Synthesis of Novel Tetrahydroisoquinoline Chiral Ligands for Application in Asymmetric Transfer Hydrogenation

by

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As the candidate's supervisors I have / have not approved this dissertation for submission

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Abstract

Several tetrahydroisoquinoline (TIQ) diamine derivatives were prepared for use as ligands in asymmetric transfer hydrogenation (ATH) of acetophenone of which 17 intermediates and the eight target ligands were novel compounds. The initial design followed that of Noyori, who presented the efficiency of his monotosylated diamine in ATH. A series of eight novel secondary amine derivatives (**78a-g** and **88**) were prepared with substituents that influenced the electronics and the sterics of and around the nitrogen donor. Ligand **71** was shown to have no activity for the ATH of acetophenone. It was apparent from experimental observations that a balance between the electronic and steric characteristics of the substituent was necessary to facilitate activity. It was found that ligand **78d** possessing a benzyl group, had the greatest activity (81 % conv.). The greatest selectivity was obtained with ligand **78f** (77 % *ee*) having a chiral phenylmethyl substituent. It was discovered in the case of the active diamine ligands that an optimised 1500 equivalents of water was required in order to demonstrate any enantioselectivity. The exact role of the water has never been ascertained, although there are many publications in which the effect of water has been examined. The most active metal precursor was also investigated and $[RhCl_2(Cp^*)]_2$ was found to be the best for these TIQ diamine ligands in the specified model reactions. This work has recently been accepted for publication and has established criteria for further rational design on this system.

Declaration

The experimental work described in this dissertation was carried out at the School of Chemistry, University of KwaZulu-Natal, Durban from January 2009 to December 2009, under the supervision of Dr. Thavendran Govender, Prof. Gert Kruger and Dr. Glenn Maguire.

These studies represent original work by the author and have not otherwise been submitted in any form for any degree or diploma to any tertiary institution. Where use has been made of the work of others it is duly acknowledged in the text.

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Byron Kennedy Peters

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Date

Publication from this project

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Chapter 1

1.1 Origin & Importance of Chirality

Chirality is an expression of asymmetry, where an entity of any kind possesses a certain geometry which when casting a reflection of itself in a mirror, neither perspective can be superimposed on the other. There are many examples to demonstrate this concept; however by far the most extensively used is that of the left and right hand. When held up against one another (see Figure 1), the left hand can be said to be a reflection of the right hand and *visa versa* the right a reflection of the left. However, despite their similarities it is clear that it is impossible to superimpose one upon the other.[1-2]

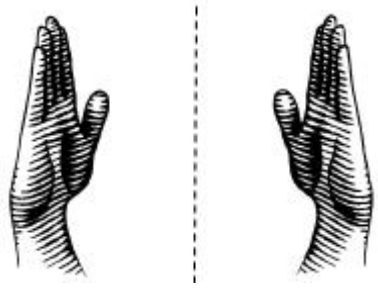


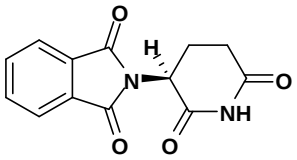
Figure 1: Representation of chirality

The term "chirality" was coined by the French chemist and microbiologist Louis Pasteur in 1848 whilst studying sodium ammonium tartrate crystals. By careful observation of the crystals, Pasteur was able to differentiate between the two forms. Pasteur discovered that the two crystalline forms rotated plane polarised light in opposite directions to one another but to the same degree. The term "enantiomer" was used to describe these molecules that possess no plane of symmetry and are non-superimposable mirror images of one another.[1-4]

Enantiomers, as is expected display similar spectroscopic properties, observed in Nuclear Magnetic Resonance (NMR) and Infrared (IR) spectroscopy; they also share similar macro structural and physiochemical behaviour such as melting point and solubility. However enantiomers differ greatly in the direction they rotate plane-polarised light and in the way they interact with other chiral species.[1, 4-6]

A variety of molecular components within biological organisms, are composed of or possess chiral molecules. These molecules are present almost entirely as one particular enantiomer;

examples of such are proteins, DNA, RNA and enzymes. Chirality plays an important role in senses such as smell, taste and in the way a drug or hormone will bind to an inherently chiral enzyme or protein. A biological response between enantiomers can differ, particularly with drugs and fragrances, examples are thalidomide **1** and carvone **2**. The (*S*)-(-) enantiomer of thalidomide **1a** in addition to relieving nausea leads to birth defects to the foetuses of pregnant women users, whilst the other (*R*)-()+ enantiomer **1b** only has a sedative effect. Carvone produced by the caraway plant, has an anise type odour indicative of the (*S*)-(-) enantiomer **2a** and also a spearmint type odour attributed to the (*R*)-(+)-enantiomer **2b**.[1, 3]



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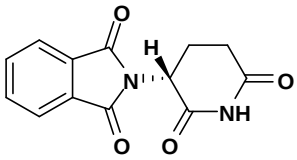
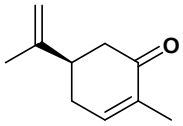
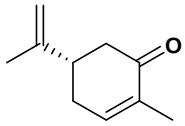


1b



2a



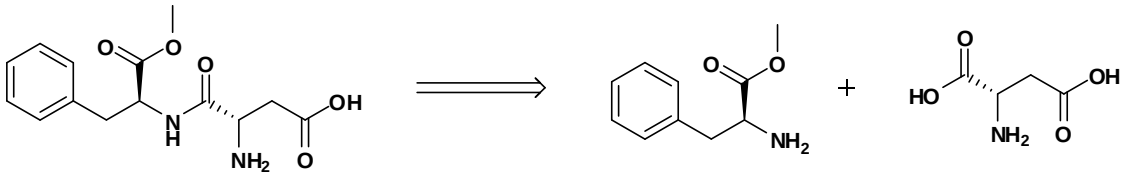
2b

1.2 Routes to Obtain Optically Pure Compounds

There are three basic strategies to obtain optically pure compounds. They are namely: the "chiral pool", resolution of racemates and asymmetric synthesis. The first two will be discussed briefly.

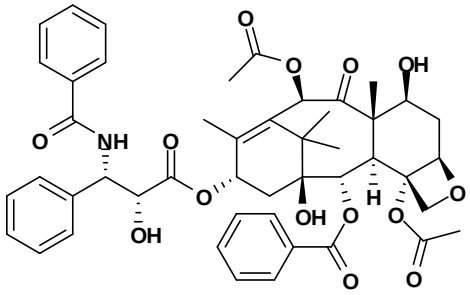
1.3 The "Chiral Pool" Strategy

This strategy utilises the abundant and diverse list of enantiomerically pure compounds that nature produces routinely, for the required application. Typical members are amino acids, sugars and terpenes among others, these all fall within the "chiral pool". An example of a synthetic application of this strategy would be the preparation of aspartame **3**, an artificial sweetener whose structure is a relatively simple dipeptide. Employing a retro-synthetic approach, it can be seen that two natural amino acids; (*S*)-phenylalanine methyl ester **4** and (*S*)-aspartic acid **5** can be condensed (using an orthogonal protection strategy) to form the desired aspartame.[7]



3 **4** **5**

In this instance, the chiral pool appears to be an attractive solution to obtain enantiomerically pure compounds. However this is not always the case, although nature has a large supply of these chiral derivatives, one that suits the needs or at least mimics the desired structural features closely enough is not always available. Another drawback is that these chiral compounds are often in small amounts within a plant or animal, sometimes requiring the organism to be destroyed to isolate enough material. Despite these short comings the chiral pool still has application in this regard *i.e.* the anti-cancer drug Taxol **6**, which is extracted from the yew tree.[8]



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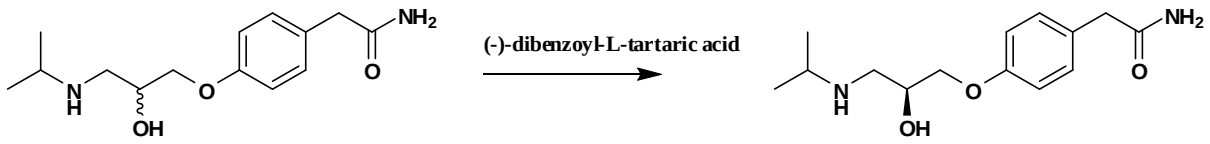
1.4 Resolution of Racemates

Resolution in essence is the separation of an equimolar mixture of two enantiomers (racemate), a difficult task given that they possess virtually identical properties. There are several means of resolving racemates; (i) enzymatic methods which are naturally selective, (ii) conversion of the enantiomers into diastereomers with the use of a chiral resolving agent, making them amenable to chromatography or recrystallisation, and finally there is (iii) chiral chromatography.[1, 9] Fodor *et al.* in 1949 showed that they were able to demonstrate resolution by method (i) *via* selectively hydrolysing one enantiomer (L) from a racemic mixture of *N*-acetylated amino acids with the use of an enzyme extracted from a hog kidney.[10-12] The beta blocker (*S*)-(-)-propanolol **8**, which possesses one chiral centre can be purified from a racemic **7** mixture by selective precipitation of the (*S*)-isomer as a salt formed with (-)-dibenzoyl-L-tartaric acid, in this respect the (-)-dibenzoyl-L-tartaric acid acts as the chiral resolving agent, even though a covalent bond is not formed.[13] This is an example of method (ii).



7 **8**

Chiral resolution is indeed an attractive means to obtain optically pure compounds. However the major drawback in this approach is the poor yields, theoretically only 50 % can be obtained from a racemic mixture. Attempts have been made to solve this problem, such as forcing the compound back to a racemic mixture so that the process can be repeated to obtain more of the desired enantiomer.[14-15]

1.5 Asymmetric Synthesis

Asymmetric synthesis involves the preparation of a substance with one or more chiral centres, however in a fashion that regulates the absolute stereochemistry of these centres to a single desired configuration. There are several approaches that can be undertaken which fall under this strategy:

Substrate-Controlled

The starting material possesses both a prochiral site and a sterogenic centre. Chiral induction is said to be substrate controlled when conversion of the prochiral centre to a chiral centre is influenced by the existing chiral centre either by steric effects, or by aiding in the chiral inducing reaction. Figure 2 shows the "Active" and "Passive" pathways for substrate controlled asymmetric synthesis. As it is seen, passage is said to be active when the chiral component of the substrate takes part in the transition state or intermediate formation step, in turn influencing the stereochemical outcome of the reaction. During the epoxidation of the unsaturated cyclopentane alcohol, a hydrogen atom is shared between the alcohol group and the *m*-chloroperbenzioc acid (*m*-CPBA) epoxidation reagent (shown in box). The pathyway is said to be passive if the existing chiral centre of the substrate does not partake in the formation or destruction of the transition state or intermediate species. However, only acts to mediate the geometry of how the another molecule or substrate itself can interact with one another (steric argument). This is illustrated in the passive manor in which the stereochemically defined methyl group of the cyclic pentanone influences the means of attack of the Grignard reagent (PhMgBr). Since the phenyl group is large, it is easier to attack *trans* to the methyl group and hence the ratio of 99:1 *trans*:*cis*.[1, 16-19]

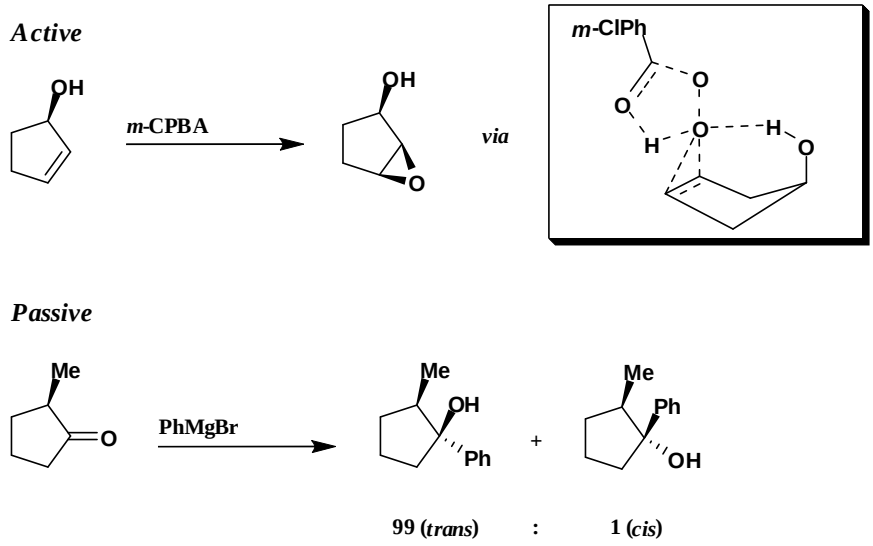


Figure 2: Substrate controlled asymmetric synthesis

Auxiliary-Controlled

A chiral auxiliary is attached to the molecule; the auxiliary is enantiomerically pure and serves to assist in the chiral inducing reaction. The auxiliary is then removed after the reaction or at a later stage of the synthesis.[1, 20-25] From Figure 3, the cyclic compound (red), which has an existing chiral centre of known stereochemistry is used to build another molecule. At a crucial step of the synthesis, the existing chiral centre on the auxiliary molecule influences the sterochemical outcome of the conjugate addition reaction using benzylbromide and lithiumdiisopropylamide (LDA). After the auxiliary molecule has achieved its purpose, it can subsequently be removed to generate either the target molecule or one of the building blocks. In the example the aldehyde (blue) is generated in 95 % enatiomeric excess (*ee*) and the auxiliary is also regenerated.[26-27]

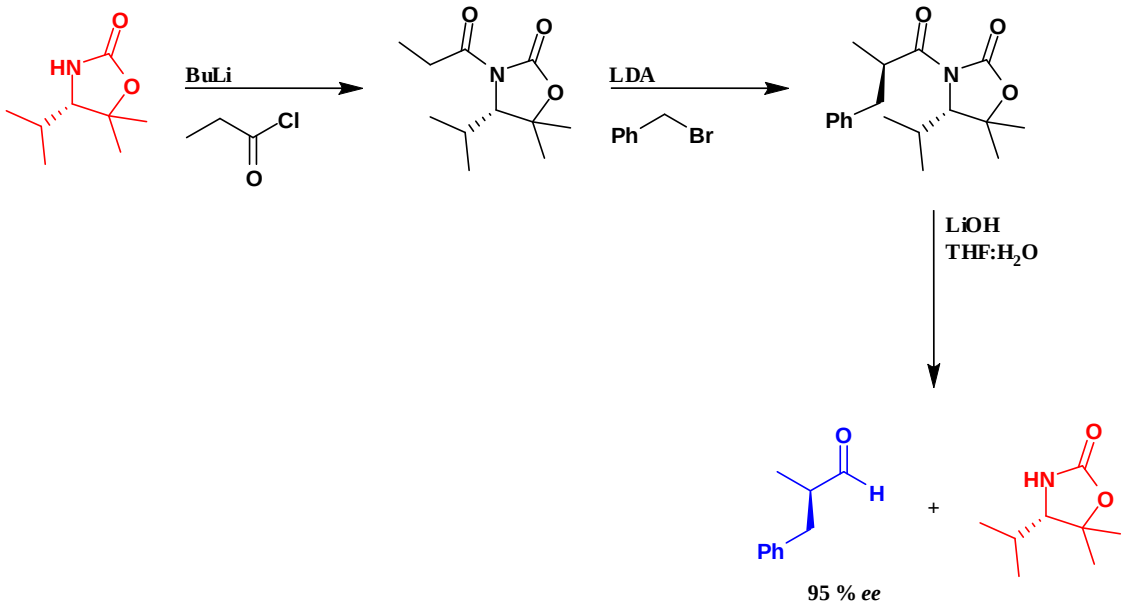


Figure 3: Auxiliary controlled asymetric synthesis

Reagent-Controlled

The reagent used to introduce chirality to the substrate is itself chiral, and therefore chirality in this instance is said to be reagent controlled.[1, 28-29] This method is expensive and impractical if the reagents are consumed during the reaction. An example of this demonstrated in Figure 4, where an aldehyde undergoes a Corey-Chaykovsky transformation to an epoxide. Using the chiral (+)-ylide, the authors were able to achieve up to 99 % *ee* in some cases. The is converted into its corresponding sulphide derivative after the reaction *i.e.* it is consumed.[30]

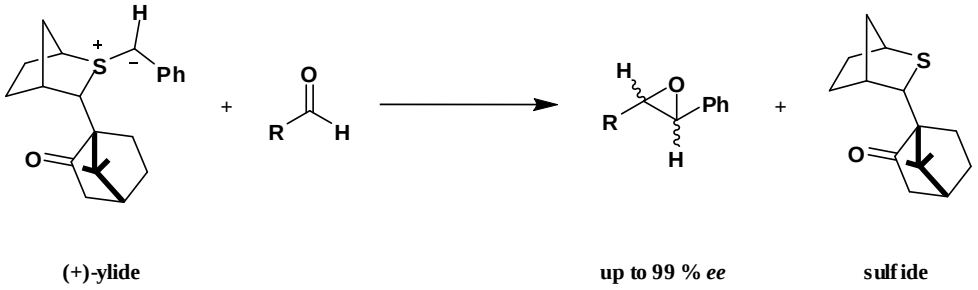


Figure 4: Reagent controlled epoxidation of aldehydes with sulphur ylides[30]

Catalyst Controlled

A chiral catalyst with known absolute stereochemistry is used in small quantity, to convert the achiral substrate to a chiral one.[1, 28, 31-33]

1.6 Asymmetric Catalysis

These can be grouped into three main classes, namely; biocatalysis, organocatalysis, and metal ligand complexes as catalysts:

Biocatalysts

This approach uses naturally occurring enzymes and proteins to carry out asymmetric transformations on unnatural substrates. Because the catalyst is derived from nature, selectivity is high (>95 %), however this method is not without its drawbacks. Reaction rates are readily slow, the reaction conditions for the catalyst to operate are stringent and obtaining sufficient quantities of the catalyst is difficult.[15, 34-36] The enzymes are also in most cases very specific with the result that a narrow range of substrates only can be used. The field is still being developed and new methods are appearing in literature, albeit at a relative slow pace. The selective hydrolysis of *N*-acetylated amino acids using an enzyme found in a hog's kidney shown by Fodor *et al* mentioned earlier is an example of biocatalysis (Figure 5).

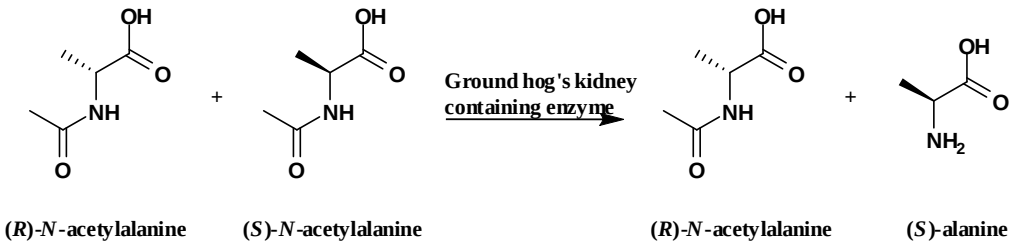


Figure 5: Selective deacetylation of racemic acetylalanine: an example of biocatalysis

Organocatalysts

In this approach the catalytic process is completely controlled by the action of a chiral organic compound. This has become an attractive area of research with many recent publications and reviews detailing the scope of these types of catalysts. Some of the drawbacks are the high catalyst loading and often the reaction times are over a period of several days. However, despite these shortcomings the use of organic molecules over expensive metal catalysts has received much attention and is certainly an important field of research.[33, 37-40] In many was organocatalysis mimics a reagent controlled approach, where the transformation and process is influenced by the two. However, the fundamental difference between a reagent controlled and organocatalytised reaction, is that the organocatalyst is regenerated after partaking and is free to repeat the process, whereas the reagent is not.

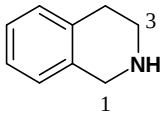
Metal-Ligand Complexes as Catalysts

This approach employs both a metallic and an organic species to catalyse the reaction transforming the achiral substrate to a chiral product with preference to a particular enantiomeric form.[1, 9] Contrary to many organocatalytic reactions, metal-ligand catalysts typically require only minuscule molecular loading, the reactions can be fast and the catalysts in some cases recoverable. Some of the drawbacks are the use of expensive and rare metals such as ruthenium, rhodium and iridium.[1, 41-45]

Metal-chiral ligand complexes and their ability to enantioselectively catalyse reactions that transform an achiral substrate to a chiral product is an integral part of this work. Therefore this subject will be discussed with relevance to the project within proceeding sections.

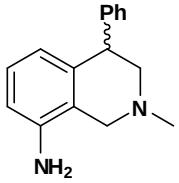
1.7 Tetrahydroisoquinoline Compounds

The tetrahydroisoquinoline (TIQ) skeleton provides useful a scaffold that has found applications in a diverse range of chemistry. The basic structure of the 1,2,3,4-tetrahydroisoquinoline **9** is shown. A six membered heterocyclic ring fused to an aromatic species are the basic features for TIQ classification.



9

Most of the earlier exploitations of the TIQ framework were directed towards pharmaceutical applications.[46-53] Interest in their activity as antiparkinson‘s disease drugs *i.e.* Nomifensine **10**, was noticed in the 70’s.[54] One very popular example of a TIQ based drug is Praziquantel **11**, an anthelmintic which is used for the treatment of human schistosomiasis (bilharzias).[55] There are many other biologically active TIQ compounds.[56]



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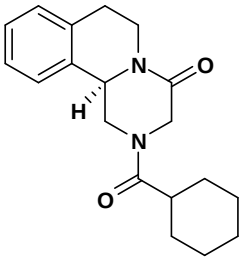

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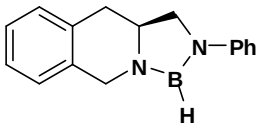
Recently, TIQ's have also been found to act as ligands in a number of asymmetric reactions.[57-61] Basavaiah *et al.* (2009) demonstrated a TIQ oxazaborolidine **12**, similar to the Corey-Bukshi-Shibata (CBS) catalyst **91**, for the reduction of prochiral ketones.[59, 62] The catalyst was able to reduce the substrates to the alcohol products in high yields (> 90 %), but in poor to good enantiomeric excess (19 – 91 %). Another catalyst, an aminophosphine-oxazoline **13** was used by Blanc *et al.* to carry out asymmetric allylic alkylation reactions. The catalyst was able to deliver the chiral products in quantitative yields and in good enantioselectivity (89 – 93 % *ee*).[57] Our group has recently reported the use of the TIQ amino alcohol **14** derivative for asymmetric transfer hydrogenation of prochiral ketones with high reaction rates (< 60 minutes) and moderate to good selectivities (65 – 94 % *ee*).[61] Our group reported the activity of several 3- and 1,3-substituted TIQ amino alcohol ligands. The investigation revealed ligand **14a** (3-substituted) to possess poor activity (28 % conv.) with poor selectivity (35 % *ee*) for ATH of some aromatic ketones. Ligand **14b** was found to have no activity. In the case of the 1,3-substituted TIQ ligands, the *cis* isomer **14c** was found to give good conversion (80 %) but as a racemic mixture. However, the other derivative **14d** was found to have good activity (94 % conv.) and excellent selectivity (94 % *ee*).[61]



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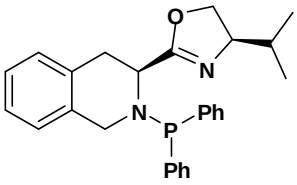

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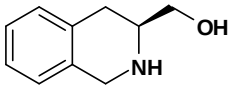
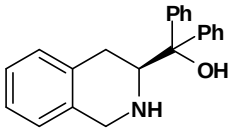
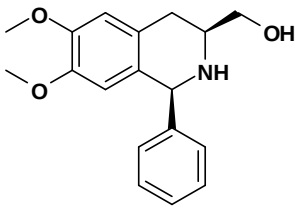


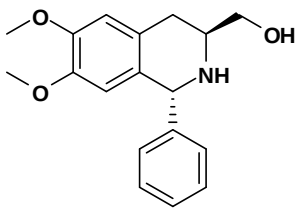
14a



14b



14c

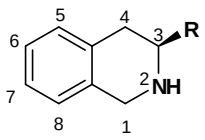


14d

This project follows on from our recently published work with the reduction of prochiral ketones, using instead chiral TIQ diamine donors as ligands for asymmetric transfer hydrogenation reactions.

1.8 Scope of Investigation Pertaining to Asymmetric Catalysis

This project is focused towards utilizing novel 3- and 1,3-substituted *N,N* donor 1,2,3,4-tetrahydroisoquinoline (TIQ) compounds for asymmetric transfer hydrogenation (ATH) of acetophenone. Many TIQ compounds are prepared from precursors with existing chirality such as phenylalanine and dihydroxyphenylalanine (L-DOPA) making chirality appendable on the TIQ backbone.[63] Given the versatility in tethering the TIQ structure and the rigidity provided by the backbone, it holds the potential to be a useful ligand in asymmetric transfer hydrogenation reactions. Figure 6 represents the 3-substituted **15** and 1,3-substituted **16** TIQ skeletons that were used in this study.



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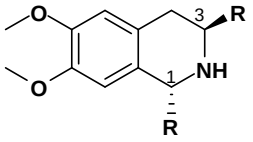

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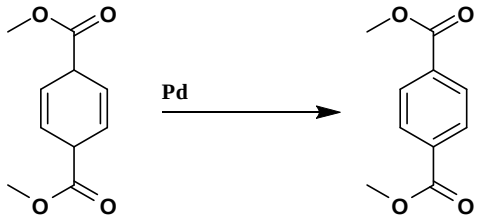
Figure 6: TIQ backbones used in this study

1.9 Asymmetric Transfer Hydrogenation (ATH)

One of the first chemists to notice that hydrogen can be supplied from another source other than hydrogen gas was Knoevenagel[64-65] in 1903, when he found that in the presence of palladium black (elemental palladium), dimethyl 1,4-dihydroterephthalate (**17**) was converted to dimethyl terephthalate (**18**). This irreversible process inspired thoughts of a safe and environmentally benign hydrogen fuel. Braude *et al*. in 1952, applied this observation to reduce ethylene and acetylene type groups with palladium black employing cyclohexene as the hydrogen source.[65-66]



17 **18**

ATH was first inspired by the Meerwein-Ponndorf-Verley reduction, discovered in 1924 by Meerwein *et al*. The reaction involves the reduction of aldehydes and ketones with aluminium

isopropoxide in isopropanol (IPA), as shown in Figure 7.[67] The hydrogen source (HS) is IPA, upon which the aluminium isopropoxide facilitates the hydride transfer from the IPA to the substrate. Since the discovery, there have been many recent publications increasing the scope of this reaction.[68-70]

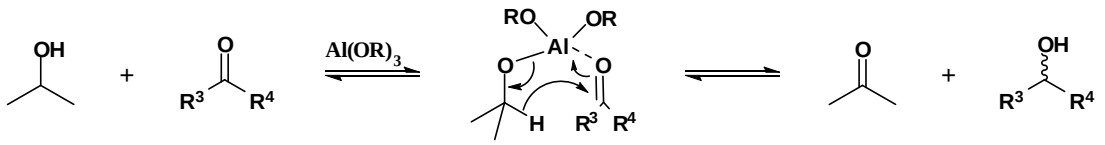


Figure 7: Meerwein-Ponndorf-Verley reaction [71]

Originally the honours go to Willy Marckwald in 1904, for identifying that catalysis lent itself to asymmetric control.[72] Marckwald demonstrated the enantioselective decarboxylation of 2-ethyl-2-methylmalonic acid to 2-methylbutanoic acid using the alkaloid brucine.[73] William Knowles and Ryoji Noyori have pioneered and contributed significantly to the field of asymmetric transfer hydrogenation over the past two decades. Knowles was the first to introduce asymmetric hydrogenation on an industrial scale, with the enantioselective reduction of a precursor to L-DOPA, an anti-Parkinsons drug.[73] These advances have lead to increased investigations into the scope of ATH reactions.[74]

An accepted mechanism for ATH is represented in Figure 8 using the (1*S*,2*S*)-*N*-(*p*-toluenesulfony1)-1,2-diphenylethylenediamine (1*S*,2*S*-Ts-DPEN) as a ligand[+].[74-77] The ligand first coordinates to the ruthenium metal precursor to form **19**. Available base removes a proton from the amine and a chloride from the Ru centre, HCl is liberated and the unstable 16 electron species **20** is generated. A molecule of IPA **21** is attacked by **20** and a hydride is transferred to the metal and a proton to the amine (shown by **22**). The loss of the hydride leads to oxidation of the IPA forming acetone and rendering the metal hydride **23**. The hydride species **23** reacts with the prochiral ketone (acetophenone) **24** as shown by **25**, where the hydrides are transferred to the substrate along with chiral information from the catalyst. After the transfer is complete the alcohol product (1-phenylethanol) **26** is released and the 16 electron species **20** is reformed. Not only in this instance, but on any occasion when IPA is employed as the hydrogen source the reaction is subject to reversibility.

[+] Structure of the ligand also shown later on in the text, Chapter 2, p18.

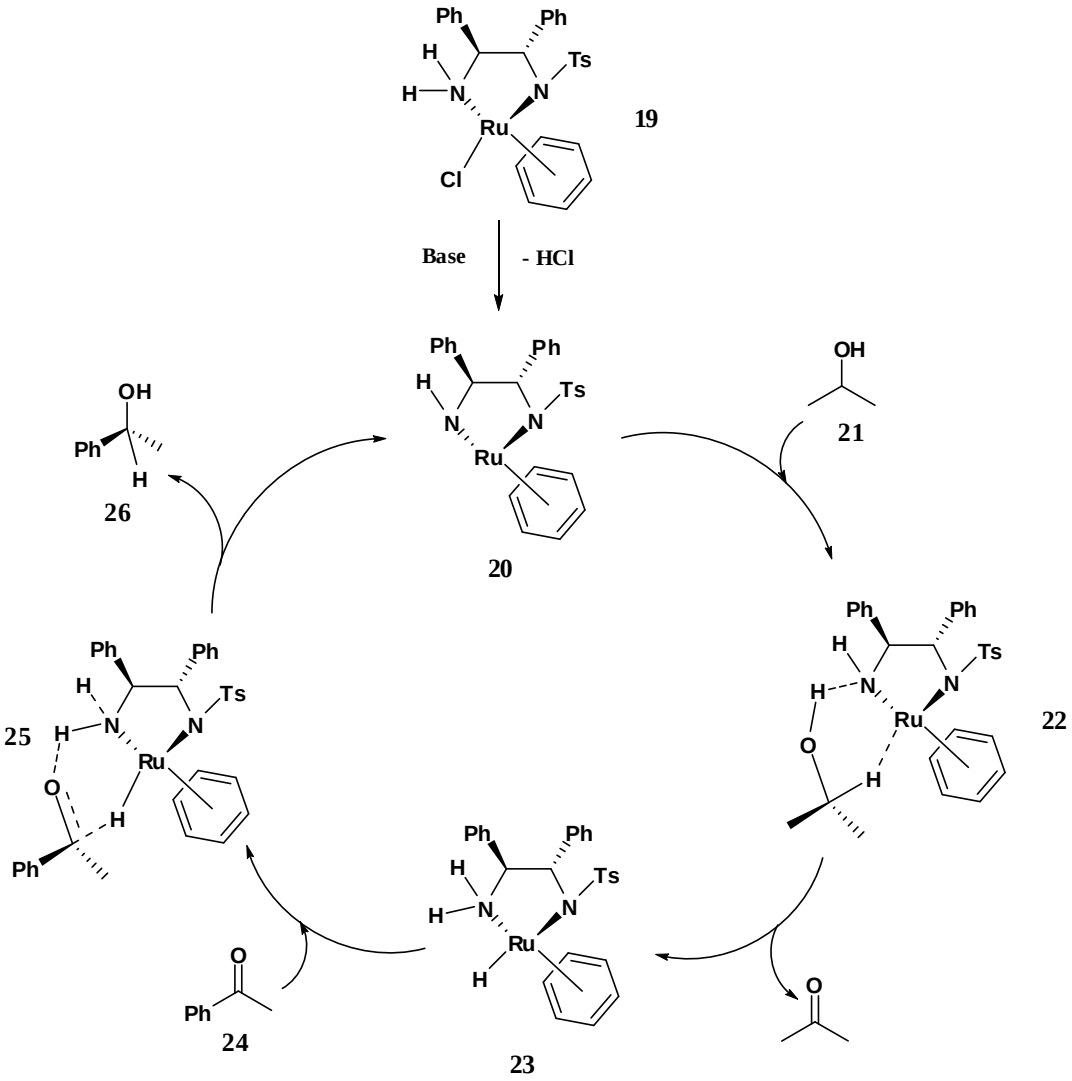


Figure 8: Pathway of ATH[78, *]

The addition of a base was found to accelerate reaction rates and increase turnover numbers (TON) of these reactions. To contend with, an earlier discovery by Parnes *et al.* in 1960 revealed that an azeotropic mixture of formic acid and triethylamine (TEAF) could also be used as a source of hydrogen, but at the time was used with only moderate success.[79] Fujii *et al.* in 1996 found the advantages of TEAF in place of the IPA HS with their catalyst, obtaining quantitative yields and optical purities of greater than 90 %, demonstrating TEAF to be an attractive alternative.[78] The mechanism for TEAF is similar to that of the IPA with the exception that an irreversible oxidation to carbon dioxide occurs upon hydride removal from the formic

[*] The mechanism is adapted from reference 78, and is widely accepted in the literature. It is noted that the stereochemical outcome of the reaction going from transition state 25 to compound 26 appears to be wrong, and that the other enantiomer should have been produced given the representation.

acid. Although a useful alternative, ATH reactions using TEAF often require longer reaction times than those with IPA.[78]

1.10 Substrates Covered by ATH

Asymmetric transfer hydrogenation has been applied to a diverse range of substrates which can be categorised into three groups; ketones, α,β-unsaturated compounds and imines. It should be noted that the catalyst designs and choice of metal precursors used will be outlined in more detail in Chapter 2.

Ketones

Prochiral ketones have been the most extensively studied substrates for ATH, more specifically aromatic ketones such as acetophenone (**25**).[80-81] Most of these aromatic and some aliphatic ketones are reduced to the chiral alcohol products in excellent yield and optical purity.[78, 82-85] These simple ketones are typically the bench mark when screening any new catalysts for activity in ATH. Figure 9 shows some of the more "exotic" and difficult ketone substrates that have been reduced with at least a significant degree of success in ATH.[74, 86]

Watanabe *et al*. in 2002, investigated ATH of α-functionalised-acetophenones such as **27**, the (*S,S*)-TsDPEN ligand was employed with a $[Ru(p\text{-cymene})Cl_2]_2$ metal precursor (MP) and TEAF HS.[87] The catalyst produced the chiral alcohols in enantiomeric excess > 90 % (*ee*). Subsequent reduction of azide, nitro and cyano groups, using palladium on carbon or borane dimethylsulphide complex gave the amino alcohols without change in optical purity.[74, 87] Later work by Hamada *et al*. in 2004 focused more on the ATH of α-chloroacetophenone derivatives **28**, which served as intermediates for enantiomerically pure epoxides.[88]

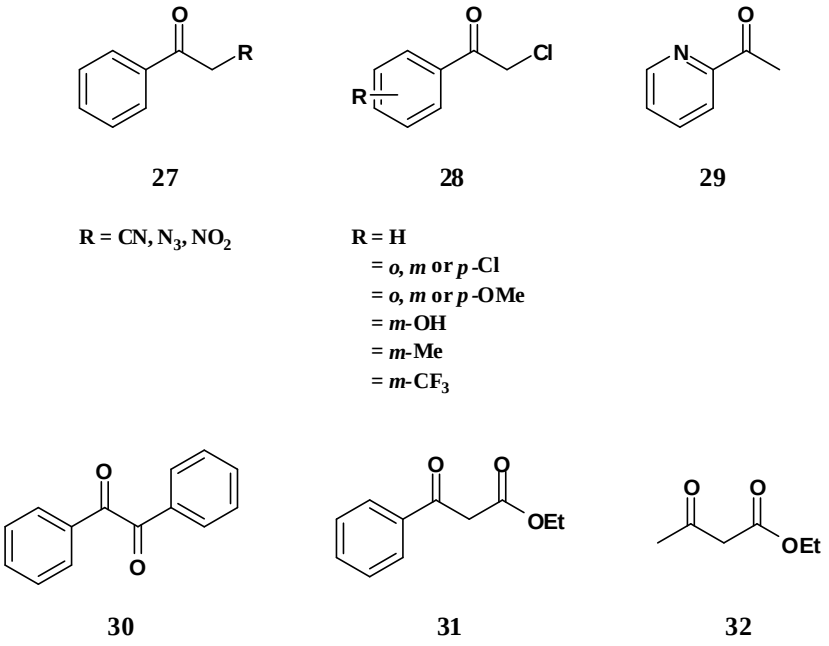


Figure 9: Ketone substrates used in ATH

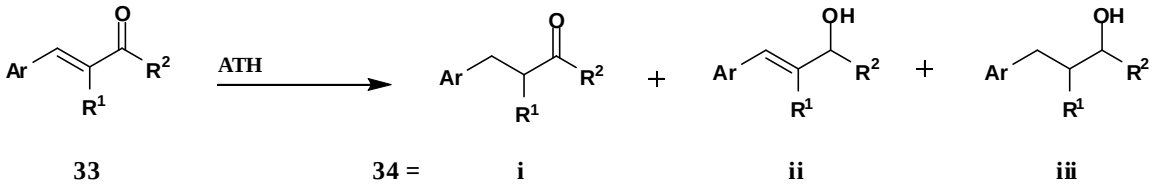
With the (*R,R*)-TsDPEN, $[RhCp^*Cl]_2$ MP and TEAF HS, Hamada and co-workers obtained selectivities in the region of 88 % to 97 % *ee* with good conversion. The study revealed the catalyst to be insensitive to the functional group, or its location on the aromatic ring *i.e. o, p* or *m*-Cl or OMe.[74, 88] Using a similar system as mentioned for Hamada's work, Okano *et al.* illustrated that pyridyl ketone **29** derivatives are also amenable to ATH when a ruthenium MP was employed.[89] Benzils **30** and ketoesters **31** and **32** have also been also been subjected to ATH reactions.[90-92]

Olefins

Based on all recognized and accepted mechanisms proposed for ATH, it is not unreasonable to say that the reduction of non-activated olefins is challenging. Without a functional group to activate the olefin the hydrogen transfer process is difficult.[93-95] Olefins of this nature are partial to other forms of transfer hydrogenation as mentioned earlier *i.e.* Braude.[66] There are many activated olefin compounds that lend themselves more susceptible to ATH, these are naturally the α,β-unsaturated olefins.

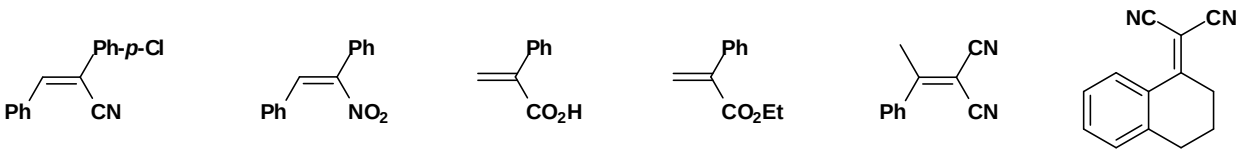
Xue and co-workers investigated the extent of ATH with α,β-unsaturated ketones, esters, nitro and cyano substrates shown in Figure 10. [96-97] For unsaturated ketones it was observed that in some cases three possible products could be obtained; either the C=C group was reduced, leaving the C=O intact (**i**), alternatively, only the C=O group was reduced and not the C=C (**ii**) or both the C=O and C=C were reduced (**iii**). They were able to show that for derivatives **33a -**

d, the reduction favoured the formation of (**ii**), this seemed to hold true so long as the R^1 and R^2 groups were either both methyl *i.e.* **33b - d**, or alternatively R^2 was methyl substituted while R^1 was hydrogen. When R^2 was then changed to an aromatic group, and R^1 left as a hydrogen **3e**, the reduction gave both (**i**) and (**iii**) products. Further, changing R^1 to a ketone or ester **33f - g**, favoured formation of (**i**) type products. Only moderate enantioselectivities of 39 % - 76 % *ee* for **33a - d** were obtained.[97] The authors inferred that the change from C=O to C=C reduction through **33a - g**, arises from an increase of polarisation when a more electron withdrawing group is added to either R^1 or R^2 or both.[97]



33 **34 =** **i** **ii** **iii**

a: Ar = Ph, R^1 = H, R^2 = Me
b: Ar = Ph, R^1 = R^2 = Me
c: Ar = *p*-$NO_2C_6H_4$, R^1 = R^2 = Me
d: Ar = *p*-$MeOC_6H_4$, R^1 = R^2 = Me
e: Ar = Ph, R^1 = H, R^2 = Ph
f: Ar = Ph, R^1 = MeCO, R^2 = Me
g: Ar = Ph, R^1 = COOEt, R^2 = Ph



35 **36** **37** **38** **39** **40**

Figure 10: α,β-Unsaturated compounds tested in ATH

The same authors attempted ATH on olefins activated by other functional groups, compounds **35 - 40**. These substrates were reduced in good yield but unfortunately poor selectivity, ranging from 0 % to 54 % *ee*.[97]

Imines

Imines are important intermediates in organic synthesis for the preparation of amines. In addition to this they loan themselves amenable to asymmetric reduction. Undoubtedly they are an invaluable tool for the preparation of chiral amine based drugs, hence they have also been extensively studied substrates in the ATH field.[77, 98-105]

In 1996 Uematsu reported the enantioselective reduction of imines. The authors used imine containing tetrahydroisoquinoline (TIQ) and some other imine containing compounds as

substrates for ATH with a ruthenium catalyst.[106] As shown in Figure 11, substrates with varying R-groups were reduced with high enantioselectivity ranging from 84 % to 95 % *ee*. It was also found that a TEAF HS was necessary for ATH of imines while IPA was not a feasible donor as determined by deuterium exchange studies.[77, 106]

The same group reported the reduction of tryptophan TIQ derivatives **41** and **42** in good enantioselectivity of up to 97 % *ee*. Less complex imines **43** and **44** were also reduced with *ee*'s of 77 % and 89 % respectively.[106] Heteroatomic aromatic substrates possessing imine groups were also investigated *i.e.* compound **45**, **46** and **47**, still employing the same catalyst the reduced products were obtained in good enantiomeric excess of 85 % and 88 % respectively in acetonitrile.[106] Praziquantel **11**, proceeds *via* an ATH of an imine from **48** to **49**.[77]

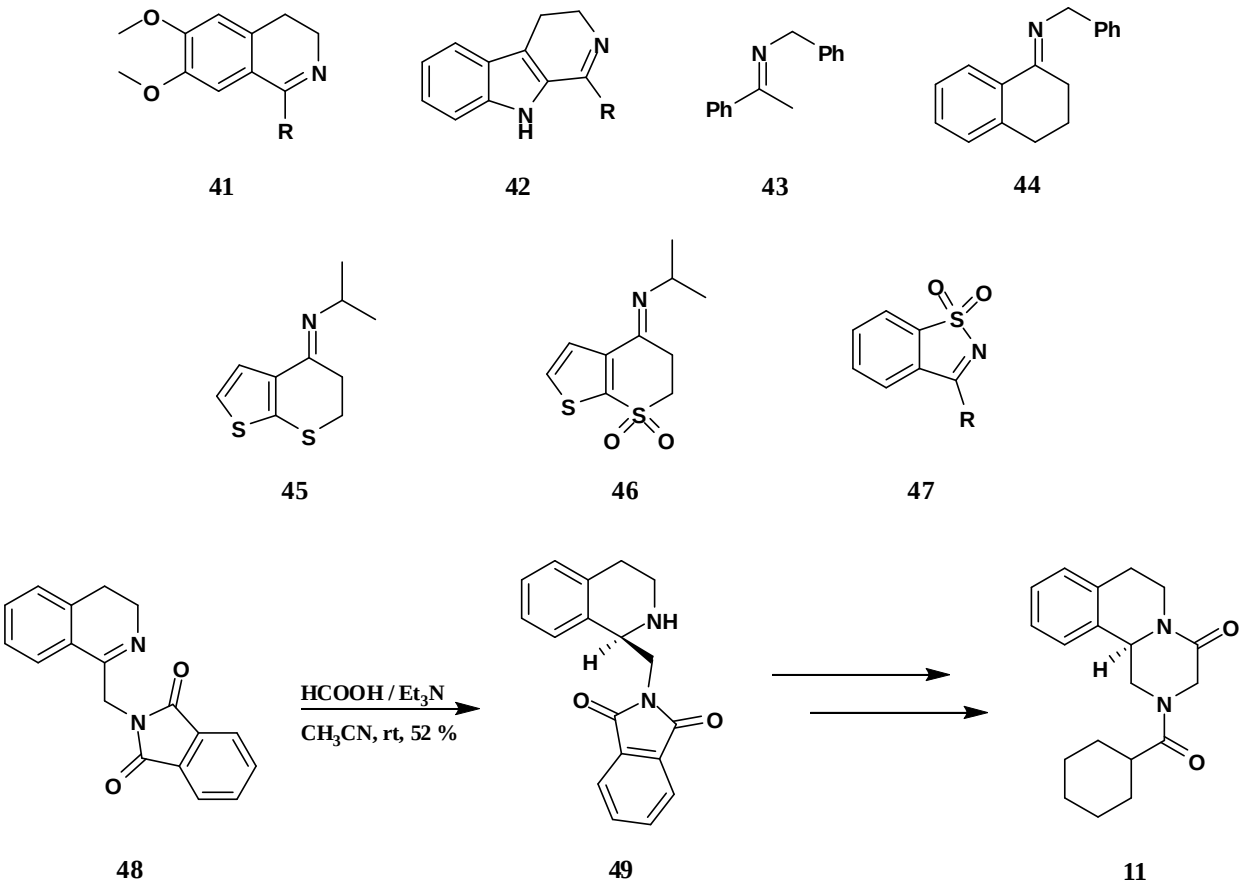


Figure 11: Imine substrates explored for amenability to ATH

Chapter 2 will briefly discuss some of the most successful catalysts developed for ATH. The logic and design behind our ligands will also be explained. The synthesis and testing will follow these sections. Results will be discussed in Chapter 3.

Chapter 2

2.1 Ligands for ATH Reactions

It has been shown in the literature that amine and diamine based ligands are useful auxiliaries in various asymmetric catalytic reactions.[85, 107-111] Noyori *et al.* tested a variety of simple amino alcohols and diamines with a ruthenium metal precursor (MP) using an isopropanol (IPA) hydrogen source (HS) and a KOH co-catalyst for the reduction of acetophenone (see Figure 12) and other ketones.[83, 85] It was noted that a two-carbon bridge between the donors (heteroatoms) formed the ideal metal chelator, and that unlike the amino alcohols, the diamines required one of the amines to be functionalized with an electron withdrawing group such as a *p*-toluenesulfonyl (Ts). Hence (1*S*,2*S*)-*N*-(*p*-toluenesulfony1)-1,2-diphenylethylenediamine (Ts-DPEN) **50** was found to have a good catalytic performance in ATH when coupled with a ruthenium MP.[85] This catalyst was able to convert acetophenone **24** to (*S*)-1-phenylethanol **26** in 97 % *ee* (Figure 12) *via* an ATH reaction.

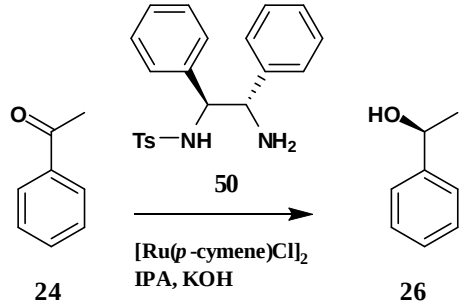
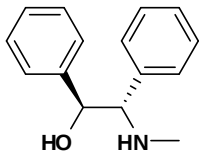


Figure 12: Reduction of acetophenone using the Ts-DPEN ligand and a ruthenium metal precursor

There have been many successful ligands developed for ATH reactions, the structures of some are shown by compounds **50** – **57**. Noyori *et al.* in 1995 shortly after their use of TsDPEN as a ligand for ATH, demonstrated that the amino alcohol **51** had a similar high performance.[82] With a $[RuCl_2(C_6Me_6)]_2$ precursor in IPA the ligand performed equally as well as **50** producing the (*S*)-1-phenylethanol product in high enantiomeric excess (*ee*). However the reaction times with **51** were greatly reduced in comparison to **50**.[82, 84-85] Puntener *et al.* who worked on chiral ferrocene compounds as ligands for asymmetric catalysis, introduced the diamine **52**.[112] This ligand coupled with $[RuCl_2(p\text{-cymene})]_2$ in IPA[113-114] gave moderate enantioselectivity in favour of the (*R*)-isomer. Following Noyori's monotosylated diamine design, Knochel also explored commercially available chiral cyclohexyl diamine derivatives for ATH. He showed that monotosylation of one of the amine groups to give **53**, and utilizing the same $[RuCl_2(p\text{-cymene})]_2$ MP as before with a TEAF HS rapidly rendered (*R*)-**26** in excellent *ee*.[112] Schiffers *et*

al. used this simple and easily accessible backbone as an auxiliary for the amino alcohol **54**.[115] Similar to the case of Noyori, both the amino alcohol (**51** *vs* **54**) and the diamine (**50** *vs* **53**) versions behaved analogously in terms of selectivity. However, contrast in rapid conversion was merely attributed to the TEAF HS over the IPA used for Noyori's diamine. Another economical design by Palmer *et al*. also employed an amino alcohol **55** using an indanol as a rigid scaffolding for ATH.[116] Moderate conversions and high *ee*'s with the $[RuCl_2(p\text{-cymene})]_2$ and IPA HS has added this ligand as another tool for ATH of prochiral ketones. Thereafter Alanso *et al*. in 2000 used the bicycle **56**, and was able to obtain good selectivity for the reduction of ketones with *ee*'s around 90 %.[117] In 2001 Rhyoo used an amino amide **57**, derived from proline, as a source of chirality. They reported that in aqueous media high conversions were achieved with moderate selectivity using a formate HS.[118]

Table 1 represents the results obtained for ligands (**50-57**) in the ATH of acetophenone. There has since been work done on these ligands, conditions have been optimised with better results achieved.[87-88, 119-124]



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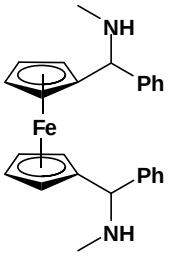

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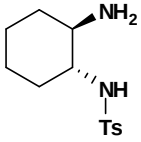

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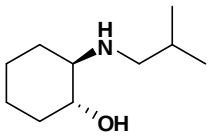

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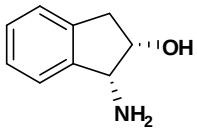

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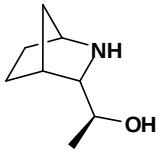

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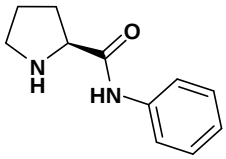


57

Other studies have attempted to optimise the performance of these catalysts, by varying sterics, electronics and the solubility properties.[112, 115-116, 118, 125-127] 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.[78, 118] 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.

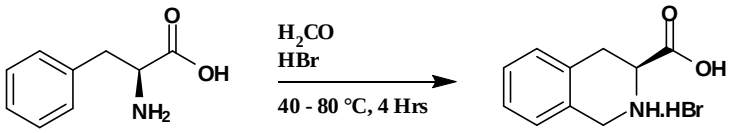
Table 1: Table of results for ATH of acetophenone for some successful diamine and amino alcohol ligands

Ligand	HS	Temp	Time /h	Metal	% Conv.	% *ee*	Isomer
50	IPA	RT	15	$[RuCl_2(mesitylene)]_2$	95	97	S[82]
51	IPA	28	1	$[RuCl_2(C_6Me_6)]_2$	94	92	S[82, 84-85]
52	IPA	22	0.5	$[RuCl_2(p\text{-cymene})]_2$	98	71	R[112-114]
53	TEAF	30	24	$[RuCl_2(p\text{-cymene})]_2$	99	94	R[112]
54	IPA	RT	1	$[RuCl_2(p\text{-cymene})]_2$	94	92	S[115]
55	IPA	RT	1.5	$[RuCl_2(p\text{-cymene})]_2$	70	91	S[116]
56	IPA	RT	0.7	$[RuCl_2(p\text{-cymene})]_2$	97	94	S[117]
57	$NaCO_2H$	30	4	$[RuCl_2(p\text{-cymene})]_2$	99.4	61	R[118]

Herein we report a systematic study of novel diamine ligands possessing the tetrahydroisoquinoline (TIQ) as a rigid and tunable chiral backbone for pre-catalysts to the asymmetric reduction of acetophenone.

2.2 Synthesis of TIQ Diamine Ligands

It should be noted that the syntheses of all 3- and 1,3-substituted 1,2,3,4-tetrahydroisoquinoline (TIQ) diamine ligands originated from common starting materials prepared as shown in Scheme 1 and 2. The 3-substituted TIQ is prepared by an acid catalysed Pictet-Spengler reaction using hydrobromic acid (HBr). The imine formed by condensation of the formaldehyde and the amine group of the *(S)*-phenylalanine **58** then undergoes nucleophilic attack by the aromatic ring to form the cyclised product **59**, which precipitates as the HBr salt.[128]

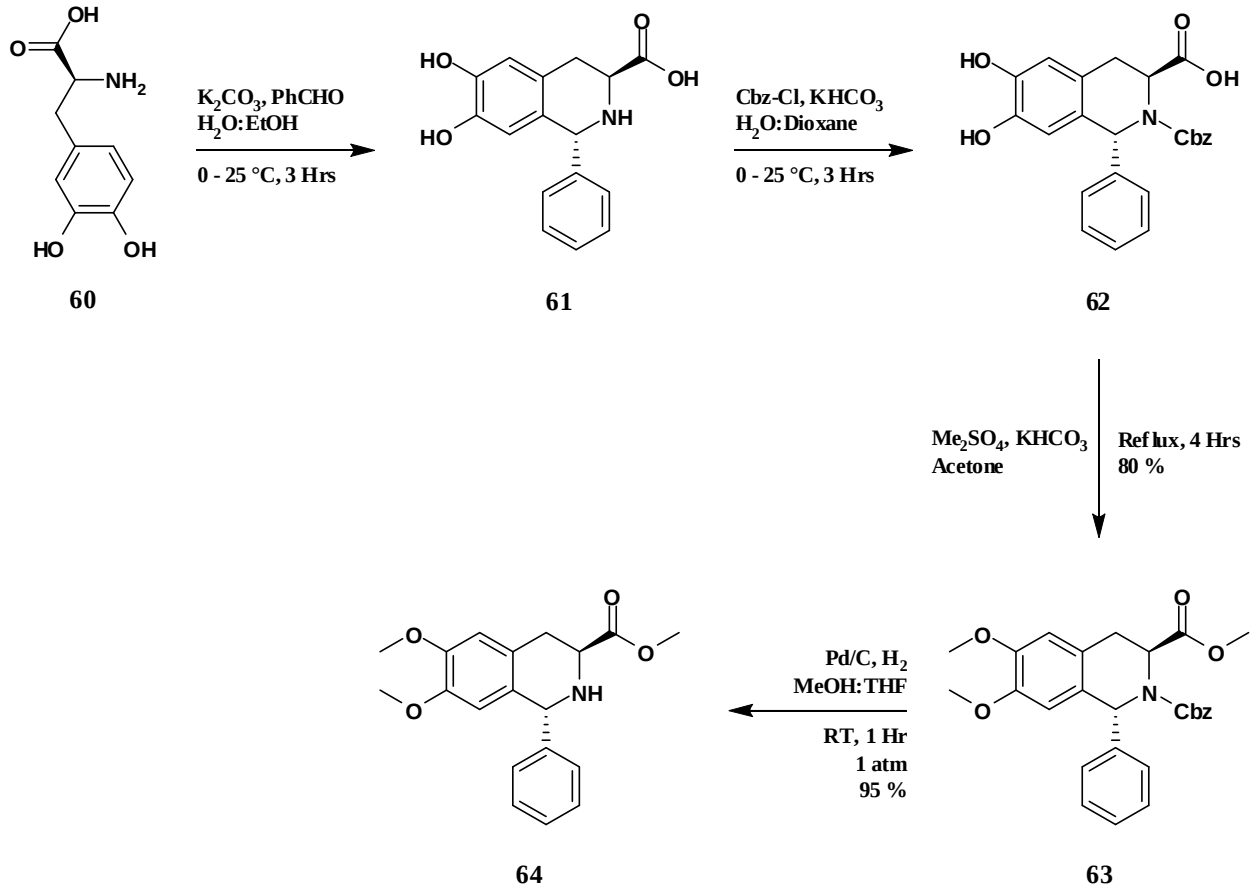


58 **59**

Scheme 1: Synthesis of 3-substituted TIQ precursor

Preparation of the 1,3-substituted 1,2,3,4-tetrahydroisoquinoline precursors involved a slightly more demanding synthesis. This was due to generation of a second chiral centre at the 1-position. The starting material L-DOPA (dihydroxyphenylalanine) **60** was treated with

potassium carbonate (K_2CO_3) in a 50:50 mixture ethanol:water and chilled in an ice bath. Benzaldehyde was then added and the reaction left to reach room temperature.



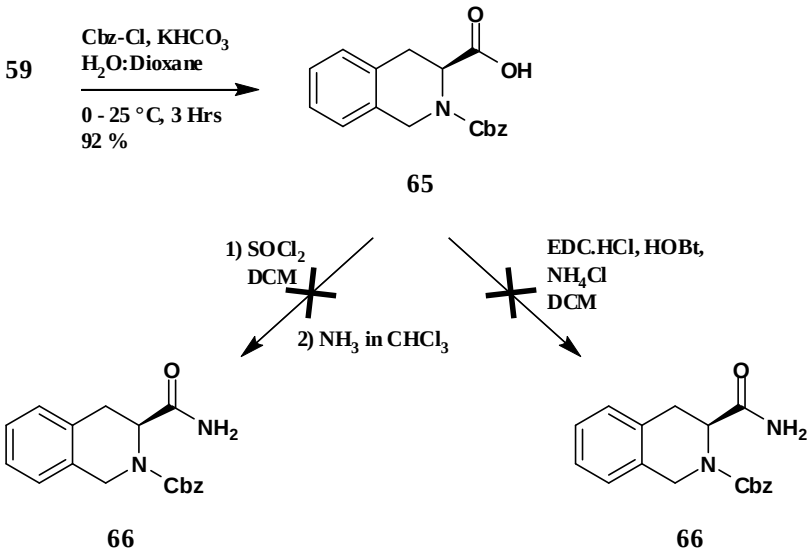
Scheme 2: Synthesis of 1,3-substituted TIQ precursor

After three hours the solid precipitate formed is filtered and carefully washed with a chilled mixture of 50:50 ethanol:water, ensuring that only the insoluble *trans* isomer **61** was obtained. Protection of the nitrogen with a benzyloxycarbonyl (Cbz) group under standard Schotten-Bauman conditions yielded **62**. It was desirable to block the phenolic hydroxy groups by methylation using dimethyl sulphate to form **63** allowing for subsequent synthesis. Removal of the Cbz by treatment of **63** with Pd/C and H_2 gas gave the desired precursor **64**.[61, 63]

2.3 Preparation of Mono-Tosylated TIQ Compounds

As it has been shown in the literature, monotosylated diamines serve as effective ligands in ATH; therefore this design served as a starting point to the synthesis of our diamine TIQ ligands. Standard protection of **59** (Scheme 3) with Cbz was carried out to block the nitrogen forming **65**.[129] Two synthetic procedures to obtain the amide were explored: i) acid chloride formation

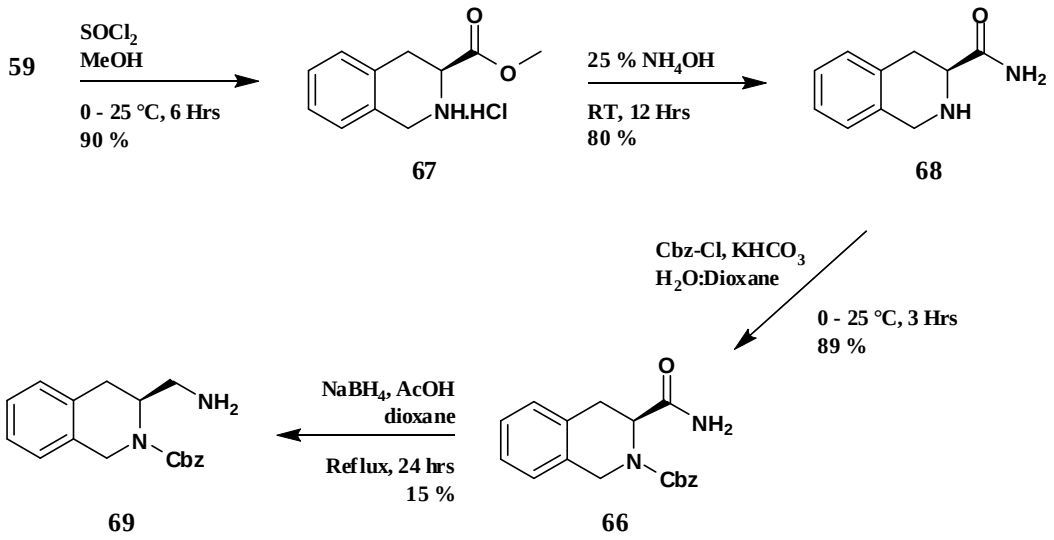
from the acid followed by treatment with a solution of ammonia in chloroform, ii) activation of the acid with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) hydrochloride (EDC.HCl) and hydroxybenzotriazole (HOBt) then substitution by NH_3 sourced from ammonium chloride (NH_4Cl) to form the amide. Unfortunately, neither of these methods issued the desired amide **66**.



Scheme 3: Synthesis of amide precursor to primary, secondary diamine ligand

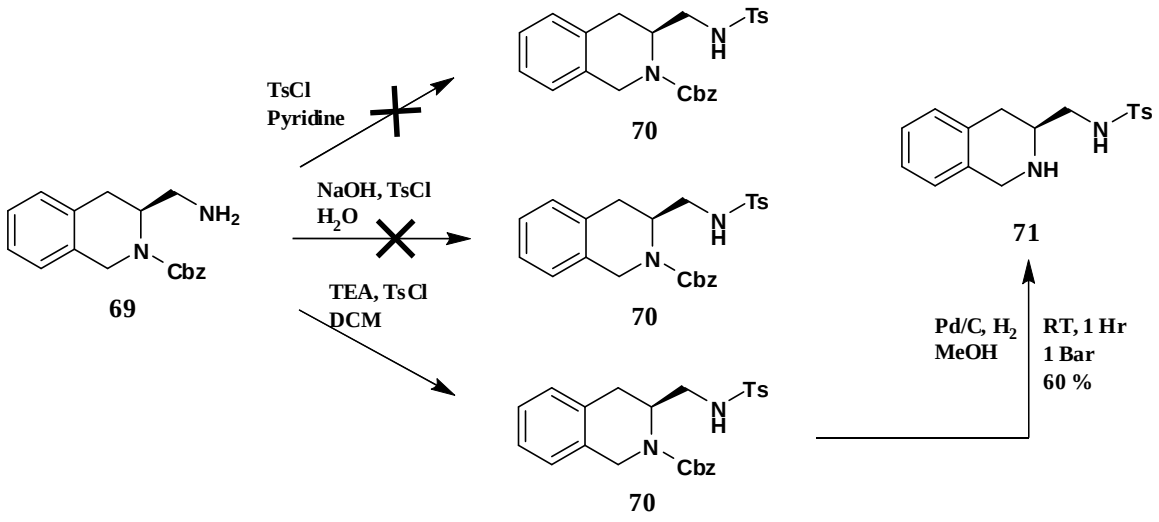
The proposed compound was necessary to the investigation of TIQ diamines as ligands for ATH, therefore alternative synthetic approaches were sought. A procedure was found to prepare the amide without protection of the amine.[56] Precursor **59** (Scheme 4) is converted to the ester; the authors did so by bubbling HCl through a solution of **59** in MeOH for 24 hours. However two alternative esterification methods were carried out in an effort to shorten this step. First **59** was refluxed in MeOH with a catalytic amount of sulfuric acid for three hours and second **59** in MeOH was treated with thionyl chloride and stirred at room temperature for three hours. The thionyl chloride method was chosen as the preferred route because the ester was obtained in high yield as the HCl salt of the product **67**, necessary for the next reaction. The amide **68** was rendered by conversion of the ester to amide from exposure of **67** with a large excess of 25 % ammonium hydroxide, and required no further purification. Amine protection of **68** with Cbz to form **66**, meant that special reduction conditions were required to convert the amide to an amine without cleavage of the Cbz group. The use of a more robust benzyl protection was attempted, however opening at the 1- and 2-positions was observed with long exposure to Pd/C with H_2 gas. Therefore a mixture of acetic acid and sodium borohydride in dioxane was engaged which

provided the Cbz protected TIQ primary amine **69**. Yields for this reduction were extremely low and despite addition of excess reducing agent and extended periods under reflux conditions, the reaction did not proceed further than 20 % conversion.[130]



Scheme 4: Synthetic route to 3-substituted Ts-diamine

Several procedures were attempted to add the tosyl group (Ts) onto **69**; these are shown in Scheme 5. Both tosylation by sodium hydroxide in water and in neat pyridine proved ineffective. When carried out in DCM with TEA as the base the reaction proceeded to form the Ts product **70**. Removal of the Cbz group provided the desired mono tosylated diamine compound **71** as the first of our novel TIQ diamine ligands to be tested in ATH.

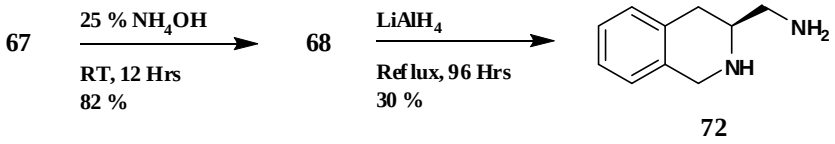


Scheme 5: Synthetic routes used to add Ts group onto 3-substituted TIQ

Preparation of 3-substituted **71** involved many synthetic steps, synthesis of a 1,3-substituted TIQ derivative would require several more steps. Therefore it did not seem feasible to prepare a 1,3-substituted TIQ version for use as a ligand in ATH.

