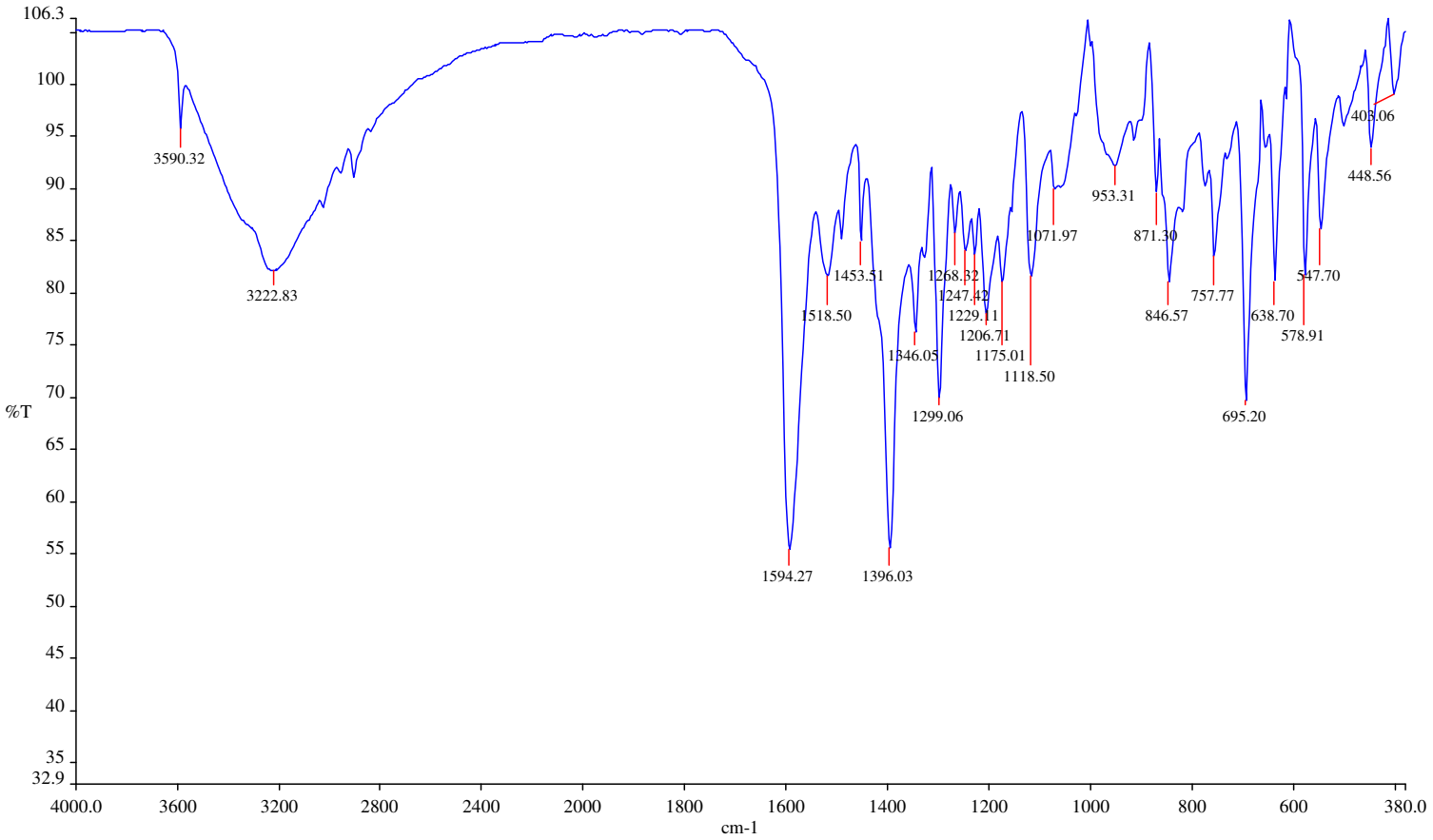


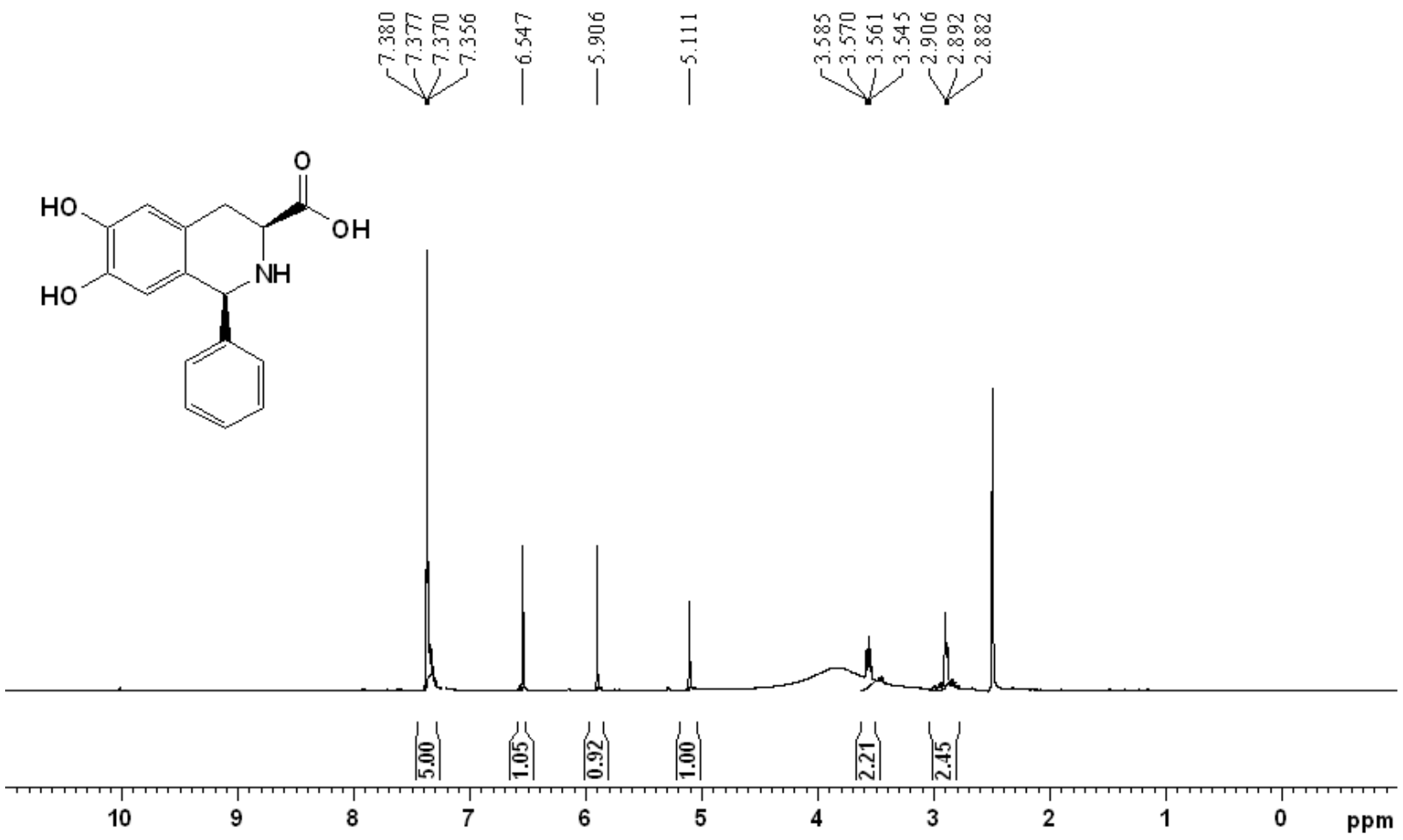
^{1}H NMR (400 MHz) Spectrum of Compound **10** in D_2O



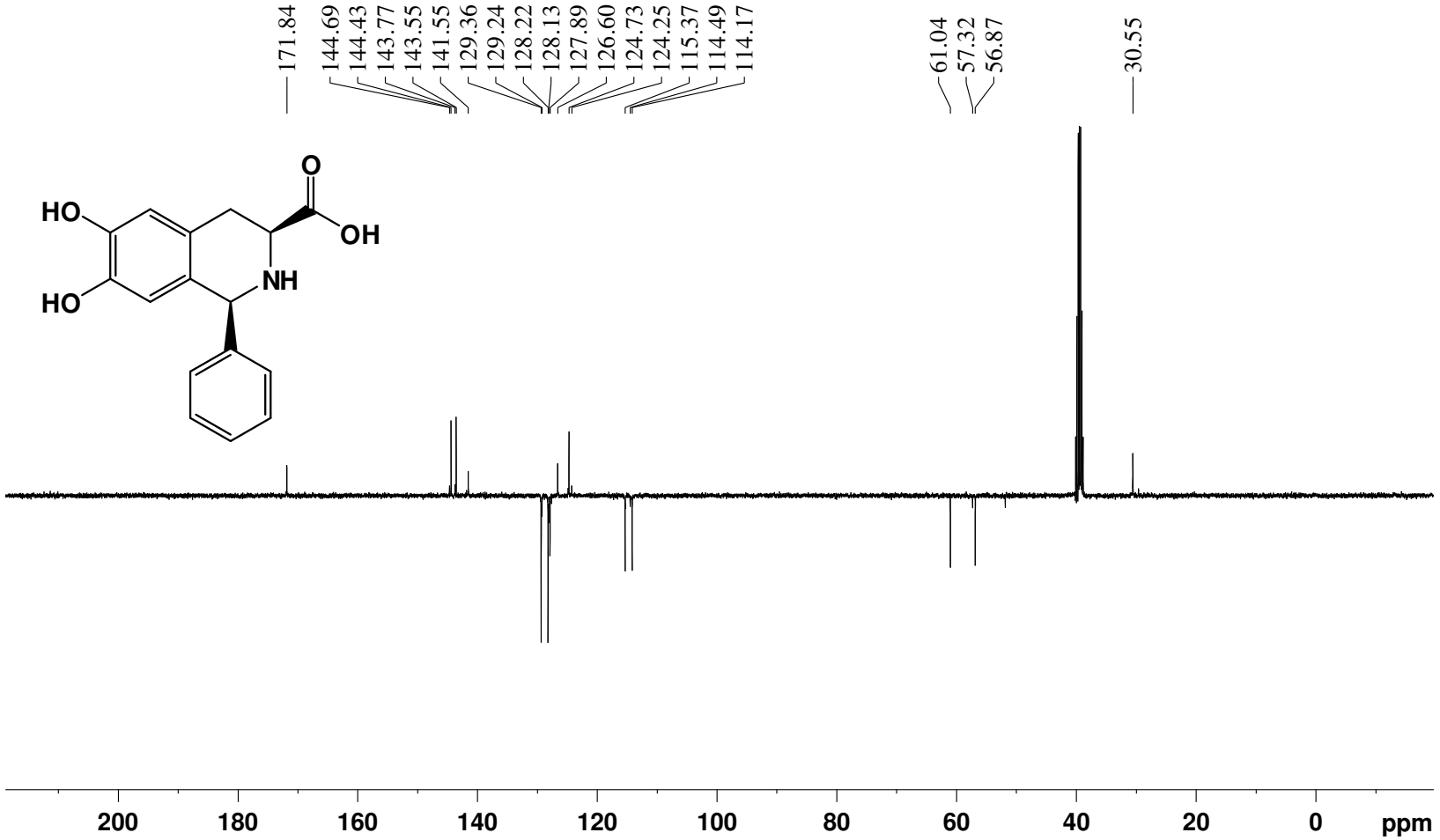
^{13}C (400 MHz) Spectrum of Compound **10** in D_2O



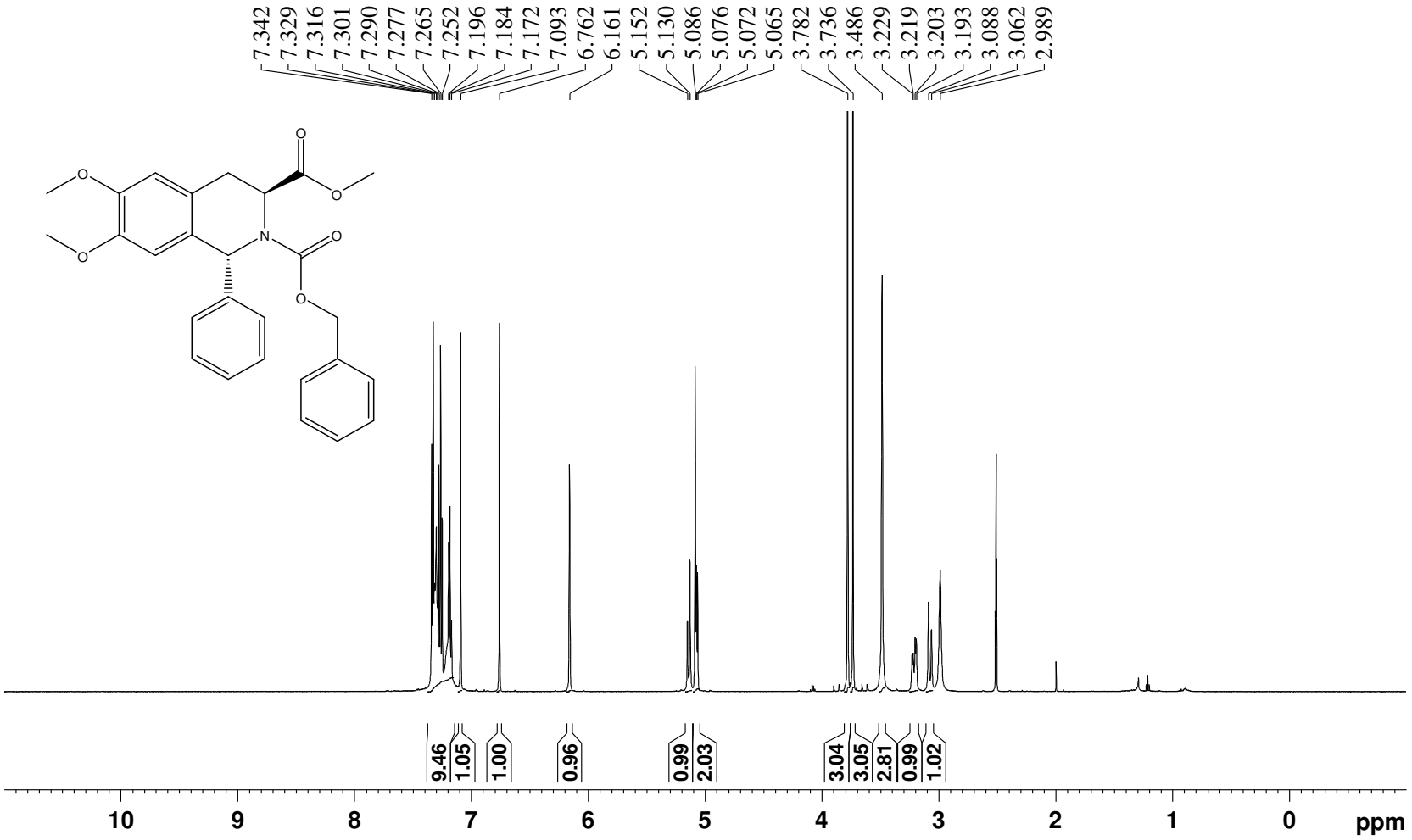
IR Spectrum of Compound **10**



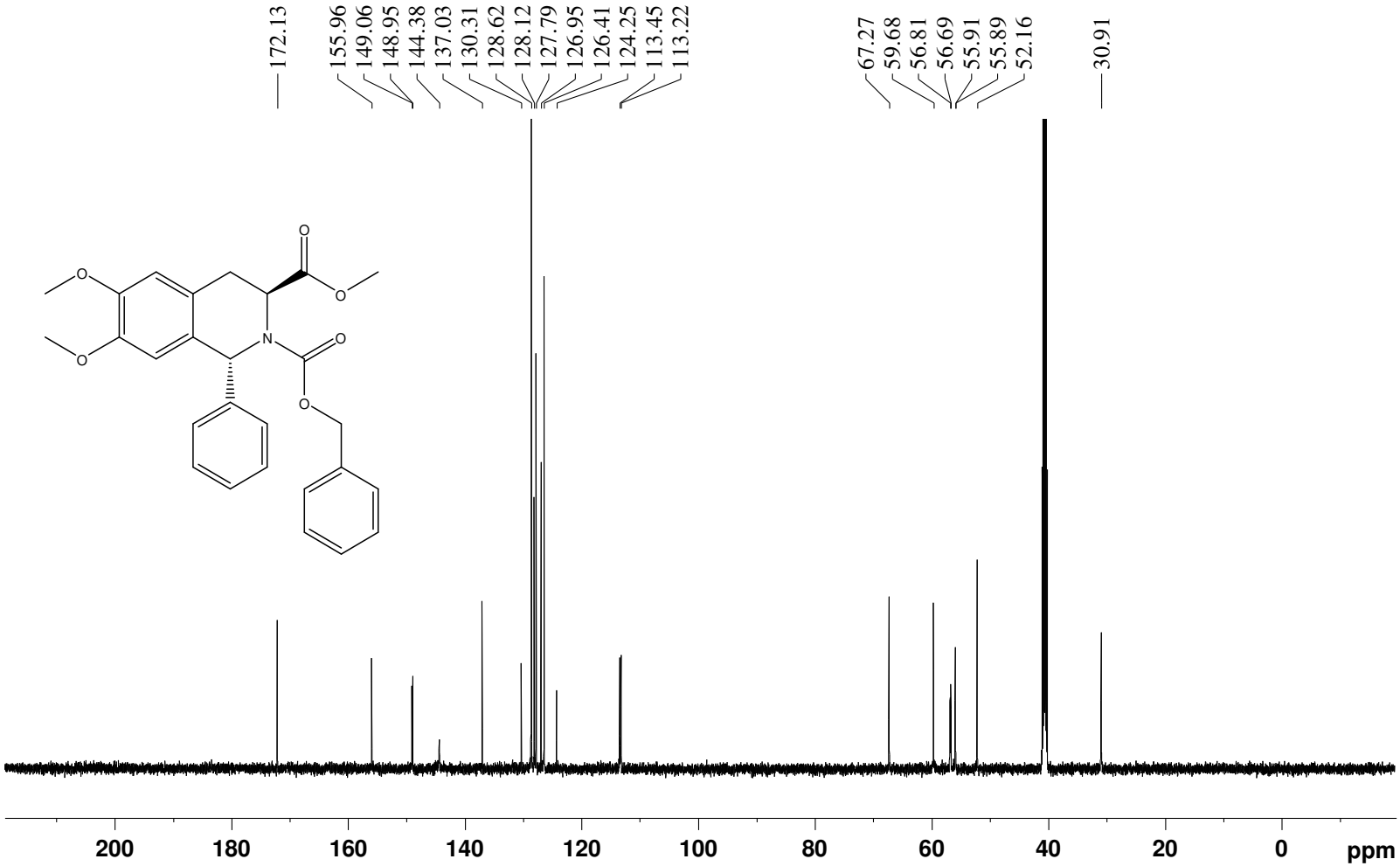
^{1}H NMR (400 MHz) Spectrum of Compound **11** in DMSO



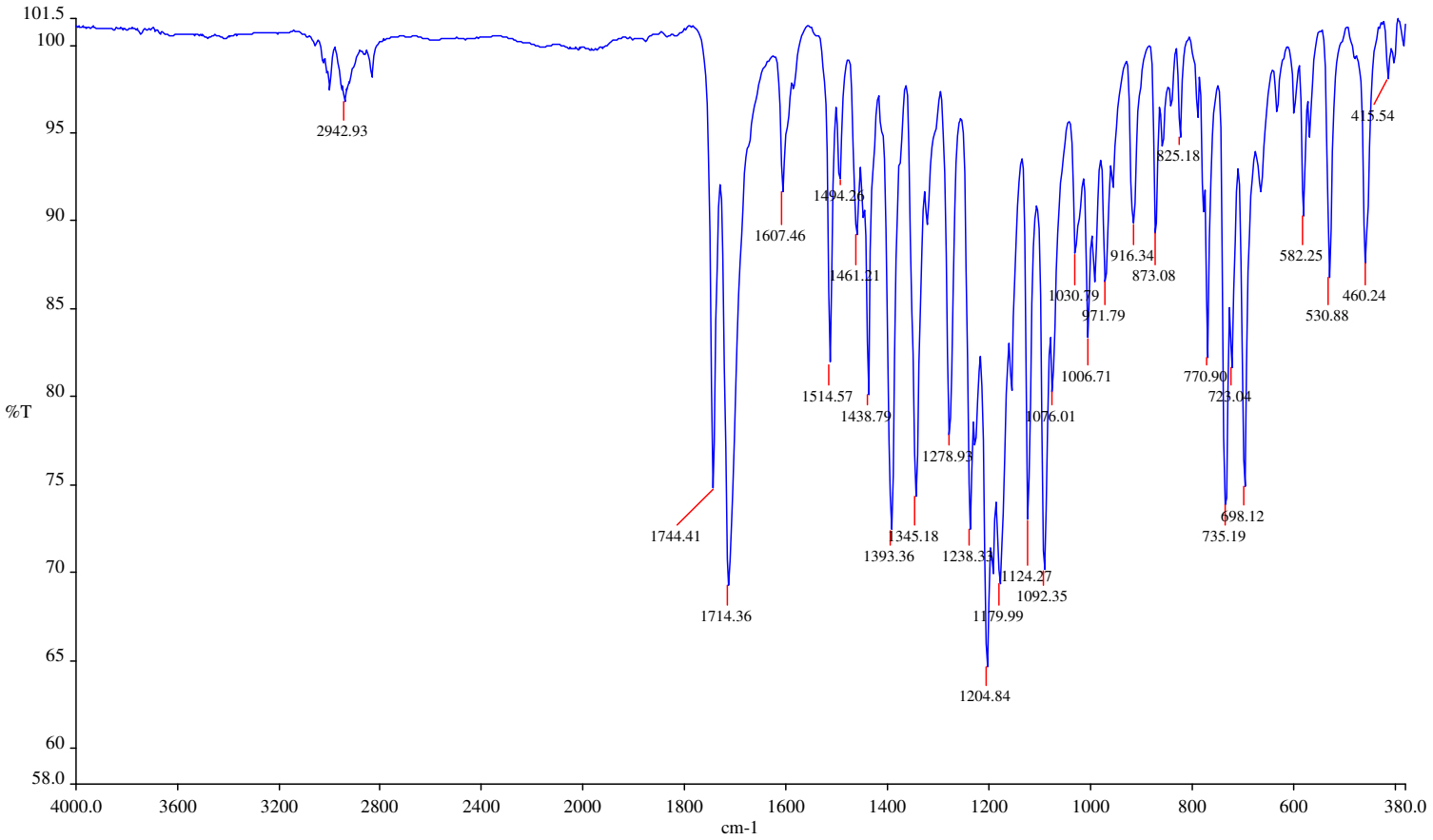
^{13}C (400 MHz) Spectrum of Compound **11** in DMSO



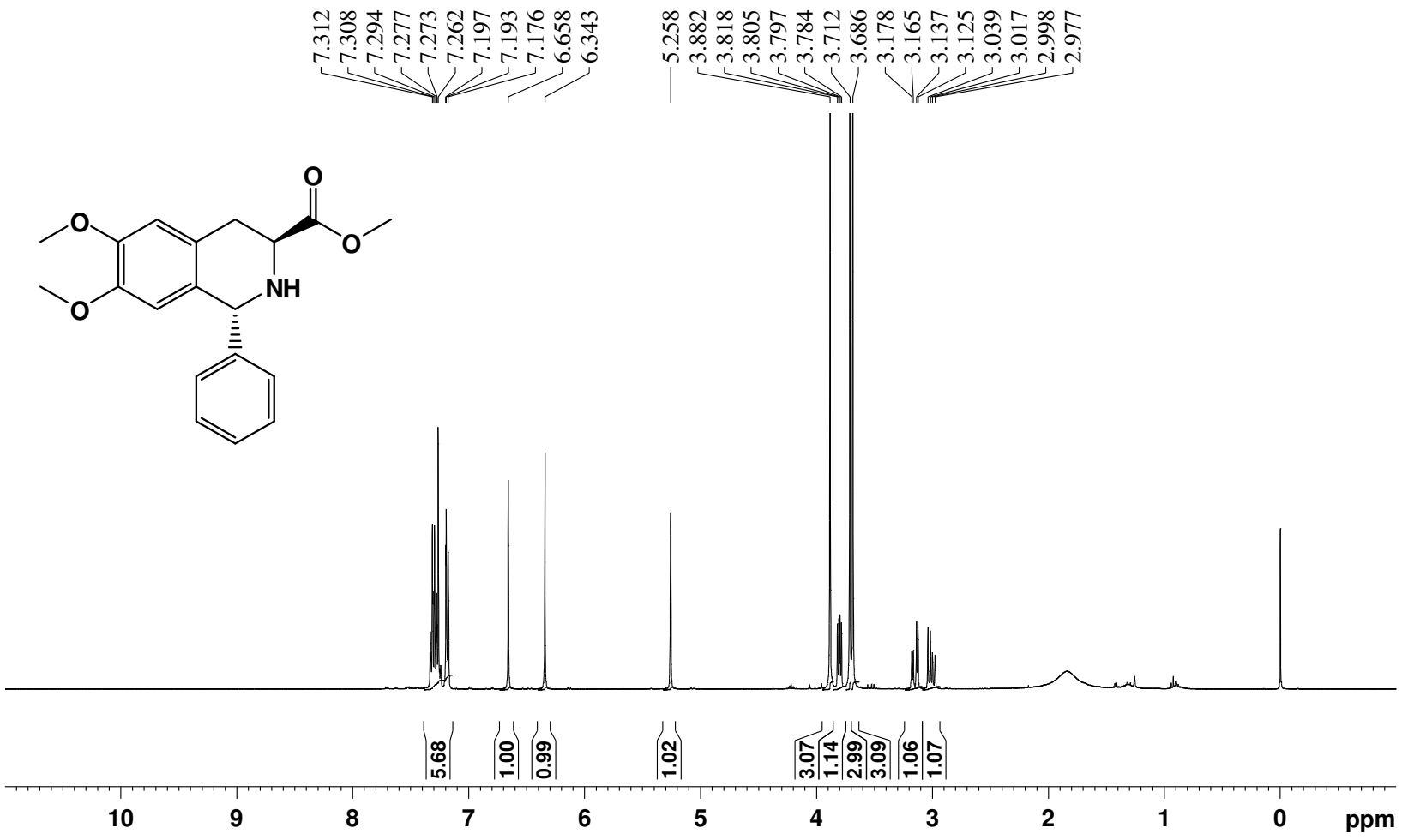
^{1}H NMR (400 MHz) Spectrum of Compound **12** in $CDCl_3$



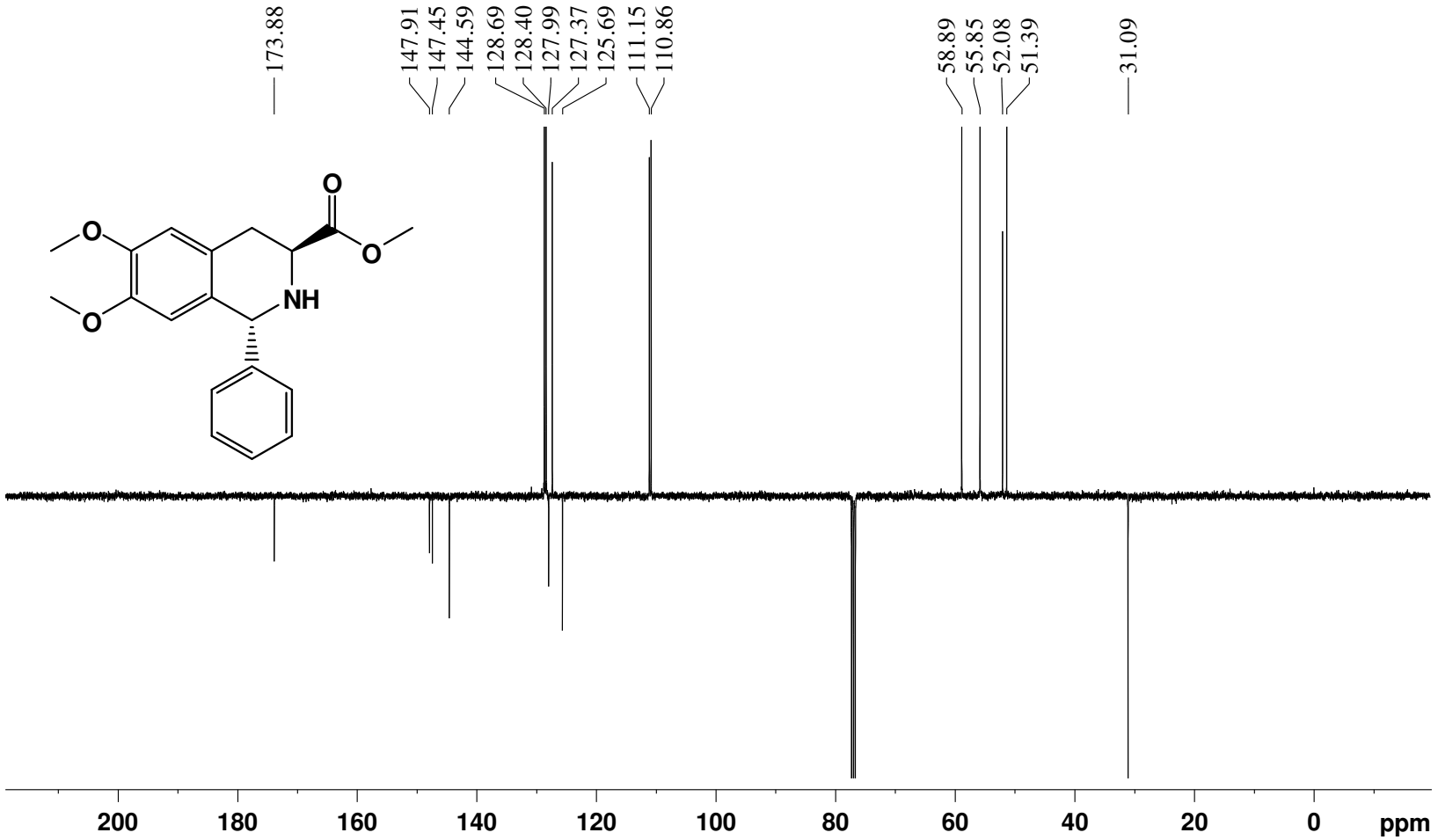
^{13}C (400 MHz) Spectrum of Compound **12** in $CDCl_3$



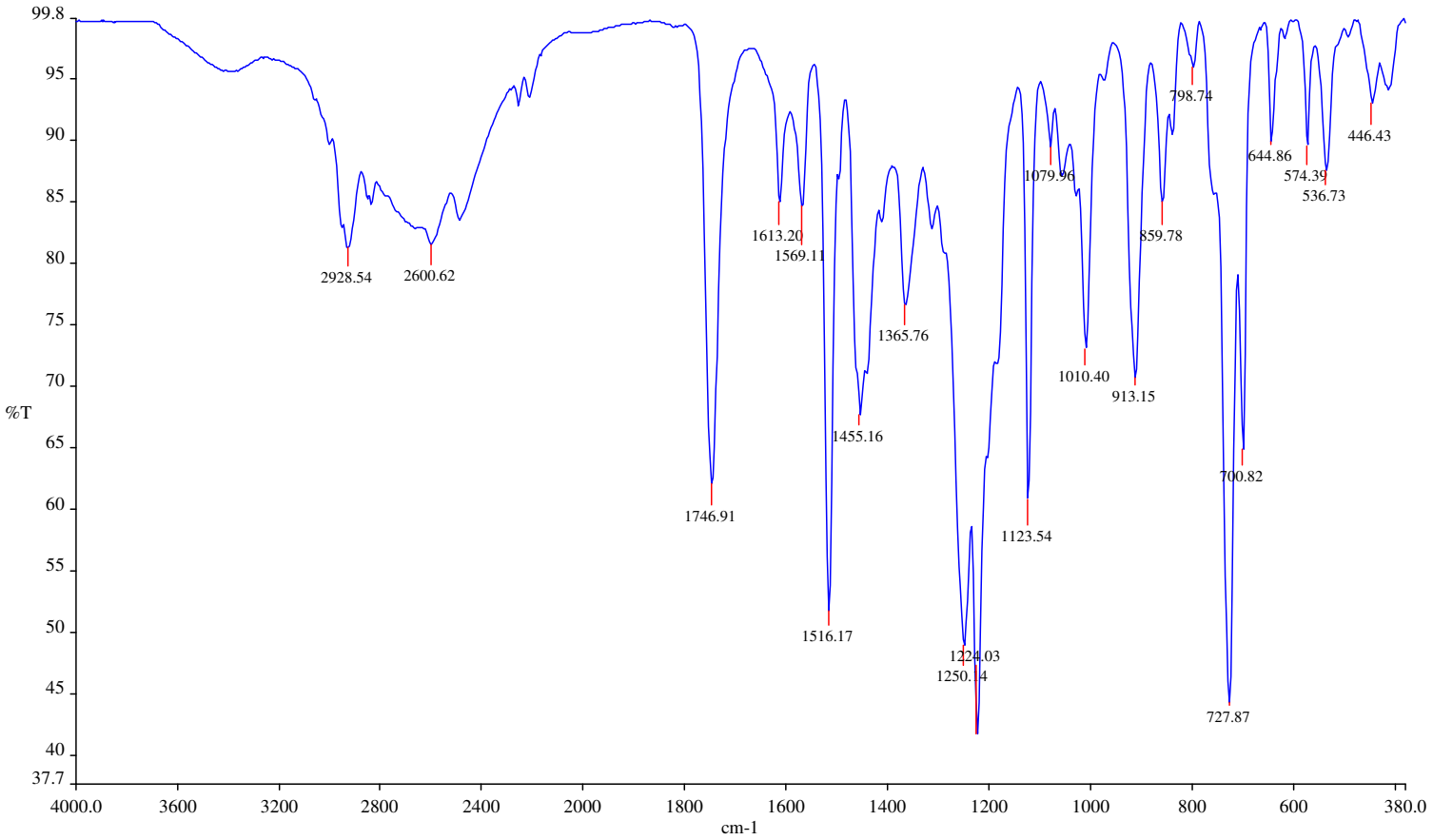
IR Spectrum of Compound **12**



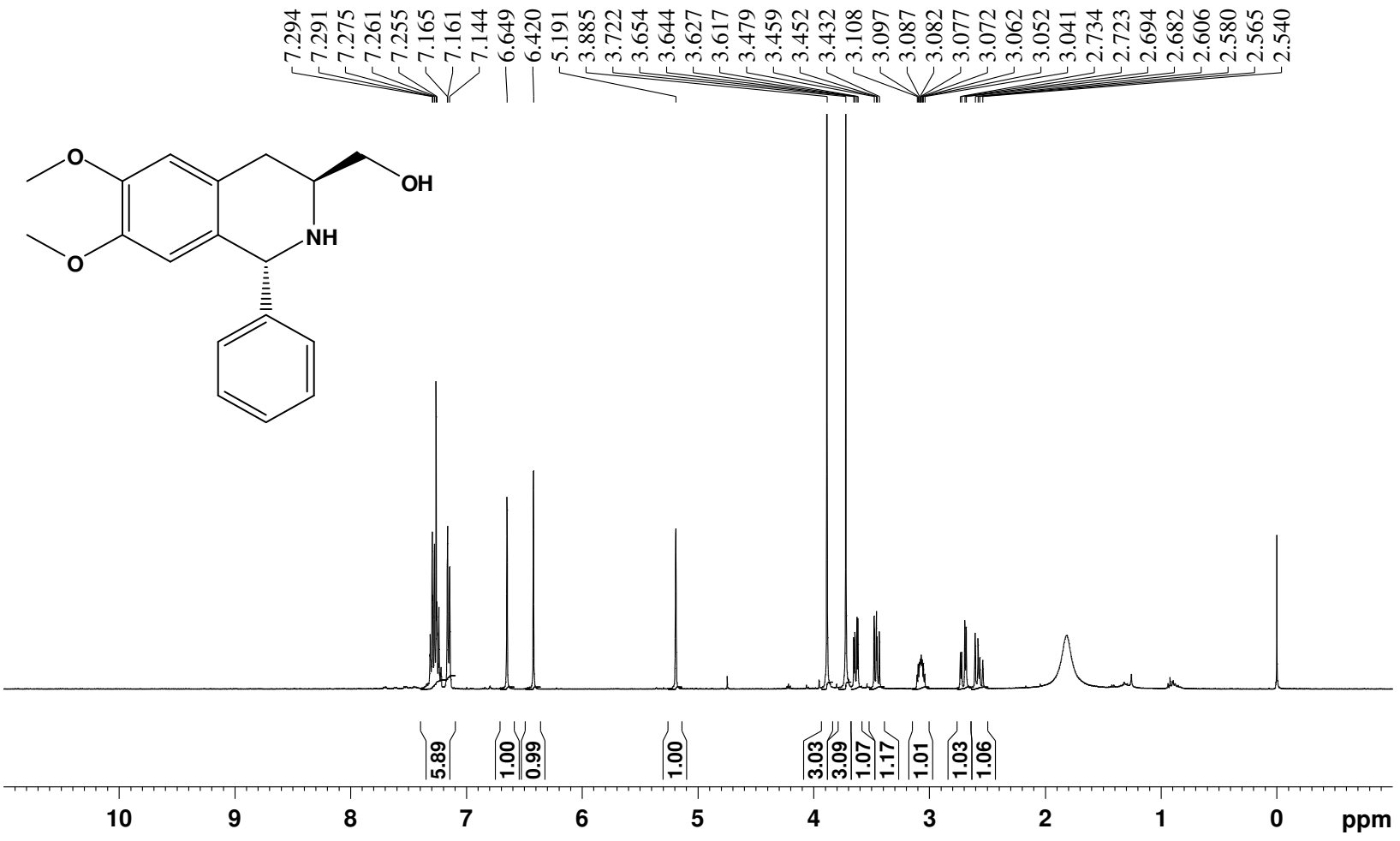
^{1}H NMR (400 MHz) Spectrum of Compound **13** in $CDCl_3$



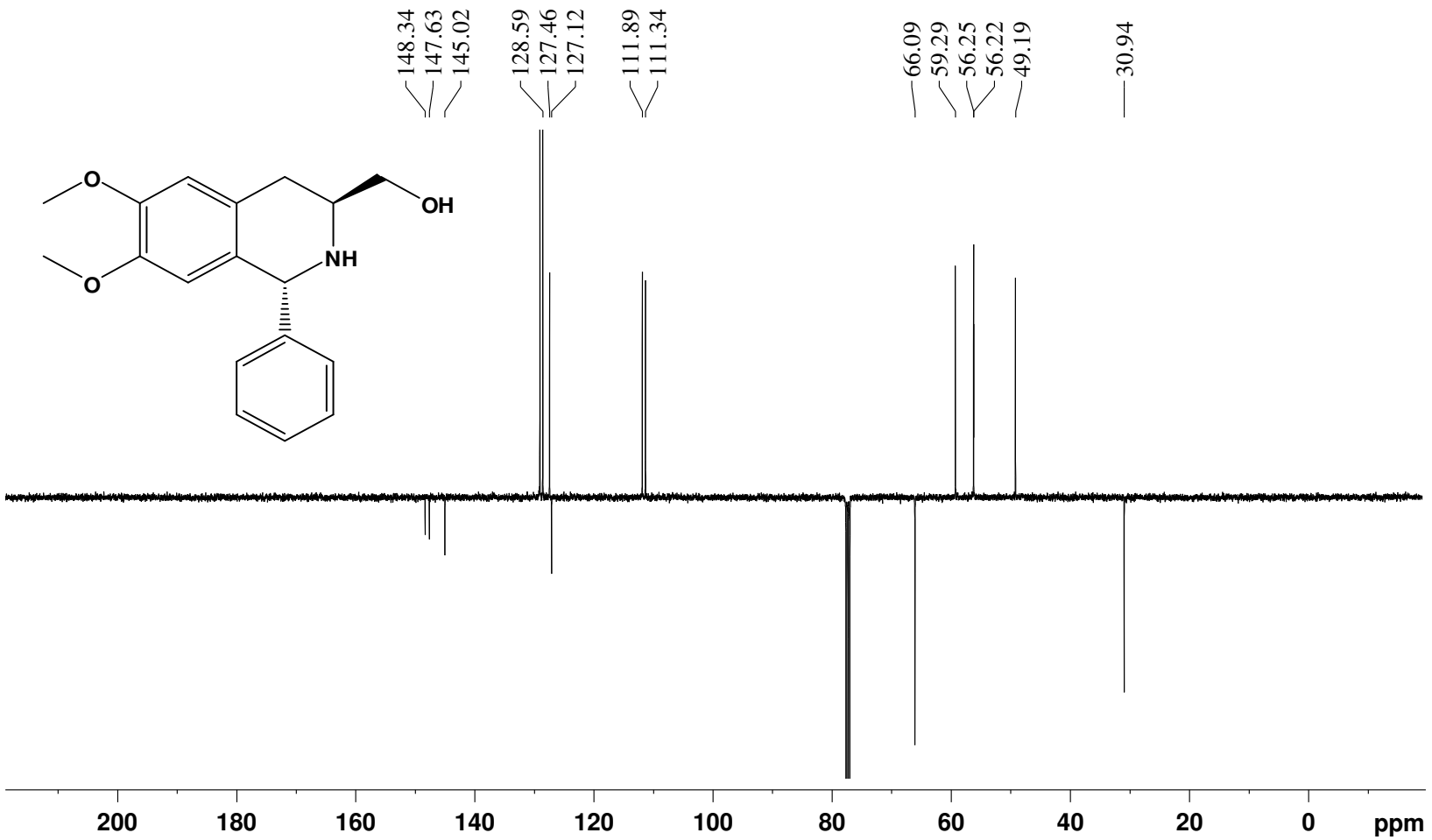
^{13}C (400 MHz) Spectrum of Compound **13** in $CDCl_3$



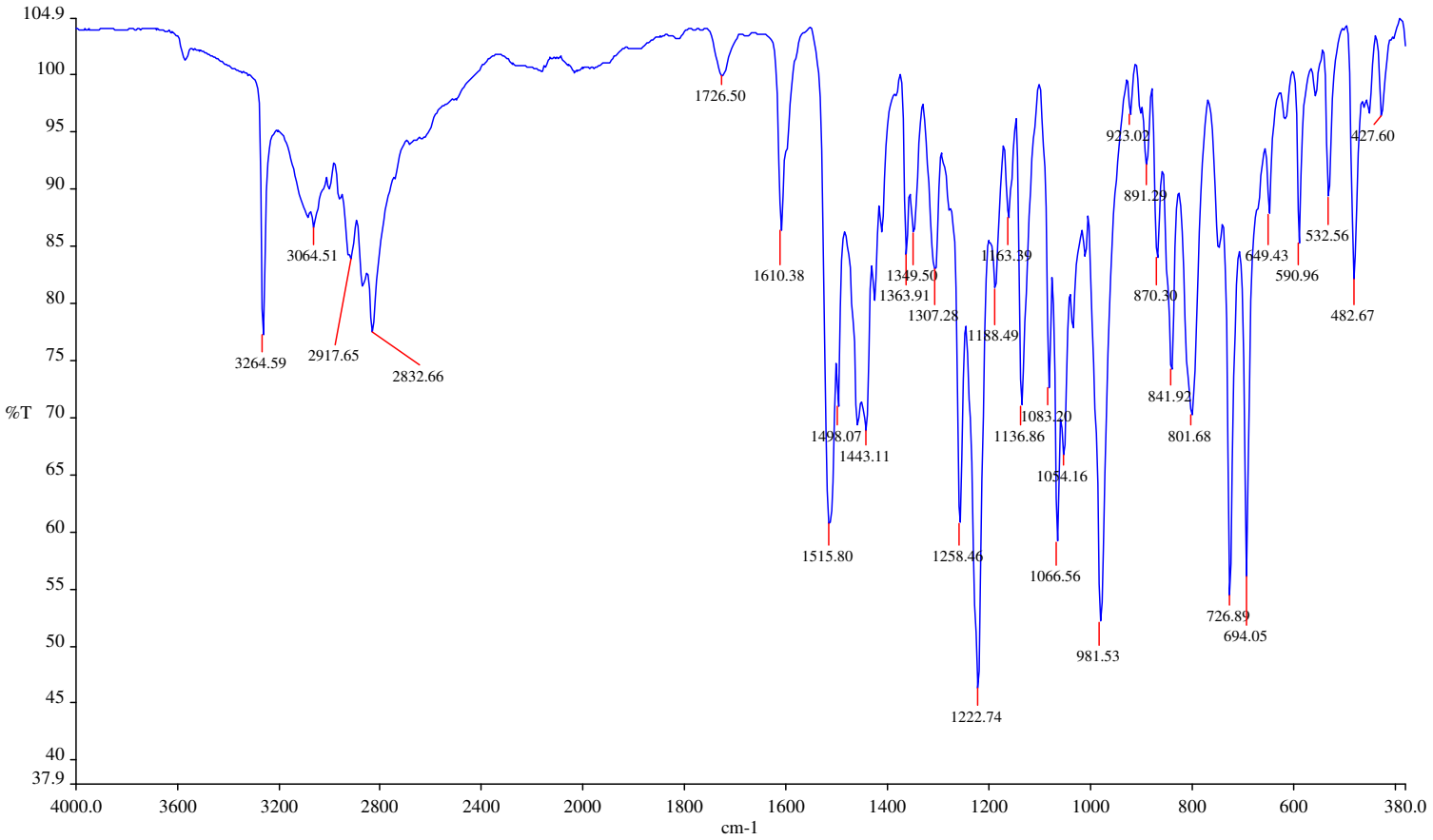
IR Spectrum of Compound **13**



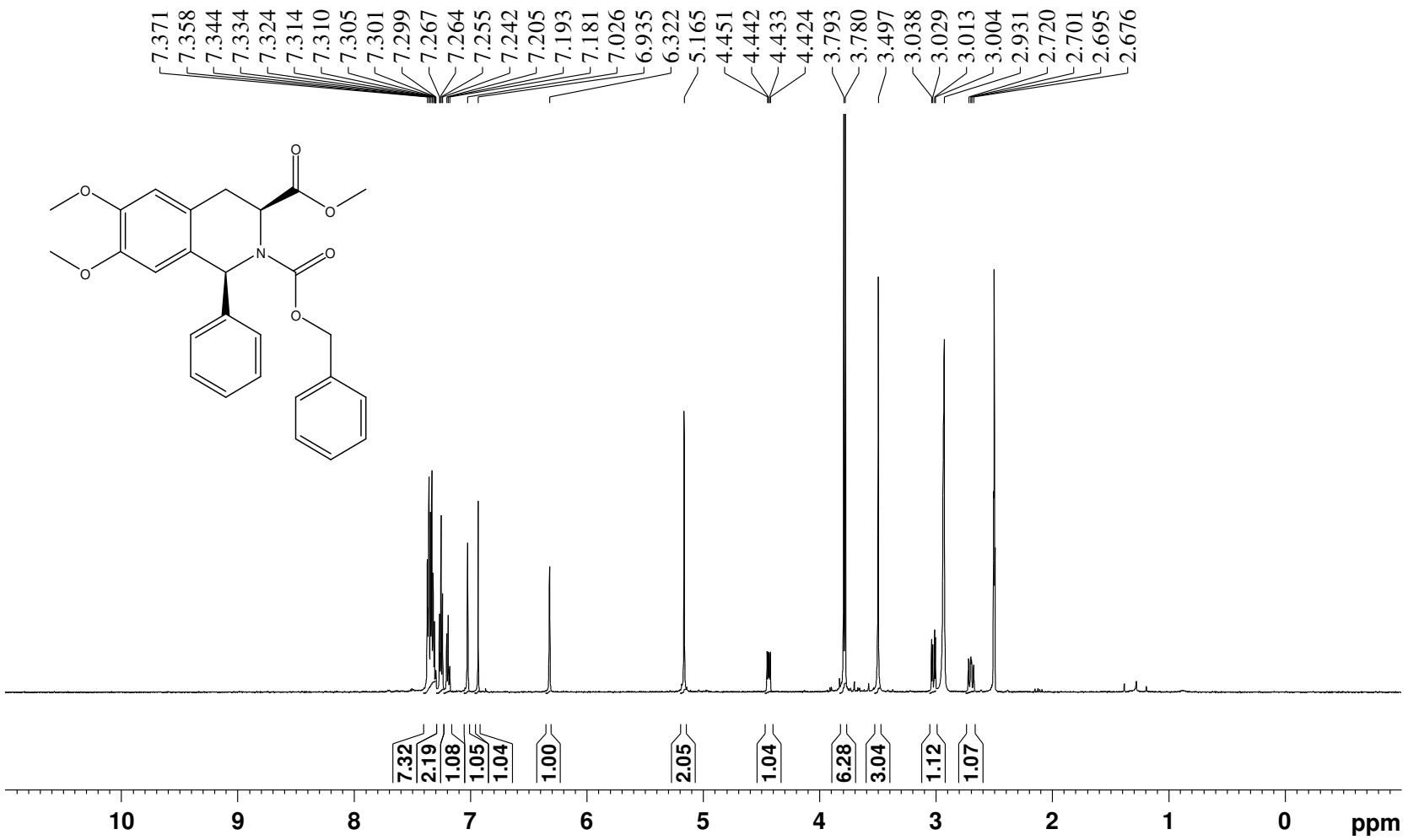
^{1}H NMR (400 MHz) Spectrum of Compound **14** in $CDCl_3$



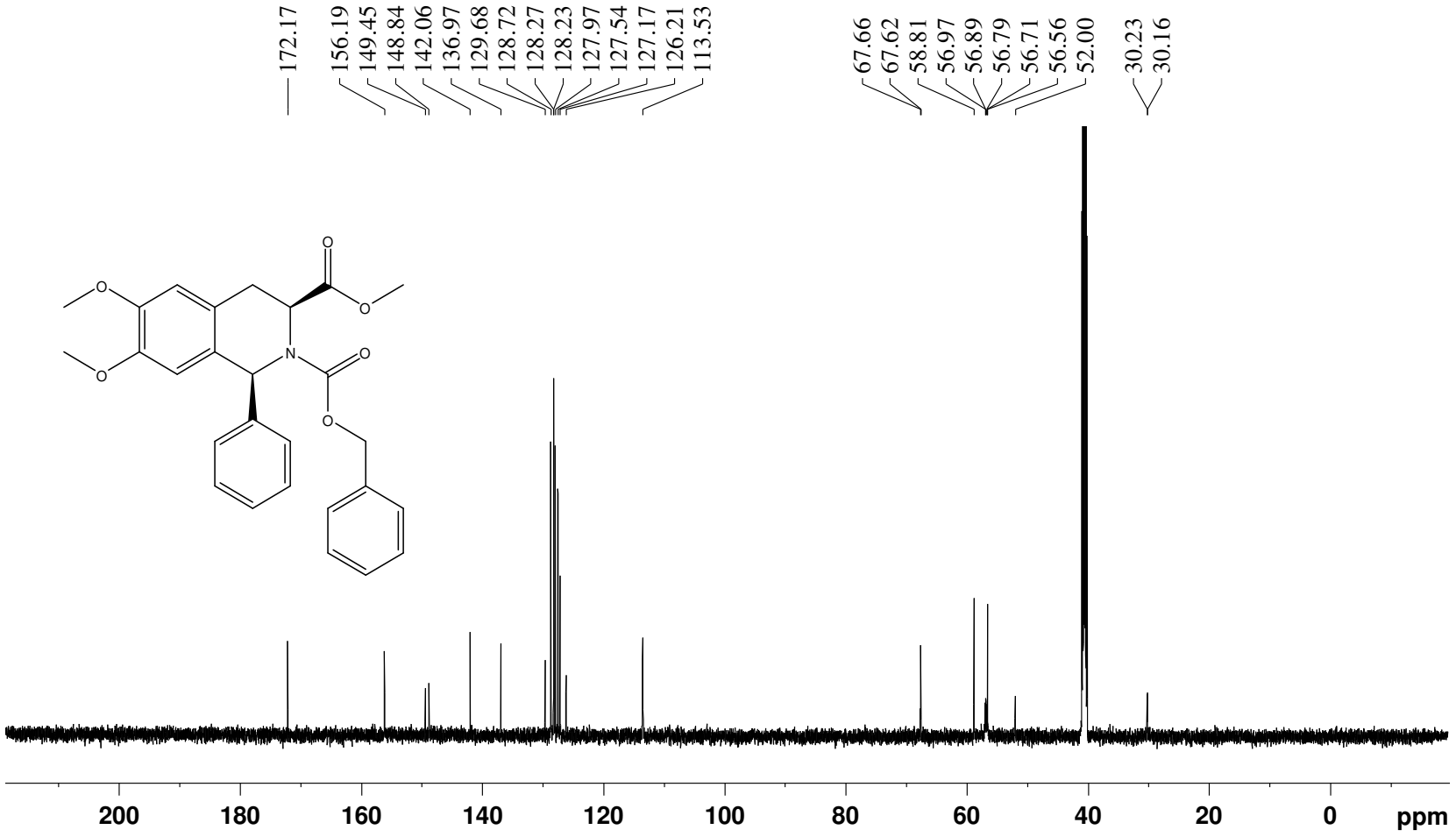
^{13}C (400 MHz) Spectrum of Compound **14** in $CDCl_3$



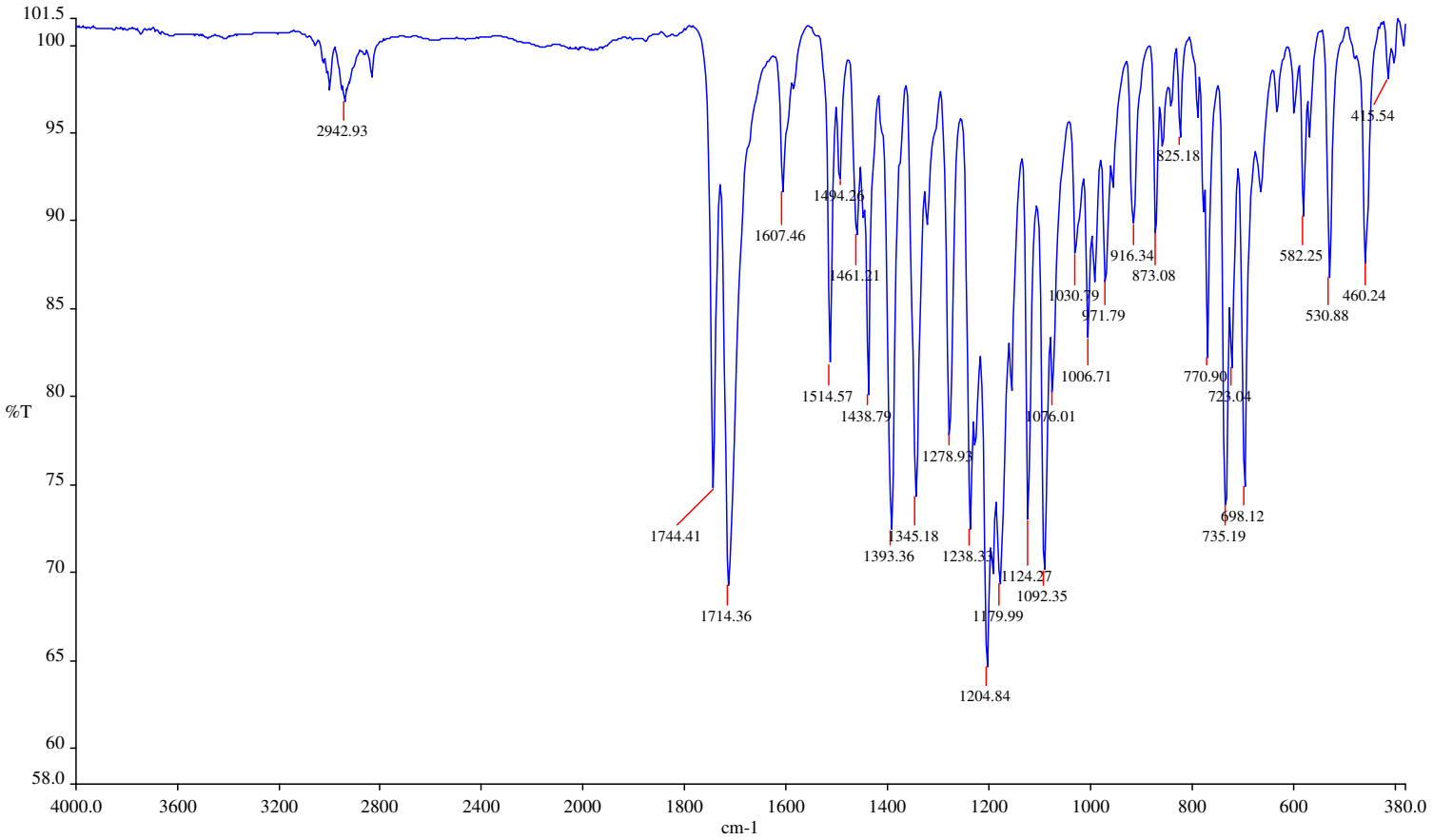
IR Spectrum of Compound **14**



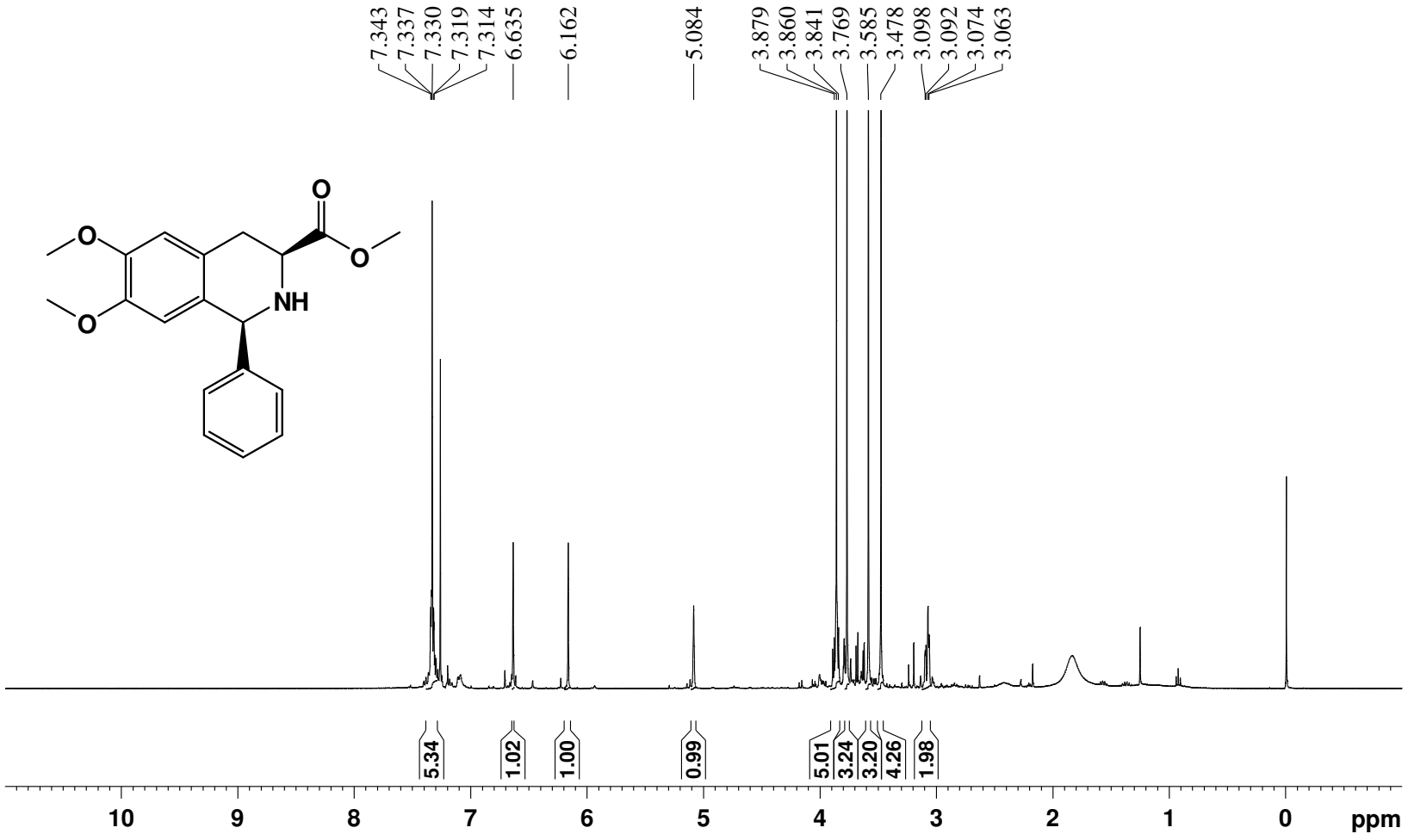
^{1}H NMR (400 MHz) Spectrum of Compound **15** in $CDCl_3$



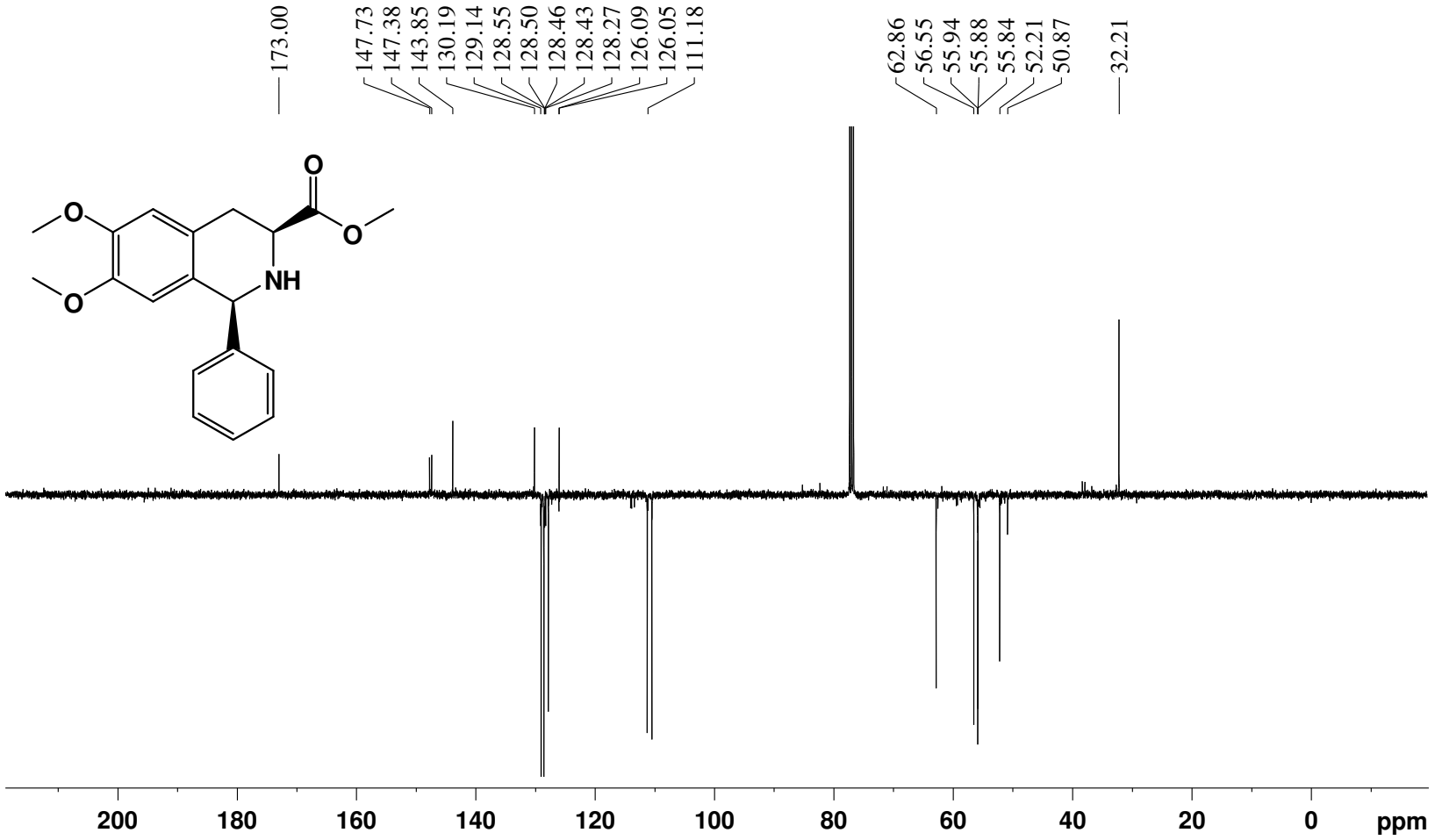
^{13}C (400 MHz) Spectrum of Compound **15** in $CDCl_3$



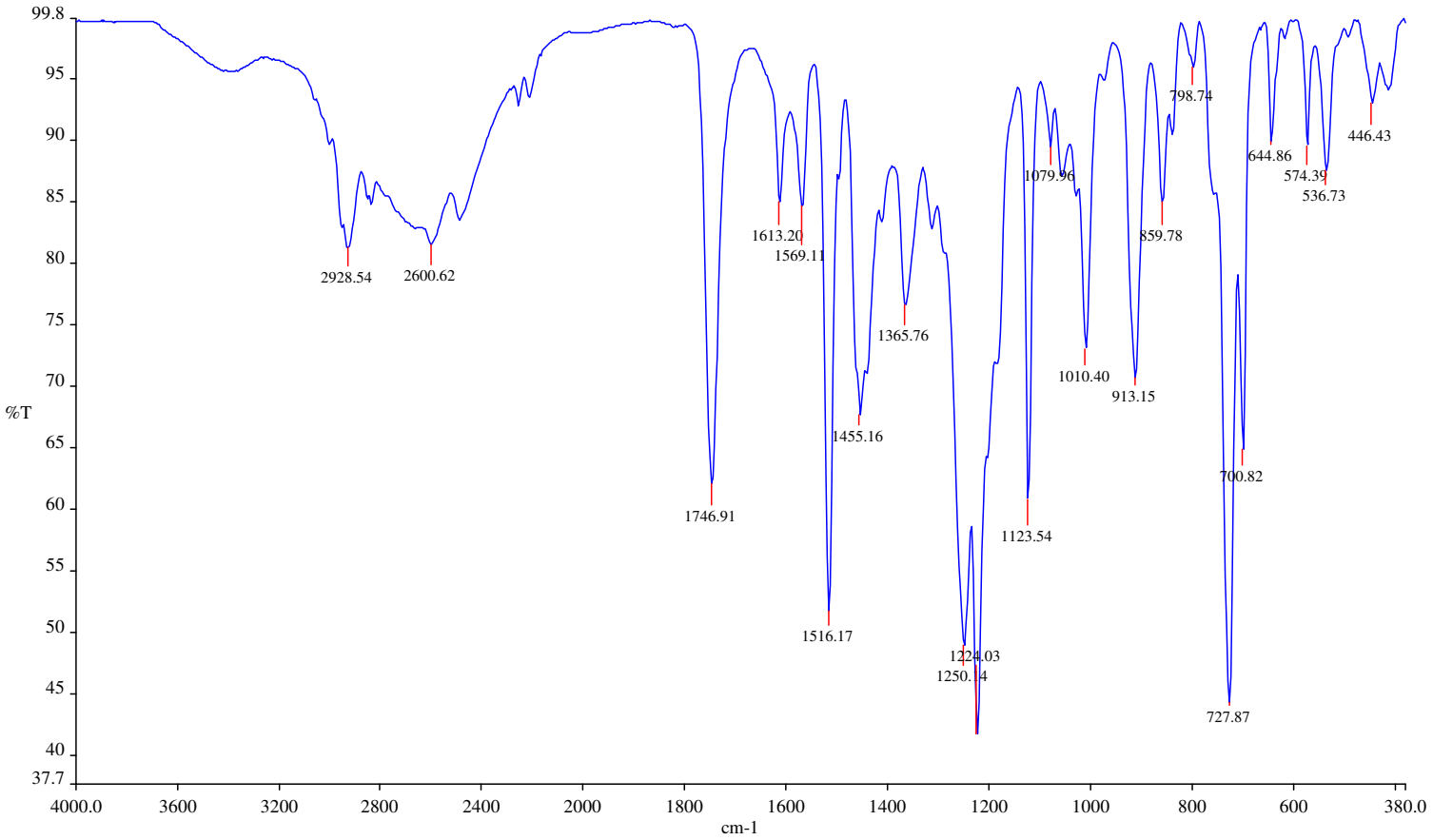
IR Spectrum of Compound **15**



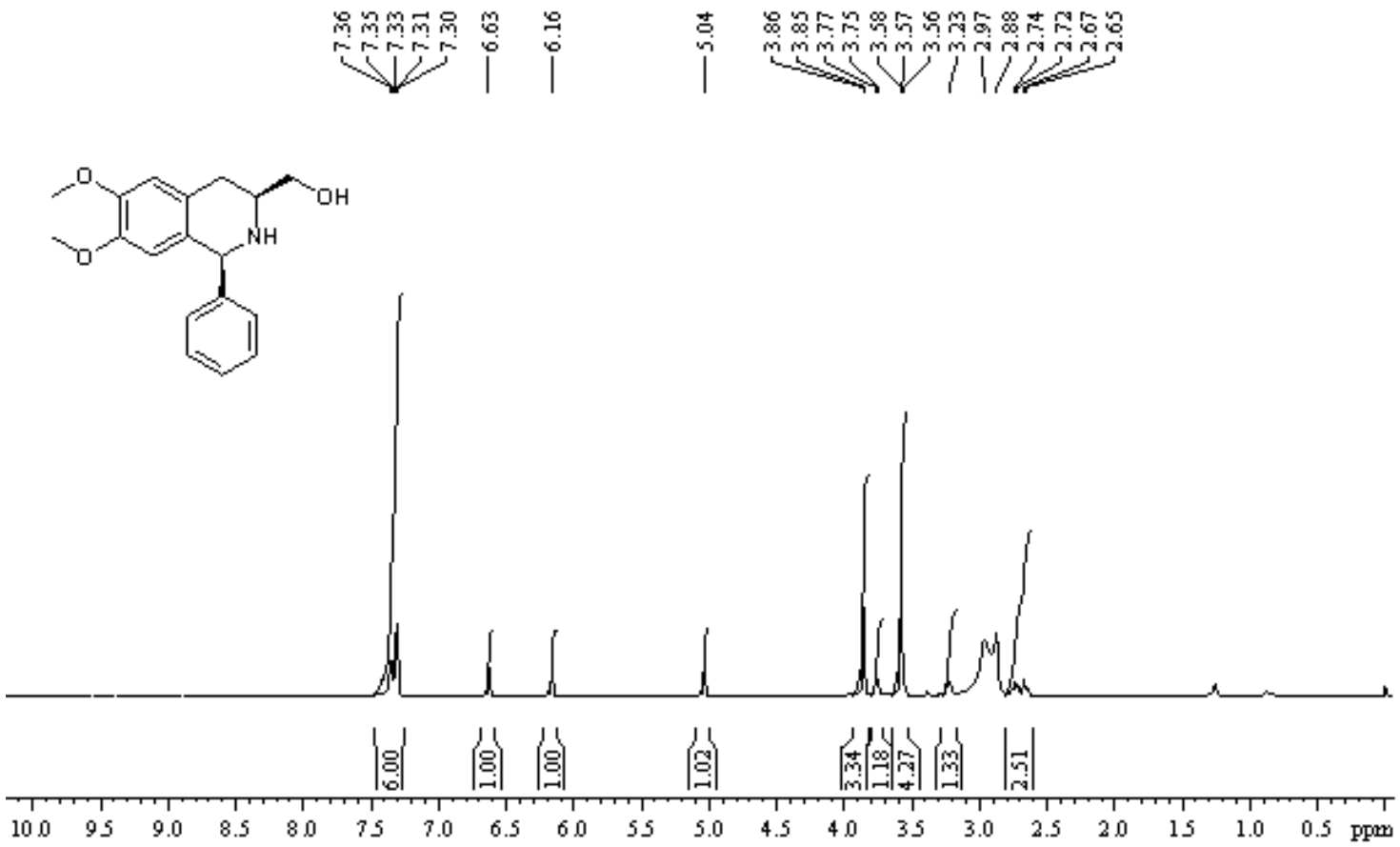
^{1}H NMR (400 MHz) Spectrum of Compound **16** in $CDCl_3$



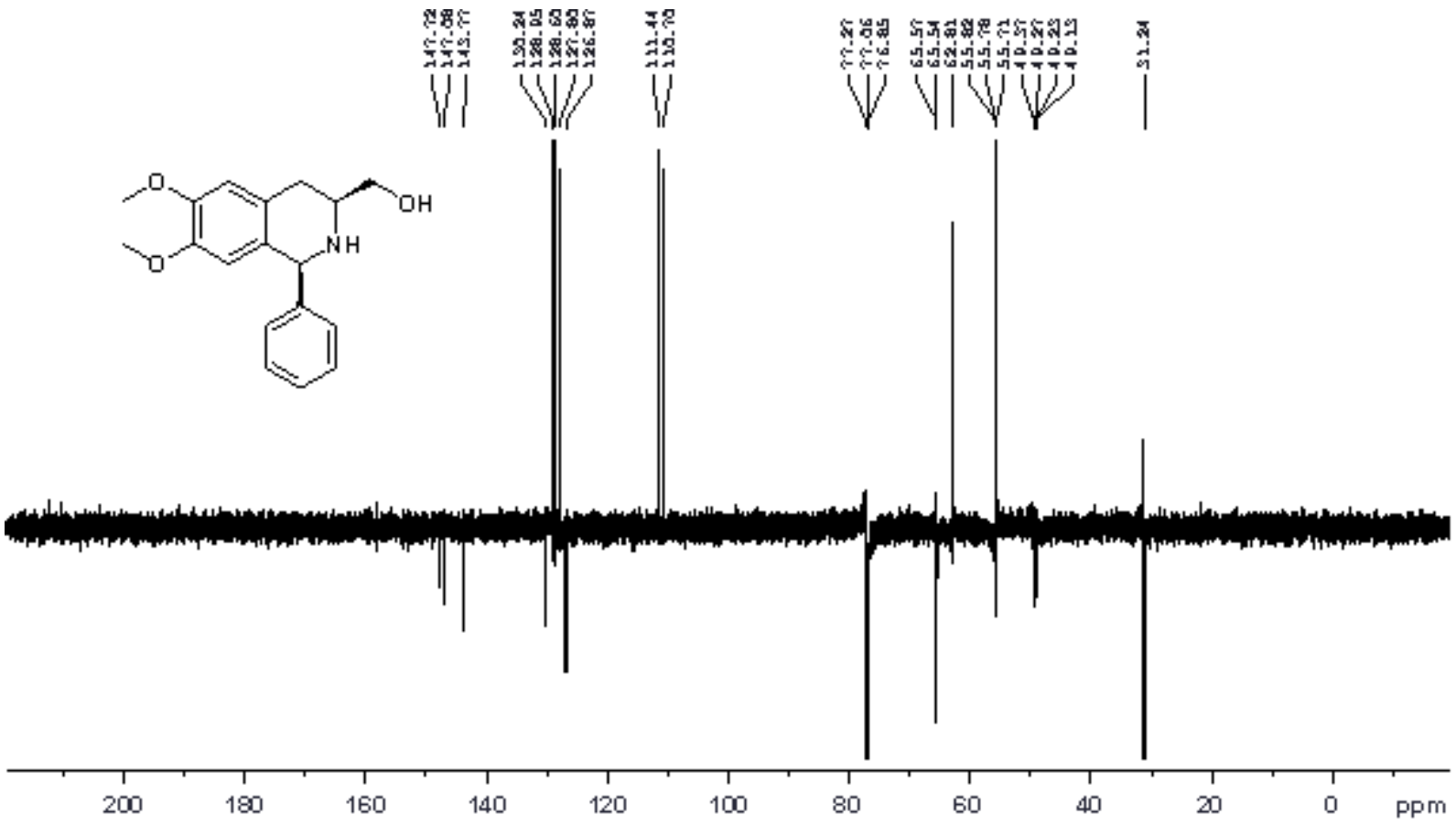
^{13}C (400 MHz) Spectrum of Compound **16** in $CDCl_3$



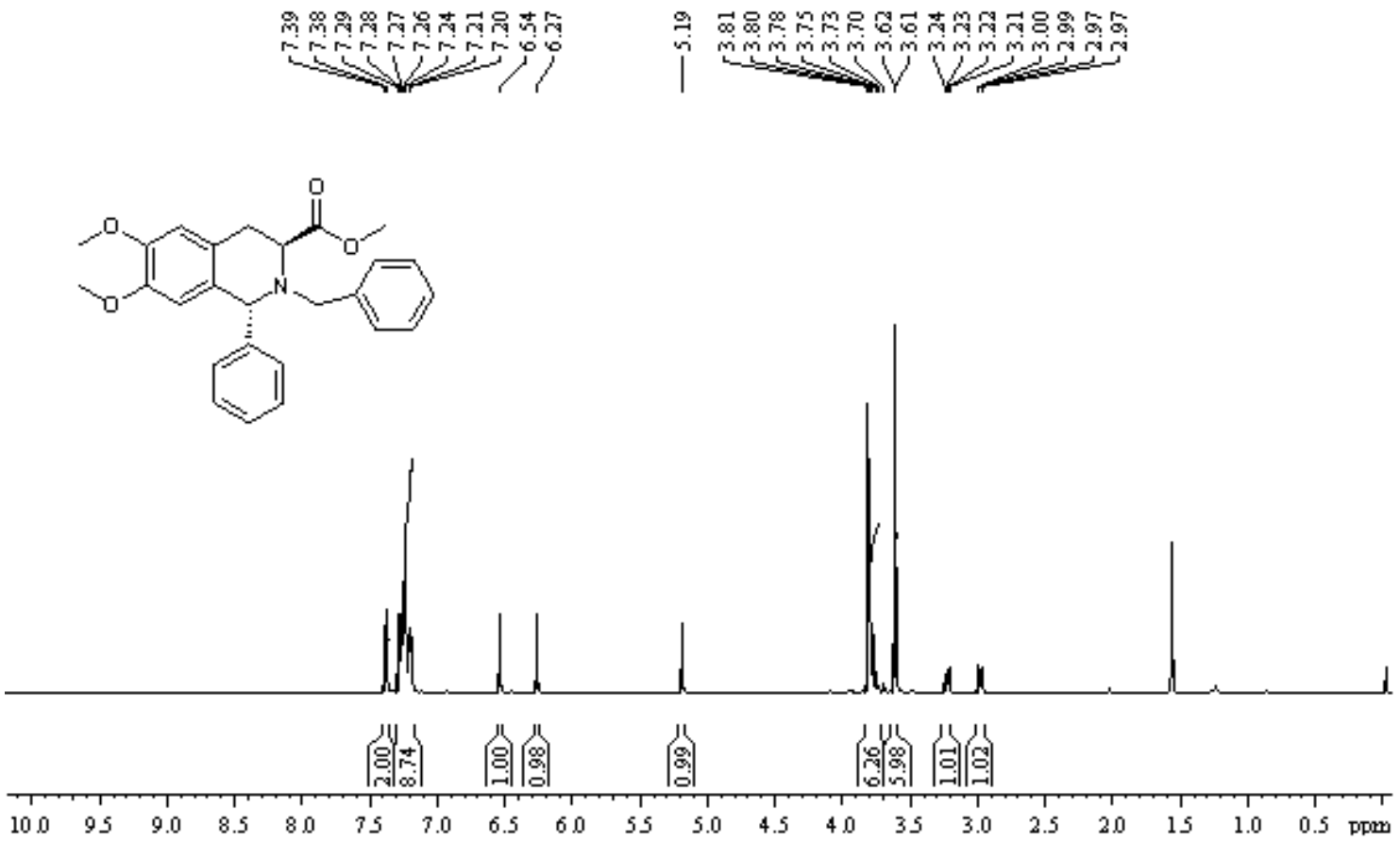
IR Spectrum of Compound **16**



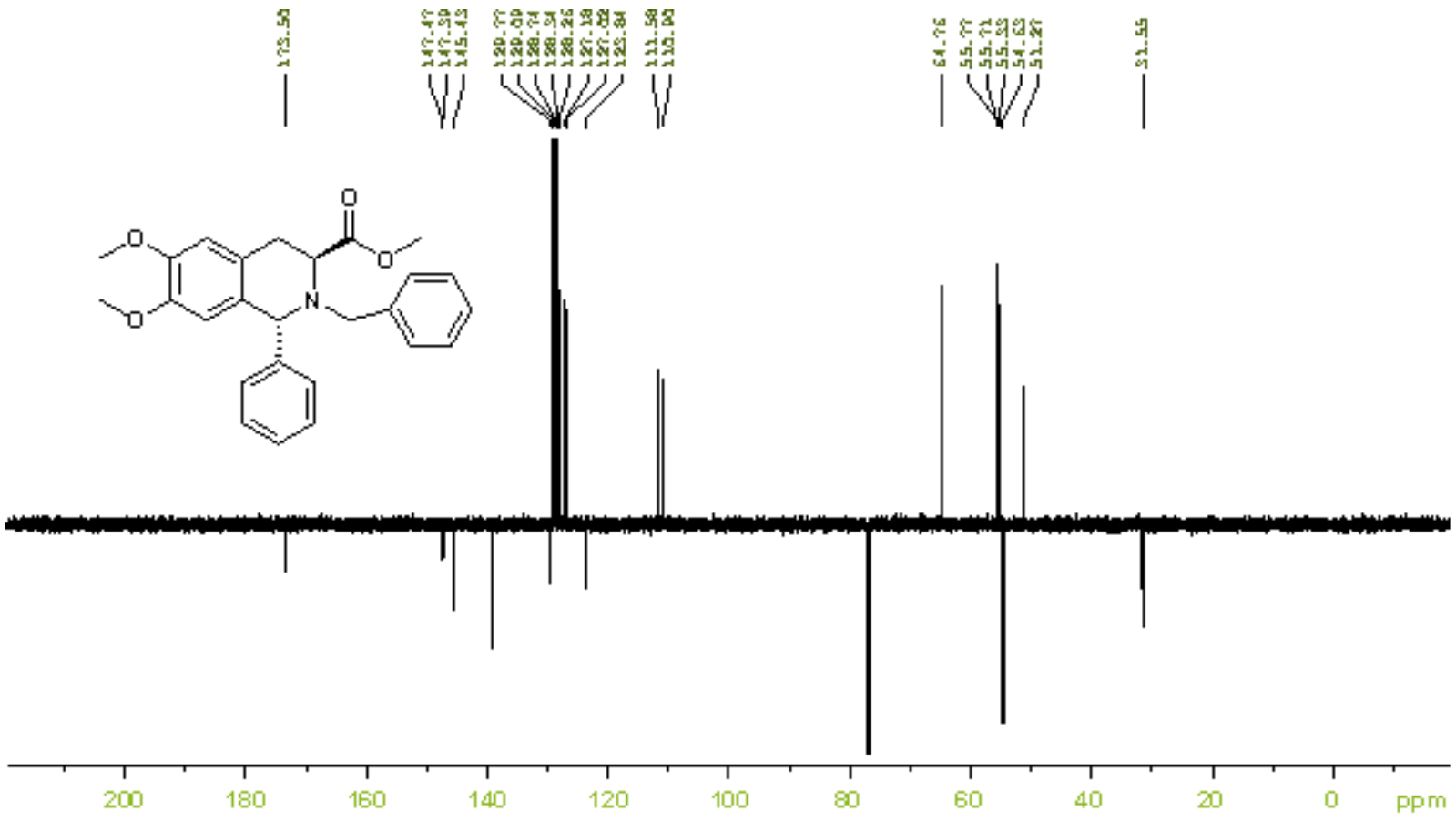
^{1}H NMR (400 MHz) Spectrum of Compound **17** in $CDCl_3$



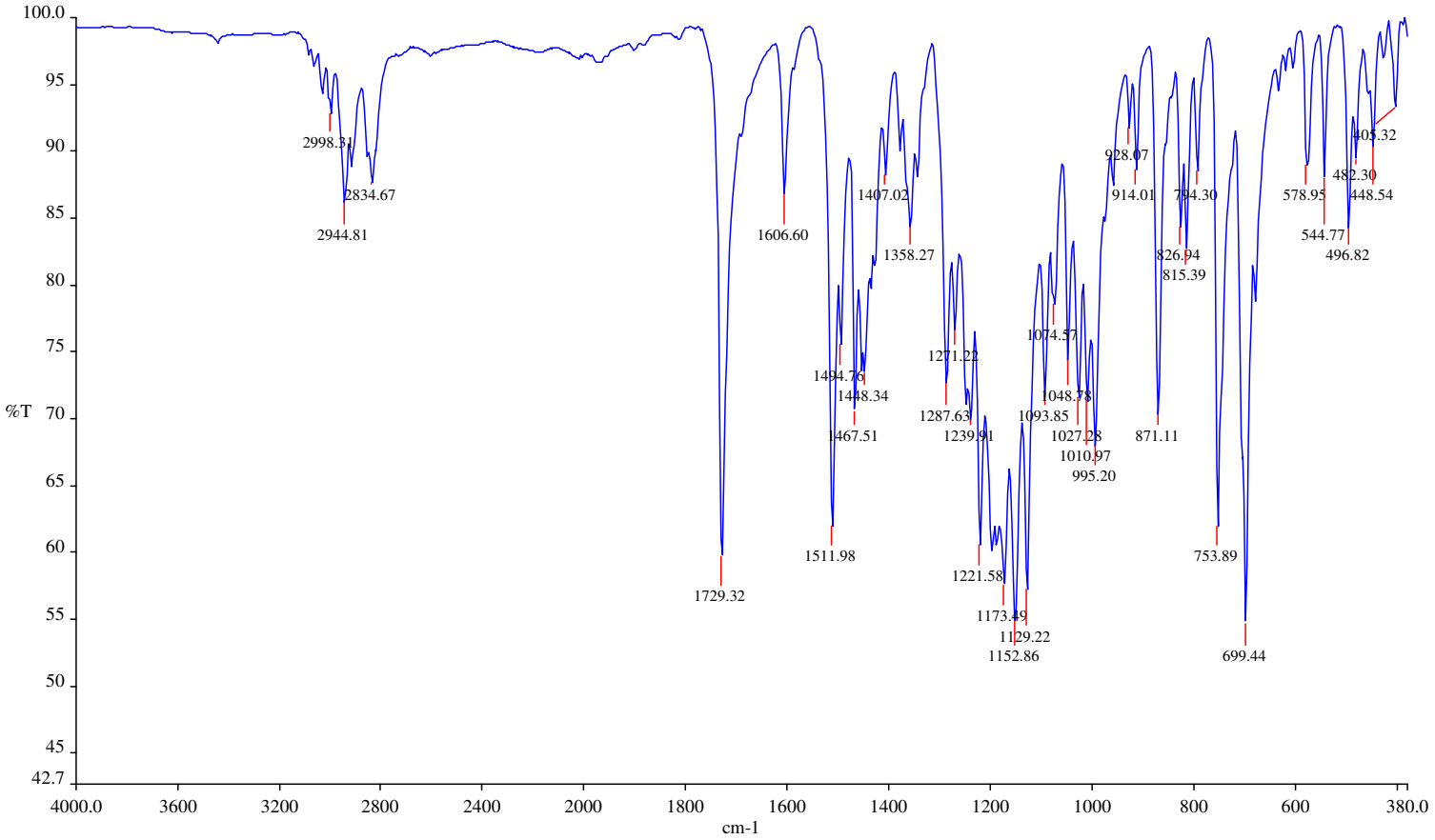
^{13}C (400 MHz) Spectrum of Compound **17** in $CDCl_3$



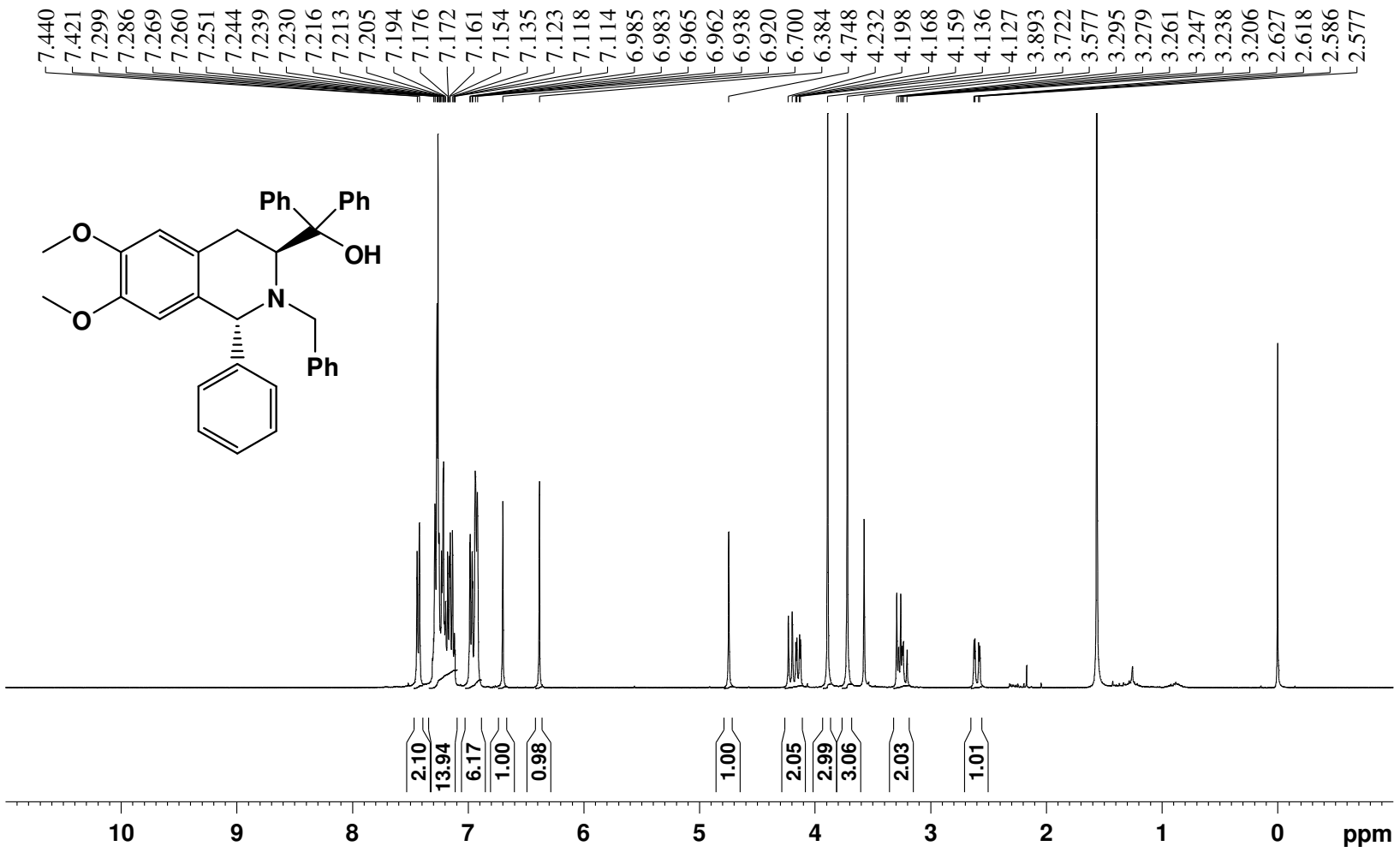
^{1}H NMR (400 MHz) Spectrum of Compound **18** in $CDCl_3$



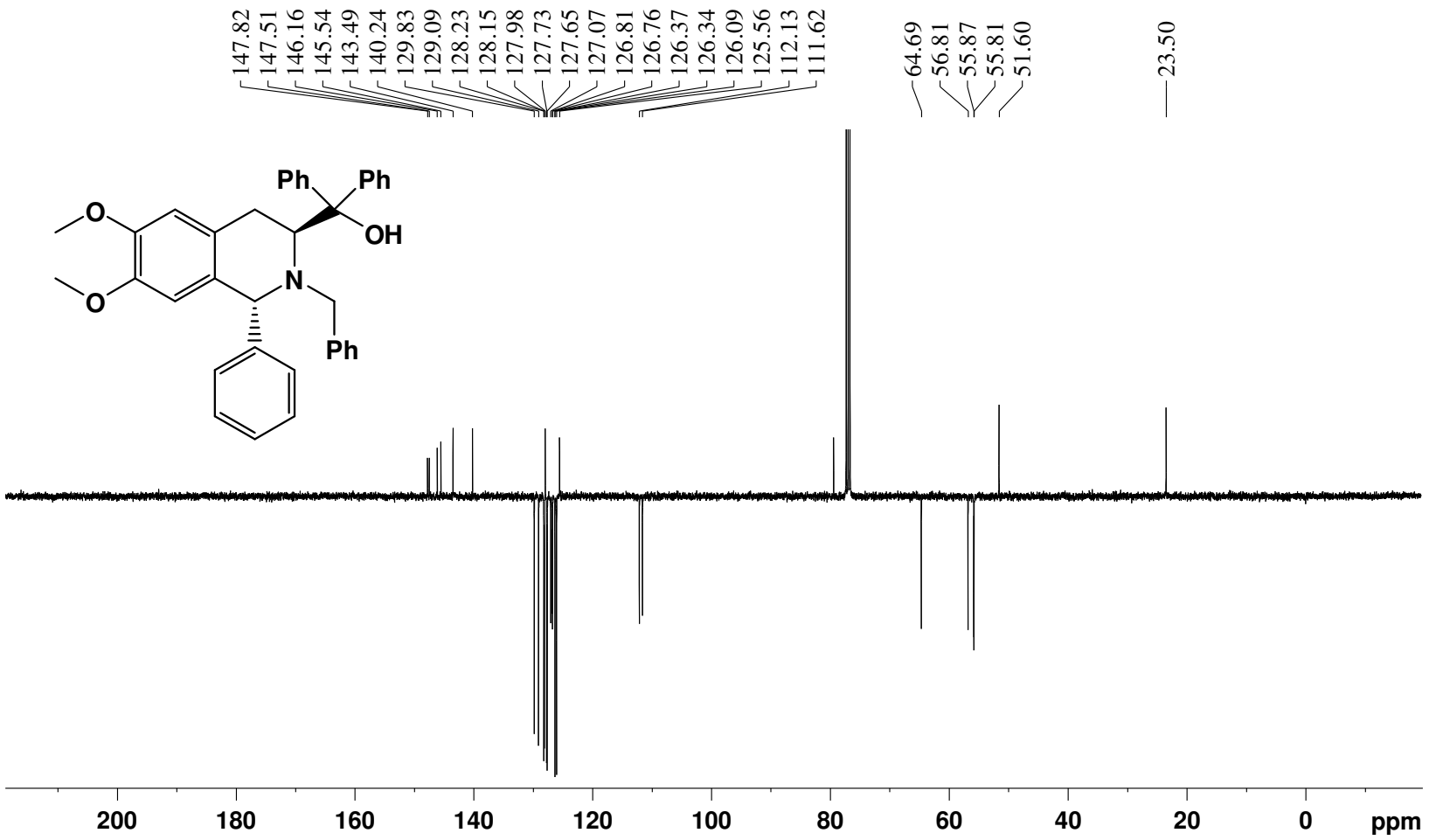
^{13}C (400 MHz) Spectrum of Compound **18** in $CDCl_3$



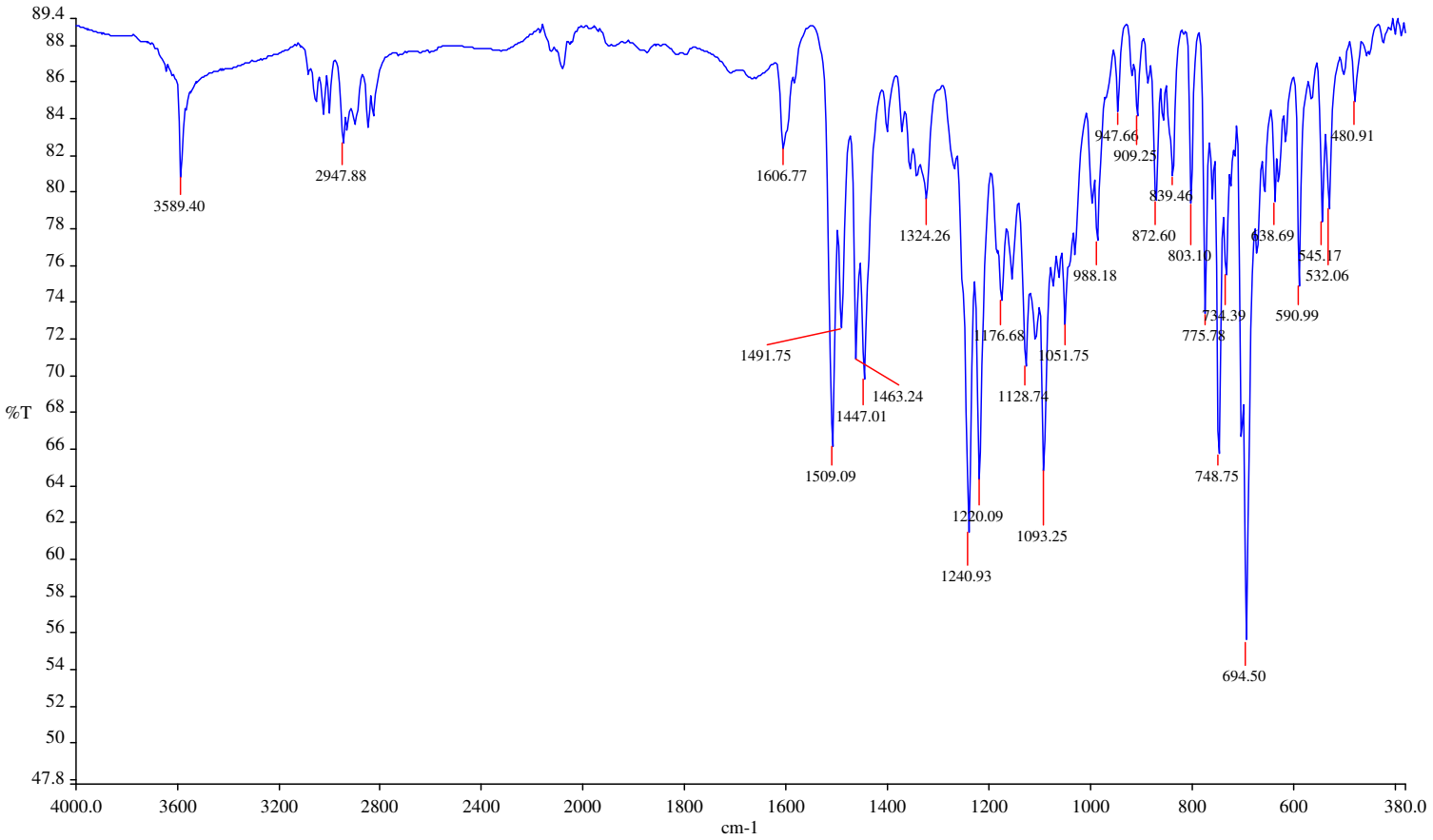
IR Spectrum of Compound **18**



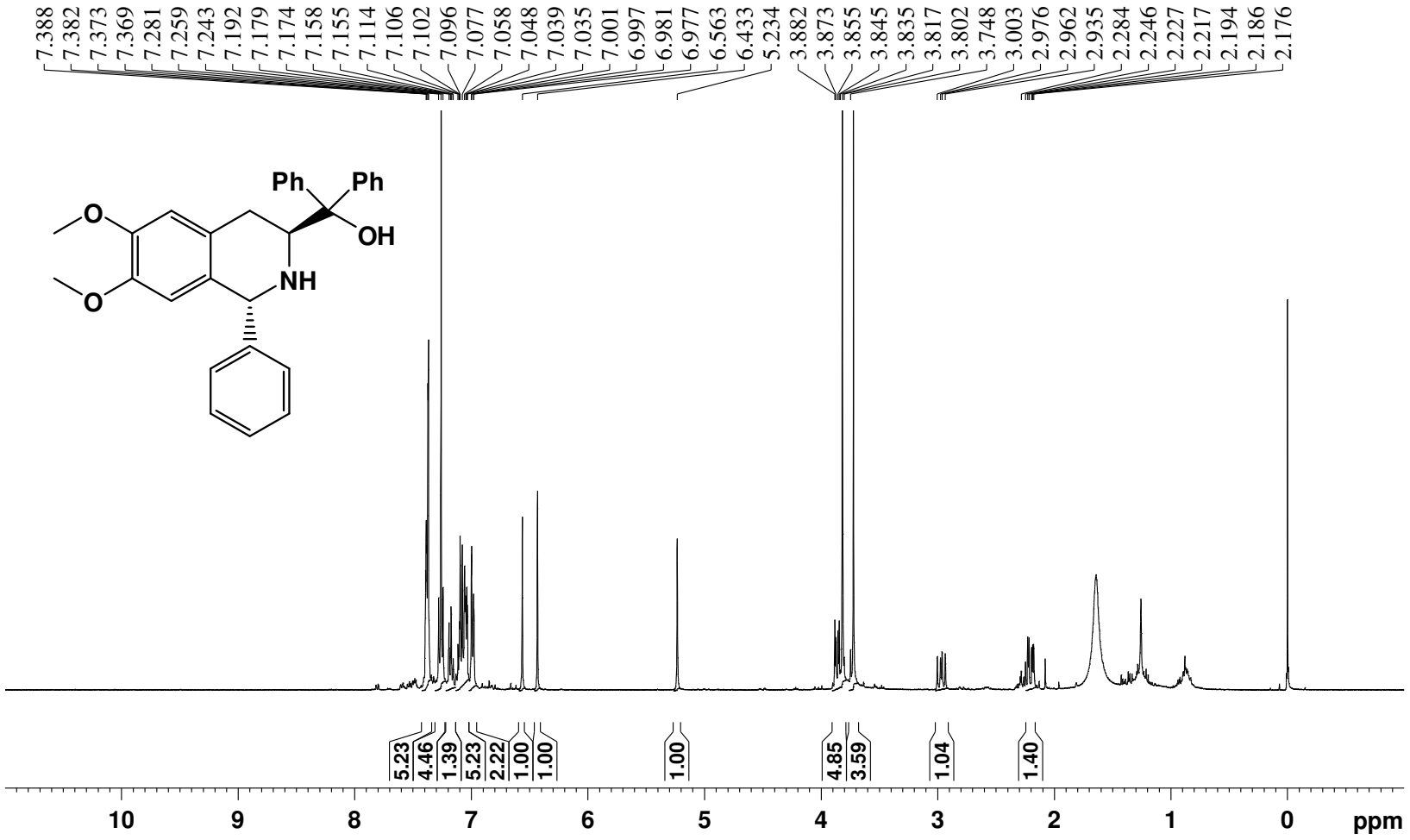
^{1}H NMR (400 MHz) Spectrum of Compound **19** in $CDCl_3$



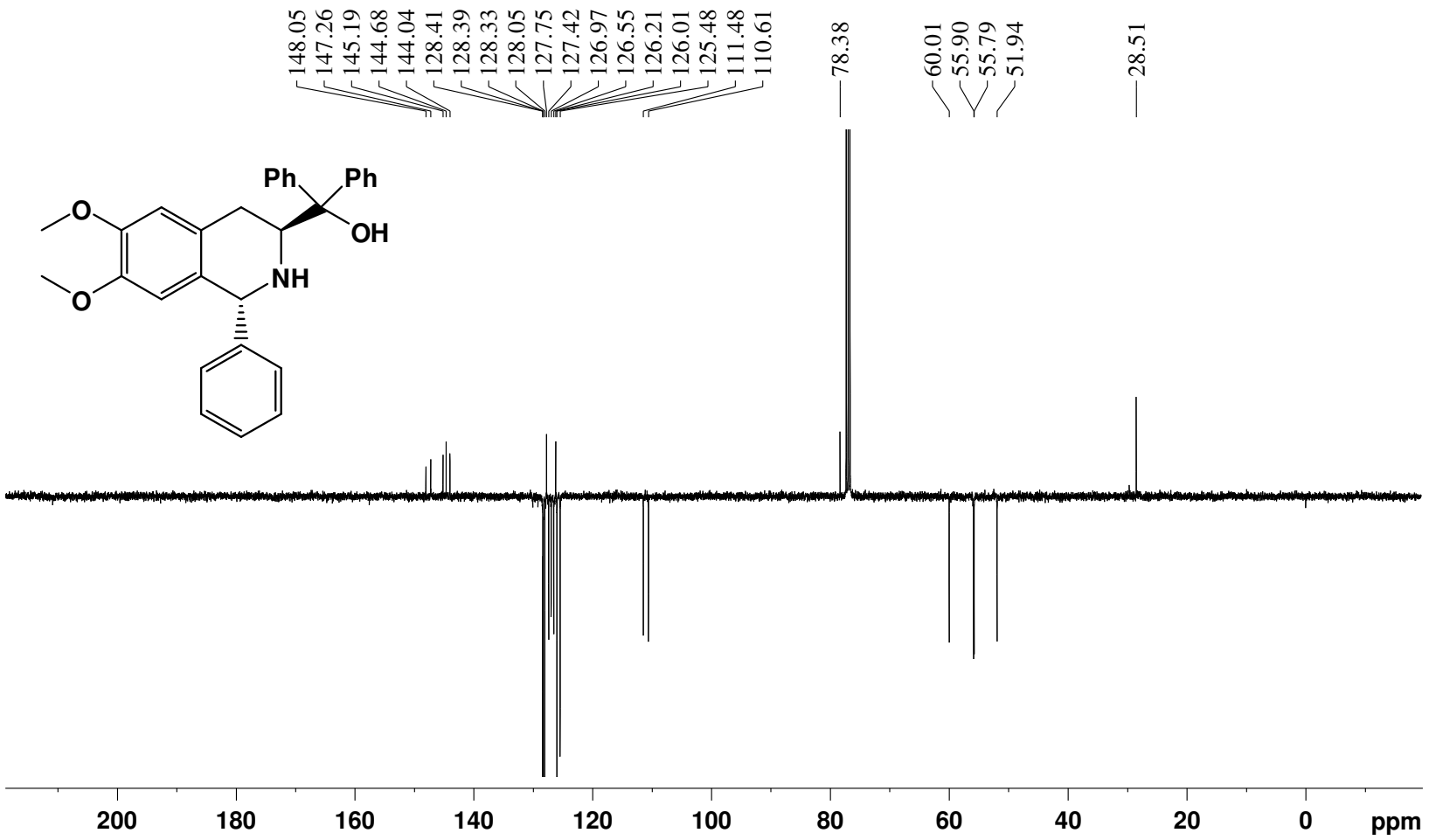
^{13}C (400 MHz) Spectrum of Compound **19** in $CDCl_3$



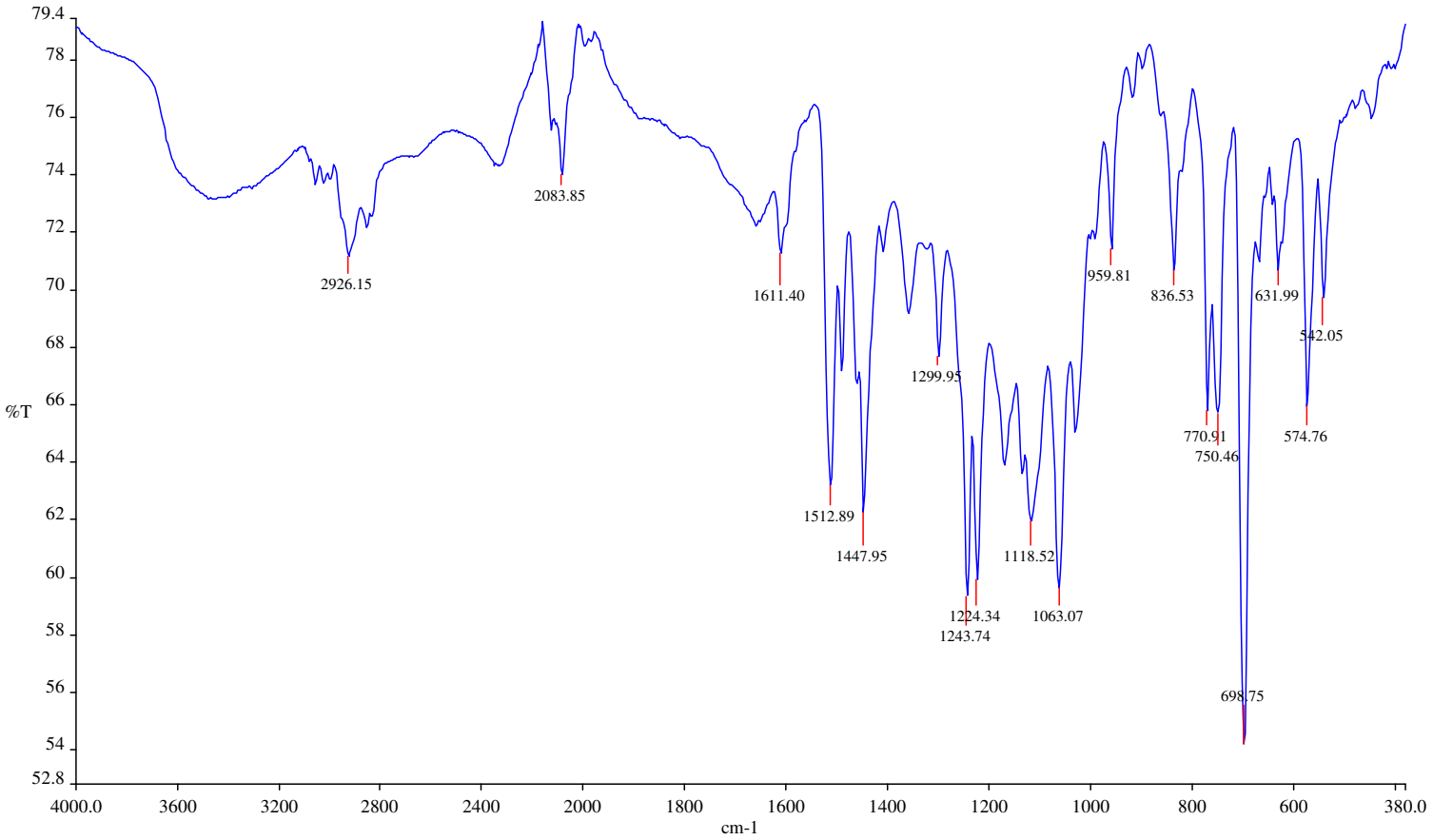
IR Spectrum of Compound **19**



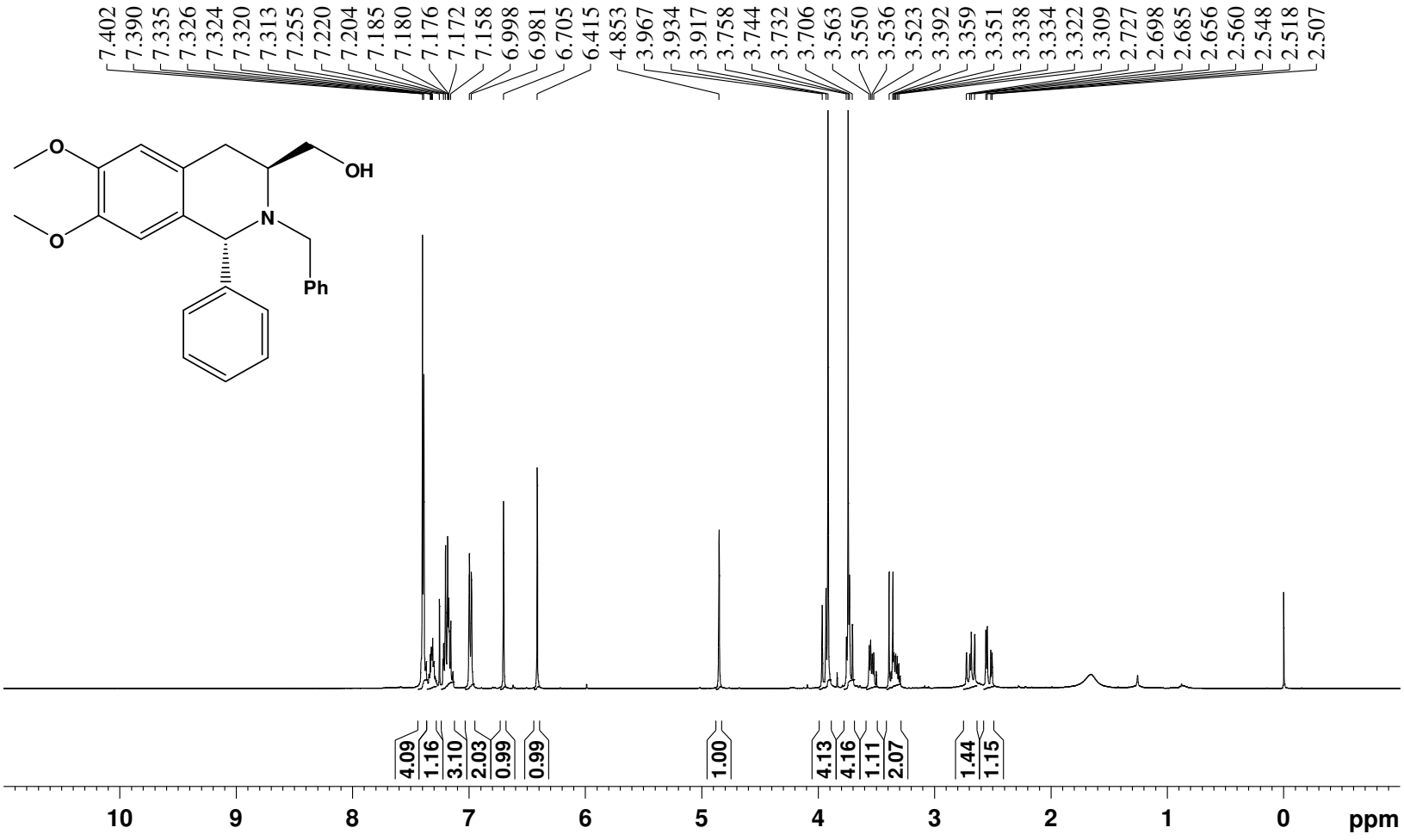
^{1}H NMR (400 MHz) Spectrum of Compound **20** in $CDCl_3$



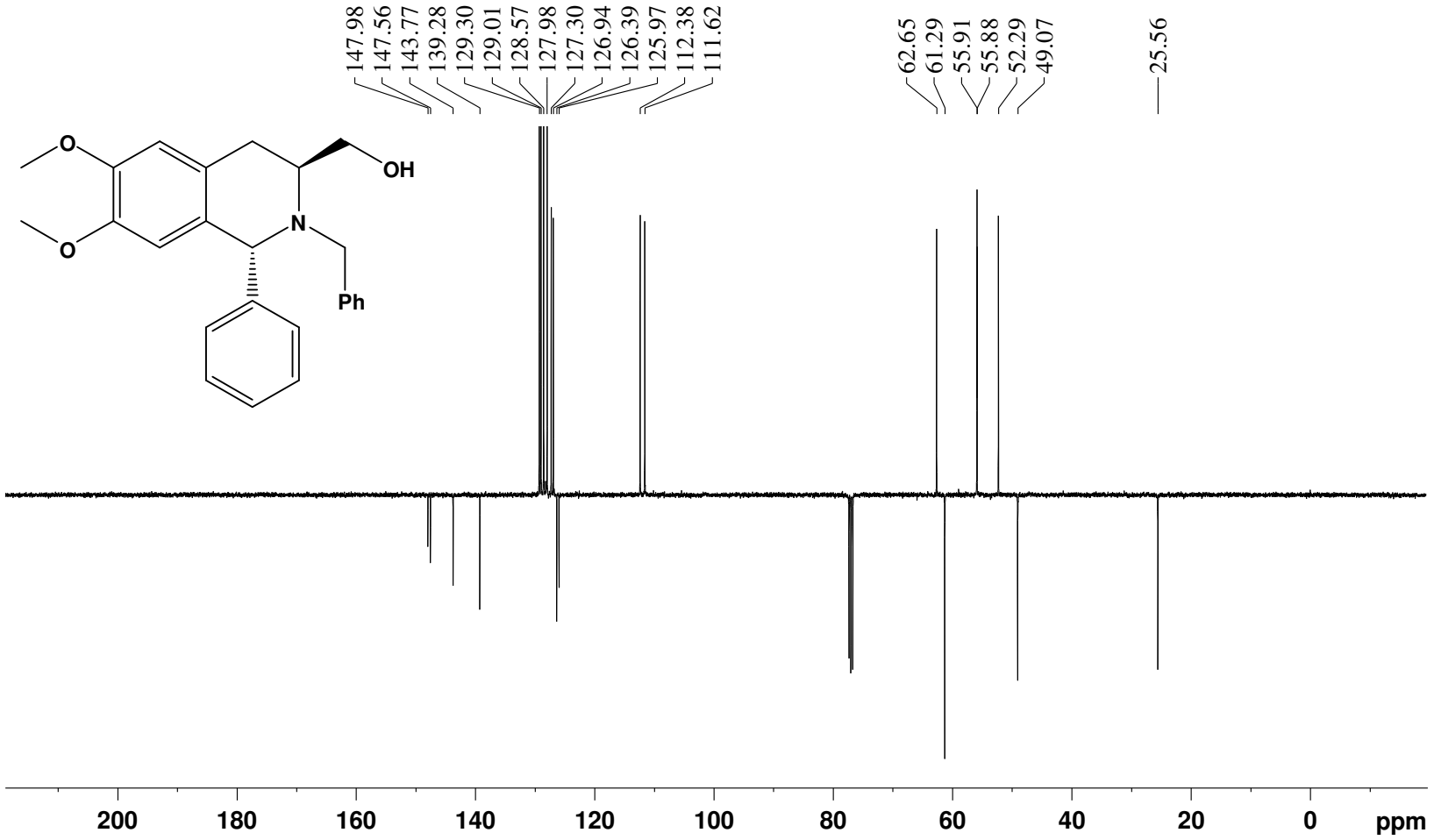
^{13}C (400 MHz) Spectrum of Compound **20** in $CDCl_3$



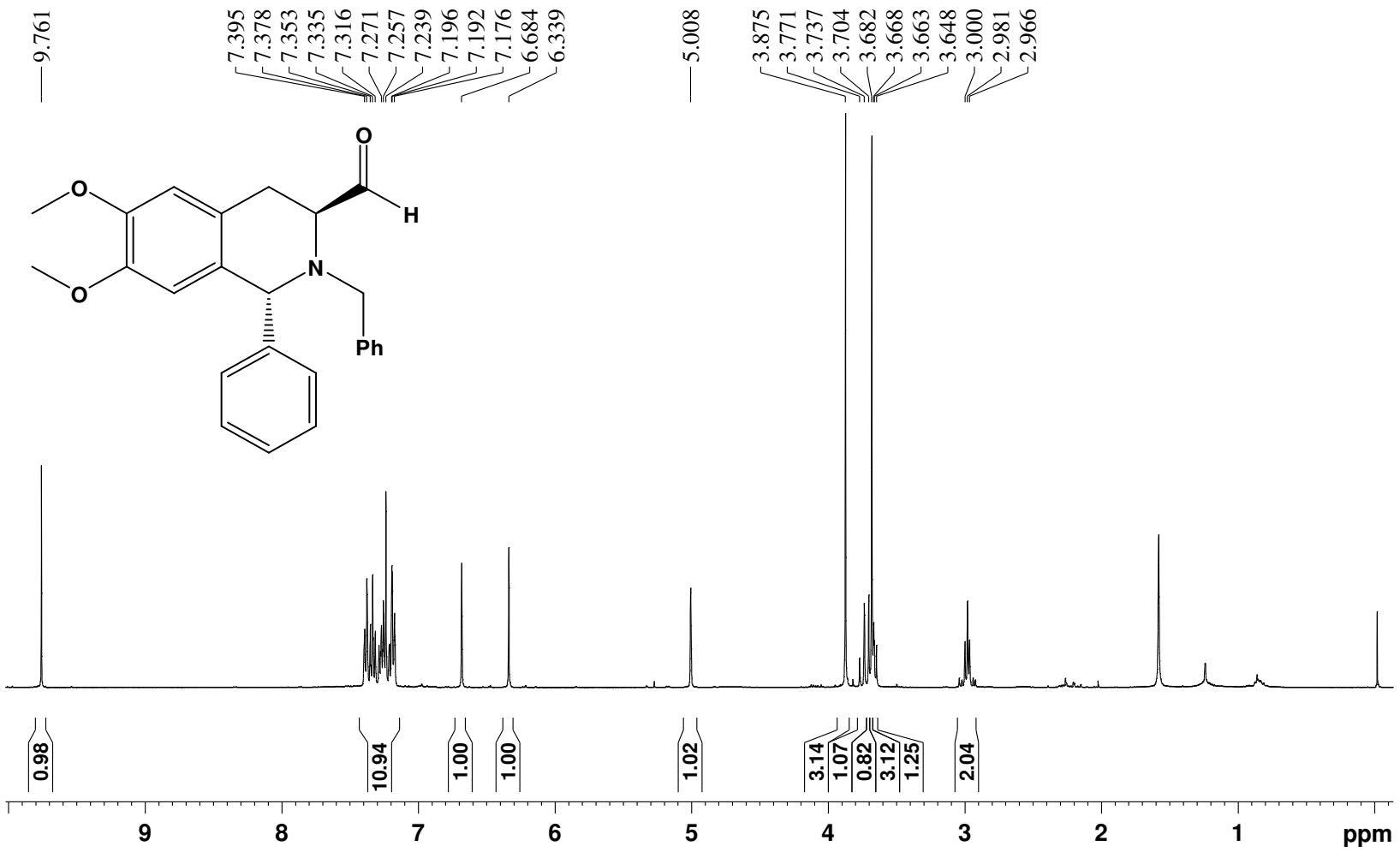
IR Spectrum of Compound **20**



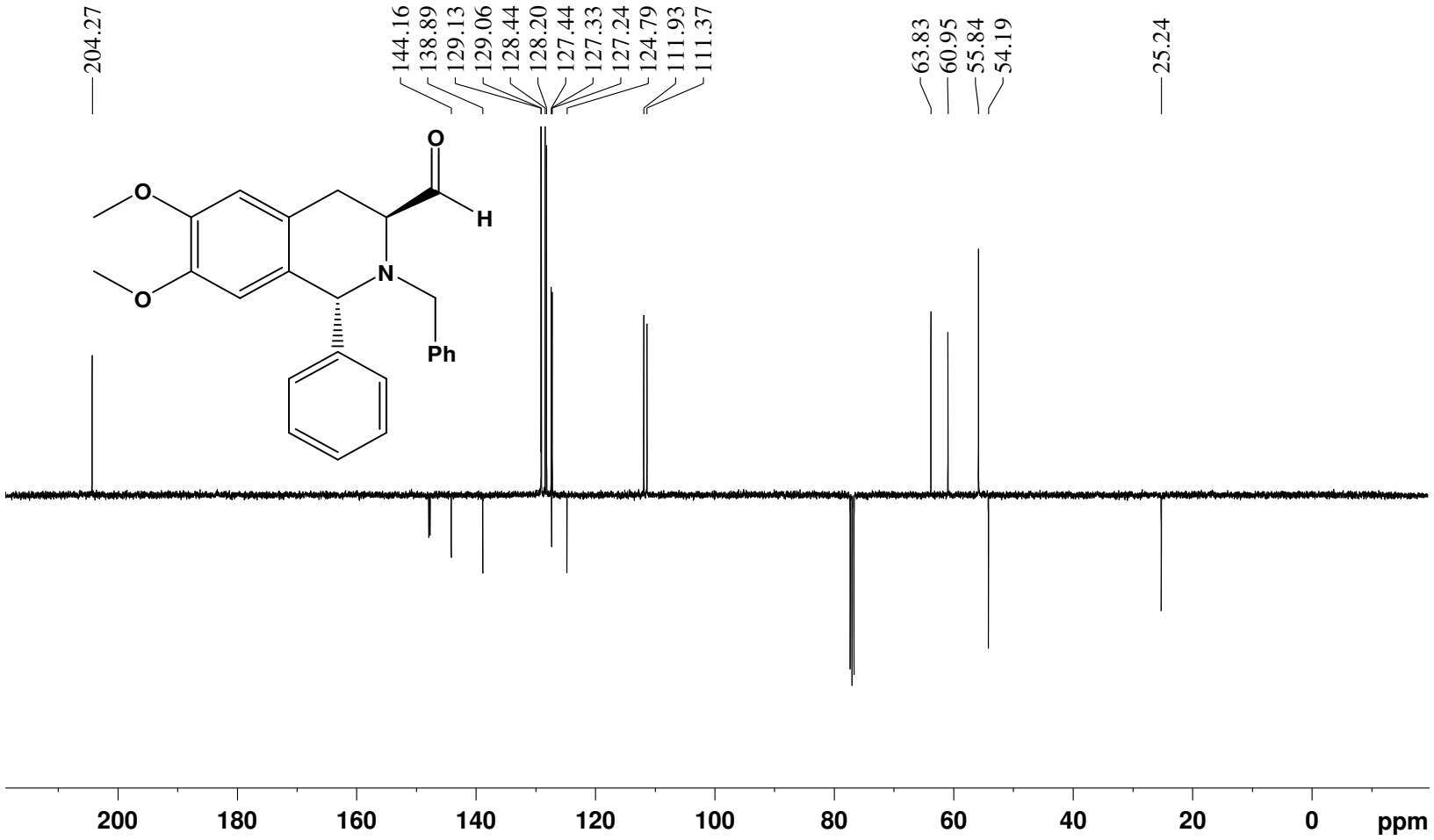
^{1}H NMR (400 MHz) Spectrum of Compound **21** in $CDCl_3$



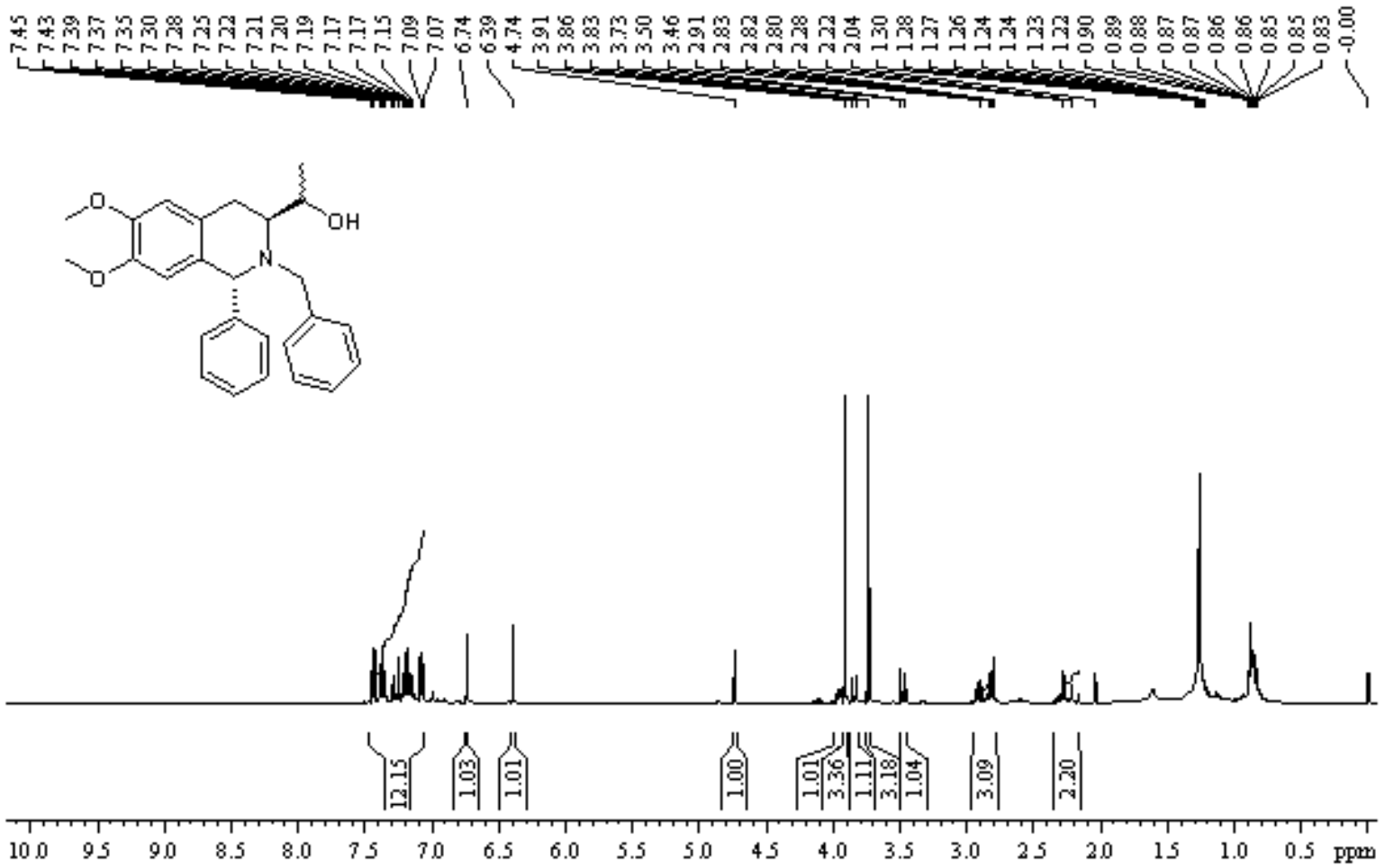
^{13}C (400 MHz) Spectrum of Compound **21** in $CDCl_3$



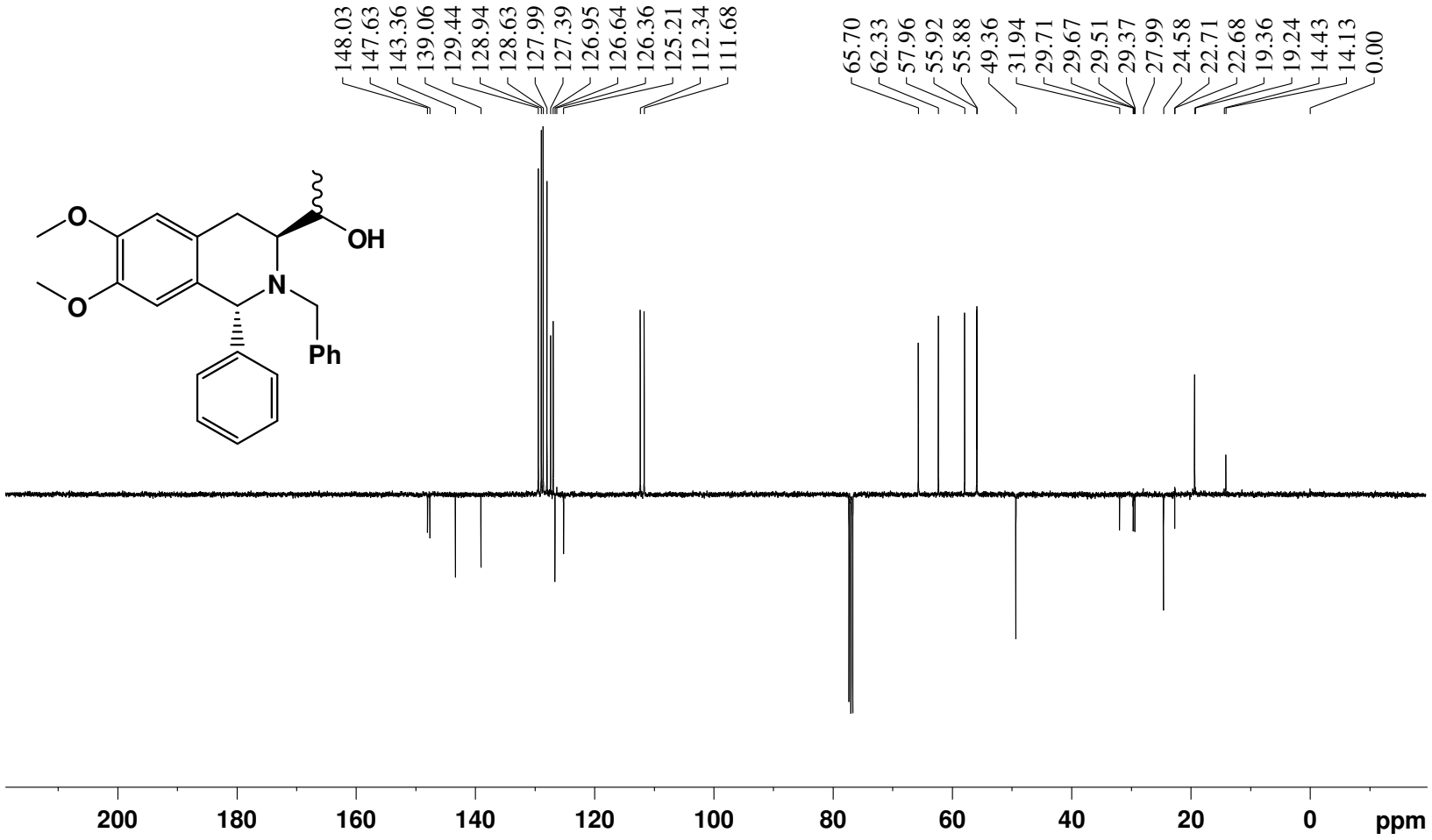
^{1}H NMR (400 MHz) Spectrum of Compound **22** in $CDCl_3$



