KJE-3900

MASTER'S THESIS IN CHEMISTRY

Synthesis of 5-,6-, and 7-membered heterocycles from barbituric acid derivatives.

David Guyader

June, 2011

FACULTY OF SCIENCE AND TECHNOLOGY

Department of Chemistry

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This thesis is dedicated to Julien Lassaux, Sandrine Quere and my future niece.

" When you don't know where you go, remember where you come from"
African citation

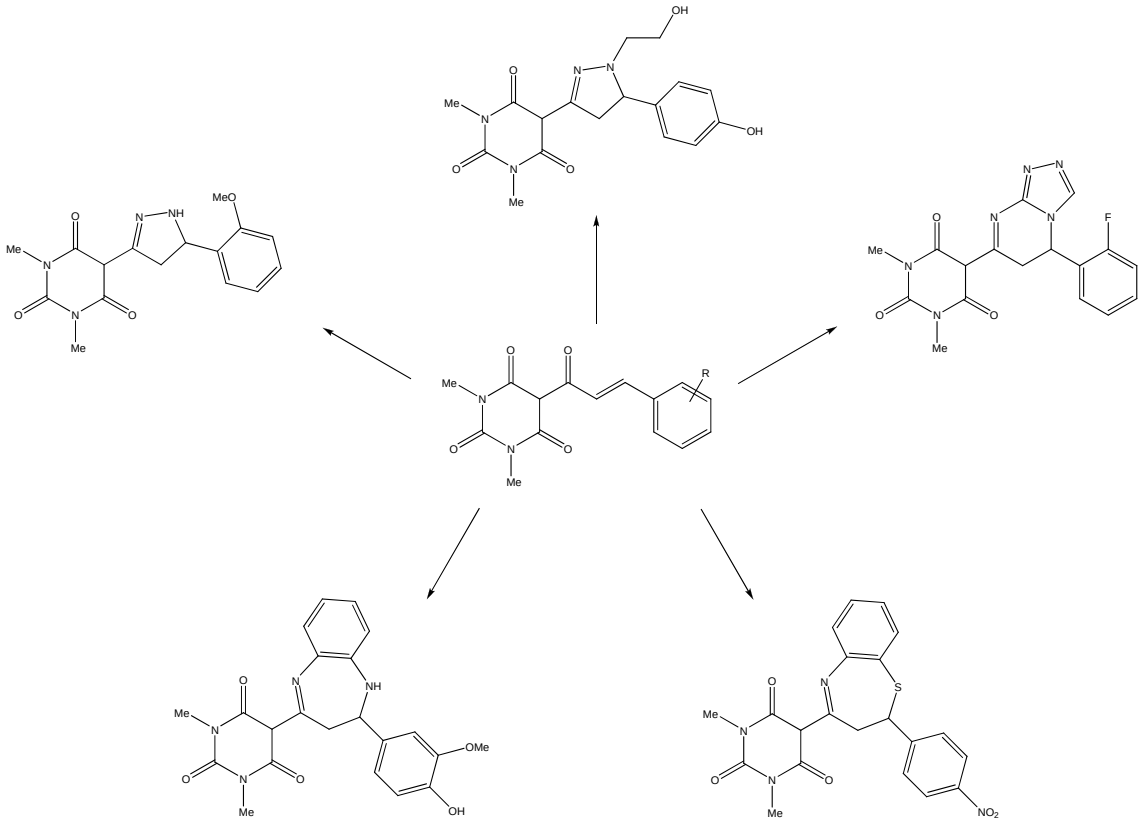
SUMMARY

A new procedure has been developed for the synthesis of barbituric acid derivatives. The reactions were performed under solvent free conditions without any catalyst. Employing this synthetic route, a large number of chalconoids and 5-,6-, and 7-membered heterocycles have been successfully synthesized in a very short time.

The chalconoids have been synthesized from a barbituric derivative and substituted benzaldehydes. The effect of different substituents on the yield of the reaction has been observed. This study revealed that electron-donating groups were more efficient in general than electron-withdrawing groups as substituents. The position of the substituents at the benzene ring of the chalconoids also seems to affect the yield of this reaction. Using experimental design optimize the reactions in a significant manner.

5-, 6-, and 7-membered heterocycles have been produced by reacting the chalconoids and a range of dinucleophiles.

Structure of some of the derivatives have been obtained by X-ray analysis and complete the spectroscopic investigations. Biological activity of some compounds has been highlighted from kinase testing.



Keywords: barbituric acid, chalconoids, benzaldehydes, solvent free reaction, experimental design, heterocycles, dinucleophiles, kinase testing.

SYMBOLS AND ABBREVIATIONS

°C	degree Celsius
calcd	calculated
cm^{-1}	wave number, reciprocal centimeter
δ	chemical shift [ppm]
d	doublet
Cl	chlorine
$CDCl_3$	deuterated chloroform
DMSO	dimethyl sulphoxyde
DMSO-d_6	deuterated dimethyl sulphoxyde
EtOH	ethanol
g	gram
h	hour
Hz	hertz
iPrOH	isopropanol
IR	infrared spectroscopy
J	coupling constant
m	multiplet
Me	methyl
mg	milligram
MHz	mega Hertz
min	minutes
mL	milliliter
mmol	milli mole
µmol	microliter
m .p.	melting point
MS	Mass spectroscopy
ν	frequency
$NaBH_4$	sodium borohydride
NMR	nuclear magnetic resonance spectroscopy
ppm	part per million
R	part per million
rt	room temperature
s	singlet
t	triplet
UV	ultra violet

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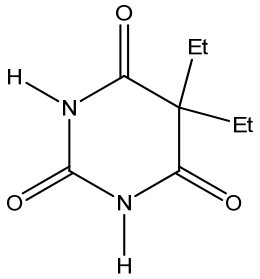
1 INTRODUCTION

1.1 History of barbituric acid.

Synthesizing the barbituric acid in 1864, the parent compound of the barbiturates, the German chemist Adolf von Baeyer[1] paved the way for the barbituric acid chemistry. In 1903, Emil Fischer and Joseph von Mering[2] synthesized 5,5-diethylbarbituric acid (**IV** also called ''barbital''), the first compound of this class with medical effect as barbituric acid was pharmacologically inactive. One century of constant progress in the barbituric acid chemistry enabled chemists to synthesize a large number of CNS active barbiturates since then.

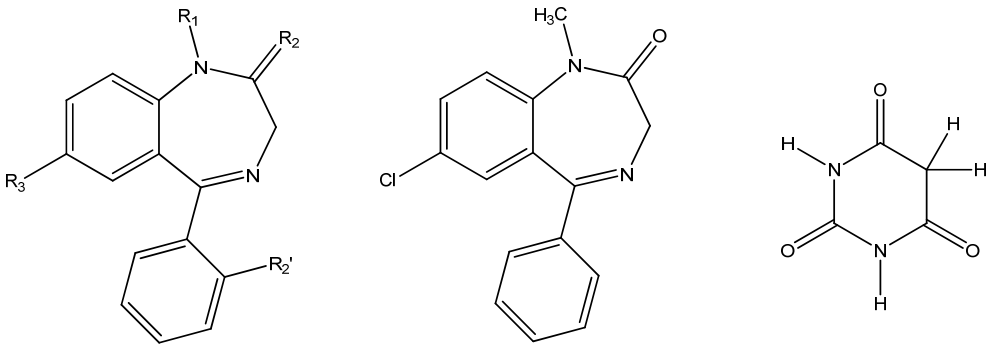


IV

***Figure 1.1**: Structure of the barbital **IV**.*

Many chemists contributed in the chemistry of barbituric acid. Historically, W.J. Doran released a book in 1959[3], a complete bibliography on the preparation and pharmacological activity of barbiturates. In 1960, Levina and Velichko[4] published a review dealing with their synthesis and reactivity. In the late 70's, B. Bobrański[5] reviewed studies about structure and conformation, spectral properties, and structure-activity relationships before Bojarski[6], reviewed basic properties of the barbiturates and advances in the chemistry of barbituric acid in 1985. Brown released an important series of book about the pyrimidine chemistry and the preparations of derivatives from 1962 to 1994[7].

Barbiturates have been widely used in the past because of their biological properties. Acting on the central nervous system, barbiturates lead to anxiolytics, hypnotics or anticonvulsants. On the other hand, facing the addiction potential of these drugs and the high risk of overdose, this type of compounds started to be replaced. Less dependent and less dangerous than its predecessor, benzodiazepines **(I)** started to take over the market. Nowadays, one of its derivatives, the diazepam, better known as Valium **(II)**, is widely commercialized worldwide. The discovery of benzodiazepines encouraged chemists exploring new pathway leading to more efficient barbiturates.



I II III

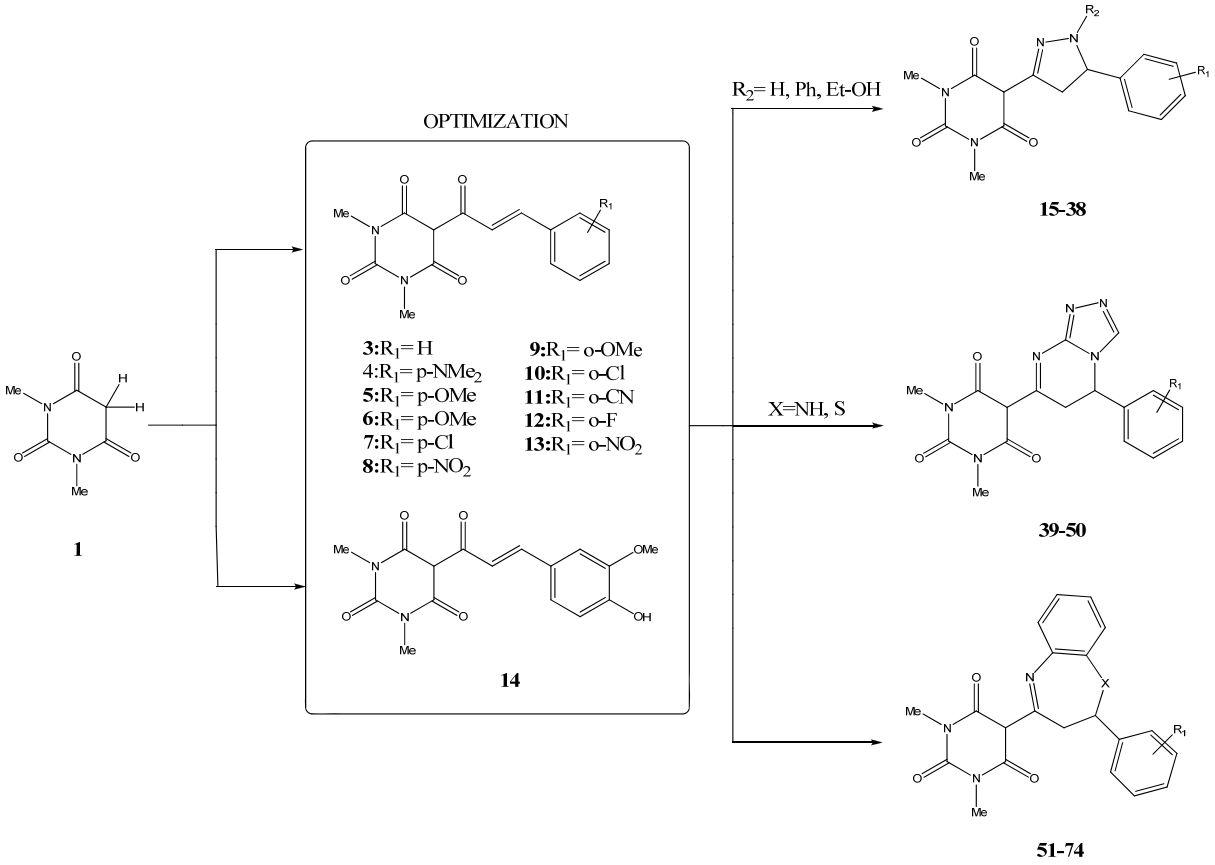
Figure 1.2*: The core structure of benzodiazepines* ***(I)****, and the structure of diazepam* ***(II)*** *and barbituric acid* ***(III)****.*

Since then, neuroscientists, toxicologists and pharmacologists found interests in new applications for barbiturates. Among these research, studies can be read on new concepts of hypnotics and antiepileptic drugs,[8] fluorinated barbituric acids,[9] and developments of barbiturates in the control of intracranial hypertension or their effects on the GABA receptors[10] (a class of receptors responding to the chief neurotransmitter in the vertebrate central nervous system.

The chemistry of barbituric acid is still relevant today…

1.2 Main objectives and approach

The interest of the group was to synthesize small focused libraries by investigating a new synthetic route. From earlier research of A.S. Gorovoi,[11,12] it was decided to take advantage of the two acidic protons at C-5 of the pyrimidine ring of the barbituric acid and thereby explore new reactions. Thus, synthesis of biologically active compounds could be possible. From 1,3-dimethylbarbituric acid **(1)**, the synthesis of a large number of chalconoids was attempt under solvent-free conditions resulting in substituted barbituric acid derivatives. Then, reaction between dinucleophiles and chalconoids was explored to synthesize new heterocyclic compounds. Experimental design was used in order to optimize experimental procedures and kinase testing was performed to highlight potentially biological activity of those barbiturates derivatives.



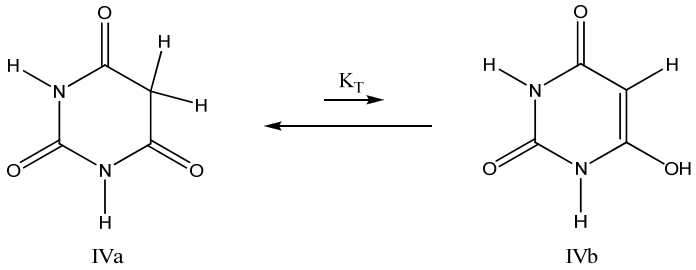
Scheme 1.1*: Overview of the synthetic route in the construction of new libraries of barbiturates containing heterocycles.*

2 THEORY

2.1 Barbituric acid properties

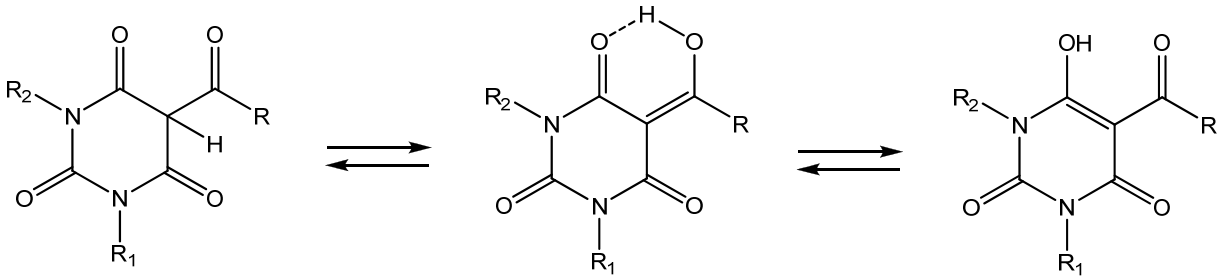
2.1.1 Tautomerism and solvation of the barbituric acid ring

The barbituric acid and its derivatives exist in different as verified by X-ray, IR and NMR spectroscopy investigations.
The barbituric acid is found in the trioxo form in the solid state.[13,14,15] The presence of the oxo-hydroxy equilibrium has been demonstrated in solution. In DMSO, only the oxo form is observable[16,17] and in water-free acid, the oxo form predominates over the hydroxyl form (Scheme 2.1).[18,19]



Scheme 2.1*: Relation between the oxo form (IVa) and the hydroxyl form (IVb) of the barbituric acid in water-free acid. The value of K_T comes from UV measurements.*

In the solid state, when the hydrogens are replaced by an ethyl group at both nitrogen, giving the 1,3-diethylbarbituric acid, the compound exists in the trioxo form. When the nitrogens are replaced by sulfur atoms, the compound is in the mono hydroxy form.
For the N,N-disubstituted-5-acyl derivatives of barbituric acid, the acyl group is involved in a keto-enol equilibrium. A proton transfer may occur through an intramolecular hydrogen bond inducing the mono hydroxy form (Scheme 2.2). [20]



***Scheme 2.2**: Keto-enol equimibrium for N,N-disubstituted-5-acyl derivatives of barbituric acid.*

2.1.2 Infrared spectroscopy

IR and Raman spectroscopical investigation of barbituric acid ring focus on N-H and C=O bonds.[21-27] For the N-H stretching bonds, the degree of hydrogen bonding influences the position and the intensity of the bands.[28-32] In the solid state, two bands appears at 3200 and 3090 cm^{-1}.[22,29,30] In highly dilute solutions and in argon matrices, the monomeric form of the molecule shows an N-H stretching vibration at ≈3400 cm^{-1} while the dimeric form reveals two broad bands at 3250-3100 cm^{-1}.[29,30,33,34] For the C=O bonds, three bands between 1770 and 1680 cm^{-1} can be seen. The highest band corresponds to the 4,6-CO symmetric vibration, the middle band to the 4,6-CO antisymmetric stretch and the lowest band to the 2-CO stretch (Figure 2.1).[29-30]

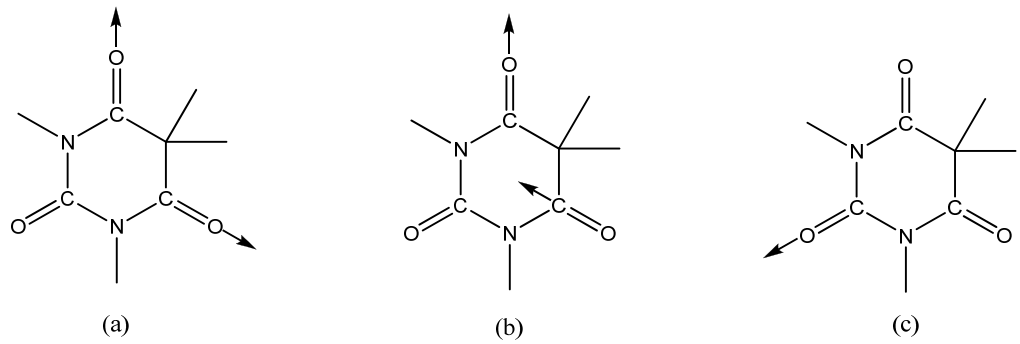


***Figure 2.1**: Carbonyl stretching vibrations of the barbituric acid ring: (a) 4,6-CO symmetric, (b) 4,6-CO antisymmetric, (c) 2-CO.*

2.1.3 ^{1}H-NMR spectroscopy

In ^{1}H-NMR spectroscopy, electronic effects of substituents at the nitrogens and the C-5 atoms, and the effect of the solvents have also highlighted for di- and trisubstituted barbiturates.[16,20,35-42] The electronic effects of the substituents at the C-5 atom cause changes to the chemical shift of the (NH) protons depending on the substituents. In the presence of electron donating or withdrawing groups attached to the substituent, a long-range magnetic effect occurs. Solvents have interesting effects that must be taken into account. It has been shown that solvents may interact with the nucleus of barbituric acid through a hydrogen bond. In DMSO, the anisotropic effect of the C-4 and C-6 carbonyl group induces differences in the chemical shift of the N-1 and N-3 ethyl groups (one imide proton is engaged in intermolecular hydrogen bonding with the solvent. Proton-donating solvents cause a downfield shift for the alkyl group attached to C-5[36-39] induced by the deformation of the planarity of the ring, and the solute-solvent hydrogen-bond interactions.[39]

2.1.4 ^{13}C-NMR spectroscopy

For ^{13}C-NMR spectroscopy, tables can be found in literature.[6] Barbiturates **V** and **VI** (Figure 2.2) can be used as the basis for ^{13}C interpretation.

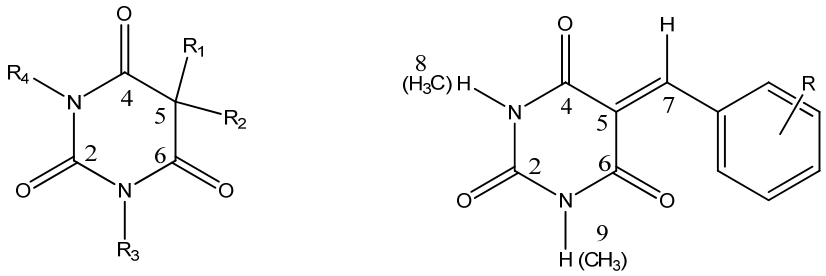


Figure 2.2 *: Two different classes of bariturates: (**V**) 1,3-dimethyl-5,5-disubstituted barbituric acid. (**VI**) 5-arylidenebarbituric acid.*

For the derivative **V**, the substituents R_1 and R_2 affect the chemical shift of the C-5 atom by 6-11 ppm compared to the C-2, C-4 and C-6 carbonyl group atoms chemical shifts that vary 1,5-2,5 ppm.[42-53] If there is a chiral center at C-5 ($R_1 \neq R_2$), C-4 and C-6 show separate resonances, if not, the difference in the chemical shifts are 0,1-1,1 ppm. In addition, when $R_3=R_4$=Me, the difference in the chemical shifts for these carbons is 0,5-1,5 ppm.

For the *meta*- and *para*-substituted derivatives of **VI**, C-4 and C-6, but not C-2, are conjugated. Interchanging an electron-donating group by an electron-attracting group at the R substituent shifts upfield C-7 by 4,5 ppm and downfield C-5 by 13 ppm.[54,55] The C-6 atom is more shielded than the C-4 atom considering interactions through bonds. It should be noted that the NMe carbon is not affected the substituent at the C-5 atom.

The symmetry in both examples also plays a role in the interpretation of spectra, influences both chemical shifts change and the resonance. On the first hand, the C-4 and C-6 atoms show different resonances when: 1. C-5 is a chiral center in derivative **V** ($R_1 \neq R_2$ and $R_3 = R_4$),[44,46,50,52] 2. $R_3 \neq R_4$ in derivative **V**,[51] 3. there is E,Z isomerism coming from the C=C bond in derivative **VI**.[54,55] On the other hand, the C-4 and C-6 atoms show a single resonance when $R_1 = R_2$ and $R_3 = R_4$ in derivative **V**. The non-equivalence of these two carbons depends on the R_2 substituent for the derivative **V** and the R substituent for the derivative **VI**.

2.1.5 Conformation in solution

Alkyl and/or alkenyl substituents at the C-5 atom have the same conformations in the solid state as in solution, based quantum mechanical calculations (MINDO/3) and confirmed by NMR spectroscopy.[41,56,57] The associated conformations in solution are not related to the ionization state of the pyrimidine ring.[41] Still if considering the example of 5-(3'-phenylpropyl)barbituric acid, the phenyl ring lies above the barbituric acid ring because of weak intramolecular interaction in the molecule (Figure 2.3). The strength of the interaction between the two rings depends on the type of the substituent attached to the aromatic ring.[58]

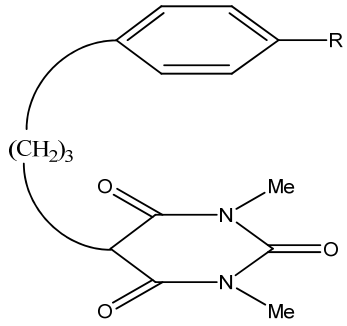


Figure 2.3: Weak intramolecular interaction in the the 5-(3'-phenylpropyl)barbituric acid as evidenced by UV-VIS and ^{1}H-NMR.

^{1}H-NMR investigations of the phenyl ring in arylidenebarbiturates reveals a twist of this ring in relation to the plane of the pyrimidine ring.[59,60] The value of dihedral angle **(**ϑ) depends on the type and position of the substituent on the phenyl ring (Figure 2.4).

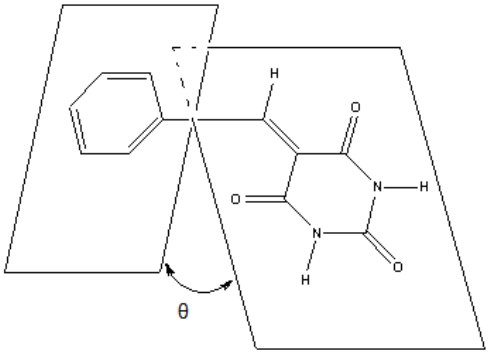


***Figure 2.4**: Conformation of 5-arylidenebarbituric acid: ϑ, dihedral angle between the phenyl and pyrimidine ring.*

Also, *ortho*-substitution in the aromatic ring induces hindrance of rotation, leading to two possible conformations conformer (Figure 2.5).

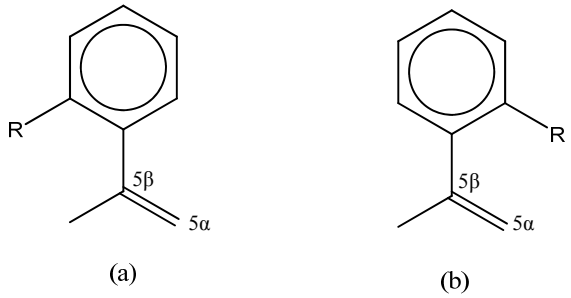
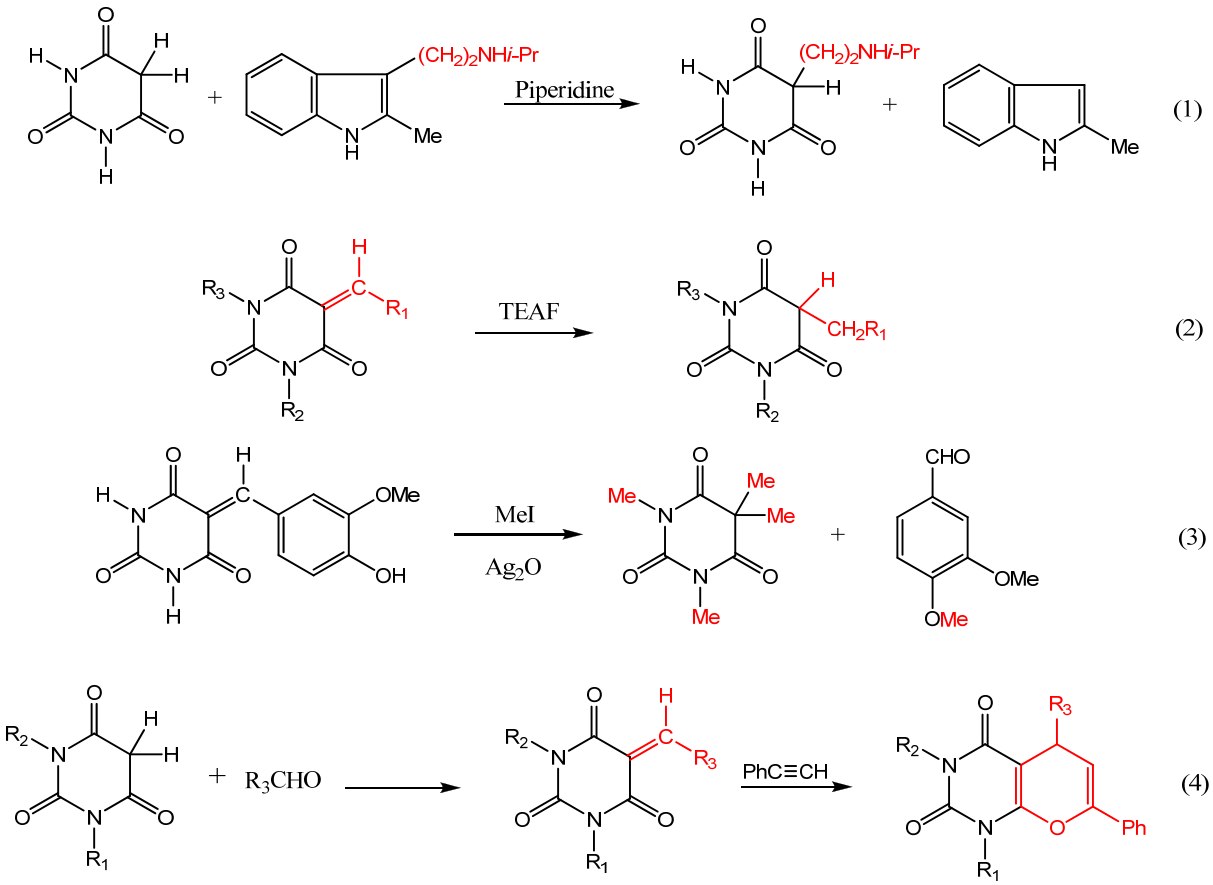


***Figure 2.5**: Two conformations of 5-arylidenebarbituric acid ortho-substituted in the phenyl ring (arylidene moiety).*

2.1.6 Reactions at the C-5 position

As shown, it is obvious that the C-5 atom plays an important role in the barbituric acid chemistry. The two hydrogens attached to the C-5 atom are very acidic and can be easily replaced in order to synthesize biologically active compounds.[61,62] Reaction between barbituric acid and indole derivatives results in the introduction of complex in the presence of piperidine [Scheme 2.3, Eq. (1)].[63] Reduction of barbituric acid derivatives with a methylene bond at the C-5 atom by TEAF results in the synthesis of 5-alkyl and 5-arylmethylbarbituric acids [Scheme 2.3, Eq. (2)].[64-66] Oxidative methylation of a 5-vanillydenebarbituric acid (and 5-benzylidenebarbituric acids) occurs in DMF by reacting with methyl iodide in the presence of Ag_2O and leads to 1,3,5,5-tetramethylbarbituric acid [Scheme 2.3, Eq. (3)].[67] Cyclization reactions are also possible. Condensation of barbituric acids (N°; R_1=H, Me, Ph; R_2=H, Me, Ph, p-NO2-C_6H_4) with and phenylacetylene.[68] 5-ylidenebarbiturates intermediates, formed during the condensation,undergo a 1,4-cycloaddition with phenylacetylene and leads to a condensed pyran system [S



***Scheme 2.3**: Examples of some reactions with barbituric acid derivatives.*

2.2 Chalcones

Chalcones contain the core 1,3-diphenyl-2-propene-1-one and are biologically active. It is an aromatic ketone with two aromatic rings linked by a three carbon α, β-unsaturated carbonyl (Figure 2.5). The conjugated double bonds and the delocalized π-electron system on both aromatic rings can lead to electron transfer reactions.[69]

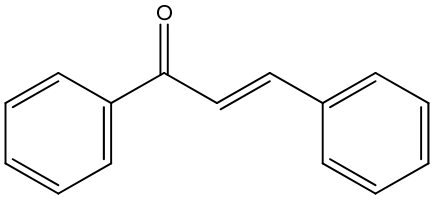
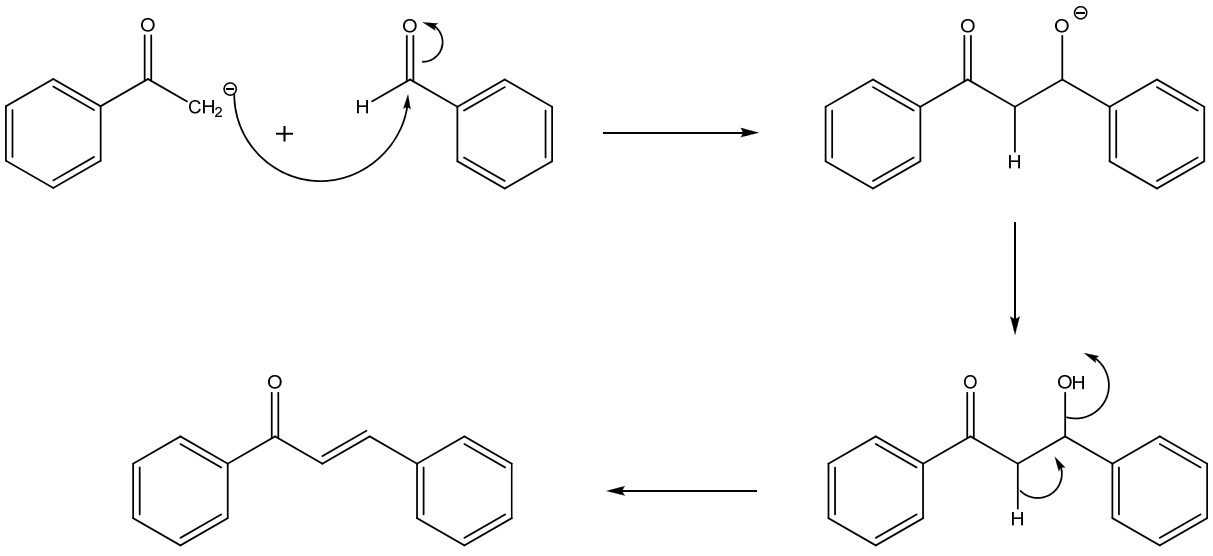


***Figure 2.5**: The 1,3-diphenyl-2-propene-1-one.*

The base catalyzed reaction consist in the aldol condensation between a benzaldehyde and an acetophenone with sodium hydroxide under solvent free conditions.[70] The first step consists of a nucleophilic addition to the carbonyl group of the benzaldehyde after deprotonation of the methyl at the acetophenone. This is followed by the protonation of the anion and the last step results in an enone (Scheme 2.4).[69]



***Scheme 2.4**: Synthesis of chalcone from aldol condensation reaction.*

2.3 Experimental design[71]

When an experiment is run, the measured result, ***y***, is called the response. The result of an experiment depends on the manner it has been run. It can therefore be assumed that there is some kind of functional relationship between the observed result, *y*, and the experimental conditions:

$$y = f(\text{experimental conditions}) \qquad 2.1$$

The experimental conditions are defined by the settings of the experimental variables, x_i, where ***x*** is the setting of ***i***. It can be written as:

$$y = f(x_1, x_2, \ldots, x_n) \qquad 2.2$$

However, any experimentally determined value contains an error, ***e***. Denoting the true value of the response, ***η***, it gives the equation (2.3):

$$y = \eta + e \qquad 2.3$$

At the best the error, ***e***, is a random error due to random fluctuations of the experimental settings and ***y*** is then an unbiased estimation of ***η***. Sometimes, the error term contains a systematic error and the method used to determine ***y***, underestimates or overestimates ***η***. Under such conditions, ***y*** is a biased estimation of ***η***. With random errors in experiments, it is reasonable to assume that they are normally distributed. An error term has to be added to the functional relationship:

$$y = f(x_1, x_2, \ldots, x_n) + e \qquad 2.4$$

A significant variable will produce a response variation above the error value, the noise level. In most cases, it is very difficult to derive an analytical expression for the function ***f***. Provided that the range of variation of the experimental conditions is not too large (the experimental domain is limited) an approximation of ***f*** by a Taylor expansion is possible if it is expressed as polynomial of the experimental variables. The term ***R*** contains the contributions of the omitted tems in the Taylor expansion. In most cases, it is sufficient to omit terms of degree 3 and higher if the rest term is less than the error term, ***e***. A sufficiently good approximation is obtained:

$$y = b_0 + b_1x_1 + b_2x_2 + \ldots + b_nx_n + b_{12}x_1x_2 + \ldots + b_{ij}x_ix_j + b_{11}x_1^2 + \ldots + b_{nn}x_n^2 + e \qquad 2.5$$

A term in the model is significant it produces a variation above the noise level on the error.

2.3.1 Screening

In any synthesis, there are many experimental variables that can influence the result. However, it is not likely that they are equally important. A screening experiment is at revealing which variables are really important.

2.3.2 Optimization

Optimization with respect to the yield of a reaction means finding the combination of the experimental variable settings that produces the highest possible yield. Close to an optimum the response function is curved. For this, it is necessary to assign a quadratic Taylor polynomial so that the curvature of the function in any ***x*** dimension can be described. The role of a multivariate statistical experimental design is to specify how the settings of the experimental variables should be varied over a series of experiments so that the coefficient of the Taylor polynomial can be estimated. In screening experiments with linear coefficient, b_i, and rectangular coefficient, b_{ij}, it is sufficient to test each variable at only two levels, (-) low level and (+) high level. Useful designs for this are factorial and fractional factorial design.

2.3.3 Factorial design

The experiments are carried out at fixed levels of the experimental variables and a factorial design contains all the possible variation of the variable settings. Assuming that there are ***k*** variables for which there are ***r*** levels of the setting, a full factorial design will thus contain r^k possible combinations. With many levels and many variables, this will be an absurd number. To keep the number of experiments manageable, two-level designs are convenient: for example with three variables and two levels there are 2^3 experiments. To compute the coefficient of the Taylor model, the design matrix is raised into a model matrix that contains columns for every term in the model. With two variables, an interaction model is:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_1x_2 \text{ (with } b_0 \text{ a constant).} \qquad 2.6$$

Design			Model					Response
x_1	x_2		x_0	x_1	x_2	x_3		
-1	-1		1	-1	-1	1		y_1
1	-1		1	1	-1	-1		y_2
-1	1		1	-1	1	-1		y_3
1	1		1	1	1	1		y_4

The constant term, b_0, is the average of the response:

$$b_0 = ¼ (y_1 + y_2 + y_3 + y_4) \quad (2.7)$$

The variable coefficients are compared to the variable settings from the columns and correspond respectively to the average response of the variable settings they are related to:

$$b_1 = ¼ (-1.y_1 + 1.y_2 - 1.y_3 + 1.y_4) \text{ (column } x_1) \quad (2.8)$$

The other coefficients are compared analogically from the other columns.

2.3.4 Fractional Factorial design

It is obvious that the number of experiments increases rapidly when the number of variables increases. In screening experiments it is sufficient to fit with interaction model and this can be made from a subselection of the experiments of a full experimental design. It is to select 1/2,1/4 , 1/8, …, $1/2^p$, of a full design and such designs are called fractional factorial designs. For an optimization with three variables and assuming that a linear model is sufficient, four experiments are needed:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + e \quad (2.9)$$

2.3.5 The three-dimension variable span

The fractional factorial design is obtained from the model matrix of a small full factorial design containing more experimental runs than the number of variables to investigate. Seven variables can be investigated in eight experiments. This will be 1/16 of the full 2^7 factorial design and these eight experiments span as much as possible of the variations in the seven-dimensional variable space.

2.3.6 Response surface design

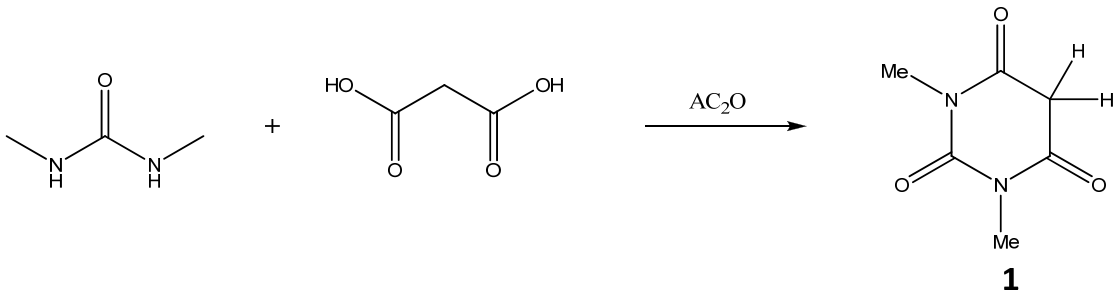
The response surface design enables to locate the optimum conditions and to analyse the effect of variations in the settings of the experimental variables on the optimum conditions. Relations between the response and the experimental variables can be interpreted from graphic illustrations of the shape of the surfaces provided by this method.

3 RESULTS AND DISCUSSIONS

This thesis is divided in five parts. The first part relates the synthesis of starting compound 5-acetyl-1,3-dimethylbarbituric acid **2**. The second and the third part present the investigation of a new synthetic route for the synthesis of chalconoids and the synthesis of 5-, 6-, and 7-membered heterocycles. The two last parts deal with experimental design and biological testing. The experimental procedures and characterization of new structures are given in **Chapter 5**. All spectra are enclosed in Appendices.

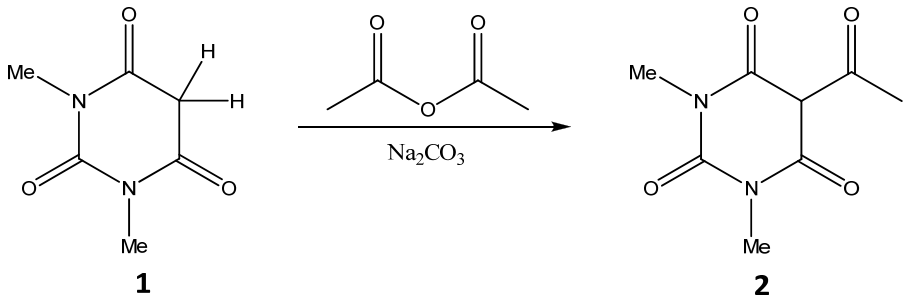
3.1 Preparation of the starting material

Starting compound, 5-acetyl-1,3-dimethylbarbituric acid **2**, was prepared in a two-step procedure. 1,3-dimethylbarbituric acid **1** was first prepared from N,N-dimethylurea and malonic acid in acetic acid (Scheme 3.1). The method used was as published by Adolf von Bayer[1] with some minor modifications. Compound **1** was obtained in quantitative yield.



Scheme 3.1**: Synthesis of 1,3-dimethylbarbituric acid **1

1,3-dimethylbarbituric acid **1** was then acetylated by reaction with acetic anhydride to yield 5-acetyl-1,3-dimethylbarbituric **2** quantitatively (Scheme 3.2). Purification was not necessary as **2** could be used directly in the next step. However, purification of **2** can be done by re-precipitation (acid/base) if necessary. Structure of **1** and **2** were confirmed by NMR spectroscopy and were in accordance with the literature.



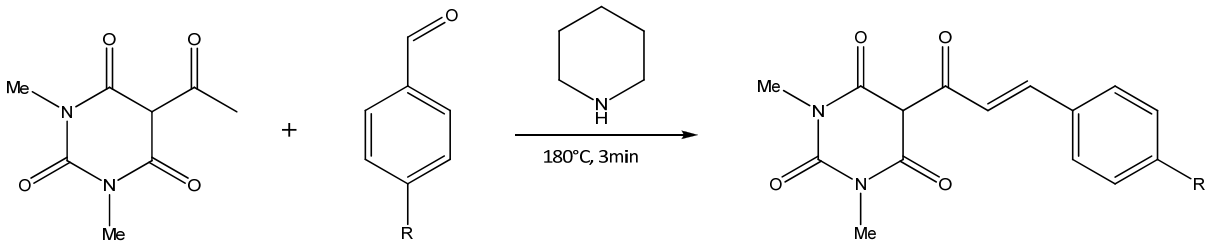
***Scheme 3.2**: Acetylation of 1,3-dimethylbarbituric acid **1**.*

3.2 Synthesis of chalconoids

The purpose of this series of experiments was to prepare barbituric acid derivatives from a wide range of substituted benzaldehydes. This study includes electron-donating and electron-withdrawing groups as substituents, in order to investigate the scope and limitations of the reactions. This type of reaction consists in reacting **2** with benzaldehydes yielding chalconoids **3-14**.

A first reaction consisted in reacting benzaldehyde with **2** under solvent-free condition before addition of base yielding **3**. Investigation of different bases (pyridine, piperidine and triethyl amine) revealed that piperidine was the most efficient (*vide infra* **PART 3.4**).

A series of synthesis was first conducted on para-substituted benzaldehydes including NMe_2, OMe, OH, Cl and NO_2 substituents. It was been observed that changing the parameters of the reaction had an influence on the yield. Investigation of these parameters on one derivative enabled to define optimal experimental conditions for this reaction (*vide infra* **PART 3.4**) and this new experimental procedure was then applied to all the following reactions. The chalconoids **3-8** were successfully synthesized, confirmed by NMR, IR and MS (see Appendices), and obtained as pure powder after washing with EtOH. The isolated yields of chalconoids with donor groups were higher than those with acceptor groups. **3-6** gave respectively 78% 84%, 89% and 76% and, **7** and **8,** both gave 31% (Scheme 3.3).

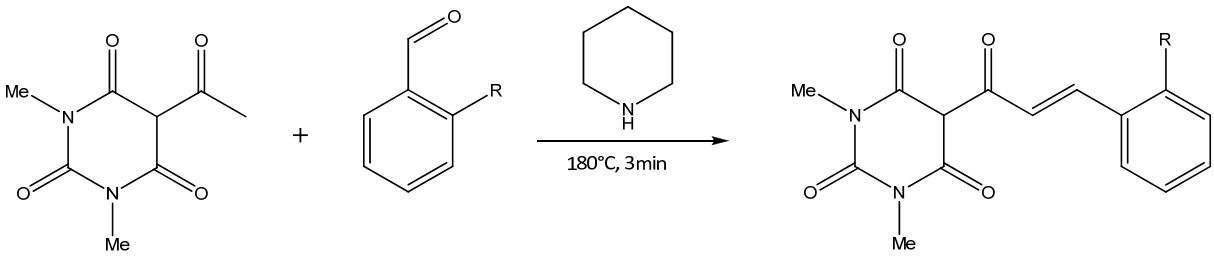


2

3:R=H	76 %
4:R=NMe_2	84 %
5:R= OMe	89 %
6:R=OH	76 %
7:R=Cl	31 %
8:R=NO_2	31%

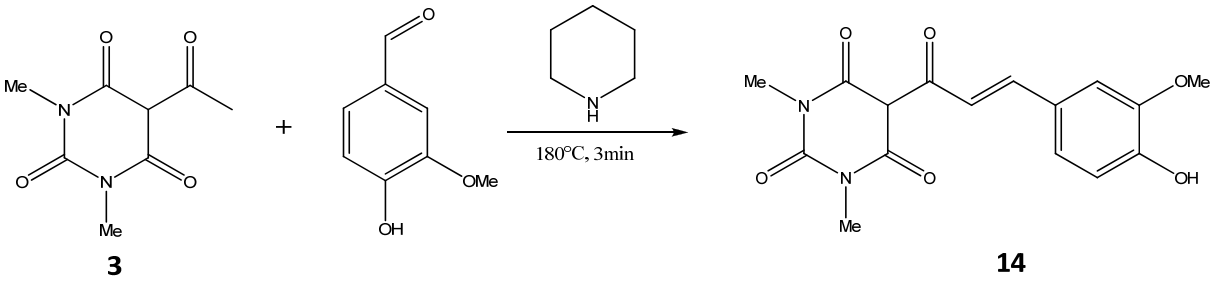
Scheme 3.3*: Synthesis of para-substituted chalconoids* ***3-8****.*

The scope of reactions was extended to *ortho*-substituted benzaldehydes. Reagents included OMe, Cl, F, CN and NO_2 substituents (Scheme 3.5). The chalconoids **9-13** were successfully synthesized, verified by NMR, IR and MS (see Appendices), and obtained as pure powders after washing with EtOH. The isolated yields of the chalconoids **12-13** with electron-withdrawing groups as substituents once again gave the lowest yields, but it has also been observed that **10-11** gave the same results as **9** (Scheme 3.4).



***Scheme 3.5**: Synthesis of ortho-substituted chalconoids **9-13**.*

Finally, the synthesis of a disubstituted chalconoid was included in the study. Vanillin and **2** were reacted following the same procedure, and yielded **14** (Scheme 3.5). Compound **14** was successfully synthesized and verified by NMR, IR and MS (see Appendices). Comparing with **6**, introduction of the methoxy group in the *meta* position affected the isolated yield.



***Scheme 3.6**: Synthesis of the disubstituted chalconoid **14**.*

Compounds **4**,**5** and **7** were analysed by X-ray analysis. Recrystallization was performed from chloroform or pentane. Compounds crystallized from dichloromethane exploded during analyses. Compound **8** was insoluble in chloroform, dichloromethane, pentane, ethanol or methanol. Keto-enol equilibrium exists in the molecule (**Scheme 3.3**). By analyzing X-ray analyses of the compound **4**, **5** and **7**, we have seen that the position of the hydrogen depends of the aryl substituent.

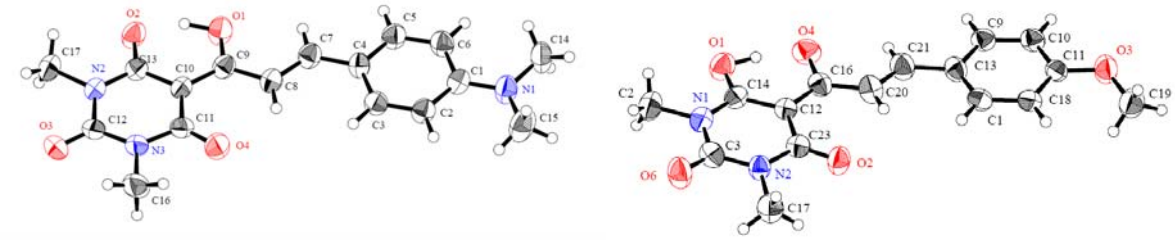


Figure 3.1**: ORTEP drawing of X-ray structure of **4** and **5

The *trans* conformation was the major. The NMR spectra, were confirmed by the X-ray analysis of the compound **7**. X-ray data indicates the presence of both conformations in the same crystal (Figure 3.2). Additionally, it also indicates the presence of the *p*-Cl substituent involve weak intramolecular interaction in **7.** However, the next step was independent of this problem with *cis*/*trans* conformation.

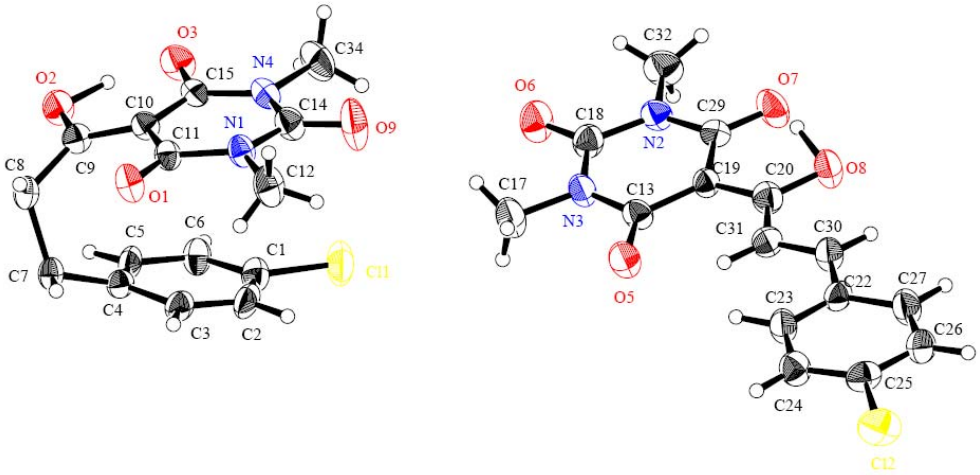


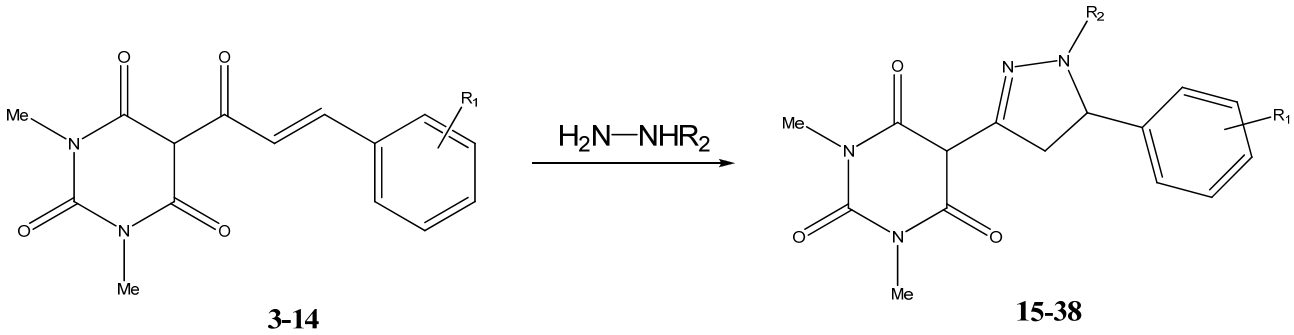
***Figure 3.2**: ORTEP drawing of X-ray structures of **7**.*

3.3 Synthesis of 5-,6-, and 7-membered heterocycles.

The next step of this project was to build a library of new heterocycles. A new synthetic route was investigated. The reactions were conducted under solvent-free conditions without any catalyst. Reactions of **3-14** with dinucleophilic reagents yielded 5-, 6- and 7-membered heterocyles. New compounds were synthesized in a short time employing cheap starting materials. The acryloyl (allyl) group in the middle of the side chain of the chalconoids enables dinucleophilic attack leading to bigger molecules very fast and very easily.

3.3.1 Synthesis of pyrazole derivatives

Two dinucleophiles were selected for the synthesis of 5-membered nitrogen containing heterocycles. Hydrazine hydrate and 2-hydroxyethyl hydrazine were reacted with **3-14** (Scheme 3.6). The results are given in Table 3.1.



*Scheme 3.6 : Synthesis of pyrazole derivatives **15-38**.*

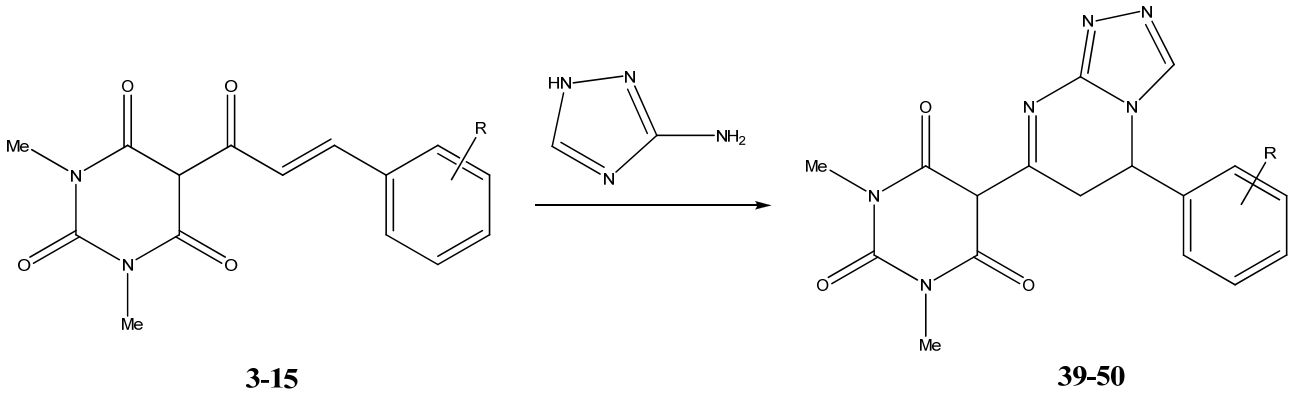
Compounds	R_1	R_2	Yield
15	H	H	24%
16	*p*-NMe_2	H	38%
17	*p*-OMe	H	34%
18	*p*-OH	H	96%
19	*p*-Cl	H	43%
20	*p*-NO_2	H	65%
21	*o*-OMe	H	49%
22	*o*-Cl	H	33%
23	*o*-F	H	51%
24	*o*-CN	H	21%
25	*o*-NO_2	H	54%
26	2-methoxy, 3-hydroxy	H	56%
27	H	EtOH	54%
28	*p*-NMe_2	EtOH	55%
29	*p*-OMe	EtOH	38%
30	*p*-OH	EtOH	48%
31	*p*-Cl	EtOH	47%
32	*p*-NO_2	EtOH	5%
33	*o*-OMe	EtOH	44%
34	*o*-Cl	EtOH	52%
35	*o*-F	EtOH	58%
36	*o*-CN	EtOH	29%
37	*o*-NO_2	EtOH	20%
38	2-methoxy, 3-hydroxy	EtOH	10%

***Table 3.1**: Results for the synthesis of 5-membered heterocycles.*

Excess of dinucleophiles was used for each reaction in order to consume 100% of the starting material. All the compounds, except **24**, were successfully synthesized as expected. Reactions with phenylhydrazine was also performed but gave <1% isolated yield products.

3.3.2 Synthesis of triazole derivatives.

To synthesize 6-membered nitrogen containing heterocycles, 3-amino-1H-1,2,4-triazole was selected to react with **3-14** (Scheme 3.7). Results of the reaction are given in Table 3.2.



3-15 **39-50**

Scheme 3.7**: Synthesis of triazole derivatives **39-50

All the compounds were successfully synthesized as expected, except **48** and **49** .

Compounds	R_1	Yield
39	H	70%
40	*p*-NMe_2	61%
41	*p*-OMe	63%
42	*p*-OH	43%
43	*p*-Cl	62%
44	*p*-NO_2	60%
45	*o*-OMe	63%
46	*o*-Cl	45%
47	*o*-F	18%
48	*o*-CN	Not synthesized
49	*o*-NO_2	Not synthesized
50	2-methoxy, 3-hydroxy	62%

***Table 3.2**: Results from the synthesis of 6-membered heterocycles.*

X-ray analysis has provided the possible structure in crystalline form of **40** (Figure 3.3).

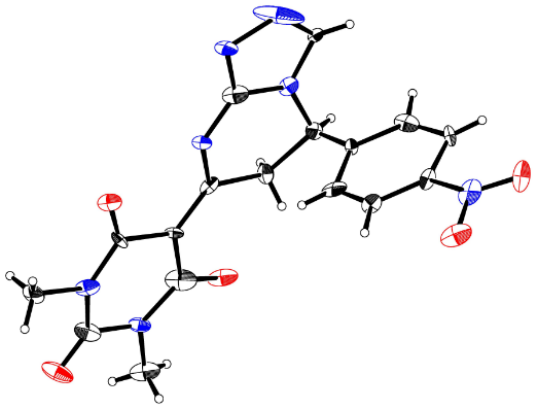
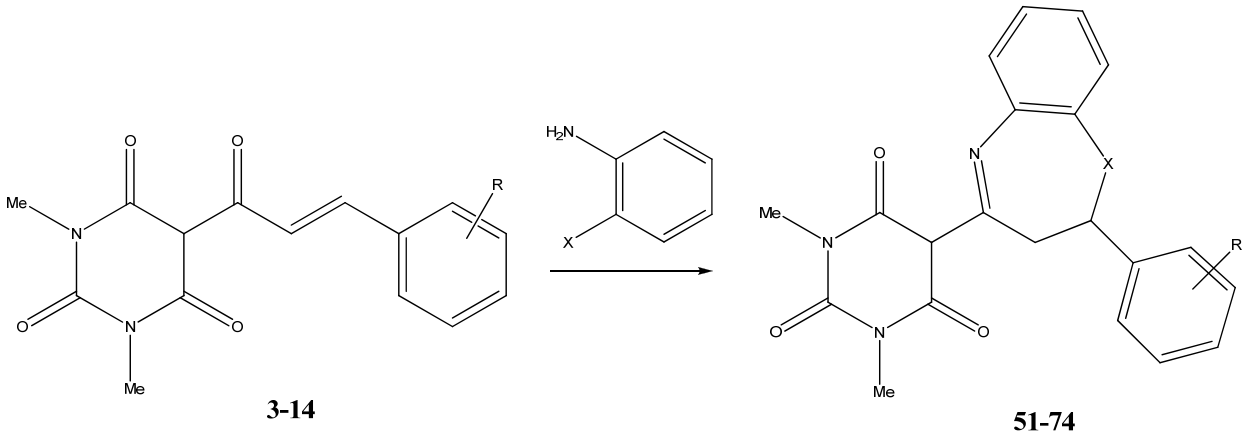


Figure 3.3: ORTEP drawing of x-ray structure of **40**.

3.3.3 Synthesis of diazepine and thiazepine derivatives.

7-membered nitrogen containing heterocycles were synthesized from reactions of 2-aminothiophenol and 1,2-phenylendiamin and **3-14** (Scheme 3.8). All the compounds, were successfully synthesized as expected except **60**, **61** and **72**. Results of the reaction are given in Table 3.3.



Scheme 3.8*: Synthesis of azepine derivatives* ***51-74***

Compounds	R_1	X	Yield
51	H	NH	61%
52	*p*-NMe_2	NH	24%
53	*p*-OMe	NH	31%
54	*p*-OH	NH	25%
55	*p*-Cl	NH	66%
56	*p*-NO_2	NH	67%
57	*o*-OMe	NH	26%
58	*o*-Cl	NH	24%
59	*o*-F	NH	48%
60	*o*-CN	NH	Not synthesized
61	*o*-NO_2	NH	Not synthesized
62	2-methoxy, 3-hydroxy	NH	50%
63	H	S	81%
64	*p*-NMe_2	S	49%
65	*p*-OMe	S	64%
66	*p*-OH	S	72%
67	*p*-Cl	S	89%
68	*p*-NO_2	S	43%
69	*o*-OMe	S	72%

70	*o*-Cl	S	38%
71	*o*-F	S	60%
72	*o*-CN	S	Not synthesized
73	*o*-NO_2	S	71%
74	2-methoxy, 3-hydroxy	S	57%

X-ray analysis have provided two possible structures in crystalline form of **53** (Figure 3.4 and Figure 3.5).

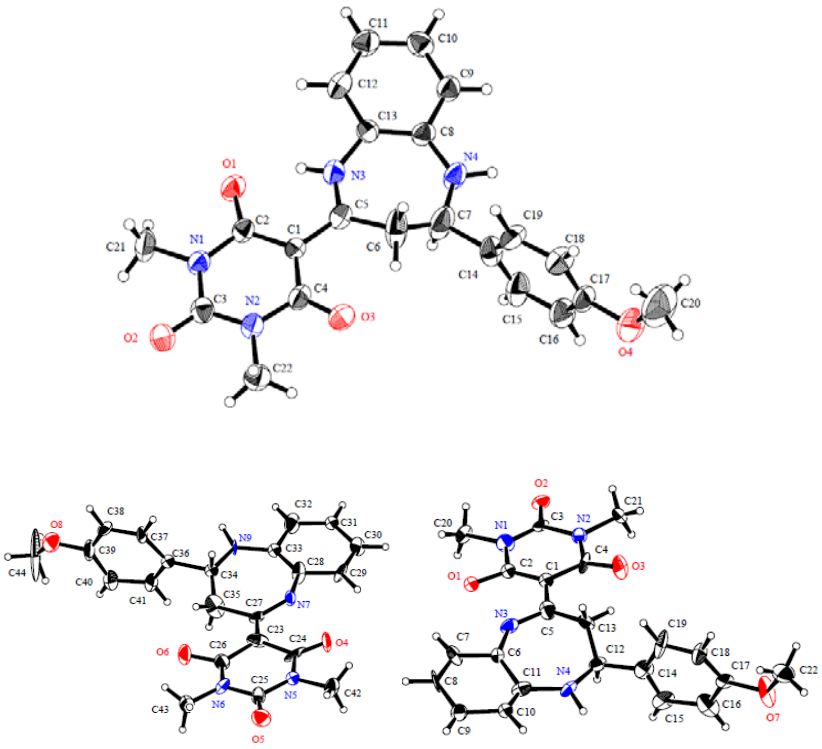


Figure 3.5: *ORTEP drawing of x-ray structure of* ***53****.*

3.4 Experimental design and base investigation

Series of optimization have been realized in order to determine the optimal experimental conditions concerning the reaction of **2** and substituted benzaldehydes for the synthesis of **3-14**. This investigation was first carried out on the synthesis of **5** and then continued with the optimization of the synthesis of **13**. Finally, the study was extended to all the chalconoids. The concept of optimization has been described in Chapter 2.

3.4.1 Optimization of 5

This optimization consisted of two steps: 1. a screening of the reaction resulting in the determination of the important variables of the reactions, 2. the optimization of the reaction to determine the optimal experimental conditions.

The importance of three variables was investigated in the screening: 1. the temperature of the oil bath fixed and monitored by a thermocouple, 2. The ratio of p-anisaldehyde to **2**, 3. The time of the reaction after addition of piperidine. Each variable was set at two levels, (-) low level and (+) high level (Table 4.1).

Variables	*Settings*	*Level (-)*	*Level (+)*
Ratio[a] (eq)	X_1	1,2	2
Time[b] (min)	X_2	1	3
Temperature[c] (°C)	X_3	120	180

Table 4.1: *Screening experimental domain of the synthesis of* ***5***

[a]Ratio of aldehyde
[b]Time after addition of piperidine
[C]Temperature of the oil bath

It was decided to run a full factorial design and $r^k=2^3$ experiments were run (*r* is the number of levels of settings and *k* the number of variables). The response of the full factorial design was the isolated yield of each experiment.

Number of the experiments	X_1	X_2	X_3	Yield
1	-	-	-	31%
2	+	-	-	50%
3	-	+	-	72%
4	+	+	-	75%
5	-	-	+	63%
6	+	-	+	85%
7	-	+	+	75%
8	+	+	+	88%

Table 4.2**: Full factorial design of the screening of the synthesis of **5

From the results of the Table 4.2, the constant term b_i of each variable settings has been calculated as described in Chapter 2.

b_1= (-31+50-72+75-63+85-75+88)/8 = +7,125

b_2= (-31-50+72+75-63-85+75+88)/8 = +10,125

b_3= (-31-50-72-75+63+85+75+88)/8 = +10,375

The result of each equation gives a clue about the importance of the variables and the position of the optimum response (that is the optimum yield of the reaction). First, the three variables have an influence on the reaction because the response of each variable setting is high. However, the temperature (of the oil bath) and the time reaction have a larger influence on the reaction than the ratio of **2**. Secondly, the sign of each average response are positives. Which means that the optimum yield will be reached around the level (+) of each variable. Nine experiments were run following the same procedure as the screening. The level (0) is the value of the variables between the level (+) and the level (-). It consists in determining the combination of the experimental variable settings that produces the highest possible yield.

Number of the experiments	X_1	X_2	X_3	Yield
9	0	0	-	34%
10	+	0	0	78%
11	0	0	+	69%
12	-	0	0	75%
13	0	-	0	63%
14	0	+	0	81%
15	0	0	0	91%

***Table 4.3**: Result of the optimization of the synthesis of **5**.*

The combination resulting from the experimental variable settings of the experiment **5** were considered good enough. The same experimental procedure was used for the other syntheses. The yield was raised by 184% (regarding the initial experimental conditions).

3.4.2 Optimization of 13

When it was decided to enlarge the study to *ortho*-substituents, a second optimization was performed on the reaction of **13**. A second screening was run with the same variable settings but different values of the variable settings (Table 4.4), taking into account the result of the optimization of **5**.

Variables	*Settings*	*Level (-)*	*Level (+)*
Ratio[a] (eq)	X_1	1	3
Time[b] (min)	X_2	1	5
Temperature[c] (°C)	X_3	160	200

***Table 4.4:** Screening experimental domain of the synthesis of **13**.*

[a]Ratio of aldehyde
[b]Time after addition of piperidine
[C]Temperature of the oil bath

A full factorial design was run the same way as the optimization of **5**.

Number of the experiments	X_1	X_2	X_3	Yield
1	-	-	-	24%
2	+	-	-	24%
3	-	+	-	29%
4	+	+	-	38%
5	-	-	+	8%
6	+	-	+	21%
7	-	+	+	18%
8	+	+	+	26%

Table 4.5*: Full factorial design of the screening of the synthesis of* ***13****.*

From the results obtained Table 4.5, in order to determine the important variables, b_i of each variable was calculated as described in Chapter 2.

b_1= (-24+24-29+38-8+21-18+26)/8 = +3,75
b_2= (-24-24+29+38-8-21+18+26)/8 = +4,25
b_3= (-24-24-29-38+8+21+18+26)/8 = -5,25

The result of these equations shows that the temperature is the most important variable. The temperature had to be lowered and both time reaction and ratio had to be raised. At that stage, five new experiments were run to observe the steepest ascent of the yield.

1. 4eq/140°/7min 43%
2. 4eq/120°/7min 52%
3. 5eq/120°/9min 50%
4. 4eq/120°/9min 52%
5. 4eq/100°/7min 50%

The 52% yield obtained was considered good enough. The yield was raised by 125% (from the initial experimental conditions).

3.4.3 Application of the optimization to the other syntheses

Regarding the previous optimizations, the optimum experimental conditions could be different for each chalconoid. A final investigation was carried out to highlight how the yields were affected by the characteristics of the benzaldehydes used. Two synthesis of each

chalconoid were performed considering both optimum experimental conditions of the optimization of **5** and **13** (Table 4.6).

Chalcone synthesized	Yield	
	1[a]	2[b]
3	23%	42%
4	38%	55%
5	36%	54%
7	19%	42%
8	36%	53%
9	28%	49%
10	31%	48%
12	3%	27%

Table 4.6*: Investigation of the variation of the yield of chalcanoids by running two different experimental procedure.*

[a]X_1: 2eq, X_2: 3min, X_3: 180°C.

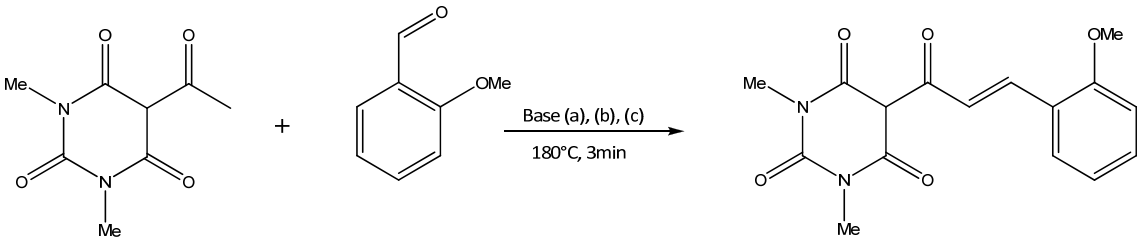
[a]X_1: 4eq, X_2: 7min, X_3: 120°C.

The first observation is that the optimal conditions N°2 gives the best results. The substituents have no effect on it, neither their position nor their type. Still there is contradiction. The two first optimizations and this investigation give different results. One of the explanations could be that one important variable has been neglected in the optimization: the amount of piperidine. Because this investigation has been performed on a very small scale (≈100-110mg) a small change in the amount of piperidine added could affect the yield more. Indeed, the temperature of boiling of piperidine is 106°C so when the synthesis is performed at 180°C on a small scale, piperidine is consumed faster. Secondly, because all the best yields correspond to one experimental condition, an explanation could be that not repeating the experiment with the same glassware, scale of the experiments, experimental procedure …) gives different results.

Some conclusions can be done and verified. The amount of piperidine is an important variable that has been omitted in the study. Secondly, each synthesis is characterized by different optimum experimental conditions. An individual optimization is required for each synthesis as observed in the screening of the synthesis of **5** and **13**. In order to give acceptable results, the optimization of the synthesis of **5** and **13** has to be realized again. All the optimizations have to be performed under the same conditions and include the amount piperidine as variable setting.

3.4.4 Investigation of influence by base

The influence of different bases on the synthesis of chalconoids was investigated. Piperidine, pyridine and triethylamine were selected for the synthesis of **9**. Their boiling temperature respectively is 106°C, 115.2°C and 88.7°C. The study revealed that piperidine gave the best. Highest boiling temperature of piperidine can explain why it gives a better yield than triethylamine for this reaction. No explanation is given why pyridine didn't react. It has been decided then to conserve piperidine as the base for the other synthesis of chalconoids (Scheme 4.1).



2

9a : 45%
9b : 0%
9c : 34%

Scheme 4.1*: Investigation of influence base on the synthesis of* ***9****: (a) piperidine, (b) yridine, (c) triethylamine.*

3.4 Biological testing

The majority of the compounds were conducted under kinase testing. A quantity of 1 mg of each compound were analysed but the bad solubility couldn't give good results. The only compounds having biological activity were the those synthesized from the chalconoids and phenylhydrazine. Because no any good spectroscopy analysis could be done, it can be prooved that the expecting compounds were synthesized. In that case, no results can't be published.

5 CONCLUSIONS

A new cheap, fast and efficient new synthetic route has been developed complex molecule in few steps. This simple gives access to a large number of new compounds with potential biological activity. Even if only a few of them revealed biological activity, these compounds form the foundations of more elaborate molecules of pharmaceutical and biological interests, leading to dozens of new derivatives.

Optimization revealed to be essential in the development of this project and the combination of statistics and chemistry proved a very powerful tool in the elaboration of this research plan.

5 EXPERIMENTAL SECTION

1. General

All reagents and solvents were of synthetic grade and were used as received. Reagents were purchased from Sigma-Aldrich, Fluka, Aesar, Merck, Janssen Chimica, SAFC, and BDH laboratory reagents. Solvents were purchased from Sigma-Aldrich, Fluka and Kenetyl.

The general procedure of each type of reaction is described. The experimental conditions are described for each synthesis and come along with the characterization of the related compound. All spectra are enclosed in the Appendices in the same order than the compounds have been presented.

Spectra for ^{1}H NMR and ^{13}C NMR were recorded on a Varian Mercury400 plus (399.65/100.54 Mhz) spectrometer. All samples were dissolved in $CDCl_3$ and DMSO-d_6. Chemical shift (δ) are reported in part per million (ppm), relative to TMS (δ = 0.00ppm) as internal standard. Coupling constant (J) are measured in Hertz (Hz). Signals multiplicity is quoted as s (singlet), d (doublet), t (triplet), m (multiplet) or as combination of these.

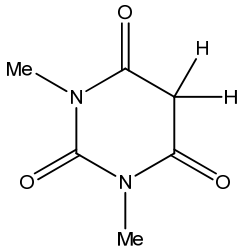
Infrared spectra were obtained on a Varian 7000e FT-IR spectrometer. Frequencies (ν) are reported in reciprocal centimeters (cm^{-1}).

Mass spectra were recorded on a Thermo electron LTQ Orbitrap+ Electrospray ion source (ION-MAX).

Melting points were either recorded on a Büchi 535 instrument or a hotplate.

2. Synthesis of Starting Materials

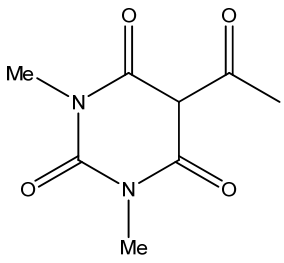
Synthesis of 1,3-dimethylbarbituric acid (1)



1

Dimethylurea (7,50 g; 85 mmol; 1 eq) and malonic acid (9,70 g; 93 mmol; 1,1 eq) were mixed in an Erlenmeyer flask, and acetic anhydride (16 ml) was added. The stirred reaction mixture was heated slowly to 80°C. When the exothermique reaction started, the oil bath was removed immediately from the hot plate; the reaction temperature rose to 125°C. The solution was allowed to cool to 100°C and was heated to 125°C one more time. Then, the solution was allowed to cool to room temperature. Isopropanol was added to the solution causing a white precipitate to appear. The white precipitate was filtered, washed with cold isopropanol and allowed to dry at room temperature;

Synthesis of 5-acetyl-1,3-dimethylbarbituric acid (2)

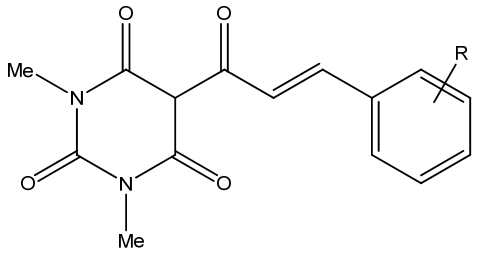


2

Compound **1** (23,51 g; 151 mmol; 1 eq) was suspended in a small amount of water and sodium bicarbonate (12,66 g; 151 mmol; 1 eq) as a concentrated water solution was added to barbituric acid in a round bottom flask. After gas evolution ceased, the insoluble part was filtered out and acetic anhydride (28,53 ml; 302 mmol; 2,00 eq) was added to the stirred reaction and a white precipitate usually formed after 5-10 minutes. The reaction was stirred overnight. The white precipitate was filtered, washed with a little of water and dissolved in 10% of ammonium hydroxide. Hydrochloric acid was added until pH=0: the temperature of the solution rose and a white precipitate was formed. The precipitate was filtered and allowed to dry at room temperature.

3. Synthesis of chalconoids

General procedure



Compound **2** was mixed with required benzaldehydes. The mixture was heated to 180°C in an oil bath for 2 minutes and 0,1mL of piperidine was added. The mixture was heated for an additional 3 minutes and was allowed to cool. Then, EtOH was added to the mixture and the solution was heated to the boiling point. The solution was allowed to cool. The precipitate was filtered out and washed with EtOH. The resulting solid compounds **3-14** were allowed to dry at room temperature.

5-cinnamoyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (3):

From **2** (5,00 g; 25 mmol) and benzaldehyde (5,15 mL; 50 mmol): 5,65 g (89 %); paled yellow solid.
m.p. 179-181 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.02 (d, *J* = 1.4 Hz, 1H), 8.58 (dd, *J* = 15.9, 1.4 Hz, 1H), 8.00 (d, *J* = 15.9 Hz, 1H), 7.76 – 7.57 (m, 2H), 7.42 (dd, *J* = 5.1, 2.0 Hz, 3H), 3.40 (s, 3H), 3.37 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 183.96, 169.98, 161.44, 150.49, 146.78, 134.84, 131.41, 129.29, 129.12, 120.56, 97.47, 28.28, 28.06 ppm.
IR (ν_{max}): 3109, 3057, 2952, 1716, 1656, 1612, 1525, 1483, 1425, 1217, 989, 920, 796, 750, 697 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{13}O_4N_2$ [M^-] 285.0875; found 285.0881.

(E)-5-(3-(4-(dimethylamino)phenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (4):

Starting from **2** (5,00 g; 25 mmol) and 4-dimethylaminobenzaldehyde (7,54 g; 50 mmol): 6,95 g (84 %); bright red solid.
m.p 229-231 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 16.78 (s, *J* = 1.2 Hz, 1H), 8.38 (d, *J* = 15.5, 1.4 Hz, 1H), 8.03 (d, *J* = 15.5 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 3.40 – 3.36 (d, 6H), 3.08 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 183.76, 169,81, 161.77, 152.85, 150.77, 148.55, 131.92, 122.77, 114.23, 114.21, 111.84, 93.01, 40.21, 28.18, 27.95 ppm.
IR (ν_{max}): 3105, 2914, 2827, 1706, 1654, 1580, 1525, 1477, 1413, 1274, 1220, 1355, 1171, 1010, 977, 814, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{20}O_4N_3$ [$M+H^+$] 330.1455, found. 330.1448.

(E)-5-(3-(4-methoxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5):

From **2** (4,00 g; 20 mmol) and *p*-anisaldehyde (4,90 mL; 40 mmol): 5,69 g (89 %); bright yellow solid.
m.p. 190-192 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 16.95 (d, *J* = 1.4 Hz, 1H), 8.46 (dd, *J* = 15.7, 1.4 Hz, 1H), 7.99 (d, *J* = 15.8 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.38 (d, *J* = 9.7 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 184.11, 170.02, 162.65, 161.68, 147.05, 131.41, 127.76, 117.99, 114.71, 93.97, 77.16, 55.64, 28.30, 28.09 ppm.
IR (ν_{max}): 3108, 2955, 2845, 1711, 1654, 1622, 1598, 1506, 1481, 1418, 1257, 1168, 1017, 976, 824, 758 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{15}O_5N_2$ [M^-] 315.0980, found 315.0986.

(E)-5-(3-(4-hydroxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (6):

From **2** (4,00 g; 20 mmol) and 4-hydroxybenzaldehyde (9,86 g; 80 mmol): 4,61 g (76 %); yellow solid.
m.p. >230 °C
^{1}H NMR (DMSO, 400 MHz): δ = 16.96 (s, 1H), 10.34 (s, 1H), 8.31 (d, *J* = 15.8 Hz, 1H), 7.91 (d, *J* = 15.8 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 3.19 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 182.15, 161.20, 149.94, 146.40, 131.37, 125.59, 116.27, 116.14, 93.72, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.90, 27.74 ppm.
IR (ν_{max}): 3235, 3109, 2960, 1711, 1618, 1596, 1478, 1428, 1272, 1166, 838 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{14}O_5N_2$ [$M+Na^+$] 325.0801, found 325.0795.

(E)-5-(3-(4-chlorophenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (7):

Starting from **2** (5,00 g; 25 mmol) and 4-chlorobenzaldehyde (7,10 g; 50 mmol): 3,31 g (41 %); yellow solid.
m.p. 201-203 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.03 (d, *J* = 1.4 Hz, 1H), 8.55 (dd, *J* = 15.9, 1.4 Hz, 1H), 7.94 (d, *J* = 15.9 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 3.39 (d, *J* = 12.7 Hz, 6H) ppm.
IR (ν_{max}): 3104, 3053, 2958, 1716, 1655, 1619, 1524, 1476, 1426, 1404, 1217, 1087, 1011, 975, 823, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{12}O_4N_2Cl$ [M^-] 319.0484, found 319.0491.

(E)-1,3-dimethyl-5-(3-(4-nitrophenyl)acryloyl)pyrimidine-2,4,6(1H,3H,5H)-trione (8):

From **2** (5,00 g; 25 mmol) and 4-nitrobenzaldehyde (7,62 g; 50 mmol): 2,60 g (41 %); yellow solid.
m.p. >250 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.11 (d, *J* = 1.4 Hz, 1H), 8.69 (dd, *J* = 15.9, 1.4 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 15.9 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 3.40 (d, *J* = 14.4 Hz, 6H) ppm.
IR (ν_{max}): 3101, 3079, 2962, 1716, 1654, 1622, 1599, 1483, 1336, 1210, 1018, 989, 848, 793, 750, 699 cm^{-1}.
HRMS (MS): calcd. for $C_{15}H_{12}O_6N_3$ [M^-] 330.0725, found 330.0732.

(E)-5-(3-(2-methoxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (9):

From **2** (9,00 g; 45 mmol) and 2-methoxybenzaldehyde (12,39 g; 90 mmol): 9,29 g (65 %); yellow solid.
m.p. 214-215 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 16.97 (s, 1H), 8.60 (d, *J* = 16.0 Hz, 1H), 8.43 (d, *J* = 16.0 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.31 (t, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.38 (d, *J* = 10.8 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 184.72, 174.87, 170.34, 166.38, 163.34, 161.86, 159.43, 151.91, 150.96, 142.38, 133.31, 129.58, 124.19, 121.34, 120.71, 111.71, 94.57, 91.45, 77.80, 77.48, 77.16, 77.16, 56.11, 28.61, 28.38, 28.30, 28.10, 26.38 ppm.
IR (ν_{max}): 3107, 3013, 2960, 2927, 2838, 1711, 1657, 1612, 1595, 1527, 1468, 1424, 1246, 1216, 1161, 1106, 991, 793, 747 cm^{-1}.
HRMS (EI): calcd. for $C_{16}H_{17}O_5N_2$ [M^+] 317.1138, found 317.1132.

(E)-5-(3-(2-chlorophenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (10):

From **2** (9,00 g; 45 mmol) and 2-chlorobenzaldehyde (12,65 g; 90 mmol): 9,63 g (66 %); paled yellow solid.
m.p. 194-195 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.06 (s, 1H), 8.57 (d, *J* = 16.0 Hz, 1H), 8.43 (d, *J* = 15.9 Hz, 1H), 7.87 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 – 7.27 (m, 2H), 3.39 (d, *J* = 14.8 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 183.52, 174.56, 169.95, 166.03, 163.00, 161.43, 151.56, 150.45, 141.92, 136.02, 132.94, 132.01, 130.38, 128.49, 127.34, 122.80, 94.85, 91.09, 77.48, 77.16, 76.84, 28.32, 28.13, 27.96, 27.76, 26.01 ppm.
IR (ν_{max}): 3110, 3066, 2956, 1717, 1651, 1617, 1515, 1424, 1216, 922, 793, 752, 724 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{14}O_4N_2Cl$ [M^+] 321.0642, obs. 321.0637.

(E)-5-(3-(2-fluorophenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (11):

From **2** (4,00 g; 20 mmol) and 2-fluorobenzaldehyde (4,25 mL; 40 mmol): 3,72 g (60 %); yellow solid.
m.p. 181-183 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.02 (s, 1H), 8.61 (d, *J* = 16.0 Hz, 1H), 8.17 (d, *J* = 16.0 Hz, 1H), 7.76 (td, *J* = 7.7, 1.3 Hz, 1H), 7.40 (td, *J* = 7.3, 1.5 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.15 – 7.07 (m, 1H), 3.38 (d, *J* = 12.5 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ= 183.67, 170.02, 163.16, 161.42, 160.62, 150.50, 138.58, 138.54, 132.94, 132.86, 129.22, 129.20, 124.75, 124.71, 122.50, 116.51, 116.29, 94.78, 28.34, 28.13 ppm.
IR (ν_{max}): 3141, 3112, 3070, 2957, 1715, 1656, 1605, 1523, 1478, 1426, 1214, 997, 766, 751 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{13}O_4N_2FNa$ [M+Na^+] 327.0757, found 327.0752.

(E)-2-(3-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-3-oxoprop-1-enyl)benzonitrile (12):

From **2** (3,91 g; 20 mmol) and 2-cyanobenzaldehyde (5,18 g; 40 mmol): 2,13 g (35 %); dark brown solid.
m.p. >214 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.06 (s, 1H), 8.71 (d, *J* = 15.8 Hz, 1H), 8.31 (t, *J* = 16.8 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 3.40 (dd, *J* = 16.1, 5.8 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 182.75, 169.94, 161.44, 140.55, 137.73, 133.65, 133.18, 130.90, 127.54, 125.04, 117.13, 113.78, 77.48, 77.16, 76.84, 28.84, 28.71, 28.41, 28.23 ppm.
IR (ν_{max}): 3108, 3064, 3029, 2963, 2225, 1716, 1647, 1624, 1519, 1474, 1423, 1371, 1213, 1110, 1016, 980, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{16}H_{13}O_4N_3Na$ [M+Na^+] 334.0804, found 334.0798.

(E)-1,3-dimethyl-5-(3-(2-nitrophenyl)acryloyl)pyrimidine-2,4,6(1H,3H,5H)-trione (13):

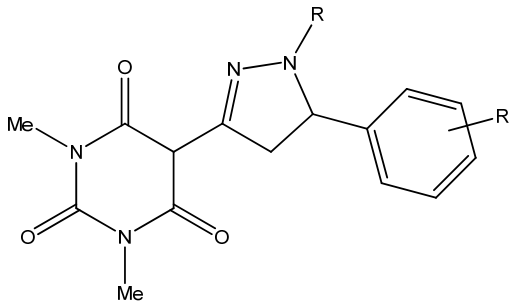
From **2** (9,00 g; 45 mmol) and 2-nitrobenzaldehyde (13,60 g; 90 mmol): 4,48 g (30 %); paled yellow solid.
m.p. 215-216 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.08 (s, 1H), 8.50 (d, *J* = 15.7 Hz, 1H), 8.40 (d, *J* = 15.7 Hz, 1H), 8.05 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.68 (m, *J* = 7.8, 1.2, 0.7 Hz, 1H), 7.57 (td, *J* = 8.1, 1.4 Hz, 1H), 3.38 (d, *J* = 19.2 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 183.01, 169.96, 161.42, 150.41, 148.86, 141.00, 133.69, 130.97, 130.87, 129.73, 125.38, 125.14, 95.29, 77.48, 77.16, 76.84, 28.38, 28.21 ppm.
IR (ν_{max}): 3105, 3079, 2963, 1721, 1672, 1623, 1571, 1514, 1473, 1421, 1353, 1339, 1298, 1212, 1016, 974, 925, 791, 752, 745 cm^{-1}.

(E)-5-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (14):

From **2** (4,03 g; 20 mmol) and vanillin (6,19 g; 40 mmol): 3,83 g (57 %); yellow solid.
m.p. >218 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 16.98 (d, *J* = 1.2 Hz, 1H), 8.43 (dd, *J* = 15.7, 1.1 Hz, 1H), 7.98 (d, *J* = 15.7 Hz, 1H), 7.22 (d, *J* = 19.7 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.00 (s, 1H), 3.98 (s, 3H), 3.39 (d, *J* = 10.0 Hz, 6H) ppm.
IR (ν_{max}): 3444, 3105, 3026, 2955, 1707, 1651, 1620, 1578, 1515, 1490, 1422, 1284, 1270, 1161, 1117, 1020, 975, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{16}H_{16}O_6N_2Na$ [M+Na^+] 355.0906, found 355.0901.

4. Synthesis of pyrazoles

General procedure



Chalconoids **3-14** were mixed with required hydrazine derivatives. The mixture was heated for 3 min. The mixture was allowed to cool. Then, water was added to the mixture and the solution was heated to the boiling point. The solution was allowed to cool. The precipitate was filtered out and washed with water. The resulting solid compound was allowed to dry at room temperature.

1,3-dimethyl-5-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (15):

From **3** (200 mg; 699 µmol) and hydrazine hydrate (0,50 mL; excess): 50 mg (24 %); paled yellow solid.
m.p. 158-160 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.16 (s, 1H), 8.22 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 4.94 (dd, *J* = 9.6, 7.5 Hz, 1H), 4.07 (dd, *J* = 18.6, 9.8 Hz, 1H), 3.44 (dd, *J* = 18.6, 7.5 Hz, 1H), 3.18 (s, 1H), 3.12 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 166.49, 162.50, 152.08, 139.40, 129.29, 128.67, 126.48, 86.54, 77.56, 77.24, 76.92, 73.18, 59.82, 43.07, 27.93, 27.86 ppm.
IR (ν_{max}): 3225, 3032, 2953, 2361, 2337, 1699, 1608, 1457, 1416, 1354, 1262, 1136, 1001, 864, 786, 753, 698 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{15}O_3N_4$ [M^-] 299.1143, found. 299.1150.

5-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (16):

From **4** (200 mg; 607 µmol) and hydrazine hydrate (0,50 mL; excess): 80 mg (38 %); brown orange solid.
m.p. >240 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.96 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 4.77 (t, *J* = 8.9 Hz, 2H), 4.08 (dd, *J* = 18.9, 8.9 Hz, 1H), 3.72 (dd, *J* = 18.9, 8.7 Hz, 4H), 3.33 (d, *J* = 10.3 Hz, 6H), 2.96 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 166.83, 160.86, 152.03, 150.73, 129.94, 127.51, 125.83, 112.70, 112.17, 111.82, 86.31, 59.91, 42.41, 40.56, 40.45, 40.30, 27.82 ppm.
IR (ν_{max}): 3221, 2951, 2891, 2810, 1666, 1611, 1542, 1433, 1363, 1196, 1054, 944, 810, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{20}O_3N_5$ [M^-] 342.1565, found 342.1572.

5-(5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (17):

From **5** (200 mg; 632 µmol) and hydrazine hydrate (0,50 mL; excess):70mg (34%); paled yellow solid.
m.p. 179-181 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.85 (t, *J* = 8.7 Hz, 1H), 4.11 (dd, *J* = 18.9, 9.0 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 19.0, 8.2 Hz, 1H), 3.32 (d, *J* = 6.8 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 166.65, 165.17, 162.43, 159.84, 152.01, 130.97, 127.77, 114.55, 86.44, 77.16, 59.54, 55.49, 42.80, 27.88, 27.76 ppm.
IR (ν_{max}): 3250, 3184, 3087, 2947, 2909, 2842, 1693, 1635, 1606, 1563, 1511, 1454, 1354, 1245, 1181, 1148, 1036, 894, 834, 786, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{16}H_{17}O_4N_4$ [M^-] 329.1249, found 329.1255.

5-(5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (18):

From **6** (331 mg; 1 mmol) and hydrazine hydrate (1,09 mL; excess): 333 mg (96 %); white solid.
m.p. >230 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.05 (s, 1H), 9.39 (s, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.73 (d, *J* = 7.6 Hz, 3H), 4.65 (d, *J* = 6.5 Hz, 1H), 3.92 (dd, *J* = 18.4, 9.2 Hz, 1H), 3.13 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 161.79, 156.79, 151.36, 130.90, 127.76, 115.20, 84.35, 58.01, 43.57, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.22 ppm.

IR (ν_{max}): 3283, 3203, 3189, 3025, 2965, 2899, 2361, 1695, 1621, 1556, 1519, 1479, 1436, 1345, 1221, 1147, 787, 753, 677 cm^{-1}.
HRMS (HRMS): calcd. for $C_{15}H_{16}O_4N_4$ [M+Na^+] 339.1070, found 339.1064.

5-(5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (19):

From **7** (200 mg; 624 µmmol) and hydrazine hydrate (0,50 mL; excess): 90mg (43 %); paled yellow solid.
m.p. 212-214 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.99 (s, 1H), 7.38 – 7.28 (m, 4H), 5.06 (s, 1H), 4.86 (dd, *J* = 9.0, 7.2 Hz, 1H), 4.10 (dd, *J* = 18.9, 9.2 Hz, 1H), 3.75 (dd, *J* = 18.9, 7.0 Hz, 1H), 3.32 (d, *J* = 14.6 Hz, 6H) ppm.
IR (ν_{max}): 3223, 3173, 2950, 2910, 2361, 2337, 1692, 1616, 1568, 1457, 1356, 1151, 897, 817, 786, 756 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{14}O_3N_4Cl$ [M^-] 333.0754, found 333.0760.

1,3-dimethyl-5-(5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (20):

From **8** (200 mg; 604 µmol) and hydrazine hydrate (0,50 mL; excess): 140 mg; 65 %; brown orange solid.

5-(5-(2-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (21):

From **9** (217 mg; 655 µmol) and hydrazine hydrate (0,68 mL; excess): 112 mg (49%); white solid.
m.p. 190-192 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.10 (s, 1H), 7.35 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.92 (dd, *J* = 7.9, 7.1 Hz, 1H), 6.77 (d, *J* = 6.1 Hz, 1H), 4.89 (dd, *J* = 15.6, 6.3 Hz, 1H), 3.90 (dd, *J* = 18.7, 9.6 Hz, 1H), 3.83 (s, 4H), 3.37 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.12 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 162.19, 156.22, 151.31, 129.25, 128.56, 125.96, 120.22, 110.87, 84.43, 55.47, 52.99, 42.91, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.19 ppm.
IR (ν_{max}): 3230, 3014, 2958, 2836, 1704, 1644, 1610, 1573, 1455, 1357, 1240, 1027, 787, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{16}H_{19}O_4N_4$ [M^+] 331.1407, found 331.1401.

5-(5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (22):

From **10** (307 mg; 957 µmol) and hydrazine hydrate (0,95 mL; excess): 107 mg (33 %); white solid.
m.p. 123-125 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 11.12 (s, 1H), 7.51 (dd, *J* = 33.1, 6.5 Hz, 2H), 7.33 (d, *J* = 6.6 Hz, 2H), 4.99 (s, 1H), 4.01 (dd, *J* = 18.3, 9.7 Hz, 1H), 3.54 – 3.23 (m, 2H), 3.11 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 162.32, 161.45, 151.29, 139.29, 131.41, 129.51, 129.05, 127.41, 127.23, 84.54, 54.87, 43.16, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.19 ppm.
IR (ν_{max}): 3227, 2953, 1697, 1609, 1464, 1413, 1353, 1262, 886, 751 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{16}O_3N_4Cl$ [M^+] 335.0912, found 335.0905.

5-(5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (23):

From **11** (296 mg; 973 µmmol) and hydrazine hydrate (0,97 mL; excess): 157 mg (51 %); white solid.
m.p. 214-216 °C.
^{1}H NMR (DMSO, 400 MHz): δ= 12.11 (s, 1H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.33 (d, *J* = 6.0 Hz, 1H), 7.25 – 7.10 (m, 2H), 6.96 (d, *J* = 5.8 Hz, 1H), 4.97 (d, *J* = 6.4 Hz, 1H), 3.99 (dd, *J* = 18.5, 9.7 Hz, 1H), 3.47 (dd, *J* = 18.5, 6.3 Hz, 1H), 3.11 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 161.76, 161.03, 158.60, 151.28, 129.44, 129.36, 128.60, 128.47, 127.67, 127.63, 124.48, 124.45, 115.53, 115.32, 84.45, 52.14, 42.86, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.90, 27.18 ppm.
IR (ν_{max}): 3274, 3200, 2962, 2887, 1693, 1609, 1455, 1416, 1357, 1264, 1135, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{16}O_3N_4F$ [$M+H^+$] 319.1207, found 319.1201.

2-(3-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile (24):

From **12** (255 mg; 819 µmol) and hydrazine hydrate (0,52 mL; excess): 57 mg (21 %); light brown solid.

1,3-dimethyl-5-(5-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (25):

From **13** (215 mg; 649 µmol) and hydrazine hydrate (0,65 mL; excess): 121 mg (54 %); paled yellow solid.
m.p. 231-233 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.09 (s, 1H), 8.11 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.54 – 7.41 (m, 1H), 5.68 – 5.54 (m, 1H), 5.38 (d, *J* = 6.9 Hz, 1H), 4.23 (dd, *J* = 19.5, 10.0 Hz, 1H), 3.84 (dd, *J* = 19.5, 4.3 Hz, 1H), 3.30 (d, *J* = 25.3 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 161.42, 151.27, 147.59, 137.06, 134.00, 128.76, 128.17, 124.84, 84.52, 53.99, 44.16, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.19 ppm.
IR (ν_{max}): 3336, 3260, 3232, 3030, 2963, 3947, 2838, 2362, 2337, 1695, 1647, 1607, 1570, 1525, 1455, 1363, 1343, 1295, 1137, 1009, 916, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{15}H_{15}O_5N_5Na$ [M+Na^+] 368.0971, found 368.0965.

5-(5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (26):

From **14** (308 mg; 627 µmol) and hydrazine hydrate (0,92 mL; excess): 179 mg (56 %); white solid.
m.p. 213-215 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.07 (s, 1H), 8.93 (s, 1H), 7.00 (s, 1H), 6.75 (q, *J* = 7.7 Hz, 4H), 4.66 (dd, *J* = 15.4, 8.5 Hz, 1H), 3.95 (dd, *J* = 18.5, 9.2 Hz, 1H), 3.76 (s, 4H), 3.44 – 3.23 (m, 3H), 3.13 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 161.73, 151.35, 147.57, 145.97, 131.32, 119.00, 115.26, 110.81, 84.31, 58.40, 55.59, 43.65, 40.14, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.20 ppm.
IR (ν_{max}): 3476, 3264, 3005, 2959, 2903, 2835, 1708, 1613, 1565, 1528, 1465, 1261, 1215, 1125, 1033, 754 cm^{-1}.
HRMS (EI): calcd. for $C_{16}H_{19}O_5N_4$ [M+H^+] 347.1356, found 347.1350.

5-(1-(2-hydroxyethyl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (27):

From **3** (403 mg; 1,41 mmol) and 2-hydroxyethylhydrazine (0,95 mL; excess): 260 mg (54%); white solid.
m.p. >228 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.70 (s, 1H), 7.49 (d, *J* = 6.3 Hz, 2H), 7.37 (dd, *J* = 16.1, 6.0 Hz, 4H), 5.59 (s, 1H), 4.32 – 4.19 (m, 1H), 4.14 (dd, *J* = 18.0, 8.5 Hz, 1H), 3.68 (s, 2H), 3.13 (s, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 158.48, 151.29, 138.24, 128.70, 128.47, 128.15, 127.65, 126.43, 83.89, 68.16, 60.72, 55.96, 42.29, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.20 ppm.
IR (ν_{max}): 3419, 3179, 2954, 2901, 2881, 2821, 1696, 1612, 1455, 1366, 1106, 1085, 1060, 750, 699 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{20}O_4N_4Na$ [M+Na^{+}] 367.1383, found 367.1377.

5-(5-(4-(dimethylamino)phenyl)-1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (28):

From **4** (407 mg; 1,24 mmol) and 2-hydroxyethylhydrazine (0,84 mL; excess): 265 mg (55 %); paled orange solid.
m.p. 228-230 °C.
IR (ν_{max}): 3422, 3173, 2947, 2903, 2885, 2808, 1699, 1636, 1610, 1525, 1471, 1453, 1361, 1061, 813, 751 cm^{-1}.
HRMS (EI): calcd. for $C_{19}H_{26}O_4N_5Na$ [M^{+}] 388.1985, found 388.1979.

5-(1-(2-hydroxyethyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (29):

From **5** (392 mg; 1,24 mmol) and 2-hydroxyethylhydrazine (0,84 mL; excess): 175 mg (38 %); white solid.
m.p. 192-194 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.69 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.59 (s, 1H), 4.11 (m, *J* = 26.5, 14.8, 8.8 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 1H), 3.71 – 3.56 (m, 2H), 3.11 (dd, *J* = 18.4, 10.7 Hz, 6H), 2.77 (d, *J* = 3.7 Hz, 2H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 159.29, 158.59, 151.40, 132.79, 129.69, 129.14, 127.84, 114.17, 113.95, 84.46, 83.95, 68.06, 60.88, 57.91, 55.71, 55.20, 55.17, 43.70, 42.22, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.29 ppm.
IR (ν_{max}): 3418, 3177, 2955, 2910, 2836, 1697, 1610, 1513, 1455, 1360, 1249, 1177, 1085, 1038, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{18}H_{22}O_5N_4Na$ [M+Na^{+}] 397.1488, found 397.1482.

5-(1-(2-hydroxyethyl)-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (30):

From **6** (328 mg; 1,09 mmol) and 2-hydroxyethylhydrazine (0,74 mL; excess): 189 mg (48%); white solid.
m.p. >238 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.68 (s, 1H), 9.49 (s, 1H), 7.28 (d, *J* = 7.7 Hz, 3H), 6.77 (d, *J* = 7.6 Hz, 3H), 5.57 (s, 1H), 4.28 – 3.85 (m, 2H), 3.66 (t, *J* = 16.8 Hz, 2H), 3.34 (s, 2H), 3.13 (s, 6H) ppm
^{13}C NMR (DMSO, 101 MHz): δ = 158.52, 157.41, 151.31, 129.04, 127.76, 127.70, 115.42, 115.19, 83.85, 68.18, 60.81, 55.55, 42.10, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.21 ppm.
IR (ν_{max}): 3489, 3314, 3217, 2920, 2881, 2838, 2362, 2337, 1700, 1612, 1594, 1516, 1463, 1451, 1362, 1345, 1267, 1230, 1092, 796 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{20}O_5N_4Na$ [M+Na^{+}] 383.1332, found 383.1326.

5-(5-(4-chlorophenyl)-1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (31):

From **7** (390 mg; 1,22 mmol) and 2-hydroxyethylhydrazine (0,83 mL; excess): 217 mg (47 %); white solid.
m.p. >240°C.
^{1}H NMR (DMSO, 400 MHz): δ = 7.52 (d, *J* = 7.0 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 4.28 (t, *J* = 10.3 Hz, 1H), 4.14 (dd, *J* = 18.0, 8.6 Hz, 1H), 3.67 (s, 2H), 3.12 (s, 6H), 2.80 (s, 2H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 158.45, 151.28, 137.46, 132.68, 129.53, 128.66, 83.92, 67.31, 60.67, 56.04, 42.19, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.20 ppm.
IR (ν_{max}): 3424, 3165, 2955, 2916, 2888, 2831, 1698, 1613, 1473, 1457, 1361, 1086, 815, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{19}O_4N_4ClNa$ [M+Na^{+}] 401.0993, found 401.0987.

5-(1-(2-hydroxyethyl)-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (32):

From **8** (200 mg; 604 µmol) and 2-hydroxyethylhydrazine (excess): 12g (5 %)
^{1}H NMR (DMSO, 400 MHz): δ = 8.23 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 4.46 (t, *J* = 10.5 Hz, 1H), 4.20 (dd, *J* = 18.2, 9.2 Hz, 1H), 3.67 (s, 2H), 3.19 – 3.02 (m, 1+3H), 2.95 – 2.76 (m, 2H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 162.79, 158.76, 151.72, 147.66, 147.15, 129.25, 124.22, 104.99, 84.42, 67.40, 61.01, 56.94, 42.74, 27.64.

5-(1-(2-hydroxyethyl)-5-(2-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (33):

From **9** (402 mg; 1,27 mmol) and 2-hydroxyethylhydrazine (0,86 mL; excess): 211 mg; (44 %); white solid.
m.p. 195-197 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.69 (s, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 5.56 (s, 1H), 4.49 (t, *J* = 10.4 Hz, 1H), 4.16 (dd, *J* = 18.4, 9.1 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 2H), 3.12 (s, 6H), 2.96 (dd, *J* = 18.3, 11.9 Hz, 1H), 2.84 (s, 2H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 158.92, 156.92, 151.30, 128.94, 126.65, 126.57, 120.66, 111.05, 83.97, 62.30, 60.64, 56.67, 55.55, 40.78, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.18 ppm.
IR (ν_{max}): 3430, 3174, 2954, 2940, 2903, 2876, 2840, 2822, 1712, 1642, 1602, 1565, 1476, 1454, 1360, 1250, 1106, 1023, 794, 750 cm^{-1}.
HRMS (EI): calcd. for $C_{18}H_{22}O_5N_4Na$ [M+Na$^+$] 397.1488, found 397.1482.

5-(5-(2-chlorophenyl)-1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (34):

From **10** (414 mg; 1,29 mmol) and 2-hydroxyethylhydrazine (0,88 mL; excess): 252mg (52%); white solid.
m.p. >234 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.67 (s, 1H), 7.69 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.51 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.43 – 7.33 (m, 2H), 5.56 (s, 1H), 4.65 (t, *J* = 10.2 Hz, 1H), 4.28 (dd, *J* = 18.5, 9.4 Hz, 1H), 3.72 (d, *J* = 10.8 Hz, 2H), 3.12 (s, 6H), 3.05 (dd, *J* = 18.6, 11.2 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.87 (d, *J* = 13.2 Hz, 1H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 158.58, 151.27, 136.67, 132.31, 129.65, 129.51, 128.12, 127.81, 84.07, 64.33, 60.52, 56.77, 40.82, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.90, 27.20 ppm.
IR (ν_{max}): 3491, 3197, 3073, 2945, 2891, 2829, 1697, 1645, 1623, 1476, 1467, 1364, 1091, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{19}O_4N_4ClNa$ [M+Na$^+$] 401.0993, found 401.0987.

5-(5-(2-fluorophenyl)-1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (35):

From **11** (396 mg; 1,30 mmol) and 2-hydroxyethylhydrazine (0,88 mL; excess): 276 mg (58 %); white solid.
m.p. 219-221 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 12.68 (s, 1H), 7.61 (t, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 5.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.57 (s, 1H), 4.55 (t, *J* = 10.4 Hz, 1H), 4.15 (dd, *J* = 18.3, 9.2 Hz, 1H), 3.70 (s, 2H), 3.20 (d, *J* = 11.7 Hz, 1H), 3.12 (d, *J* = 15.1 Hz, 6H), 2.98 – 2.78 (m, 2H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 163.39, 161.67, 161.41, 159.23, 158.78, 158.72, 151.28, 130.02, 129.93, 128.67, 128.63, 125.71, 125.59, 124.88, 115.71, 115.50, 84.00, 61.40, 60.58, 56.55, 40.82, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 27.20 ppm.
IR (ν_{max}): 3444, 3196, 2970, 2898, 2882, 2821, 2362, 2336, 1697, 1613, 1455, 1359, 1088, 751 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{19}O_4N_4FNa$ [M+Na$^+$] 385.1288, found 385.1283.

2-(3-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile (36):

From **12** (351 mg; 1,13 mmol) and 2-hydroxyethylhydrazine (0,76 mL; excess): 119 mg (29 %); brown solid.
m.p. >234 °C.
IR (ν_{max}): 3296, 3103, 2957, 2909, 2845, 2362, 2335, 2220, 1689, 1621, 1475, 1365, 1090, 755 cm^{-1}.
HRMS (EI): calcd. for $C_{18}H_{19}O_4N_5Na$ [M+Na$^+$] 392.1335, found. 392.1329.

5-(1-(2-hydroxyethyl)-5-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (37)

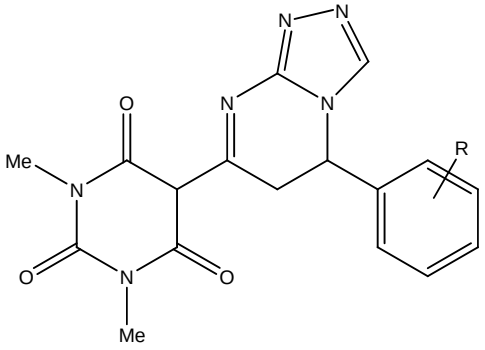
From **13** (411 mg; 1,24 mmol) and 2-hydroxyethylhydrazine (0,84 mL; excess): 35 mg (20 %)
m.p. >230 °C.
IR (ν_{max}): 3358, 2955, 2886, 2827, 2361, 2336, 1677, 1640, 1609, 1578, 1480, 1416, 1384, 1350, 1222, 750 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{19}O_6N_5Na$ [M+Na$^+$] 412.1233, found 412.1228.

5-(5-(4-hydroxy-3-methoxyphenyl)-1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (38):

From **14** (200 mg; 1,28 mmol) and 2-hydroxyethylhydrazine (0,87 mL; excess): 42g (10 %).
^{1}H NMR (DMSO, 400 MHz): δ = 12.67 (s, 1H), 9.01 (s, 2H), 7.04 (d, *J* = 1.6 Hz, 2H), 6.88 – 6.79 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 2H), 4.13 – 3.96 (m, 4H), 3.76 (s, 6H), 3.65 (dd, *J* = 20.8, 10.0 Hz, 4H), 3.12 (s, 15H), 2.76 (t, *J* = 14.7 Hz, 4H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 158.95, 151.77, 148.18, 147.02, 128.75, 120.90, 115.75, 111.93, 84.30, 68.92, 61.25, 56.03, 42.58, 27.65ppm.

6. Synthesis of triazoles

General procedure



Chalconoids **3-14** were mixed with 3-amino-1H-1,2,4-triazole. The mixture was heated for 3 min. The mixture was allowed to cool. Then, EtOH was added to the mixture and the solution was heated to the boiling point. The solution was allowed to cool. The precipitate was filtered out and washed with EtOH. The resulting solid compound was allowed to dry at room temperature.

1,3-dimethyl-5-(5-phenyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (39):

From **3** (200 mg; 699 µmol) and 3-amino-1H-1,2,4-triazole (64 mg; 7µmol): 120 mg (70%); pinked white solid.
m.p. 170-172 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 14.47 (s, 1H), 7.83 (s, 1H), 7.35 (d, *J* = 6.9 Hz, ?H), 7.07 (dd, *J* = 7.5, 1.8 Hz, 2H), 5.64 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.80 (dd, *J* = 18.4, 5.0 Hz, 1H), 4.03 (dd, *J* = 18.4, 7.0 Hz, 1H), 3.33 (d, *J* = 22.2 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.94, 164.25, 162.21, 151.08, 150.62, 146.61, 136.91, 129.49, 129.20, 126.08, 93.77, 77.48, 77.16, 76.84, 56.18, 33.57, 28.41, 28.26 ppm.
IR (ν_{max}): 3141, 3033, 2962, 1716, 1623, 1553, 1528, 1510, 1453, 1442, 1411, 1347, 1330, 1249, 1184, 1110, 695 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{16}O_3N_6Na$ [M+Na^+] 375.1182, found 375.1176.

5-(5-(4-(dimethylamino)phenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (40):

From **4** (200 mg; 607 µmol) 3-amino-1H-1,2,4-triazole (160 mg): 200 mg (61 %); orange solid.
m.p. 159-161 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 14.44 (s, 1H), 7.80 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.86 (s, 2H), 5.56 (t, *J* = 6.0 Hz, 1H), 4.75 (dd, *J* = 18.3, 5.3 Hz, 1H), 4.02 (dd, *J* = 18.3, 6.8 Hz, 1H), 3.34 (d, *J* = 20.9 Hz, 6H), 2.97 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ= 165.89, 164.94, 162.13, 150.77, 150.74, 150.64, 146.22, 127.06, 123.78, 112.63, 93.50, 77.48, 77.16, 76.84, 55.83, 40.38, 33.49, 28.31, 28.14 ppm.
IR (ν_{max}): 3126, 3030, 2955, 2890, 2807, 1712, 1647, 1618, 1558, 1524, 1514, 1442, 1413, 1348, 1188, 1113, 814 cm^{-1}.
HRMS (EI): calcd. for $C_{19}H_{22}O_3N_7$ [M^+] 396.1785, found 396.1779.

5-(5-(4-methoxyphenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (41):

From **5** (200mg; 632mmol) and 3-amino-1H-1,2,4-triazole (165 mg): 250mg (63%); paled yellow solid.
m.p. 200-202 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 14.43 (s, 1H), 7.78 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.56 (t, *J* = 6.1 Hz, 1H), 4.70 (dd, *J* = 18.3, 5.4 Hz, 1H), 4.03 (dd, *J* = 18.3, 6.8 Hz, 1H), 3.76 (s, 3H), 3.32 (d, *J* = 20.6 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.89, 164.45, 162.17, 160.11, 150.91, 150.59, 146.40, 128.70, 127.46, 114.76, 93.65, 77.48, 77.16, 76.84, 55.72, 55.42, 33.54, 28.35, 28.19 ppm.
IR (ν_{max}): 3068, 3028, 3004, 2959, 2910, 2837, 1720, 1656, 1623, 1571, 1542, 1512, 1439, 1409, 1367, 1355, 1247, 1191, 1177, 829 cm^{-1}.
HRMS (EI): calcd. for $C_{18}H_{19}O_4N_6$ [M^+] 383.1469, found 383.1462.

5-(5-(4-hydroxyphenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (42):

From **6** (379 mg; 1,25 mmol) and 3-amino-1H-1,2,4-triazole (211 mg; 2,51 mmol): 200 mg (43%); yellow solid.
m.p. >228 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 14.30 (s, 1H), 9.58 (s, 1H), 7.92 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 2H), 5.71 (s, 1H), 4.49 (dd, *J* = 18.1, 4.9 Hz, 1H), 4.15 (dd, *J* = 18.0, 6.3 Hz, 1H), 3.17 (d, *J* = 29.1 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 165.90, 165.19, 161.62, 157.56, 150.27, 150.13, 145.93, 128.17, 127.65, 115.63, 92.86, 54.83, 40.14, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 33.38, 27.87, 27.77 ppm.
IR (ν_{max}): 3221, 2970, 2900, 2817, 2595, 2454, 2361, 1713, 1644, 1614, 1582, 1553, 1517, 1451, 1419, 1366, 1263, 1237, 1187, 1109, 961, 843, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{17}O_4N_6$ [M^+] 369.1312, found 369.1306.

5-(5-(4-chlorophenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (43):

From **7** (200 mg; 624 µmol) and 3-amino-1H-1,2,4-triazole (156 mg): 100 mg (62 %); paled yellow solid.
m.p. 196-198 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 14.46 (s, 1H), 7.83 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.70 – 5.55 (m, 1H), 4.81 (dd, *J* = 18.3, 5.1 Hz, 1H), 4.02 (dd, *J* = 18.3, 6.9 Hz, 1H), 3.34 (d, *J* = 21.0 Hz, 6H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.85, 163.75, 162.14, 151.19, 150.49, 146.58, 135.32, 135.18, 131.20, 129.65, 129.43, 127.49, 93.82, 77.48, 77.16, 76.84, 55.52, 33.26, 28.39, 28.22 ppm.
IR (ν_{max}): 3141, 3050, 2962, 1718, 1648, 1626, 1558, 1534, 1513, 1445, 1413, 1348, 1247, 1190, 1113, 800 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{16}O_3N_6Cl$ [M^+] 387.0973, found 387.0967.

1,3-dimethyl-5-(5-(4-nitrophenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (44):

From **8** (200 mg; 604 µmol) and 3-amino-1H-1,2,4-triazole (162mg): 90 mg (60 %); yellow orange solid.
m.p. >225 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 14.34 (s, 1H), 8.25 (d, *J* = 8.7 Hz, 2H), 8.02 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 6.04 (t, *J* = 6.4 Hz, 1H), 4.50 (dd, *J* = 18.2, 6.0 Hz, 1H), 4.33 (dd, *J* = 18.2, 7.0 Hz, 1H), 3.30 – 3.22 (m, 3H), 3.21 (s, 3H), 3.16 (d, *J* = 3.8 Hz, 2H), 3.12 (s, 3H) ppm.
IR (ν_{max}): 3109, 3075, 3011, 2975, 2901, 1718, 1657, 1624, 1574, 1548, 1524, 1473, 1448, 1416, 1363, 1346, 1316, 1195, 1106, 858, 750 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{16}O_7N_5$ [M^+] 398.1214, found 398.1207.

5-(5-(2-methoxyphenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (45):

From **9** (307 mg; 971 µmol) and 3-amino-1H-1,2,4-triazole (128 mg; 152 µmol): 234 mg (63%); white solid.
m.p. >234 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 14.40 (s, 1H), 7.93 (s, 1H), 7.41 – 7.29 (m, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 6.5 Hz, 1H), 5.94 (dd, *J* = 8.2, 3.9 Hz, 1H), 4.54 (dd, *J* = 18.6, 4.0 Hz, 1H), 4.10 (dd, *J* = 18.6, 8.3 Hz, 1H), 3.75 (s, 3H), 3.17 (d, *J* = 41.0 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 165.99, 165.54, 161.58, 156.19, 150.39, 150.12, 146.26, 130.06, 127.26, 126.18, 120.65, 111.72, 92.34, 55.52, 51.61, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 31.83, 27.83, 27.77 ppm.

IR (ν_{max}): 3278, 3143, 3038, 2998, 2959, 2896, 2838, 1716, 1641, 1567, 1515, 1466, 1439, 1414, 1349, 1249, 1195, 1110, 1028, 769 cm^{-1}.
HRMS (EI): calcd. for $C_{18}H_{18}O_4N_6$ [M^+] 383.1468, found 383.1462.

5-(5-(2-chlorophenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (46):

From **10** (303 mg; 944 µmol) and 3-amino-1H-1,2,4-triazole (122 mg; 145 µmol): 165 mg (45 %); paled yellow solid.
m.p. >236 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 14.39 (s, 1H), 8.00 (s, 1H), 7.57 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.40 (td, *J* = 7.7, 1.6 Hz, 1H), 7.34 (td, *J* = 7.6, 1.0 Hz, 1H), 6.85 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.10 (t, *J* = 6.6 Hz, 1H), 4.45 (dd, *J* = 18.4, 6.1 Hz, 1H), 4.35 (dd, *J* = 18.4, 7.3 Hz, 1H), 3.17 (d, *J* = 36.5 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 165.89, 164.32, 161.58, 150.75, 150.07, 146.78, 135.10, 131.39, 130.42, 130.14, 128.07, 127.66, 92.98, 52.79, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 31.88, 27.86, 27.78 ppm.
IR (ν_{max}): 3280, 3251, 3044, 2959, 2884, 2826, 1720, 1651, 1618, 1565, 1538, 1517, 1440, 1410, 1365, 1346, 1248, 1190, 1107, 835, 749 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{16}O_3N_6$ [M^+] 387.0973, found 387.0967.

5-(5-(2-fluorophenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (47):

From **11** (308 mg; 1,01 mmol) and 3-amino-1H-1,2,4-triazole (128 mg; 1,52 mmol; 1,5 eq): 68 mg (18 %); paled yellow solid.
m.p. 180-182 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 14.37 (s, 1H), 7.97 (s, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.25 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.1 Hz, 1H), 6.06 (t, *J* = 6.6 Hz, 1H), 4.45 (dd, *J* = 18.4, 6.0 Hz, 1H), 4.33 (dd, *J* = 18.3, 7.3 Hz, 1H), 3.17 (d, *J* = 36.0 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 165.90, 164.63, 161.60, 160.72, 158.27, 150.58, 150.08, 146.36, 131.00, 130.92, 128.22, 128.19, 125.12, 125.08, 124.94, 124.81, 116.15, 115.94, 92.85, 50.23, 50.20, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 32.06, 27.85, 27.78 ppm.
IR (ν_{max}): 3284, 3260, 3136, 3039, 2968, 2892, 2835, 1707, 1652, 1635, 1560, 1536, 1514, 1441, 1414, 1366, 1350, 1247, 1188, 851, 754 cm^{-1}.
HRMS (EI): calcd. for $C_{17}H_{16}O_3N_6F$ [M^+] 371.1269, found 371.1262.

2-(7-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)benzonitrile (48)

Starting from **12** (257 mg; 826 µmol) and 3-amino-1H-1,2,4-triazole (148 mg; 1,24 mmol): 165 mg (45%); dark solid.

Compound not synthesized

1,3-dimethyl-5-(5-(2-nitrophenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (49)

Starting from **13** (303 mg; 915 µmol) and 3-amino-1H-1,2,4-triazole (118 mg; 1,40 mmol): 165 mg (36%); dark yellow solid.