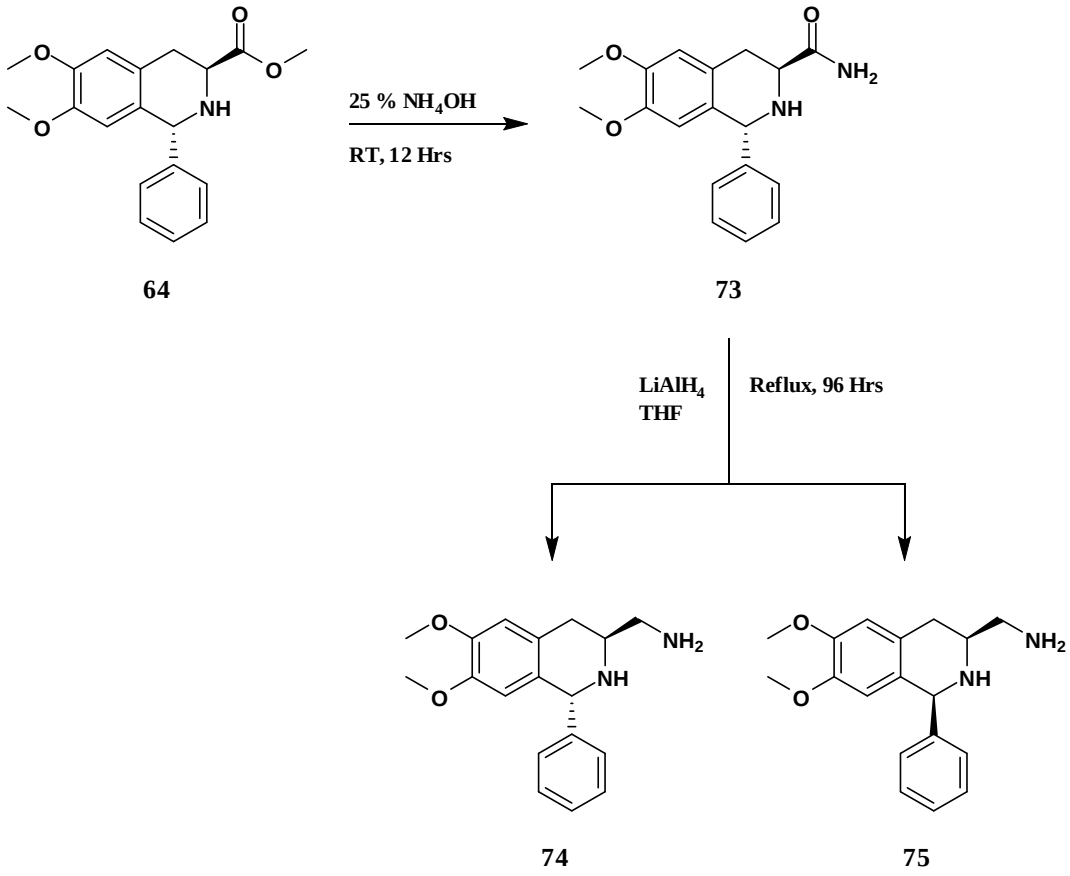
2.4 Preparation of Primary, Secondary Amine TIQ Compounds

Preparation of the 3-substituted TIQ **72** shared similar reactions steps to **71**, as shown in Scheme 6. Lithium aluminum hydride ($LiAlH_4$) was employed as the reducing agent, which unfortunately required a long reaction time (96 hours) under reflux conditions to afford the amine **72** in low yield. Despite numerous attempts to reproduce the yields and reaction times (3 hours) reported for this compound in literature, our efforts were unsucessful.[56, 131] The polar nature of **72** made purification by gravity chromatography using silica-gel difficult. Semi-preparative liquid chromatography using a C18 stationary phase was attempted with little success in obtaining the compound in good purity. Finally, it was discovered that precipitation of **72** as the HCl salt was sufficient for purification.



Scheme 6: Preparation of primary, secondary amine ligand 72

The same procedure was utilized in an effort to obtain the 1,3-substituted diamine TIQ **74** (Scheme 7). However, epimerisation at the 1-position occurred whilst reducing **73**. This is typical of dibenzylic systems rendering the proton at that 1 position moderately labile when using $LiAlH_4$ under reflux conditions.

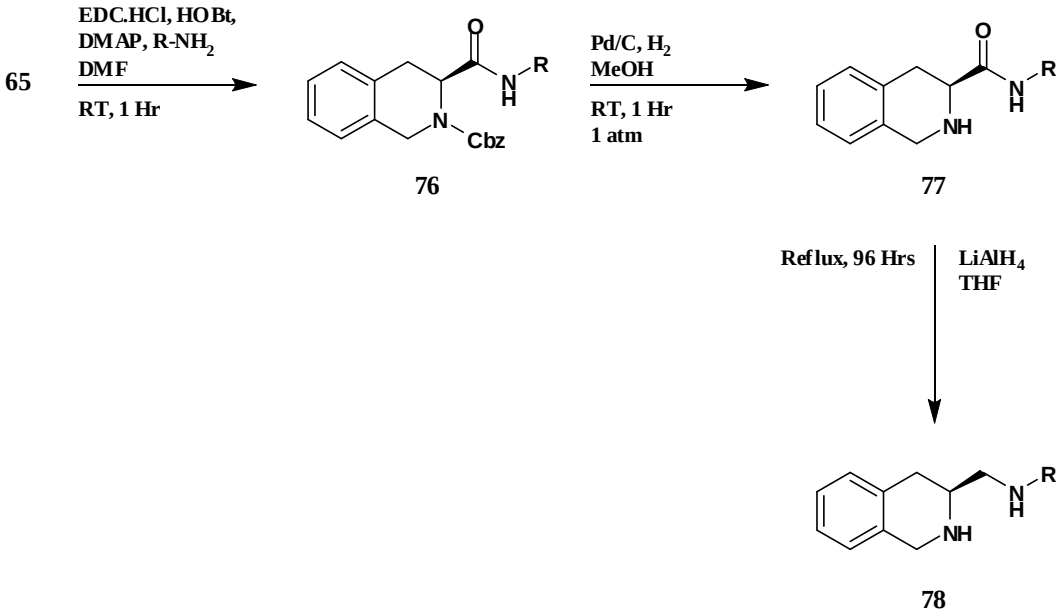


Scheme 7: Preparation of 1,3-substituted TIQ primary, secondary amine ligand

Attempts to separate the diastereomers were unsuccessful, as well as achieving adequate purification for characterization. Therefore this ligand was abandoned and was not tested for activity in ATH.

2.5 Synthesis of Secondary, Secondary Amines

The secondary, secondary amine system was employed as a means of introducing steric bulk to the molecule at the 3-position. The respective amines were coupled to the acid **65** *via* a condensation reaction using EDC.HCl, HOBt and a catalytic amount of DMAP to form the corresponding amides **76a - g**. Removal of the Cbz group with Pd/C and H_2 gas at one atmosphere afforded **77a - g**, which were then treated with $LiAlH_4$ for 96 hours in THF under reflux conditions to form the desired secondary amine compounds **78a - g**. *In situ* removal of the Cbz group with $LiAlH_4$ was attempted, but other side products were formed, therefore it was preferred to remove the Cbz group prior to amide reduction (Scheme 8).



R =	a	b	c	d	e	f	g
76 =	68 %	85 %	83 %	75 %	71 %	78 %	89 %
77 =	77 %	92 %	88 %	85 %	80 %	72 %	76 %
78 =	15 %	46 %	57 %	31 %	21 %	30 %	35 %

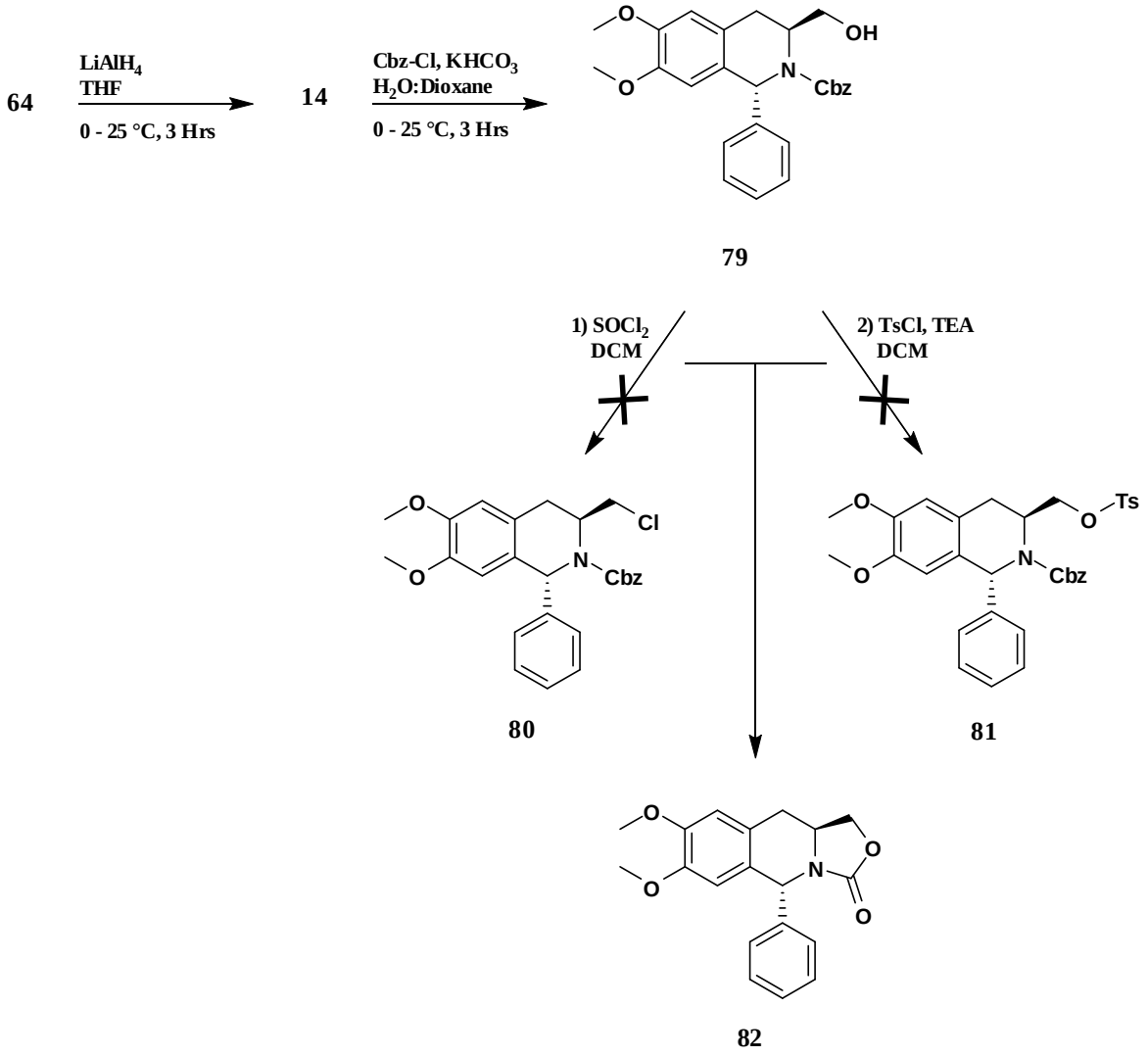
Scheme 8: Preparation of secondary amines

This scheme was successful in delivering all of the final ligands (**78a-g**).

2.6 Preparation of 1,3-Substituted TIQ Secondary, Secondary Amine Ligand

The synthesis of the 1,3 substituted diamine version did not follow that of the 3-substituted version (Scheme 9) this was due to racemisation that was observed as mentioned for the preparation of **74**. Therefore another strategy employing the addition of a leaving group at the 3-position and hence a substitution reaction using benzylamine could be carried out. Initially the alcohol was prepared by reduction of **64** to give the amino alcohol **14d** which could then be Cbz protected to give **79**. The protected alcohol served as a precursor for addition of the leaving groups, the first of which was an attempted replacement with a chloride to give **80**. However this was unsuccessful and cyclisation rendering **82** occurred. A second attempt, this time adding a tosyl group to **79** to form **81** was tried, but again cyclisation occurred to form **82**. This was

tracked using low resolution mass spectrometry. It was apparent that an alternative means to prepare the 1,3-substituted TIQ was necessary.

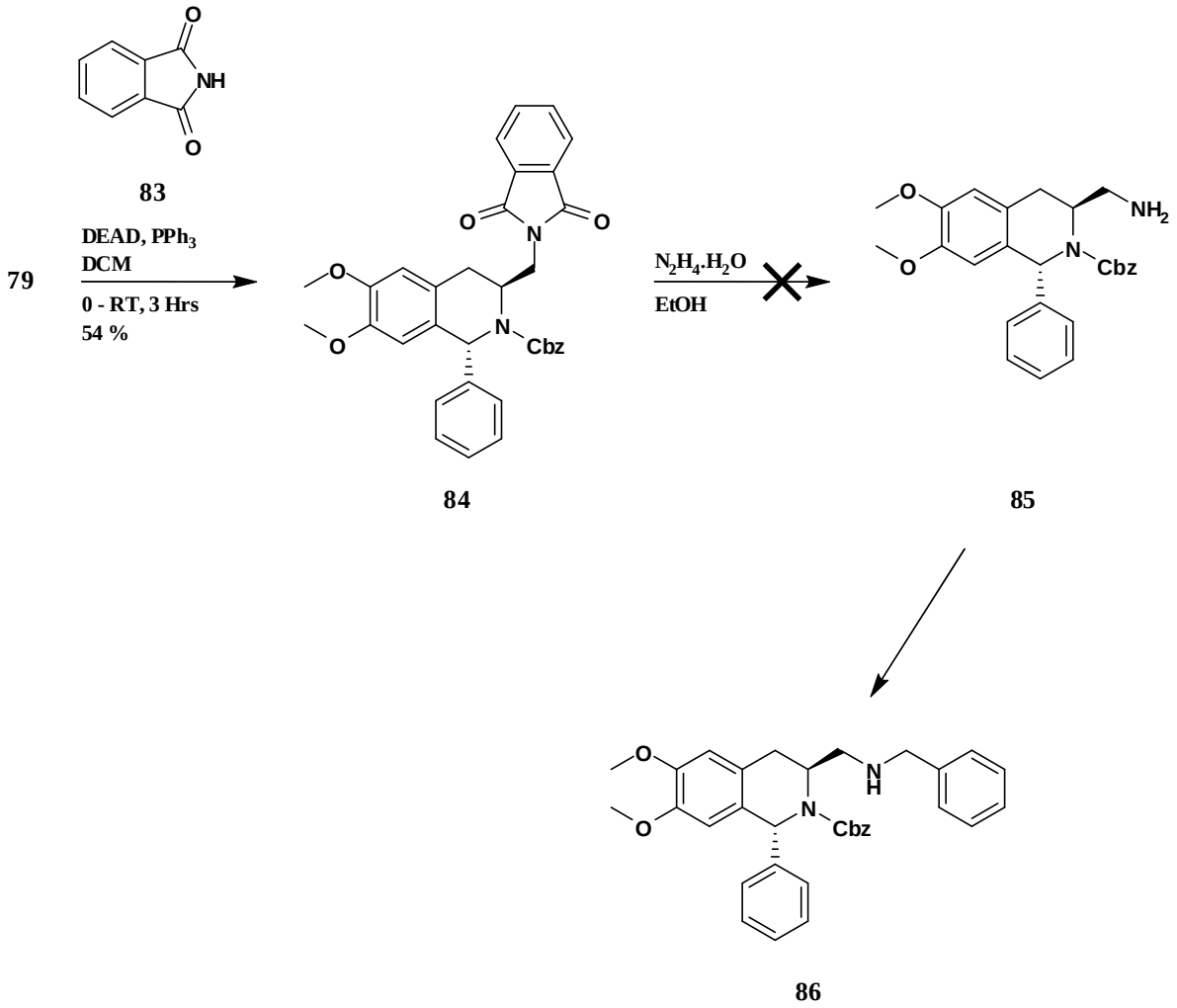


Scheme 9: Attempted synthesis of 1,3-benzyl sustituted TIQ ligand

Another route (Scheme 10) which places a phthalimide group **83** onto **79** using the Mitsonubu reaction[132] with diethylazidodicarboxylate (DEAD) to produce **84** was tried. This would produce the primary amine **85** upon removal of the phthalimide protection. In turn, reductive amination with benzaldehyde could be used to insert the benzyl group to form **86** which would require only a deprotection step to form the product. However the synthesis did not proceed beyond **84** due to problems incurred during the phthalimide deprotection step.

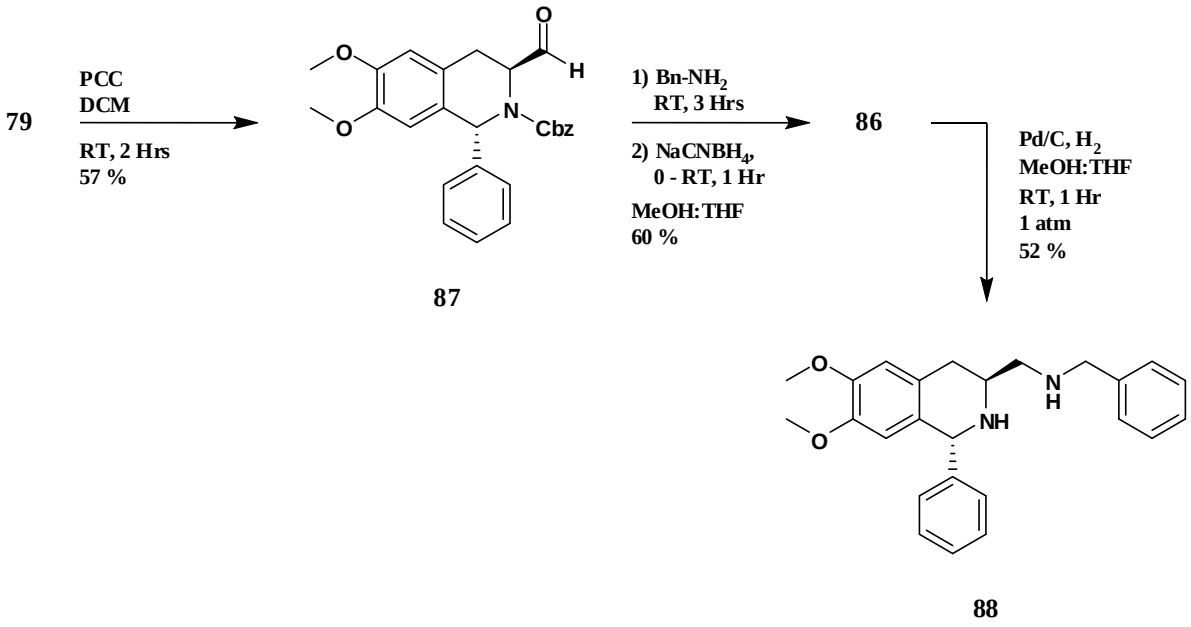
After that attempt the same strategy (Scheme 4) for the conversion of **66** to **69** was used to convert the Cbz-protected amide to the Cbz-protected amine. However the same problems of long reaction times and low yields were encountered and not enough could be obtained to carry

out the two additional steps to achieve the desired benzyl 1,3-substituted TIQ diamine ligand. Therefore, an alternative synthetic procedure was sought once more.



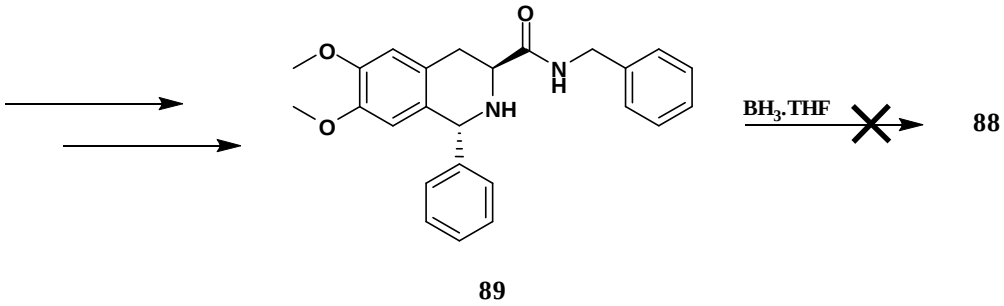
Scheme 10: Attempted synthesis of 1,3-benzyl substituted TIQ ligand

Eventually, preparation of diamine **88** (Scheme 11) was carried out by oxidation of the alcohol **79** with pyridinium chlorochromate (PCC) to produce **87**. A reductive amination using benzylamine (Bn-NH_2) to form the imine with subsequent reduction to the amine using sodium cyanoborohydride ($NaCNBH_4$) producing **86**. Final and selective deprotection of the Cbz group was closely monitored to insure that both the benzyl and the Cbz group were not removed to give the desired final compound **88**.



Scheme 11: Preparation of 1,3-substituted TIQ ligand 88

An alternative route was attempted for preparation of the 1,3-substituted amine from the corresponding amide. This method involved the use of borane (BH_3) in tetrahydrofuran (THF), BH_3 is able to reduce amides and acids in a different manner to that of $LiAlH_4$. The BH_3 is mild relative to $LiAlH_4$ with regards to its basic nature (Lewis base) and this appeared to present a probable solution.[19] However, when the reduction was carried out on the amide precursor **89** (Scheme 12), only very little of the desired **88** was formed[133-135]

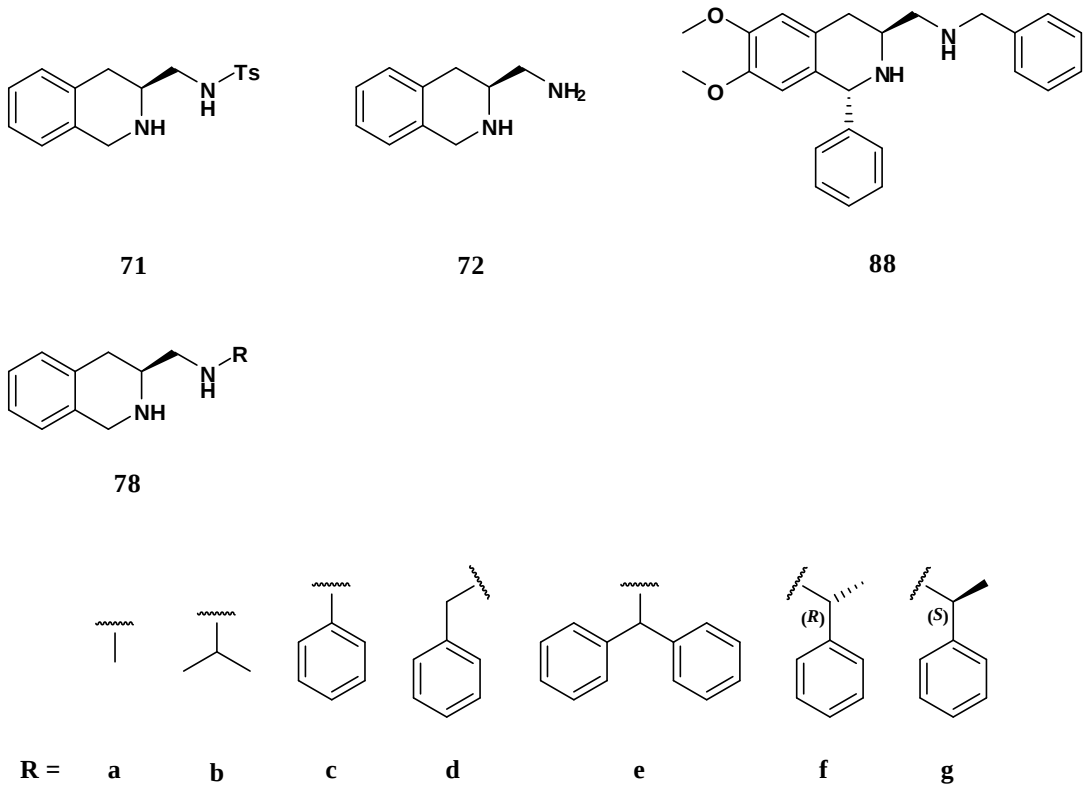


Scheme 12: Attempted reduction of amide precursor using BH_3.THF complex

Chapter 3

3.1 Results & Discussion

The following ligands were tested for activity in ATH using IPA as the hydrogen source, potassium *t*-butoxide (KO*t*Bu) as the base and the following metal precursors; [Ru(*p*-cymene)Cl_2]$_2$, [$IrCl_2$(Cp*)]$_2$ and [$RhCl_2$(Cp*)]$_2$. These conditions were chosen based on those employed most commonly in the literature. The ligands tested in this investigation are represented in Figure 13.

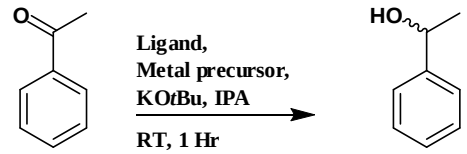


71 72 88

78

Figure 13: Ligands tested for performance in ATH of acetophenone

The model reaction used in this investigation was the asymmetric transformation of acetophenone to 1-phenylethanol using a chiral catalyst, as represented in Figure 14.



24 26

Figure 14: Model reaction used in this investigation

Key: from here on in, the term "activity" refers to the catalysts ability to convert (conversion) acetophenone to 1-phenylethanol. The term "performance" describes both the catalysts ability to convert acetophenone to 1-phenylethanol and its selectivity in doing so. The terms "good", "poor" and "moderate" are also used extensively in the discussion. These terms have no fixed meaning, but are simply used in relative tense with regard to another catalyst to which it is being compared.

Monotosylated Diamine TIQ Ligand 71

The monotosylated diamine **71** as the first of the ligands prepared, showed no activity for the transformation of acetophenone **24** to 1-phenylethanol **26** using any of the metals precursors.

Primary, Secondary Amine Ligand 72

Ligand **72** possessing a primary amine extending from the 3-position and a secondary amine located on the TIQ backbone at the 2-position demonstrated little activity for ATH of acetophenone when $[IrCl_2(Cp^*)]_2$ was used as the metal precursor. The reduction was monitored over a 24 hour period and was found to reach a maximum conversion of 10 % with no enantioselectivity.

Secondary, Secondary Amine Ligands 78a-g & 88

Ligands **71** and **72** share a similar design to Noyori's diamine and monotosylated diamine. However, unlike Noyori's which possess a di-primary or primary and tosylated secondary amine, our ligands have a cyclic secondary amine in a six-membered ring. Ligand **71** was found to be completely inactive, whilst **72** demonstrated only poor activity when using an Iridium MP. Therefore, as our system differs from that of Noyori's, as expected we needed to perform structural modifications in order to achieve activity. The secondary amine on the TIQ back bone is "fixed"; therefore only the 3-position remained free to functionalise. In order to study the effect of both steric and electronic influence on activity, several secondary amine derivatives were prepared (**78a – g**).

Ligands **78a** and **b** possessing a methyl and isopropyl group respectively are inherently both electron-donating groups differing only in size from one another. The results for the ATH of acetophenone for these ligands (Table 2) revealed **78a** to have no activity at all, whilst **78b** was moderately active, giving a conversion of 67 % to the *(S)*-1-phenylethanol product. As a result of this positive response in activity from the larger isopropyl group (**78b**), a more bulky **78c** was prepared giving an aniline group. **78c** possessed no activity, demonstrating that there must be a balance between the steric and electronic behaviour of the substituent on the nitrogen.

To test this, ligand **78d** was synthesised. **78d** possessing a benzyl group, is poorly electron-withdrawing , can be considered to be nearly neutral in its electronic contribution. With ligand **78d** an 81 % conversion of acetophenone to *(S)*-1-phenylethanol was obtained. This confirmed the view that a balance between the sterics and electronics must be obtained for there to be activity. To further investigate the extent of this idea, a dibenzyl substituent (**78e**) was synthesised for comparison to ligand **78d**. The dibenzyl is only slightly more electron-releasing than a benzyl group, so its electronic difference is not significant. However, sterically the two substituents differ greatly. It was observed that ligand **78e** shows poor activity with a conversion of 22 % to *(S)*-1-phenylethanol, a considerable change from the 81 % conversion obtained for **78d**.

As discussed earlier, it was noted that the isopropyl group is slightly bulkier than the benzyl, however, not much activity is lost on going from the benzyl to the isopropyl, and in addition, a slight gain in selectivity is observed. Therefore we decided to add a chiral substituent to the nitrogen in order to achieve better selectivity. Based on the comparisons and conclusions drawn, it was decided that chiral phenylmethyl groups should be used (ligands **78f** and **g**). The electronic influence of the methyl (electron donating) is counteracted by that of the phenyl group (slightly electron withdrawing) and *vice versa*. Therefore the electronic character of the group lies between that of an isopropyl and a benzyl moiety. The phenylmethyl substituent is slightly larger than both the isopropyl and the benzyl and therefore a slight drop in activity was anticipated. From the results it was shown that both **78f** and **g** gave poor activities, 24 % and 5.5 % respectively. The difference in activity of the chiral isomers is likely to be due to the orientation *i.e. cis* and *trans* relative to the pre-existing chiral centre on the TIQ, when complexed to the metal. This is supported by the choice of isomer for each ligand *(R)*-isomer for **78f** and *(S)*-isomer for **78g**. The anticipated increase in selectivity was observed for ligand **78f**, with an enantiomeric excess of 77 % for the *(R)*-isomer. The same was not true for the other chiral phenylmethyl isomer **78g**, which had an enantiomeric excess of 51 % for the *(S)*-isomer.

Previously our group has reported the activity of some 3- and 1,3-substituted TIQ amino alcohol ligands *i.e.* ligand **14d**. This prompted us, having screened a variety of 3-substituted diamines, to investigate whether adding a phenyl ring to the 1-position would have any value in increasing the selectivity. Therefore, a benzyl substituent was added to the 3-position yielding ligand **88**. Surprisingly, the diamine mimic of **14d** did not demonstrate any activity at all.

Table 2: Asymmetric transfer hydrogenation of acetophenone by ligand 78a-g & 88 rhodium complexes

Entry	Ligand	% Conv.	% *ee*	Isomer
1	**78a**	-	-	-
2	**78b**	67	71	*S*
3	**78c**	-	-	-
4	**78d**	81	70	*S*
5	**78e**	22	11	*S*
6	**78f**	24	77	*R*
7	**78g**	5.5	51	*S*
8	**88**	-	-	-

All reactions were carried out at 25 °C.
IPA was used as the solvent when employed as the HS along with *t*-BuOK as the base. Testing was carried out using a substrate to catalyst ratio (S/C) of 100.
Measured by GC with chiral capillary column *β*-DEX™ 120.

In the case of the secondary amine ligands, a certain amount of water was required in order for selectivity to be observed in the ATH reaction. This is not uncommon, and as stated in Chapters 1 and 2, water is often employed as the reaction solvent. It has been demonstrated in the literature that water has potential to influence the performance of a catalyst in ATH reactions.[118, 121, 125, 136-140] The results in Table 2 reflect the optimised amount of water found using the benzyl ligand **78d**. Table 3 presents results regarding the optimised water content. Adding one equivalent of water to the metal complex was found to increase activity relative to no water (27 %, entry 1). Progressively increasing the amount of water from 2 to 400 equivalents showed an improvement in selectivity (entries 2 – 6). Thereafter, raising the amount of water to a 1000 and further to 3000 equivalents a maximum was reached with an optimum of 70 % enantioselectivity (entries 7 – 9). Increasing the amount of water to 50:50 water:IPA (many times excess) destroyed the reactivity completely (entry 10). Since reactivity dropped significantly at 3000 equivalents, 1500 equivalents was taken as the best compromise between reactivity and selectivity for subsequent testing.

Table 3: Results of the effect on the enantioselectivity in varying the water content added to the ATH reaction of acetophenone catalysed by the rhodium-78d complex

Entry	Molar eqv H_2O	Conv. %	*ee* %
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[a]	50:50	-	-

All reactions were carried out at 25 °C.
IPA 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.
Measured by GC with chiral capillary column *β*-DEX™ 120.
[a] A 50/50 mixture of water and IPA was used.

Further study of the effect of metal precursor and HS for ligand **78d** was carried out (Table 4). Entries 1 and 4 show that very little activity is observed when the ATH reaction is performed in water using a potassium formate hydrogen source (2 %, entry 1), and no activity with the IPA (entry 4) when $[Ru(p\text{-cymeme})Cl_2]_2$ 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 HS was changed to IPA (40 %, entry 5) for the $[IrCl_2(Cp^*)]_2$ MP. 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 IPA was used instead (90 %, entry 6). The results for the $[RhCl_2(Cp^*)]_2$ prompted us to investigate whether using a TEAF HS could increase the activity. Unfortunately this proved unsuccessful (entry 7). Changing from the $[RhCl_2(Cp^*)]_2$ (arene) to the $RhPPh_3COH$ (hydride) did not give an improvement 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 IPA.

Table 4: Asymmetric transfer hydrogenation of acetophenone by different hydrogen sources and ligand 78d metal complexes

Entry	Metal Complex	HS	Conv. %[a]	*ee* %[a]	Isomer
1	$[Ru(p\text{-cymene})Cl_2]_2$	KCO_2H	2	10	*R*
2	$[IrCl_2(Cp^*)]_2$	KCO_2H	10	25	*R*
3	$[RhCl_2(Cp^*)]_2$	KCO_2H	43	50	*R*
4	$[Ru(p\text{-cymene})Cl_2]_2$	IPA	-	-	-
5	$[IrCl_2(Cp^*)]_2$	IPA	40	-	-
6	$[RhCl_2(Cp^*)]_2$	IPA	90	-	-
7	$[RhCl_2(Cp^*)]_2$	TEAF	-	-	-
8	$RhPPh_3COH$	IPA	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.
IPA 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.

In previous work on ATH reactions using amino alcohols by our group, the 3 substituted ligands were found to perform poorly. The 1,3-substituted ligands however, under the same conditions gave a range of performance from poor to good.[61] In the case of our diamine ligands, a reverse scenario was observed. Several 3-substituted ligands were identified as reasonable catalysts namely; **78b**, **d** and **f**.

It was also noted from previous investigations of the TIQ amino alcohols, that the ligands functioned best under anhydrous conditions. However, in the diamine system water was crucial in order to obtain selectivity.

In the case of the TIQ amino alcohols ligands, both the $[RhCl_2(Cp^*)]_2$ and the $[Ru(p\text{-cymeme})Cl_2]_2$ precursors produced very active catalysts when IPA was used as the HS. However, the highest selectivity was achieved with the $[Ru(p\text{-cymeme})Cl_2]_2$ precursor. In the case of our diamines, $[Ru(p\text{-cymeme})Cl_2]_2$ was observed to have poor activity with these ligands but better activity was achieved when using the $[RhCl_2(Cp^*)]_2$ precursor.

3.2 Conclusions

In our investigation 24 TIQ diamine derivatives were prepared for use as ligands in ATH of acetophenone. Ligand **71** was shown to have no activity for the ATH of acetophenone. To elaborate on this the primary amine derivative, ligand **72** was also prepared to simulate ethylenediamine, an active ligand for transfer hydrogenation. However, this too was unsuccessful. It was inferred to be as a result of the difference in the electronic character of the secondary amine at the 2-position of the TIQ as opposed to the primary amine in Noyori's and the ethylenediamine case. Therefore we decided to change the structure at the position where modification was easiest, namely the 3-position. A series of secondary amines derivatives were prepared with substituent's that influenced the electronics and the sterics of and around the nitrogen donor, ligands **78a-g**. Several of these ligands were found to be active and selective for the ATH of acetophenone (**78b**, **d**, **e**, **f** and **g**), whilst others possessed no activity (**78a** and **c**). We found that **78d** (81 % conv.) possessing a benzyl substituent, had the greatest activity, thus it seems creating the appropriate balance of sterics and electronics to a greater extent than the other substituents. The highest selectivity achieved was when a phenylmethyl derivative (**78f**) was employed (77 % *ee*), however, the activity of this ligand was low (24 % conv.). Our structural investigation of the TIQ diamines concluded with a 1-(phenyl) 3-substituted ligand (**88**) that gave no activity. It was discovered in the case of our active diamine ligands that an optimised 1500 equivalents of water was necessary to be added in order for there to be optimum enantioselectivity. The exact role of the water was never ascertained. Many publications on the possible mechanism of water in ATH reactions have appeared and due to the increased scope of such an investigation, it was decided to exclude that in the current project. A range of metal precursors were also investigated and $[RhCl_2(Cp^*)]_2$ was found to be the best for our TIQ diamine ligands.

The ligand with the greatest overall performance was **78d**, yielding a conversion of 81 % and an enantioselectivity of 70 % *ee* for the *(S)*-1-phenylethanol product. We have successfully studied the use of TIQ diamine compounds as ligands for the ATH of acetophenone, and have established criteria for the further rational design of this system.

The investigation also revealed that the *N,O*-TIQ system differs from the *N,N*-TIQ ligand in several ways; First, the choice of active metal precursor is different, Ruthenium *versus* Rhodium. Second, water is not required for activity in the *N,O*-TIQ, but essential for the *N,N*-ligand system.

Chapter 4

4.1 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 MHz or 600 MHz instruments. Chemical shifts are expressed in ppm and referenced to the TMS signal, which the NMR solvents purchased, had been pre-spiked. Coupling constants are reported in Hz. NMR spectra were obtained at room temperature, except if stated differently. Thin layer chromatography (TLC) was performed using Merck Kieselgel 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 from Vogel.[130] 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 Model 341. All melting points (MP) are uncorrected. High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument, with a sample concentration of approximately 1 ppm. All gas chromatography (GC) was carried out on an Agilent 6820 with a chiral capillary column, β-DEX™ 120.

Spectral data are provided for all non novel compounds with appropriate references. All novel compounds were prepared following synthetic strategies and procedures found in literature for which the relevant reference has been provided.

General Procedure for Transfer Hydrogenation of Acetophenone[85]

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

IPA hydrogen source in water: The reaction was carried out as reported above with the exception that 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:[118] The metal precursor and ligand were complexed as described above. Water was then added (2 mL), and the reaction mixture heated to 40 °C and stirred for 30 minutes. 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, which were then used for GC analysis.

TEAF hydrogen source:[78] The metal precursor and ligand were stirred in DCM for 30 minutes, followed by the addition of acetophenone (S/C = 100) and TEAF (0.9 mL). The reaction was monitored similar to that when using the IPA hydrogen source.

(*S*)-2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid 65[129]

To a suspension of **59** (5.00 g, 19.45 mmoles) in dioxane (80 mL) and water (40 mL) was added $NaHCO_3$ (77.80 mmoles) at 0 °C following Schotten-Baumann conditions. After addition of the base, Cbz-Cl (3.64 g/ 3.01 mL, 21.40 mmoles) was added and the reaction was allowed to stir at 0 °C for 1.5 hours and then at room temperature for a further 1.5 hours. The product was extracted twice with ethyl acetate (~ 25 ml), the organic layer dried with anhydrous magnesium sulphate and concentrated to dryness affording **65** (5.56 g, 92 % yield) that was carried forward without any purification. ^{1}H and ^{13}C NMR were used to confirm **65**.

General Procedure for the Preparation of 76a-g

Method adapted from literature.[141] (*S*)-2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **65** (1.50 g, 4.80 mmoles) was dissolved in DMF (15.00 mL) followed by addition of EDC.HCl (1.10 g, 5.80 mmoles), HOBt (0.81 g, 5.30 mmoles), a catalytic amount of DMAP and the appropriate amines (5.30 mmols). The reaction was then stirred at room temperature until no more starting material could be detected by TLC analysis (solvent 50:50 EtOAc:Hex) approximately one hour. The reaction was poured into 30 volumes of chilled water. The mixture was then extracted twice with ethyl acetate (25.00 ml). The extracts were combined, washed with 10 % HCl (aq) to remove latent EDC urea, dried over anhydrous magnesium sulphate and then concentrated to dryness affording the crude product which was purified by column chromatography.

General Procedure for the Preparation of 77a-g

The method was adapted from the literature.[129] The precursors **77a-g** (0.80 g) in 50:50 MeOH:THF (12:12 mL) with half an equivalent by mass (0.40 g) of 10 % palladium on carbon Pd/C was stirred under hydrogen (approximately 1 atm) for two hours. The reaction was limited to this period as additional 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 78a-g

The amine amides **77a-g** (0.25 g) were reduced with four equivalents of $LiAlH_4$ (~ 0.11 g) in refluxing dry THF (~ 9 mL) 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 hours. The reactions were quenched by slow addition of saturated sodium sulphate solution and the white aluminium sulphate precipitate was then filtered. The filtrate was washed with water (~ 5 mL), dried over anhydrous magnesium sulphate and concentrated to dryness affording the crude product which was purified by column chromatography.

(1*R*,3*S*)-6,7-dihydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid 61[56, 131]

This compound was prepared as reported previously. ^{1}H NMR (400 MHz, D_2O) δ = 7.37 – 7.24 (m, 3H), 7.21-7.13 (m, 2H), 6.67 (s, 1H), 6.29 (s, 1H), 5.30 (s, 1H), 3.58 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.04 (dd, *J* = 16.7, 5.1 Hz, 1H), 2.81 (dd, *J* = 16.6, 10.2 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ = 178.4, 145.6, 144.5, 141.6, 129.2, 128.6, 128.2, 125.2, 124.8, 115.2, 114.5, 58.1, 52.0 and 29.9.

(1*R*,3*S*)-2-Benzyl-3-methyl-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate 63[61]

This compound was prepared as it has been reported in the literature. $[\alpha]^{20}_D$ = + 9.54 (*c* = 0.26 g/100mL, $CHCl_3$); IR ν_{max}: 2942 cm^{-1}, 1744 cm^{-1}, 1714 cm^{-1}, 1204 cm^{-1}, 735 cm^{-1}, 698 cm^{-1}. HRMS calculated for $C_{27}H_{28}NO_6$ $(M + H)^+$ = 462.1896 *m/z*, found 462.1916 *m/z*. ^{1}H NMR (400 MHz, d6-DMSO, 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* = 15.7, 6.0 Hz, 1H), 3.13–3.04 (m, 2H).

(1*R*,3*S*)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 64[61]

This compound was prepared as it has been reported in literature. Colourless oil; $[\alpha]^{20}_{D}$ = + 15.38 (*c* = 0.26/100 mL, $CHCl_3$). IR ν_{max}: 2928 cm^{-1}, 2600 cm^{-1}, 1746 cm^{-1}, 1516 cm^{-1}, 1250 cm^{-1}, 1123 cm^{-1} and 727 cm^{-1}. HRMS calculated for $C_{19}H_{22}NO_4$ $(M + H)^+$ = 328.1548 *m/z*, found 328.1547 *m/z*. ^{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* = 8.6, 5.1 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.15 (dd, *J* = 5.1 Hz, 1H) 3.01 (dd, *J* = 8.7 Hz, 1H)..

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

This compound was prepared as it has been reported in literature.[61] IR: 3264 cm^{-1}, 2832 cm^{-1}, 1515 cm^{-1}, 1222 cm^{-1}, 1066 cm^{-1}, 981 cm^{-1}, 726 cm^{-1}, 694 cm^{-1}. $[\alpha]^{20}_{D}$ = + 3.7 (*c* = 0.27/100 mL, CH_2Cl_2). HRMS calculated for $C_{28}H_{22}NO_3$ $(M + H)^+$ = 300.1600 *m/z*, found 300.1622 *m/z*. Pale yellow solid; mp 115 – 117 °C. ^{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* = 4.56 Hz, 1H), 2.57 (dd, *J* = 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 and 30.5.

(S)-2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 66

Compound **68** (0.40 g, 2.27 mmoles) was protected with a Cbz group, under the conditions described in the general procedure to afford **66** (0.63 g, 89 %), a colourless oil after column chromatography (EtOAc/Hex = 20:80, R_f ~ 0.5). $[\alpha]^{20}_{D}$ = - 2.3 (c = 0.59 g/100 mL, CH_2Cl_2). IR ν_{max}: 427 cm^{-1}, 593 cm^{-1}, 675 cm^{-1}, 697 cm^{-1}, 740 cm^{-1}, 908 cm^{-1}, 983 cm^{-1}, 1027 cm^{-1}, 1038 cm^{-1}, 1091 cm^{-1}, 1119 cm^{-1}, 1216 cm^{-1}, 1348 cm^{-1}, 1403 cm^{-1}, 1496 cm^{-1}, 1605 cm^{-1}, 1661 cm^{-1}, 2158 cm^{-1}, 2586 cm^{-1}, 2882 cm^{-1} 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).[142] ^{1}H 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.rotamers

(S)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 68[56]

This compound was prepared according to the literature. Yield 82 % ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 6.96 (m, 4H), 5.66 (s, 1H), 4.11 – 3.94 (m, 1H), 3.59 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.22 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.87 (dd, *J* = 16.5, 10.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.9, 135.6, 134.0, 129.2, 126.6, 126.2, 125.6, 56.5, 47.6 and 30.8.

(*S*)-benzyl 3-(aminomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 69

To a solution of **66** (0.50 g, 1.50 mmoles) in dioxane (3 mL) was added $NaBH_4$ (0.17 g, 4.50 mmoles). The mixture was then cooled to 0 °C and acetic acid (0.18 g, 4.50 mmoles) was added dropwise. After addition the reaction was set to reflux for 48 hours to yield **69** as yellow oil.[130] Due to stability problems (decomposition) with the crude product **69** (0.07 g, 15 % in ~ 90 % pure by TLC) was carried forward without further purification. $[\alpha]^{20}_{D}$ = - 15.00 (c = 0.16 g/100 mL, CH_2Cl_2). IR ν_{max}: 426 cm^{-1}, 495 cm^{-1}, 548 cm^{-1}, 565 cm^{-1}, 658 cm^{-1}, 705 cm^{-1}, 746 cm^{-1}, 810 cm^{-1}, 850 cm^{-1}, 880 cm^{-1}, 1071 cm^{-1}, 1093 cm^{-1}, 1154 cm^{-1}, 1314 cm^{-1}, 1450 cm^{-1}, 1494 cm^{-1}, 1598 cm^{-1}, 1722 cm^{-1}, 2853 cm^{-1}, 2922 cm^{-1}, 3031 cm^{-1} 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).[142] ^{1}H 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* = 8.0, 13.2 Hz, 1 H), 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 71

Compound **69** (0.06 g, 0.20 mmoles) was treated with TsCl (0.042 g, 0.22 mmoles) and triethylamine (TEA) (0.05 g, 0.45 mmoles) in CH_2Cl_2 (1.50 mL) for 12 hours at room temperature. Water was then added, and the organic layer washed with 1 N HCl (~ 10 mL) 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 **71** (0.04 g, 60 %) as a pale yellow oil: $[\alpha]^{20}_{D}$ = - 13.82 (c = 0.17 g/100 mL, 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 cm^{-1}, 457 cm^{-1}, 594 cm^{-1}, 696 cm^{-1}, 735 cm^{-1}, 808 cm^{-1}, 912 cm^{-1}, 1020 cm^{-1}, 1095 cm^{-1}, 1117 cm^{-1}, 1217 cm^{-1}, 1249 cm^{-1}, 1320 cm^{-1}, 1418 cm^{-1}, 1495 cm^{-1}, 1678 cm^{-1}, 2927 cm^{-1}, 3030 cm^{-1}, 3315 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.14 – 6.96 (m, 4H), 3.94 (d, *J* =

4.7 Hz, 2H), 3.19 (dd, *J* = 3.9, 12.7 Hz, 1H), 3.00 (m, 1H), 2.84 (dd, *J* = 9.0, 12.7 Hz, 1H), 2.71 (dd, *J* = 4.4, 16.3 Hz, 1 H), 2.49 (dd, *J* = 10.9, 16.8 Hz, 1 H), 2.41 (s, 3 H), 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.

(*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 72[56]

This compound was prepared as it has been reported in the literature. Yield 30 % $[\alpha]^{20}_D$ = – 35.0 (*c* = 0.17, in 1 N HCl). IR ν_{max}: 764 cm^{-1}, 1102 cm^{-1}, 1453 cm^{-1}, 1496 cm^{-1}, 1528 cm^{-1}, 1582 cm^{-1} and 2879 cm^{-1}. MP 224 - 226 °C. HRMS calculated for $C_{10}H_{15}N_2$ $(M + H)^+$ = 163.1230 *m/z*, found 163.1192 *m/z*. ^{1}H NMR (400 MHz, D_2O) *δ* = 7.09-7.20 (m, 4H), 4.15 (s, 2H), 3.48 (m, 1H), 3.15 (d, 1H), 2.99 (dd, *J* = 21.2 Hz, 1H) and 2.75 (dd, *J* = 10.8, 10.4 Hz, 1H).

Synthesis of (*S*)-benzyl 3-(methylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76a

The resultant product from condensation with methylamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.4) to afford the methyl substituted TIQ derivative **76a** (1.06 g, 68 %) light yellow oil. $[\alpha]^{20}_D$ = - 6.452 (c = 0.62 g/100 mL, CH_2Cl_2). IR ν_{max}: 495 cm^{-1}, 616 cm^{-1}, 696 cm^{-1}, 742 cm^{-1}, 908 cm^{-1}, 1011 cm^{-1}, 1120 cm^{-1}, 1215 cm^{-1}, 1302 cm^{-1}, 1323 cm^{-1}, 1406 cm^{-1}, 1536 cm^{-1}, 1655 cm^{-1}, 1695 cm^{-1}, 2939 cm^{-1}, 3031 cm^{-1}, 3065 cm^{-1} 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.[142] ^{1}H NMR (400 MHz, d6-DMSO) δ = 7.85 (m, 1 H), 7.58 – 7.08 (m, 9 H), 5.36 – 4.98 (m, 2 H), 4.86 – 4.28 (m, 2 H), 3.22 – 2.89 (m, 2 H), 2.60 – 2.52 (m, 1H), 2.47 (d, 4.66 Hz, 3 H). ^{13}C NMR (101 MHz, d6-DMSO) δ = 170.8, 136.7 - 125.9, 66.4, 54.1, 44.4, 31.3 and 25.6.

Synthesis of (*S*)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 77a

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 **77a** (0.36 g, 77 %) as a white solid. $[\alpha]^{20}_D$ = - 222.5 (c = 0.20 g/100 mL, CH_2Cl_2). IR ν_{max}: 399 cm^{-1}, 435 cm^{-1}, 515 cm^{-1}, 609 cm^{-1}, 674 cm^{-1}, 738 cm^{-1}, 797 cm^{-1}, 963 cm^{-1}, 1129 cm^{-1}, 1225 cm^{-1}, 1413 cm^{-1}, 1562 cm^{-1}, 1643 cm^{-1}, 2835 cm^{-1}, 2877 cm^{-1}, 2940 cm^{-1} 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 and 5.1 Hz, 1H), 3.24 (dd, *J* = 16.5 and 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 78a

After reduction **78a** 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 effective, 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 **78a** (0.03 g, 15 %) a light brown solid. $[\alpha]^{20}_D$ = - 1.3 (c = 0.1 g/100 mL, MeOH). IR ν_{max}: 428 cm^{-1}, 448 cm^{-1}, 763 cm^{-1}, 1025 cm^{-1}, 1451 cm^{-1}, 2598 cm^{-1}, 2717 cm^{-1}, 2941 cm^{-1} 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, 4 H), 4.42 (s, 2 H), 3.94 (m, 1 H), 3.46 (dd, *J* = 13.6 & 6.5 Hz, 1 H), 3.37 (dd, *J* = 13.6 and 5.6 Hz, 1 H), 3.24 (m, 1 H), 3.03 (dd, *J* = 17.1 & 11.0 Hz, 1 H) and 2.76 (s, 3 H), 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 and 30.4.

Synthesis of (*S*)-benzyl 3-(isopropylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76b

The resultant product from the reaction with isopropylamine and **65** was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.45) to afford **76b** (1.43 g, 85 %) as a beige powder. $[\alpha]^{20}_D$ = - 3.5 (c = 0.58 g/100 mL, THF). IR ν_{max}: 695 cm^{-1}, 733 cm^{-1}, 749 cm^{-1}, 1124 cm^{-1}, 1212 cm^{-1}, 1311 cm^{-1}, 1408 cm^{-1}, 1546 cm^{-1}, 1644 cm^{-1}, 1701 cm^{-1}, 2970 cm^{-1} and 3299 cm^{-1}. MP = 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.[142] ^{1}H NMR (400 MHz, d6-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, d6-DMSO) δ = 169.6, 155.2 - 125.8, 67.0, 55.2, 44.6, 40.5, 31.8 and 22.1.

Synthesis of (*S*)-*N*-isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 77b

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 **77b** (0.46 g, 92 %) as a white solid. $[\alpha]^{20}_D$ = - 105.7 (c = 0.35 g/100 mL, CH_2Cl_2). IR ν_{max}: 402 cm^{-1}, 406 cm^{-1}, 619 cm^{-1}, 683 cm^{-1}, 734 cm^{-1}, 1159 cm^{-1}, 1219 cm^{-1}, 1365 cm^{-1}, 1451 cm^{-1}, 1493 cm^{-1}, 1544 cm^{-1}, 1640 cm^{-1}, 2929 cm^{-1},

2973 cm^{-1} 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.

Synthesis of (*S*)-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)propan-2-amine 78b

After reduction of **77e**, the crude compound was purified by column chromatography (EtOAc:MeOH = 95:5, R_f ~ 0.5), yielding an off white-solid **78b** (0.11 g, 46 %). $[\alpha]^{20}_D$ = - 8.3 (c = 0.12 g/100 mL, CH_2Cl_2). IR ν_{max}: 695 cm^{-1}, 729 cm^{-1}, 1118 cm^{-1}, 1216 cm^{-1}, 1302 cm^{-1}, 1322 cm^{-1}, 1400 cm^{-1}, 1650 cm^{-1}, 1680 cm^{-1}, 3029 cm^{-1} and 3331 cm^{-1}. MP = 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, 2 H), 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, 125.7, 53.9, 52.9, 49.0, 48.3, 33.5, 23.1 and 23.0.

Synthesis of (*S*)-benzyl 3-(phenylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76c

The resultant product from condensation with aniline was purified by column chromatography (EtOAc/Hex = 40:60, R_f ~ 0.5) to afford the aniline substituted TIQ derivative **76c** (1.54 g, 83 %) as a light-yellow oil. $[\alpha]^{20}_D$ = - 38.1 (c = 0.42 g/100 mL, CH_2Cl_2). IR ν_{max}: 487 cm^{-1}, 693 cm^{-1}, 736 cm^{-1}, 749 cm^{-1}, 960 cm^{-1}, 1099 cm^{-1}, 1127 cm^{-1}, 1184 cm^{-1}, 1413 cm^{-1}, 1546 cm^{-1}, 1665 cm^{-1}, 1701 cm^{-1}, 3027 cm^{-1} and 3301 cm^{-1}. MP = 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.[142] ^1H NMR (400 MHz, d6-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, d6-DMSO) δ = 169.9, 155.3 - 119.2, 66.5, 54.9, 44.8 and 31.8.

Synthesis of (*S*)-*N*-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 77c

Removal of Cbz group from the aniline amide TIQ **77c** (0.46 g, 88 %) formed as a white solid, which required no further purification. $[\alpha]^{20}_{D}$ = - 144.7 (c = 0.38 g/100 mL, CH_2Cl_2). IR ν_{max}: 440 cm^{-1}, 551 cm^{-1}, 695 cm^{-1}, 736 cm^{-1}, 1060 cm^{-1}, 1190 cm^{-1}, 1258 cm^{-1}, 1364 cm^{-1}, 1408 cm^{-1}, 1496 cm^{-1}, 1597 cm^{-1}, 1697 cm^{-1}, 2891 cm^{-1}, 2927 cm^{-1}, 2968 cm^{-1}, 3045 $cm^{-11}$and 3299 cm^{-1}. MP = 183 – 192 °C. HRMS calculated for $C_{16}H_{17}N_2O$ $(M + H)^+$ = 253.1317 *m/z*, found 253.1335 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.39 (s, 1 H), 7.60 (d, *J* = 7.8 Hz, 2 H), 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 5.3 Hz, 1H), 2.95 (dd, *J* = 16.4 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.

Synthesis of (*S*)-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)aniline 78c[62]

After reduction of **77c**, the crude compound was purified by column chromatography (100 % diethyl ether, R_f ~ 0.5), yielding a white solid **78c** (0.13 g, 57 %). $[\alpha]^{20}_{D}$ = - 64.29 (c = 0.14 g/100 mL, CH_2Cl_2). IR ν_{max}: 435 cm^{-1}, 488 cm^{-1}, 513 cm^{-1}, 585 cm^{-1}, 690 cm^{-1}, 743 cm^{-1}, 805 cm^{-1}, 1258 cm^{-1}, 1346 cm^{-1}, 1494 cm^{-1}, 1600 cm^{-1}, 2792 cm^{-1}, 2929 cm^{-1}, 3218 cm^{-1} and 3301 cm^{-1}. MP = 90 – 92 °C. HRMS calculated for $C_{16}H_{19}N_2$ $(M + H)^+$ = 239.1543 *m/z*, found 239.1543 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 6.99 (m, 6 H), 6.76 – 6.62 (m, 3H), 4.23 (br s, NH, 1H), 4.07 (br s, 2H), 3.36 (d, *J* = 12.1 Hz, 1H), 3.22 (m, 1H), 3.10 (m, 1H), 2.85 (dd, *J* = 16.3 and 4.1 Hz, 1H), 2.66 (dd, *J* = 16.3 and 10.5 Hz, 1H), only a single NH proton was 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.

Synthesis of (*S*)-benzyl 3-(benzylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76d

The crude product **76d** was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~ 0.45), isolated as a white powder (1.44 g, 75 %). $[\alpha]^{20}_{D}$ = - 8.3 (c = 0.12 g/100 mL, CH_2Cl_2). IR ν_{max}: 695 cm^{-1}, 729 cm^{-1}, 1118 cm^{-1}, 1216 cm^{-1}, 1302 cm^{-1}, 1322 cm^{-1}, 1400 cm^{-1}, 1650 cm^{-1}, 1680 cm^{-1}, 3029 cm^{-1} and 3331 cm^{-1}. MP = 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).[142] ^{1}H NMR (400 MHz, d6-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, d6-DMSO) δ = 170.6, 139.2 - 126.1, 66.4, 54.5, 44.7, 41.8 and 31.8.

Synthesis of (*S*)-*N*-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 77d

Removal of Cbz from **76d**, after purification by column chromatography (DCM/MeOH/10 % NH_3 in $CHCl_3$ = 87:3:10, R_f ~ 0.4) gave the benzyl amide TIQ **77d** (0.45 g, 85 %) as a white solid. $[\alpha]^{20}_D$ = - 54.76 (c = 0.42 g/100 mL, CH_2Cl_2). IR ν_{max}: 435 cm^{-1}, 467 cm^{-1}, 613 cm^{-1}, 694 cm^{-1}, 736 cm^{-1}, 797 cm^{-1}, 1029 cm^{-1}, 1222 cm^{-1}, 1453 cm^{-1}, 1546 cm^{-1}, 1643 cm^{-1}, 2925 cm^{-1}, 3033 cm^{-1}, 3057 cm^{-1}, 3279 cm^{-1} and 3330 cm^{-1}. MP = 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 Hz, 2H), 4.05 – 3.91 (d, *J* = 6.5 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.

Synthesis of (*S*)-*N*-benzyl-1-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 78d

After reduction of **77d** (0.25 g), 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 **78d** (0.07 g, 31 %) as an off-white/yellow solid. $[\alpha]^{20}_D$ = - 70.93 (c = 0.43 g/100 mL, CH_2Cl_2). IR ν_{max}: 695 cm^{-1}, 729 cm^{-1}, 1118 cm^{-1}, 1216 cm^{-1}, 1302 cm^{-1}, 1322 cm^{-1}, 1400 cm^{-1}, 1650 cm^{-1}, 1680 cm^{-1}, 3029 cm^{-1} and 3331 cm^{-1}. MP = 85 – 87 °C. HRMS calculated for $C_{17}H_{21}N_2$ $(M + H)^+$ = 253.1699 *m/z*, found 253.1708 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 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.

Synthesis of (*S*)-benzyl 3-(benzhydrylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76e

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 **76e** (1.62 g, 71 %) light yellow oil. $[\alpha]^{20}_D$ = - 11.43 (c = 0.36 g/100 mL, CH_2Cl_2). IR ν_{max}: 528 cm^{-1}, 546 cm^{-1}, 604 cm^{-1}, 616 cm^{-1}, 639 cm^{-1}, 695 cm^{-1}, 738 cm^{-1}, 909 cm^{-1}, 1001 cm^{-1},

1028 cm^{-1}, 1094 cm^{-1}, 1120 cm^{-1}, 1215 cm^{-1}, 1303 cm^{-1}, 1346 cm^{-1}, 1403 cm^{-1}, 1453 cm^{-1}, 1494 cm^{-1}, 1658 cm^{-1}, 1696 cm^{-1}, 2851 cm^{-1}, 2925 cm^{-1}, 3029 cm^{-1} 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.[142] ^{1}H NMR (400 MHz, d6-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, d6-DMSO) δ = 170.2, 155.3 - 125.9, 86.6, 66.4, 54.8, 44.8 and 32.1.

Synthesis of (*S*)-*N*-benzhydryl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 77e

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 TIQ **77e** (0.46 g, 80 %) as a light brown solid. $[\alpha]^{20}_D$ = - 105.7 (c = 0.35 g/100 mL, CH_2Cl_2). IR ν_{max}: 402 cm^{-1}, 406 cm^{-1}, 619 cm^{-1}, 683 cm^{-1}, 734 cm^{-1}, 1159 cm^{-1}, 1219 cm^{-1}, 1365 cm^{-1}, 1451 cm^{-1}, 1493 cm^{-1}, 1544 cm^{-1}, 1640 cm^{-1}, 2929 cm^{-1}, 2973 cm^{-1} and 3292 cm^{-1}. HRMS calculated for $C_{23}H_{22}N_2O$ $(M + H)^+$ = 343.1795 *m/z*, found 343.1805 *m/z*. ^{1}H 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 spectra. ^{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

Synthesis of (*S*)-1,1-diphenyl-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)methanamine 78e

After the reduction of **77e** (0.25 g), the crude compound was purified by column chromatography (MeOH/Et_2O = 5:95, R_f ~ 0.6) to afford the *N*-diphenylmethanamine amine derivative **78e** (0.05 g, 21 %) as a yellow solid. $[\alpha]^{20}_D$ = - 55.77 (c = 0.52 g/100 mL, CH_2Cl_2). IR ν_{max}: 430 cm^{-1}, 696 cm^{-1}, 706 cm^{-1}, 743 cm^{-1}, 800 cm^{-1}, 1027 cm^{-1}, 1429 cm^{-1}, 1447 cm^{-1}, 1490 cm^{-1}, 1580 cm^{-1}, 1595 cm^{-1}, 2780 cm^{-1}, 2911 cm^{-1}, 3289 cm^{-1}, and 3324 cm^{-1}. MP = 89 – 91 °C. HRMS calculated for $C_{23}H_{25}N_2$ $(M + H)^+$ = 329.2012 *m/z*, found 329.2004 *m/z*. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.43 – 6.98 (m, 14 H), 4.87 (s, 1 H), 4.06 (s, 2 H), 3.00 (m, 1 H), 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, 127.0, 126.1, 126.0, 125.7, 67.7, 53.7, 53.6, 48.3 and 33.4.

Synthesis of (*S*)-benzyl 3-((*R*)-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76f

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 **76f** (1.55 g, 78 %) as a light-yellow oil. $[\alpha]^{20}_D$ = + 10.7 (c = 1.03 g/100 mL, CH_2Cl_2). IR ν_{max}: 491 cm^{-1}, 599 cm^{-1}, 696 cm^{-1}, 740 cm^{-1}, 905 cm^{-1}, 1001 cm^{-1}, 1093 cm^{-1}, 1119 cm^{-1}, 1214 cm^{-1}, 1302 cm^{-1}, 1322 cm^{-1}, 1347 cm^{-1}, 1400 cm^{-1}, 1448 cm^{-1}, 1522 cm^{-1}, 1638 cm^{-1}, 1697 cm^{-1}, 2932 cm^{-1}, 3029 cm^{-1}, 3062 cm^{-1} 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.[142] ^{1}H NMR = (400 MHz, d6-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* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, d6-DMSO) δ = 170.1, 144.1 - 125.6, 66.4, 54.4, 47.5, 44.7, 32.0 and 22.0.

Synthesis of (*S*)-*N*-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 77f

Removal of Cbz and purification by column chromatography (Et_2O:Acetone = 80:20, R_f ~ 0.5) gave the (*R*)-1-phenylethanamide TIQ **77f** (0.39 g, 72 %) as a white solid. $[\alpha]^{20}_D$ = - 33.8 (c = 0.34 g/100 mL, CH_2Cl_2). IR ν_{max}: 430 cm^{-1}, 583 cm^{-1}, 617 cm^{-1}, 695 cm^{-1}, 733 cm^{-1}, 748 cm^{-1}, 790 cm^{-1}, 803 cm^{-1}, 1180 cm^{-1}, 1221 cm^{-1}, 1446 cm^{-1}, 1492 cm^{-1}, 1544 cm^{-1}, 1643 cm^{-1}, 2838 cm^{-1}, 2926 cm^{-1} and 3284 cm^{-1}. MP = 119 – 121 °C. HRMS calculated for $C_{18}H_{21}N_2O$ $(M + H)^+$ = 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* = 11.8 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.

Synthesis of (*R*)-1-phenyl-*N*-(((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine 78f

After reduction of **77f** (0.25 g), 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 **78f** (0.07 g, 30 %), a light-yellow oil. $[\alpha]^{20}_D$ = - 43.55 (c = 0.93 g/100 mL, CH_2Cl_2). IR ν_{max}: 431 cm^{-1}, 543 cm^{-1}, 695 cm^{-1}, 783 cm^{-1}, 1118 cm^{-1}, 1451 cm^{-1}, 1492 cm^{-1}, 2789 cm^{-1}, 2918 cm^{-1}, 2960 cm^{-1}, 3026 cm^{-1} and 3240 cm^{-1}. HRMS calculated for $C_{18}H_{23}N_2$ $(M + H)^+$ = 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* = 16.8 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 Hz, 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.

