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Synthesis of nitrogen heterocycles via palladium-catalyzed annulation of acetylenes

by

Kevin Ray Roesch

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of
DOCTOR OF PHILOSOPHY

Major: Organic Chemistry
Major Professor: Richard C. Larock

Iowa State University
Ames, Iowa
1999

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Major Professor

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For the Graduate College

To Julie, for always being there through the best and worst of times (and for putting up with me), and my parents for all of the support from the beginning. Thank you.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
br	broad
br m	broad multiplet
br s	broad singlet
Bu	butyl
t-Bu	*tert*-butyl
cat.	catalytic
concd	concentrated
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
dddd	doublet of doublets of doublets of doublets
dm	doublet of multiplets
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dq	doublet of quartets
dt	doublet of triplets
eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)

HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
m	multiplet
Me	methyl
mL	milliliters
mol	mole(s)
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
q	quartet
s	singlet
t	triplet
TBAC	tetra-*n*-butylammonium chloride
td	triplet of doublets
tq	triplet of quartets
tert	tertiary
Ts	*p*-toluenesulfonyl
tt	triplet of triplets

ABSTRACT

A wide variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[*f*]isoquinoline, pyrindine, and pyridine heterocycles have been prepared via annulation of internal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst. The best results are obtained by employing 5 mol % $Pd(OAc)_2$, an excess of the alkyne, one equivalent of sodium carbonate as a base, and 10 mol % PPh_3 in DMF as the solvent. This annulation methodology is particularly effective for aryl- or alkenyl-substituted alkynes. Trimethylsilyl-substituted alkynes also undergo this annulation process to afford mono-substituted heterocyclic products. Other acetylenes, however, fail to undergo this annulation process.

Mono-substituted isoquinolines and pyridines have been prepared via coupling of terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes. In addition, isoquinolines have been prepared in excellent yields via copper-catalyzed cyclization of iminoalkynes. The choice of cyclization conditions is dependent upon the nature of the terminal acetylene that is employed, as only aryl and alkenyl acetylenes cyclize under the palladium-catalyzed reaction conditions that have been developed. However, aryl, vinylic, and alkyl substituted acetylenes undergo palladium-catalyzed coupling and subsequent copper-catalyzed cyclization in excellent yields. Finally, the total synthesis of the isoquinoline natural product

decumbenine B has been accomplished in 7 steps and 20% overall yield by employing this palladium-catalyzed coupling and cyclization methodology.

A wide variety of substituted isoindolo[2,1-*a*]indoles have been prepared via annulation of internal alkynes by imines derived from *o*-iodoanilines in the presence of a palladium catalyst. This methodology provides an extremely efficient route for the synthesis of these tetracyclic heterocycles from readily available starting materials. The mechanism of this interesting annulation process appears to involve either electrophilic palladation of a σ-palladium intermediate onto the adjacent aromatic ring of the internal alkyne, or oxidative addition of the neighboring aryl carbon-hydrogen bond. A variety of internal acetylenes have been employed in this annulation process in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.

GENERAL INTRODUCTION

Transition metal-catalyzed processes have proved to be extremely effective in organic synthesis. More specifically, palladium-catalyzed methodology has been extensively utilized in recent years.[1] The ability to create multiple carbon-carbon bonds from simple starting materials, the regio- and stereospecificity of the reactions, the exceptional tolerance for functionality, the insensitivity to air or moisture, and the procedural ease with which the reactions can be carried out have all contributed to the success of this methodology in organic synthesis.

The Larock group has recently shown in a number of recent papers that palladium-catalyzed internal alkyne annulation methodology can be effectively employed for the synthesis of a variety of carbo- and heterocycles, such as indoles,[2] benzofurans,[3] benzopyrans,[3] isocoumarins,[3] indenones,[4] α-pyrones,[5] and polycyclic aromatic hydrocarbons.[6] In this dissertation, the scope of this alkyne annulation methodology has been expanded by employing *tert*-butylimines derived from *o*-iodobenzaldehydes and 3-halo-2-alkenals in internal and terminal alkyne annulations to provide access to a variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[*f*]isoquinoline, pyrindine, and pyridine heterocycles. In addition, substituted isoindolo[2,1-*a*]indole heterocycles have been prepared in good to excellent yields via annulation of internal alkynes by imines derived from *o*-iodoanilines. The author of this manuscript was the primary investigator and the author of each of the papers reported in this dissertation.

Dissertation Organization

This dissertation is divided into three chapters. Each of the chapters presented herein is written by following the guidelines for a full paper in the *Journal of Organic Chemistry* and are composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgment, and references.

Chapter 1 discusses the synthesis of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[*f*]isoquinoline, pyrindine, and pyridine heterocycles by the palladium-catalyzed iminoannulation of internal alkynes by employing *tert*-butylimines derived from *o*-iodobenzaldehydes and 3-halo-2-alkenals. Interestingly, when employing trimethylsilyl-substituted alkynes, monosubstituted heterocycles are obtained. A mechanism involving desilylation of the acetylene and subsequent palladium-catalyzed coupling and cyclization of the intermediate iminoalkynes is proposed.

Chapter 2 presents an extension of the internal alkyne methodology described in Chapter 1. The palladium-catalyzed coupling of terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals with subsequent copper-catalyzed cyclization of the intermediate iminoalkynes affords a variety of isoquinoline and pyridine heterocycles. The mechanism of this interesting isoquinoline synthesis has been studied and will be presented in detail. In addition, the total synthesis of the isoquinoline natural product decumbenine B will be discussed.

Chapter 3 describes the synthesis of substituted isoindolo[2,1-*a*]indole heterocycles via annulation of internal acetylenes with imines derived from *o*-

iodoanilines in the presence of a palladium catalyst. This reaction provides a novel and efficient route to the isoindole skeleton from simple and readily available starting materials. The mechanism of this remarkable process is believed to proceed via (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and insertion of the acetylene, (4) addition of the vinylpalladium intermediate across the carbon-nitrogen double bond, (5) either electrophilic palladation of the σ-palladium intermediate onto the adjacent aromatic ring, or oxidative addition of the neighboring aryl carbon-hydrogen bond to the σ-palladium intermediate to form a Pd(IV) intermediate, and subsequent elimination of HI by base, and (6) regeneration of the Pd(0) catalyst by reductive elimination to form the isoindole.

Finally, all of the ^{1}H and ^{13}C spectra for the imine starting materials and the palladium-catalyzed reaction products have been compiled in appendices A-C following the general conclusions for this dissertation.

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2. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
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CHAPTER 1. SYNTHESIS OF ISOQUINOLINES AND PYRIDINES VIA PALLADIUM-CATALYZED IMINOANNULATION OF INTERNAL ALKYNES

A paper to be submitted to the *Journal of Organic Chemistry*

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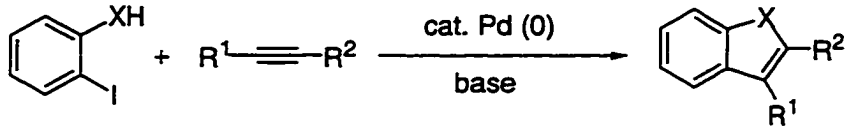
Abstract

A wide variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[*f*]isoquinoline, pyrindine, and pyridine heterocycles have been prepared via annulation of internal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst. The best results are obtained by employing 5 mol % $Pd(OAc)_2$, an excess of the alkyne, one equivalent of sodium carbonate as a base, and 10 mol % PPh_3 in DMF as the solvent. This annulation methodology is particularly effective for aryl- or alkenyl-substituted alkynes. Trimethylsilyl-substituted alkynes also undergo this annulation process to afford mono-substituted heterocyclic products. Other acetylenes, however, fail to undergo this annulation process.

Introduction

Annulation processes have found numerous applications in organic synthesis, primarily due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed.[1] In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology can be effectively employed for the synthesis of indoles,[2] benzofurans,[3] benzopyrans,[3] isocoumarins,[3] indenones,[4] polycyclic aromatic hydrocarbons,[5] and α-pyrones[6] (eq 1).



(1)

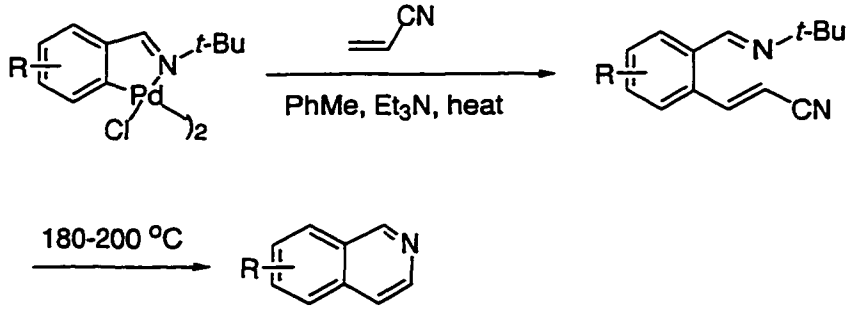
XH = $C(CO_2Et)_2$, NR, O, CO, CO_2Et

R^1, R^2 = alkyl, aryl, silyl, alkenyl

The synthesis of isoquinoline heterocycles has received considerable attention in the literature due to the fact that the isoquinoline ring system is present in numerous naturally-occurring alkaloids. Although the classical methods for the synthesis of this important ring system, the Bischler-Napieralski reaction,[7] the Pomeranz-Fritsch reaction,[7a,8] and the Pictet-Spengler reaction[7a,9] have been frequently employed in the total synthesis of isoquinoline alkaloids, they are all quite limited synthetically. For example, all of these methods are based on electrophilic cyclizations of a β-phenylethylamine to form the nitrogen-containing

ring, and therefore suffer the disadvantages of employing strong acids for their ring closure steps, and the synthesis of appropriate starting materials is often difficult. Furthermore, the Bischler-Napieralski and Pictet-Spengler reactions require dehydrogenations of dihydro- and tetrahydroisoquinolines, respectively.

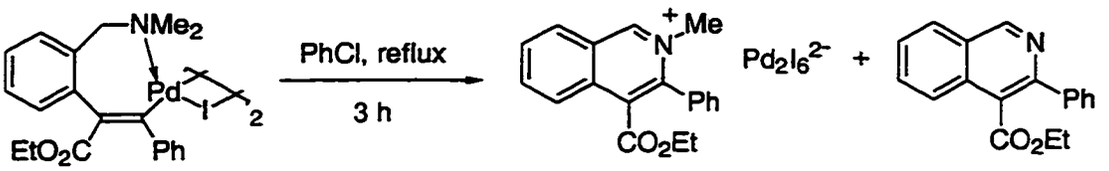
Substituted isoquinoline heterocycles have also been synthesized by employing palladium methodology. For instance, Widdowson reported the synthesis of isoquinoline derivatives from cyclopalladated *N-tert*-butylarylaldimines in yields from 10 to 56% (eq 2).[10] However, this synthesis suffers from the disadvantages that stoichiometric amounts of palladium salts are required for the preparation of the intermediate iminoalkenes, and a final pyrolysis step in a diphenyl ether/mesitylene solvent at 180-200 °C greatly limits the synthetic utility.



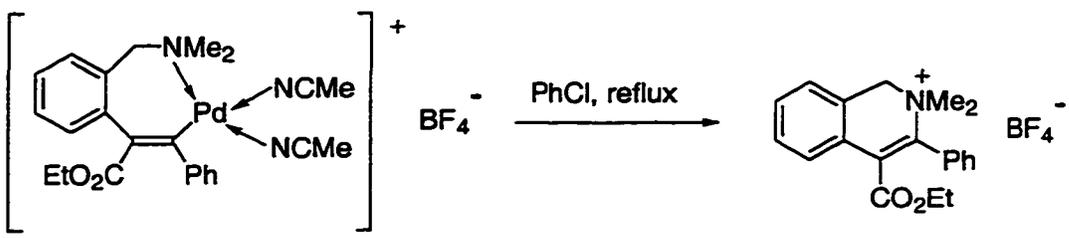
(2)

Pfeffer has reported the formation of the isoquinolinium salt **1** in 14% yield, as well as the disubstituted isoquinoline derivative **2** in 60% yield from a cyclopalladated *N,N*-dimethylbenzylamine complex (eq 3).[11] Moreover, an entirely different heterocycle (**4**) was obtained by the thermal depalladation of the cationic tetrafluoroborate palladium complex **3** (eq 4). These syntheses also have the

disadvantage that they use stoichiometric amounts of palladium salts for the preparation of the starting cyclopalladated complexes.

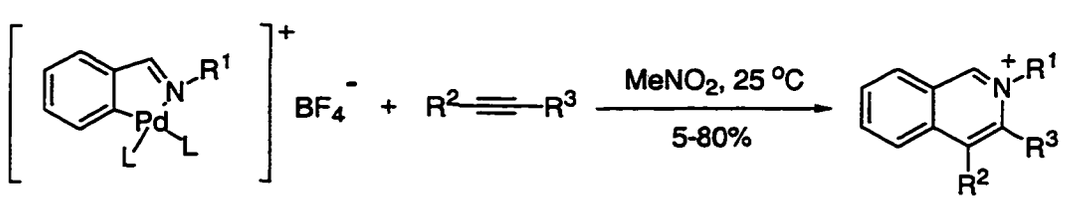


1 2 (3)

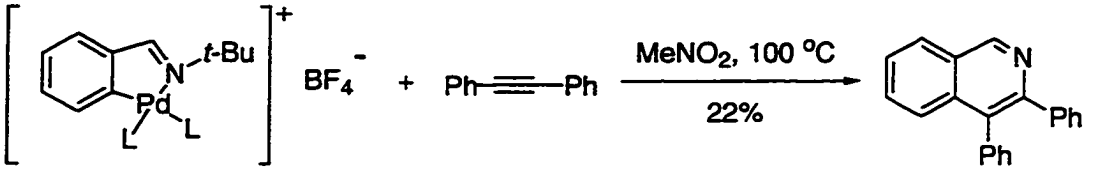


3 4 (4)

Heck has also reported the synthesis of isoquinolinium tetrafluoroborate salts in moderate yields from the reaction of cyclopalladated arylaldimine tetrafluoroborates and internal alkynes (eq 5).[12] In one instance, Heck observed the formation of 3,4-diphenylisoquinoline in 22% yield from the reaction of a cationic, tetrafluoroborate *N-tert*-butylbenzaldimine palladium complex and diphenylacetylene (eq 6). These two syntheses, however, also suffer from the use of stoichiometric amounts of palladium salts.



(5)

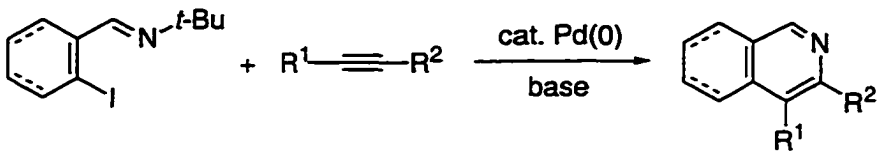


(6)

Our own interest in this type of annulation reaction has prompted us to investigate a catalytic version of these isoquinoline syntheses. Herein, we report that our catalytic annulation chemistry can also be applied to the synthesis of a wide variety of nitrogen heterocycles including isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[*f*]isoquinolines, pyrindines, and pyridines. A variety of aryl-, alkenyl-, and silyl-substituted alkynes have been employed in the palladium-catalyzed annulations with *tert*-butylimines derived from *o*-iodobenzaldehydes and 3-halo-2-alkenals.

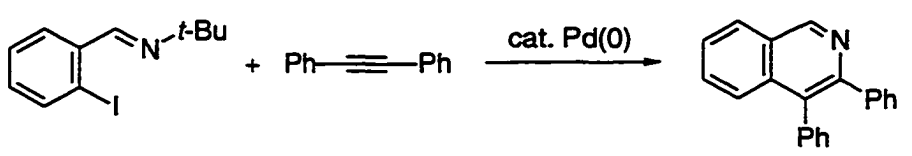
Results and Discussion

Our initial studies focused on the palladium-catalyzed annulation of internal alkynes employing the methyl imine of *o*-iodobenzaldehyde. However, this substrate failed to produce any of the desired isoquinoline even at elevated temperatures. Furthermore, use of the corresponding isopropyl, allyl, and benzyl imines also afforded none of the desired heterocyclic products. The reaction of the α-methylbenzyl imine with diphenylacetylene did produce the desired product, 3,4-diphenylisoquinoline, albeit in low yields (6-11%). By employing the *tert*-butylimine, however, we were able to obtain substantially improved results with a variety of alkynes, after optimization of the reaction conditions (eq 7).



(7)

The reaction of diphenylacetylene and the *tert*-butylimine of *o*-iodobenzaldehyde was chosen as the model system for the optimization of this annulation process (eq 8). In the early stages of this work, the reaction conditions that were chosen were similar to the conditions employed in our other alkyne annulation chemistry (Table 1).[2-6] For example, 0.5 mmol of the *tert*-butylimine, 1.0 mmol of diphenylacetylene, 0.5 mmol of LiCl, with 0.5 mmol of Na_2CO_3 as a base in 10 mL of DMF at 100 °C afforded 3,4-diphenylisoquinoline in 76% yield after a 53 hour reaction time (entry 1). By increasing the temperature to 110 °C, the reaction time was reduced, while the yield was comparable to that of entry 1 (entry 2). It was also observed that chloride salts significantly increased the reaction times when employing Na_2CO_3 as a base (compare entries 1-4 and entry 5). Upon removal of the chloride salts from the reaction mixture, we were able to isolate the desired product in a relatively short reaction time, and in yields comparable to the reactions in which chloride salts were employed (compare entries 1-4 and entry 5).



(8)

5 **6**

Table 1. Optimization of the Palladium-catalyzed Formation of 3,4-Diphenylisoquinoline (eq 8).

entry	chloride source (equiv)	base (equiv)	10% PPh_3	temp (°C), time (h)	% isolated yield of **6**
1	LiCl (1)	Na_2CO_3 (1)	-	100, 53	76
2	LiCl (1)	Na_2CO_3 (1)	-	110, 25	71
3	LiCl (2)	Na_2CO_3 (1)	-	100, 115	69
4	*n*-Bu_4NCl (1)	Na_2CO_3 (1)	-	100, 86	81
5	-	Na_2CO_3 (1)	-	100, 23	80
6	-	Na_2CO_3 (1)	+	100, 25	96
7	-	$NaHCO_3$ (1)	+	100, 32	77
8	-	NaOAc (1)	+	100, 25	87
9	-	K_2CO_3 (1)	+	110, 88	69
10	-	*i*-Pr_2NEt (1)	+	100, 9	68
11	-	Et_3N (1)	+	100, 8	76
12	-	Na_2CO_3 (1)	+	80, 115	70
13	-	Et_3N (1)	+	80, 21	63
14	-	Na_2CO_3 (1)	+	100, 96	77[a]

[a]Two mol % $Pd(OAc)_2$, and 4 mol % PPh_3 were used.

The effect of triphenylphosphine on the reaction was then investigated. The yield of 3,4-diphenylisoquinoline was observed to increase upon addition of a catalytic amount of triphenylphosphine (10 mol %) to the reaction mixture (compare entries 5 and 6). Presumably, the added phosphine disrupts the coordination of the neighboring imine substituent to the palladium atom in the arylpalladium intermediate (see the latter mechanistic discussion). Other inorganic bases were also employed in the reaction with triphenylphosphine. However, poorer yields were observed with other bases, and in the case of K_2CO_3, a significant increase in the reaction time was observed (compare entries 7-9 with entry 6). When tertiary organic amine bases were employed, a reduction in the reaction time was observed, in addition to the yield of the product (entries 10 and 11).

Additional attempts to optimize this annulation process included the investigation of two additional reaction variables. First of all, based on the success with Na_2CO_3 and triphenylphosphine (entry 6), the reaction temperature was lowered to 80 °C in order to determine the effect on the reaction rate and yield (entry 12). Unfortunately, the reduction in the temperature of the reaction was accompanied by an increase in the reaction time, and a decrease in the product yield. Furthermore, since the reaction times were relatively short with the organic amine bases employed, a reaction was run with Et_3N at 80 °C (entry 13). Although the reaction time with this base was relatively short, the yield was significantly less than that with Na_2CO_3 at 100 °C (compare entries 6 and 13).

Finally, in an effort to reduce the amount of the palladium catalyst, one reaction was run in which the amount of $Pd(OAc)_2$ was reduced from 5 mol % to 2 mol % (entry 14). However, both a decrease in the reaction rate as well as the yield was observed. These results have led to the development of the following general reaction procedure for our heterocycle synthesis. One equiv of the *tert*-butylimine, 2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 1 equiv of Na_2CO_3 in DMF as the solvent at 100 °C give the best results. We then wanted to determine the scope and limitations of this methodology by annulating a wide variety of acetylenes with a number of aryl and vinylic imines. The results from this study are summarized in Table 2.

The annulation of a variety of aryl-substituted alkynes by the *tert*-butylimine of *o*-iodobenzaldehyde (**5**) has afforded the desired disubstituted isoquinoline heterocycles in moderate to excellent yields with high regioselectivity (Table 2, entries 1-6). The regiochemistry of the products is based on analogy with our previous alkyne annulation chemistry[2-6] and comparison of the spectral and physical data for compounds **7**[11] and **8**[13] with those already in the literature.

The annulation of a relatively unhindered diyne and enyne by imine **5** also afforded the anticipated isoquinoline products in good yields, although mixtures of regioisomers were obtained (entries 7-9). This is interesting due to the fact that the products **6-11** were isolated as single regioisomers, while the attempted annulation of other substituted alkynes, namely 4-octyne, 3-hexyne, 4,4-dimethyl-2-butyne, and 3,3-dimethyl-1-phenyl-1-butyne by imine **5** failed to produce any of the

Table 2. Synthesis of Nitrogen Heterocycles by the Pd-Catalyzed Annulation of Internal Acetylenes (eq 7).[a]

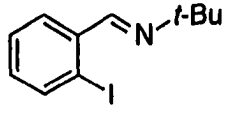
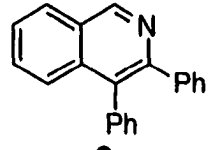
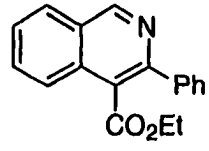
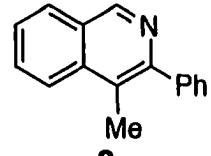
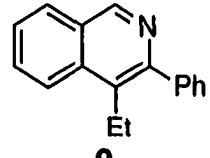
entry	imine	alkyne	time (h)	product	% yield
1	 **5**	Ph—≡—Ph	24	 **6**	96
2		Ph—≡—CO_2Et	5	 **7**	99
3		Ph—≡—Me	21	 **8**	84
4		Ph—≡—Et	16	 **9**	93

Table 2. (continued)

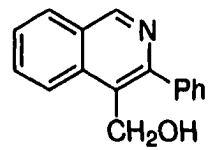
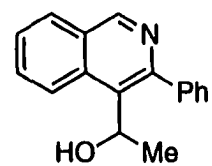
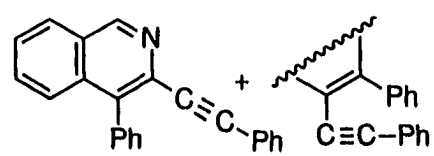
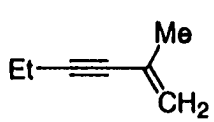
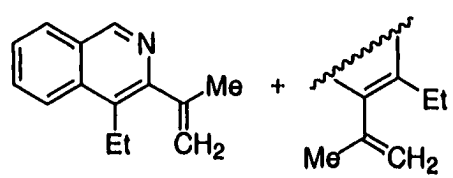
entry	imine	alkyne	time (h)	product	% yield
5		Ph—≡—CH_2OH	7	 **10**	100
6		Ph—≡—CH(Me)OH	4	 **11**	65
7		Ph—≡—≡—Ph	25	 **12** **13**	72 + 13
8			21	 **14** **15**	69[b]

Table 2. (continued)

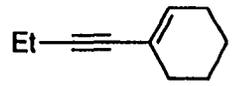
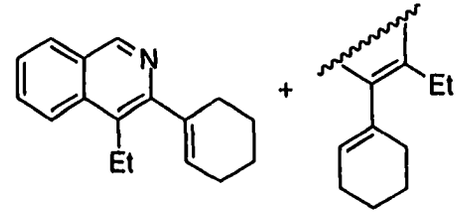
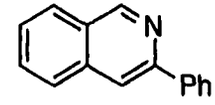
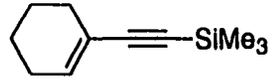
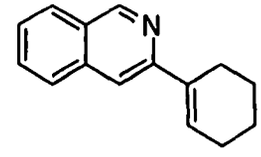
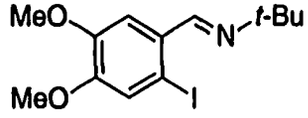
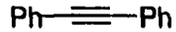
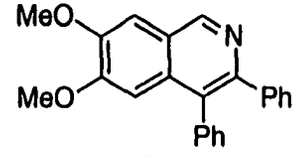
entry	imine	alkyne	time (h)	product	% yield
9			10	 **16** **17**	69[c]
10			21	 **18**	85
11			78	 **19**	77
12	 **20**		24	 **21**	82

Table 2. (continued)

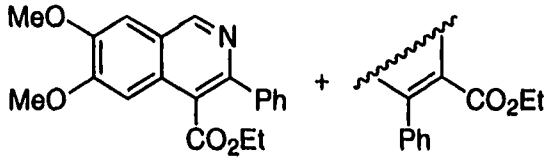
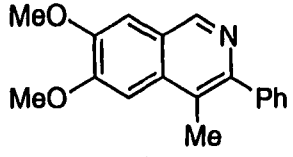
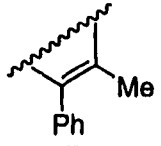
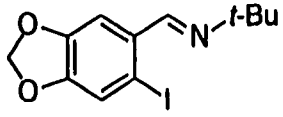
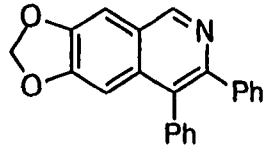
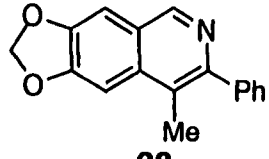
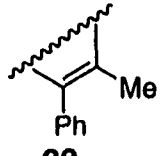
entry	imine	alkyne	time (h)	product	% yield
13		Ph—≡—CO_2Et	29	 **22** + **23**	95 + 5
14		Ph—≡—Me	29	 **24** +  **25**	67 + 17
15	 **26**	Ph—≡—Ph	44	 **27**	83
16		Ph—≡—Me	44	 **28** +  **29**	77 + 14

Table 2. (continued)

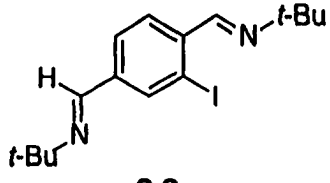
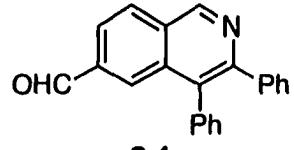
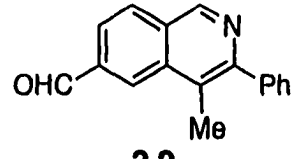
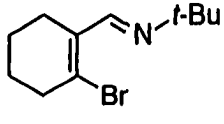
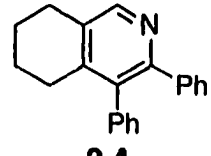
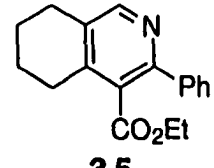
entry	imine	alkyne	time (h)	product	% yield
17	 **30**	Ph—≡—Ph	36	 **31**	69
18		Ph—≡—Me	36	 **32**	69
19	 **33**	Ph—≡—Ph	16	 **34**	72
20		Ph—≡—CO_2Et	14	 **35**	99

Table 2. (continued)

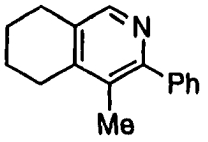
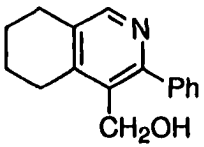
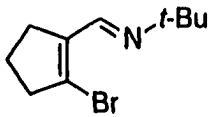
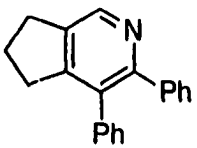
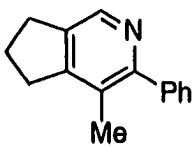
entry	imine	alkyne	time (h)	product	% yield
21		Ph—≡—Me	14	 **36**	74
22		Ph—≡—CH_2OH	3	 **37**	100
23	 **38**	Ph—≡—Ph	4	 **39**	71
24		Ph—≡—Me	3	 **40**	96

Table 2. (continued)

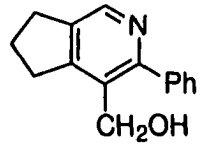
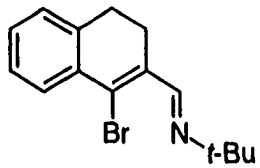
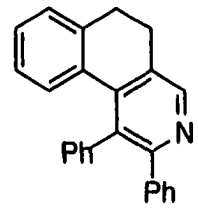
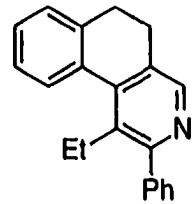
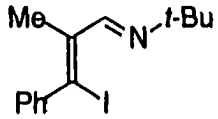
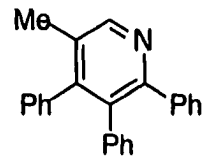
entry	imine	alkyne	time (h)	product	% yield
25		Ph—≡—CH_2OH	2	 **41**	72
26	 **42**	Ph—≡—Ph	11	 **43**	85
27		Ph—≡—Et	3	 **44**	94
28	 **45**	Ph—≡—Ph	17	 **46**	68

Table 2. (continued)

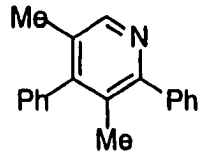
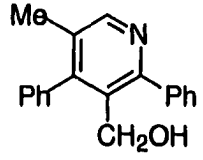
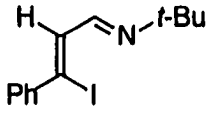
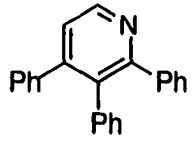
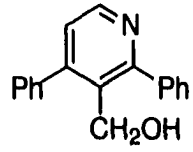
entry	imine	alkyne	time (h)	product	% yield
29		Ph—≡—Me	15	 **47**	65
30		Ph—≡—CH_2OH	2	 **48**	95
31	 **49**	Ph—≡—Ph	4	 **50**	52
32		Ph—≡—CH_2OH	2	 **51**	79

Table 2. (continued)

[a]A representative procedure for the annulation of internal acetylenes: 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, Na_2CO_3 (0.5 mmol), the acetylene (1.0 mmol), the imine (0.5 mmol), and DMF (10 ml) were placed in a 4 dram vial and were heated at 100 °C for the indicated time. [b]Isolated in an 85:15 ratio of **14** to **15** as an inseparable mixture of isomers. [c]Isolated in a 95:5 ratio of **16** to **17** as an inseparable mixture of isomers.

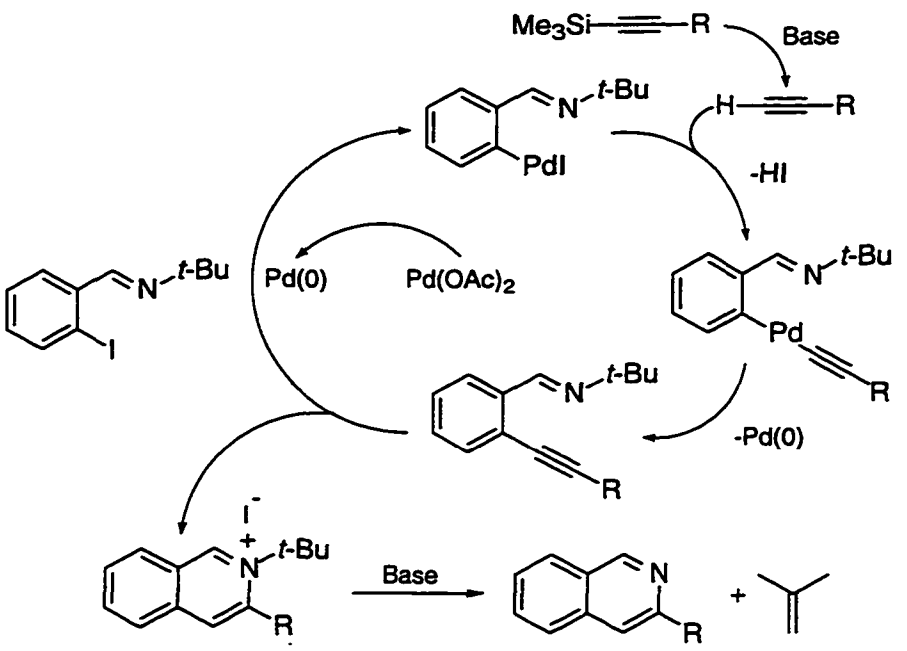
desired heterocycles. Based on the observations of Heck,[12] it is presumed that multiple alkyne insertion products are being formed with these alkynes, although none of these products have been identified. Alternatively, the presumed vinylpalladium intermediate (see the latter mechanistic discussion) may simply be undergoing beta hydride elimination to allenes.

The annulation of 1,4-diphenylbutadiyne by imine **5** has been observed to give an unexpected major product bearing the more hindered phenyl group in the 4-position (entry 7). This is in contrast to the regiochemical outcome of much of our other alkyne annulation chemistry in which the palladium adds to the more hindered end of the alkyne.[2-6] The regiochemistry of the products from this annulation has been confirmed by comparison of the ^{1}H NMR spectral properties of compounds **12** and **13** with the spectral properties of 3-phenyl-4-(phenylethynyl)-isoquinoline, which has been isolated as a minor product from the annulation of imine **5** by phenylacetylene.

This annulation methodology has also been extended to trimethylsilyl-substituted alkynes. To our surprise, the 3-monosubstituted isoquinolines were isolated from these reactions (entries 10 and 11). These are rather surprising results, since the expected products were either the 3,4-disubstituted products retaining the silyl group, or the corresponding 4-substituted isoquinolines arising from desilylation of the 3,4-disubstituted isoquinolines. Based on the results from an extensive investigation of this reaction, it appears that the trimethylsilyl acetylenes are being desilylated by the base in the reaction (see Scheme 1). The terminal alkynes, which are thus produced, are apparently then undergoing

palladium-catalyzed coupling and subsequent cyclization. A full account of this investigation is presented in chapter 2 of this dissertation (Roesch and Larock, 1999).

Scheme 1



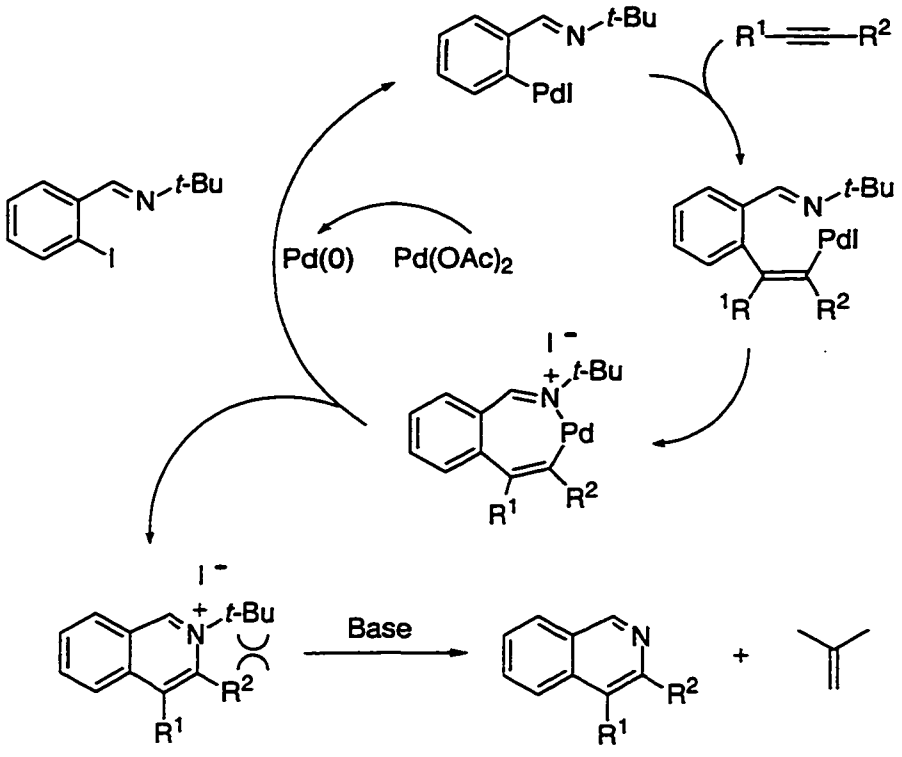
Surprisingly, when a more electron-rich imine, such as **20** or **26**, was employed in a reaction that previously gave only a single regioisomer, a mixture of regioisomers was observed (compare entries 13, 14, and 16 with entries 2 and 3). In the case of the imine **30** bearing an electron-withdrawing group, only a single regioisomer were obtained (entry 18), with hydrolysis of the imines presumably occurring during the work-up of the reaction.

This annulation chemistry has also been extended to vinylic imines. For example, the tetrahydroisoquinoline derivatives **34-37** have been synthesized by

annulation with the cyclic vinylic imine **33** (entries 19-22). In addition, the pyrindine derivatives **39-41** and the dihydrobenzoisoquinoline derivatives **43** and **44** have been synthesized from vinylic imines **38** and **42**, respectively (entries 23-27). Finally, the acyclic vinylic imines **45** and **49** have also been successfully employed in this annulation process to produce highly substituted pyridine derivatives (entries 28-32). It is interesting to note that the compounds derived from the vinylic imines were all isolated as single regioisomers. Surprisingly, the imine **49** works quite well in this pyridine synthesis, whereas the corresponding ethyl ester (*Z*-PhCl=CHCO$_2$Et) fails to undergo annulation of this same alkyne to produce the corresponding α-pyrone, a process with which we have recently had considerable success.[6]

We propose a mechanism for this process which is similar to our other alkyne annulation chemistry (Scheme 2). Specifically, oxidative addition of the aryl or vinylic halide to Pd(0) produces an organopalladium intermediate, which then inserts the acetylene, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a 7-membered palladacyclic ammonium salt. Subsequent reductive elimination produces a *tert*-butylisoquinolinium salt and regenerates Pd(0). As previously suggested by Heck,[12] the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.

Scheme 2



Conclusion

An efficient, palladium-catalyzed synthesis of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[*f*]isoquinolines, pyrindines, and pyridines has been developed. A wide variety of aryl acetylenes undergo this process in moderate to excellent yields, with high regioselectivity being observed in most cases. In addition, a relatively unhindered diyne and enyne have been employed. However, mixtures of regioisomers were observed in both cases. By employing trimethylsilyl-containing acetylenes, we have been able to synthesize monosubstituted heterocyclic products.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na_2CO_3, K_2CO_3, NaOAc, $NaHCO_3$, LiCl, DMF, THF, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh_3 was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodobenzyl alcohol, piperonal, *tert*-butylamine, diphenylacetylene, ethyl phenylpropiolate, 1-phenyl-1-propyne, 1-phenyl-2-(trimethylsilyl)acetylene, (1-cyclohexen-1-ylethynyl)trimethylsilane, Et_3N, and *i*-Pr_2NEt were purchased from Aldrich Chemical Co., Inc. 4,5-Dimethoxy-2-iodobenzoic acid and dimethyl iodoterephthalate were purchased from Trans World Chemical Co. 3-Phenyl-2-

propyn-1-ol and *n*-Bu_4NCl were purchased from Lancaster Synthesis, Inc. 1-Phenyl-1-butyne, 1,4-diphenylbutadiyne, 2-methyl-1-hexen-3-yne, 4-phenyl-3-butyn-2-ol, and 1-butynyl-1-cyclohexanol was purchased from Farchan Chemical Co. 2-Iodobenzaldehyde,[4] 2-bromopiperonal,[14] 2-bromocyclohexene-1-carboxaldehyde,[15] 2-bromocyclopentene-1-carboxaldehyde,[16] 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde,[17] (*Z*)-3-iodo-2-methyl-3-phenyl-2-propenal,[18] and (*Z*)-3-iodo-3-phenyl-2-propenal,[18] were prepared according to previous literature procedures. The following starting materials were prepared as indicated.

1-(1-Butynyl)cyclohexene. To a solution of 1-(1-butynyl)cyclohexanol (2.00 g, 13.14 mmol) in 50 mL of pyridine was added methanesulfonyl chloride (4.14 g, 36.14 mmol). The mixture was stirred for 60 h at room temperature and water (50 mL) was then added. The aqueous layer was extracted with ether (4 x 25 mL) and the extracts were combined and washed with 5% HCl, saturated aqueous $NaHCO_3$, water and brine, and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the resulting oil was purified by flash column chromatography using 10:1 hexanes/EtOAc to afford 1.3 g (74%) of the desired compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.5 Hz, 3H), 1.50-1.64 (m, 4H), 2.04-2.10 (m, 4H), 2.28 (q, J = 7.5 Hz, 2H), 5.97-6.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0, 14.2, 21.7, 22.5, 25.6, 29.6, 81.7, 88.7, 121.0, 133.2.

2-Iodopiperonal. 2-Iodopiperonal was prepared according to a modified literature procedure.[19] To a solution of *N*-(6-bromobenzo[1,3]dioxol-5-

ylmethylene)-*tert*-butylamine (1.50 g, 5.28 mmol) in 50 mL of ether at -78 °C was added 2.3 mL of *n*-BuLi (2.5 M in hexanes) dropwise over a five minute period. The solution was stirred for 30 min at -78 °C and a solution of I_2 (2.68 g, 10.6 mmol) in 5 mL of THF was added dropwise. The resulting solution was warmed to room temperature and stirred for 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (25 mL), and solid $NaHSO_3$ was added until the solution was decolorized. The layers were then separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to afford 0.80 g of the crude aldehyde. Recrystallization from 95% EtOH afforded 0.54 g (37%) of the desired compound with spectral properties identical to those previously reported.[20]

2-Iodobenzene-1,4-dicarbaldehyde. To a solution of dimethyl iodoterephthalate (2.56 g, 8 mmol) in hexanes (25 mL) and THF (25 mL) at -78 °C was added 32 mL of DIBAL-H (32 mmol, 1M in hexanes) dropwise. The solution was stirred for 6 h at -78 °C and then quenched with saturated aqueous NH_4Cl (40 mL). The mixture was warmed to room temperature and the precipitate was destroyed with 2M HCl (50 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 40 mL). The extracts were washed with 5% $NaHCO_3$ and brine, and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to afford the crude diol, which was then oxidized without further purification. The crude diol and PCC (2.53 mmol) were stirred at room temperature in CH_2Cl_2 (20 mL) for 24 h. Ether (50 mL) was added and the resulting solution

was filtered through Florisil. The solvent was removed under reduced pressure and the resulting solid was chromatographed using 15:1 hexanes/EtOAc to afford 0.53 g (25%) of the desired compound as a white solid: mp 91-92 °C; ^{1}H NMR ($CDCl_3$) δ 10.15 (d, J = 0.6 Hz, 1H), 10.04 (s, 1H), 8.44 (d, J = 0.9 Hz, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.95 (dq, J = 0.6, 6.0 Hz, 1H).

Imines Prepared

***N*-(2-Iodobenzylidene)-*tert*-butylamine (5).** To a mixture of 2-iodobenzaldehyde (1.00 g, 4.3 mmol) and H_2O (0.25 mL/mmol) was added *tert*-butylamine (12.9 mmol, 3 equivalents). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.18 g (95%) of the imine as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 7.07 (td, J = 1.5, 7.2 Hz, 1H), 7.36 (tt, J = 0.6, 7.2 Hz, 1H), 7.83 (dd, J = 0.9, 7.8 Hz, 1H), 7.94 (dd, J = 1.8, 7.8 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 58.0, 100.4, 128.5, 128.7, 131.6, 137.9, 139.4, 159.2; IR (neat, cm^{-1}) 3059, 2966, 1633; HRMS Calcd for $C_{11}H_{14}IN$: 287.0170. Found: 287.0173.

***N*-(2-Iodo-4,5-dimethoxybenzylidene)-*tert*-butylamine (20).** The imine was prepared by the same method used for **5**, but employing 2-iodo-4,5-dimethoxybenzaldehyde (1.00 g, 3.42 mmol). Removal of the solvent afforded

1.14 g (96%) of the imine **20** as a white solid: mp 80-81 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 3.89 (s, 3H), 3.94 (s, 3H), 7.22 (s, 1H), 7.53 (s, 1H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 56.1, 56.3, 57.6, 90.2, 110.3, 121.1, 130.7, 149.6, 151.3, 158.8; IR ($CHCl_3$, cm^{-1}) 3006, 2962, 1628; HRMS Calcd for $C_{13}H_{18}INO_2$: 347.0382. Found: 347.01382.

***N*-(6-Bromobenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine.** The imine was prepared by the same method used for **5**, but employing 2-bromopiperonal (2.00 g, 8.73 mmol). Removal of the solvent afforded 2.27 g (92%) of the imine as a white solid: mp 73-74 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 5.99 (s, 2H), 6.98 (s, 1H), 7.52 (s, 1H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 57.8, 102.1, 107.8, 112.5, 117.2, 129.5, 147.9, 150.1, 154.2; IR ($CHCl_3$, cm^{-1}) 3077, 2963, 1627; HRMS Calcd for $C_{12}H_{14}BrNO_2$: 283.0208. Found: 283.0205.

***N*-(6-Iodobenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (26).** The imine was prepared by the same method used for **5**, but employing 2-iodo-4,5-methylenedioxybenzaldehyde (0.54 g, 1.97 mmol). Removal of the solvent afforded 0.47 g (73%) of the imine **26** as an off-white solid: mp 89-90 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 5.99 (s, 2H), 7.24 (s, 1H), 7.50 (s, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 57.7, 90.1, 102.00, 108.2, 118.4, 131.9, 148.9, 150.3, 158.6; IR ($CHCl_3$, cm^{-1}) 3081, 2962, 1622; HRMS Calcd for $C_{12}H_{14}INO_2$: 331.0069. Found: 331.0072.

***N*-[2-Iodo-4-(*tert*-butyliminomethyl)benzylidene]-*tert*-butylamine (30).** The imine was prepared by the same method used for **5**, but employing 2-

iodobenzene-1,4-dicarbaldehyde (0.53 g, 2.04 mmol). Removal of the solvent afforded 0.75 g (100%) of the imine **30** as a white solid: mp 67-69 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.31 (s, 9H), 7.64 (d, J = 6 Hz, 1H), 7.93 (d, J = 6 Hz, 1H), 8.16 (s, 1H), 8.25 (d, J = 0.9 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 29.8, 57.8, 58.2, 100.6, 128.2, 128.5, 138.4, 139.0, 140.1, 153.3, 159.0; IR ($CHCl_3$, cm^{-1}) 2966, 1635; HRMS Calcd for $C_{16}H_{23}IN_2$: 370.0906. Found: 370.0916.

***N*-(2-Bromocyclohex-1-enylmethylene)-*tert*-butylamine (33).** The imine was prepared by the same method used for **5**, but employing 2-bromocyclohexene-1-carboxaldehyde (0.50 g, 2.64 mmol). Removal of the solvent afforded 0.59 g (92%) of the imine **33** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.65-1.75 (m, 4H), 2.38-2.43 (m, 2H), 2.62-2.66 (m, 2H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.8, 27.3, 29.9, 38.2, 57.6, 131.7, 133.9, 157.0; IR (neat, cm^{-1}) 2964, 1624; HRMS Calcd for $C_{11}H_{18}BrN$: 243.0623. Found: 243.0616.

***N*-(2-Bromocyclopent-1-enylmethylene)-*tert*-butylamine (38).** The imine was prepared by the same method used for **5**, but employing 2-bromocyclopentene-1-carboxaldehyde (0.75 g, 4.31 mmol). Removal of the solvent afforded 0.89 g (90%) of the imine **38** as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.97 (quintet, 2H), 2.59 (tt, J = 2.1, 7.5 Hz, 2H), 2.79 (tt, J = 2.4, 7.5 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 29.8, 31.1, 41.6, 57.7, 127.9, 139.1, 151.8; IR (neat, cm^{-1}) 2965, 1630; HRMS Calcd for $C_{10}H_{16}BrN$: 229.0466. Found: 229.0460.

***N*-(1-Bromo-3,4-dihydronaphthalen-2-ylmethylene)-*tert*-butylamine (42).** The imine was prepared by the same method used for **5**, but employing 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde (0.77 g, 3.26 mmol). Removal of the solvent afforded 0.85 g (89%) of the imine **42** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.81-2.83 (m, 4H), 7.16 (dd, J = 1.8, 6.9 Hz, 1H), 7.22-7.31 (m, 2H), 7.79 (dd, J = 1.8, 7.2 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 27.7, 30.0, 58.1, 126.8, 127.3, 127.6, 128.6, 129.1, 134.2, 135.9, 138.3, 157.0; IR (neat, cm^{-1}) 3063, 2965, 1612; HRMS Calcd for $C_{15}H_{18}BrN$: 291.0623. Found: 290.0548 (M-H).

***N*-[(*Z*)-3-Iodo-2-methyl-3-phenylallylidene]-*tert*-butylamine (45).** The imine was prepared by the same method used for **5**, but employing *Z*-3-iodo-2-methyl-3-phenyl-2-propenal (0.61 g, 2.22 mmol). Removal of the solvent afforded 0.70 g (96%) of the imine **45** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.88 (s, 3H), 7.24-7.28 (m, 3H), 7.34-7.39 (m, 2H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 29.9. 57.9, 107.0, 128.2, 128.3, 128.4, 139.0, 144.5, 162.8; IR (neat, cm^{-1}) 3075, 2966, 1618; HRMS Calcd for $C_{14}H_{18}IN$: 327.0484. Found: 327.0477.

***N*-[(*Z*)-3-Iodo-3-phenylallylidene]-*tert*-butylamine (49).** The imine was prepared by the same method used for **5**, but employing *Z*-3-iodo-3-phenyl-2-propenal (0.60 g, 2.33 mmol). Removal of the solvent afforded 0.64 g (87%) of the imine **49** as a yellow solid: mp 81-83 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 6.77 (d, J = 7.8 Hz, 1H), 7.32-7.35 (m, 3H), 7.56-7.60 (m, 2H), 8.15 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 58.4, 113.6, 128.5, 128.8, 129.6, 134.9, 142.0, 161.4; IR

($CHCl_3$, cm^{-1}) 3078, 2967, 1614; HRMS Calcd for $C_{13}H_{16}IN$: 313.0328. Found: 313.0332.

General Procedure for the Palladium-Catalyzed Formation of Isoquinolines and Pyridines. DMF (10 mL), $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (13 mg, 0.05 mmol), Na_2CO_3 (53 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. The contents were then stirred for 1 minute and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 30 mL of ether, washed with 45 mL of saturated NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3,4-Diphenylisoquinoline (6). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 135 mg (96%) of the indicated compound with spectral properties identical to those previously reported[12a]: mp 154-155 °C (lit.[12a] mp 155-156 °C).

Ethyl 3-phenylisoquinoline-4-carboxylate (7). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 138 mg (99%) of the

indicated compound with spectral properties identical to those previously reported.[11]

4-Methyl-3-phenylisoquinoline (8). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 92 mg (84%) of the indicated compound as a white solid: mp 101-102 °C (lit.[13] mp 103-104 °C); ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H), 7.38-7.53 (m, 3H), 7.57-7.63 (m, 3H), 7.74 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 8.04 (dd, J = 0.6, 8.4 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.6, 123.7, 124.1, 126.7, 127.3, 127.7, 128.16, 128.21, 129.9, 130.5, 136.3, 141.4, 150.3, 151.9; MS *m/z* (rel intensity) 219 (50, M^+), 218 (100), 217 (22). Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.30; H, 6.09; N, 6.32.

4-Ethyl-3-phenylisoquinoline (9). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 109 mg (93%) of the indicated compound as a white solid: mp 117-118 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 3.07 (q, J = 7.5 Hz, 2H), 7.39-7.56 (m, 5H), 7.62 (ddd J = 1.2, 6.9, 8.4 Hz, 1H), 7.77 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.7, 21.9, 123.7, 126.6, 127.6, 127.9, 128.2, 128.5, 129.3, 130.4, 130.5, 135.3, 141.6, 150.2, 151.9; IR ($CHCl_3$, cm^{-1}) 3027, 2976, 1653, 1559; MS *m/z* (rel intensity) 233 (76, M^+), 232 (100), 217 (44). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.48; H, 6.68; N, 5.91.

4-Hydroxymethyl-3-phenylisoquinoline (10). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 118 mg (100%) of the

indicated compound as a white solid: mp 175-176 °C (hexanes/EtOAc); ^{1}H NMR (CD_3OD) δ 4.89 (br s, 1H), 4.96 (s, 2H), 7.44-7.54 (m, 3H), 7.65 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.72 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.88 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (CD_3OD) δ 57.9, 124.2, 126.9, 127.3, 127.9, 128.0, 128.0, 128.1, 129.6, 131.3, 136.2, 139.9, 151.7, 152.1; IR ($CHCl_3$, cm^{-1}) 3270, 1622, 1576; MS *m/z* (rel intensity) 235 (100, M^+), 262 (100). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.57; H, 5.84; N, 5.88.

4-(1-Hydroxyethyl)-3-phenylisoquinoline (11). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 80 mg (65%) of the indicated compound as a white solid: mp 146-147 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.75 (d, *J* = 6.6 Hz, 3H), 2.49 (br s, 1H), 5.44 (q, *J* = 6.6 Hz, 1H), 7.41 (s, 5H), 7.62 (t, *J* = 6 Hz, 1H), 7.74 (ddd, *J* = 1.2, 5.7, 6.9 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 8.82 (d, *J* = 8.7 Hz, 1H), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.9, 67.9, 126.6, 126.8, 127.7, 128.1, 128.5, 128.7, 129.2, 130.0, 131.1, 134.5, 140.7, 150.6, 151.5; IR ($CHCl_3$, cm^{-1}) 3266, 1621, 1574, 1497; HRMS calcd for $C_{17}H_{15}NO$: 249.1154. Found: 249.1151.

4-Phenyl-3-(phenylethynyl)-isoquinoline (12). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 110 mg (72%) of the indicated compound as an off-white solid: mp 113-114 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.25 (br s, 5H), 7.49-7.68 (m, 8H), 7.99-8.02 (m, 1H), 9.26 (s, 1H);

^{13}C NMR ($CDCl_3$) δ 89.4, 92.5, 122.8, 125.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 130.8, 131.0, 131.8, 135.0, 135.5, 136.4, 136.5, 152.3; IR ($CHCl_3$, cm^{-1}) 2213, 1610, 1554, 1489; HRMS calcd for $C_{23}H_{15}N$: 305.1205. Found: 305.1197.

3-Phenyl-4-(phenylethynyl)-isoquinoline (13). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 20 mg (13%) of the indicated compound as an off-white solid: mp 115-116 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 7.35-7.40 (m, 3H), 7.43-7.57 (m, 5H), 7.68 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.85 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 8.04 (dd, J = 0.9, 7.2 Hz, 1H), 8.12-8.16 (m, 2H), 8.50 (dd, J = 0.9, 7.5 Hz, 1H), 9.30 (d, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 85.9, 99.3, 112.6, 123.3, 125.8, 126.7, 127.7, 128.0, 128.0, 128.6, 128.7, 128.8, 130.1, 131.4, 131.6, 136.8, 140.1, 151.6, 154.5; IR ($CHCl_3$, cm^{-1}) 2210, 1653, 1558, 1495; HRMS calcd for $C_{23}H_{15}N$: 305.1205. Found: 305.1196.

4-Ethyl-3-isopropenylisoquinoline (14) and 3-ethyl-4-isopropenylisoquinoline (15). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 68 mg (69%) of the indicated compounds as a yellow oil (85:15 inseparable mixture of isomers). **4-Ethyl-3-isopropenylisoquinoline** (major isomer): ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 2.20-2.21 (m, 3H), 3.10 (q, J = 7.5 Hz, 2H), 5.04-5.05 (m, 1H), 5.36-5.38 (m, 1H), 7.52 (ddd, J = 0.9, 7.2, 8.1 Hz, 1H), 7.68 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 8.00 (dd, J = 0.6, 8.4 Hz, 1H), 9.09 (s, 1H). **3-Ethyl-4-isopropenylisoquinoline** (minor isomer): ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7.5 Hz,

3H), 2.10-2.11 (t, J = 0.9 Hz, 3H), 2.92 (dq, J = 2.1, 7.5 Hz, 2H), 4.97-4.98 (m, 1H), 5.49-5.51 (m, 1H), 7.48 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.61 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.85 (t, J = 6.3 Hz, 1H), 8.05 (dd, J = 1.5, 6.3 Hz, 1H), 9.15 (s, 1H). Additional spectral data for the product mixture: ^{13}C NMR ($CDCl_3$) δ 15.1, 16.1, 21.8, 24.0, 25.0, 28.6, 115.6, 117.4, 123.6, 124.6, 126.0, 126.3, 127.6, 127.7, 128.3, 128.6, 129.0, 130.2, 131.6, 131.8, 134.6, 135.2, 141.7, 145.4, 150.1, 151.2, 152.5, 153.7; IR ($CHCl_3$, cm^{-1}) 3076, 1619, 1569, 1495; HRMS calcd for $C_{23}H_{15}N$: 197.1205. Found: 197.1203.

3-(Cyclohex-1-enyl)-4-ethylisoquinoline (16) and 4-(Cyclohex-1-enyl)-3-ethylisoquinoline (17). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 82 mg (69%) of the indicated compounds as a yellow oil (96:4 inseparable mixture of isomers). **3-(Cyclohex-1-enyl)-4-ethylisoquinoline** (major isomer): ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 1.71-1.89 (m, 4H), 2.21-2.27 (m, 2H), 2.37-2.42 (m, 2H), 3.07 (q, J = 7.5 Hz, 2H), 5.77 (dddd, J = 1.8, 1.8, 3.6, 3.6 Hz, 1H), 7.51 (ddd, J = 0.9, 6.9, 7.8 Hz, 1H), 7.67 (ddd, J = 1.2, 6.9, 9.9 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 9.08 (s, 1H). **4-(Cyclohex-1-enyl)-3-ethylisoquinoline** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3H), 2.90 (dq, J = 1.5, 14.7 Hz, 2H), 5.68 (dddd, J = 2.1, 2.1, 3.3, 3.3 Hz, 1H), 7.47 (ddd, J = 0.9, 6.9, 7.8 Hz, 1H), 7.60 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 11.7 Hz, 1H), 9.13 (s, 1H). Additional spectral data for the product mixture: ^{13}C NMR ($CDCl_3$) δ 16.1, 21.8, 22.2, 23.1, 25.4, 26.6, 123.6, 126.1, 126.9, 127.6, 128.3, 129.3, 130.1, 135.3, 138.7, 150.1, 154.5; IR

($CHCl_3$, cm^{-1}) 3059, 3025, 2929, 1619, 1569; HRMS calcd for $C_{17}H_{19}N$: 237.1518. Found: 237.1515.

3-Phenylisoquinoline (18). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 88 mg (85%) of the indicated compound with spectral properties identical to those previously reported[21]: mp 102-103 °C (lit.[21] mp 101-102 °C).

3-(Cyclohex-1-enyl)isoquinoline (19). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 81 mg (77%) of the indicated compound as a yellow solid: mp 114-115 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.67-1.75 (m, 2H), 1.81-1.89 (m, 2H), 2.29-2.36 (m, 2H), 2.54-2.60 (m, 2H), 7.02 (tt, J = 2.4, 3.6 Hz, 1H), 7.48 (dt, J = 0.6, 14.4 Hz, 1H), 7.57 (s, 1H), 7.63 (dd, J = 1.2, 6.9 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.1, 26.1, 26.2, 114.2, 126.4, 126.8, 127.6, 128.4, 130.3, 135.7, 136.7, 151.7, 152.5 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3060, 2919, 1621, 1574; MS *m/z* (rel intensity) 209 (100, M^+), 208 (89), 194 (42), 180 (51). Anal. Calcd for $C_{15}H_{15}N$: C, 86.09; H, 7.23; N, 6.69. Found: C, 86.03; H, 7.30; N, 6.73.

6,7-Dimethoxy-3,4-diphenylisoquinoline (21). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 138 mg (82%) of the indicated compound as a white solid (mp 181-182 °C): ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.03 (s, 3H), 6.91 (s, 1H), 7.16-7.18 (m, 3H), 7.23-7.26 (m, 3H), 7.33-7.36 (m, 5H), 9.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 56.2, 104.0, 105.3, 123.7, 126.9, 127.4,

127.6, 128.5, 129.7, 130.3, 131.1, 132.6, 137.8, 141.2, 149.2, 149.7, 150.1, 153.0; IR ($CHCl_3$, cm^{-1}) 3055, 3021, 2960, 1620, 1501; MS (CI) *m/z* 342 (M+1). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.74; H, 5.69; N, 3.99.

Ethyl 6,7-dimethoxy-3-phenylisoquinoline-4-carboxylate (22). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 146 mg (95%) of the indicated compound as a white solid: mp 110-111 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 7.17 (s, 1H), 7.31 (s, 1H), 7.34-7.40 (m, 3H), 7.62 (dd, *J* = 1.5, 6.6 Hz, 2H), 9.08 (s,1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 56.1, 56.2, 61.6, 102.5, 105.5, 121.9, 123.3, 128.2, 128.3, 128.7, 130.4, 140.9, 150.5, 150.7, 150.8, 154.1, 169.2; IR ($CHCl_3$, cm^{-1}) 3068, 2978, 1716, 1620, 1578, 1505; MS *m/z* (rel intensity) 337 (82, M^+), 308 (100), 292 (38). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.85; H, 5.70; N, 4.02.

Ethyl 6,7-dimethoxy-4-phenylisoquinoline-3-carboxylate (23). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 7 mg (5%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.2 Hz, 3H), 3.77 (s, 3H), 4.06 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 6.83 (s, 1H), 7.25 (s, 1H), 7.33 (dd, *J* = 1.8, 7.5 Hz, 2H), 7.44-7.56 (m, 3H), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 56.0, 56.3, 61.3, 104.7, 105.4, 127.9, 128.4, 128.5, 129.5, 132.0, 132.1, 132.2, 132.3, 151.5, 153.4; HRMS calcd for $C_{20}H_{19}NO_4$: 337.1315. Found: 337.1314.

6,7-Dimethoxy-4-methyl-3-phenylisoquinoline (24). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 94 mg (67%) of the indicated compound as a white solid: mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 7.16 (s, 1H), 7.19 (s, 1H), 7.36 (ddd, J = 1.2, 7.2, 8.4 Hz, 1H), 7.44 (ddd, J = 1.8, 5.1, 7.5 Hz, 2H), 7.55 (dd, J = 1.5, 8.4 Hz, 2H), 8.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.8, 56.1, 102.1, 105.8, 122.8, 123.4, 127.4, 128.1, 129.9, 132.8, 141.7, 147.7, 149.9, 151.0, 153.0 (one sp^3 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3058, 2942, 1620, 1579, 1506; MS (CI) *m/z* 280 (M+1). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.14; H, 6.20; N, 4.95.

6,7-Dimethoxy-3-methyl-4-phenylisoquinoline (25). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 24 mg (17%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.74 (s, 3H), 4.02 (s, 3H), 6.62 (s, 1H), 7.20 (s, 1H), 7.30 (dt, J = 1.8, 6.6 Hz, 2H), 7.41-7.55 (m, 3H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 55.9, 56.1, 103.3, 105.3, 123.0, 127.6, 128.5, 128.8, 130.0, 132.1, 132.2, 132.7, 138.1, 147.6, 148.4, 149.7, 153.1; HRMS calcd for $C_{18}H_{17}NO_2$: 279.1259. Found: 279.1256.

7,8-Diphenyl-1,3-dioxolo[4,5-*g*]isoquinoline (27). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 135 mg (83%) of the indicated compound as an off-white solid: mp 234-235 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 2H), 6.90 (s, 1H), 7.15-7.33 (m, 11H), 9.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 101.7, 102.1, 103.0, 124.9, 127.0, 127.4, 127.6, 128.4, 130.2, 131.1,

134.5, 137.7, 140.9, 148.1, 149.5, 150.1, 151.3; IR ($CDCl_3$, cm^{-1}) 3082, 3060, 1457; HRMS calcd for $C_{22}H_{15}NO_2$: 325.1103. Found: 325.1098.

8-Methyl-7-phenyl-1,3-dioxolo[4,5-*g*]isoquinoline (28). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 101 mg (77%) of the indicated compound as an off-white solid: mp 153-154 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H), 6.05 (s, 2H), 7.15 (s, 1H), 7.23 (s, 1H), 7.35 (ddd, J = 1.8, 5.4, 6.6 Hz, 1H), 7.43 (t, J = 5.4 Hz, 2H), 7.52 (dd, J = 0.9, 6.3 Hz, 2H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.0, 100.2, 101.7, 103.5, 123.6, 124.6, 127.5, 128.1, 129.8, 134.6, 141.4, 147.8, 148.0, 151.2, 151.3; IR ($CHCl_3$, cm^{-1}) 1584, 1486, 1462; MS *m/z* (rel intensity) 263 (47, M^+), 262 (100). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.95; H, 5.19; N, 5.29.

7-Methyl-8-phenyl-1,3-dioxolo[4,5-*g*]isoquinoline (29). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 18 mg (14%) of the indicated compound as a viscous yellow oil: ^1H NMR ($CDCl_3$) δ 2.41 (s, 3H), 6.03 (s, 2H), 6.64 (s, 1H), 7.19 (s, 1H), 7.25 (dt, J = 1.5, 6.6 Hz, 2H), 7.41-7.54 (m, 3H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.0, 101.5, 101.6, 102.9, 124.2, 127.6, 128.8, 130.0, 130.9, 134.4, 138.2, 147.5, 148.2, 149.0, 151.1; IR ($CDCl_3$, cm^{-1}) 1653, 1540, 1521, 1456; HRMS calcd for $C_{17}H_{13}NO_2$: 263.0946. Found: 263.0943.

3,4-Diphenyl-6-isoquinolinecarboxaldehyde (31). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 134 mg (87%) of the indicated compound as a white solid: mp 154-155 °C; ^1H NMR ($CDCl_3$) δ 7.19-7.29 (m, 5H), 7.35-7.43 (m, 5H), 8.04-8.17 (m, 3H), 9.45 (d, J = 0.6 Hz, 1H), 10.02

(s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.8, 127.6, 127.9, 128.0, 128.8, 128.9, 129.4, 130.3, 131.2, 131.7, 132.1, 135.8, 136.4, 137.5, 140.2, 151.9, 152.2, 192.1; IR ($CDCl_3$, cm^{-1}) 3055, 2962, 1699, 1558; MS *m/z* (rel intensity) 309 (62, M^+), 308 (100). Anal. Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.09; H, 5.04; N, 4.47.

4-Methyl-3-phenyl-6-isoquinolinecarboxaldehyde (32). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 86 mg (69%) of the indicated compound as an off-white solid: mp 126-127 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.73 (s, 3H), 7.39-7.52 (m, 3H), 7.59 (dd, J = 1.5, 8.4 Hz, 2H), 8.03-8.10 (m, 2H), 8.54 (s, 1H), 9.27 (s, 1H), 10.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.7, 124.0, 125.5, 128.1, 128.3, 129.4, 129.4, 129.5, 129.9, 136.0, 137.2, 140.7, 150.3, 153.4, 192.2 ; IR ($CHCl_3$, cm^{-1}) 1696, 1684, 1577, 1417; HRMS calcd for $C_{17}H_{13}NO$: 247.0997. Found: 247.0991.

3,4-Diphenyl-5,6,7,8-tetrahydroisoquinoline (34). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 103 mg (72%) of the indicated compound as an off-white solid: mp 143-144 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.71-1.84 (m, 4H), 2.46 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.3 Hz, 2H), 7.05-7.08 (m, 2H), 7.12-7.15 (m, 3H), 7.22-7.27 (m, 5H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.9, 26.8, 28.2, 126.98, 127.00, 127.5, 128.2, 129.8, 130.3, 131.5, 135.4, 138.4, 141.0, 145.2, 149.3, 154.6; IR ($CHCl_3$, cm^{-1}) 1552, 1449, 1433; MS *m/z* (rel intensity) 285 (50, M^+), 284 (100). Anal. Calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.32; H, 6.76; N, 4.99.

Ethyl 3-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxylate (35). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 140 mg (99%) of the indicated compound as a red solid: mp 77-78 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 6.9 Hz, 3H), 1.81 (tt, J = 3.6, 6.0 Hz, 4H), 2.77-2.81 (m, 4H), 4.10 (q, J = 7.2 Hz, 2H), 7.31-7.41 (m, 3H), 7.53-7.57 (m, 2H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.1, 22.3, 26.4, 26.5, 61.4, 128.3, 128.3, 128.4, 128.6, 131.5, 140.2, 144.1, 150.8, 153.6, 168.9; IR ($CHCl_3$, cm^{-1}) 2977, 1718, 1558; MS *m/z* (rel intensity) 281 (39, M$^+$), 252 (100), 209 (40). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.92; H, 6.85; N, 4.93.

4-Methyl-3-phenyl-5,6,7,8-tetrahydroisoquinoline (36). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 83 mg (74%) of the desired compound as a white solid: mp 49-50 °C; ^{1}H NMR ($CDCl_3$) δ 1.76-1.92 (m, 4H), 2.17 (s, 3H), 2.66 (t, J = 6.0 Hz, 2H), 2.78 (t, J = 6.3 Hz, 2H), 7.34-7.48 (m, 5H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.9, 22.3, 23.0, 26.9, 127.5, 128.1, 128.9, 129.3, 131.2, 141.5, 145.4, 147.4, 156.0; IR (Et_2O, cm^{-1}) 3026, 2931, 1653, 1558; MS *m/z* (rel intensity) 223 (39, M$^+$), 222 (100). Anal. Calcd for $C_{16}H_{17}N$: C, 86.06; H, 7.67; N, 6.27. Found: C, 85.90; H, 7.83; N, 6.25.

4-Hydroxymethyl-3-phenyl-5,6,7,8-tetrahydroisoquinoline (37). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 120 mg (100%) of the desired compound as a white solid: mp 175-176 °C; ^{1}H NMR ($CDCl_3$) δ 1.79-1.83 (m, 4H), 2.77 (t, J = 6.0 Hz, 2H), 2.91 (t, J = 5.4 Hz, 2H) 4.53 (s, 2H), 7.34-7.41 (m, 3H), 7.50-7.53 (m, 2H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2,

22.7, 25.7, 26.8, 59.0, 127.9, 128.2, 129.3, 130.7, 132.1, 140.4, 147.2, 149.4, 156.8; IR ($CHCl_3$, cm^{-1}) 3232, 2933, 1558; HRMS calcd for $C_{16}H_{17}NO$: 239.1310. Found: 239.1307.

6,7-Dihydro-5*H*[2]-3,4-diphenylpyrindine (39). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 96 mg (71%) of the indicated compound with spectral properties identical to those previously reported[22]: mp 101-102 °C (lit.[22] mp 104-105 °C); ^1H NMR ($CDCl_3$) δ 2.10 (quintet, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 7.10-7.14 (m, 2H), 7.16-7.20 (m, 3H), 7.22-7.33 (m, 5H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 30.8, 32.9, 127.0, 127.3, 127.7, 128.2, 129.9, 130.0, 132.7, 138.6, 138.9, 140.7, 144.2, 153.7, 155.1; HRMS calcd for $C_{20}H_{16}N$: 270.1283. Found: 270.1283.

6,7-Dihydro-5*H*[2]-4-methyl-3-phenylpyrindine (40). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 100 mg (96%) of the indicated compound as an off-white solid: mp 60-61 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.15 (quintet, 2H), 2.25 (s, 3H), 2.90 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 7.33-7.51 (m, 5H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 24.8, 30.7, 32.0, 127.0, 127.6, 128.1, 129.2, 138.4, 141.1, 142.6, 153.9, 156.4; IR ($CHCl_3$, cm^{-1}) 1591, 1459, 1437, 1397; MS *m/z* (rel intensity) 209 (34, M^+), 208 (100). Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.12; H, 7.40; N, 6.71.

6,7-Dihydro-5*H*[2]-4-hydroxymethyl-3-phenylpyrindine (41). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 81 mg (72%) of the indicated compound as a white solid: mp 158-159 °C

(hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.93 (br s, 1H), 2.18 (quintet, J = 7.5 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 4.64 (s, 2H), 7.36-7.46 (m, 3H), 7.55-7.58 (m, 2H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 30.5, 31.5, 60.4, 128.1, 128.3, 129.0, 129.2, 139.4, 140.1, 144.7, 155.1, 156.8; IR (CH_2Cl_2, cm^{-1}) 3207, 2915, 1594, 1432; MS *m/z* (rel intensity) 225 (58, M^+), 224 (100). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.91; H, 6.72; N, 6.33.

1,2-Diphenyl-5,6-dihydrobenzo[*f*]isoquinoline (43). The reaction mixture was chromatographed using hexanes/EtOAc to afford 142 mg (85%) of the desired compound as a white solid: mp 198-199 °C; ^{1}H NMR ($CDCl_3$) δ 2.90 (dddd, J = 3.3, 7.5, 13.8, 13.8 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.79 (ddd, J = 1.2, 1.2, 8.1 Hz, 1H), 7.06 (dd, J = 1.8, 7.5 Hz, 1H), 7.09-7.26 (m, 10H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.9, 29.5, 125.7, 127.0, 127.1, 127.6, 127.8, 128.3, 128.5, 129.8, 131.3, 131.7, 132.1, 132.4, 132.9, 139.2, 140.4, 141.2, 141.4 147.5, 158.0; HRMS Calcd for $C_{25}H_{19}N$: 333.1441. Found: 332.1439 (M-H).

1-Ethyl-2-phenyl-5,6-dihydrobenzo[*f*]isoquinoline (44). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 135 mg (94%) of the indicated compound as a white solid: mp 121-122 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 2.79 (dddd, J = 3.9, 6.6, 11.4, 11.4 Hz, 4H), 3.06 (t, J = 7.5 Hz, 2H), 7.31-7.35 (m, 3H), 7.37-7.52 (m, 5H) 7.80 (ddd, J = 1.2, 1.2, 3.9 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 23.2, 27.2, 29.8, 126.5, 127.6, 128.2, 128.2, 128.3, 128.6, 129.0, 133.0, 133.2, 140.7, 142.2, 142.2, 145.3, 160.1;

IR ($CHCl_3$, cm^{-1}) 3062, 2938, 1559, 1440; HRMS calcd for $C_{21}H_{19}N$: 285.1518. Found: 284.1446 (M-H).

5-Methyl-2,3,4-triphenylpyridine (**46**). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 110 mg (68%) of the indicated compound as a white solid: mp 119-120 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 6.81-6.85 (m, 2H), 6.95-7.00 (m, 5H), 7.14-7.29 (m, 8H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 126.3, 127.0, 127.2, 127.4, 127.7, 128.0, 129.3, 129.9, 130.2, 131.3, 134.8, 138.2, 138.3, 141.0, 149.6, 149.9, 155.9; IR ($CHCl_3$, cm^{-1}) 3055, 3026, 2971, 1560, 1431; HRMS calcd for $C_{24}H_{19}N$: 321.1518. Found: 321.1510.

3,5-Dimethyl-2,4-diphenylpyridine (**47**). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 85 mg (65%) of the indicated compound as a white solid: mp 84-85 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.06 (s, 3H), 7.17 (dt, J = 1.5, 8.1 Hz, 2H), 7.34-7.55 (m, 8H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.6, 18.1, 127.6, 127.7, 128.2, 128.2, 128.5, 128.9, 129.2, 129.9, 139.0, 141.4, 147.7, 150,7, 157.1; IR ($CHCl_3$, cm^{-1}) 3057, 2924, 1604, 1577, 1458; HRMS calcd for $C_{19}H_{17}N$: 259.1361. Found: 258.1288 (M-H).

3-(Hydroxymethyl)-5-methyl-2,4-diphenylpyridine (**48**). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 131 mg (95%) of the indicated compound as a white solid: mp 152-153 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.24 (br s, 1H), 4.24 (s, 2H), 7.24 (dd, J = 1.2, 6.3 Hz, 2H), 7.35-7.47 (m, 6H), 7.65 (dd, J = 1.5, 6.3 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$)

δ 17.5, 59.5, 127.9, 128.1, 128.2, 128.4, 128.8, 129.3, 130.6, 130.7, 137.6, 140.2, 149.5, 151.5, 157.9; IR ($CHCl_3$, cm^{-1}) 3237, 3058, 2967, 1574, 1545, 1441; MS *m/z* (rel intensity) 275 (61, M^+), 274 (100). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.84; H, 6.32; N, 5.17.

2,3,4-Triphenylpyridine (50). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 81 mg (52%) of the indicated compound with spectral properties identical to those previously reported[23]: mp 188-189 °C (lit.[23] mp 189-190 °C).

3-(Hydroxymethyl)-2,4-diphenylpyridine (51). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 104 mg (79%) of the desired compound as a white solid: mp 153-154 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.59 (br s, 1H), 4.51 (d, J = 5.4 Hz, 2H), 7.24 (d, J = 5.1 Hz, 1H), 7.44-7.54 (m, 8H), 7.70 (dd, J = 1.8, 6.3 Hz, 2H), 8.66 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 59.4, 123.9, 128.3, 128.4, 128.4, 128.5, 129.0, 129.3, 130.8, 138.9, 140.2, 148.3, 152.1, 160.9; IR ($CHCl_3$, cm^{-1}) 3246, 3059, 2975, 1576, 1496, 1443; MS *m/z* (rel intensity) 261 (62, M^+), 260 (100). Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.43; H, 5.72; N, 5.36.

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CHAPTER 2. SYNTHESIS OF ISOQUINOLINES AND PYRIDINES VIA PALLADIUM- AND COPPER-CATALYZED COUPLING AND CYCLIZATION OF TERMINAL ACETYLENES: THE TOTAL SYNTHESIS OF DECUMBENINE B

A paper to be submitted to the *Journal of Organic Chemistry*

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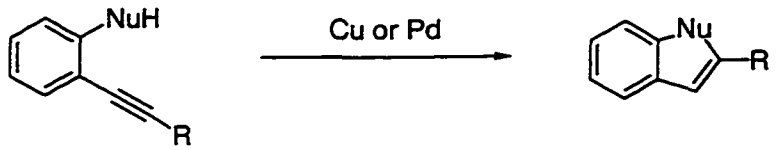
Abstract

Mono-substituted isoquinolines and pyridines have been prepared in good to excellent yields via coupling of terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes. In addition, isoquinoline heterocycles have been prepared in excellent yields via copper-catalyzed cyclization of iminoalkynes. The choice of cyclization conditions is dependent upon the nature of the terminal acetylene that is employed, as only aryl and alkenyl acetylenes cyclize under the palladium-catalyzed reaction conditions that have been developed. However, aryl-, vinylic-, and alkyl-substituted acetylenes undergo palladium-catalyzed coupling and subsequent copper-catalyzed cyclization in excellent yields. Finally, the total synthesis of the isoquinoline natural product decumbenine B has been accomplished in 7 steps

and 20% overall yield by employing this palladium-catalyzed coupling and cyclization methodology.

Introduction

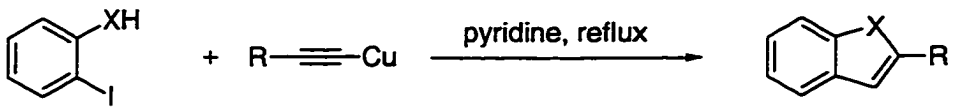
The palladium-catalyzed annulation of alkynes has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles. For example, the annulation of internal alkynes has been employed by Larock and co-workers for the synthesis of indoles,[1] benzofurans,[2] benzopyrans,[2] isocoumarins,[2] indenones,[3] isoquinolines,[4] α-pyrones,[5] and polycyclic aromatic hydrocarbons.[6] The transition metal-catalyzed cyclization of disubstituted alkynes (formed from coupling of aryl and vinylic halides with terminal alkynes), which possess a nucleophile in proximity to the triple bond, by either copper or palladium-based methodologies, has also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles (eq 1).



(1)

The copper-promoted cyclization of disubstituted alkynes containing nucleophilic sites in the ortho position was first reported by Castro and co-workers in 1963 for the synthesis of benzofurans, indoles, and phthalides (eq 2).[7] However, the synthesis of these heterocycles suffers the disadvantage of requiring

harsh reaction conditions (110-120 °C) and stoichiometric amounts of copper acetylides. In subsequent years, considerable attention has been given to the development of other transition metal-based methods for the synthesis of the indole nucleus from substituted *o*-alkynyl and *o*-arylethynylanilines.[8] However, the procedures that have been developed also suffer from the use of stoichiometric amounts of organometallic intermediates, elevated temperatures, and the inability to accomodate a wide variety of functionality.

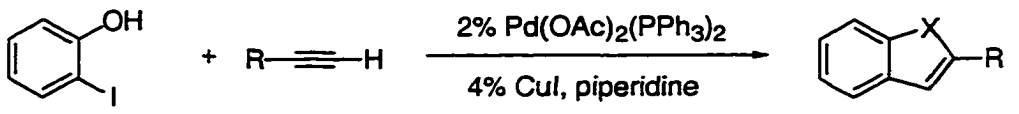


(2)

R = aryl
X = O, NH, COO

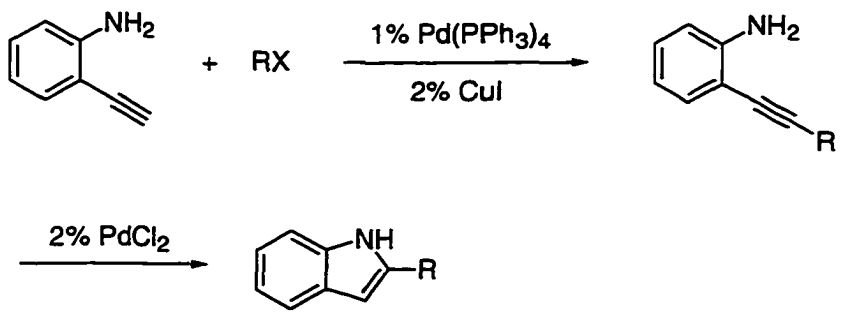
The synthesis of the aforementioned heterocycles was considerably improved by the use of palladium-catalyzed coupling and cyclization methodology. Cacchi and co-workers subsequently reported improved procedures for the benzofuran and indole syntheses by employing catalytic amounts of palladium and copper salts. The synthesis of the benzofuran nucleus has been accomplished by the palladium-catalyzed coupling of *o*-iodophenol and terminal alkynes, followed by a Pd(II)-catalyzed cyclization of the resulting disubstituted alkynes (eq 3),[9] while the indole synthesis has been achieved by the coupling of *o*-ethynylaniline with aryl and vinylic halides, followed by a Pd(II)-catalyzed cyclization of the resulting disubstituted alkynes (eq 4).[10] The

advantages of these processes over previously reported syntheses are the ready availability of starting materials, the decreased need for the synthesis of organometallic starting materials, and exceptional tolerance of functionality. Since the first reports of this palladium-catalyzed coupling and cyclization methodology, numerous syntheses of carbo- and heterocycles have been reported by employing this methodology with a wide variety of nucleophiles,[11] as well as syntheses employing solid supports.[12]



(3)

R = alkyl, aryl

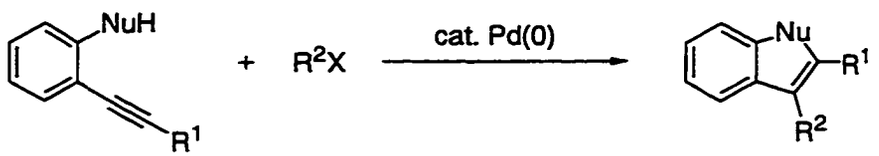


(4)

R = aryl, vinylic, heteroaryl
X = iodide, bromide, triflate

The cyclization of disubstituted alkynes promoted by σ-vinyl-, σ-aryl-, and σ-alkynylpalladium complexes generated *in situ* from unsaturated halides or triflates is also currently of great interest (eq 5). The utilization of readily available

acetylenic and unsaturated triflate and halide precursors, in addition to the ability to generate complex molecular skeletons regio- and stereoselectively, has made this methodology especially attractive.



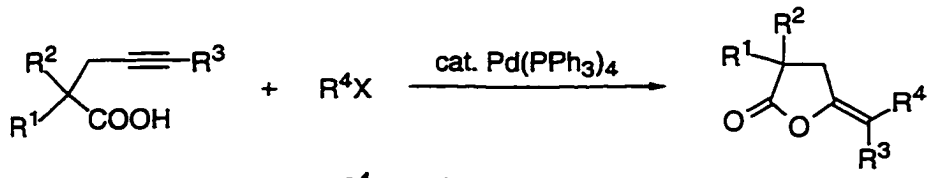
(5)

R^1 = alkyl, aryl, vinylic

R^2 = aryl, alkenyl, vinylic

X = halide, triflate

In the first reports of this type of cyclization reaction, it was shown that enol lactones **2** could be produced regio- and stereoselectively from the palladium-catalyzed reaction of pentynoic acids (**1**) and aryl halides or vinylic triflates (eq 6).[13] Moreover, as an extension of the palladium-catalyzed indole synthesis discussed previously, a two-component approach to the synthesis of 2,3-disubstituted indoles based on the palladium-catalyzed heteroannulation of *o*-alkynyltrifluoroacetanilides with aryl halides and vinylic triflates has been reported (eq 7).[14] In addition to these examples, this methodology has been employed in the synthesis of a wide variety of functionalized carbo- and heterocycles.[15]

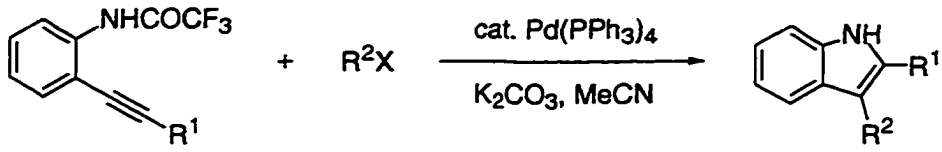


(6)

1 **2**

R^4 = aryl, vinylic

X = halide, triflate



(7)

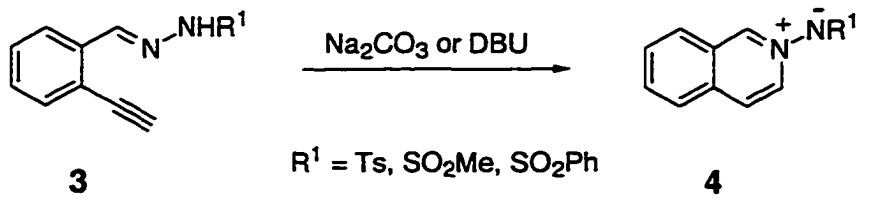
R^1 = alkyl, aryl, vinylic

R^2 = aryl, vinylic

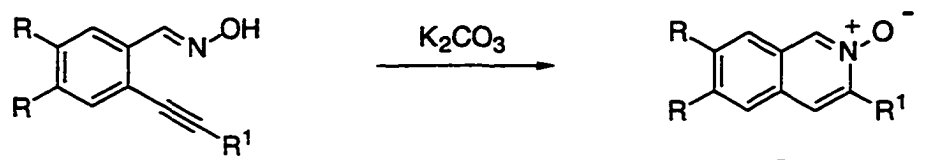
X = halide, triflate

Isoquinoline derivatives have been synthesized via base-catalyzed cyclization of terminal and disubstituted alkynes. For example, Sharp reported the synthesis of *N*-*p*-toluenesulfonylimine isoquinoline, *N*-methanesulfonylimine isoquinoline, and *N*-benzenesulfonyl isoquinoline heterocycles (**4**) in modest yields (40-77%) from the base-induced cyclization of *o*-ethynyl hydrazones **3** (eq 8).[16] The synthesis of these heterocycles is not general, however, as only terminal acetylenes could be cyclized under the reaction conditions employed. The synthesis of isoquinoline *N*-oxides has also been reported using similar methodology (eq 9).[17] Treatment of *o*-alkynyl oximes **5** with K_2CO_3 afforded isoquinoline *N*-oxides **6** in modest yields (39-78%). Finally, the synthesis of 3-substituted isoquinolines has been reported from *o*-ethynylbenzaldehydes and ammonia in modest to excellent yields (45-95%) (eq 10).[18] Few examples of the

latter two syntheses were reported. Therefore, the synthetic utility of these processes cannot be fully determined at this time.

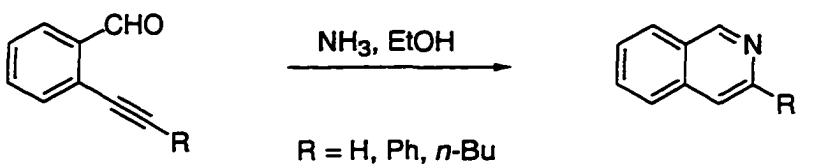


3 4 (8)



5 6 (9)

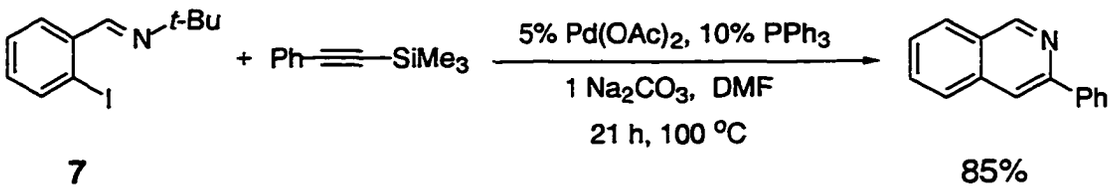
R = H, OMe
R^1 = Ph, *n*-Bu, $SiMe_3$



R = H, Ph, *n*-Bu (10)

During the course of our investigation of the iminoannulation of internal alkynes, we also observed an interesting isoquinoline synthesis (eq 11).[4] To our surprise, 3-phenylisoquinoline, and not the expected disubstituted heterocycle, 4-phenyl-3-(trimethylsilyl)isoquinoline, was isolated in 85% yield from the palladium-catalyzed reaction of *N*-(2-iodobenzylidene)-*tert*-butylamine (**7**) and 1-phenyl-2-(trimethylsilyl)acetylene. Herein, we report a full investigation of this intriguing

reaction and the application of this methodology to the synthesis of the naturally-occurring isoquinoline alkaloid decumbenine B (**46**).

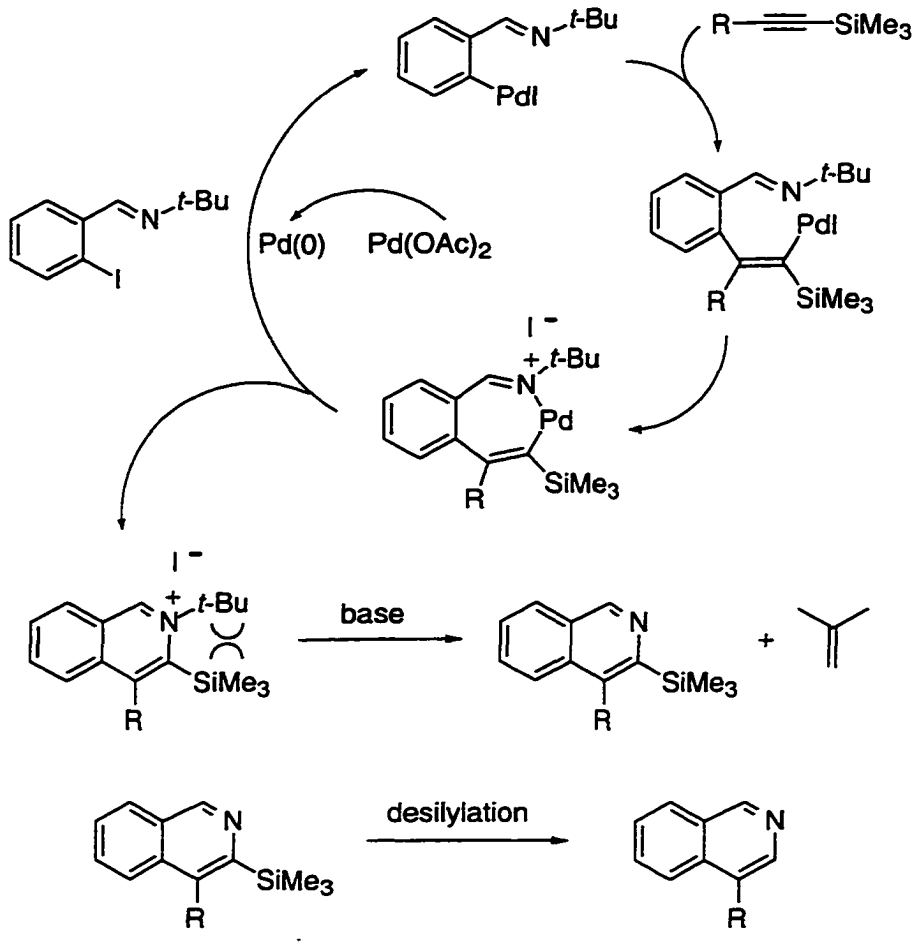


7 85% (11)

Results and Discussion

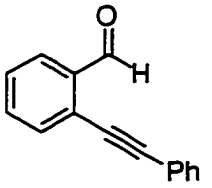
From the results of our internal alkyne annulation investigation, we were compelled to determine the mechanism of this interesting transformation and to define the scope and limitations of this new isoquinoline synthesis. Based on the regiochemical outcome of much of our other alkyne annulation chemistry in which the palladium adds to the more hindered end of the alkyne (Scheme 1), the expected products from the reaction with trimethylsilyl-substituted alkynes were either the 3,4-disubstituted products retaining the silyl group, or the corresponding 4-substituted isoquinoline arising from desilylation of the 3,4-disubstituted isoquinoline.

Scheme 1



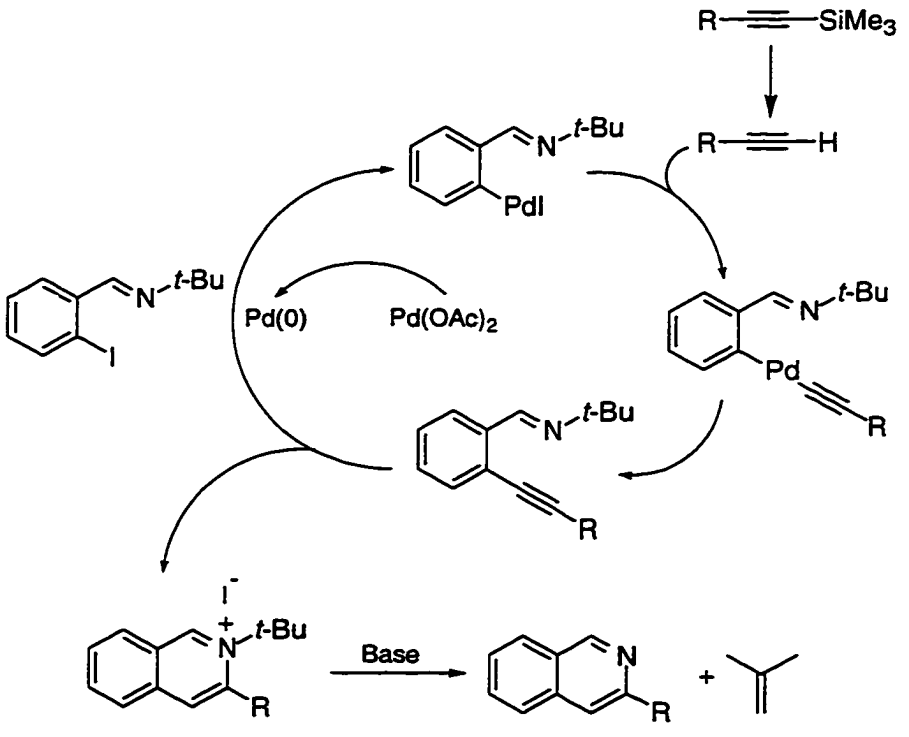
However, since a product was isolated from this reaction in which the trimethylsilyl substituent was not incorporated, and the phenyl substituent was in the 3-position of the isoquinoline, other mechanisms must be operating in this system. This was confirmed by the observation that aldehyde **8** could be isolated if the reactions were not allowed to proceed to completion. Therefore, an alternative mechanistic picture was envisioned for this transformation (Scheme 2). Specifically, oxidative addition of the aryl halide to Pd(0) produces an organopalladium intermediate, which then couples with a terminal acetylene or

acetylide that is formed *in situ*. The disubstituted alkyne that is subsequently produced can then be cyclized by palladium catalysis, thus producing a *tert*-butylisoquinolinium salt. As in our internal alkyne annulation chemistry, the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.[4]



8

Scheme 2



To gain additional insight into this process, iminoalkyne **9** was independently synthesized by a palladium-catalyzed coupling of 2-bromobenzaldehyde and phenylacetylene, followed by imine formation (Scheme 3). Imine **9** was then subjected to a variety of reaction conditions in order to effect its cyclization to 3-phenylisoquinoline (**10**) (eq 12, Table 1). Under the standard palladium reaction conditions that were developed for our internal alkyne isoquinoline synthesis [5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and 1 equiv of Na_2CO_3 in 10 mL of DMF at 100 °C], isoquinoline **10** was isolated in 75% yield after a 39 h reaction time (entry 1). Thus, our assumptions about the mechanism of this process appeared to be correct. We then were interested in optimizing the yield and reaction time for this process.

Scheme 3

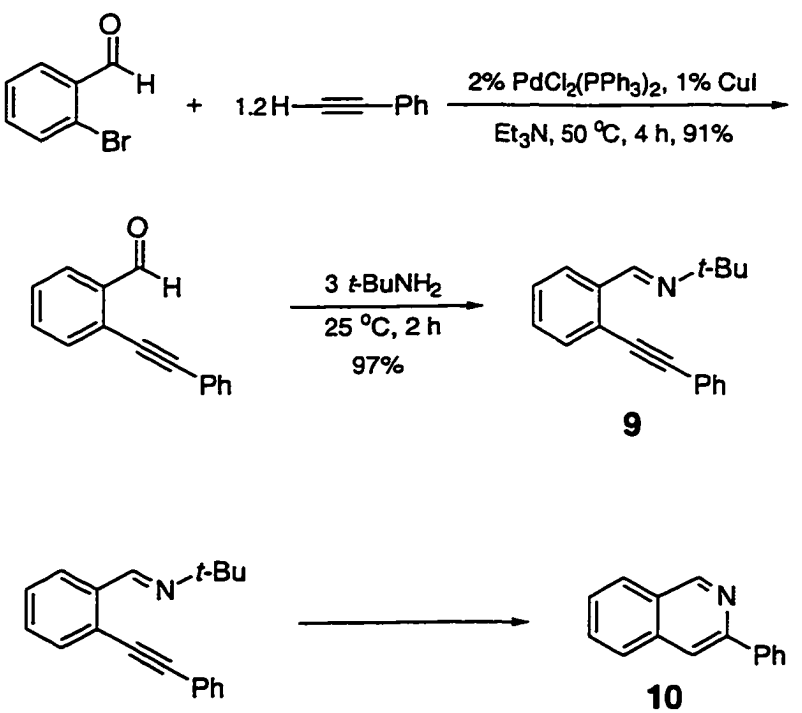


Table 1. Synthesis of 3-Phenylisoquinoline (eq 12).[a]

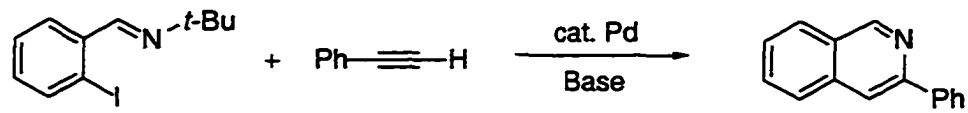
entry	5 mol% Pd cat.	1 equiv Na_2CO_3	10 mol % PPh_3	temp (°C), time (h)	% yield
1	$Pd(OAc)_2$	+	+	100 (39)	75
2	$Pd(OAc)_2$	-	-	100 (14)	78
3	$PdCl_2$	-	-	100 (15)	65
4	$PdCl_2$	+	-	100 (36)	69
5	$PdCl_2(PhCN)_2$	+	-	100 (48)	88
6	$PdCl_2(PhCN)_2$	-	-	100 (42)	58
7	-	-	-	100 (6)	100[b]
8	-	-	-	100 (6)	77[c]
9	-	-	-	130 (45)	57
10	-	+	-	130 (45)	63

[a]All reactions were run with 0.25 mmol of the imine in 5 mL of DMF. [b] 10 mol % CuI was added. [c]5 mol % CuI was added.

Upon removal of the base and the phosphine from the reaction, the desired product was isolated in 78% yield in a shorter reaction time (compare entries 1 and 2). $PdCl_2$ was also observed to promote the cyclization, although a decrease in yield was observed (entries 3 and 4). By employing $PdCl_2(PhCN)_2$ as the palladium catalyst and Na_2CO_3, the desired product was isolated in 88% yield after a 48 hour reaction time (entry 5). Removal of the base from the $PdCl_2(PhCN)_2$ catalyzed reaction, however, resulted in a lower isolated yield of the desired product (entry 6). Interestingly, by employing only CuI as a catalyst, the desired product was obtained in quantitative yield in a short reaction time (entry 7). In an effort to reduce the amount of catalyst that was employed in the reaction, 5 mol % of CuI was added, but a decrease in the yield was observed (entry 8). Finally, this iminoalkyne can also be cyclized thermally, although the yields are lower than either of the palladium or copper-catalyzed cyclizations (entries 9 and 10).

Based on the mechanistic picture that we envisioned for this process, it was expected that terminal acetylenes would also undergo this annulation. Indeed, phenylacetylene was subsequently observed to participate in this palladium-catalyzed annulation (eq 13). However, under the standard internal alkyne annulation conditions, 3-phenylisoquinoline could only be obtained in 62% isolated yield. Thus, we again were interested in optimizing the yield and reaction time for this process. The results of this investigation are shown in Table 2. After optimization of the reaction conditions, we found that by employing 1 equiv of **7**, 1.1 equiv of phenylacetylene, 5 mol % $PdCl_2(PhCN)_2$, and 1 equiv of Na_2CO_3 in DMF at 100 °C, isoquinoline **10** could be isolated in 85% yield after a 14 h

reaction time (entry 10). It is interesting to note that CuI was not required as a co-catalyst for this annulation.



(13)

Table 2. Synthesis of 3-Phenylisoquinoline by Pd-Catalyzed Coupling and Cyclization (eq 13).[a]

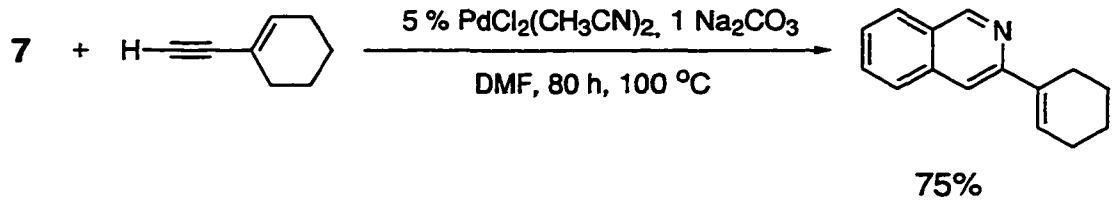
entry	base (equiv)	5 mol % Pd catalyst	5 mol % CuI	10 mol % PPh_3	temp (°C), time (h)	% yield
1	Na_2CO_3 (1)	$Pd(OAc)_2$	-	+	100 (58)	62
2	Na_2CO_3 (1)	$Pd(OAc)_2$	+	+	rt (12), 100 (75)	68
3	NEt_3 (2)	$Pd(OAc)_2$	+	+	rt (12), 100 (22)	60
4	*i*-Pr_2NEt (2)	$Pd(OAc)_2$	+	+	rt (1), 100 (14)	50
5	Na_2CO_3 (1)	$Pd(OAc)_2$	-	-	100 (11)	83[b]
6	NEt_3 (2)	$PdCl_2(PPh_3)_2$	+	-	rt (3), 100 (15)	59
7	Na_2CO_3 (1)	$PdCl_2(PPh_3)_2$	-	-	100 (12)	77[b]
8	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	-	+	100 (72)	78

Table 2. (continued)

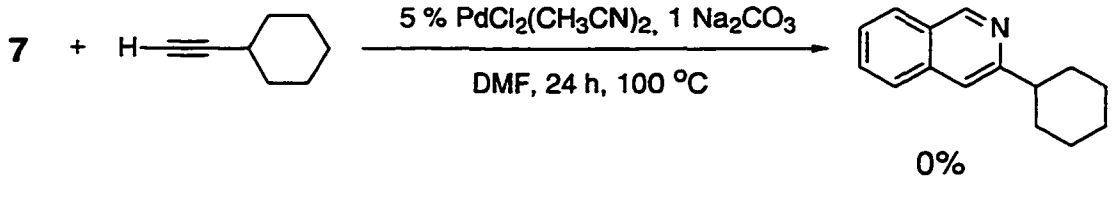
9	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	-	-	100 (30)	60
10	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	-	-	100 (14)	85[b]
11	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	+	-	100 (12)	75[b]
12	Na_2CO_3 (1)	$PdCl_2(PhCN)_2$	-	+	100 (23)	85[b]

[a]All reactions were run with 0.5 mmol of the imine and 1.0 mmol of phenylacetylene in 10 mL of DMF unless otherwise noted. [b]1.1 Equiv of phenylacetylene were used. [c]10 Mol % CuI was added.

After optimization of the reaction conditions with phenylacetylene, we then proceeded to define the scope and limitations of the terminal acetylene annulation. The reaction in which 1-ethynylcyclohexene was employed also afforded the desired isoquinoline in good yield (eq 14). Unfortunately, when cyclohexyl acetylene was employed, none of the desired isoquinoline was obtained (eq 15). In addition, the standard isoquinoline internal alkyne annulation conditions also afforded none of the desired heterocycle. Therefore, we again were interested in finding reaction conditions that would increase the generality of this annulation process.



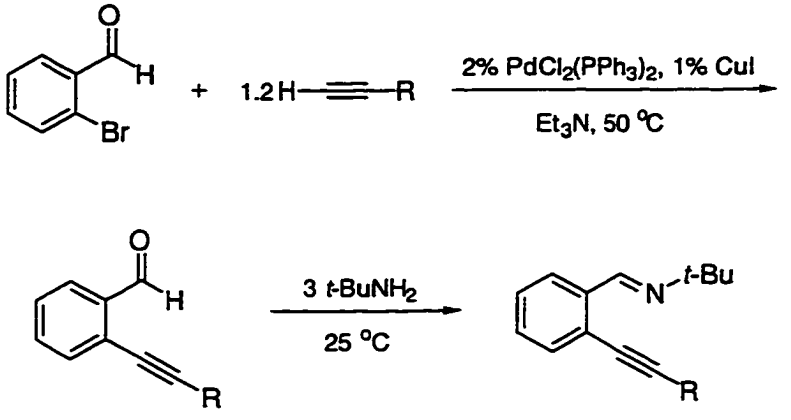
75% (14)



0% (15)

Due to the success of the copper-catalyzed cyclization of iminoalkyne **9** (Table 1, entry 7), the cyclization of iminoalkynes with differing functionality was investigated (Table 3). All of the iminoalkynes employed in this cyclization process were synthesized in excellent yields by the same sequence of transformations used for alkyne **9** (Scheme 4). Although limited success was obtained from the terminal acetylene coupling/cyclization chemistry discussed previously, the copper-catalyzed cyclization proved to be more general with respect to the functionality that can be introduced into the products. For example, iminoalkynes containing aryl, alkenyl, and alkyl substituents afford excellent yields of the desired monosubstituted isoquinoline heterocycles (Table 3, entries 1-4). However, free hydroxy groups are not tolerated in these cyclization reactions (entries 5 and 6), nor were highly hindered iminoalkynes (entry 7).