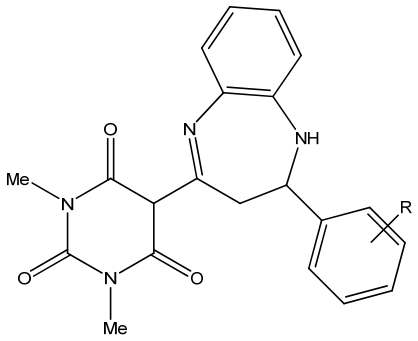
Compound not synthesized

5-(5-(4-hydroxy-3-methoxyphenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (50):

From **14** (300 mg; 903 µmol) and 3-amino-1H-1,2,4-triazole (118 mg; 1,40 mmol): 222 mg (62 %); yellowsolid.
m.p. >230 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 14.30 (s, 1H), 9.15 (s, 1H), 7.93 (s, 1H), 6.86 (s, 1H), 6.73 (d, *J* = 7.1 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 5.68 (s, 1H), 4.51 (dd, *J* = 18.2, 4.2 Hz, 1H), 4.19 (dd, *J* = 17.6, 5.1 Hz, 1H), 3.71 (s, 3H), 3.18 (d, *J* = 28.8 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 165.90, 165.26, 161.64, 150.21, 150.12, 147.81, 146.77, 145.99, 128.61, 118.74, 115.53, 110.78, 92.81, 55.59, 55.10, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.90, 33.35, 27.87, 27.77 ppm.
IR (ν_{max}): 3148, 3017, 2958, 2901, 2840, 1712, 1657, 1634, 1583, 1531, 1512, 1461, 1368, 1279, 1269, 1196, 1027, 855, 753 cm^{-1}.
HRMS (EI): calcd. for $C_{18}H_{19}O_5N_6$ [M^+] 399.1418, found 399.1411.

6. Synthesis of diazepines

General procedure



Chalcanoids **3-14** were mixed with 1,2-phenylendiamin. The mixture was heated for 3 min. The mixture was allowed to cool. Then, EtOH was added to the mixture and the solution was heated to the boiling point. The solution was allowed to cool. The precipitate was filtered out and washed with EtOH. The resulting solid compound was allowed to dry at room temperature.

1,3-dimethyl-5-(2-phenyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (51):

From **3** (200 mg; 699 µmol) and 1,2-phenylendiamin (300 mg; 2,77 mmol): 70 mg (27 %); yellow solid.
m.p. 165-167 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.83 (s, 1H), 7.43 – 7.38 (m, 2H), 7.35 (dd, *J* = 8.1, 6.4 Hz, 2H), 7.31 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.24 – 7.13 (m, 2H), 7.03 (td, *J* = 7.9, 1.2 Hz, 1H), 6.94 – 6.89 (m, 1H), 5.29 (dd, *J* = 10.8, 3.4 Hz, 1H), 4.66 – 4.37 (m, 1H), 3.97 (s, 1H), 3.35 (d, *J* = 19.7 Hz, 6H), 2.95 (dd, *J* = 12.3, 10.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.15, 166.40, 162.98, 151.37, 144.90, 140.31, 129.02, 128.41, 128.19, 127.15, 125.87, 124.57, 121.96, 121.70, 90.80, 77.48, 77.16, 77.16, 68.38, 36.66, 28.18, 27.87 ppm.
IR (ν_{max}): 3354, 3213, 3032, 2959, 2905, 2797, 1690, 1643, 1614, 1593, 1571, 1462, 1421, 1367, 749 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{19}O_3N_4$ [M^-] 375.1456, found 375.1463.

5-(2-(4-(dimethylamino)phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (52):

From **4** (200 mg; 607 µmol) and 1,2-phenylendiamin (260 mg; 2,40 mmol): 60 mg (24 %); yellow orange solid.
m.p. 223-225 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.82 (s, 1H), 7.24 (s, 1H), 7.17 (dd, *J* = 15.4, 7.9 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 7.3 Hz, 2H), 5.19 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 12.2 Hz, 1H), 3.91 (s, 1H), 3.35 (dd, *J* = 17.9, 1.6 Hz, 6H), 2.94 (d, *J* = 1.4 Hz, 6H), 2.84 (t, *J* = 12.2 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.34, 166.46, 162.99, 151.46, 140.46, 128.31, 126.93, 126.71, 124.52, 121.71, 121.65, 112.78, 90.77, 77.48, 77.16, 76.84, 68.14, 40.76, 36.92, 28.18, 27.86 ppm.
IR (ν_{max}): 3343, 3044, 2890, 2858, 2808, 1684, 1638, 1608, 1576, 1518, 1466, 1424, 1369, 1326, 1224, 1012, 900, 756, 749 cm^{-1}.
HRMS (EI): calcd. for $C_{23}H_{24}O_3N_5Na$ [M^-] 418.1878, found 418.1885.

5-(2-(4-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (53):

From **5** (200 mg; 632 µmol) and 1,2-phenylendiamin (280 mg; 2,59 mmol): 70 mg (27 %); yellow green solid.
m.p. 165-167 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.82 (s, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.22 – 7.13 (m, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 11.1, 4.4 Hz, 3H), 5.24 (dd, *J* = 10.8, 3.3 Hz, 1H), 4.54 – 4.36 (m, 1H), 3.81 – 3.78 (s, 3H), 3.39 – 3.29 (d, 6H), 2.95 – 2.85 (t, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.13, 166.37, 162.97, 159.40, 151.36, 140.23, 137.23, 128.37, 127.02, 124.54, 121.87, 121.69, 114.24, 101.64, 90.75, 77.48, 77.16, 76.84, 67.89, 55.44, 36.80, 28.17, 27.86 ppm.
IR (ν_{max}): 3337, 3031, 2956, 2914, 2839, 1680, 1609, 1575, 1515, 1466, 1414, 1372, 1254, 1173, 1023, 829, 746 cm^{-1}.
HRMS (EI): calcd. for $C_{22}H_{21}O_4N_4$ [M^-] 405.1562, found 405.1568.

5-(2-(4-hydroxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (54):

From **6** (354 mg; 1,17 mmol) and 1,2-phenylendiamin (509 mg; 4,71 mmol): 114 mg (25 %); yellow solid.
m.p. 185-187 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.69 (s, 1H), 9.37 (s, 1H), 7.10 (dd, *J* = 20.0, 8.4 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 2H), 6.49 (s, 1H), 6.37 (s, 1H), 6.02 (s, 1H), 5.01 (d, *J* = 9.3 Hz, 1H), 4.37 (s, 2H), 4.25 (d, *J* = 12.2 Hz, 1H), 3.17 (s, 6H), 2.94 (t, *J* = 11.1 Hz, 1H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 170.35, 156.74, 150.46, 141.00, 135.58, 134.92, 127.84, 126.86, 125.34, 124.22, 121.16, 119.94, 117.28, 115.05, 114.53, 89.72, 65.89, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 36.71, 27.57 ppm.
IR (ν_{max}): 3448, 3346, 3329, 3022, 2971, 2891, 2361, 2335, 1707, 1695, 1618, 1606, 1588, 1566, 1510, 1458, 1423, 1371, 1266, 1194, 1008, 837, 752, 739 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{20}O_4N_4Na$ [M+Na^{+}] 415.1383, found 415.1377.

5-(2-(4-chlorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (55):

From **7** (200 mg; 624 µmol) and 1,2-phenylendiamin (270 mg; 2,50 mmol): 170 mg (66 %); paled yellow solid.
m.p. 178-180 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.65 (s, 1H), 7.37 (dd, *J* = 23.0, 8.1 Hz, 4H), 7.23 – 7.04 (m, 3H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.18 (s, 1H), 5.14 (d, *J* = 9.1 Hz, 1H), 4.09 (d, *J* = 12.2 Hz, 1H), 3.35 (s, 6H), 3.14 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.12, 166.67, 163.29, 151.63, 143.49, 140.24, 134.21, 129.43, 128.81, 127.65, 124.95, 122.63, 122.07, 91.16, 77.79, 77.48, 77.16, 68.01, 36.77, 28.51, 28.21 ppm.
IR (ν_{max}): 3354, 3031, 2959, 1693, 1645, 1616, 2592, 1568, 1460, 1421, 1365, 1322, 1092, 1010, 834, 819, 748 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{18}O_3N_4Cl$ [M^{-}] 409.1067, found 409.1073.

1,3-dimethyl-5-(2-(4-nitrophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (56):

From **8** (200 mg; 604 µmol) and 1,2-phenylendiamin (260 mg; 2,40 mmol): 170 mg (67 %); yellow solid.
m.p. 228-230 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.83 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.22 (m, 1H), 7.19 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.96 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.43 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.46 – 4.17 (m, 1H), 3.34 (d, *J* = 29.5 Hz, 6H), 3.18 (dd, *J* = 12.4, 10.2 Hz, 1H) ppm.
IR (ν_{max}): 3402, 3360, 3059, 2946, 1702, 1639, 1620, 1571, 1522, 1427, 1376, 1348, 1108, 835, 750 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{18}O_5N_5$ [M^-] 420.1307, found 420.1313.

5-(2-(2-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (57):

From **9** (211 mg; 667 µmol) and 1,2-phenylendiamin (288 mg; 2,66 mmol): 70 mg (26 %); yellow solid.
m.p. 97-99 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.85 (s, 1H), 7.31 – 7.20 (m, 2H), 7.13 (dd, *J* = 16.4, 7.7 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.89 (dd, *J* = 16.1, 7.9 Hz, 2H), 6.71 (d, *J* = 7.5 Hz, 1H), 5.59 (d, *J* = 8.2 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.06 (s, 1H), 3.86 (s, 3H), 3.34 (dd, *J* = 29.7, 16.2 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 172.20, 166.35, 162.82, 156.61, 151.40, 140.59, 131.01, 129.15, 128.09, 127.61, 126.51, 124.28, 121.95, 121.81, 120.53, 110.81, 90.92, 77.48, 77.16, 76.84, 62.80, 55.51, 33.18, 28.08, 27.86 ppm.
IR (ν_{max}): 3340, 3303, 3000, 2948, 2837, 2361, 2336, 1703, 1643, 1568, 1465, 1425, 1369, 1242, 1028, 1012, 749 cm^{-1}.
HRMS (EI): calcd. for $C_{22}H_{23}O_4N_4$ [M^+] 407.1720, found 407.1714.

5-(2-(2-chlorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (58):

From **10** (219 mg; 683 mmol) and 1,2-phenylendiamin (295 mg; 2,73 mmol): 68mg (24 %); yellow solid.
m.p. 182-184 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.86 (s, 1H), 7.45 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.24 – 7.13 (m, 4H), 7.06 – 6.99 (m, 1H), 6.83 – 6.78 (m, 1H), 5.73 (m, *J* = 8.4, 3.8, 1.8 Hz, 1H), 4.09 (dd, *J* = 12.5, 3.9 Hz, 1H), 3.91 (s, 1H), 3.70 (dd, *J* = 12.5, 8.5 Hz, 1H), 3.27 (d, *J* = 59.6 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 170.93, 166.32, 162.54, 151.25, 140.03, 132.76, 129.98, 129.19, 128.32, 127.68, 127.35, 126.98, 124.50, 122.33, 121.80, 91.09, 77.48, 77.16, 76.84, 64.39, 33.22, 28.09, 27.87 ppm.
IR (ν_{max}): 3338, 3029, 2965, 2838, 2362, 2336, 1690, 1637, 1611, 1591, 1570, 1464, 1423, 1370, 1242, 1012, 746 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{19}O_3N_4ClNa$ [M+Na^+] 433.1044, found 433.1038.

5-(2-(2-fluorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (59):

From **11** (295 mg; 969 µmol) and 1,2-phenylendiamin (419 mg; 3,87mmol): 184 mg (48 %); yellow solid.
m.p. 161-163 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.70 (s, 1H), 7.41 (t, *J* = 7.1 Hz, 1H), 7.32 (dd, *J* = 13.3, 6.1 Hz, 1H), 7.25 – 7.09 (m, 4H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.10 (s, 1H), 5.40 (d, *J* = 7.9 Hz, 1H), 3.98 (d, *J* = 10.1 Hz, 1H), 3.56 (dd, *J* = 12.4, 8.9 Hz, 1H), 3.12 (d, *J* = 44.2 Hz, 6H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 170.03, 160.36, 157.92, 150.34, 141.00, 130.72, 130.59, 129.35, 129.27, 127.86, 125.59, 124.23, 124.18, 124.15, 121.12, 120.32, 115.41, 115.19, 89.93, 60.22, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 33.68, 27.50 ppm.
IR (ν_{max}): 3385, 3085, 3051, 2958, 2887, 2836, 1685, 1609, 1588, 1577, 1463, 1422, 1372, 747 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{20}O_3N_4F$ [M^+] 395.1520,found 395.1514.

2-(4-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)benzonitrile (60)

Starting from **12** (261 mg; 838 µmol) and 1,2-phenylendiamin (382 mg; 3,36 mmol) : 3 mg (1%) dark solid.

Compound not synthesized

1,3-dimethyl-5-(2-(2-nitrophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (61) <u>not good</u>

Starting from **13** (207mg; 625 µmol) and 1,2-phenylendiamin (270 mg; 2,45 mmol): 170mg (65%); yellow solid.

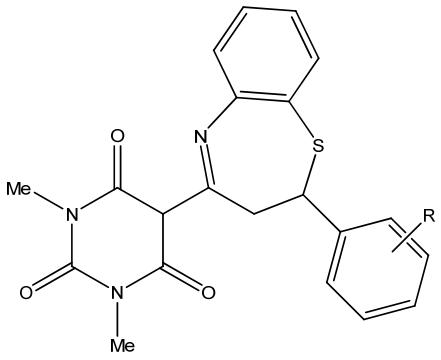
Compound not synthesized

5-(2-(4-hydroxy-3-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (62):

From **14** (304 mg; 915 µmol) and 1,2-phenylendiamin (397 mg; 3,67 mmol): 195 mg (50 %); yellow solid.
m.p. >230 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.71 (s, 1H), 8.92 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.89 (s, 2H), 6.72 (s, 2H), 6.06 (s, 1H), 5.02 (d, *J* = 8.7 Hz, 1H), 4.18 (d, *J* = 11.9 Hz, 1H), 3.71 (s, 3H), 3.18 (d, *J* = 16.2 Hz, 6H) ppm.
IR (ν_{max}): 3484, 3352, 3033, 3000, 2950, 2898, 2846, 1695, 1643, 1622, 1571, 1517, 1469, 1426, 1369, 1279, 1167, 821, 740 cm^{-1}.
HRMS (EI): calcd. for $C_{22}H_{22}O_5N_4Na$ [M+Na$^+$] 445.1488, found 445.1482.

7. Synthesis of thiazepines

General procedure



Chalcanoids **3-14** were mixed with 2-aminothiophenol. The mixture was heated for 3 min. The mixture was allowed to cool. Then, EtOH was added to the mixture and the solution was heated to the boiling point. The solution was allowed to cool. The precipitate was filtered out and washed with EtOH. The resulting solid compound was allowed to dry at room temperature.

1,3-dimethyl-5-(2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (63):

From **3** (200 mg; 699 µmol) and 2-aminothiophenol (0,26 mL; 2,10 mmol): 200 mg (81 %); grey white solid.
m.p. 231-233 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.96 (s, 1H), 7.74 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.50 (td, *J* = 7.7, 1.5 Hz, 1H), 7.41 – 7.22 (m, 2H), 5.19 (dd, *J* = 12.4, 4.5 Hz, 1H), 4.44 (m, *J* = 11.8, 4.5, 1.4 Hz, 1H), 3.39 (d, *J* = 8.2 Hz, 6H), 2.68 (t, *J* = 12.1 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.71, 166.95, 162.99, 151.67, 144.21, 140.29, 136.48, 130.72, 129.16, 128.84, 128.62, 128.17, 126.74, 125.16, 91.64, 77.80, 77.48, 77.16, 56.31, 39.73, 28.60, 28.30 ppm.
IR (ν_{max}): 3399, 3342, 3078, 3055, 3025, 3002, 2957, 1699, 1644, 1610, 1573, 1544, 1457, 1422, 1359, 1321, 1216, 1181, 1009, 819, 753, 700 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{18}O_3N_3S$ [M^-] 392.1068, found 392.1074.

5-(2-(4-(dimethylamino)phenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (64):

From **4** (200 mg; 607 µmol) and 2-aminothiophenol (0,40 mL; 3,74 mmol): 130 mg (47 %); white solid.
m.p. >238 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.94 (s, 1H), 7.72 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.48 (td, *J* = 7.7, 1.5 Hz, 1H), 7.32 (m, *J* = 15.9, 7.9, 1.3 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 7.5 Hz, 2H), 5.15 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.40 (m, *J* = 11.7, 4.5, 1.4 Hz, 1H), 3.38 (d, *J* = 9.7 Hz, 6H), 2.93 (s, 6H), 2.68 (t, *J* = 12.1 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.54, 166.68, 162.63, 151.41, 139.93, 136.21, 130.13, 129.00, 128.14, 127.13, 124.73, 112.63, 91.30, 77.48, 77.16, 76.84, 56.07, 40.71, 39.54, 28.25, 27.94 ppm.
IR (ν_{max}): 3405, 3345, 2990, 2952, 2883, 2858, 2806, 1703, 1645, 1610, 1577, 1546, 1521, 1458, 1422, 1356, 812, 771, 756 cm^{-1}.
HRMS (EI): calcd. for $C_{23}H_{23}O_3N_4S$ [M^-] 435.1490, found 435.1496.

5-(2-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (65):

From **5** (200 mg; 632 µmol) and 2-aminothiophenol (0,50 mL; 4,67 mmol): 170 mg (64 %); white solid.
m.p. 240-242 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.94 (s, 1H), 7.86 – 7.60 (d, 1H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38 – 7.27 (m, 4H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.16 (dd, *J* = 12.3, 4.4 Hz, 1H), 4.41 (m, *J* = 11.7, 4.4, 1.1 Hz, 1H), 3.78 (s, 3H), 3.39 (d, *J* = 9.3 Hz, 6H), 2.66 (t, *J* = 12.1 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.38, 166.67, 162.69, 159.19, 151.37, 139.96, 136.31, 136.15, 130.33, 128.65, 128.25, 127.54, 124.82, 114.15, 91.32, 77.48, 77.16, 76.84, 55.65, 55.45, 39.56, 28.27, 27.97 ppm.
IR (ν_{max}): 3396, 3337, 3003, 2962, 2936, 2915, 2839, 1700, 1642, 1612, 1580, 1553, 1510, 1464, 1426, 1364, 1250, 1180, 1033, 827, 757 cm^{-1}.
HRMS (EI): calcd. for $C_{22}H_{20}O_4N_3S$ [M^-] 422.1174, found 422.1180.

5-(2-(4-hydroxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (66):

From **6** (357 mg; 1,18 mmol) and 2-aminothiophenol (0,51 mL; 4,77 mmol): 349 mg (72 %); yellow solid.
m.p. >236 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.71 (s, 1H), 9.44 (s, 1H), 7.68 – 7.62 (m, 1H), 7.62 – 7.54 (m, 1H), 7.49 (d, *J* = 6.9 Hz, 1H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.04 (dd, *J* = 12.4, 4.2 Hz, 1H), 4.23 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.21 (d, *J* = 18.0 Hz, 6H), 2.58 (t, *J* = 12.2 Hz, 1H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 170.37, 165.78, 161.91, 156.81, 150.48, 139.40, 135.40, 134.22, 131.37, 130.47, 128.19, 127.21, 127.11, 125.17, 116.27, 115.22, 90.49, 55.01, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 38.38, 27.79, 27.54 ppm.
IR (ν_{max}): 3329, 3109, 3067, 3027, 2962, 2890, 2830, 1703, 1618, 1547, 1461, 1425, 1370, 1216, 1011, 833, 764, 756 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{19}O_4N_3NaS$ [M+Na$^+$] 432.0994, found 432.0988.

5-(2-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (67):

From **7** (200 mg; 624 µmol) and 2-aminothiophenol (0,30 mL; 2,80 mmol): 240mg (89 %); white solid.
m.p. 230-232°C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.95 (s, 1H), 7.71 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.51 (td, *J* = 7.7, 1.5 Hz, 1H), 7.39 – 7.26 (m, 6H), 5.16 (dd, *J* = 12.4, 4.5 Hz, 1H), 4.41 (m, *J* = 11.8, 4.5, 1.4 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 6H), 2.63 (t, *J* = 12.1 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.03, 166.61, 162.72, 151.31, 142.34, 139.95, 136.10, 133.54, 130.61, 128.97, 128.39, 128.11, 127.87, 124.95, 91.36, 77.48, 77.16, 76.84, 55.18, 39.29, 28.30, 28.00 ppm.
IR (ν_{max}): 3412, 3348, 3059, 3011, 2953, 2809, 1708, 1641, 1610, 1578, 1553, 1463, 1424, 1361, 1274, 1213, 1179, 1090, 1014, 821, 763, 754 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{17}O_3N_3ClS$ [M$^-$] 426.0678, found 426.0685.

1,3-dimethyl-5-(2-(4-nitrophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (68):

From **8** (200 mg; 604 µmol) and 2-aminothiophenol (0,20 mL; 1,87 mmol): 120 mg (43 %); yellow solid.
m.p. 204-206 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.97 (s, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.72 (td, *J* = 8.0, 1.4 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.42 – 7.28 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 5.19 (m, *J* = 52.9, 12.4, 4.5 Hz, 1H), 4.52 – 4.33 (m, 1H), 3.39 (dd, *J* = 9.8, 5.4 Hz, 6H), 2.65 (dd, *J* = 14.2, 10.1 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.42, 170.45, 166.59, 166.50, 162.72, 162.59, 151.32, 151.17, 150.66, 147.37, 145.99, 139.95, 139.86, 136.09, 135.98, 134.12, 130.91, 130.15, 128.78, 128.51, 128.12, 127.50, 127.45, 127.35, 125.09, 124.71, 124.15, 115.17, 91.42, 91.23, 77.48, 77.16, 76.84, 55.94, 54.79, 39.50, 38.91, 28.26, 28.21, 27.97, 27.90 ppm.
IR (ν_{max}): 3449, 3366, 3102, 3061, 2953, 2936, 2848, 1713, 1635, 1620, 1576, 1550, 1520, 1463, 1424, 1363, 1344, 1275, 1260, 1177, 1012, 828, 751 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{17}O_5N_4S$ [M^-] 437.0919, found 437.0925.

5-(2-(2-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (69):

From **9** (198 mg; 598 µmol) and 2-aminothiophenol (0,27 mL; 2,50 mmol): 191 mg (72%) white solid.
m.p. 191-193 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.98 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.46 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.22 (dd, *J* = 11.1, 4.6 Hz, 1H), 7.06 – 6.96 (m, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 5.51 (dd, *J* = 12.7, 4.2 Hz, 1H), 4.36 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.81 (s, 3H), 3.36 (d, *J* = 22.7 Hz, 6H), 2.94 (t, *J* = 12.1 Hz, 1H), 1.65 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 172.24, 166.64, 162.55, 156.18, 151.37, 139.86, 136.21, 131.35, 130.00, 129.27, 128.85, 127.90, 125.73, 124.58, 120.40, 110.99, 91.27, 77.48, 77.16, 76.84, 55.51, 49.95, 35.40, 28.21, 27.94 ppm.
IR (ν_{max}): 3411, 3354, 3056, 3003, 2933, 2867, 2835, 1710, 1654, 1576, 1556, 1465, 1424, 1360, 1283, 1260, 1104, 1030, 819, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{22}H_{21}O_4N_3NaS$ [$M+Na^+$] 446.1151, found 446.1145.

5-(2-(2-chlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (70):

From **10** (205 mg; 639 µmol) and 2-aminothiophenol (0,28 mL; 2,56 mmol): 105 mg (38 %); white solid.
m.p. >232 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.98 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.24 (m, 2H), 7.16 (dt, *J* = 14.8, 7.2 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 5.63 (dd, *J* = 12.4, 3.9 Hz, 1H), 4.41 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.36 (d, *J* = 23.8 Hz, 6H), 2.90 (t, *J* = 12.0 Hz, 1H), 1.68 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.17, 166.60, 162.51, 151.28, 140.31, 140.07, 136.31, 132.83, 130.55, 130.19, 128.85, 128.17, 127.95, 127.08, 126.07, 124.78, 91.46, 77.48, 77.16, 76.84, 51.12, 35.88, 28.24, 27.96 ppm.
IR (ν_{max}): 3336, 3030, 2966, 2940, 2838, 2362, 2336, 1705, 1645, 1616, 1570, 1464, 1425, 1369, 1242, 1013, 752 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{18}O_3N_3ClNaS$ [M+Na^+] 450.0655, found 450.0650.

5-(2-(2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (71):

From **11** (305 mg; 1 mmol) and 2-aminothiophenol (0,43 mL; 4 mmol): 247 mg (60 %); white solid.
m.p. 191-193 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.75 (s, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.37 (dd, *J* = 14.2, 6.9 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 5.33 (dd, *J* = 12.4, 3.5 Hz, 1H), 4.25 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.21 (d, *J* = 28.8 Hz, 6H), 2.89 (t, *J* = 12.2 Hz, 1H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 170.19, 165.82, 162.03, 160.06, 157.62, 150.54, 139.44, 135.48, 130.83, 130.09, 129.96, 129.78, 129.70, 128.21, 127.08, 127.04, 126.53, 125.31, 124.73, 124.71, 115.88, 115.66, 90.77, 48.11, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 35.44, 27.80, 27.60 ppm.
IR (ν_{max}): 3396, 3340, 3113, 3089, 3065, 2958, 2893, 1701, 1650, 1609, 1574, 1546, 1456, 1422, 1357, 1009, 824, 754 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{19}O_3N_3FS$ [M^+] 412.1132, found 412.1126.

2-(4-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-2-yl)benzonitrile (72)

Starting from **12** (264 mg; 848 µmol) and 2-aminothiophenol (0,36mL; 2,33mmol: 162mg (46%); brown solid.

Compound not synthesized

1,3-dimethyl-5-(2-(2-nitrophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (73):

From **13** (209 mg; 631 µmol) and 2-aminothiophenol (0,27 mL; 2,52 mmol): 195 mg (71 %); paled yellow solid.
m.p. >238 °C.
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.98 (s, 1H), 7.98 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.45 – 7.39 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.9, 1.0 Hz, 1H), 5.76 (dd, *J* = 12.4, 4.1 Hz, 1H), 4.44 (m, *J* = 11.4, 4.1, 1.0 Hz, 1H), 3.35 (d, *J* = 36.4 Hz, 6H), 2.95 (t, *J* = 12.0 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 170.61, 166.59, 162.51, 151.23, 147.28, 140.00, 137.64, 136.18, 133.49, 132.23, 130.80, 128.56, 128.28, 128.02, 127.90, 126.71, 126.05, 125.49, 124.90, 121.07, 118.96, 91.48, 77.48, 77.16, 76.84, 48.67, 36.12, 28.25, 27.99 ppm.
IR (ν_{max}): 3338, 2997, 2947, 2837, 2362, 2337, 1708, 1654, 1616, 1578, 1556, 1517, 1464, 1427, 1350, 825, 751 cm^{-1}.
HRMS (EI): calcd. for $C_{21}H_{18}O_5N_4NaS$ [M+Na^+] 461.0896, found 461.0890.

5-(2-(4-hydroxy-3-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (74):

From **14** (301 mg; 906 µmol) and 2-aminothiophenol (0,39 mL; 3,62 mmol): 210 mg (57 %); yellow solid.
m.p. >234 °C.
^{1}H NMR (DMSO, 400 MHz): δ = 13.72 (s, 1H), 9.02 (s, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H), 6.68 (q, *J* = 8.1 Hz, 2H), 5.05 (dd, *J* = 12.3, 4.3 Hz, 1H), 4.27 (dd, *J* = 11.8, 4.1 Hz, 1H), 3.69 (s, 3H), 3.23 (d, *J* = 18.2 Hz, 5H), 2.65 (t, *J* = 12.1 Hz, 1H) ppm.
^{13}C NMR (DMSO, 101 MHz): δ = 170.44, 165.81, 161.94, 150.52, 147.47, 146.13, 139.49, 135.48, 134.79, 130.57, 128.17, 127.28, 125.24, 118.25, 115.18, 110.18, 90.55, 55.47, 55.29, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 38.25, 27.80, 27.55 ppm.
IR (ν_{max}): 3474, 3056, 3022, 2958, 2923, 2845, 1704, 1633, 1622, 1580, 1550, 1514, 1462, 1422, 1367, 1267, 1212, 819, 756 cm^{-1}.
HRMS (EI): calcd. for $C_{22}H_{21}O_5N_3NaS$ [M+Na^+] 462.1100, found 462.1094.

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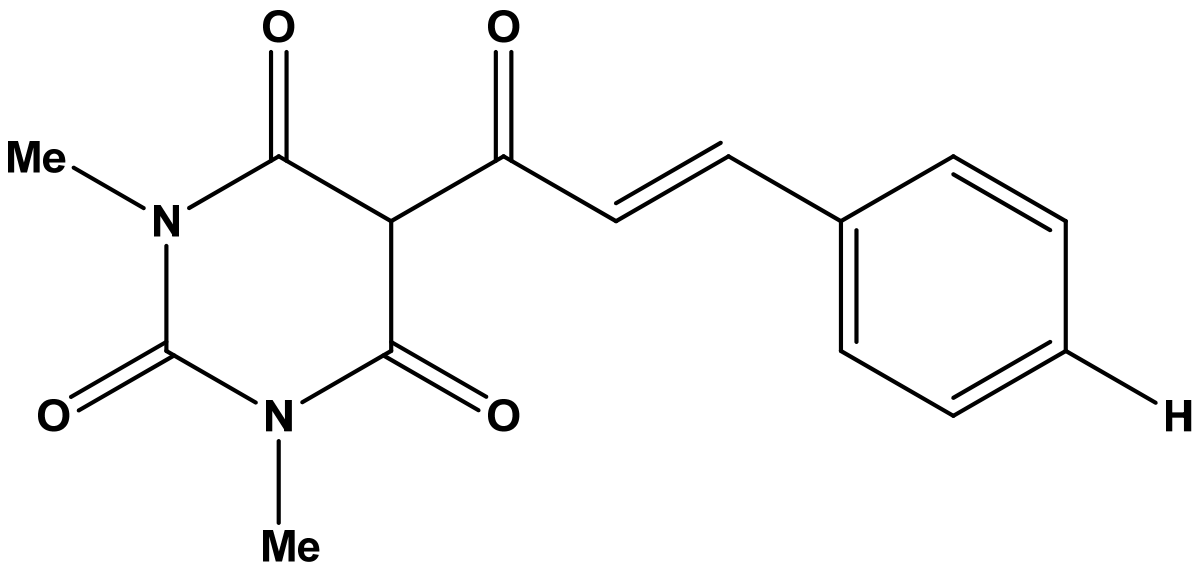
APPENDICES

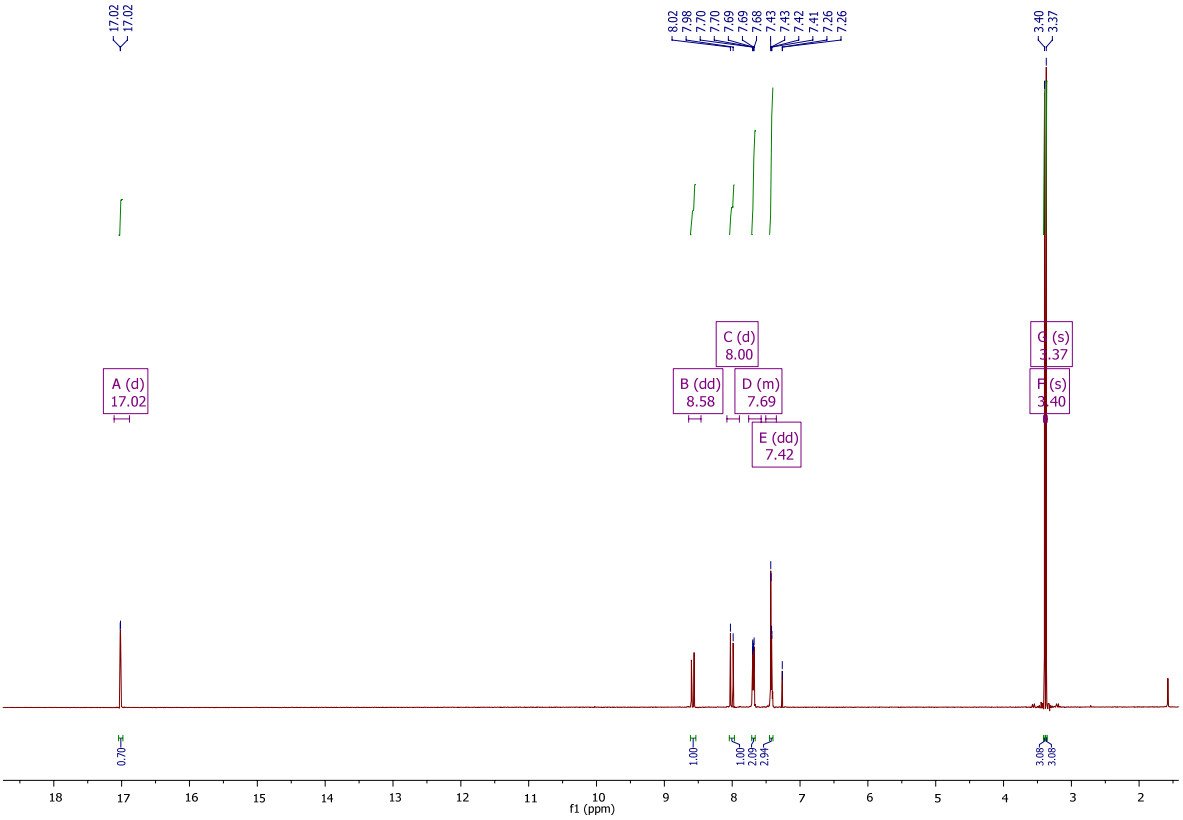
A Spectroscopic data for chalconoids 3-14

A.1 Spectroscopic data for 3

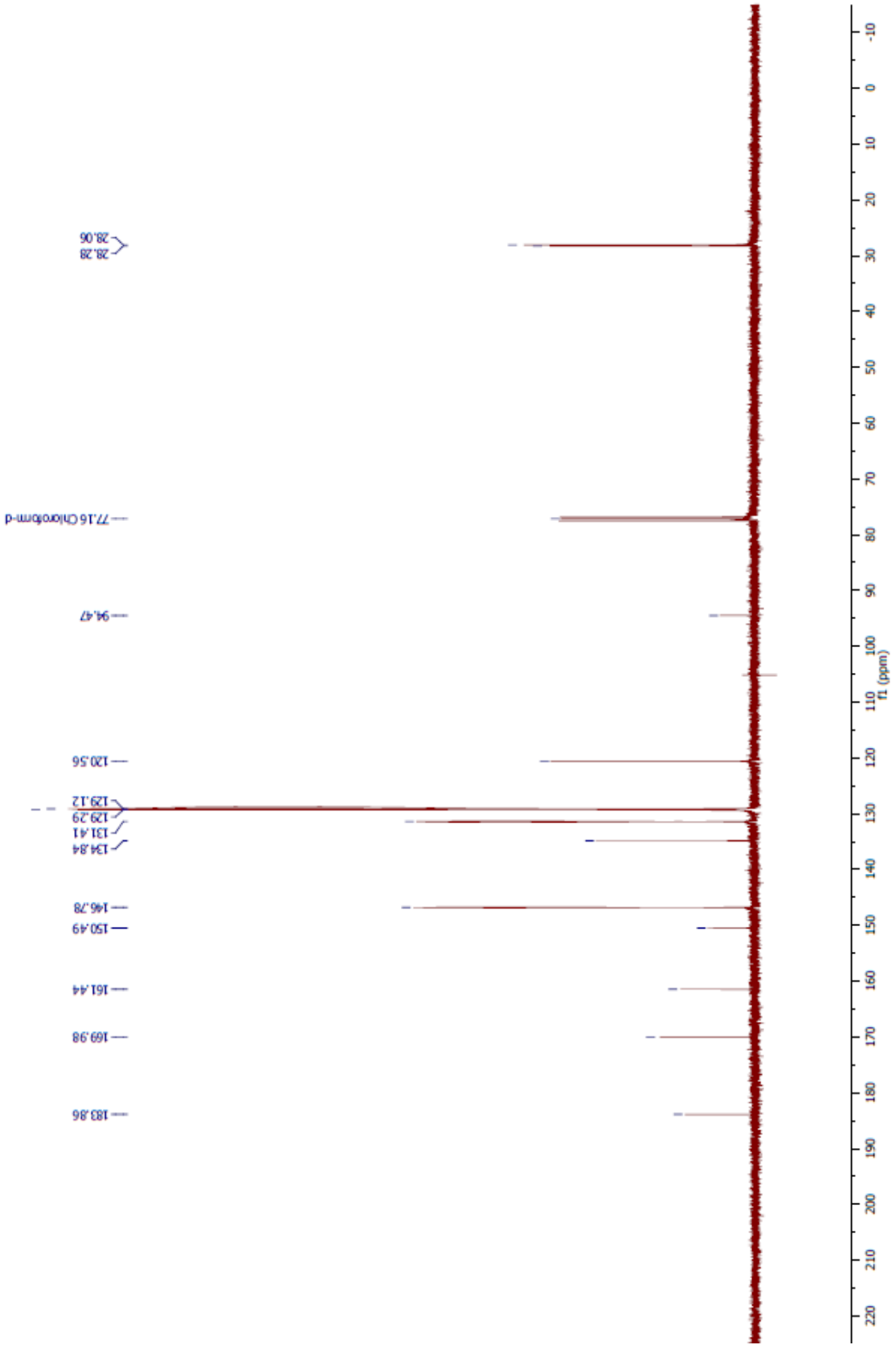


3

A.1.1 ^{1}H NMR spectrum of 3

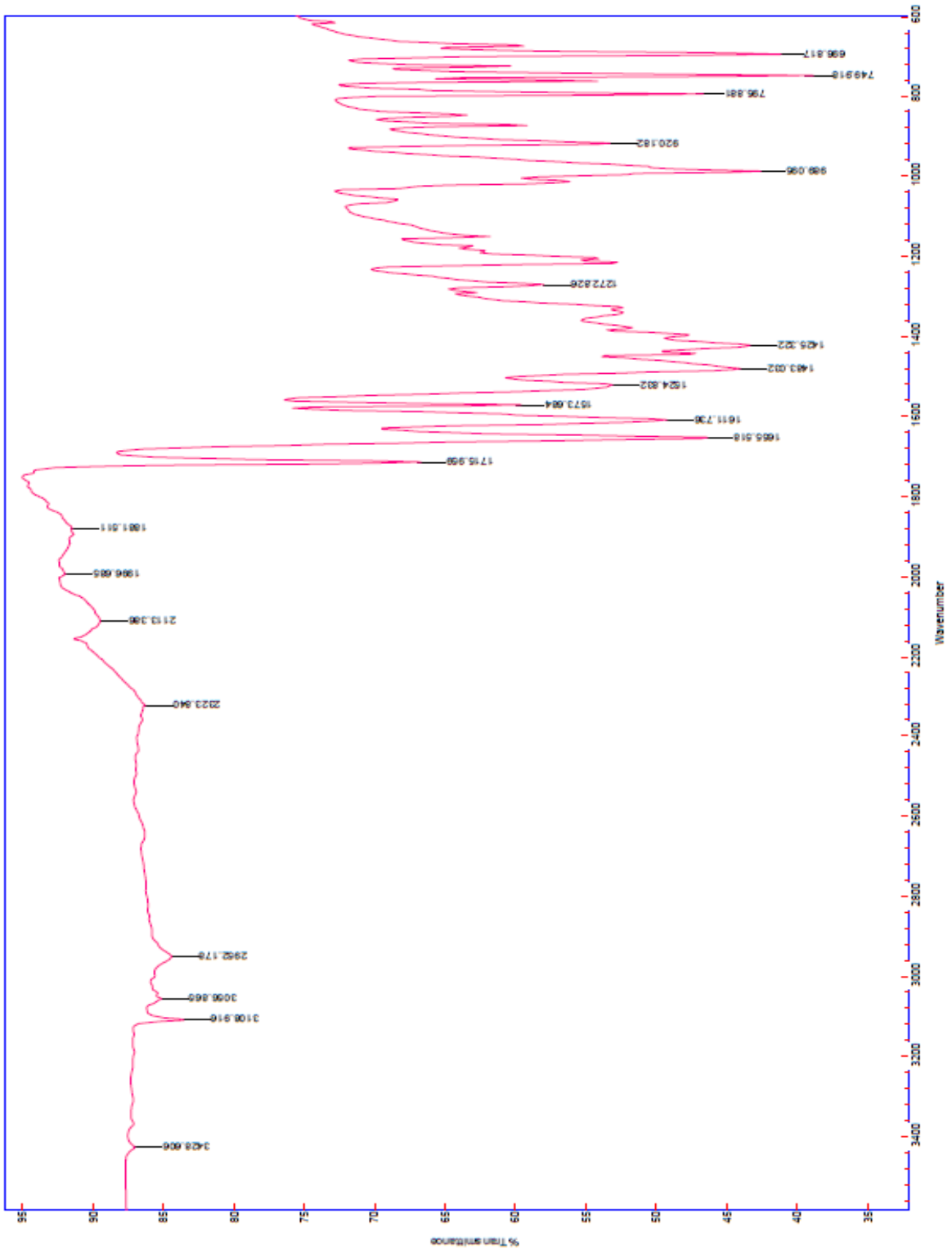


A.1.2 ^{13}C NMR spectrum of

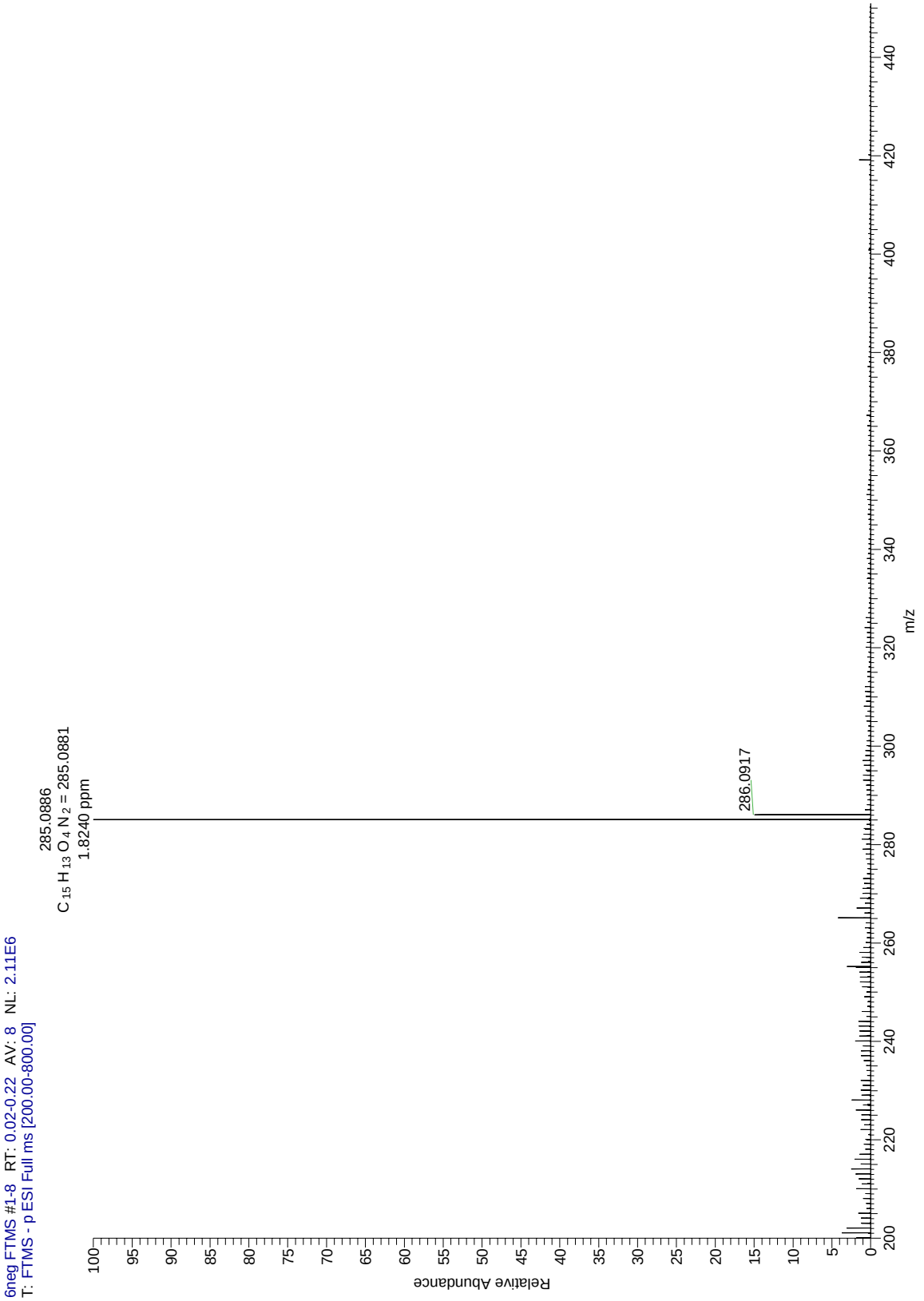


3

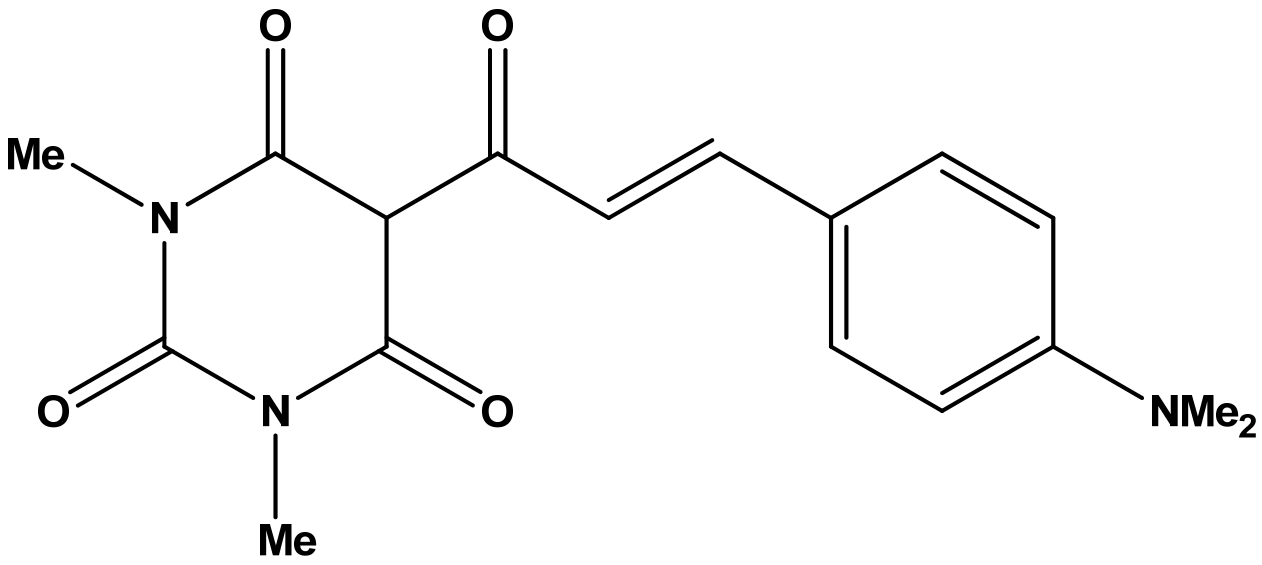
A.1.3 IR spectrum of 3



A.1.4 HRMS of 3

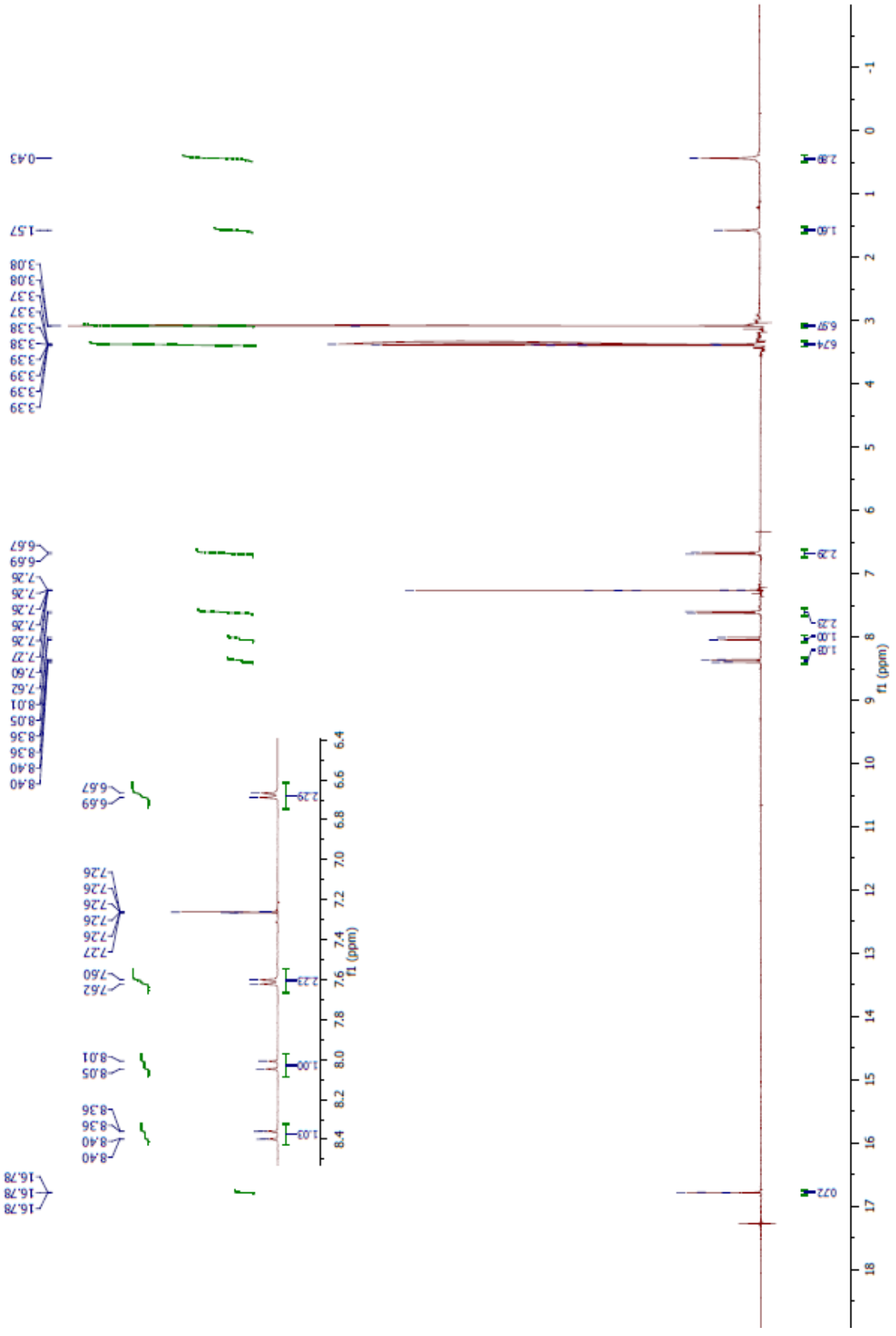

6neg FTMS #1-8 RT: 0.02-0.22 AV: 8 NL: 2.11E6
T: FTMS - p ESI Full ms [200.00-800.00]
285.0886
C 15 H 13 O 4 N 2 = 285.0881
1.8240 ppm
286.0917
Relative Abundance
m/z

A.2 Spectroscopic data for 4

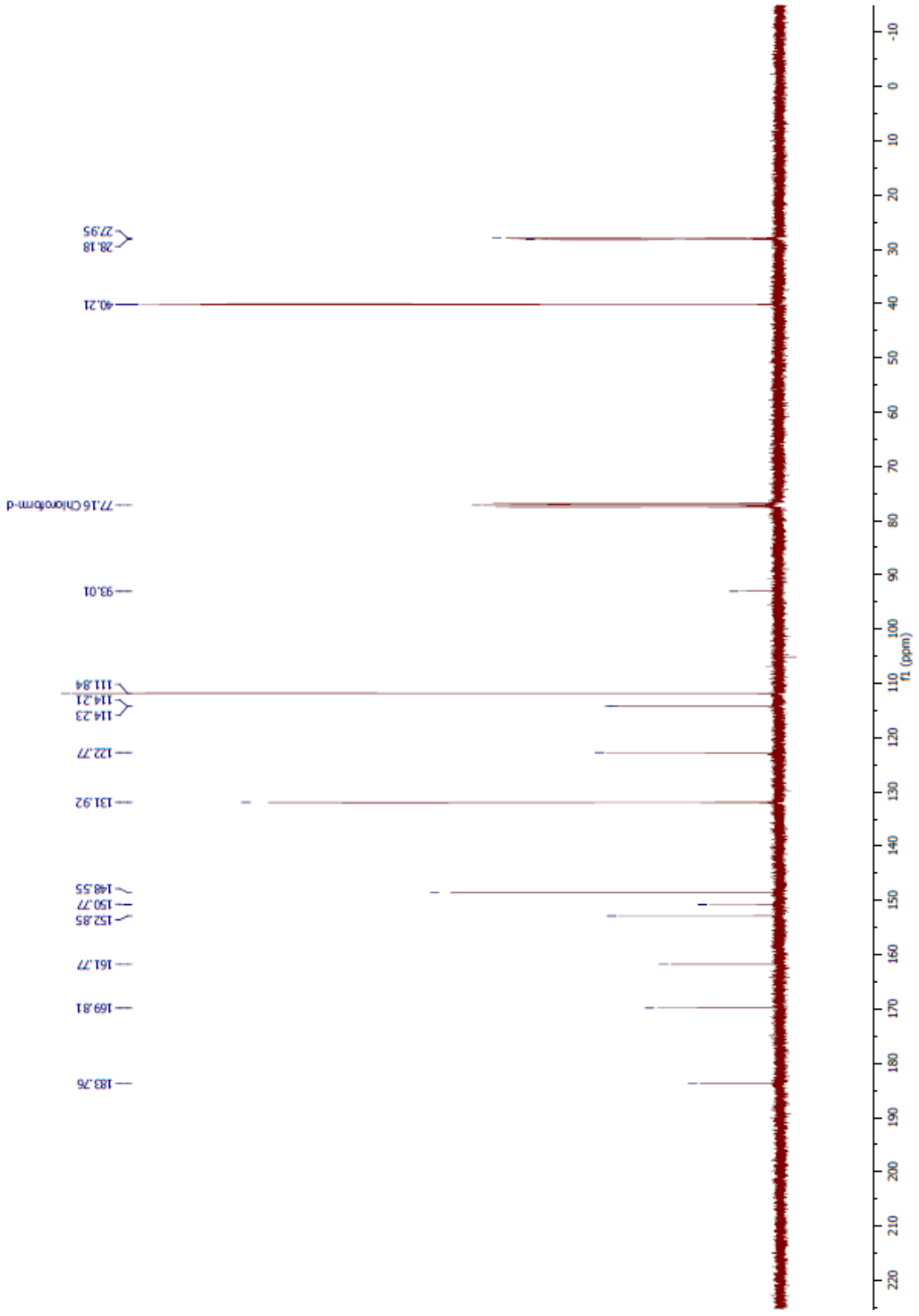


4

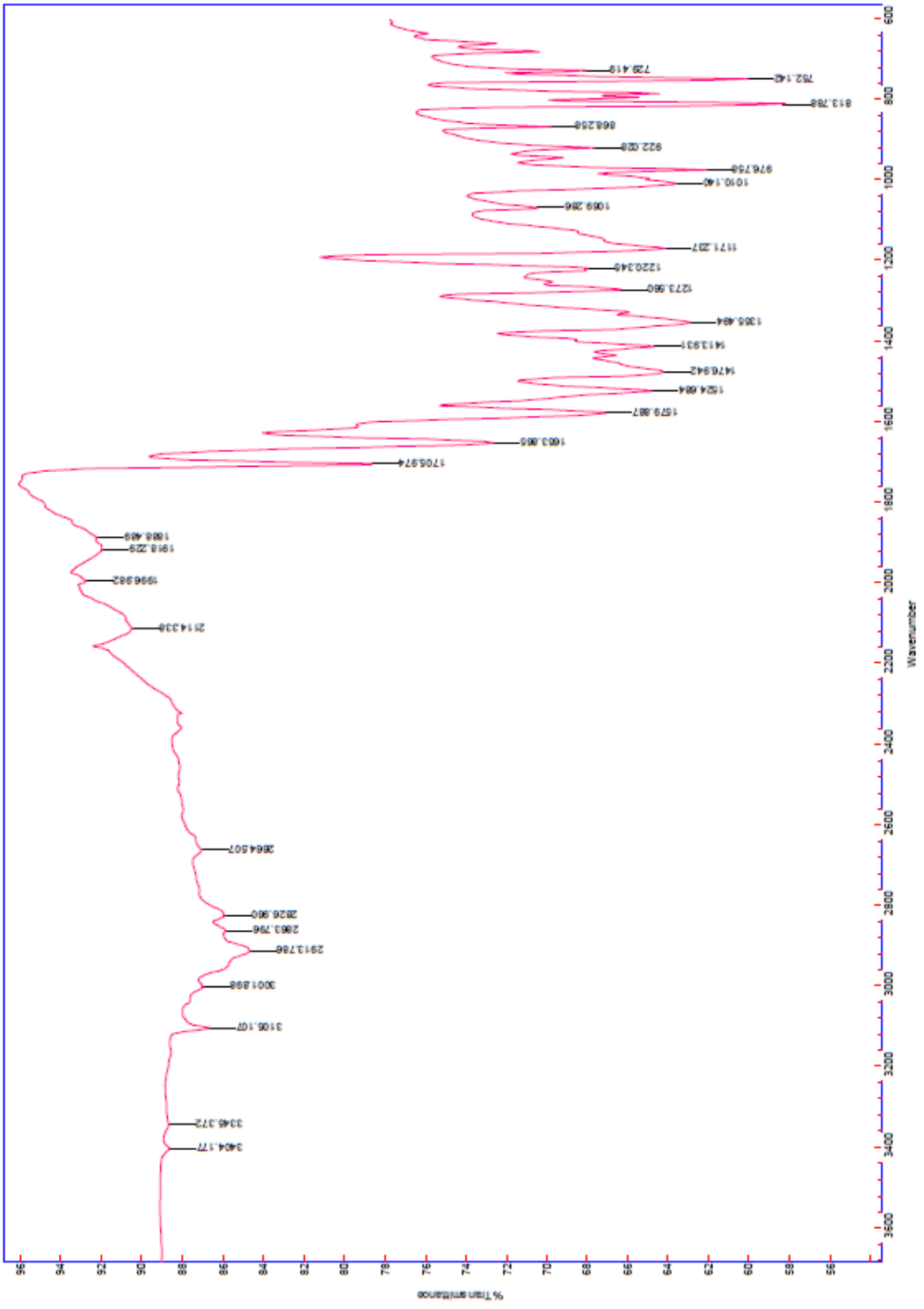
A.2.1 ^{1}H NMR spectrum of 4



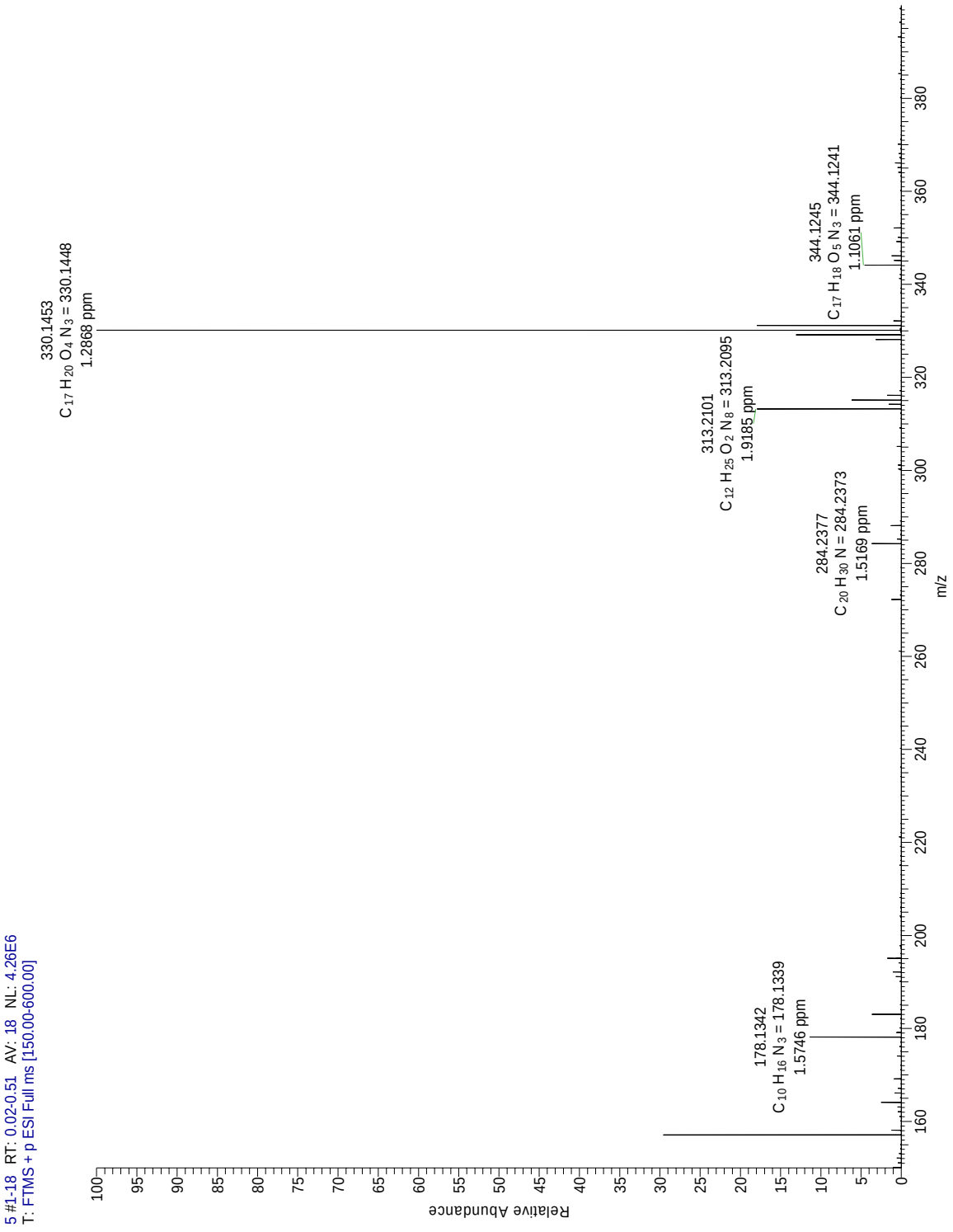
A.2.2 ^{13}C NMR spectrum of 4



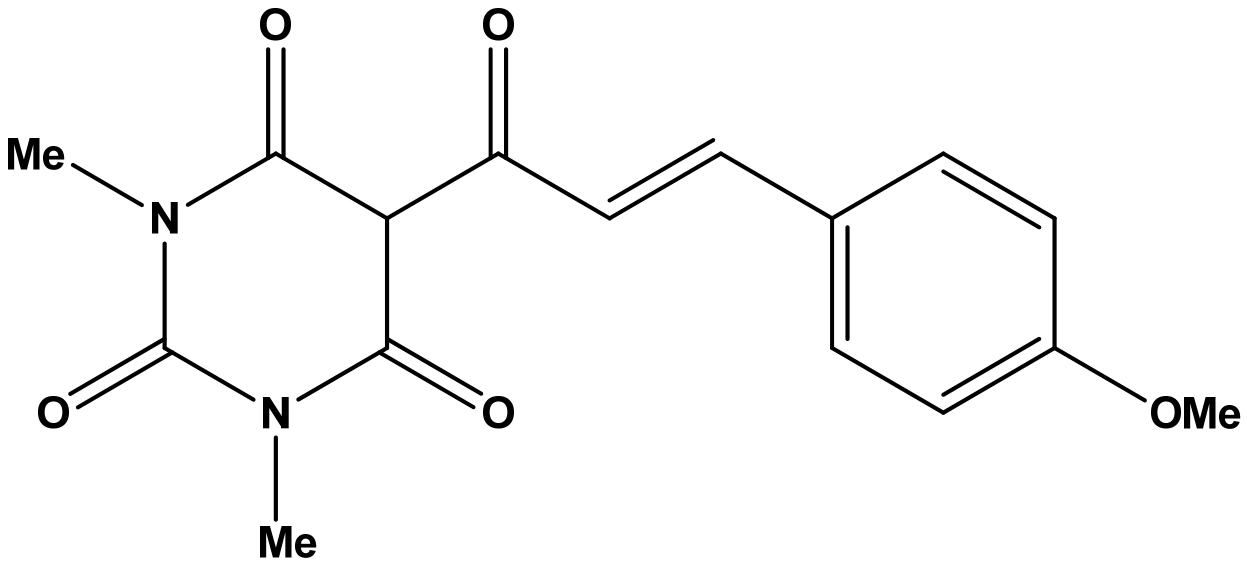
A.1.3 IR spectrum of 4



A.2.4 HRMS of 4

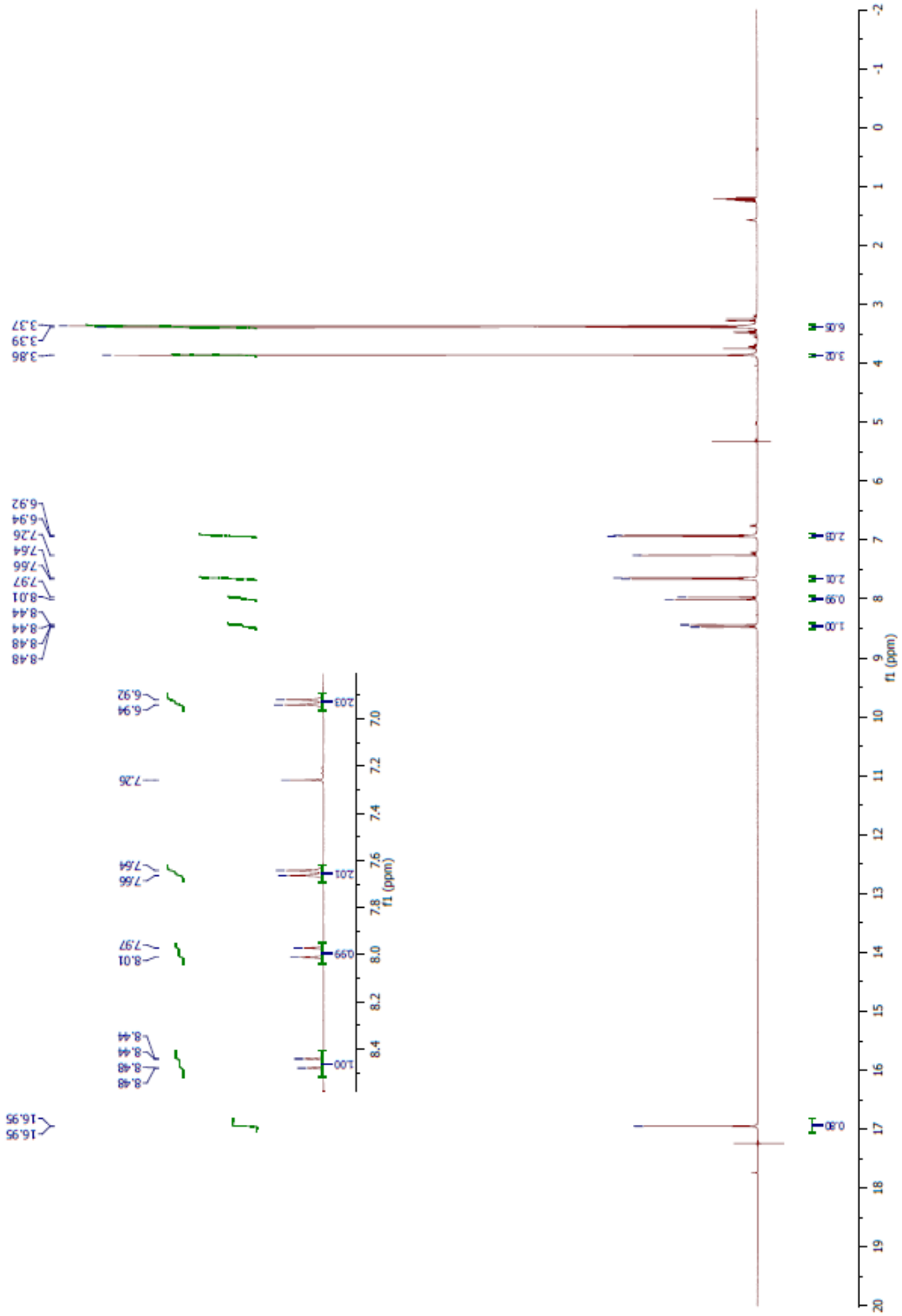

5 #1-18 RT: 0.02-0.51 AV: 18 NL: 4.26E6
T: FTMS + p ESI Full ms [150.00-600.00]
330.1453
C17 H20 O4 N3 = 330.1448
1.2868 ppm
313.2101
C12 H25 O2 N8 = 313.2095
1.9185 ppm
344.1245
C17 H18 O5 N3 = 344.1241
1.1061 ppm
284.2377
C20 H30 N = 284.2373
1.5169 ppm
178.1342
C10 H16 N3 = 178.1339
1.5746 ppm
Relative Abundance
m/z

A.3 Spectroscopic data for 5

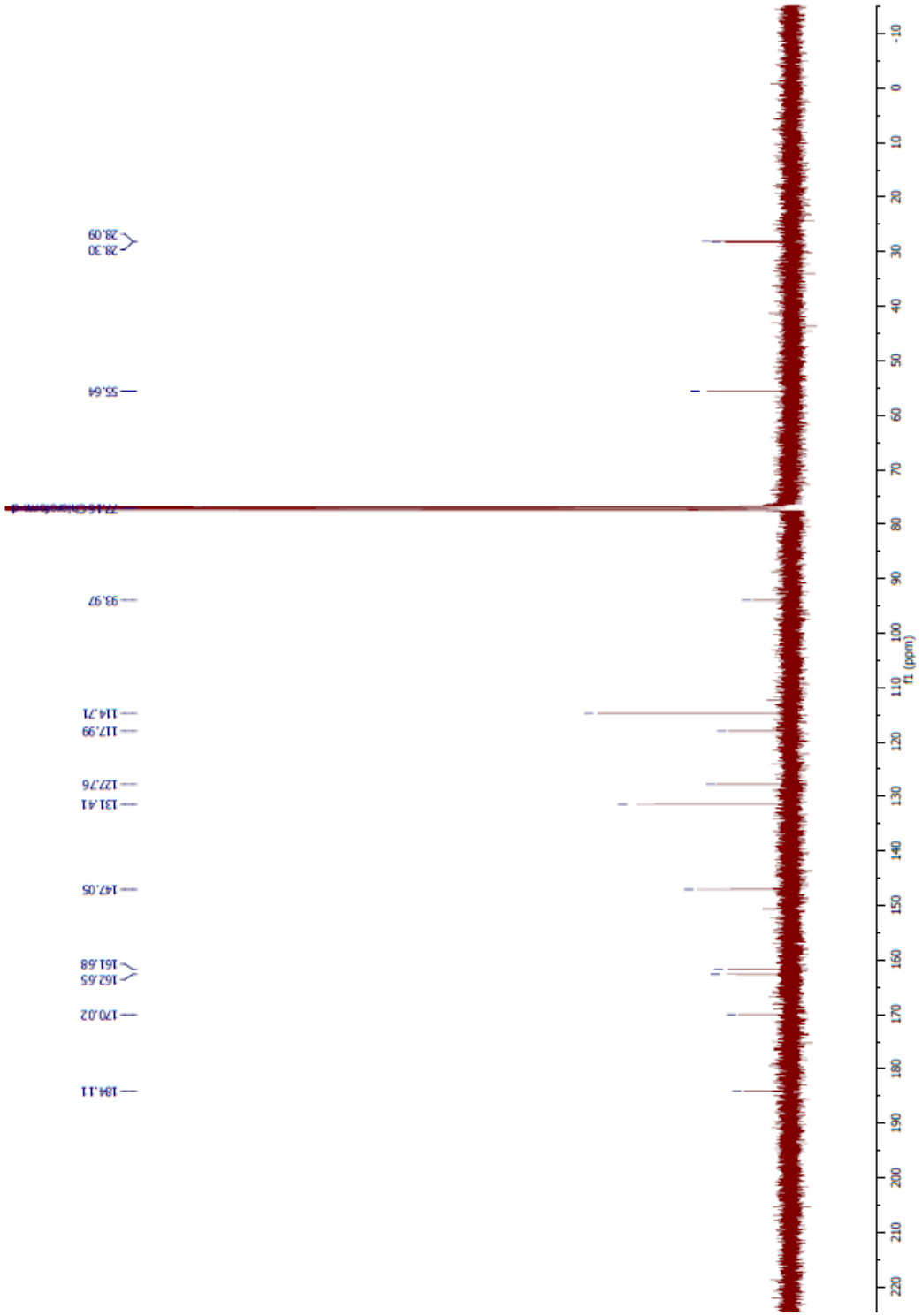


5

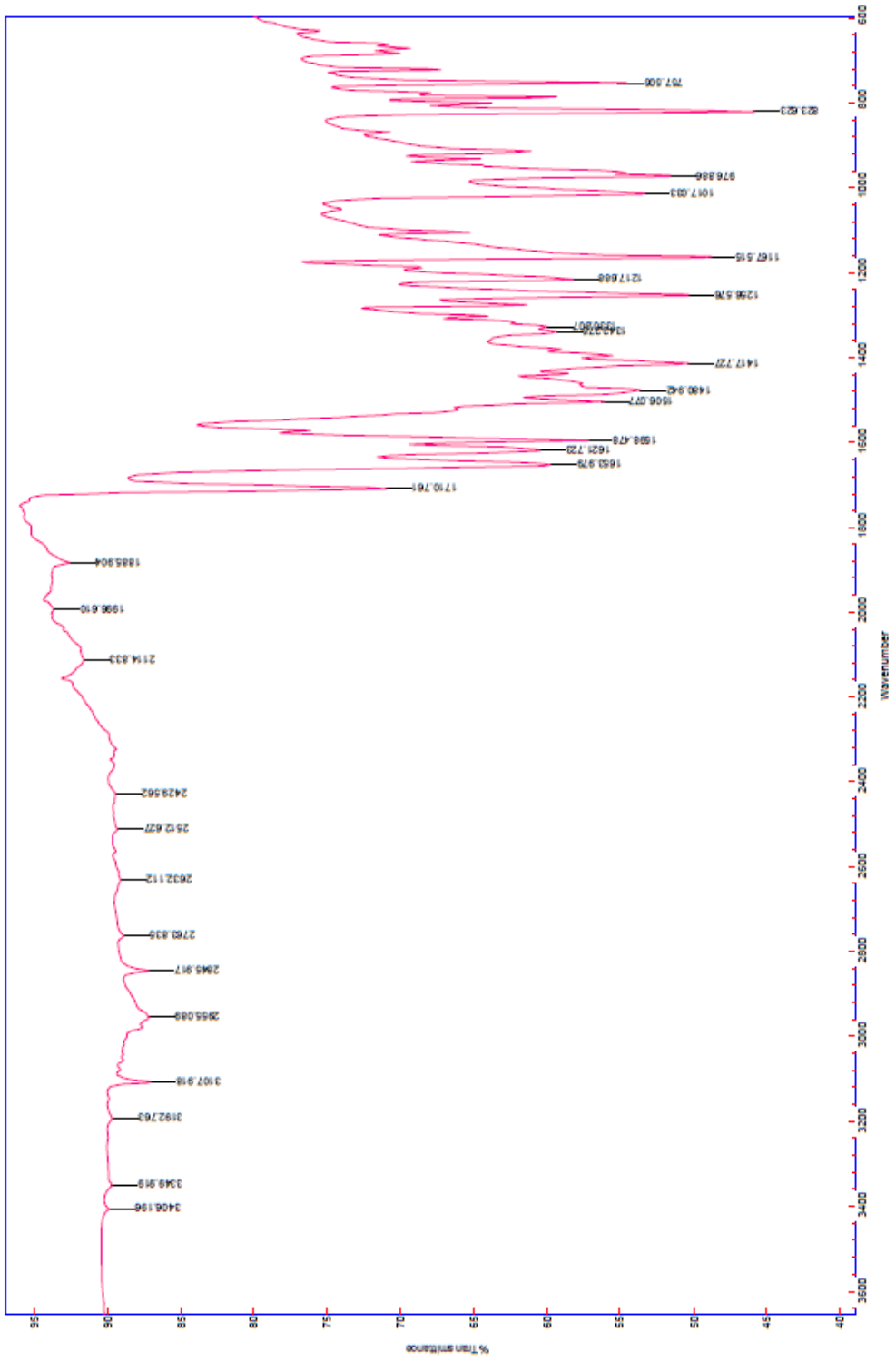
A.3.1 ^{1}H NMR spectrum of 5



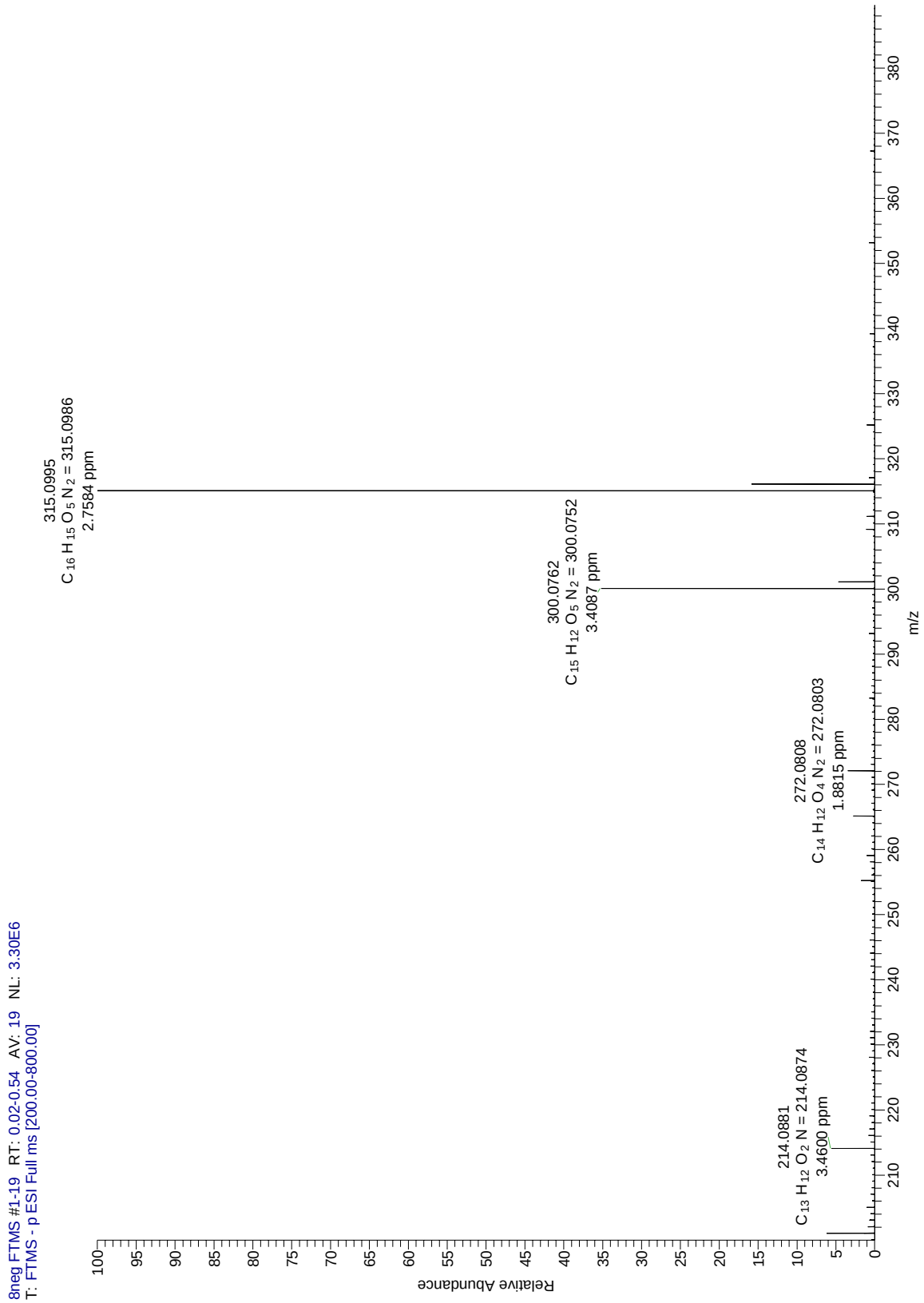
A.3.2 ^{13}C NMR spectrum of 5



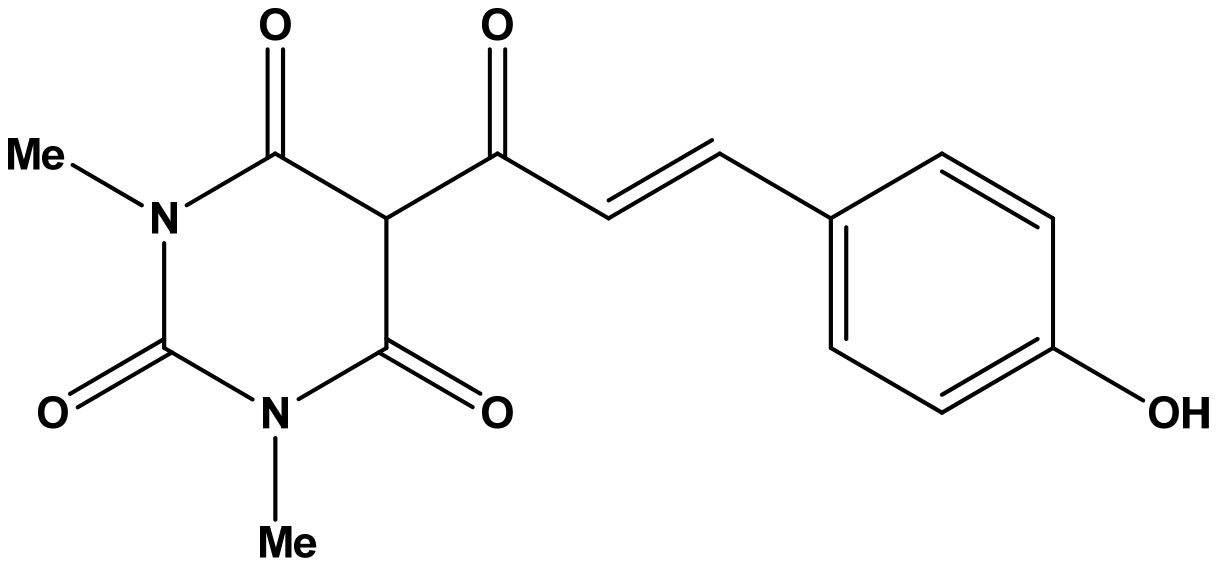
A.3.2 IR spectrum of 5



A.3.4 HRMS of 5

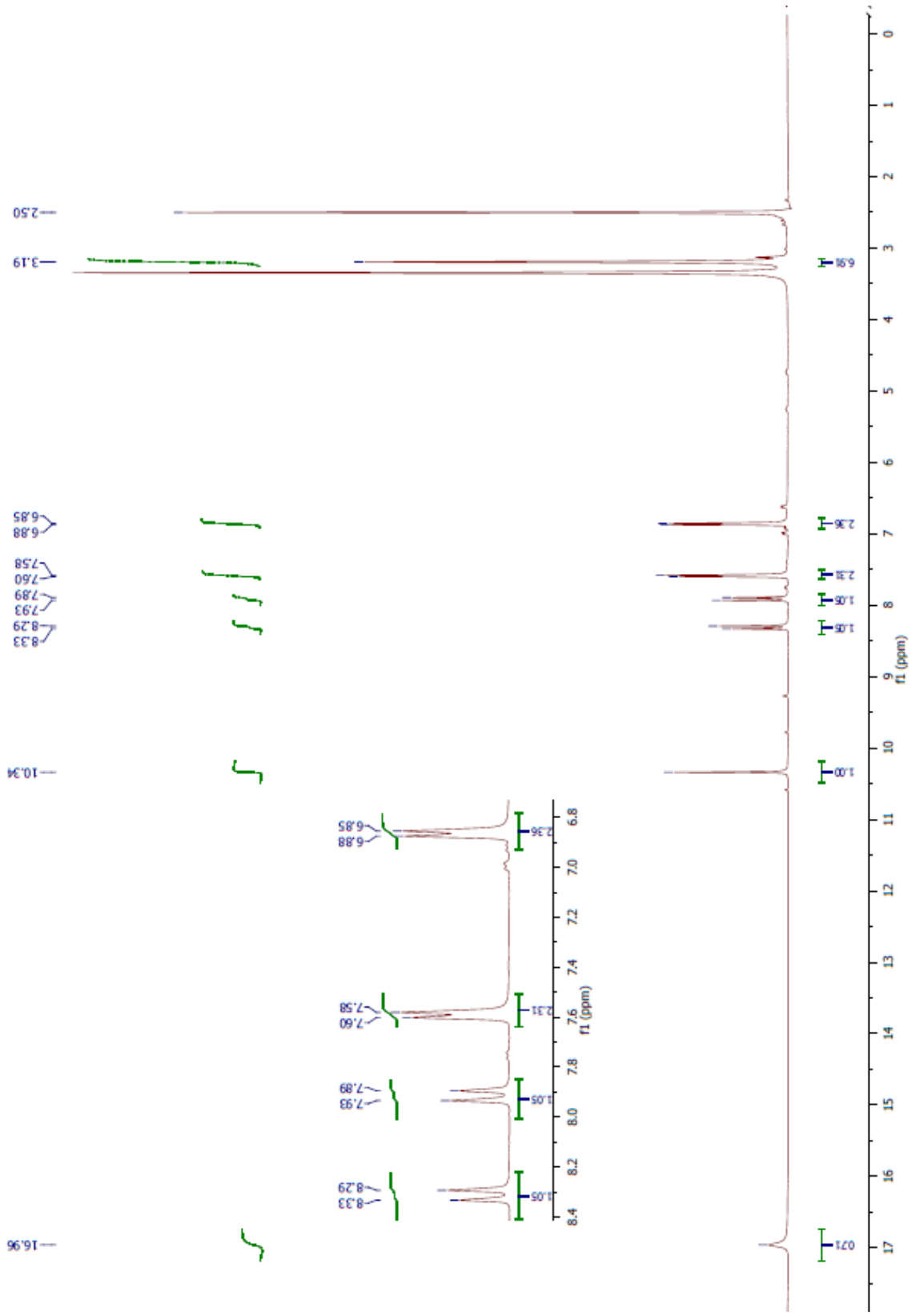

8neg FTMS #1-19 RT: 0.02-0.54 AV: 19 NL: 3.30E6
T: FTMS - p ESI Full ms [200.00-800.00]
315.0995
C 16 H 15 O 5 N 2 = 315.0986
2.7584 ppm
300.0762
C 15 H 12 O 5 N 2 = 300.0752
3.4087 ppm
272.0808
C 14 H 12 O 4 N 2 = 272.0803
1.8815 ppm
214.0881
C 13 H 12 O 2 N = 214.0874
3.4600 ppm
Relative Abundance
m/z

A.4 Spectroscopic data for 6

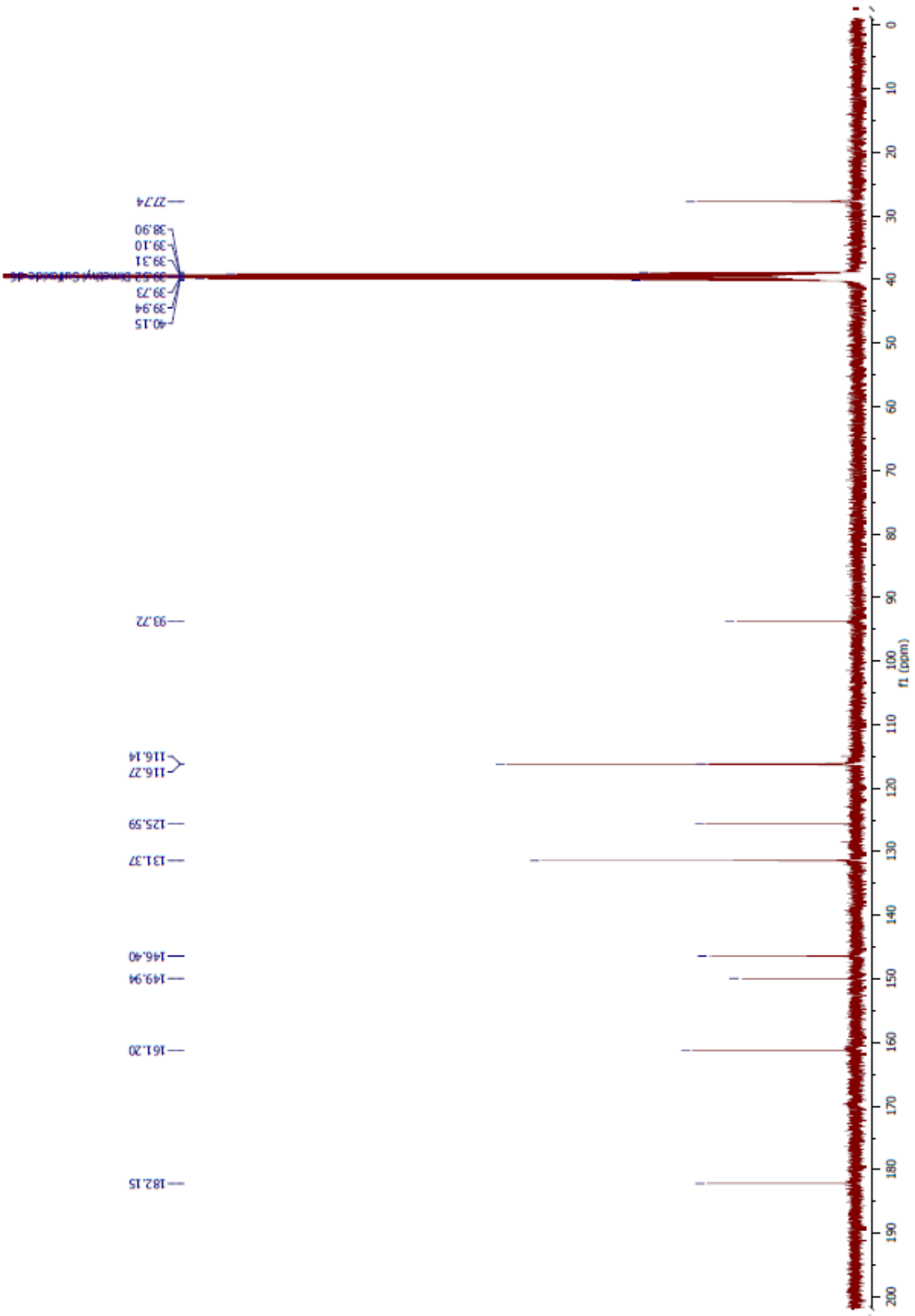


6

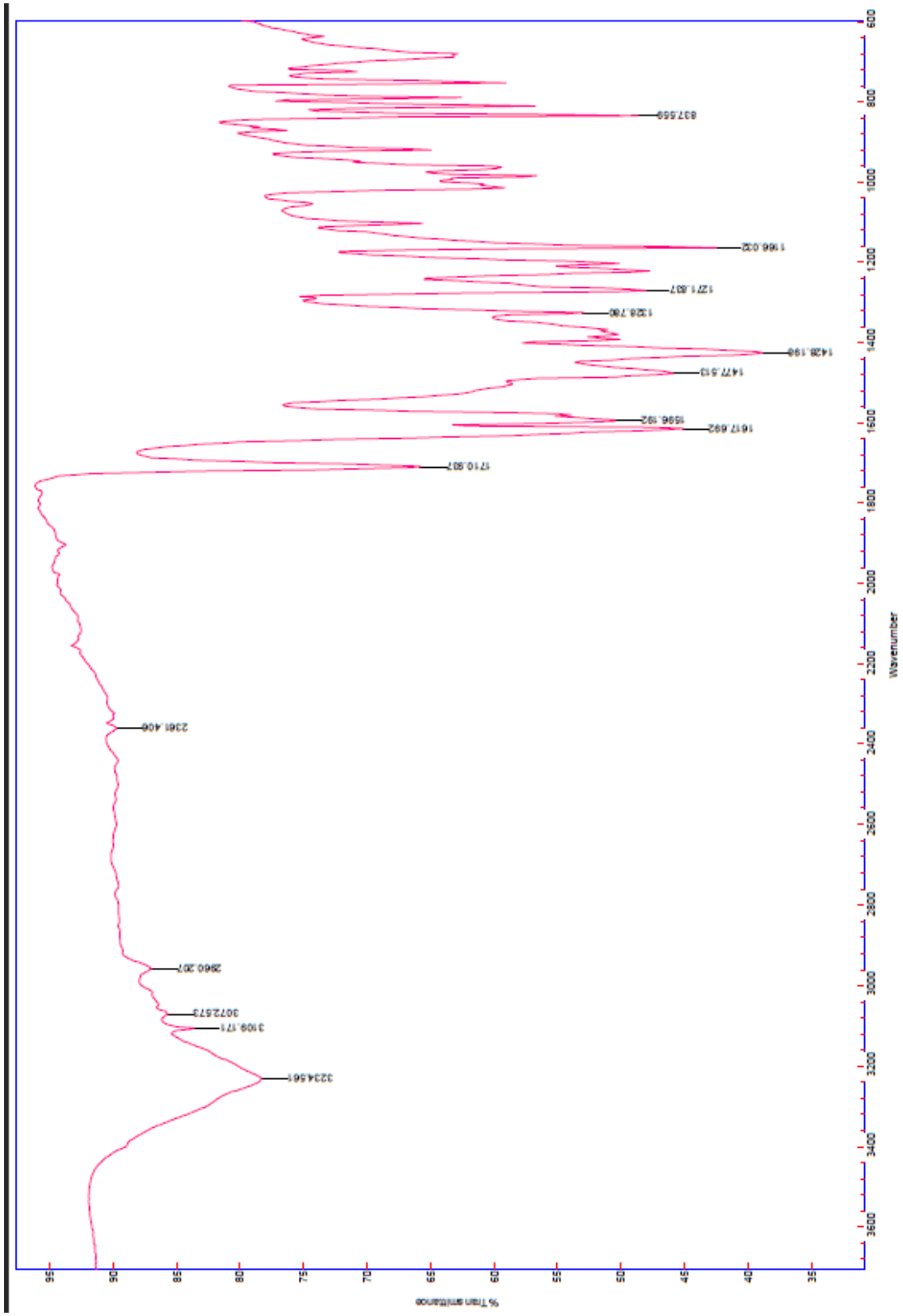
A.4.1 ^{1}H NMR spectrum of 6



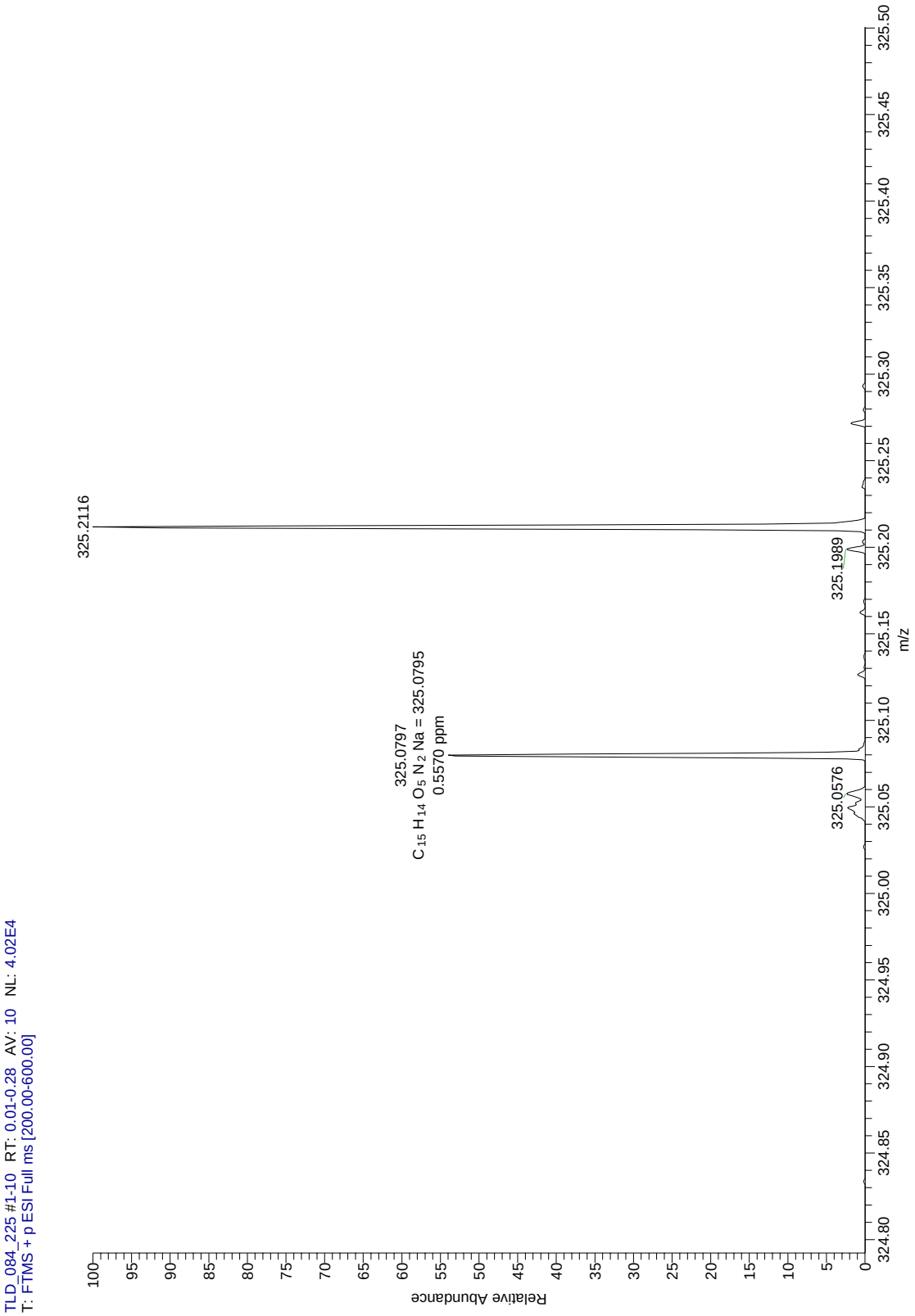
A.4.2 ^{13}C NMR spectrum of 6



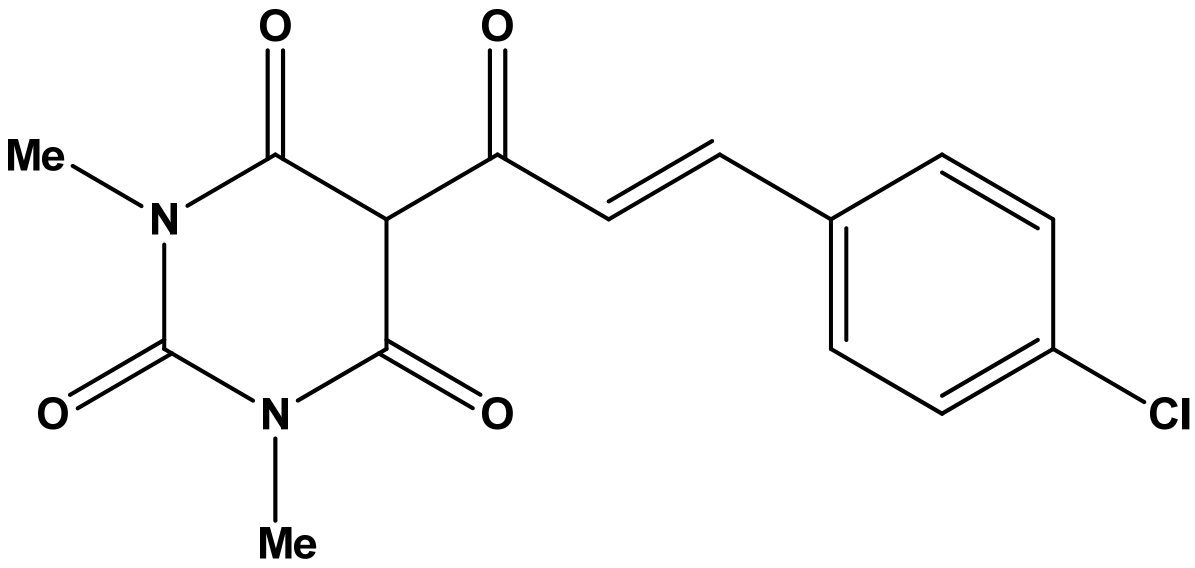
A.4.3 IR spectrum of 6



A.4.4 HRMS of 6

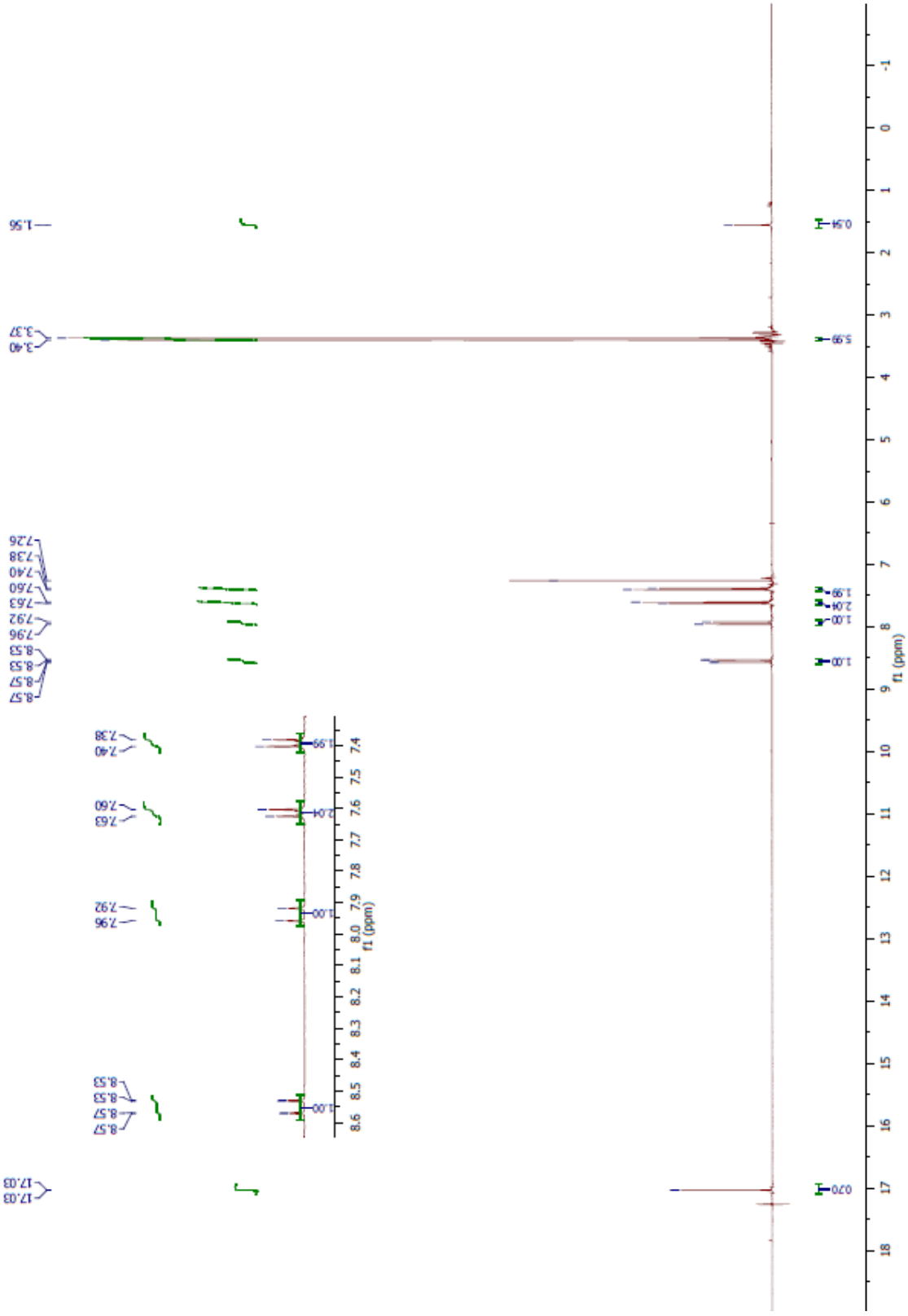

TLD_084_225 #1-10 RT: 0.01-0.28 AV: 10 NL: 4.02E4
T: FTMS + p ESI Full ms [200.00-600.00]
325.2116
325.1989
325.0797
C15 H14 O5 N2 Na = 325.0795
0.5570 ppm
325.0576
Relative Abundance
m/z

A.5 Spectroscopic data for 7

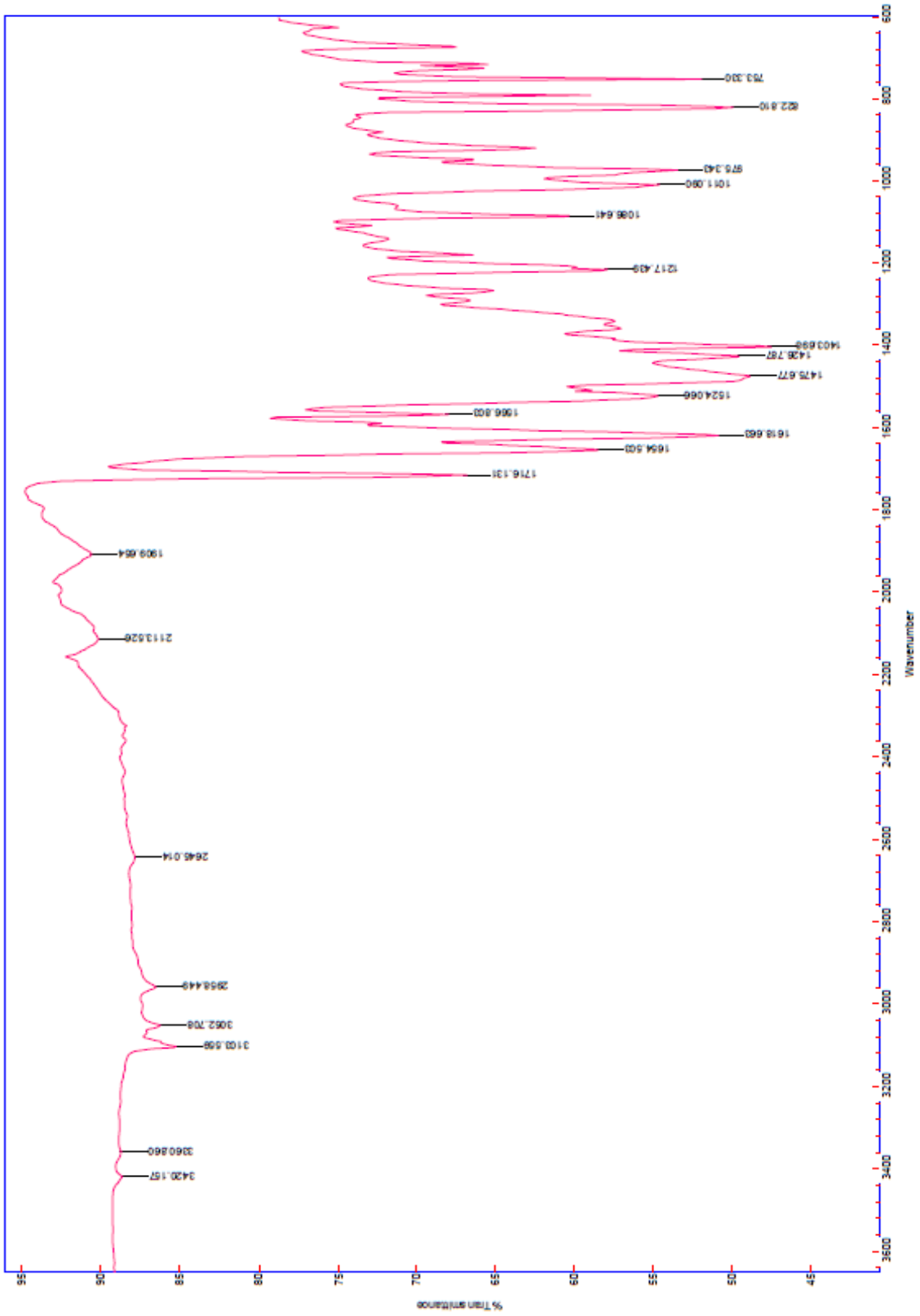


7

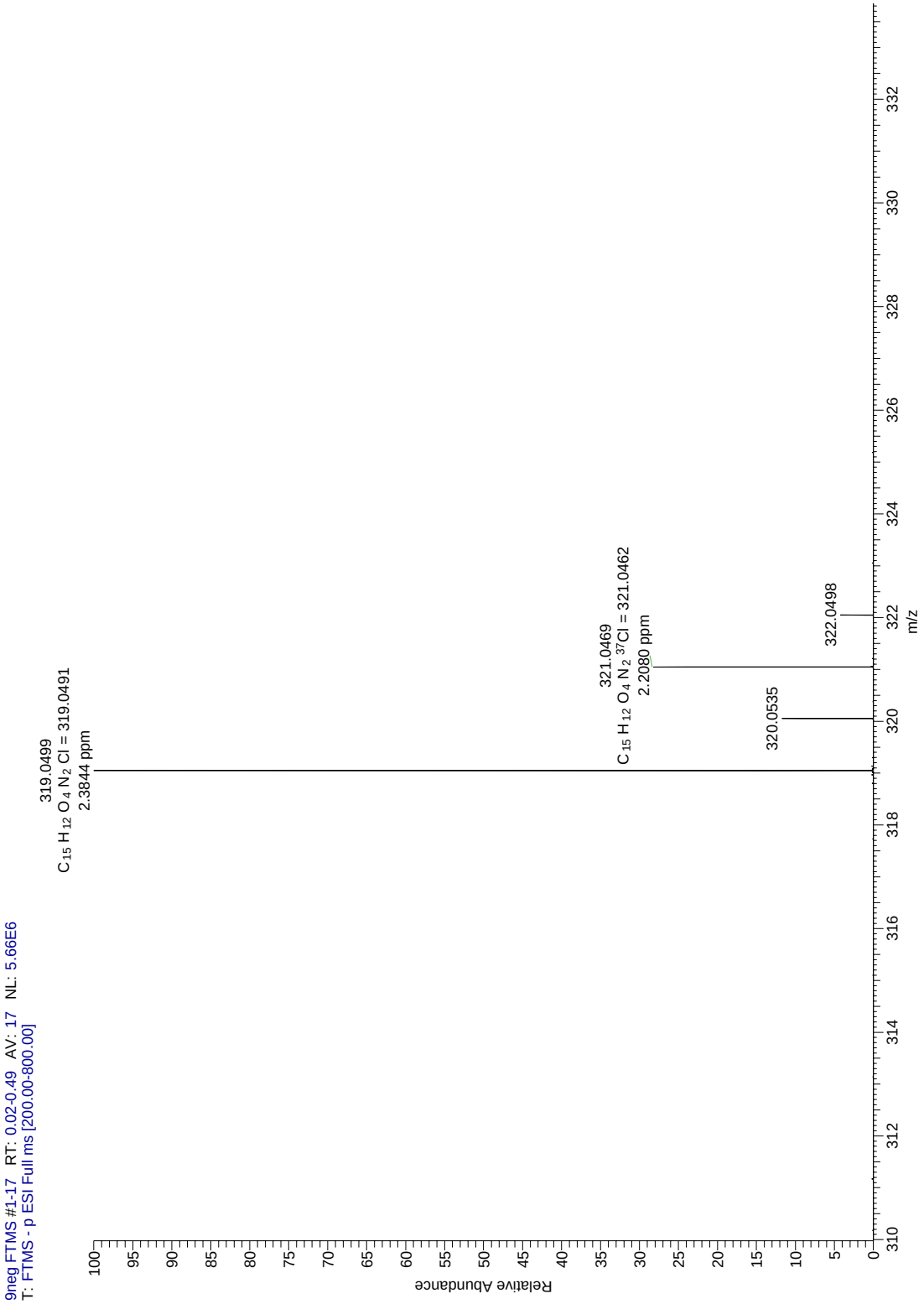
A.5.1 ^{1}H NMR spectrum of 7



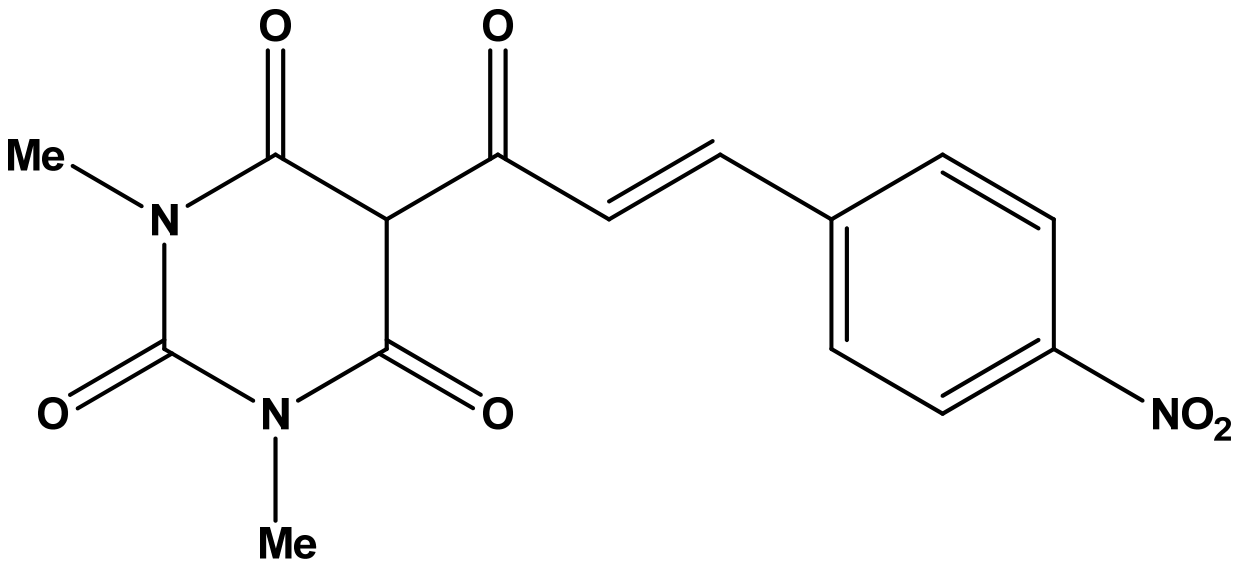
A.5.2 IR spectrum of 7



A.5.3 HRMS of

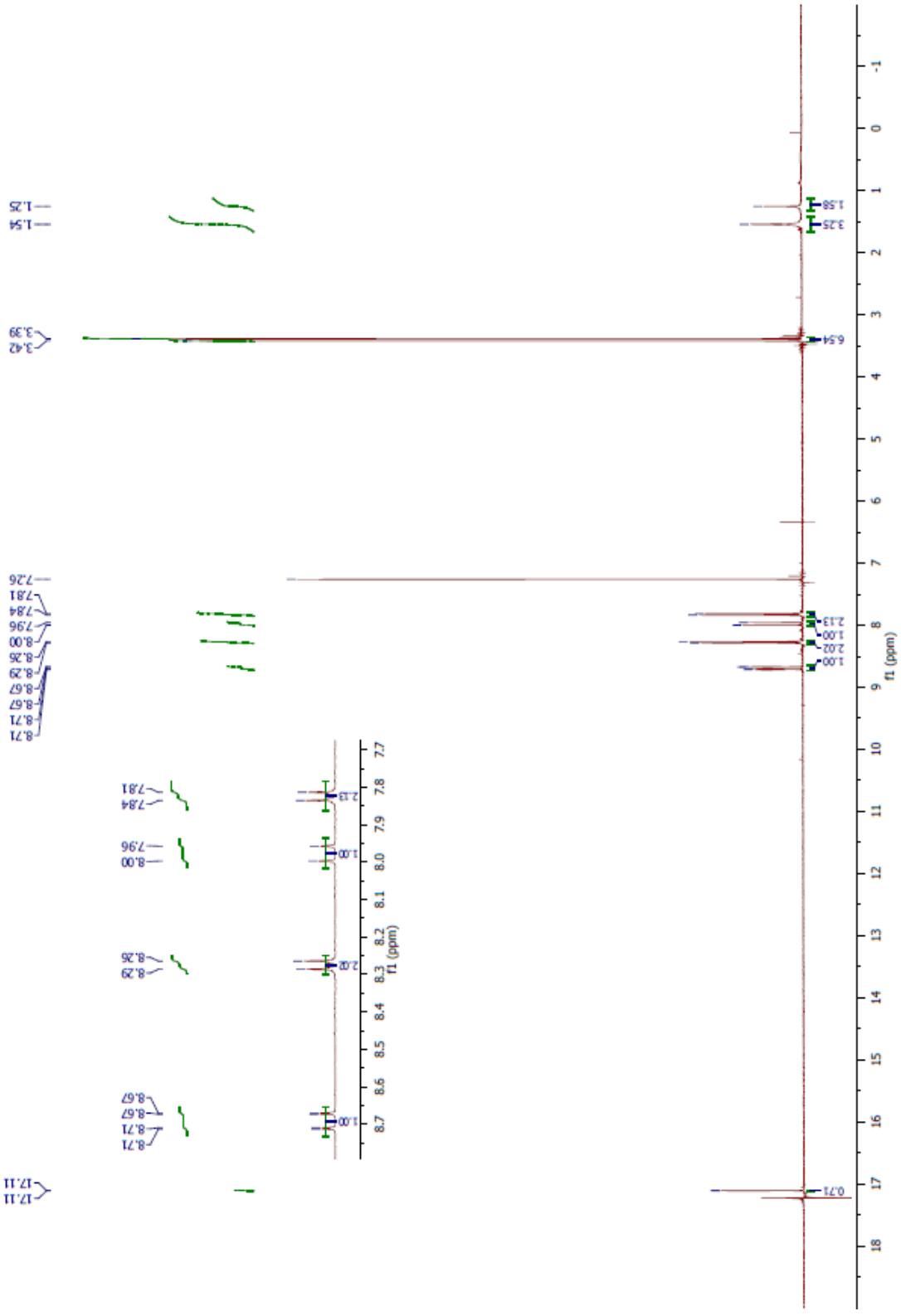

9neg FTMS #1-17 RT: 0.02-0.49 AV: 17 NL: 5.66E6
T: FTMS - p ESI Full ms [200.00-800.00]
319.0499
C15 H12 O4 N2 Cl = 319.0491
2.3844 ppm
321.0469
C15 H12 O4 N2 37Cl = 321.0462
2.2080 ppm
320.0535
322.0498
Relative Abundance
m/z