Synthesis of (*S*)-benzyl 3-((*S*)-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 76g

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 **76g** (1.77 g, 89 %) as a light-yellow oil. $[\alpha]^{20}_D$ = - 21.4 (c = 0.70 g/100 mL, CH_2Cl_2). IR ν_{max}: 696 cm^{-1}, 738 cm^{-1}, 1059 cm^{-1}, 1119 cm^{-1}, 1213 cm^{-1}, 1303 cm^{-1}, 1329 cm^{-1}, 1407 cm^{-1}, 1449 cm^{-1}, 1495 cm^{-1}, 1534 cm^{-1}, 1656 cm^{-1}, 1697 cm^{-1}, 2972 cm^{-1}, 3029 cm^{-1}, 3062 cm^{-1} and 3299 cm^{-1}. HRMS calculated for $C_{26}H_{27}N_2O_3$ $(M + H)^+$ = 415.2016 *m/z*, found 415.2009 *m/z*. NMR spectra are reported for a mixture of two rotamers.[142] ^{1}H NMR (400 MHz,d6- 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, d6-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 77g

Removal of Cbz and purification by column chromatography (Et_2O:Acetone = 80:20, R_f ~ 0.5) afforded the (*S*)-1-phenylethanamide TIQ **77g** (0.41 g, 76 %) as a beige solid. $[\alpha]^{20}_D$ = - 100.7 (c = 0.36 g/100 mL, CH_2Cl_2). IR ν_{max}: 428 cm^{-1}, 449 cm^{-1}, 525 cm^{-1}, 551 cm^{-1}, 609 cm^{-1}, 643 cm^{-1}, 697 cm^{-1}, 734 cm^{-1}, 750 cm^{-1}, 780 cm^{-1}, 1077 cm^{-1}, 1137 cm^{-1}, 1225 cm^{-1}, 1248 cm^{-1}, 1493 cm^{-1}, 1533 cm^{-1}, 1646 cm^{-1}, 2926 cm^{-1}, 2966 cm^{-1} and 3333 cm^{-1}. MP = 119 – 121 °C. HRMS calculated for $C_{18}H_{21}N_2O$ $(M + H)^+$ = 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* = 16.5 and 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.

Synthesis of (*S*)-1-phenyl-*N*-(((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine 78g

After reduction of **77g** (0.25 g), 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 **78g** (0.08 g, 35 %), as a light-yellow oil, which was then also stored as the dihydrochloride salt. $[\alpha]^{20}_D$ = - 43.6 (c = 0.93 g/100 mL, CH_2Cl_2). IR ν_{max}: 431 cm^{-1}, 543 cm^{-1}, 695 cm^{-1}, 783 cm^{-1}, 1118 cm^{-1}, 1451 cm^{-1}, 1492 cm^{-1}, 2789 cm^{-1}, 2918 cm^{-1}, 2960 cm^{-1}, 3026 cm^{-1} and 3240 cm^{-1}. HRMS calculated for $C_{18}H_{23}N_2$ $(M + H)^+$ = 267.1856 *m/z*, found 267.1846 *m/z*. ^{1}H NMR (400 MHz, MeOD) δ = 7.58 – 7.10 (m, 9 H), 4.52 – 4.31 (m, 3 H), 3.87 (m, 1 H), 3.49 (m, 1 H), 3.19 – 3.01 (m, 3 H), 1.71 (d, *J* = 6.7, 3 H). ^{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.

Synthesis of (1*R*,3*S*)-benzyl 3-(hydroxymethyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 79

Compound **9**[143] (1.00 g, 3.34 mmoles) was protected with a Cbz group under the conditions described in the general procedure to afford **79** (1.31 g, 91 %) as a light-yellow oil after column chromatography (EtOAc/Hex = 60:40, R_f ~ 0.5). $[\alpha]^{20}_D$ = + 40.38 (c = 0.26 g/100 mL, CH_2Cl_2). IR ν_{max}: 697 cm^{-1}, 1088 cm^{-1}, 1220 cm^{-1}, 1285 cm^{-1}, 1337 cm^{-1}, 1404 cm^{-1}, 1516 cm^{-1}, 1638 cm^{-1}, 1688 cm^{-1}, 2247 cm^{-1}, 3301 cm^{-1} and 3553 cm^{-1}. HRMS calculated for $C_{26}H_{28}NO_5$ $(M + H)^+$ = 434.1928 *m/z*, found 434.1962 *m/z*. NMR spectra are reported for a mixture of two rotamers.[142] ^{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-((1,3-dioxoisoindolin-2-yl)methyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 84

Compound **79** (0.36 g, 0.83 mmoles), phthalimide (0.18 g, 1.25 mmoles) and triphenylphosphine (0.63 g, 2.41 mmoles) were first taken up in 11.50 mL of DCM. The mixture was kept stirring whilst cooled to 0 °C, after which diethyl azidodicarboxylate (0.30 mL, 2.49 mmoles) in 3.00 mL of DCM was added dropwise. Thereafter the mixture was allowed to reach room temperature and stirred for a further three hours.[144] The DCM was then removed under vacuum and water was added, the aqueous layer was extracted three times with DCM, followed by a

typical work up procedure as outlined in the general procedures. The product **84** was obtained as a yellow oil (55 %)after column chromatography (EtOAc/Hex, 40:60 R_f ~ 0.7). HRMS calculated for $C_{34}H_{31}N_2O_6$ $(M + H)^+$ = 563.2177 *m/z*, found 563.2180 *m/z*. IR ν_{max}: 430 cm^{-1}, 457 cm^{-1}, 594 cm^{-1}, 696 cm^{-1}, 735 cm^{-1}, 808 cm^{-1}, 912 cm^{-1}, 1020 cm^{-1}, 1095 cm^{-1}, 1117 cm^{-1}, 1217 cm^{-1}, 1249 cm^{-1}, 1320 cm^{-1}, 1418 cm^{-1}, 1495 cm^{-1}, 1678 cm^{-1}, 2927 cm^{-1}, 3030 cm^{-1}, 3315 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.51 (m, 4H), 7.56 – 7.02 (m, 9H), 6.87 (m, 1H), 6.47 - 6.68 (m, 2H), 5.92 (m, 1H), 5.27 – 4.76 (m, 3H), 4.01 (m, 1H), 3.93 - 3.53 (m, 7H), 3.22 (m, 1H), 2.81 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 156.1, 147.6, 144.6, 136.4, 133.6, 132.1, 131.8, 128.8, 128.5, 128.3, 128.1, 127.5, 126.5, 125.9, 125.5, 123.7, 122.6, 112.1, 110.3, 77.3, 77.0, 76.7, 67.5, 67.1, 59.7, 55.8, 55.7, 51.2, 40.7 and 31.1.

Synthesis of (1*R*,3*S*)-benzyl 3-formyl-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 87

Oxidation of **79** (0.80 g, 1.84 mmoles) with PCC (3 equivalents) and $MgSO_4$ (3 equivalents) in dry DCM[145] gave **87** (0.45 g, 57 %) as a yellow oil after treatment with wet diethyl ether and filtration through a small plug of silica to remove excess PCC and other metal species. $[\alpha]^{20}_D$ = + 41.5 (c = 0.41 g/100 mL, CH_2Cl_2). IR ν_{max}: 594 cm^{-1}, 697 cm^{-1}, 737 cm^{-1}, 994 cm^{-1}, 1028 cm^{-1}, 1092 cm^{-1}, 1221 cm^{-1}, 1264 cm^{-1}, 1339 cm^{-1}, 1397 cm^{-1}, 1513 cm^{-1}, 1692 cm^{-1}, 2838 cm^{-1} 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.[142] ^{1}H NMR (400 MHz, CDCl3) 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, CDCl3) δ = 148.5 - 126.0, 110.7, 67.5, 60.6, 56.0, 55.9 and 29.7.

Synthesis of (1*R*,3*S*)-benzyl 3-((benzylamino)methyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 86

To a 50 % mixture of dry THF in MeOH (6.00 mL) was added compound **11** (0.30 g, 0.69 mmoles), followed by benzylamine (0.23 g, 2.00 mmoles) and the mixture was allowed to stir at room temperature for 3 hours. The reaction mixture was then cooled to 0 °C with an ice bath, followed by slow addition of $NaCNBH_4$ (~ 0.30 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. $[\alpha]^{20}_D$ = + 27.3 (c = 0.44 g/100 mL, CH_2Cl_2). IR ν_{max}: 593 cm^{-1}, 697 cm^{-1}, 736 cm^{-1}, 999 cm^{-1}, 1028 cm^{-1}, 1092 cm^{-1},

1219 cm^{-1}, 1338 cm^{-1}, 1397 cm^{-1}, 1452 cm^{-1}, 1514 cm^{-1}, 1689 cm^{-1}, 2931 cm^{-1} 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.[142] ^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, CDCl3) 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.

Synthesis of N-benzyl-1-((1R,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 88

Compound **12** (0.1 g, 0.19 mmoles) 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 **88** (0.038 g, 52 %) as a colourless oil. $[\alpha]^{20}_D$ = - 26.8 (c = 0.41 g/100 mL, CH_2Cl_2). IR ν_{max}: 573 cm^{-1}, 699 cm^{-1}, 753 cm^{-1}, 819 cm^{-1}, 1057 cm^{-1}, 1127 cm^{-1}, 1224 cm^{-1}, 1293 cm^{-1}, 1449 cm^{-1}, 1519 cm^{-1}, 1609 cm^{-1}, 2832 cm^{-1}, 2920 cm^{-1}, 2994 cm^{-1} and 3060 cm^{-1}. HRMS calculated for $C_{25}H_{29}N_2O_2$ $(M + H)^+$ = 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), 3.55 (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, 128.3, 128.3, 128.3, 128.2, 128.1, 127.0, 126.9, 111.4, 111.1, 59.3, 55.9, 55.8, 53.9, 53.5, 46.2 and 33.1.

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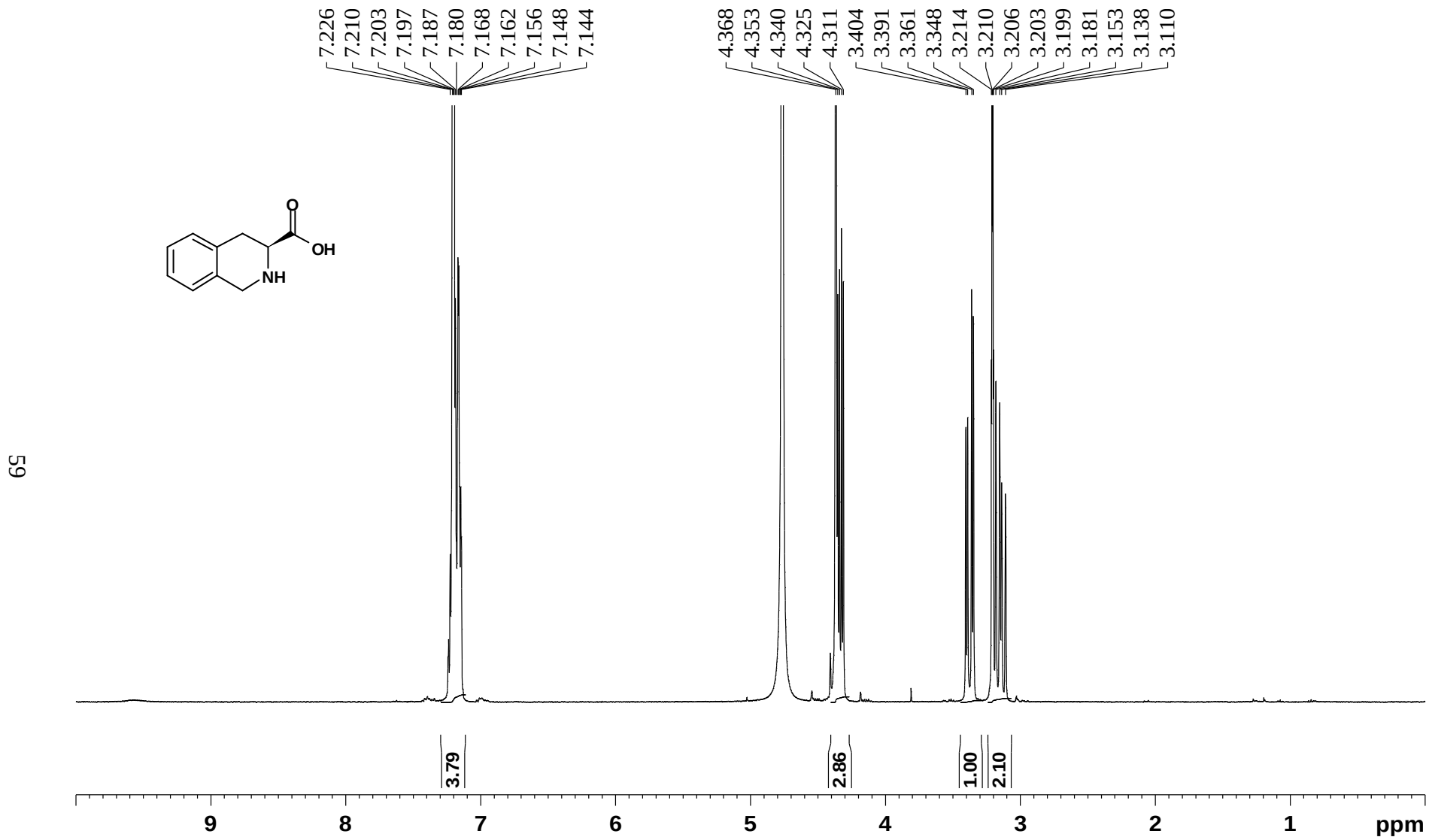
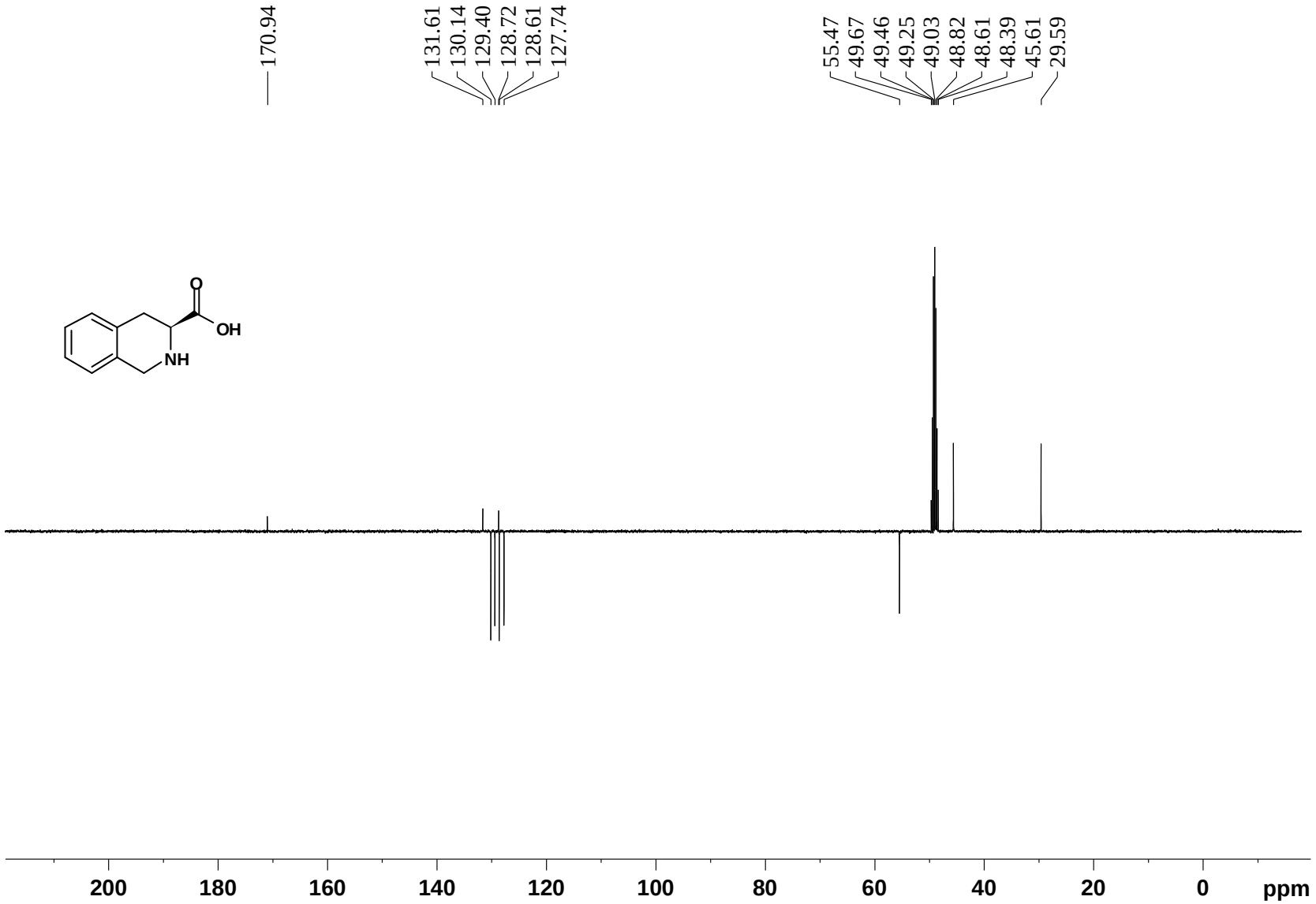
Appendix A

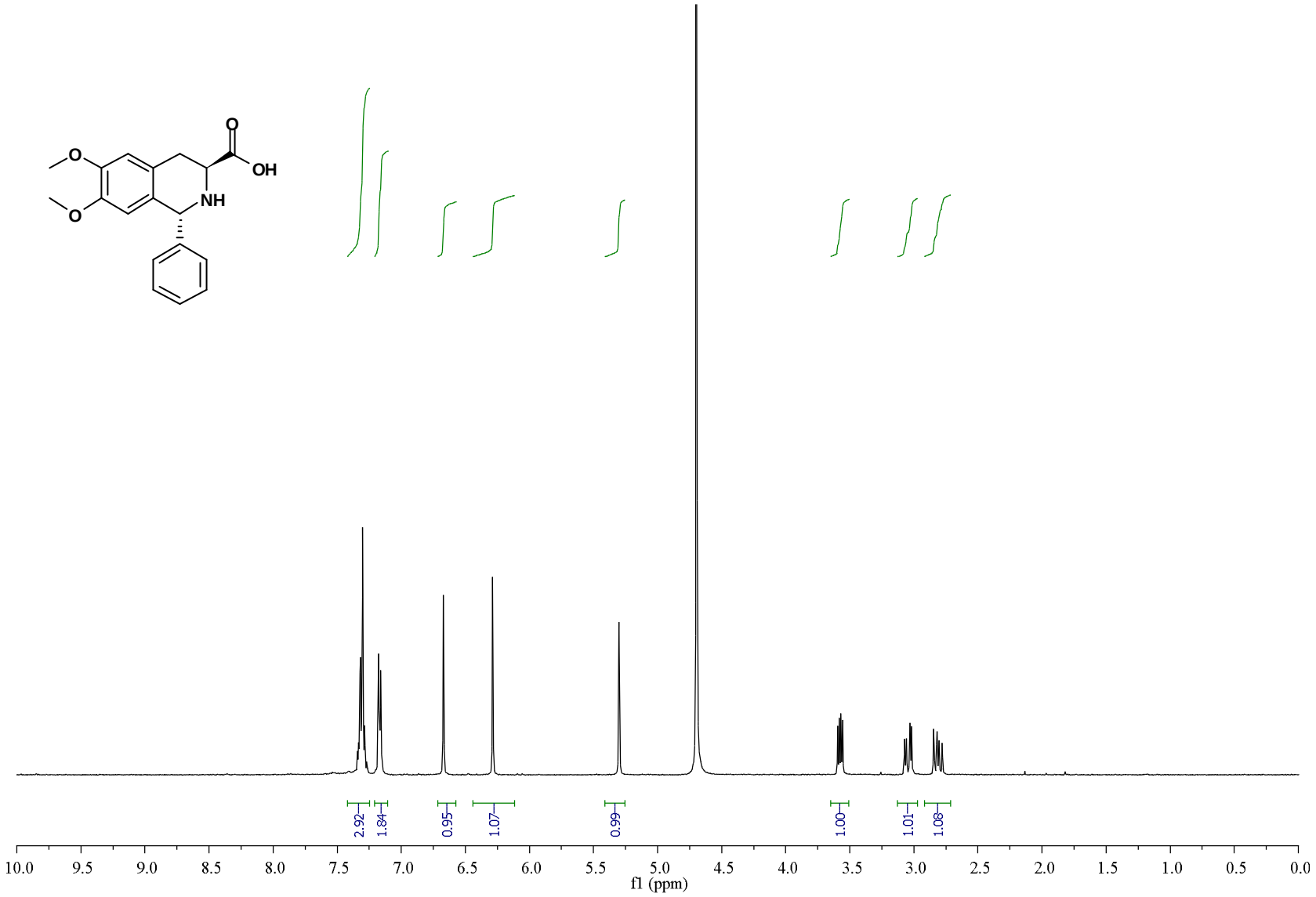
- **NMR spectra**
- **IR spectra**
- **GC chromatographs**



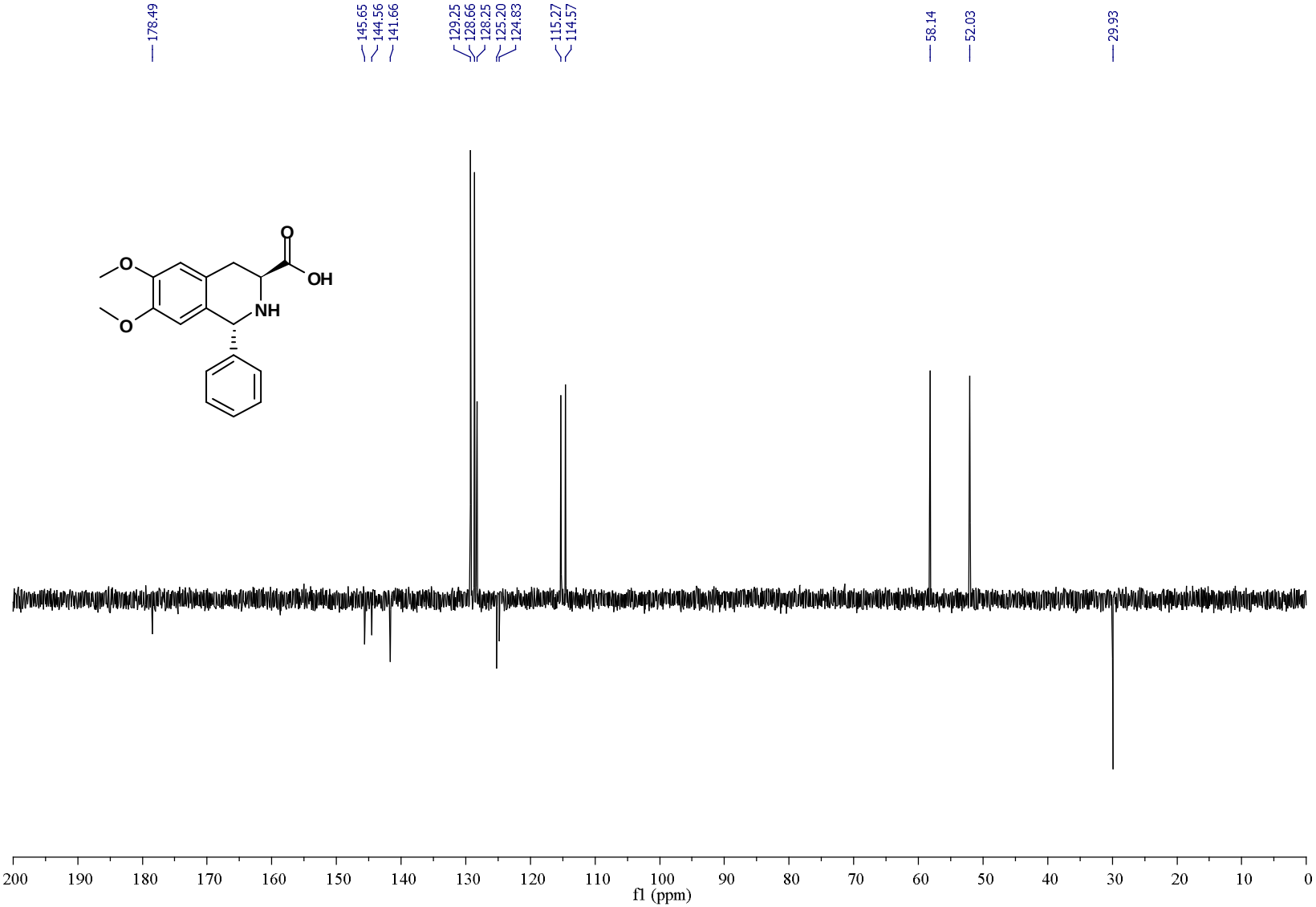
^{1}H NMR Spectrum of Compound 59 in $CDCl_3$



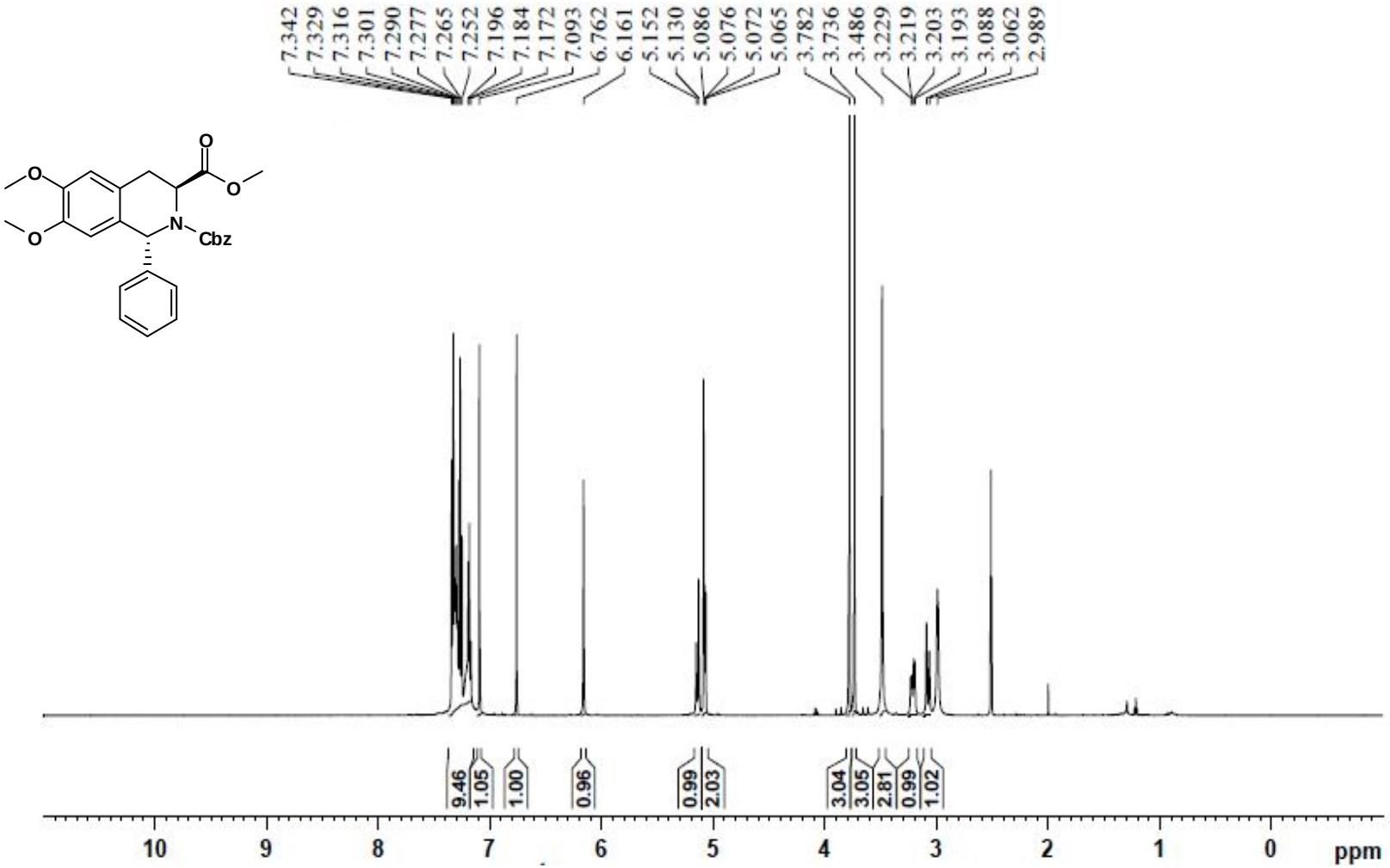
^{13}C NMR Spectrum of Compound 59 in $CDCl_3$



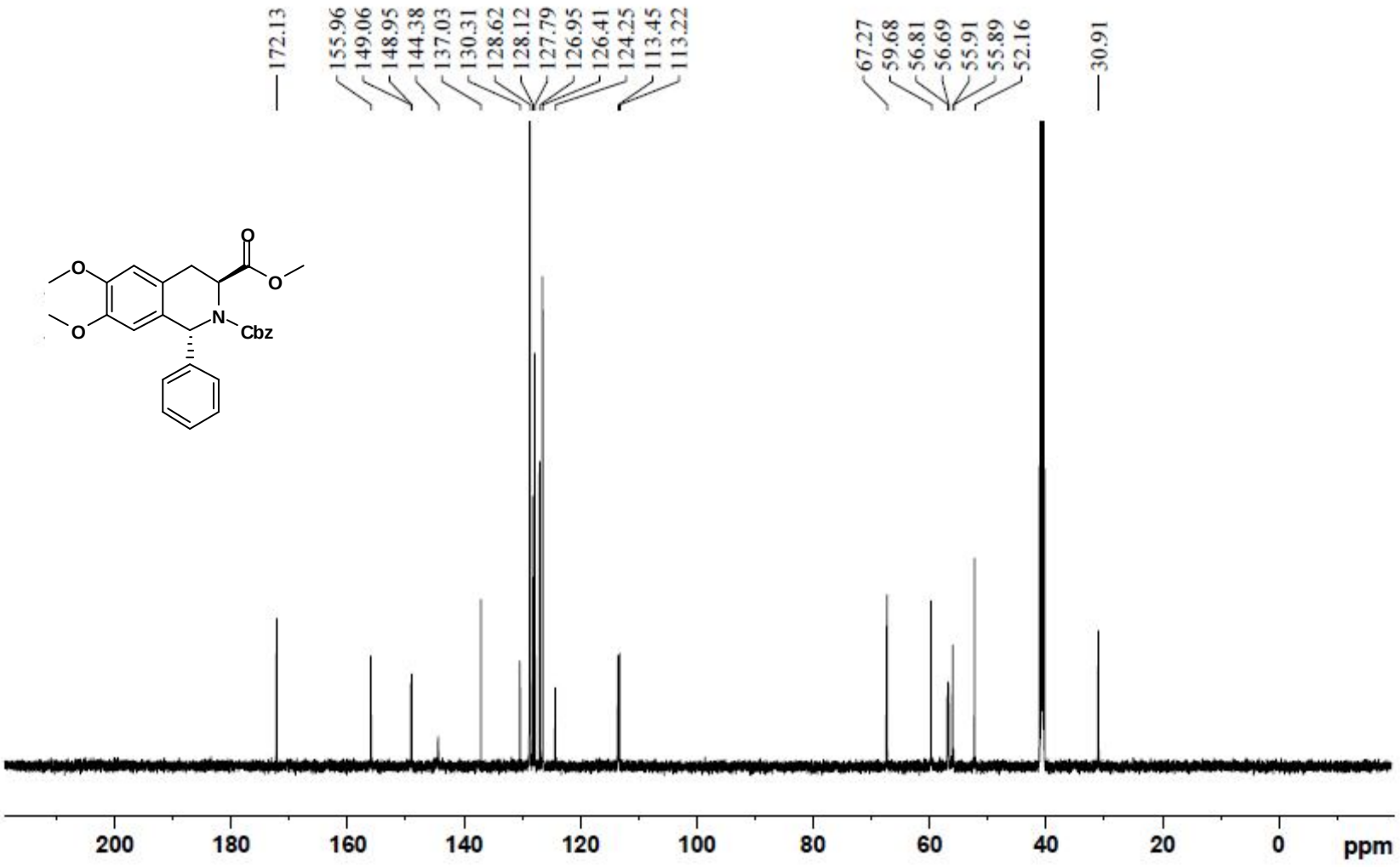
^{1}H NMR Spectrum of Compound 61 in $CDCl_3$



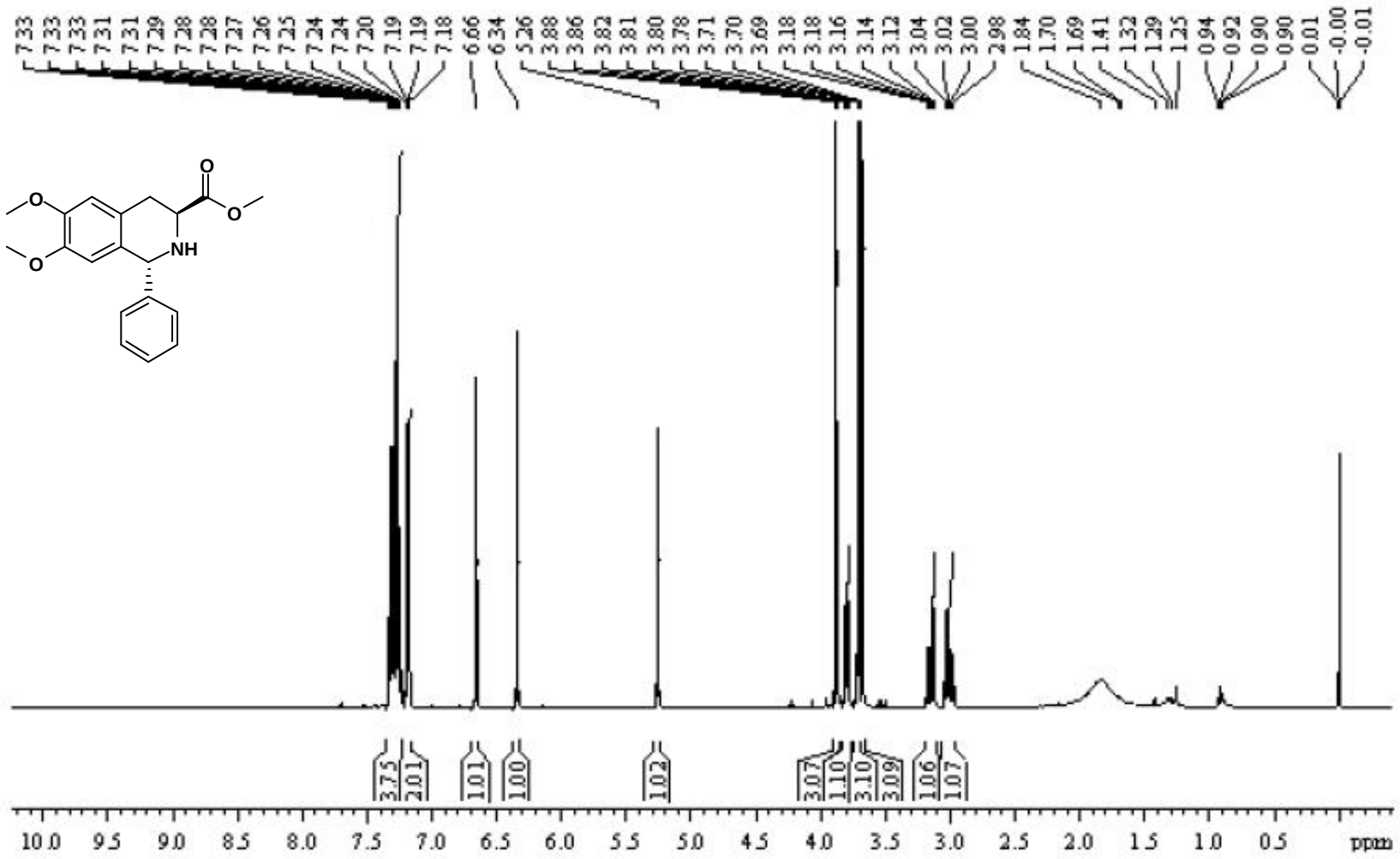
^{13}C NMR Spectrum of Compound 61 in $CDCl_3$



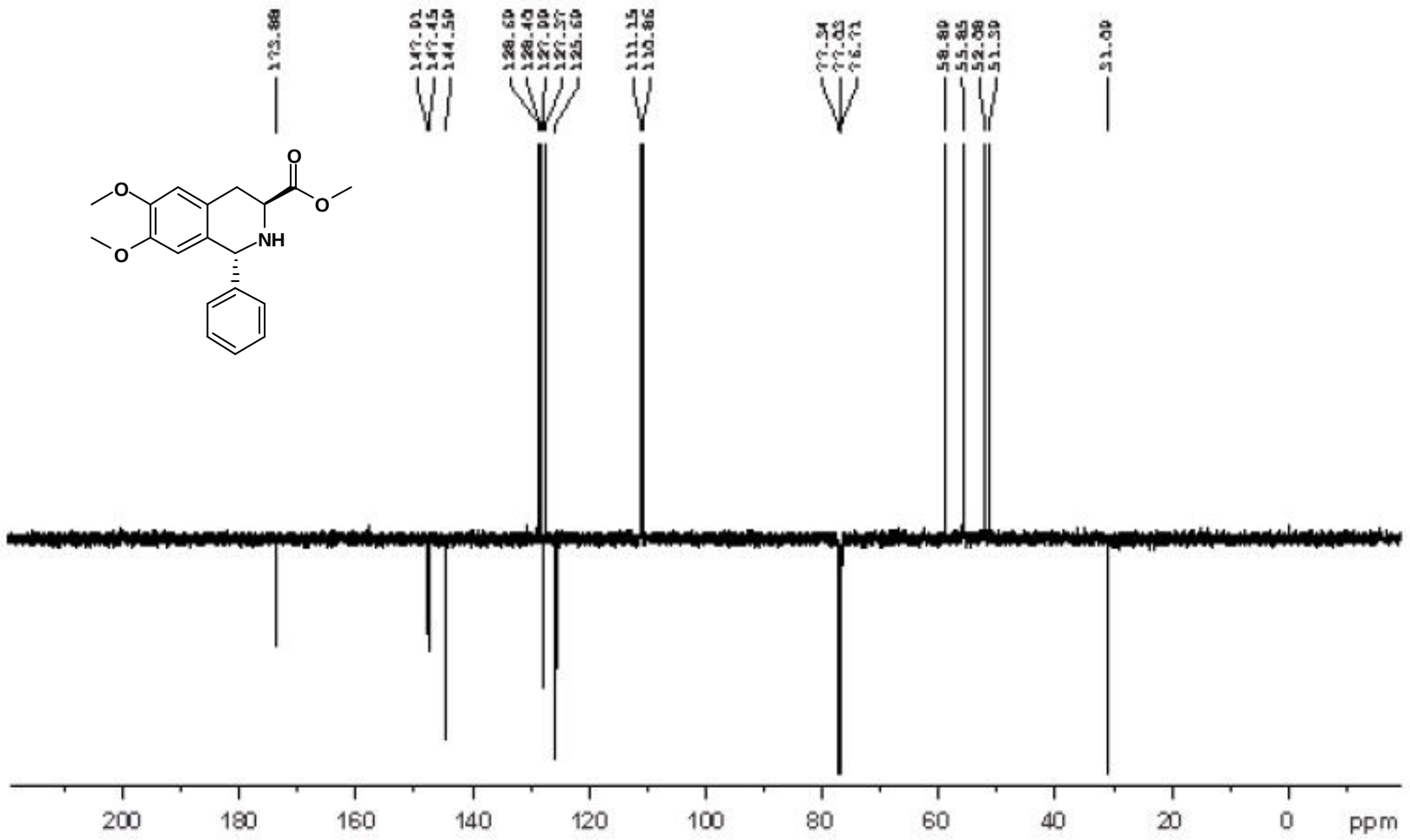
^{1}H NMR Spectrum of Compound 63 in $CDCl_3$



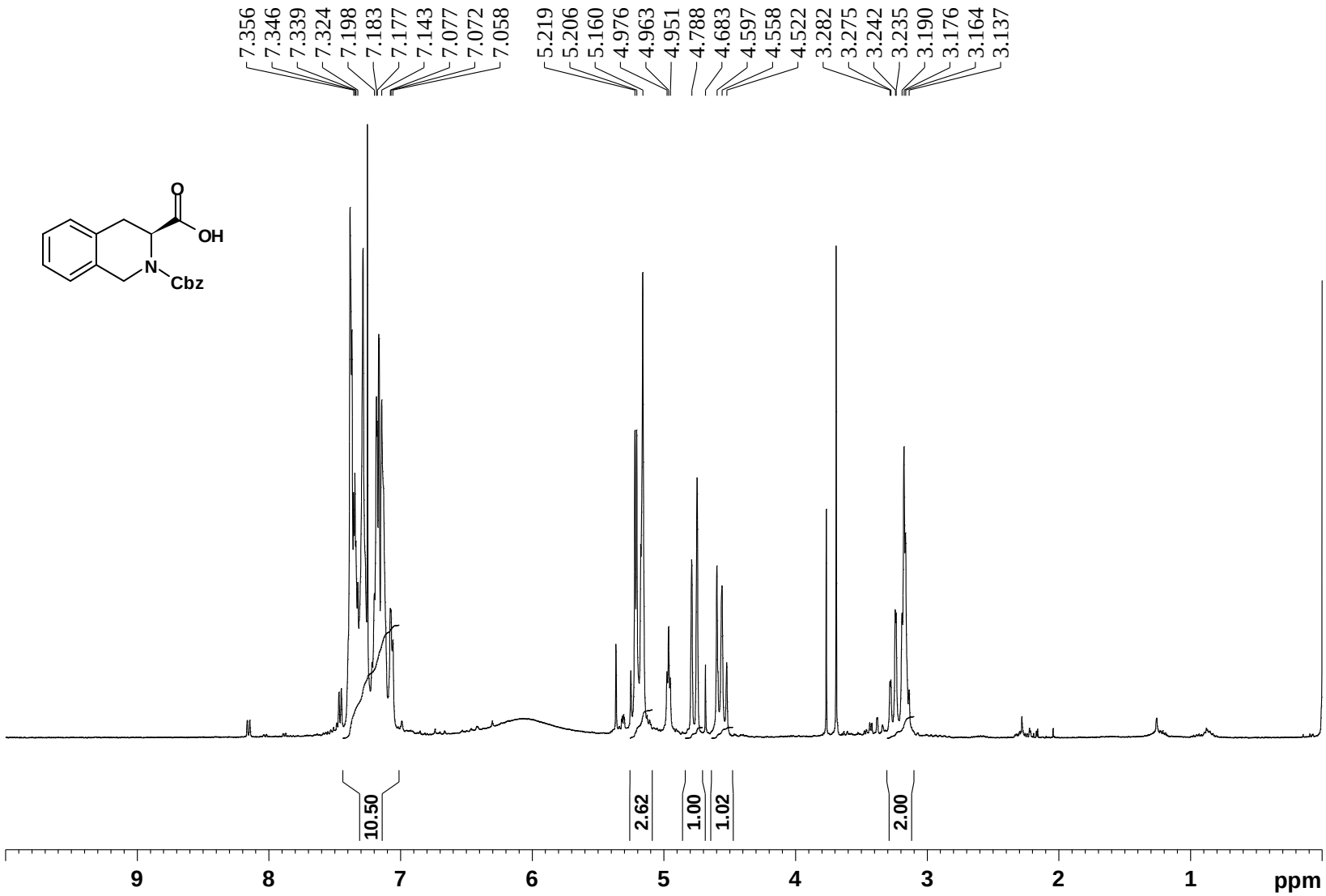
^{13}C NMR Spectrum of Compound 63 in $CDCl_3$



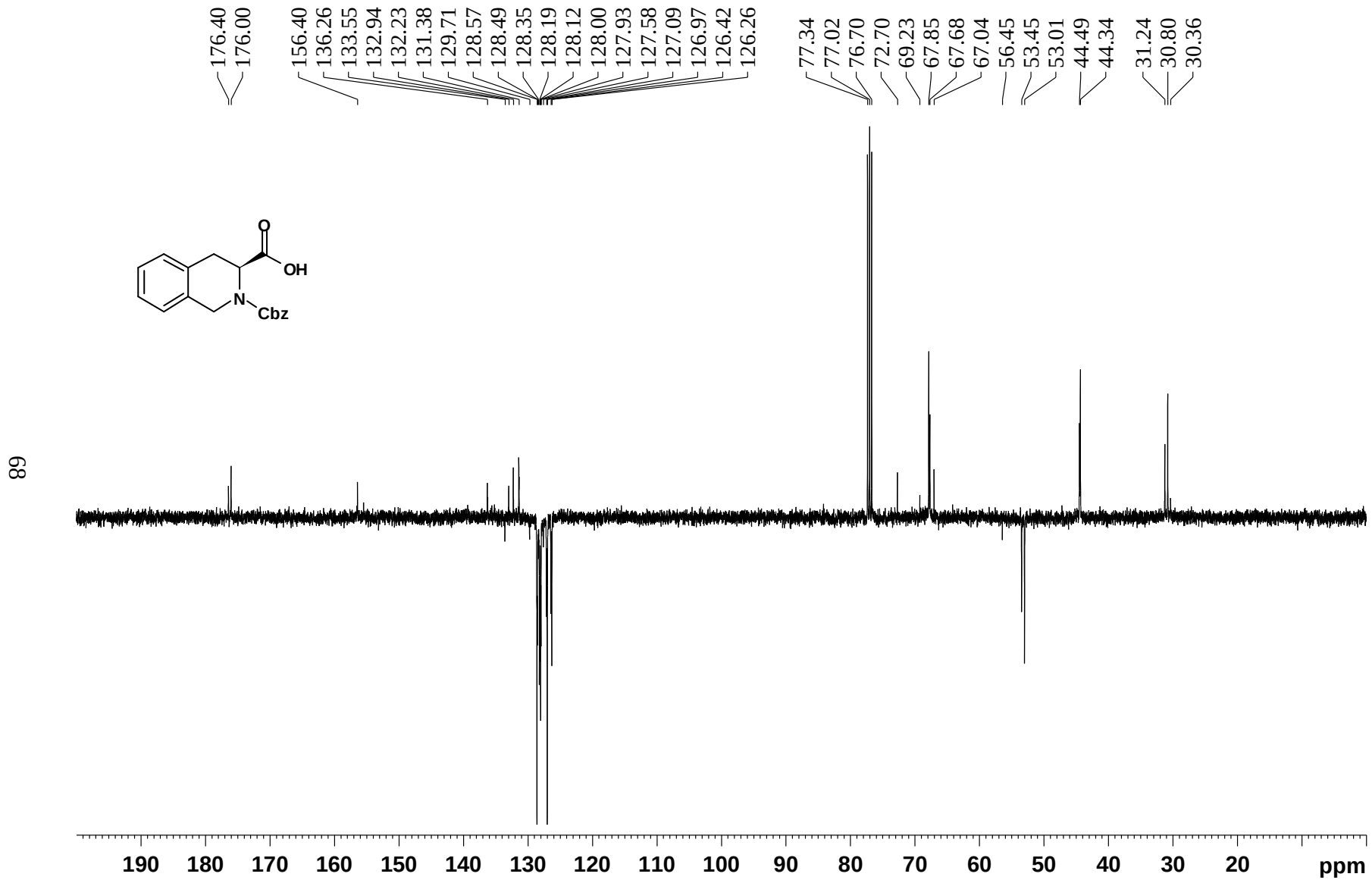
^{1}H NMR Spectrum of Compound 64 in $CDCl_3$



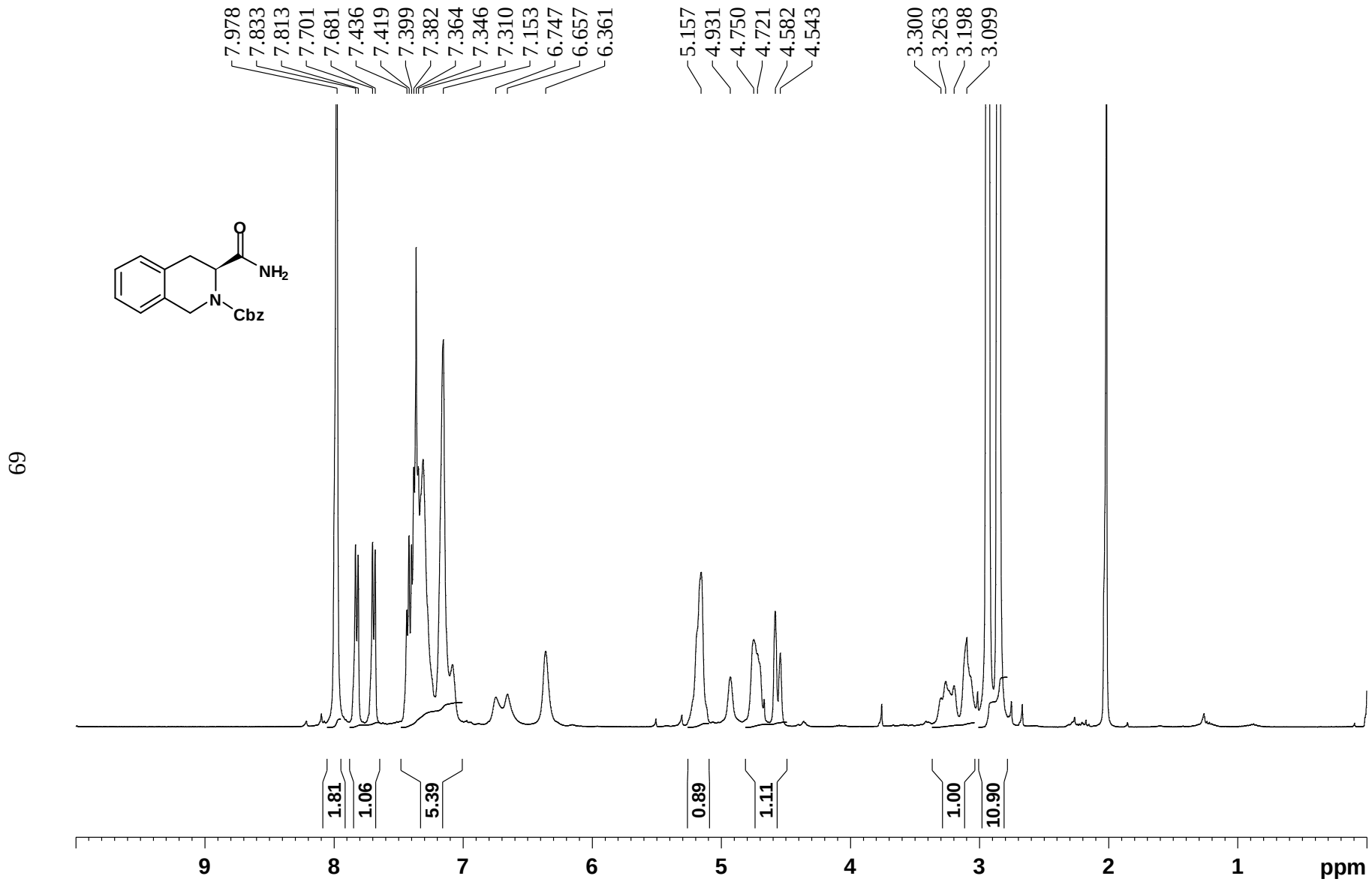
^{13}C NMR Spectrum of Compound 64 in $CDCl_3$



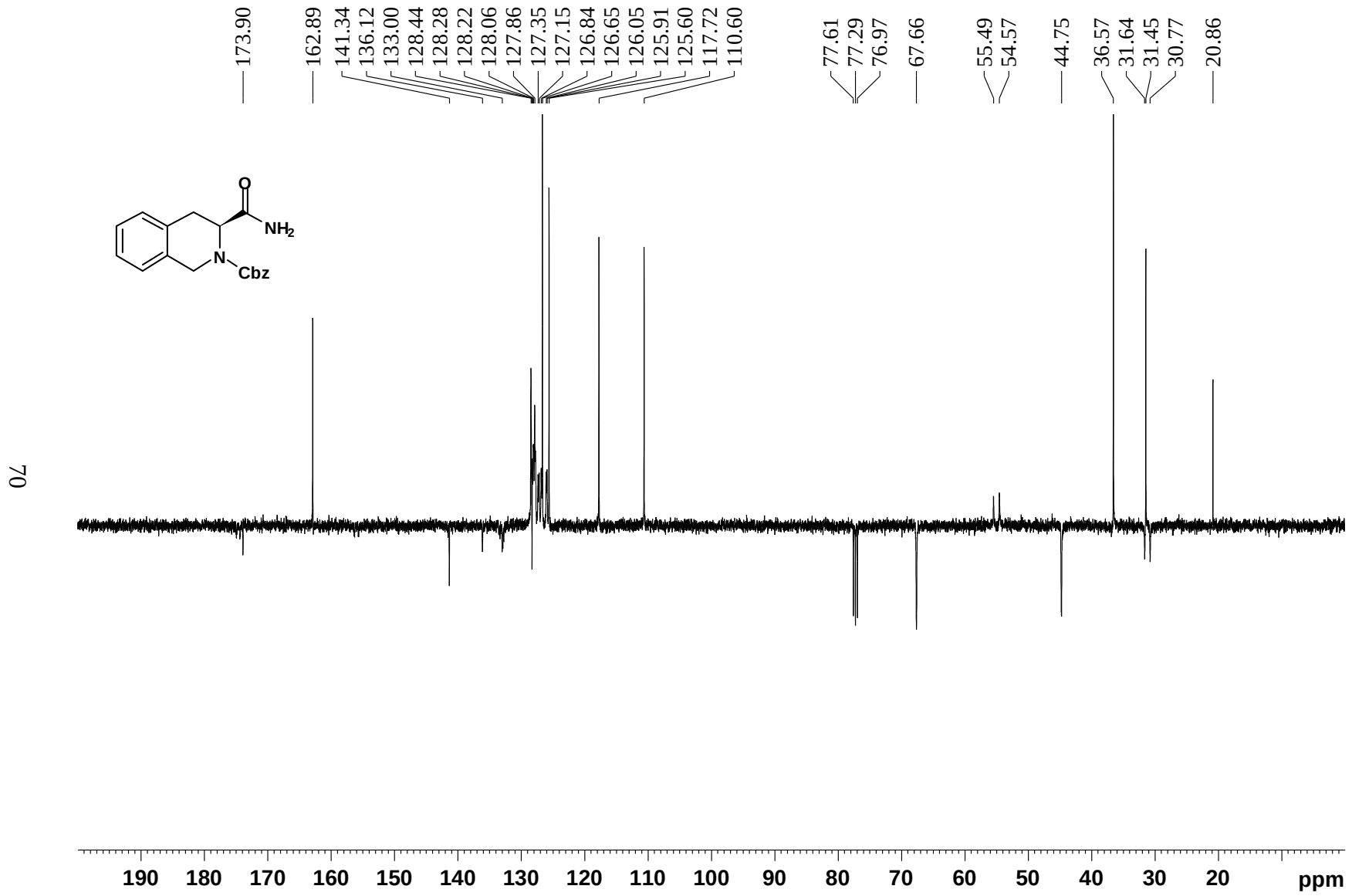
^{1}H NMR Spectrum of Compound 65 in $CDCl_3$



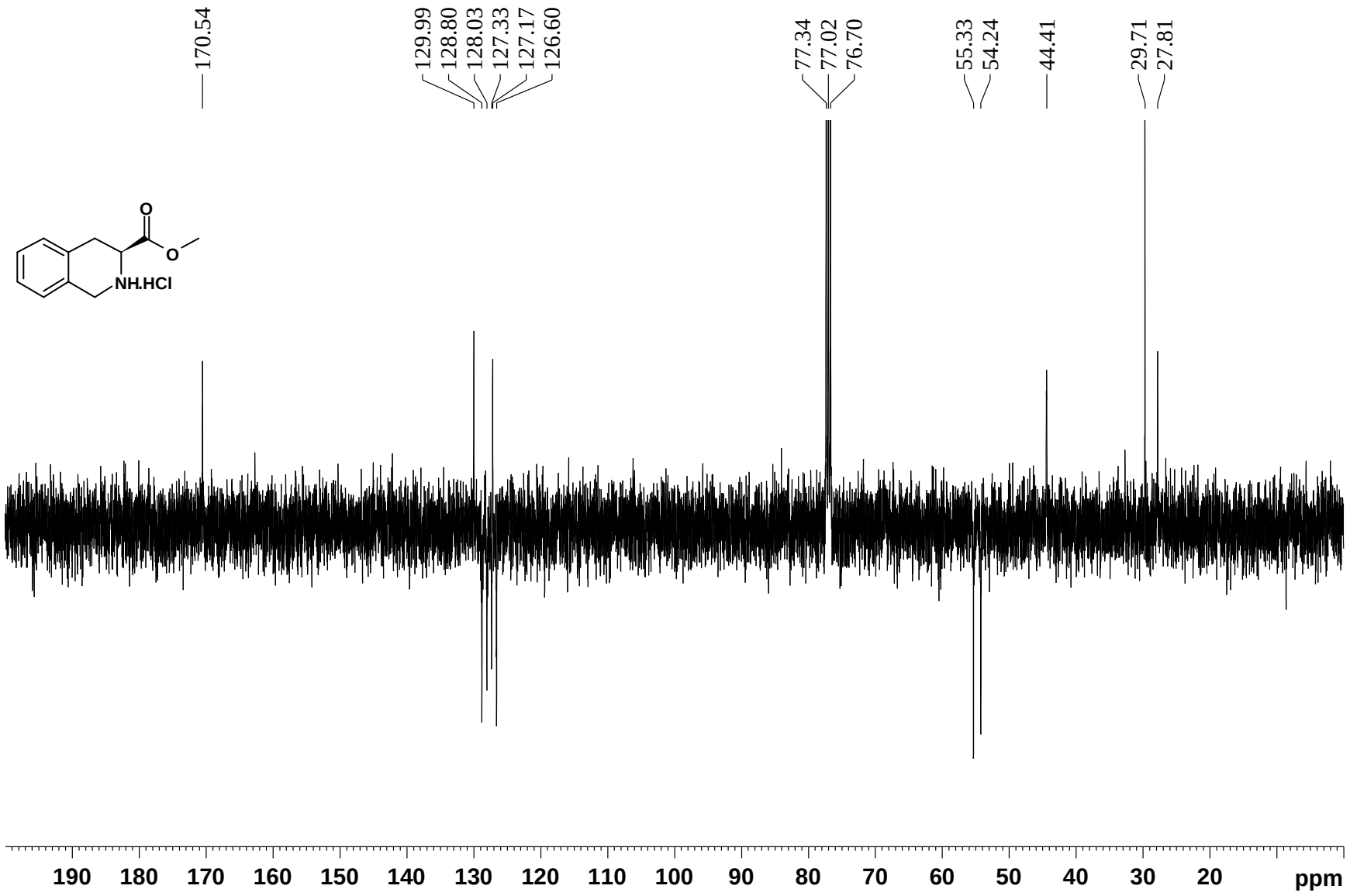
^{13}C NMR Spectrum of Compound 65 in $CDCl_3$



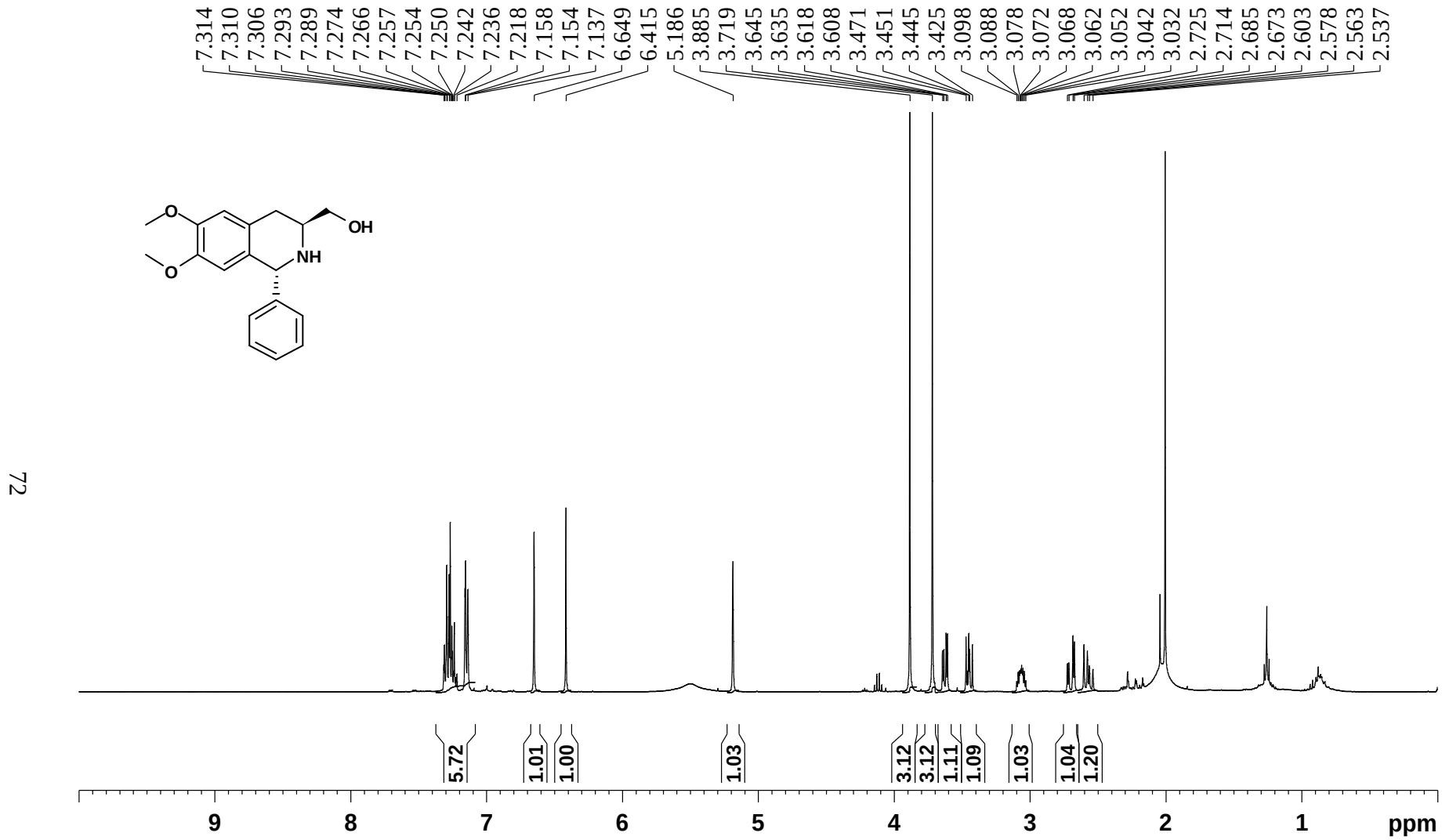
^{1}H NMR Spectrum of Compound 66 in $CDCl_3$



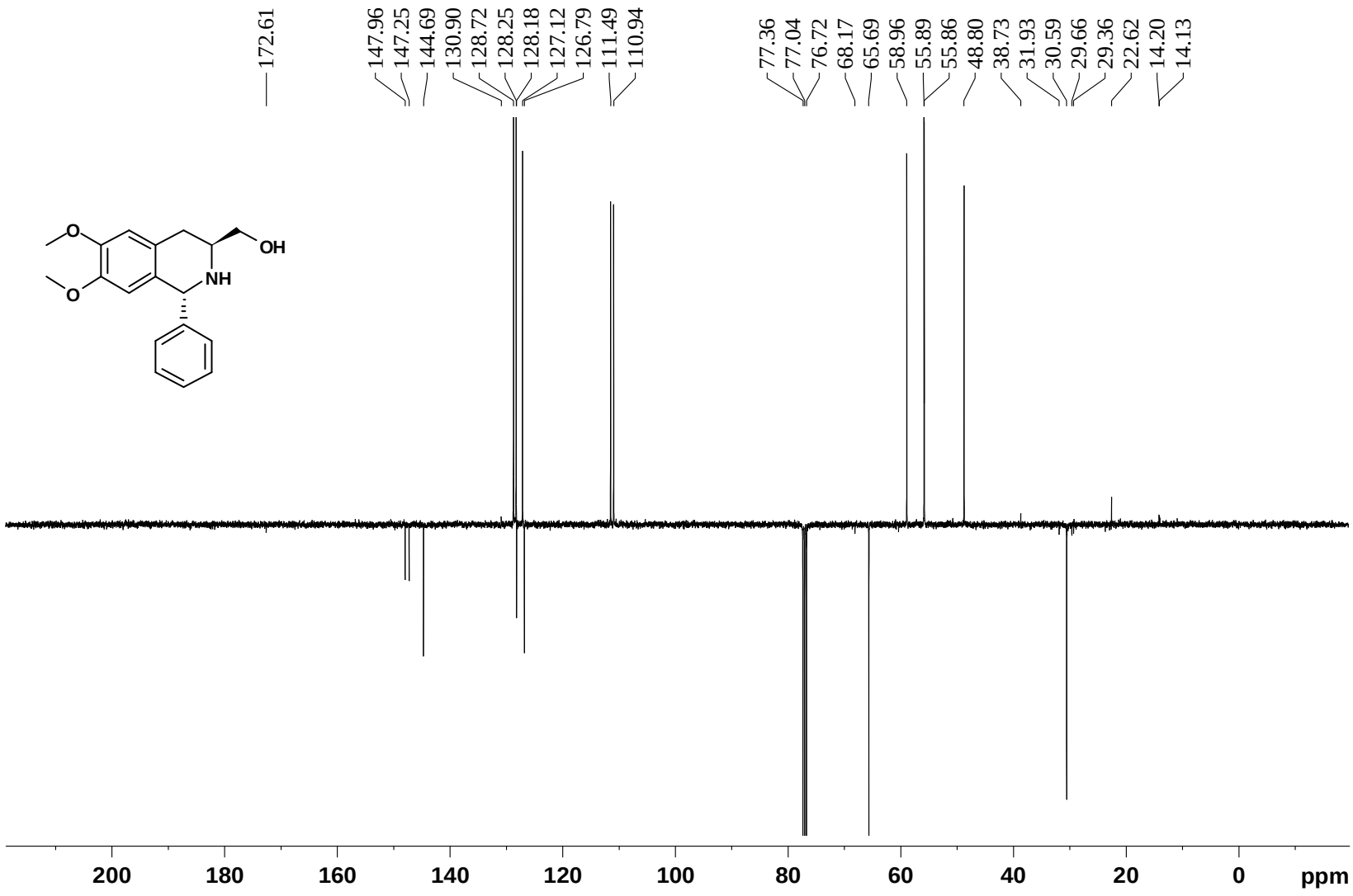
^{13}C NMR Spectrum of Compound 66 in $CDCl_3$