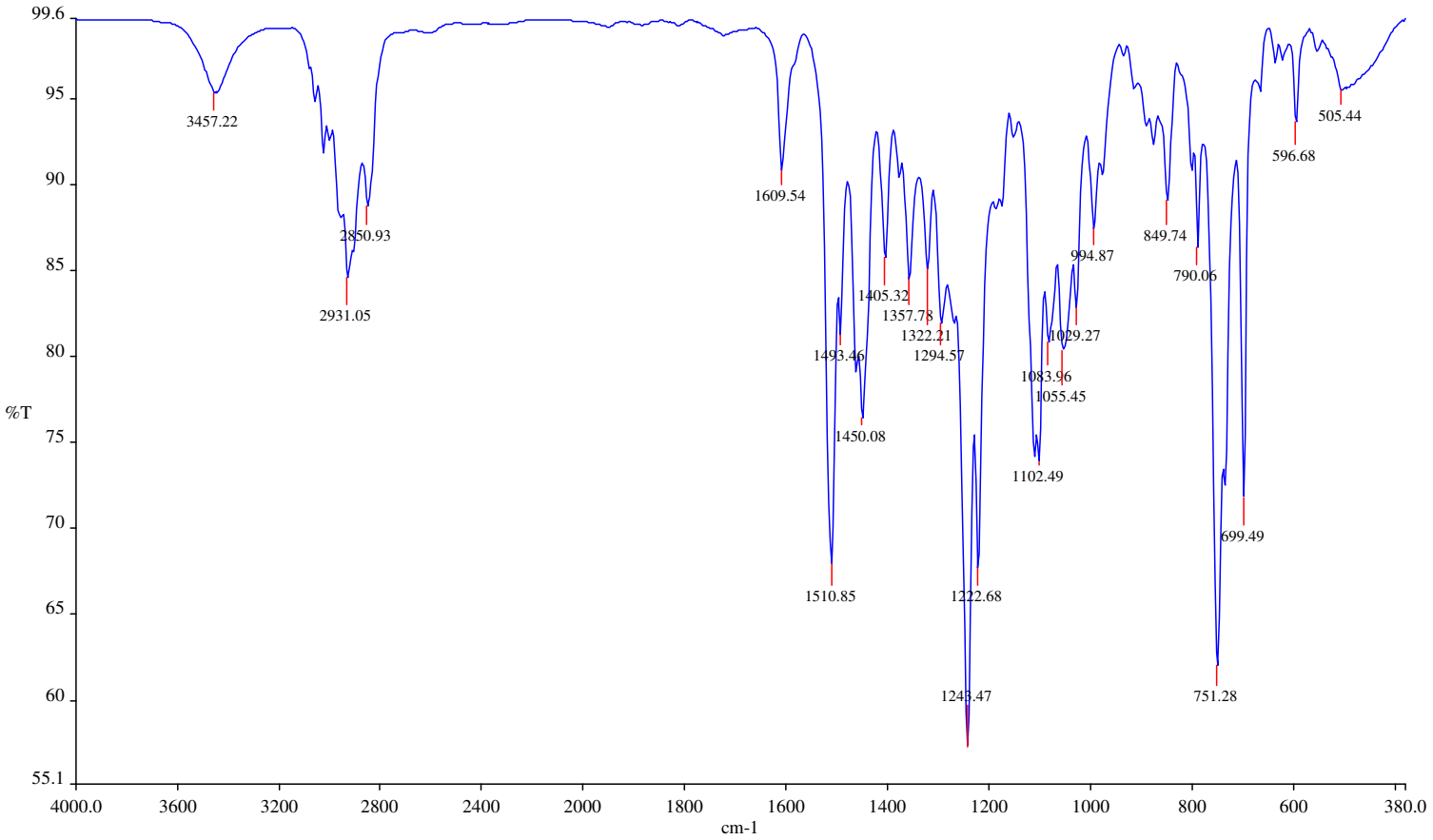
^{13}C (400 MHz) Spectrum of Compound **22** in $CDCl_3$



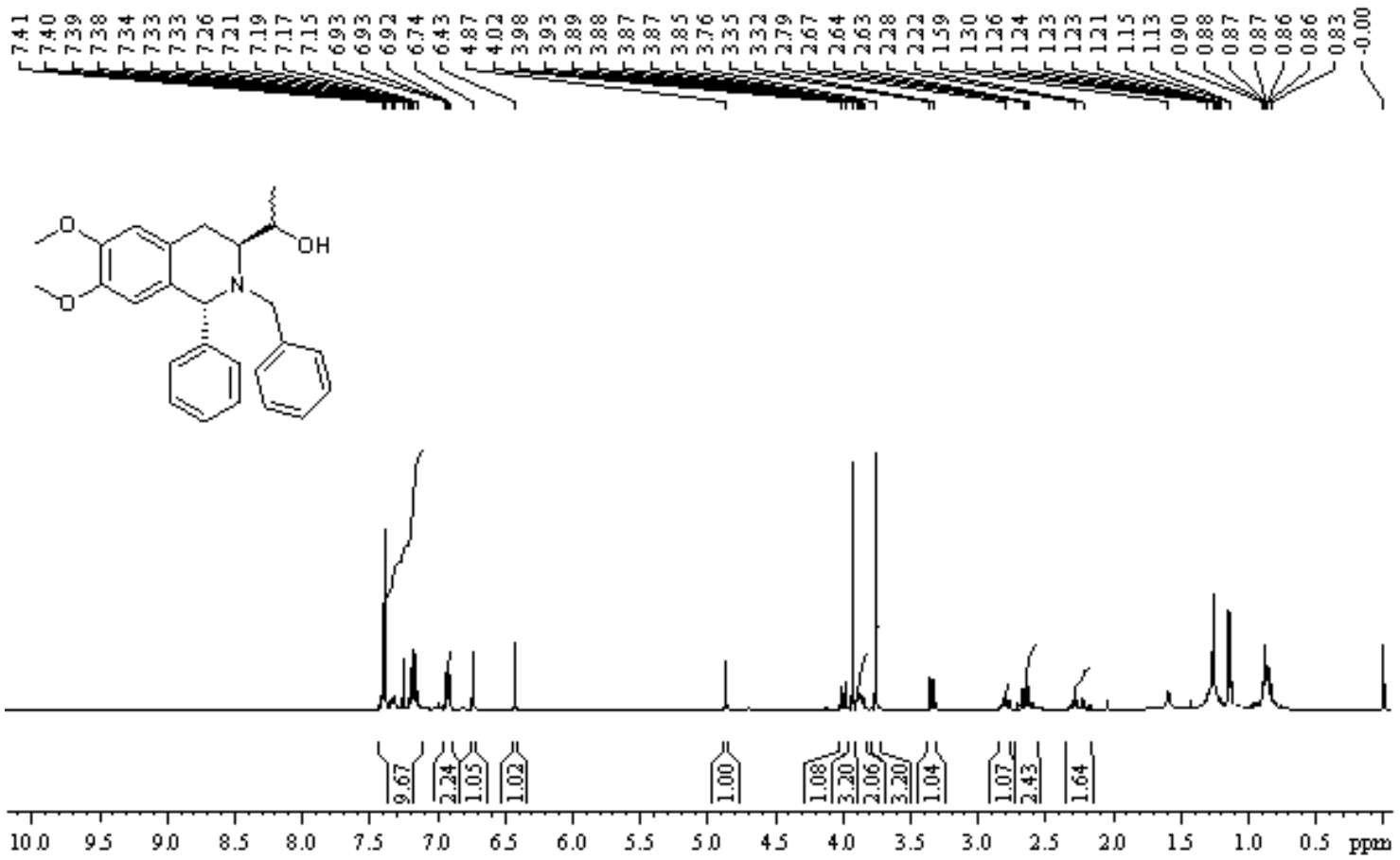
^{1}H NMR (400 MHz) Spectrum of Compound Major **23** in $CDCl_3$



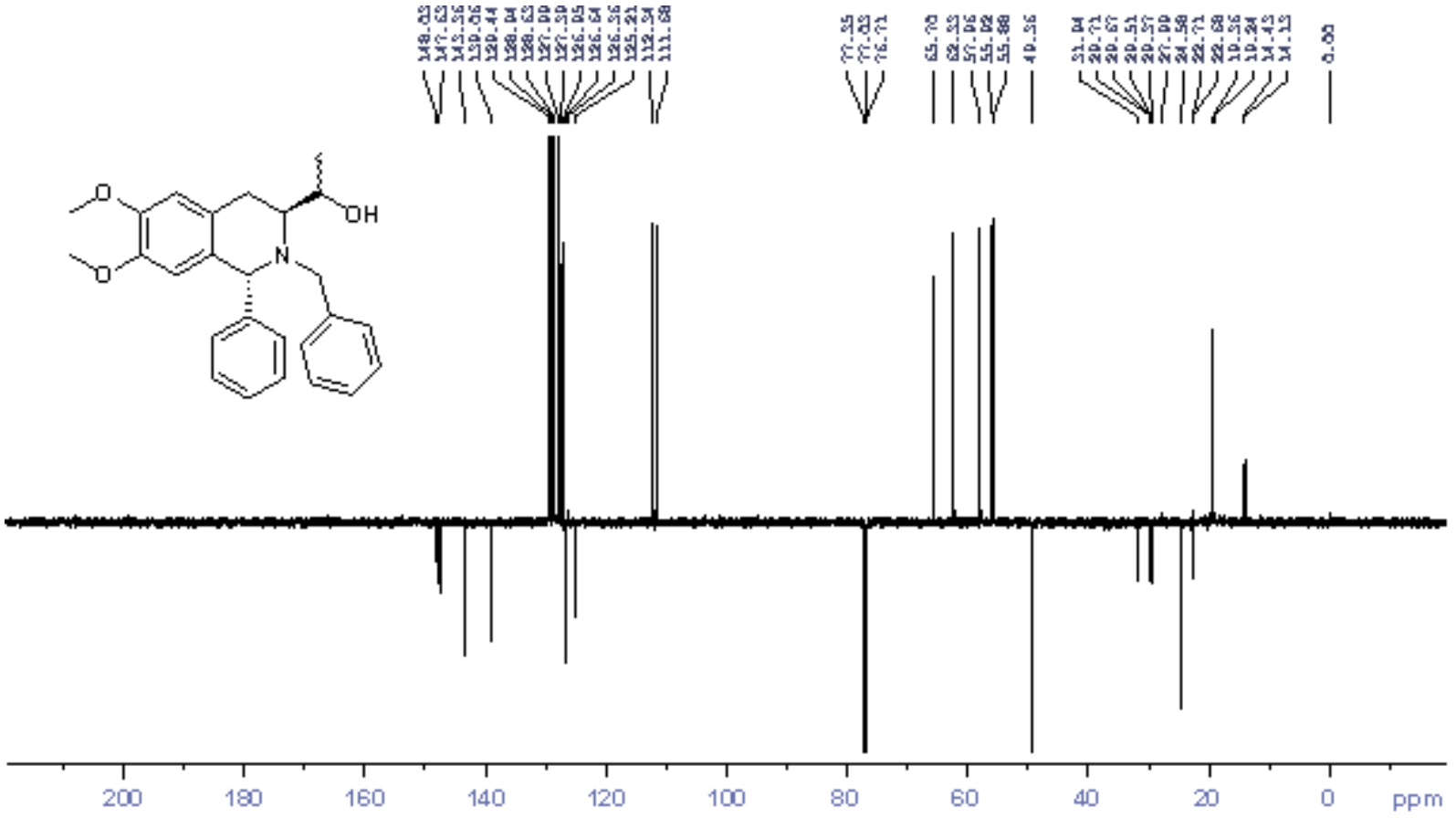
^{13}C (400 MHz) Spectrum of Compound Major **23** in $CDCl_3$



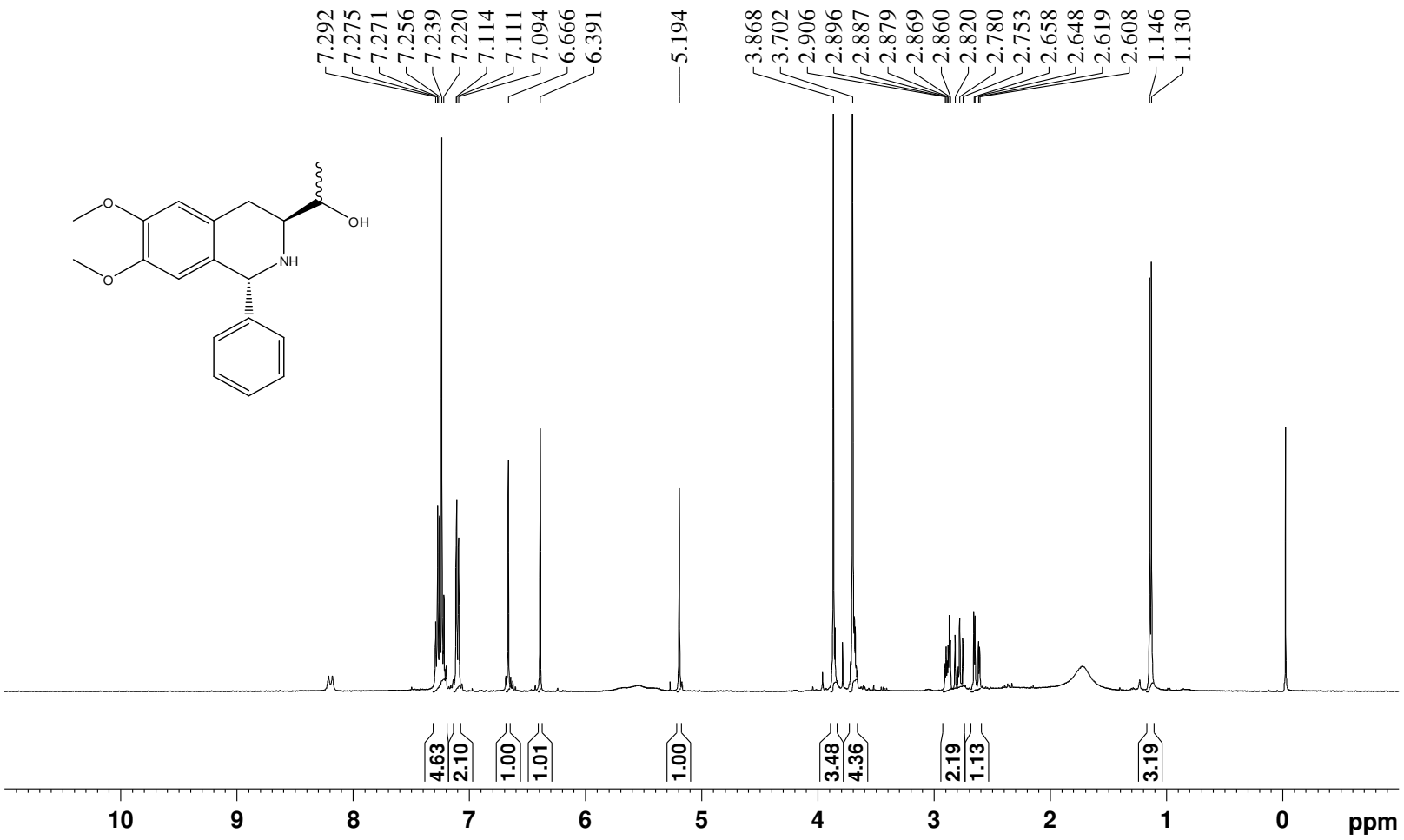
IR Spectrum of Compound Major **23**



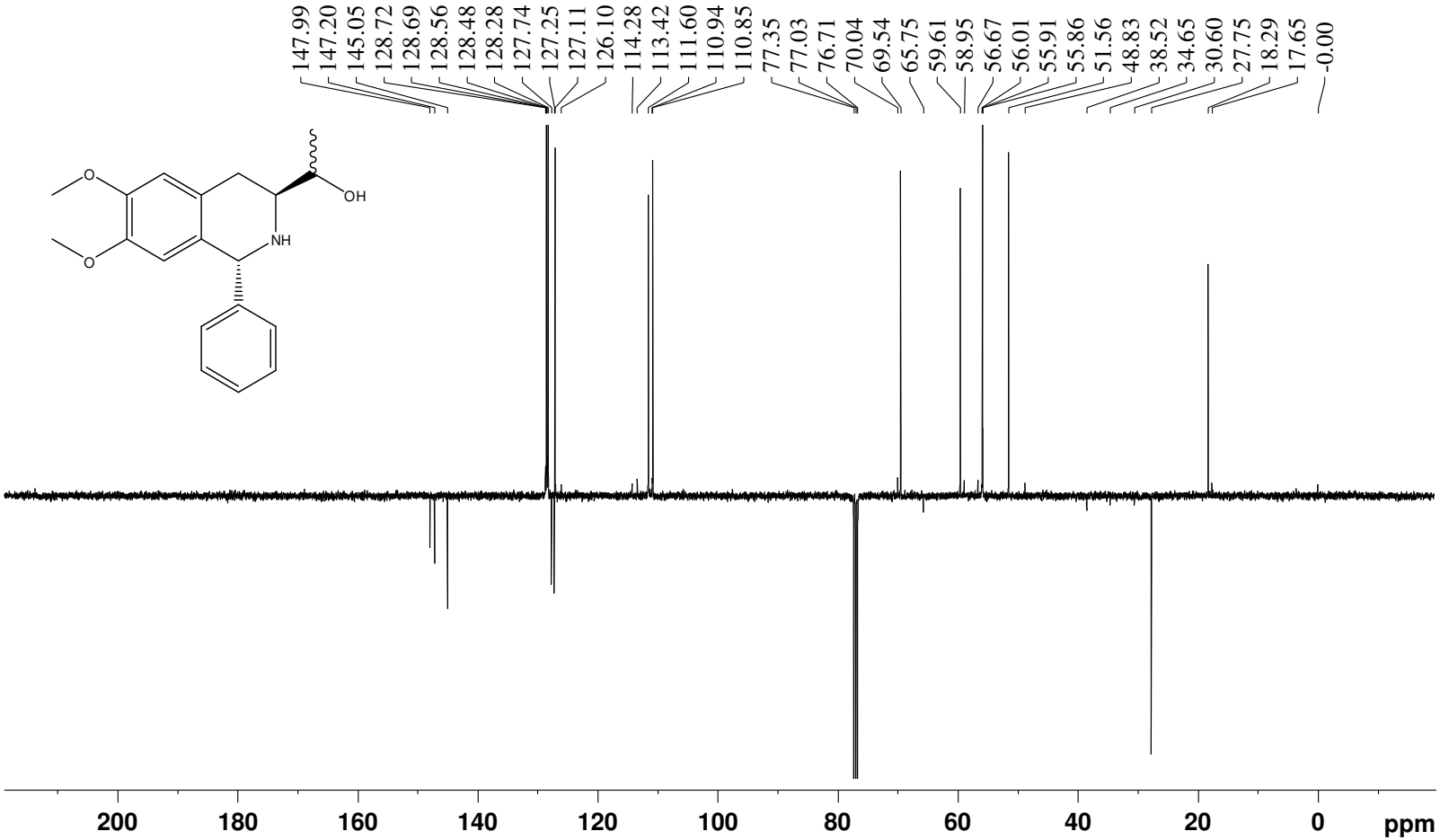
^{1}H NMR (400 MHz) Spectrum of Compound Minor **23** in $CDCl_3$



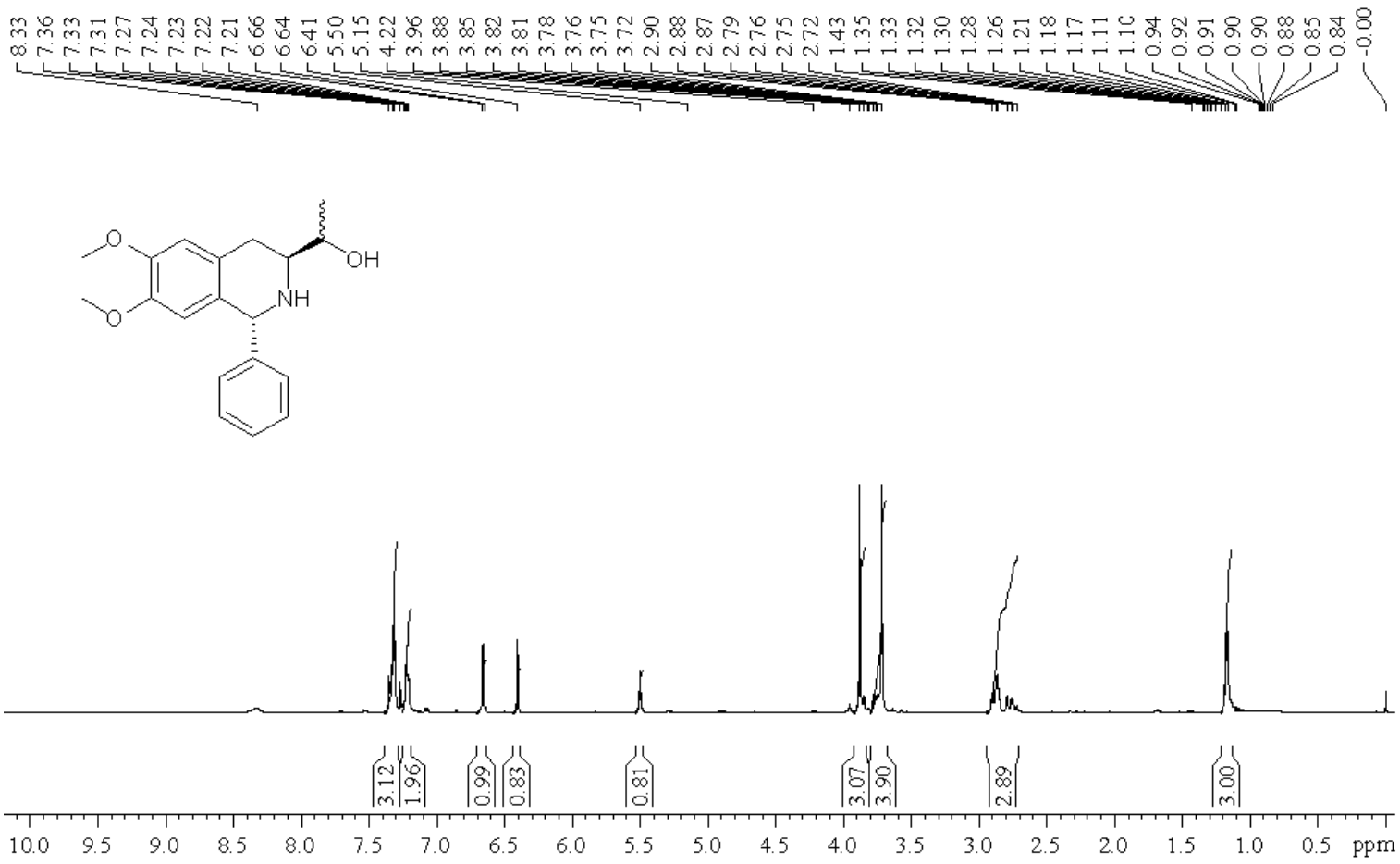
^{13}C (400 MHz) Spectrum of Compound Minor **23** in $CDCl_3$



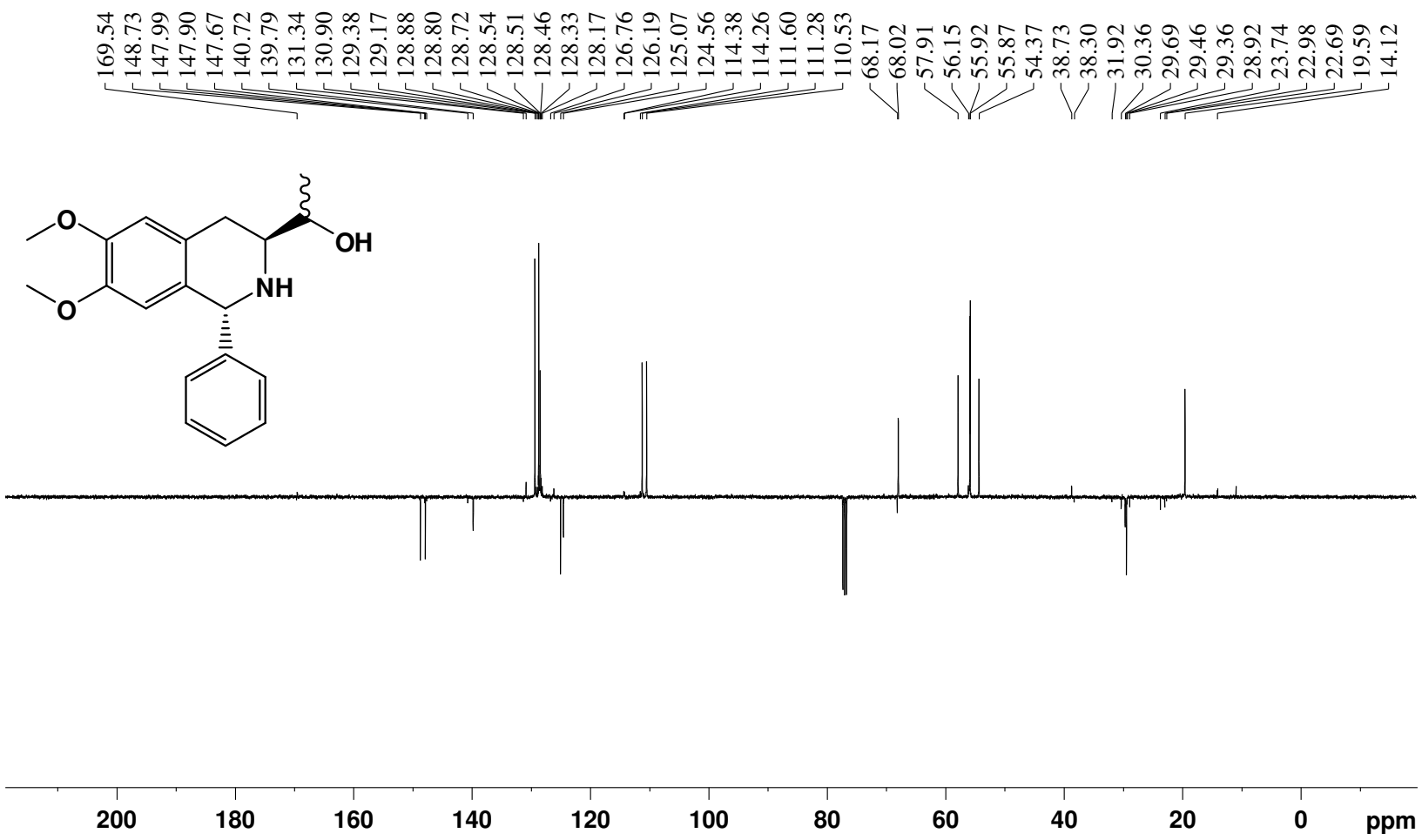
^{1}H NMR (400 MHz) Spectrum of Compound Major **24** in $CDCl_3$



^{13}C (400 MHz) Spectrum of Compound Major **24** in $CDCl_3$



^{1}H NMR (400 MHz) Spectrum of Compound Minor **24** in $CDCl_3$



^{13}C (400 MHz) Spectrum of Compound Minor **24** in $CDCl_3$

Display Report

Analysis Info

Analysis Name	D:\Data\sai\tiq000018.d	Acquisition Date	9/23/2009 7:50:12 PM
Method	tune_wide_expert.m	Operator	BDAL@DE
Sample Name	tiq	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

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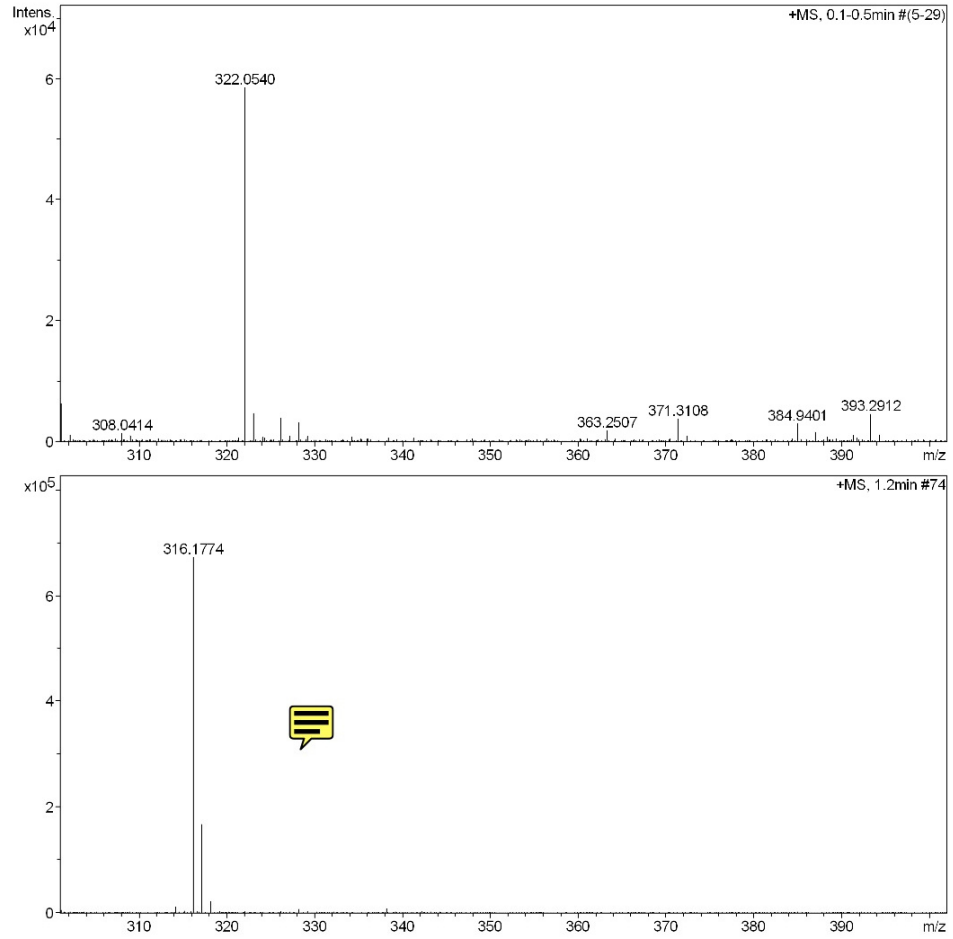
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 9/23/2009 8:41:50 PM Page 1 of 1

High Resolution Mass Spectrum of Compound **8**

Display Report

Analysis Info

Analysis Name	D:\Data\sai\tiq000016.d	Acquisition Date	9/23/2009 7:40:42 PM
Method	tune_wide_expert.m	Operator	BDAL@DE
Sample Name	tiq	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
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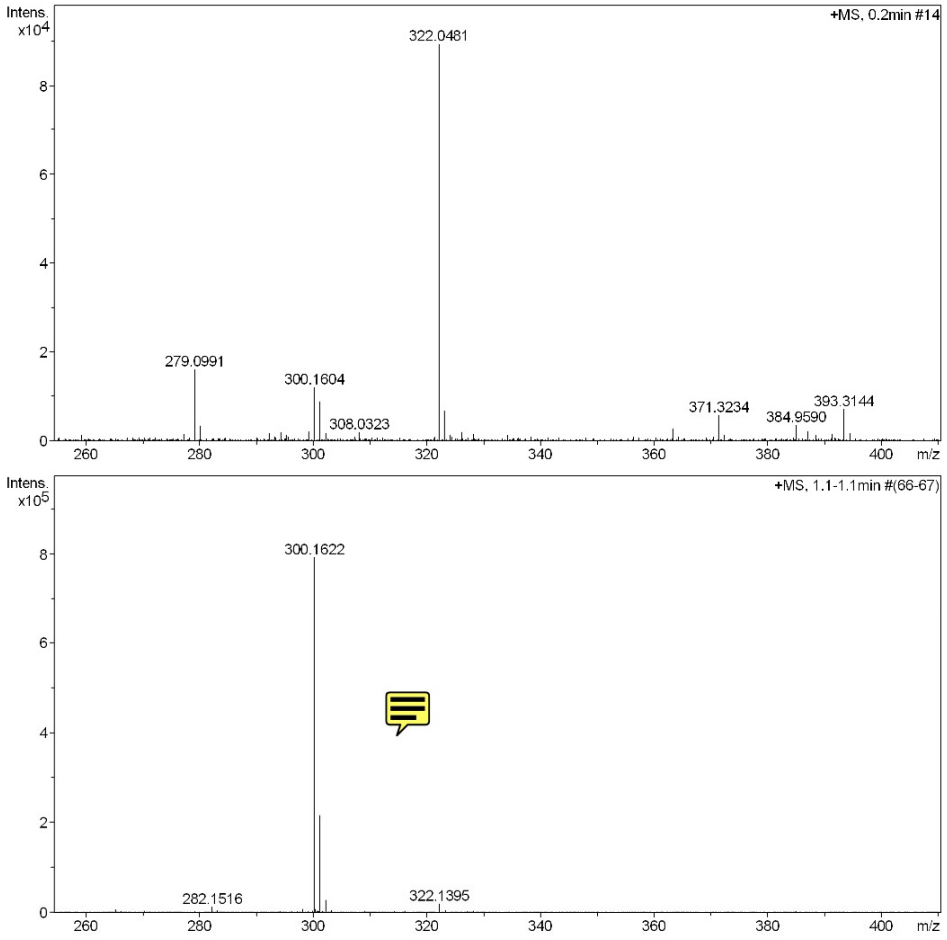
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 9/23/2009 8:27:56 PM Page 1 of 1

High Resolution Mass Spectrum of Compound **14**

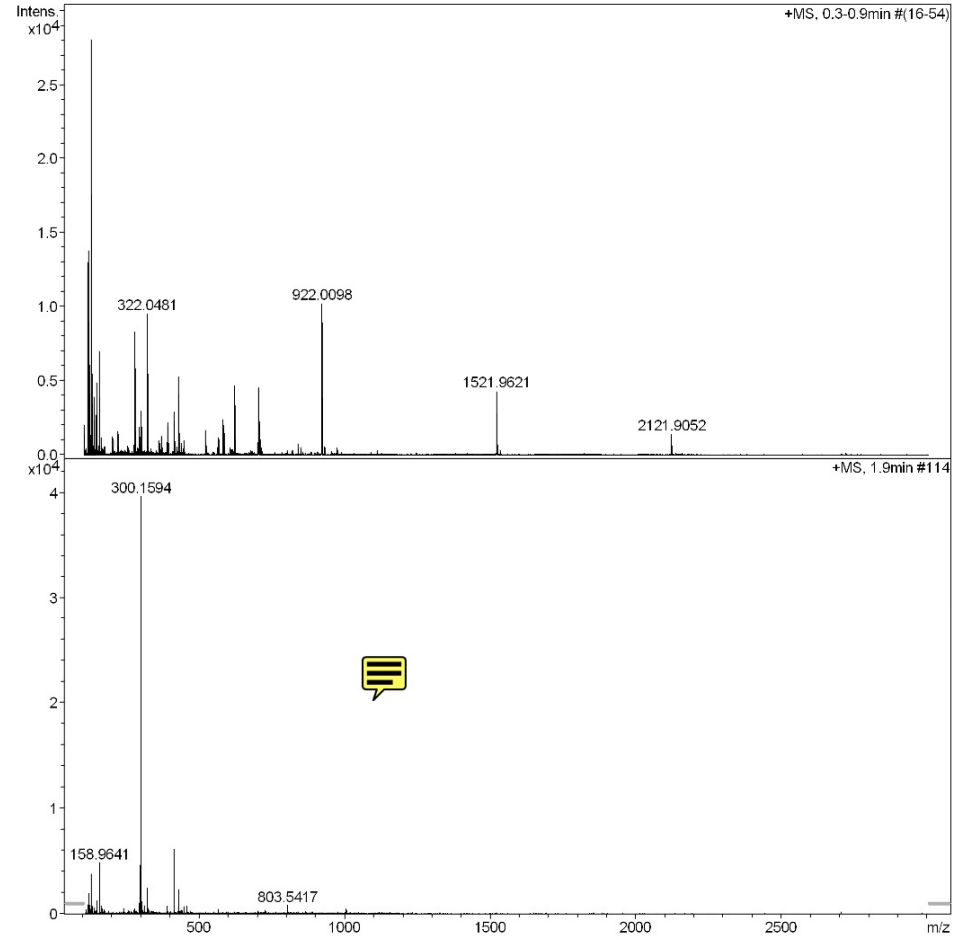
Display Report

Analysis Info

Analysis Name	D:\Data\sai\tiq000006.d	Acquisition Date	6/20/2009 2:46:36 PM
Method	tune_low_expert.m	Operator	BDAL@DE
Sample Name	tiq	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 9/23/2009 5:13:10 PM Page 1 of 1

High Resolution Mass Spectrum of Compound **17**

Display Report

Analysis Info

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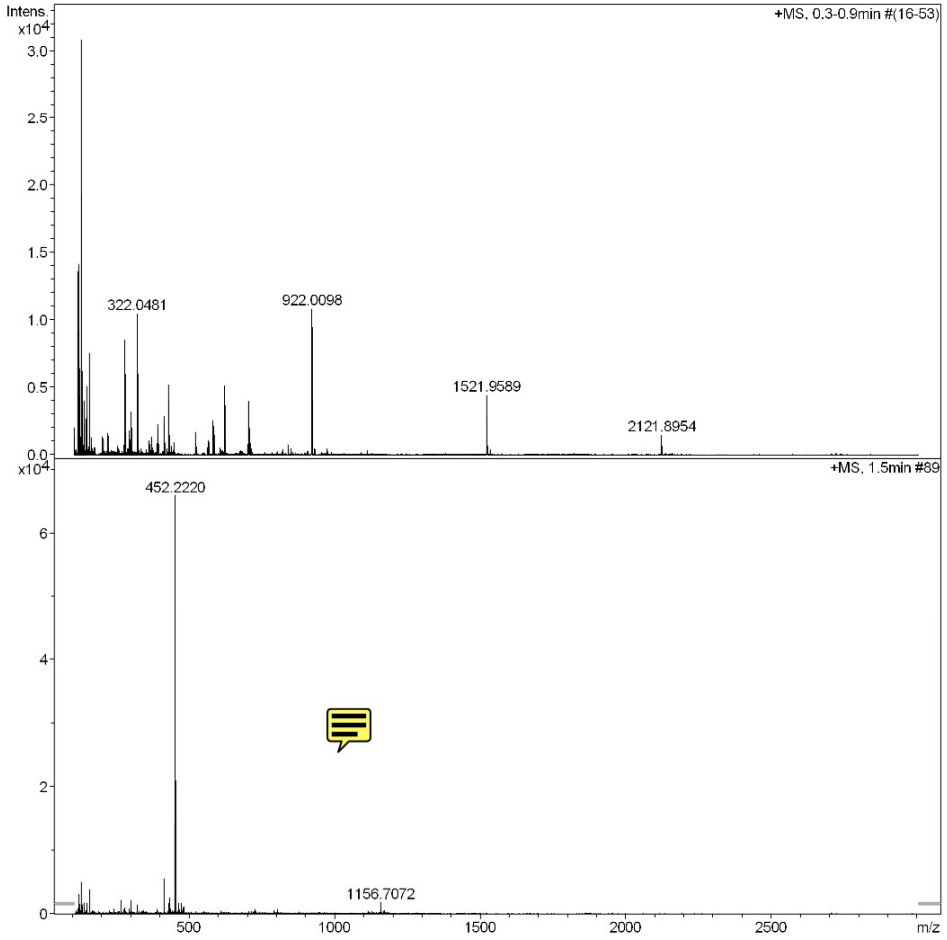
Method	tune_low_expert.m	Operator	BDAL@DE
Sample Name	tiq	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 9/23/2009 5:17:11 PM Page 1 of 1

High Resolution Mass Spectrum of Compound **20**

Display Report

Analysis Info

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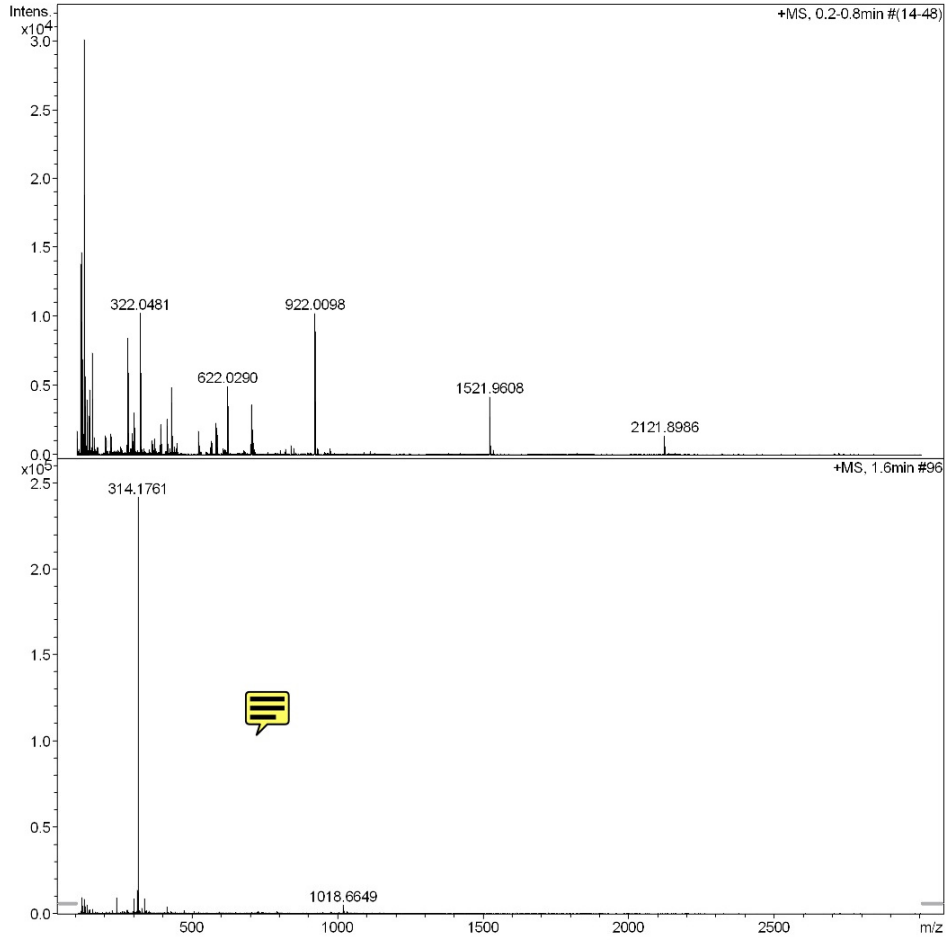
Method	tune_low_expert.m	Operator	BDAL@DE
Sample Name	tiq	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 9/23/2009 5:28:20 PM Page 1 of 1

High Resolution Mass Spectrum of Compound **Major 24**

Display Report

Analysis Info

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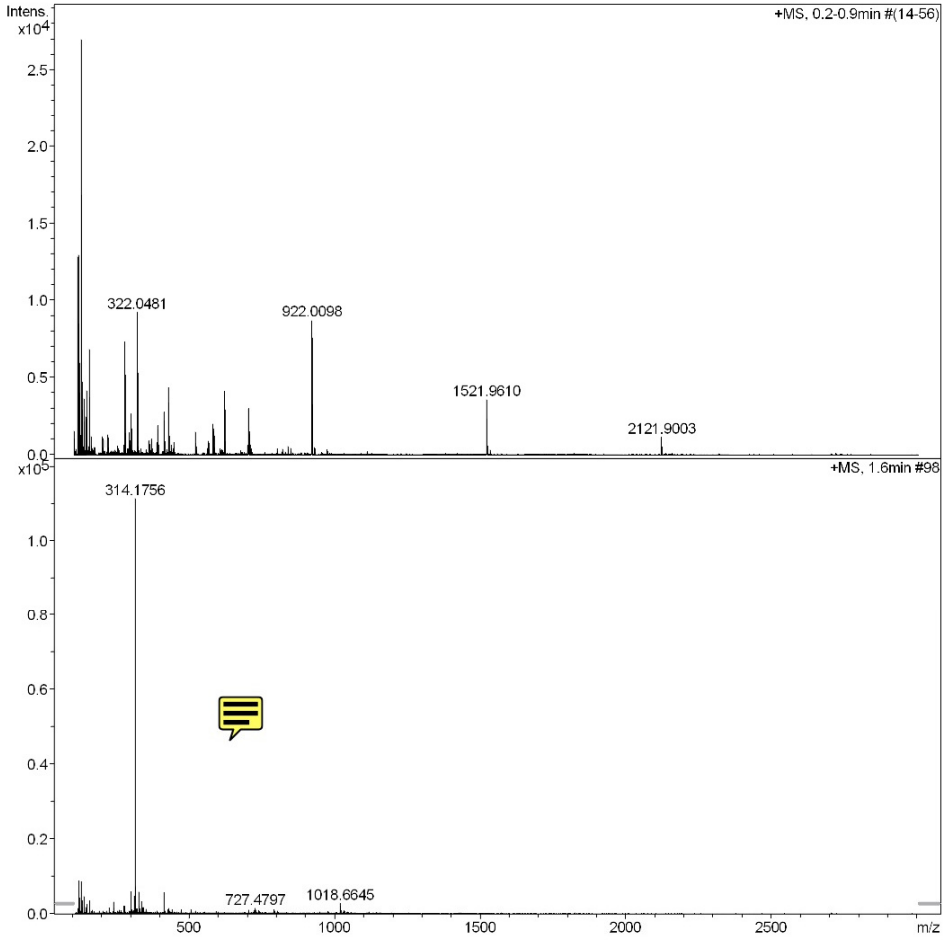
Method	tune_low_expert.m	Operator	BDAL@DE
Sample Name	tiq	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 9/23/2009 5:29:20 PM Page 1 of 1

High Resolution Mass Spectrum of Compound **Minor 24**

APPENDIX 2

SYNTHESIS OF TETRAHYDROISOQUINOLINE-DIAMINE LIGANDS AND THEIR APPLICATION IN ASYMMETRIC TRANSFER HYDROGENATION

SUPPLAMENTARY INFORMATION FOR CHAPTER 3

Byron K. Peters,[a] Sai Kumar Chakka,[a] Tricia Naicker,[a] Pher G. Andersson,[b] Glenn E. M. Maguire,[a] Hendrik G. Kruger,*[a] and Thavendran Govender*[c]

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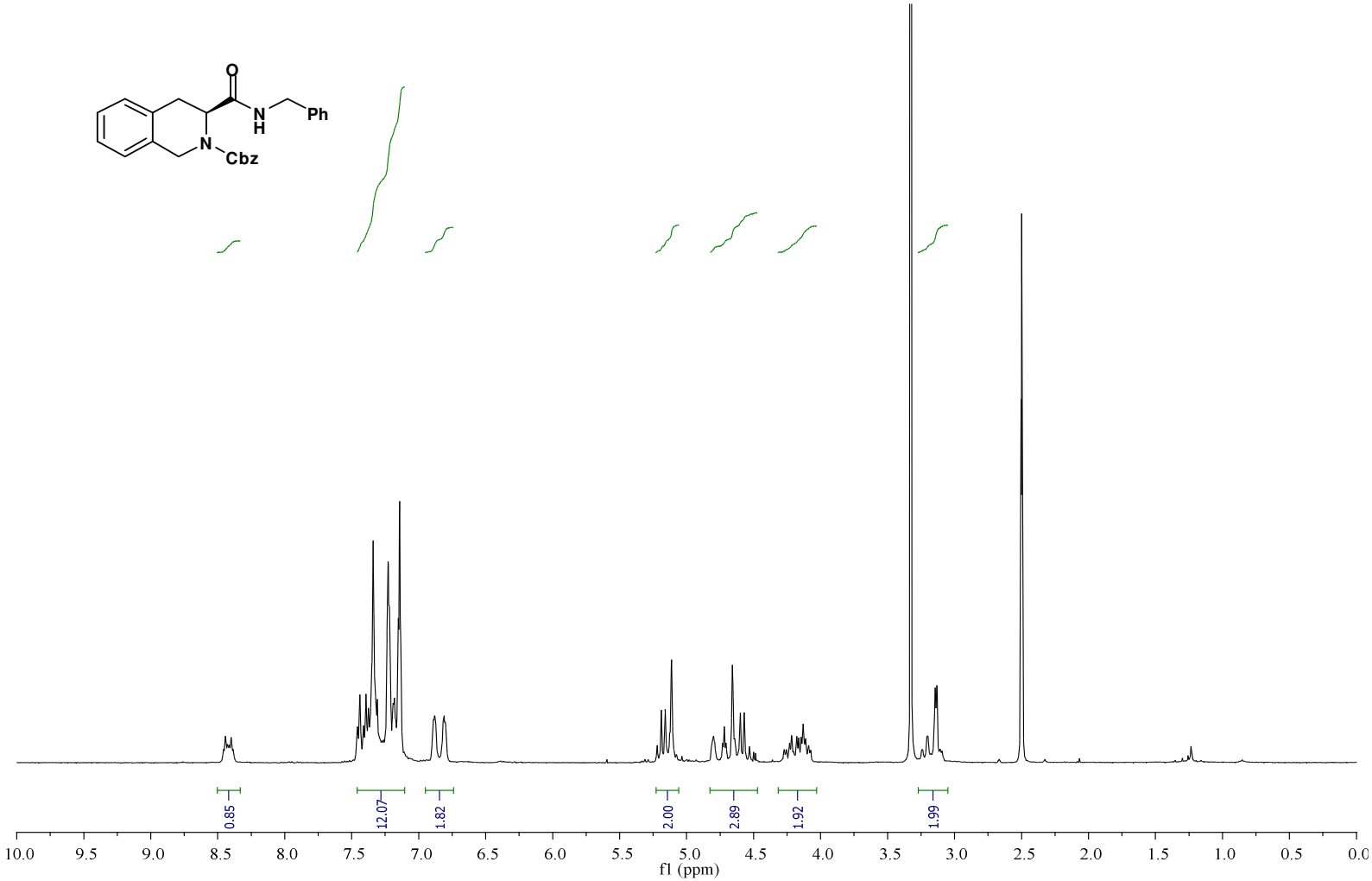
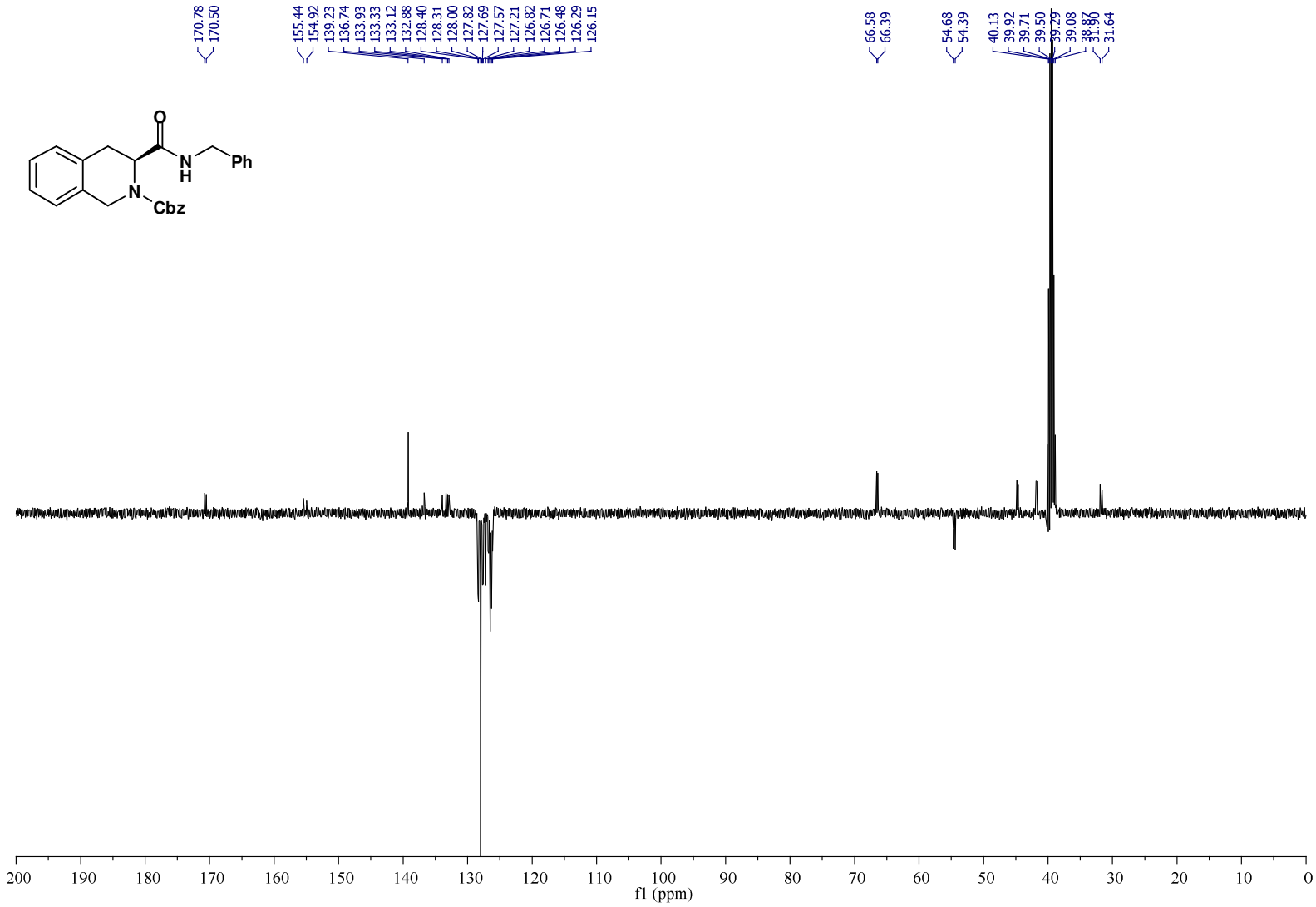
bDepartment of Organic Chemistry, Uppsala University, Uppsala, Sweden

cDepartment of Pharmacy, University of KwaZulu-Natal, Durban, South Africa

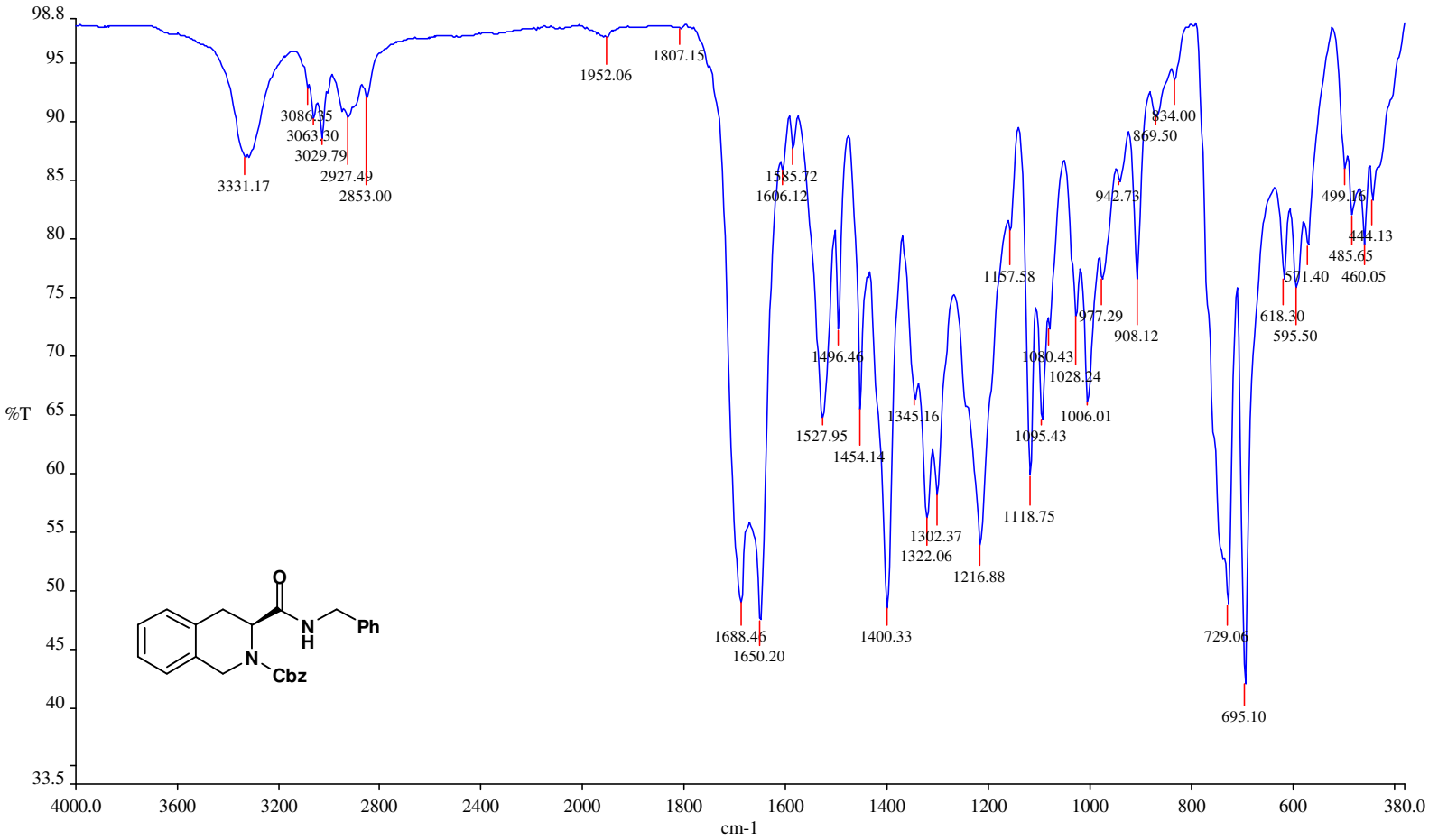
***Corresponding Author: email: govenderthav@ukzn.ac.za**



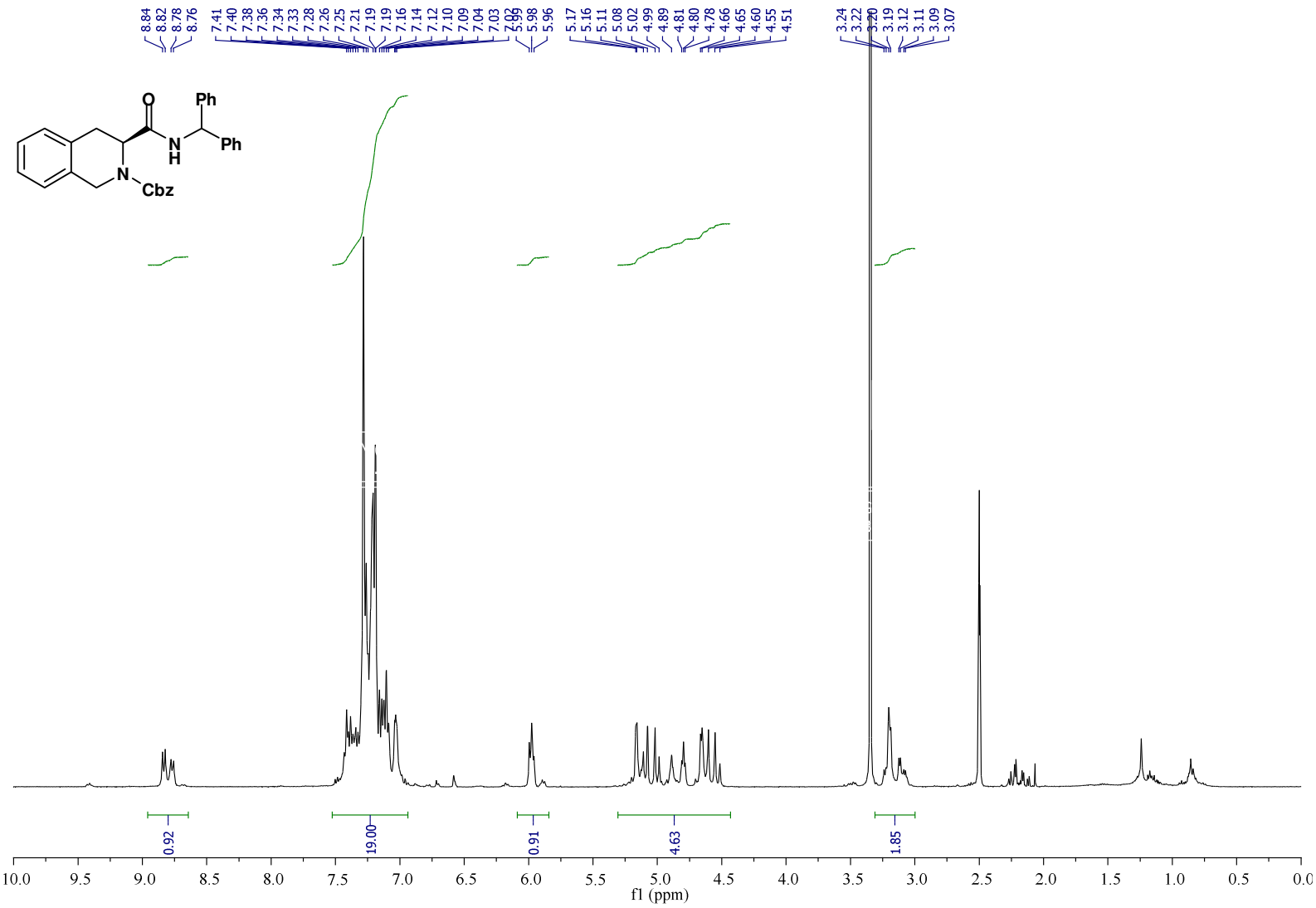
^{1}H NMR (400 MHz) Spectrum of Compound **5a** in d6-DMSO



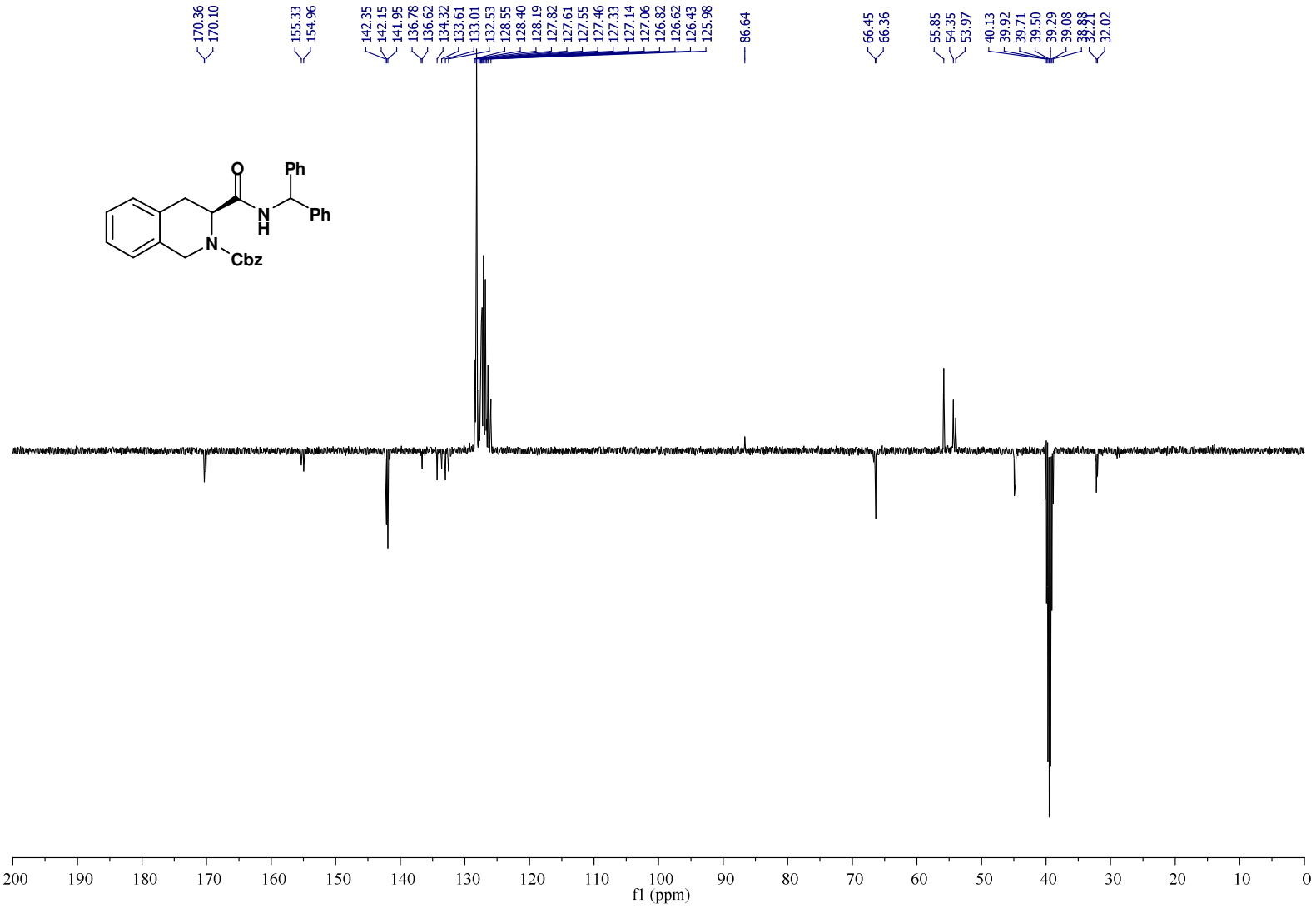
^{13}C NMR (400 MHz) Spectrum of Compound **5a** in d6-DMSO



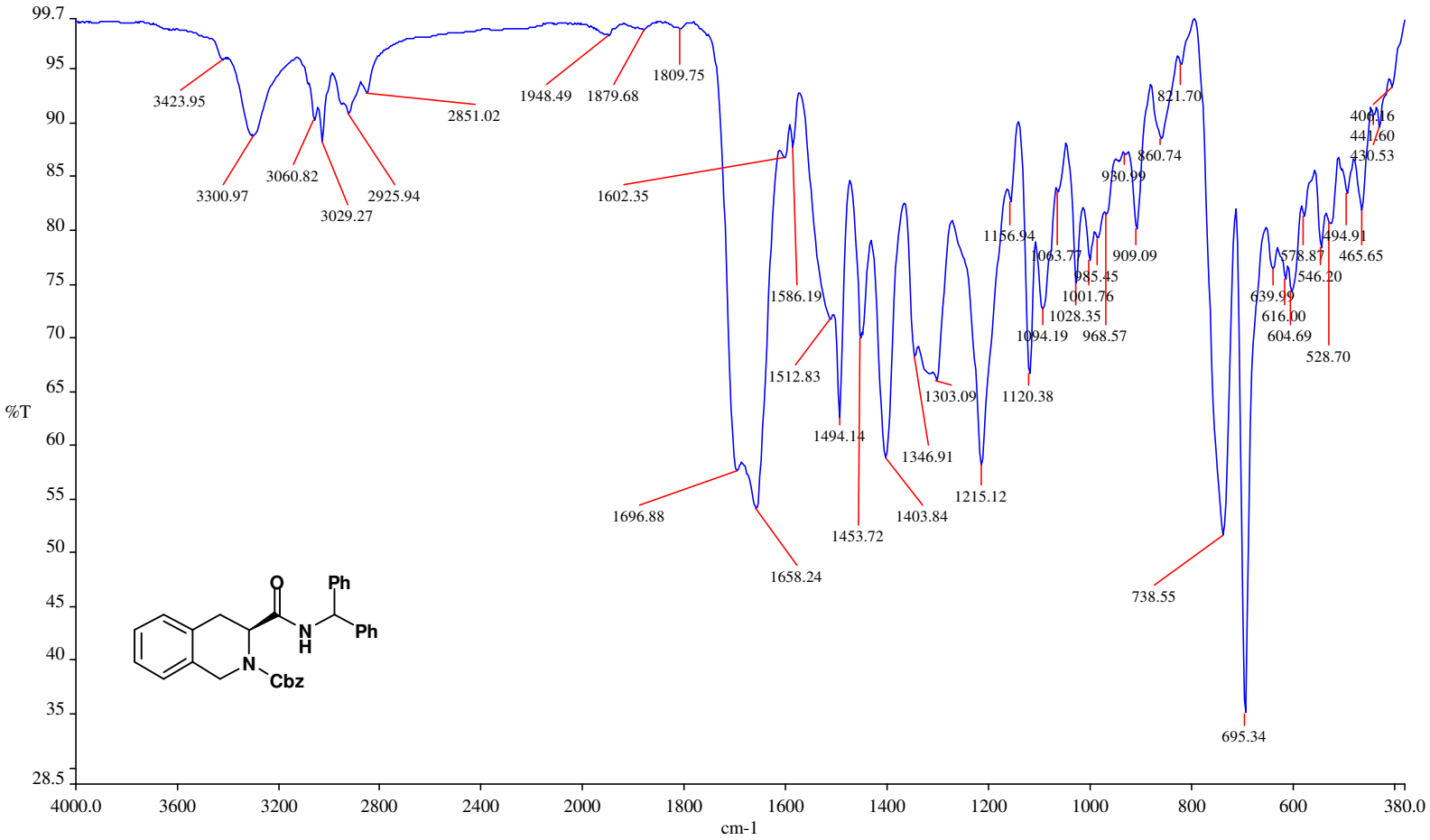
IR Spectrum of Compound **5a**



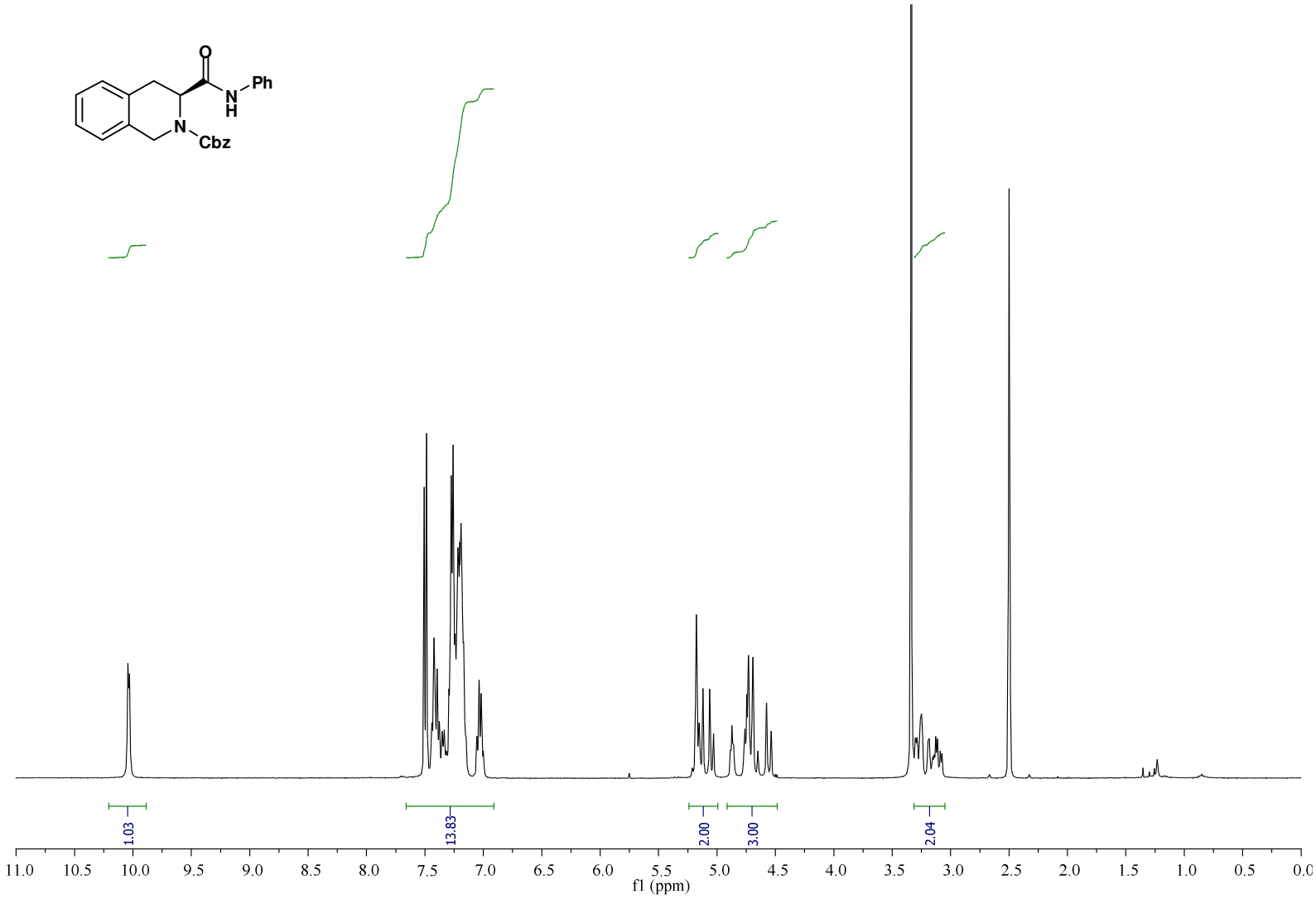
^{1}H NMR (400 MHz) Spectrum of Compound **5b** in d6-DMSO



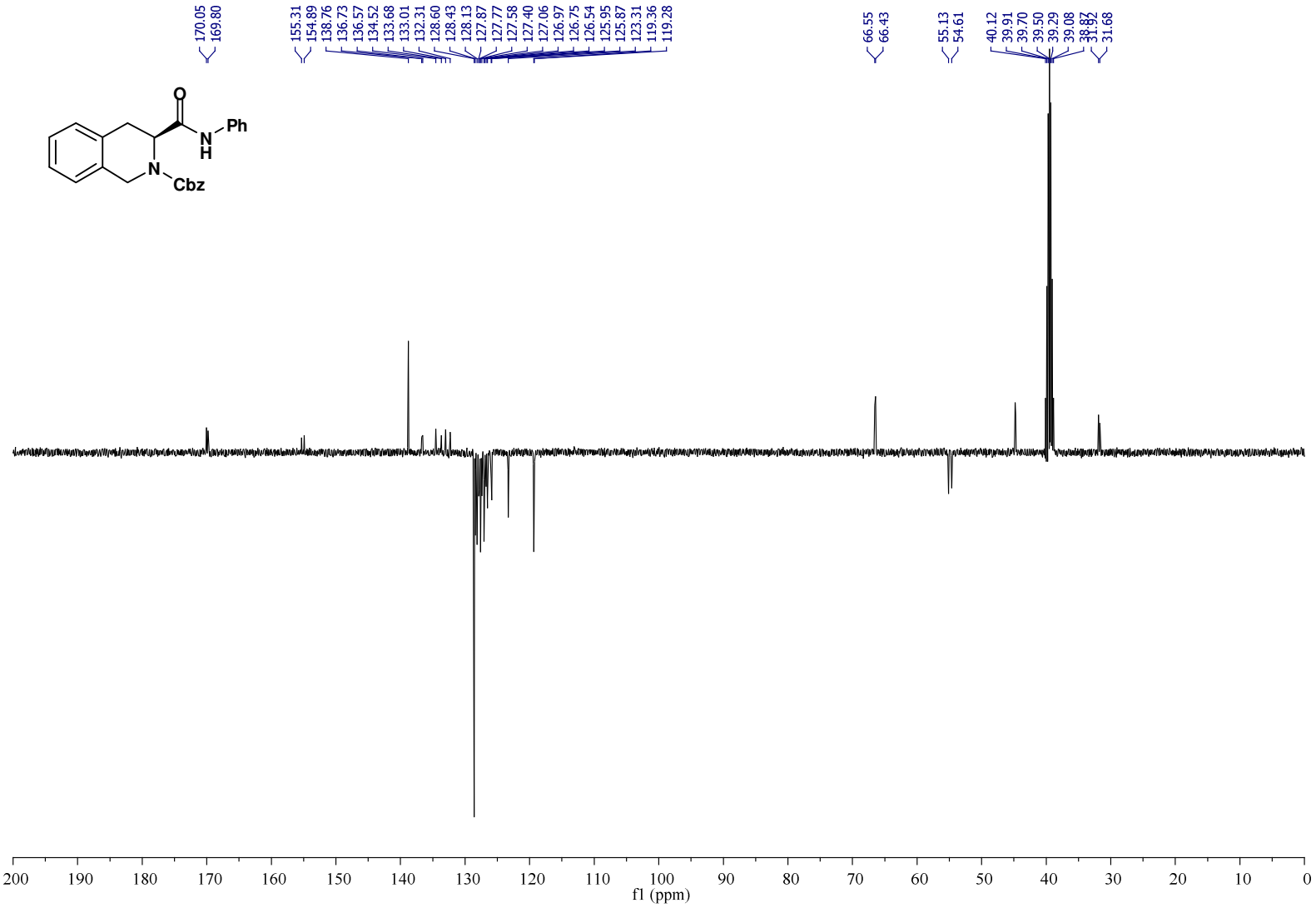
^{13}C NMR (400 MHz) Spectrum of Compound **5b** in d6-DMSO



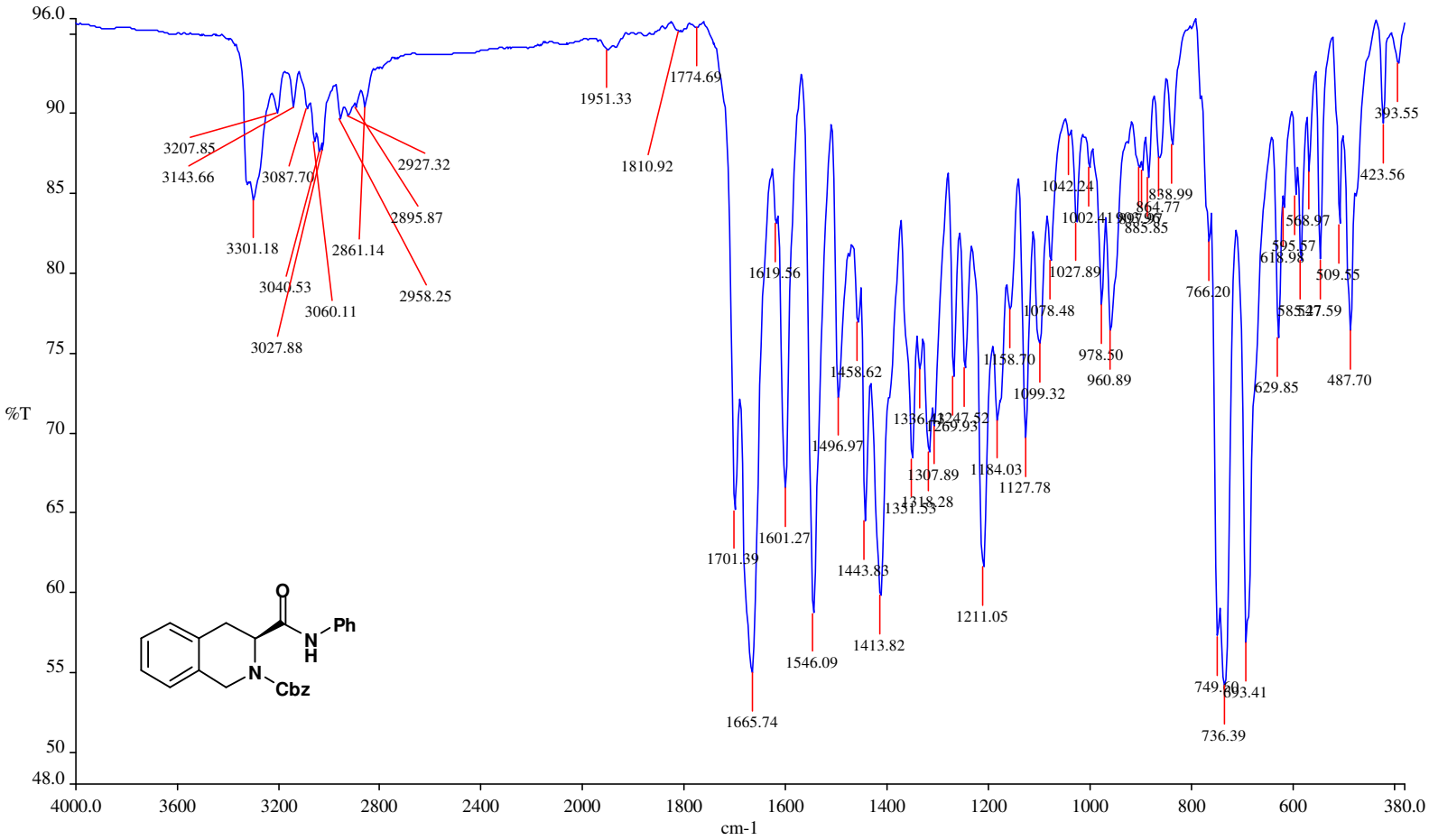
IR Spectrum of Compound **5d**



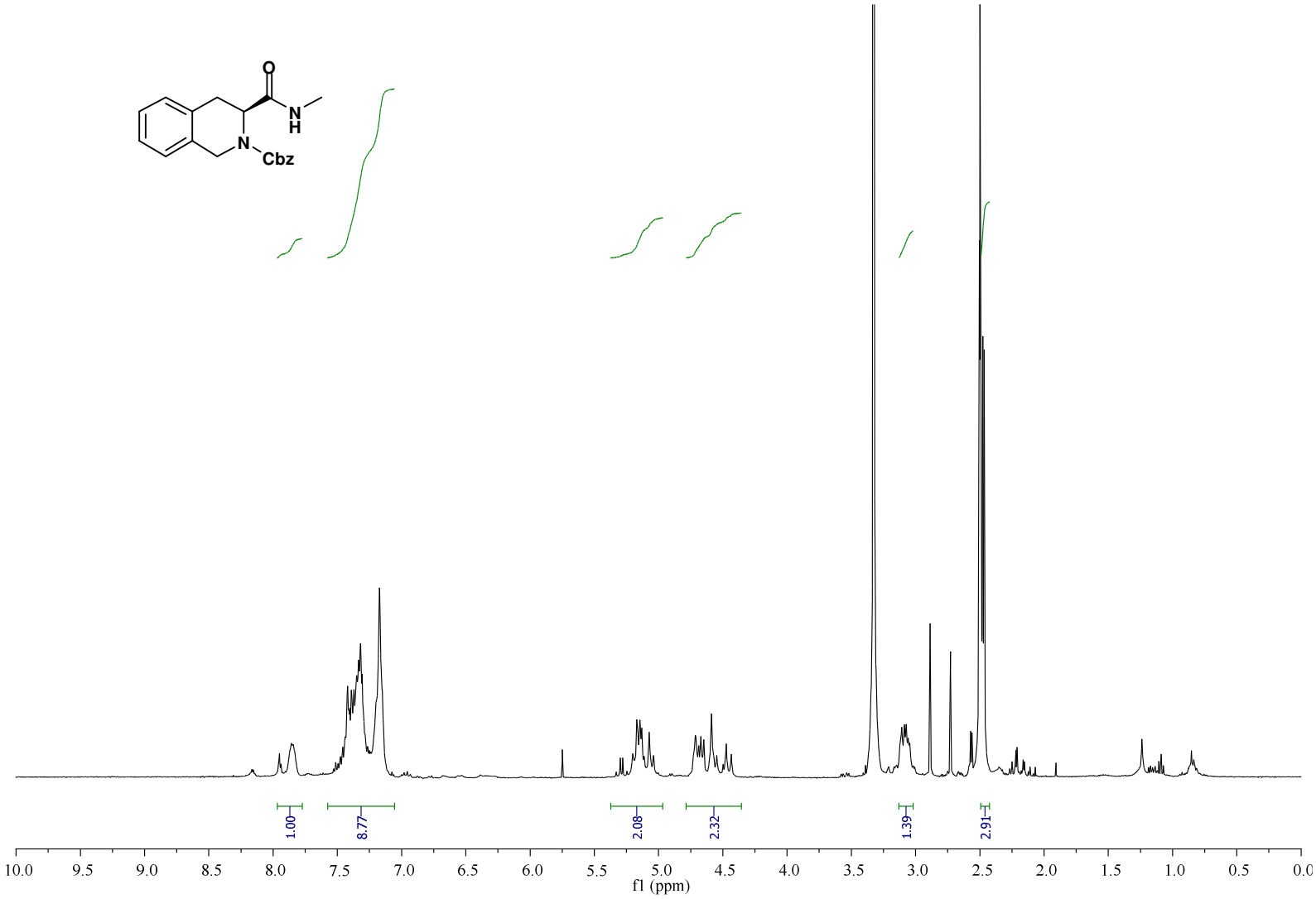
^{1}H NMR (400 MHz) Spectrum of Compound **5c** in d6-DMSO



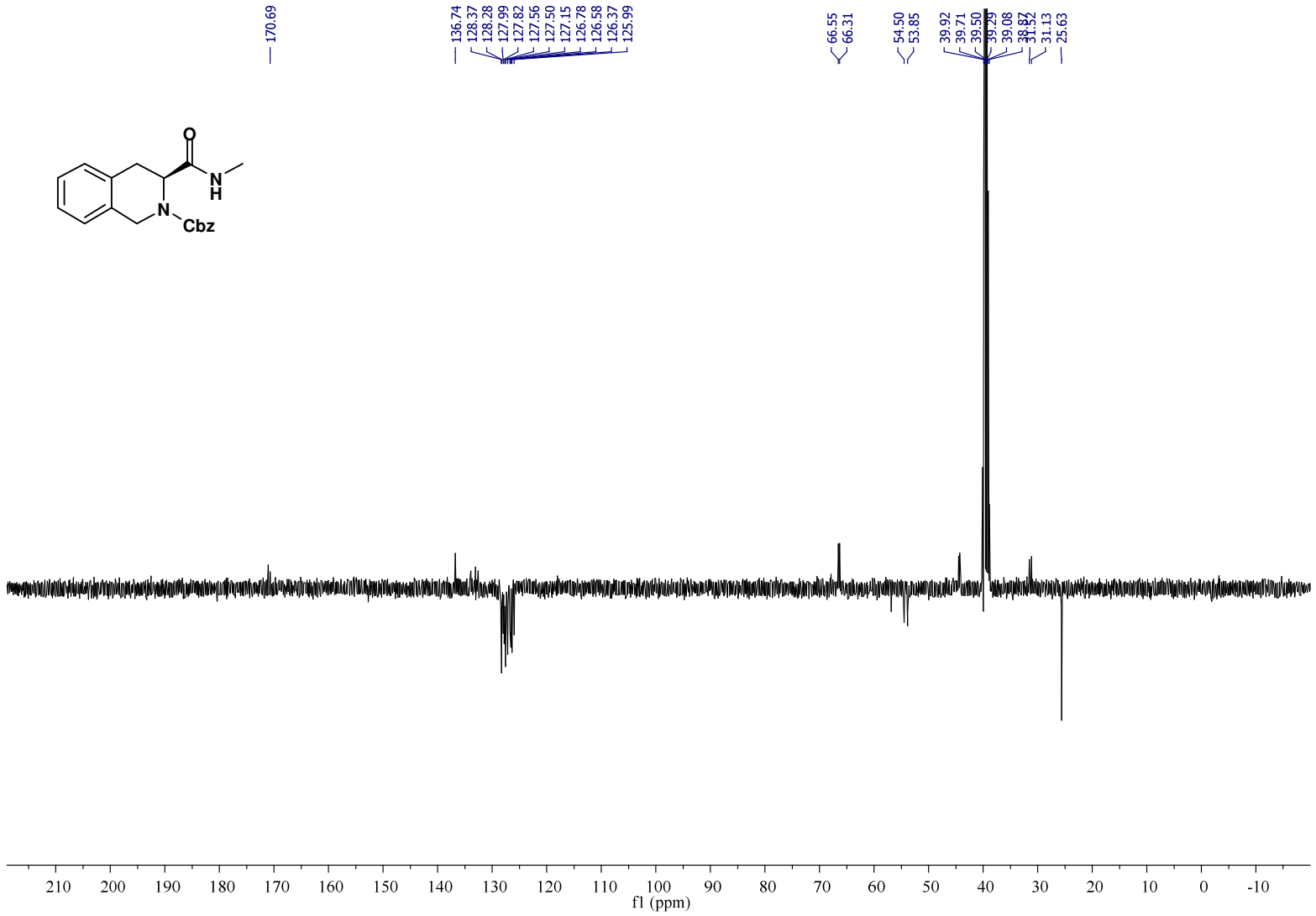
^{13}C NMR (400 MHz) Spectrum of Compound **5c** in d6-DMSO



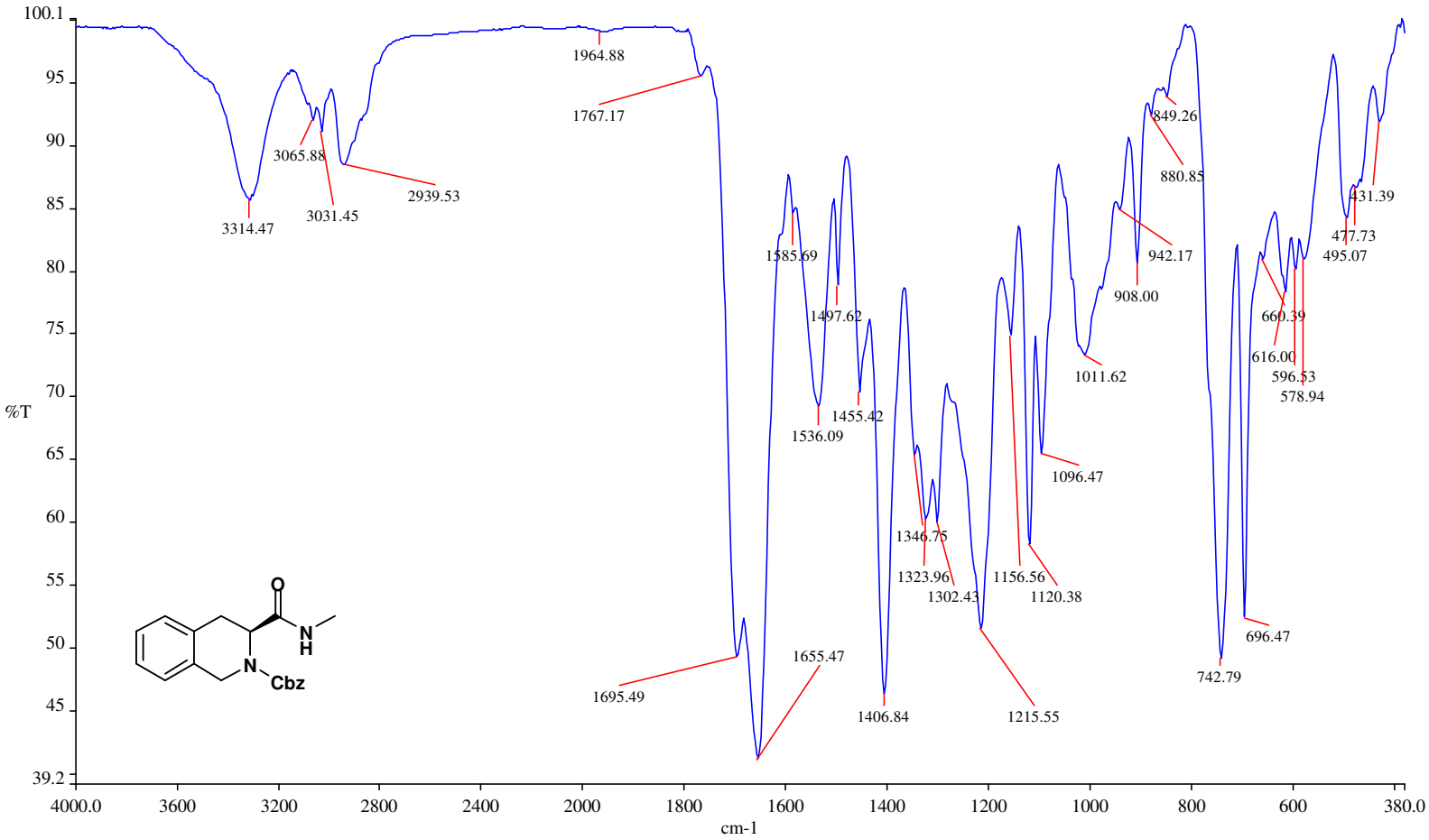
IR Spectrum of Compound **5c**



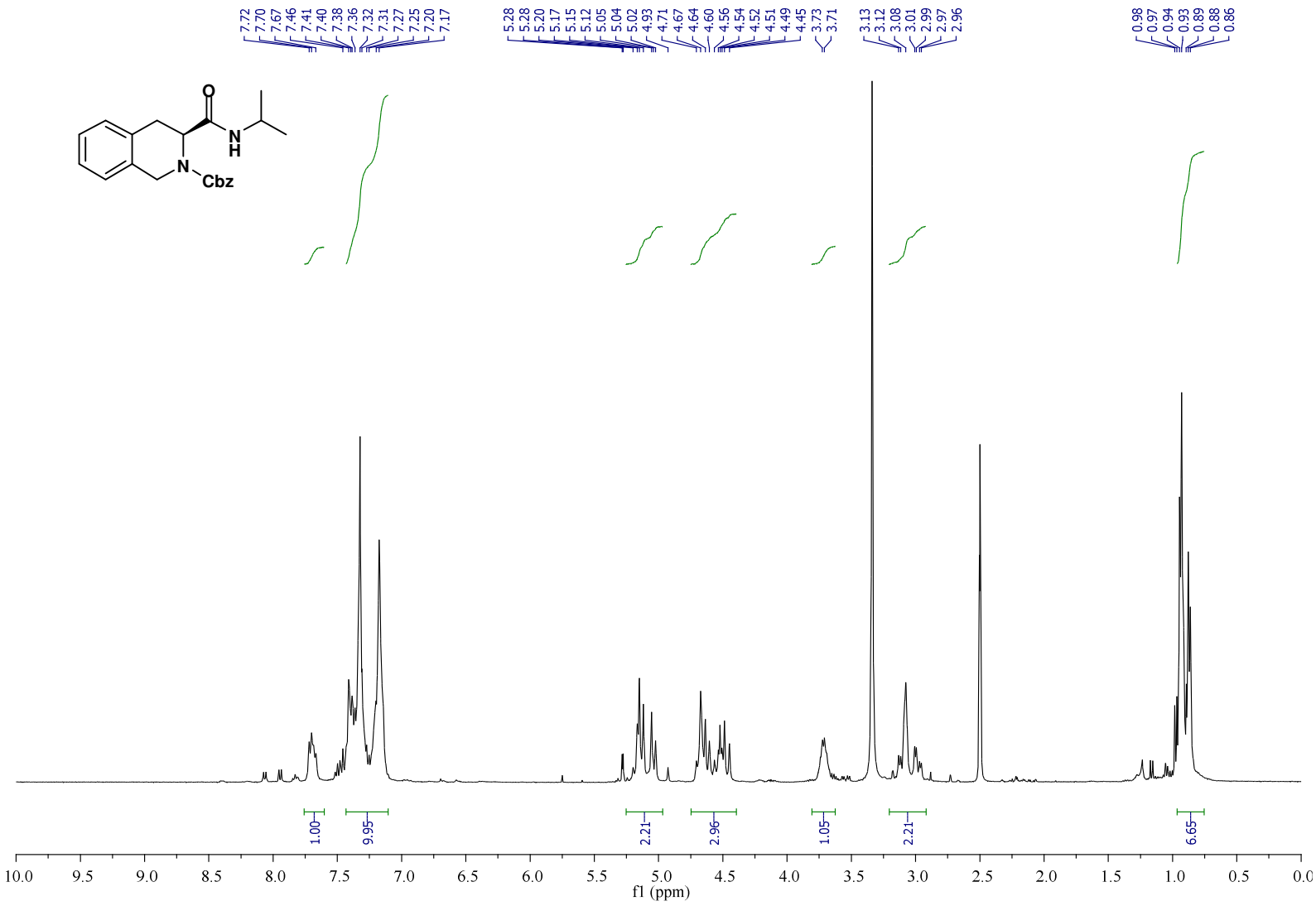
^{1}H NMR (400 MHz) Spectrum of Compound **5d** in d6-DMSO



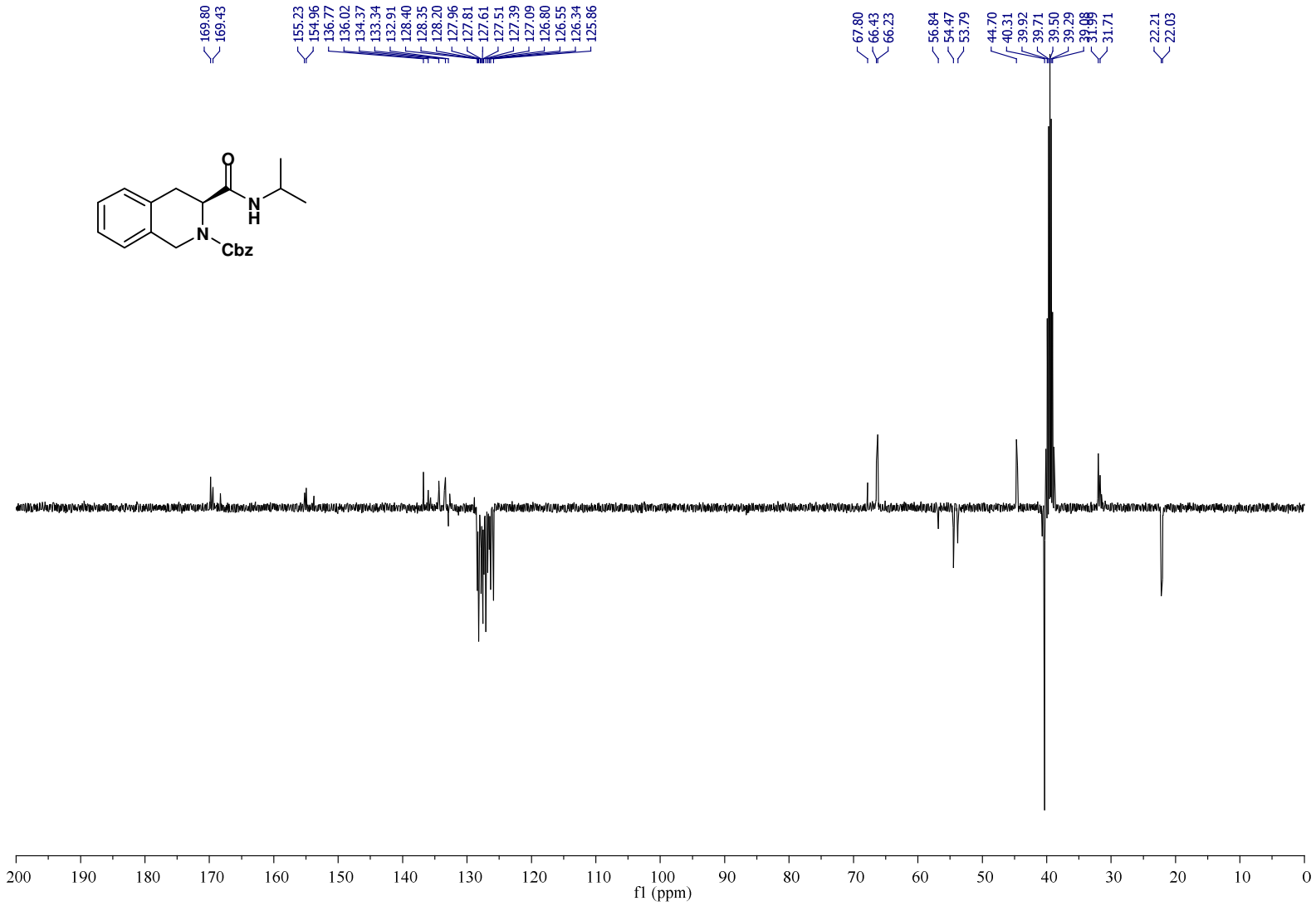
^{13}C NMR (400 MHz) Spectrum of Compound **5d** in d6-DMSO



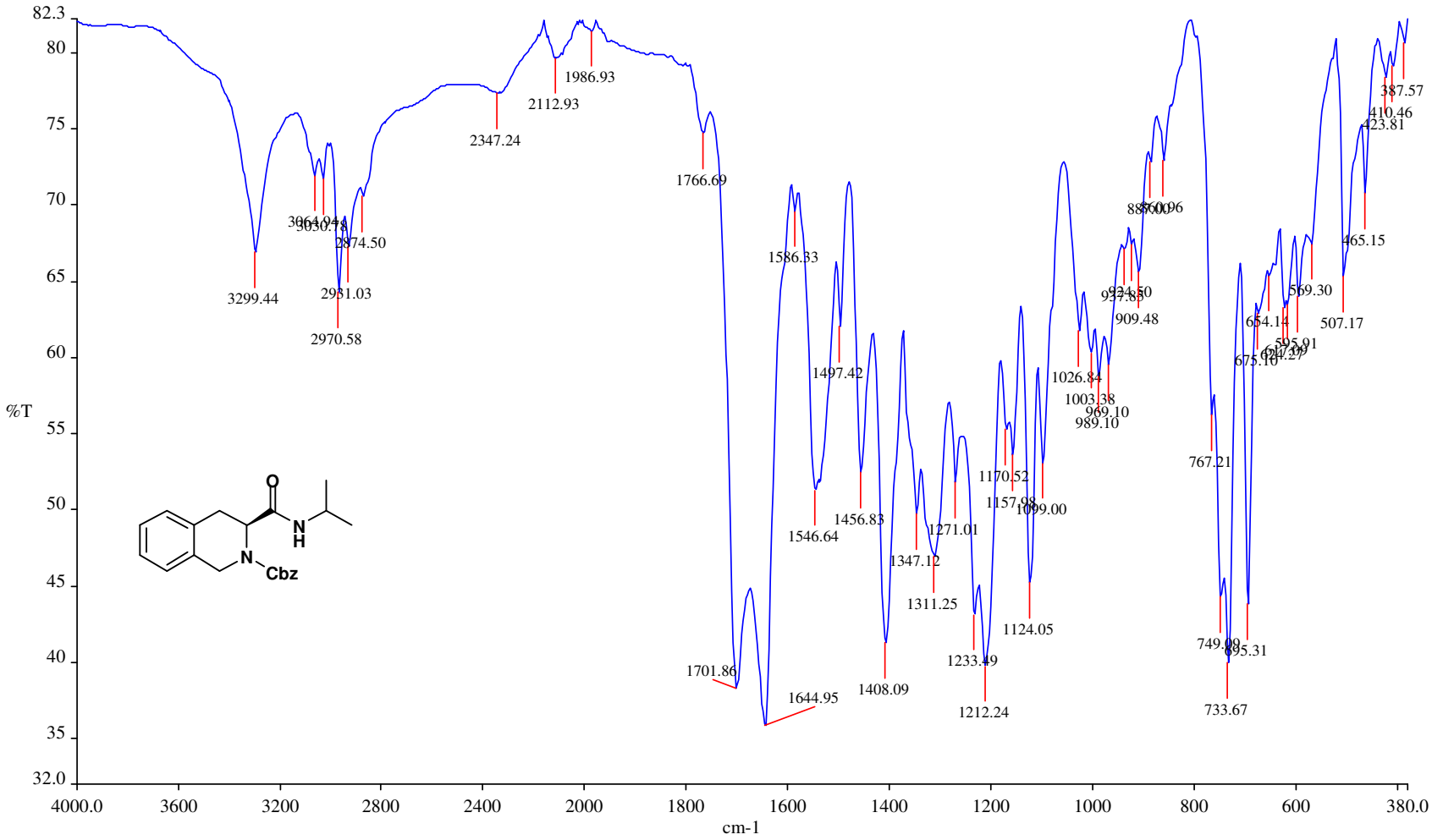
IR Spectrum of Compound **5d**



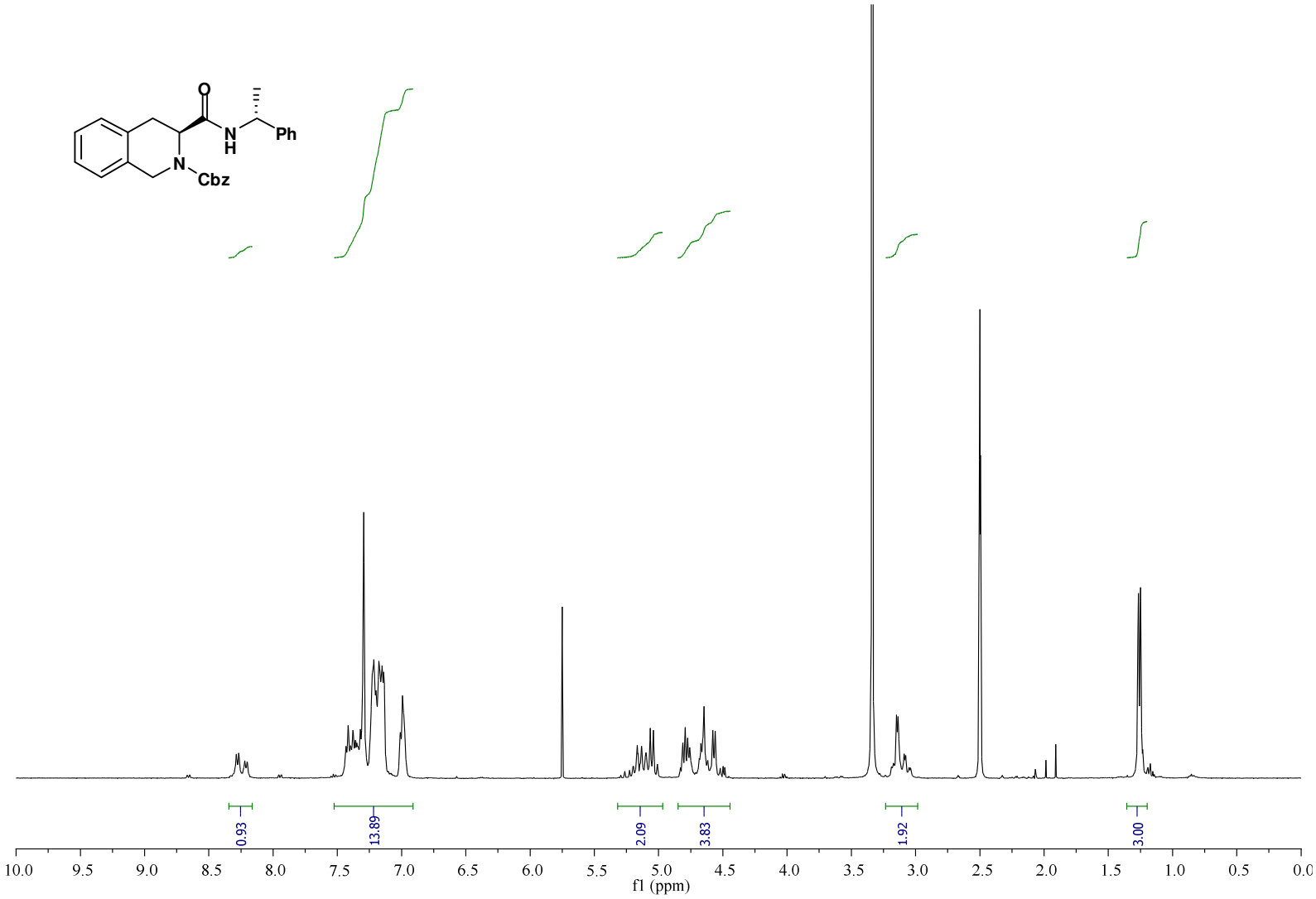
^{1}H NMR (400 MHz) Spectrum of Compound **5e** in d6-DMSO



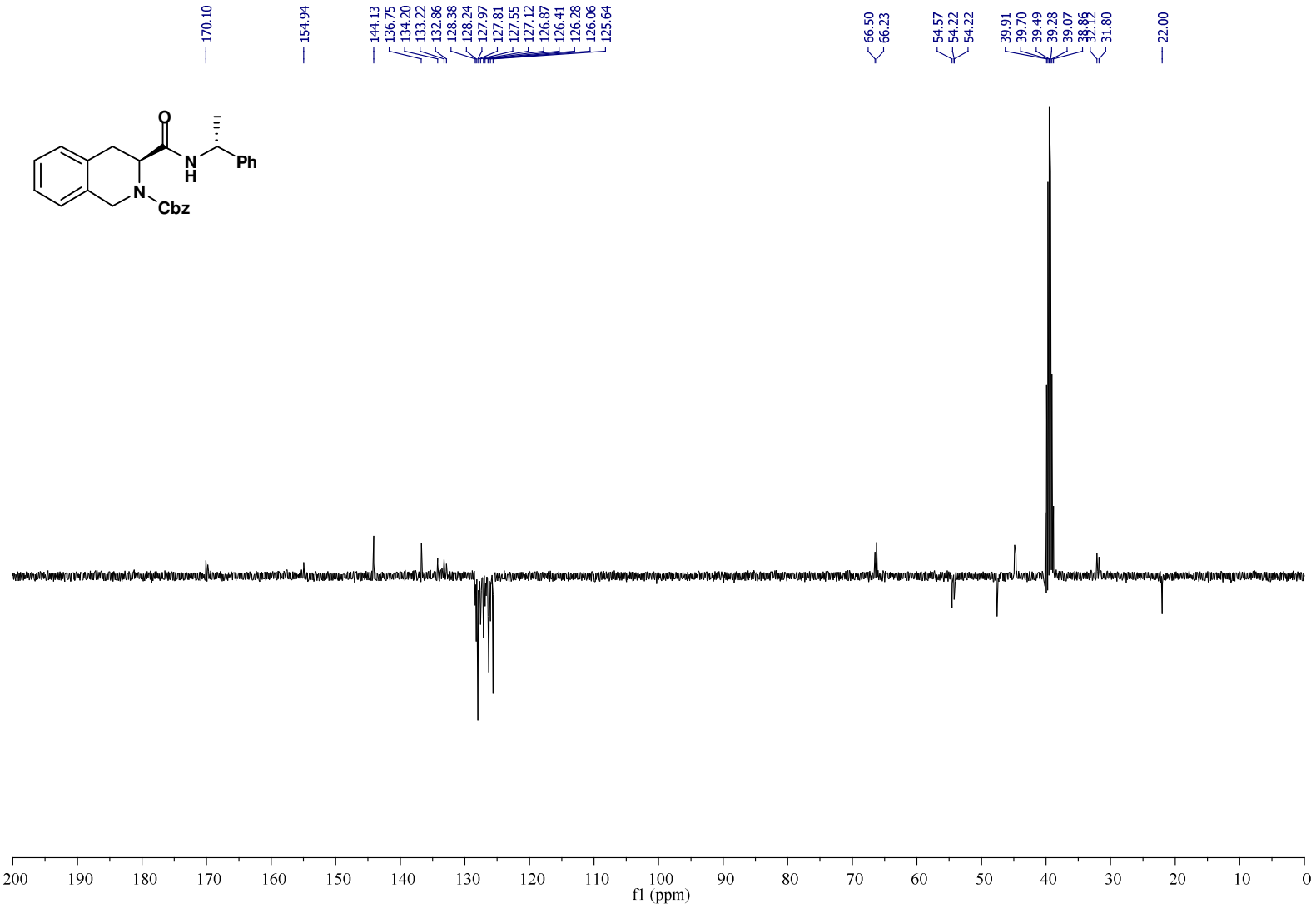
^{13}C NMR (400 MHz) Spectrum of Compound **5e** in d6-DMSO



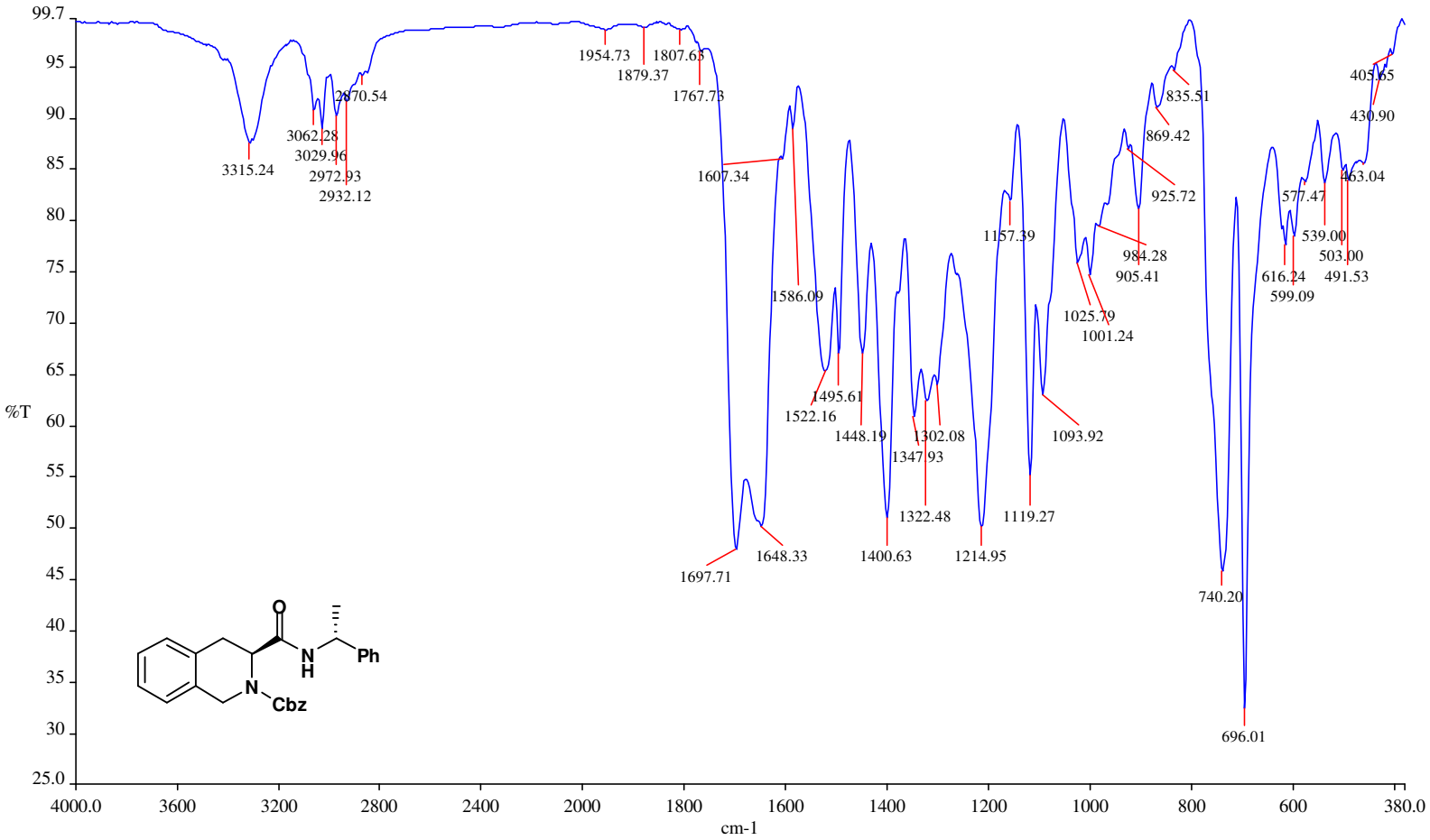
IR Spectrum of Compound **5e**



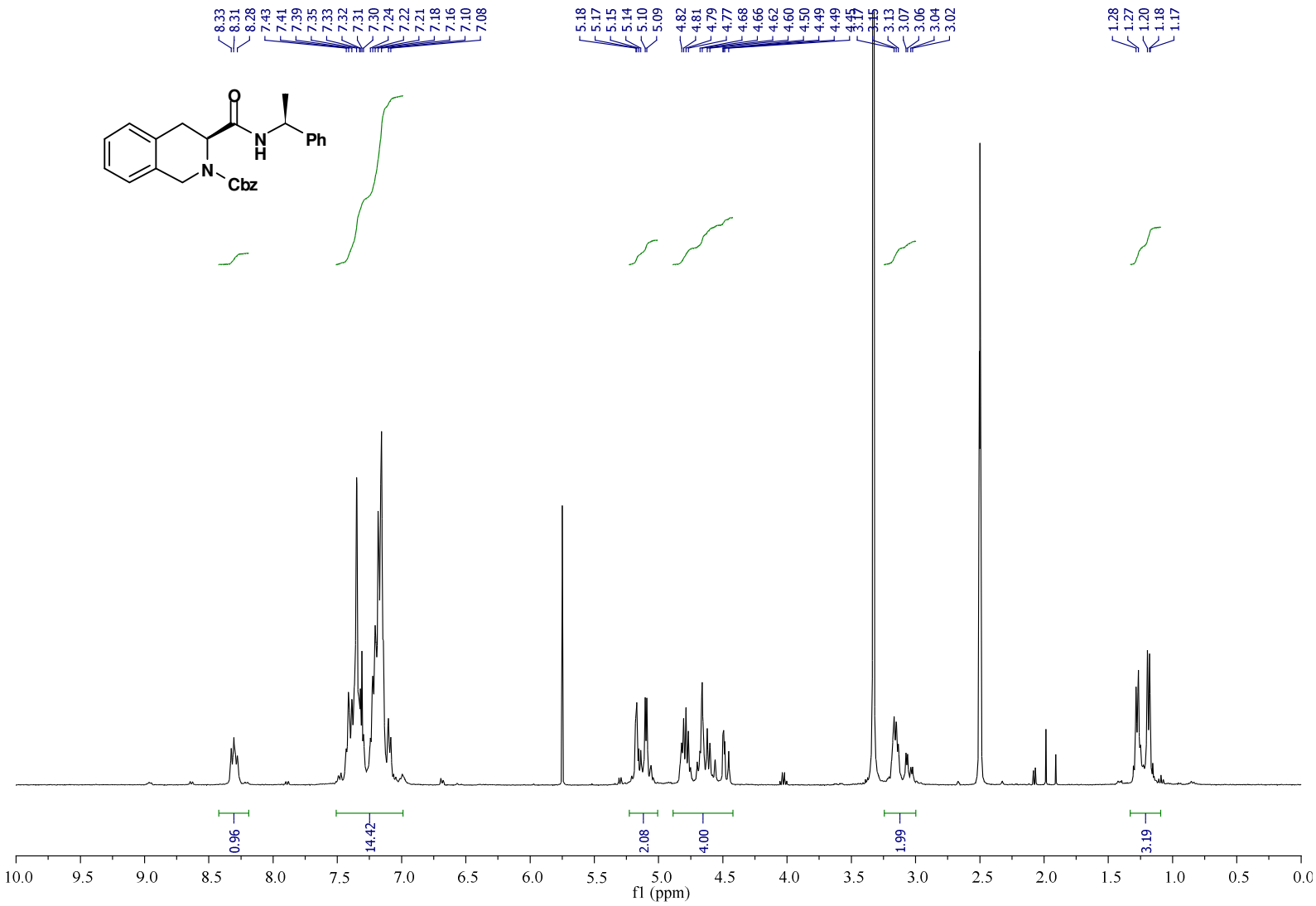
^{1}H NMR (400 MHz) Spectrum of Compound **5f** in d6-DMSO



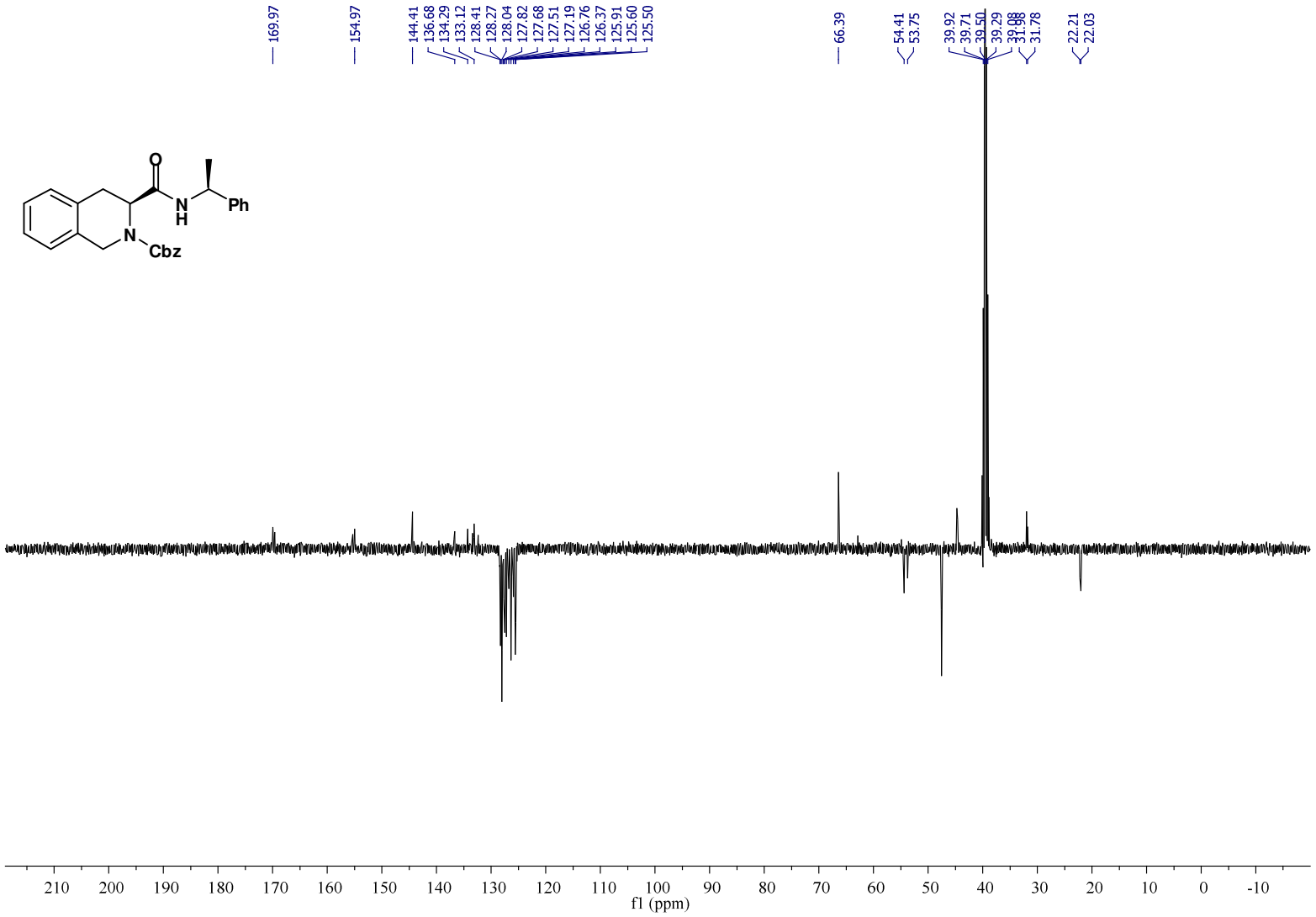
^{13}C NMR (400 MHz) Spectrum of Compound **5f** in d6-DMSO



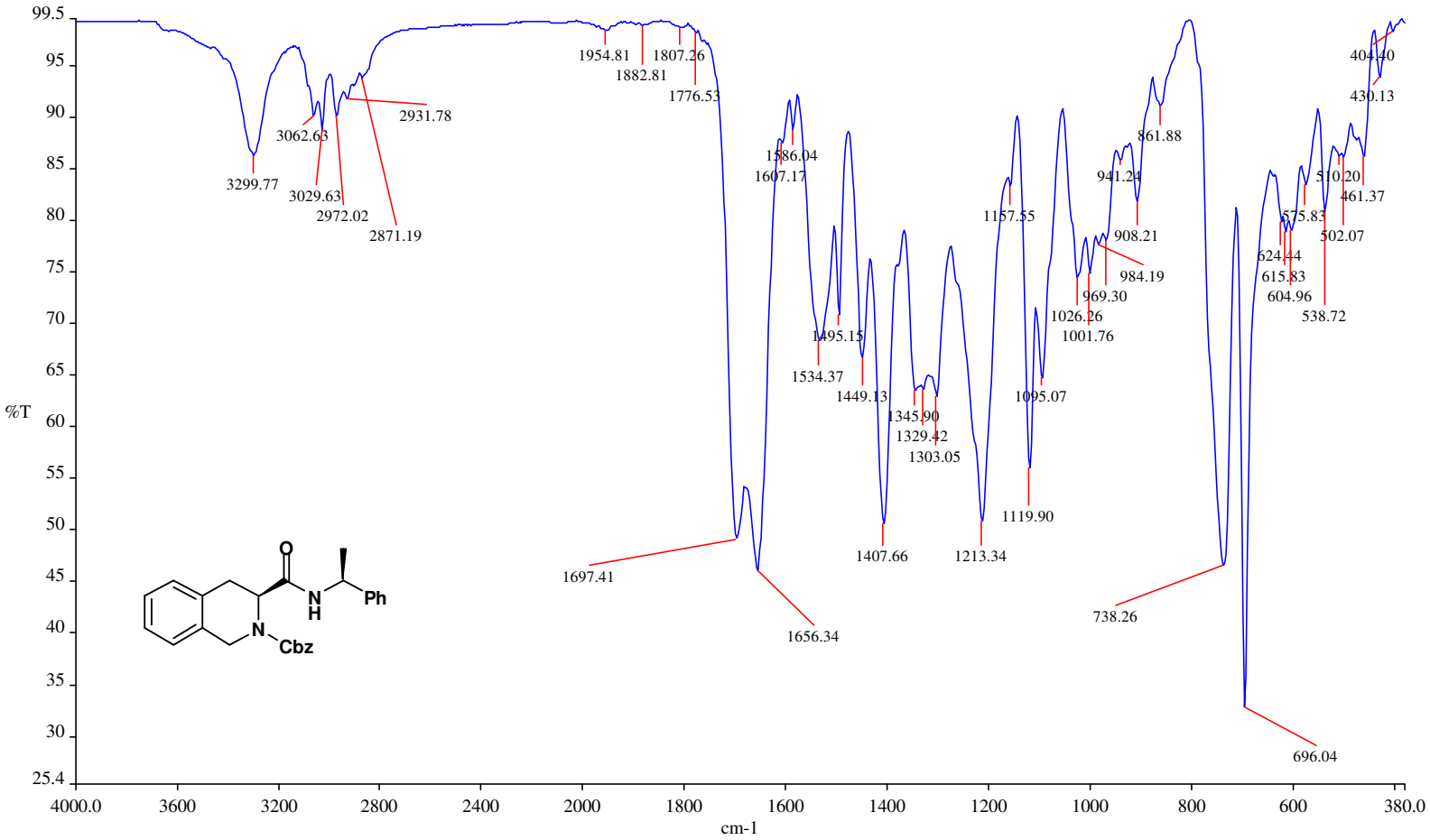
IR Spectrum of Compound **5f**



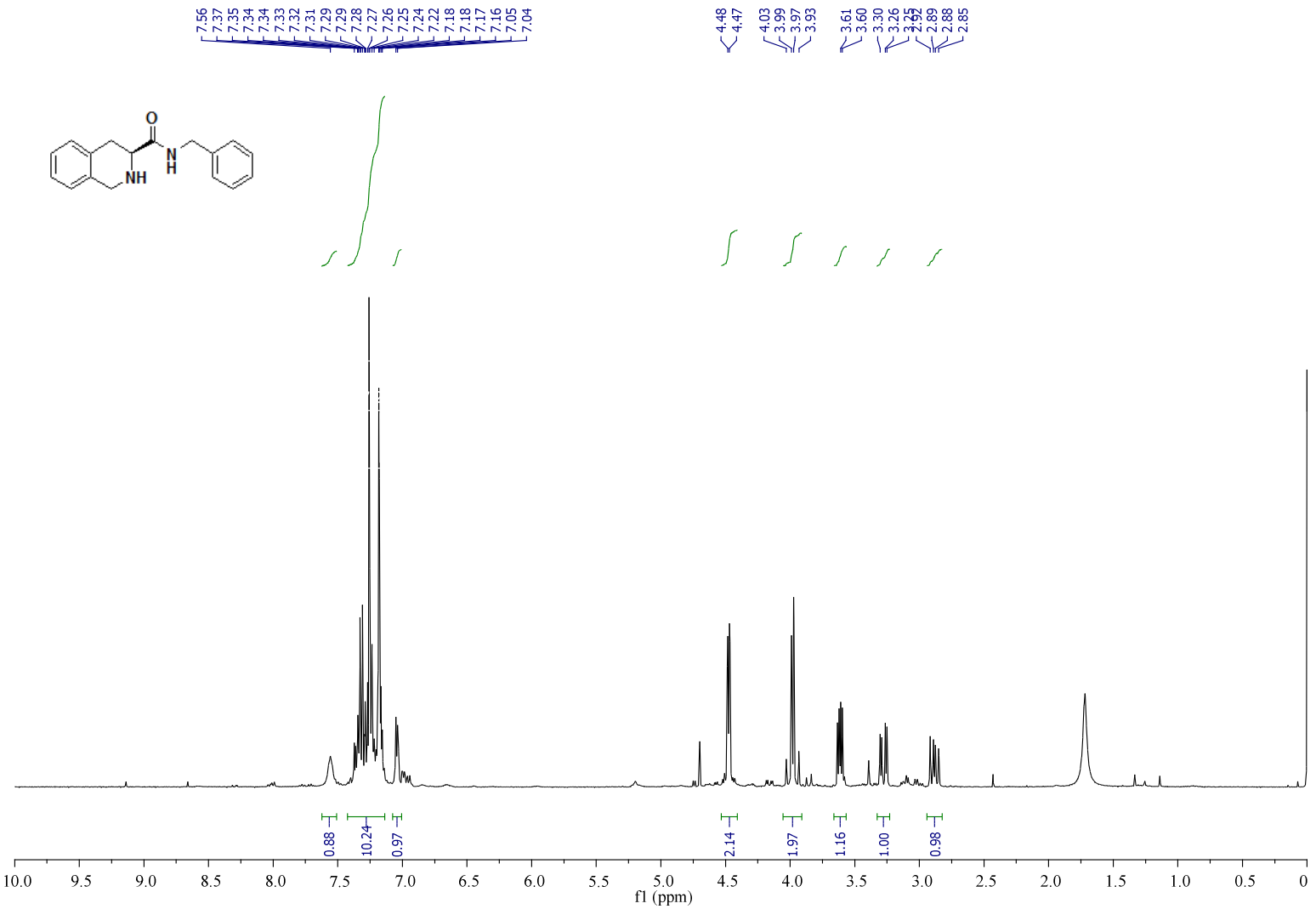
^{1}H NMR (400 MHz) Spectrum of Compound **5g** in d6-DMSO



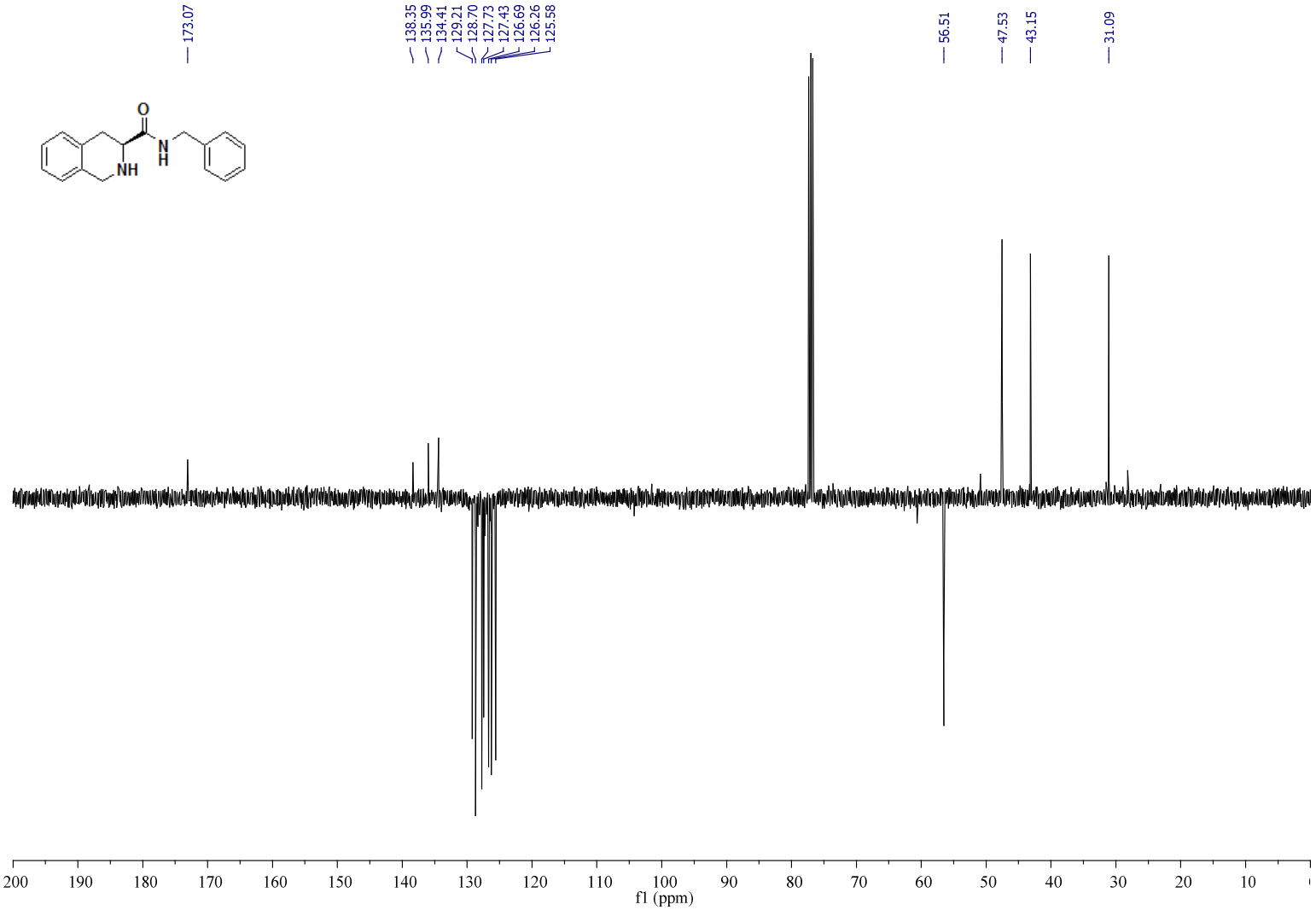
^{13}C NMR (400 MHz) Spectrum of Compound **5g** in d6-DMSO