Scheme 4



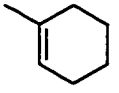
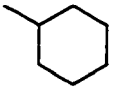
	R	% yield		% yield
11		95	**17**	96
12		95	**18**	95
13	$(CH_2)_2OTHP$	99	**19**	94
14	CH_2OH	89	**20**	96
15	CMe_2OH	96	**21**	97
16	$Si(i\text{-}Pr)_3$	92	**22**	97

Table 3. Synthesis of Isoquinoline Heterocycles by the Cu-Catalyzed Cyclization of Iminoalkynes.[a]

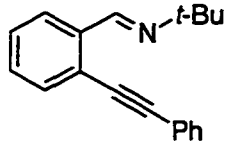
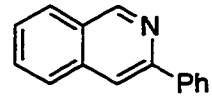
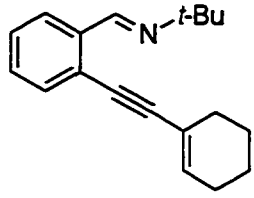
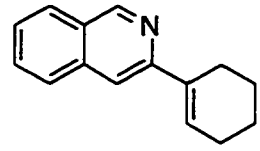
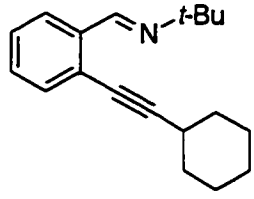
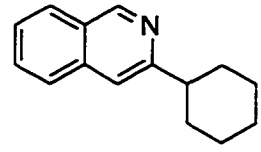
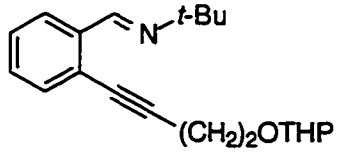
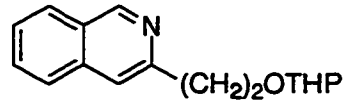
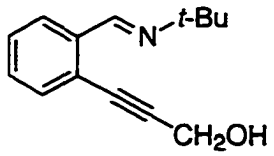
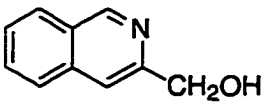
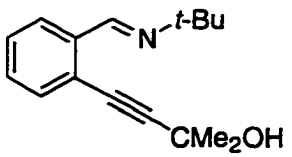
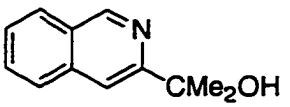
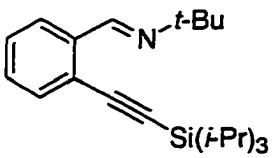
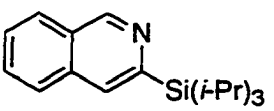
entry	imine	time (h)	product	% yield
1	 **9**	3	 **10**	100
2	 **17**	3	 **23**	81
3	 **18**	6	 **24**	93
4	 **19**	5	 **25**	83

Table 3. (continued)

5	 **20**	12	 **26**	0
6	 **21**	12	 **27**	0
7	 **22**	24	 **28**	0[b]

[a]A representative procedure for the cyclization of iminoalkynes: 10 mol % CuI, the imine (0.25 mmol), and DMF (5 mL) were placed in a 2 dram vial and heated at 100 °C for the indicated time. [b]100% of the starting material was recovered.

Although the copper-catalyzed synthesis was more general than the palladium-catalyzed terminal acetylene coupling/cyclization reactions with respect to the types of functionality that could be incorporated into the isoquinoline, this synthesis was still not as efficient as the one-pot reaction discussed previously (eqs 13 and 14), since three transformations (coupling, imine formation, and

copper-catalyzed cyclization) were required. Consequently, we more closely examined the reaction of imine **7** and cyclohexyl acetylene with different bases and palladium catalysts (Table 4). By employing Et_3N, instead of Na_2CO_3, as a base in the presence of 5 mol % $Pd(OAc)_2$ and 2.5 mol % CuI, 3-cyclohexylisoquinoline could be isolated in low yield (entry 3). By increasing the amount of CuI to 10 mol %, a slight increase in yield was observed (entry 4). All additional attempts to increase the yield by changing bases and palladium catalysts in this reaction, however, proved futile (entries 5-11).

Table 4. Synthesis of Compound 24 by the Pd-Catalyzed Coupling and Cyclization of Imine 7 and Cyclohexyl Acetylene.[a]

entry	base (equiv)	5 mol % Pd catalyst	CuI (mol %)	temp (°C), time (h)	% yield
1	Na_2CO_3 (1)	$Pd(OAc)_2$	0	100 (24)	0
2	Na_2CO_3 (1)	$Pd(OAc)_2$	10	100 (24)	0
3	Et_3N (1)	$Pd(OAc)_2$	2.5	100 (12)	20
4	Et_3N (1)	$Pd(OAc)_2$	10	100 (12)	26
5	Et_3N (1)	$Pd(OAc)_2$	10	100 (12)	19[b]
6	Et_3N (0.15)	$Pd(OAc)_2$	10	100 (12)	18
7	*i*-Pr_2NEt (1)	$Pd(OAc)_2$	10	100 (11)	15

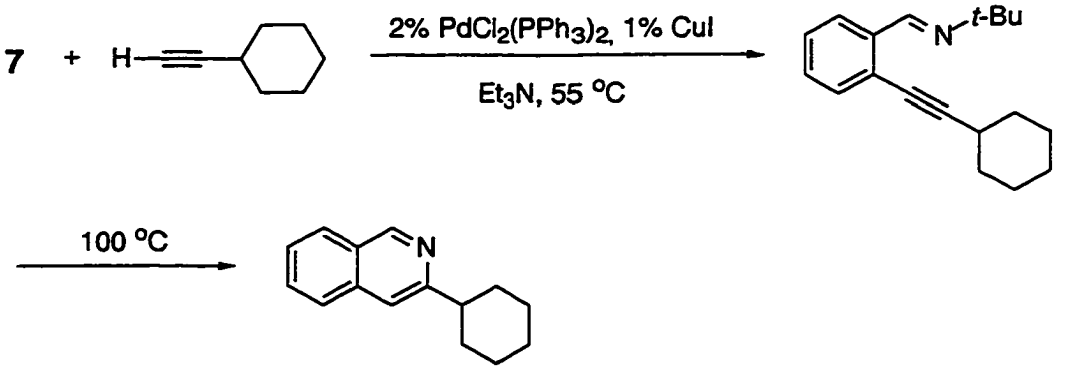
Table 4. (continued)

8	pyridine (1)	$Pd(OAc)_2$	10	100 (11)	10
9	Et_3N (1)	$Pd(dba)_2$	10	100 (10)	14
10	Et_3N (1)	$PdCl_2(CH_3CN)_2$	10	100 (10)	12
11	Et_3N (1)	$PdCl_2(PPh_3)_2$	10	100 (10)	13

[a]All reactions were run with 0.25 mmol of the imine and 1.1 mmol of cyclohexyl acetylene in 5 mL of DMF unless otherwise noted. [b]1.1 Mmol of the imine and 1.0 mmol of cyclohexyl acetylene were employed.

Based on our work up to this point, it was felt that a reasonable mechanism had been formulated for this annulation process (Scheme 2). Specifically, coupling of the aryl halide and terminal acetylene must first occur to produce the intermediate iminoalkyne, followed by a cyclization step to produce the isoquinoline. Therefore, the reaction conditions employed for a one-pot synthesis must be compatible with both steps in the catalytic cycle. Since we had considerable success with the palladium-catalyzed coupling of *o*-bromobenzaldehyde and terminal acetylenes (Scheme 4), and also with the copper-catalyzed cyclization of iminoalkynes (Table 3), we felt that by an appropriate choice of reaction conditions, it should be possible to efficiently synthesize the desired isoquinolines.

We then investigated the use of the coupling conditions employed in Scheme 4 for both the coupling and cyclization steps (eq 16), since triethylamine was employed for the coupling reactions and afforded the best yield of isoquinoline **24** (Table 4, entry 4). The results of this investigation are shown in Table 5. The reactions were run with 2 mol % $PdCl_2(PPh_3)_2$ and 1 mol % CuI in Et_3N at 50 °C to effect the coupling, and then 100 °C to promote the cyclization of the intermediate iminoalkyne **18**. Although only a trace of product was observed under these reactions conditions, it was possible to recover 95% of the intermediate coupled product, thus indicating an efficient coupling step (entry 1). Based on this result, an additional 10 mol % of CuI was added to the reaction mixture after the coupling step had gone to completion, in hopes of promoting the cyclization step. Unfortunately, this also was quite inefficient, although some product was observed (entry 2). Finally, two reactions were run in which an additional 10 mol % of CuI and 3 mL of a solvent were added after the coupling was complete. Unfortunately, this also afforded only trace amounts of the desired isoquinoline (entries 3 and 4).



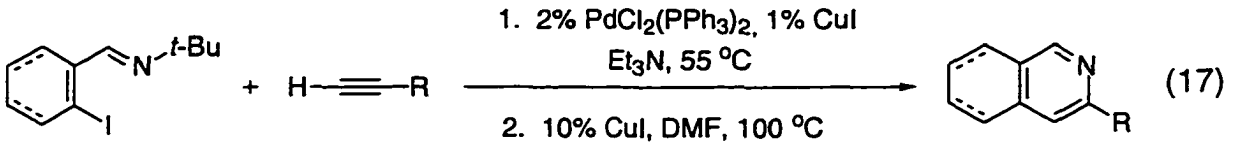
(16)

Table 5. Synthesis of 3-Cyclohexylisoquinoline (eq 16).[a]

entry	coupling time (h)	cyclization time (h)	% yield
1	1	48	trace[b]
2	1	48	22[c]
3	1	48	0[d]
4	1	48	trace[e]

[a]All reactions were run with 0.5 mmol of the imine, 0.6 mmol of cyclohexyl acetylene, 2 mol % of $PdCl_2(PPh_3)_2$, and 1 mol % of CuI in 2 mL of Et_3N unless otherwise noted. [b]A 95% yield of the intermediate alkyne was recovered. [c]An additional 10 mol % of CuI was added after the coupling step was complete. [d]An additional 10 mol % of CuI and 3 mL of Et_3N was added after the coupling step. [e]An additional 10 mol % of CuI and 3 mL of DMF was added after the coupling step.

Based on the results in Table 5, it appeared that the coupling of imine **7** and cyclohexyl acetylene was proceeding in high yield to produce iminoalkyne **18**. However, under the reaction conditions employed, **18** was not efficiently cyclized to isoquinoline **24**. Thus, since the coupling reaction proceeded in high yield in Et_3N, which serves as both the solvent and the base, and our considerable success with the copper-catalyzed cyclization in DMF, modified reaction conditions were developed to incorporate both of these transformations into a single reaction sequence (eq 17).



(17)

We then employed the following reaction conditions for the isoquinoline synthesis: the imine (0.5 mmol), the terminal acetylene (0.6 mmol), 2 mol % of $PdCl_2(PPh_3)_2$, and 1 mol % of CuI in 2 mL of Et_3N were heated at 55 °C until the coupling was judged complete by thin-layer chromatography. The solvent and the precipitates were subsequently removed, and DMF (5 mL) and 10 mol % of CuI were added to the residue. The resulting mixtures were then heated at 100 °C until the cyclization was judged complete by thin-layer chromatography. By employing this reaction sequence, a variety of isoquinolines have been synthesized in good to excellent yields (Table 6).

A variety of functionalized terminal acetylenes has been employed in this palladium and copper-catalyzed process. For example, the reaction of imine **7** with aryl-, alkenyl-, and alkyl-substituted acetylenes affords the desired isoquinolines in good to excellent yields (Table 6, entries 1-7). As in our copper-catalyzed cyclization of iminoalkynes, free hydroxy groups are not tolerated, as the reaction of **7** with 3-butyn-1-ol afforded none of the desired heterocycle. Protection of the free hydroxy group as the tetrahydropyranyl ether on the acetylene, however, afforded the desired isoquinoline in 95% yield (entry 4). Acetal and nitrile functional groups were also tolerated (entries 5 and 6). Using 1,6-heptadiyne as the terminal acetylene afforded bis-isoquinoline **31** in 56% yield. Unfortunately, when the highly hindered terminal alkyne 3,3-dimethyl-1-butyne was employed, aldehyde **45** (imine hydrolysis occurred during purification) was isolated in 95% yield after a 24 hour cyclization time. Thus, this isoquinoline synthesis appears to also be limited to the use of relatively unhindered acetylenes. Finally, isoquinolines **33** and **34** and naphthyridines **36** and **37** have also been synthesized in good yields from imines **32** and **35**, respectively (entries 8-11).

Table 6. Synthesis of Isoquinolines and Pyridines by the Pd-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes (eq 17).[a]

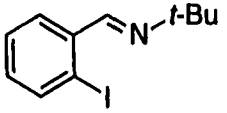
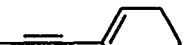
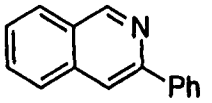
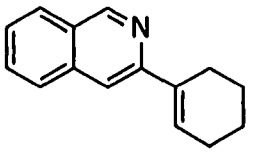
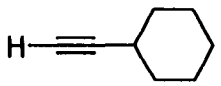
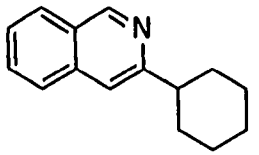
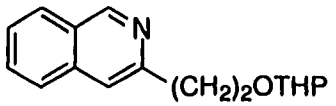
entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
1	 **7**		2	1	 **10**	91
2			1	5	 **23**	81
3			1	2	 **24**	88
4			6	2	 **25**	95

Table 6. (continued)

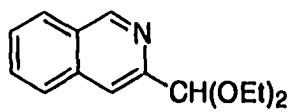
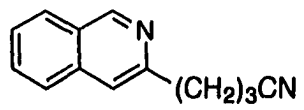
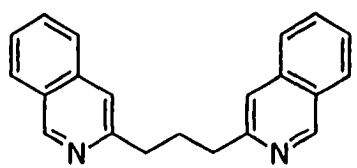
entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
5		H—≡—$CH(OEt)_2$	1	2	 **29**	84
6		H—≡—$(CH_2)_3CN$	1	3	 **30**	87
7		H—≡—$(CH_2)_3$—≡—H	7	8	 **31**	56

Table 6. (continued)

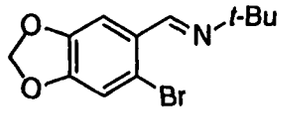
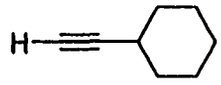
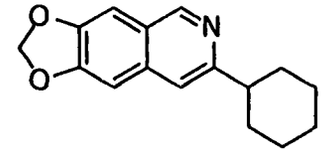
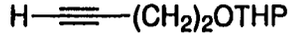
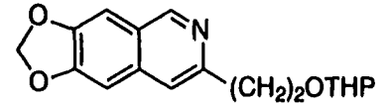
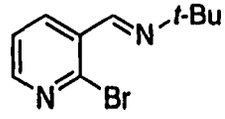
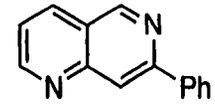
entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
8	 **32**		2	12	 **33**	76
9			8	12	 **34**	81
10	 **35**		2	15	 **36**	85

Table 6. (continued)

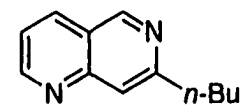
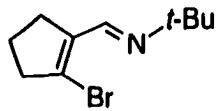
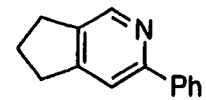
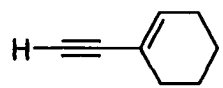
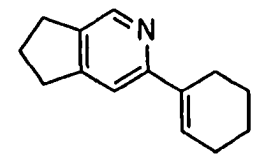
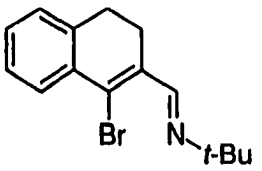
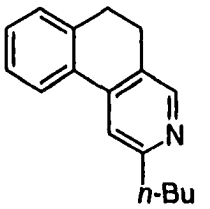
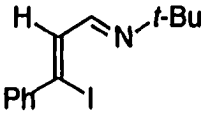
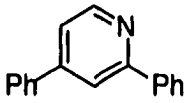
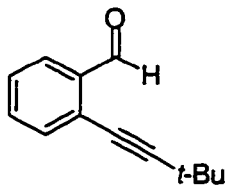
entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
11		H—≡—*n*-Bu	2	15	 **37**	72
12	 **38**	H—≡—Ph	1	24	 **39**	69
13			1	60	 **40**	55

Table 6. (continued)

entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
14	 **41**	H—≡—*n*-Bu	1	48	 **42**	46
15	 **43**	H—≡—Ph	1	36	 **44**	57

[a]All reactions were run using 2 mol % of $PdCl_2(PPh_3)_2$ and 1 mol % of CuI in 2 mL of Et_3N to effect the coupling step, and 10 mol % of CuI in 5 mL of DMF to effect cyclization to the nitrogen heterocycle.



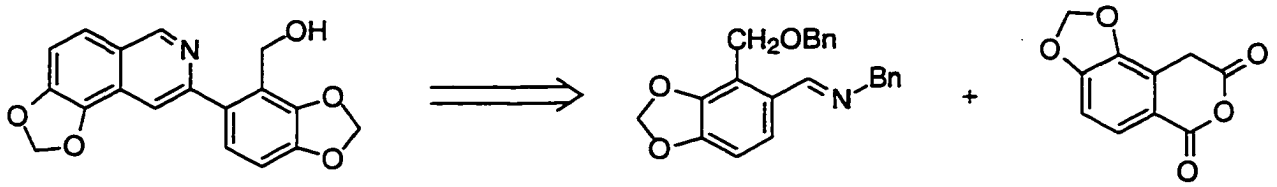
45

As in our isoquinoline synthesis from internal alkynes (Chapter 1), pyridines can be synthesized by employing vinylic imines. Pyridines **36** and **37** have been synthesized from cyclic imine **35**. Unfortunately, this pyridine synthesis appears to be limited to aryl- and alkenyl-substituted acetylenes, since the reaction of imine **35** and *N*-(2-bromocyclohex-1-enylmethylene)-*tert*-butylamine with various alkyl-substituted acetylenes afforded only low yields of the desired pyridines (~10%). Interestingly, the reaction of 1-hexyne and imine **38** did afford pyridine **38** in 46% yield. Finally, pyridine **40** has been synthesized from the acyclic imine **39** in 57% yield.

To demonstrate the utility of this annulation methodology, we have applied this coupling/cyclization process to the synthesis of the naturally-occurring isoquinoline alkaloid decumbenine B (**46**). Decumbenine B was recently isolated in small amounts from the plant tubers of *Corydalis decumbens*, which have been used in Chinese folk herbal medicine for the treatment of paralytic stroke and rheumatic arthritis.[19] One total synthesis of this alkaloid has recently appeared.[20] However, the reported synthesis was accomplished in a low overall yield and 18 steps, by employing as a key step, the condensation of benzyl imine **47** with 5,6-(methylenedioxy)homophthalic anhydride **48** (Scheme 5). Upon observation of

the structure of decumbenine B, we felt that it could be efficiently synthesized by employing the palladium-catalyzed coupling and cyclization methodology discussed previously.

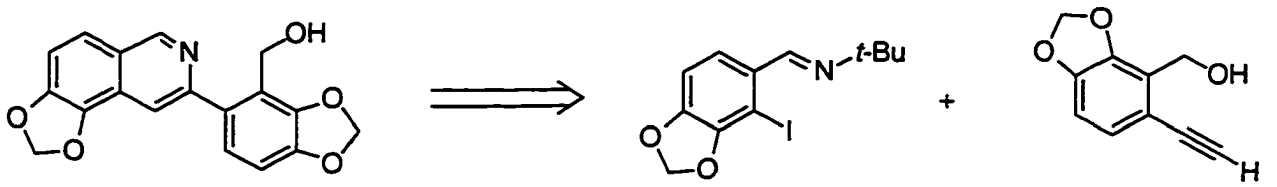
Scheme 5



46 **47** **48**

The retrosynthetic analysis for the synthesis of **46** is shown in Scheme 6. It was envisioned that decumbenine B could be synthesized by the palladium-catalyzed coupling of imine **49** and alkyne **50** with subsequent cyclization of the intermediate iminoalkyne. The starting materials required for the synthesis of decumbenine B were easily prepared in a minimal number of synthetic transformations from the commercially available aldehydes piperonal and 2,3-(methylenedioxy)benzaldehyde.

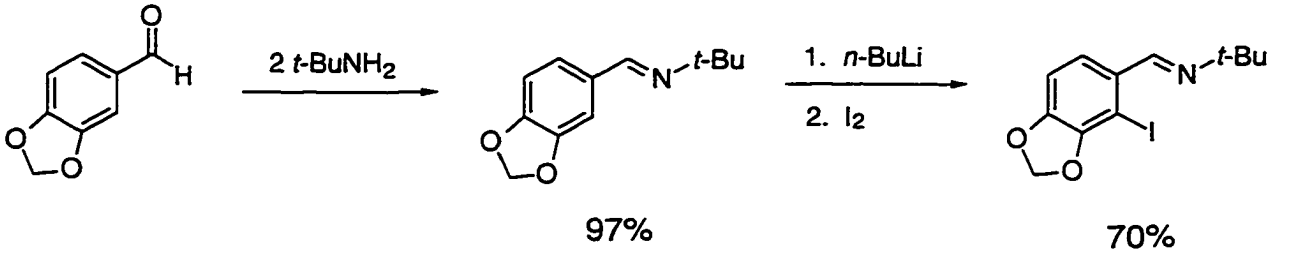
Scheme 6



49 **50**

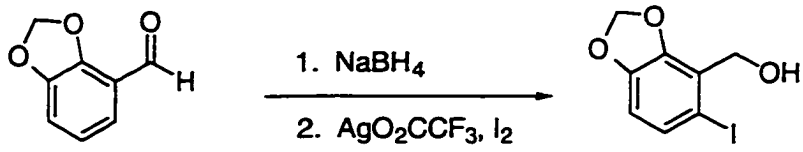
The synthesis of imine **49** was accomplished in two steps as shown in Scheme 7. The *tert*-butyl imine of piperonal was synthesized in high yield and was subjected to previously reported reaction conditions for the metallation of cyclohexylimines derived from piperonal.[21] Treatment of the imine with *n*-BuLi and subsequent quenching with iodine afforded the desired iodinated imine in 70% yield. It is interesting to note that the *tert*-butyl imine served as an excellent protecting group for the lithiation reaction, with no addition products of *n*-BuLi to the imine being observed. In addition, by employing the *tert*-butyl imine, rather than the cyclohexylimine as was reported, several steps involving imine formation and hydrolysis were avoided.

Scheme 7

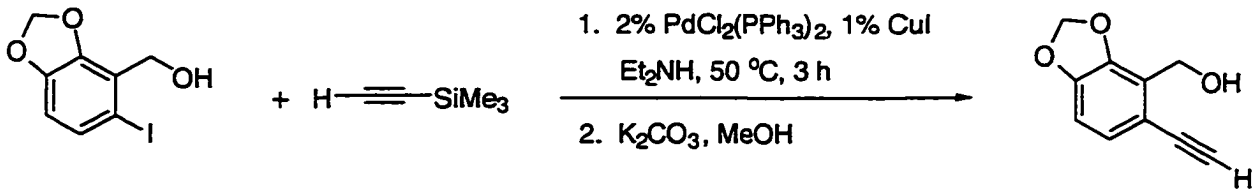


The synthesis of alkyne **50** was accomplished in four steps by the synthetic route shown in Scheme 8. Reduction of 3,4-(methylenedioxy)benzaldehyde to the benzyl alcohol and subsequent iodination afforded the intermediate iodide in 57% overall yield. Alkyne **50** was then synthesized in 98% overall yield by a palladium-catalyzed coupling of the aryl iodide with trimethylsilylacetylene and subsequent desilylation with potassium carbonate.

Scheme 8

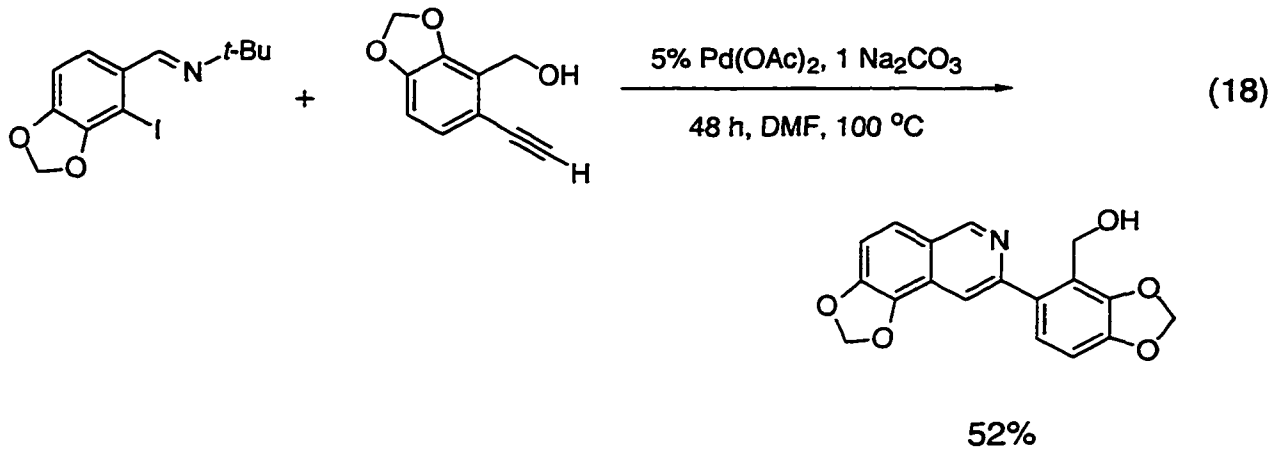


57%



98%

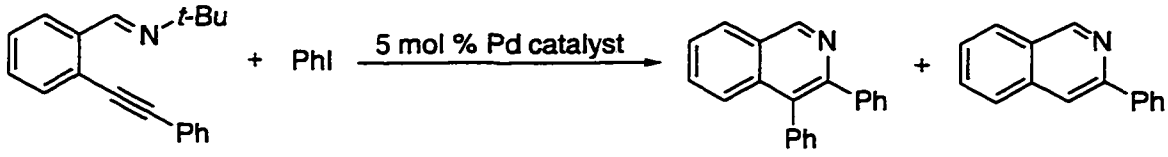
With imine **49** and alkyne **50** in hand, the synthesis of decumbenine B was completed in 52% yield by employing the palladium-catalyzed methodology developed previously (eq 18). In spite of the low yield for the key palladium-catalyzed reaction, this synthesis of decumbenine B was completed in 7 steps and 20% overall yield, which demonstrates the functionality tolerance and effectiveness of this methodology.



(18)

52%

The palladium-catalyzed cyclization/coupling of iminoalkynes and aryl halides has also been investigated for the synthesis of 3,4-disubstituted isoquinolines (eq 19). The reaction of **9** and iodobenzene was chosen as the model system for optimization of the reaction conditions, since the product 3,4-diphenylisoquinoline (**51**) had been synthesized previously via our internal alkyne methodology. The results of those preliminary studies are summarized in Table 7.



(19)

9 **51** **10**

Table 7. Synthesis of 3,4-Diphenylisoquinoline by the Pd-Catalyzed Cyclization of Iminoalkynes (eq 19).[a]

entry	PhI (equiv)	5 mol % Pd catalyst	base	temp (°C)	time (h)	% isolated yield (**51** + **10**)
1	2	$Pd(OAc)_2$	Na_2CO_3	100	10	36 + 4[b]
2	1.1	$Pd(dba)_2$	Na_2CO_3	100	3	54 + 14
3	2	$Pd(dba)_2$	Na_2CO_3	100	2	80 + 16
4	2	$Pd(dba)_2$	Na_2CO_3	80	8	73 + 0
5	3	$Pd(dba)_2$	Na_2CO_3	100	9	84 + 4
6	3	$Pd(dba)_2$	Na_2CO_3	90	5	70 + 4
7	2	$Pd(dba)_2$	Na_2CO_3	100	3	64 + 10[c]
8	2	$Pd(dba)_2$	Na_2CO_3	100	4	60 + 16[d]
9	2	$Pd(dba)_2$	Na_2CO_3	100	4	51 + 16[e]
10	2	$Pd(dba)_2$	Na_2CO_3	100	21	29 + 16[f]
11	2	$Pd(dba)_2$	Li_2CO_3	100	7	66 + 14
12	2	$Pd(dba)_2$	K_2CO_3	100	3	70 + 7

Table 7. (continued)

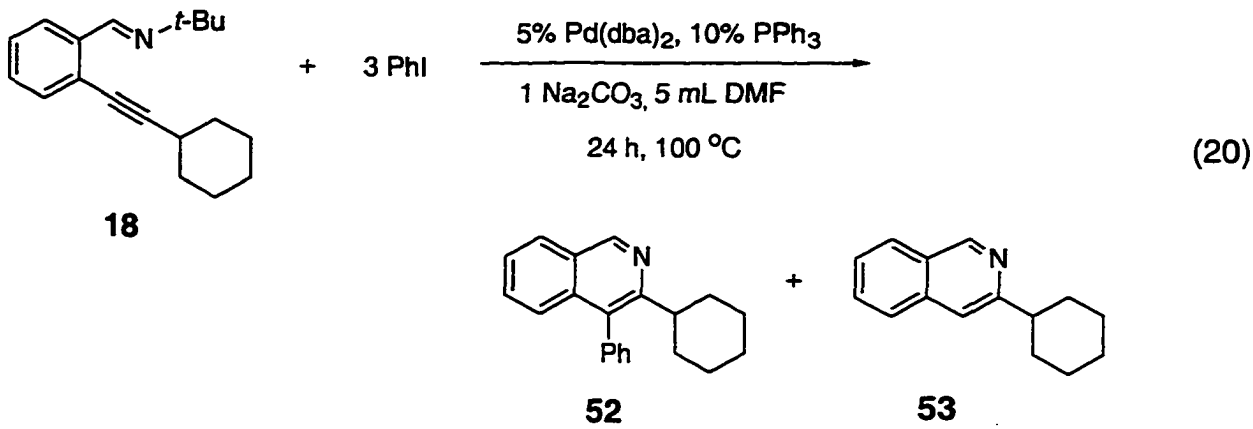
13	2	$Pd(dba)_2$	Cs_2CO_3	100	4	33 + 0
14	2	$Pd(dba)_2$	NaOAc	100	3	51 + 18
15	2	$Pd(dba)_2$	Et_3N	80	93	26 + 6
16	2	$Pd(dba)_2$	-	80	93	25 + 5
17	2	$Pd(OAc)_2$	Na_2CO_3	80	8	53 + 6

[a]All reactions were run with 0.25 mmol of the imine, 10 mol % PPh_3, and 1 equivalent of a base in 5 mL of DMF unless otherwise noted. [b]0.5 Mmol of the imine and 10 mL of DMF were used. [c]No PPh_3 was added. [d]2 Ml of DMF were used. [e]10 Ml of DMF were used. [f]One equiv of LiCl was added.

In all reactions two products were observed, 3-phenylisoquinoline and 3,4-diphenylisoquinoline. After a thorough investigation of this reaction, the following reaction conditions were observed to give the best ratio of **51** to **10**, as well as the highest overall yield: 0.25 mmol of the imine, 0.75 mmol of iodobenzene, 5 mol % $Pd(dba)_2$, 10 mol % PPh_3, and 1 equiv of Na_2CO_3 at 100 °C in 5 mL DMF. By employing these conditions, we were able to obtain **51** in an 84% yield (entry 5). Unfortunately, no reactions conditions were found that exclusively formed disubstituted heterocycle **51**. Isoquinoline **10** is presumably being formed from the thermal cyclization of iminoalkyne **9**, as had been observed during the optimization

studies for the palladium- and copper-catalyzed cyclizations (Table 1). Therefore, the reaction temperature was lowered for two reactions that were run. Upon lowering the reaction temperature to 80 °C, isoquinoline **51** was the only observed product, but the yield was considerably lower when compared to the reaction that was run at 100 °C (Table 7, entry 4). A reaction was also run at 90 °C. However, only a moderate yield of isoquinoline **51** was obtained, in addition to minor amounts of isoquinoline **10** (Table 7, entry 6).

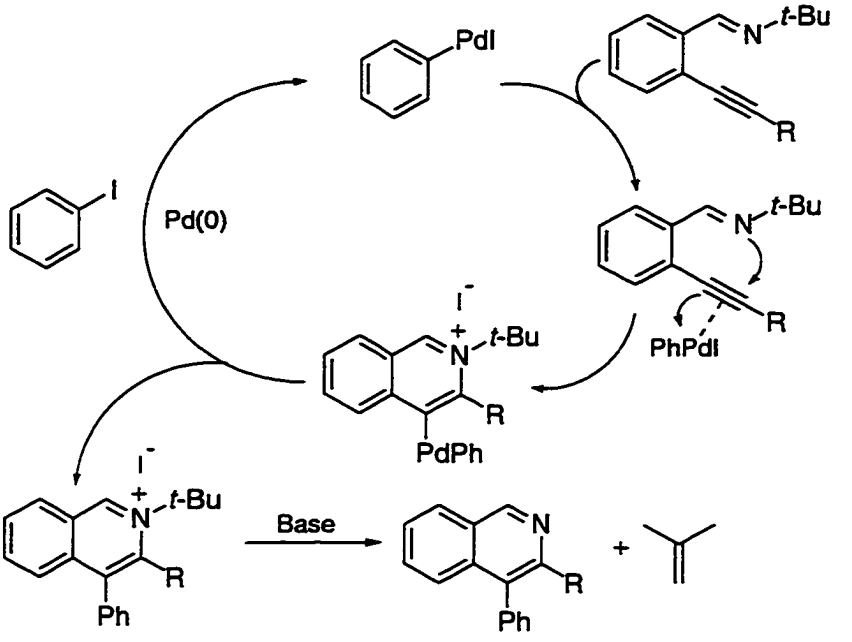
Reactions have also been run with imine **9** and other aryl iodides, namely 2-iodotoluene, 4-iodoanisole, and ethyl 4-iodobenzoate. However, the reactions with these substrates were much slower than the reactions with iodobenzene and afforded mixtures (~50:50) of the coupled products and **10**. Also, one reaction was run with imine **18** under the conditions that were developed for imine **9**. Unfortunately, none of the desired product **52** or the cyclization product **53** were observed from this reaction.



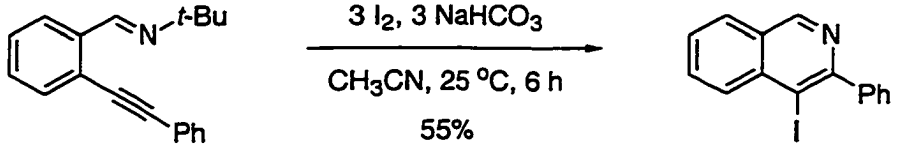
(20)

This palladium-catalyzed cyclization/coupling process is believed to proceed mechanistically as illustrated in Scheme 9. Specifically, oxidative addition of the aryl halide to Pd(0) produces an arylpalladium intermediate, which then coordinates to the alkyne. Subsequent attack of the neighboring imine substituent onto the coordinated alkyne then forms a diarylpalladium intermediate, which undergoes reductive elimination, thus producing a *tert*-butylisoquinolinium salt and regenerating Pd(0). As in our internal alkyne annulation chemistry, the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.[4]

Scheme 9



We have also discovered that electrophilic cyclizations of iminoalkyne **9** also produce substituted isoquinolines. For example, the reaction of **9** with 3 equiv of iodine and 3 equiv of $NaHCO_3$ in CH_3CN at 25 °C afforded the halogenated isoquinoline **54** in 55% yield. The mechanism of this process also appears to involve nucleophilic attack of the neighboring imine substituent onto the coordinated alkyne.



54

(21)

Conclusion

Efficient, palladium and copper-catalyzed syntheses of isoquinolines and pyridines have been developed. Only aryl and alkenyl-substituted alkynes cyclize by employing the palladium-catalyzed reaction conditions that have been developed. However, a wide variety of functionalized terminal acetylenes participate in a palladium-catalyzed coupling and copper-catalyzed cyclization process to afford the desired nitrogen heterocycles in moderate to excellent yields. The effectiveness of the palladium-catalyzed terminal acetylene annulation methodology has been demonstrated by the total synthesis of the isoquinoline alkaloid decumbenine B in 7 steps and 20% overall yield. Finally, diaryl iminoalkynes afforded diarylisoquinolines and a halogenated isoquinoline from palladium-catalyzed cyclization/coupling reactions and electrophilic cyclizations, respectively.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High

resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na_2CO_3, Li_2CO_3, K_2CO_3, Cs_2CO_3, NaOAc, DMF, THF, methanol, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. $Pd(OAc)_2$ and $PdCl_2$ were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh_3 was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodobenzyl alcohol, 2-bromobenzaldehyde, phenylacetylene, 1-ethynylcyclohexene, 2-(3-butynyloxy)tetrahydro-2*H*-pyran, propargyl alcohol, 2-methyl-3-butyn-2-ol, 3-butyn-1-ol, (triisopropylsilyl)acetylene, (trimethylsilyl)acetylene, propiolaldehyde diethyl acetal, 3,3-dimethyl-1-butyne, piperonal, 2,3-(methylenedioxy)benzaldehyde, *tert*-butylamine, copper iodide, Et_3N, and *i*-Pr_2NEt were purchased from Aldrich Chemical Co., Inc. 1,6-Heptadiyne was purchased from Lancaster Synthesis, Inc. Cyclohexylacetylene and 5-cyano-1-pentyne were purchased from Farchan Chemical Co. 2-Iodobenzaldehyde,[3] 2-bromopiperonal,[22] 2-bromocyclopentene-1-carboxaldehyde,[23] 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde,[24] (*Z*)-3-iodo-3-phenyl-2-propenal[25] and 2-bromo-3-formylpyridine[26] were prepared according to previous literature procedures. The following starting materials were prepared as indicated.

Aldehydes Prepared

2-(2-Phenylethynyl)benzaldehyde (8). To a solution of 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %). The mixture was stirred for 5 min and CuI (20 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 20:1 hexanes/EtOAc to afford 1.88 g (91%) of the compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.35-7.44 (m, 4H), 7.52-7.64 (m, 4H), 7.94 (dd, J = 0.3, 7.8 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 85.1, 96.5, 122.4, 126.9, 127.3, 128.6, 128.7, 129.2, 131.8, 133.3, 133.9, 135.9, 191.7.

2-(2-Cyclohex-1-enylethynyl)benzaldehyde (11). The aldehyde was prepared by the same method used for **8**, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and 1-ethynylcyclohexene (1.27 g, 12.0 mmol) for 3 h. Column chromatography using 25:1 hexanes/EtOAc afforded 2.00 g (95%) of the compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.57-1.72 (m, 4H), 2.11-2.18 (m, 2H), 2.20-2.25 (m, 2H), 6.27 (dddd, J = 1.8, 1.8, 6.0, 6.0 Hz, 1H), 7.33-7.39 (m, 1H), 7.49-7.51 (m, 2H), 7.87 (dt, J = 1.2, 7.8 Hz, 1H), 10.52 (d, J = 0.9

Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.3, 25.9, 29.0, 82.5, 98.6, 120.4, 127.1, 127.7, 128.1, 133.1, 133.8, 135.7, 136.9, 192.0.

2-(2-Cyclohexylethynyl)benzaldehyde (12). The aldehyde was prepared by the same method used for **8**, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and cyclohexyl acetylene (1.29 g, 12.0 mmol) for 2 h. Column chromatography using 25:1 hexanes/EtOAc afforded 2.01 g (95%) of the compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.34-1.45 (m, 3H), 1.52-1.63 (m, 3H), 1.71-1.78 (m, 2H), 1.87-1.92 (m, 2H), 2.68 (dddd, J = 3.6, 3.6, 12.6, 12.6 Hz, 1H), 7.34-7.39 (m, 1H), 7.48-7.54 (m, 2H), 7.88 (d, J = 8.1 Hz, 1H), 10.56 (d, J = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 25.9, 29.9, 32.5, 76.3, 102.2, 126.9, 127.9, 128.1, 133.3, 133.7, 136.0, 192.3.

2-[4-(Tetrahydropyran-2-yloxy)but-1-ynyl]benzaldehyde (13). The aldehyde was prepared by the same method used for **8**, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and 2-(3-butynyloxy)tetrahydro-2*H*-pyran (1.85 g, 12.0 mmol) for 2 h. Column chromatography using 10:1 hexanes/EtOAc afforded 2.56 g (99%) of the compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.48-1.66 (m, 4H), 1.67- 1.89 (m, 2H), 2.78 (t, J = 6.9 Hz, 2H), 3.49-3.56 (m, 1H), 3.57 (ddd, J = 6.9, 9.6 Hz, 1H), 3.85-3.98 (m, 2H), 3.45-3.41 (m, 1H), 7.49-7.51 (m, 2H), 7.87 (ddd, J = 0.6, 0.6, 7.2 Hz, 1H) 10.54 (d, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.5, 21.2, 25.5, 30.6, 62.3, 65.5, 77.2, 94.9, 98.9, 127.0, 127.6, 128.2, 133.3, 133.8, 136.2, 192.2.

2-(3-Hydroxyprop-1-ynyl)benzaldehyde (14). The aldehyde was prepared by the same method used for **8**, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and propargyl alcohol (0.67 g, 12.0 mmol) for 6 h. Column chromatography using 1:1 hexanes/EtOAc afforded 1.43 g (89%) of the compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.68 (br s, 1H), 4.51 (s, 2H), 7.34 (dddd, J = 0.6, 3.9, 3.9, 8.7 Hz, 1H), 7.45 (ddd, J = 1.2, 1.2, 5.1 Hz, 2H), 7.80 (ddd, J = 0.9, 0.9, 7.8 Hz, 1H), 10.41 (d, J = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.3, 81.0, 94.9, 126.2, 127.5, 128.8, 133.5, 133.9, 135.9, 192.1.

2-(3-Hydroxy-3-methylbut-1-ynyl)benzaldehyde (15). The aldehyde was prepared by the same method used for **8**, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and 2-methyl-3-butyn-2-ol (1.01 g, 12.0 mmol) for 2 h. Column chromatography using 3:1 hexanes/EtOAc afforded 1.80 g (96%) of the compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 6H), 2.73 (br s, 1H), 7.36-7.42 (m, 1H), 7.48-7.51 (m, 2H), 7.86 (ddd, J = 0.9, 0.9, 6.9 Hz, 1H), 10.46 (d, J = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.4, 65.7, 77.8, 101.2, 126.4, 127.4, 128.7, 133.4, 133.8, 135.9, 191.9.

2-(2-Triisopropylsilylethynyl)benzaldehyde (16). The aldehyde was prepared by the same method used for **8**, but employing 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and (triisopropylsilyl)acetylene (2.19 g, 12.0 mmol) for 2 h. Column chromatography using 35:1 hexanes/EtOAc afforded 2.65 g (92%) of the compound as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 21H), 7.44 (dddd, J = 0.6, 0.6, 7.8, 7.8 Hz, 1H), 7.52-7.62 (m, 2H), 7.92 (ddd, J = 0.6, 0.6,

7.8 Hz, 1H), 10.62 (d, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.3, 18.7, 99.2, 102.1, 126.9, 127.2, 128.8, 133.7, 134.0, 136.3, 191.8.

Imines Prepared

***N*-(2-Iodobenzylidene)-*tert*-butylamine** (**7**). To a mixture of 2-iodobenzaldehyde (1.00 g, 4.3 mmol) and H_2O (0.25 mL/mmol) was added *tert*-butylamine (12.9 mmol, 3 equivalents). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.18 g (95%) of the imine as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 7.07 (td, J = 1.5, 7.2 Hz, 1H), 7.36 (tt, J = 0.6, 7.2 Hz, 1H), 7.83 (dd, J = 0.9, 7.8 Hz, 1H), 7.94 (dd, J = 1.8, 7.8 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 58.0, 100.4, 128.5, 128.7, 131.6, 137.9, 139.4, 159.2; IR (neat, cm^{-1}) 3059, 2966, 1633; HRMS Calcd for $C_{11}H_{14}IN$: 287.0170. Found: 287.0173.

***N*-(2-Phenylethynylbenzylidene)-*tert*-butylamine** (**9**). The imine was prepared by the same method used for **7**, but employing 2-(2-phenylethynyl)benzaldehyde (0.80 g, 3.88 mmol). Removal of the solvent afforded 1.00 g (97%) of the imine **9** as a yellow oil, which solidified upon cooling: mp 52-53 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 7.28-7.35 (m, 5H), 7.49-7.54 (m, 3H), 8.07-8.10 (m, 1H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 58.0, 86.9, 95.1, 123.3, 124.1,

126.2, 128.7, 128.7, 128.8, 129.9, 131.6, 132.4, 138.0, 154.2; IR ($CHCl_3$, cm^{-1}) 3060, 2214, 1637; HRMS Calcd for $C_{19}H_{19}N$: 261.1518. Found: 261.1518.

***N*-(2-Cyclohex-1-enylethynylbenzylidene)-*tert*-butylamine (17).** The imine was prepared by the same method used for **7**, but employing 2-(2-cyclohex-1-enylethynyl)benzaldehyde (1.05 g, 5 mmol). Removal of the solvent afforded 1.28 g (96%) of the imine **17** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.59-1.74 (m, 4H), 2.13-2.20 (m, 2H), 2.22-2.27 (m, 2H), 6.23 (dddd, J = 1.8, 1.8, 6.0, 6.0 Hz, 1H), 7.29-7.33 (m, 2H), 7.39-7.45 (m, 1H), 7.98-8.05 (m, 1H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.4, 25.9, 29.3, 29.9, 57.8, 84.2, 97.0, 120.8, 124.5, 125.9, 128.2, 129.7, 132.1, 135.6, 137.6, 154.6; IR (neat, cm^{-1}) 3062, 2200, 1637; HRMS Calcd for $C_{19}H_{23}N$: 265.1830. Found: 265.1831.

***N*-(2-Cyclohexylethynylbenzylidene)-*tert*-butylamine (18).** The imine was prepared by the same method used for **7**, but employing 2-(2-cyclohexylethynyl)benzaldehyde (0.85 g, 4 mmol). Removal of the solvent afforded 1.01 g (95%) of the imine **18** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.35-1.45 (m, 3H), 1.50-1.63 (m, 3H), 1.73-1.81 (m, 2H), 1.85-1.92 (m, 2H), 2.68 (dddd, J = 3.6, 3.6, 12.3, 12.3 Hz, 1H), 7.26-7.31 (m, 2H), 7.37-7.43 (m, 1H), 7.98-8.03 (m, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 26.0, 29.8, 29.9, 32.7, 57.8, 78.0, 100.2, 124.9, 125.8, 127.9, 129.7, 132.2, 137.8, 154.8; IR (neat, cm^{-1}) 3062, 2224, 1683; HRMS Calcd for $C_{19}H_{25}N$: 267.1987. Found: 267.1987.

***N*-[4-(Tetrahydropyran-2-yloxy)but-1-ynylbenzylidene]-*tert*-butylamine (19).** The imine was prepared by the same method used for **7**, but

employing 2-[4-(tetrahydropyran-2-yloxy)but-1-ynyl]benzaldehyde (0.78 g, 3 mmol). Removal of the solvent afforded 0.88 g (94%) of the imine **19** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.48-1.65 (m, 4H), 1.68-1.89 (m, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 3.48-3.56 (m, 1H), 3.67 (ddd, *J* = 7.2, 7.2, 9.6, Hz, 1H), 3.86-3.97 (m, 2H), 4.68 (t, *J* = 3.0 Hz, 1H), 7.26-7.31 (m, 2H), 7.37-7.42 (m, 1H), 7.97-8.03 (m, 1H), 8.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.5, 21.2, 25.5, 29.8, 30.7, 57.7, 62.3, 65.9, 78.8, 92.7, 98.9, 124.4, 125.9, 128.1, 129.7, 132.4, 137.8, 154.5; IR (neat, cm^{-1}) 3063, 2229, 1637; HRMS Calcd for $C_{20}H_{27}NO_2$: 313.2040. Found: 313.2042.

***N*-[2-(3-Hydroxyprop-1-ynyl)benzylidene]-*tert*-butylamine (20).** The imine was prepared by the same method used for **7**, but employing 2-(3-hydroxy-prop-1-ynyl)benzaldehyde (1.00 g, 6.25 mmol). Removal of the solvent afforded 1.30 g (96%) of the imine **20** as a tan solid: mp 50-51 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 4.04 (br s, 1H), 4.45 (s, 2H), 7.23-7.38 (m, 3H), 7.99 (dd, *J* = 1.8, 7.5 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 51.0, 58.1, 82.3, 93.6, 123.6, 126.1, 128.7, 129.9, 132.6, 137.6, 155.1; IR ($CHCl_3$, cm^{-1}) 3332, 3066, 2969, 1637; HRMS Calcd for $C_{14}H_{17}NO$: 215.1310. Found: 215.1310.

***N*-[2-(3-Hydroxy-3-methylbut-1-ynyl)benzylidene]-*tert*-butylamine (21).** The imine was prepared by the same method used for **7**, but employing 2-(3-hydroxy-3-methylbut-1-ynyl)benzaldehyde (0.75 g, 4 mmol). Removal of the solvent afforded 0.94 g (97%) of the imine **21** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.64 (s, 6H), 2.47 (br s, 1H), 7.27-7.36 (m, 2H),

7.38-7.43 (m, 1H), 8.01-8.04 (m, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 31.6, 58.0, 65.7, 79.5, 99.5, 123.4, 126.0, 128.7, 129.7, 132.3, 137.9, 154.3; IR (neat, cm^{-1}) 3359, 3063, 2222, 1637; HRMS Calcd for $C_{16}H_{21}NO$: 243.1619. Found: 243.1623.

***N*-(2-Triisopropylsilylethynylbenzylidene)-*tert*-butylamine (22).** The imine was prepared by the same method used for **7**, but employing 2-(2-triisopropylsilylethynyl)benzaldehyde (0.57 g, 2 mmol). Removal of the solvent afforded 0.66 g (97%) of the imine **22** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.15 (s, 21H), 1.31 (s, 9H), 7.29-7.38 (m, 2H), 7.49-7.52 (m, 1H), 8.02-8.08 (m, 1H), 8.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.37, 18.8, 29.9, 57.8, 96.5, 104.2, 124.2, 125.9, 128.7, 129.6, 133.1, 138.2, 154.3; IR (neat, cm^{-1}) 3064, 2153, 1702, 1637; HRMS Calcd for $C_{22}H_{35}NSi$: 341.2540. Found: 341.2539.

***N*-(6-Bromobenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (32).** The imine was prepared by the same method used for **7**, but employing 2-bromopiperonal (2.00 g, 8.73 mmol). Removal of the solvent afforded 2.27 g (92%) of the imine **32** as a white solid: mp 73-74 °C; ^1H NMR ($CDCl_3$) δ 1.29 (s, 9H), 5.99 (s, 2H), 6.98 (s, 1H), 7.52 (s, 1H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 57.8, 102.1, 107.8, 112.5, 117.2, 129.5, 147.9, 150.1, 154.2; IR ($CHCl_3$, cm^{-1}) 3077, 2963, 1627; HRMS Calcd for $C_{12}H_{14}BrNO_2$: 283.0208. Found: 283.0205.

***N*-(2-Bromopyridin-3-ylmethylene)-*tert*-butylamine (35).** The imine was prepared by the same method used for **7**, but employing 2-bromo-3-formylpyridine (0.51 g, 2.74 mmol). Removal of the solvent afforded 0.62 g (94%)

of the imine **35** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 7.27 (dd, J = 4.8, 7.8 Hz, 1H), 8.25 (dd, J = 1.8, 7.5, Hz, 1H), 8.34 (dd, J = 0.9, 4.5 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.6, 58.5, 123.2, 132.9, 136.9, 144.0, 151.1, 153.2; IR (neat, cm^{-1}) 3043, 2968, 1633, 1576; HRMS Calcd for $C_{10}H_{13}BrN_2$: 240.0262. Found: 240.0262.

***N*-(2-Bromocyclopent-1-enylmethylene)-*tert*-butylamine (38).** The imine was prepared by the same method used for **7**, but employing 2-bromocyclopentene-1-carboxaldehyde (0.75 g, 4.31 mmol). Removal of the solvent afforded 0.89 g (90%) of the imine **38** as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.97 (quintet, 2H), 2.59 (tt, J = 2.1, 7.5 Hz, 2H), 2.79 (tt, J = 2.4, 7.5 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 29.8, 31.1, 41.6, 57.7, 127.9, 139.1, 151.8; IR (neat, cm^{-1}) 2965, 1630; HRMS Calcd for $C_{10}H_{16}BrN$: 229.0466. Found: 229.0460.

***N*-(1-Bromo-3,4-dihydronaphthalen-2-ylmethylene)-*tert*-butylamine (41).** The imine was prepared by the same method used for **7**, but employing 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde (0.77 g, 3.26 mmol). Removal of the solvent afforded 0.85 g (89%) of the imine **41** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.81-2.83 (m, 4H), 7.16 (dd, J = 1.8, 6.9 Hz, 1H), 7.22-7.31 (m, 2H), 7.79 (dd, J = 1.8, 7.2 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 27.7, 30.0, 58.1, 126.8, 127.3, 127.6, 128.6, 129.1, 134.2, 135.9, 138.3, 157.0; IR (neat, cm^{-1}) 3063, 2965, 1612; HRMS Calcd for $C_{15}H_{18}BrN$: 291.0623. Found: 290.0548 (M-H).

***N*-[(*Z*)-3-Iodo-3-phenylallylidene]-*tert*-butylamine (43).** The imine was prepared by the same method used for **7**, but employing *Z*-3-iodo-3-phenyl-2-propenal (0.60 g, 2.33 mmol). Removal of the solvent afforded 0.64 g (87%) of the imine **43** as a yellow solid: mp 81-83 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 6.77 (d, J = 7.8 Hz, 1H), 7.32-7.35 (m, 3H), 7.56-7.60 (m, 2H), 8.15 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 58.4, 113.6, 128.5, 128.8, 129.6, 134.9, 142.0, 161.4; IR ($CHCl_3$, cm^{-1}) 3078, 2967, 1614; HRMS Calcd for $C_{13}H_{16}IN$: 313.0328. Found: 313.0332.

General Procedure for the Copper-Catalyzed Cyclization of Iminoalkynes. DMF (5 mL), the imine (0.25 mmol), and CuI (5 mg, 0.025 mmol), were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3-Phenylisoquinoline (10). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 51 mg (100%) of the indicated compound with

spectral properties identical to those previously reported[27]: mp 102-103 °C (lit.[27] mp 101-102 °C).

3-(Cyclohex-1-enyl)isoquinoline (23). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 42 mg (81%) of the indicated compound as a yellow solid: mp 114-115 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.67-1.75 (m, 2H), 1.81-1.89 (m, 2H), 2.29-2.36 (m, 2H), 2.54-2.60 (m, 2H), 7.02 (tt, *J* = 2.4, 3.6 Hz, 1H), 7.48 (dt, *J* = 0.6, 14.4 Hz, 1H), 7.57 (s, 1H), 7.63 (dd, *J* = 1.2, 6.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.1, 26.1, 26.2, 114.2, 126.4, 126.8, 127.6, 128.4, 130.3, 135.7, 136.7, 151.7, 152.5 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3060, 2919, 1621, 1574; MS *m/z* (rel intensity) 209 (100, M^+), 208 (89), 194 (42), 180 (51). Anal. Calcd for $C_{15}H_{15}N$: C, 86.09; H, 7.23; N, 6.69. Found: C, 86.03; H, 7.30; N, 6.73.

3-Cyclohexylisoquinoline (24). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 49 mg (93%) of the indicated compound as a yellow oil, which solidified upon cooling: mp 40-41 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.25-1.67 (m, 6H), 1.89 (dt, *J* = 2.7, 12.6 Hz, 2H), 2.06 (dd, *J* = 1.5, 12.9 Hz, 2H), 2.84 (tt, *J* = 3.3, 11.7 Hz, 1H), 7.45 (s, 1H), 7.50 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H), 7.62 (td, *J* = 1.2, 6.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.8, 33.2, 46.2, 116.2, 126.3, 126.4, 127.3, 127.5, 130.2, 136.7, 151.9, 160.2; IR ($CHCl_3$, cm^{-1}) 3055, 2926, 1628, 1585; HRMS Calcd for $C_{15}H_{17}N$: 211.1356. Found: 211.1361.

3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (**25**). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 53 mg (83%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.40-1.60 (m, 4H), 1.61-1.82 (m, 2H), 3.23 (t, *J* = 7.2 Hz, 2H), 3.42-3.48 (m, 1H), 3.76 (ddd, *J* = 3.3, 8.1, 11.7 Hz, 1H), 3.87 (ddd, *J* = 6.9, 9.6, 16.5 Hz, 1H), 4.18 (ddd, *J* = 6.9, 9.6, 16.8 Hz, 1H), 4.62 (ddd, *J* = 2.7, 2.7, 2.7 Hz, 1H), 7.52 (ddd, *J* = 1.2, 6.9, 9.3 Hz, 1H), 7.55 (s, 1H), 7.63 (ddd, *J* = 1.2, 6.6, 9.3 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 25.5, 30.7, 38.5, 62.3, 67.0, 98.9, 119.2, 126.2, 126.6, 127.3, 127.6, 130.3, 136.5, 152.1, 152.6; IR ($CHCl_3$, cm^{-1}) 3054, 2942, 1629, 1588; HRMS Calcd for $C_{16}H_{19}NO_2$: 257.1416. Found: 257.1415.

General Procedure for the Palladium and Copper-Catalyzed Formation of Isoquinolines and Pyridines from Terminal Acetylenes. Et_3N (2 mL), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), the imine (0.5 mmol), the terminal acetylene (0.6 mmol) and CuI (1 mg, 0.005 mmol) were placed in a 2 dram vial. The vial was flushed with nitrogen and heated in an oil bath at 55 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. For the reactions with imine **7**, the reaction mixture was cooled, the precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. For the reactions with imines **32**, **35**, **37**, and **39**, the reaction mixture was cooled, the solvent was removed under reduced pressure, the

precipitates were filtered off and washed with ether, and the solvent was removed under reduced pressure. The residue obtained was transferred to a 2 dram vial and DMF (5 mL) and CuI (10 mg, 0.05 mmol) were added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

3-Phenylisoquinoline (**10**). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 94 mg (91%) of the indicated compound, whose spectral data were identical with that reported above.

3-(Cyclohex-1-enyl)isoquinoline (**23**). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 85 mg (81%) of the indicated compound, whose spectral data were identical with that reported above.

3-Cyclohexylisoquinoline (**24**). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 93 mg (88%) of the indicated compound, whose spectral data were identical with that reported above.

3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (**25**). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 122 mg

(95%) of the indicated compound, whose spectral data were identical with that reported above.

3-(Diethoxymethyl)isoquinoline (**29**). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 97 mg (84%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (dt, J = 0.6, 13.5 Hz, 6H), 3.67 (dddd, J = 0.6, 7.2, 7.8, 16.5 Hz, 4H), 5.67 (s, 1H), 7.54 (dddd, J = 1.2, 1.2, 8.1, 8.1 Hz, 1H), 7.64 (dddd, J = 1.2, 1.2, 6.9, 6.9 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.90-7.93 (m, 2H), 9.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 62.0, 102.4, 117.7, 127.2, 127.5, 127.5, 128.4, 130.5, 136.2, 151.5, 152.2; IR (neat, cm^{-1}) 3056, 2975, 1629, 1587; HRMS Calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 232.1338 (M+H).

4-(3-Isoquinolinyl)butanenitrile (**30**). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 85 mg (87%) of the indicated compound as an off-white solid: mp 104-105 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.18 (pentet, J = 7.2 Hz, 2H), 2.36 (t, J = 7.8 Hz, 2H), 3.04 (t, J = 7.2 Hz, 2H), 7.48 (s, 1H), 7.53 (ddd, J = 1.2, 6.9, 9.3 Hz, 1H), 7.64 (dd, J = 1.2, 6.9, 9.3 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 25.3, 36.4, 118.9, 119.7, 126.2, 126.9, 127.4, 127.6, 130.7, 136.4, 152.6, 152.8; IR ($CHCl_3$, cm^{-1}) 3054, 2946, 1627, 1586; HRMS Calcd for $C_{13}H_{12}N_2$: 196.1000. Found: 196.1001.

3-[3-(3-Isoquinolinyl)propyl]isoquinoline (**31**). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 42 mg (56%) of the indicated compound as a yellow solid: mp 116-117 °C (hexanes/EtOAc); ^{1}H NMR

($CDCl_3$) δ 2.37 (pentet, J = 8.1 Hz, 2H), 3.05 (t, J = 8.4 Hz, 4H), 7.48 (s, 2H), 7.51 (ddd, J = 1.2, 6.9, 9.3 Hz, 2H), 7.62 (ddd, J = 1.2, 6.9, 9.6 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 9.19 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 30.1, 37.8, 118.3, 126.2, 126.4, 127.2, 127.5, 130.3, 136.6, 152.2, 155.3; IR ($CHCl_3$, cm^{-1}) 3054, 2946, 1627, 1586; HRMS Calcd for $C_{12}H_{18}N_2$: 298.1470. Found: 298.1469.

7-Cyclohexyl-1,3-dioxolo[4,5-*g*]isoquinoline (33). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 97 mg (76%) of the indicated compound as a yellow solid: mp 93-94 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.20-1.61 (m, 5H), 1.71-1.77 (m, 1H), 1.85 (dt, J = 3.0, 12.3 Hz, 2H), 1.97-2.02 (m, 2H), 2.74 (tt, J = 3.3, 8.1 Hz, 1H), 6.01 (s, 2H), 6.95 (s, 1H), 7.09 (s, 1H), 7.25 (s, 1H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.8, 33.3, 46.0, 101.4, 102.3, 103.0, 116.1, 124.3, 135.1, 147.7, 149.7, 150.8, 159.3; IR ($CHCl_3$, cm^{-1}) 3029, 2923, 1601, 1584, 1482, 1453; HRMS Calcd for $C_{16}H_{17}NO_2$: 255.1259. Found: 255.1254.

7-[2-(Tetrahydropyran-2-yloxy)ethyl]-1,3-dioxolo[4,5-*g*]isoquinoline (34). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 122 mg (81%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.38-1.79 (m, 6H), 3.12 (t, J = 6.9 Hz, 2H), 3.38-3.45 (m, 1H), 3.69-3.84 (m, 2H), 4.06-4.15 (m, 1H), 4.57-4.59 (m, 1H), 6.01 (s, 2H), 6.94 (s, 1H), 7.08 (s, 1H), 7.34 (s, 1H), 8.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 25.5, 30.7, 38.3, 62.3, 67.1, 98.9, 101.5, 102.2, 103.0, 119.0, 124.4, 134.9, 147.9, 149.8, 150.9,

151.7; IR ($CHCl_3$, cm^{-1}) 3051, 2942, 1604, 1481, 1456; HRMS Calcd for $C_{17}H_{19}NO_4$: 301.1314. Found: 301.1313.

7-Phenyl-1,6-naphthyridine (36). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 88 mg (85%) of the indicated compound as a yellow solid: mp 135-136 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 7.39-7.45 (m, 2H), 7.48-7.53 (m, 2H), 8.13-8.17 (m, 2H), 8.23 (d, J = 8.1 Hz, 1H), 8.31 (s, 1H), 9.04 (br s, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 117.9, 122.3, 122.7, 127.3, 129.0, 129.2, 135.6, 138.9, 151.4, 152.7, 155.1, 155.2; IR ($CDCl_3$, cm^{-1}) 3048, 1618, 1594, 1558; HRMS Calcd for $C_{14}H_{10}N_2$: 206.0844. Found: 206.0840.

7-*n*-Butyl-1,6-naphthyridine (37). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 67 mg (72%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H), 1.38 (sextet, J = 7.5 Hz, 2H), 1.77 (quintet, J = 7.5 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 7.39 (dd, J = 4.2, 8.4 Hz, 1H), 7.69 (s, 1H), 8.19 (dd, J = 0.9, 8.4 Hz, 1H), 8.99 (d, J = 2.7 Hz, 1H), 9.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 31.9, 38.0, 119.6, 121.7, 121.9, 135.6, 151.1, 152.4, 154.8, 160.4; IR (neat, cm^{-1}) 3051, 2942, 1604, 1481, 1456; HRMS Calcd for $C_{12}H_{14}N_2$: 186.1157. Found: 186.1159.

6,7-Dihydro-5*H*[2]-3-phenylpyrindine (39). The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 68 mg (69%) of the indicated compound with ^1H spectral properties identical to those previously reported[28]: mp 49-50 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 2.13 (quintet, J = 7.5 Hz, 2H), 2.95 (t, J = 7.2 Hz, 4H), 7.35-7.41 (m, 1H), 7.42-7.48 (m, 2H), 7.59 (d, J =

0.3 Hz, 1H), 7.94-7.98 (m, 2H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 30.1, 32.8, 116.9, 127.0, 128.5, 128.7, 138.8, 140.1, 145.5, 154.7, 155.5; IR ($CHCl_3$, cm^{-1}) 3067, 2950, 1611, 1556; HRMS Calcd for $C_{14}H_{13}N$: 195.1048. Found: 194.0965 (M-H).

6,7-Dihydro-5*H*[2]-3-(cyclohex-1-enyl)pyrindine (40). The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 55 mg (55%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.62-1.69 (m, 2H), 1.74-1.81 (m, 2H), 2.07 (quintet, J = 7.5 Hz, 2H), 2.22-2.25 (m, 2H), 2.47-2.49 (m, 2H), 2.88 (q, J = 6.9 Hz, 4H), 6.56-6.59 (m, 1H), 7.24 (s, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.0, 25.2, 26.0, 26.4, 30.1, 32.8, 115.2, 127.5, 136.9, 137.9, 144.5, 154.1, 157.2; IR ($CHCl_3$, cm^{-1}) 3059, 2854, 1602, 1554, 1477; HRMS Calcd for $C_{14}H_{17}N$: 199.1361. Found: 199.1361.

2-*n*-Butyl-5,6-dihydrobenzo[*f*]isoquinoline (42). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 55 mg (46%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3H), 1.42 (sextet, J = 7.5 Hz, 2H), 1.75 (quintet, J = 7.8 Hz, 2H), 2.80-2.92 (m, 6H), 7.24-7.36 (m, 3H), 7.44 (s, 1H), 7.75-7.82 (m, 1H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.1, 28.7, 32.4, 38.2, 116.5, 124.2, 127.2, 128.6, 129.0, 129.3, 132.3, 138.4, 142.0, 148.5, 161.3; IR (neat, cm^{-1}) 3061, 2933, 1603, 1544, 1483; HRMS Calcd for $C_{17}H_{19}N$: 237.1517. Found: 237.1508.

2,4-Diphenylpyridine (43). The reaction mixture was chromatographed using 15:1 hexanes/EtOAc to afford 66 mg (57%) of the indicated compound as a yellow oil with spectral properties identical to those previously reported.[29]

Total synthesis of Decumbenine B

***N*-(Benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine.** To a mixture of piperonal (2.00 g, 13.3 mmol) and H_2O (2 mL) was added *tert*-butylamine (26.6 mmol, 2 equiv). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were then dried (Na_2SO_4) and filtered. Removal of the solvent afforded 2.65 g (97%) of the imine as a white solid: mp 44-45 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 5.97 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 1.5, 8.1 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 57.0, 101.4, 106.6, 108.0, 123.9, 132.2, 148.3, 149.5, 154.3; IR ($CHCl_3$, cm^{-1}) 3060, 2214, 1637; HRMS Calcd for $C_{12}H_{15}NO_2$: 205.1100. Found: 205.1103.

***N*-(4-Iodobenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (49).** *N*-(4-Iodo-benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine was prepared according to a modified literature procedure.[21] To a solution of *N*-(benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (1.03 g, 5.00 mmol) in 40 mL of THF at -78 °C was added 5.25 mmol of *n*-BuLi (2.5 M in hexanes) dropwise over a

five minute period. The solution was stirred for 30 min at -78 °C and a solution of I_2 (2.68 g, 7.5 mmol) in 15 mL of THF was added dropwise. The resulting solution was warmed to room temperature and was stirred for 2 h. The reaction mixture was then quenched with water, extracted with ether, washed with saturated aqueous $Na_2S_2O_3$, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Recrystallization from hexanes/EtOAc afforded 0.77 g (70%) of the desired compound as an off-white solid: mp 126-127 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 6.05 (s, 2H), 6.61 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 57.8, 77.1, 100.9, 108.6, 122.7, 131.2, 147.6, 149.4, 157.4; IR ($CHCl_3$, cm^{-1}) 3062, 2965, 1596; HRMS Calcd for $C_{12}H_{14}INO_2$: 331.0069. Found: 331.0064.

(5-Iodobenzo[1,3]dioxol-4-yl)methanol. To a solution of 2,3-(methylenedioxy)benzaldehyde (1.50 g, 10.0 mmol) in 5 mL CH_2Cl_2 was added $NaBH_4$ (0.47 g, 12.5 mmol) in MeOH (5 mL). The reaction mixture was stirred for 2 h at room temperature, quenched with water, extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure to afford 1.52 g of the desired alcohol as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (br s, 1H), 4.64 (s, 2H), 5.93 (s, 2H), 6.73-6.85 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 60.0, 101.1, 108.2, 121.2, 121.8, 122.4, 145.1, 147.4. To a mixture of this alcohol and AgO_2CCF_3 (2.21 g, 10.0 mmol) in 15 mL of $CHCl_3$ was added a solution of iodine (2.54 g, 10.0 mmol) in 80 mL of $CHCl_3$. The reaction mixture was stirred for 24 h and then filtered. The filtrate was washed with saturated aqueous $NaHCO_3$, brine, dried

($MgSO_4$), and filtered. Removal of the solvent afforded a yellow oil, which was dissolved in ether. Addition of hexanes precipitated 1.58 g (57%) of the desired alcohol as a yellow solid: mp 96-97 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 (br s, 1H), 4.69 (s, 2H), 5.99 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 63.4, 88.3, 101.8, 110.2, 124.3, 132.1, 146.6, 148.2; IR ($CHCl_3$, cm^{-1}) 3358, 2891, 1460; HRMS Calcd for $C_8H_7IO_3$: 277.9444. Found: 277.9442.

(5-Ethynylbenzo[1,3]dioxol-4-yl)methanol (50). To a solution of (5-iodobenzo[1,3]dioxol-4-yl)methanol (0.56 g, 2.0 mmol) and (trimethylsilyl)acetylene (0.24 g, 2.4 mmol) in Et_2NH (10 mL) was added $PdCl_2(PPh_3)_2$ (28 mg, 2 mol %). The mixture was stirred for 5 min and CuI (4 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The crude silyl acetylene was dissolved in 30 mL of MeOH, and K_2CO_3 (0.55 g, 4 mmol) was added. The mixture was then stirred for 1 h at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 2:1 hexanes/EtOAc to afford 0.30 g (98%) of the desired compound as a brown solid: mp 64-65 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (br t, J = 5.7 Hz, 1H), 3.20 (s, 1H), 4.77 (d, J = 5.4 Hz, 2H), 5.98 (s, 2H), 6.68 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 58.1, 79.9, 81.4,

101.7, 108.0, 114.7, 124.1, 127.6, 146.0, 148.3; IR ($CHCl_3$, cm^{-1}) 3401, 3286, 2099, 1466; HRMS Calcd for $C_{10}H_8O_3$: 176.0474. Found: 176.0474.

Decumbenine B (46). DMF (5 mL), $Pd(OAc)_2$ (3 mg, 0.013 mmol), Na_2CO_3 (26 mg, 0.25 mmol), and *N*-(4-iodobenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (0.083 g, 0.25 mmol) were placed in a 2 dram vial. The contents were then stirred for 1 minute and (5-ethynylbenzo[1,3]dioxol-4-yl)methanol (42 mg, 0.28 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100° C for 48 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column using 1:1 hexanes/EtOAc to afford 42 mg (52%) of the indicated compound with spectral properties identical to those previously reported[19,20]: mp 221-222 °C (lit.[19,20] mp 222-224 °C).

3,4-Diphenylisoquinoline (51). DMF (5 mL), $Pd(dba)_2$ (7 mg, 0.013 mmol), PPh_3 (7 mg, 0.025 mmol), Na_2CO_3 (26 mg, 0.25 mmol), and iodobenzene (153 mg, 0.75 mmol) were placed in a 2 dram vial. The contents were then stirred for 1 minute and the appropriate imine (0.25 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for 9 h. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 mL of ether, washed with 30 mL of saturated NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and

the residue was chromatographed using 5:1 hexanes/EtOAc to afford 59 mg (84%) of the indicated compound with spectral properties identical to those previously reported[30]: mp 154-155 °C (lit.[30] mp 155-156 °C).

4-Iodo-3-phenylisoquinoline (54). To a mixture of iodine (190 mg, 0.75 mmol) and $NaHCO_3$ (63 mg, 0.75 mmol) in CH_3CN (1 mL) was added a soultion of *N*-(2-phenylethynylbenzylidene)-*tert*-butylamine (65 mg, 0.25 mmol) in CH_3CN (1 mL). The resulting mixture was stirred at room temperature for 6 h. Saturated aqueous $Na_2S_2O_3$ (25 mL) was added and the product was extracted with Et_2O, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column using 10:1 hexanes/EtOAc to afford 46 mg (55%) of the indicated compound as a dark brown solid. Filtration through charcoal gave a yellow solid: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.42-7.54 (m, 3H), 7.61-7.67 (m, 2H), 7.70 (ddd, *J* = 0.9, 6.9, 9.0 Hz, 1H), 7.85 (ddd, *J* = 1.5, 6.9, 9.9 Hz, 1H), 7.98 (dd, *J* = 0.3, 8.1 Hz, 1H), 8.25 (dd, *J* = 0.6, 8.4 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 98.2, 128.0, 128.1, 128.1, 128.4, 129.9, 132.3, 132.5, 138.7, 143.8, 152.1, 157.2 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3055, 1630, 1549; HRMS Calcd for $C_{15}H_{10}IN$: 330.9858. Found: 330.9852.

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CHAPTER 3. SYNTHESIS OF ISOINDOLO[2,1-*a*]INDOLES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

A paper to be submitted to the *Journal of Organic Chemistry*

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Abstract

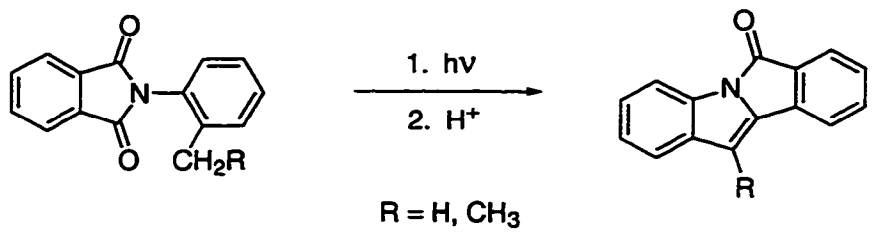
A wide variety of substituted isoindolo[2,1-*a*]indoles have been prepared via annulation of internal alkynes by imines derived from *o*-iodoanilines in the presence of a palladium catalyst. This methodology provides an extremely efficient route for the synthesis of these tetracyclic heterocycles from readily available starting materials. The mechanism of this interesting annulation process appears to involve (1) oxidative addition of the aryl iodide to Pd(0), (2) alkyne insertion, (3) addition of the resulting vinylic palladium intermediate to the C-N double bond of the imine, (4) either electrophilic palladation of the resulting σ-palladium intermediate onto the adjacent aromatic ring derived from the internal alkyne, or oxidative addition of the neighboring aryl carbon-hydrogen bond, and (5) reduction of the tetracyclic product and Pd(0). A variety of internal acetylenes have been employed in this annulation process in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.

Introduction

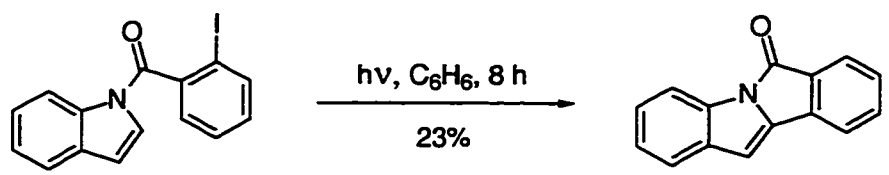
The development of efficient and selective synthetic transformations is a major challenge in organic synthesis. Consequently, tandem (domino) processes have been extensively investigated as they are among the most versatile reactions for the efficient, stereocontrolled synthesis of complex organic molecules.[1] It is not surprising, therefore, that transition metal-catalyzed alkyne annulation processes have received considerable attention for the synthesis of a variety of complex carbo- and heterocycles due to the synthetic efficiency of this methodology.[2] For example, the palladium-catalyzed annulation of internal alkynes has been employed by Larock and co-workers for the synthesis of indoles,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4] indenones,[5] isoquinolines,[6] α-pyrones,[7] and polycyclic aromatic hydrocarbons.[8]

Considerable attention has been directed towards the synthesis of compounds containing the indole nucleus, a structural subunit of a wide variety of biologically active natural products. However, the synthesis of functionalized indoles still presents a major challenge in organic synthesis. Isoindolo[2,1-*a*]indoles are a class of these functionalized indoles that have been synthesized by employing classical synthetic organic and palladium-mediated methodologies.

Various photochemical approaches to this ring system have been reported. For example, the synthesis of isoindoles **2** by irradiation of phthalimides **1**, followed by dehydration, has been reported (eq 1).[9] In addition, isoindole **4** has been synthesized in low yield by the irradiation of iodide **3** (eq 2).[10]

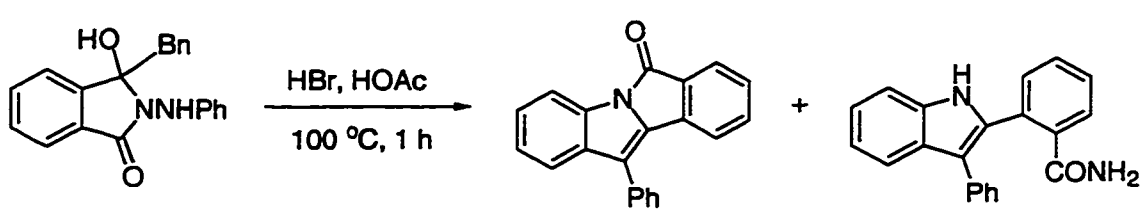


1 2 (1)



3 4 (2)

Other reports of the synthesis of these indoles have included acid- and base-catalyzed rearrangements and ring expansion reactions. For example, the synthesis of a mixture of isoindole **5** in 34% yield and indole **6** in 11% yield has been reported from the acid-catalyzed rearrangement of a phthalimidine derivative (eq 3).[11] In addition, these same researchers have reported the synthesis of isoindole **5** in low yield from the base-catalyzed rearrangement of vinylic bromide **7** (eq 4).[12]



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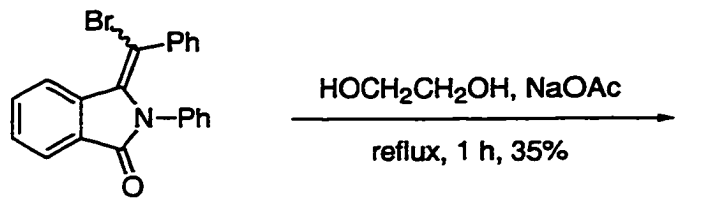
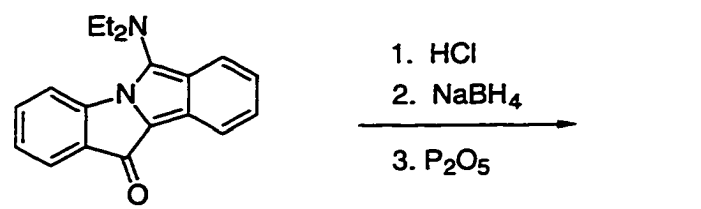


(4)

7

The synthesis of indole **4** has also been reported in low yield from the sequence of transformations shown in eq 5.[13] Finally, isoindole **8** has been synthesized as a single example in 57% yield via a thermal ring expansion (eq 6).[14] However, pyrrolophenanthridinediol **9** and indole **10** were also isolated in 12% and 8% yields, respectively from this reaction.



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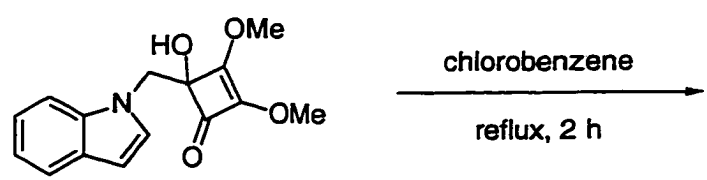

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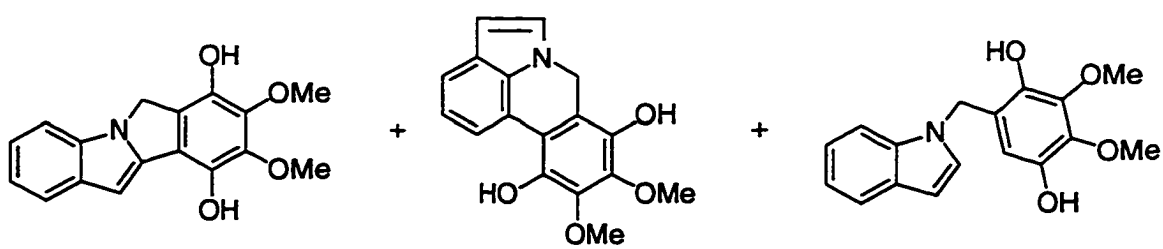
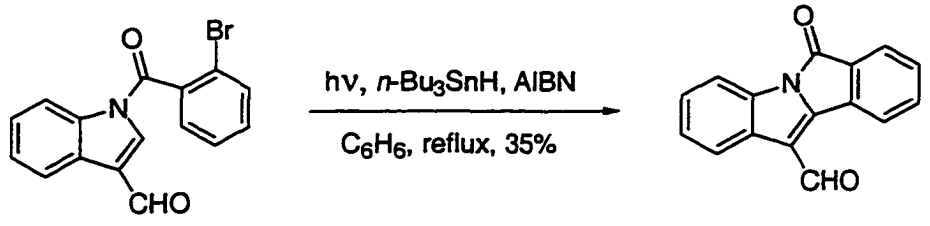
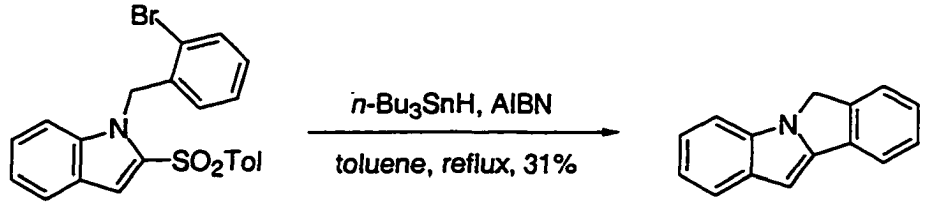


8 **9** **10**

In addition to the photochemical and rearrangement routes already discussed, radical routes to the isoindole nucleus have been reported. For example, the intramolecular radical cyclization of indole **11** employing *n*-Bu_3SnH and AIBN has been reported to give isoindole **12** in 35% yield (eq 7).[15] In addition, isoindole **14** has been synthesized in low yield from indole **13** by employing a radical ipso-substitution reaction (eq 8).[16]



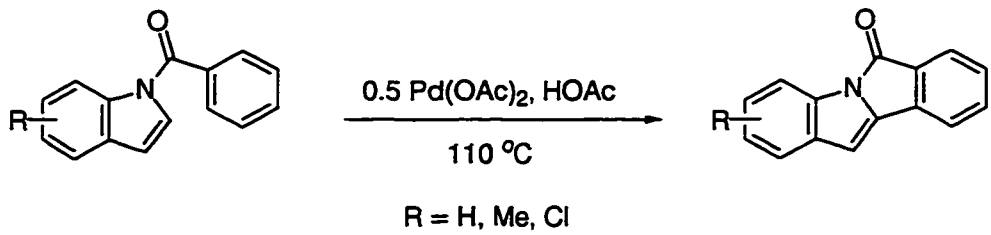
11 **12** (7)



13 **14** (8)

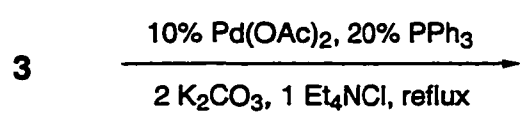
Palladium-based methodology has also been employed in the synthesis of isoindolo[2,1-*a*]indole derivatives. The synthesis of 6-oxo-6*H*-isoindolo[2,1-*a*]indoles has been accomplished in yields of 7-47% by the intramolecular dehydrogenation of 1-aroylindoles with $Pd(OAc)_2$ (eq 9).[17] However, the yields from this process are relatively low, and the use of 0.5 equiv of $Pd(OAc)_2$ greatly

limits the synthetic utility. In addition, the yields from this synthesis do not exceed 50%, suggesting that the process actually requires stoichiometric amounts of palladium salts.

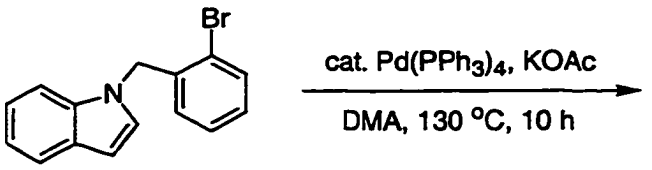


(9)

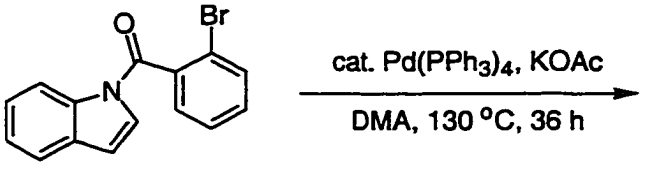
The synthesis of this class of indoles has been expanded, however, by employing additional palladium-catalyzed cyclization methodology. For example, the palladium-catalyzed cyclization of indole **3** to isoindole **4** has been reported in 80% yield (eq 10),[18] in addition to the synthesis of isoindole **11** in 86% yield (eq 11) and isoindole **4** in 72% yield by employing catalytic amounts of $Pd(PPh_3)_4$ (eq 12).[19] In addition to these examples, the synthesis of isoindole **15**, containing an acetamide moiety, has been synthesized in 74% yield by employing palladium-catalyzed methodology (eq 13).[19] The synthesis of **15** is of note due to the fact that it has been shown to display a high binding affinity for the peripheral benzodiazepine receptor, which is linked to the production of neurosteroids.[20]



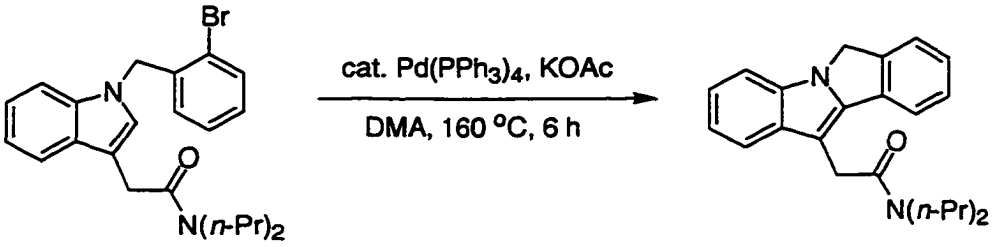
(10)



14 (11)

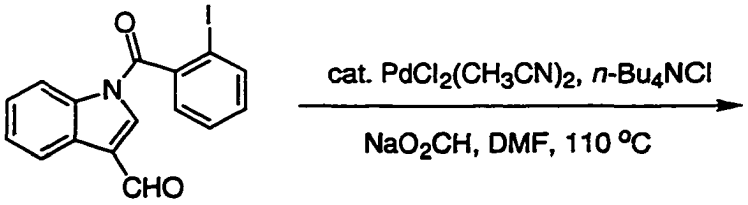


4 (12)

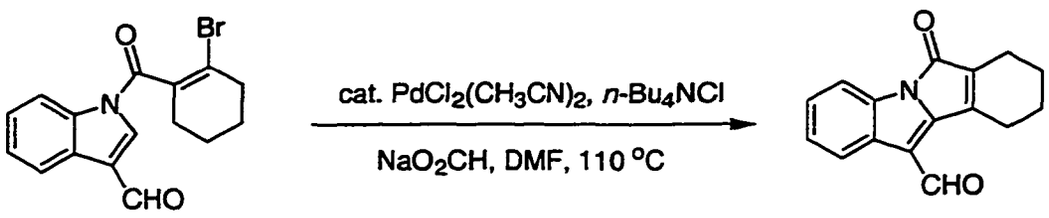


15 (13)

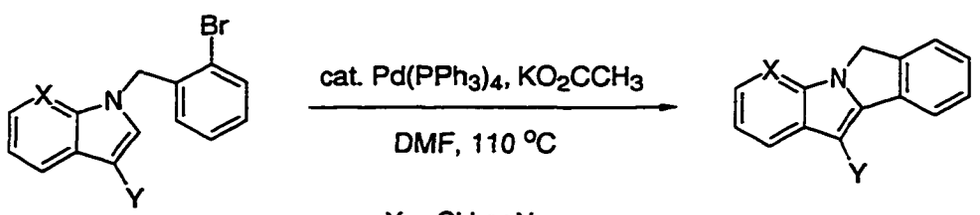
The synthesis of isoindole **12** in 70% yield from the palladium-catalyzed cyclization of iodide **16** (eq 14), and the tetrahydroisoindole derivative **18** from vinylic bromide **17** in 60% yield has also been reported (eq 15).[15] Finally, isoindoles **19** have been synthesized by in yields ranging from 25-87% by employing catalytic amounts of $Pd(PPh_3)_4$ (eq 16).[21]



16 **12** (14)



17 **18** (15)

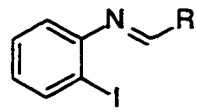


X = CH or N
Y = CHO or CN

19 (16)

The photochemical, rearrangement, and radical routes for the synthesis of these complex heterocycles all suffer the disadvantage of affording low yields of the tetracyclic products. In addition, the inclusion of additional functionality into the products has not been investigated. Efficient palladium-catalyzed cyclization methodology has been reported for the synthesis of these heterocycles. However, no reports of highly functionalized products, or indoles containing functional groups other than a carbonyl at C-6 of the isoindole[2,1-*a*]indole structure have appeared.

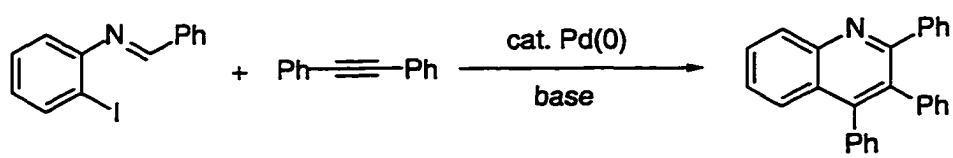
Due to our continuing interest in the palladium-catalyzed annulation of internal alkynes, we have investigated the reaction of internal alkynes and imines **20** derived from *o*-iodoanilines and aldehydes. Herein, we report that this annulation methodology very efficiently constructs the isoindolo[2,1-*a*]indole skeleton from readily prepared imines and internal acetylenes.



20

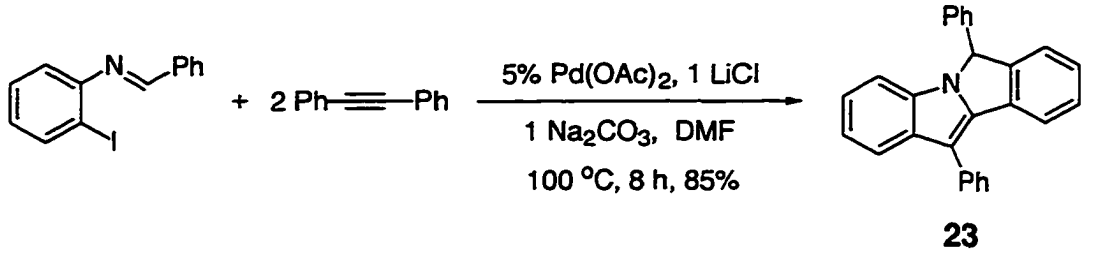
Results and Discussion

The palladium-catalyzed reaction of imine **21** and diphenylacetylene was chosen as the model system for our initial investigation of this annulation process. We anticipated that imine **21** might undergo a reaction with an internal alkyne in the presence of a palladium catalyst to produce the highly substituted quinoline derivative **22** (eq 17). However, when reaction conditions were employed that have been used in much of our previous alkyne annulation chemistry (1 equiv of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in DMF at 100 °C),[3-8] none of the anticipated quinoline derivative was observed. Instead, isoindole **23** was isolated in 85% yield after an 8 h reaction time (eq 18). This was a rather surprising result, and we therefore concentrated on defining the scope and limitations of this intriguing isoindole synthesis.



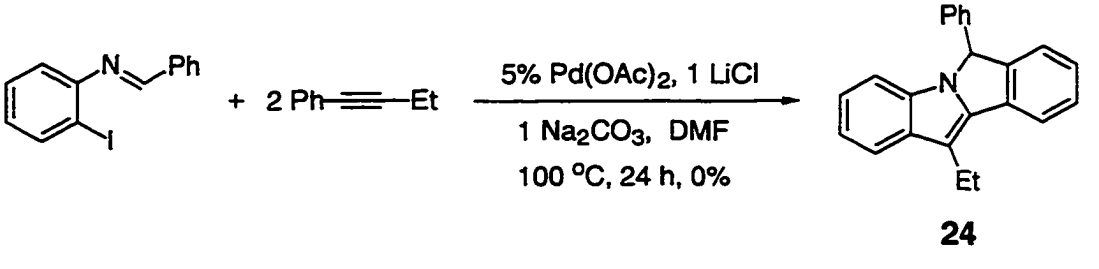
(17)

21 **22**



23 (18)

Since the reaction of imine **21** and diphenylacetylene proceeded in high yield and a short reaction time under the reaction conditions that were initially employed, we proceeded to investigate the annulation of **21** with alkynes of differing functionality to expand the scope of this isoindole synthesis. Many of the alkynes that were employed, however, failed to give as good yields as the reactions that were run with diphenylacetylene. For example, the reaction of imine **21** and 1-phenyl-1-butyne under the reaction conditions that were developed for the diphenylacetylene annulation, afforded none of the desired indole **24** (eq 19). Therefore, several optimization reactions were run in order to improve this reaction (Table 1).



24 (19)

Table 1. Synthesis of Indole 24 by the Pd-Catalyzed Annulation of Internal Acetylenes (eq 19).[a]

entry	base (equiv)	chloride source	time (h)	% isolated yield
1	Na_2CO_3 (1)	LiCl	72	0
2	Na_2CO_3 (1)	*n*-Bu_4NCl	72	65
3	Na_2CO_3 (2)	*n*-Bu_4NCl	72	68
4	*i*-Pr_2NEt (1)	*n*-Bu_4NCl	72	63
5	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	36	75
6	*i*-Pr_2NEt (3)	*n*-Bu_4NCl	36	75
7	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	36	77[b]
8	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	36	81[c]

[a]All reactions were run with 0.5 mmol of the imine, 2.0 mmol of 1-phenyl-1-butyne, and 1 equiv of the chloride source in 10 mL of DMF at 100 °C unless otherwise noted. [b]1.2 Equiv of 1-phenyl-1-butyne were used. [c]1.2 Equiv of 1-phenyl-1-butyne and 5 mL of DMF were used.

By employing *n*-Bu_4NCl as the chloride source, instead of LiCl, indole **24** was obtained in 65% yield after a 72 h reaction time (entry 1). Upon increasing the amount of Na_2CO_3 to 2 equiv, virtually no increase in yield or decrease in the reaction time was observed (entry 3). Also, no increase in yield was observed by employing *i*-Pr_2NEt as the base (entry 4). However, by increasing the amount of *i*-Pr_2NEt to 2 equiv with 1 equiv of *n*-Bu_4NCl, the yield increased to 78% and the reaction time decreased significantly (entry 5). The yield was not increased, however, by employing 3 equiv of *i*-Pr_2NEt (entry 6). By reducing the amount of the alkyne to 1.2 equiv, indole **24** was isolated in 77% yield (entry 7). Finally, by reducing the amount of alkyne and increasing the concentration of the reaction mixture, the desired product was obtained in 81% yield (entry 8).

As a consequence of the results reported in Table 1, the reaction of imine **21** and diphenylacetylene was reinvestigated (Table 2). By employing *i*-Pr_2NEt as the base, the desired isoindole was obtained in an 85% yield (entry 2). However, as in the reaction with 1-phenyl-1-butyne, reducing the amount of alkyne to 1.2 equiv increased the yield to 94% (entry 3). Upon reducing the amount of alkyne and solvent as in Table 1, the yield was reduced to 85%.

The results of these optimization studies led to the use of three general reaction procedures for the synthesis of the isoindoles. Procedure A: 0.5 mmol of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in 10 mL of DMF at 100 °C. Procedure B: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 5 mL of DMF at 100 °C. Procedure C: 0.5 mmol of the aryl

Table 2. Synthesis of Indole 23 by the Pd-Catalyzed Annulation of Diphenylacetylene.[a]

entry	base (equiv)	chloride source	time (h)	% isolated yield
1	Na_2CO_3 (1)	LiCl	8	85
2	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	12	84
3	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	12	94[b]
4	*i*-Pr_2NEt (2)	*n*-Bu_4NCl	10	85[c]

[a]All reactions were run with 0.5 mmol of the imine, 2.0 equiv of diphenylacetylene, and 1 equiv of the chloride source in 10 mL of DMF at 100 °C unless otherwise noted. [b]1.2 Equiv of diphenylacetylene were used. [c]1.2 Equiv of diphenylacetylene and 5 mL of DMF were used.

imine, 1.2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 10 mL of DMF at 100 °C. The procedure used for these reactions is dependent upon the alkyne that is employed, as one procedure may not give any of the desired indole. For example, alkyl-substituted acetylenes afford better yields when procedure B is employed and diaryl acetylenes afford better yields when procedure C is employed. The other substituted alkynes (ester, hydroxyl) afford better yields when procedure A is employed. The isoindoles that have been synthesized are shown in Table 3.

Table 3. Synthesis of Isoindolo[2,1-*a*]indoles by the Pd-Catalyzed Annulation of Internal Alkynes.[a]

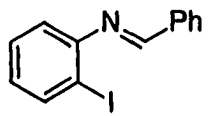
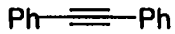
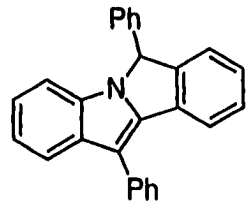
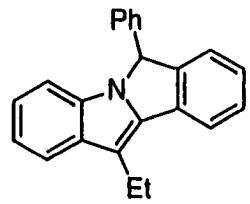
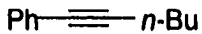
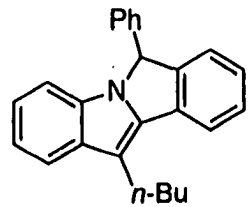
entry	imine	alkyne	procedure, time (h)	product	% yield
1			A, 8		85
2			B, 10		85
3	**21**		C, 12	**23**	94
4			A, 72		0
5			B, 36		81
6			C, 36	**24**	77
7			B, 24		81
				25	

Table 3. (continued)

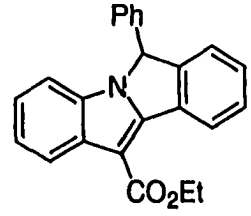
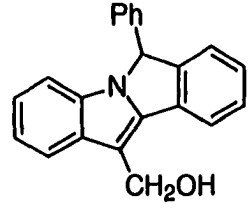
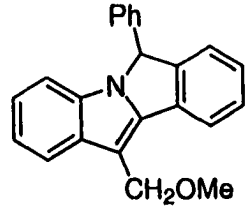
entry	imine	alkyne	procedure, time (h)	product	% yield
8		Ph—≡—CO_2Et	A, 4	 **26**	80
9		Ph—≡—CH_2OH	A, 24	 **27**	51
10		Ph—≡—CH_2OMe	B, 12	 **28**	46

Table 3. (continued)

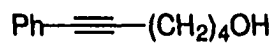
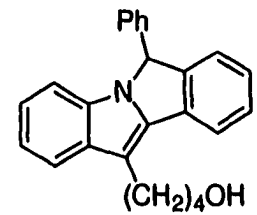
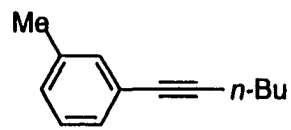
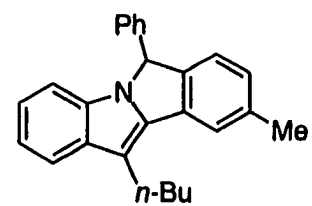
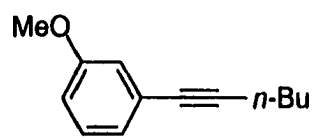
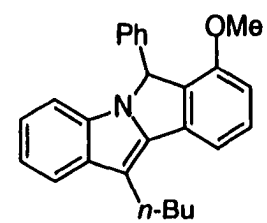
entry	imine	alkyne	procedure, time (h)	product	% yield
11			B, 10	 **29**	72
12			B, 36	 **30**	81
13			B, 36	 **31**	78

Table 3. (continued)

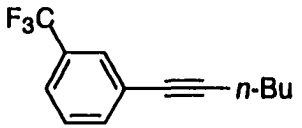
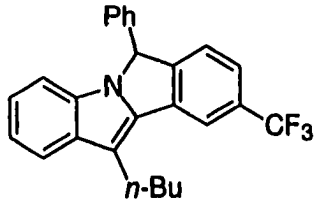
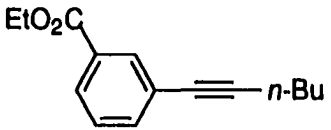
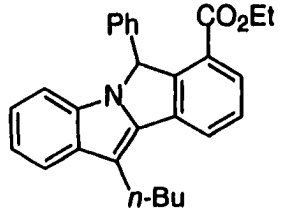
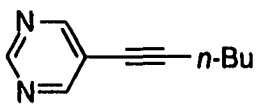
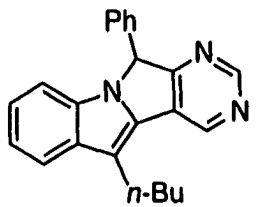
entry	imine	alkyne	procedure, time (h)	product	% yield
14			B, 18	 **32**	95
15			B, 18	 **33**	74
16			B, 10	 **34**	93

Table 3. (continued)

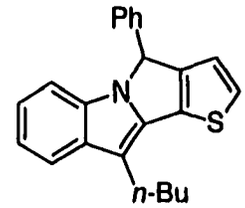
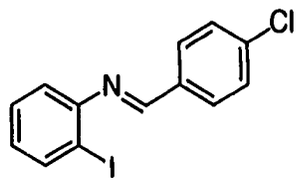
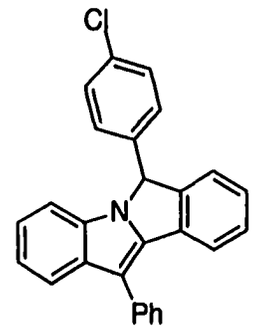
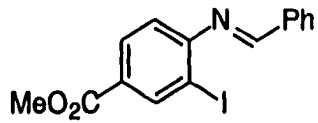
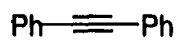
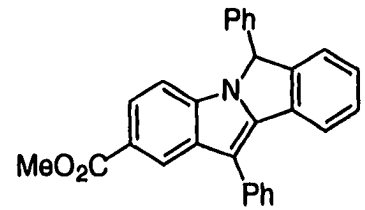
entry	imine	alkyne	procedure, time (h)	product	% yield
17			B, 19	 **35**	84
18	 **36**	Ph—≡—Ph	C, 12	 **37**	93

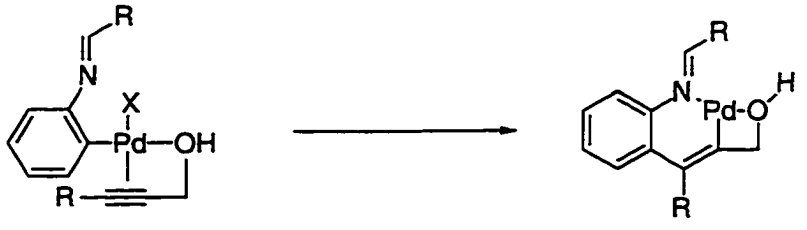
Table 3. (continued)

entry	imine	alkyne	procedure, time (h)	product	% yield
19	 **38**		C, 18	 **39**	83

[a] Procedure A: 0.5 mmol of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in 10 mL of DMF were heated at 100 °C for the indicated time. Procedure B: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 2 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 5 mL of DMF were heated at 100 °C for the indicated time. Procedure C: 1 equiv of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 2 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 10 mL of DMF were heated at 100 °C for the indicated time.

The reaction of imine **21** with a variety of functionalized alkynes has afforded the desired indoles in good to excellent yields. For example, the reaction with diphenylacetylene gave indole **23** in 94% yield by employing procedure C (entry 3). Also, the reaction of **21** with alkyl-substituted alkynes afforded the desired heterocycles in excellent yields by employing procedure B (entries 5 and 7). The annulation with ethyl phenylpropiolate afforded **26** in 80% yield (entry 8).

The reaction of 3-phenyl-2-propyn-1-ol gave **27** in only 51% yield (entry 9). The low yield associated with this alkyne can possibly be explained by a directive effect of the hydroxyl substituent on the alkyne, which has been observed previously in analogous indole chemistry[3] and the palladium-catalyzed hydroarylation of propargylic alcohols.[22] This effect appears to direct alkyne insertion so that the palladium adds to the least hindered end of the alkyne (eq 18). Consequently, the tetracyclic product cannot be formed from this vinylpalladium intermediate, which would undergo unknown side reactions, although no other products were isolated from this reaction (see the latter mechanistic discussion).



(18)

In an attempt to avoid the directive effect of the propargylic alcohol, 1-phenyl-3-methoxy-1-propyne was subsequently employed in the annulation with imine **21**. However, it appears that the effect of the methyl ether is still significant, as only a low yield of indole **28** was observed (46%, entry 10). 6-Phenyl-5-hexyn-1-ol, which has an additional three carbon spacer between the triple bond and the free hydroxyl substituent, was also employed in the reaction with imine **21**. A significant increase in yield was observed from this alkyne annulation (71%, entry 11) when compared to the propargylic alcohol or its methyl ether, although some effect of the heteroatom may still be operating, since the yield was lower than in the annulation in which 1-phenyl-1-hexyne was employed (compare entries 7 and 11).

We have also investigated the regiochemistry of ring closure onto the aryl group of the acetylene (entries 12-15). This has been done by employing alkynes which bear substituents *meta* to the ethynyl substituent. In the case of the aryl acetylene bearing a methyl group, a single regioisomer **30** was obtained in 84% yield (entry 12). Also, a single regioisomer **31** was isolated in 78% yield from the annulation using an aryl acetylene bearing an electron-donating methoxy group (entry 13). By ^{1}H NMR spectral analysis, regioisomer **30** was obtained, which has the methyl substituent in the 9-position of the isoindole. However, indole **31** has the electron-donating methoxy substituent in the 7-position. The excellent regioselectivity of this ring closure, as well as the reversal of regioselectivity upon switching from the electron-donating methoxy group to the relatively neutral methyl group were rather surprising, so we therefore investigated the use of alkynes bearing electron-withdrawing substituents.

When alkynes bearing electron-withdrawing substituents were employed with imine **21**, single regioisomers were also obtained. For example, indole **32** was obtained in which the trifluoromethyl substituent appears in the 9-position, as had been observed with the alkyne bearing the methyl group (entry 14). Surprisingly, the alkyne bearing the electron-withdrawing ester reacted in such a manner as to place the ester functionality in the 7-position, as had been observed with the alkyne bearing the electron-donating methoxy group (entry 15).

From these results, it appears that substituents on the aryl ring of the alkyne are able to control the regioselectivity of ring closure by chelation of the palladium in the σ-palladium intermediate that is formed during the reaction (see the latter mechanistic discussion). For example, products were isolated in which ring closure had occurred to place the oxygen-containing alkoxy or ester functionalities in the 7-position. However, when alkynes were employed that contained trifluoromethyl or methyl substituents, products were isolated with these substituents in the 9-position, presumably due to steric interactions that inhibit ring closure and thus place these groups in the 7-position. Nevertheless, it does appear that by the appropriate choice of functionality, it is possible to exclusively prepare one isoindole isomer.

In addition to the previous examples, ring closure onto heterocyclic rings has also been investigated. For example, 5-pyrimidyl-1-hexyne afforded a 93% yield of the desired tetracyclic indole in a short reaction time (entry 16). Also, a thienyl-

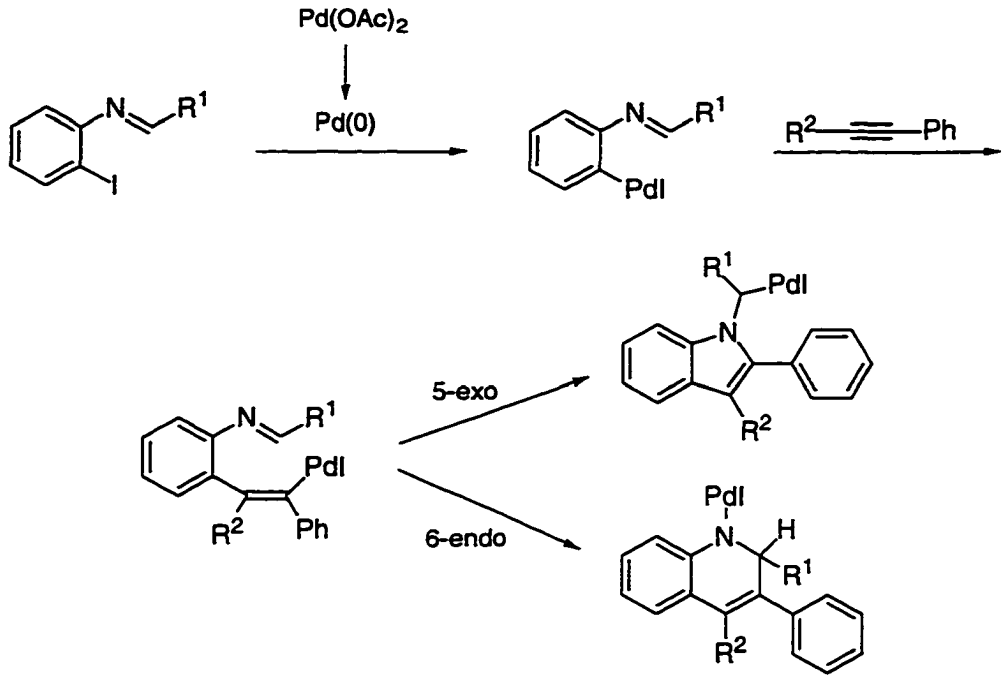
substituted acetylene also undergoes this annulation process to afford heterocycle **35** in 84% yield (entry 17).