A.6 Spectroscopic data for 8

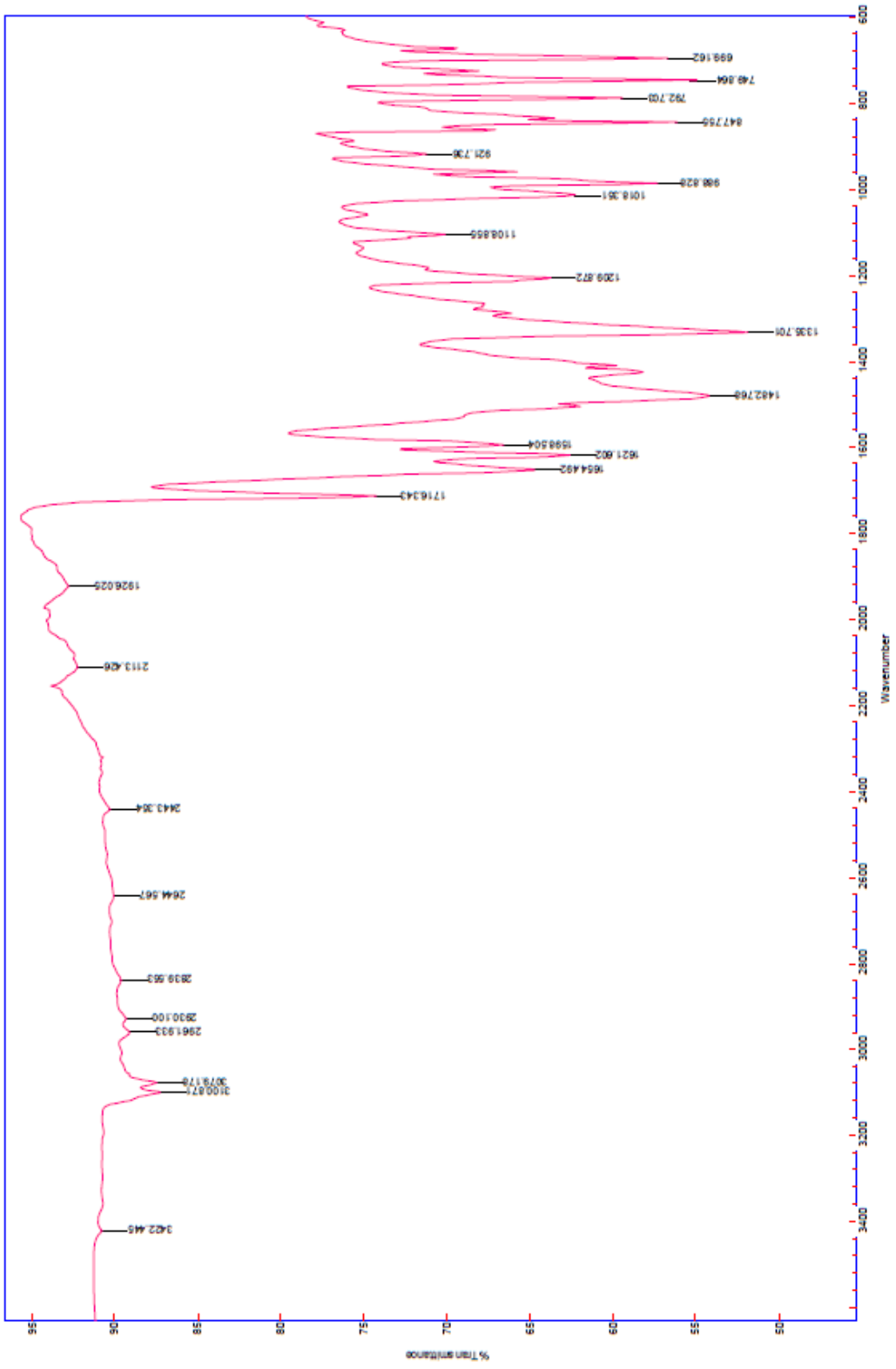


8

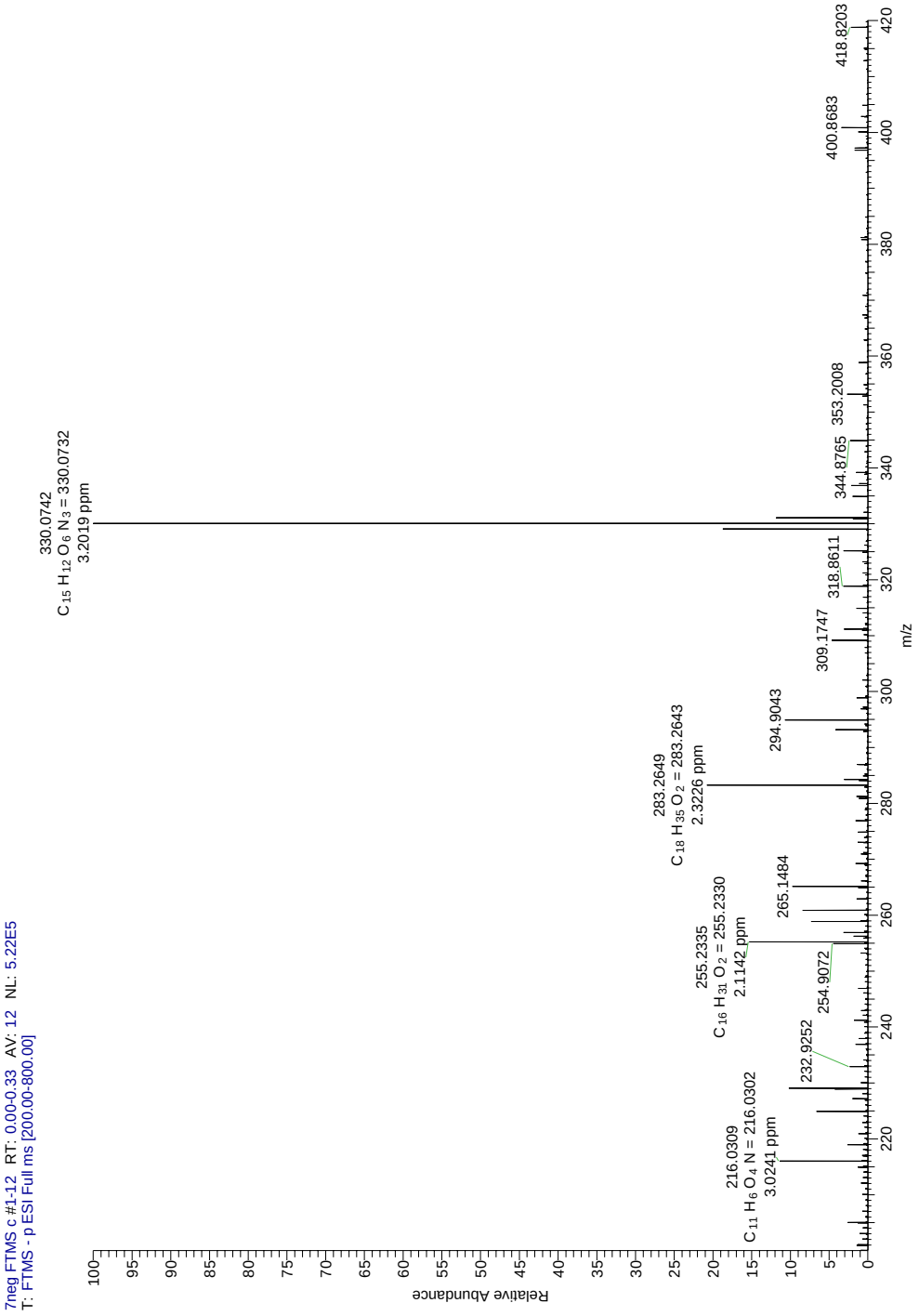
A.6.1 ^{1}H NMR spectrum of 8



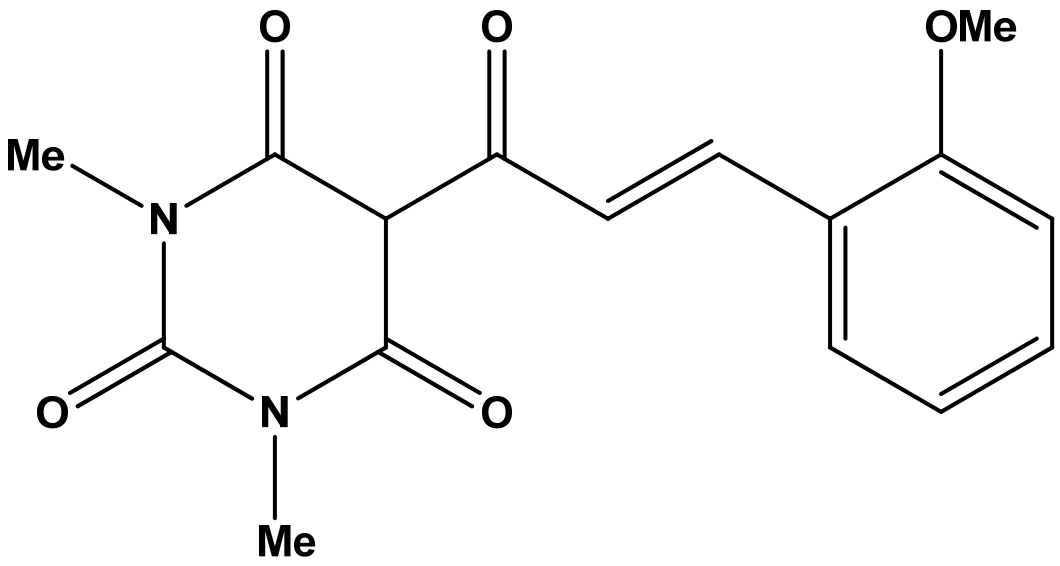
A.6.2 IR spectrum of 8



A.6.2 HRMS of 8

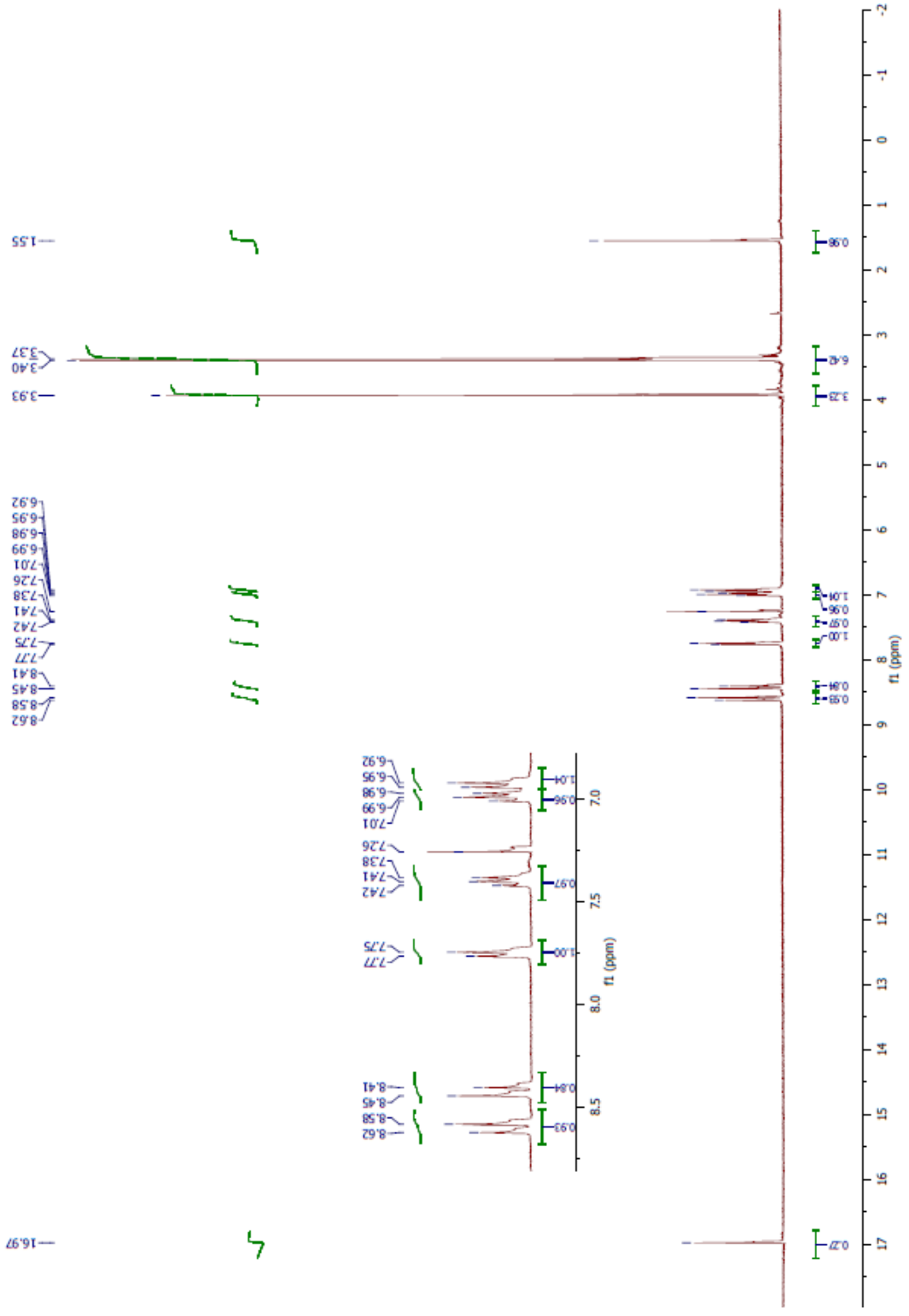

7neg FTMS c #1-12 RT: 0.00-0.33 AV: 12 NL: 5.22E5
T: FTMS - p ESI Full ms [200.00-800.00]
330.0742
C15 H12 O6 N3 = 330.0732
3.2019 ppm
283.2649
C18 H35 O2 = 283.2643
2.3226 ppm
255.2335
C16 H31 O2 = 255.2330
2.1142 ppm
216.0309
C11 H6 O4 N = 216.0302
3.0241 ppm
418.8203
400.8683
353.2008
344.8765
318.8611
309.1747
294.9043
265.1484
254.9072
232.9252
Relative Abundance
m/z

A.7 Spectroscopic data for 9

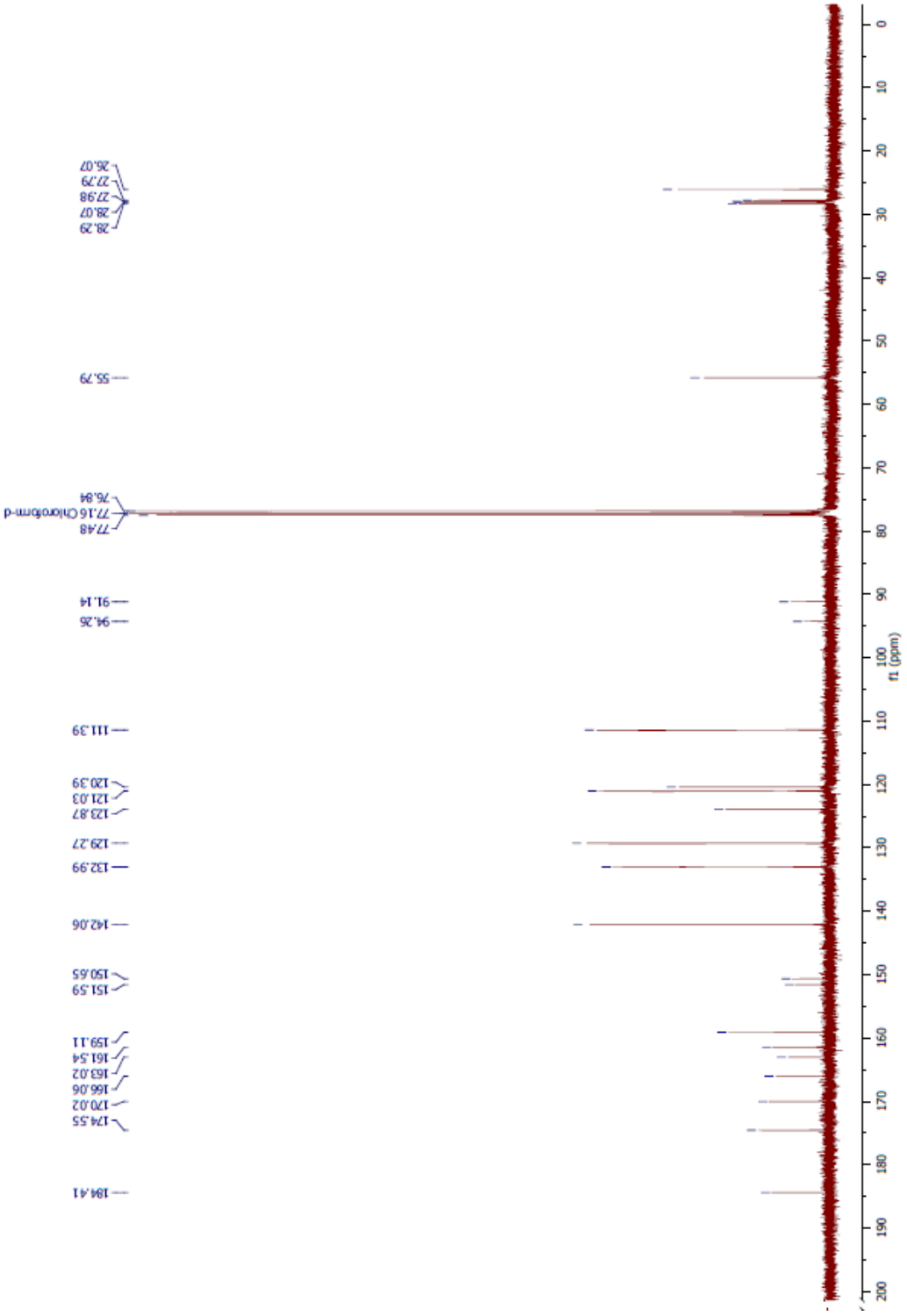


9

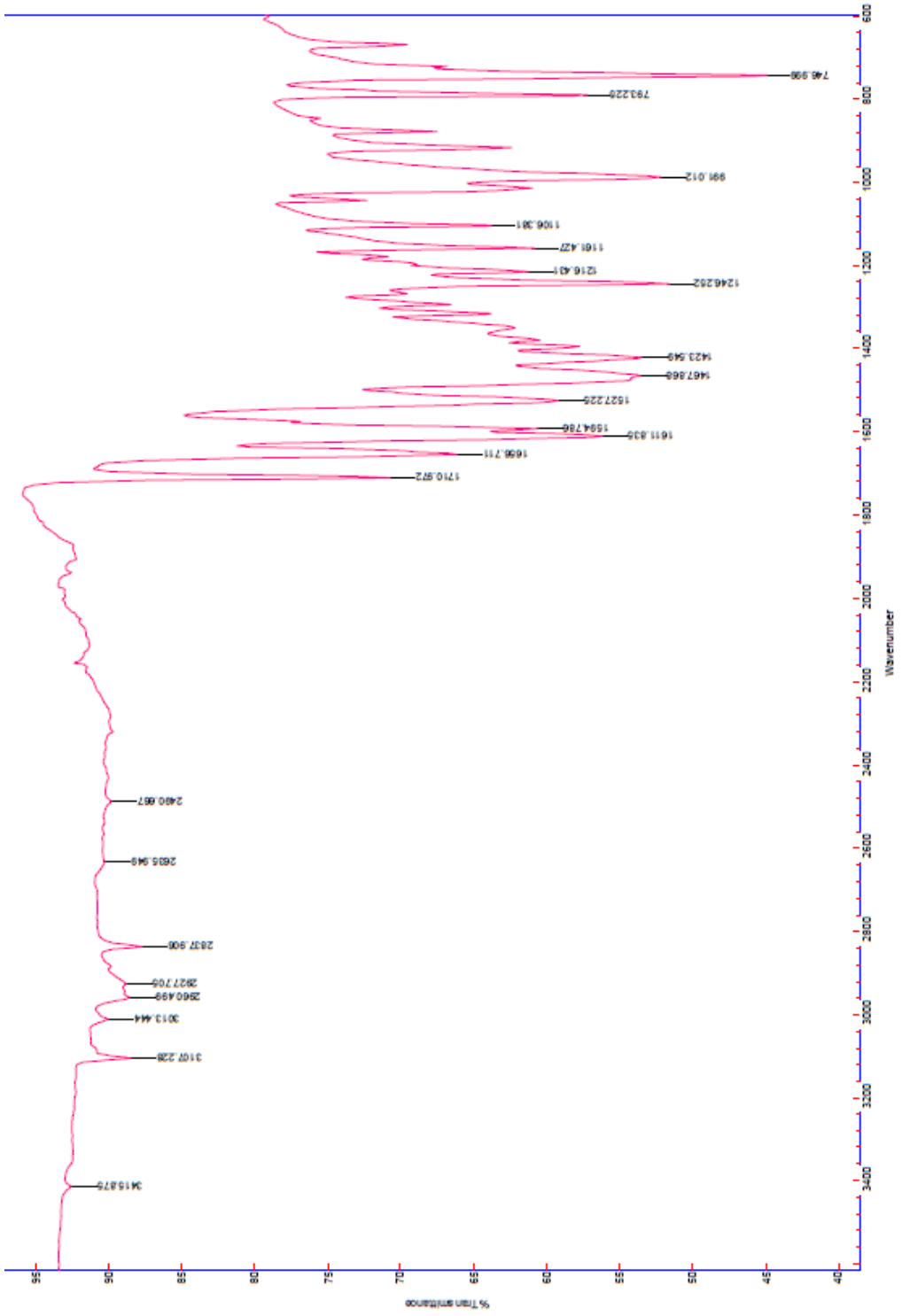
A.7.1 ^{1}H NMR spectrum of 9



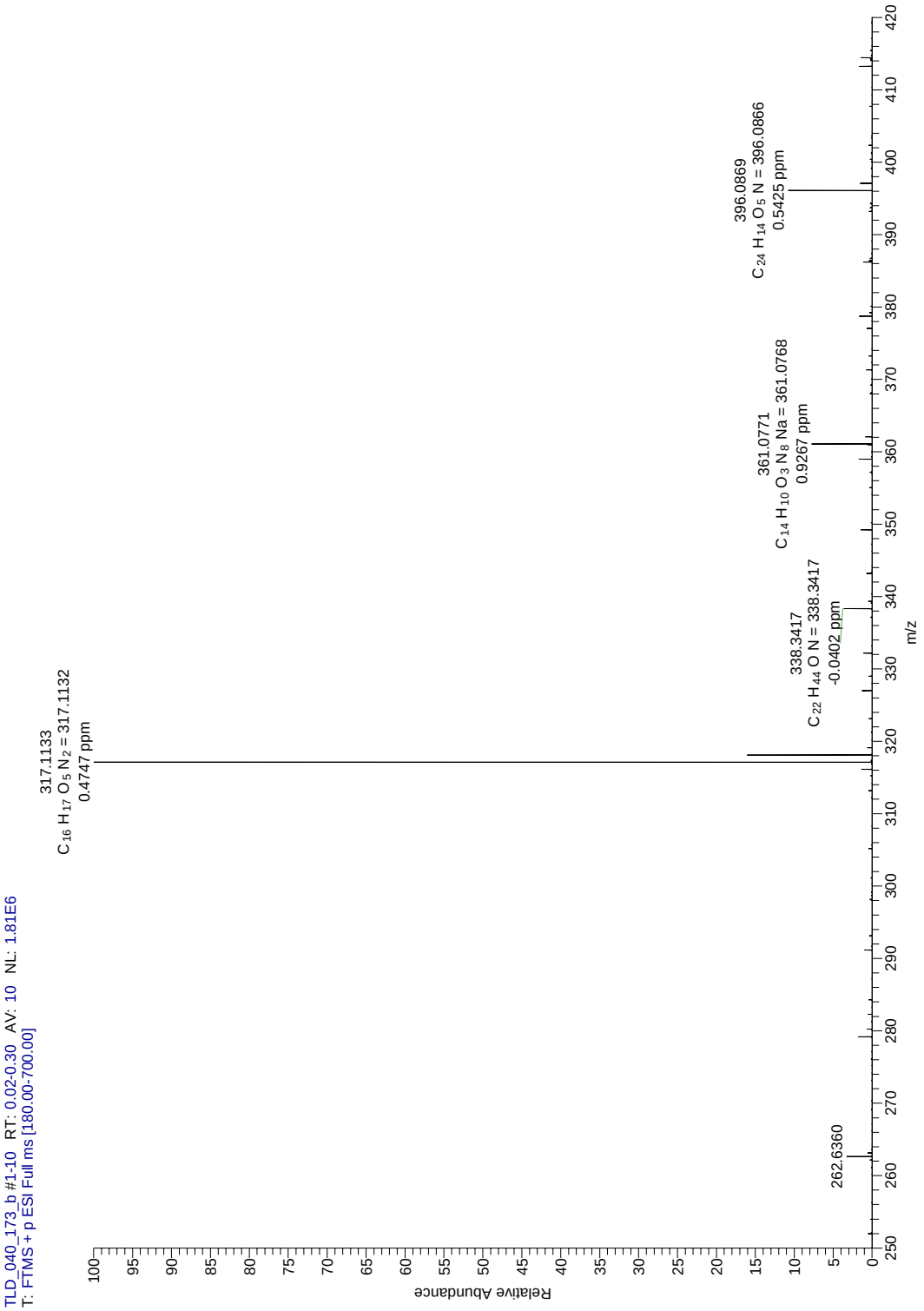
A.7.2 ^{13}C NMR spectrum of 9



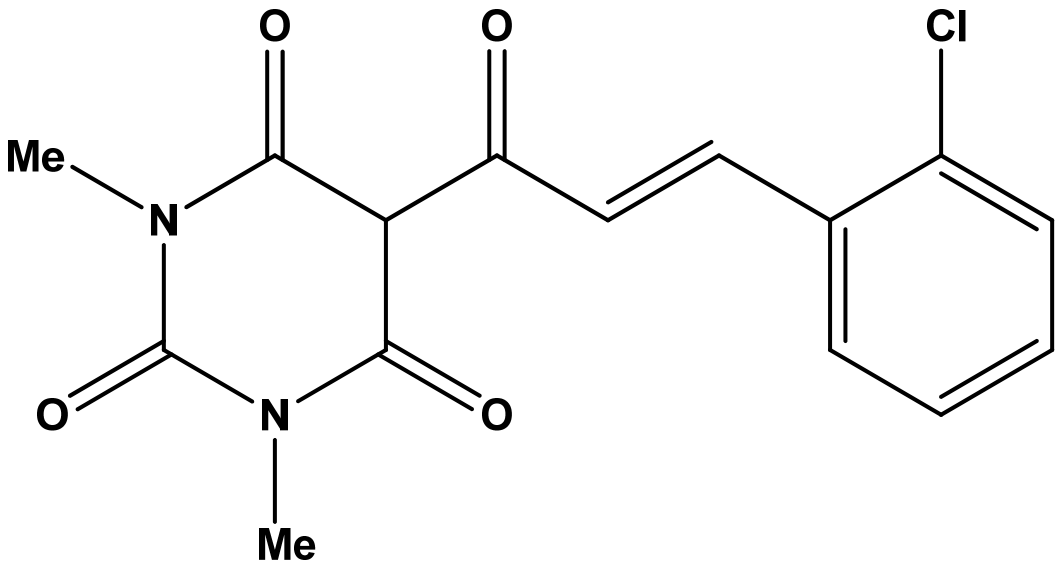
A.7.3 IR spectrum of 9



A.7.4 HRMS of 9

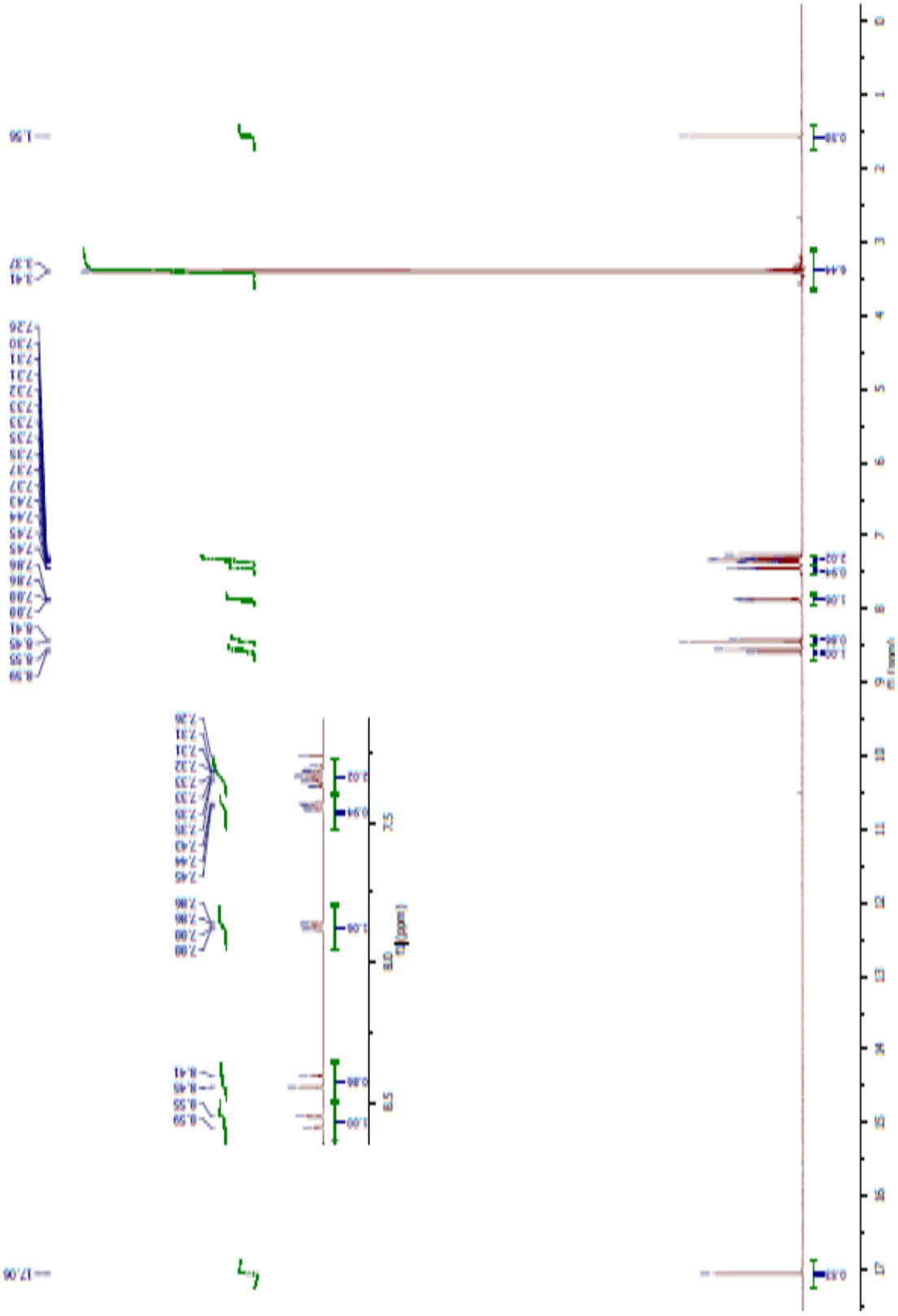

TLD_040_173_b #1-10 RT: 0.02-0.30 AV: 10 NL: 1.81E6
T: FTMS + p ESI Full ms [180.00-700.00]
317.1133
C16 H17 O5 N2 = 317.1132
0.4747 ppm
338.3417
C22 H44 O N = 338.3417
-0.0402 ppm
361.0771
C14 H10 O3 N8 Na = 361.0768
0.9267 ppm
396.0869
C24 H14 O5 N = 396.0866
0.5425 ppm
262.6360
Relative Abundance
m/z

A.8 Spectroscopic data for 10

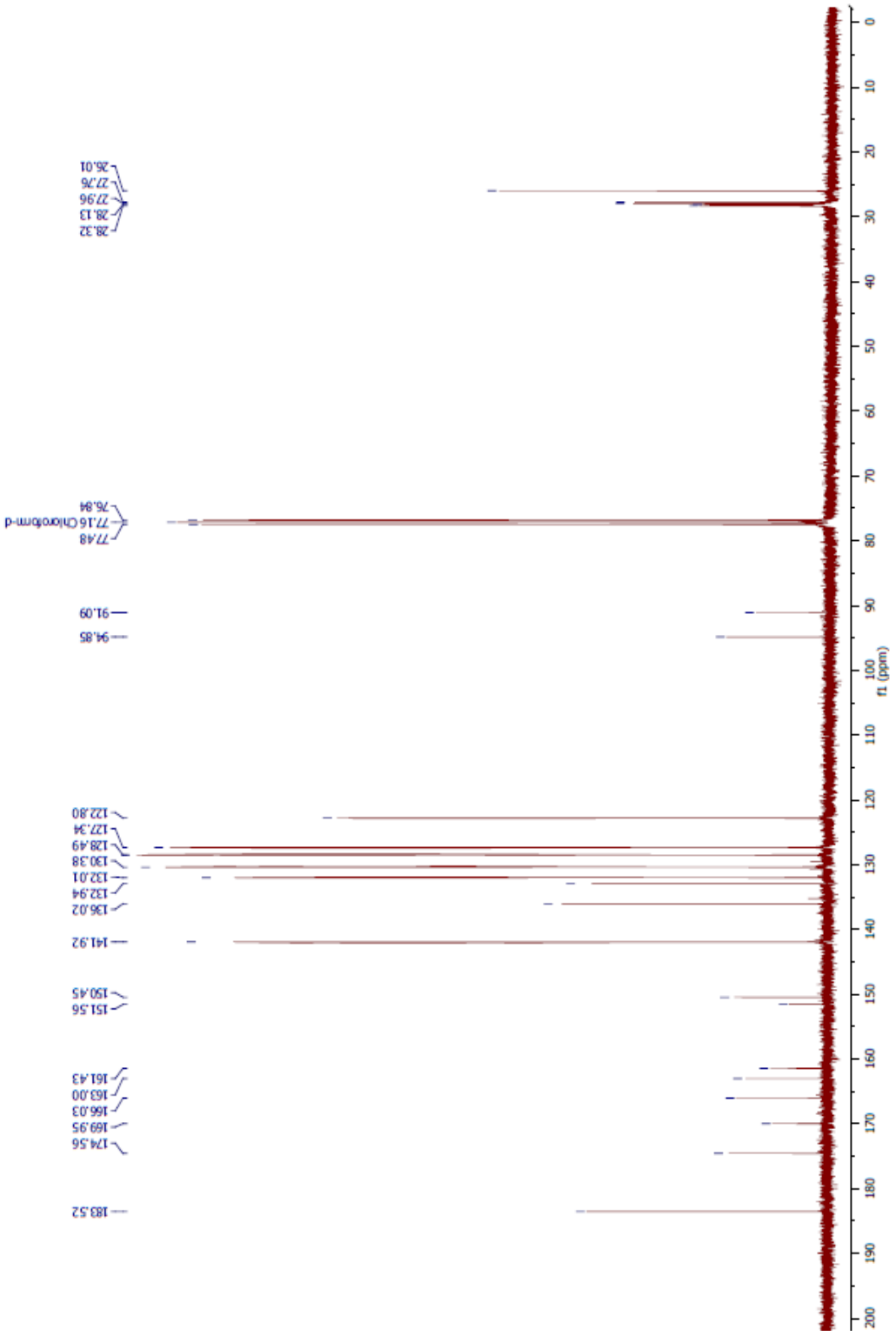


10

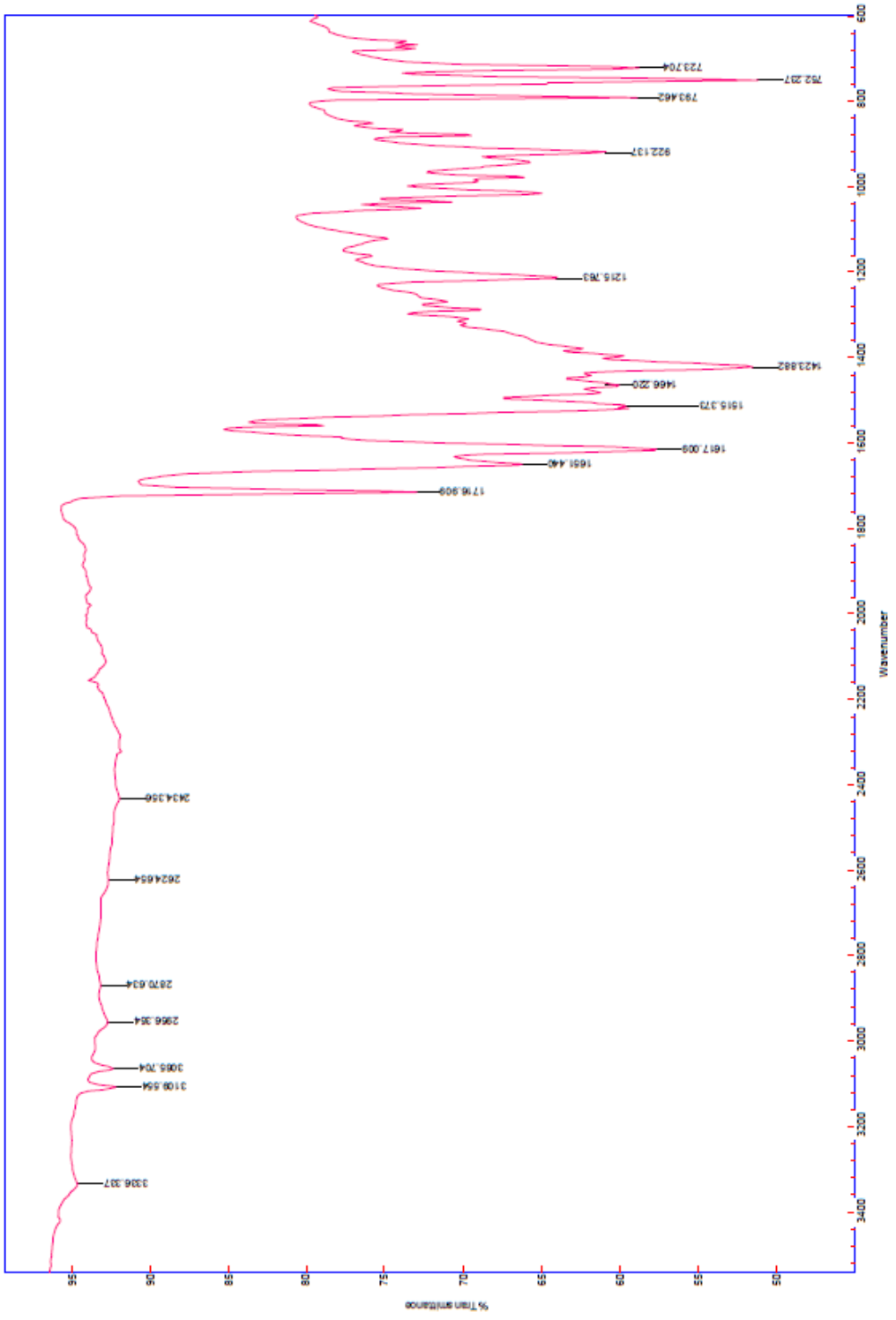
A.8.1 ^{1}H NMR spectrum of 10



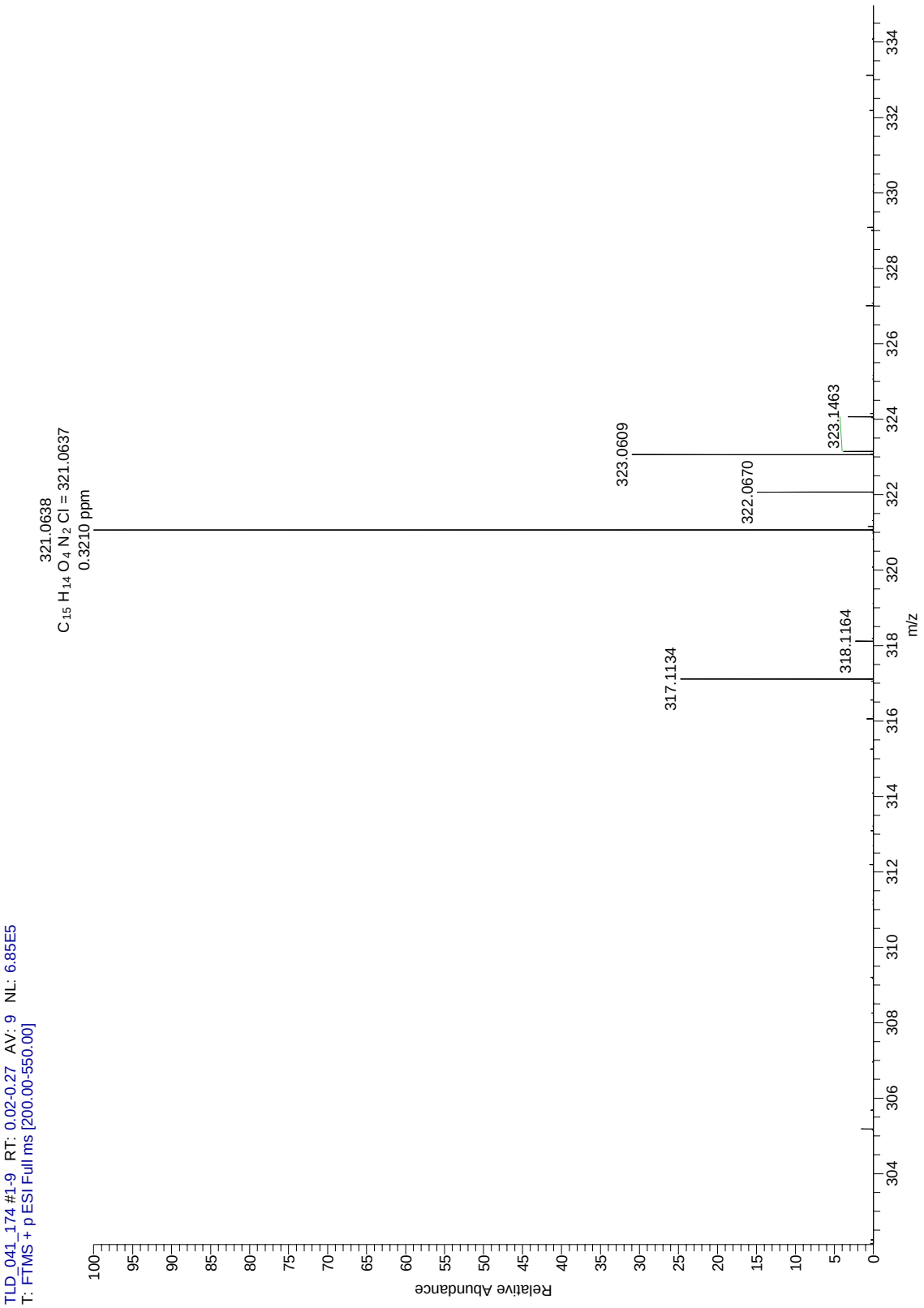
A.8.2 ^{13}C NMR spectrum of 10



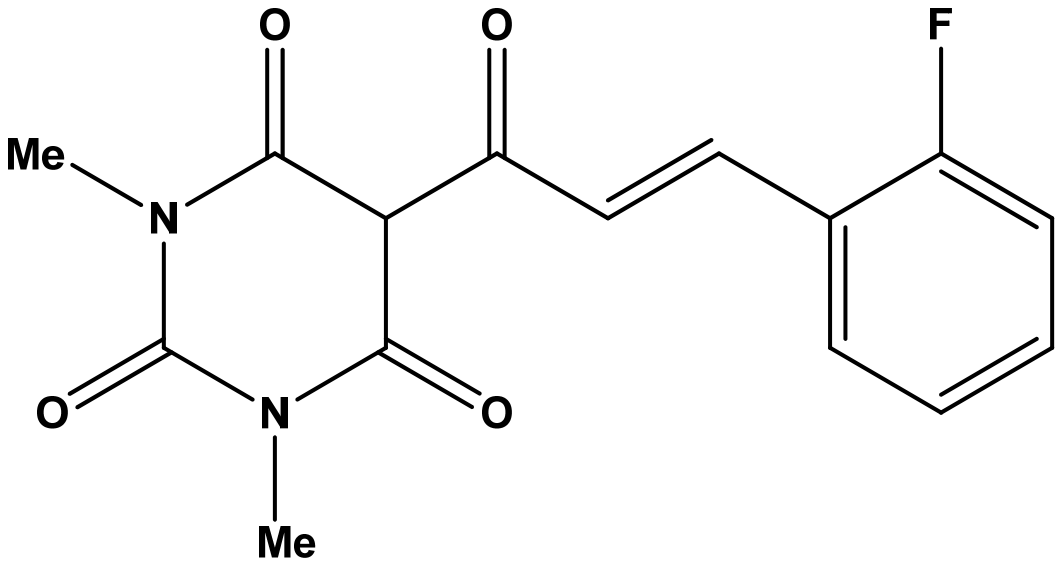
A.8.3 IR spectrum of 10



A.8.4 HRMS of 10

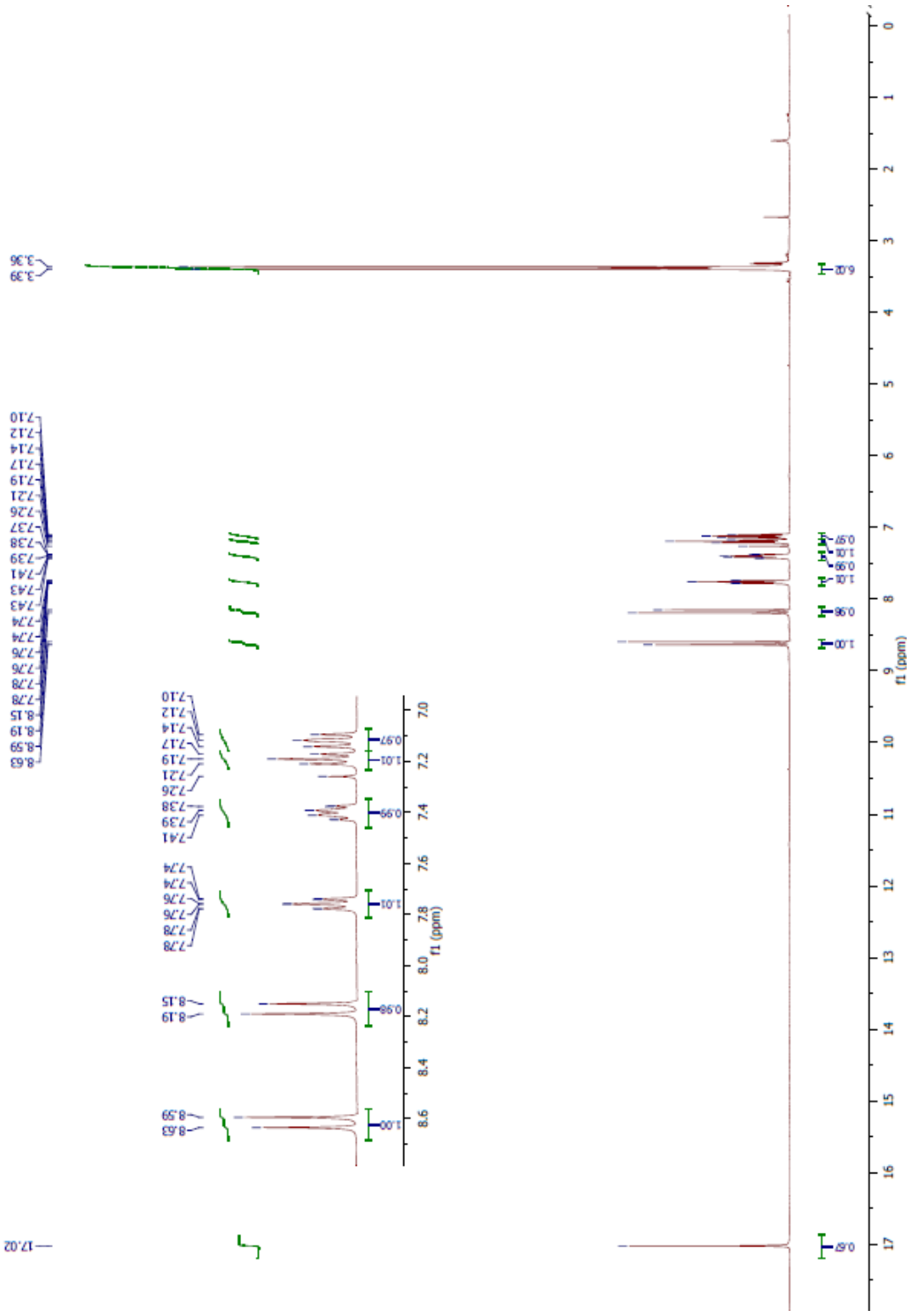


A.9 Spectroscopic data for 11

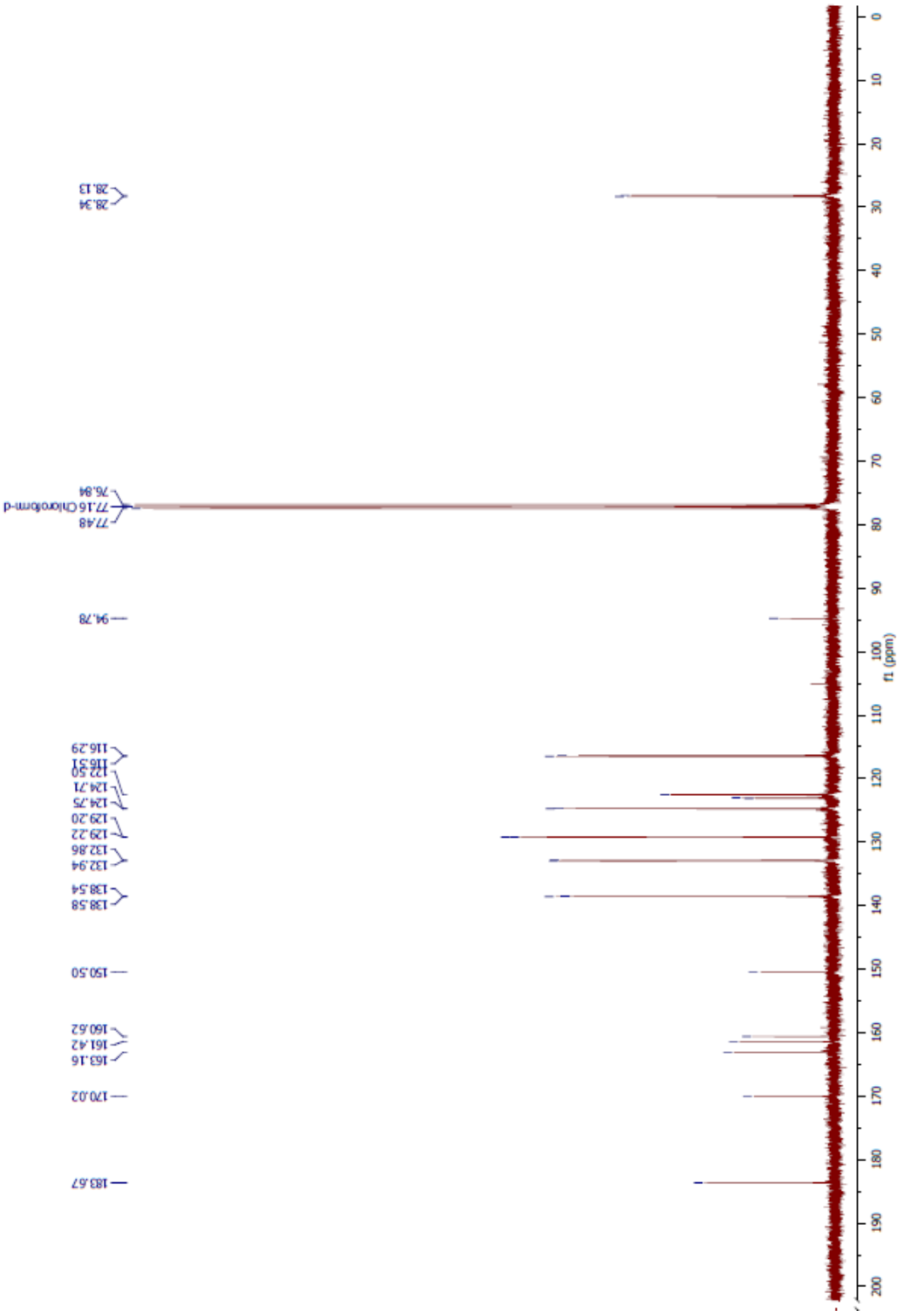


11

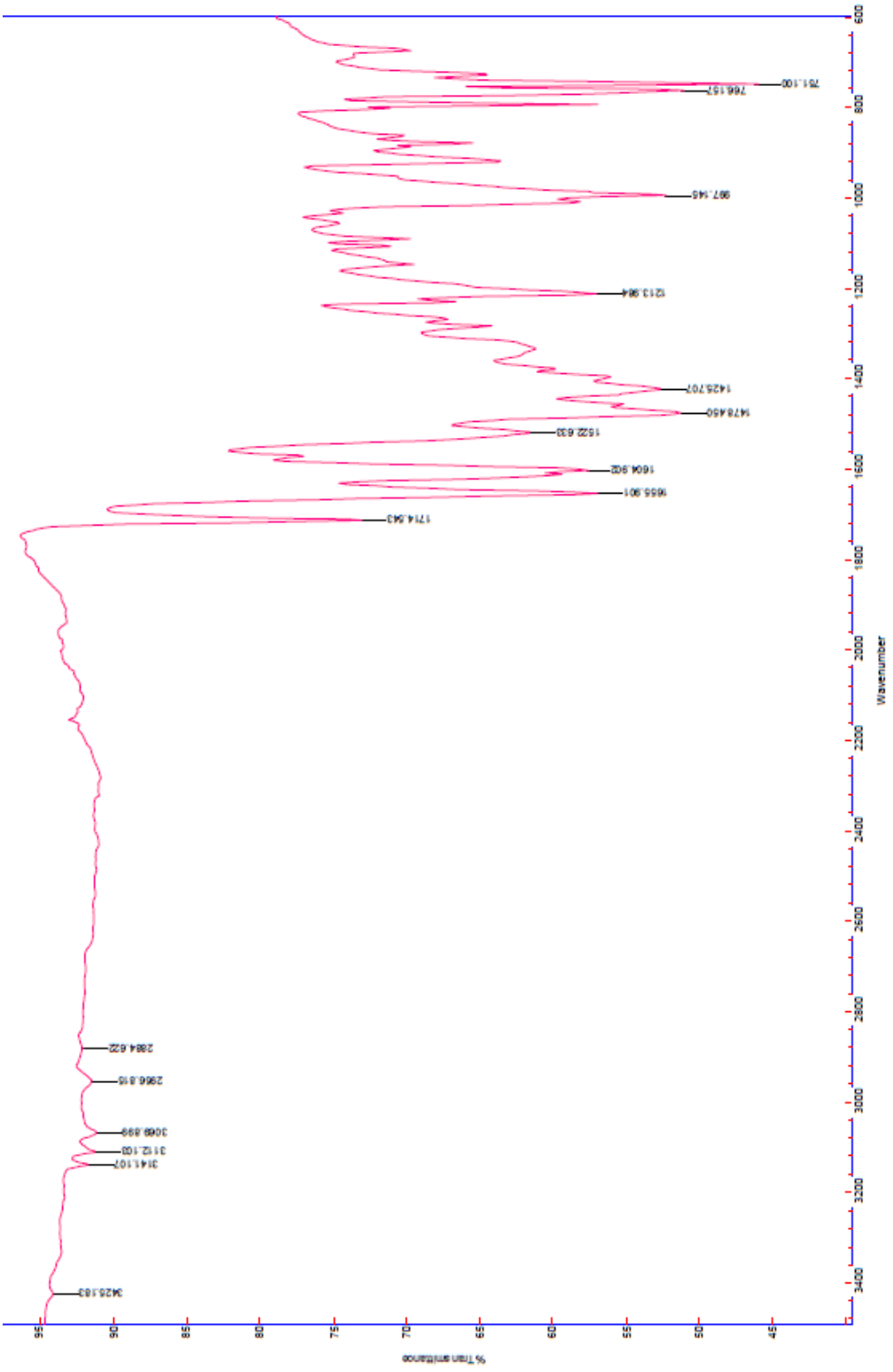
A.9.1 ^{1}H NMR spectrum of 11



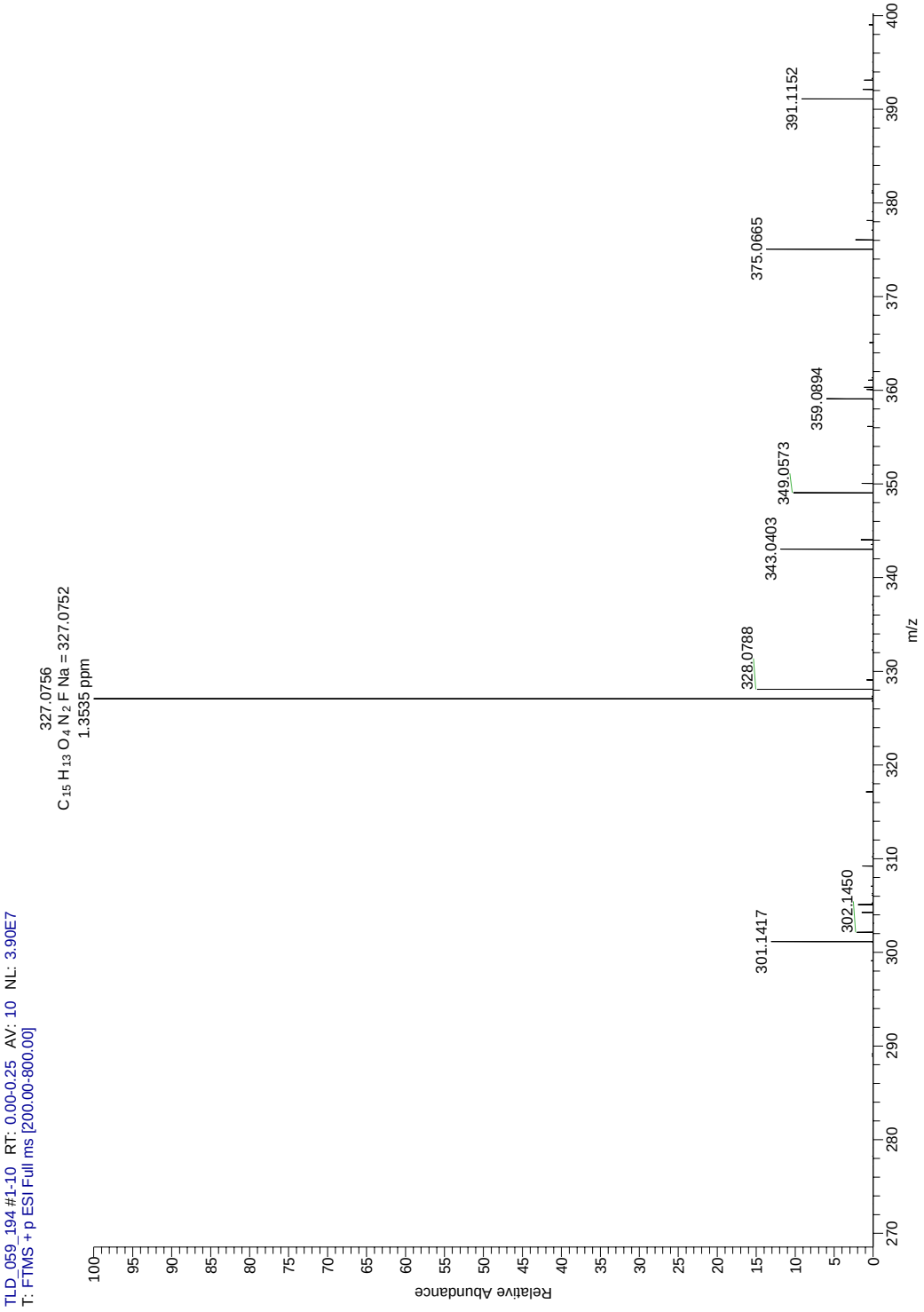
A.9.2 ^{13}C NMR spectrum of 11



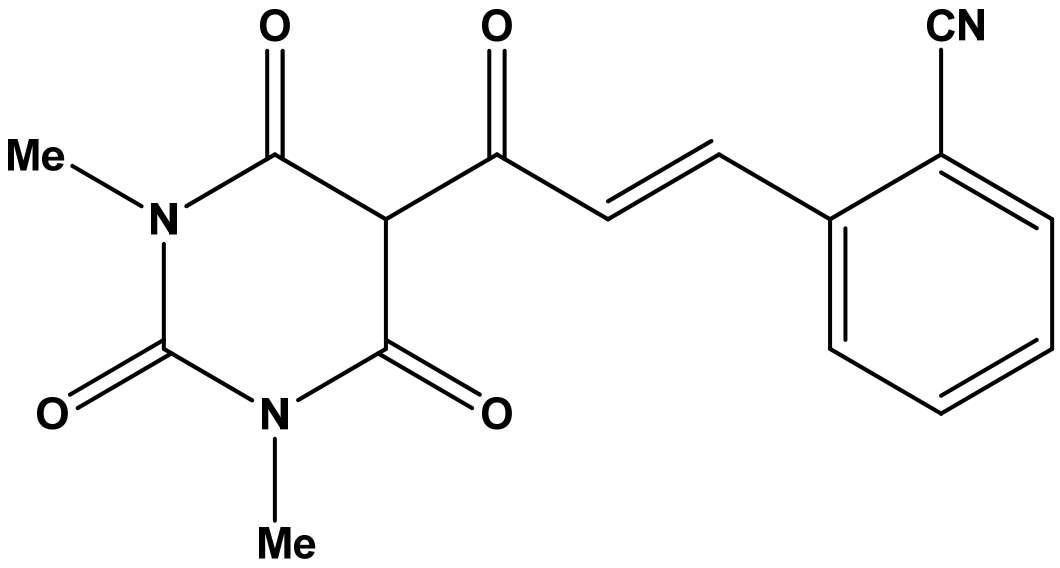
A.9.3 IR spectrum of 11



A.9.4 HRMS of 11

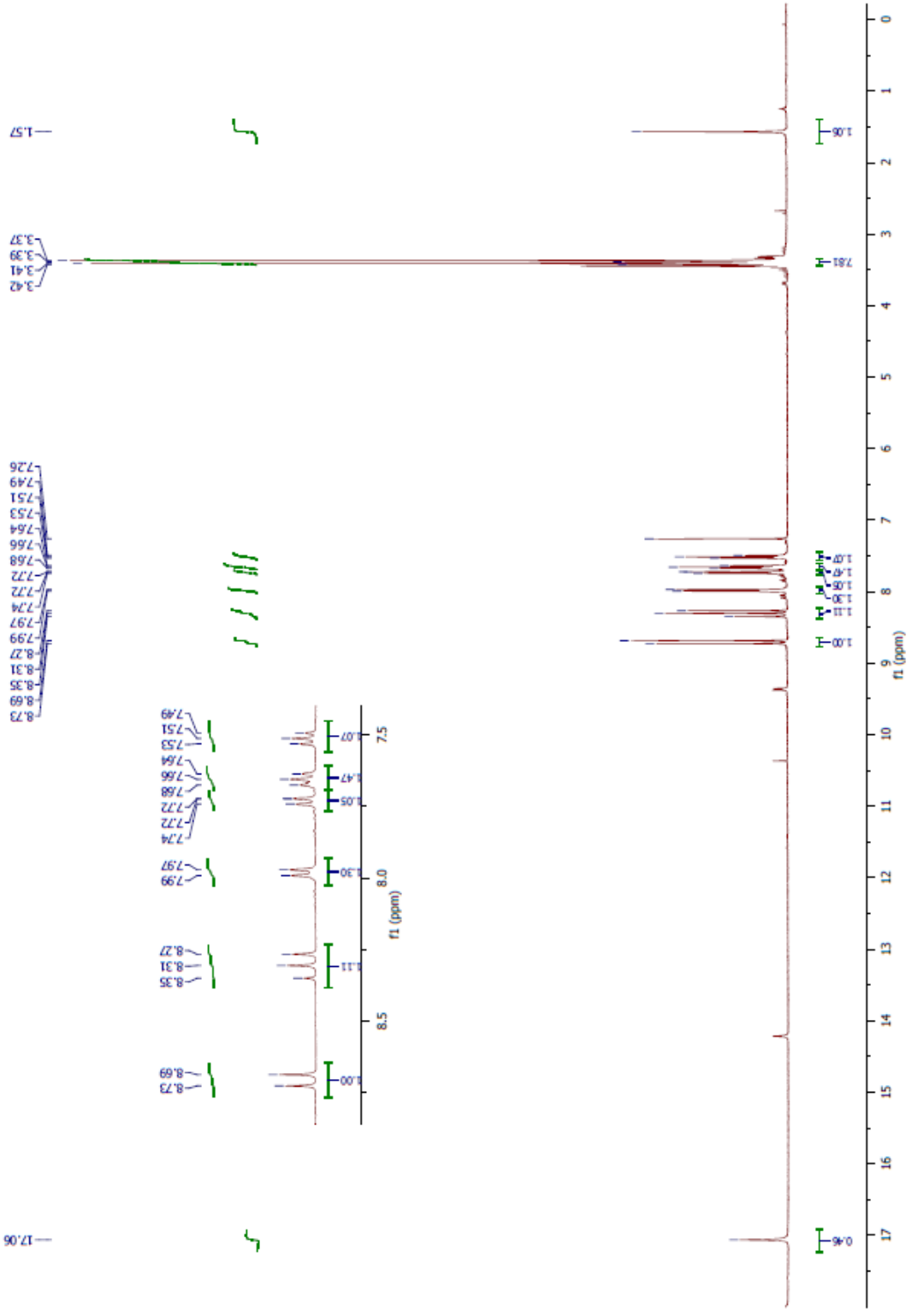


A.10 Spectroscopic data for 12

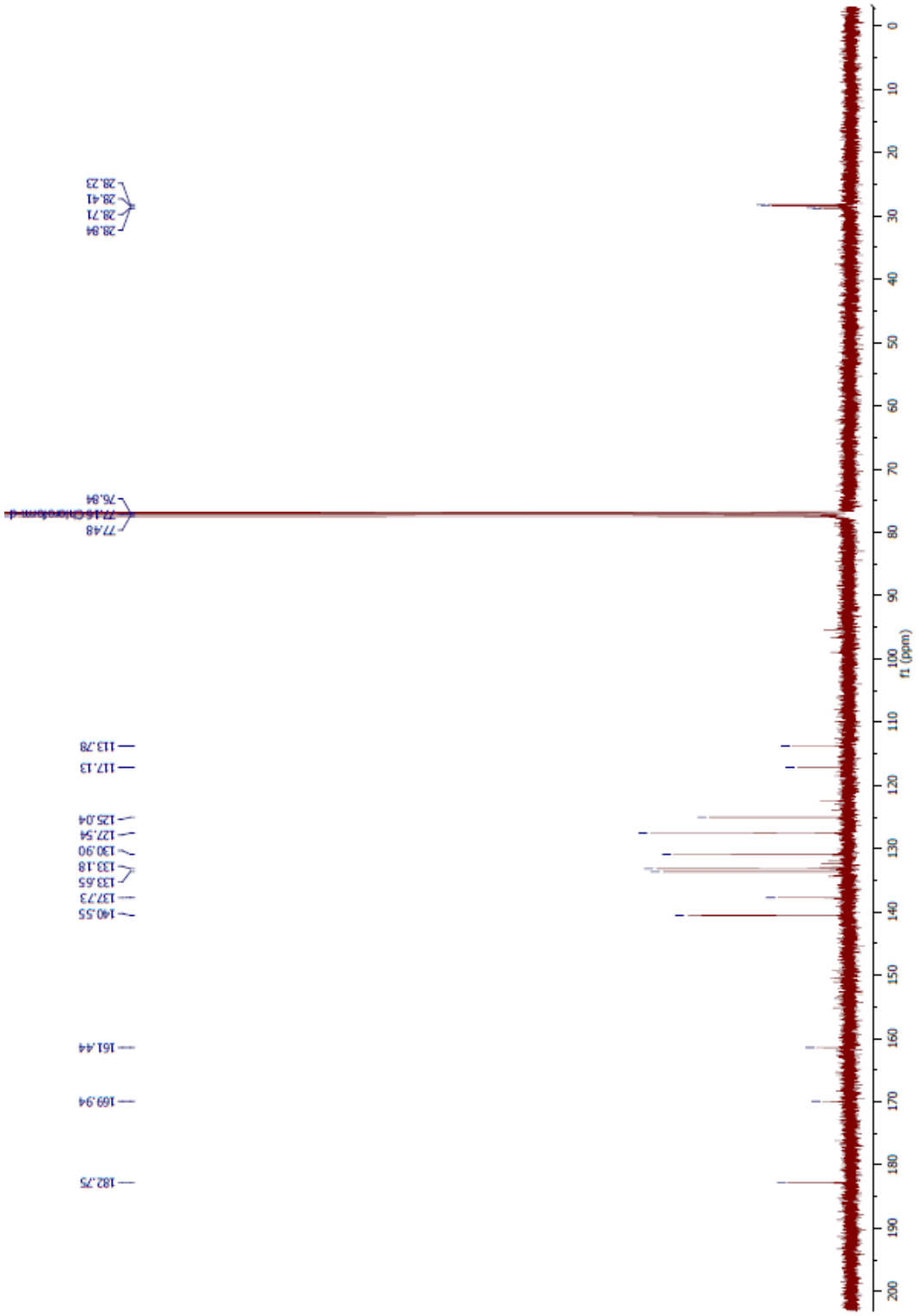


12

A.10.1 ^{1}H NMR spectrum of 12



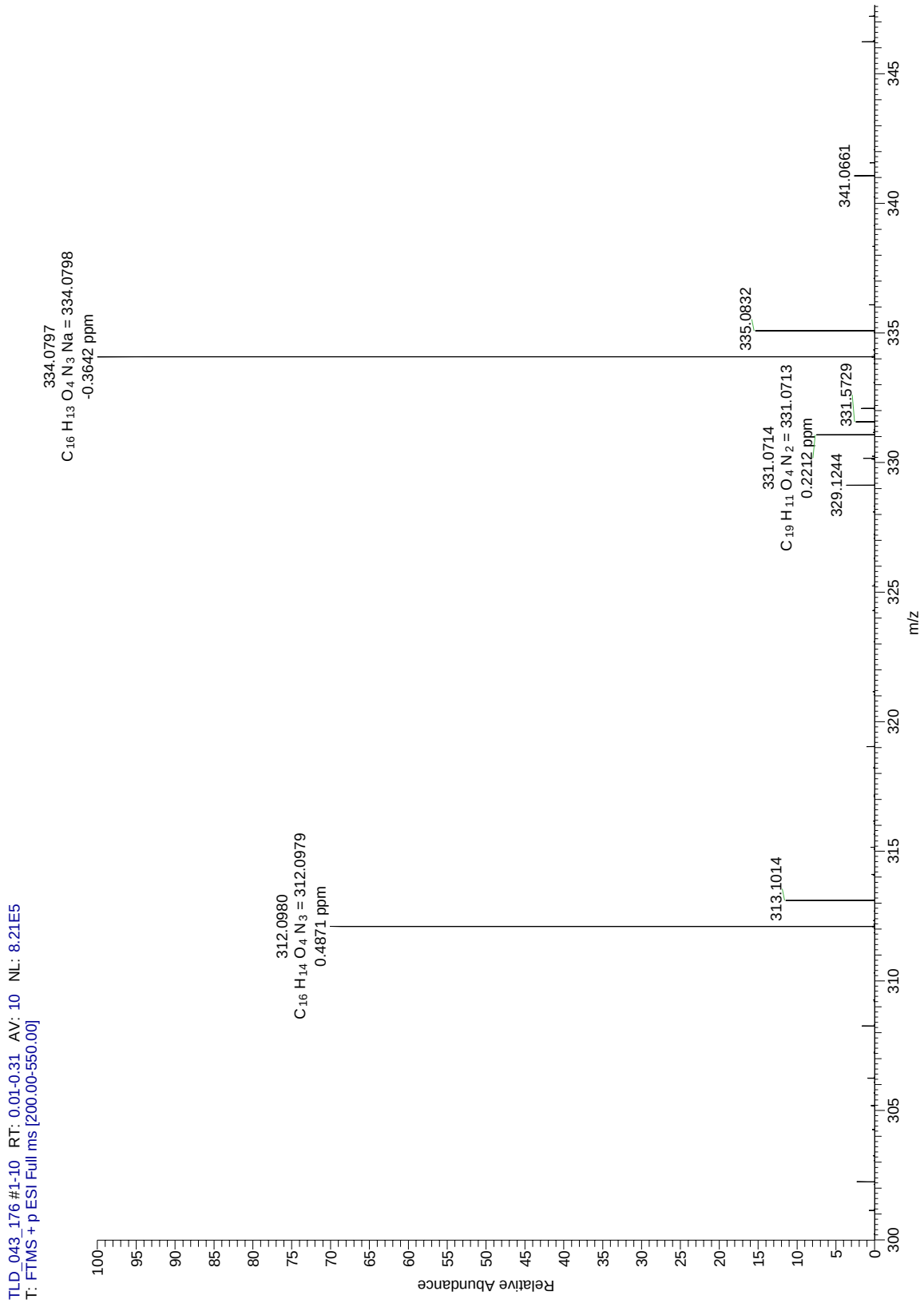
A.10.2 ^{13}C NMR spectrum of 12



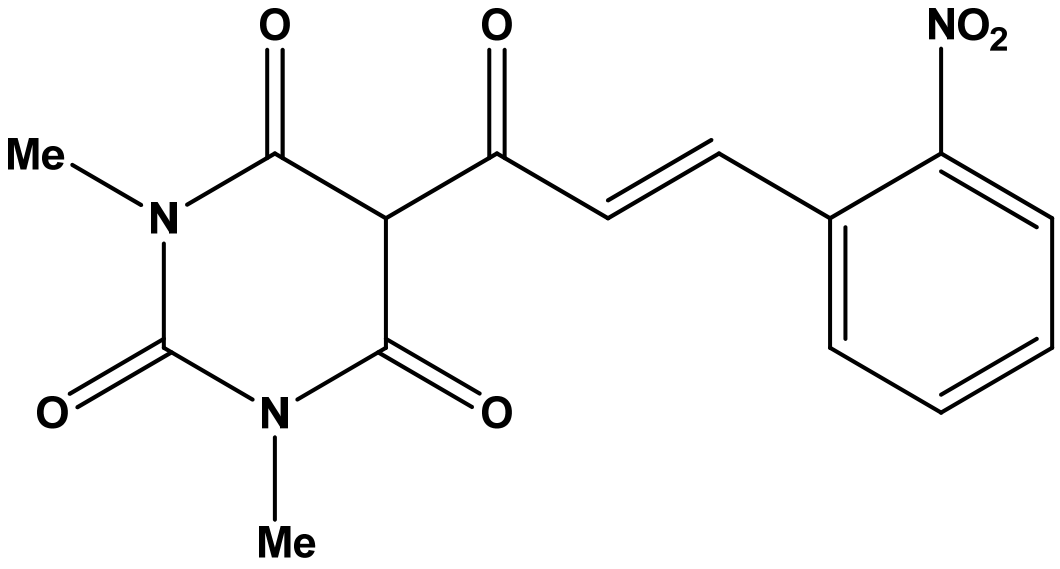
A.10.3 IR spectrum of 12

A.10.3 IR spectrum of 12

A.10.4 HRMS of 12

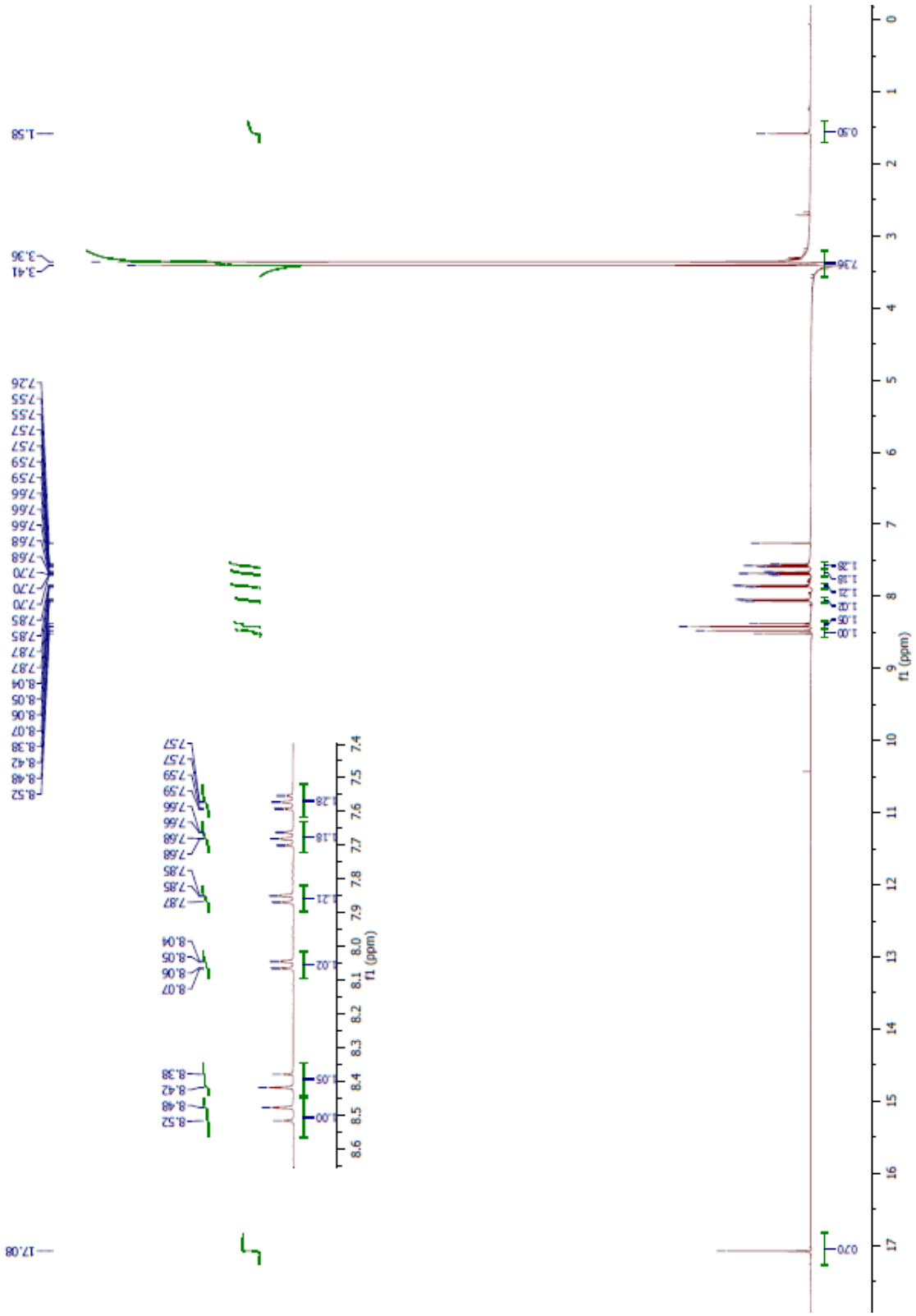


A.11 Spectroscopic data for 13

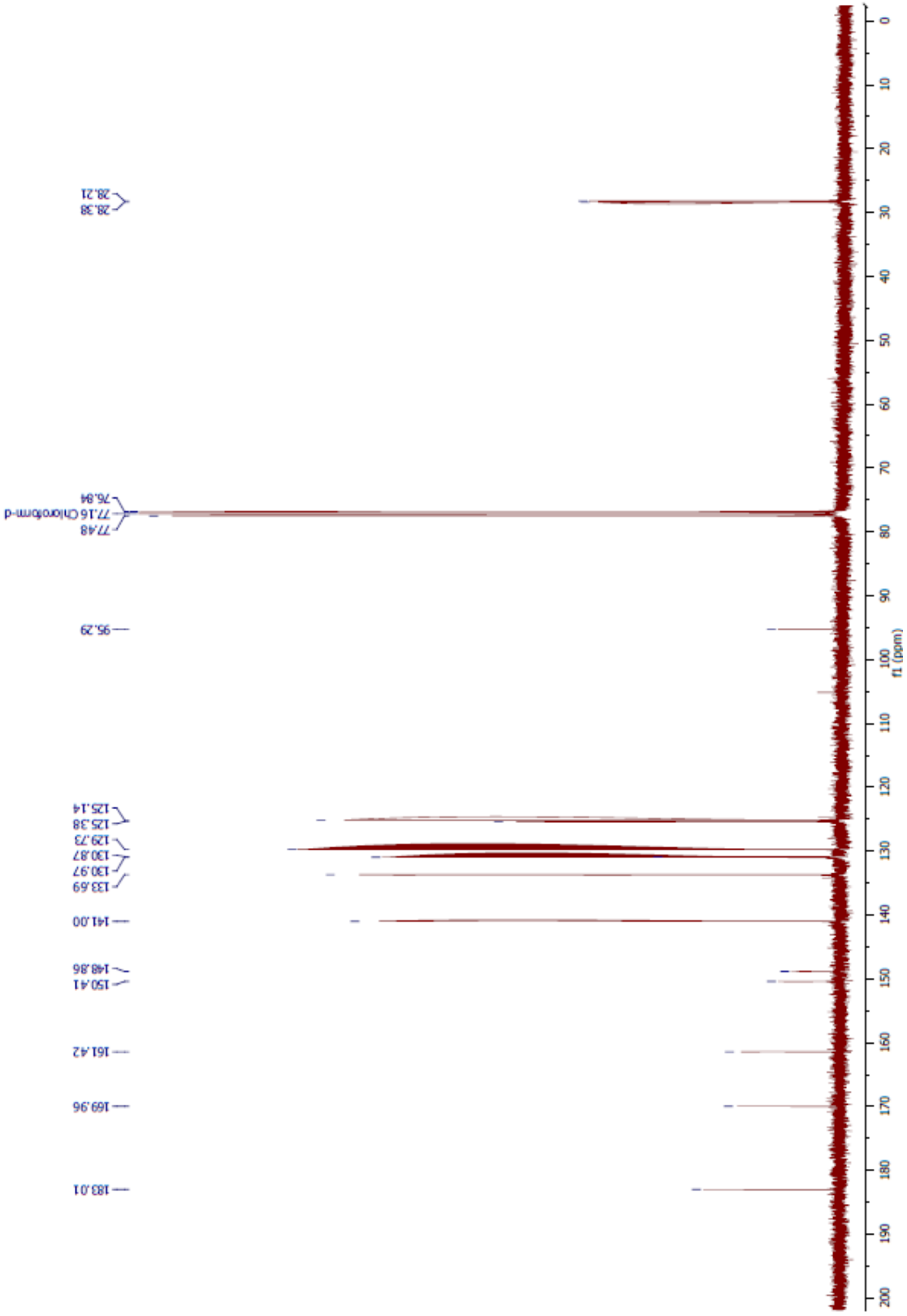


13

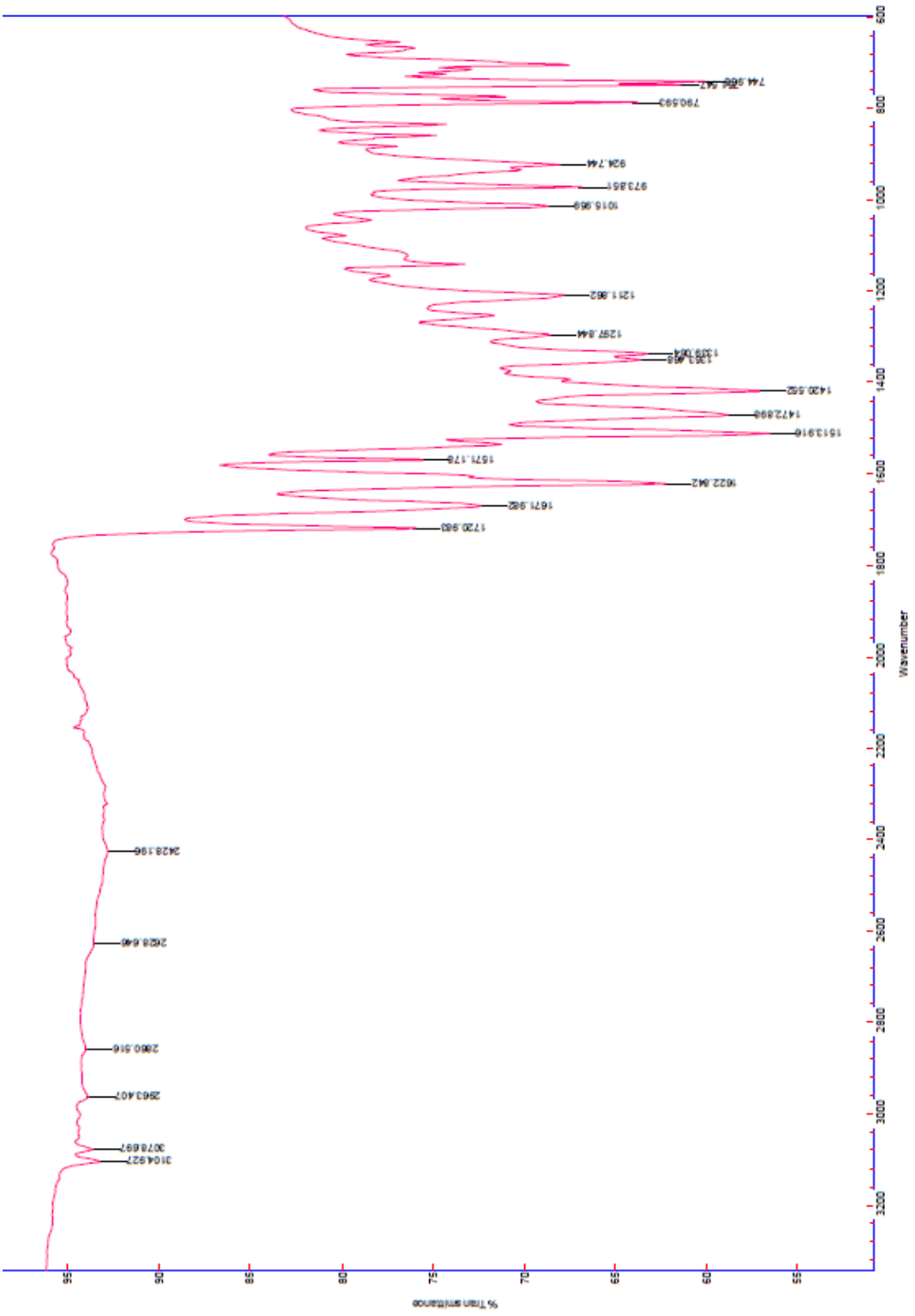
A.11.1 ^{1}H NMR spectrum of 13



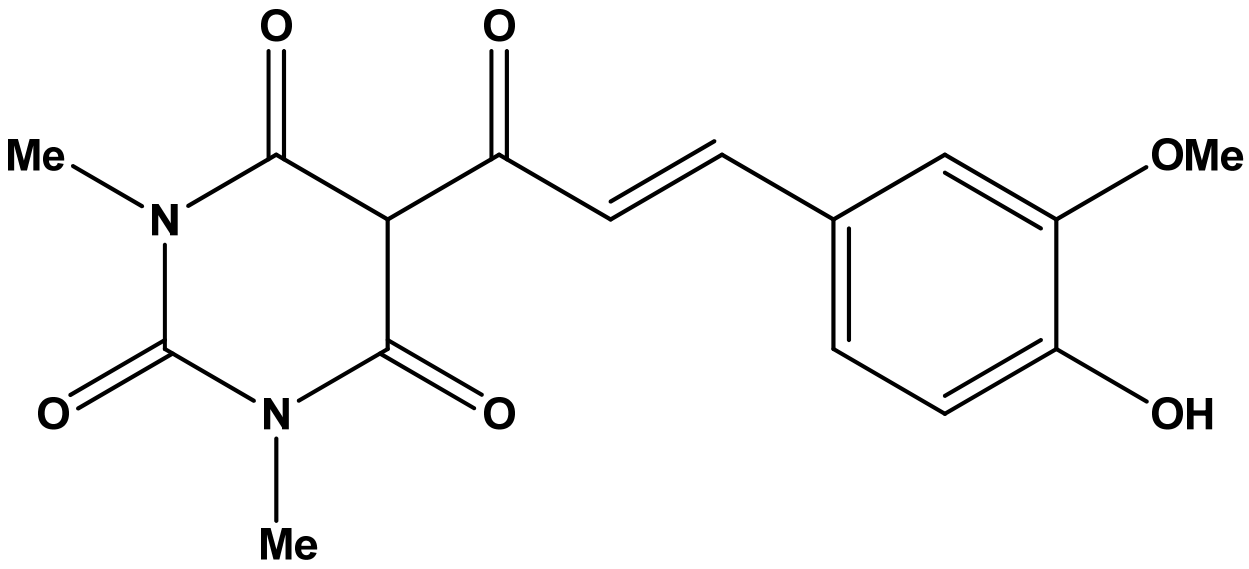
A.11.2 ^{13}C NMR spectrum of 13



A.11.3 IR spectrum of 13

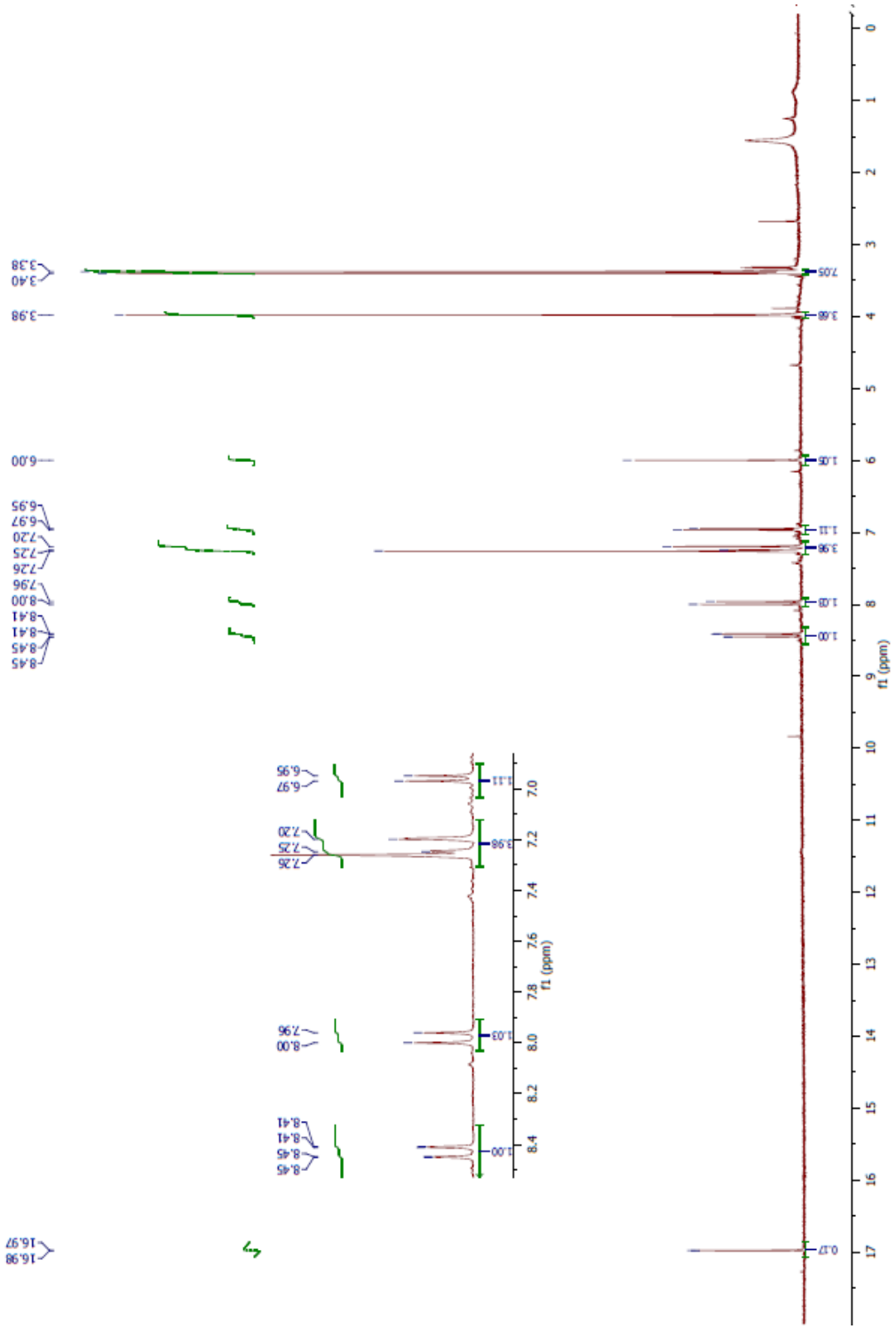


A.12 Spectroscopic data for 14

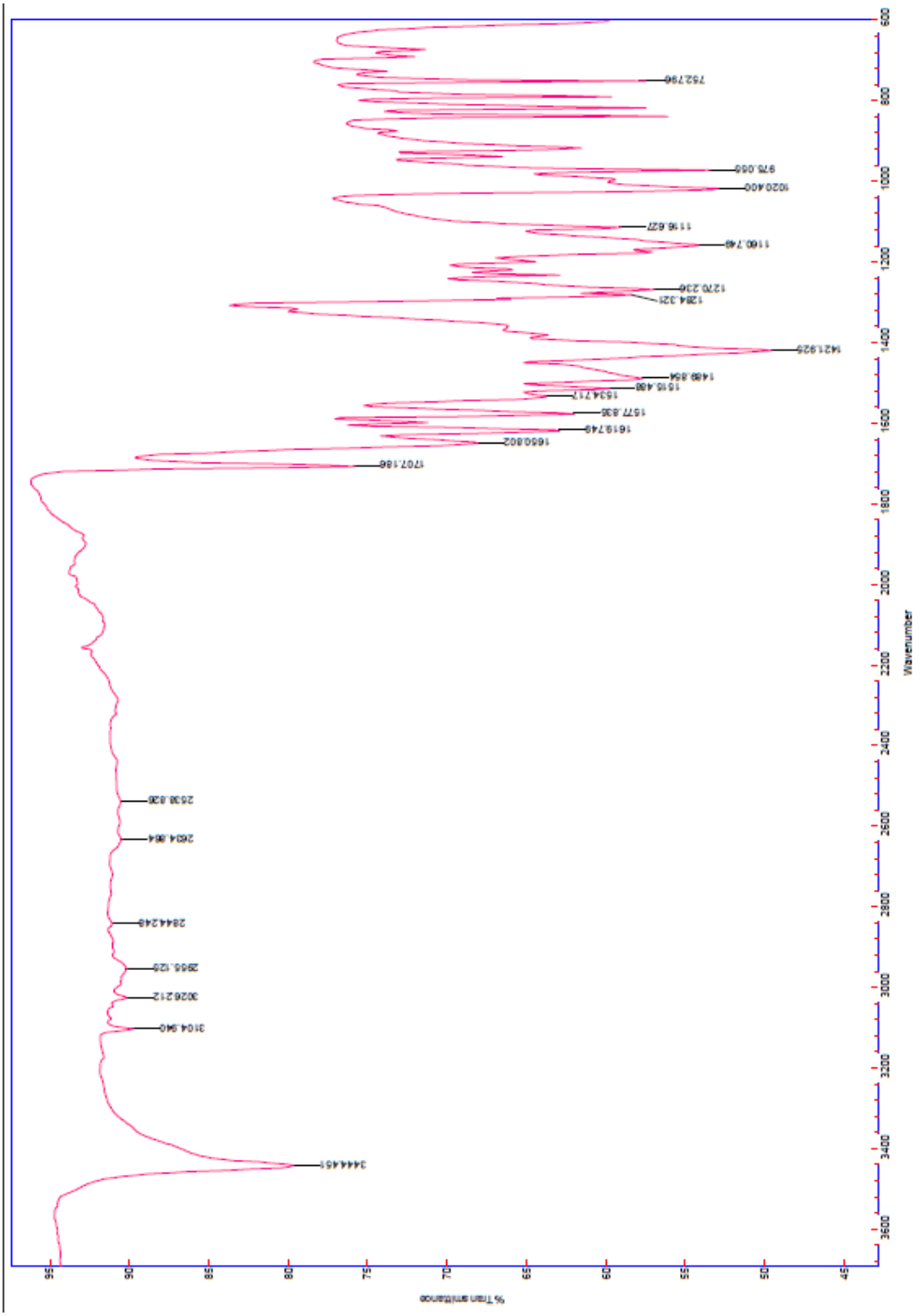


14

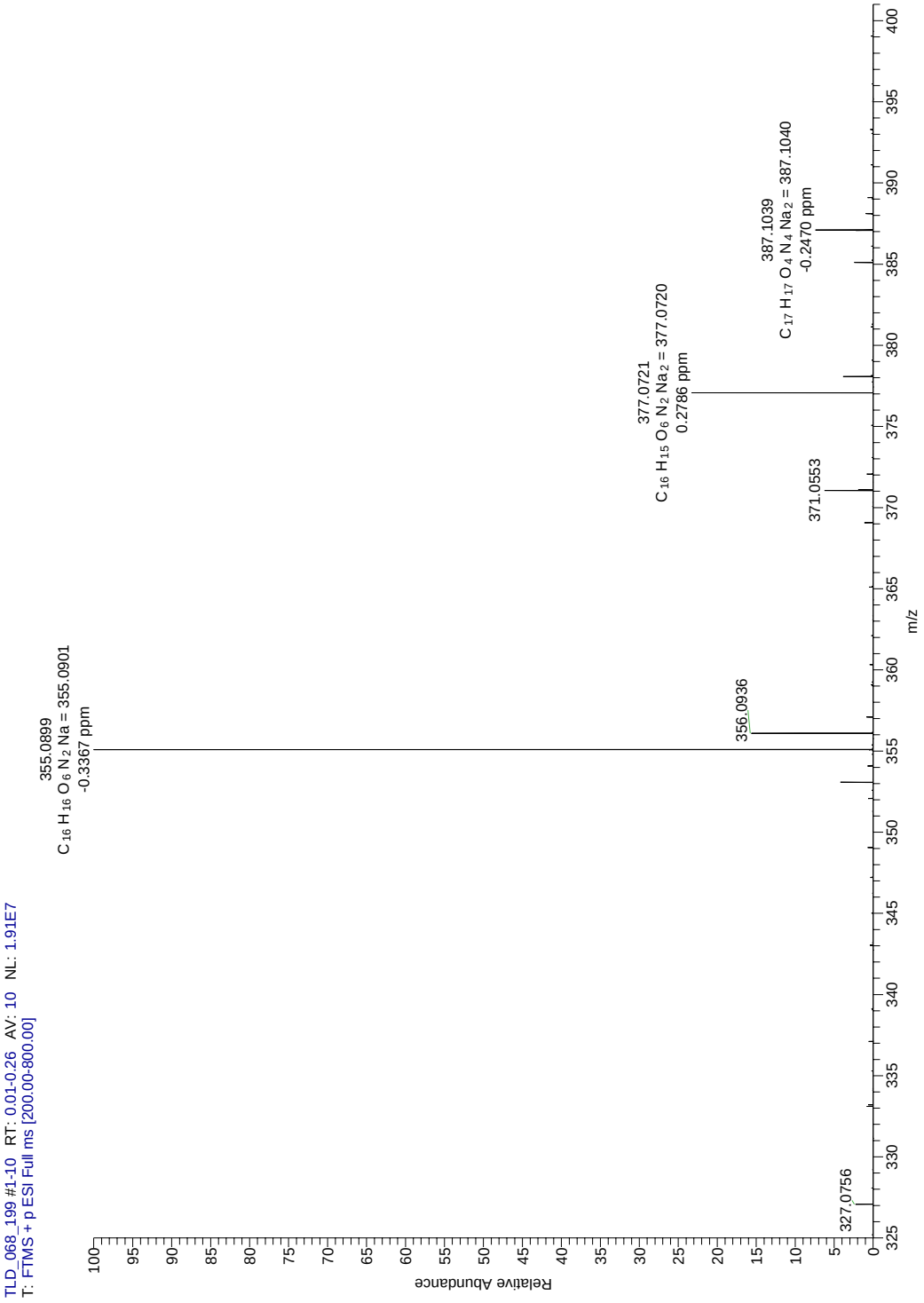
A.12.1 ^{1}H NMR spectrum of 14



A.12.2 IR spectrum of 14

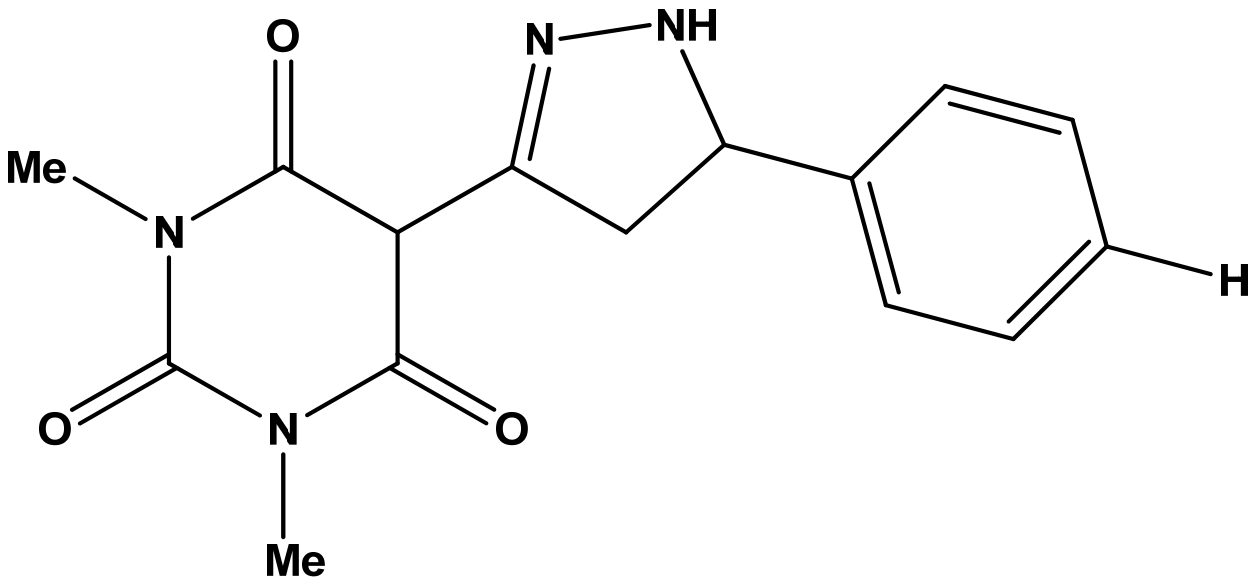


A.12.3 HRMS of 14



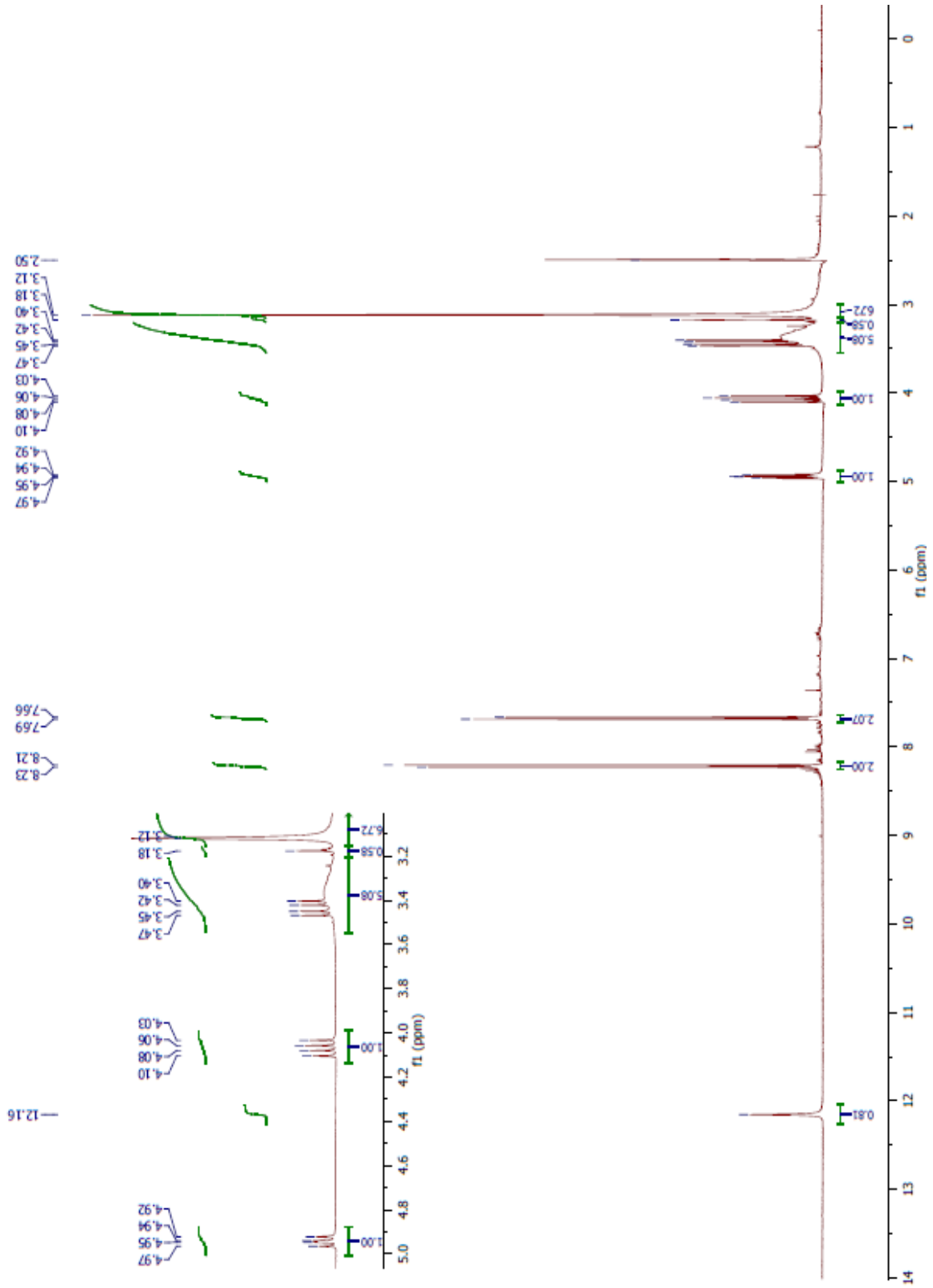
B Spectroscopic data for 5-membered heterocyles 15-38