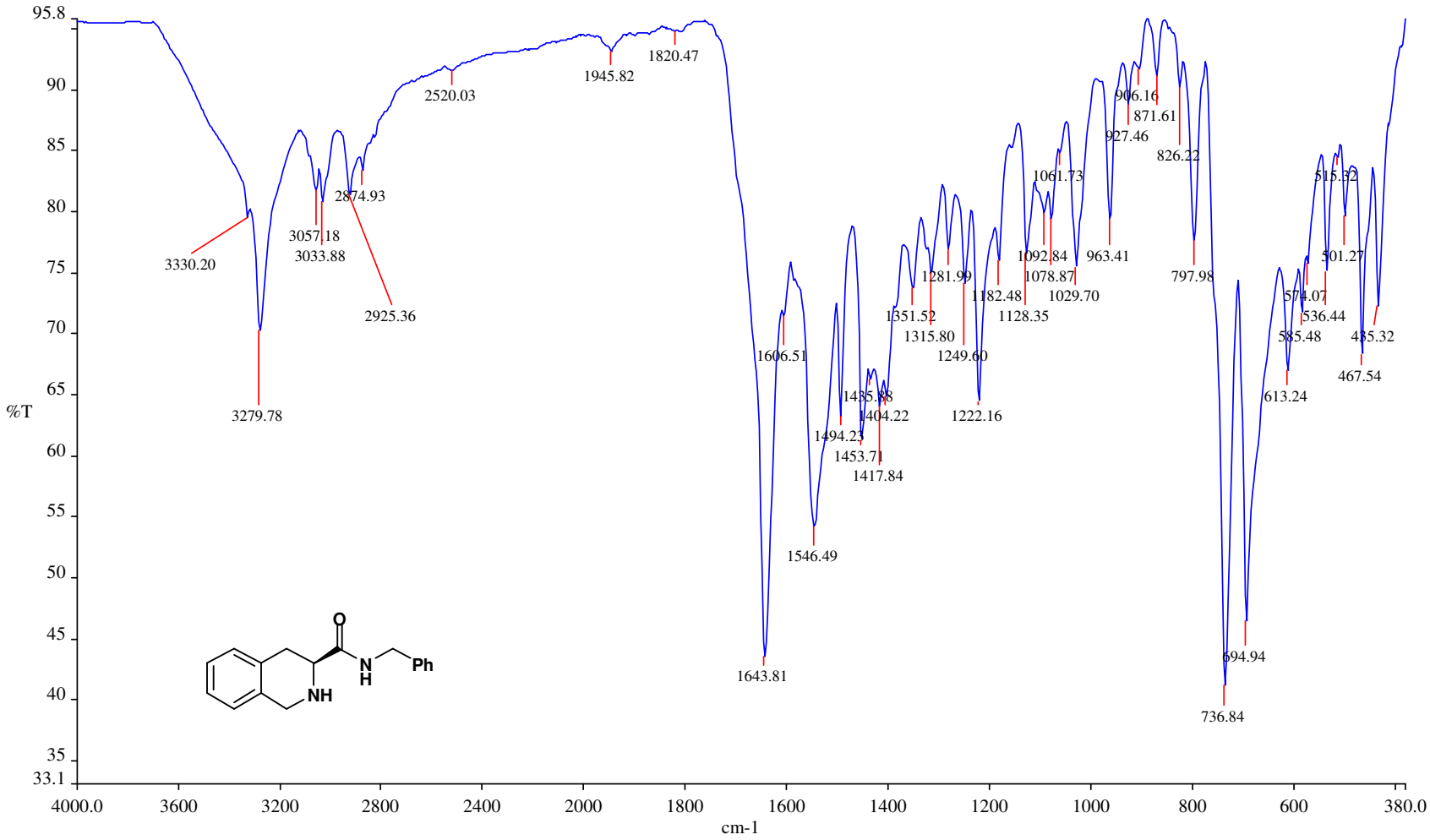
IR Spectrum of Compound **5g**



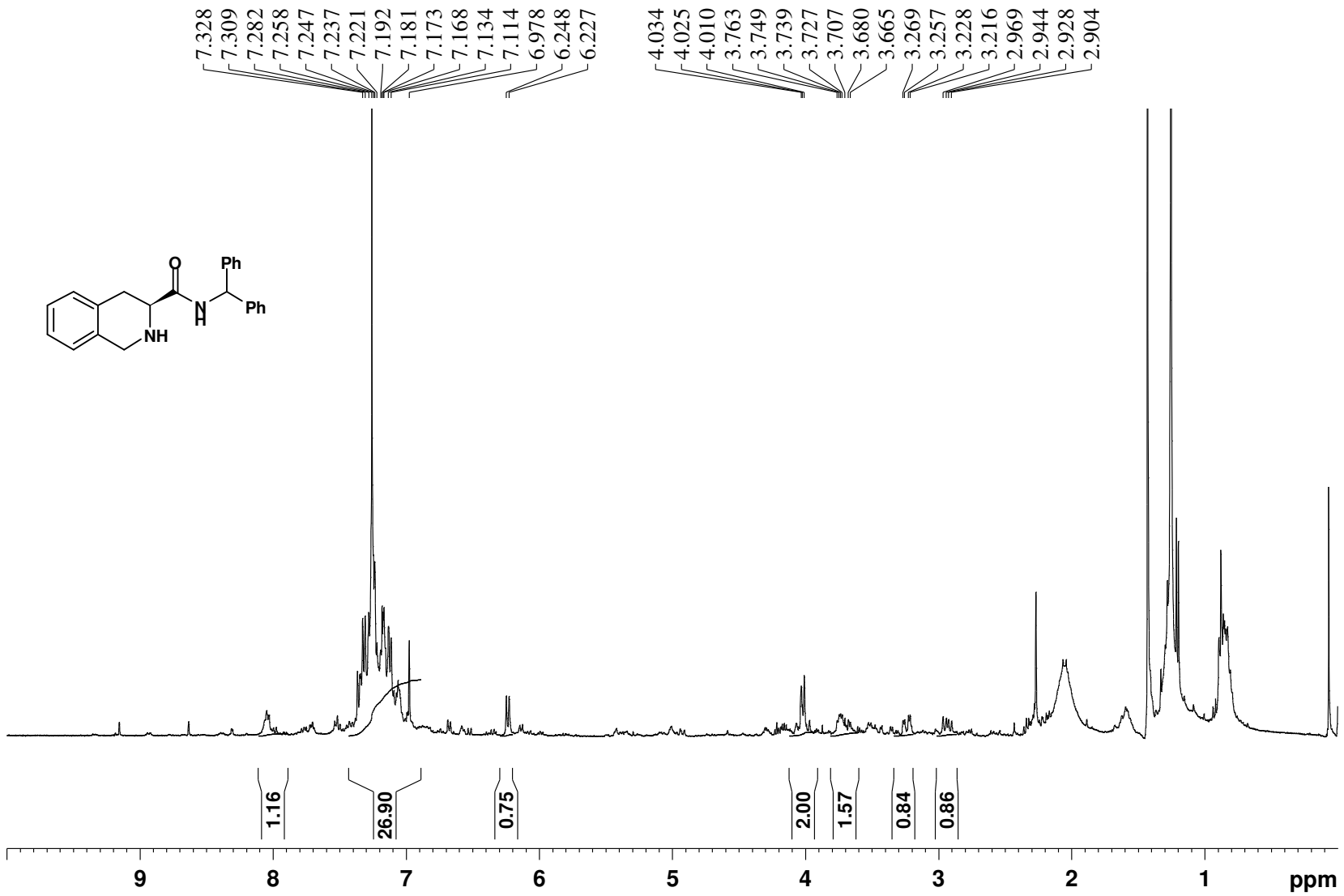
^{1}H NMR (400 MHz) Spectrum of Compound **6a** in $CDCl_3$



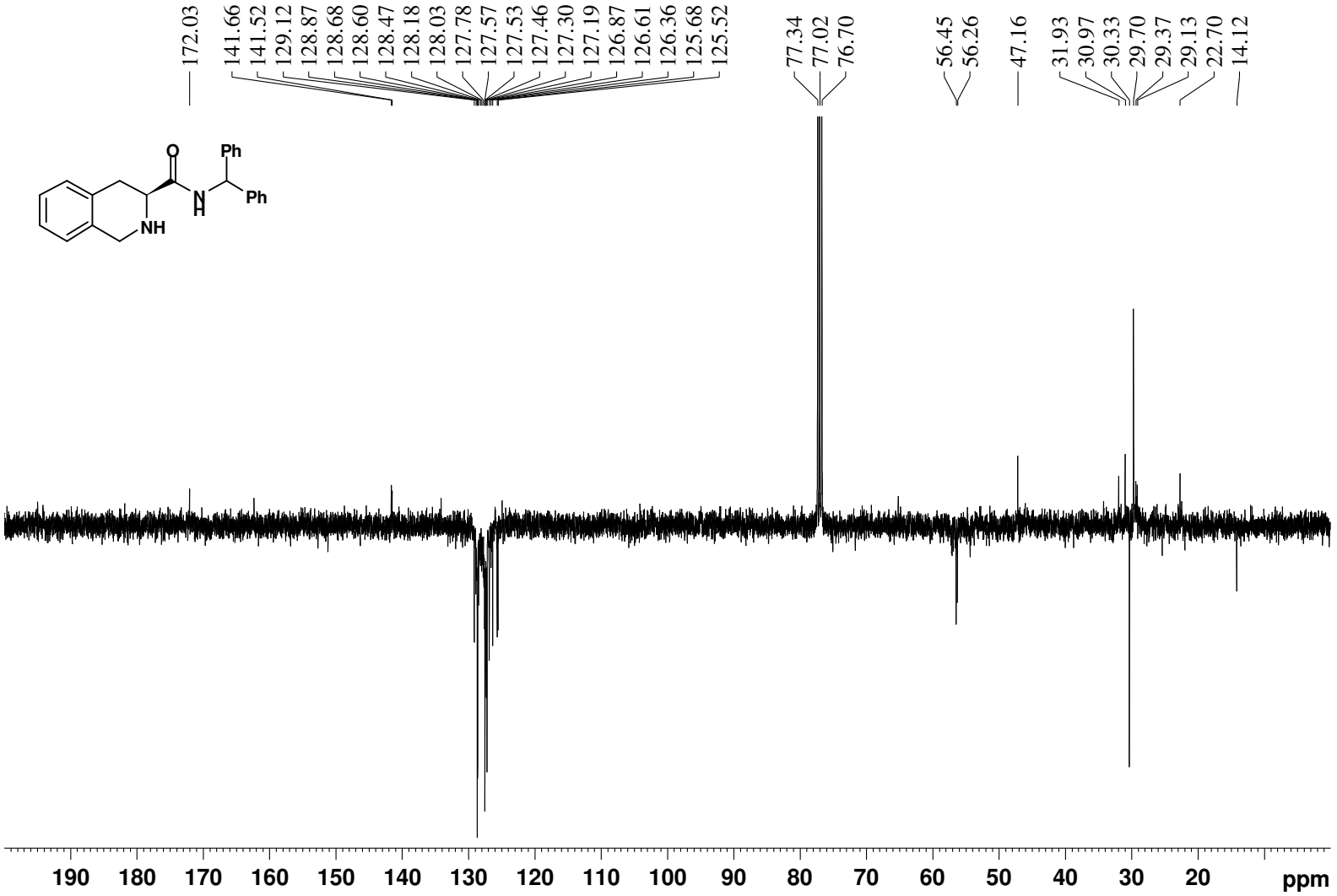
^{13}C NMR (400 MHz) Spectrum of Compound **6a** in $CDCl_3$



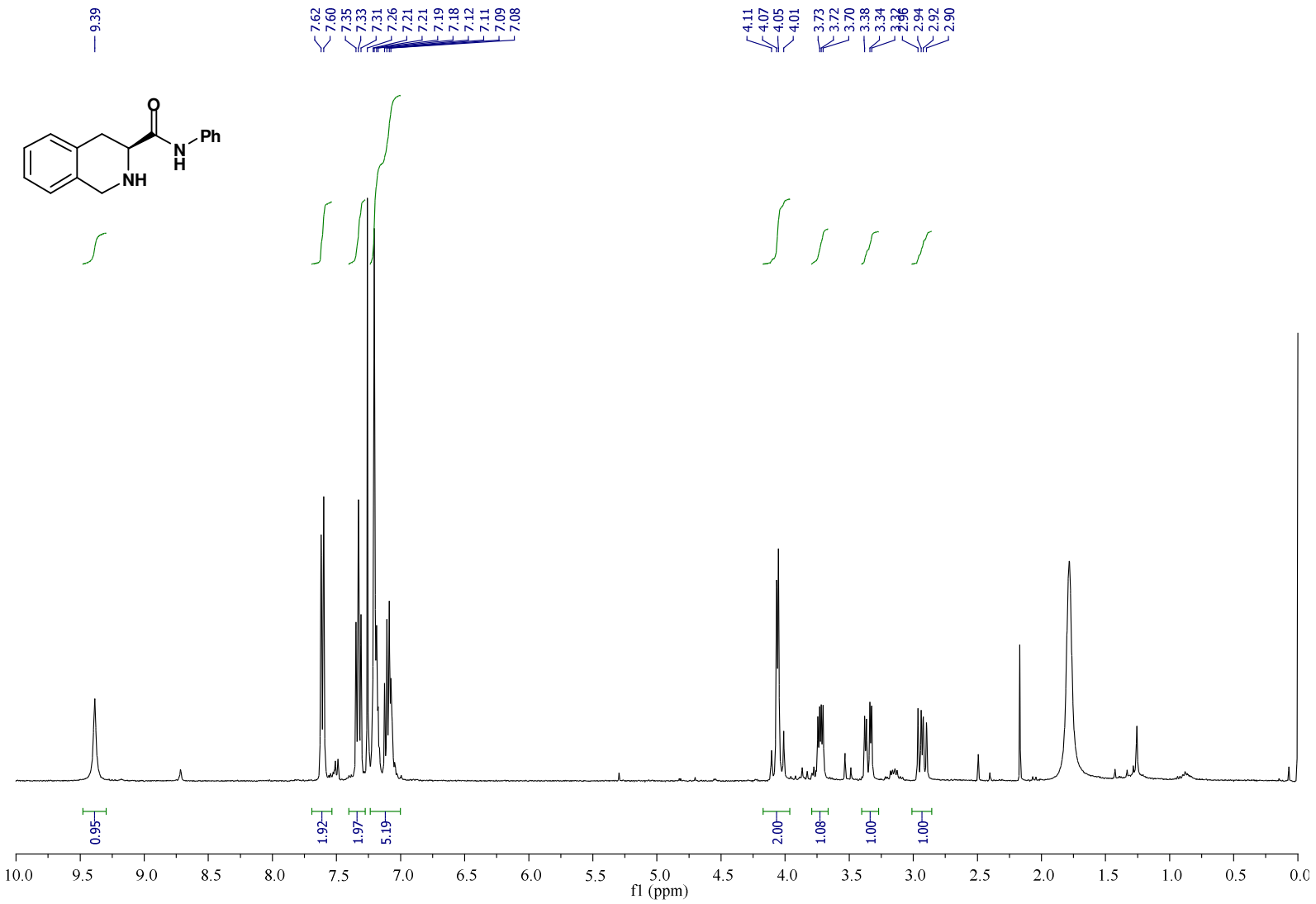
IR Spectrum of Compound **6a**



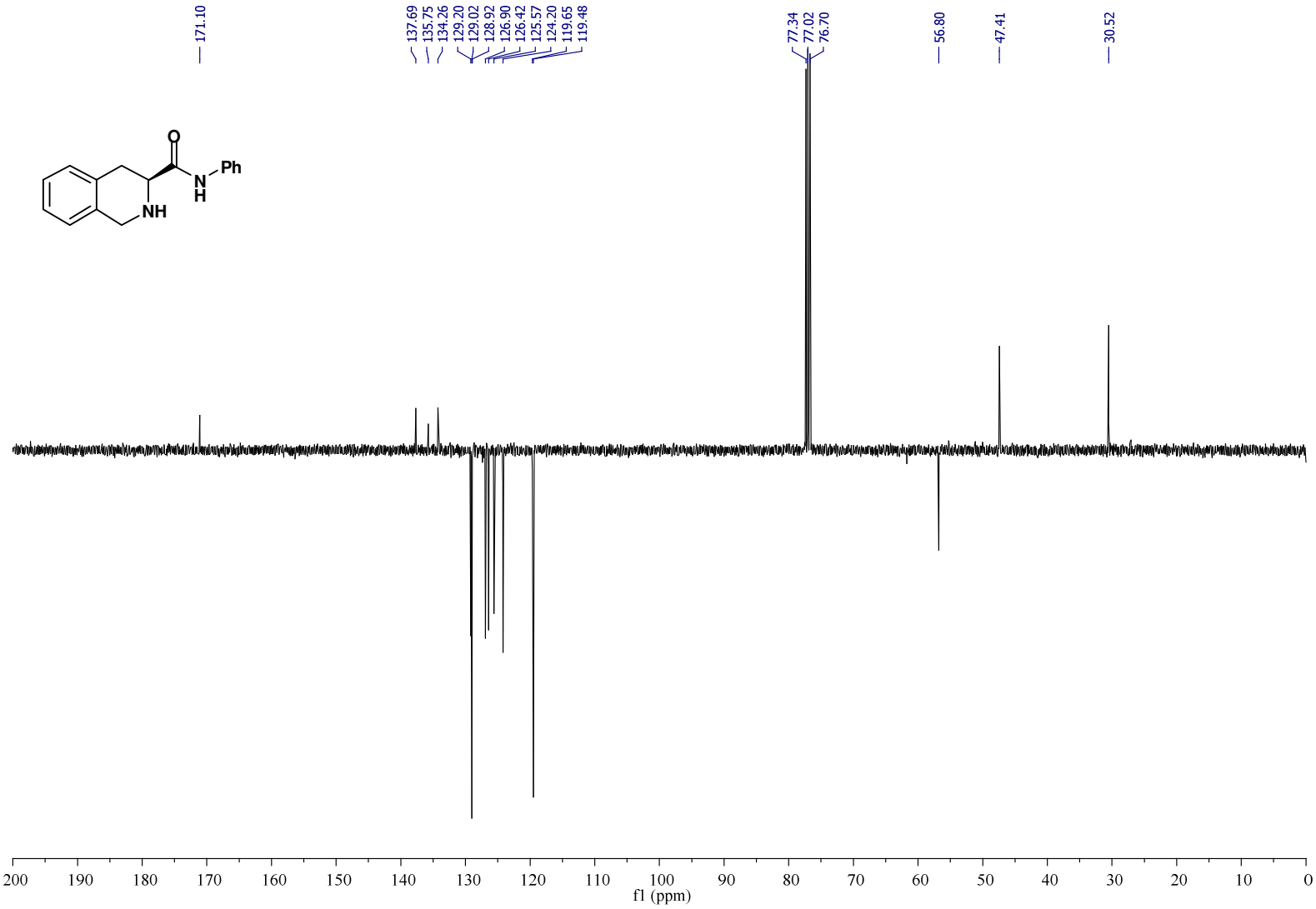
^{1}H NMR (400 MHz) Spectrum of Compound **6b** in $CDCl_3$



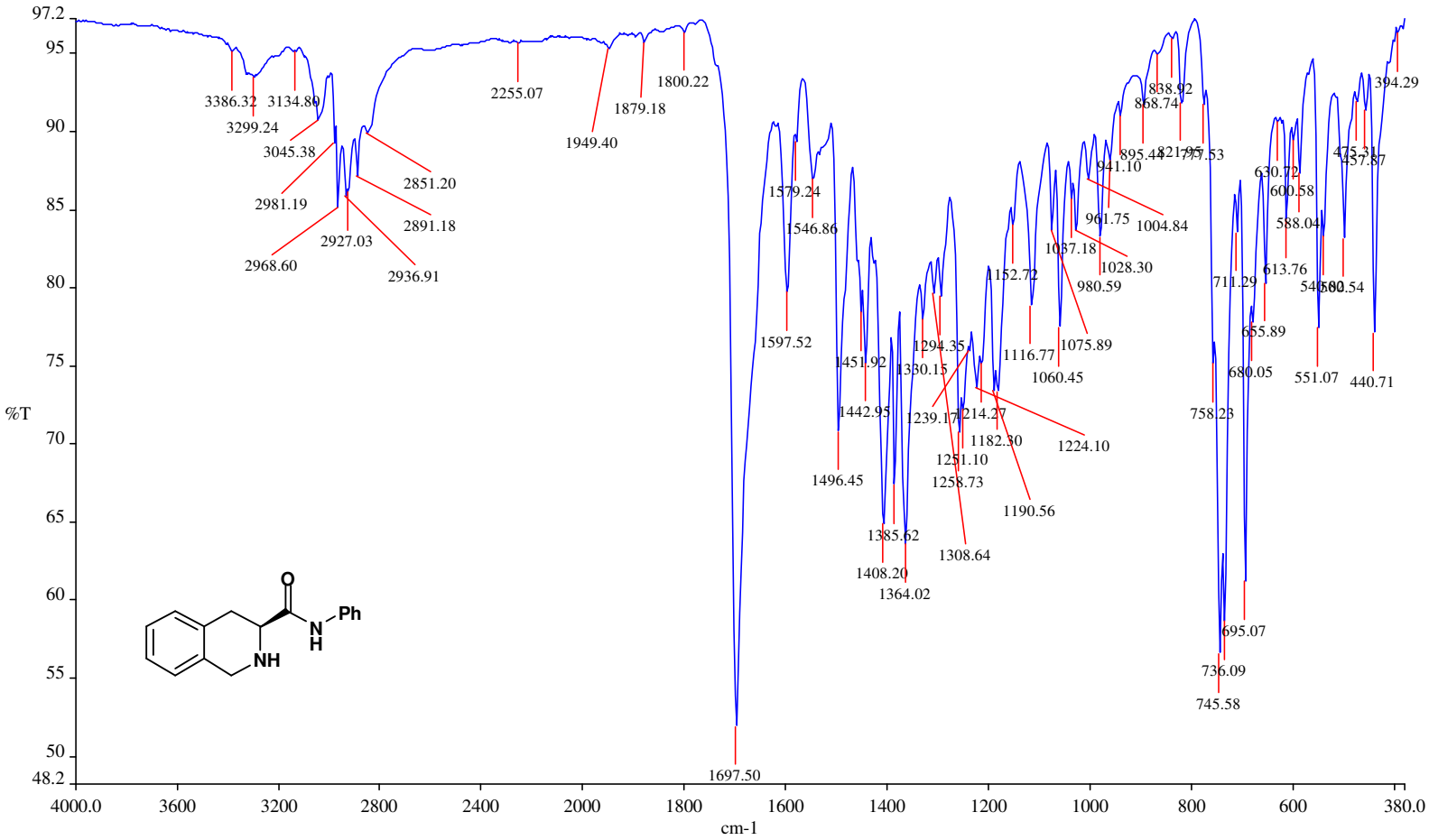
^{13}C NMR (400 MHz) Spectrum of Compound **6b** in $CDCl_3$



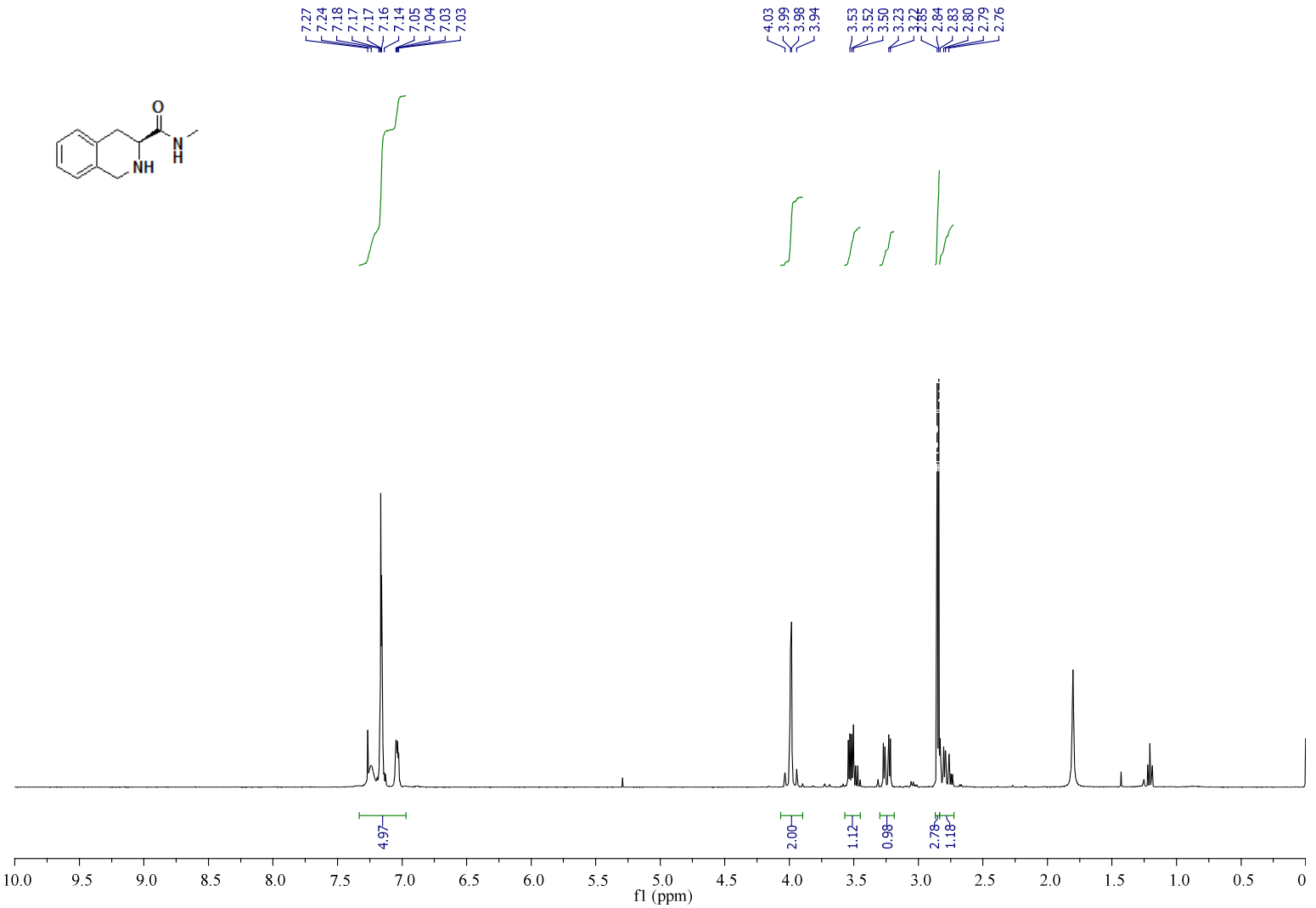
^{1}H NMR (400 MHz) Spectrum of Compound **6c** in $CDCl_3$



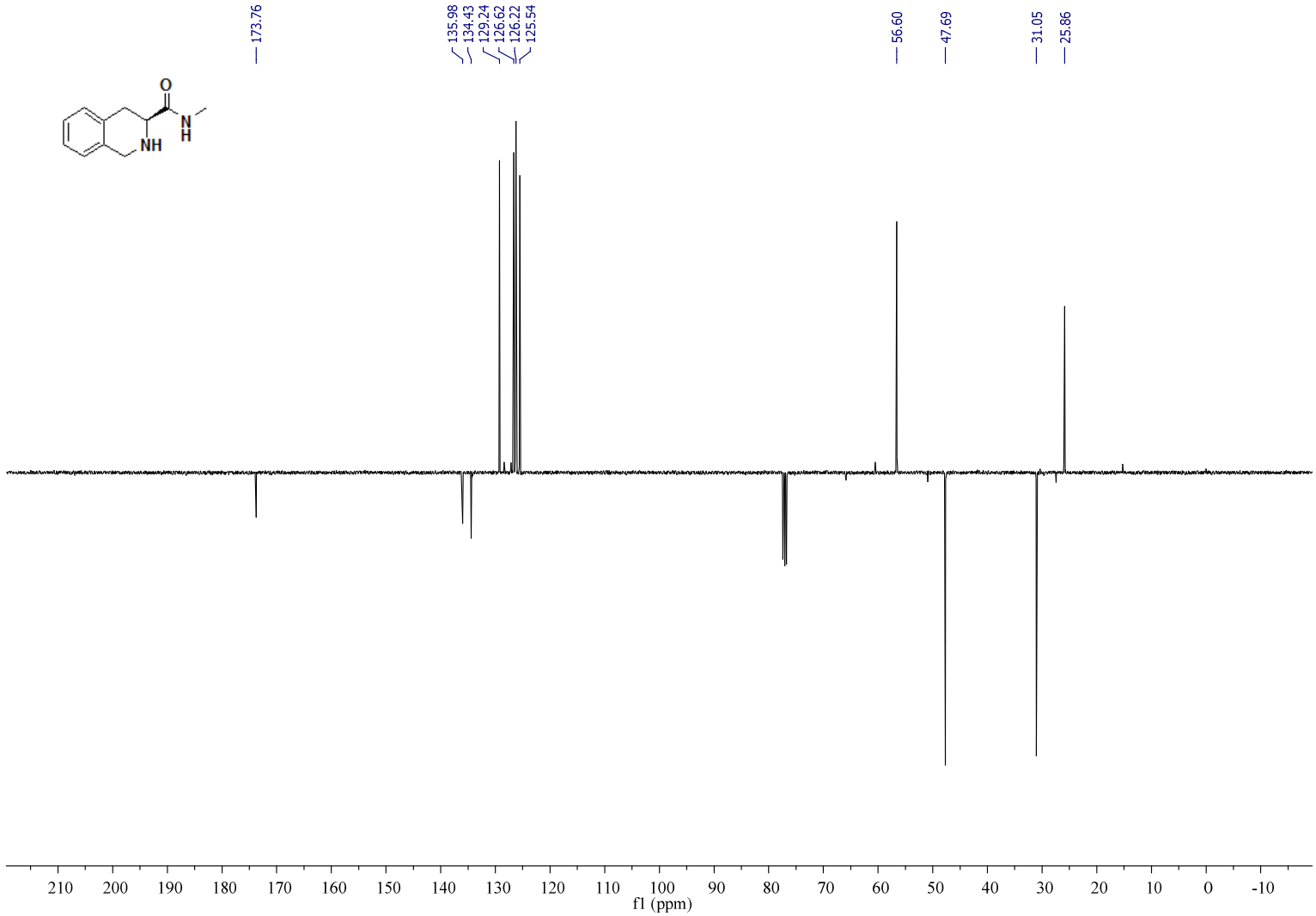
^{13}C NMR (400 MHz) Spectrum of Compound **6c** in $CDCl_3$



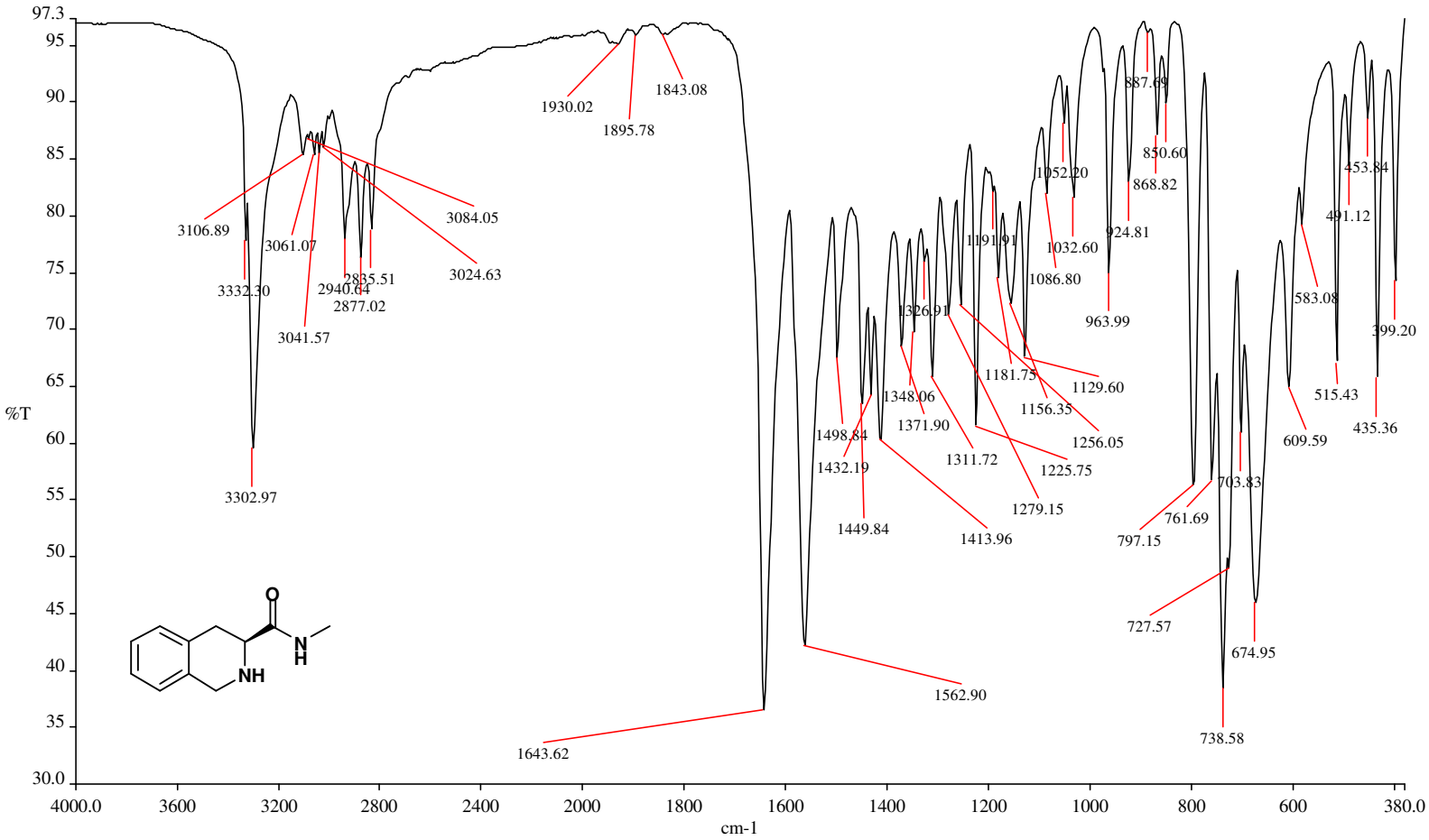
IR Spectrum of Compound **6c**



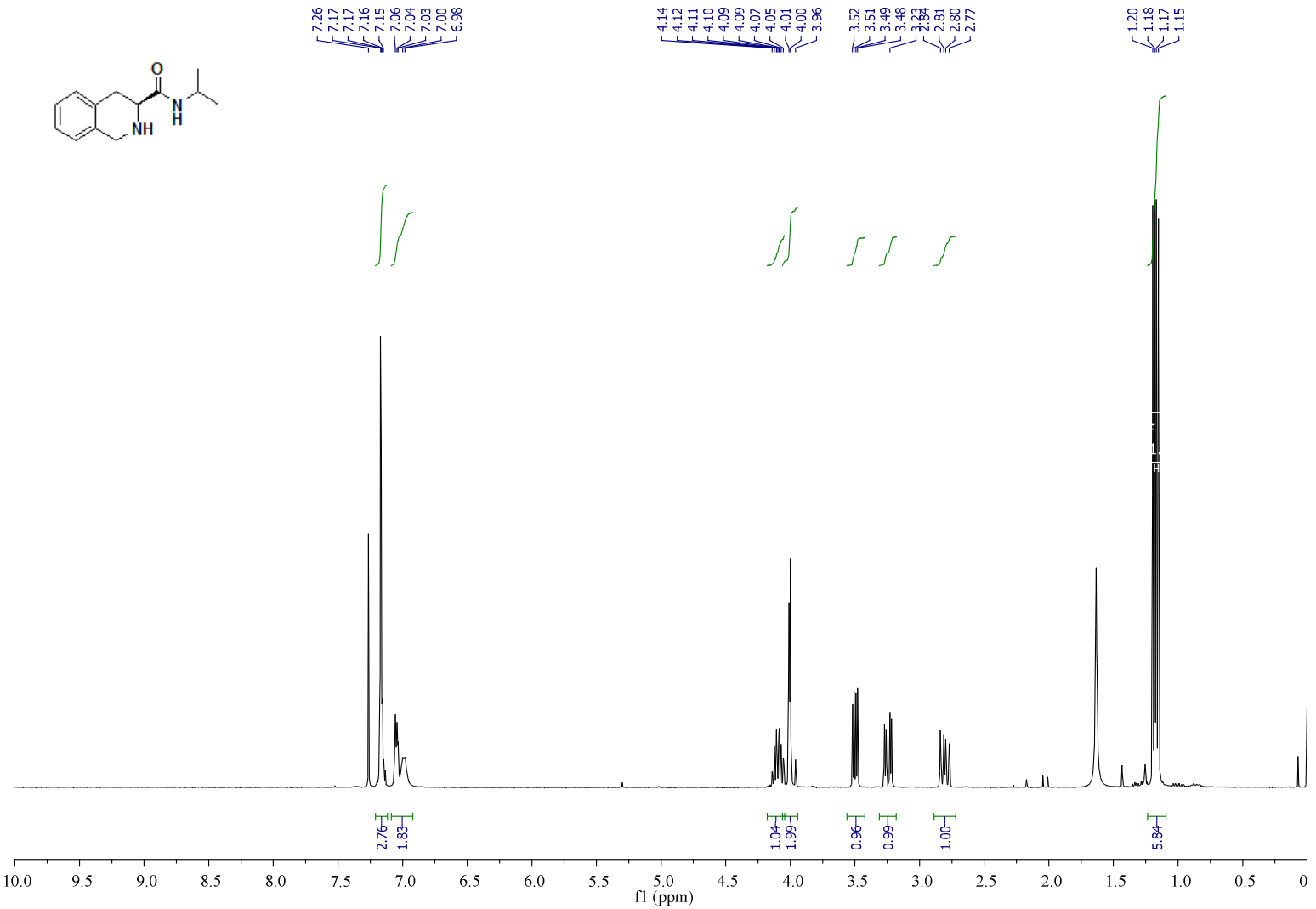
^{1}H NMR (400 MHz) Spectrum of Compound **6d** in $CDCl_3$



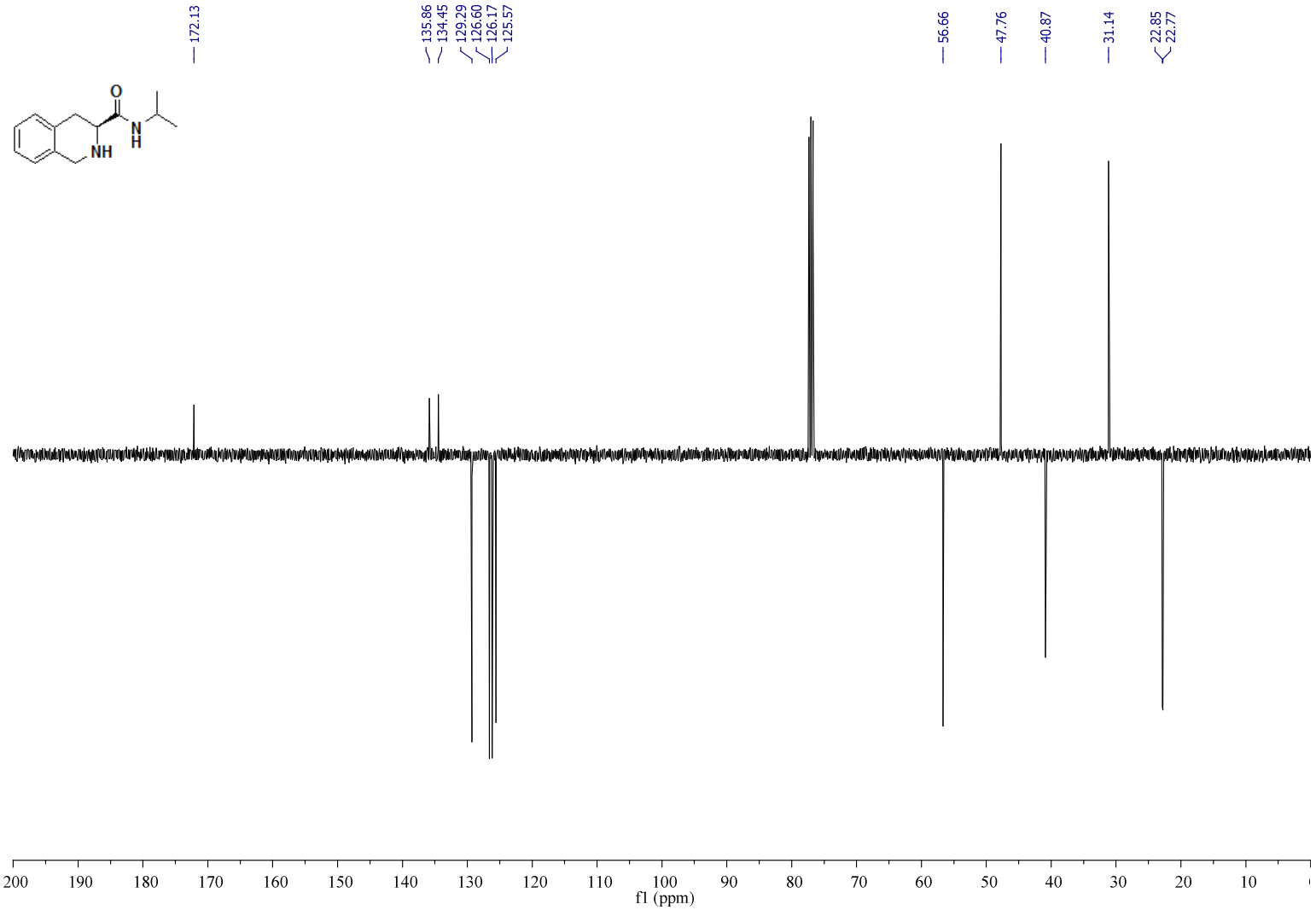
^{13}C NMR (400 MHz) Spectrum of Compound **6d** in $CDCl_3$



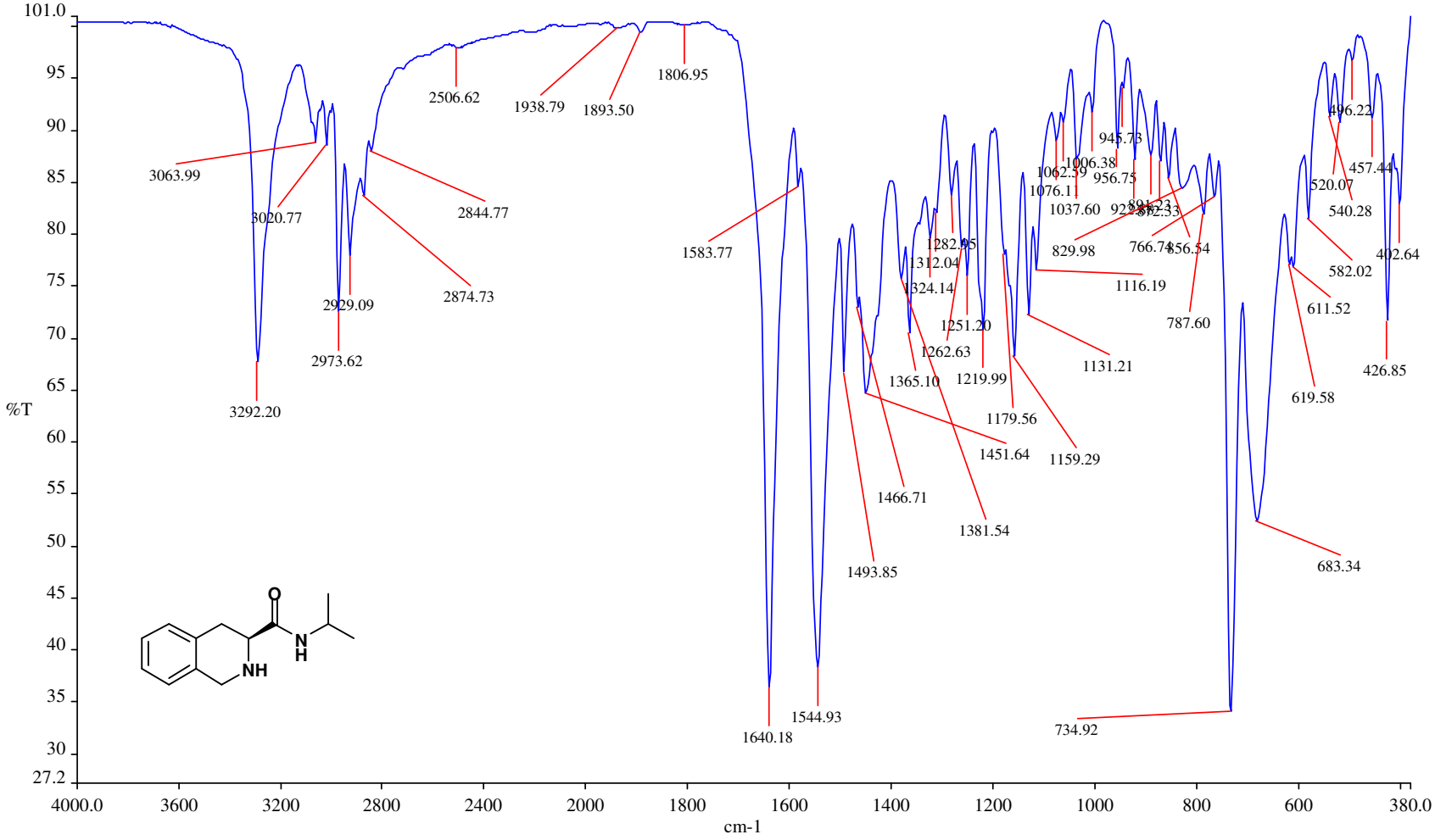
IR Spectrum of Compound **6d**



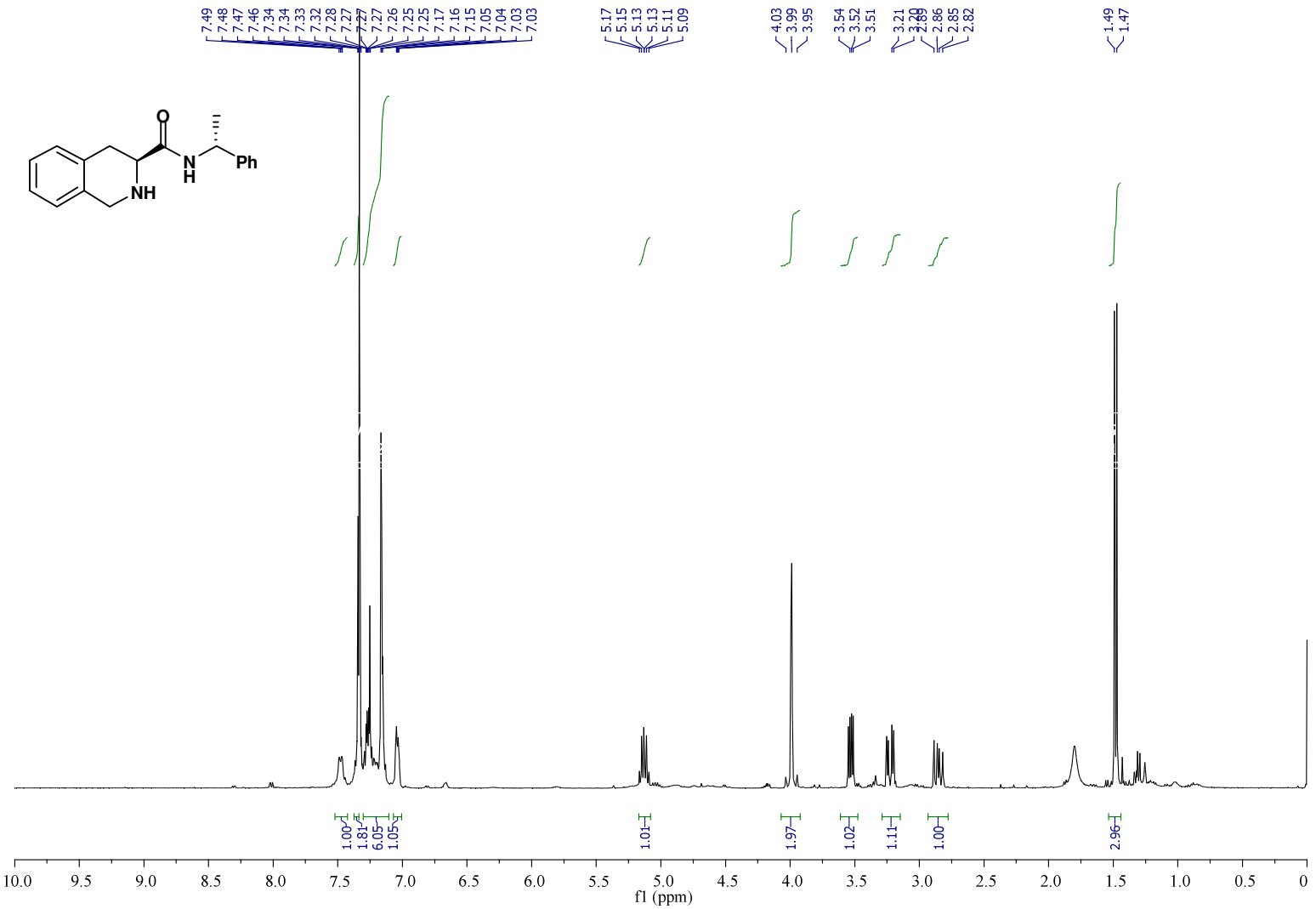
^{1}H NMR (400 MHz) Spectrum of Compound **6e** in $CDCl_3$



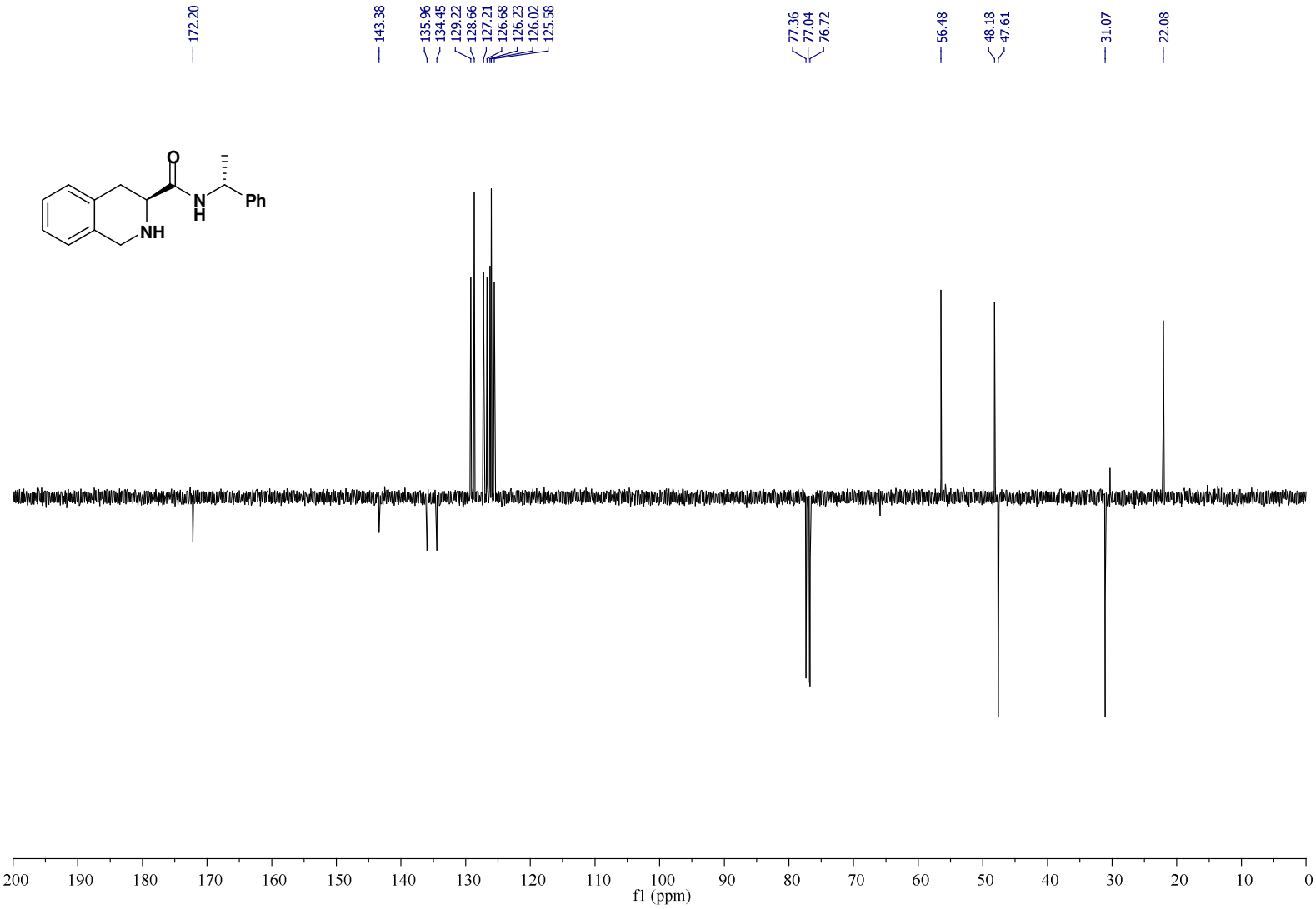
^{13}C NMR (400 MHz) Spectrum of Compound **6e** in $CDCl_3$



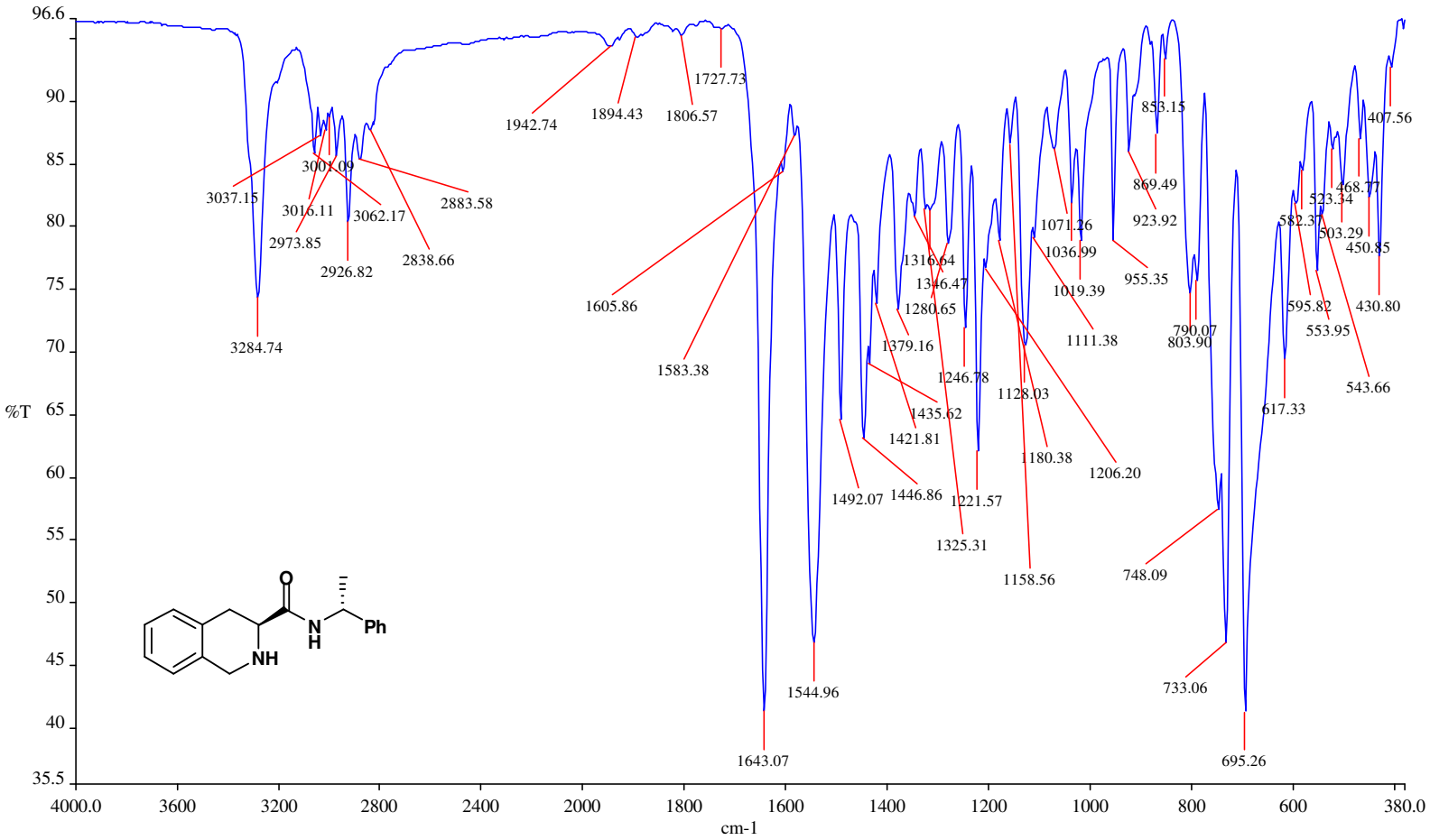
IR Spectrum of Compound **6e**



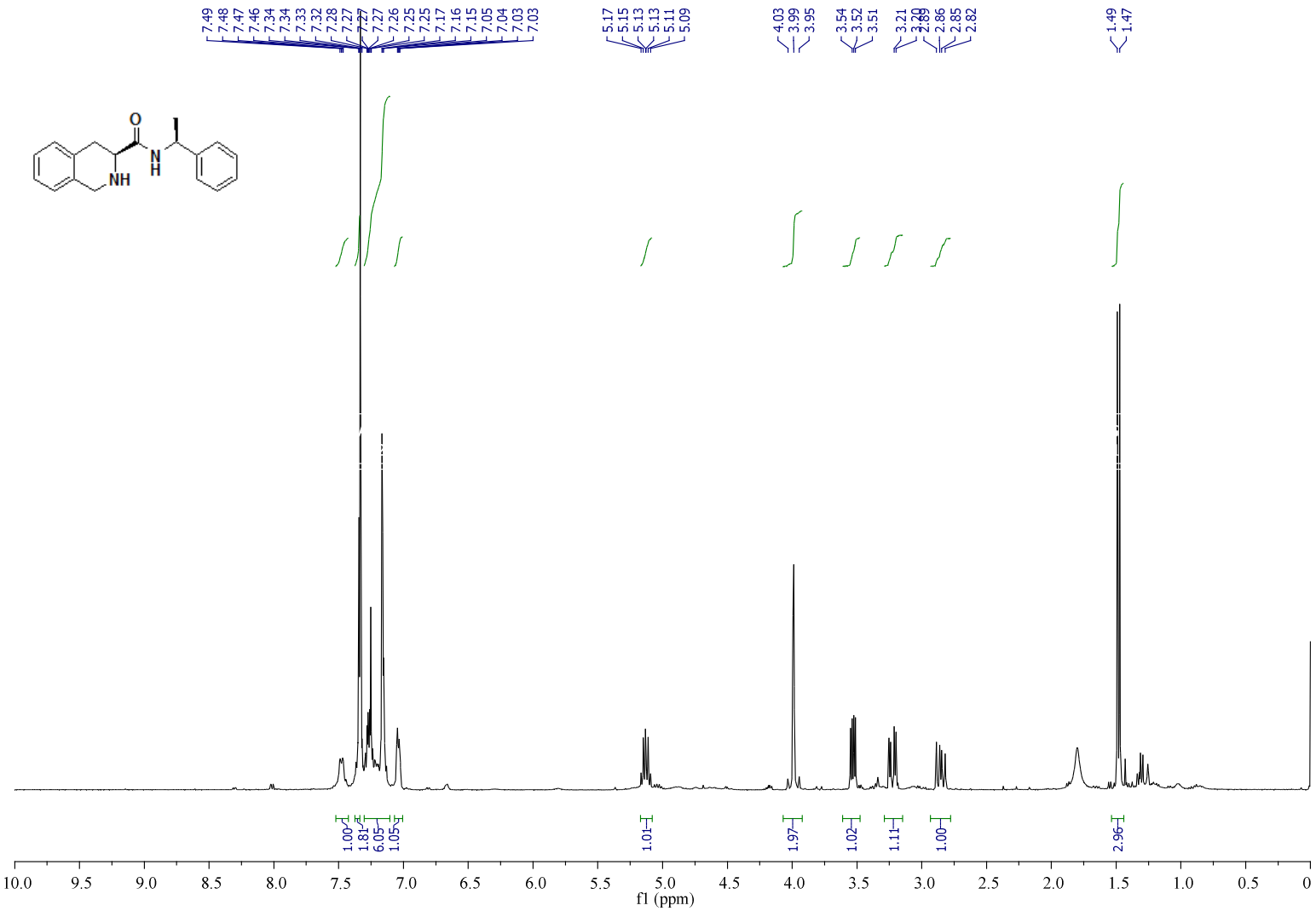
^{1}H NMR (400 MHz) Spectrum of Compound **6f** in $CDCl_3$



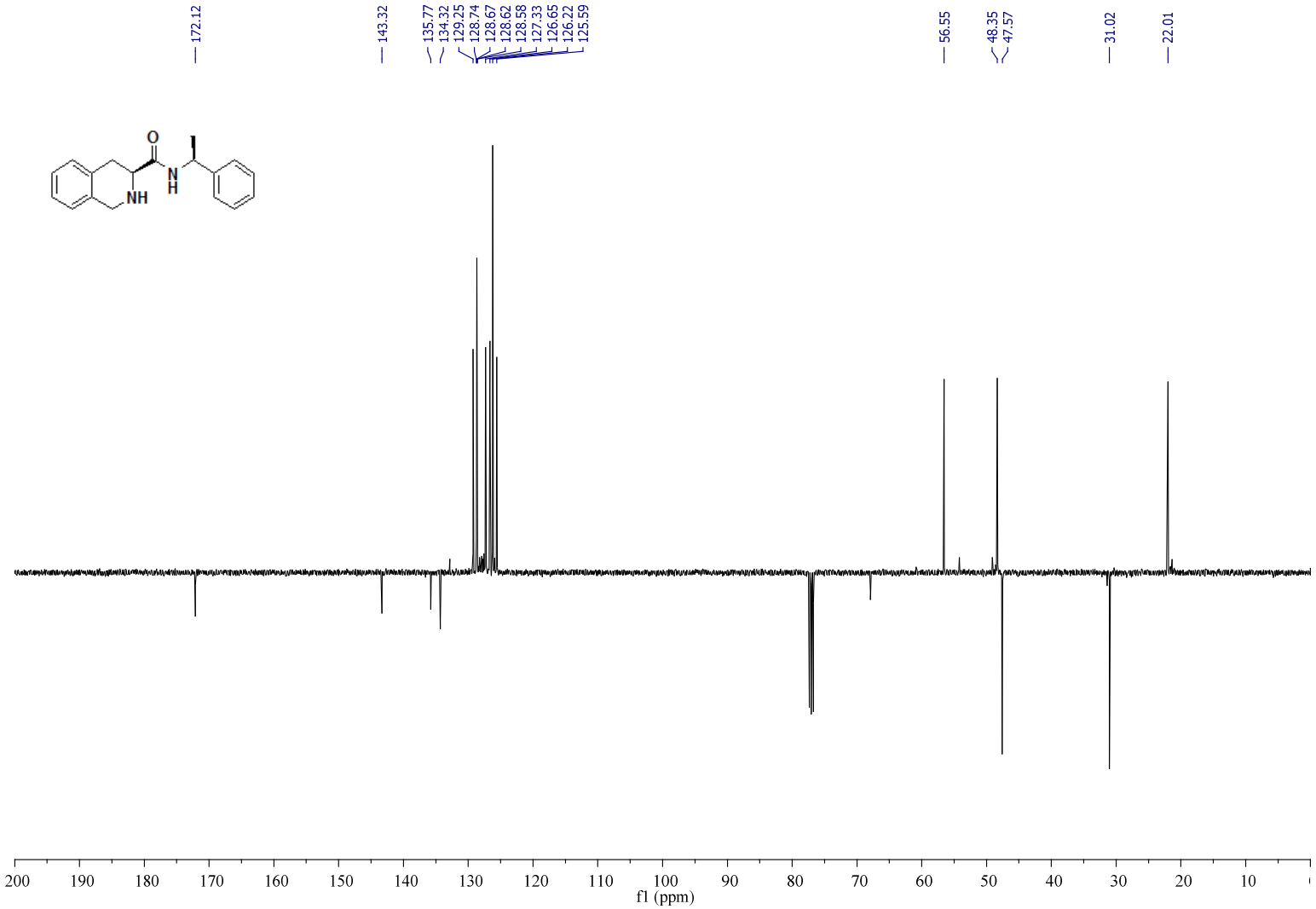
^{13}C NMR (400 MHz) Spectrum of Compound **6f** in $CDCl_3$



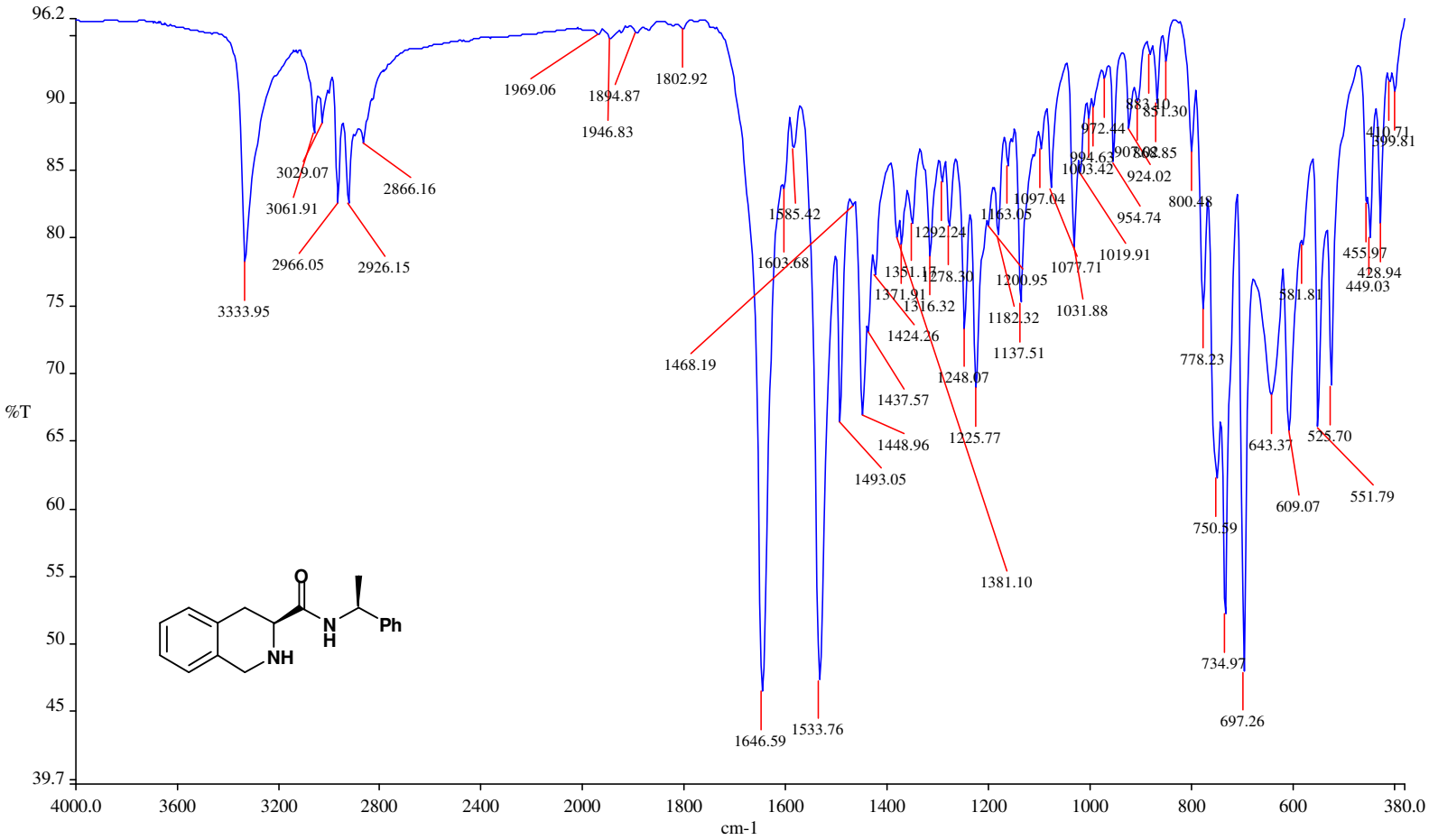
IR Spectrum of Compound **6f**



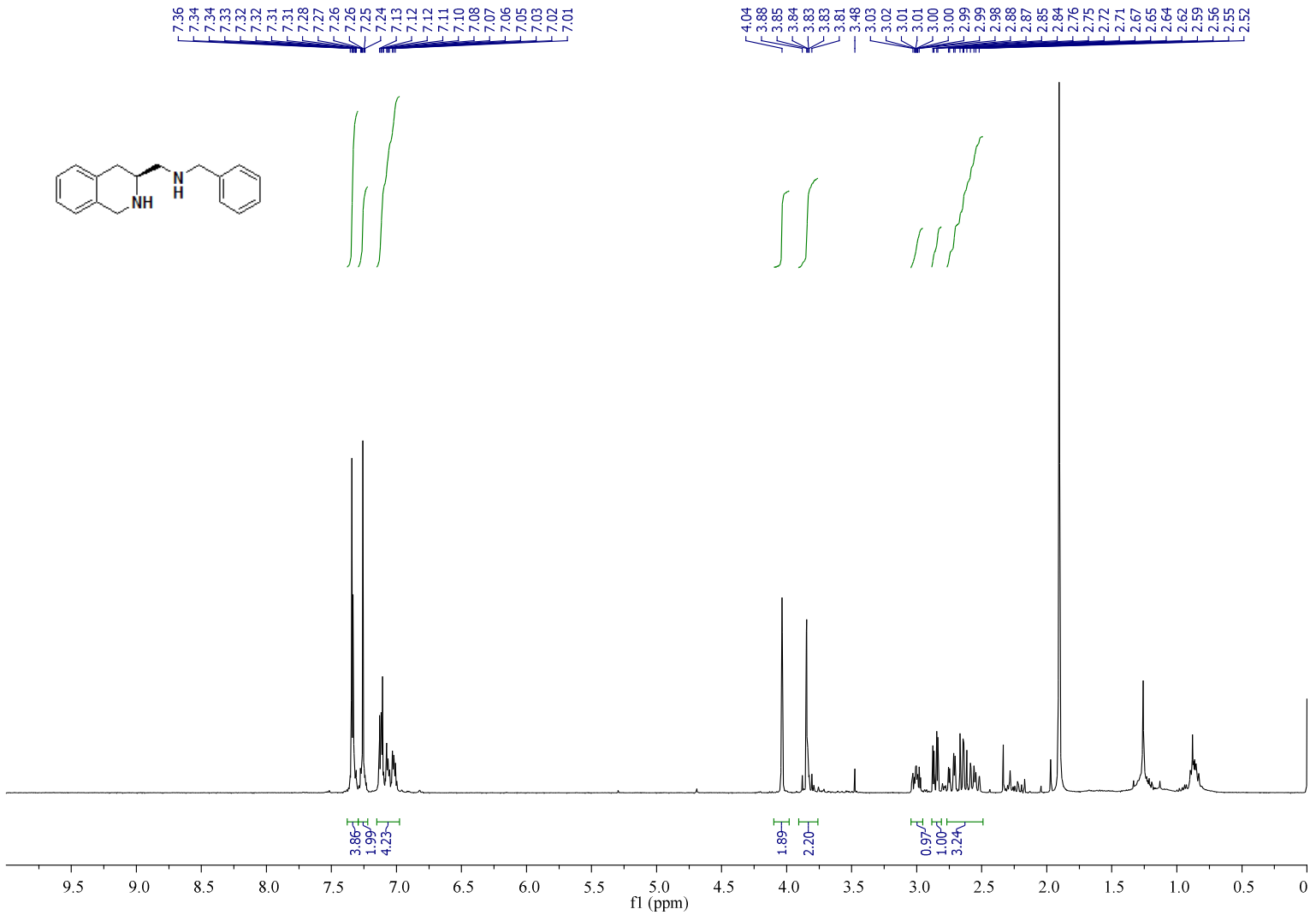
^{1}H NMR (400 MHz) Spectrum of Compound **6g** in $CDCl_3$



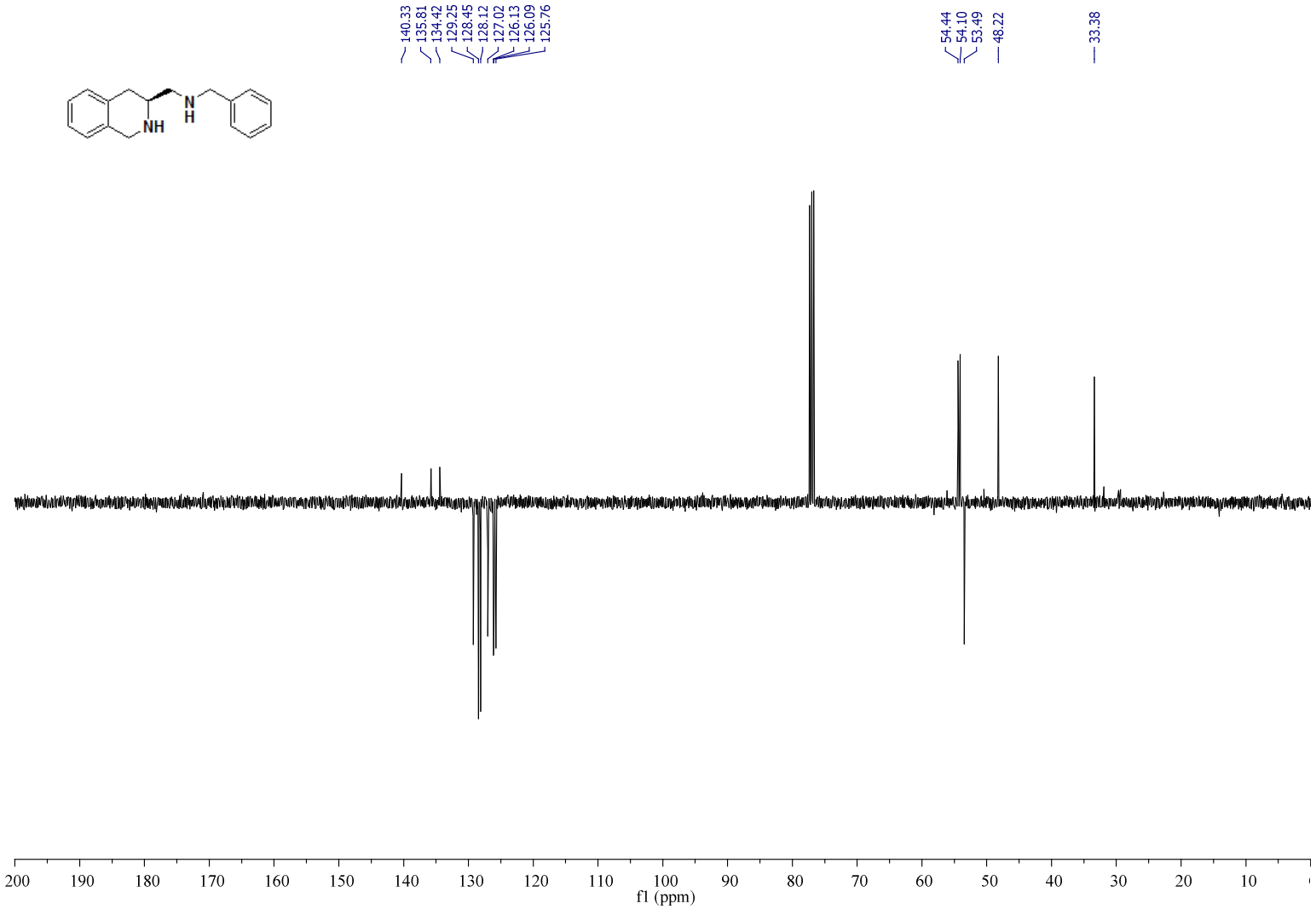
^{13}C NMR (400 MHz) Spectrum of Compound **6g** in $CDCl_3$



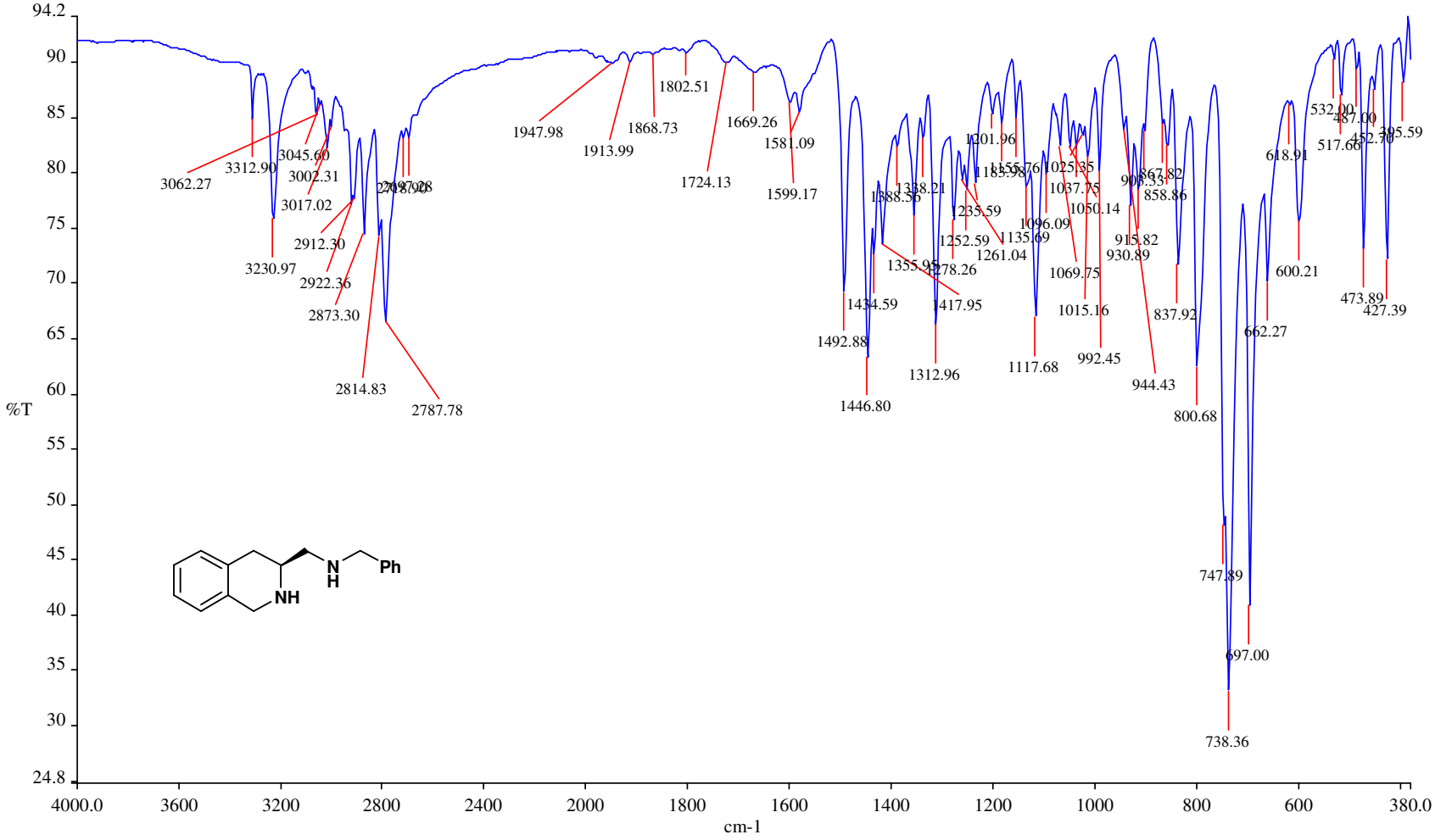
IR Spectrum of Compound **6g**



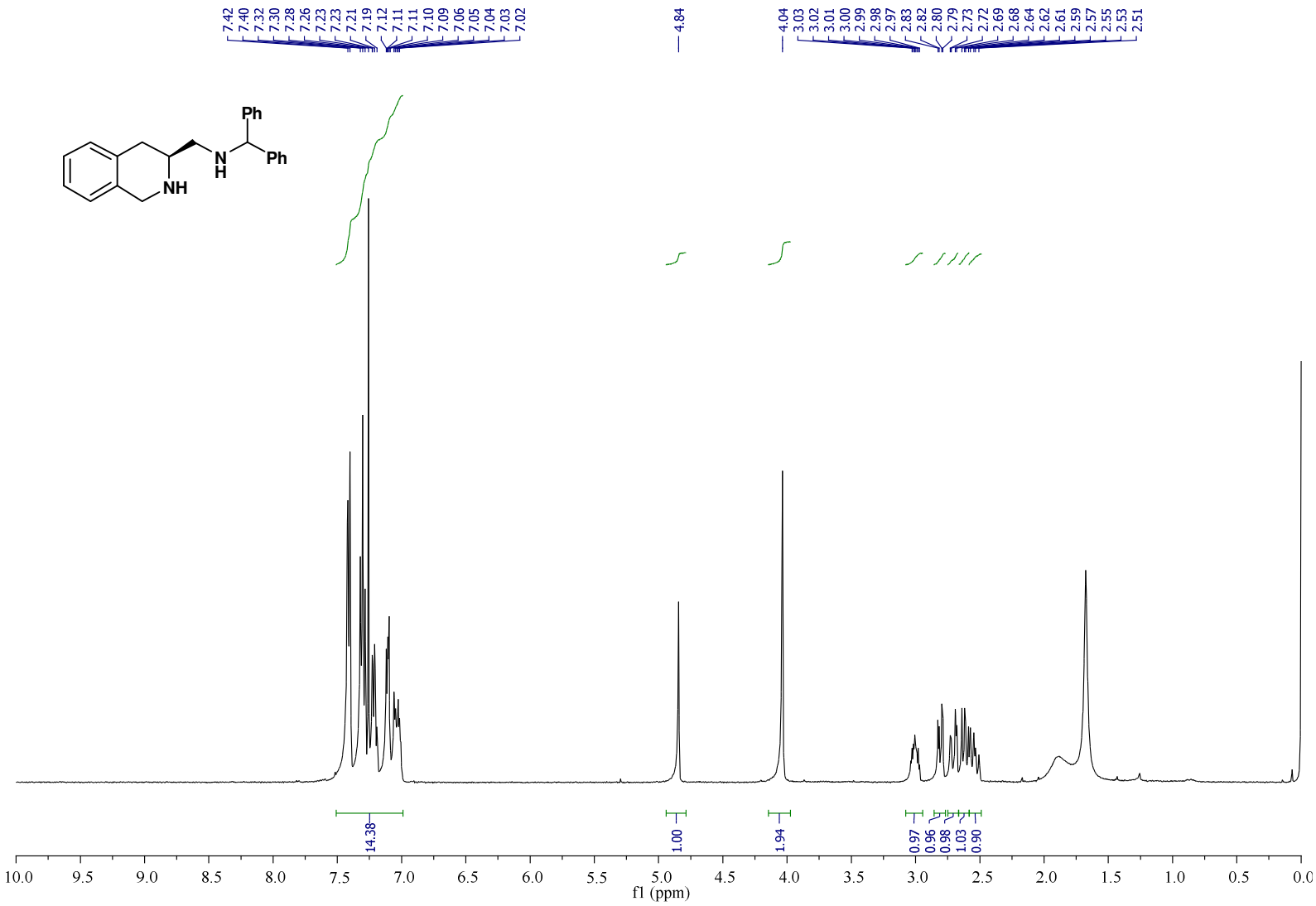
^{1}H NMR (400 MHz) Spectrum of Compound **2a** in $CDCl_3$



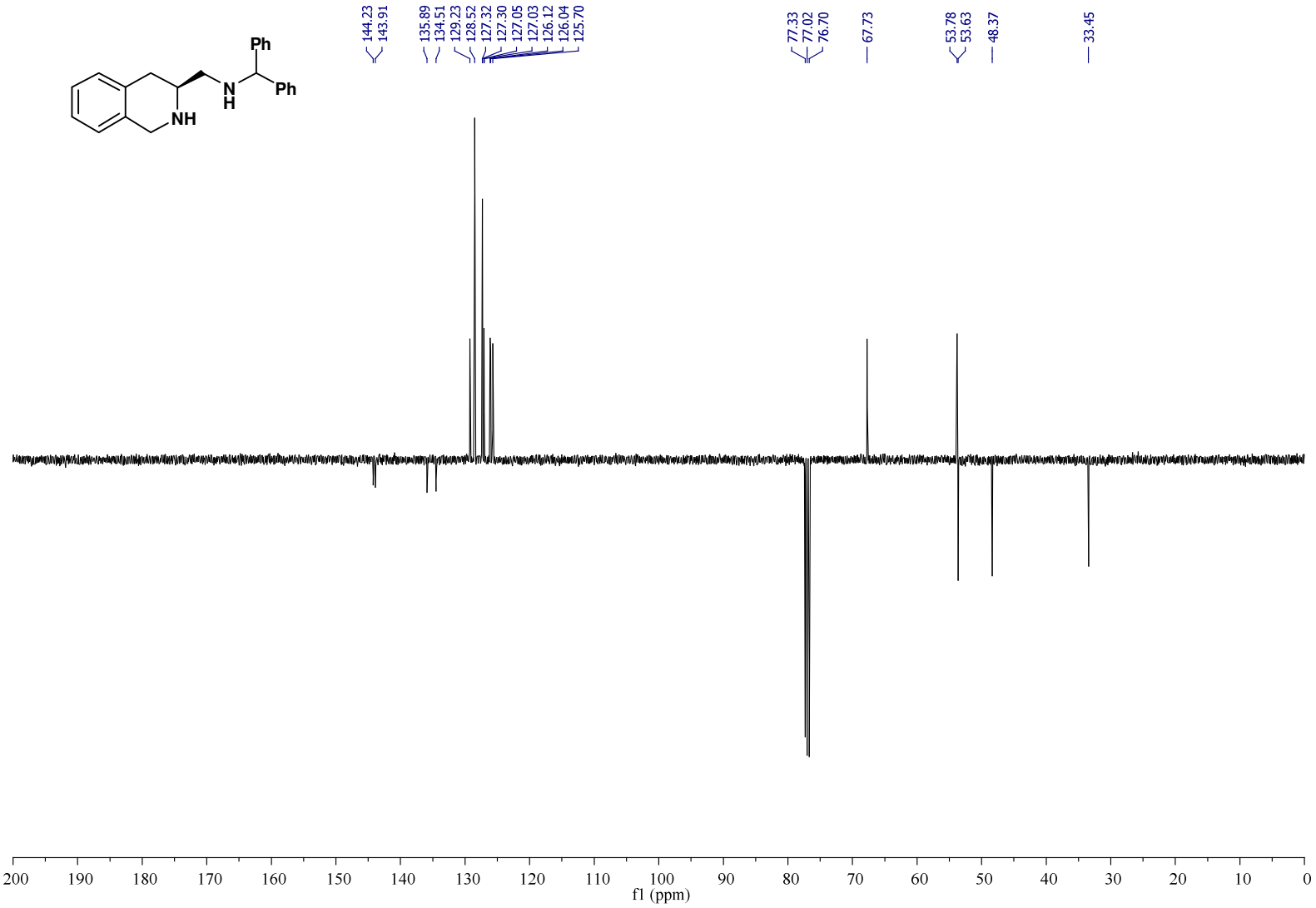
^{13}C NMR (400 MHz) Spectrum of Compound **2a** in $CDCl_3$



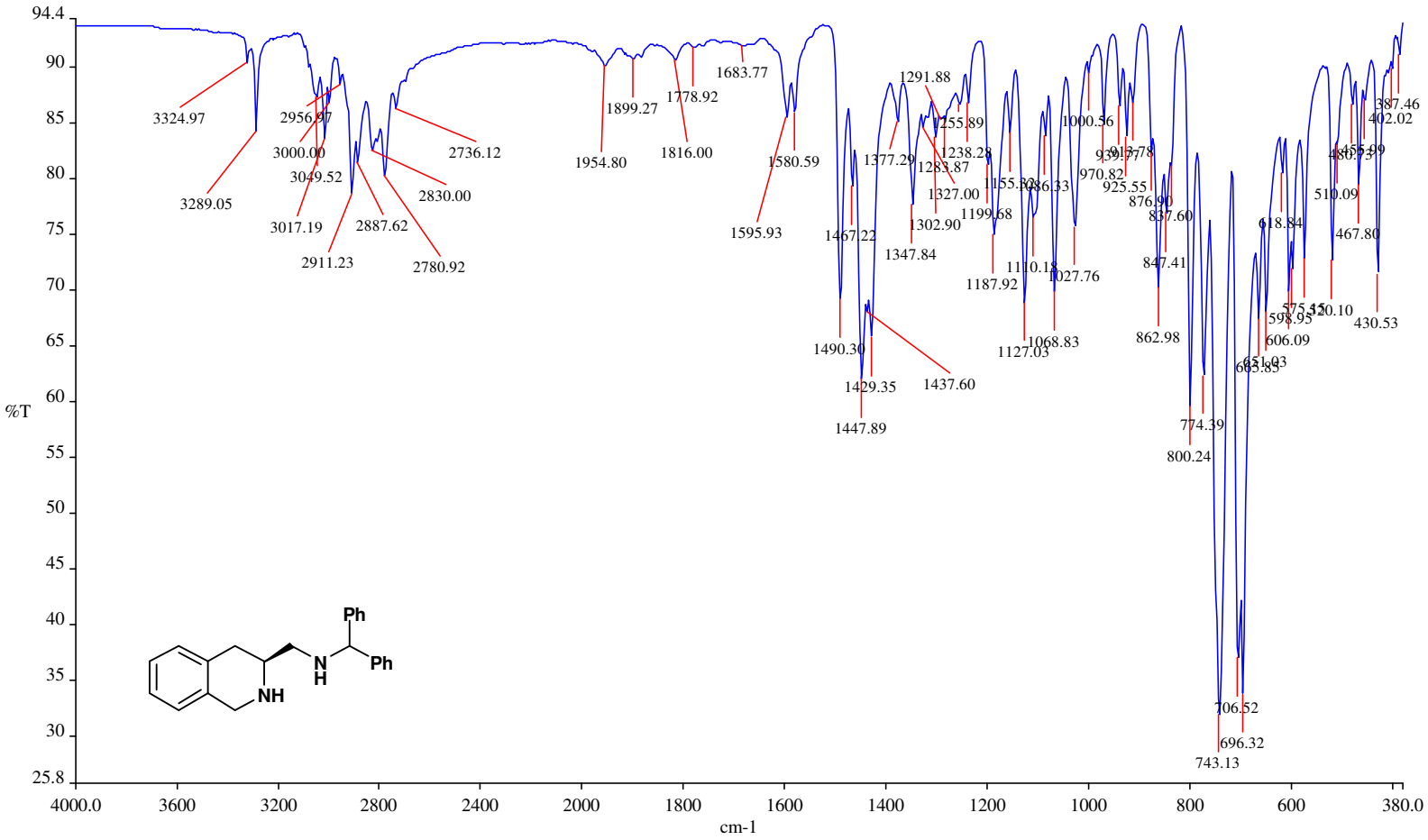
IR Spectrum of Compound **2a**



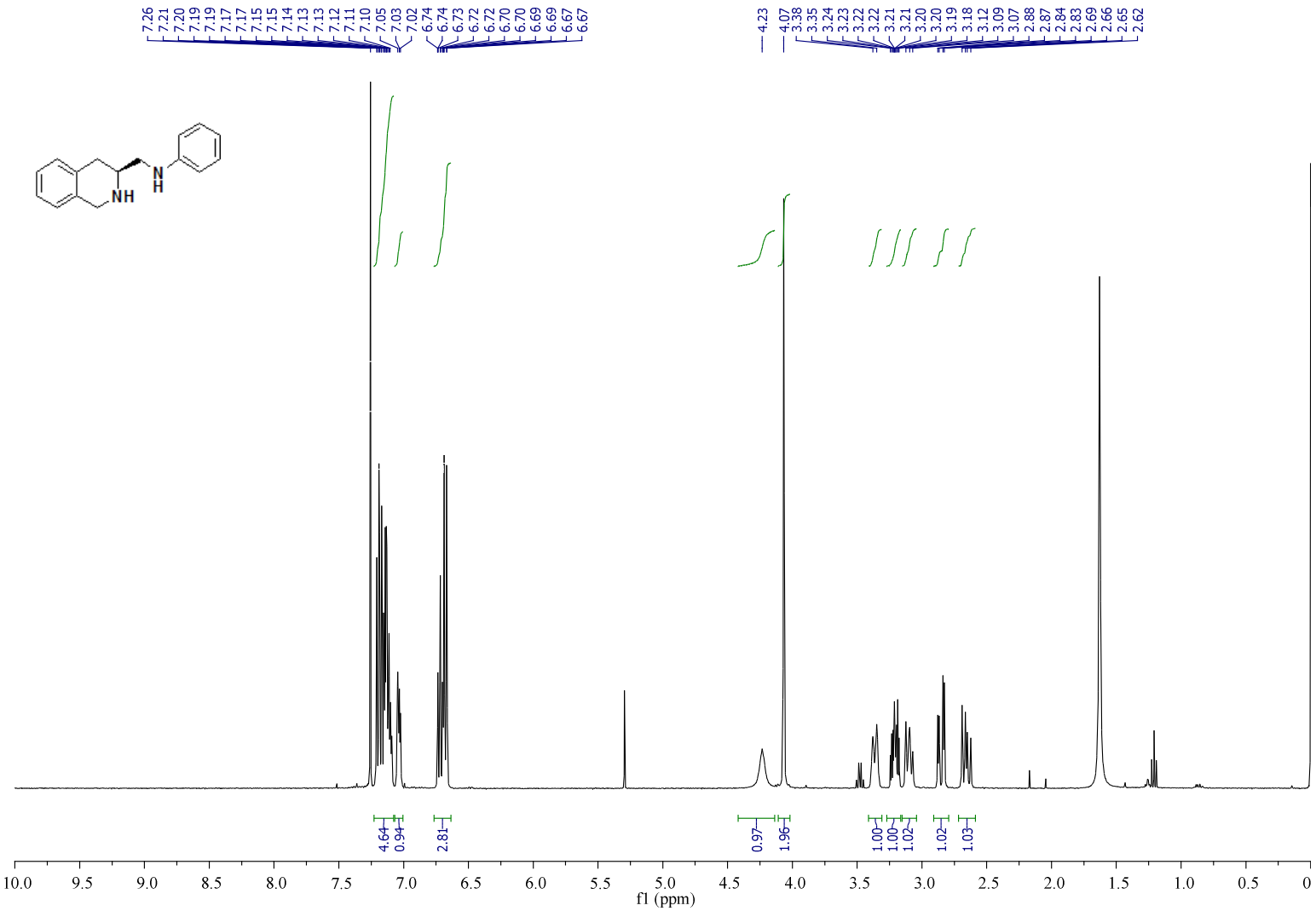
^{1}H NMR (400 MHz) Spectrum of Compound **2b** in $CDCl_3$



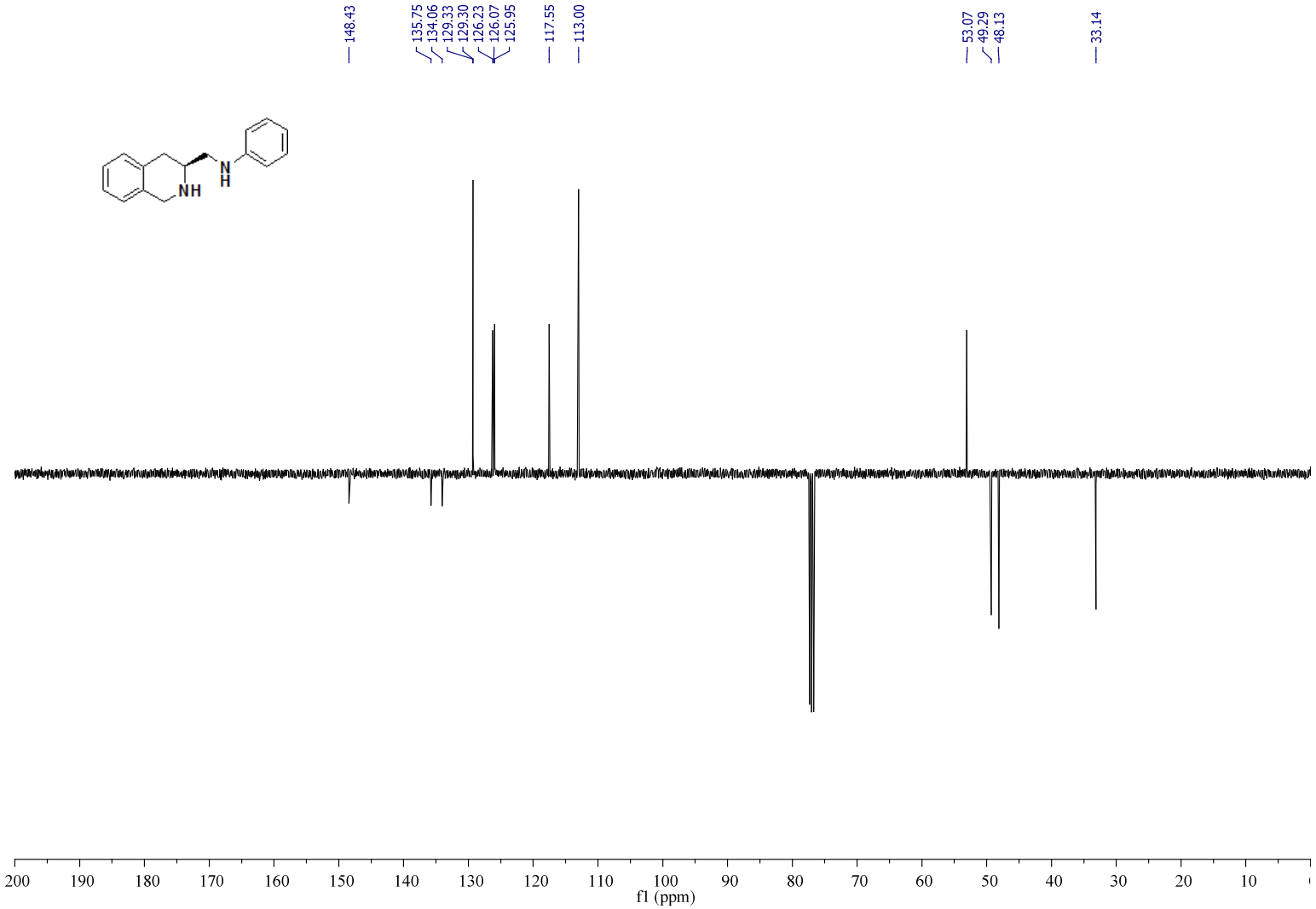
^{13}C NMR (400 MHz) Spectrum of Compound **2b** in $CDCl_3$



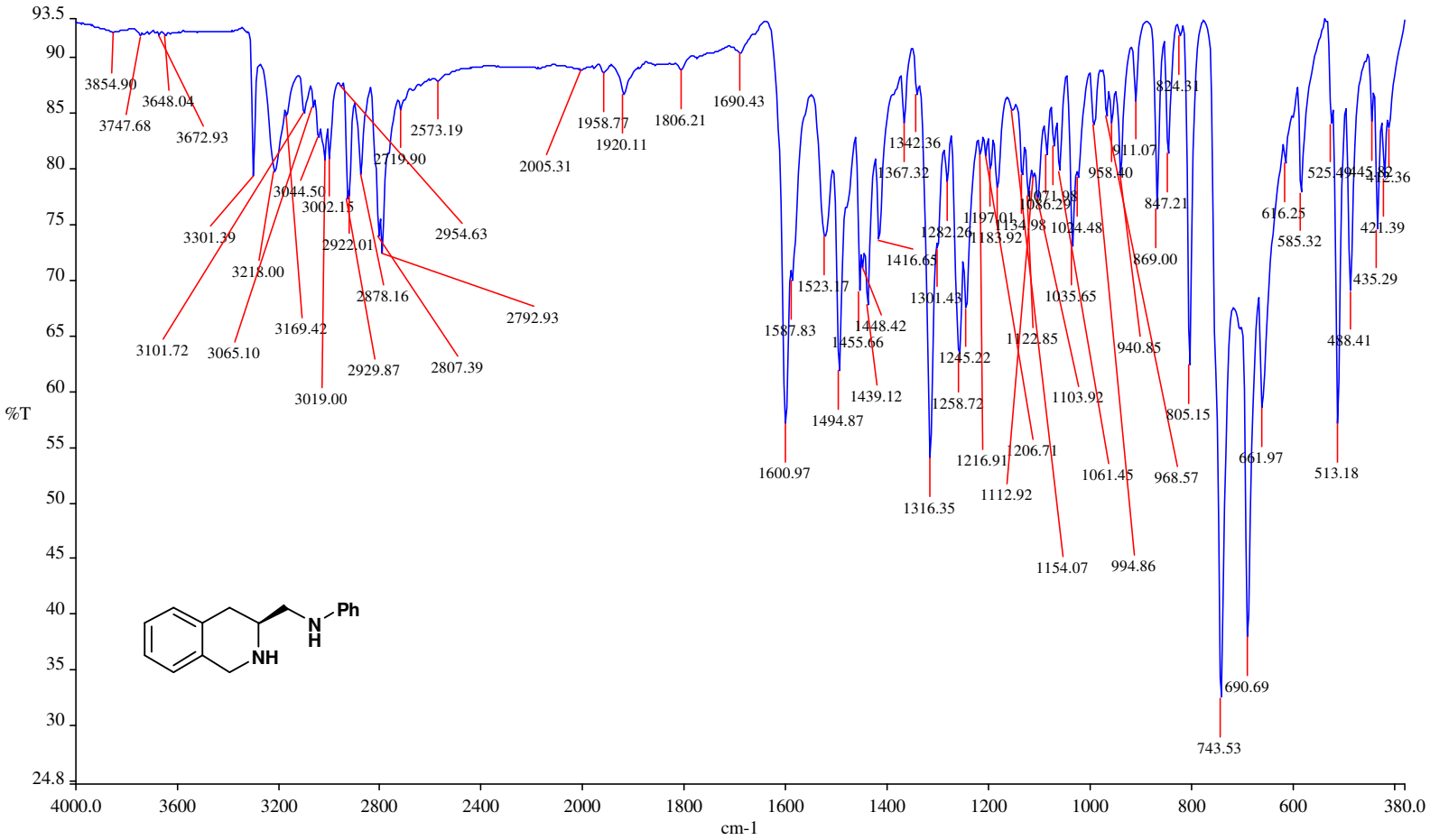
IR Spectrum of Compound **2b**



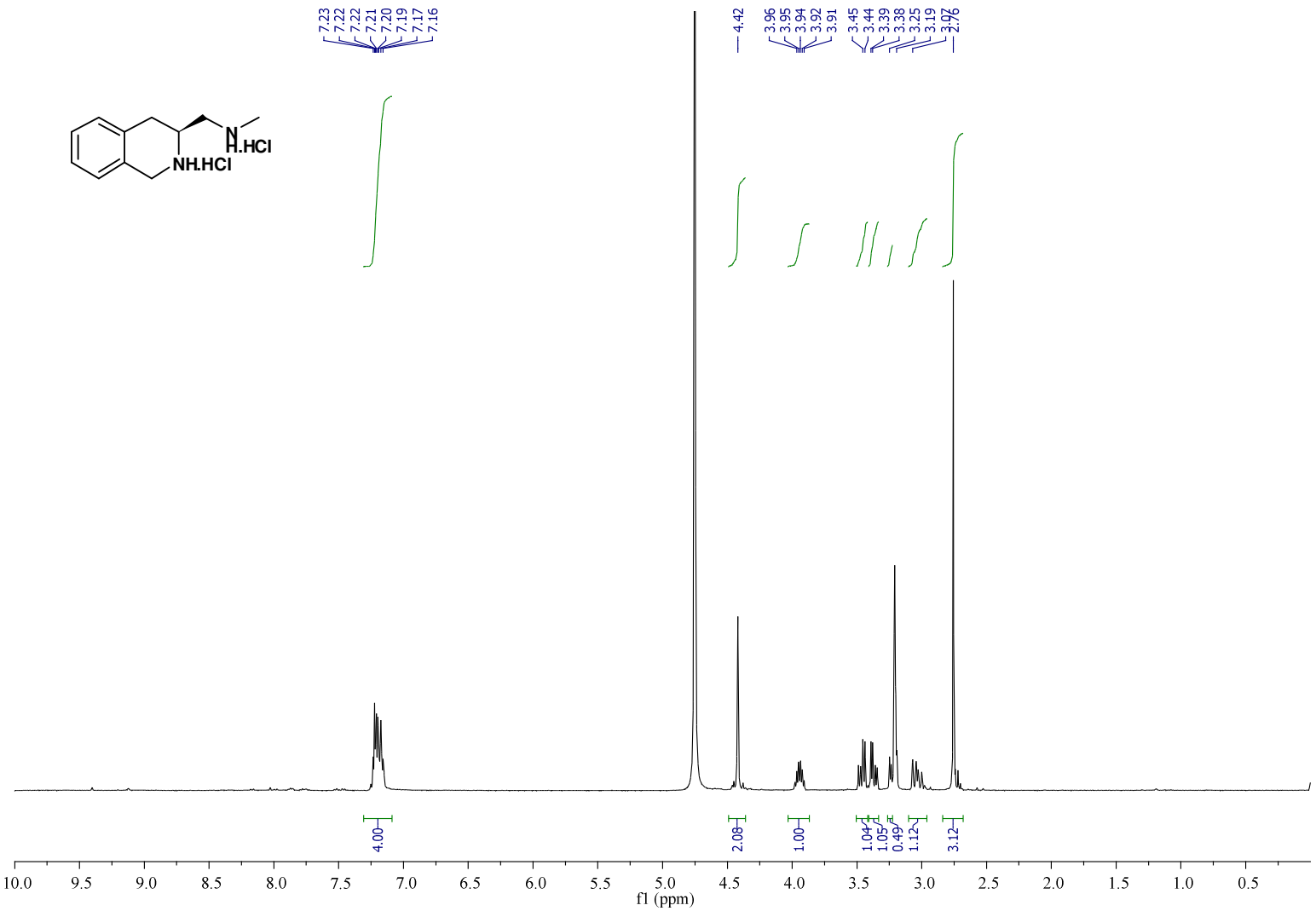
^{1}H NMR (400 MHz) Spectrum of Compound **2c** in $CDCl_3$



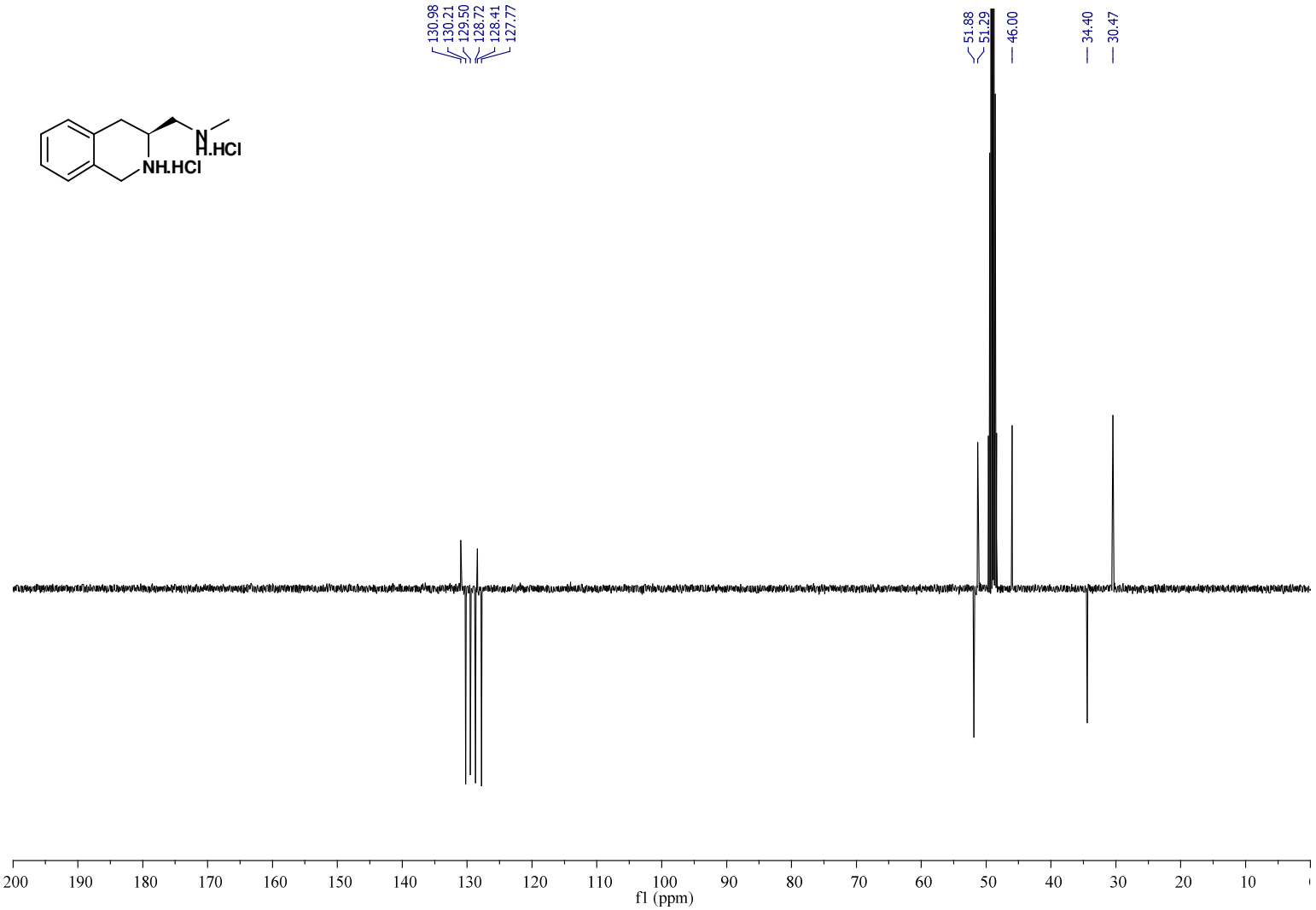
^{13}C NMR (400 MHz) Spectrum of Compound **2c** in $CDCl_3$



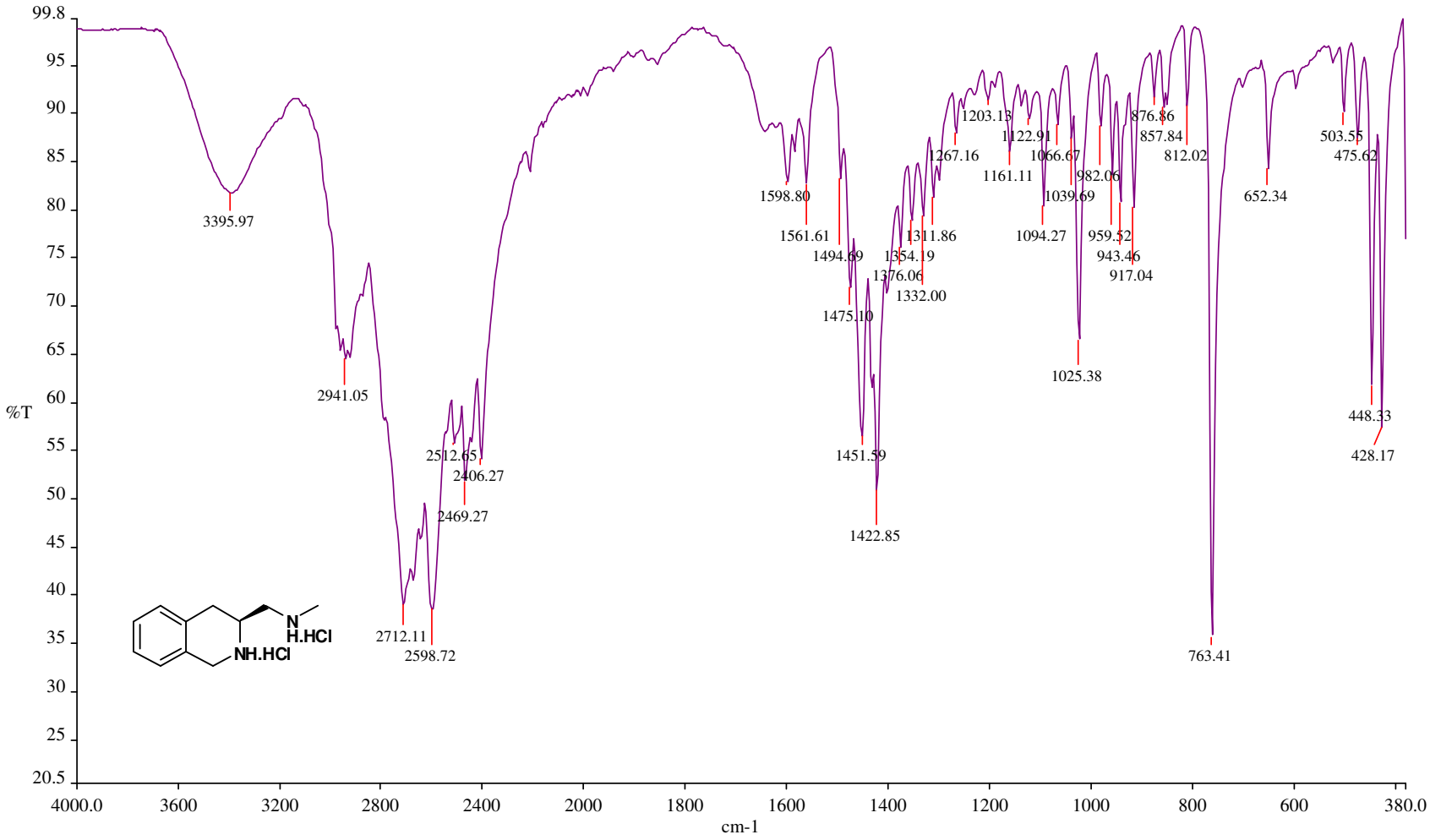
IR Spectrum of Compound **2c**



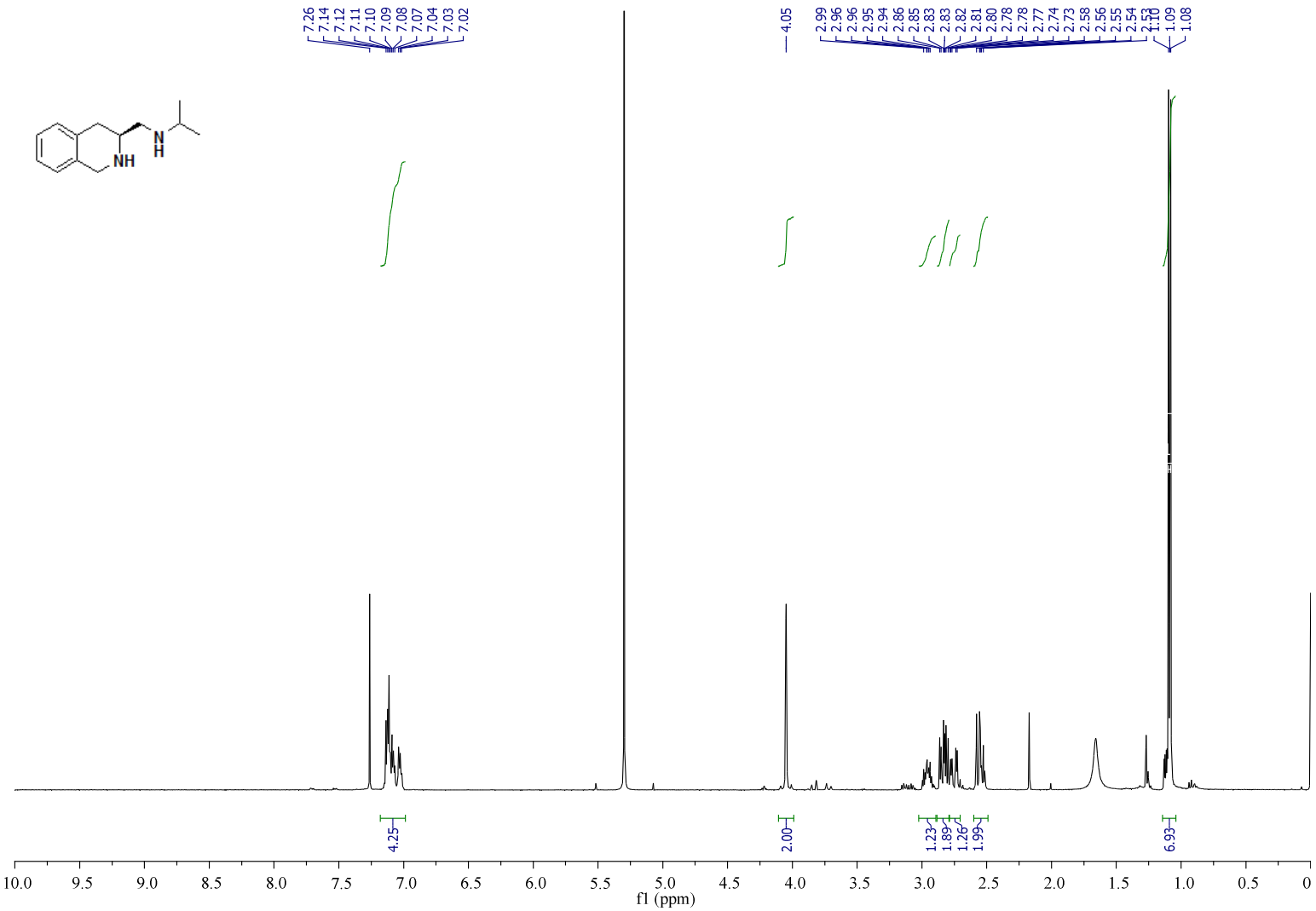
^{1}H NMR (400 MHz) Spectrum of Compound **2d** in MeOD



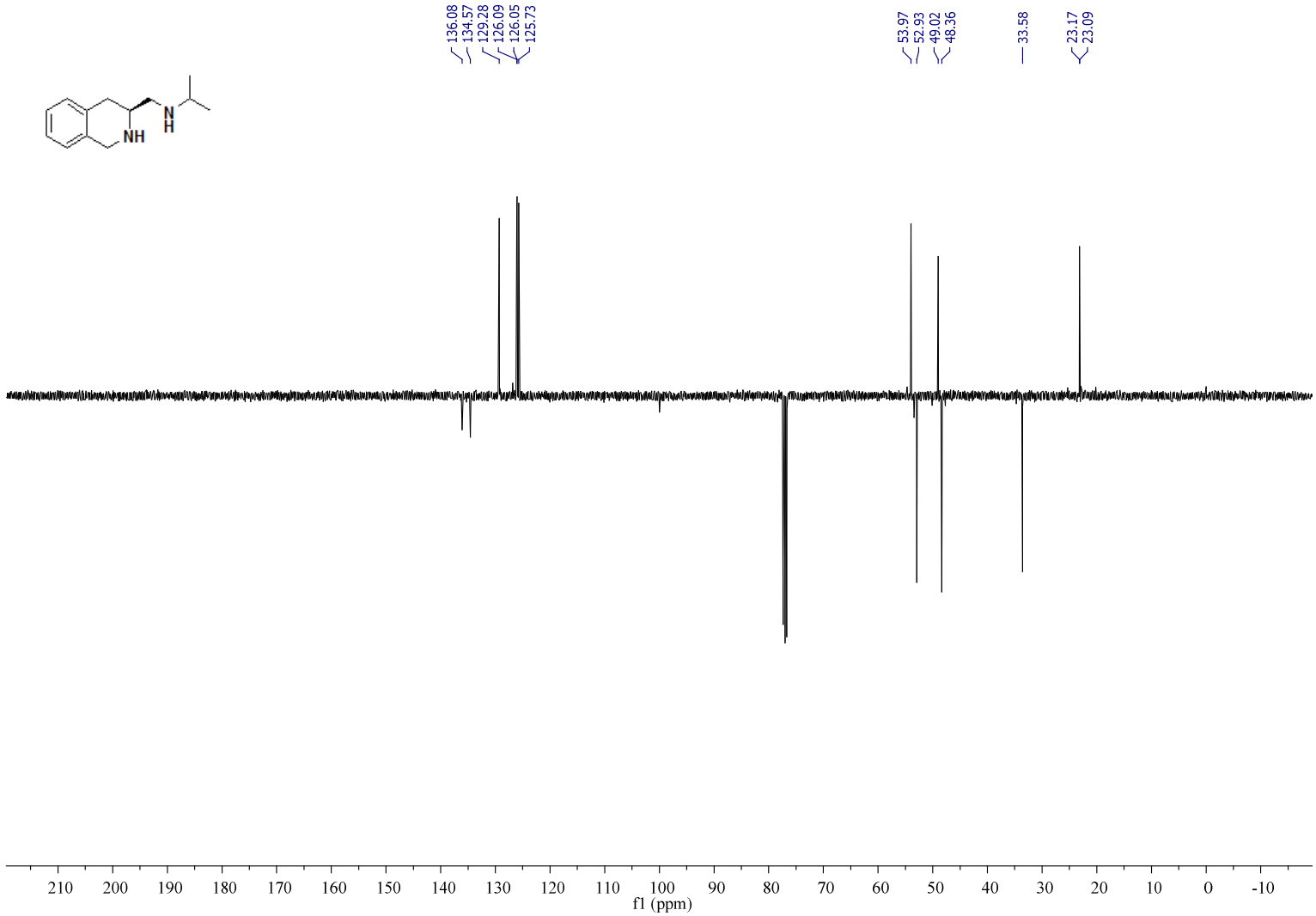
^{13}C NMR (400 MHz) Spectrum of Compound **2d** in MeOD



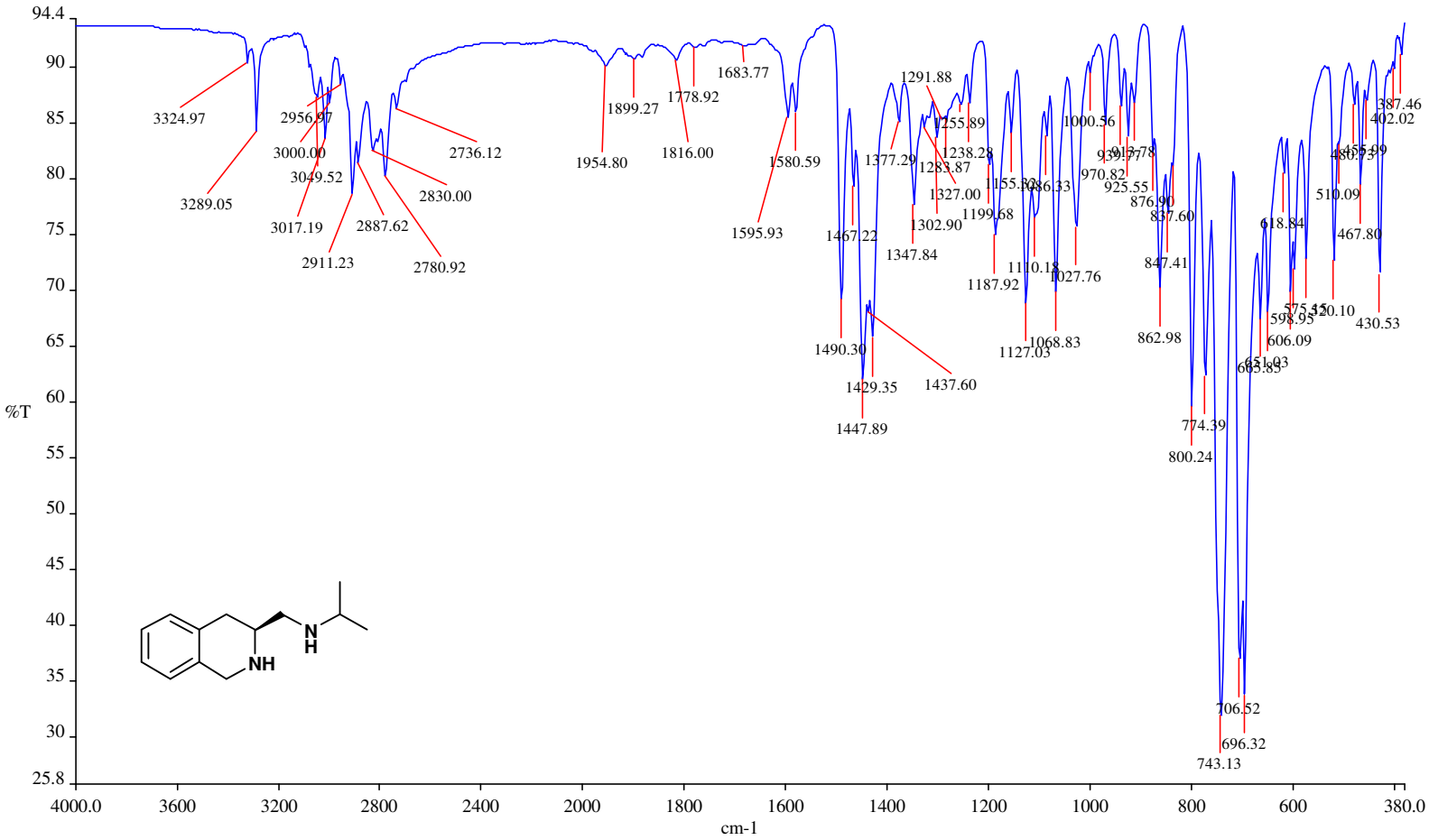
IR Spectrum of Compound **2d**



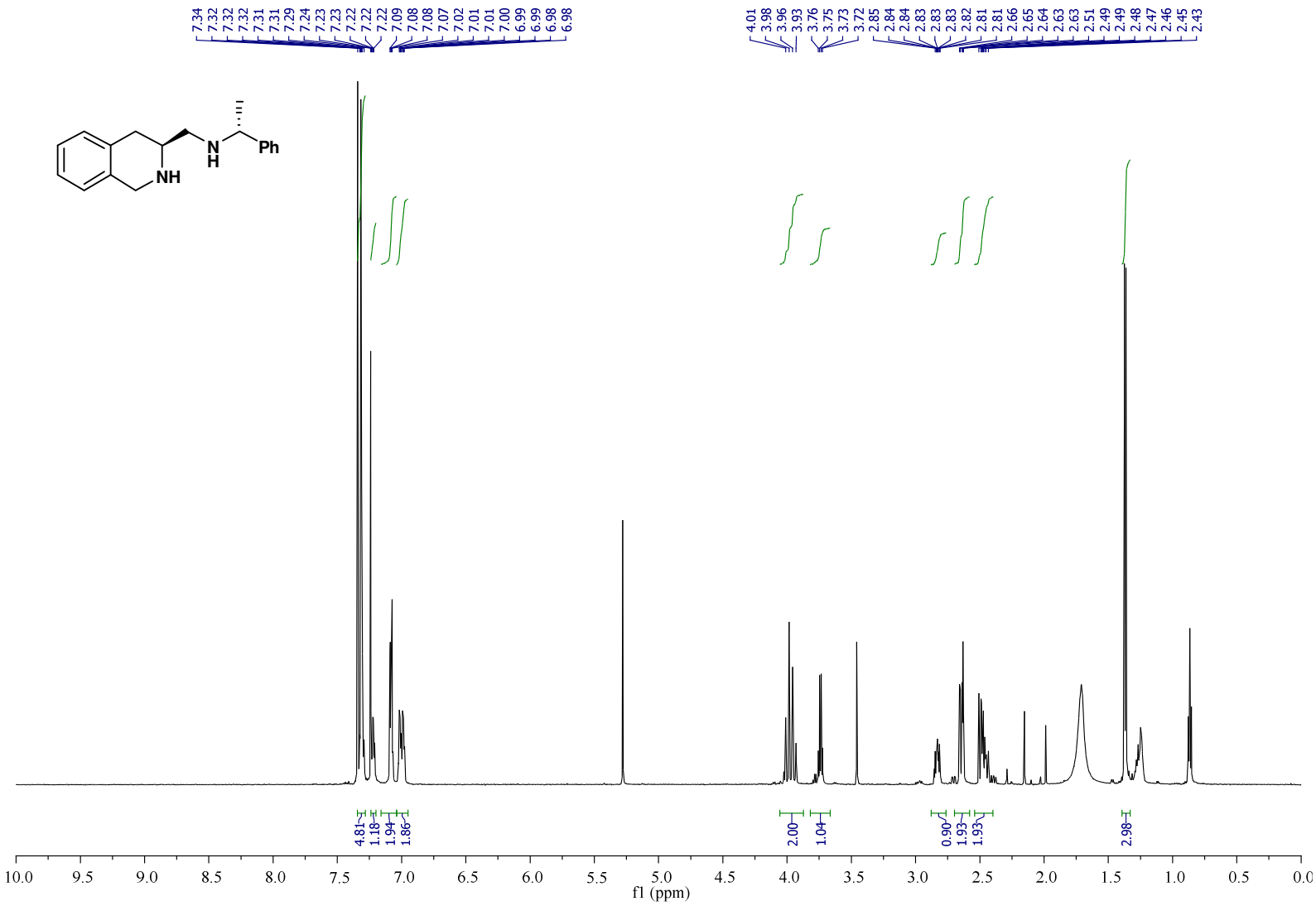
^{1}H NMR (400 MHz) Spectrum of Compound **2e** in $CDCl_3$



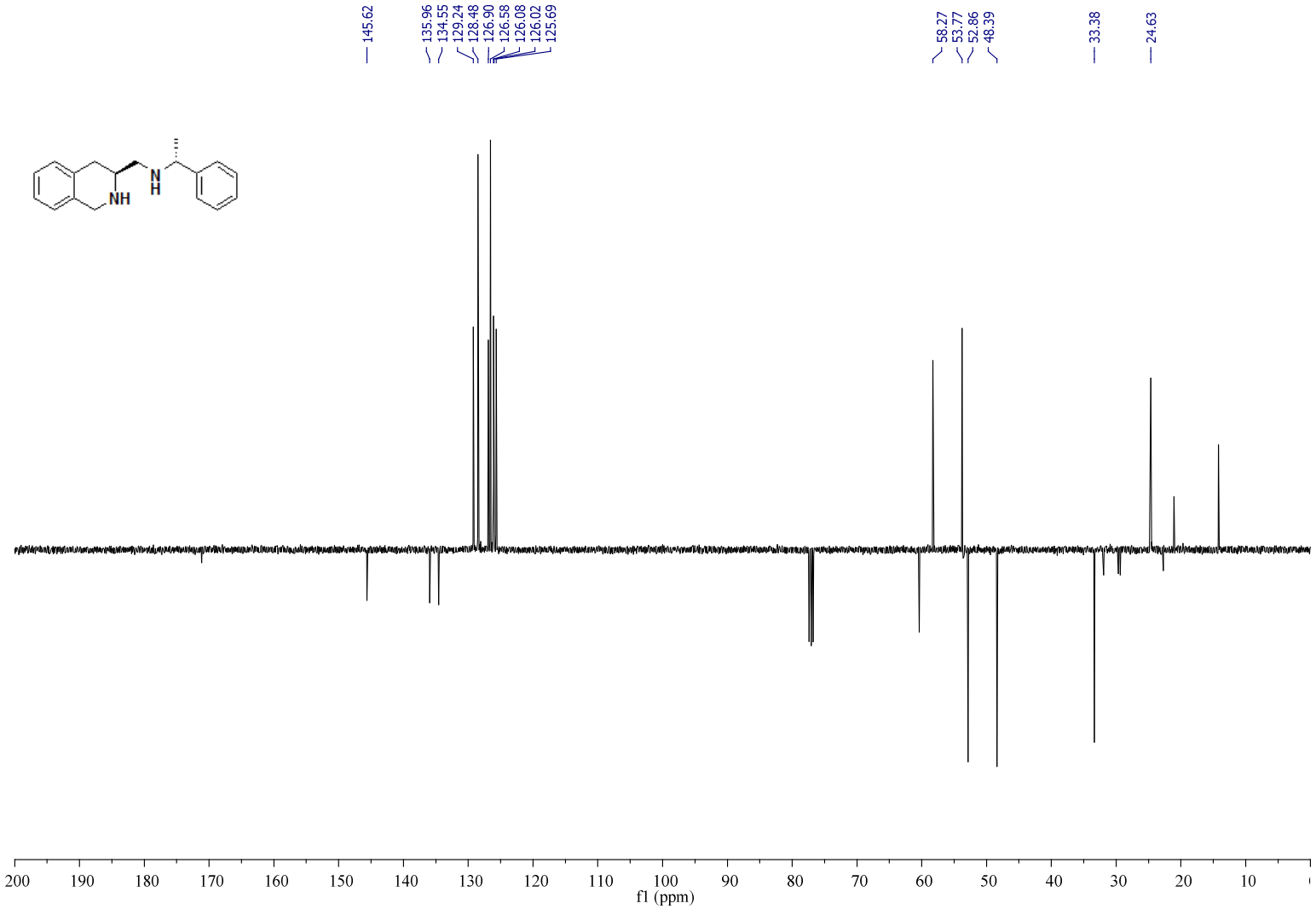
^{13}C NMR (400 MHz) Spectrum of Compound **2e** in $CDCl_3$



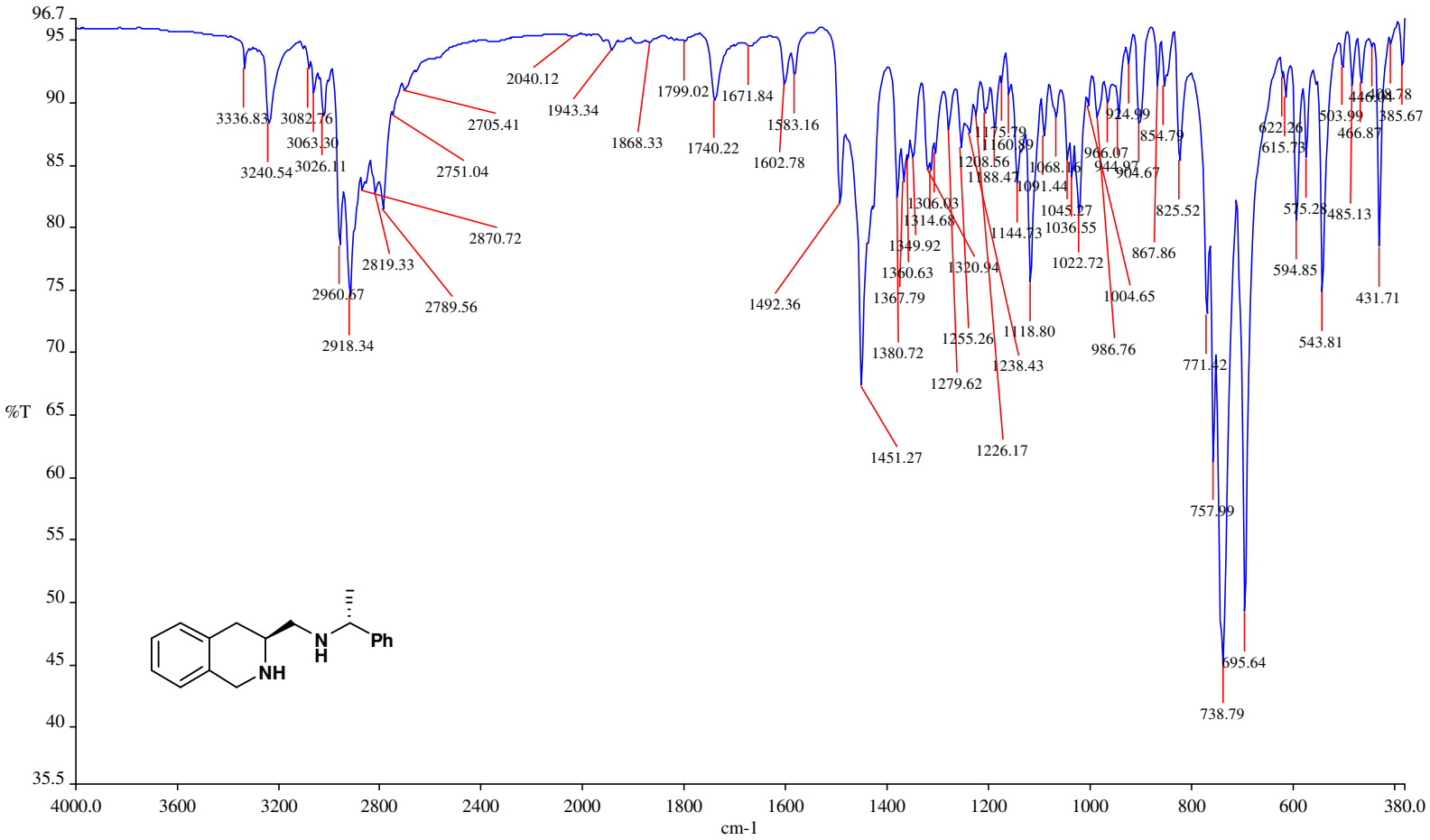
IR Spectrum of Compound **2e**



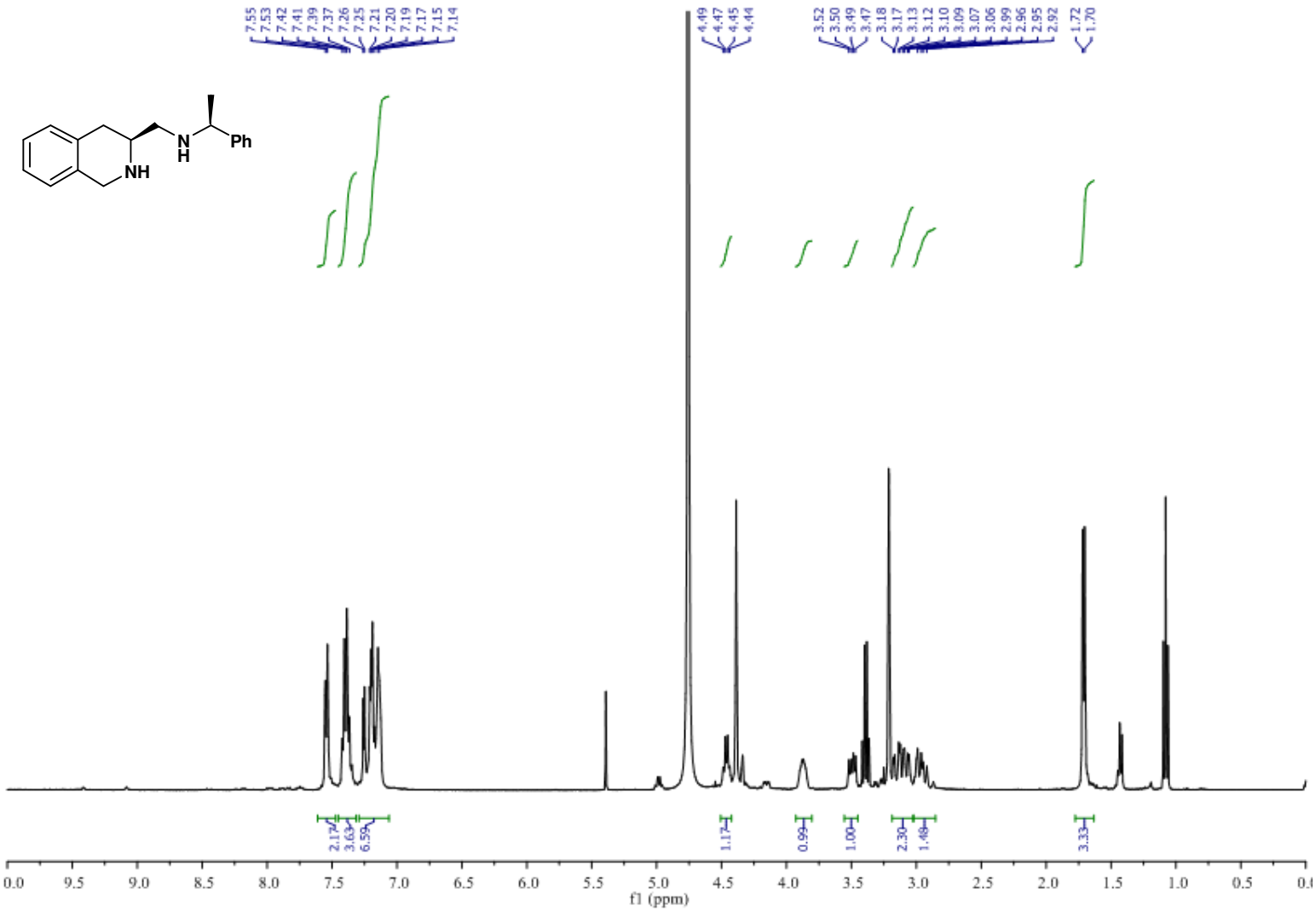
^{1}H NMR (400 MHz) Spectrum of Compound **2f** in $CDCl_3$