Finally, the annulation of functionalized imines also affords the isoindoles in good yields. For example, the annulation of imine **36** with diphenylacetylene afforded indole **37** in 93% yield (entry 18). This example not only demonstrates the ease of introduction of additional functionality into the tetracyclic structure, but it also shows the chemoselectivity of the annulation. Imine **38** bearing an electron-withdrawing methyl ester has also been employed with diphenylacetylene to afford isoindole **39** in good yield (entry 19).

As mentioned previously, the anticipated product from the annulation of imine **21** and diphenylacetylene was the highly substituted quinoline derivative **22** (eq 17). To our surprise, none of this heterocycle was observed and tetracyclic indole **23** was isolated as the only product in 85% yield. From a mechanistic standpoint, these two heterocycles can be formed from two different possible ring closure pathways as illustrated in Scheme 1. Following reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), oxidative addition of the aryl iodide to Pd(0), and coordination and subsequent insertion of the acetylene, either a 5-exo or 6-endo addition of the vinylpalladium intermediate across the adjacent carbon-nitrogen double bond can occur. The σ-palladium intermediate resulting from the 5-exo mode cyclization pathway proceeds to form the observed tetracyclic products, and the 6-endo pathway might be expected to form the anticipated quinoline derivative. In this

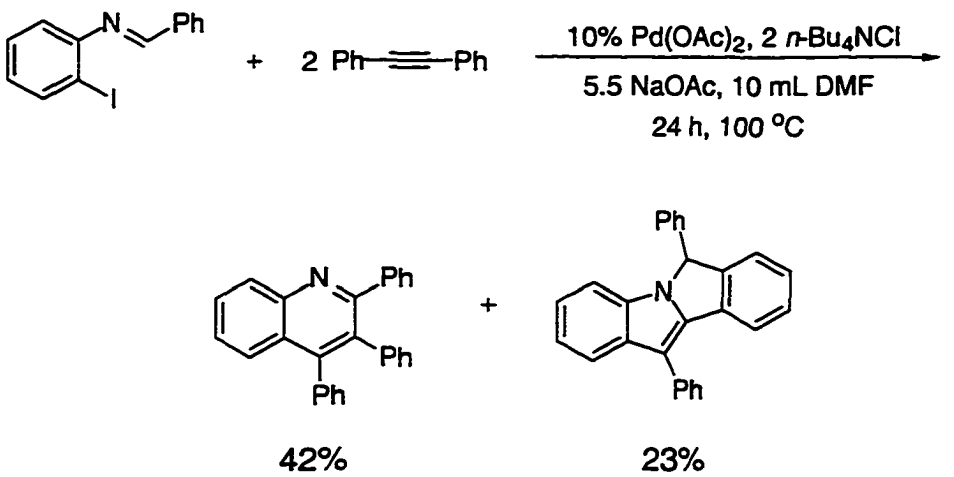
palladium-catalyzed process, however, the 5-exo pathway, which forms the tetracyclic products, occurs exclusively.

Scheme 1



Numerous examples have been reported in the literature in which palladium intermediates can cyclize via exo or endo pathways in Heck-type reactions. Although the exo mode cyclizations have generally been observed to be the dominant ring-closure pathway when substrates are employed that can cyclize via either process, various examples of the less favored endo-mode pathway have been reported.[23] Preliminary data suggests that by slightly altering the reaction conditions employed in this annulation process, it is possible to promote the formation of quinoline derivatives through the 6-exo cyclization pathway (eq 19).[24]

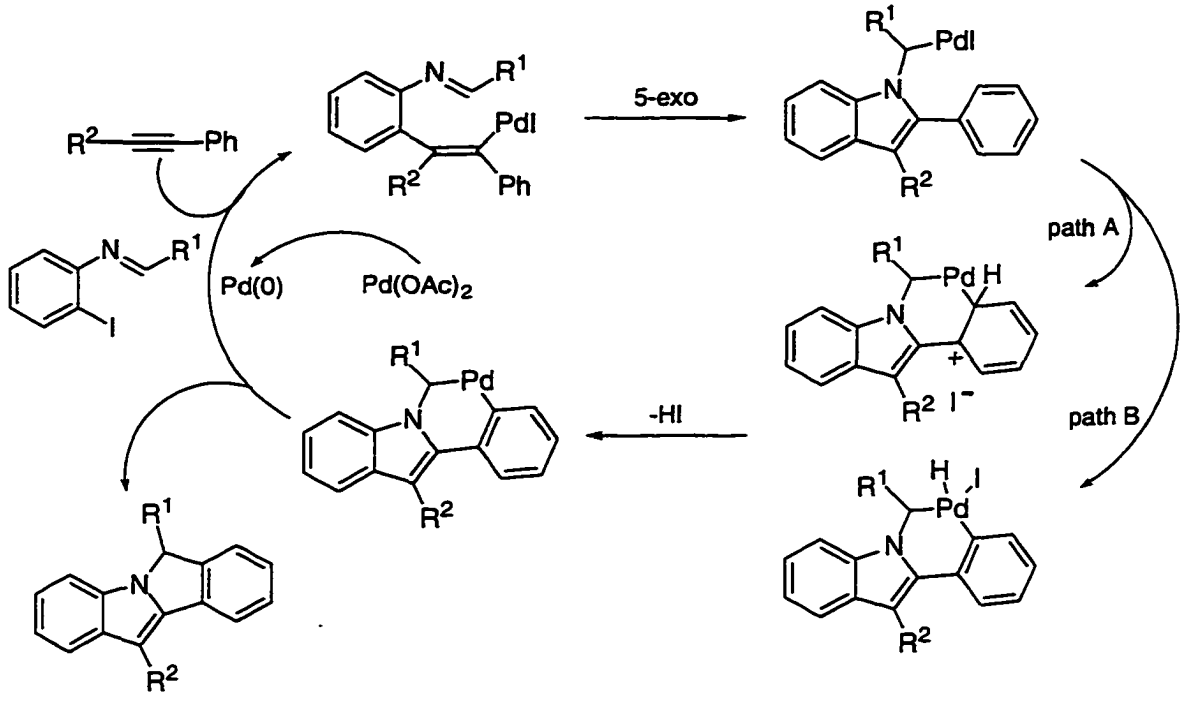
However, a significant amount of the tetracyclic product has also generally been observed. Work on this process is continuing.



(19)

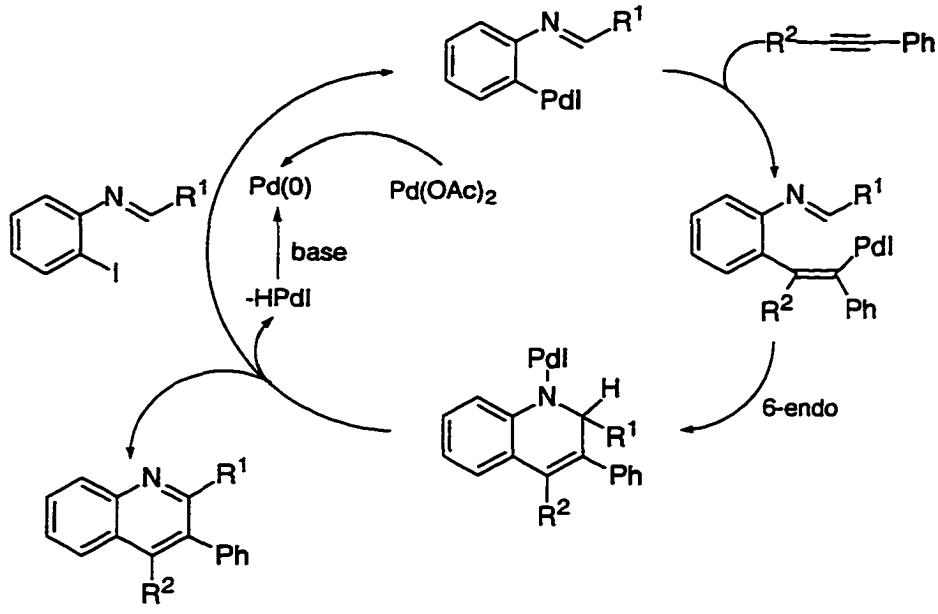
Based on the previous discussion, we propose a mechanism for this remarkable isoindole synthesis involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene, (4) a 5-exo addition of the vinylpalladium intermediate across the carbon-nitrogen double bond, (5) either electrophilic palladation of the σ-palladium intermediate onto the adjacent aromatic ring (path A), or oxidative addition of the neighboring aryl carbon-hydrogen bond of the aromatic ring to the σ-palladium intermediate to form a Pd(IV) intermediate (path B), and subsequent elimination of HI by base, and (6) regeneration of the Pd(0) catalyst by reductive elimination to form the isoindole as shown in Scheme 2.

Scheme 2



Likewise, we propose a mechanism for formation of the quinoline heterocycles involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene, (4) a 6-endo addition of the vinylpalladium intermediate across the carbon-nitrogen double bond, (5) beta hydride elimination to form the quinoline, and (6) regeneration of the Pd(0) catalyst by reductive elimination of HPdI, as shown in Scheme 3.

Scheme 3



Conclusion

We have developed an efficient, palladium-catalyzed synthesis of isoindolo[2,1-*a*]indole heterocycles from readily available starting materials. A wide variety of aryl acetylenes in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring undergo this process in moderate to excellent yields with high regioselectivity. In addition, preliminary results indicate that the formation of highly substituted quinoline heterocycles may be possible by slightly altering the reaction conditions employed.

Experimental

General Procedures. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of Na_2CO_3, K_2CO_3, NaOAc, $NaHCO_3$, LiCl, DMF, THF, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh_3 was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodoaniline, benzaldehyde, 4-chlorobenzaldehyde, methyl 4-aminobenzoate, diphenylacetylene, ethyl phenylpropiolate, 1-phenyl-1-hexyne, methyl propargyl ether, 1-hexyne, 5-hexyn-1-ol, iodobenzene, 2-iodothiophene, 5-bromopyrimidine, 3-bromotoluene, 3-iodoanisole, 3-iodobenzotrifluoride, Et_3N, and *i*-Pr_2NEt were purchased from Aldrich Chemical Co., Inc. 3-Phenyl-2-propyn-1-ol, ethyl 3-

iodobenzoate, and *n*-Bu_4NCl were purchased from Lancaster Synthesis, Inc. 1-Phenyl-1-butyne was purchased from Farchan Chemical Co. Methyl 3-iodo-4-aminobenzoate was prepared according to a previous literature procedure.[25] The following starting materials were prepared as indicated.

General Procedure for the Synthesis of the Aryl Alkynes. To a solution of the iodo- or bromoarene (10.0 mmol) and terminal alkyne (12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %). The mixture was then stirred for 5 min and CuI (20 mg, 1 mol %) was added. The resulting mixture was heated under a nitrogen atmosphere at 50 °C. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the pure alkynes.

Alkynes Prepared

1-Phenyl-3-methoxy-1-propyne. The acetylene was prepared by employing iodobenzene (2.04 g, 10 mmol) and methyl propargyl ether (0.84 g, 12 mmol). Column chromatography on silica gel using 20:1 hexanes/EtOAc afforded 1.39 g (95%) of the desired compound as a yellow oil with spectral properties identical to those previously reported.[26]

6-Phenyl-5-hexyn-1-ol. The acetylene was prepared by employing iodobenzene (2.04 g, 10 mmol) and 5-hexyn-1-ol (1.18 g, 12 mmol). Column chromatography on silica gel using 2:1 hexanes/EtOAc afforded 1.70 g (98%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.63-1.80 (m, 5H), 2.45 (t, J = 6.6 Hz, 2H), 3.70 (t, J = 6.3 Hz, 2H), 7.24-7.29 (m, 3H), 7.36-7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3, 25.1, 32.0, 62.5, 81.0, 90.0, 124.0, 127.7, 128.3, 131.6.

1-(3-Methylphenyl)-1-hexyne. The acetylene was prepared by employing 3-bromotoluene (1.71 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol) at 90 °C. Column chromatography on silica gel using hexanes afforded 1.70 g (99%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.44-1.54 (m, 2H), 1.56-1.65 (m, 2H), 2.32 (s, 3H), 2.42 (t, J = 6.9 Hz, 2H), 7.08 (d, J = 7.2 Hz, 1H), 7.15-7.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.2, 21.3, 22.1, 31.0, 80.7, 90.1, 124.0, 128.2, 128.4, 128.7, 132.3, 137.9.

1-(3-Methoxyphenyl)-1-hexyne. The acetylene was prepared by employing 3-iodoanisole (2.34 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using 25:1 hexanes/EtOAc afforded 1.88 g (100%) of the desired compound as a yellow oil with spectral properties identical to those previously reported.[27]

1-(3-Trifluoromethylphenyl)-1-hexyne. The acetylene was prepared by employing 3-iodobenzotrifluoride (2.72 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using hexanes afforded 2.26 g (100%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2

Hz, 3H), 1.41-1.65 (m, 4H), 2.42 (t, J = 6.9 Hz, 2H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H), 7.52 (d, J = 13.8 Hz, 1H), 7.54 (d, J = 13.5 Hz, 1H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.1, 22.1, 30.7, 79.3, 92.3, 123.9 (q, $^1J_{C\text{-}F}$ = 272.6 Hz), 124.1 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 125.1, 128.4 (q, $^4J_{C\text{-}F}$ = 3.8 Hz), 128.7, 130.8 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 134.7.

2-(1-Hexynyl)benzoic acid ethyl ester. The acetylene was prepared by employing ethyl 3-iodobenzoate (2.76 g, 10.0 mmol) and 1-hexyne (0.99 g, 12.0 mmol). Column chromatography on silica gel using 20:1 hexanes/EtOAc afforded 2.16 g (94%) of the desired compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.42-150 (m, 2H), 1.53-1.63 (m, 2H) 2.39 (t, J = 6.9 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 7.32 (ddd, J = 0.3, 7.8, 7.8 Hz, 1H), 7.53 (ddd, J = 1.5, 1.5, 6.3 Hz, 1H), 7.91 (ddd, J = 1.2, 1.2, 7.8 Hz, 1H), 8.05 (dd, J = 1.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.4, 19.1, 22.1, 30.8, 61.1, 79.8, 91.5, 124.6, 128.3, 128.5, 130.7, 132.7, 135.7, 166.1.

1-(5-Pyrimidyl)-1-hexyne. The acetylene was prepared by employing 5-bromopyrimidine (1.59 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol). Column chromatography on silica gel using 15:1 hexanes/EtOAc afforded 1.53 g (96%) of the desired compound as a dark yellow oil with spectral properties identical to those previously reported.[28]

1-(2-Thienyl)-1-hexyne. The acetylene was prepared by employing 2-iodothiophene (2.10 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol). Column chromatography on silica gel using 25:1 hexanes/EtOAc afforded 1.64 g (100%) of the desired compound as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t , J = 7.2 Hz,

3H), 1.41-1.65 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 6.94 (dd, J = 3.6, 5.1 Hz, 1H), 7.12 (dd, J = 1.2, 3.6 Hz, 1H), 7.17 (dd, J = 1.2, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.5, 22.1, 30.7, 73.7, 94.6, 124.4, 125.9, 126.8, 130.9.

Imines Prepared

Benzylidene(2-iodophenyl)amine (21). A mixture of 2-iodoaniline (2.19 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and *p*-toluenesulfonic acid monohydrate (1 crystal) in benzene (40 mL) was refluxed with the aid of a Dean-Stark apparatus to remove the water produced. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The oily residue was dissolved in a minimal amount of 100% ethanol and cooled. The resulting solid was collected to afford 2.15 g (70%) of the imine **21** as an off-white solid: mp 56-57 °C; ^{1}H NMR ($CDCl_3$) δ 6.94 (td, J = 1.5, 7.8 Hz, 1H), 7.02 (dd, J = 1.5, 8.1 Hz, 1H), 7.38 (td, J = 1.2, 7.5 Hz, 1H), 7.48-7.55 (m, 3H), 7.93 (dd, J = 1.2, 7.8 Hz, 1H), 7.99-8.02 (m, 2H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 95.0, 118.6, 127.2, 129.0, 129.3, 129.5, 131.9, 135.9, 139.2, 153.1, 161.1; IR ($CHCl_3$, cm^{-1}) 3052, 3001, 1626, 1573; HRMS Calcd for $C_{13}H_{10}IN$: 306.9858. Found: 306.9855.

4-Chlorobenzylidene(2-iodophenyl)amine (36). The imine was prepared by the same method used for imine **21** by employing 2-iodoaniline (2.19 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). Crystallization from

100% ethanol afforded 2.46 g (72%) of the imine **36** as a yellow solid: mp 44-45 °C; ^{1}H NMR ($CDCl_3$) δ 6.94 (td, J = 0.9, 5.7 Hz, 1H), 7.00 (dd, J = 1.2, 6.0 Hz, 1H), 7.37 (td, J = 0.9, 6.0 Hz, 1H), 7.47 (dt, J = 1.5, 6.6 Hz, 2H), 7.90-7.93 (m, 3H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 95.0, 118.3, 127.4, 129.2, 129.4, 130.3, 134.3, 137.9, 139.2, 152.7, 159.5; IR ($CHCl_3$, cm^{-1}) 3056, 2997, 1628, 1569; HRMS Calcd for $C_{13}H_9ClIN$: 340.9468. Found: 340.9472.

4-Benzylideneamino-3-iodobenzoic acid methyl ester (38). The imine was prepared by the same method used for imine **21** by employing methyl 3-iodo-4-aminobenzoate (4.27 g, 15.4 mmol) and benzaldehyde (2.45 g, 23.1 mmol). Crystallization from 100% ethanol afforded 1.46 g (40%) of the imine **38** as an off-white solid: mp 64-65 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.00 (d, J = 8.1 Hz, 1H), 7.45-7.57 (m, 3H), 7.98 (dd, J = 1.5, 6.3 Hz, 2H), 8.04 (dd, J = 1.5, 8.1 Hz, 1H), 8.30 (s, 1H), 8.5 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.4, 93.6, 118.2, 128.5, 129.0, 129.4, 131.0, 132.3, 135.5, 140.5, 157.2, 162.0, 165.6; IR ($CHCl_3$, cm^{-1}) 3060, 2949, 1720, 1631, 1585; HRMS Calcd for $C_{15}H_{12}INO_2$: 364.9913. Found: 364.9921.

General Procedure for the Palladium-Catalyzed Formation of Isoindolo[2,1-*a*]indoles. Procedure A: DMF (10 mL), $Pd(OAc)_2$ (6 mg, 0.027 mmol), LiCl (21 mg, 0.5 mmol), Na_2CO_3 (56 mg, 0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. Procedure B: DMF (5 mL), $Pd(OAc)_2$ (6 mg, 0.027 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), *i*-Pr_2NEt (130 mg, 1.0 mmol), and the alkyne (0.6 mmol) were placed in a 2 dram vial. Procedure C: DMF (10 mL),

$Pd(OAc)_2$ (6 mg, 0.027 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), *i*-Pr_2NEt (130 mg, 1.0 mmol), and the alkyne (1.2 mmol) were placed in a 4 dram vial. The chemicals for procedures A-C were mixed and the appropriate imine (0.5 mmol) was added. The vial was flushed with nitrogen and heated in an oil bath at 100 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, diluted with 30 ml of ether, washed with 45 mL (Procedures A and C) or 30 mL (Procedure B) of saturated aqueous NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

6,11-Diphenylisoindolo[2,1-*a*]indole (Compound **23**, Table 3, entry 3). The reaction was run using procedure C and was chromatographed using 25:1 hexanes/EtOAc to afford 168 mg (94%) of the indicated compound as a white solid: mp 168-169 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 6.20 (s, 1H), 7.02 (dt, J = 0.6, 8.1 Hz, 1H), 7.16 (dddd, J = 1.5, 7.2, 7.2, 22.2 Hz, 2H), 7.25-7.49 (m, 9H), 7.63 (t, J = 7.5 Hz, 2H), 7.87-7.94 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 64.5, 109.8, 110.3, 120.3, 120.5, 121.1, 122.4, 124.1, 126.5, 127.3, 127.7, 128.4, 128.6, 128.9, 129.3, 129.5, 131.9, 132.0, 133.7, 135.1, 138.9, 139.5, 147.5; IR ($CHCl_3$, cm^{-1}) 3065, 3028, 1602,

1450; MS *m/z* (rel intensity) 358 (28, M+1), 357 (100, M^+), 356 (26), 280 (78). Anal. Calcd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.39; H, 5.61; N, 3.94.

11-Ethyl-6-phenylisoindolo[2,1-*a*]indole (Compound **24**, Table 3, entry 5). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 126 mg (81%) of the indicated compound as a white solid: mp 144-145 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 7.5 Hz, 3H), 3.18 (q, J = 7.5 Hz, 2H), 6.14 (s, 1H), 6.97 (dd, J = 1.8, 7.8 Hz, 1H), 7.06-7.16 (m, 2H), 7.22-7.26 (m, 4H), 7.35-7.47 (m, 4H), 7.75 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.9, 18.1, 64.3, 109.9, 110.1, 119.1, 119.8, 120.9, 121.7, 124.1, 126.8, 127.2, 128.4, 128.5, 129.1, 132.5, 132.8, 133.6, 139.1, 139.4, 147.2; IR ($CHCl_3$, cm^{-1}) 3057, 2926, 1611, 1451; HRMS Calcd for $C_{23}H_{19}N$: 309.1518. Found: 309.1516. Anal. Calcd for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53. Found: C, 88.95; H, 6.47; N, 4.66.

11-*n*-Butyl-6-phenylisoindolo[2,1-*a*]indole (25). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 137 mg (81%) of the indicated compound as a white solid: mp 135-136 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3H), 1.56 (sextet, J = 7.5 Hz, 2H), 1.86 (quintet, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 6.14 (s, 1H), 6.93 (dd, J = 0.9, 7.5 Hz, 1H), 7.09 (dddd, J = 1.2, 7.2, 7.2, 17.7 Hz, 2H), 7.18-7.24 (m, 4H), 7.33-7.44 (m, 4H), 7.71 (dd, J = 0.6, 8.1 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 24.5, 33.5, 64.3, 108.3, 110.0, 119.1, 119.9, 120.9, 121.6, 124.1, 126.8, 127.2, 128.3, 128.4, 129.1, 132.5, 133.1, 133.5, 139.4, 139.5, 147.2;

IR ($CHCl_3$, cm^{-1}) 3046, 2922, 1610, 1450; HRMS Calcd for $C_{25}H_{23}N$: 337.1831. Found: 337.1831. Anal. Calcd for $C_{25}H_{23}N$: C, 88.98; H, 6.87; N, 4.15. Found: C, 88.72; H, 7.00; N, 4.26.

Ethyl 6-phenylisoindolo[2,1-*a*]indole-11-carboxylate (26). The reaction was run using procedure A and was chromatographed using 7:1 hexanes/EtOAc to afford 141 mg (80%) of the indicated compound as a white solid: mp 181-182 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.57 (t, J = 7.2 Hz, 3H), 4.55 (q, J = 7.2 Hz, 2H), 6.02 (s, 1H), 6.90 (d, J = 8.1 Hz, 1H), 7.06-7.13 (m, 3H), 7.24 (dt, J = 0.9, 14.4 Hz, 2H), 7.30-7.37 (m, 4H), 7.49 (dt, J = 0.6, 14.7 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.78 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 60.0, 64.9, 99.9, 110.4, 122.0, 122.9, 123.4, 125.7, 127.2, 128.8, 129.2, 129.3, 130.7, 131.2, 133.1, 137.5, 148.3, 148.6, 165.8 (two sp^2 carbons missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3056, 2980, 1688, 1559; HRMS Calcd for $C_{24}H_{19}NO_2$: 353.1416. Found: 353.1416.

11-Hydroxymethyl-6-phenylisoindolo[2,1-*a*]indole (27). The reaction was run using procedure A and was chromatographed using 1:1 hexanes/EtOAc to afford 80 mg (51%) of the indicated compound as a white solid: mp 182-183 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.59 (br s, 1H), 5.20 (s, 2H), 6.12 (s, 1H), 6.92 (d, J = 7.8 Hz, 1H), 7.10 (dddd, J = 1.2, 6.9, 6.9, 19.5 Hz, 2H), 7.15-7.22 (m, 2H), 7.25, (dd, J = 0.9, 5.4 Hz, 2H), 7.28-7.35 (m, 3H), 7.41 (td, J = 1.8, 8.1 Hz, 1H), 7.76 (d,J = 7.5 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.2, 64.6, 106.6, 110.2, 119.7, 120.0, 121.8, 122.1, 124.0, 127.2, 127.6, 128.5, 128.6, 129.2, 131.5,

132.1, 133.4, 138.7, 141.3, 147.3; IR ($CHCl_3$, cm^{-1}) 3382, 3047, 1614, 1450; HRMS Calcd for $C_{22}H_{17}NO$: 311.1310. Found: 311.1307.

11-Methoxymethyl-6-phenylisoindolo[2,1-*a*]indole (28). The reaction was run using procedure B and was chromatographed using 10:1 hexanes/EtOAc to afford 75 mg (46%) of the indicated compound as a white solid: mp 144-145 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 3.53 (s, 3H), 5.03 (s, 2H), 6.12 (s, 1H), 6.94 (dd, J = 0.3, 7.8 Hz, 1H), 7.11 (dddd, J = 1.2, 7., 7.2, 21.6 Hz, 2H), 7.19 (dd, J = 3.6, 7.5 Hz, 2H), 7.25-7.27 (m, 2H), 7.33-7.36 (m, 3H), 7.43 (td, J = 2.4, 8.1 Hz,1H), 7.78 (dd, J = 0.6, 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.6, 64.5, 65.3, 103.8, 110.2, 119.90, 119.94, 121.9, 122.0, 124.0, 127.2, 127.5, 128.5, 128.6, 129.2, 131.8, 132.9, 133.4, 138.83, 141.9, 147.4; IR ($CHCl_3$, cm^{-1}) 3055, 2923, 1612, 1451; HRMS Calcd for $C_{23}H_{19}NO$: 325.1467. Found: 325.1466. Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.88; N, 4.30. Found: C, 84.82; H, 6.16; N, 4.36.

11-(4-Hydroxybutyl)-6-phenylisoindolo[2,1-*a*]indole (29). The reaction was run using procedure B and was chromatographed using 1:1 hexanes/EtOAc to afford 127 mg (72%) of the indicated compound as a white solid: mp 136-137 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.61 (br s, 1H), 1.73-1.82 (m, 2H), 1.89-1.99 (m, 2H), 3.16 (t, J = 7.2 Hz, 2H), 3.71 (t, J = 6.6 Hz, 2H), 6.13 (s, 1H), 6.93 (dd, J = 1.2, 7.2 Hz, 1H), 7.08 (dddd, J = 1.2, 7.2, 7.2, 15.9 Hz, 2H), 7.17-7.26 (m, 4H), 7.31-7.43, (m, 4H), 7.68 (dd, J = 1.2, 6.9 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 27.3, 32.7, 63.1, 64.2, 107.6, 110.1, 119.2, 119.8, 120.8, 121.7, 124.1, 126.9, 127.2, 128.3, 128.4, 129.1, 132.4, 133.0, 133.5, 139.3, 139.6,

147.1; IR ($CHCl_3$, cm^{-1}) 3046, 2922, 1610, 1450; IR ($CHCl_3$, cm^{-1}) 3365, 3049, 2935, 1610, 1450; HRMS Calcd for $C_{25}H_{23}NO$: 353.1780. Found: 353.1787.

11-*n*-Butyl-9-methyl-6-phenylisoindolo[2,1-*a*]indole (30). The reaction was run using procedure B and was chromatographed using 50:1 hexanes/EtOAc to afford 142 mg (81%) of the indicated compound as a yellow solid: mp 122-124 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 1.61 (sextet, J = 7.5 Hz, 2H), 1.90 (quintet, J = 7.2 Hz, 2H), 2.51 (s, 3H), 3.18 (t, J = 7.5 Hz, 2H), 6.11 (s, 1H), 6.95 (dd, J = 1.2, 6.9 Hz, 1H), 7.05-7.17 (m, 4H), 7.20-7.25 (m, 2H), 7.32-7.40 (m, 3H), 7.65 (s, 1H), 7.74 (dd, J = 0.6, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.8, 22.9, 24.5, 33.5, 64.1, 108.2, 110.0, 119.0, 119.9, 121.5, 121.6, 123.8, 127.2, 127.7, 128.3, 129.1, 132.7, 133.2, 133.6, 138.2, 139.6, 139.7, 144.6; IR ($CDCl_3$, cm^{-1}) 3058, 2954, 1620, 1452; HRMS Calcd for $C_{26}H_{25}N$: 351.1987. Found: 351.1987.

11-*n*-Butyl-7-methoxy-6-phenylisoindolo[2,1-*a*]indole (31). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (78%) of the indicated compound as a white solid: mp 153-154 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.5 Hz, 3H), 1.52 (sextet, J = 7.5 Hz, 2H), 1.81 (quintet, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 3.88 (s, 3H), 6.08 (s, 1H), 6.75 (dd, J = 2.4, 8.4 Hz, 1H), 6.89 (dddd, J = 0.9, 0.9, 0.9, 8.1 Hz, 1H), 7.04 (dddd, J = 1.2, 6.9, 6.9, 22.2 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.14-7.20 (m, 2H), 7.28-7.36 (m, 4H), 7.65 (dddd, J = 0.9, 0.9, 0.9, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 24.5, 33.5, 55.7, 63.8, 106.7, 108.5, 110.0, 112.3, 119.1,

120.0, 121.7, 124.7, 127.2, 128.3, 129.1, 133.1, 133.6, 133.8, 139.3, 139.6, 139.8, 160.2; IR ($CHCl_3$, cm^{-1}) 3043, 2925, 1626, 1456; HRMS Calcd for $C_{26}H_{25}NO$: 367.1936. Found: 367.1936.

11-*n*-Butyl-9-trifluoromethyl-6-phenylisoindolo[2,1-*a*]indole (32). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 193 mg (95%) of the indicated compound as a yellow solid: mp 139-140 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.52 (sextet, J = 7.5 Hz, 2H), 1.83 (quintet, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 6.23 (s, 1H), 6.90 (dd, J = 1.2, 6.3 Hz, 1H), 7.09 (dddd, J = 1.5, 7.2, 7.2, 14.1 Hz, 2H), 7.15 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 4.2 Hz, 1H), 7.29-7.37 (m, 4H), 7.46 (dd, J = 0.6, 8.1 Hz, 1H), 7.70 (dd, J = 1.5, 6.9 Hz, 1H), 7.96 (s,1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.8, 24.4, 33.3, 64.1, 109.7, 110.1, 117.4 (q, $^3J_{C\text{-}F}$ = 2.8 Hz), 119.4, 120.3, 122.3, 123.6 (q, $^4J_{C\text{-}F}$ = 2.7 Hz), 124.2 (q, $^1J_{C\text{-}F}$ = 204.1 Hz), 124.4, 127.1, 128.7, 129.3, 130.0 (q, $^2J_{C\text{-}F}$ = 24.2 Hz), 133.0, 133.2, 133.5, 137.9, 138.4, 150.3; IR ($CHCl_3$, cm^{-1}) 3049, 2926, 1455, 1438; HRMS Calcd for $C_{26}H_{22}F_3N$: 405.1704. Found: 405.1705.

Ethyl 11-*n*-butyl-6-phenylisoindolo[2,1-*a*]indole-7-carboxylate (33). The reaction was run using procedure B and was chromatographed using 10:1 hexanes/EtOAc to afford 151 mg (74%) of the indicated compound as a yellow solid: mp 120-121 °C (hexanes/EtOAc); ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.53 (sextet, J = 7.5 Hz, 2H), 1.84 (quintet, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 6.15 (s, 1H), 6.90 (ddd, J = 0.9, 0.9,

8.1 Hz, 1H), 7.07 (dddd, J = 1.2, 7.2, 7.2, 14.7 Hz, 2H), 7.15-7.18 (m, 2H), 7.26 (d, J = 8.1 Hz, 1H), 7.31-7.36 (m, 3H), 7.68 (ddd, J = 1.5, 6.6 Hz, 1H), 7.90 (dd, J = 1.5, 8.1 Hz, 1H), 8.41 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 22.8, 24.4, 33.4, 61.3, 64.3, 109.3, 110.1, 119.4, 120.2, 121.8, 122.1, 123.9, 127.2, 128.2, 128.6, 129.2, 131.0, 132.9, 133.1, 133.5, 138.4, 138.7, 151.5, 166.4; IR ($CDCl_3$, cm^{-1}) 3056, 2967, 1720, 1437; HRMS Calcd for $C_{26}H_{27}NO_2$: 409.2042. Found: 409.2048.

Compound 34 (Table 3, entry 16). The reaction was run using procedure B and was chromatographed using 1:1 hexanes/EtOAc to afford 158 mg (93%) of the indicated compound as an off-white solid: mp 200-201 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3H), 1.49 (sextet, J = 7.5 Hz, 2H), 1.82 (quintet, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 6.17 (s, 1H), 6.96 (dddd, J = 3.6, 3.6, 7.8, 7.8 Hz, 1H), 7.13 (dddd, J = 1.2, 1.2, 8.1, 8.1 Hz, 2H), 7.19 (dd, J = 3.6, 7.5 Hz, 2H), 7.35-7.38 (m, 3H), 7.71 (dddd, J = 3.3, 3.3, 11.1, 11.1 Hz, 1H), 9.00 (s, 1H), 9.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.8, 24.9, 33.2, 64.6, 110.7, 112.4, 120.0, 120.5, 123.2, 125.5, 127.2, 129.0, 129.3, 132.1, 133.5, 134.1, 135.9, 147.8, 156.0, 173.6; IR ($CHCl_3$, cm^{-1}) 3028, 2953, 1495, 1456; HRMS Calcd for $C_{23}H_{21}N_3$: 339.1736. Found: 339.1738.

Compound 35 (Table 3, entry 17). The reaction was run using procedure B and was chromatographed using 25:1 hexanes/EtOAc to afford 144 mg (84%) of the indicated compound as an off-white solid: mp 104-105 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.50 (sextet, J = 7.5 Hz, 2H), 1.85 (quintet, J

= 7.2 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 6.07 (s, 1H), 6.86-6.89 (m, 2H), 7.04 (dddd, J = 1.5, 6.9, 6.9, 13.8 Hz, 2H), 7.20 (dddd, J = 4.2, 4.2, 4.2, 6.3 Hz, 2H), 7.27 (d, J = 4.8 Hz, 1H), 7.30-7.37 (m, 3H), 7.62 (dddd, J = 0.6, 0.6, 0.6, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 24.9, 32.8, 63.2, 105.8, 109.3, 118.9, 120.0, 121.5, 121.7, 127.1, 128.3, 128.4, 129.2, 132.5, 133.0, 134.5, 136.7, 138.6, 151.1; IR ($CHCl_3$, cm^{-1}) 3041, 2925, 1552, 1454; HRMS Calcd for $C_{23}H_{21}NS$: 343.1395. Found: 343.1395.

11-Phenyl-6-(3-chlorophenyl)isoindolo[2,1-*a*]indole (37). The reaction was run using procedure C and was chromatographed using 25:1 hexanes/EtOAc to afford 182 mg (93%) of the indicated compound as a white solid: mp 165-166 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1H), 6.99 (dd, J = 1.2, 7.2 Hz, 1H), 7.13-7.39 (m, 9H), 7.47 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 2H), 7.86-7.93 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 63.7, 110.0, 110.2, 120.5, 120.6, 121.2, 122.5, 123.9, 126.6, 127.8, 128.6, 128.7, 129.0, 129.5, 129.5, 131.8, 132.0, 133.6, 134.4, 134.9, 137.5, 139.3, 147.0; IR ($CHCl_3$, cm^{-1}) 3051, 3016, 1602, 1489; HRMS Calcd for $C_{27}H_{18}ClN$: 391.1128. Found: 391.1121.

Methyl 6,11-diphenylisoindolo[2,1-*a*]indole-2-carboxylate (39). The reaction was run using procedure C and was chromatographed using 15:1 hexanes/EtOAc to afford 172 mg (83%) of the indicated compound as a white solid: mp 170-171 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.22 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.21-7.47 (m, 9H), 7.60 (t, J = 7.5 Hz, 2H), 7.77-7.88 (m, 4H), 8.55 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.9, 64.5, 109.8, 110.9, 121.3, 122.2,

123.3, 123.8, 124.1, 126.9, 127.2, 128.2, 128.5, 128.7, 129.1, 129.3, 129.5, 131.2, 131.6, 134.1, 136.0, 138.4, 140.7, 147.3, 168.2; IR ($CDCl_3$, cm^{-1}) 3063, 2947, 1711, 1621, 1437; HRMS Calcd for $C_{29}H_{21}NO_2$: 415.1572. Found: 415.1574.

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GENERAL CONCLUSION

In this dissertation, the scope and limitations of several palladium-catalyzed processes have been presented. Specifically, the scope of the palladium-catalyzed internal alkyne methodology that has been employed by Larock and co-workers for the synthesis of a variety of carbo- and heterocycles has been expanded by employing *tert*-butylimines derived from *o*-iodobenzaldehydes and 3-halo-2-alkenals for the synthesis of isoquinolines and pyridines. In addition, imines derived from *o*-iodoanilines have been employed for the synthesis of isoindolo[2,1-*a*]indoles.

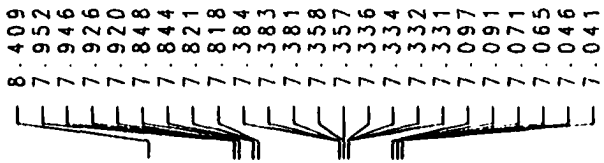
Chapter 1 describes the synthesis of a variety of substituted isoquinoline, tetrahydroisoquinoline, 5,6-dihydrobenz[*f*]isoquinoline, pyrindine, and pyridine heterocycles by the palladium-catalyzed annulation of internal alkynes. These heterocycles have been synthesized in moderate to excellent yields by employing mild reaction conditions and short reaction times. Also, during the development of this annulation methodology, an interesting isoquinoline synthesis was discovered when trimethylsilyl-substituted acetylenes were employed. A mechanism involving desilylation of the acetylene and subsequent palladium-catalyzed coupling and cyclization of the intermediate iminoalkynes is proposed for this annulation process.

Chapter 2 describes in detail, a related terminal acetylene annulation process that was discovered during the development of the internal alkyne methodology presented in chapter 1. It was subsequently discovered that, in addition to trimethylsilyl-substituted alkynes, terminal acetylenes could also be

employed in this palladium-catalyzed coupling and cyclization process. Also, a palladium-catalyzed coupling of the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals with terminal acetylenes and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes were employed for the synthesis of a variety of isoquinolines and pyridines. Finally, the effectiveness of this palladium-catalyzed terminal acetylene annulation methodology was demonstrated by the total synthesis of the isoquinoline natural product decumbenine B.

Chapter 3 presents the synthesis of a variety of substituted isoindolo[2,1-*a*]indoles via annulation of internal aryl acetylenes with imines derived from *o*-iodoanilines. This methodology very efficiently constructs these tetracyclic indoles in good to excellent yields by employing mild reaction conditions, readily prepared imines, and a variety of internal alkynes which contain either phenyl or heterocyclic rings. In addition, preliminary results indicate that the formation of highly substituted quinoline heterocycles may be possible by slightly altering the reaction conditions employed.

APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA



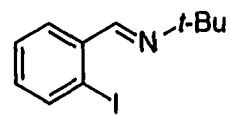


Table 2, Compound **5**

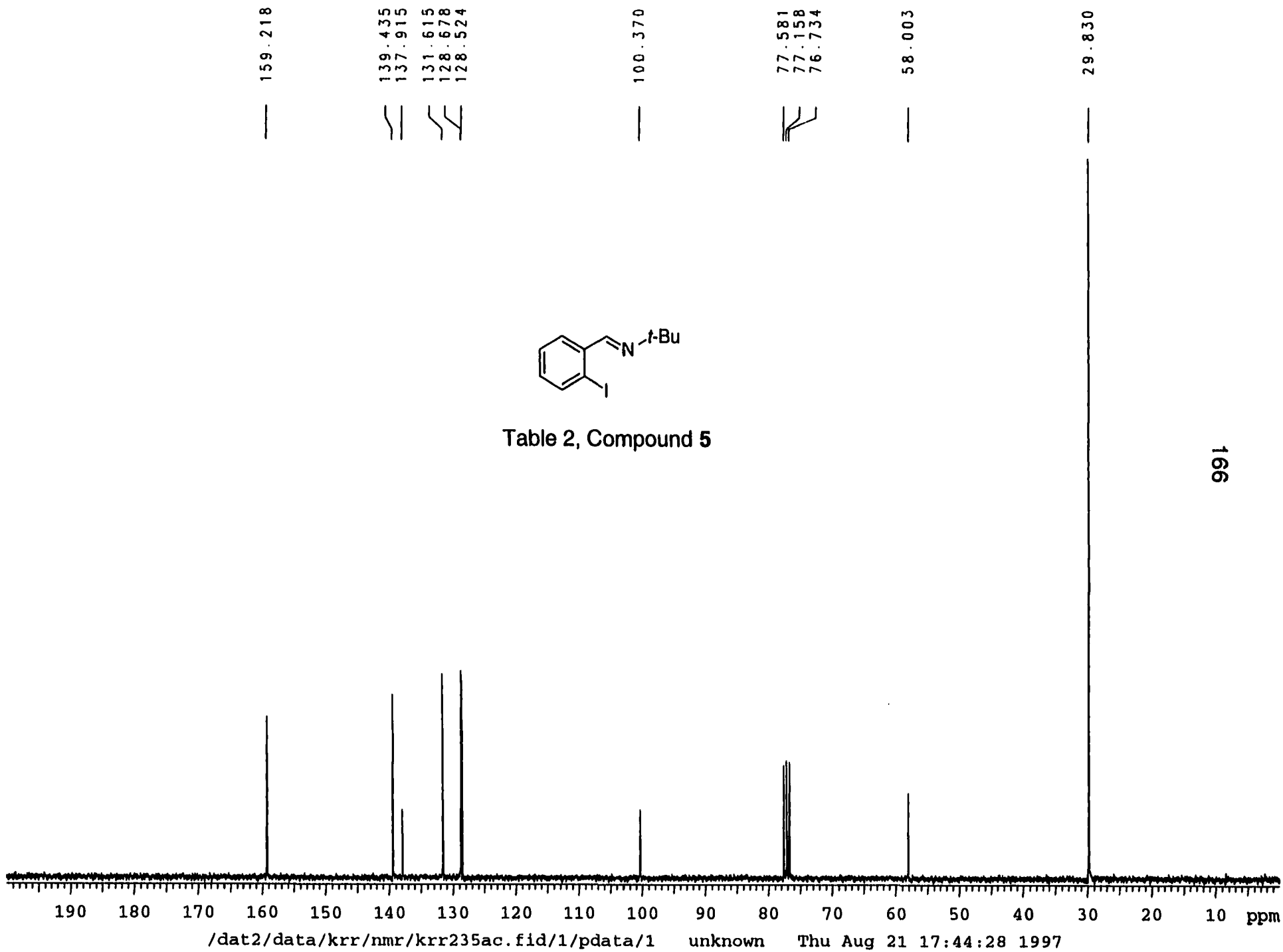


Table 2, Compound **5**

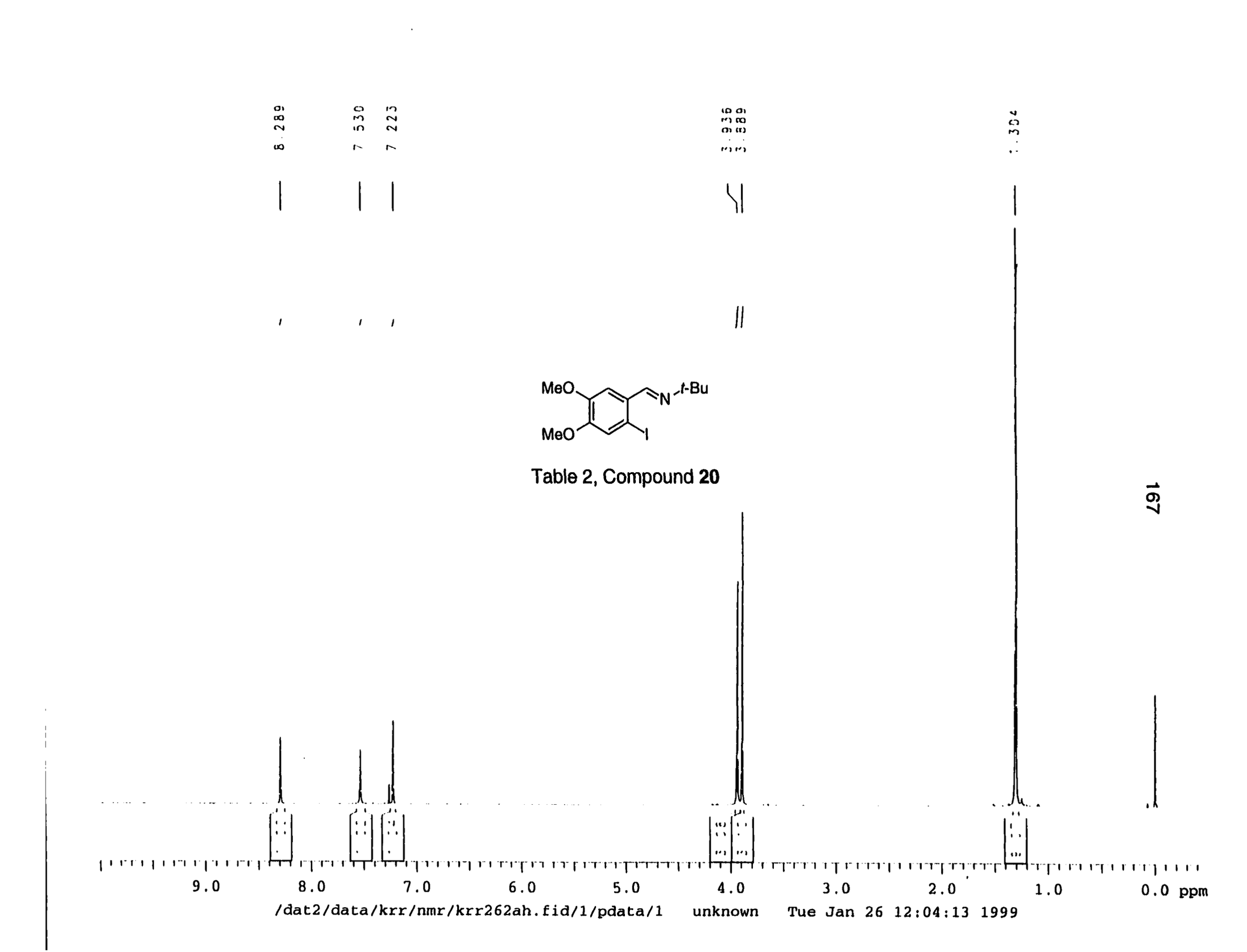
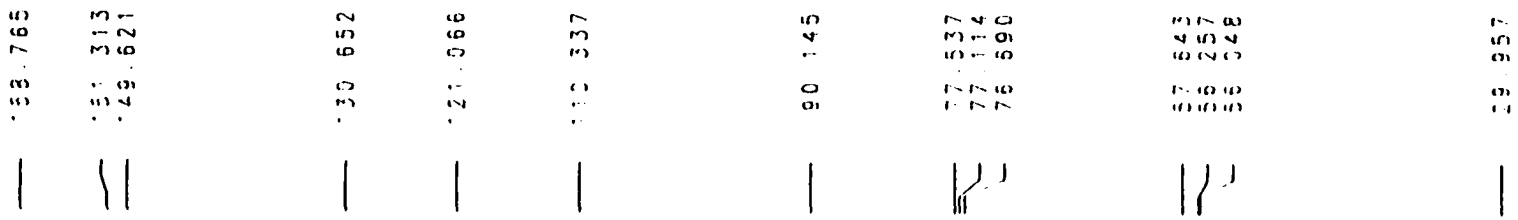
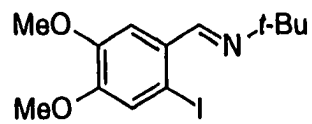


Table 2, Compound **20**





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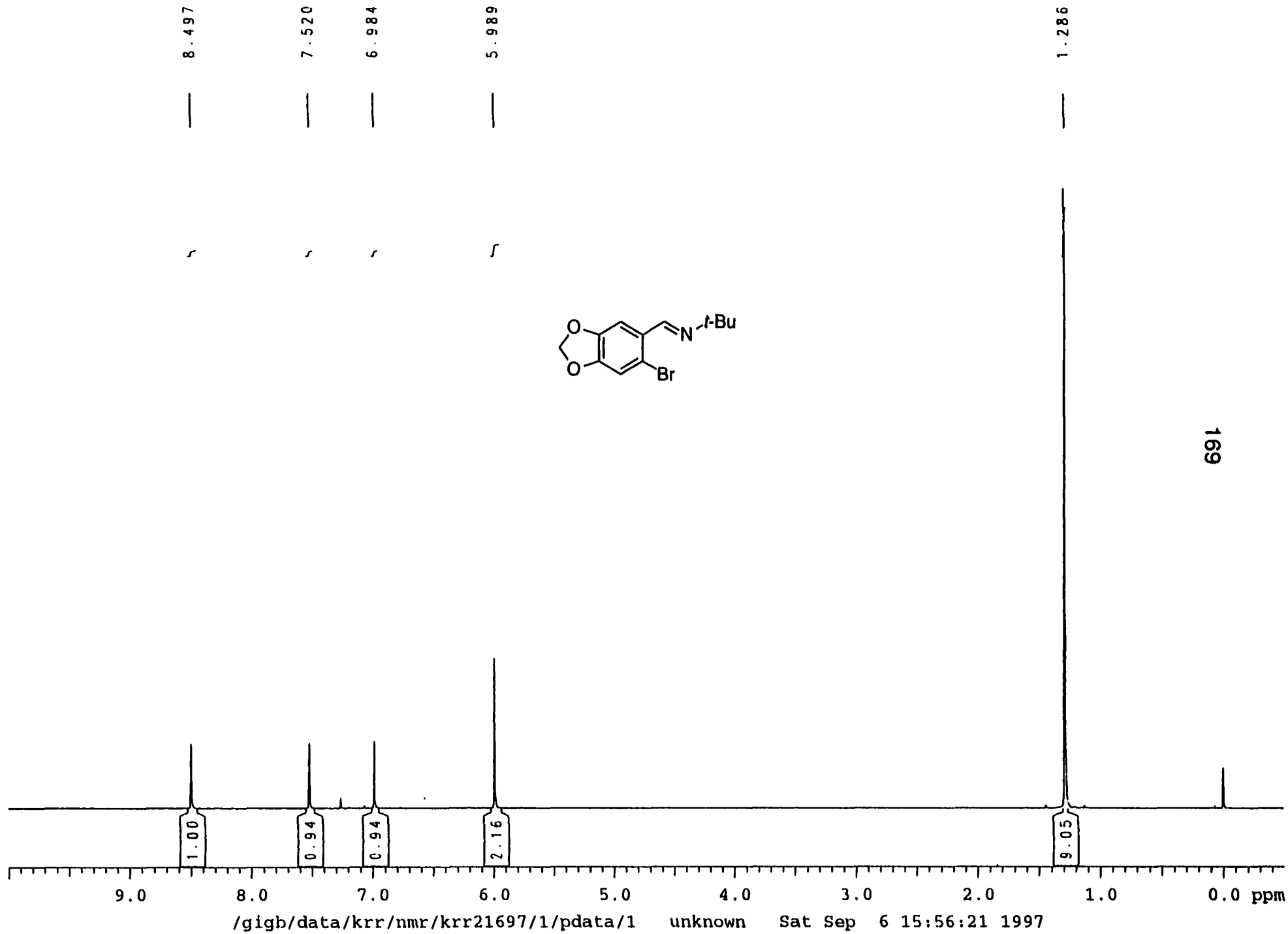

8.497
7.520
6.984
5.989
1.286
O
O
N
t-Bu
Br
1.00
0.94
0.94
2.16
9.05
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/gigb/data/krr/nmr/krr21697/1/pdata/1 unknown Sat Sep 6 15:56:21 1997

/gigb/data/krr/nmr/krr21697c.fid/1/pdata/1 unknown Sat Sep 6 16:02:00 1997
ppm
180
160
140
120
100
80
60
40
20
154.176
150.046
147.845
129.484
117.204
112.463
107.764
102.053
77.539
77.115
76.691
57.782
29.840
Br
N
t-Bu

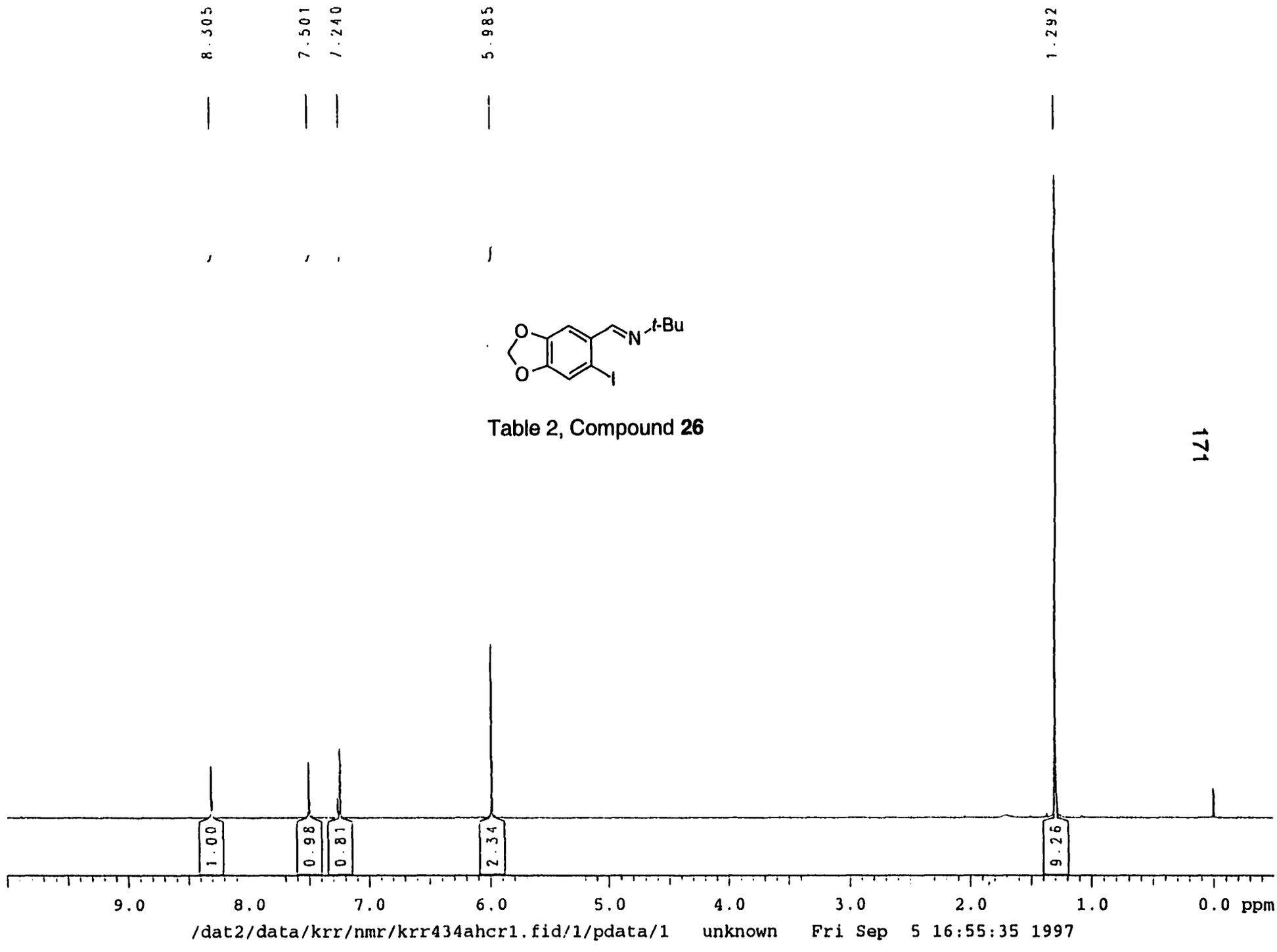


Table 2, Compound **26**

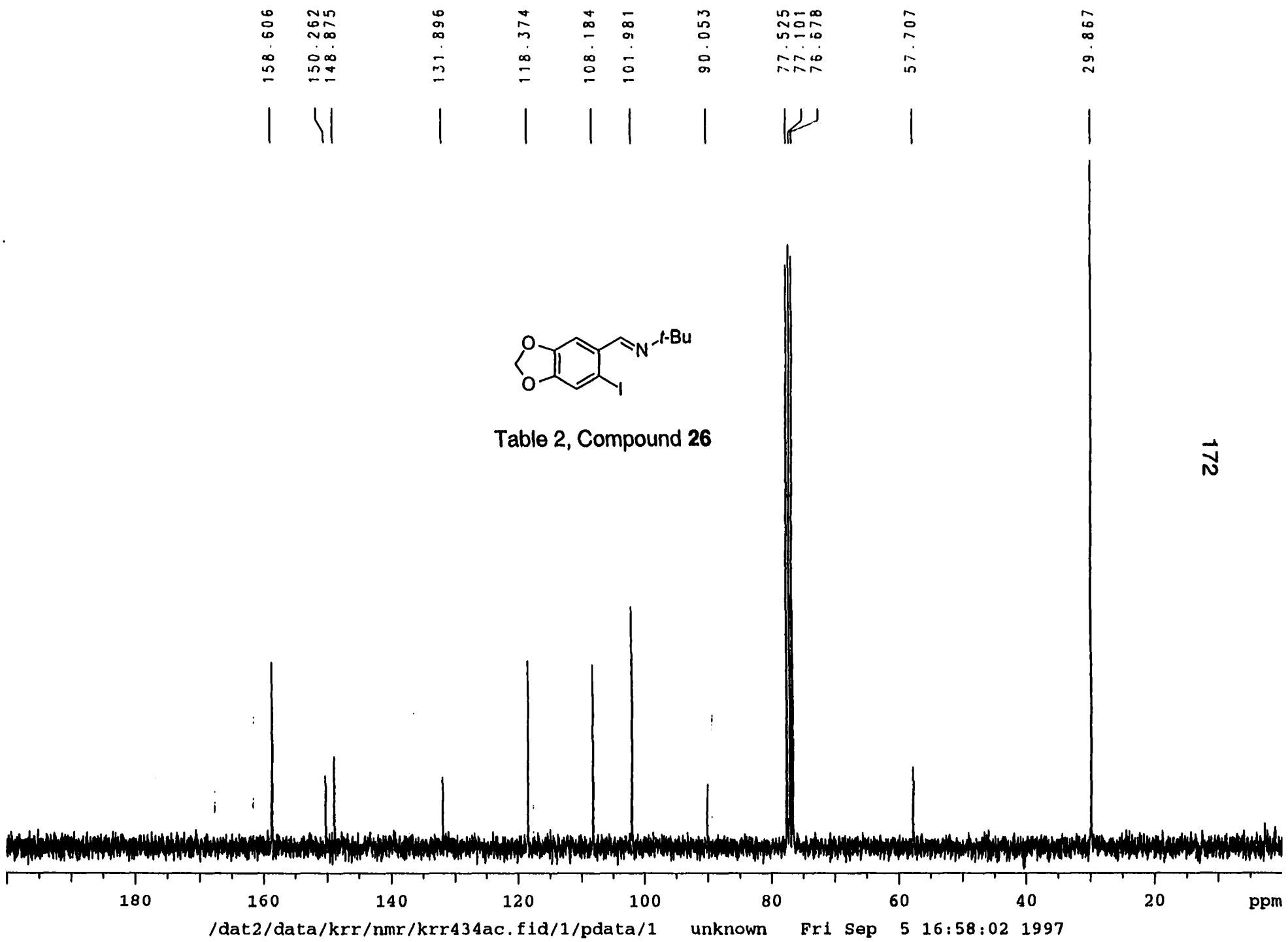


Table 2, Compound **26**

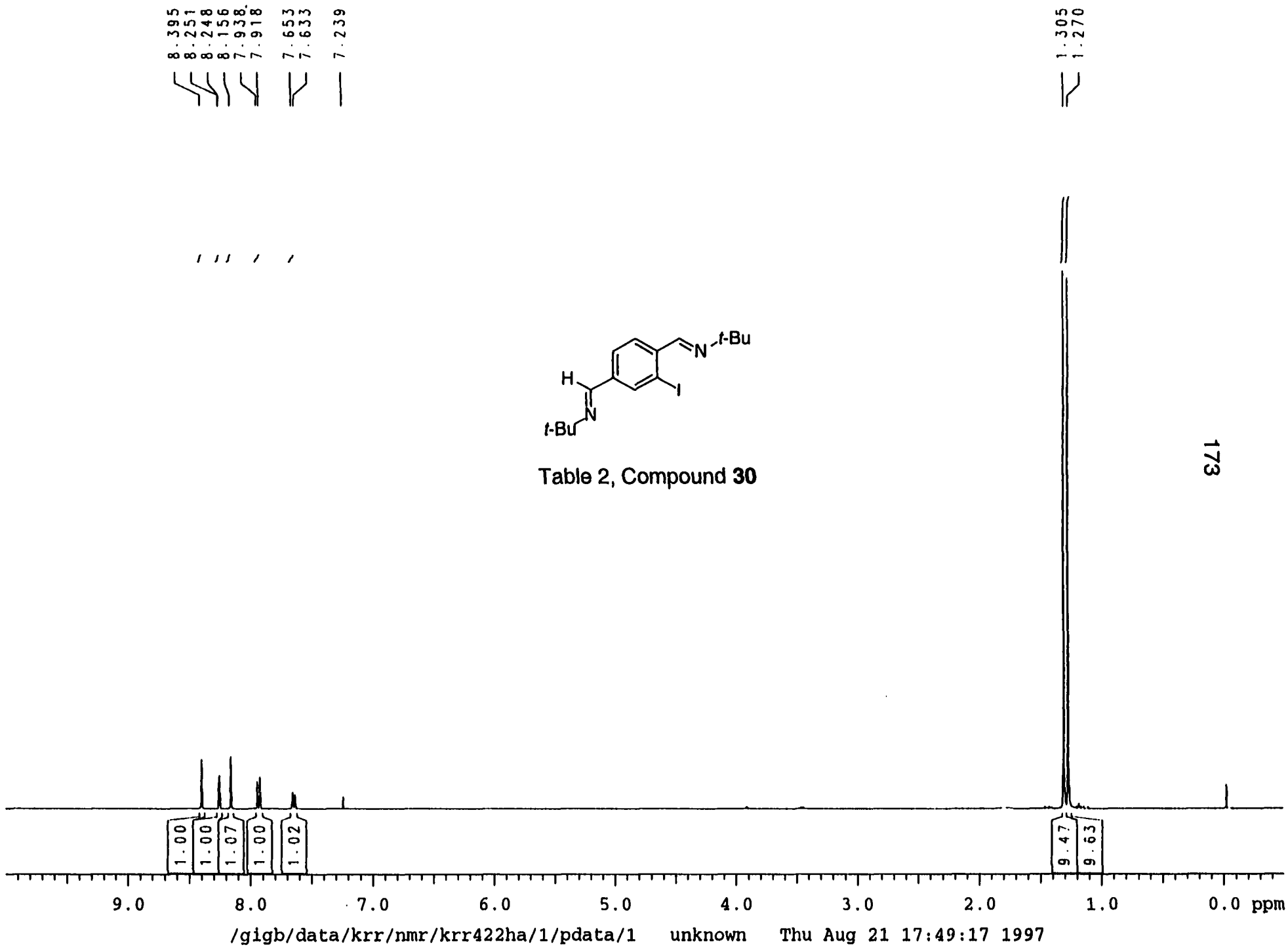


Table 2, Compound **30**

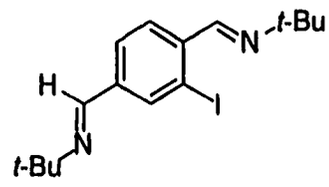


Table 2, Compound **30**

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

/gigb/data/krr/nmr/krr422ca.fid/1/pdata/1 unknown Sat Aug 9 14:12:03 1997

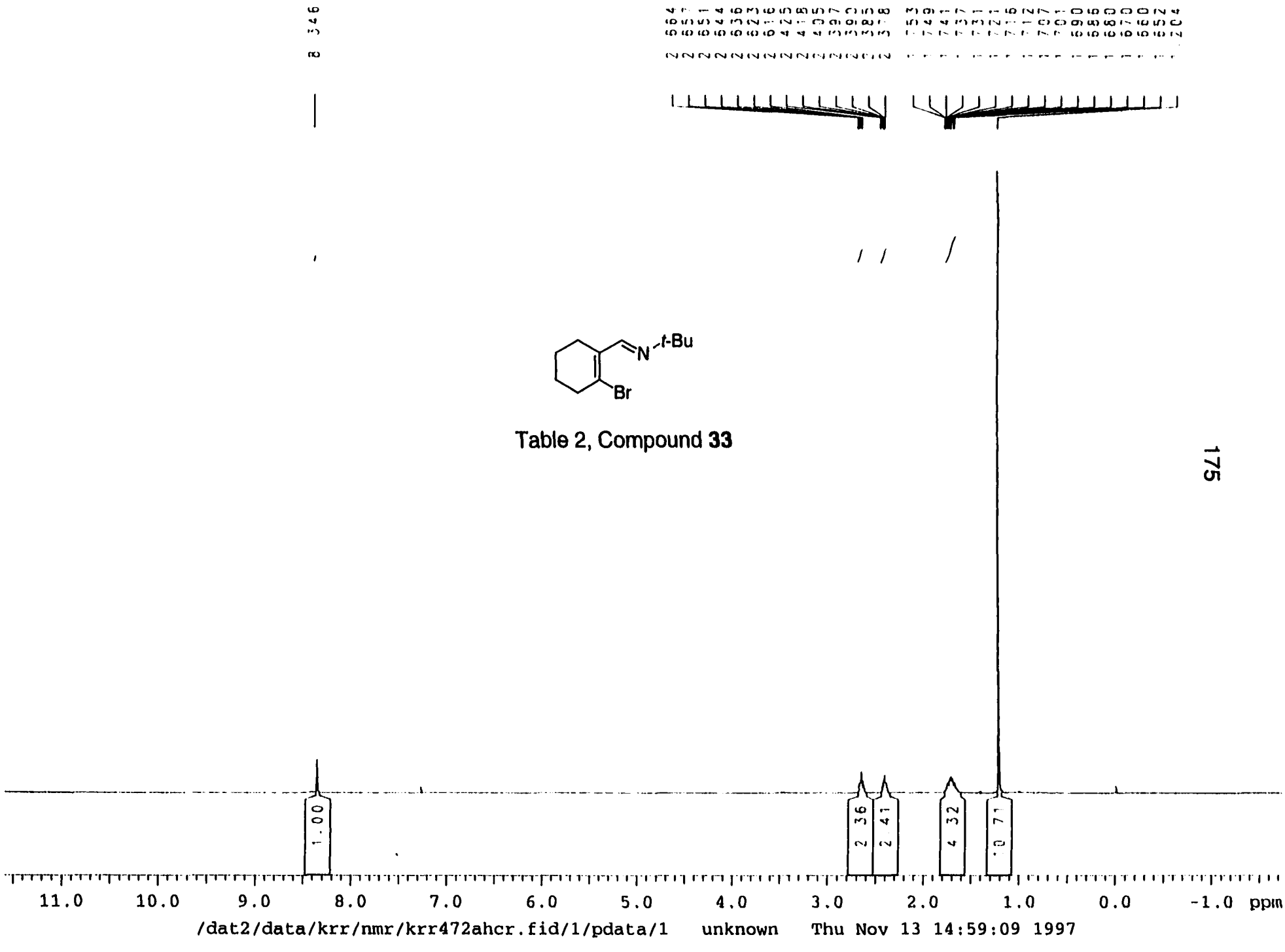


Table 2, Compound **33**

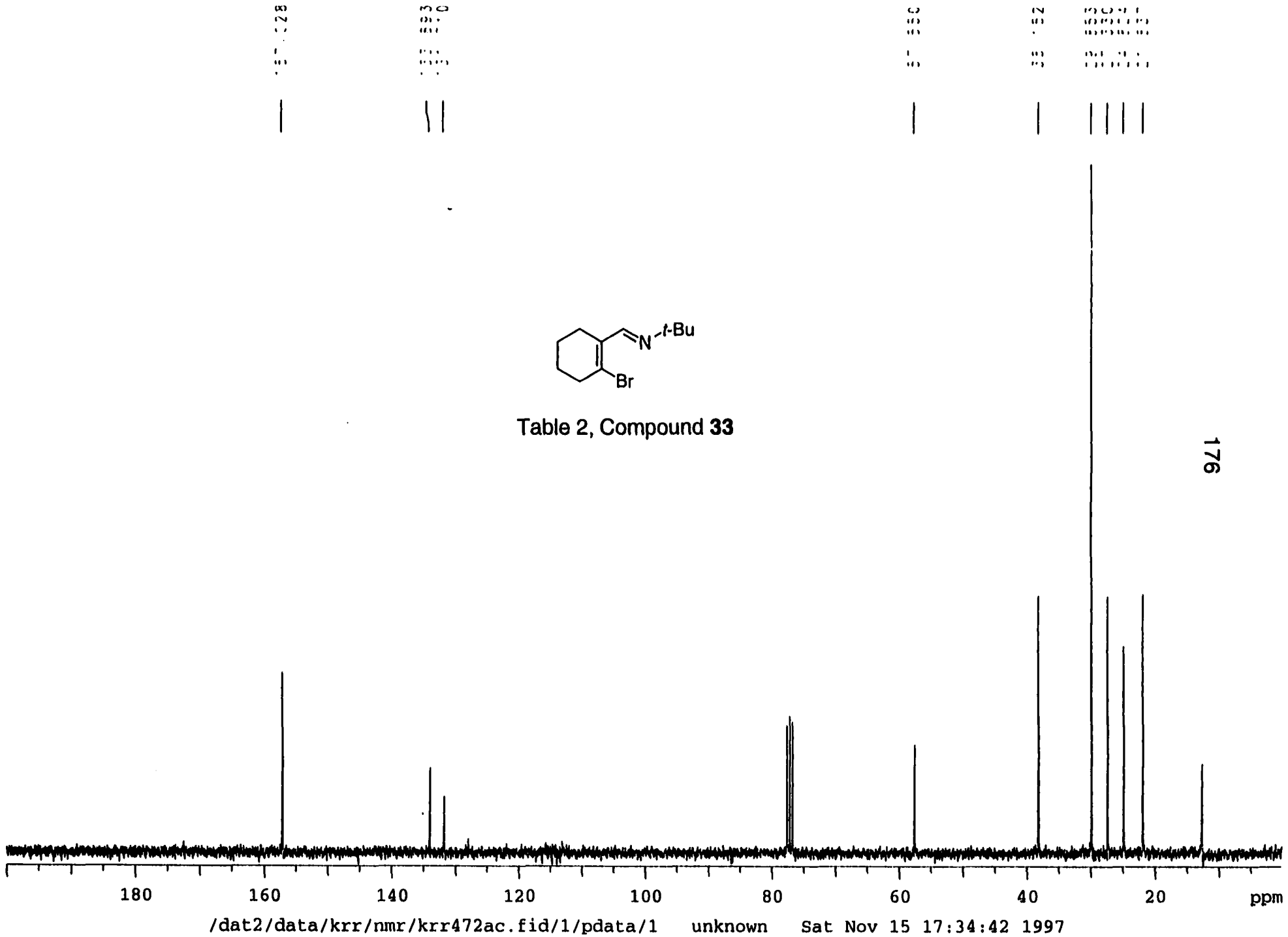


Table 2, Compound **33**

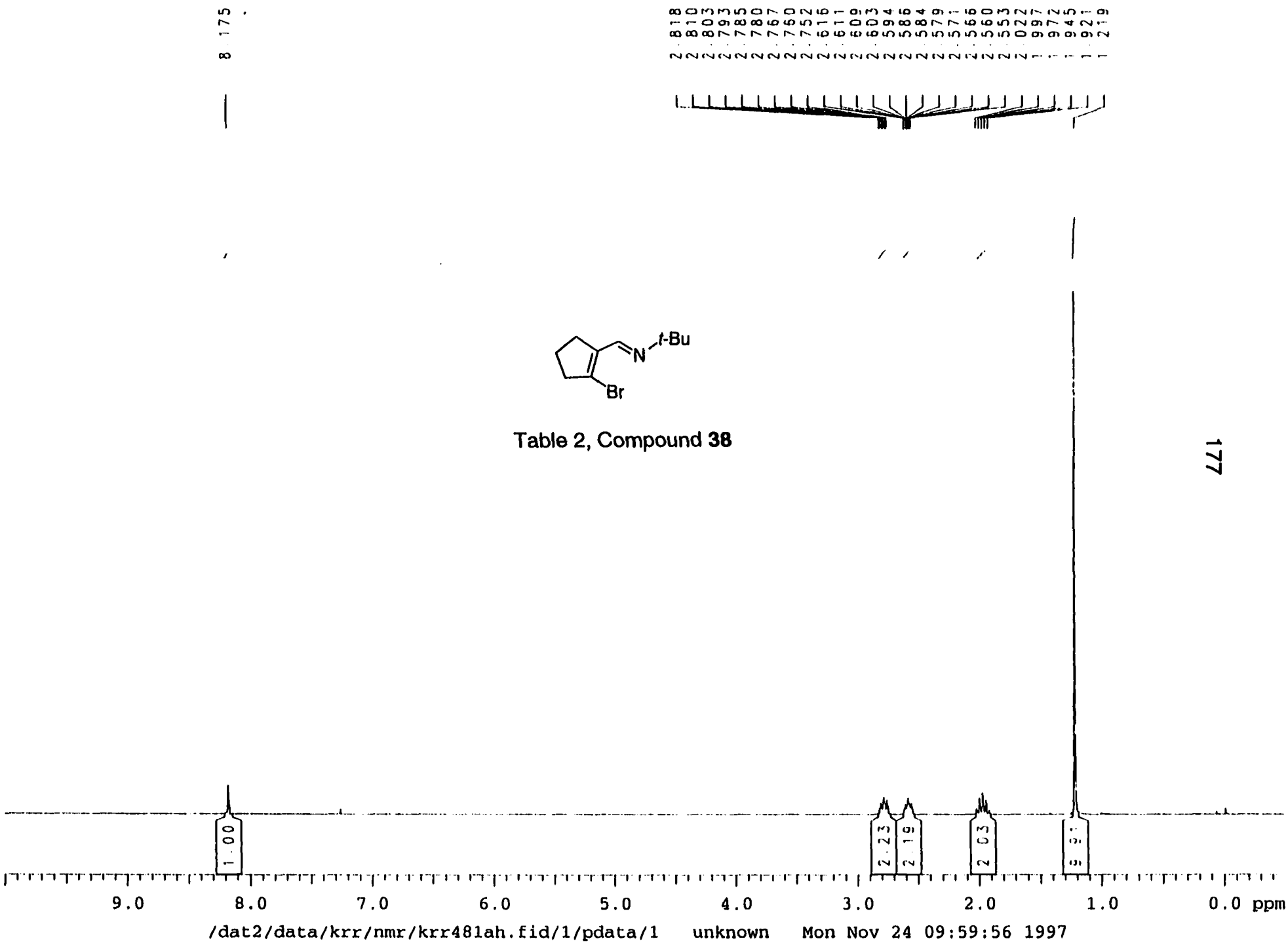


Table 2, Compound **38**

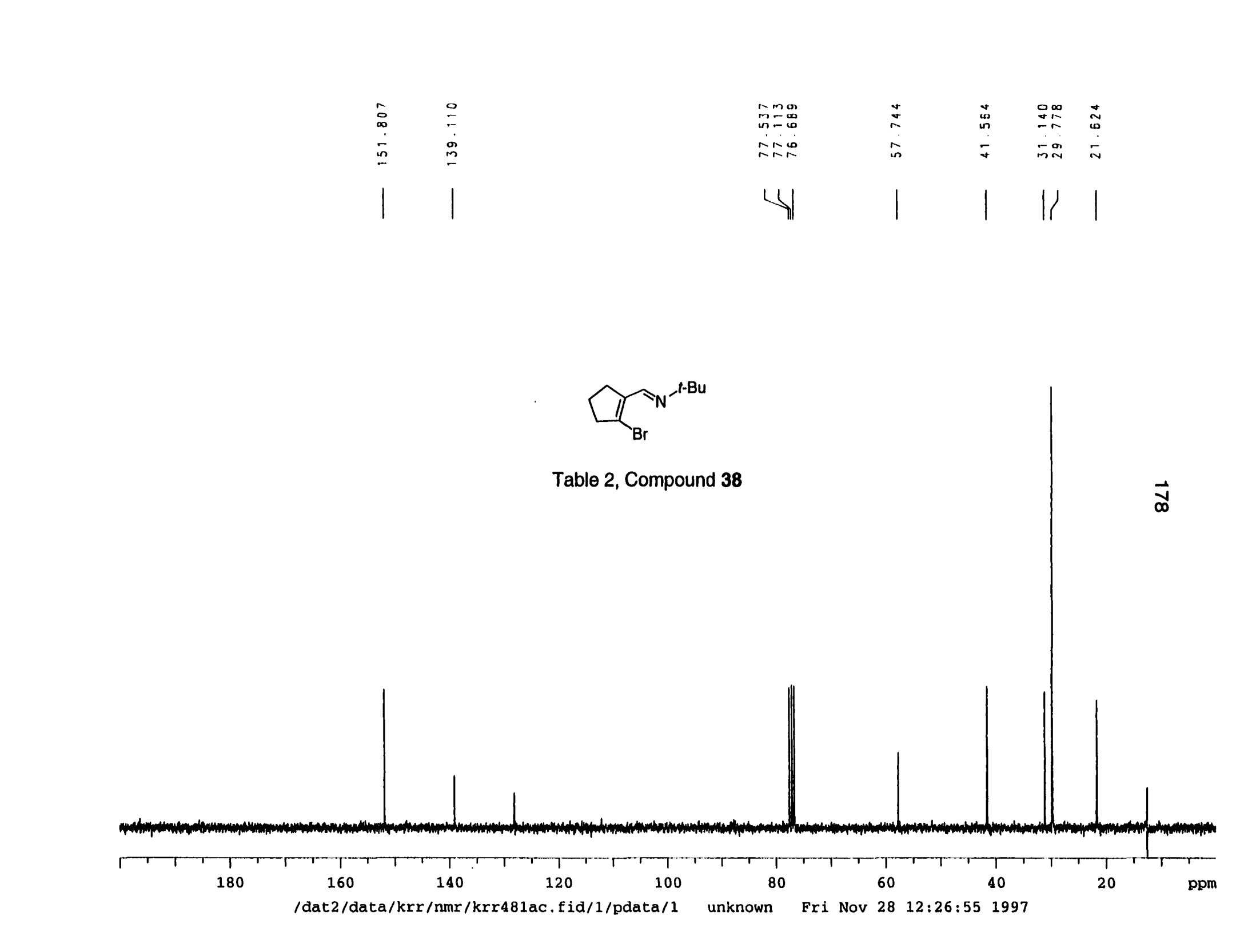

151.807
139.110
77.537
77.113
76.689
57.744
41.564
31.140
29.778
21.624
t-Bu
N
Br
Table 2, Compound 38
178
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr481ac.fid/1/pdata/1 unknown Fri Nov 28 12:26:55 1997

Table 2, Compound **42**

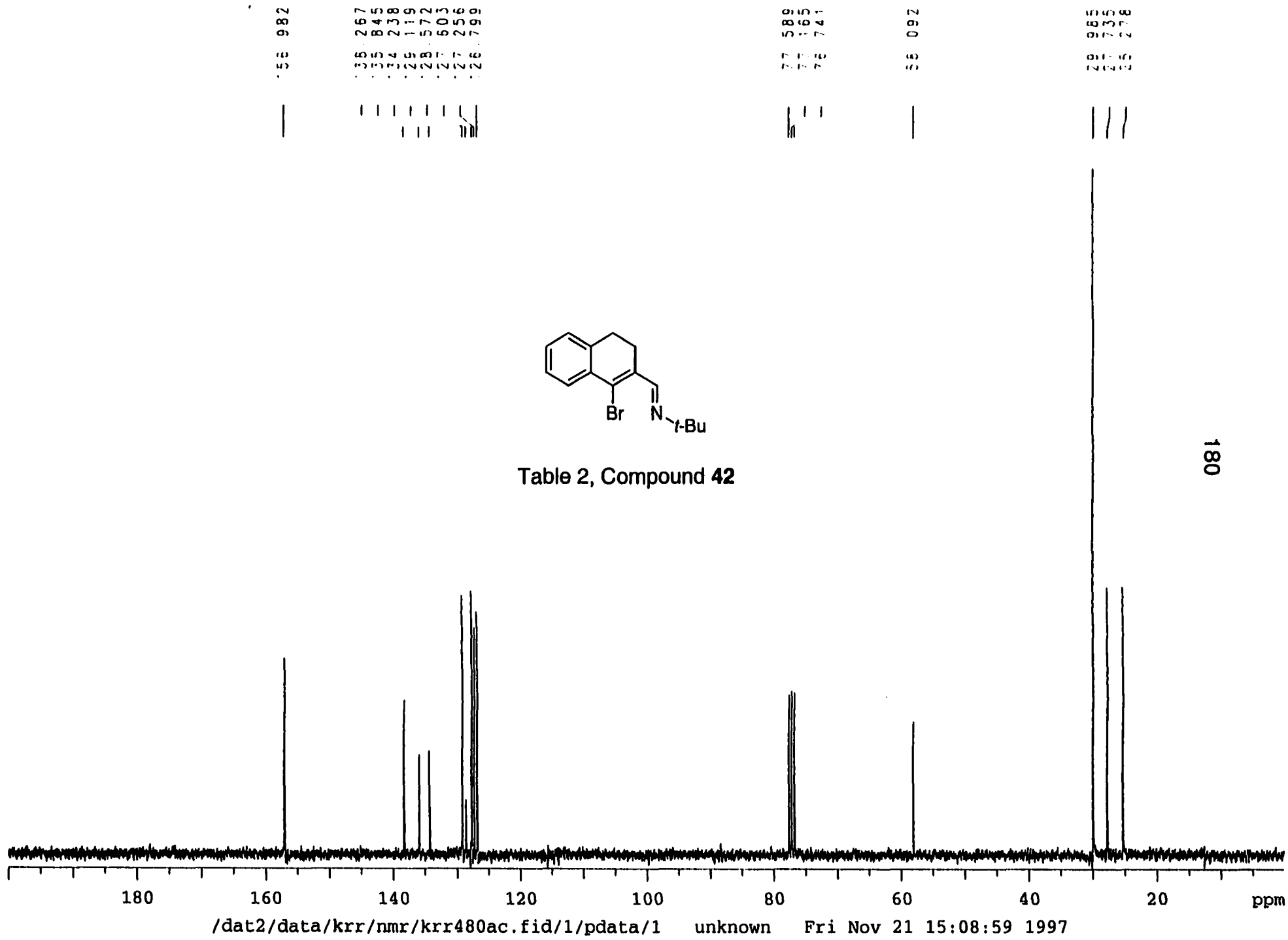


Table 2, Compound **42**

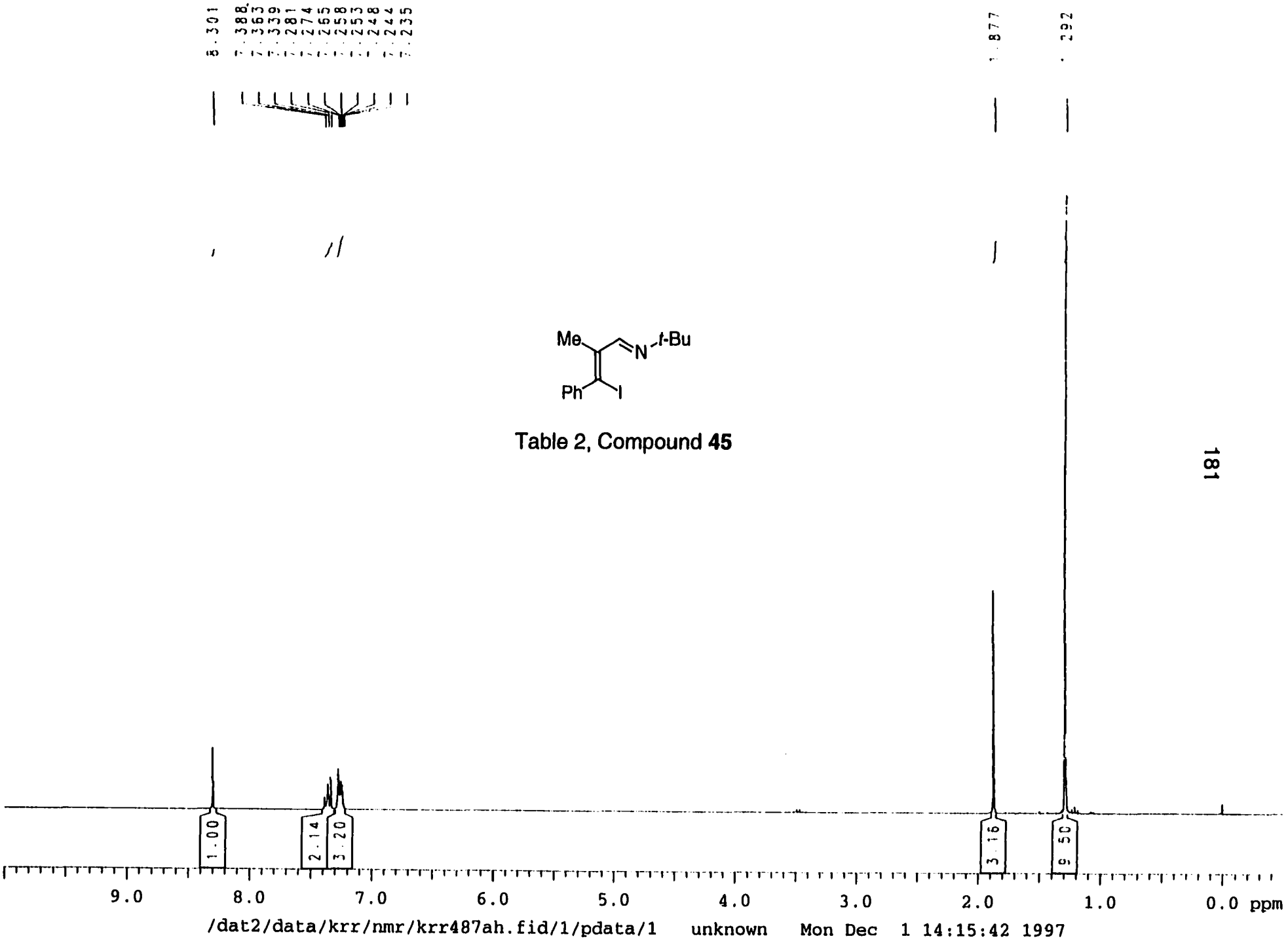


Table 2, Compound **45**

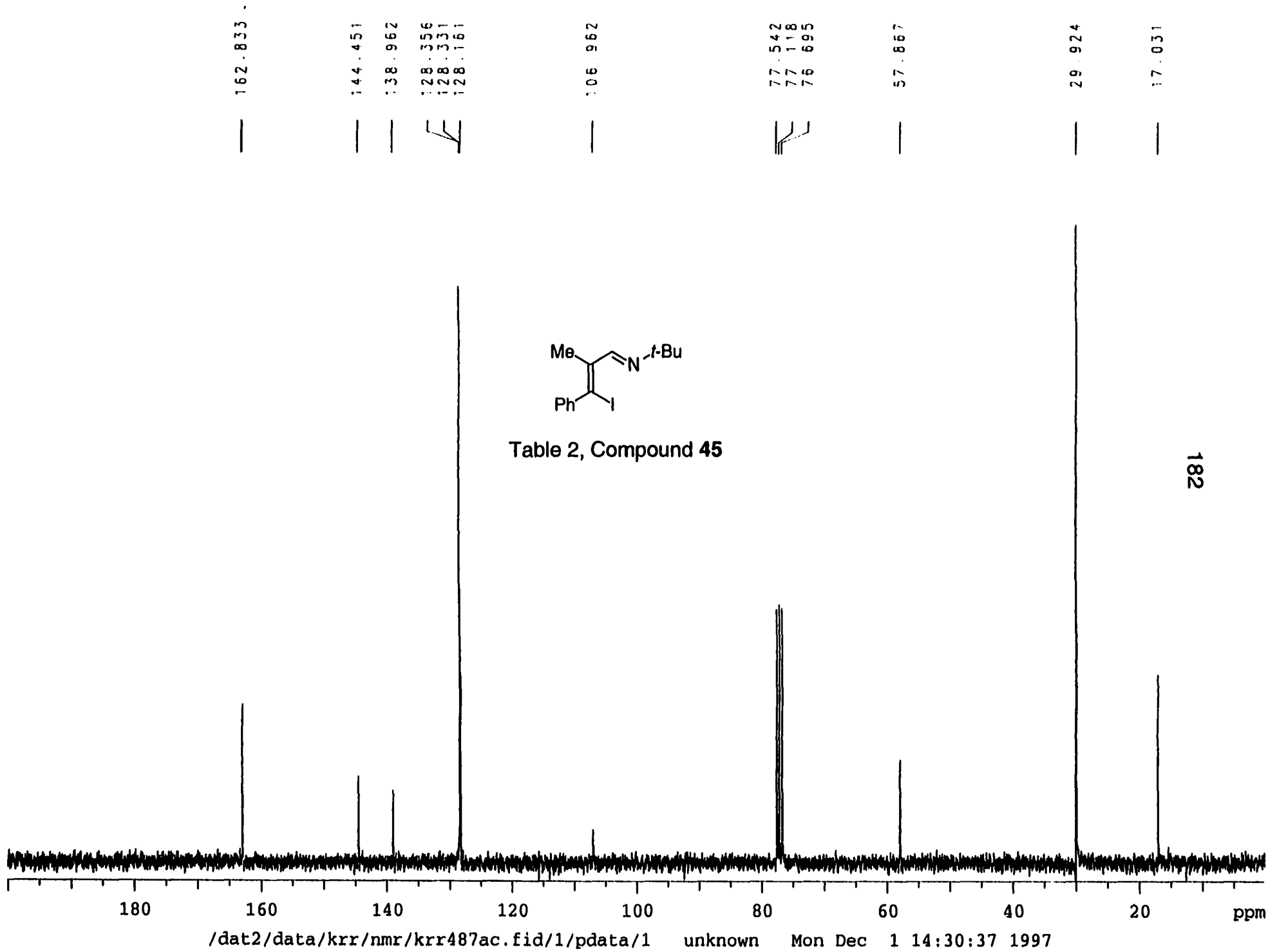
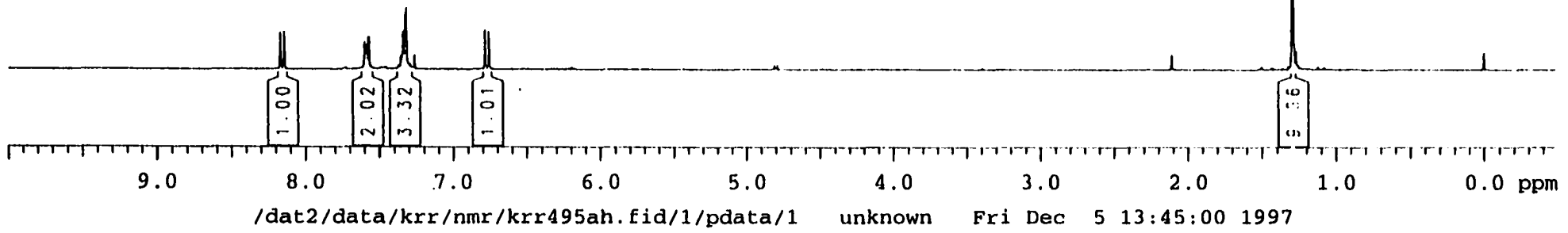

162.833
144.451
138.962
128.356
128.331
128.161
106.962
77.542
77.118
76.695
57.867
29.924
17.031
Me
N
t-Bu
Ph
I
Table 2, Compound 45
182
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr487ac.fid/1/pdata/1 unknown Mon Dec 1 14:30:37 1997

Table 2, Compound **49**



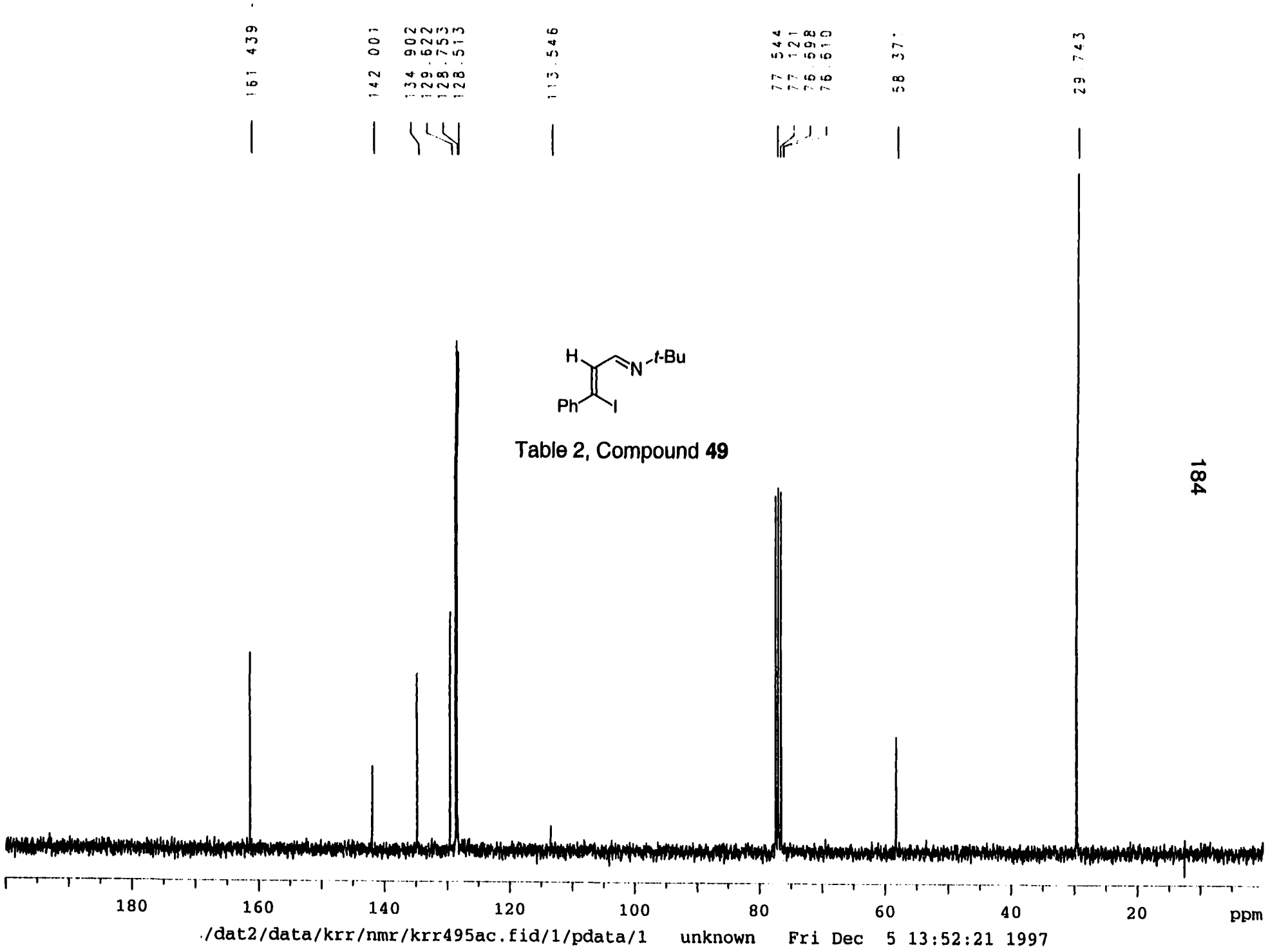


Table 2, Compound **49**

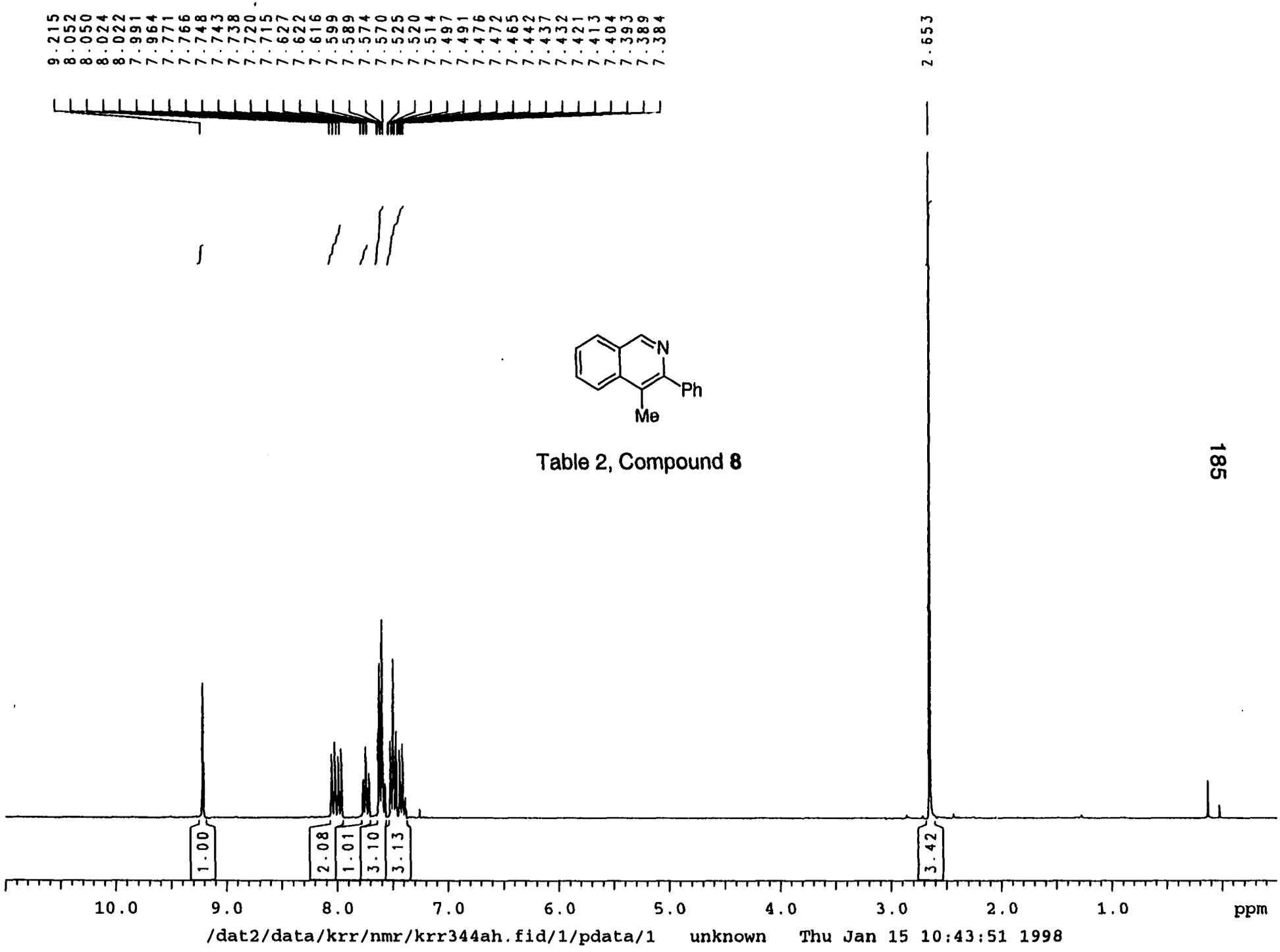


Table 2, Compound **8**

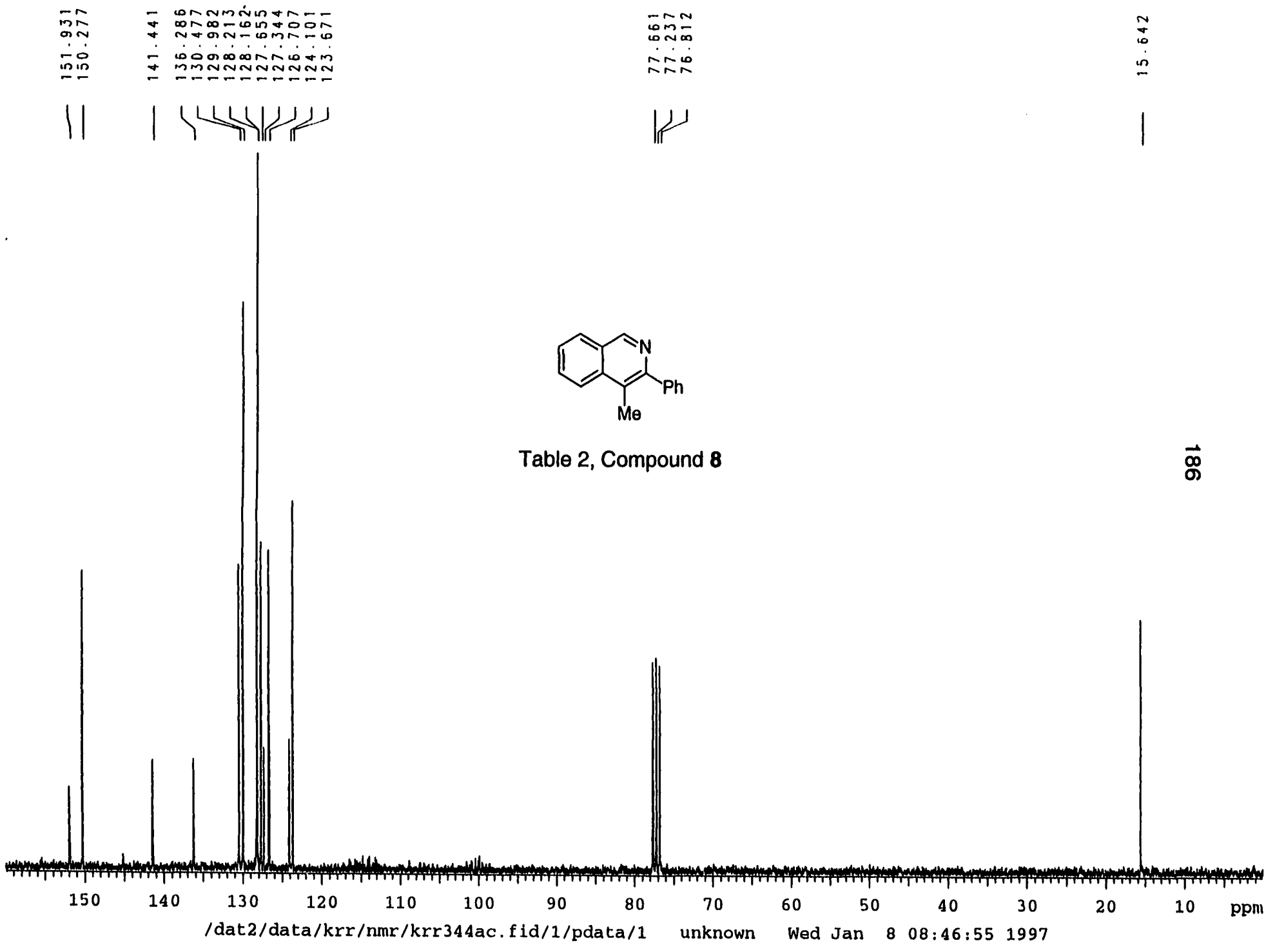
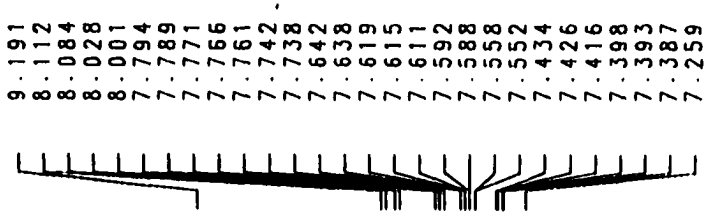
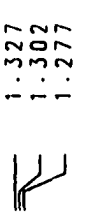


Table 2, Compound **8**

t e x t X





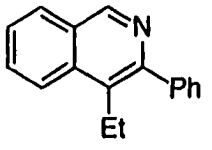
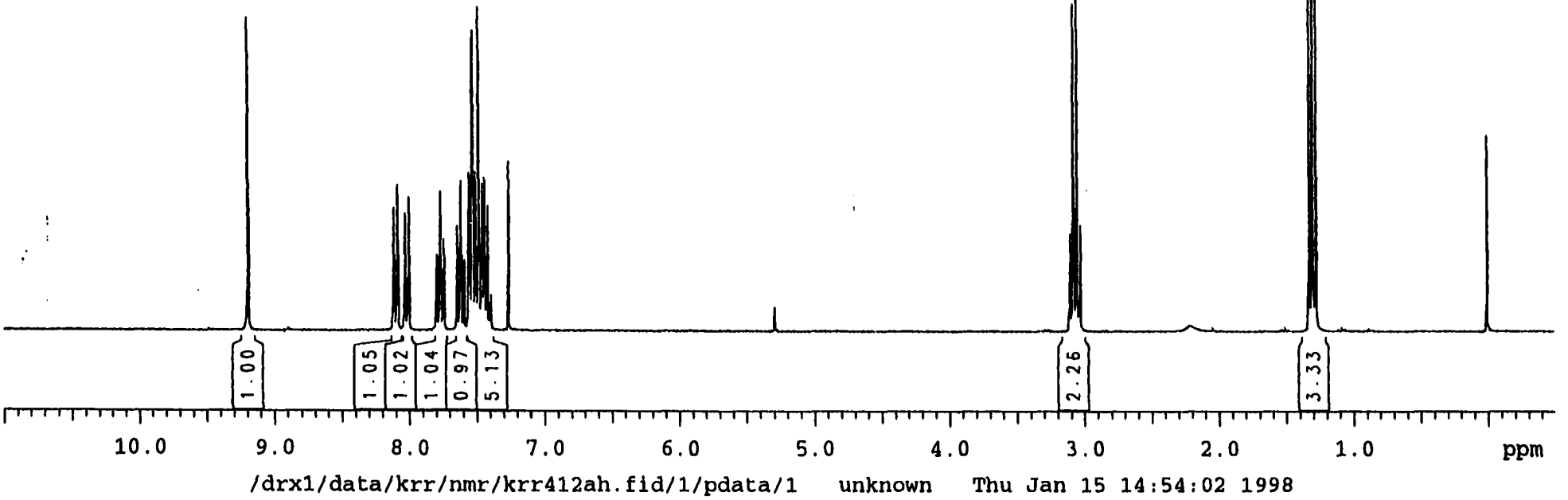
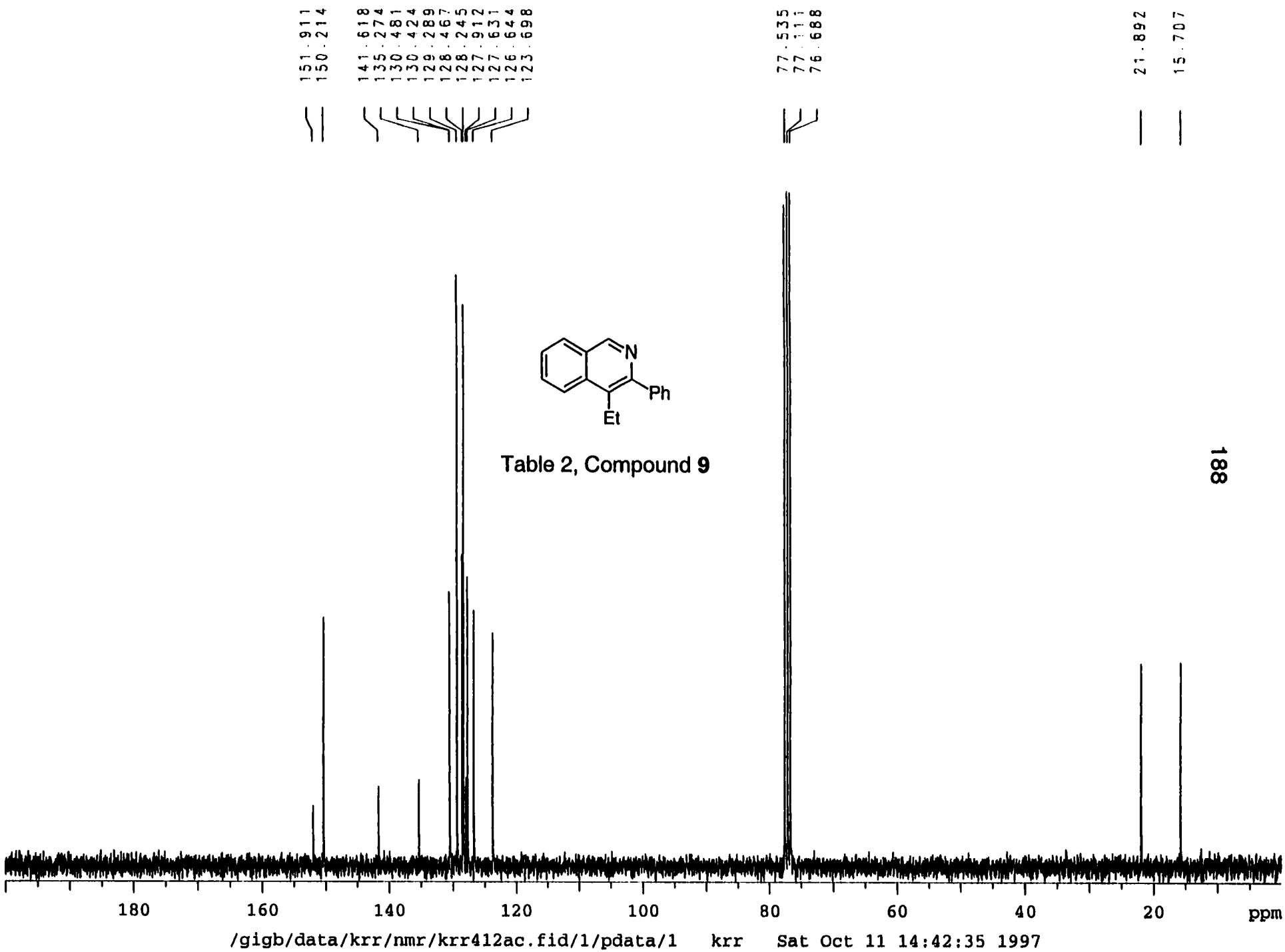