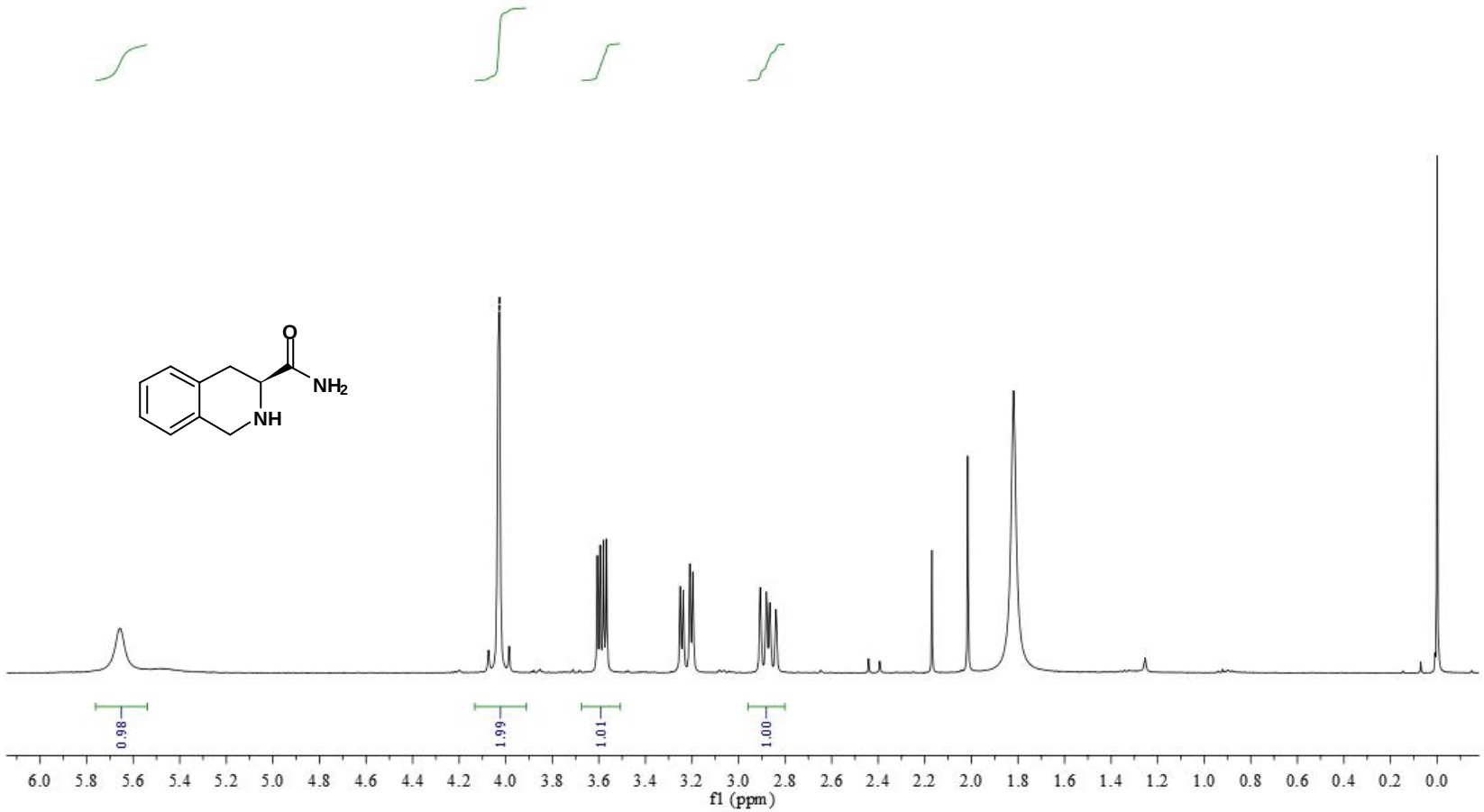
^{13}C NMR Spectrum of Compound 67 in $CDCl_3$



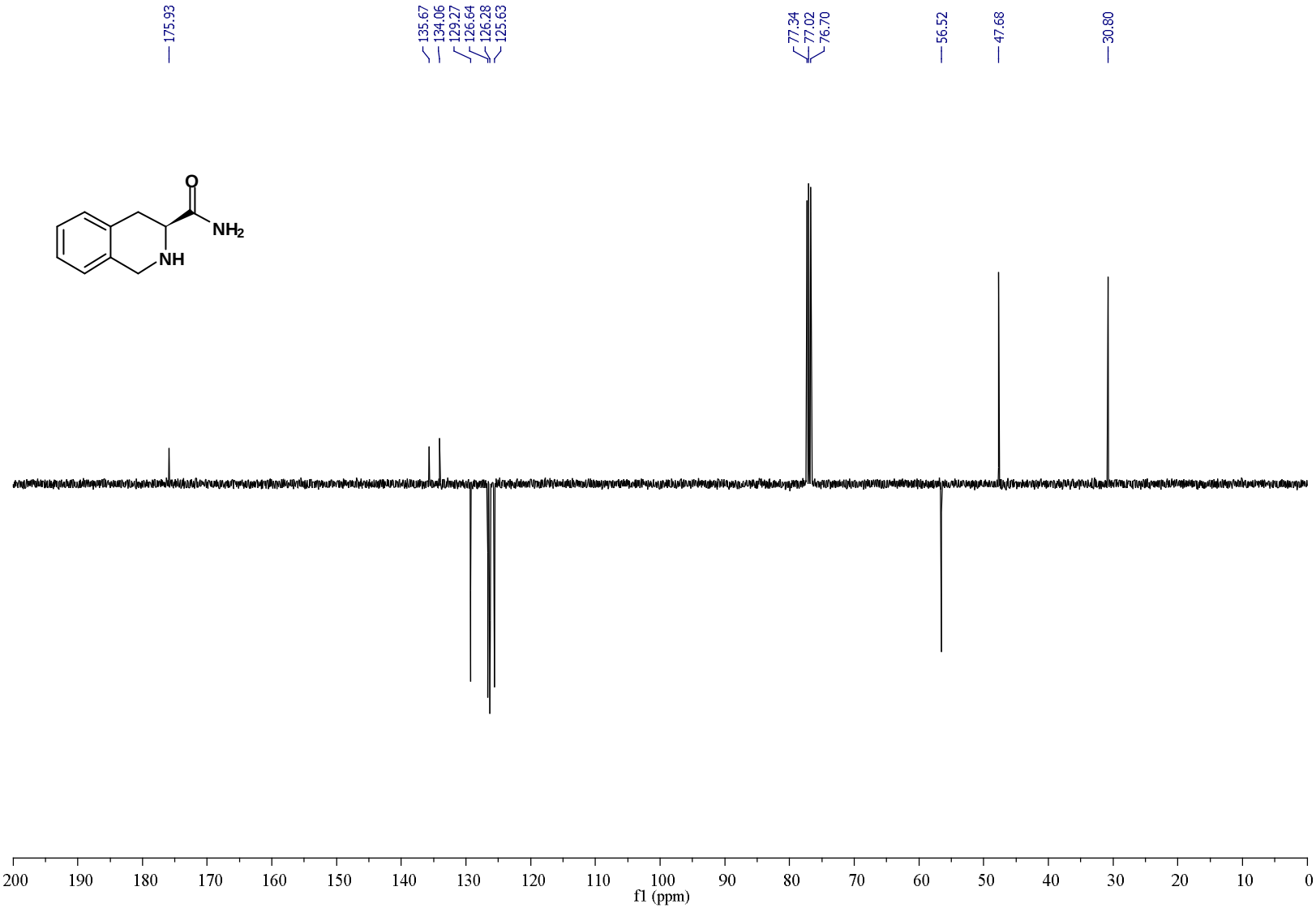
^{1}H NMR Spectrum of Compound 14 in $CDCl_3$



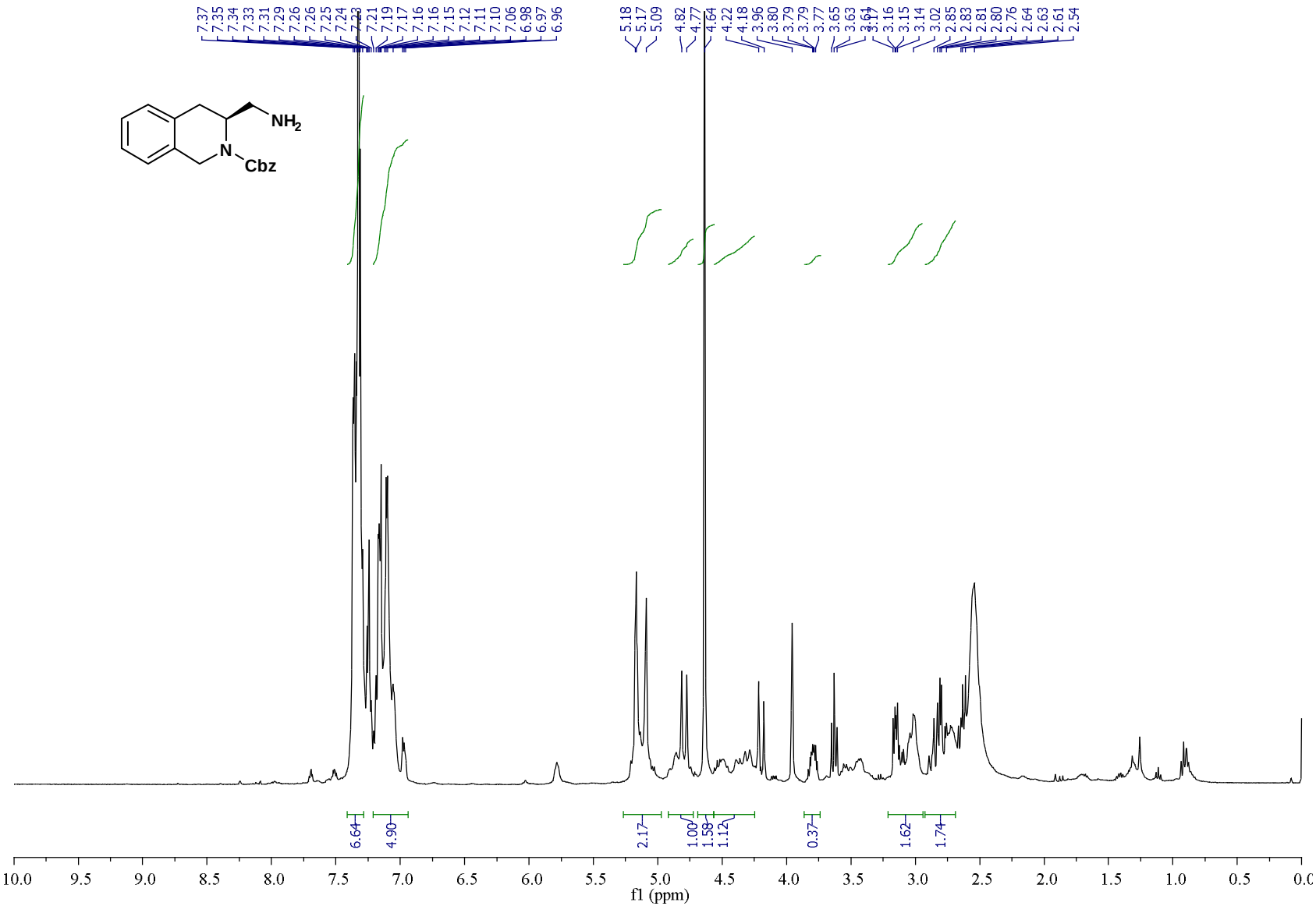
^{13}C NMR Spectrum of Compound 14 in $CDCl_3$



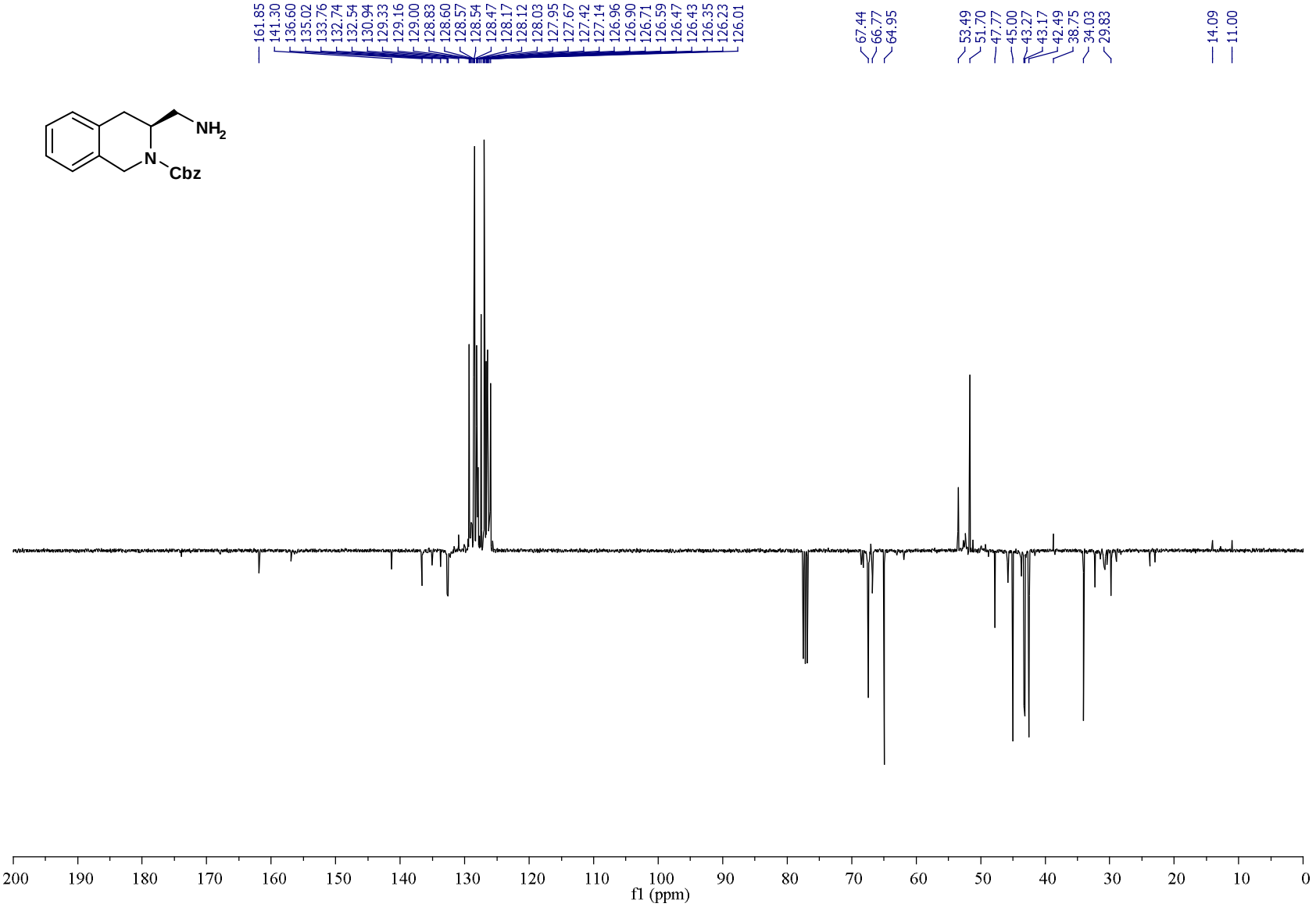
^{1}H NMR Spectrum of Compound 68 in $CDCl_3$



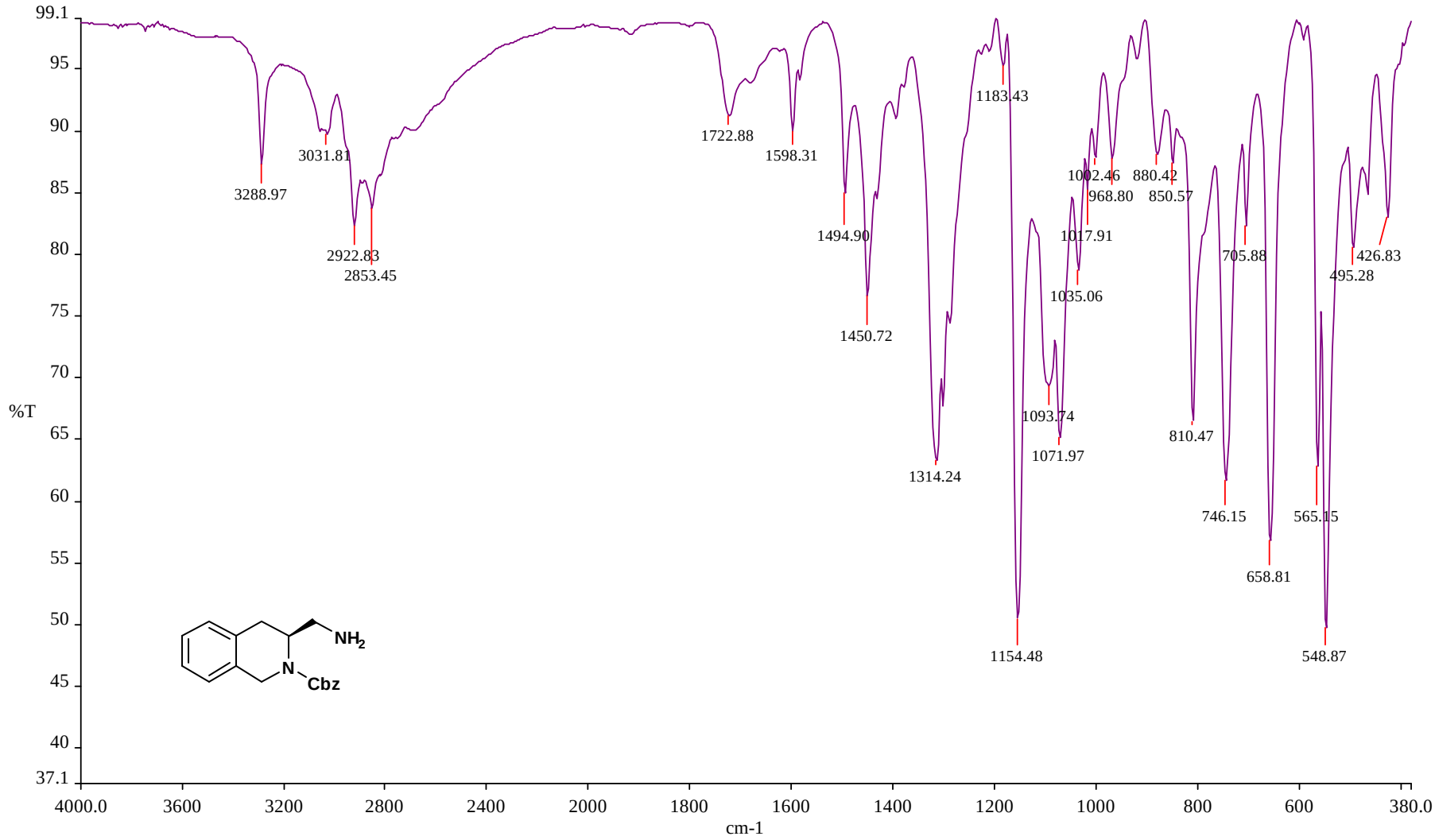
^{13}C NMR Spectrum of Compound 68 in $CDCl_3$



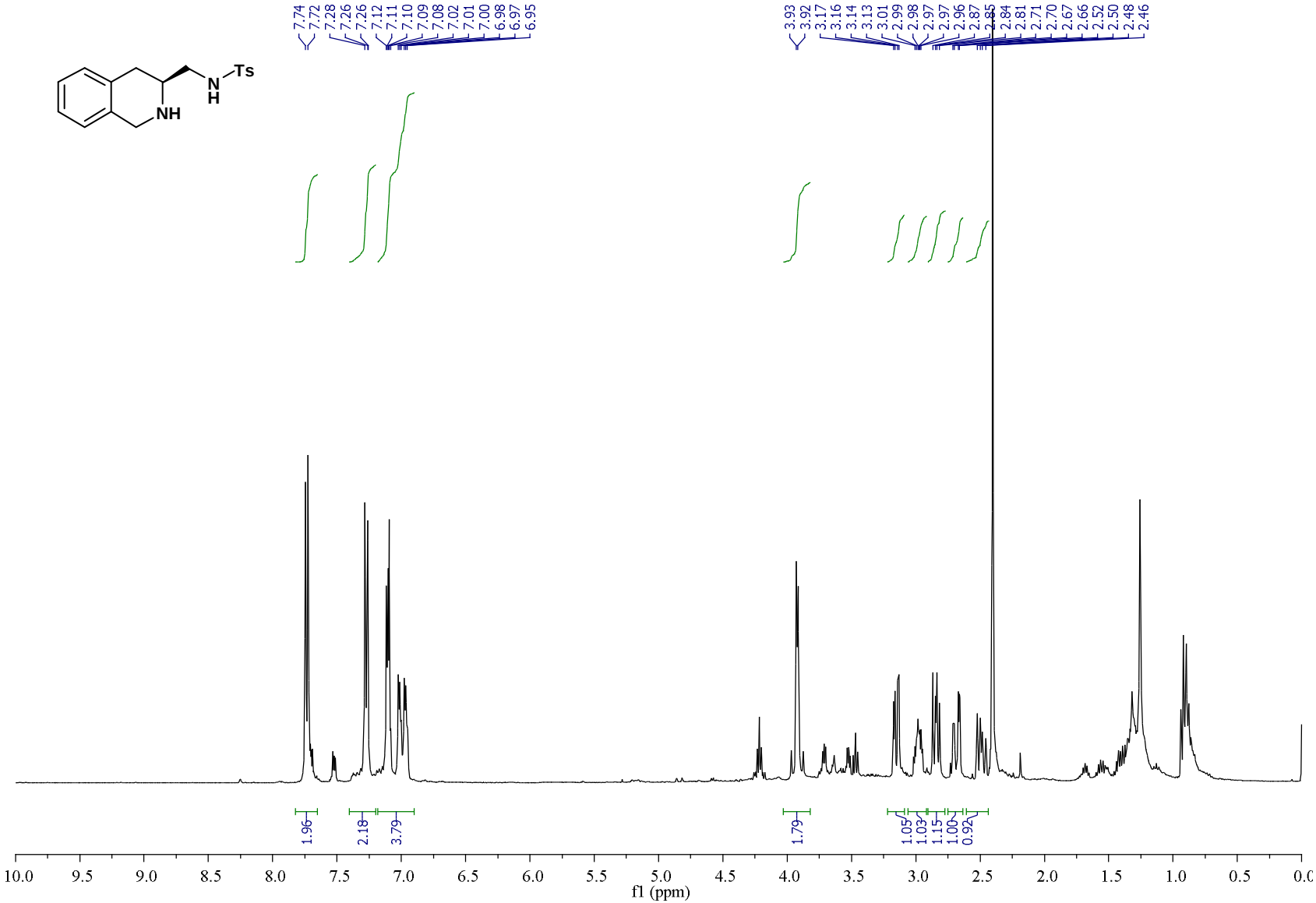
^{1}H NMR Spectrum of Compound 69 in $CDCl_3$



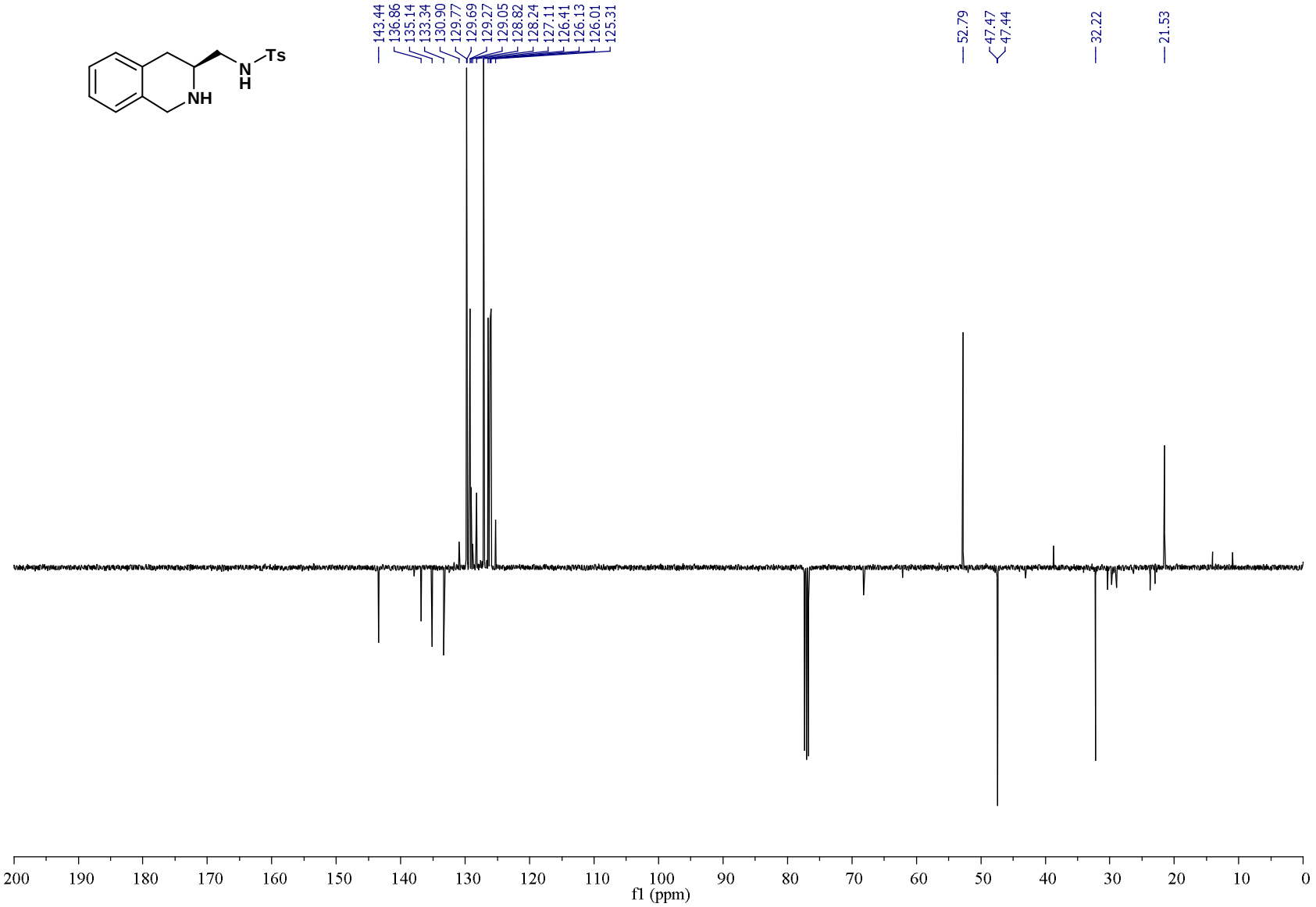
^{13}C NMR Spectrum of Compound 69 in $CDCl_3$



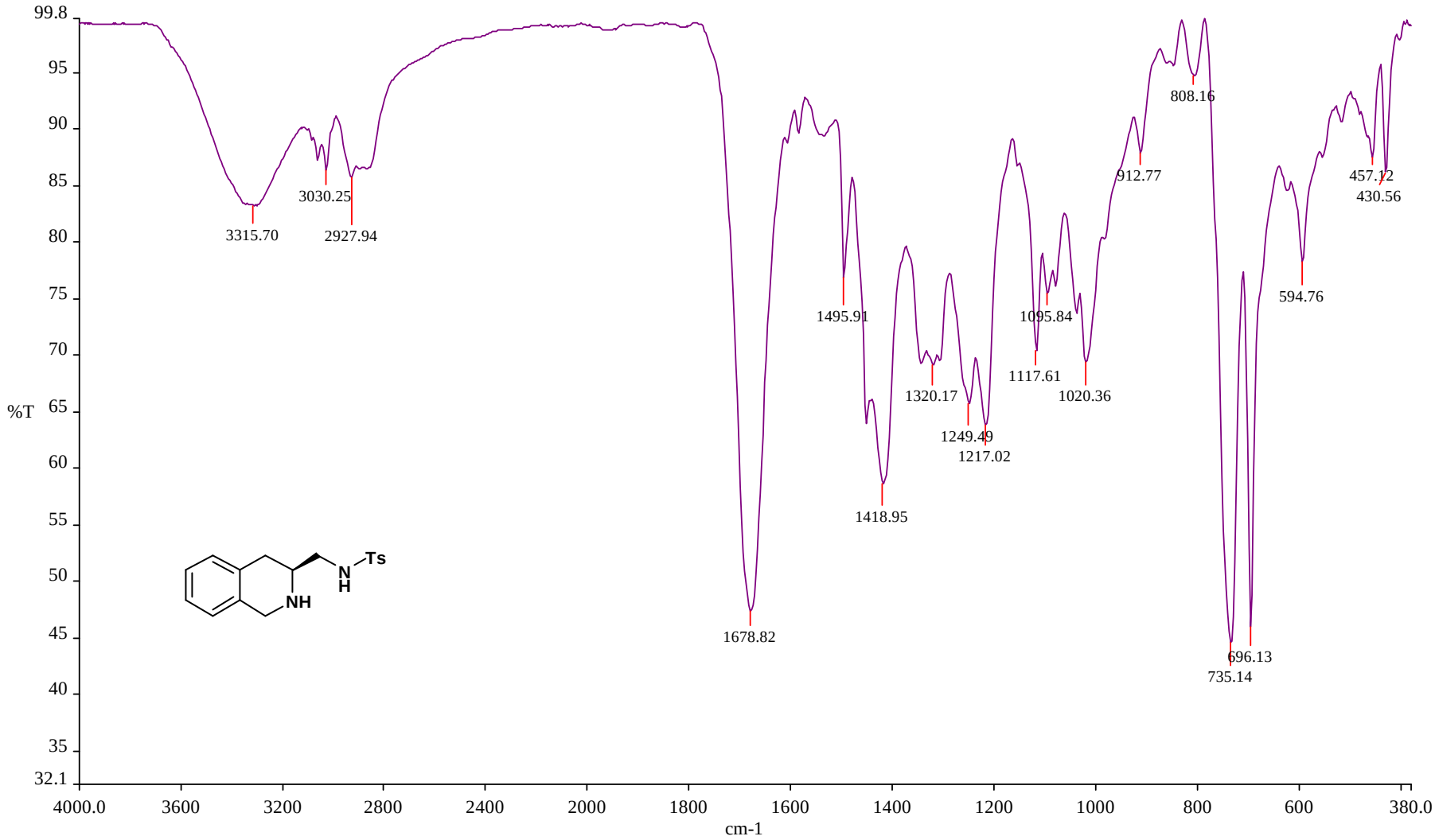
IR Spectrum of Compound 69



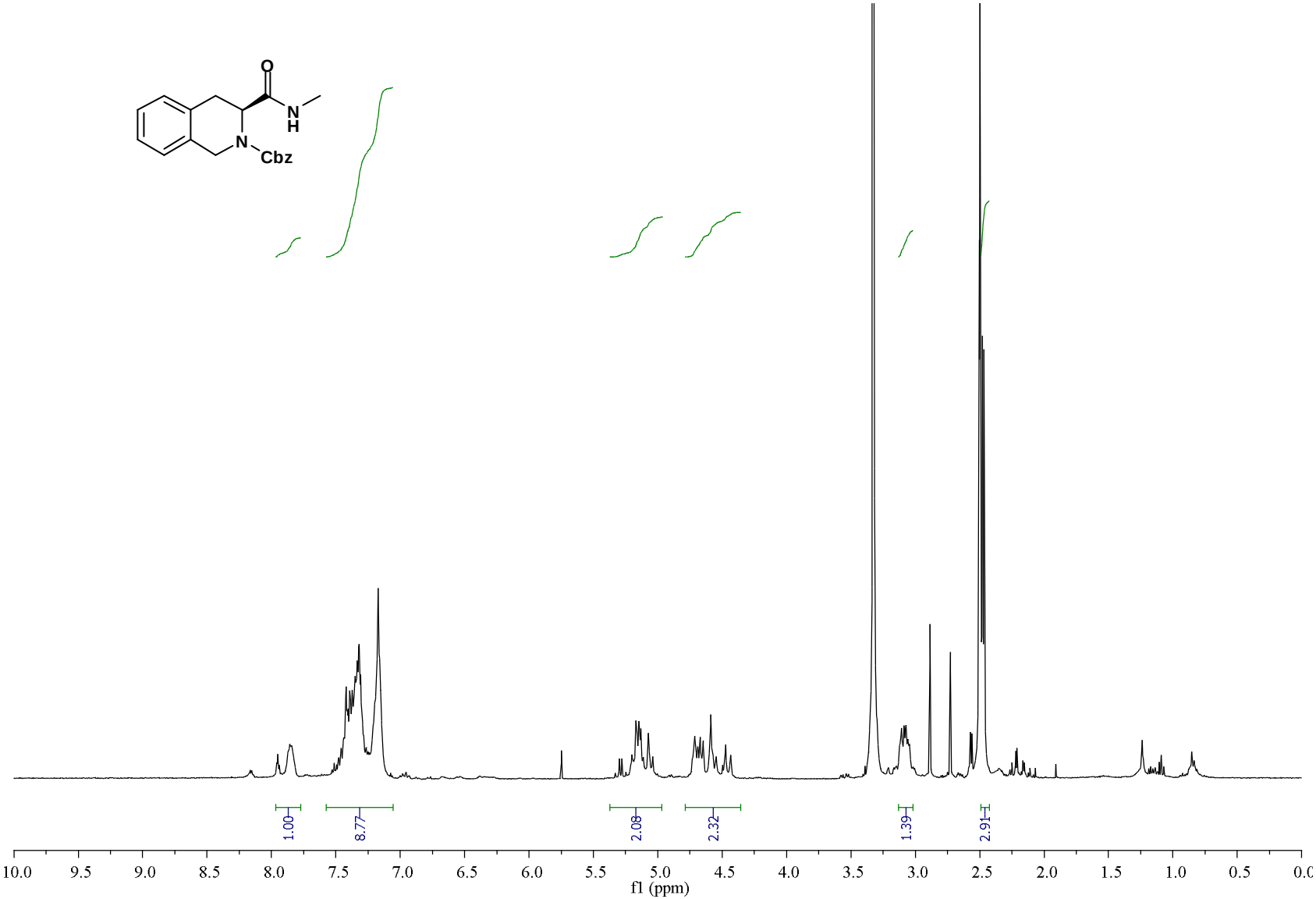
^{1}H NMR Spectrum of Compound 71 in $CDCl_3$



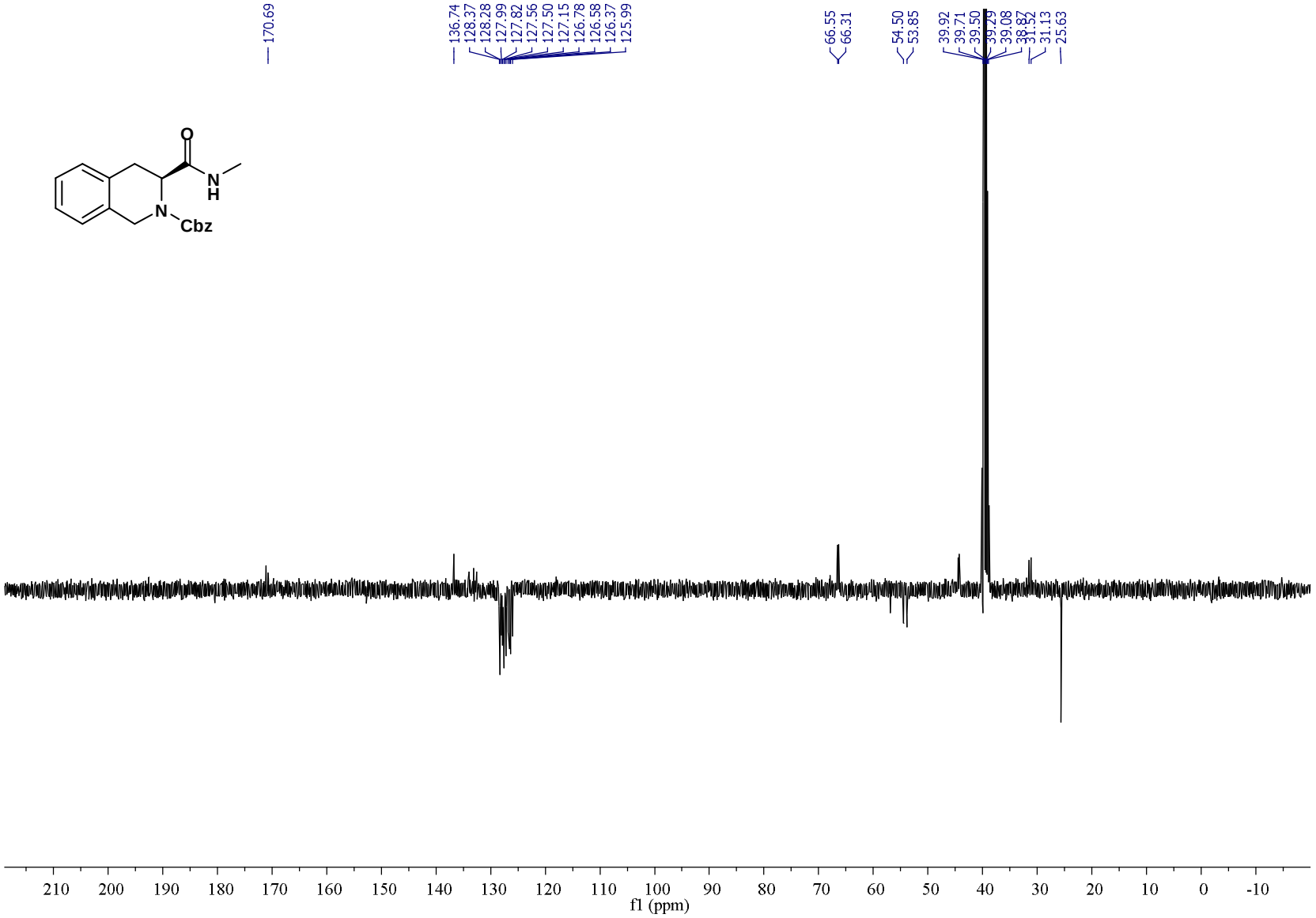
^{13}C NMR Spectrum of Compound 71 in $CDCl_3$



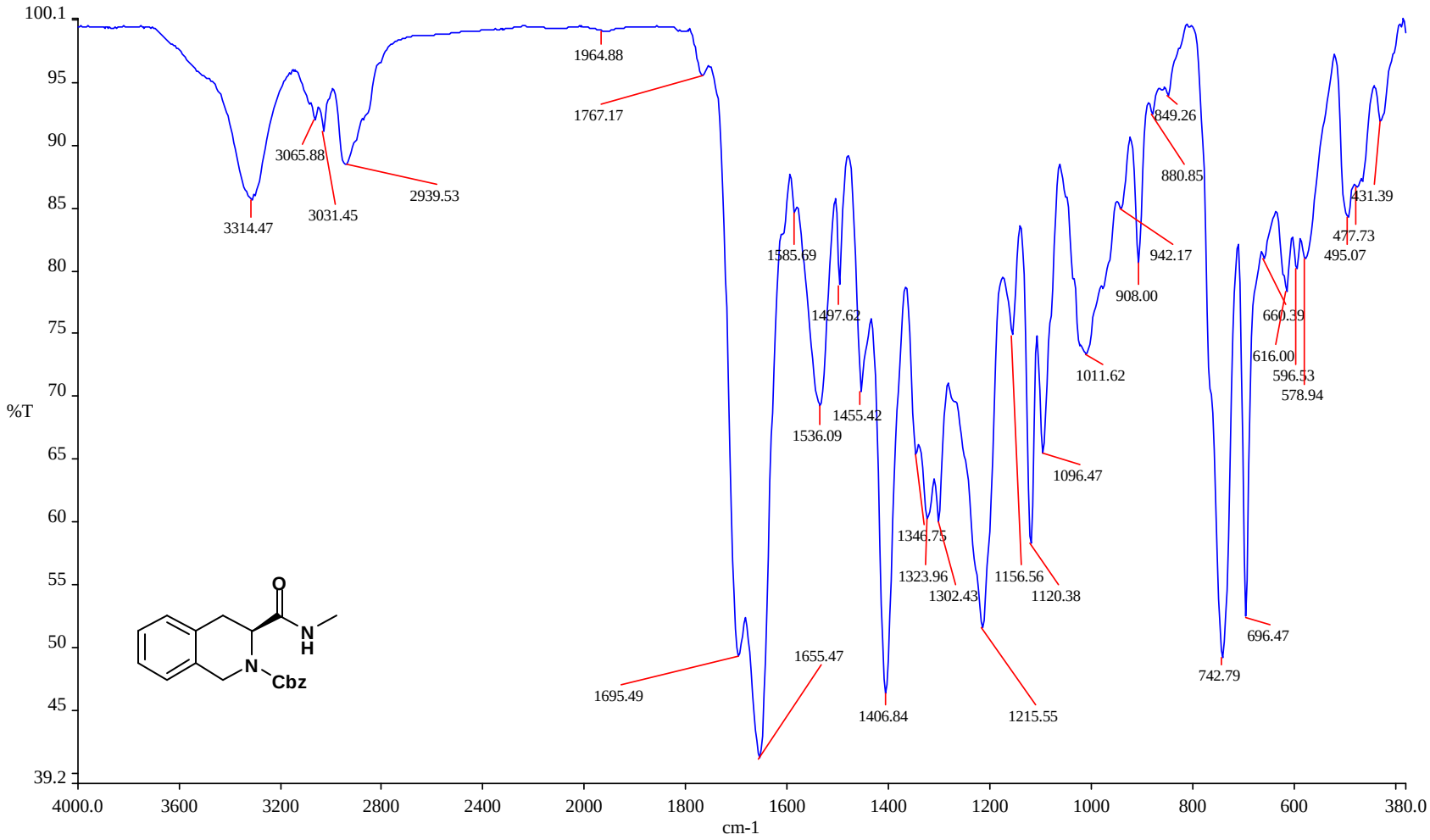
IR Spectrum of Compound 71



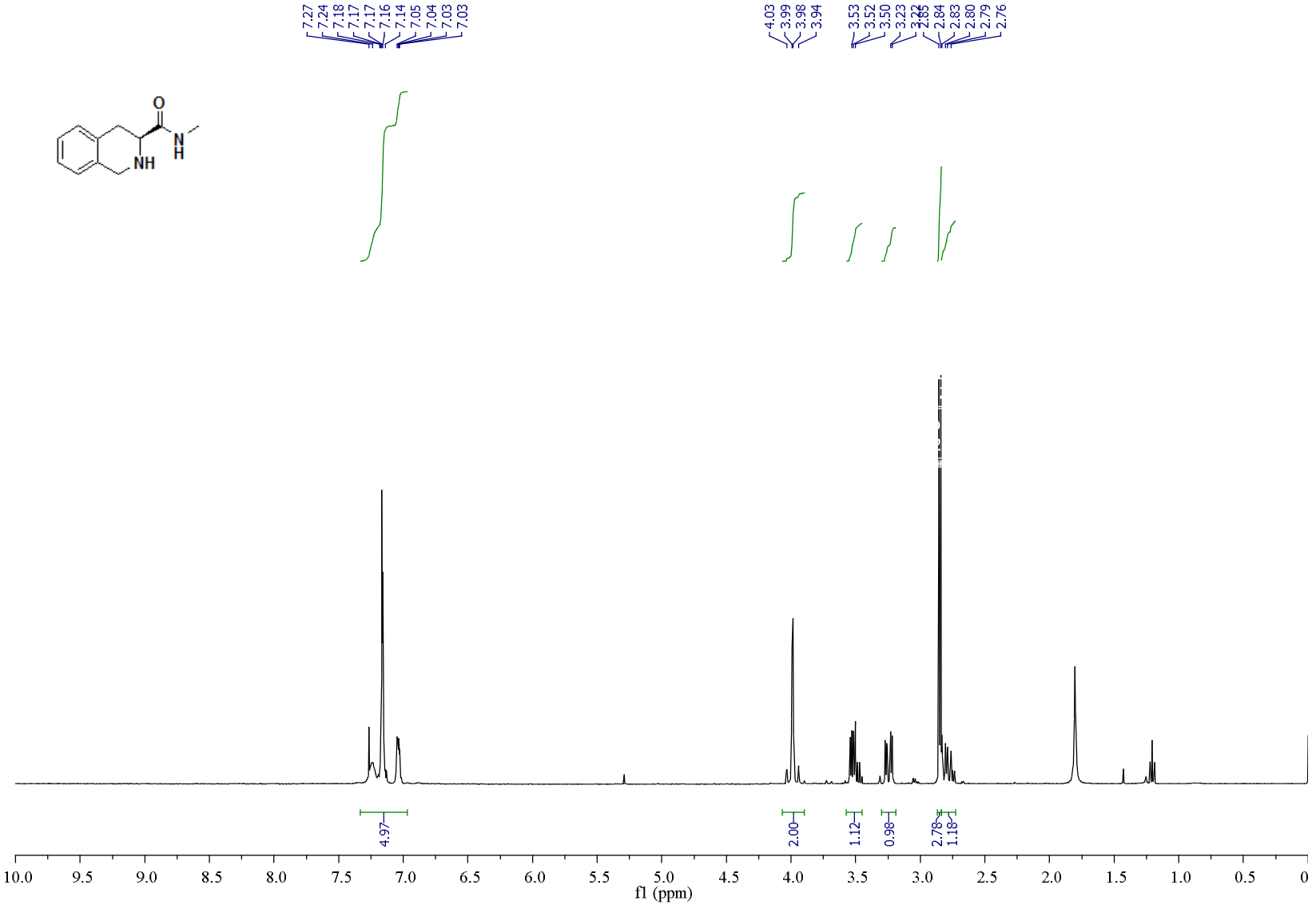
^{1}H NMR Spectrum of Compound 76a in d6-DMSO



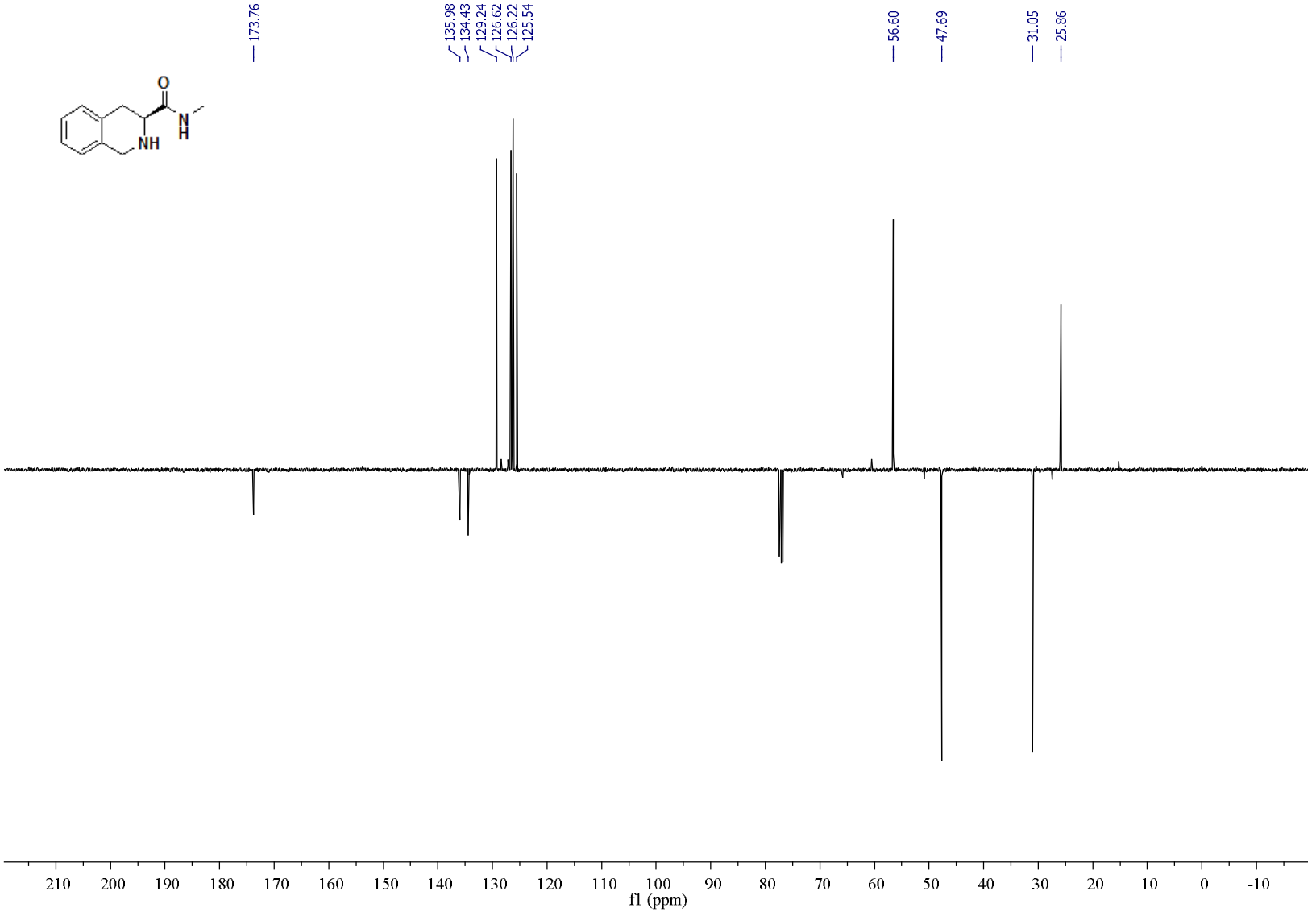
^{13}C NMR Spectrum of Compound 76a in d6-DMSO



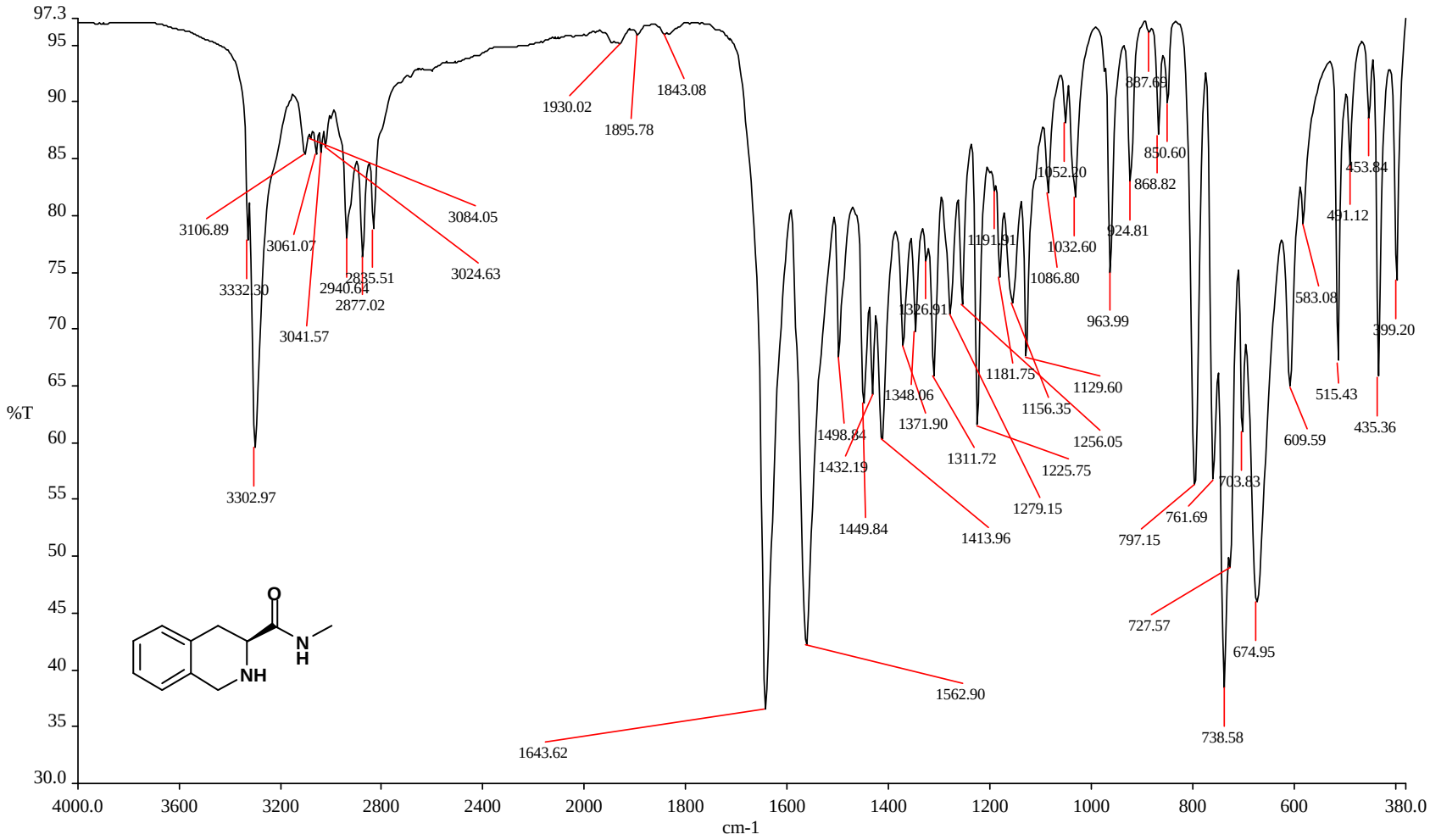
IR Spectrum of Compound 76a



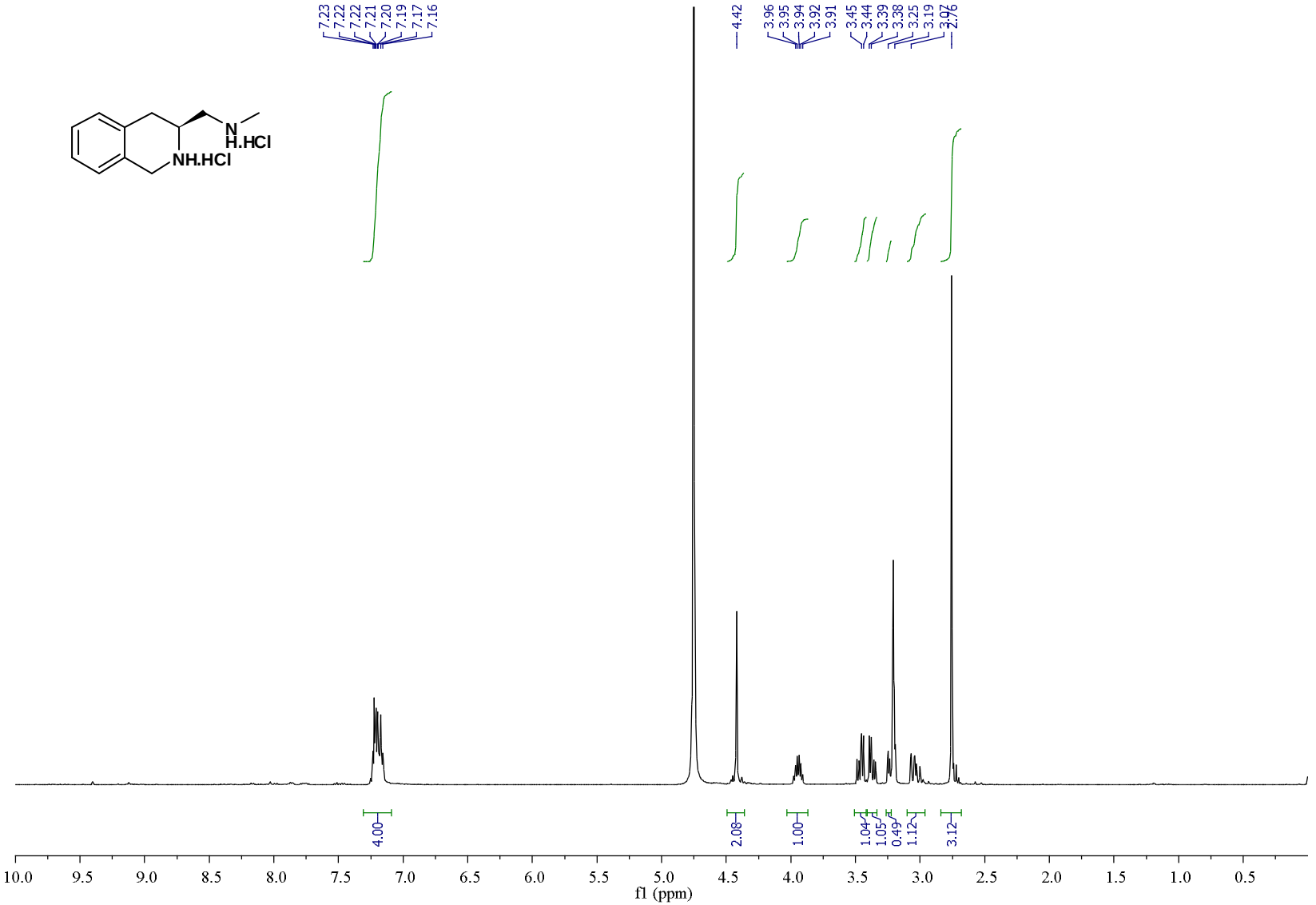
^{1}H NMR Spectrum of Compound 77a in $CDCl_3$



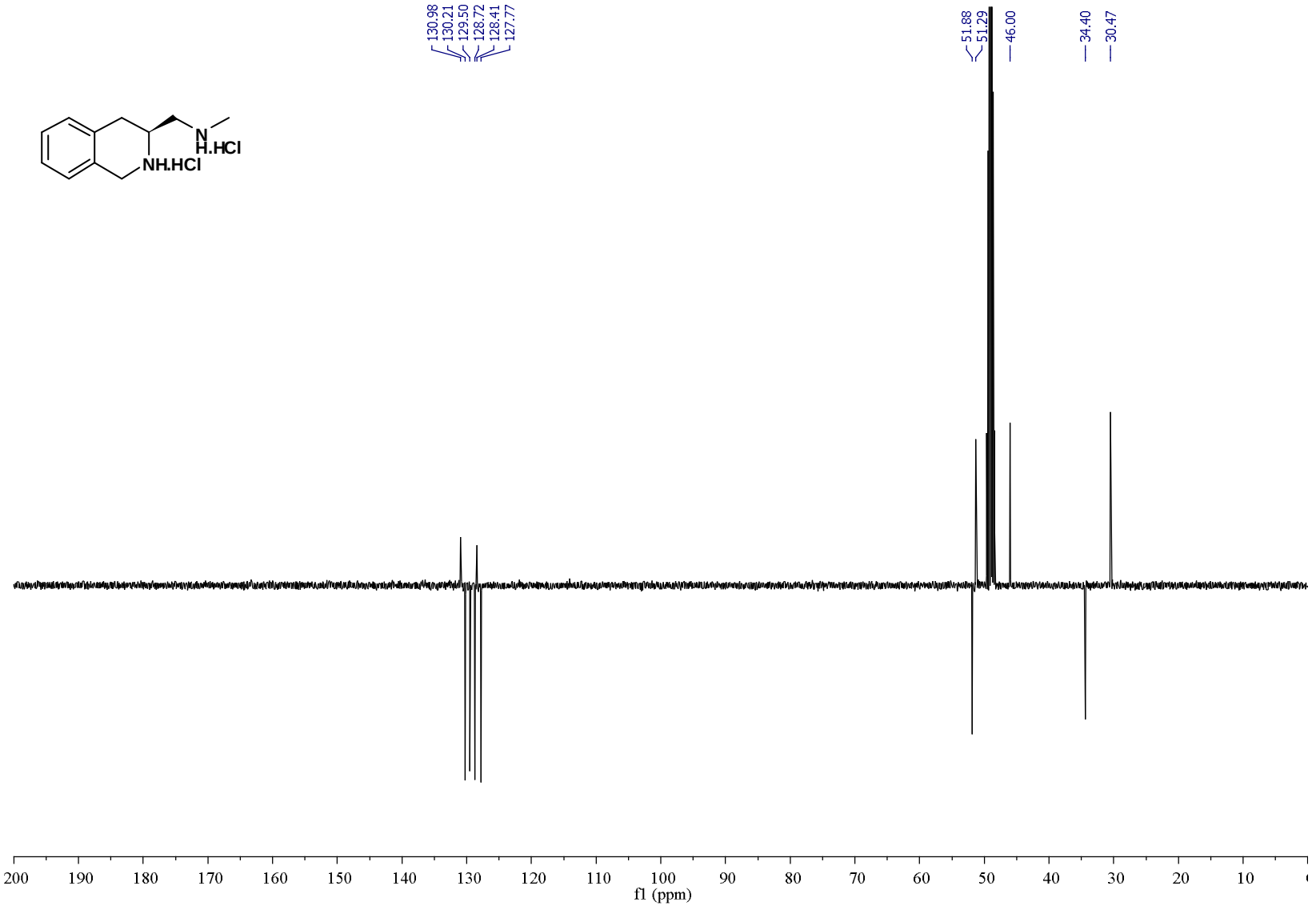
^{13}C NMR Spectrum of Compound 77a in $CDCl_3$



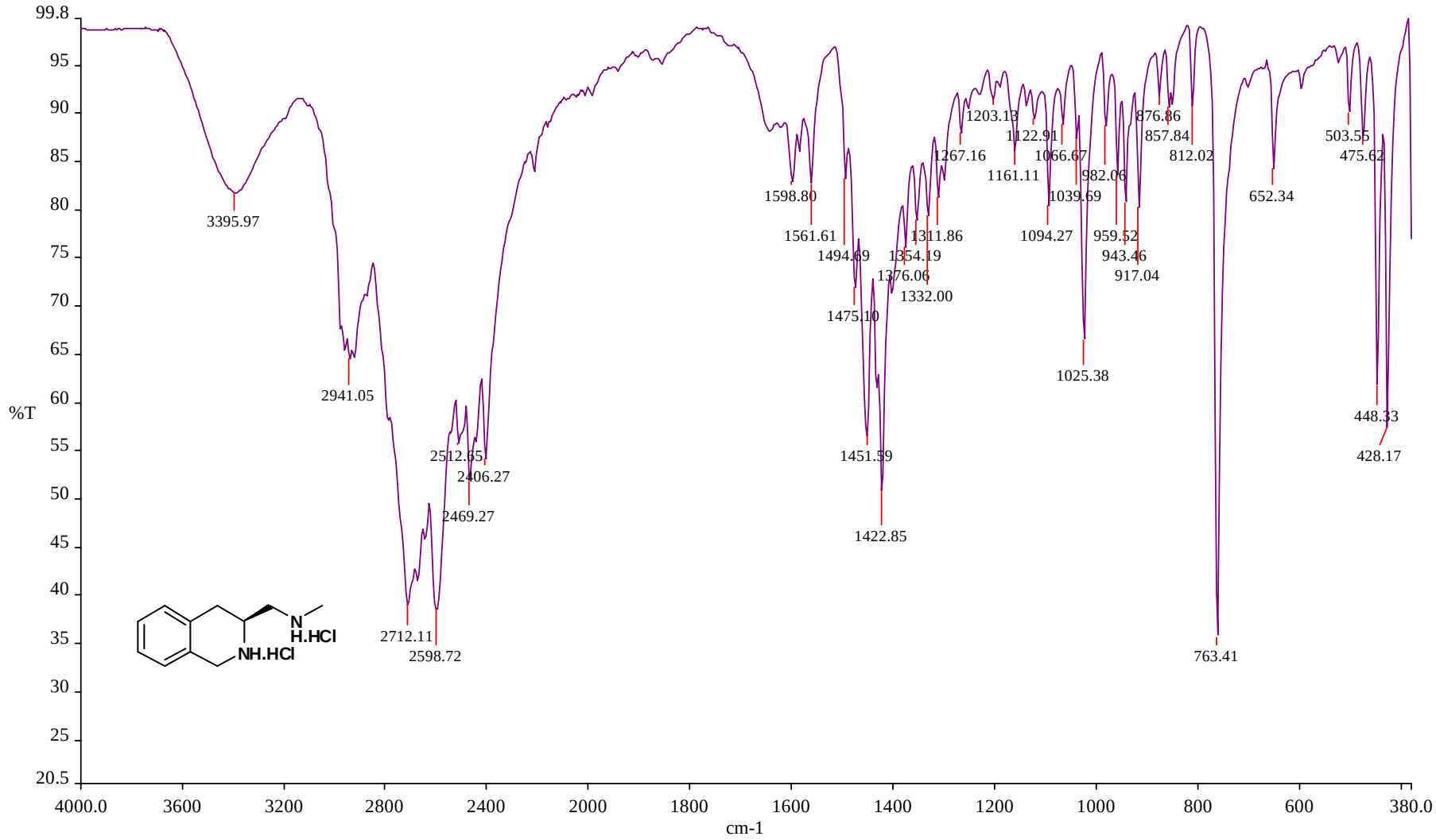
IR Spectrum of Compound 77a



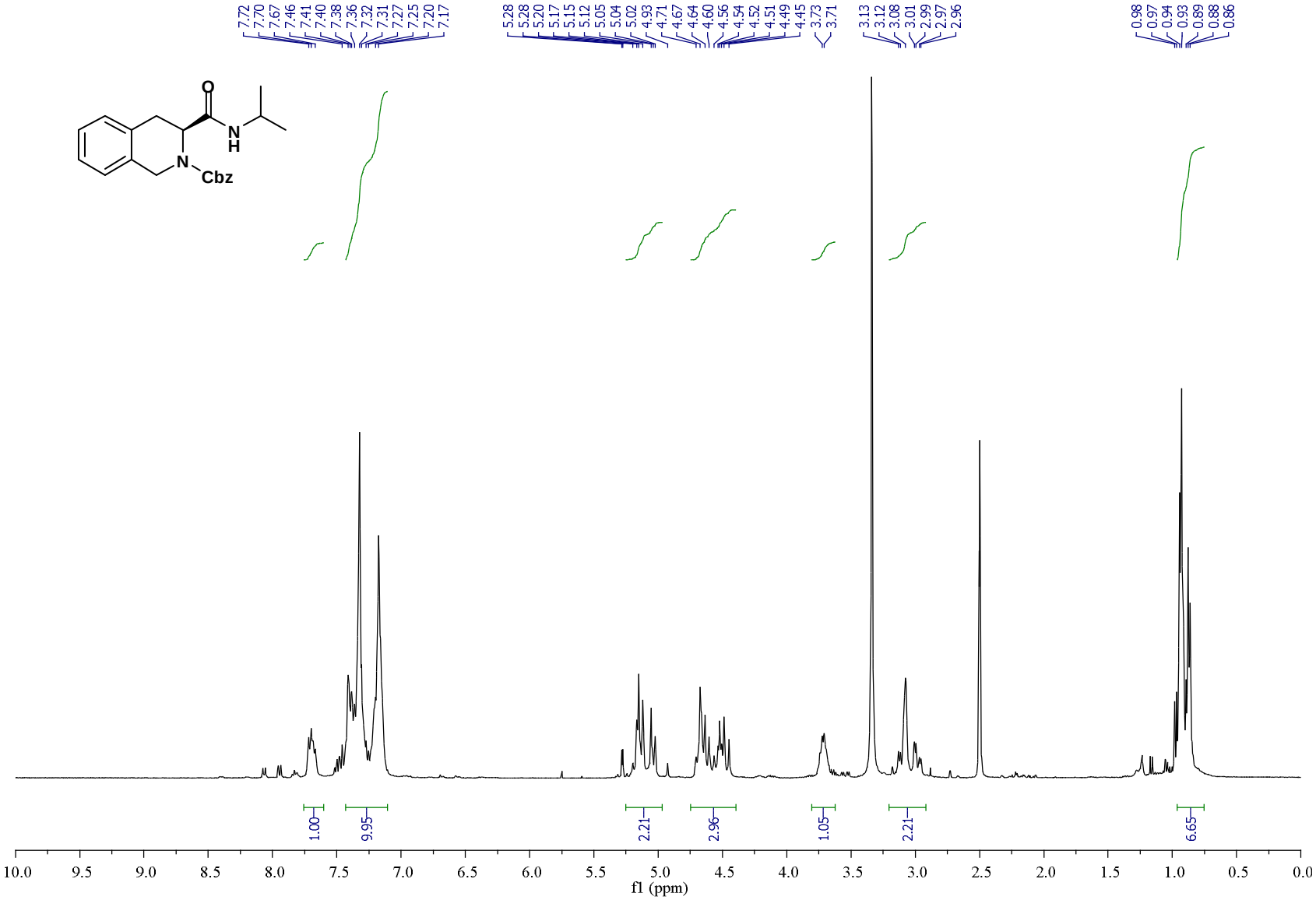
^{1}H NMR Spectrum of Compound 78a in MeOD