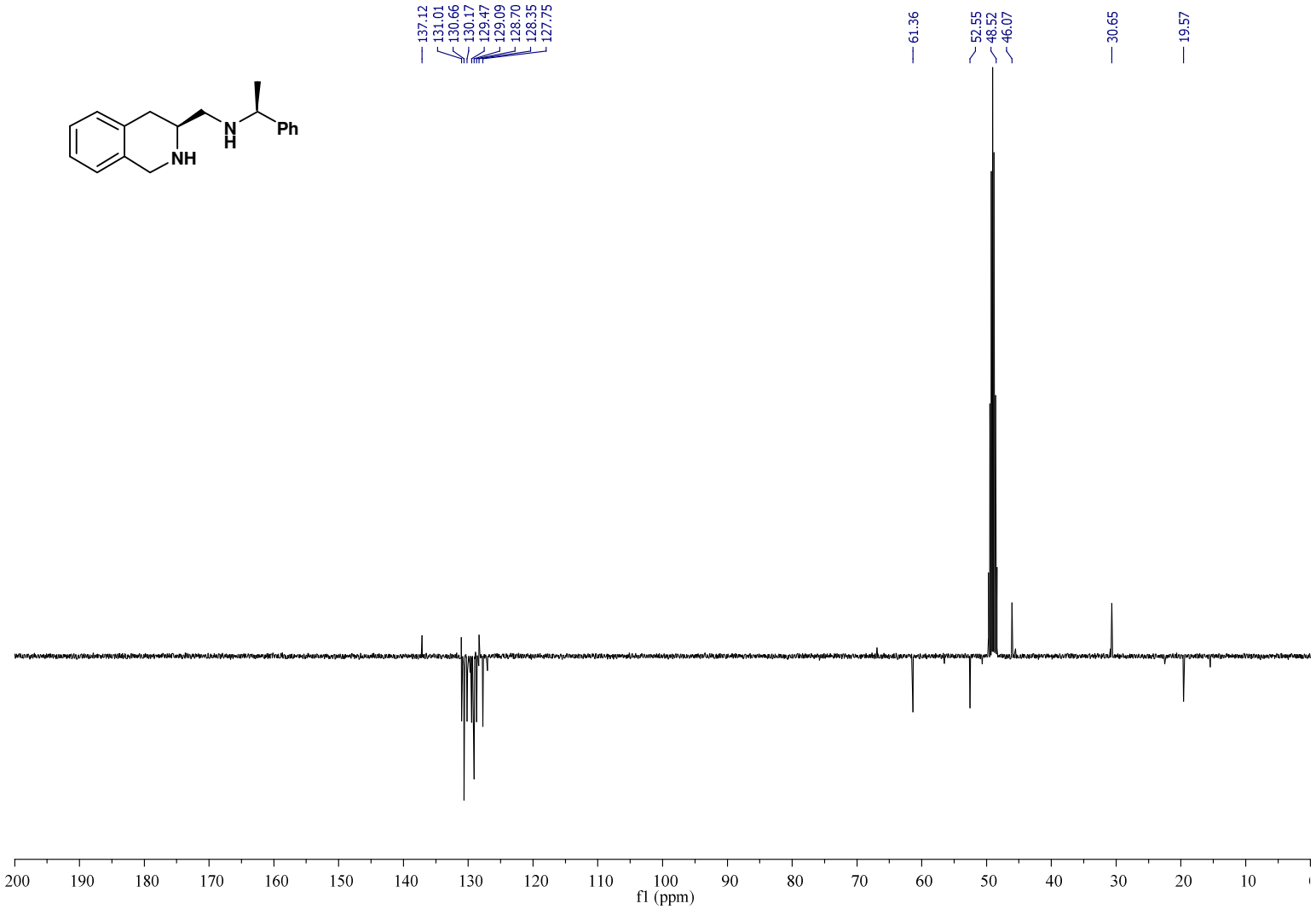
^{13}C NMR (400 MHz) Spectrum of Compound **2f** in $CDCl_3$



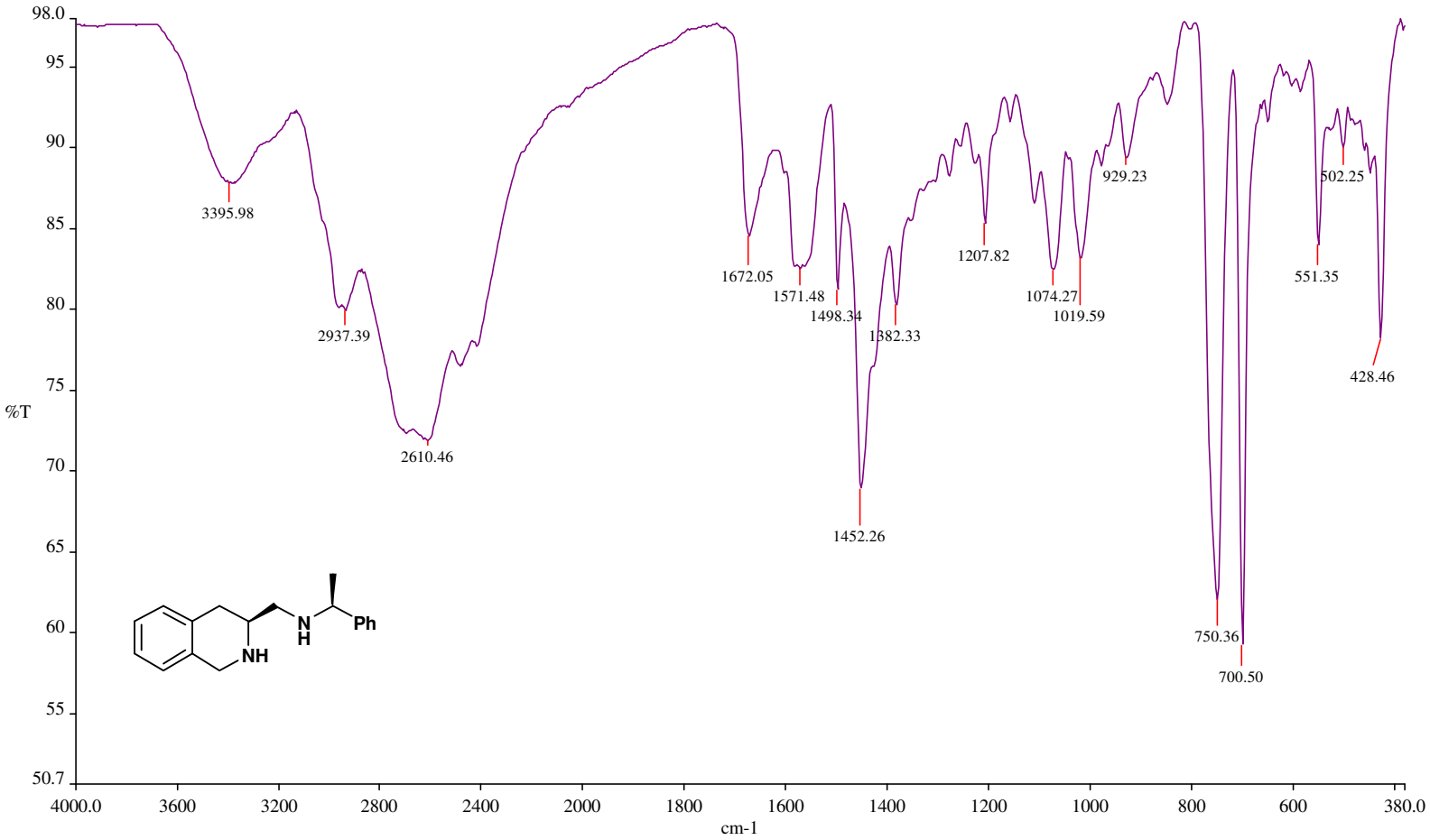
IR Spectrum of Compound **2f**



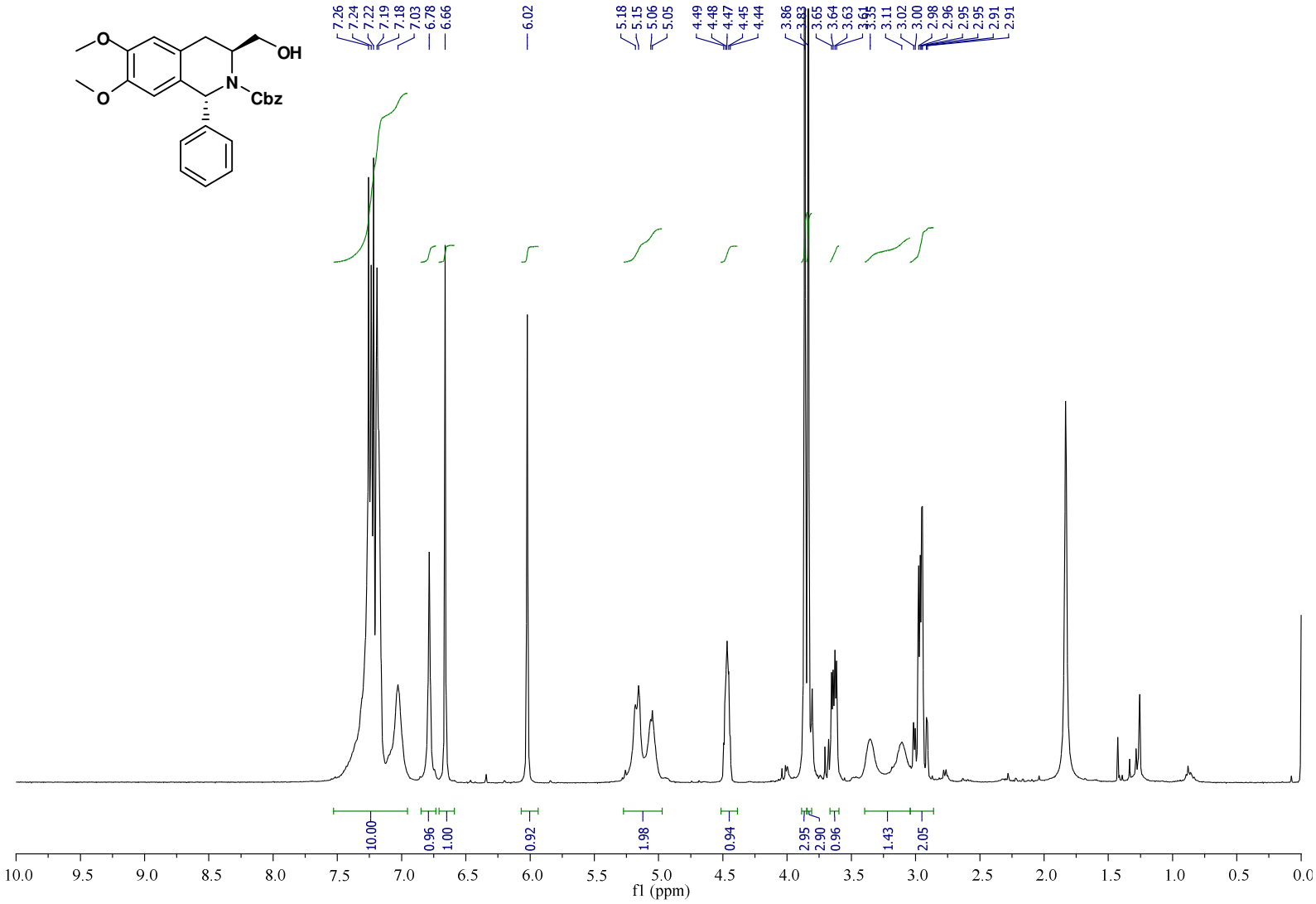
^{1}H NMR (400 MHz) Spectrum of Compound **2g** in MeOD



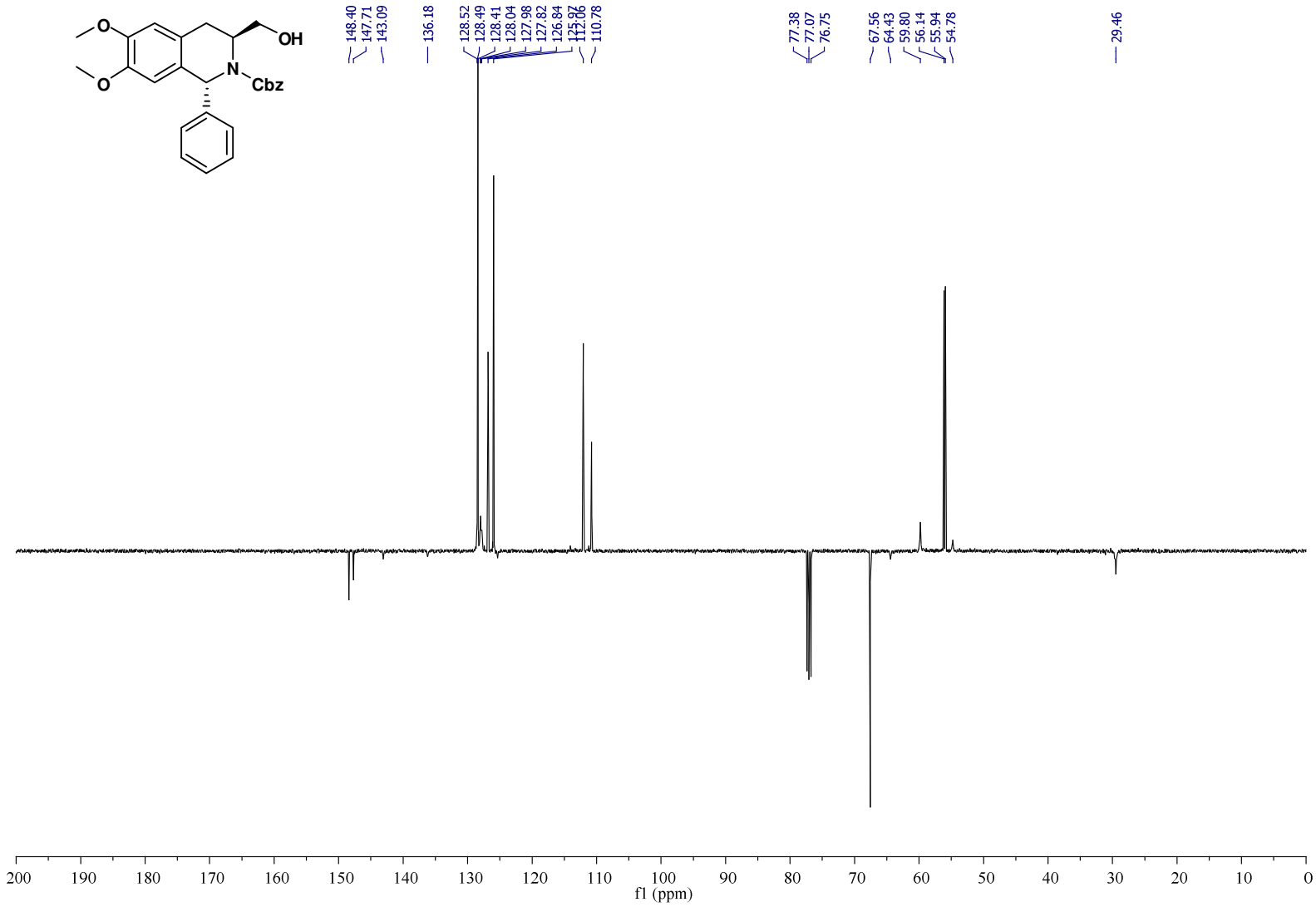
^{13}C NMR (400 MHz) Spectrum of Compound **2g** in MeOD



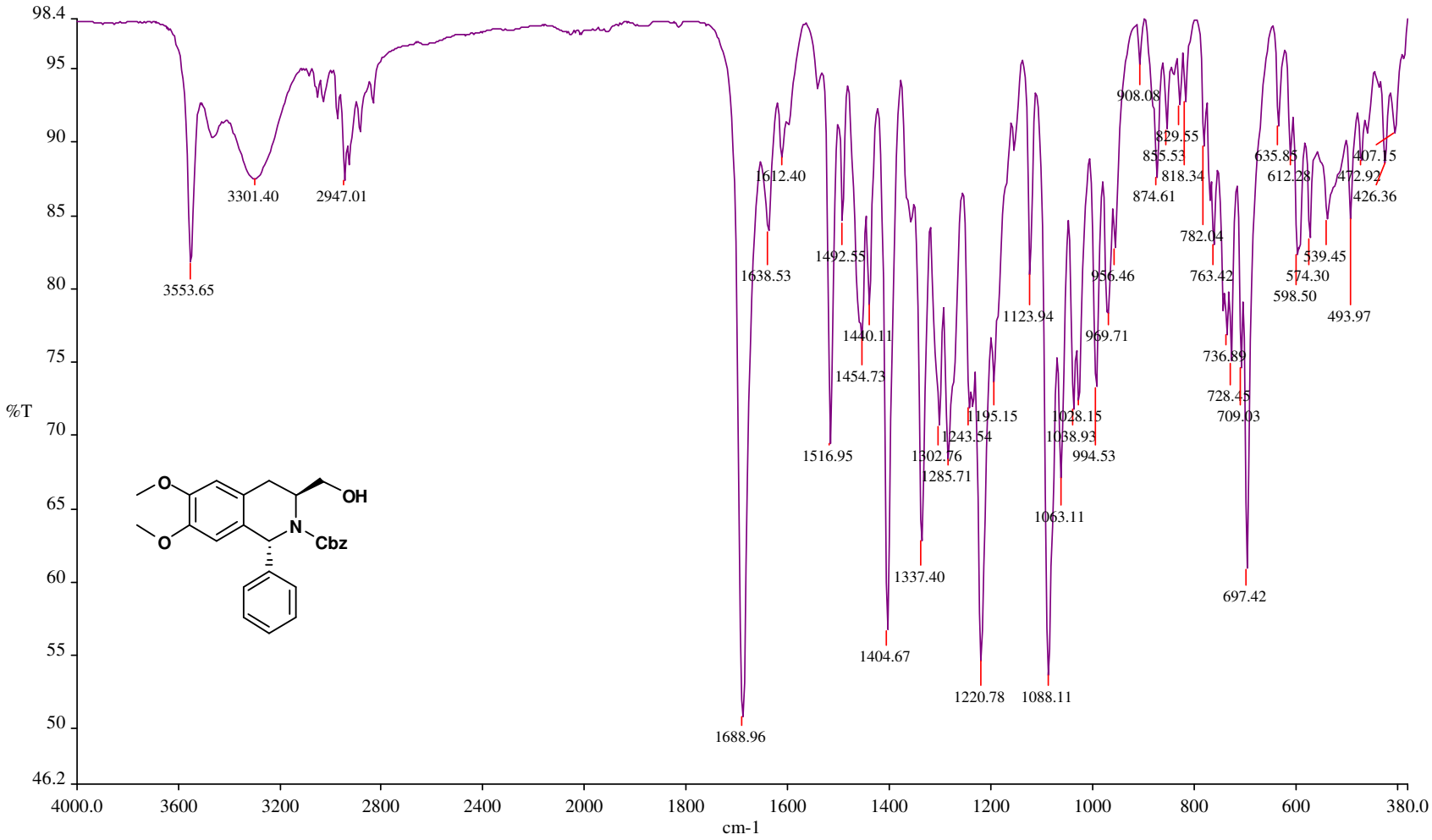
IR Spectrum of Compound **2g**



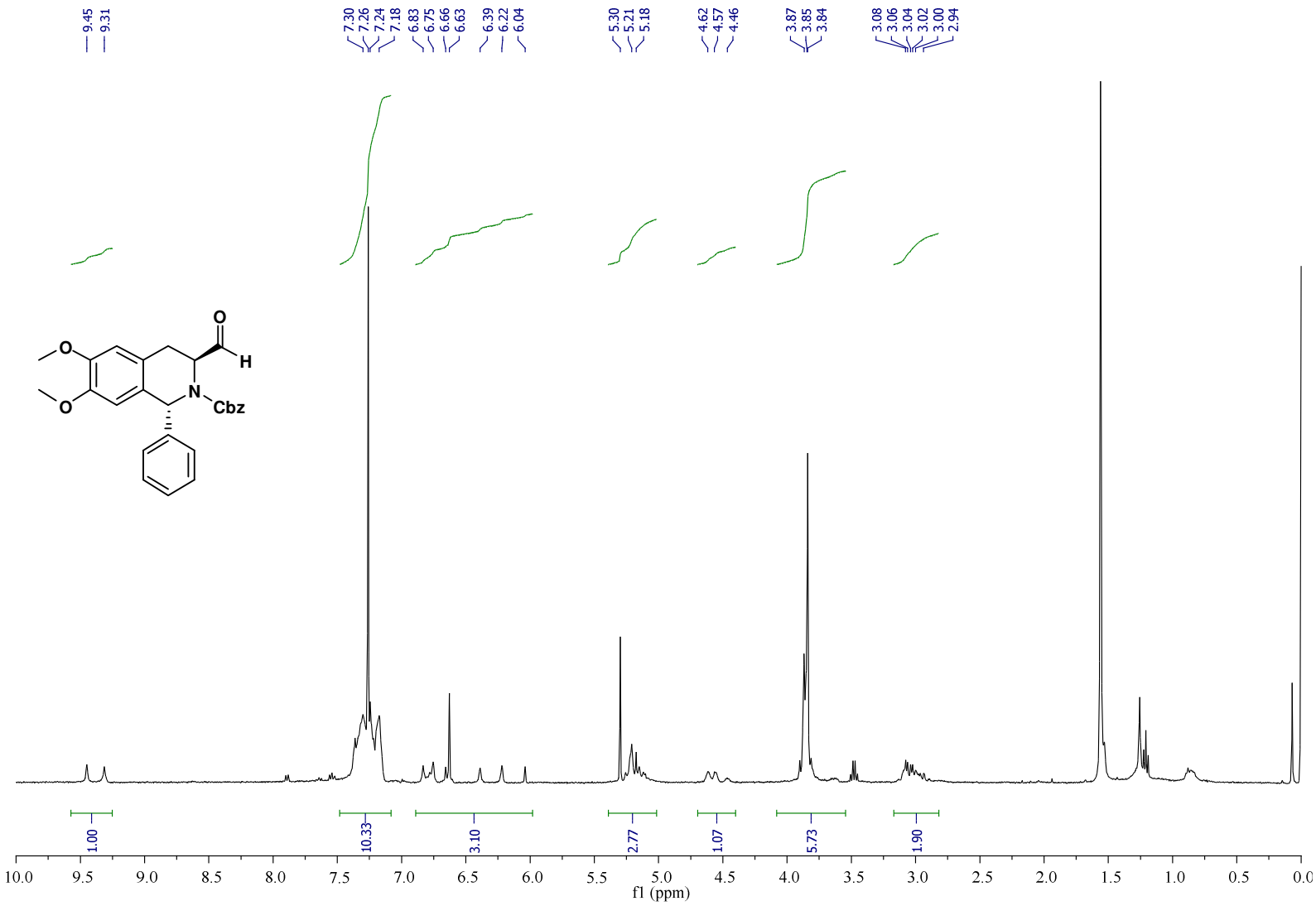
^{1}H NMR (400 MHz) Spectrum of Compound **10** in $CDCl_3$



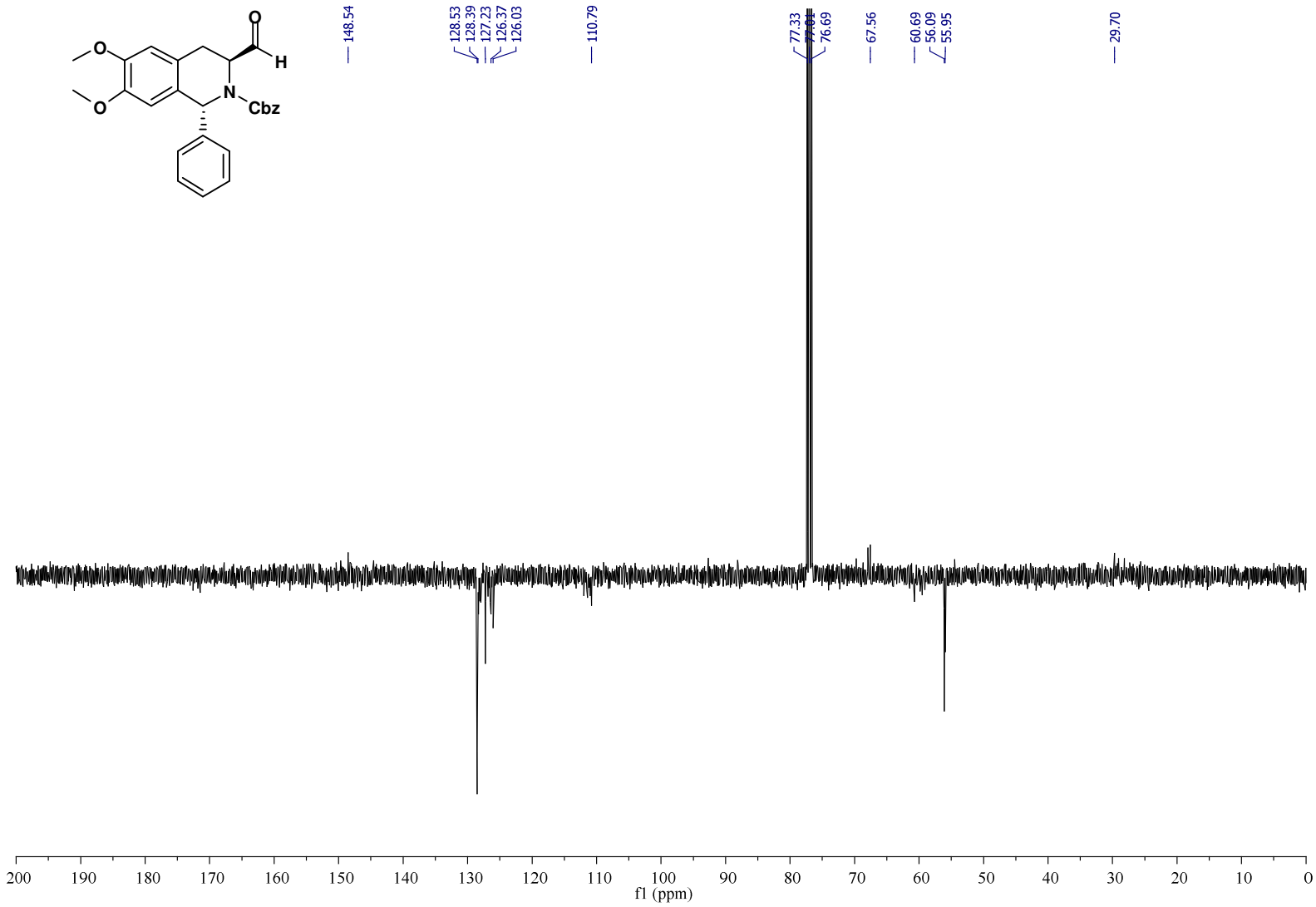
^{13}C NMR (400 MHz) Spectrum of Compound **10** in $CDCl_3$



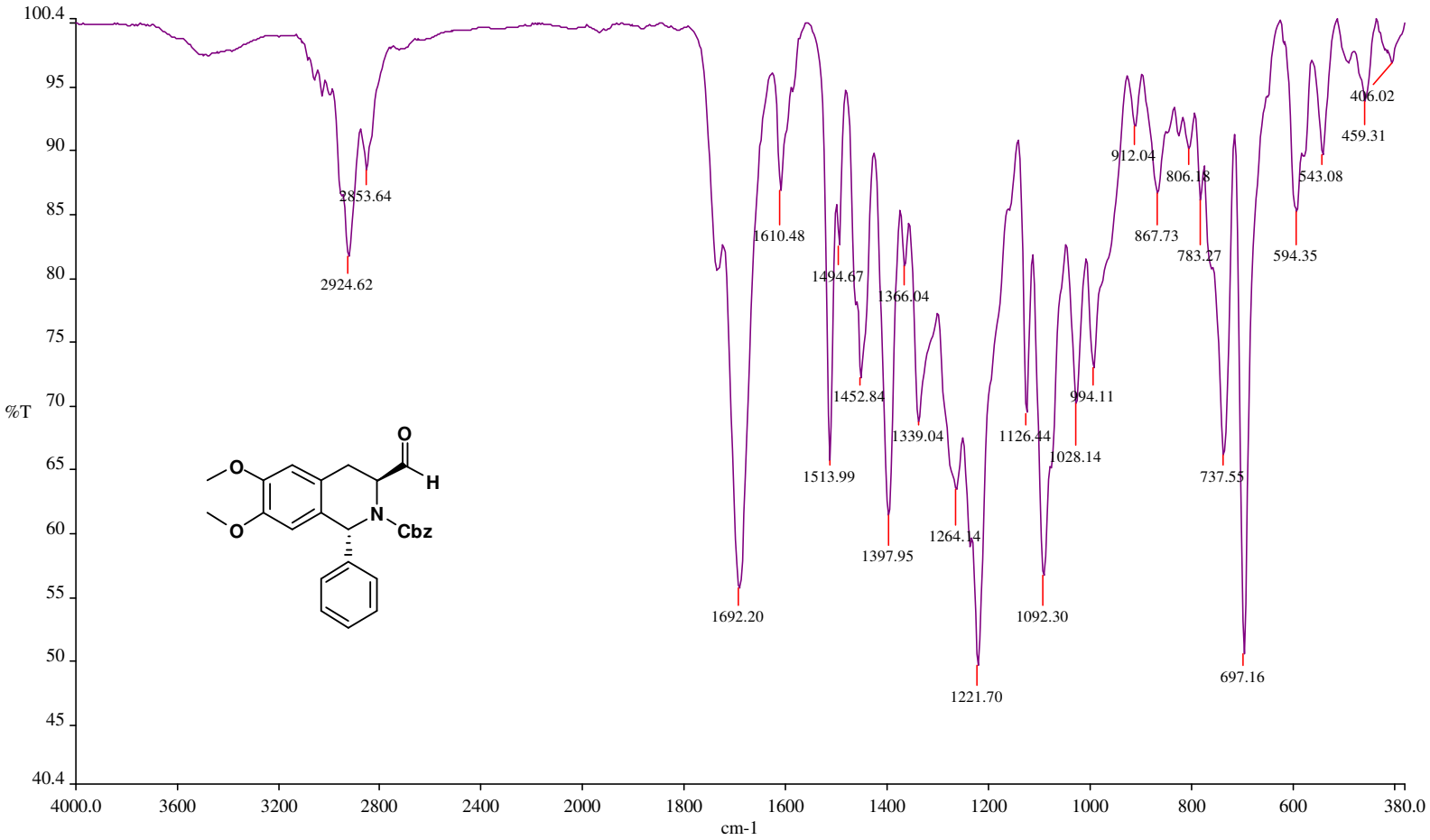
IR Spectrum of Compound **10**



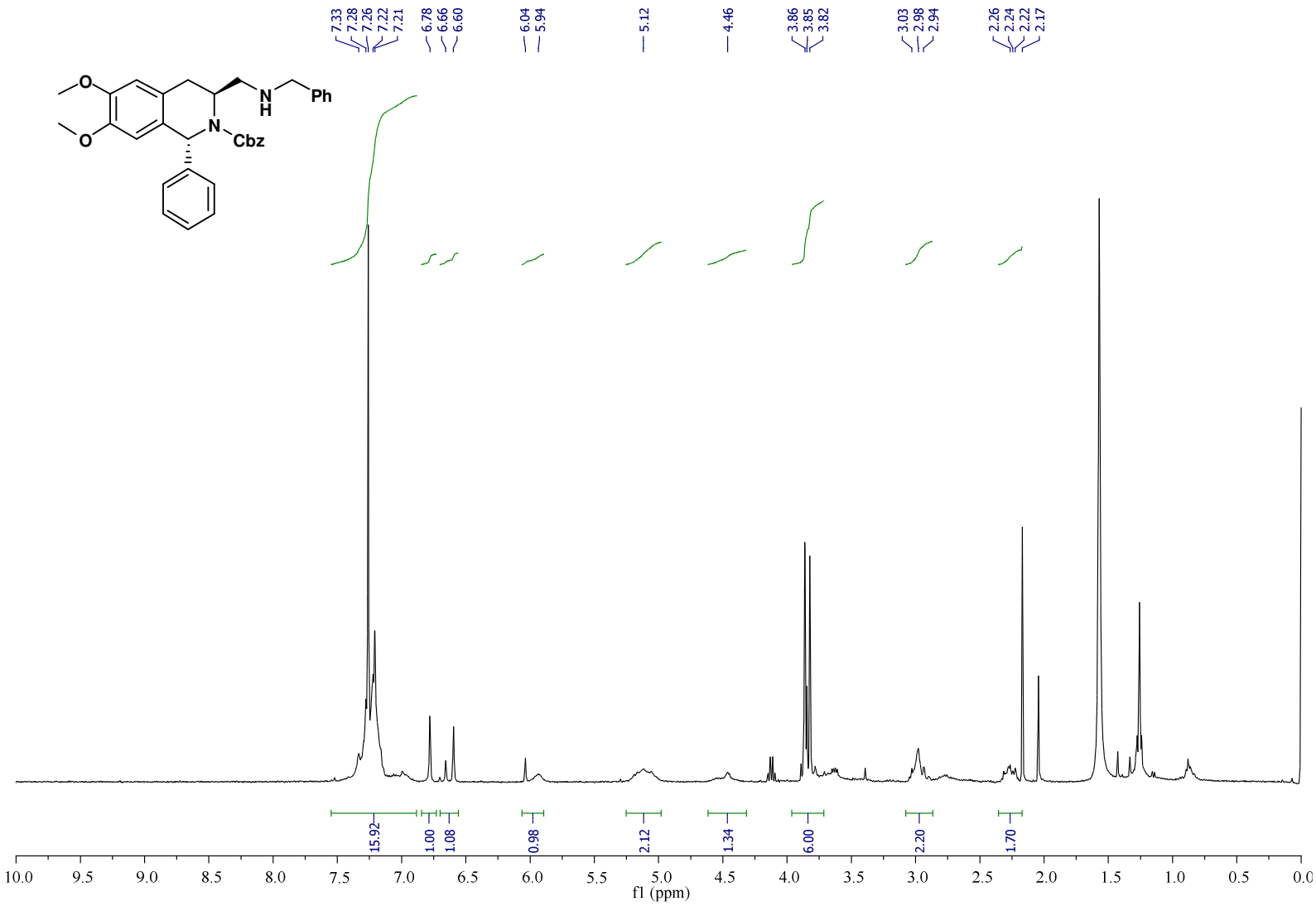
^{1}H NMR (400 MHz) Spectrum of Compound **11** in $CDCl_3$



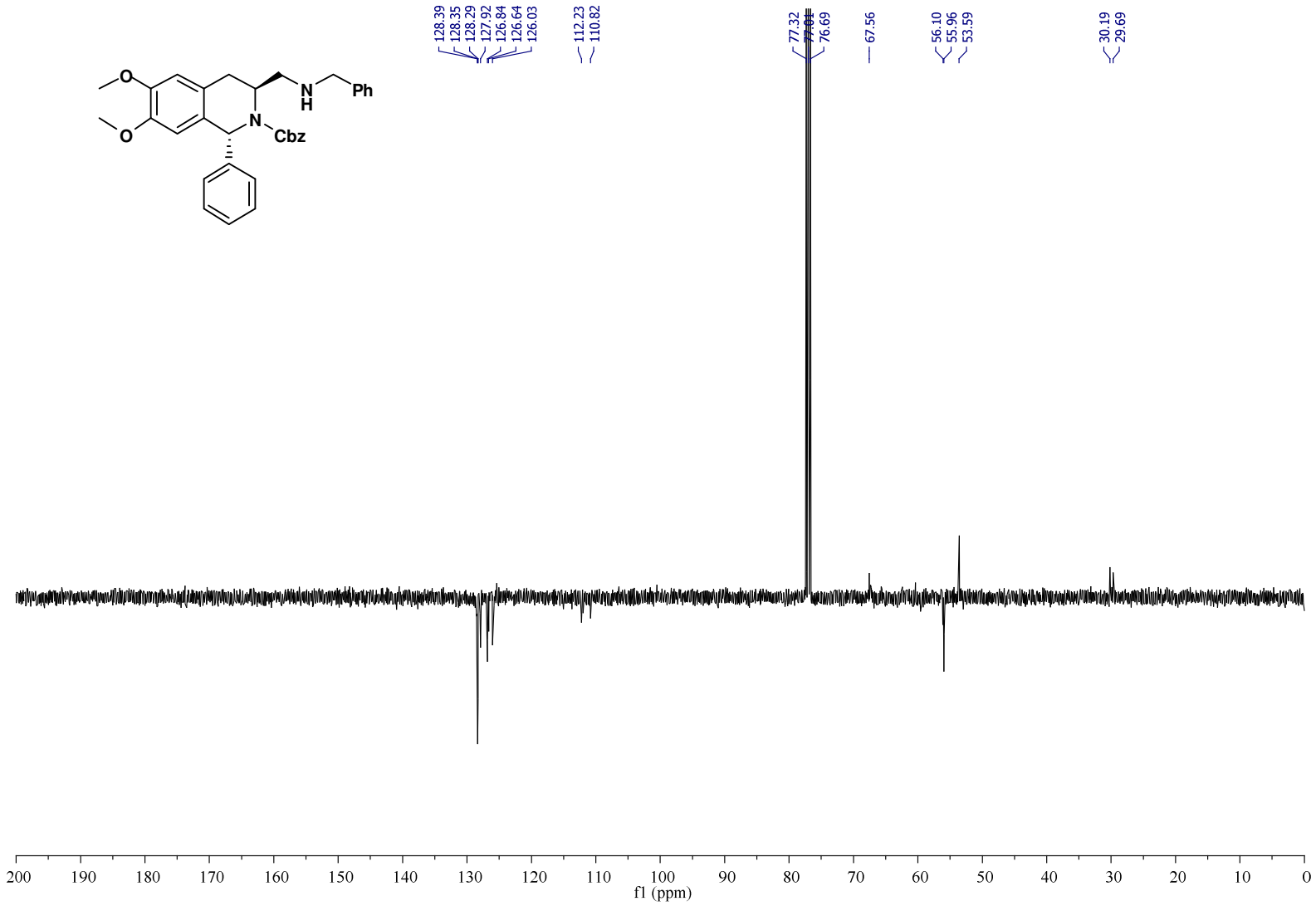
^{13}C NMR (400 MHz) Spectrum of Compound **10** in $CDCl_3$



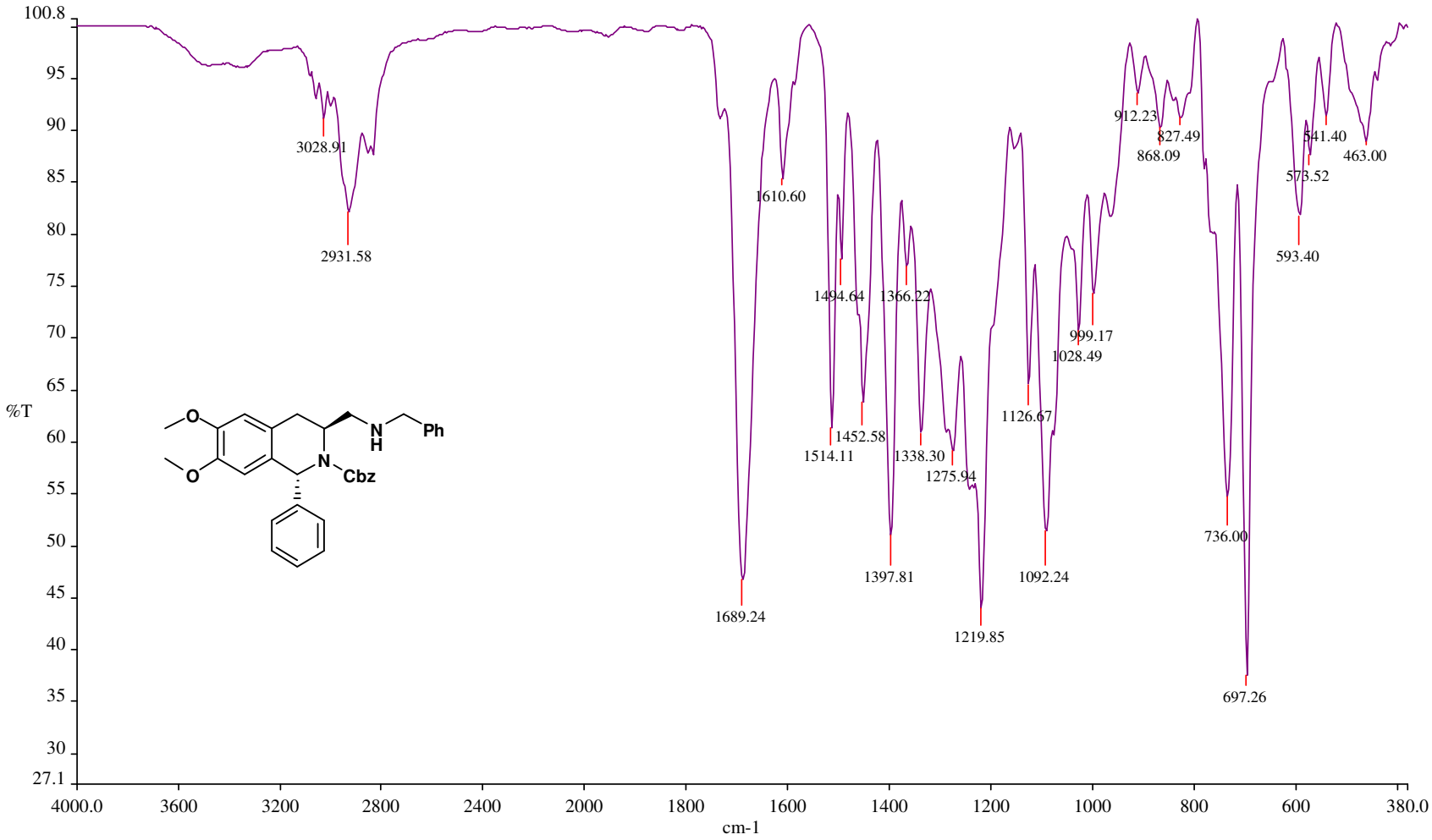
IR Spectrum of Compound **10**



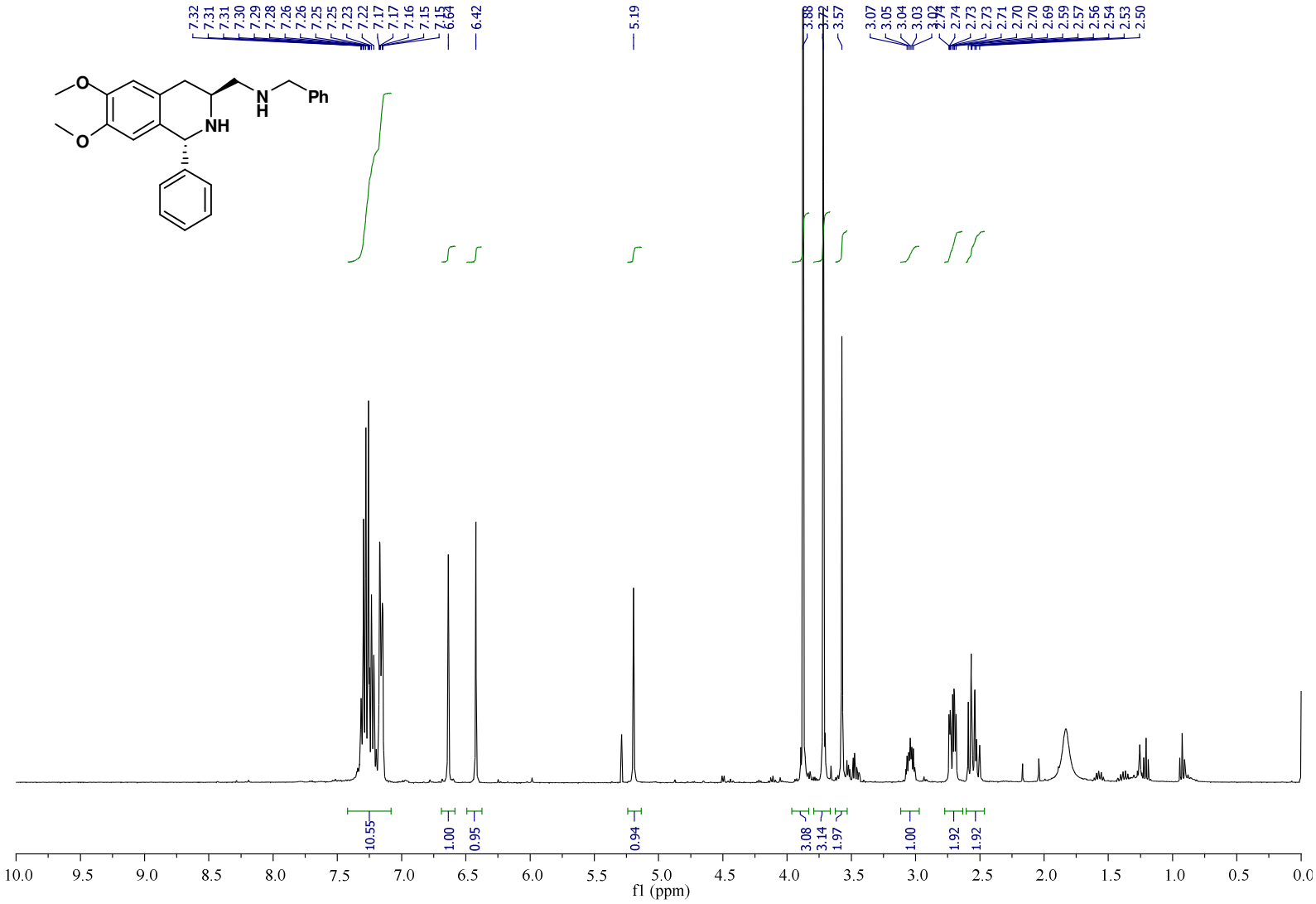
^{1}H NMR (400 MHz) Spectrum of Compound **12** in $CDCl_3$



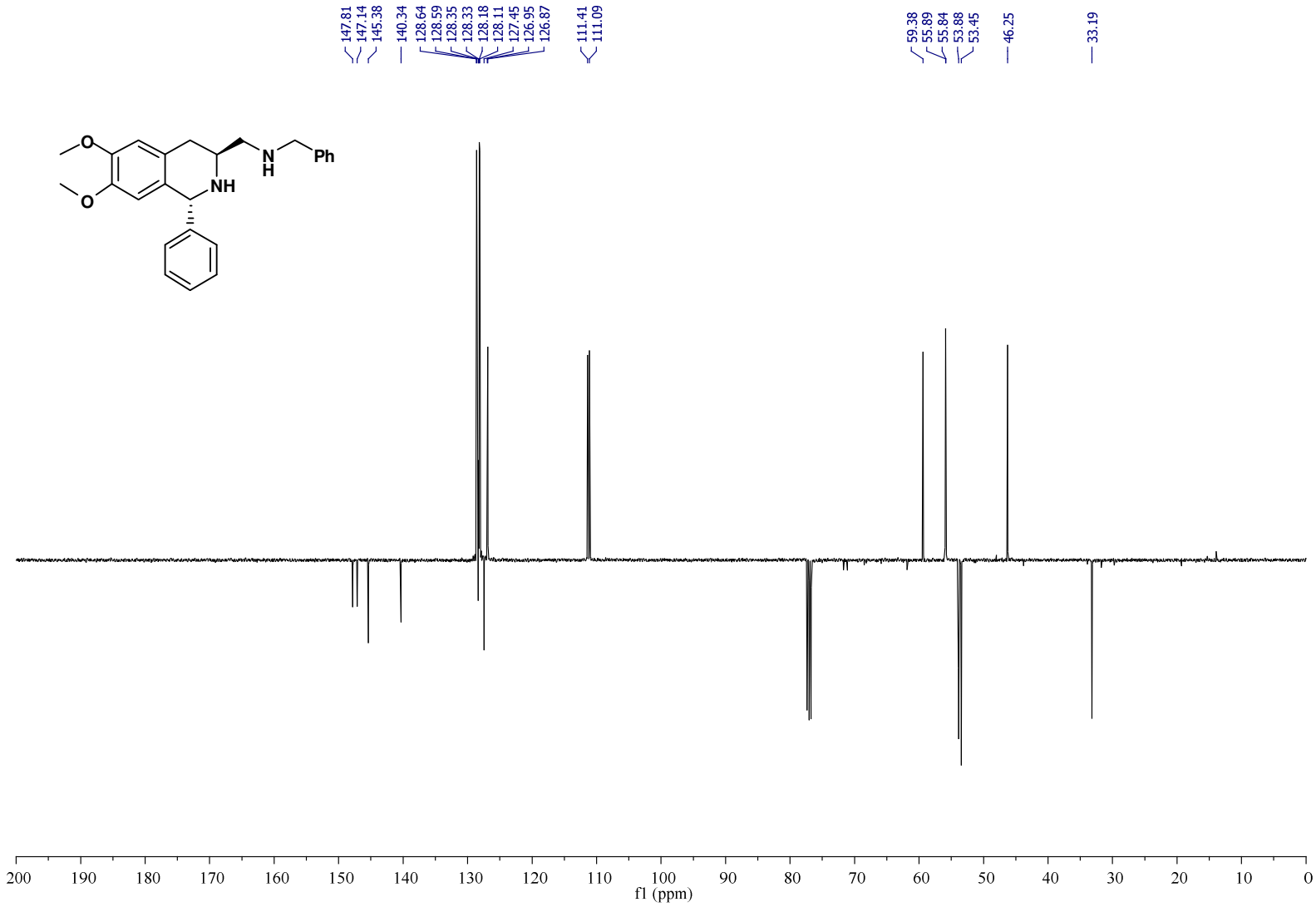
^{13}C NMR (400 MHz) Spectrum of Compound **12** in $CDCl_3$



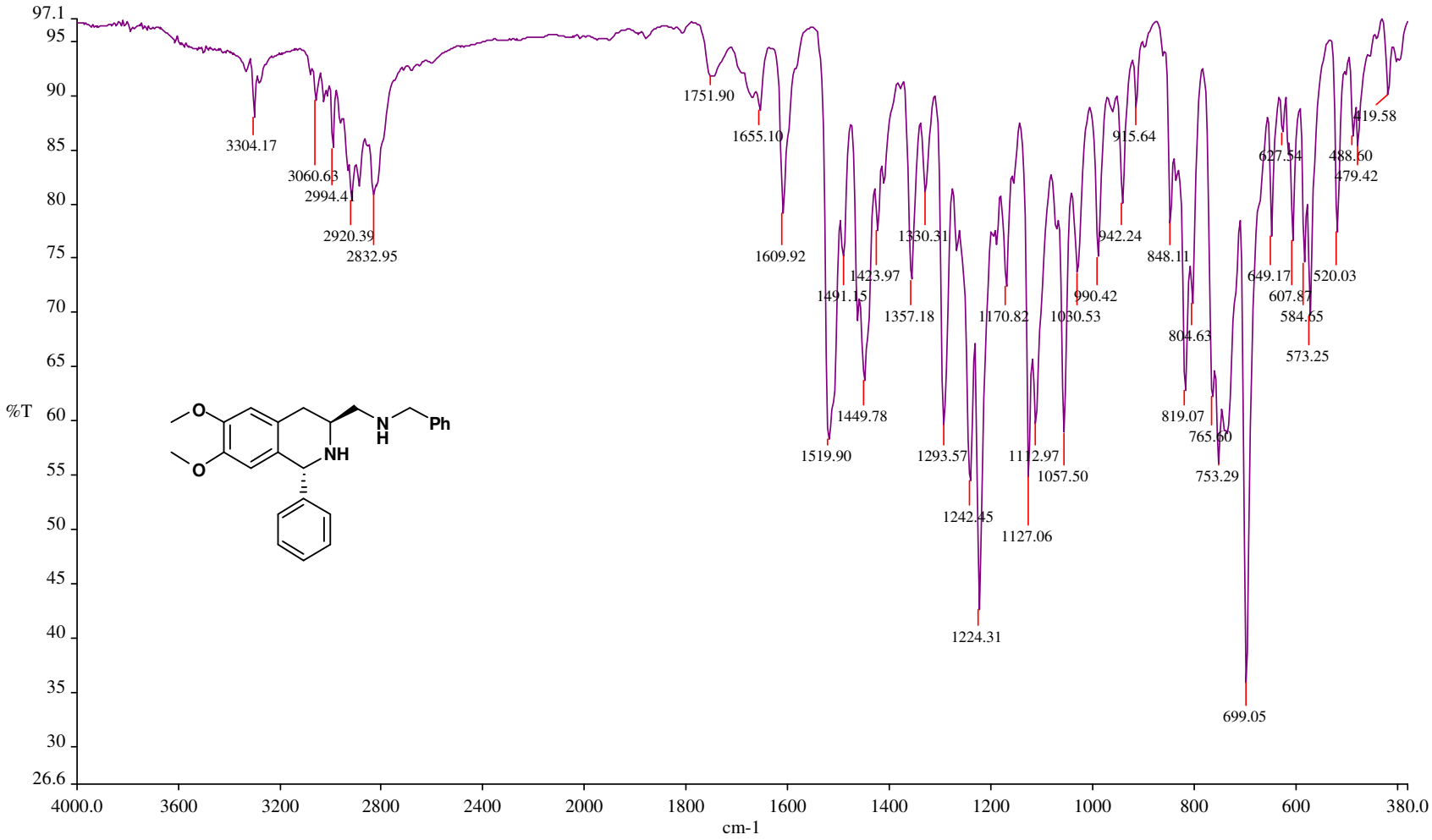
IR Spectrum of Compound **12**



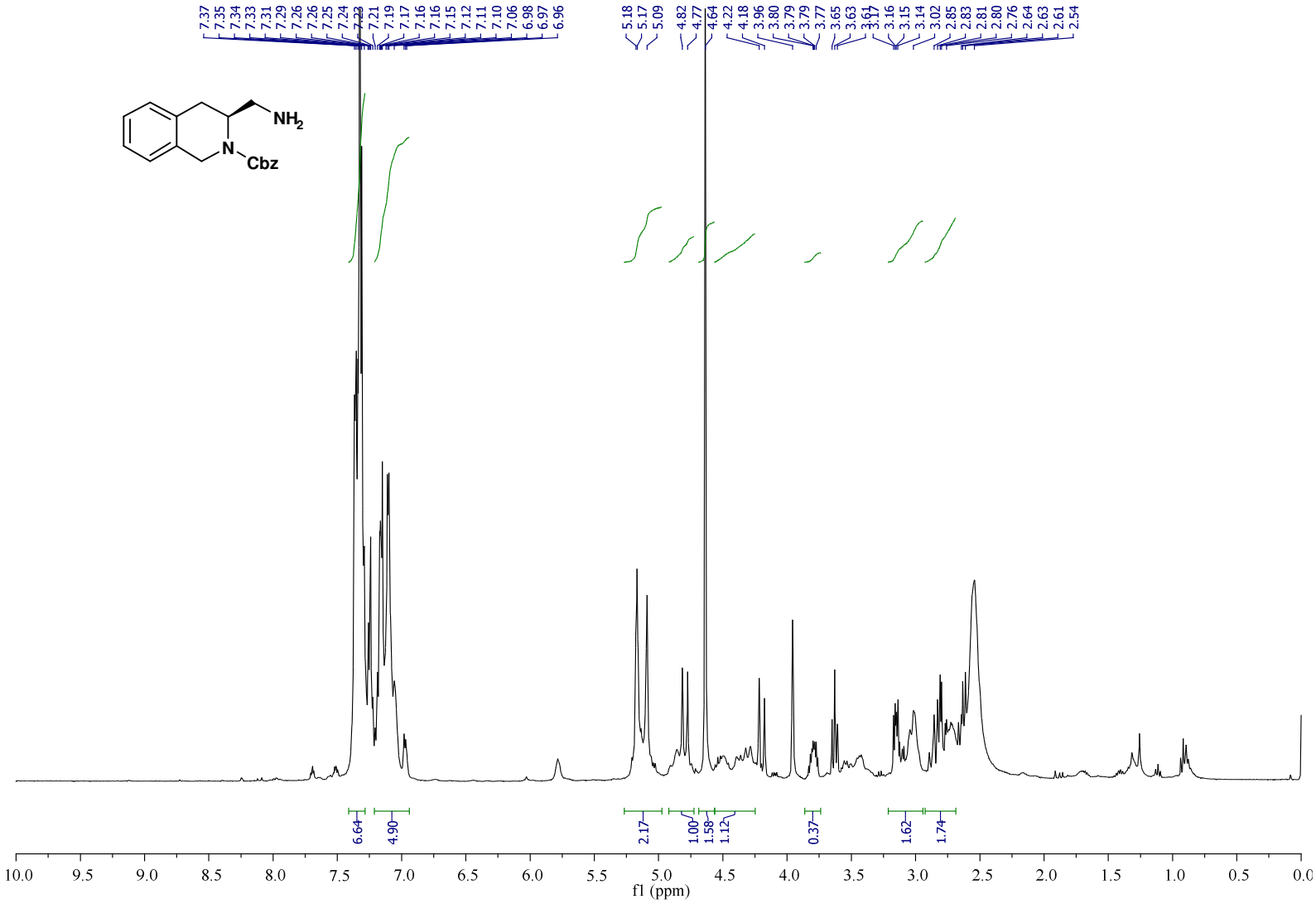
^{1}H NMR (400 MHz) Spectrum of Compound **2i** in $CDCl_3$



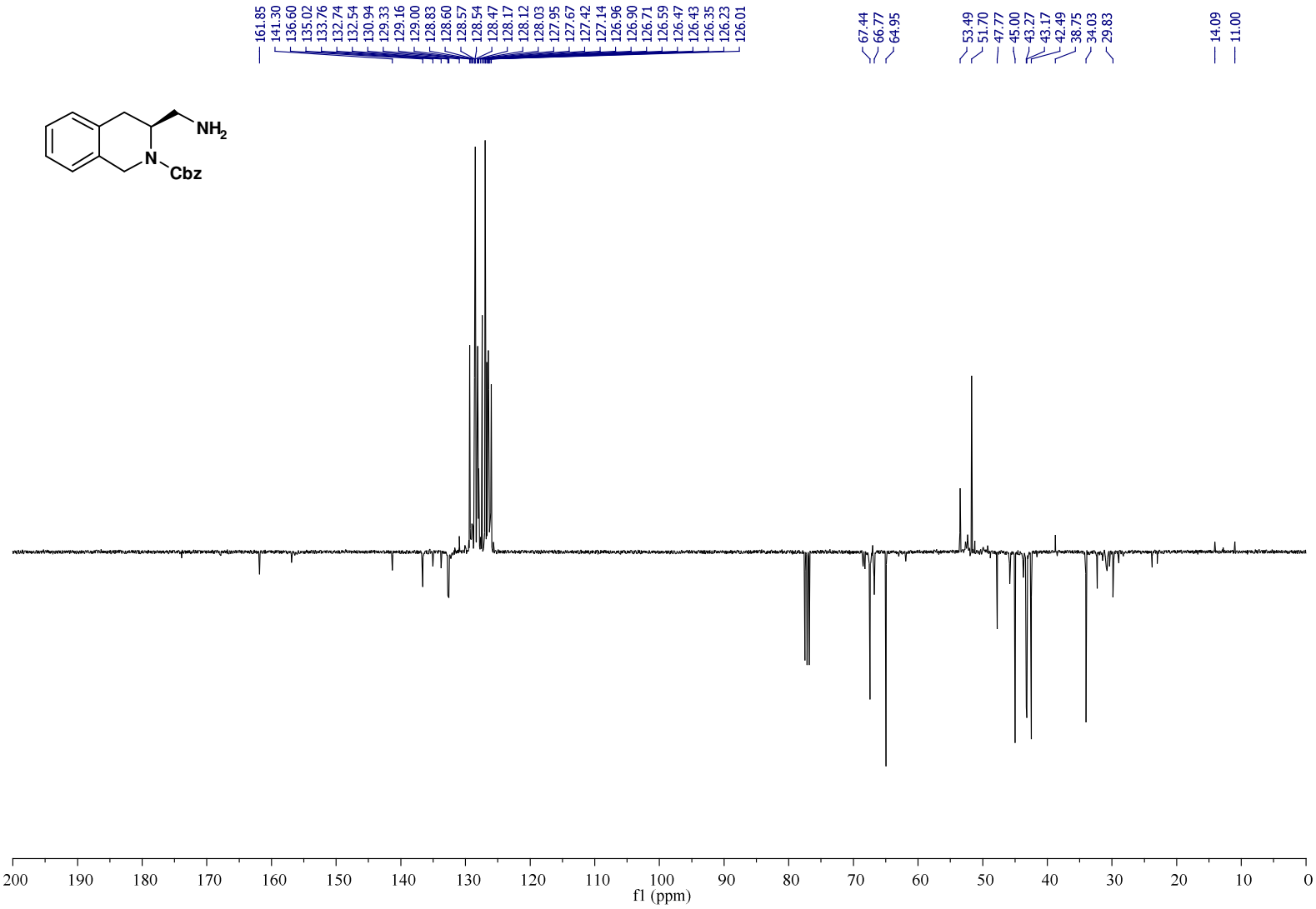
^{13}C NMR (400 MHz) Spectrum of Compound **2i** in $CDCl_3$



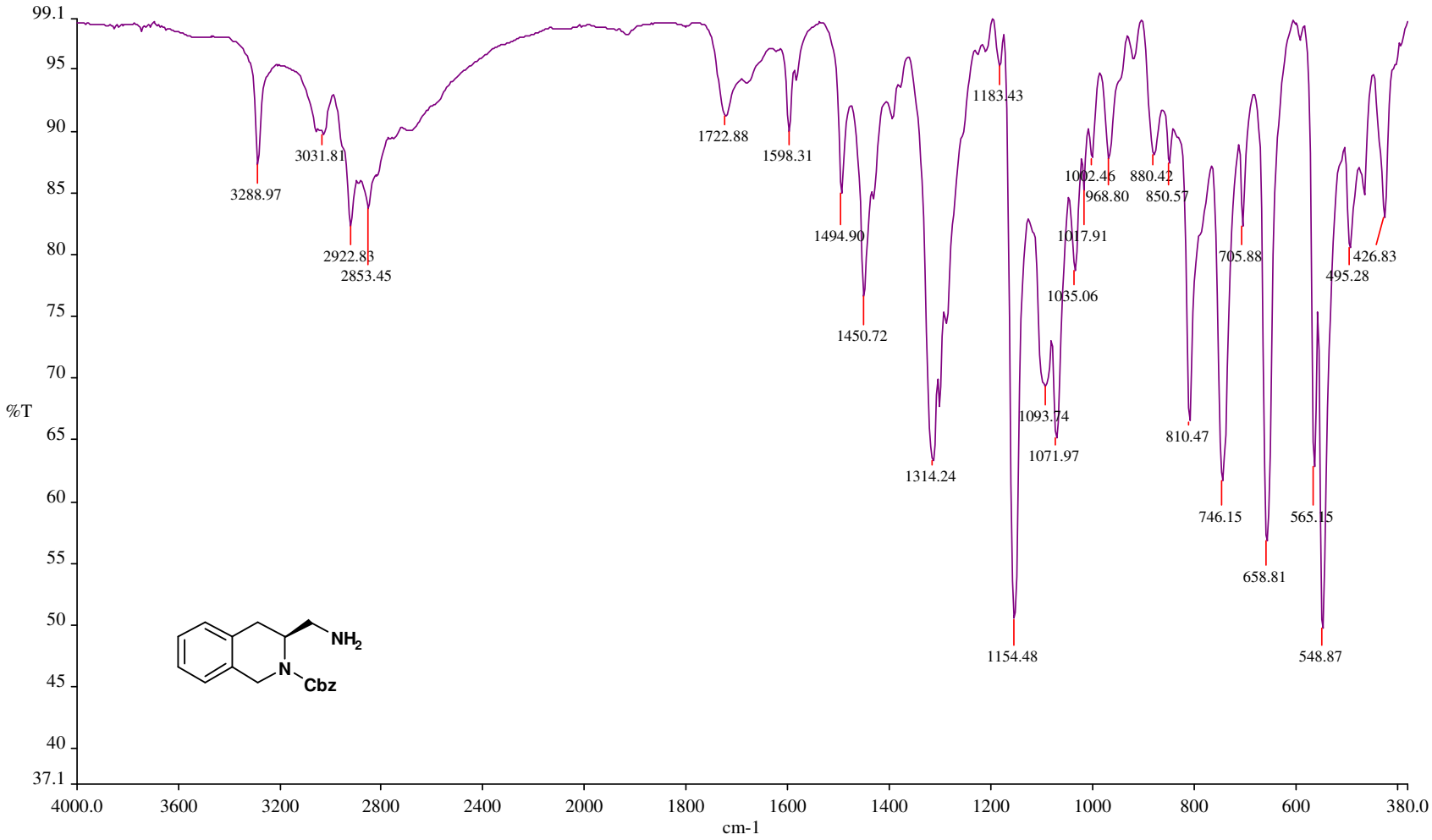
IR Spectrum of Compound **2i**



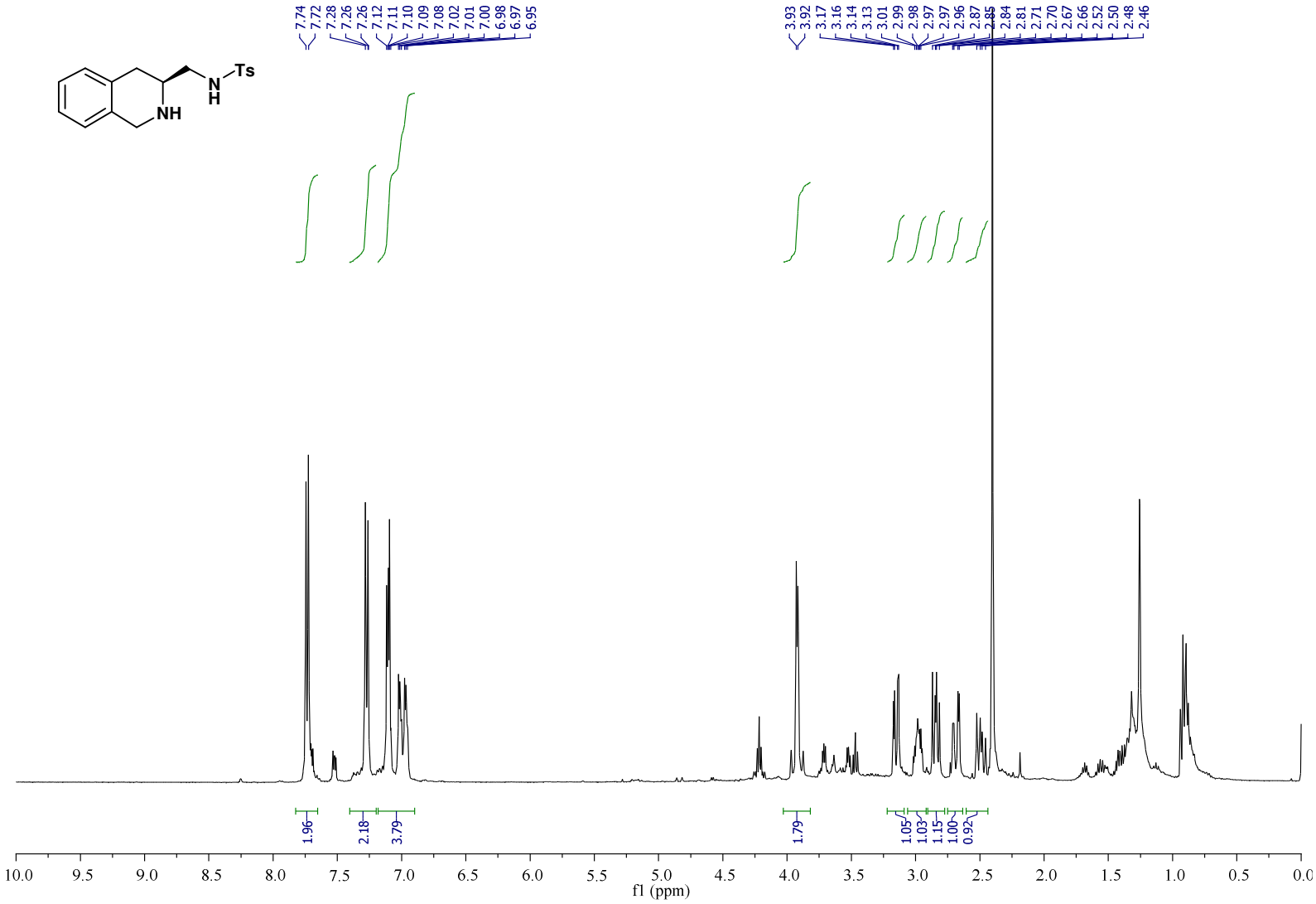
^{1}H NMR (400 MHz) Spectrum of Compound **14** in $CDCl_3$



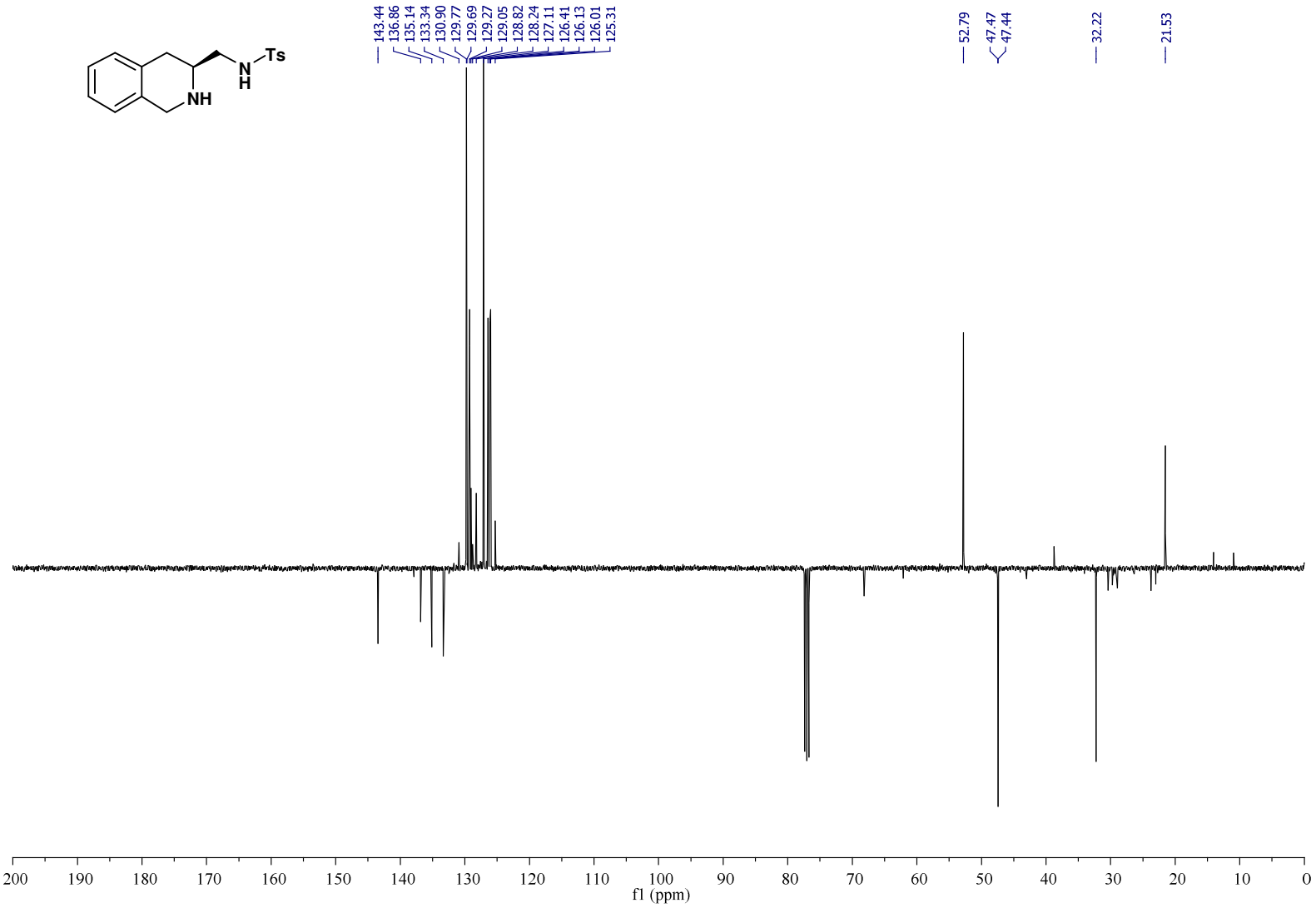
^{13}C NMR (400 MHz) Spectrum of Compound **14** in $CDCl_3$



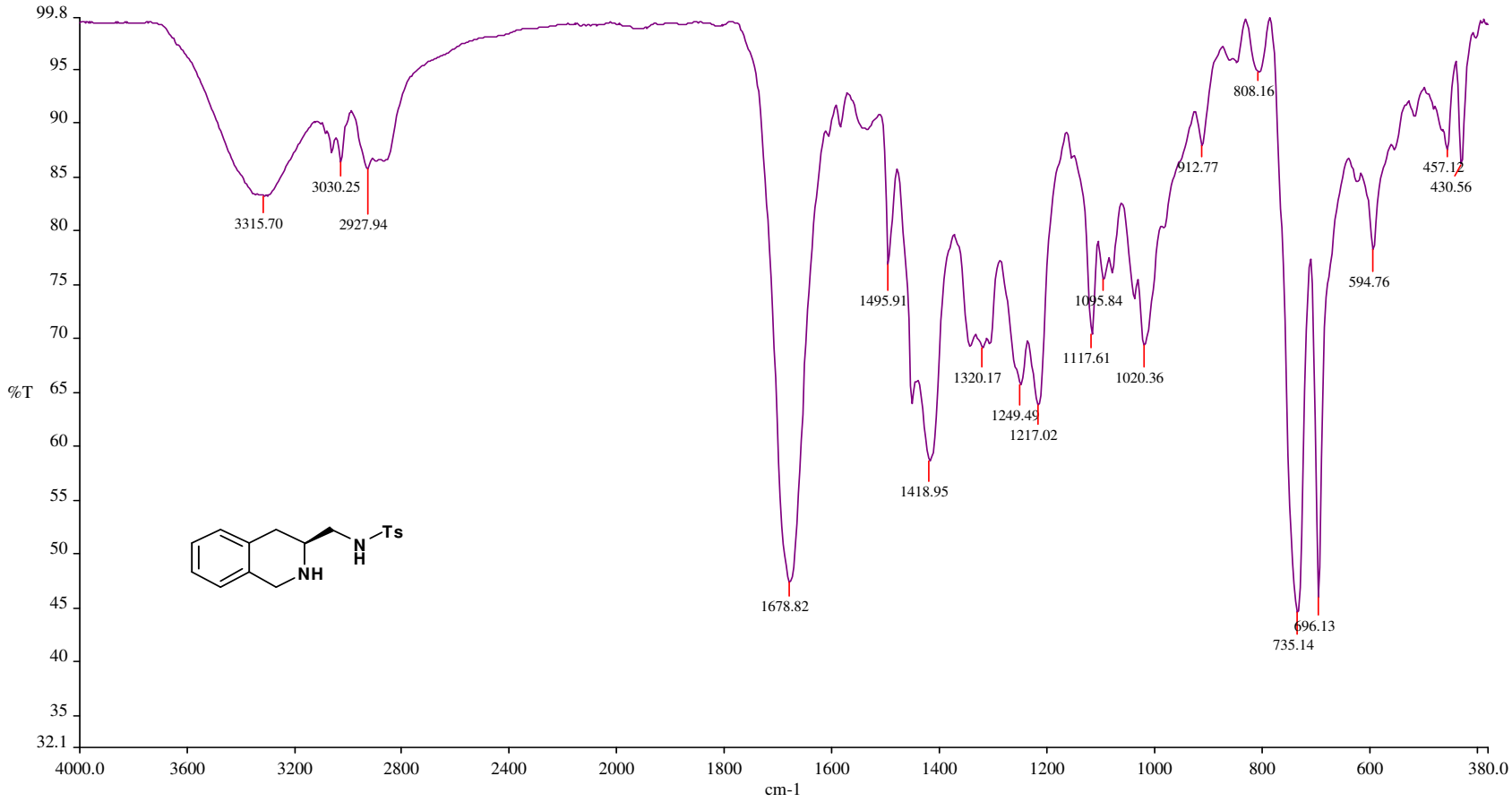
IR Spectrum of Compound **14**



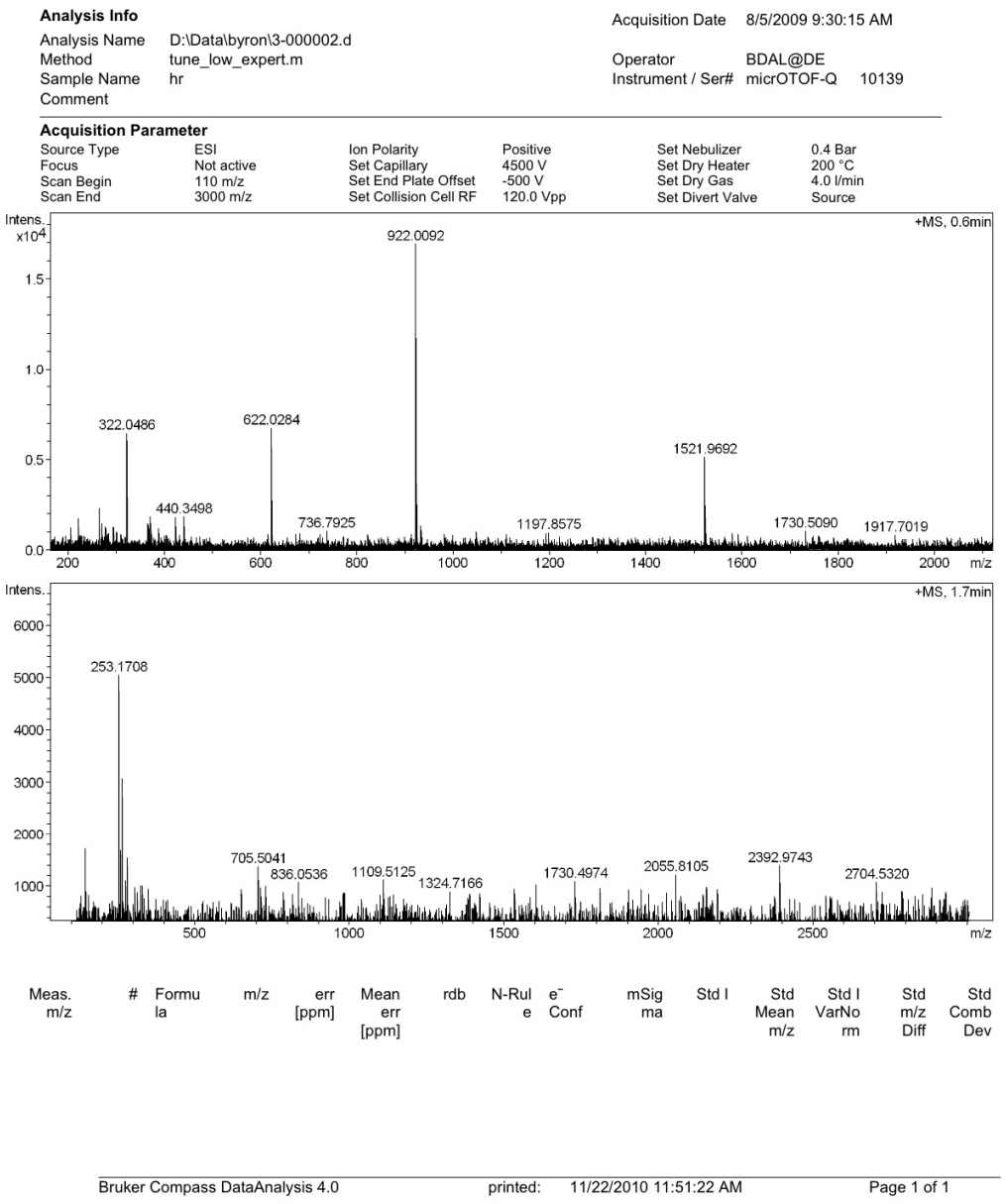
^{1}H NMR (400 MHz) Spectrum of Compound **2j** in $CDCl_3$



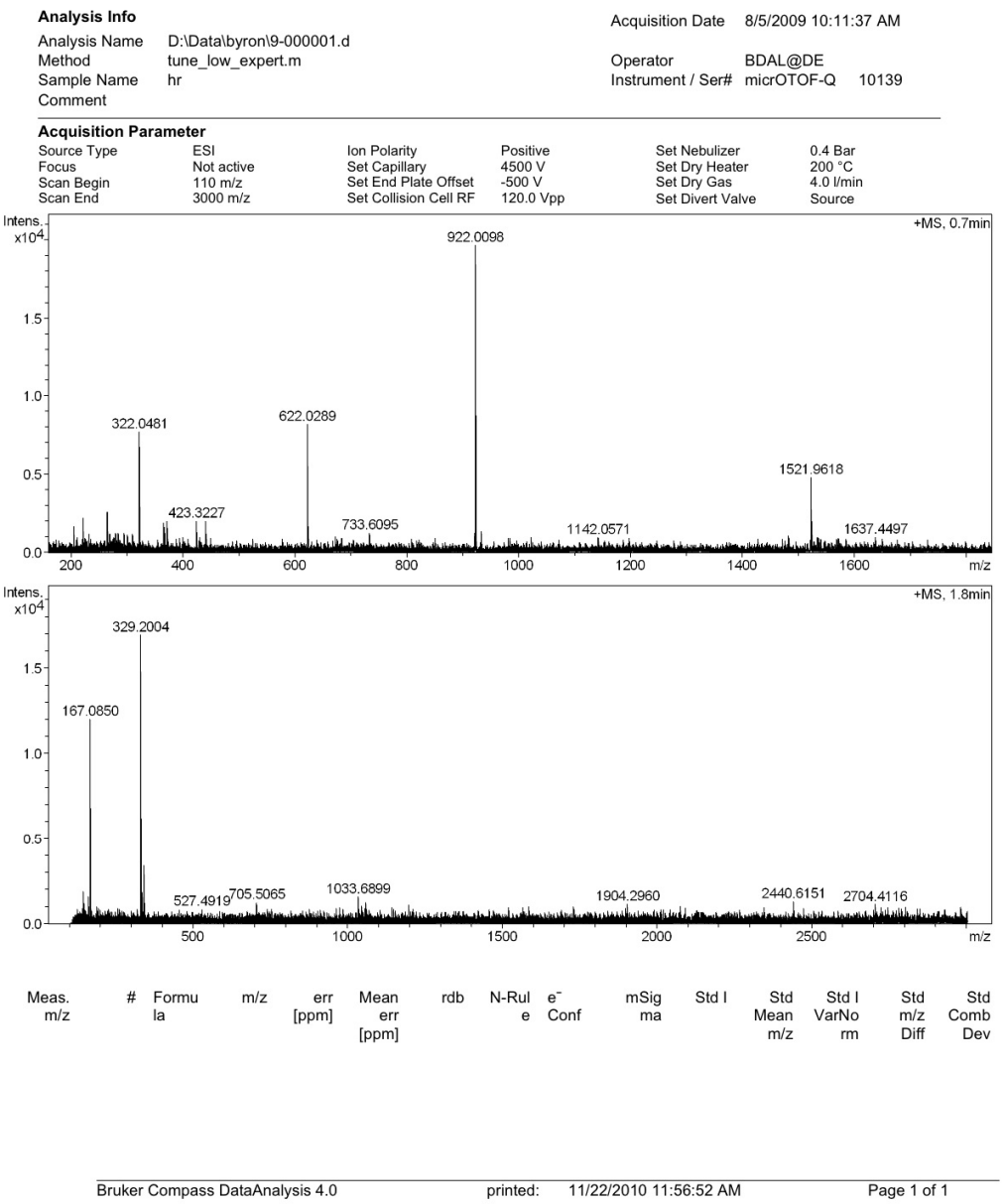
^{13}C NMR (400 MHz) Spectrum of Compound **2j** in $CDCl_3$



IR Spectrum of Compound **2j**



High resolution Mass Spectrum of Compound **2a**



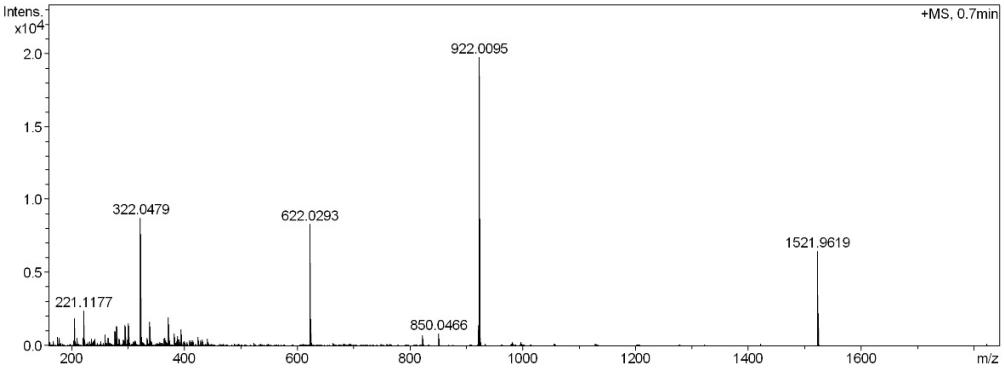
High Resolution Mass Spectrum of Compound **2b**

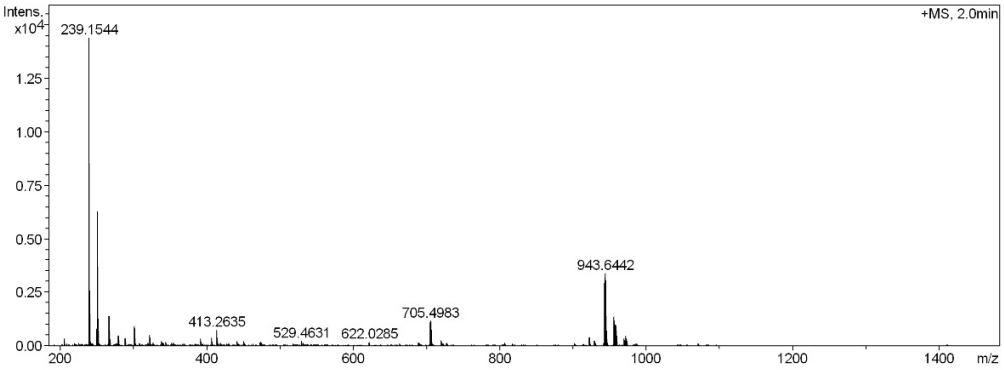
Analysis Info

Analysis Name	D:\Data\byron\21000003.d	Acquisition Date	8/12/2009 6:52:16 AM
Method	tune_low_expert.m		
Sample Name	21	Operator	BDAL@DE
Comment		Instrument / Ser#	micrOTOF-Q 10139

Acquisition Parameter

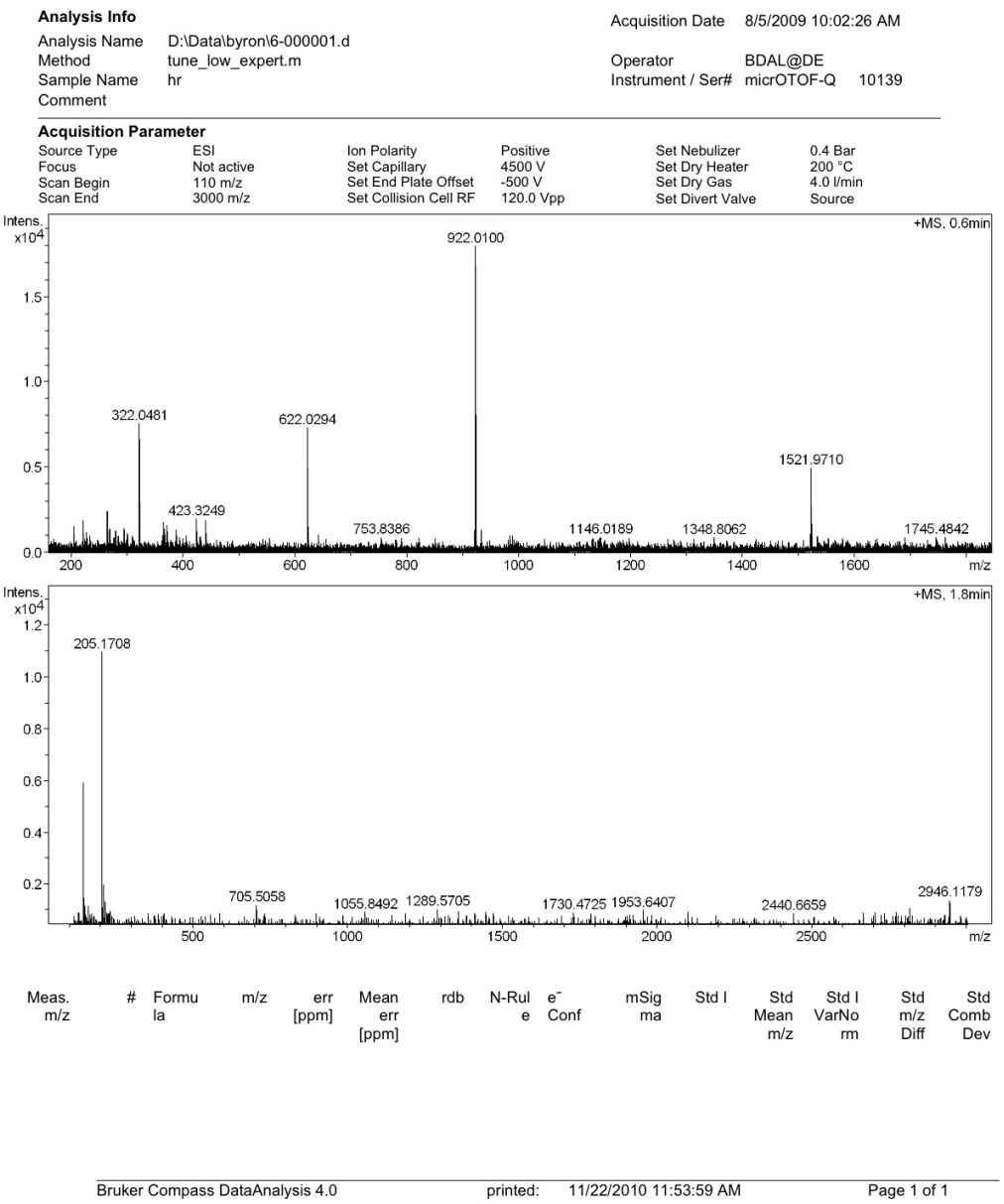
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



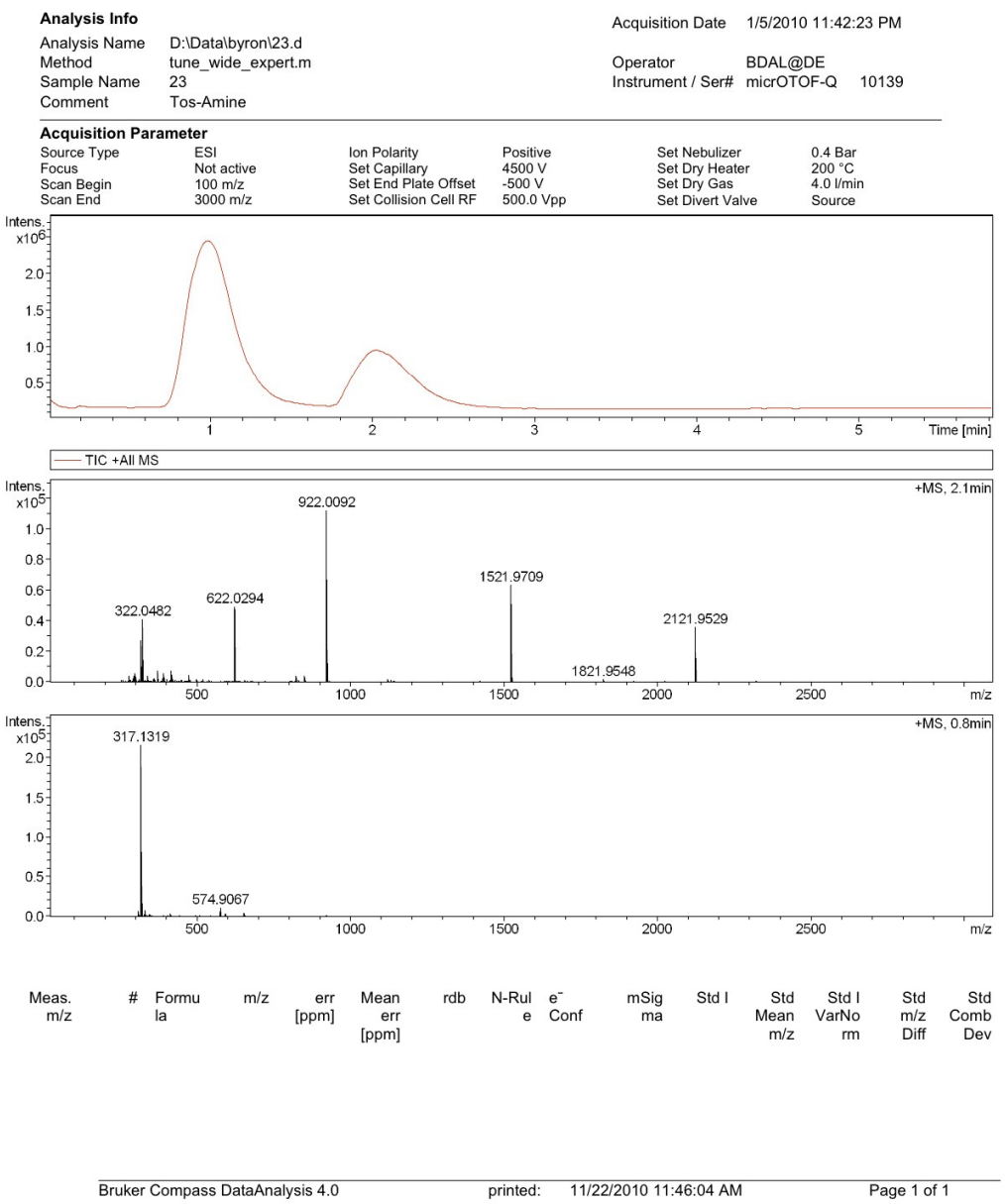


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev

High Resolution Mass Spectrum of Compound **2c**



High Resolution Mass Spectrum of Compound **2e**



High Resolution Mass Spectrum of Compound **2j**

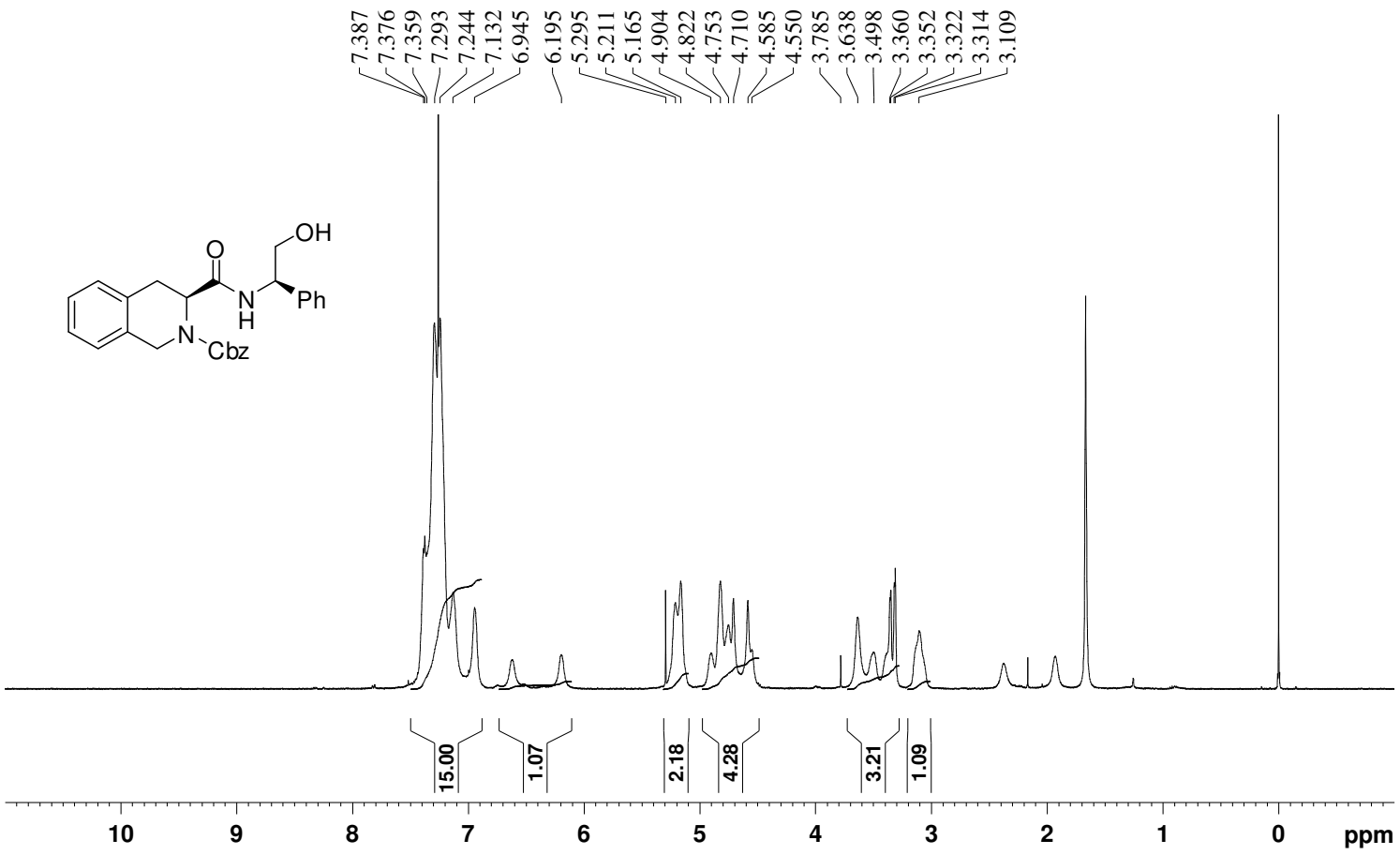
APPENDIX 3

IRIDIUM CATALYZED ASYMMETRIC HYDROGENATION OF OLEFINS USING TIQ PHOSPHINE-OXAZOLINE LIGANDS

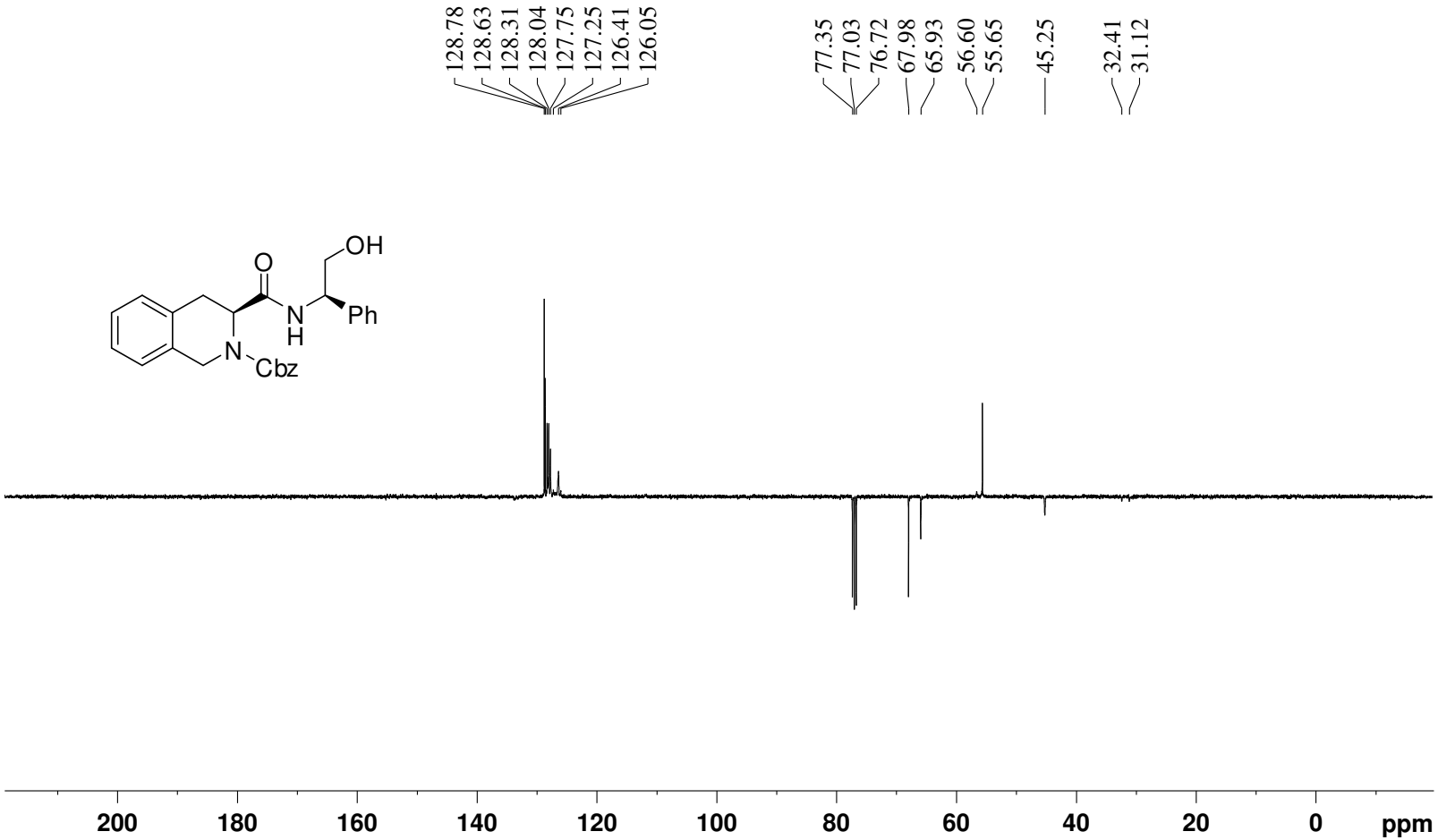
SUPPLAMENTARY INFORMATION FOR CHAPTER 4

Sai Kumar Chakka,[a] Byron K. Peters,[a] Pher G. Andersson,[c] Glenn E. M. Maguire,[a] Hendrik G. Kruger[a]* and Thavendran Govender[b]*

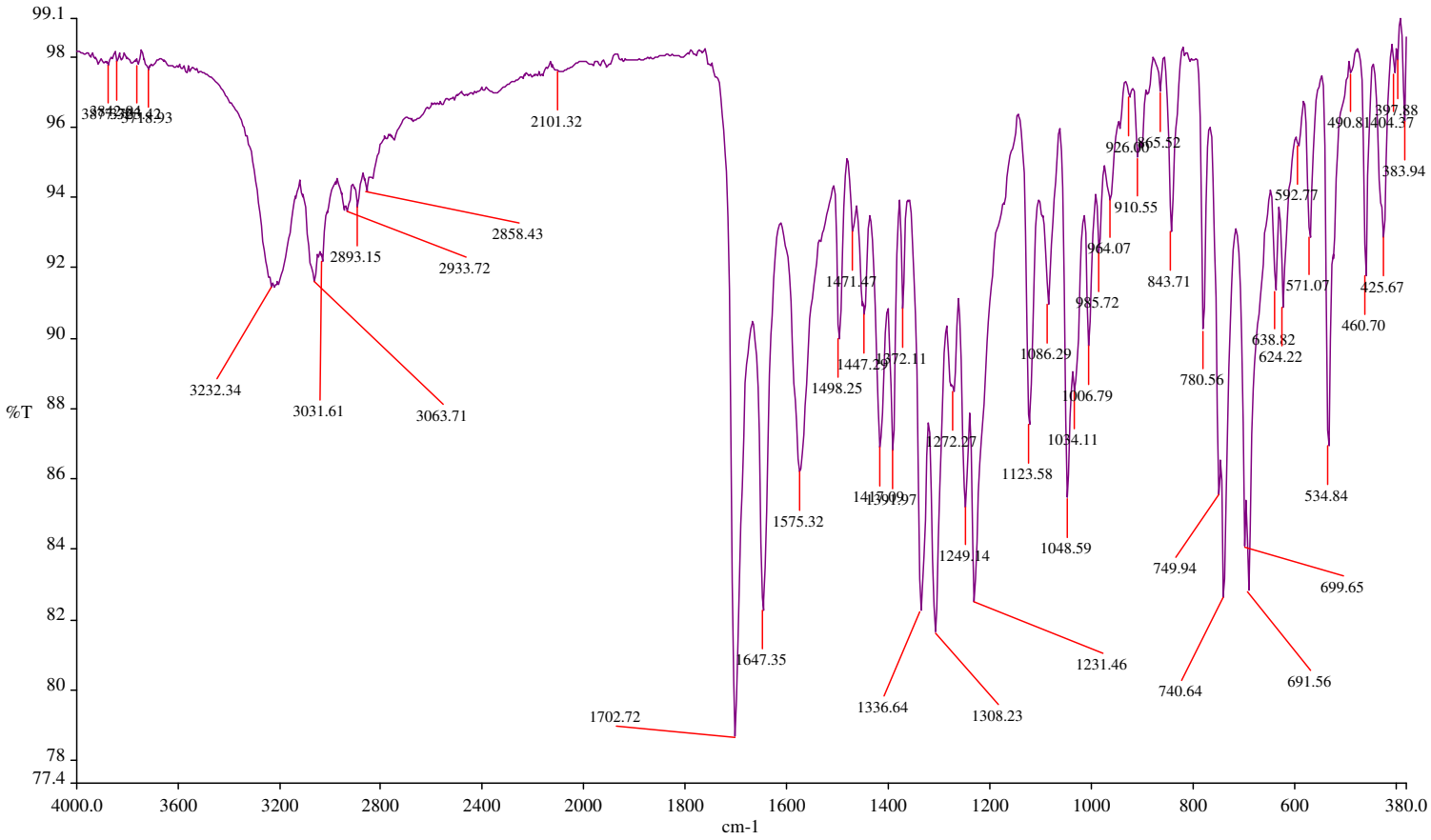
aSchool of Chemistry, University of KwaZulu-Natal, Durban, South Africa. bSchool of Pharmacy and Pharmacology, University of KwaZulu-Natal, Durban, South Africa. cDepartment of Organic chemistry, Uppsala University, Uppsala, Sweden.



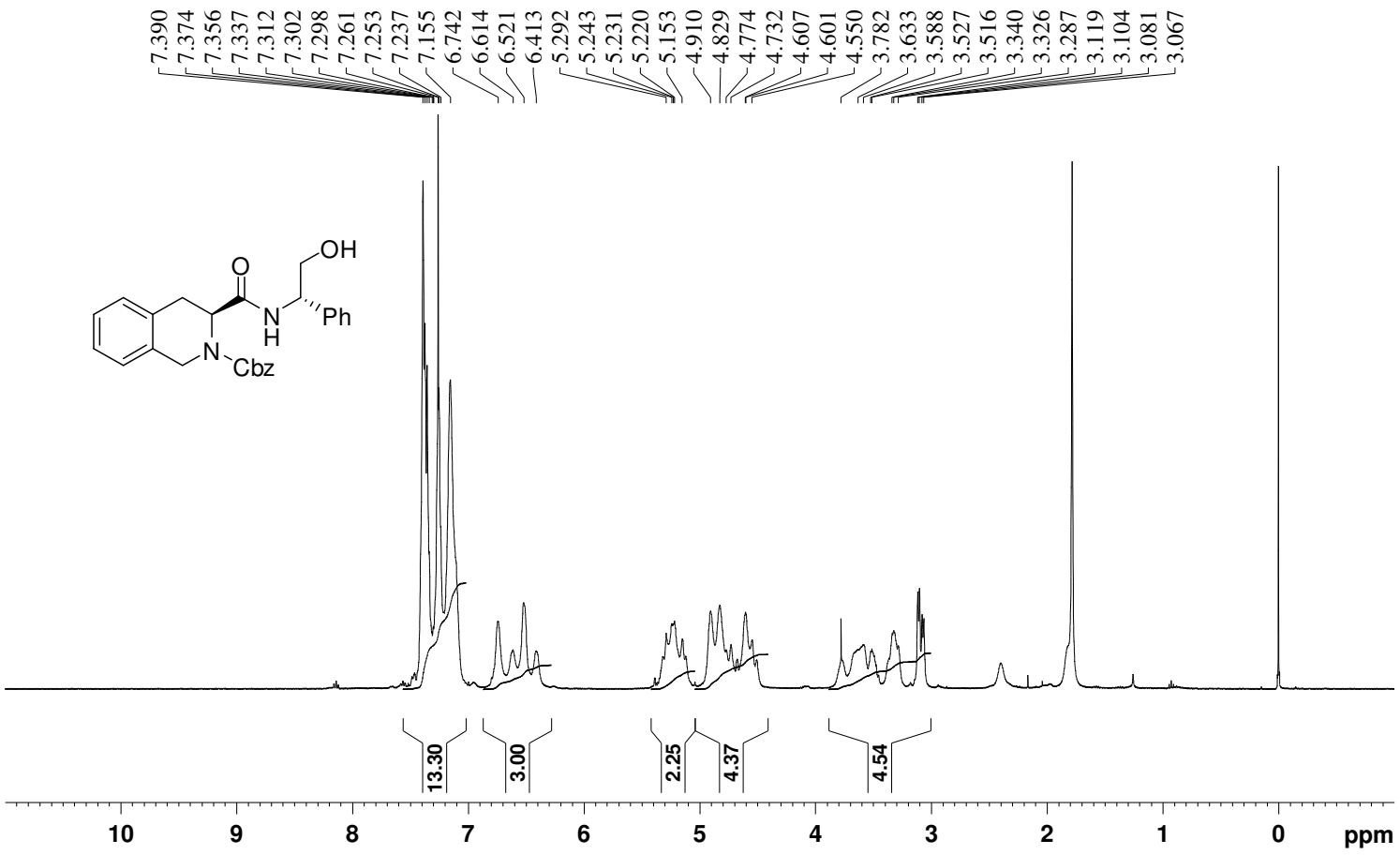
^{1}H NMR (400 MHz) Spectrum of Compound **5** in $CDCl_3$



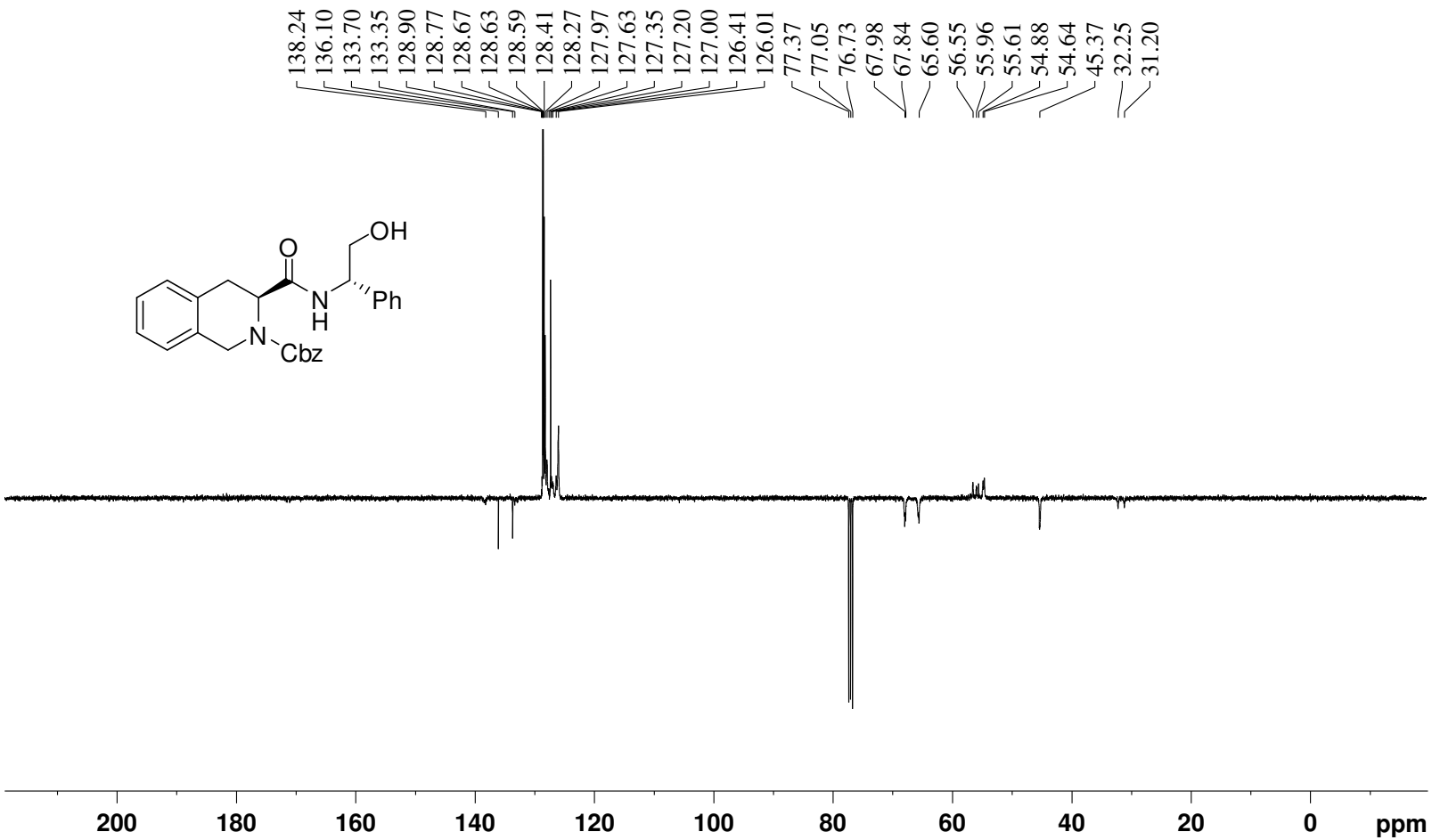
^{13}C (400 MHz) Spectrum of Compound **5** in $CDCl_3$



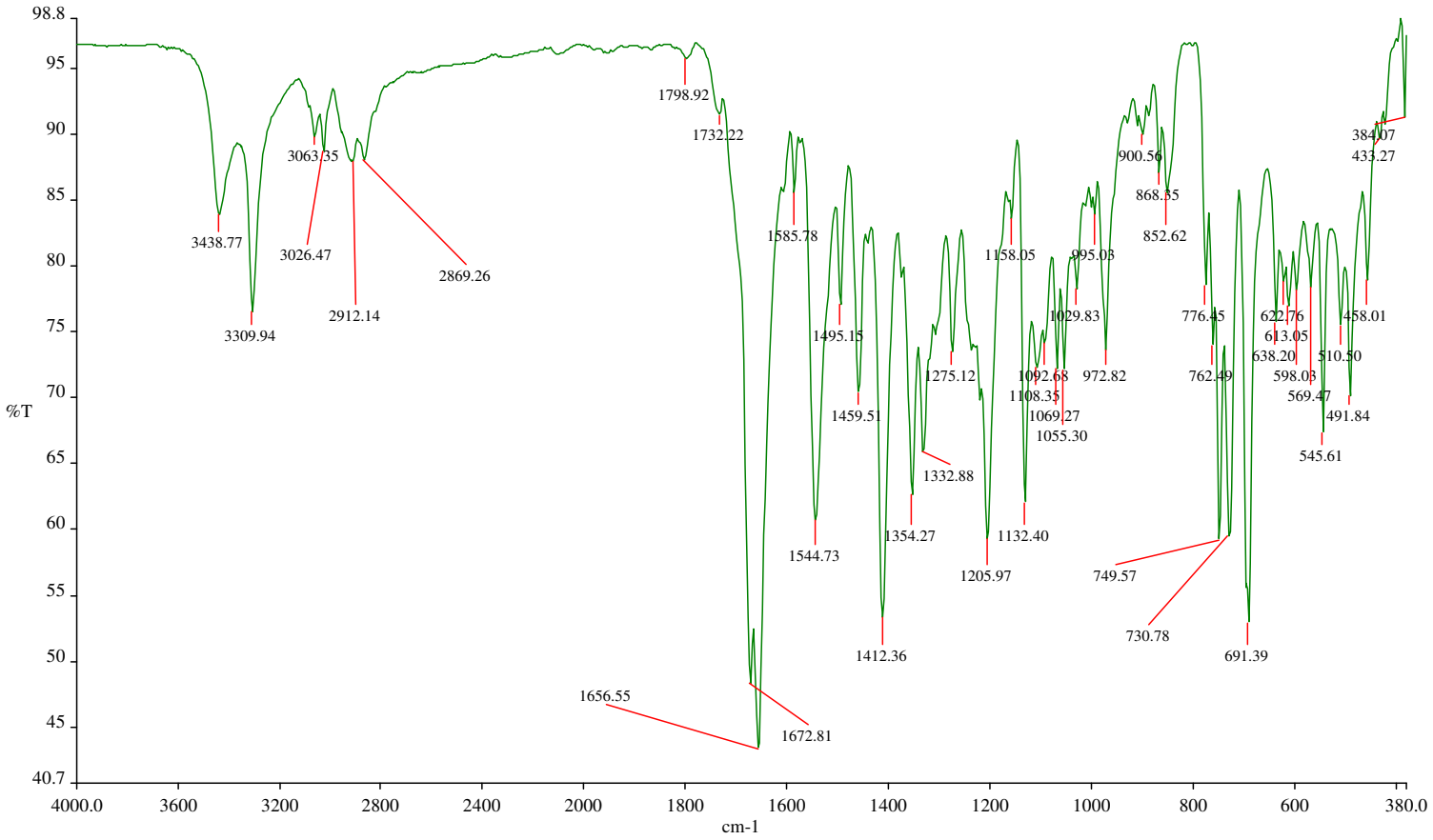
IR Spectrum of Compound **5**



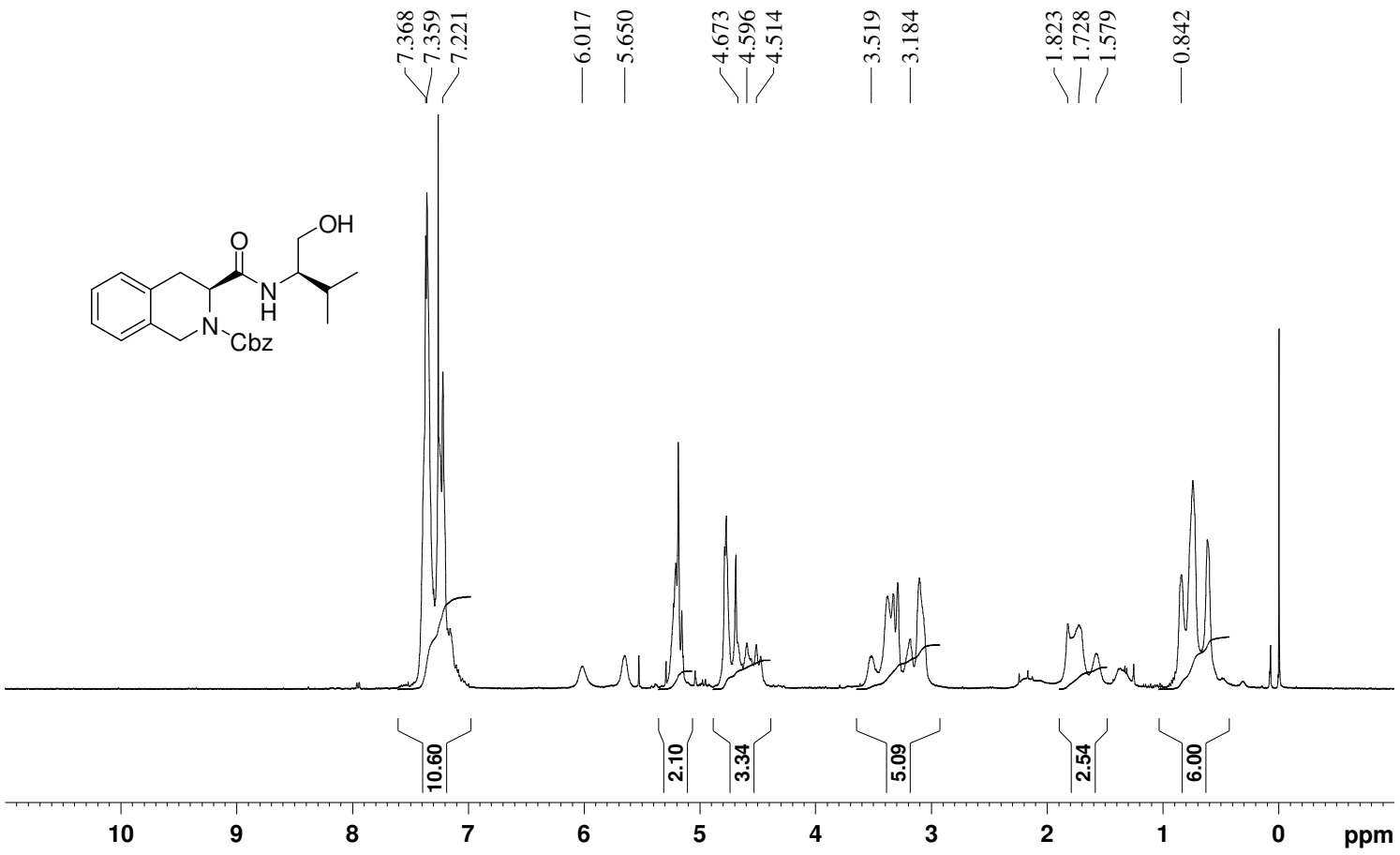
^{1}H NMR (400 MHz) Spectrum of Compound **6** in $CDCl_3$



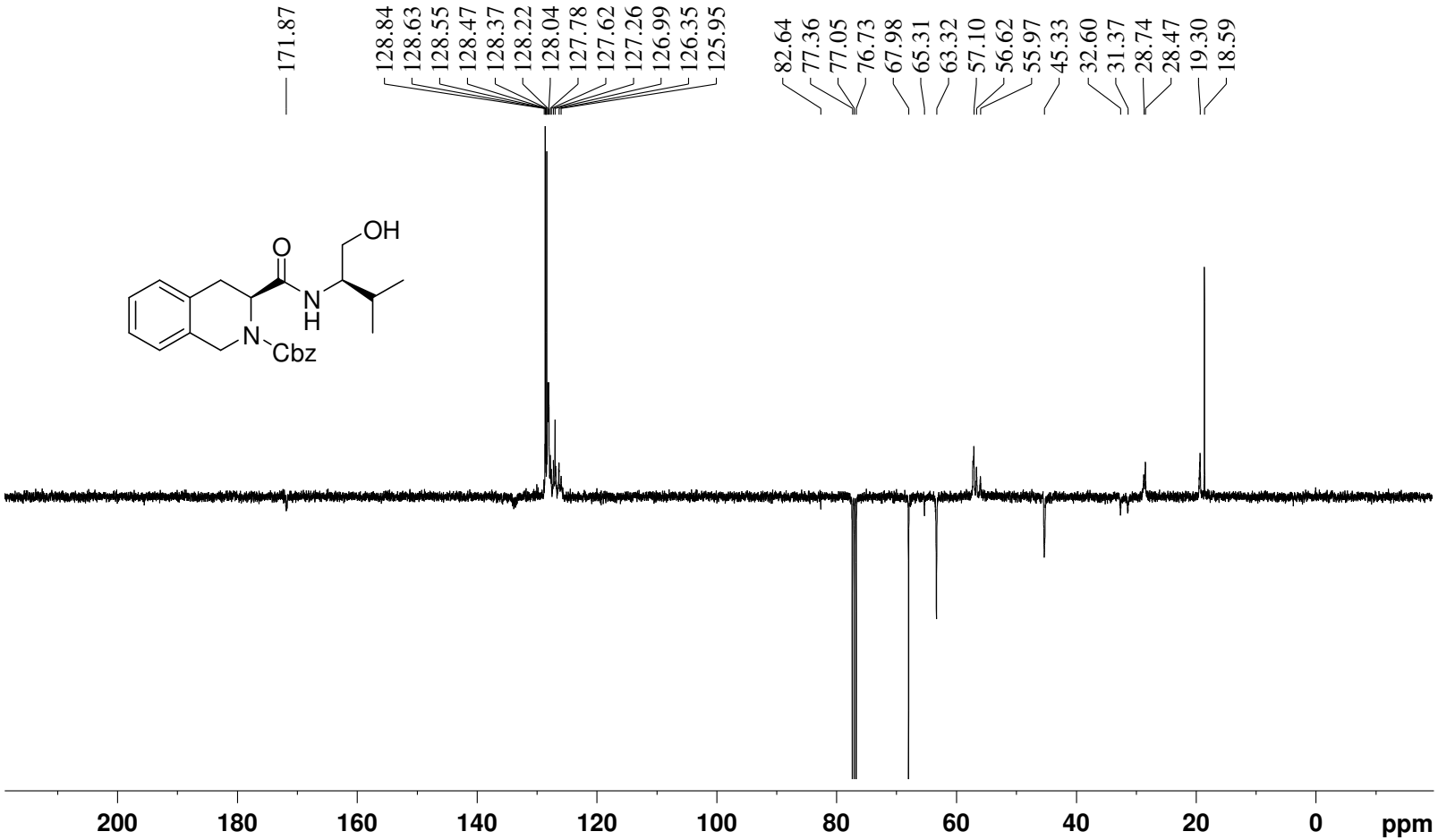
^{13}C (400 MHz) Spectrum of Compound **6** in $CDCl_3$



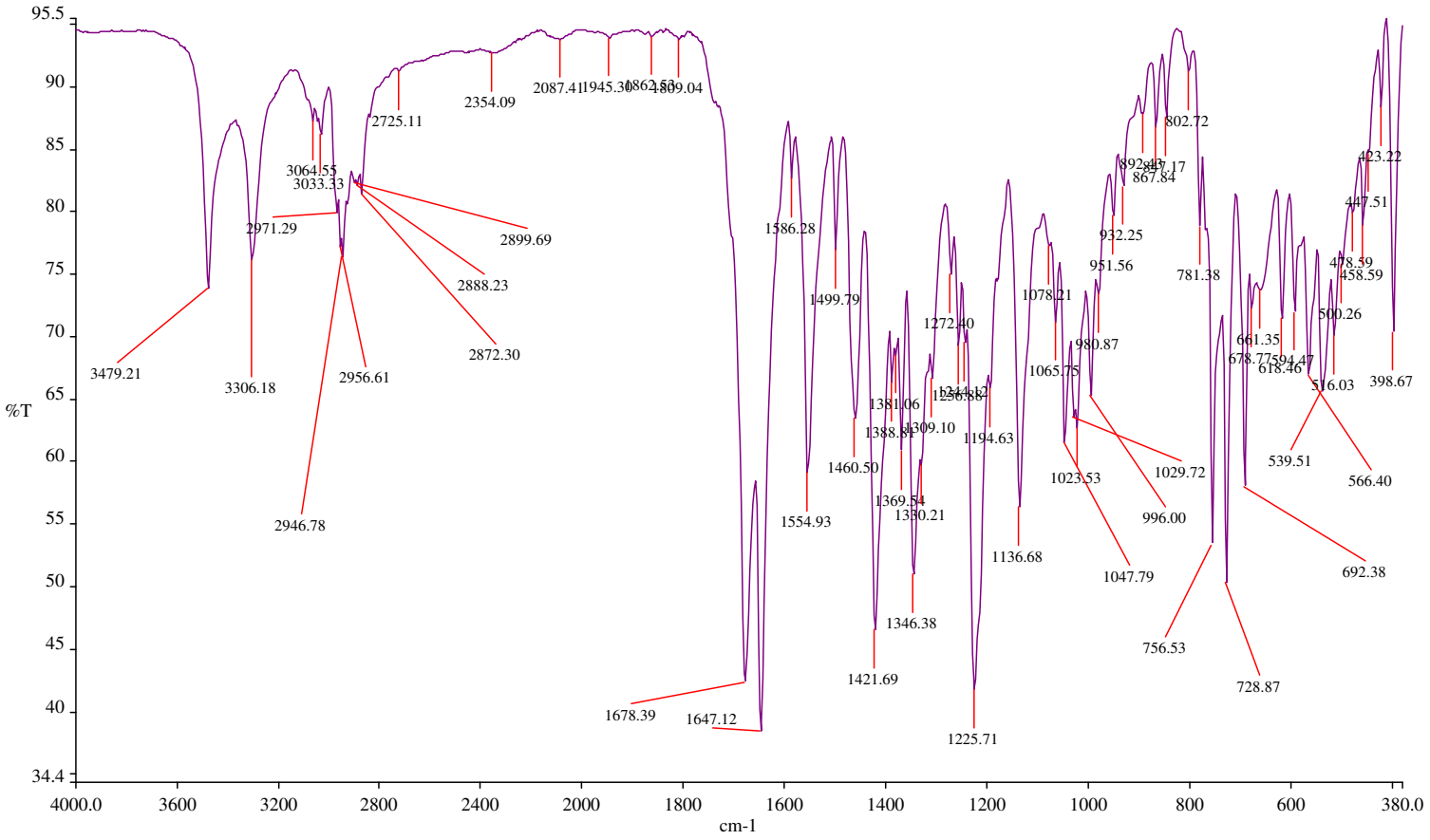
IR Spectrum of Compound **6**



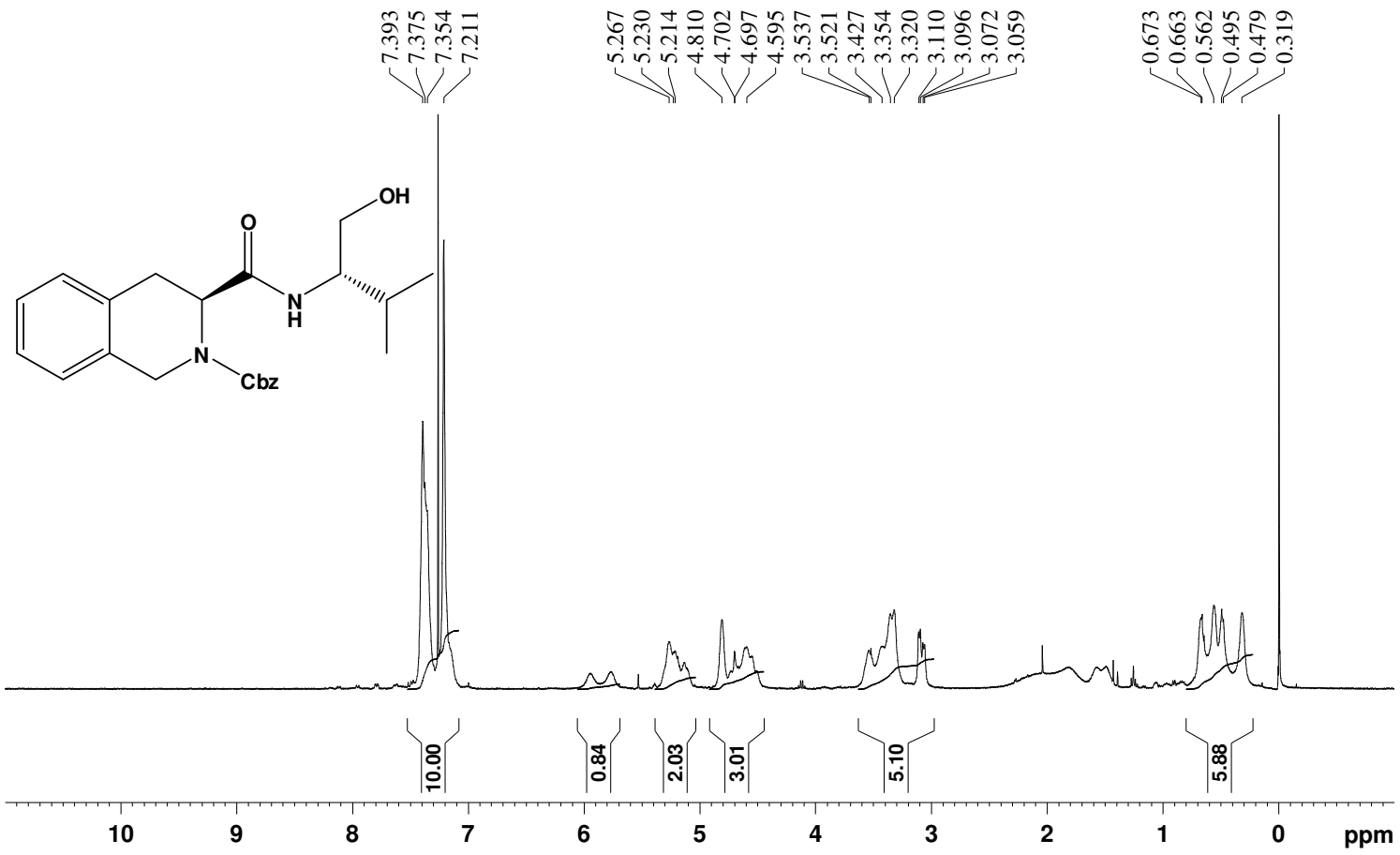
^{1}H NMR (400 MHz) Spectrum of Compound **7** in $CDCl_3$