B.1 Spectroscopic data for 15

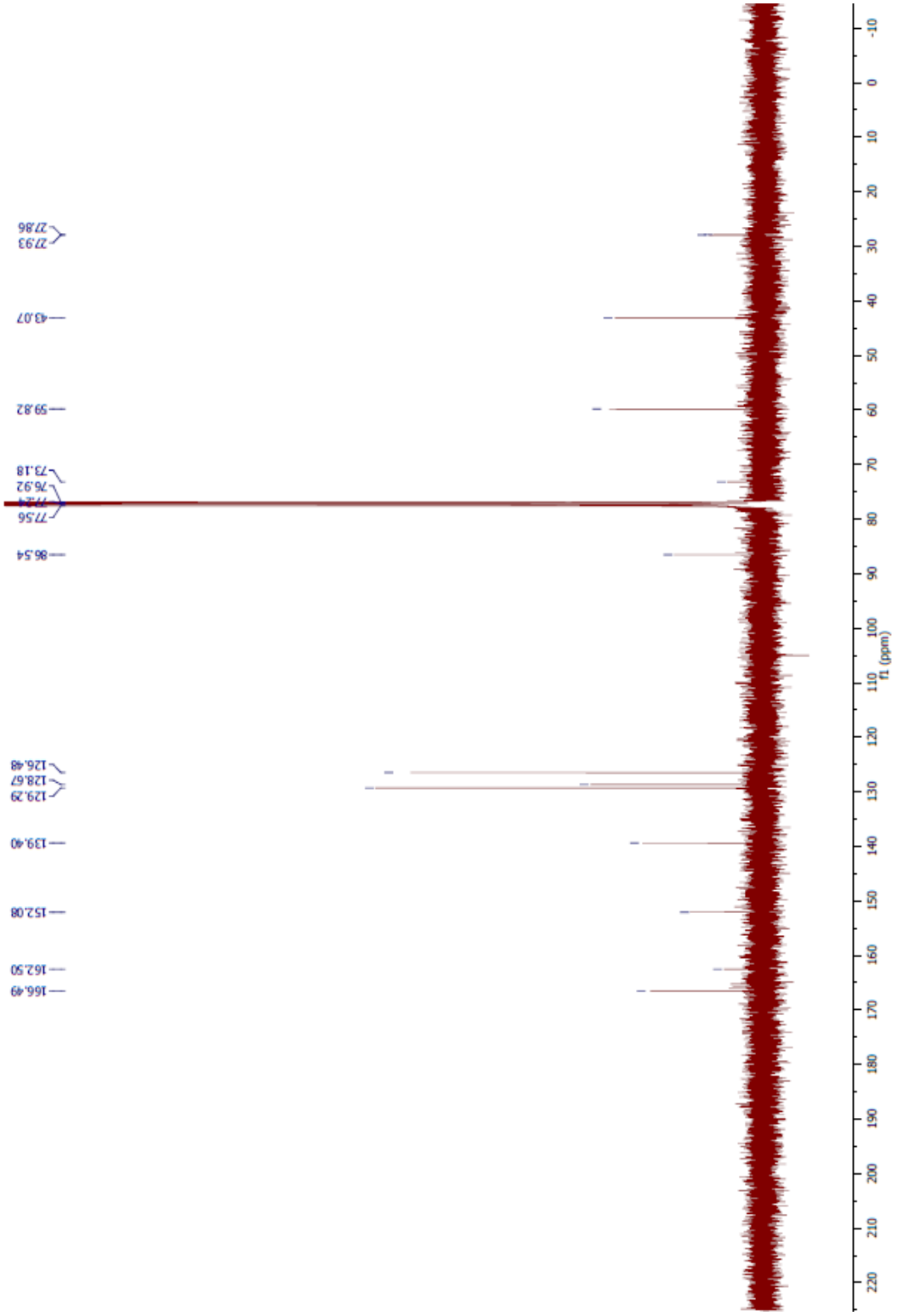


15

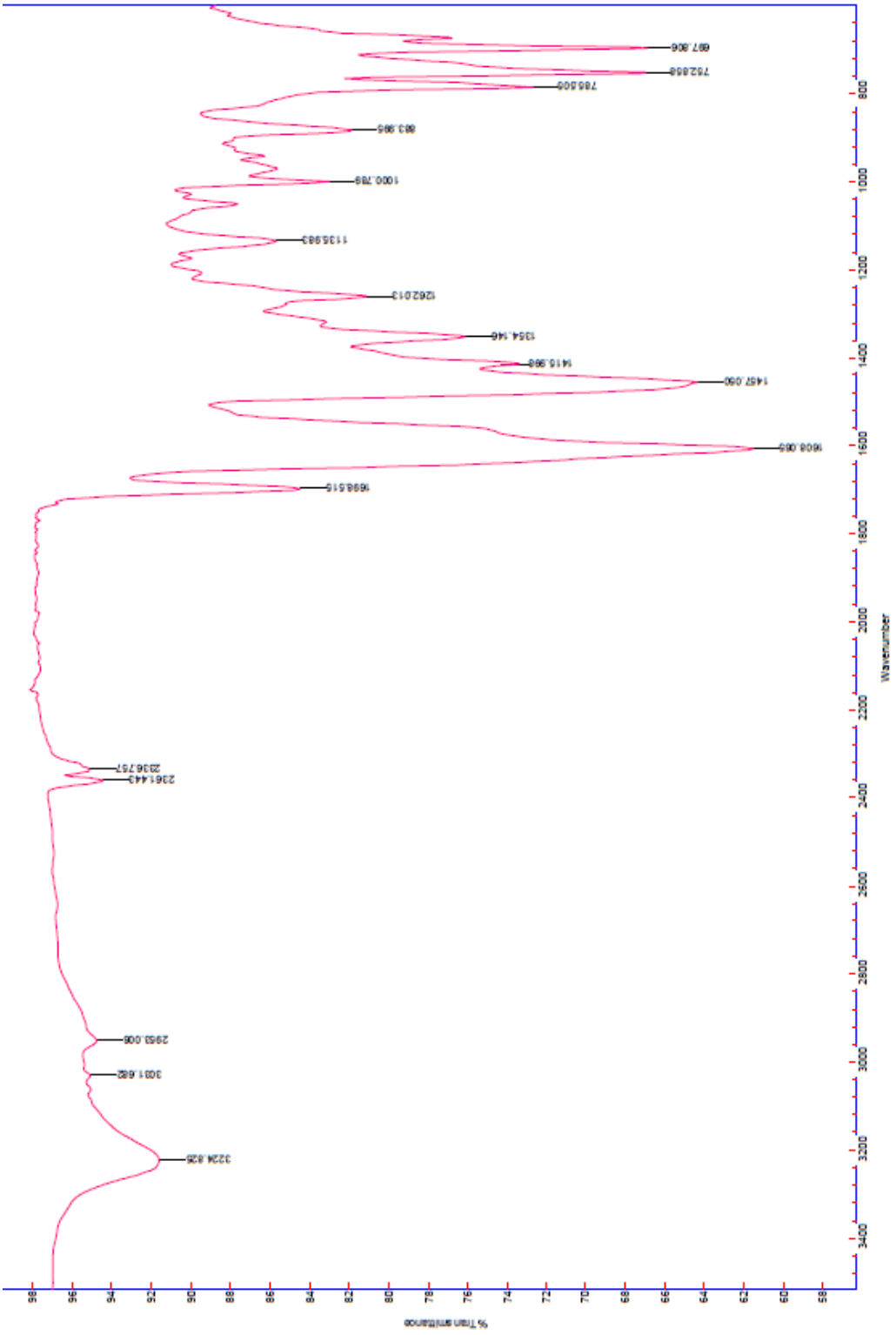
B.1.1 ^{1}H NMR spectrum of 15



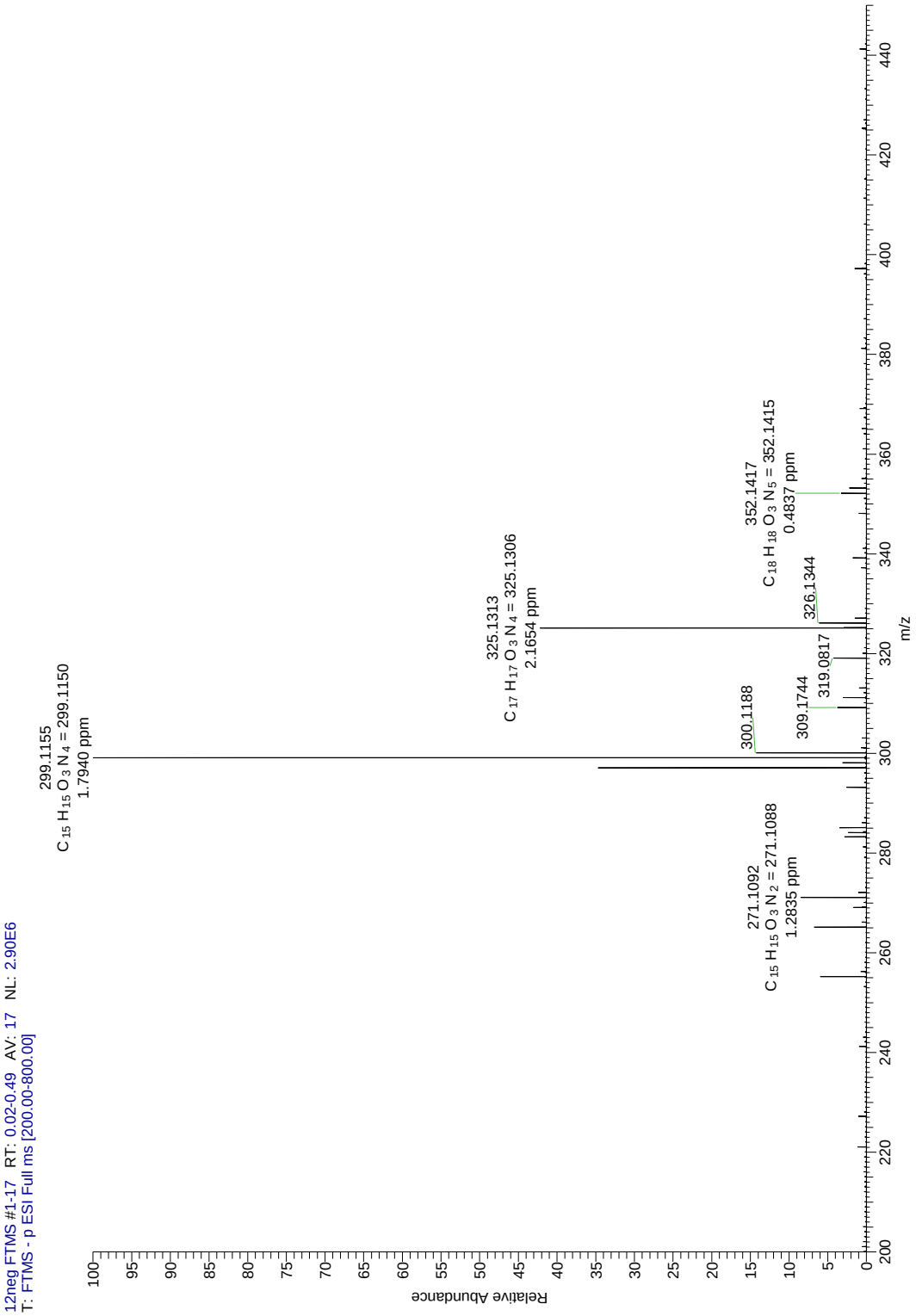
B.1.2 ^{13}C NMR spectrum of 15



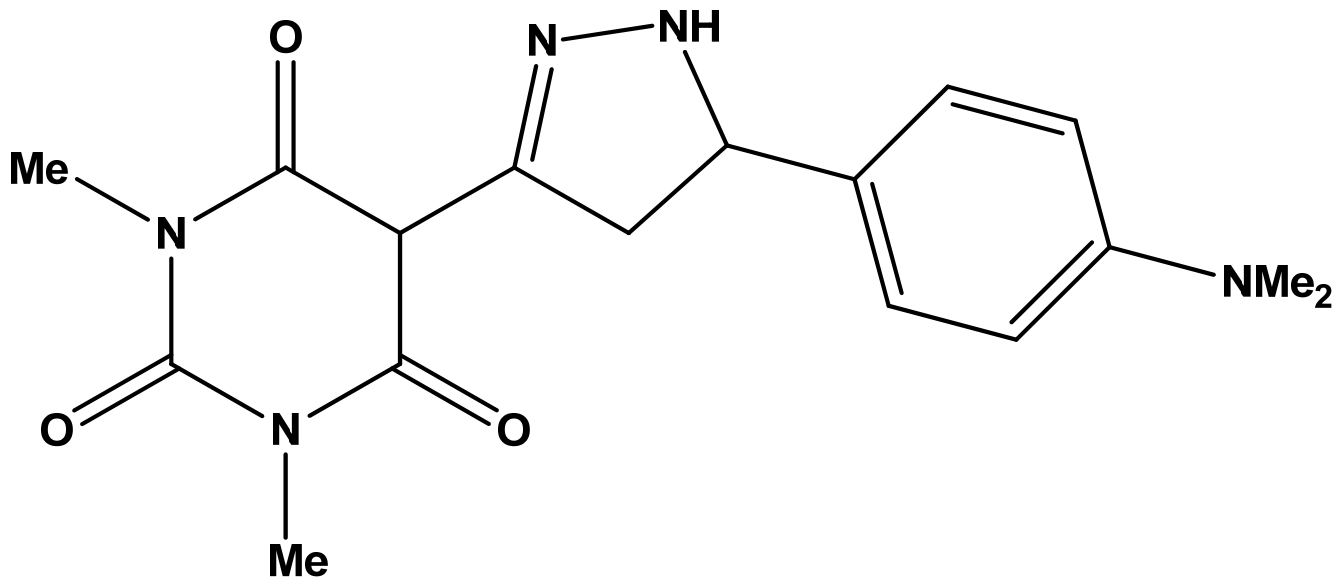
B.1.3 IR spectrum of 15



B.1.4 HRMS of 15

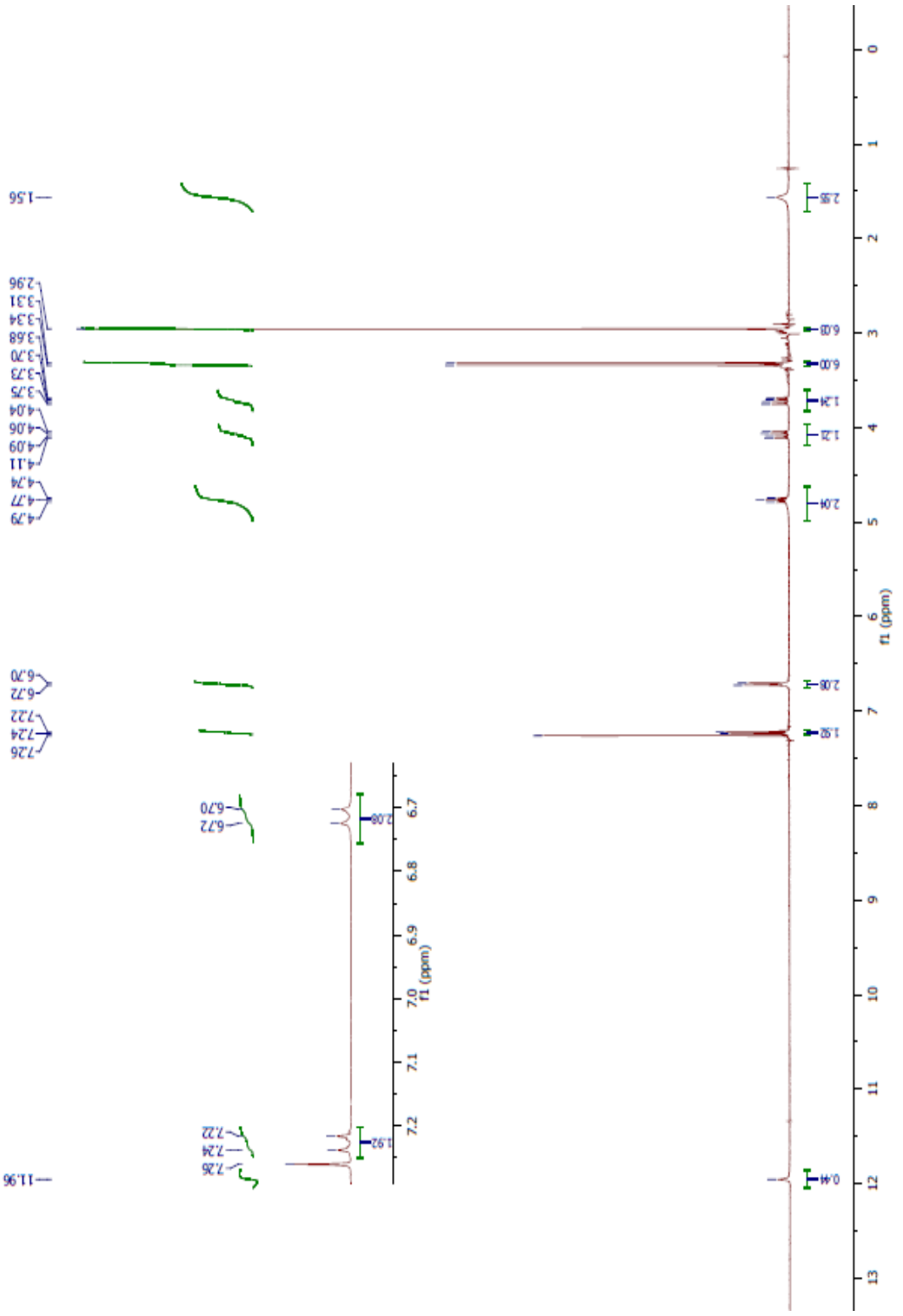


B.2 Spectroscopic data for 16

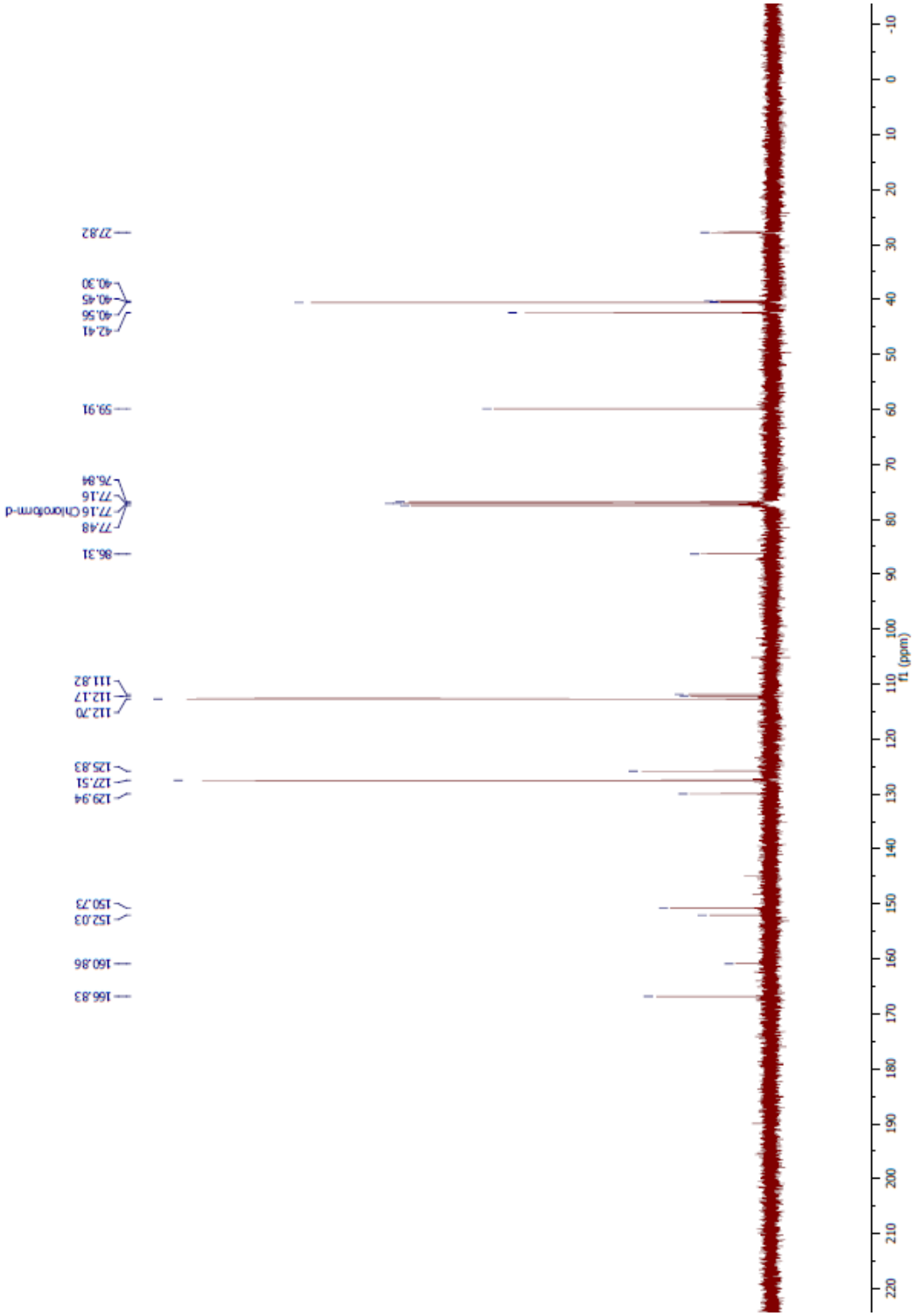


16

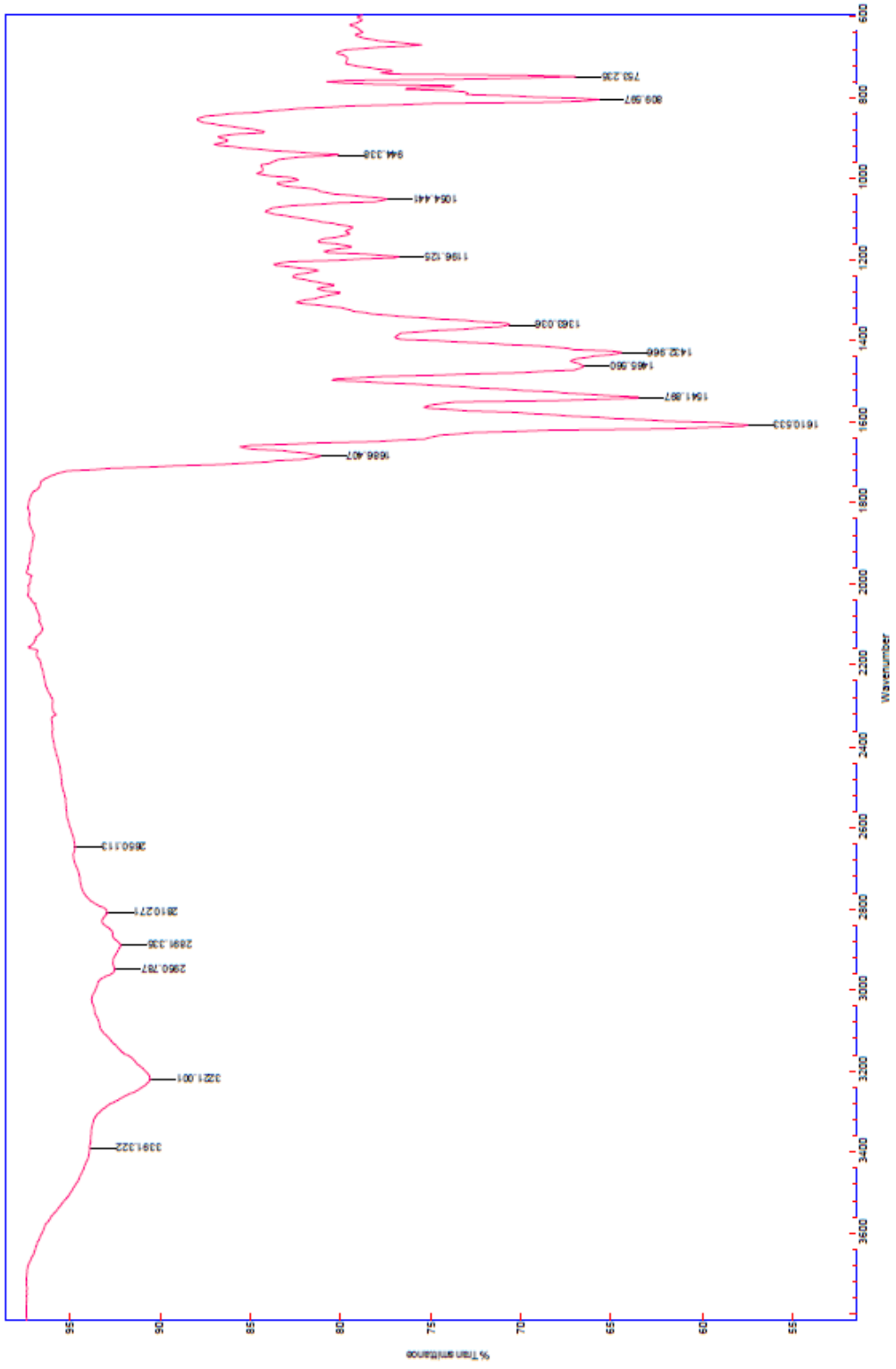
B.2.1 ^{1}H NMR spectrum of 16



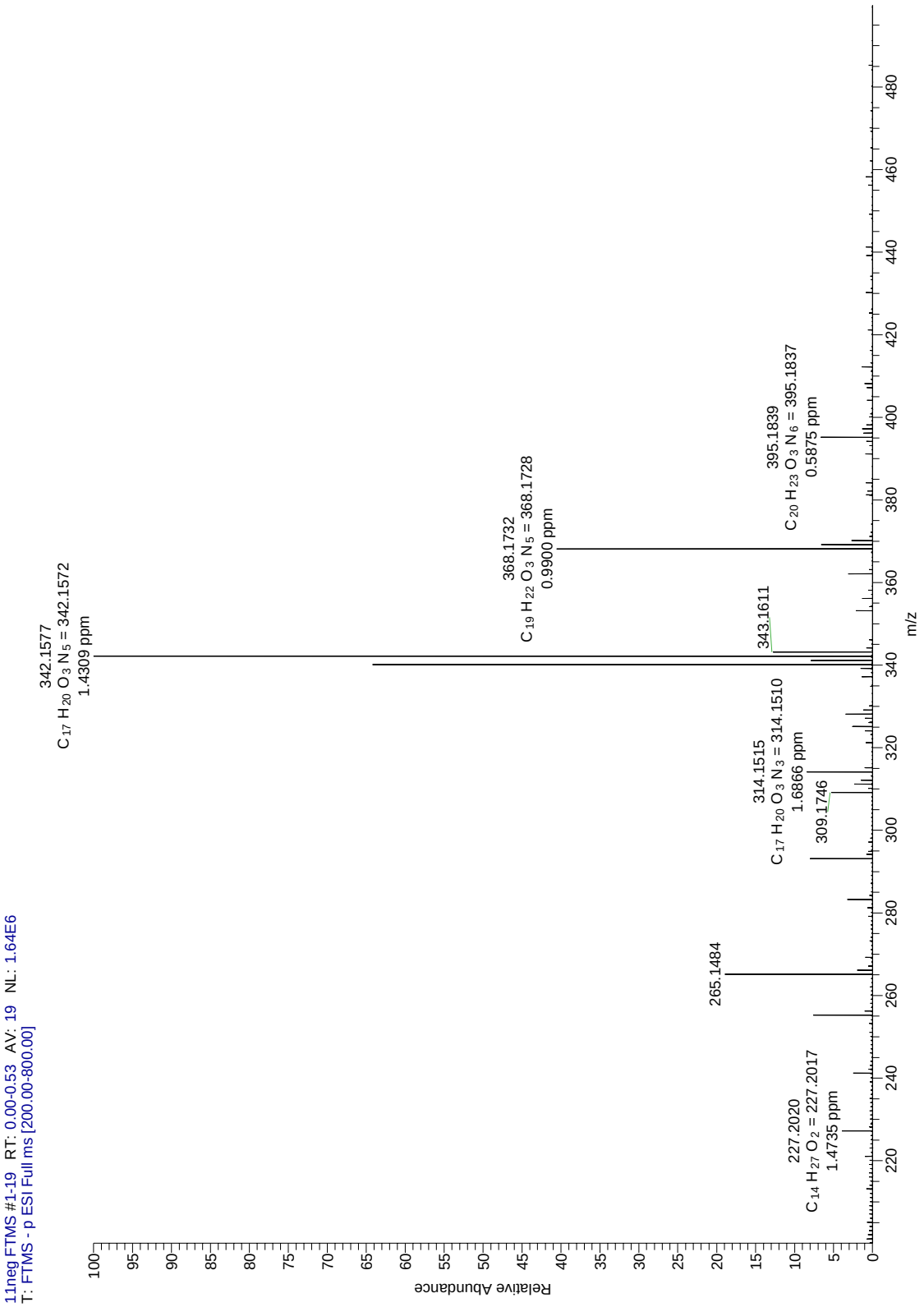
B.2.2 ^{13}C NMR spectrum of 16



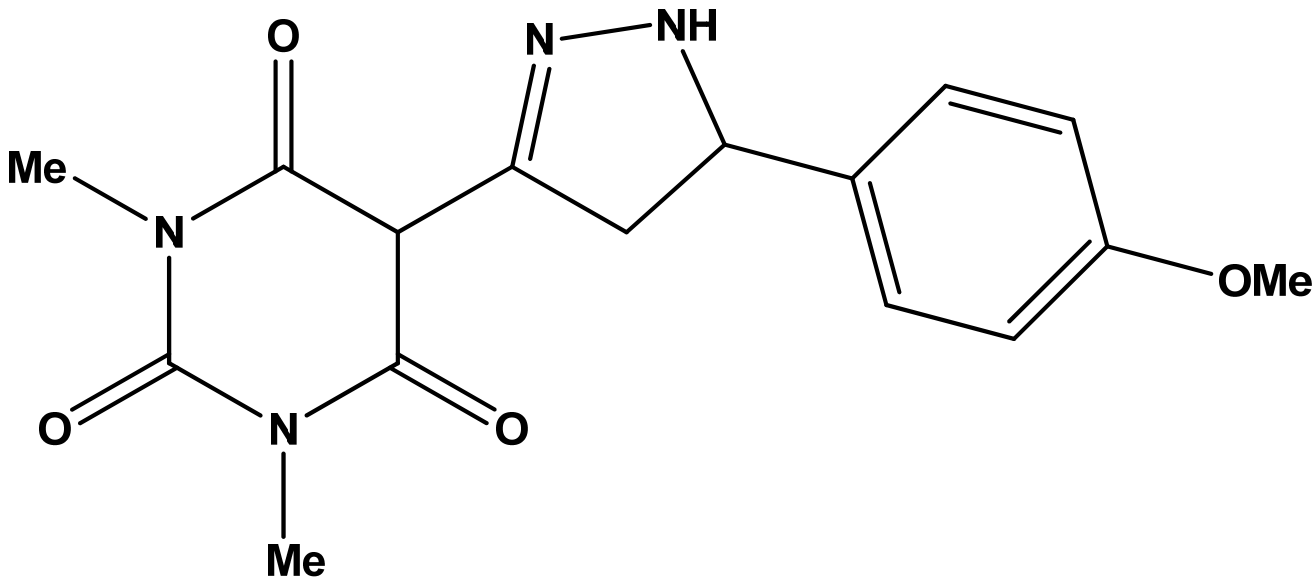
B.2.3 IR spectrum of 16



B.2.4 HRMS of 16

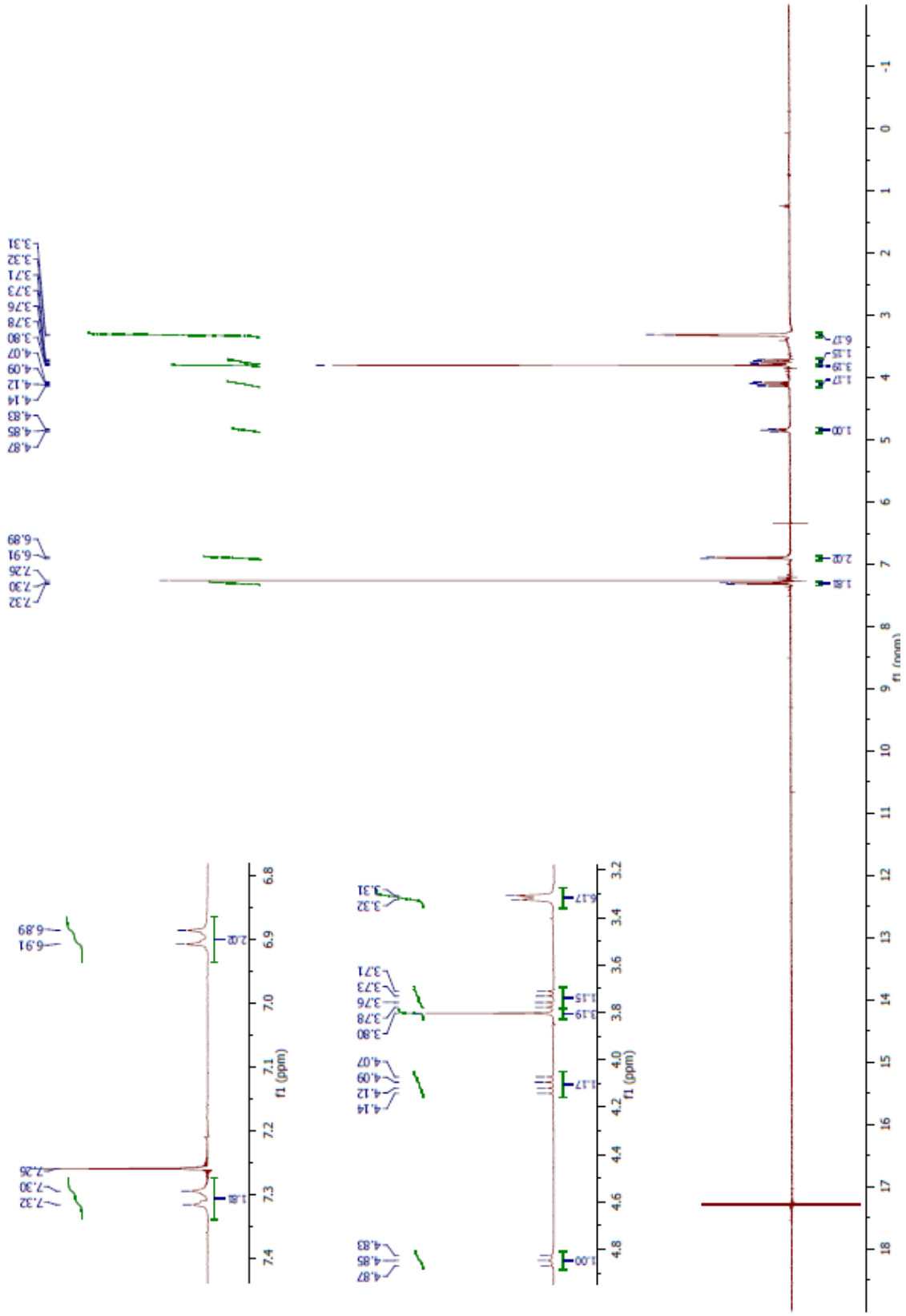


B.3 Spectroscopic data for 17

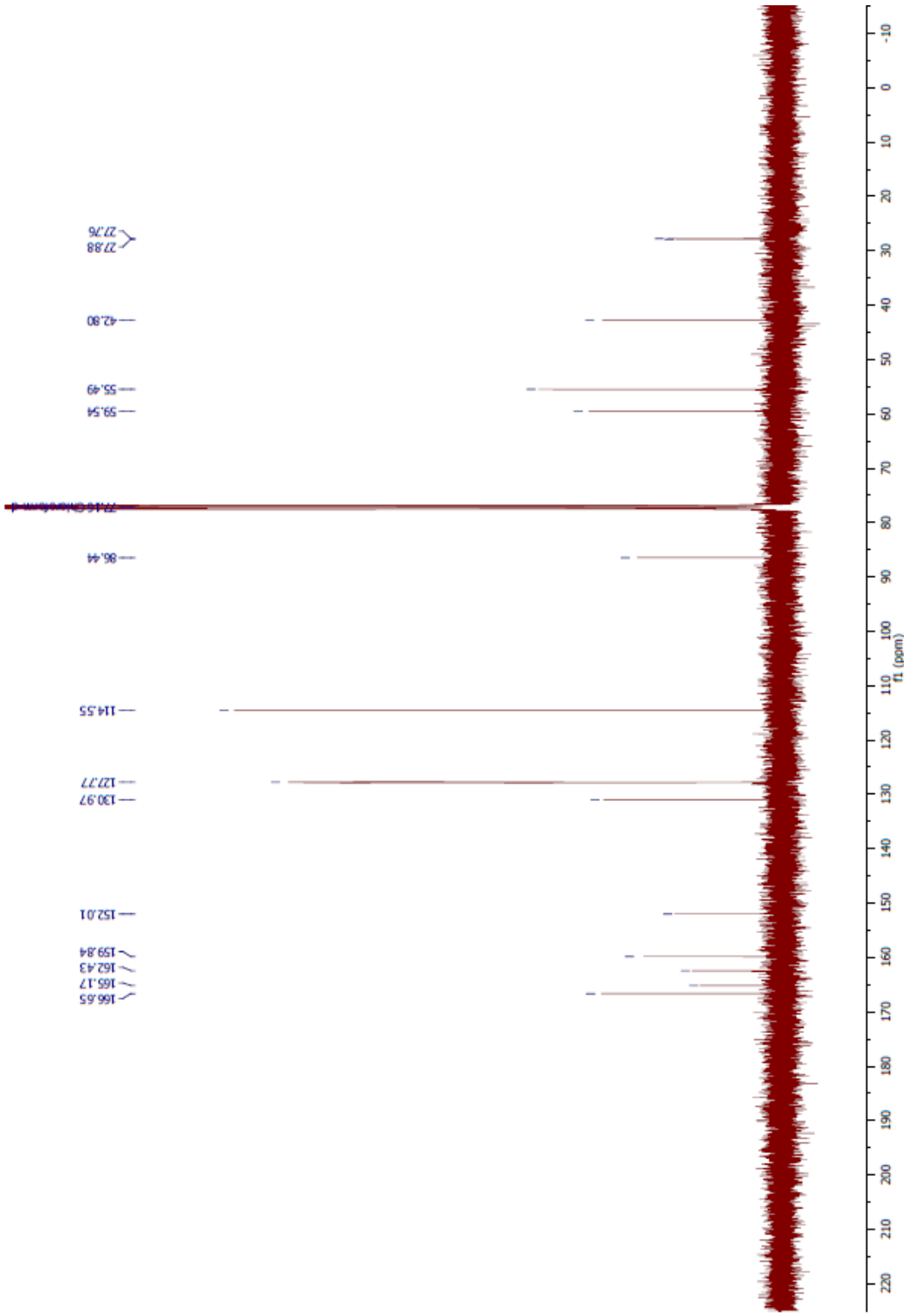


17

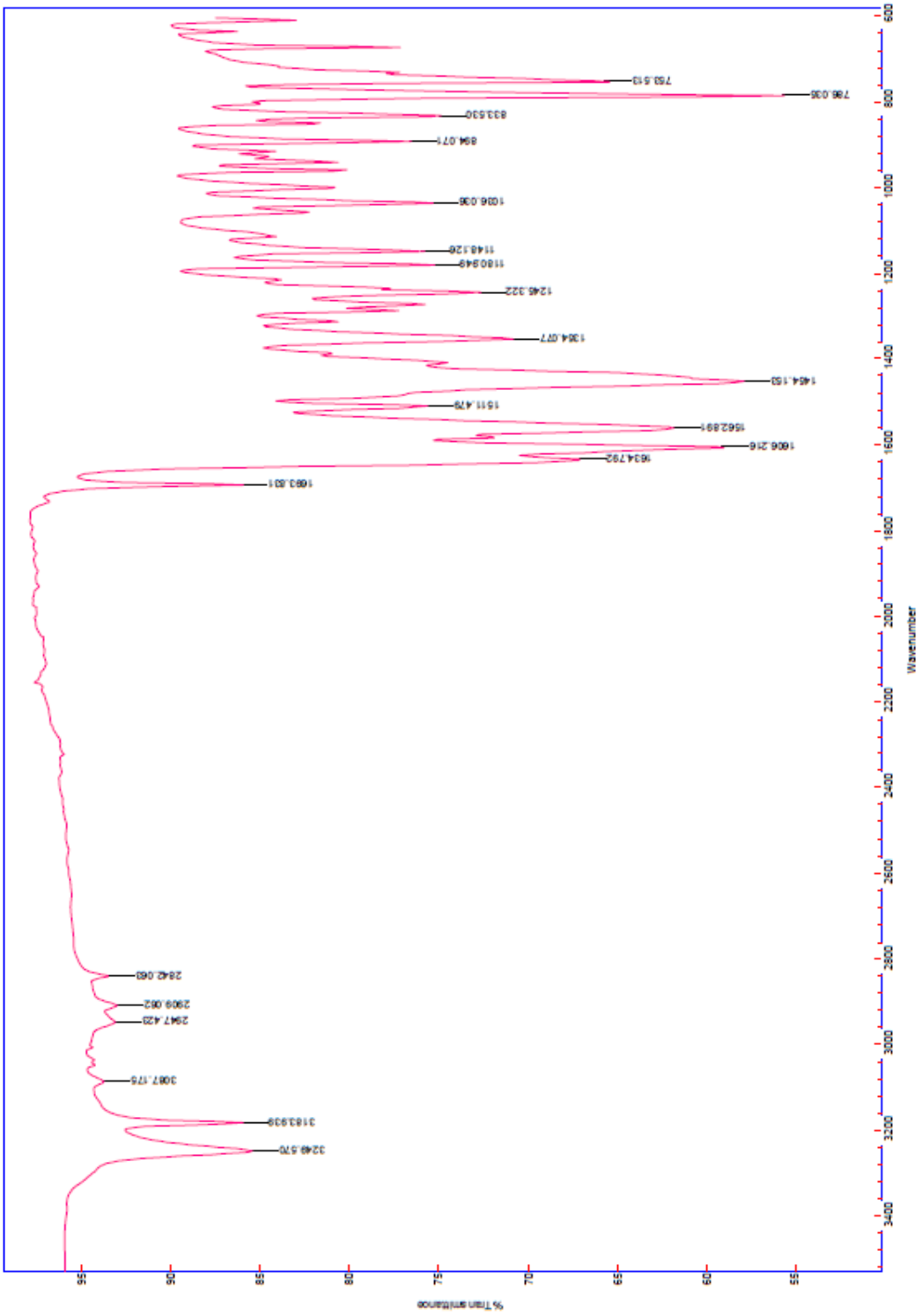
B.3.1 ^{1}H NMR spectrum of 17



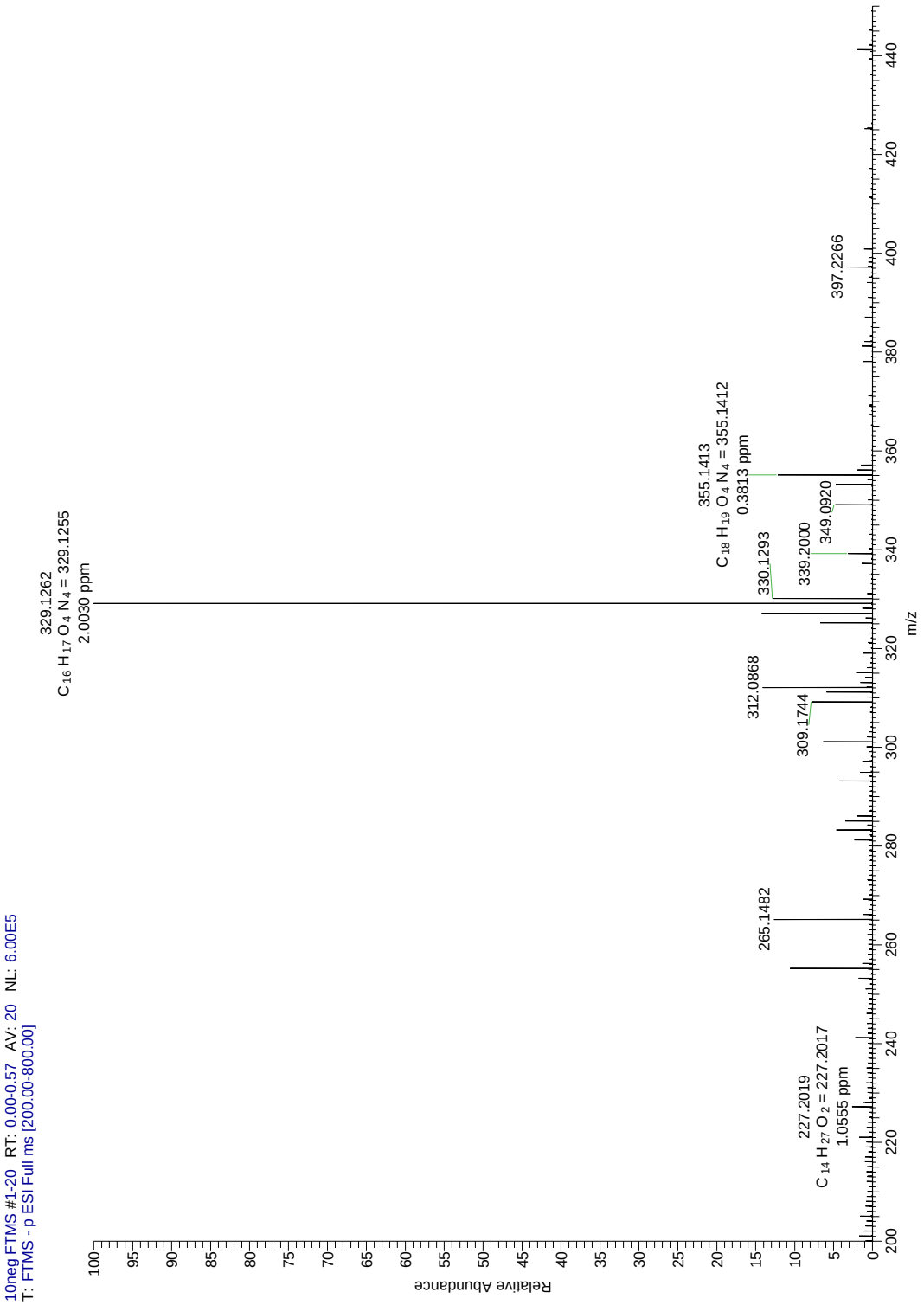
B.3.2 ^{13}C NMR spectrum of 17



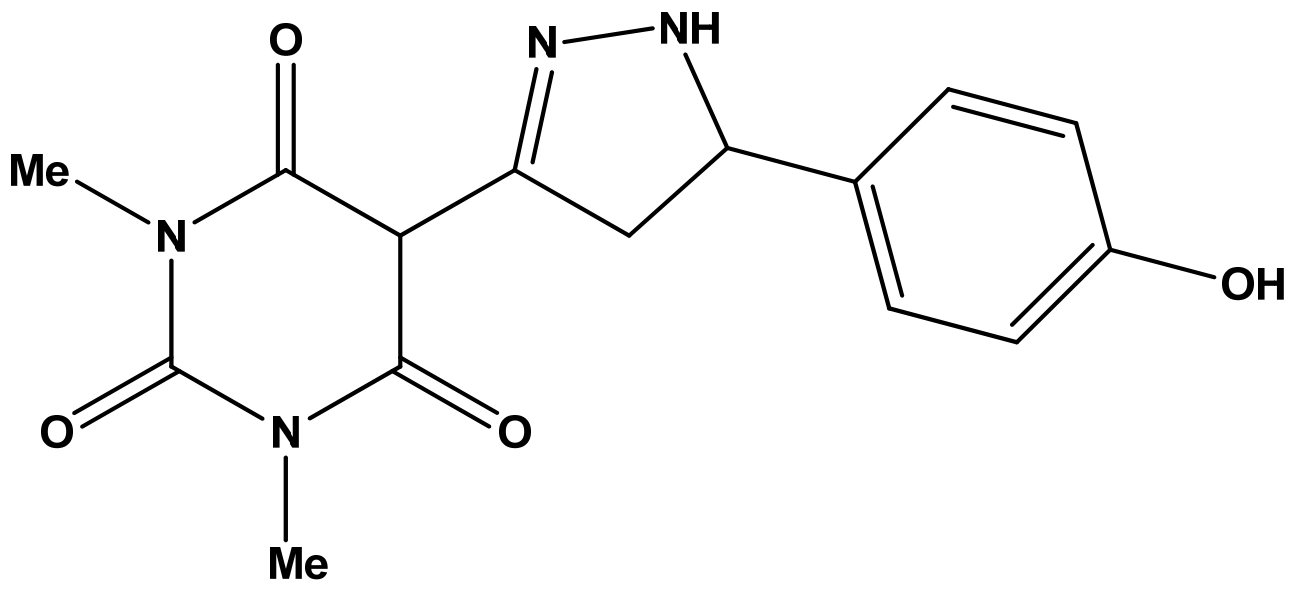
B.3.3 IR spectrum of 17



B.3.4 HRMS of 17

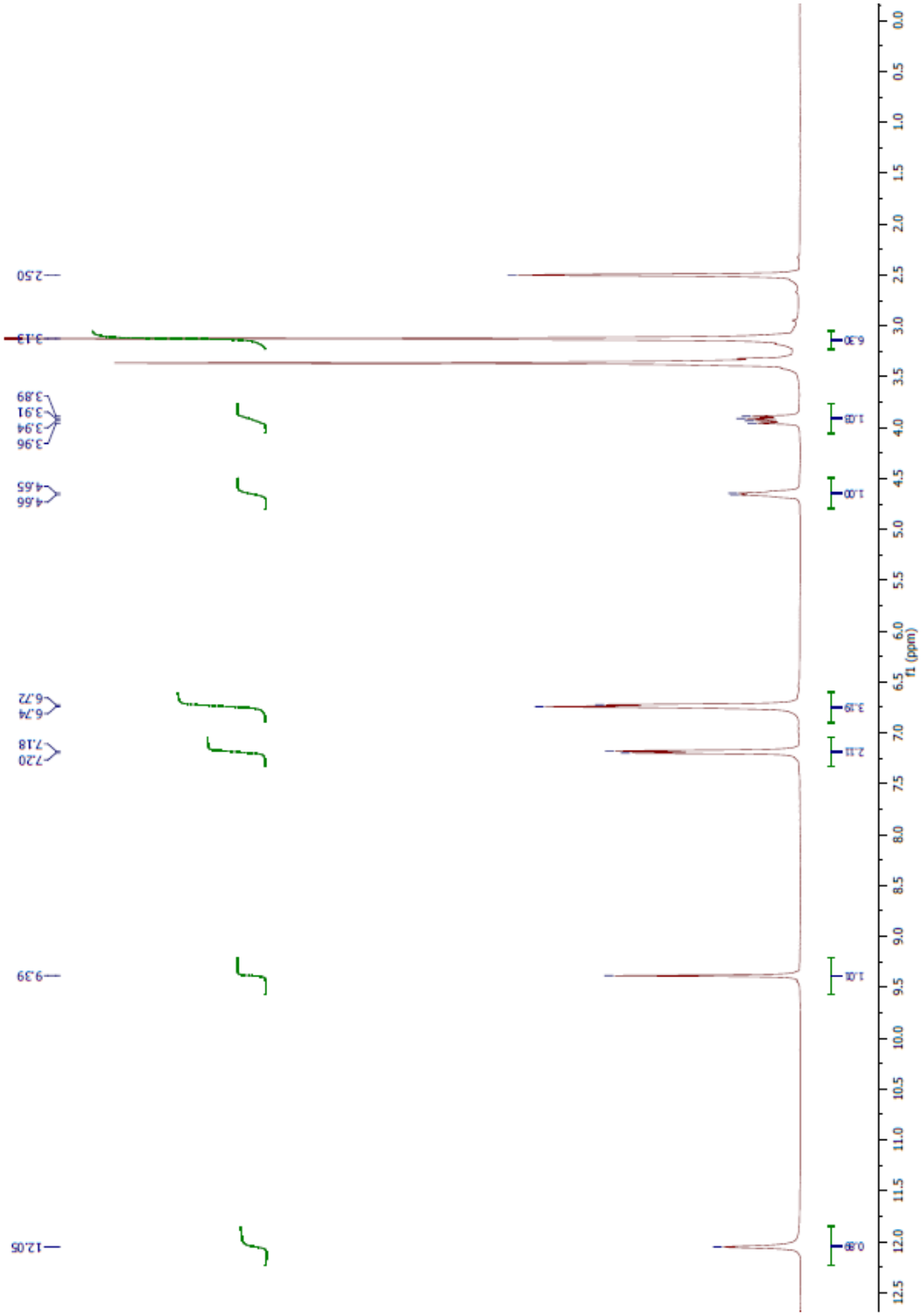


B.4 Spectroscopic data for 18

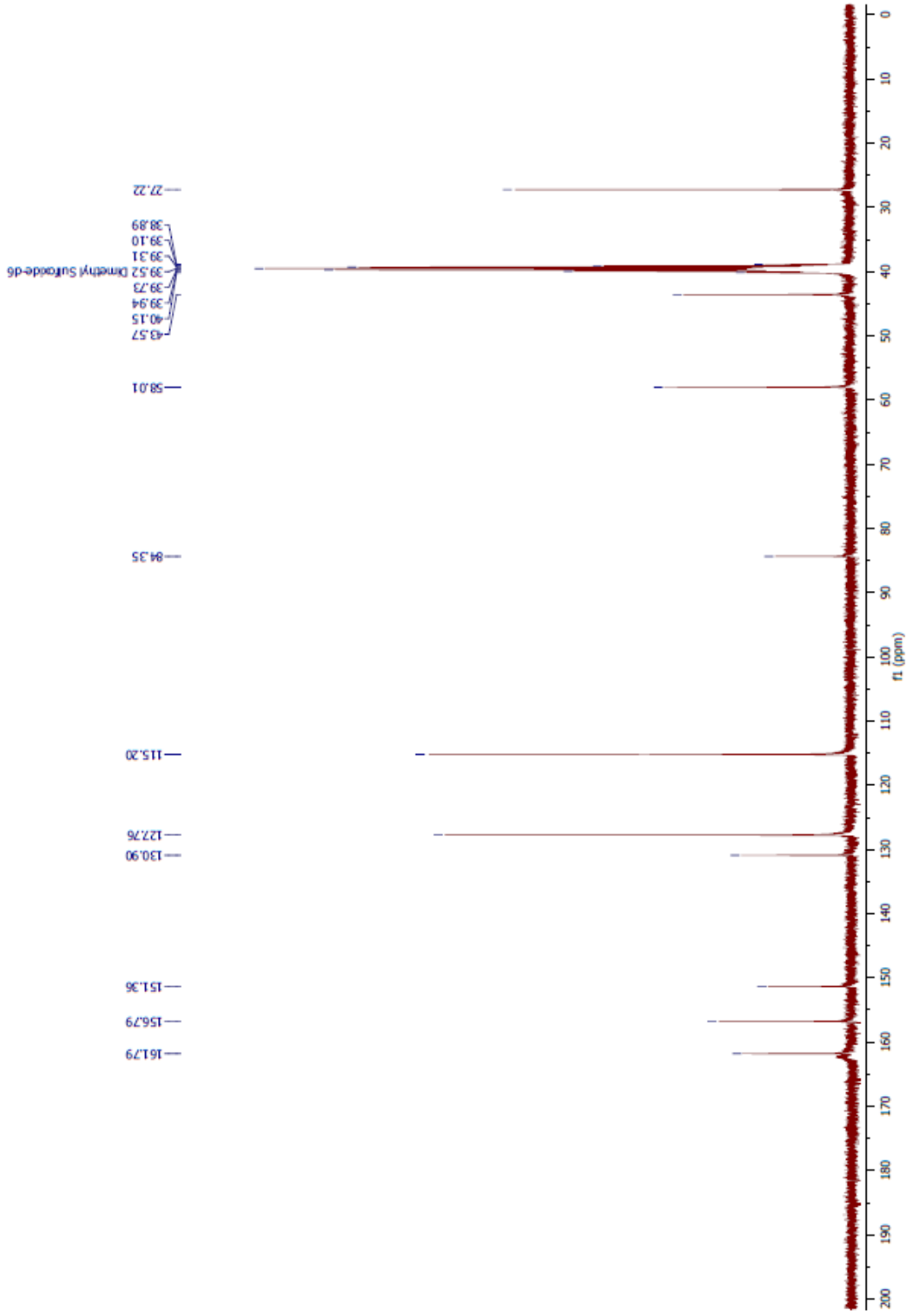


18

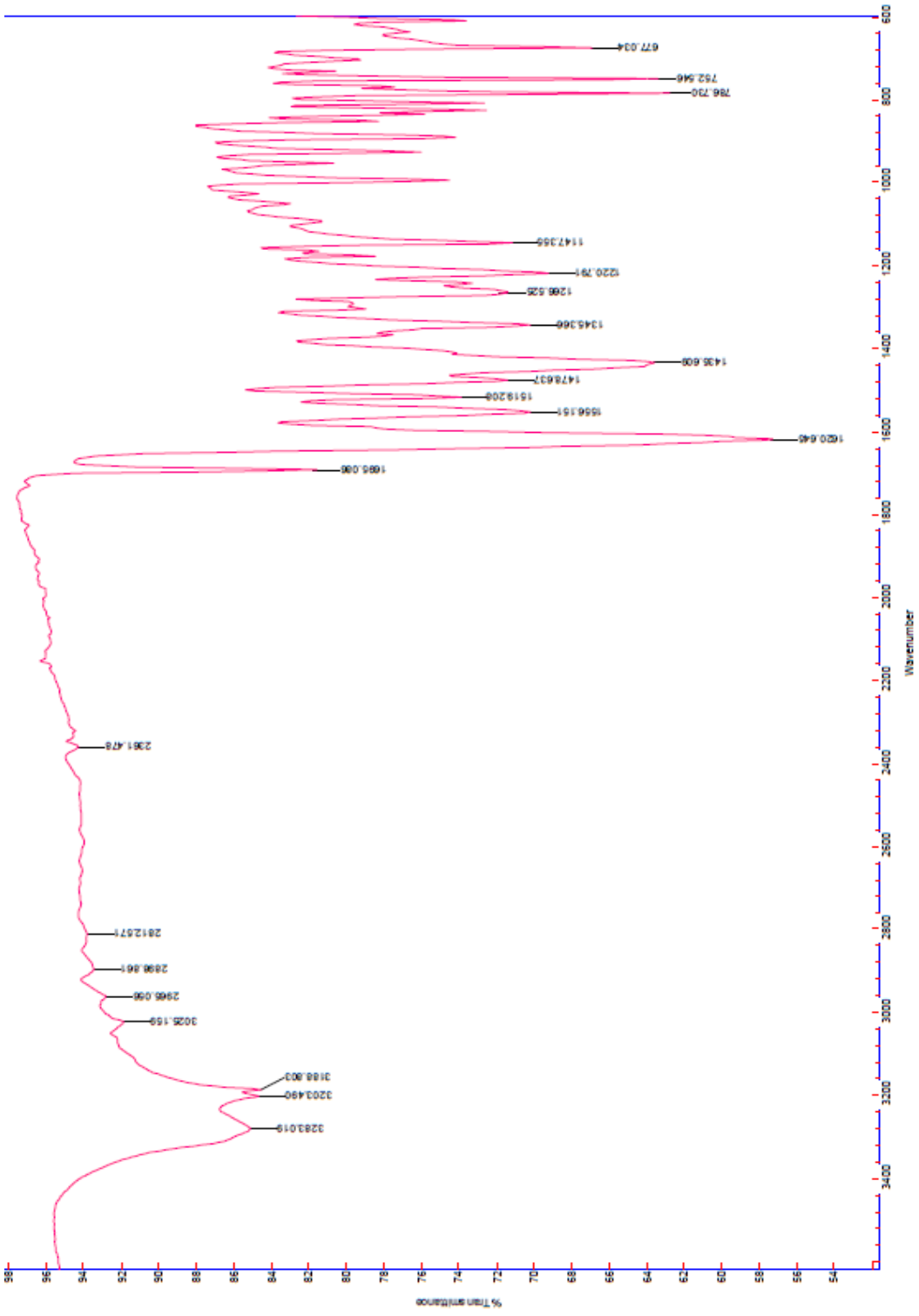
B.4.1 ^{1}H NMR spectrum of 18



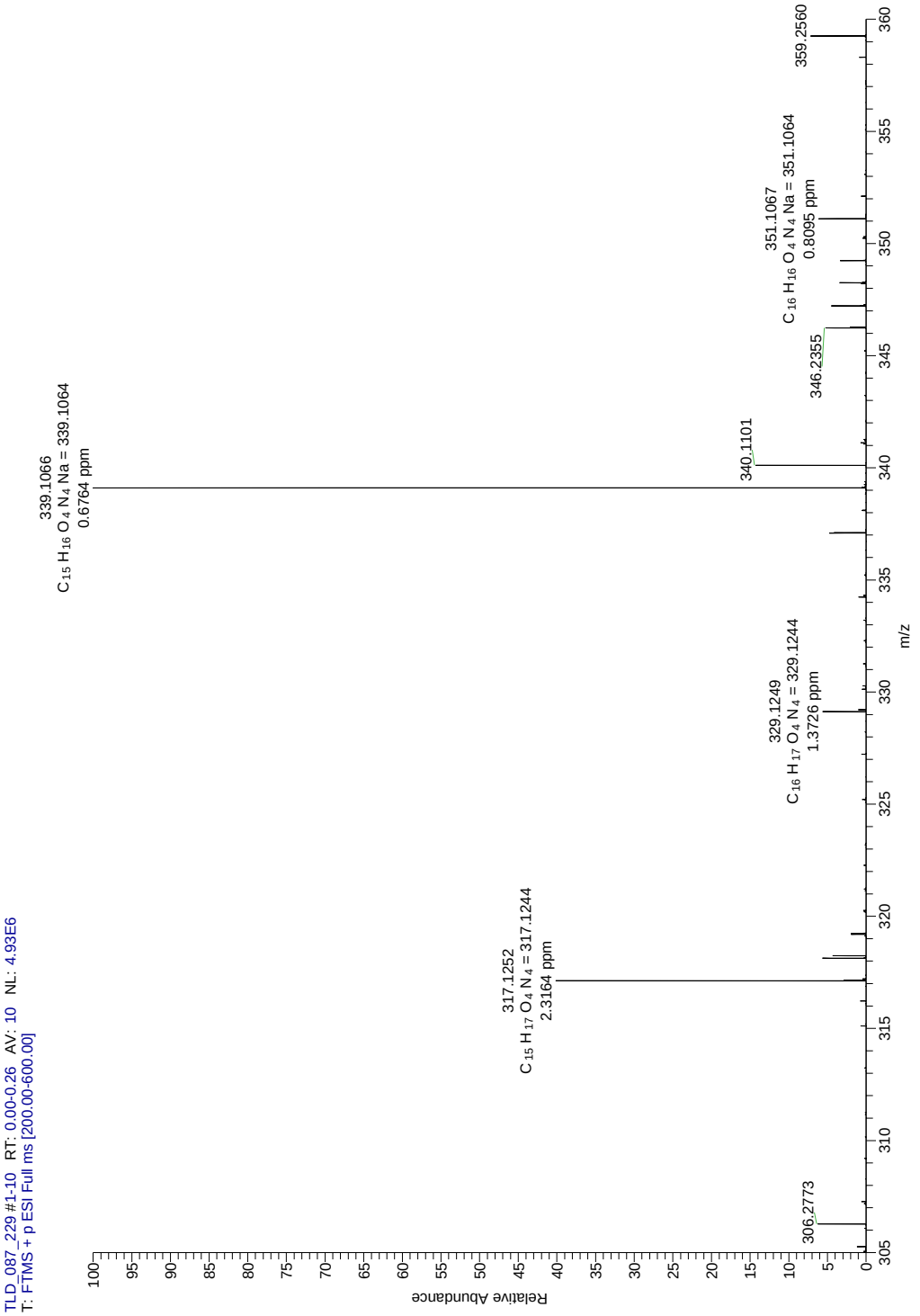
B.4.2 ^{13}C NMR spectrum of 18



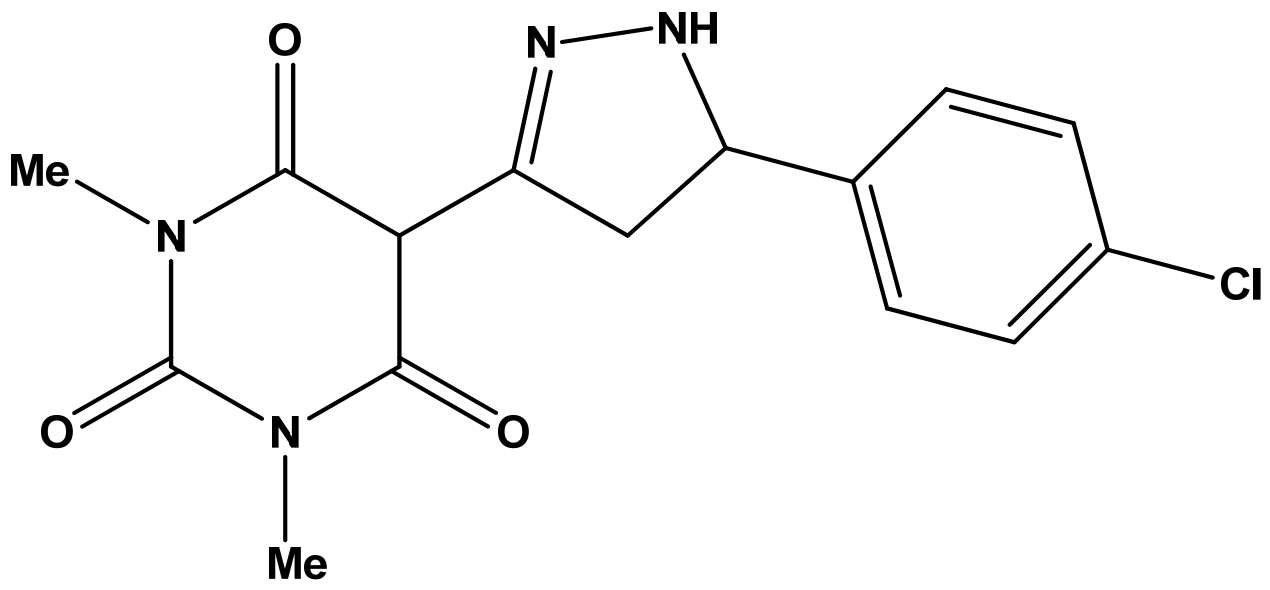
B.4.3 IR spectrum of 18



B.4.4 HRMS of 18

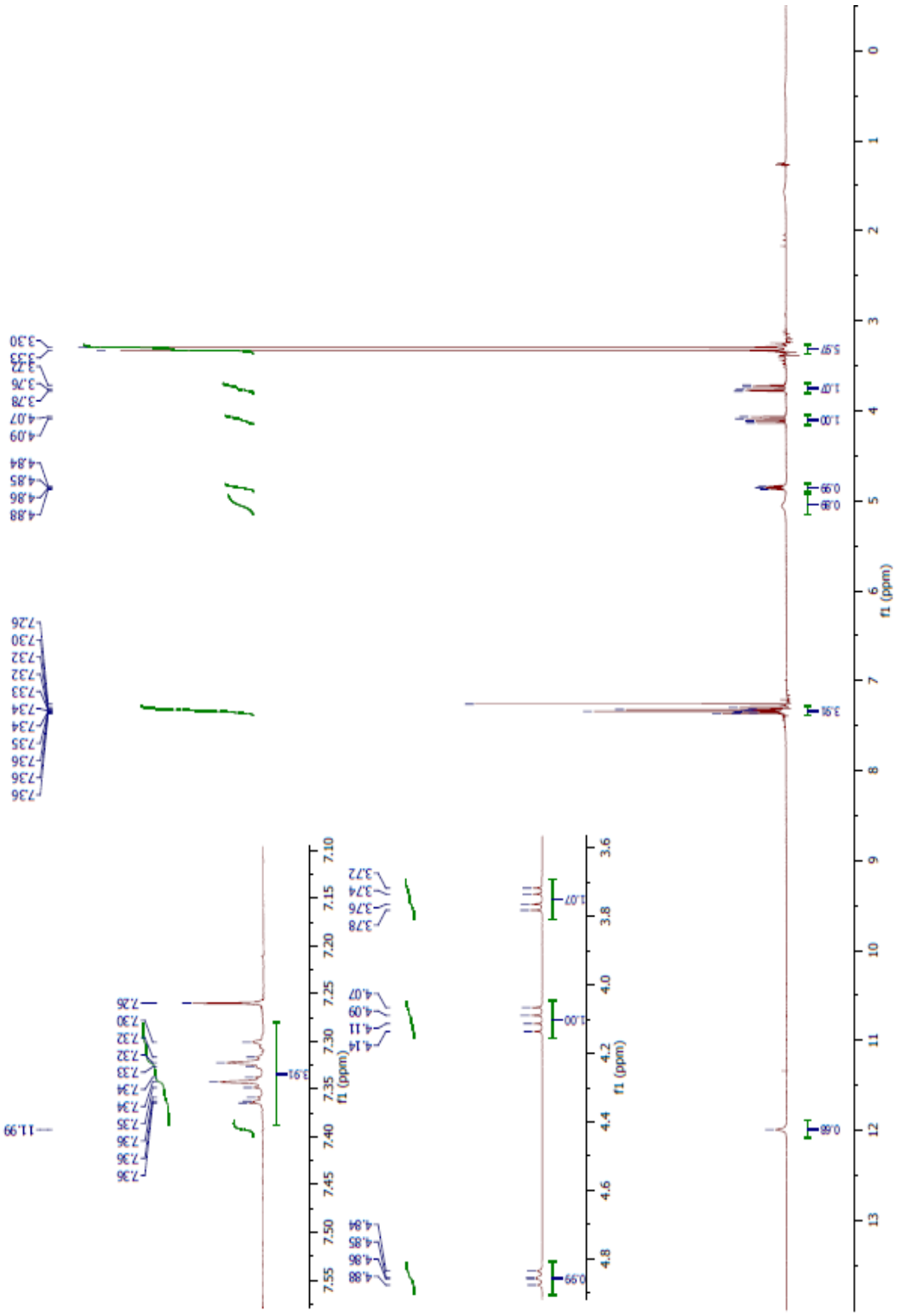


B.5 Spectroscopic data for 19

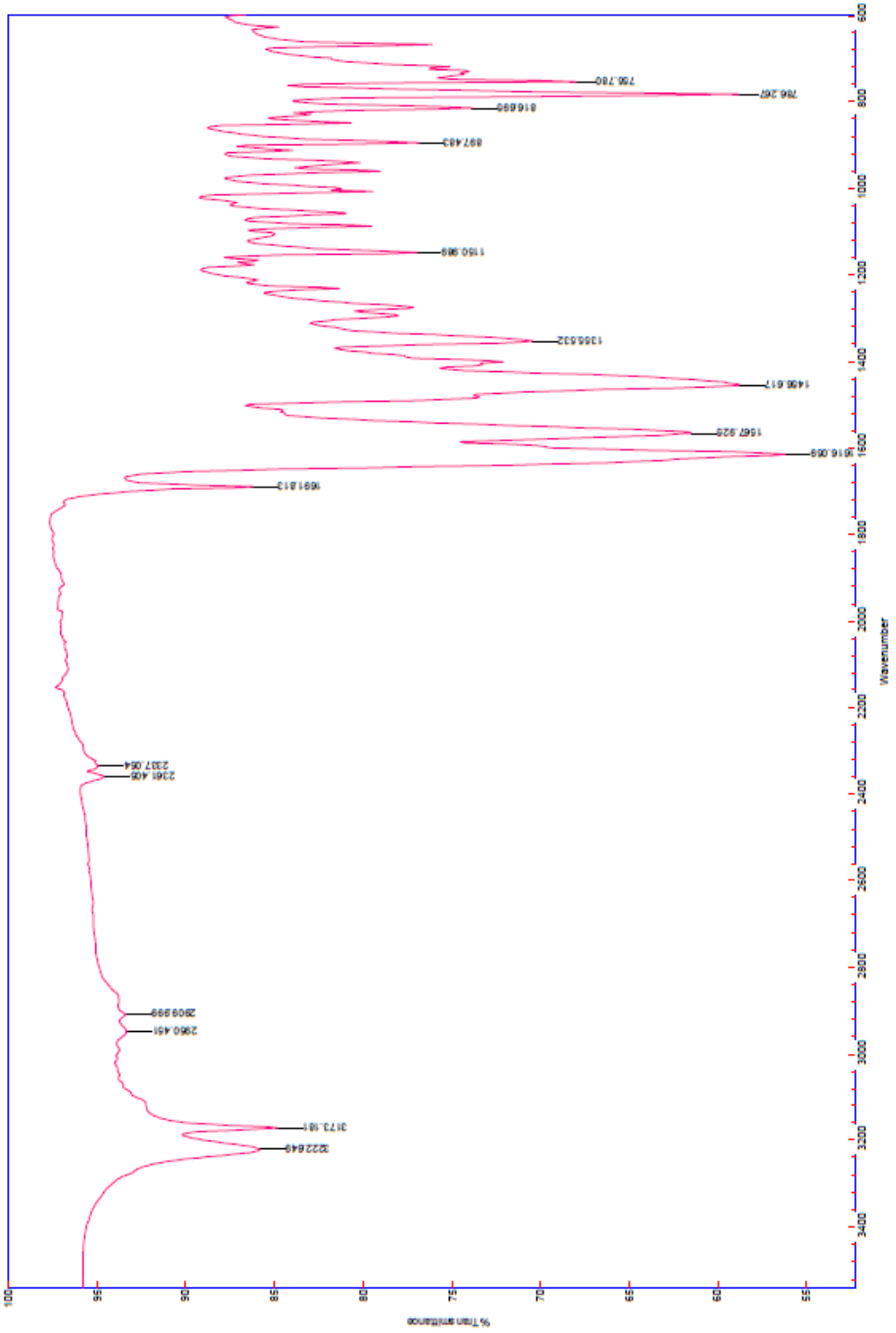


19

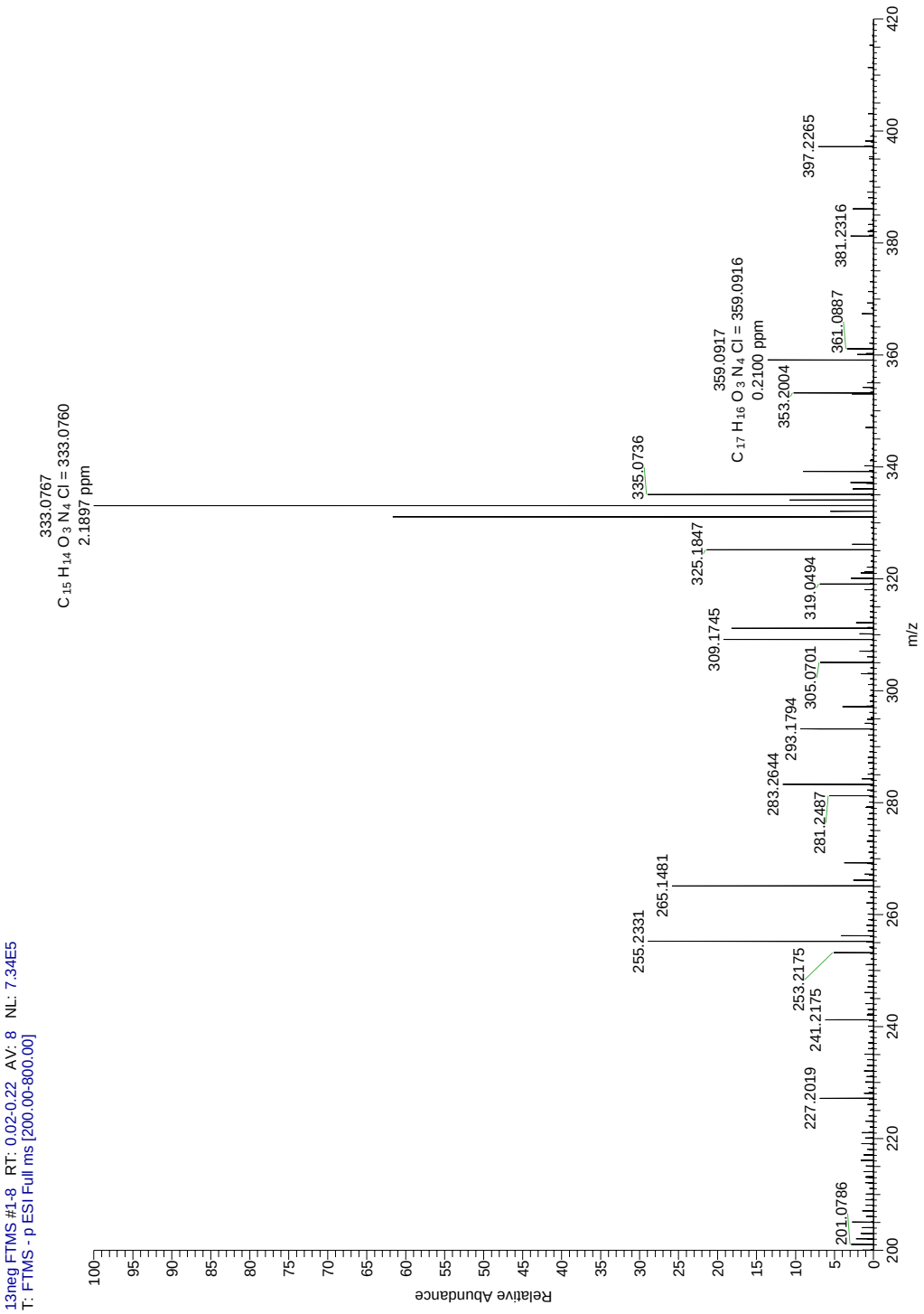
B.5.1 ^{1}H NMR spectrum of 19



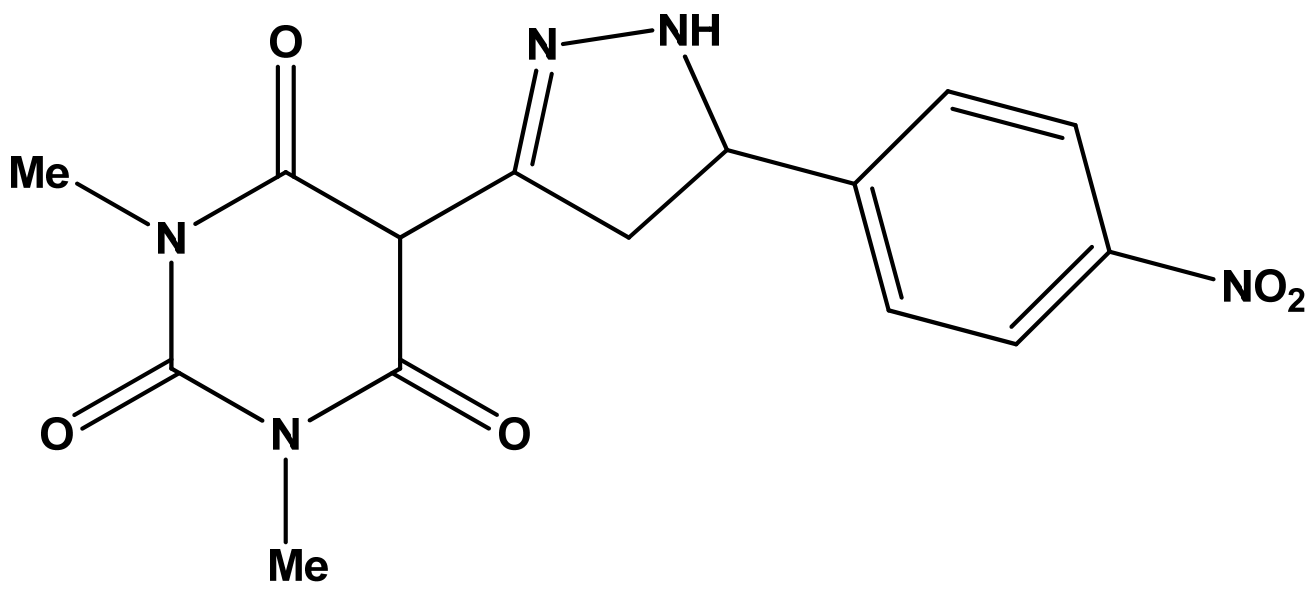
B.5.2 IR spectrum of 19



B.5.2 HRMS of 19

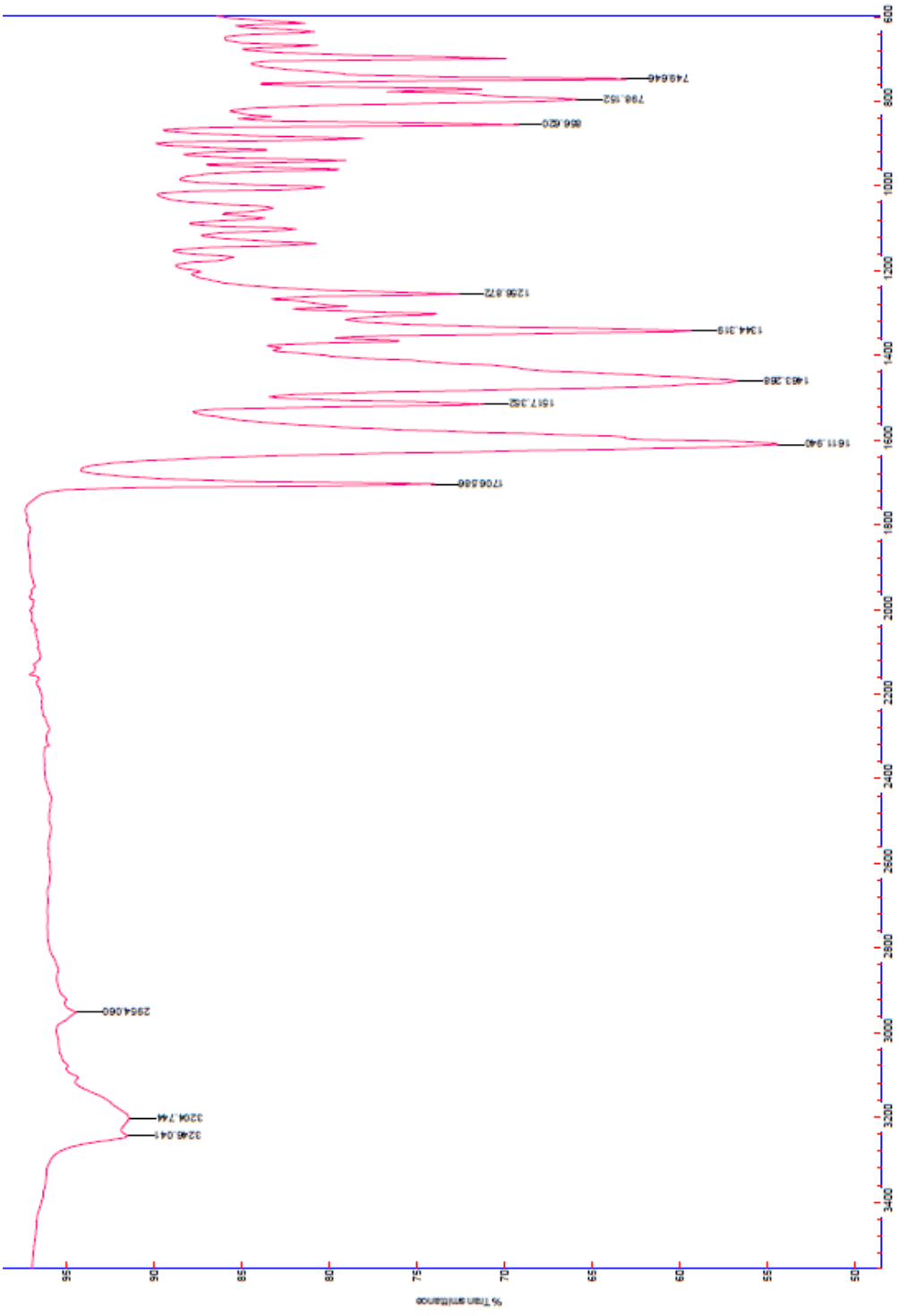


B.6 Spectroscopic data for 20

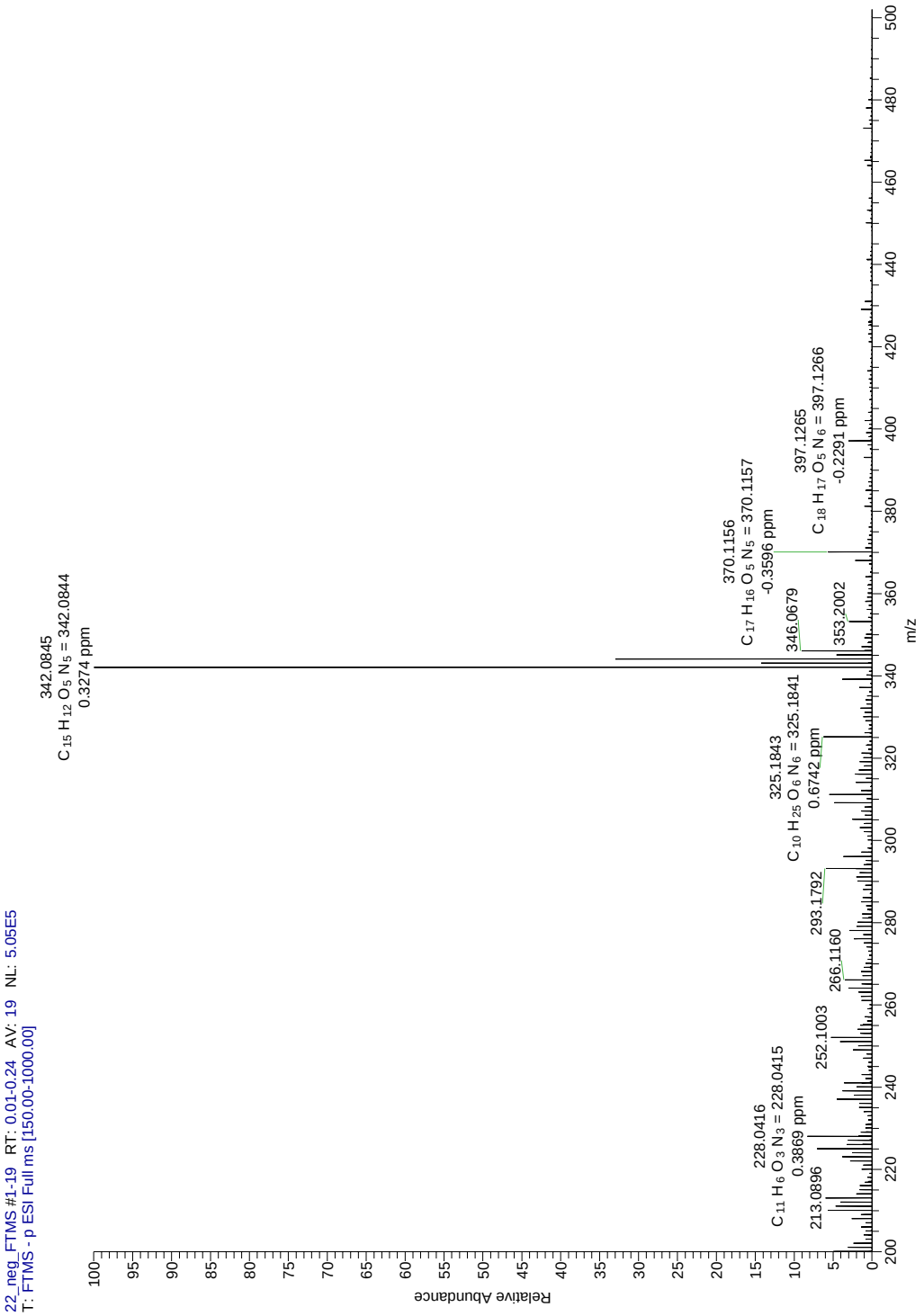


20

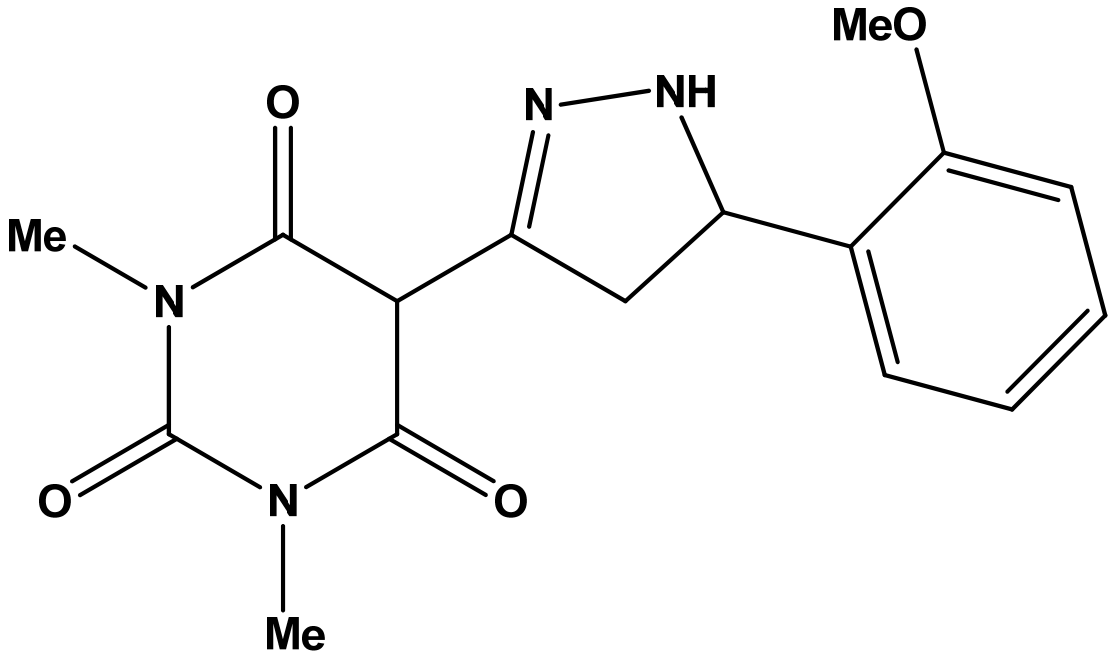
B.6.1 IR spectrum of 20



B.6.2 HRMS of 20

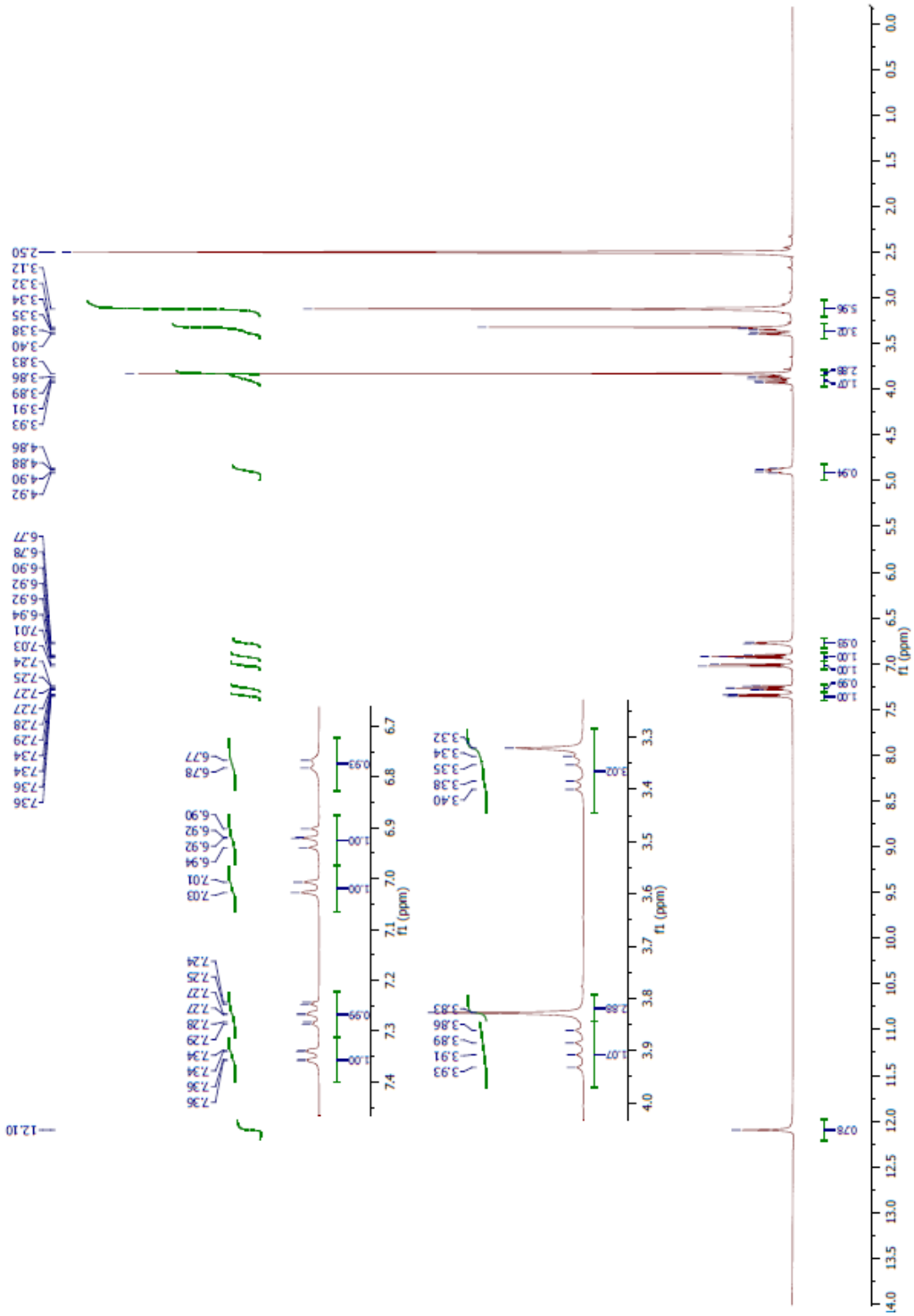


B.7 Spectroscopic data for 21

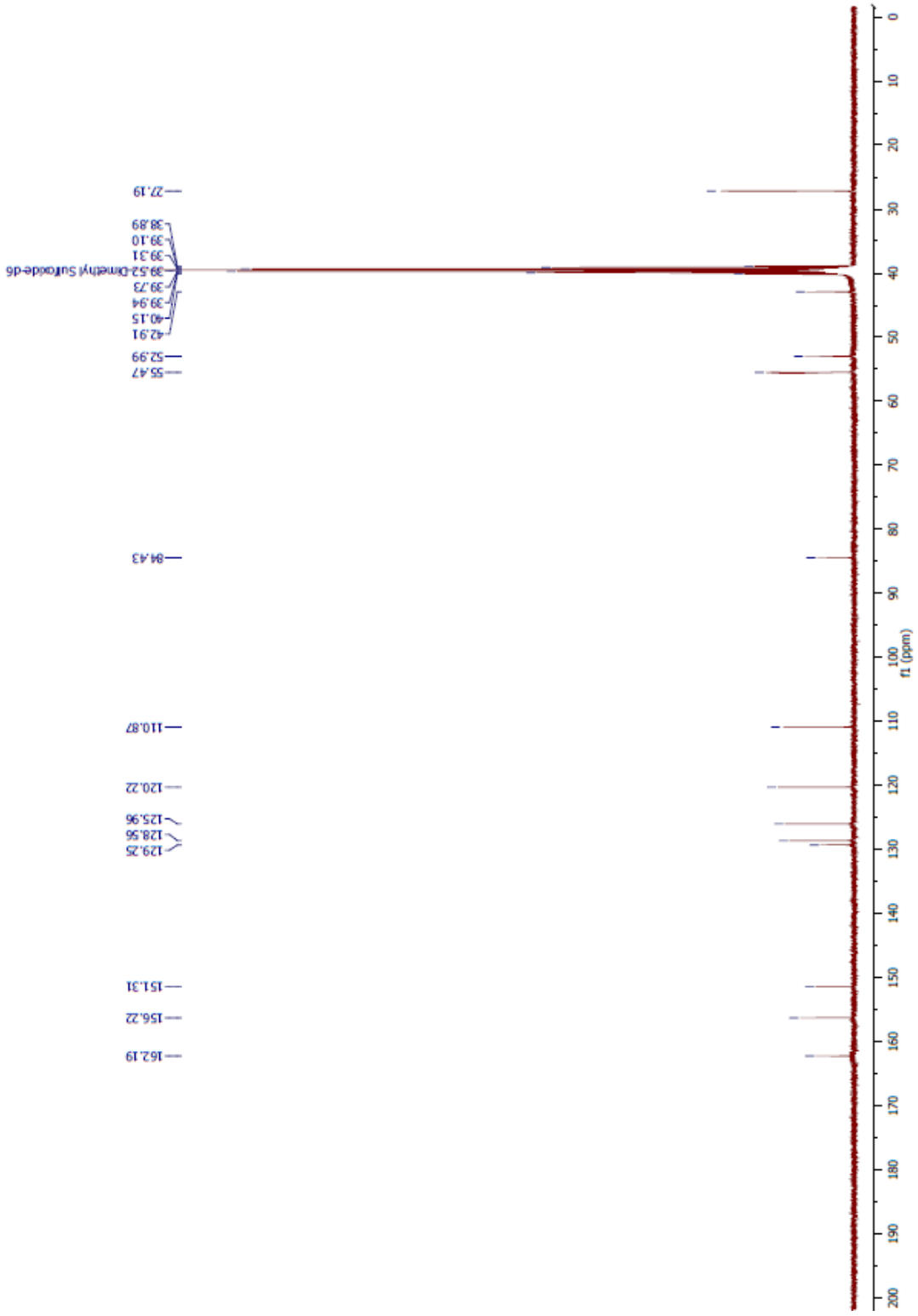


21

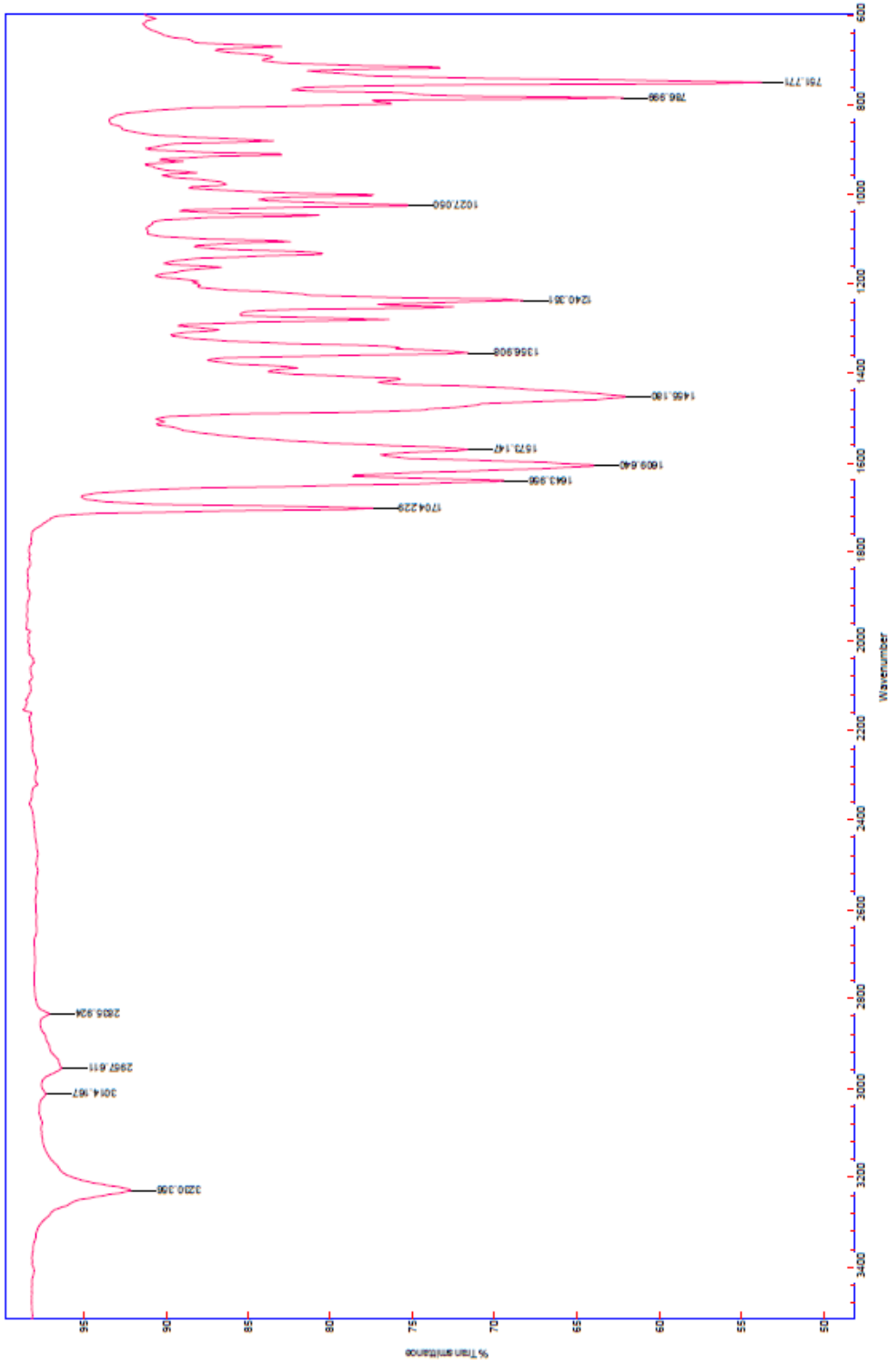
B.7.1 ^{1}H NMR spectrum of 21



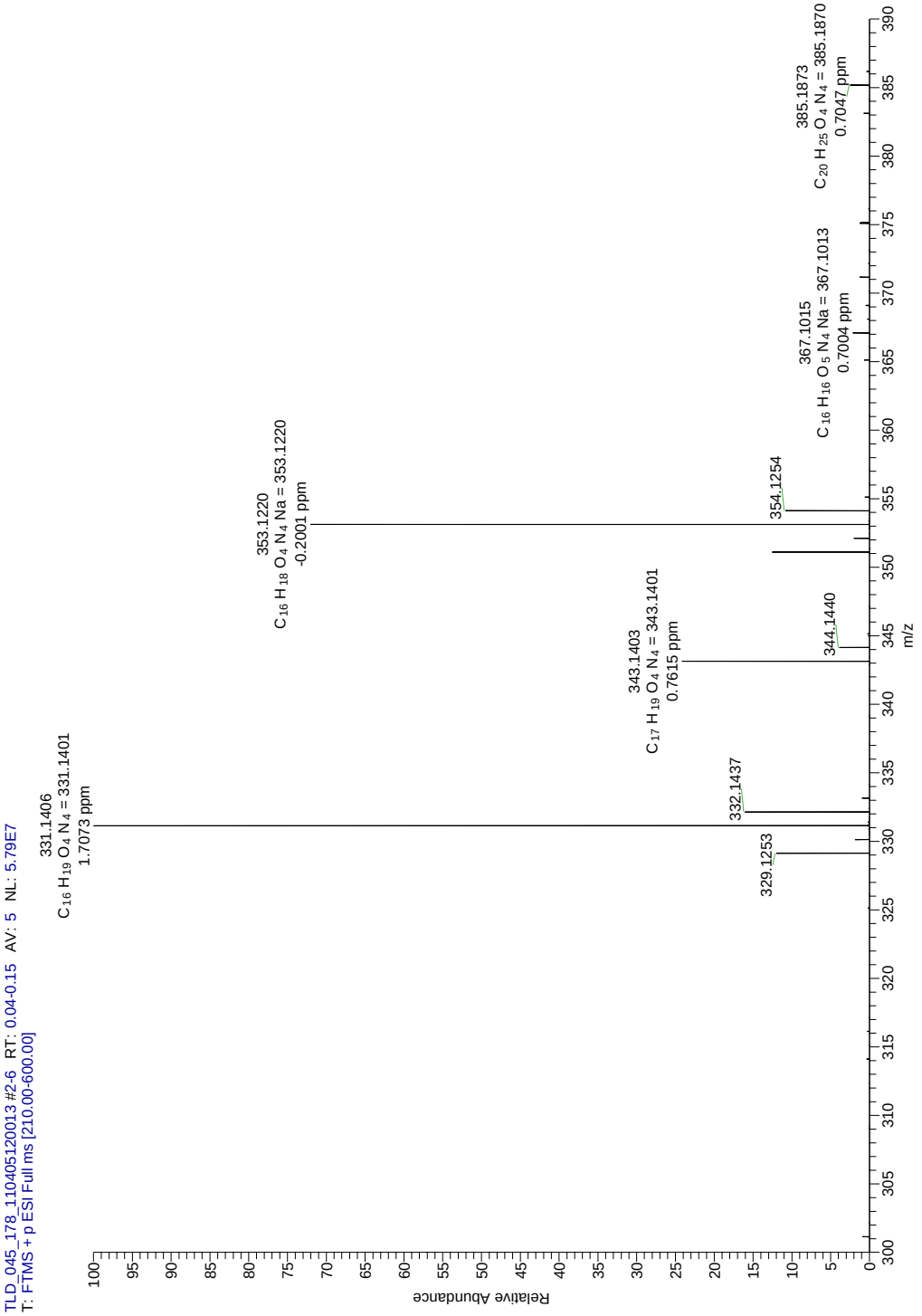
B.7.2 ^{13}C NMR spectrum of 21



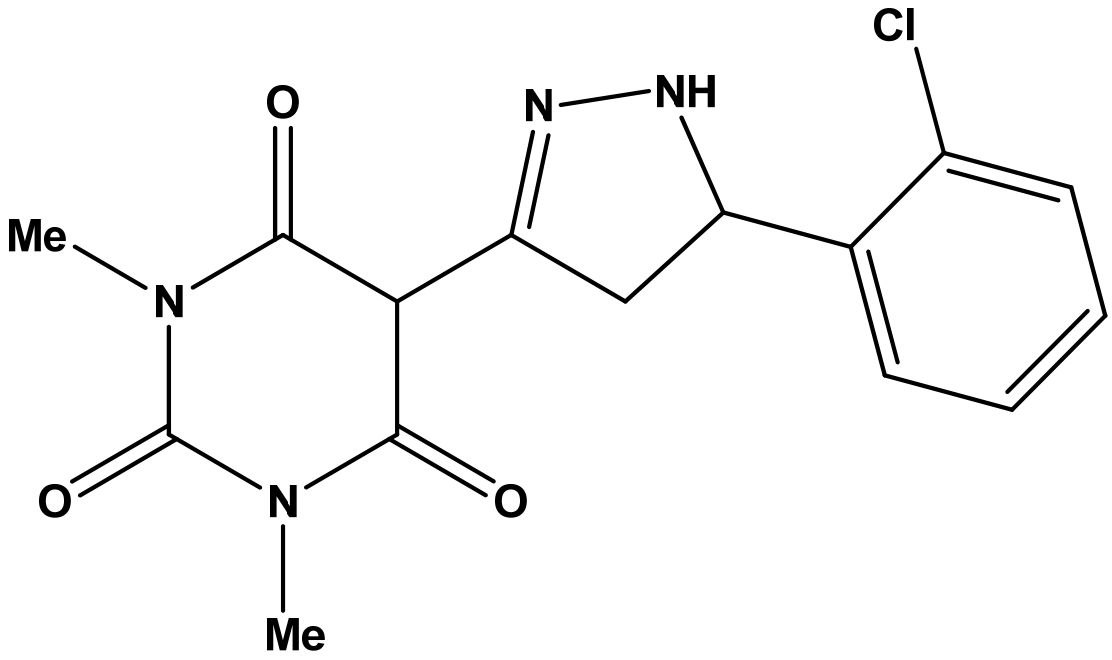
B.7.3 IR spectrum of 21



B.7.4 HRMS of 21

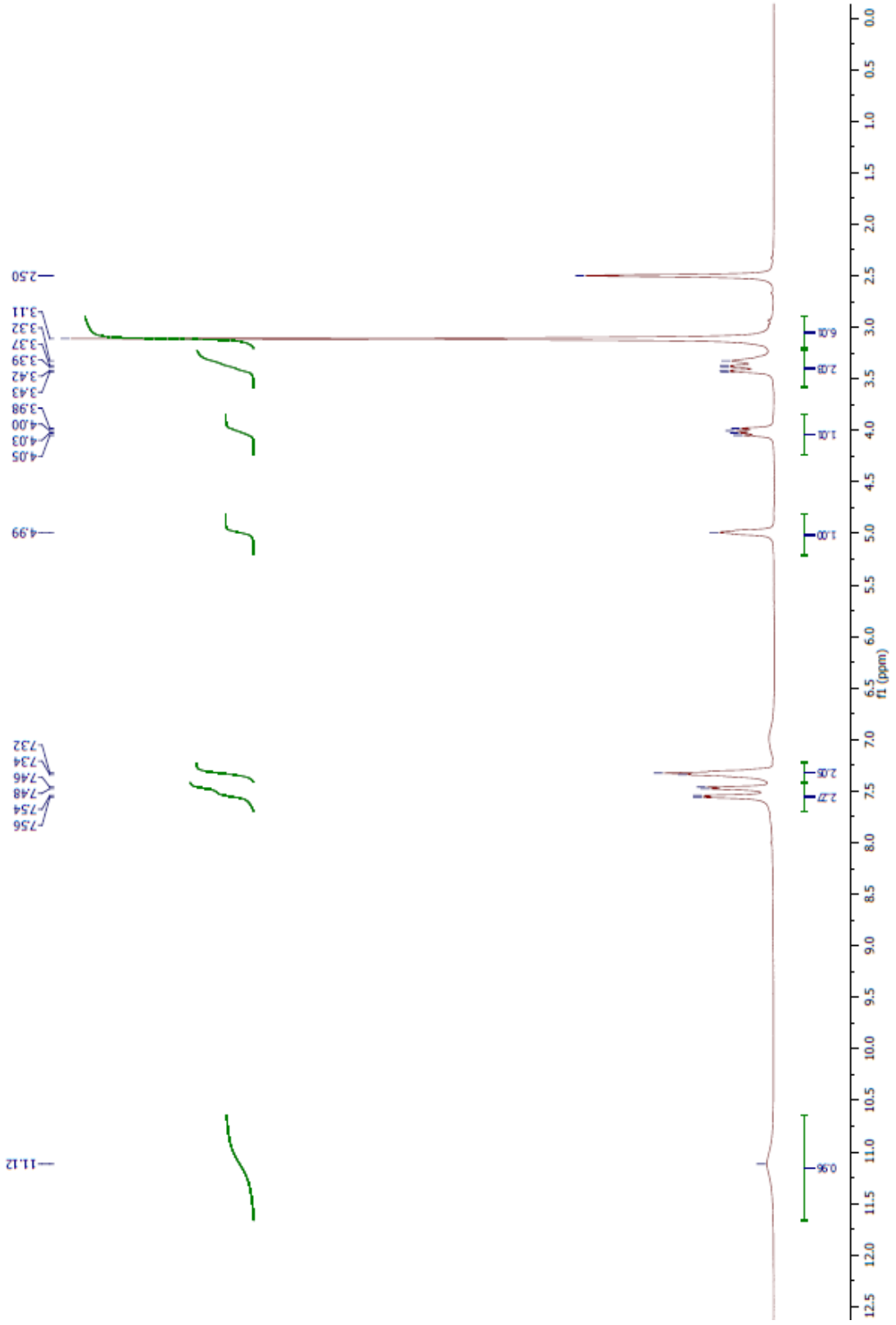


B.8 Spectroscopic data for 22