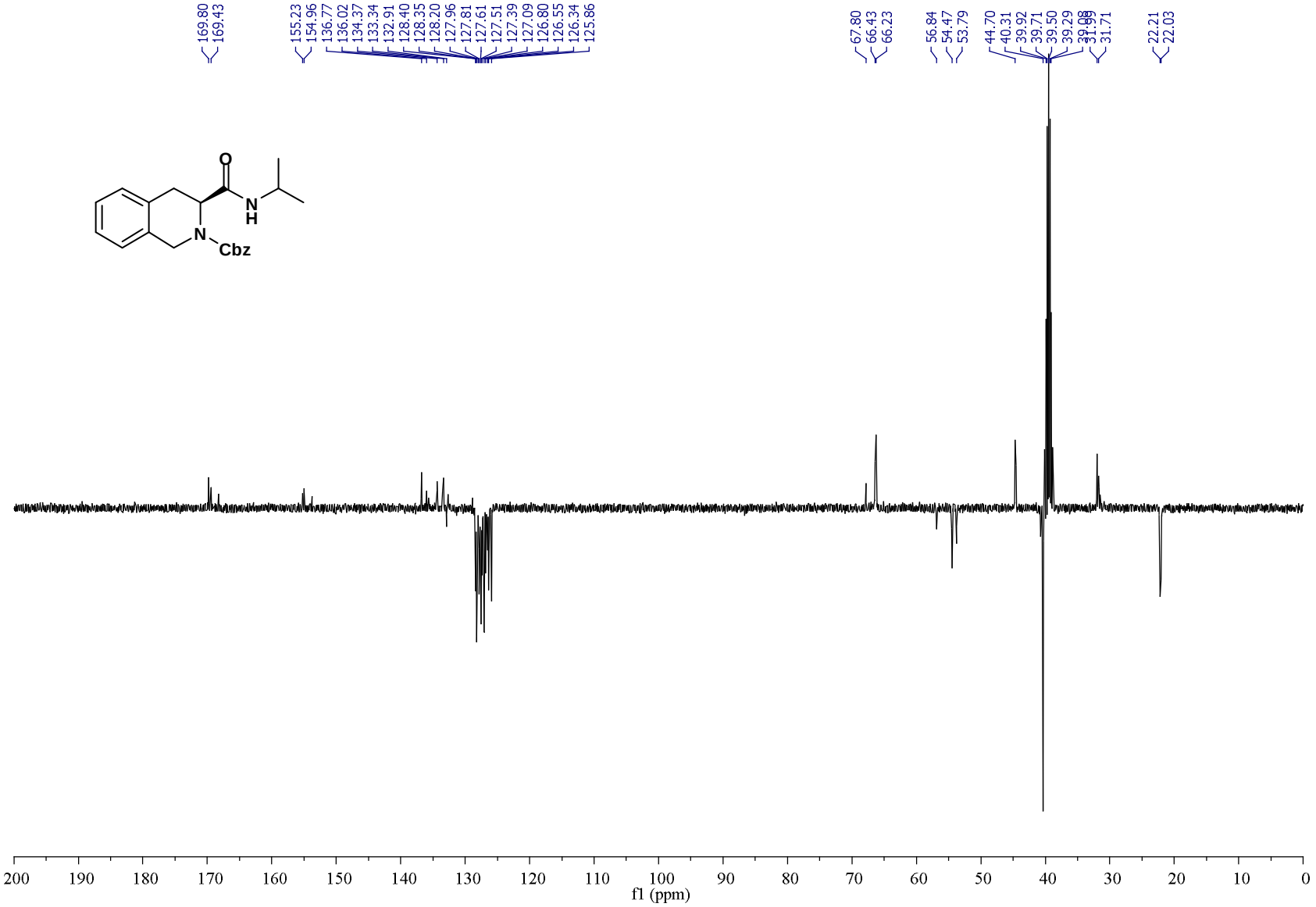
^{13}C NMR Spectrum of Compound 78a in MeOD



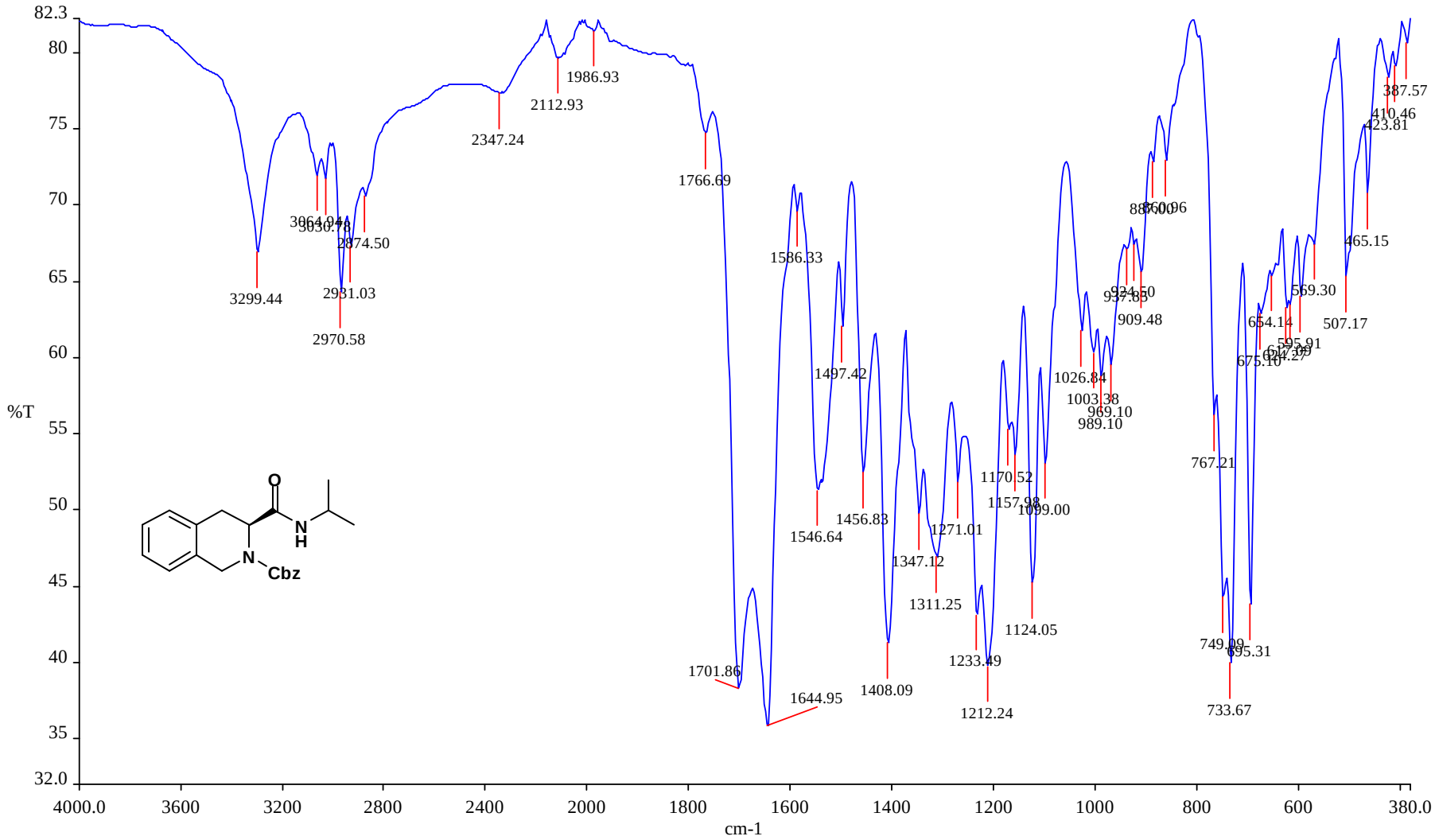
IR Spectrum of Compound 78a



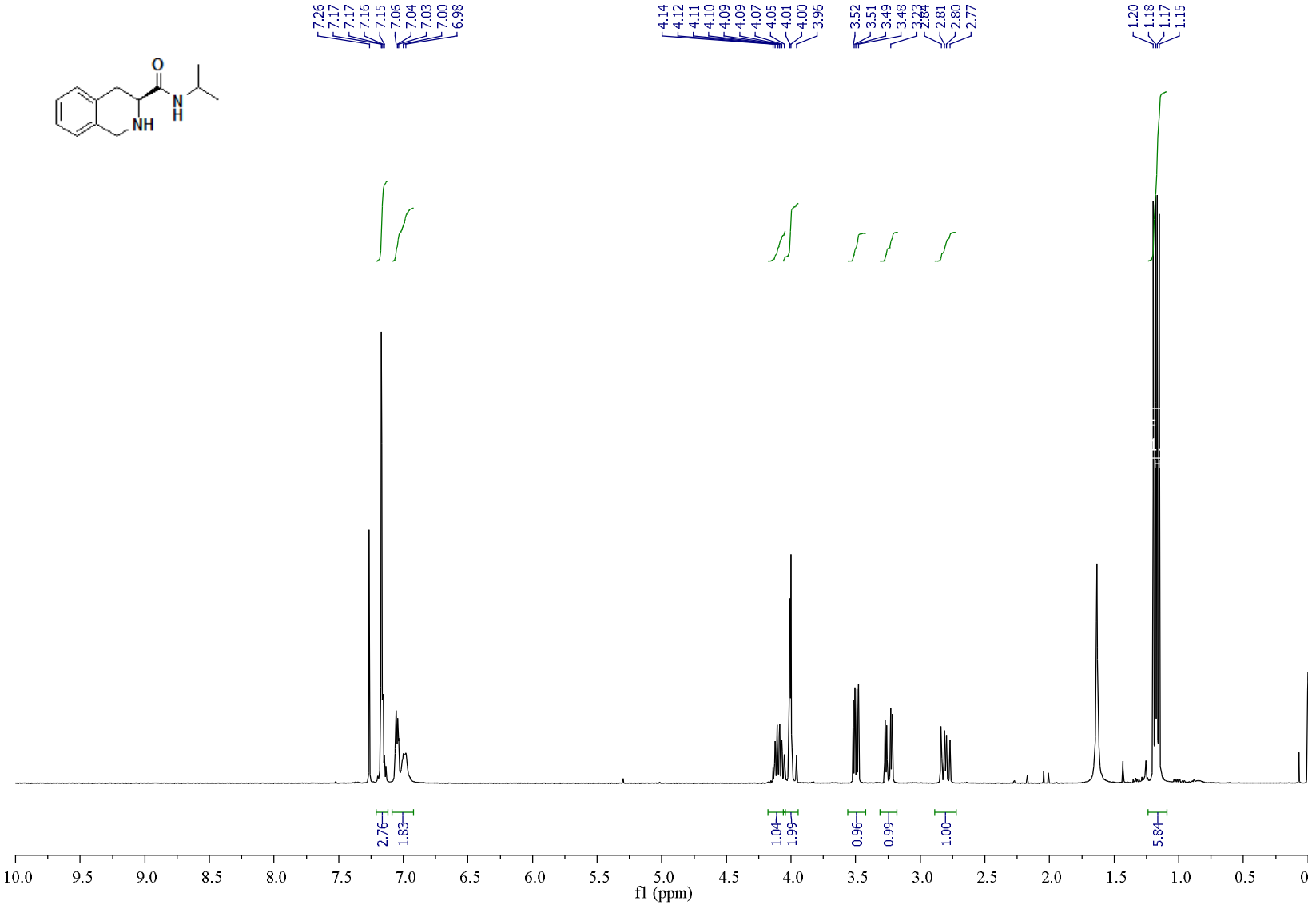
^{1}H NMR Spectrum of Compound 76b in d6-DMSO



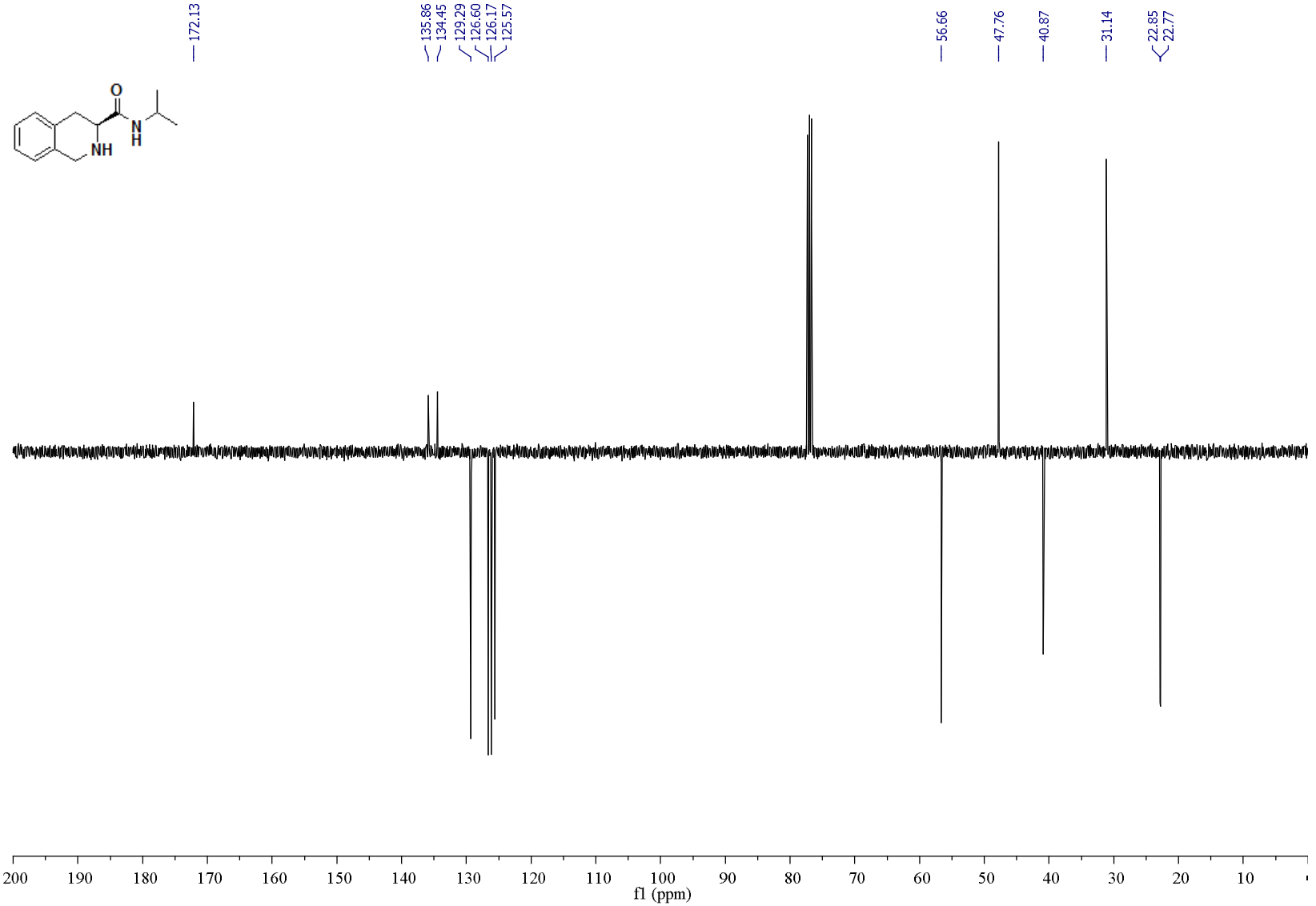
^{13}C NMR Spectrum of Compound 76b in d6-DMSO



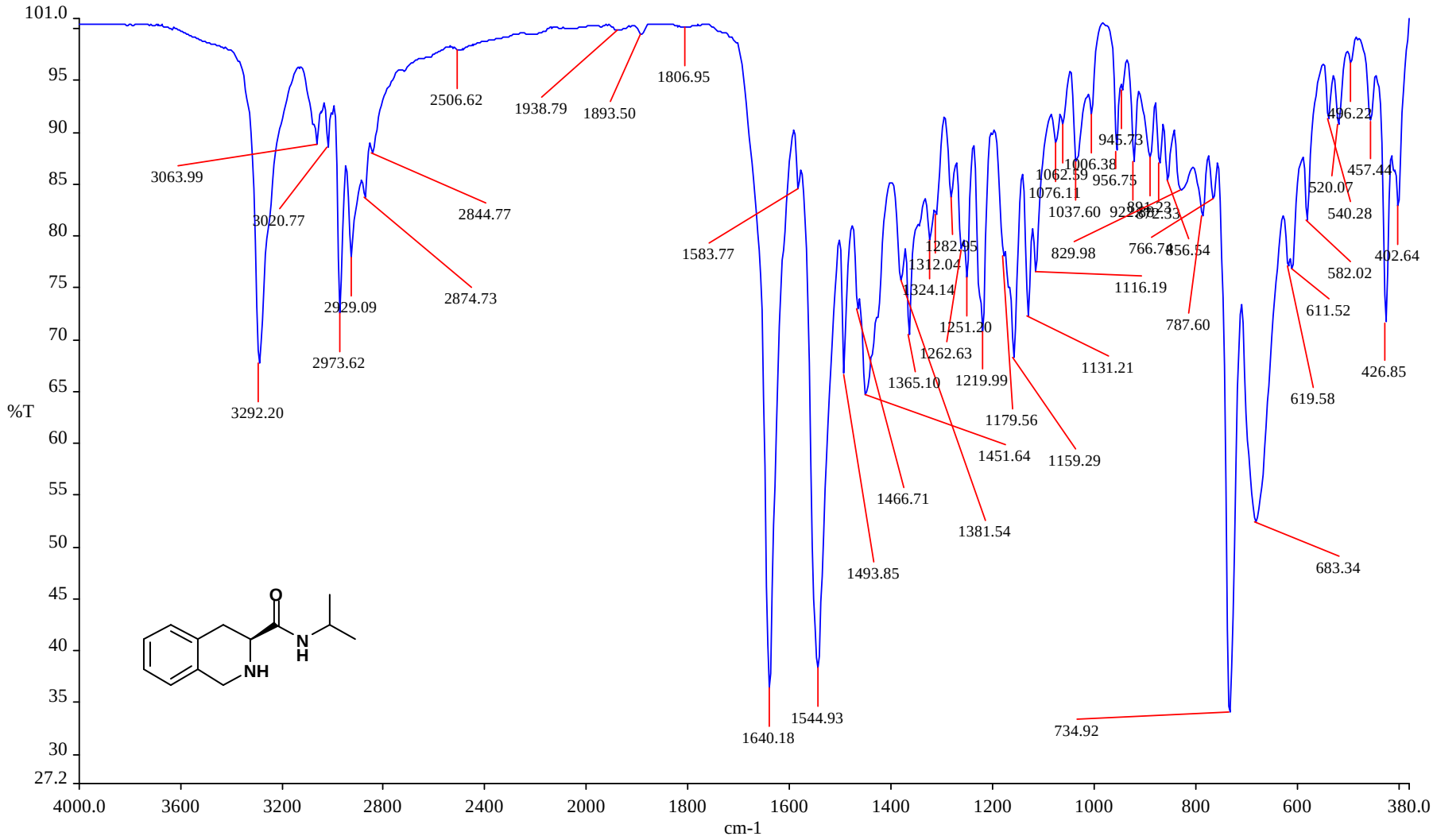
IR Spectrum of Compound 76b



^{1}H NMR Spectrum of Compound 77b in $CDCl_3$



^{13}C NMR Spectrum of Compound 77b in $CDCl_3$



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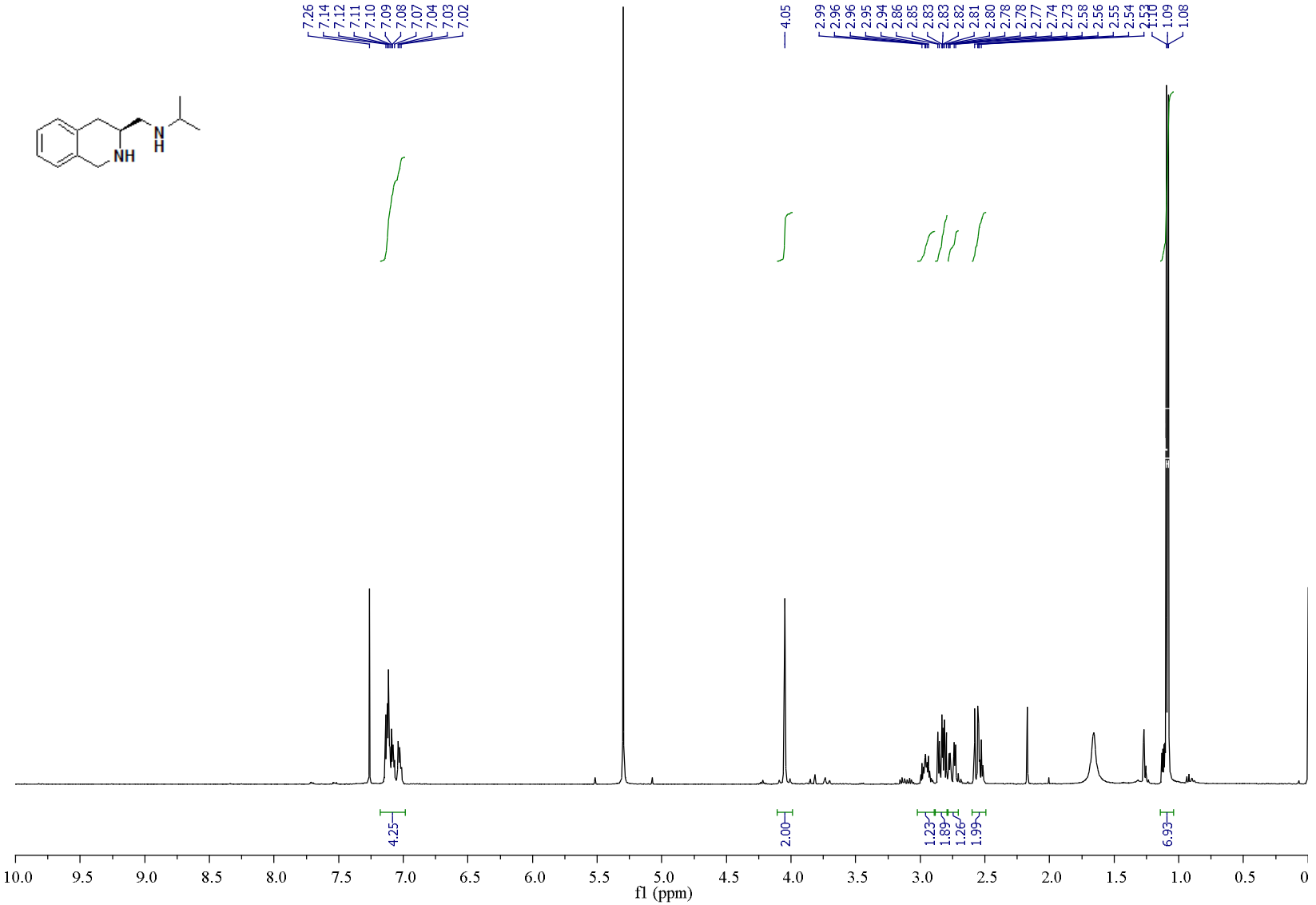
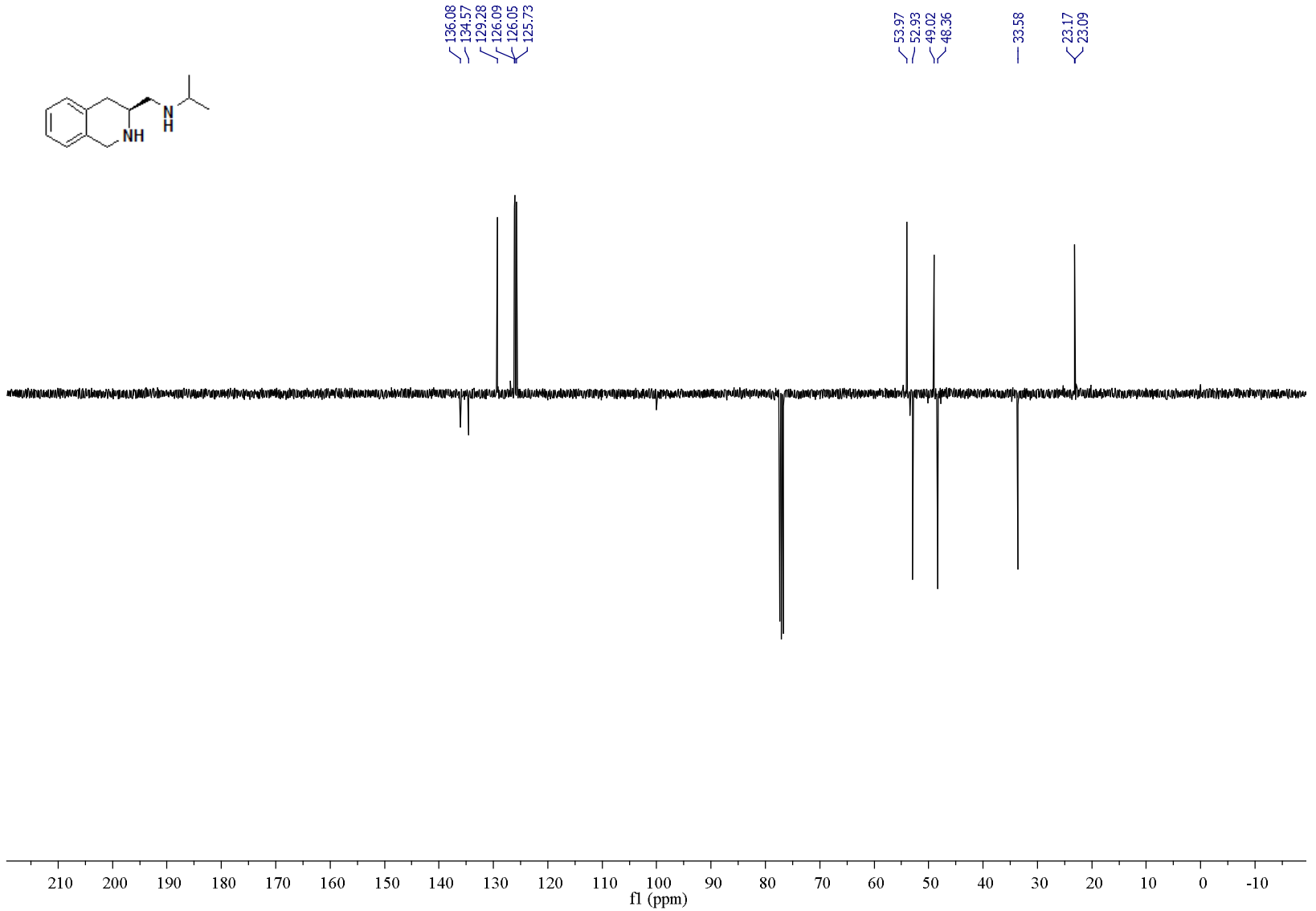
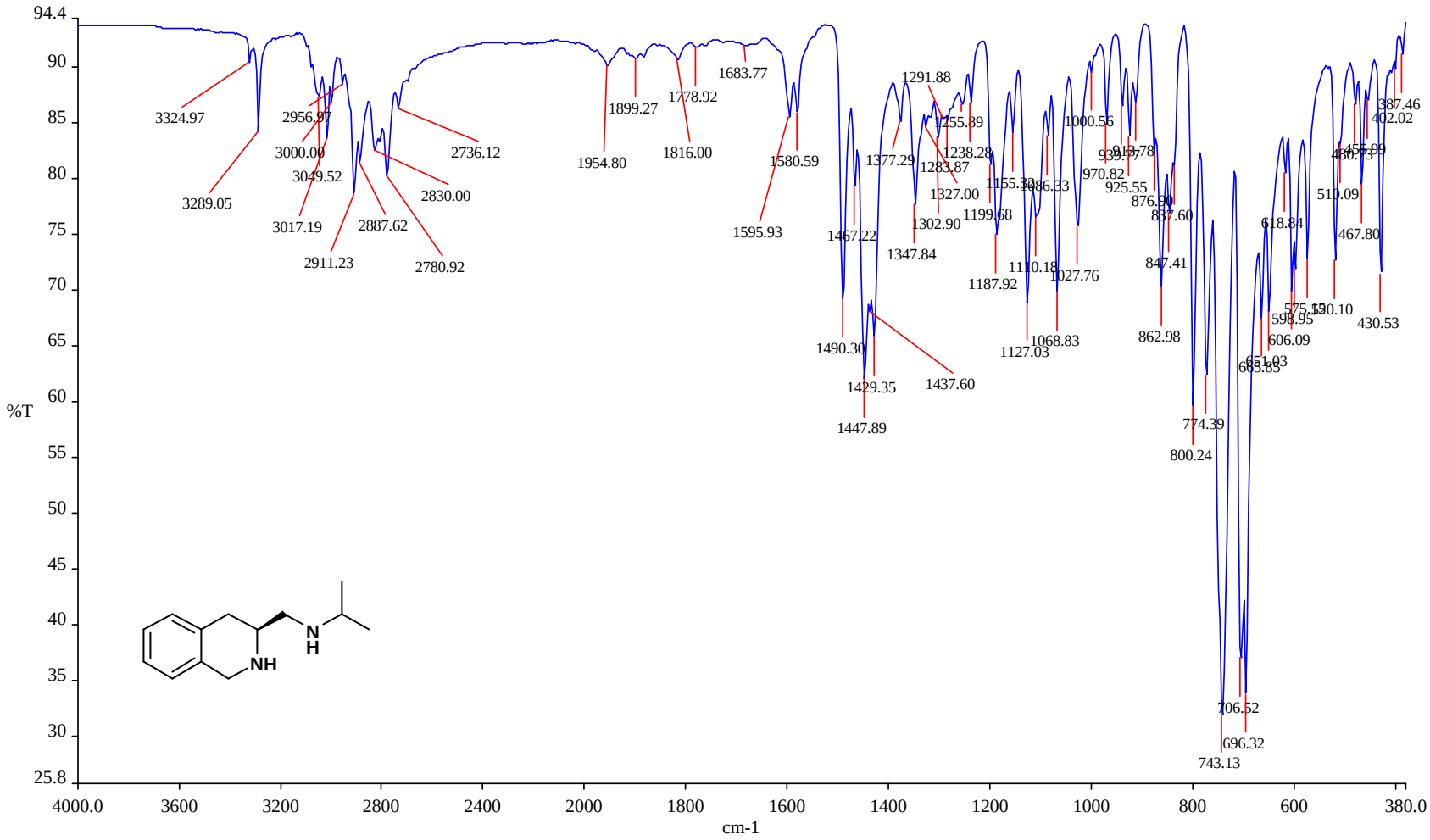
IR Spectrum of Compound 77b



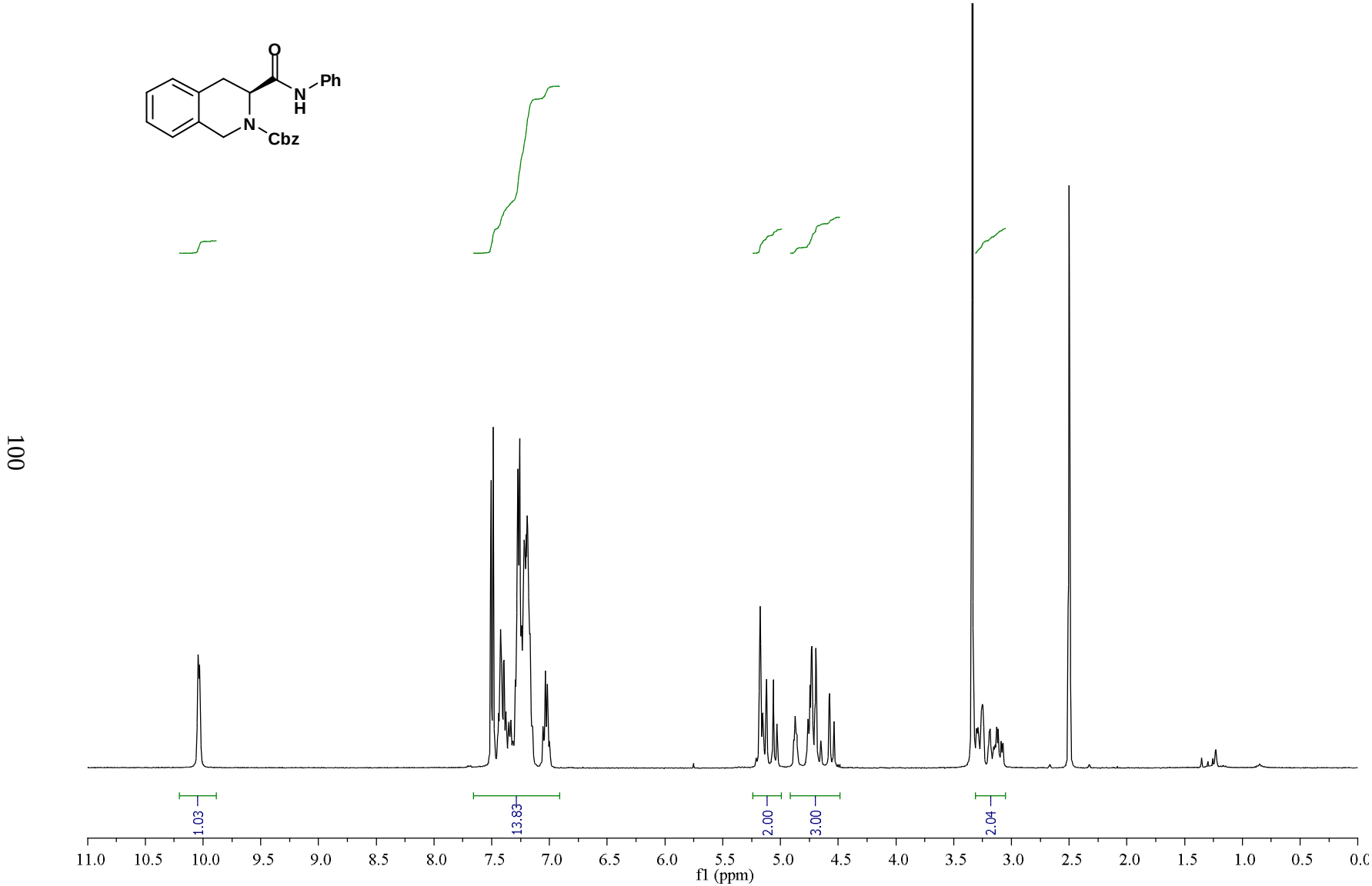
^{1}H NMR Spectrum of Compound 78b in $CDCl_3$



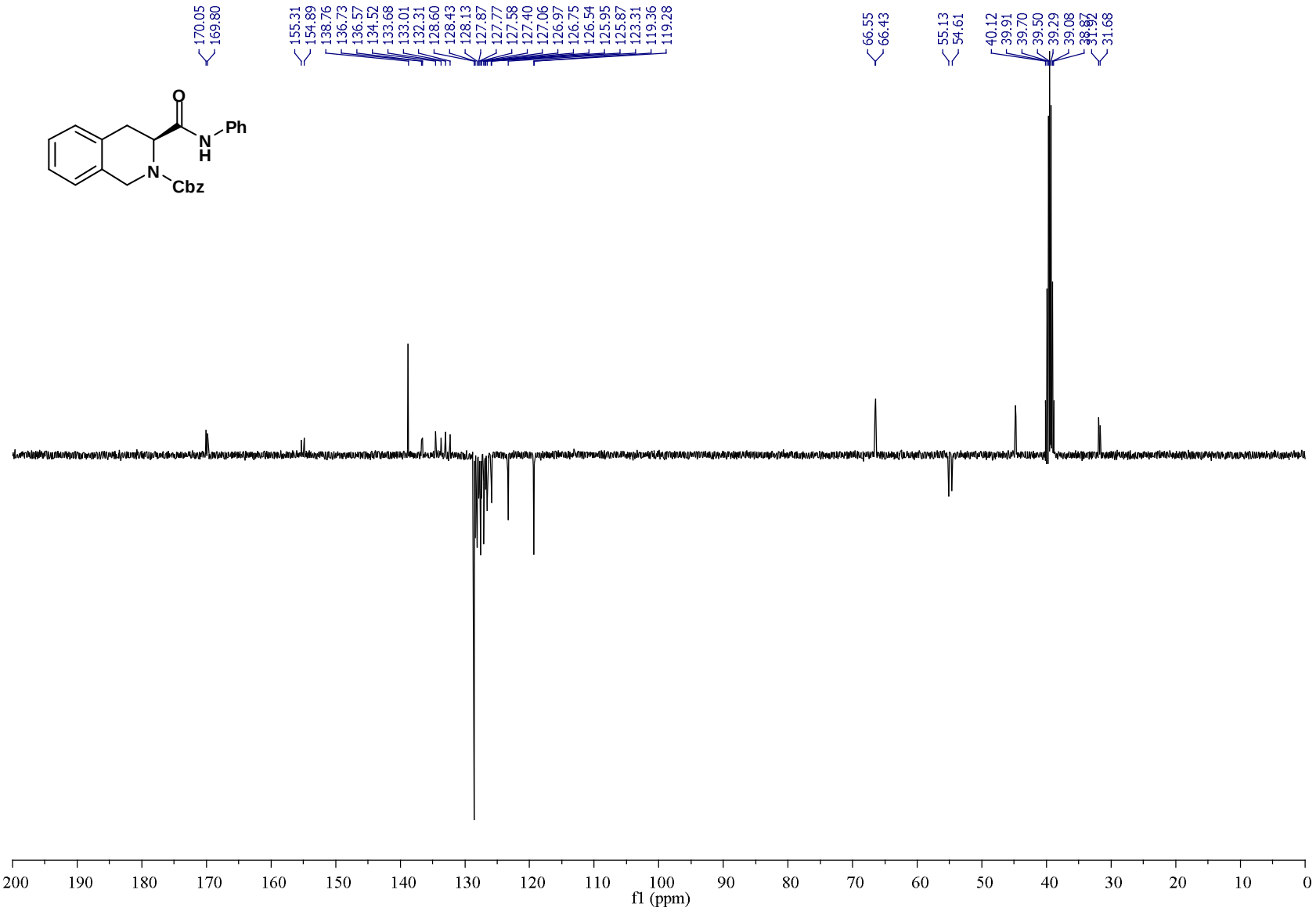
^{13}C NMR Spectrum of Compound 78b in $CDCl_3$



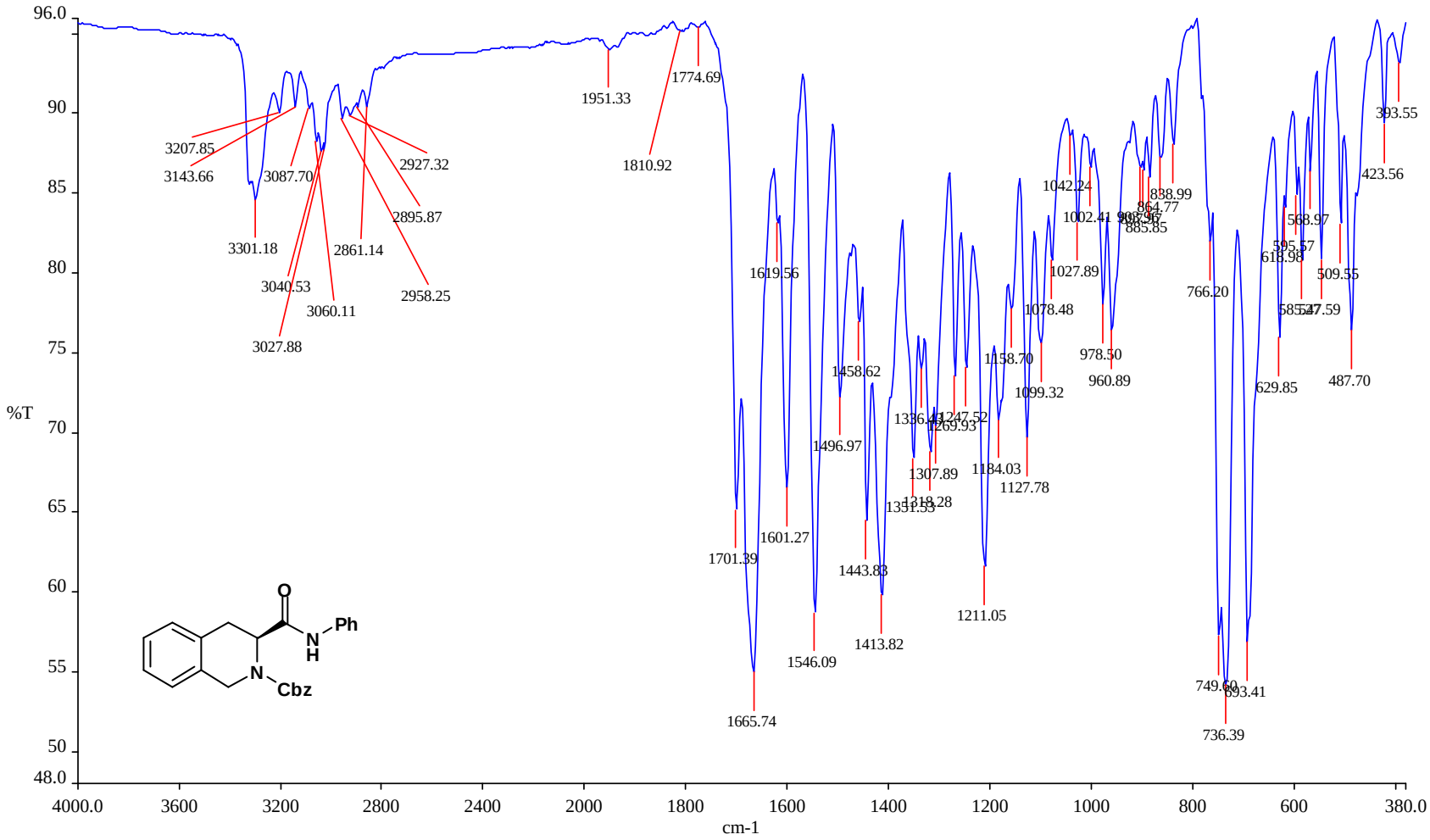
IR Spectrum of Compound 78b



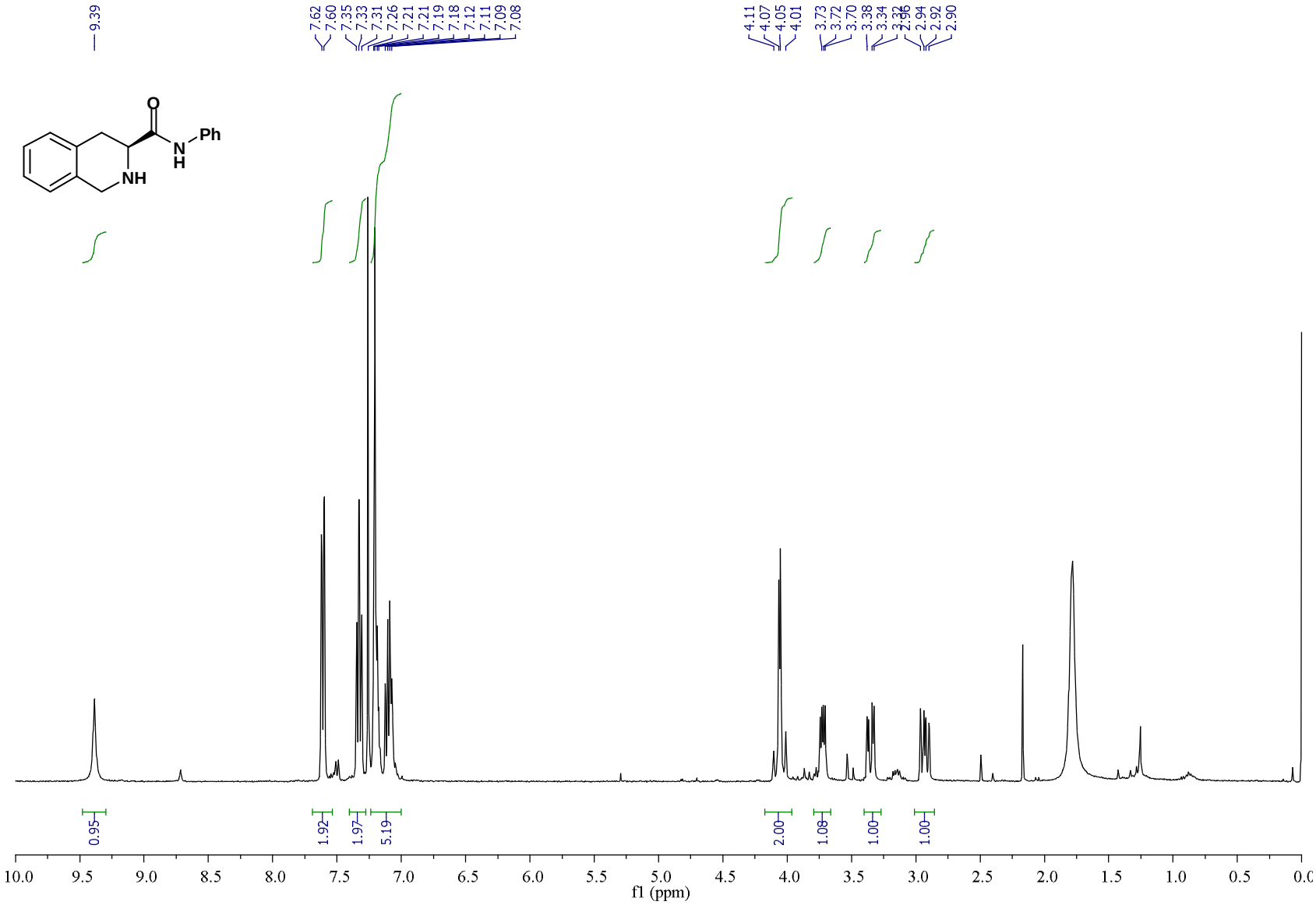
^{1}H NMR Spectrum of Compound 76c in d6-DMSO



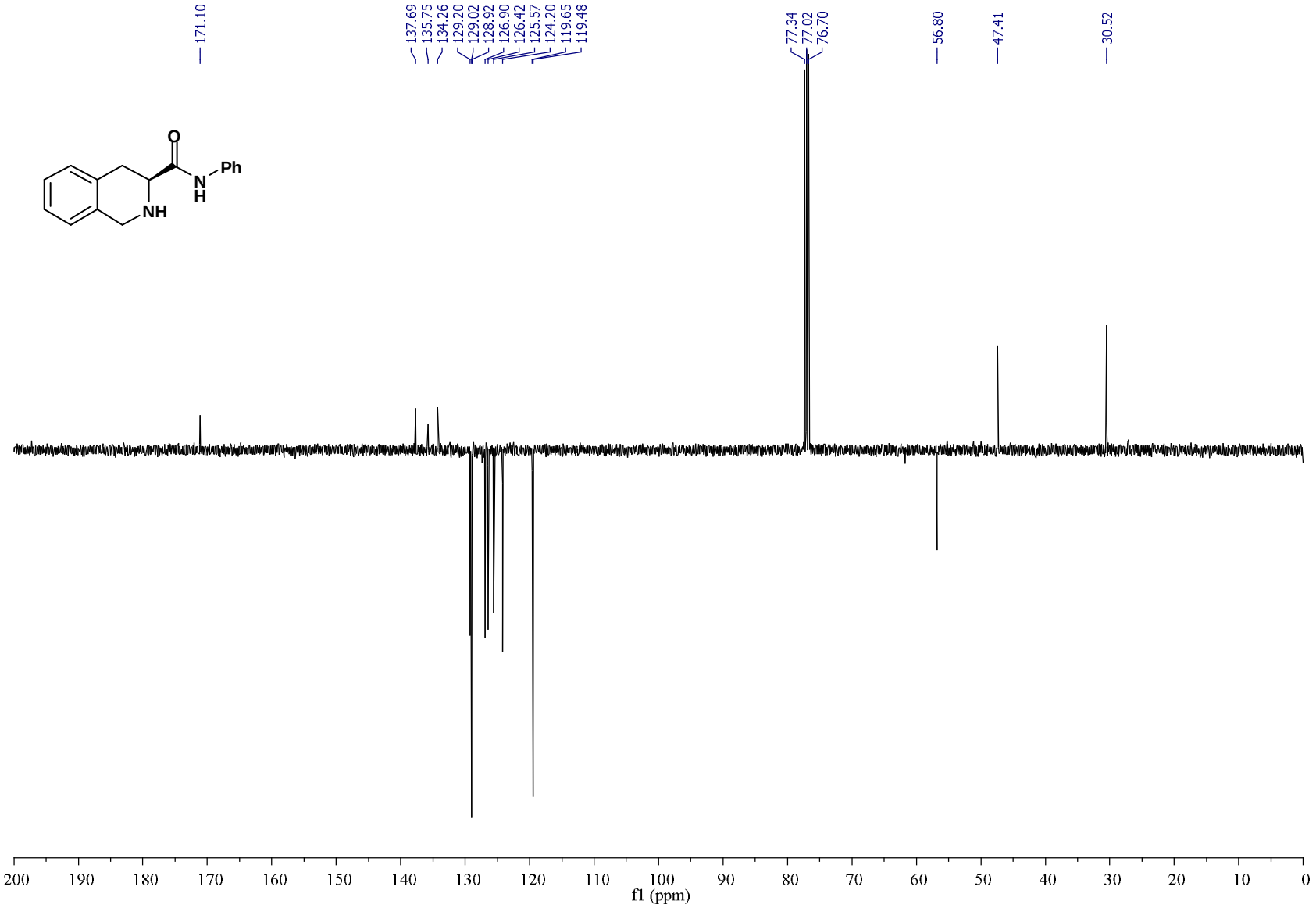
^{13}C NMR Spectrum of Compound 76c in d6-DMSO



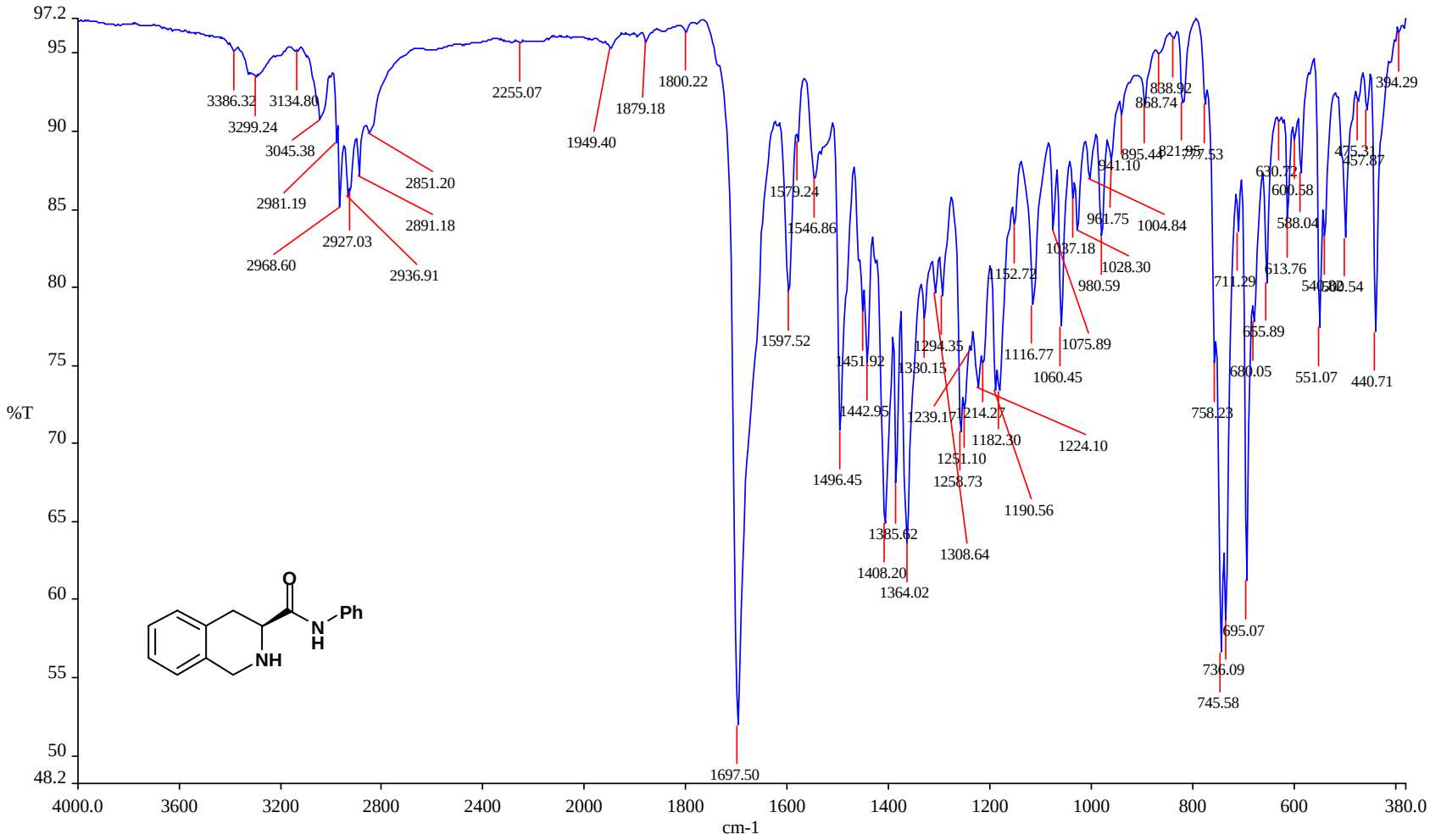
IR Spectrum of Compound 76c



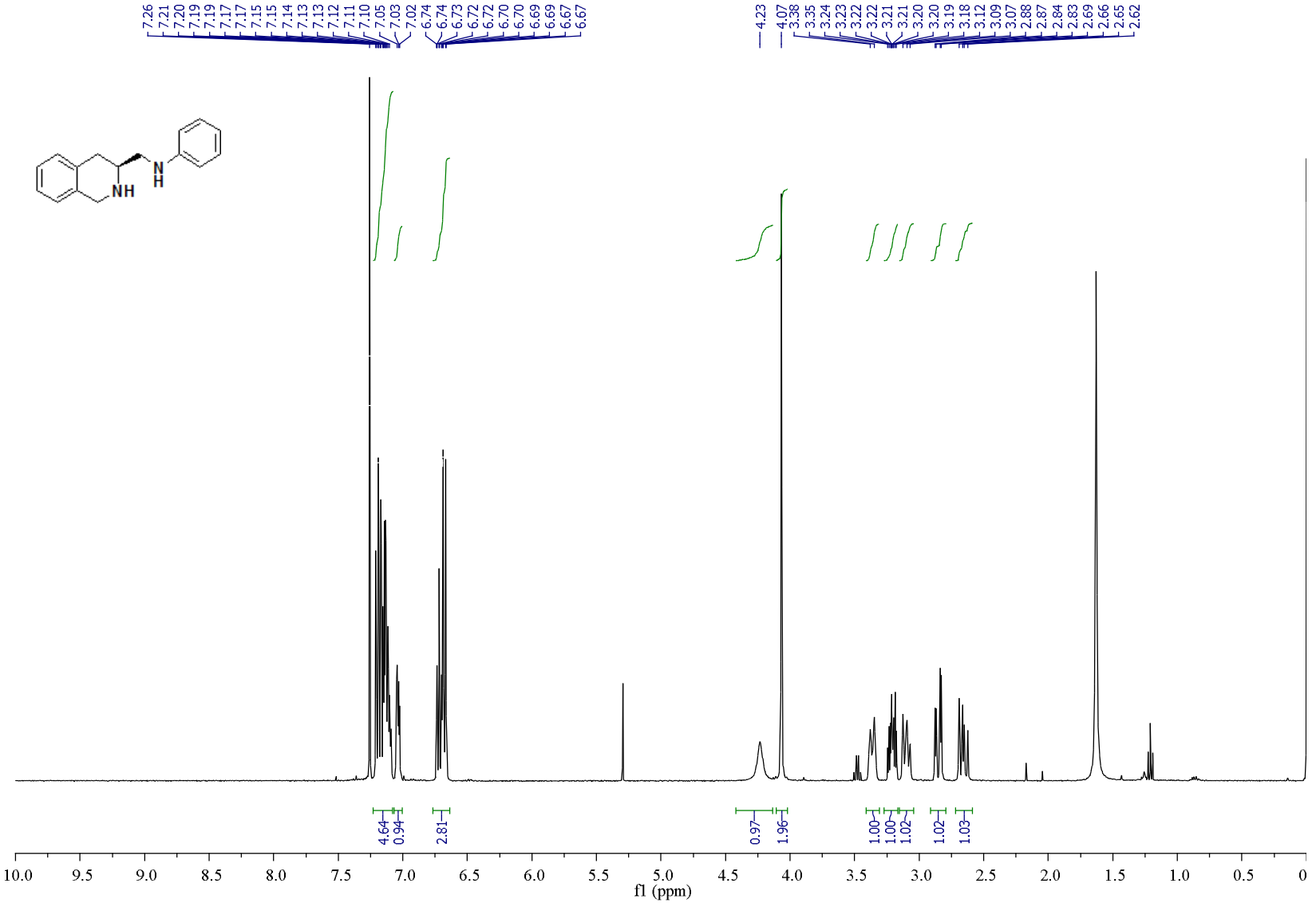
^{1}H NMR Spectrum of Compound 77c in $CDCl_3$



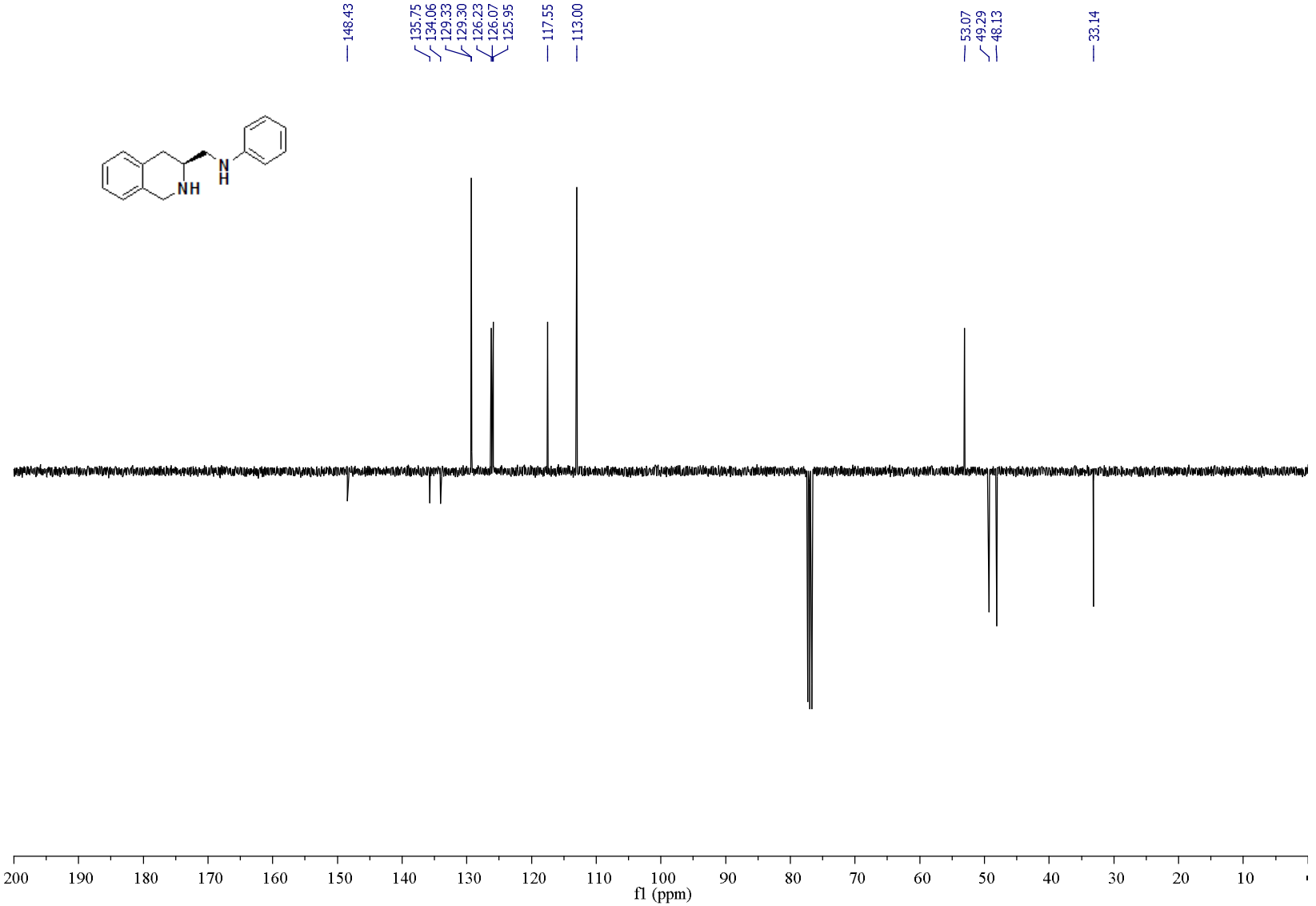
^{13}C NMR Spectrum of Compound 77c in $CDCl_3$