^{13}C (400 MHz) Spectrum of Compound **7** in $CDCl_3$

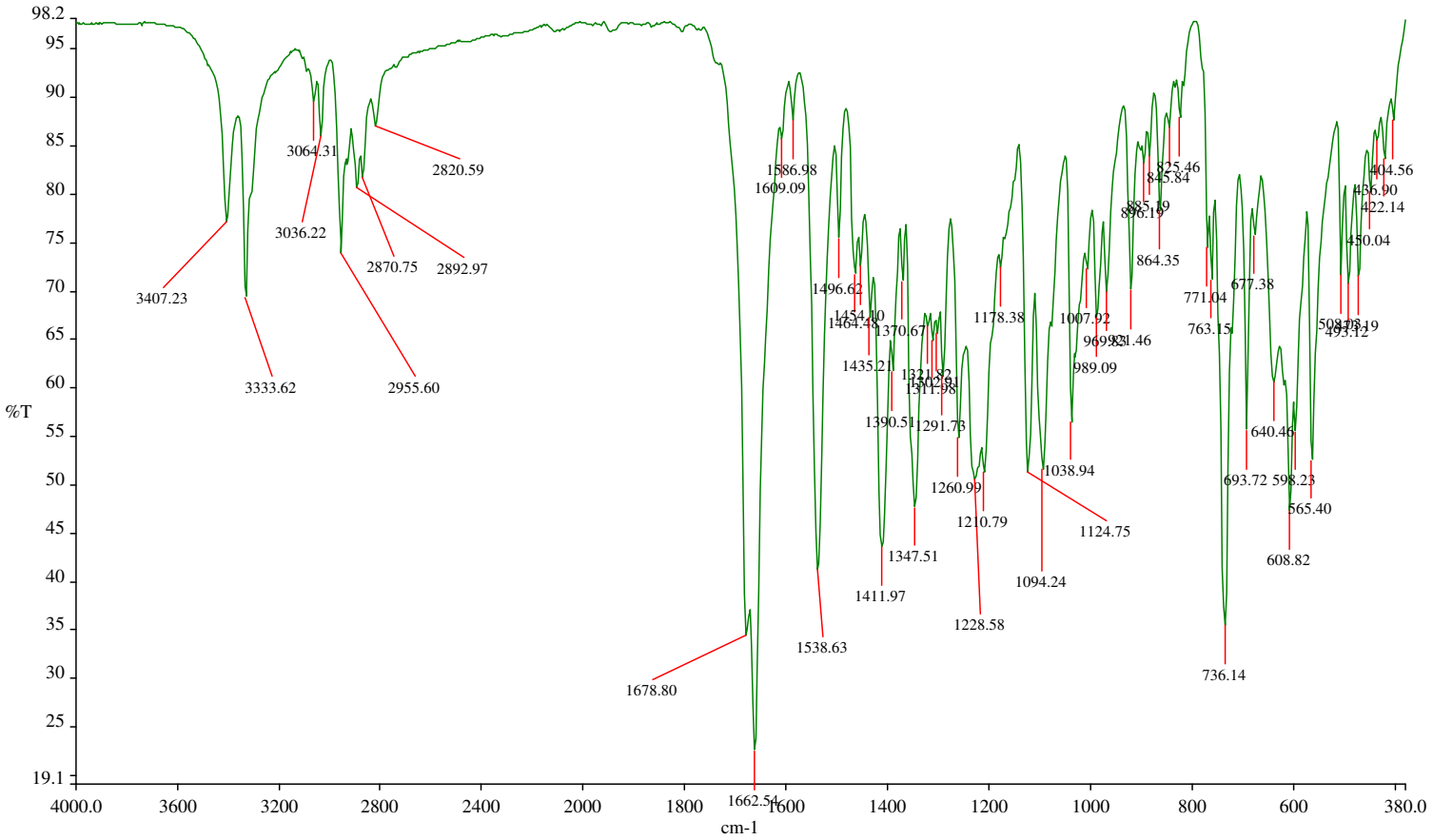


IR Spectrum of Compound **7**

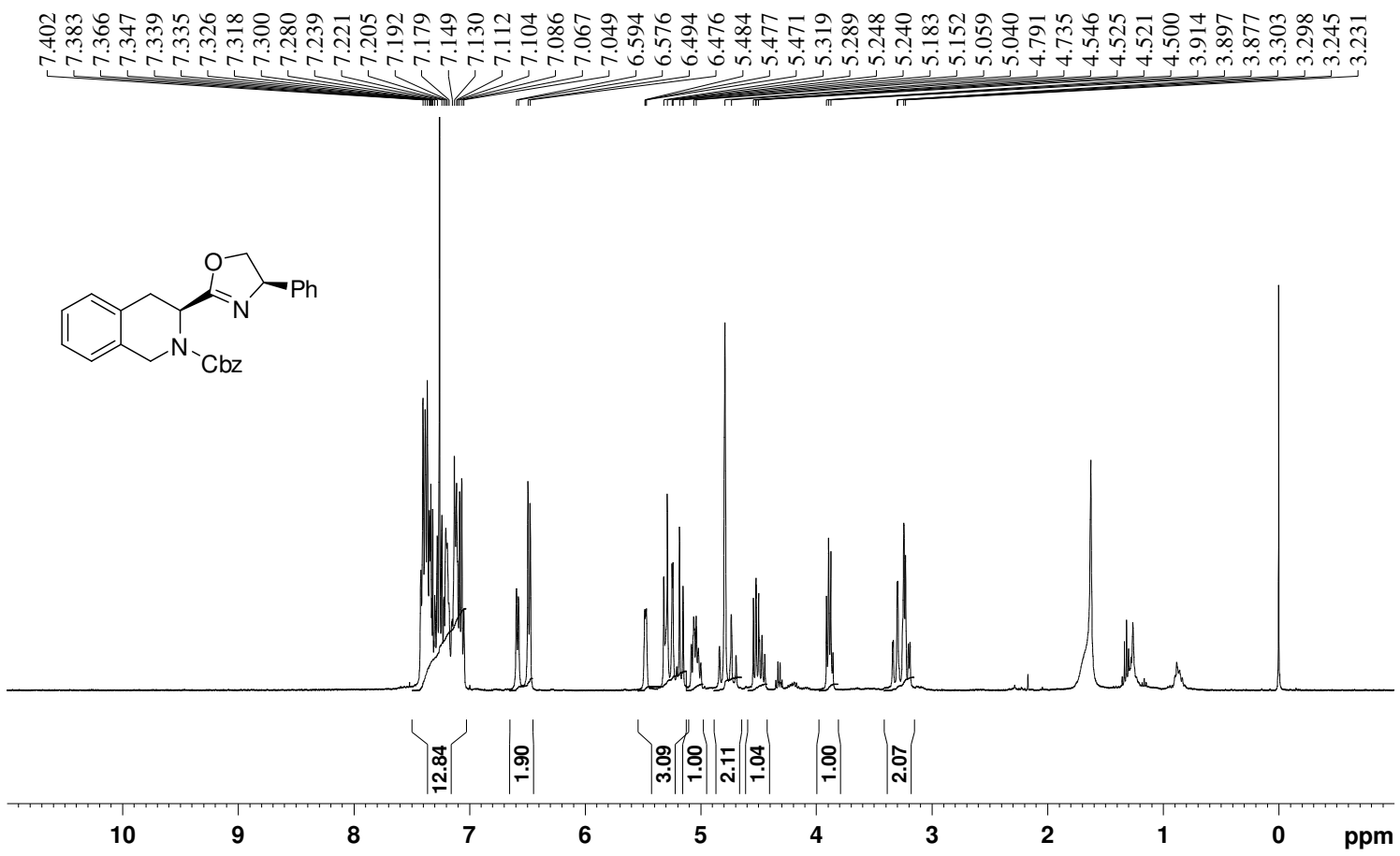


^{1}H NMR (400 MHz) Spectrum of Compound **8** in $CDCl_3$

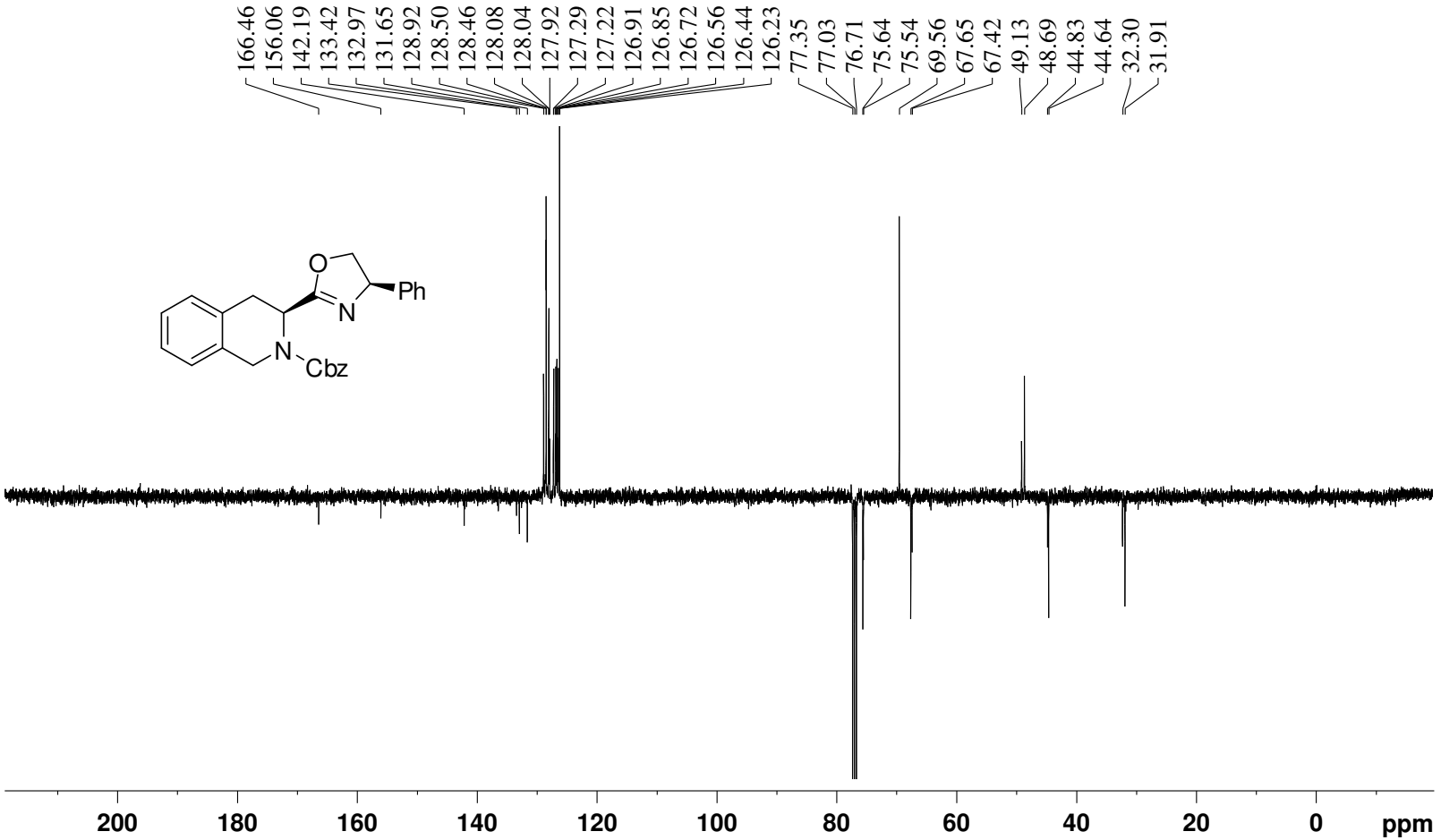
^{13}C (400 MHz) Spectrum of Compound **8** in $CDCl_3$



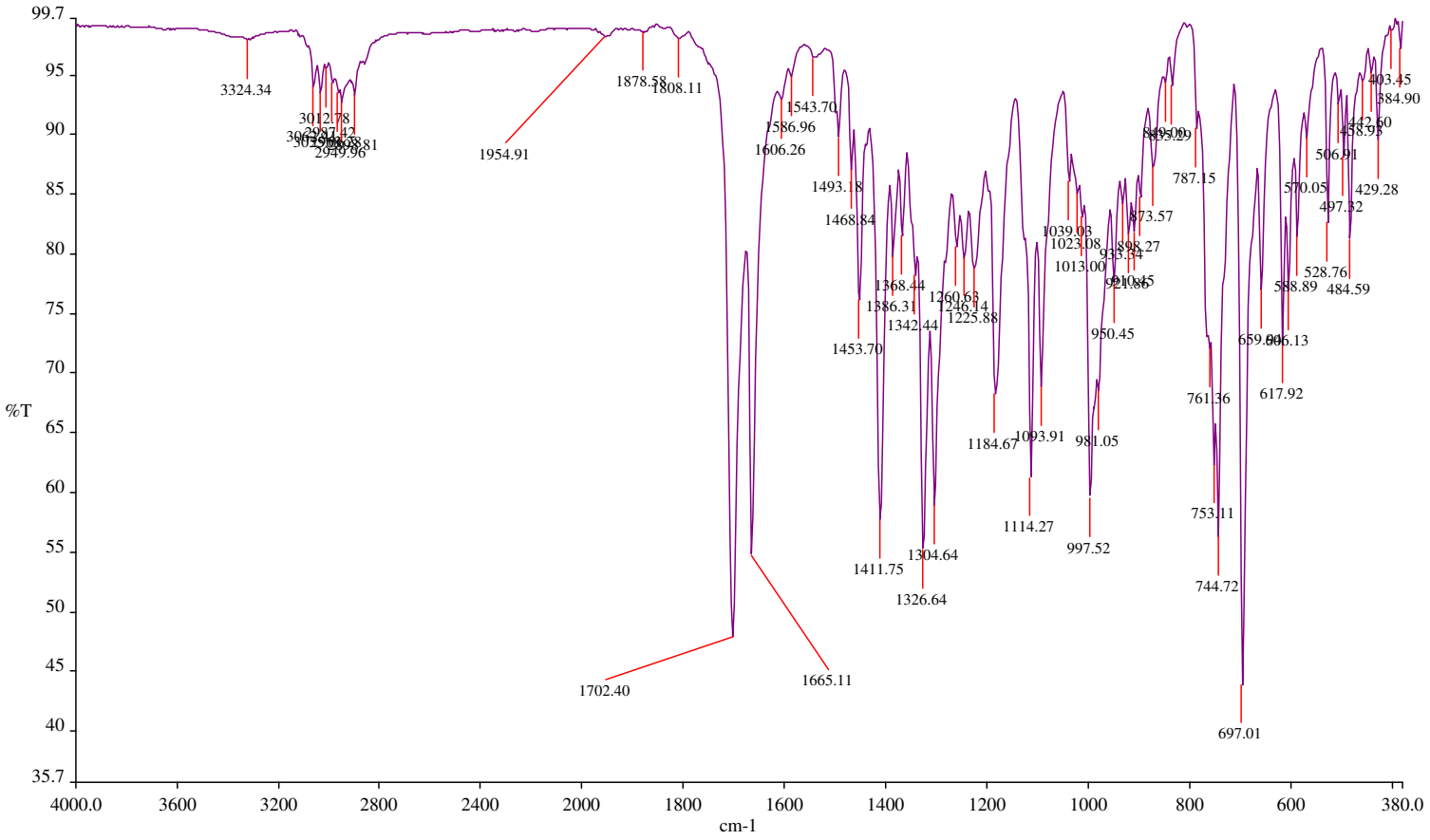
IR Spectrum of Compound **8**



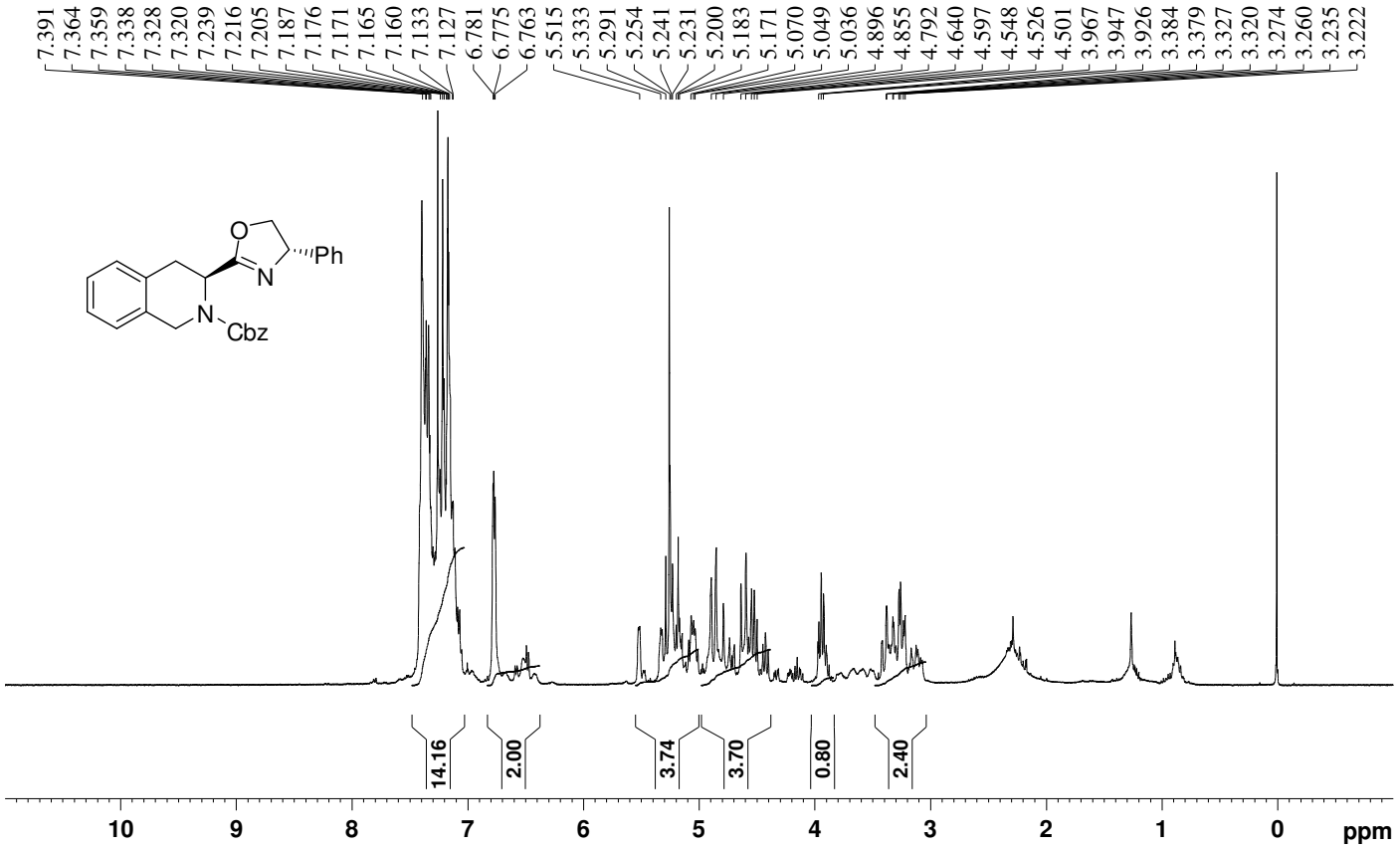
^{1}H NMR (400 MHz) Spectrum of Compound **9** in $CDCl_3$



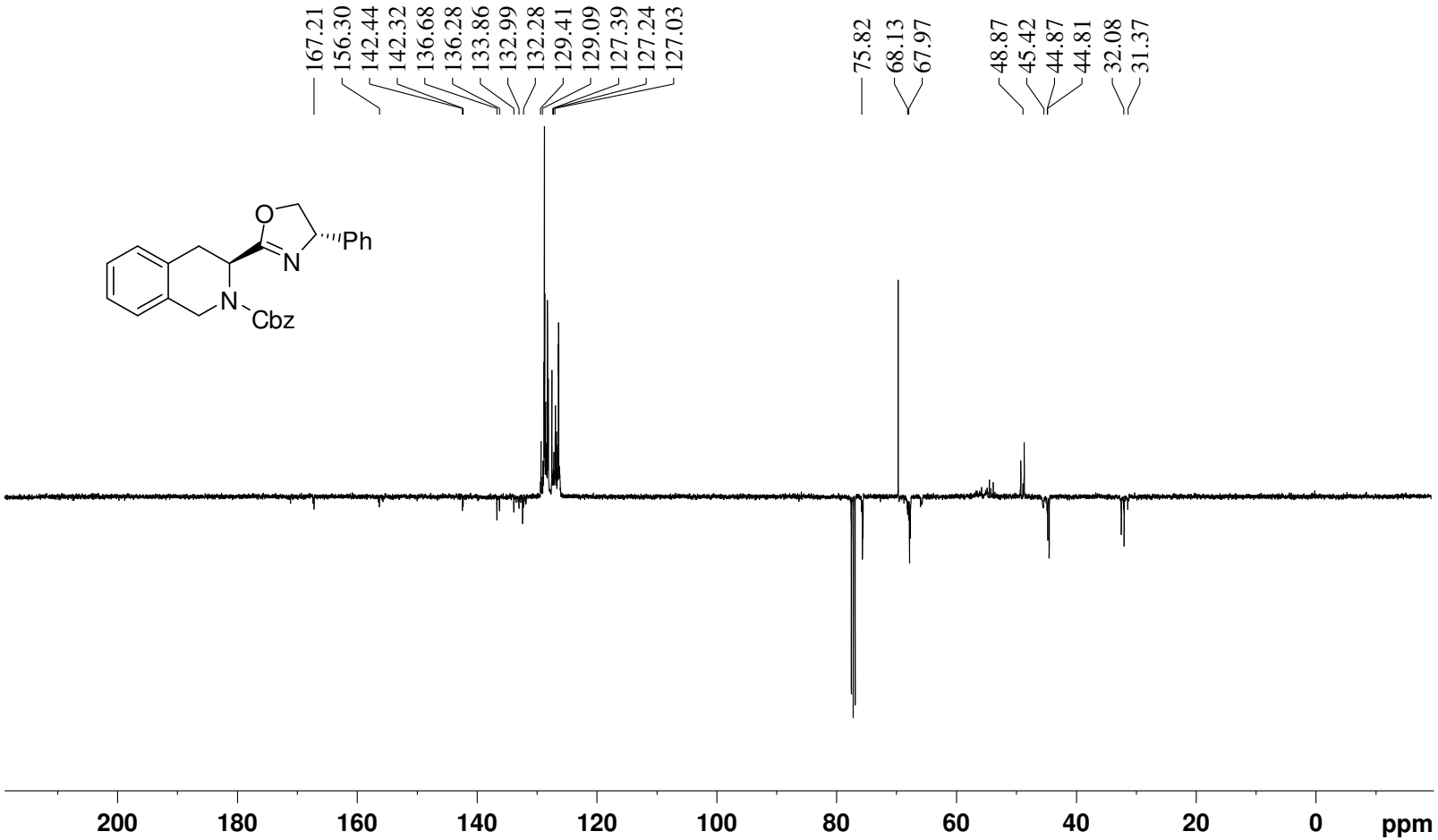
^{13}C (400 MHz) Spectrum of Compound **9** in $CDCl_3$



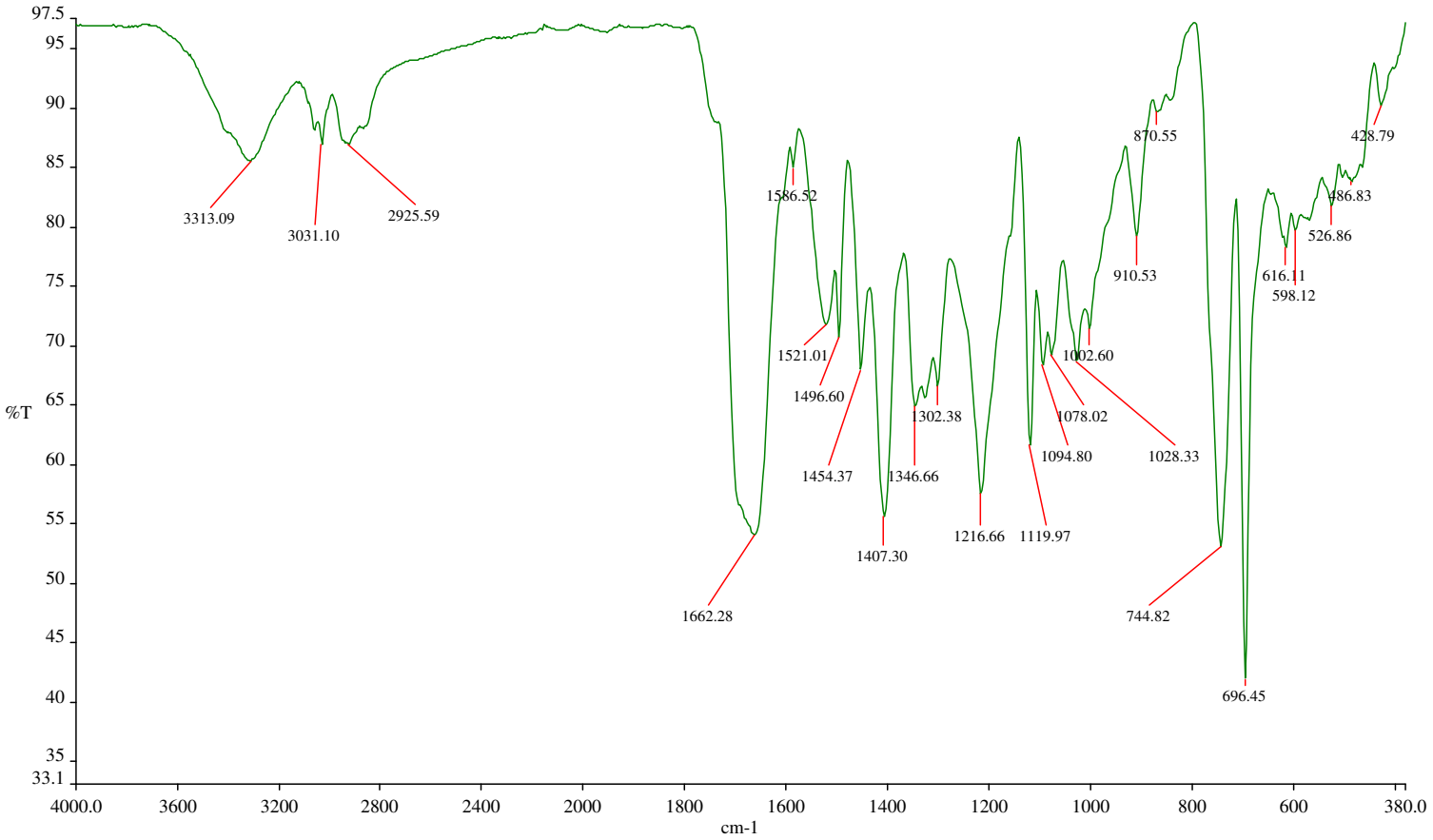
IR Spectrum of Compound **9**



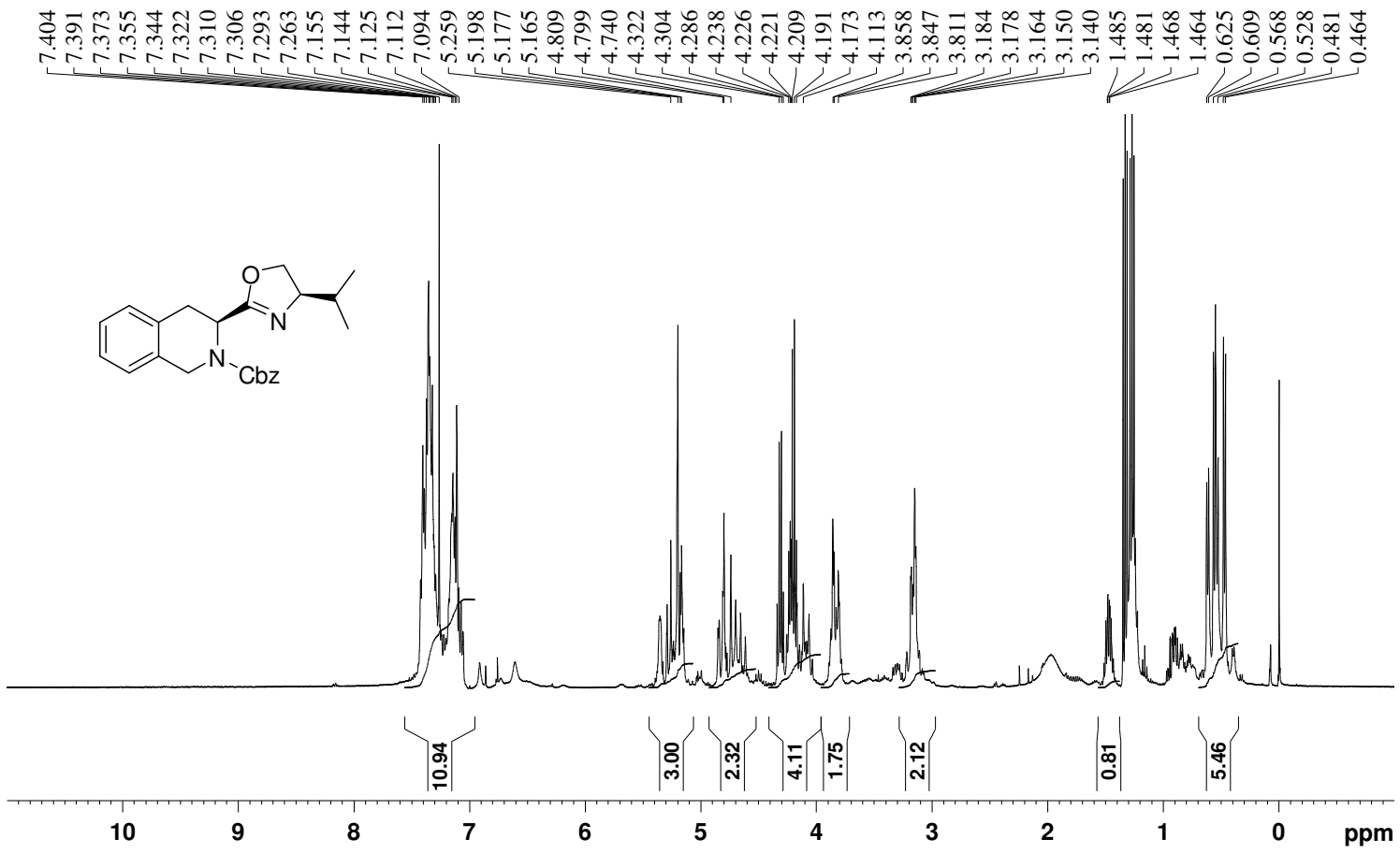
^{1}H NMR (400 MHz) Spectrum of Compound **10** in $CDCl_3$



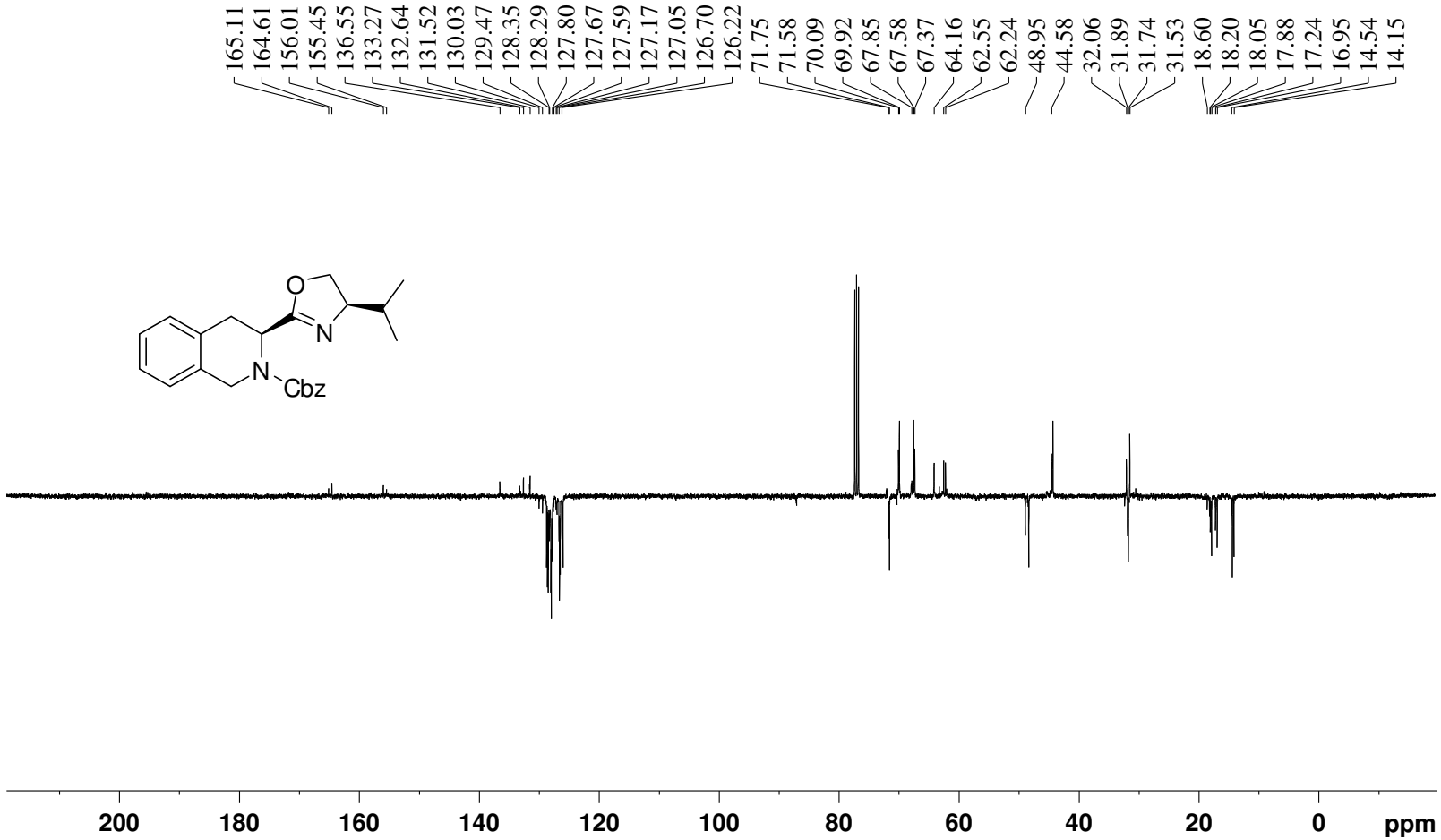
^{13}C (400 MHz) Spectrum of Compound **10** in $CDCl_3$



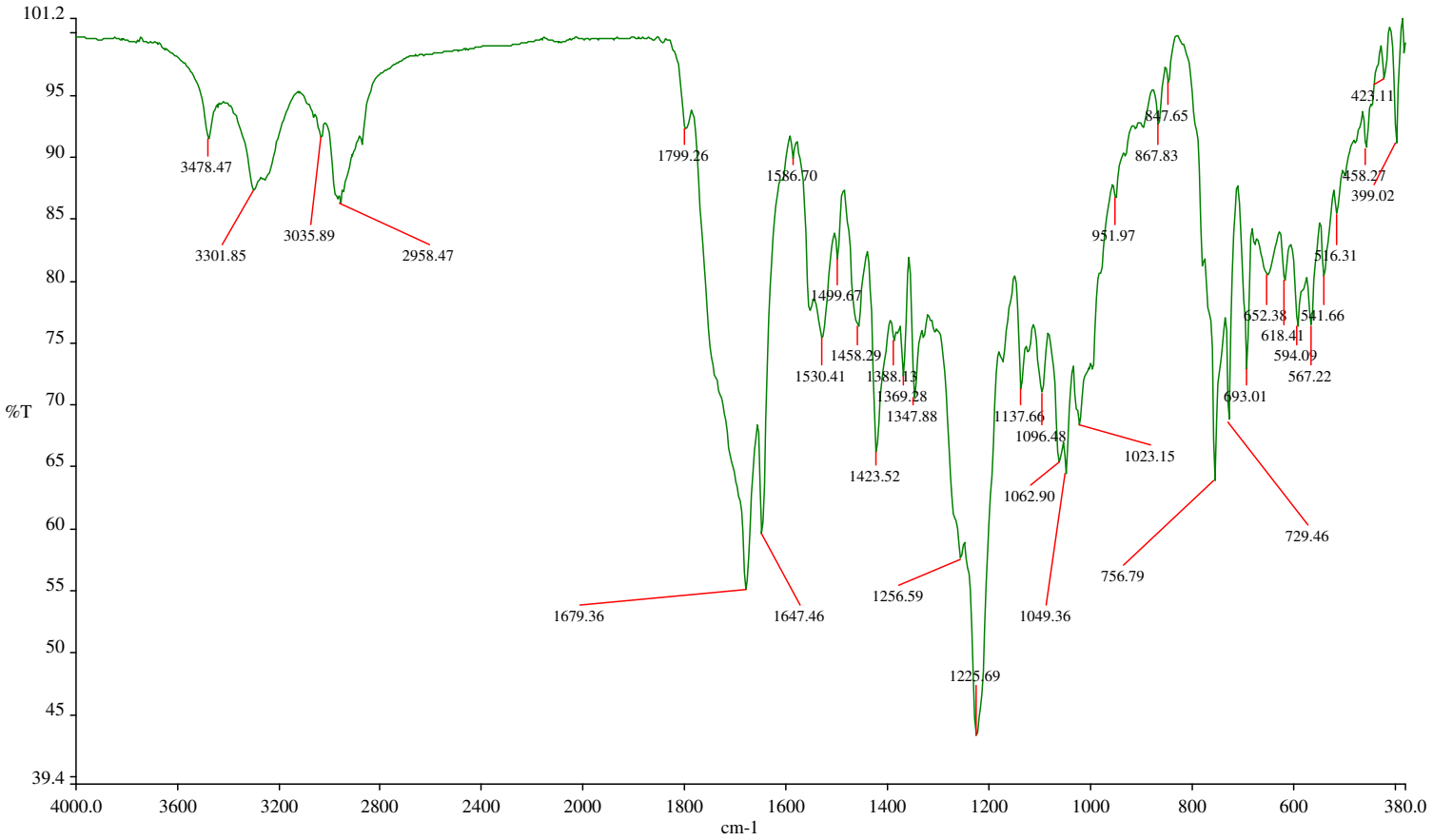
IR Spectrum of Compound **10**



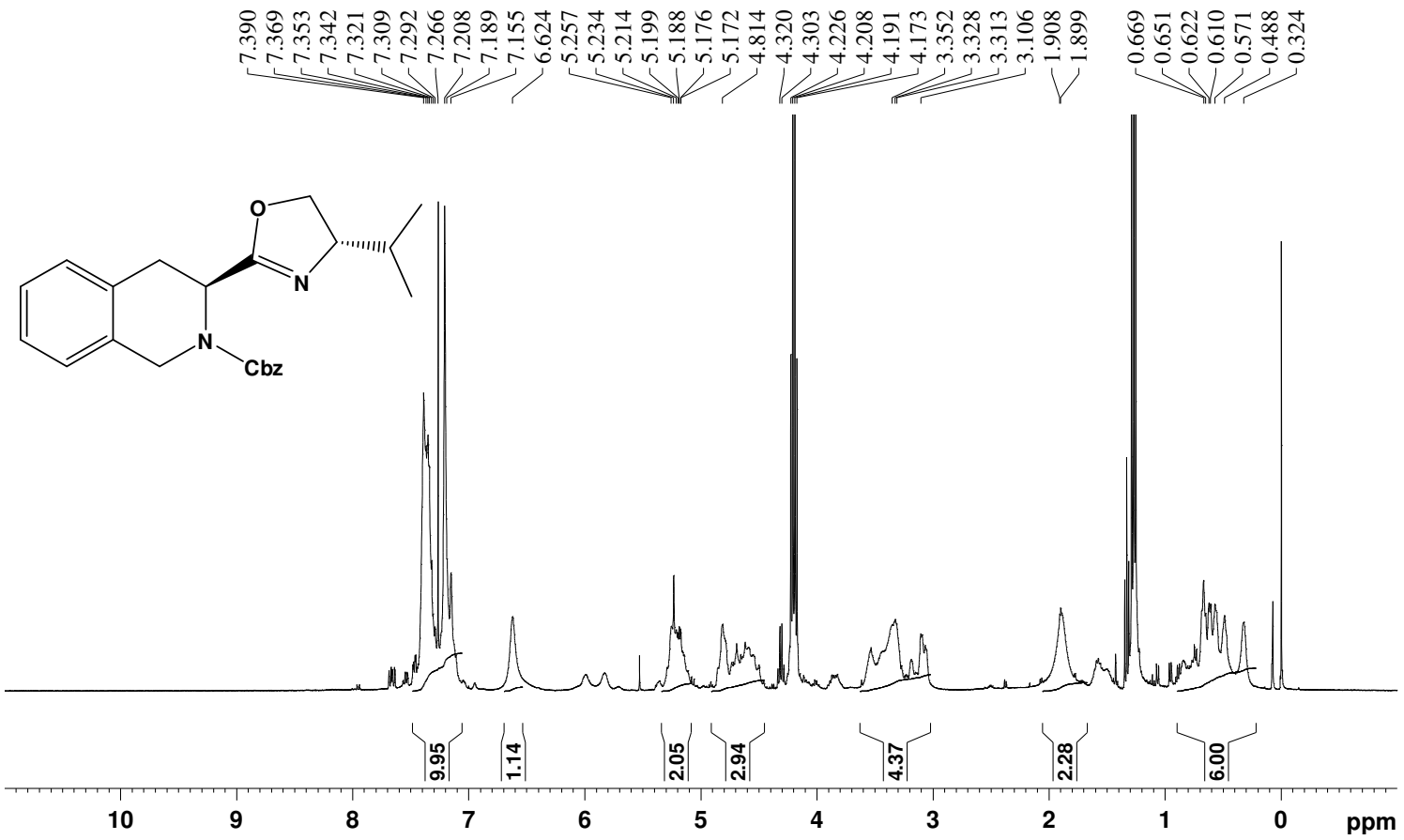
^{1}H NMR (400 MHz) Spectrum of Compound **11** in $CDCl_3$



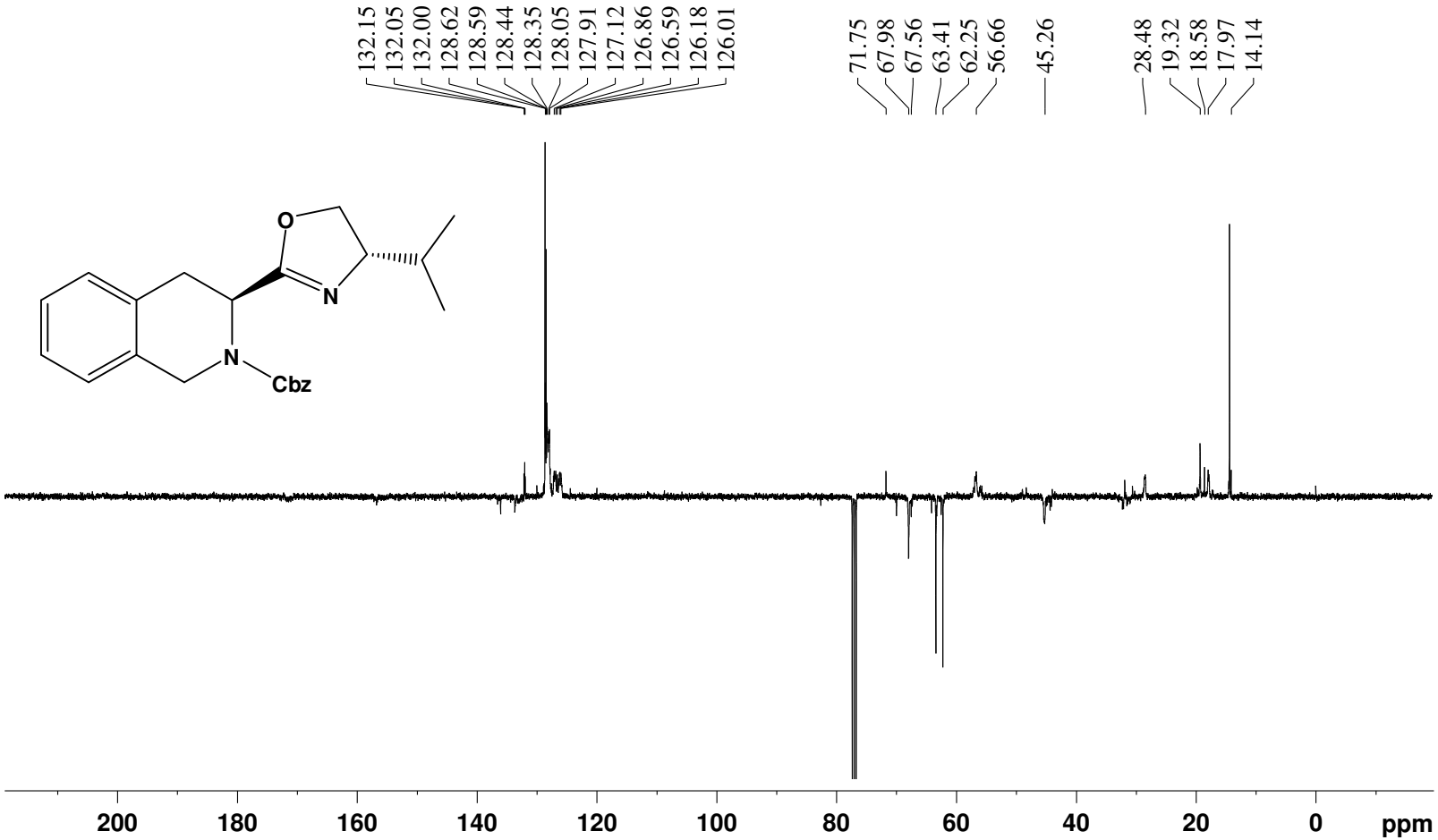
^{13}C (400 MHz) Spectrum of Compound **11** in $CDCl_3$



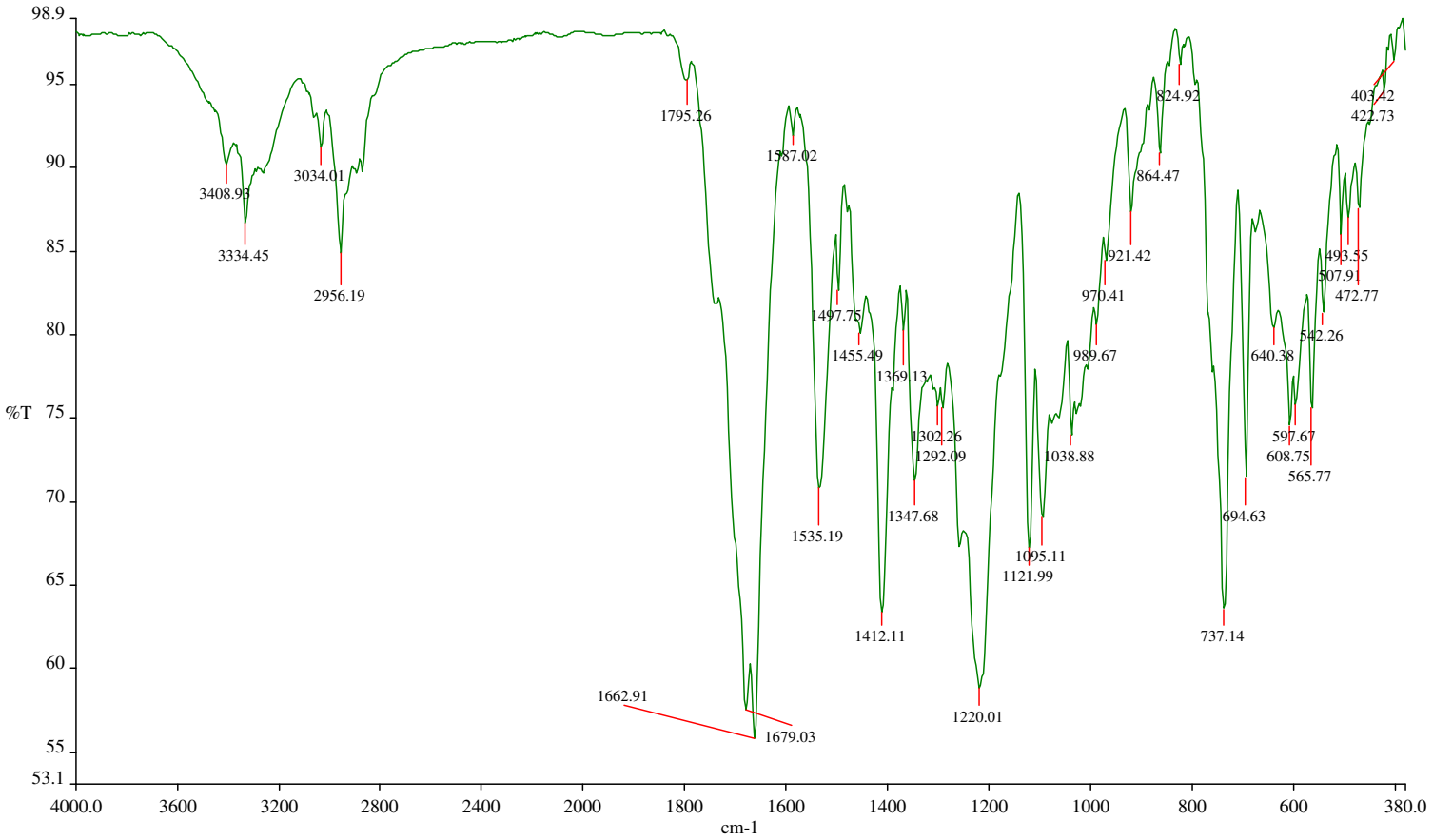
IR Spectrum of Compound **11**



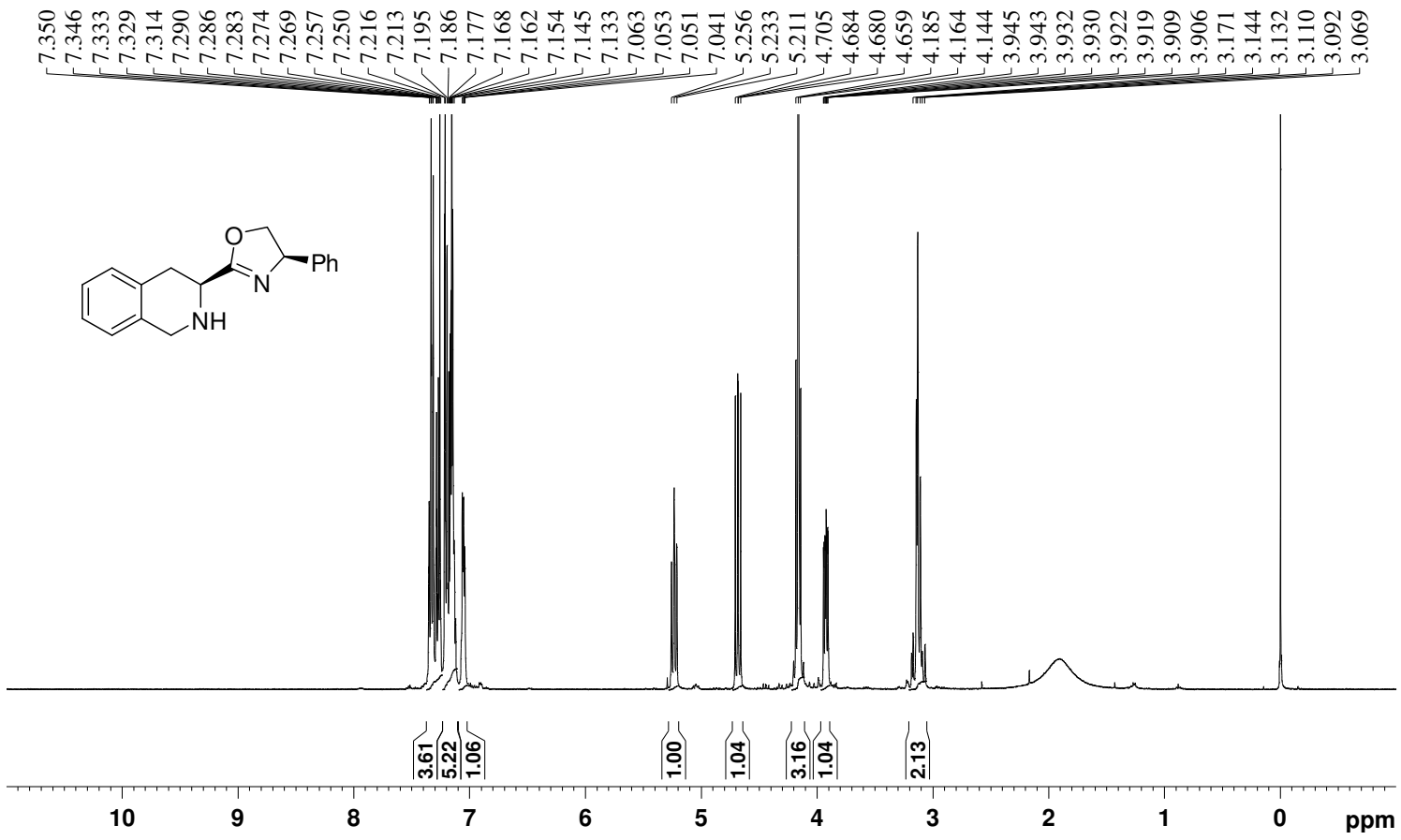
^{1}H NMR (400 MHz) Spectrum of Compound **12** in $CDCl_3$



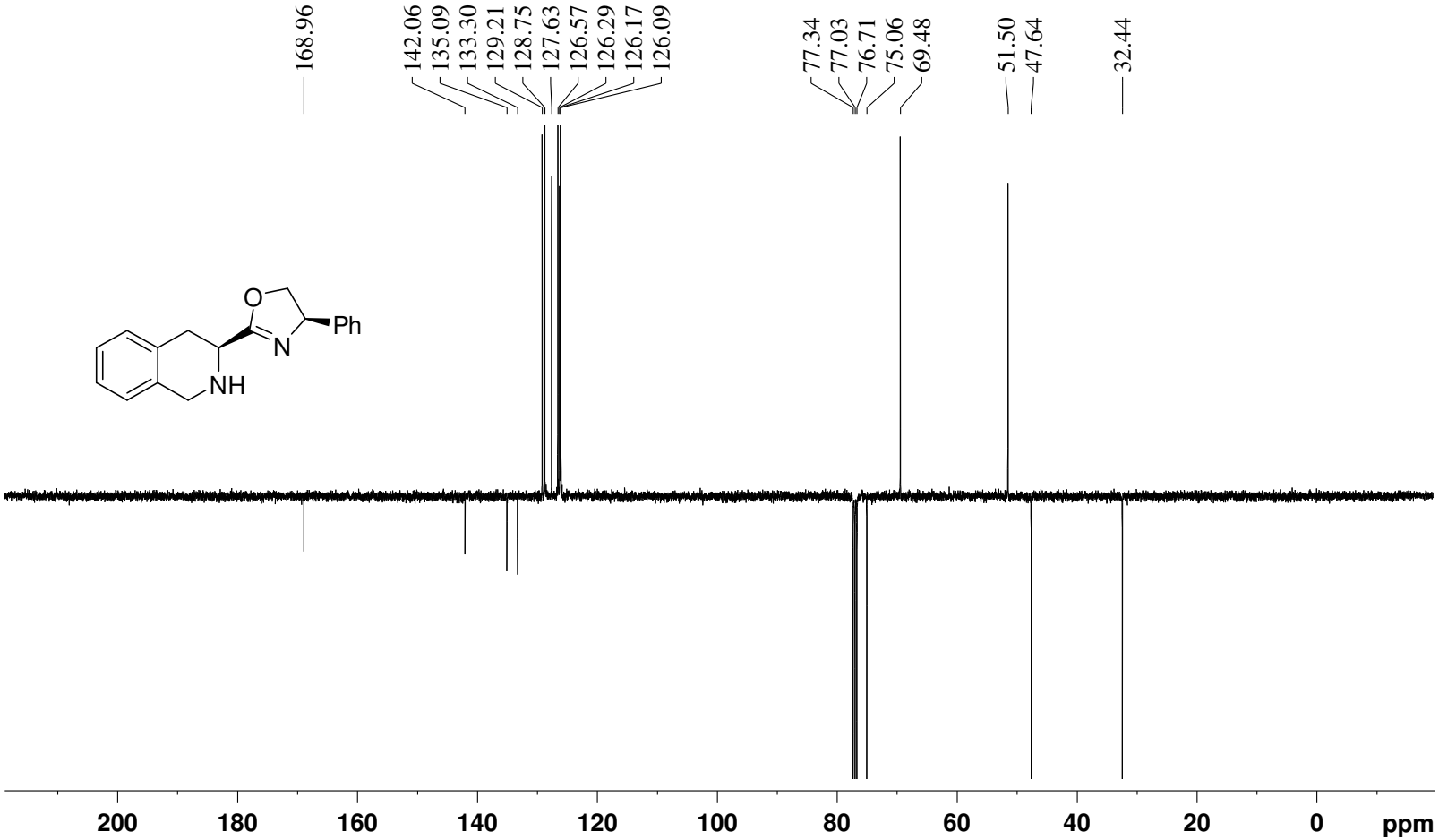
^{13}C (400 MHz) Spectrum of Compound **12** in $CDCl_3$



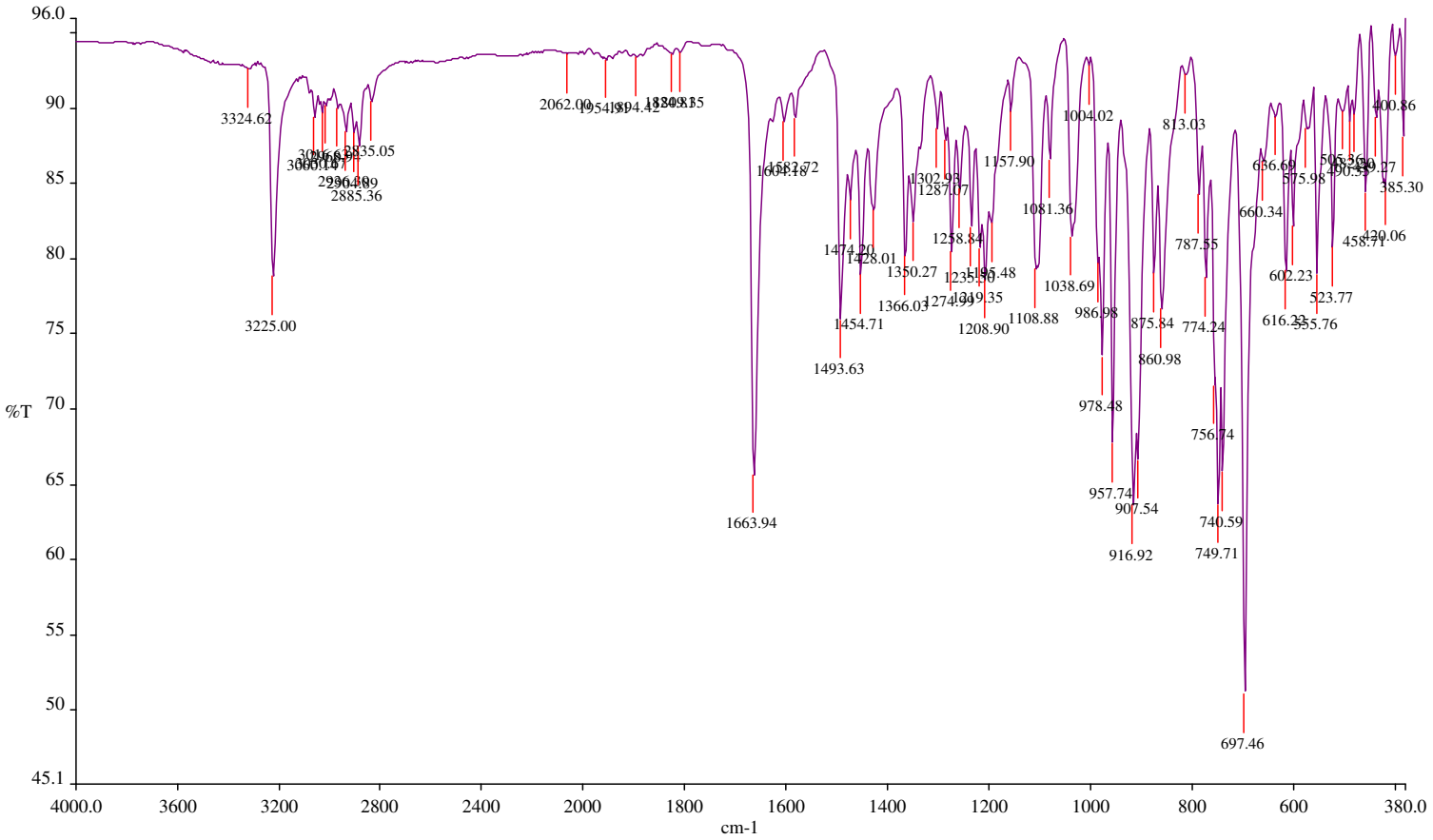
IR Spectrum of Compound **12**



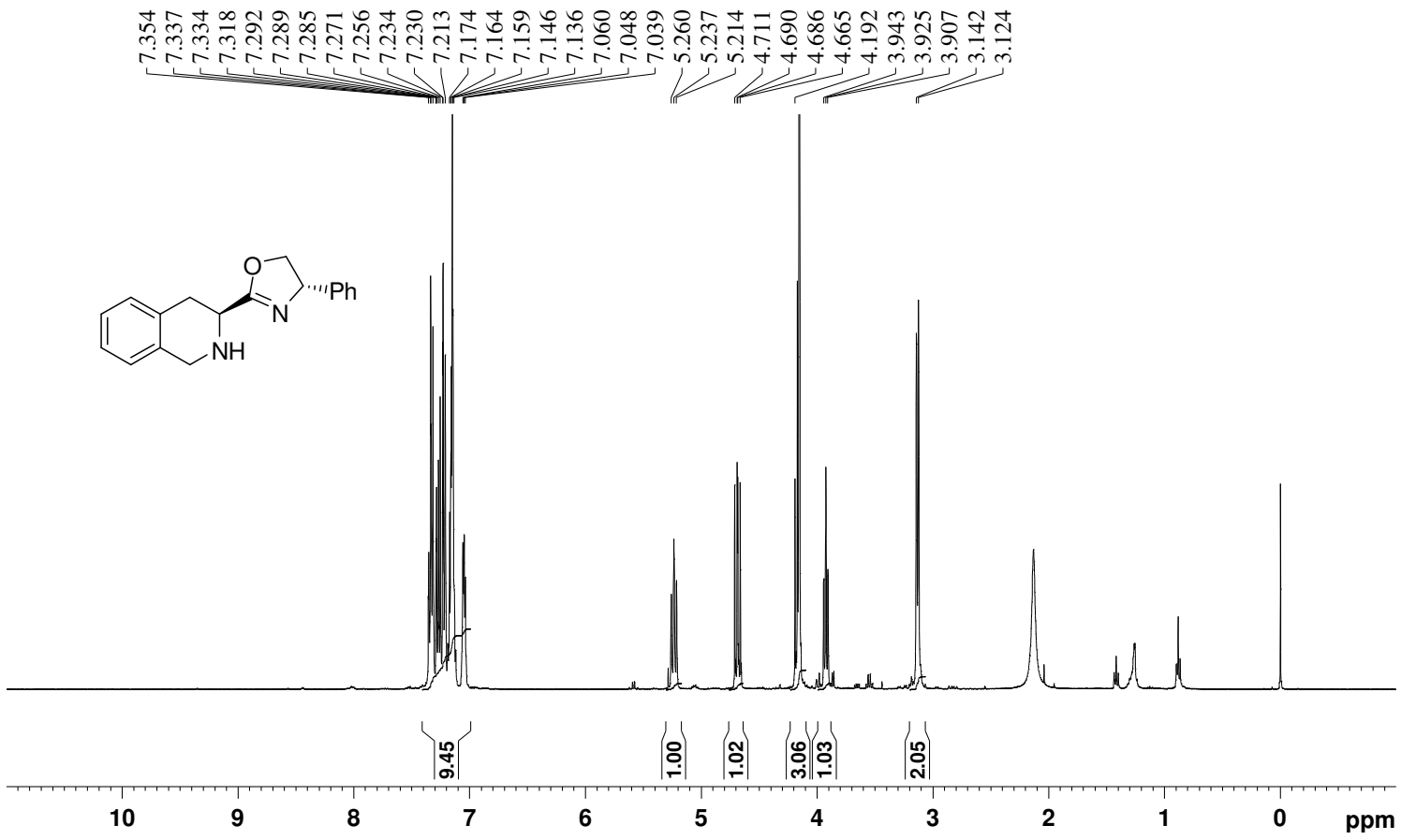
^{1}H NMR (400 MHz) Spectrum of Compound **13** in $CDCl_3$



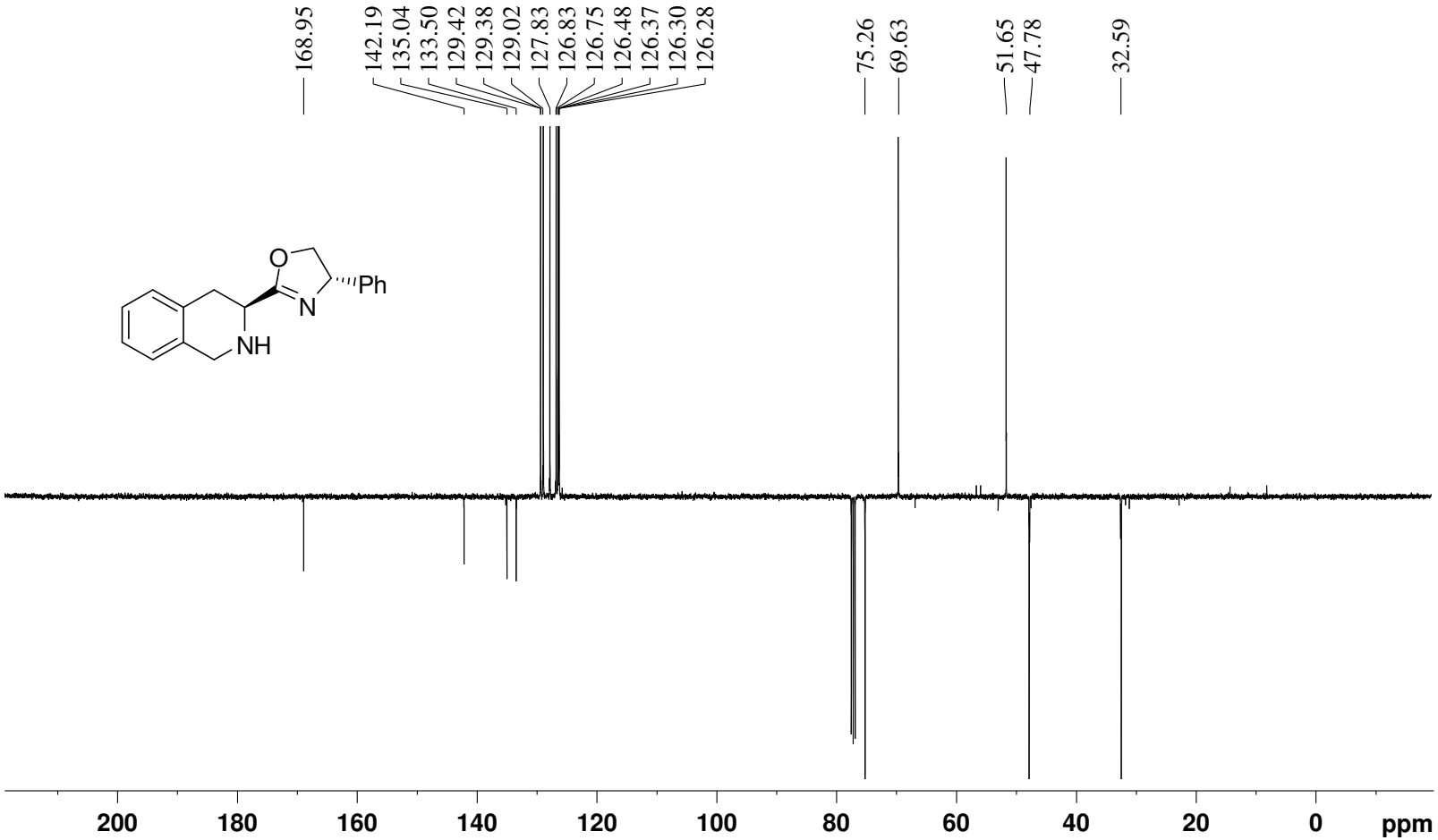
^{13}C (400 MHz) Spectrum of Compound **13** in $CDCl_3$



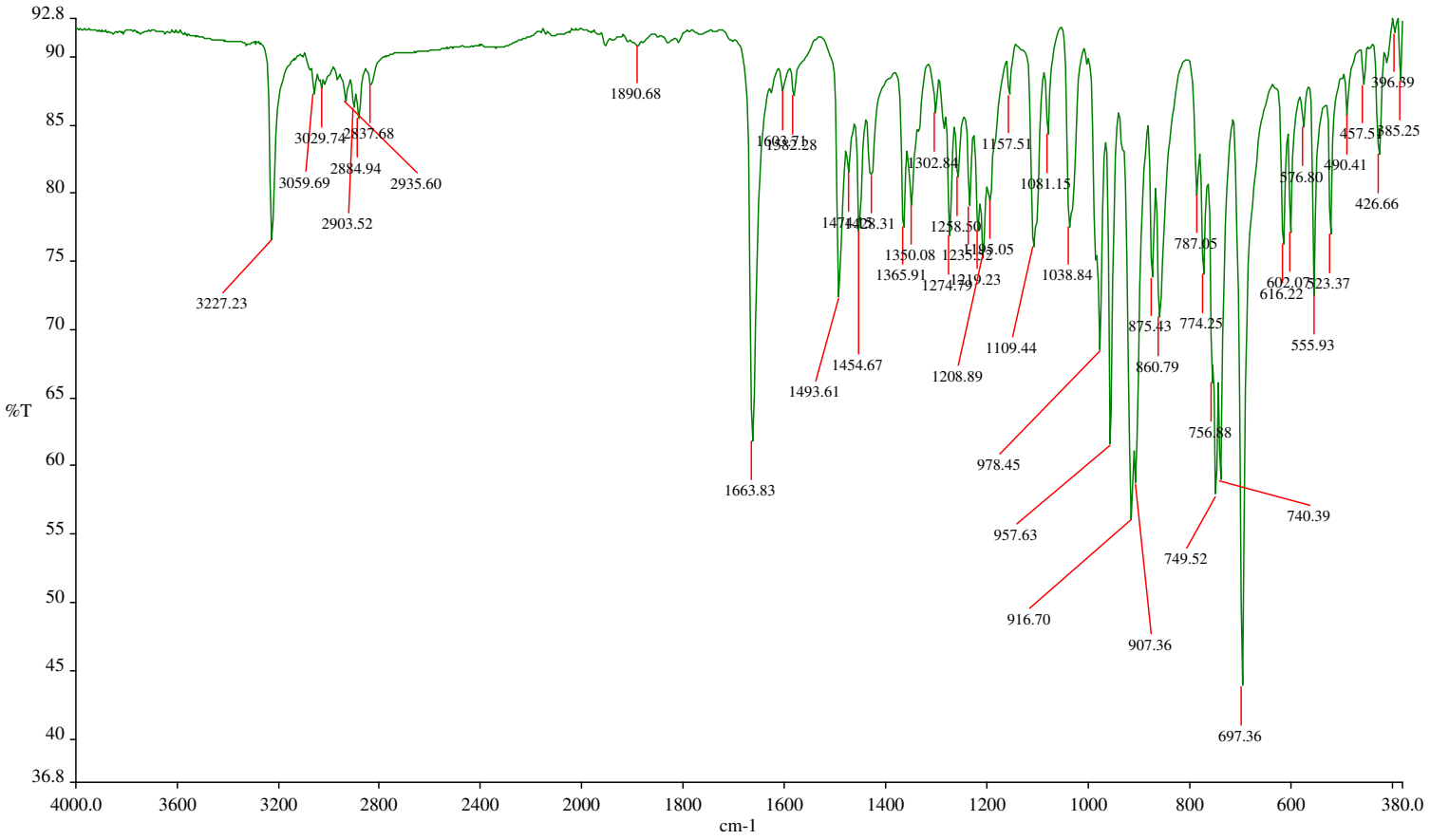
IR Spectrum of Compound **13**



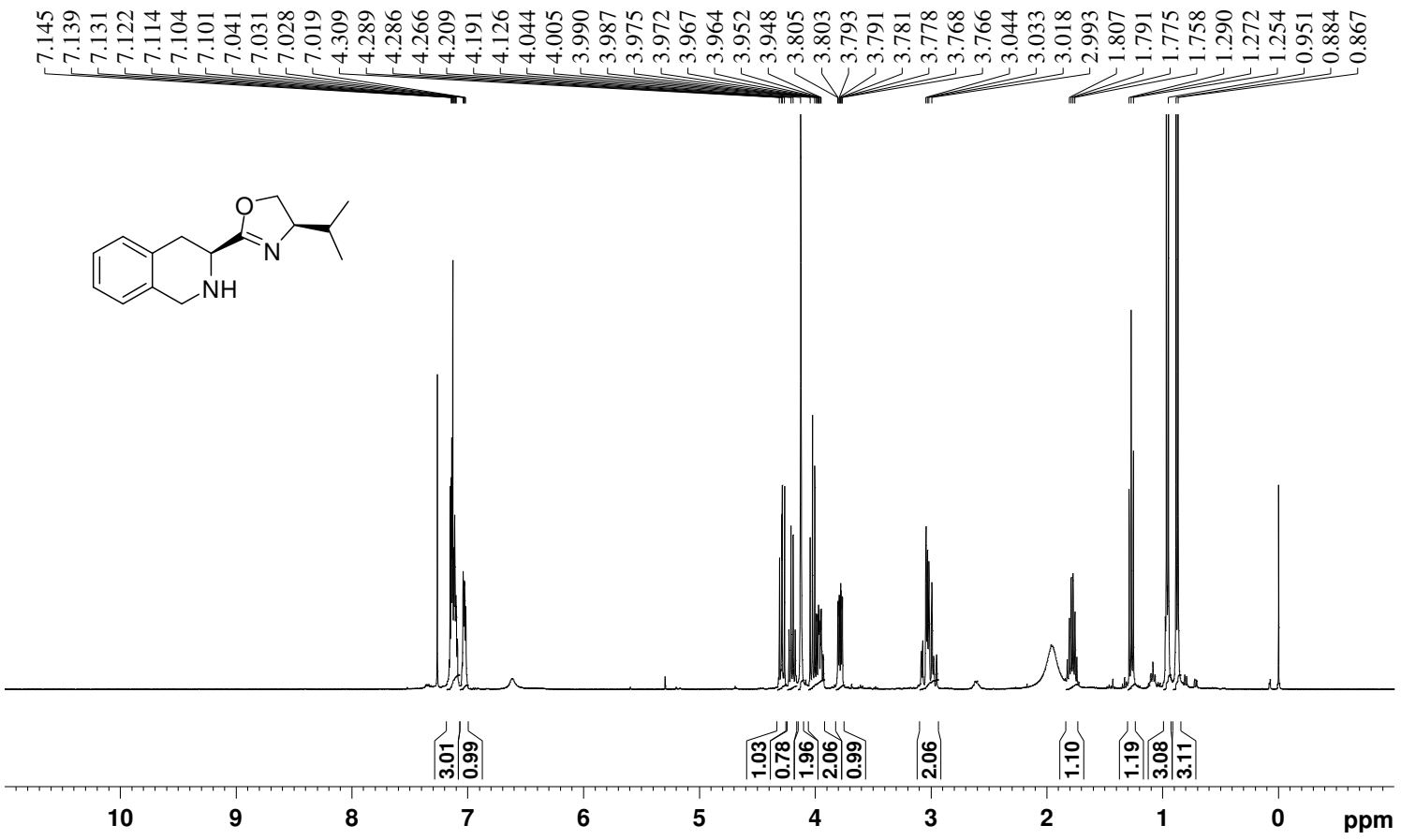
^{1}H NMR (400 MHz) Spectrum of Compound **14** in $CDCl_3$



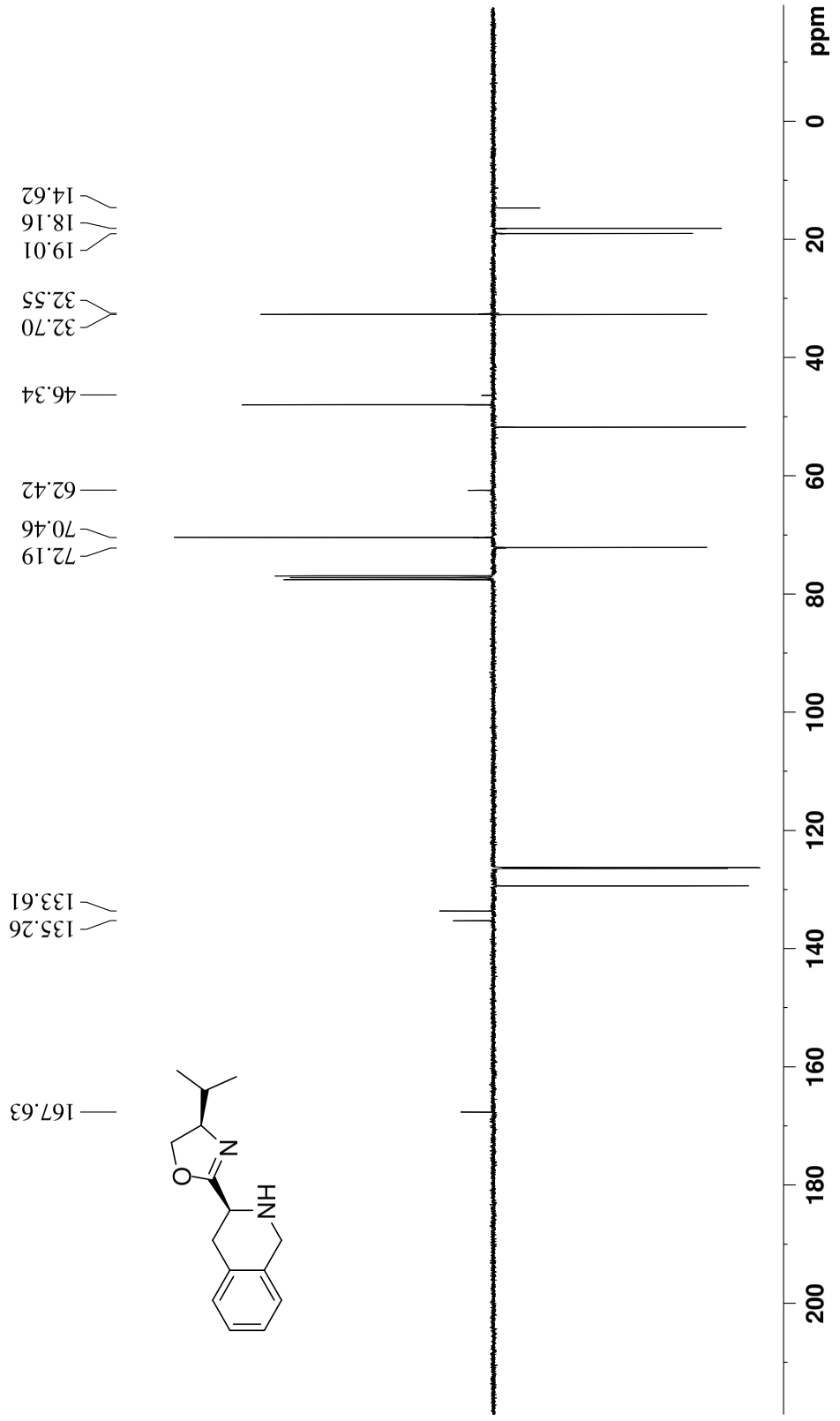
^{13}C (400 MHz) Spectrum of Compound **14** in $CDCl_3$



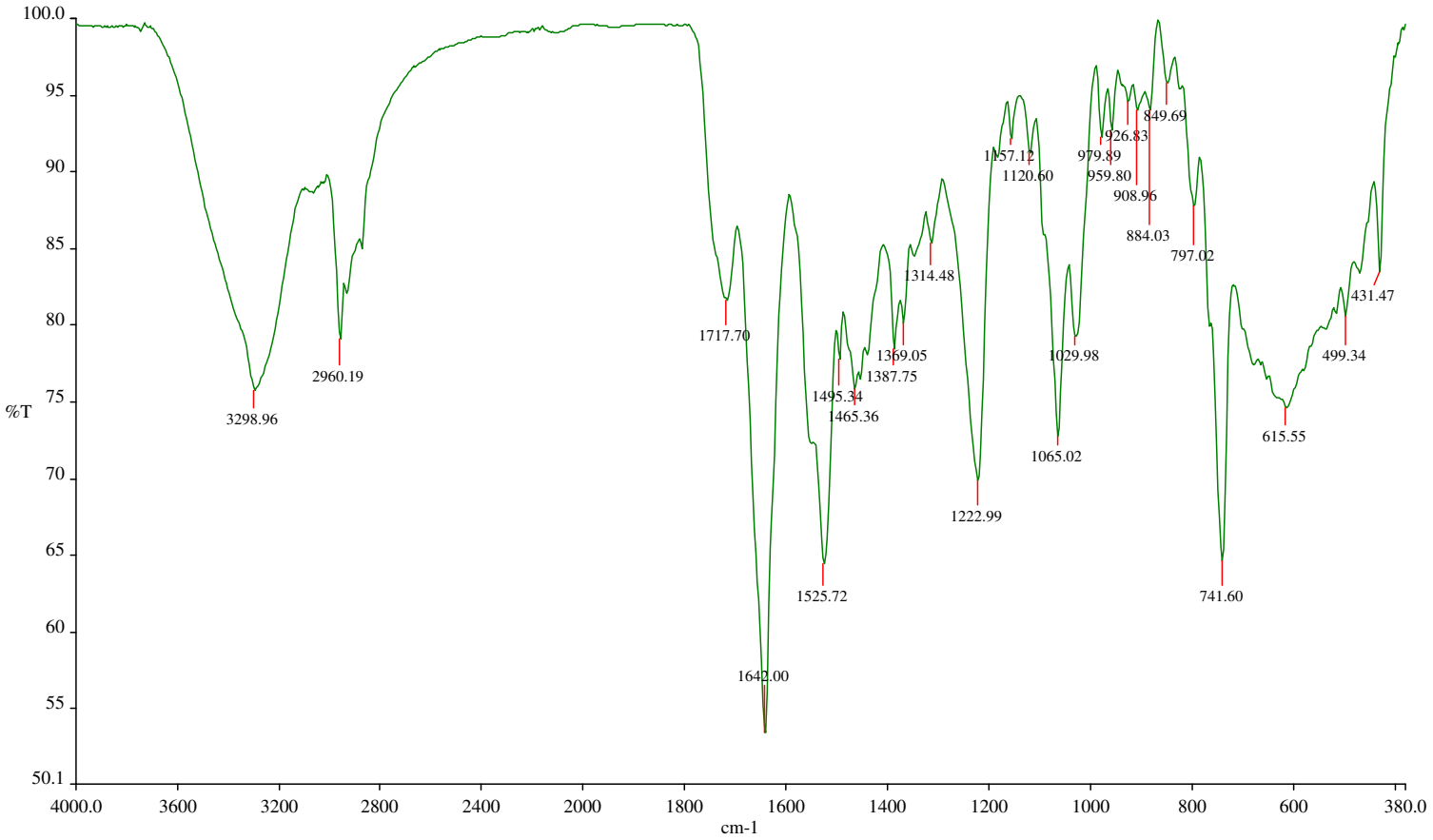
IR Spectrum of Compound **14**



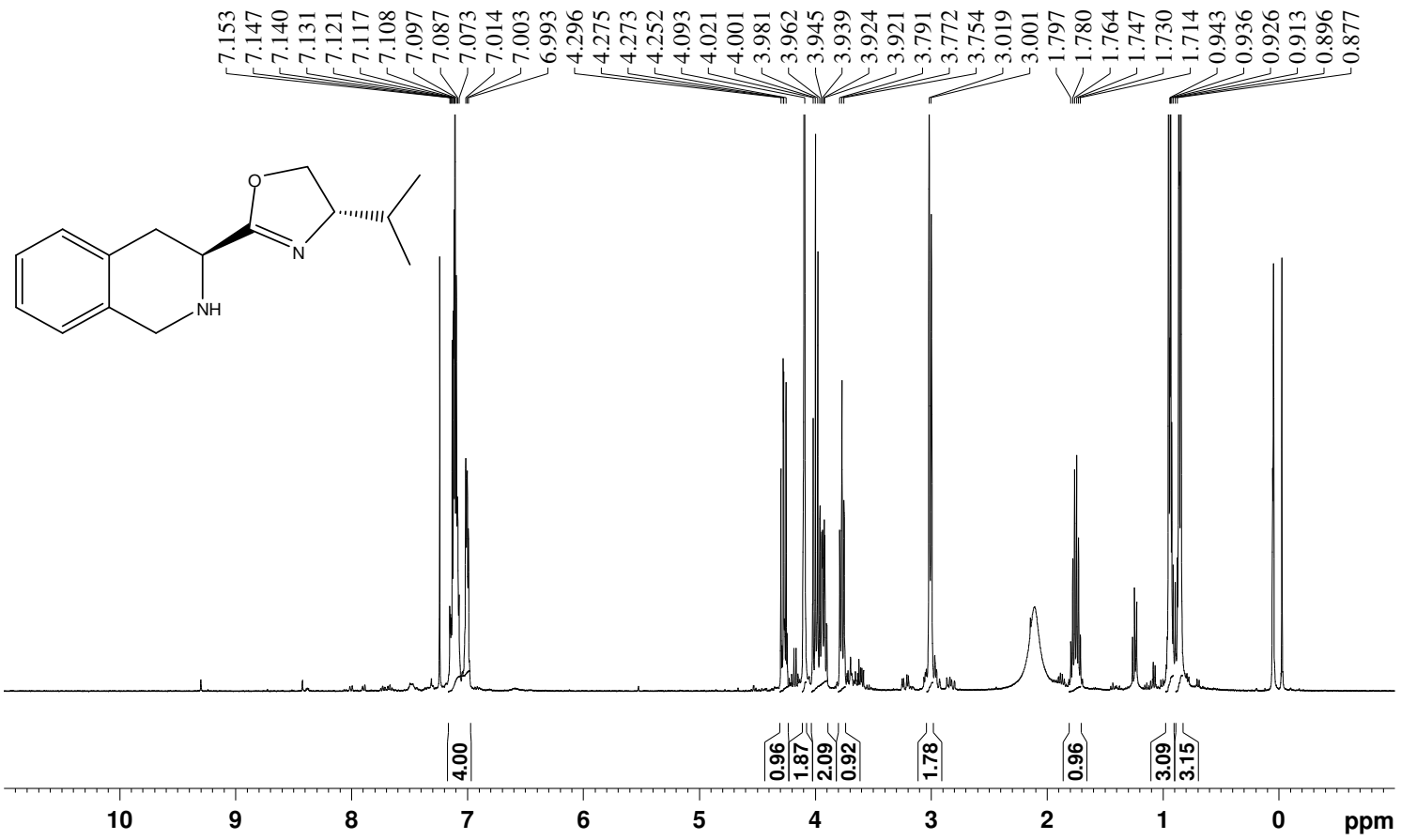
^{1}H NMR (400 MHz) Spectrum of Compound **15** in $CDCl_3$



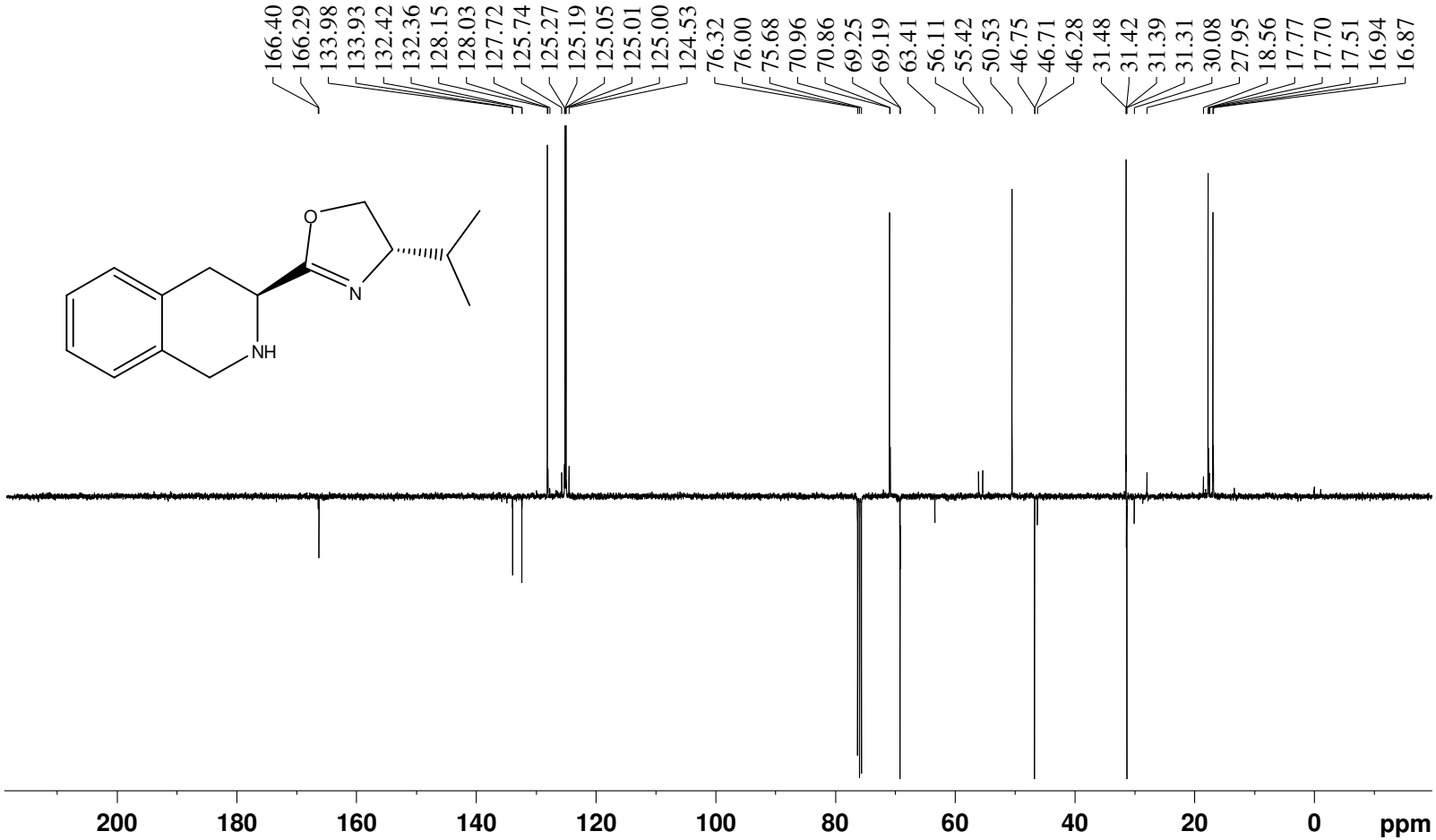
^{13}C (400 MHz) Spectrum of Compound **15** in $CDCl_3$



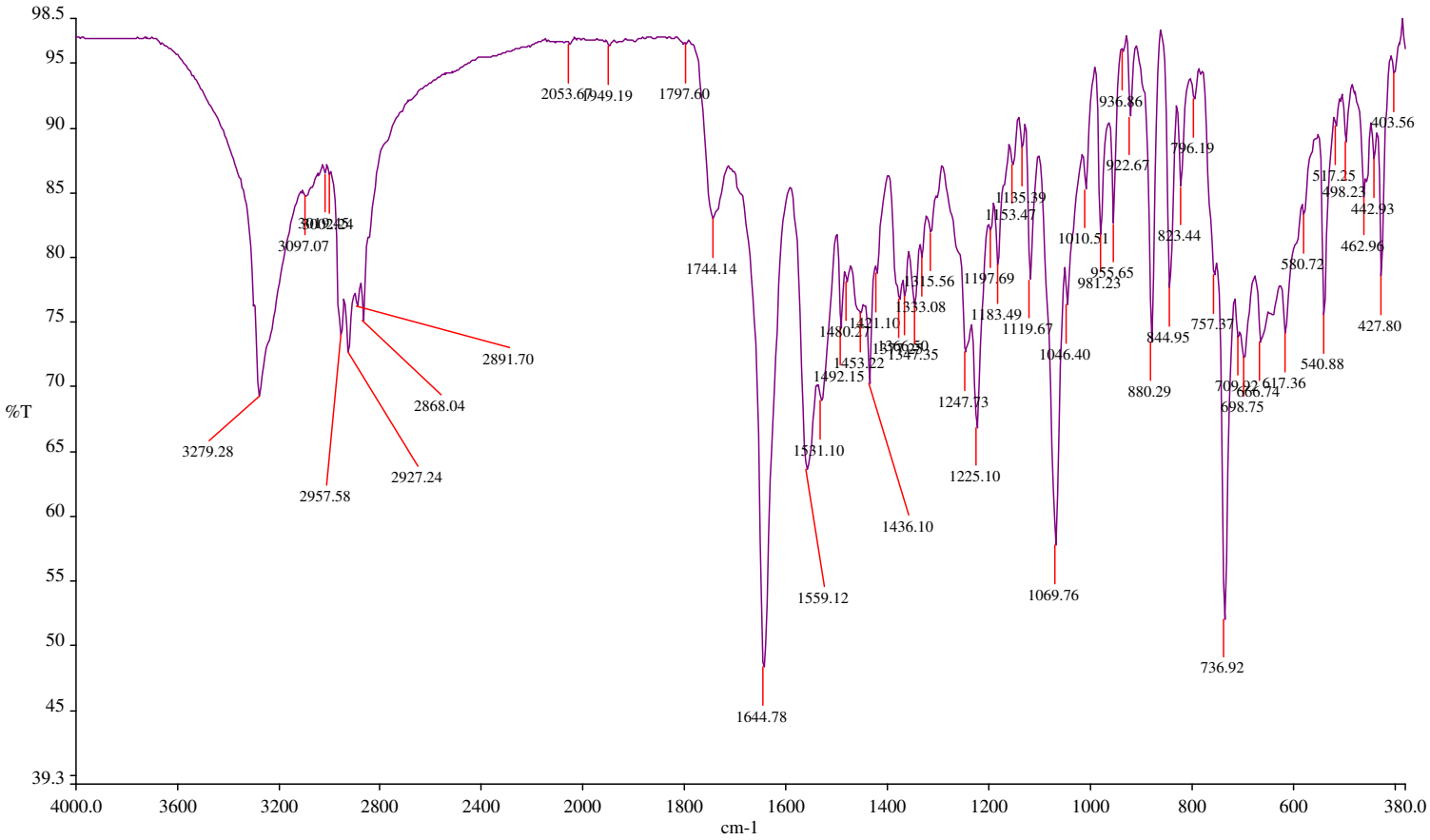
IR Spectrum of Compound **15**



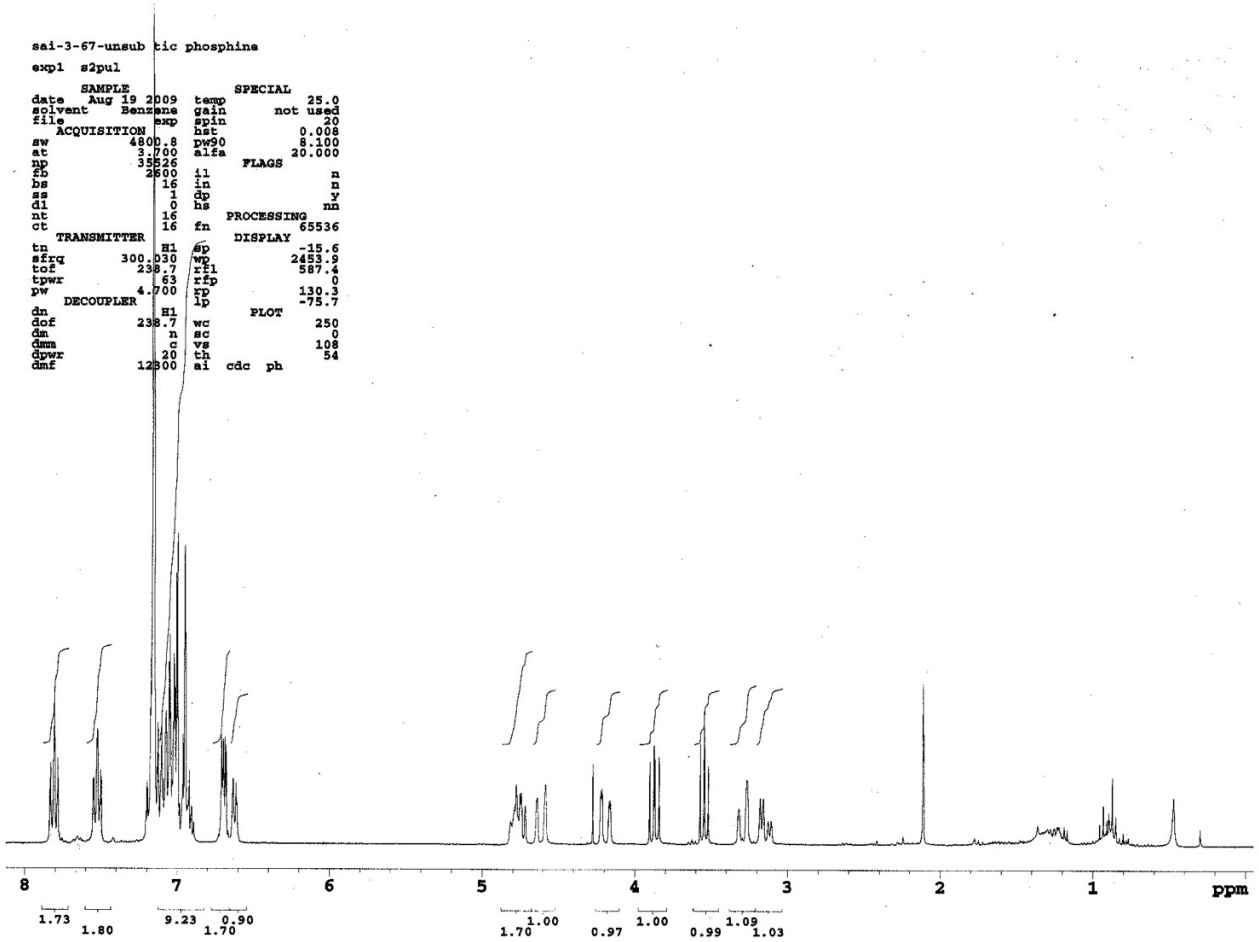
^{1}H NMR (400 MHz) Spectrum of Compound **16** in $CDCl_3$



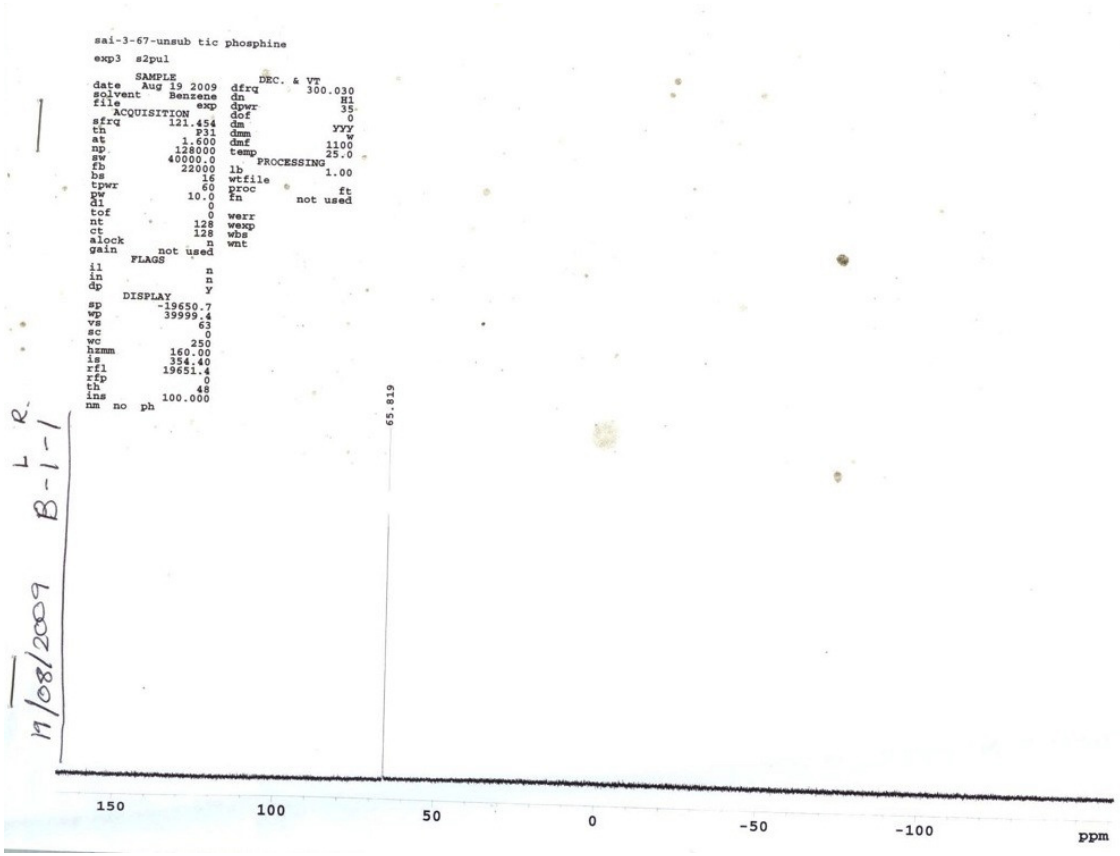
^{13}C (400 MHz) Spectrum of Compound **16** in $CDCl_3$



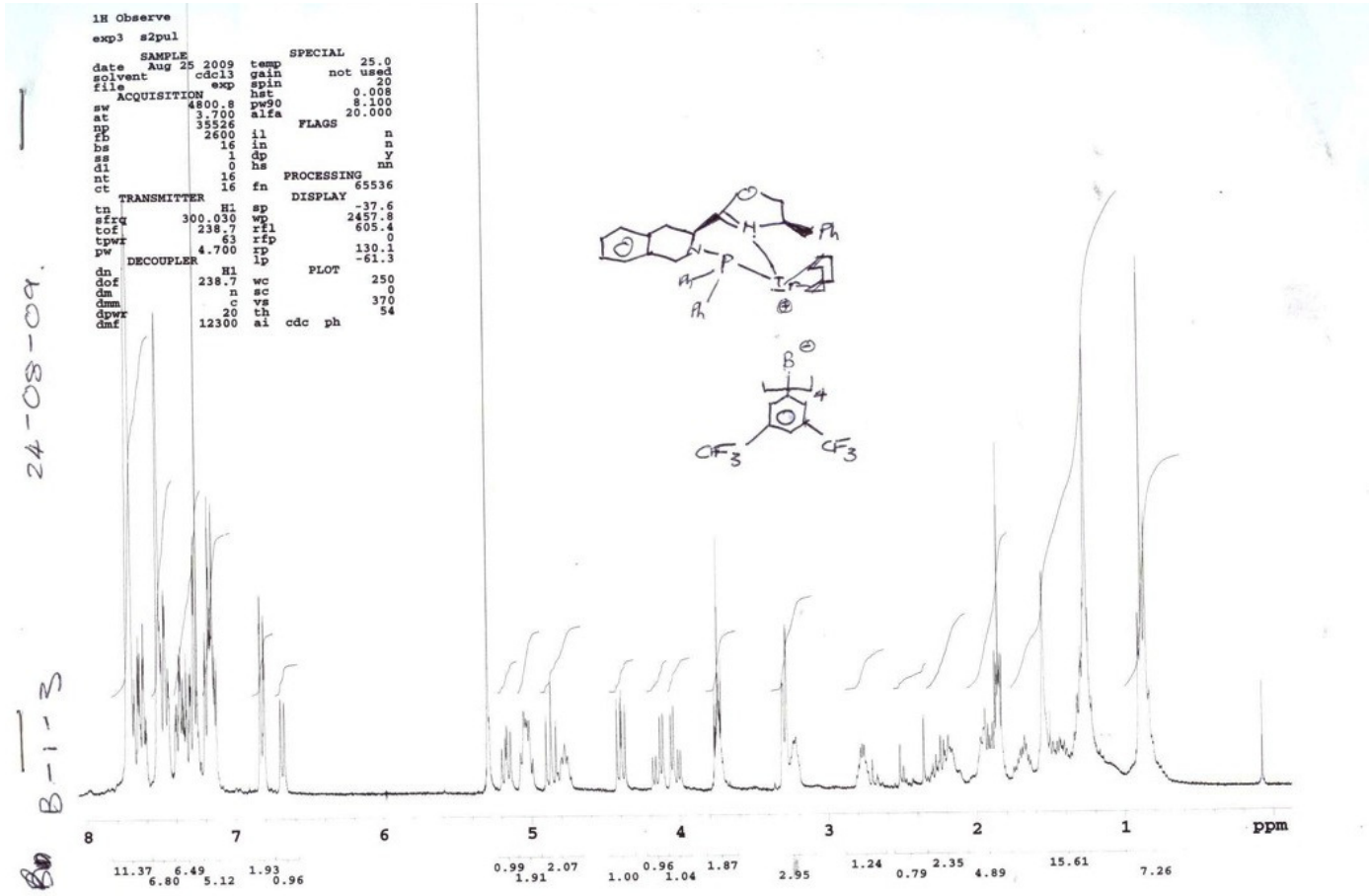
IR Spectrum of Compound **16**



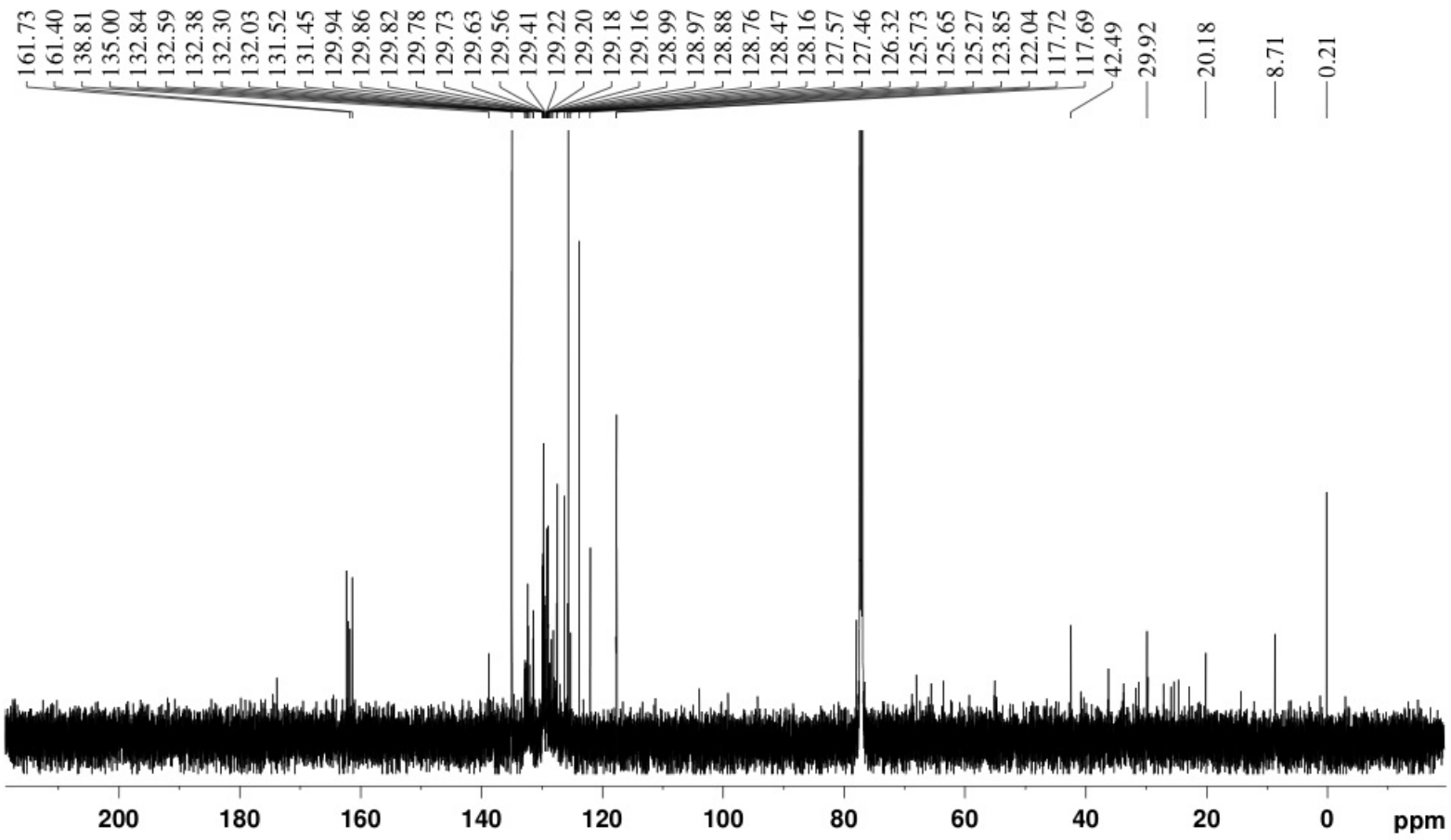
^{1}H NMR (400 MHz) Spectrum of Compound **17** in $CDCl_3$



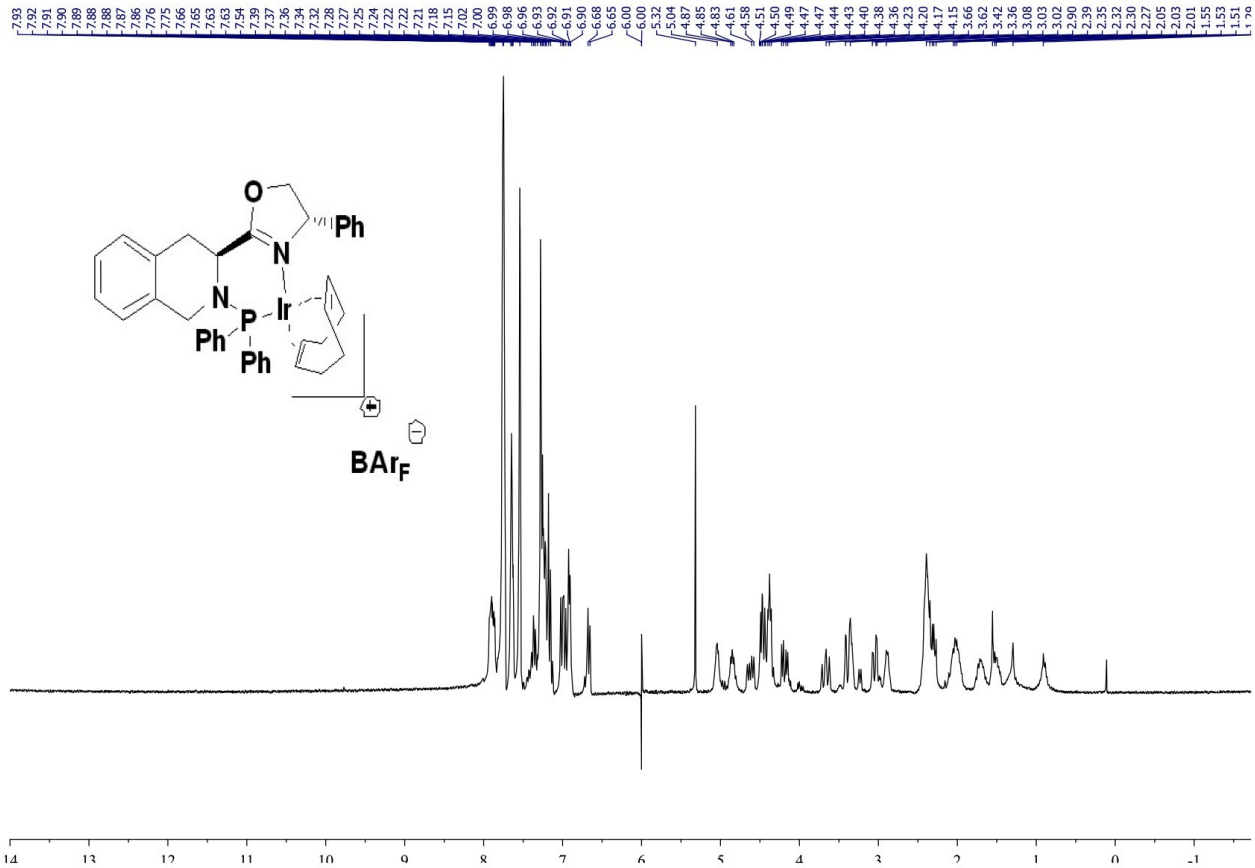
^{31}P NMR (400 MHz) Spectrum of compound **17** in $CDCl_3$



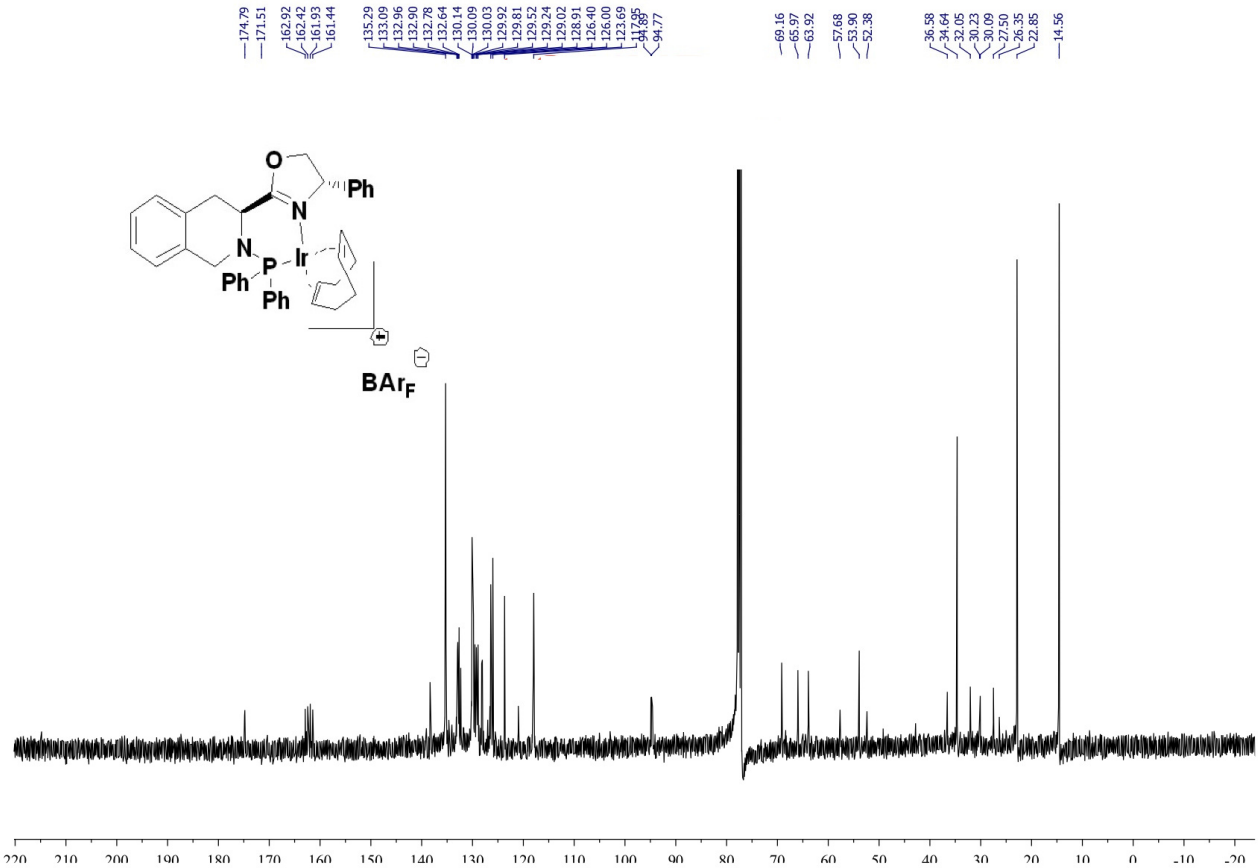
^{1}H NMR (400 MHz) Spectrum of Compound **21** in $CDCl_3$



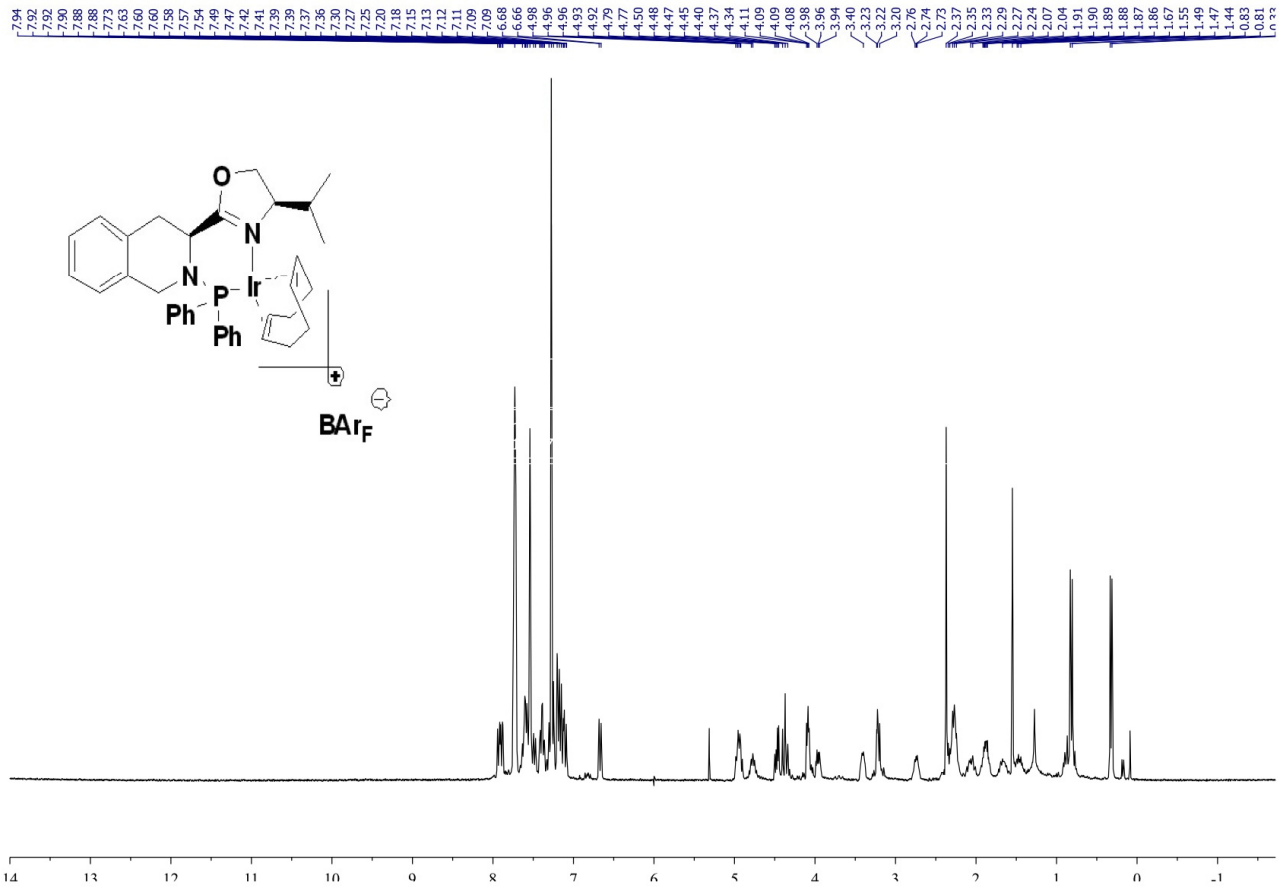
^{13}C NMR (400 MHz) Spectrum of Compound **21** in $CDCl_3$



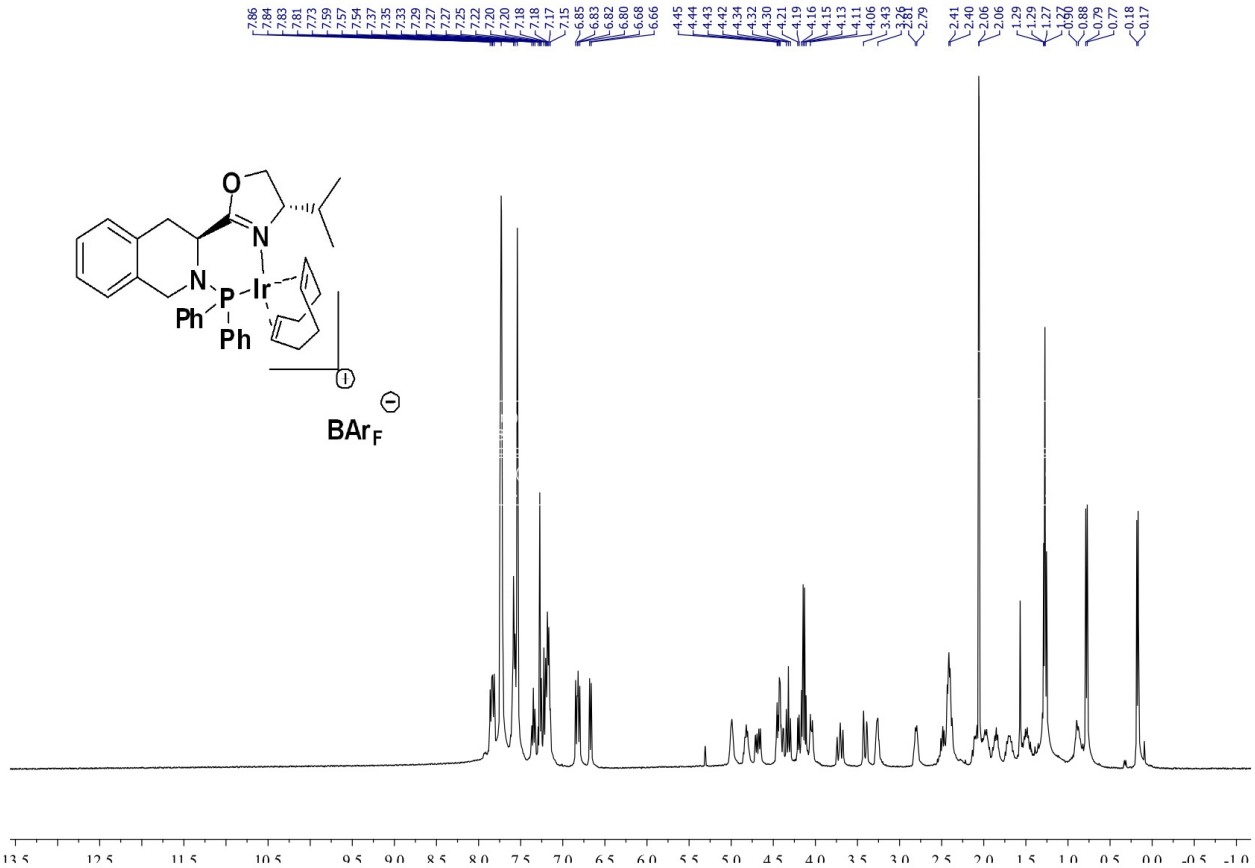
^{1}H NMR (400 MHz) Spectrum of Compound **22** in $CDCl_3$



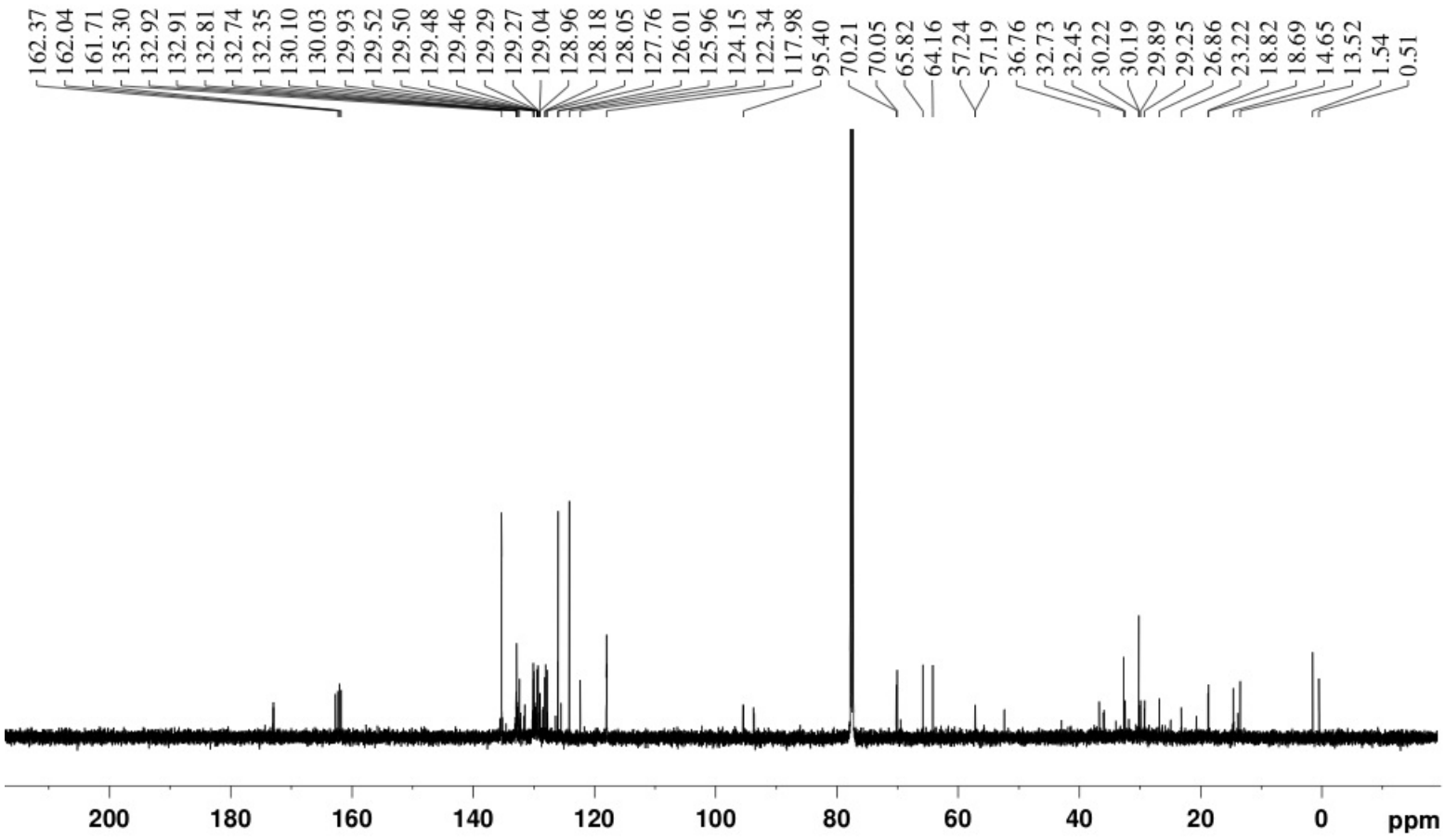
^{13}C NMR (400 MHz) Spectrum of Compound **22** in $CDCl_3$



^{1}H NMR (400 MHz) Spectrum of Compound **23** in $CDCl_3$



^{1}H NMR (400 MHz) Spectrum of Compound **24** in $CDCl_3$



^{13}C NMR (400 MHz) Spectrum of Compound **24** in $CDCl_3$

Analysis Info

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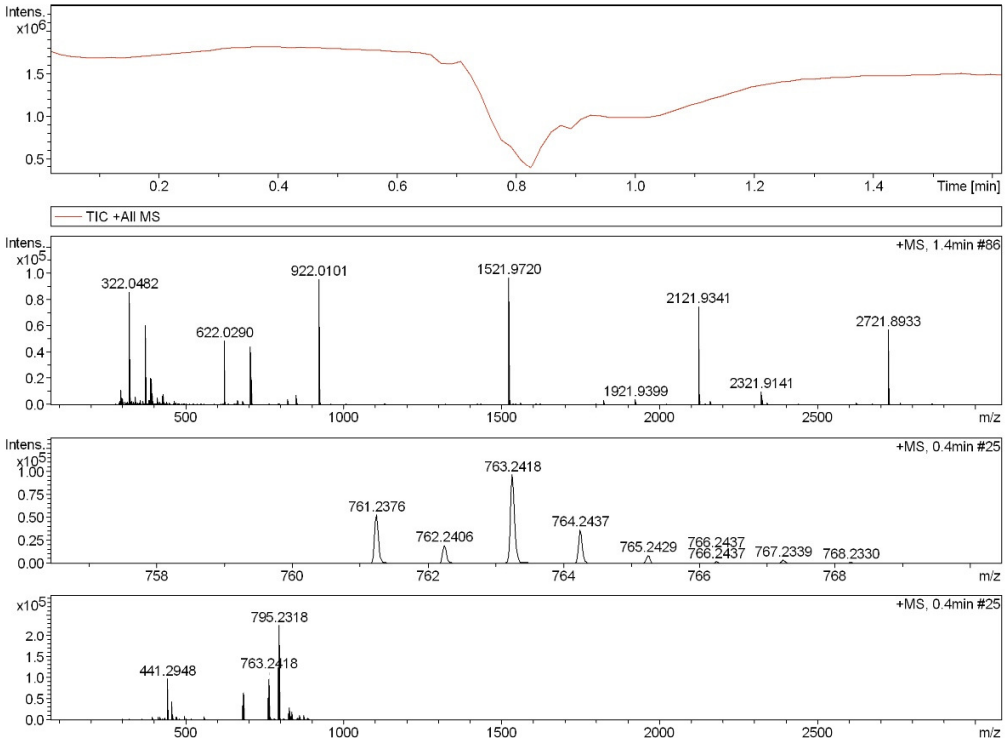
Method	tune_high_expert.m	Operator	BDAL@DE
Sample Name	1st_phgly_Cmplx_oxa	Instrument / Ser#	micrOTOF-Q 10139
Comment	mass = 795		

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	150 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	600.0 Vpp	Set Divert Valve	Source



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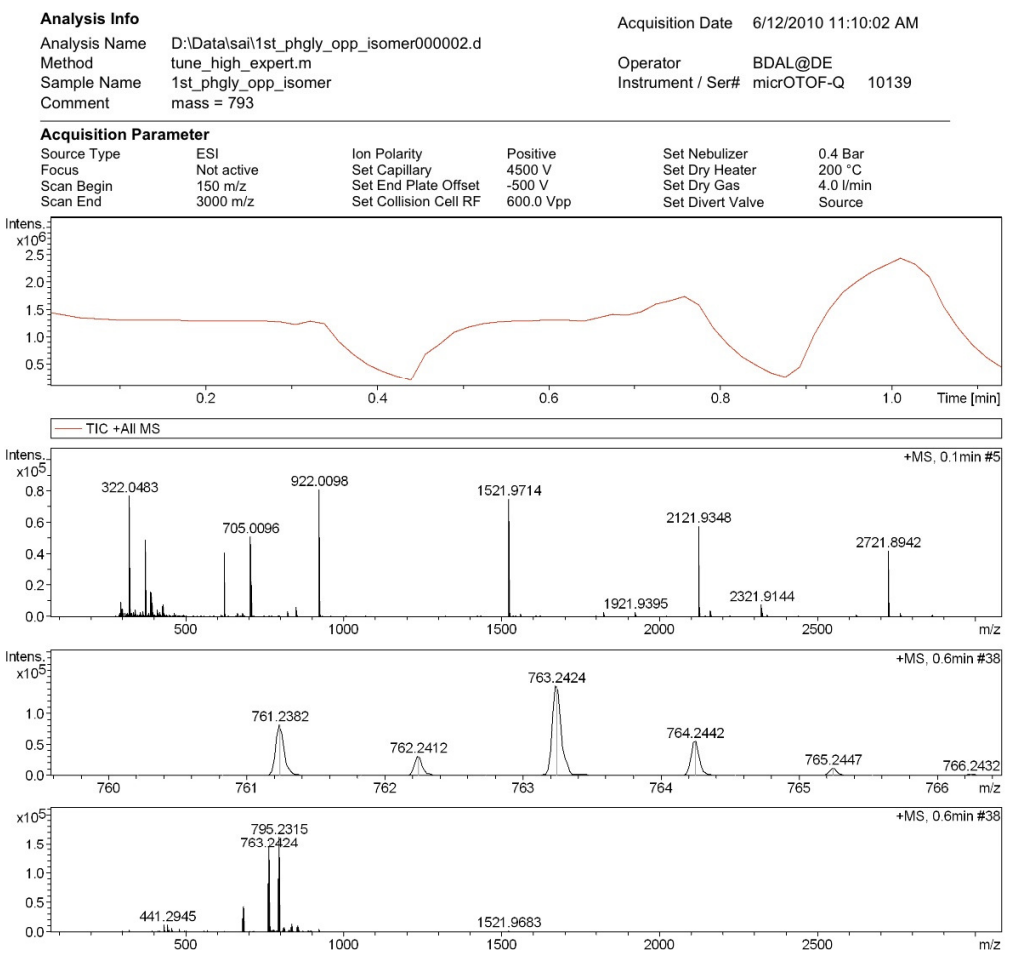
763.2418														
	1	C 35 H 41 Ir N O 4 P	763.2397	-2.8	-1.1	17.0	ok	odd	11.78	0.0122	0.0016	0.0047	0.0025	0.7228
	2	C 36 H 44 Ir O 2 P 2	763.2440	2.9	4.6	16.5	ok	even	13.14	0.0131	0.0038	0.0052	0.0025	0.8439
	3	C 33 H 39 Ir N 4 O 3 P	763.2384	-4.6	-2.9	17.5	ok	even	14.00	0.0160	0.0026	0.0060	0.0025	0.8098