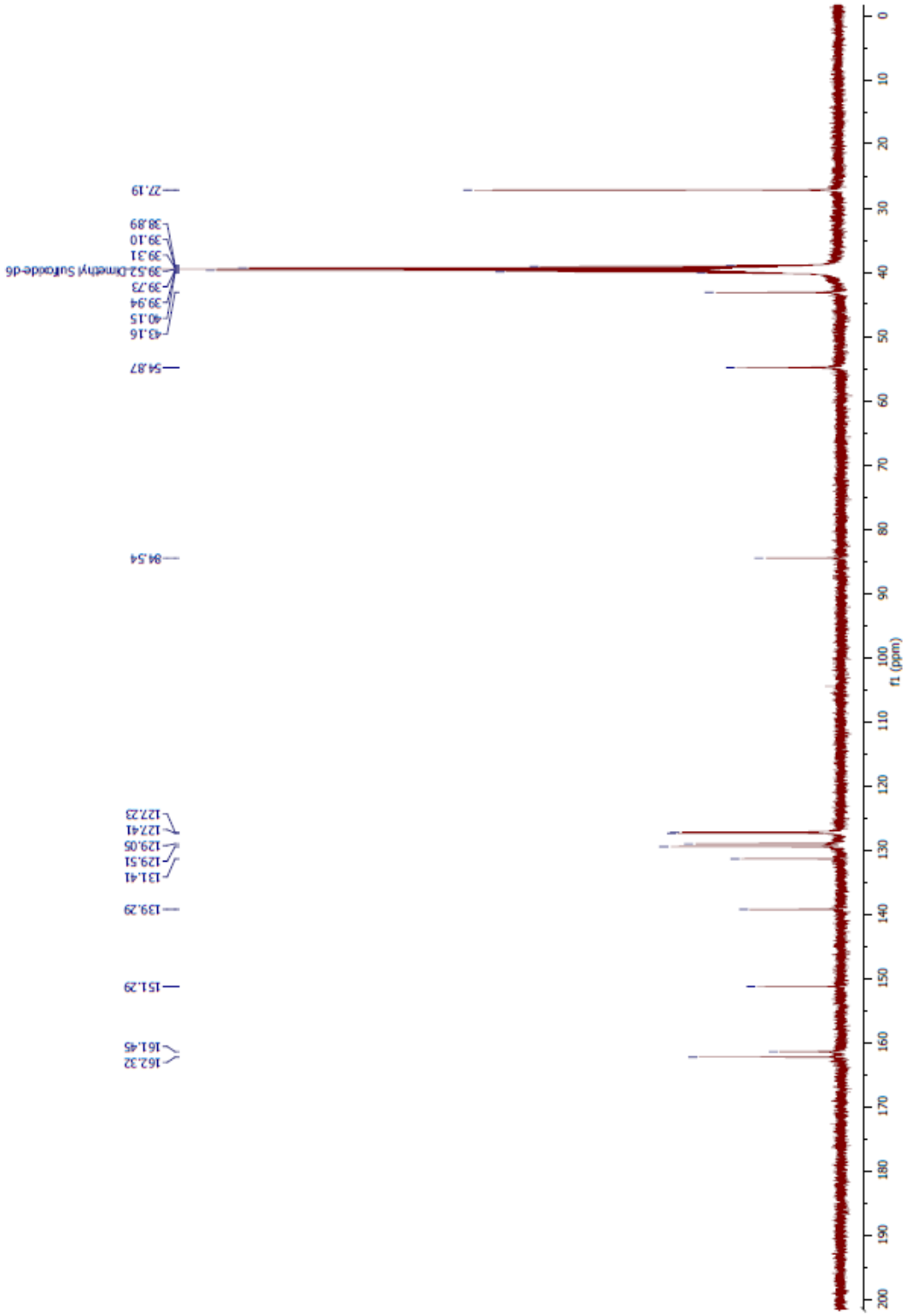


22

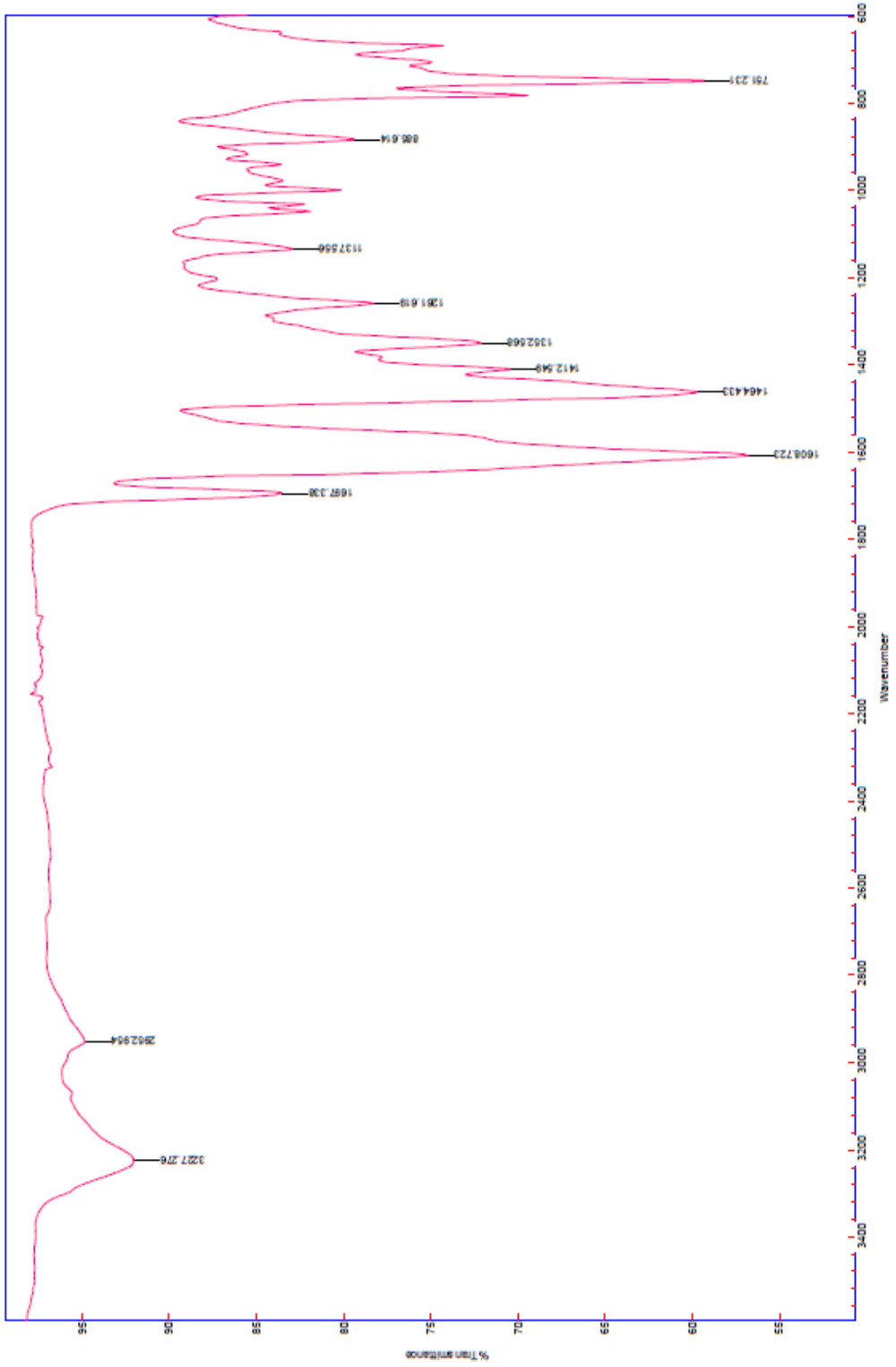
B.8.1 ^{1}H NMR spectrum of 22



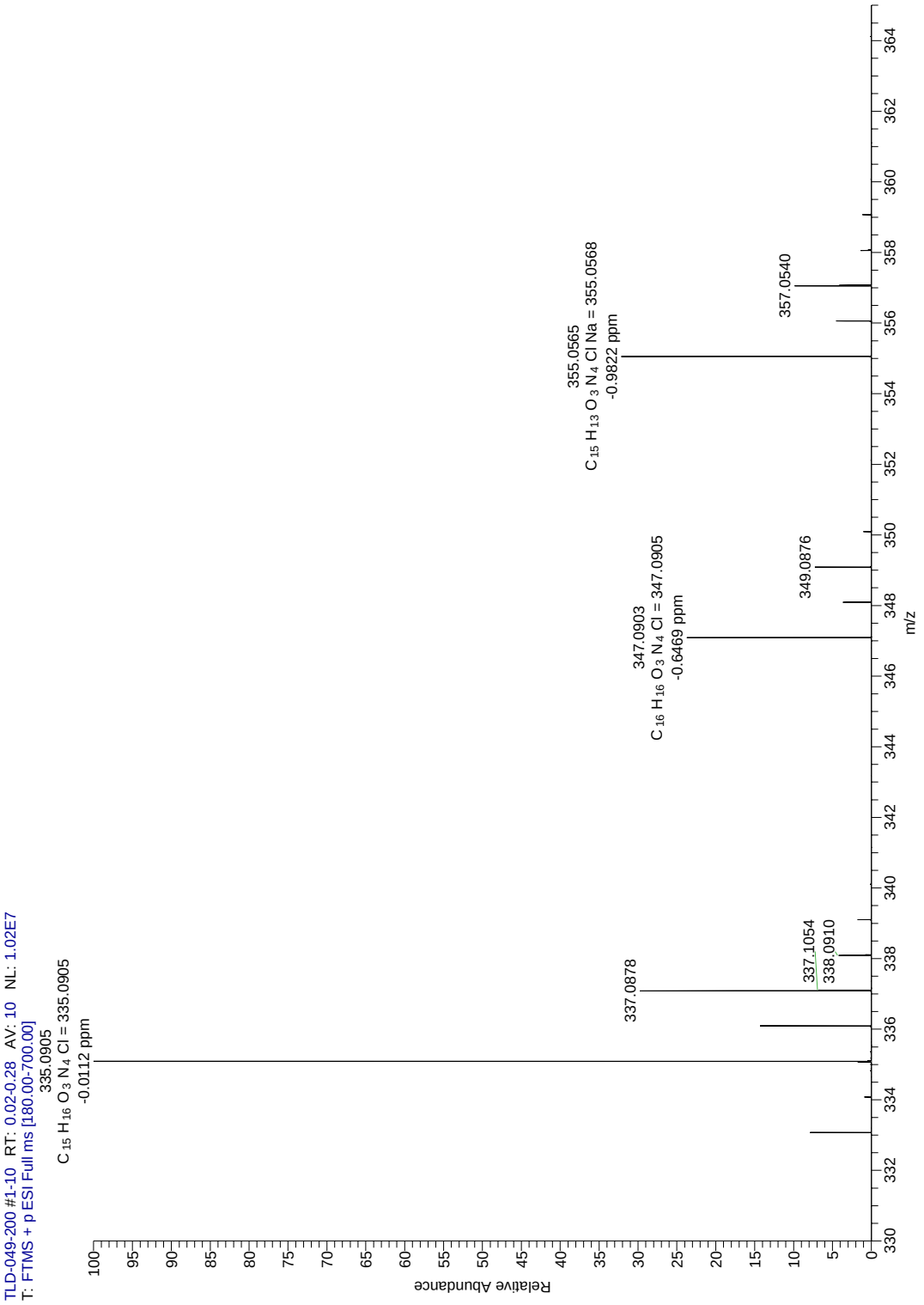
B.8.2 ^{13}C NMR spectrum of 22



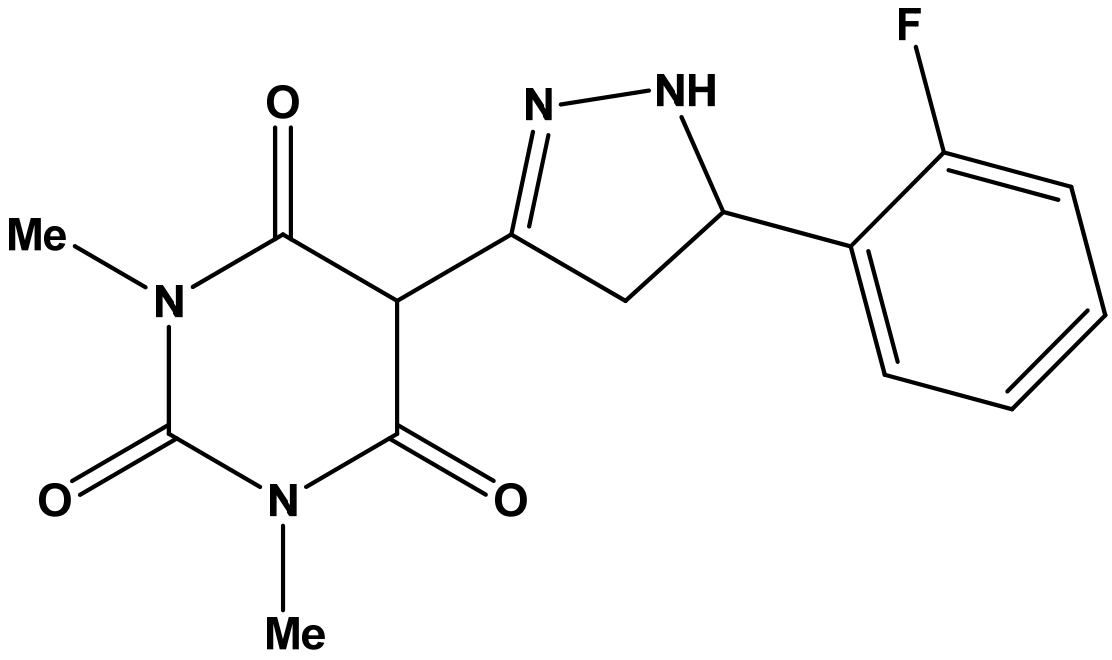
B.8.3 IR spectrum of 22



B.8.3 HRMS of 22

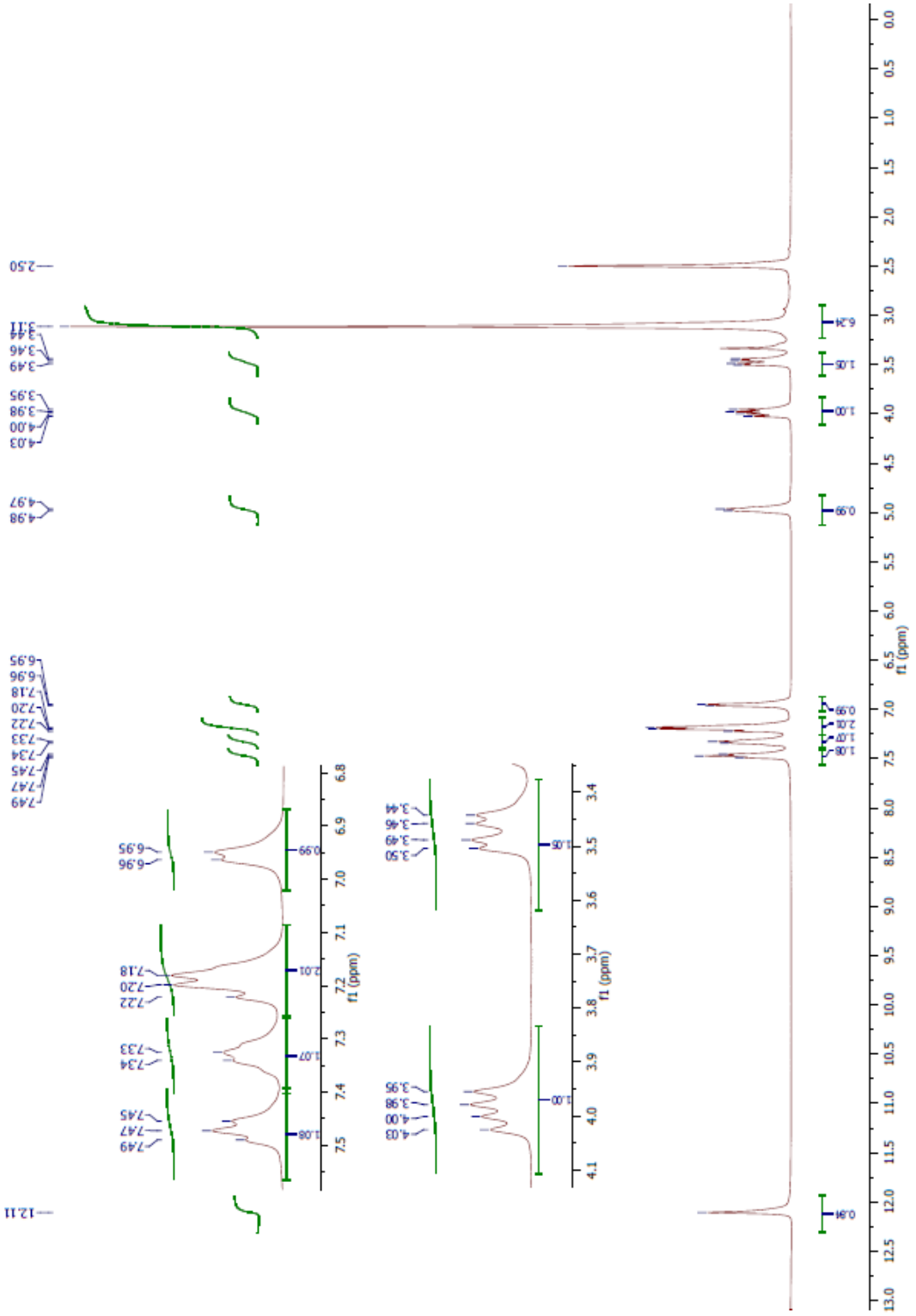


B.9 Spectroscopic data for 23

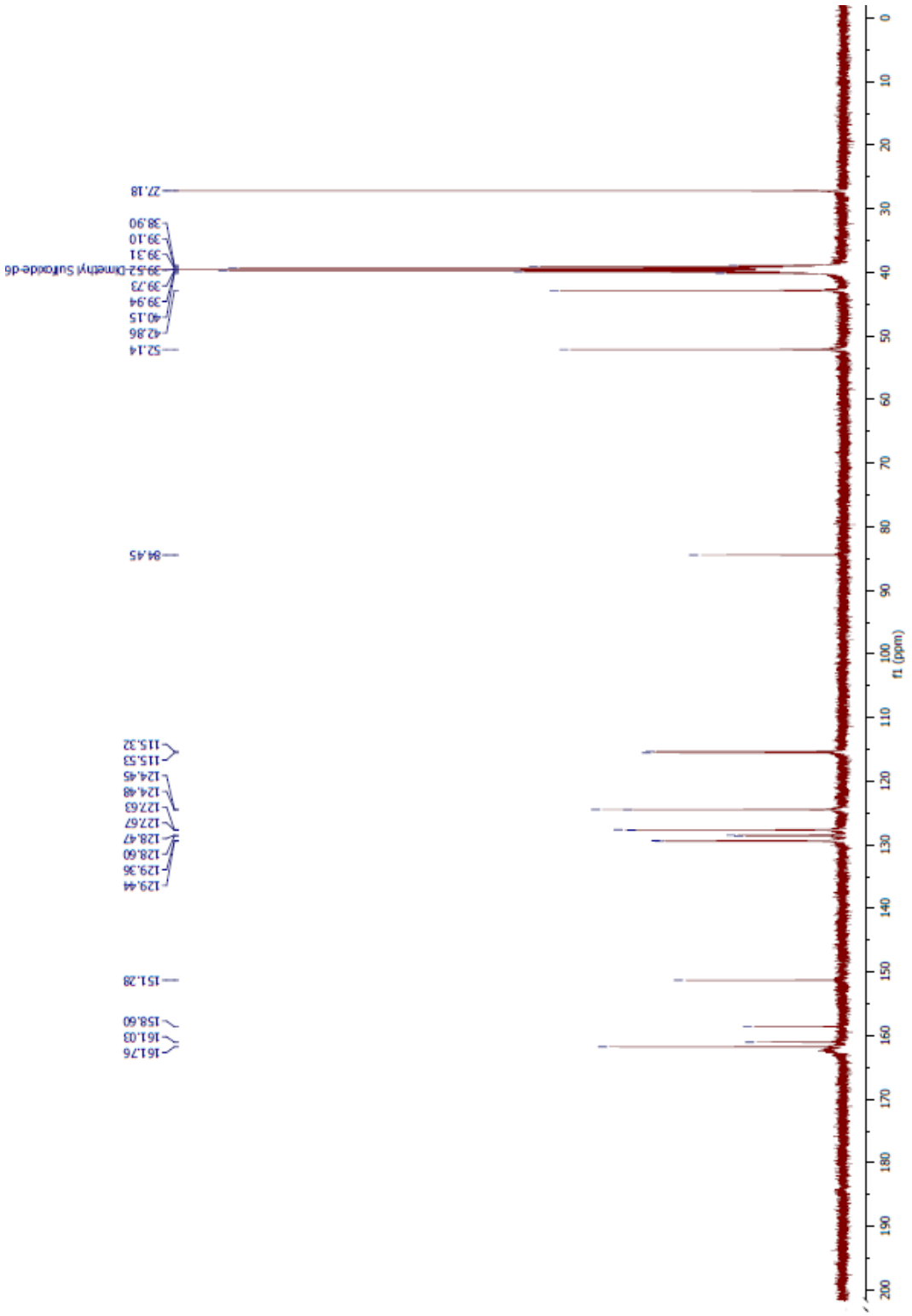


23

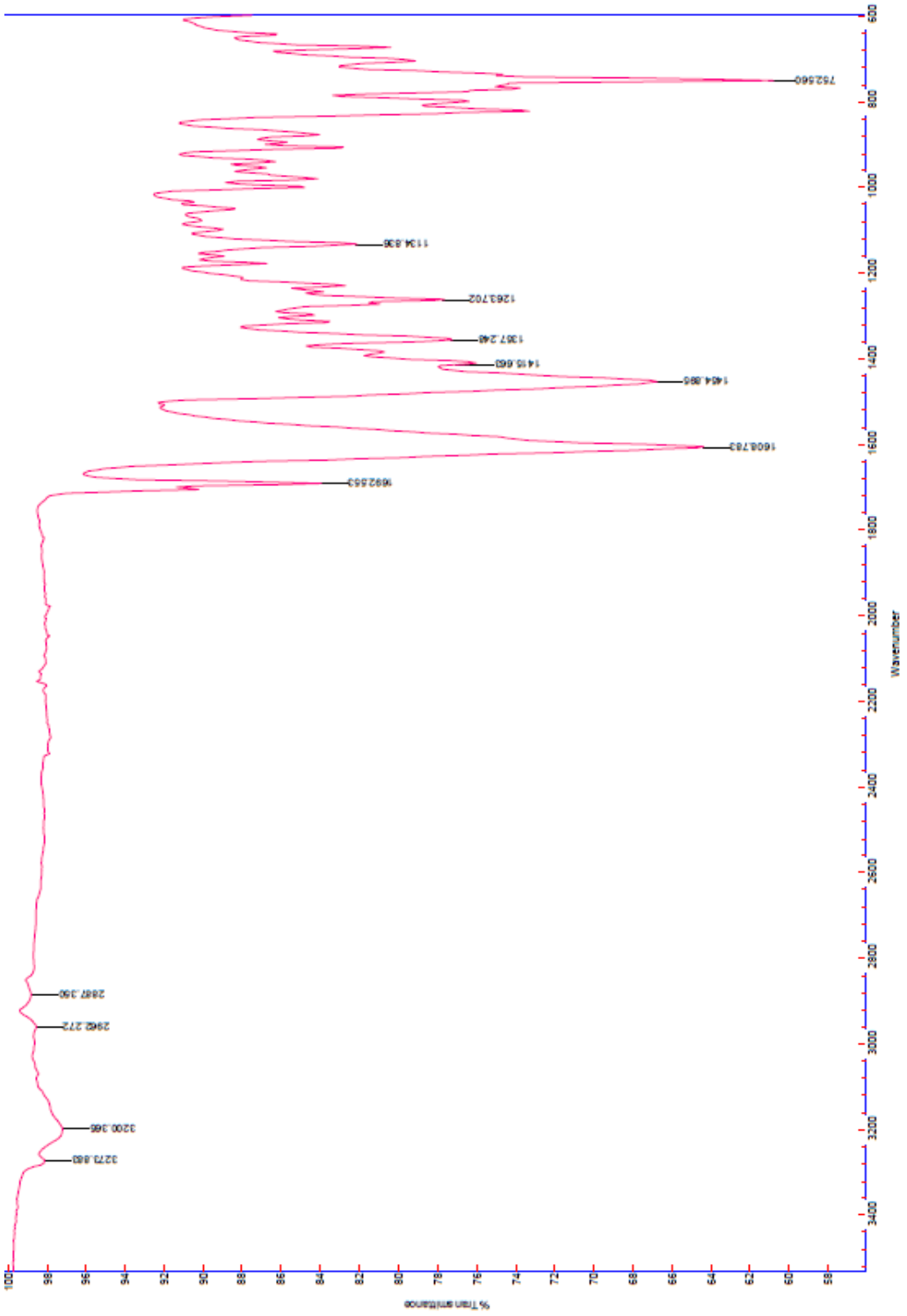
B.9.1 ^{1}H NMR spectrum of 23



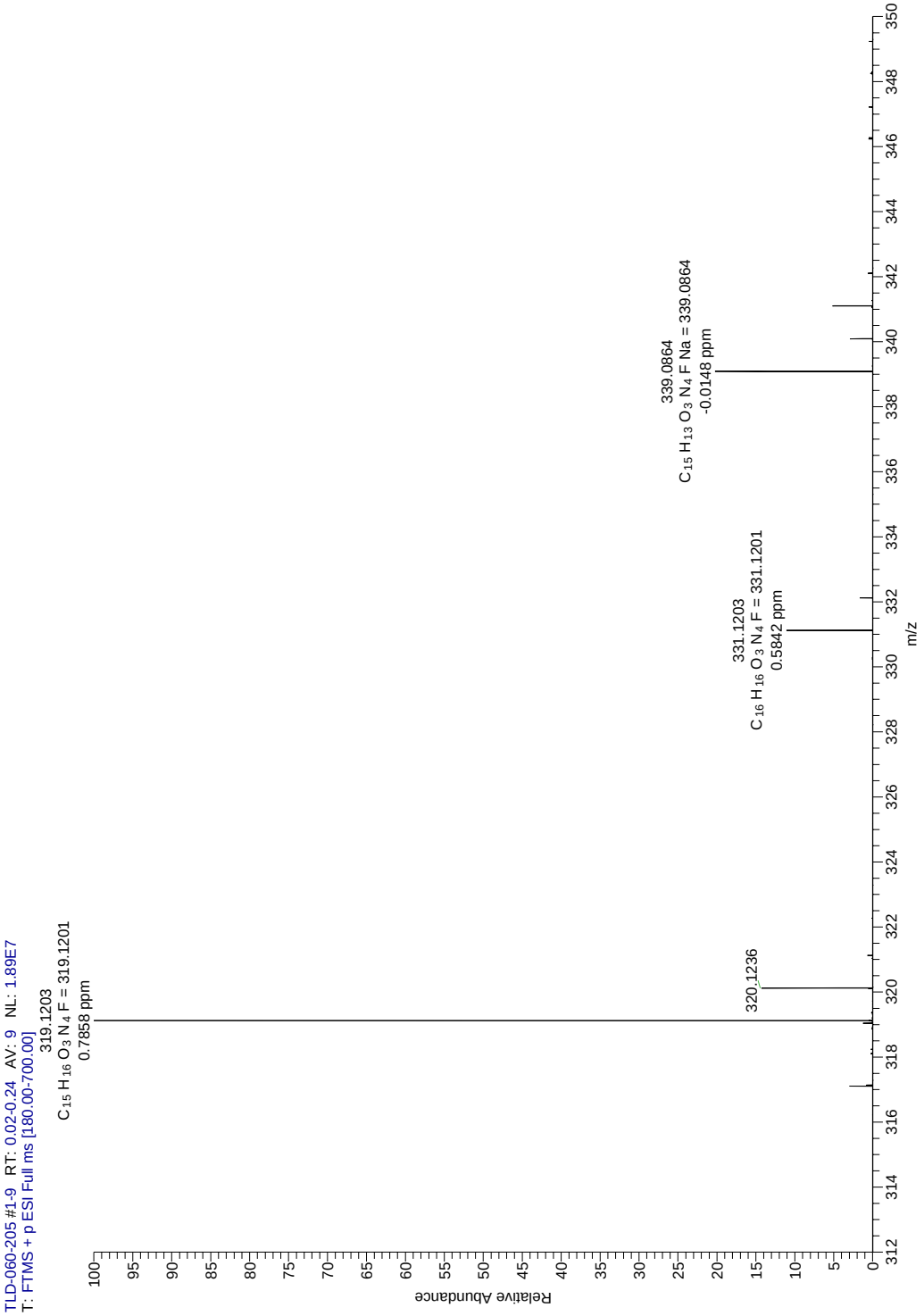
B.9.2 ^{13}C NMR spectrum of 23



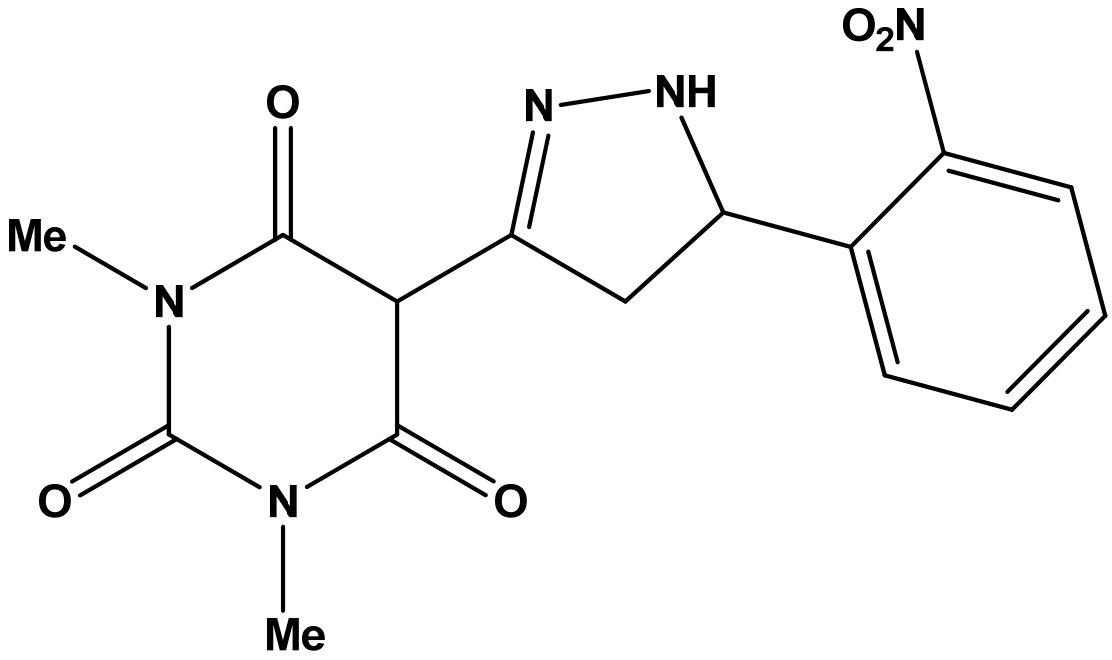
B.9.3 IR spectrum of 23



B.9.4 HRMS of 23

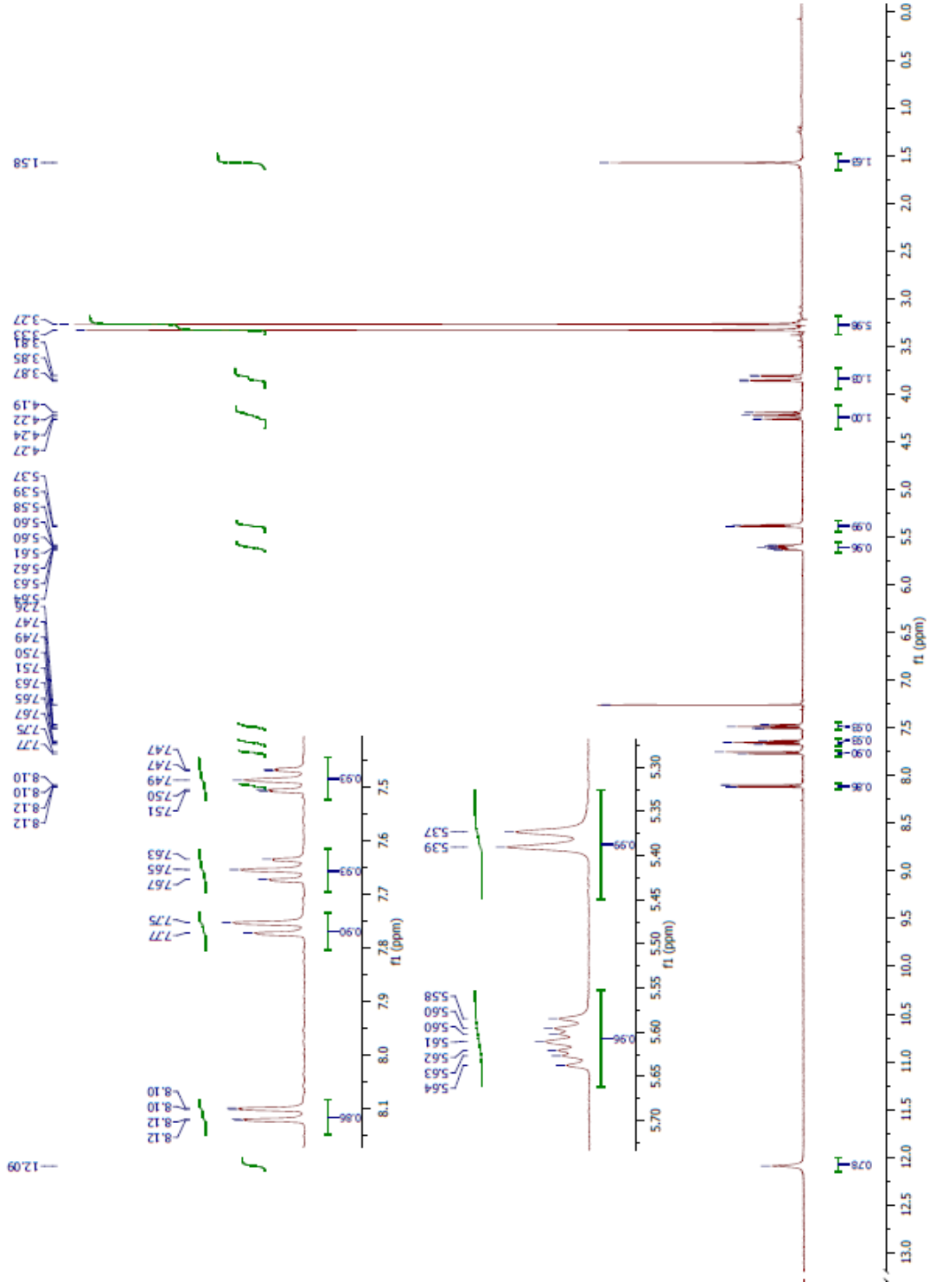


B.10 Spectroscopic data for 25

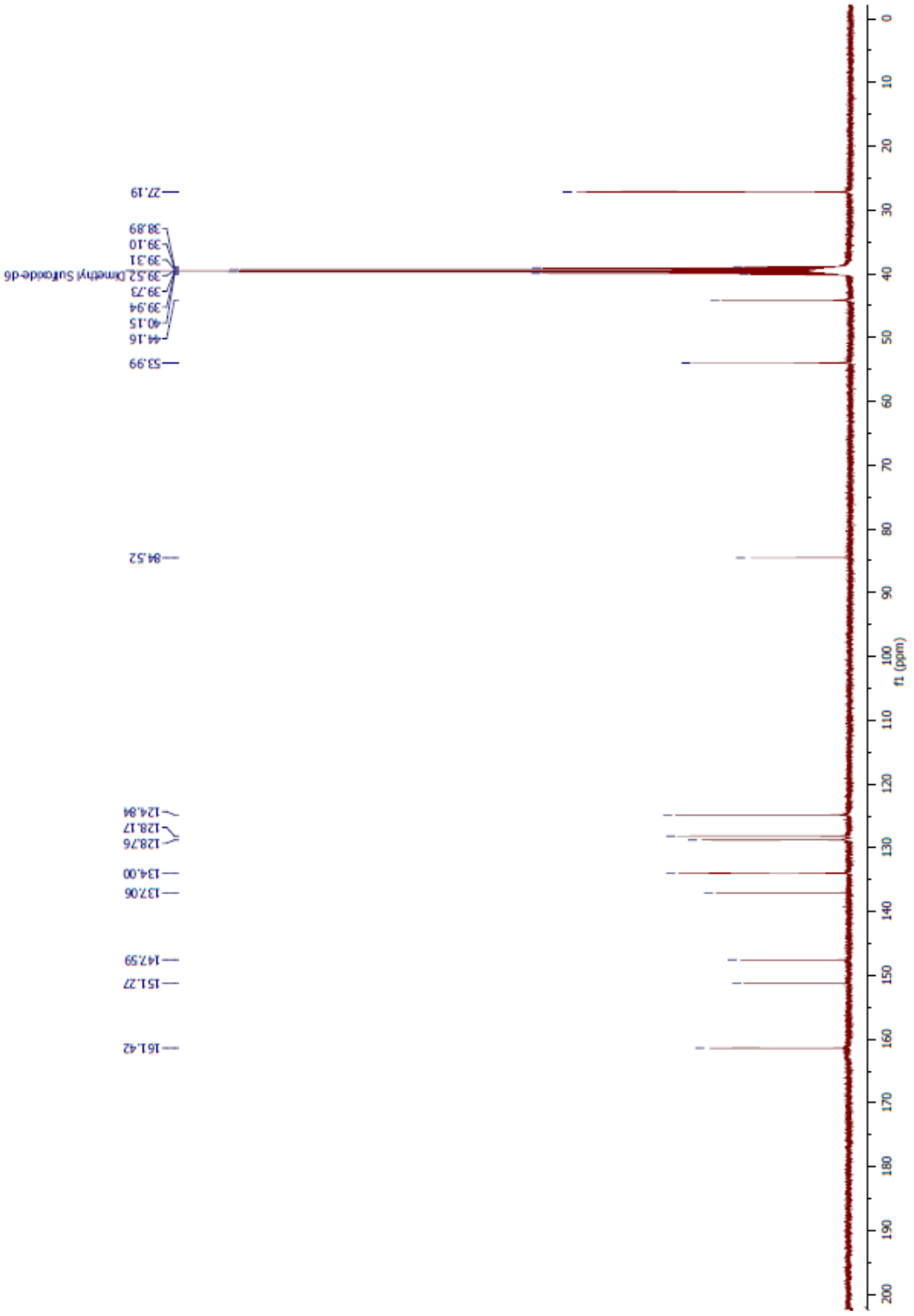


25

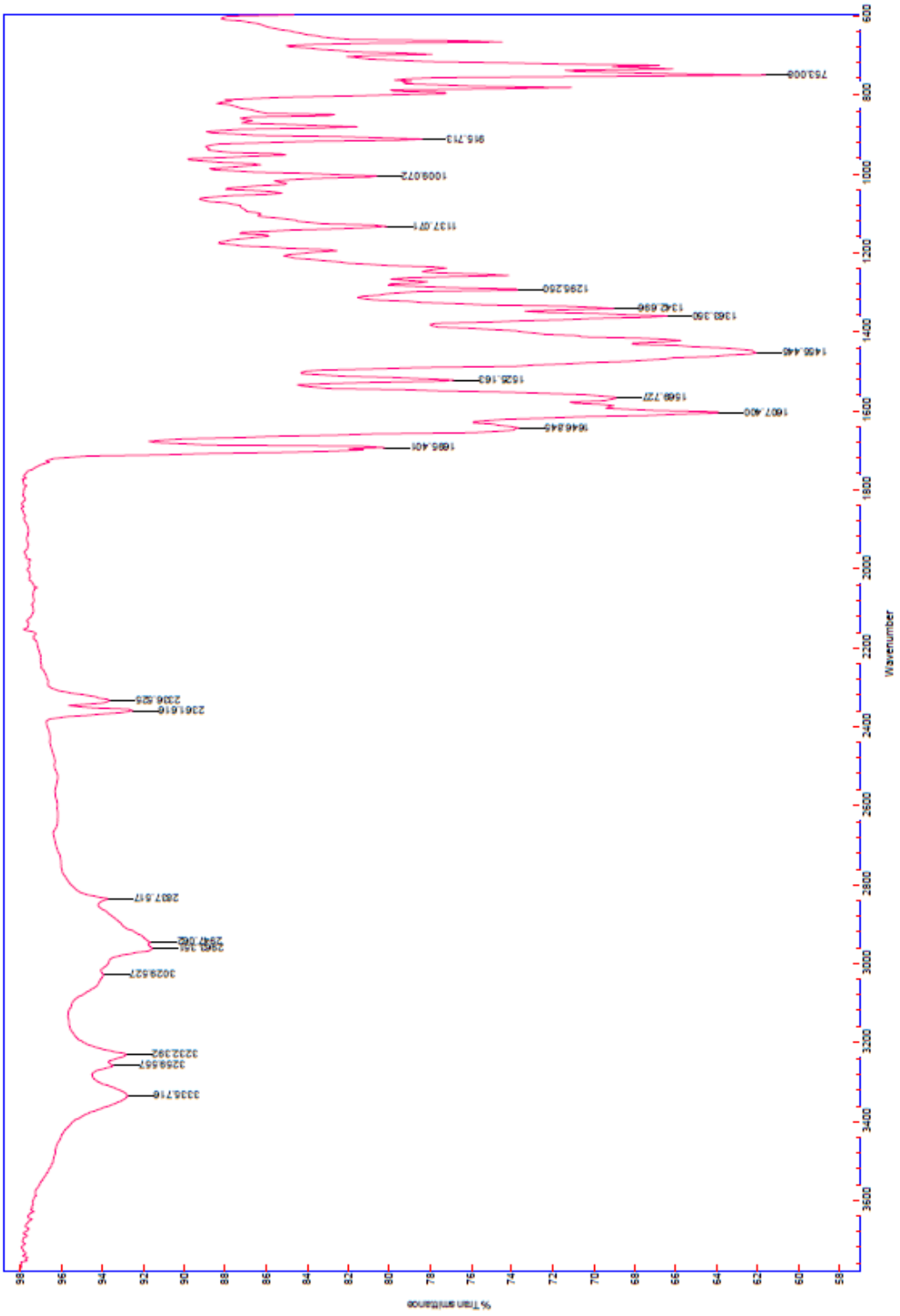
B.10.1 ^{1}H NMR spectrum of 25



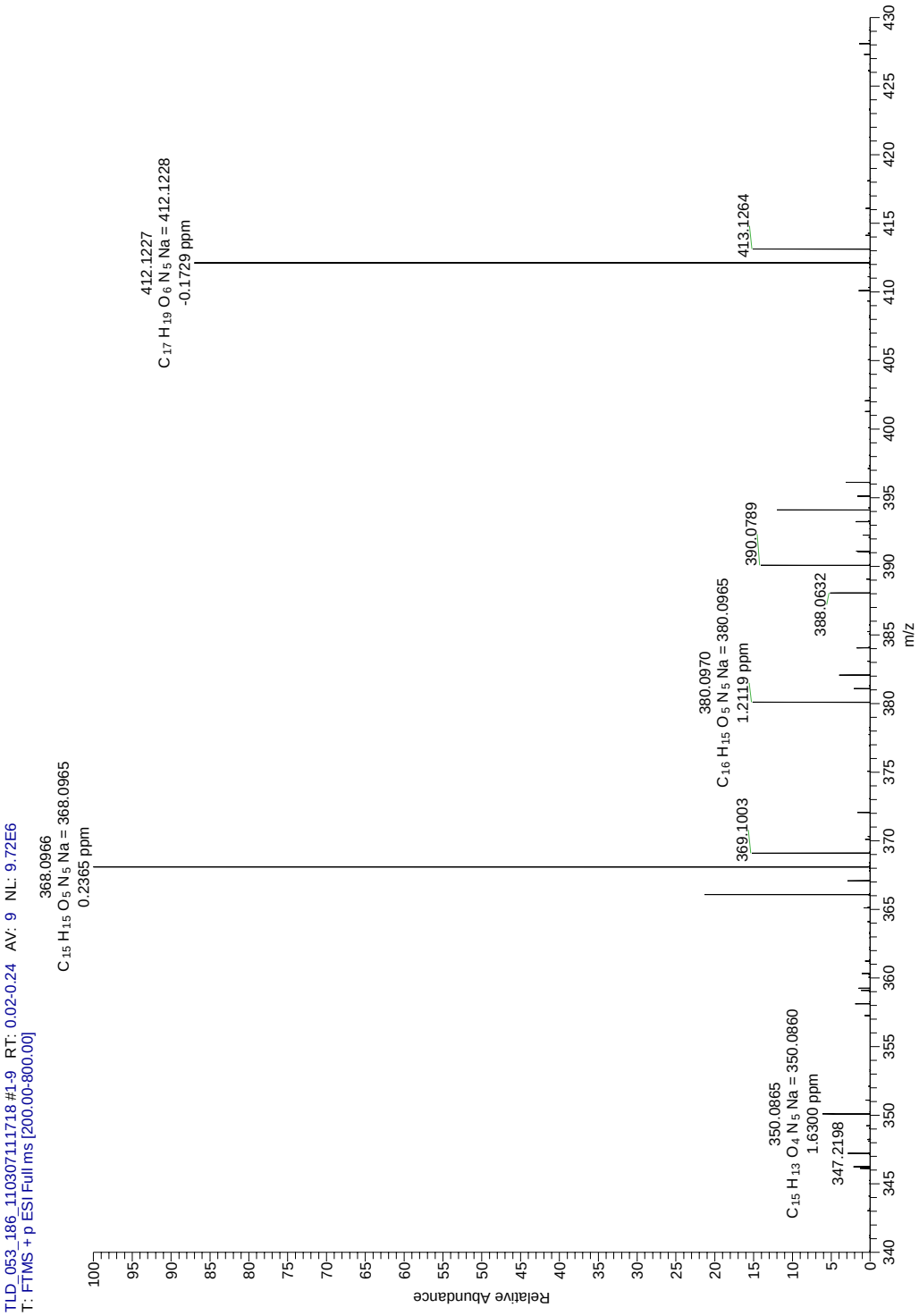
B.10.2 ^{13}C NMR spectrum of 25



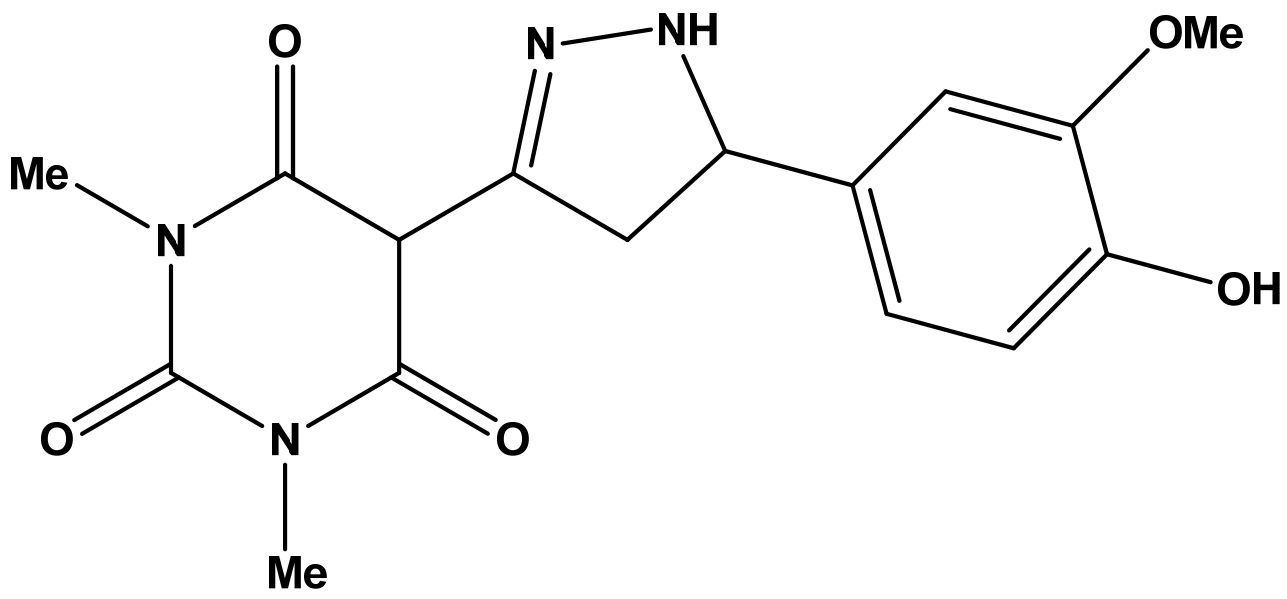
B.10.3 IR spectrum of 25



B.10.4 HRMS of 25

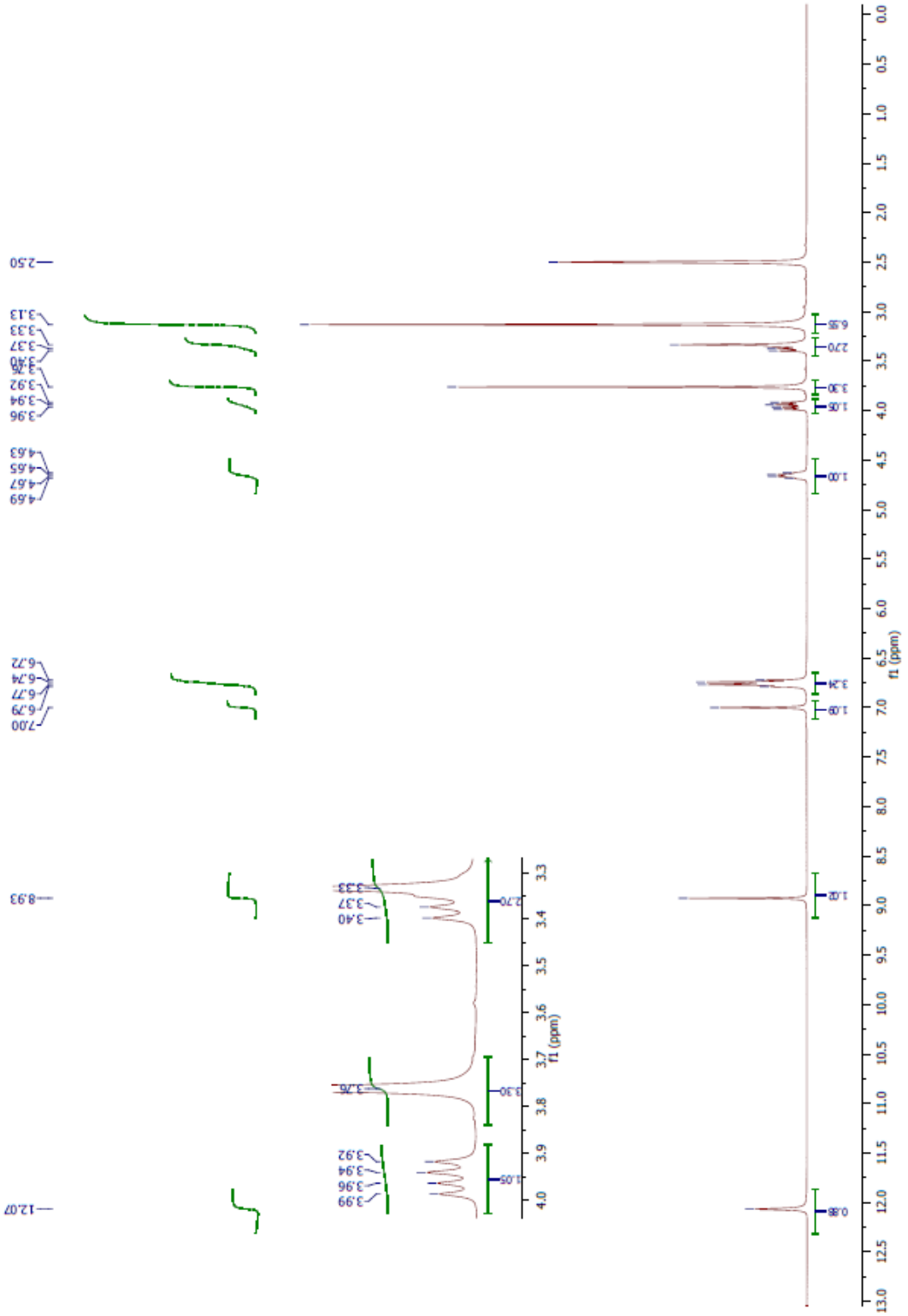


B.11 Spectroscopic data for 26

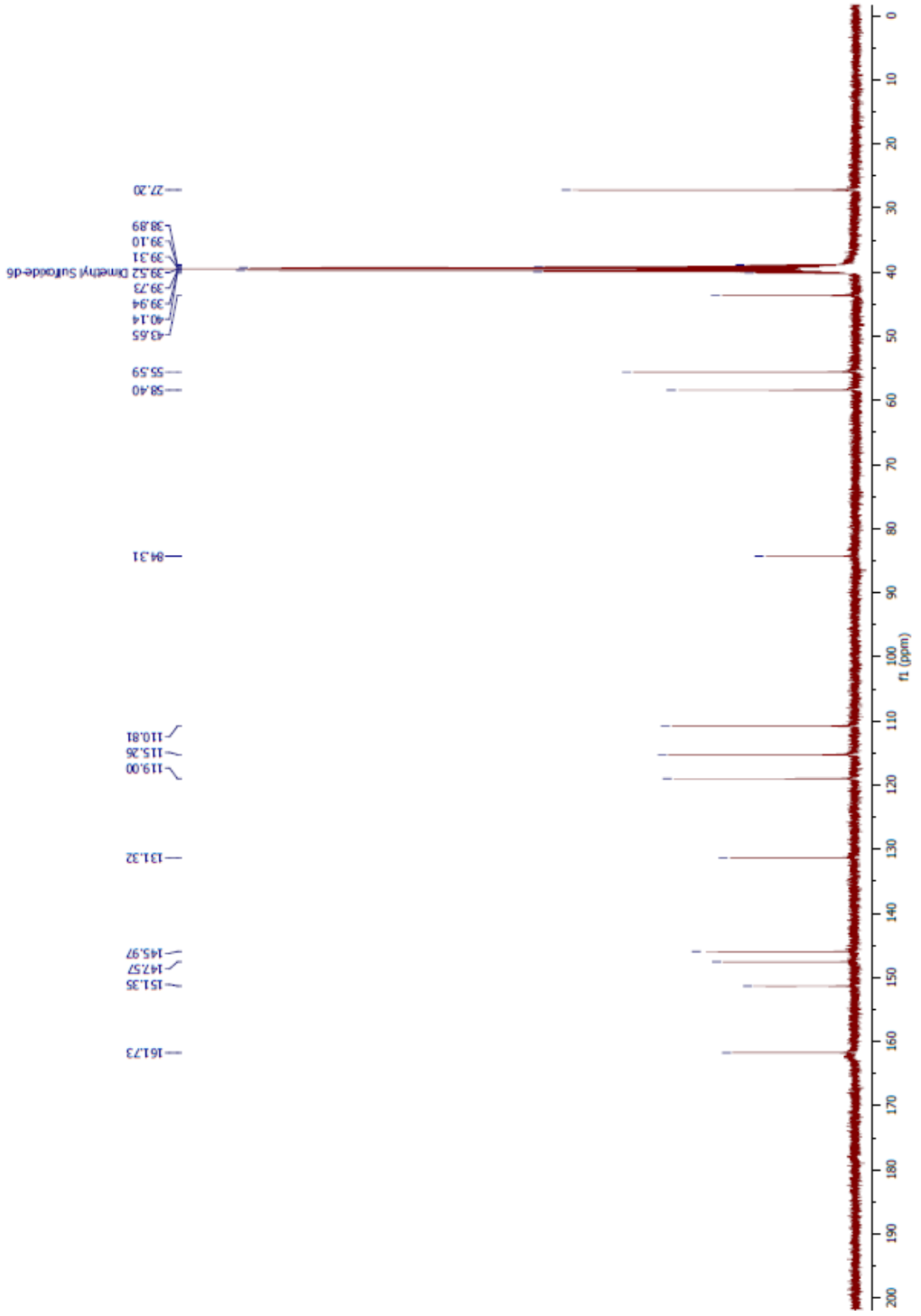


26

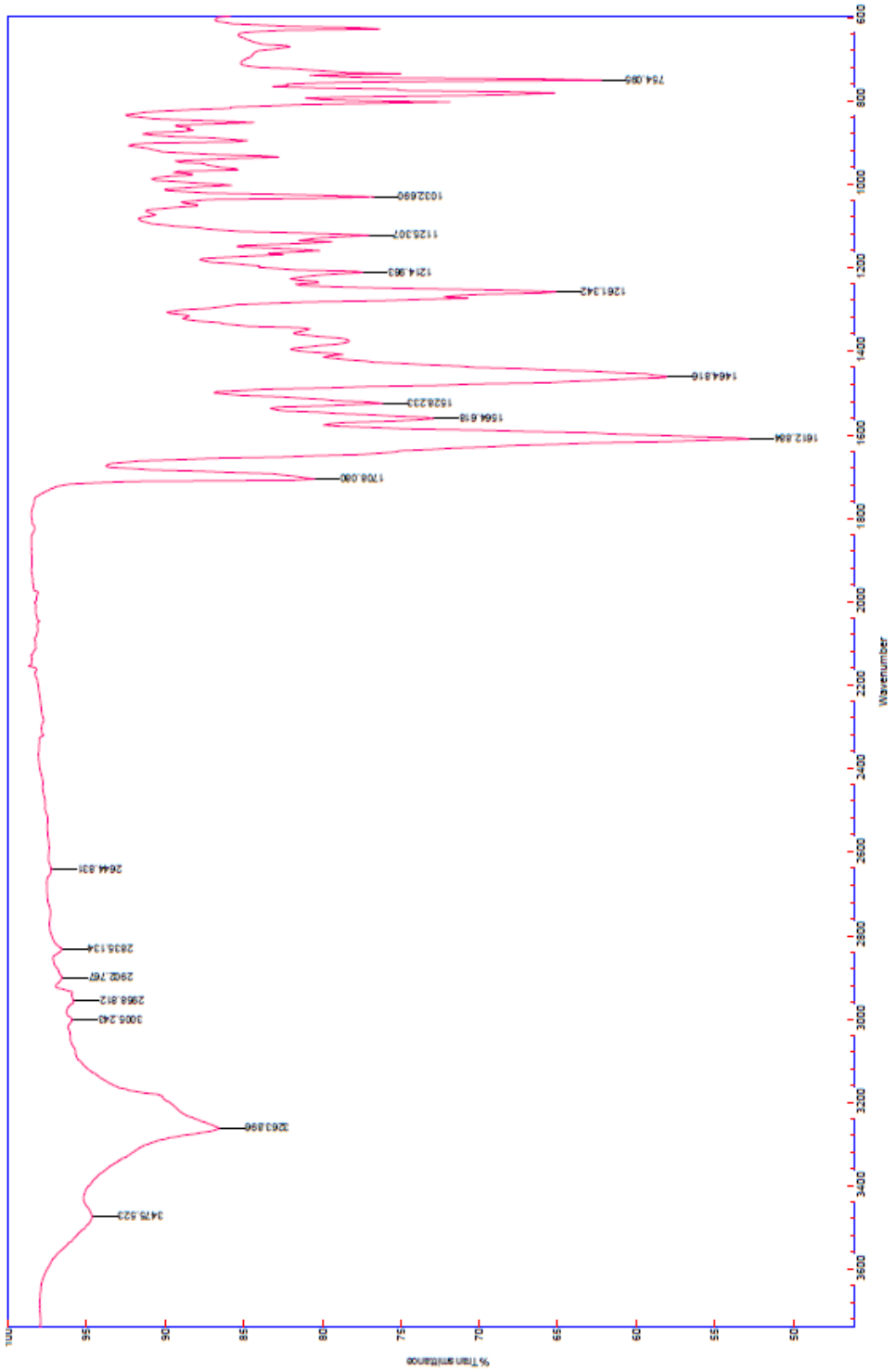
B.11.1 ^{1}H NMR spectrum of 26



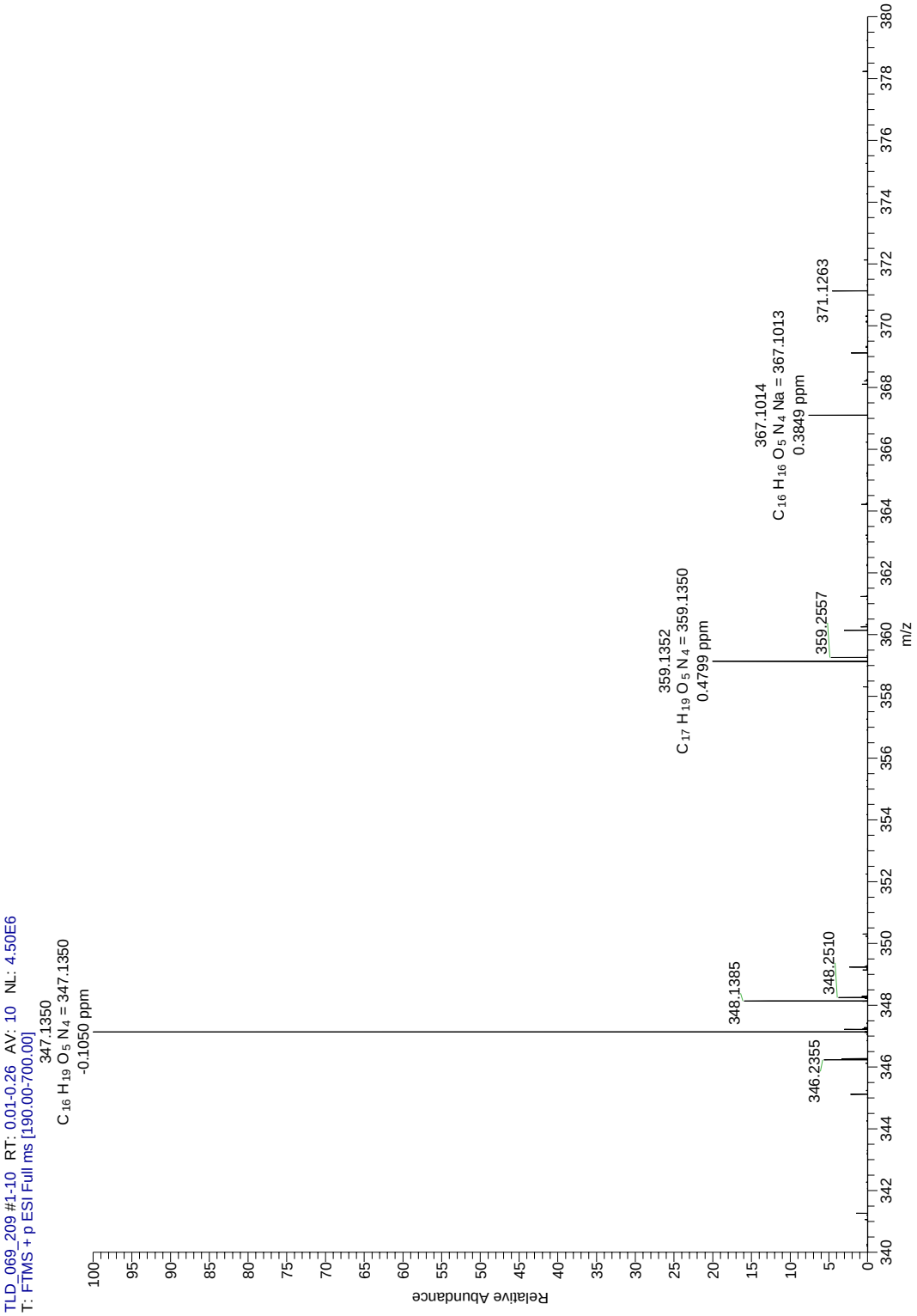
B.11.2 ^{13}C NMR spectrum of 26



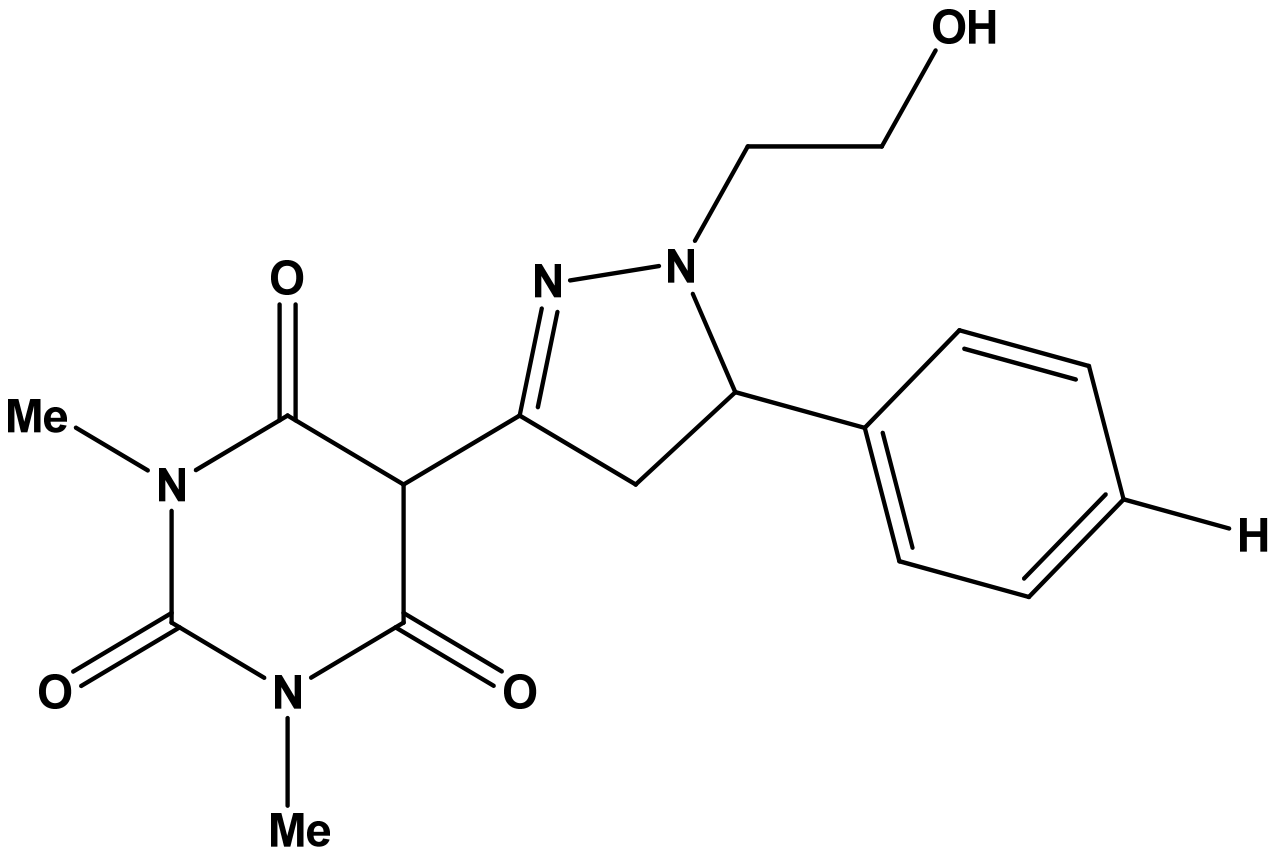
B.11.3 IR spectrum of 26



B.11.4 HRMS of 26

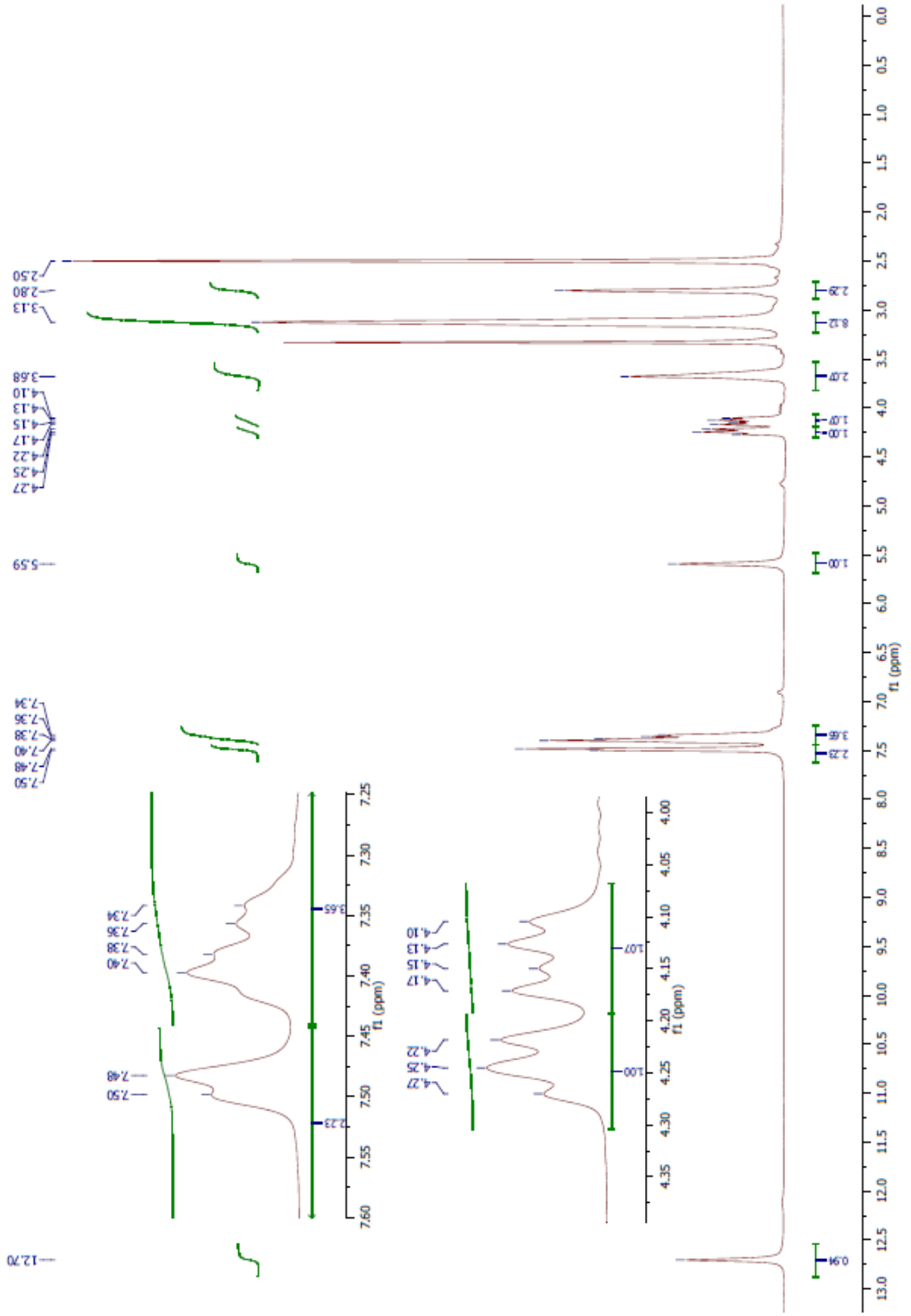


B.12 Spectroscopic data for 27

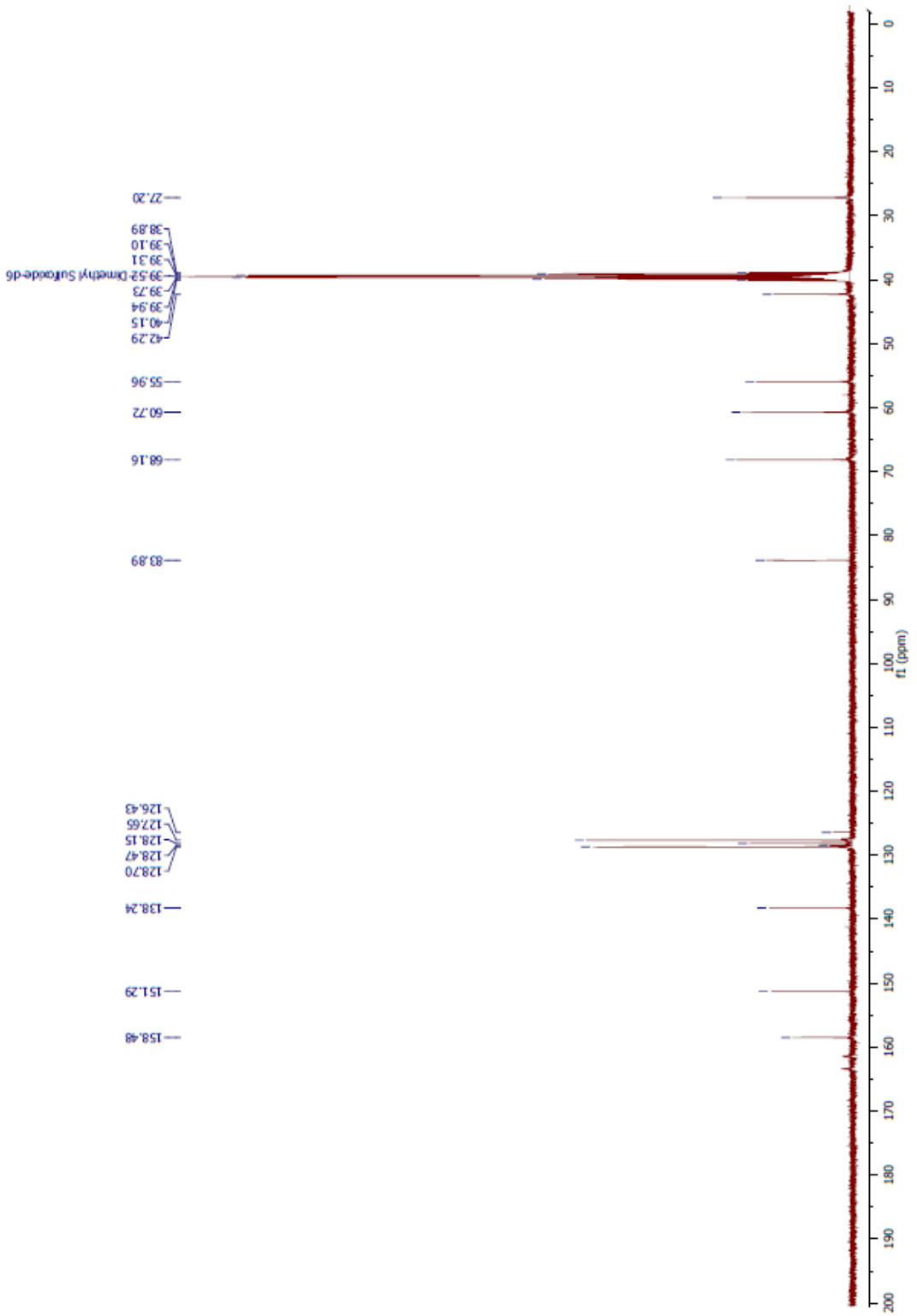


27

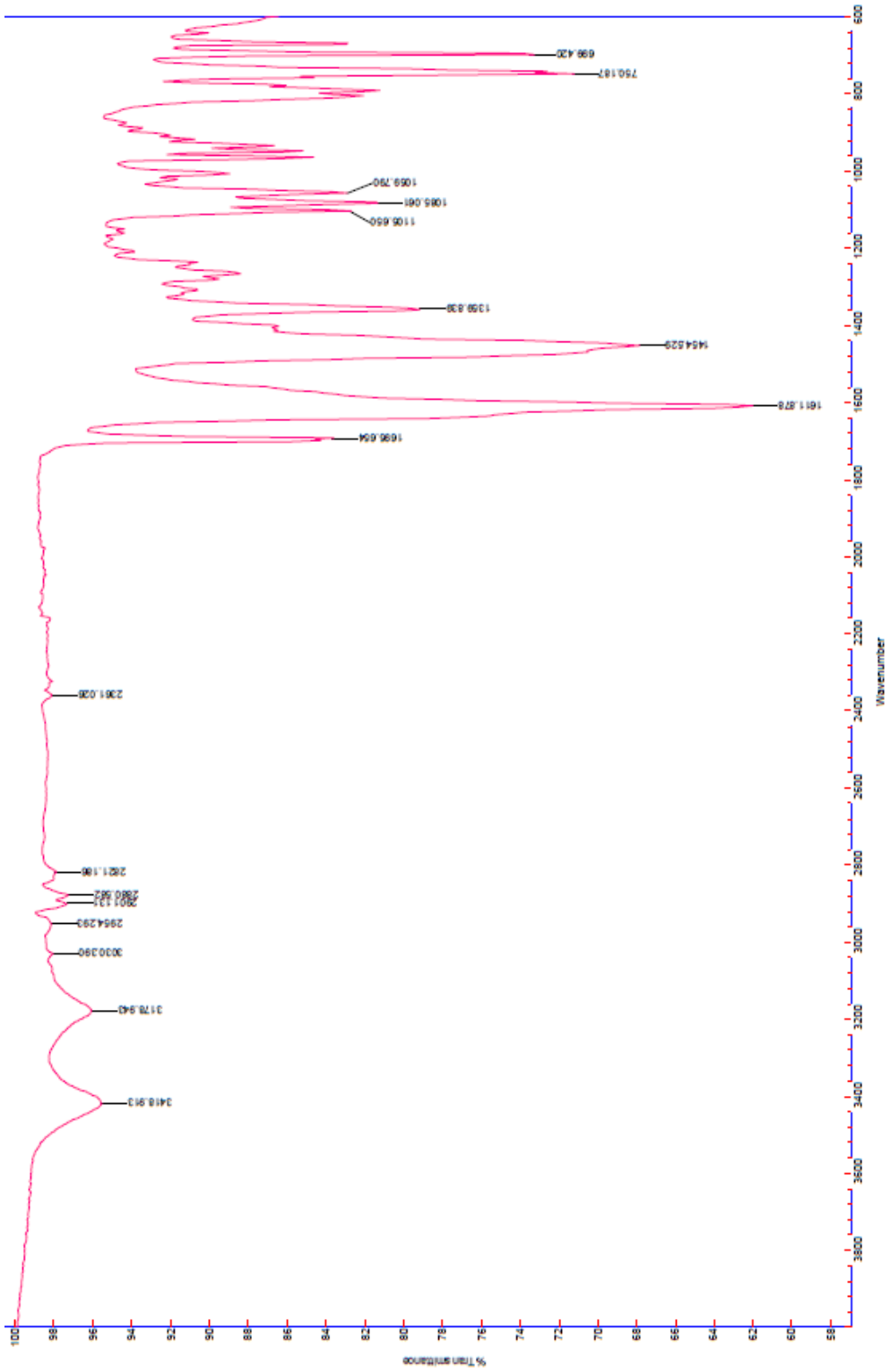
B.12.1 ^{1}H NMR spectrum of 27



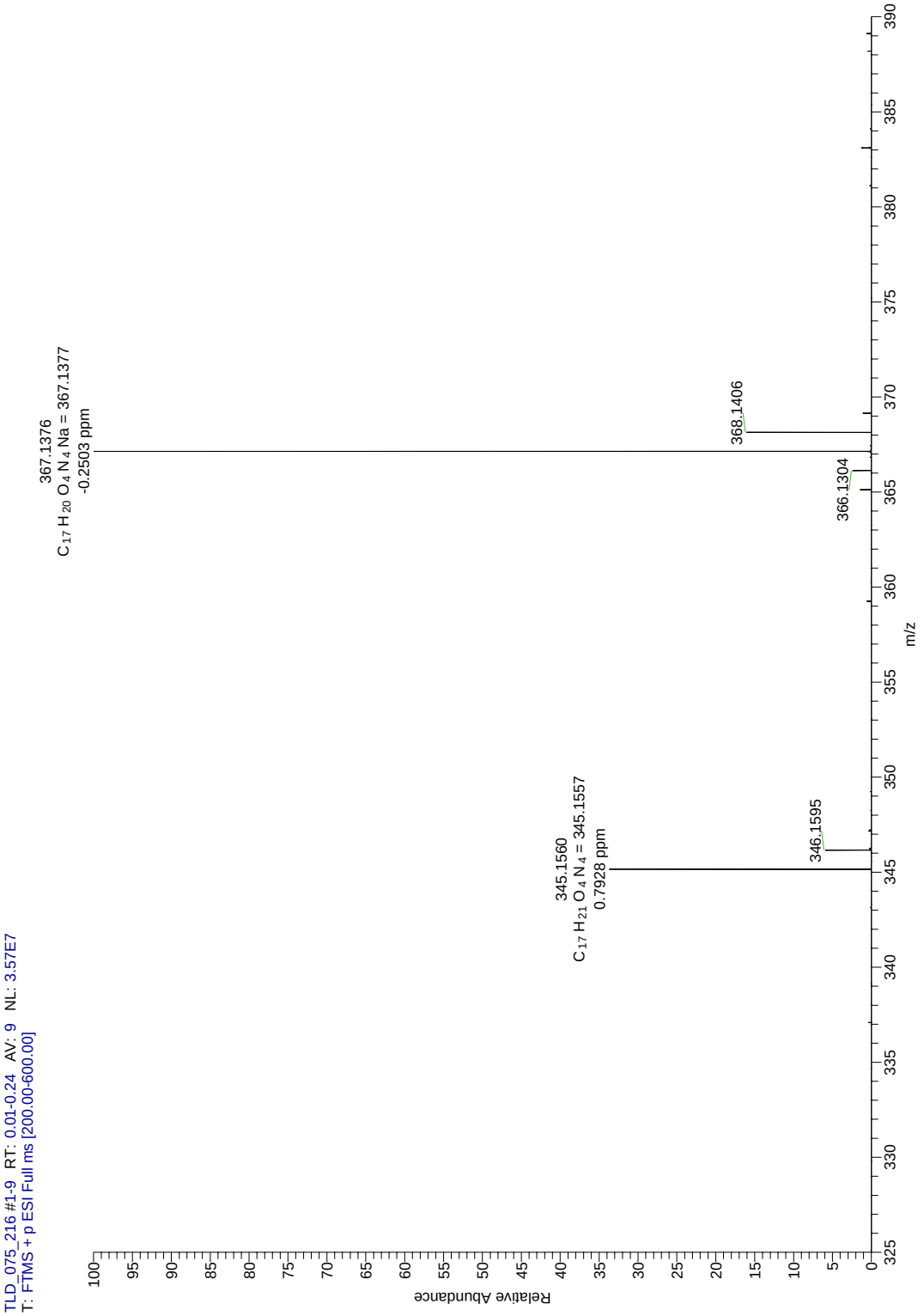
B.12.2 ^{13}C NMR spectrum of 27



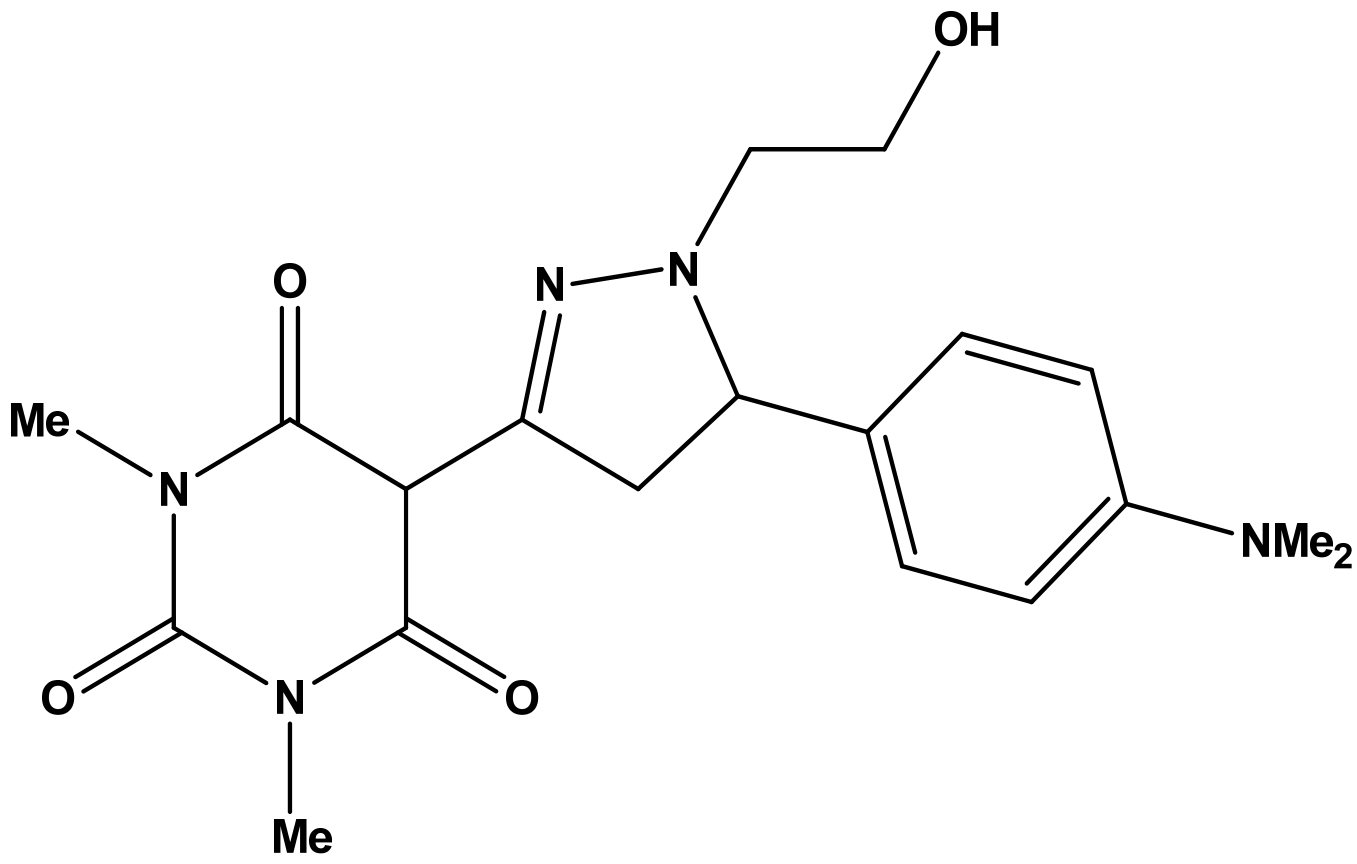
B.12.3 IR spectrum of 27



B.12.4 HRMS of 27

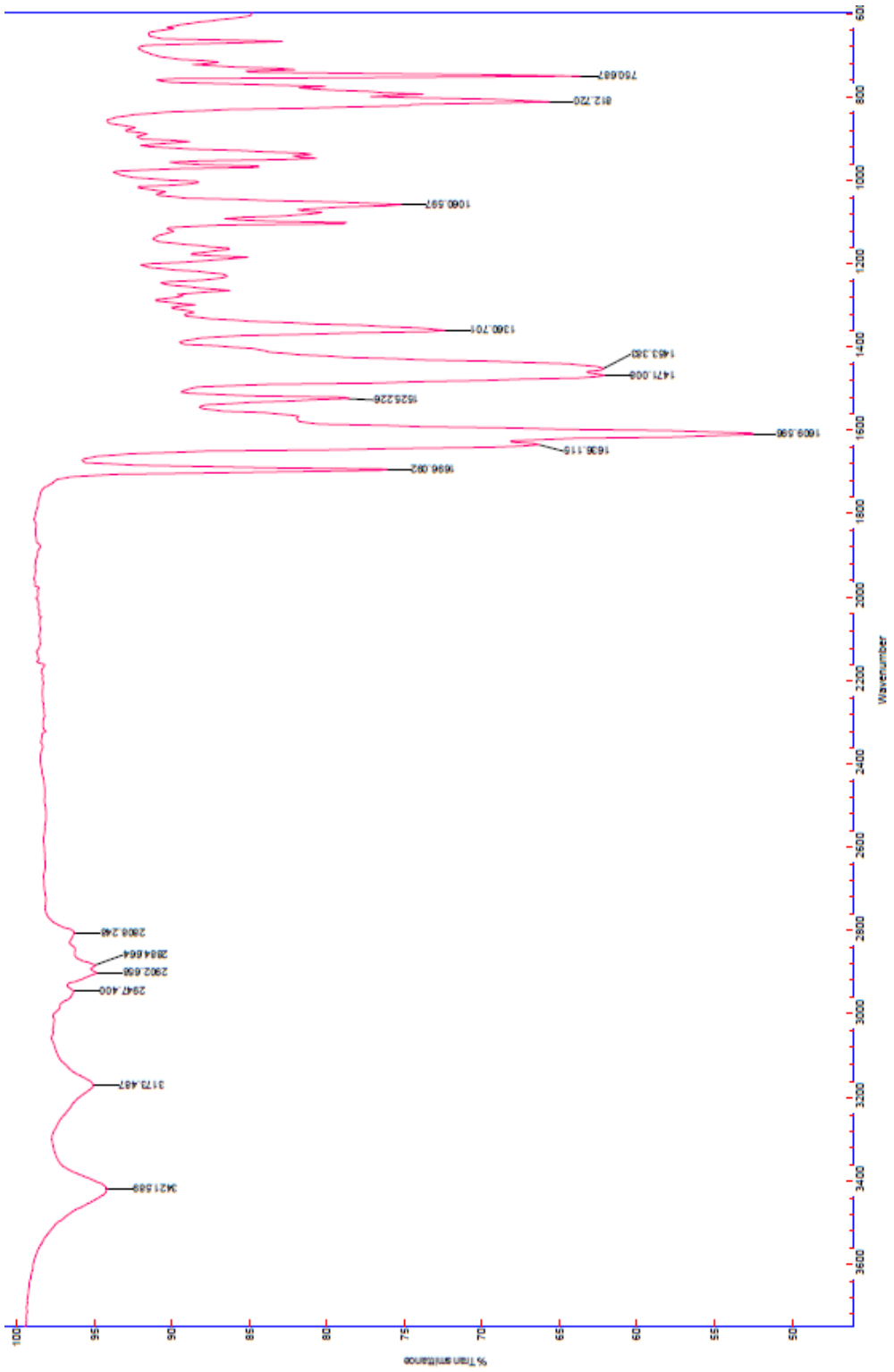


B.13 Spectroscopic data for 28

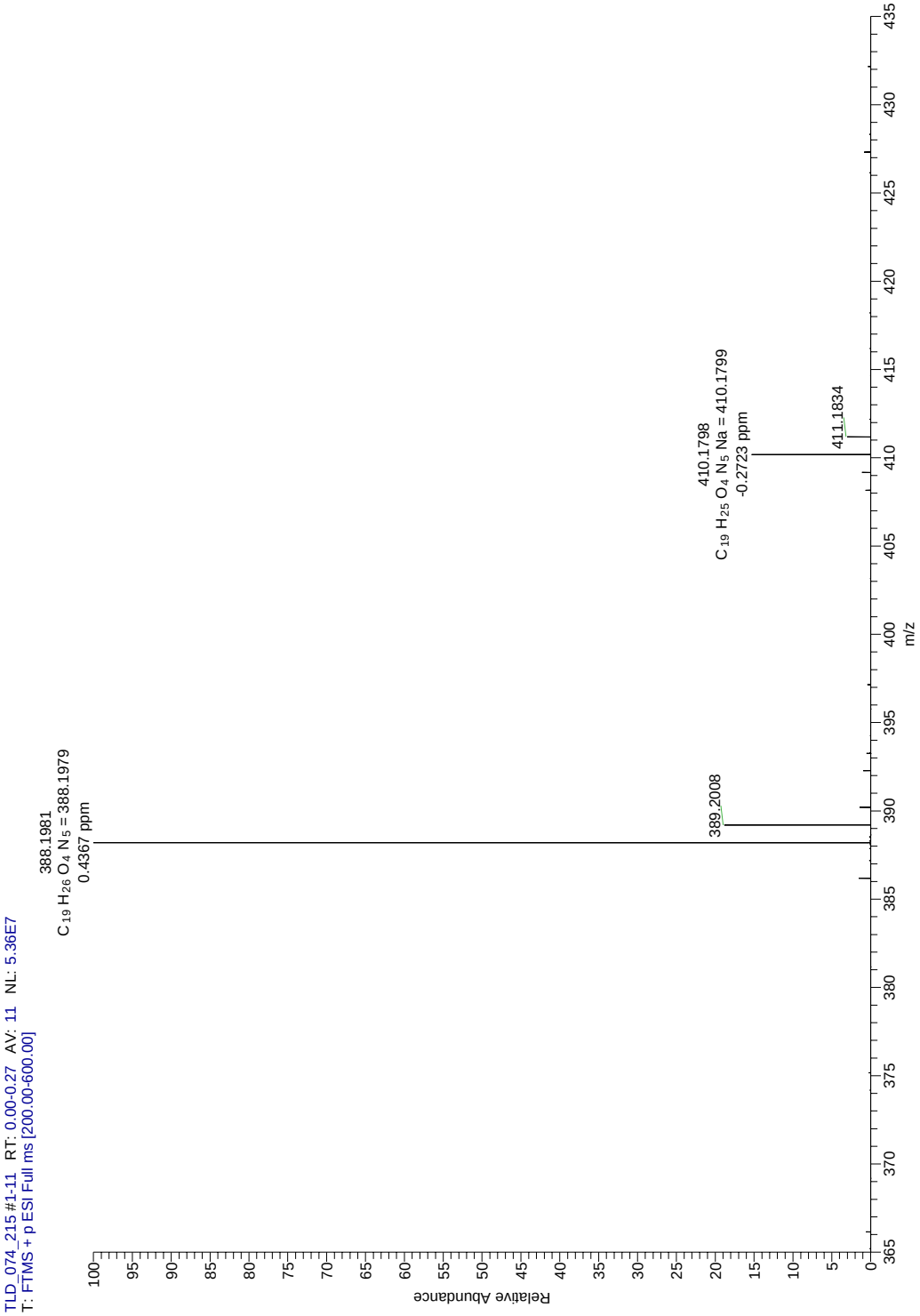


28

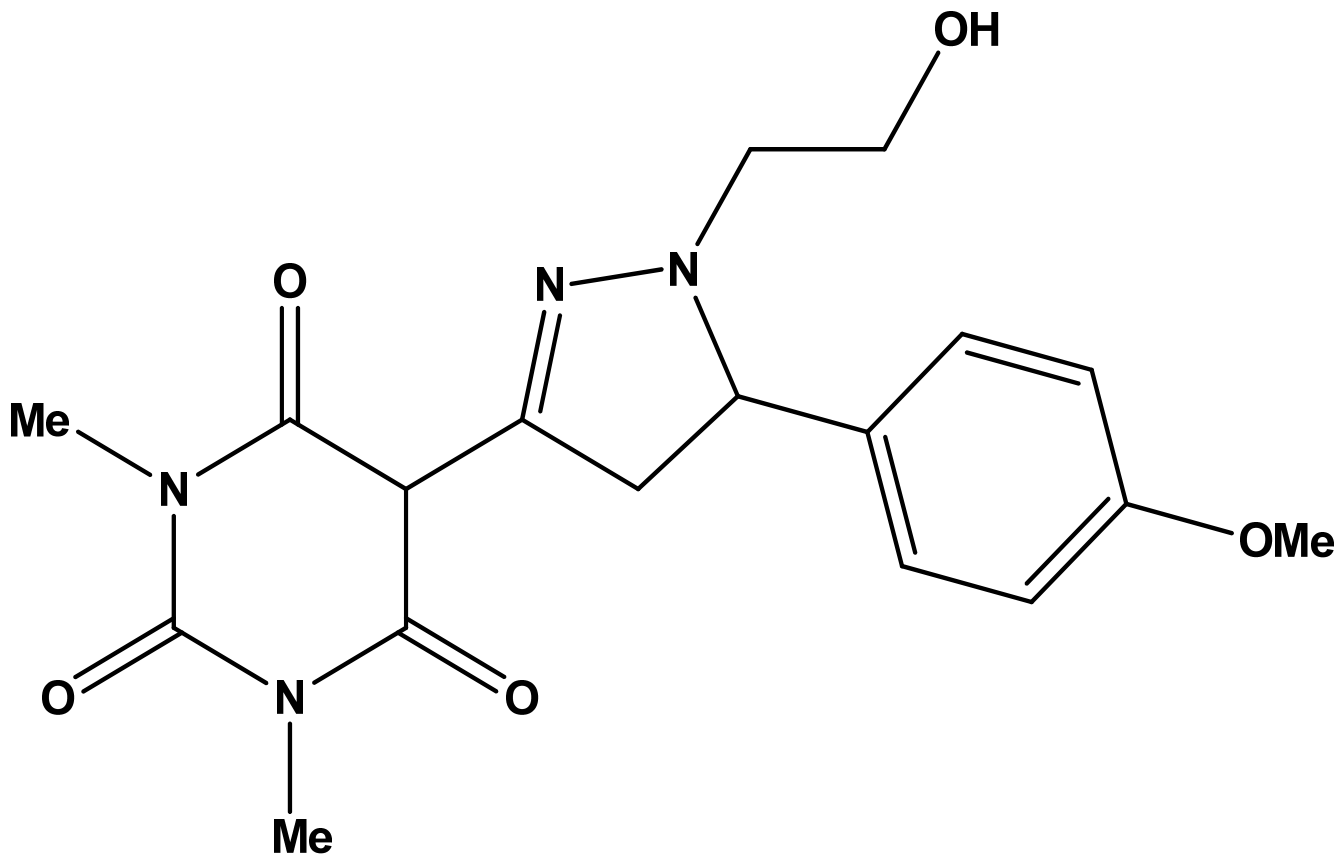
B.1.1 IR spectrum of 28



B.1.2 HRMS of 28

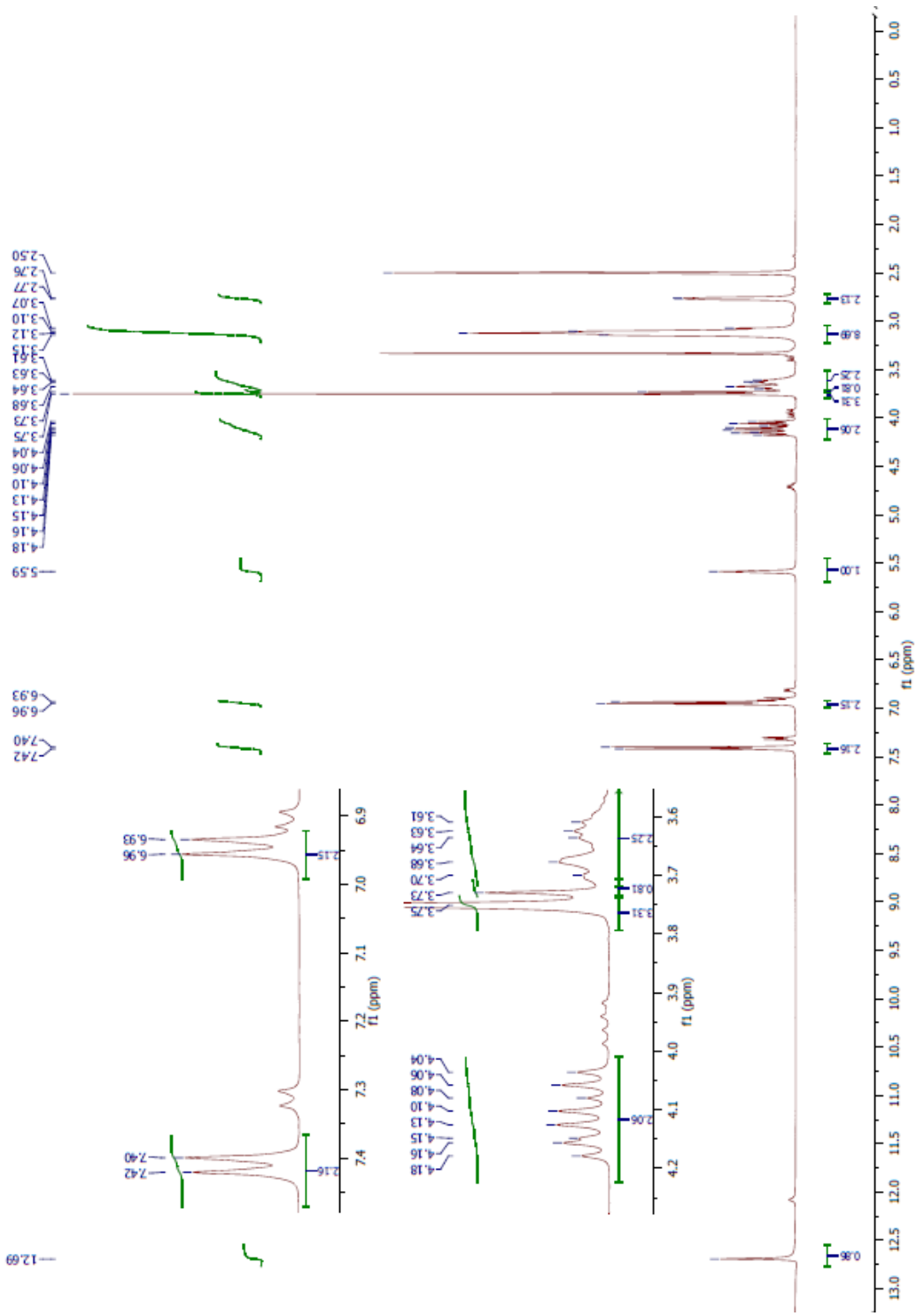


B.14 Spectroscopic data for 29

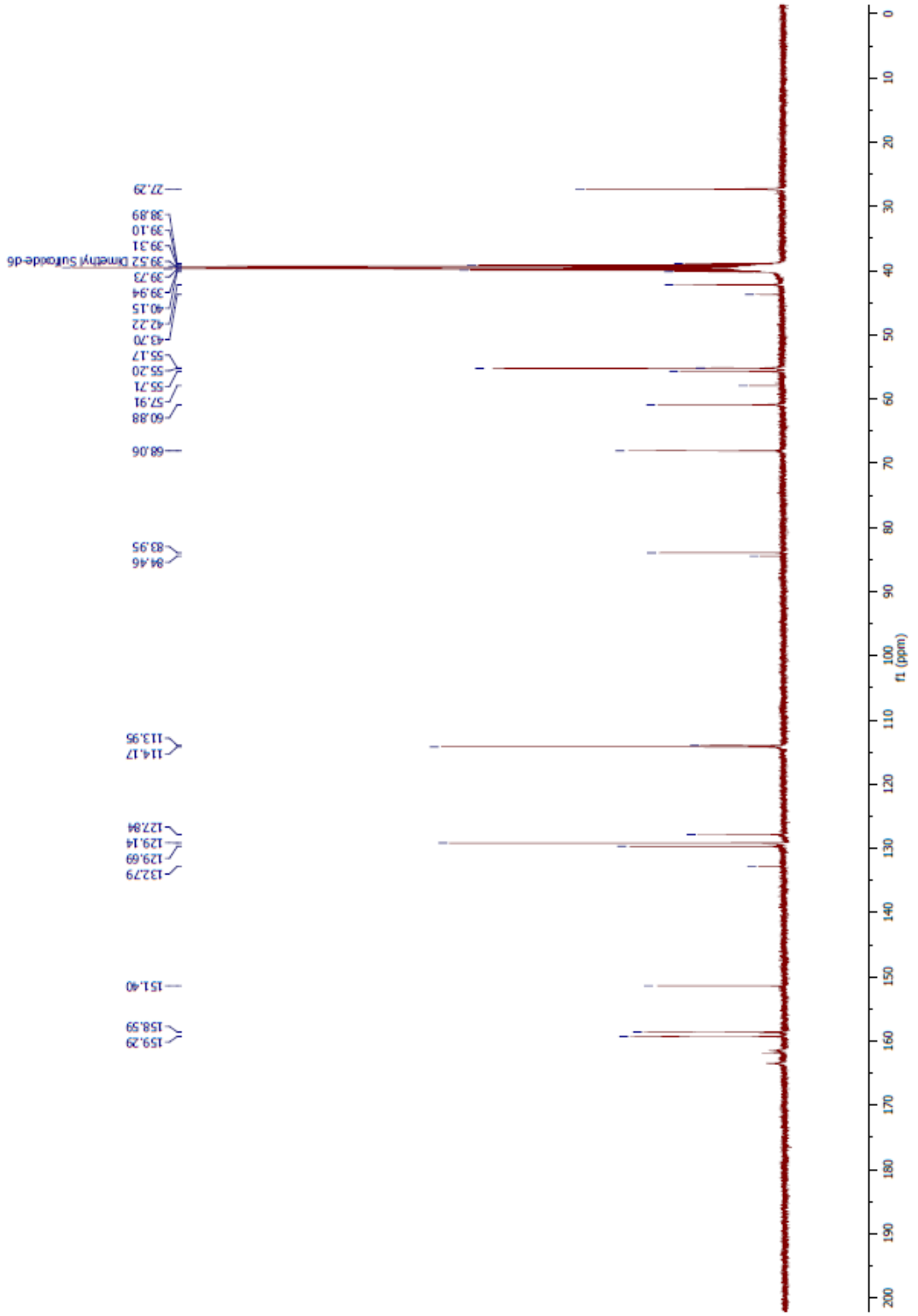


29

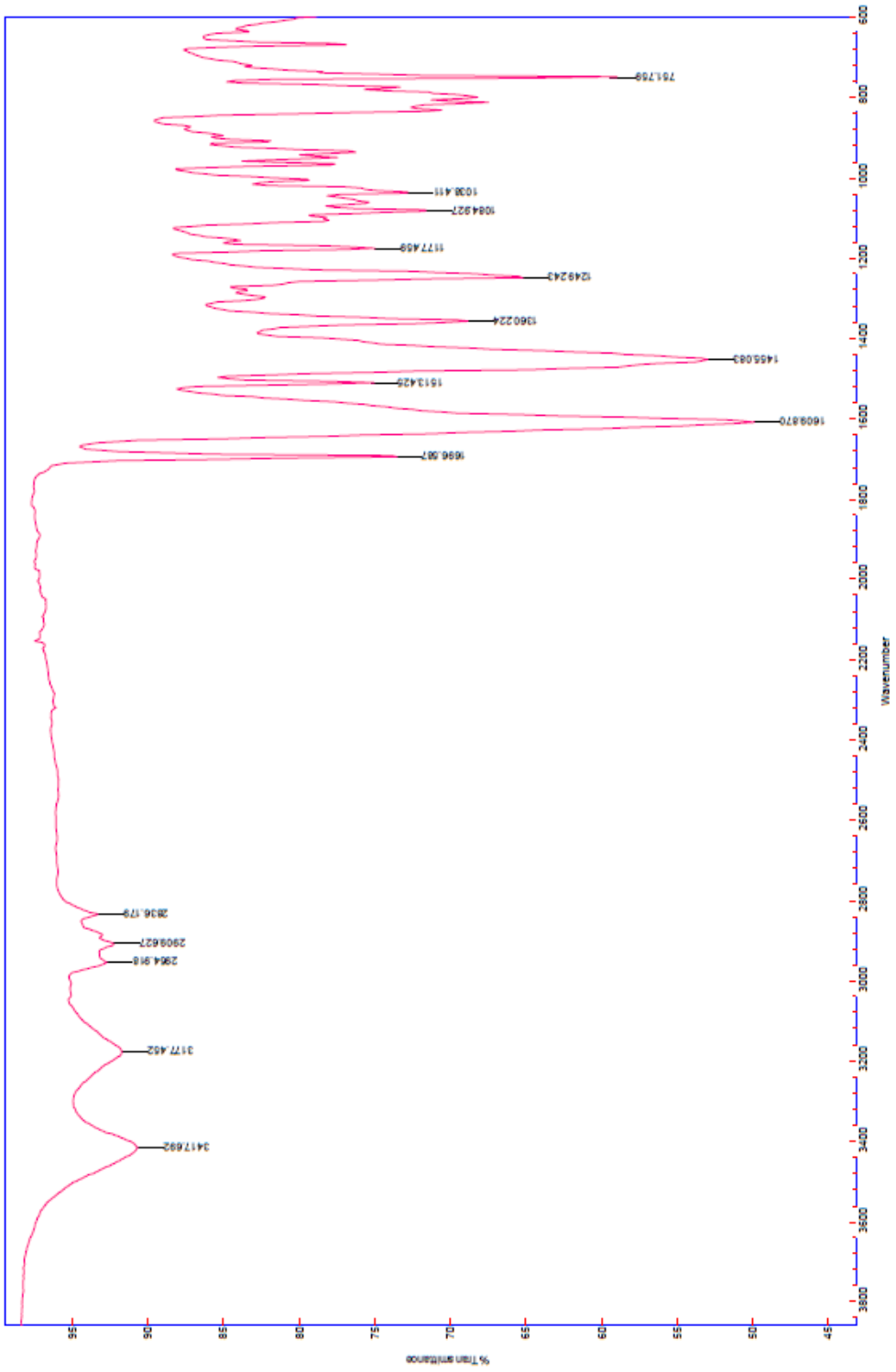
B.14.1 ^{1}H NMR spectrum of 29



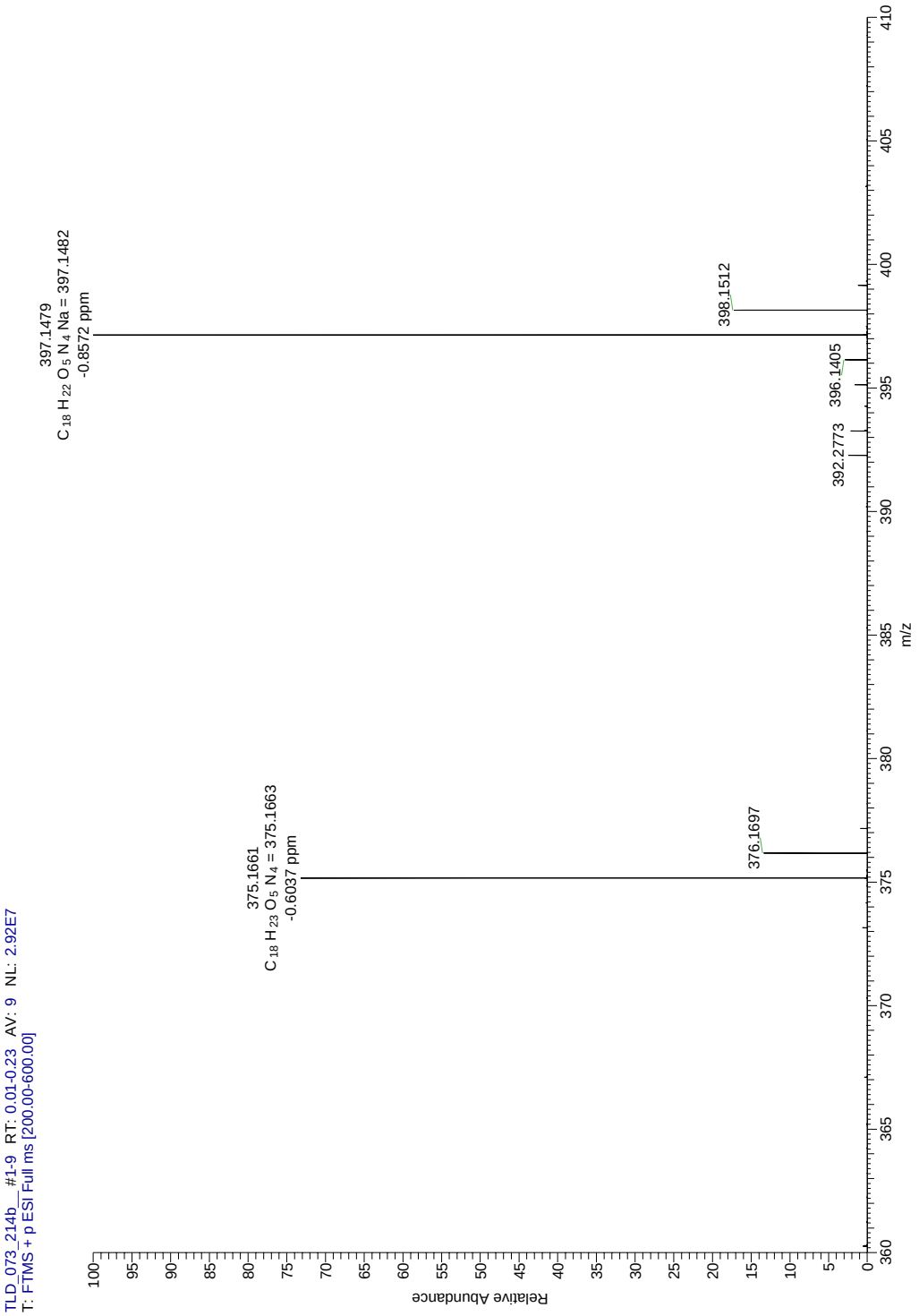
B.14.2 ^{13}C NMR spectrum of 29



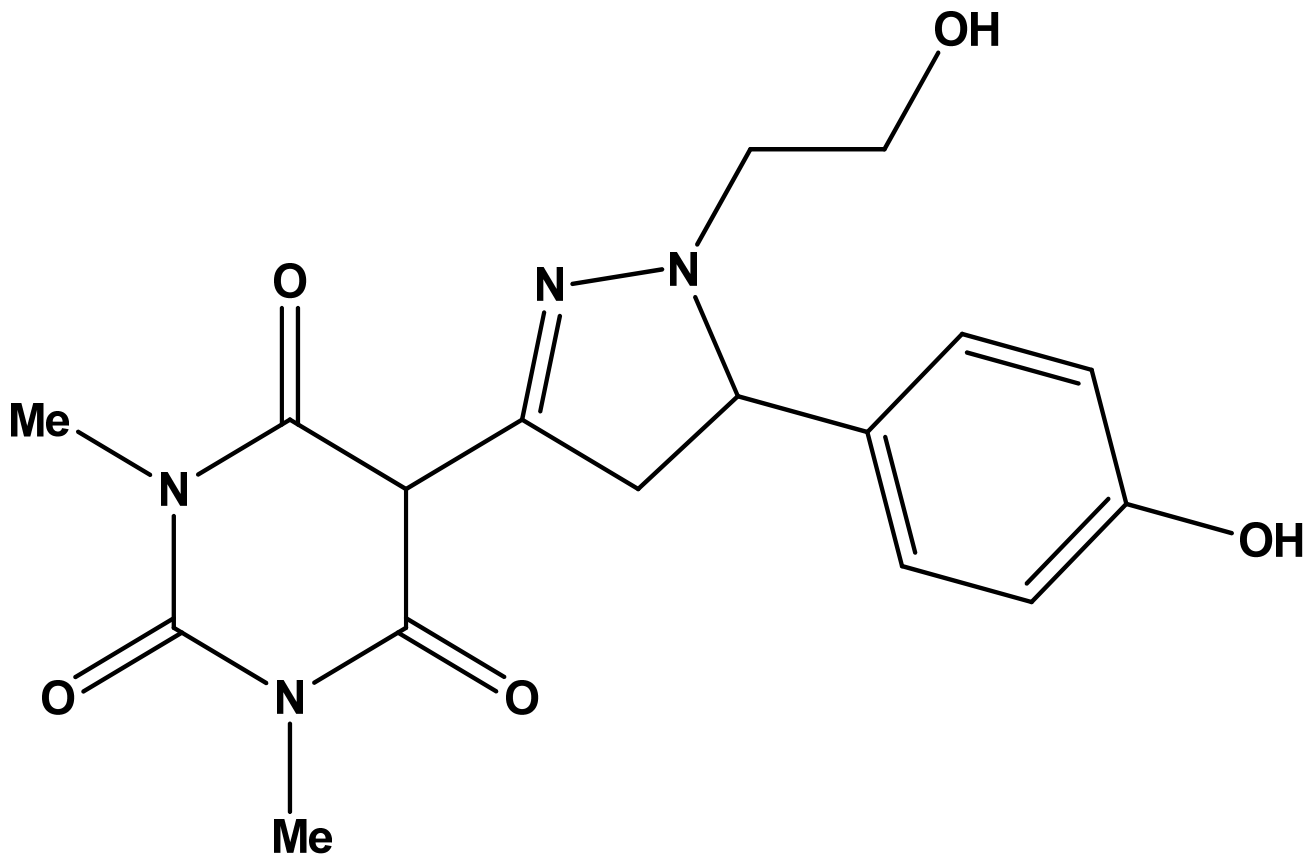
B.14.3 IR spectrum of 29



B.14.4 HRMSof 29