Table 2, Compound **9**

187



/drx1/data/krr/nmr/krr412ah.fid/1/pdata/1 unknown Thu Jan 15 14:54:02 1998


151.911
150.214
141.618
135.274
130.481
130.424
129.289
128.467
128.245
127.912
127.631
126.644
123.698
77.535
77.111
76.688
21.892
15.707
N
Ph
Et
Table 2, Compound 9
188
180
160
140
120
100
80
60
40
20
ppm
/gigb/data/krr/nmr/krr412ac.fid/1/pdata/1 krr Sat Oct 11 14:42:35 1997

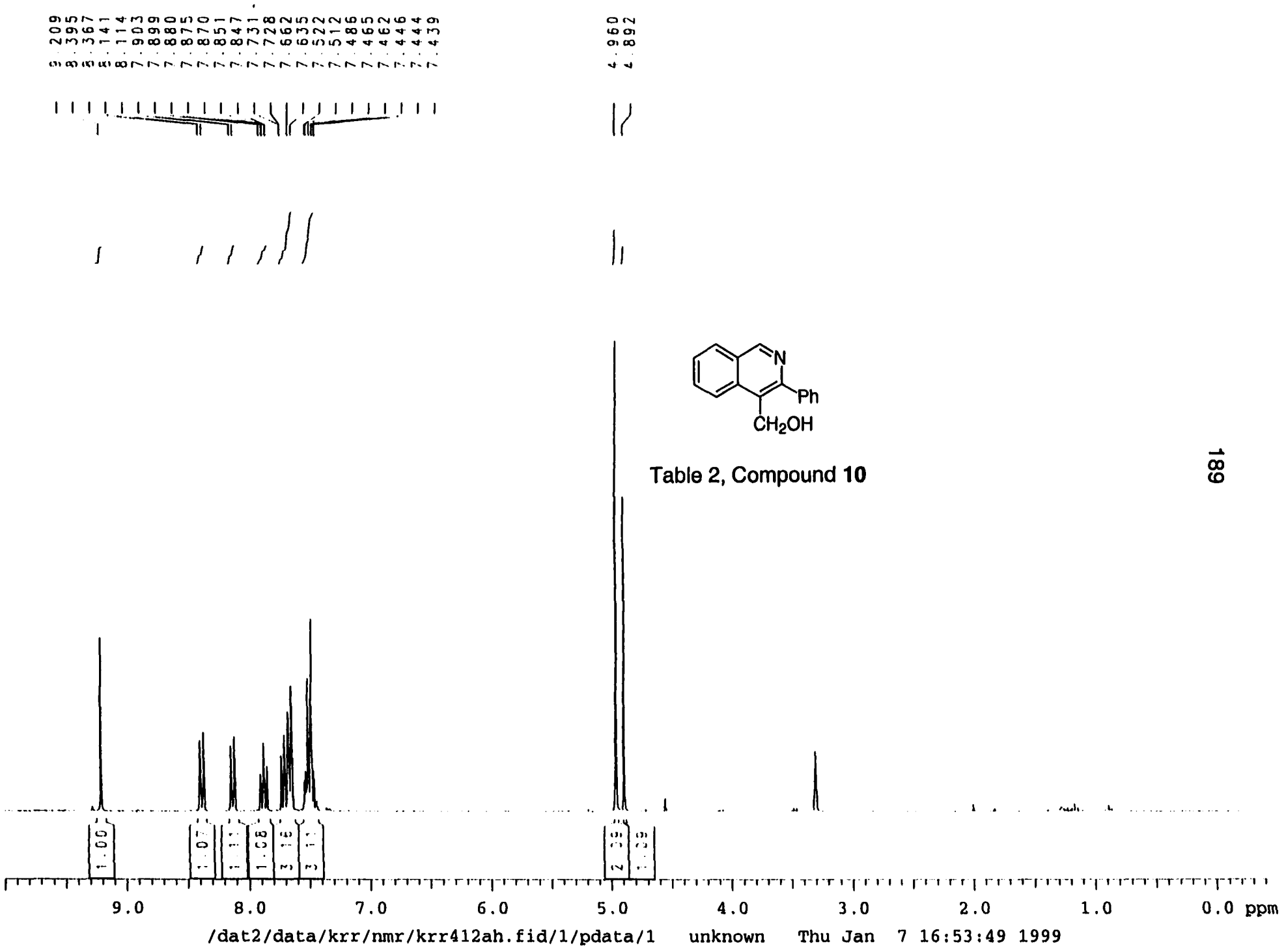


Table 2, Compound **10**

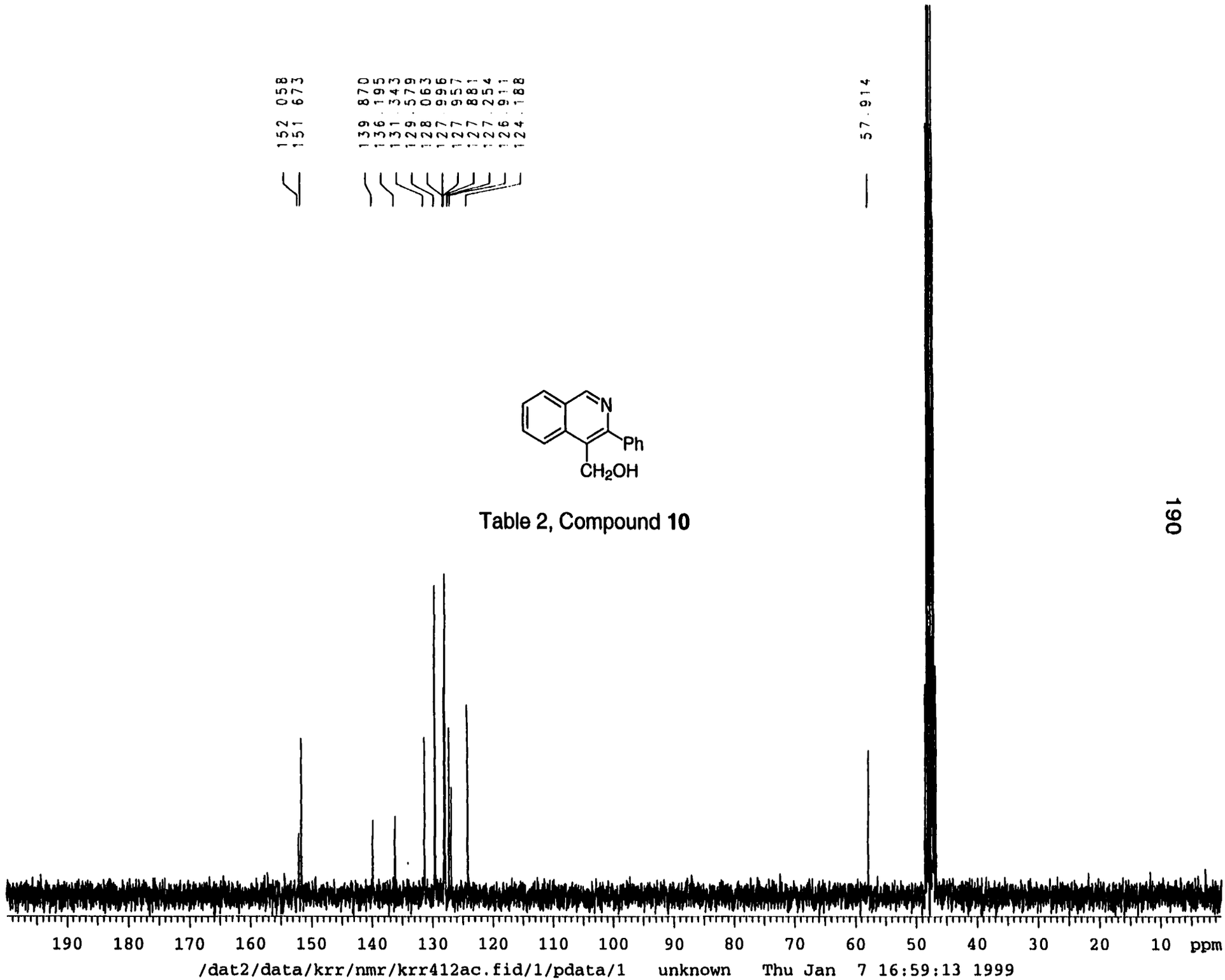


Table 2, Compound **10**

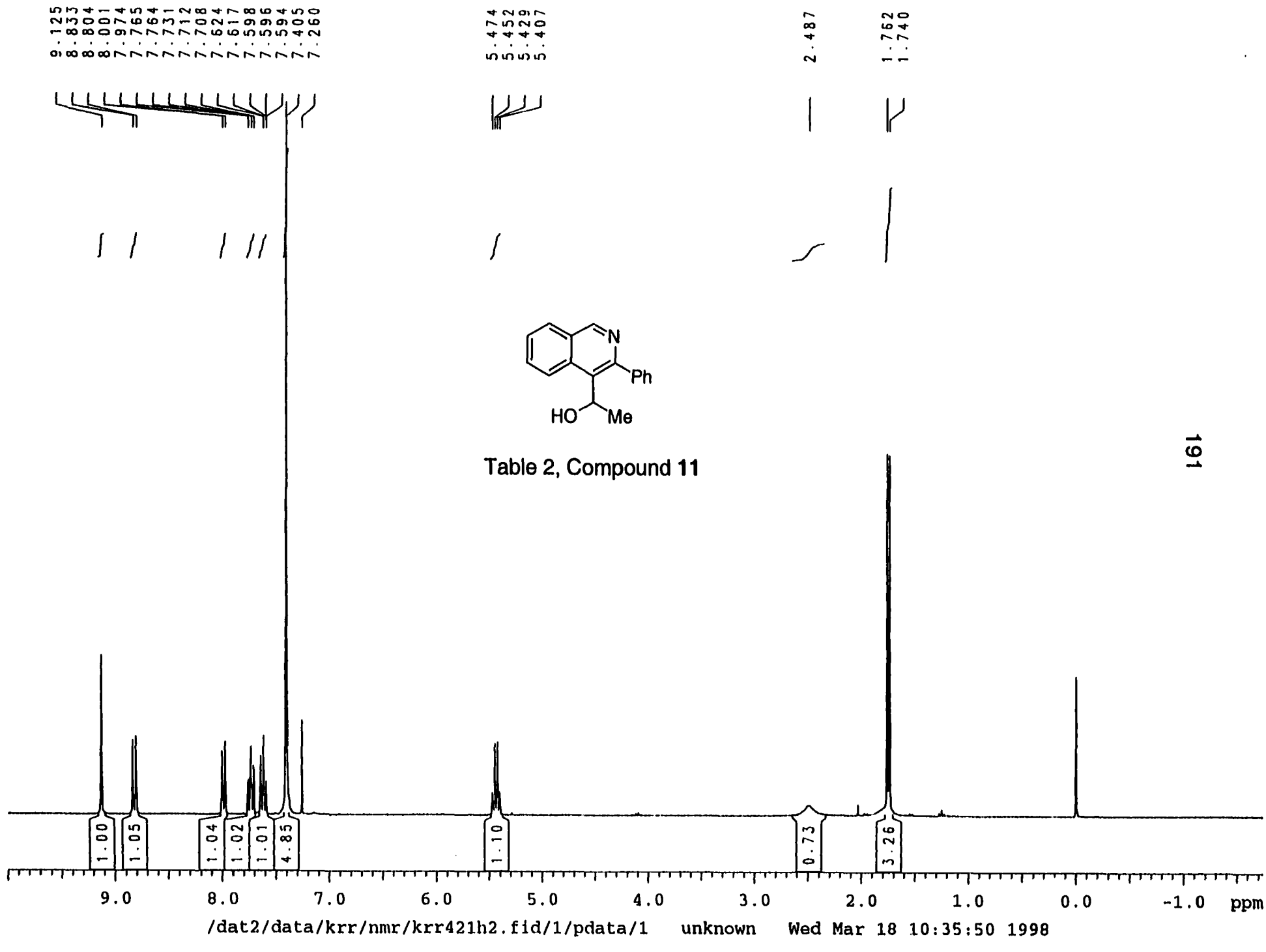


Table 2, Compound **11**

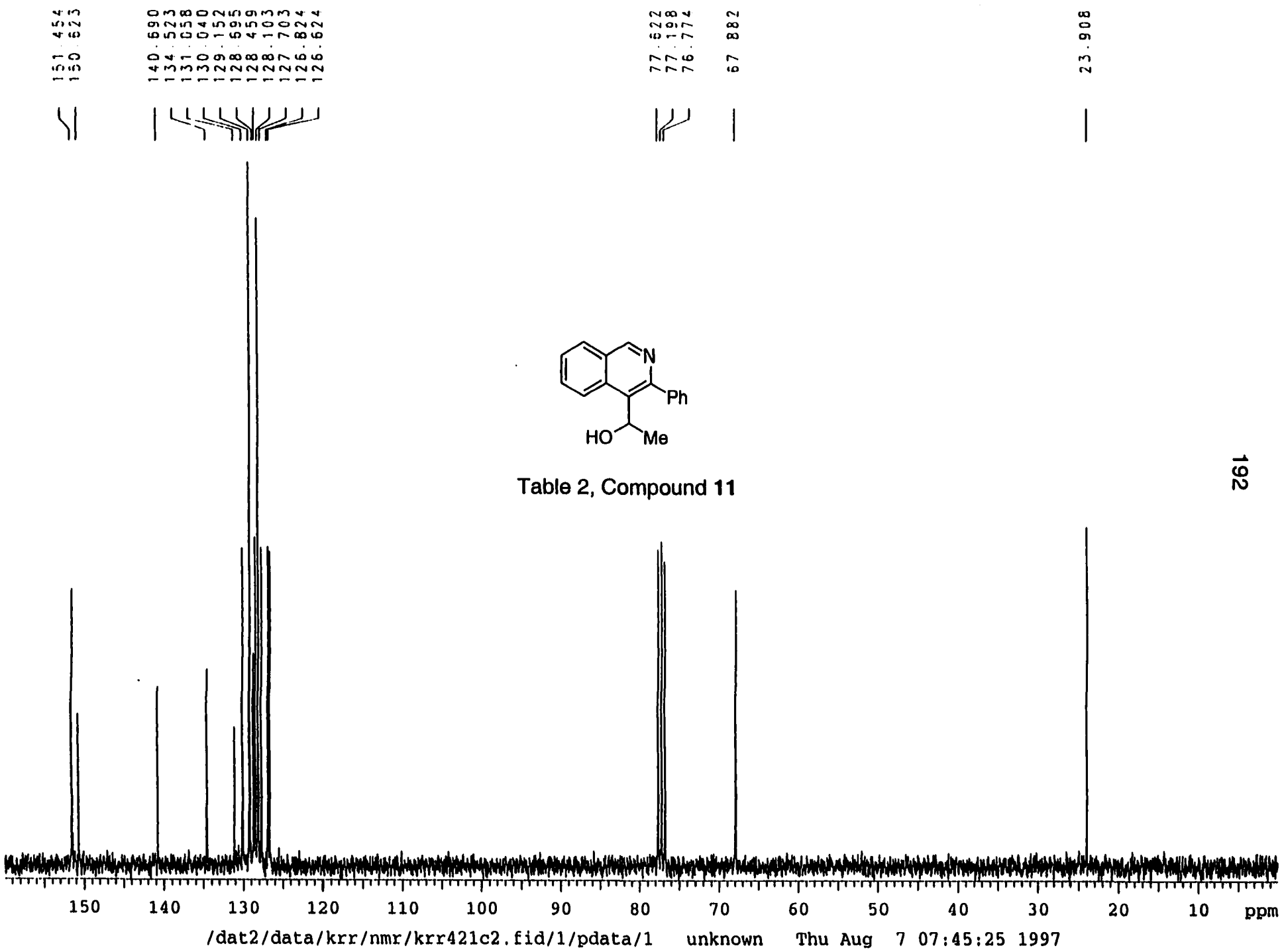


Table 2, Compound **11**

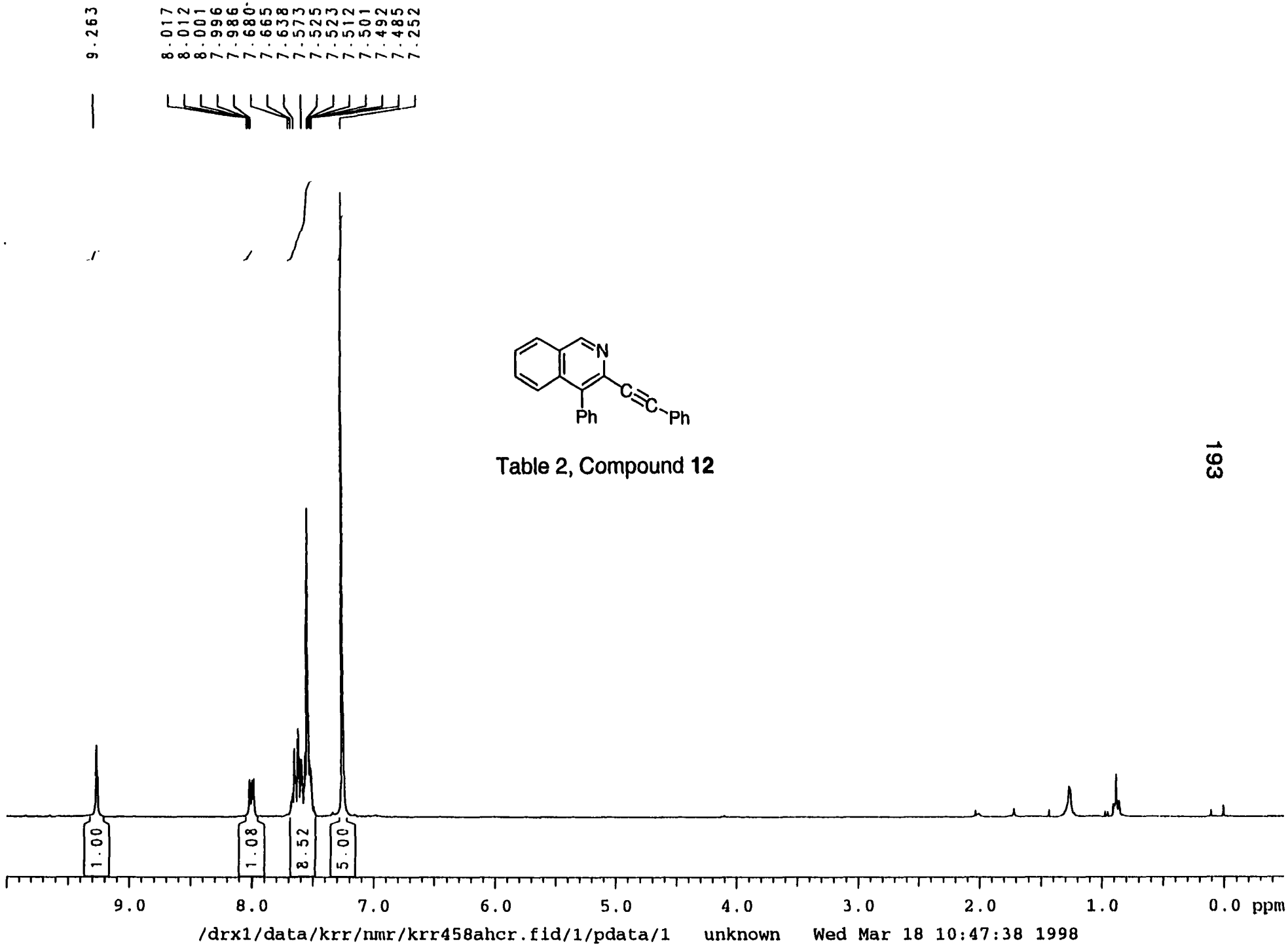


Table 2, Compound **12**

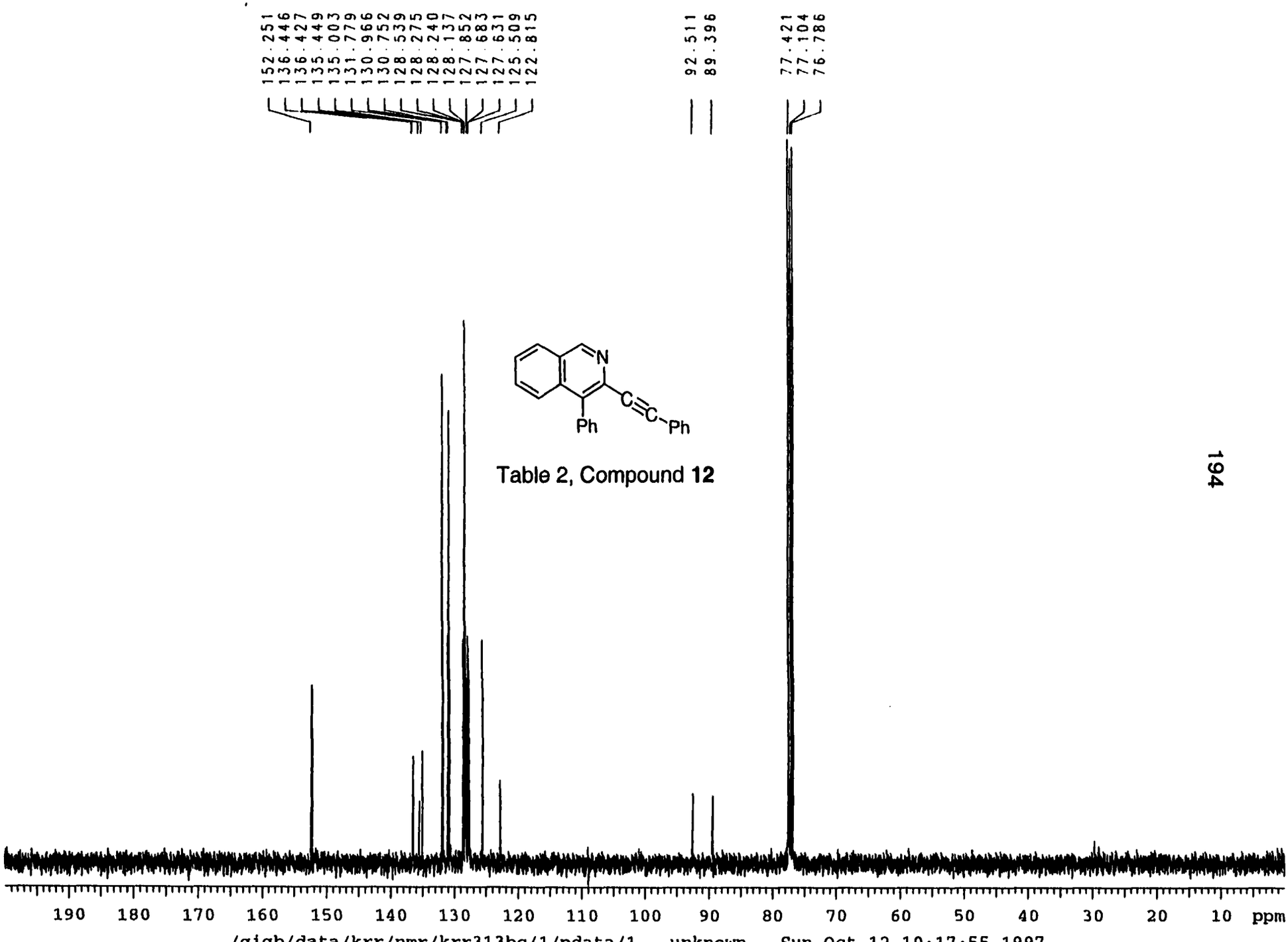


Table 2, Compound **12**

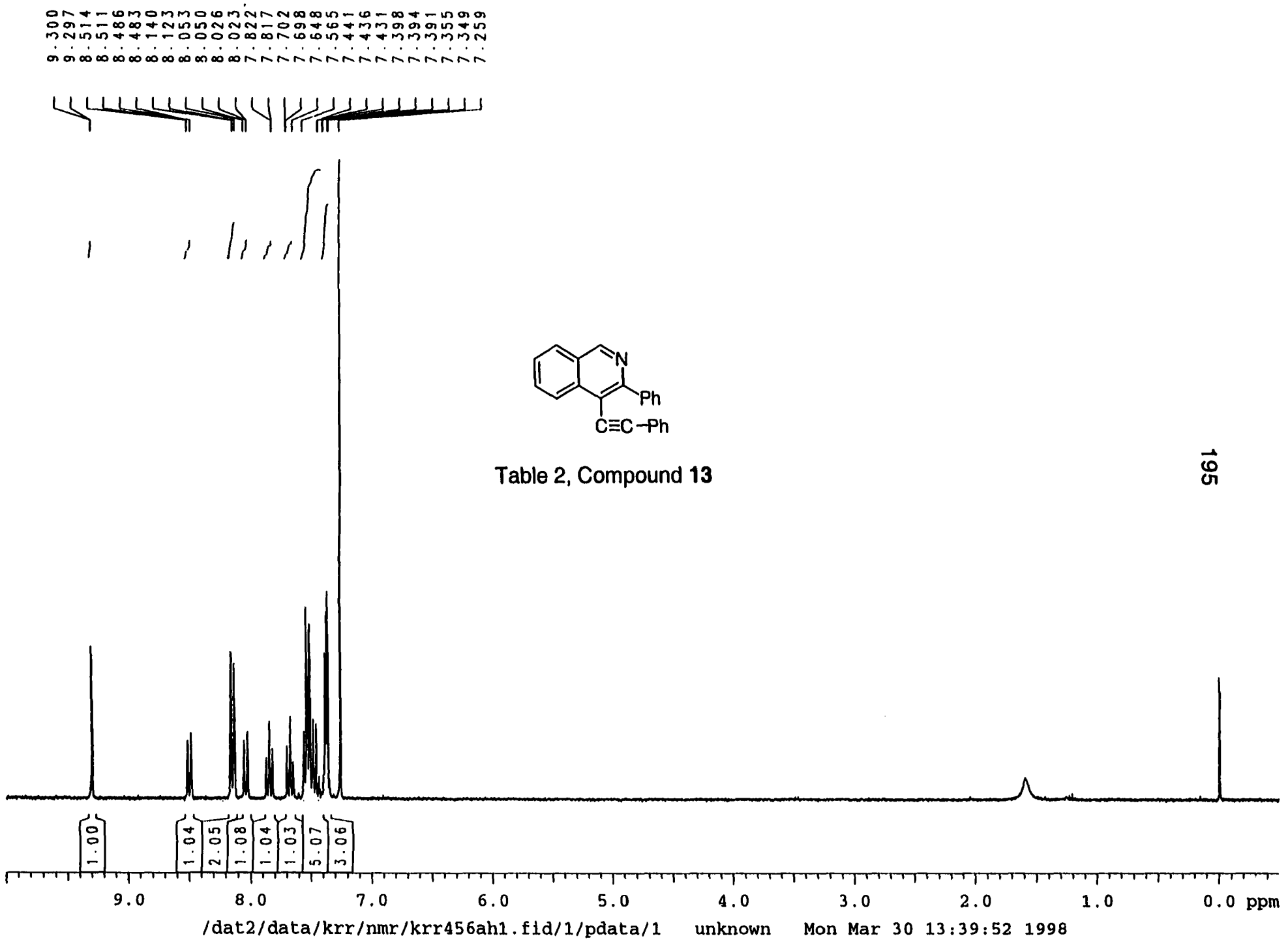
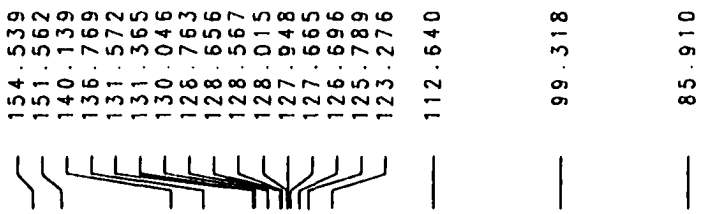


Table 2, Compound **13**



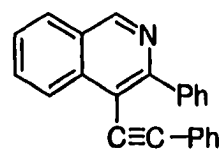


Table 2, Compound **13**

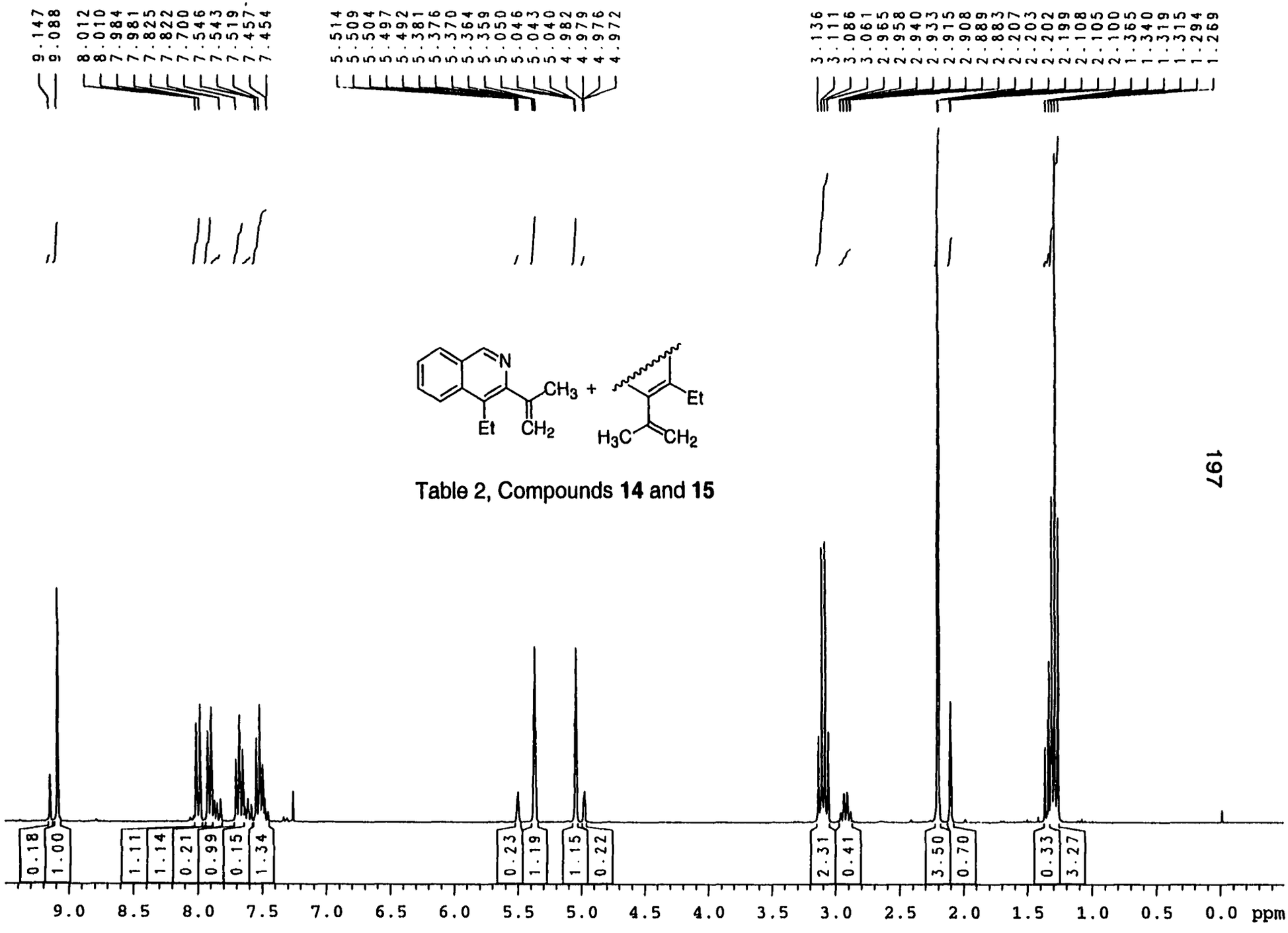


Table 2, Compounds **14** and **15**

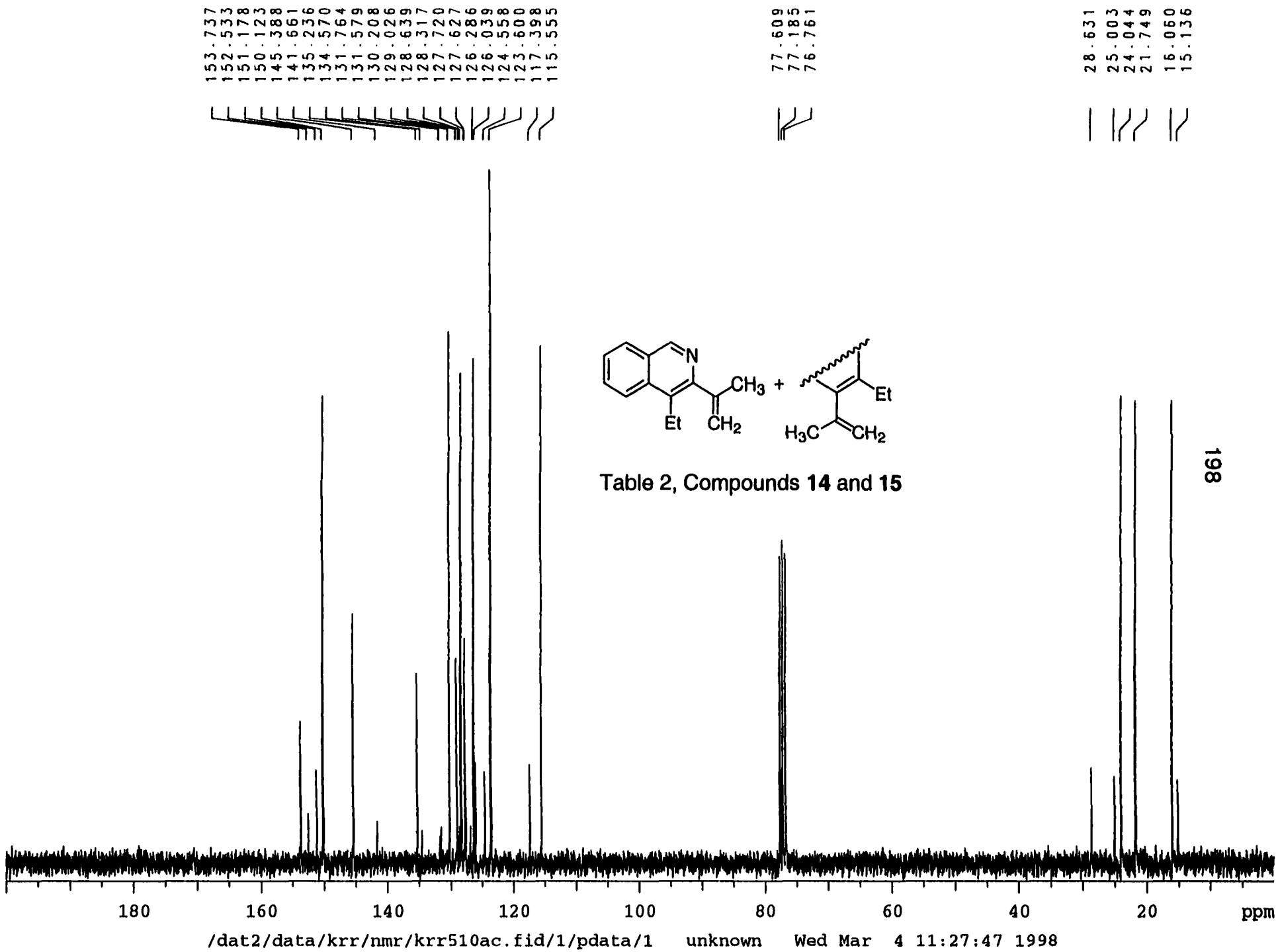


Table 2, Compounds **14** and **15**

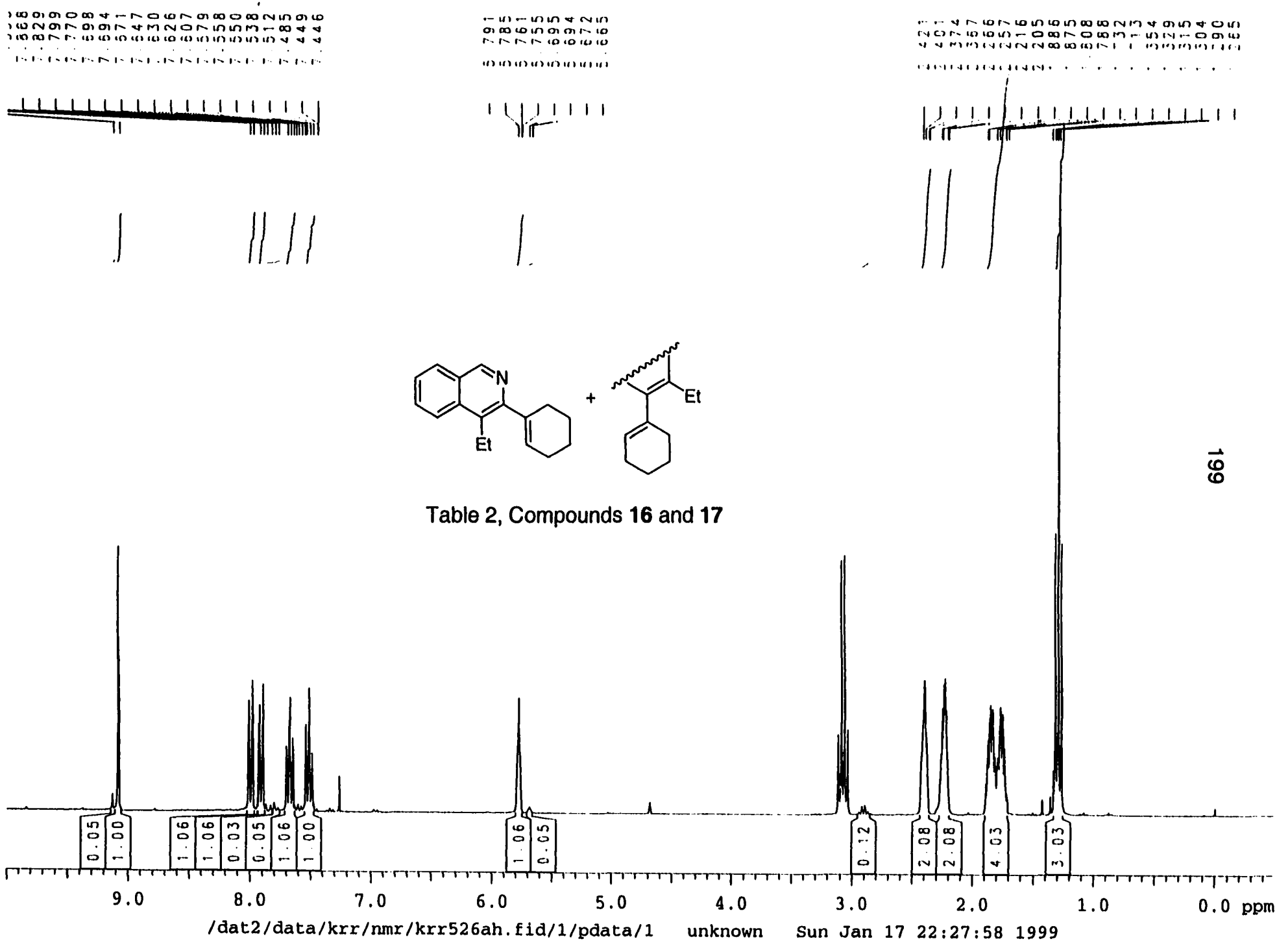


Table 2, Compounds **16** and **17**

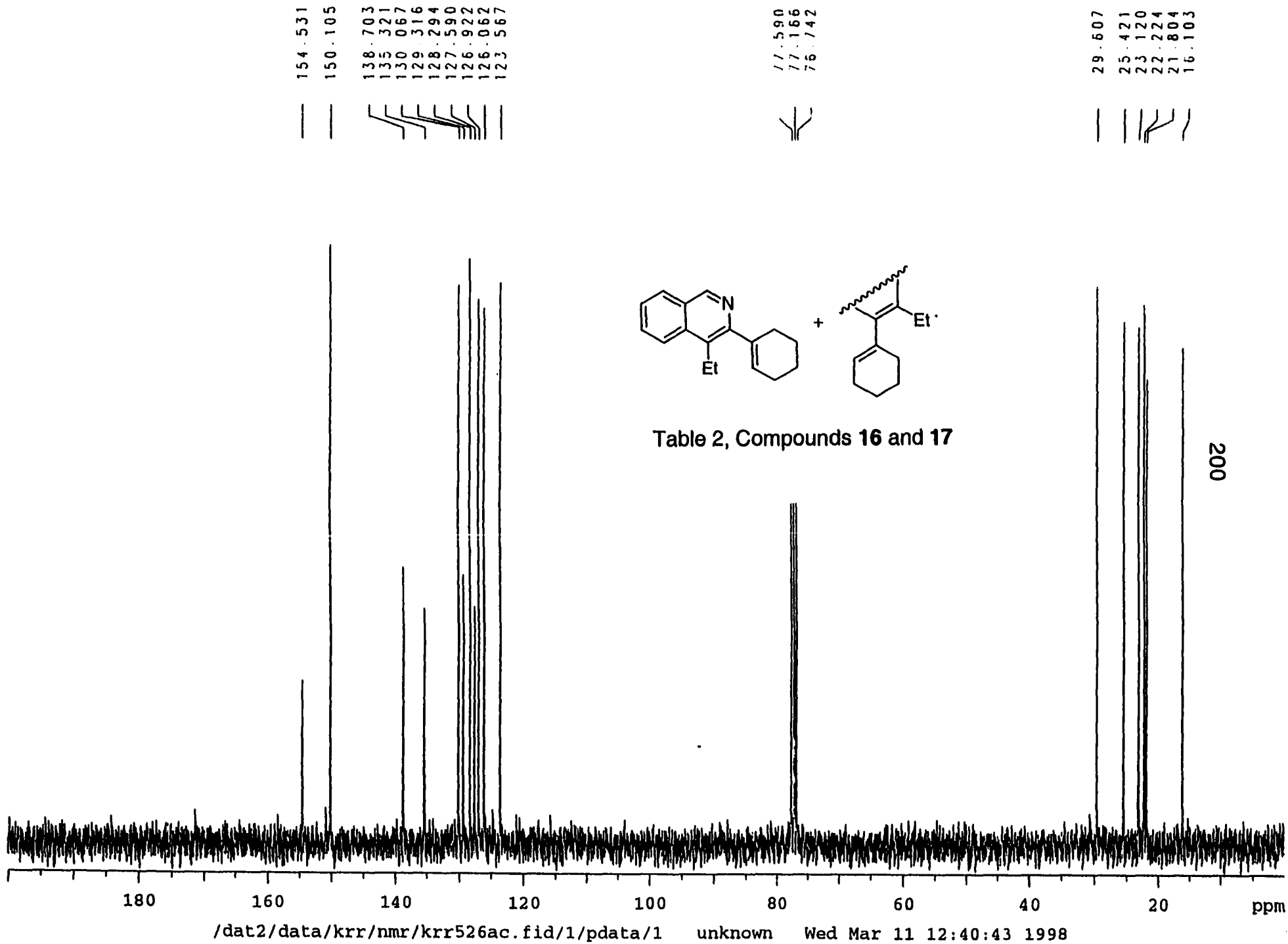


Table 2, Compounds **16** and **17**

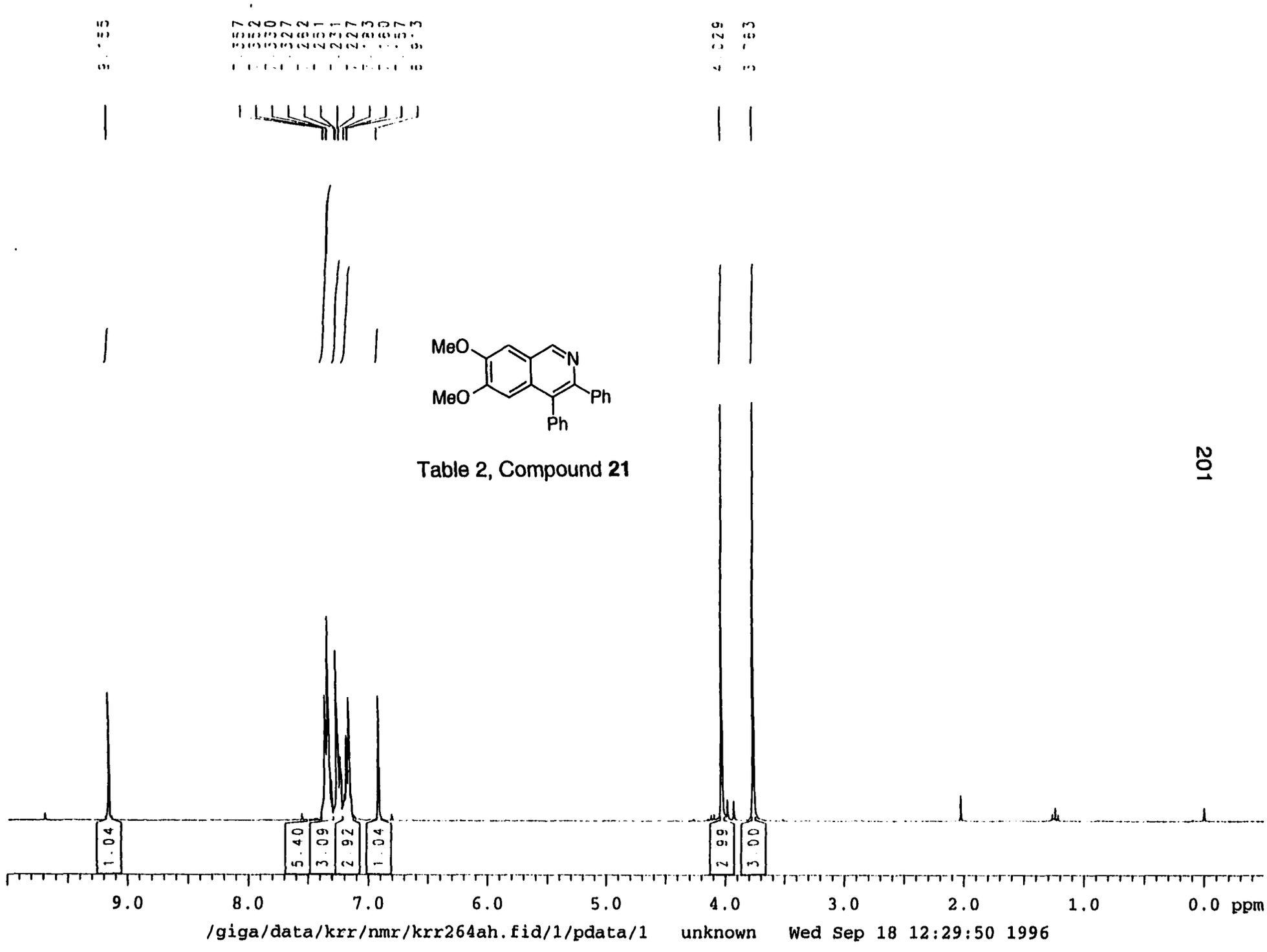


Table 2, Compound **21**

153.024
150.135
149.740
149.205
141.159
137.773
132.545
131.134
130.247
129.679
128.456
127.627
127.375
126.886
123.703
105.294
103.357
77.654
77.230
76.805
56.163
55.874

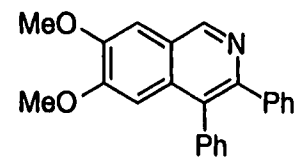


Table 2, Compound **21**

202

150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

/giga/data/krr/nmr/krr264ac.fid/1/pdata/1 unknown Wed Sep 18 10:22:23 1996

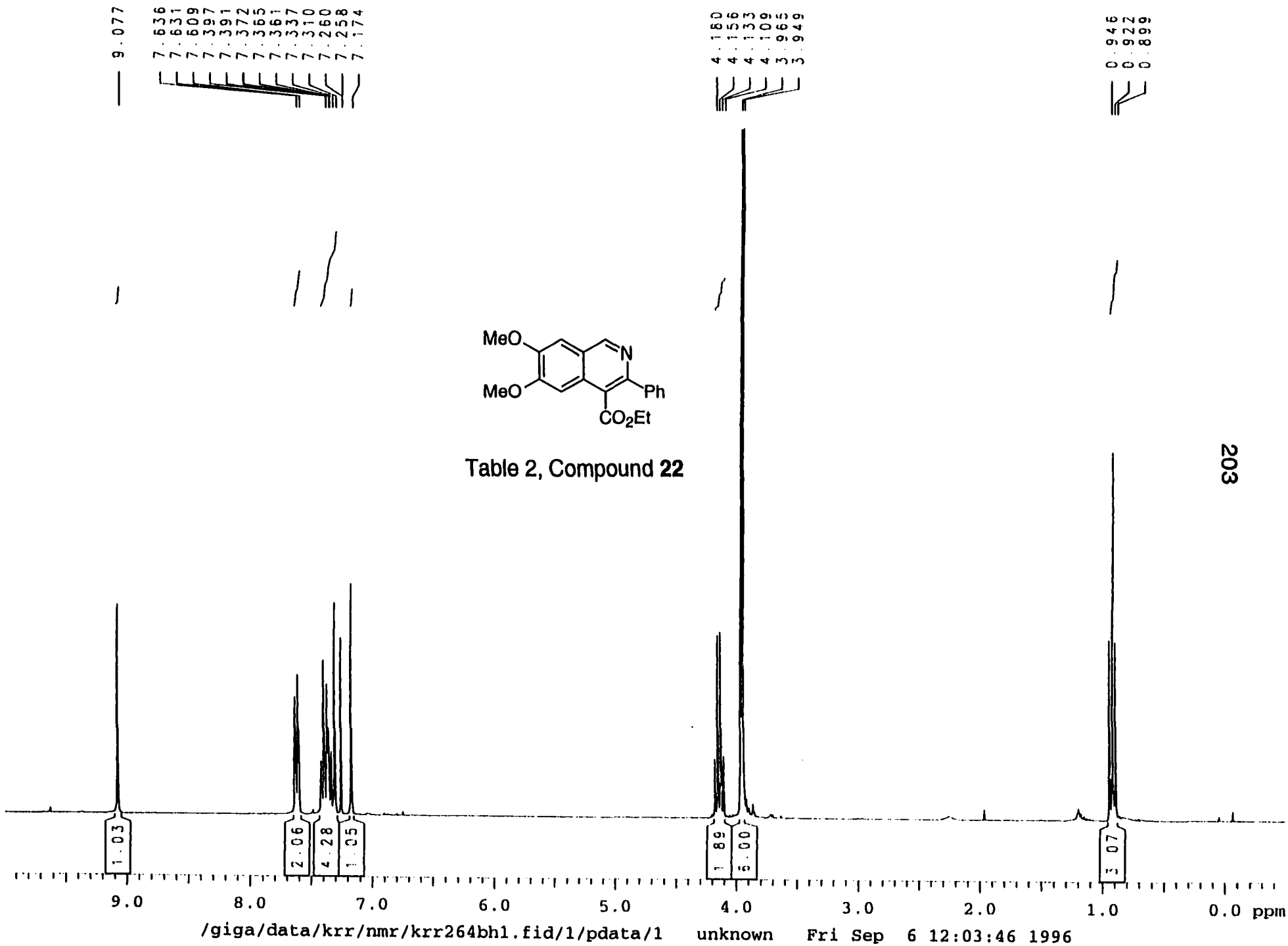


Table 2, Compound **22**

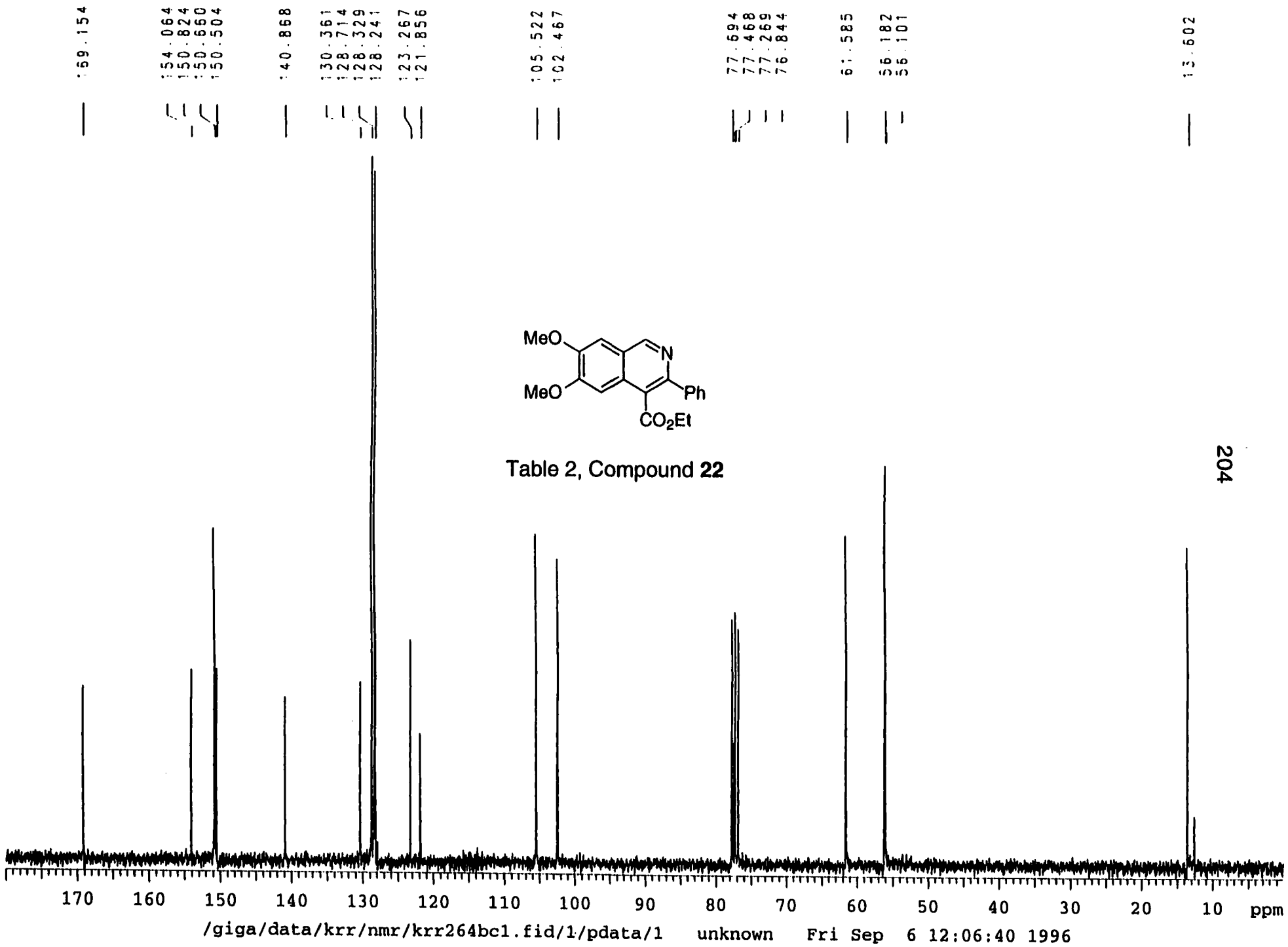
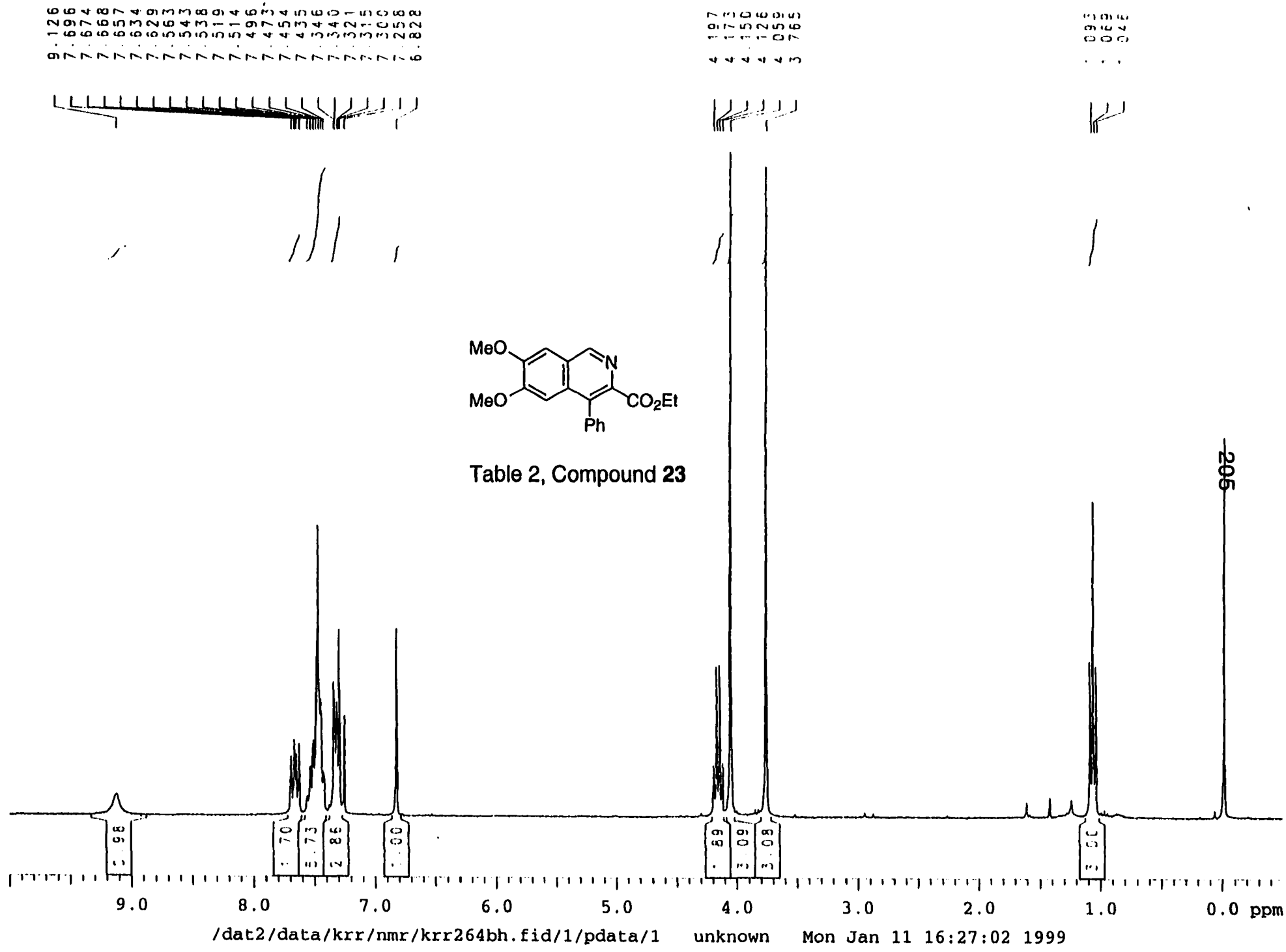


Table 2, Compound **22**


MeO
MeO
N
CO2Et
Ph
Table 2, Compound 23
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/dat2/data/krr/nmr/krr264bh.fid/1/pdata/1 unknown Mon Jan 11 16:27:02 1999

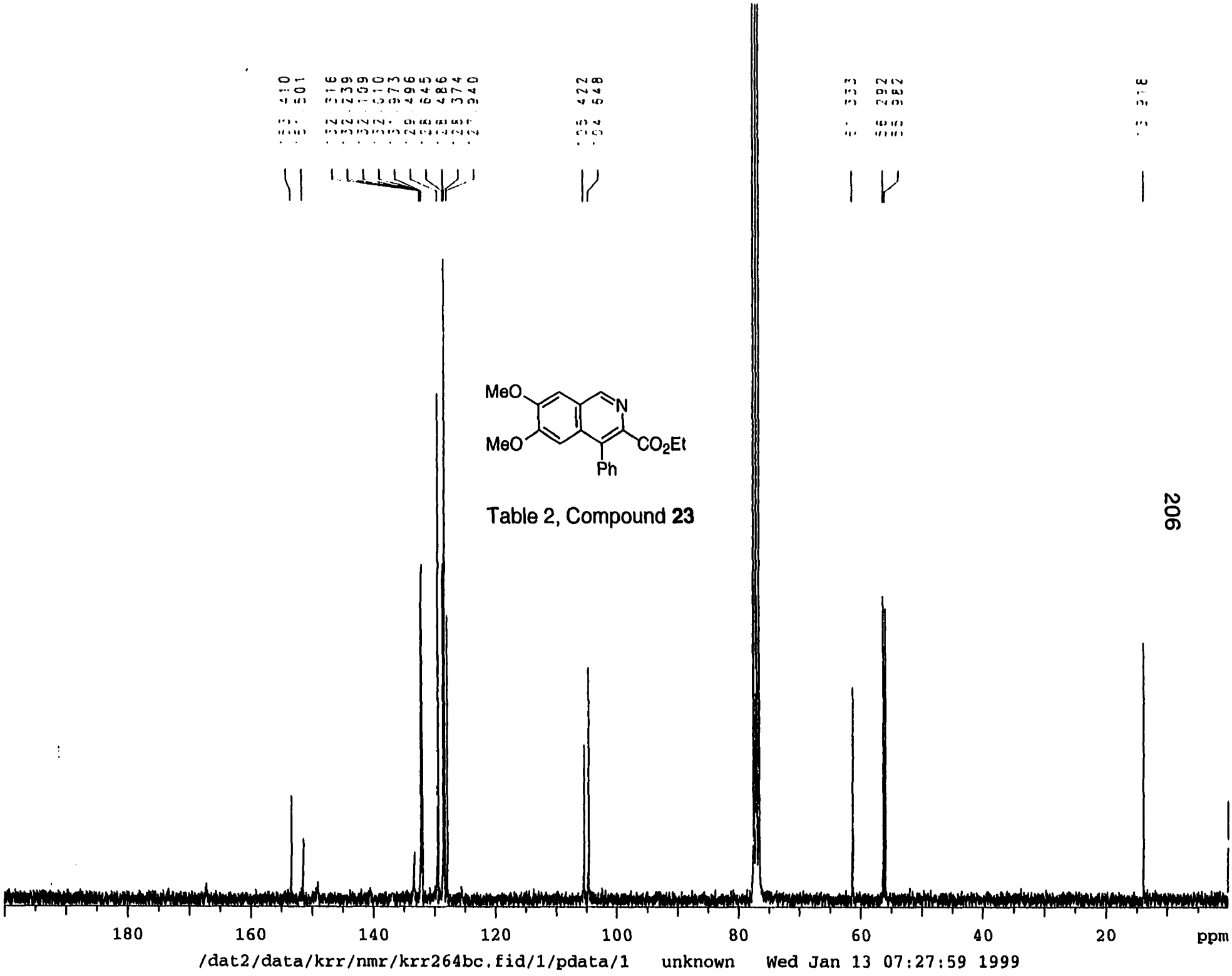


Table 2, Compound **23**

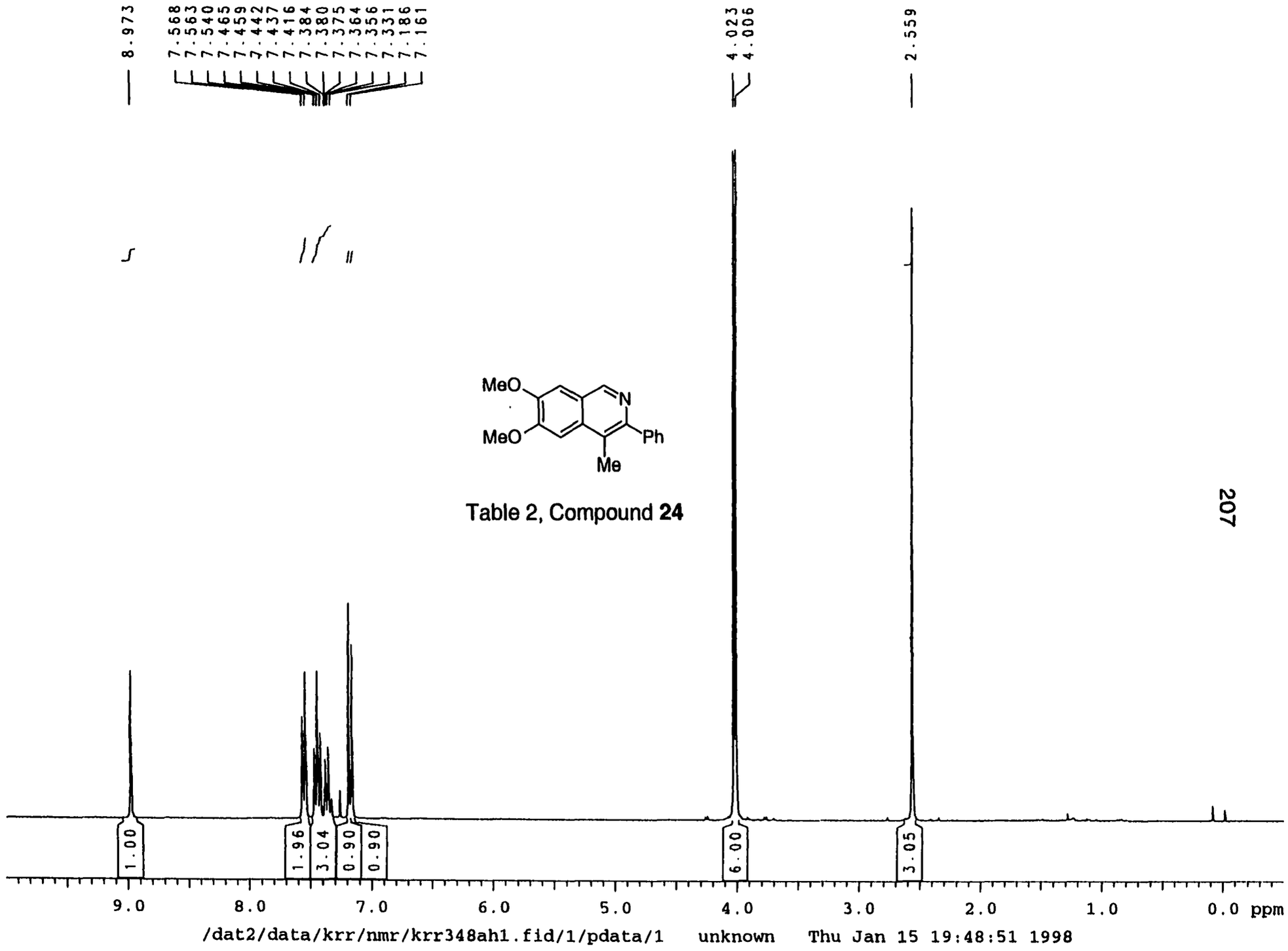


Table 2, Compound **24**

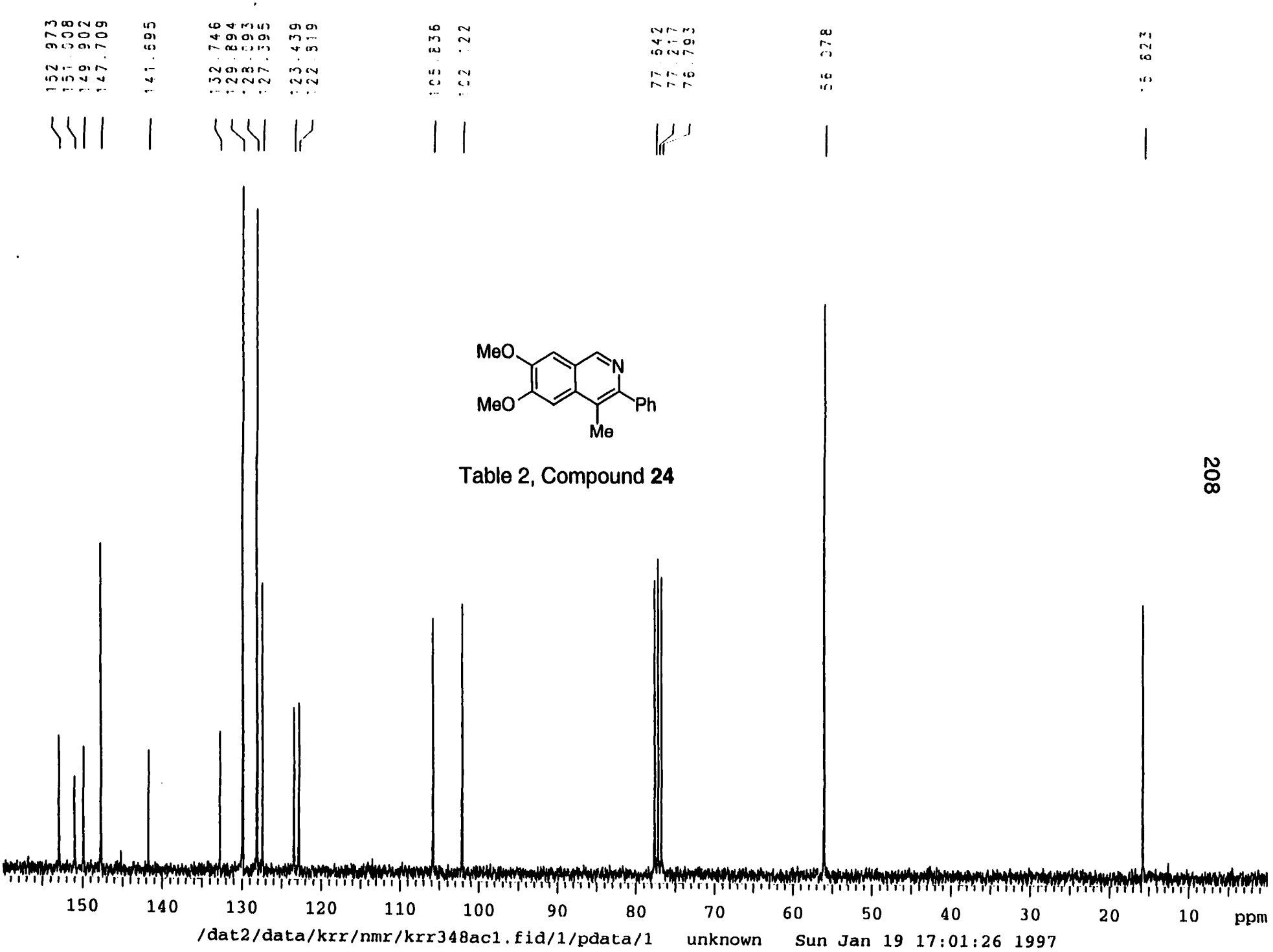


Table 2, Compound **24**

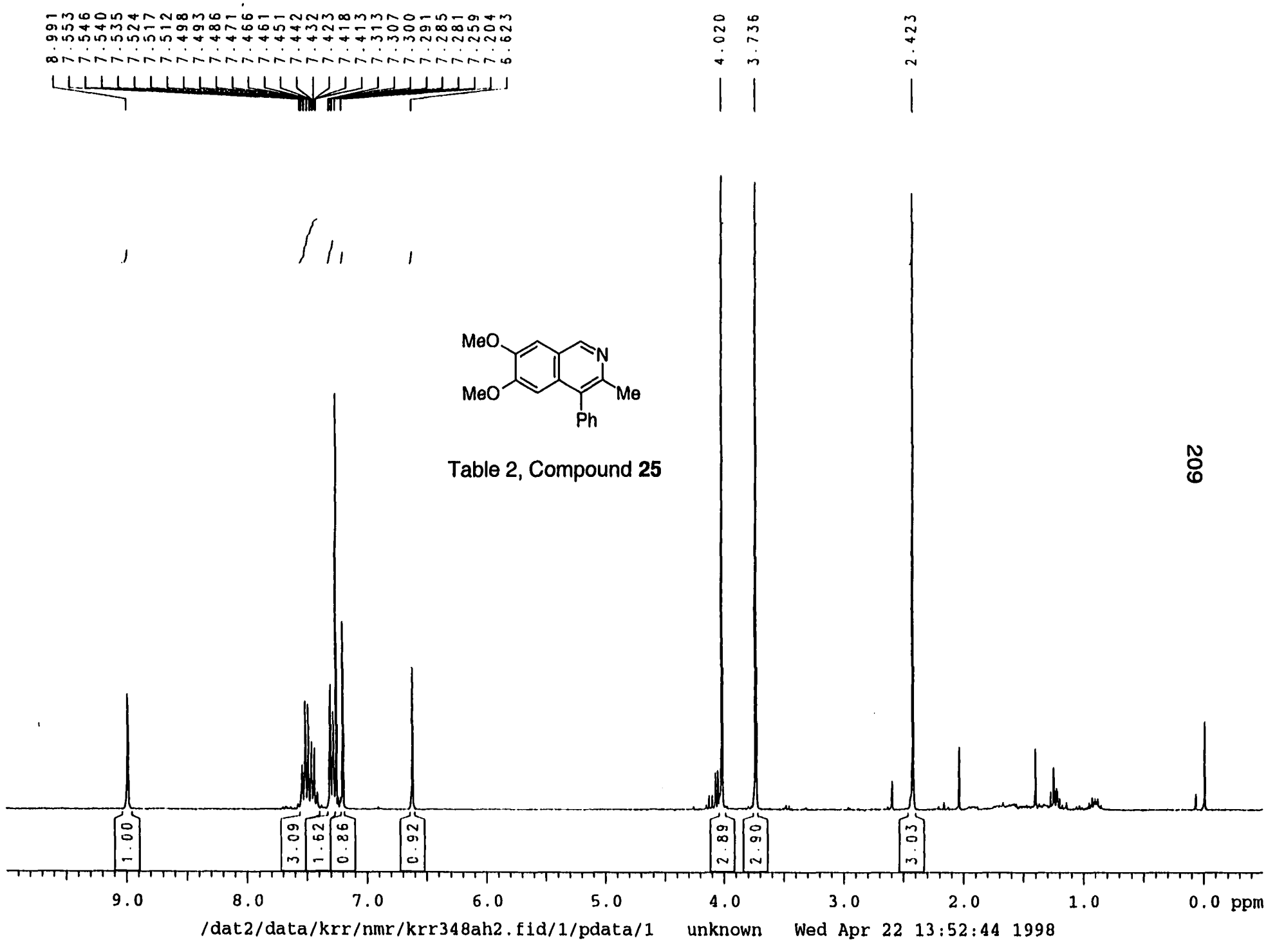
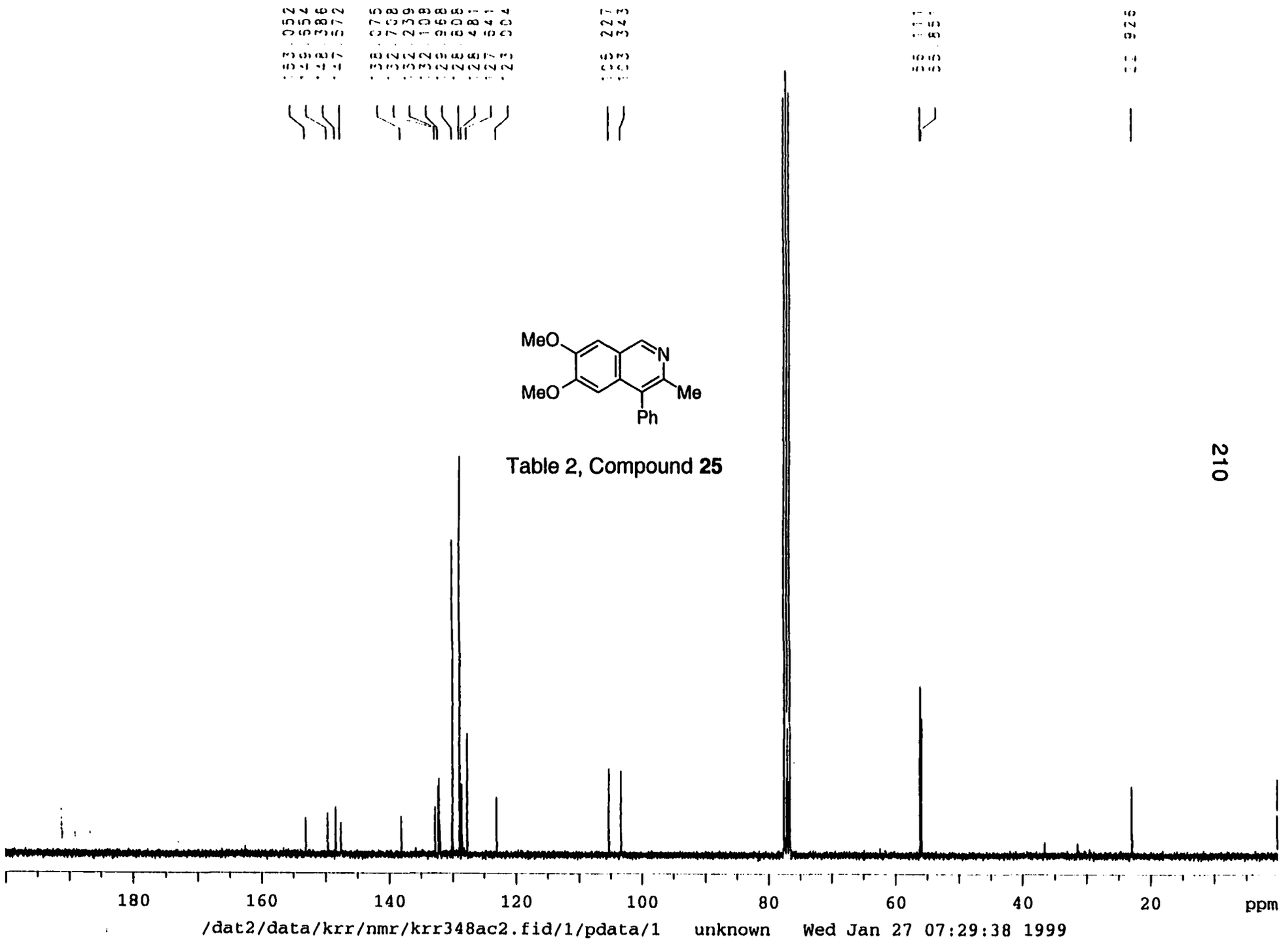


Table 2, Compound **25**


MeO
MeO
N
Me
Ph
Table 2, Compound 25
210
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr348ac2.fid/1/pdata/1 unknown Wed Jan 27 07:29:38 1999