High Resolution Mass Spectrum of Complex **21**



Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
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	2	C 36 H 44 Ir O 2 P 2	763.2440	2.2	3.8	16.5	ok	even	5.22	0.0056	0.0031	0.0025	0.0020	0.8134
	3	C 34 H 42 Ir N 3 O P 2	763.2427	0.4	2.0	17.0	ok	odd	7.15	0.0090	0.0020	0.0038	0.0020	0.7817

High Resolution Mass Spectrum of Complex **22**

Analysis Info

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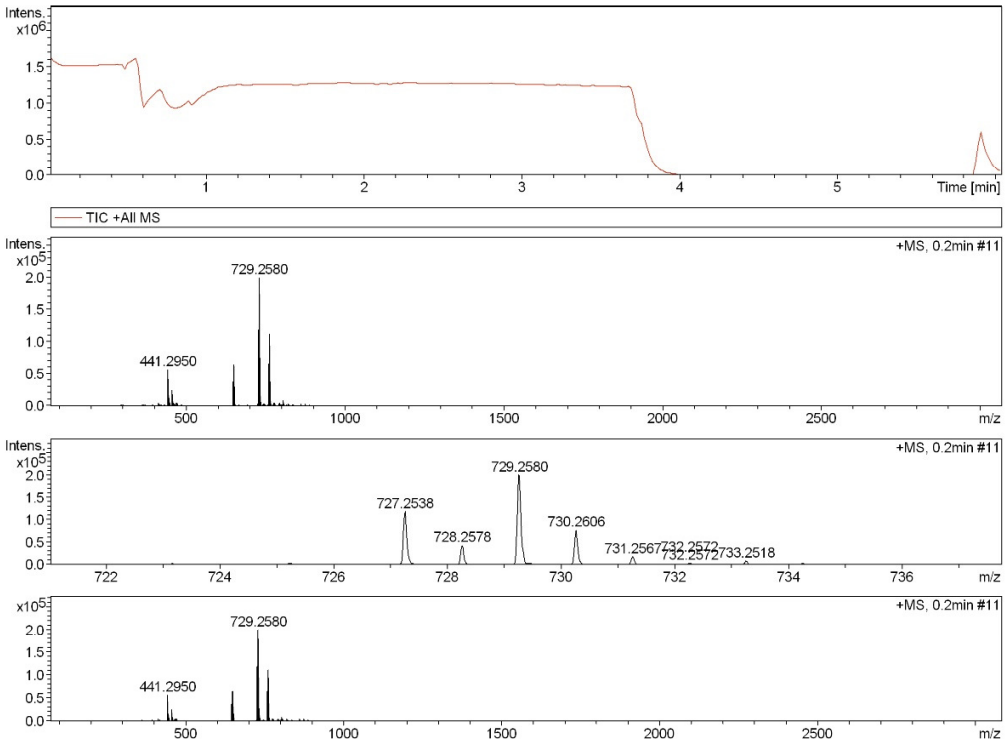
Sample Name	D_Valine_Cmplx_oxa	Instrument / Ser#	micrOTOF-Q 10139
Comment	mass = 762		

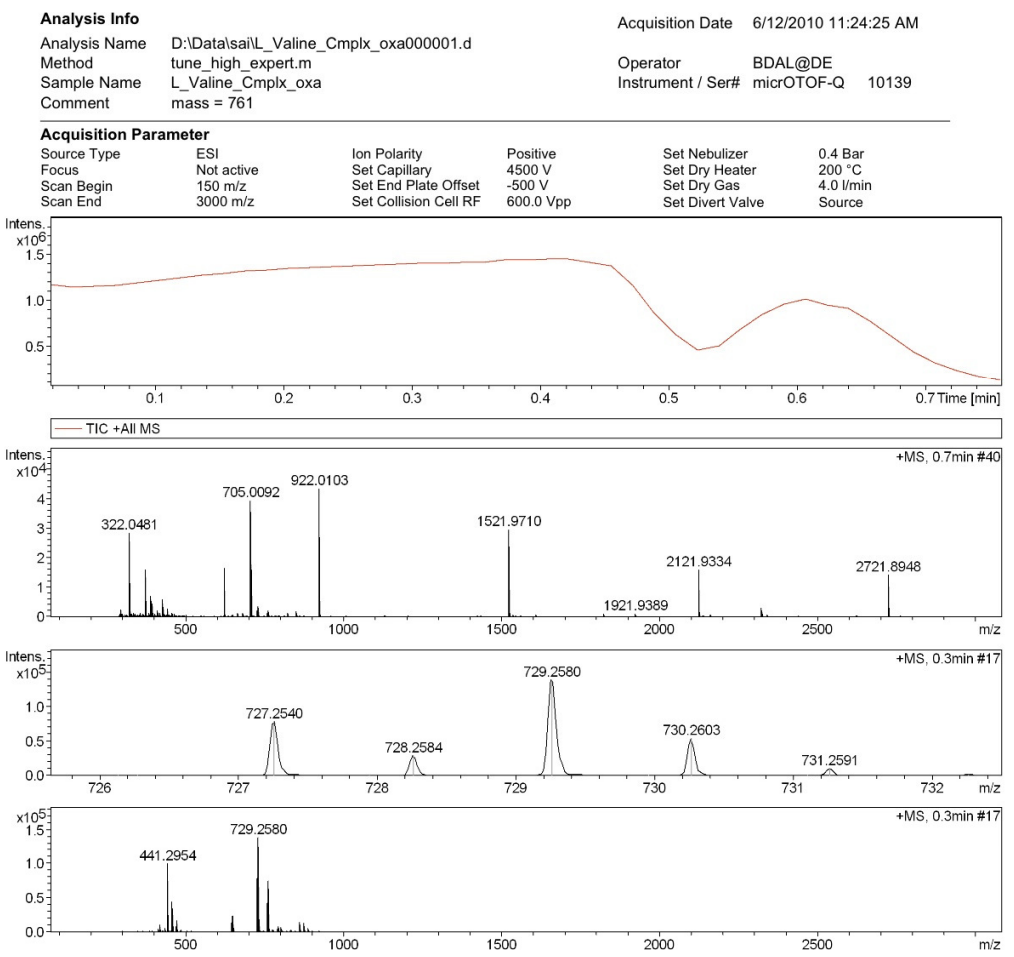
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	150 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	600.0 Vpp	Set Divert Valve	Source



Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
729.2580														
	1	C 35 H 41 Ir N 2 O P	729.2580	0.0	1.6	17.5	ok	even	12.21	0.0132	0.0021	0.0047	0.0032	0.7637
	2	C 33 H 39 Ir N 5 P	729.2567	-1.8	-0.2	18.0	ok	odd	14.22	0.0161	0.0017	0.0055	0.0032	0.7564
	3	C 33 H 46 Ir O 2 P 2	729.2597	2.3	3.9	12.5	ok	even	19.22	0.0222	0.0033	0.0068	0.0032	0.8573

High Resolution Mass Spectrum of Complex **23**



Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
729.2580														
	1	C 35 H 41 Ir N 2 O P	729.2580	0.1	1.4	17.5	ok	even	8.89	0.0097	0.0015	0.0033	0.0022	0.7408
	2	C 33 H 39 Ir N 5 P	729.2567	-1.7	-0.5	18.0	ok	odd	10.28	0.0114	0.0012	0.0038	0.0022	0.7231
	3	C 33 H 46 Ir O 2 P 2	729.2597	2.4	3.7	12.5	ok	even	15.34	0.0175	0.0029	0.0053	0.0022	0.8658

High Resolution Mass Spectrum of Complex **24**

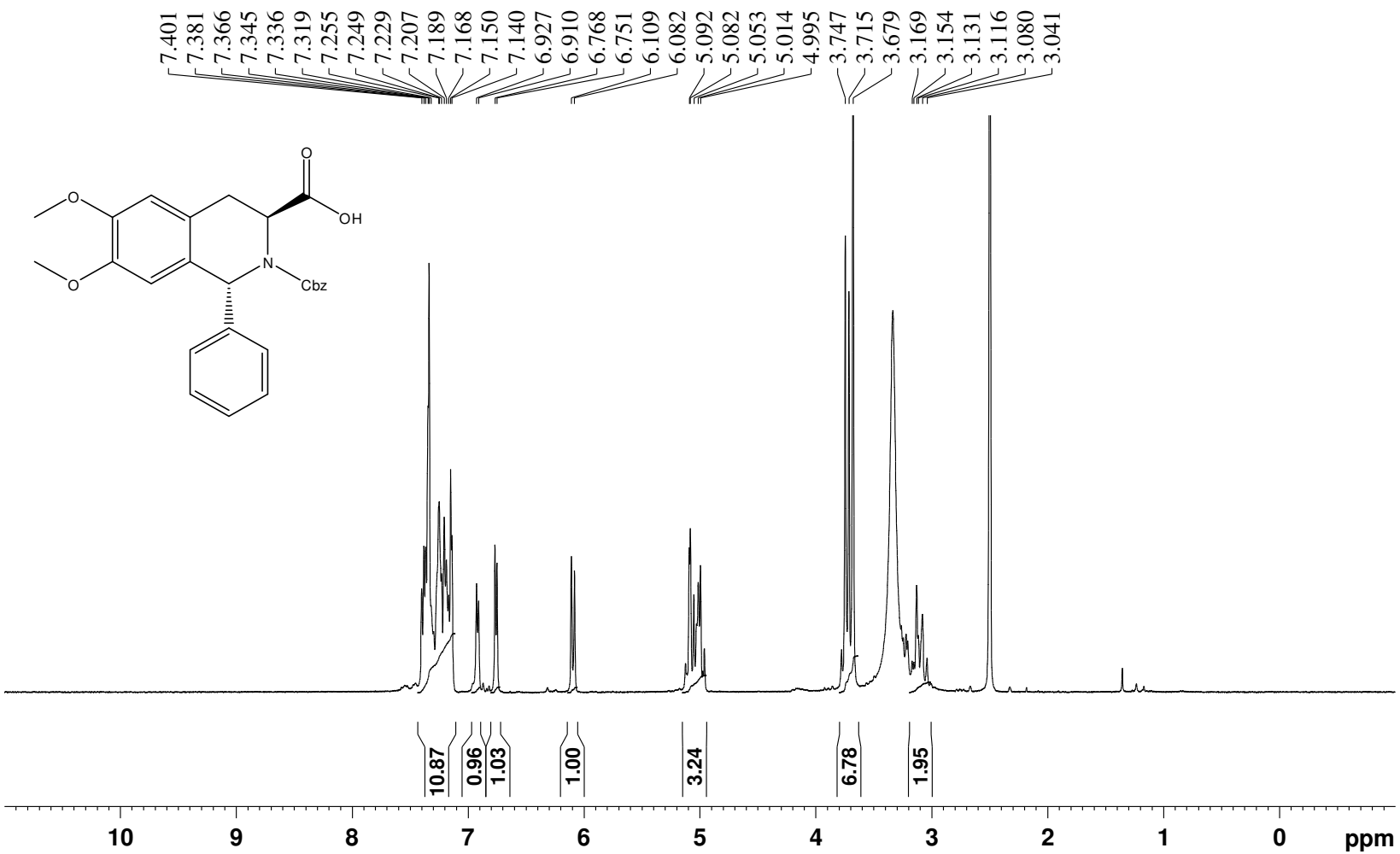
APPENDIX 4

SYNTHESIS OF TETRAHYDROISOQUINOLINE (TIQ)-OXAZOLINE LIGANDS AND THEIR APPLICATION IN ENANTIOSELECTIVE HENRY REACTIONS

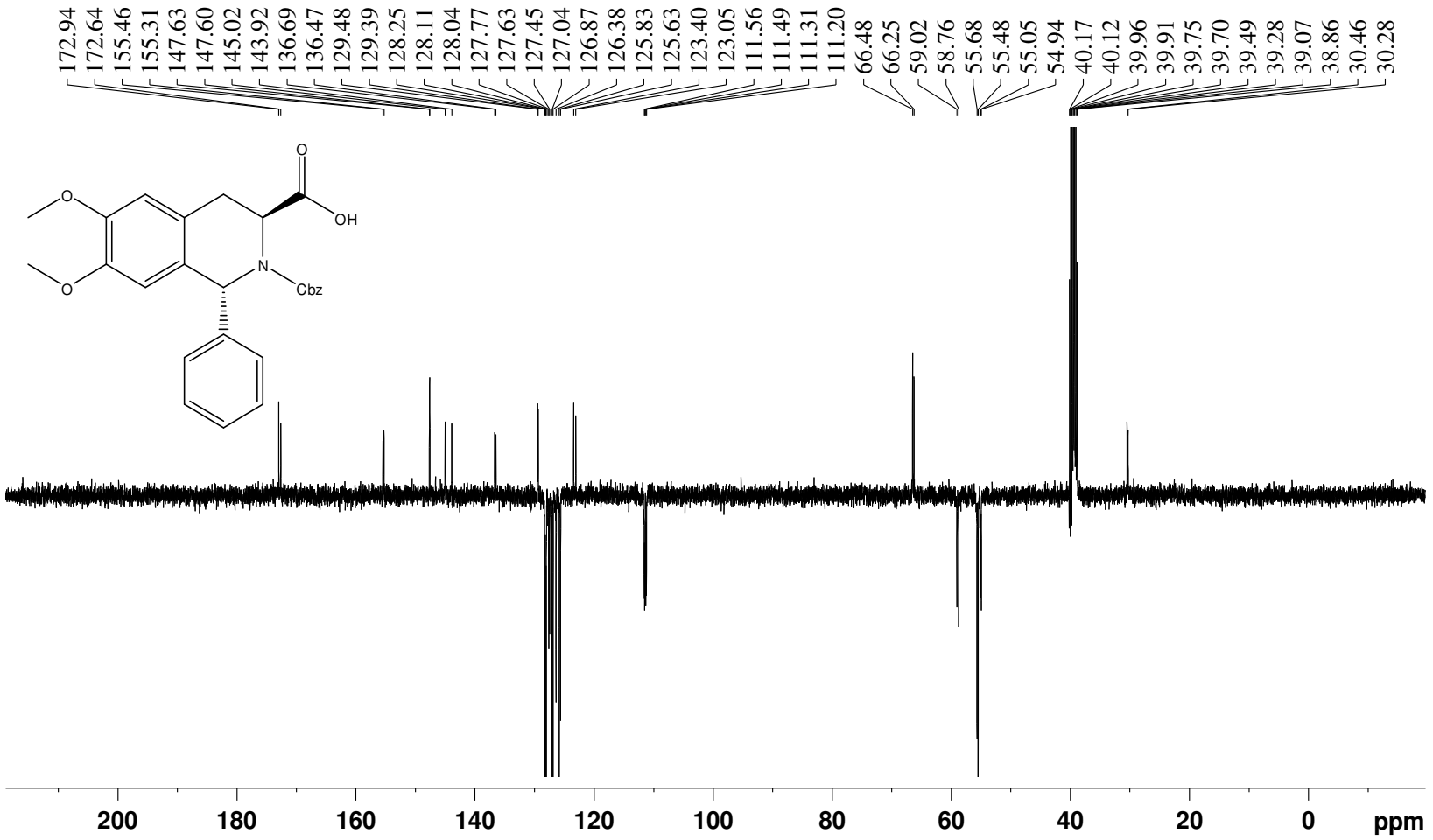
SUPPLAMENTARY INFORMATION FOR CHAPTER 5

Rahul B. Kawthekar,[a] Sai Kumar Chakka,[a] Vivian Francis,[a] Pher G. Andersson,[c] Hendrik G. Kruger,[a*] Glenn E. M. Maguire[a] and Thavendran Govender[b*]

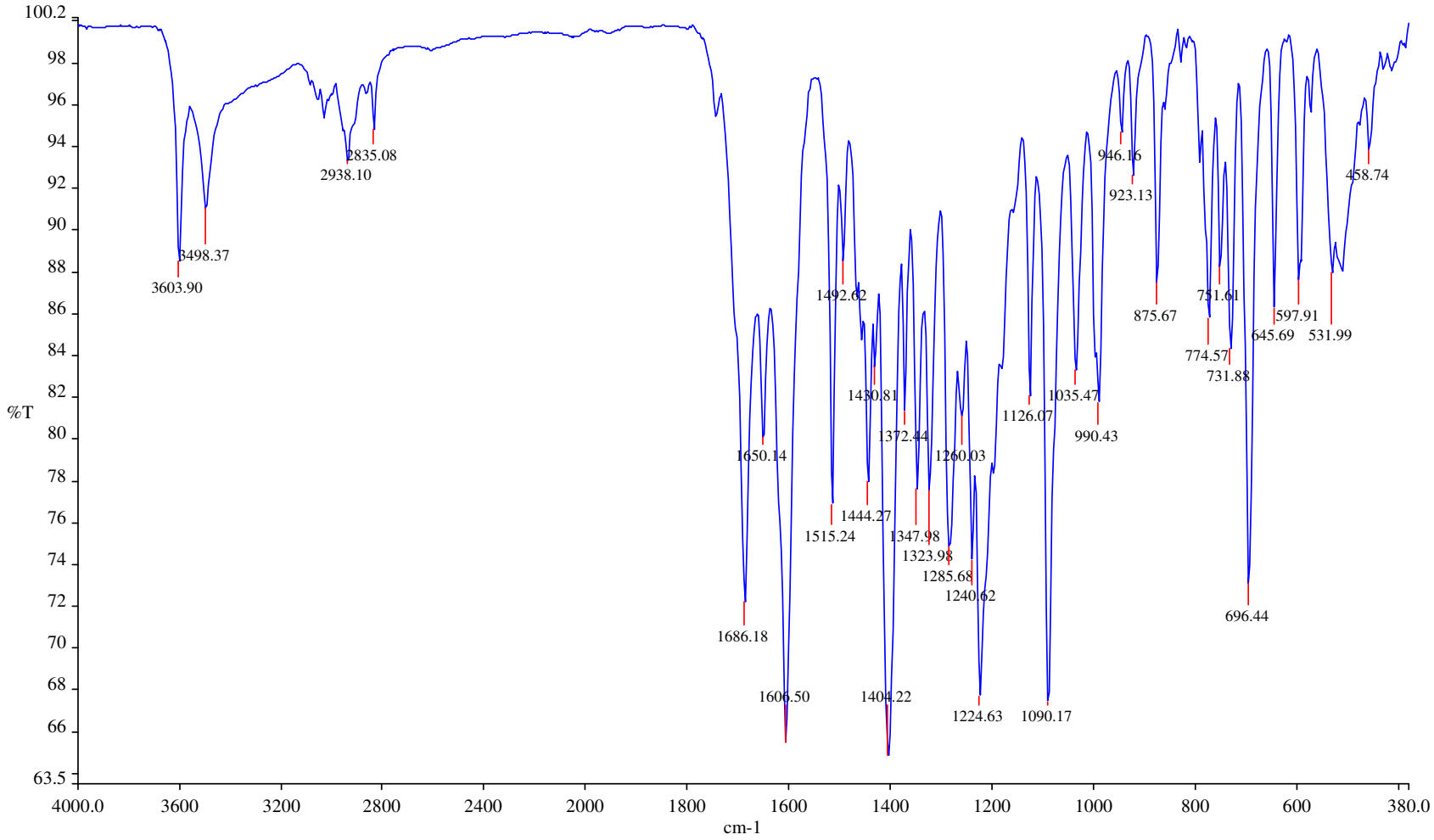
[a]School of Chemistry, University of KwaZulu-Natal, Durban, South Africa.
[b]School of Pharmacy and Pharmacology, University of KwaZulu-Natal, Durban, South Africa. [c]Department of Organic chemistry, Uppsala University, Uppsala, Sweden.
[*]Corresponding Author: email: govenderthav@ukzn.ac.za



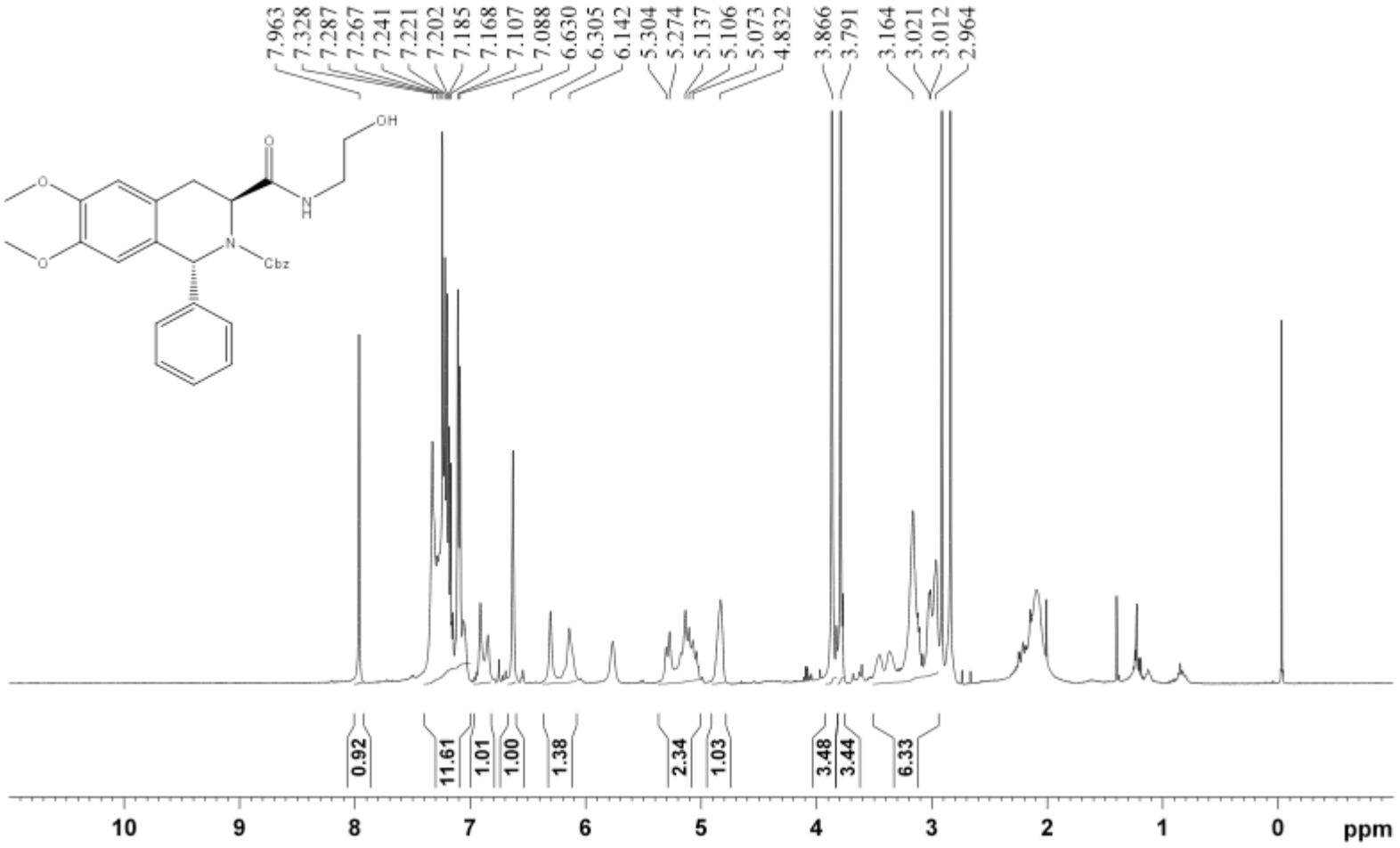
^{1}H NMR (400 MHz) Spectrum of Compound **8** in $CDCl_3$



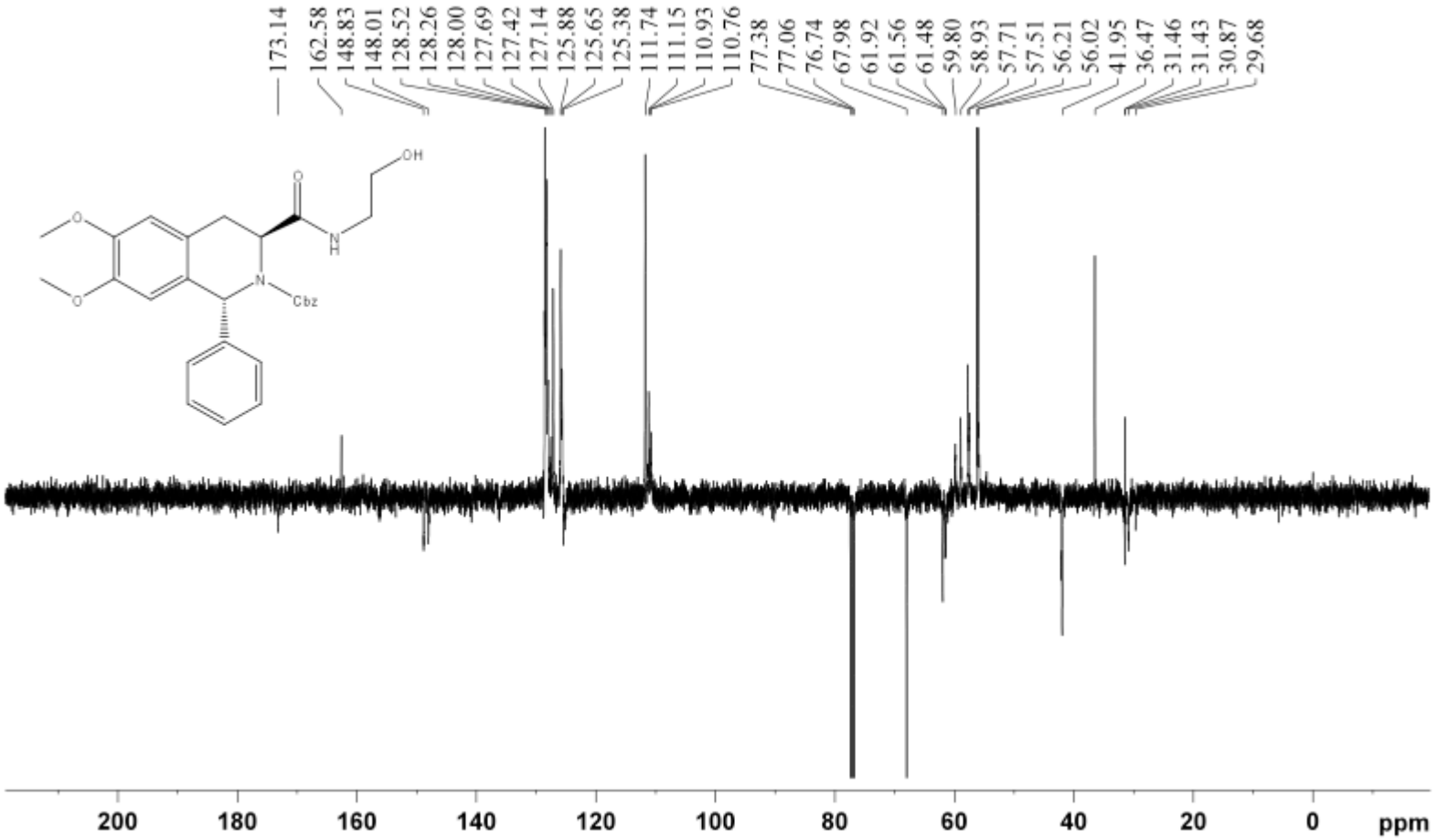
^{13}C (400 MHz) Spectrum of Compound **8** in $CDCl_3$



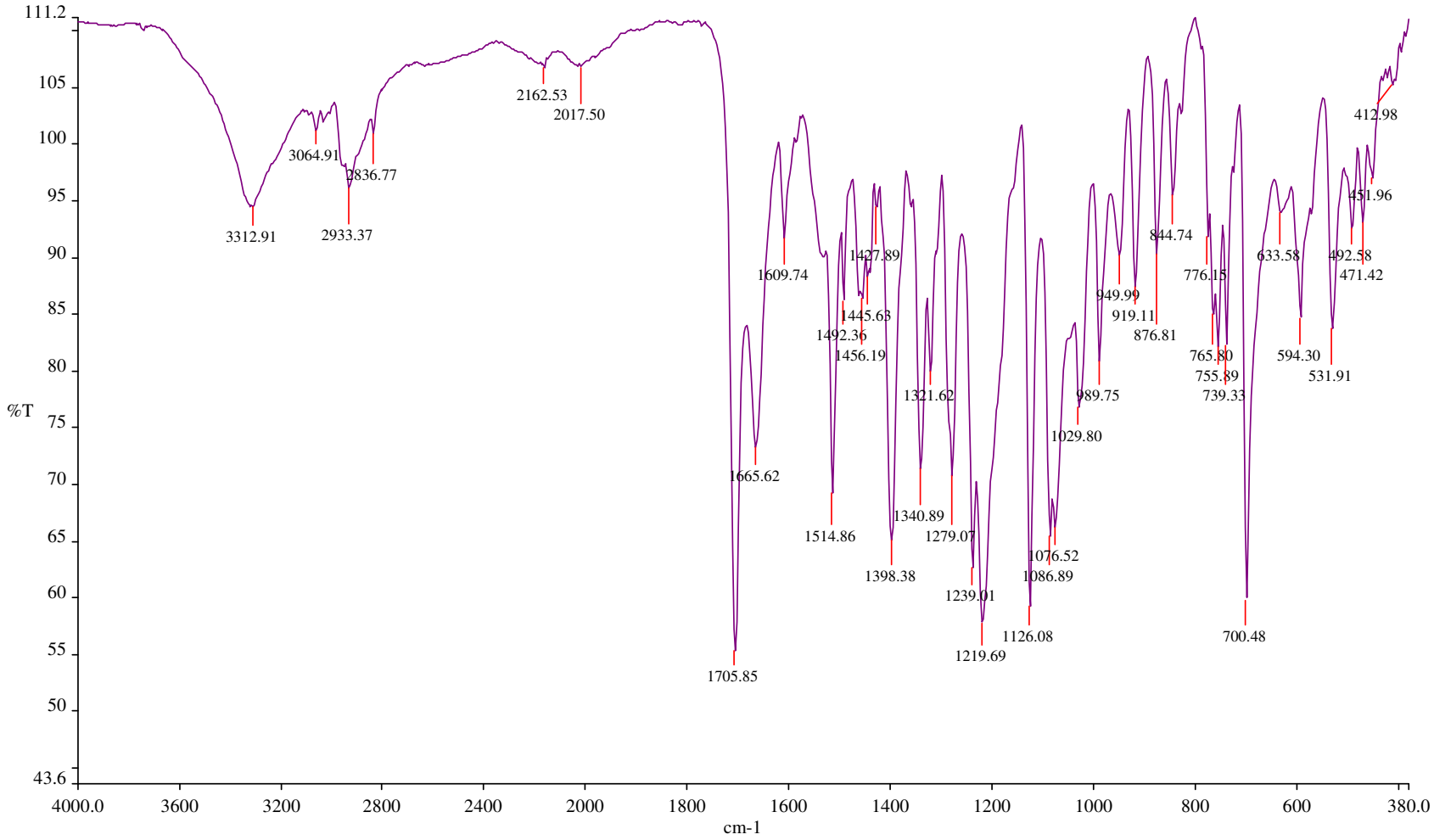
IR Spectrum of Compound **8**



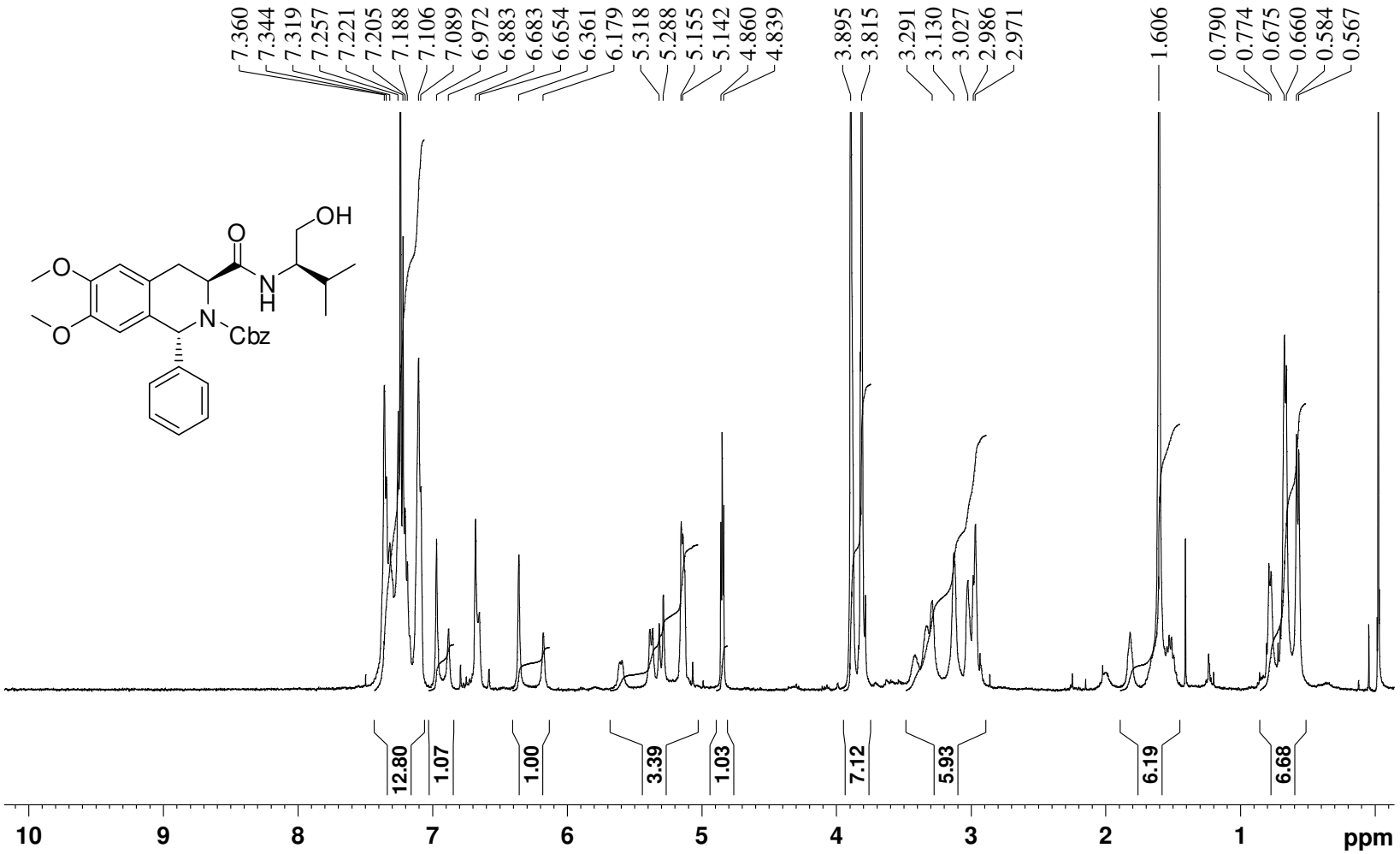
^{1}H NMR (400 MHz) Spectrum of Compound **9** in $CDCl_3$



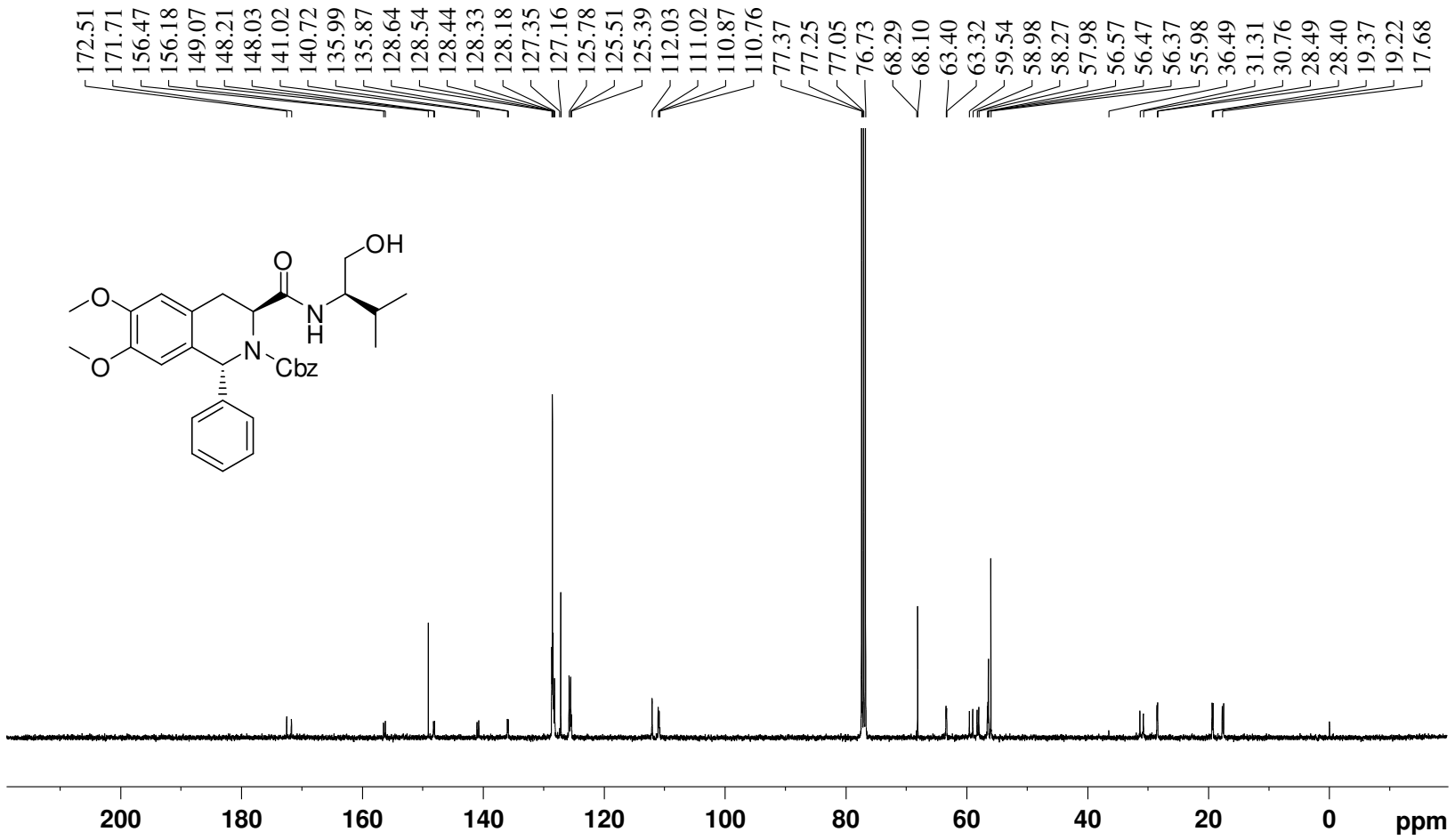
^{13}C (400 MHz) Spectrum of Compound **9** in $CDCl_3$



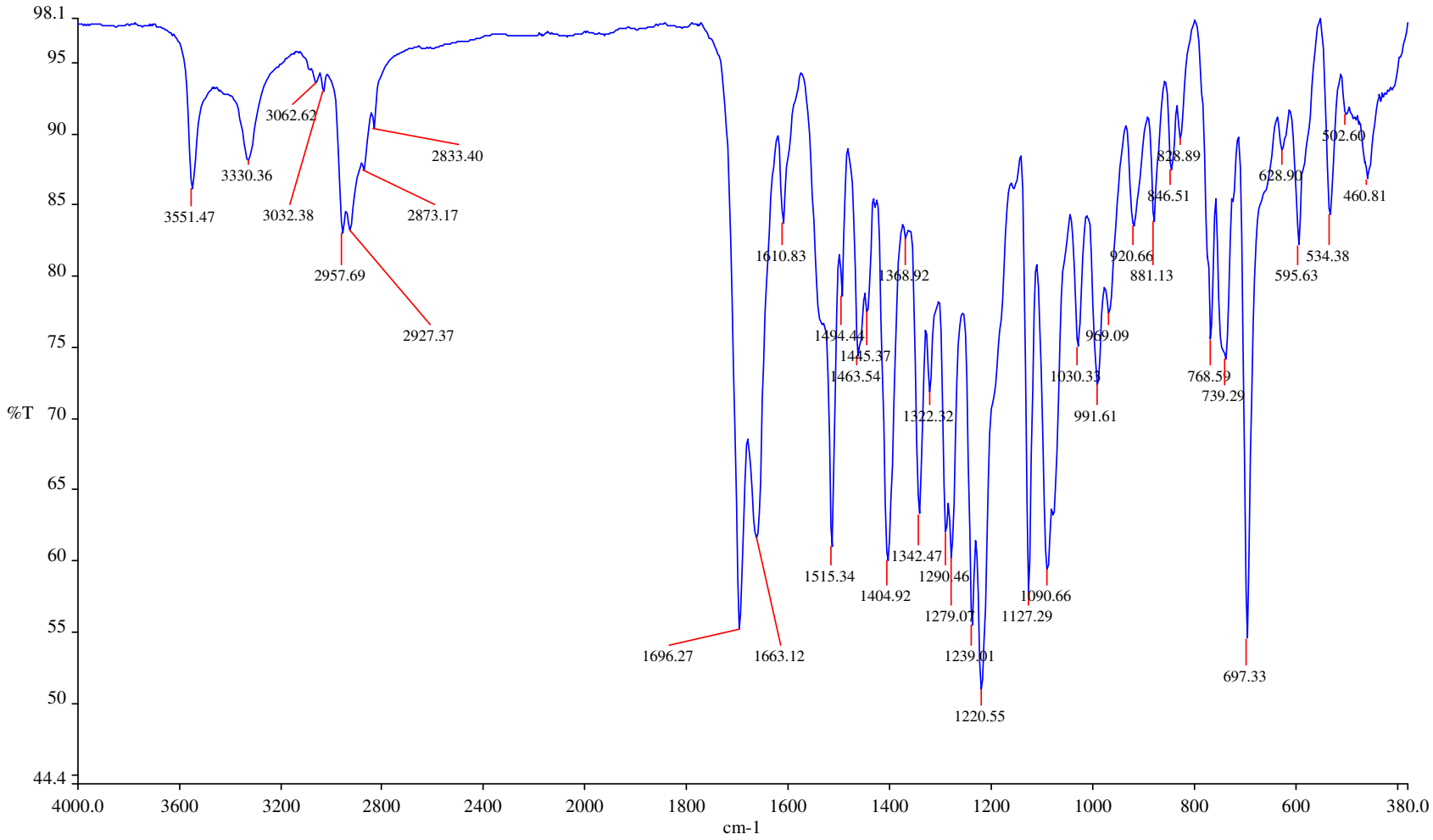
IR Spectrum of Compound **9**



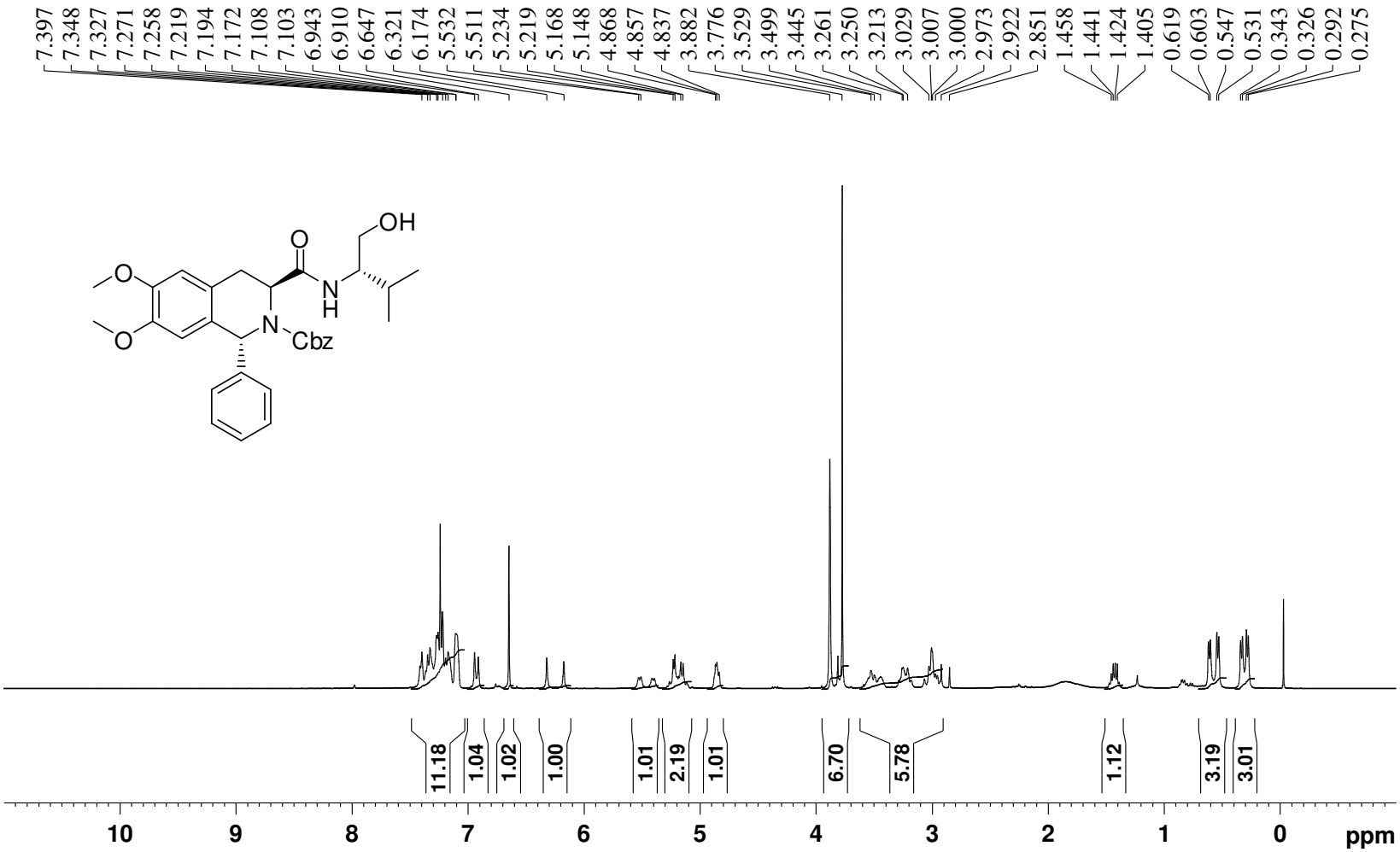
^{1}H NMR (400 MHz) Spectrum of Compound **10a** in $CDCl_3$



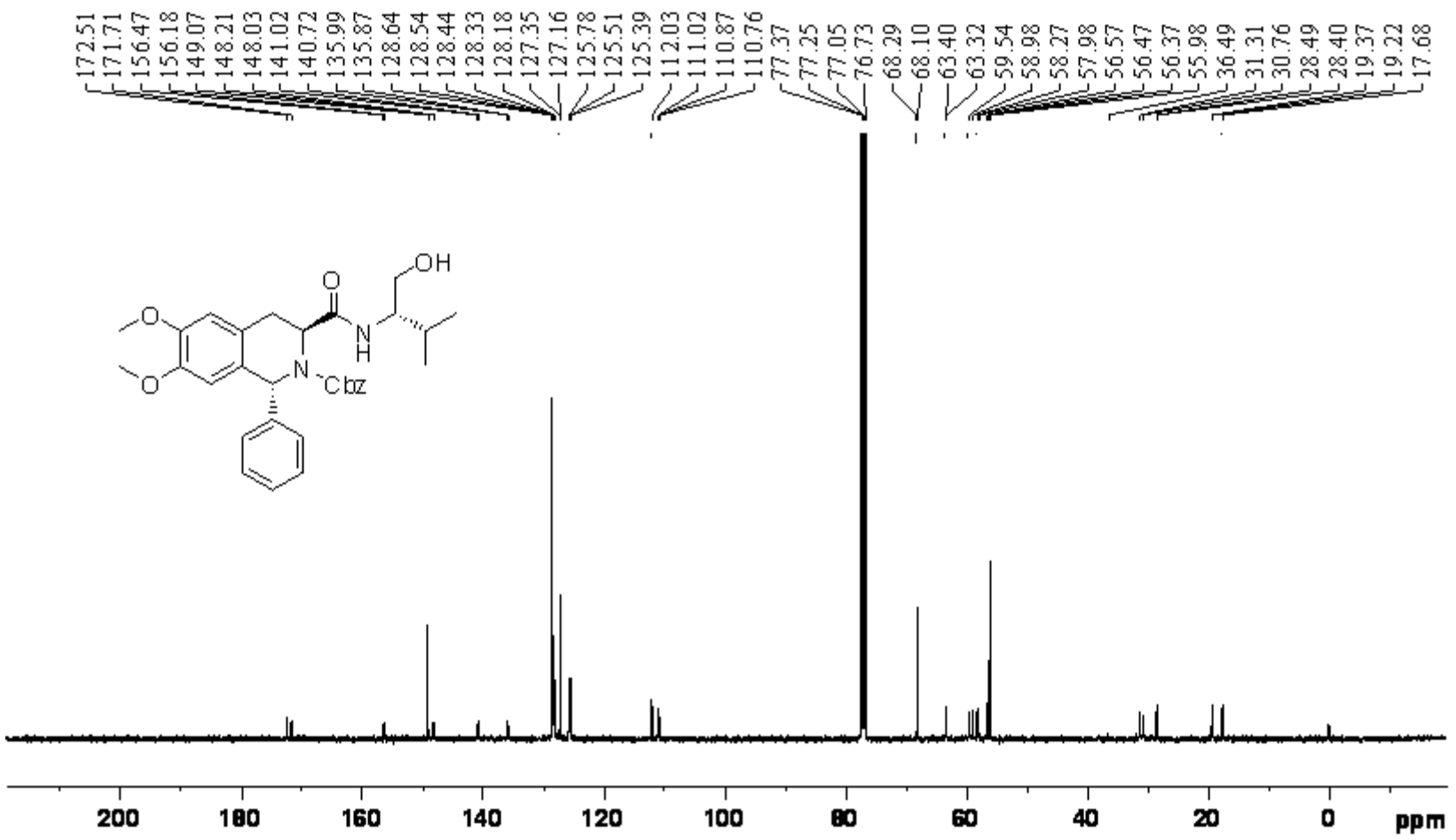
^{13}C (400 MHz) Spectrum of Compound **10a** in $CDCl_3$



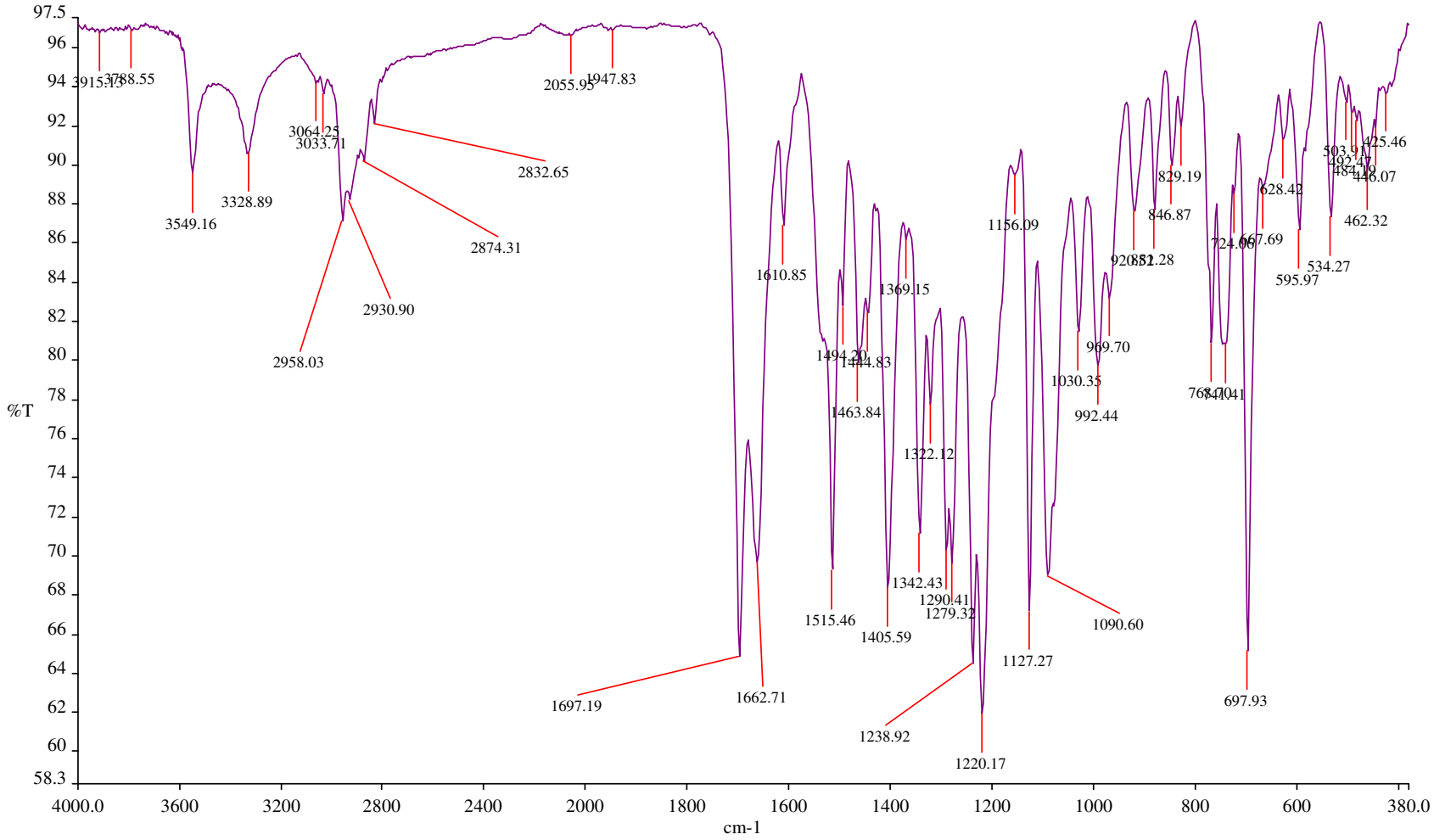
IR Spectrum of Compound **10a**



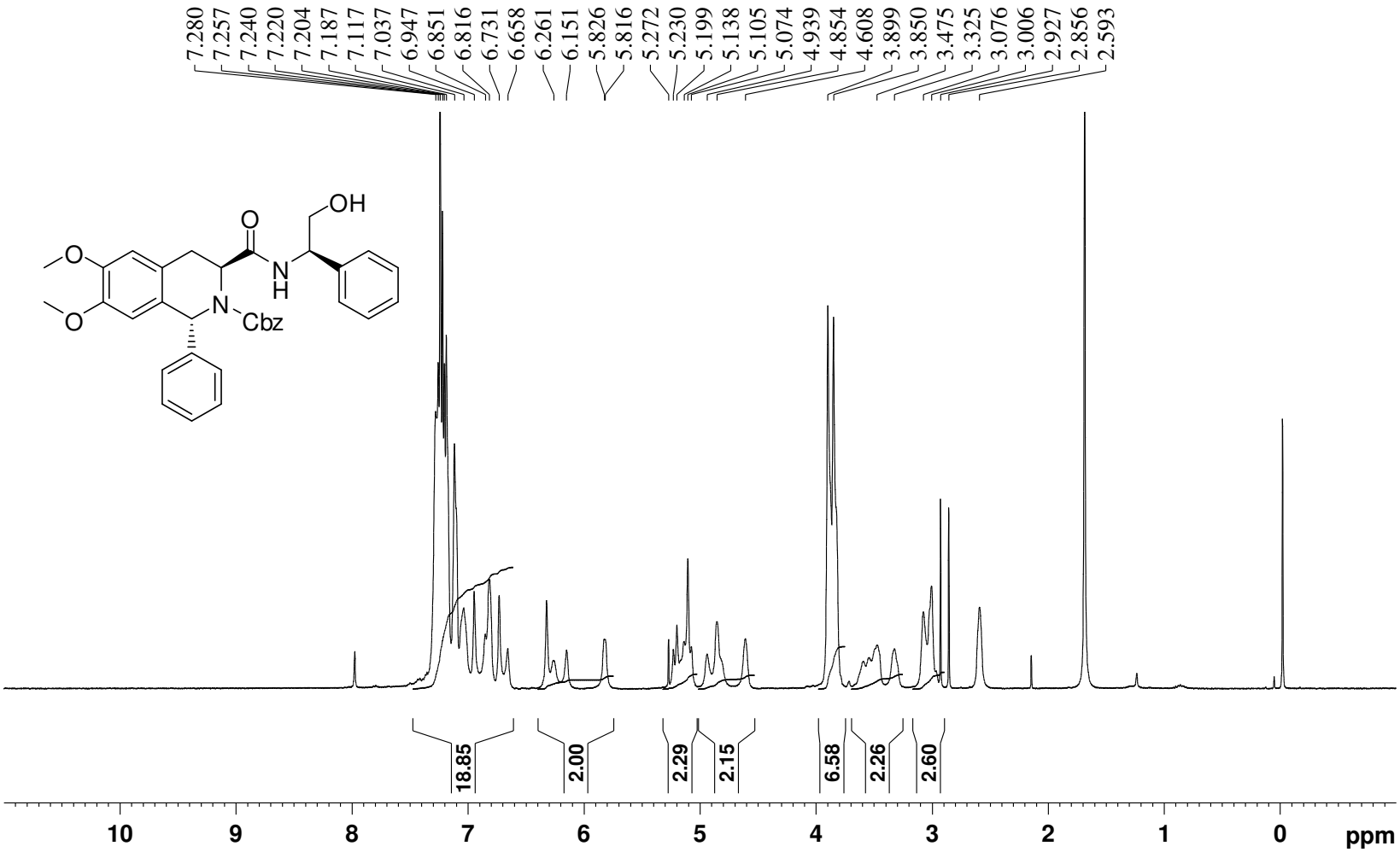
^{1}H NMR (400 MHz) Spectrum of Compound **10b** in $CDCl_3$



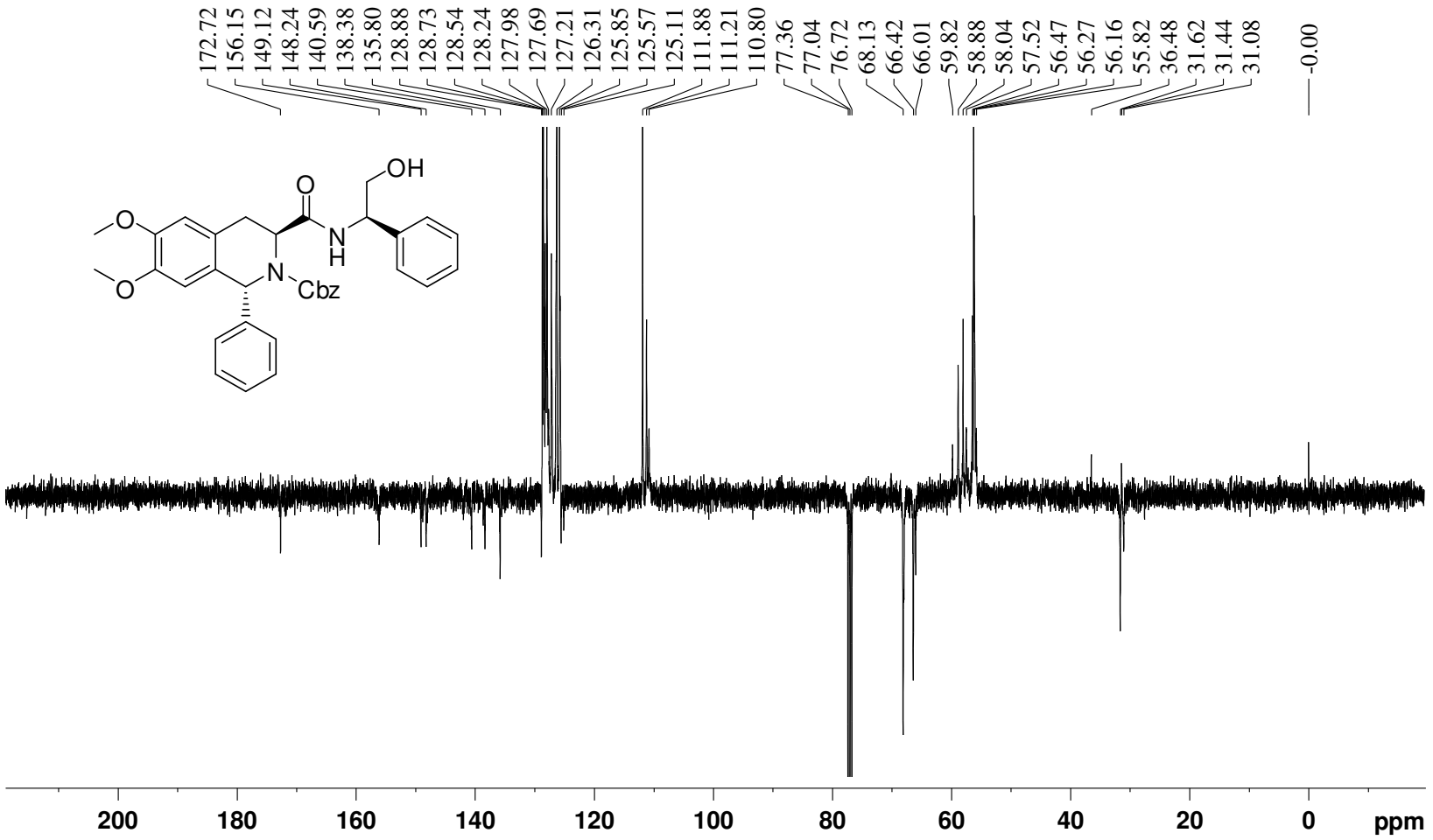
^{13}C (400 MHz) Spectrum of Compound **10b** in $CDCl_3$



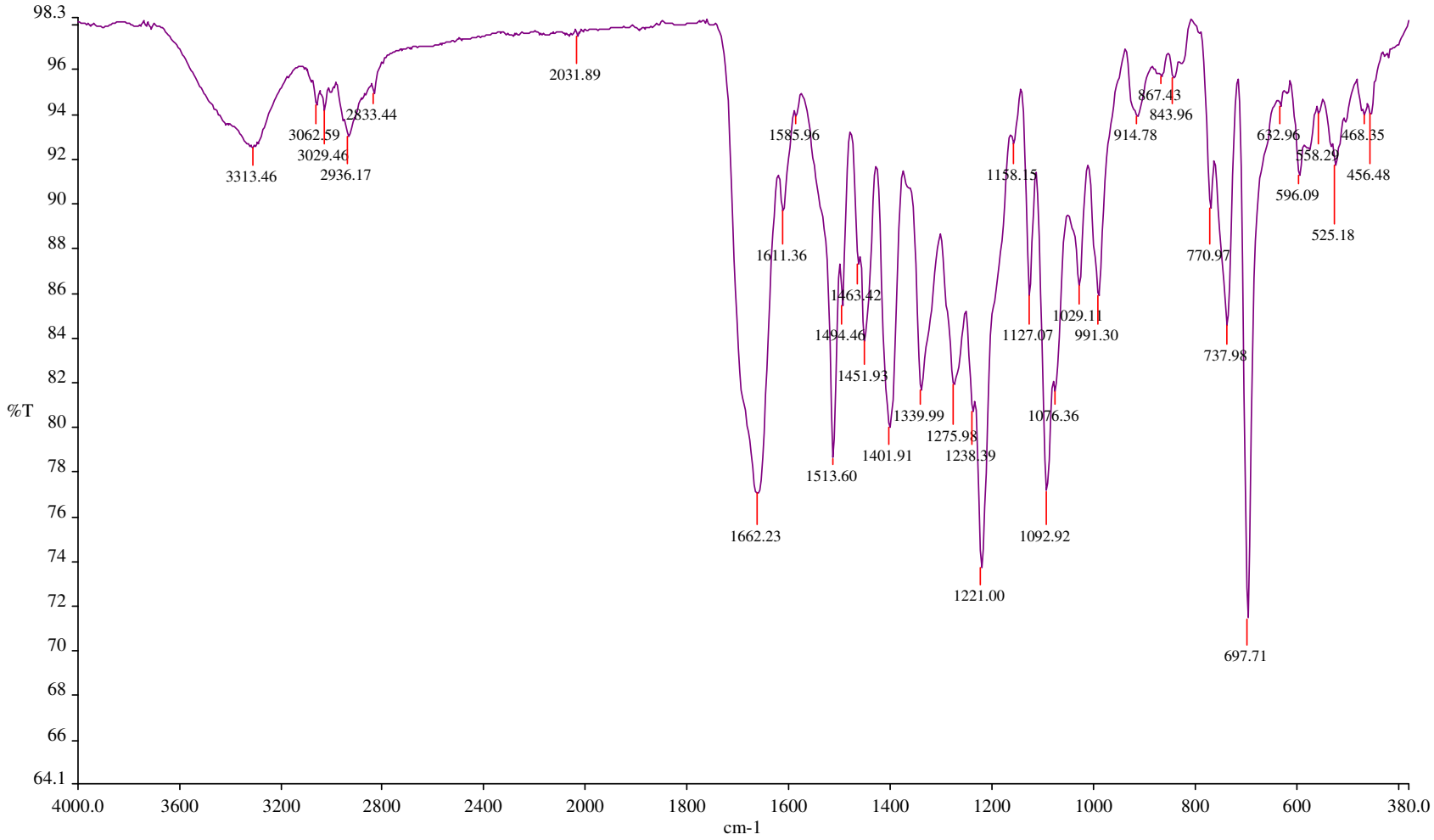
IR Spectrum of Compound **10b**



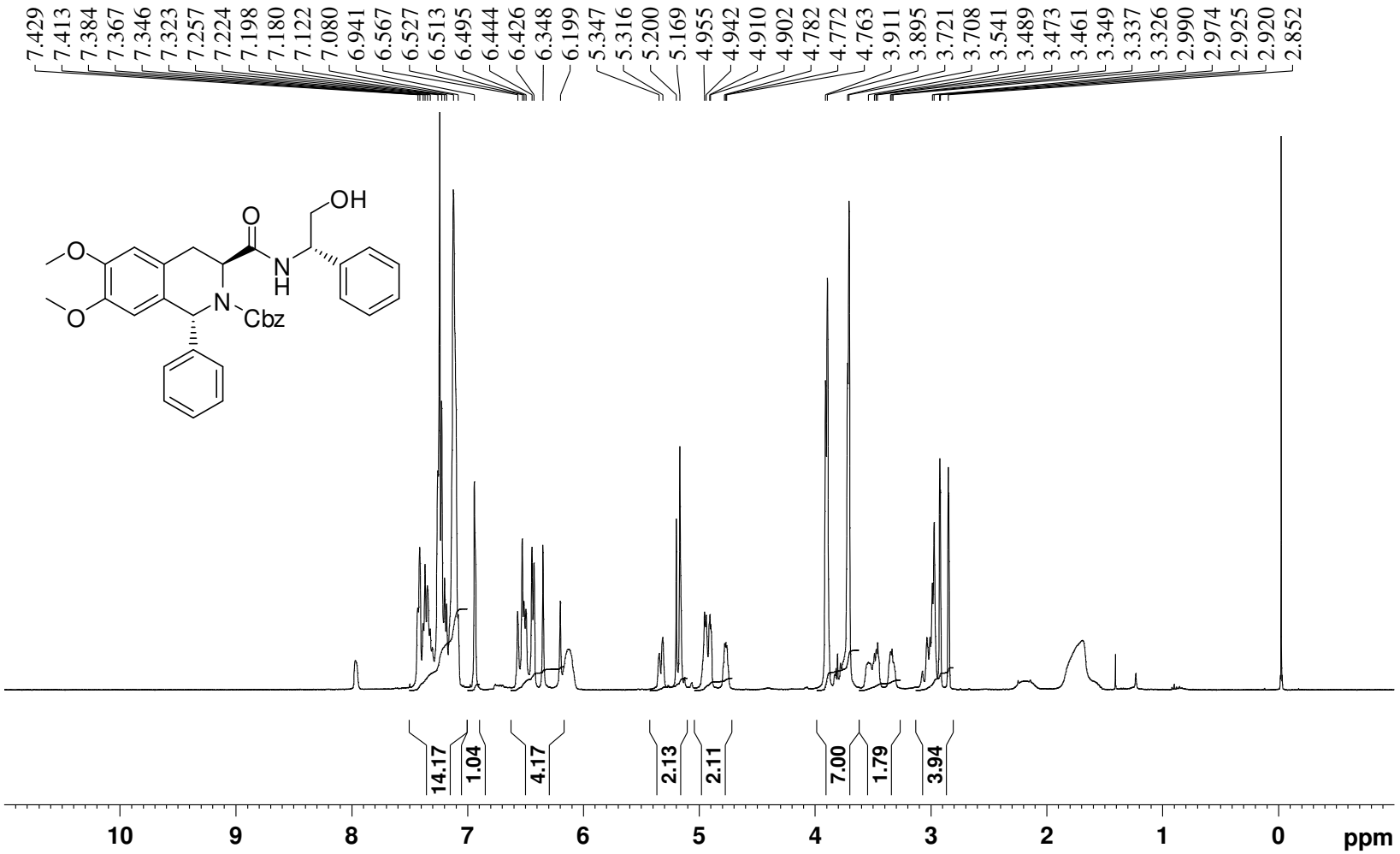
^{1}H NMR (400 MHz) Spectrum of Compound **11a** in $CDCl_3$



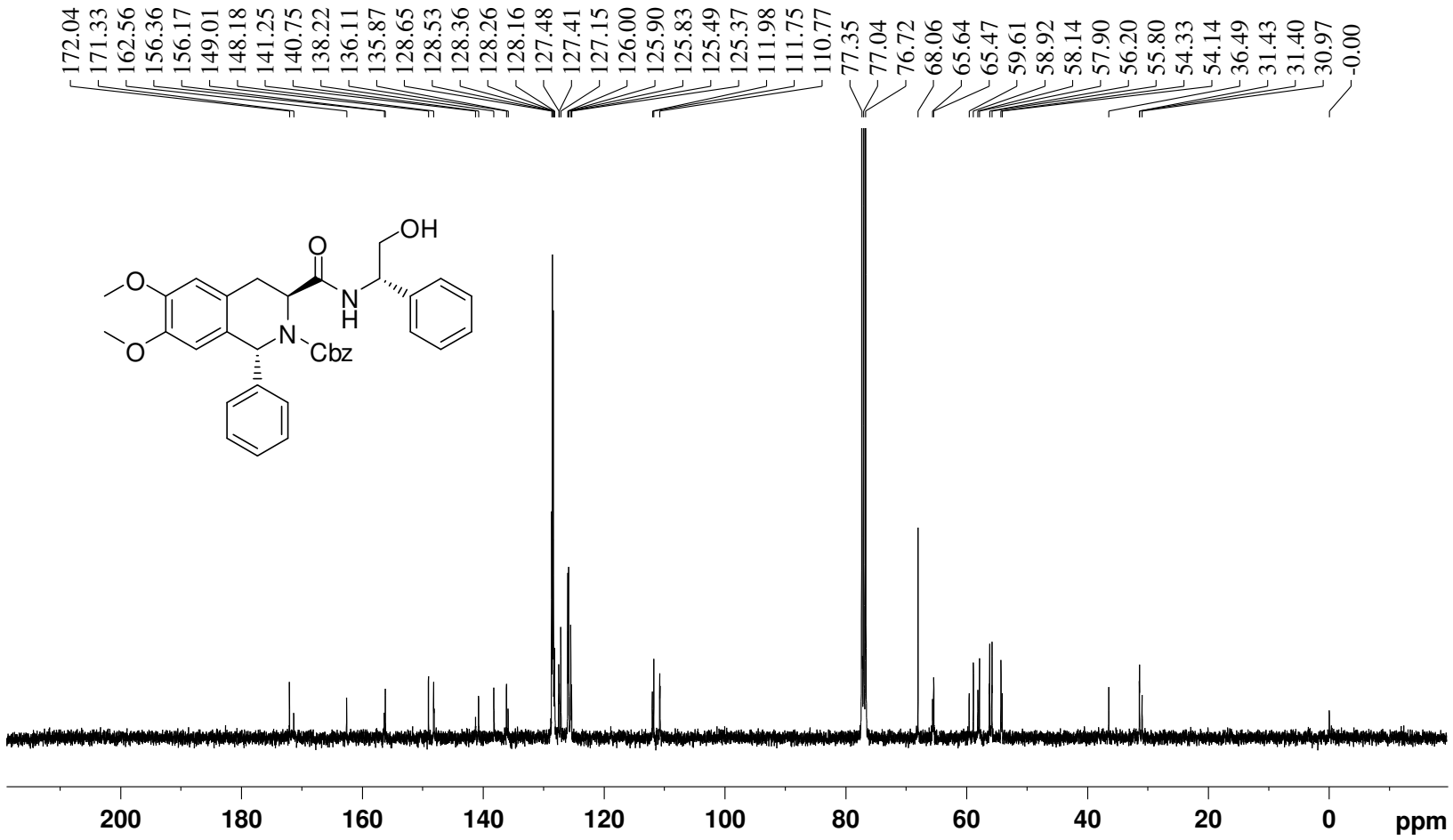
^{13}C (400 MHz) Spectrum of Compound **11a** in $CDCl_3$



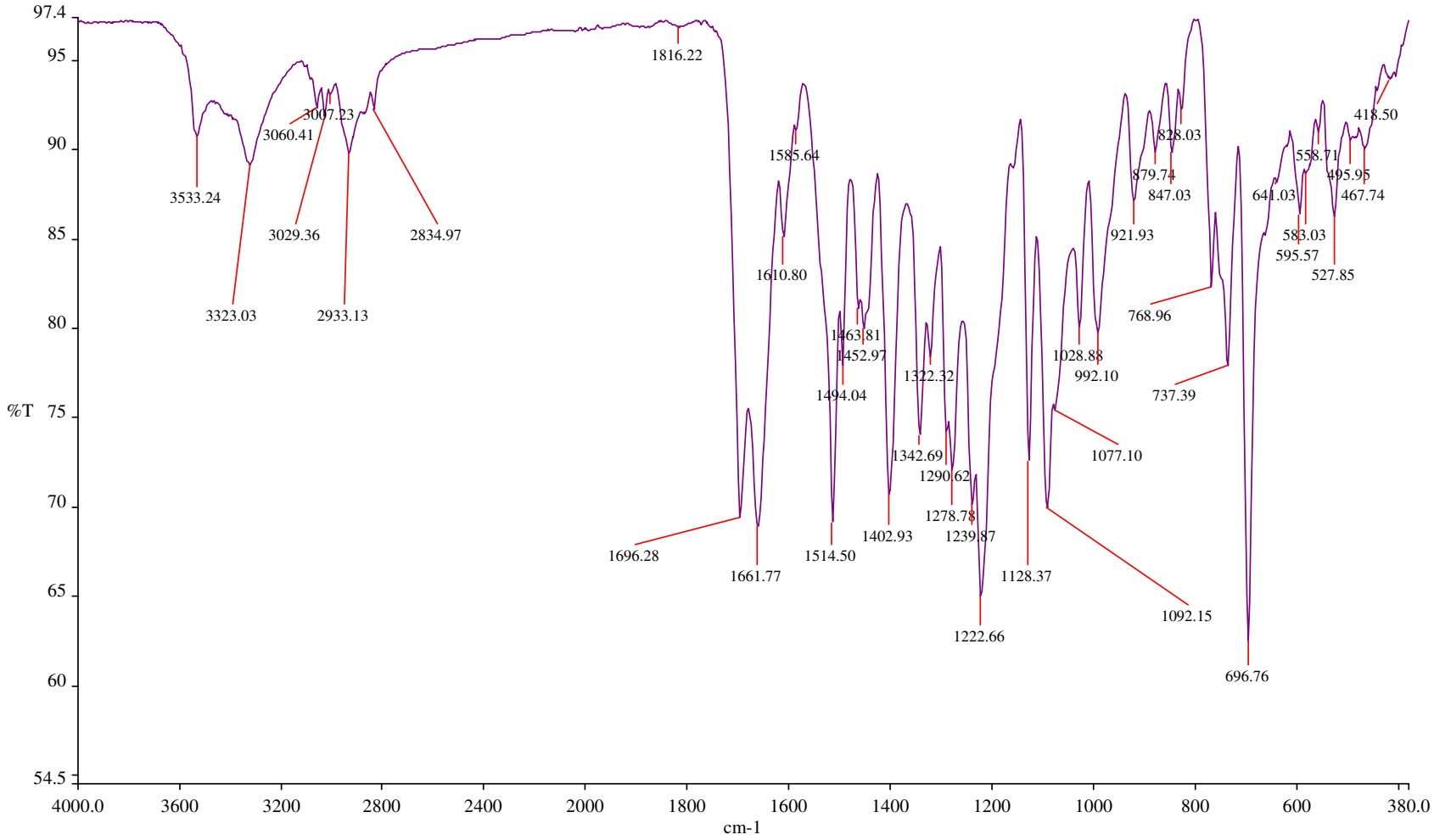
IR Spectrum of Compound **11a**



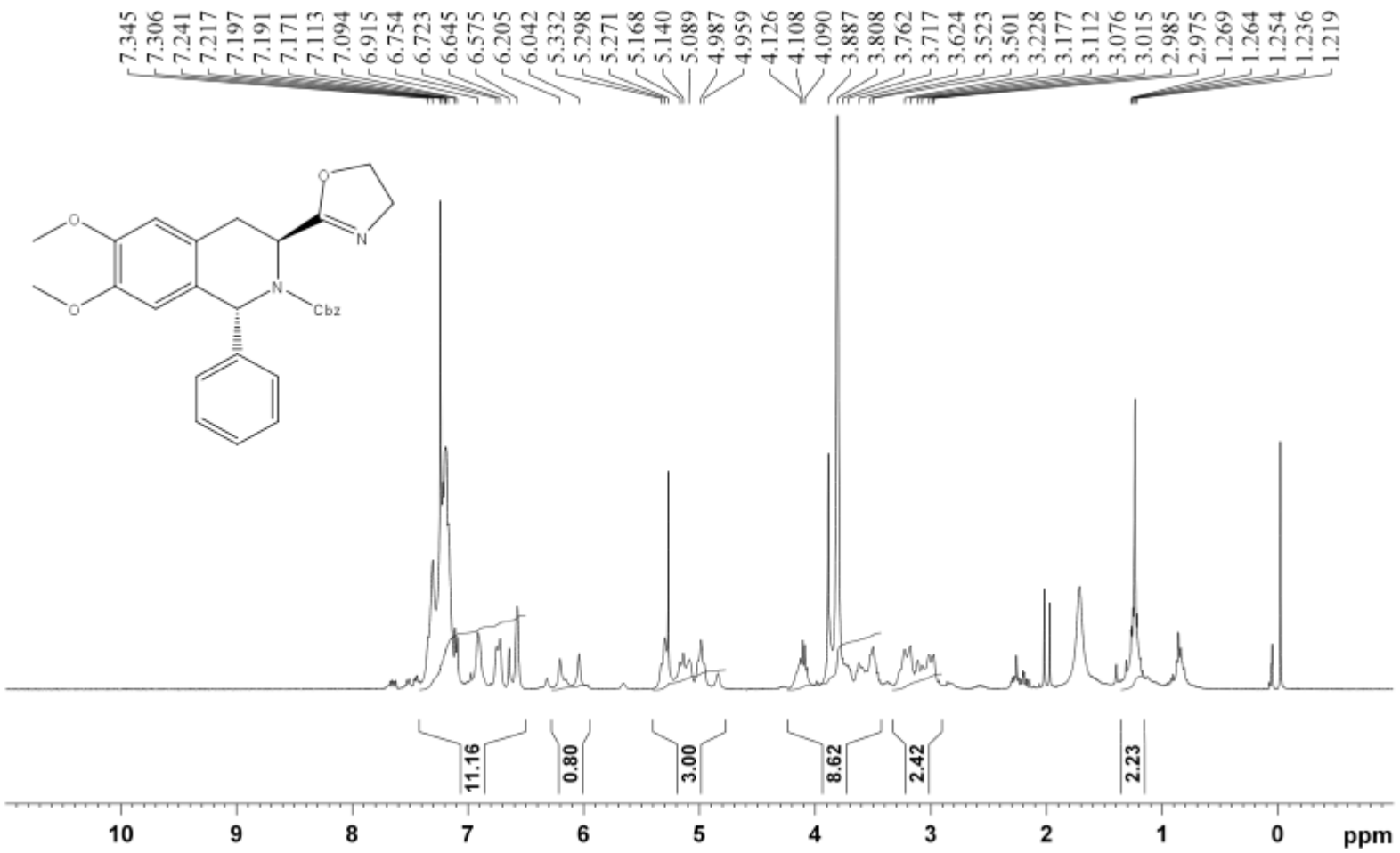
^{1}H NMR (400 MHz) Spectrum of Compound **11b** in $CDCl_3$



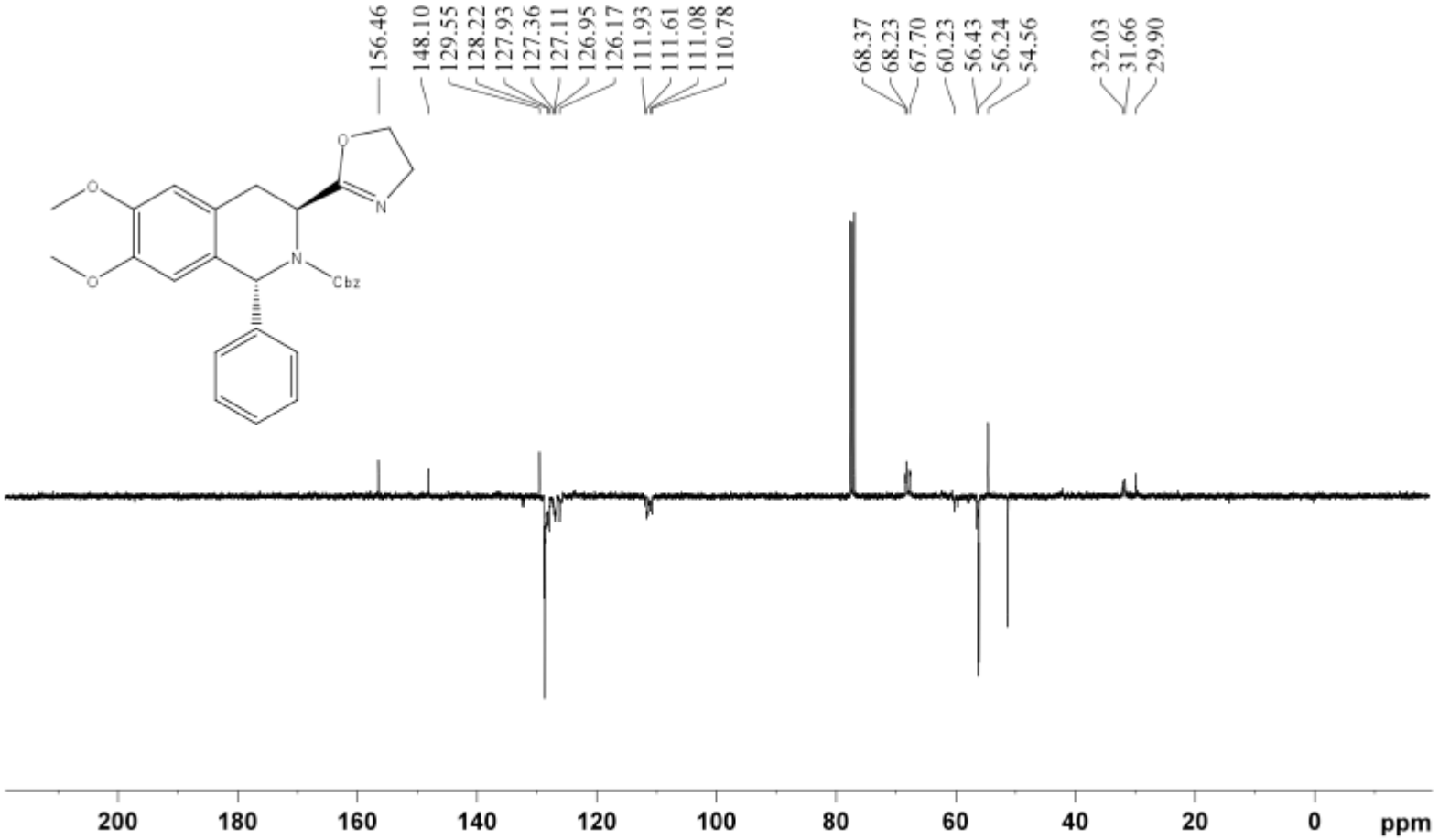
^{13}C (400 MHz) Spectrum of Compound **11b** in $CDCl_3$



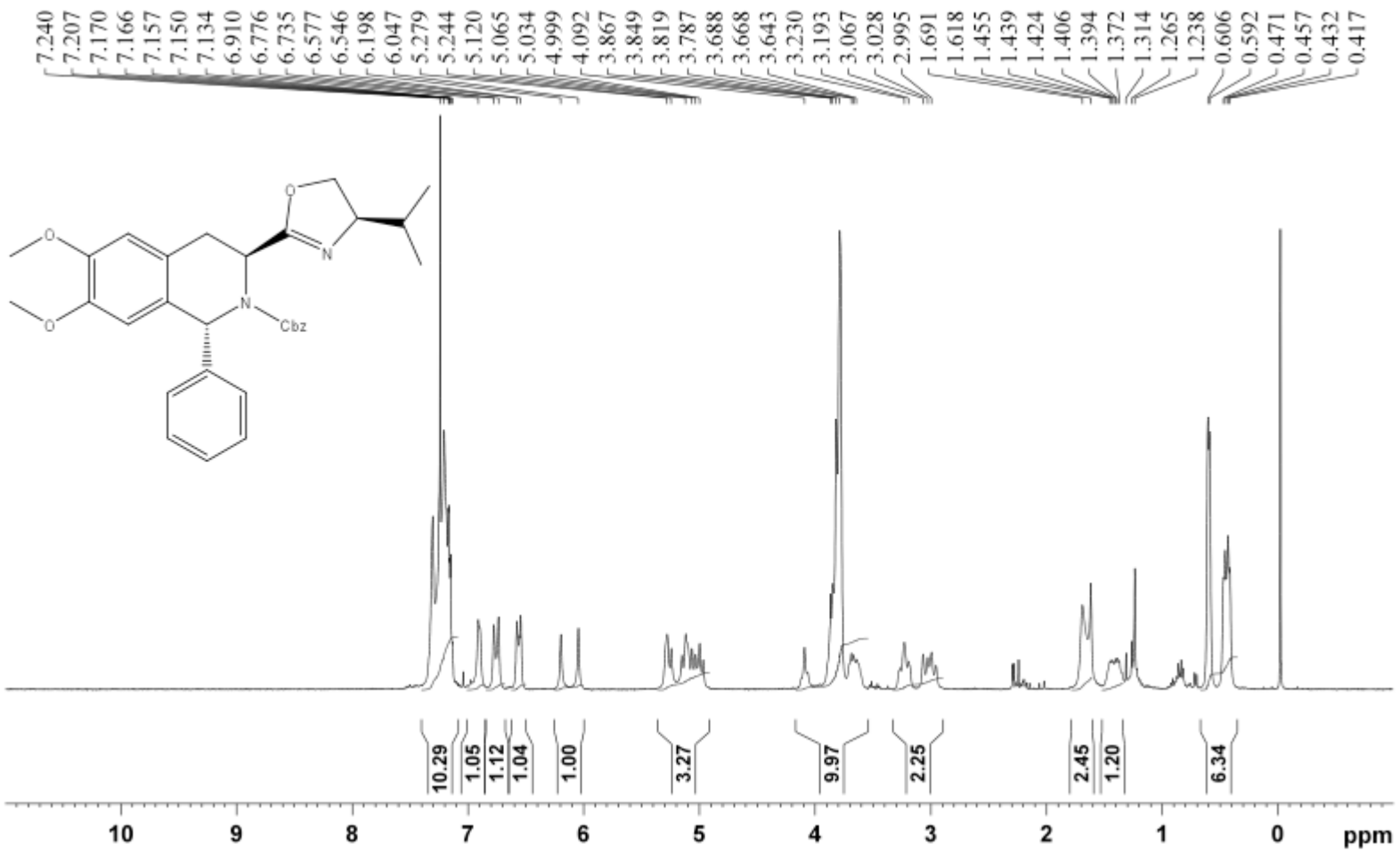
IR Spectrum of Compound **11b**



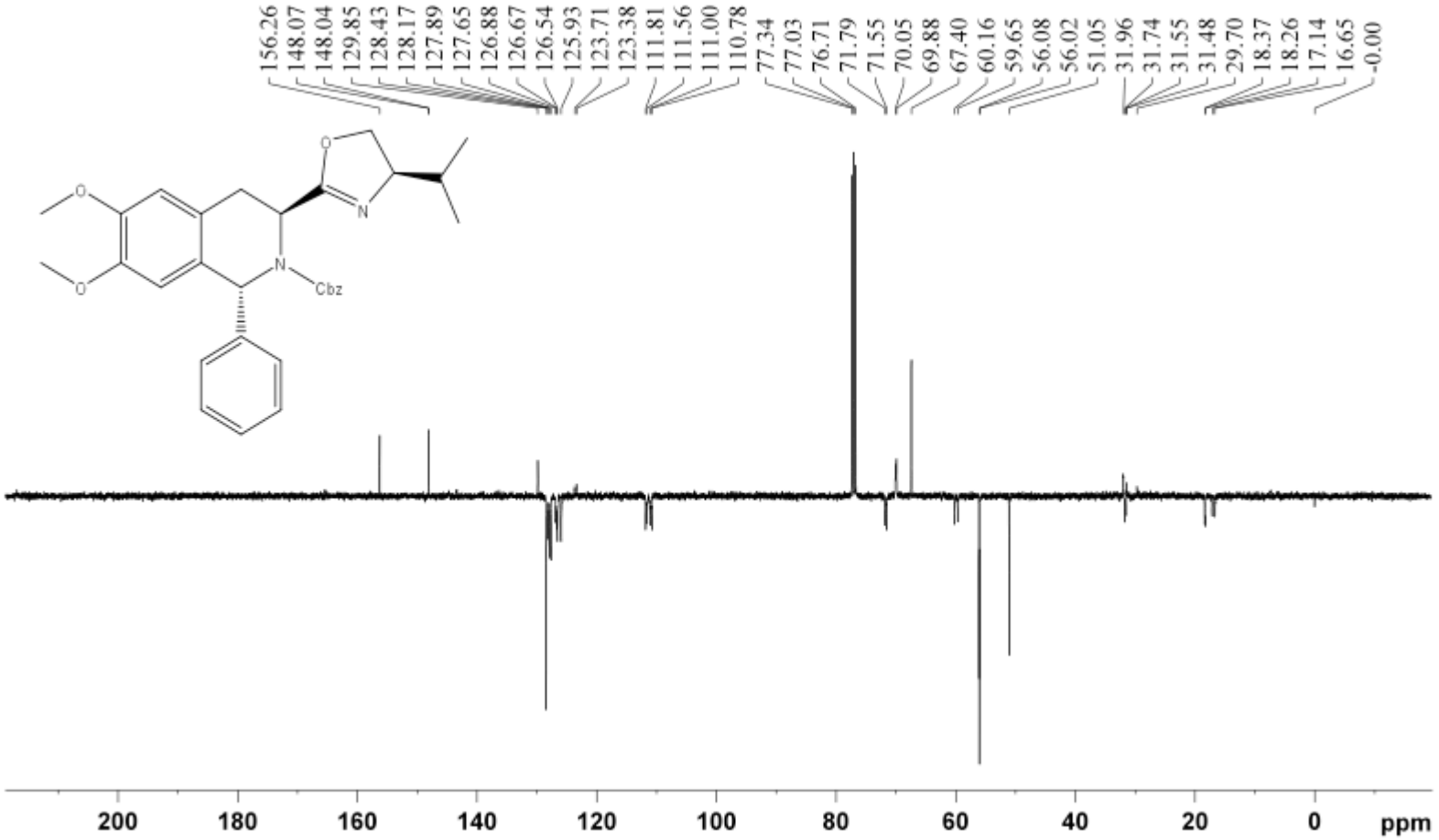
^{1}H NMR (400 MHz) Spectrum of Compound **12** in $CDCl_3$



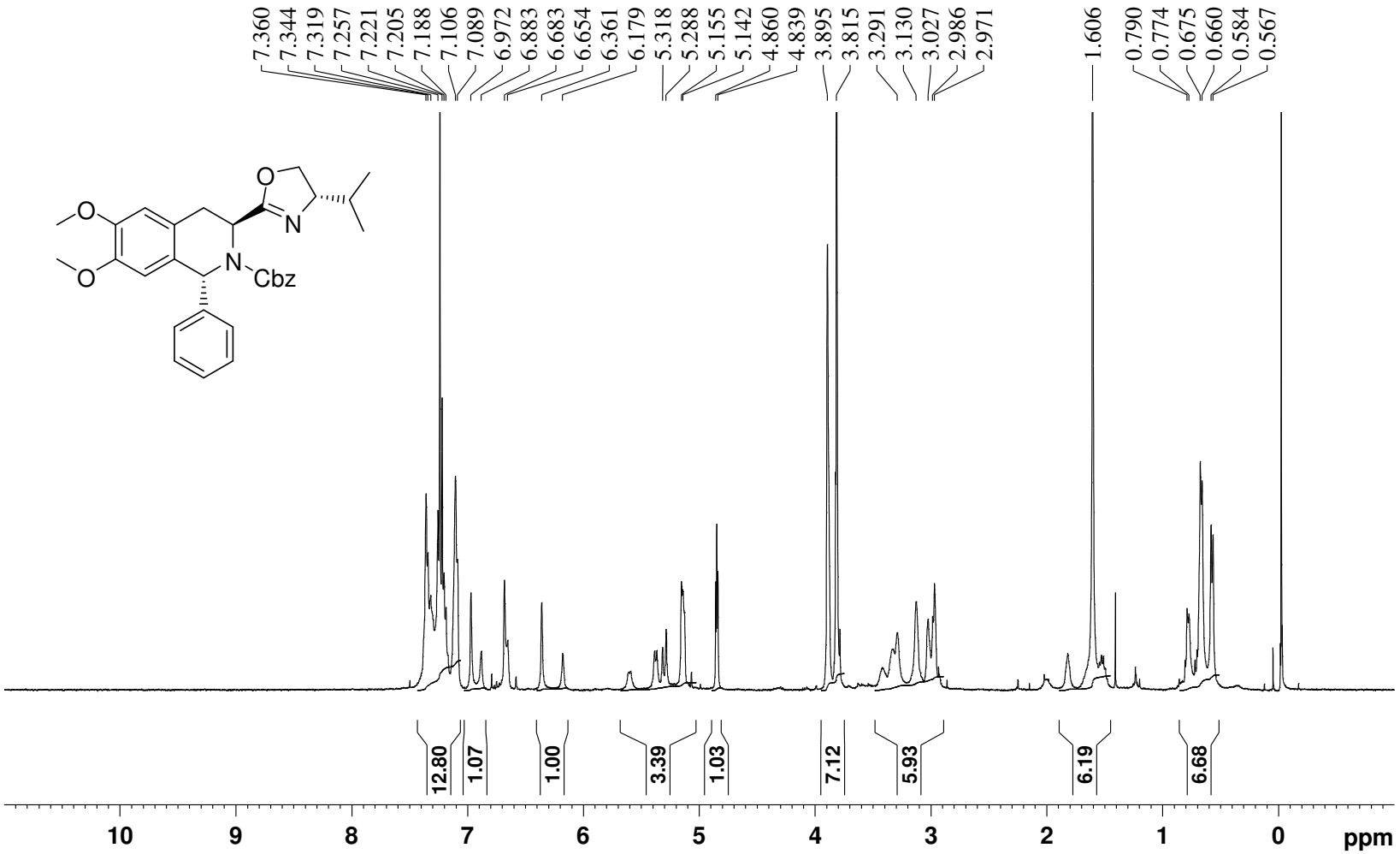
^{13}C (400 MHz) Spectrum of Compound **12** in $CDCl_3$



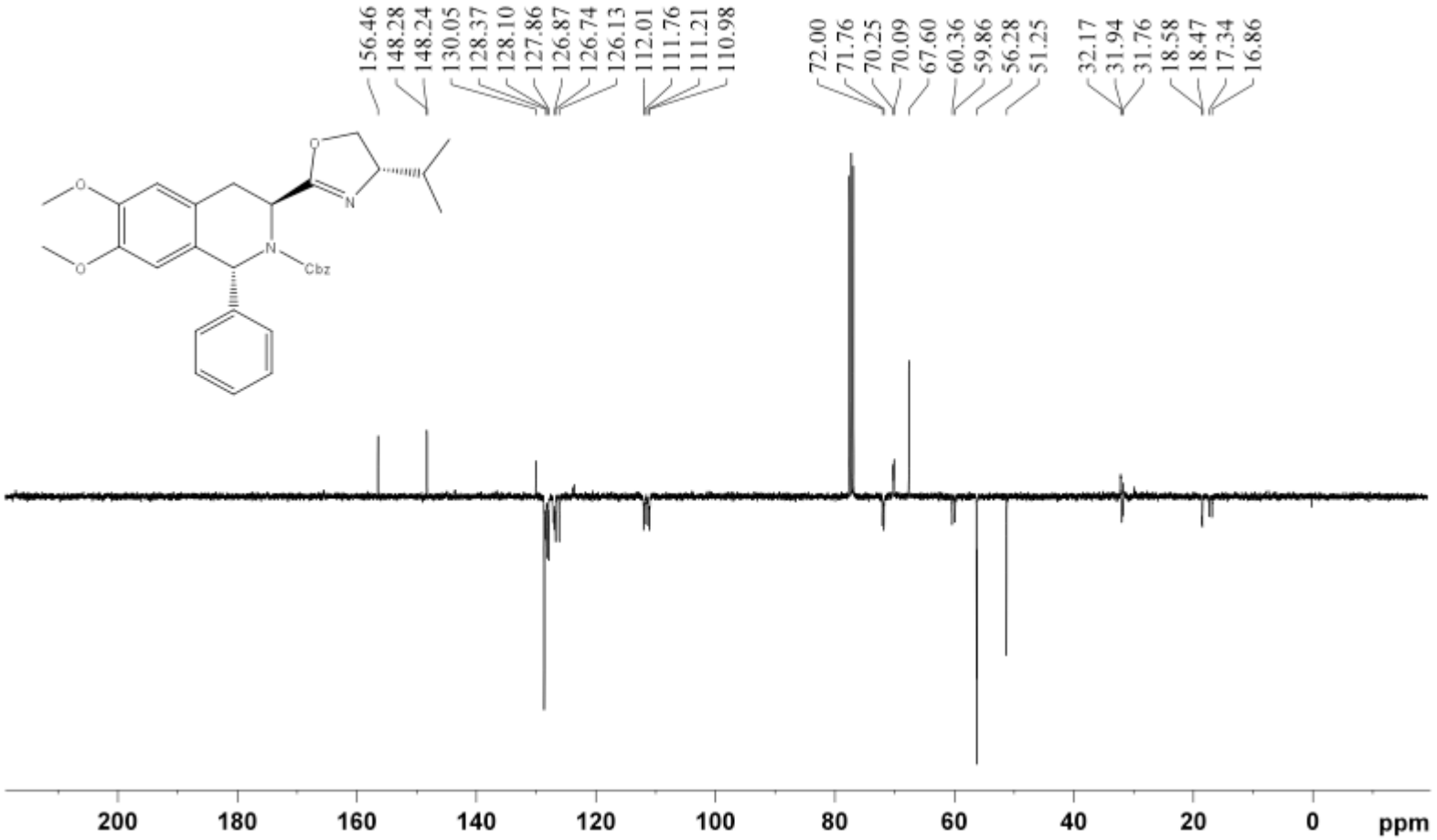
^{1}H NMR (400 MHz) Spectrum of Compound **13a** in $CDCl_3$



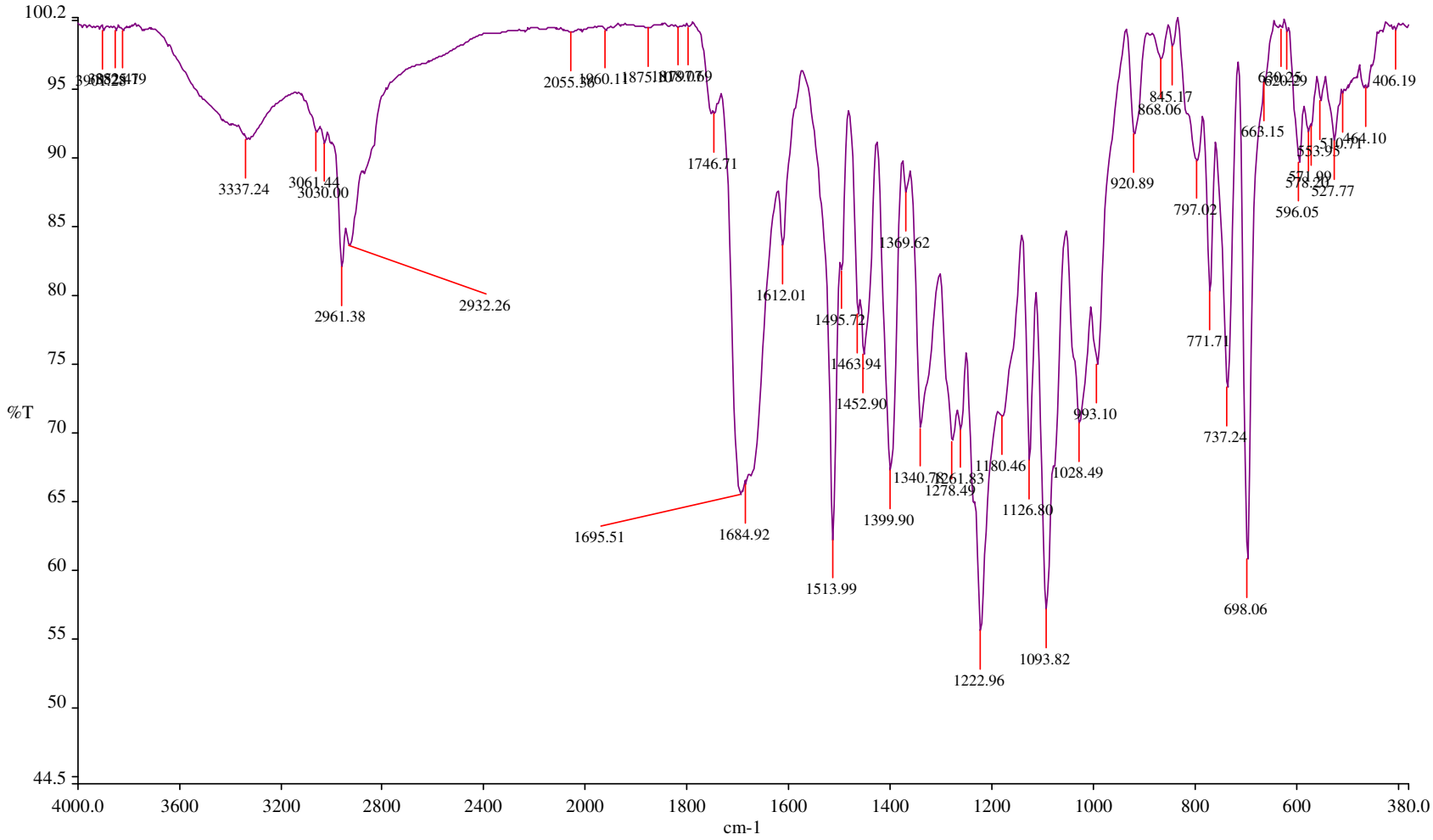
^{13}C (400 MHz) Spectrum of Compound **13a** in $CDCl_3$



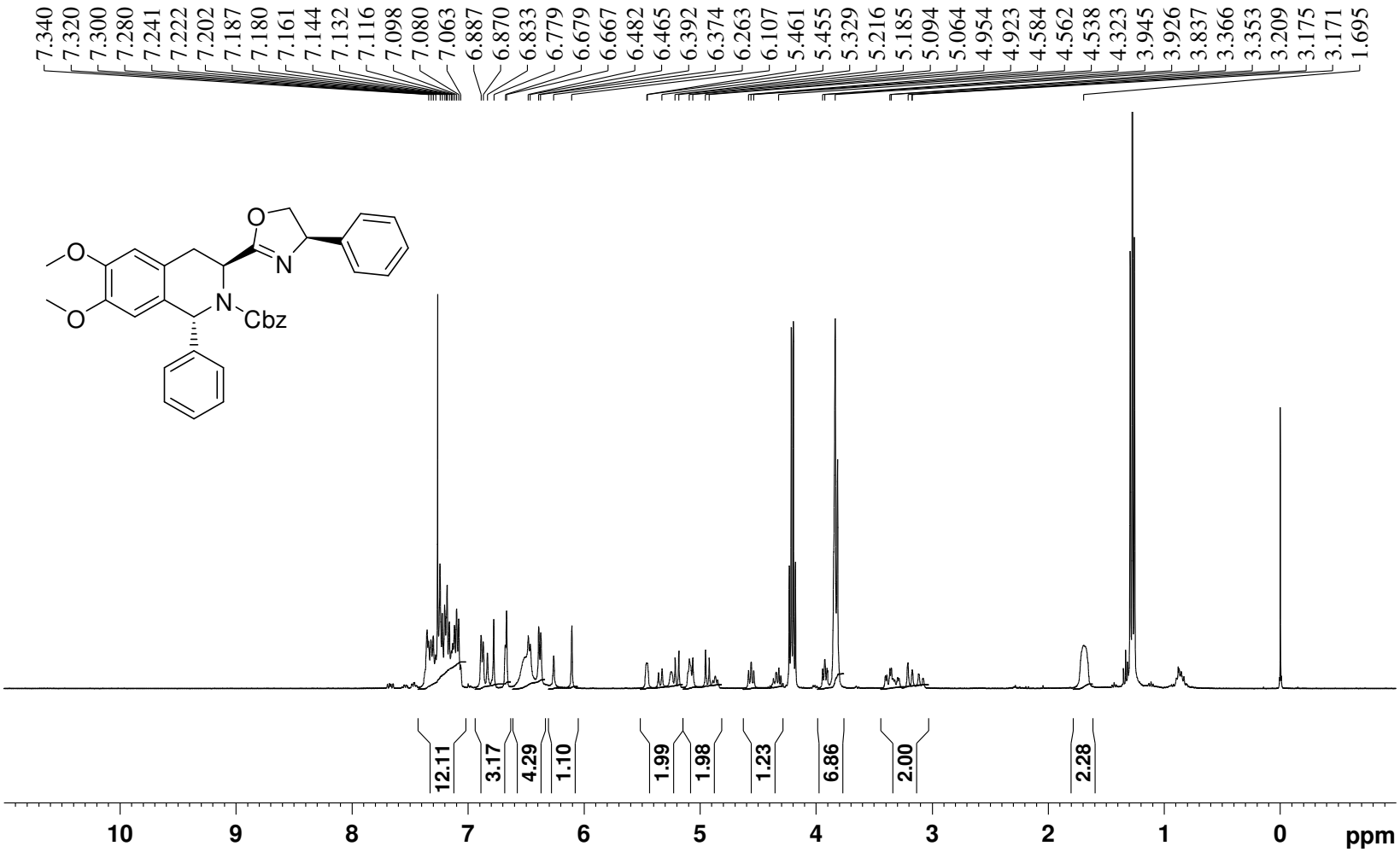
^{1}H NMR (400 MHz) Spectrum of Compound **13b** in $CDCl_3$



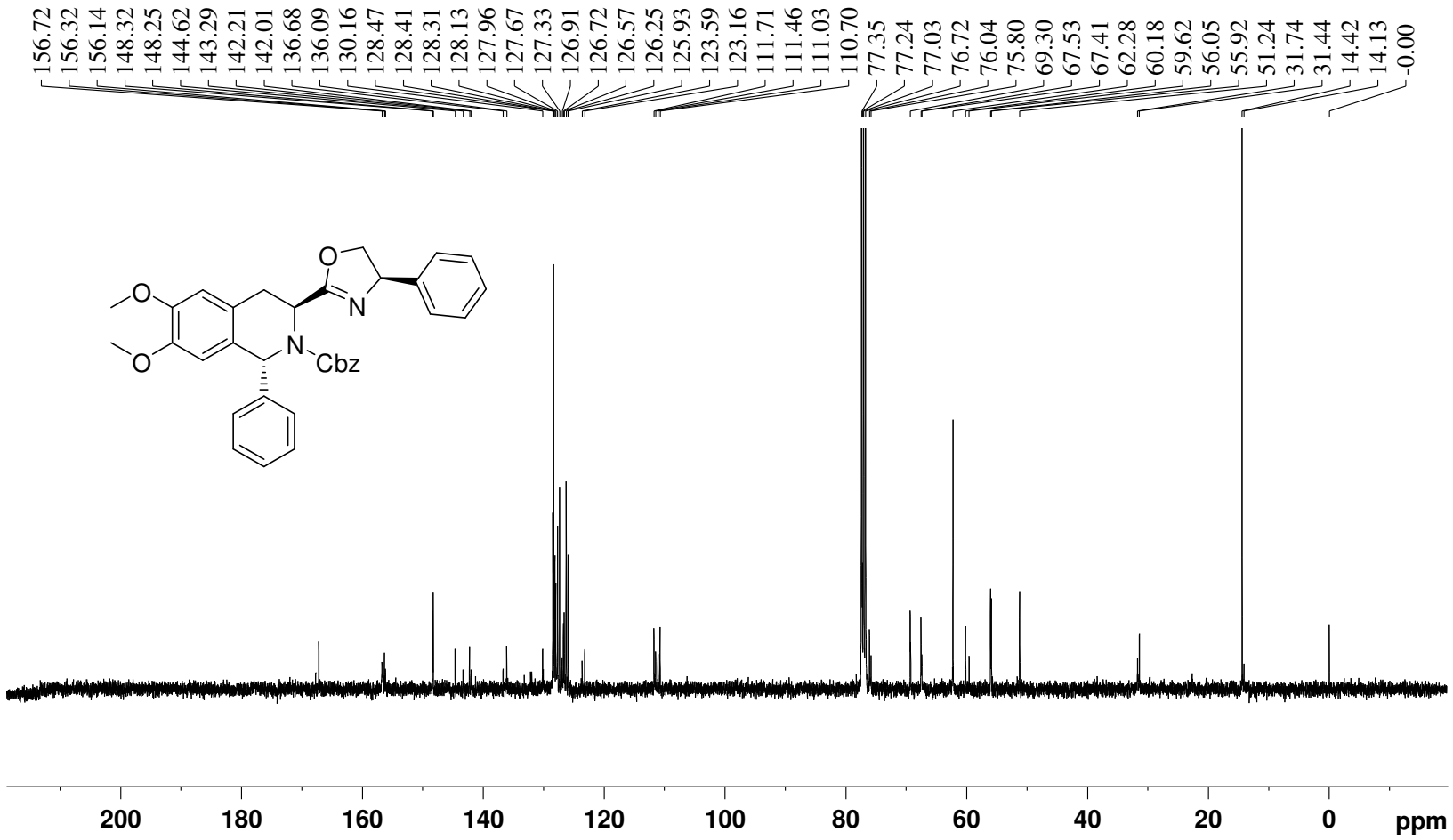
^{13}C (400 MHz) Spectrum of Compound **13b** in $CDCl_3$



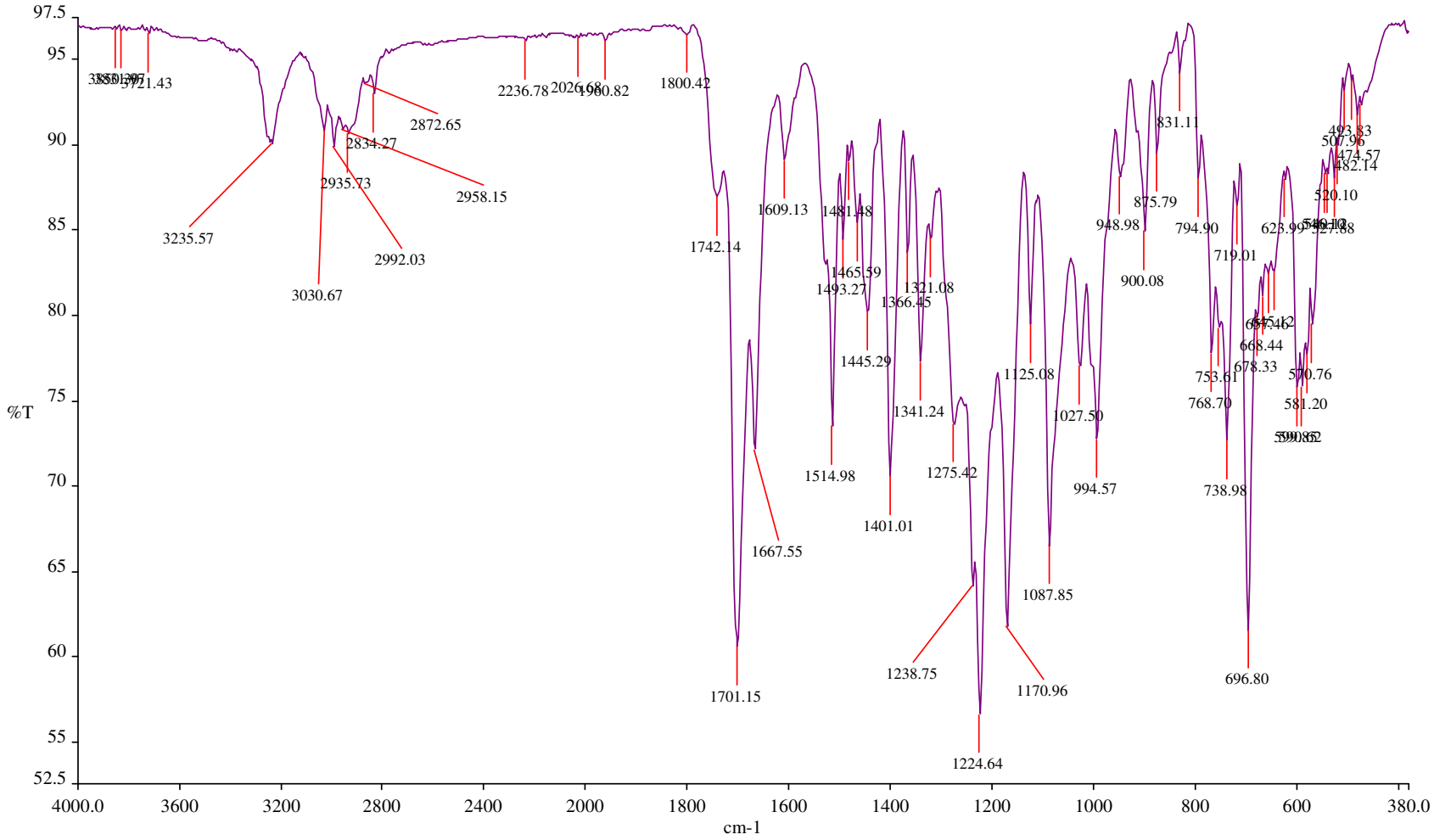
IR Spectrum of Compound **13b**



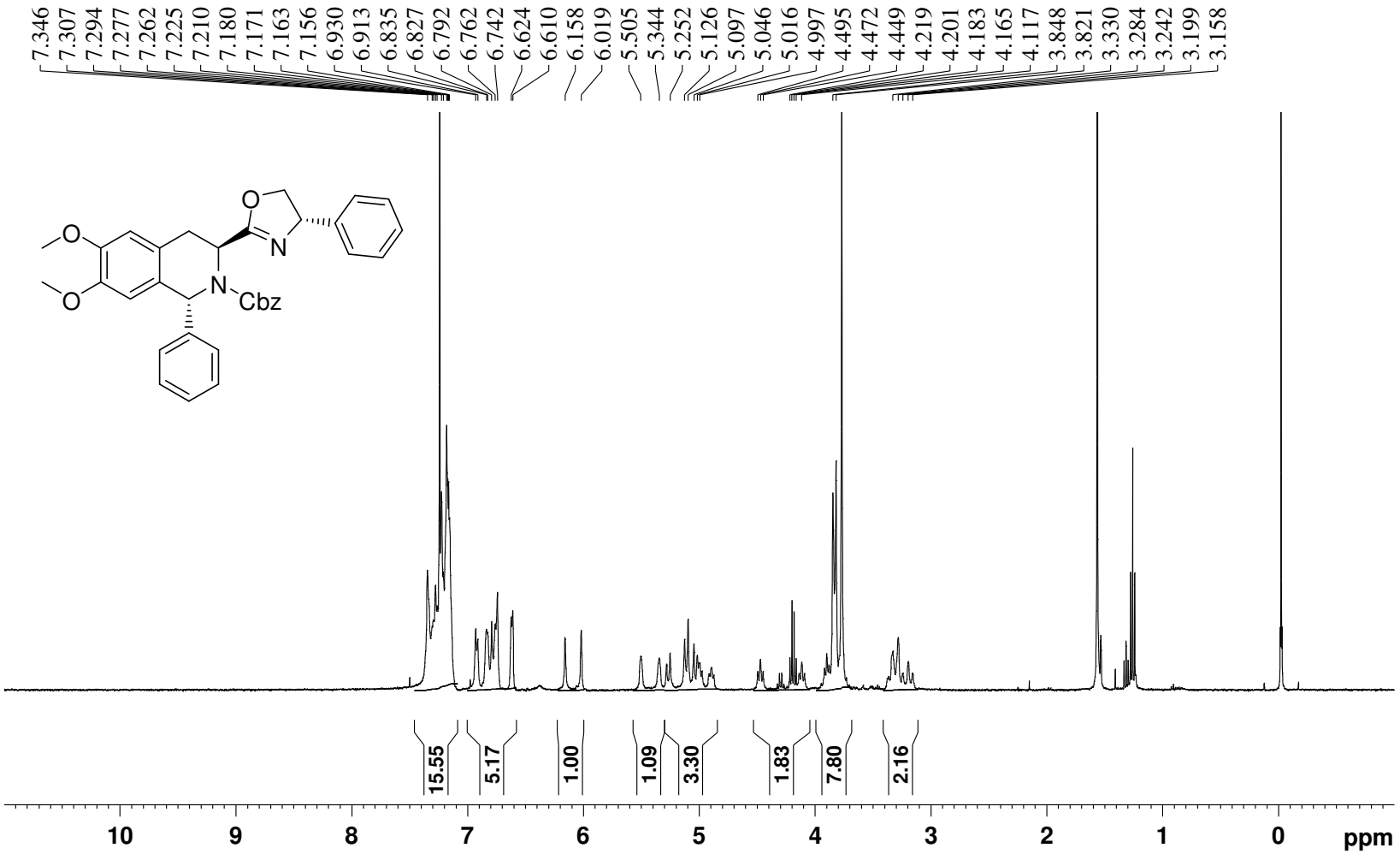
^{1}H NMR (400 MHz) Spectrum of Compound **14a** in $CDCl_3$



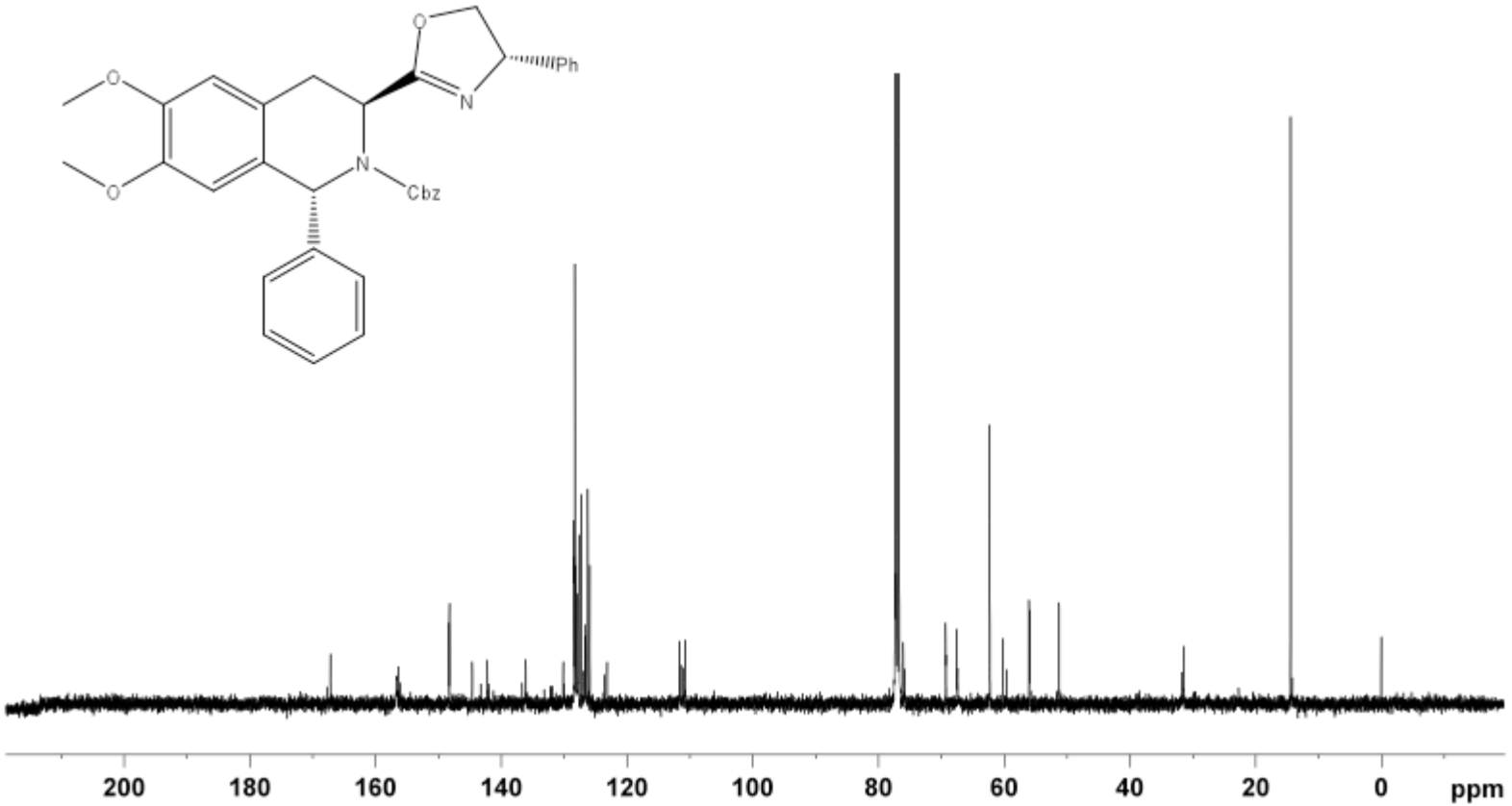
^{13}C (400 MHz) Spectrum of Compound **14a** in $CDCl_3$



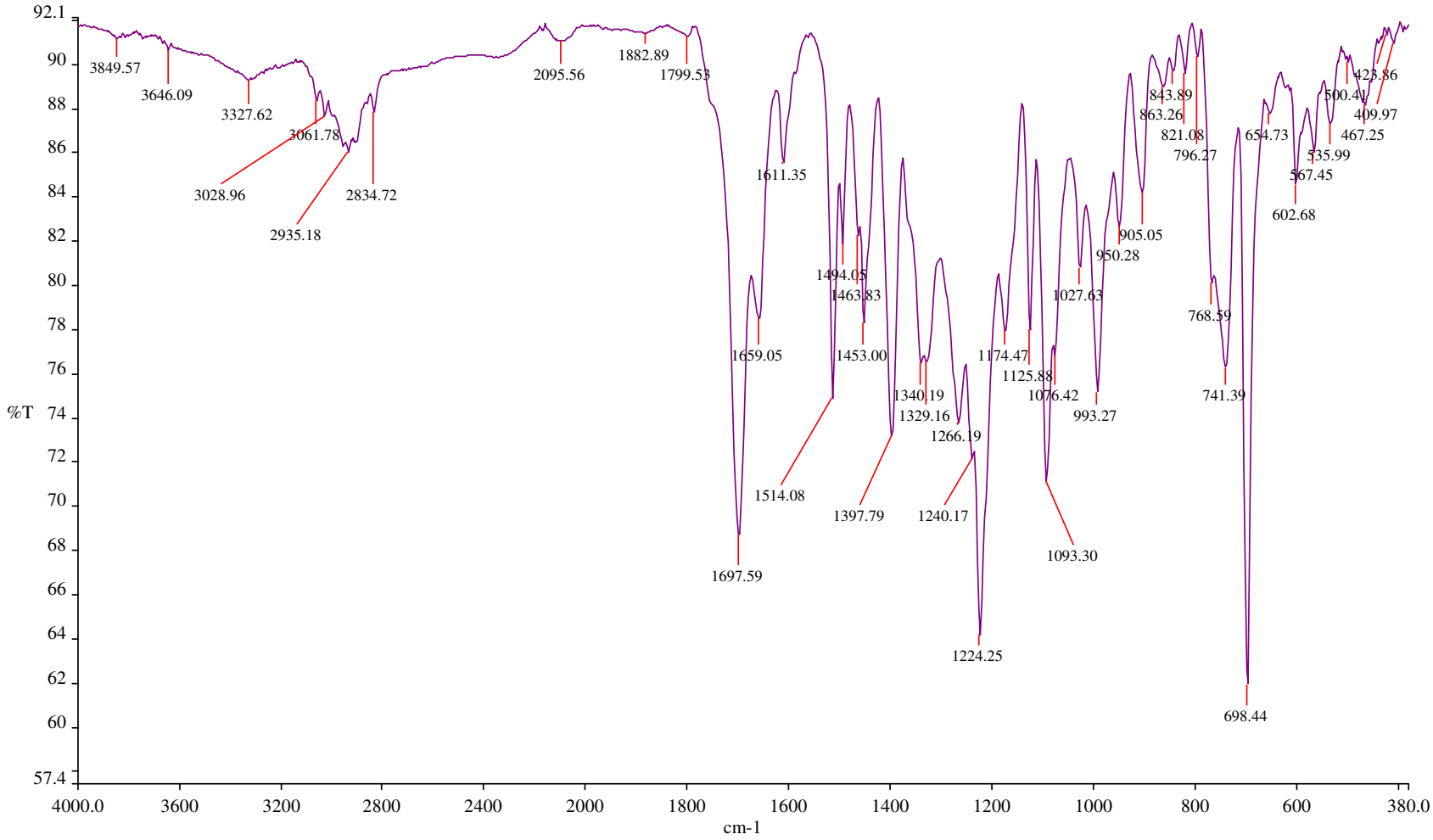
IR Spectrum of Compound **14a**



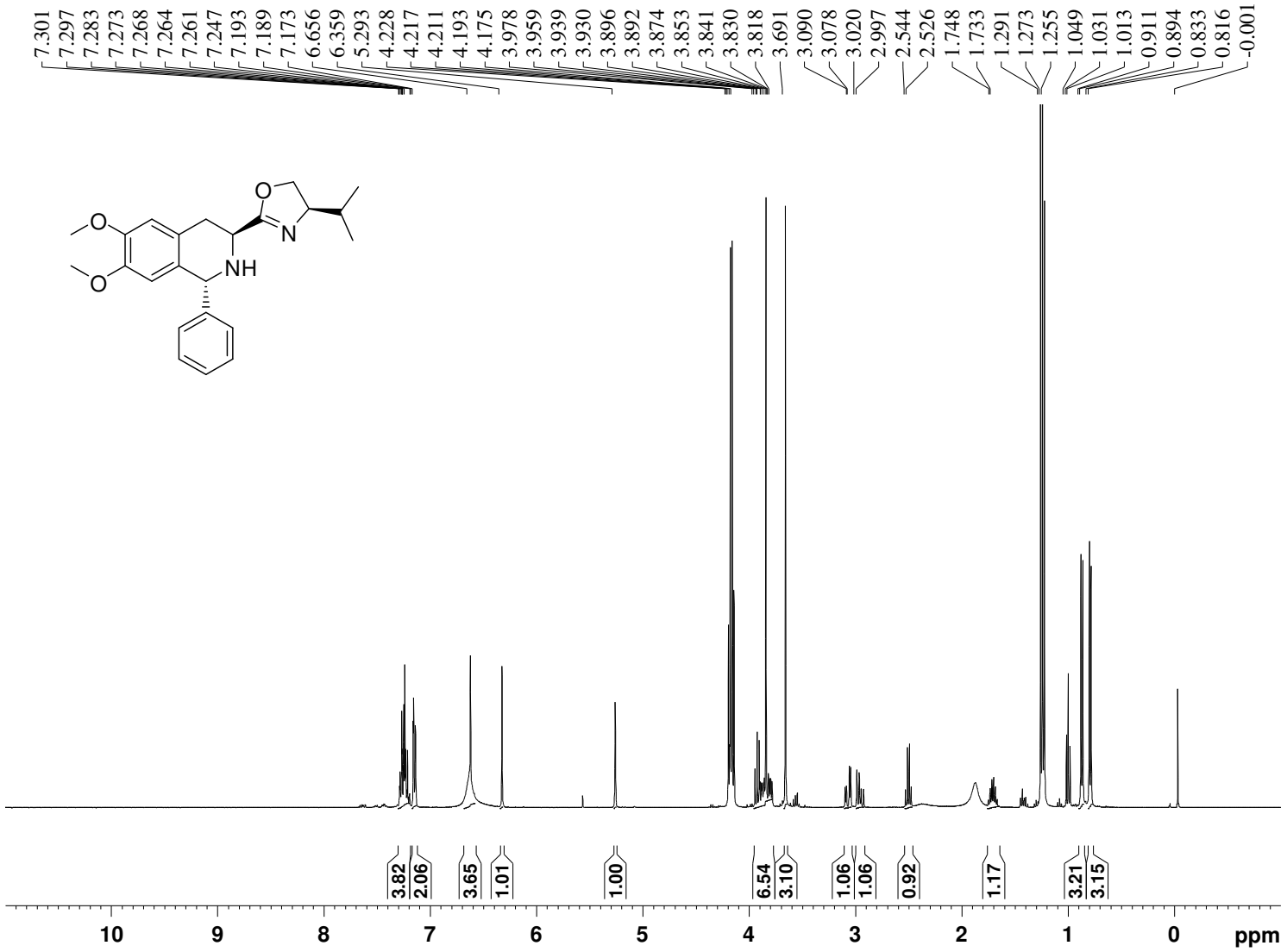
^{1}H NMR (400 MHz) Spectrum of Compound **14b** in $CDCl_3$



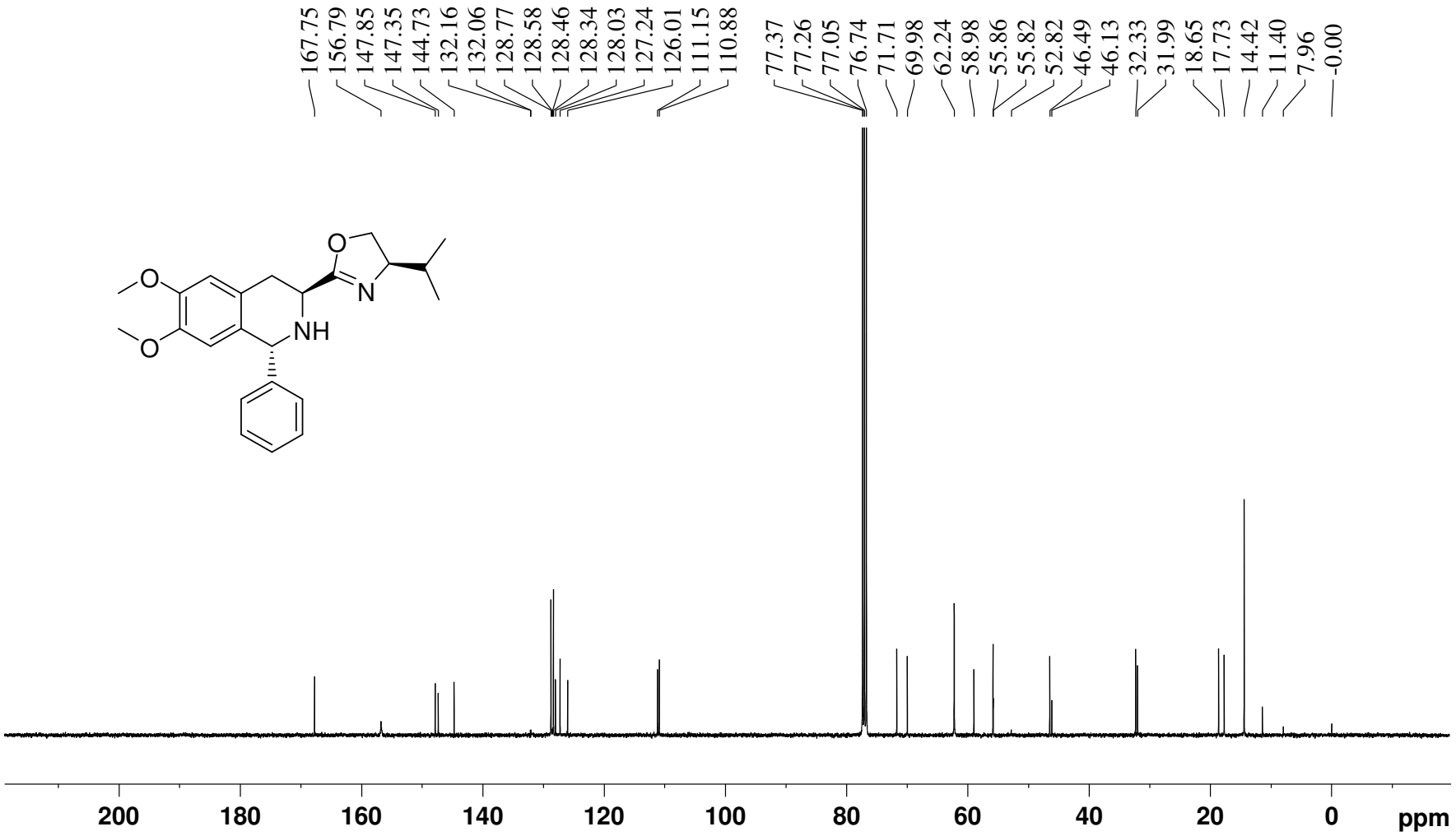
^{13}C (400 MHz) Spectrum of Compound **14b** in $CDCl_3$