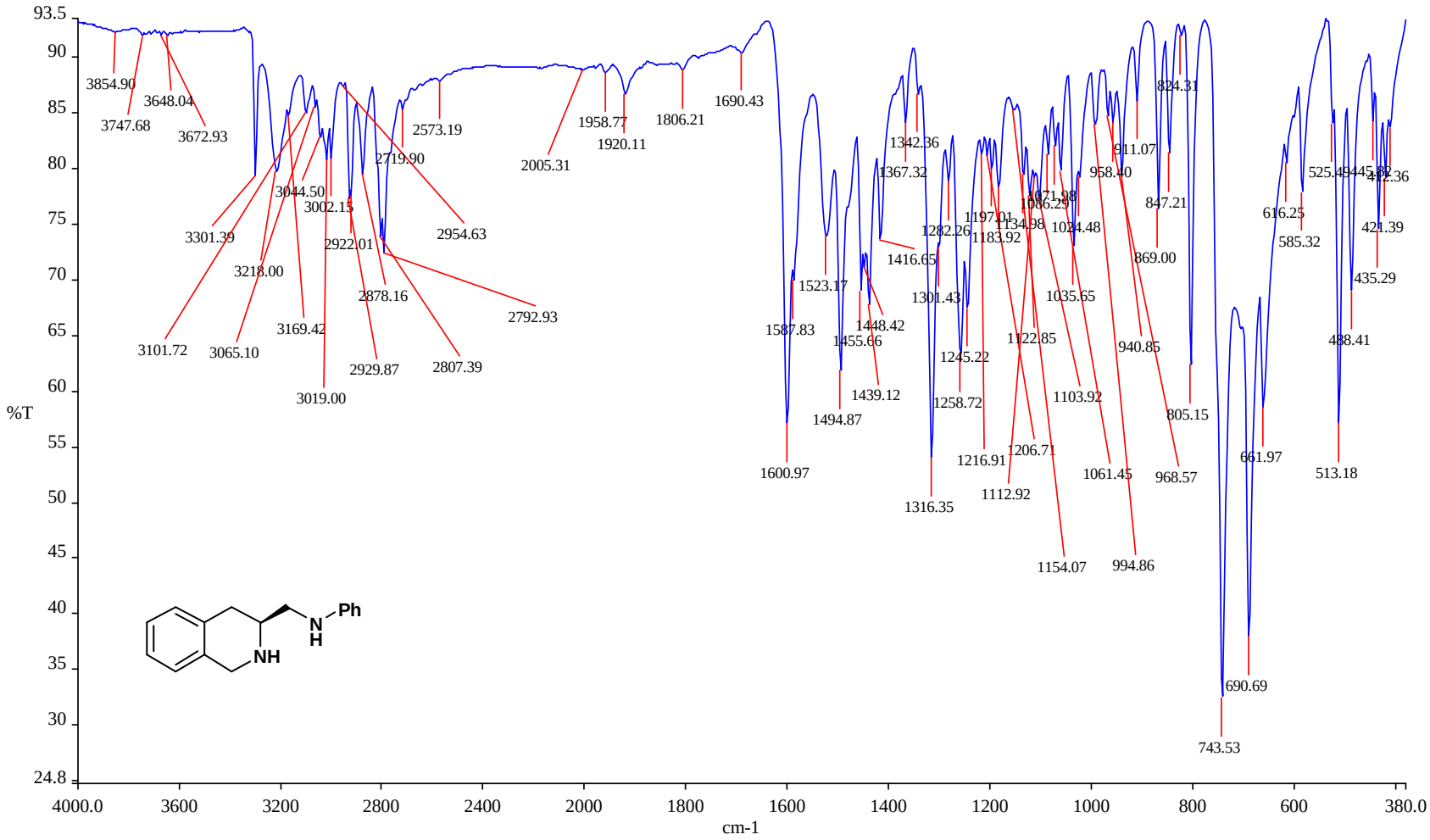
IR Spectrum of Compound 77c



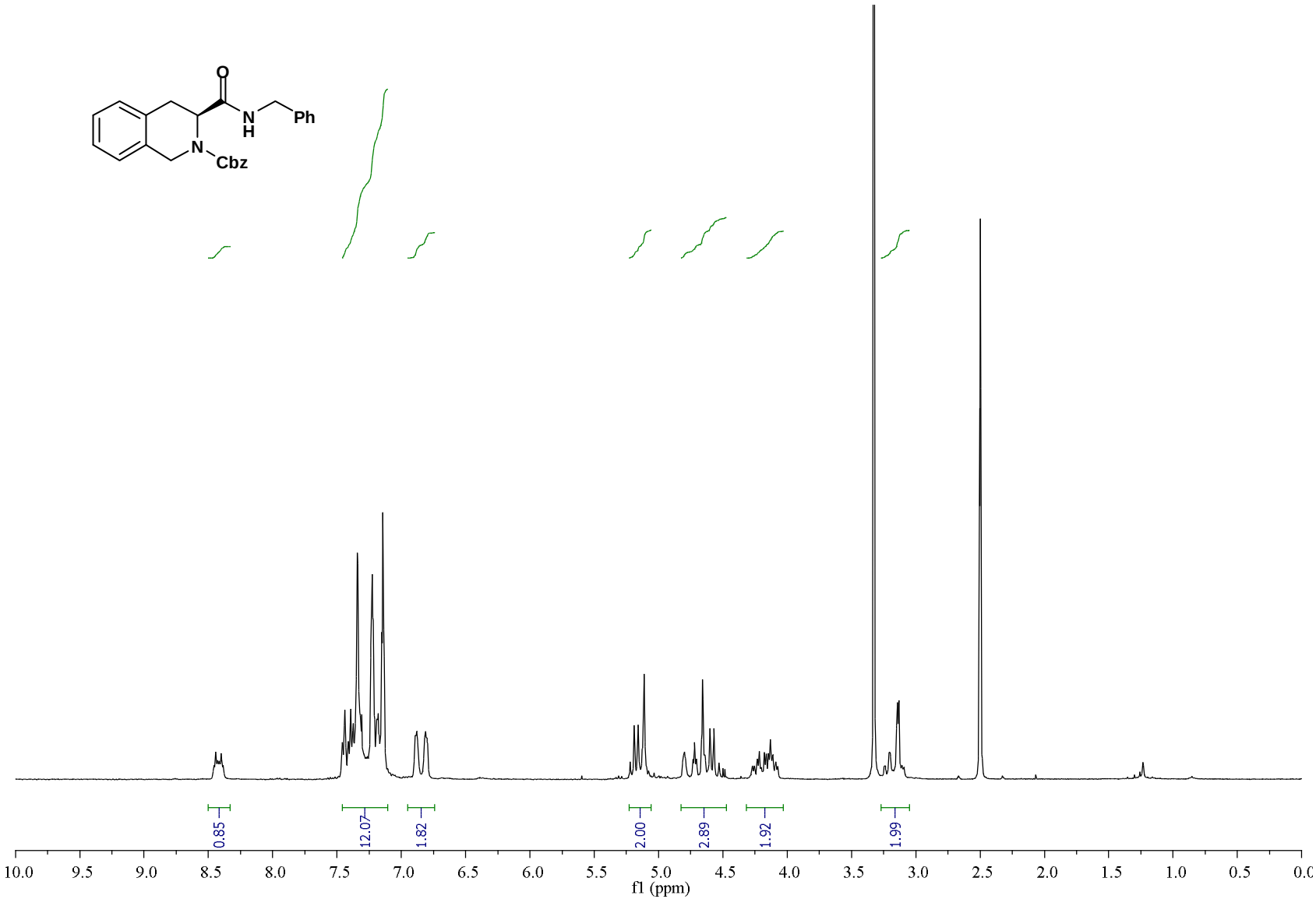
^{1}H NMR Spectrum of Compound 78c in $CDCl_3$



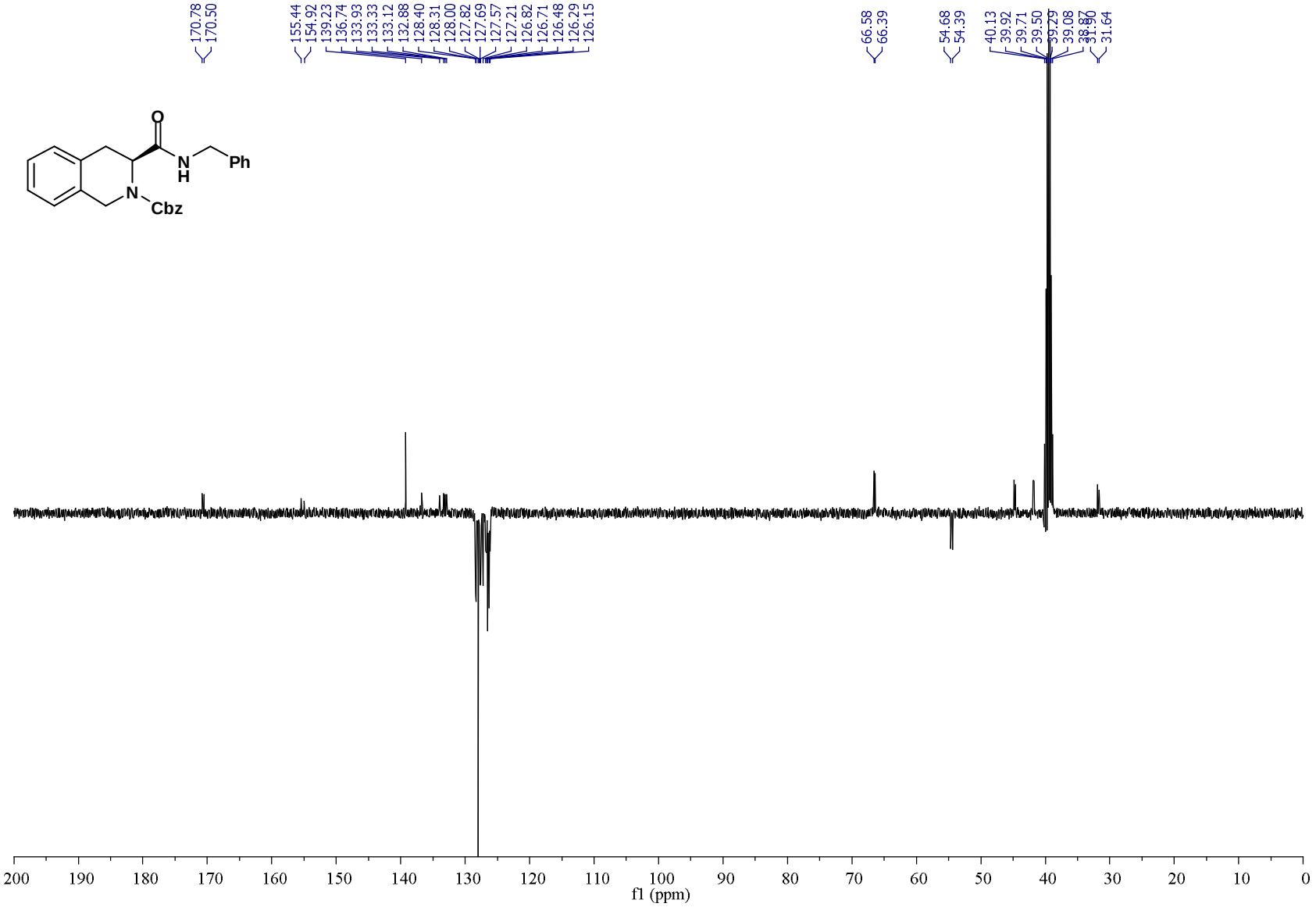
^{13}C NMR Spectrum of Compound 78c in $CDCl_3$



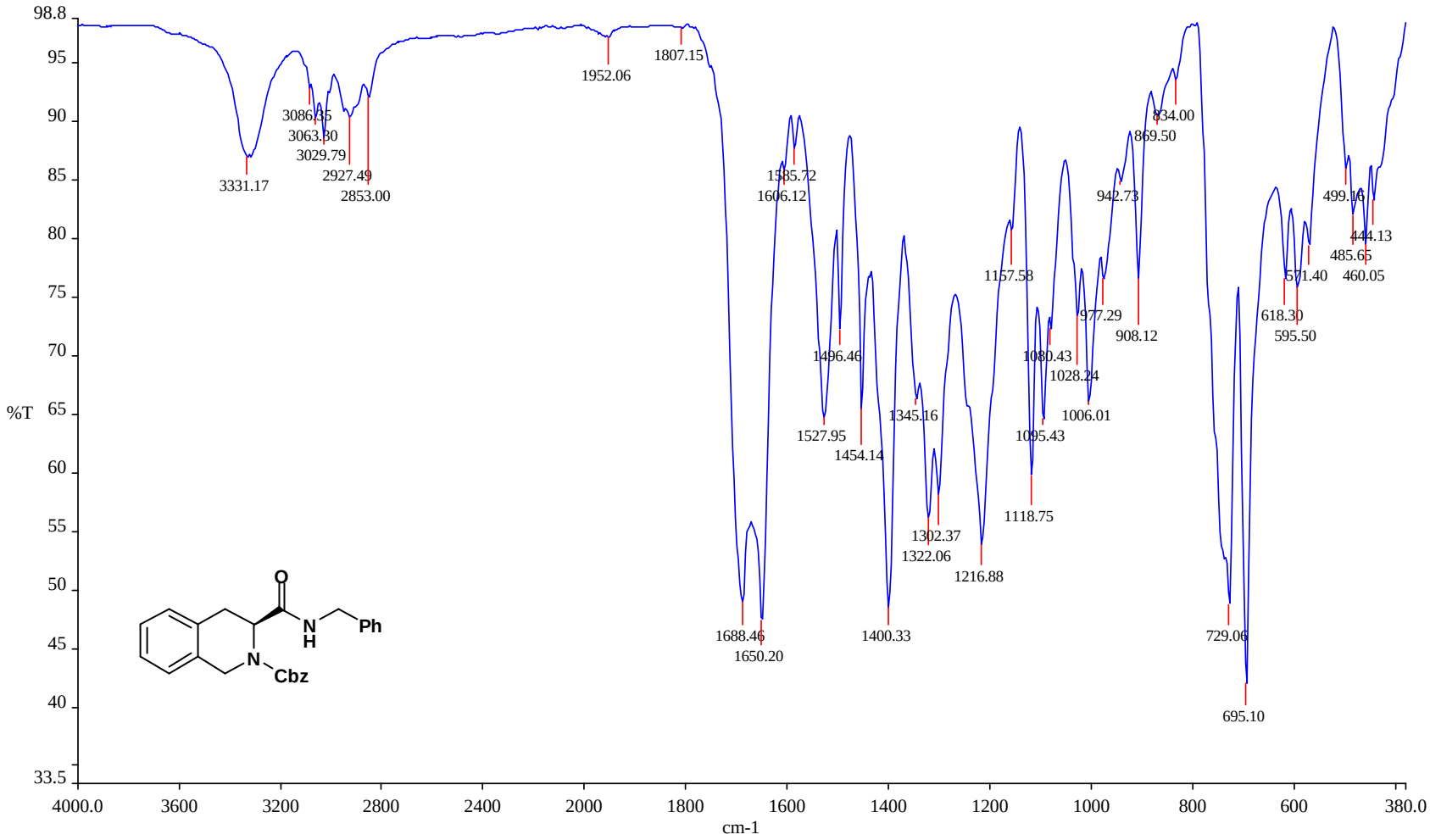
IR Spectrum of Compound 78c



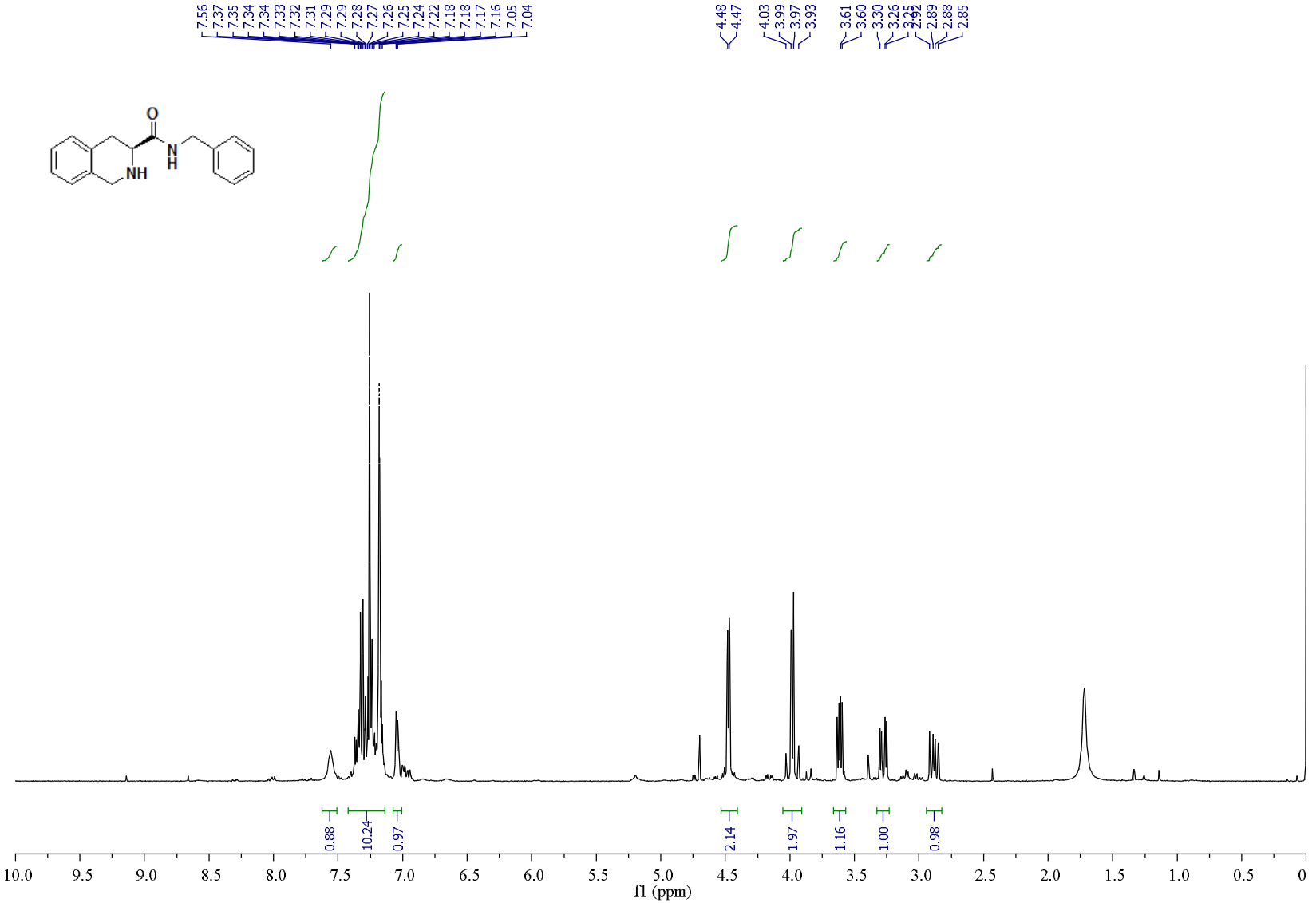
^{1}H NMR Spectrum of Compound 76d in d6-DMSO



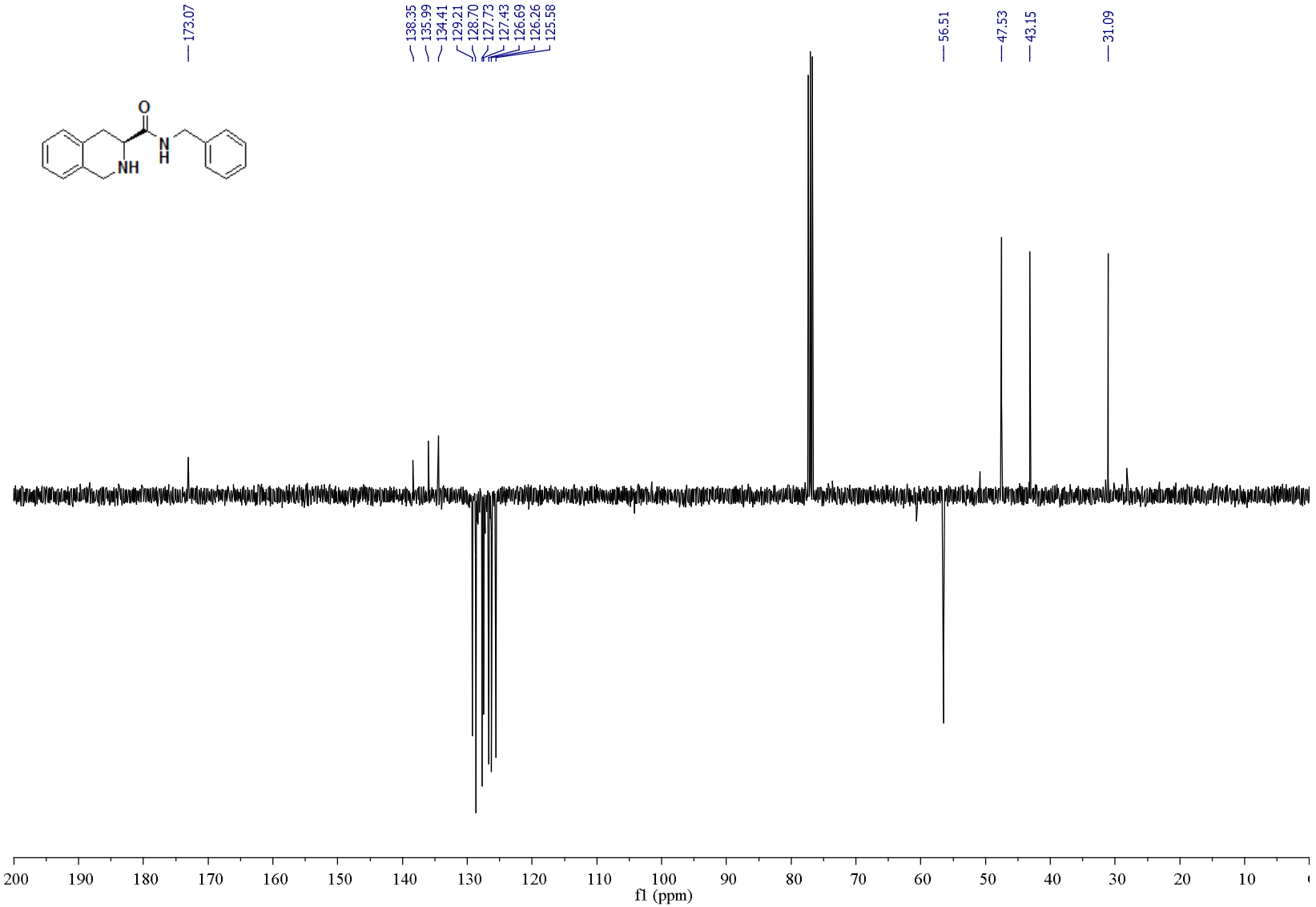
^{13}C NMR Spectrum of Compound 76d in d6-DMSO



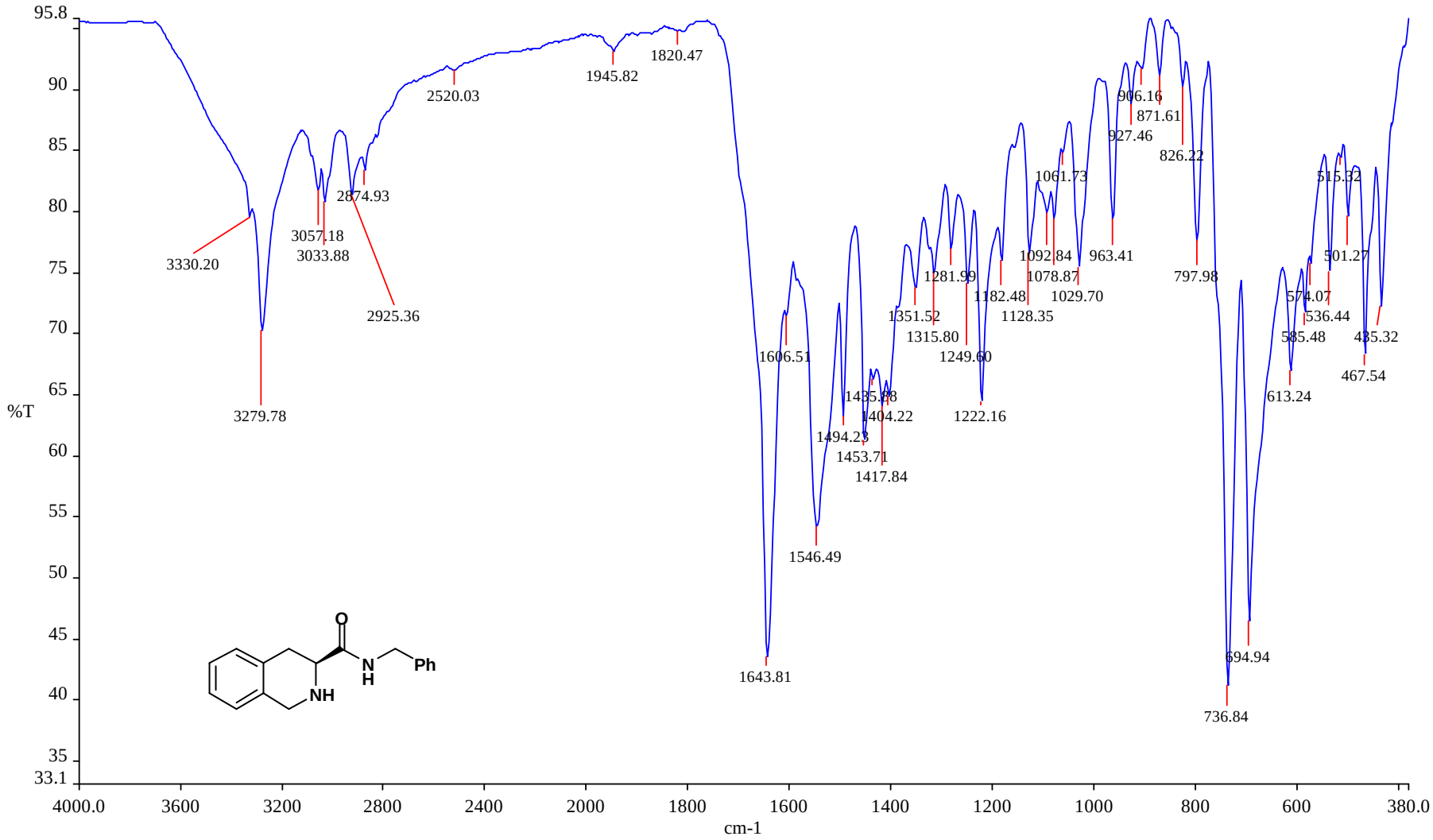
IR Spectrum of Compound 76d



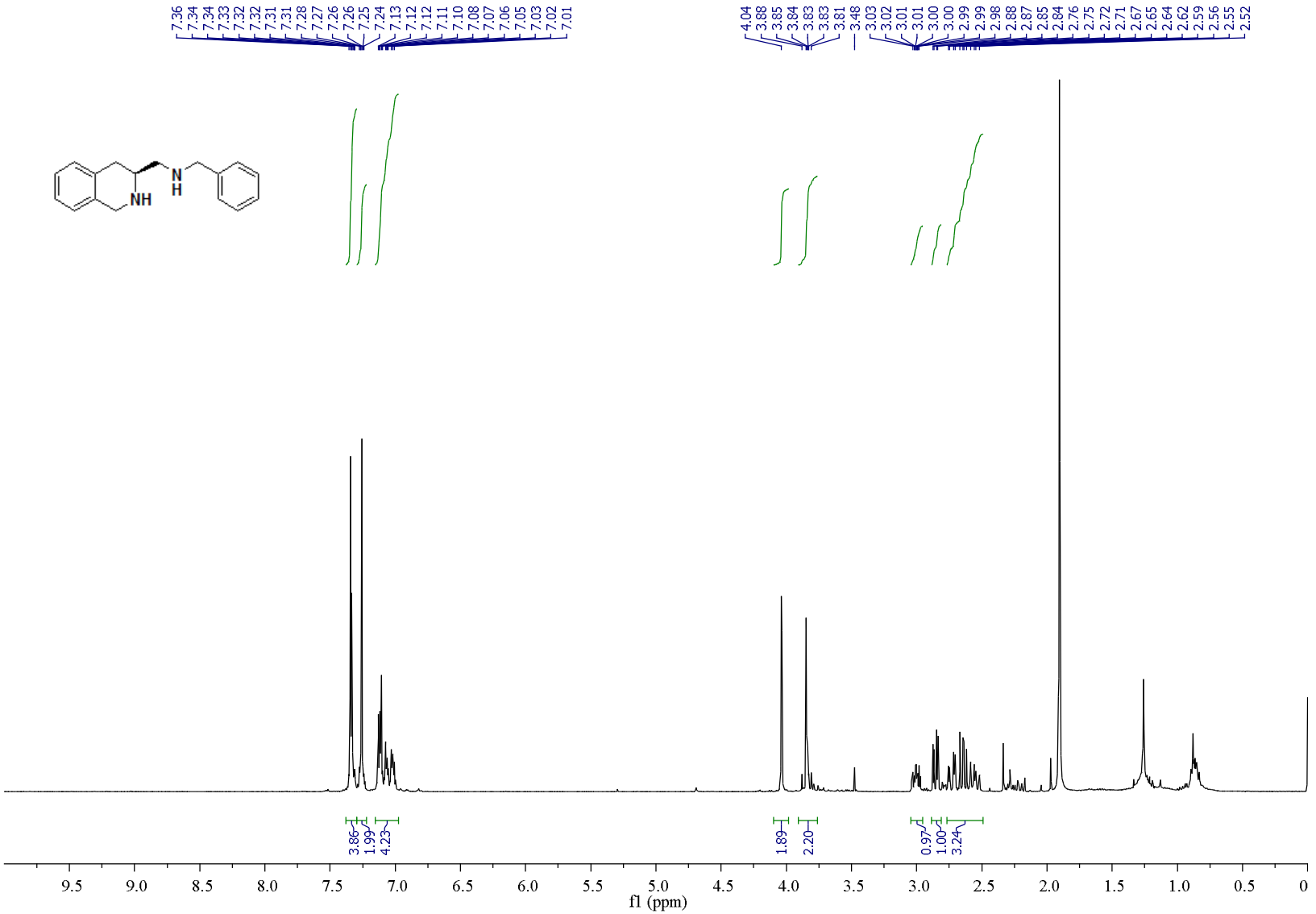
^{1}H NMR Spectrum of Compound 77d in $CDCl_3$



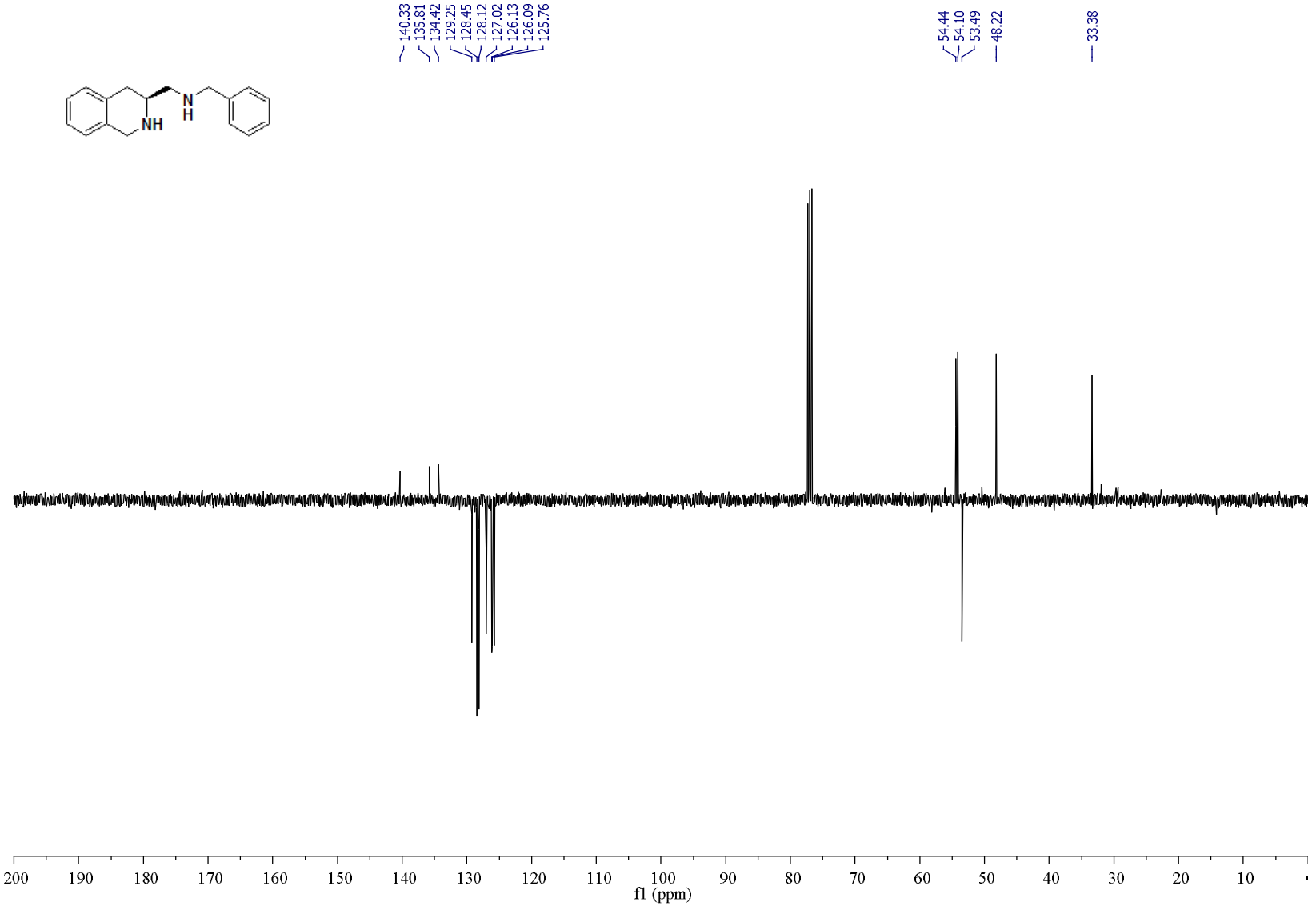
^{13}C NMR Spectrum of Compound 77d in $CDCl_3$



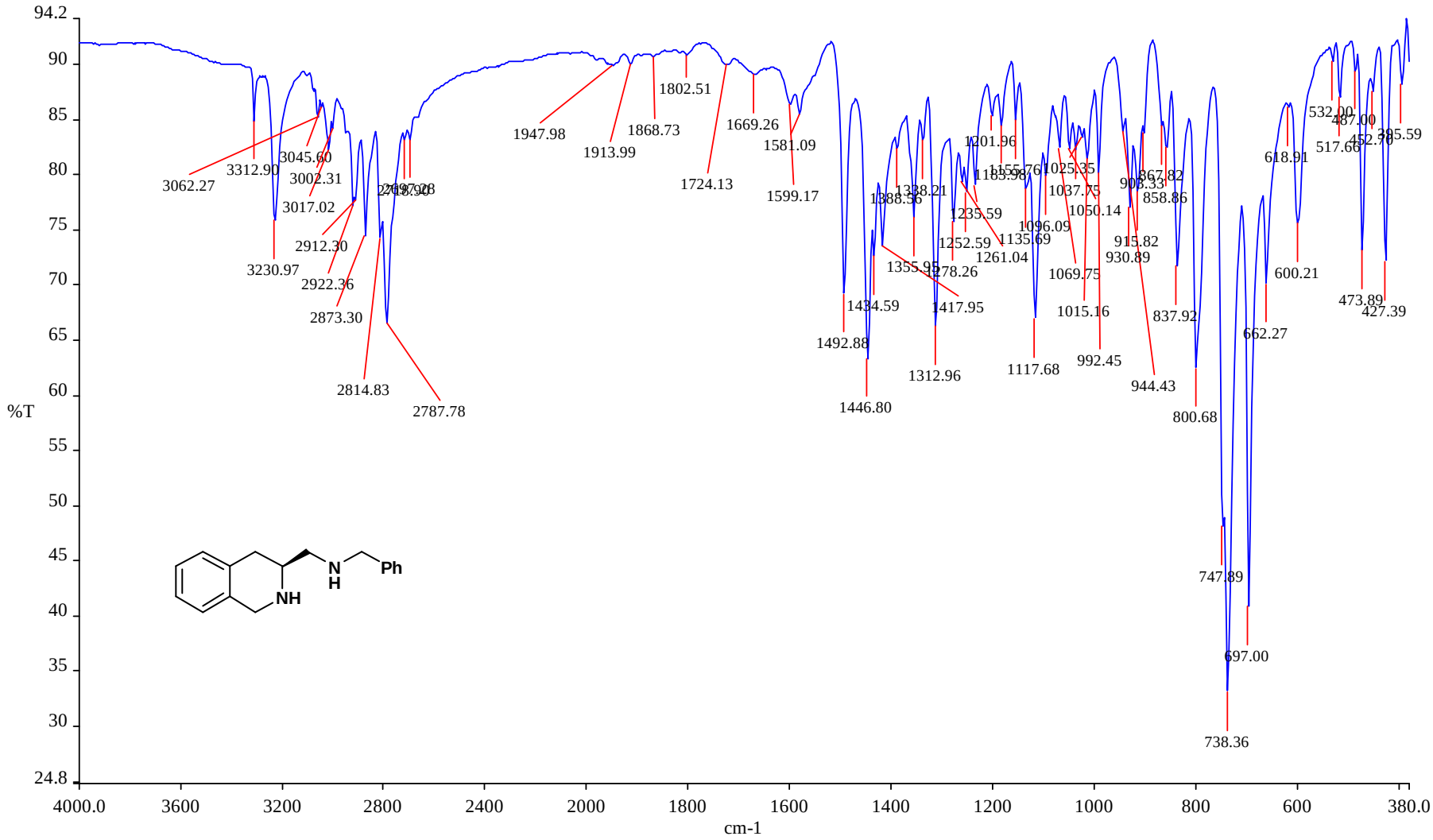
IR Spectrum of Compound 77d



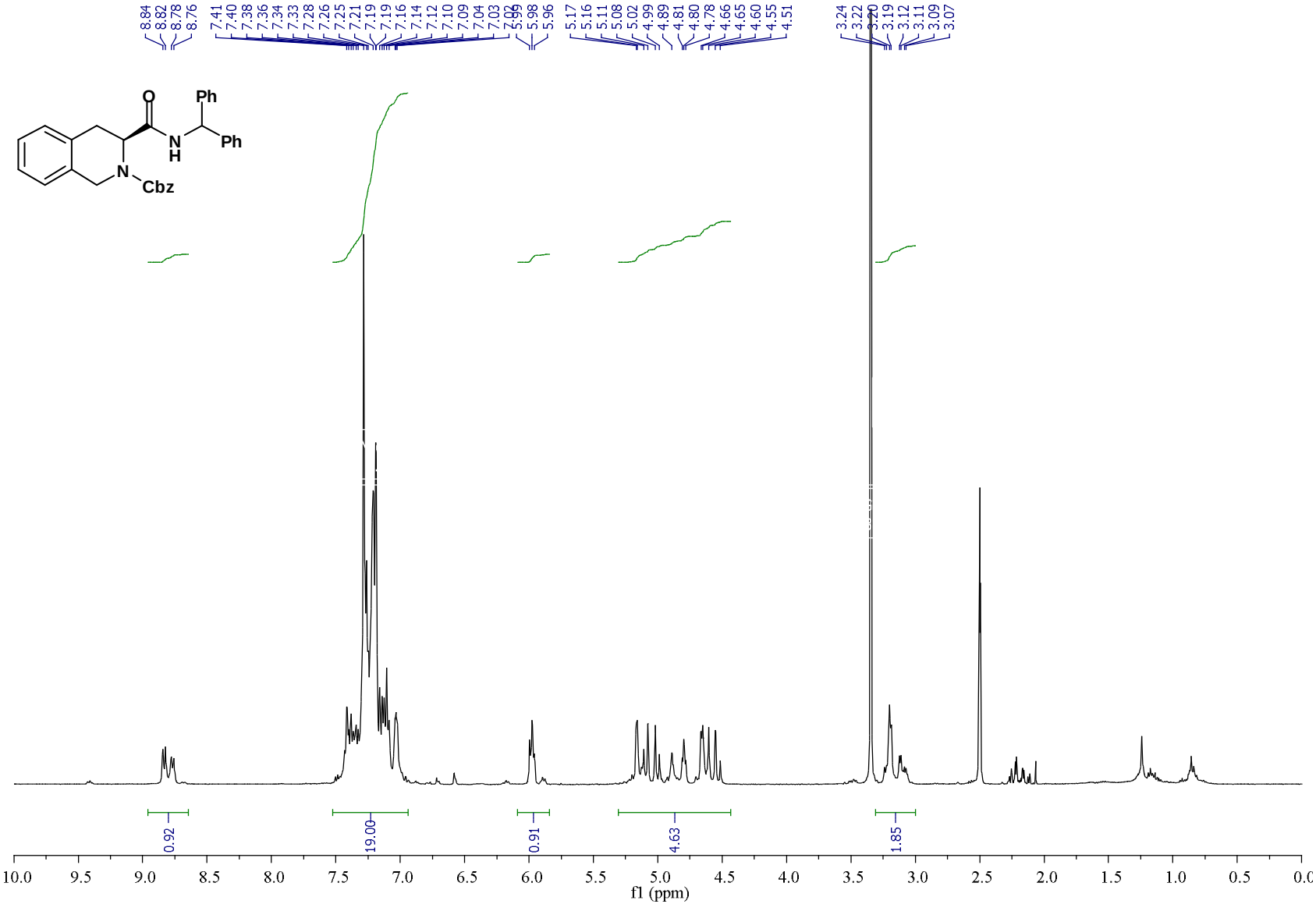
^{1}H NMR Spectrum of Compound 78d in $CDCl_3$



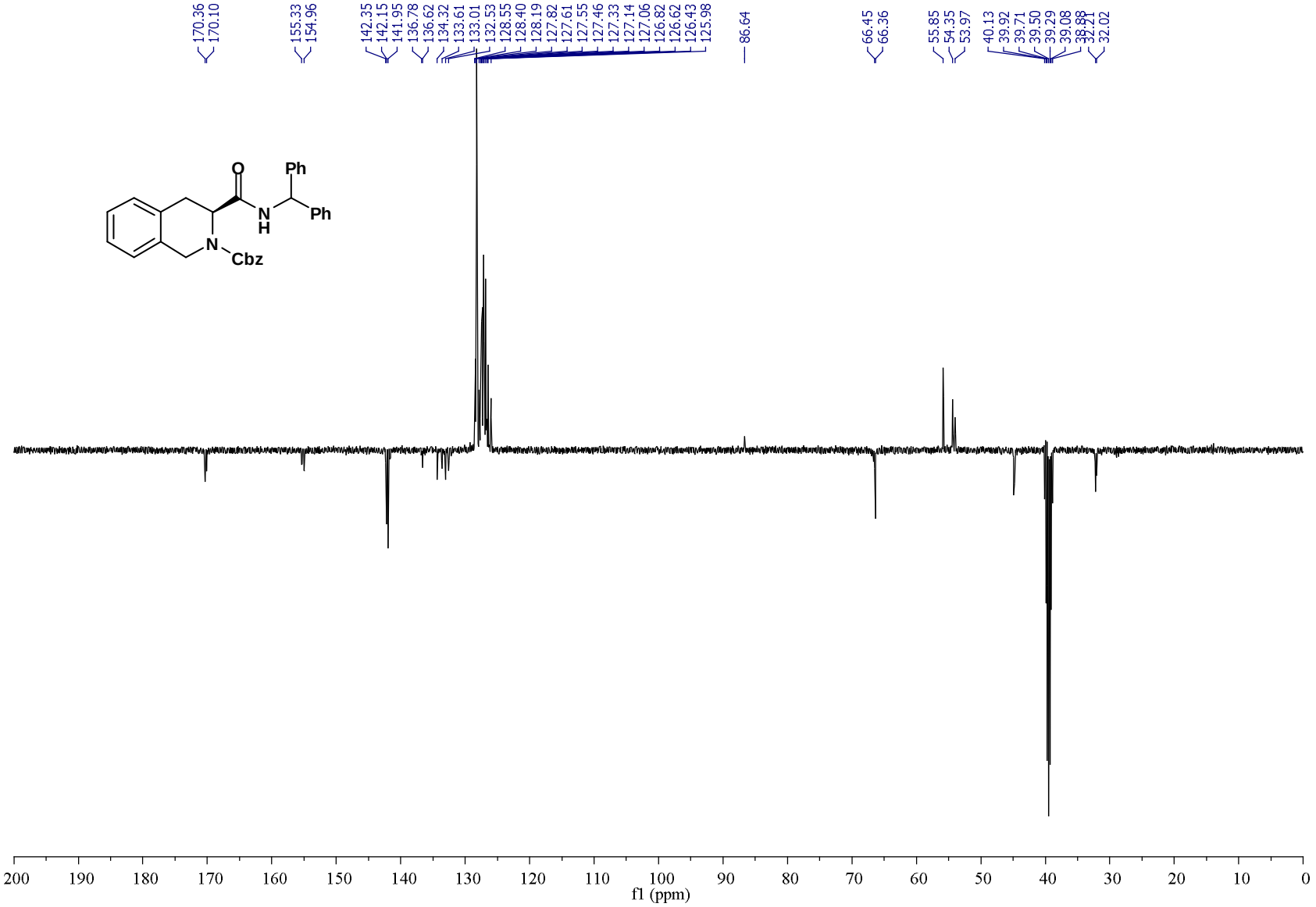
^{13}C NMR Spectrum of Compound 78d in $CDCl_3$



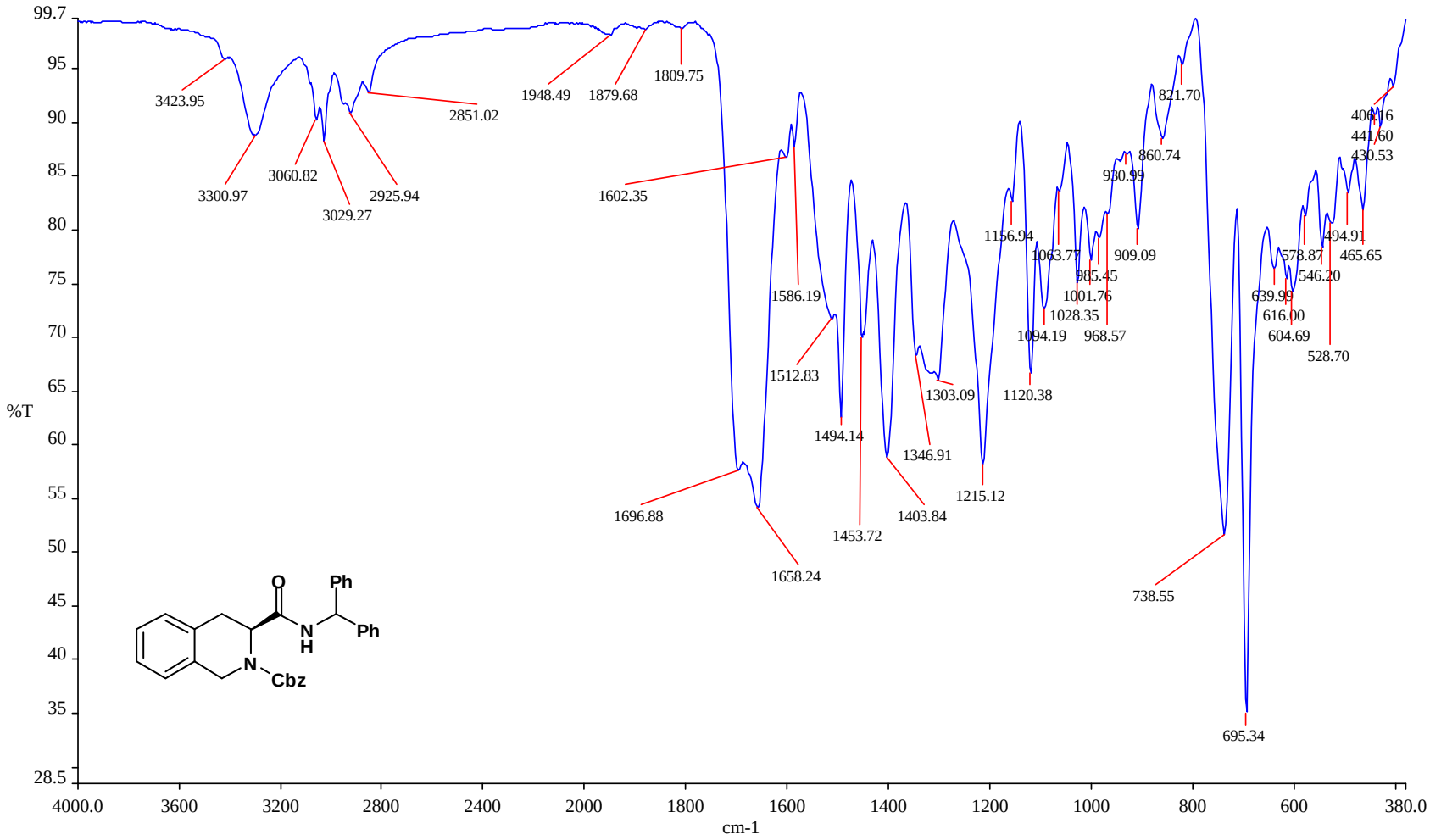
IR Spectrum of Compound 78d



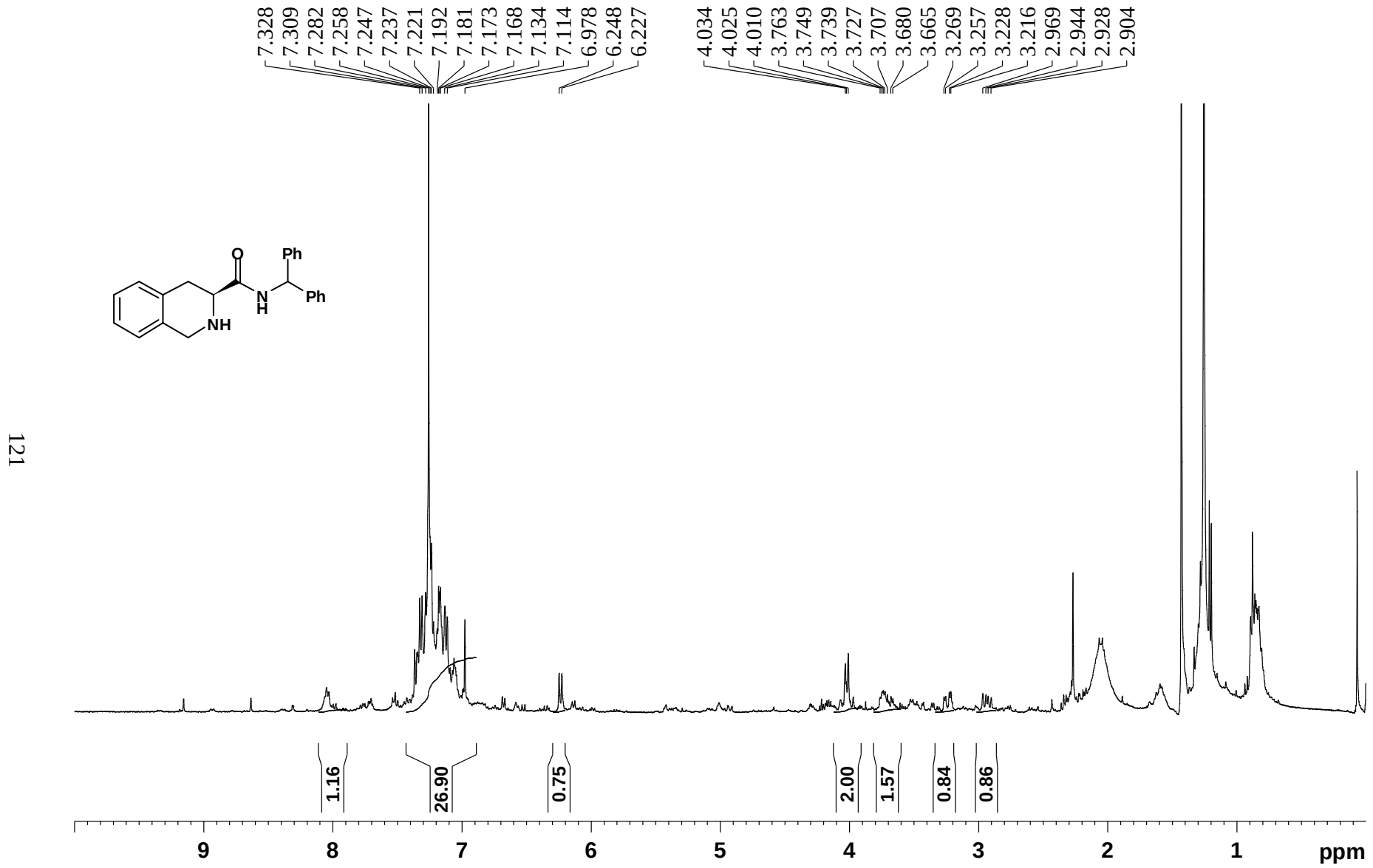
^{1}H NMR Spectrum of Compound 76e in d6-DMSO



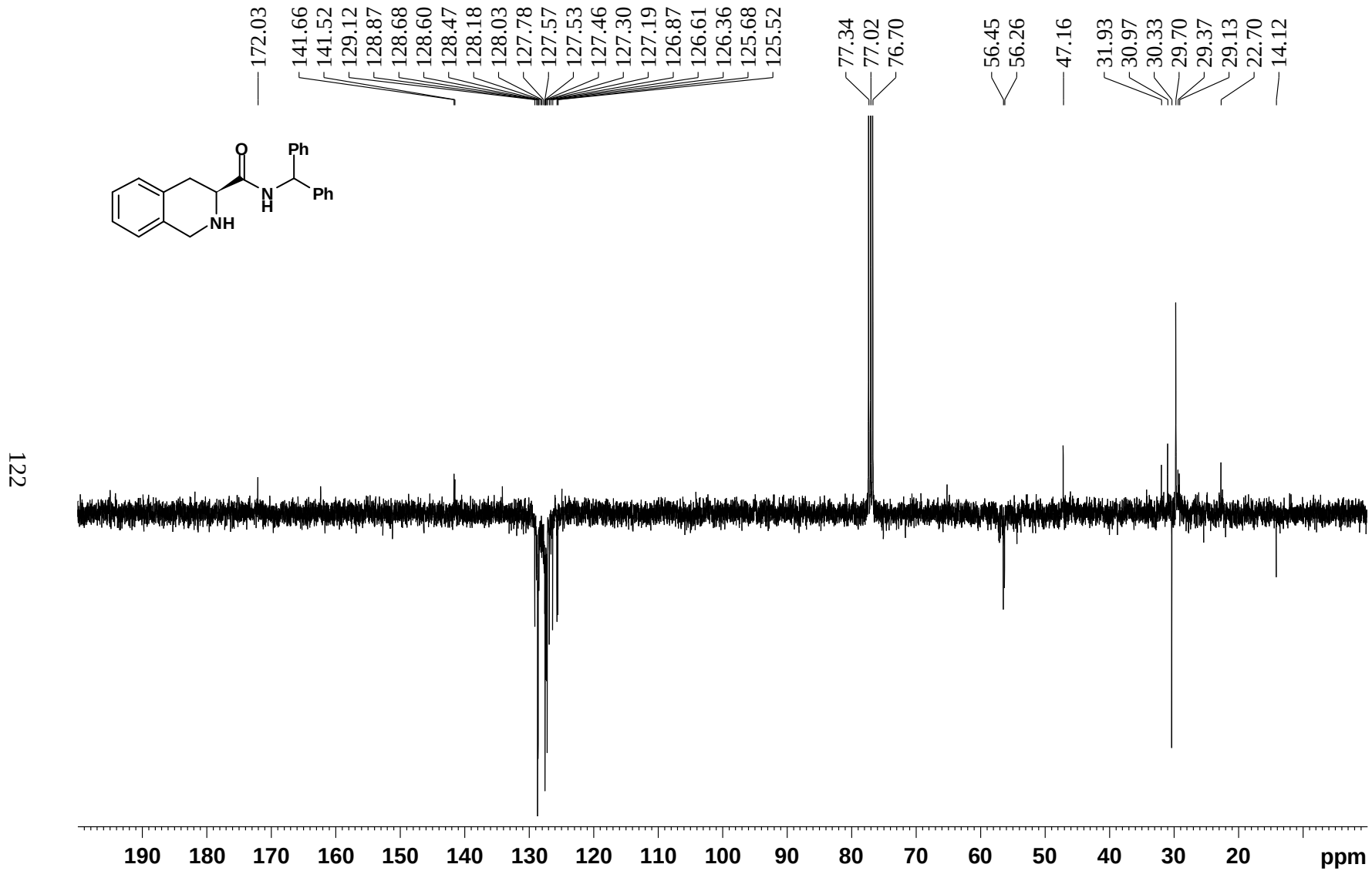
^{13}C NMR Spectrum of Compound 76e in d6-DMSO



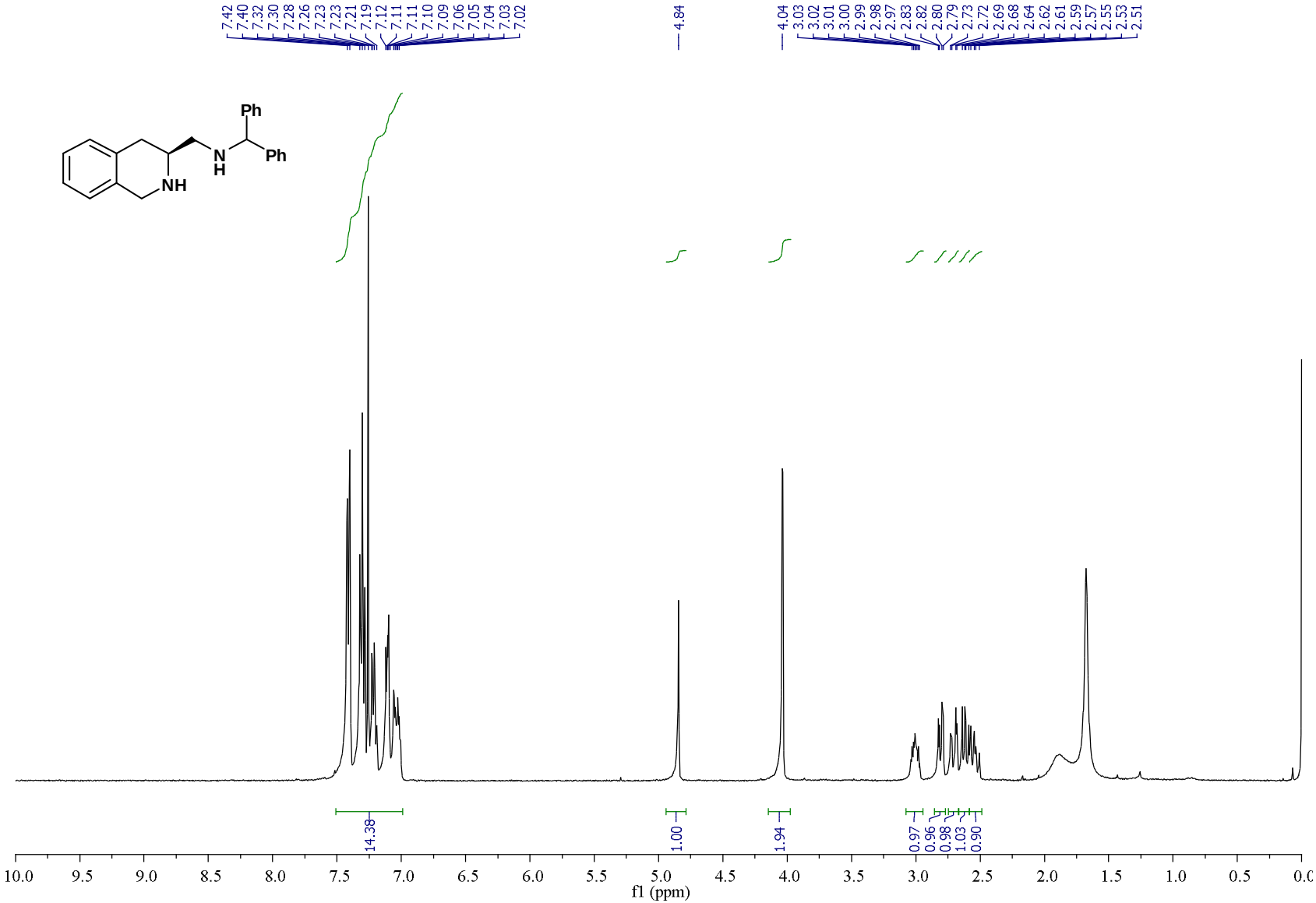
IR Spectrum of Compound 76e



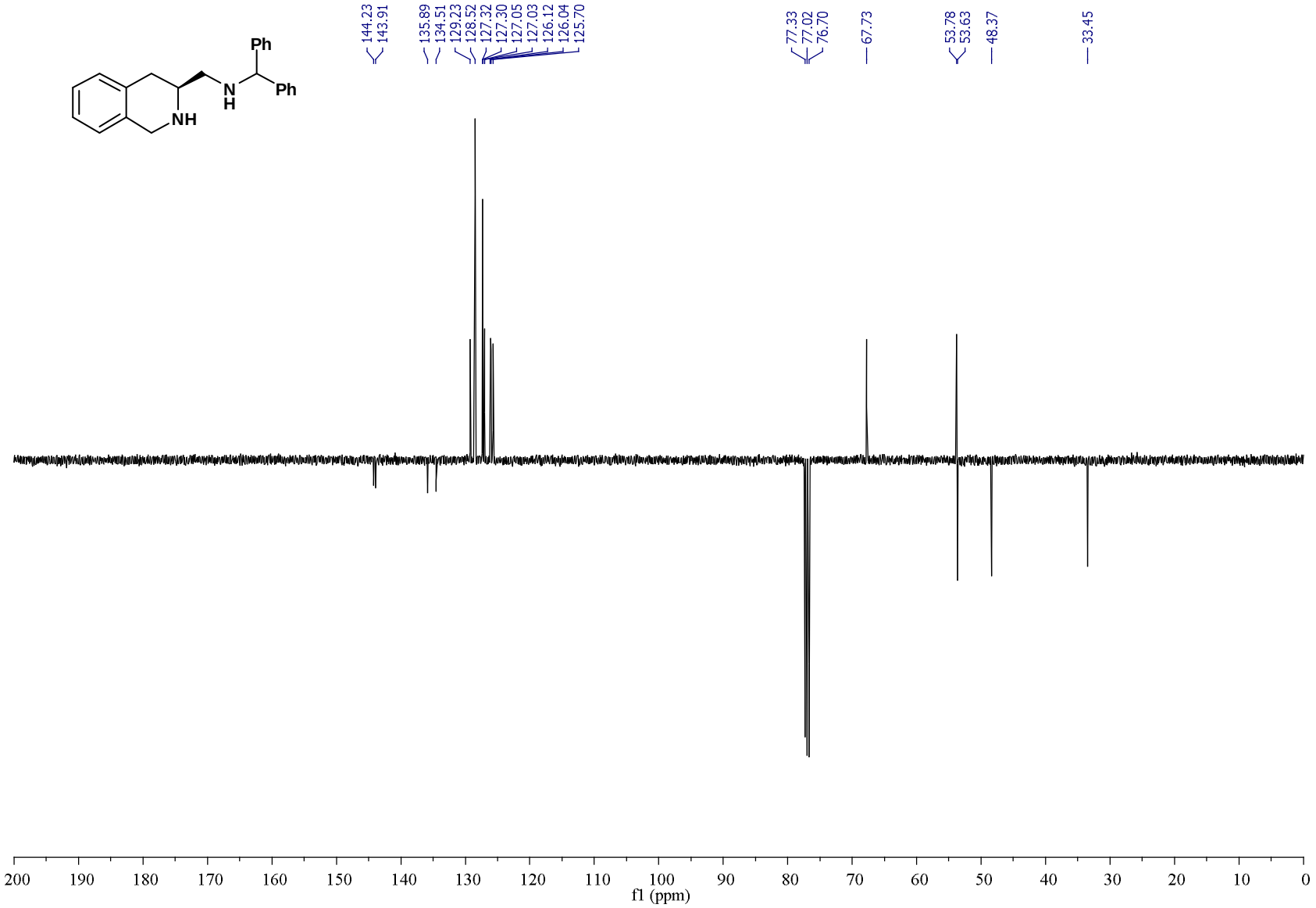
^{1}H NMR Spectrum of Compound 77e in $CDCl_3$



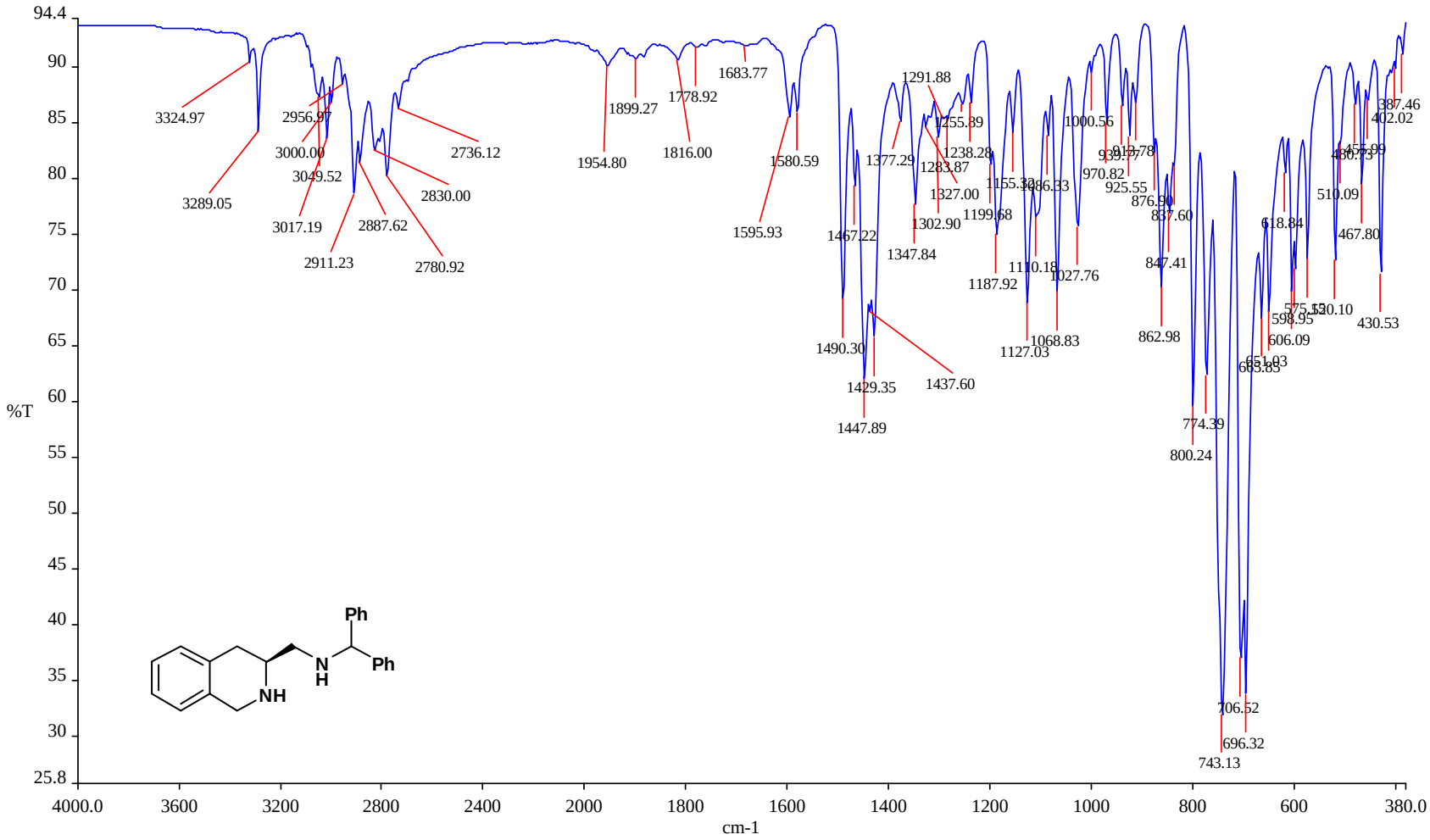
^{13}C NMR Spectrum of Compound 77e in $CDCl_3$