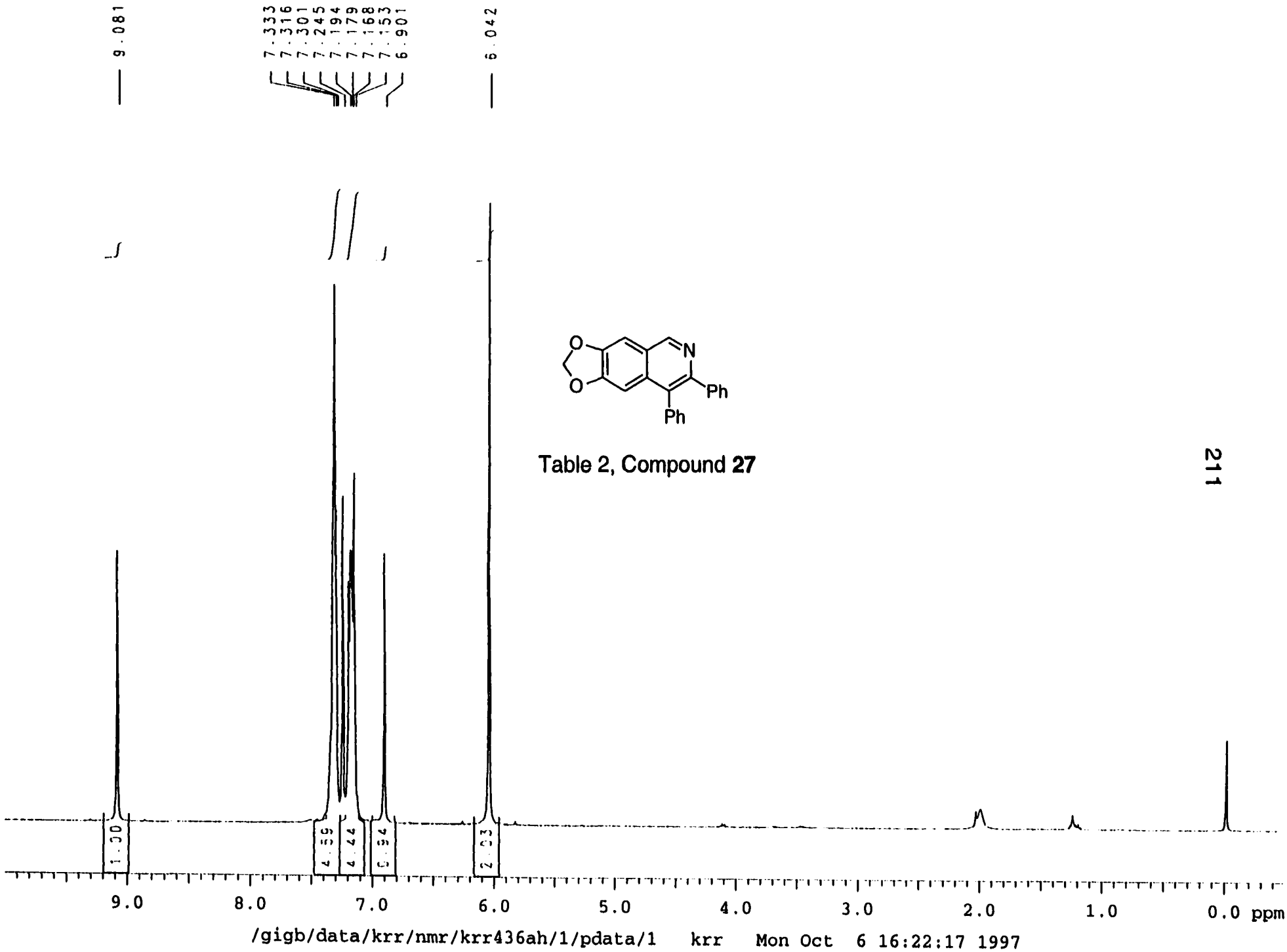


Table 2, Compound **27**

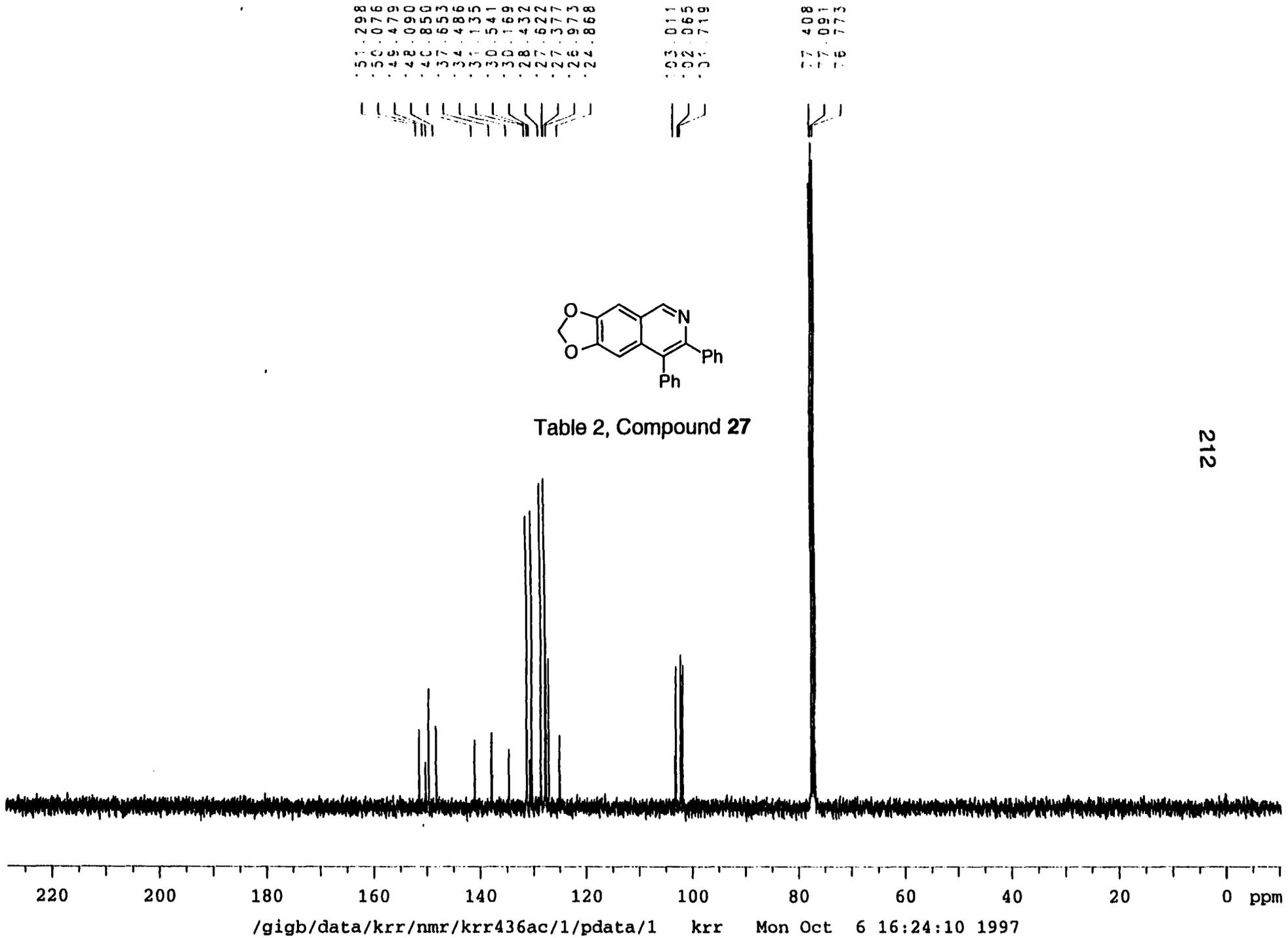


Table 2, Compound **27**

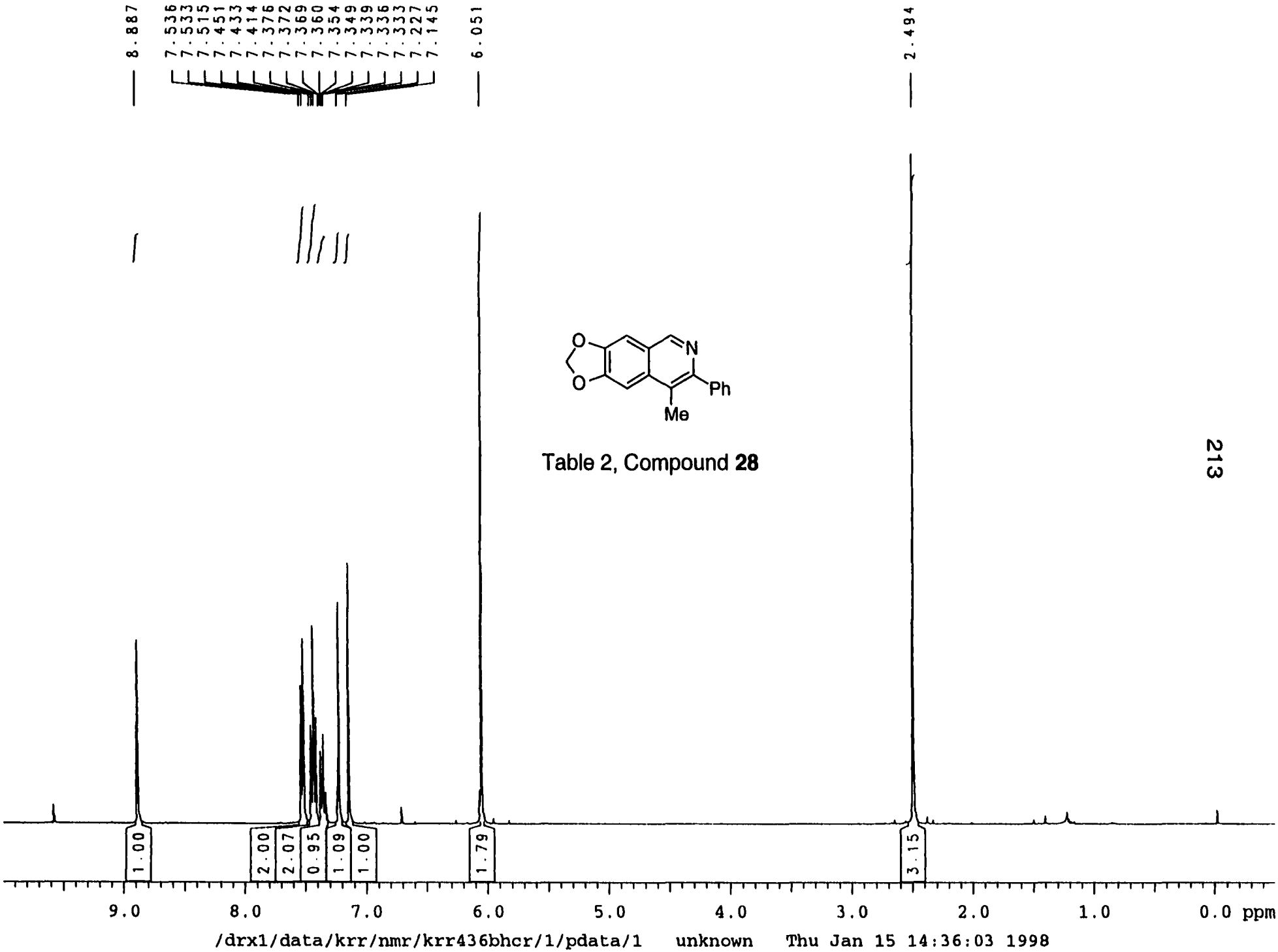


Table 2, Compound **28**

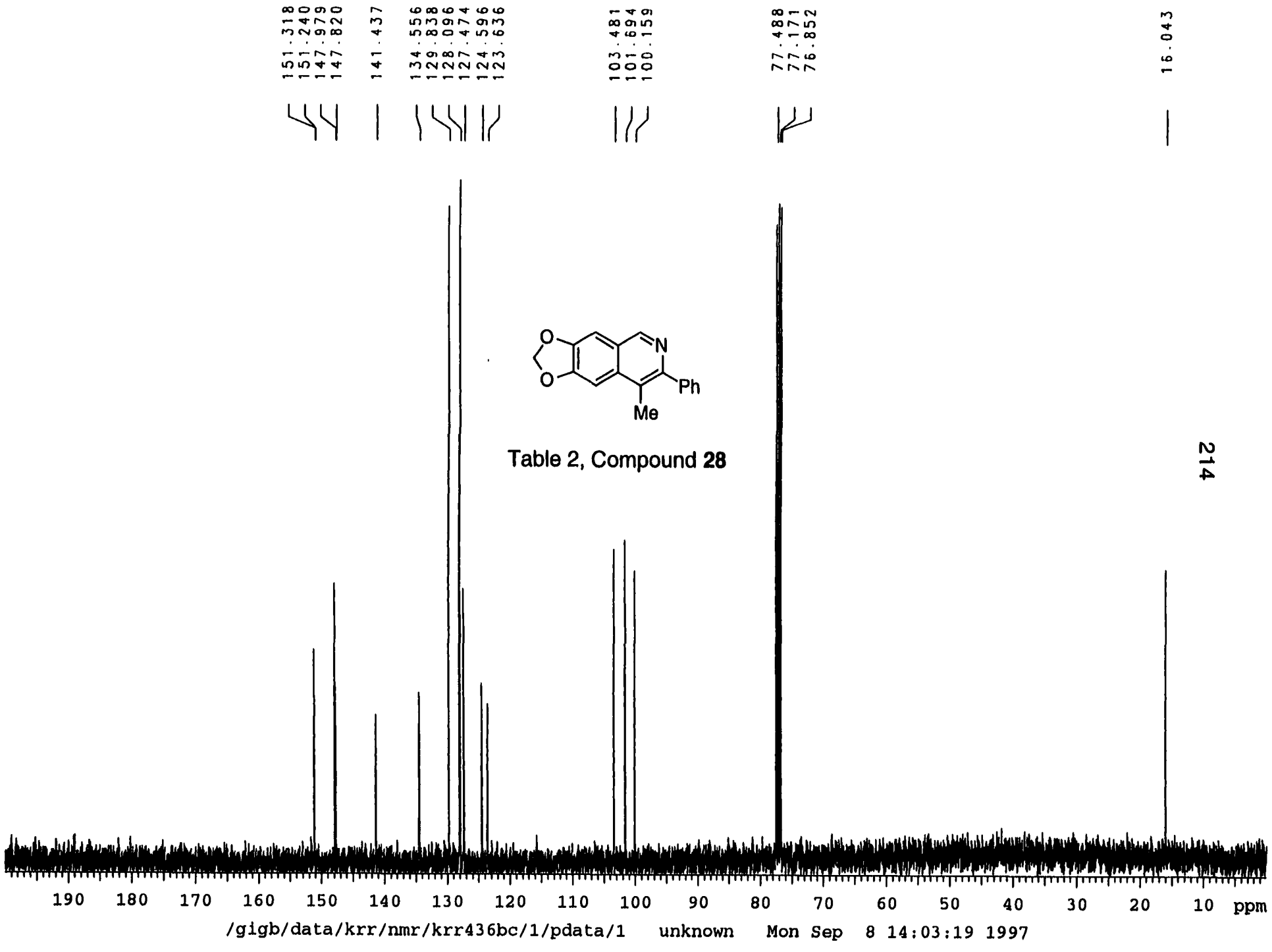


Table 2, Compound **28**

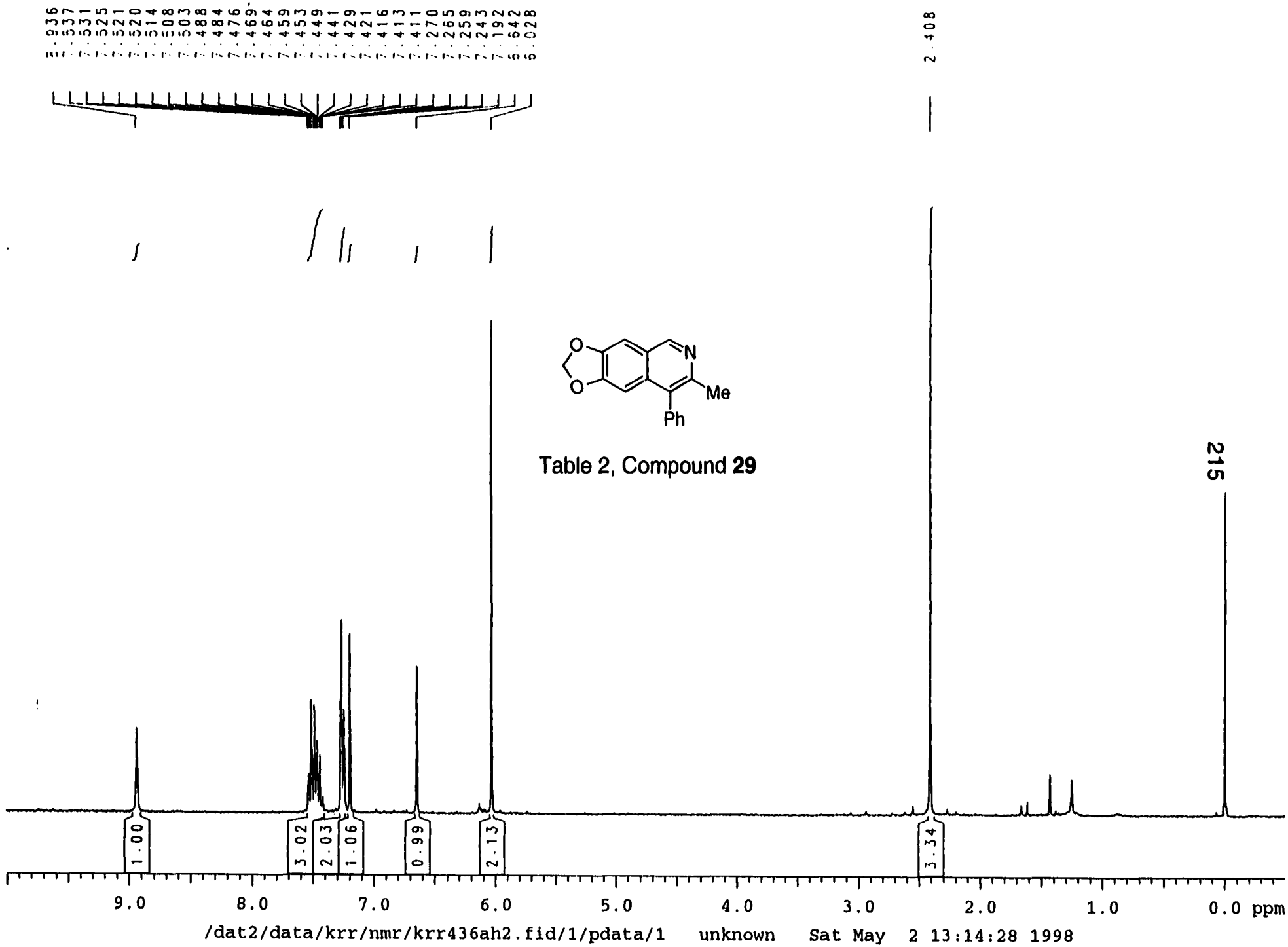


Table 2, Compound **29**

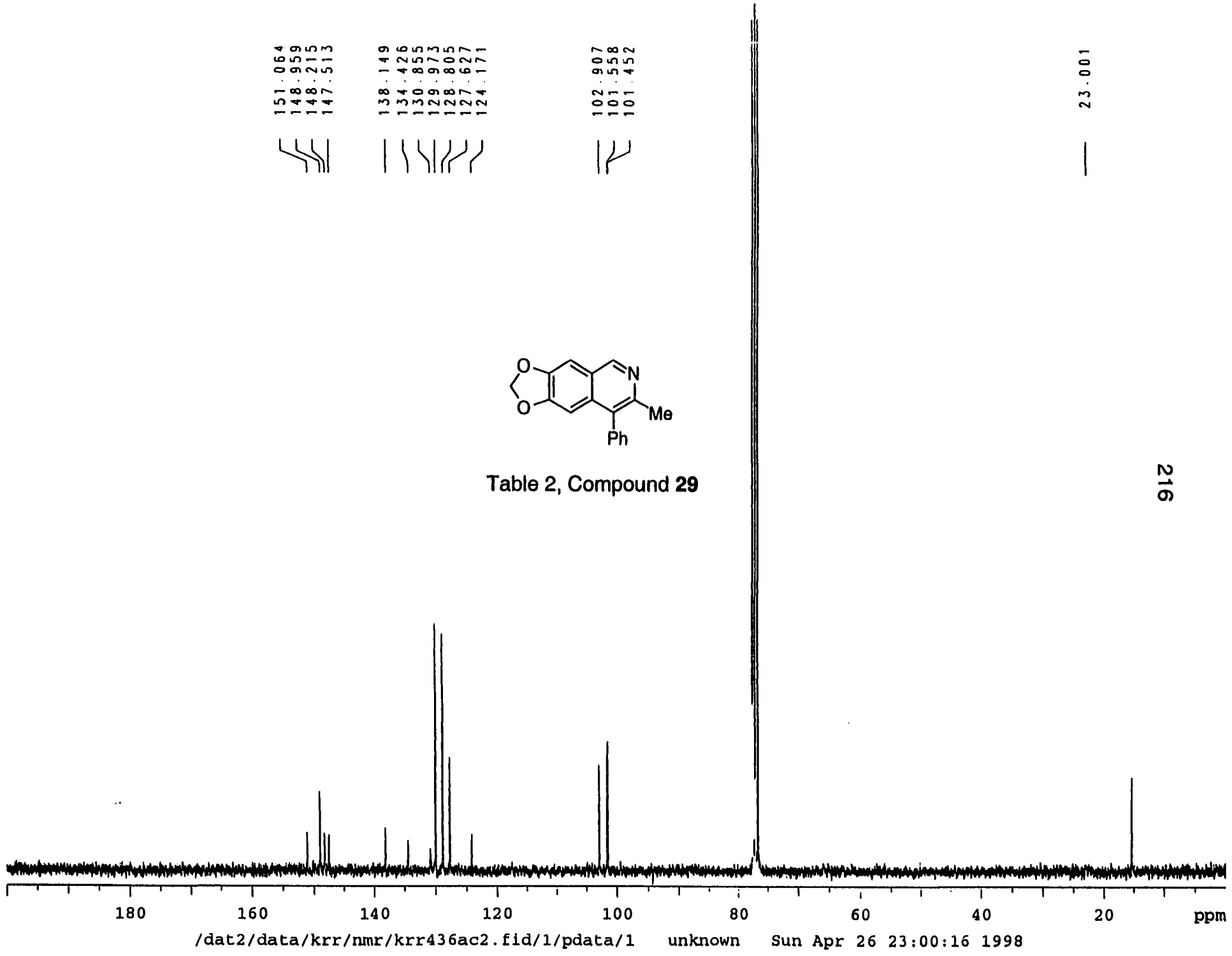


Table 2, Compound **29**

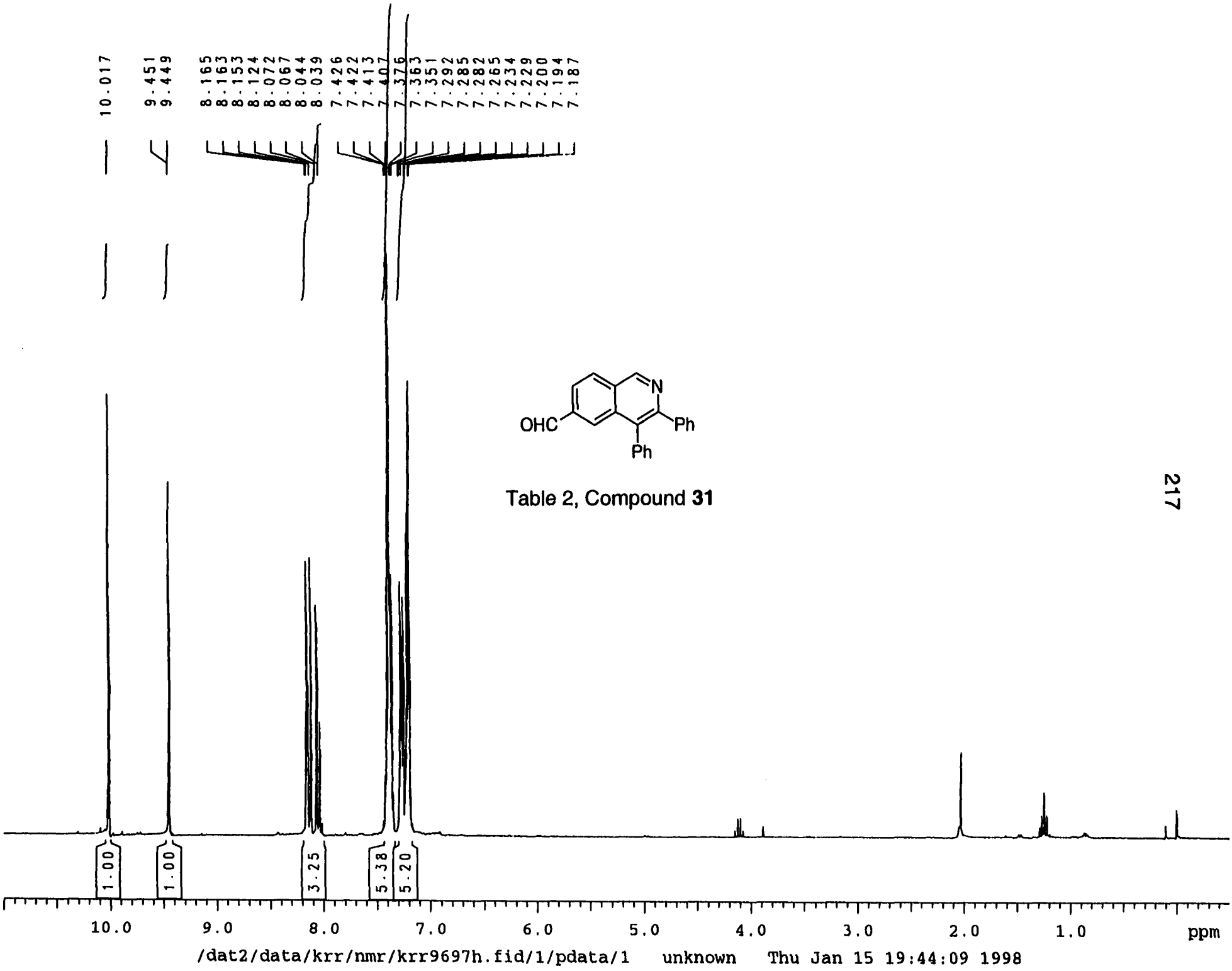


Table 2, Compound **31**

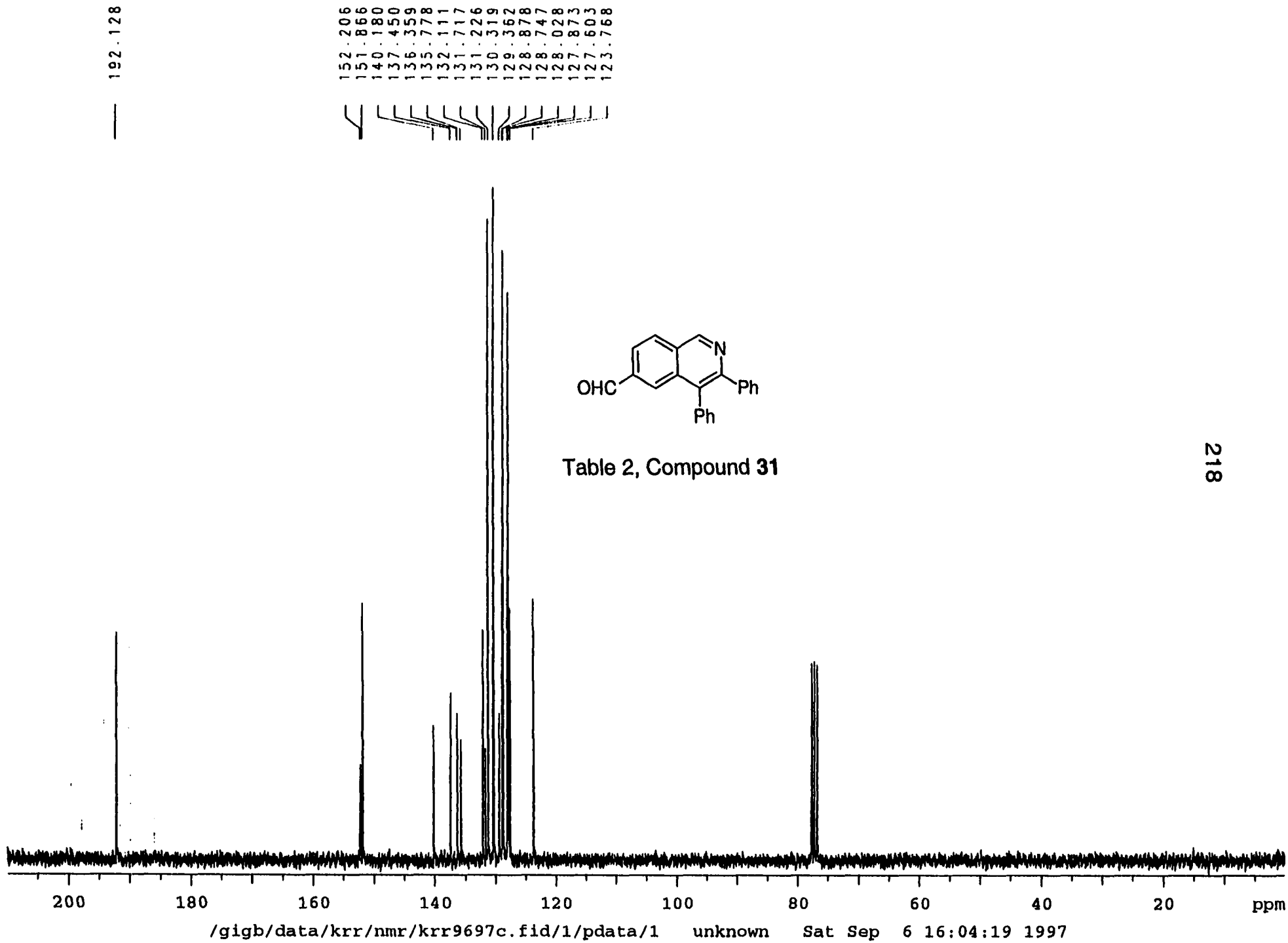


Table 2, Compound **31**

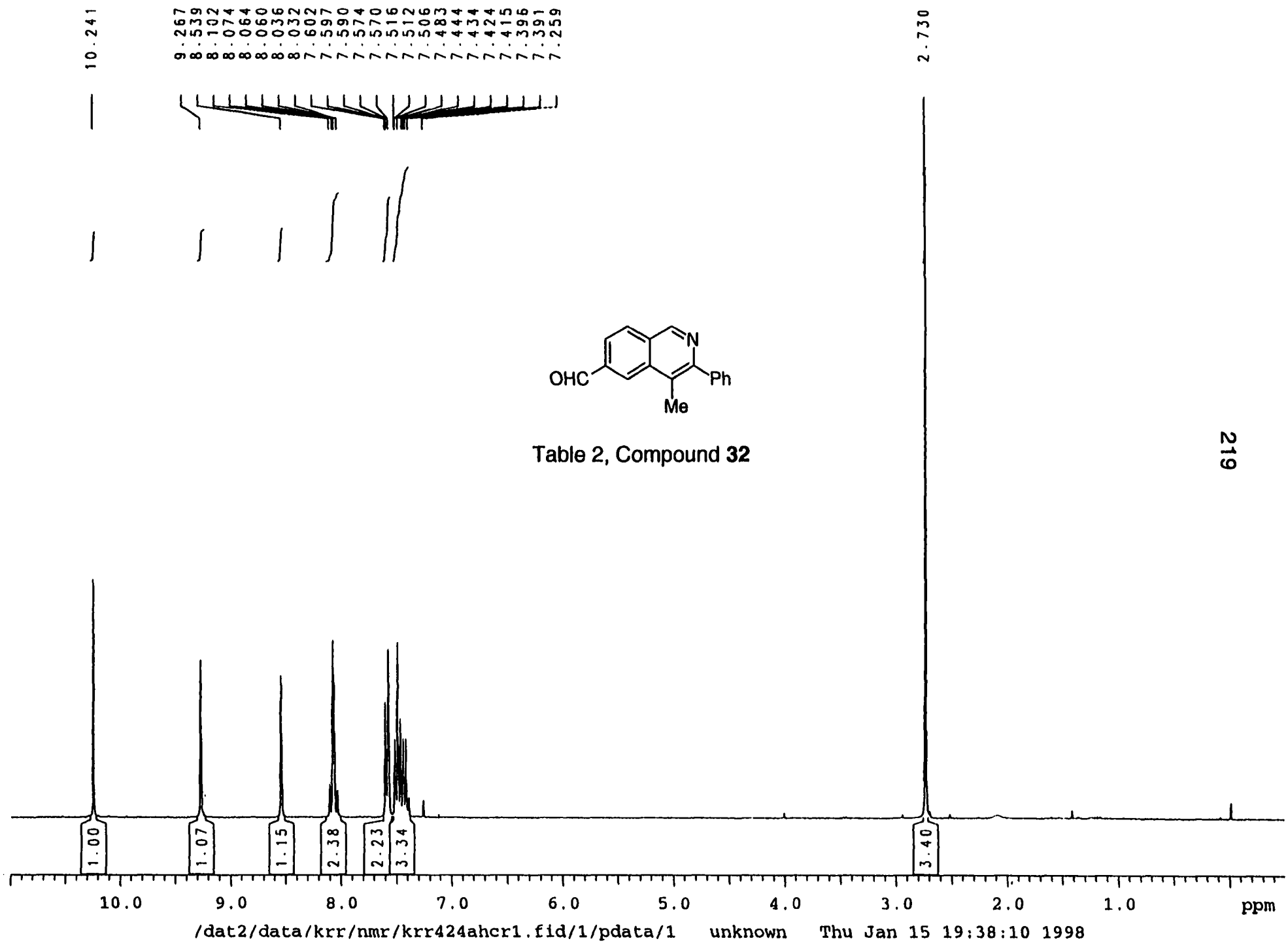


Table 2, Compound **32**

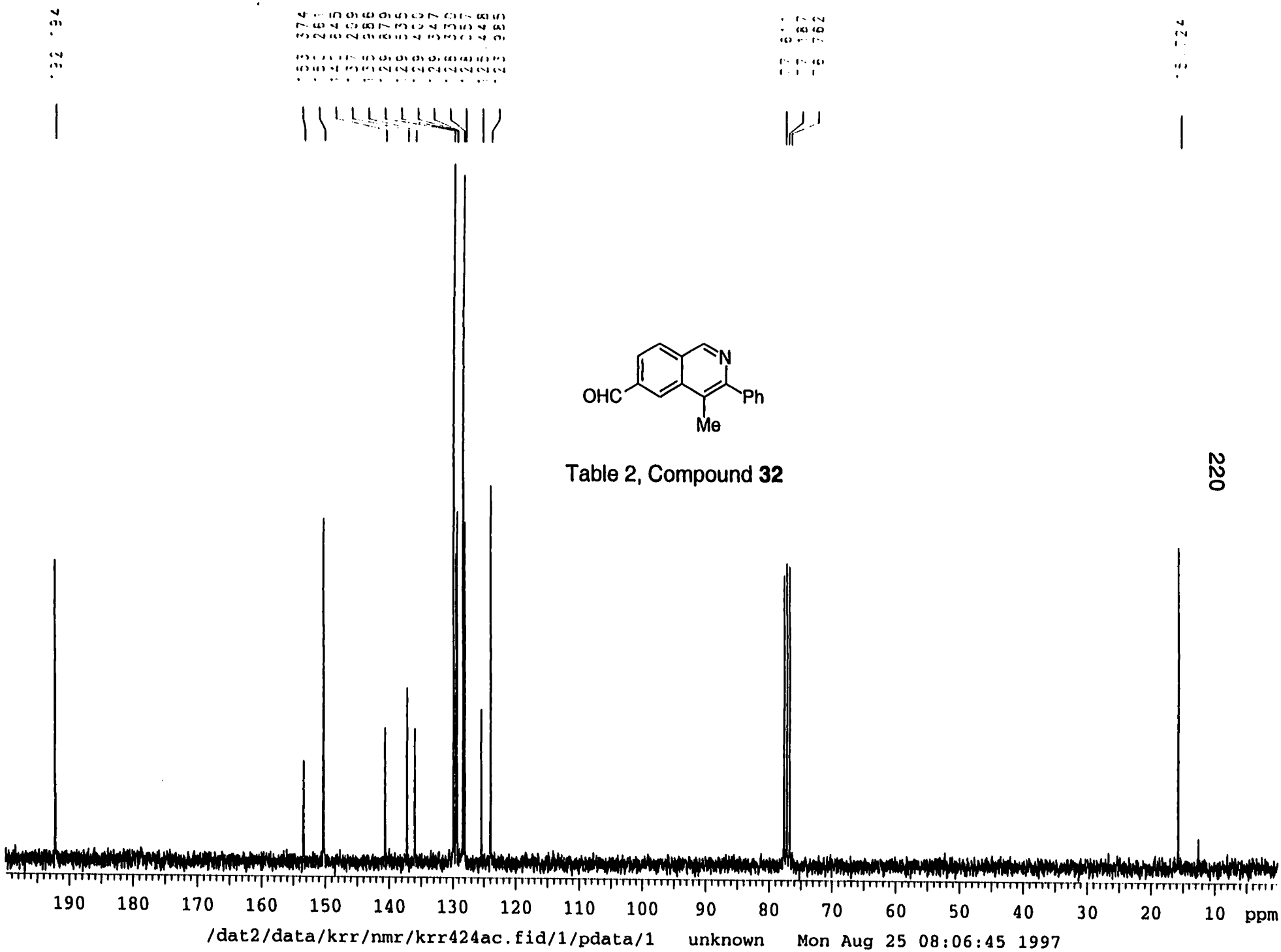


Table 2, Compound **32**

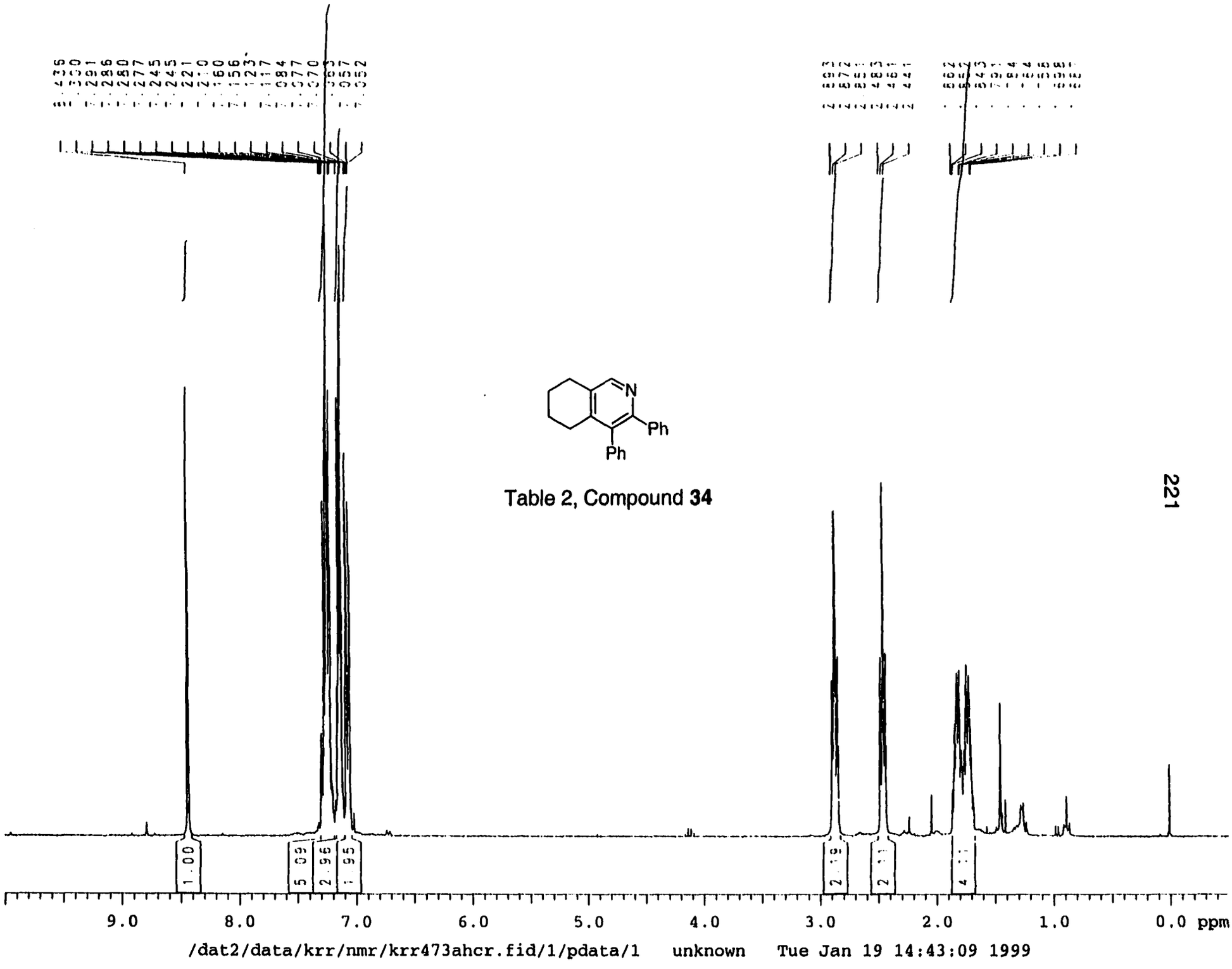


Table 2, Compound **34**

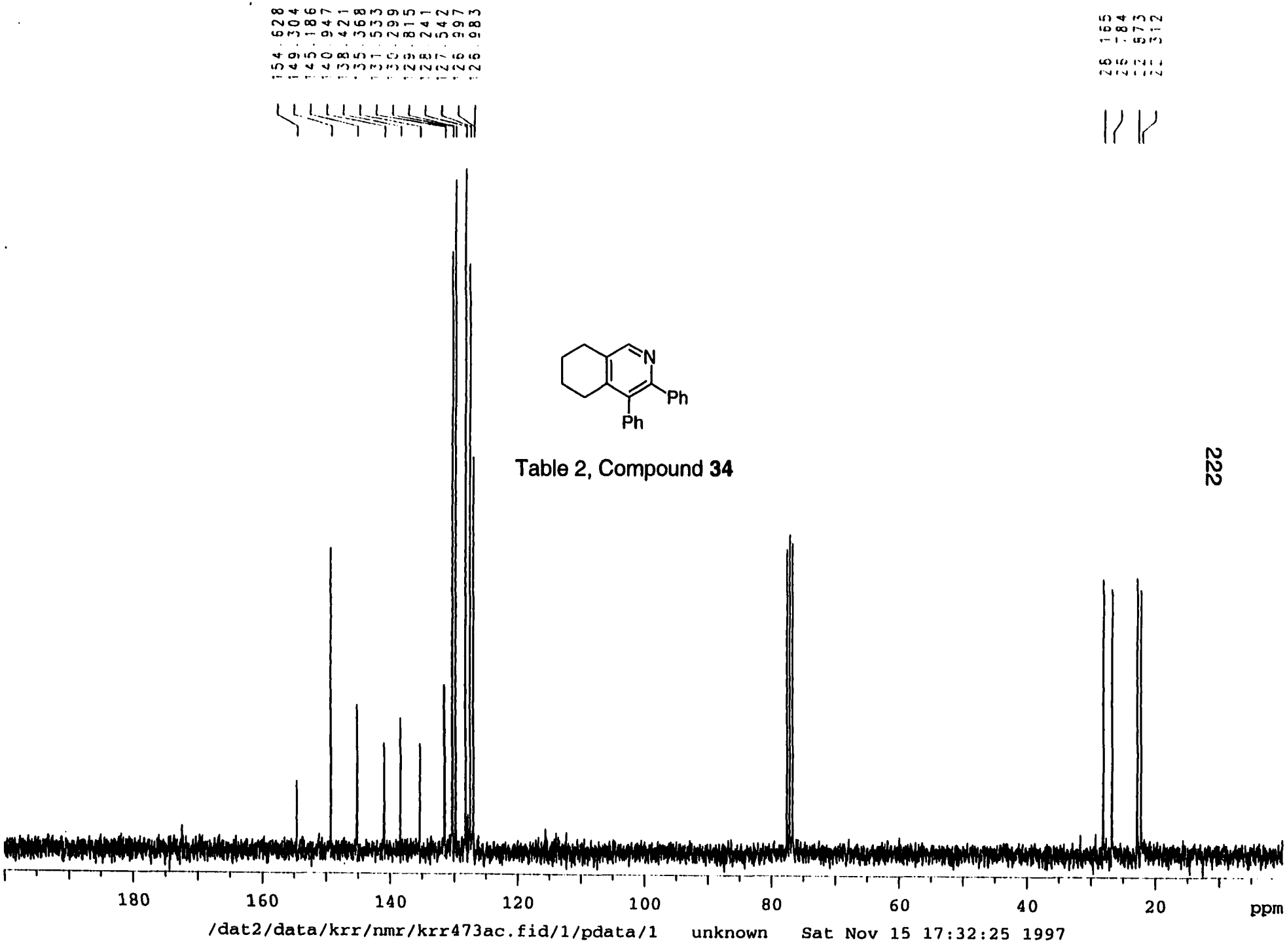
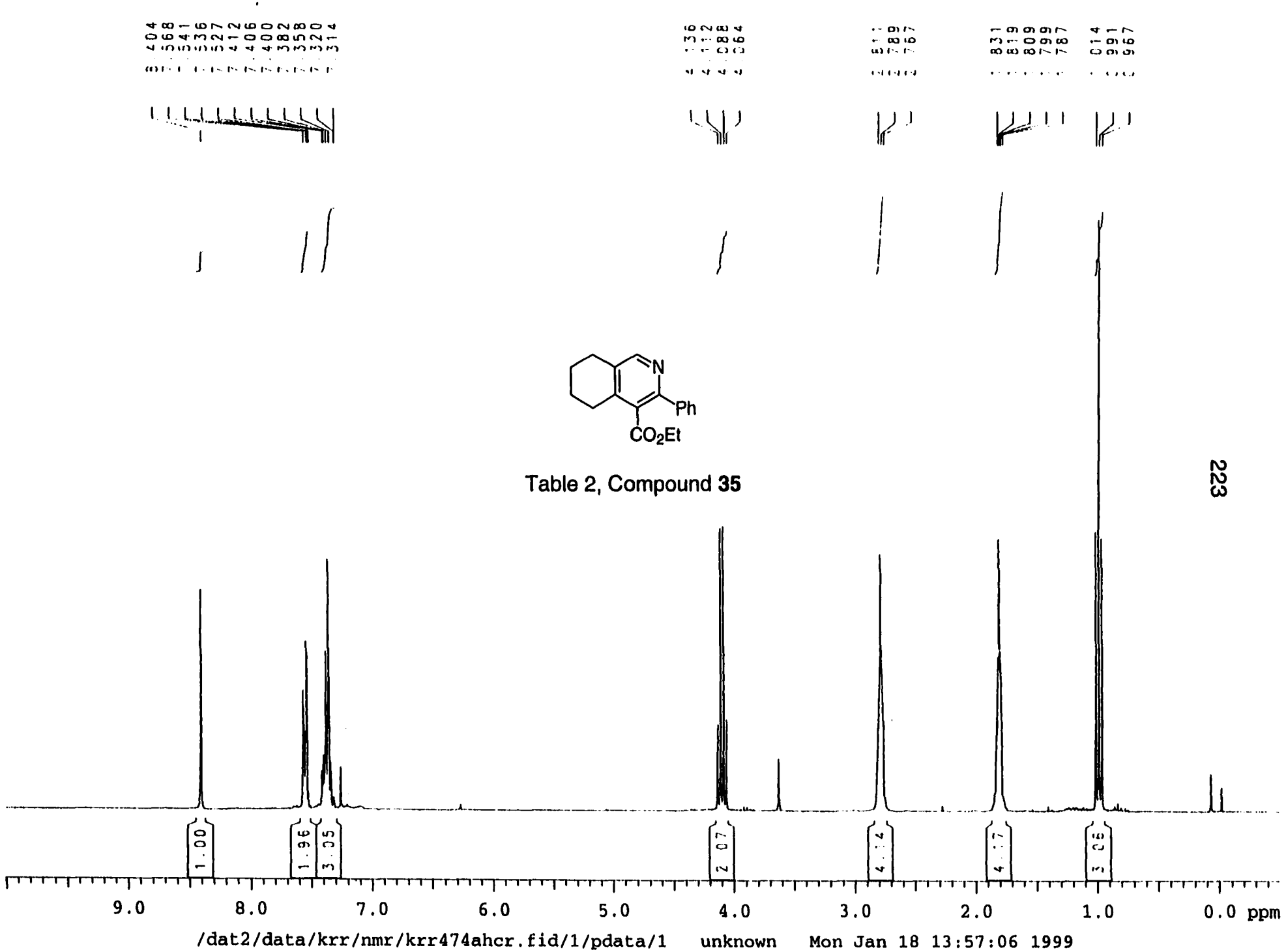


Table 2, Compound **34**


8.404
8.368
8.341
7.336
7.327
7.412
7.406
7.400
7.382
7.358
7.320
7.314
4.136
4.112
4.088
4.064
1.611
1.589
1.567
0.831
0.819
0.809
0.799
0.787
0.014
0.991
0.967
N
Ph
CO2Et
Table 2, Compound 35
223
1.00
1.96
3.05
2.07
4.14
4.17
3.06
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/dat2/data/krr/nmr/krr474ahcr.fid/1/pdata/1 unknown Mon Jan 18 13:57:06 1999

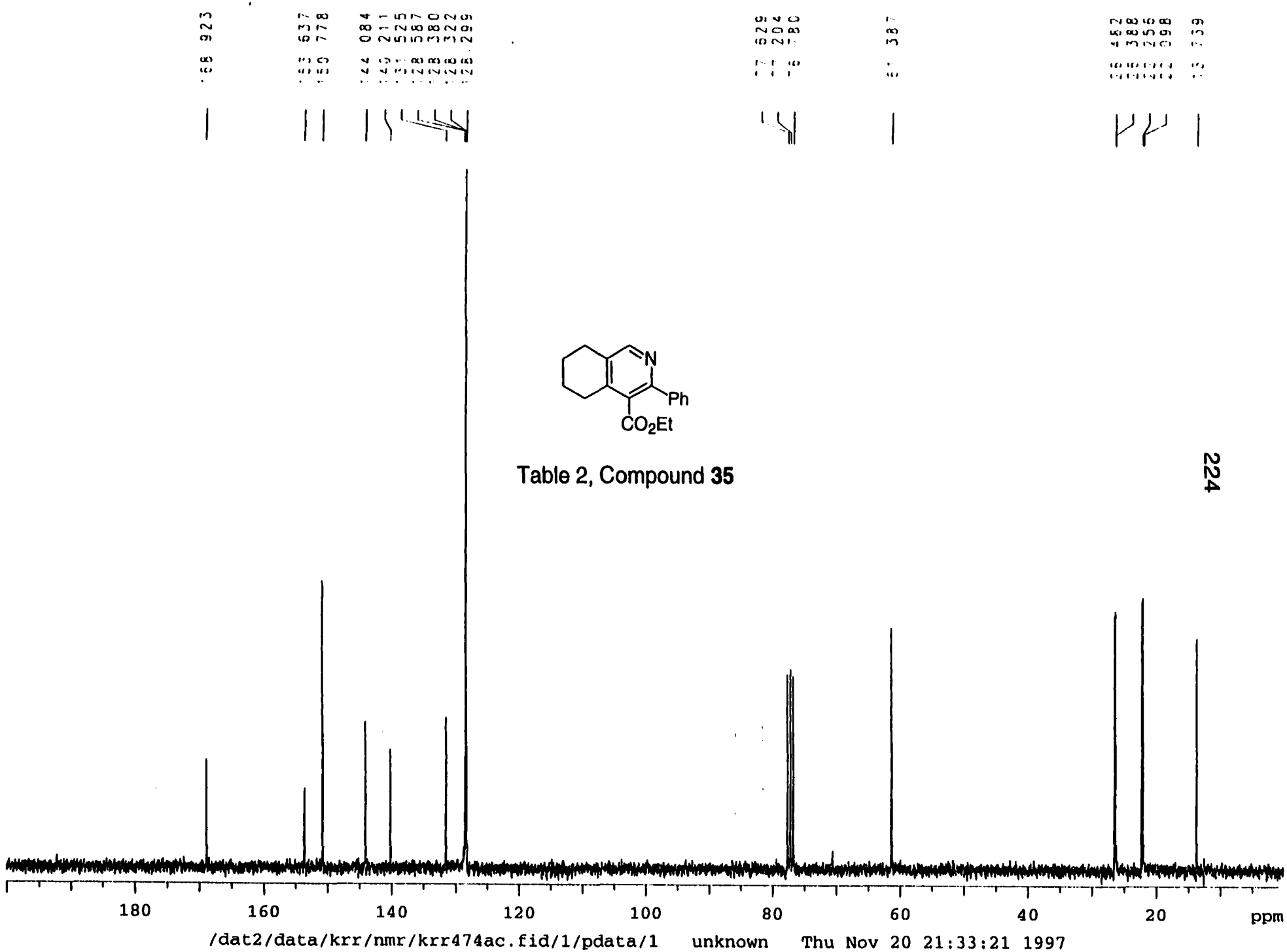
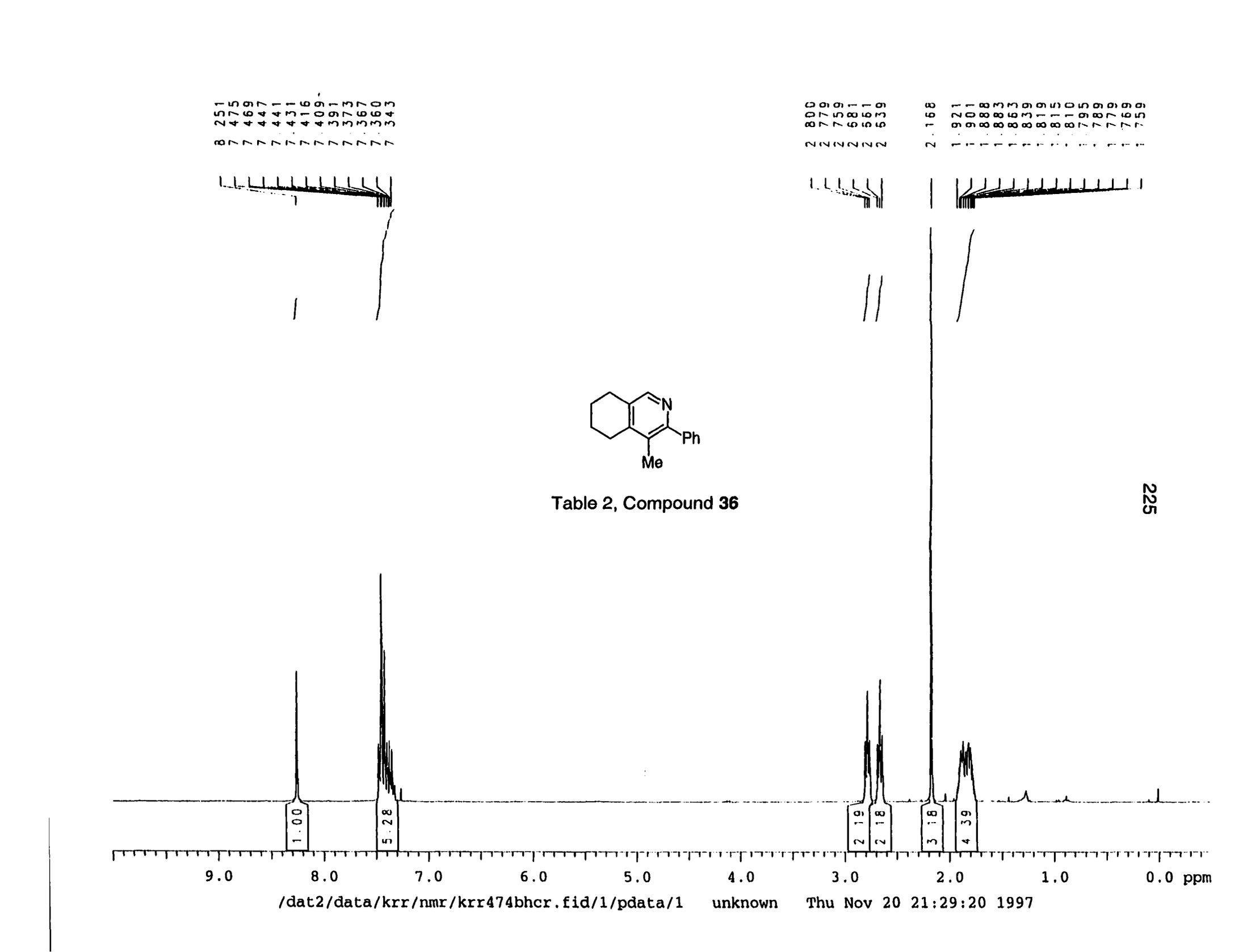
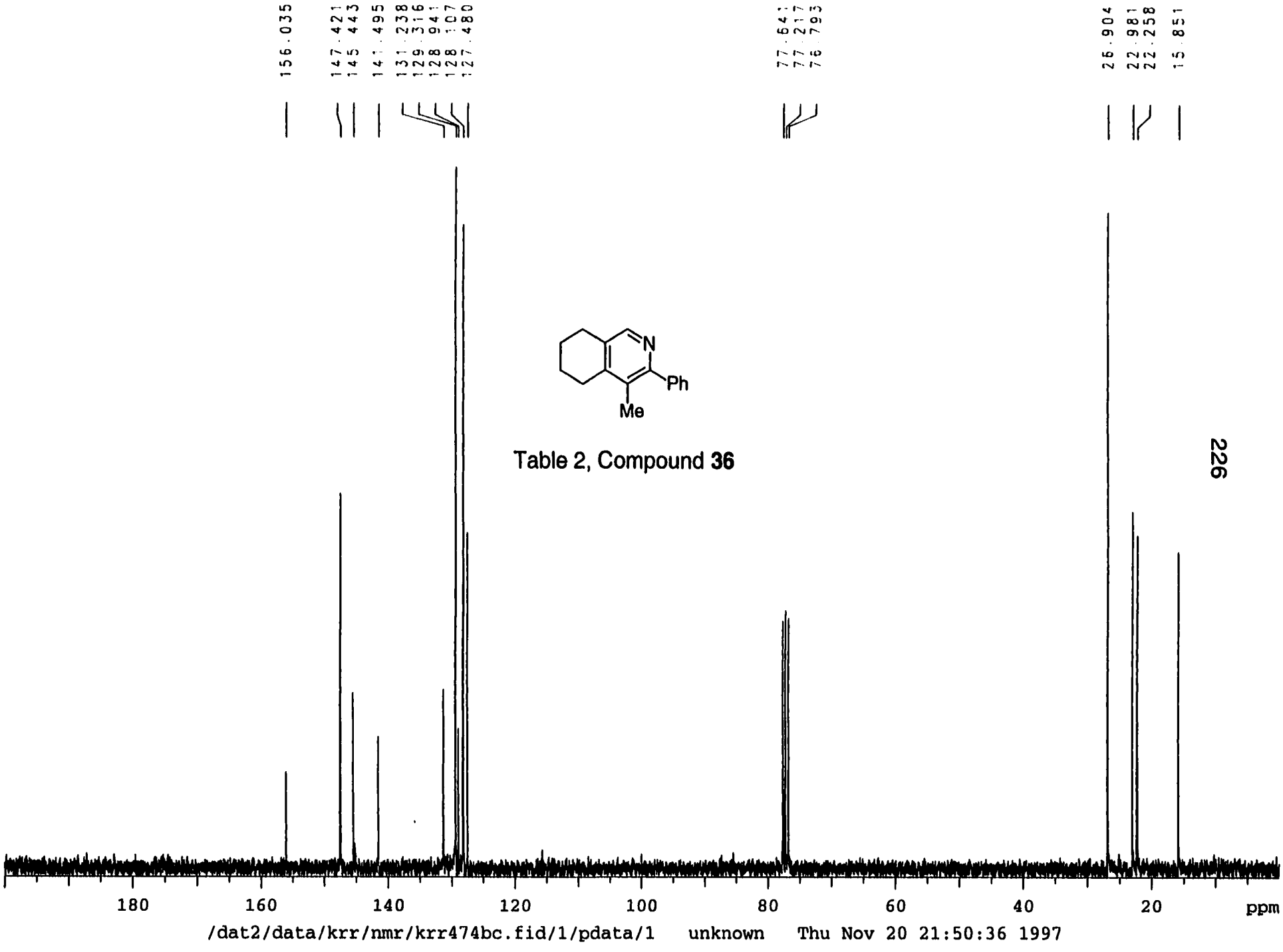


Table 2, Compound **35**


8.251
7.475
7.469
7.447
7.441
7.431
7.416
7.409
7.391
7.373
7.367
7.360
7.343
2.800
2.779
2.759
2.681
2.561
2.539
2.168
1.921
1.901
1.888
1.883
1.863
1.839
1.819
1.815
1.810
1.795
1.789
1.779
1.769
1.759
N
Ph
Me
Table 2, Compound 36
225
1.00
5.28
2.19
2.18
3.18
4.39
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/dat2/data/krr/nmr/krr474bhcr.fid/1/pdata/1 unknown Thu Nov 20 21:29:20 1997


156.035
147.421
145.443
141.495
131.238
129.316
128.941
128.107
127.480
77.641
77.217
76.793
26.904
22.981
22.258
15.851
N
Ph
Me
Table 2, Compound 36
226
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr474bc.fid/1/pdata/1 unknown Thu Nov 20 21:50:36 1997

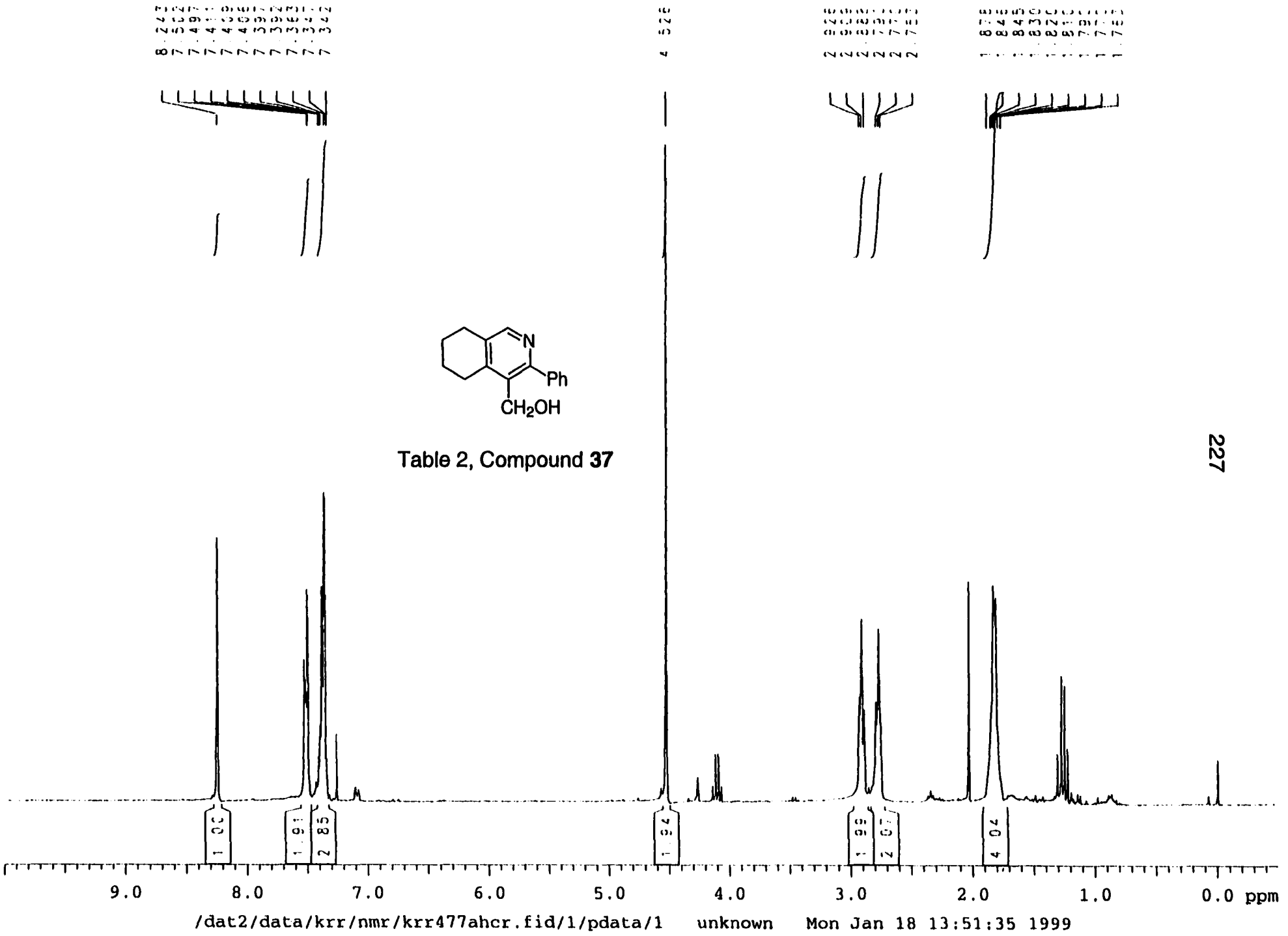
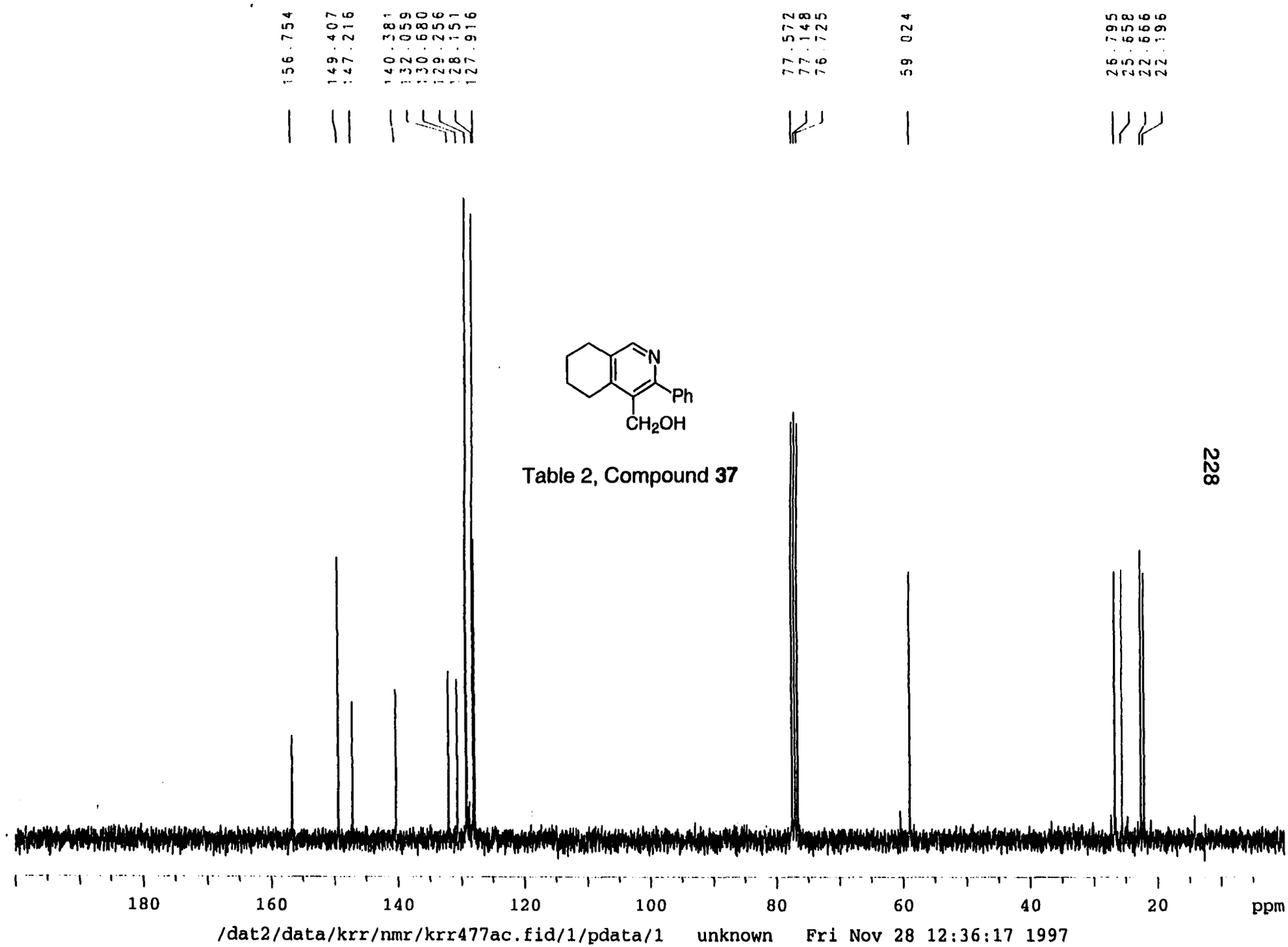
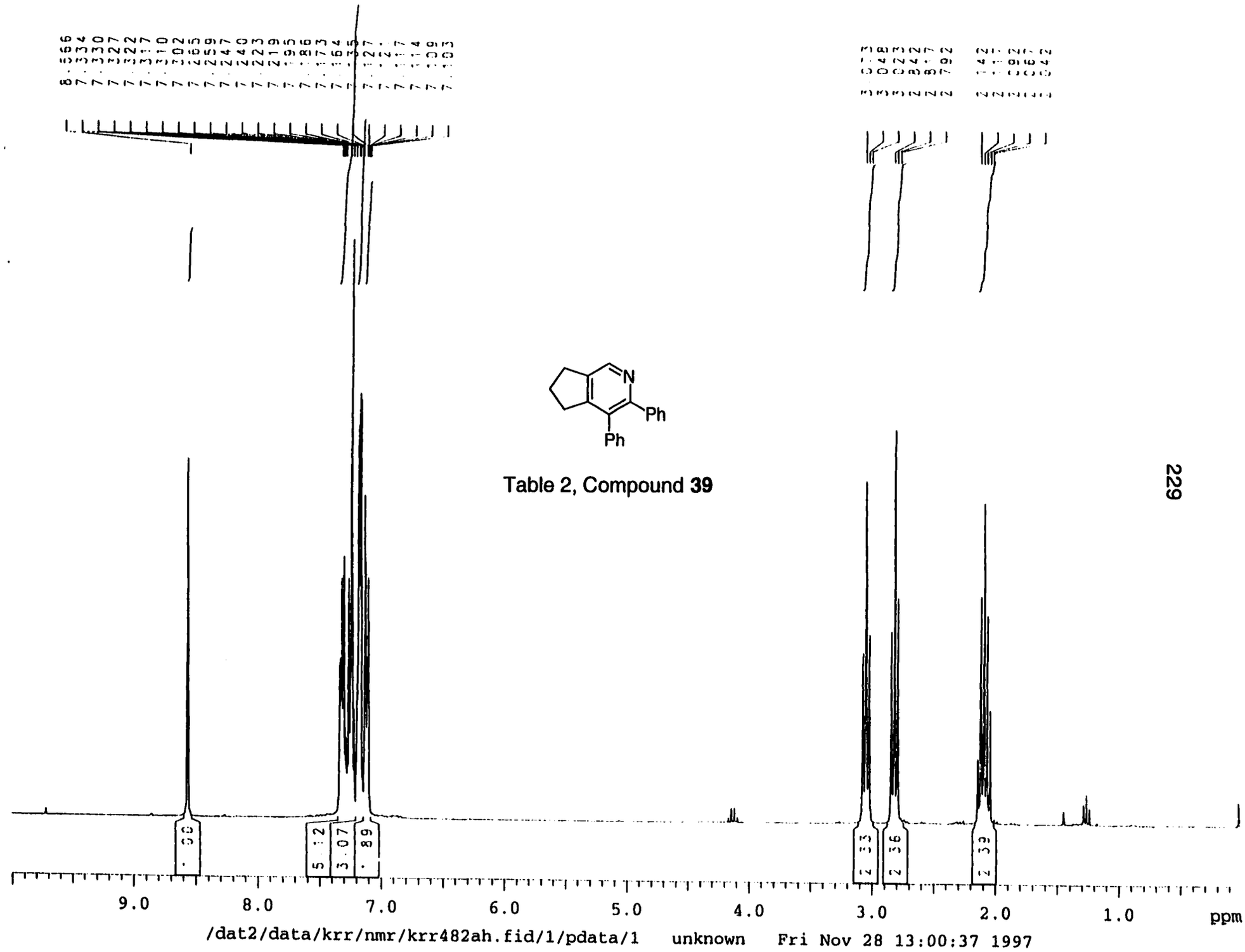


Table 2, Compound **37**


156.754
149.407
147.216
140.381
132.059
130.680
129.256
128.151
127.916
77.572
77.148
76.725
59.024
26.795
25.658
22.666
22.196
N
Ph
CH2OH
Table 2, Compound 37
228
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr477ac.fid/1/pdata/1 unknown Fri Nov 28 12:36:17 1997


8.366
7.334
7.330
7.327
7.322
7.317
7.310
7.302
7.265
7.259
7.247
7.240
7.223
7.219
7.195
7.186
7.173
7.164
7.135
7.127
7.117
7.114
7.109
7.103
3.348
3.323
3.317
3.292
2.442
2.392
2.342
N
Ph
Ph
Table 2, Compound 39
229
.66
5.12
3.07
.89
2.33
2.36
2.39
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm
/dat2/data/krr/nmr/krr482ah.fid/1/pdata/1 unknown Fri Nov 28 13:00:37 1997

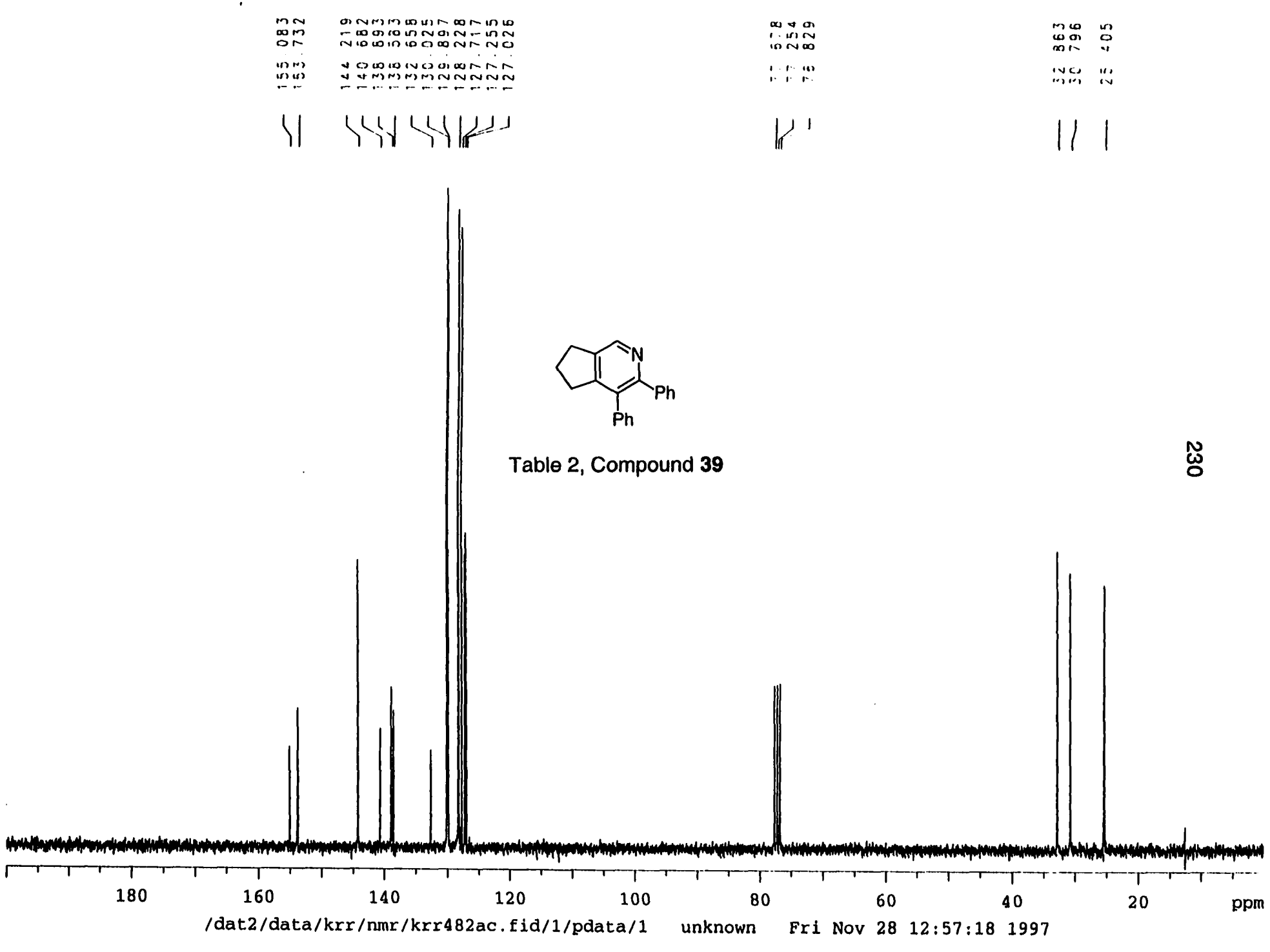


Table 2, Compound **39**

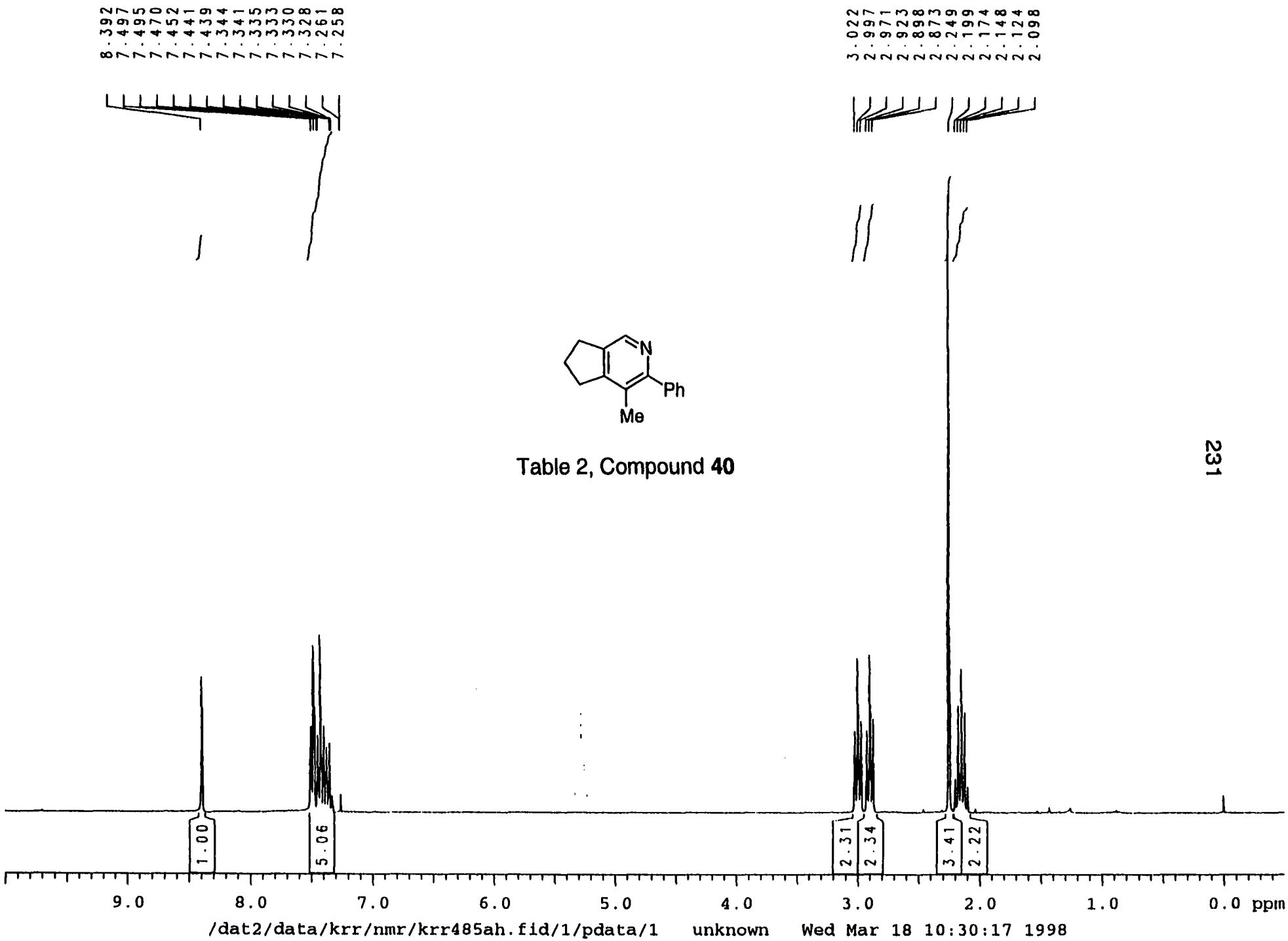
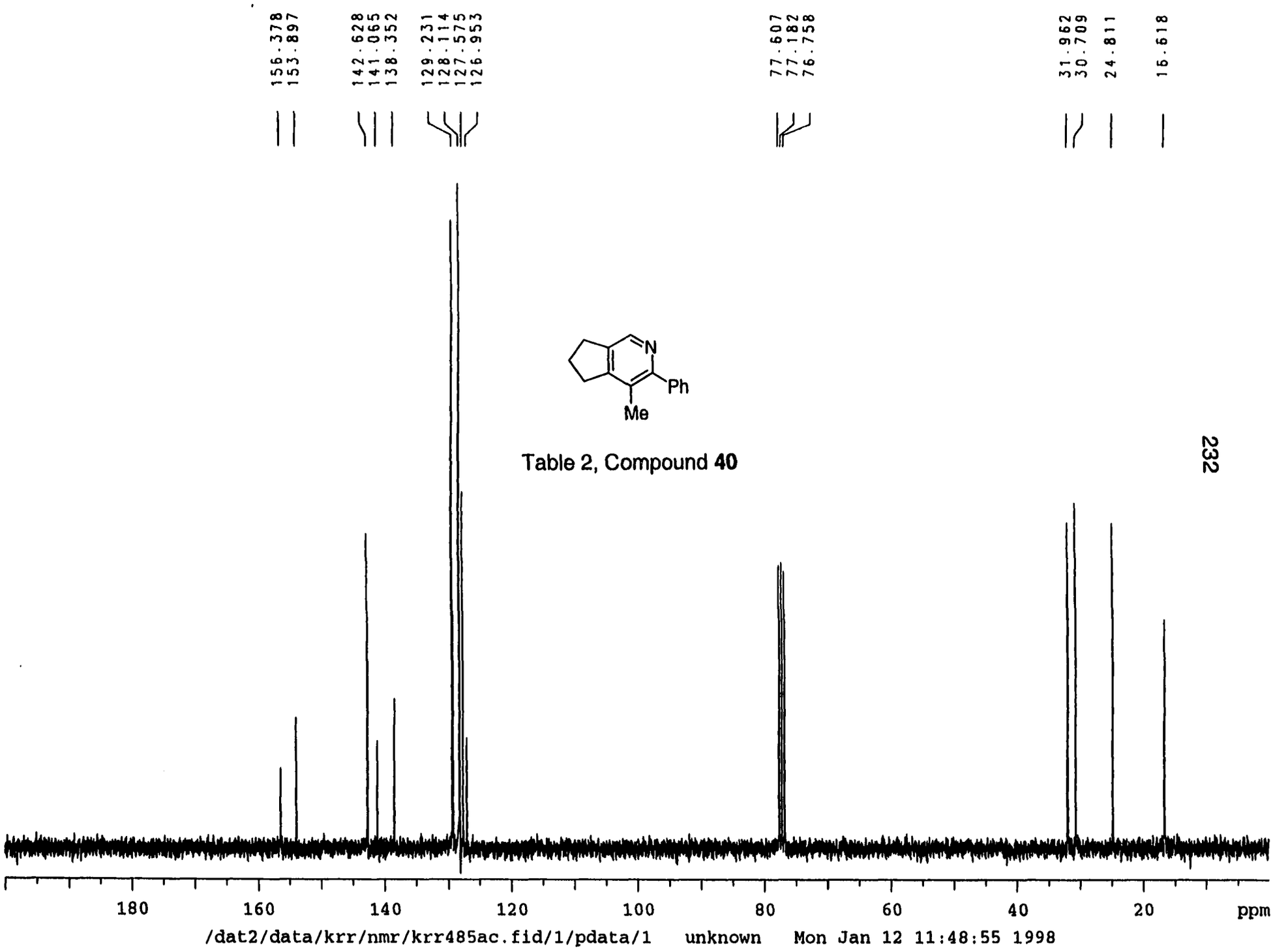


Table 2, Compound **40**


156.378
153.897
142.628
141.065
138.352
129.231
128.114
127.575
126.953
77.607
77.182
76.758
31.962
30.709
24.811
16.618
N
Ph
Me
Table 2, Compound 40
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr485ac.fid/1/pdata/1 unknown Mon Jan 12 11:48:55 1998

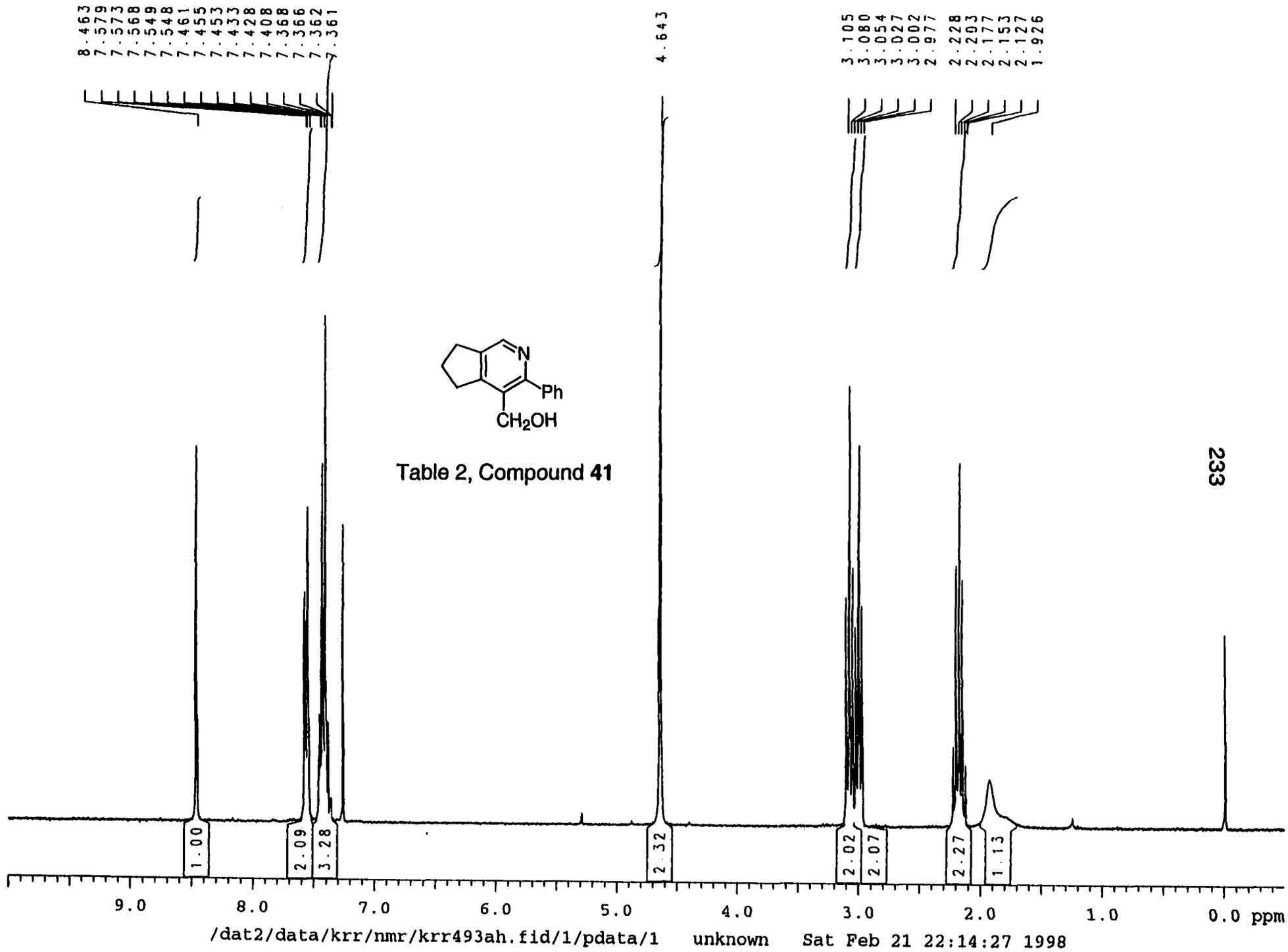


Table 2, Compound **41**

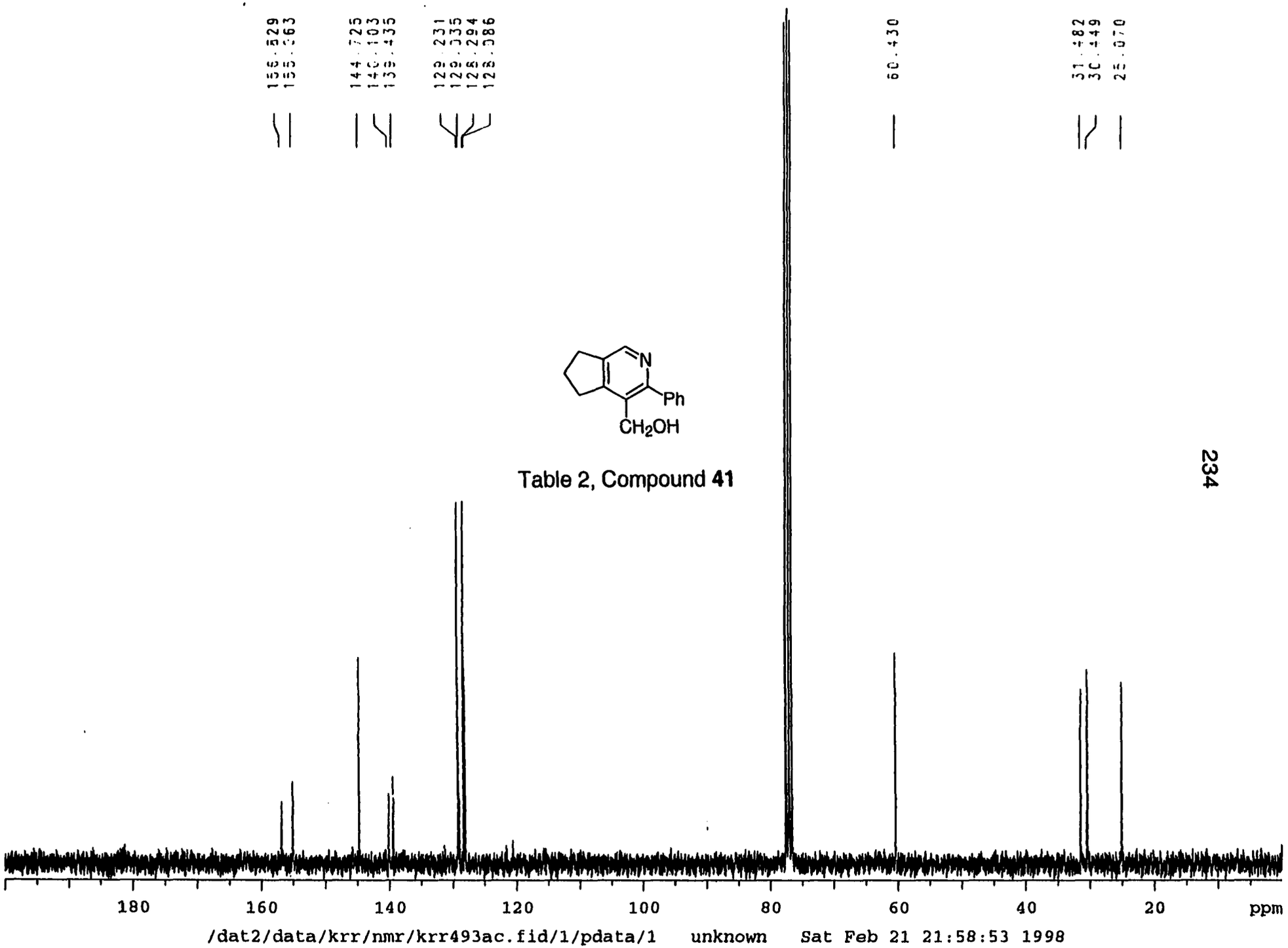


Table 2, Compound **41**

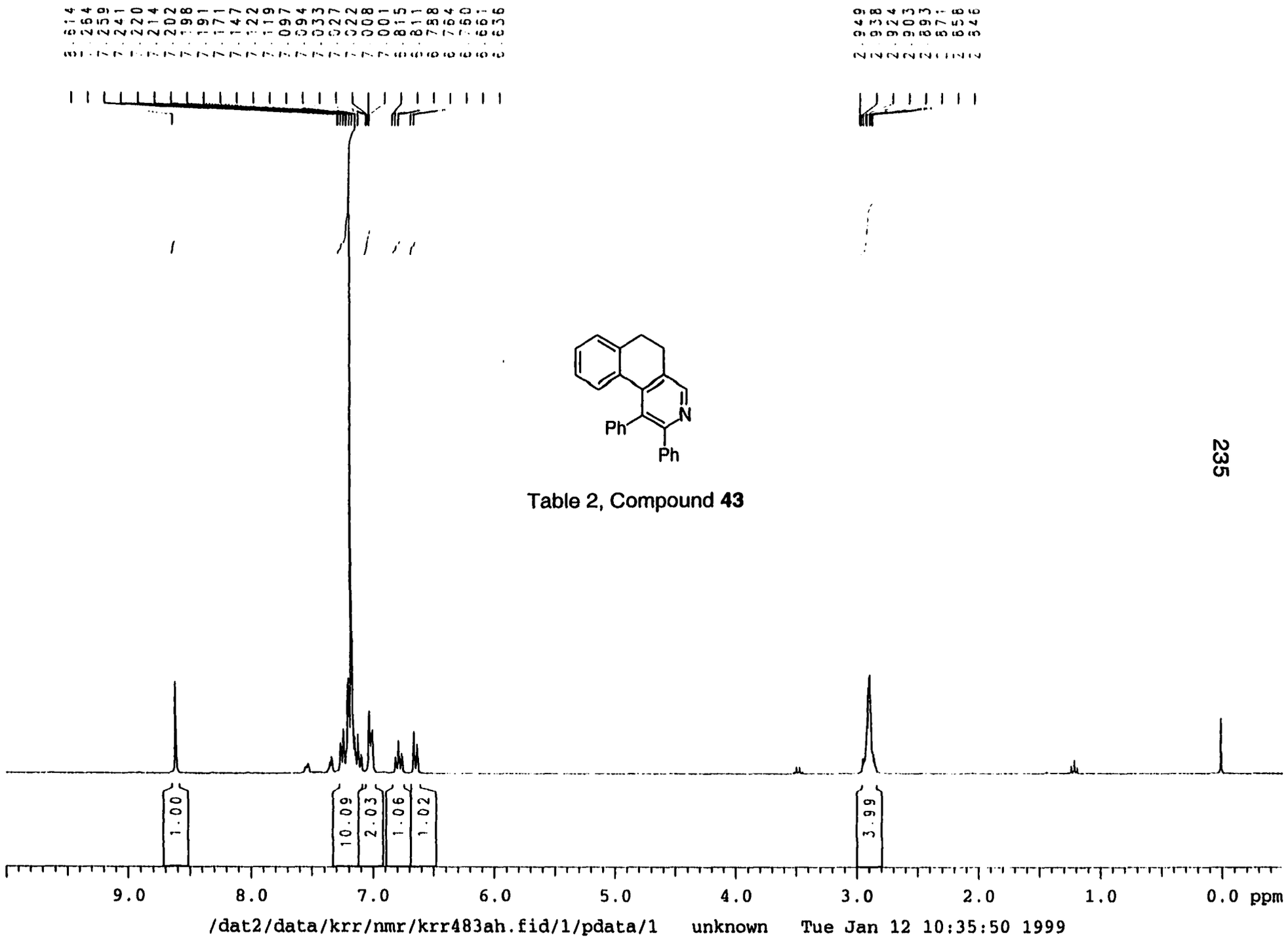


Table 2, Compound **43**

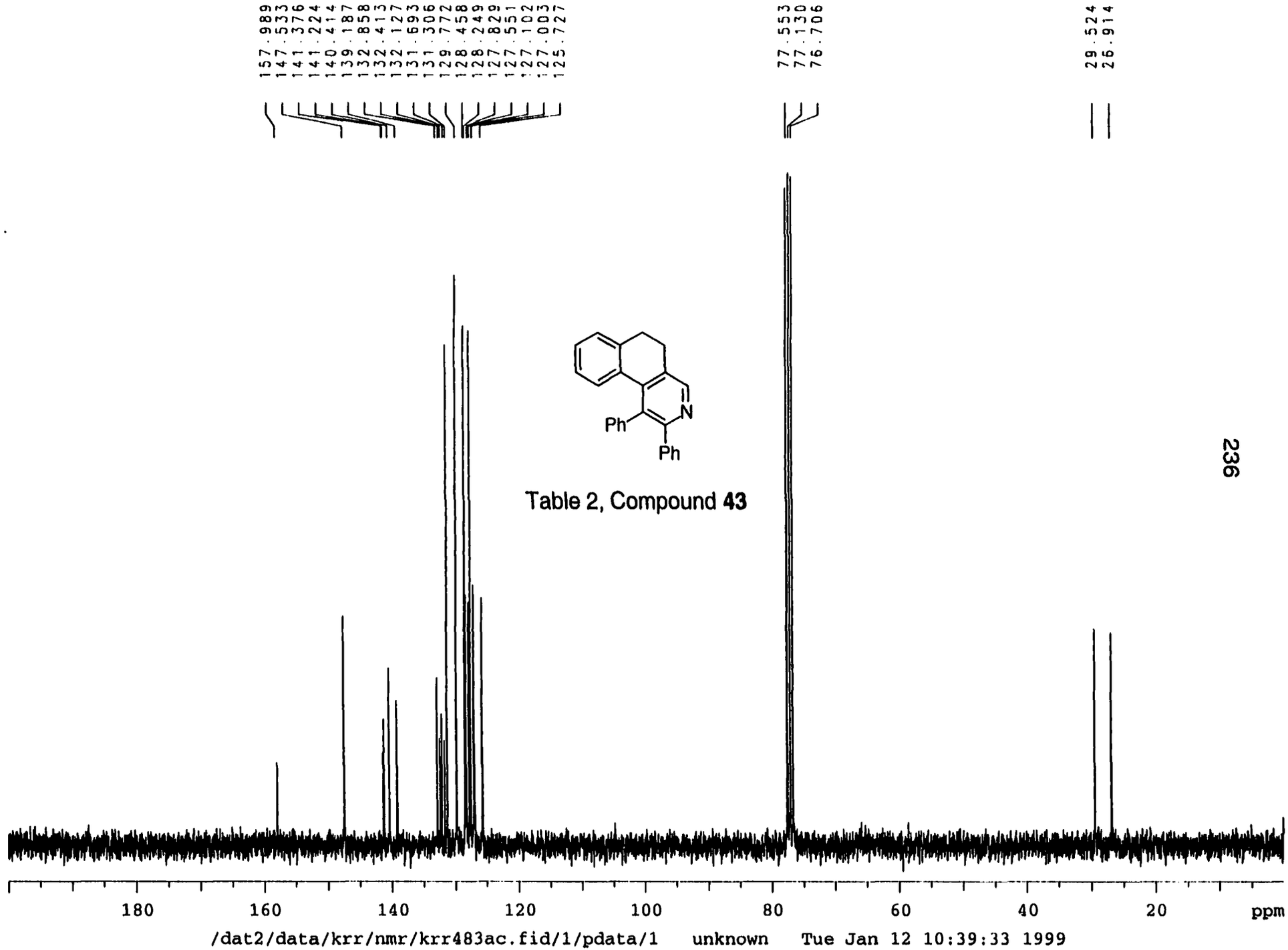


Table 2, Compound **43**

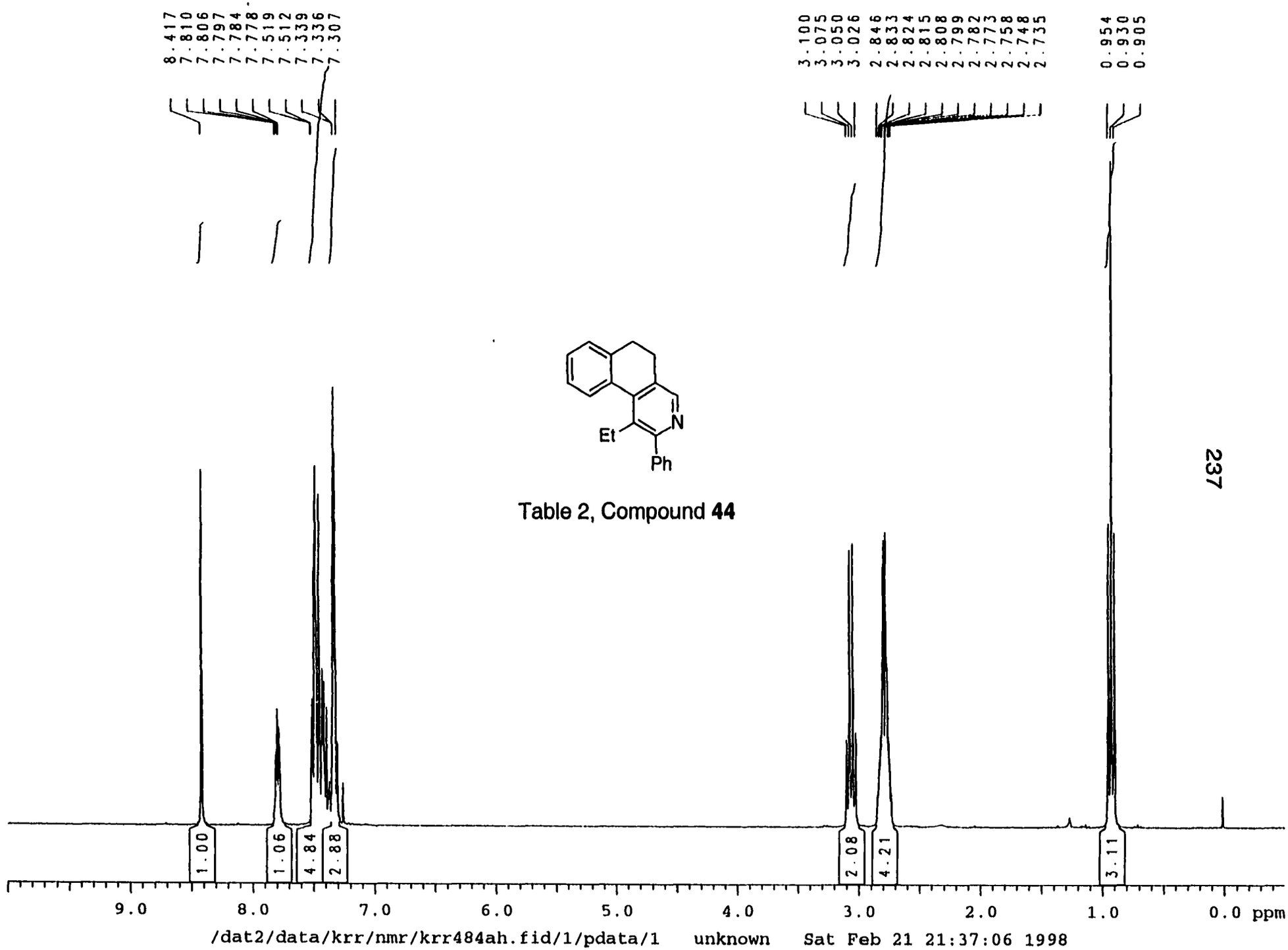
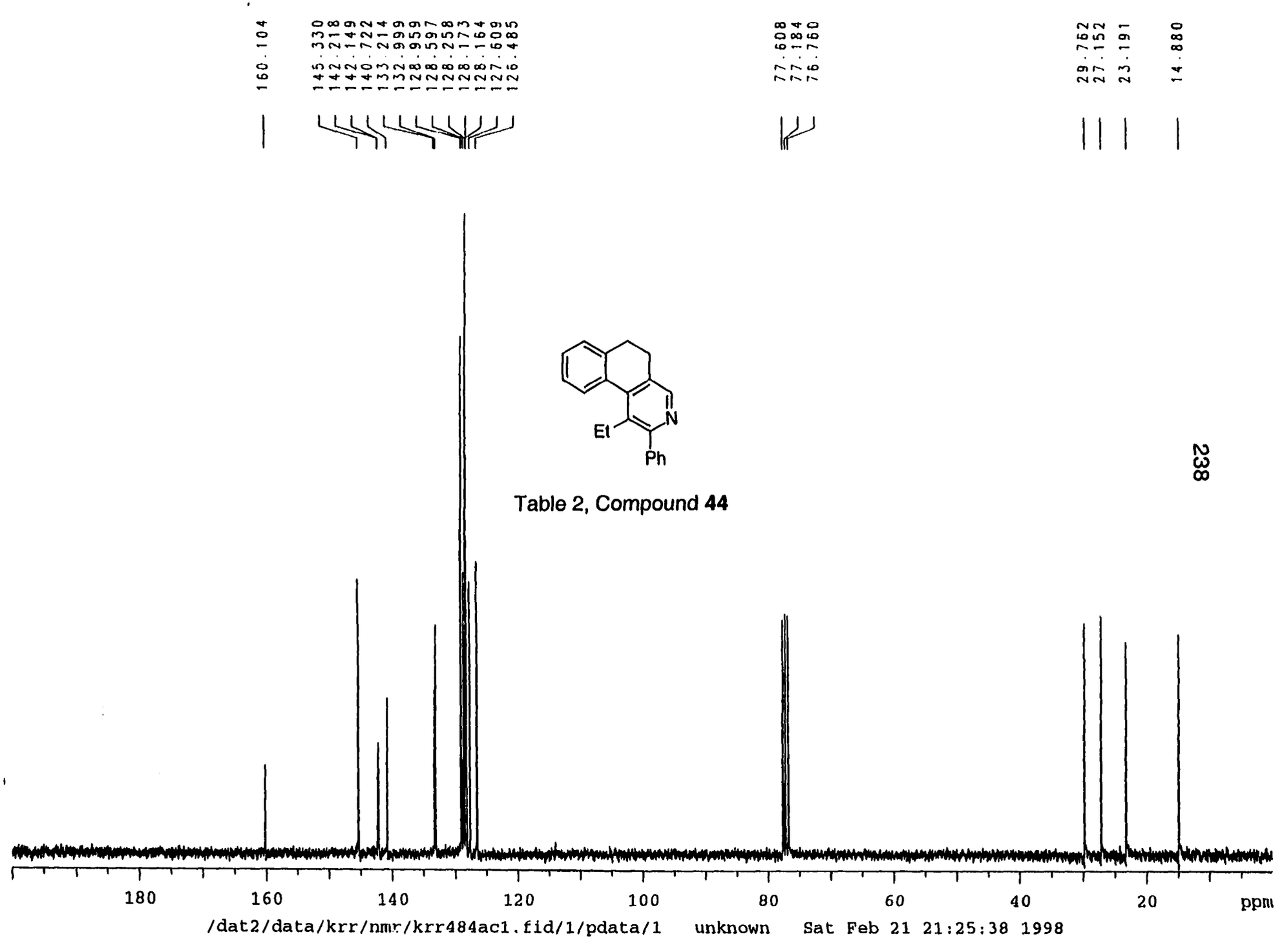


Table 2, Compound **44**


160.104
145.330
142.218
142.149
140.722
133.214
132.999
128.959
128.597
128.258
128.173
128.164
127.609
126.485
77.608
77.184
76.760
29.762
27.152
23.191
14.880
Et
N
Ph
Table 2, Compound 44
238
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr484ac1.fid/1/pdata/1 unknown Sat Feb 21 21:25:38 1998

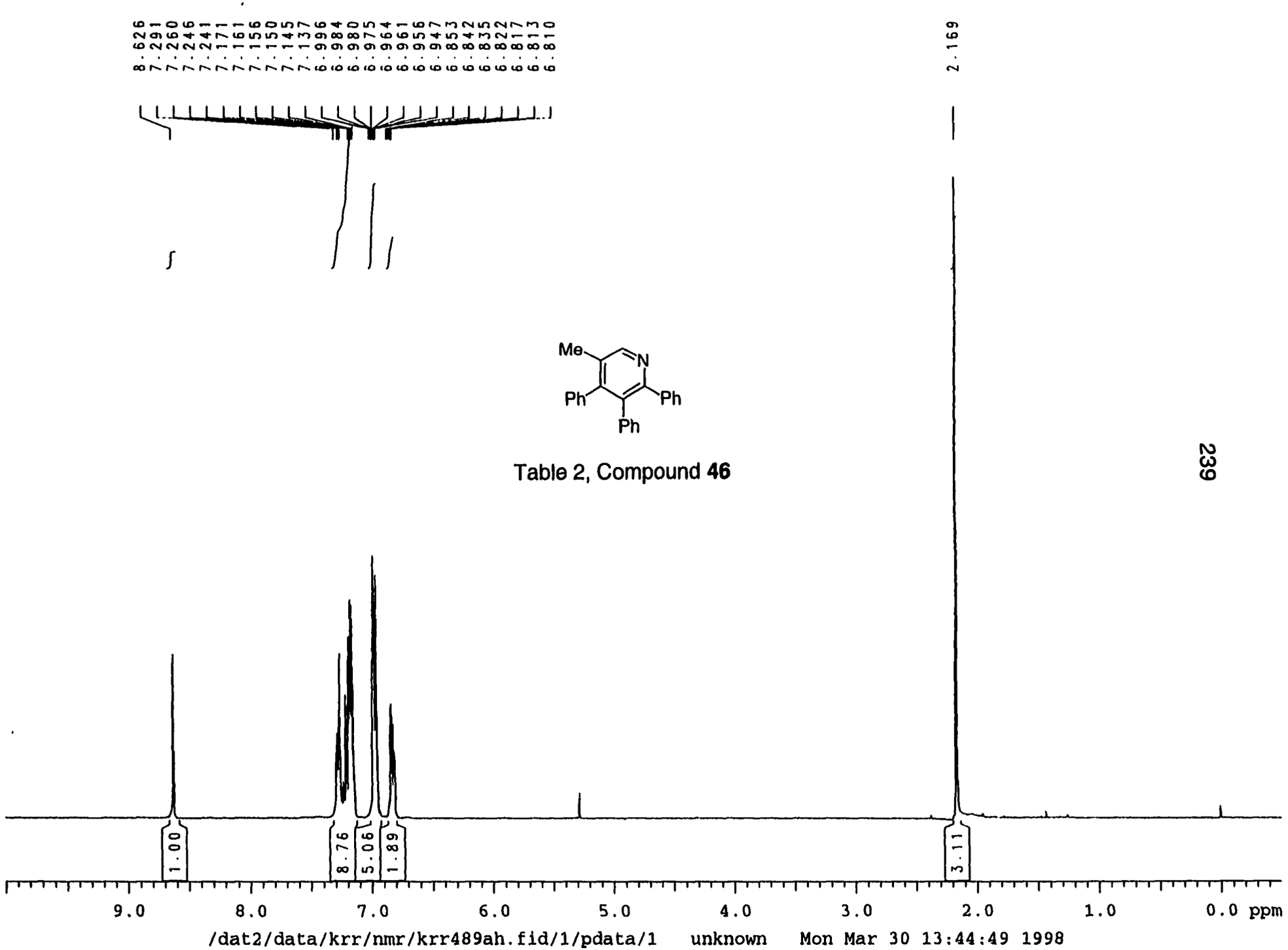
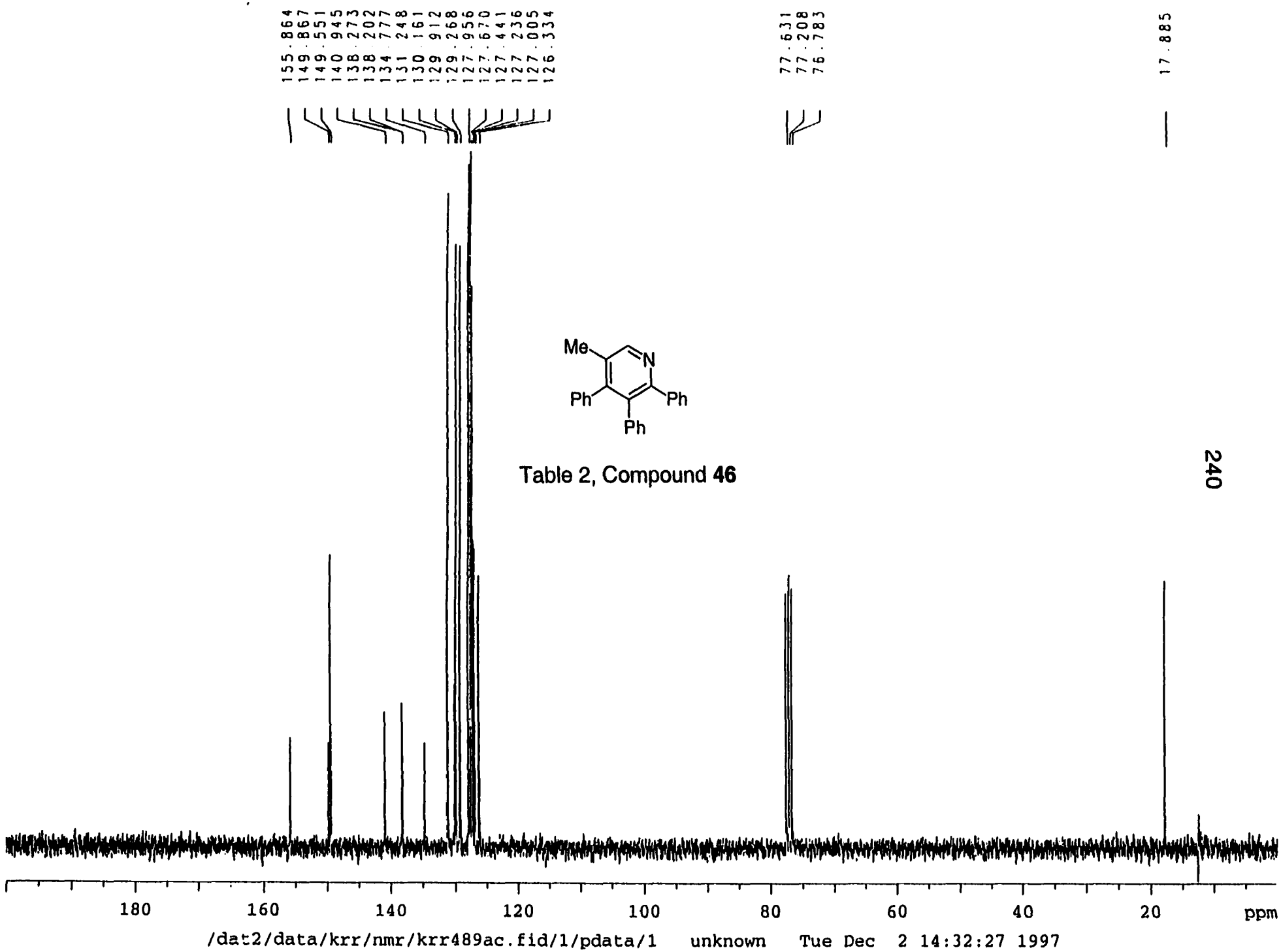


Table 2, Compound **46**


155.864
149.867
149.551
140.945
138.273
138.202
134.777
131.248
130.161
129.912
129.268
127.956
127.670
127.441
127.236
127.005
126.334
77.631
77.208
76.783
17.885
Me
N
Ph
Ph
Ph
Table 2, Compound 46
240
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr489ac.fid/1/pdata/1 unknown Tue Dec 2 14:32:27 1997

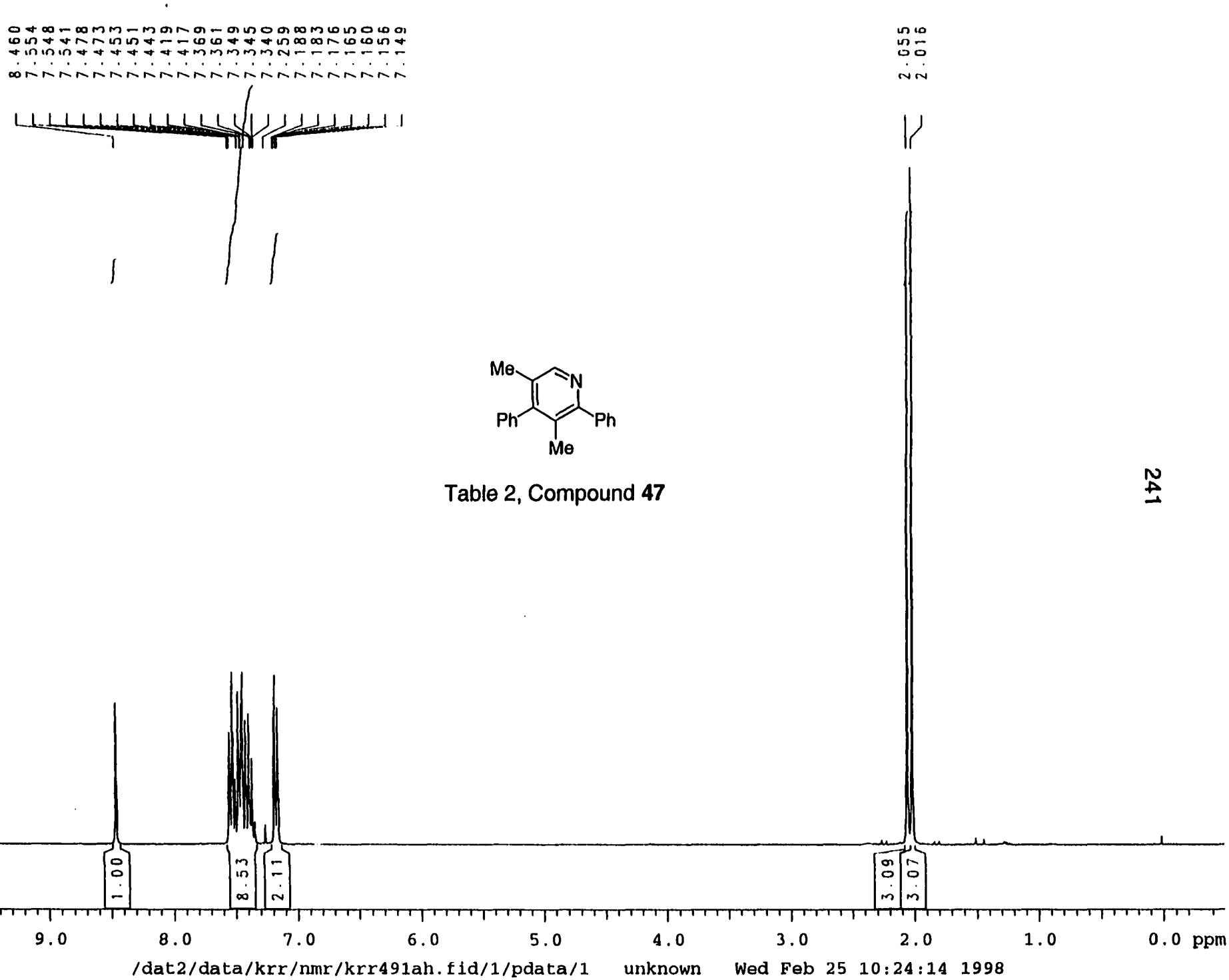


Table 2, Compound **47**

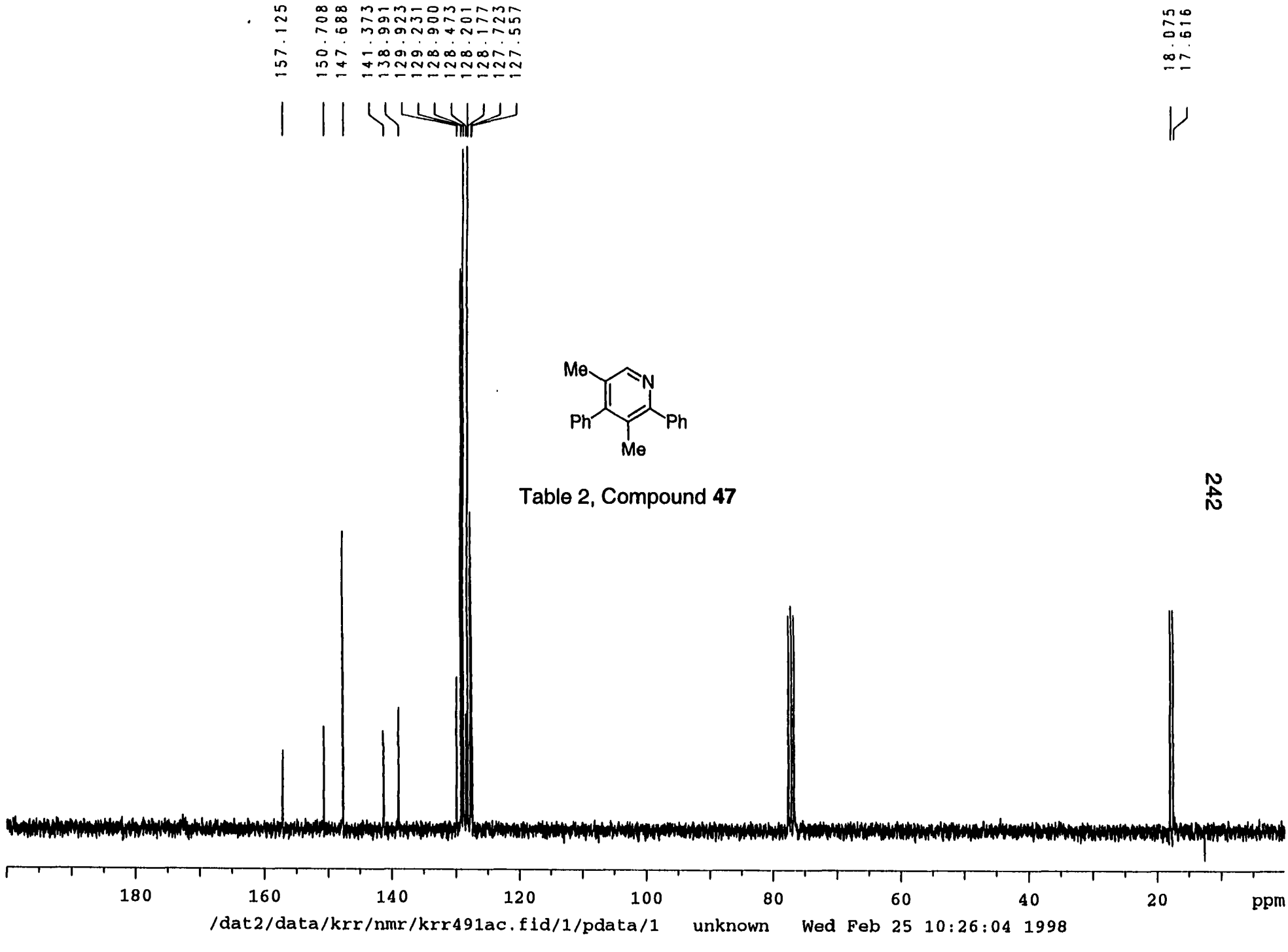


Table 2, Compound **47**

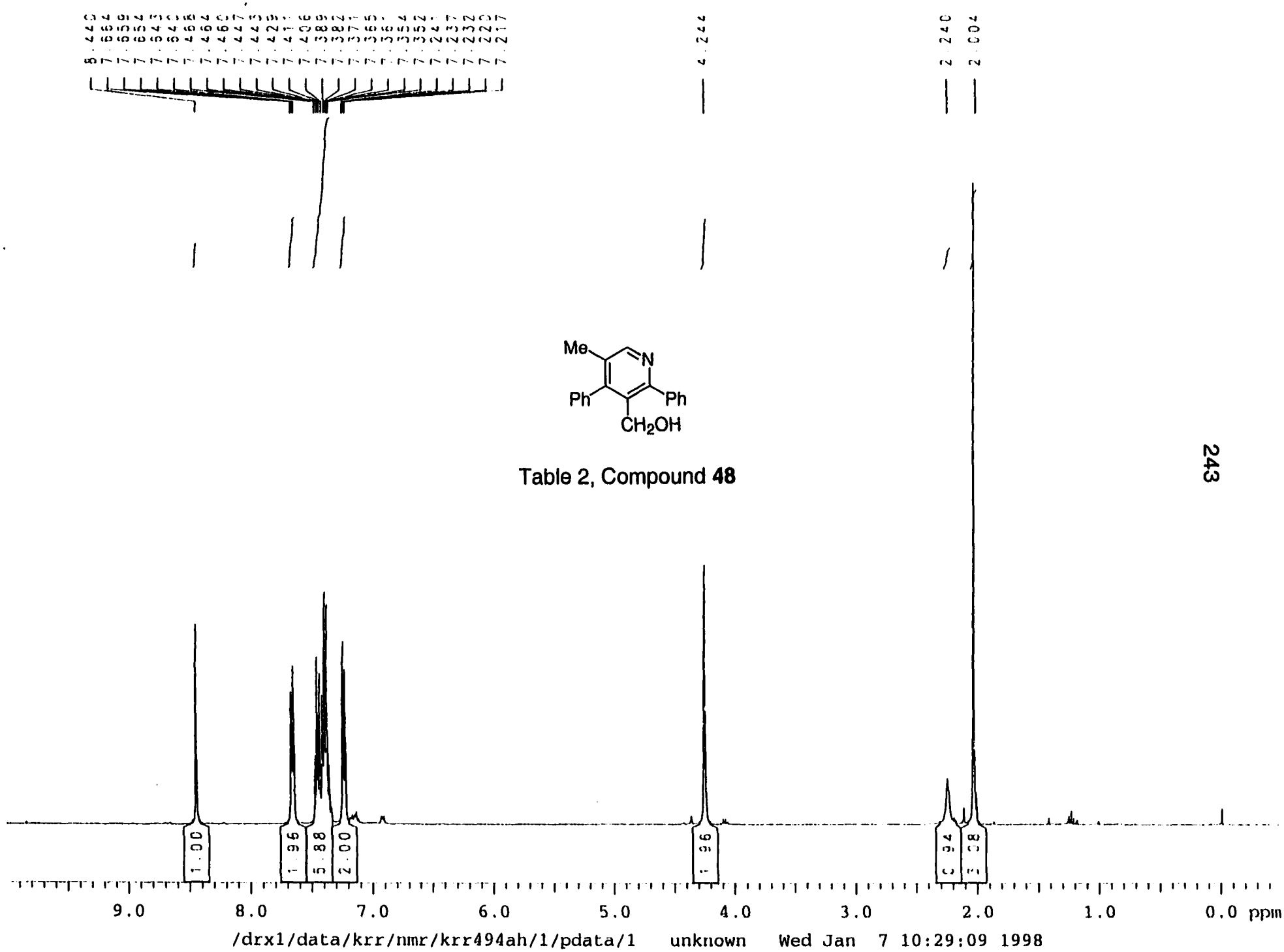
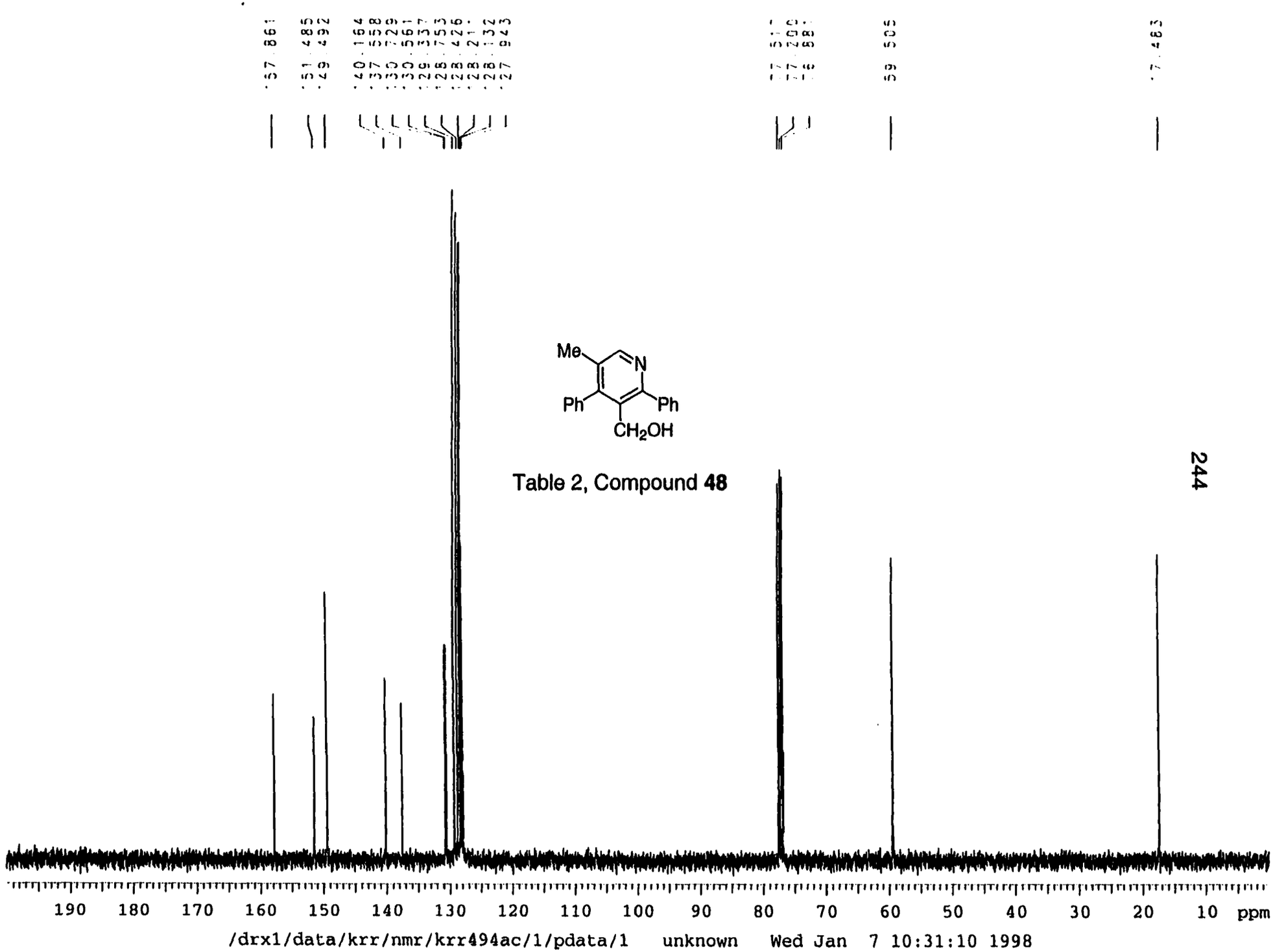


Table 2, Compound **48**


Me
N
Ph
Ph
CH2OH
Table 2, Compound 48
244
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
/drx1/data/krr/nmr/krr494ac/1/pdata/1 unknown Wed Jan 7 10:31:10 1998

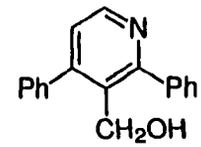
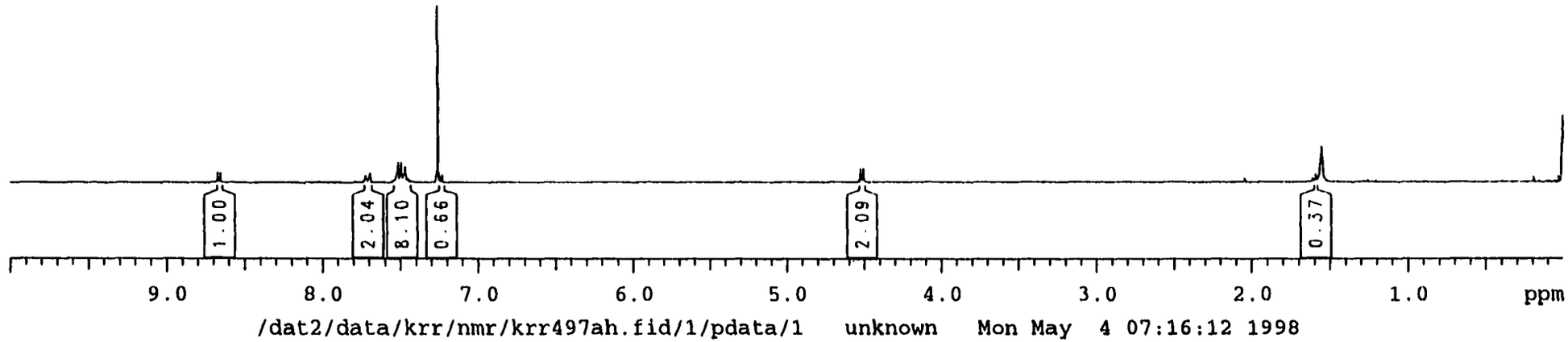


Table 2, Compound **51**



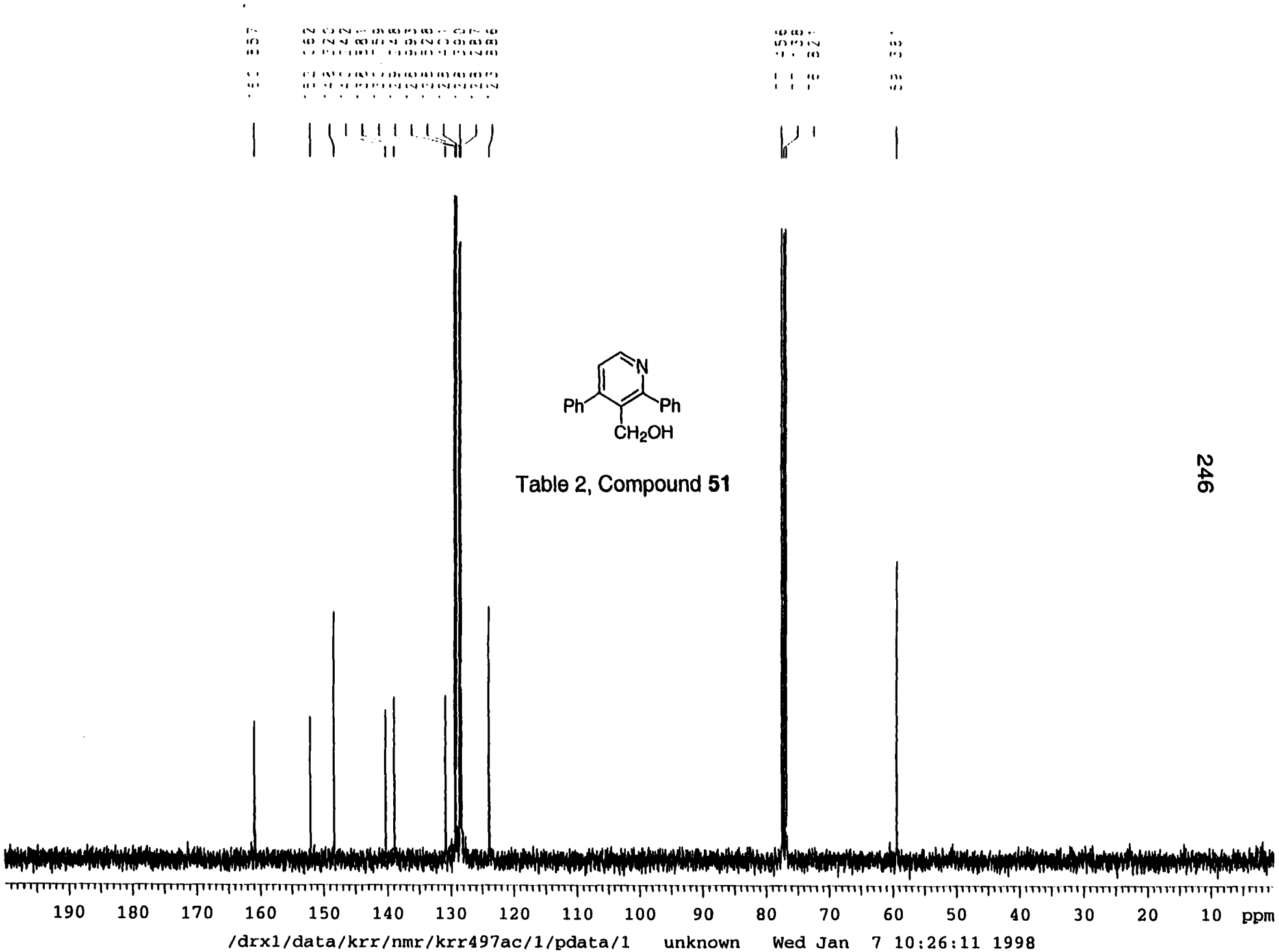
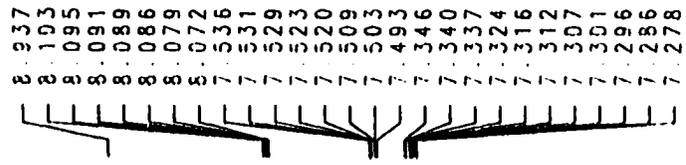