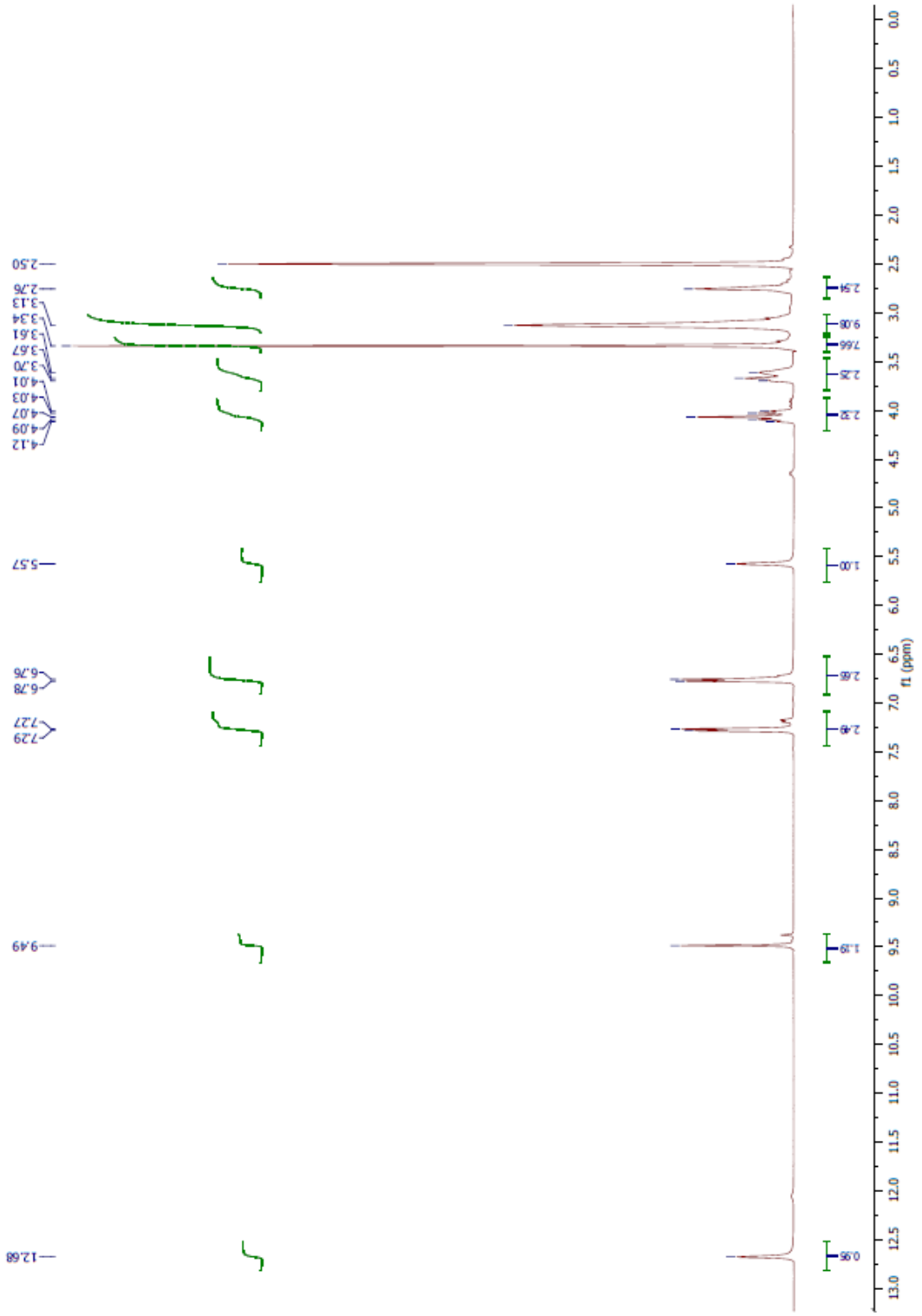


B.15 Spectroscopic data for 30

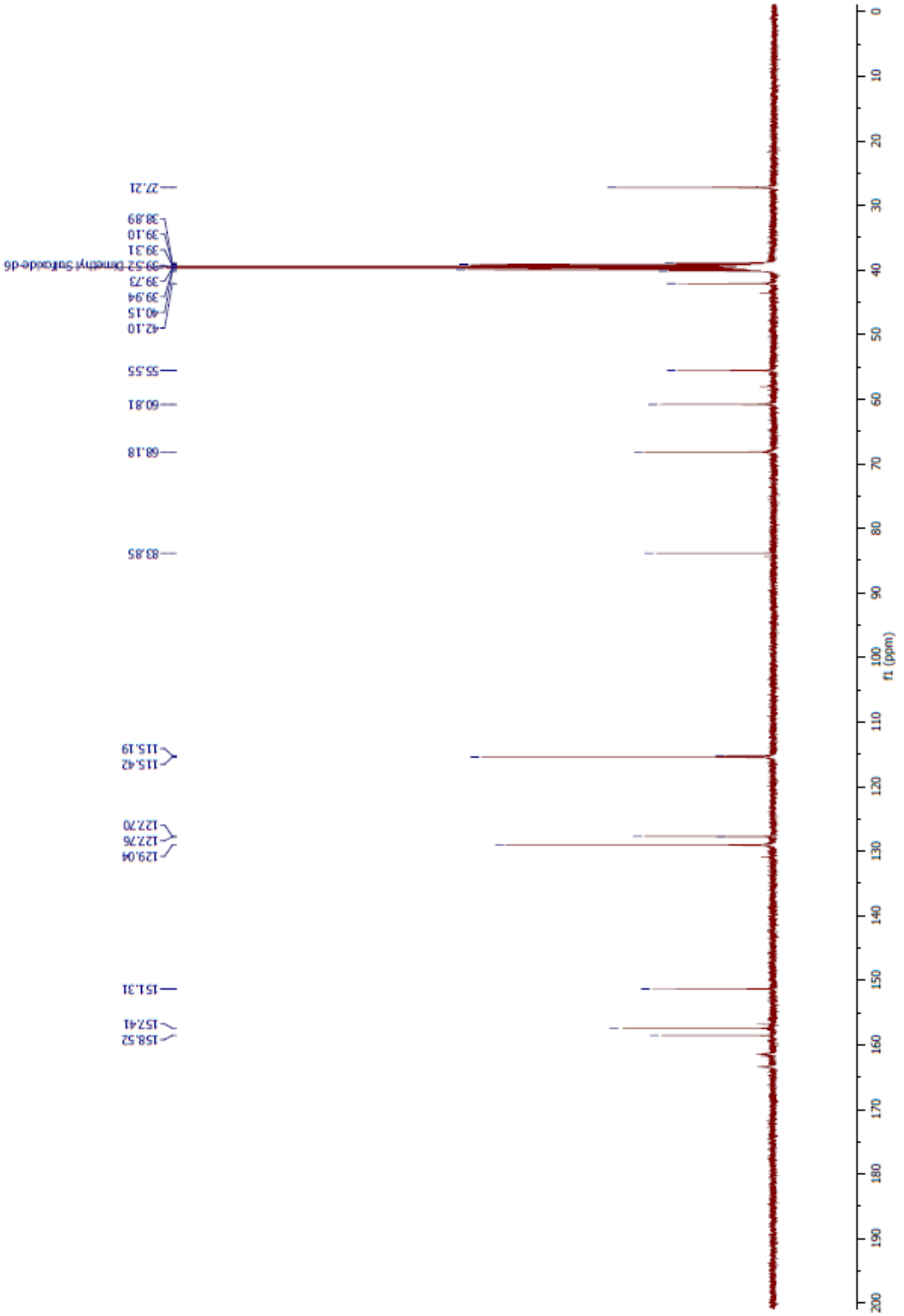


30

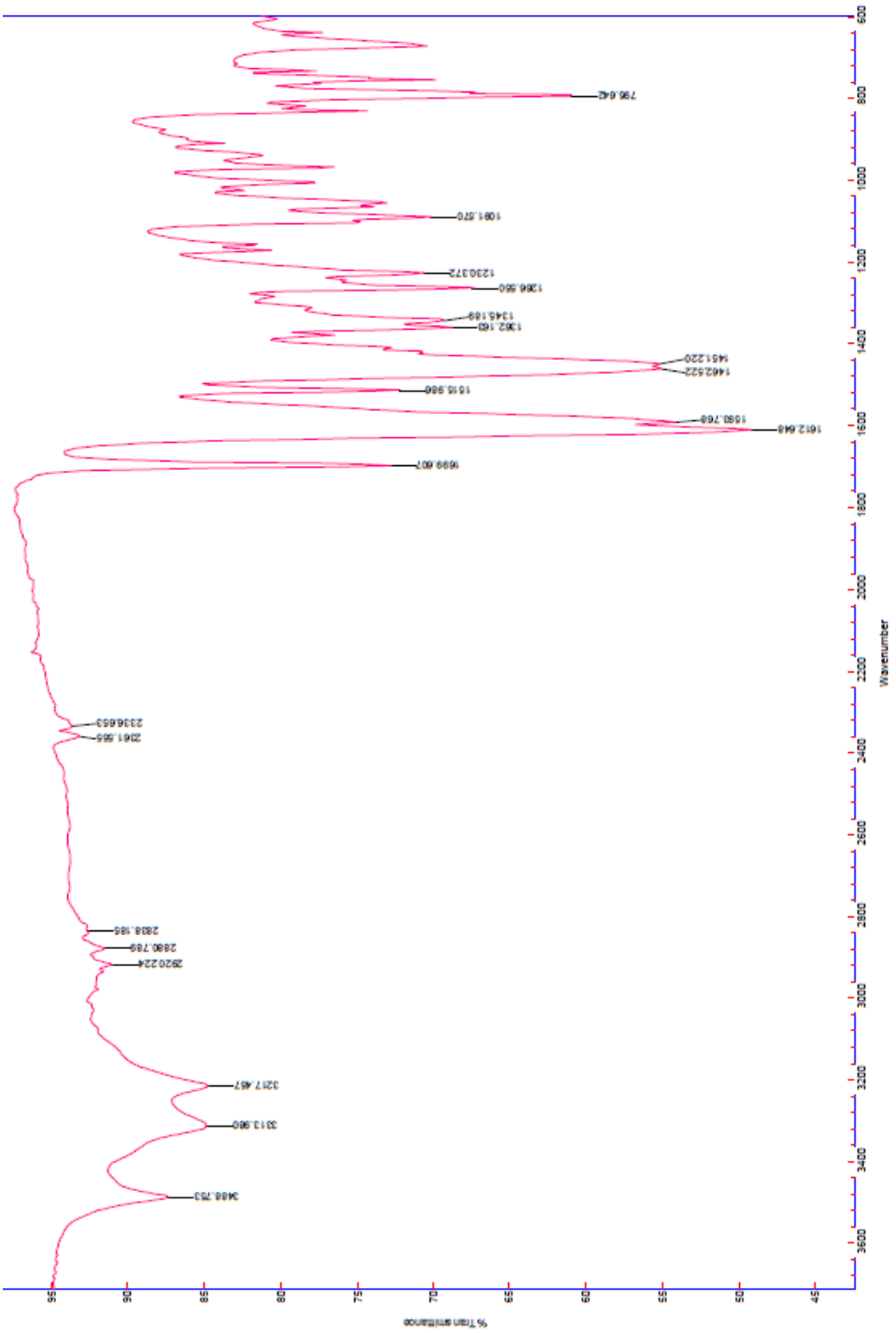
B.15.1 ^{1}H NMR spectrum of 30



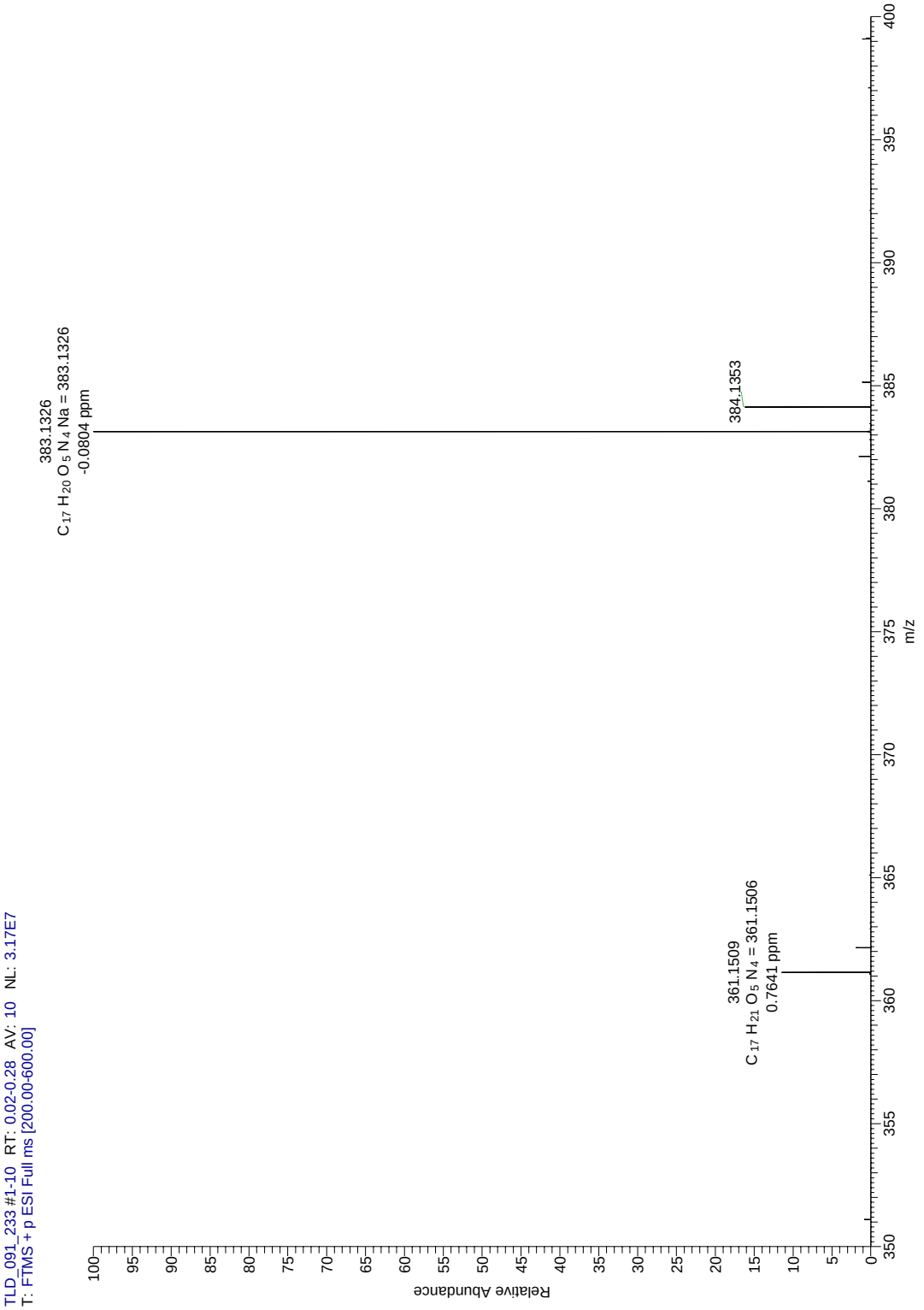
B.15.2 ^{13}C NMR spectrum of 30



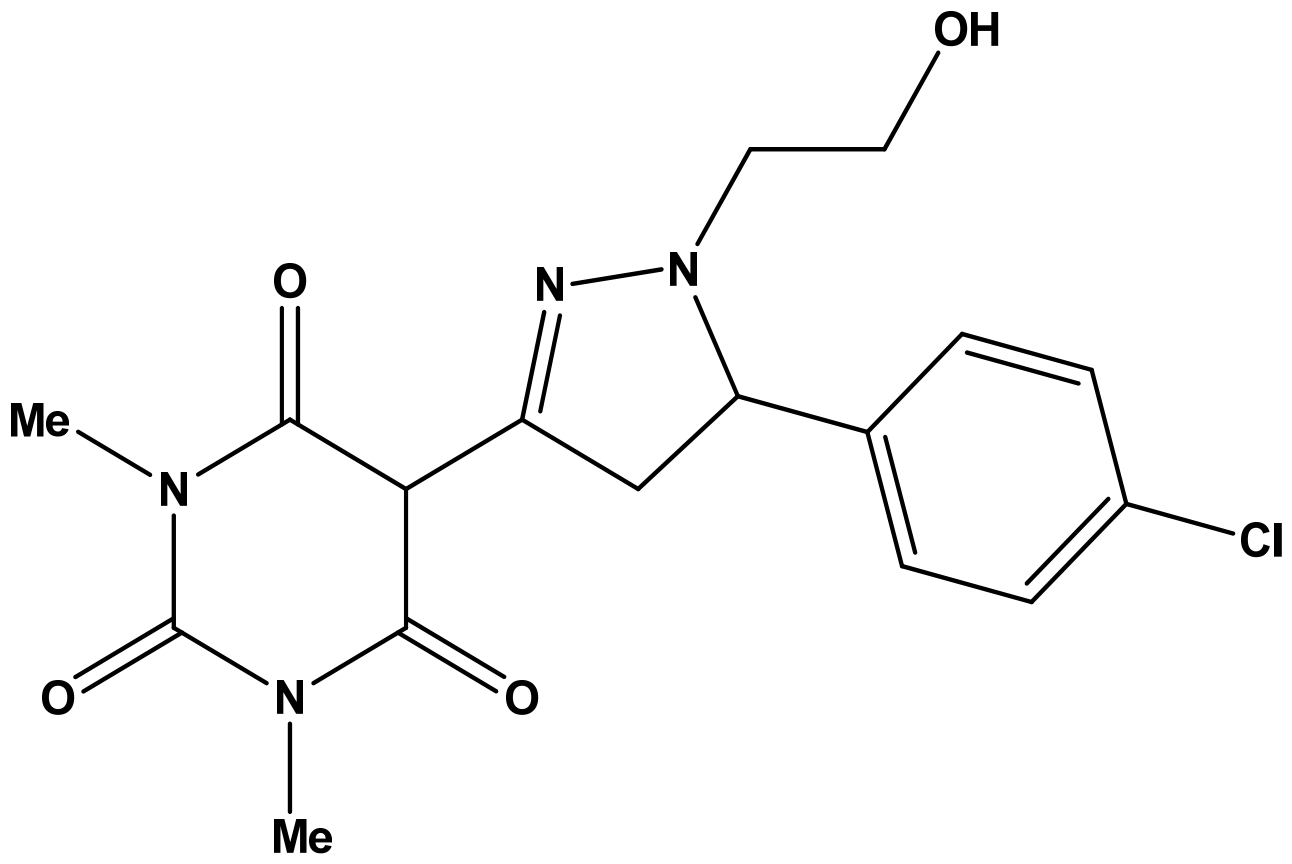
B.15.3 IR spectrum of 30



B.15.4 HRMS of 30

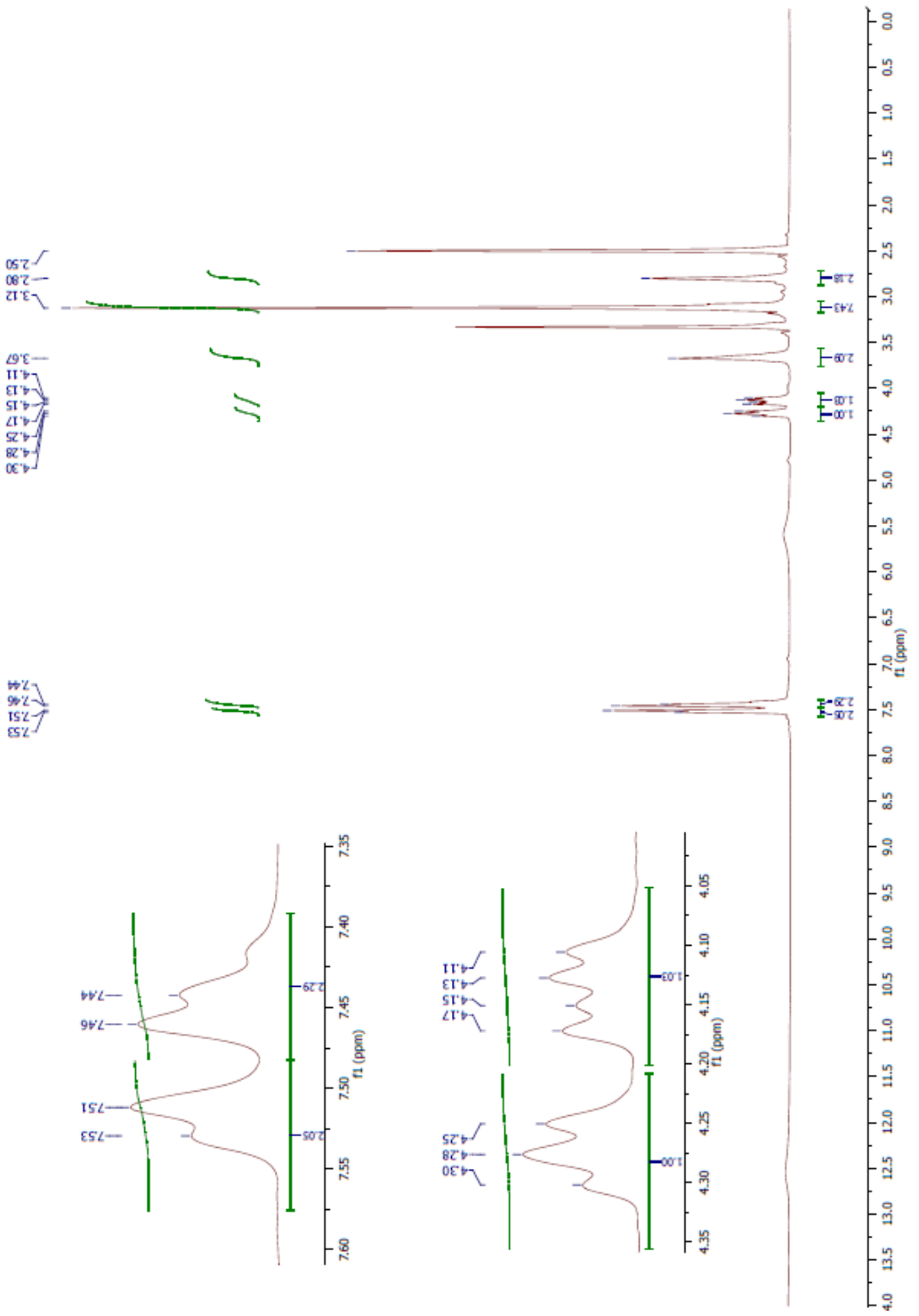


B.16 Spectroscopic data for 31

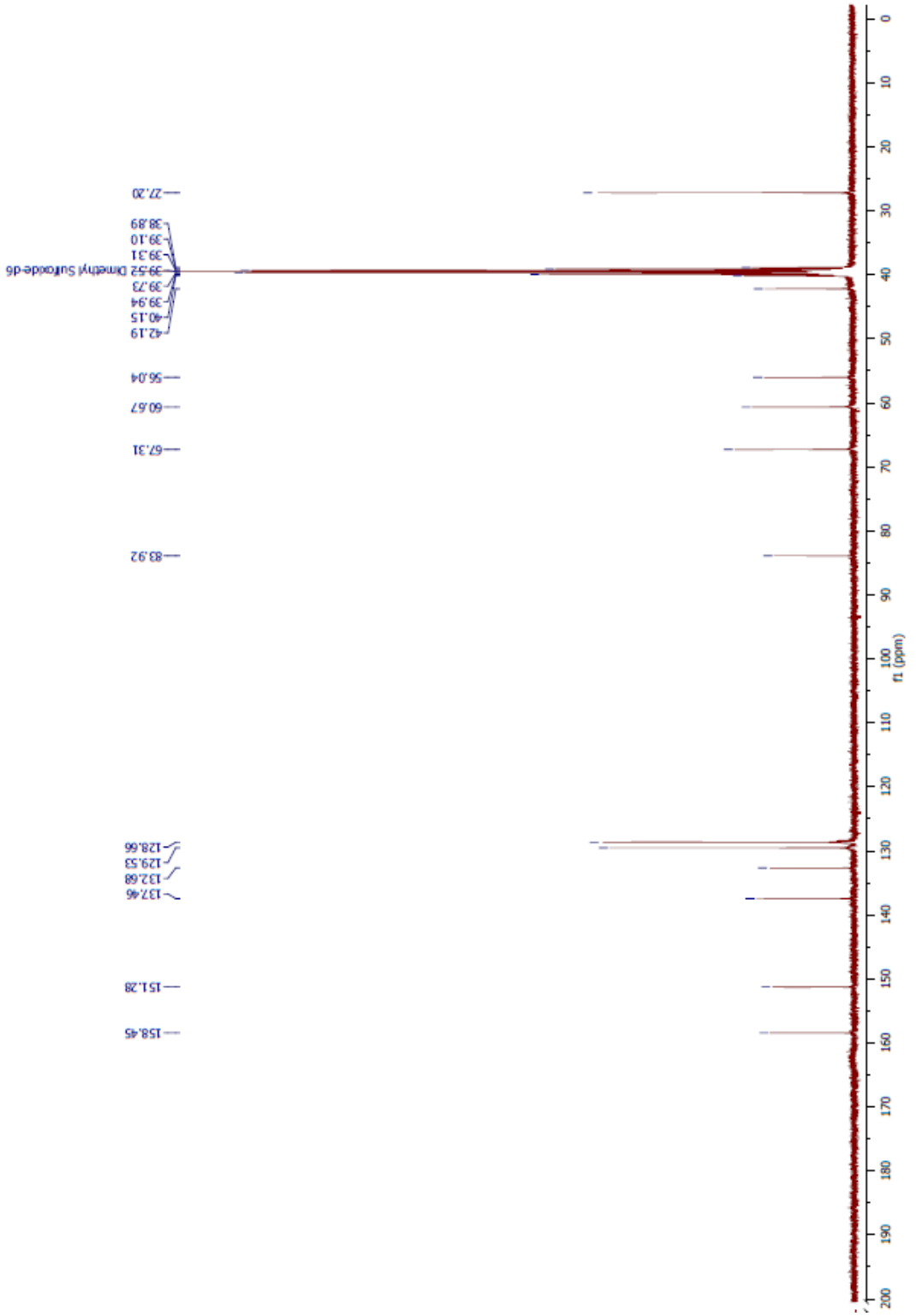


31

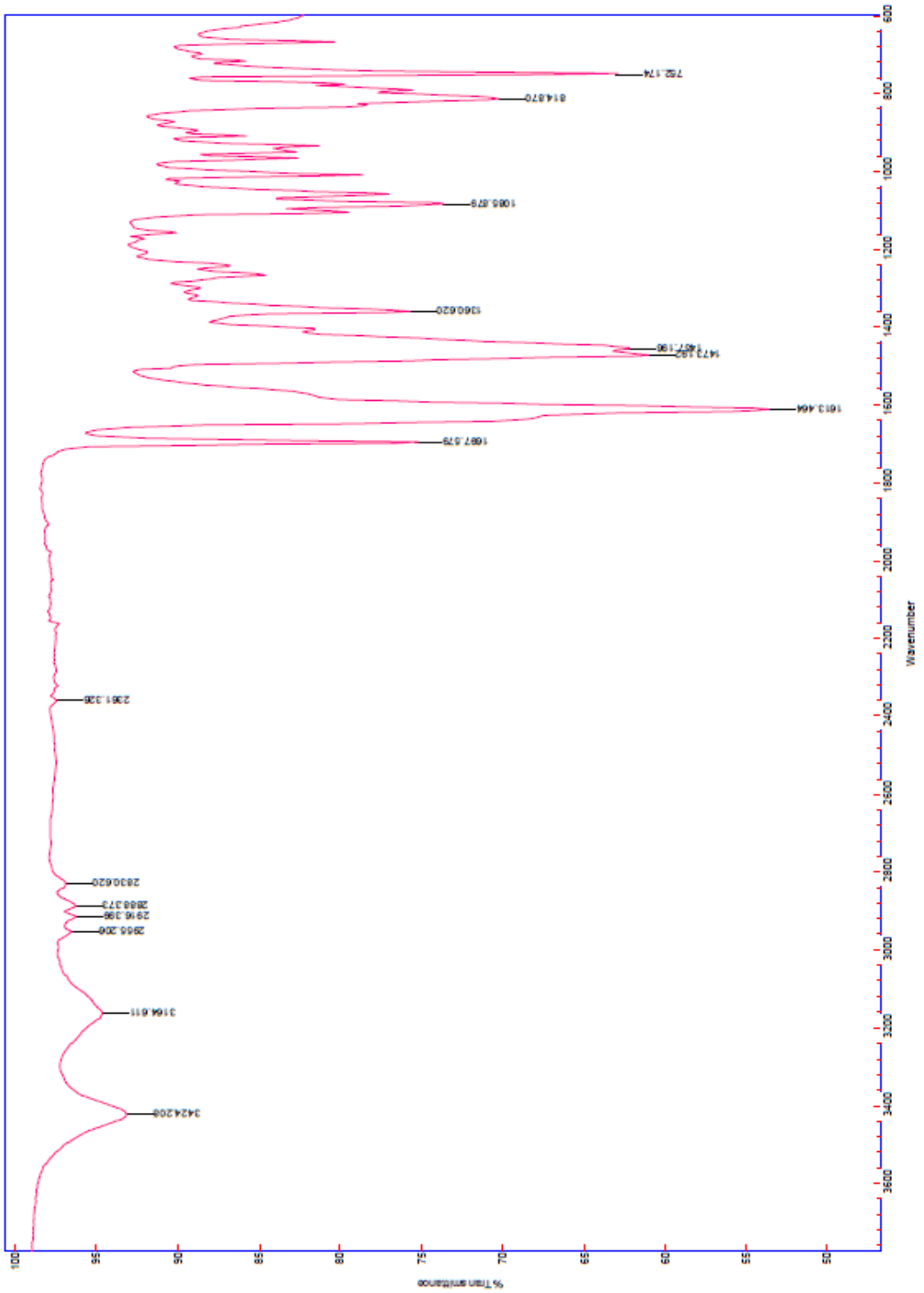
B.16.1 ^{1}H NMR spectrum of 31



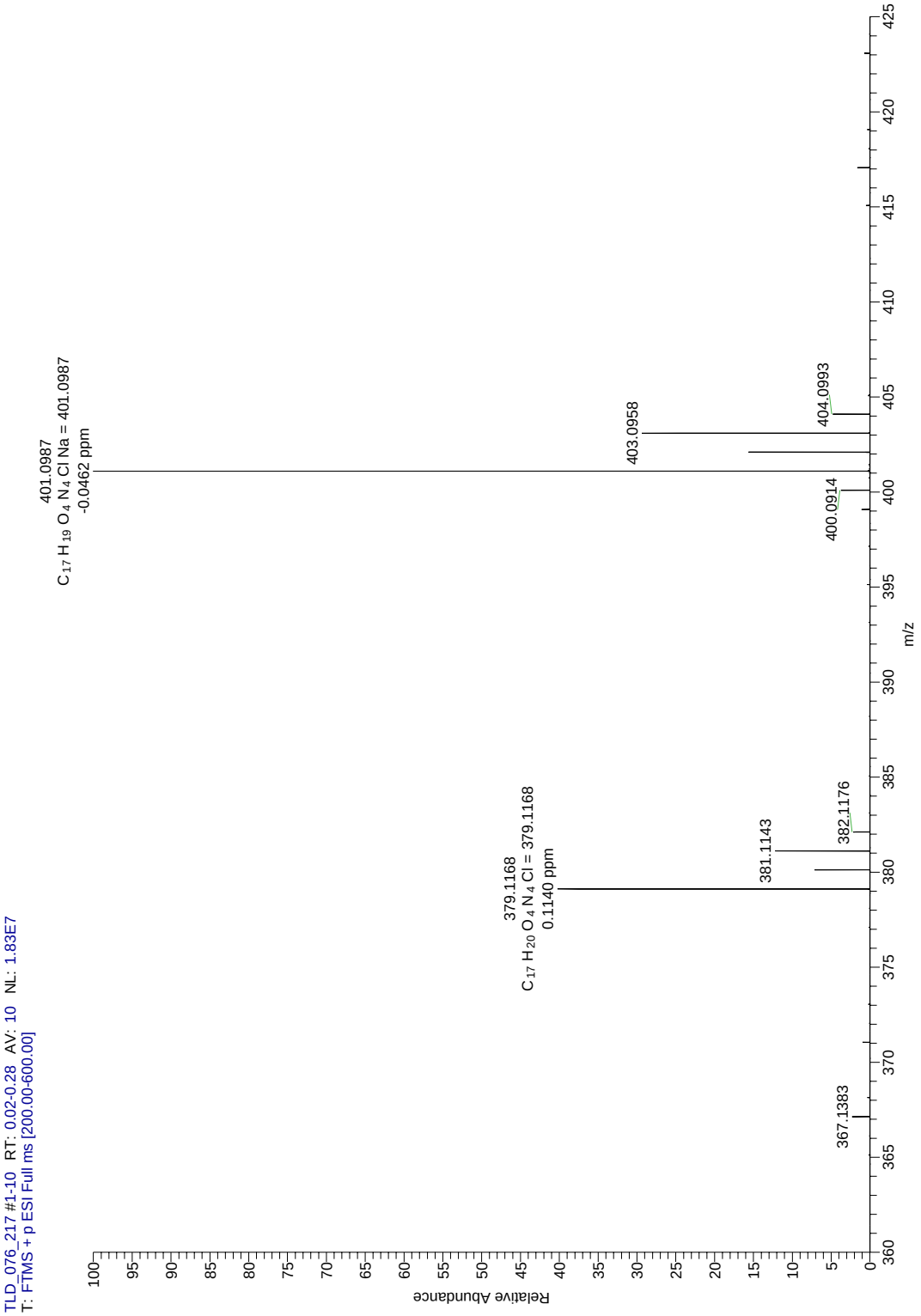
B.16.2 ^{13}C NMR spectrum of 31



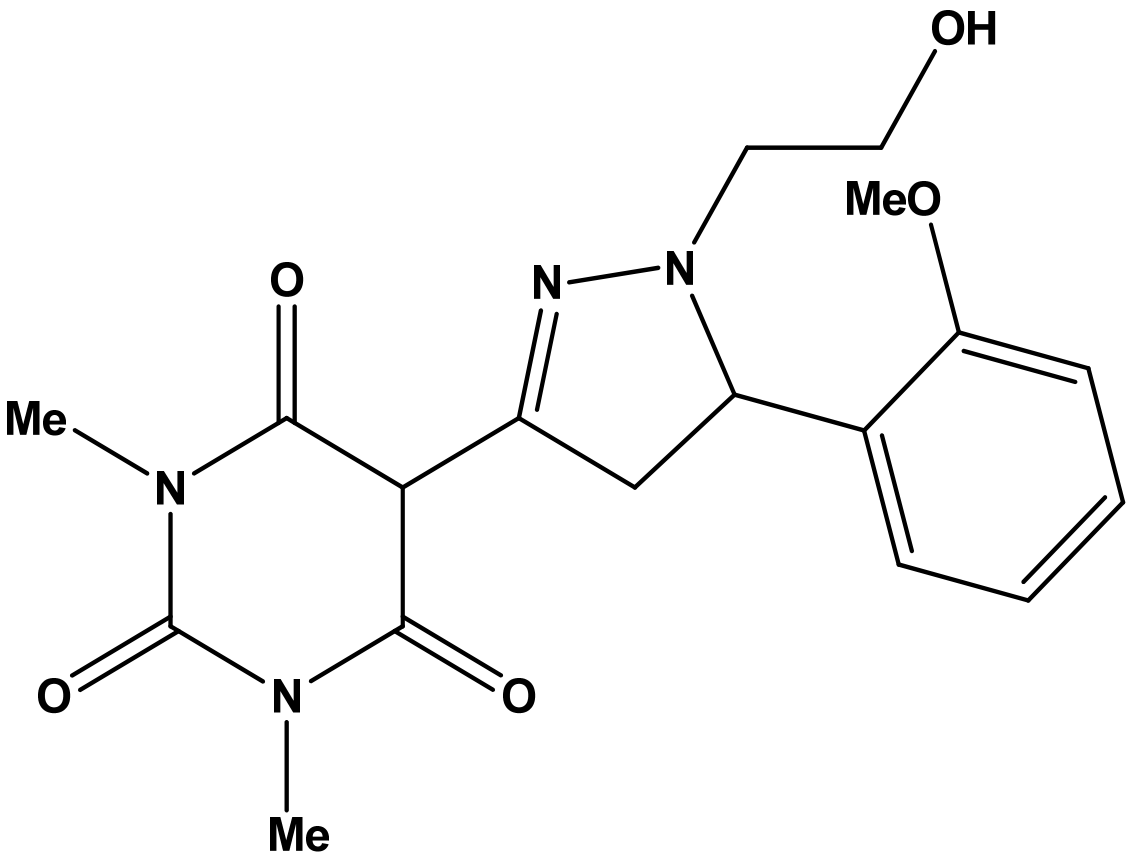
B.16.3 IR spectrum of 31



B.16.4 HRMS of 31

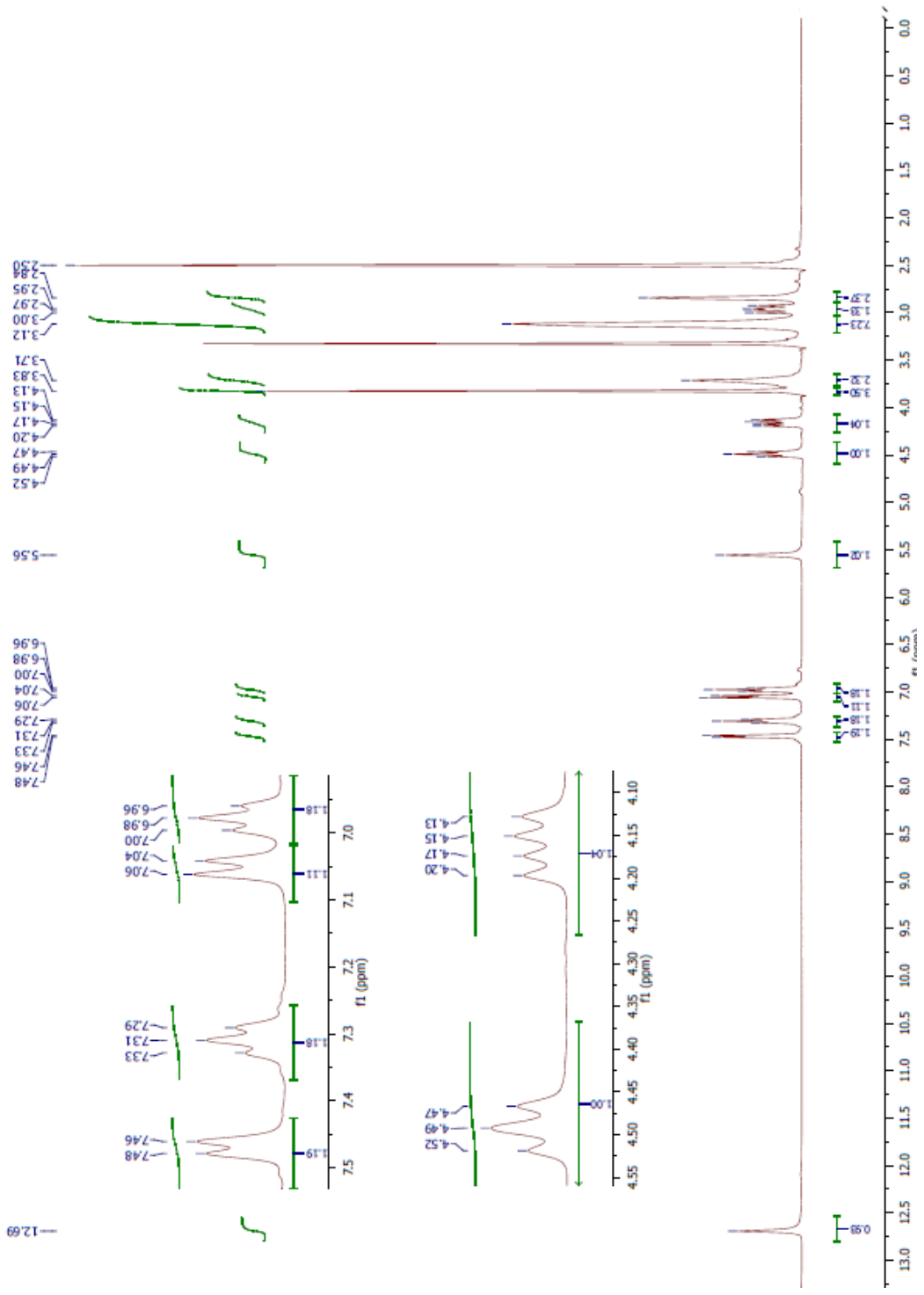


B.17 Spectroscopic data for 33

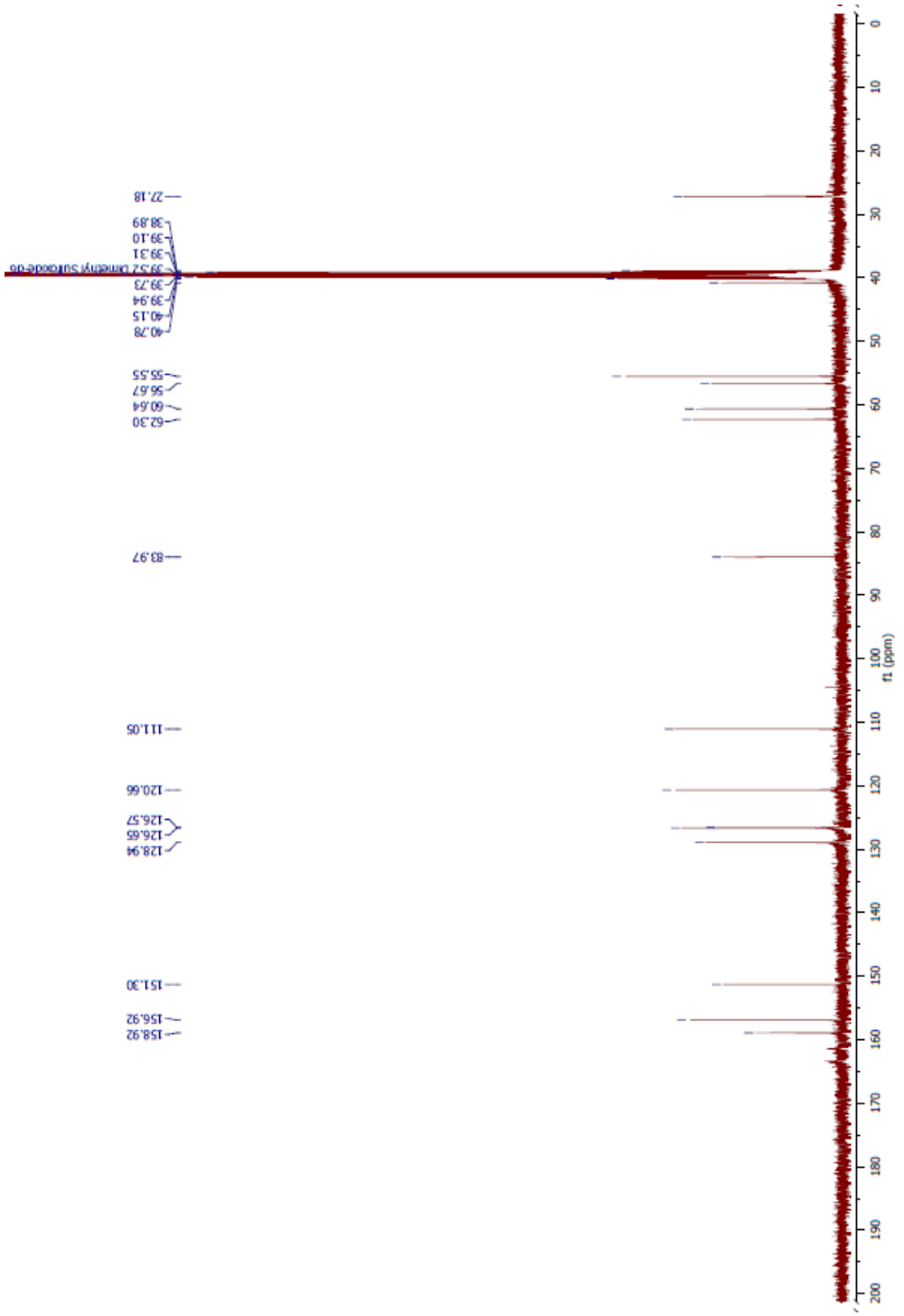


33

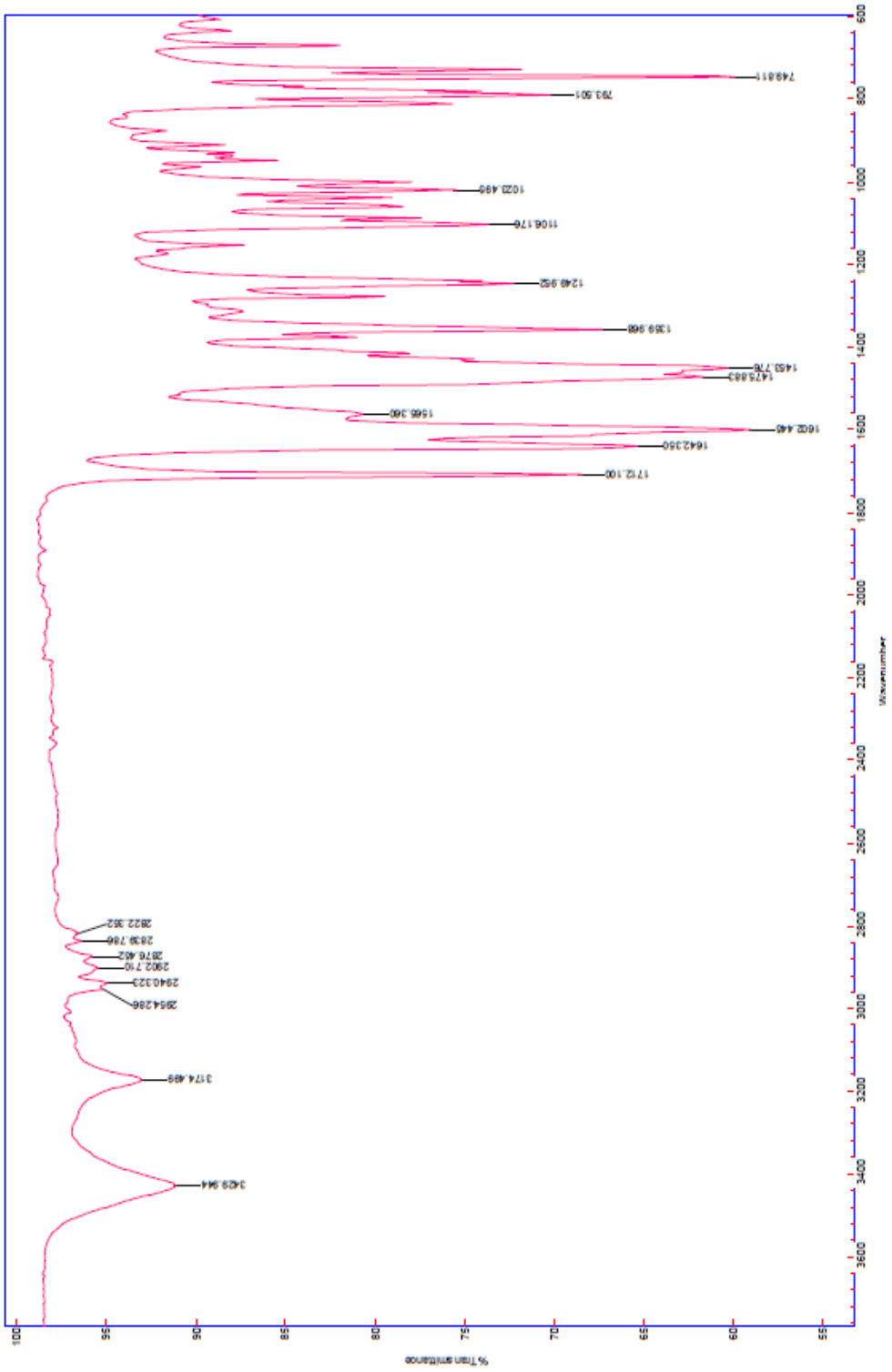
B.17.1 ^{1}H NMR spectrum of 33



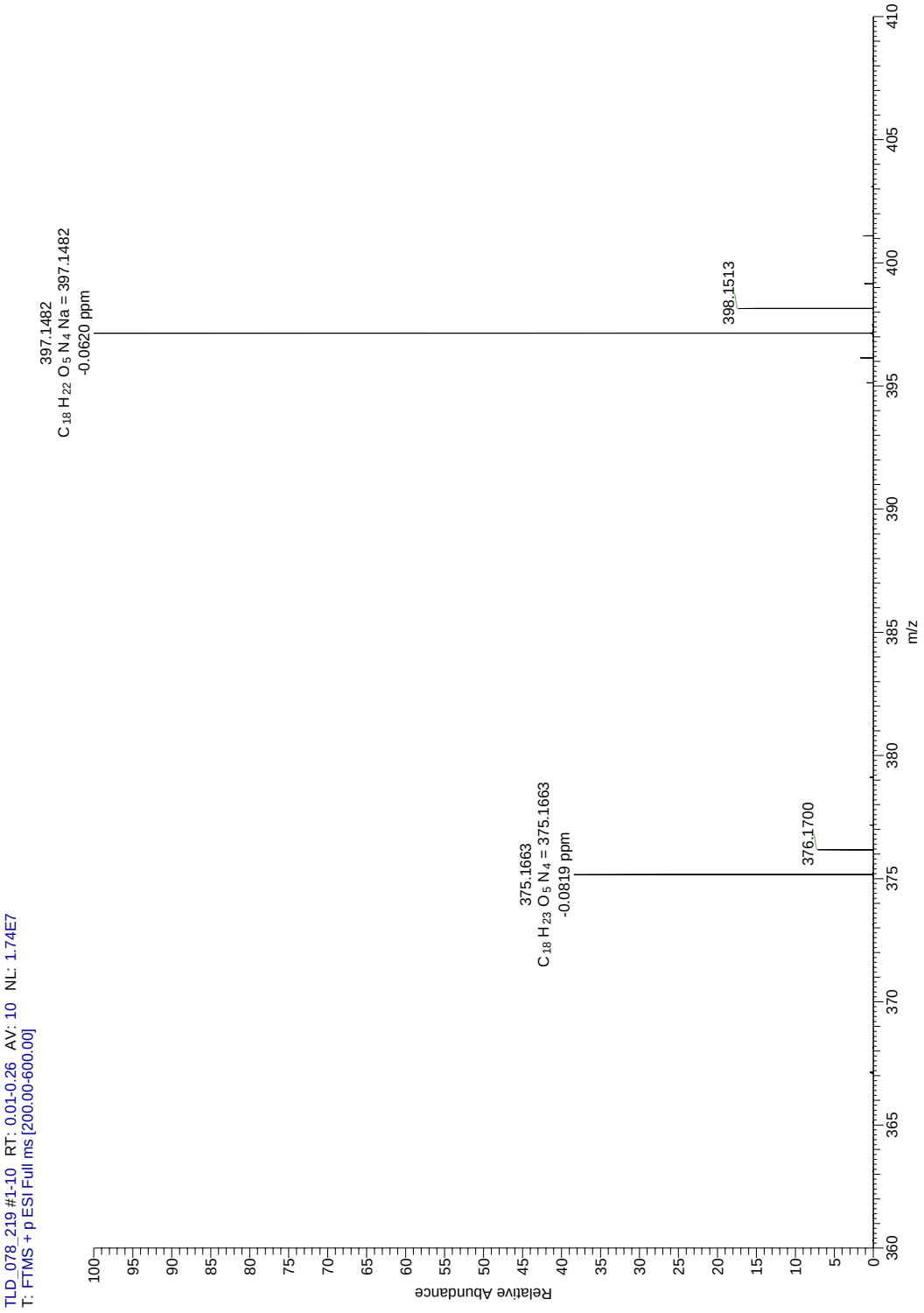
B.17.2 ^{13}C NMR spectrum of 33



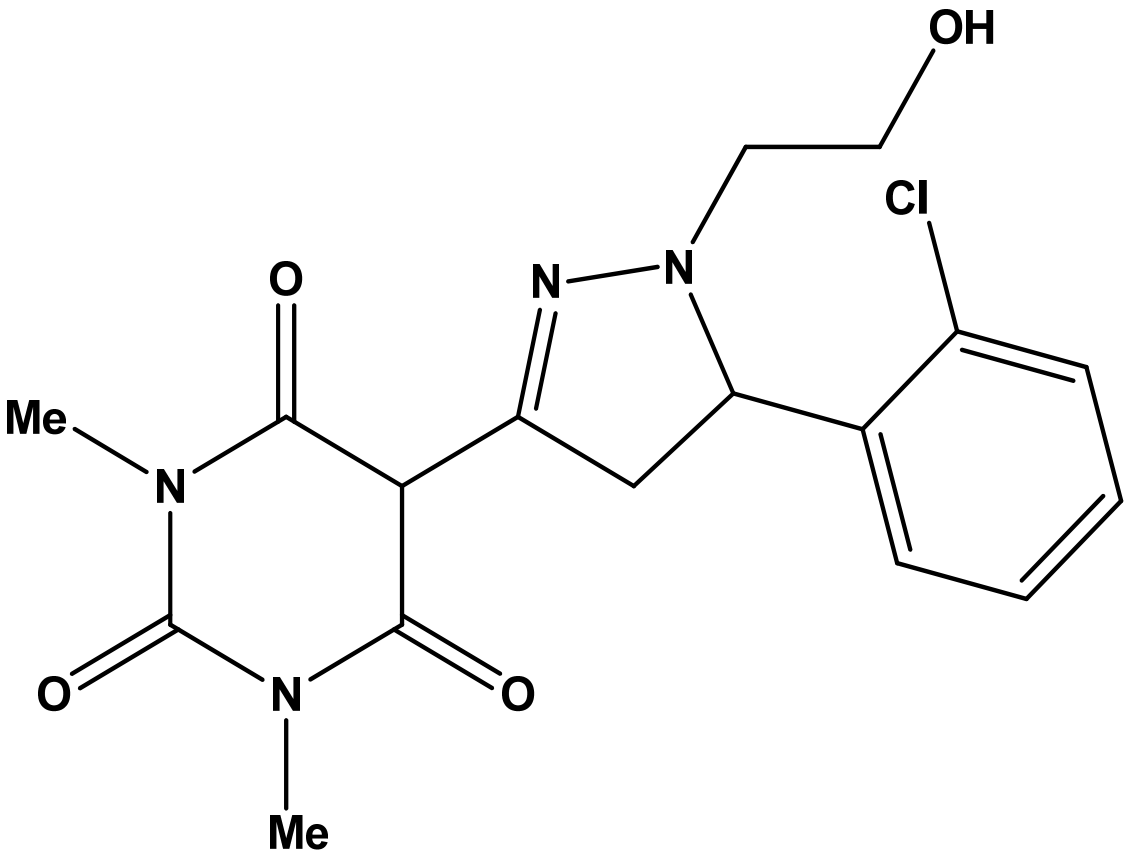
B.17.3 IR spectrum of 33



B.17. HRMS spectrum of 33

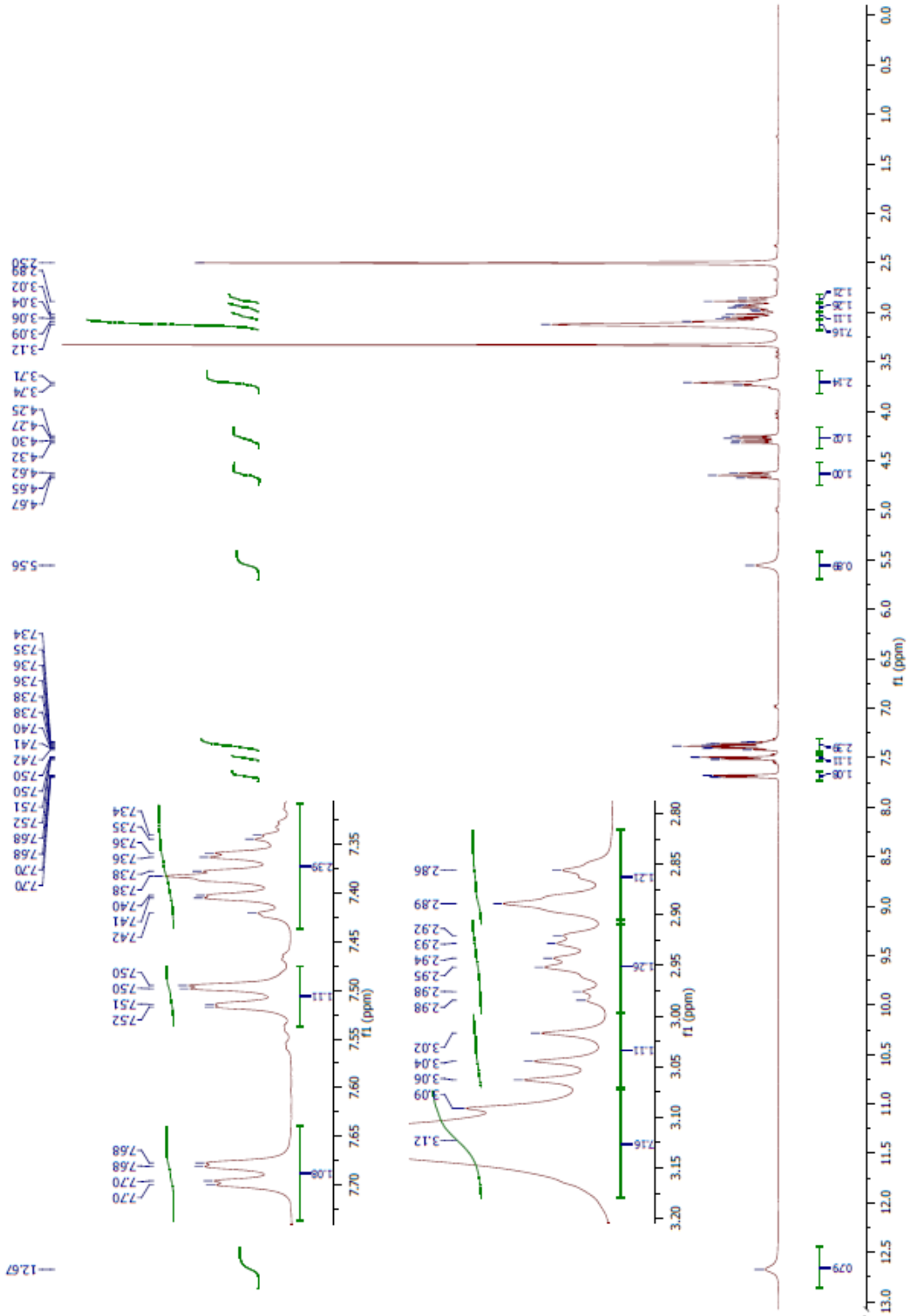


B.18 Spectroscopic data for 34

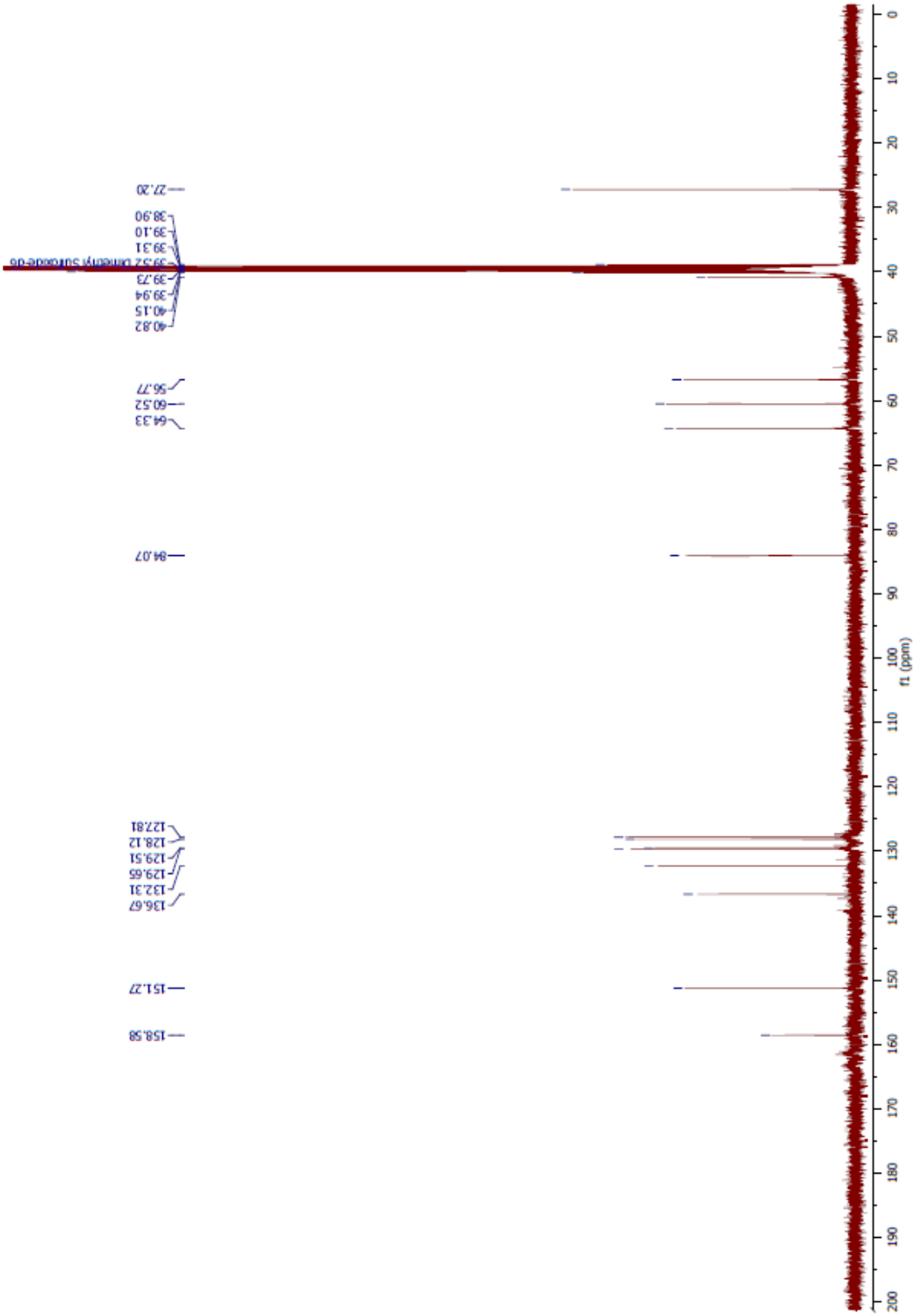


34

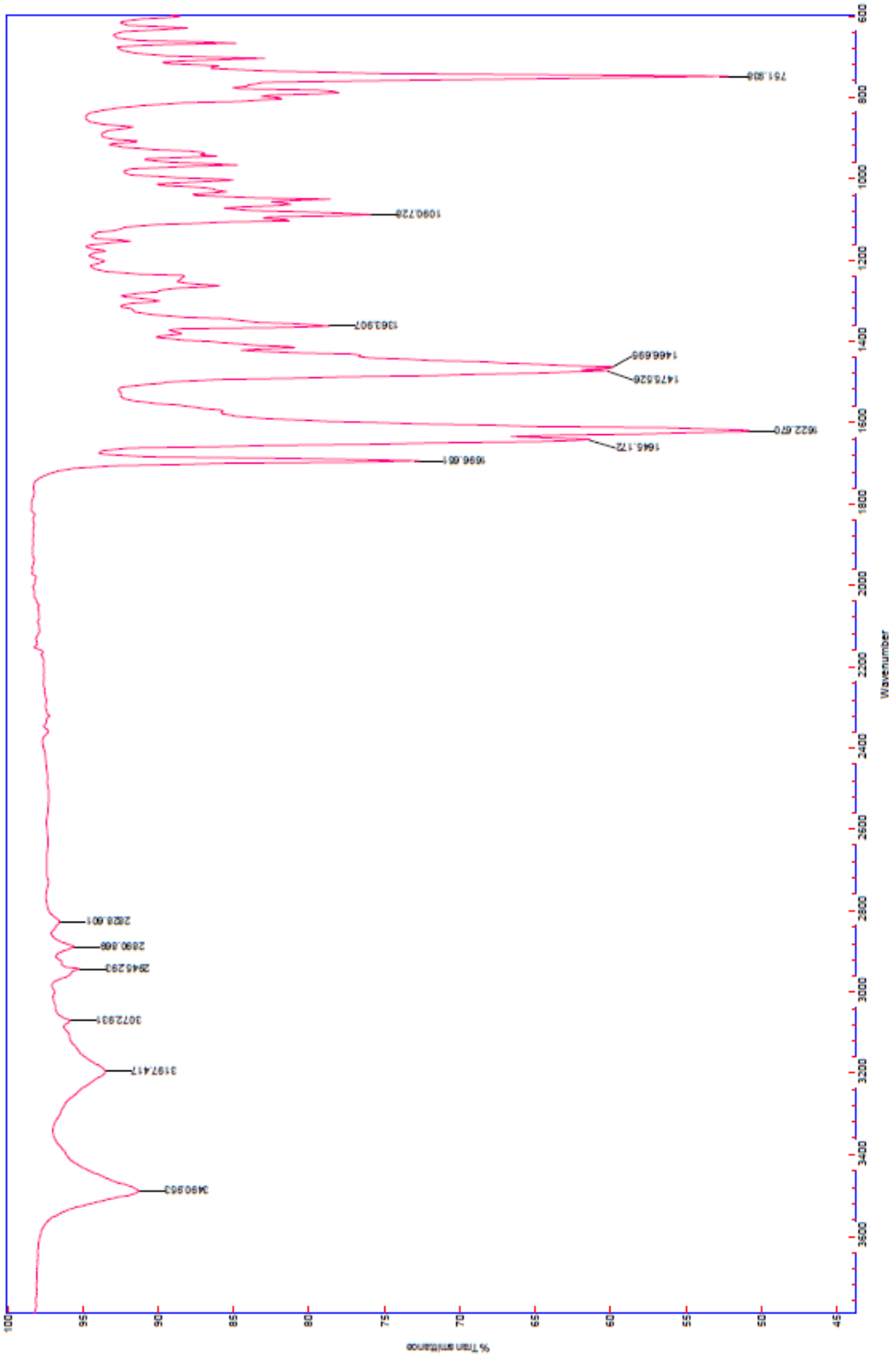
B.18.1 ^{1}H NMR spectrum of 34



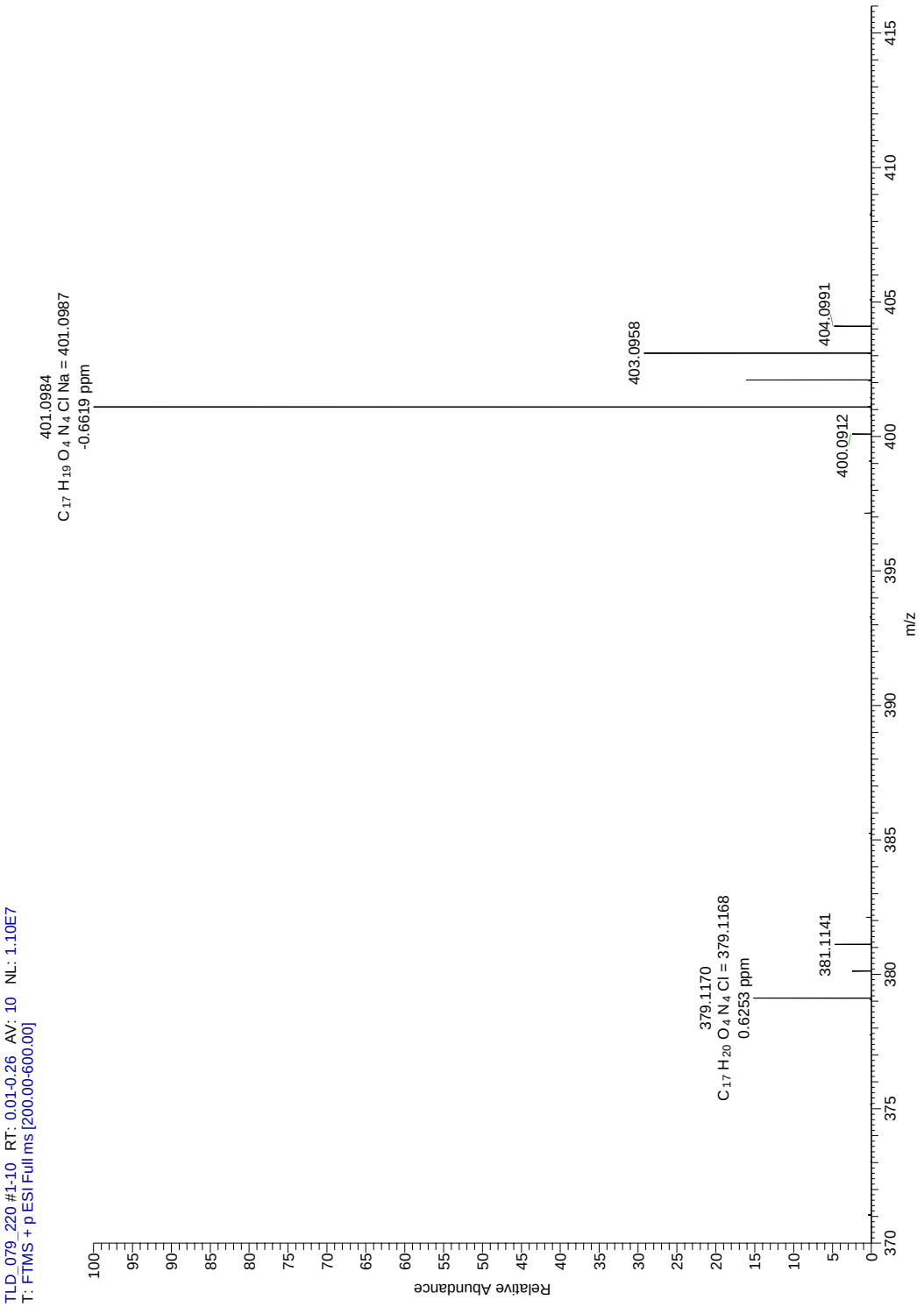
B.18.2 ^{13}C NMR spectrum of 34



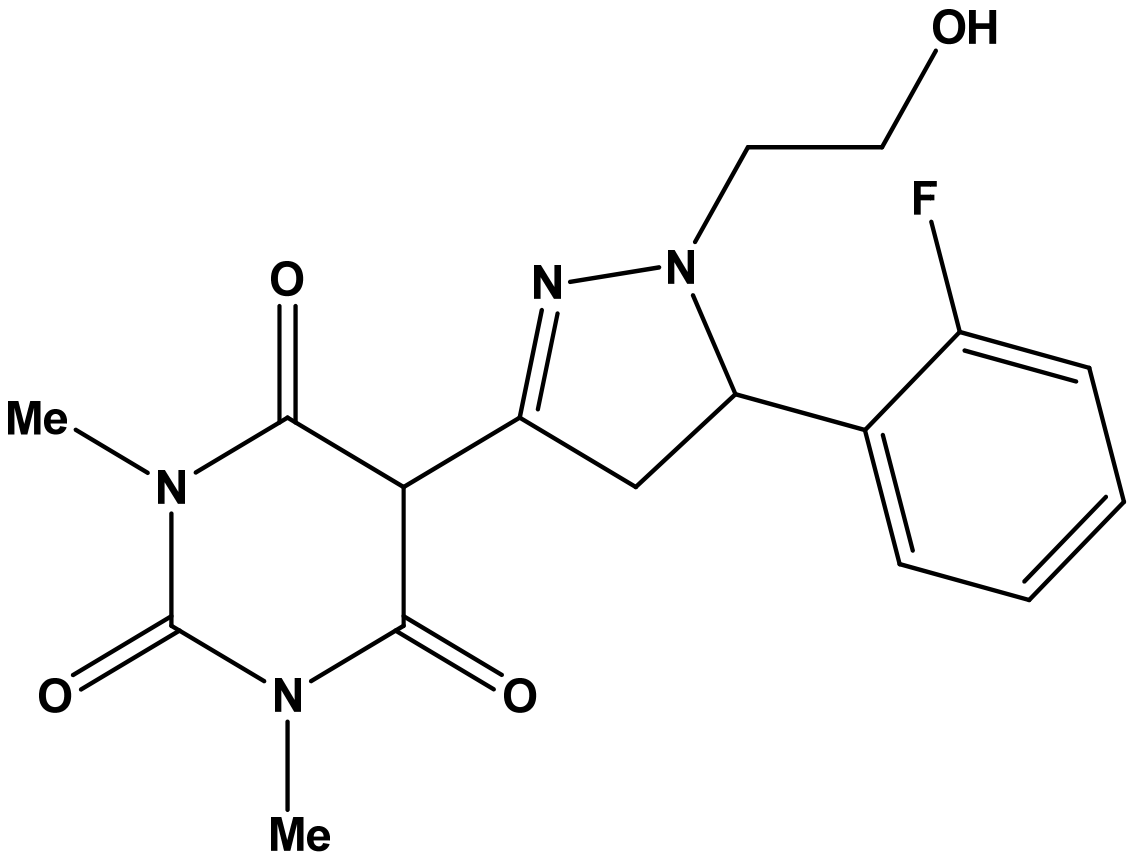
B.18.3 IR spectrum of 34



B.18.3 HRMS of 34

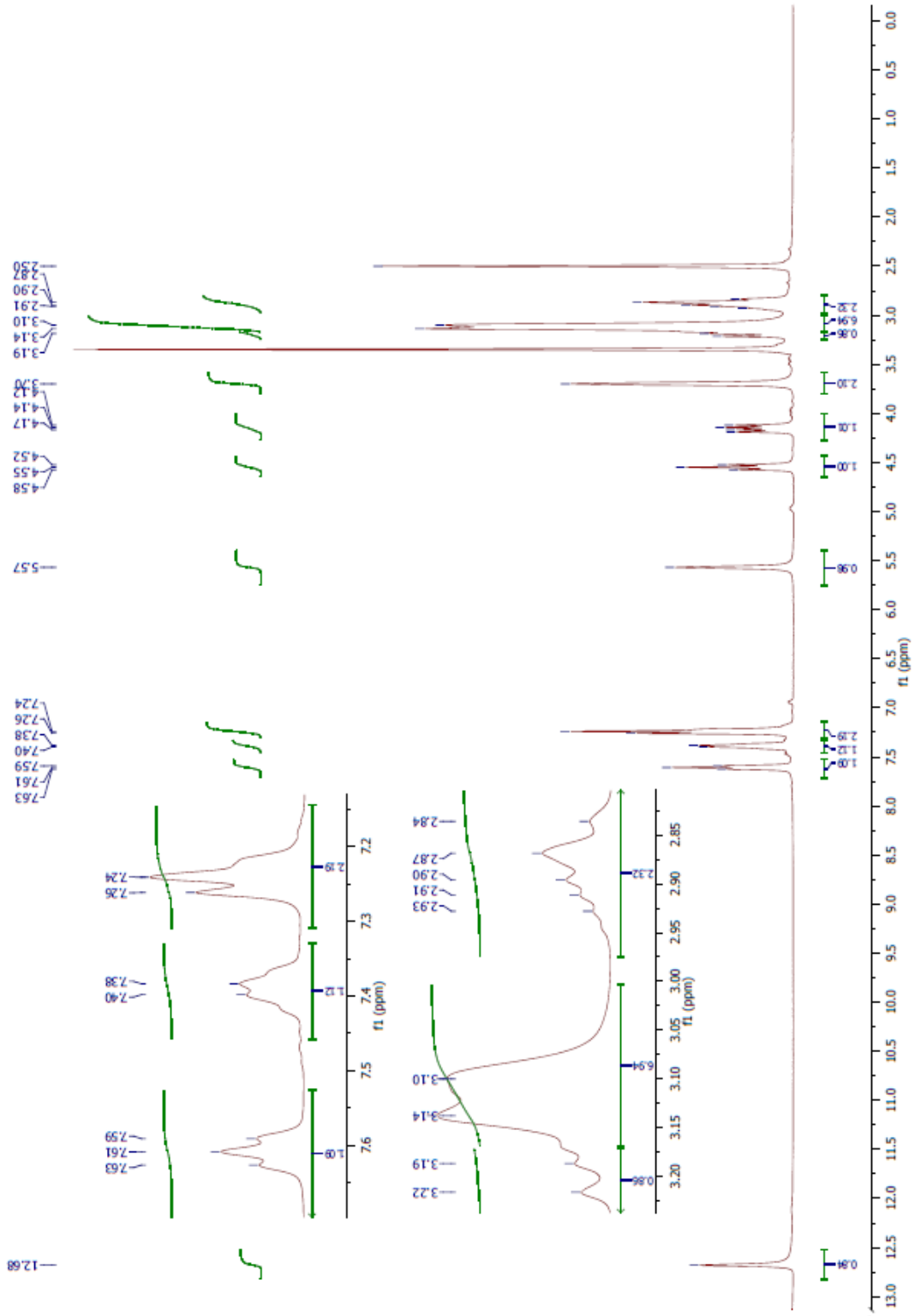


B.19 Spectroscopic data for 35

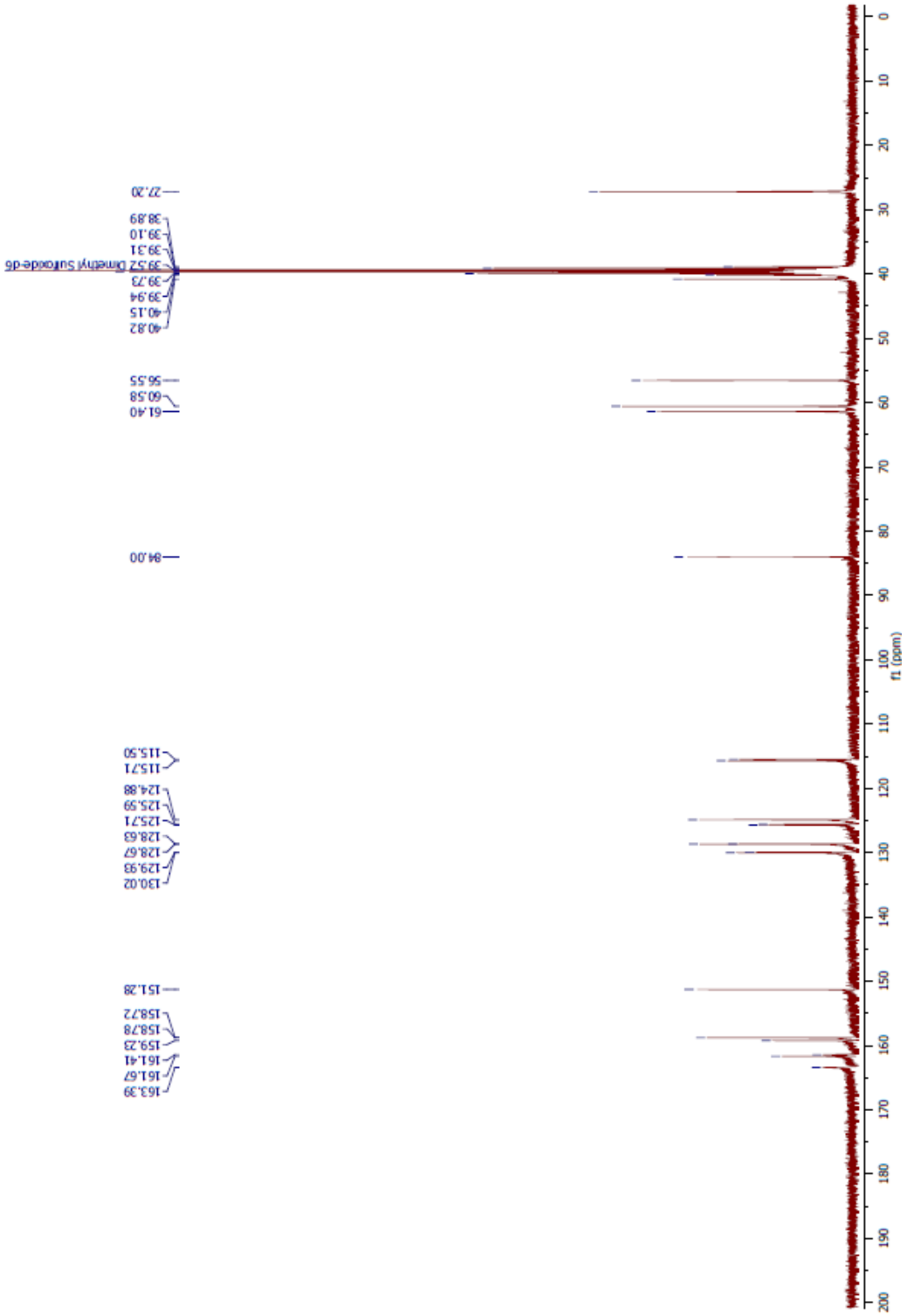


35

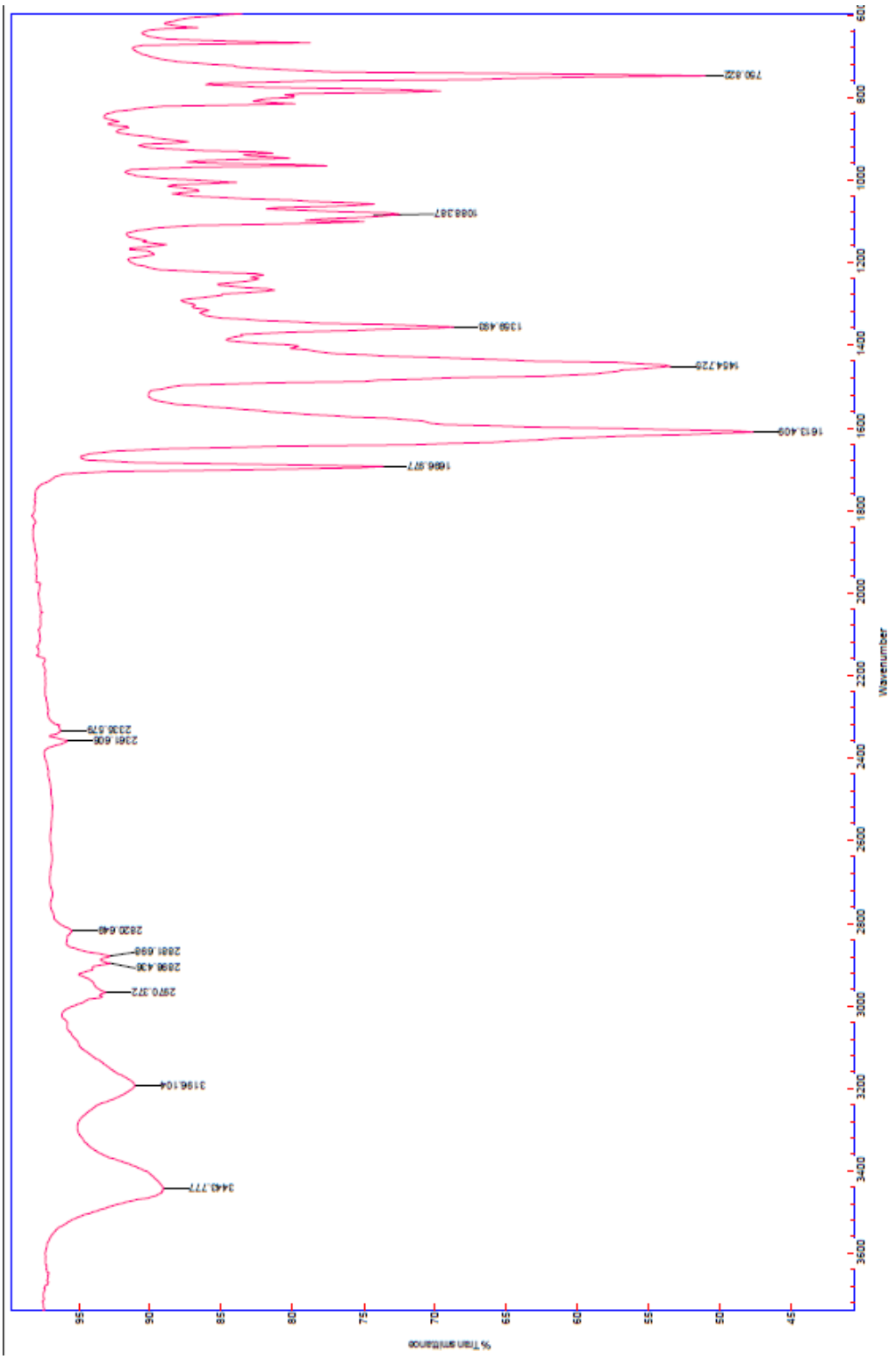
B.19.1 ^{1}H NMR spectrum of 35



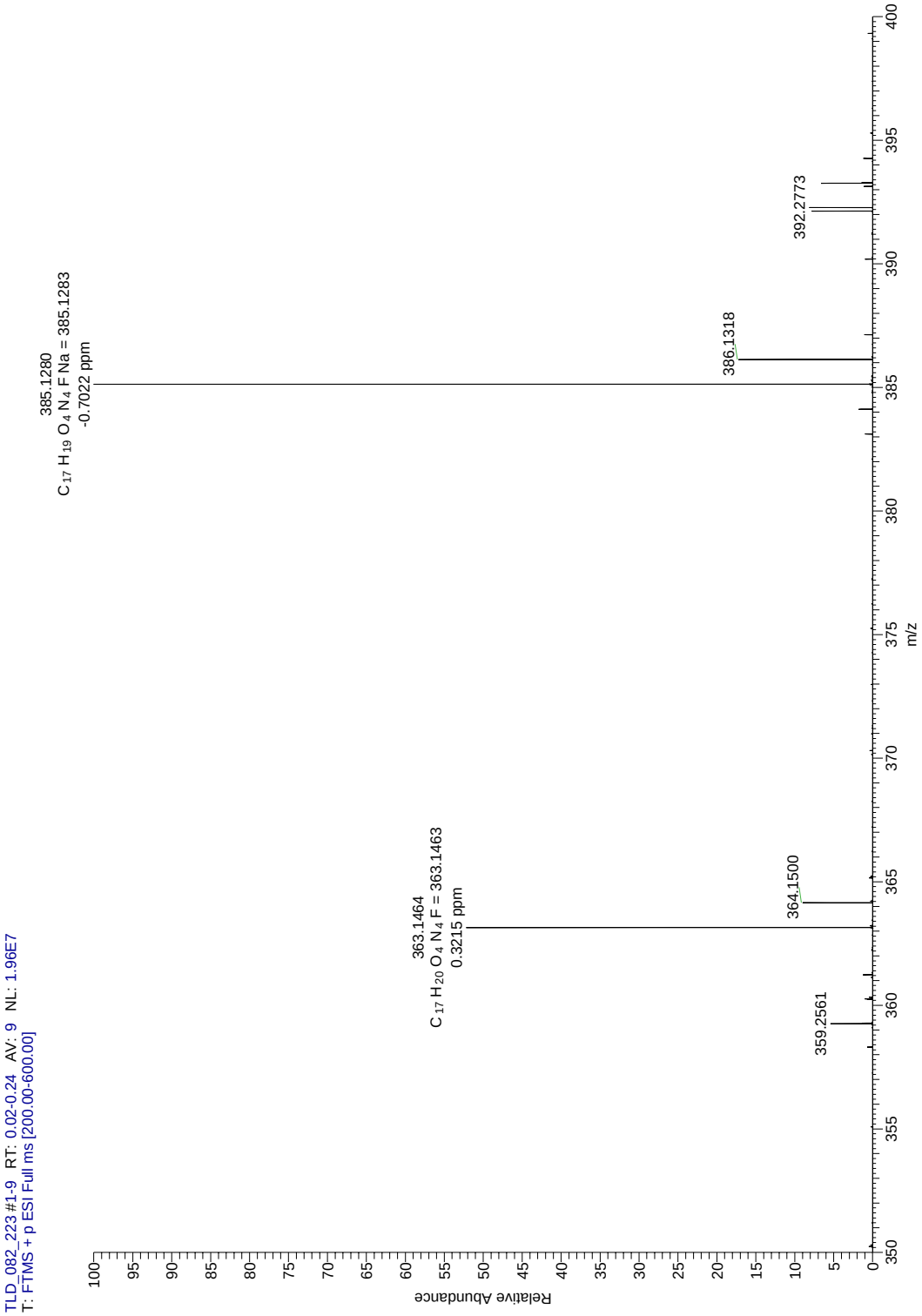
B.19.2 ^{13}C NMR spectrum of 35



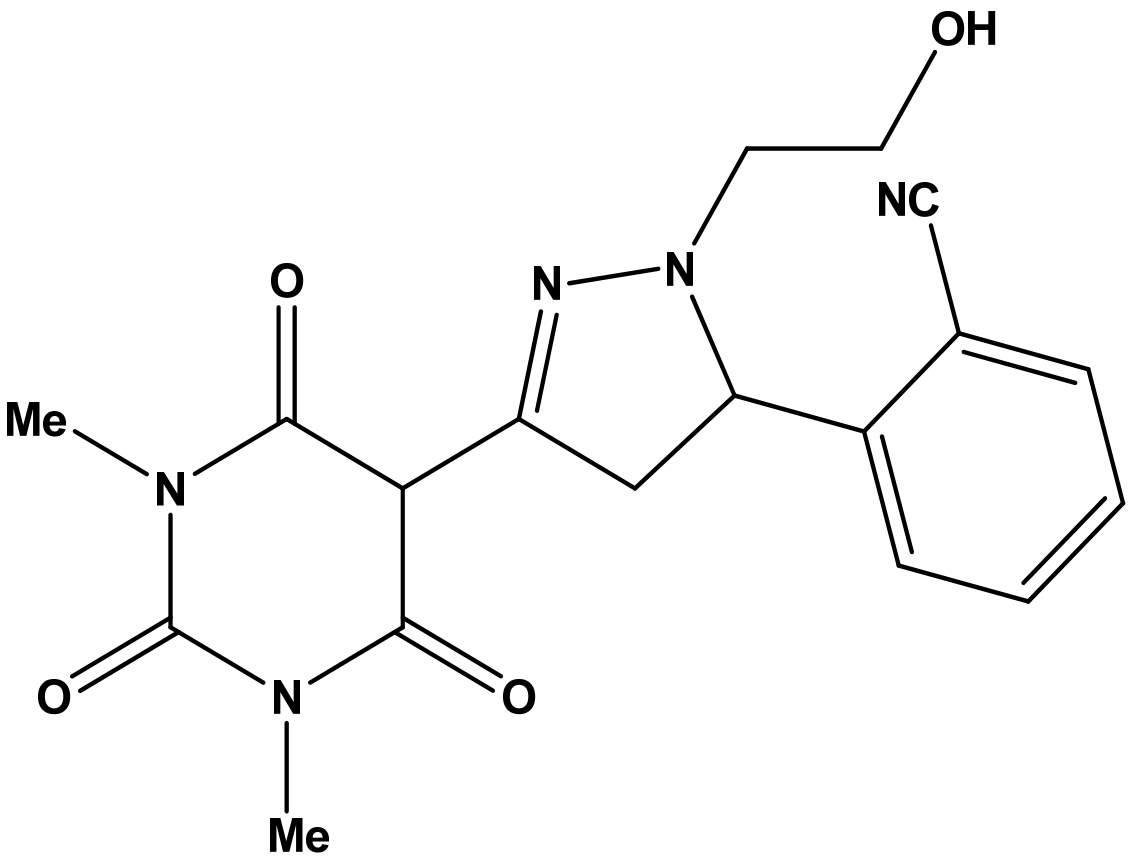
B.19.3 IR spectrum of 35



B.19.4 HRMS of 35



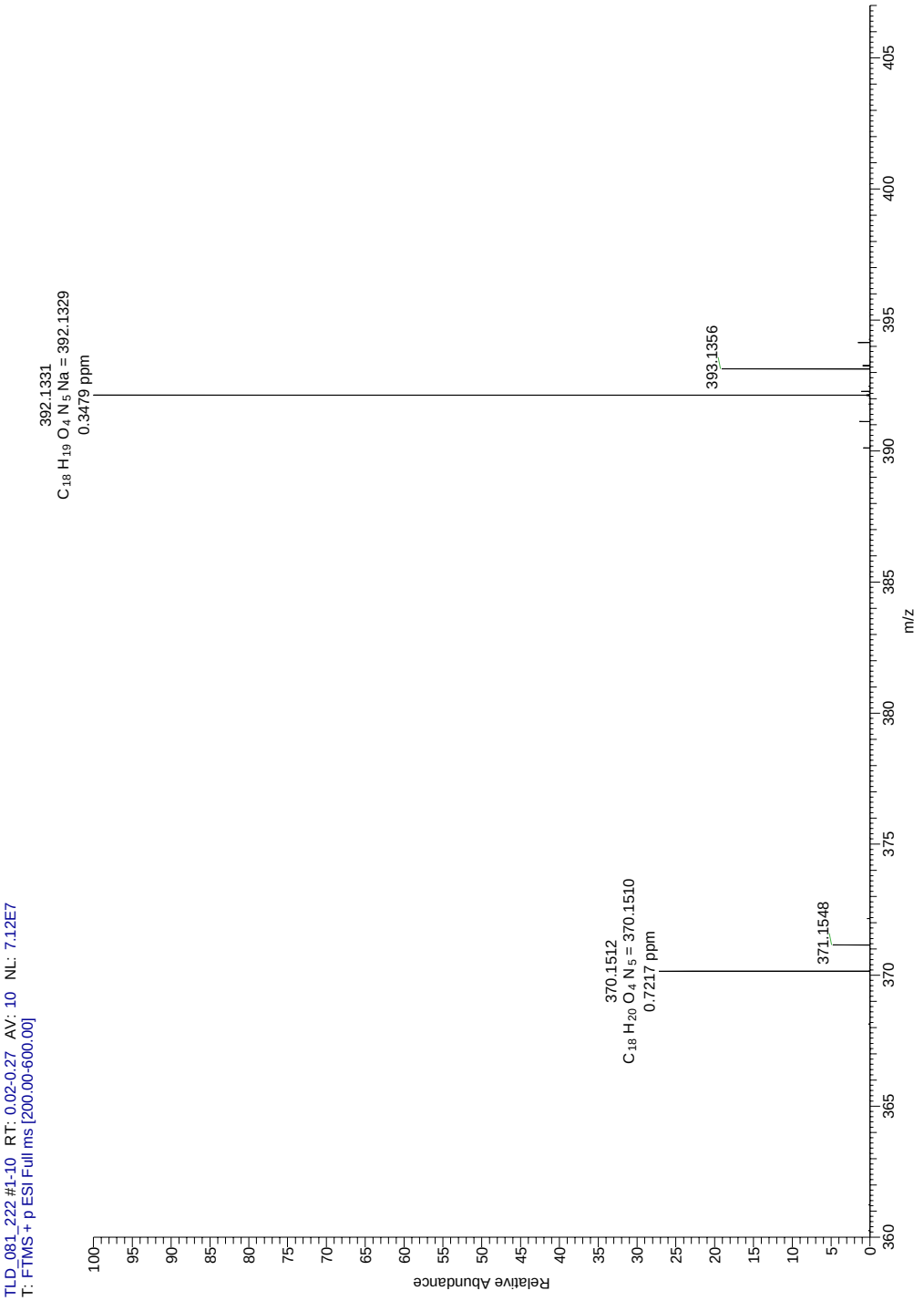
B.20 Spectroscopic data for 36



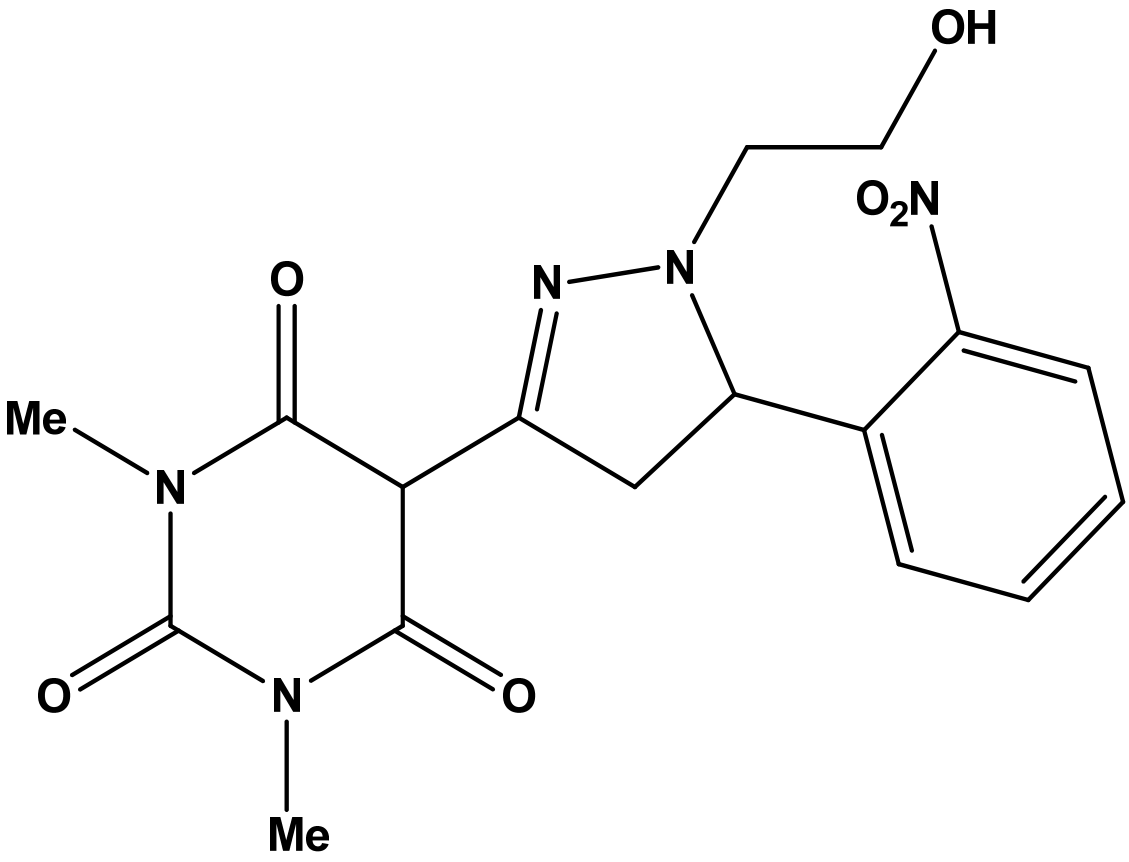
36

B.20.1 IR spectrum of 36

B.20.2 HRMS of 36

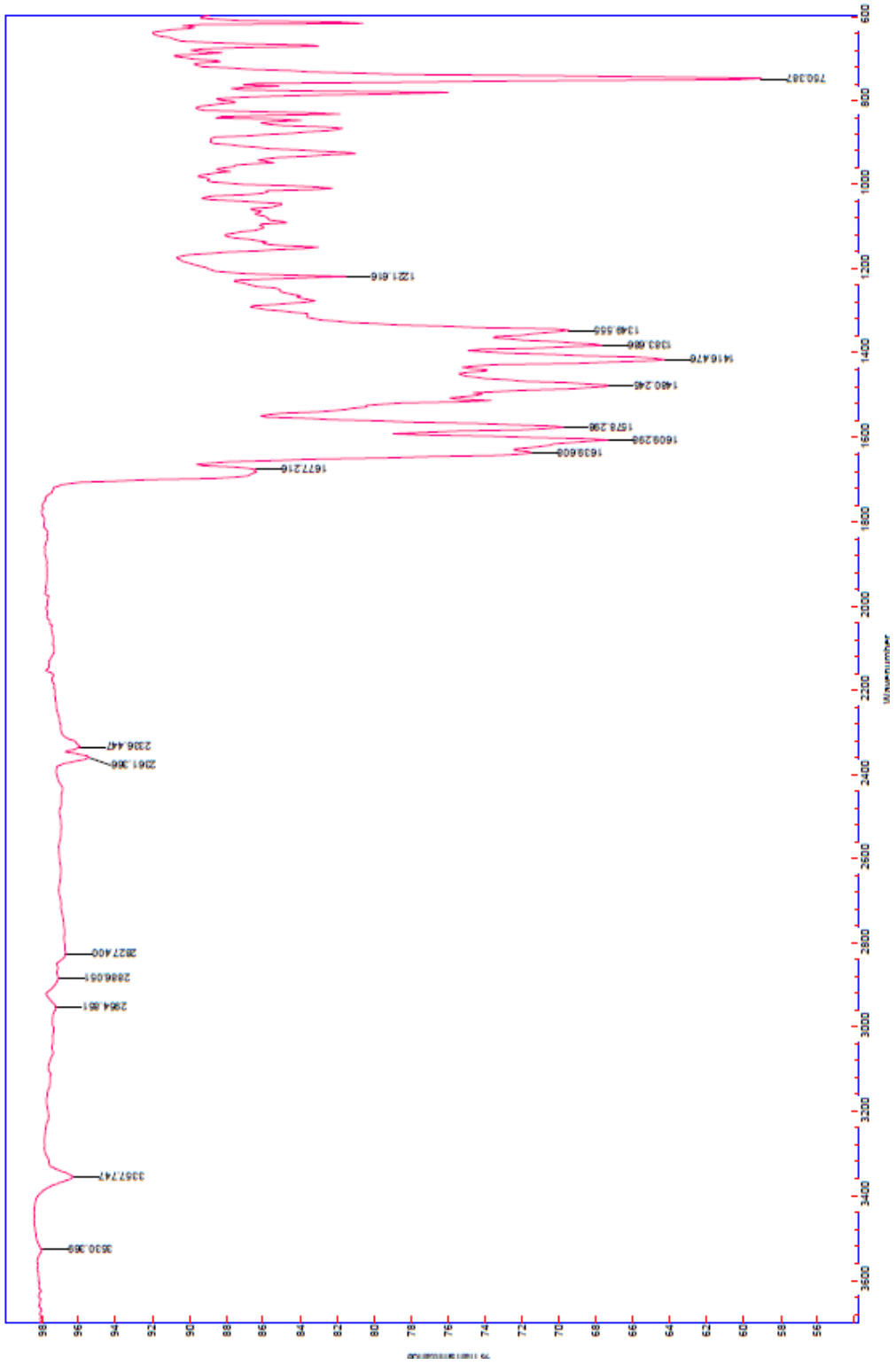


B.21 Spectroscopic data for 37

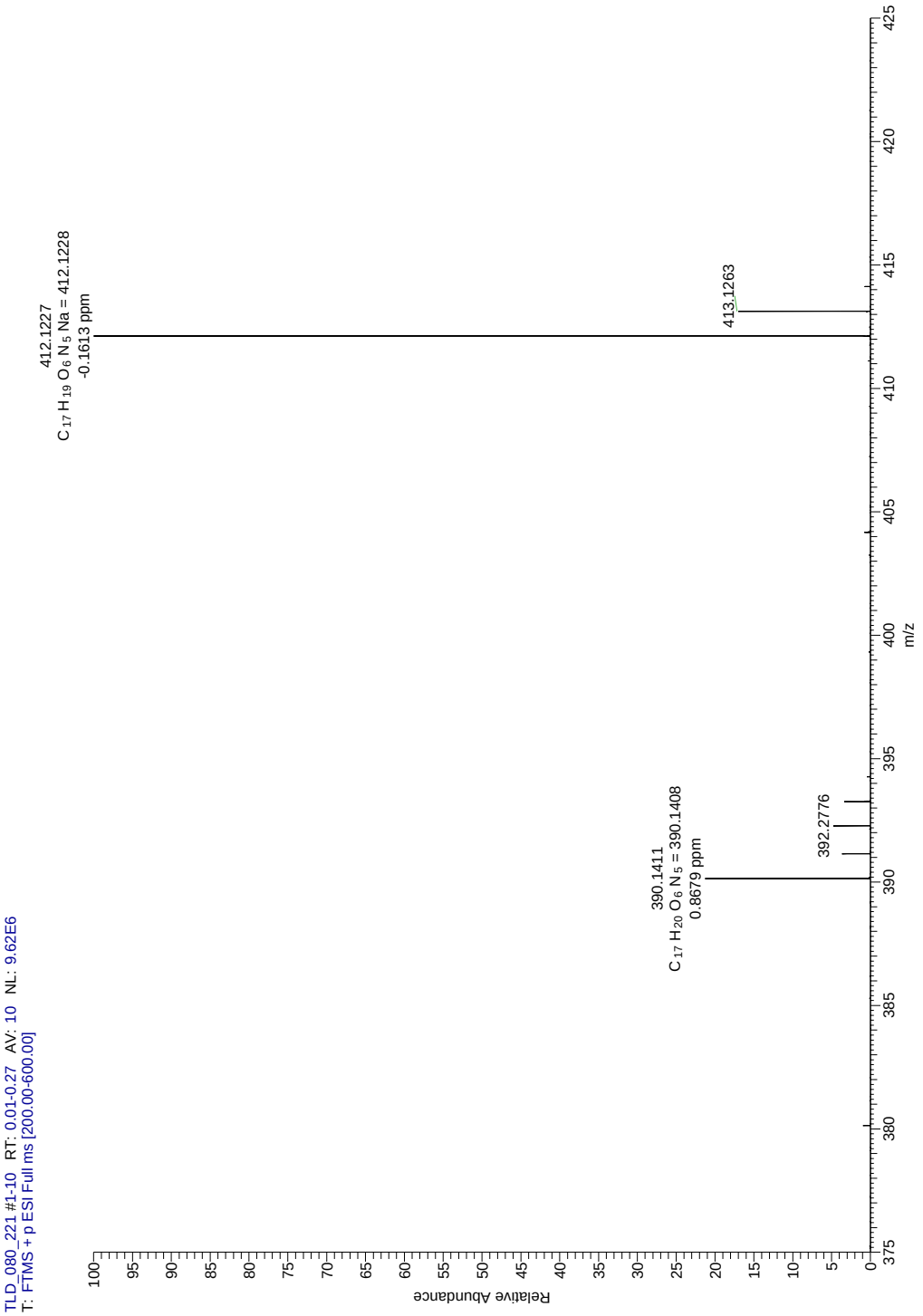


37

B.21.1 IR spectrum of 37

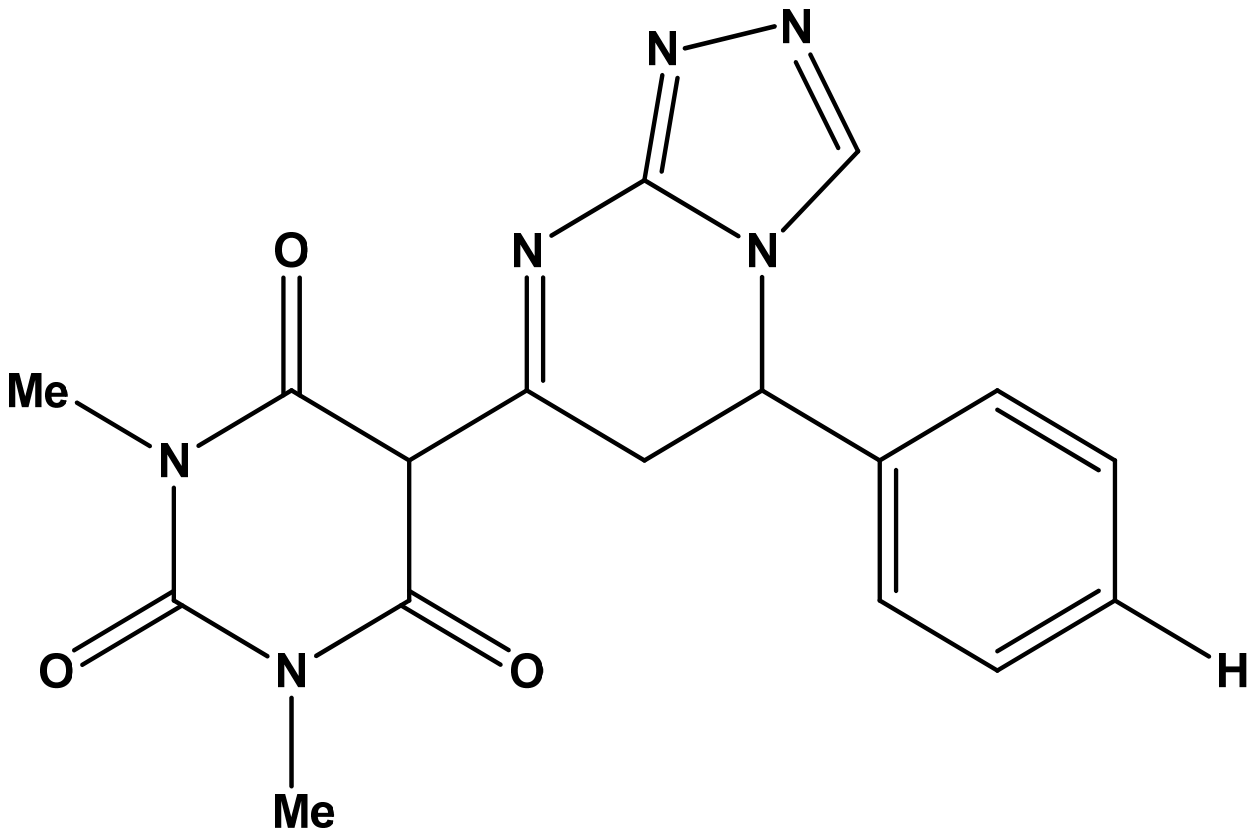


B.21.2 HRMS of 37



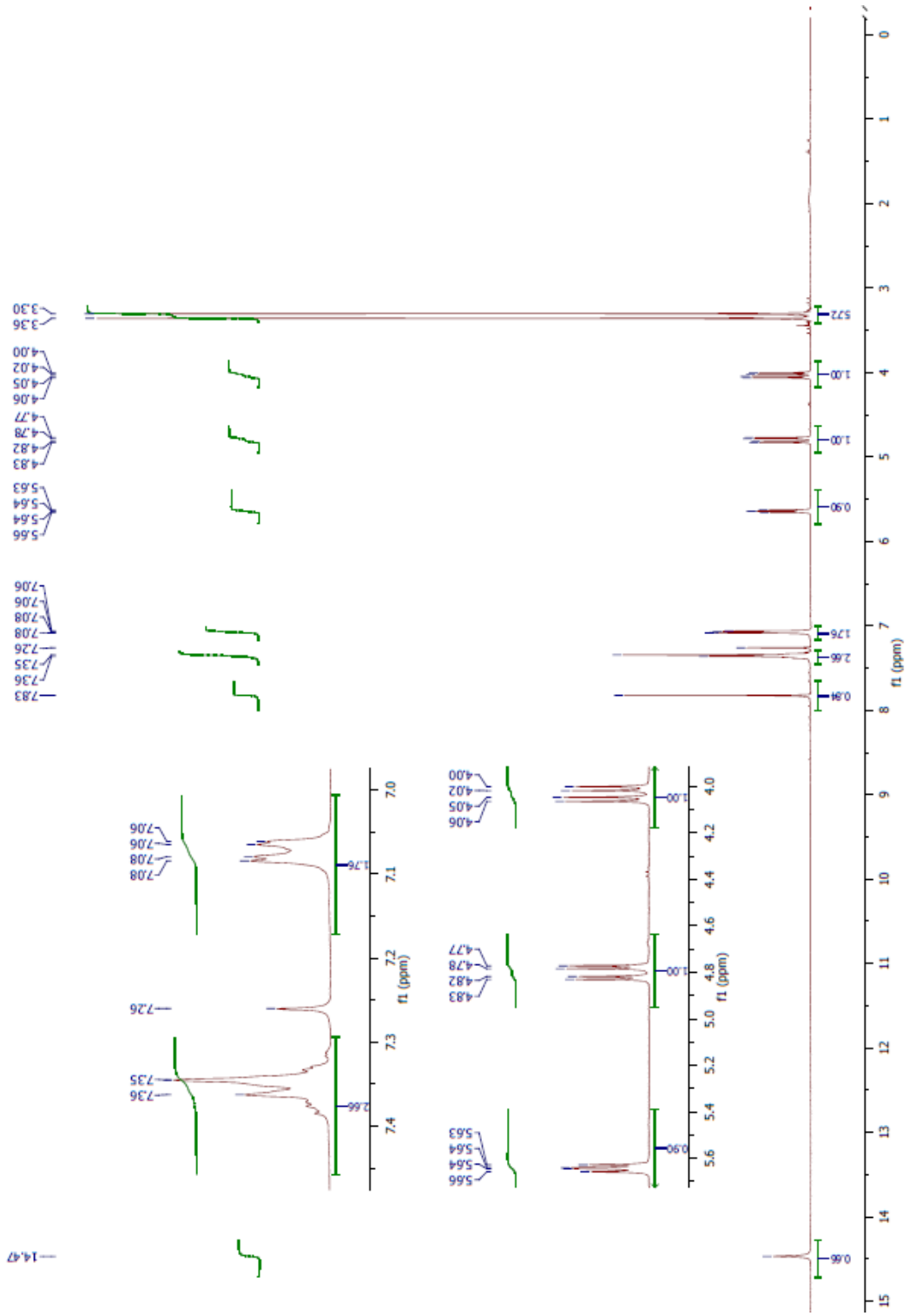
C Spectroscopic data for 6-membered heterocyles 39-50