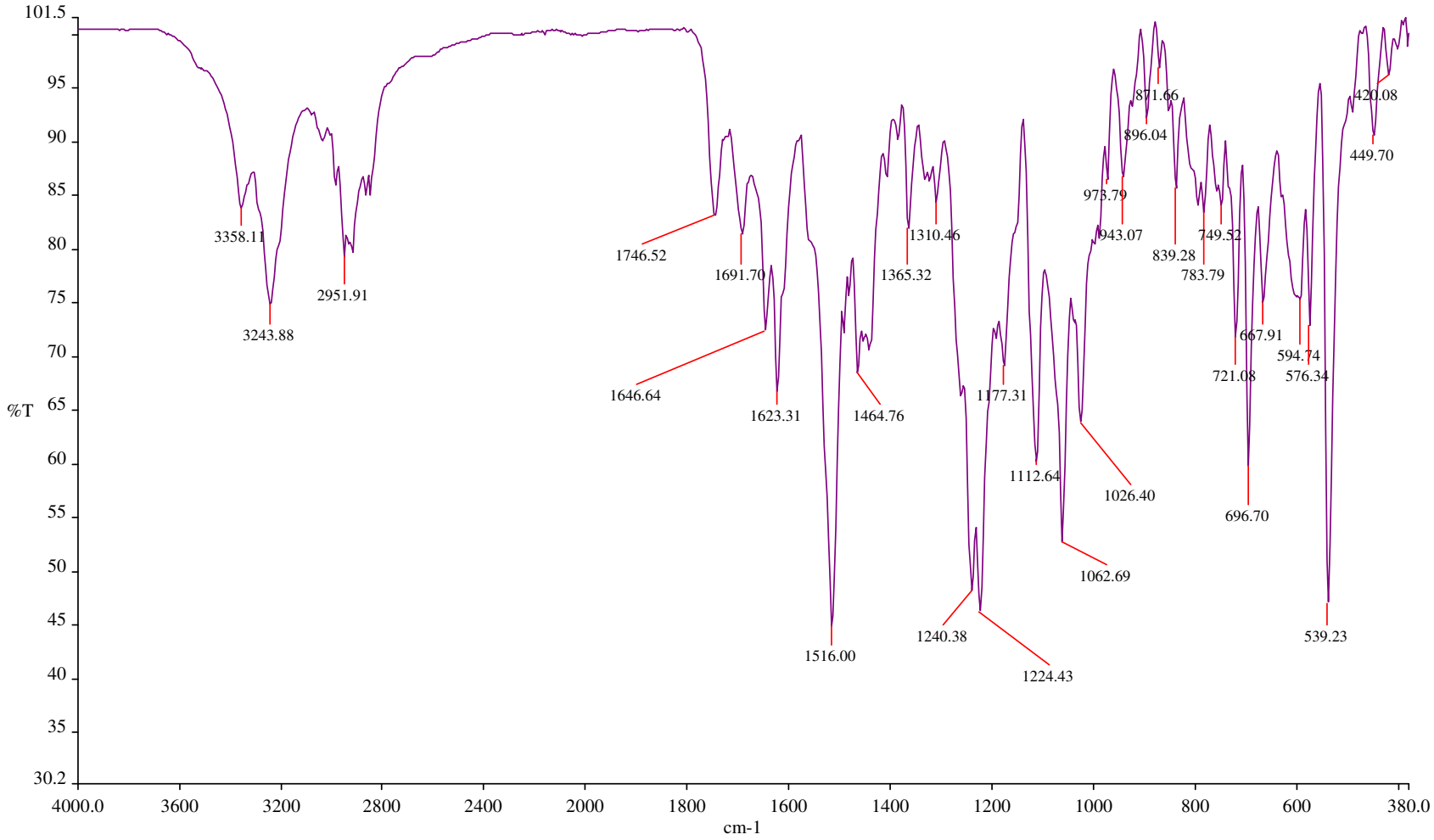
IR Spectrum of Compound **14b**



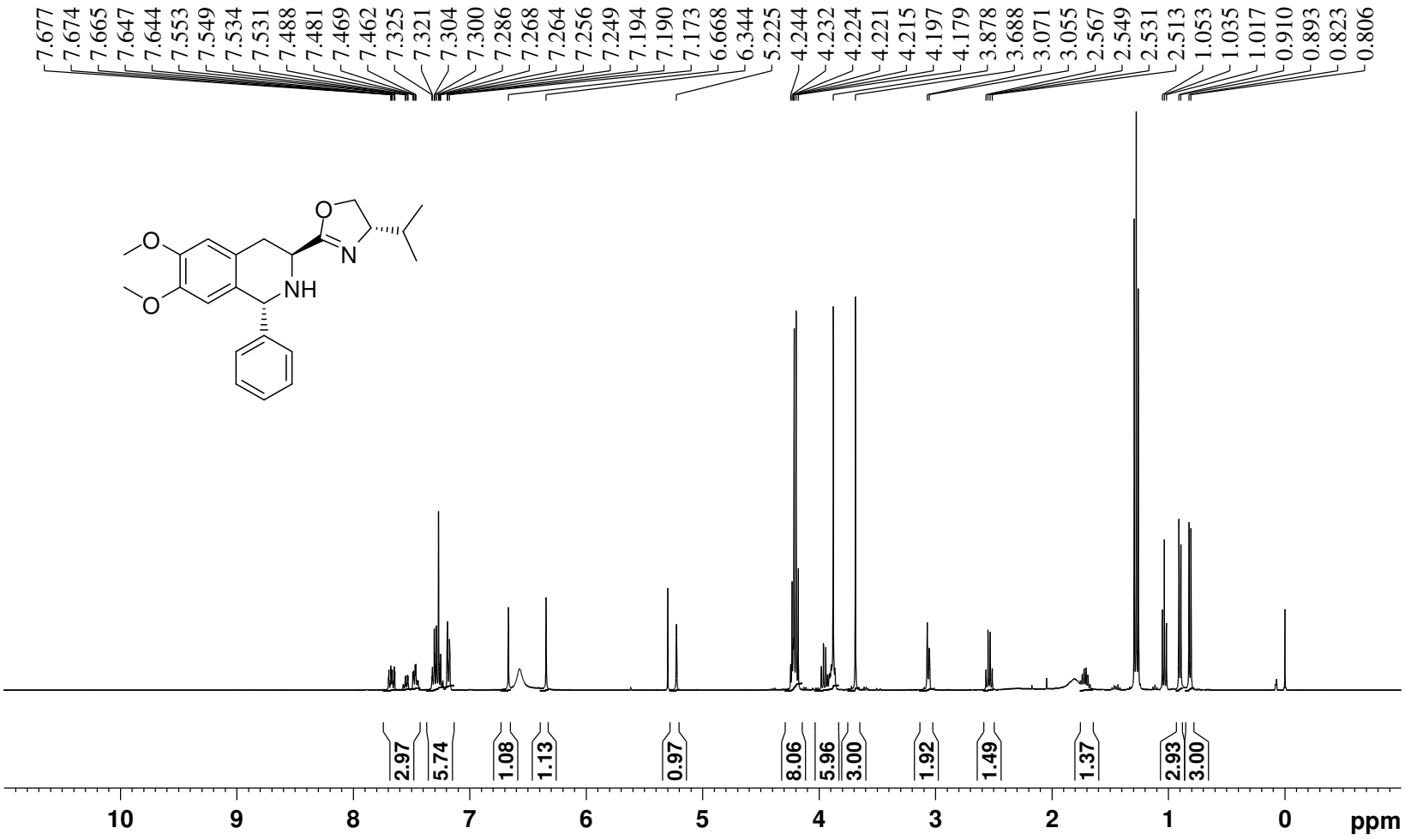
^{1}H NMR (400 MHz) Spectrum of Compound **2a** in $CDCl_3$



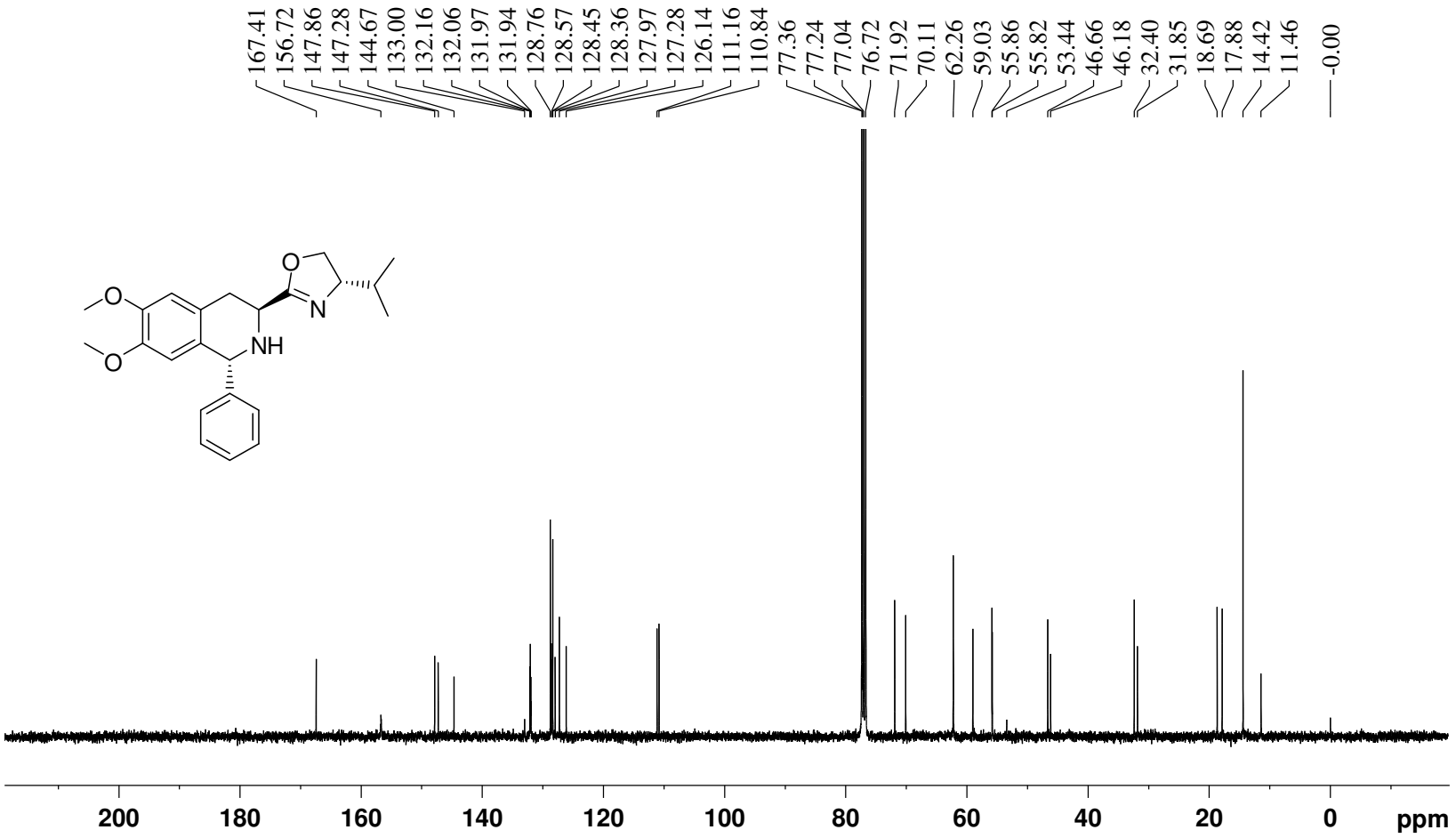
^{13}C (400 MHz) Spectrum of Compound **2a** in $CDCl_3$



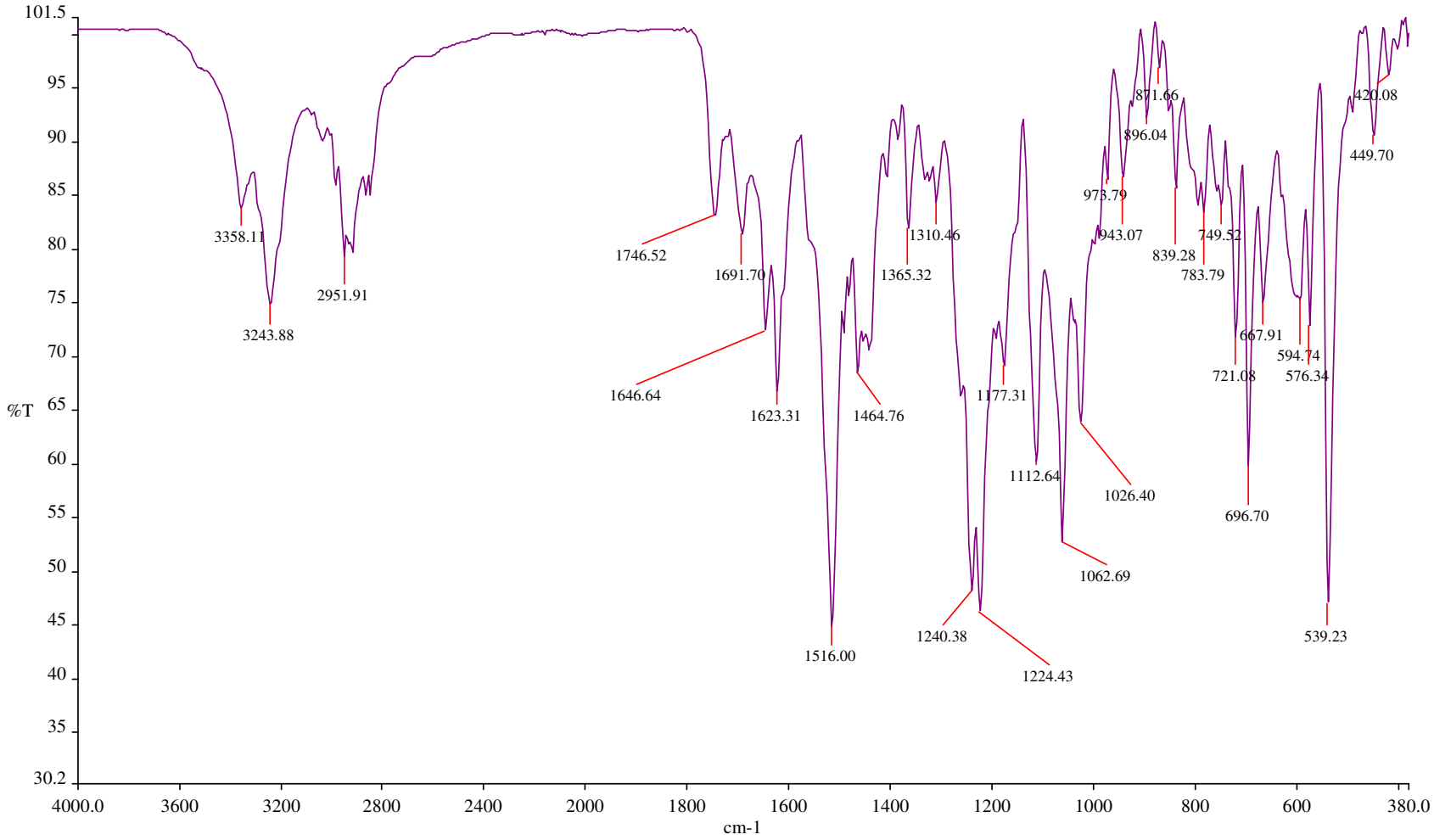
IR Spectrum of Compound **2a**



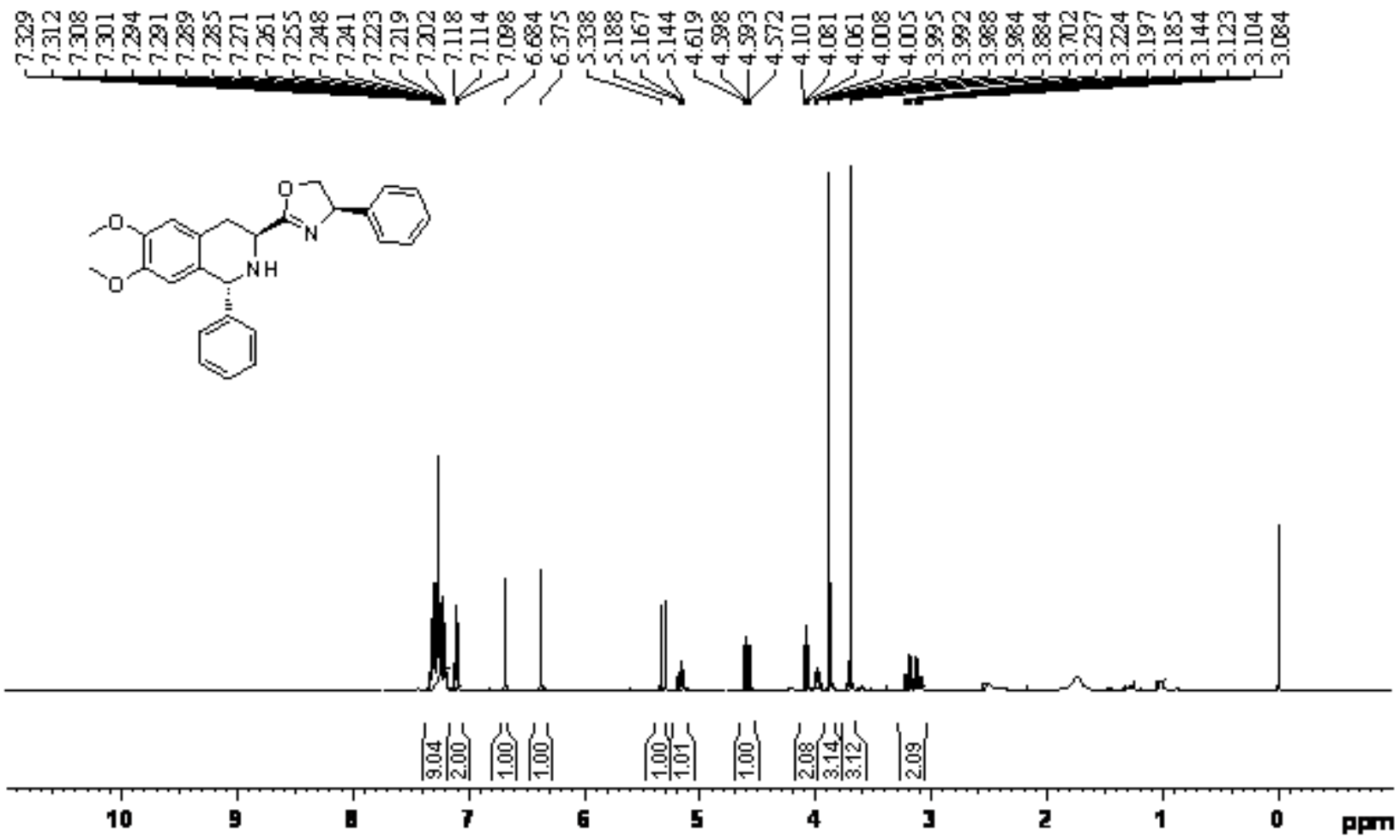
^{1}H NMR (400 MHz) Spectrum of Compound **2b** in $CDCl_3$



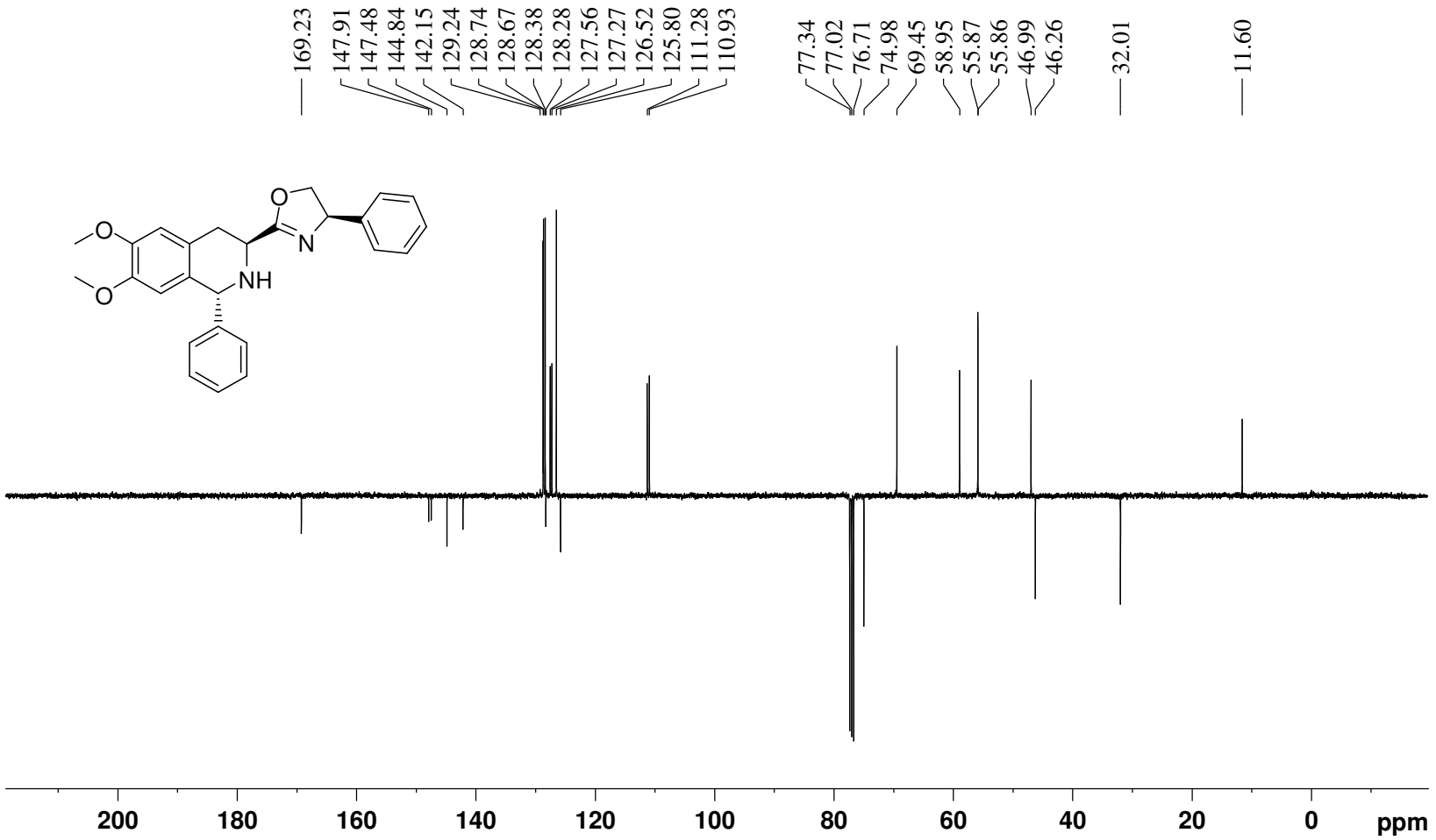
^{13}C (400 MHz) Spectrum of Compound **2b** in $CDCl_3$



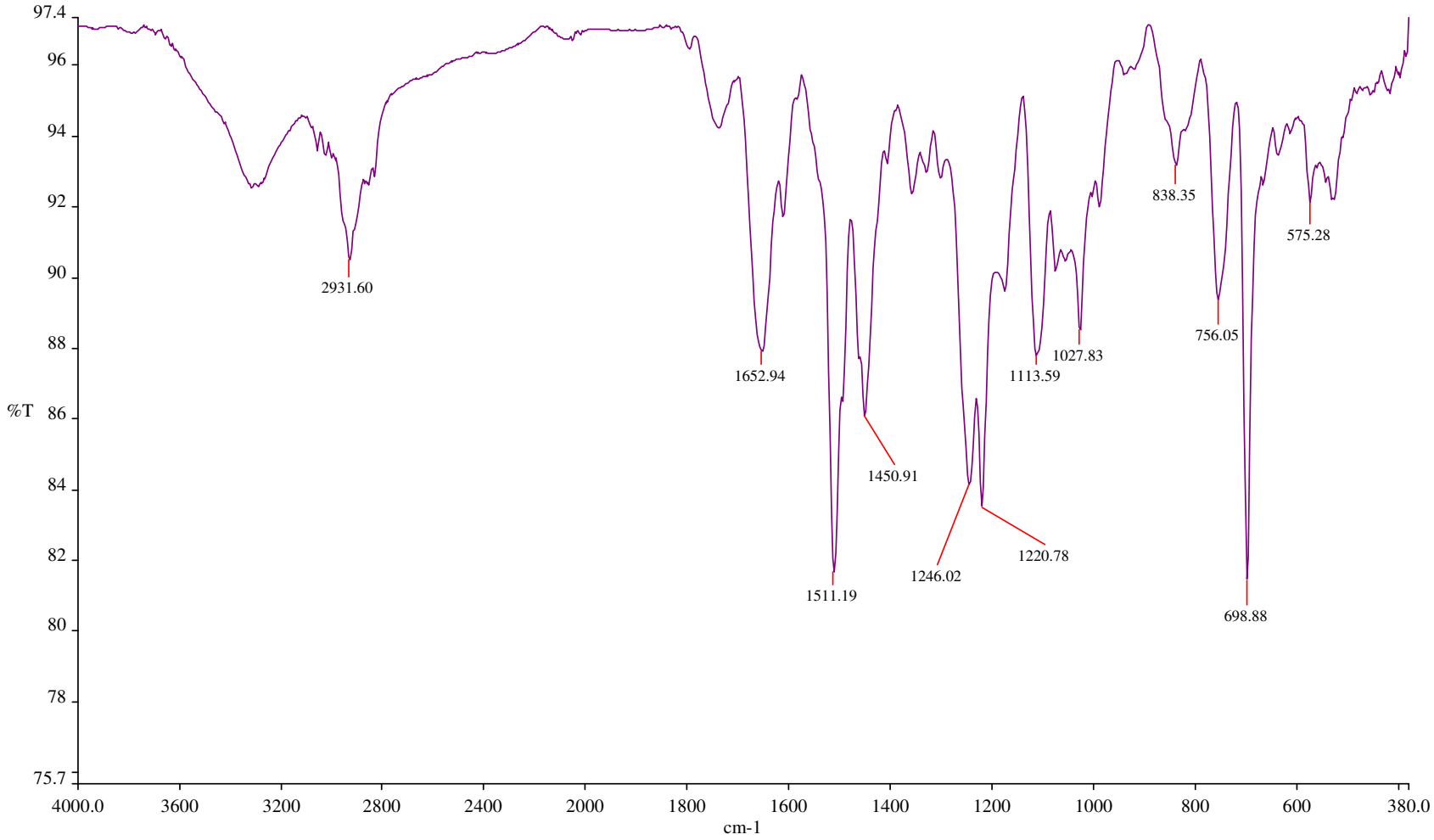
IR Spectrum of Compound **2b**



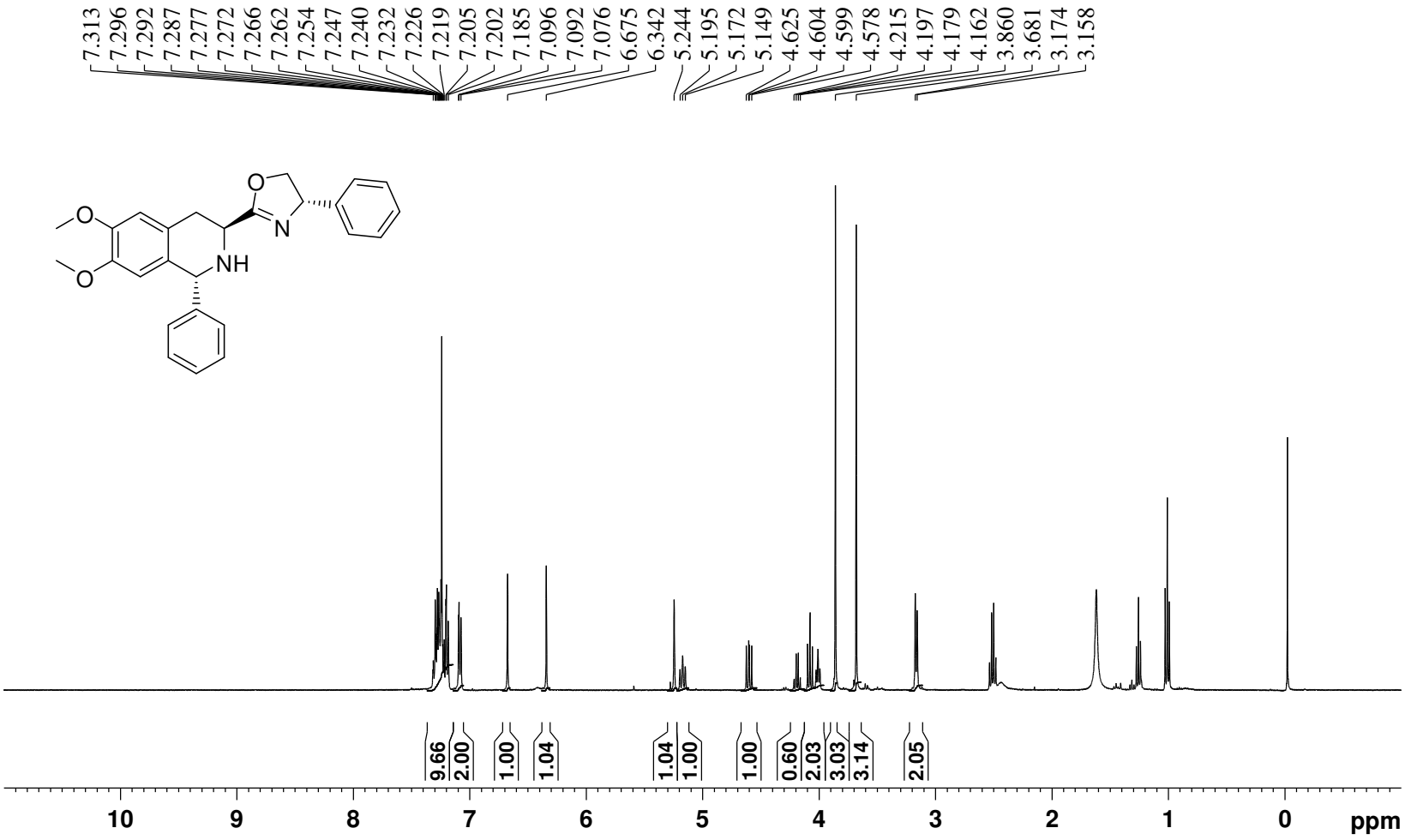
^{1}H NMR (400 MHz) Spectrum of Compound **3a** in $CDCl_3$



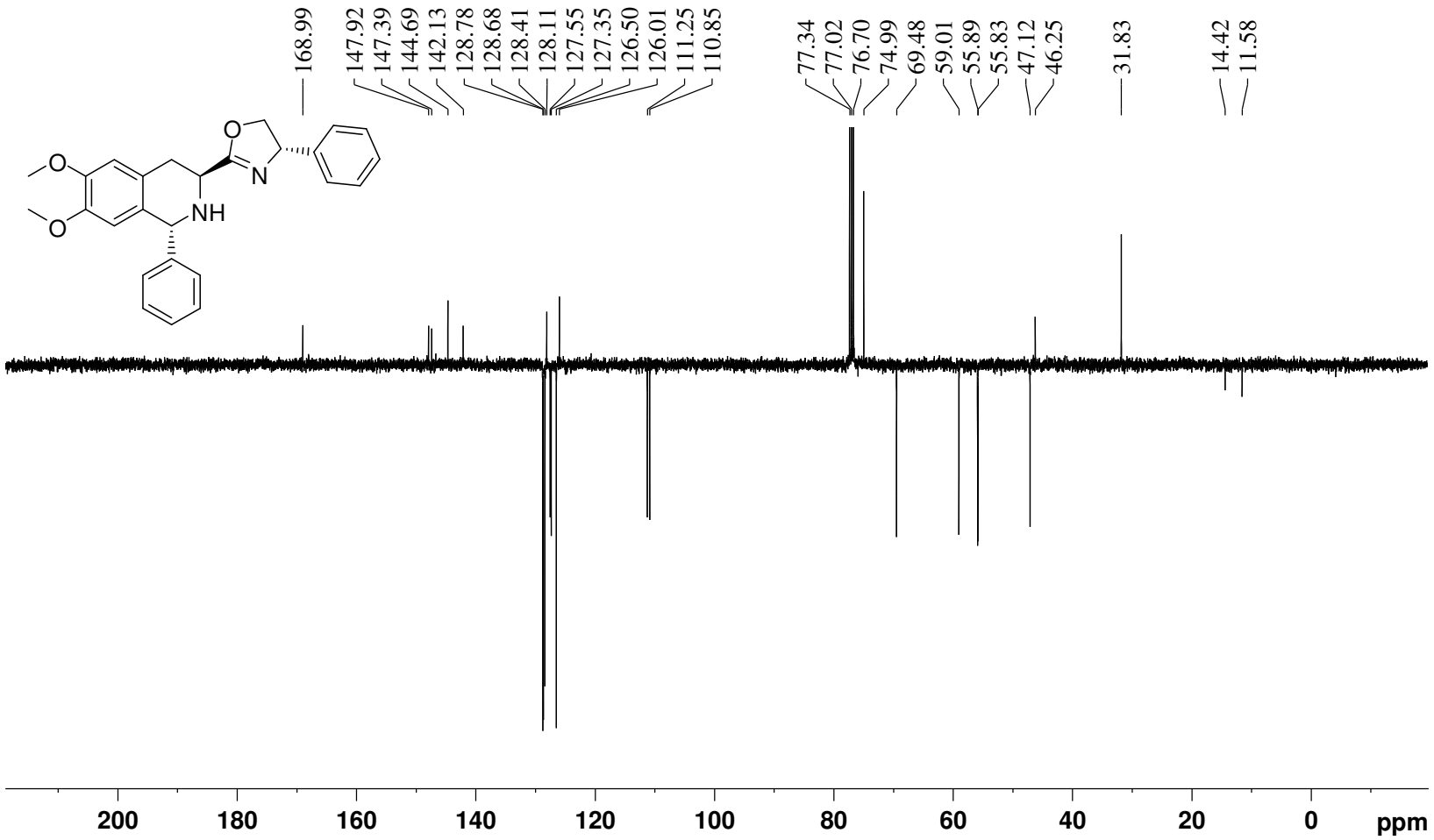
^{13}C (400 MHz) Spectrum of Compound **3a** in $CDCl_3$



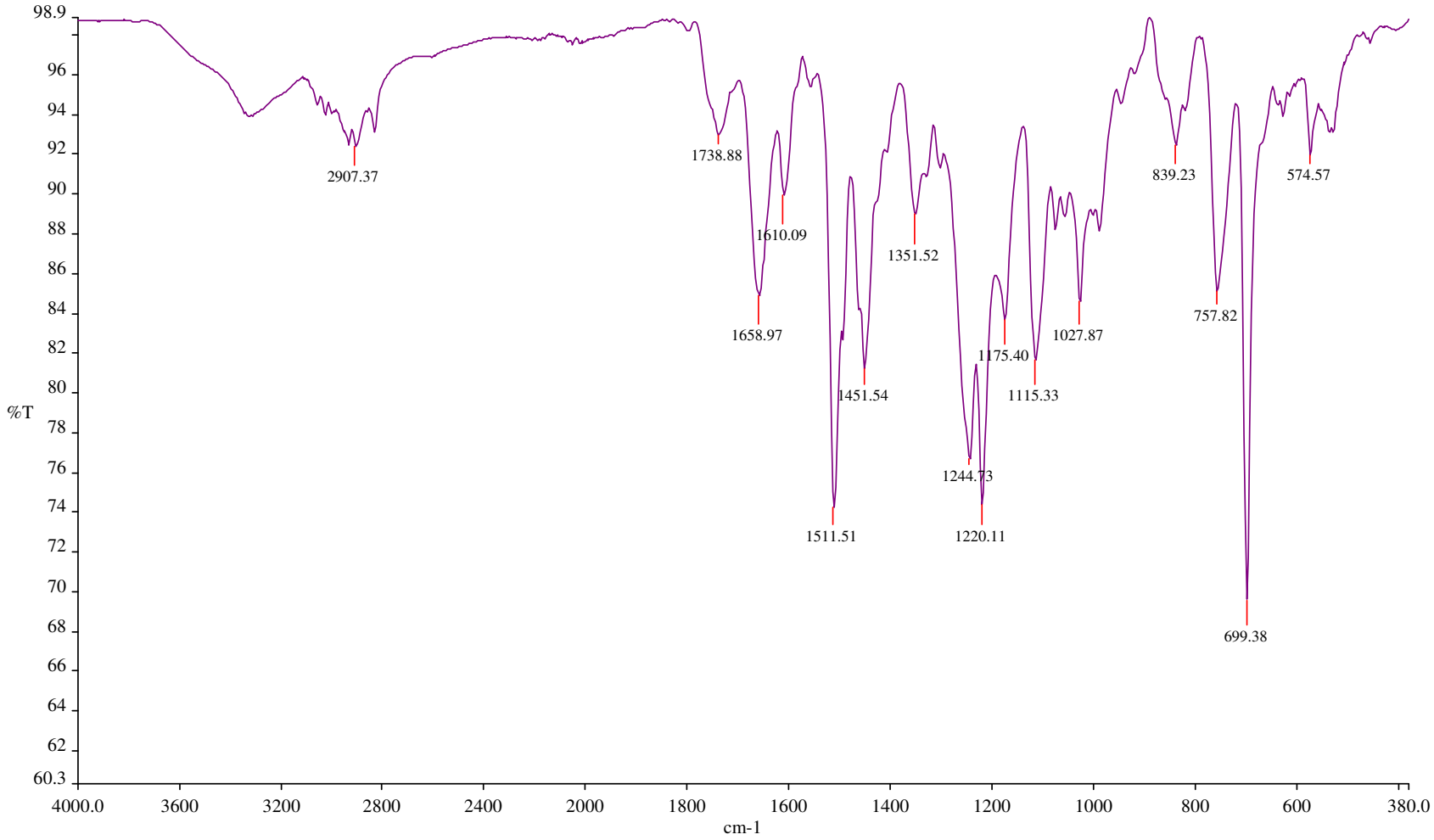
IR Spectrum of Compound **3a**



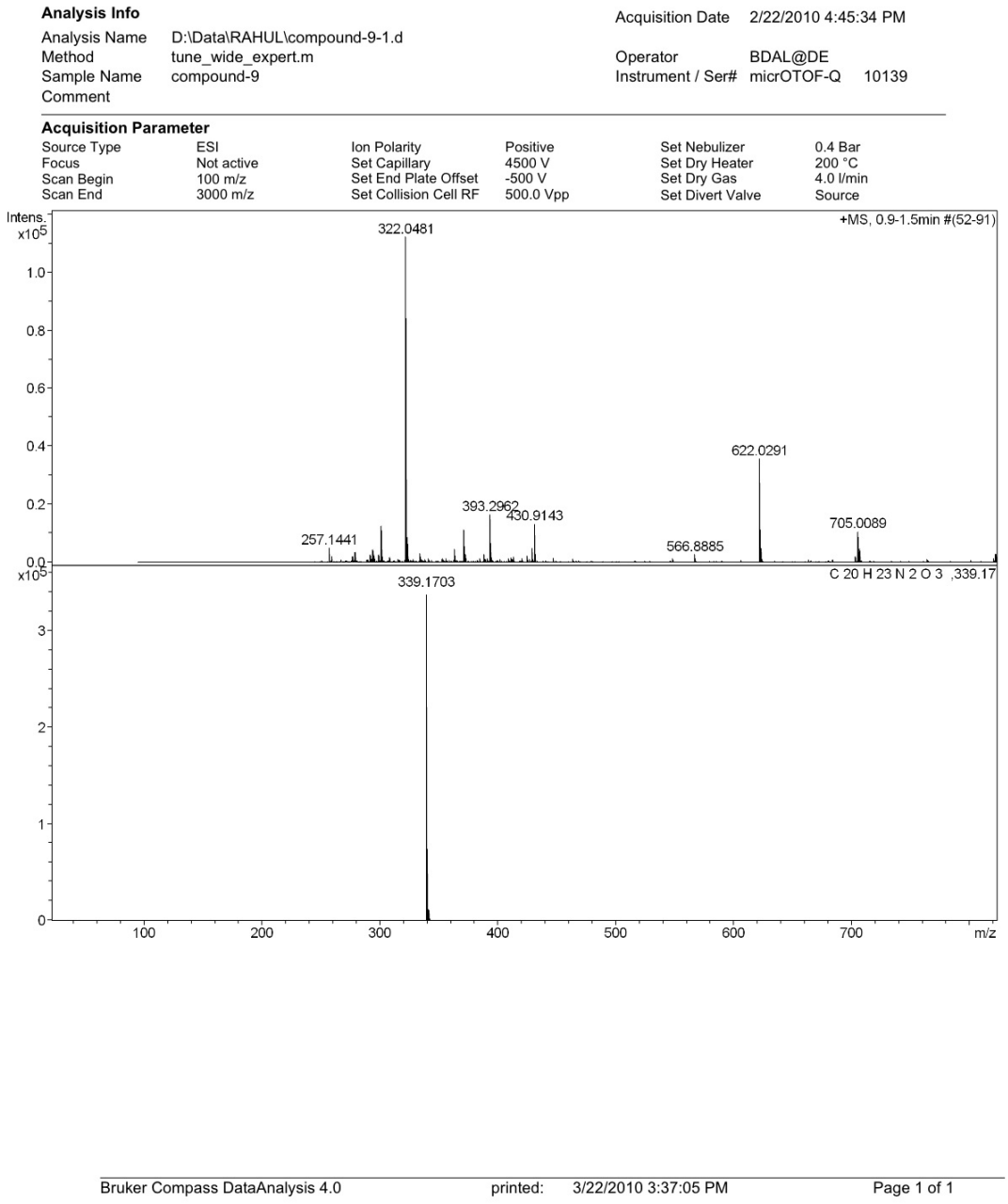
^{1}H NMR (400 MHz) Spectrum of Compound **3b** in $CDCl_3$



^{13}C (400 MHz) Spectrum of Compound **3b** in $CDCl_3$



IR Spectrum of Compound **3b**



High Resolution Mass Spectrum of Compound **1**

Analysis Info

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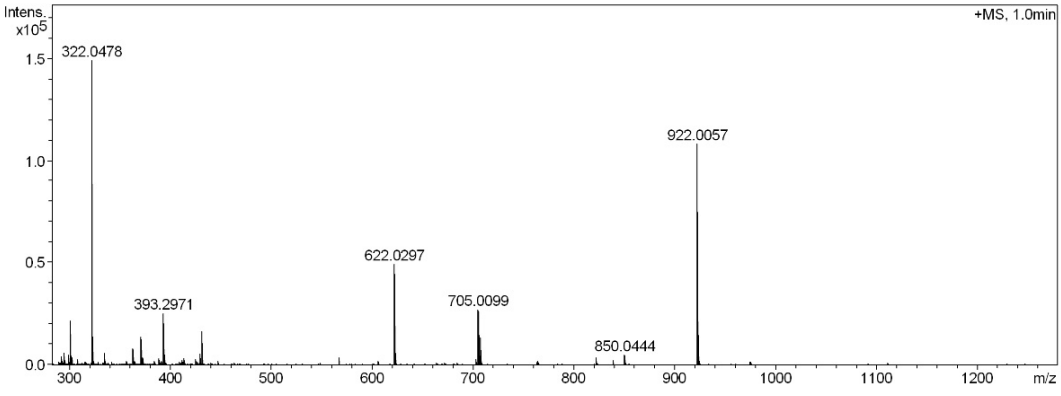
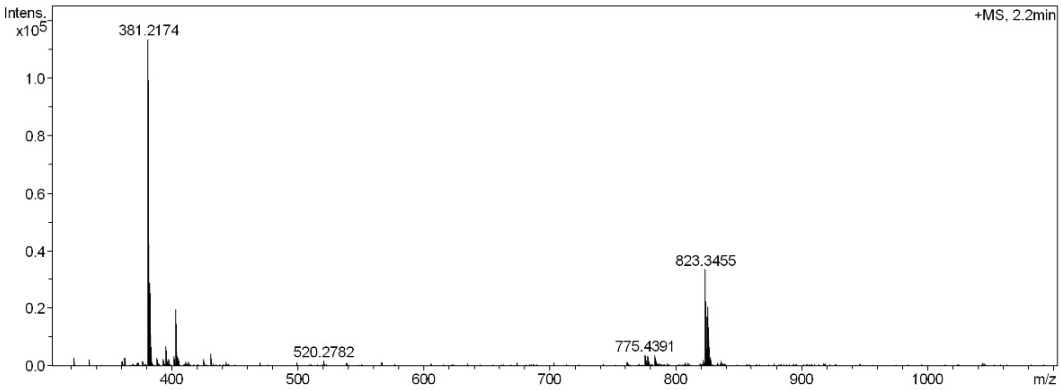
Method	tune_wide_expert.m	Operator	BDAL@DE
Sample Name	compound-2a-2	Instrument / Ser#	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source





Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev

High Resolution Mass Spectrum of Compound **2a**

Analysis Info

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Method	tune_wide_expert.m	Operator	BDAL@DE
Sample Name	compound-2b-2	Instrument / Ser#	micrOTOF-Q 10139
Comment			

Acquisition Parameter

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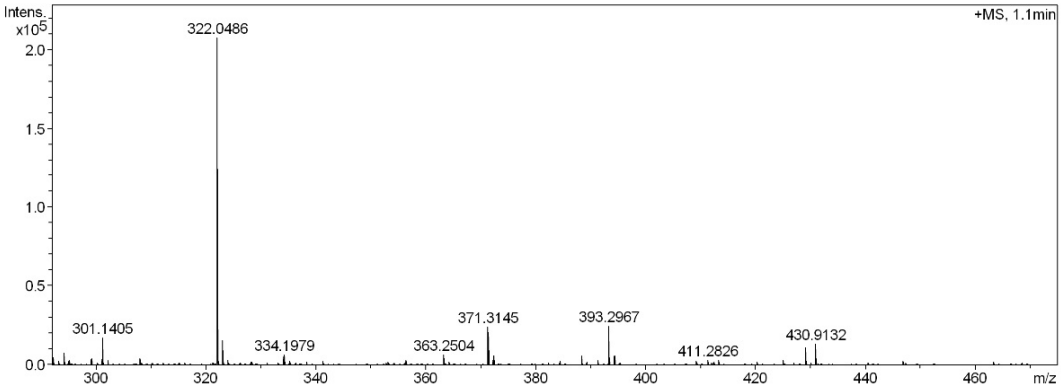
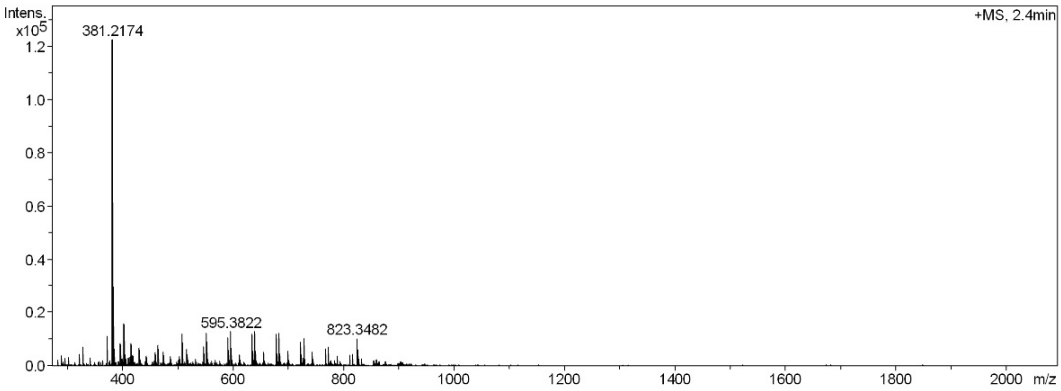
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source





Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev

High Resolution Mass Spectrum of Compound **2b**

Display Report

Analysis Info

Analysis Name	D:\Data\RAHUL\compound-3a-1.d	Acquisition Date	2/18/2010 9:50:05 AM
Method	tune_low_expert.m	Operator	BDAL@DE
Sample Name	compound-3a	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
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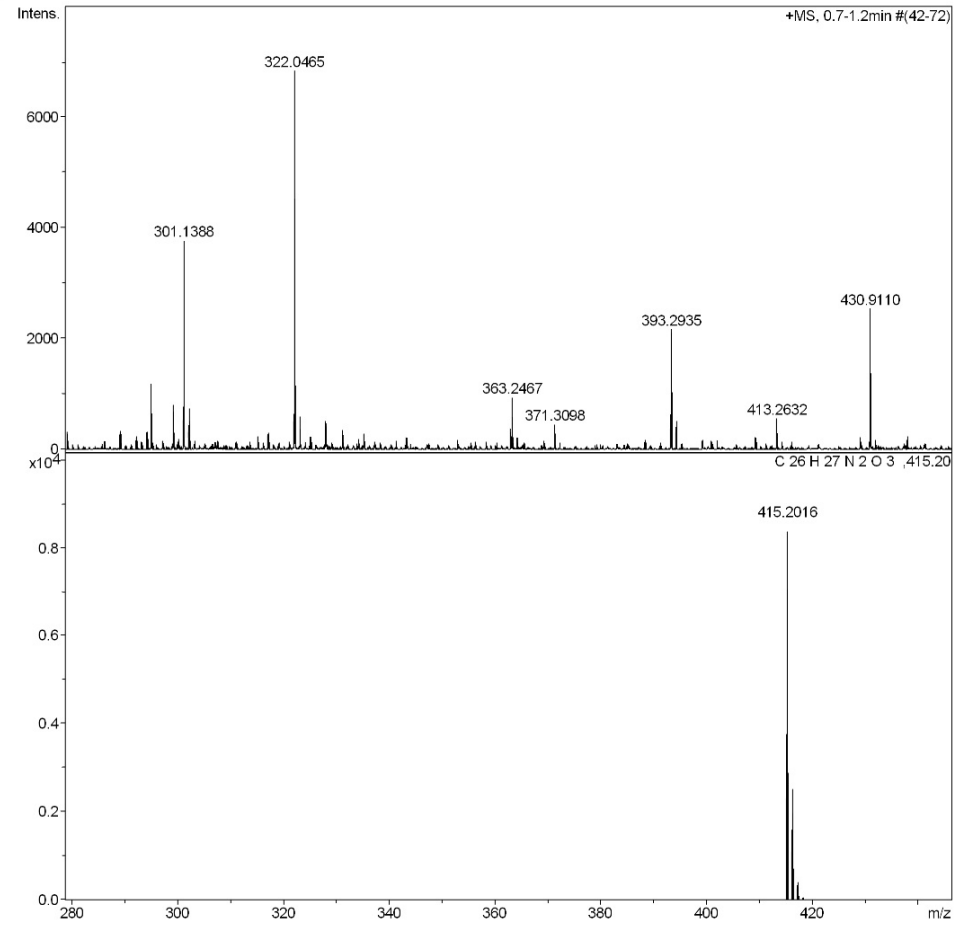
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 2/18/2010 9:55:48 AM Page 1 of 1

High Resolution Mass Spectrum of Compound **3a**

Display Report

Analysis Info

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Method	tune_low_expert.m	Operator	BDAL@DE
Sample Name	compound-3a	Instrument	micrOTOF-Q 10139
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
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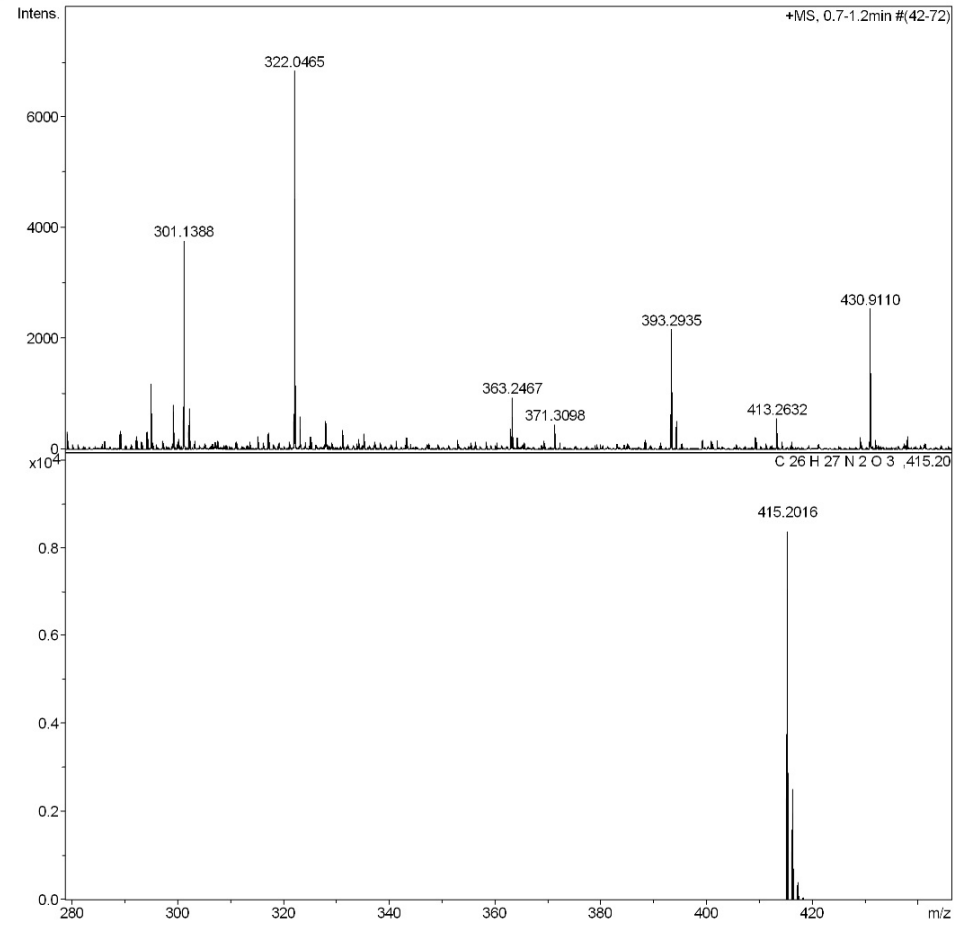
Scan Begin	110 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	120.0 Vpp	Set Divert Valve	Source



Bruker Compass DataAnalysis 4.0 printed: 2/18/2010 9:55:48 AM Page 1 of 1

High Resolution Mass Spectrum of Compound **3b**

APPENDIX 5

ASYMMETRIC CONJUGATE ADDITION OF THIOGLYCOLATE TO CHALCONE USING TETRAHYDROISOQUINOLINE (TIQ) *N,N′*-DIOXIDE LIGANDS

SUPPLAMENTARY INFORMATION FOR CHAPTER 6

Sai Kumar Chakka,[a] Vivian Francis,[a] Pher G. Andersson,[a,c] Hendrik G. Kruger,[a*] Glenn E. M. Maguire[a] and Thavendran Govender[b*]

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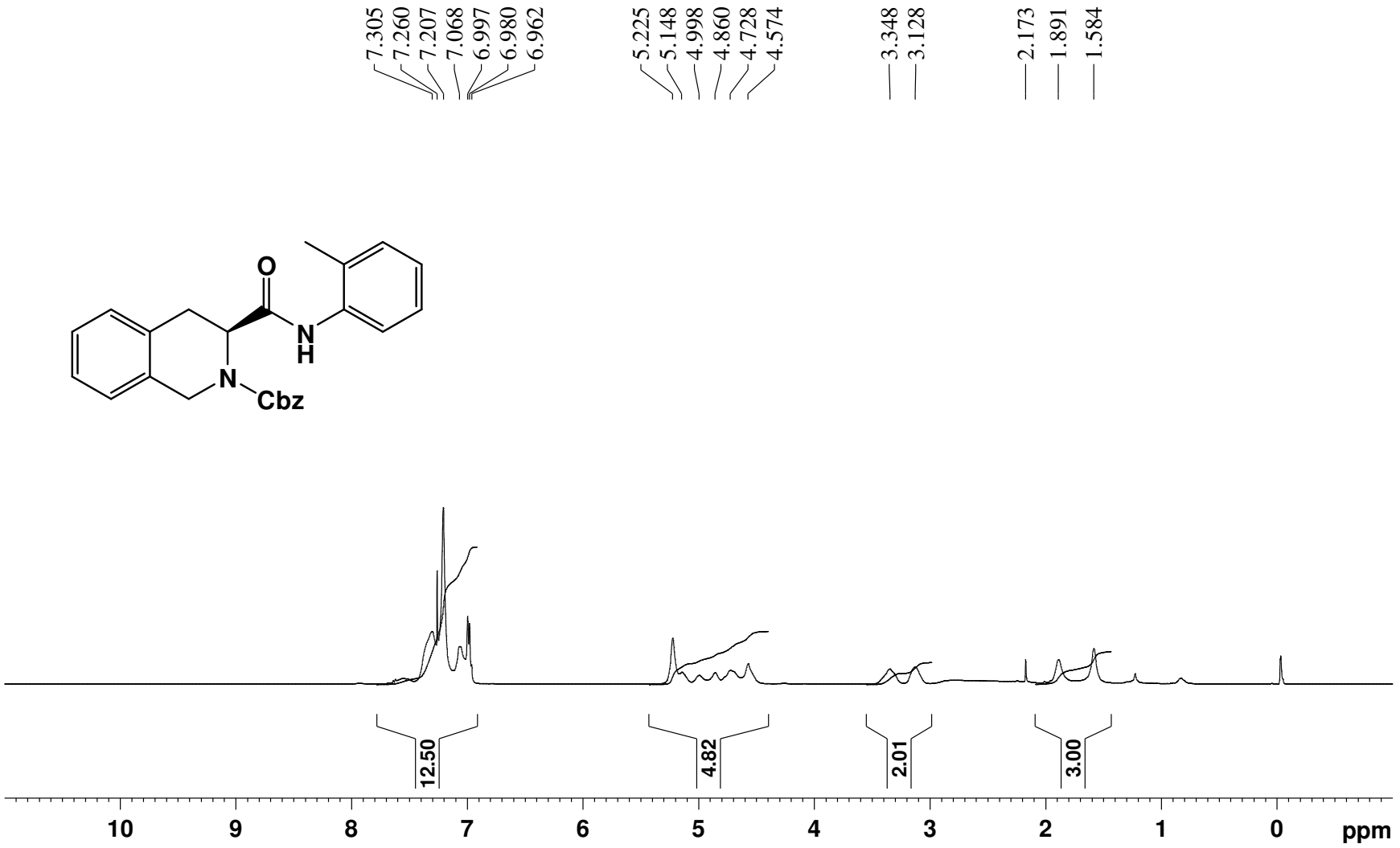
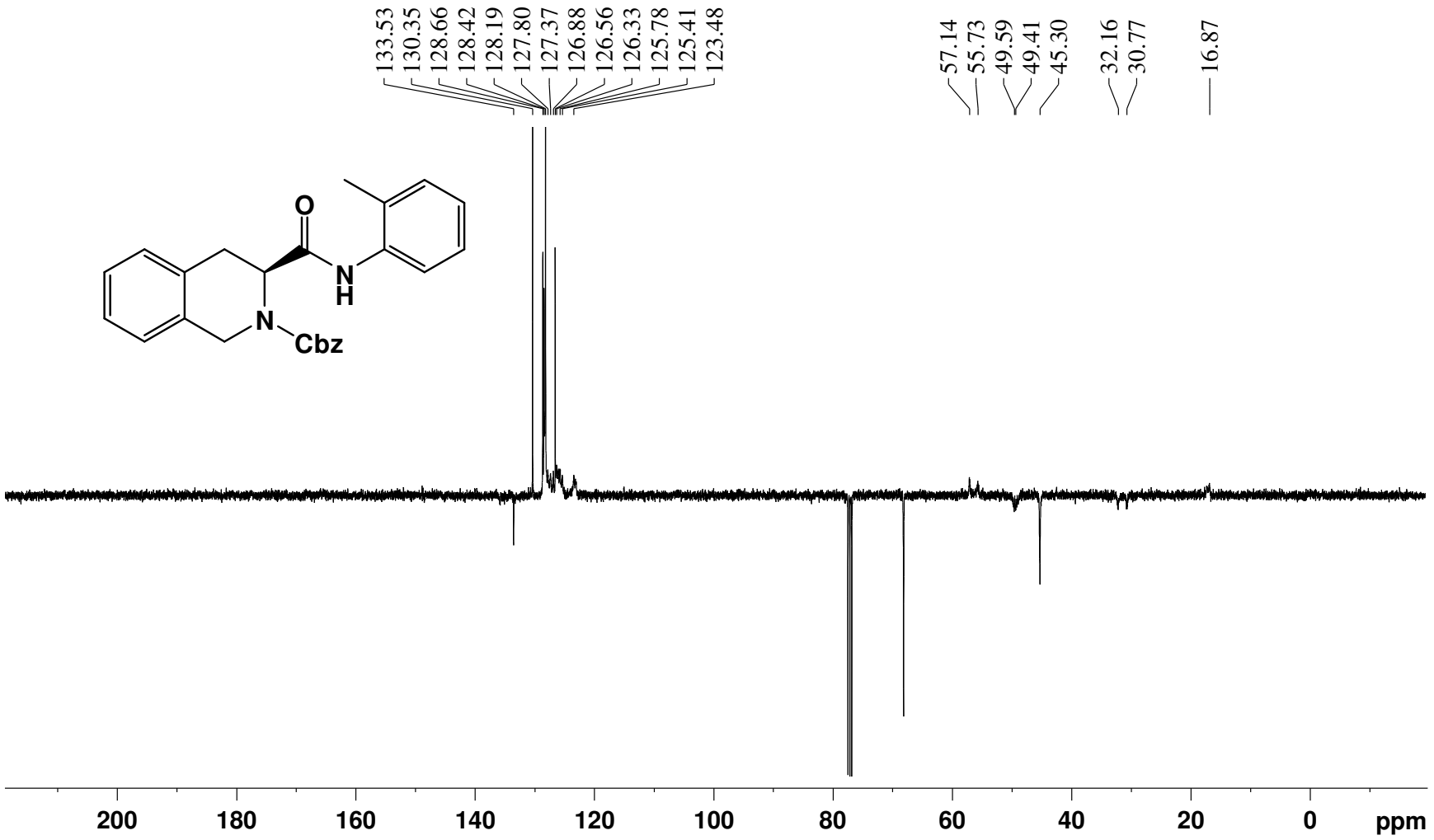
[b]School of Pharmacy and Pharmacology, University of KwaZulu-Natal, Durban, South Africa.[c]Department of Biochemistry and Organic chemistry, Uppsala University, Uppsala, Sweden.

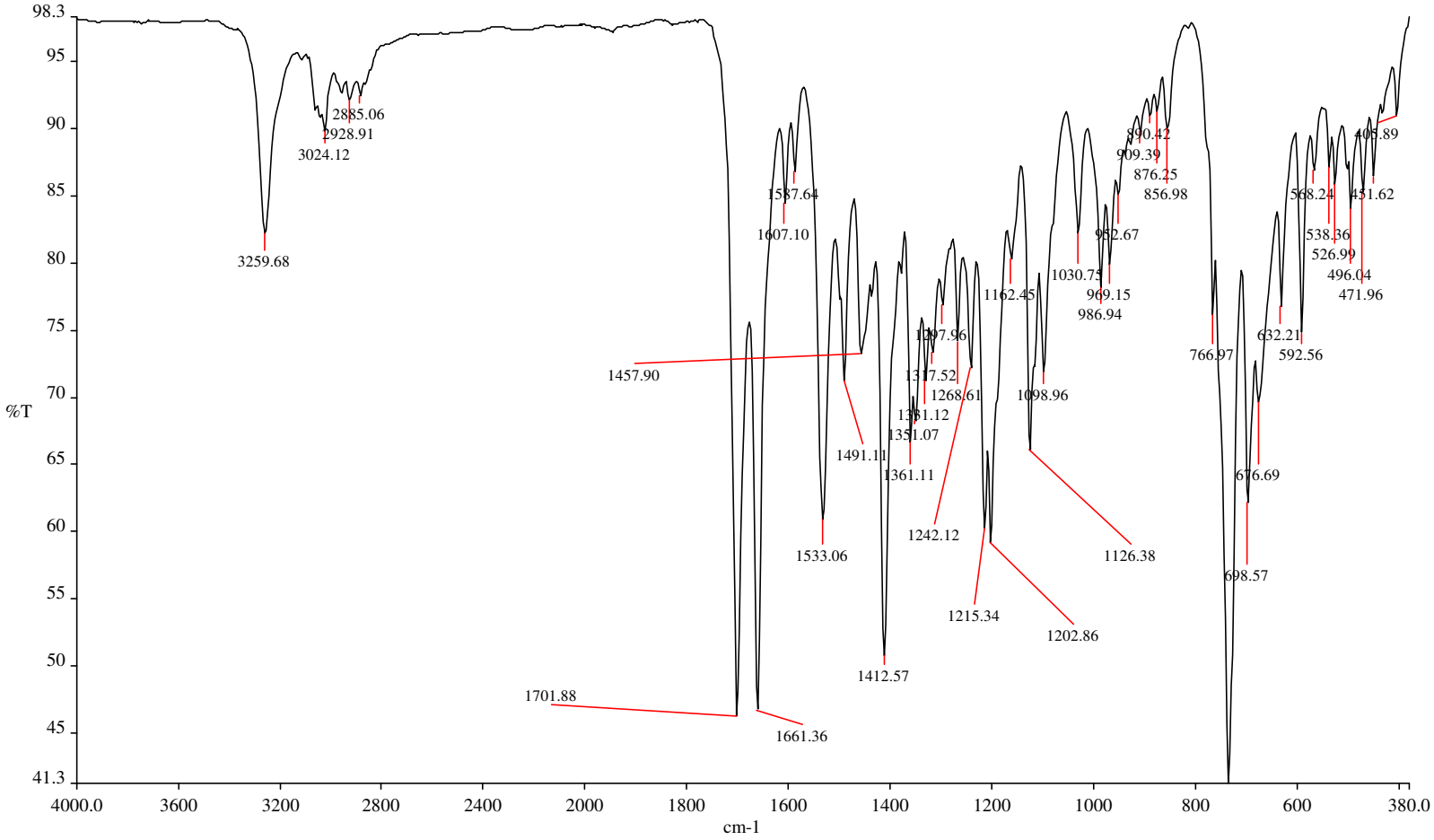
[*]Corresponding Author: email: govenderthav@ukzn.ac.za



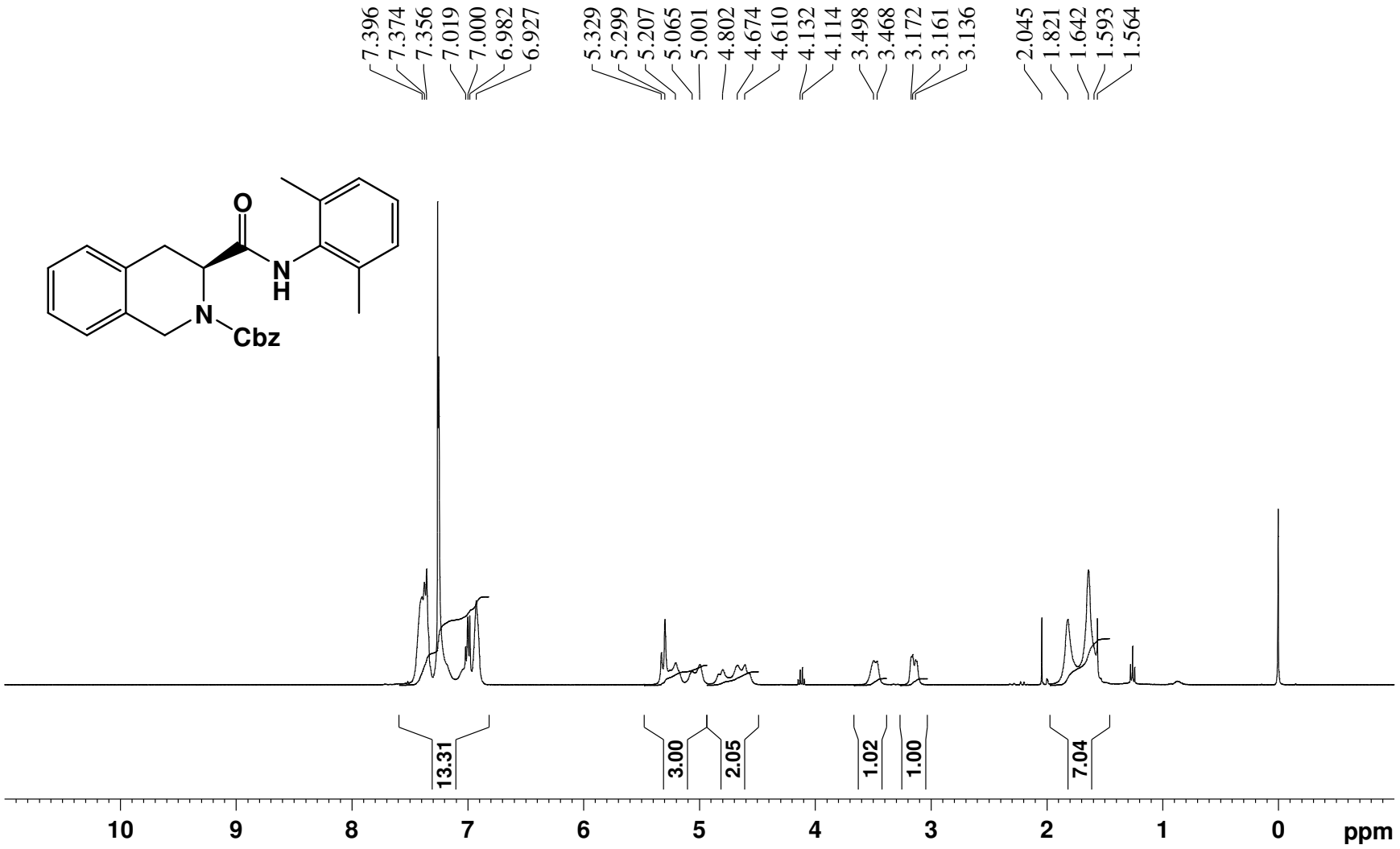
^{1}H NMR (400 MHz) Spectrum of Compound **6** in $CDCl_3$



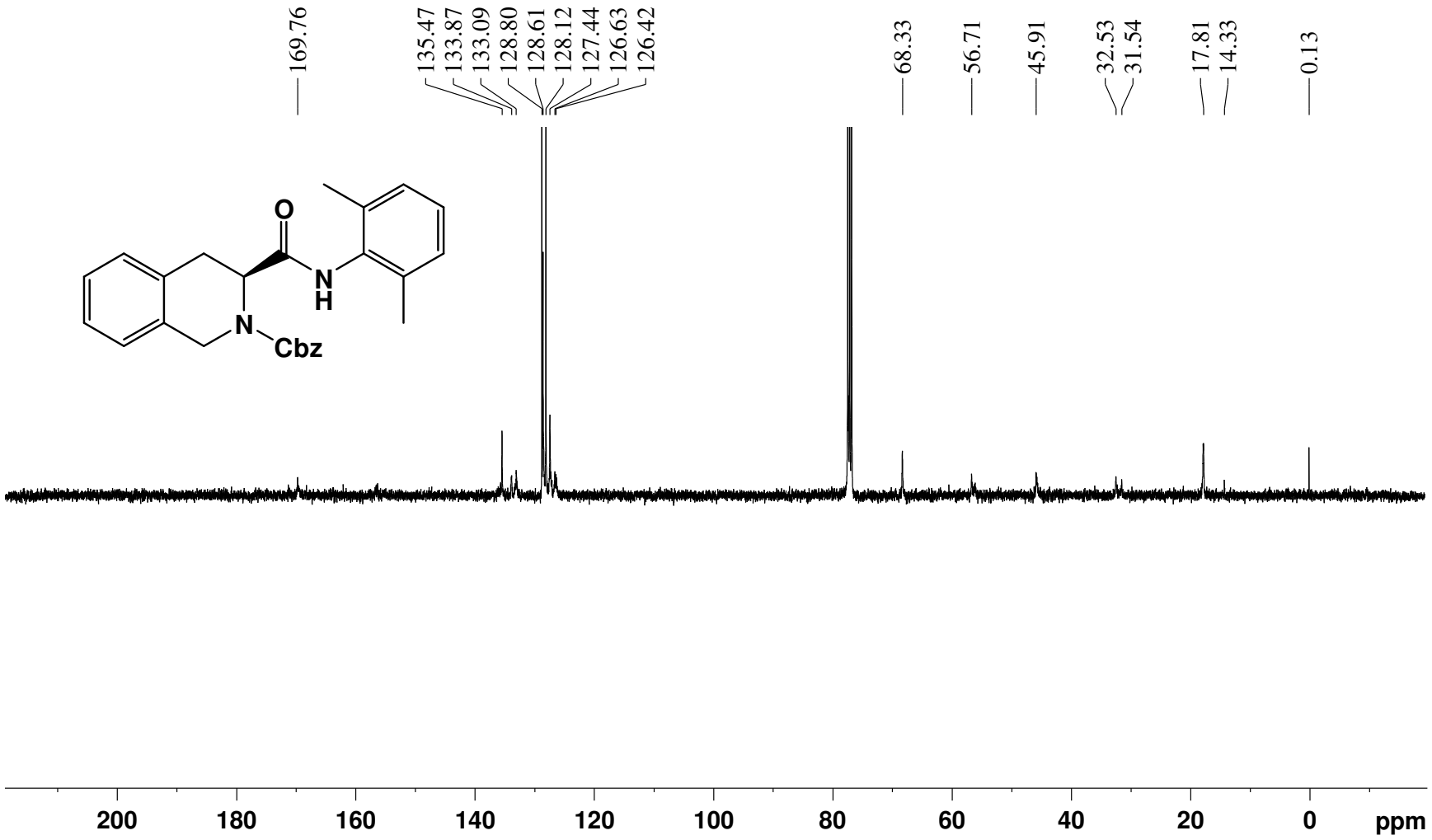
^{13}C (400 MHz) Spectrum of Compound **6** in $CDCl_3$



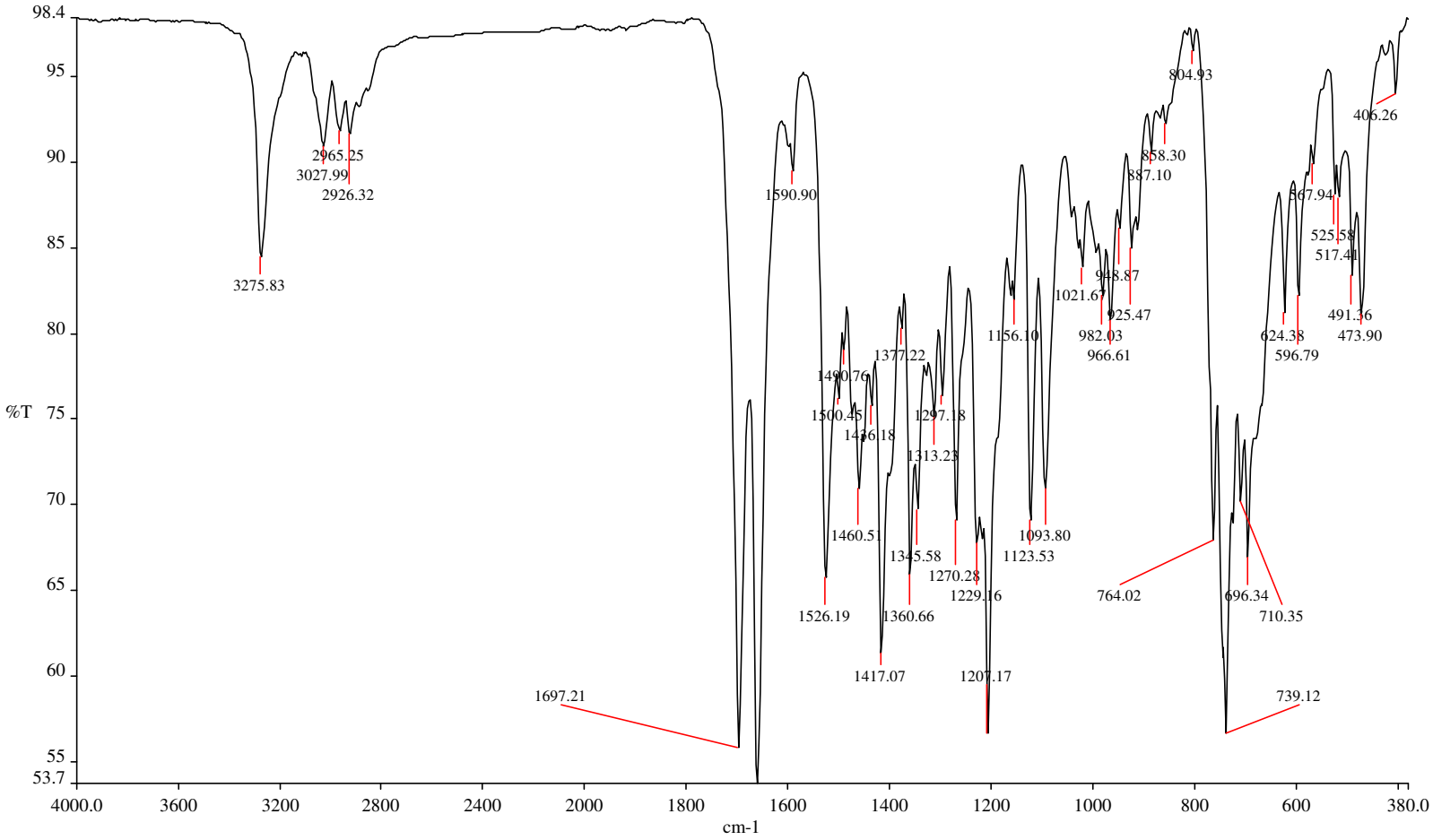
IR Spectrum of Compound **6**



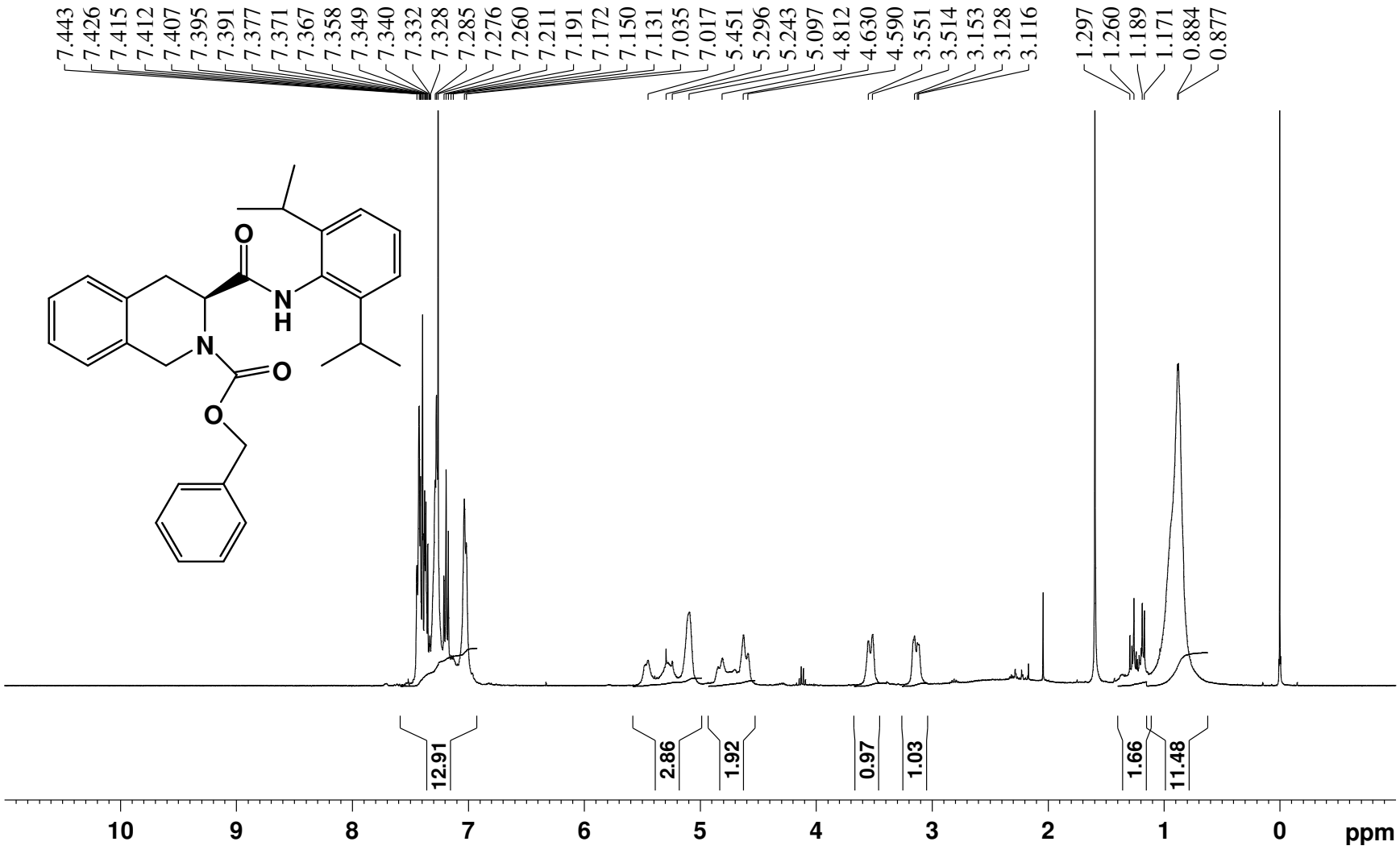
^{1}H NMR (400 MHz) Spectrum of Compound **7** in $CDCl_3$



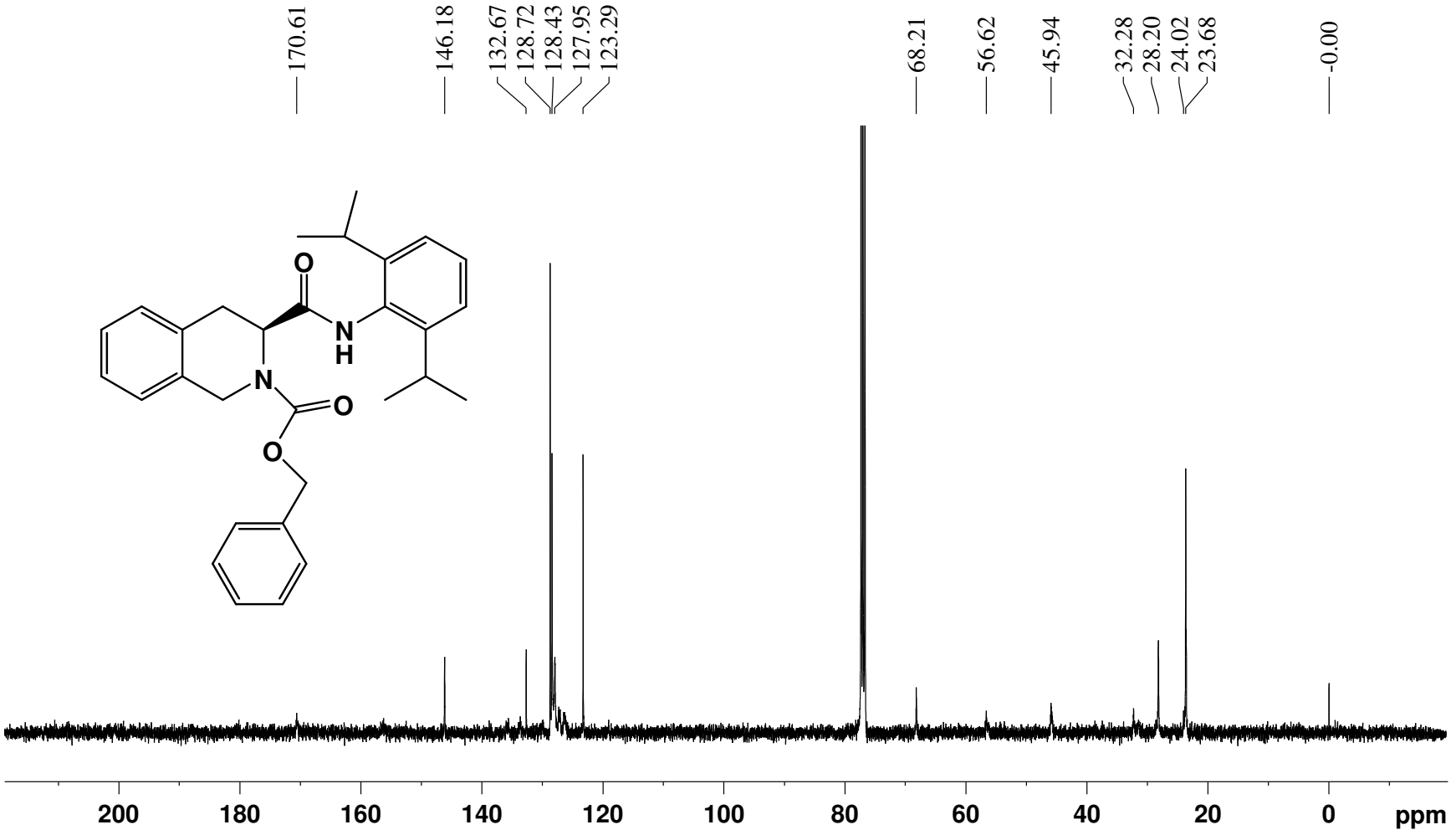
^{13}C (400 MHz) Spectrum of Compound **7** in $CDCl_3$



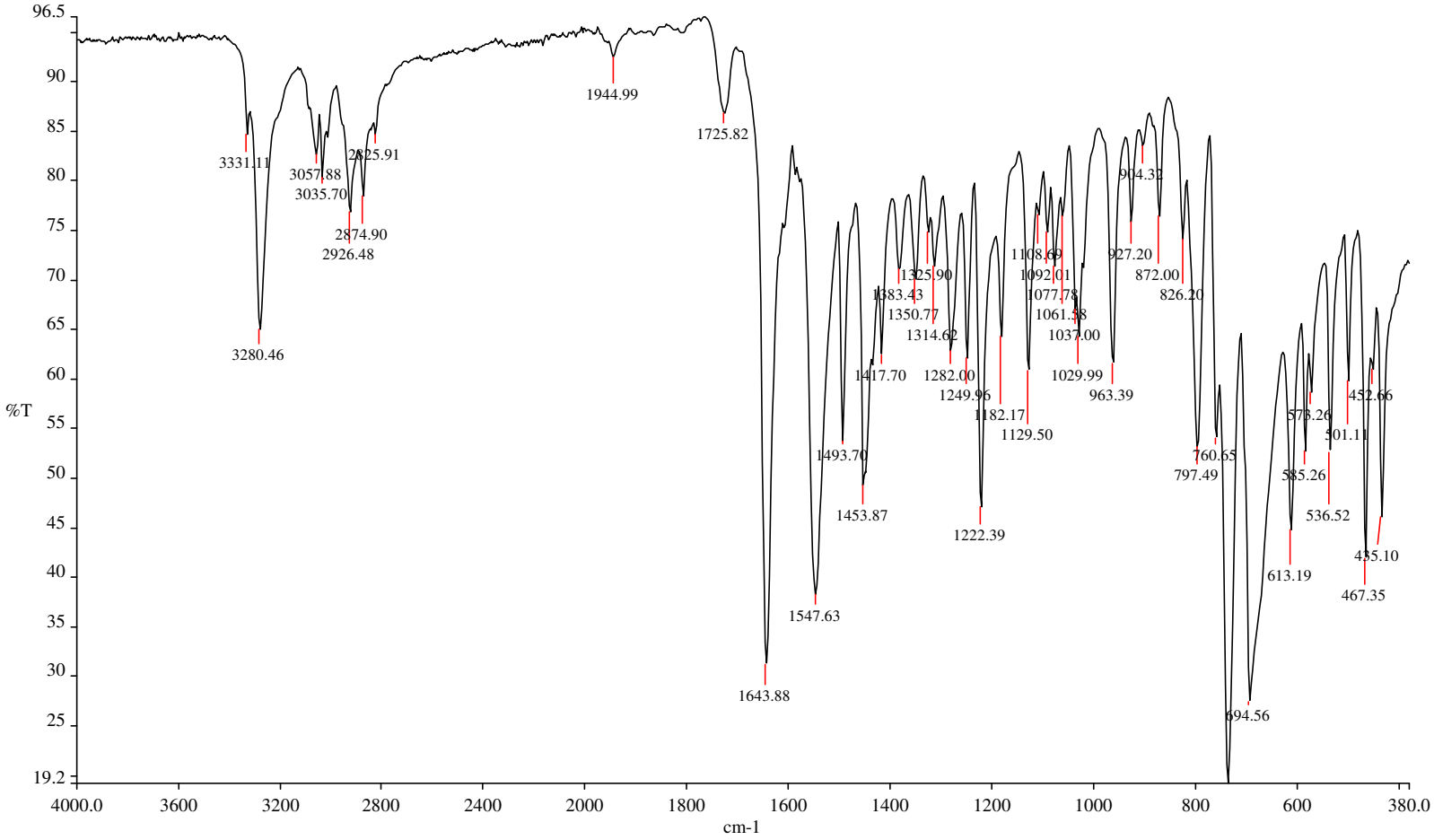
IR Spctrum of Compound **7**



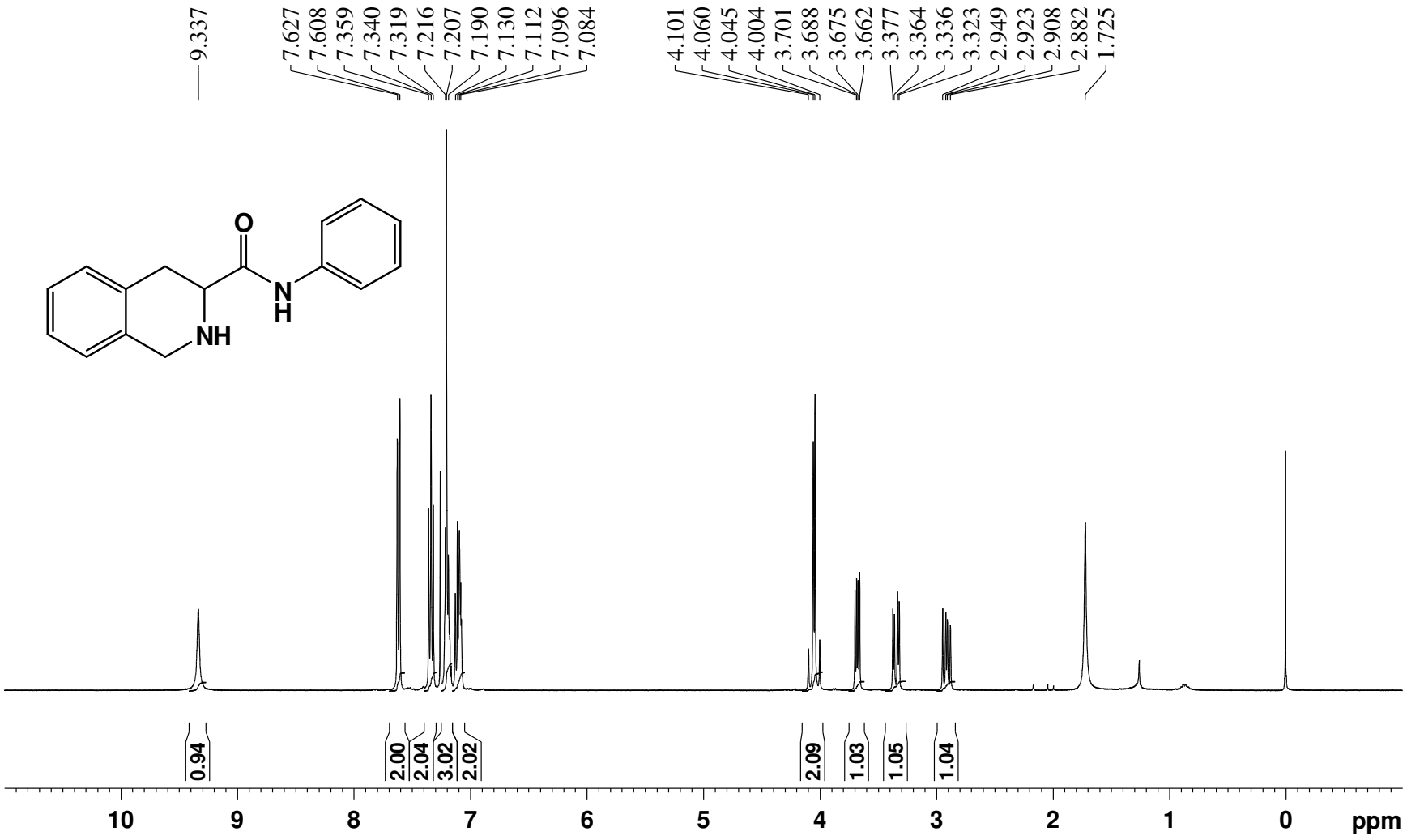
^{1}H NMR (400 MHz) Spectrum of Compound **8** in $CDCl_3$



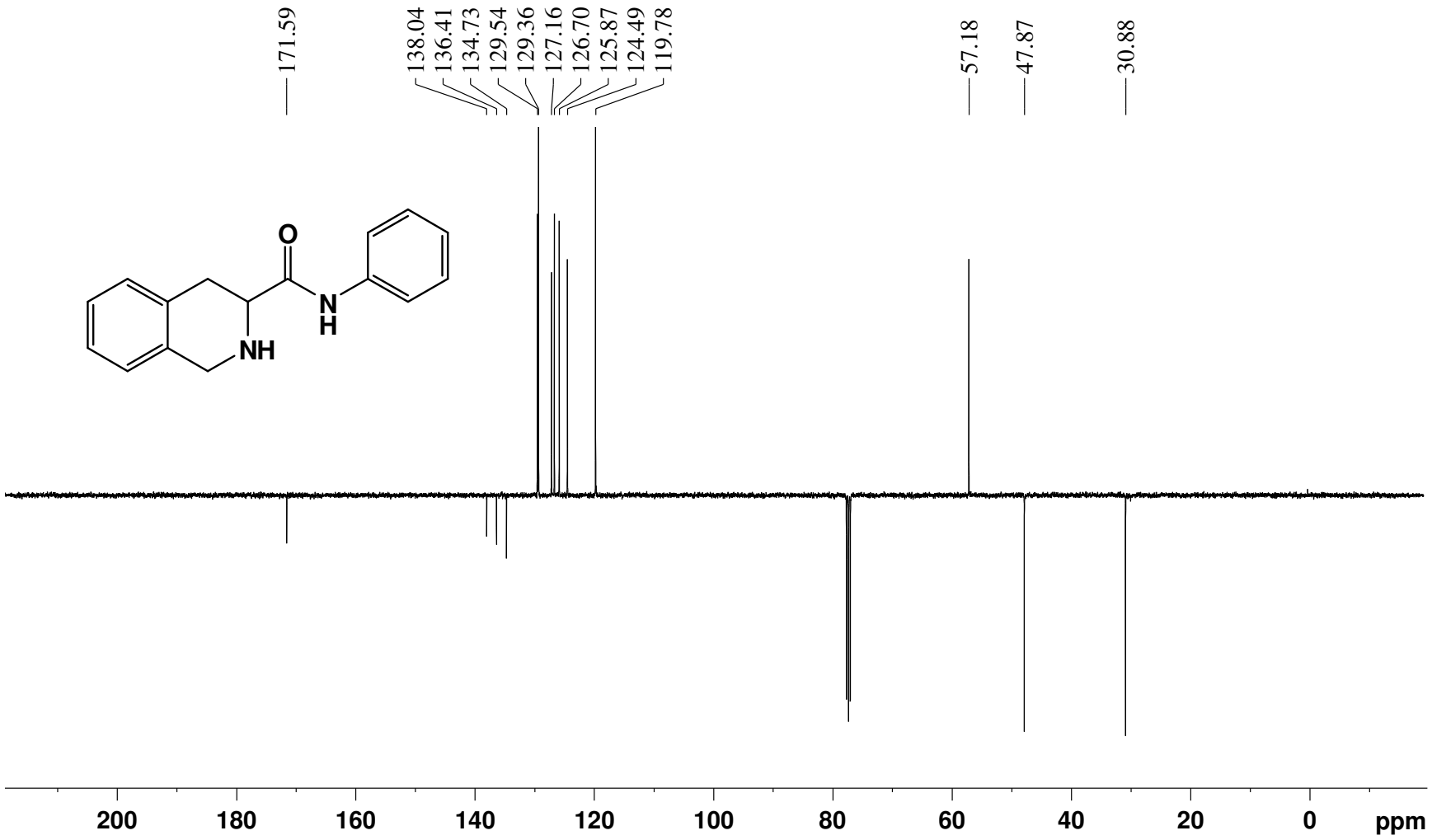
^{13}C (400 MHz) Spectrum of Compound **8** in $CDCl_3$



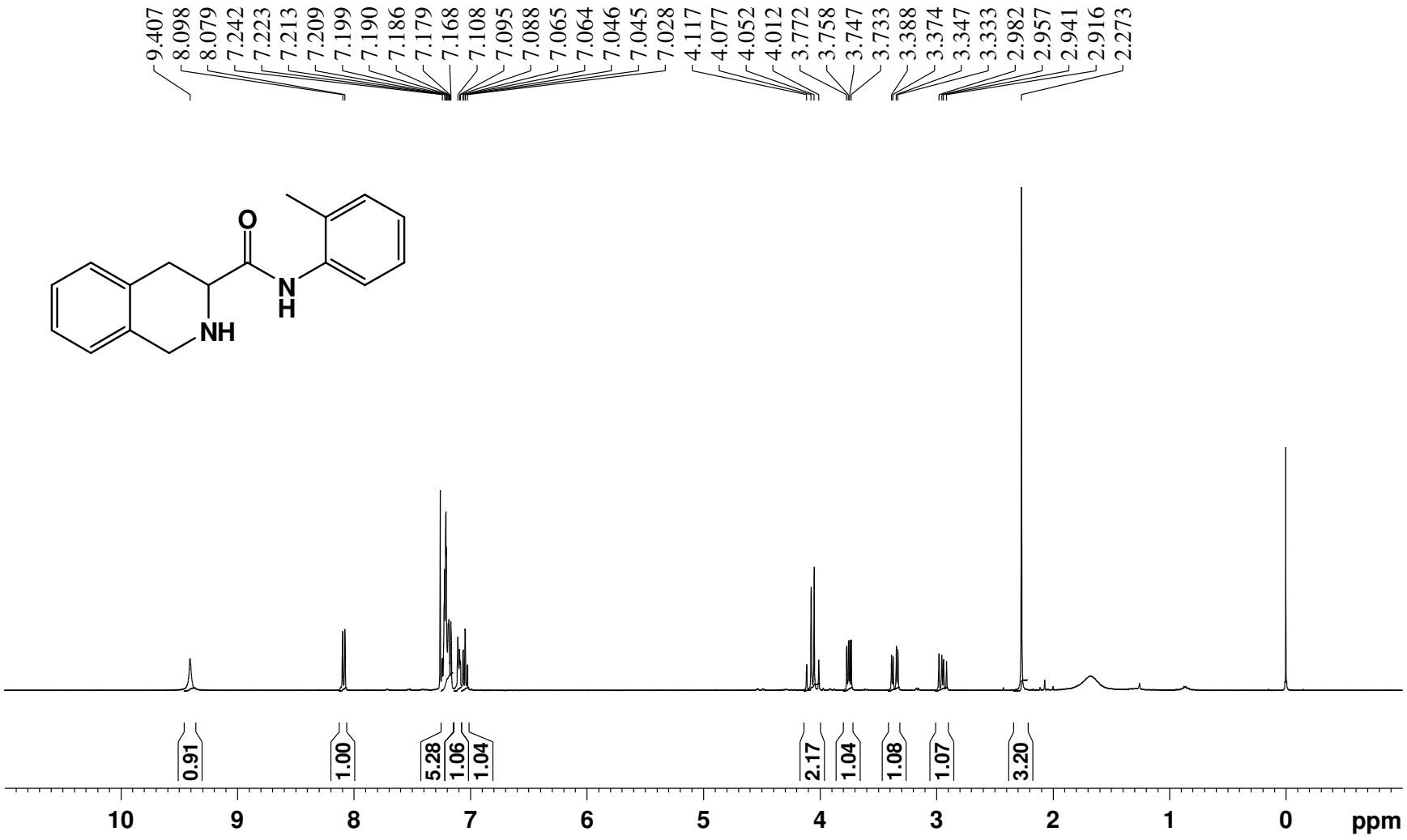
IR Spectrum of Compound **8**



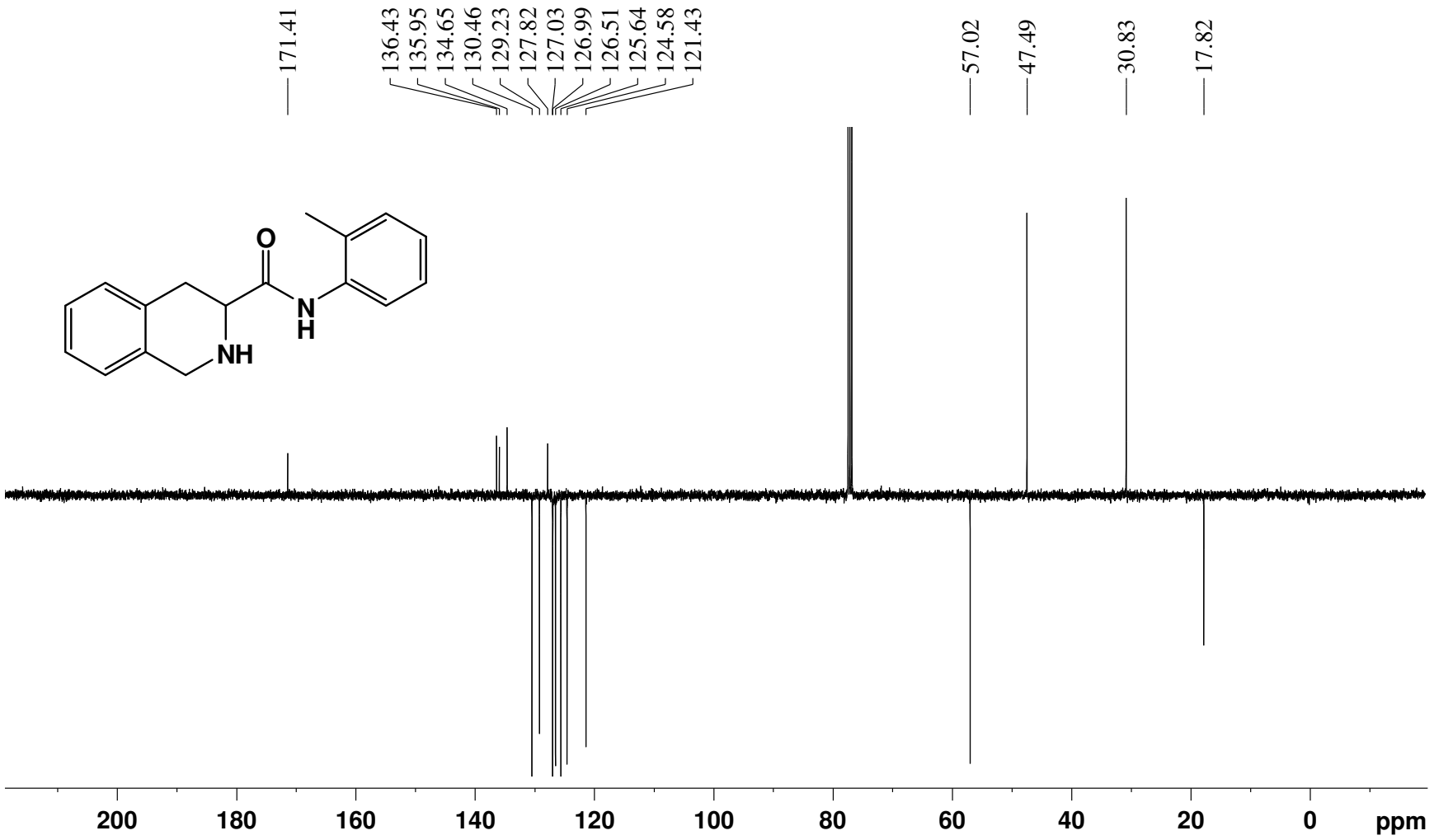
^{1}H NMR (400 MHz) Spectrum of Compound **10** in $CDCl_3$



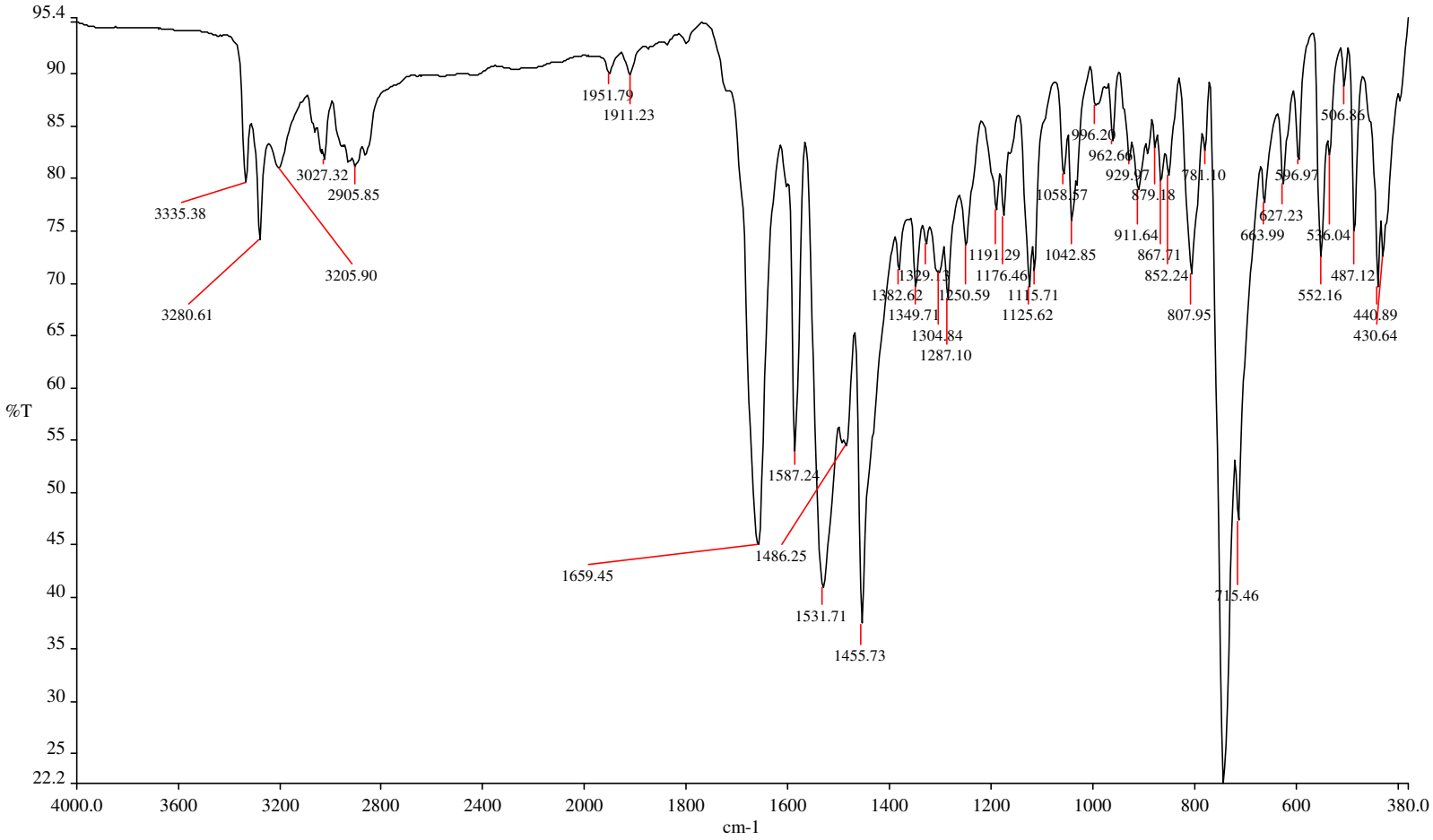
^{13}C (400 MHz) Spectrum of Compound **10** in $CDCl_3$



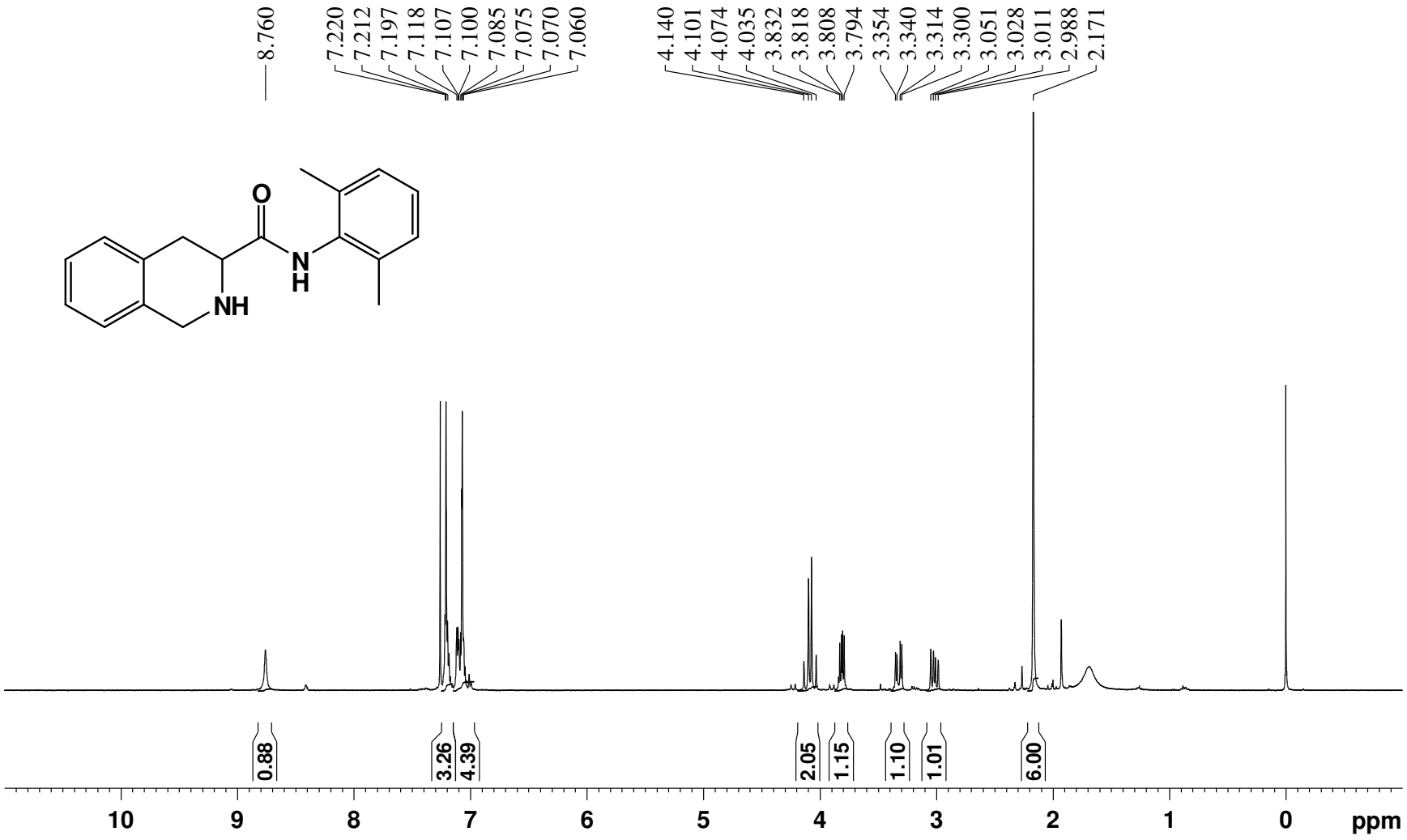
^{1}H NMR (400 MHz) Spectrum of Compound **11** in $CDCl_3$



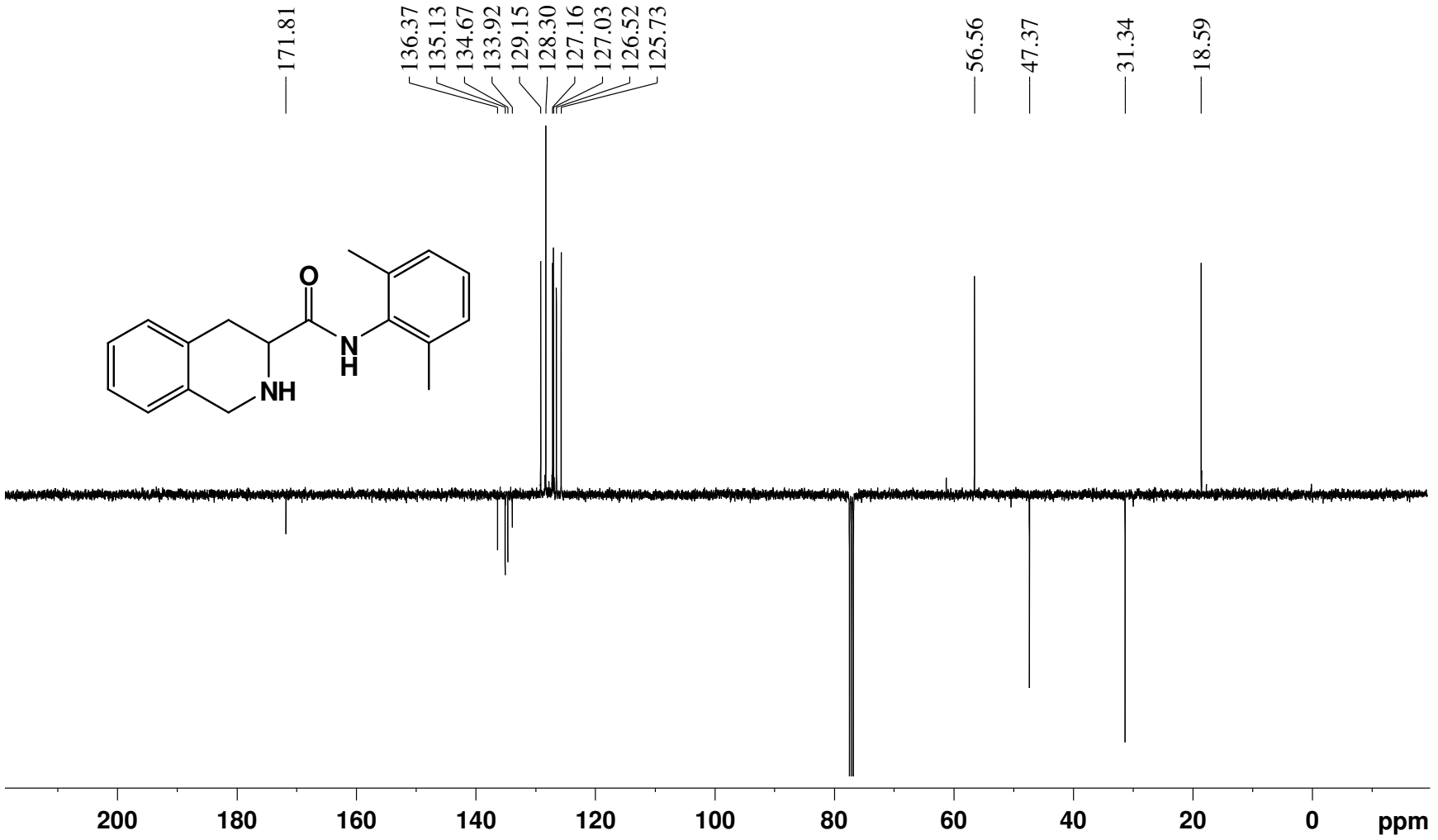
^{13}C (400 MHz) Spectrum of Compound **11** in $CDCl_3$



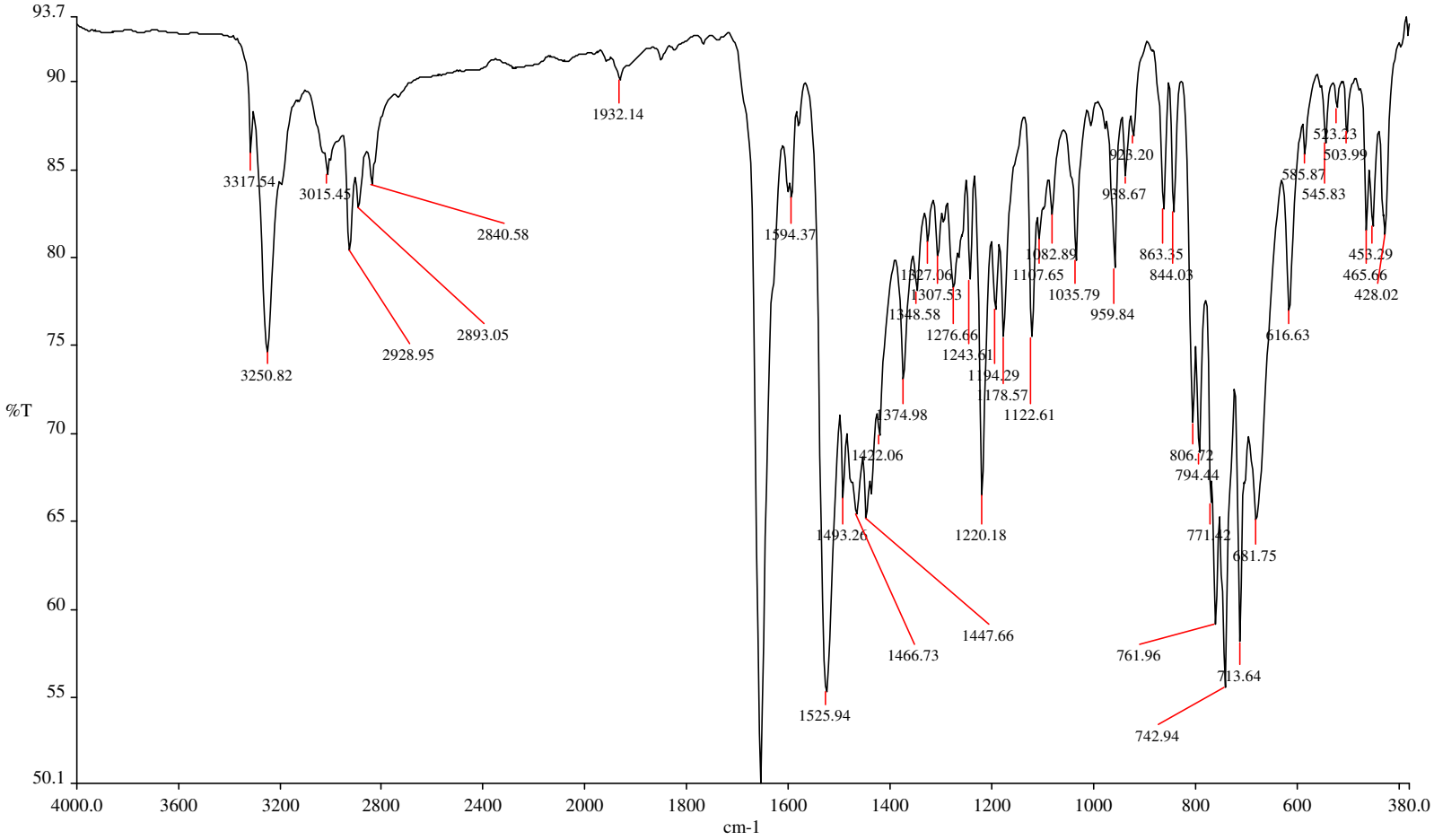
IR Spectrum of Compound **11**



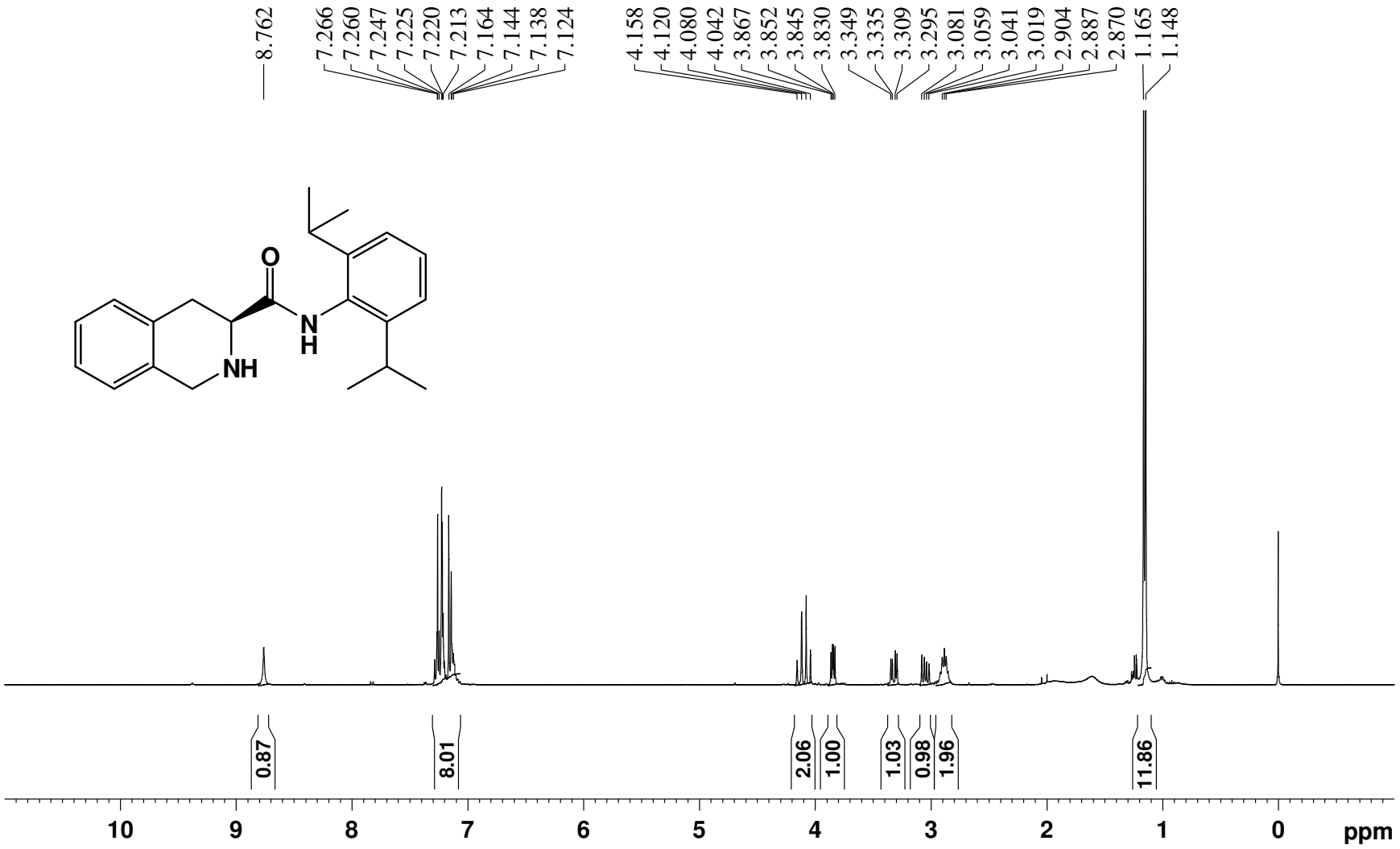
^{1}H NMR (400 MHz) Spectrum of Compound **12** in $CDCl_3$



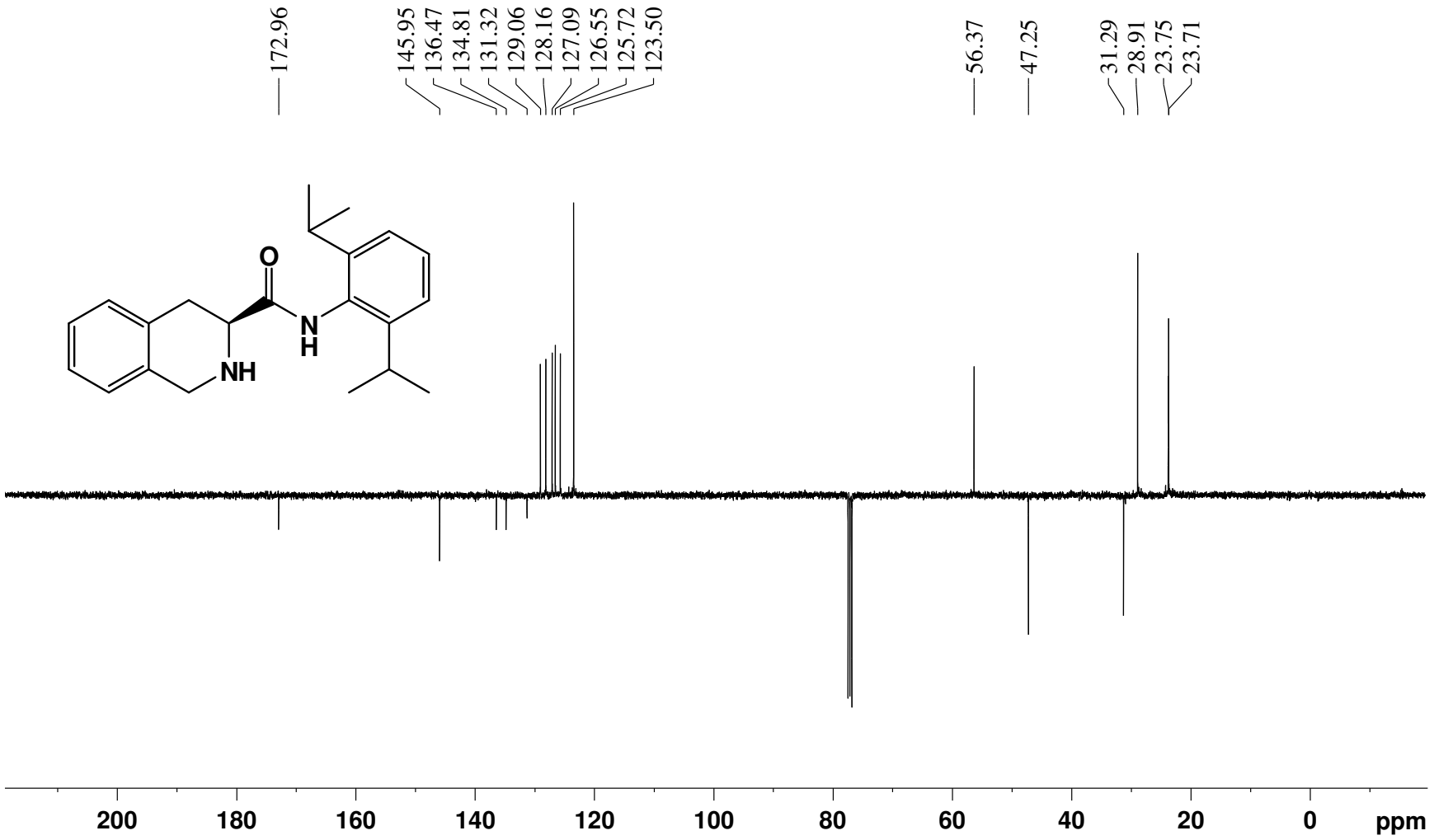
^{13}C (400 MHz) Spectrum of Compound **12** in $CDCl_3$



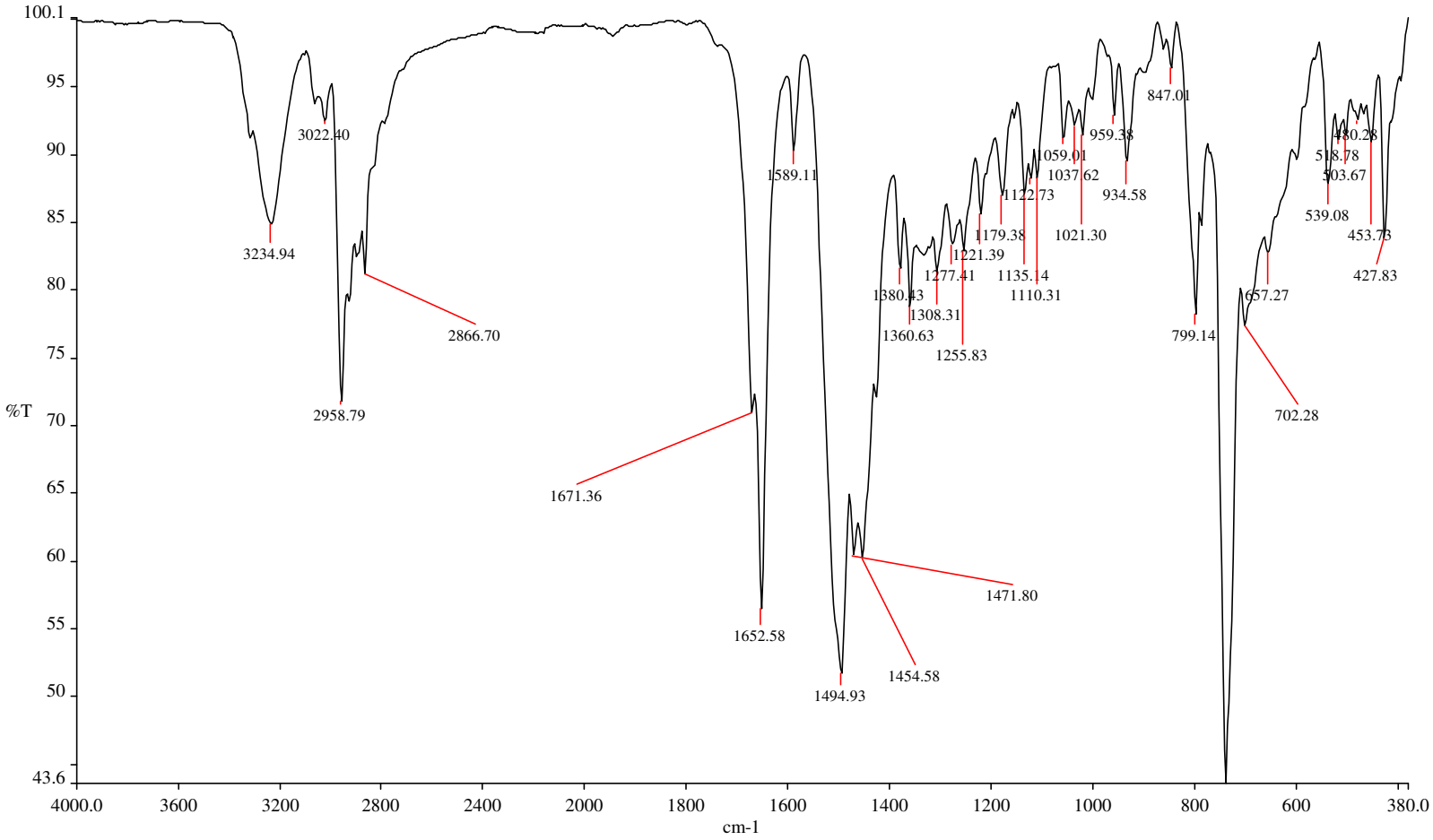
IR Spectrum of Compound **12**



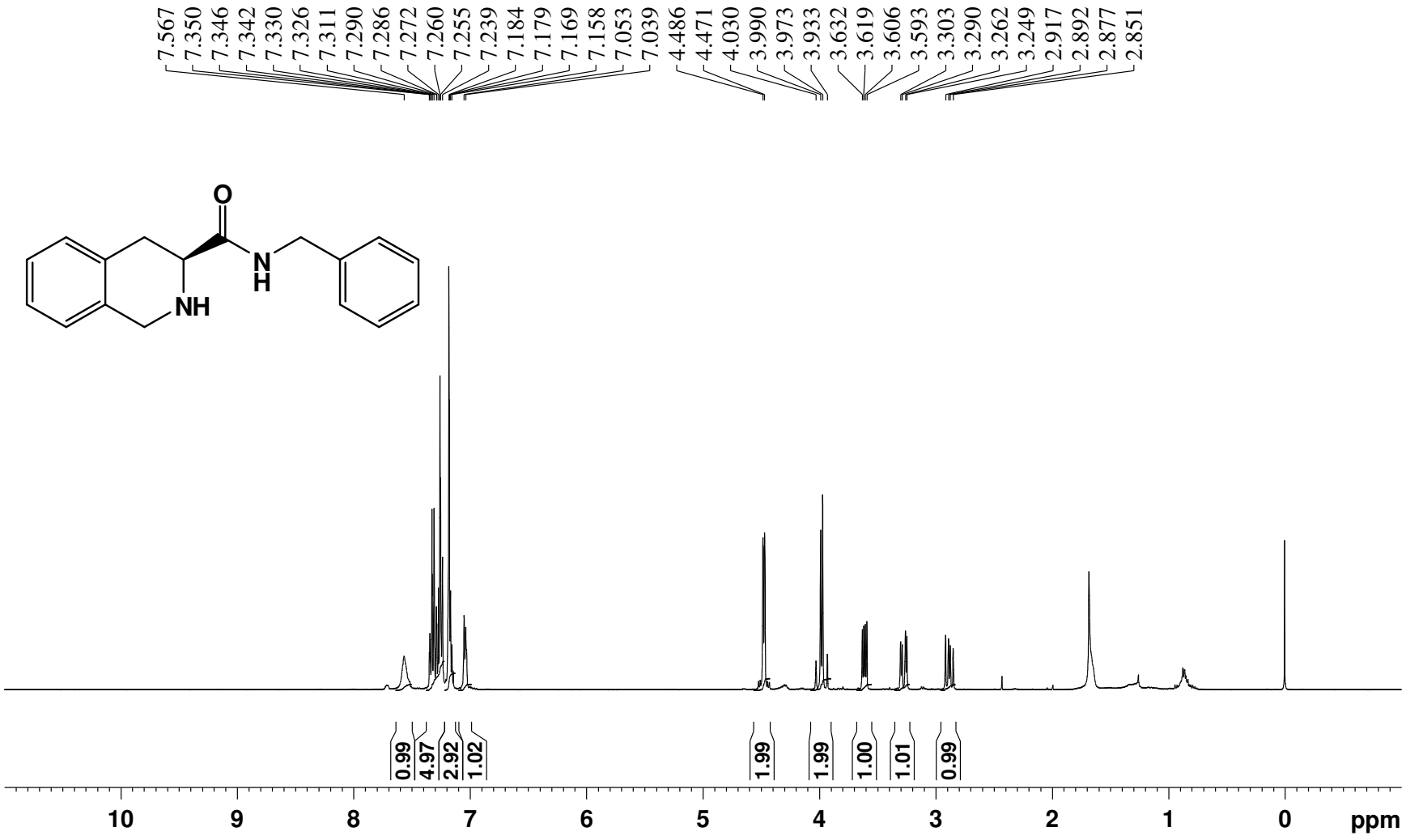
^{1}H NMR (400 MHz) Spectrum of Compound **13** in $CDCl_3$