Table 2, Compound **51**

APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

t e x t X



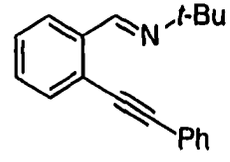


Table 3, Compound **9**

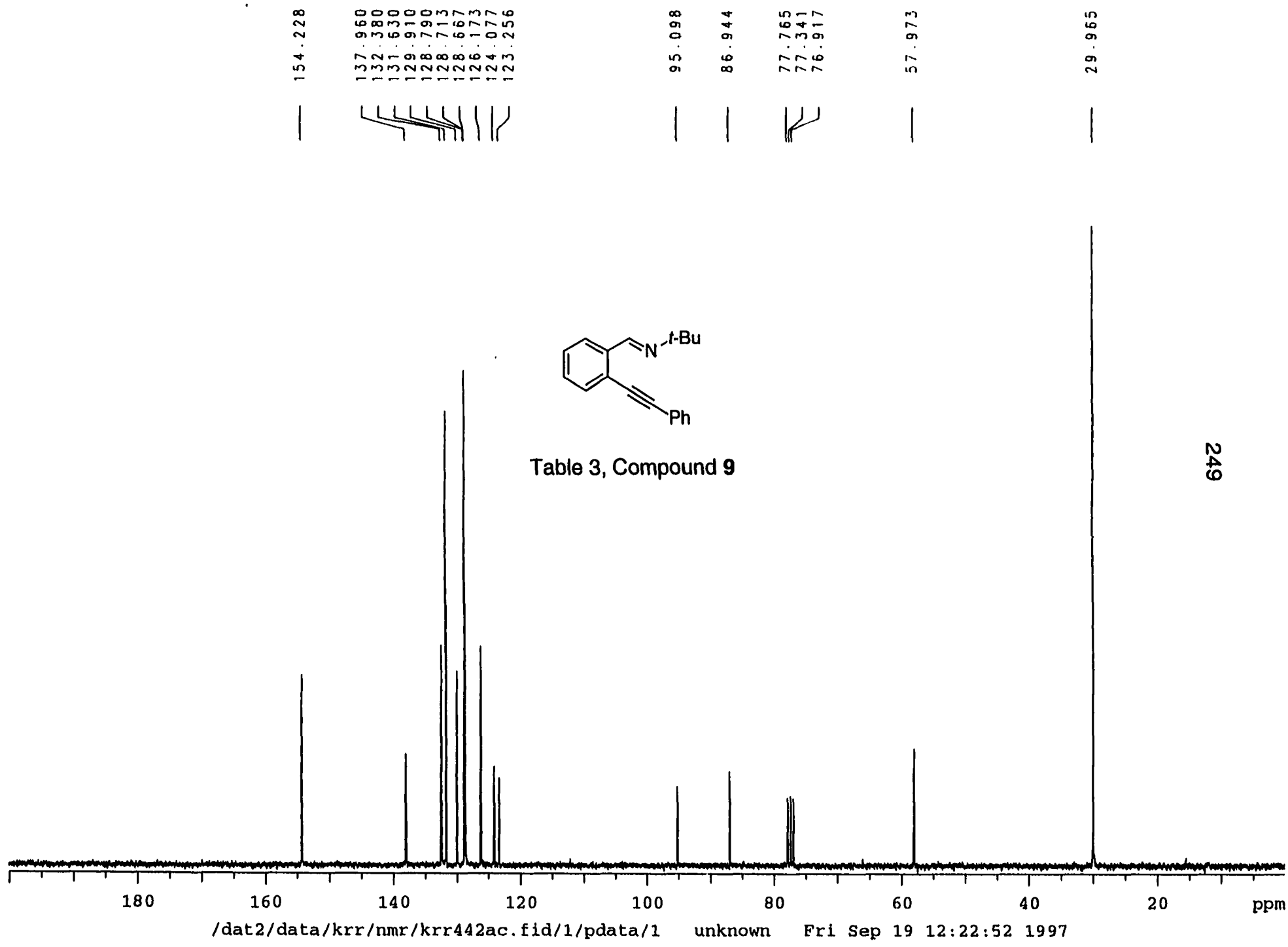


Table 3, Compound **9**

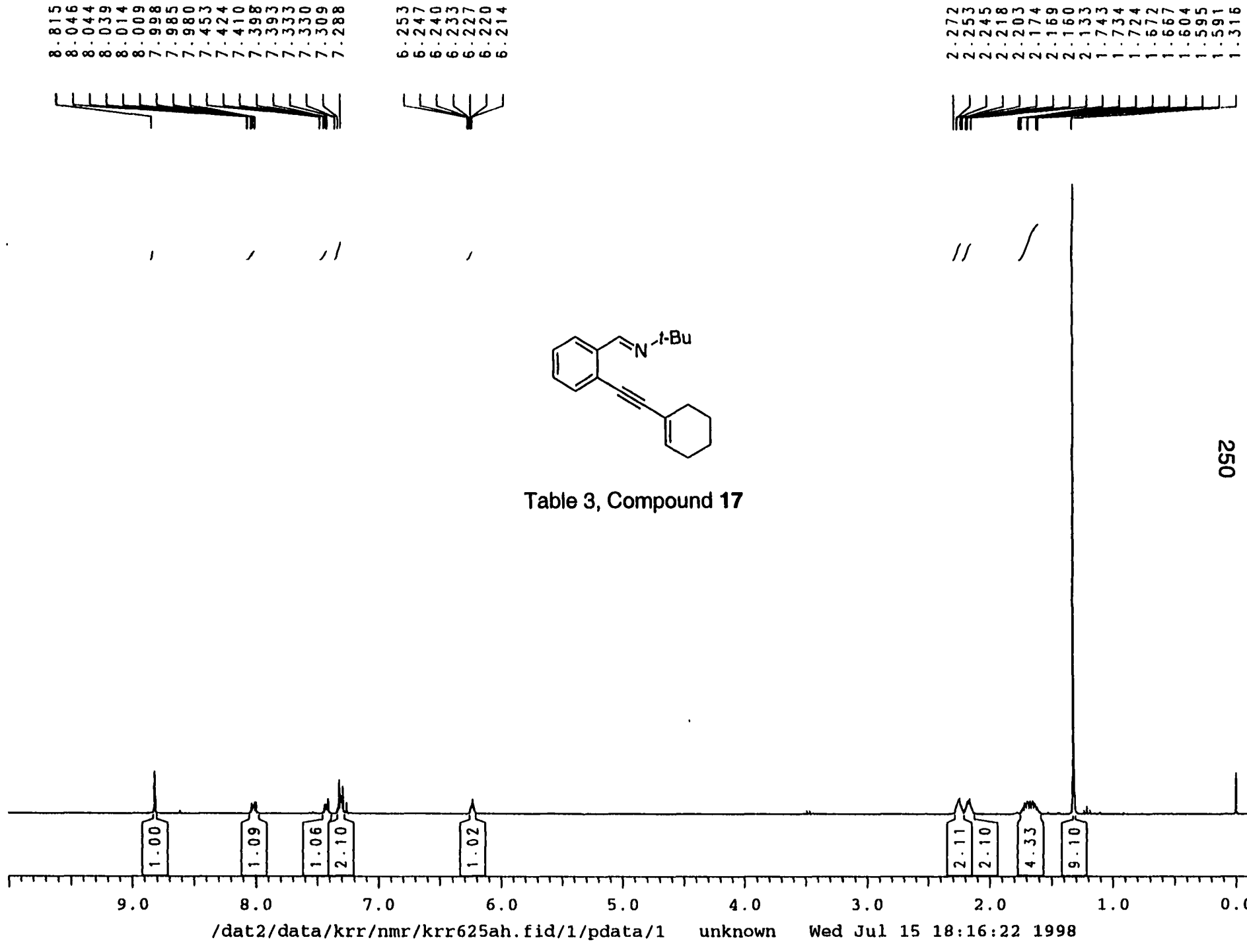


Table 3, Compound **17**

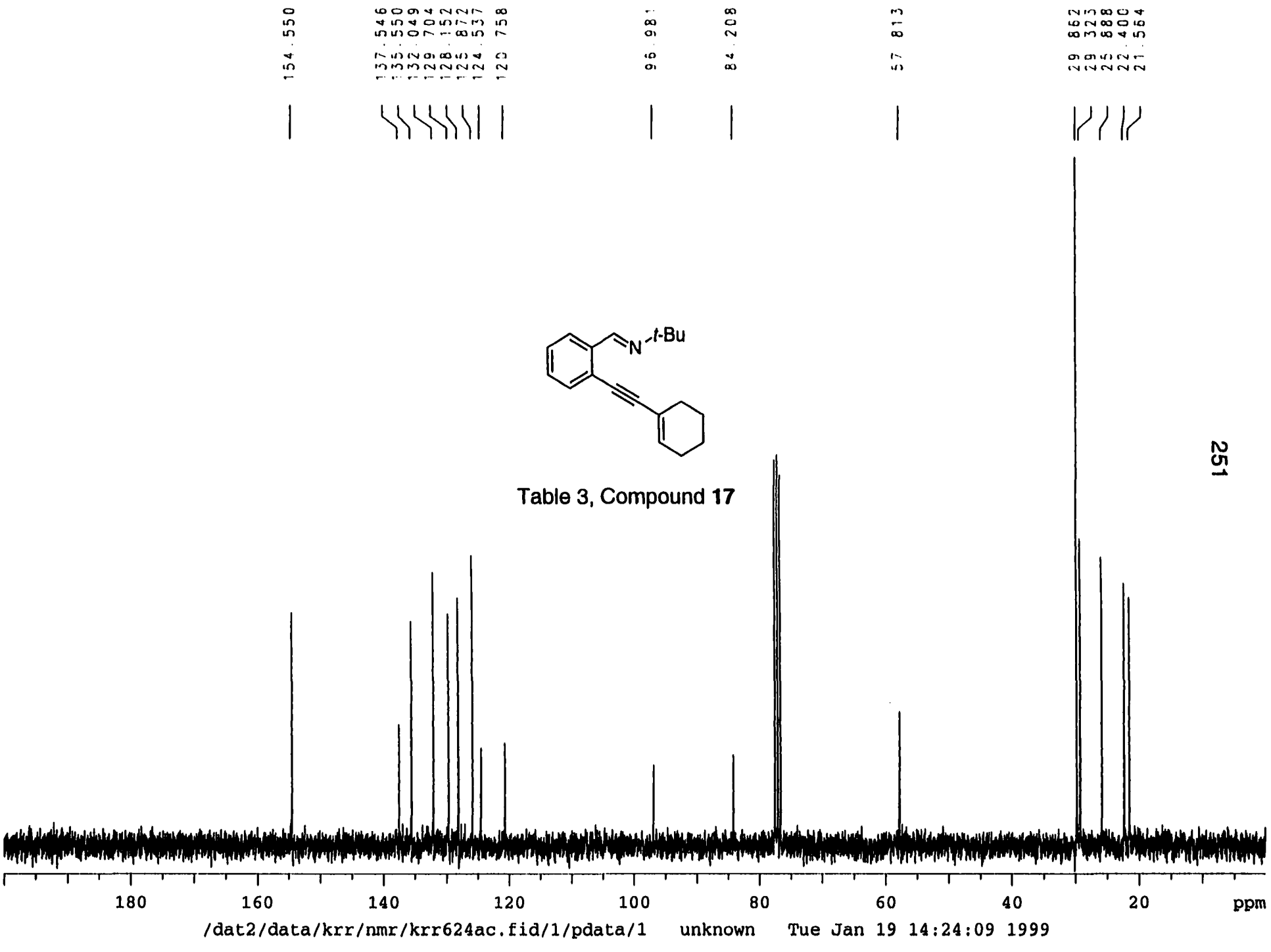


Table 3, Compound **17**

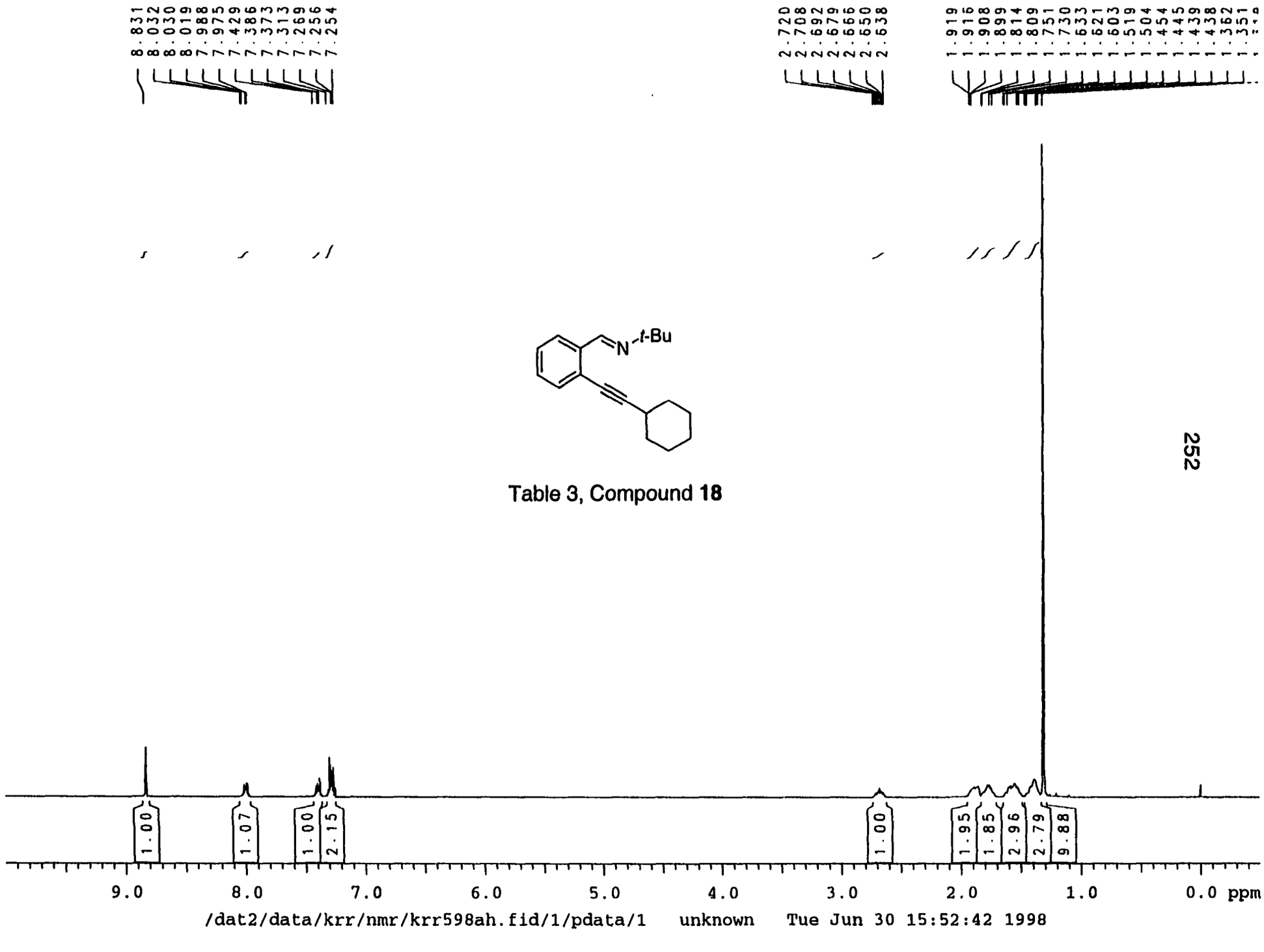


Table 3, Compound **18**

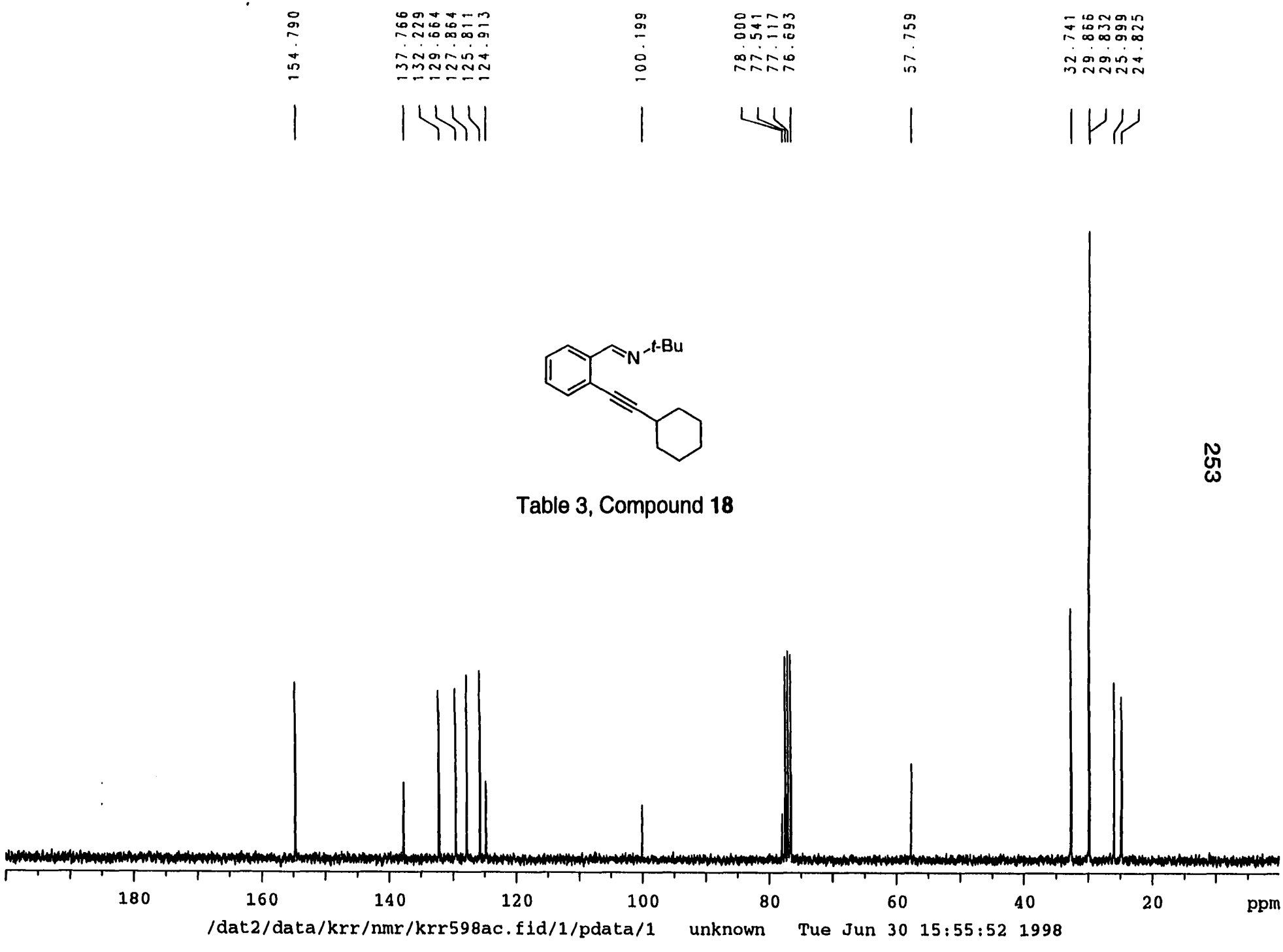


Table 3, Compound **18**

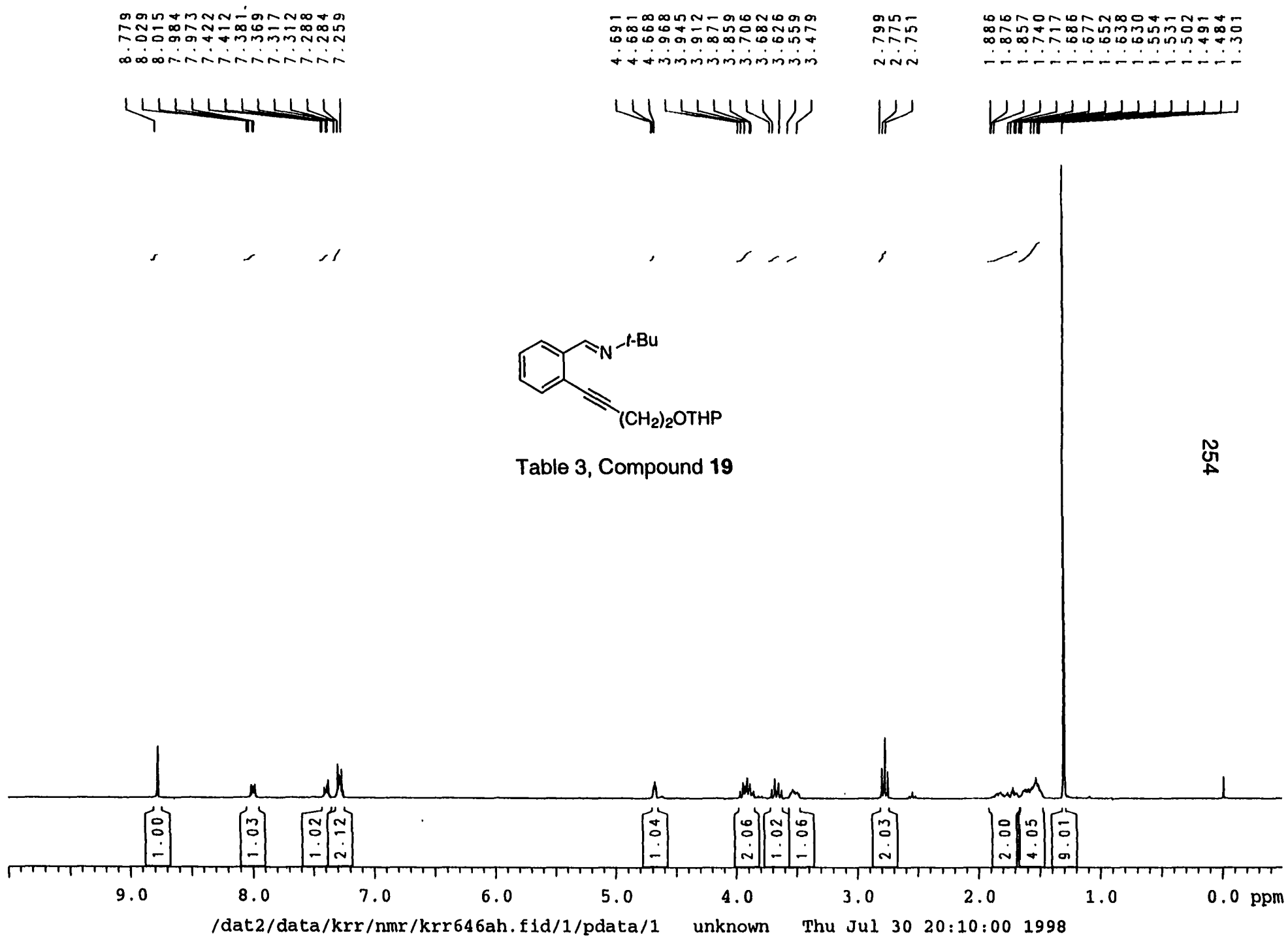


Table 3, Compound **19**

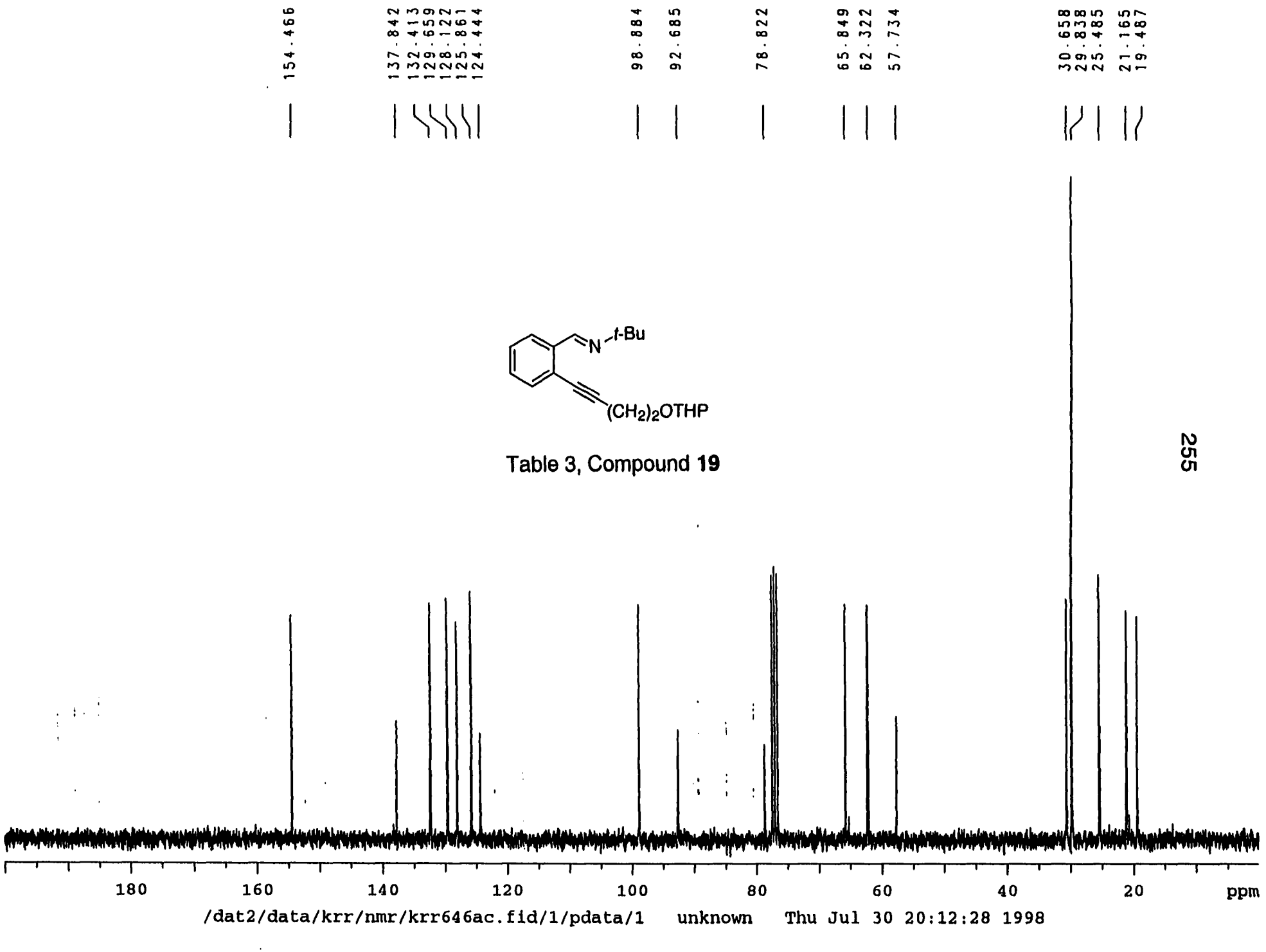
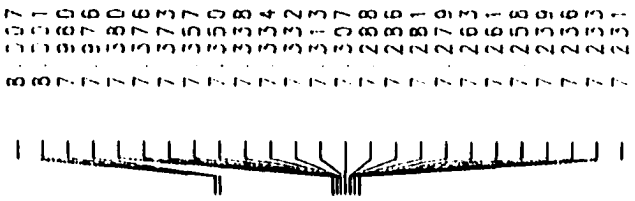
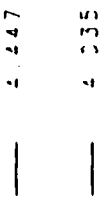
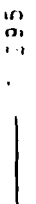


Table 3, Compound **19**







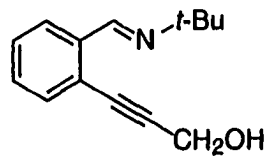
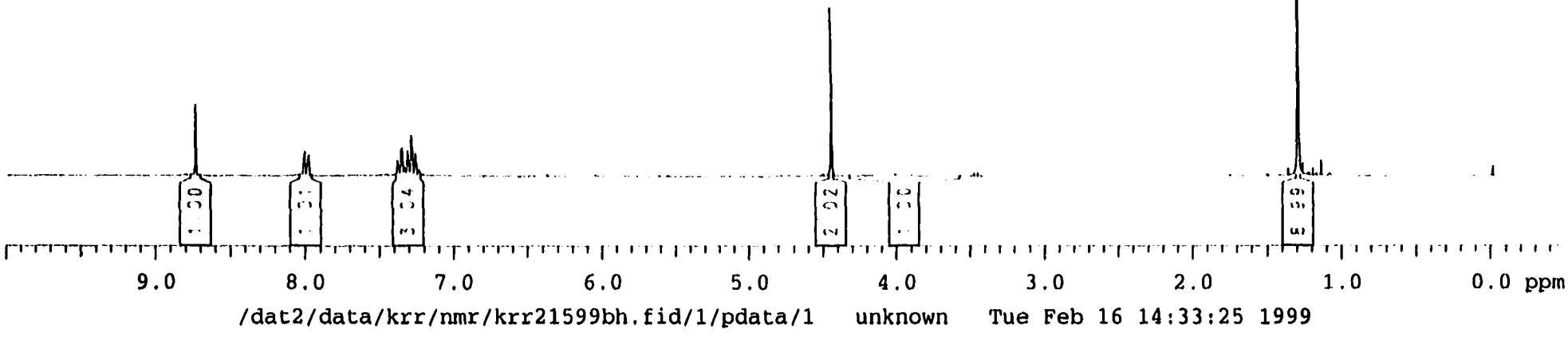


Table 3, Compound **20**



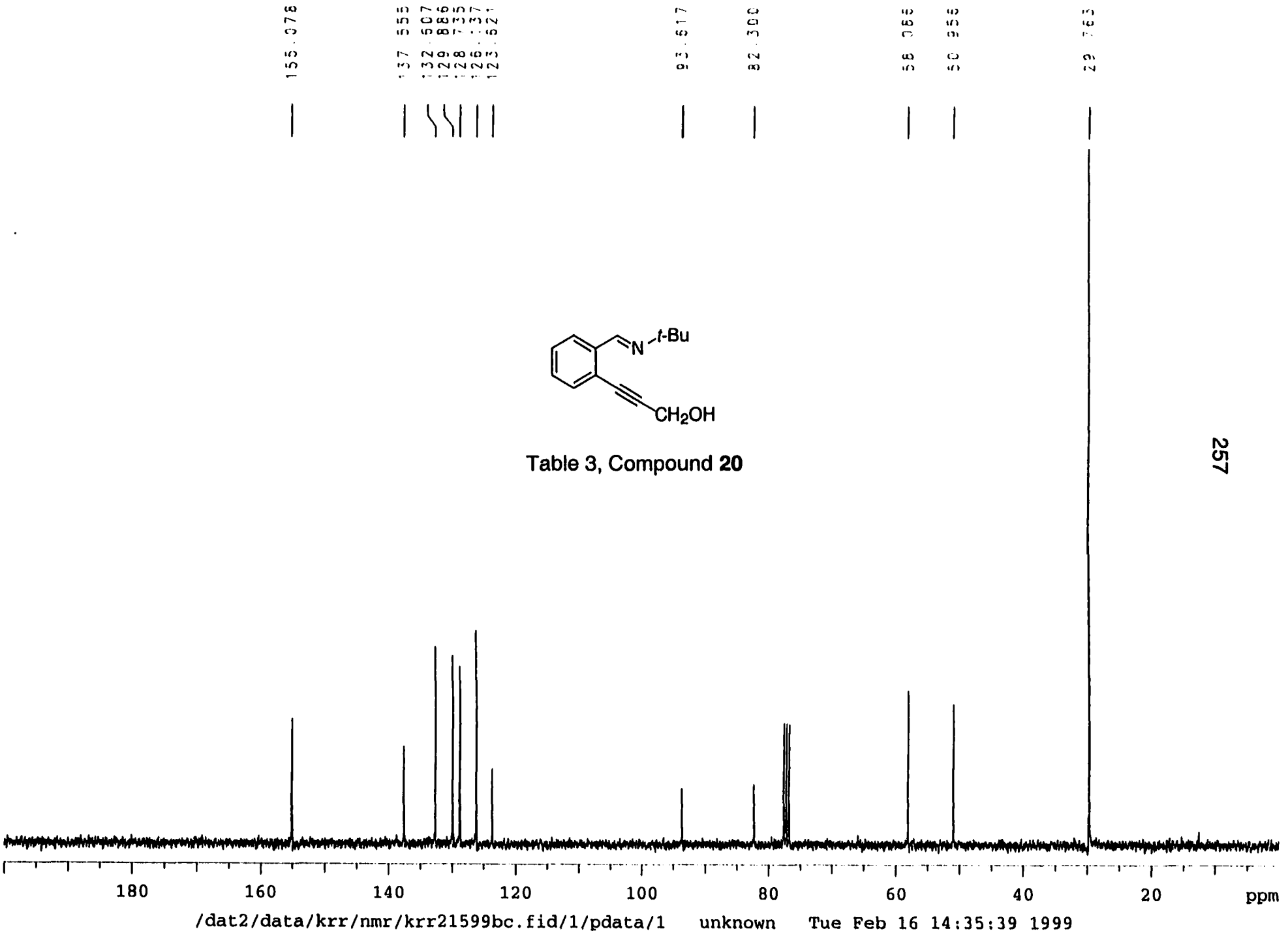


Table 3, Compound **20**

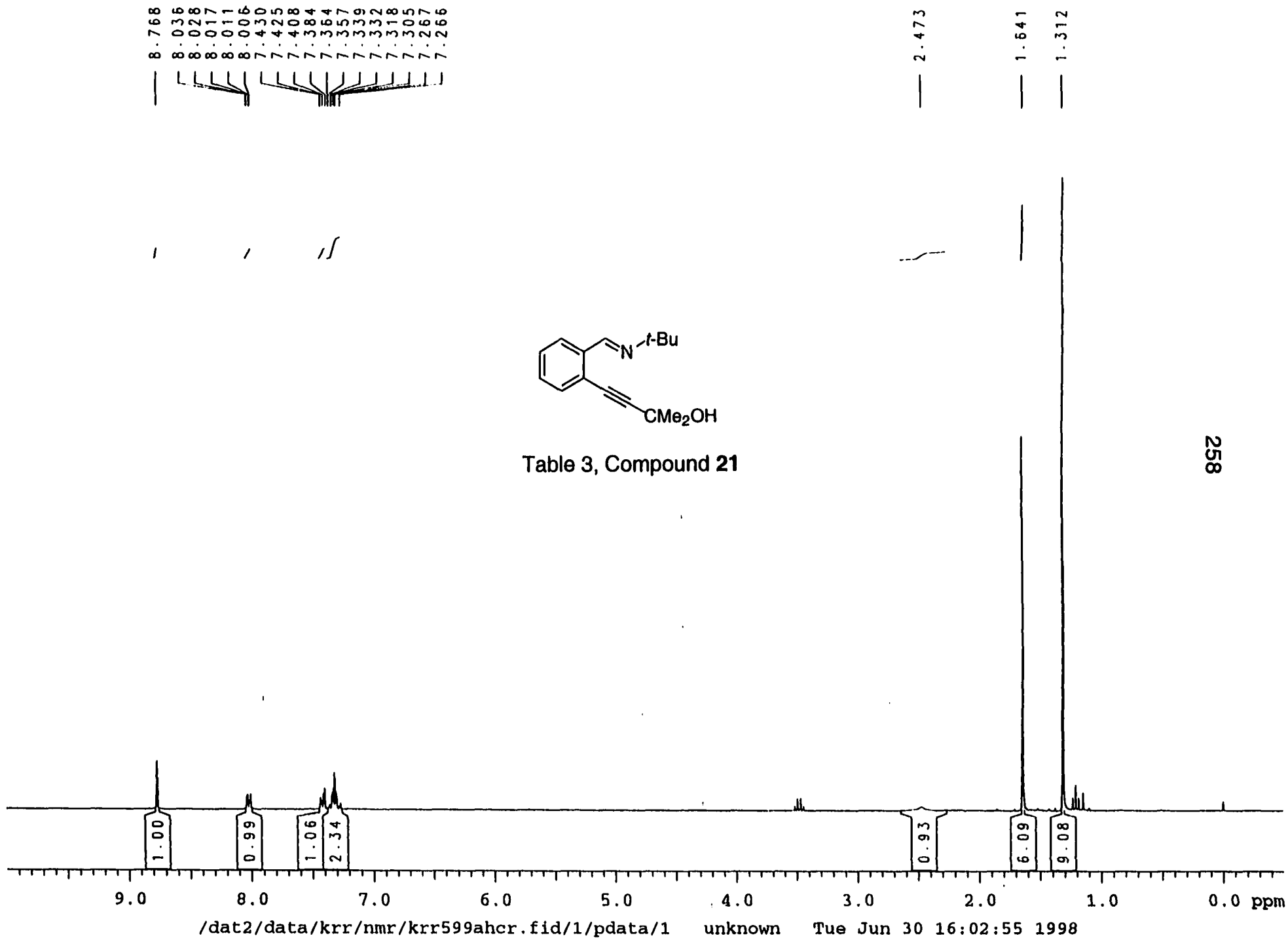


Table 3, Compound **21**

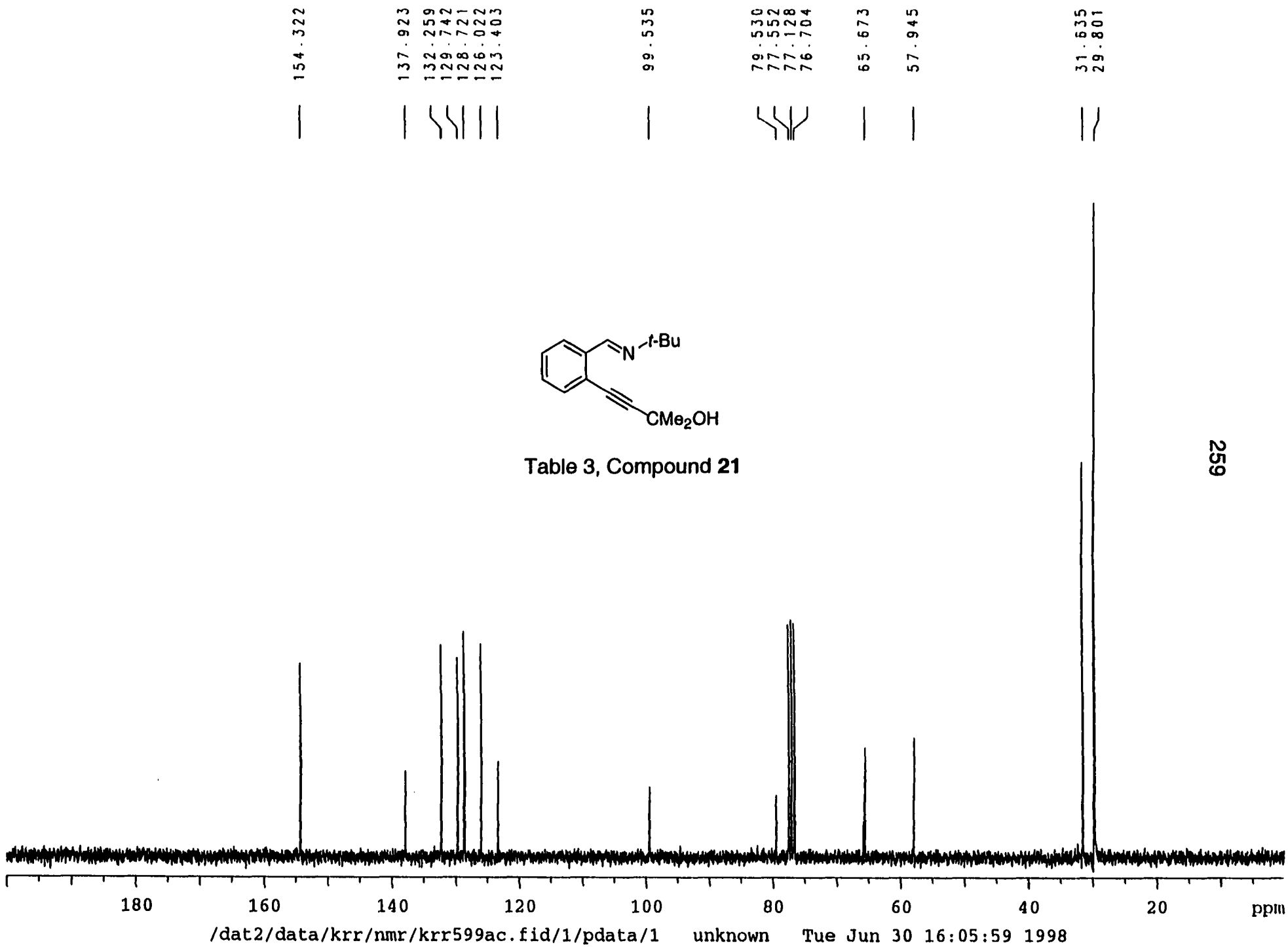
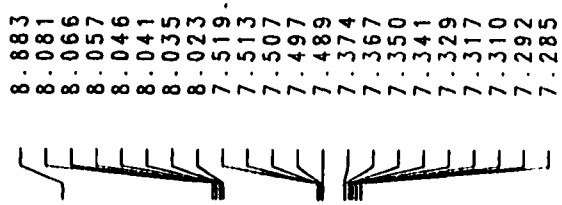


Table 3, Compound **21**



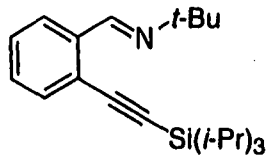


Table 3, Compound **22**

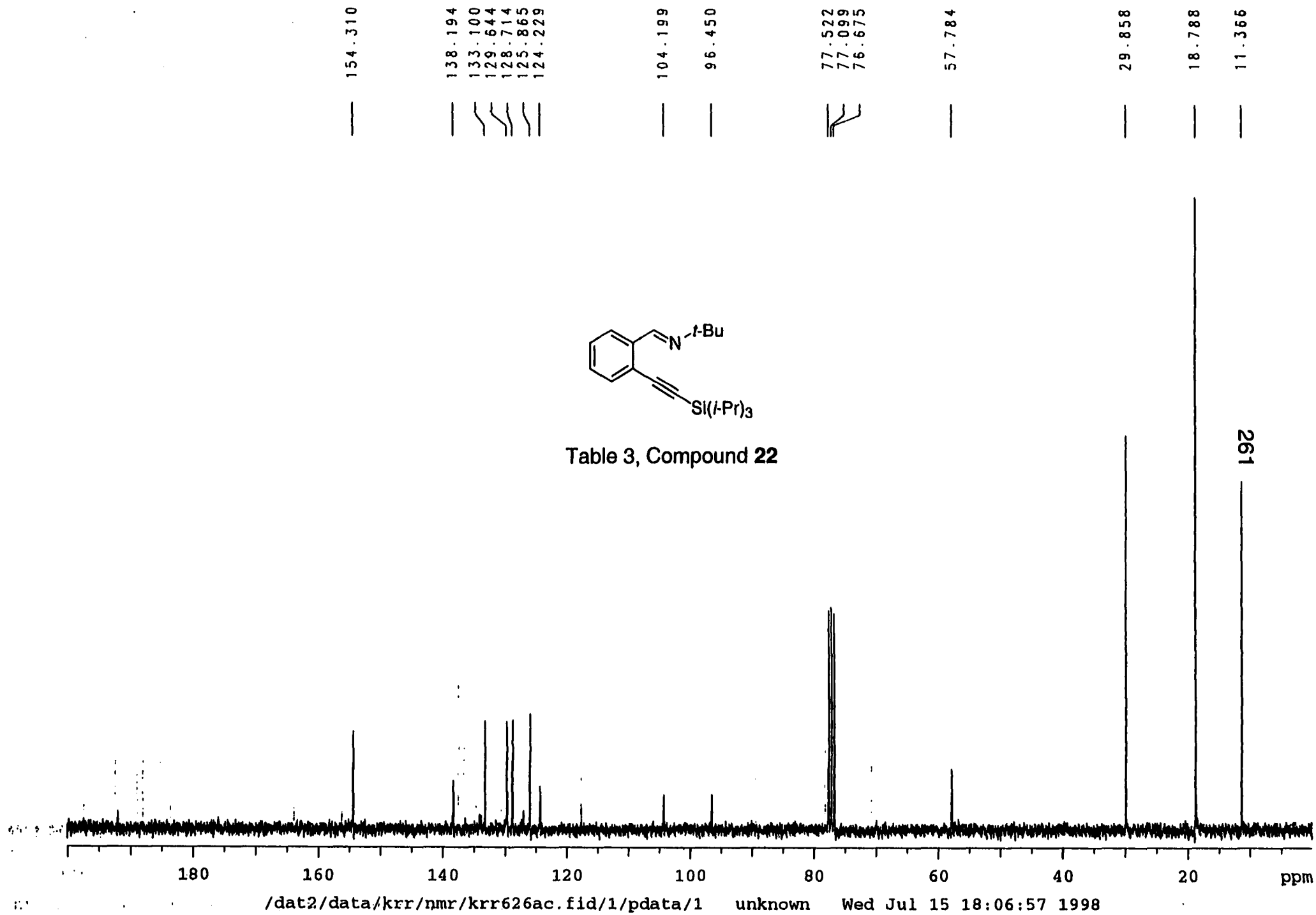


Table 3, Compound **22**

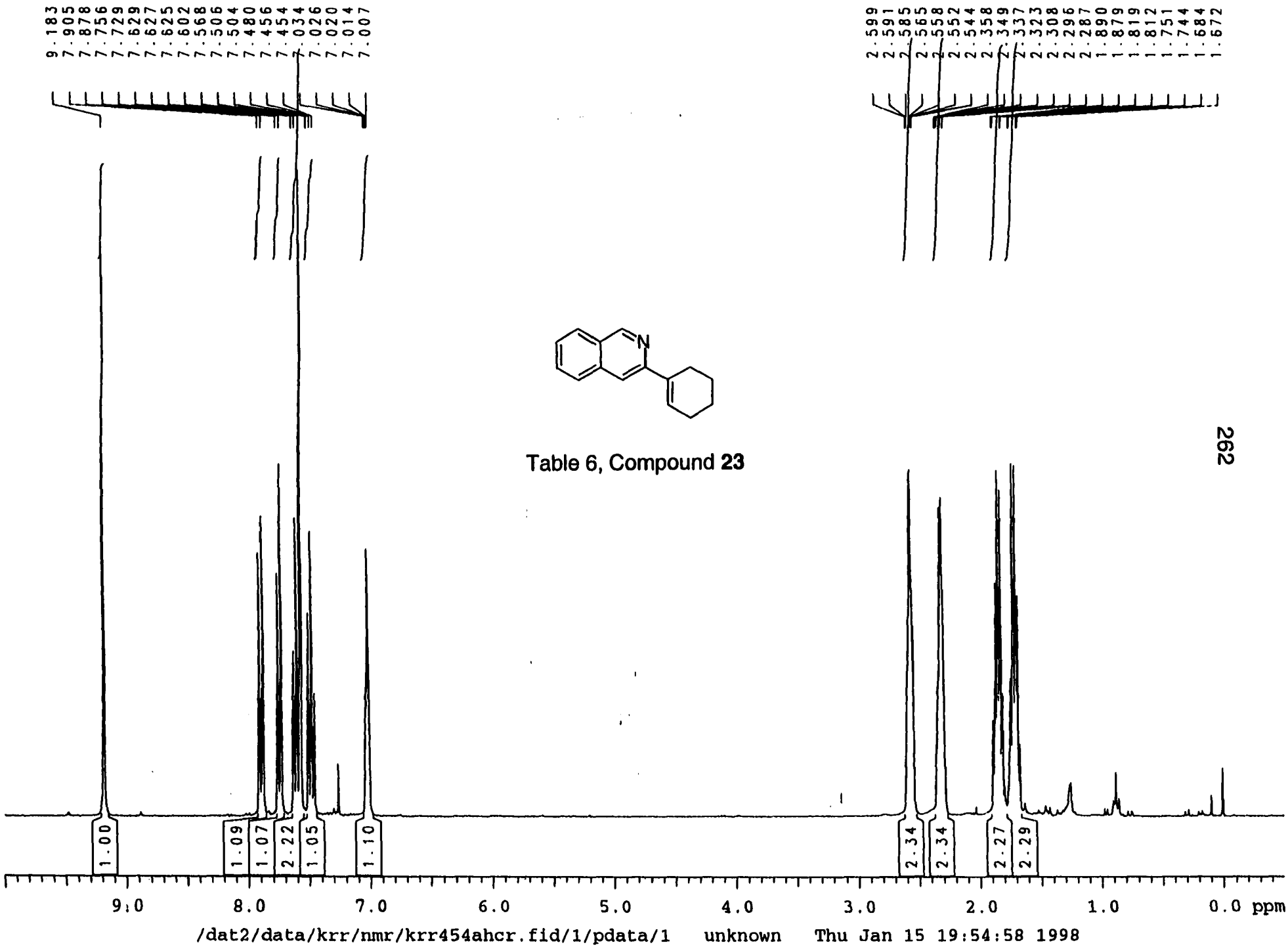
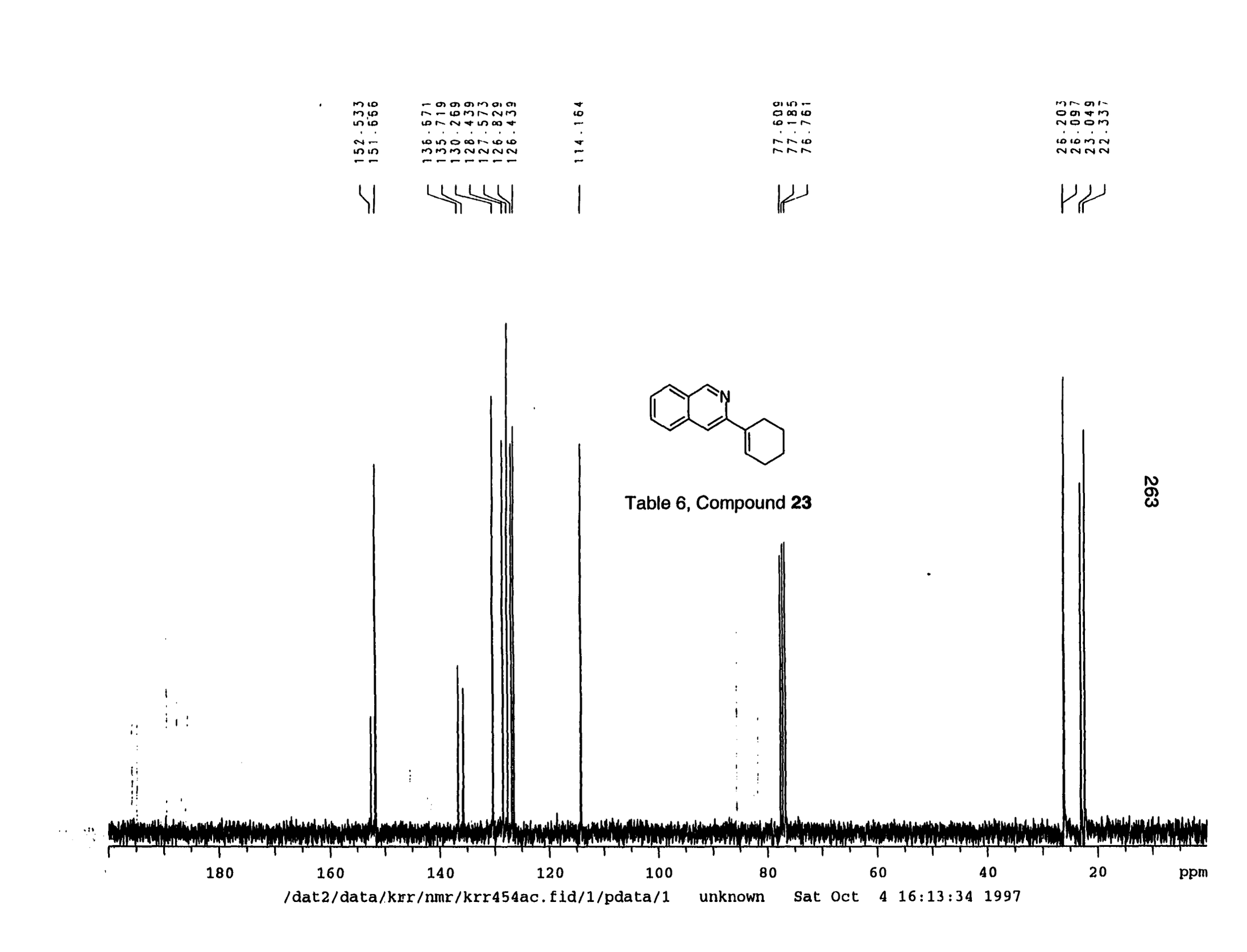


Table 6, Compound **23**


152.533
151.666
136.671
135.719
130.269
128.439
127.573
126.829
126.439
114.164
77.609
77.185
76.761
26.203
26.097
23.049
22.337
N
Table 6, Compound 23
263
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr454ac.fid/1/pdata/1 unknown Sat Oct 4 16:13:34 1997

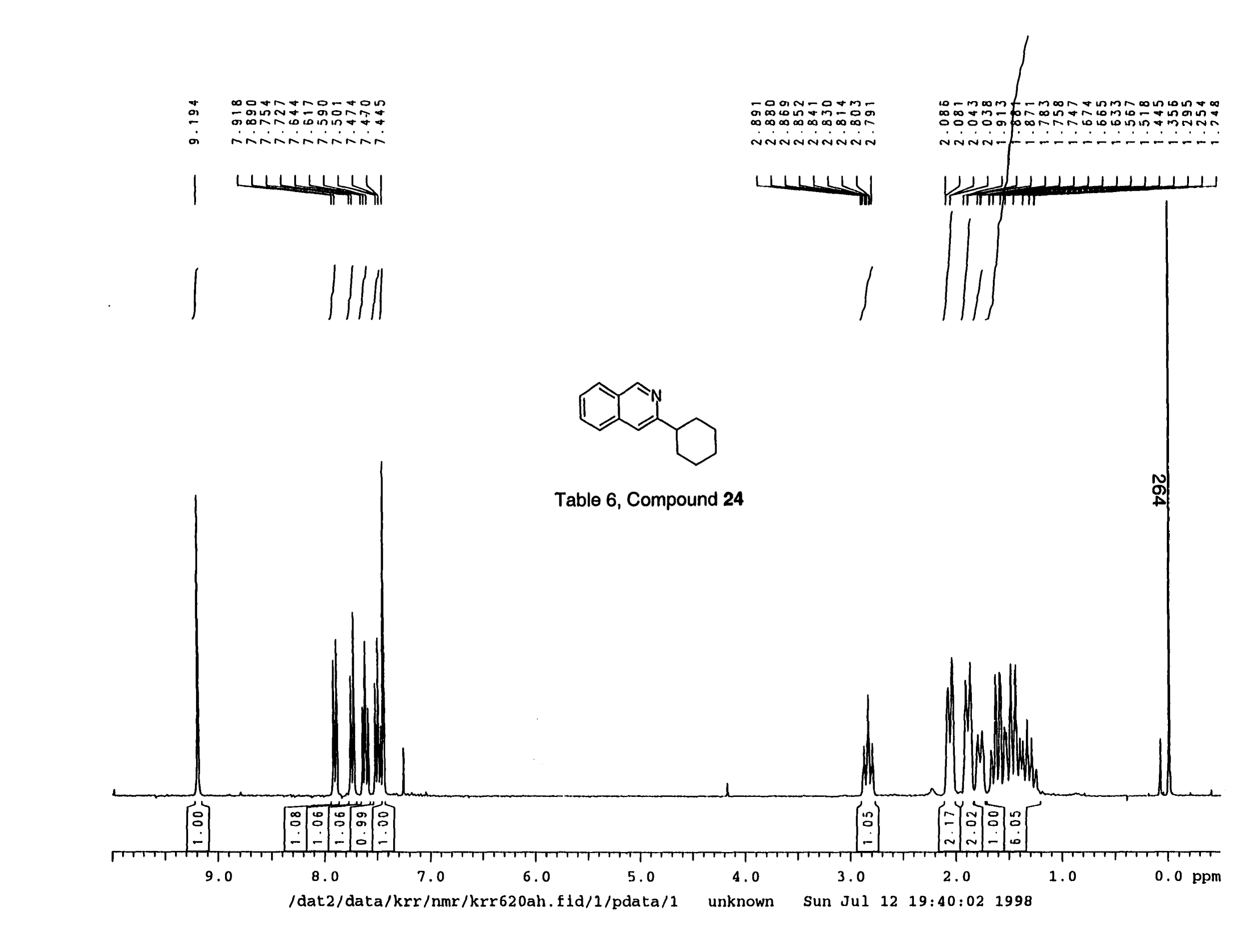


Table 6, Compound **24**

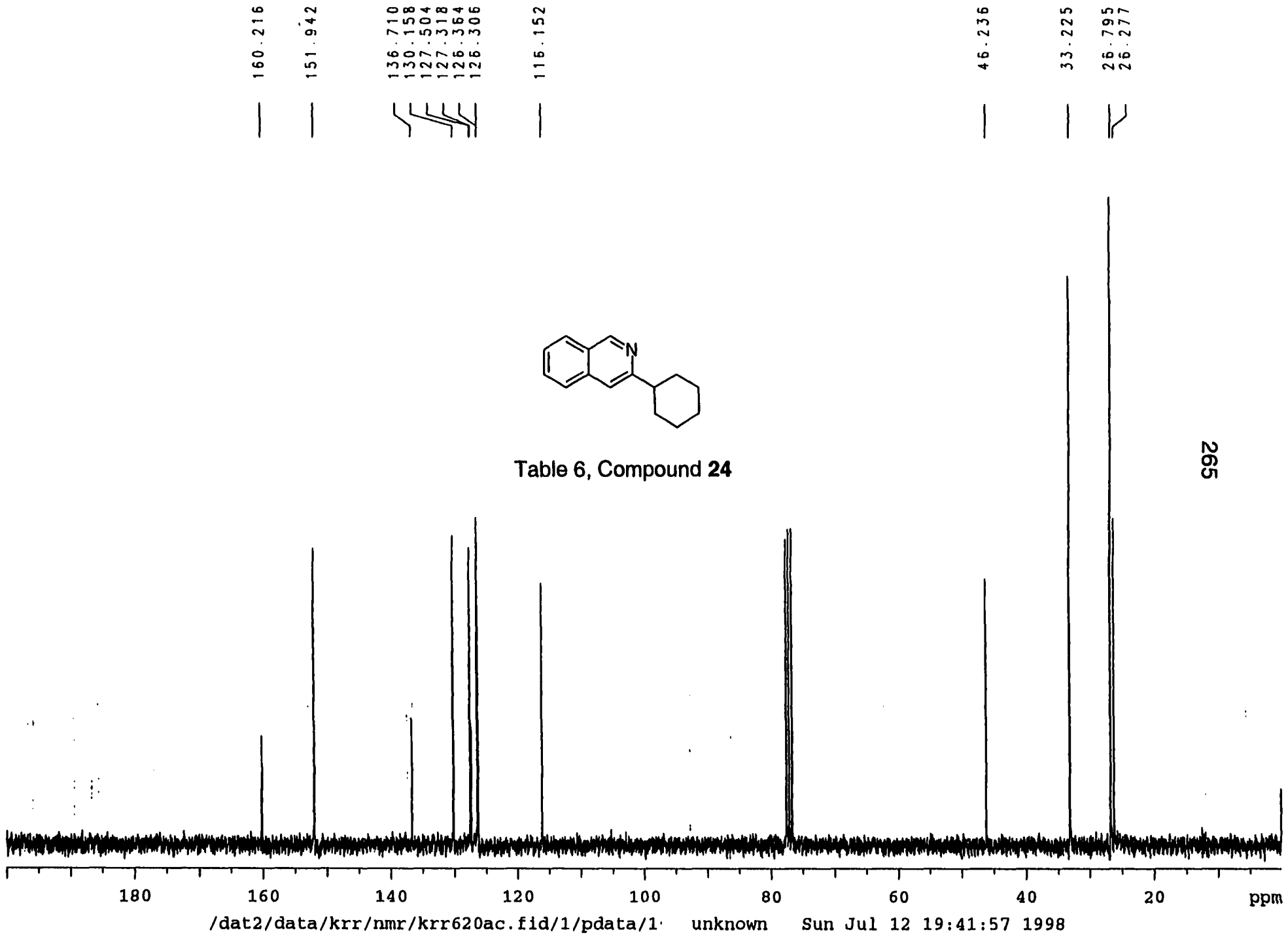


Table 6, Compound **24**

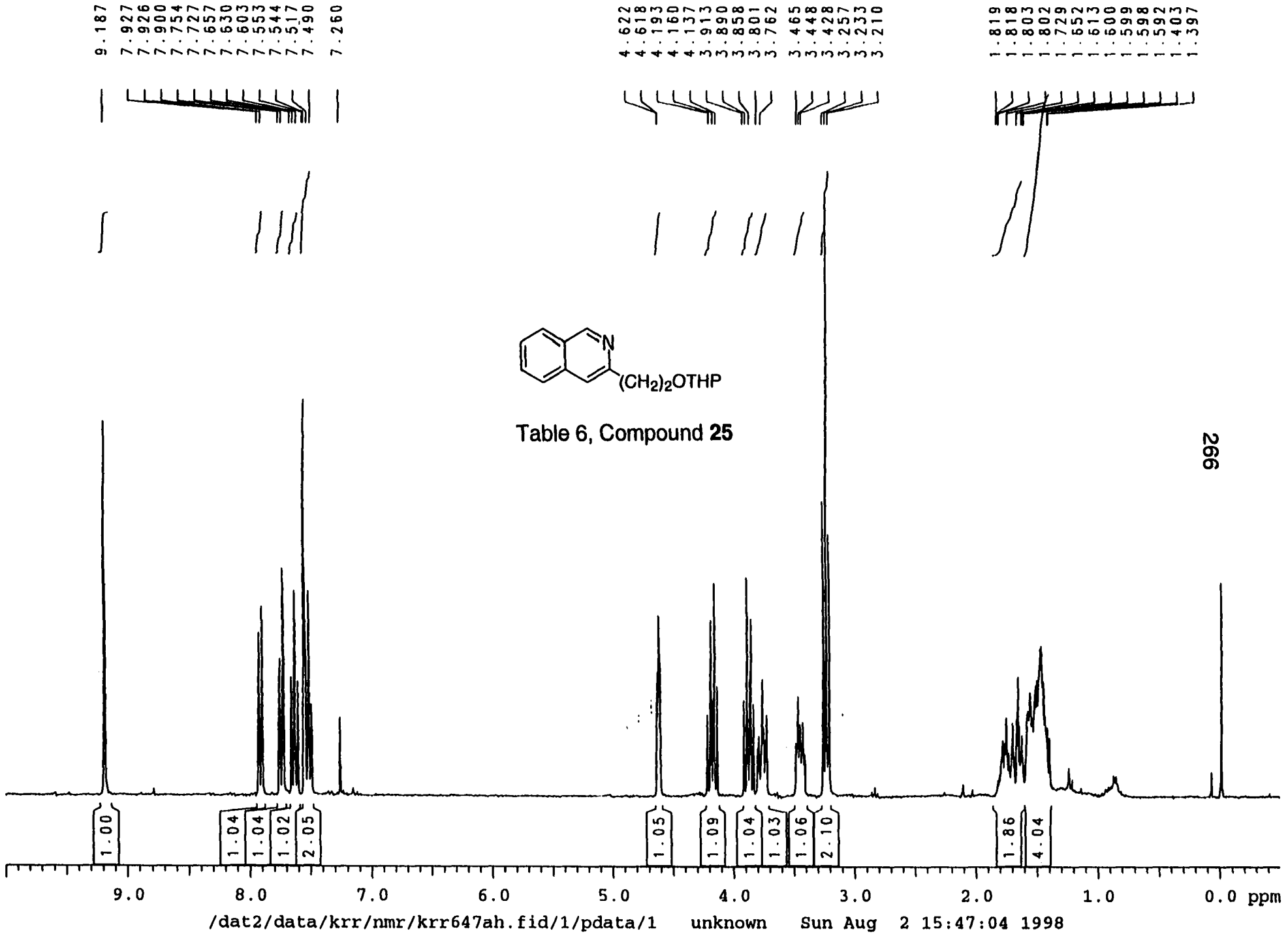
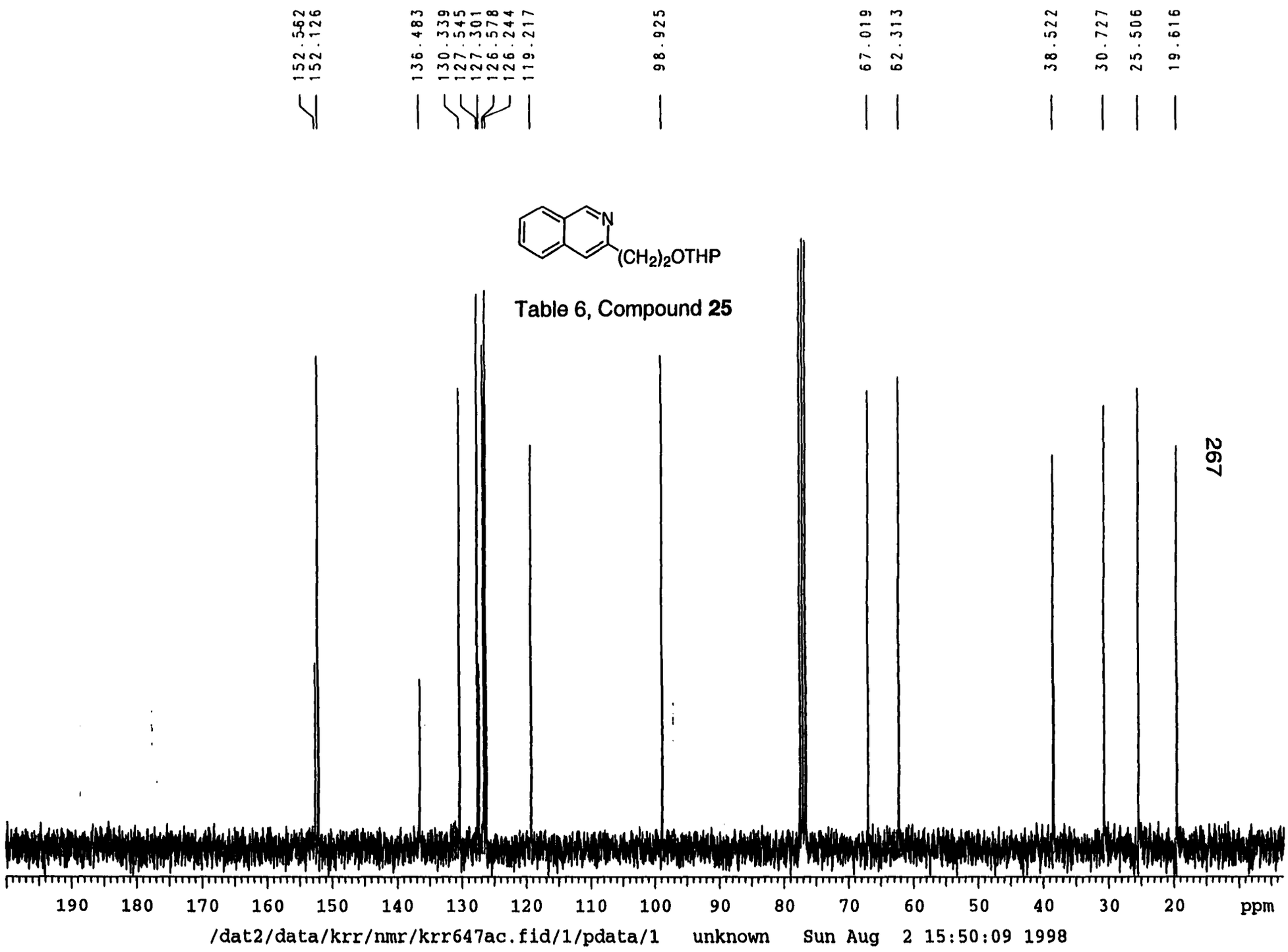


Table 6, Compound **25**


152.562
152.126
136.483
130.339
127.545
127.301
126.578
126.244
119.217
98.925
67.019
62.313
38.522
30.727
25.506
19.616
N
(CH2)2OTHP
Table 6, Compound 25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm
/dat2/data/krr/nmr/krr647ac.fid/1/pdata/1 unknown Sun Aug 2 15:50:09 1998

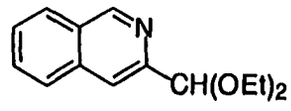
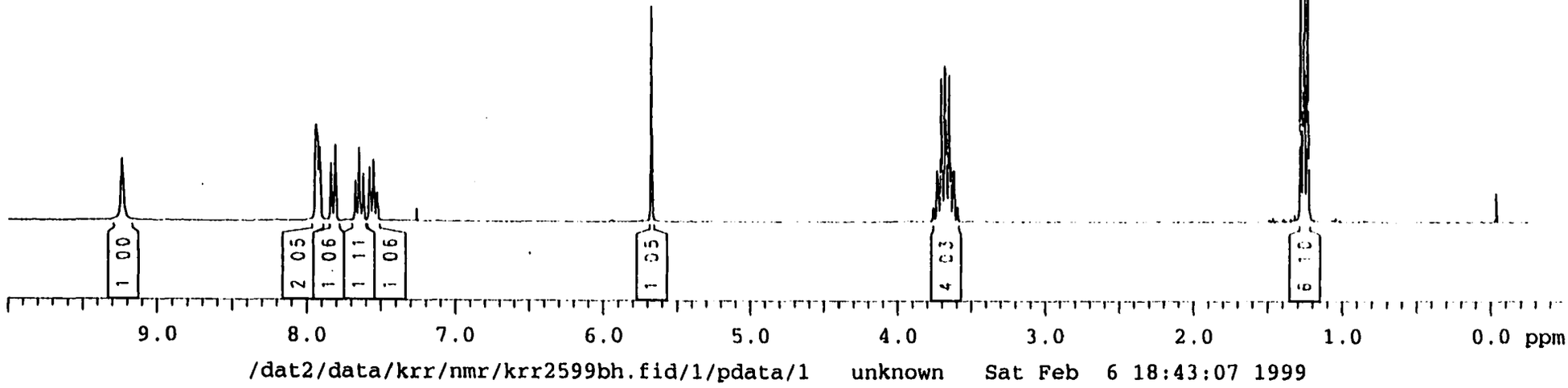
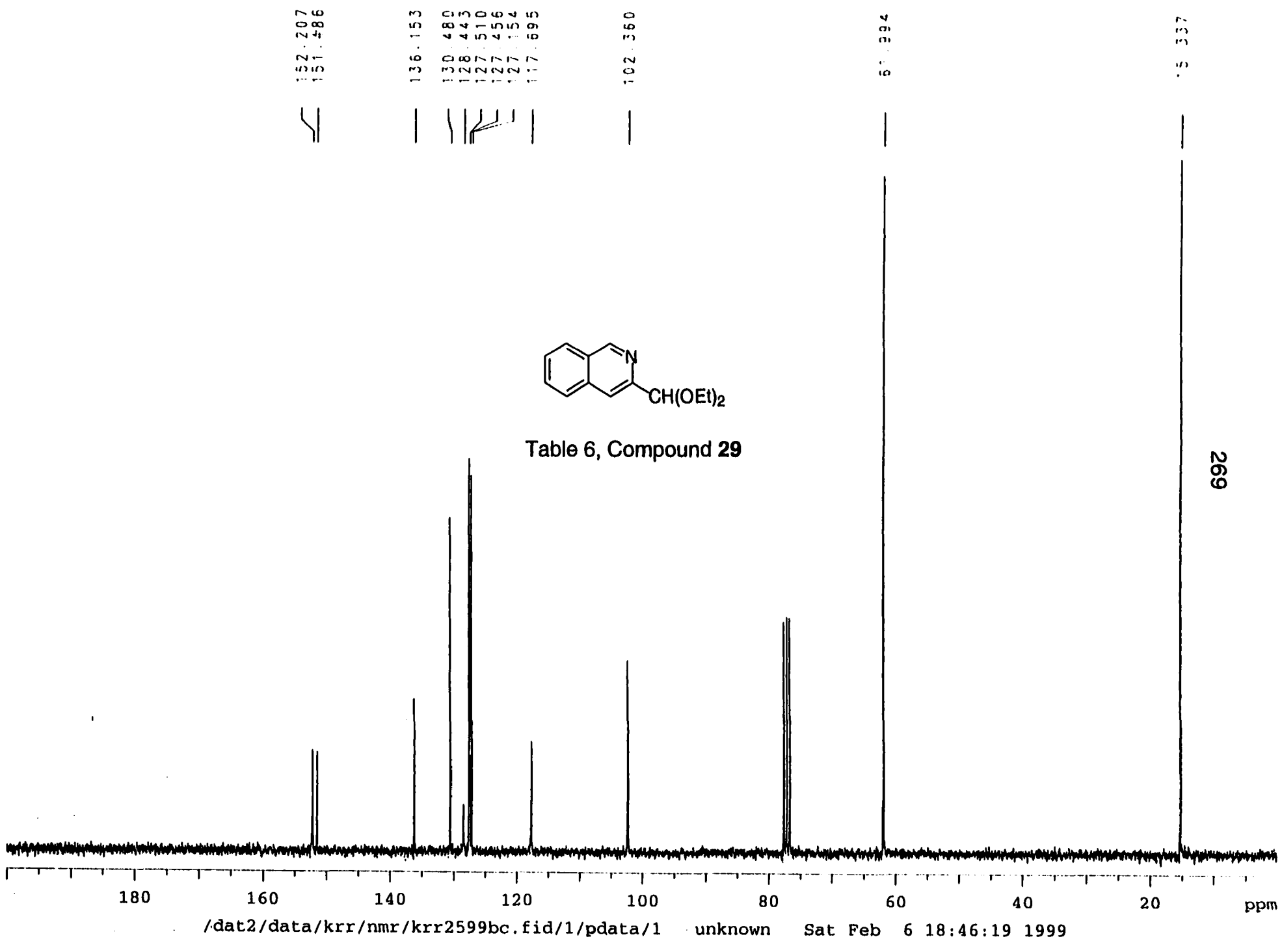


Table 6, Compound **29**




152.207
151.486
136.153
130.480
128.443
127.510
127.456
127.154
117.695
102.360
61.994
15.337
N
CH(OEt)2
Table 6, Compound 29
269
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr2599bc.fid/1/pdata/1 unknown Sat Feb 6 18:46:19 1999

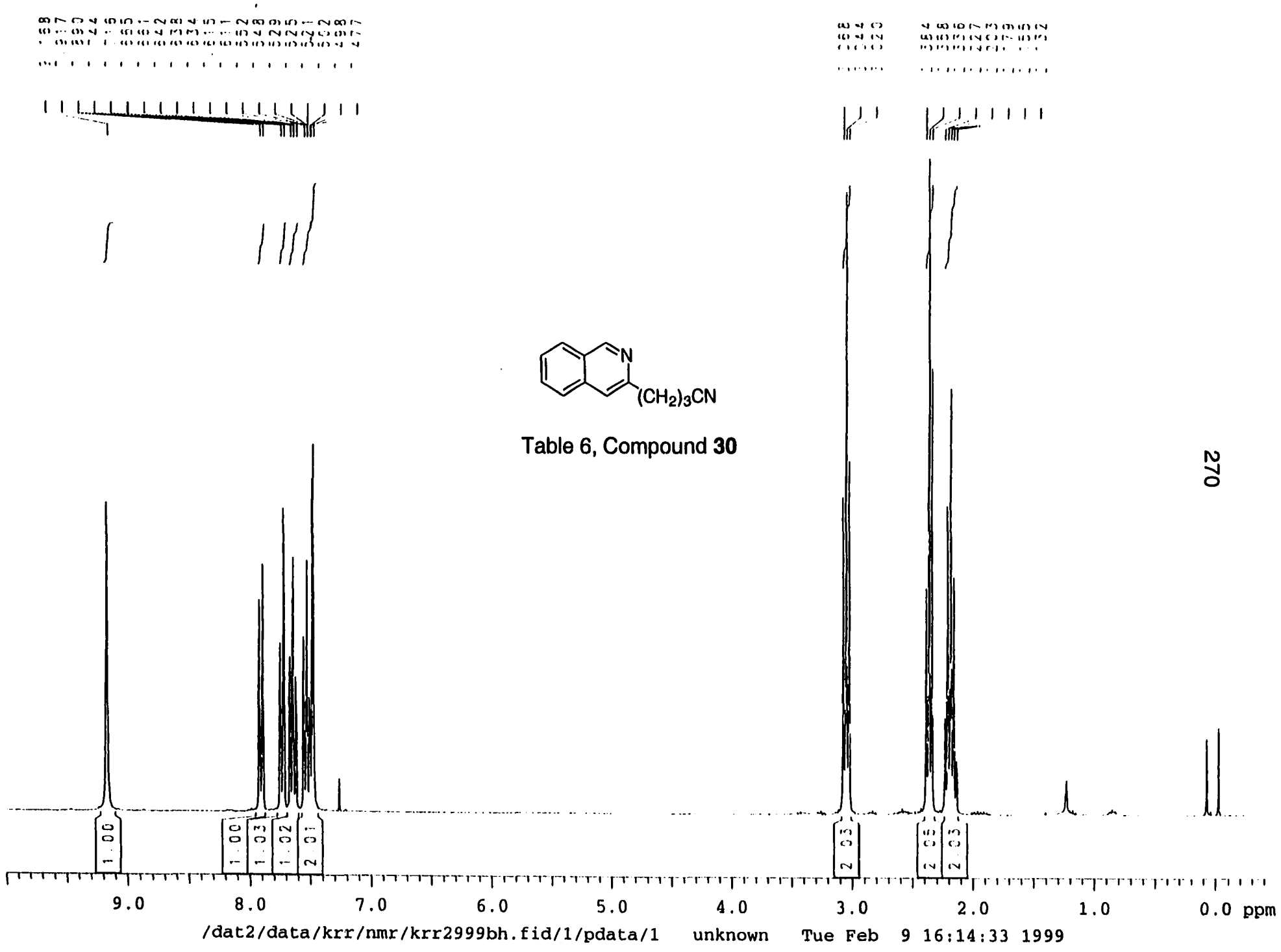
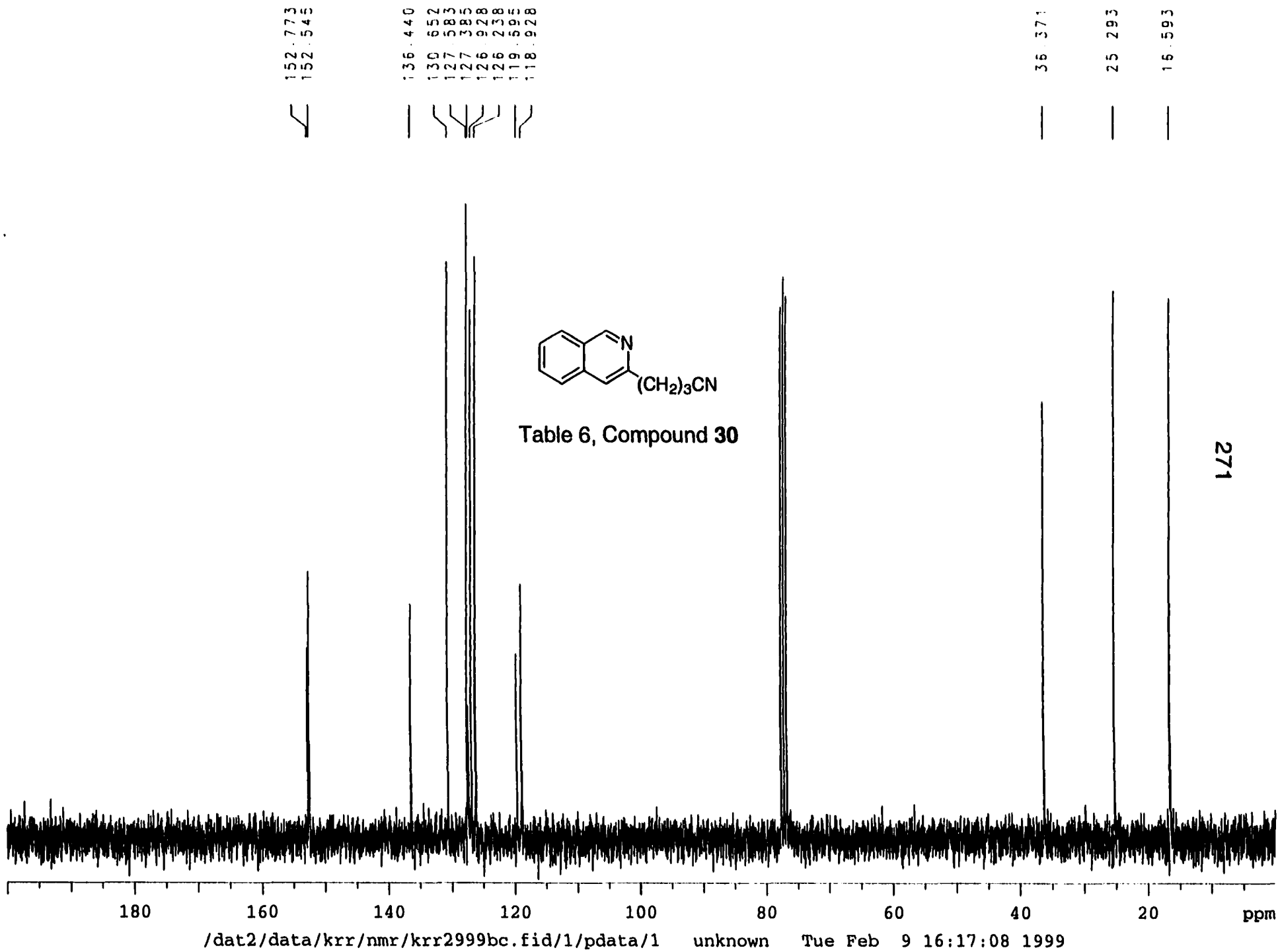


Table 6, Compound **30**


152.773
152.545
136.440
130.652
127.583
127.385
126.928
126.238
119.695
118.928
36.371
25.293
16.593
N
(CH2)3CN
Table 6, Compound 30
271
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr2999bc.fid/1/pdata/1 unknown Tue Feb 9 16:17:08 1999