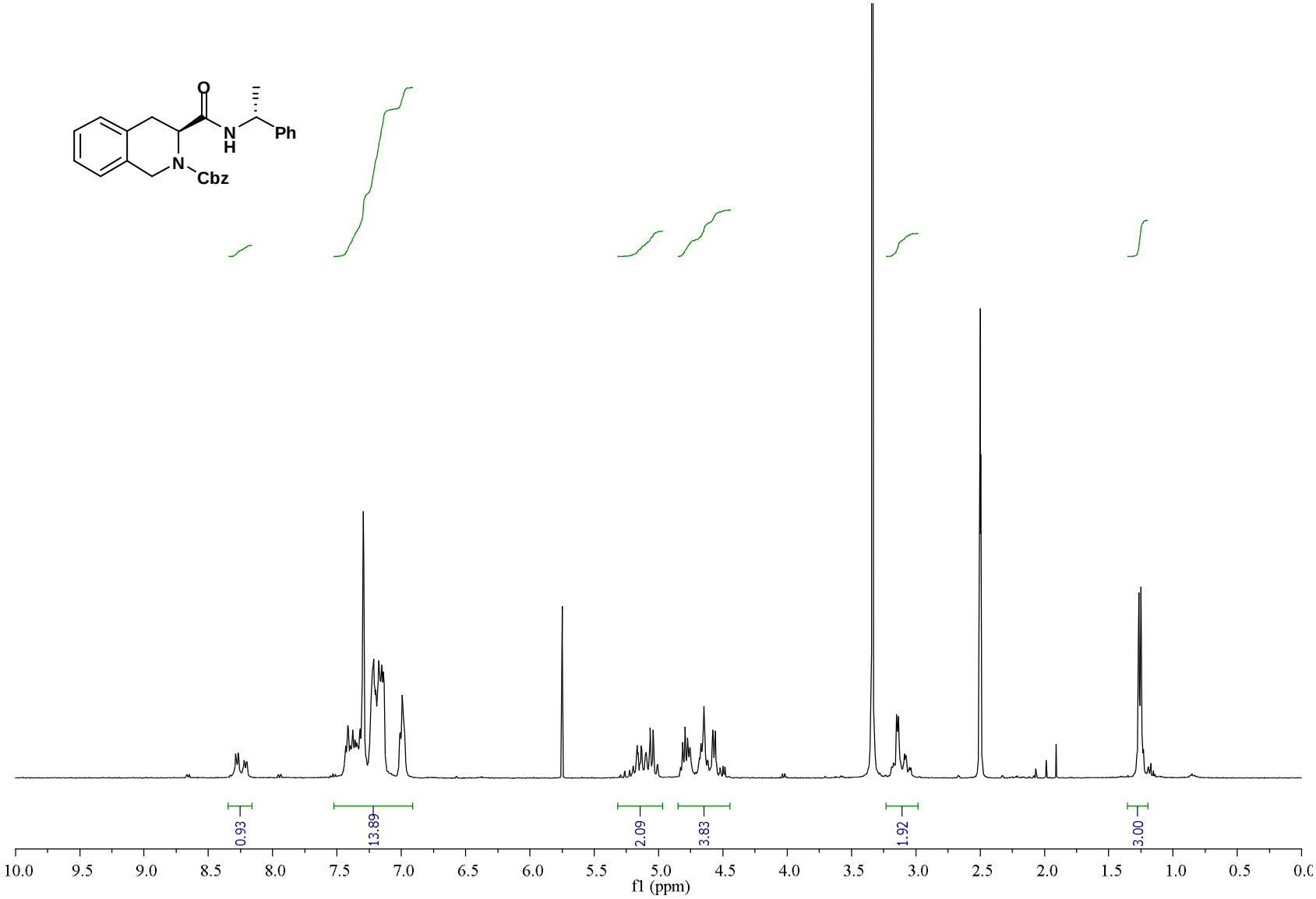
^{1}H NMR Spectrum of Compound 78e in $CDCl_3$



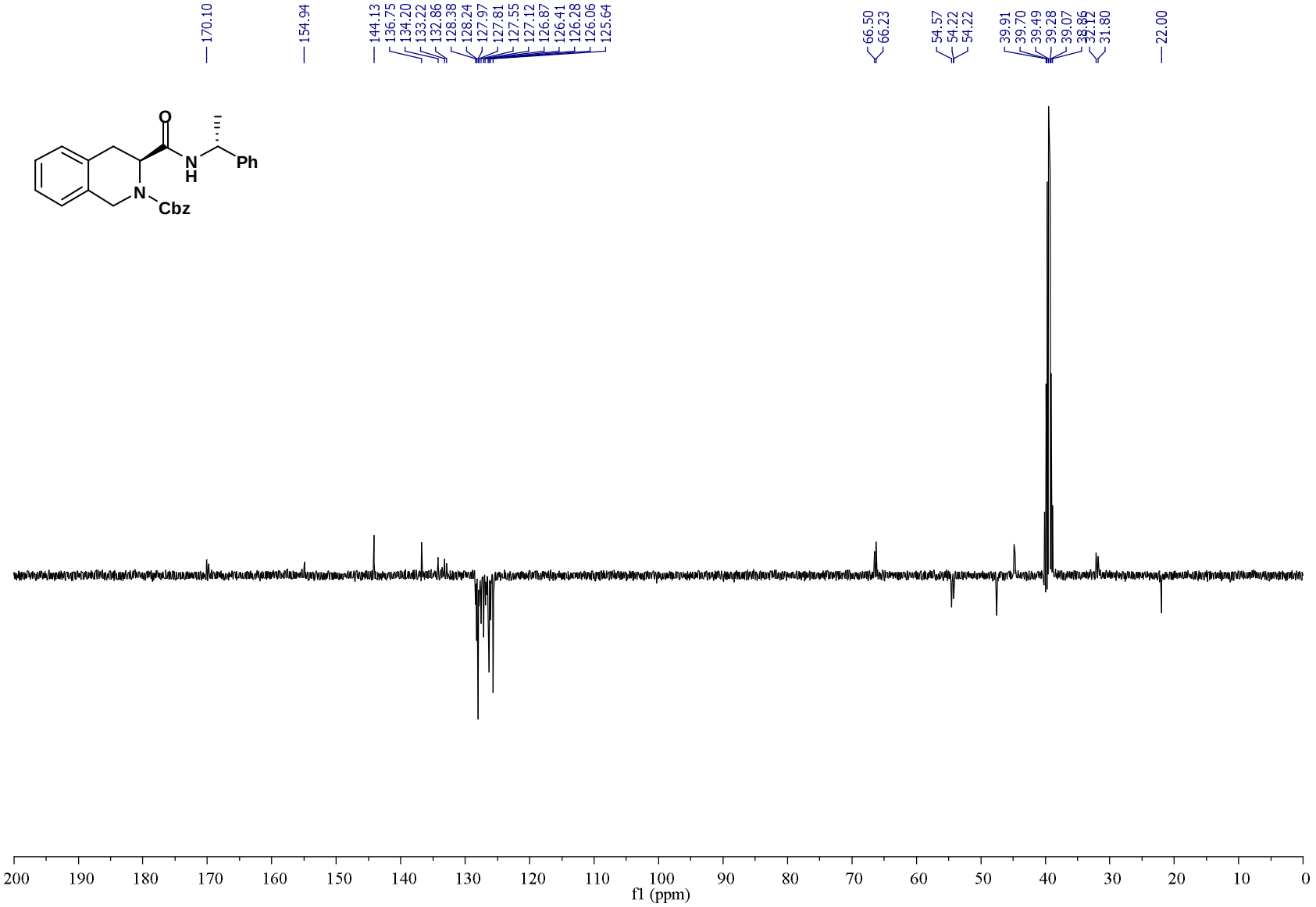
^{13}C NMR Spectrum of Compound 78e in $CDCl_3$



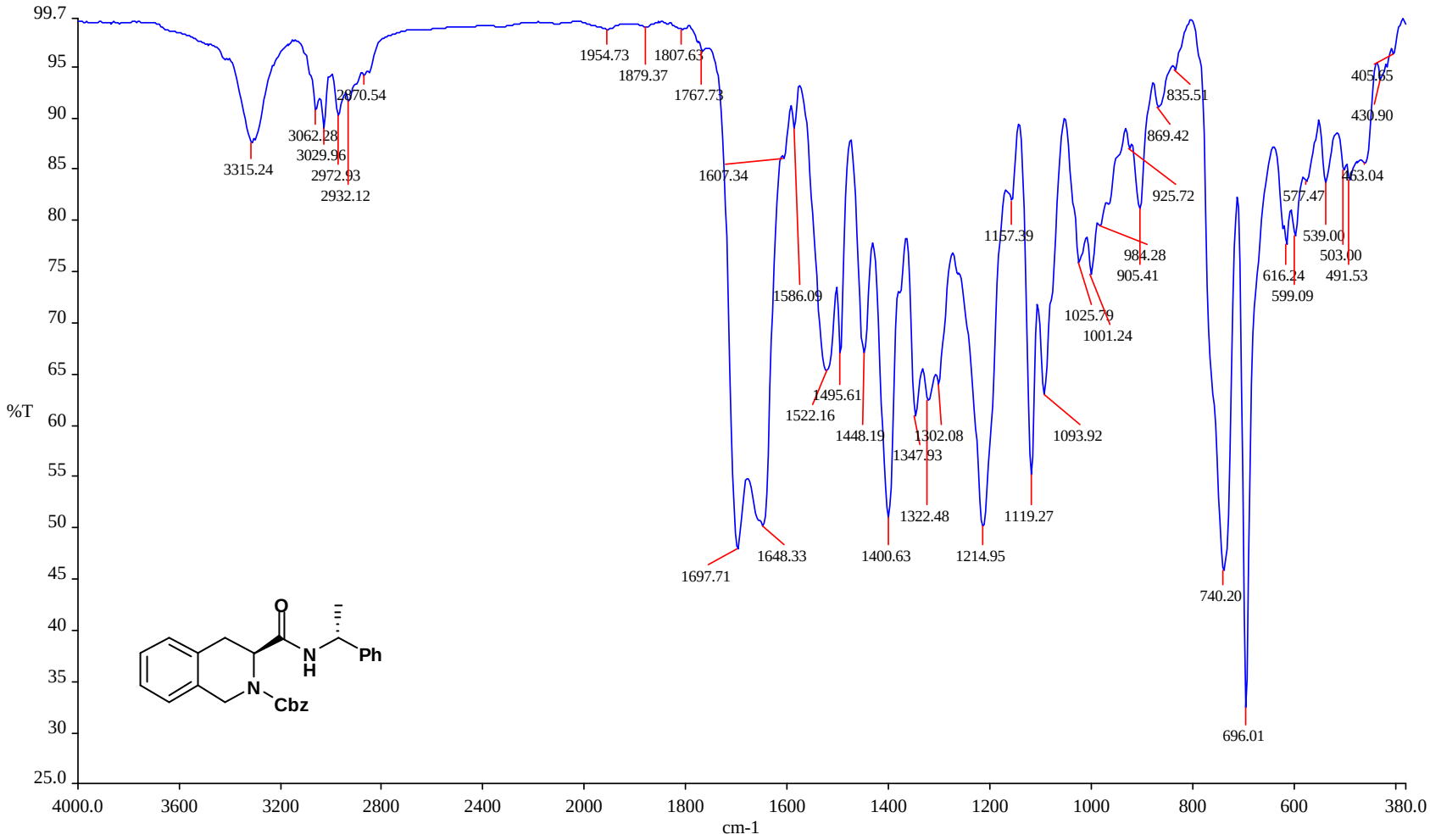
IR Spectrum of Compound 78e



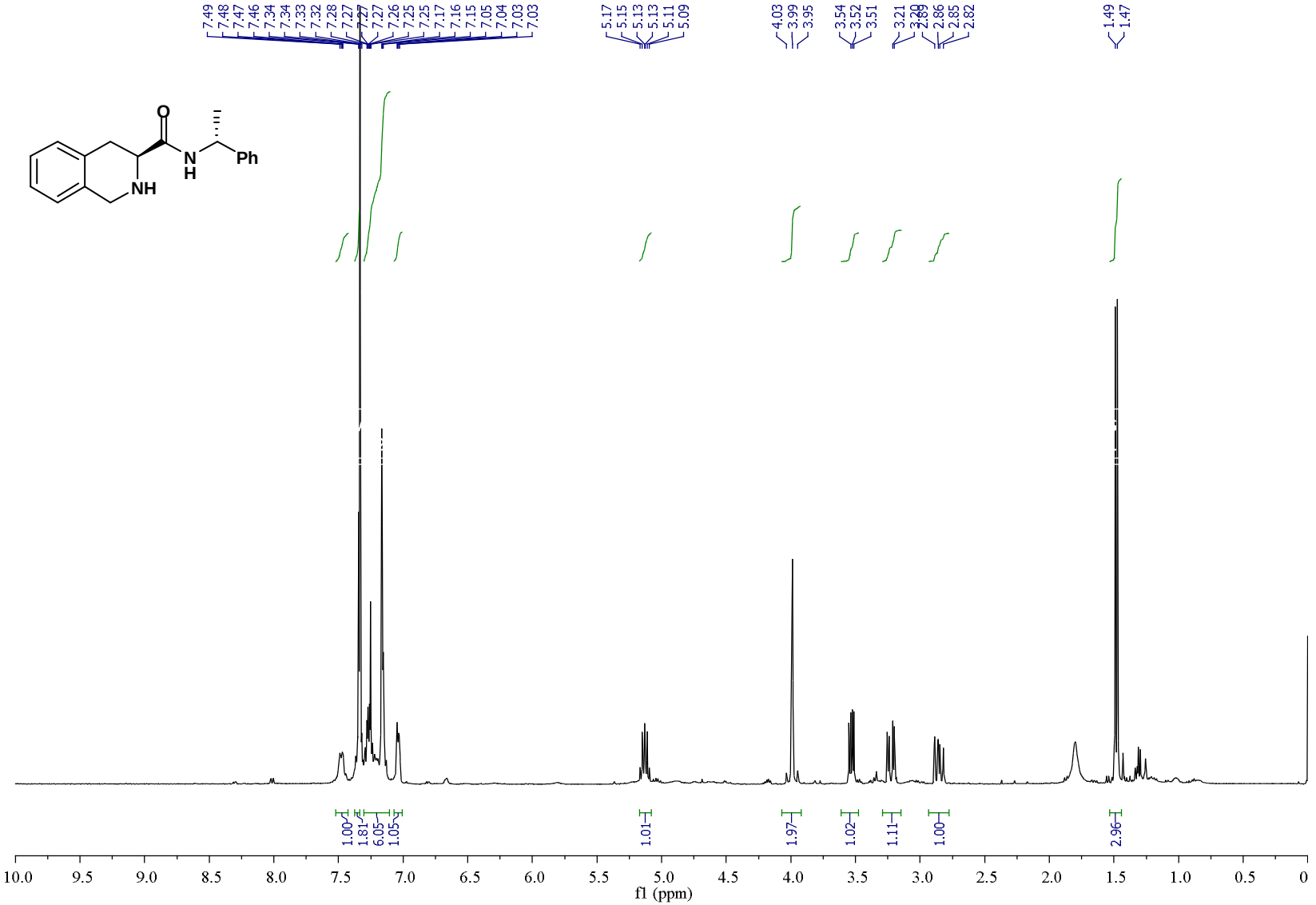
^{1}H NMR Spectrum of Compound 76f in d6-DMSO



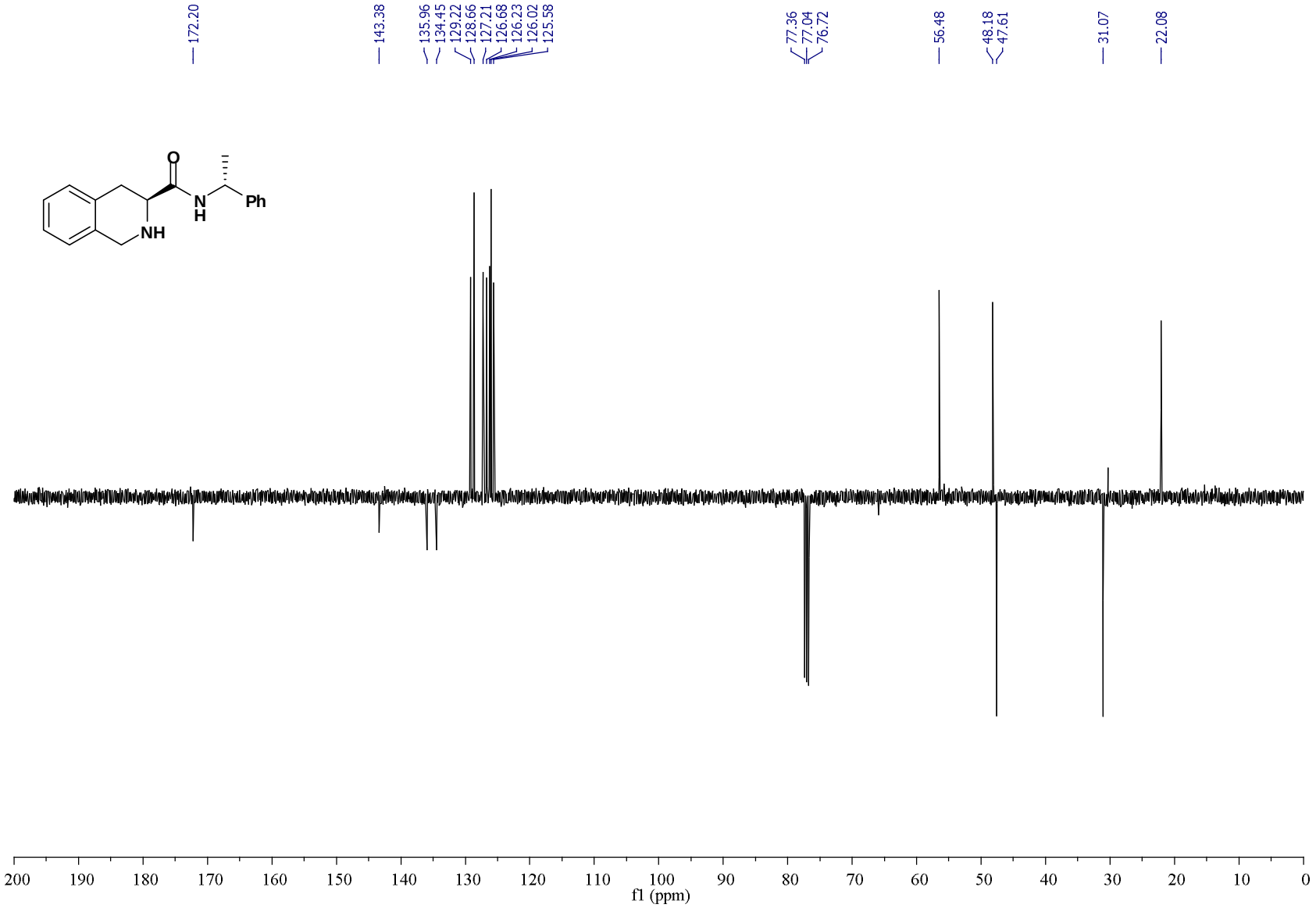
^{13}C NMR Spectrum of Compound 76f in d6-DMSO



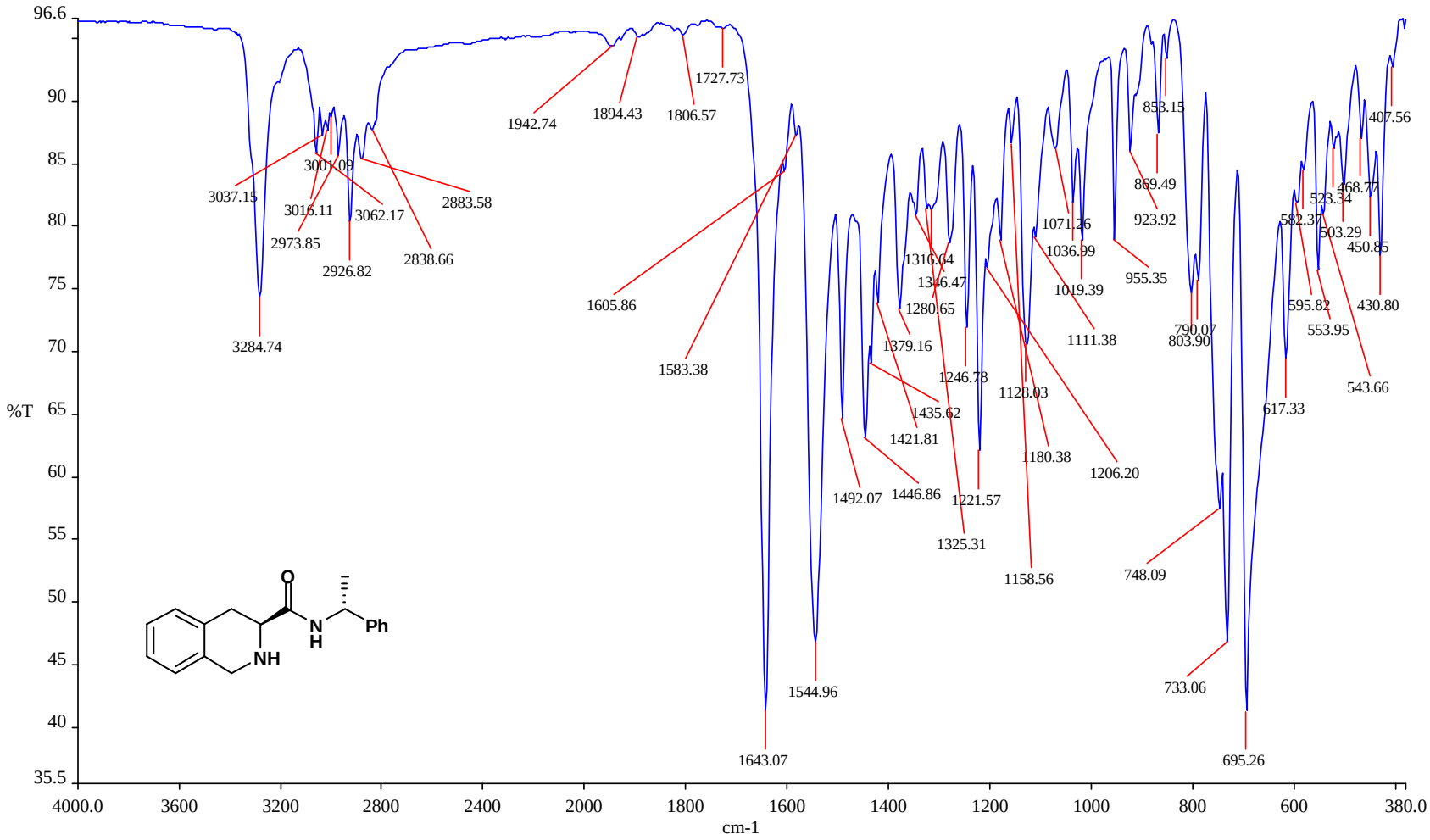
IR Spectrum of Compound 76f



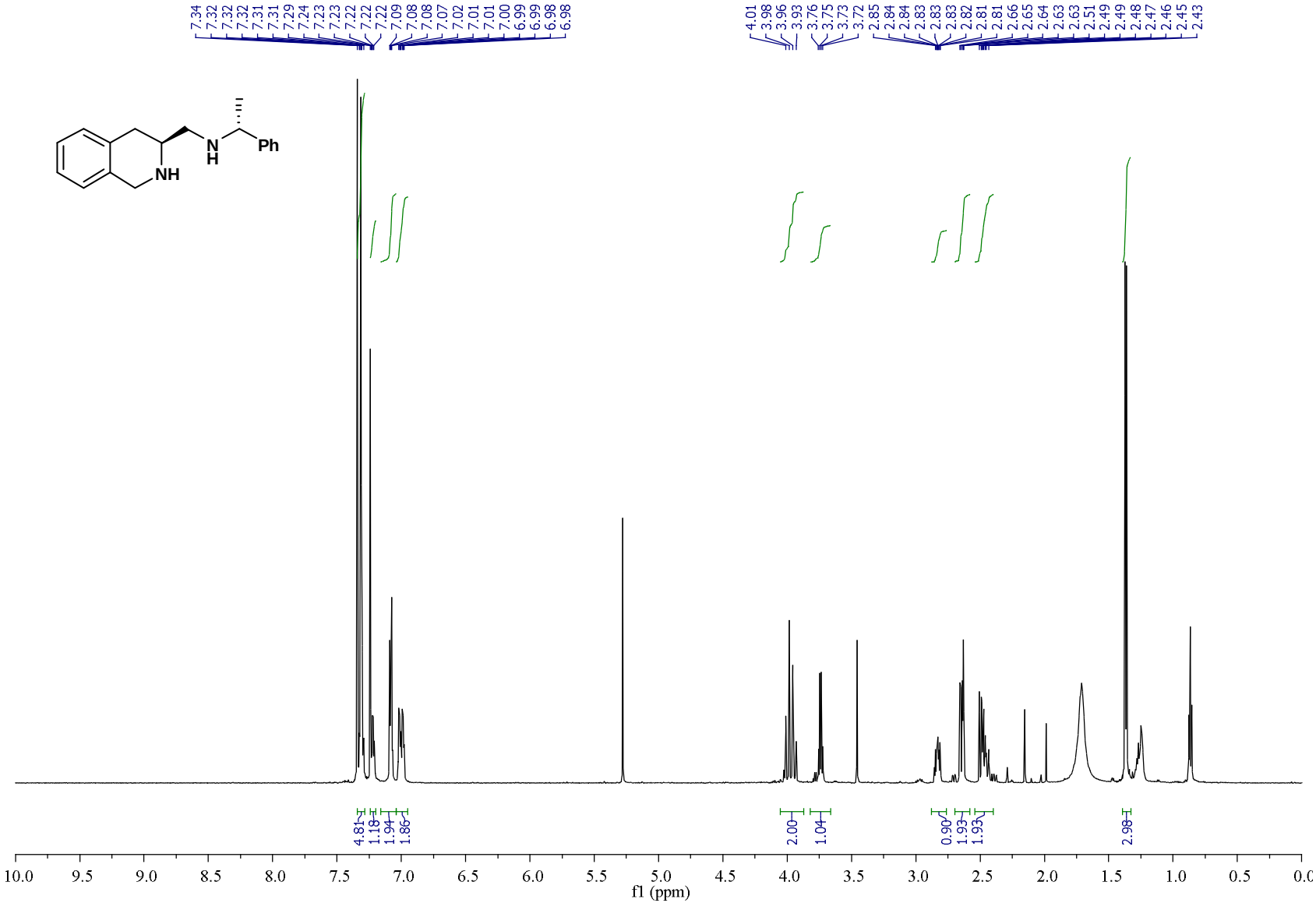
^{1}H NMR Spectrum of Compound 77f in $CDCl_3$



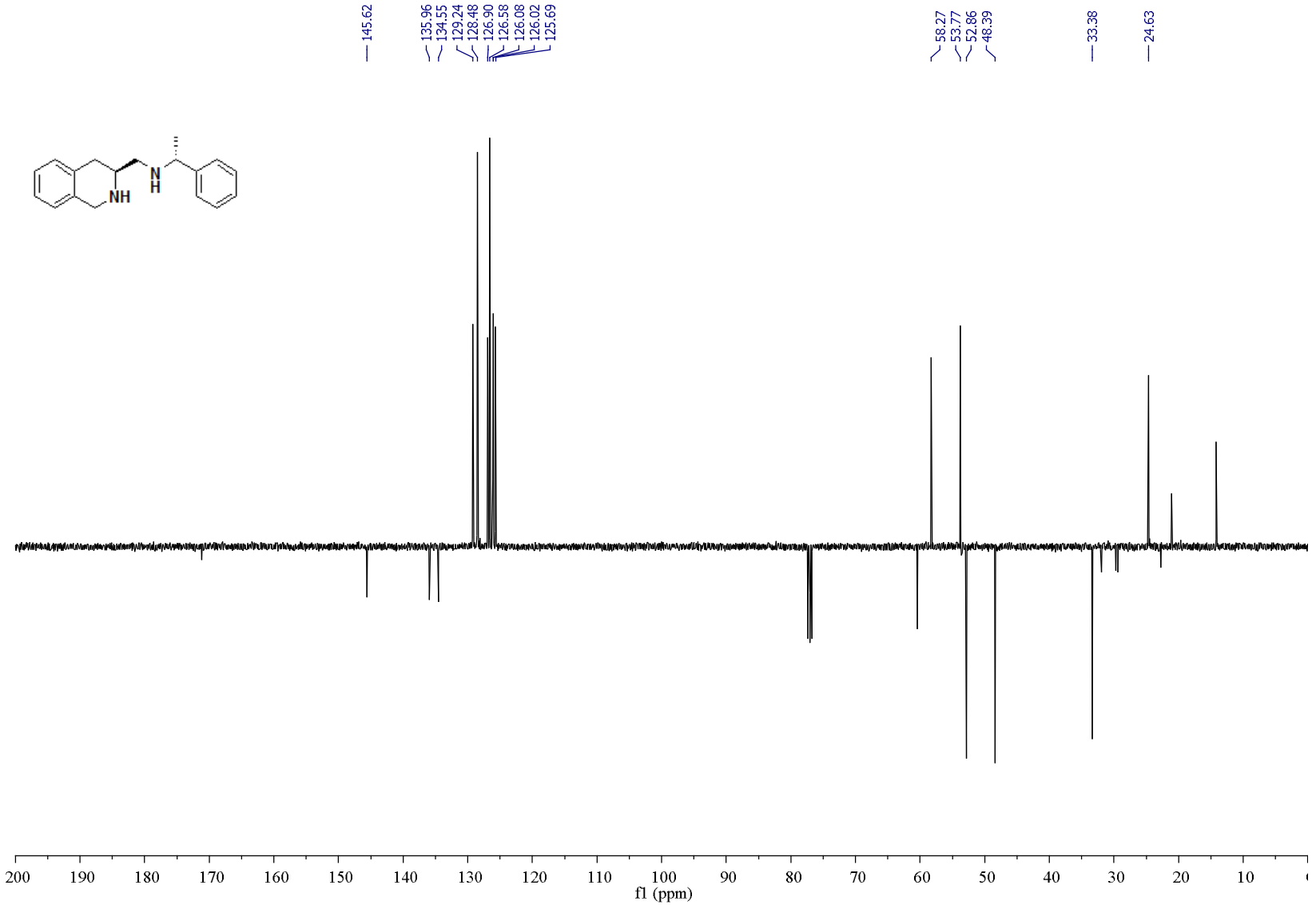
^{13}C NMR Spectrum of Compound 77f in $CDCl_3$



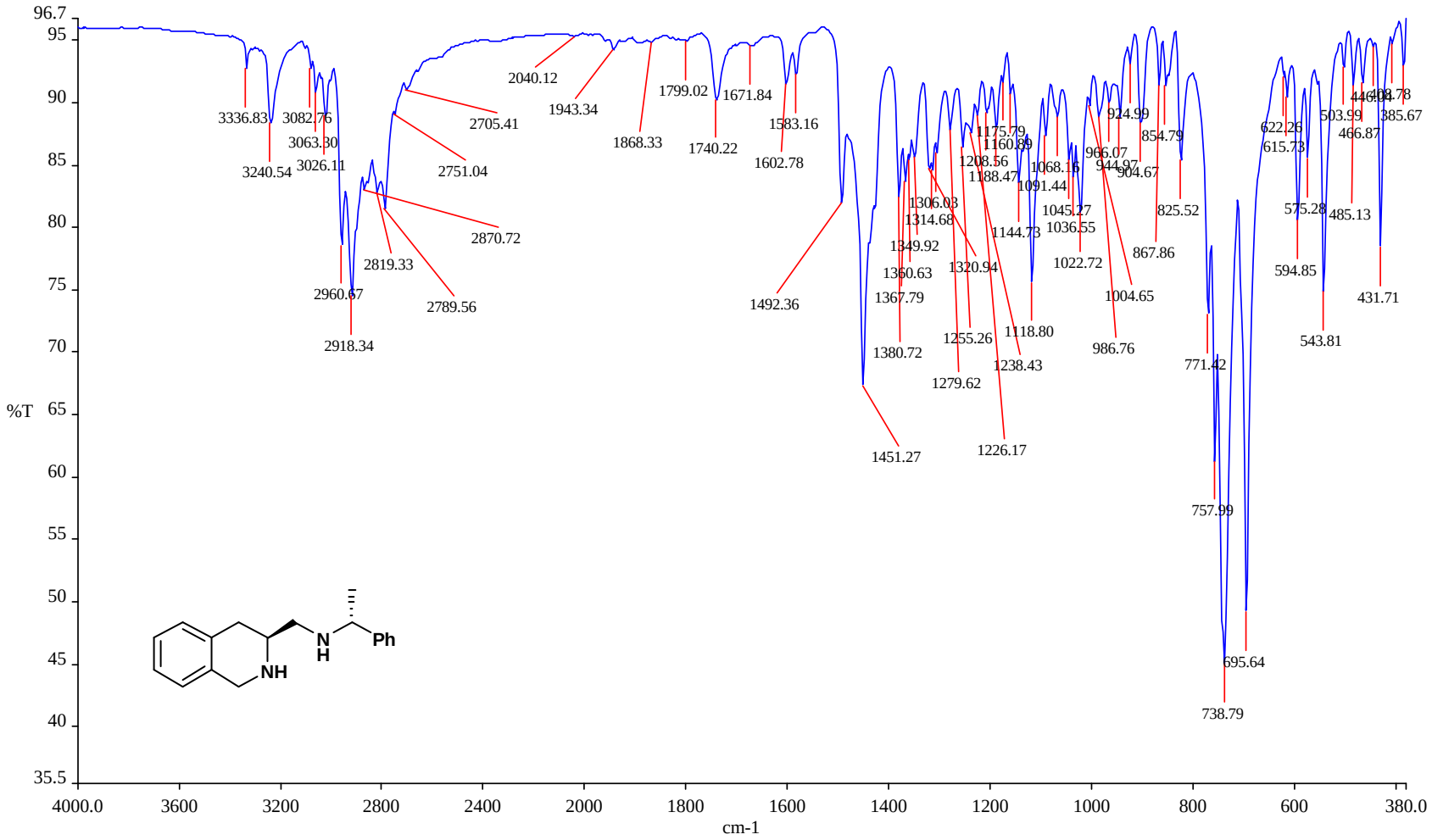
IR Spectrum of Compound 77f



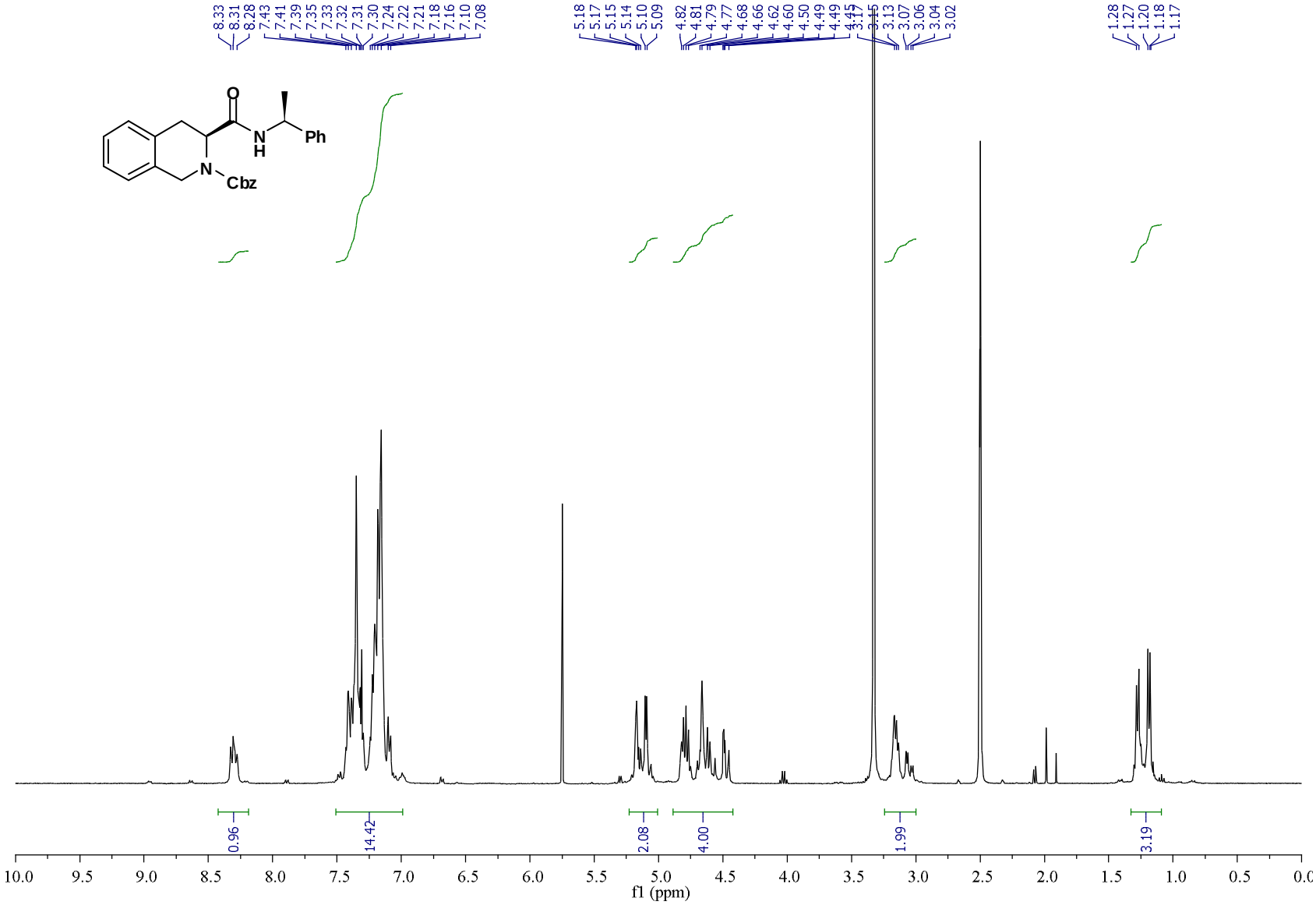
^{1}H NMR Spectrum of Compound 78f in $CDCl_3$



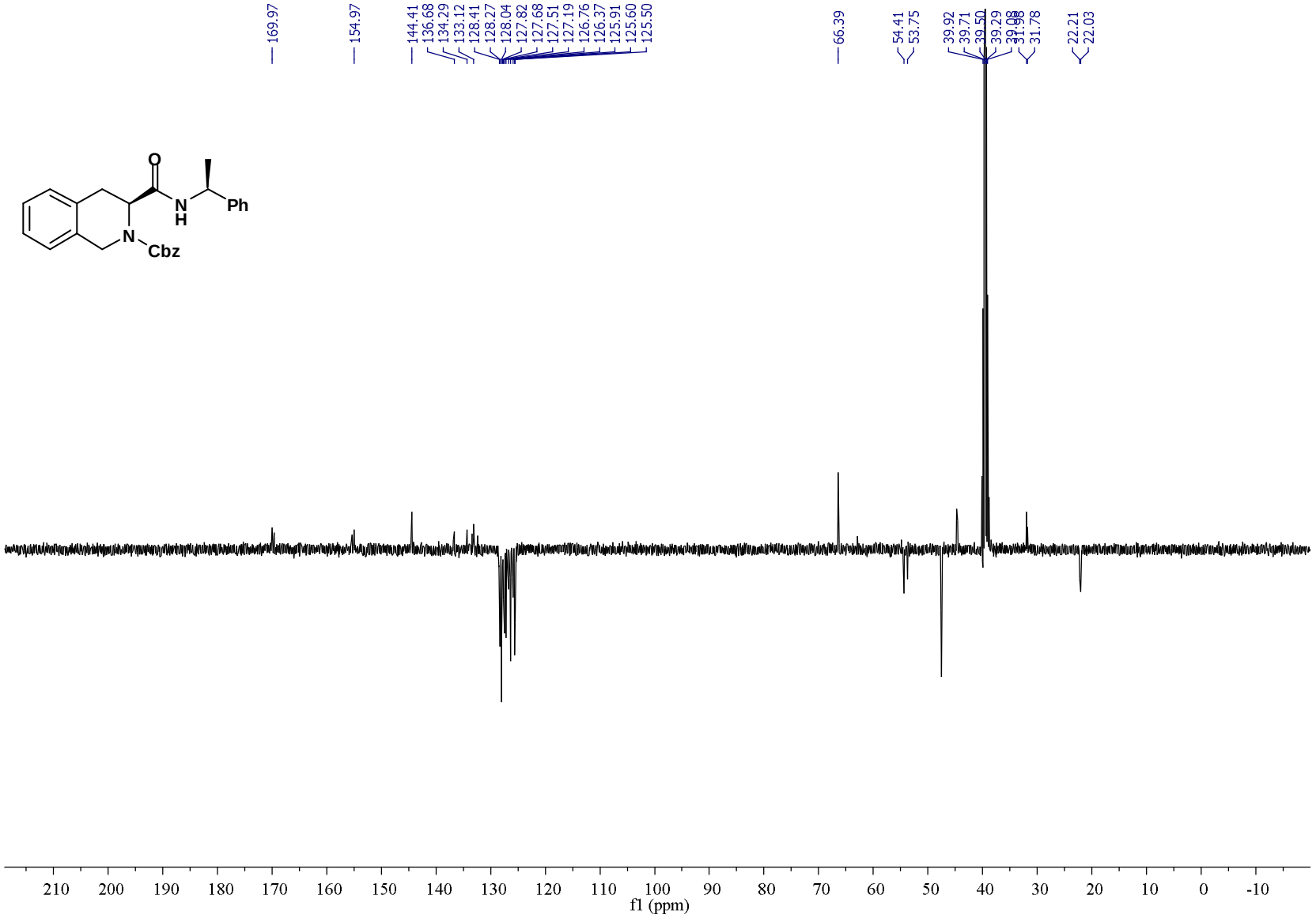
^{13}C NMR Spectrum of Compound 78f in $CDCl_3$



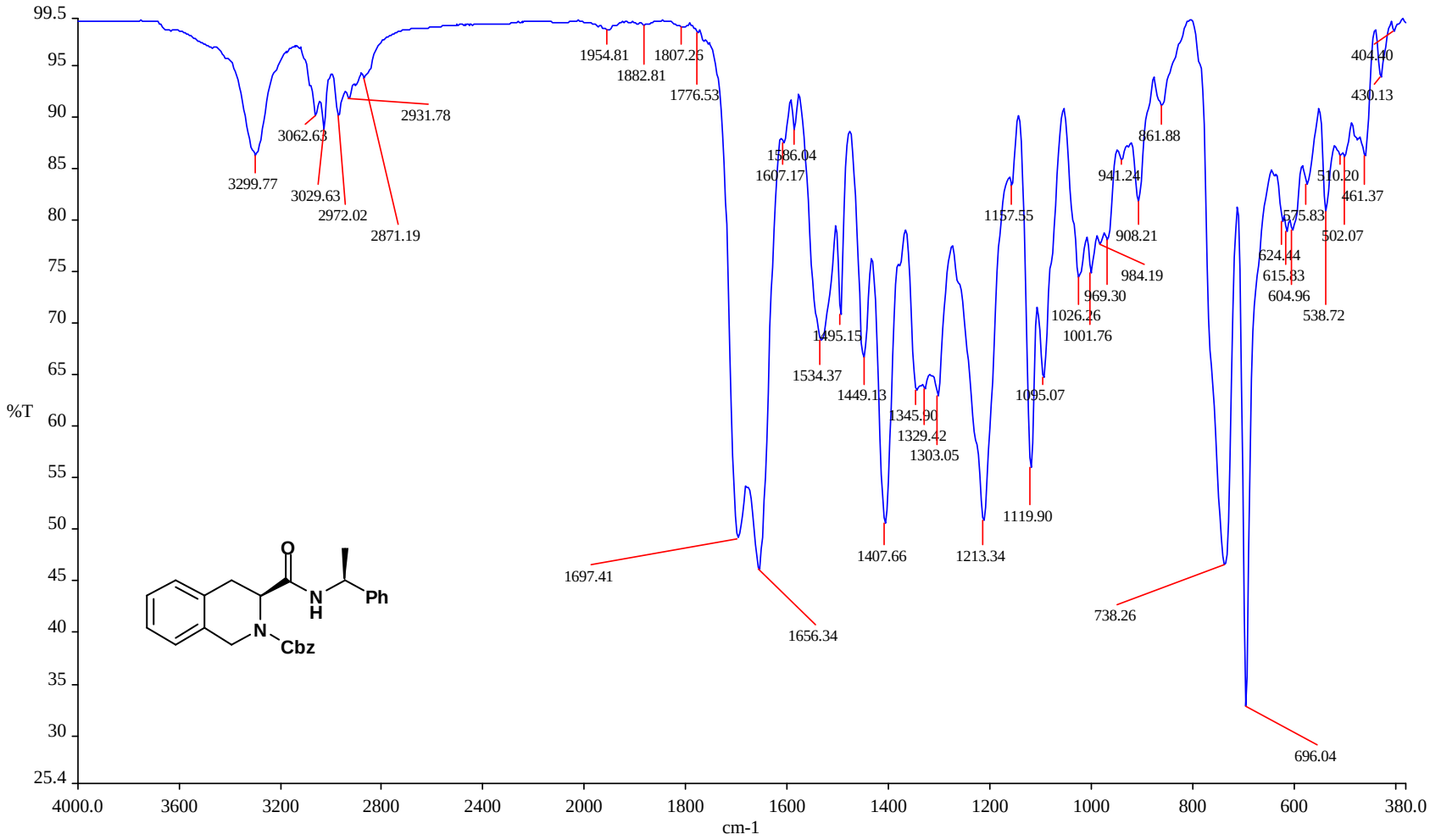
IR Spectrum of Compound 78f



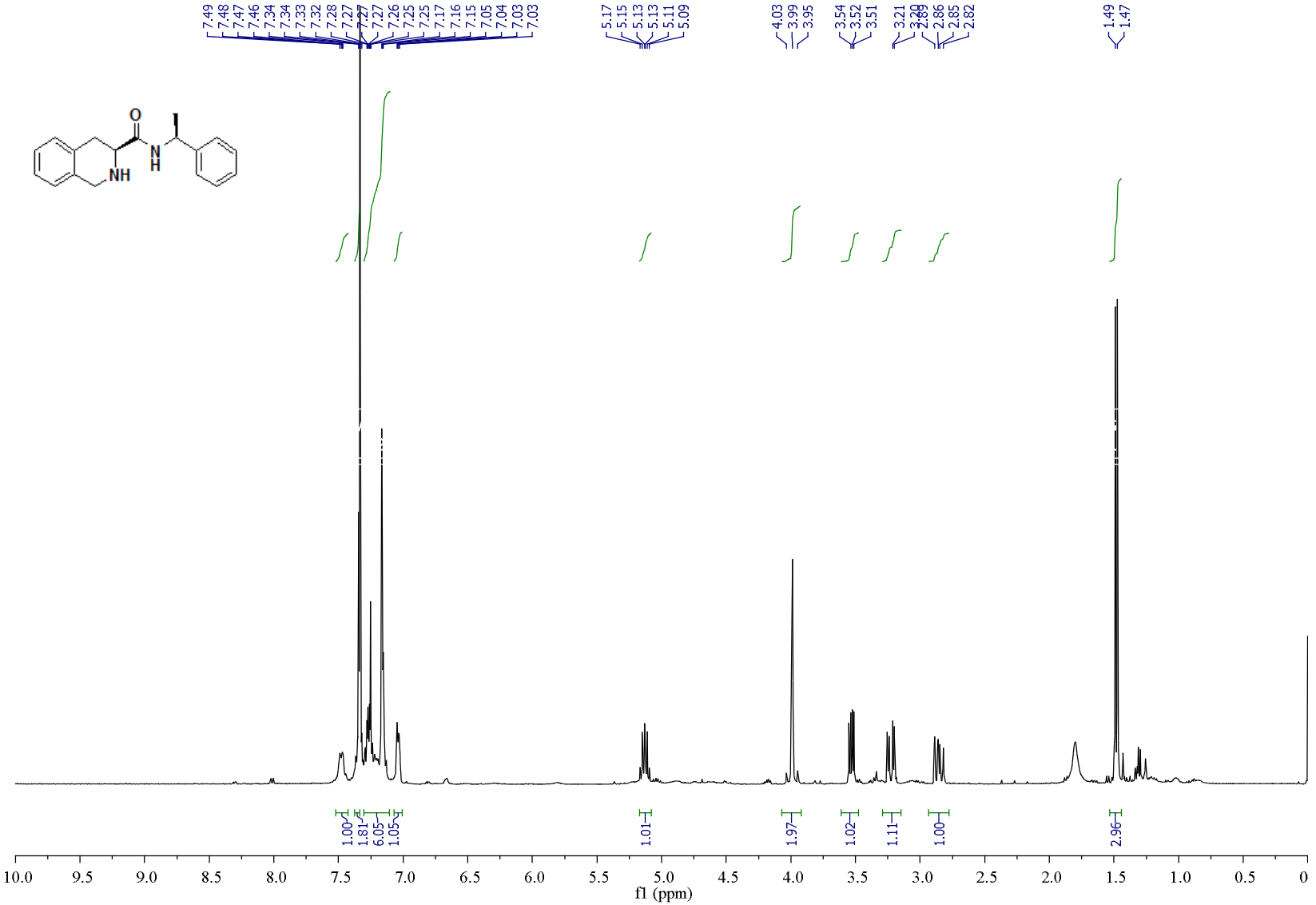
^{1}H NMR Spectrum of Compound 76g in d6-DMSO



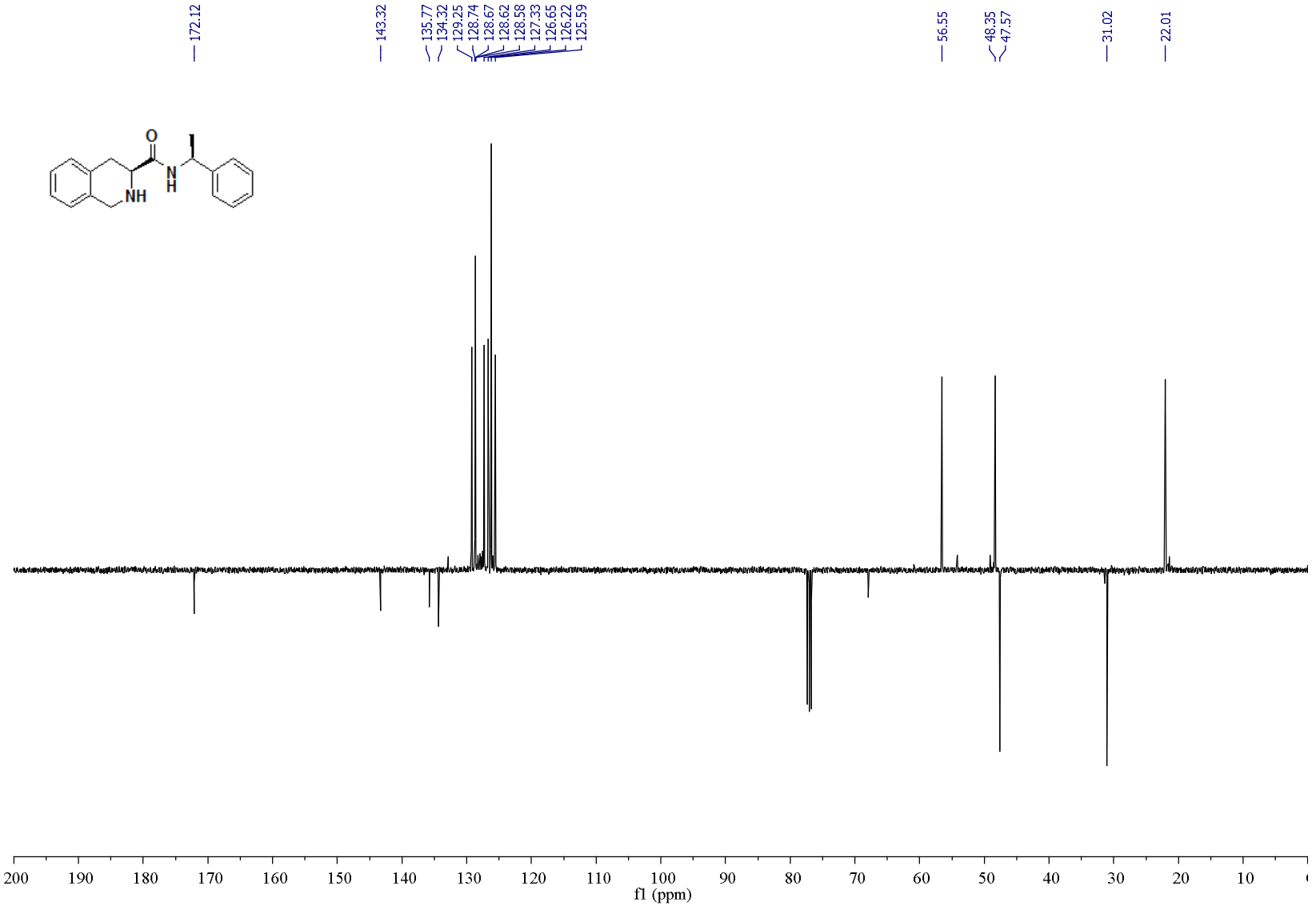
^{13}C NMR Spectrum of Compound 76g in d6-DMSO



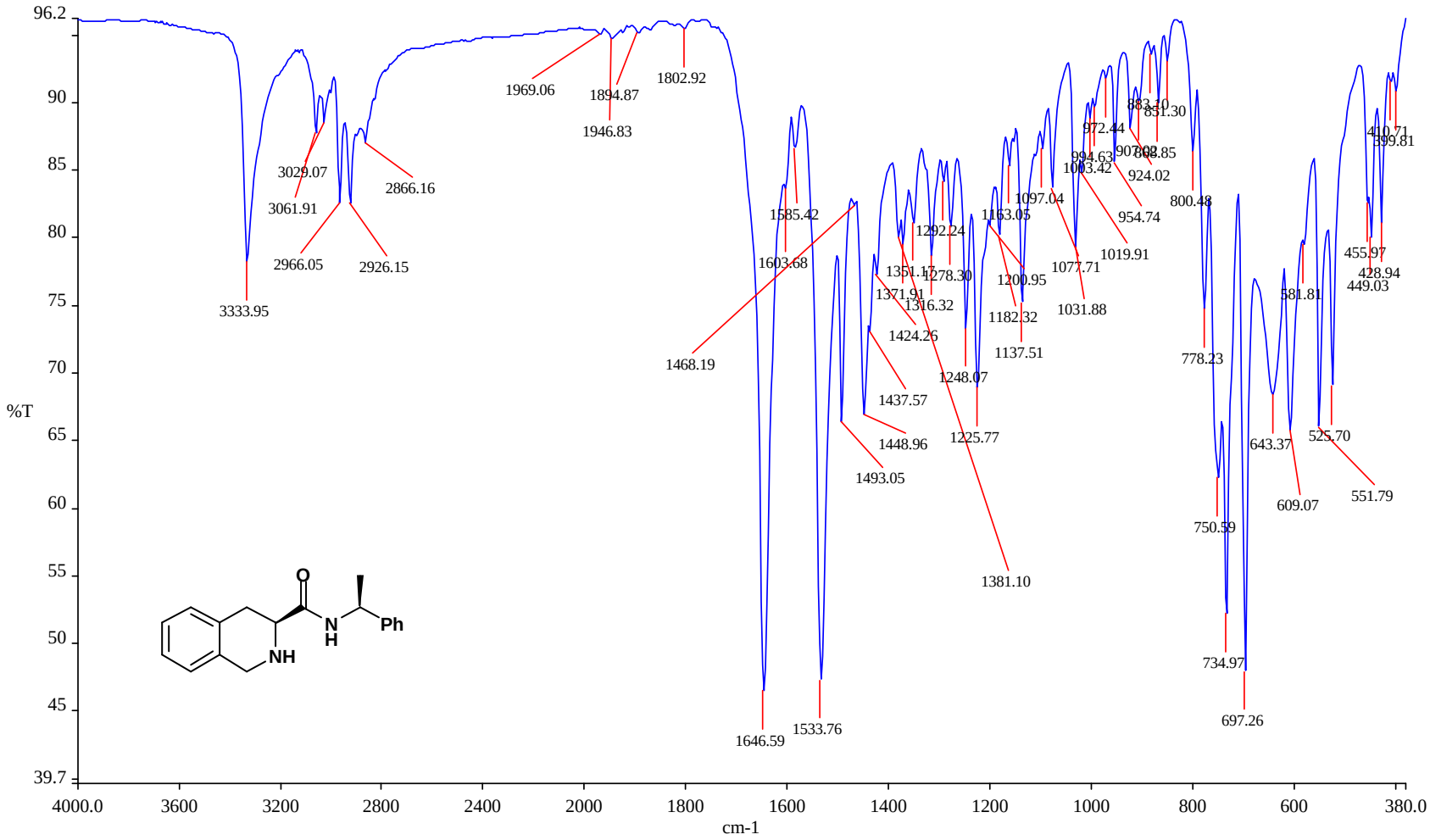
IR Spectrum of Compound 76g



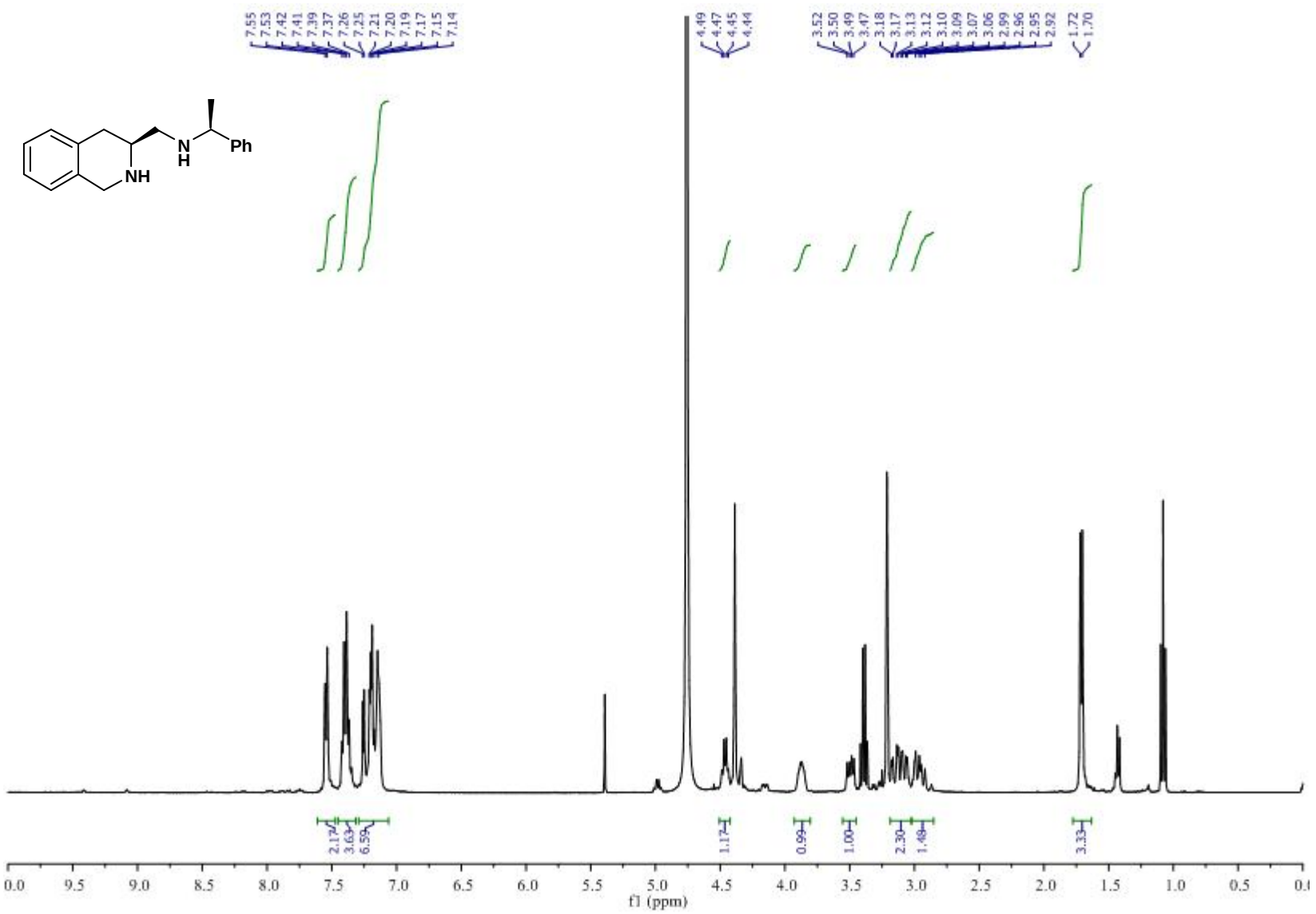
^{1}H NMR Spectrum of Compound 77g in $CDCl_3$



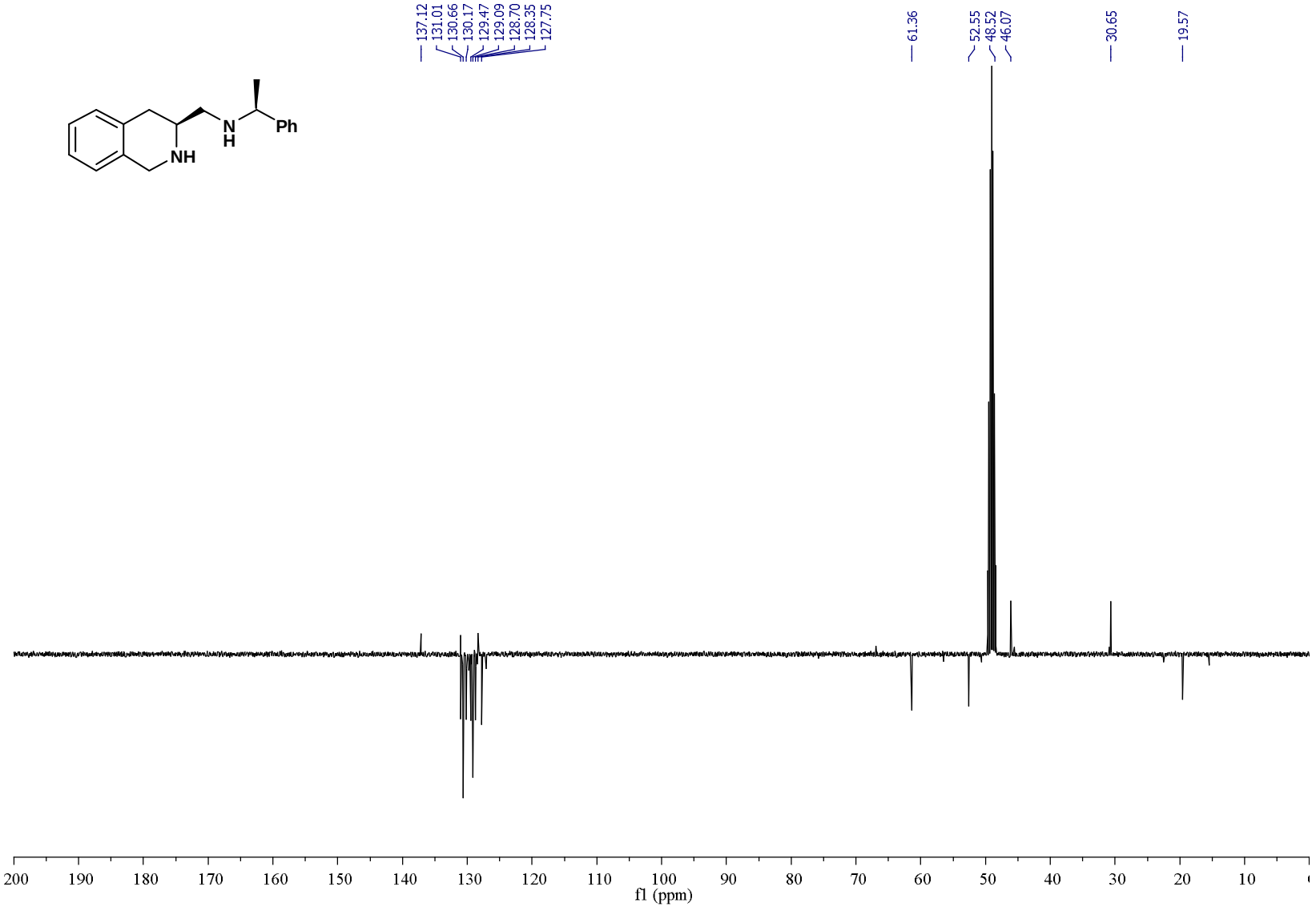
^{13}C NMR Spectrum of Compound 77g in $CDCl_3$