C.1 Spectroscopic data for 39

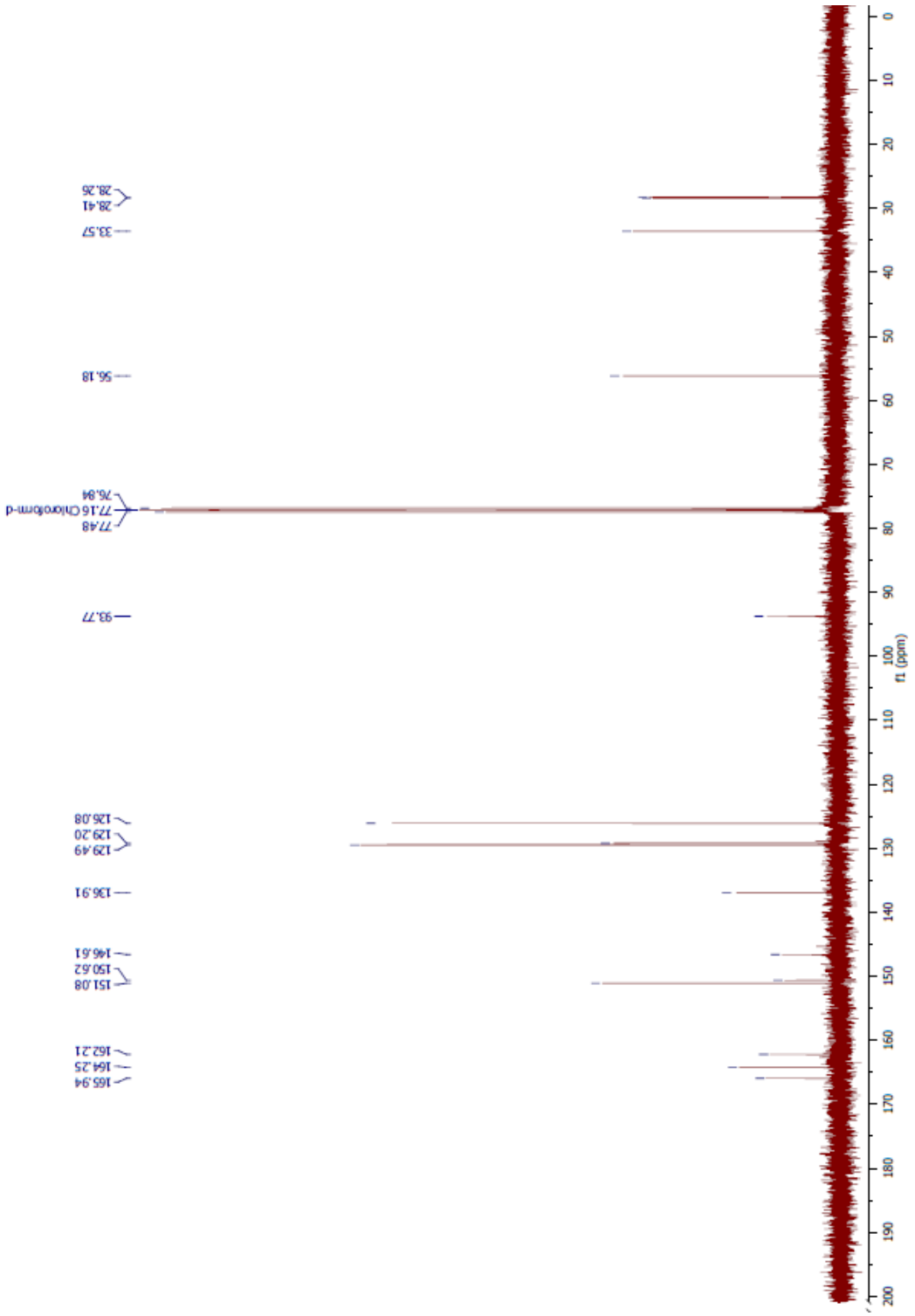


39

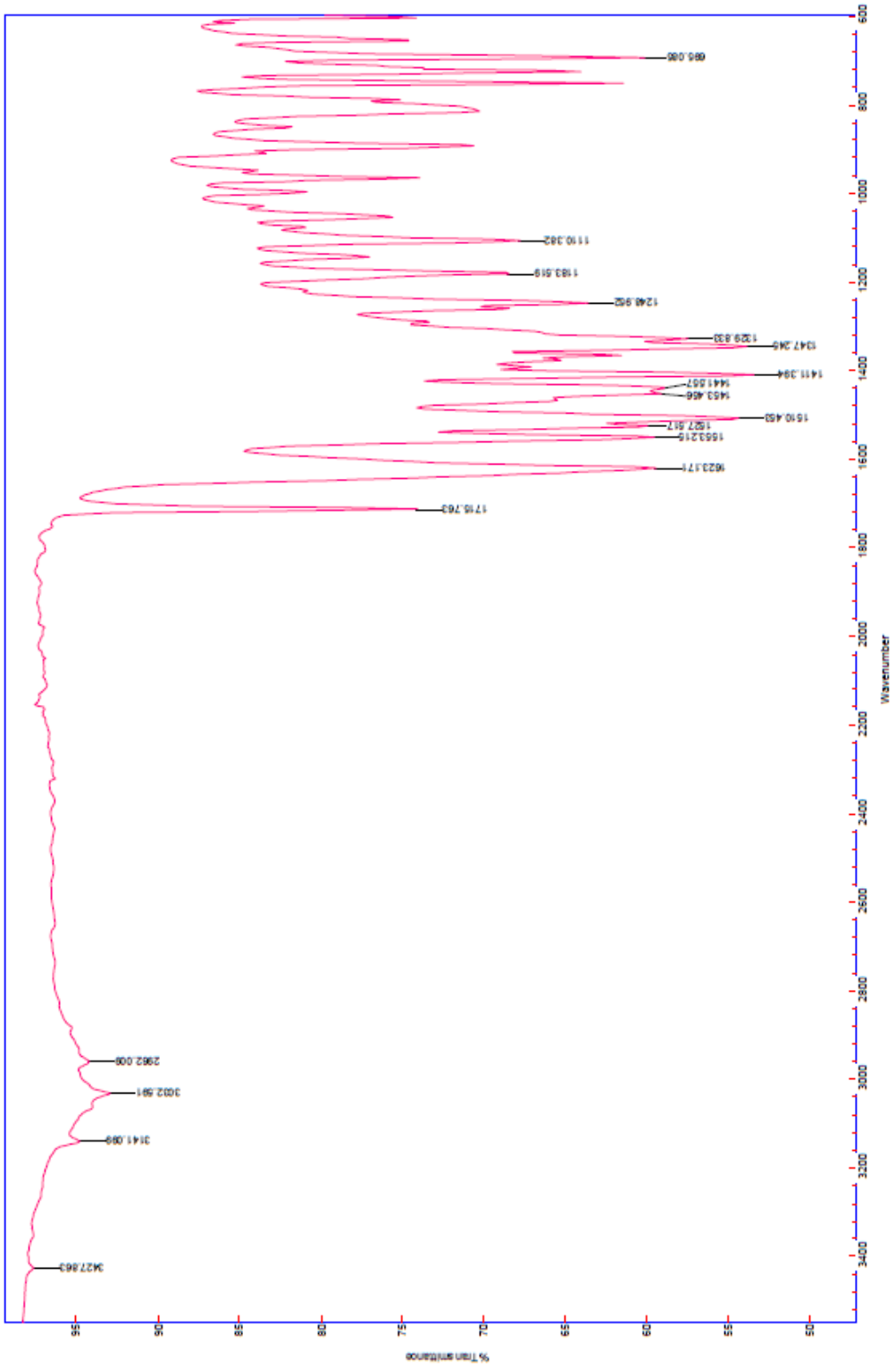
C.1.1 ^{1}H NMR spectrum of 39



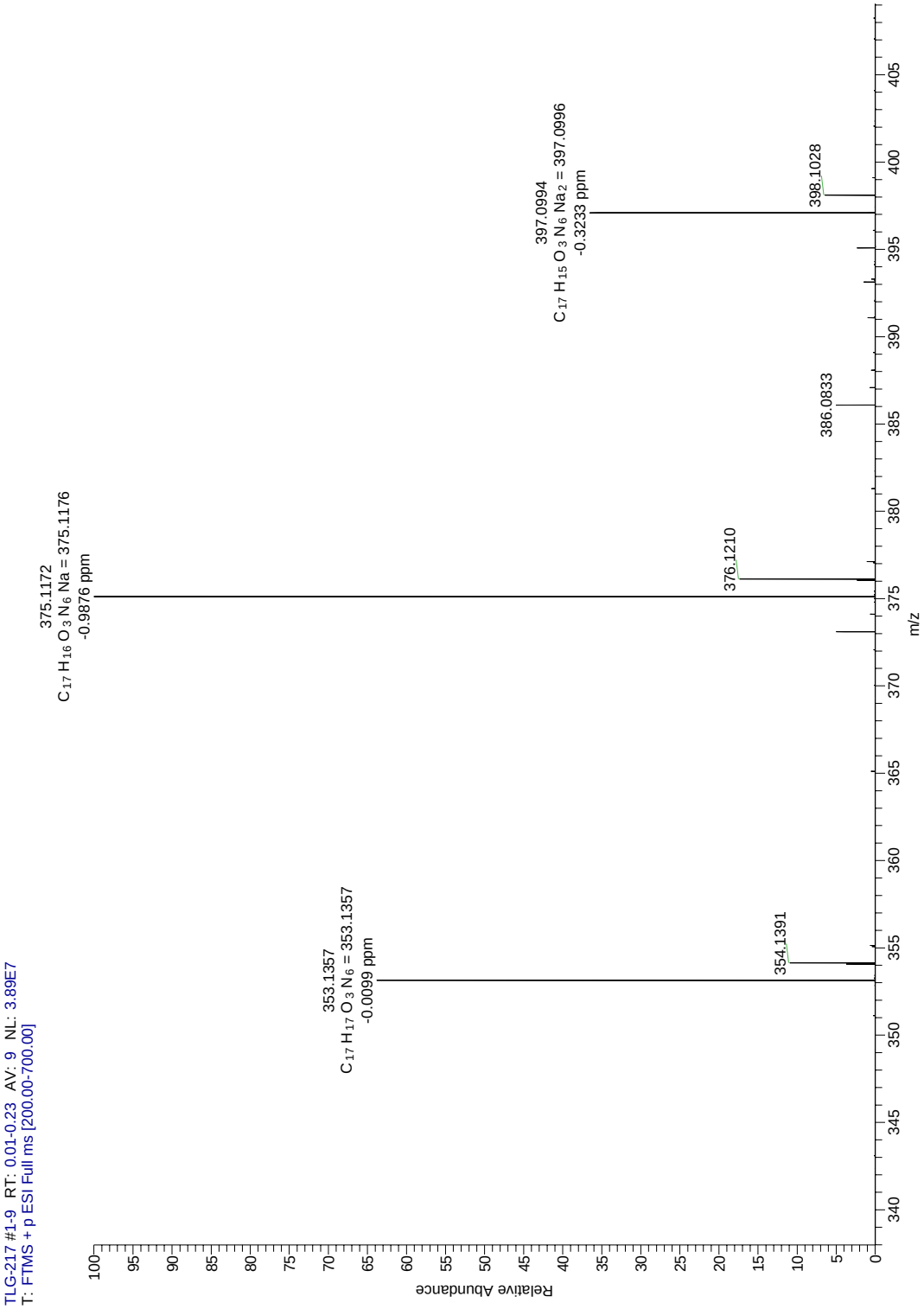
C.1.2 ^{13}C NMR spectrum of 39



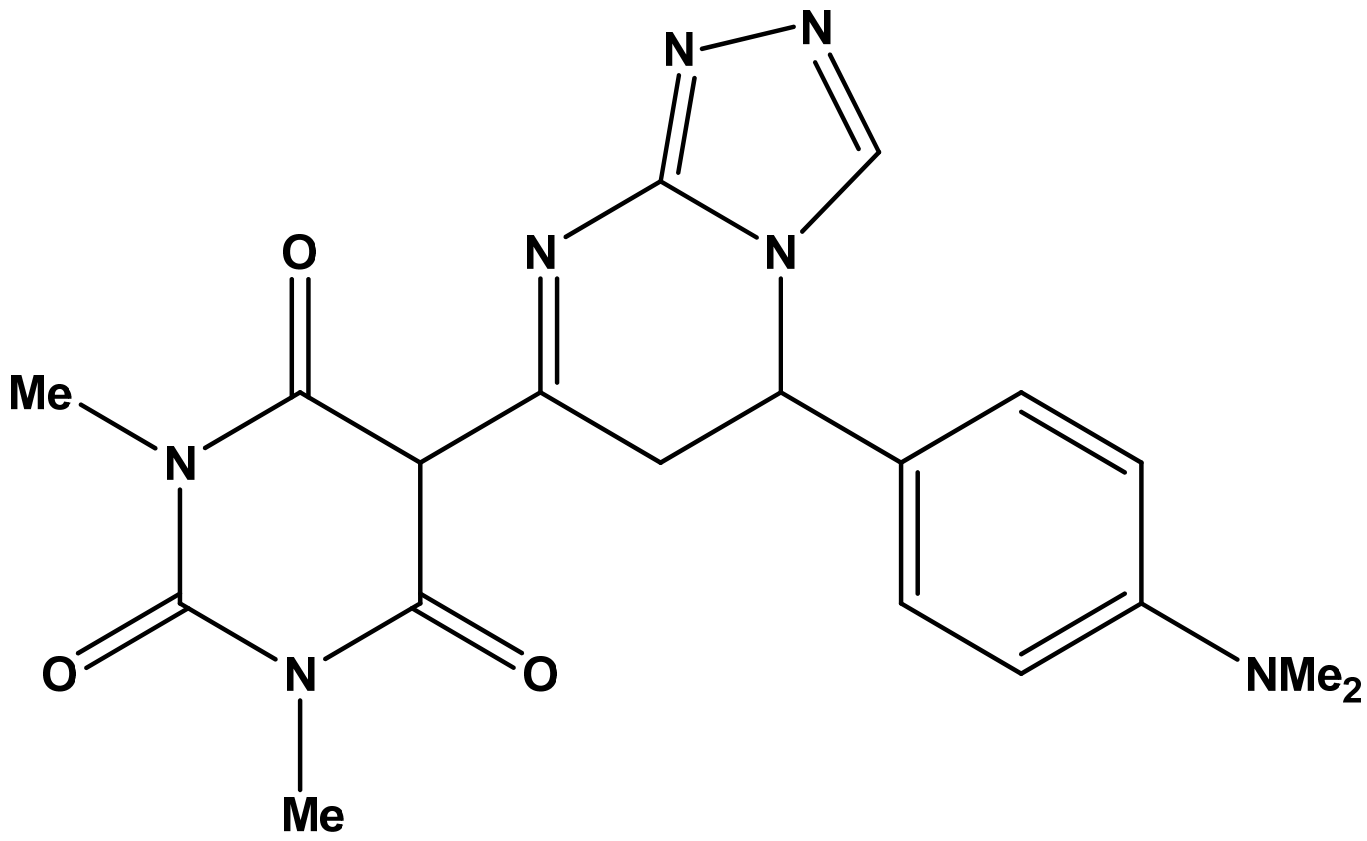
C.1.3 IR spectrum of 39



C.1.4 HRMS of 39

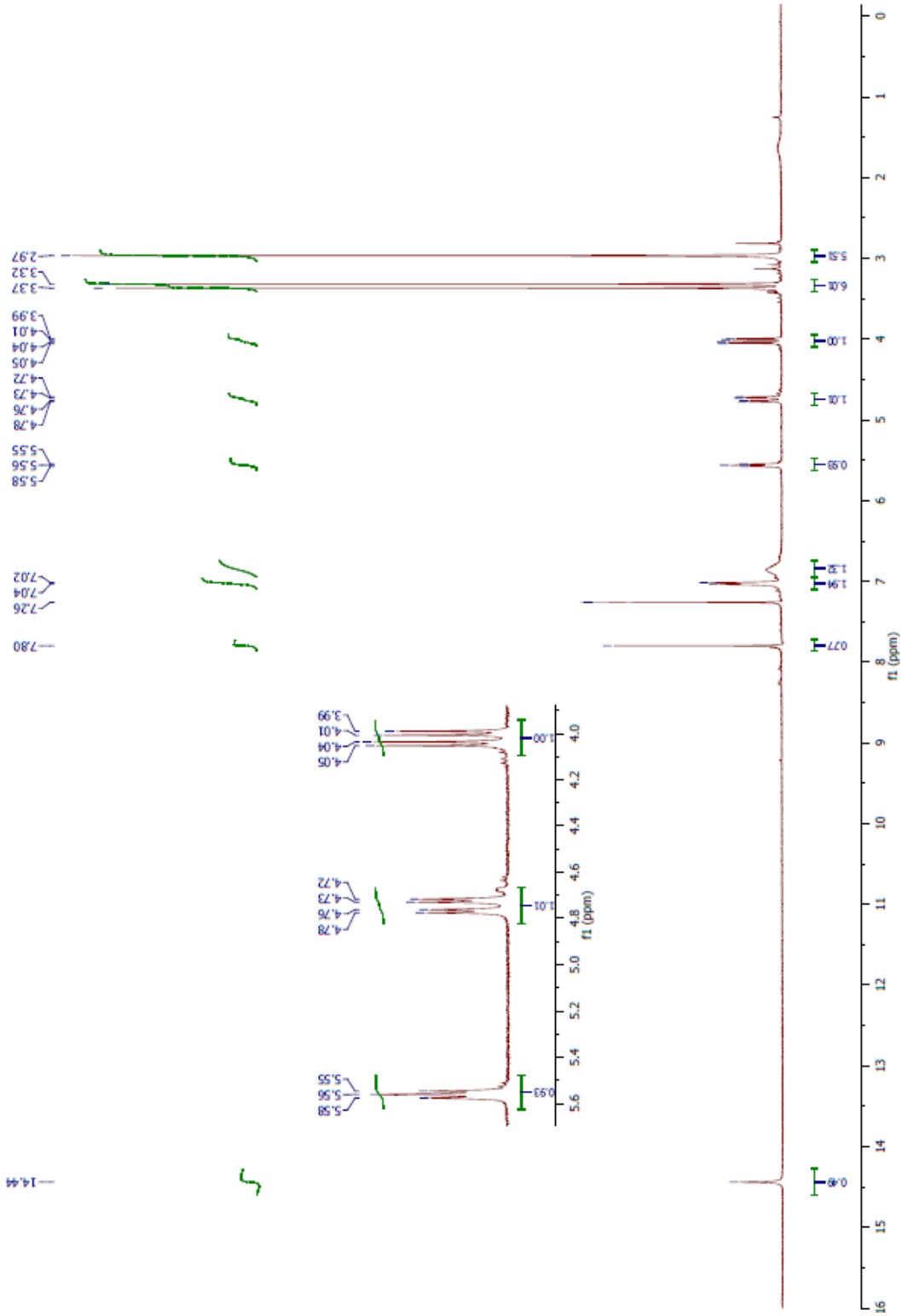


C.2 Spectroscopic data for 40

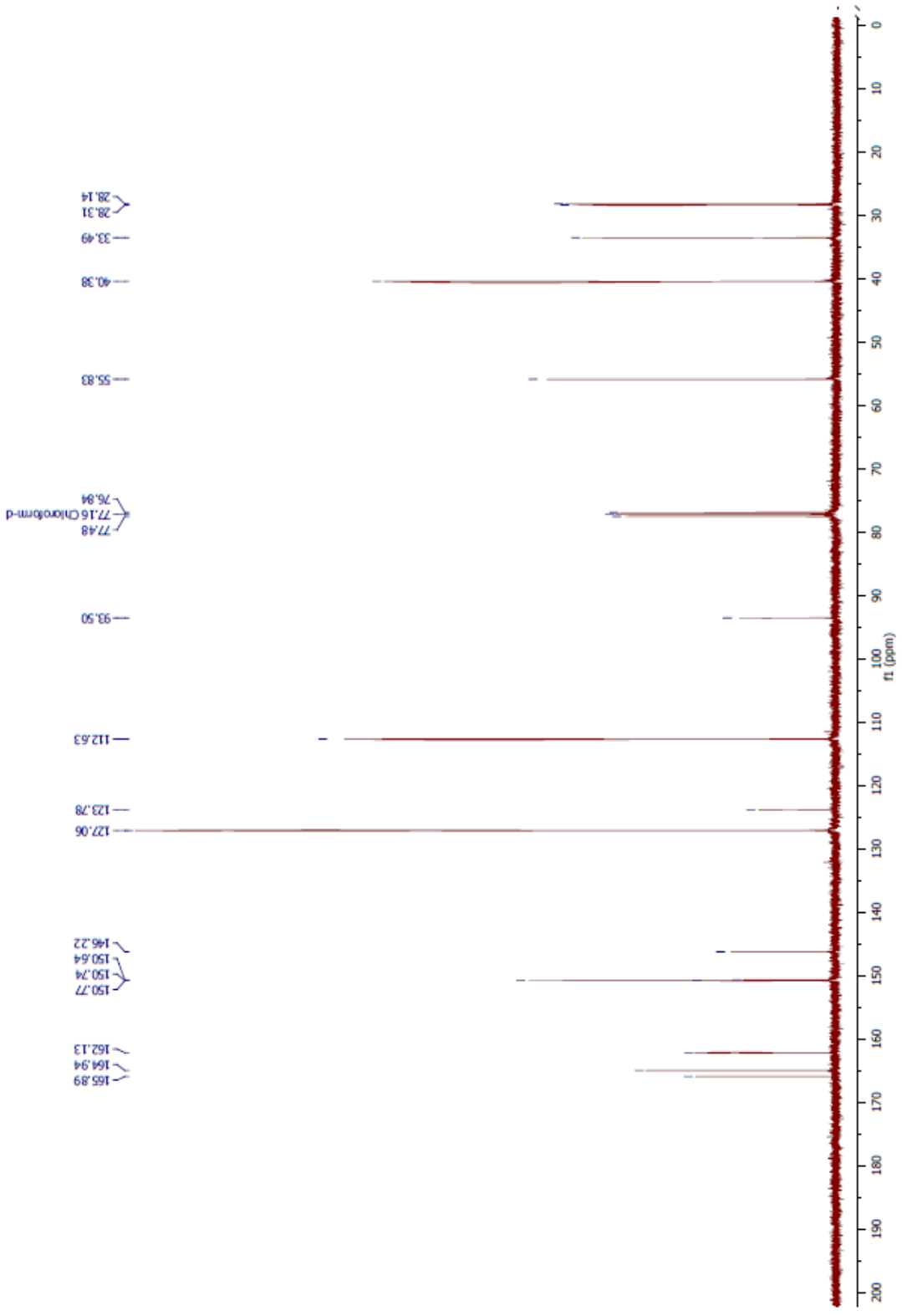


40

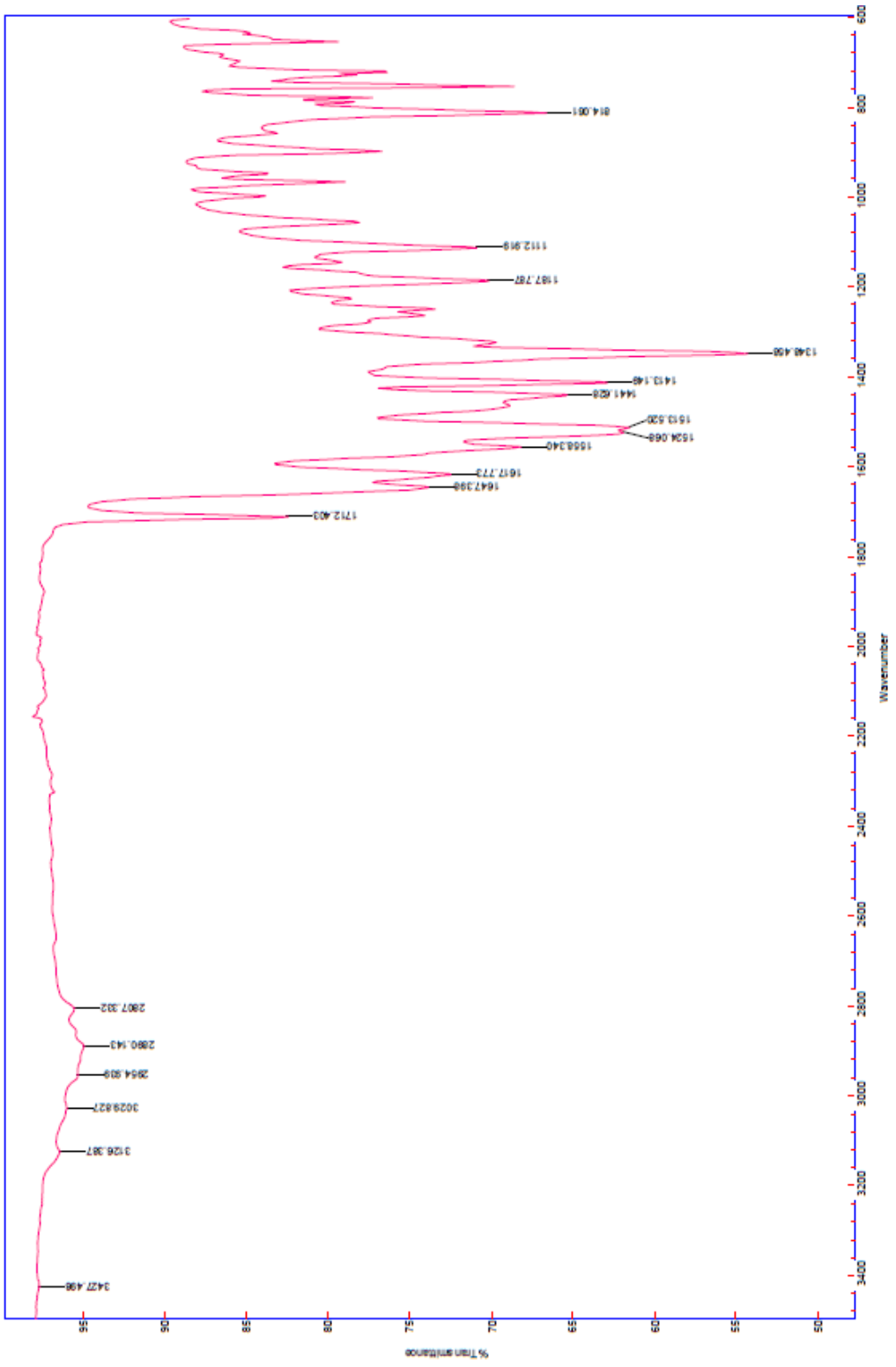
C.2.1 ^{1}H NMR spectrum of 40



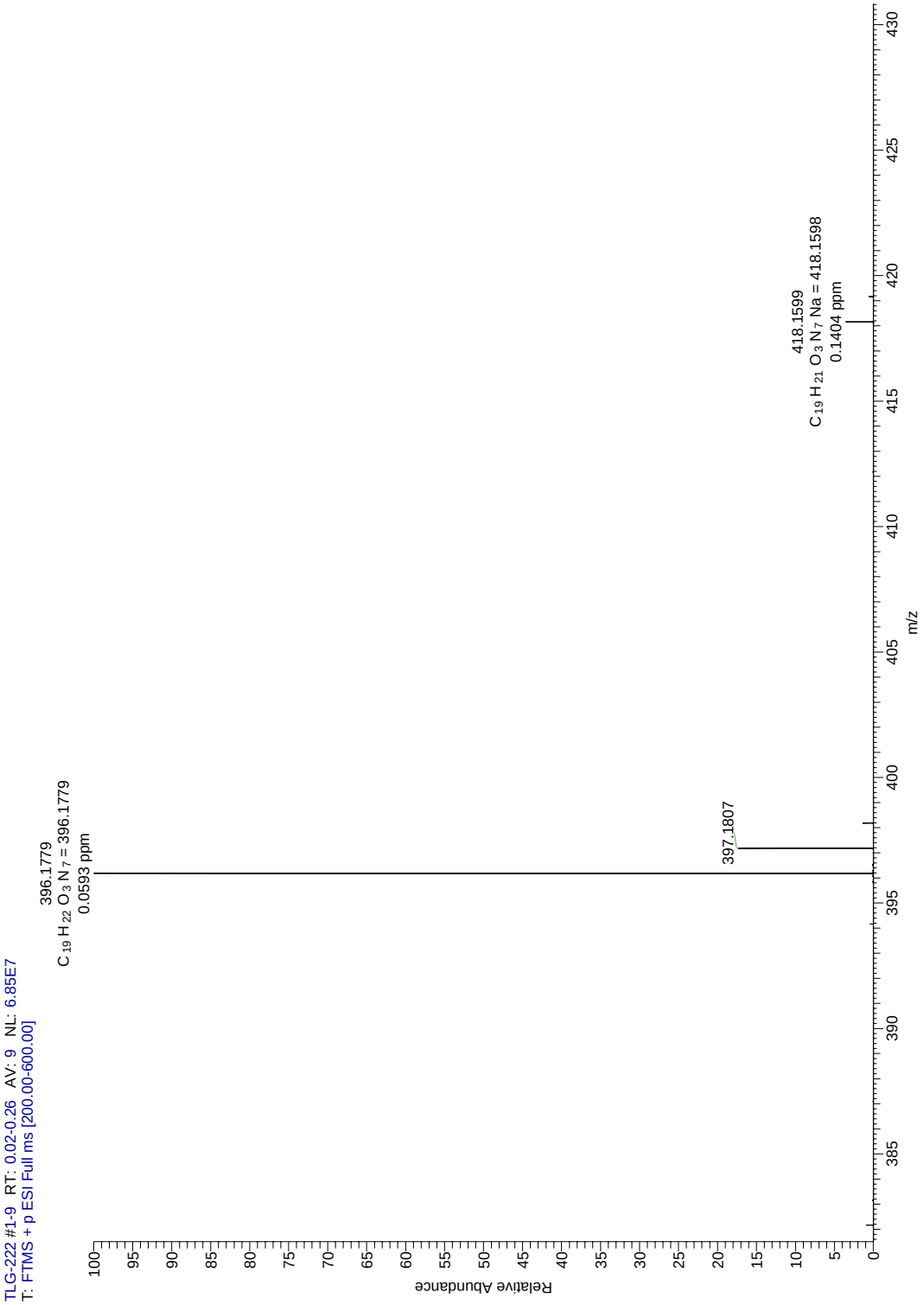
C.2.2 ^{13}C NMR spectrum of 40



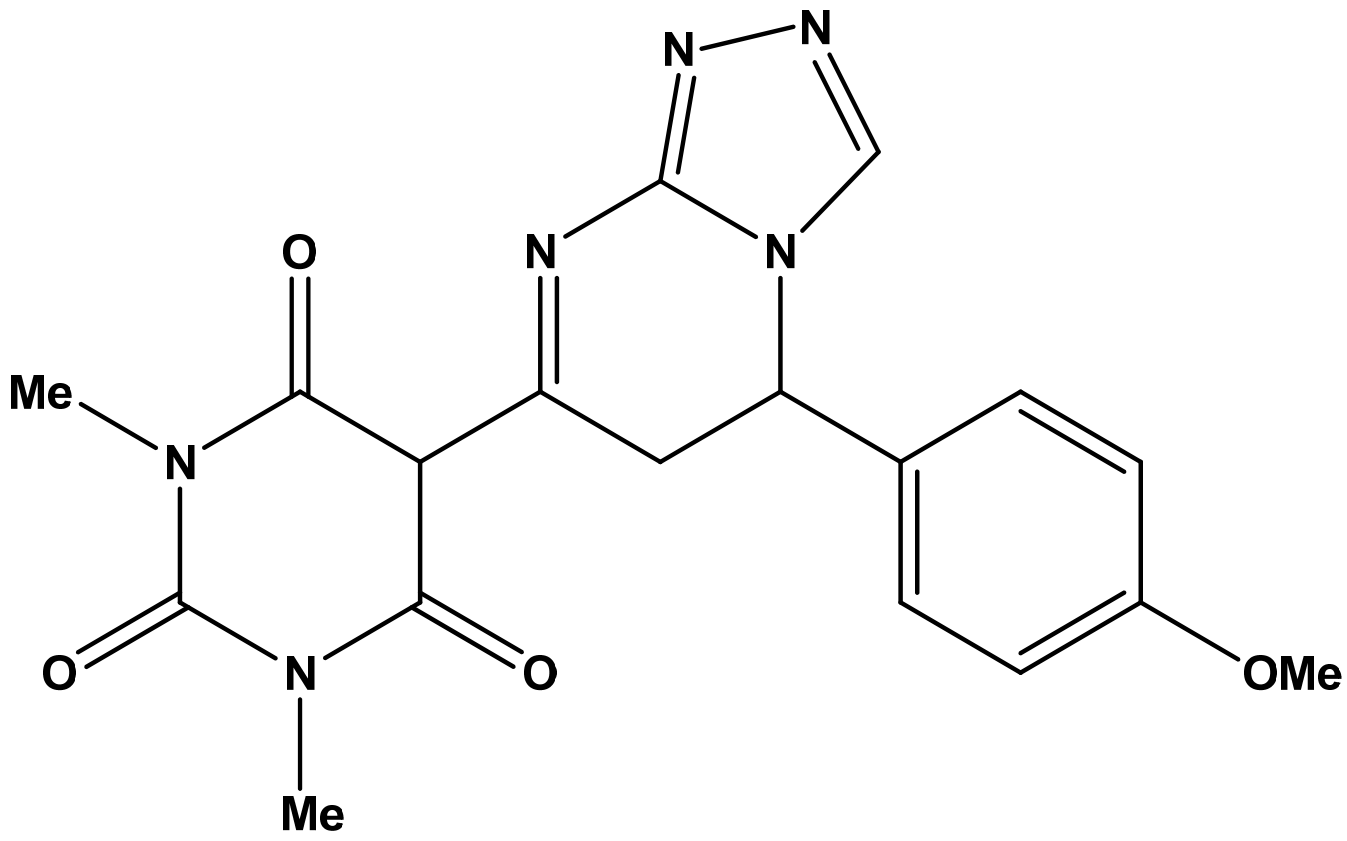
C.2.3 IR spectrum of 40



C.2.4 HRMS of 40

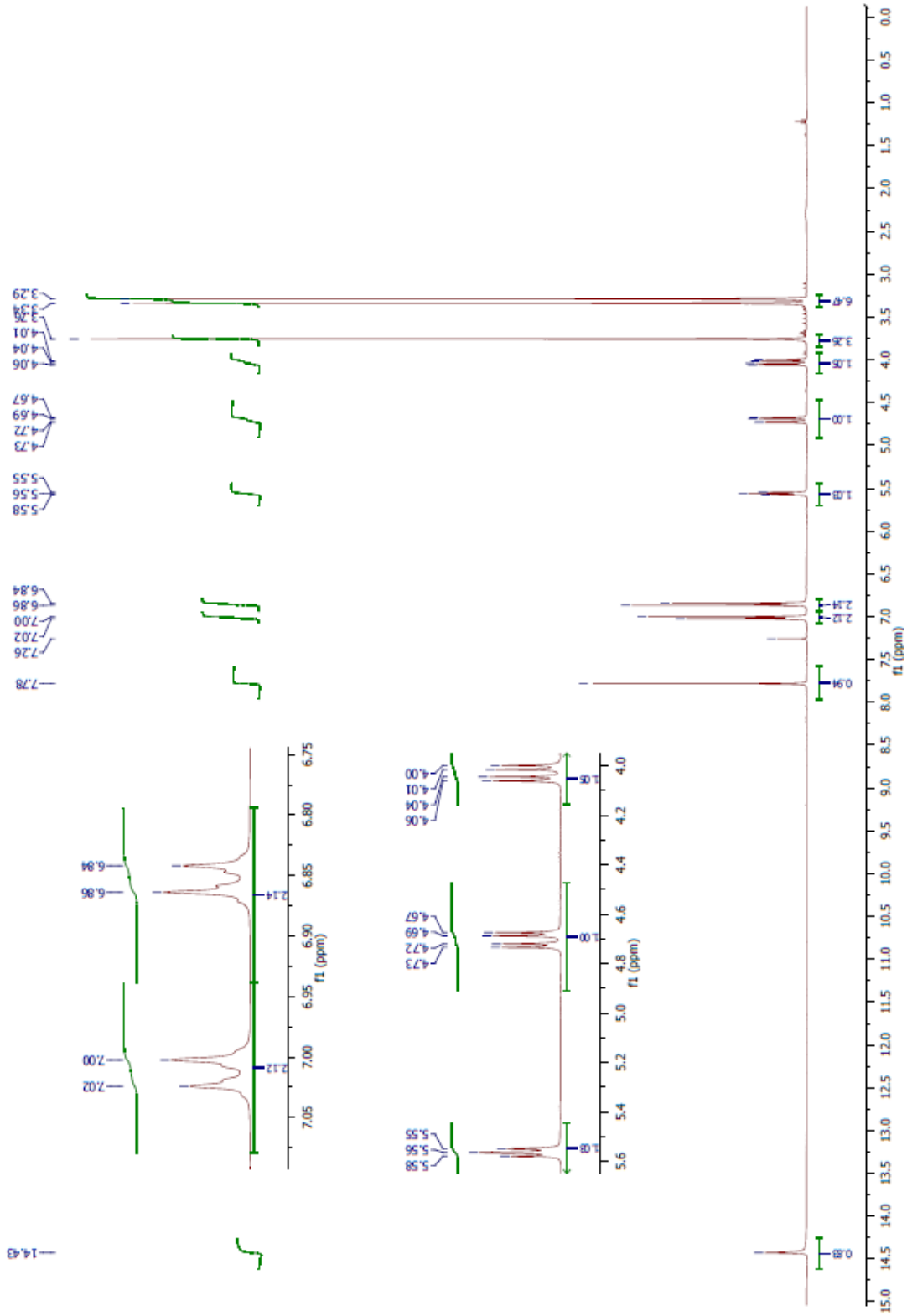


C.3 Spectroscopic data for 41

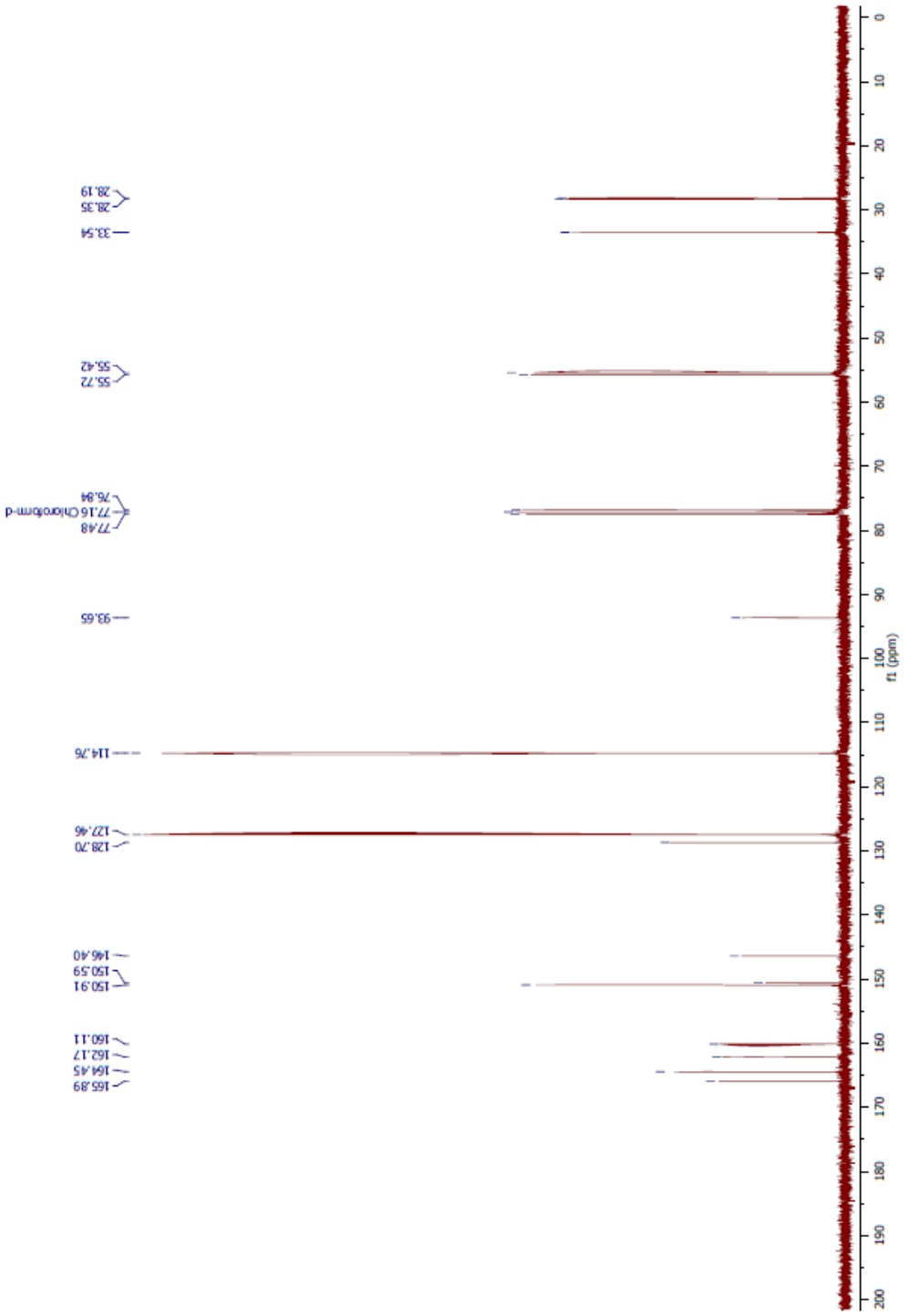


41

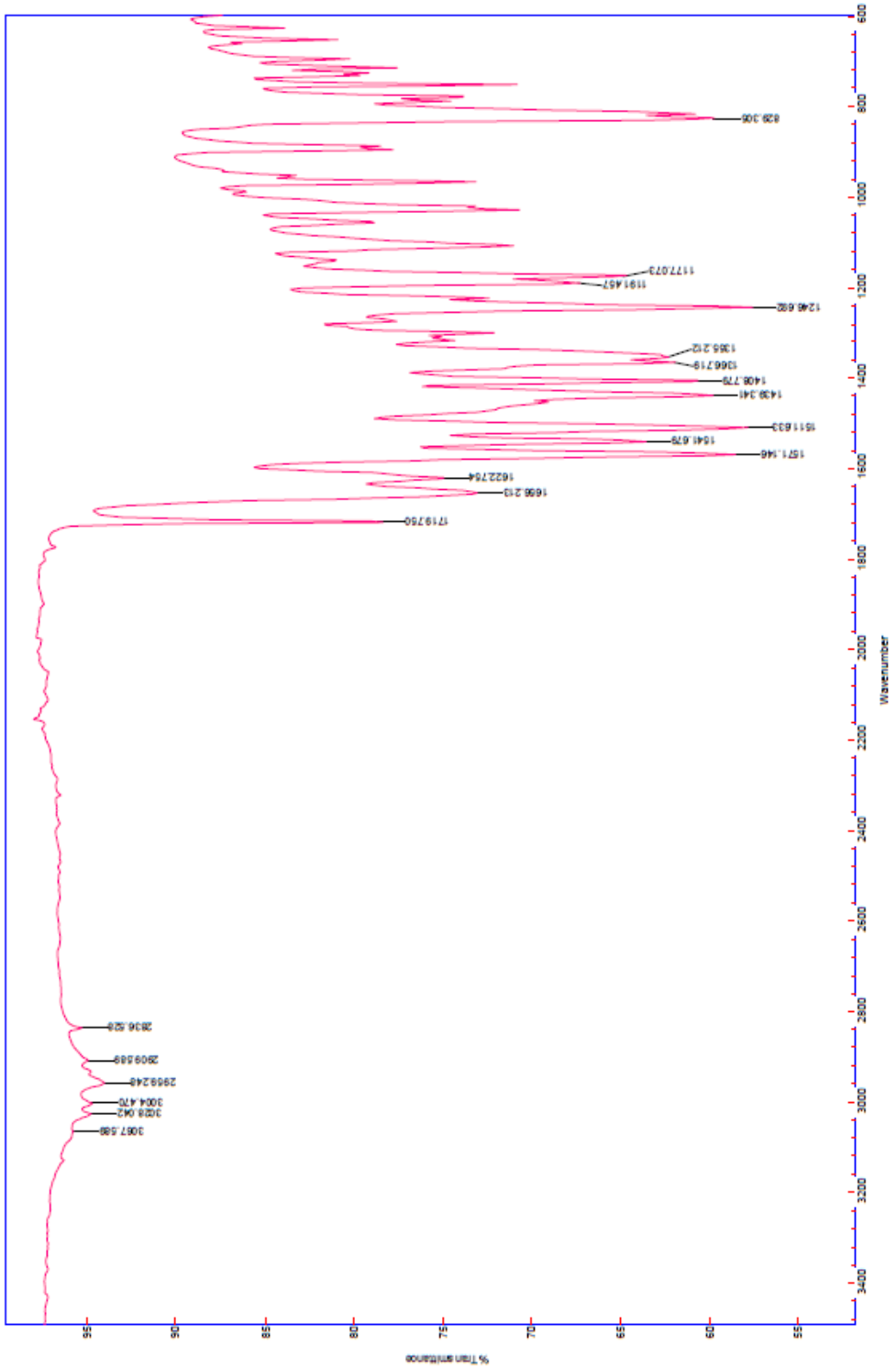
C.3.1 ^{1}H NMR spectrum of 41



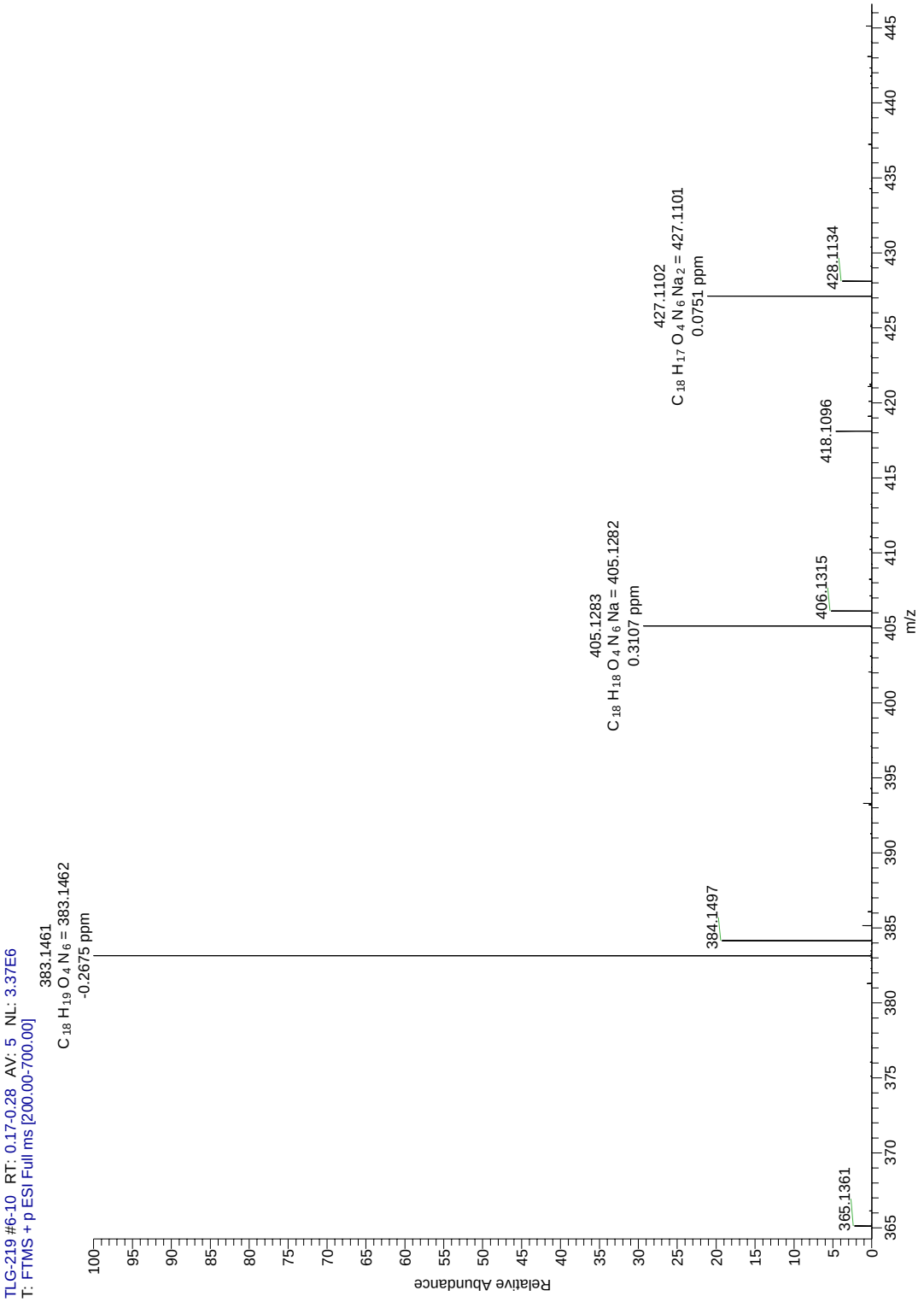
C.3.2 ^{13}C NMR spectrum of 41



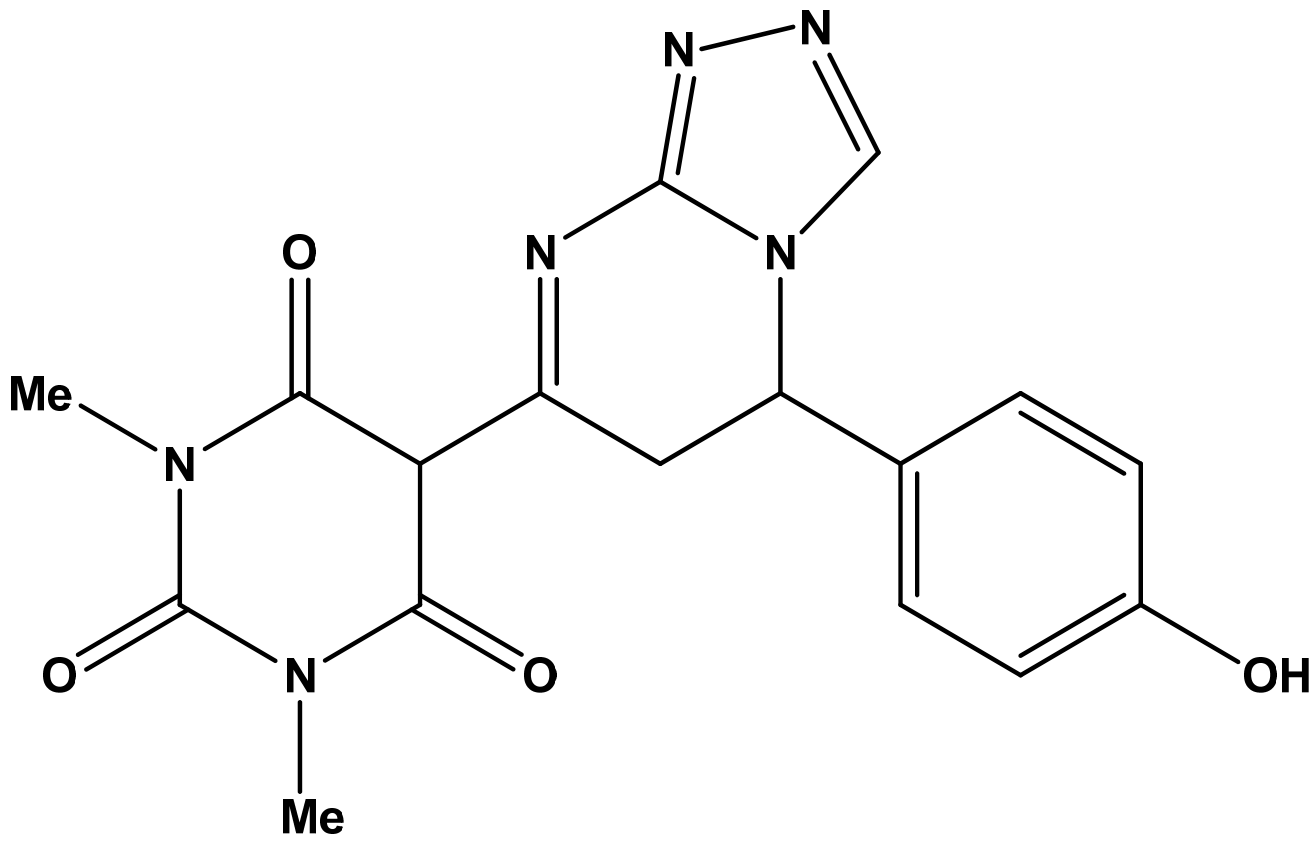
C.3.3 IR Spectrum of 41



C.3.4 HRMS of 41

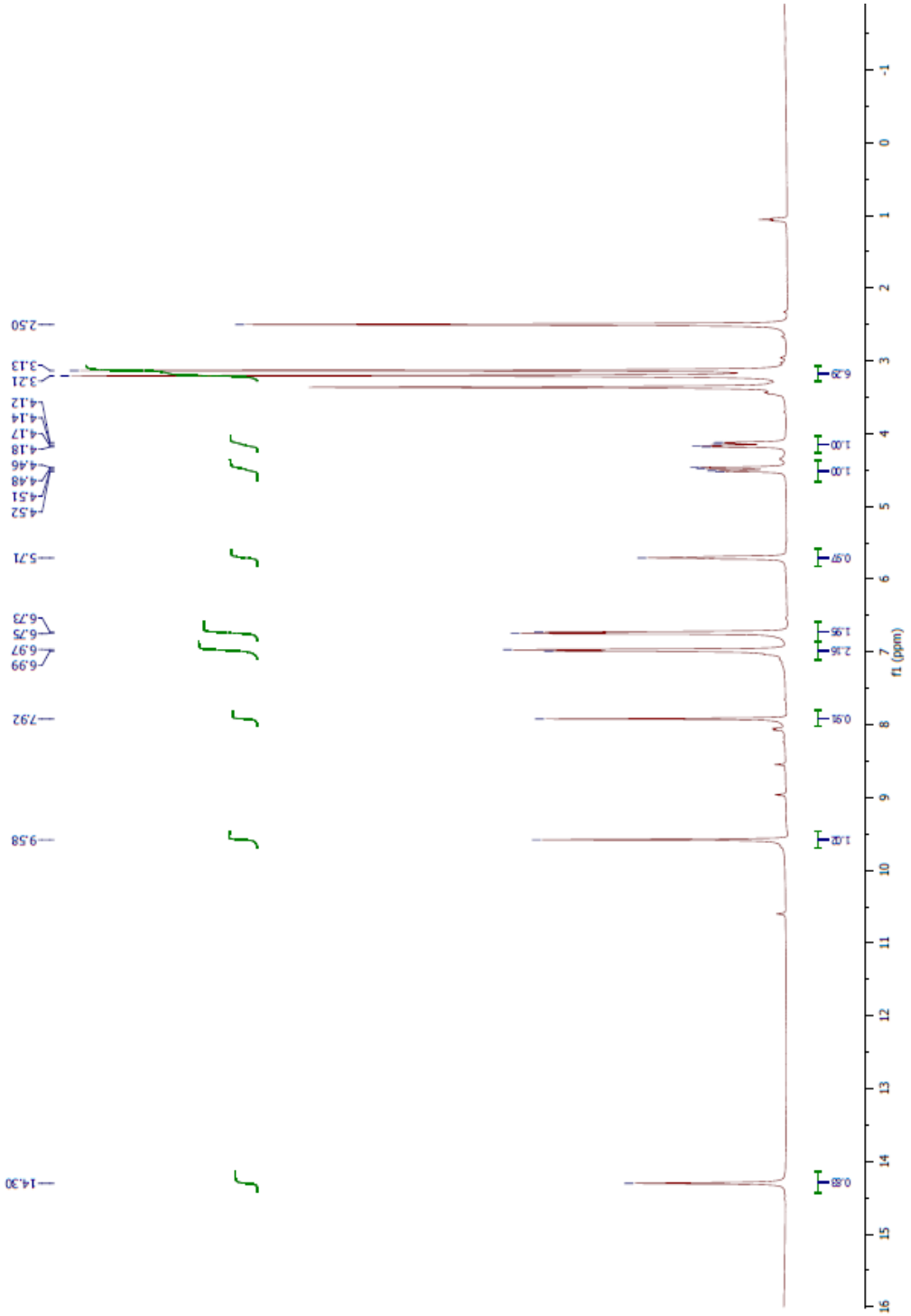


C.4 Spectroscopic data for 42

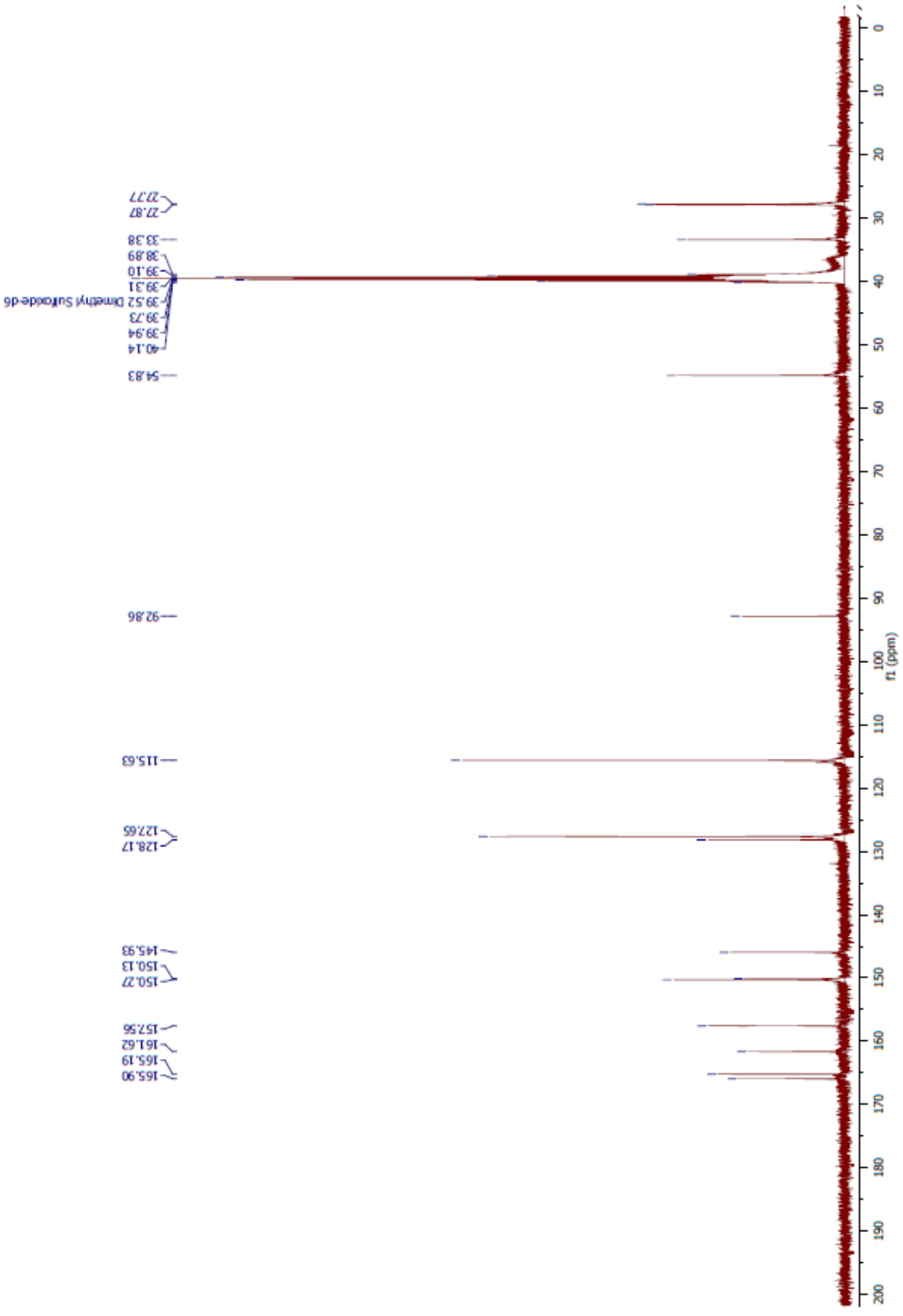


42

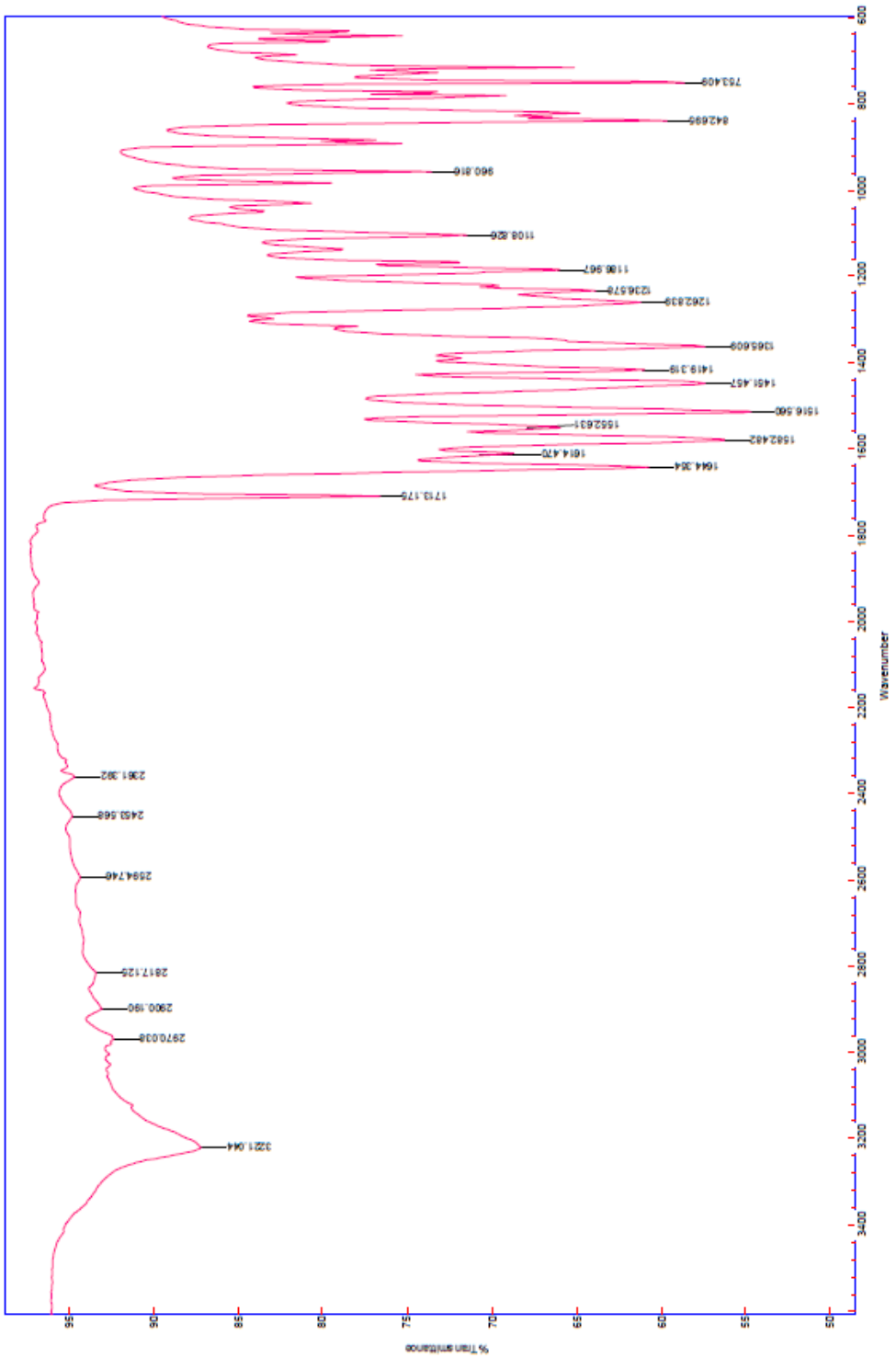
C.4.1 ^{1}H NMR spectrum of 42



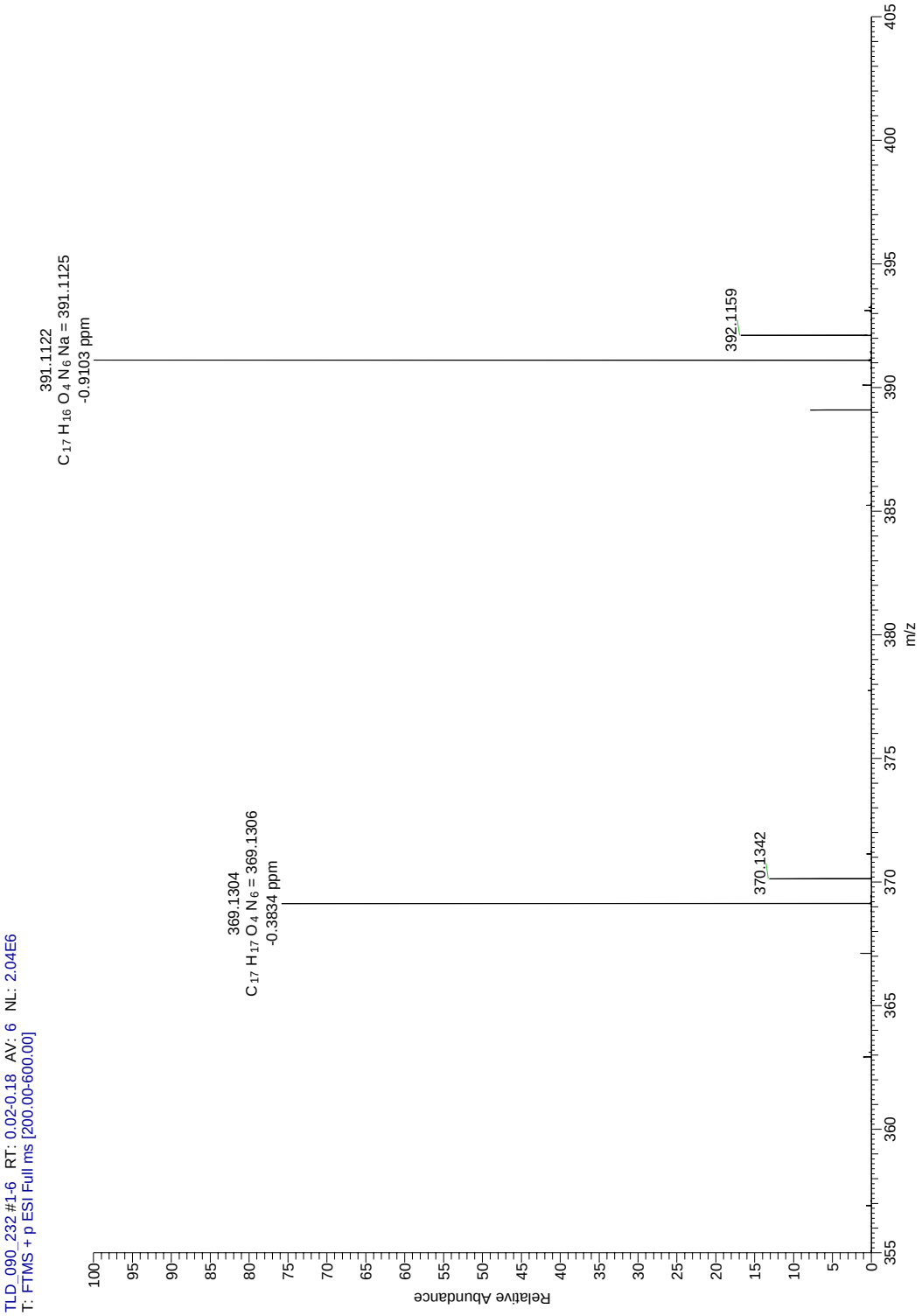
C.4.2 ^{13}C NMR spectrum of 42



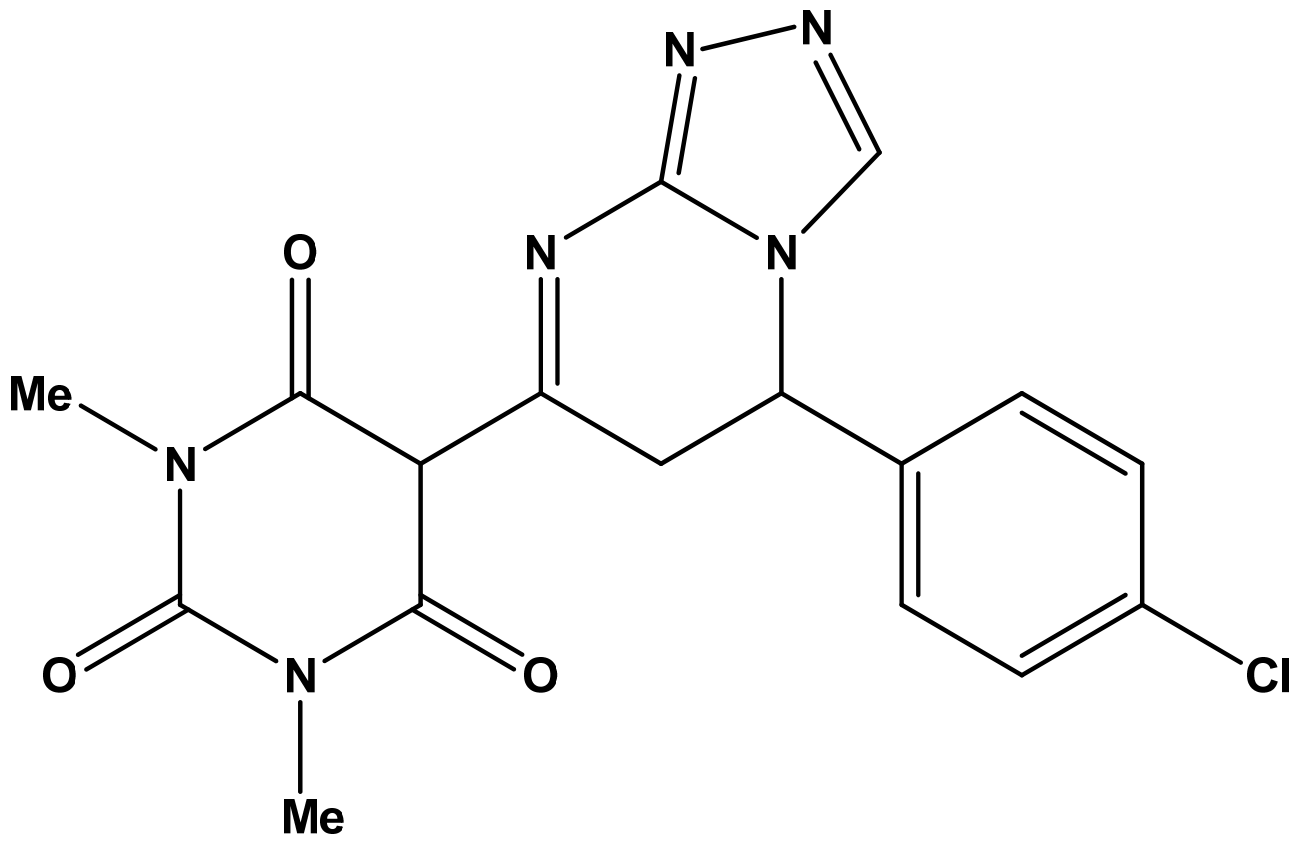
C.4.3 IR spectrum of 42



C.4.3 IR spectrum of 42

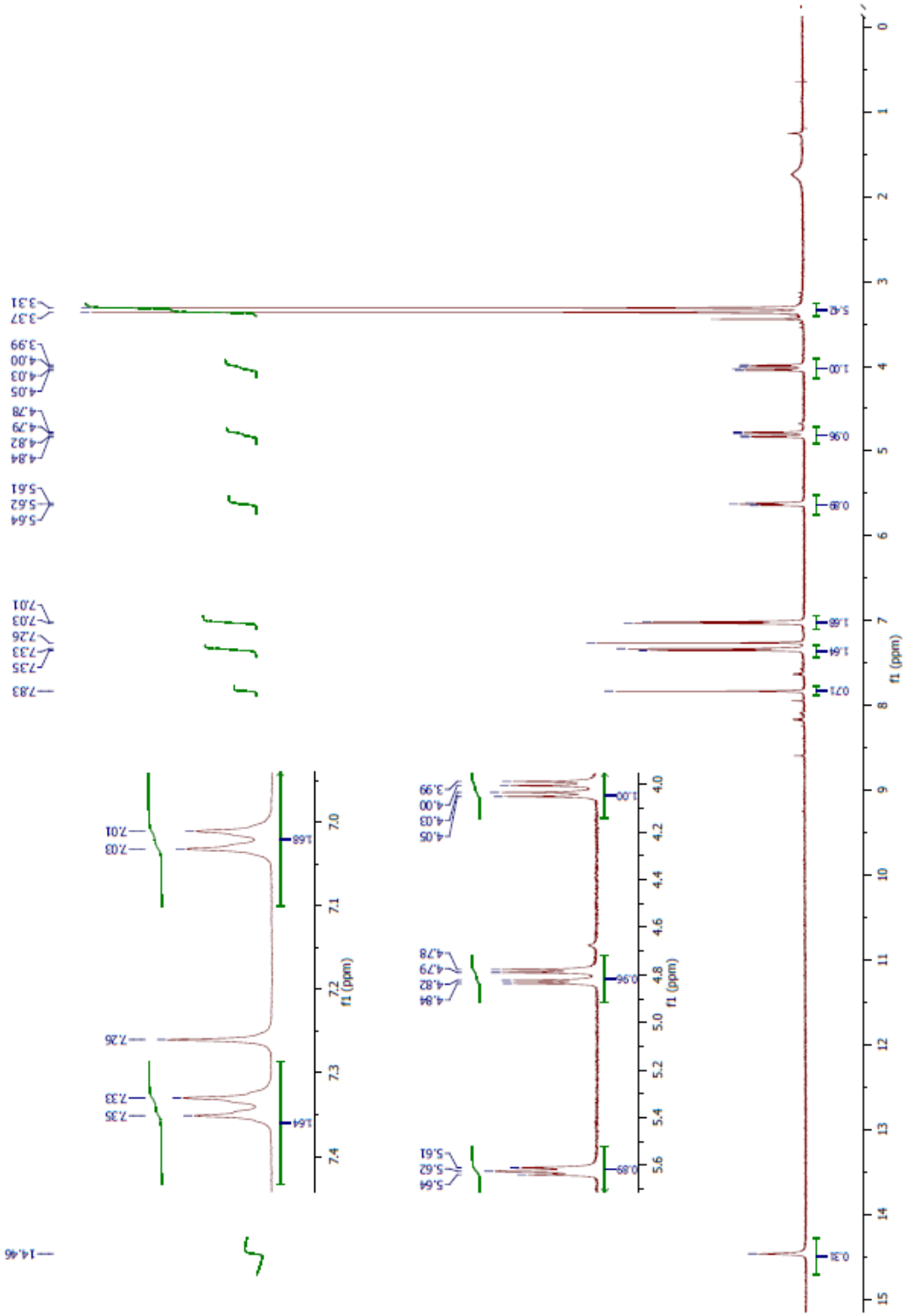


C.5 Spectroscopic data for 43

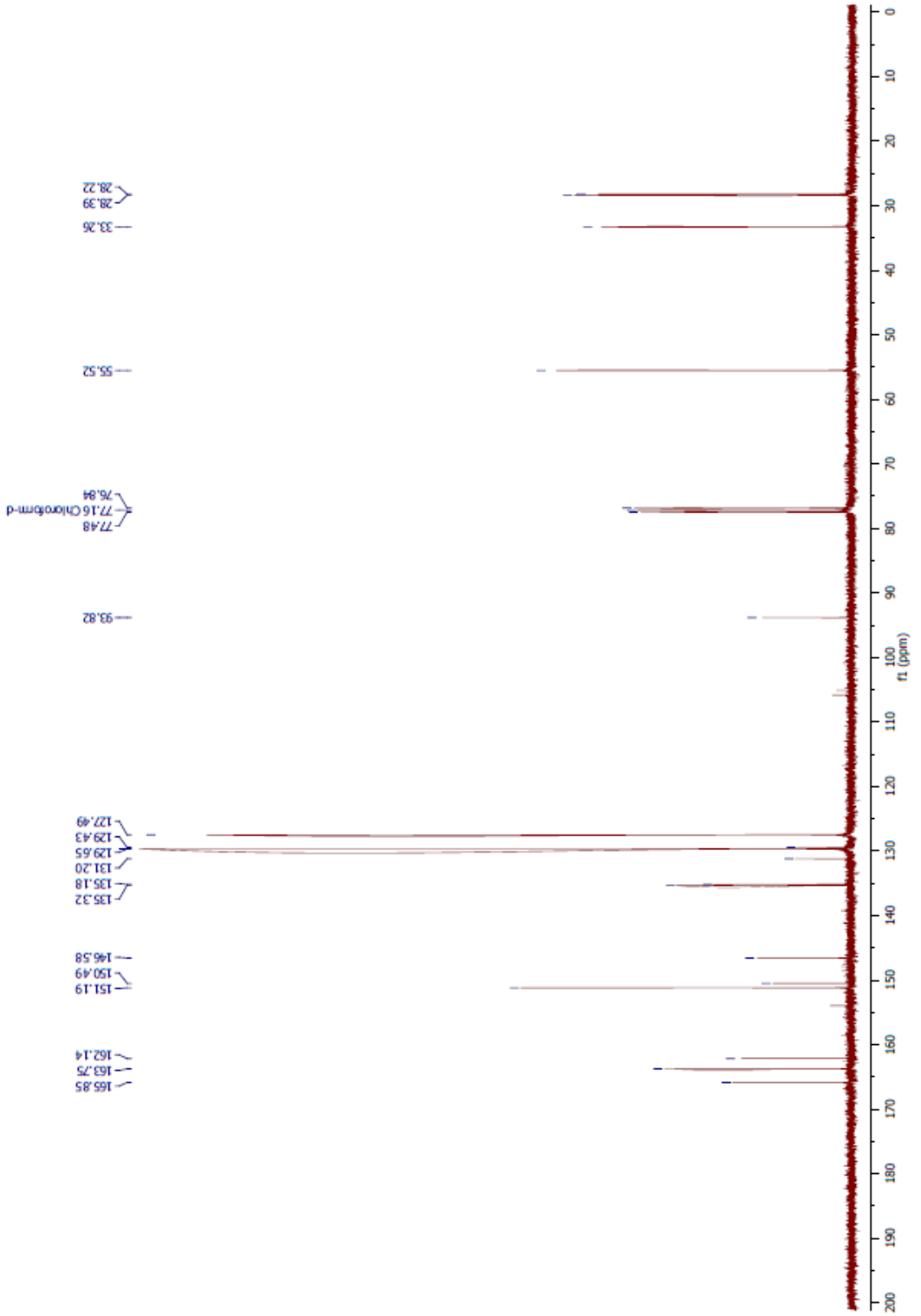


43

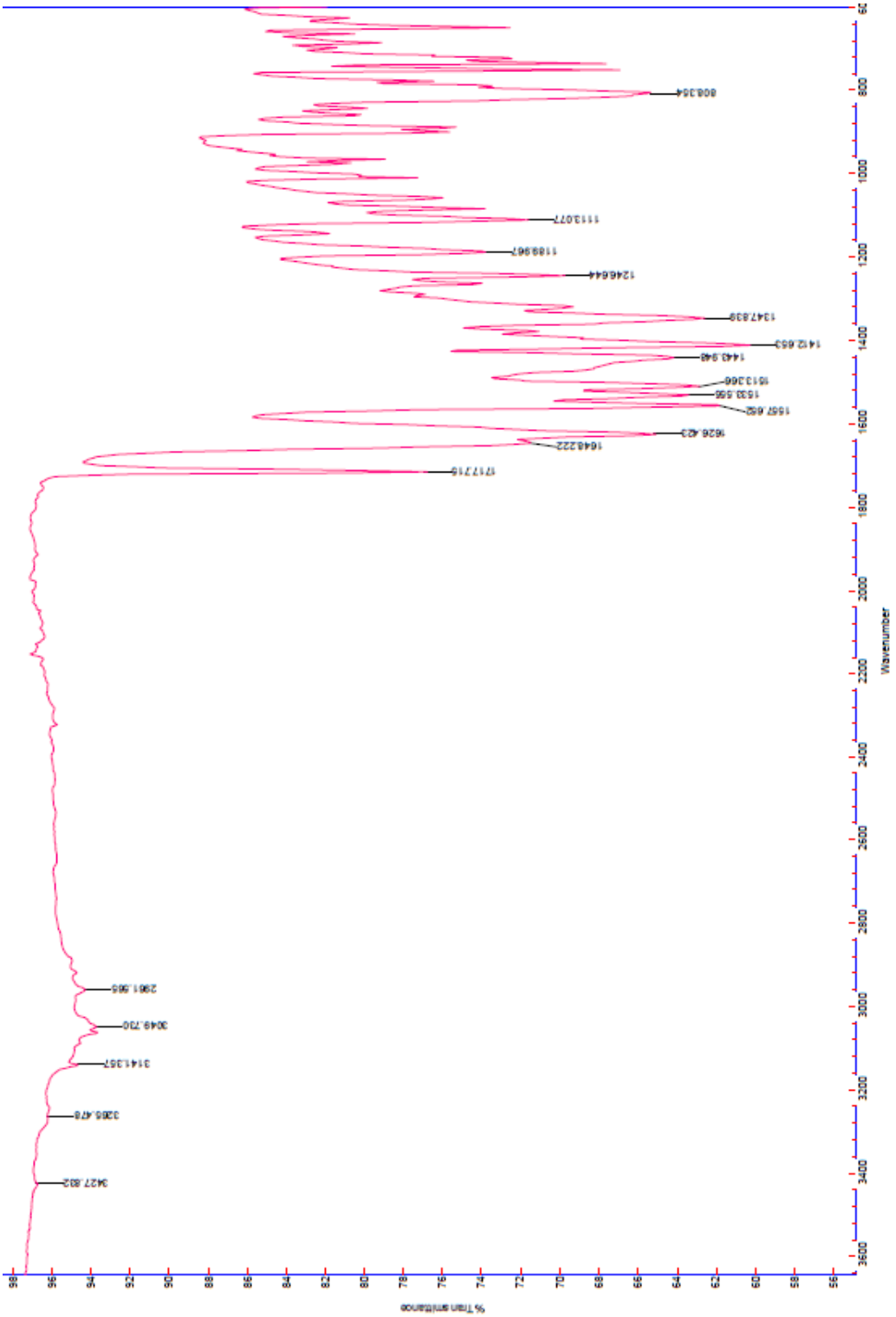
C.5.1 ^{1}H NMR spectrum of 43



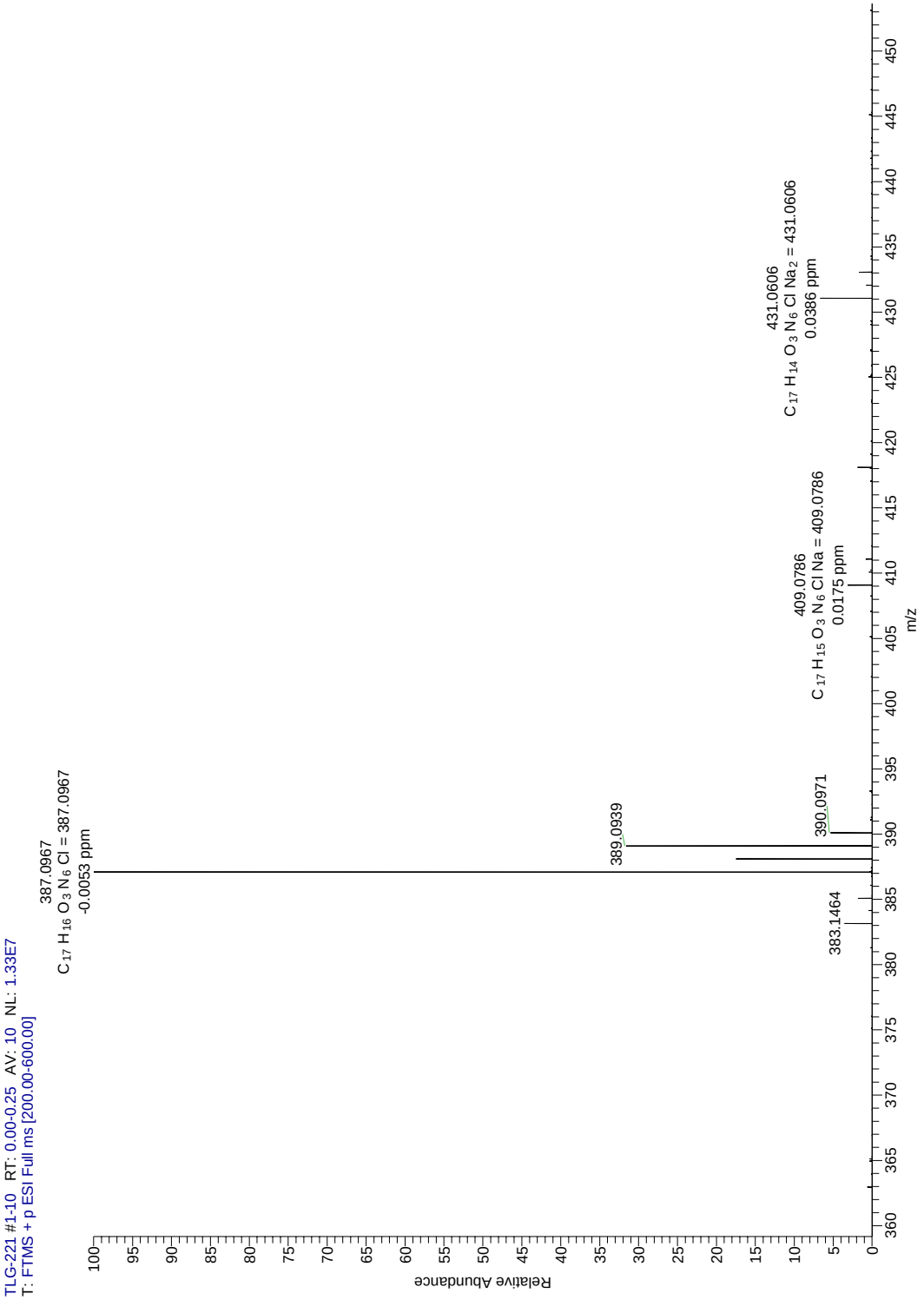
C.5.2 ^{13}C NMR spectrum of 43



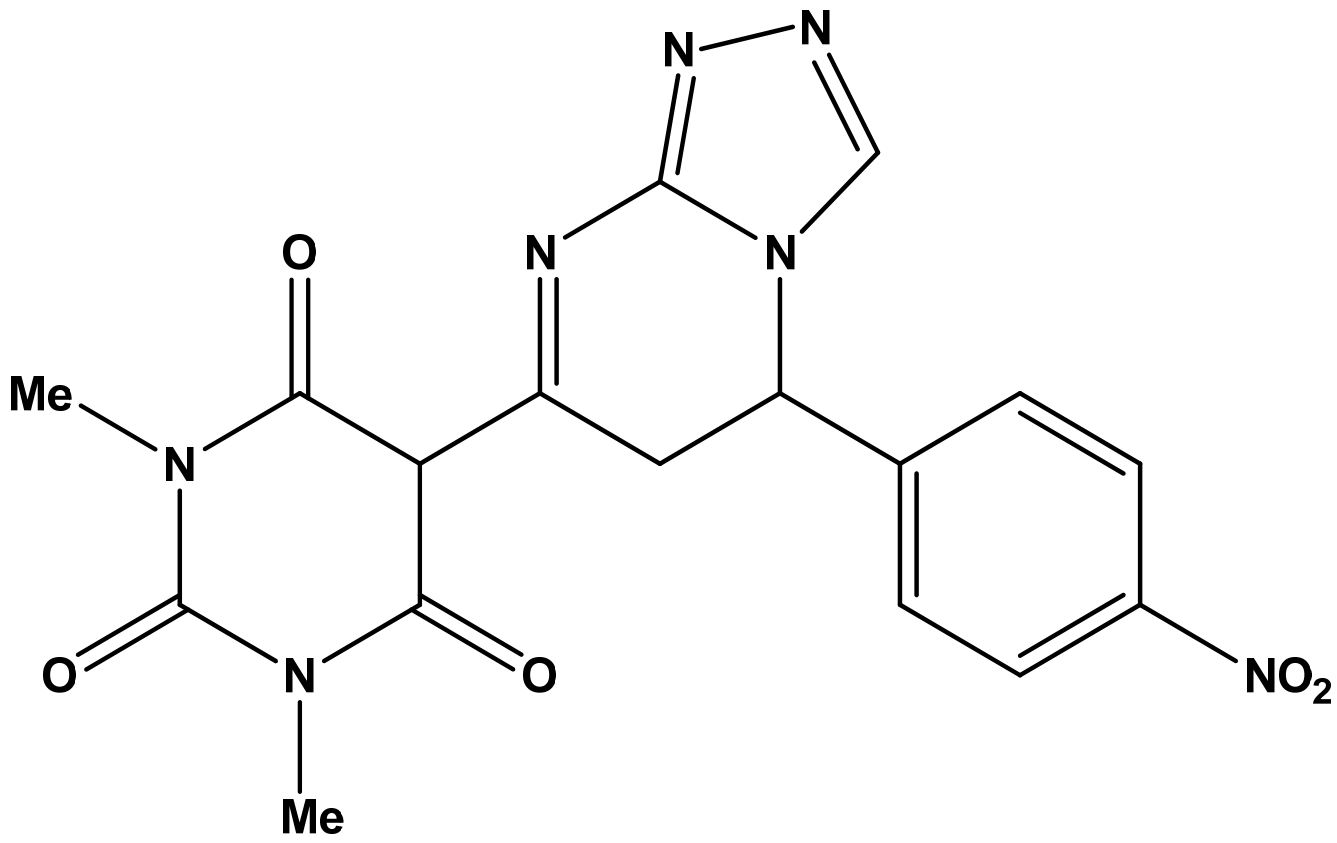
C.5.3 IR spectrum of 43



C.5.3 HRMS of 43

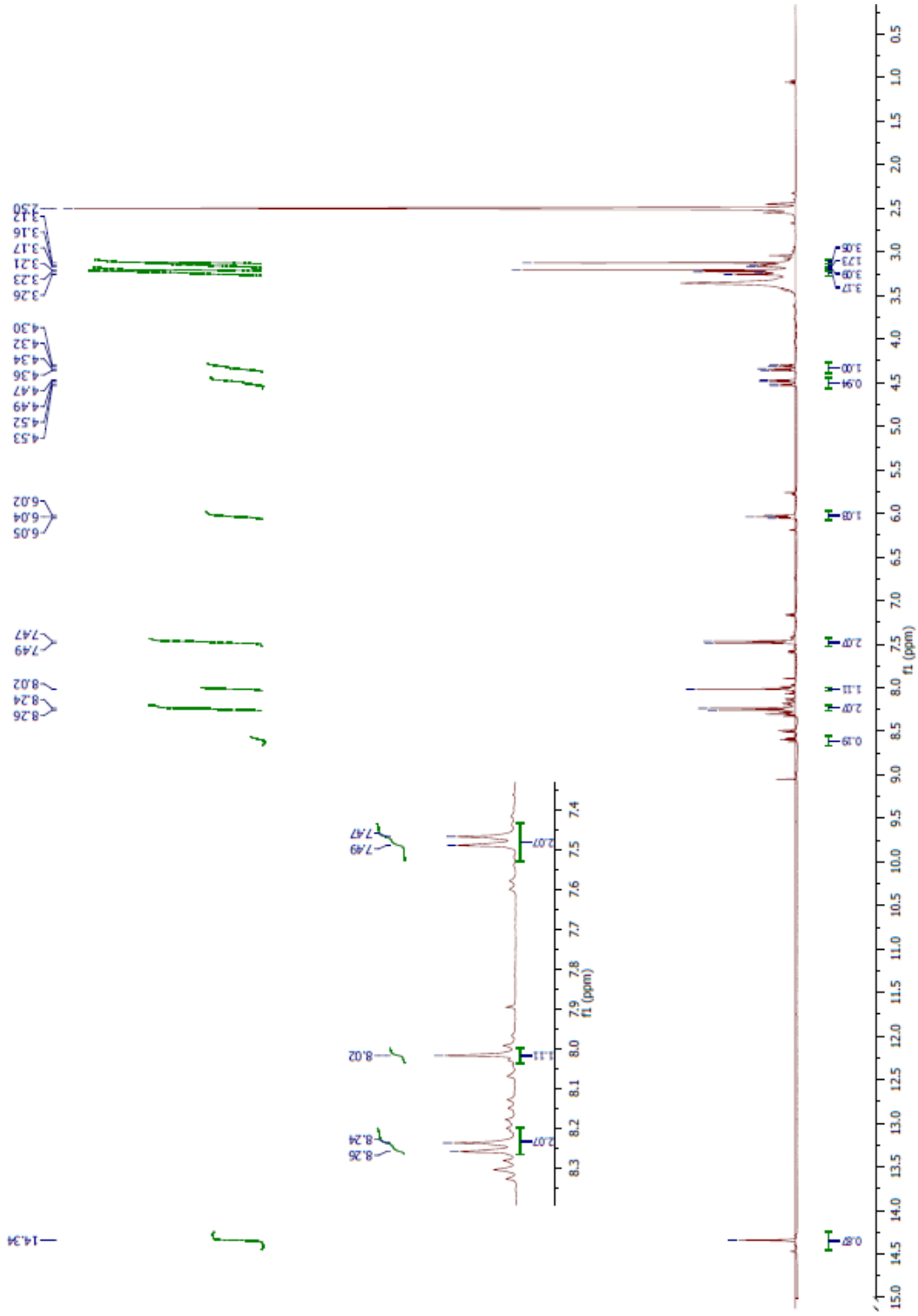


C.6 Spectroscopic data for 44

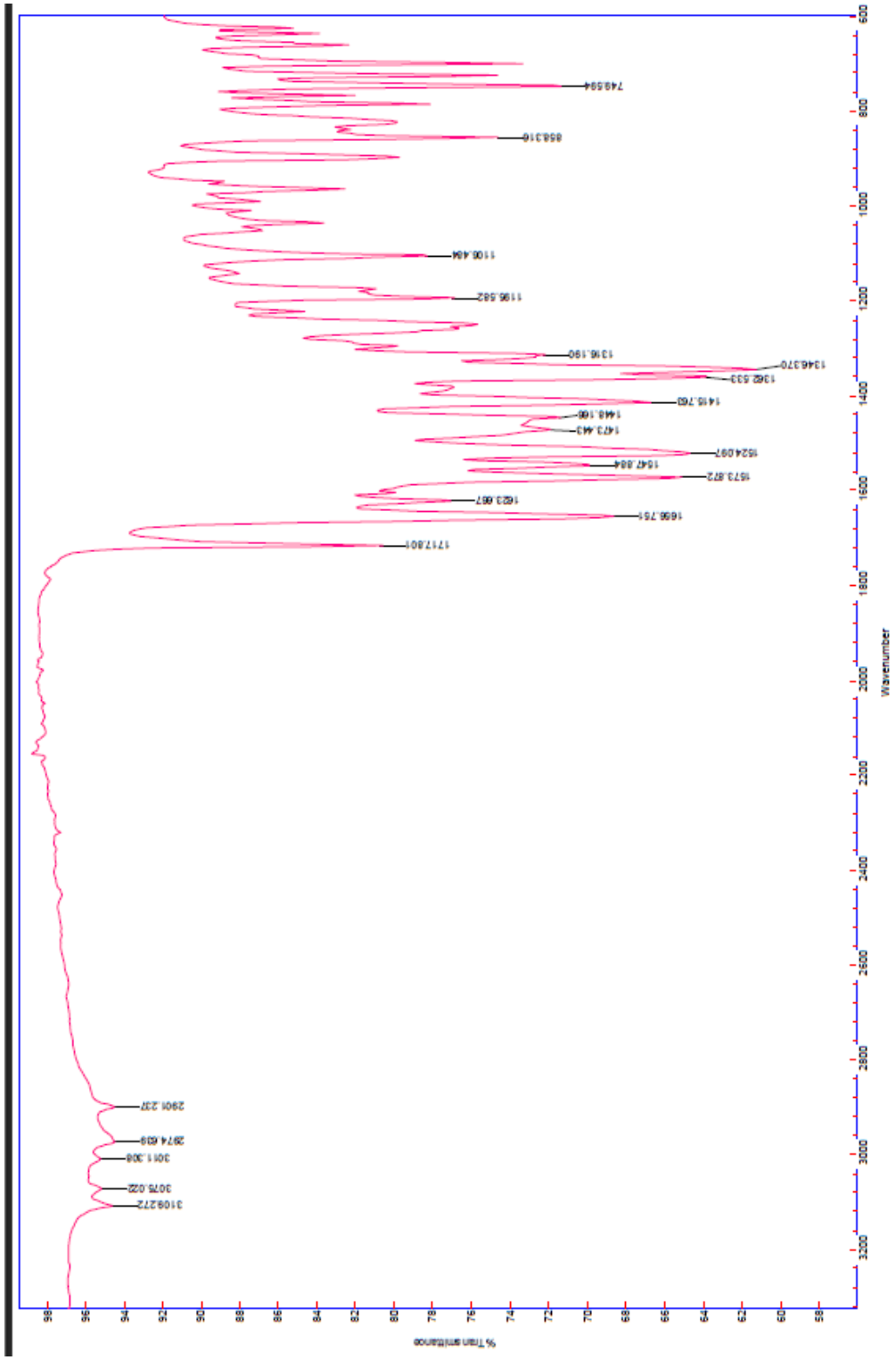


44

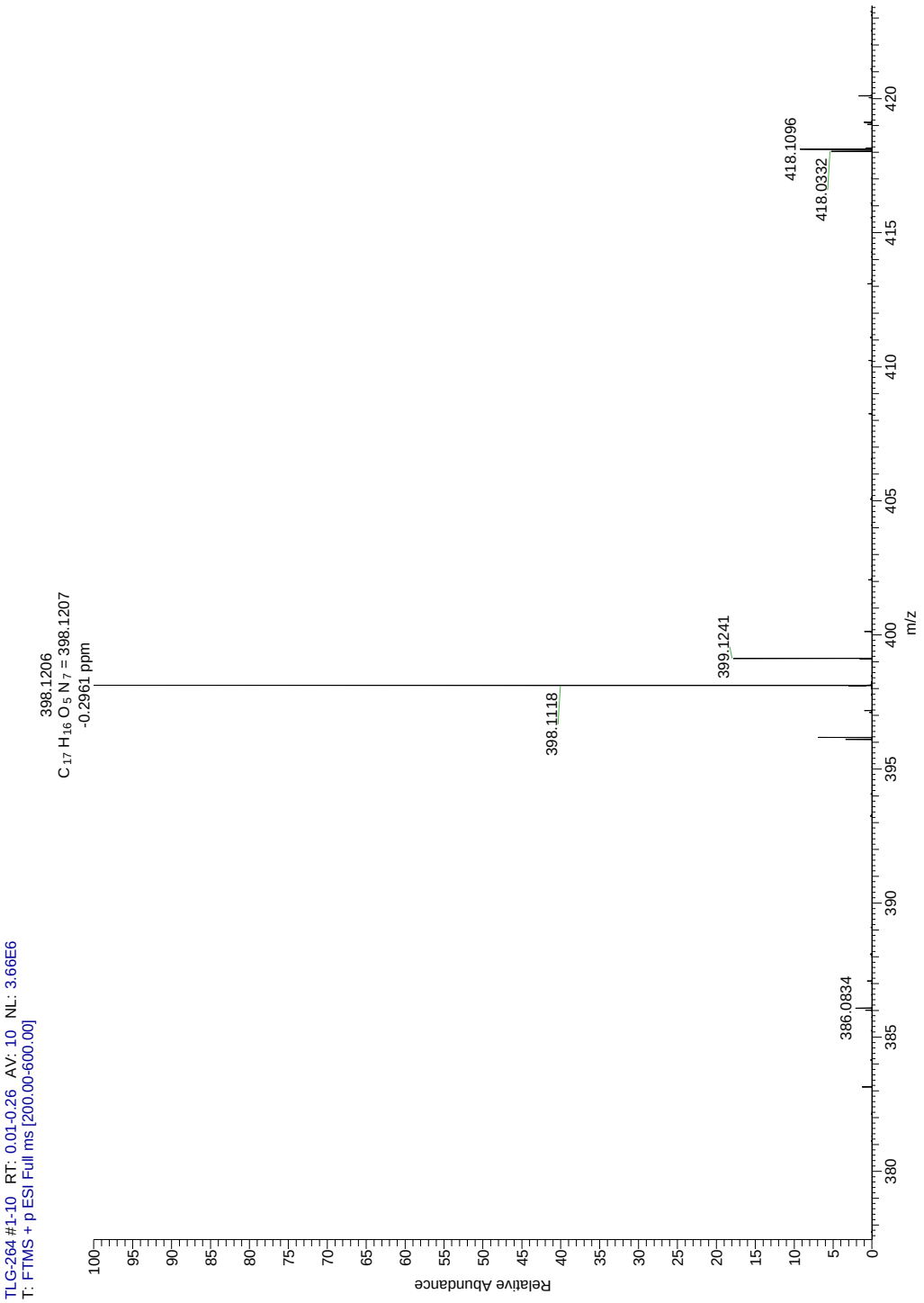
C.6.1 ^{1}H NMR spectrum of 44



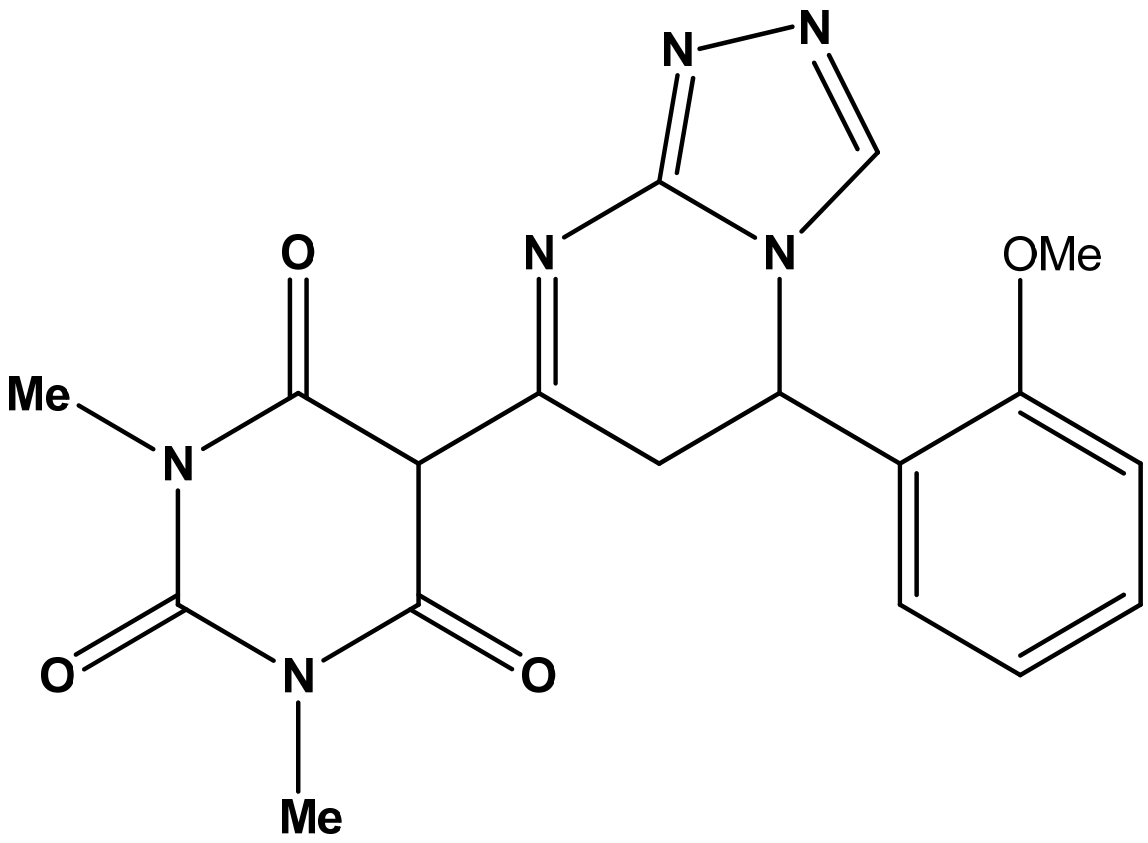
C.6.2 IR spectrum of 44



C.6. HRMS of 44

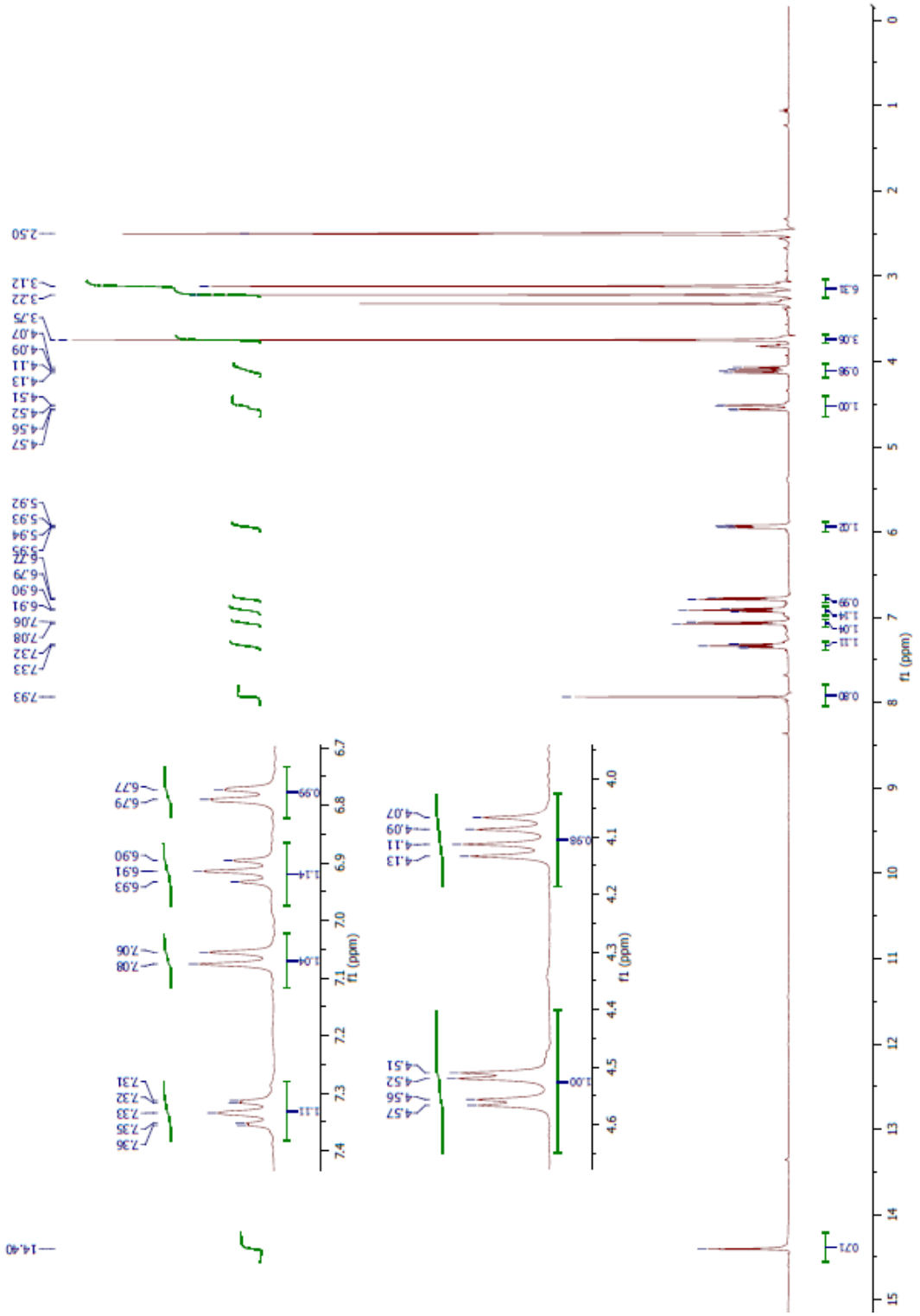

TLG-264 #1-10 RT: 0.01-0.26 AV: 10 NL: 3.66E6
T: FTMS + p ESI Full ms [200.00-600.00]
398.1206
C 17 H 16 O 5 N 7 = 398.1207
-0.2961 ppm
398.1118
399.1241
386.0834
418.1096
418.0332
Relative Abundance
m/z