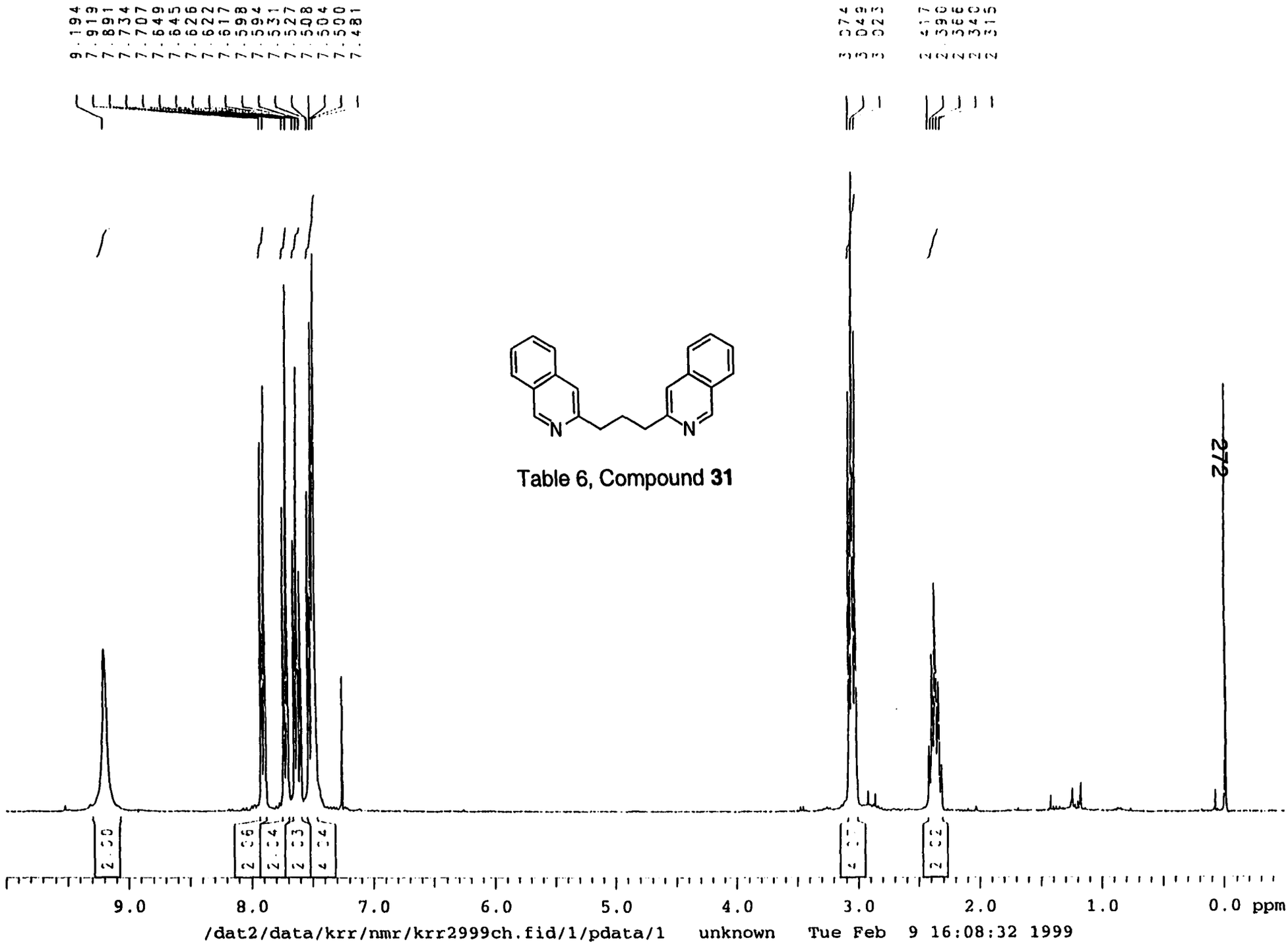


Table 6, Compound **31**

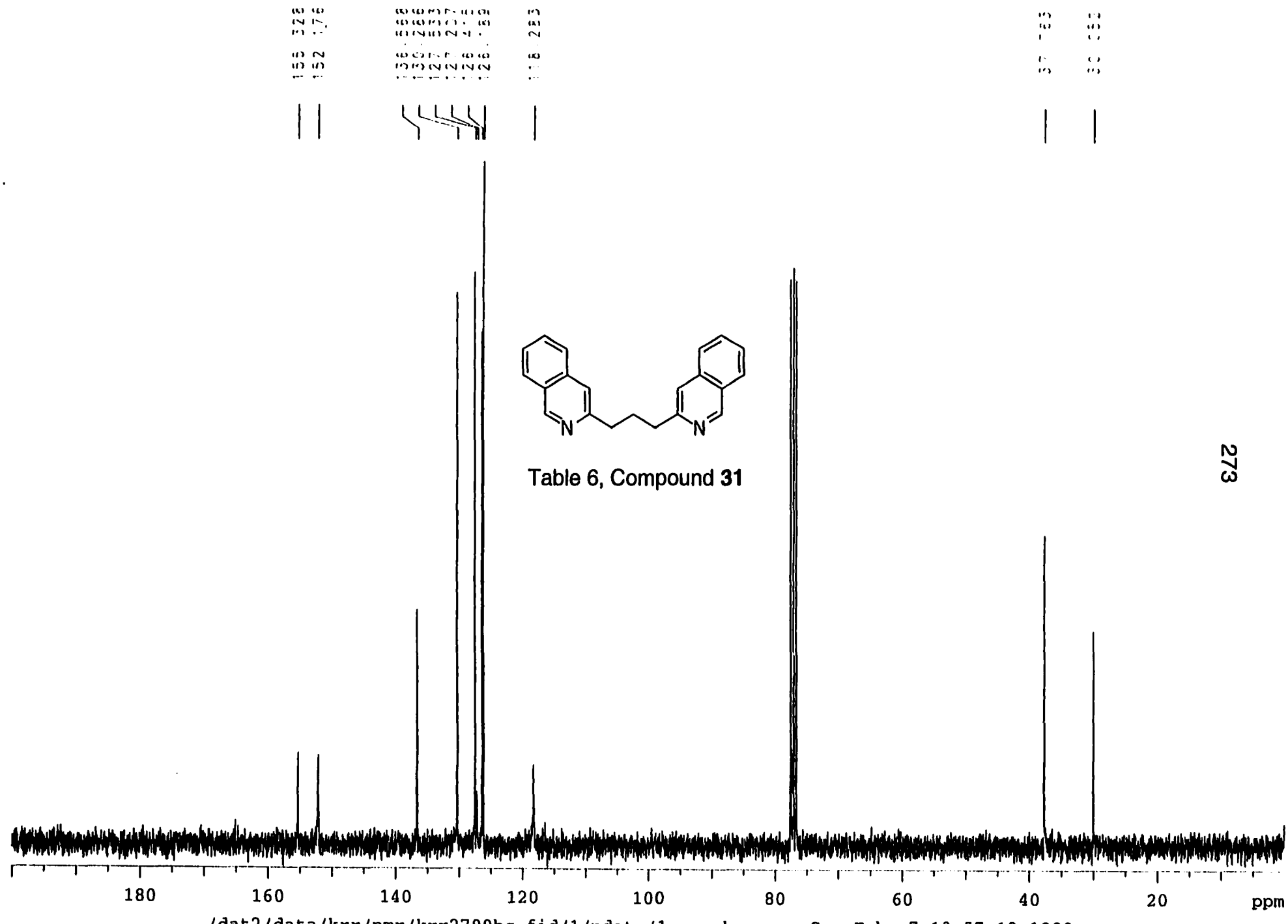


Table 6, Compound **31**

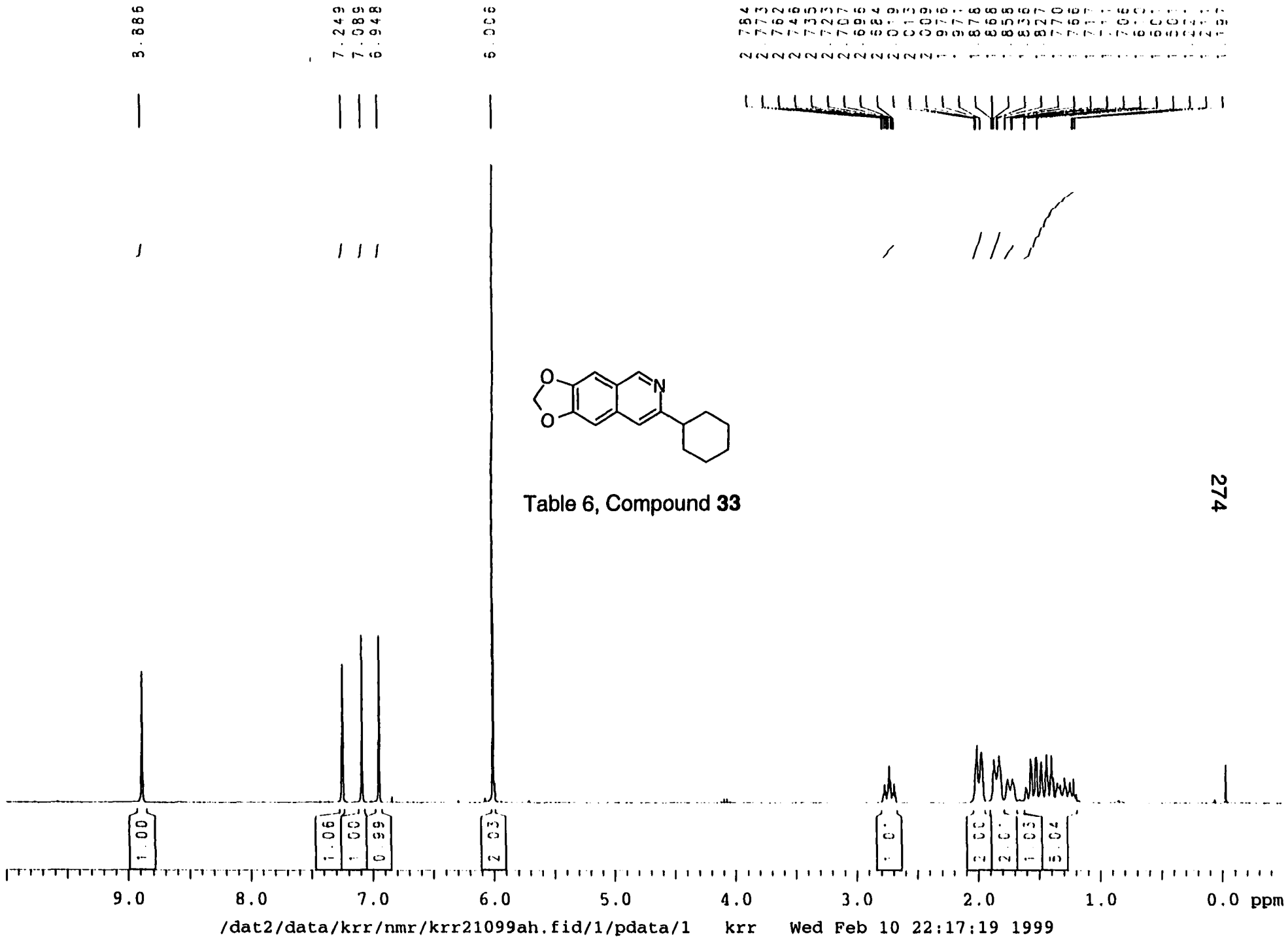


Table 6, Compound **33**

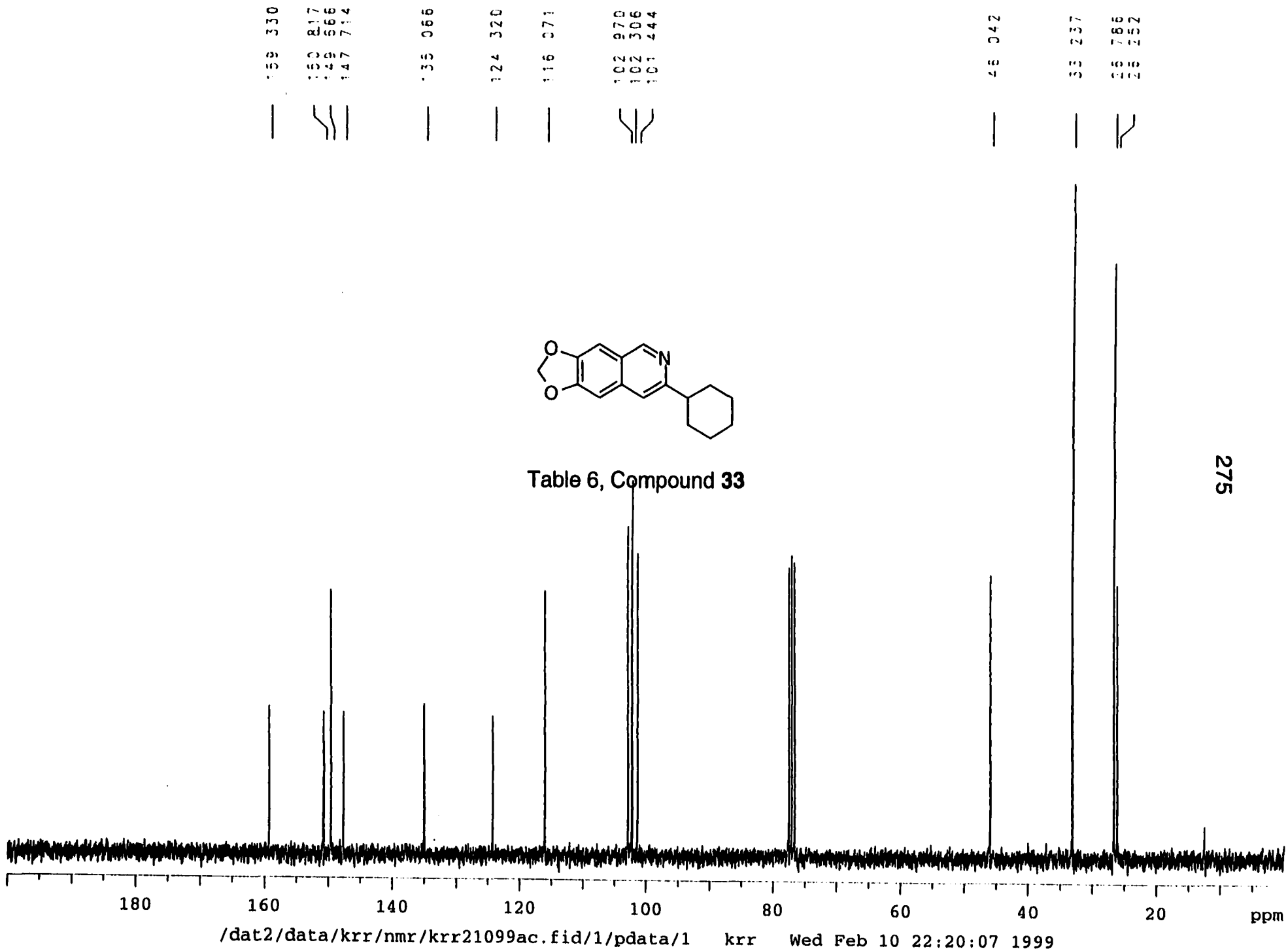


Table 6, Compound **33**

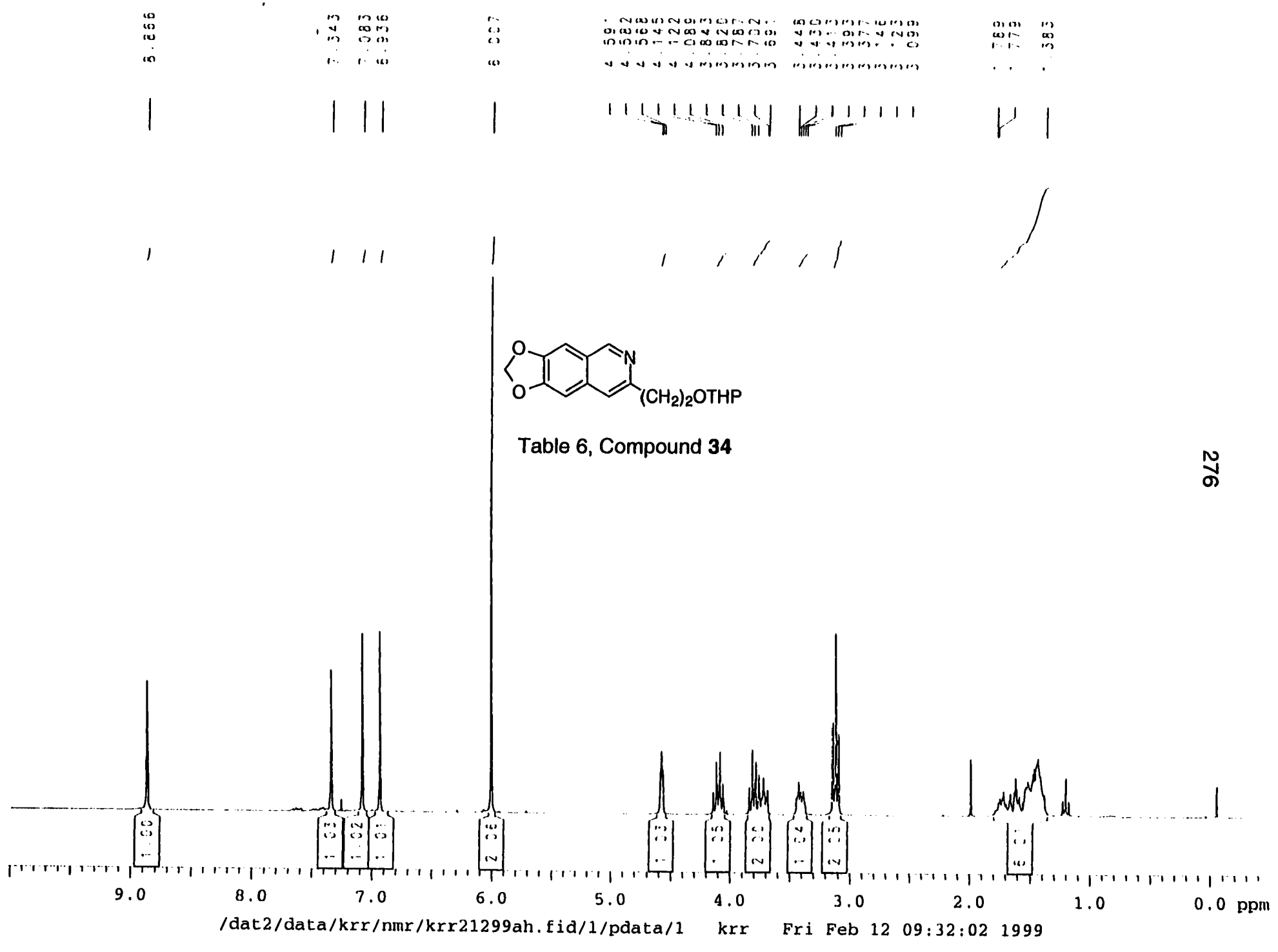


Table 6, Compound **34**

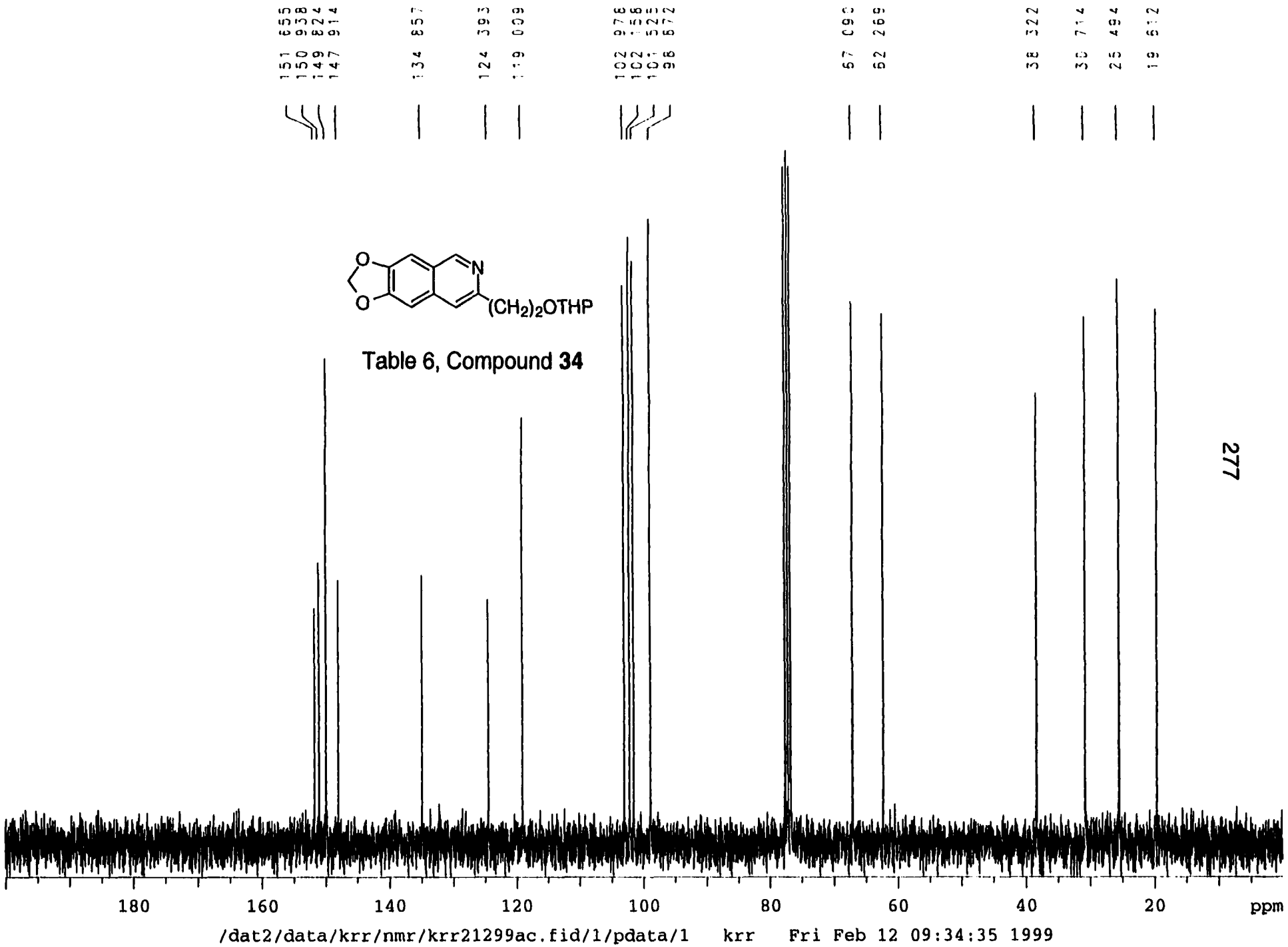


Table 6, Compound **34**

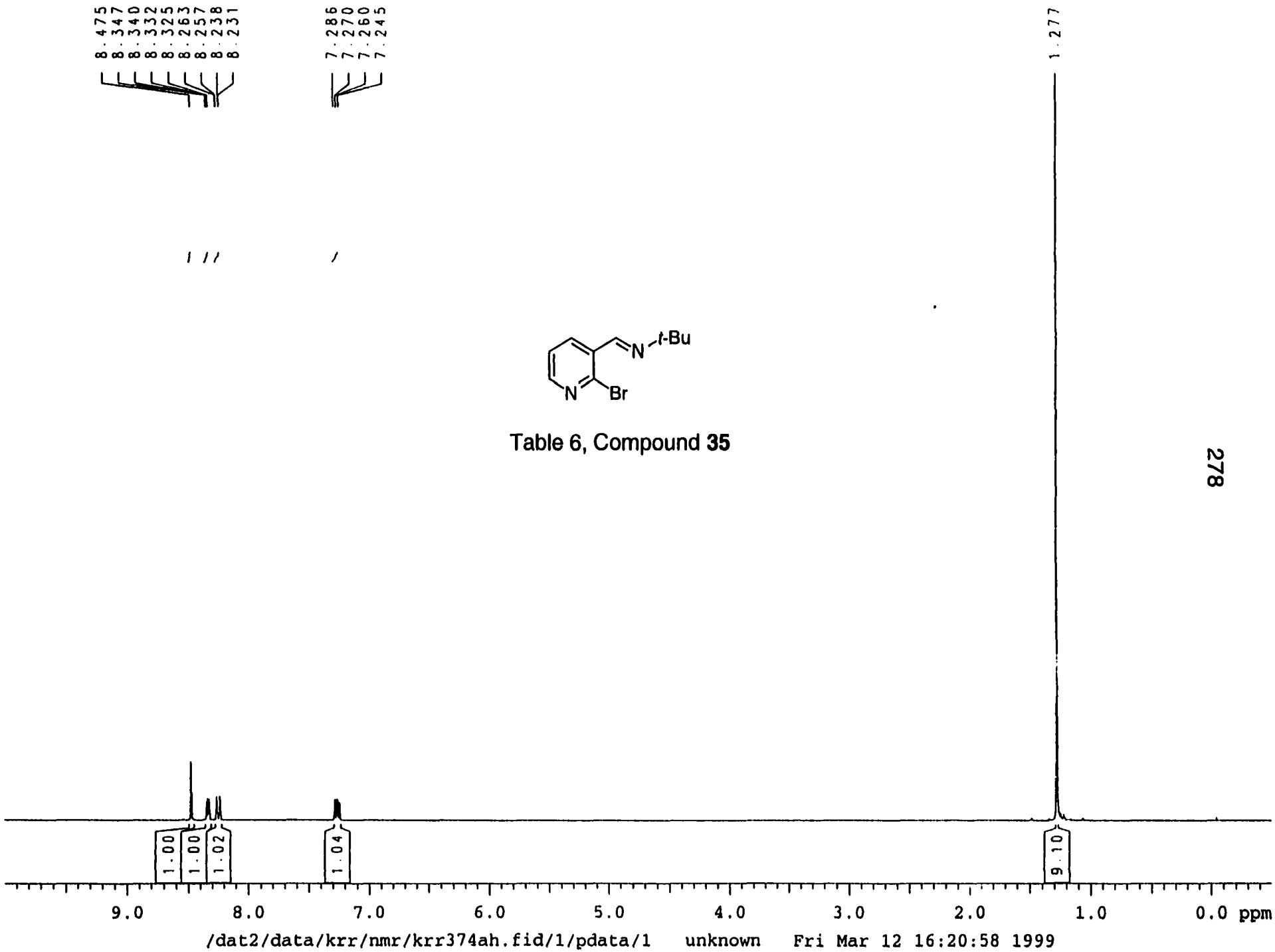


Table 6, Compound **35**

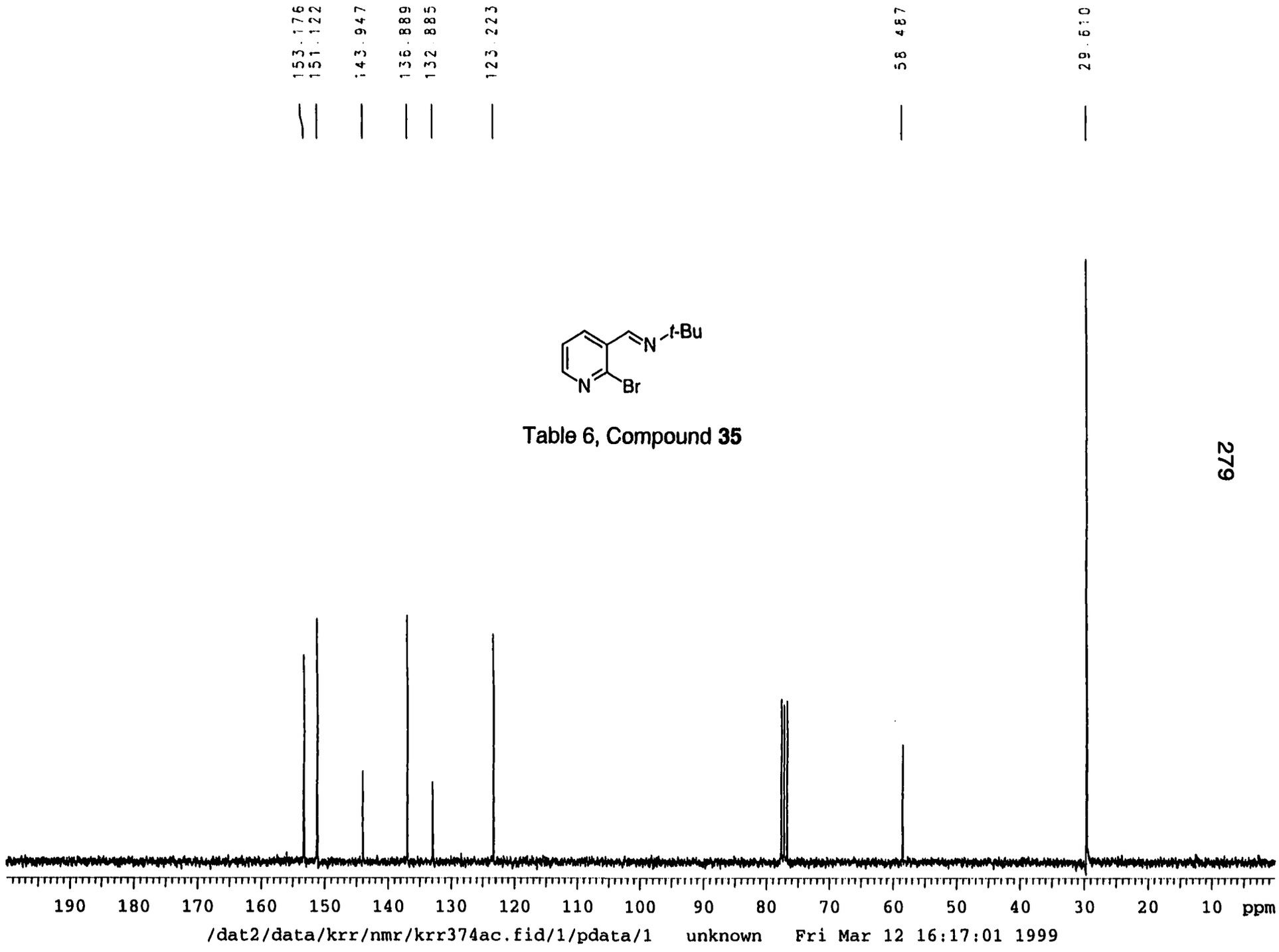


Table 6, Compound **35**

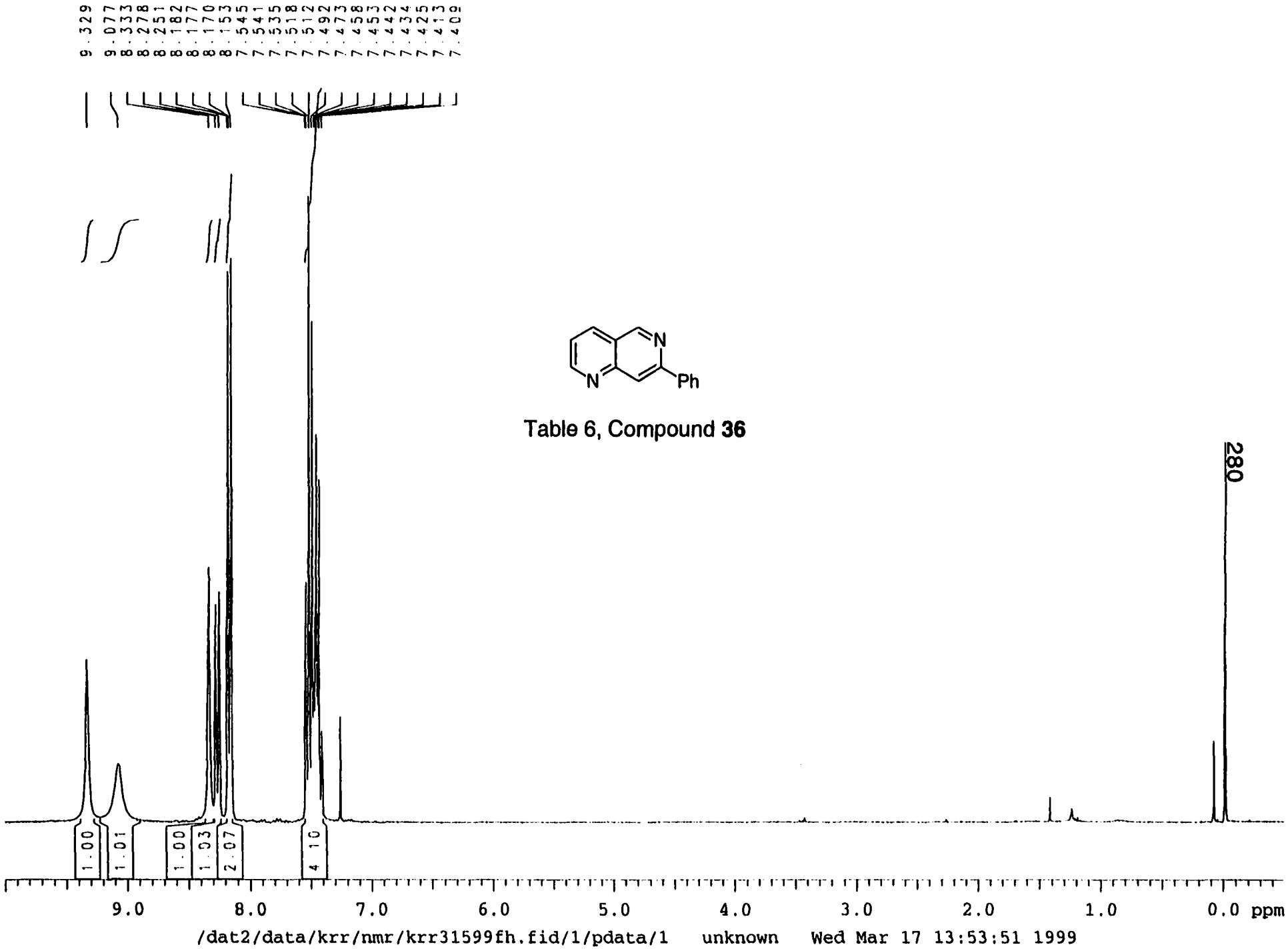


Table 6, Compound **36**

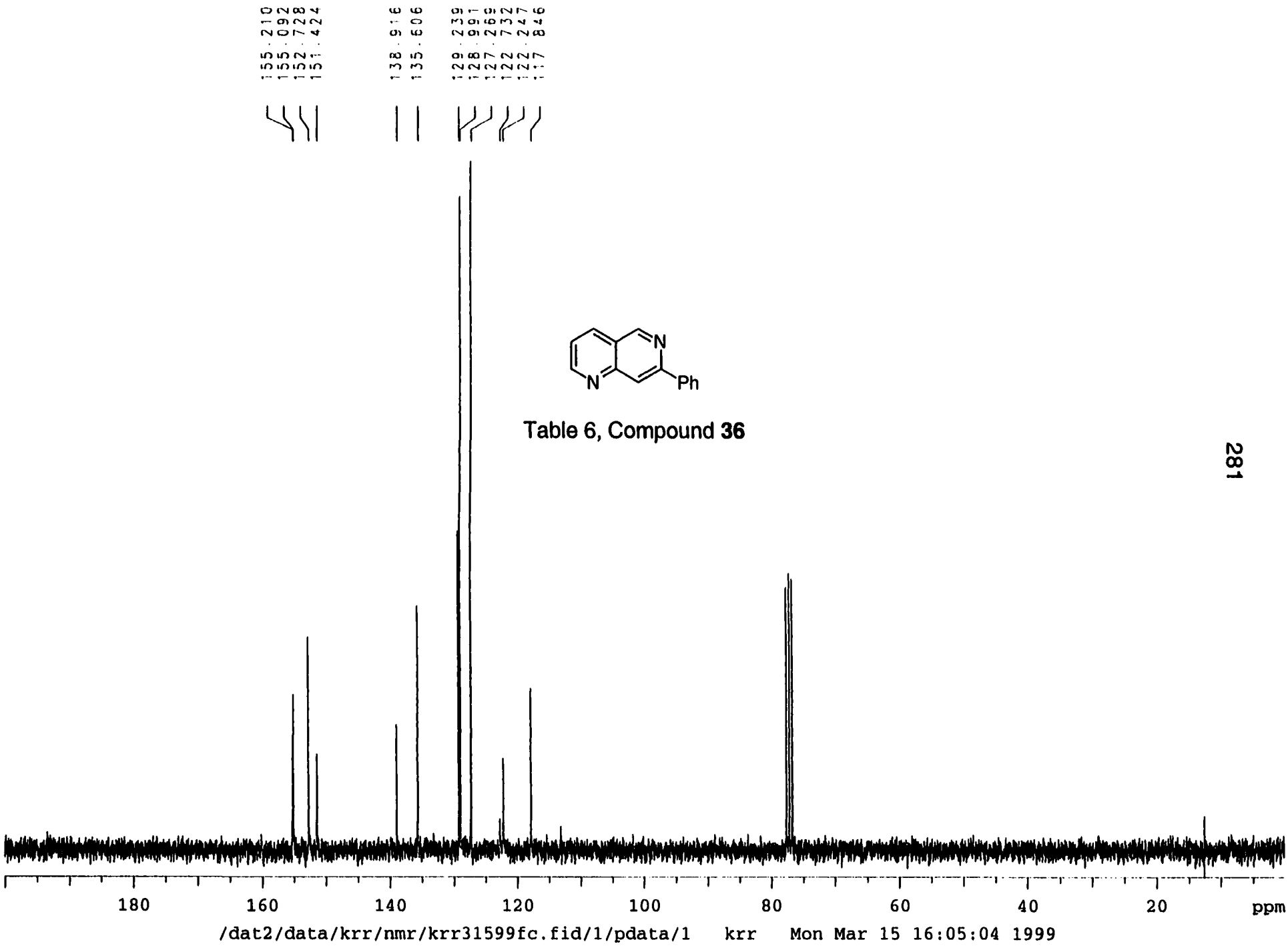


Table 6, Compound **36**

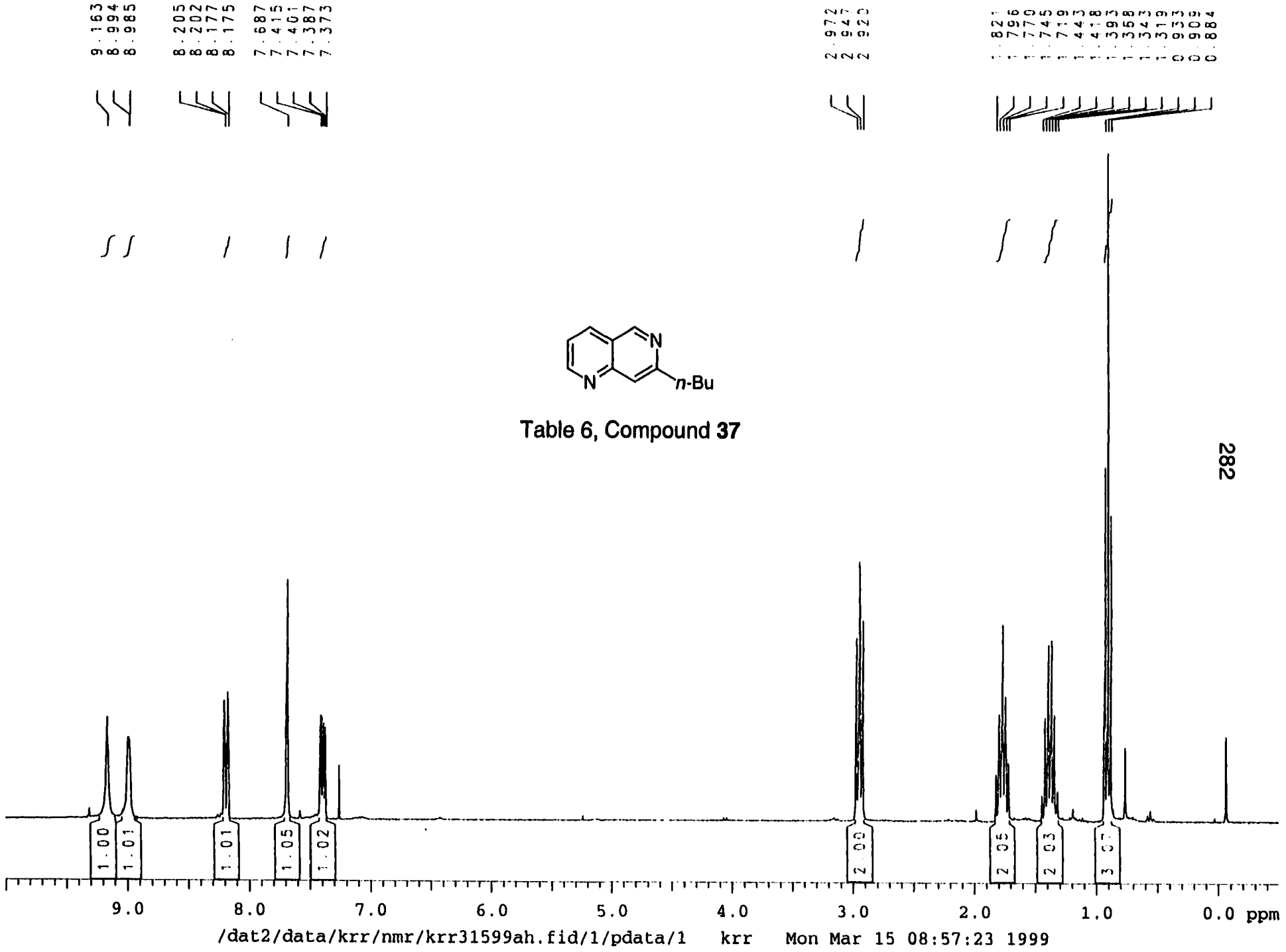


Table 6, Compound **37**

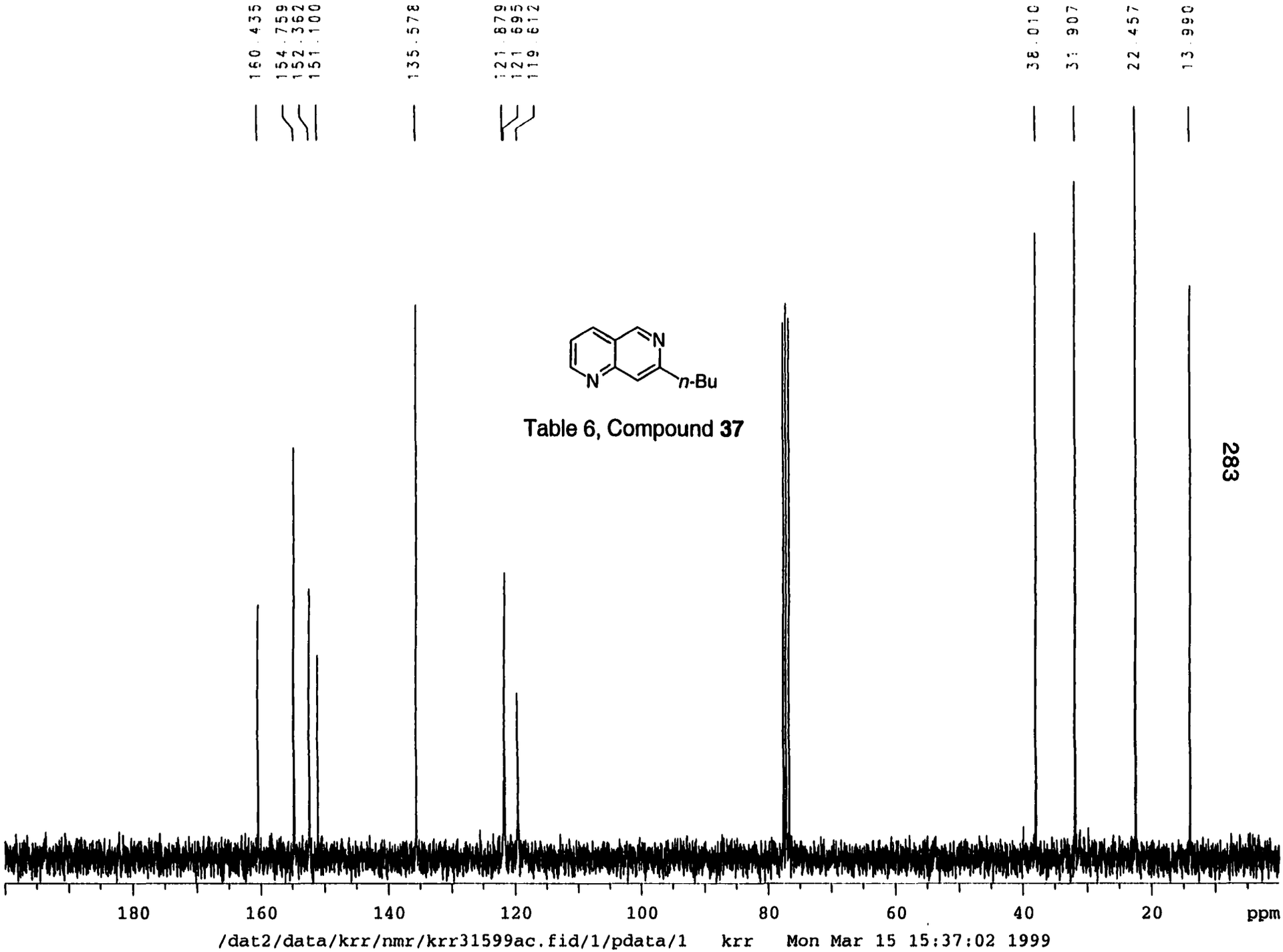


Table 6, Compound **37**

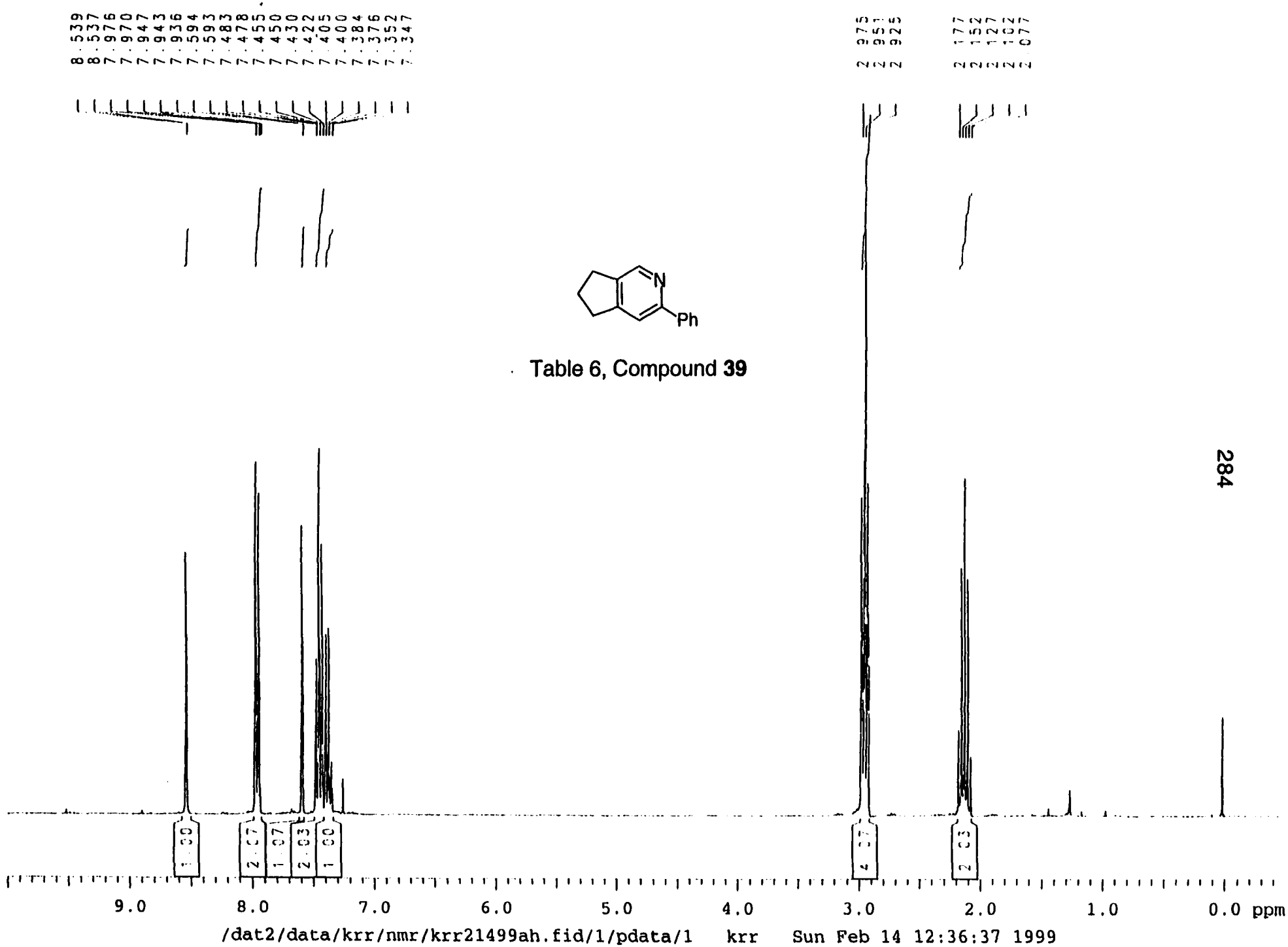


Table 6, Compound **39**

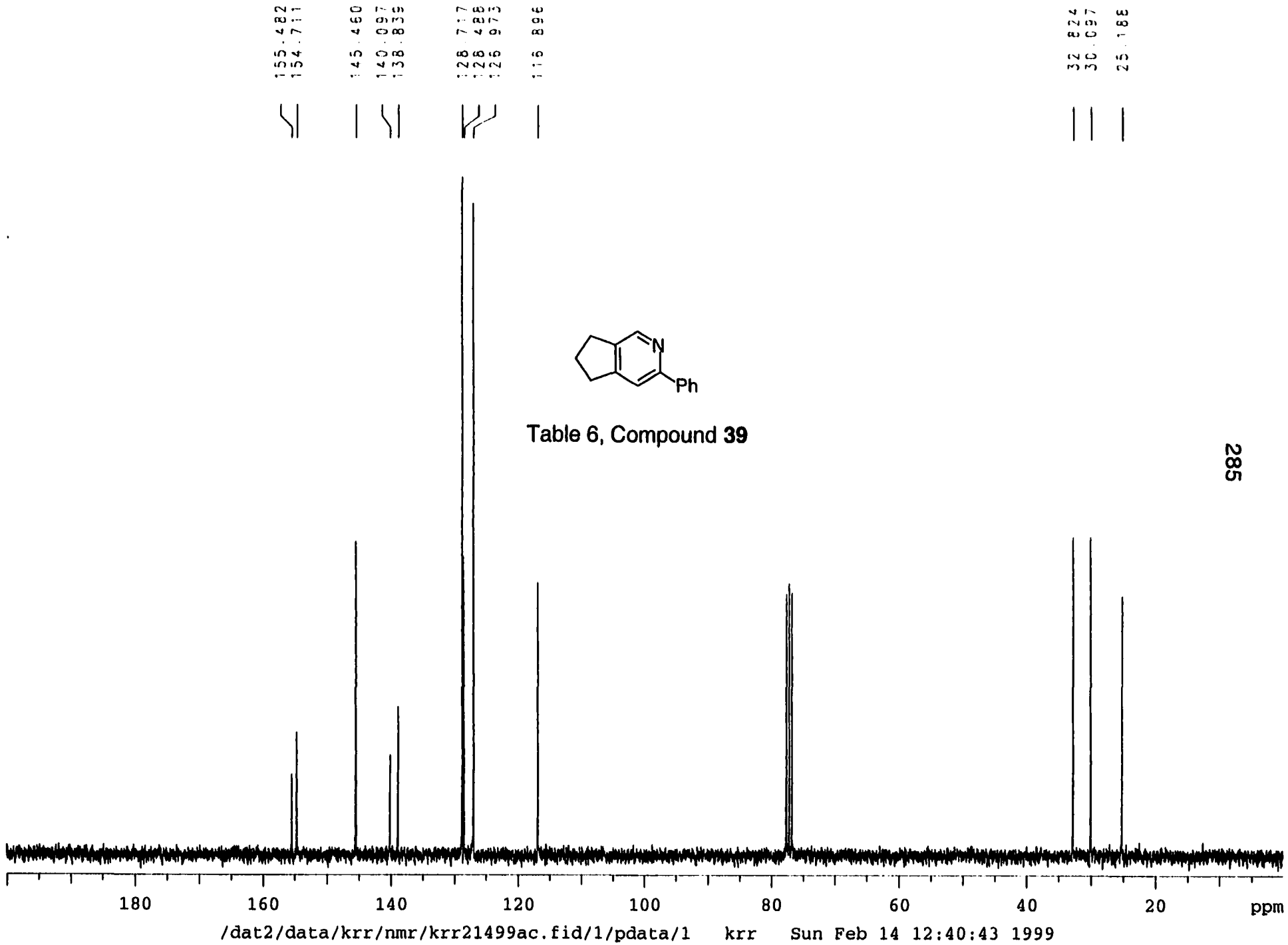


Table 6, Compound **39**

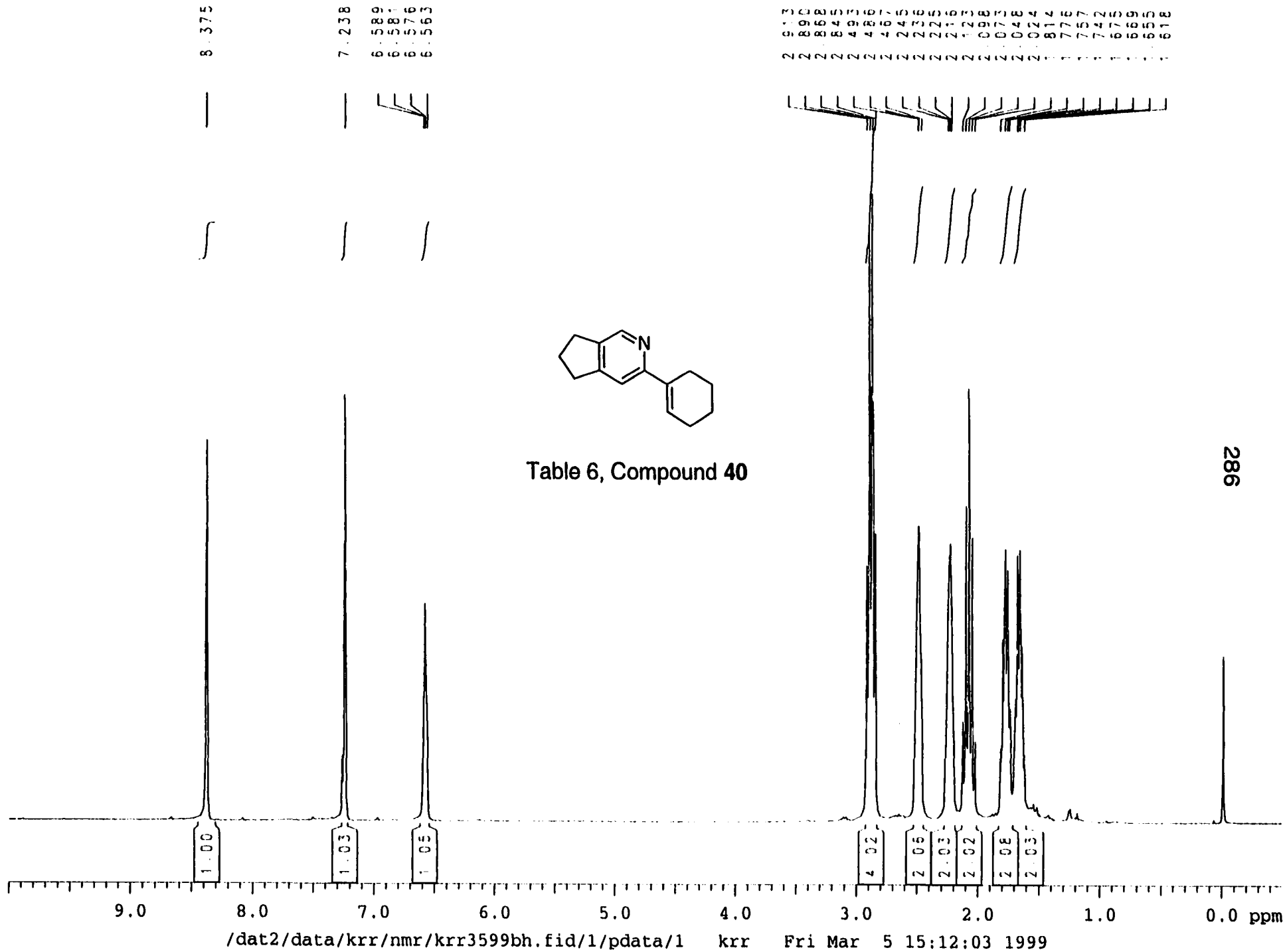


Table 6, Compound **40**

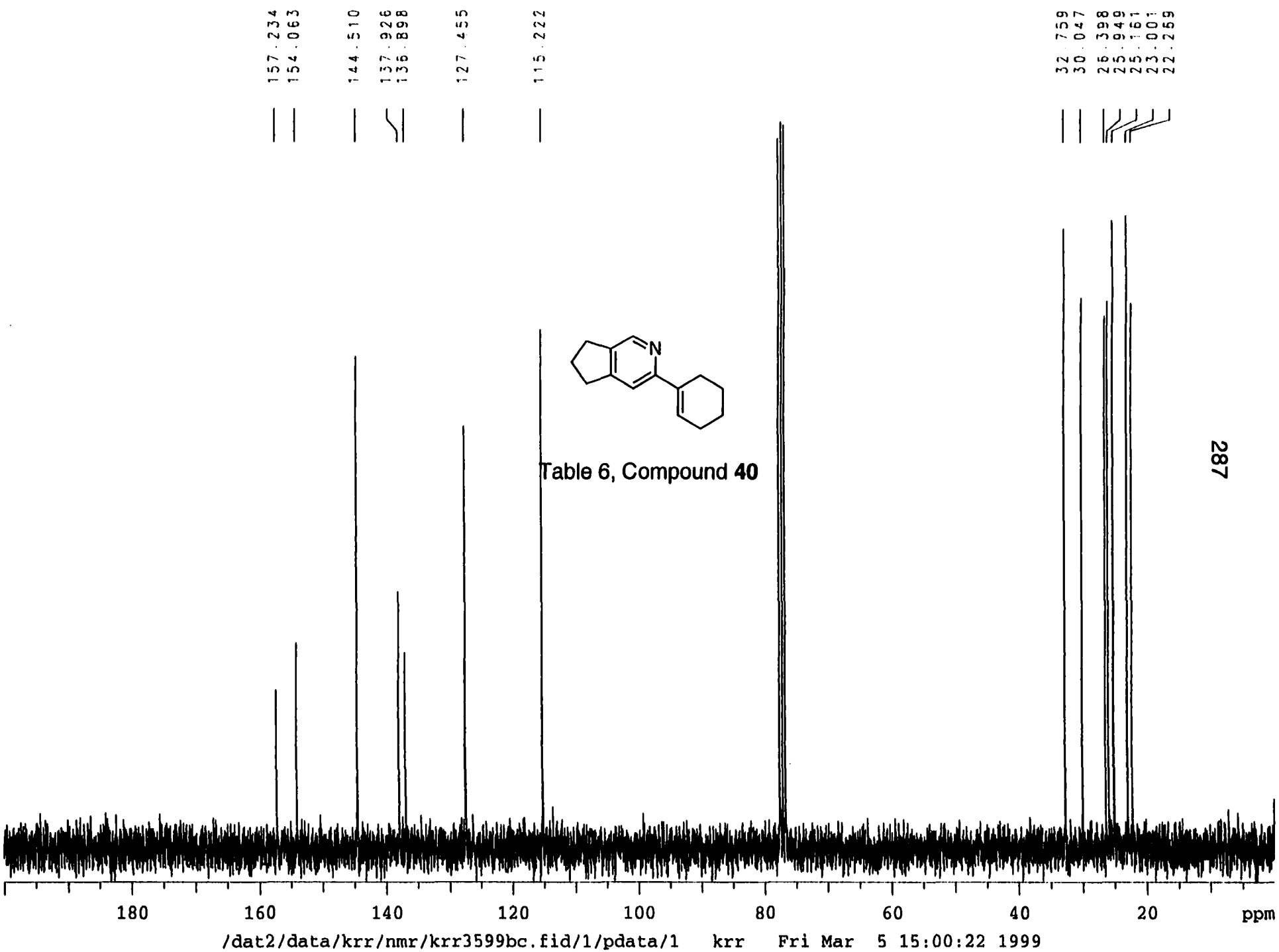


Table 6, Compound **40**

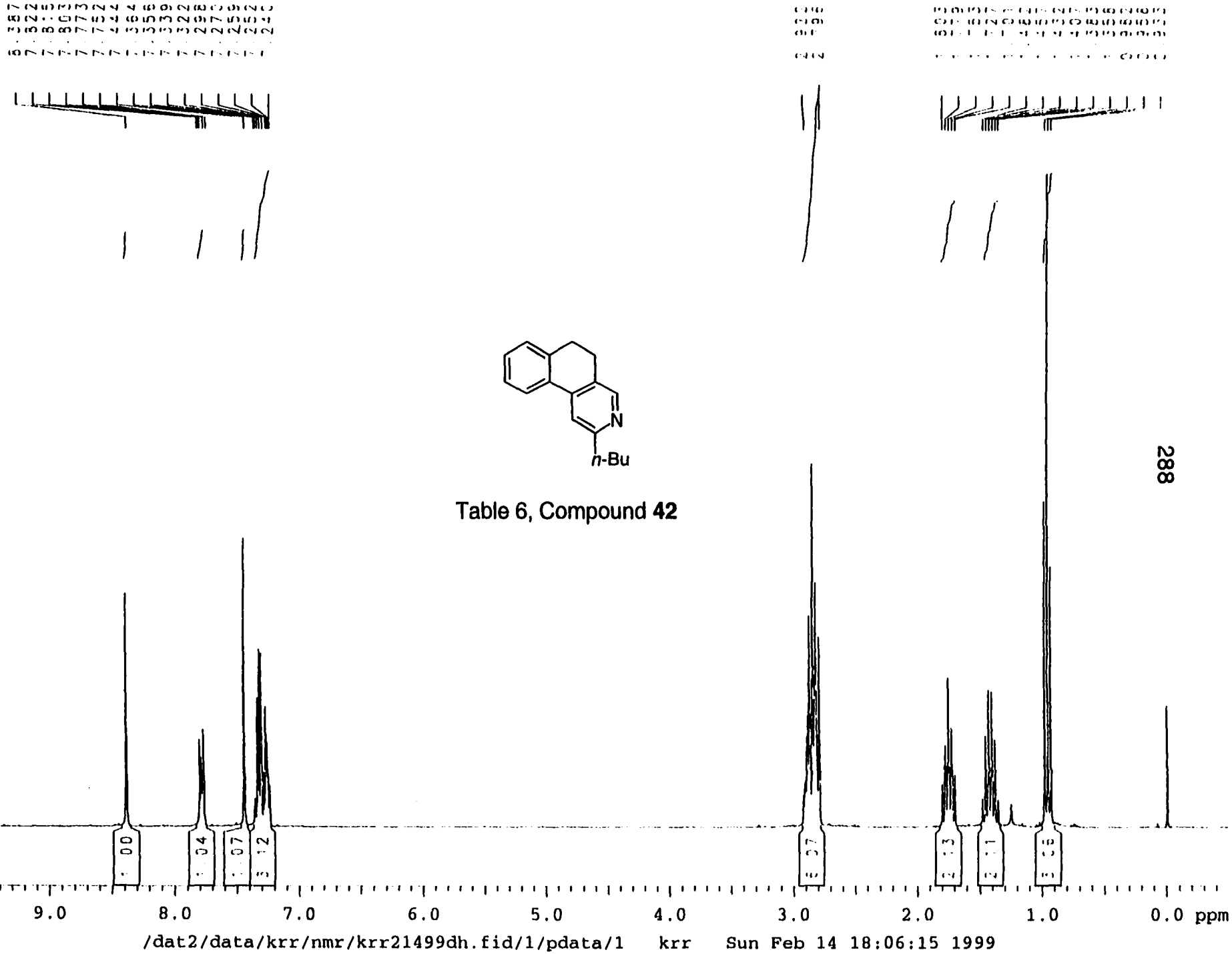
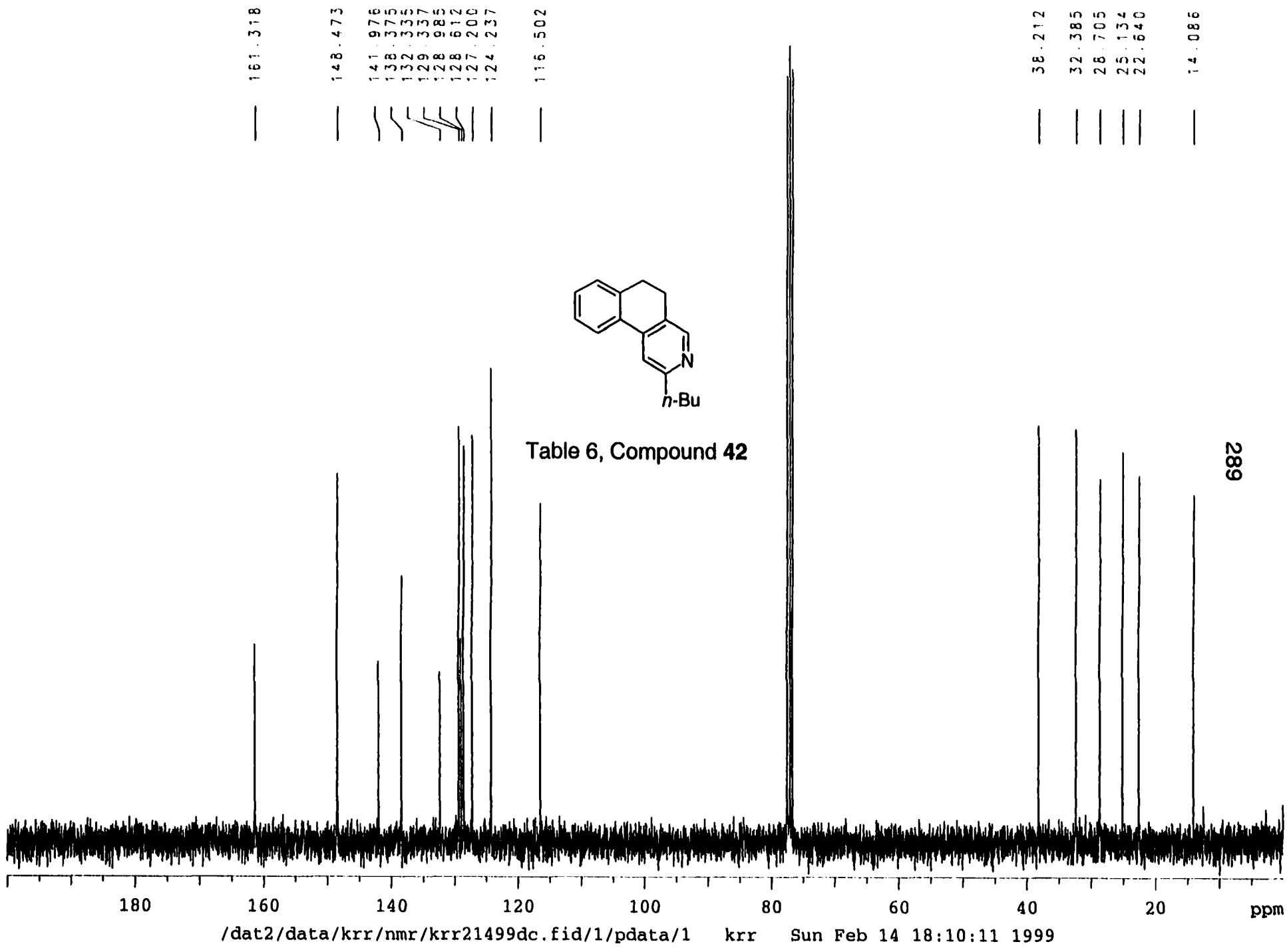
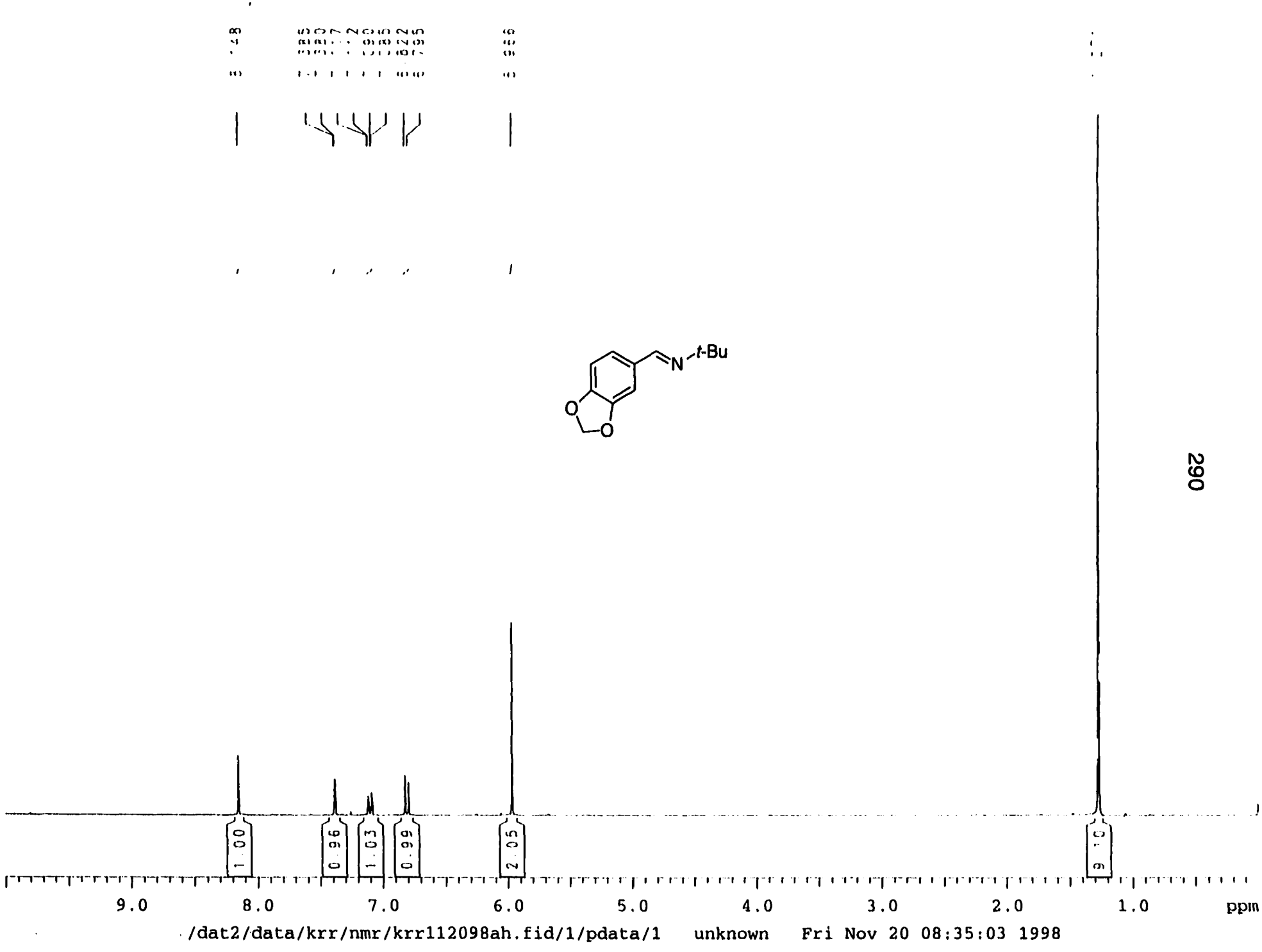
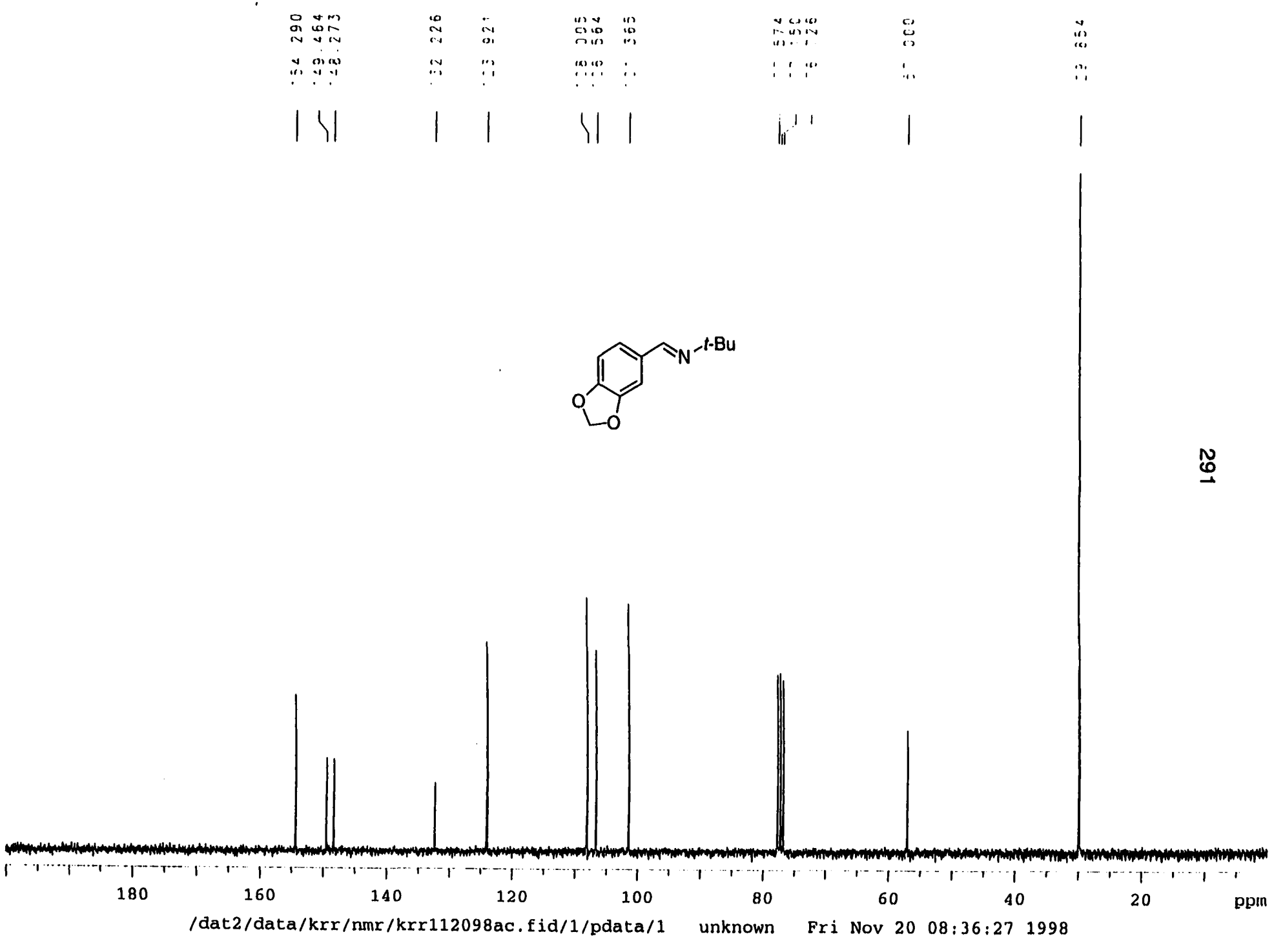
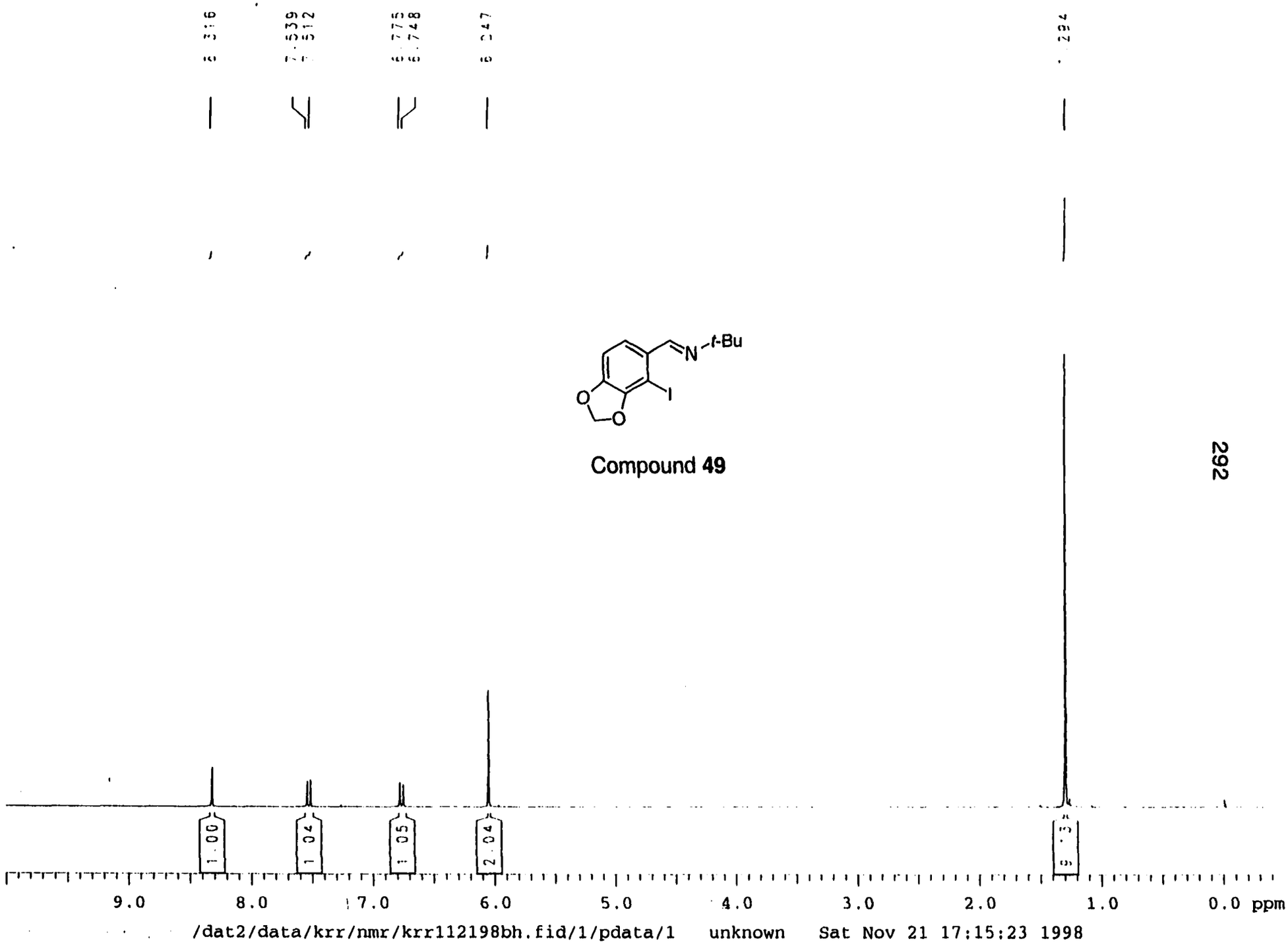


Table 6, Compound **42**

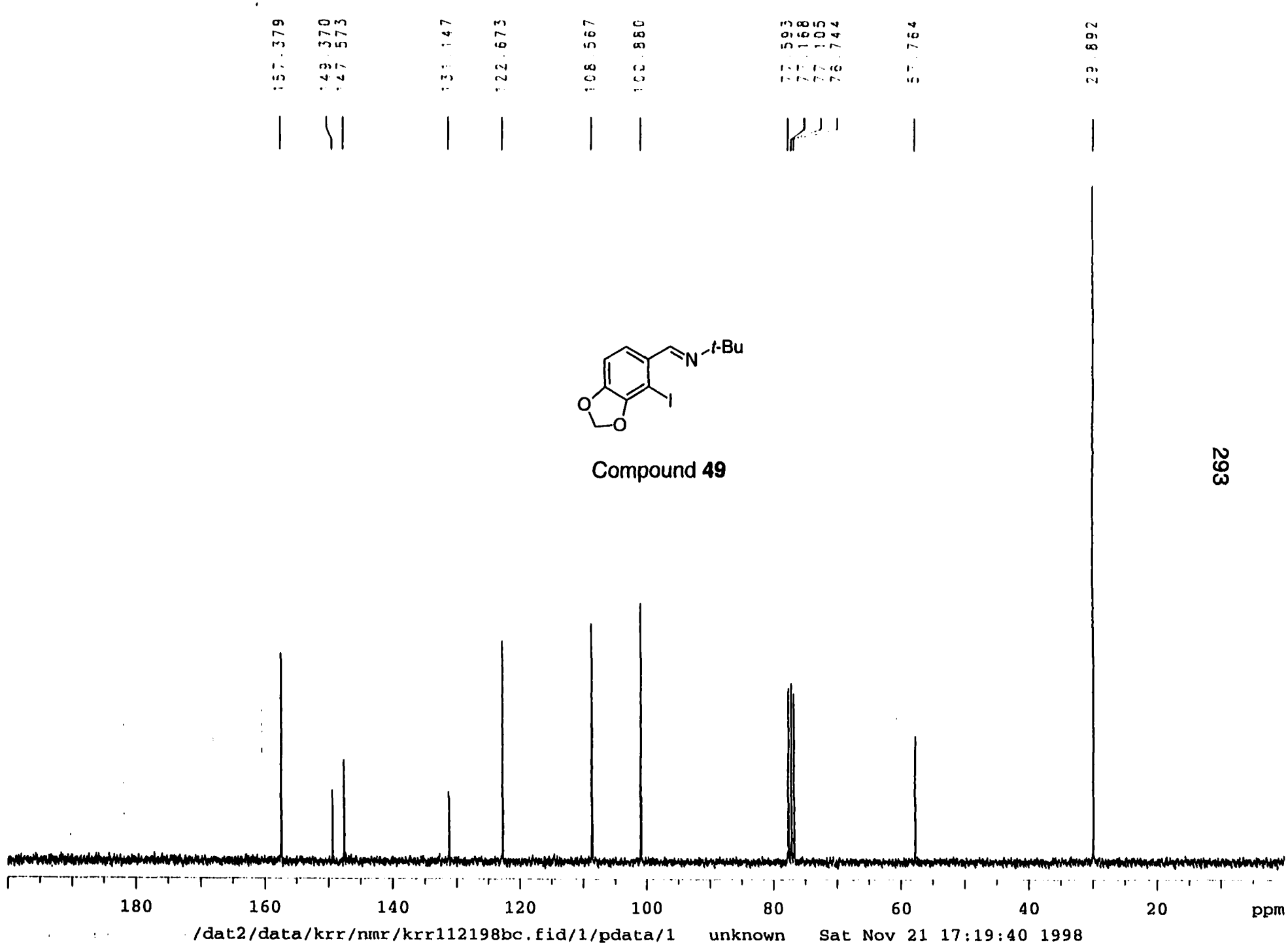

161.318
148.473
141.976
138.375
132.335
129.337
128.985
128.612
127.200
124.237
116.502
38.212
32.385
28.705
25.134
22.640
14.086
N
n-Bu
Table 6, Compound 42
289
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr21499dc.fid/1/pdata/1 krr Sun Feb 14 18:10:11 1999

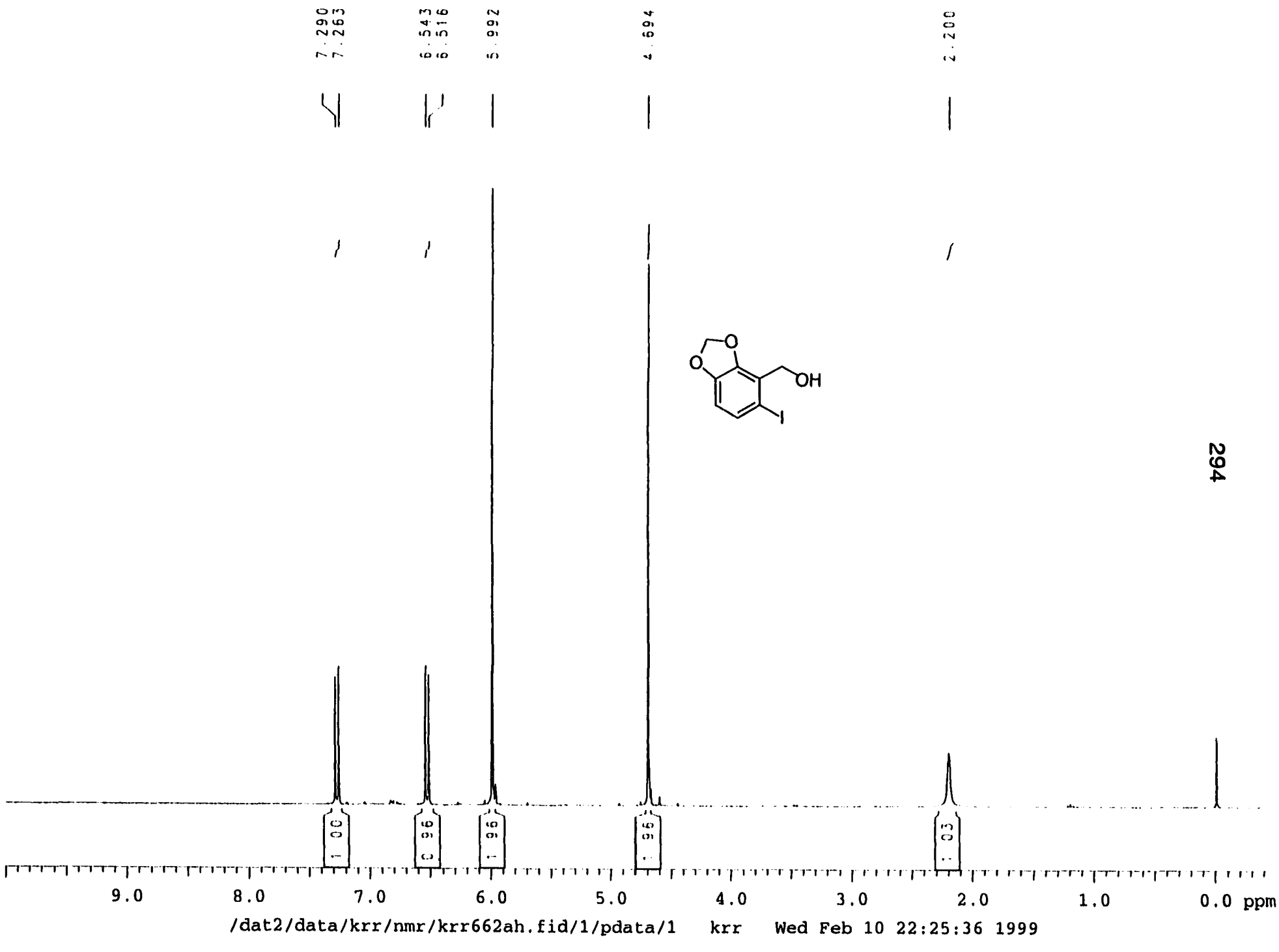

t-Bu
N
O
O
1.00
0.96
1.03
0.99
2.05
9.10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm
/dat2/data/krr/nmr/krr112098ah.fid/1/pdata/1 unknown Fri Nov 20 08:35:03 1998


154.290
129.464
128.273
132.226
123.921
128.005
126.564
101.365
77.574
77.250
76.926
61.000
29.854
N
t-Bu
O
O
291
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr112098ac.fid/1/pdata/1 unknown Fri Nov 20 08:36:27 1998

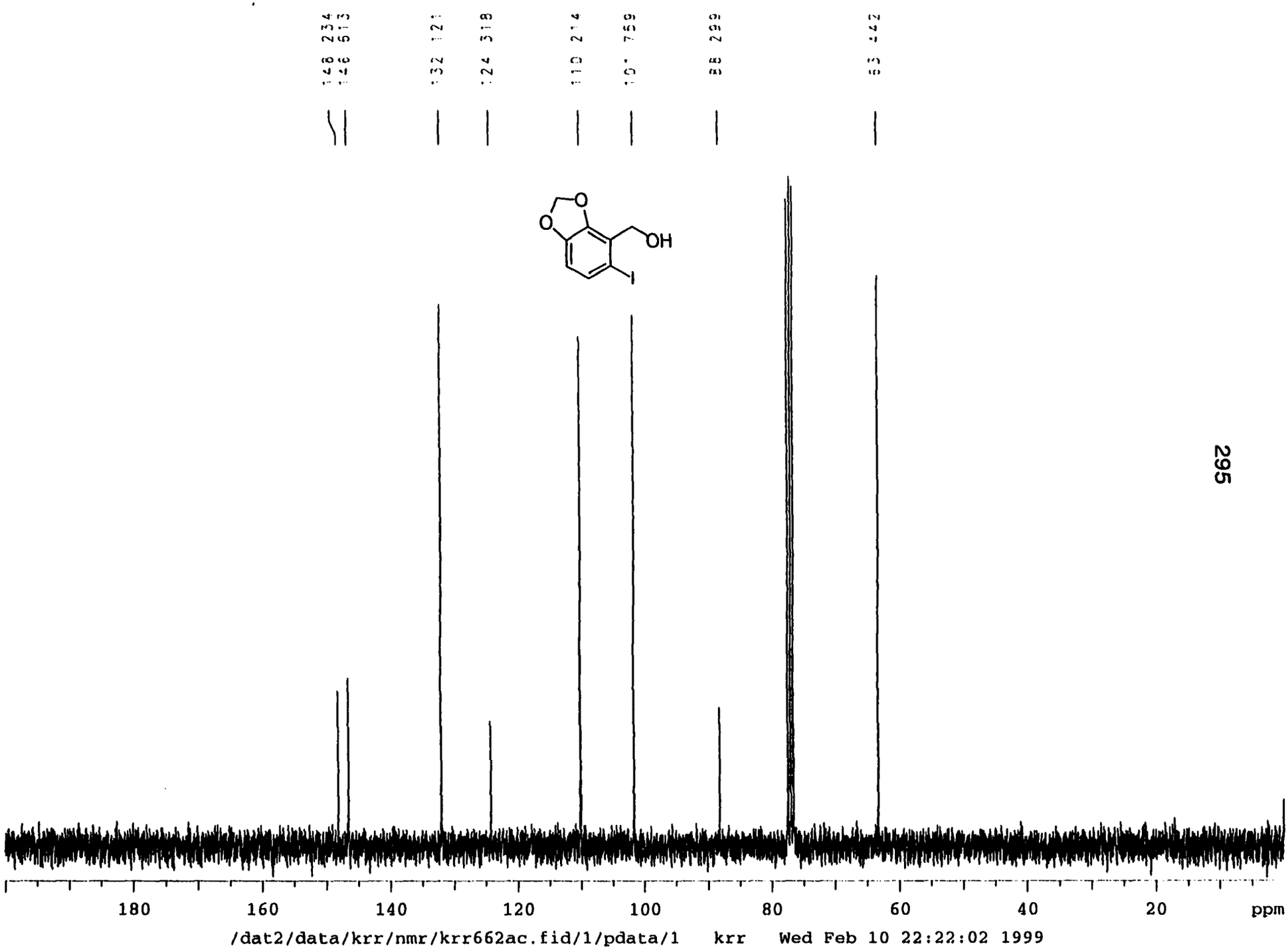

8.316
7.539
7.512
6.775
6.748
6.247
1.294
N
t-Bu
O
O
I
1.00
1.04
1.05
2.04
9.37
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/dat2/data/krr/nmr/krr112198bh.fid/1/pdata/1 unknown Sat Nov 21 17:15:23 1998

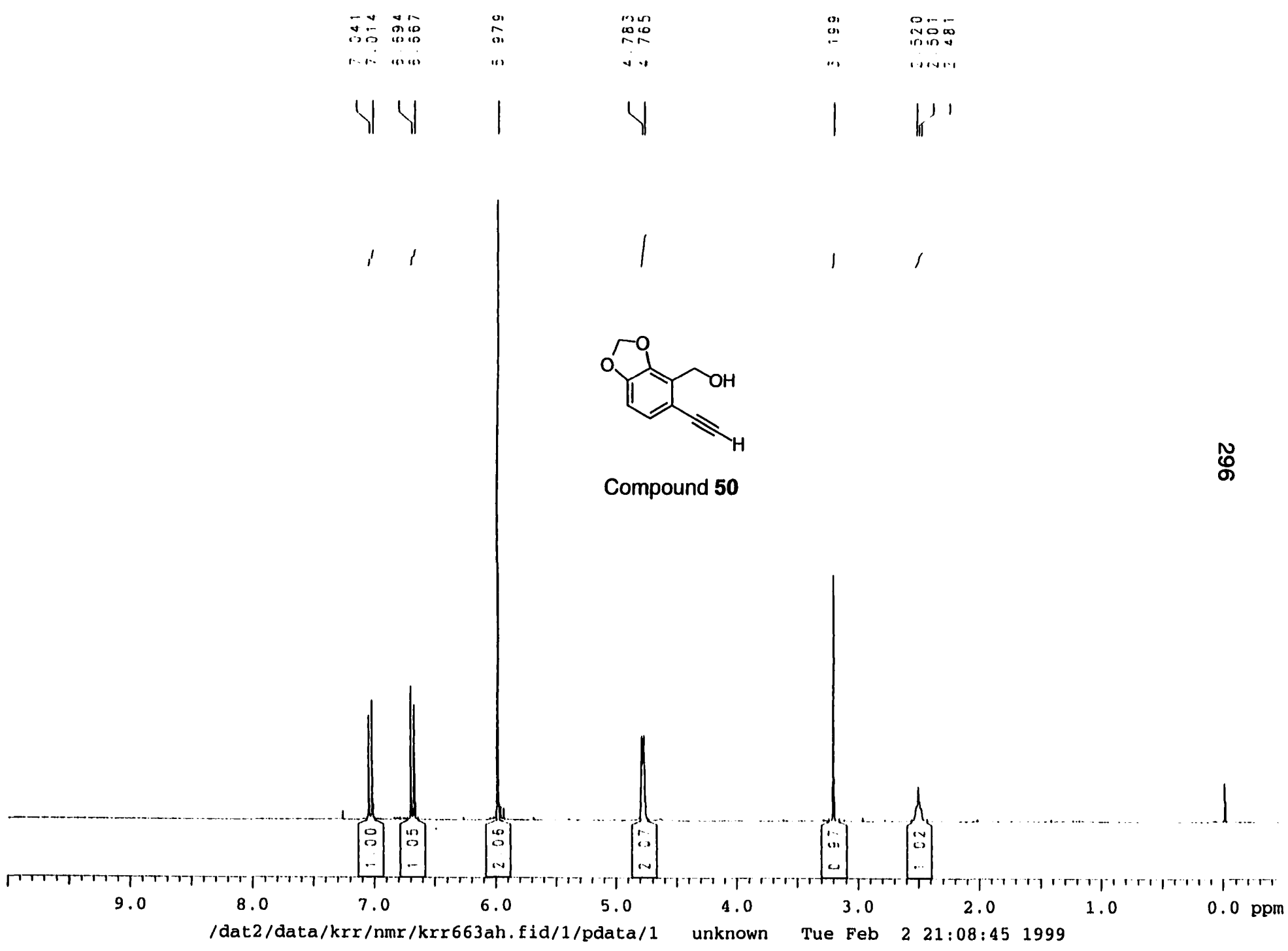
Compound **49**

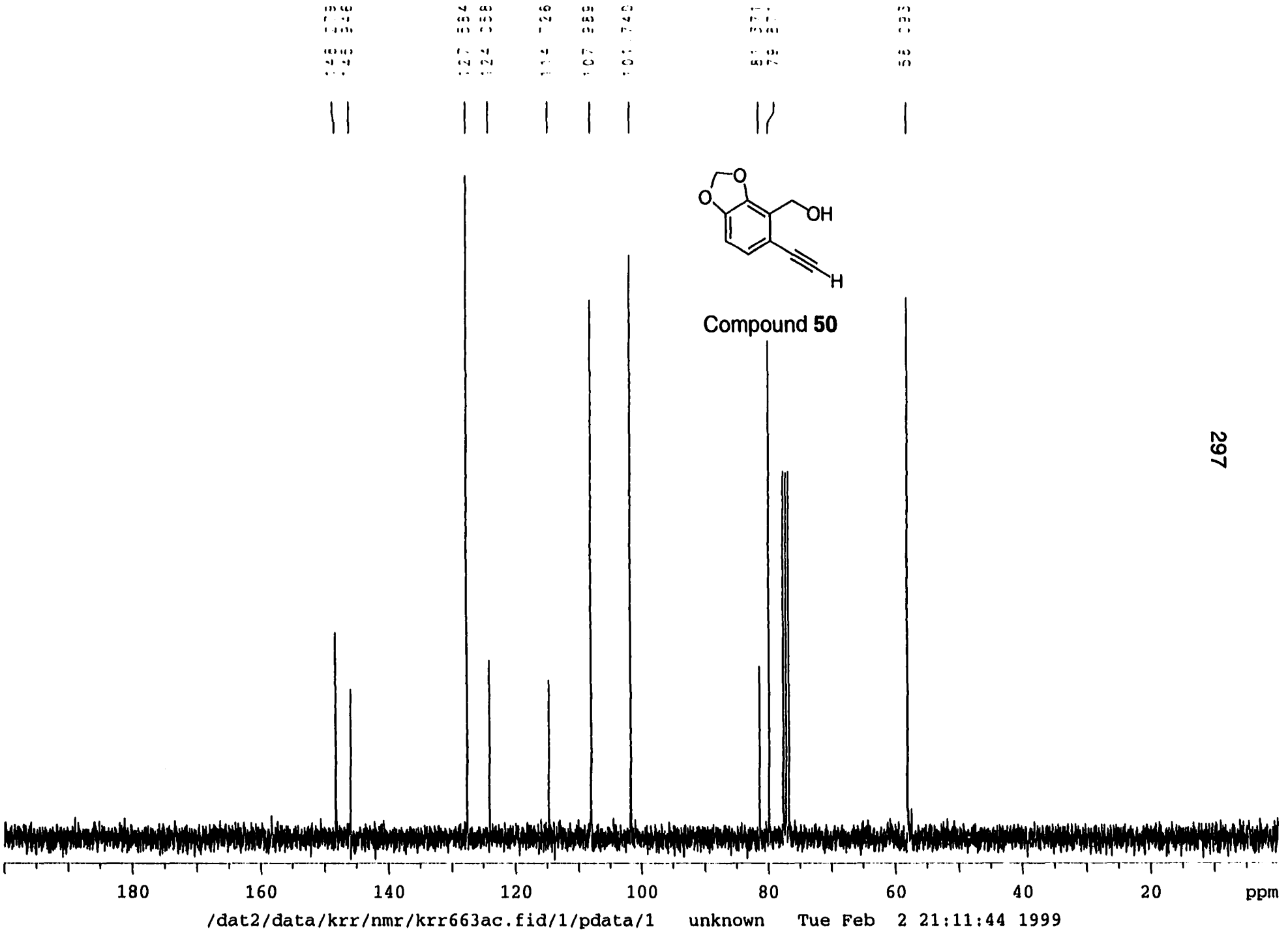

157.379
149.370
147.573
131.147
122.673
108.567
100.880
77.593
77.168
77.105
76.744
57.764
29.892
t-Bu
N
I
O
O
Compound 49
293
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr112198bc.fid/1/pdata/1 unknown Sat Nov 21 17:19:40 1998

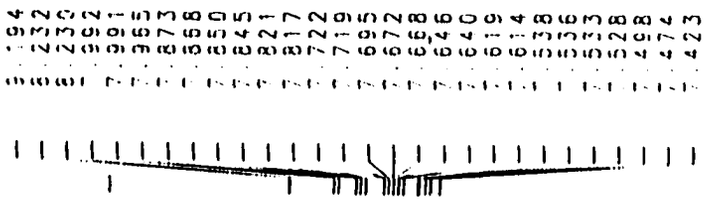

7.290
7.263
6.543
6.516
5.992
4.694
2.200
OH
I
1.00
0.96
1.96
1.96
3.03
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/dat2/data/krr/nmr/krr662ah.fid/1/pdata/1 krr Wed Feb 10 22:25:36 1999

294


148.234
146.513
132.121
124.318
110.214
101.759
88.299
63.442
OH
I
295
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr662ac.fid/1/pdata/1 krr Wed Feb 10 22:22:02 1999


7.041
7.014
6.694
6.667
5.979
4.783
4.765
3.199
2.520
2.501
2.481
OH
H
Compound 50
296
1.00
1.05
2.06
2.07
2.97
1.02
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
/dat2/data/krr/nmr/krr663ah.fid/1/pdata/1 unknown Tue Feb 2 21:08:45 1999


OH
H
Compound 50
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr663ac.fid/1/pdata/1 unknown Tue Feb 2 21:11:44 1999



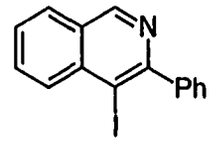
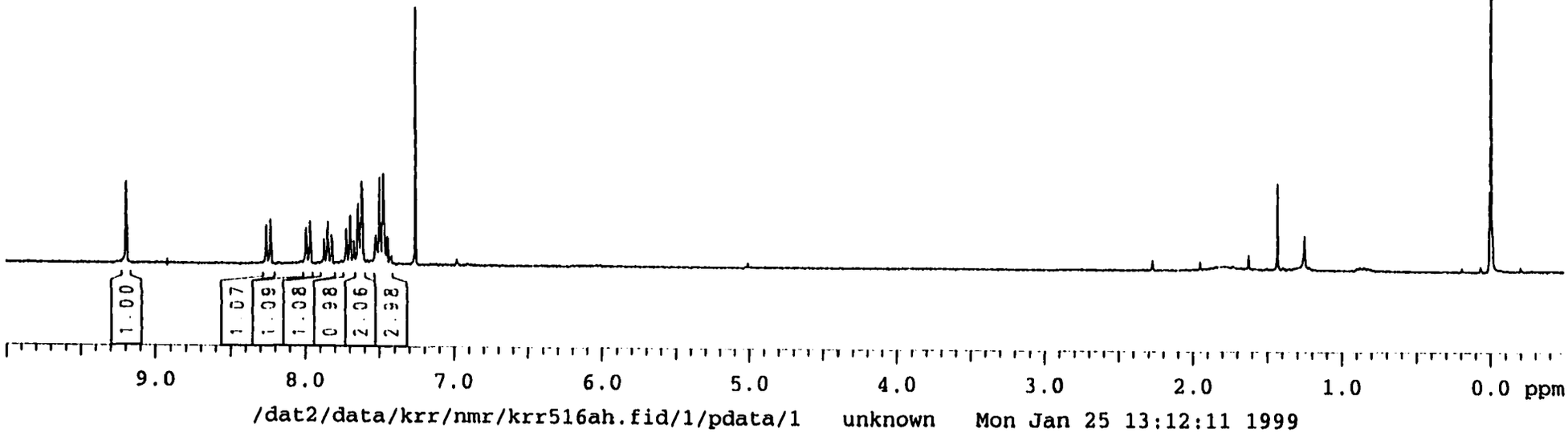


Table 6, Compound **54**



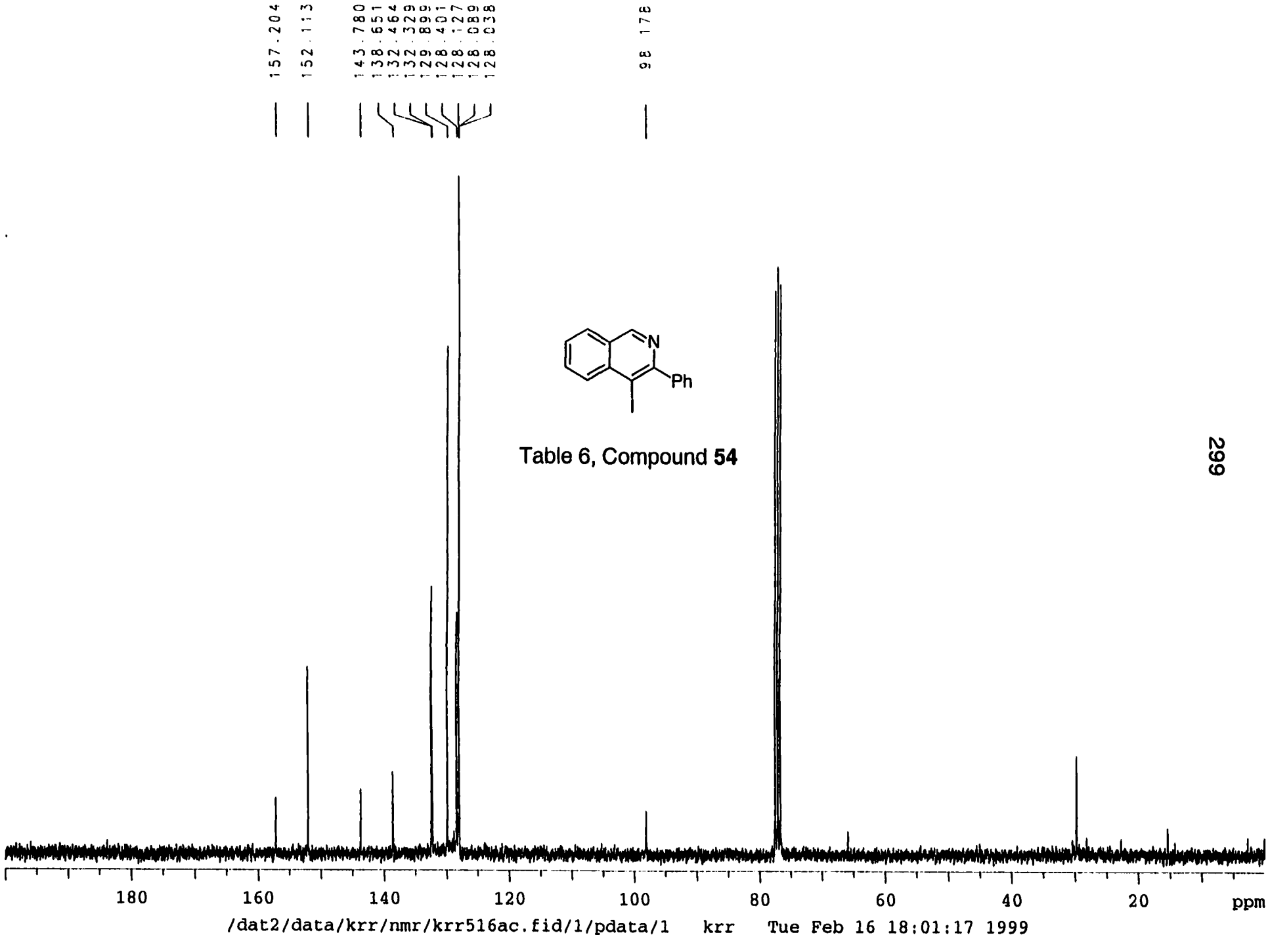
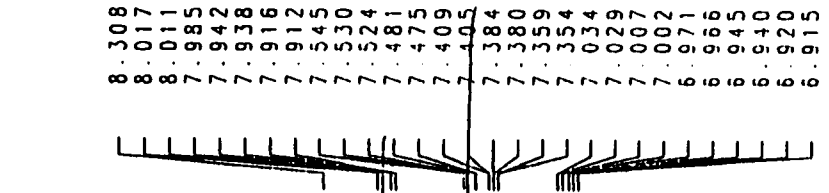


Table 6, Compound **54**

APPENDIX C. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA



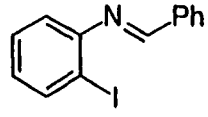
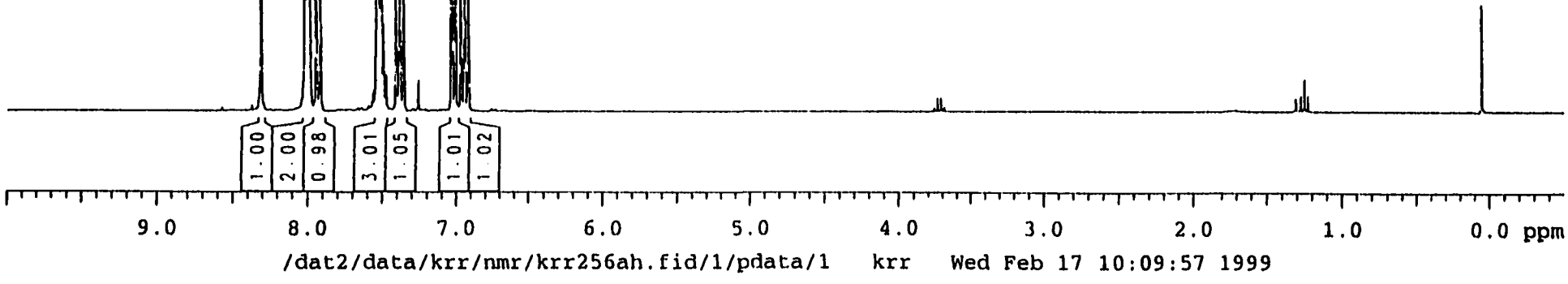


Table 3, Compound **21**

301



/dat2/data/krr/nmr/krr256ah.fid/1/pdata/1 krr Wed Feb 17 10:09:57 1999

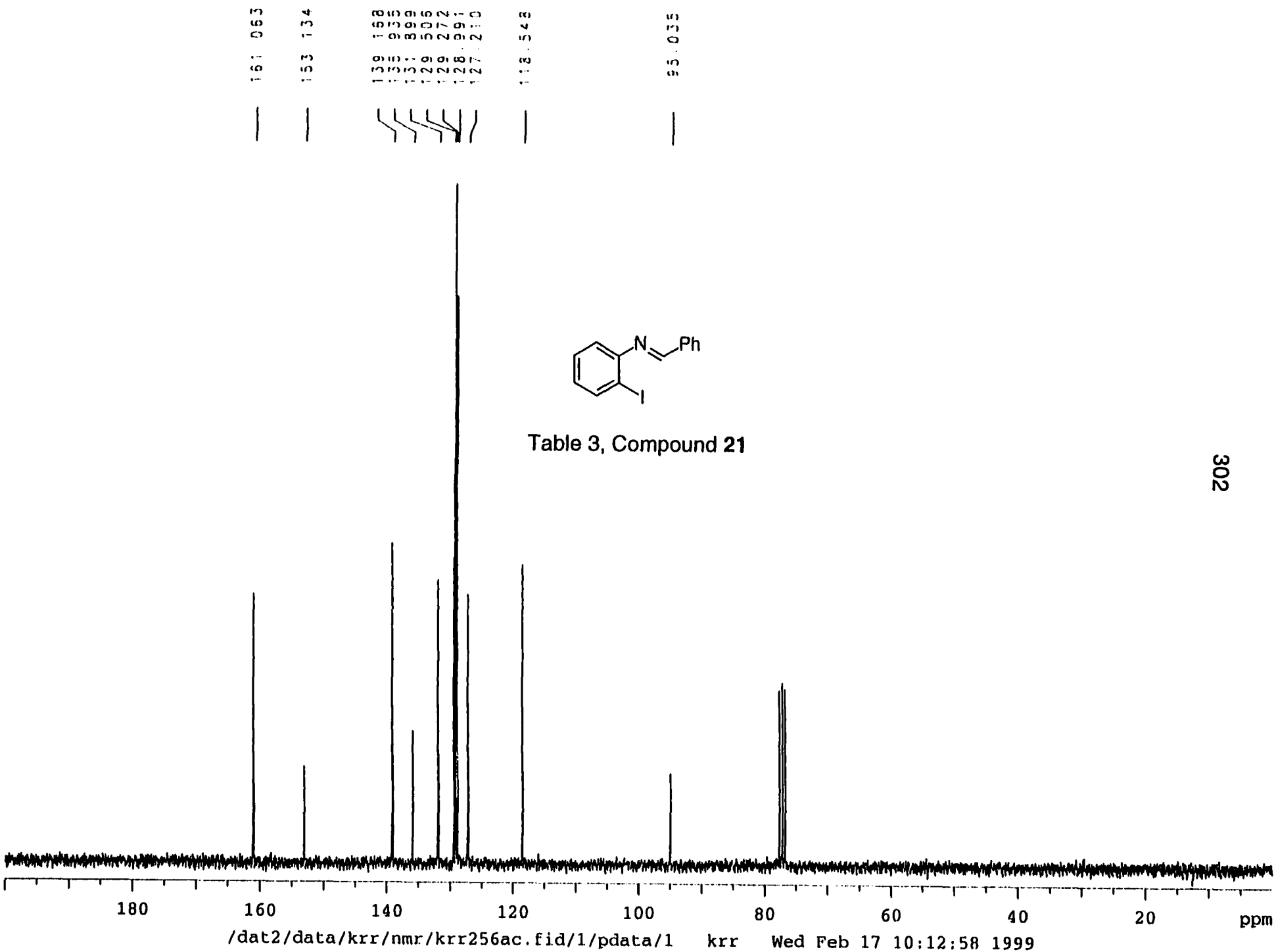
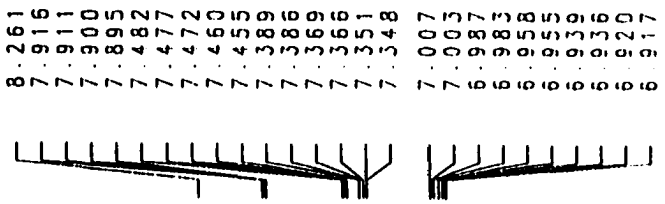


Table 3, Compound **21**



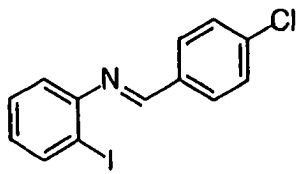


Table 3, Compound **36**

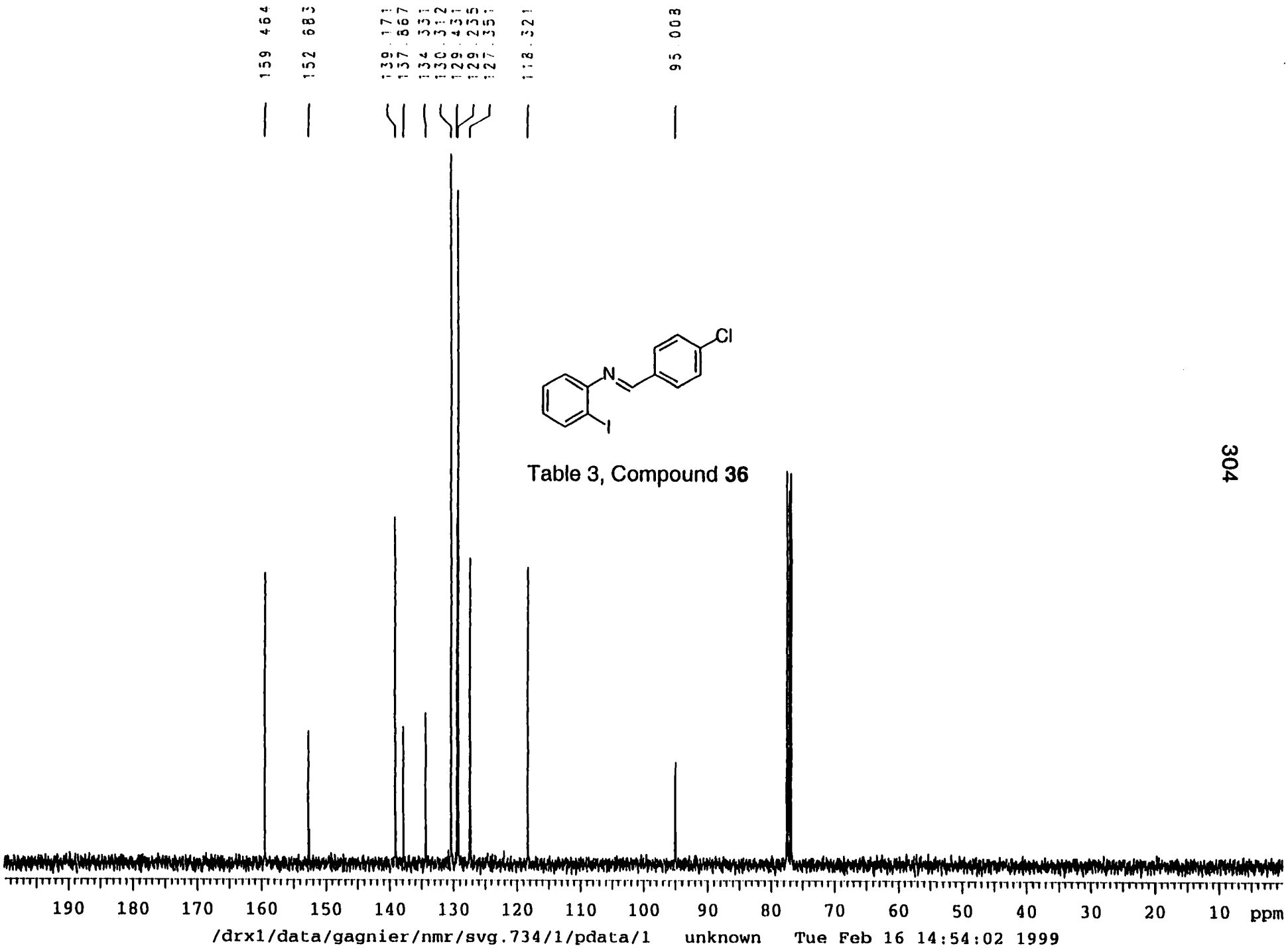


Table 3, Compound **36**

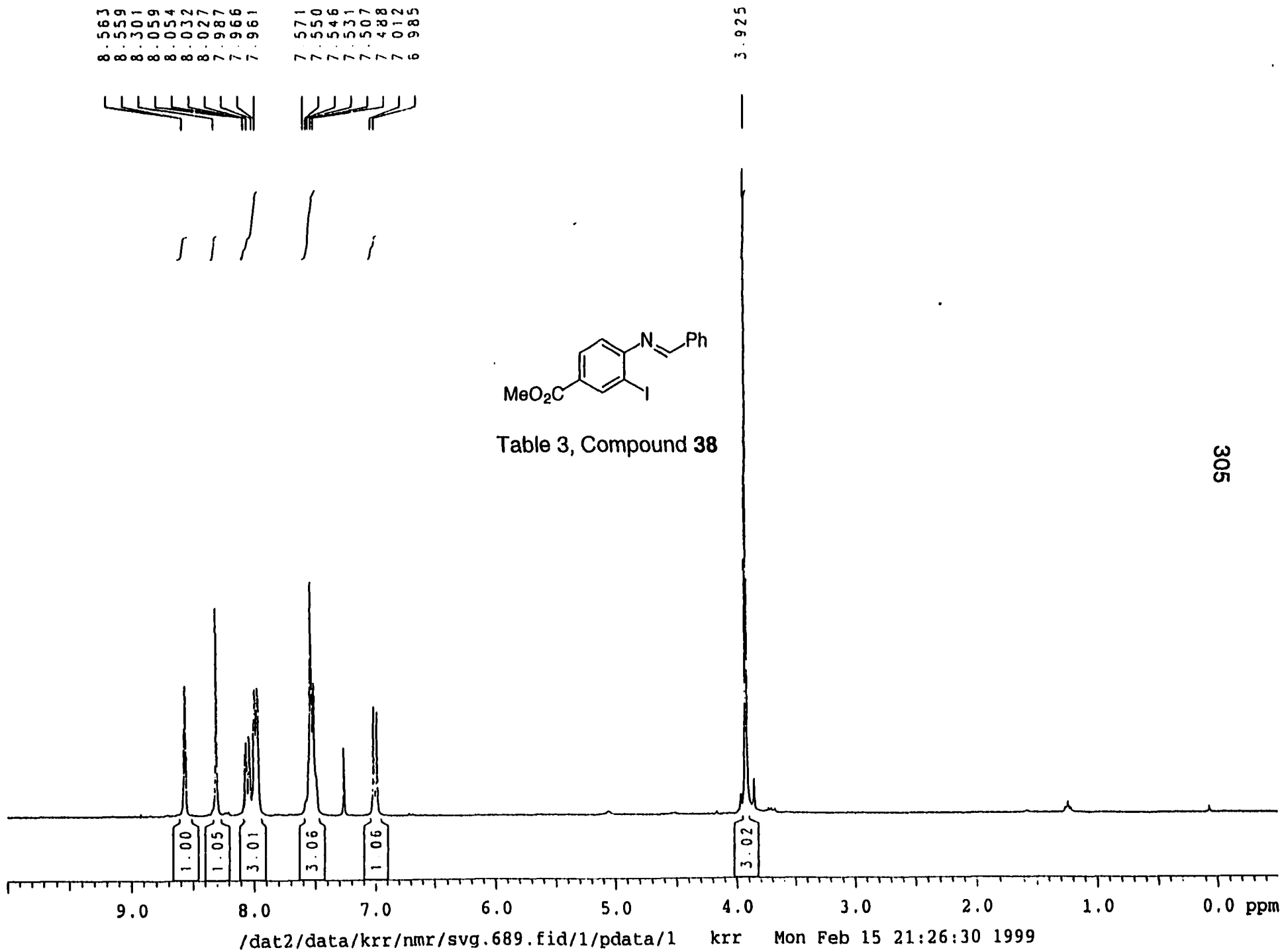


Table 3, Compound **38**

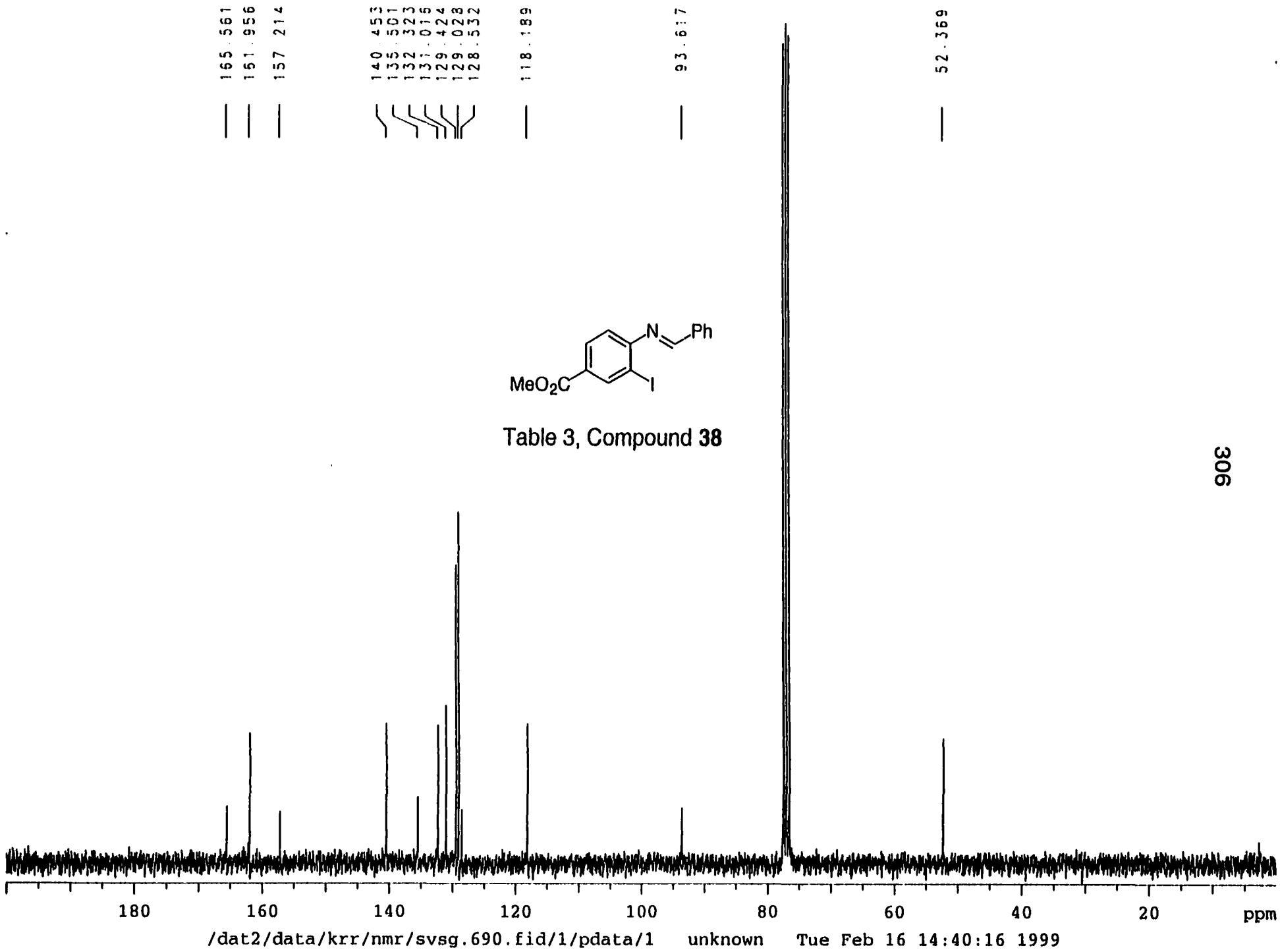
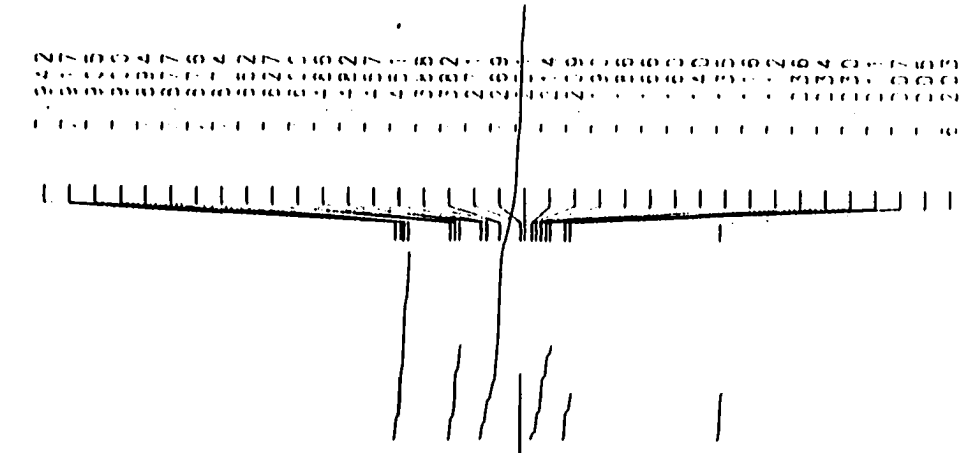


Table 3, Compound **38**



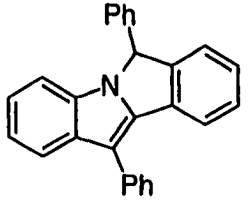


Table 3, Compound **23**

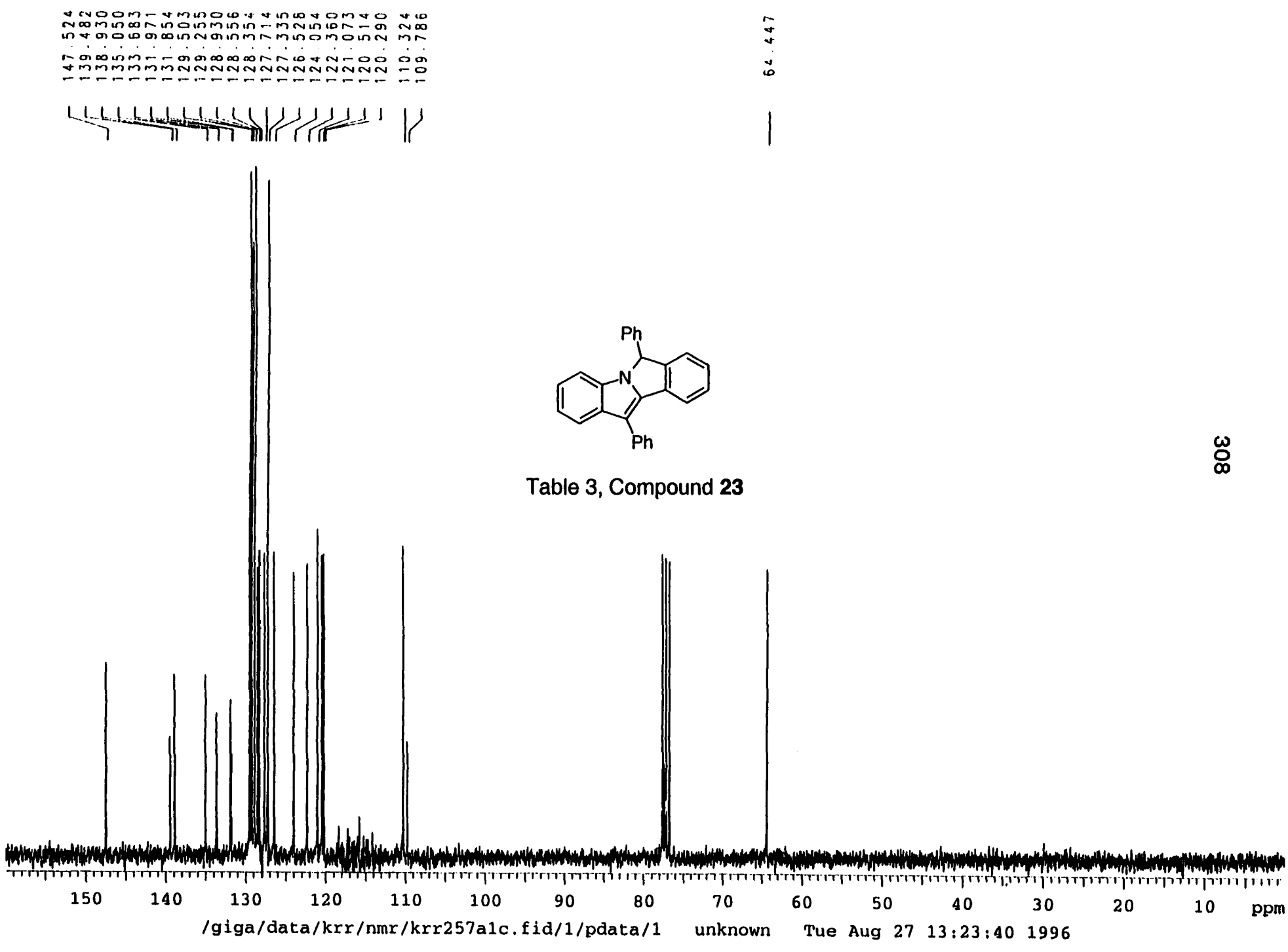


Table 3, Compound **23**

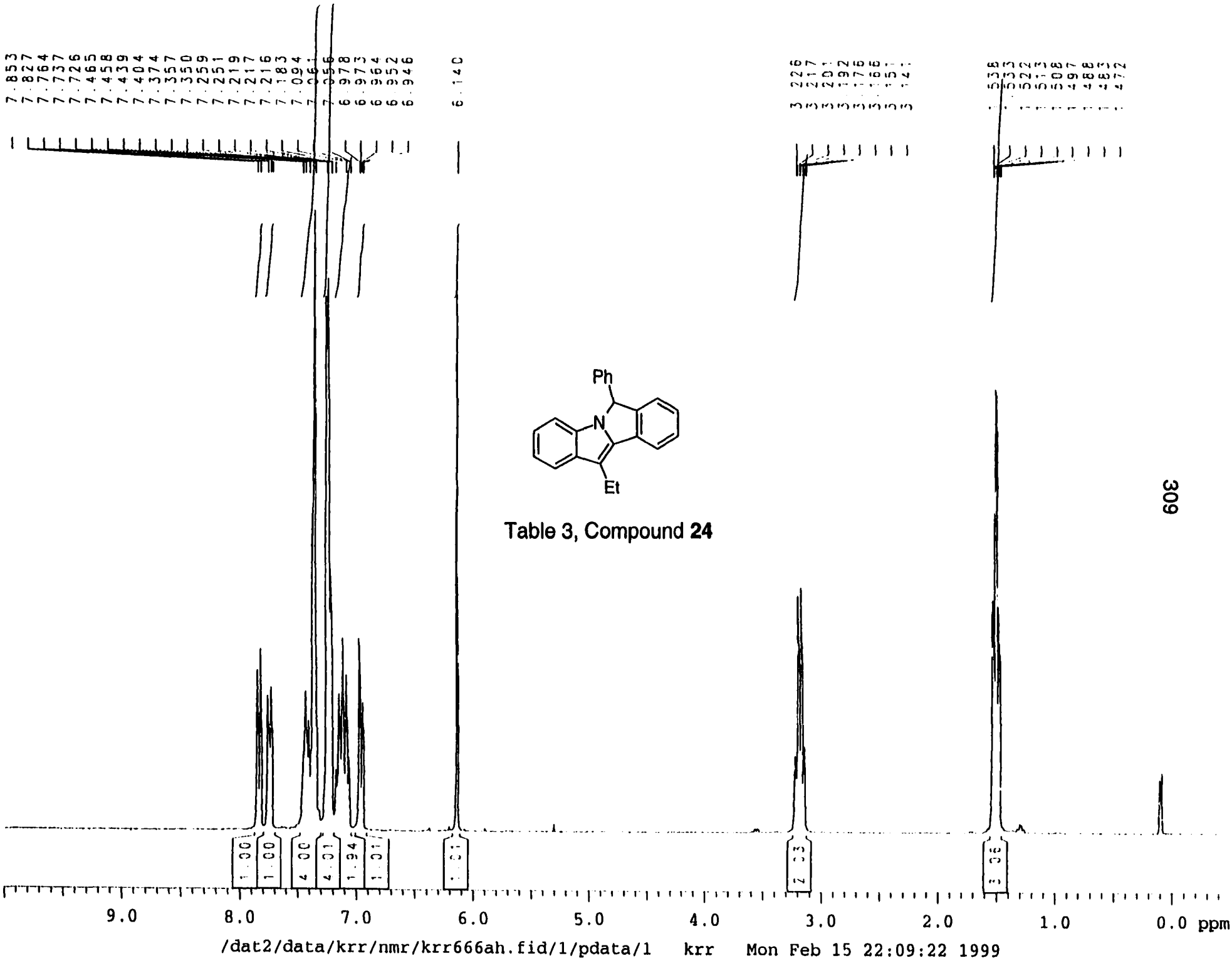
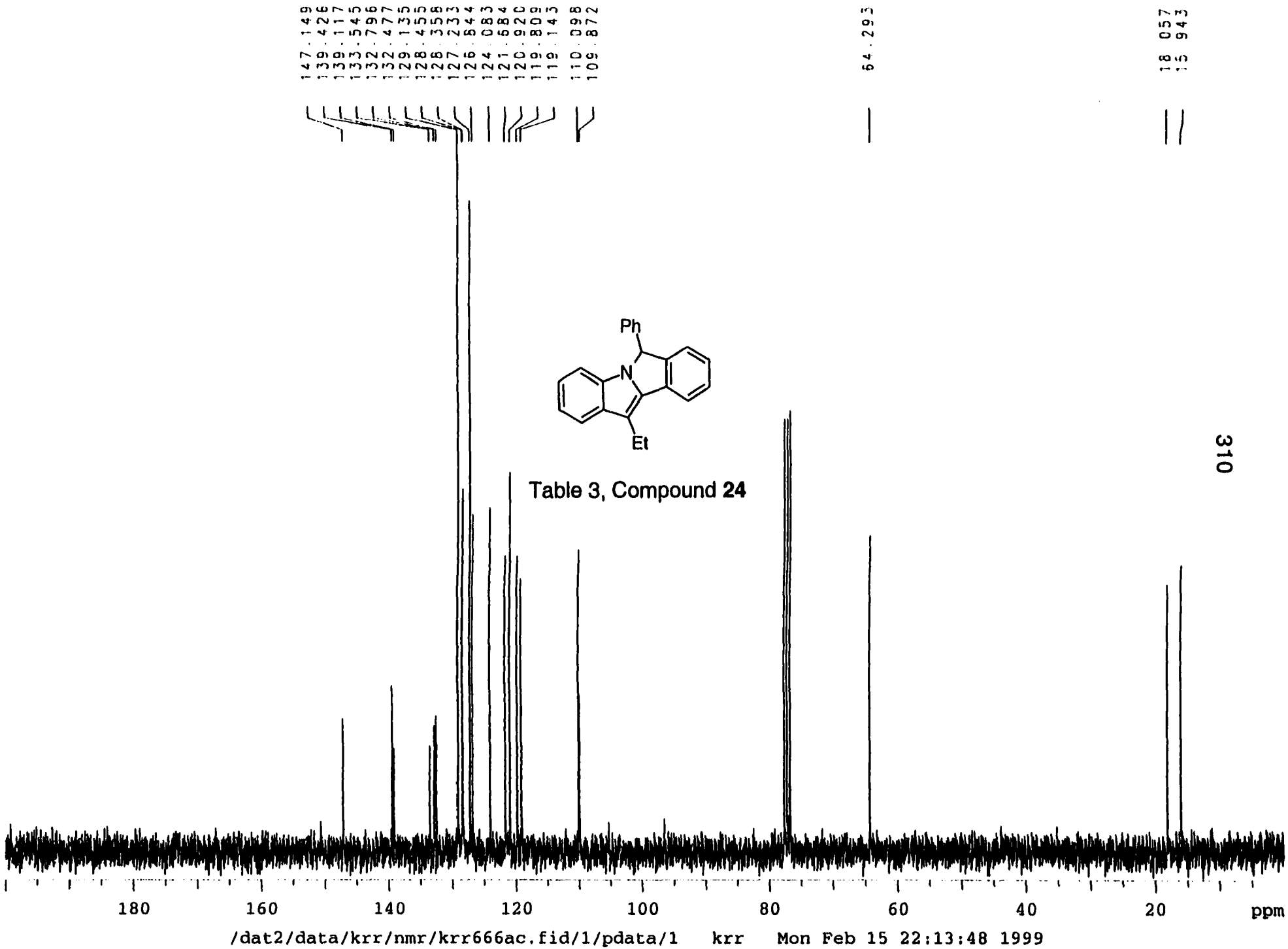