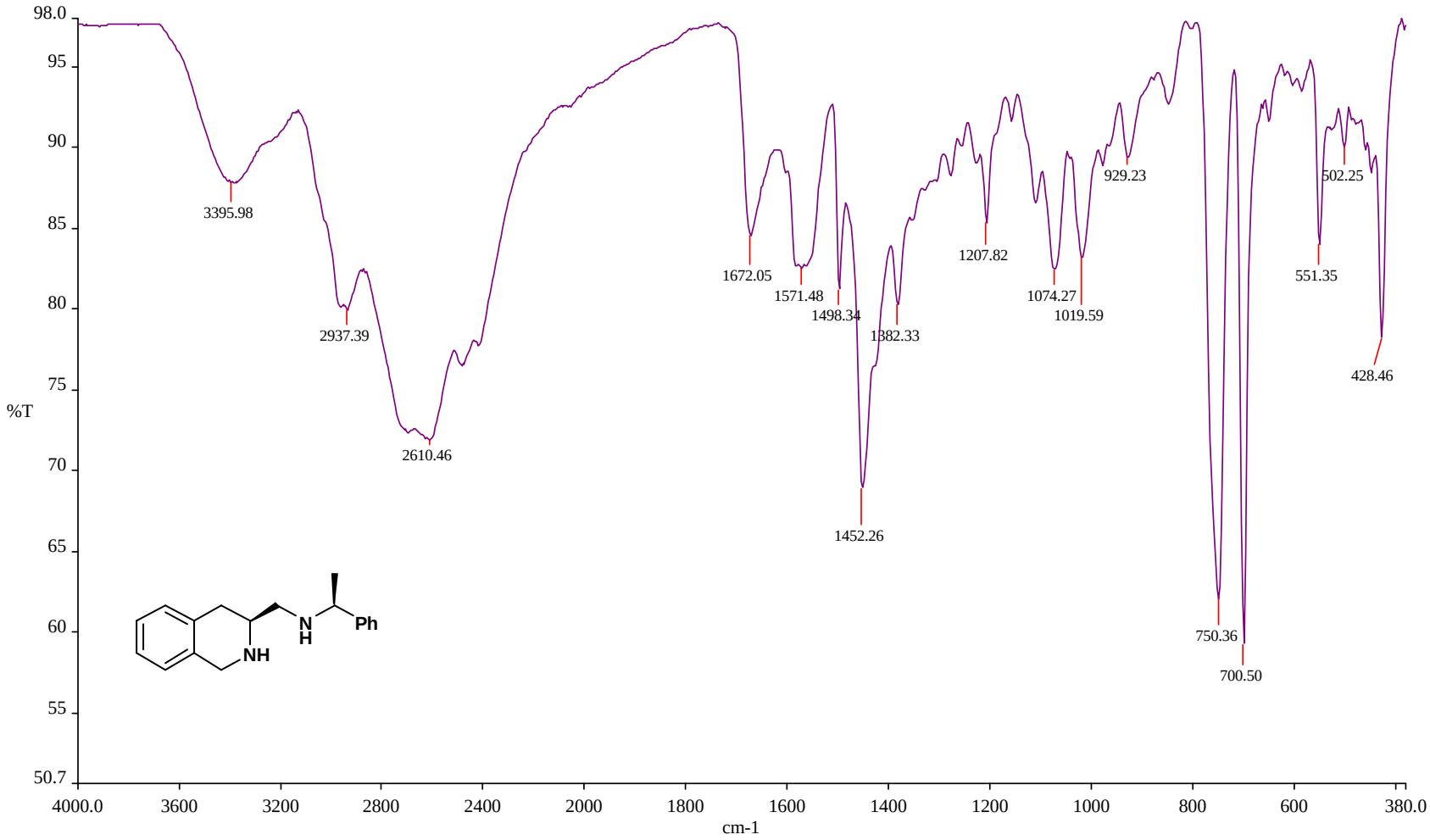
IR Spectrum of Compound 77g



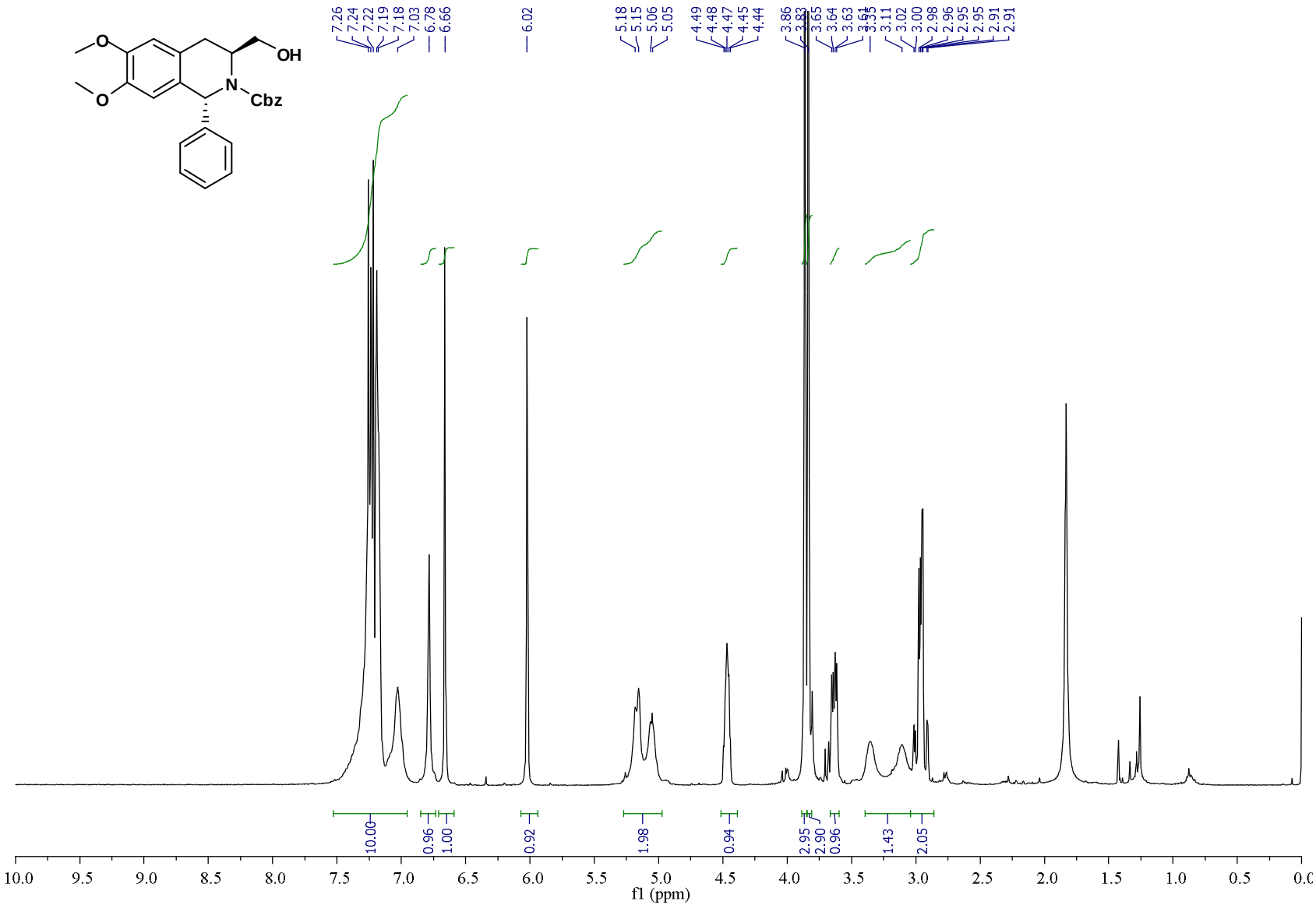
^{1}H NMR Spectrum of Compound 78g in MeOD



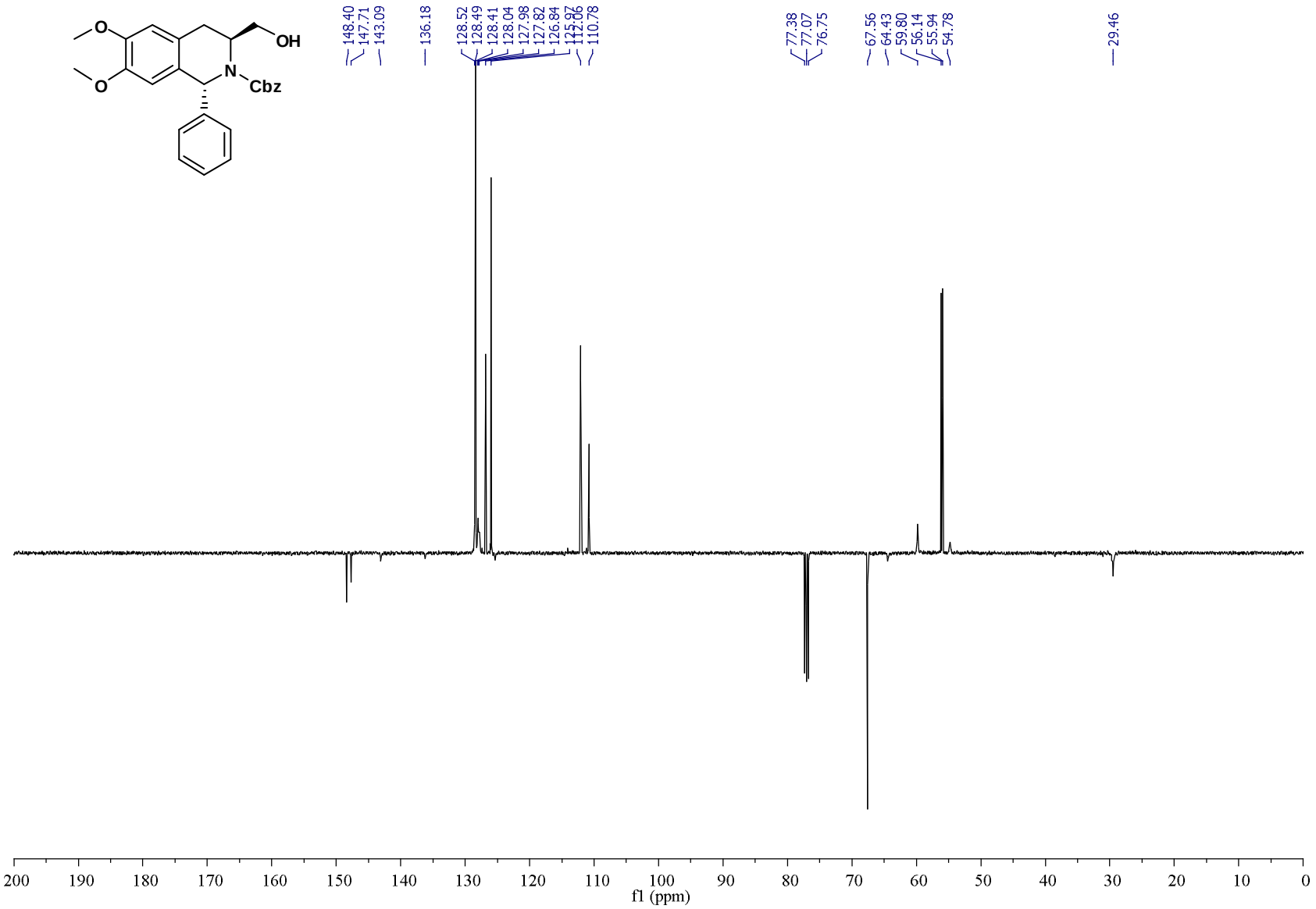
^{13}C NMR Spectrum of Compound 78g in MeOD



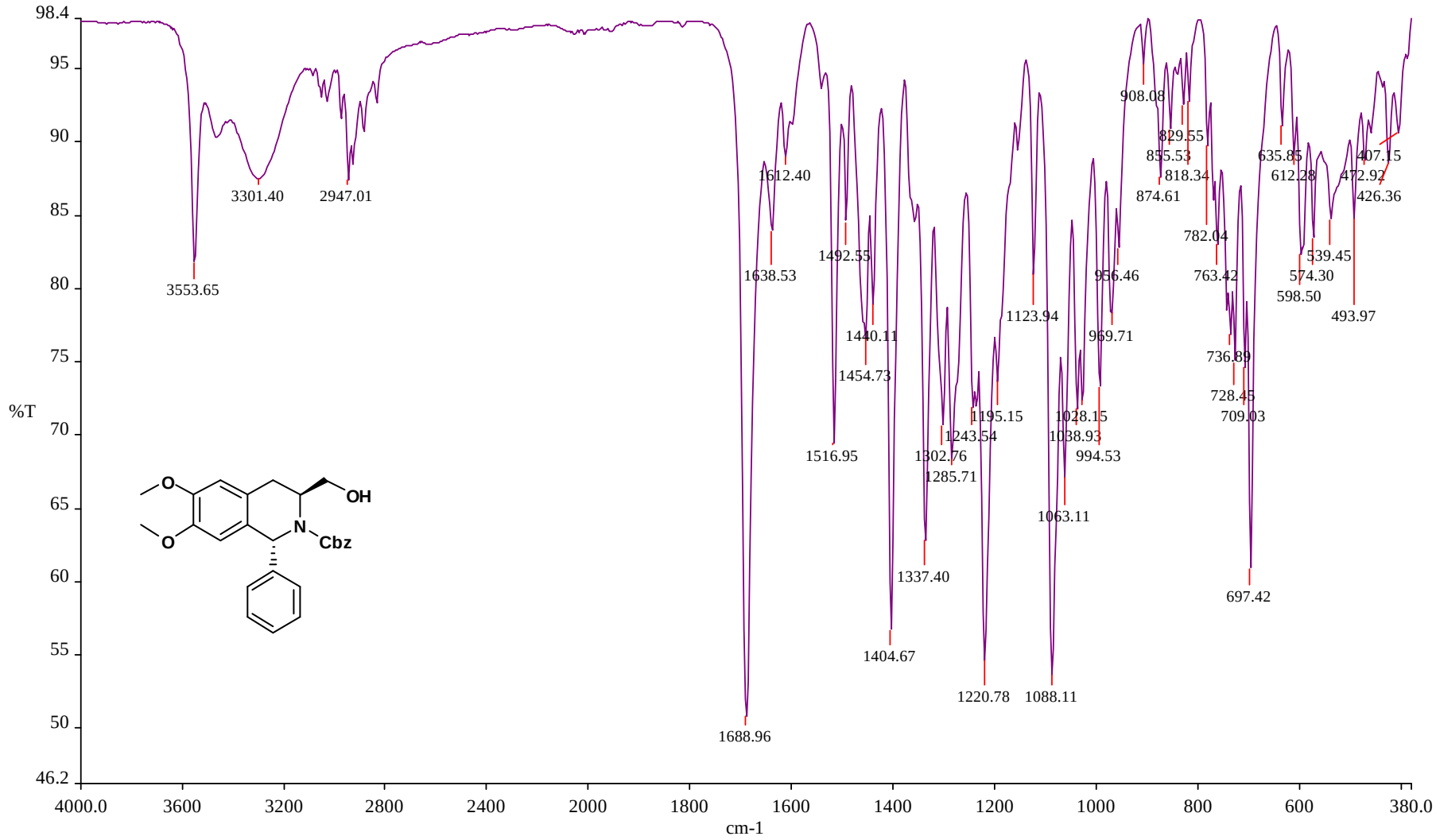
IR Spectrum of Compound 78g



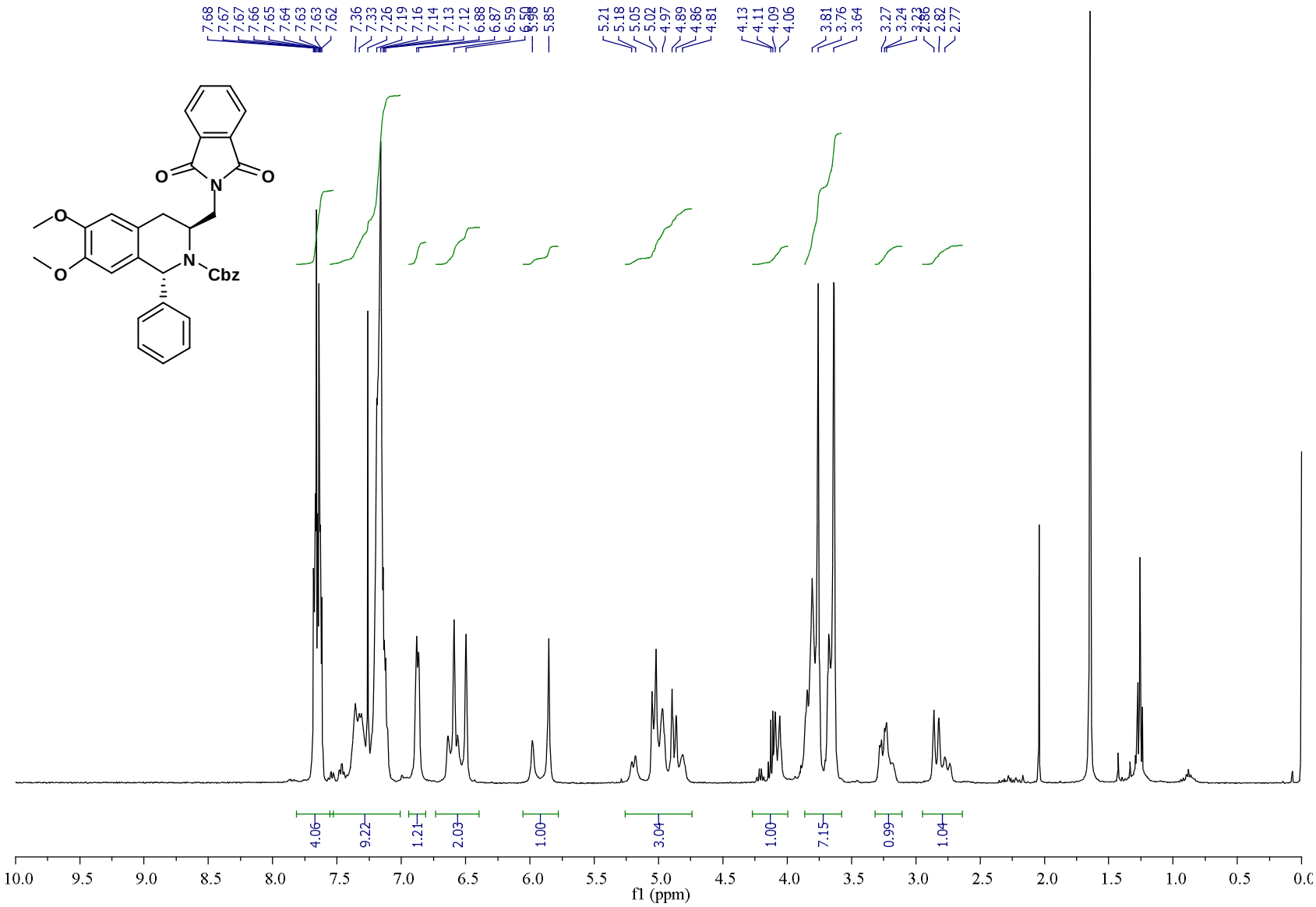
^{1}H NMR Spectrum of Compound 79 in $CDCl_3$



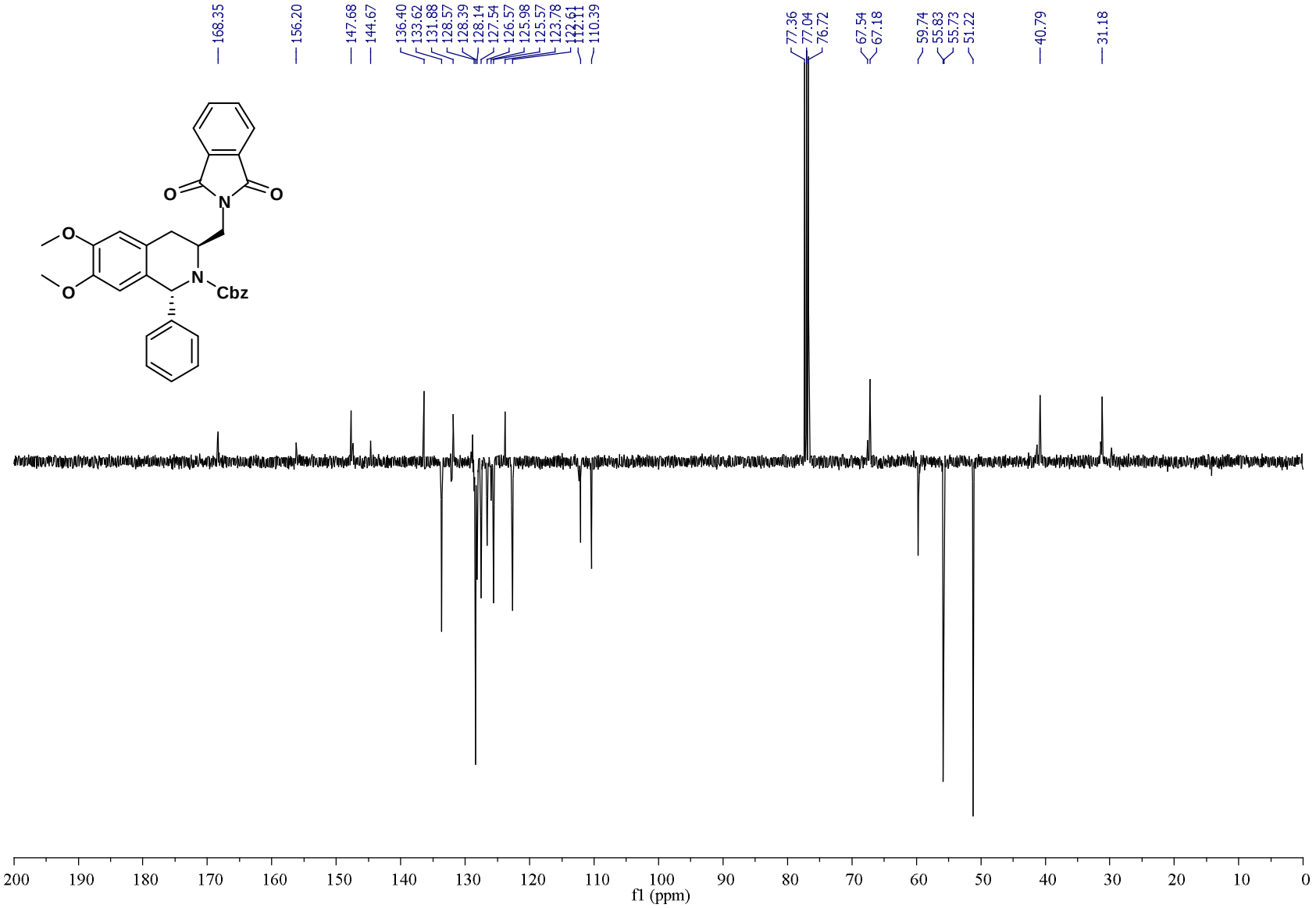
^{13}C NMR Spectrum of Compound 79 in $CDCl_3$



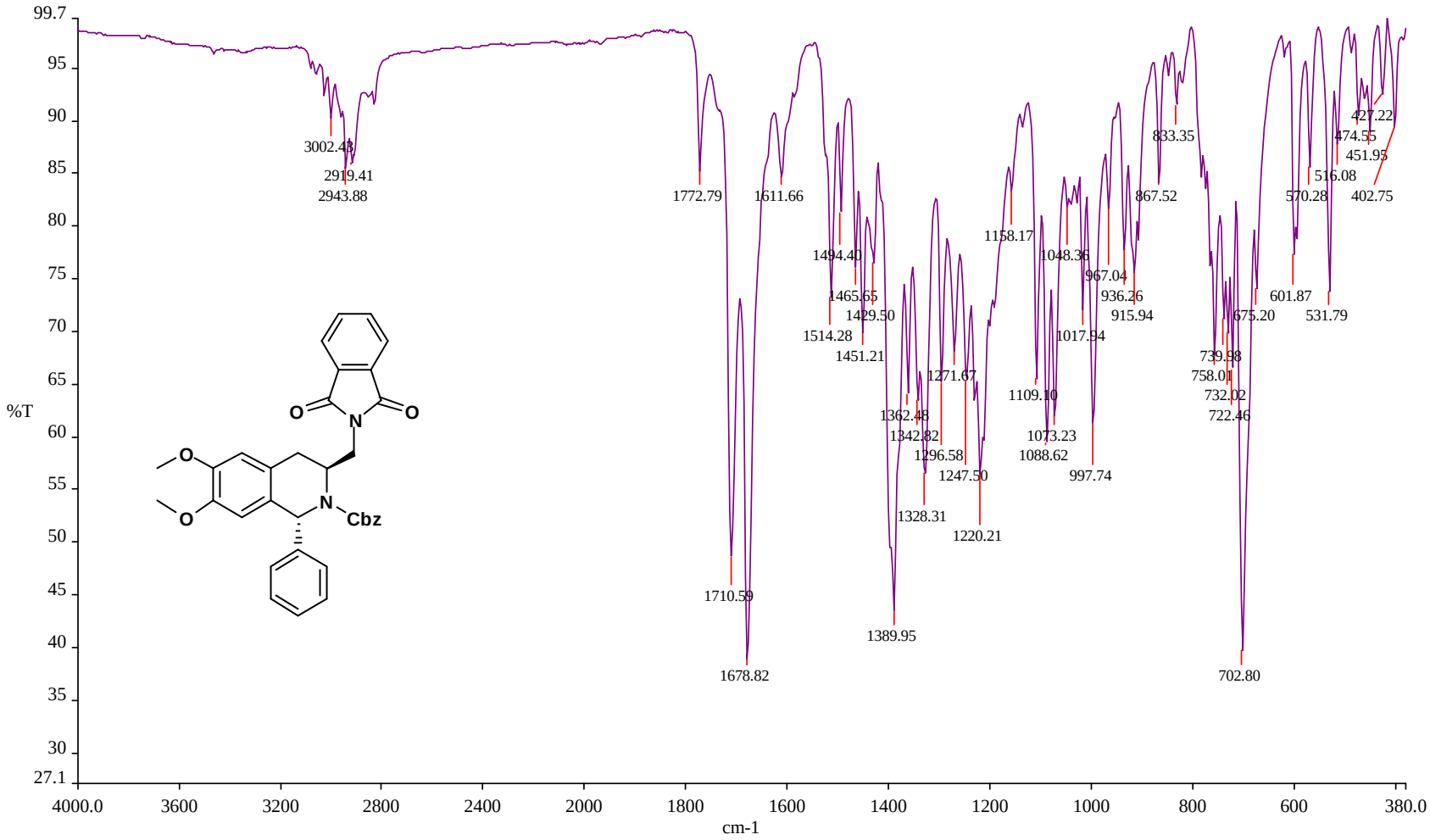
IR Spectrum of Compound 79



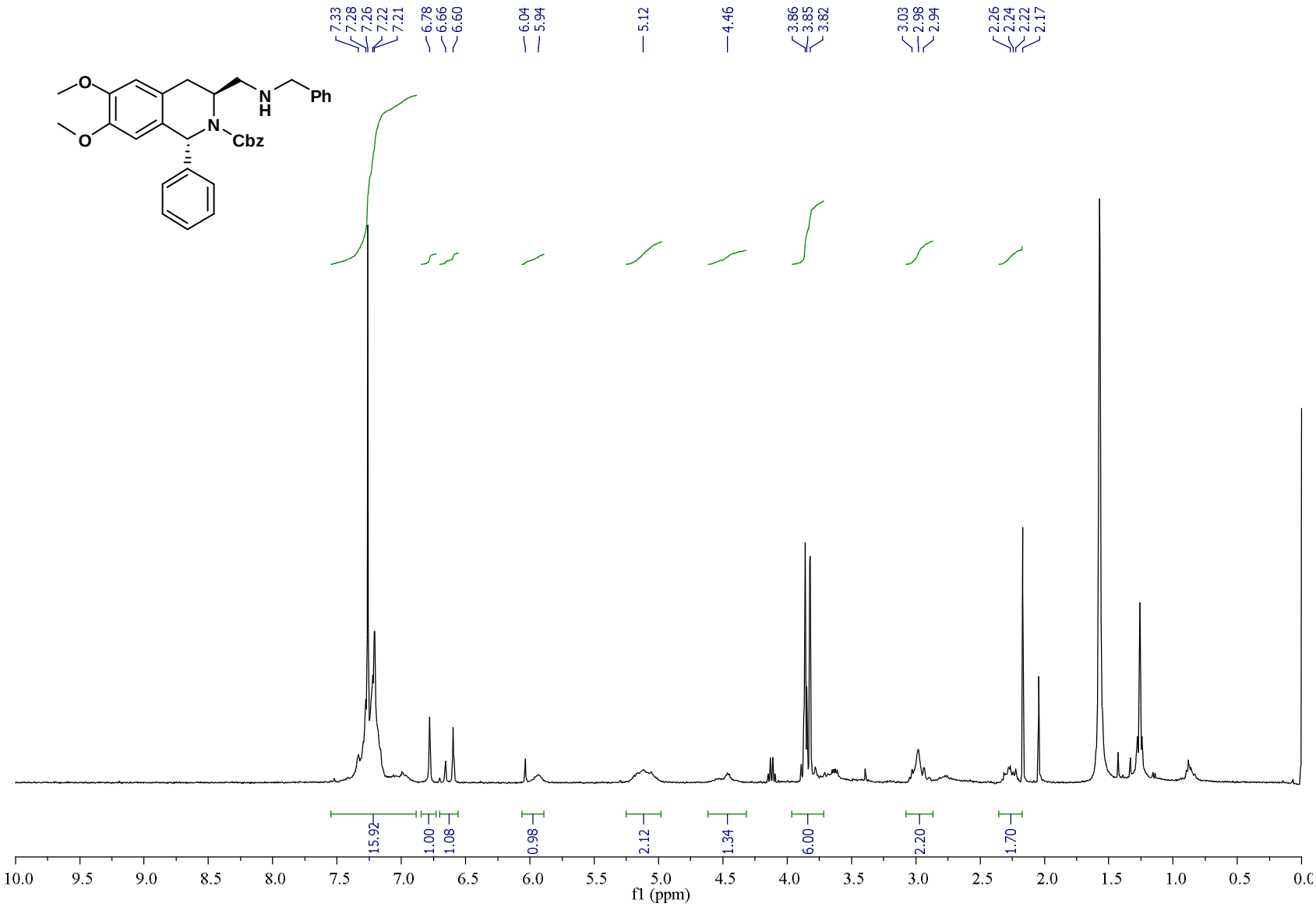
^{1}H NMR Spectrum of Compound 84 in $CDCl_3$



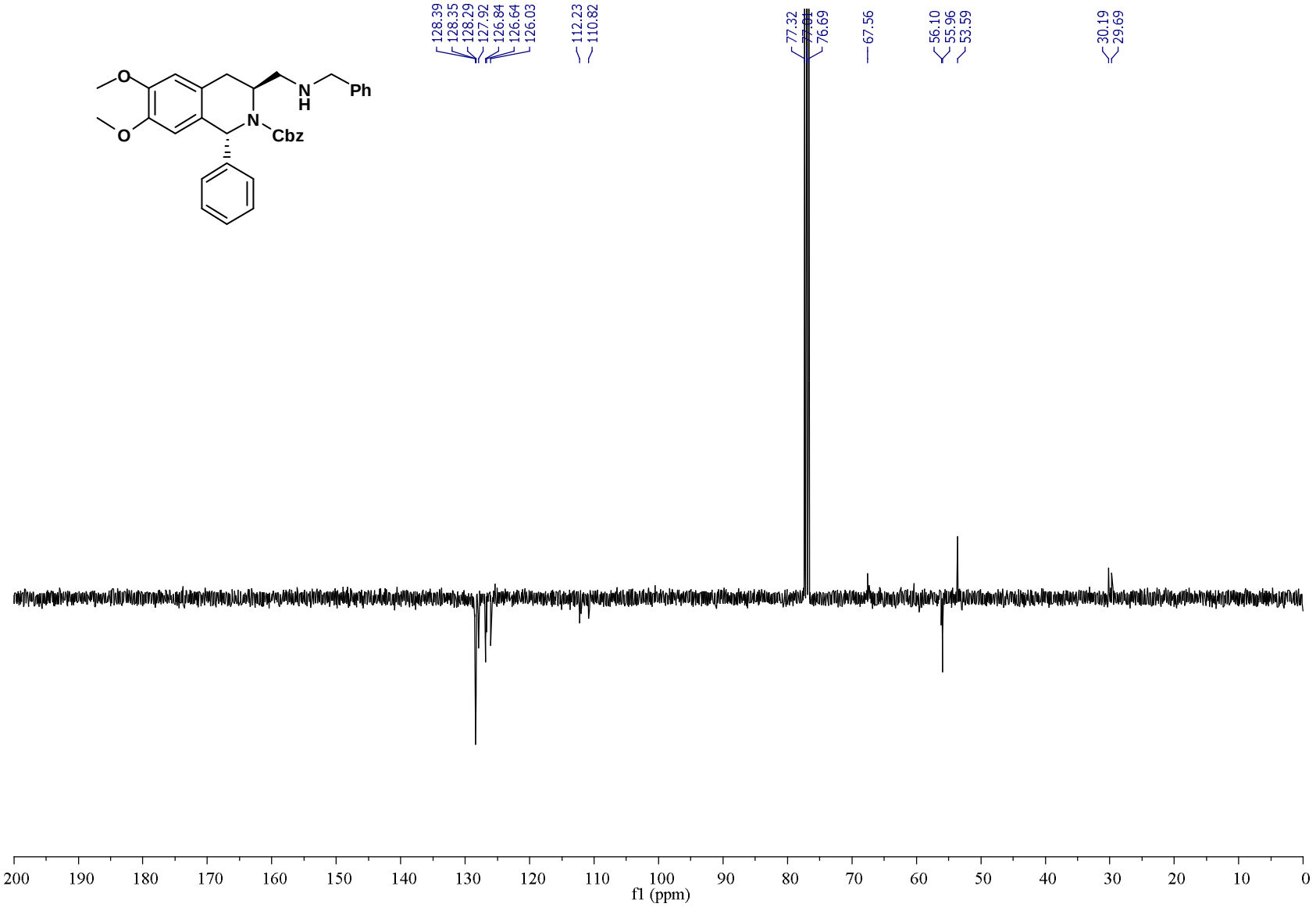
^{13}C NMR Spectrum of Compound 84 in $CDCl_3$



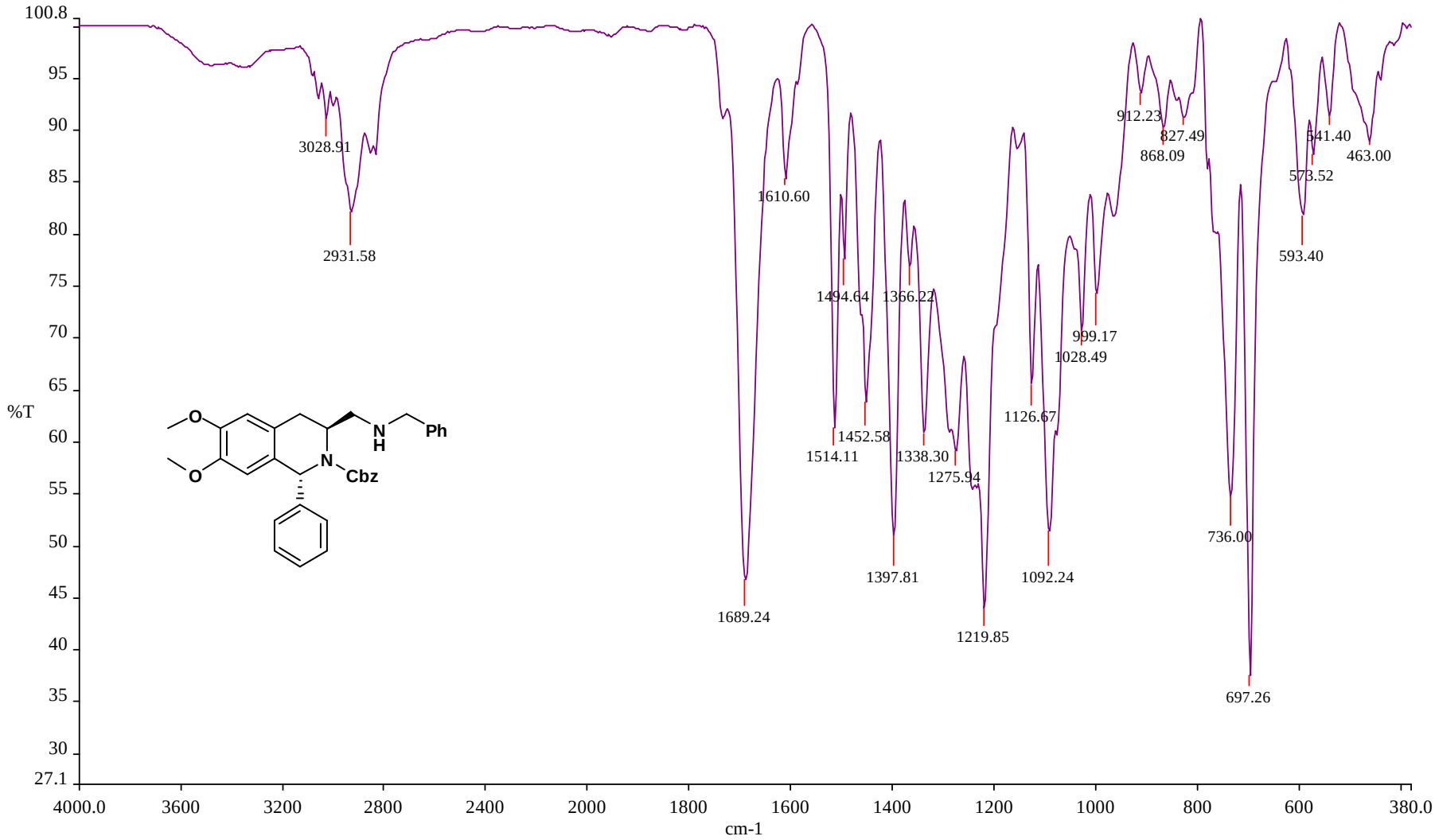
IR Spectrum of Compound 84



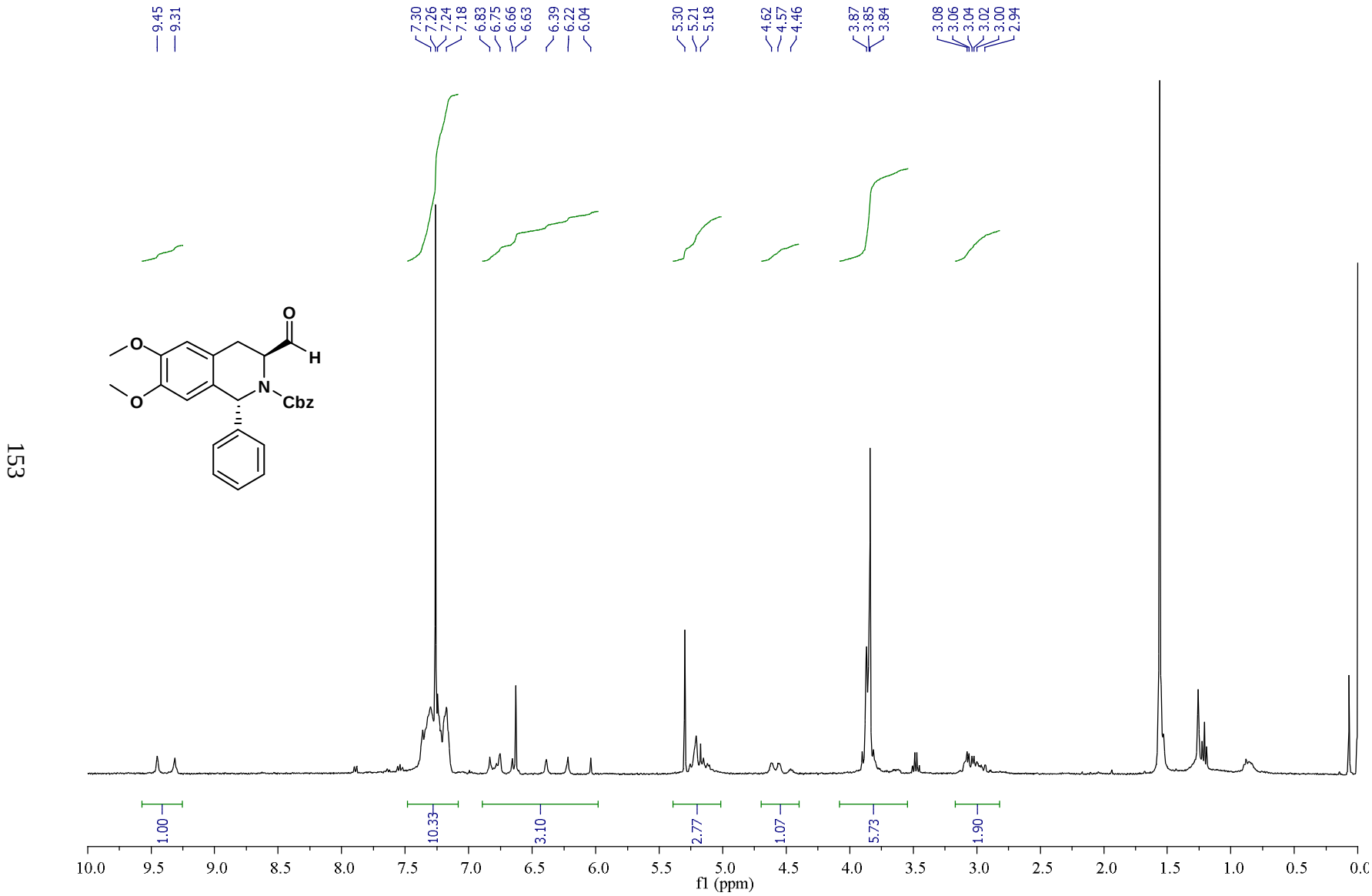
^{1}H NMR Spectrum of Compound 86 in $CDCl_3$



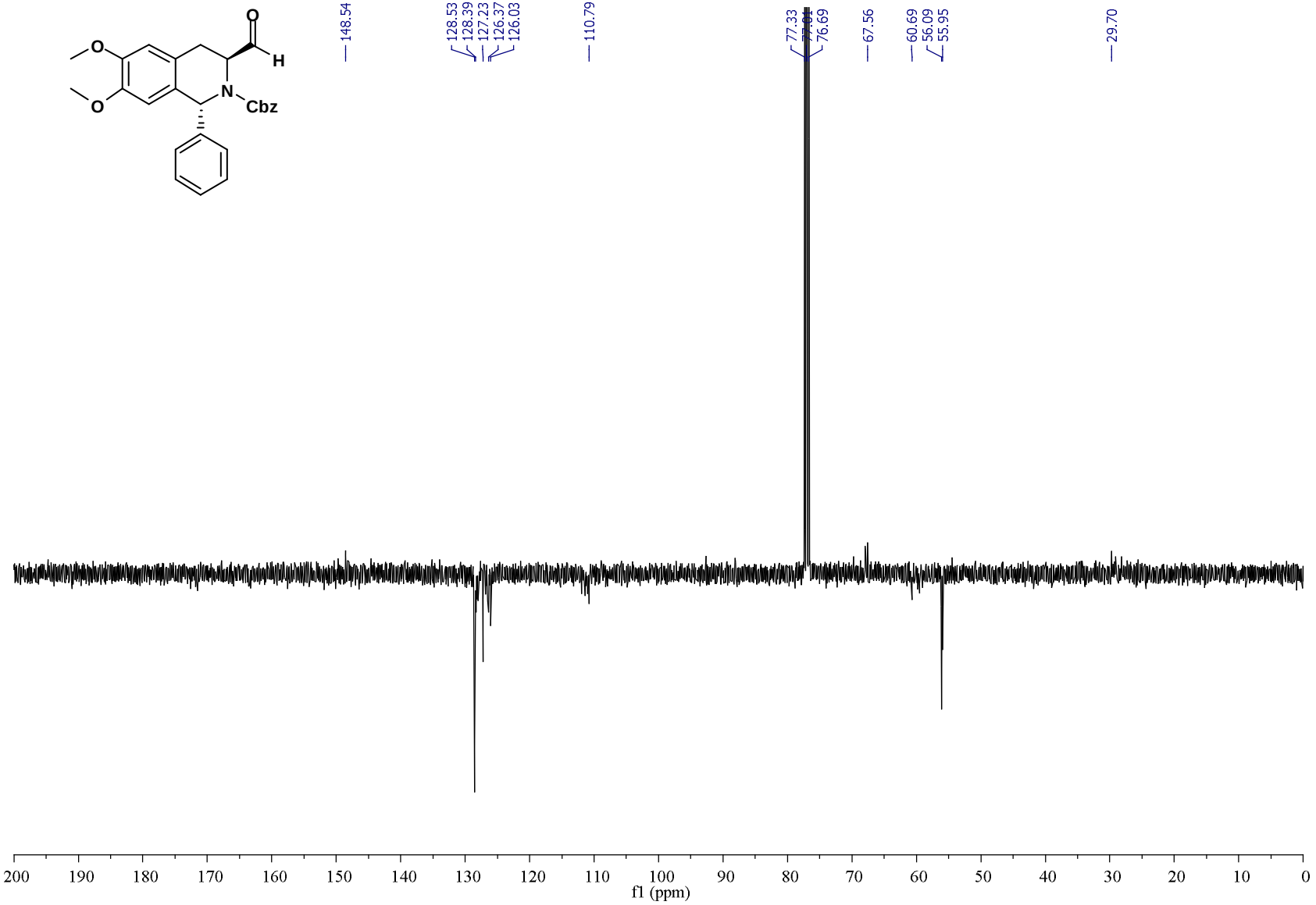
^{13}C NMR Spectrum of Compound 86 in $CDCl_3$



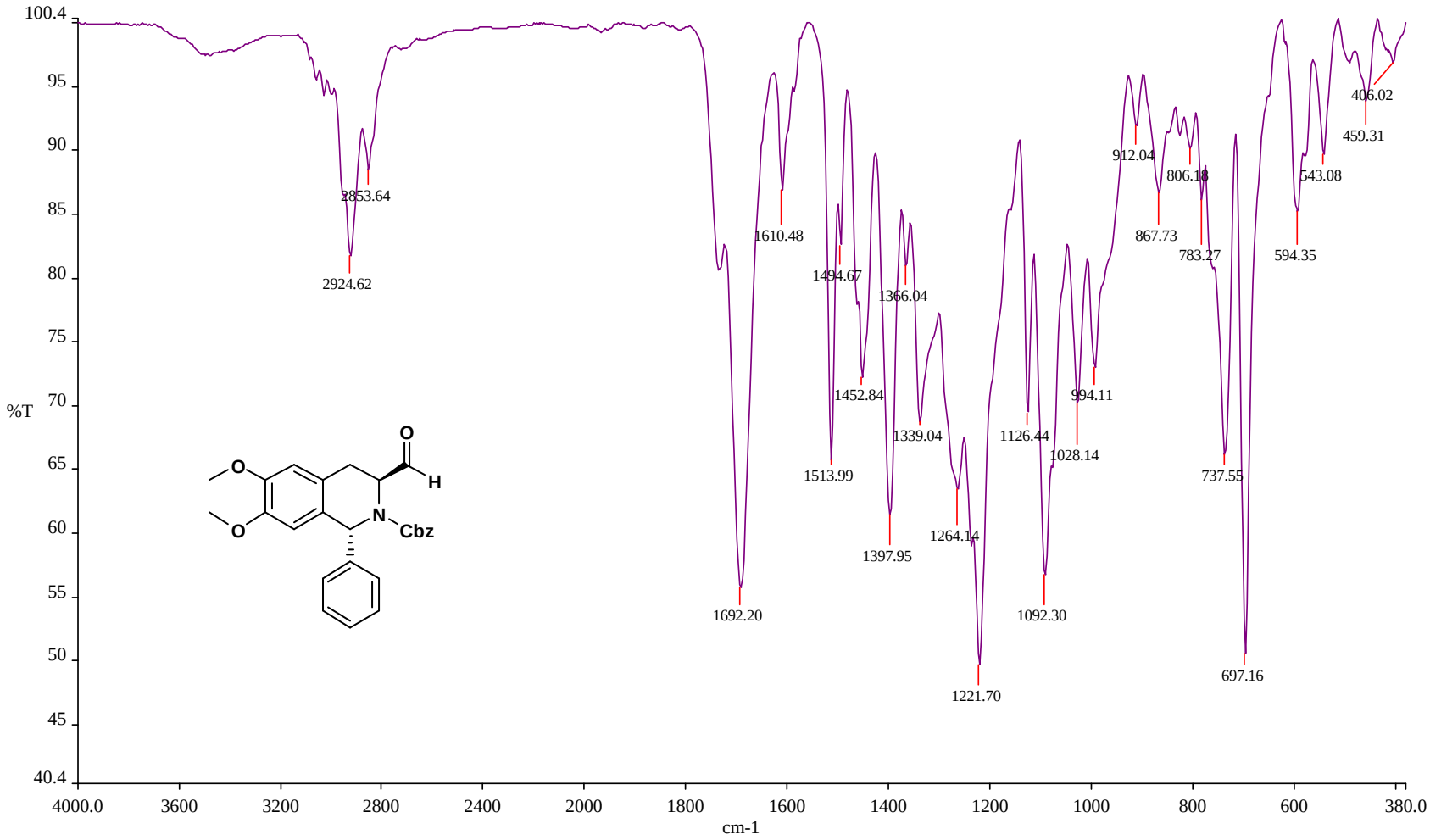
IR Spectrum of Compound 86



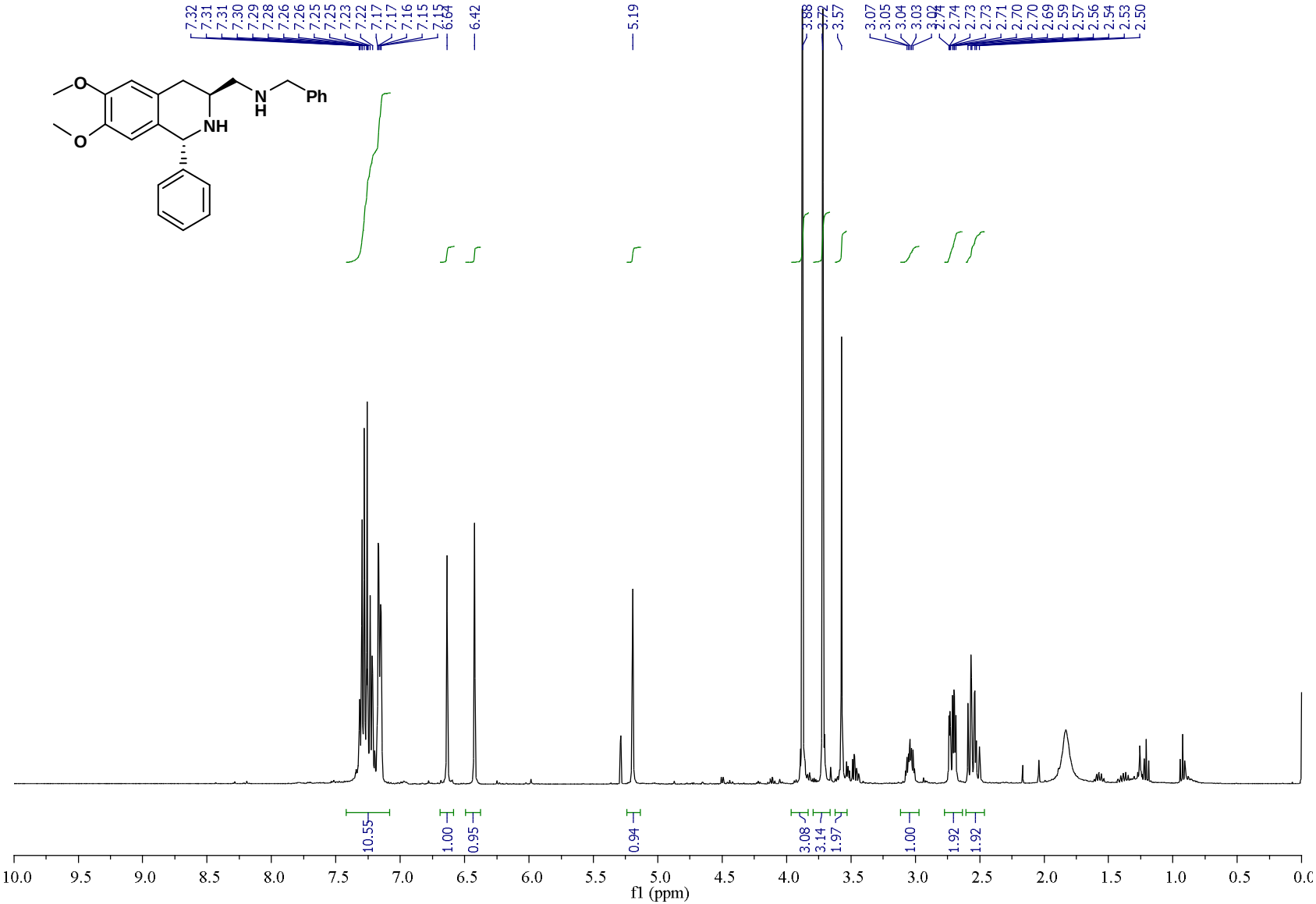
^{1}H NMR Spectrum of Compound 87 in $CDCl_3$



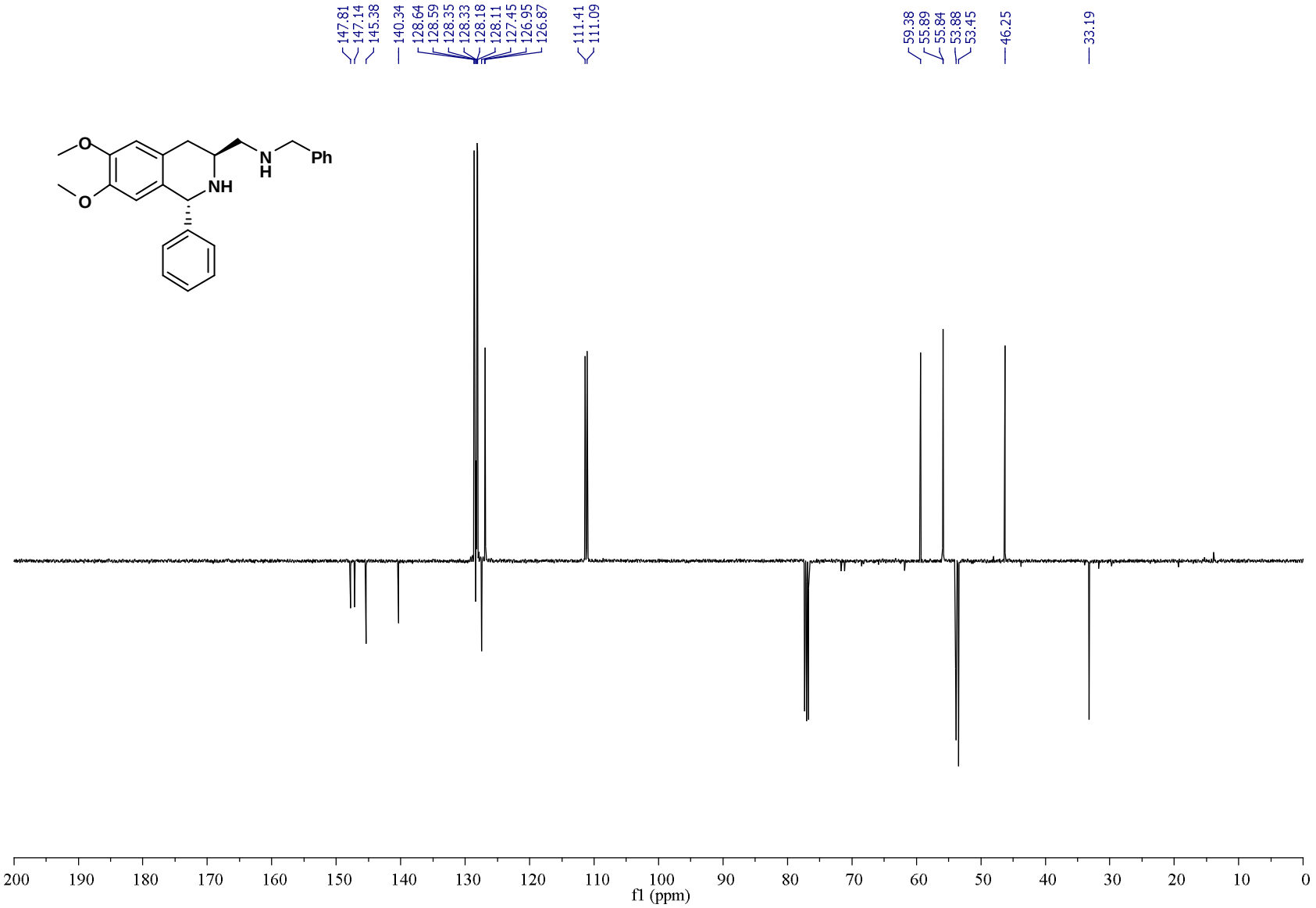
^{13}C NMR Spectrum of Compound 87 in $CDCl_3$



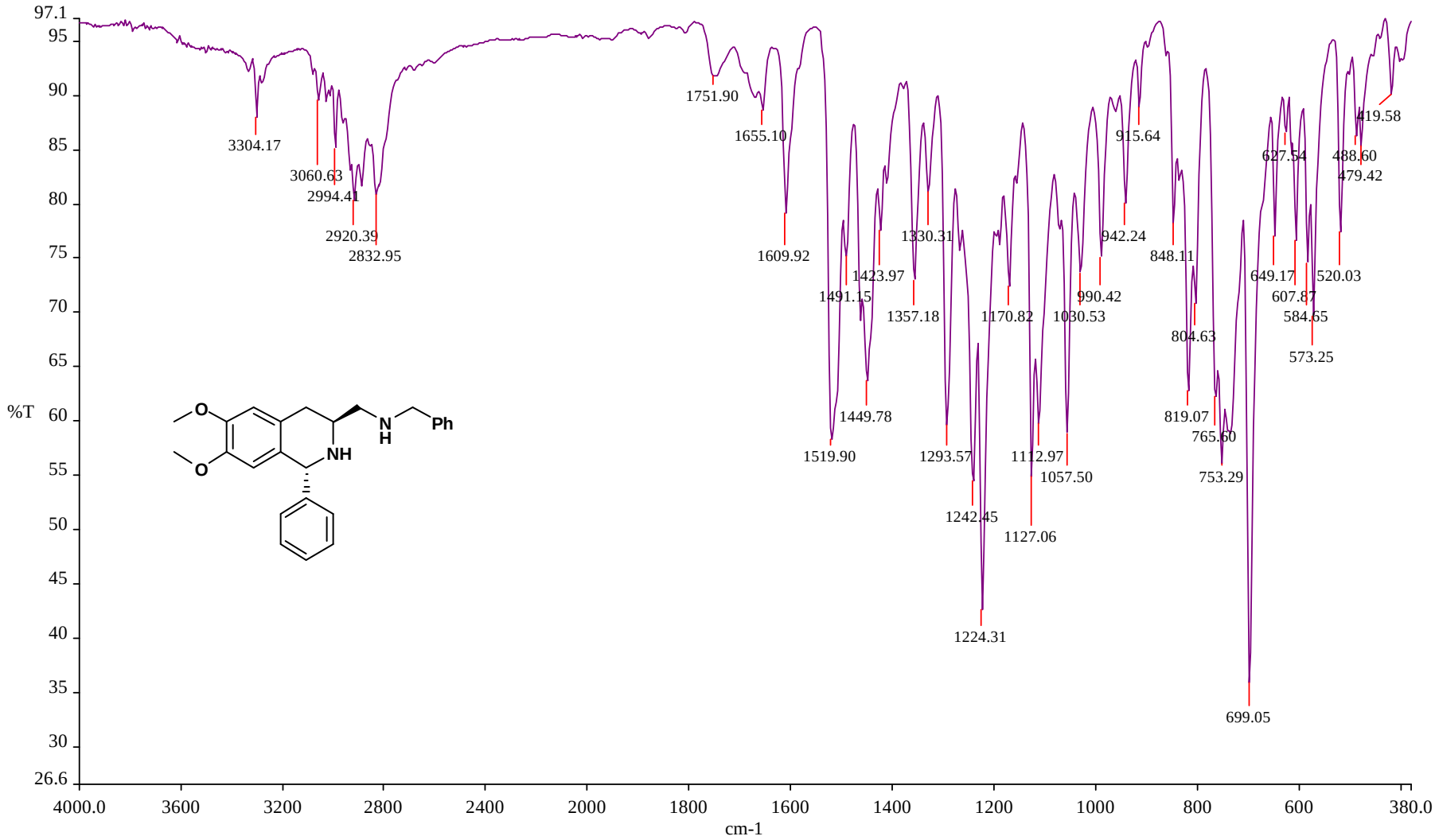
IR Spectrum of Compound 87



^{1}H NMR Spectrum of Compound 88 in $CDCl_3$



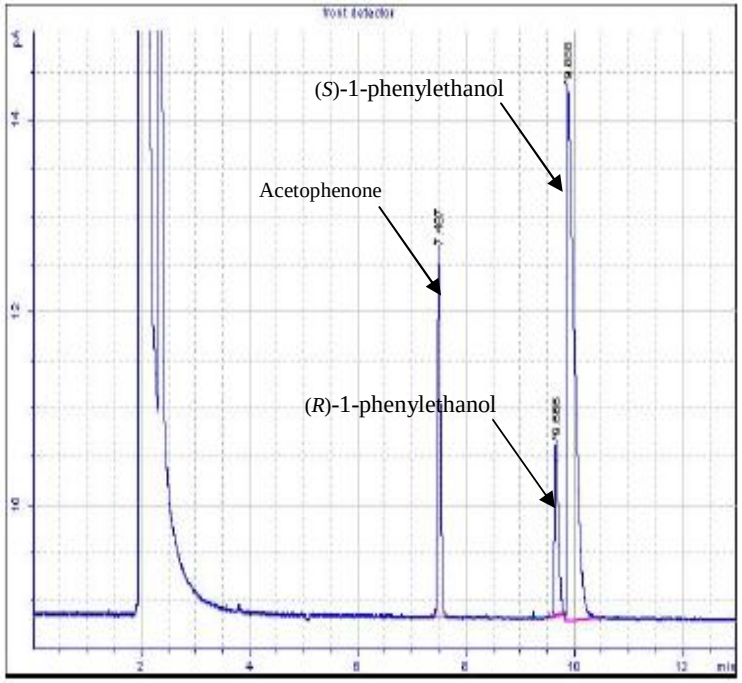
^{13}C NMR Spectrum of Compound 88 in $CDCl_3$



IR Spectrum of Compound 88

Agilent Cerity QA/QC Report

Sample name:	*Reprocessed: byron-3000 eqv water in dry iPrOH 40 min
Sample note:	
Submission time:	03 August 2009 12:24
Operator:	
Injection date:	03 August 2009 12:28
GC Description:	New1 - SN: CN10651003
Signal description:	FID1 A, front detector
Method:	SAI
Method last saved:	11 July 2009 12:34



Area Percent Report

Calibration last saved:	
Multiplier:	1.0000
Dilution:	1.0000
Sample amount:	0.0000 µL
Sample type:	Sample
Sampling source:	Manual

Signal	Retention Time [min]	Type	Width [min]	Area [pA*s]	Area %
1	7.497	BB	0.055	13.85137	18.98913
1	9.666	MM m	0.077	8.42703	11.55278
1	9.888	MM m	0.151	50.66531	69.45809

Total Area = 72.94371

Report summary:
Warning(s): Sample amount is zero. Absolute amounts calculated

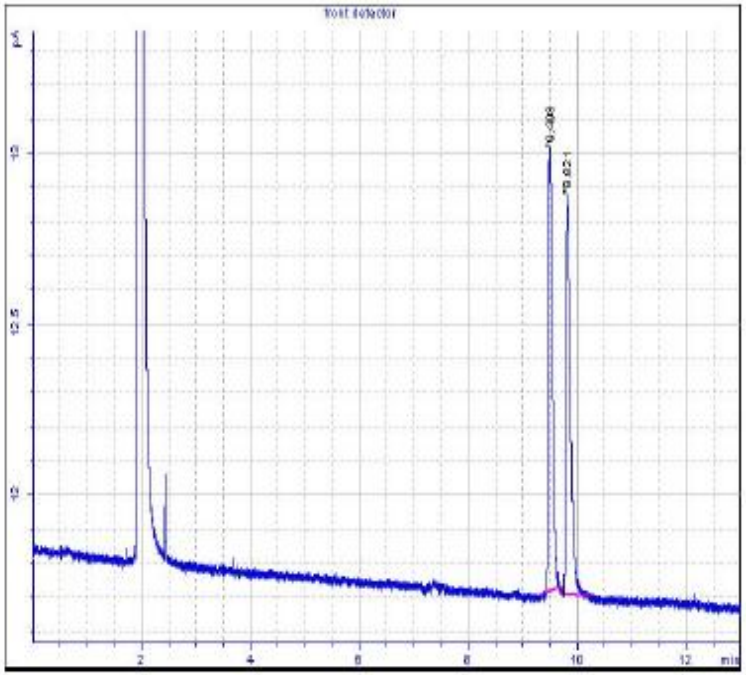
Instrument run log:

No deviations found

GC Chromatogram for a test reaction

Agilent Cerity QA/QC Report

Sample name:	*Reprocessed: 1-phenylethanol check 2
Sample note:	
Submission time:	16 November 2009 09:19
Operator:	
Injection date:	16 November 2009 09:20
GC Description:	New1 - SN: CN10651003
Signal description:	FID1 A, front detector
Method:	SAI
Method last saved:	11 July 2009 12:34



Area Percent Report

Calibration last saved:	
Multiplier:	1.0000
Dilution:	1.0000
Sample amount:	0.0000 µL
Sample type:	Sample
Sampling source:	Manual

Signal	Retention Time [min]	Type	Width [min]	Area [pA*s]	Area %
1	9.498	MM m	0.084	6.56468	48.83961
1	9.821	MM m	0.098	6.87663	51.16039

Total Area = 13.44131

Report summary:
Warning(s): Sample amount is zero. Absolute amounts calculated

Instrument run log:

No deviations found

GC Chromatogram of 1-phenylethanol (racemic)