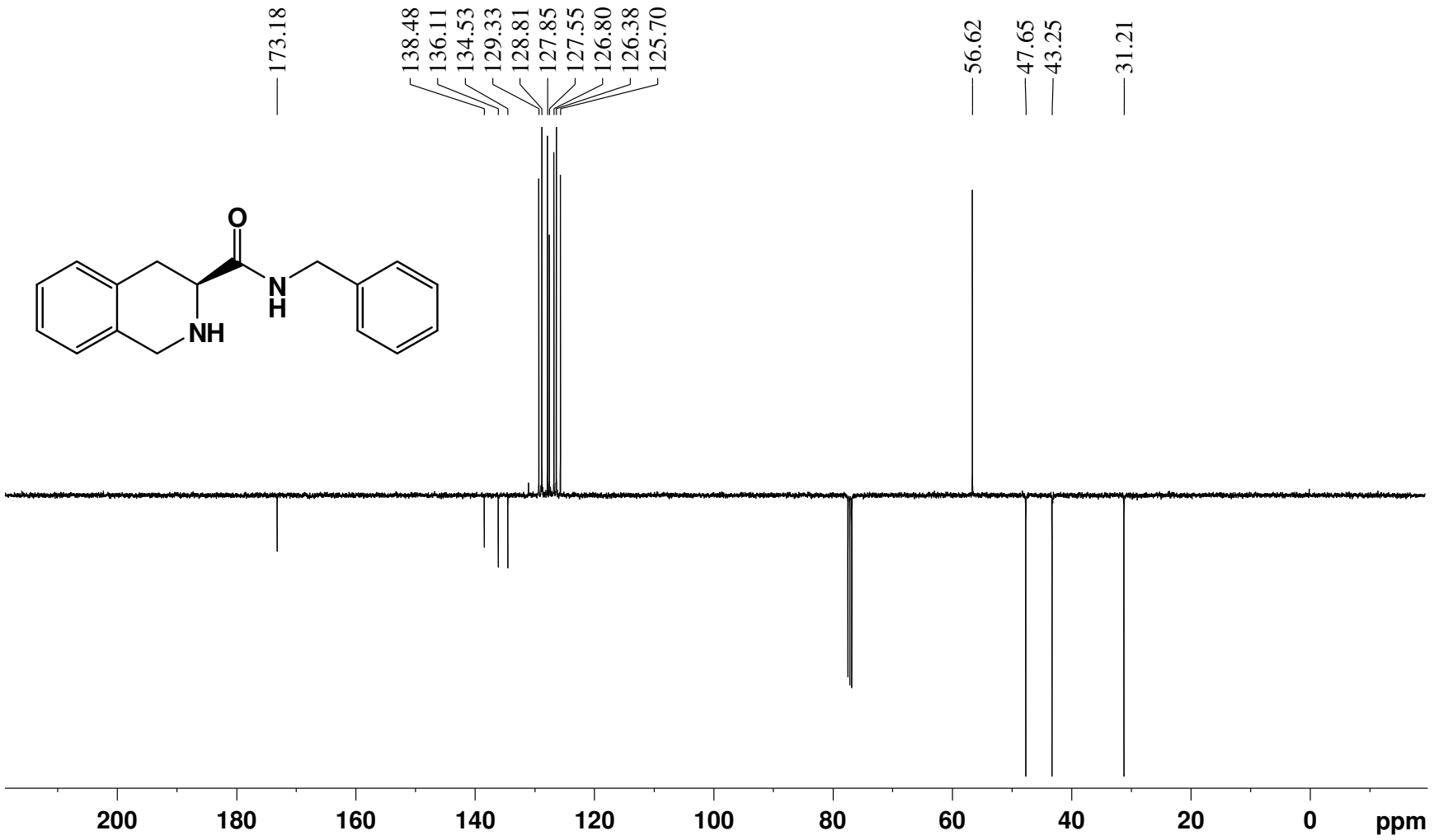
^{13}C (400 MHz) Spectrum of Compound **13** in $CDCl_3$



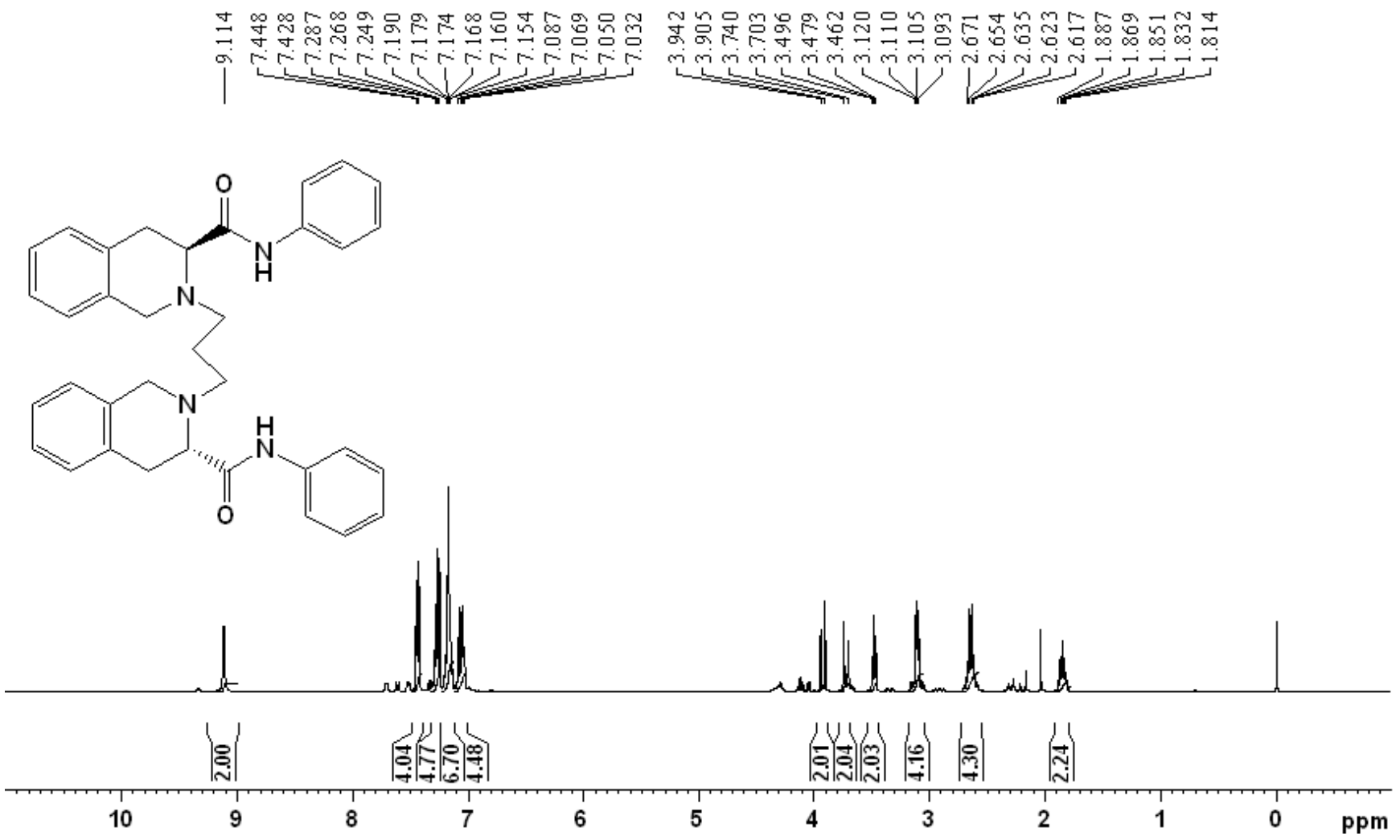
IR Spectrum of Compound **13**



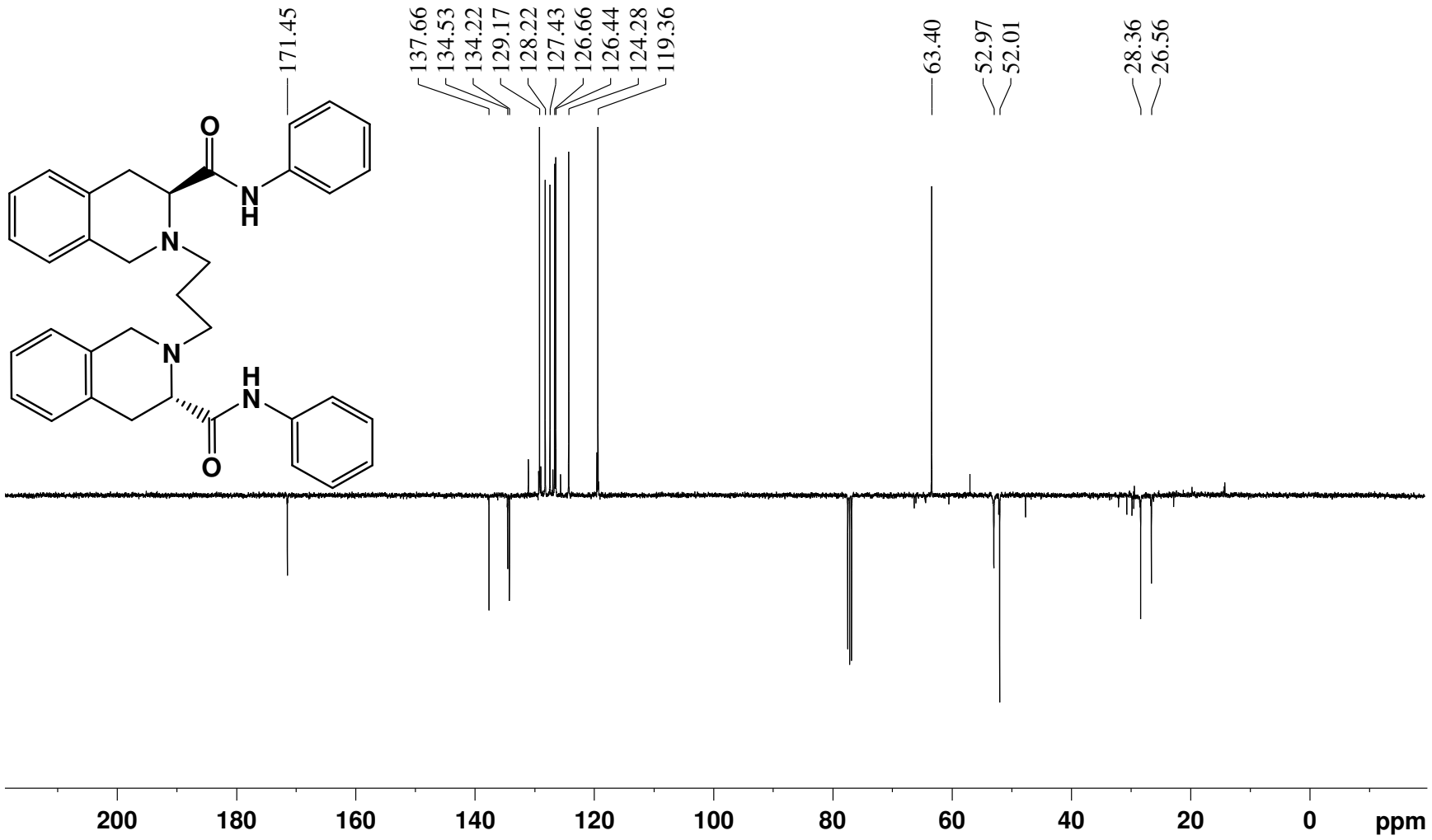
^{1}H NMR (400 MHz) Spectrum of Compound **14** in $CDCl_3$



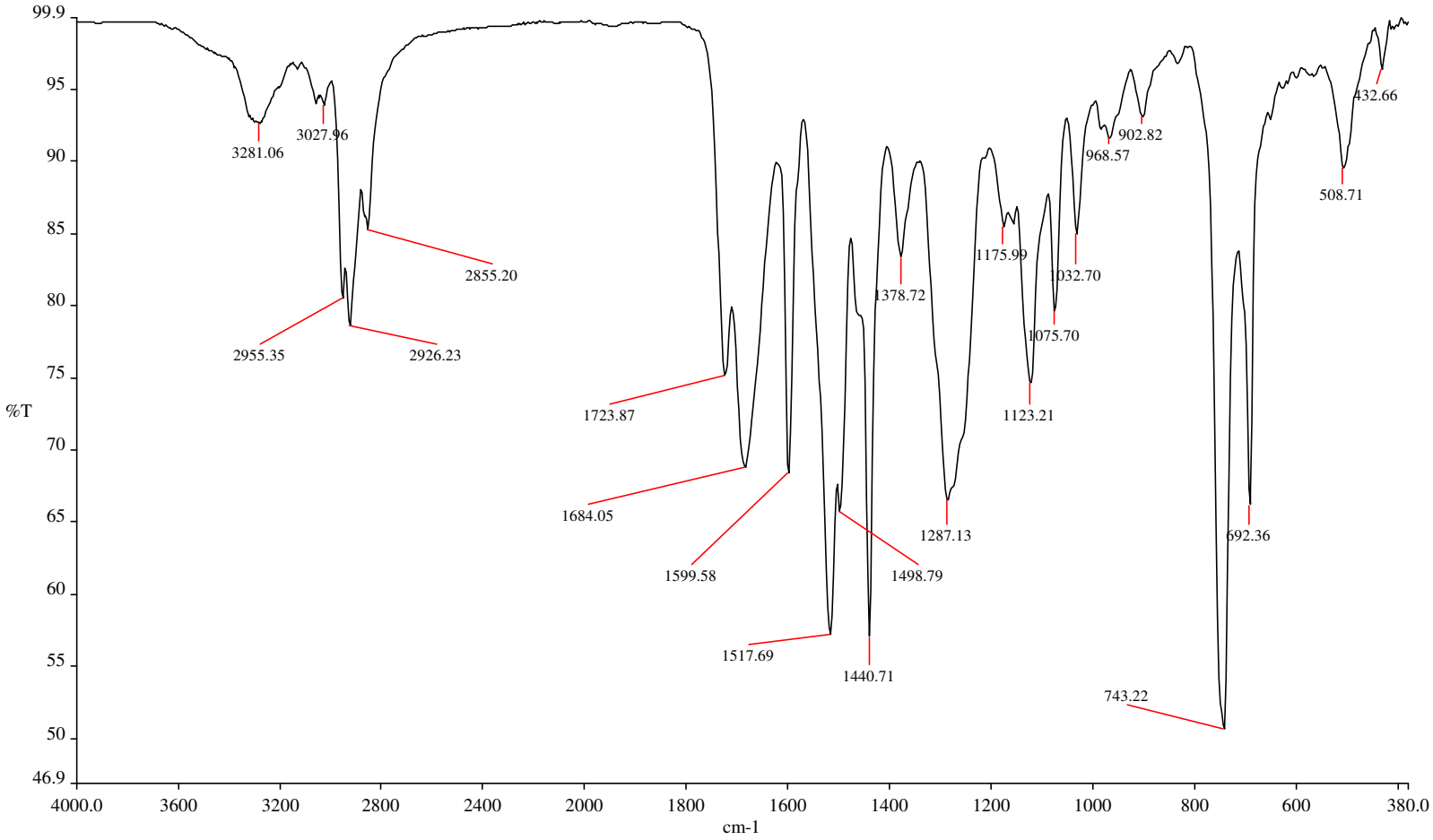
^{13}C (400 MHz) Spectrum of Compound **14** in $CDCl_3$



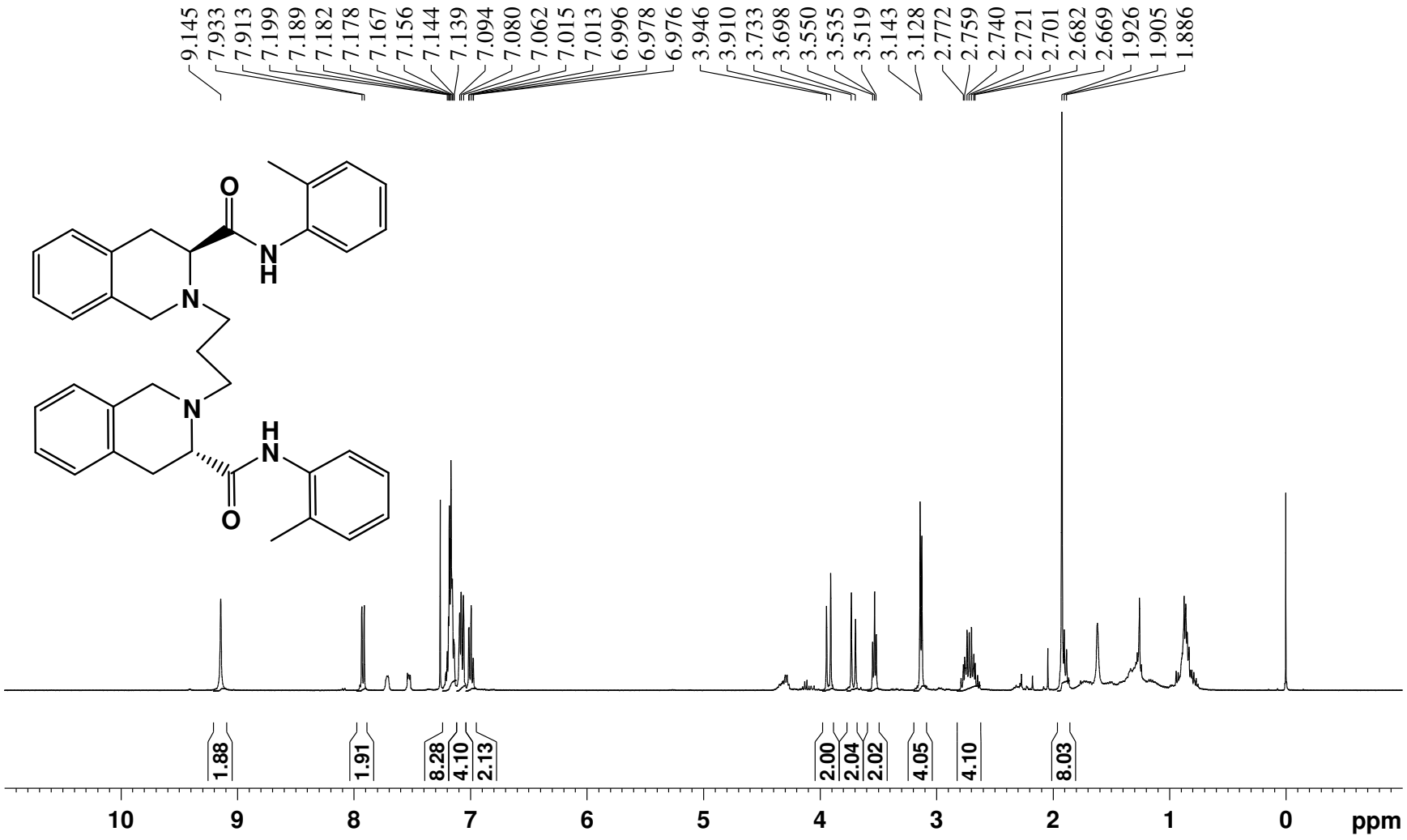
^{1}H NMR (400 MHz) Spectrum of Compound **15** in $CDCl_3$



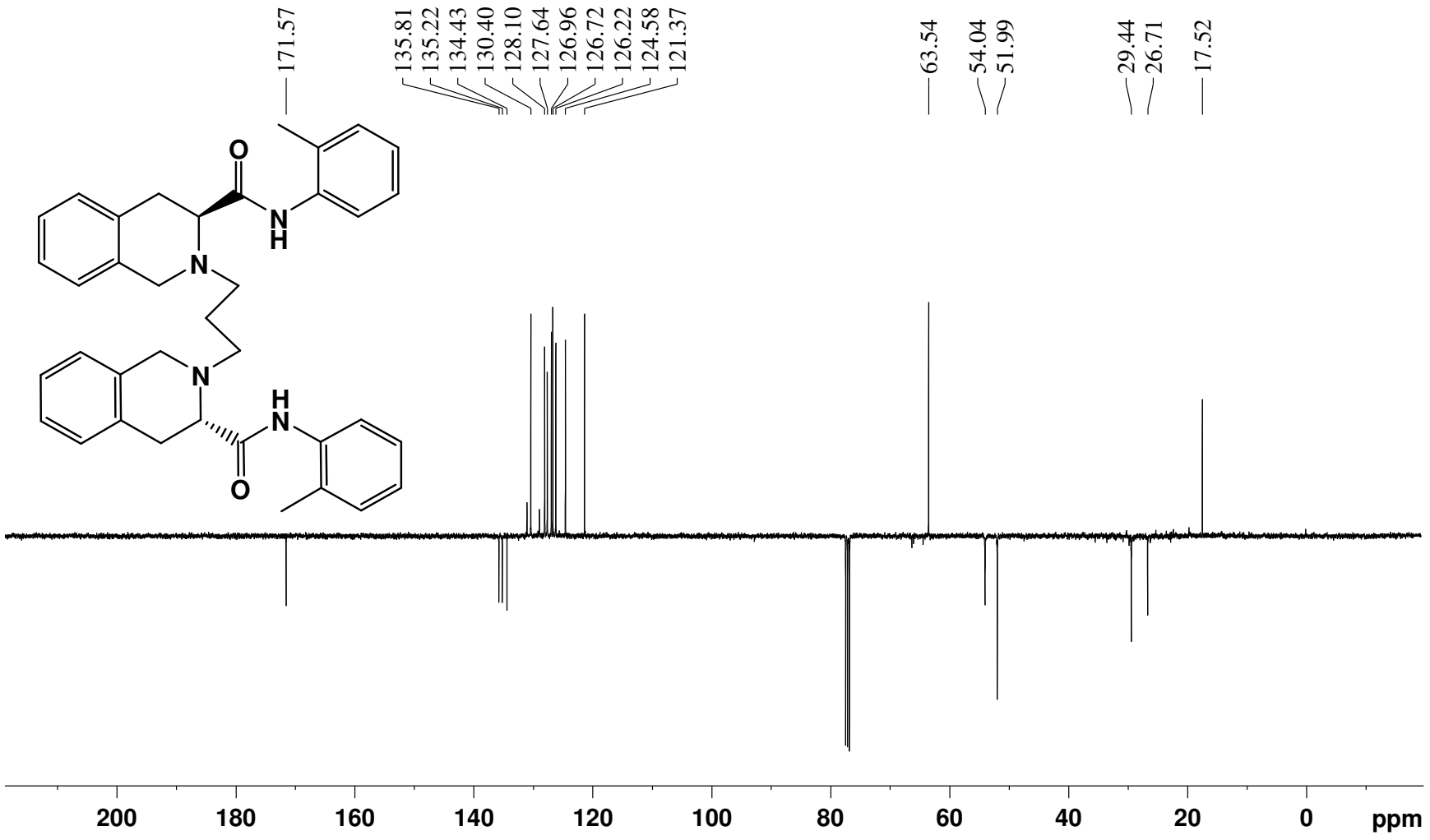
^{13}C (400 MHz) Spectrum of Compound **15** in $CDCl_3$



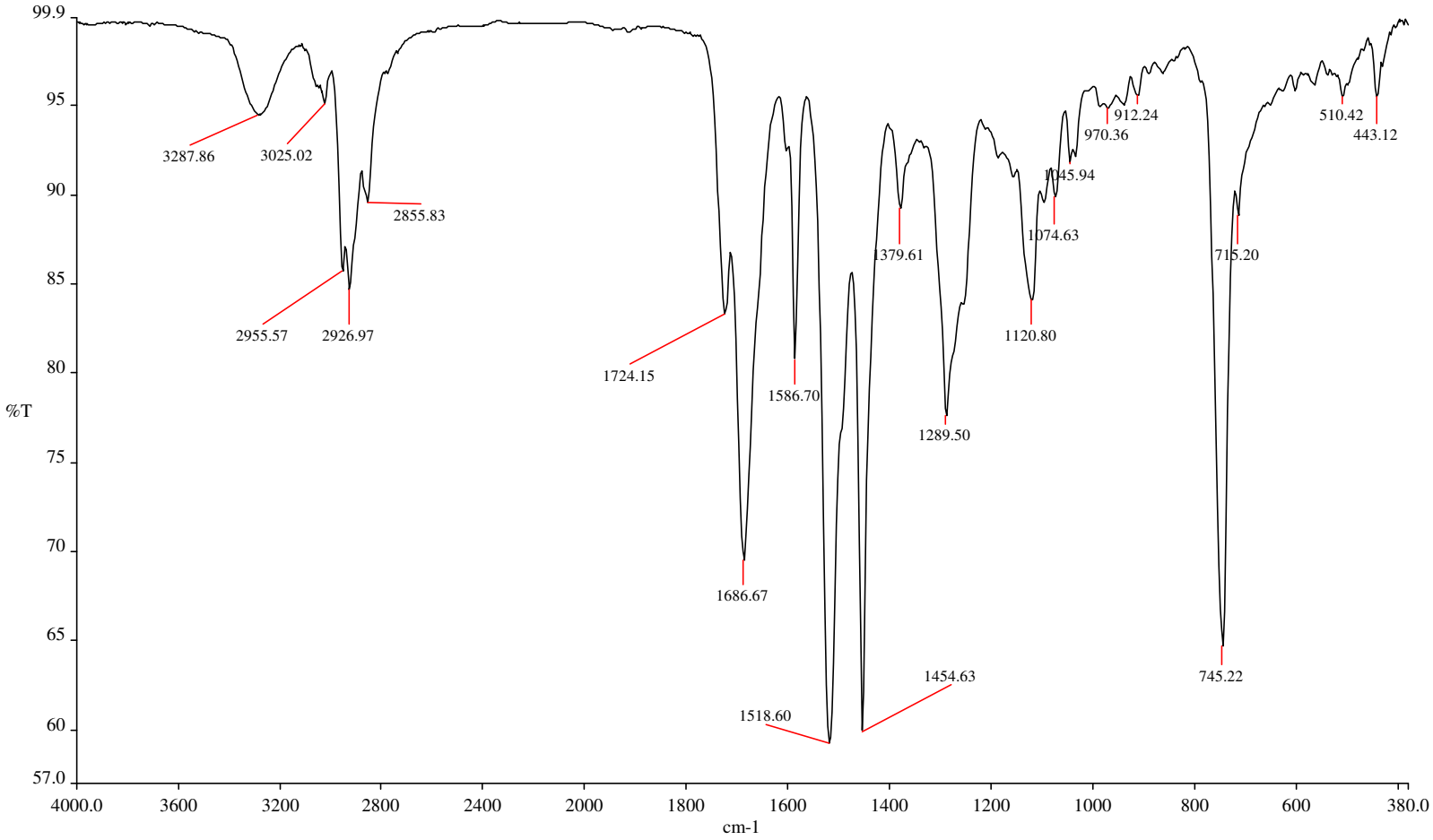
IR Spectrum of Compound **15**



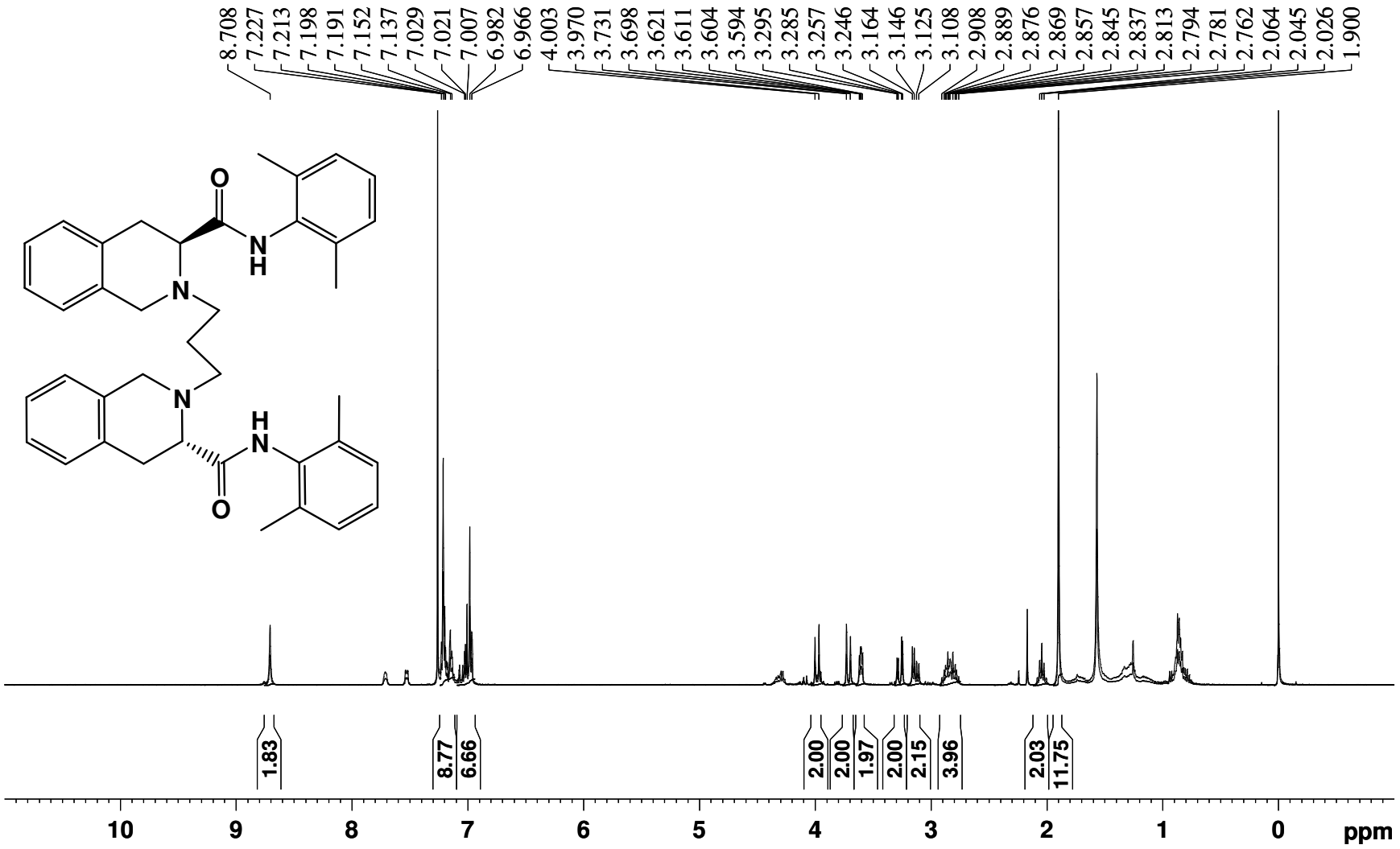
^{1}H NMR (400 MHz) Spectrum of Compound **16** in $CDCl_3$



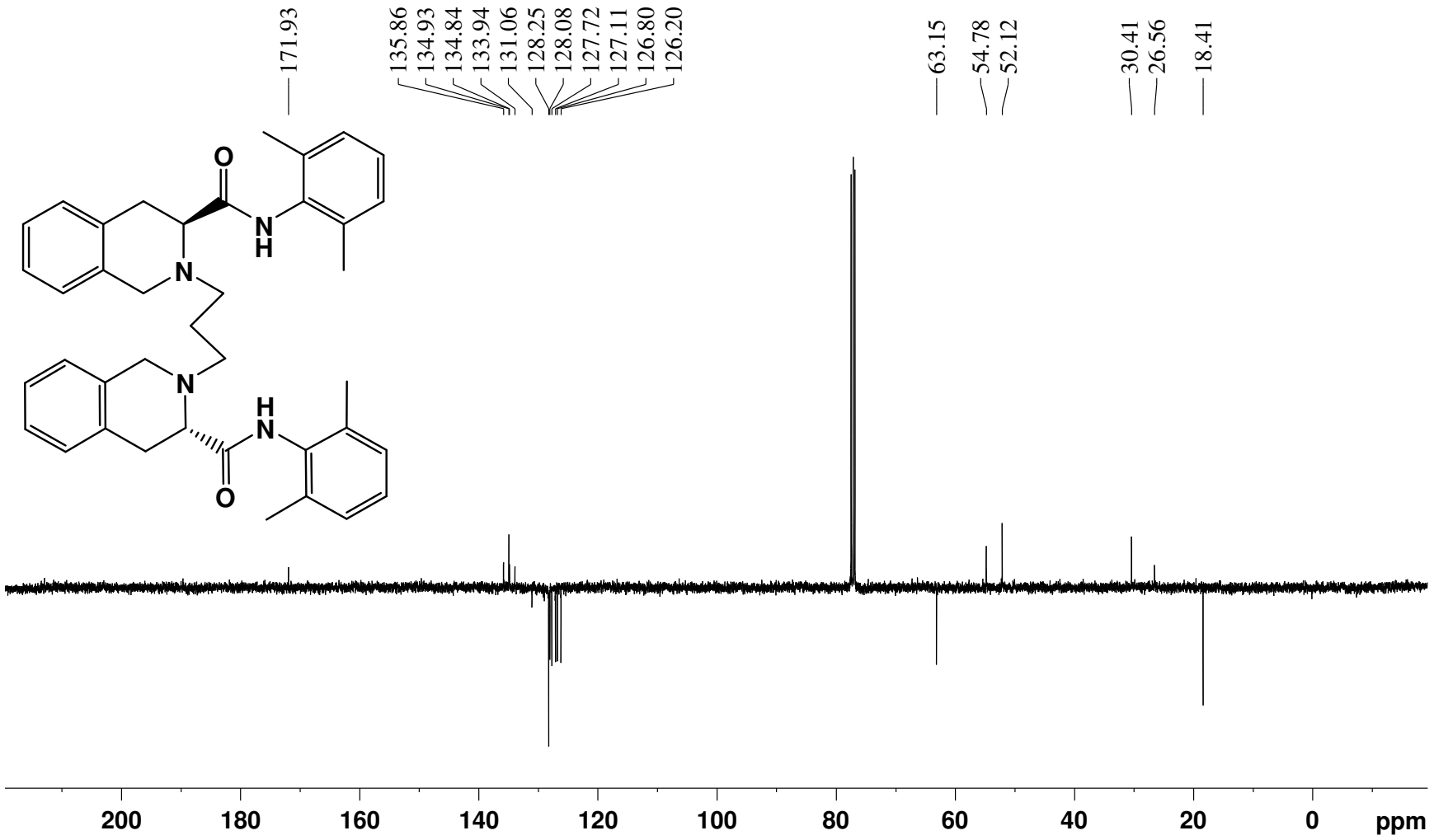
^{13}C (400 MHz) Spectrum of Compound **16** in $CDCl_3$



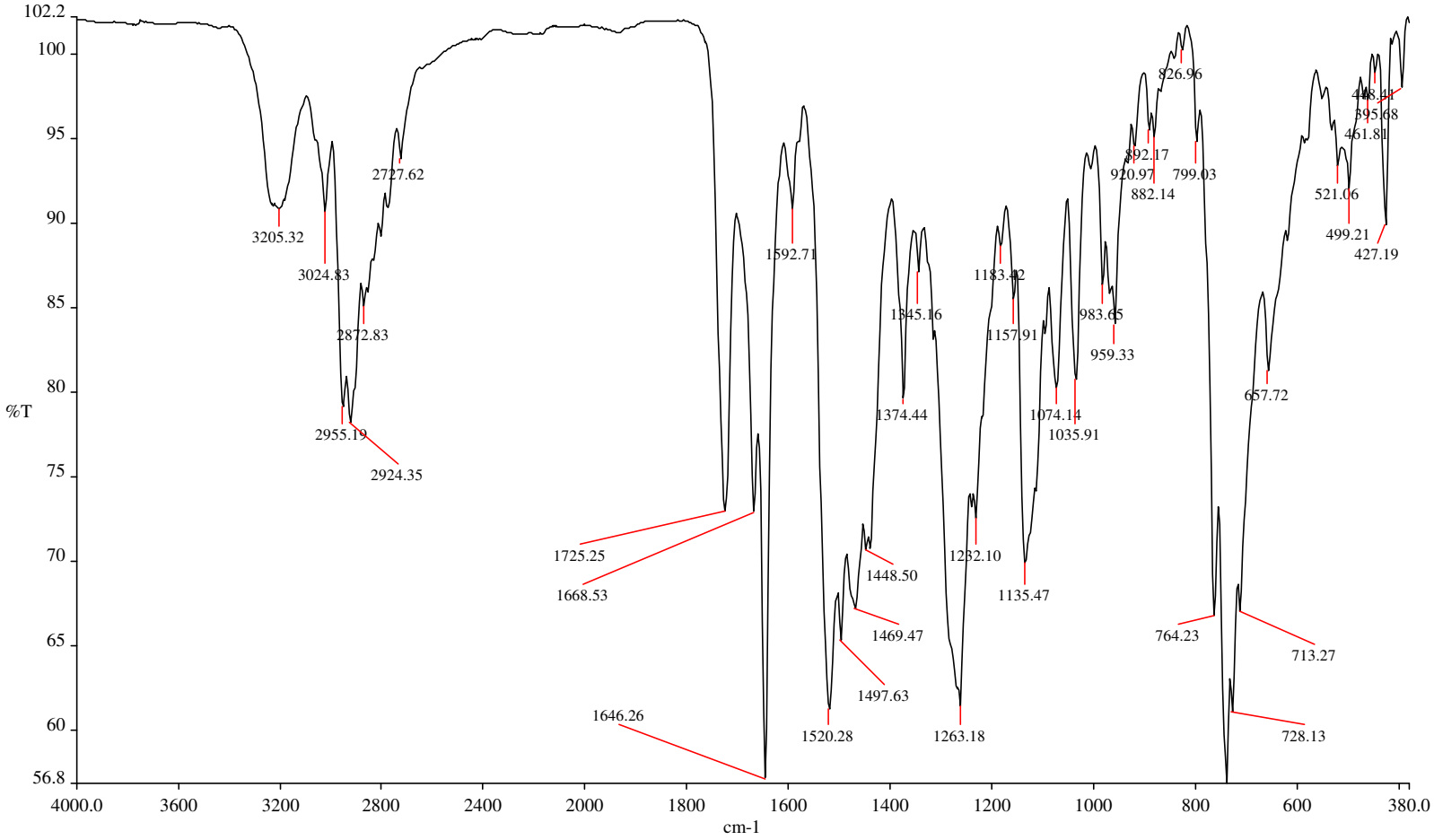
IR Spectrum of Compound **16**



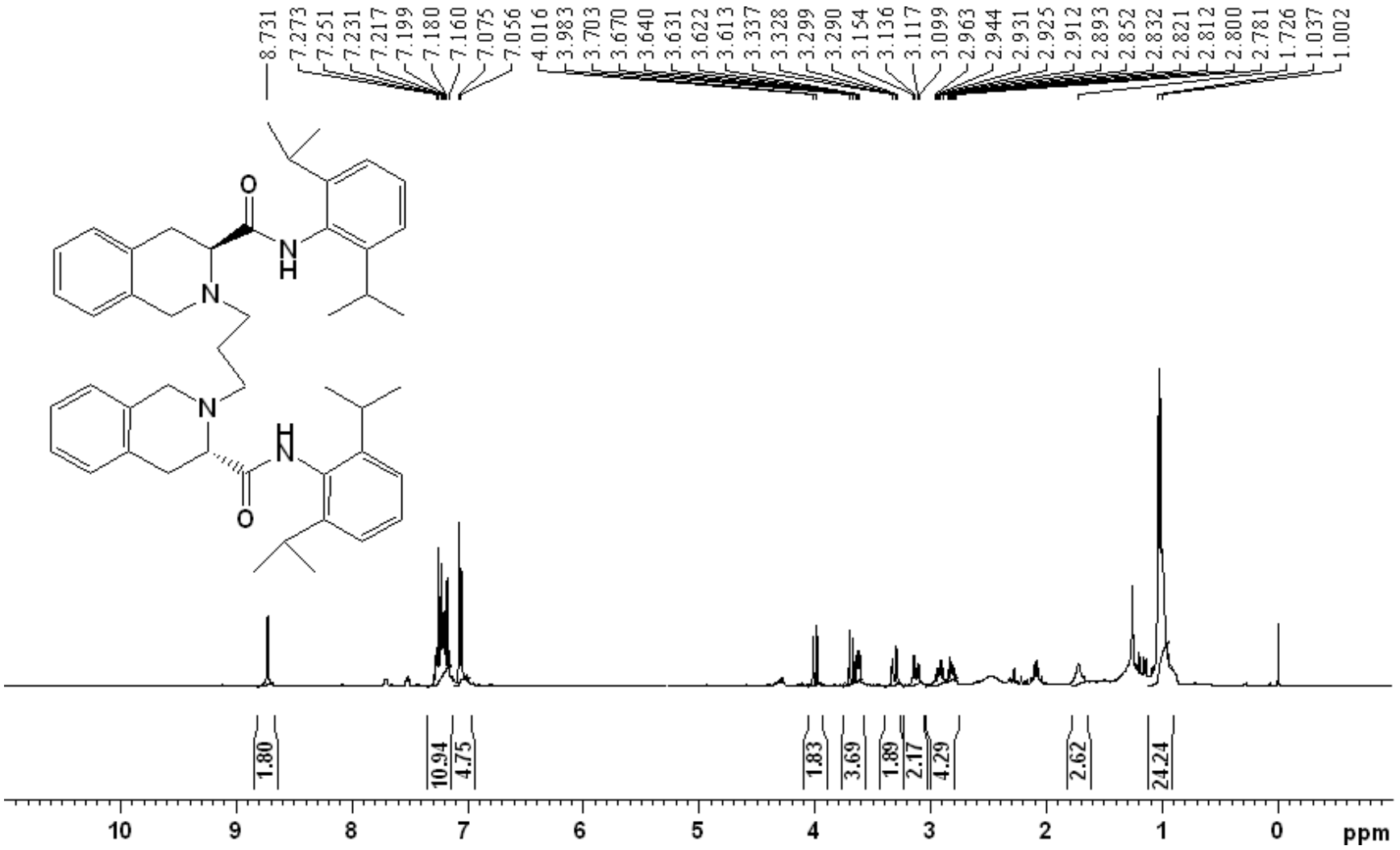
^{1}H NMR (400 MHz) Spectrum of Compound **17** in $CDCl_3$



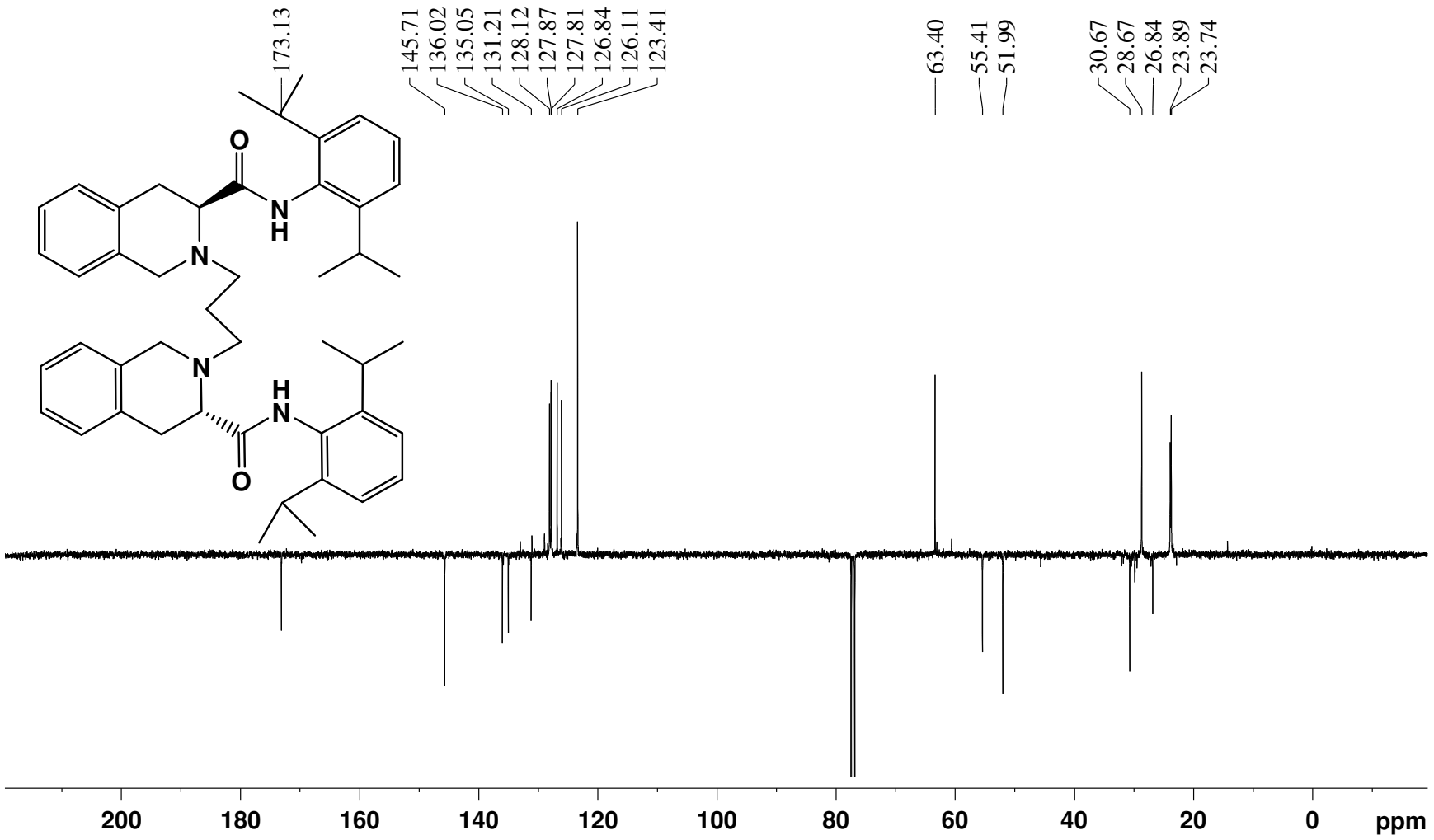
^{13}C (400 MHz) Spectrum of Compound **17** in $CDCl_3$



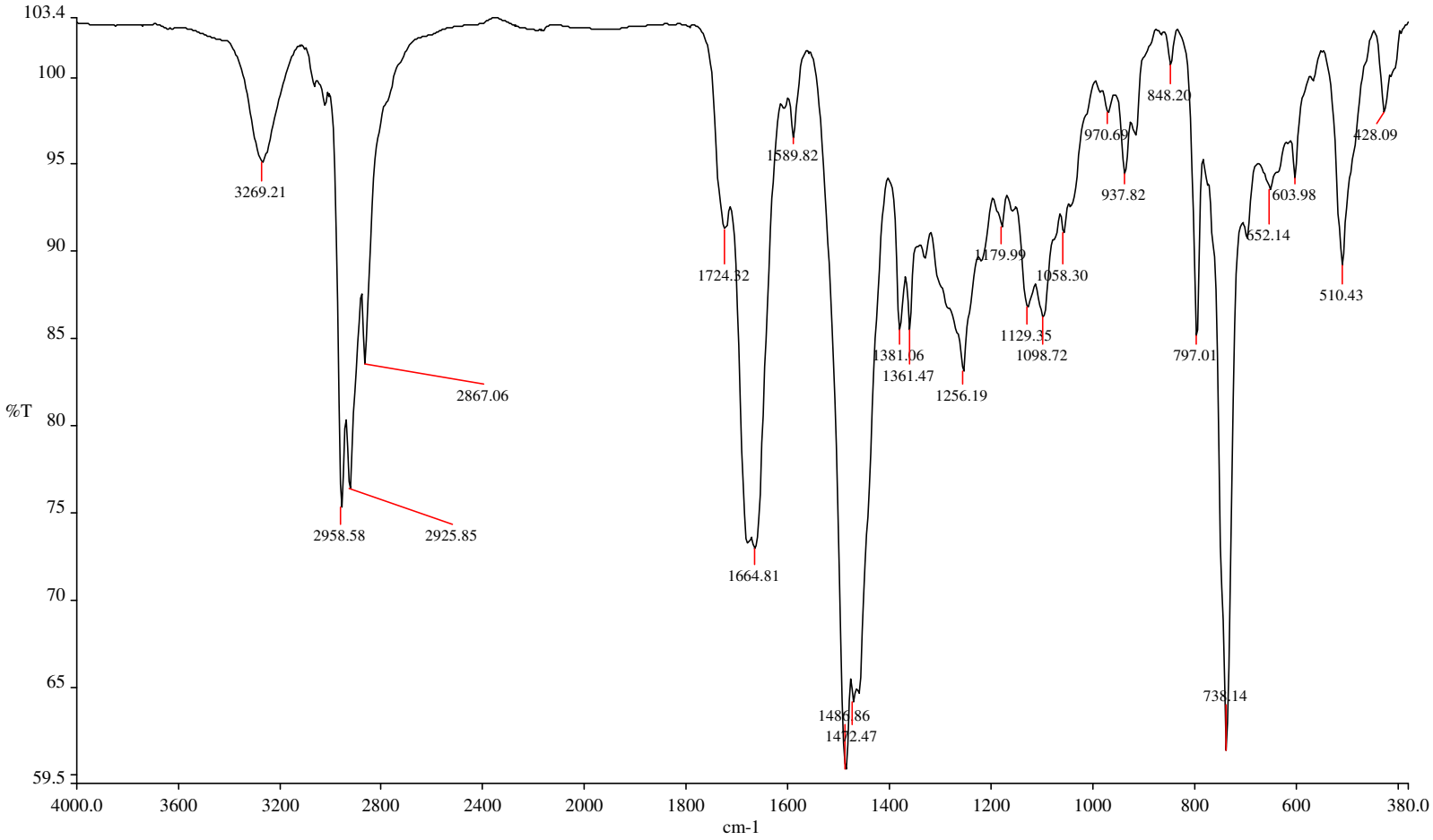
IR Spectrum of Compound **17**



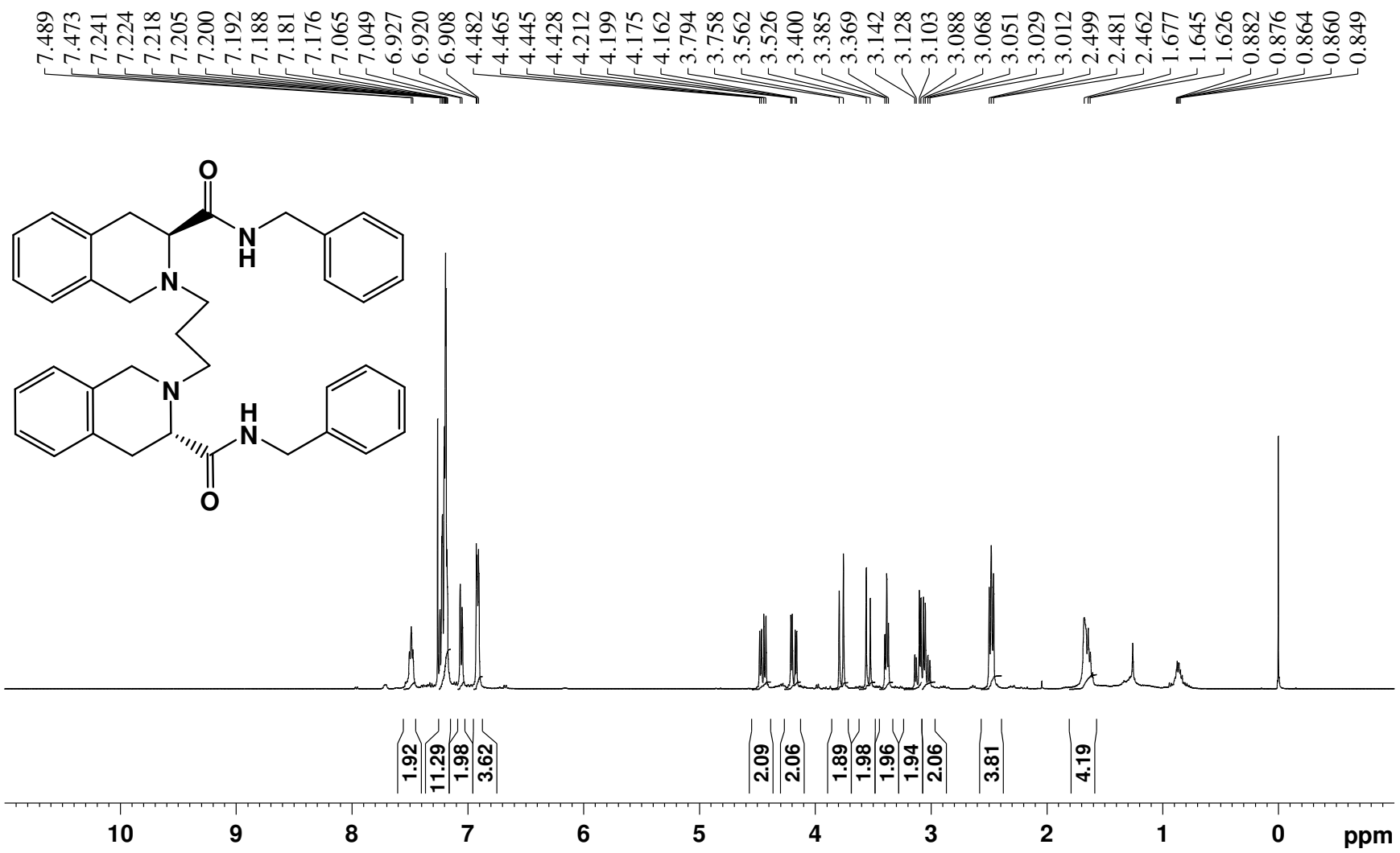
^{1}H NMR (400 MHz) Spectrum of Compound **18** in $CDCl_3$



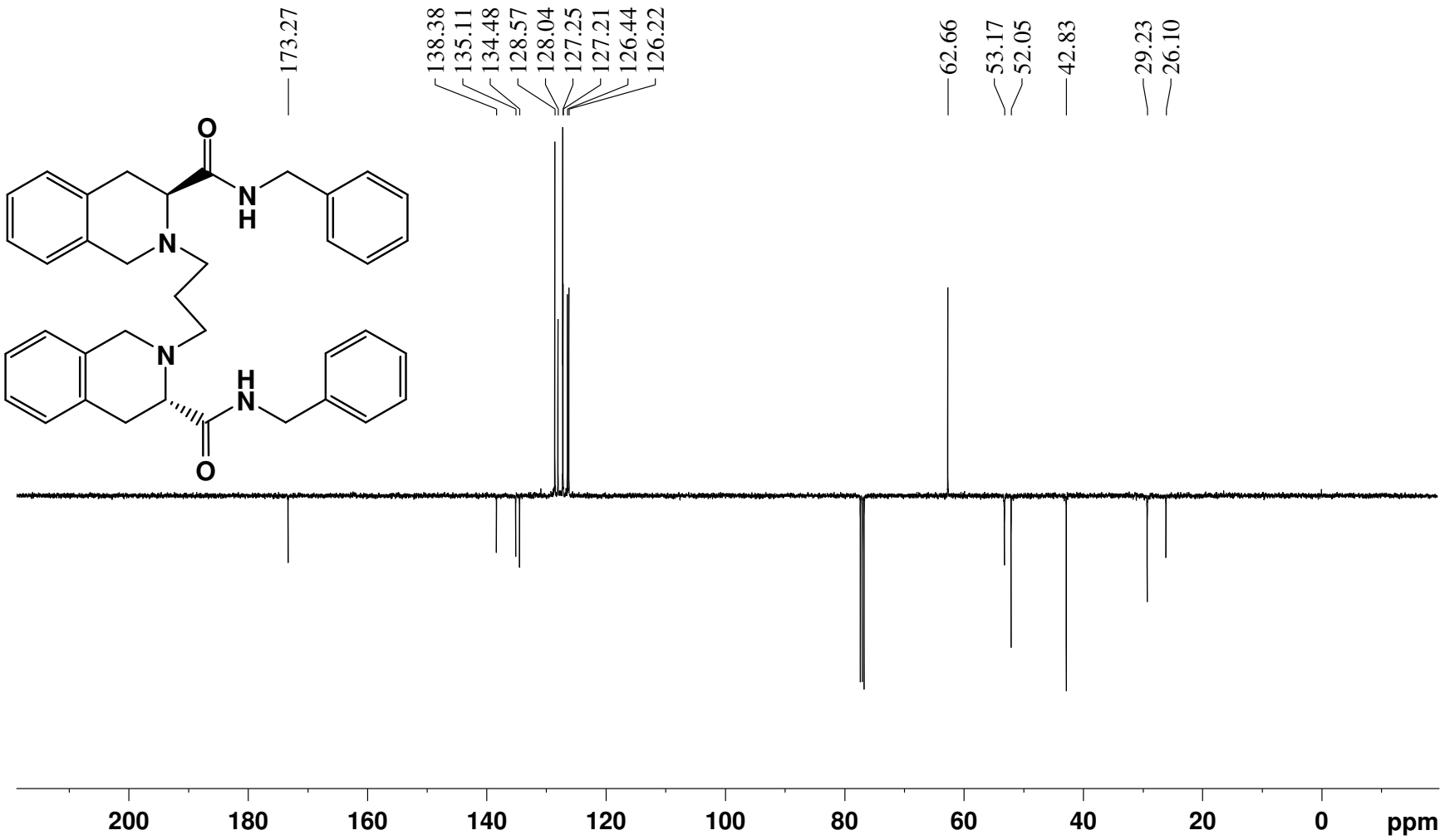
^{13}C (400 MHz) Spectrum of Compound 1**8** in $CDCl_3$



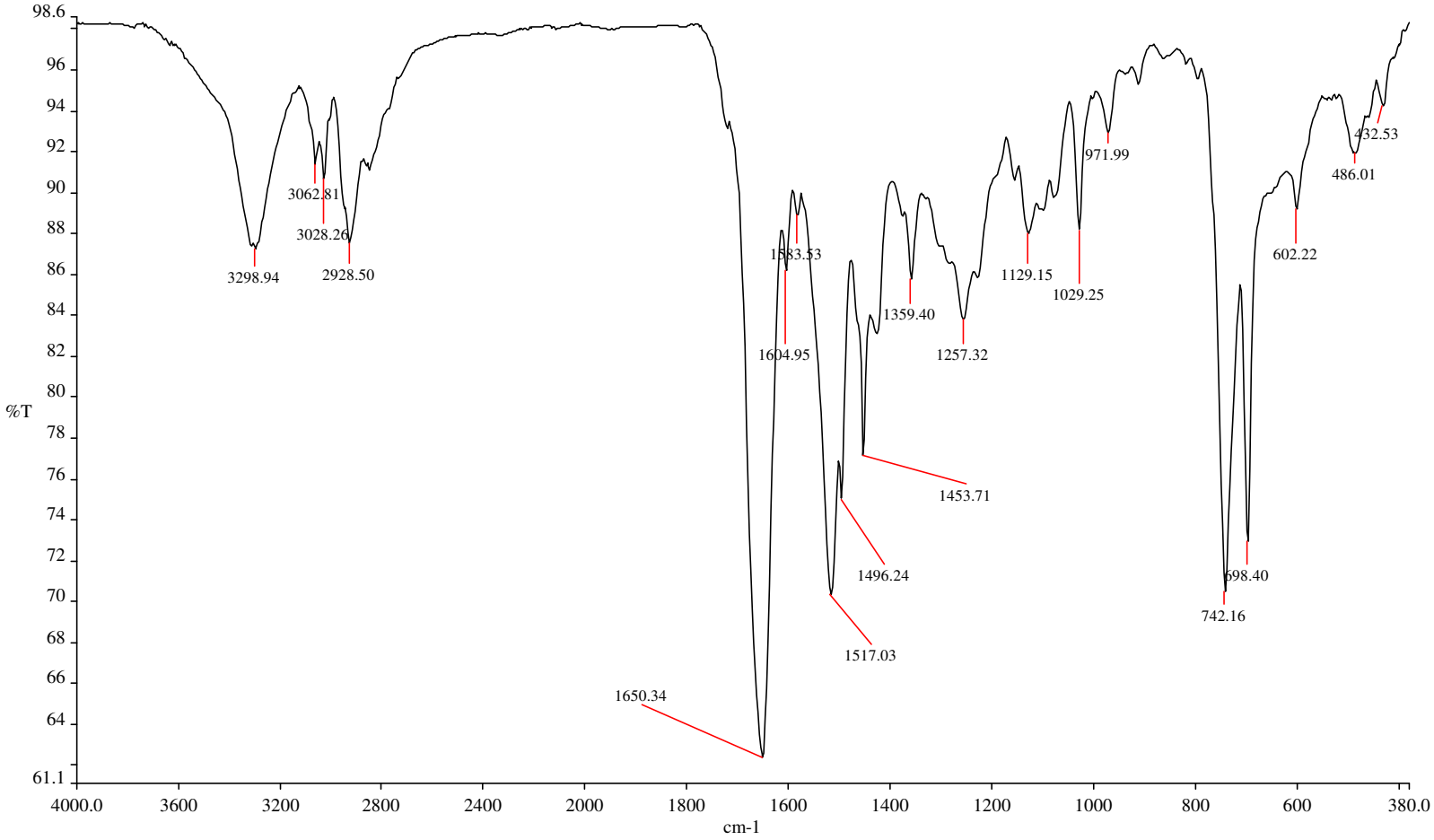
IR Spectrum of Compound **18**



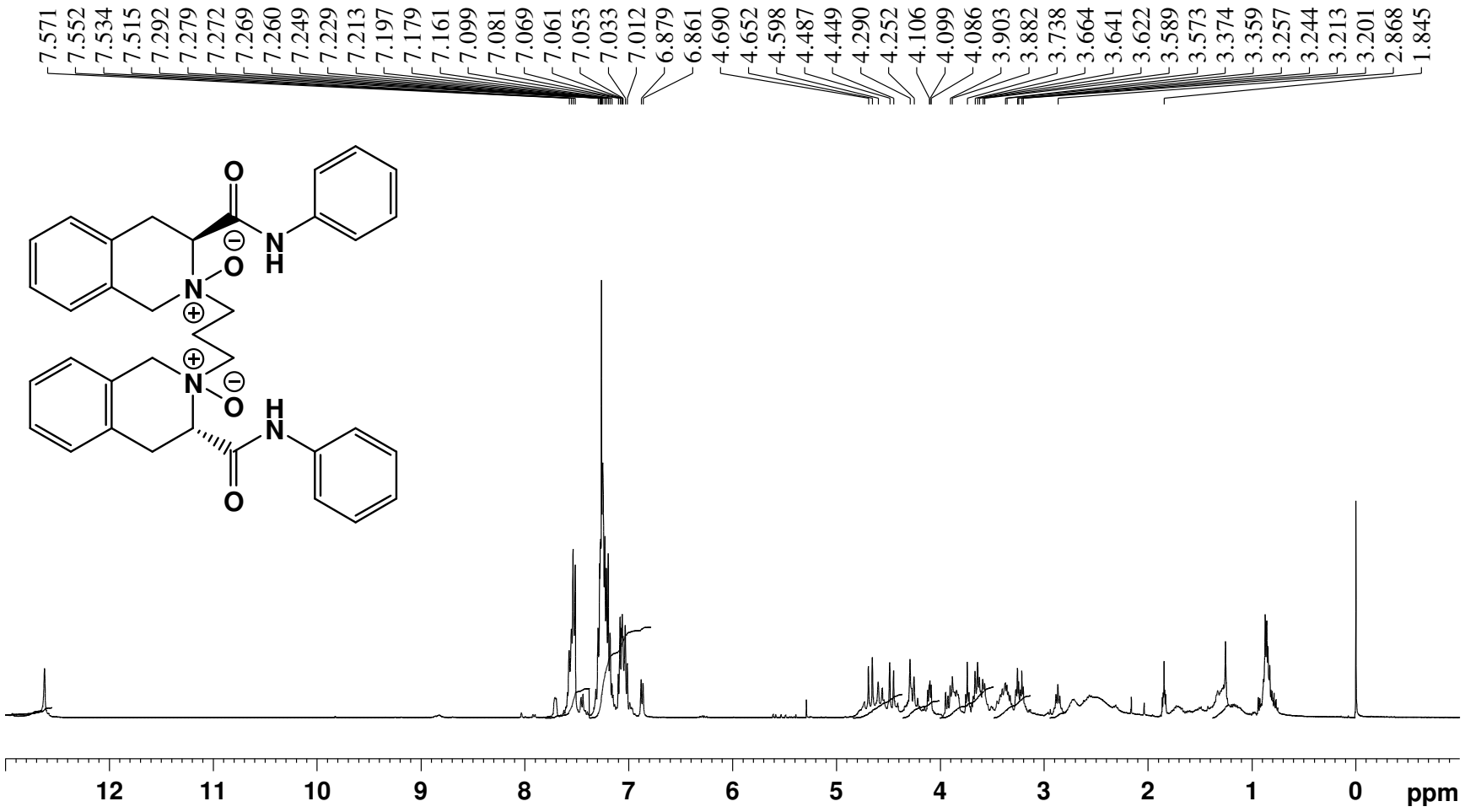
^{1}H NMR (400 MHz) Spectrum of Compound **19** in $CDCl_3$



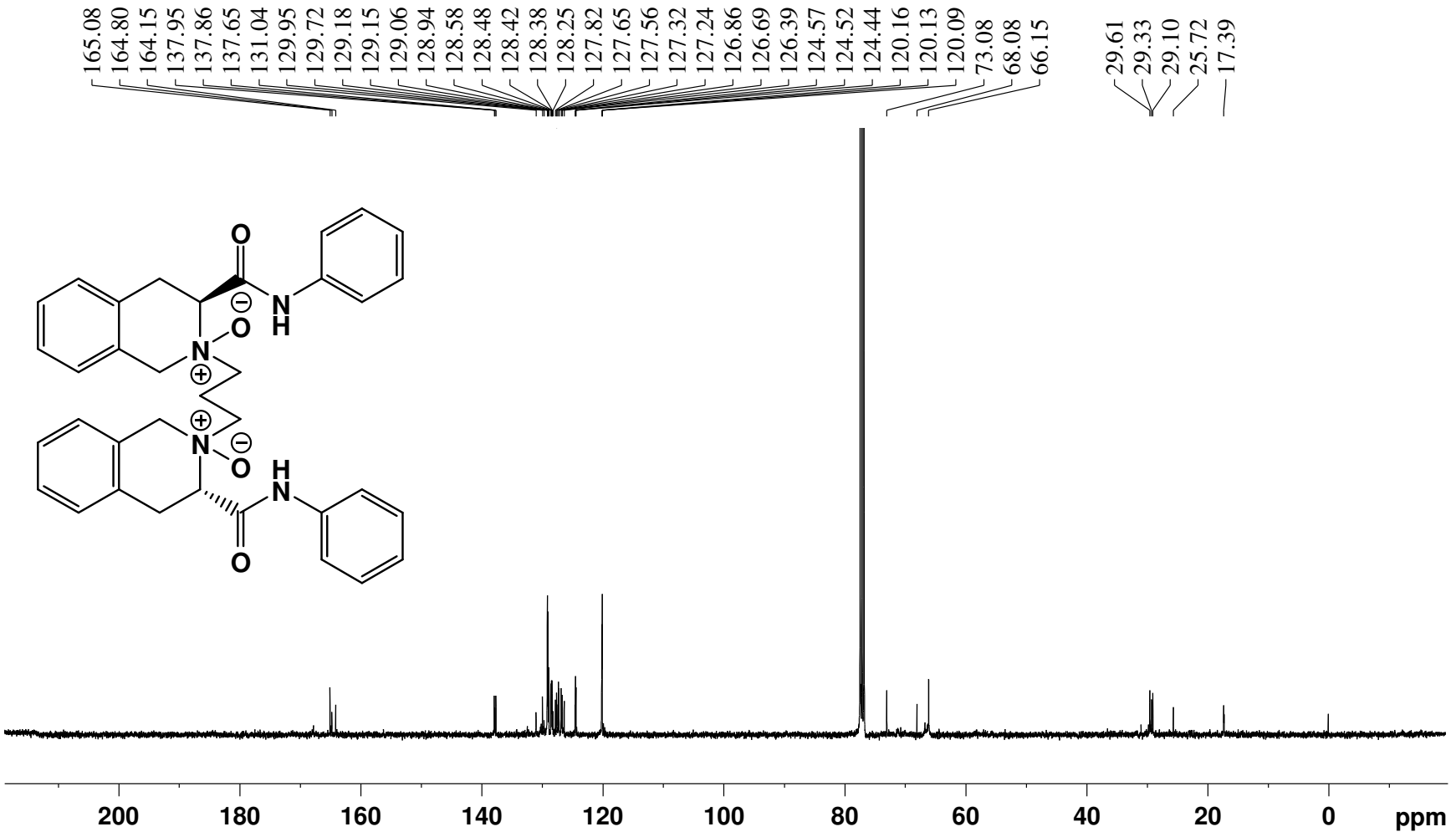
^{13}C (400 MHz) Spectrum of Compound **19** in $CDCl_3$



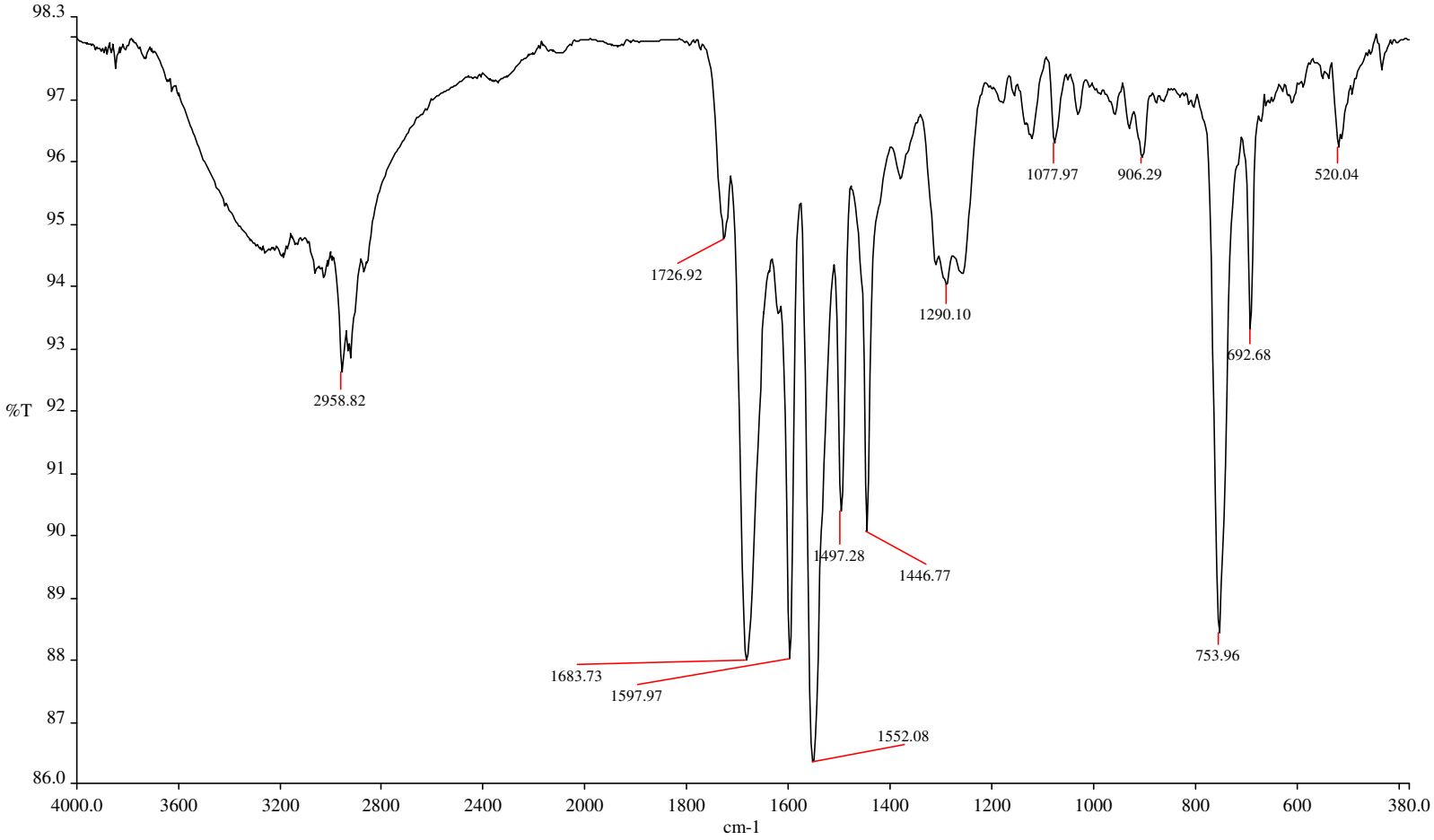
IR Spectrum of Compound **19**



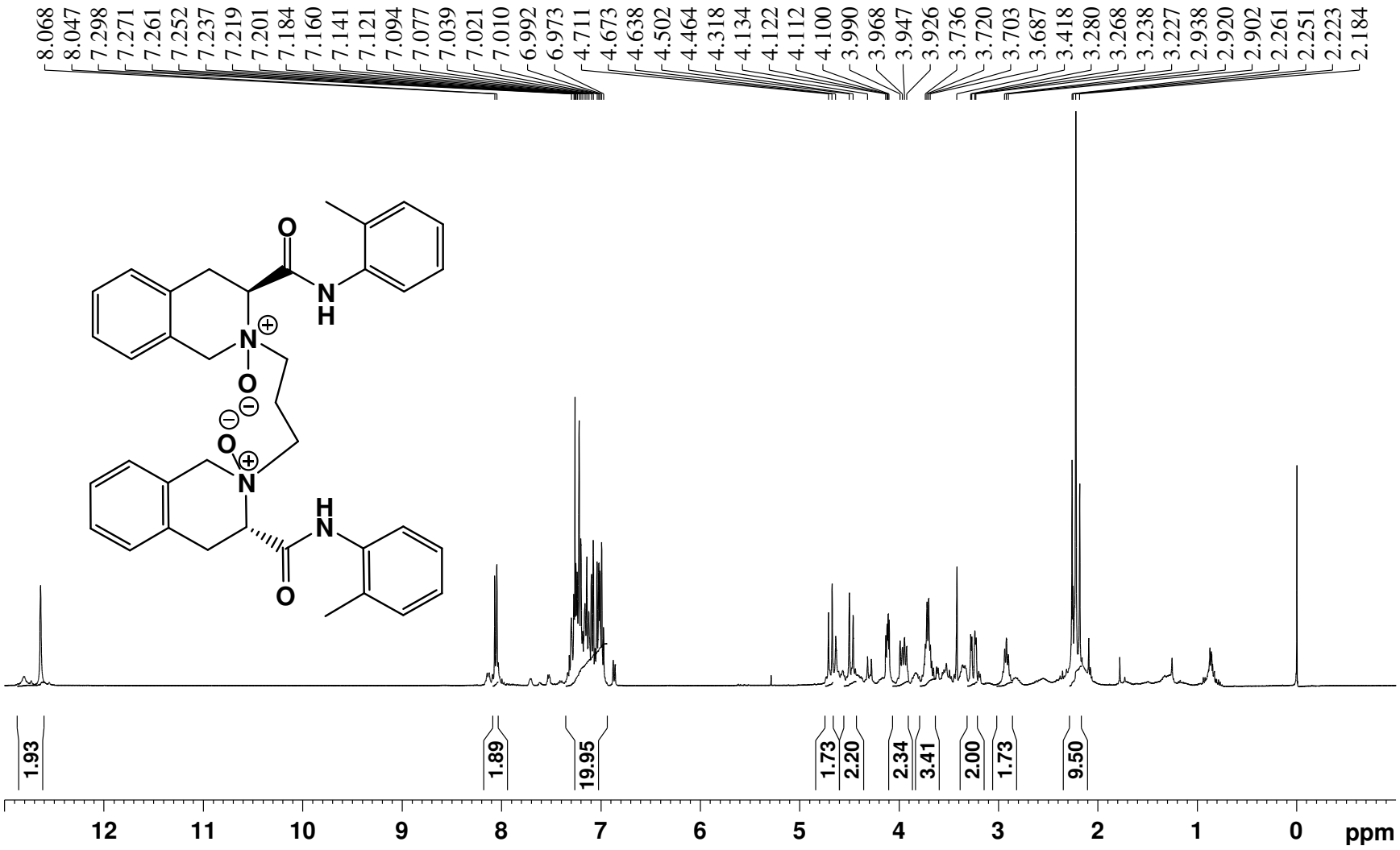
^{1}H NMR (400 MHz) Spectrum of Compound **20**



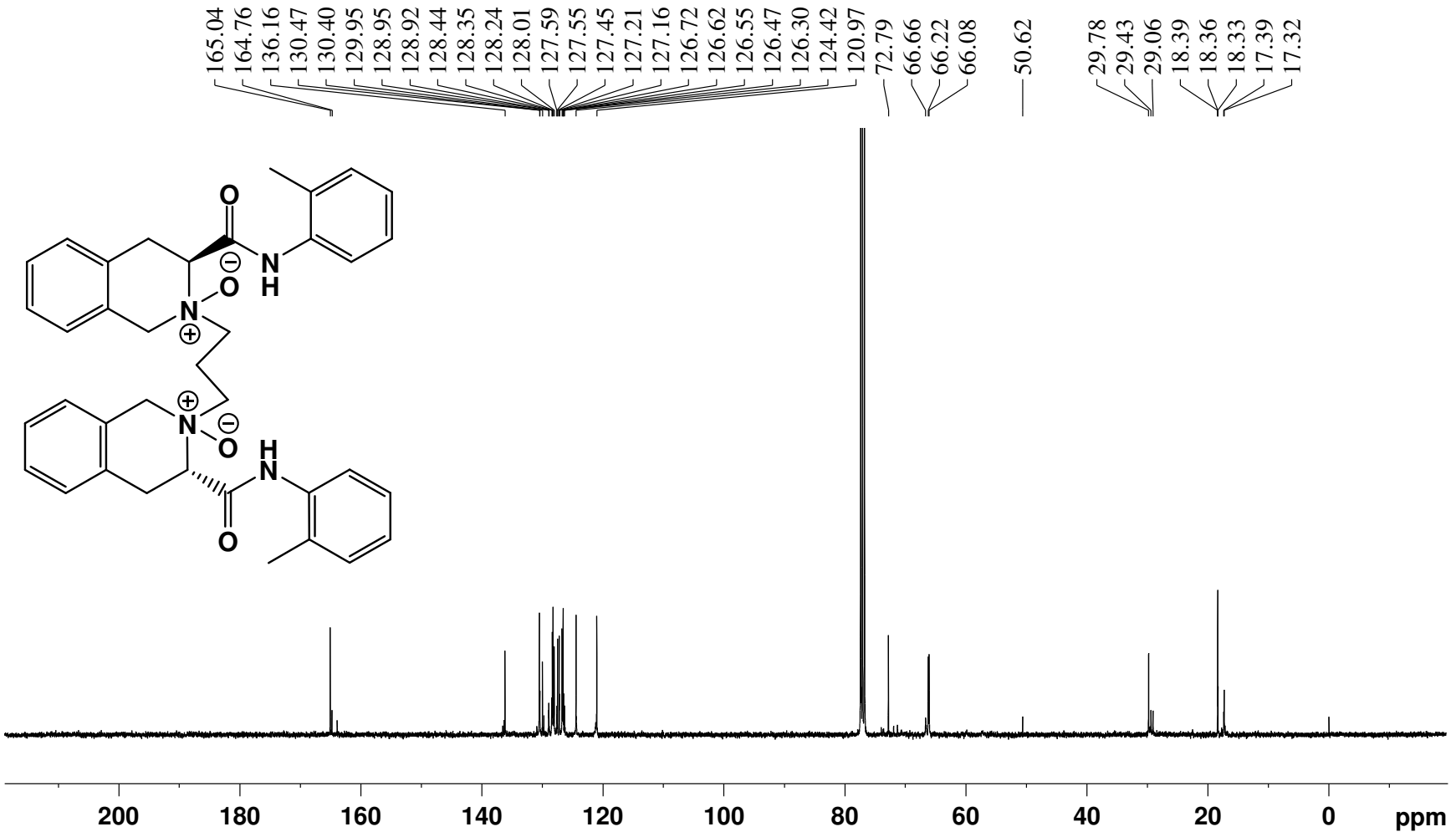
^{13}C NMR (400 MHz) Spectrum of Compound **20**



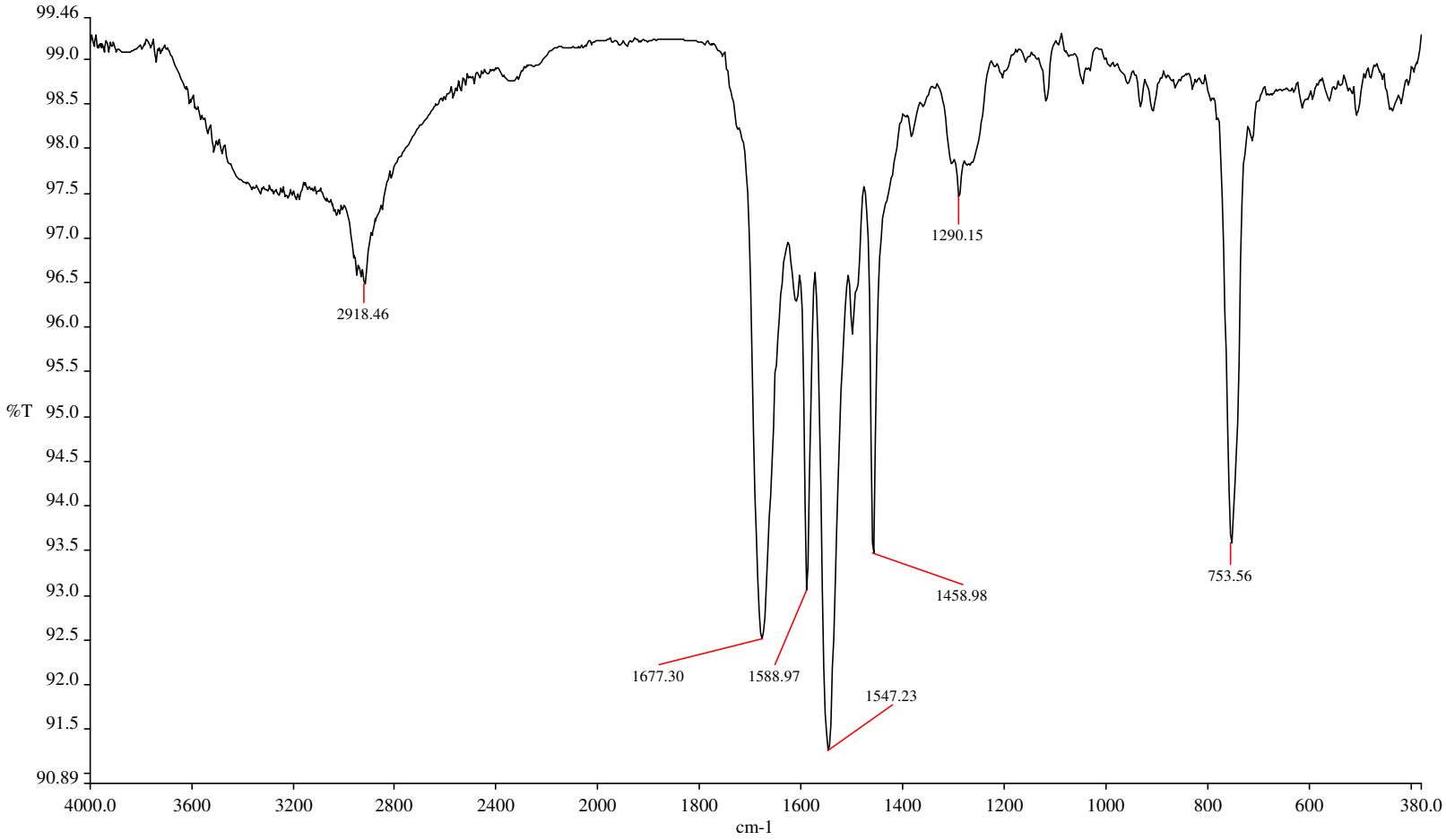
IR Spectrum of Compound **20**



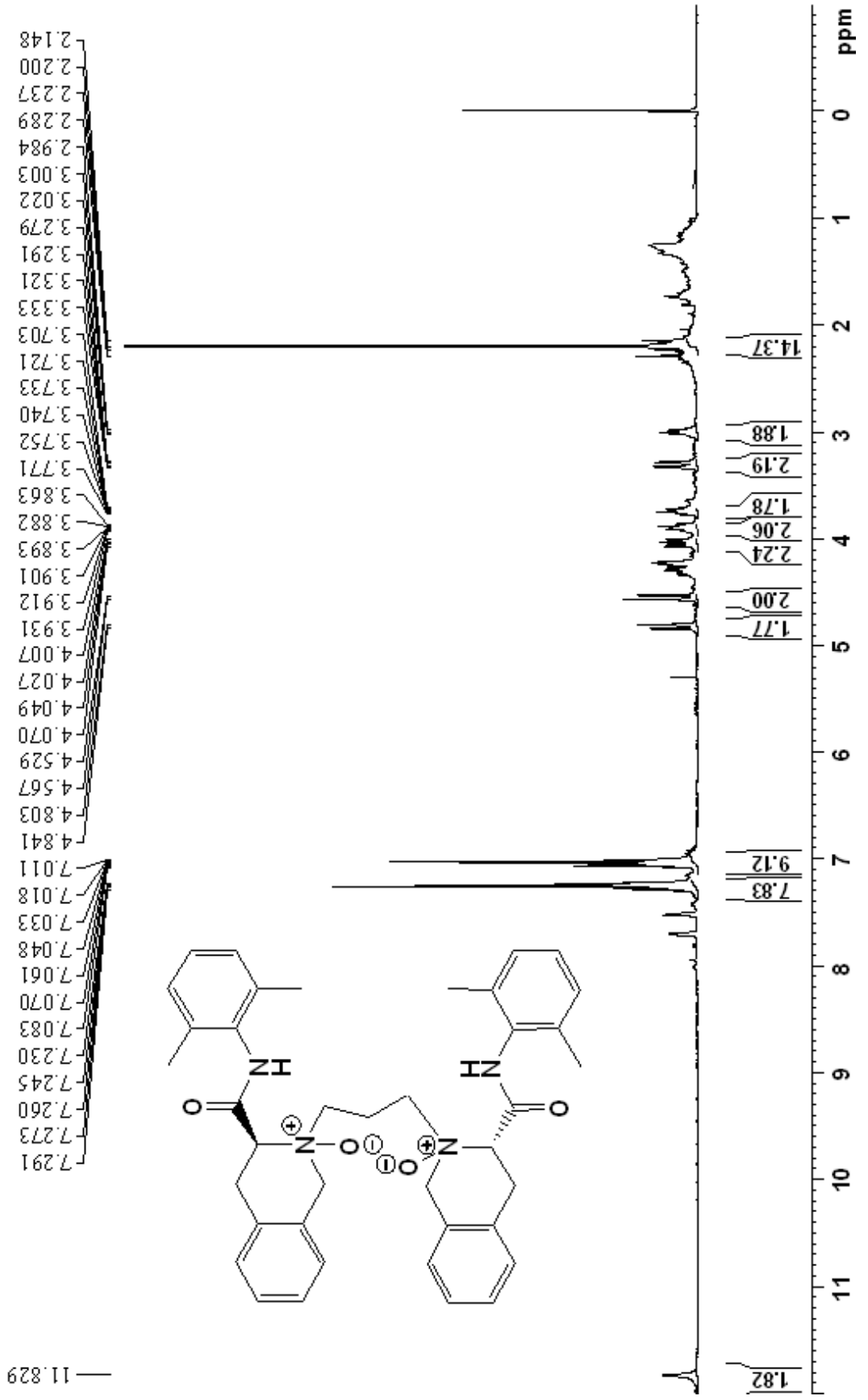
^{1}H NMR (400 MHz) Spectrum of Compound **21** in $CDCl_3$



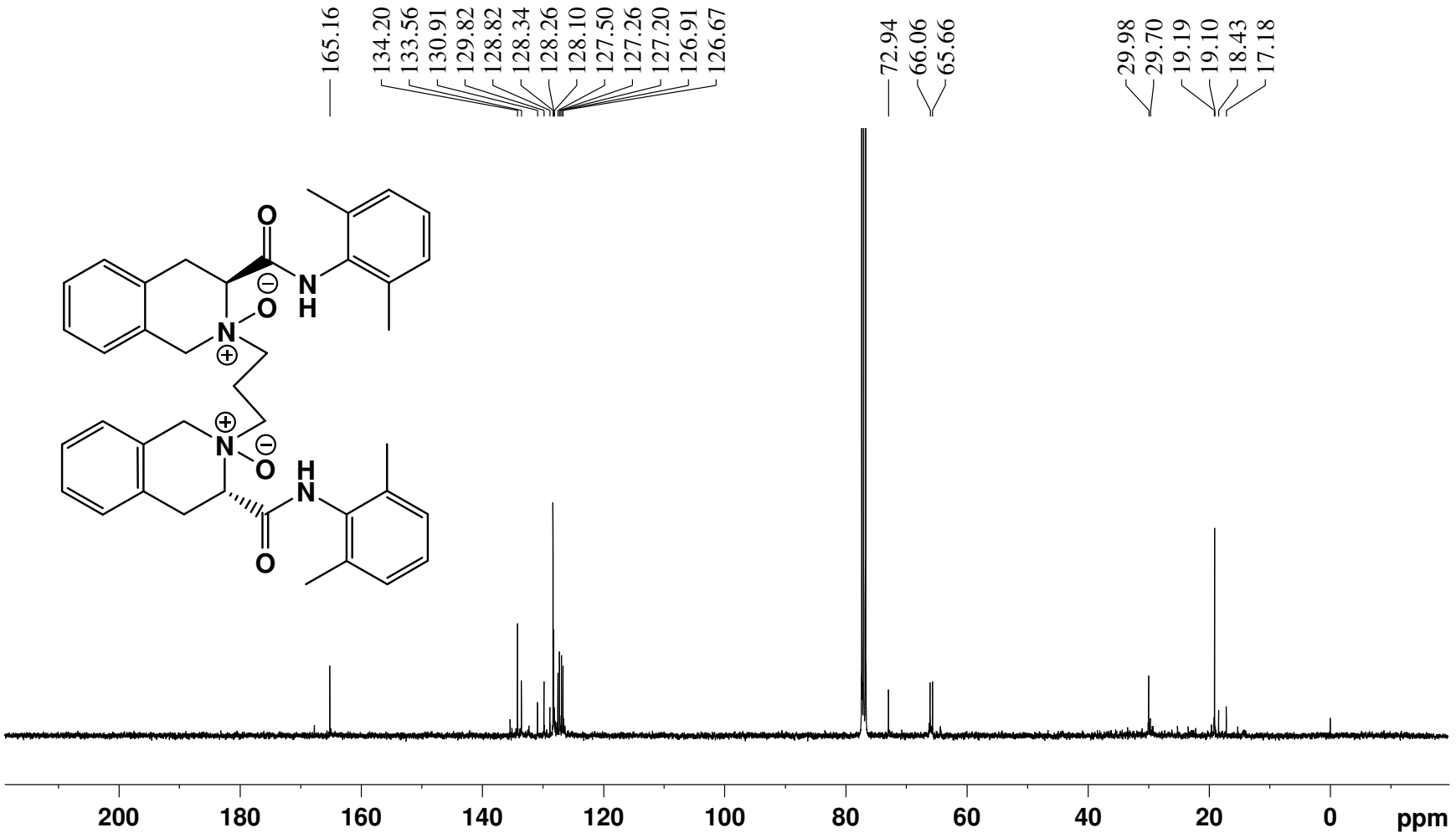
^{13}C (400 MHz) Spectrum of Compound **21** in $CDCl_3$



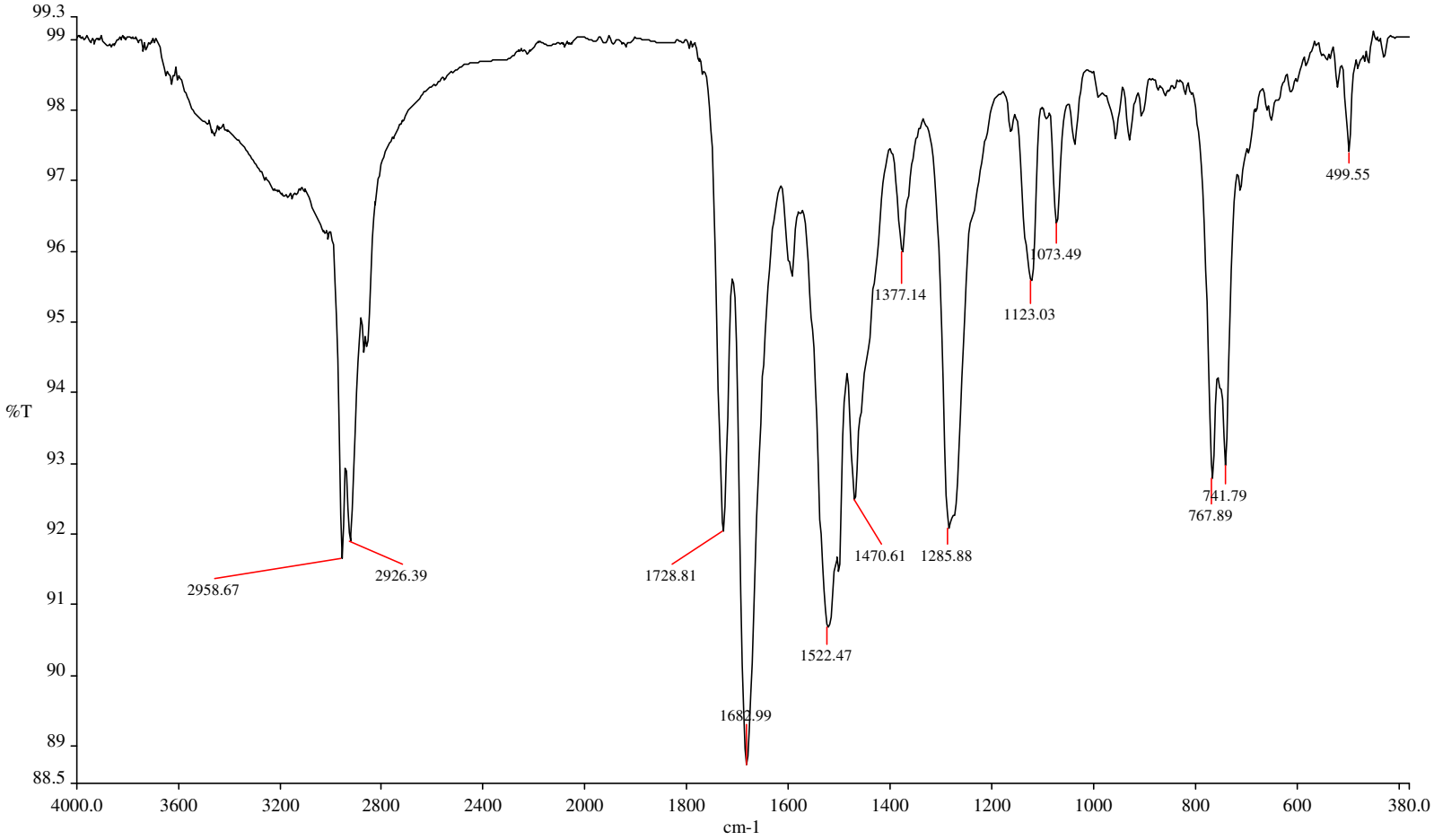
IR Spectrum of Compound **21**



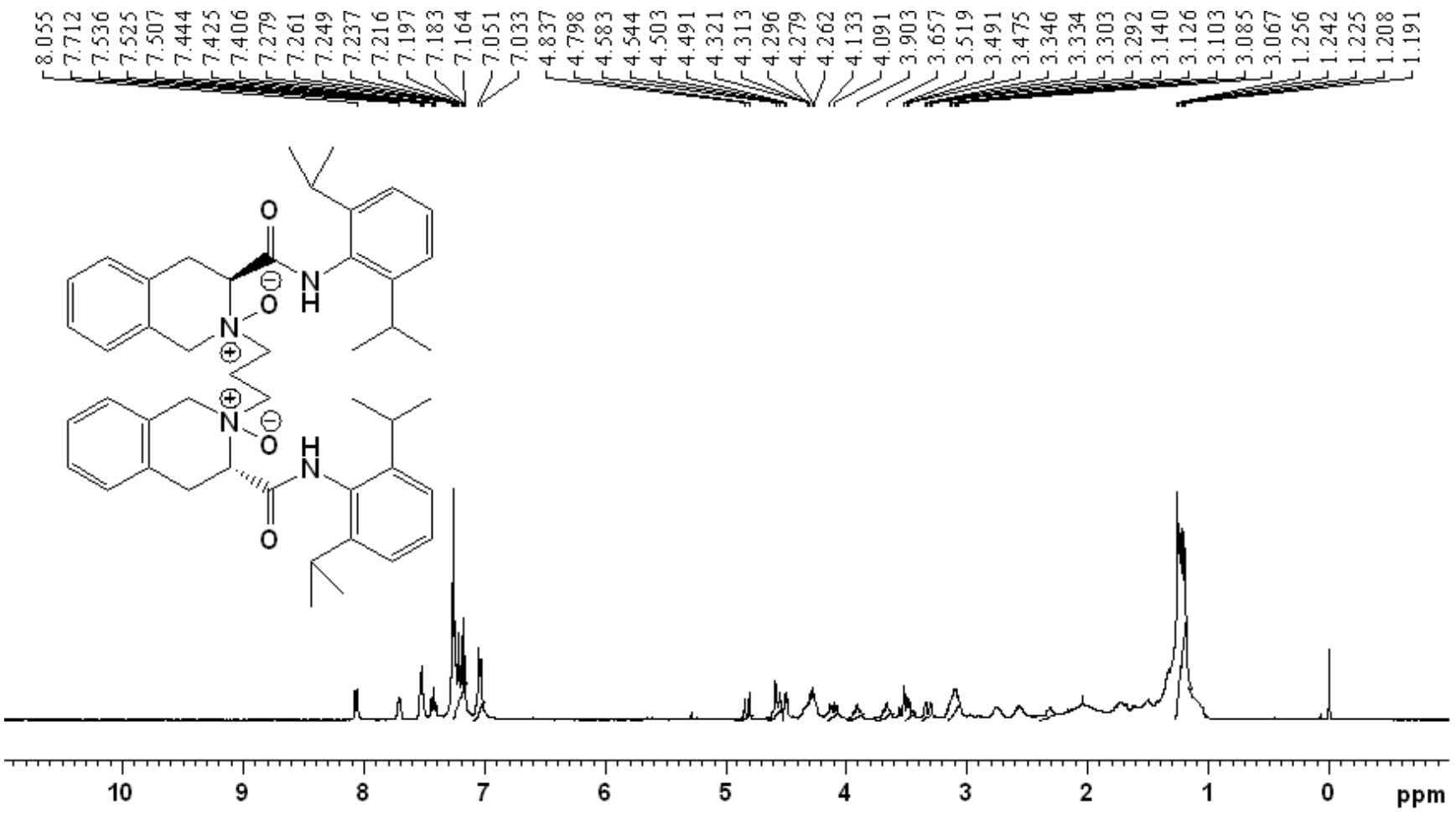
^{1}H NMR (400 MHz) Spectrum of Compound **22** in $CDCl_3$



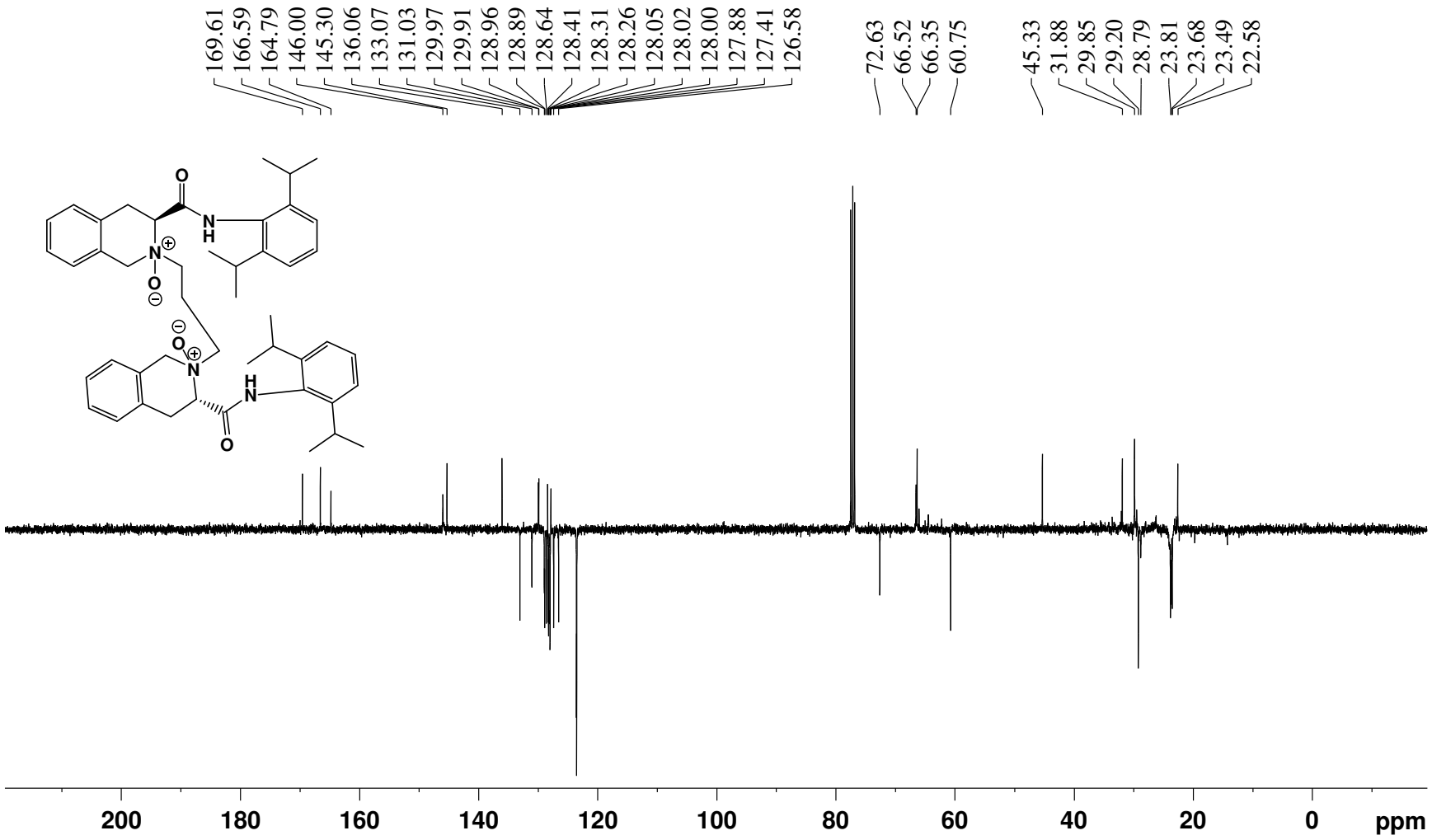
^{13}C (400 MHz) Spectrum of Compound **22** in $CDCl_3$



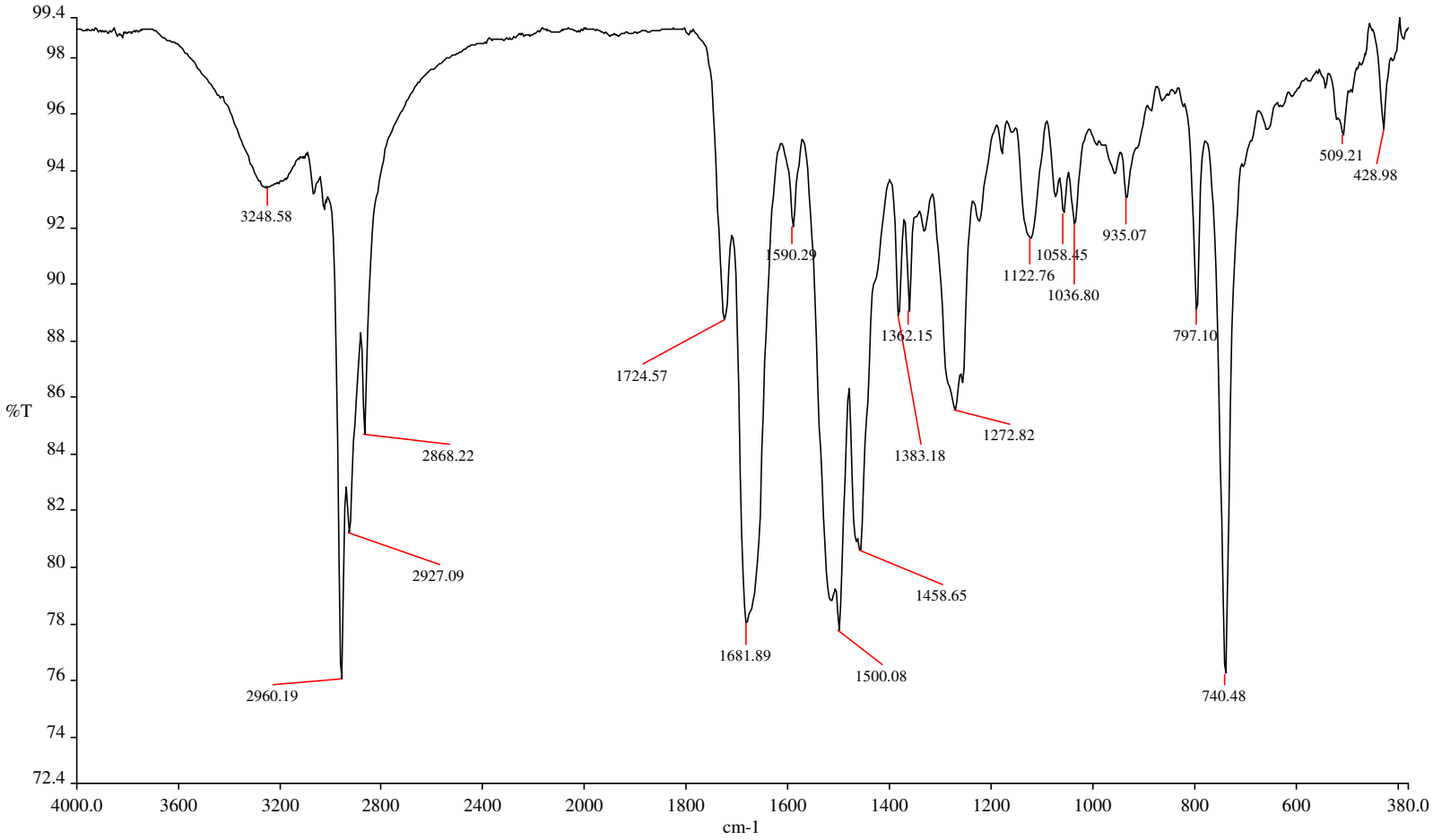
IR Spectrum of Compound **22**



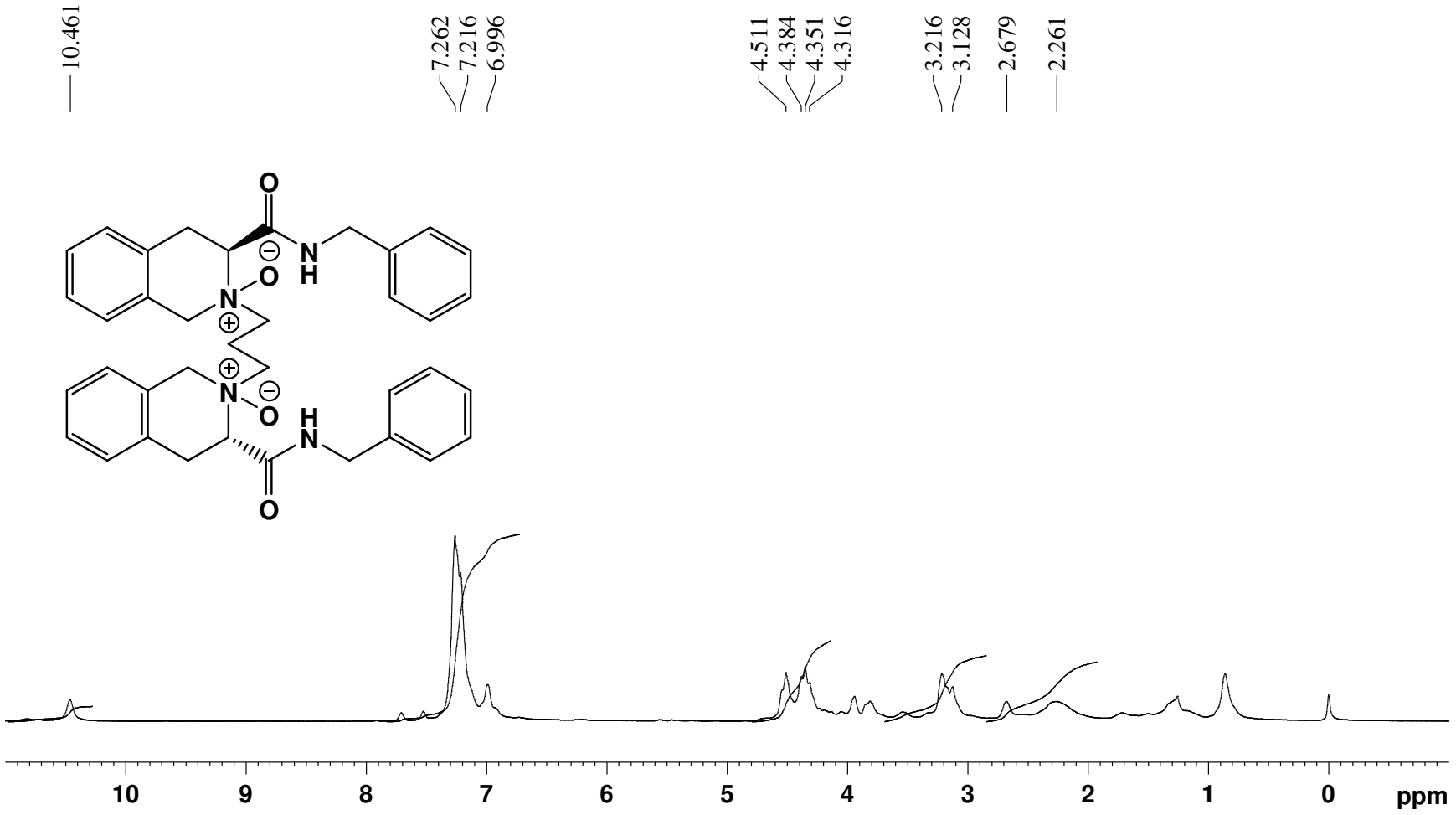
^{1}H NMR (400 MHz) Spectrum of Compound **23** in $CDCl_3$



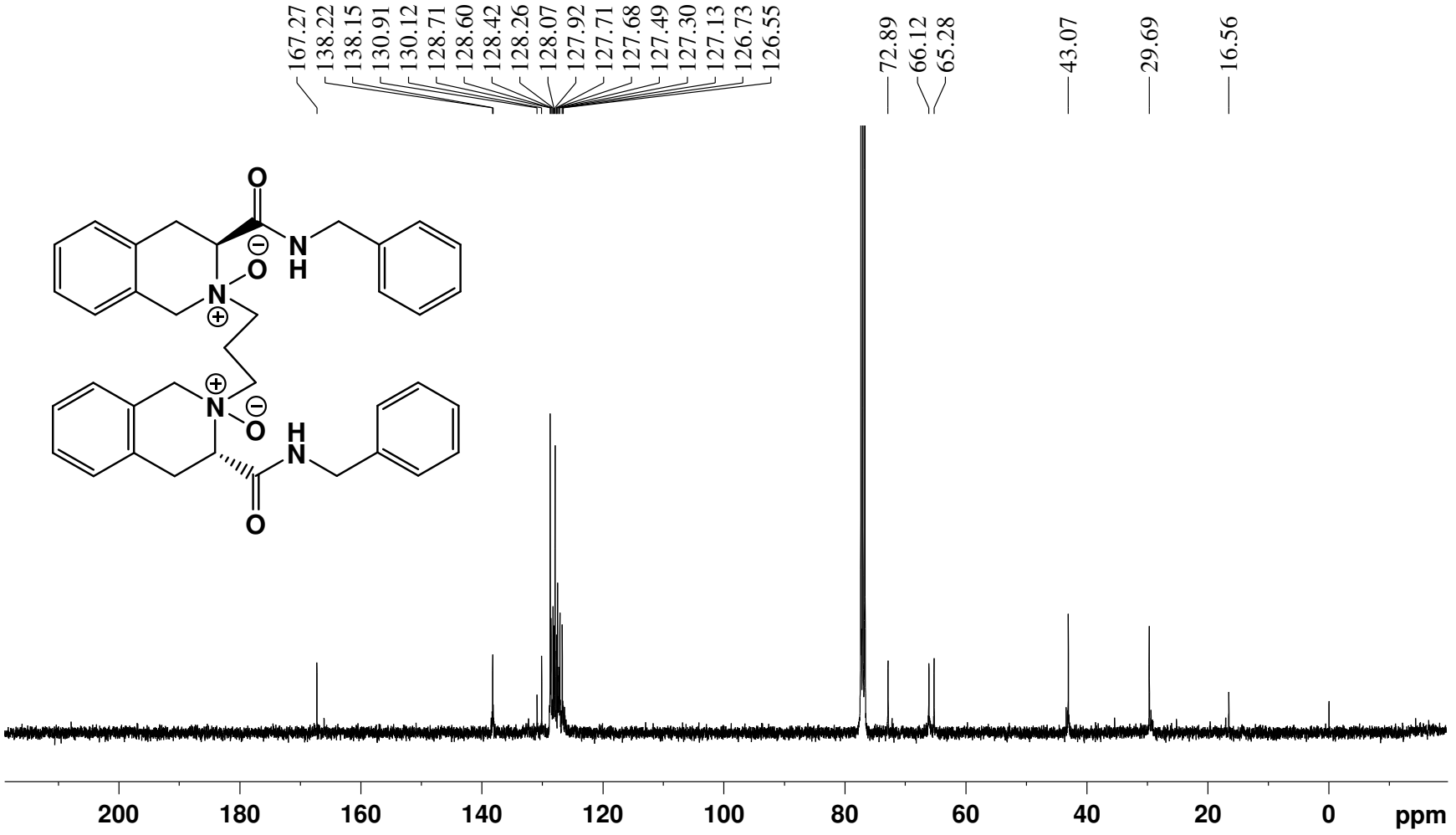
^{13}C (400 MHz) Spectrum of Compound **23** in $CDCl_3$



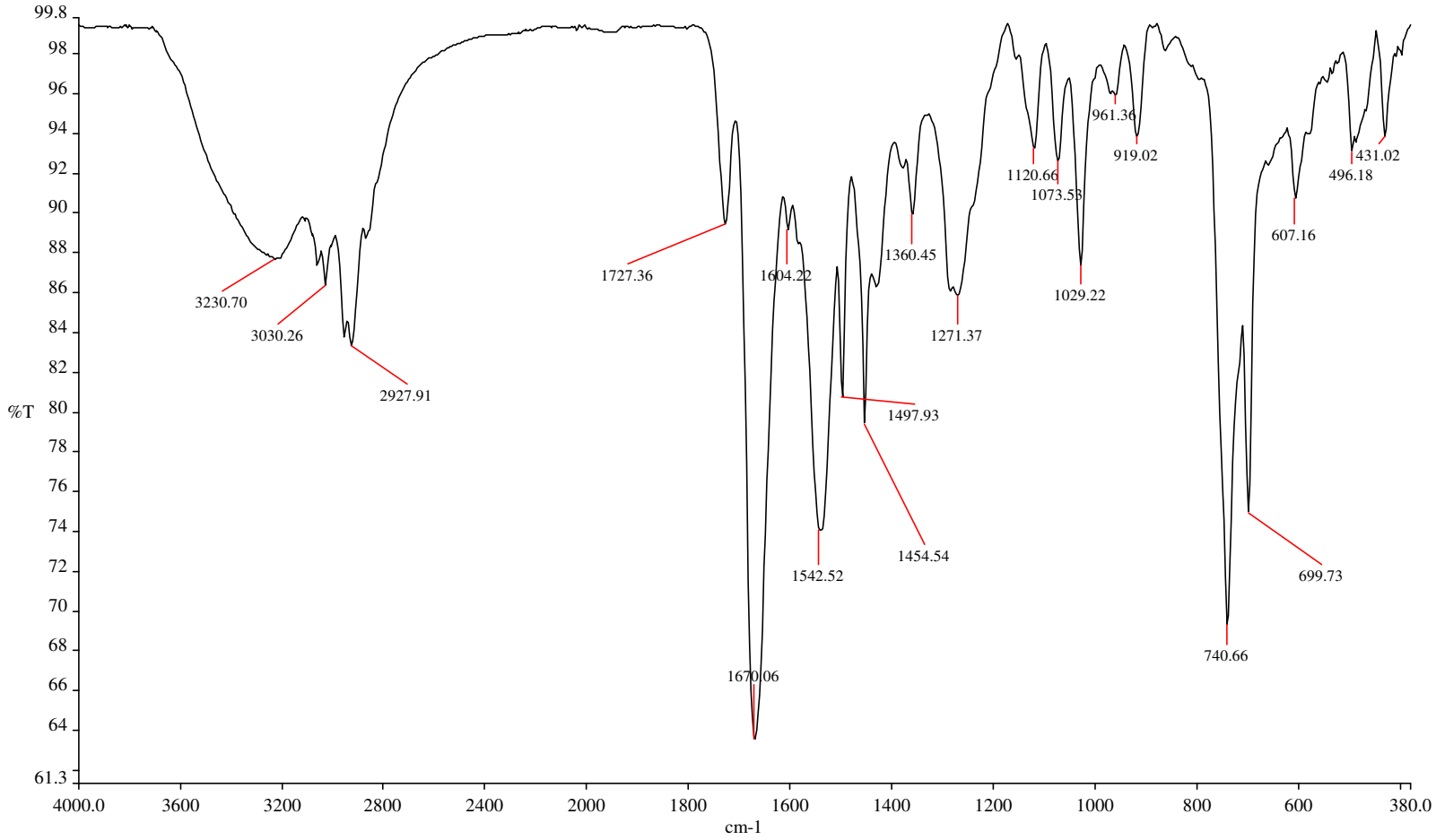
IR Spectrum of Compound **23**



^{1}H NMR (400 MHz) Spectrum of Compound **24** in $CDCl_3$



^{13}C (400 MHz) Spectrum of Compound **24** in $CDCl_3$



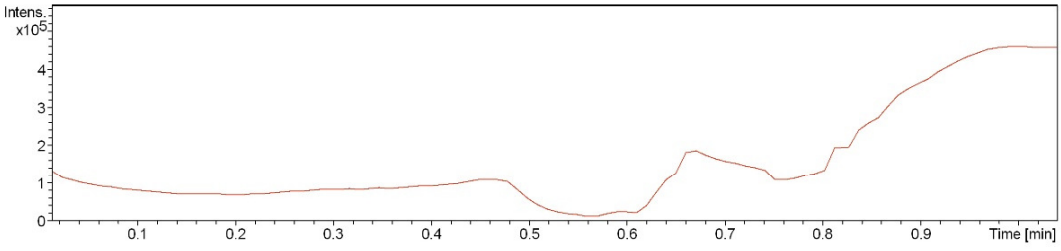
IR Spectrum of Compound **24**

Analysis Info

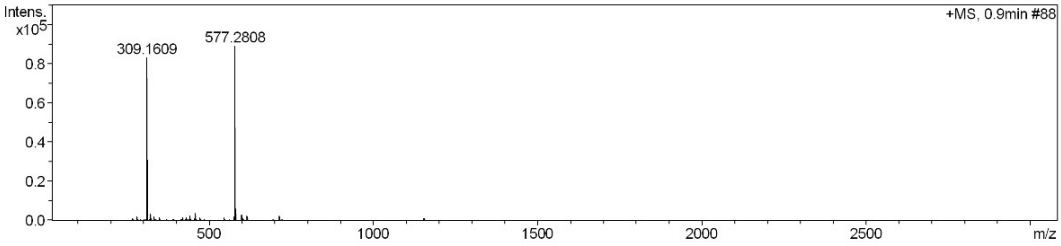
Analysis Name	D:\Data\sai\NOXIDE-PHENYL.d	Acquisition Date	10/23/2010 5:52:27 PM
Method	tune_wide_expert.m	Operator	BDAL@DE
Sample Name	NOXIDE-PHENYL	Instrument / Ser#	micrOTOF-Q 10139
Comment			

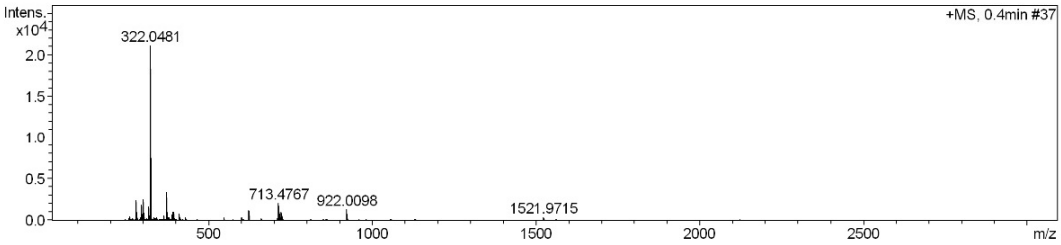
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	14.5 psi
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Source



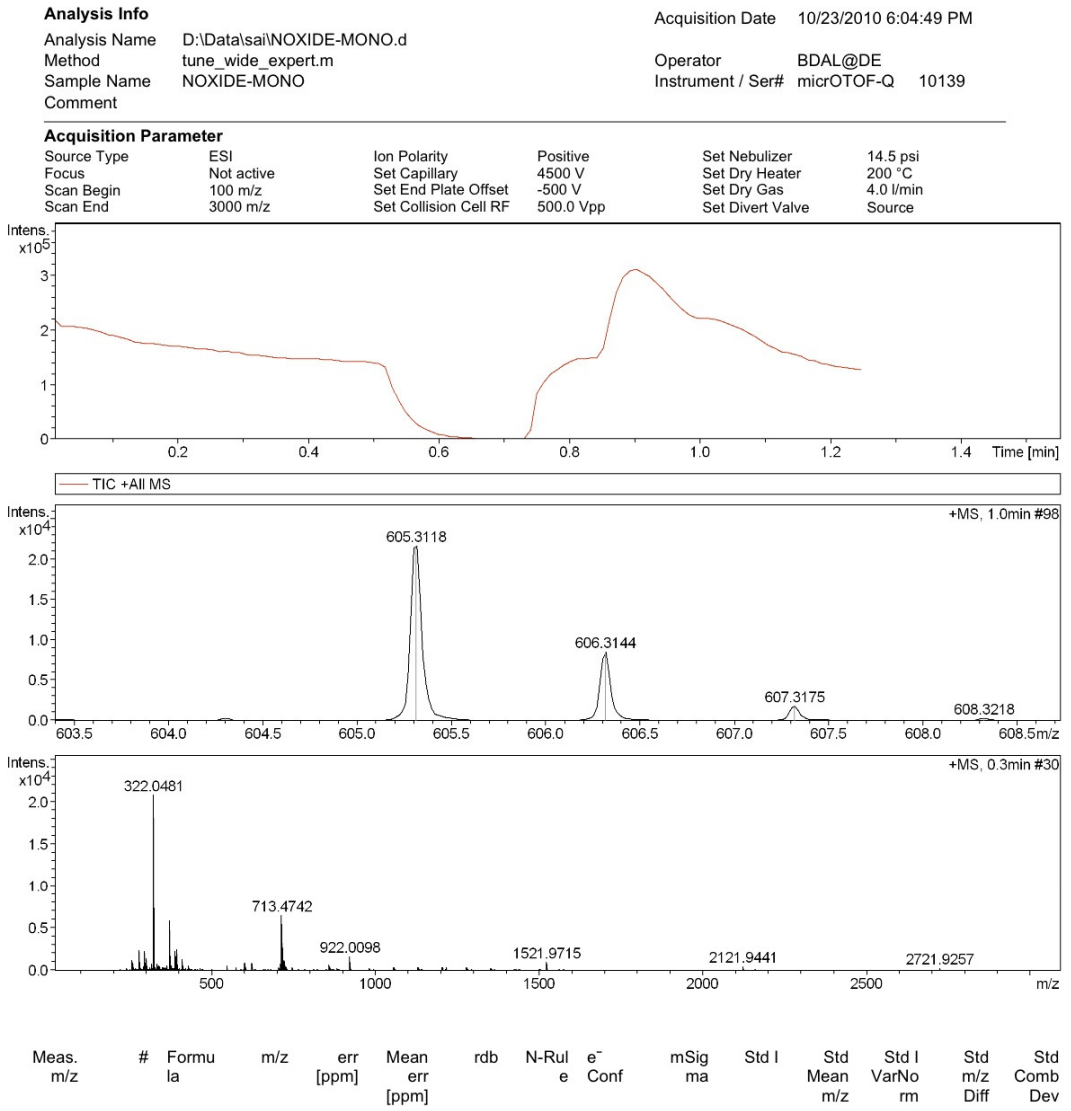
TIC +All MS



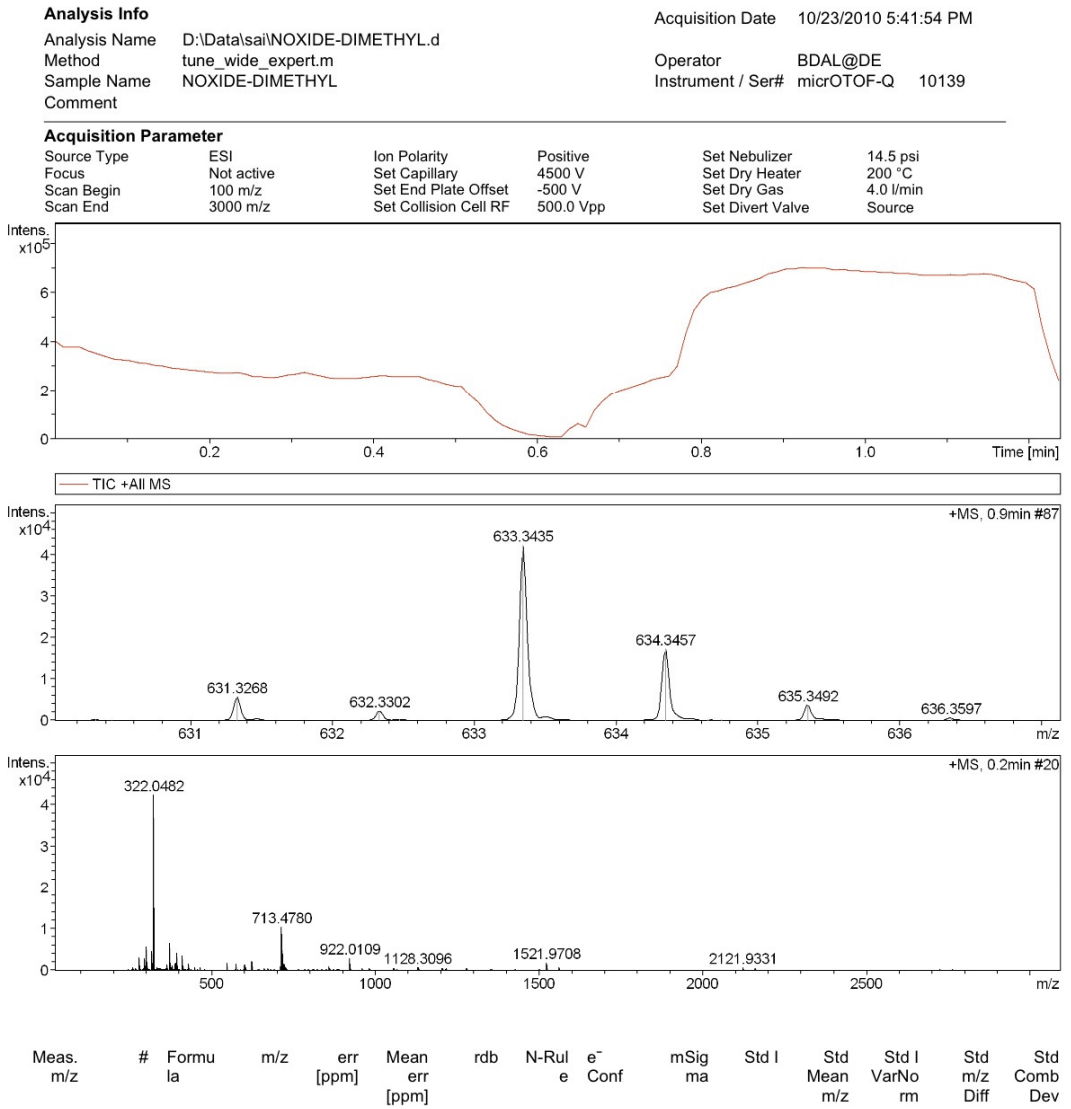


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev

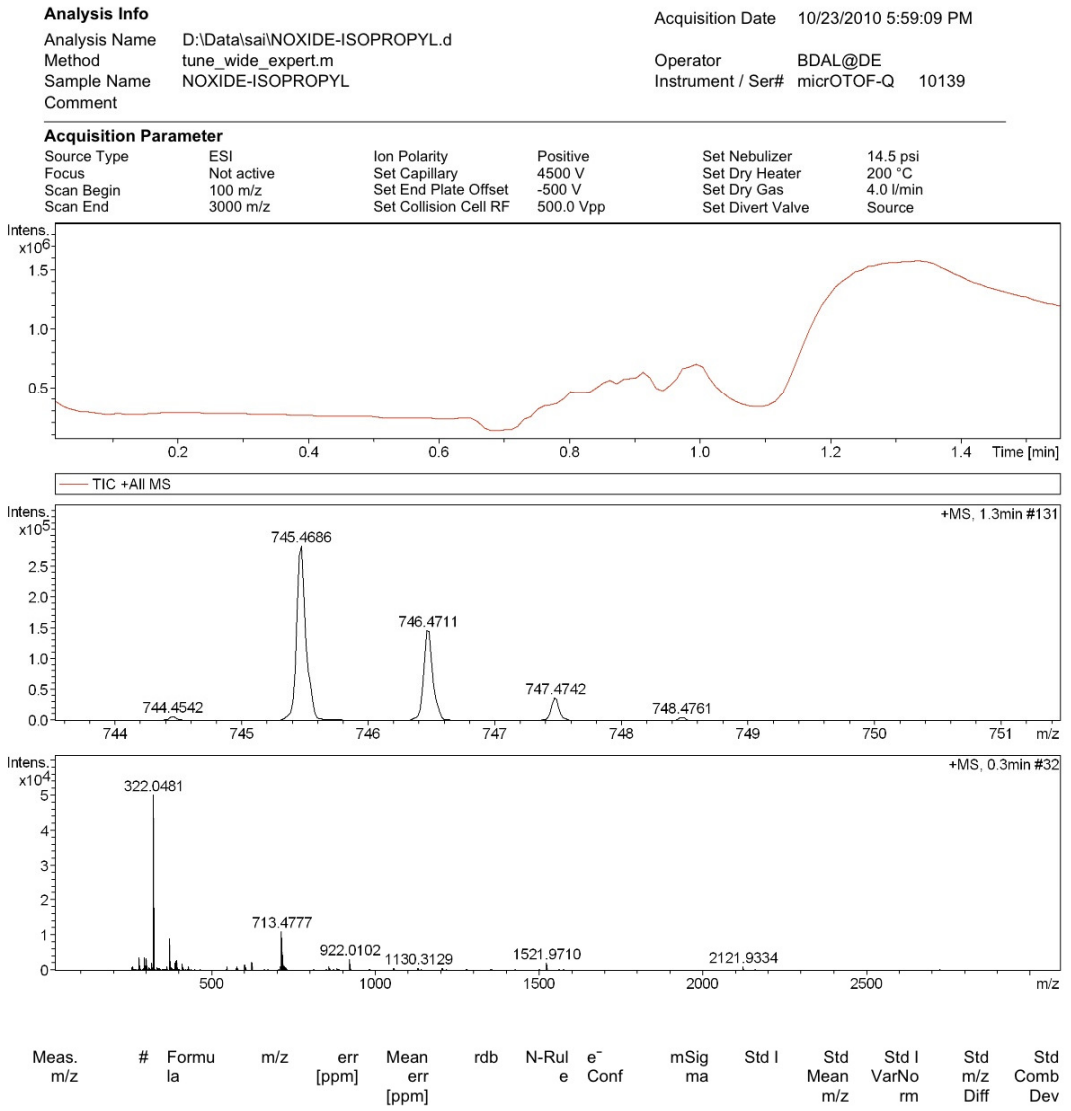
High Resolution Mass Spectrum of Compound **20**



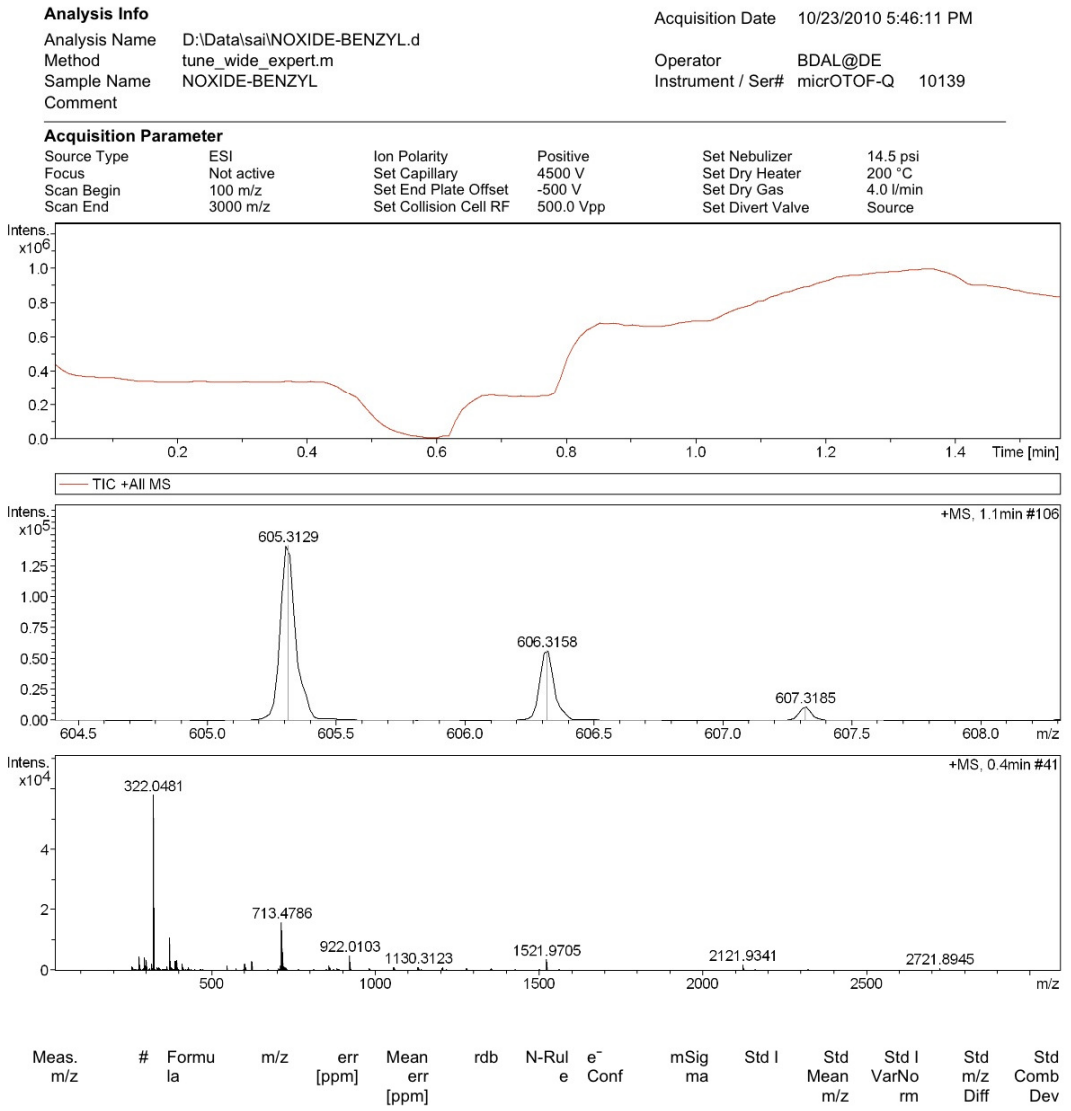
High Resolution Mass Spectrum of Compound **21**



High Resolution Mass Spectrum of Compound **22**



High Resolution Mass Spectrum of Compound **23**



High Resolution Mass Spectrum of Compound **24**