Table 3, Compound **24**


147.149
139.426
139.117
133.545
132.796
132.477
129.135
128.455
128.358
127.233
126.844
124.083
121.584
120.920
119.809
119.143
110.098
109.872
64.293
18.057
15.943
Ph
N
Et
Table 3, Compound 24
310
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr666ac.fid/1/pdata/1 krr Mon Feb 15 22:13:48 1999

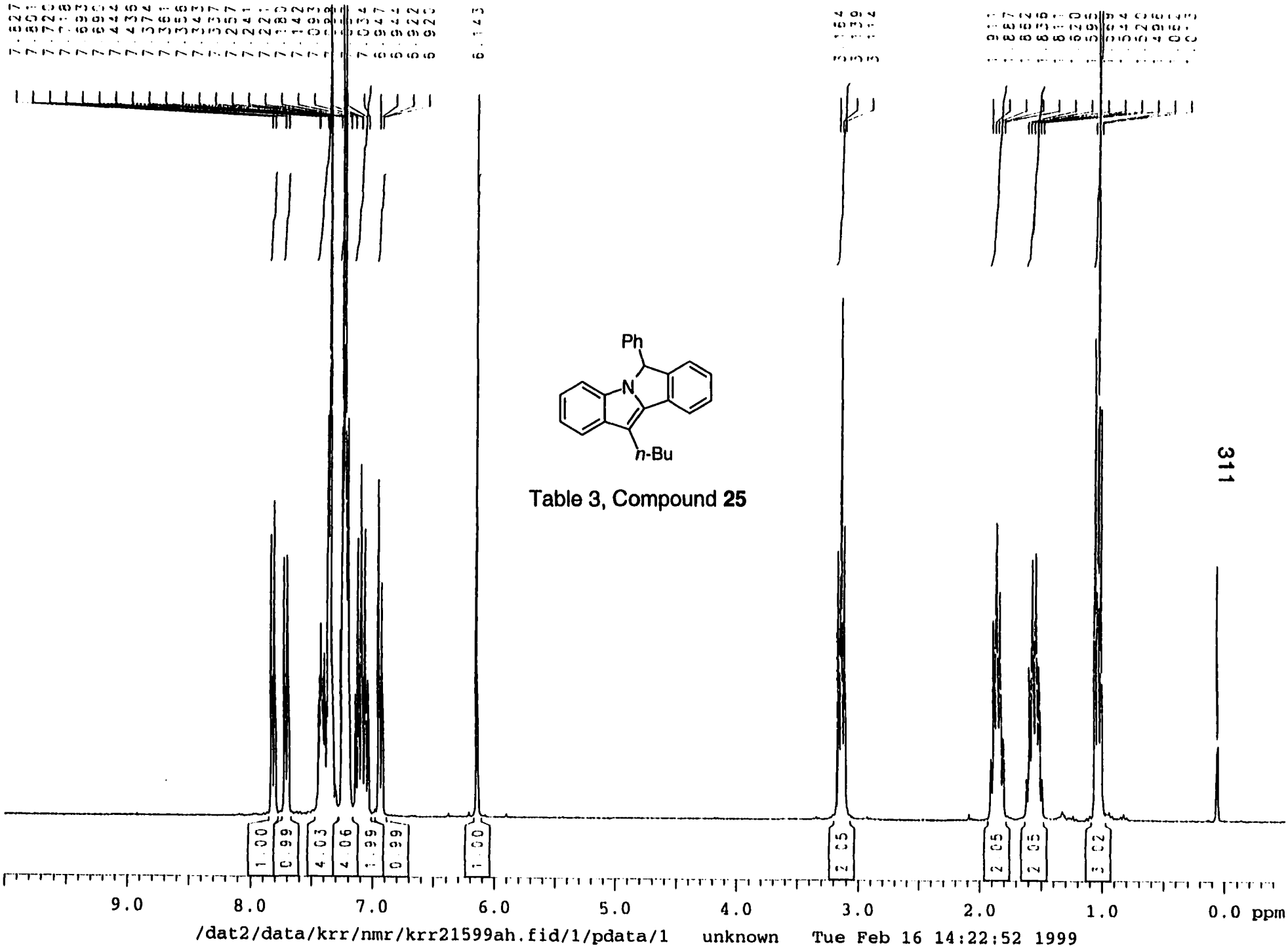
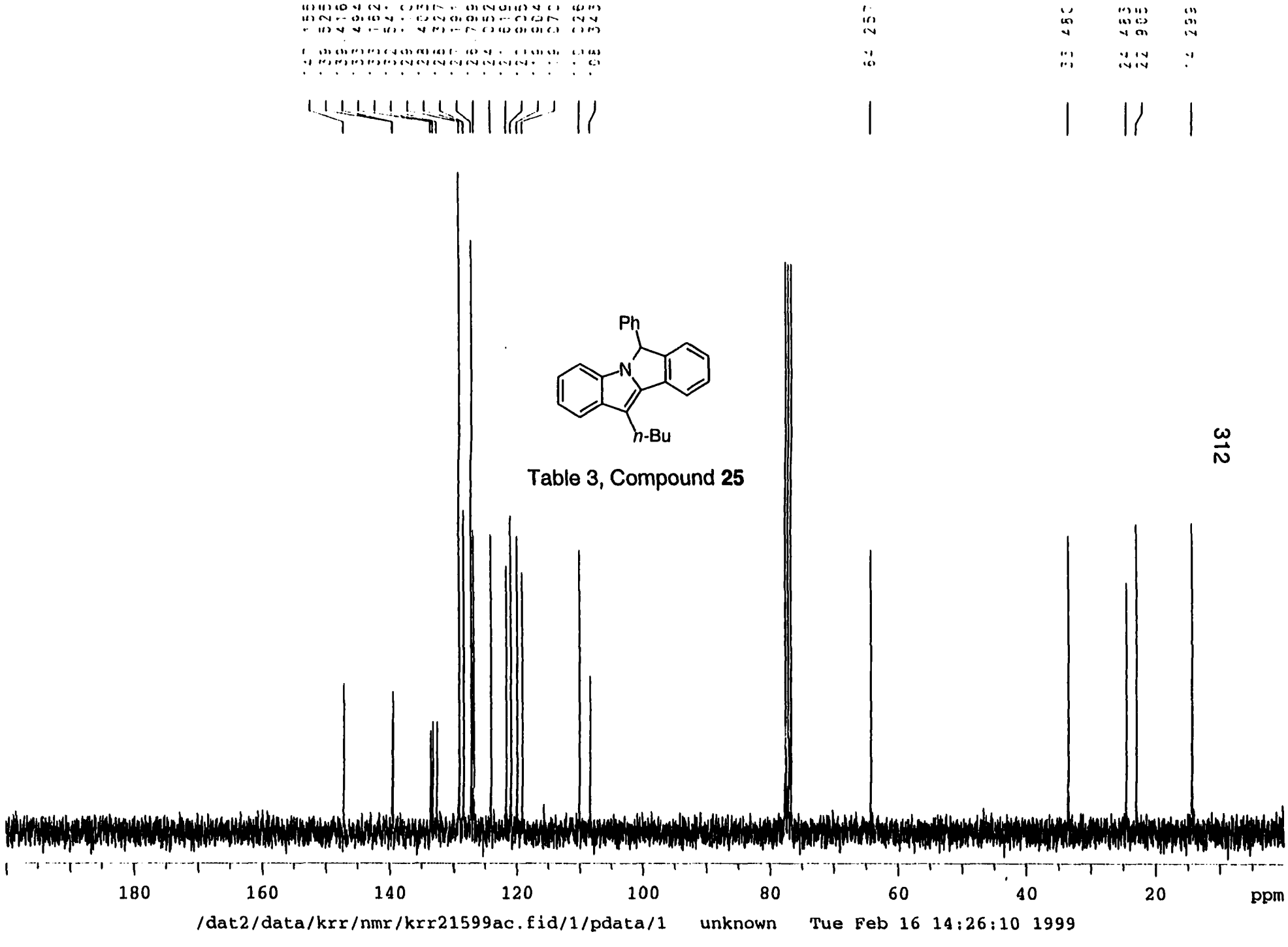


Table 3, Compound **25**


Ph
N
n-Bu
Table 3, Compound 25
312
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr21599ac.fid/1/pdata/1 unknown Tue Feb 16 14:26:10 1999

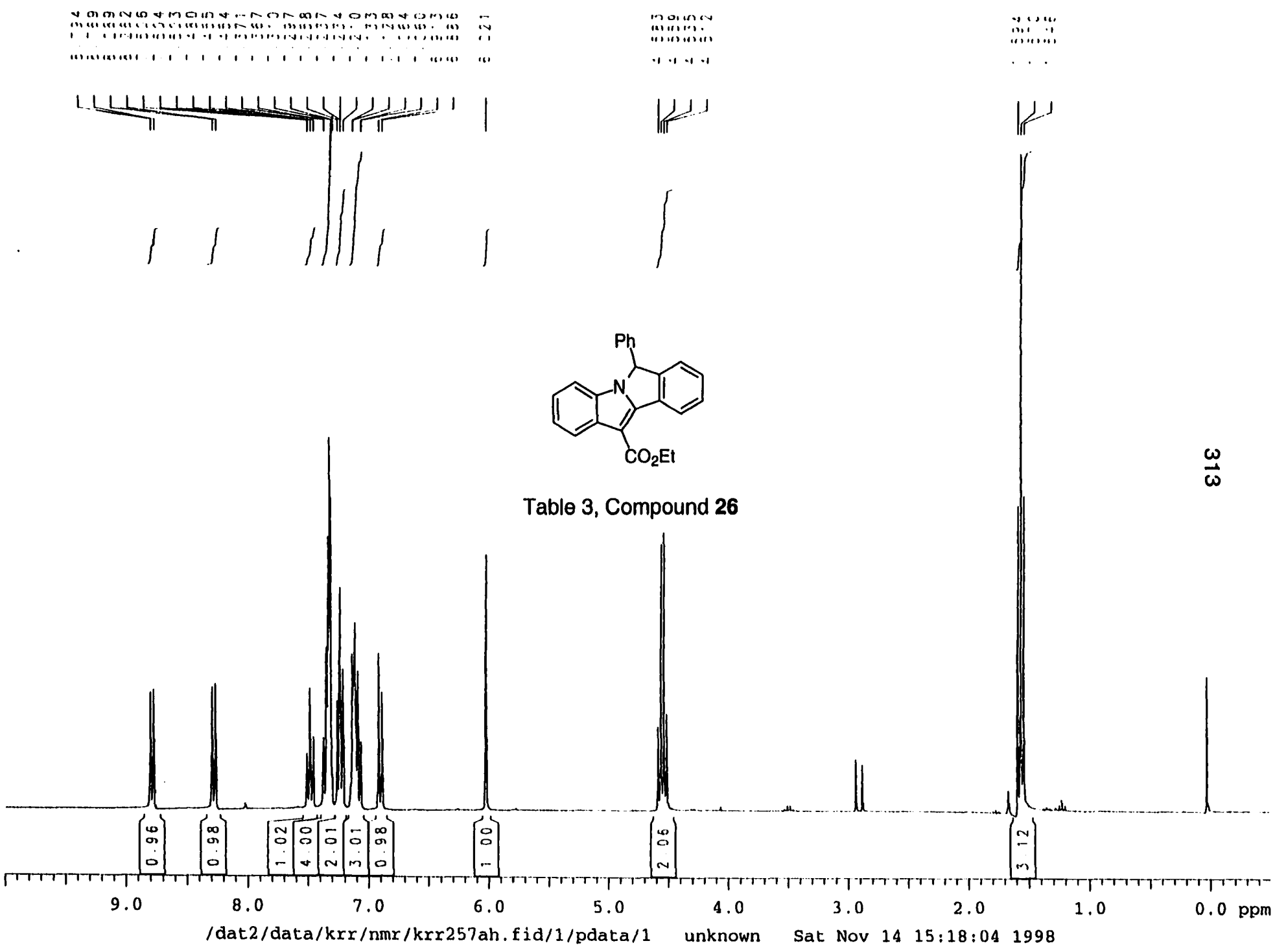


Table 3, Compound **26**

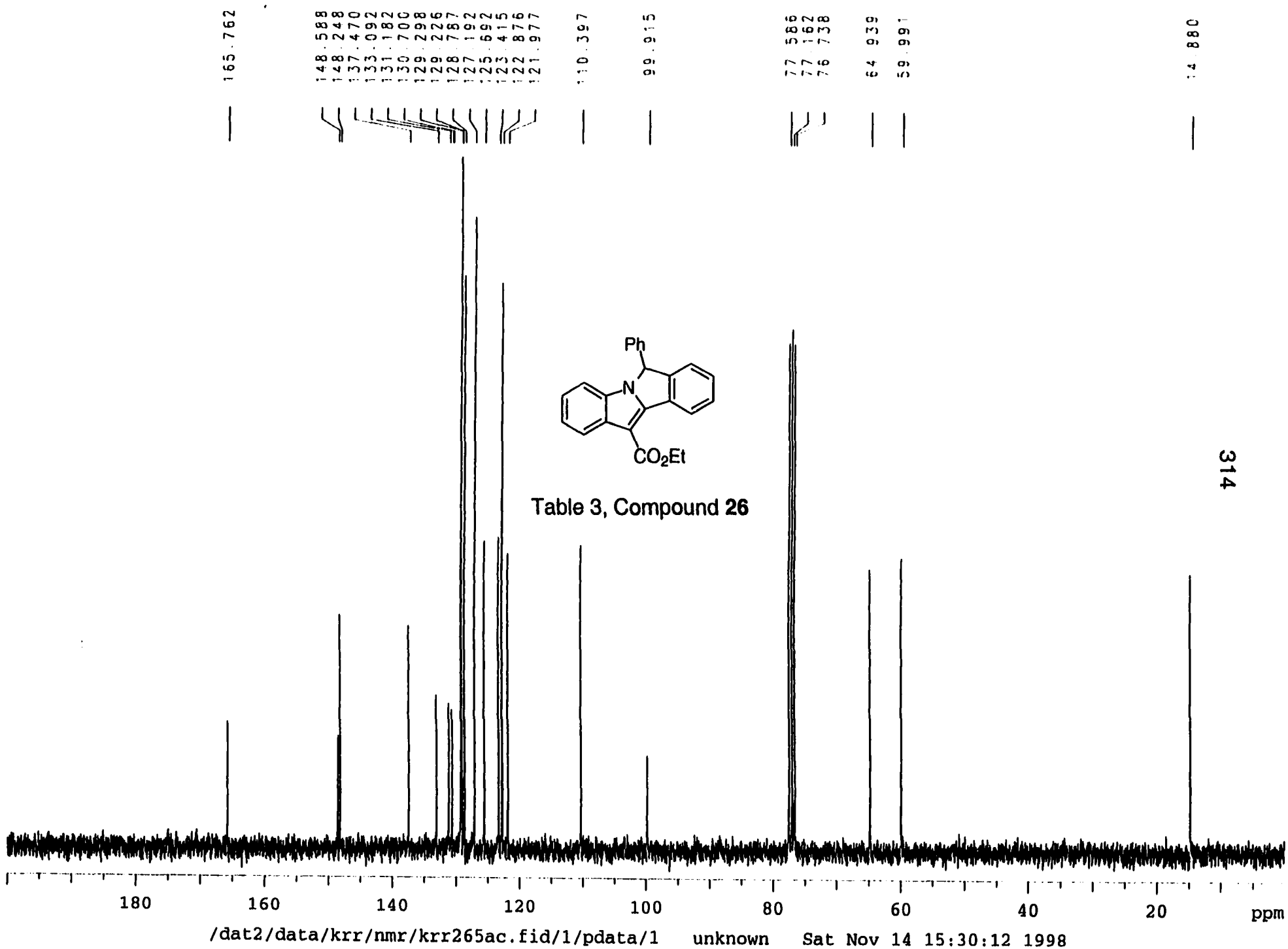


Table 3, Compound **26**

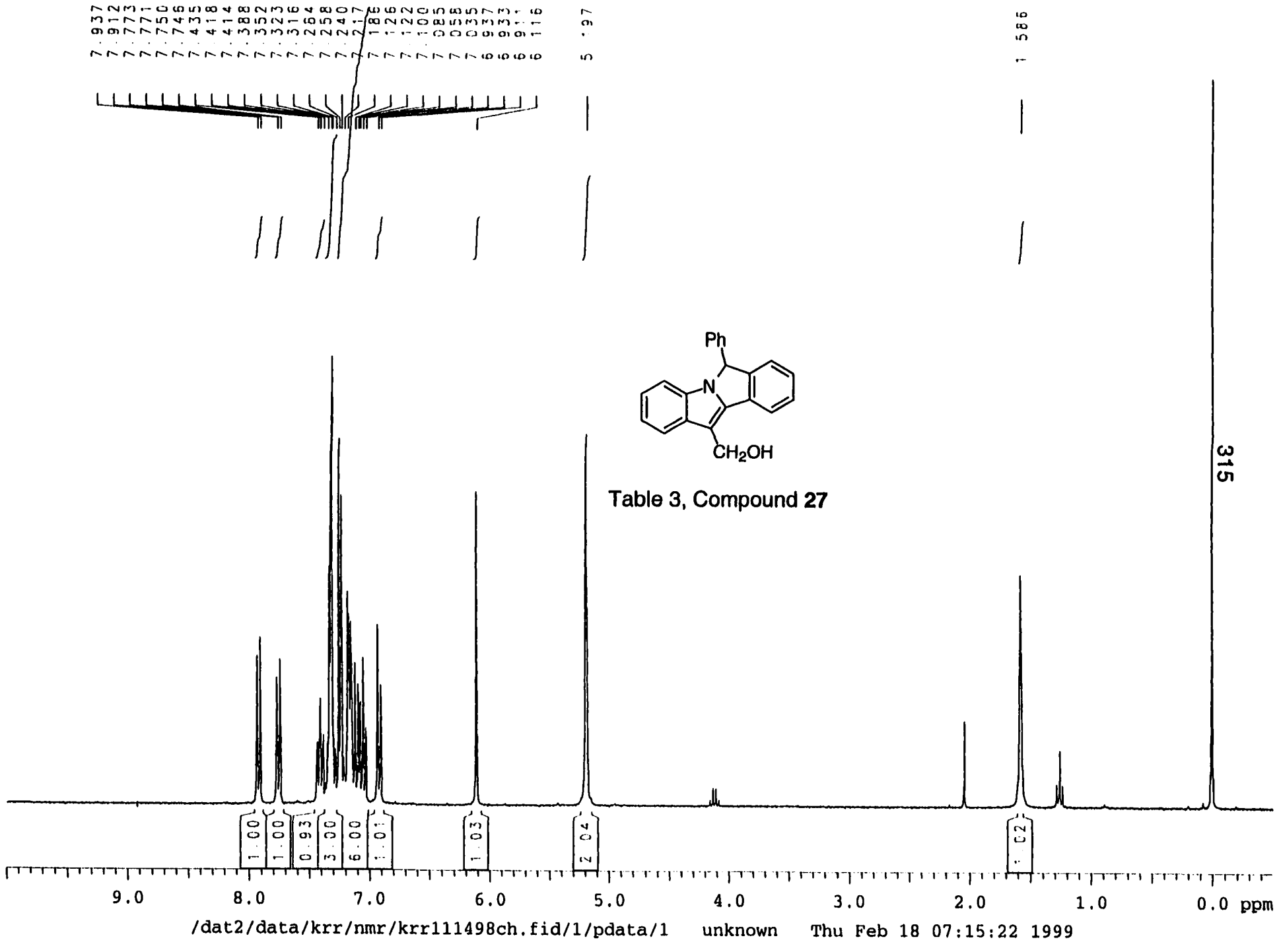


Table 3, Compound **27**

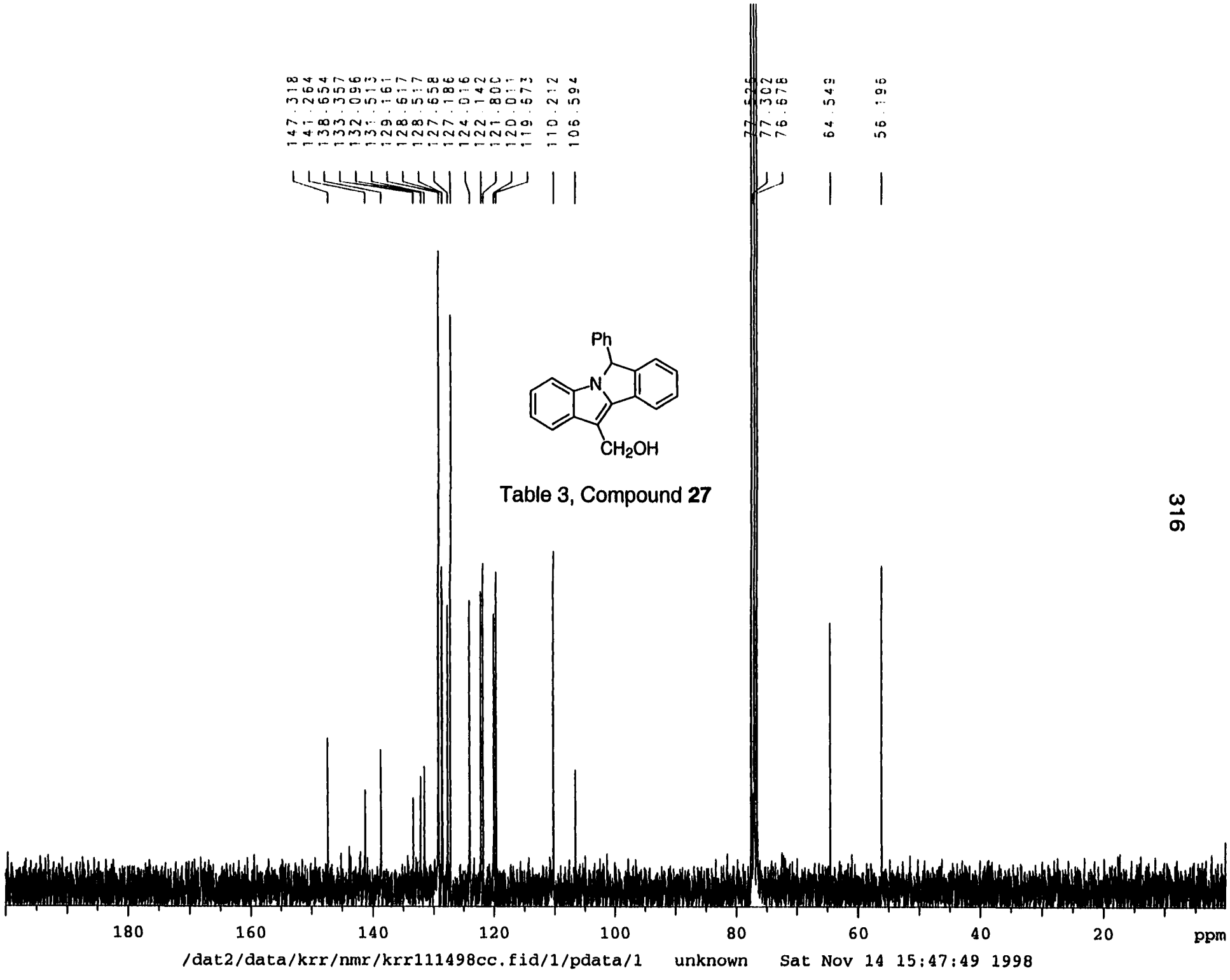


Table 3, Compound **27**

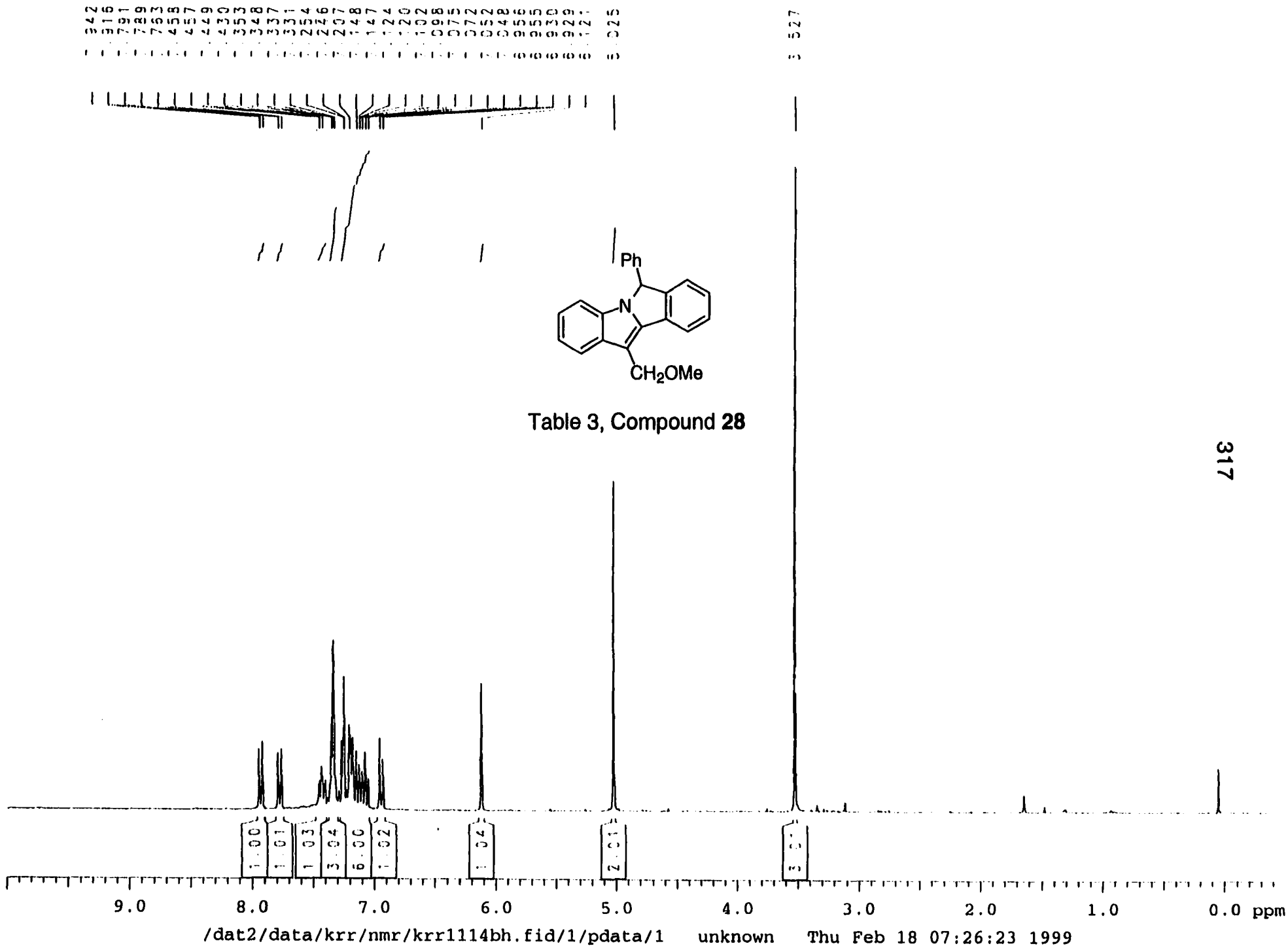


Table 3, Compound **28**

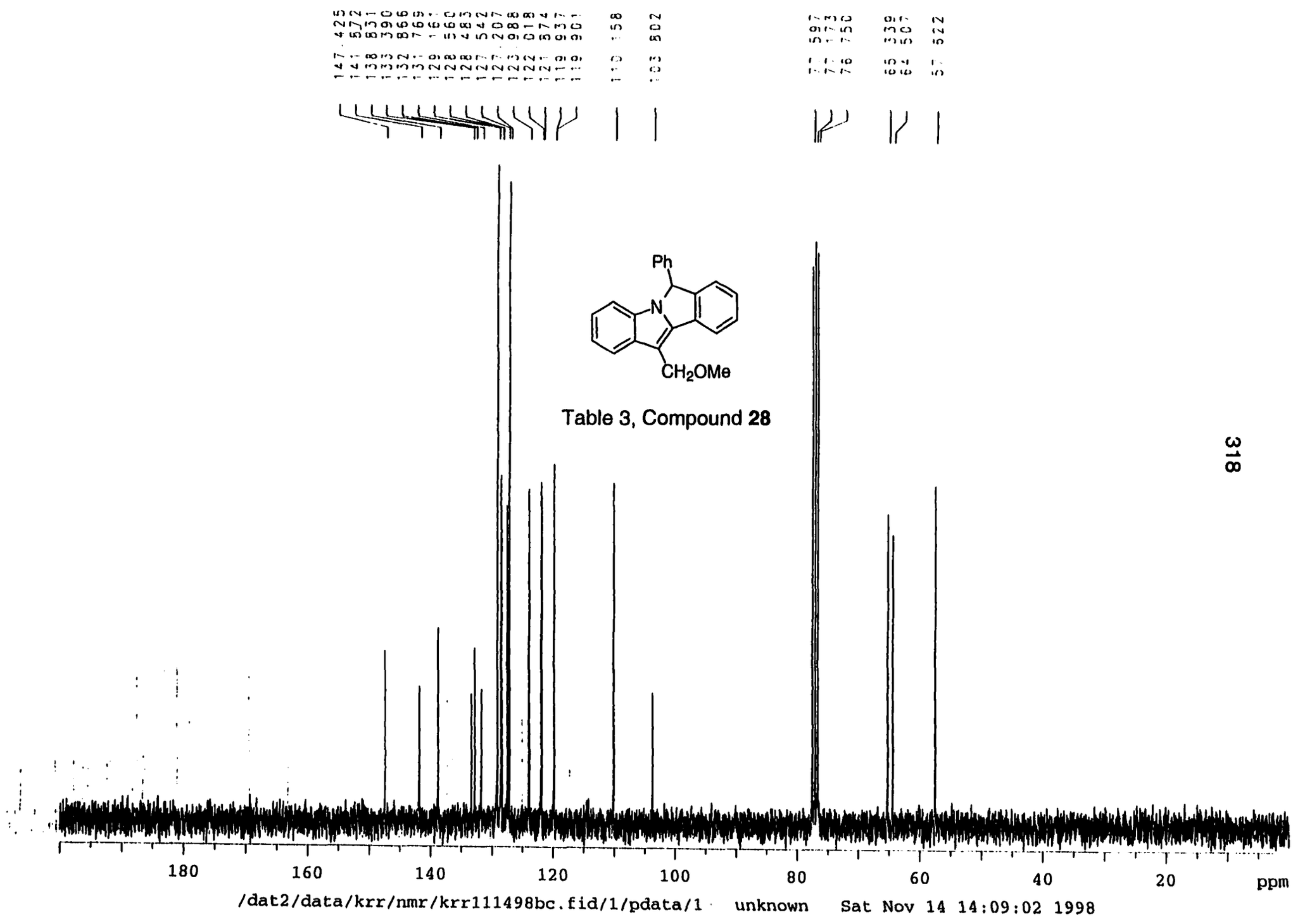


Table 3, Compound **28**

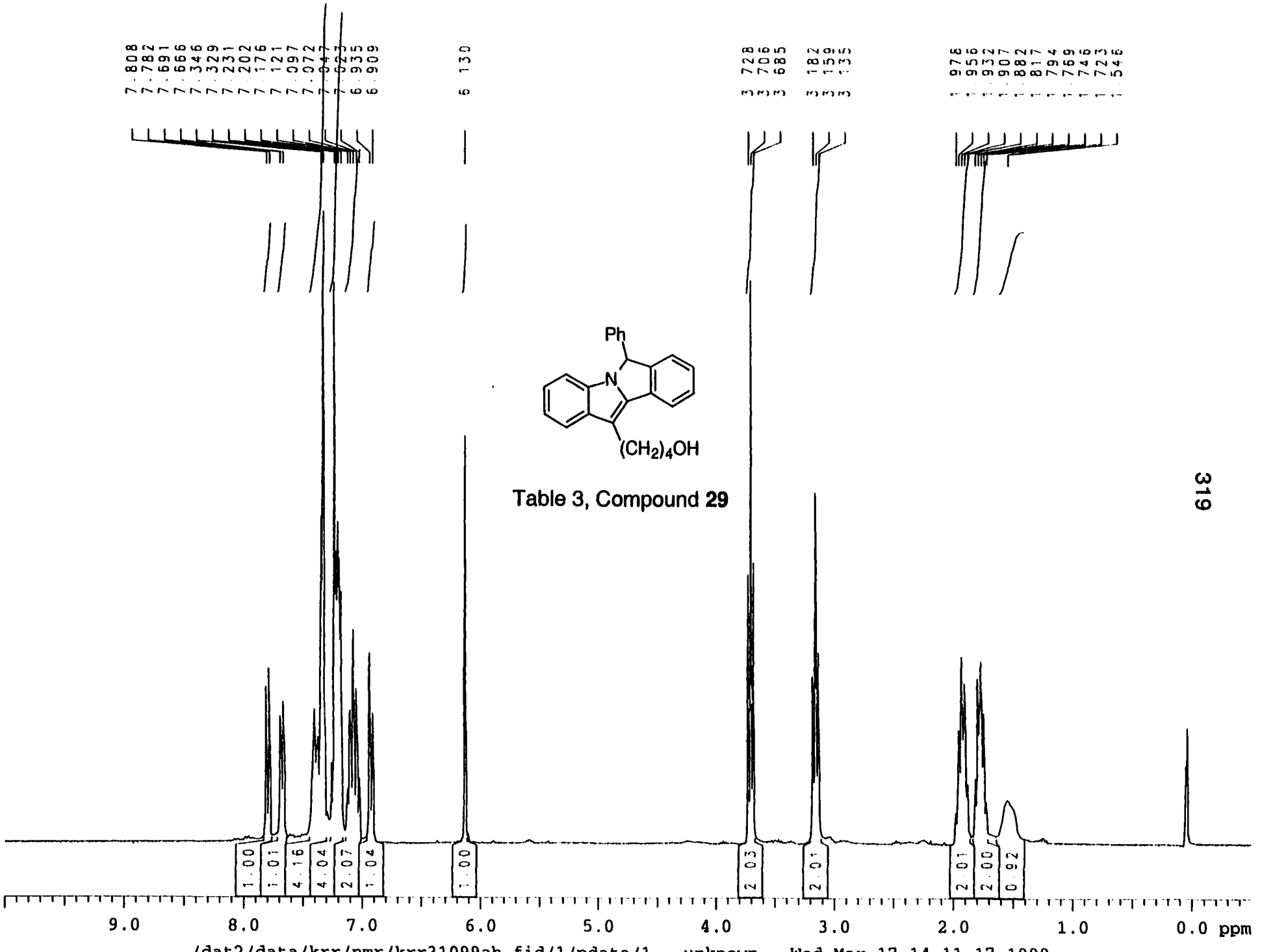
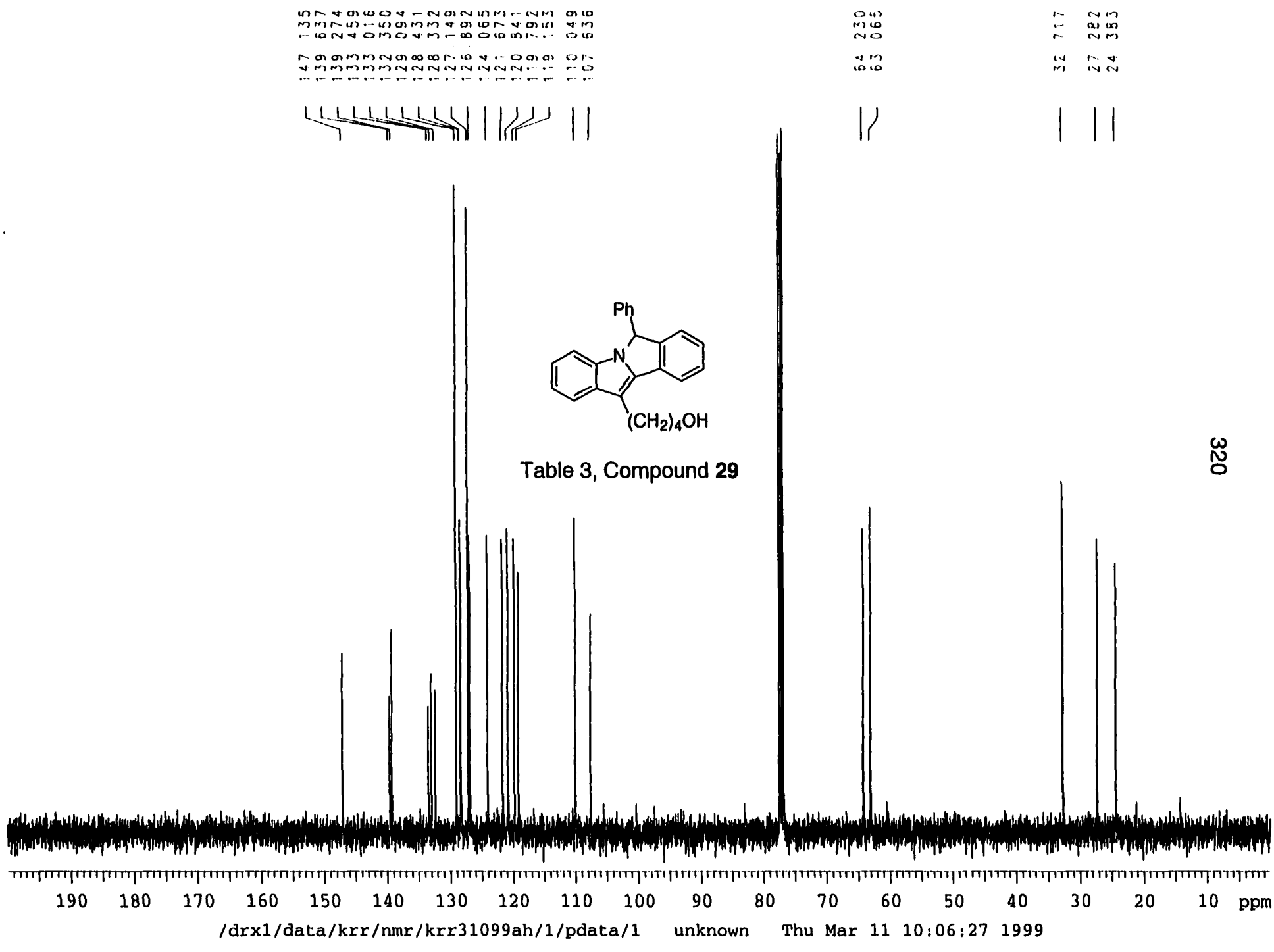


Table 3, Compound **29**


Ph
N
(CH2)4OH
Table 3, Compound 29
320
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
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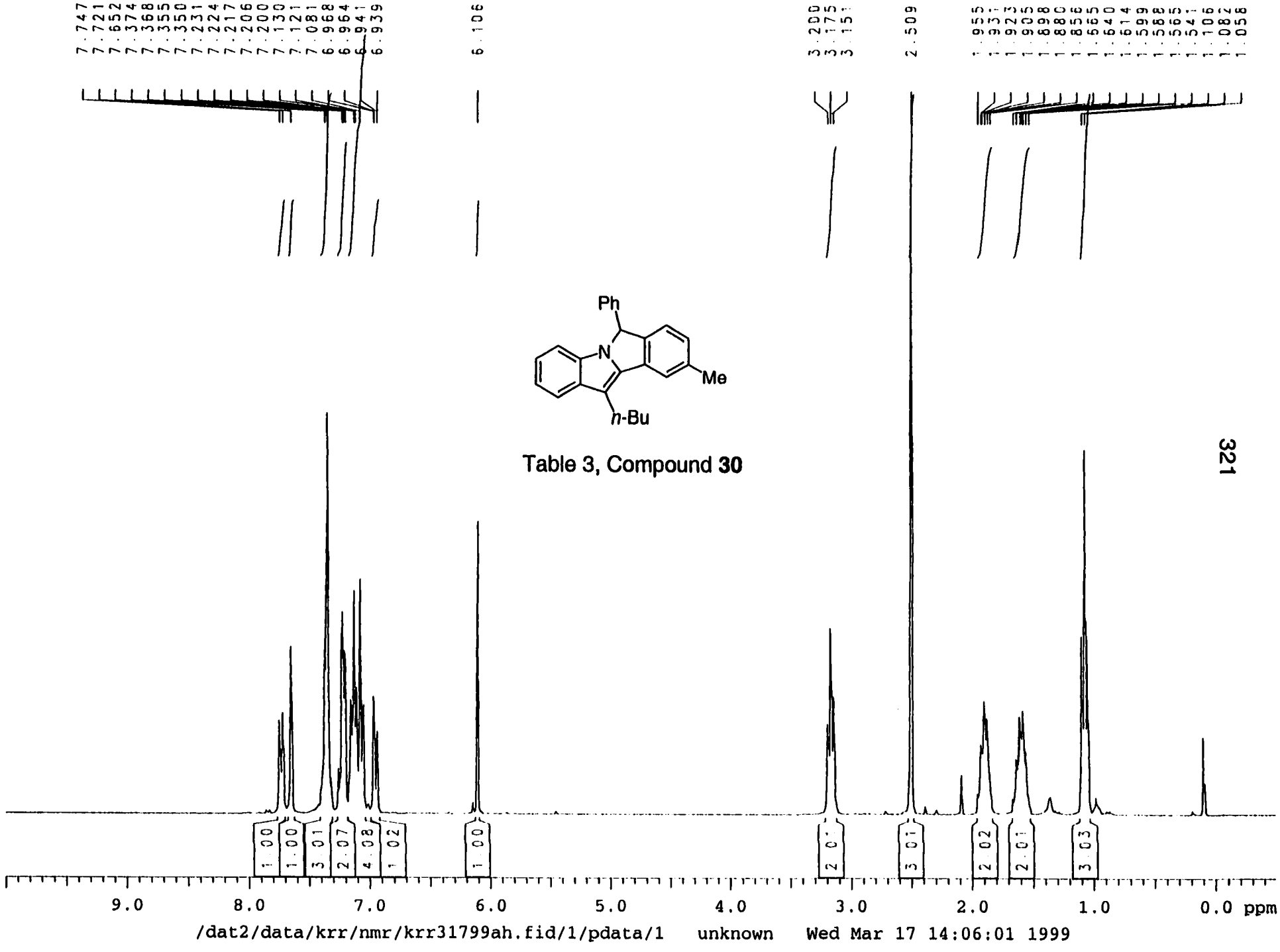
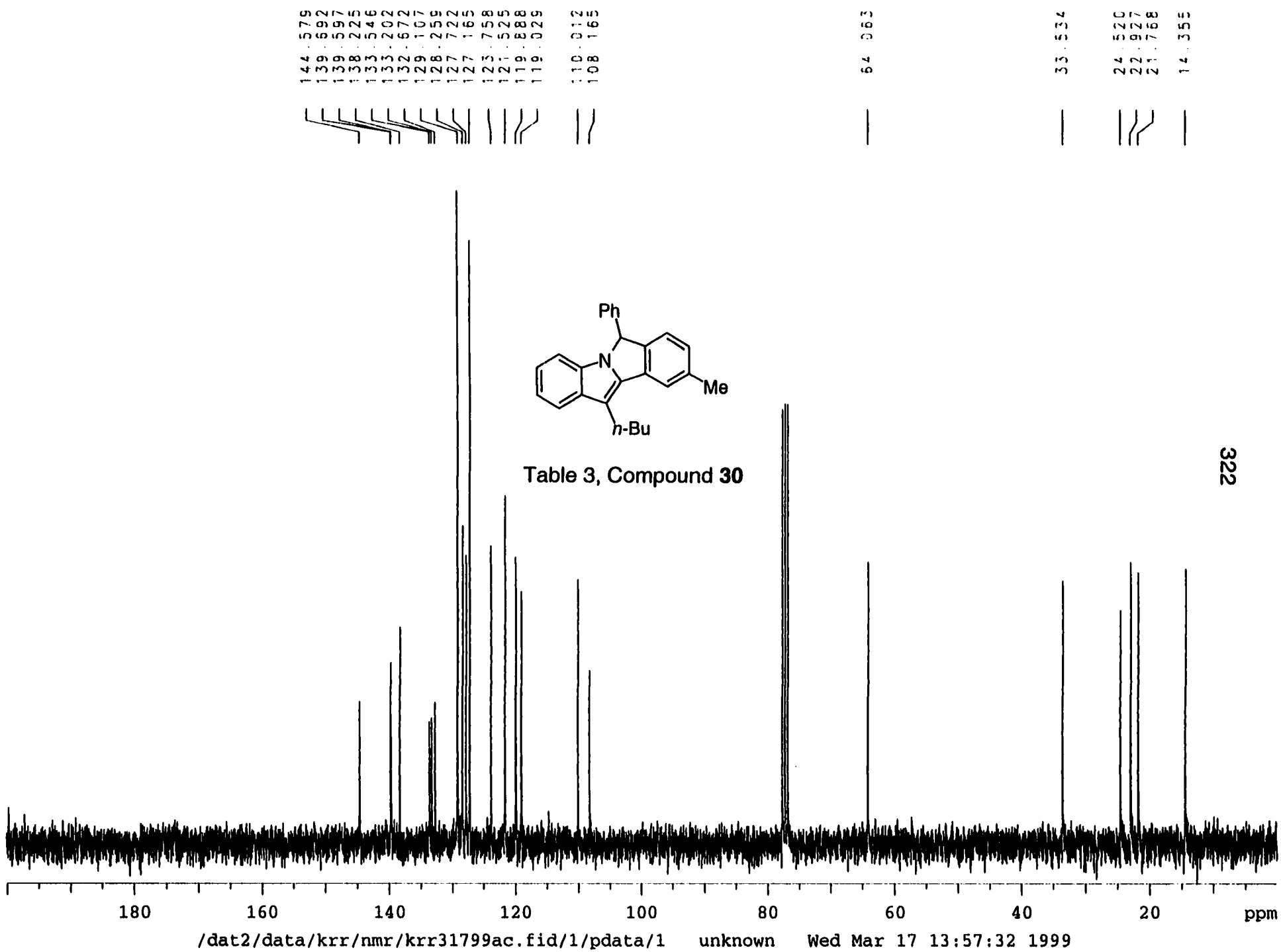


Table 3, Compound **30**


144.579
139.692
139.597
138.225
133.546
133.202
132.672
129.107
128.259
127.722
127.165
123.758
121.525
119.888
119.029
110.012
108.165
64.063
33.534
24.520
22.927
21.768
14.355
Ph
N
Me
n-Bu
Table 3, Compound 30
322
180
160
140
120
100
80
60
40
20
ppm
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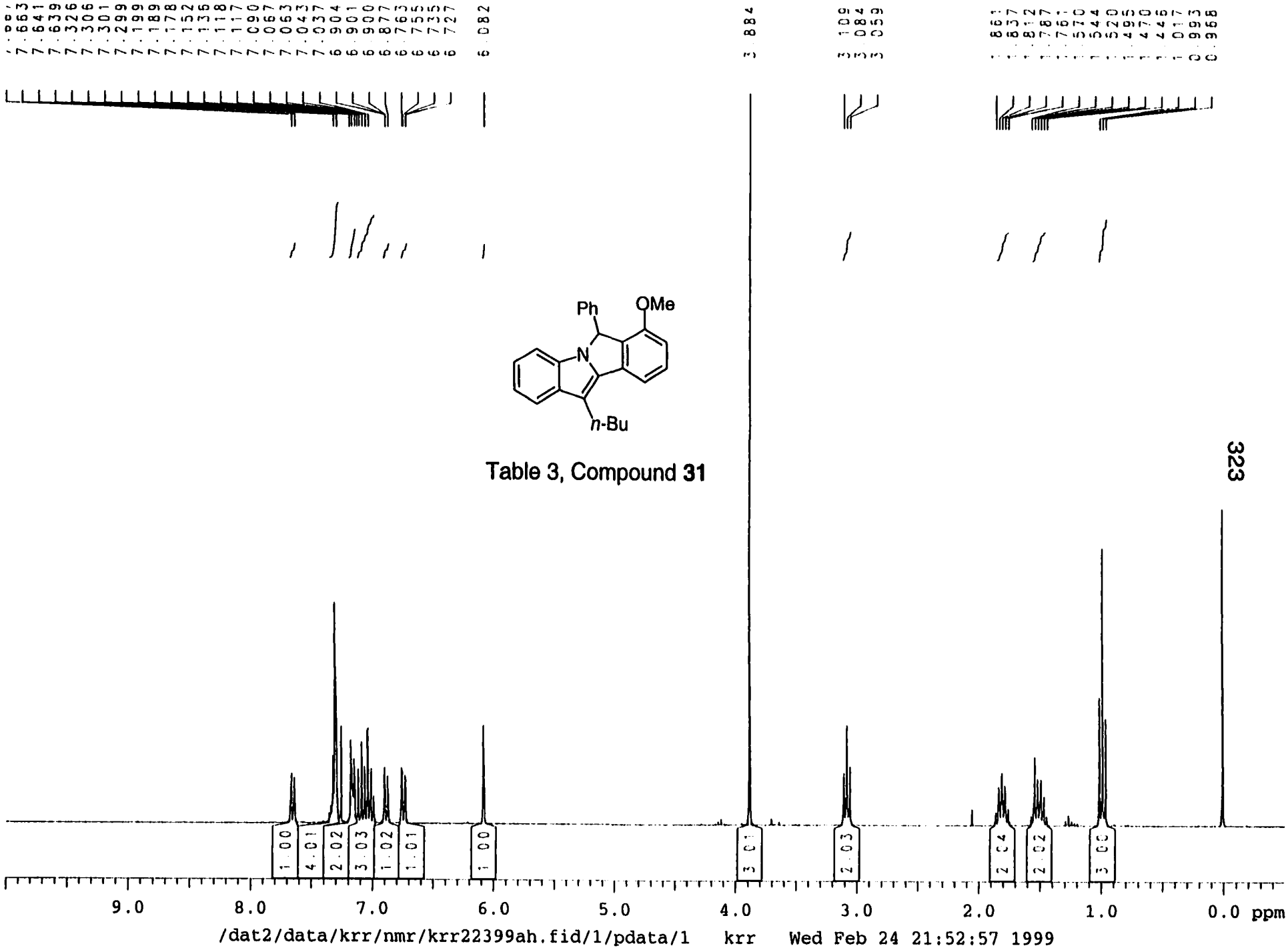

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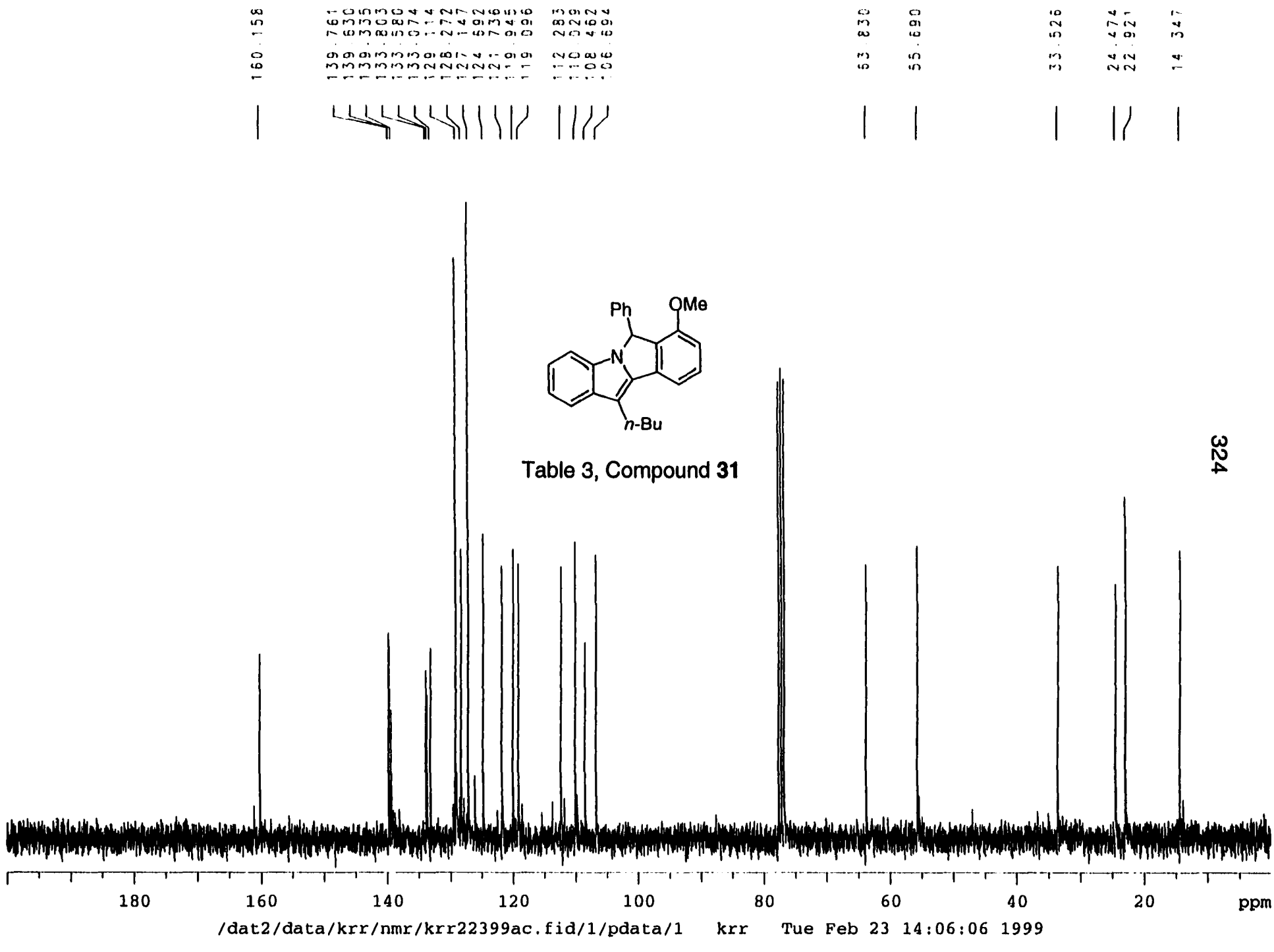
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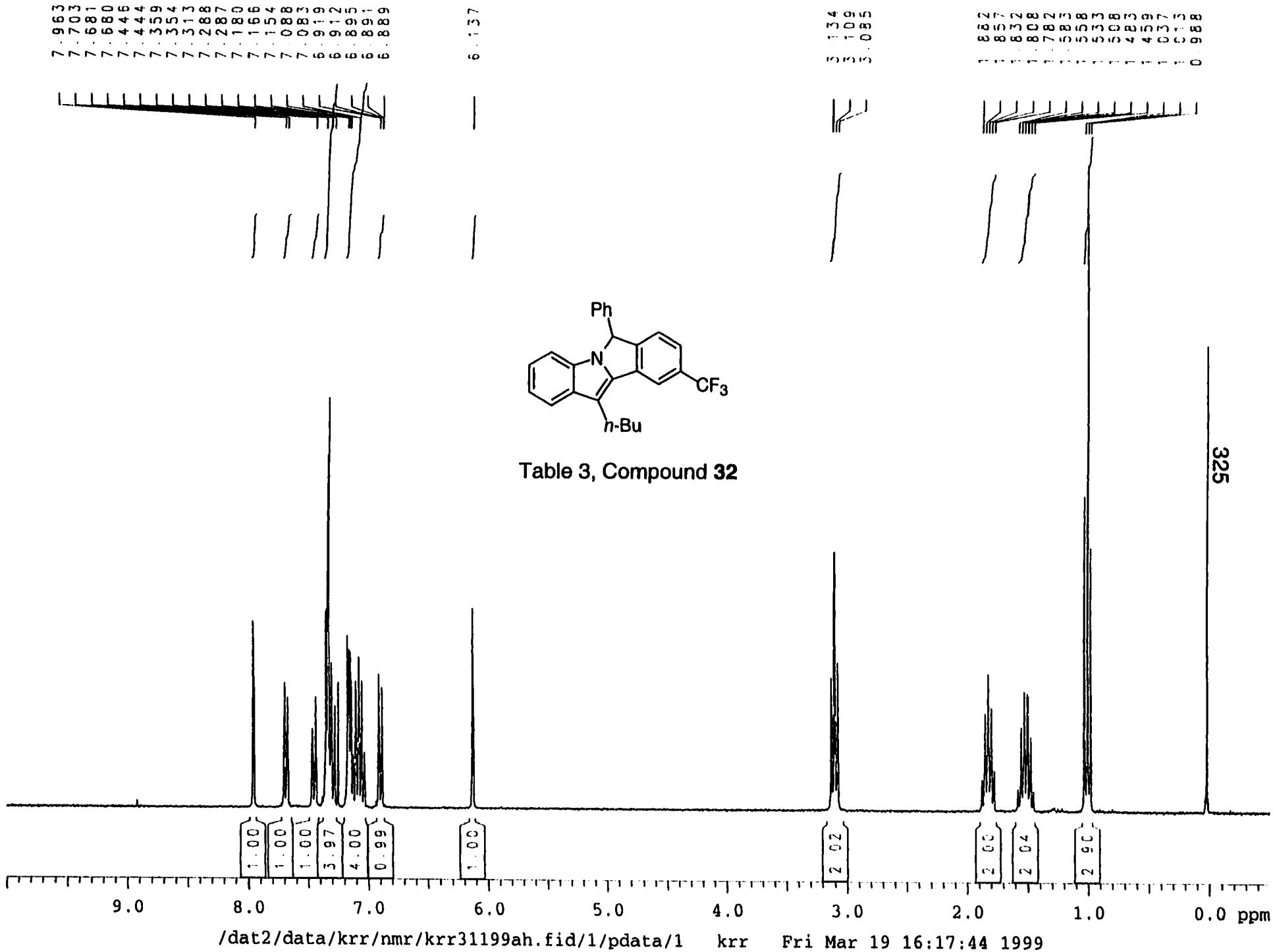
139.761
139.630
139.335
133.803
133.580
133.074
129.114
128.272
124.592
121.736
119.945
119.096
112.283
110.529
108.462
106.894
63.830
55.690
33.526
24.474
22.921
14.347
Ph
OMe
N
n-Bu
Table 3, Compound 31
324
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr22399ac.fid/1/pdata/1 krr Tue Feb 23 14:06:06 1999



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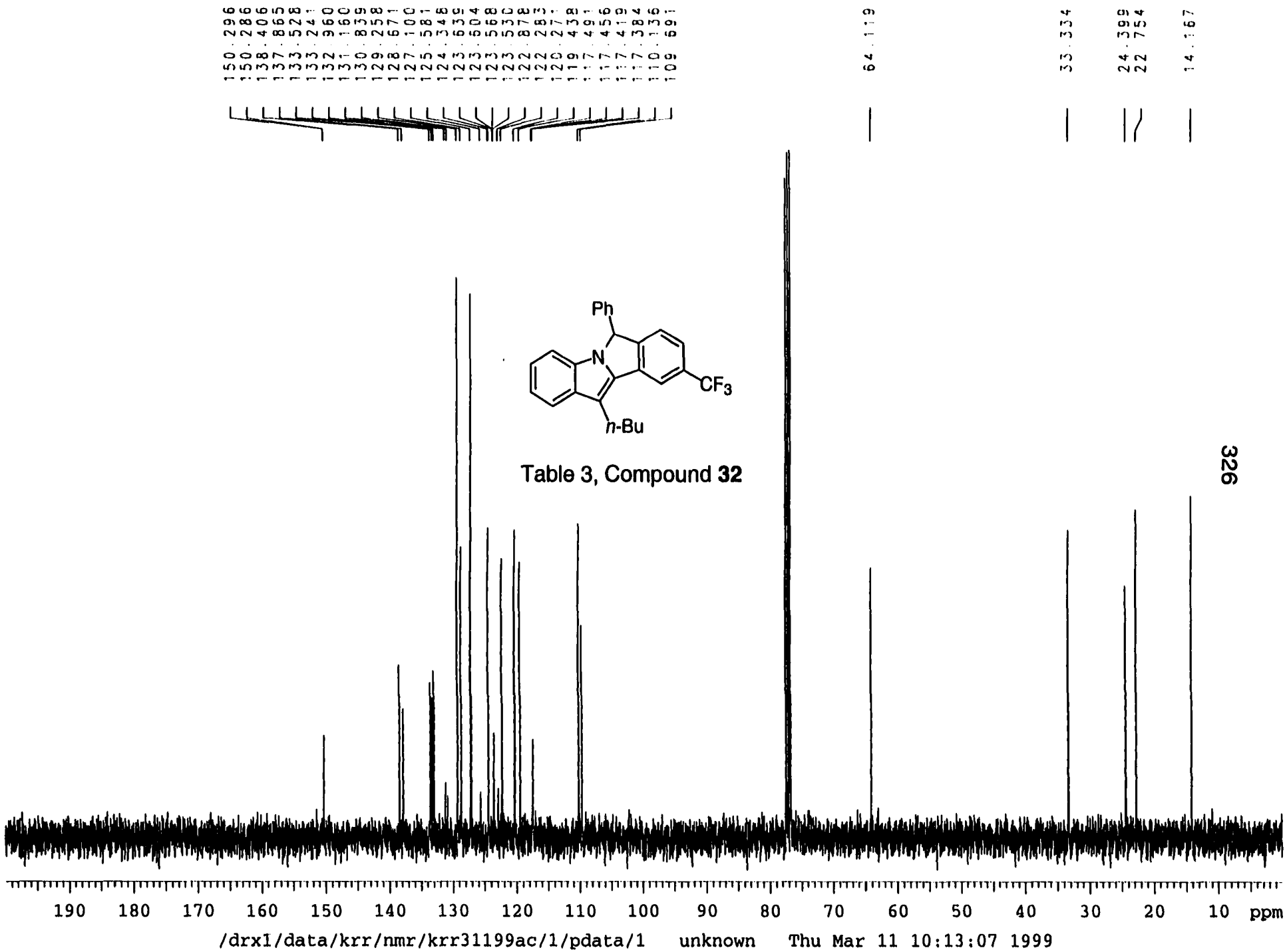
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150.286
138.406
137.865
133.528
133.241
132.960
131.160
130.839
129.258
128.671
127.100
125.581
124.346
123.639
123.604
123.568
123.535
122.878
122.283
120.27
119.438
117.491
117.456
117.419
117.384
110.136
109.691
64.119
33.334
24.399
22.754
14.167
Ph
N
CF3
n-Bu
Table 3, Compound 32
326
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
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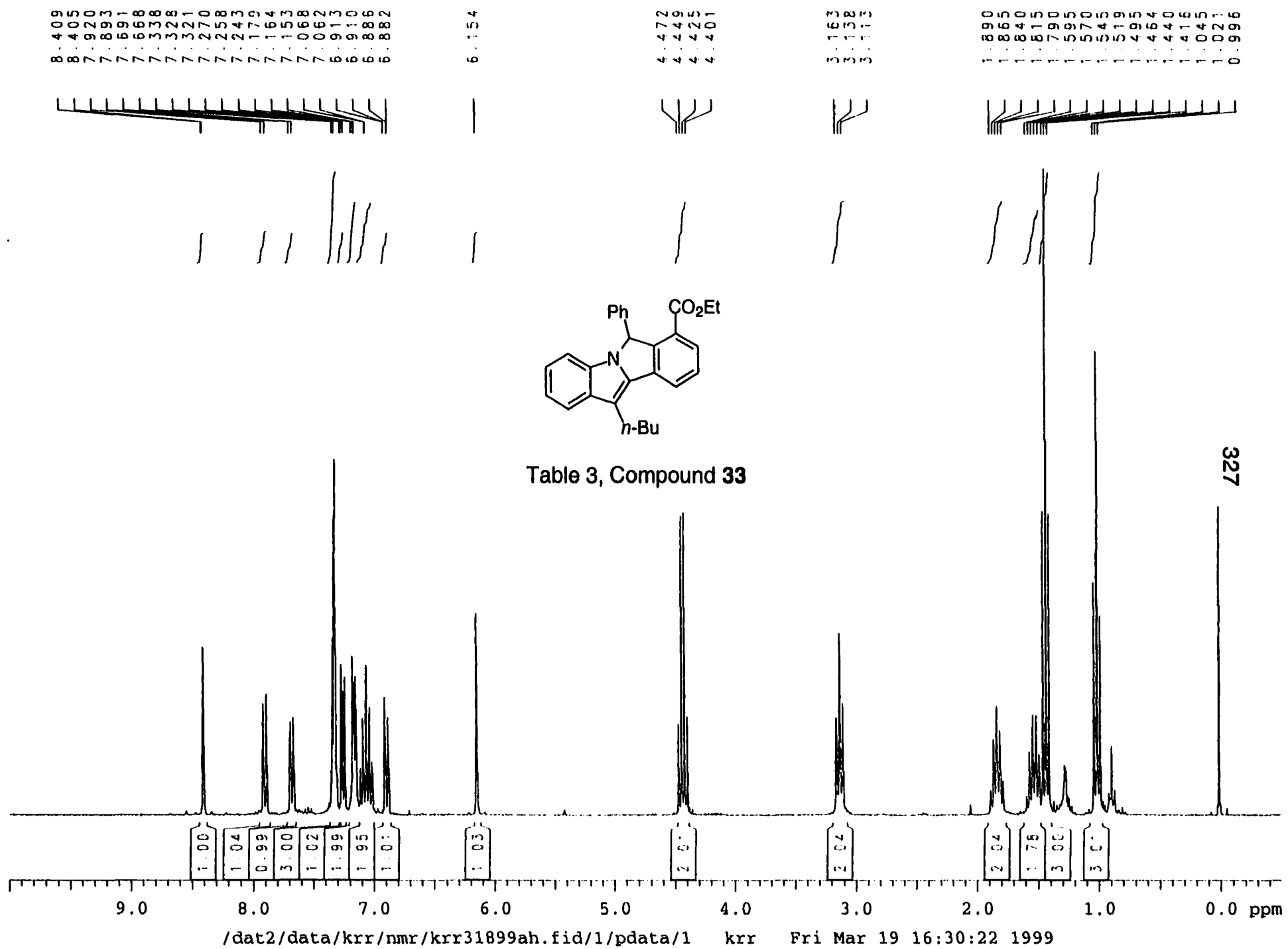
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8.405
7.920
7.893
7.691
7.668
7.338
7.328
7.321
7.270
7.258
7.243
7.175
7.164
7.153
7.068
7.062
6.913
6.910
6.886
6.882
6.154
4.472
4.449
4.425
4.401
3.163
3.138
3.113
1.890
1.865
1.840
1.815
1.790
1.595
1.570
1.545
1.519
1.495
1.464
1.440
1.416
1.045
1.021
0.996
Ph
CO2Et
N
n-Bu
Table 3, Compound 33
327
1.00
1.04
0.99
3.00
1.02
1.99
1.95
1.03
2.04
2.04
1.78
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm
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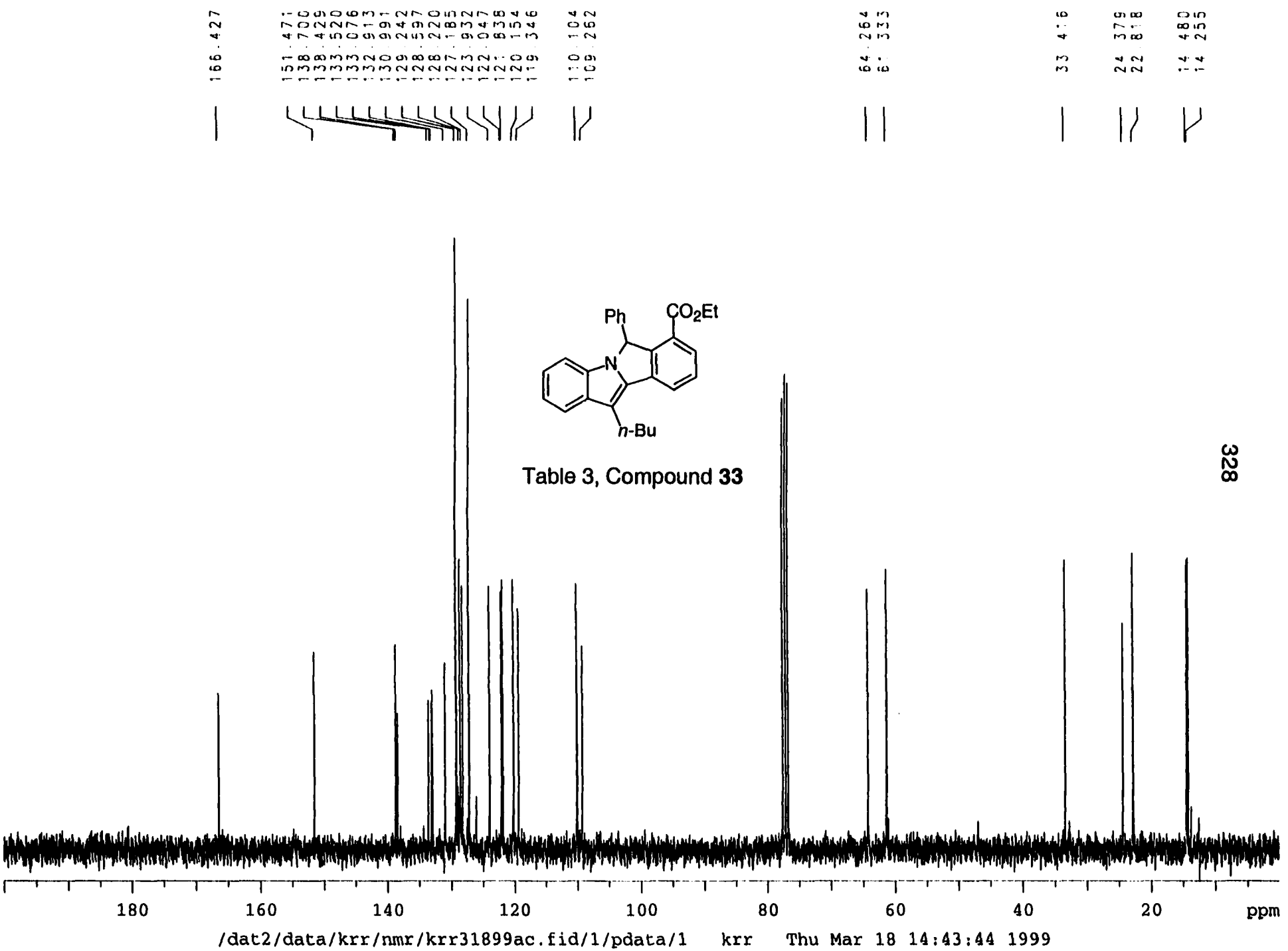
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151.471
138.700
138.429
133.520
133.076
132.913
130.991
129.242
128.597
128.220
127.185
123.932
122.047
64.264
33.416
24.379
22.818
14.480
14.255
Ph
CO2Et
N
n-Bu
Table 3, Compound 33
328
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr31899ac.fid/1/pdata/1 krr Thu Mar 18 14:43:44 1999

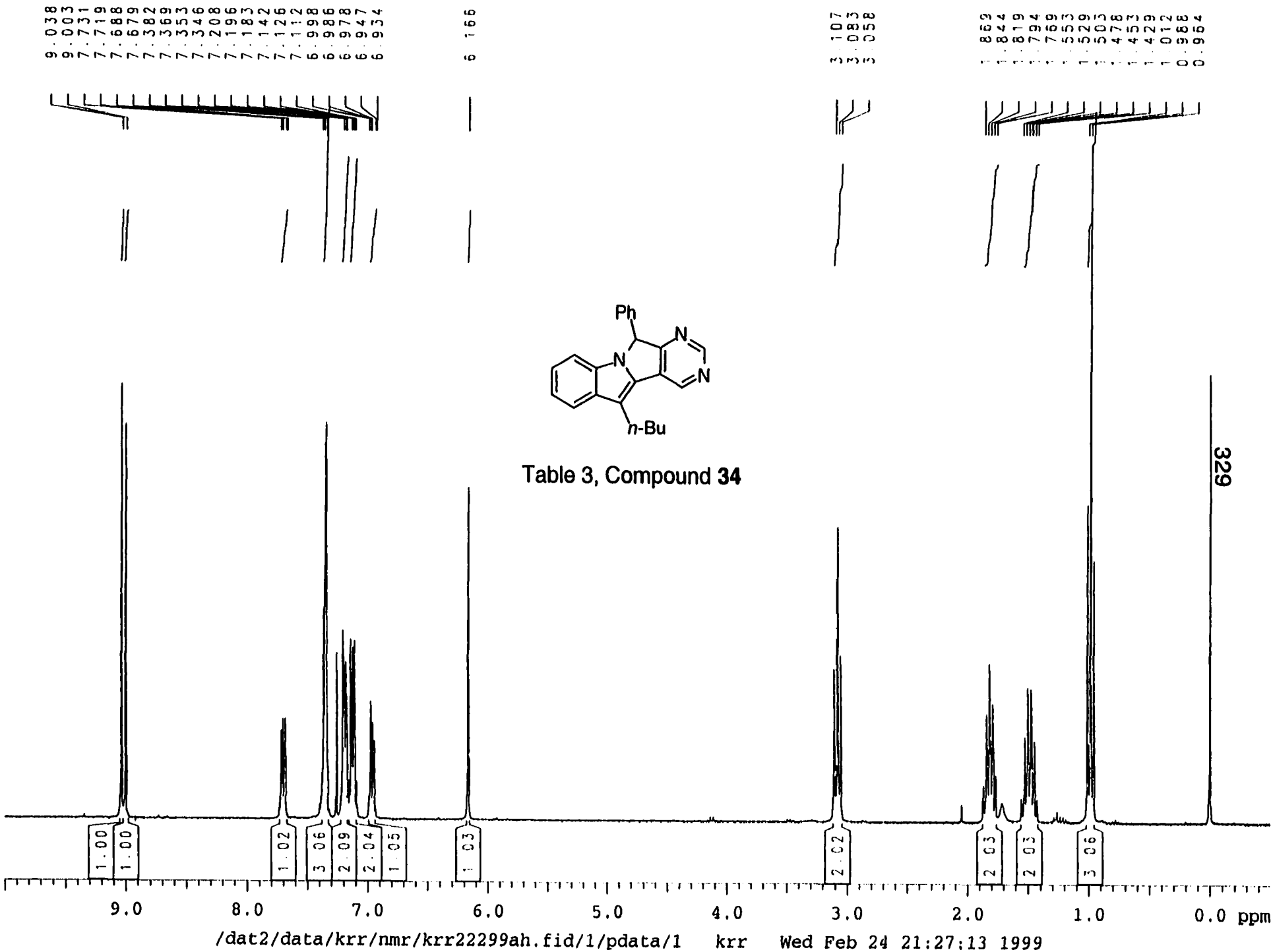
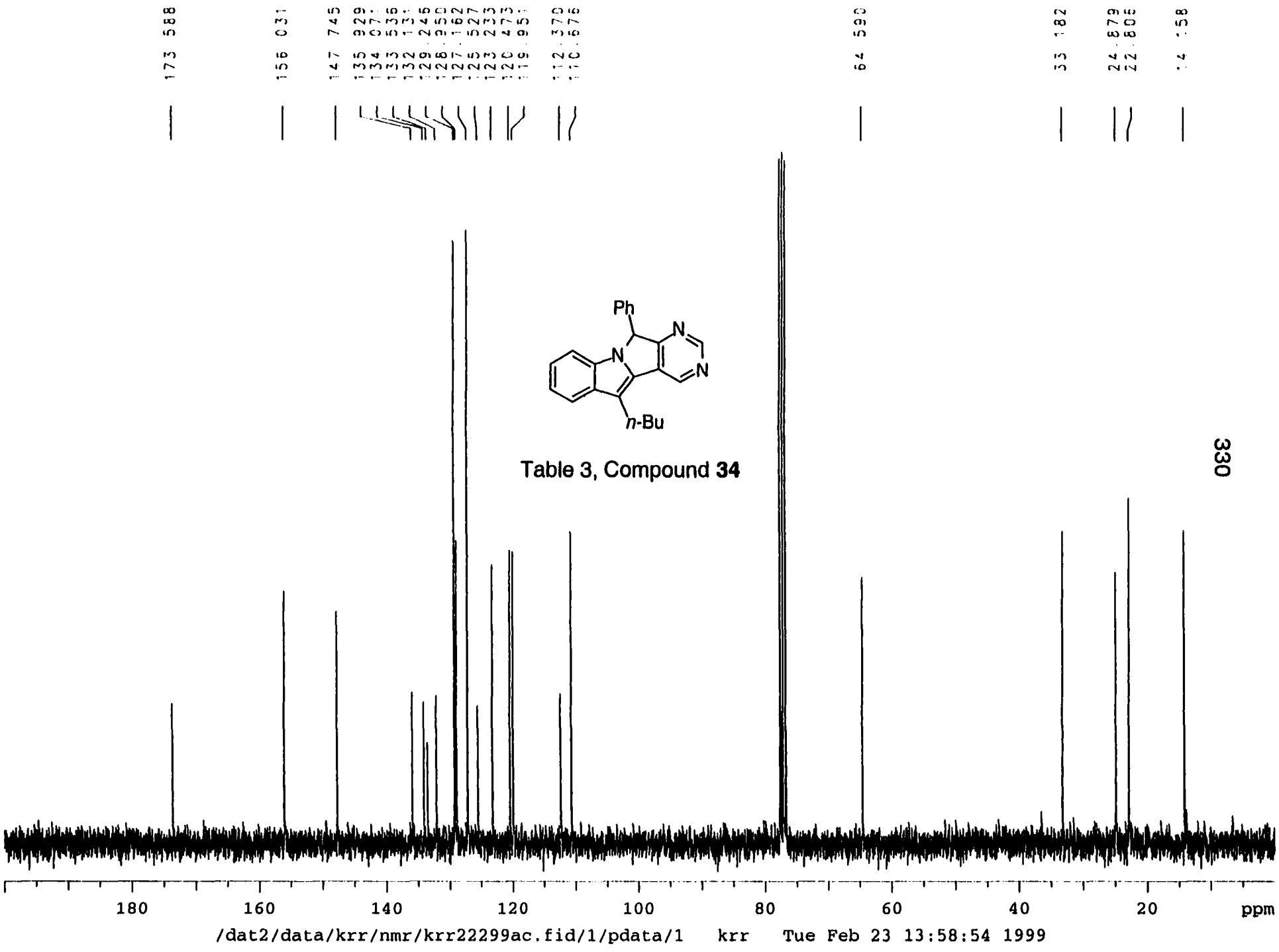
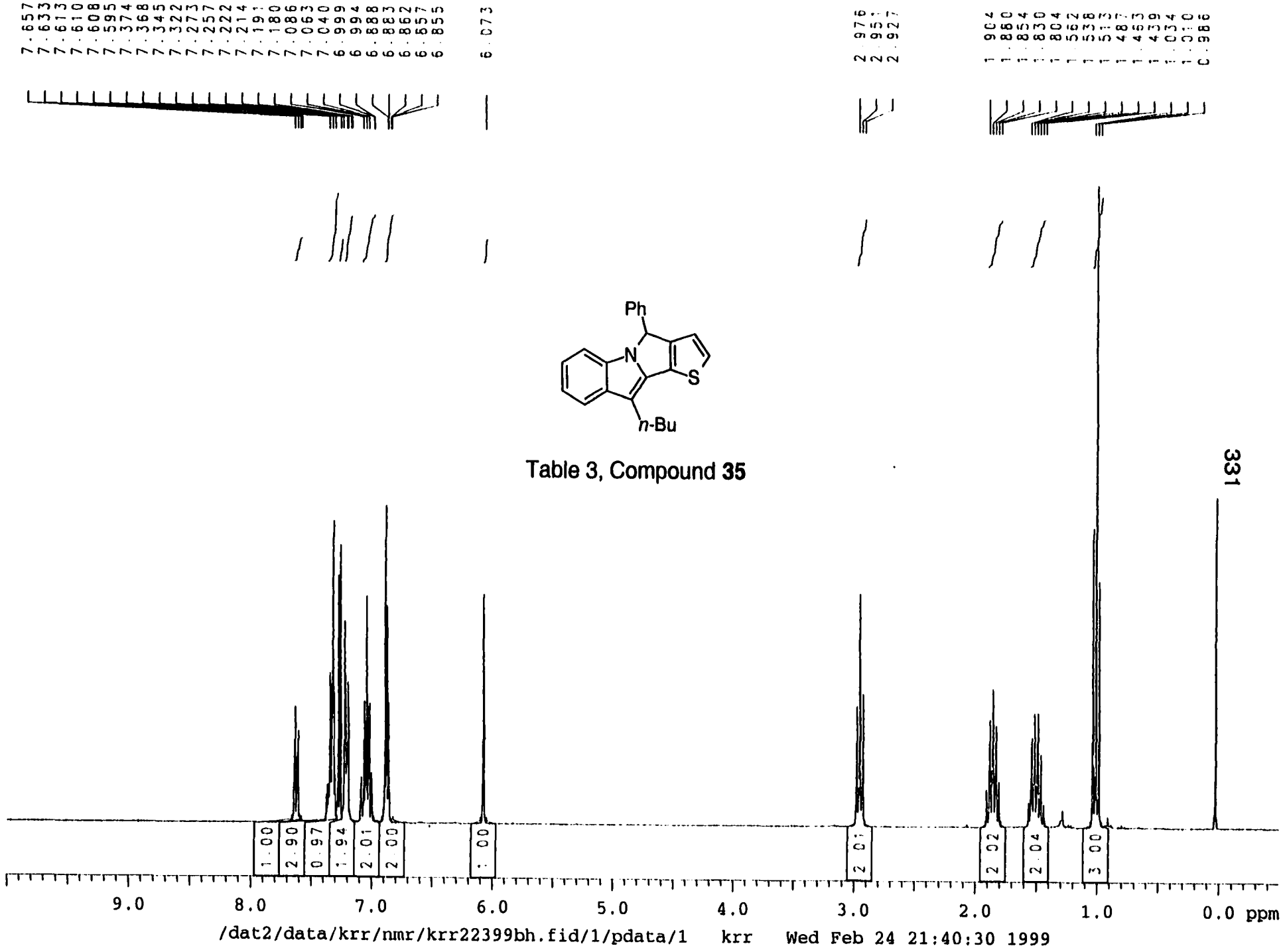


Table 3, Compound **34**


Ph
N
N
N
n-Bu
Table 3, Compound 34
330
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr22299ac.fid/1/pdata/1 krr Tue Feb 23 13:58:54 1999



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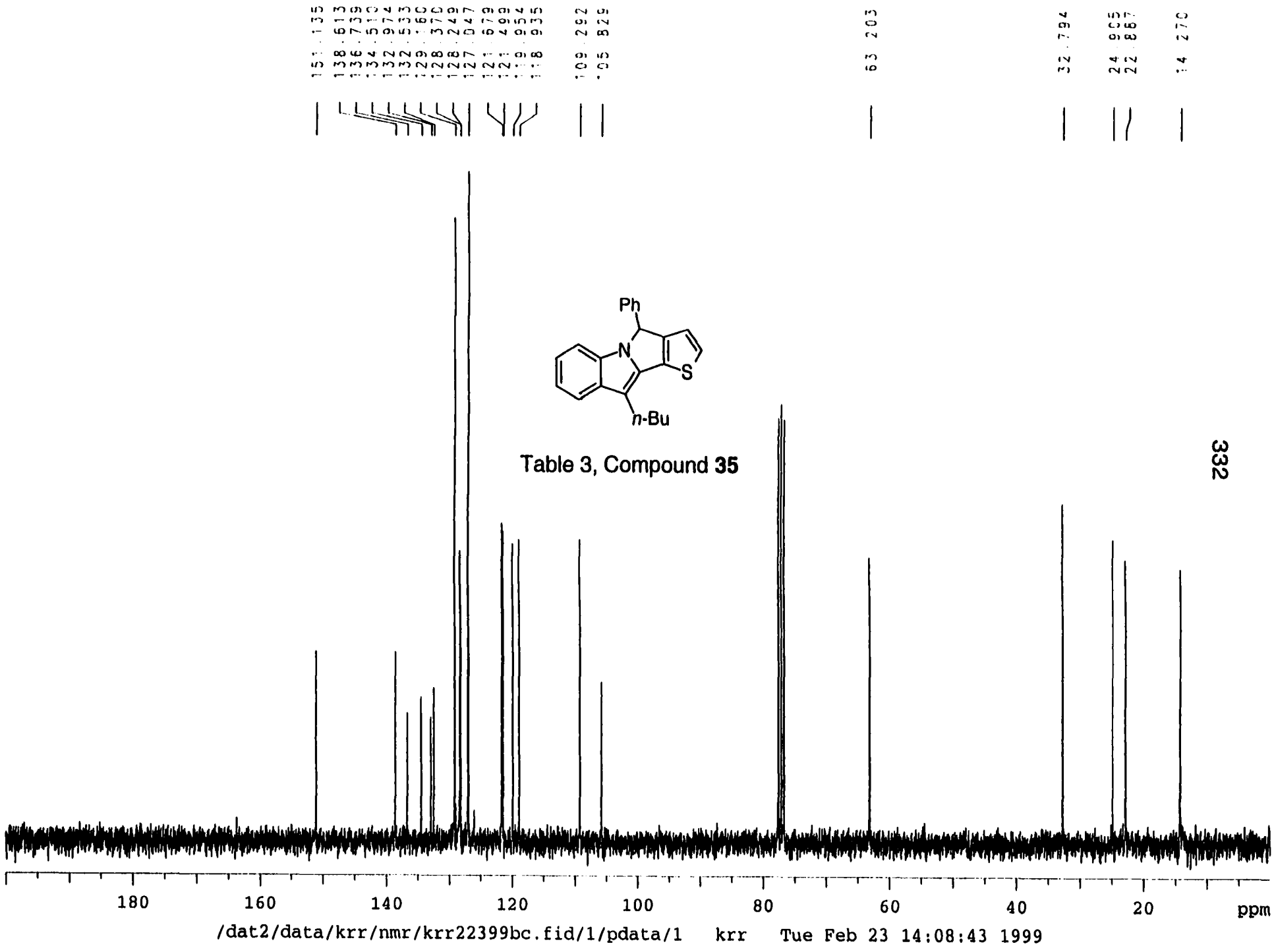
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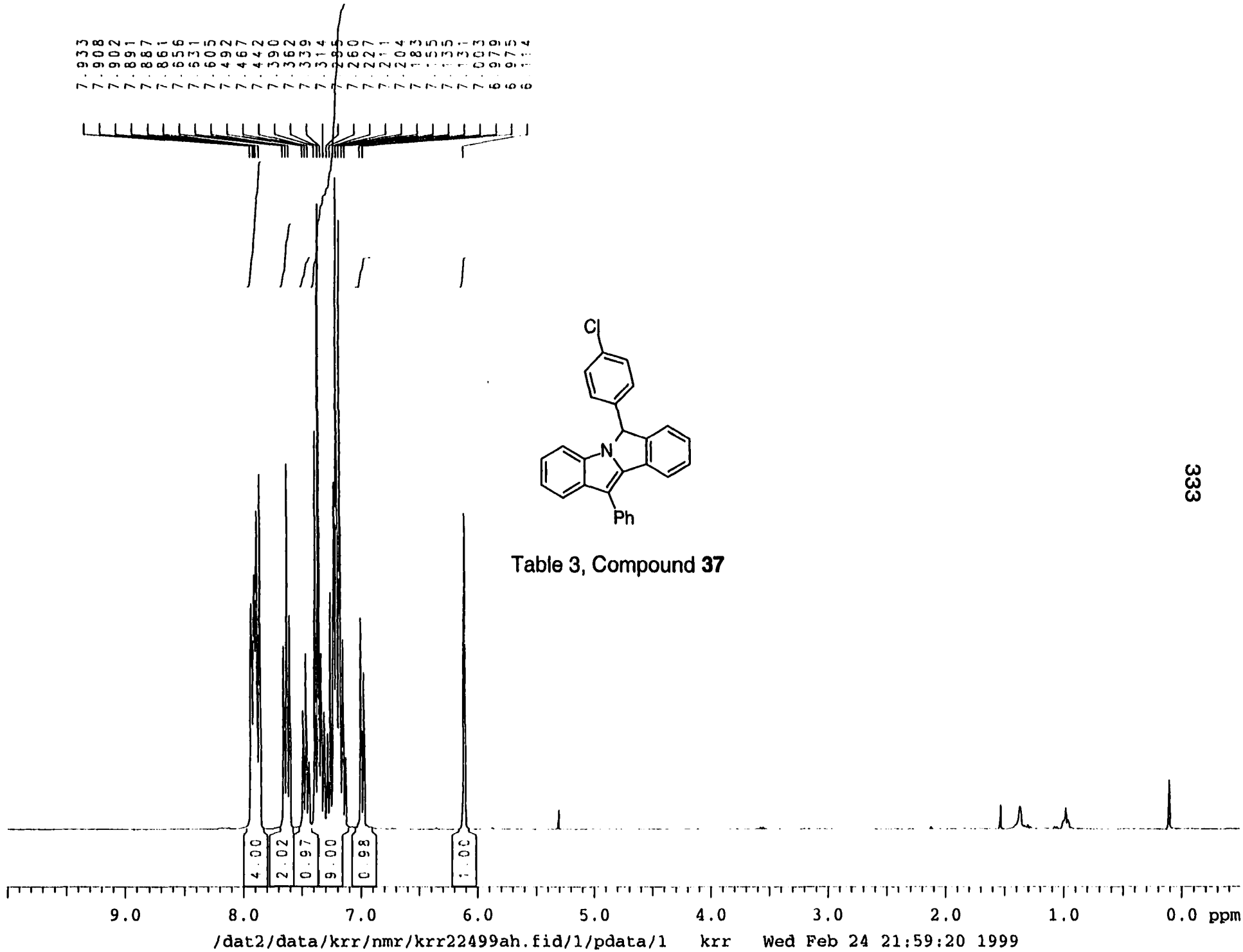
138.613
136.739
134.510
132.974
132.533
129.160
128.370
128.249
127.047
121.679
121.499
119.954
118.935
109.292
105.829
63.203
32.794
24.905
22.867
14.270
Ph
N
S
n-Bu
Table 3, Compound 35
332
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr22399bc.fid/1/pdata/1 krr Tue Feb 23 14:08:43 1999



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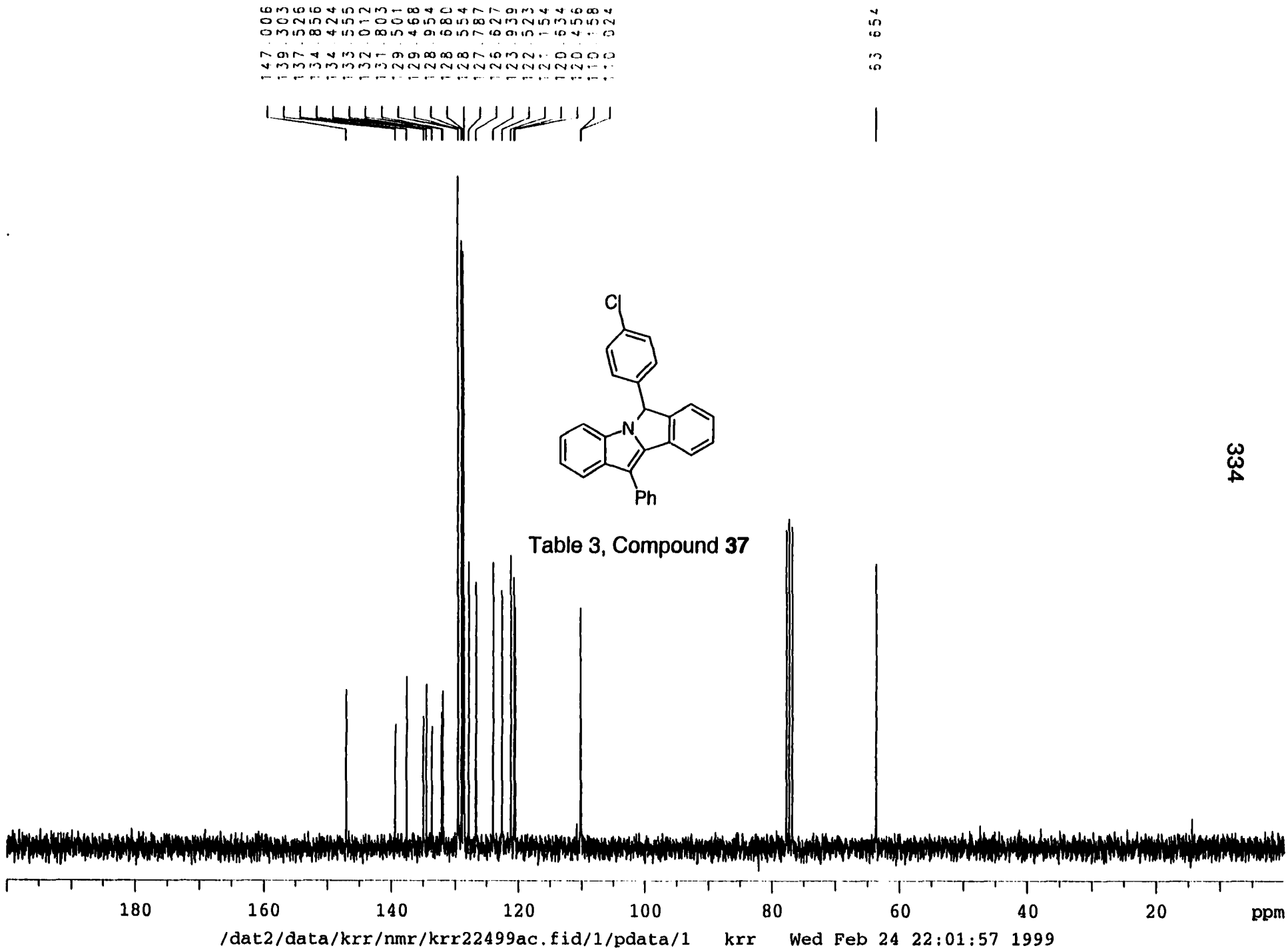
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139.303
137.526
134.856
134.424
133.555
132.012
131.803
129.501
129.468
128.954
128.680
128.554
127.787
126.627
123.939
122.523
122.154
120.634
120.456
110.158
110.024
53.654
Cl
N
Ph
Table 3, Compound 37
180
160
140
120
100
80
60
40
20
ppm
/dat2/data/krr/nmr/krr22499ac.fid/1/pdata/1 krr Wed Feb 24 22:01:57 1999

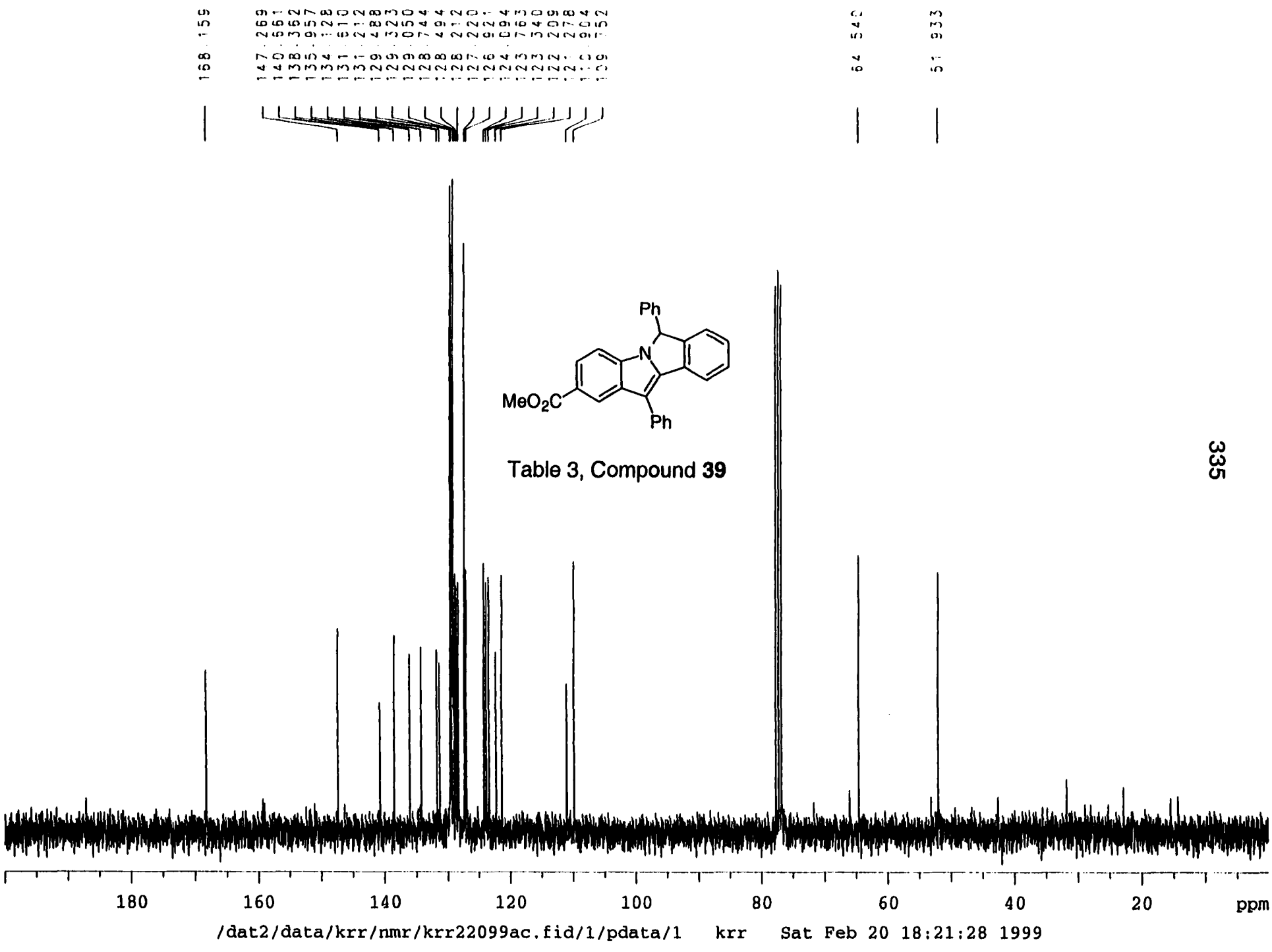


Table 3, Compound **39**

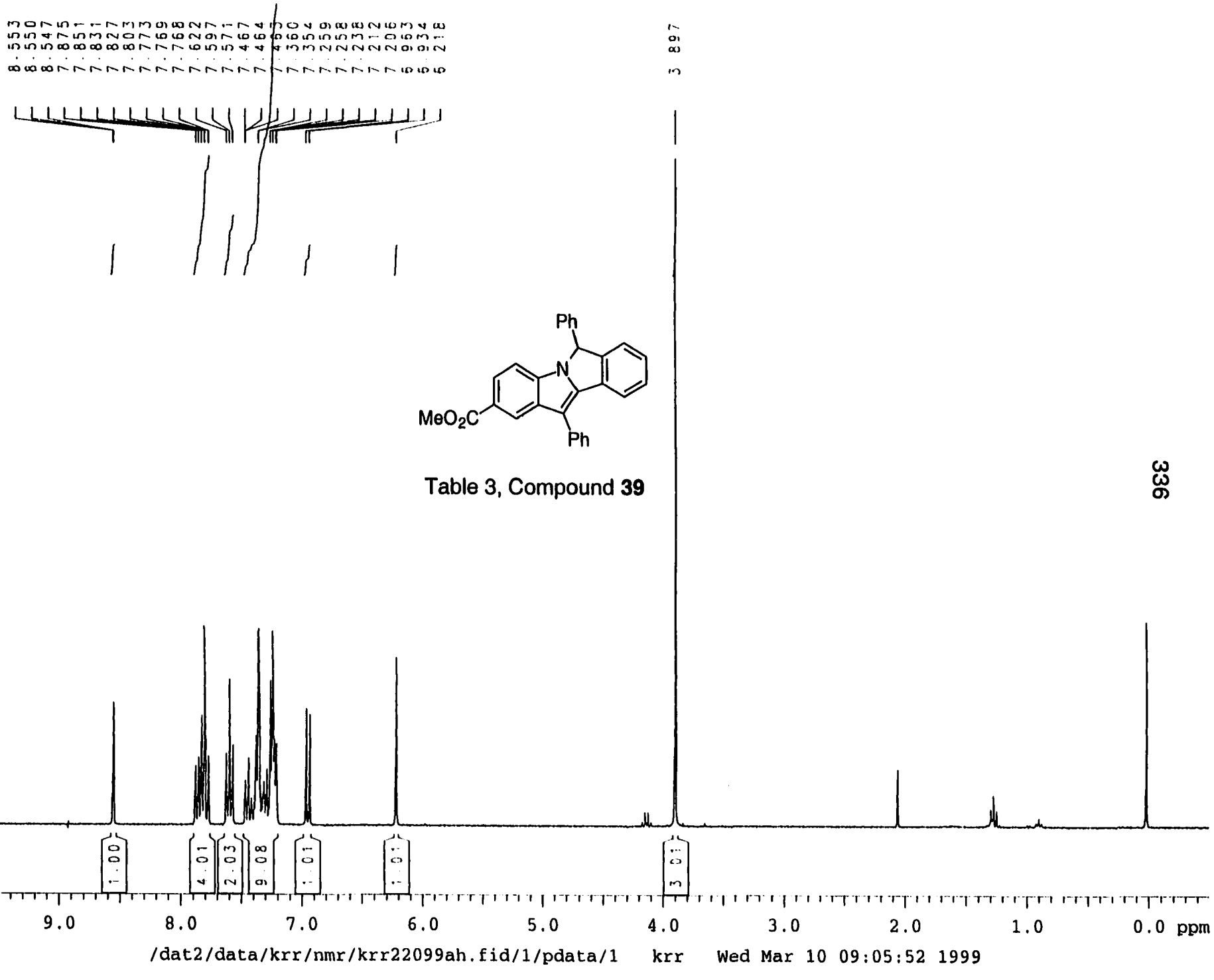


Table 3, Compound **39**

ACKNOWLEDGMENTS

I must begin this section with a sincere word of thanks to my major professor, Richard C. Larock, for his patience, excellent guidance, and financial support throughout the course of this work. Also, I have to acknowledge his willingness to listen to many of my crazy ideas, and to always offer advice as to how those ideas should be carried out.

I have met so many people during my years at Iowa State that have helped me through a number of things, and others that made the time here extremely memorable. I know for a fact that this degree would not have been possible without the assistance of a few certain people. The immense help that I received from Dr. Xiaojun Han from our start at ISU (and also during our last year at SIU) in course work and lab work in the early days, as well as the many of those memorable discussions, will always be appreciated and remembered. Dr. Mitchell Refvik pulled me through numerous tough times by offering advice in so many areas, and telling me some of the most interesting jokes I have ever heard. Without his help, I definitely would not have made it through. I cannot end this dissertation without thanking him for all of the great times that we had while he was here at Iowa State. I also must thank Melanie Refvik (are you wearing them now?) for keeping Mitch and I in line, as well as Kirsten and Samantha for teaching me so many things. Finally, I cannot forget some of the times that I had with Dr. Dan Gregory. I must thank Dan for the trips to Minnesota (although my foot still hurts when I think about them), removing my screen, helping me move, listening to David Allen Coe and Kern River, and burning rubber in the Monz.

This dissertation could not end without a few words about the infamous lunchroom crowd. Some of the most memorable discussions I ever had at Iowa State, or anywhere else, came from the lunchroom. Some of the things that I heard during that time will never be forgotten (although I wish I could forget some things). For those discussions I have to thank Dr. Mitchell (Michelena) Refvik, Dr. Dan (G-Roy) Gregory, Nate (Big Daddy) Classen, and Steve (Lance) Gagnier. A special thanks goes to Nate for taking it like a man in the lunchroom and Steve for letting me take his money at golf.

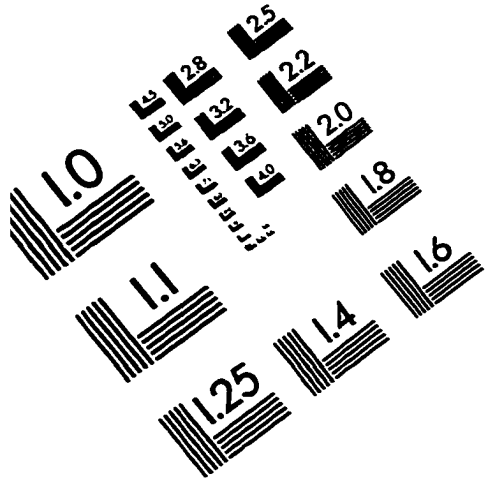
During the last year and a half of this degree, Jack Hunter has helped me immensely. I have to thank him for taking me to and from the airport, Saturday lunches, page numbering and thesis help, and again, many memorable discussions. I have also had numerous enlightening discussions, which sometimes included chemistry, with Dan Emrich, that I must thank him for. I must also thank Dan for being the racy person that he is. I also must thank Marino Campo for teaching me some things that I did not need to know. Finally, I would like to thank all other members of the Larock group, past and present, that I have had the pleasure to work with.

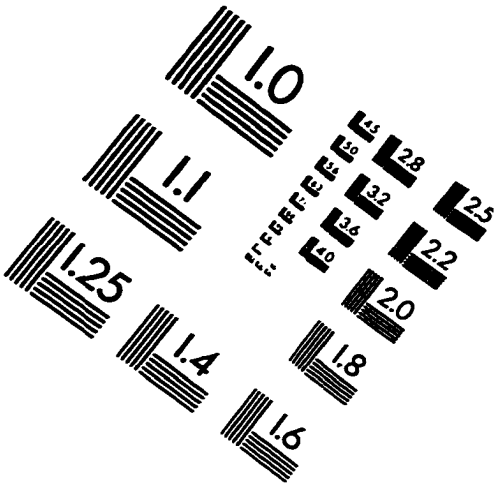
Many thanks go to my parents who have supported me throughout the completion of my degrees. I would definitely not have made it through without their unending support, which means a great deal. When I look back at some of the things that have happened to all three of us throughout the years, I can only laugh.

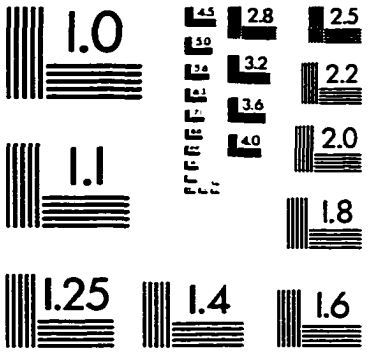
Finally, I have to thank my wife, Julie, for being there through a little bit of everything. Her support and help over these many years, and especially the last

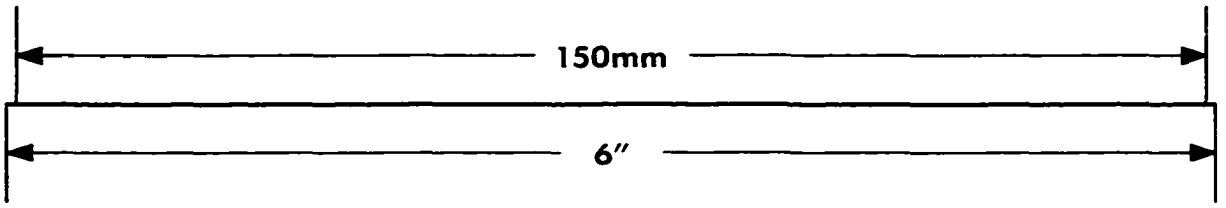
three here in Iowa, have meant more than she will ever know. Actually, I still cannot believe that she still puts up with me. I know she has spent many lonely nights waiting for me to complete this degree. For her patience and understanding, I have only one thing to say, WE DID IT!

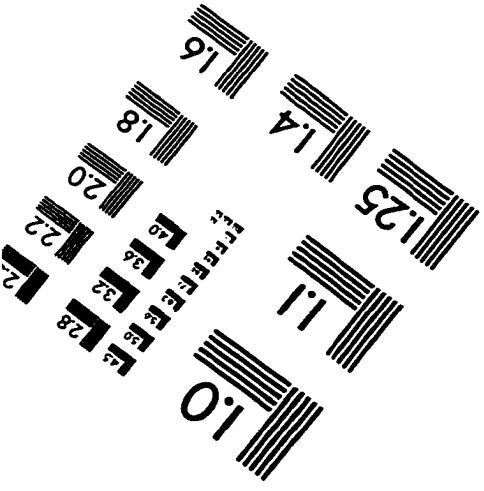
IMAGE EVALUATION
TEST TARGET (QA-3)

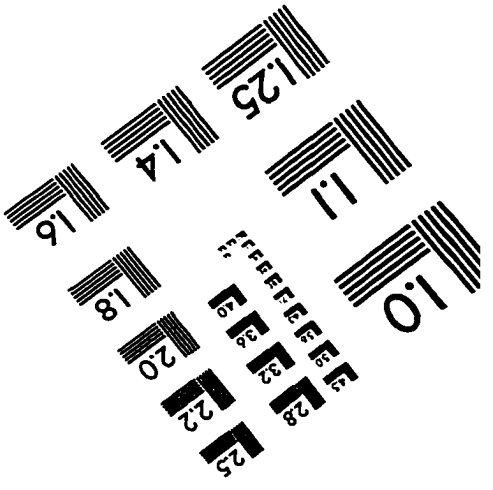












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