C.7 Spectroscopic data for 45

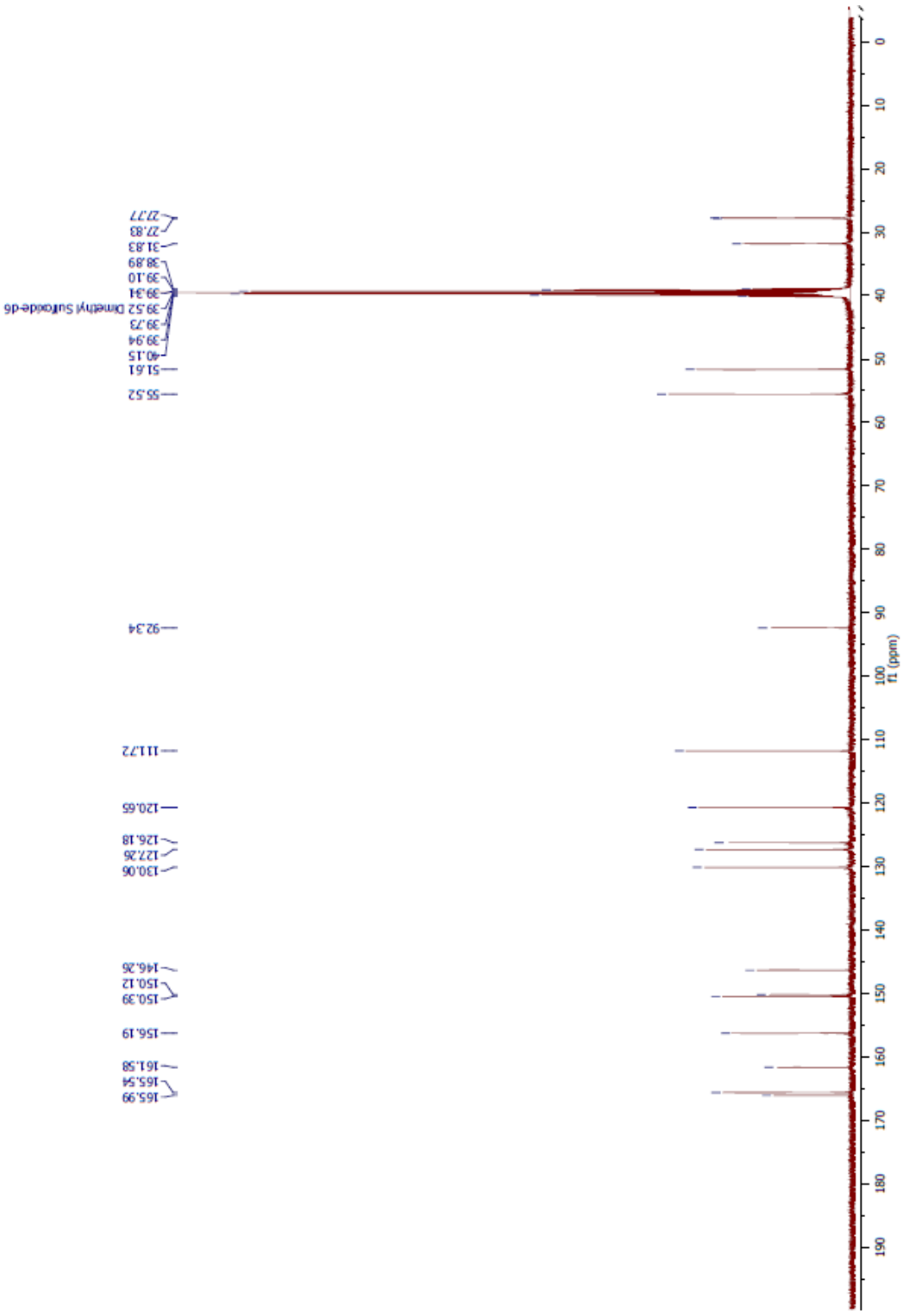


45

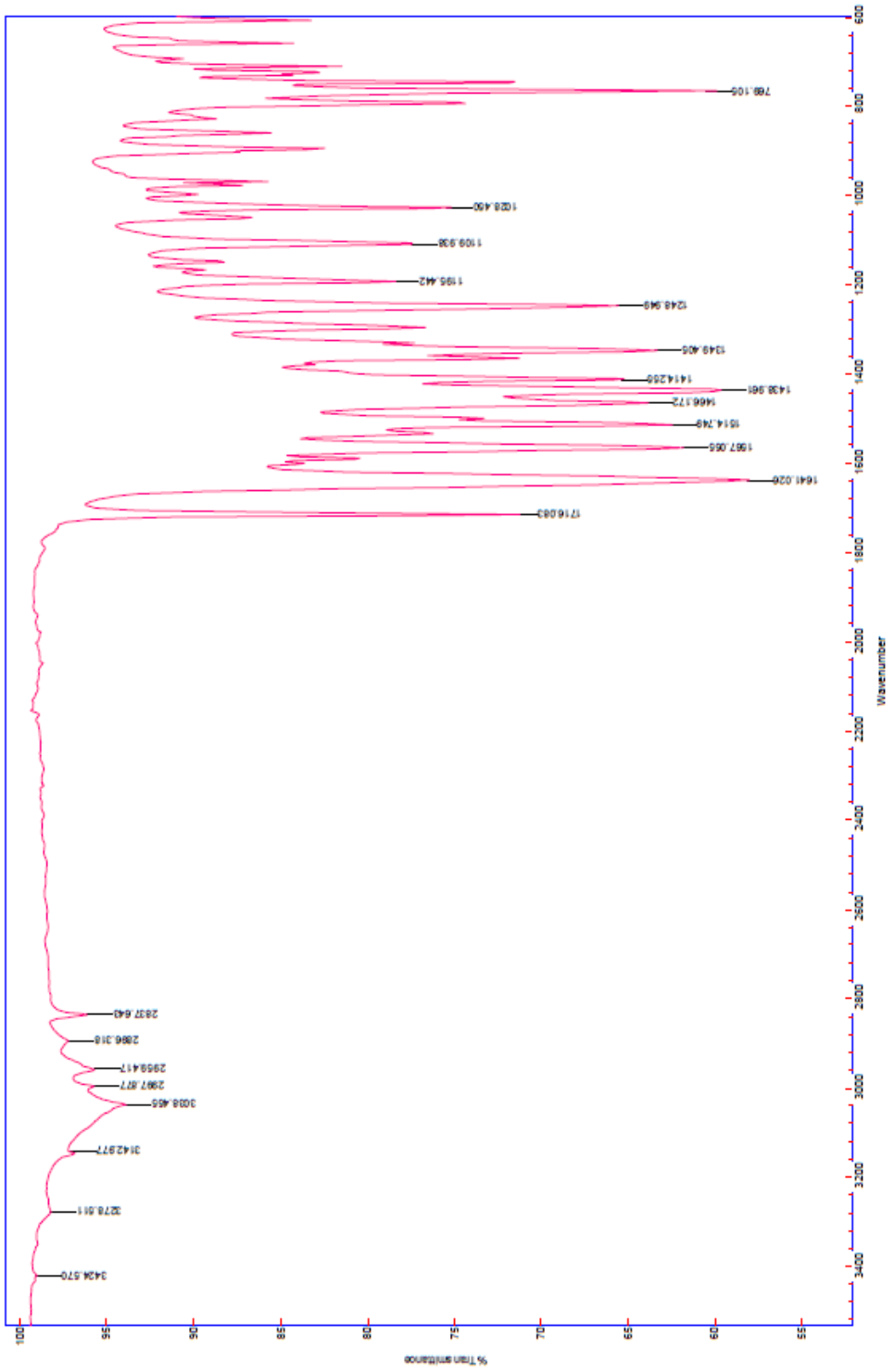
C.7.1 ^{1}H NMR spectrum of 45



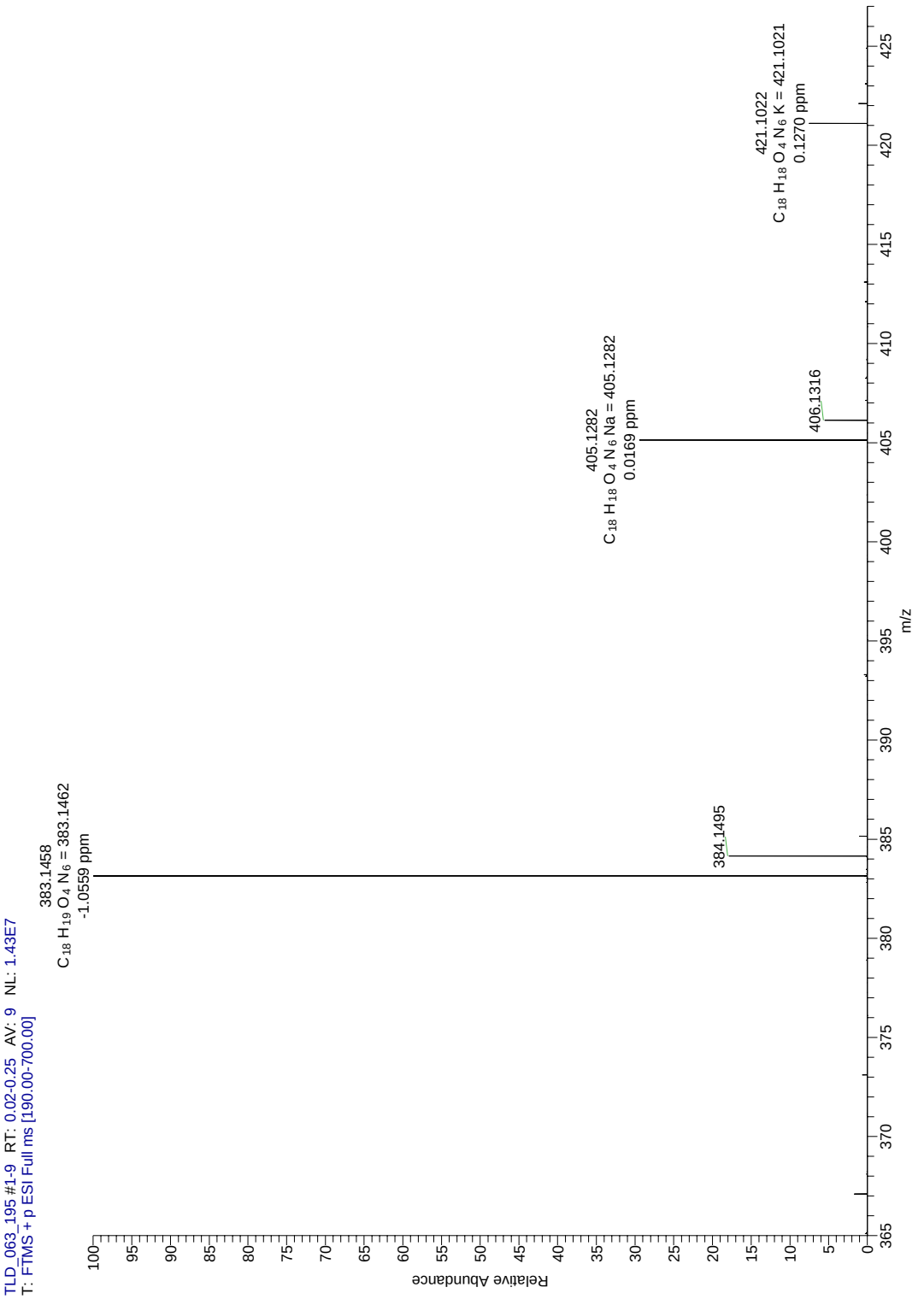
C.7.2 ^{13}C NMR spectrum of 45



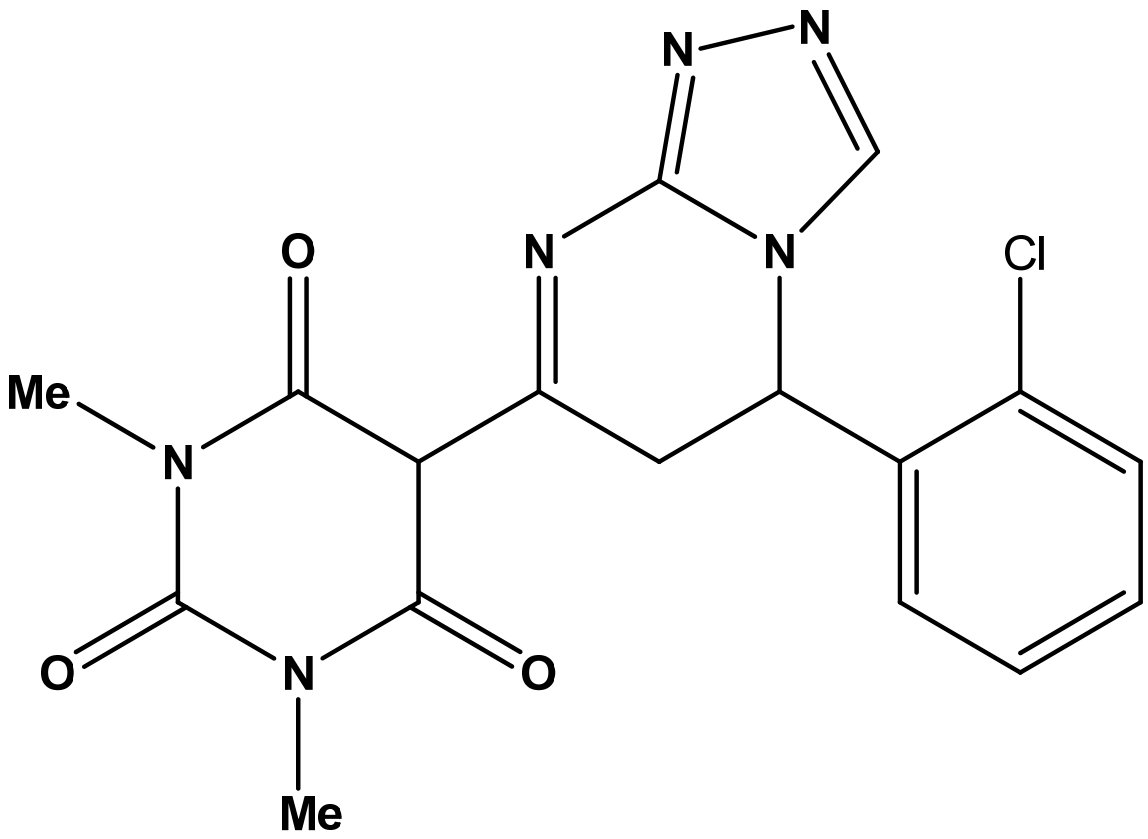
C.7.3 IR spectrum of 45



C.7.4 HRMS of 45

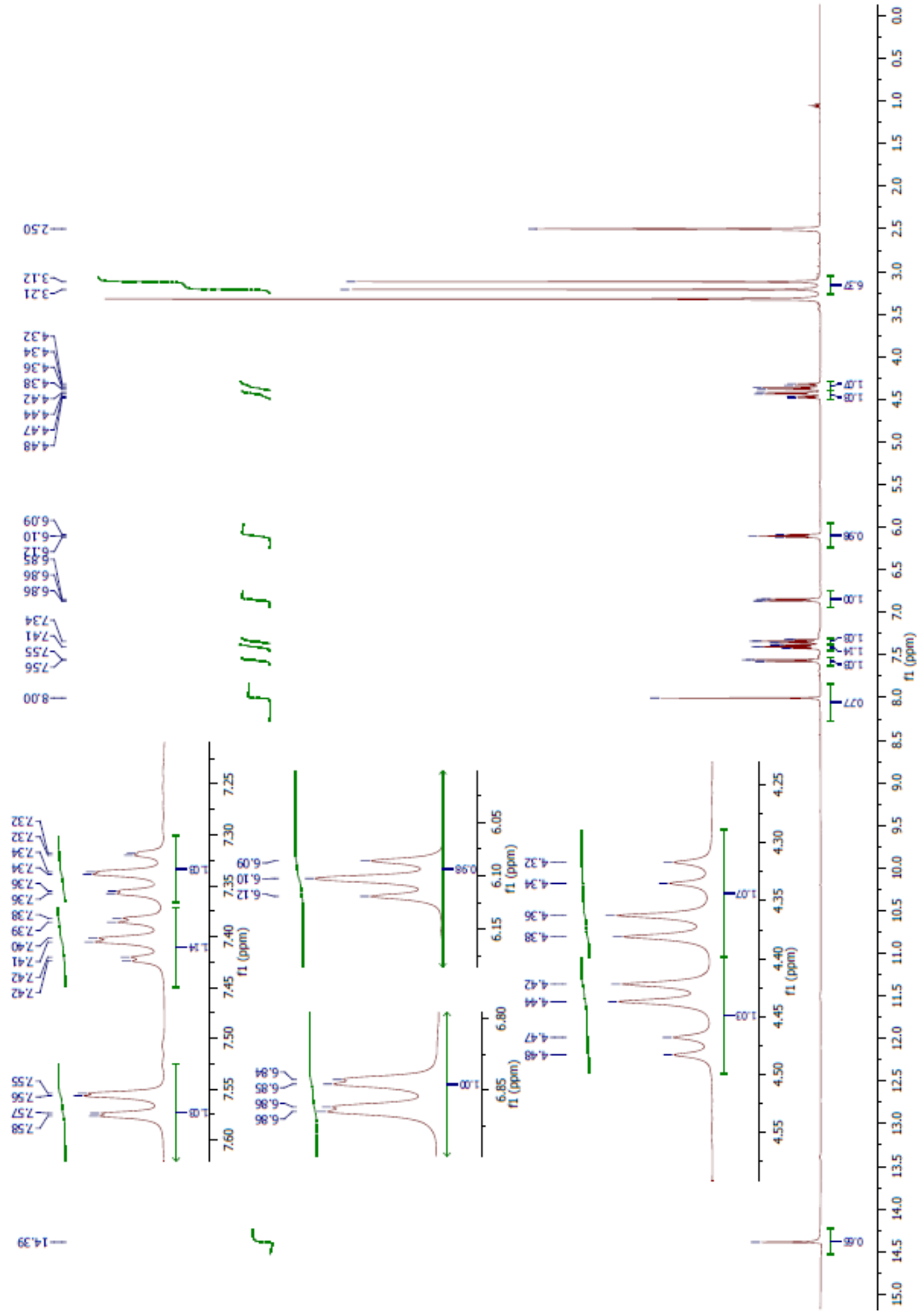


C.8 Spectroscopic data for 46

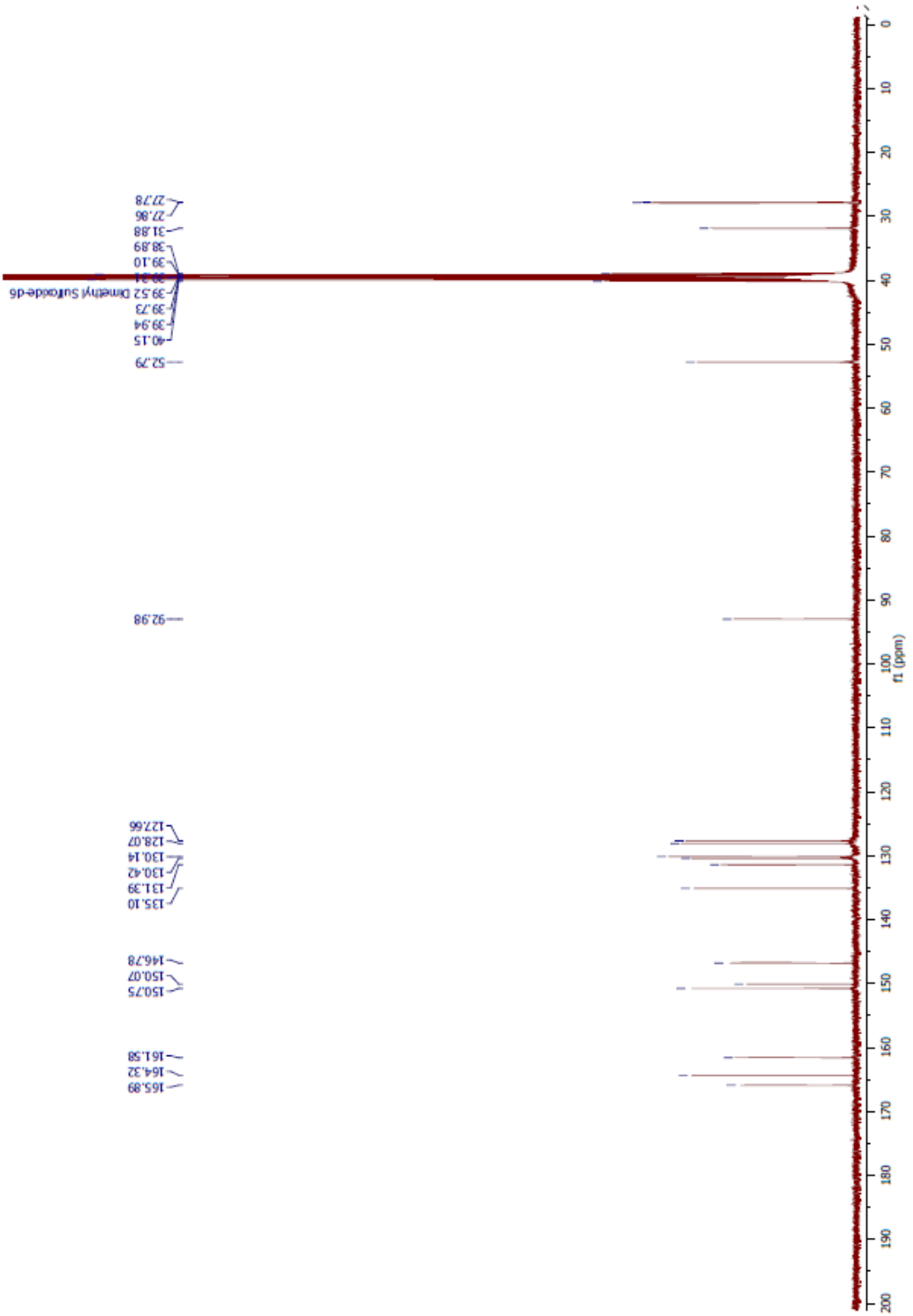


46

C.8.1 ^{1}H NMR spectrum of 46

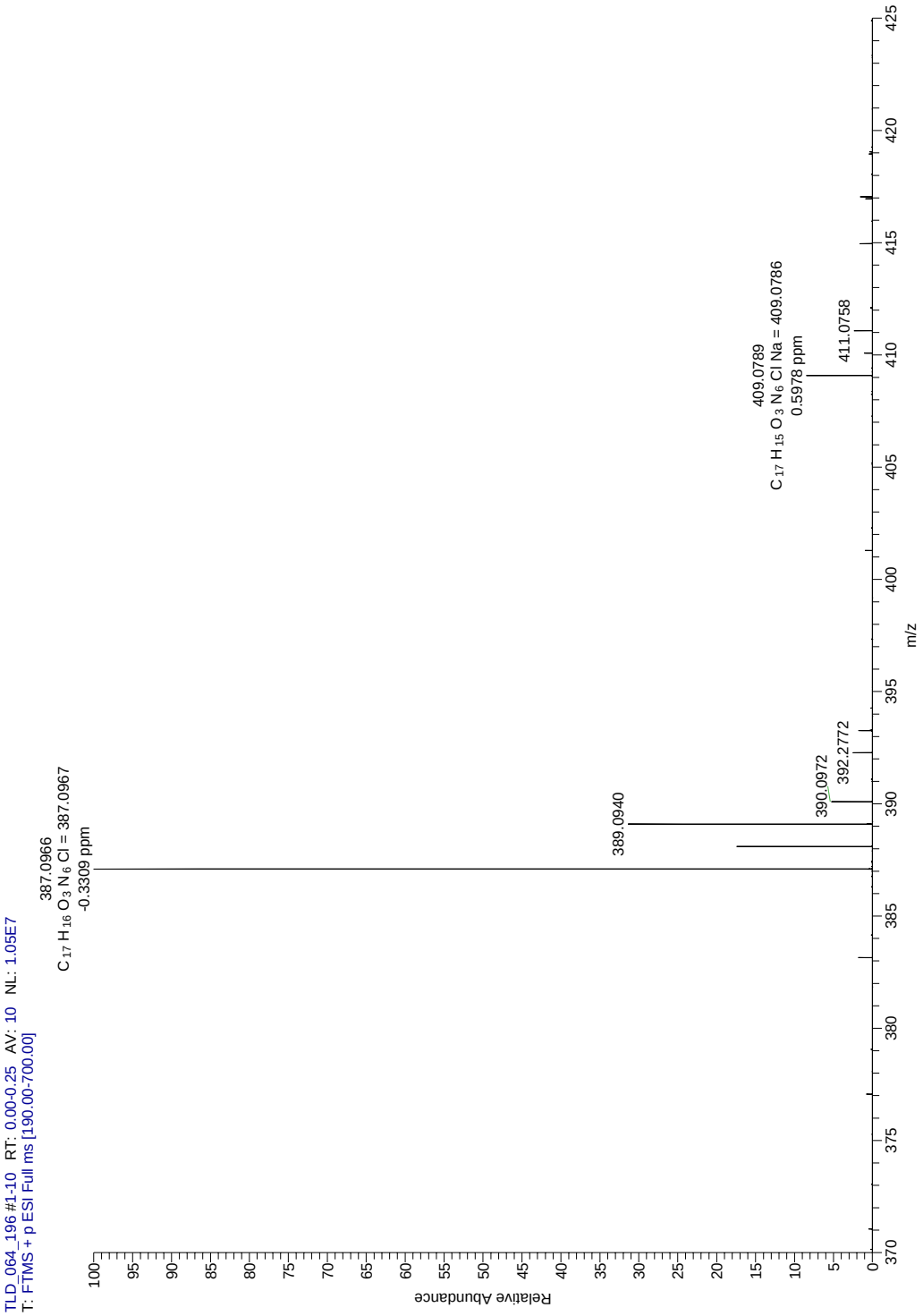


C.8.2 ^{13}C NMR spectrum of 46

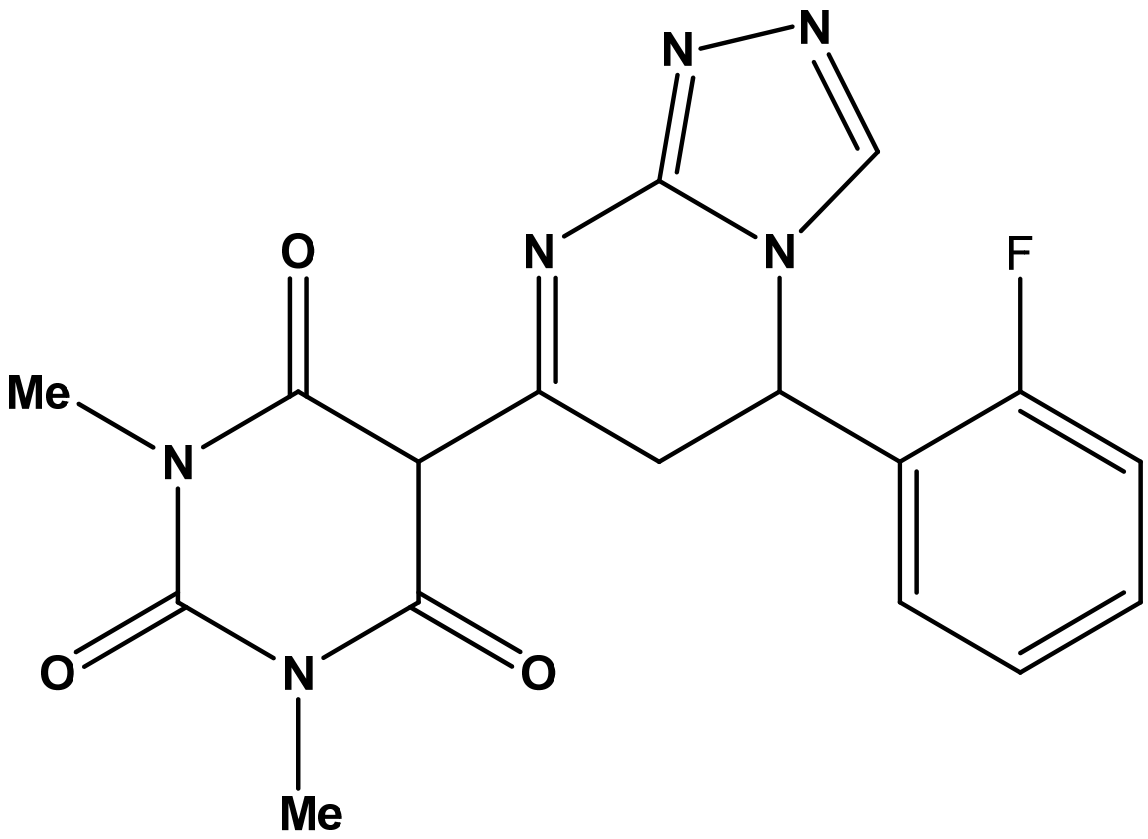


C.8.3 IR spectrum of 46

C.8.4 HRMS of 46

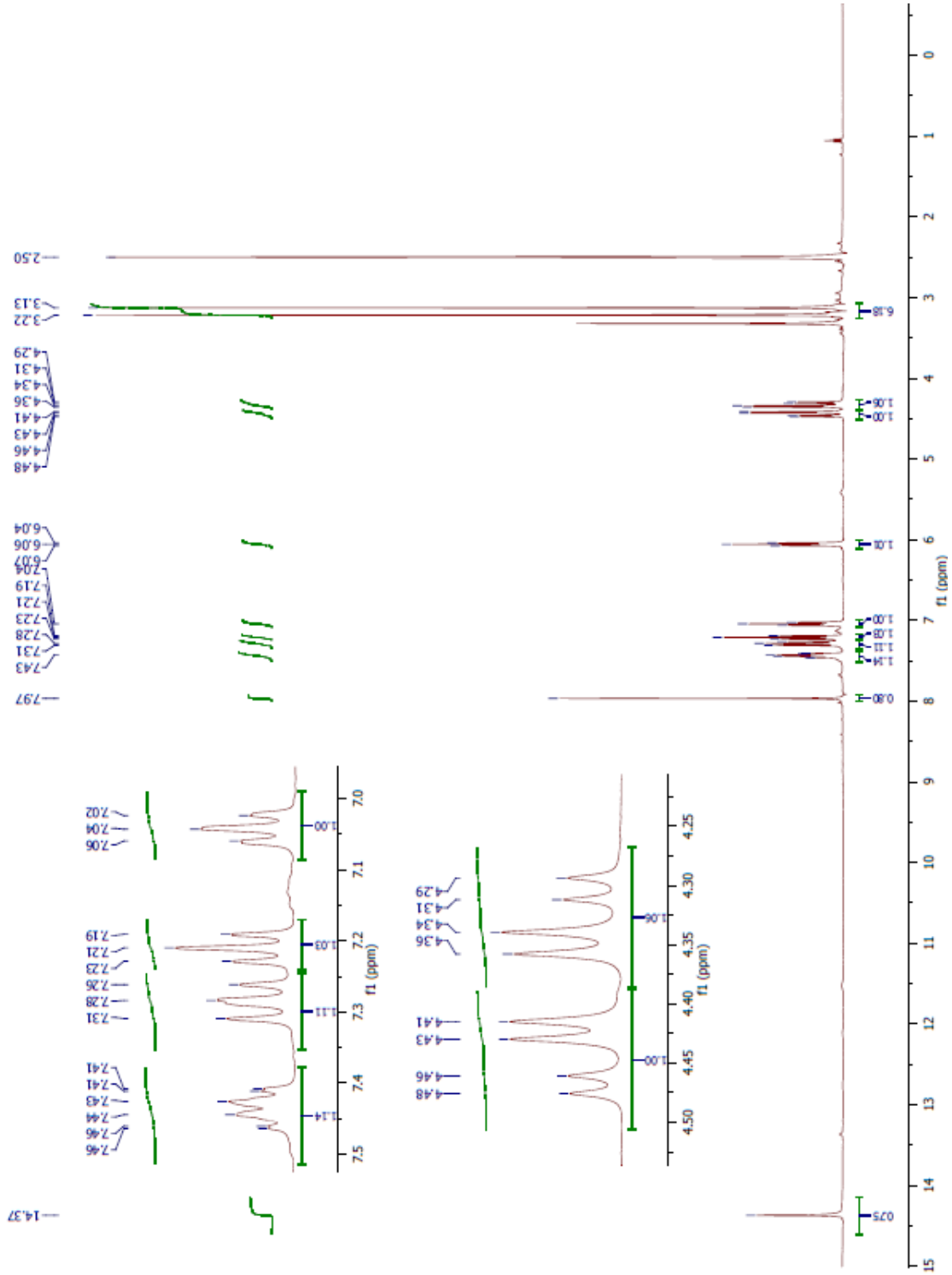


C.9 Spectroscopic data for 47

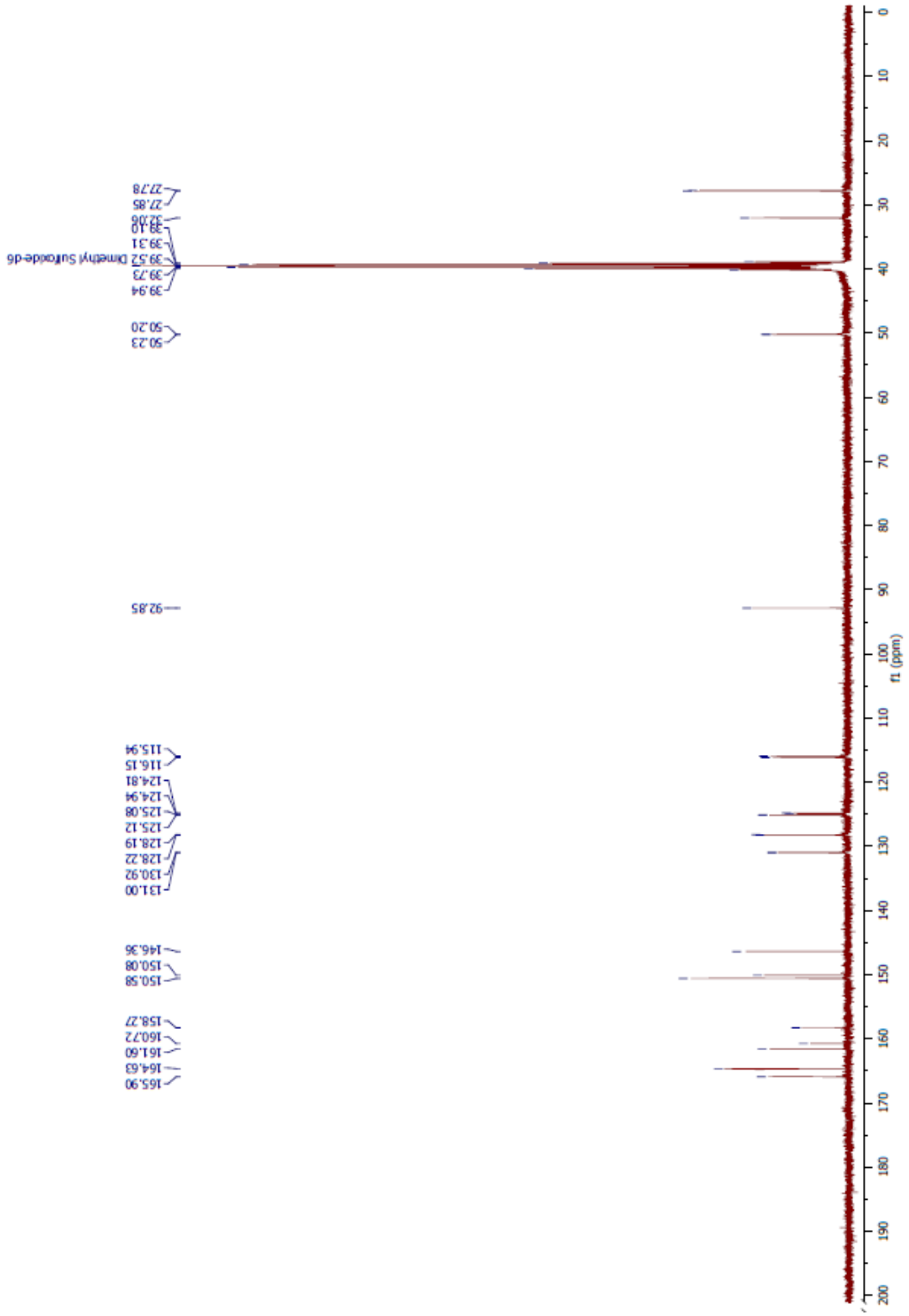


47

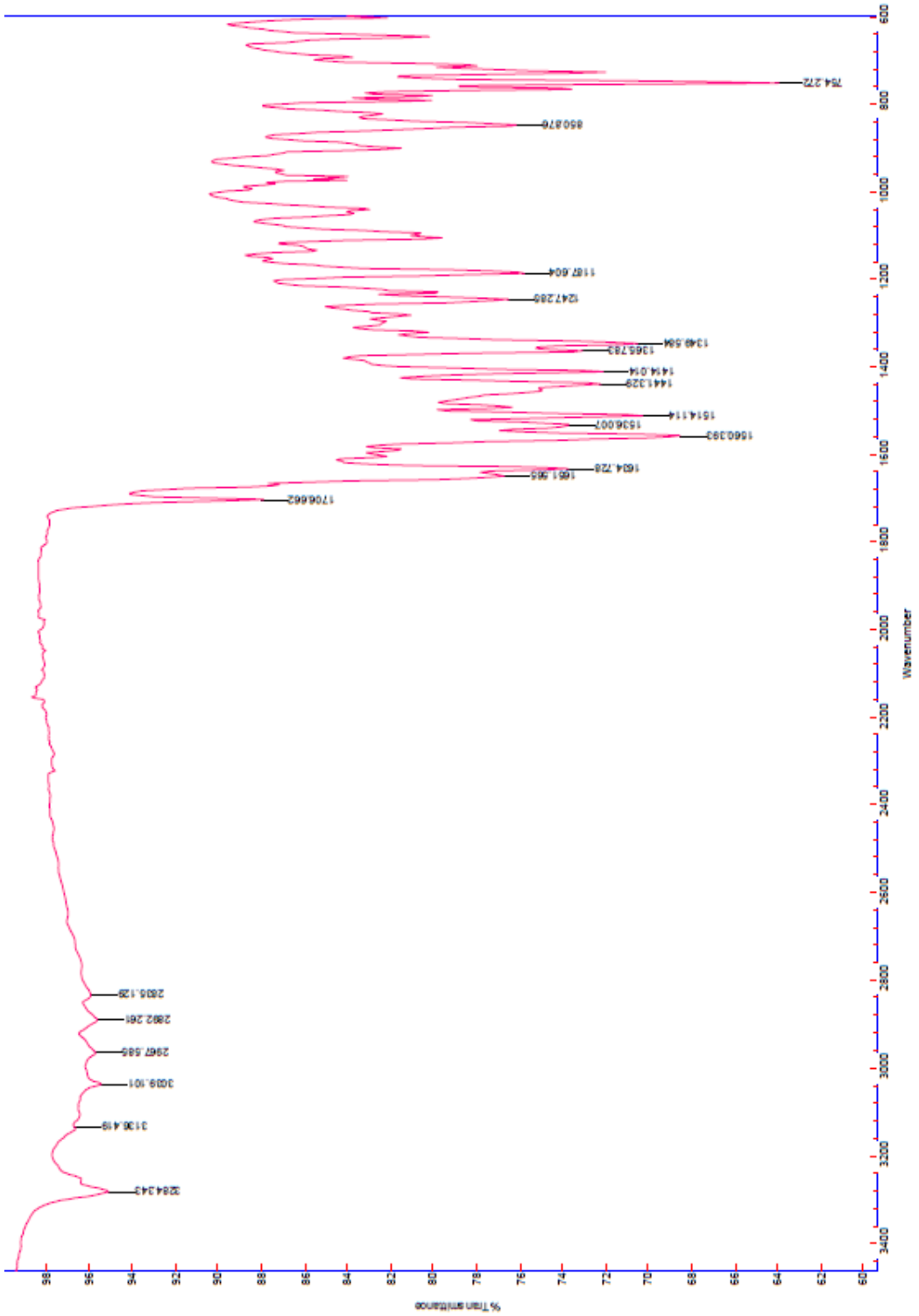
C.9.1 ^{1}H NMR spectrum of 47



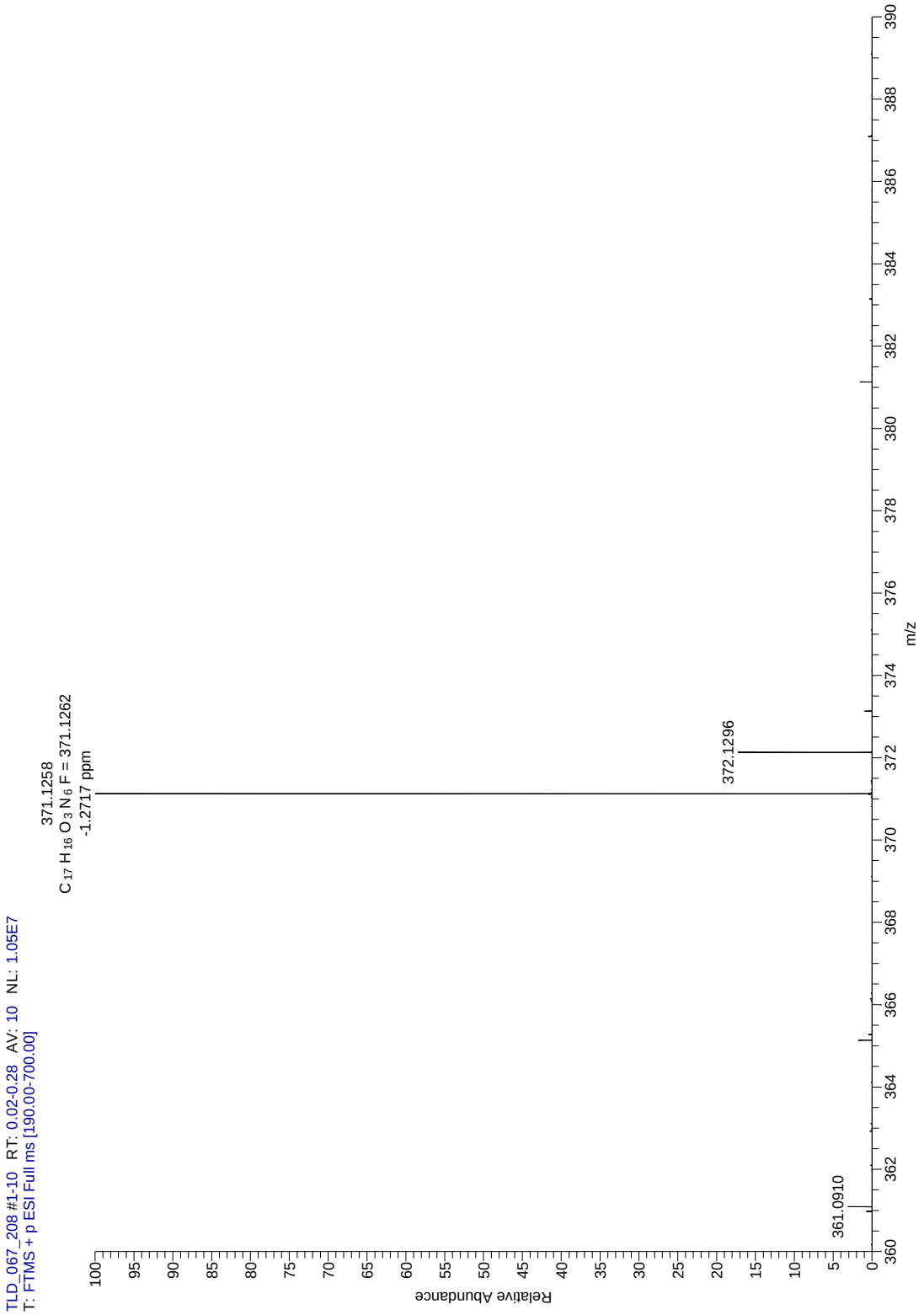
C.9.2 ^{13}C NMR spectrum of 47



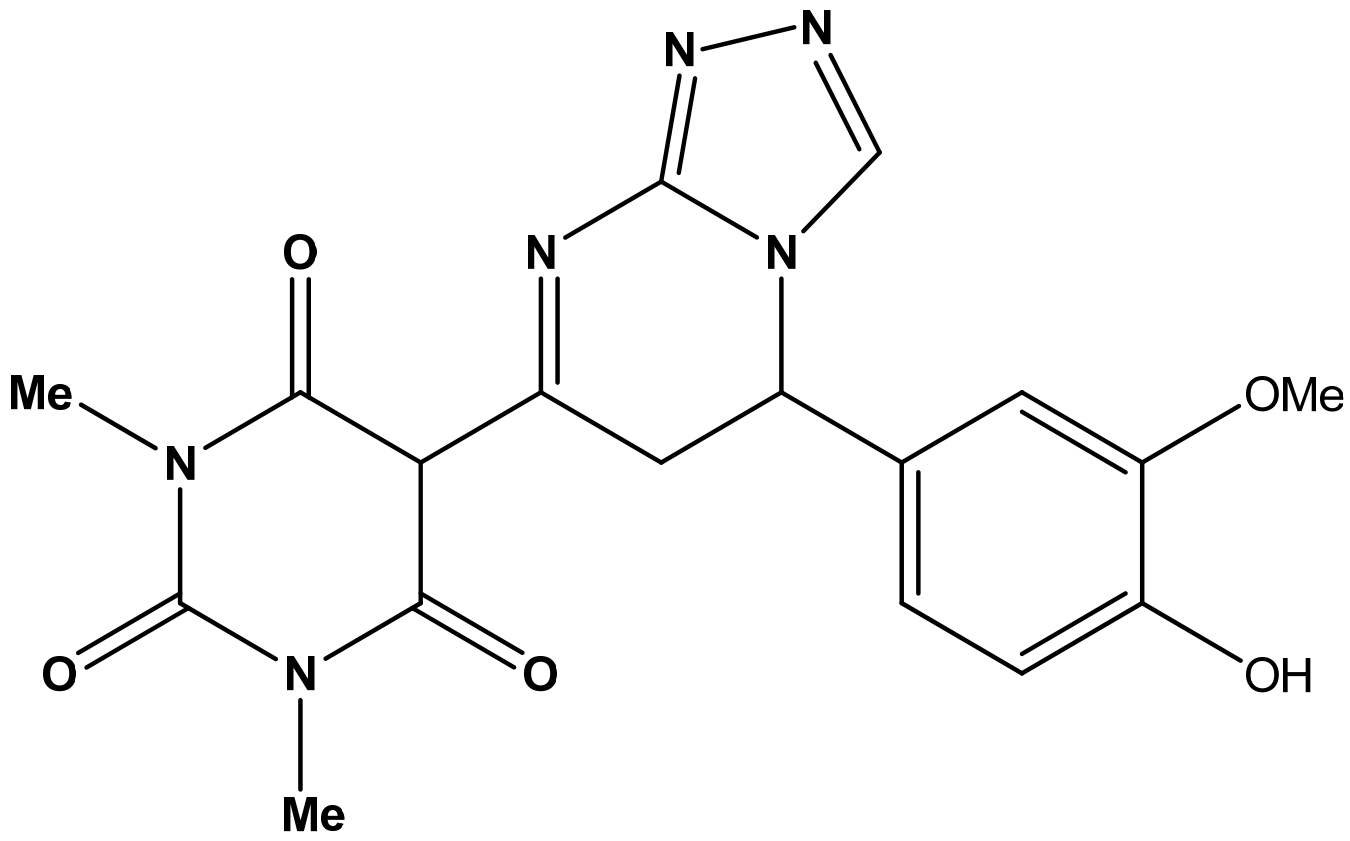
C.9.3 IR spectrum of 47



C.9.4 HRMS of 47

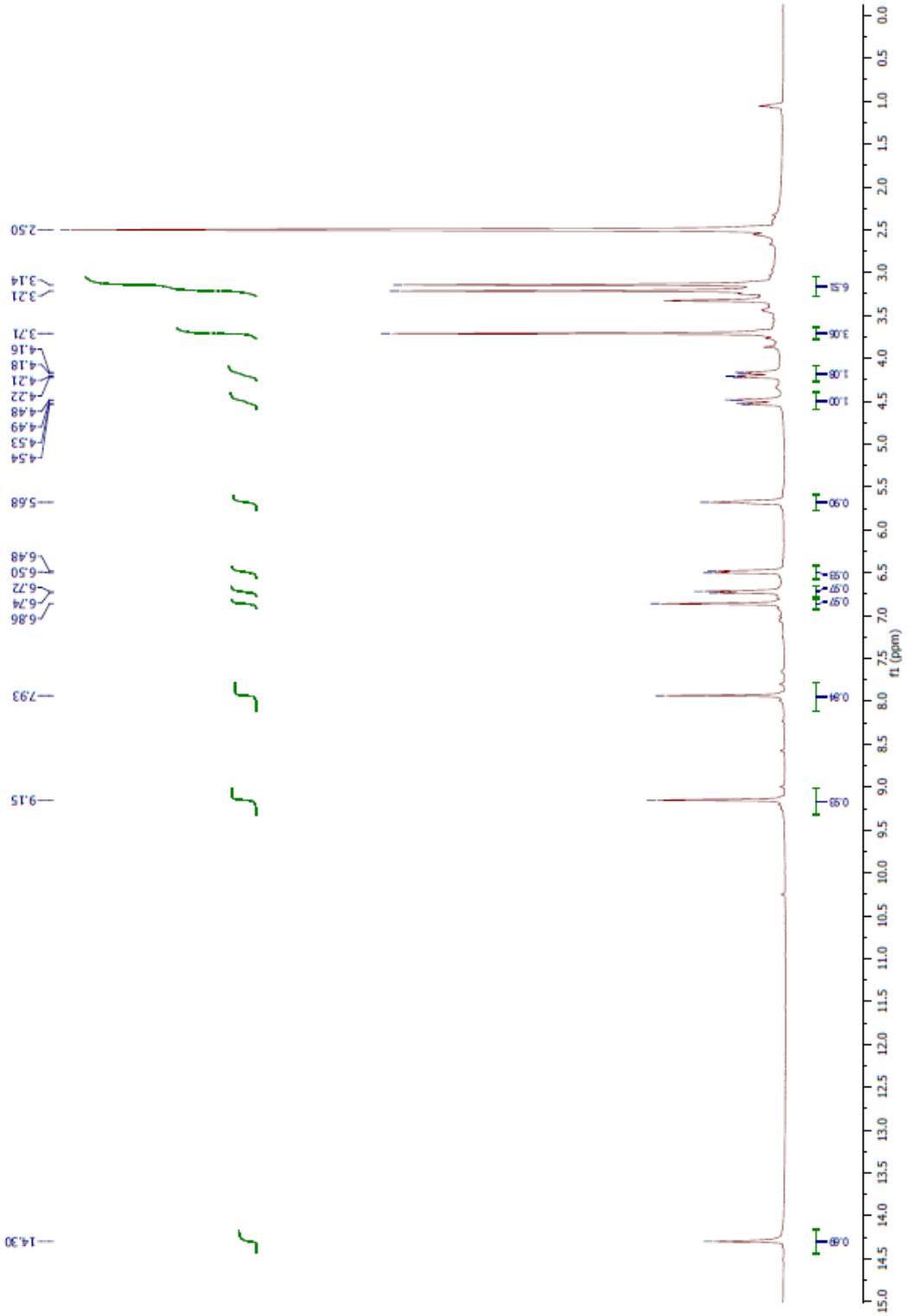


C.10 Spectroscopic data for 50

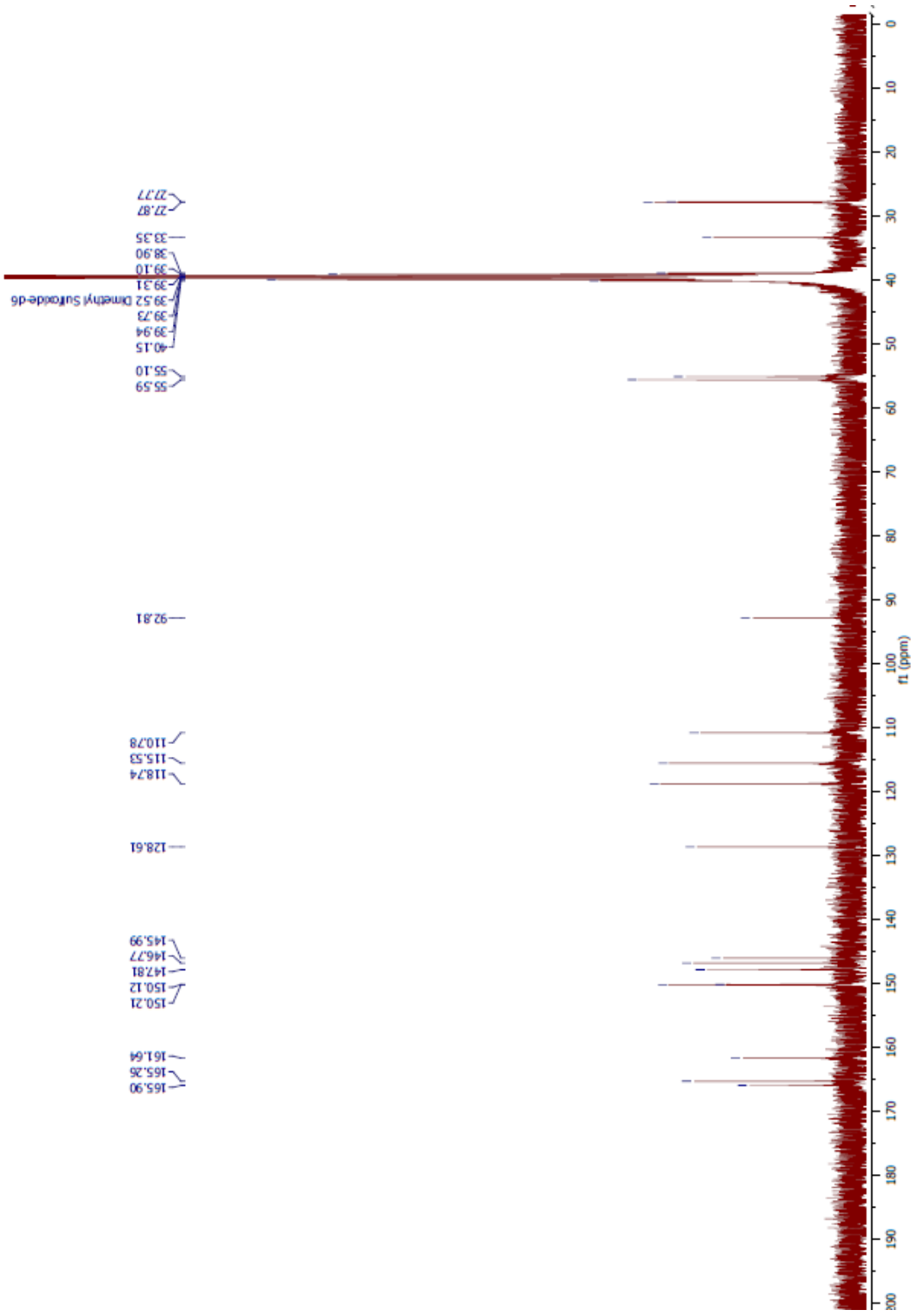


50

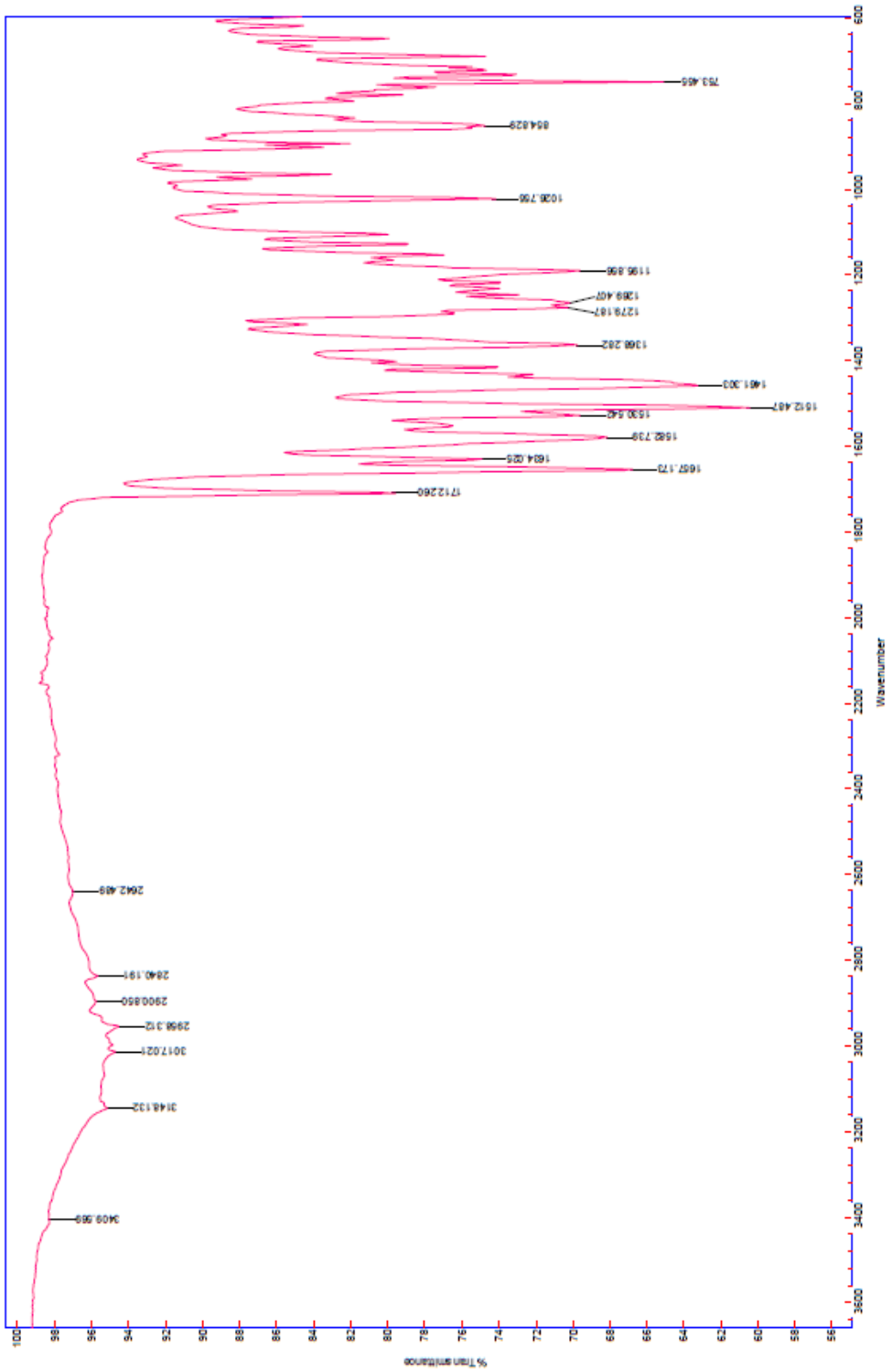
C.10.1 ^{1}H NMR spectrum of 50



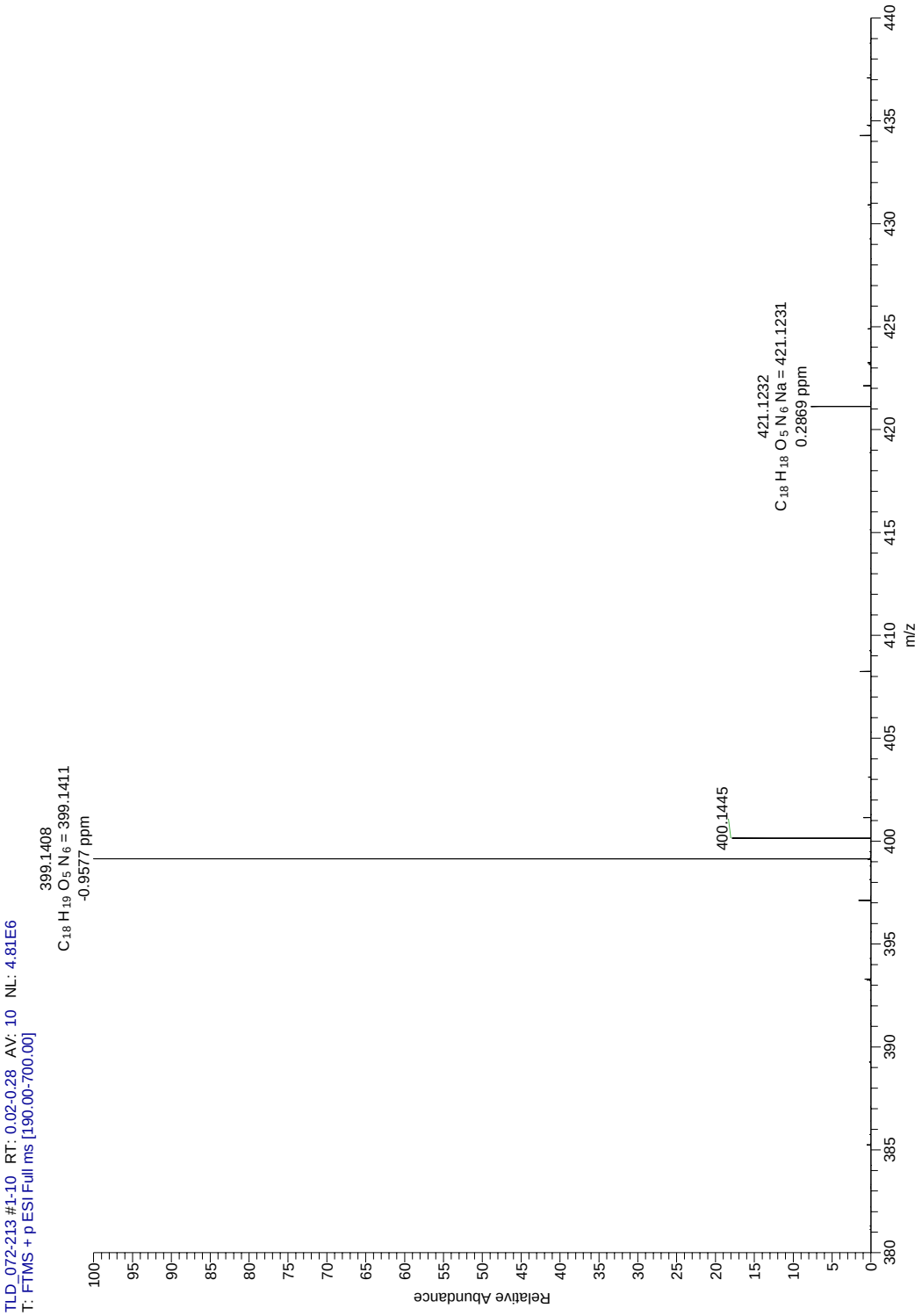
C.10.2 ^{13}C NMR spectrum of 50



C.10.3 IR spectrum of 50

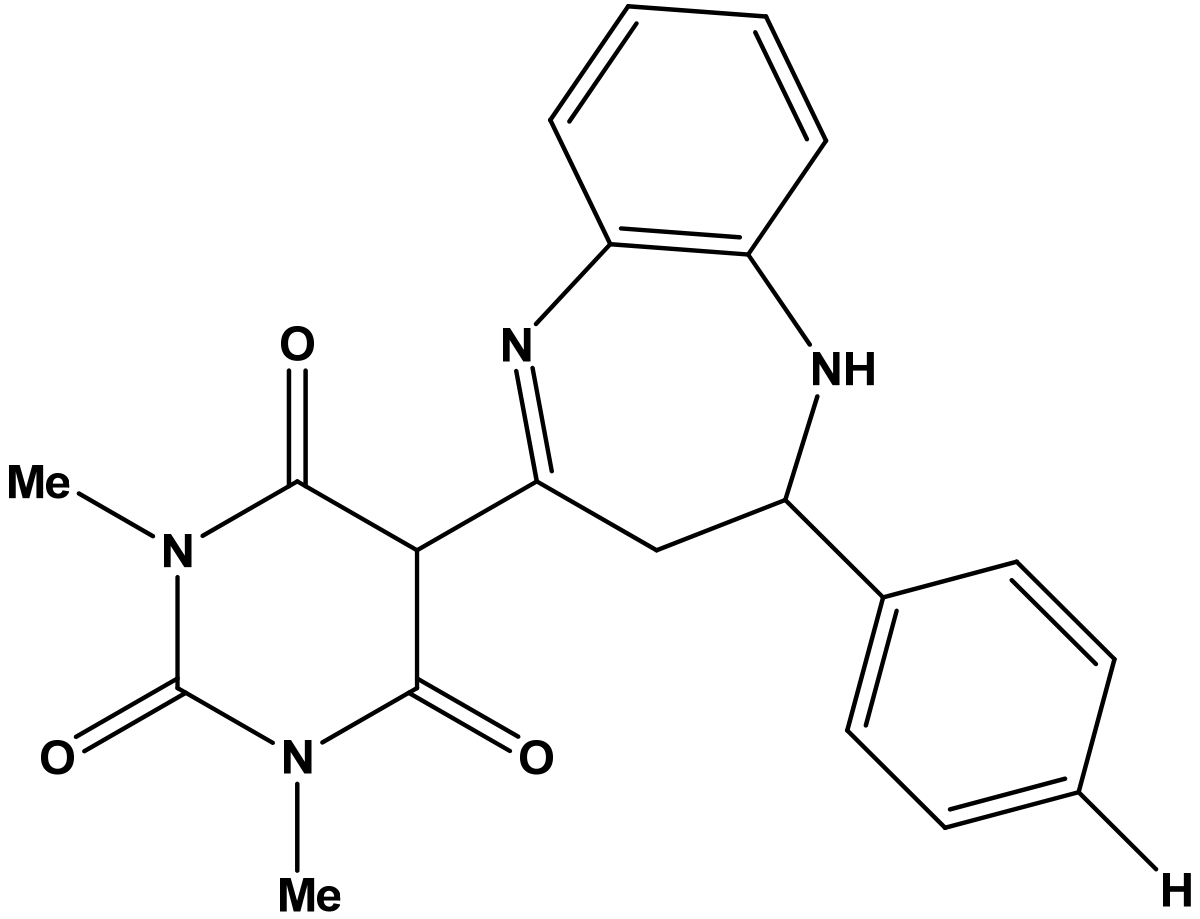


C.10.4 HRMS of 50



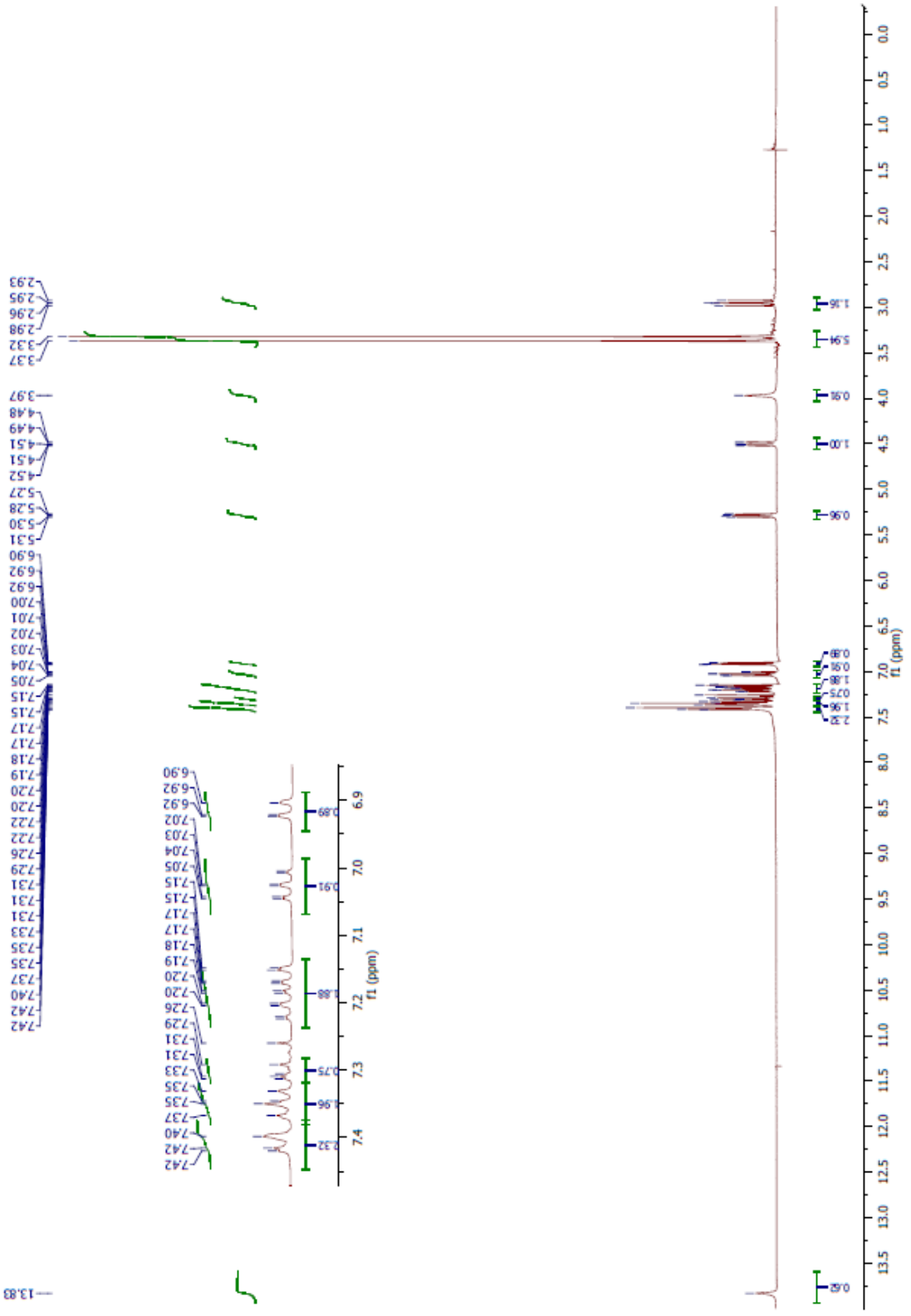
D Spectroscopic data for 6-membered heterocyles 51-74

D.1 Spectroscopic data for 51

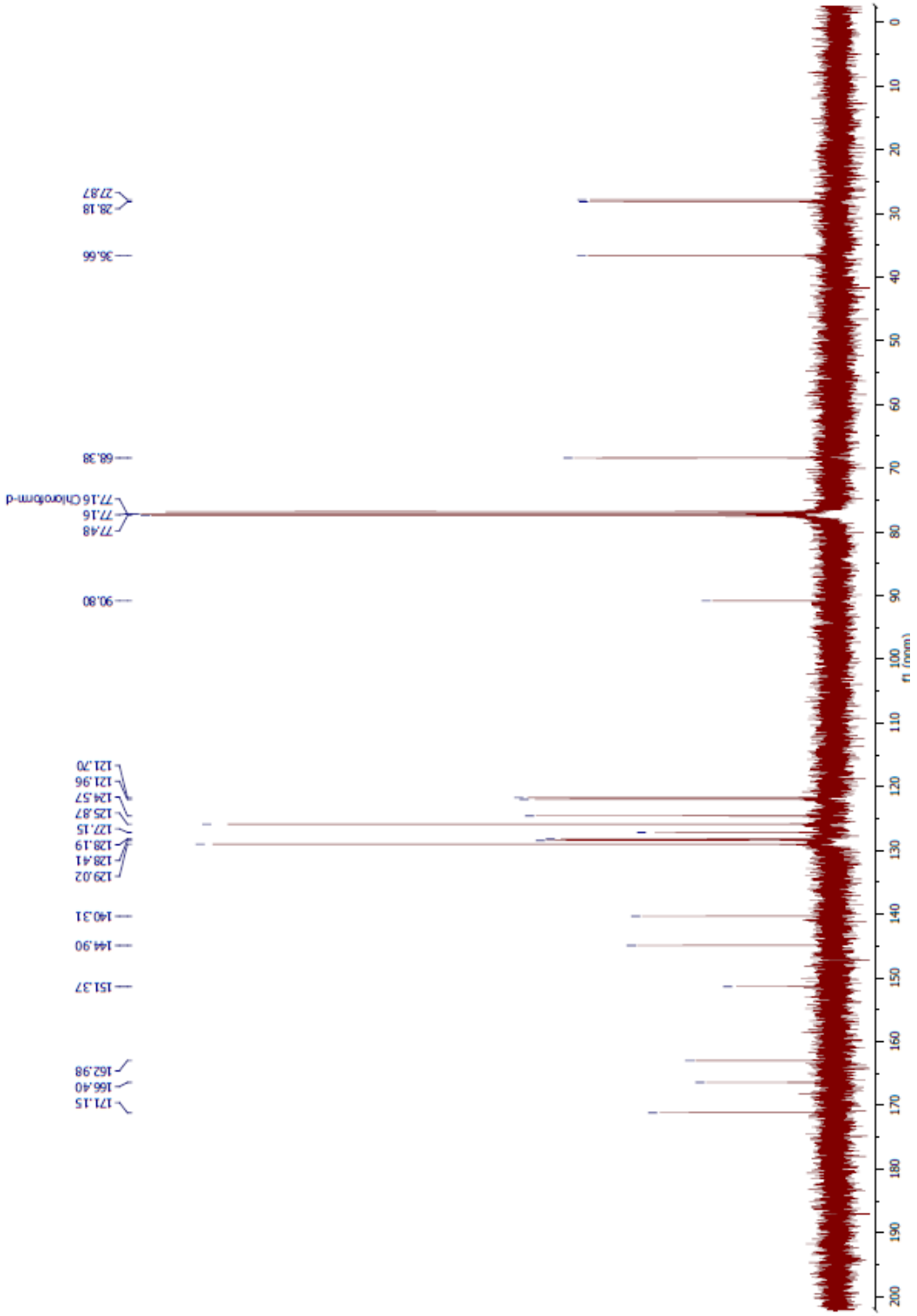


51

D.1.1 ^{1}H NMR spectrum of 51

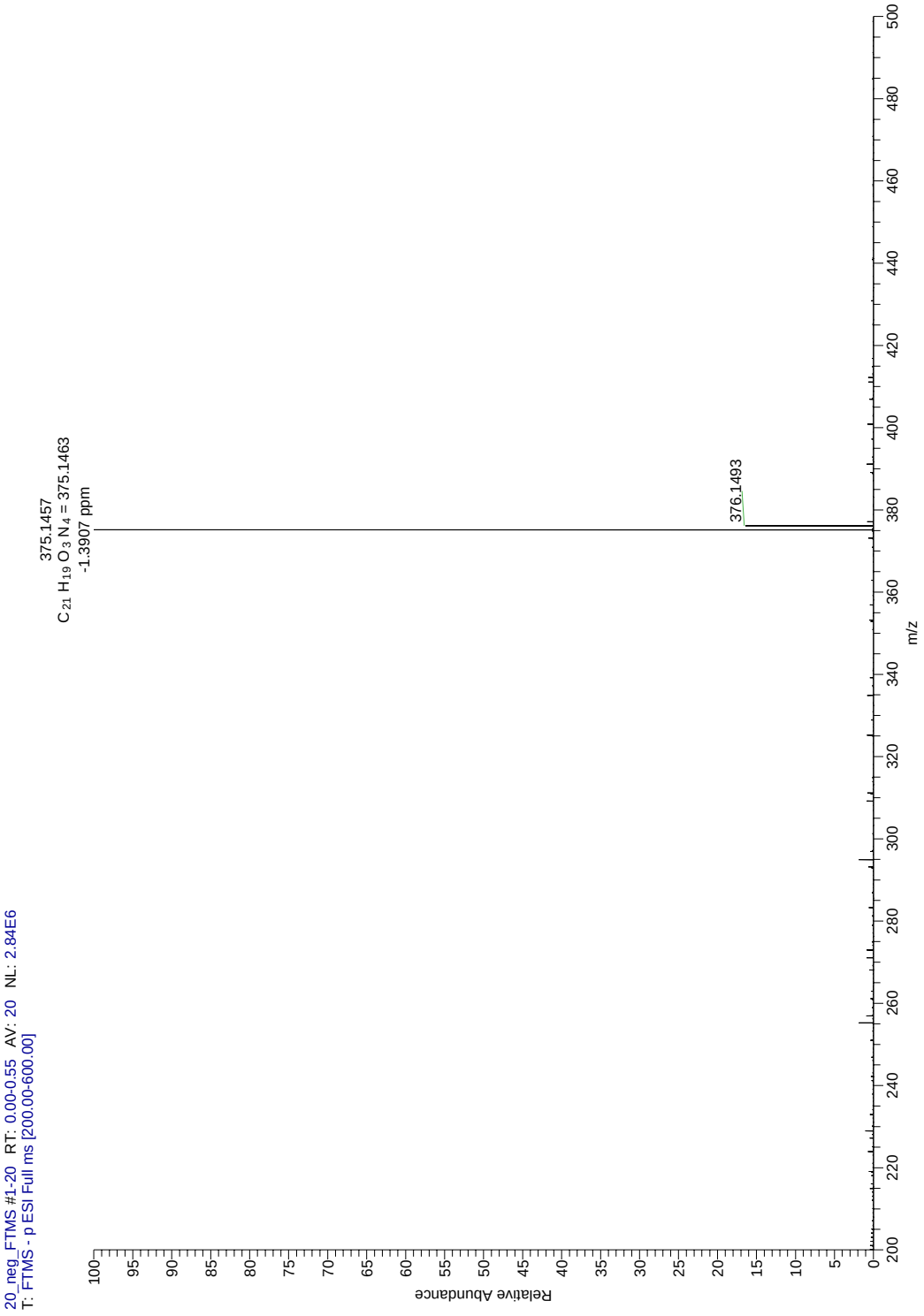


D.1.2 ^{13}C NMR spectrum of 51

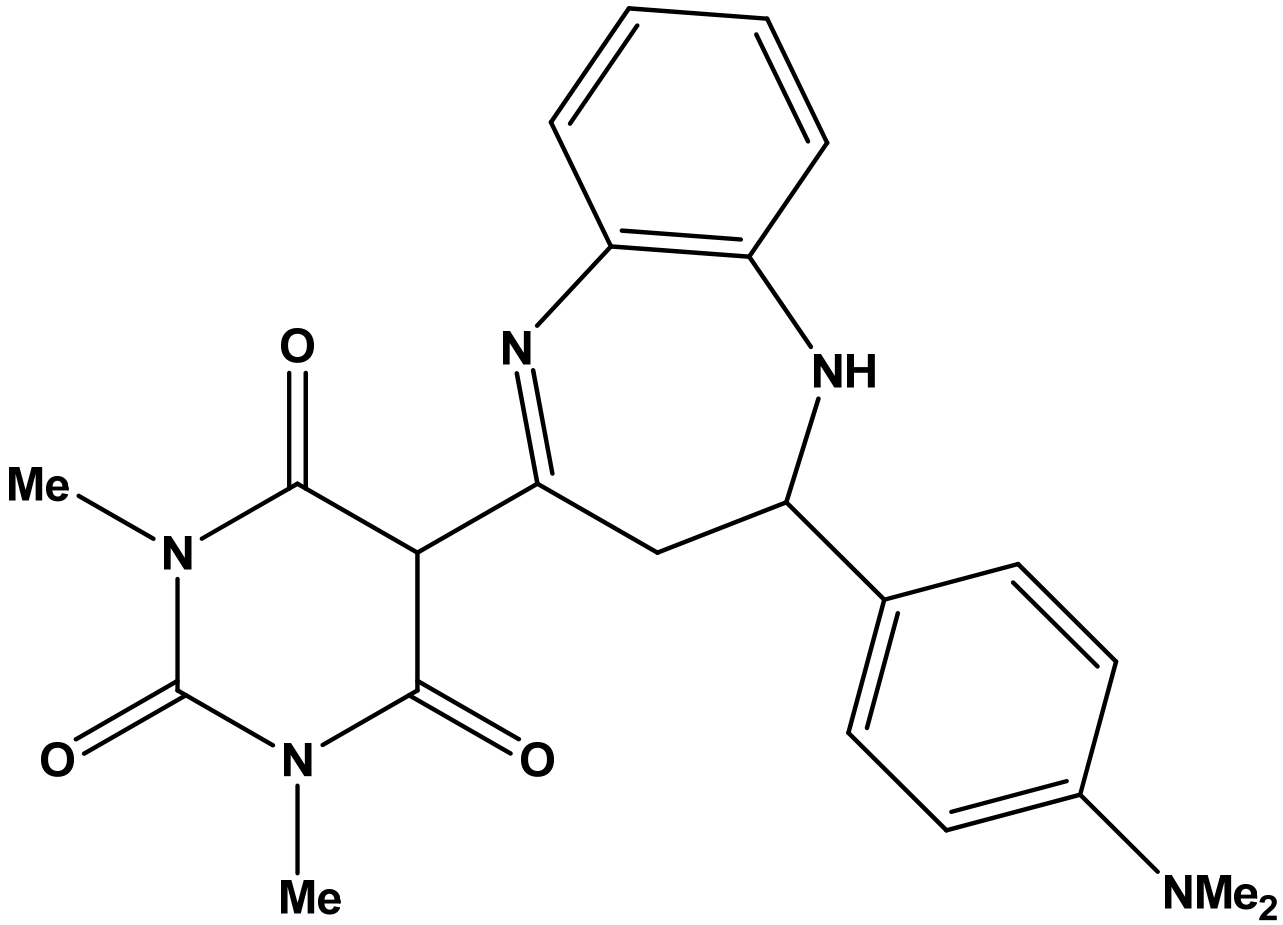


D.1.3 IR spectrum of 51

D.1.4 HRMS of 51

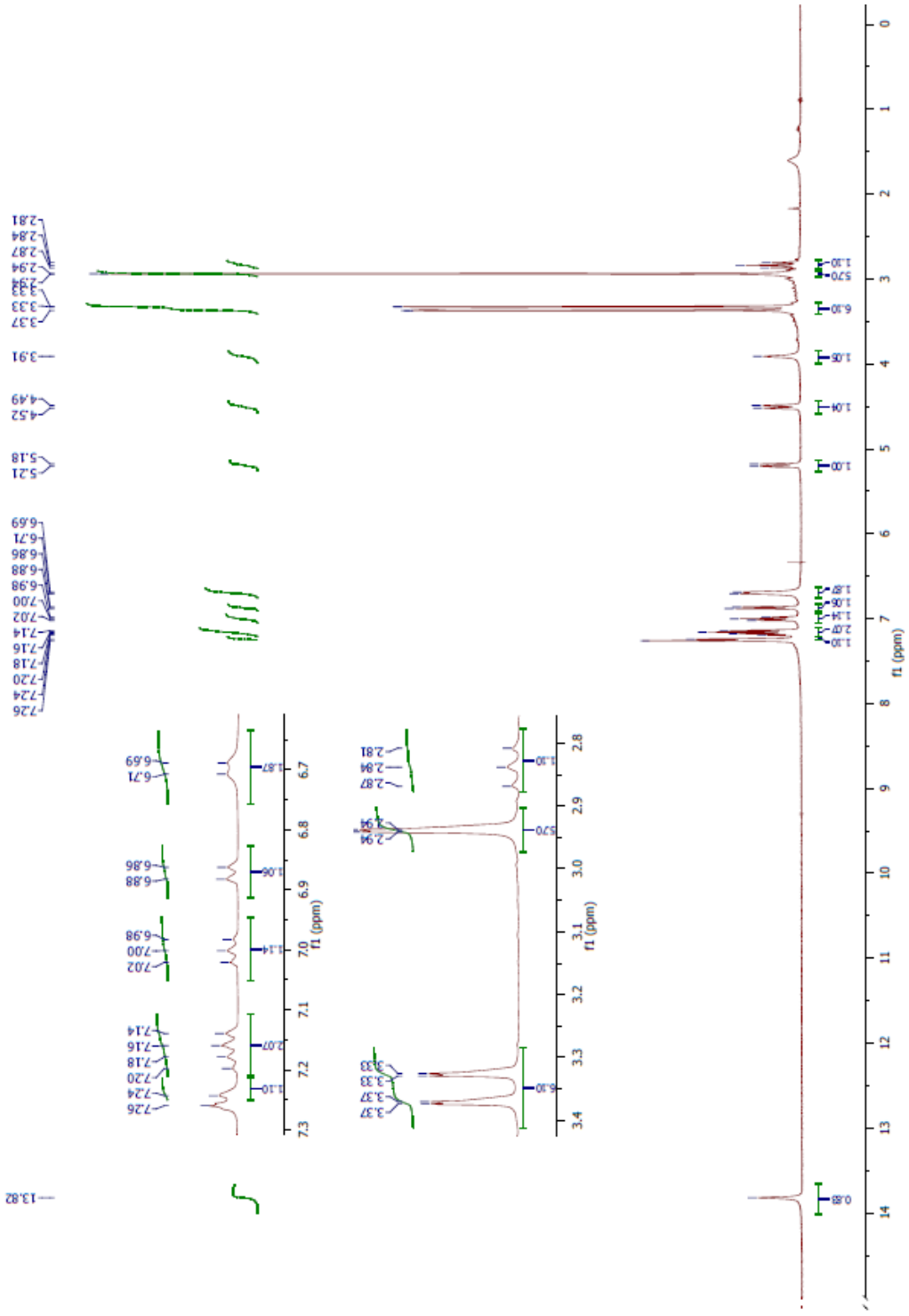


D.2 Spectroscopic data for 52

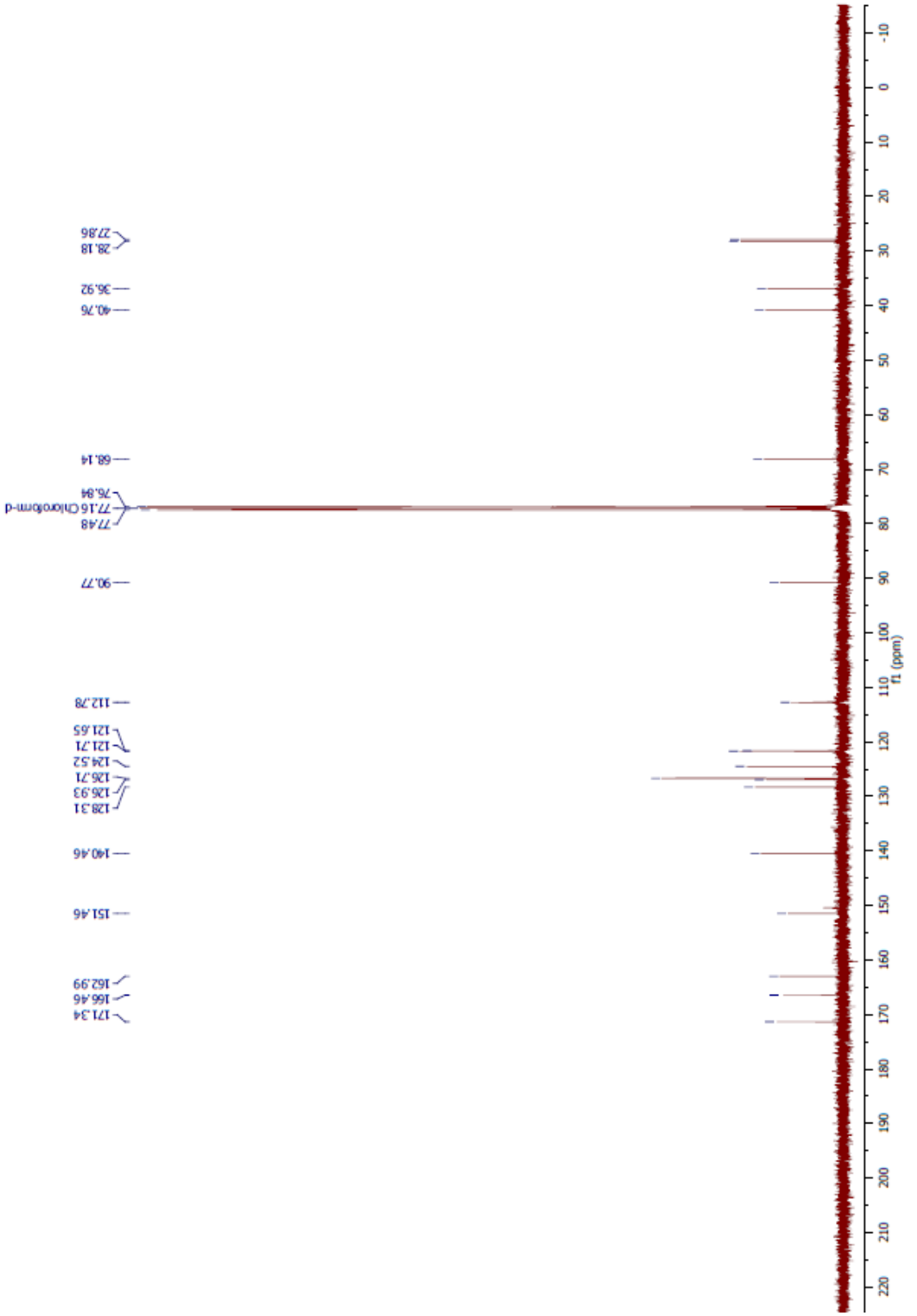


52

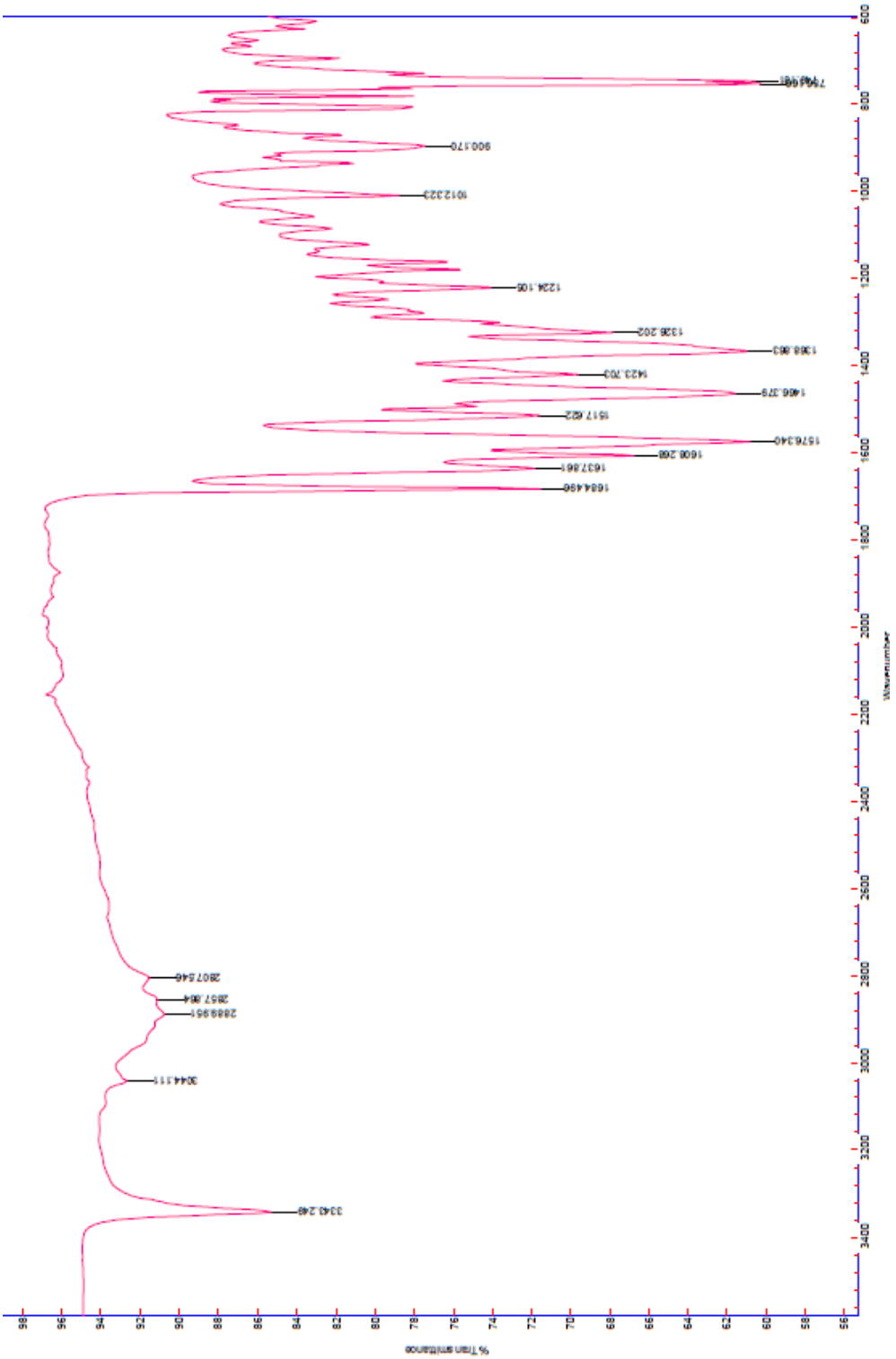
D.2.1 ^{1}H NMR spectrum of 52



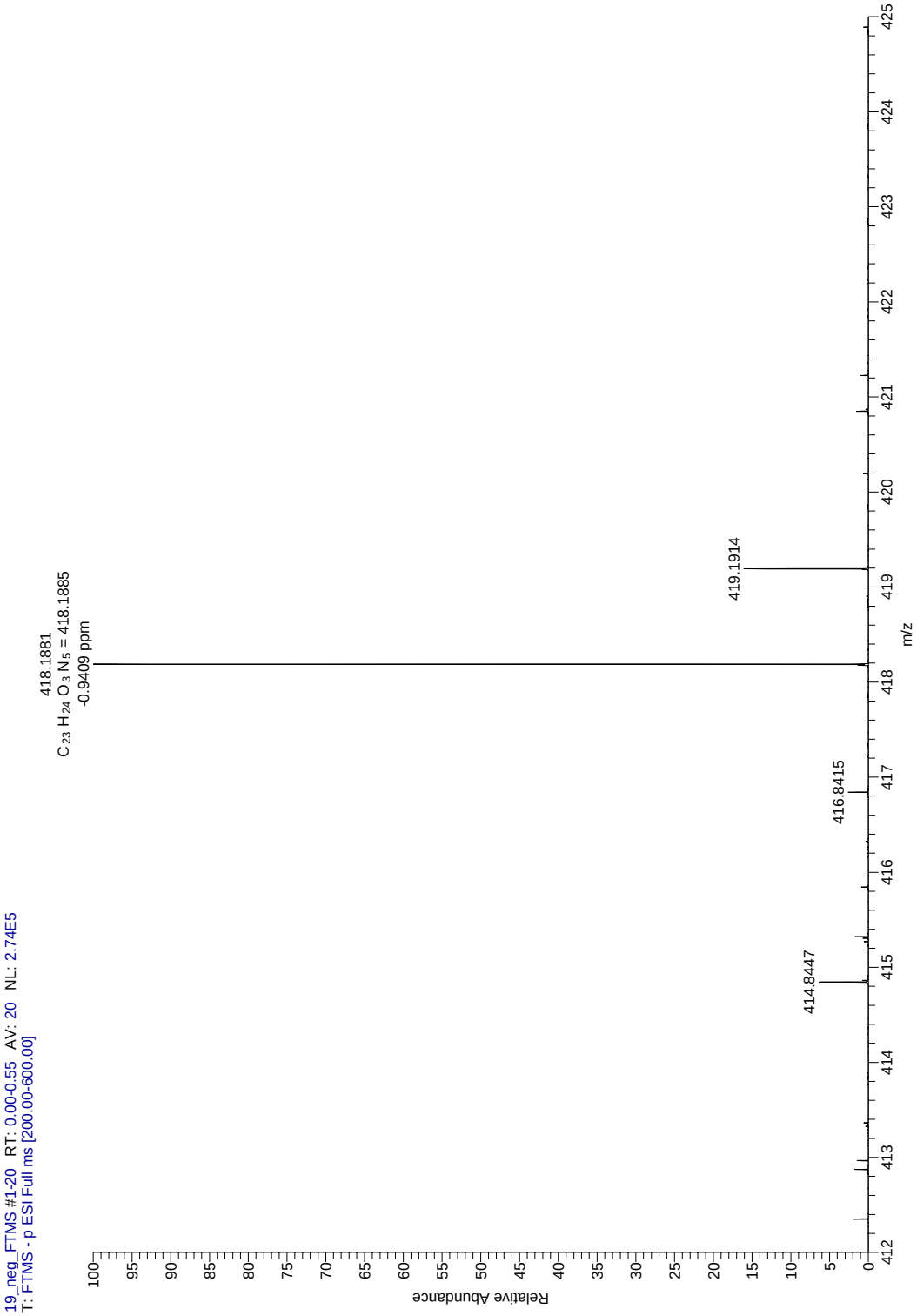
D.2.2 ^{13}C NMR spectrum of 52



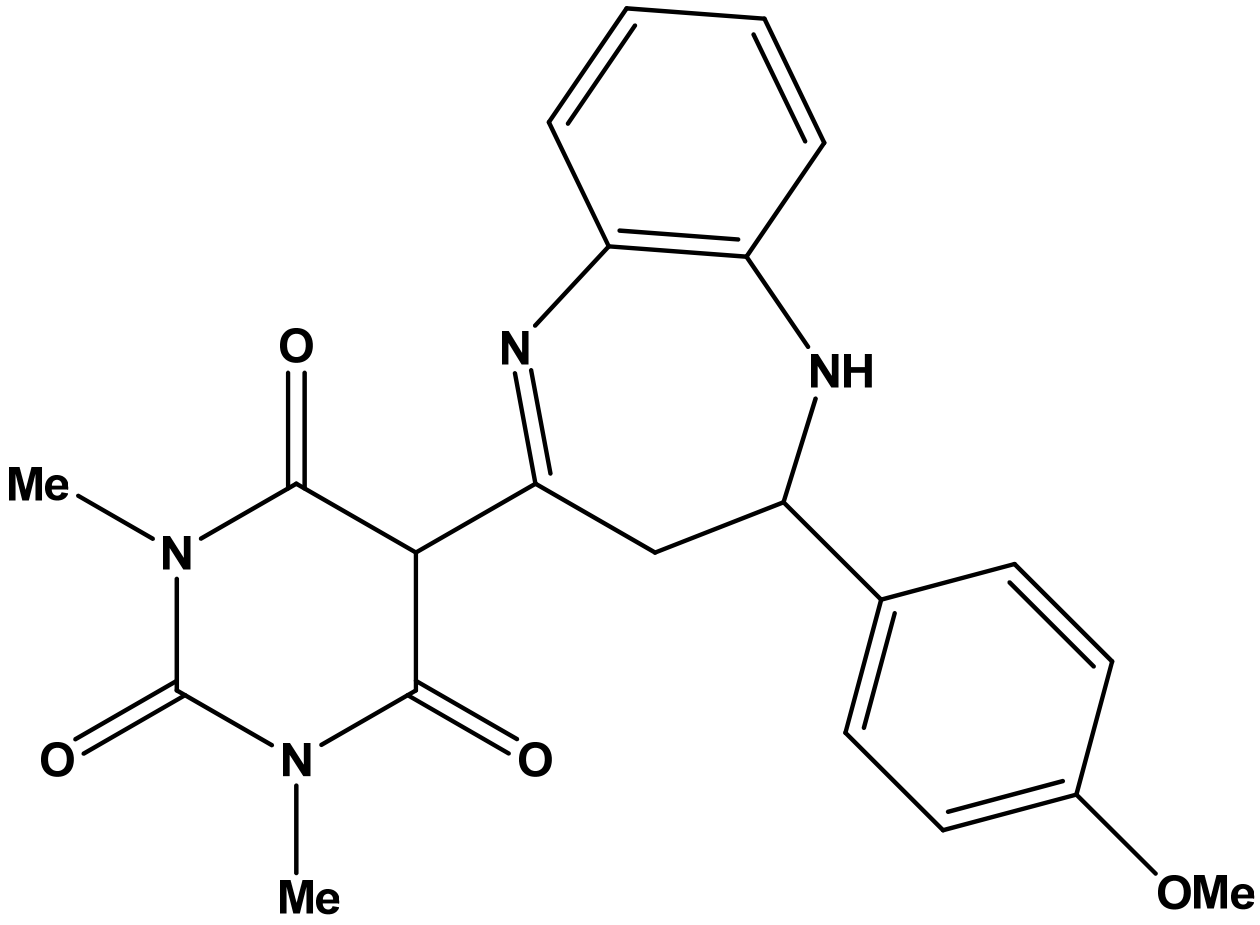
D.2.3 IR spectrum of 52



D.2.4 HRMS of 52

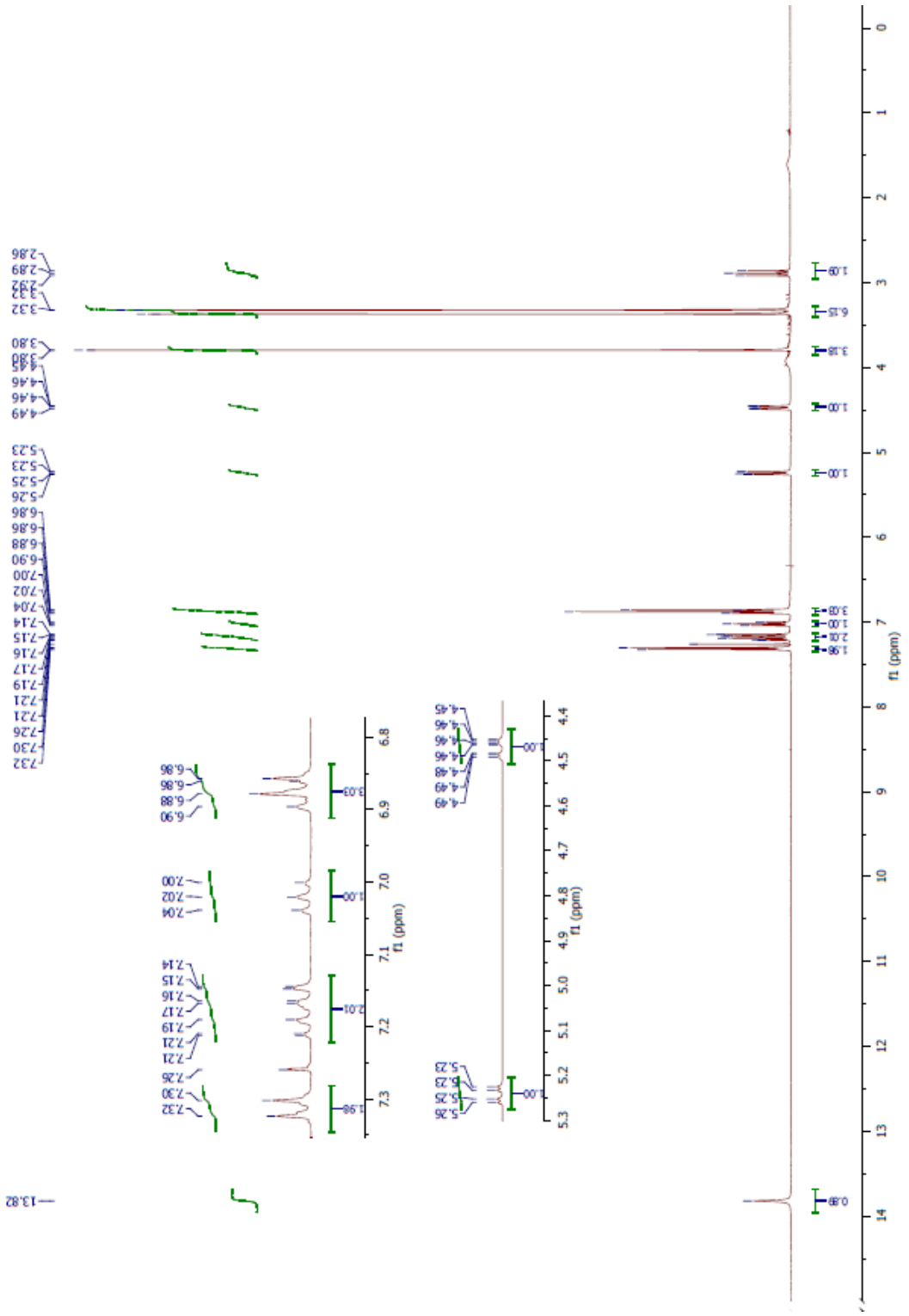


D.3 Spectroscopic data for 53

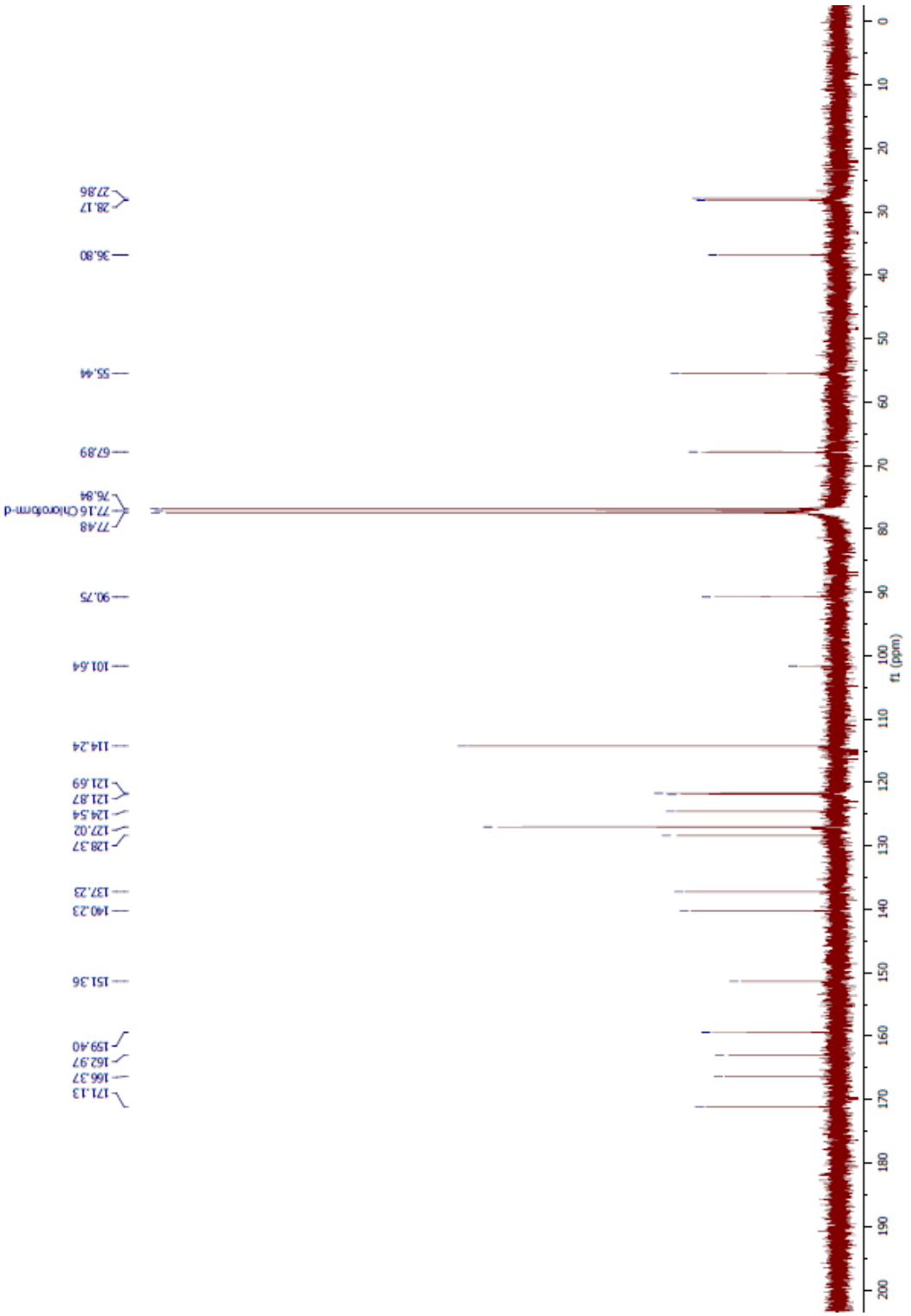


53

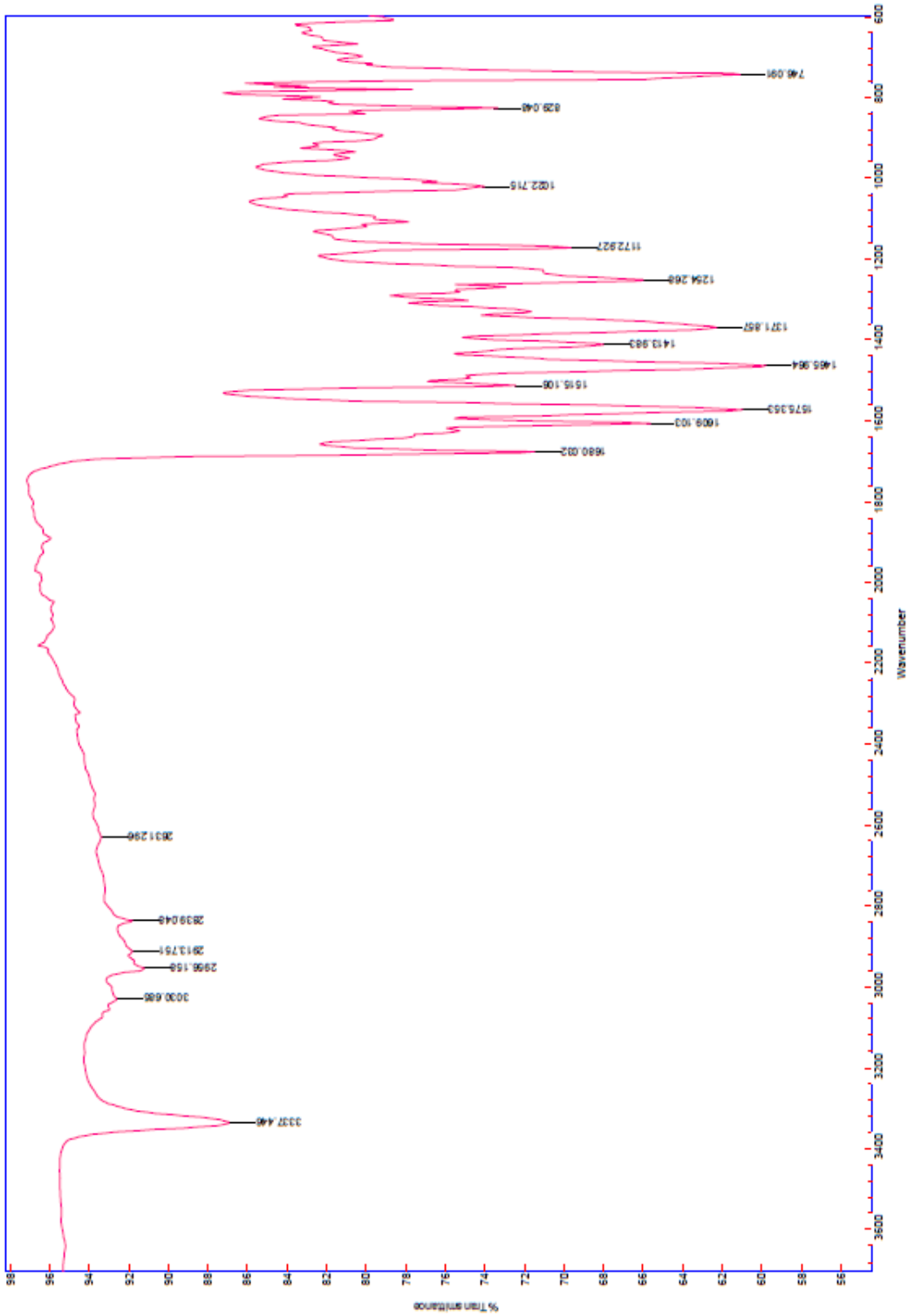
D.3.1 ^{1}H NMR spectrum of 53



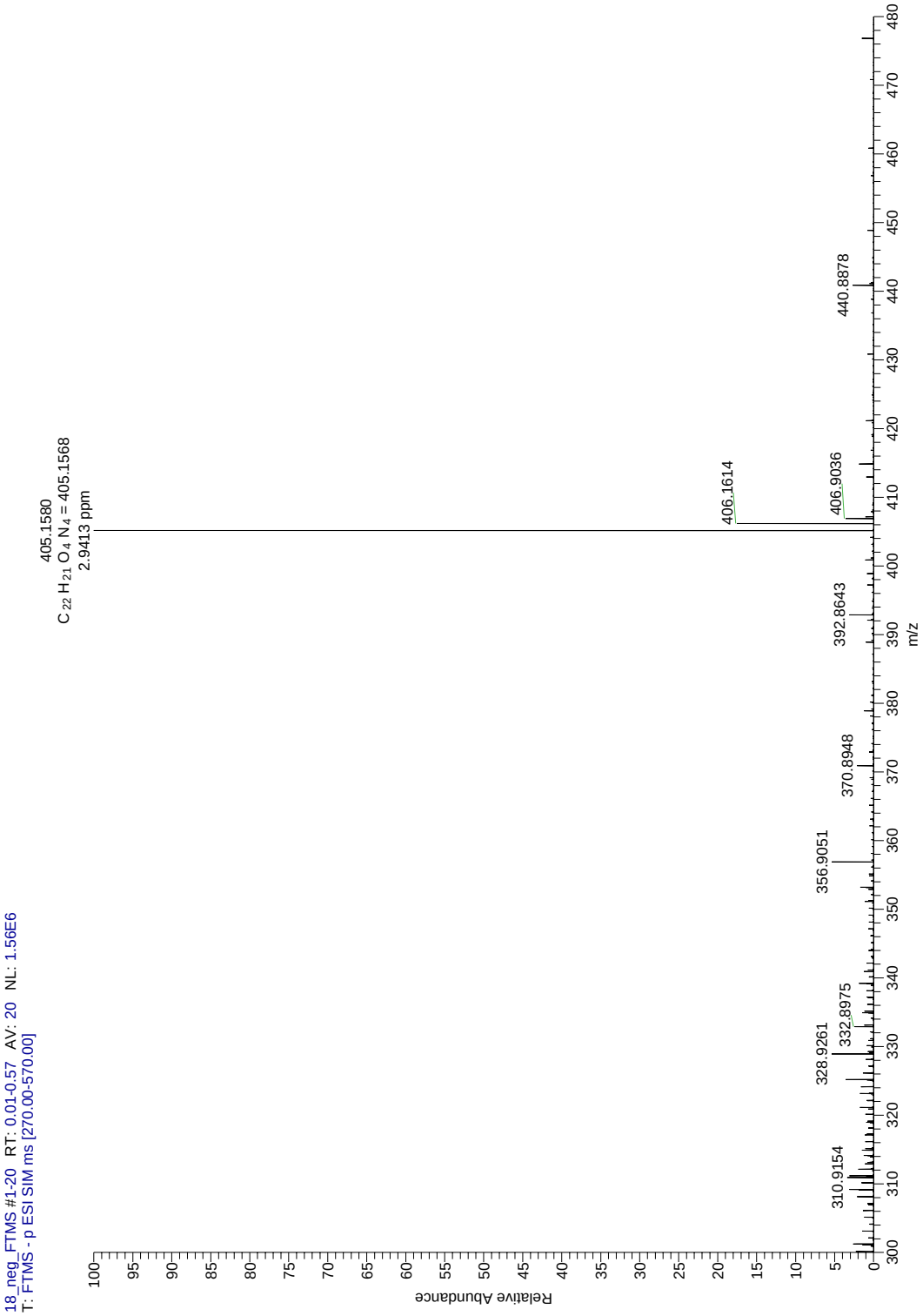
D.3.2 ^{13}C NMR spectrum of 53



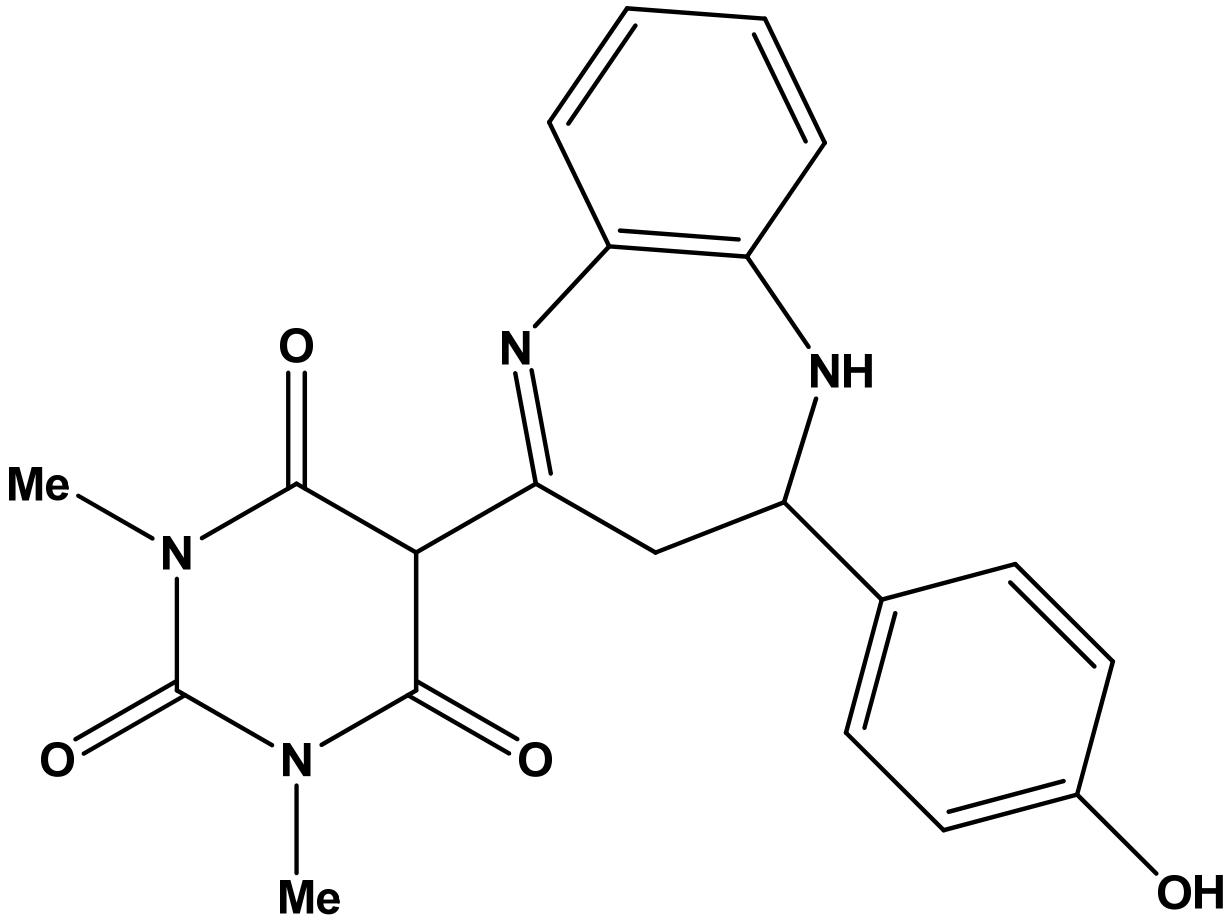
D.3.3 IR spectrum of 53



D.3.4 HRMS of 53

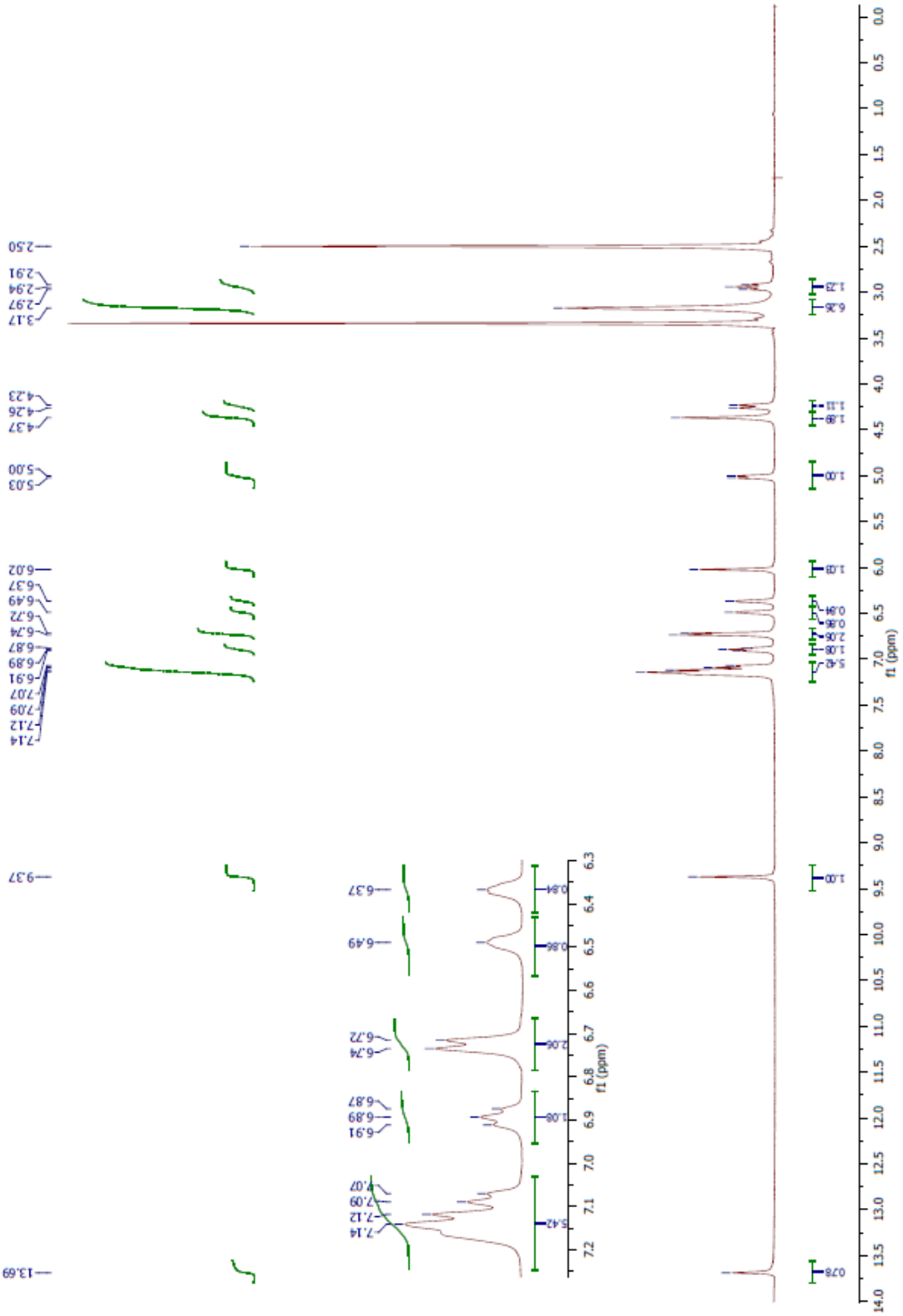


D.4 Spectroscopic data for 54

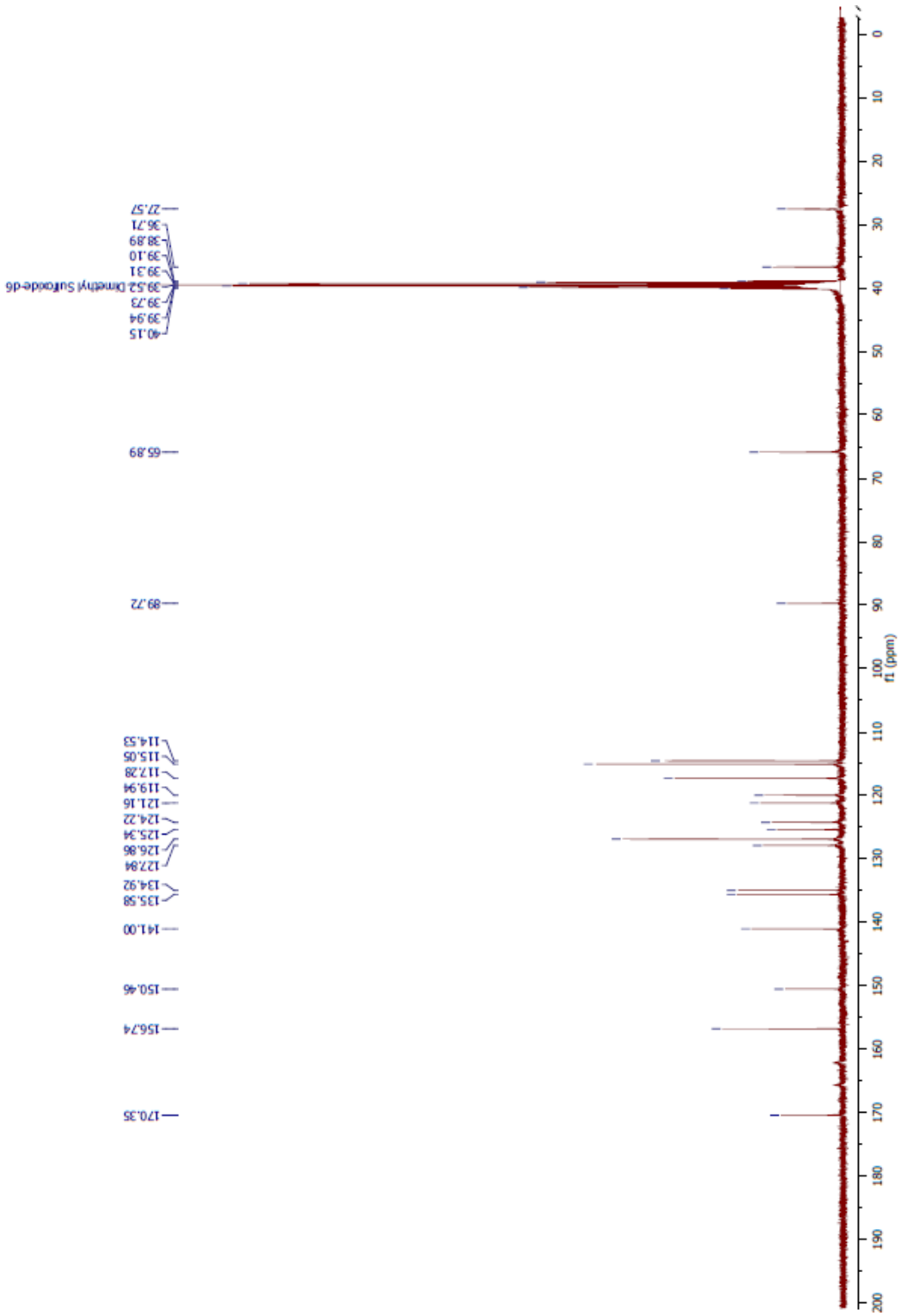


54

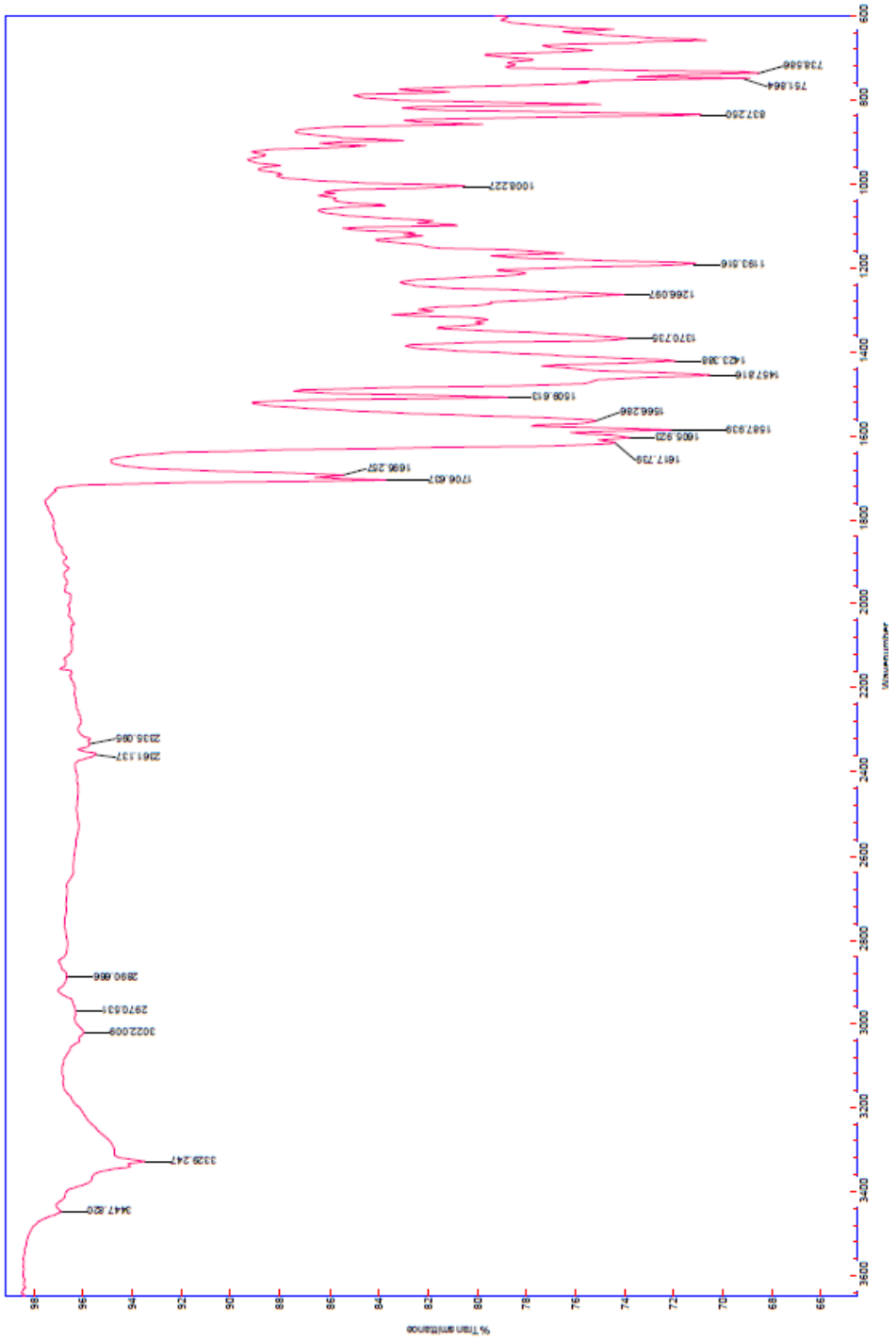
D.4.1 ^{1}H NMR spectrum of 54



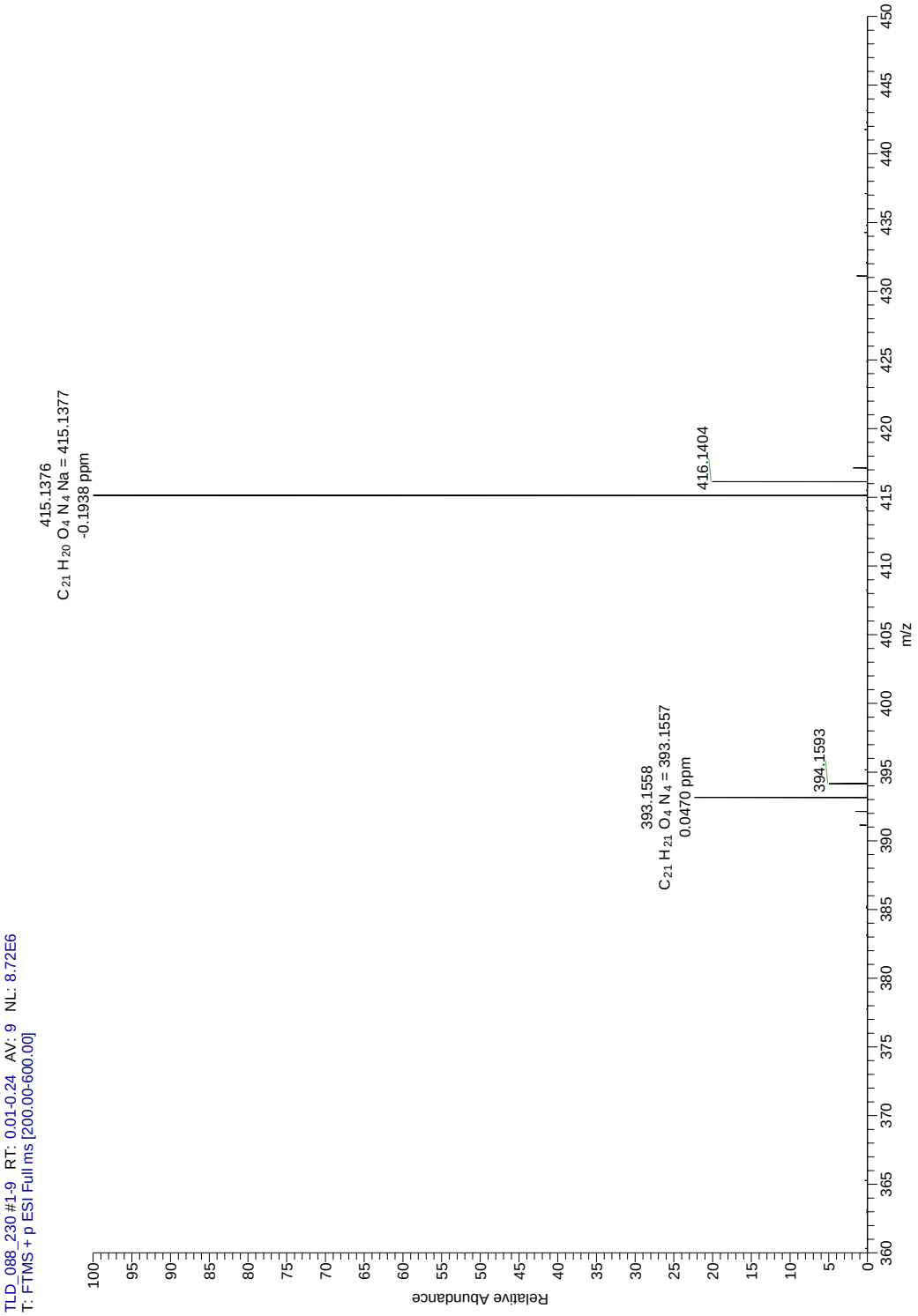
D.4.2 ^{13}C NMR spectrum of 54



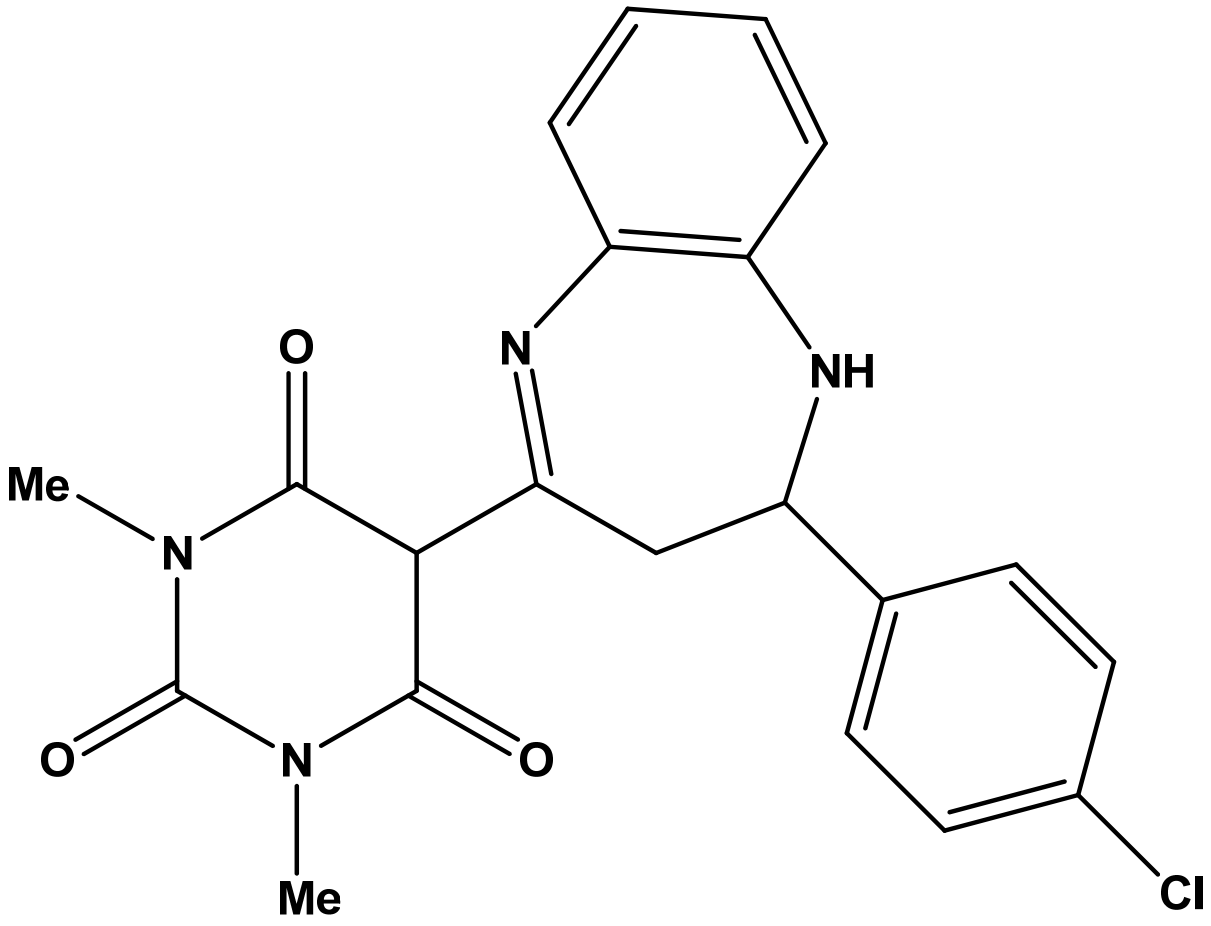
D.4.3 IR spectrum of 54



D.4.4 HRMS of 54

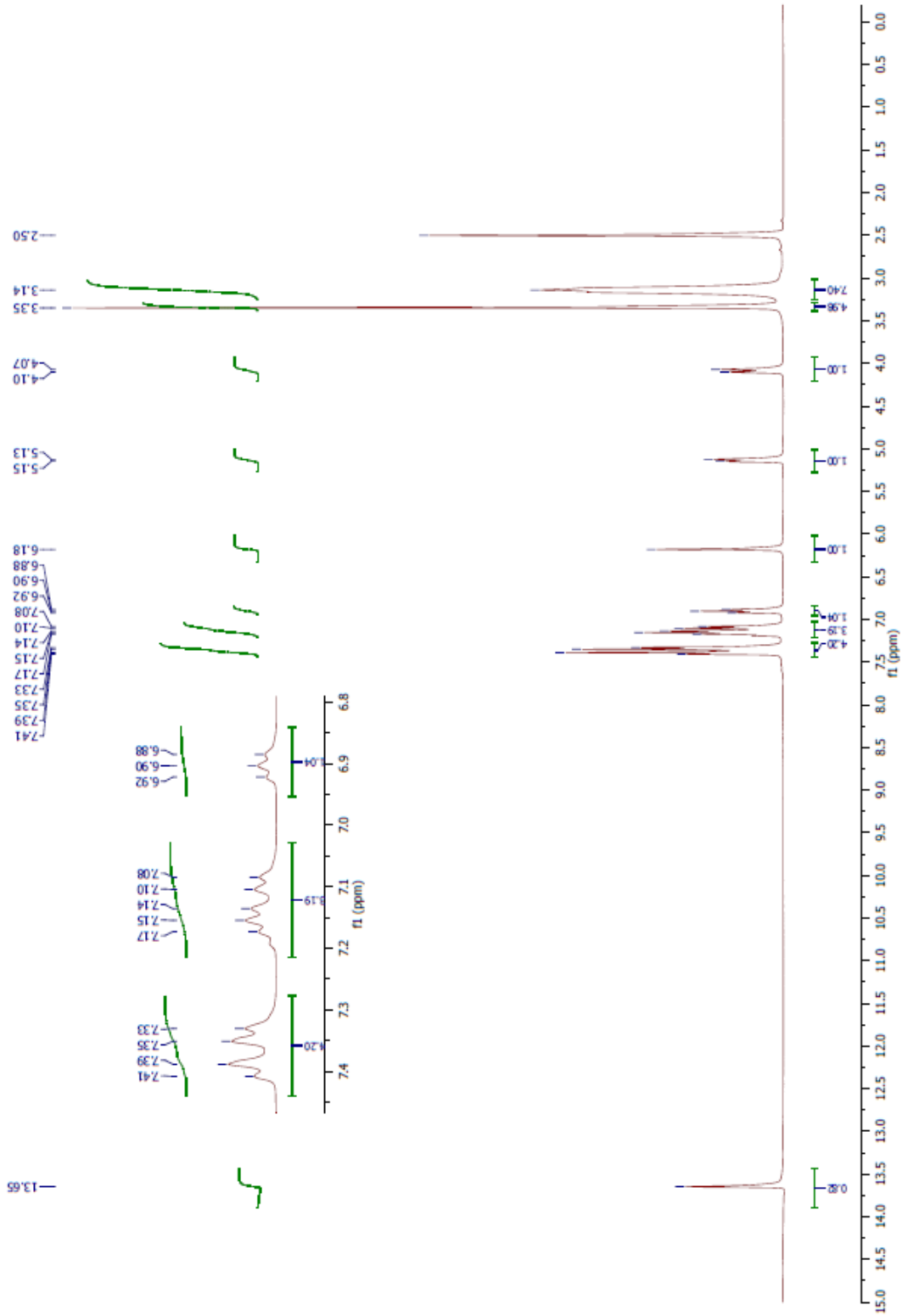


D.5 Spectroscopic data for 55

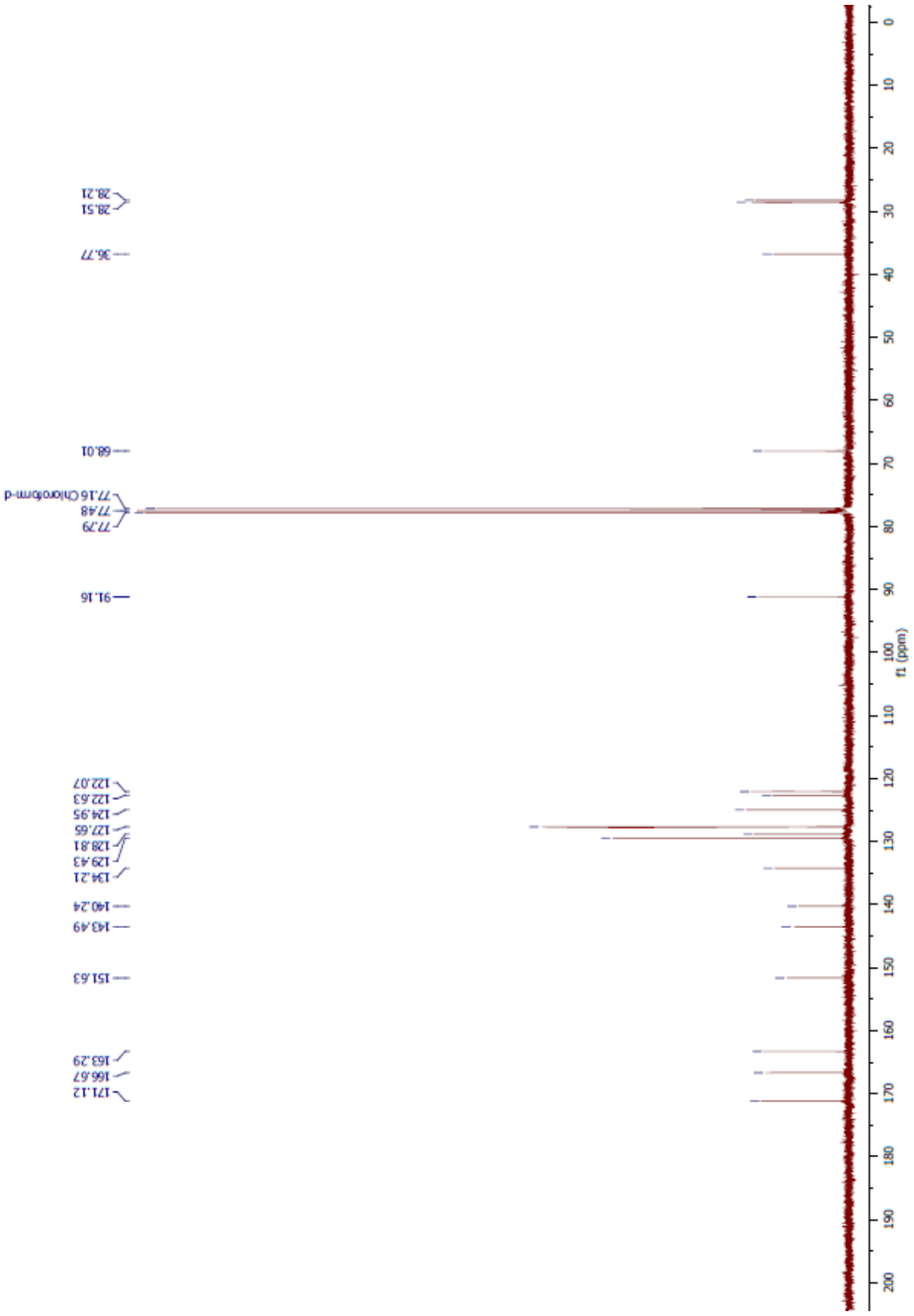


55

D.5.1 ^{1}H NMR spectrum of 55

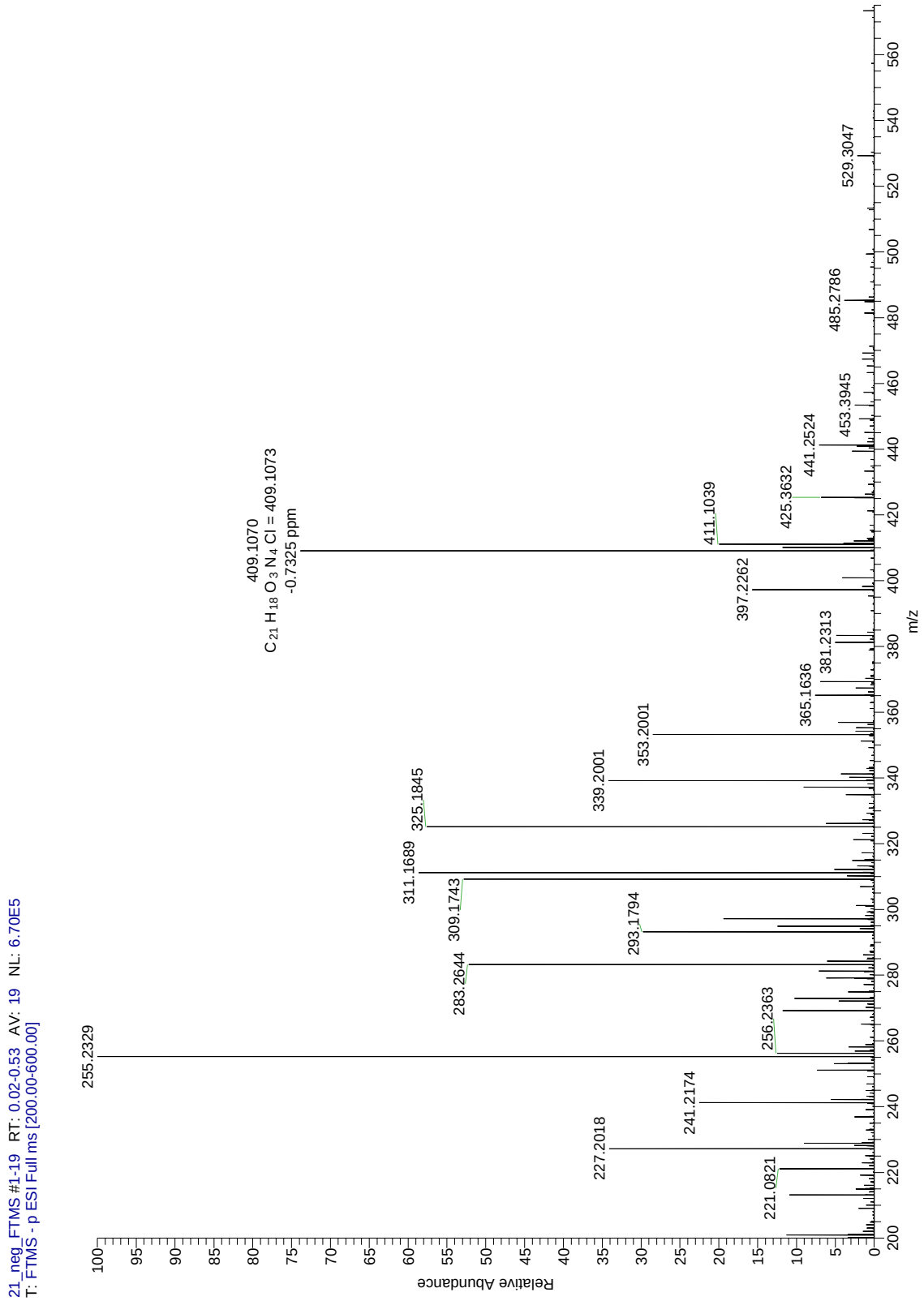


D.5.2 ^{13}C NMR spectrum of 55

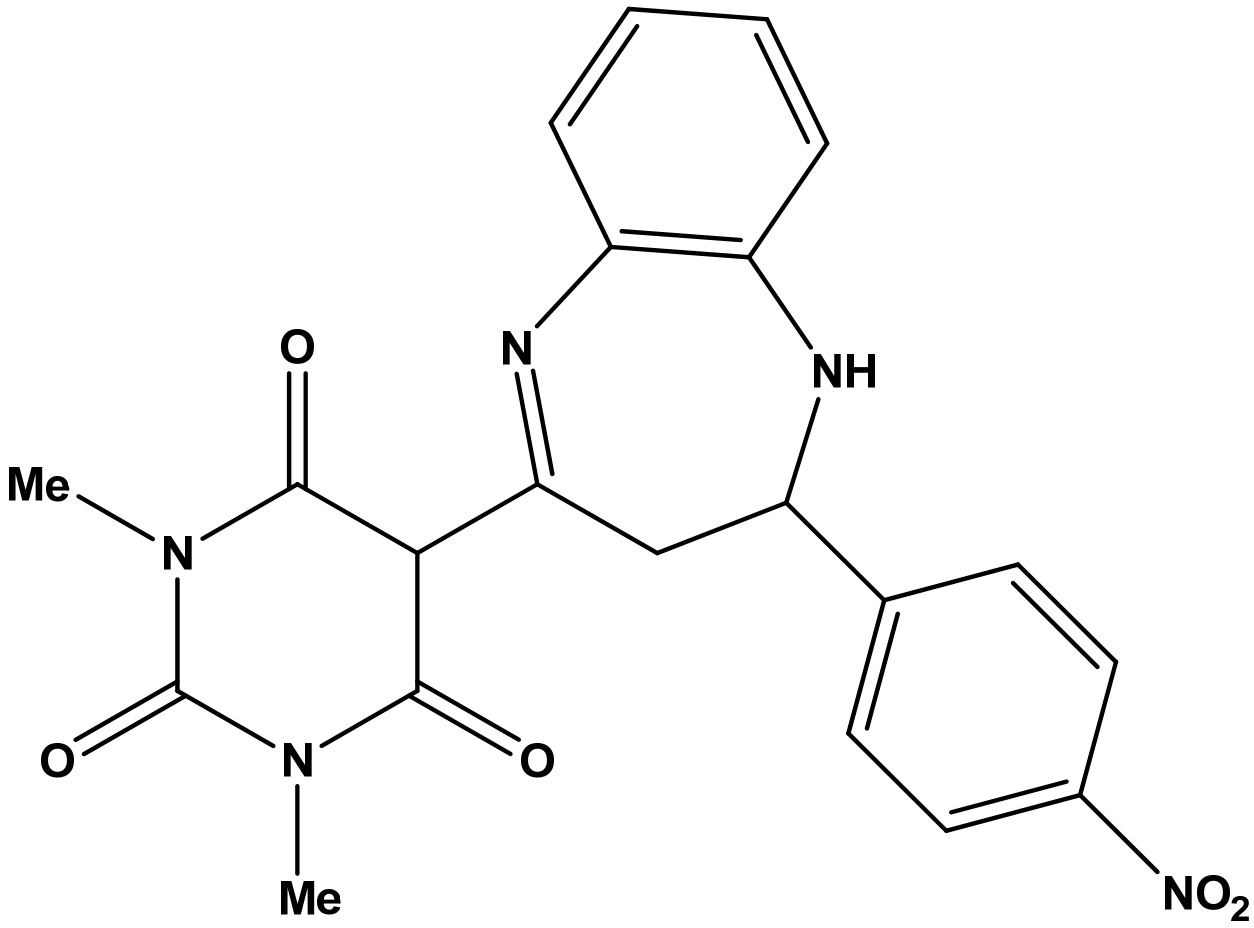


D.5.3 IR spectrum of 55

D.5.4 HRMS of 55

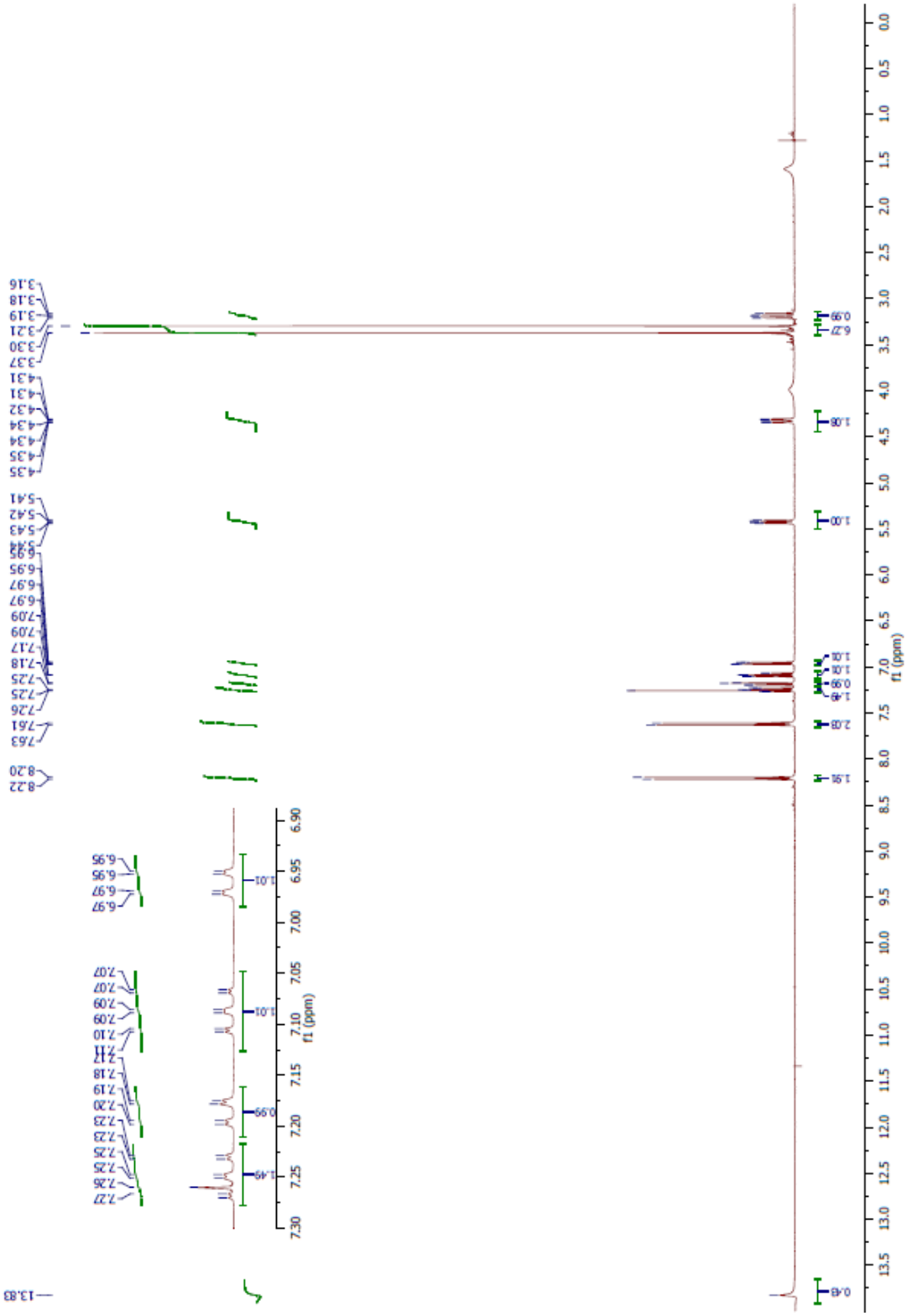


D.6 Spectroscopic data for 56

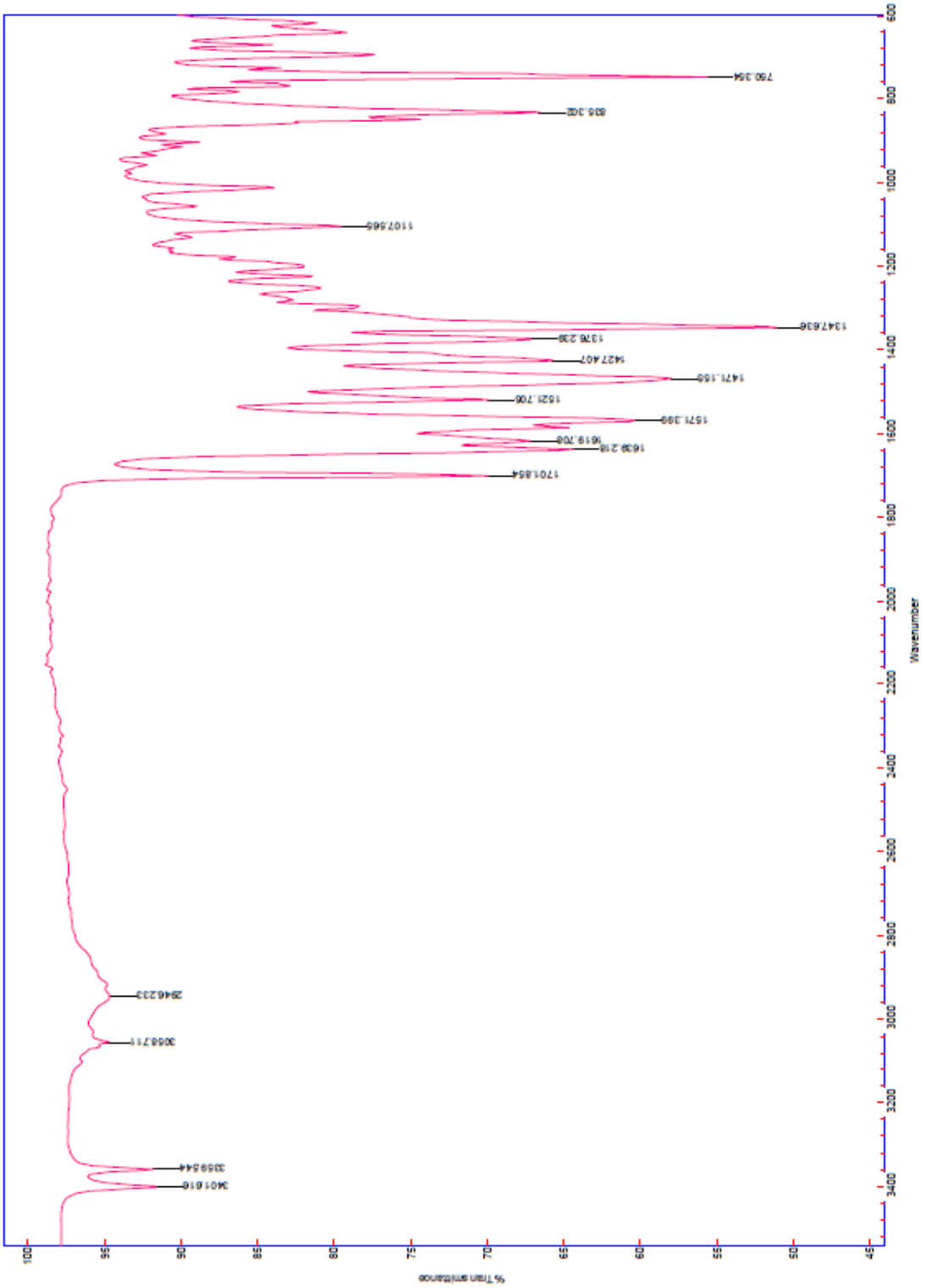


56

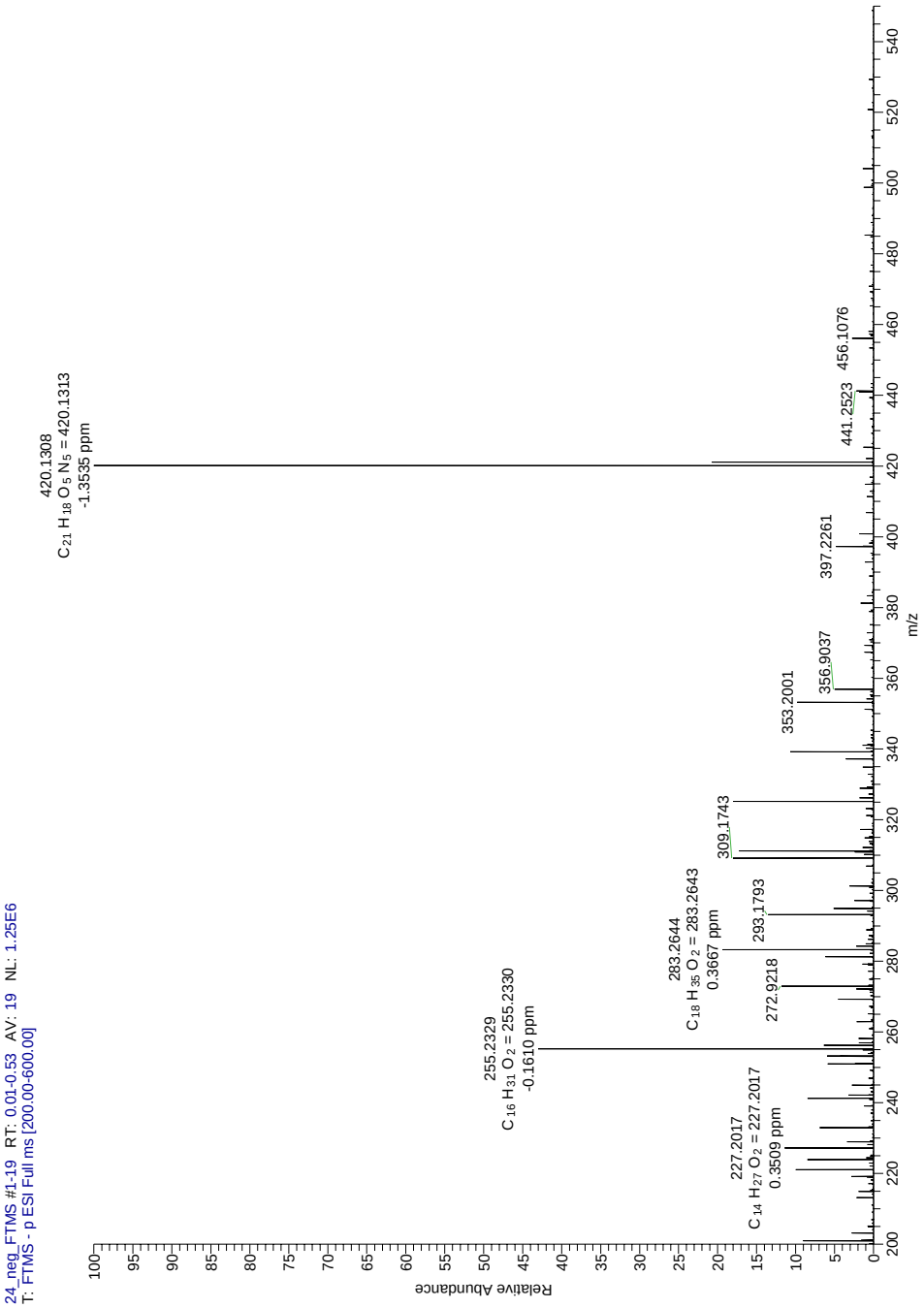
D.6.1 ^{1}H NMR spectrum of 56



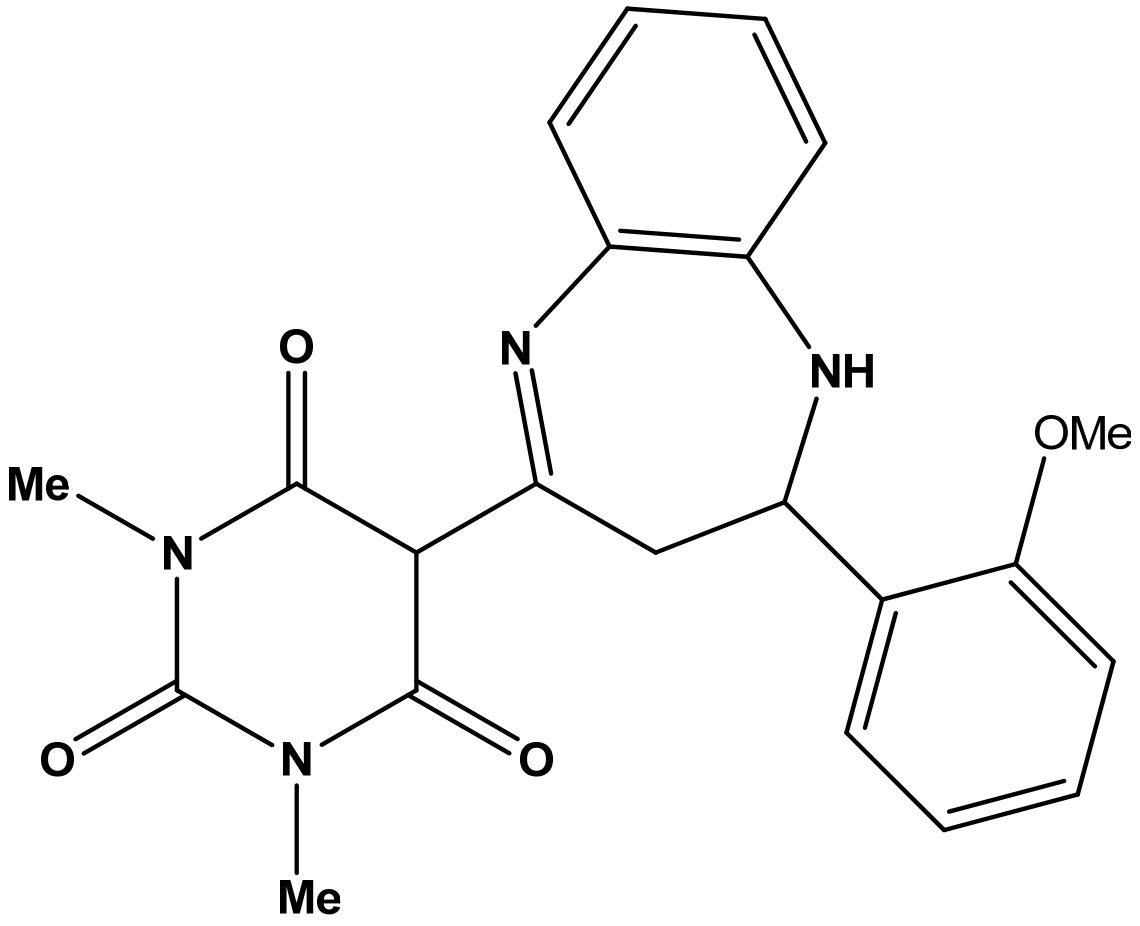
D.6.2 IR spectrum of 56



D.6.3 HRMS of 56

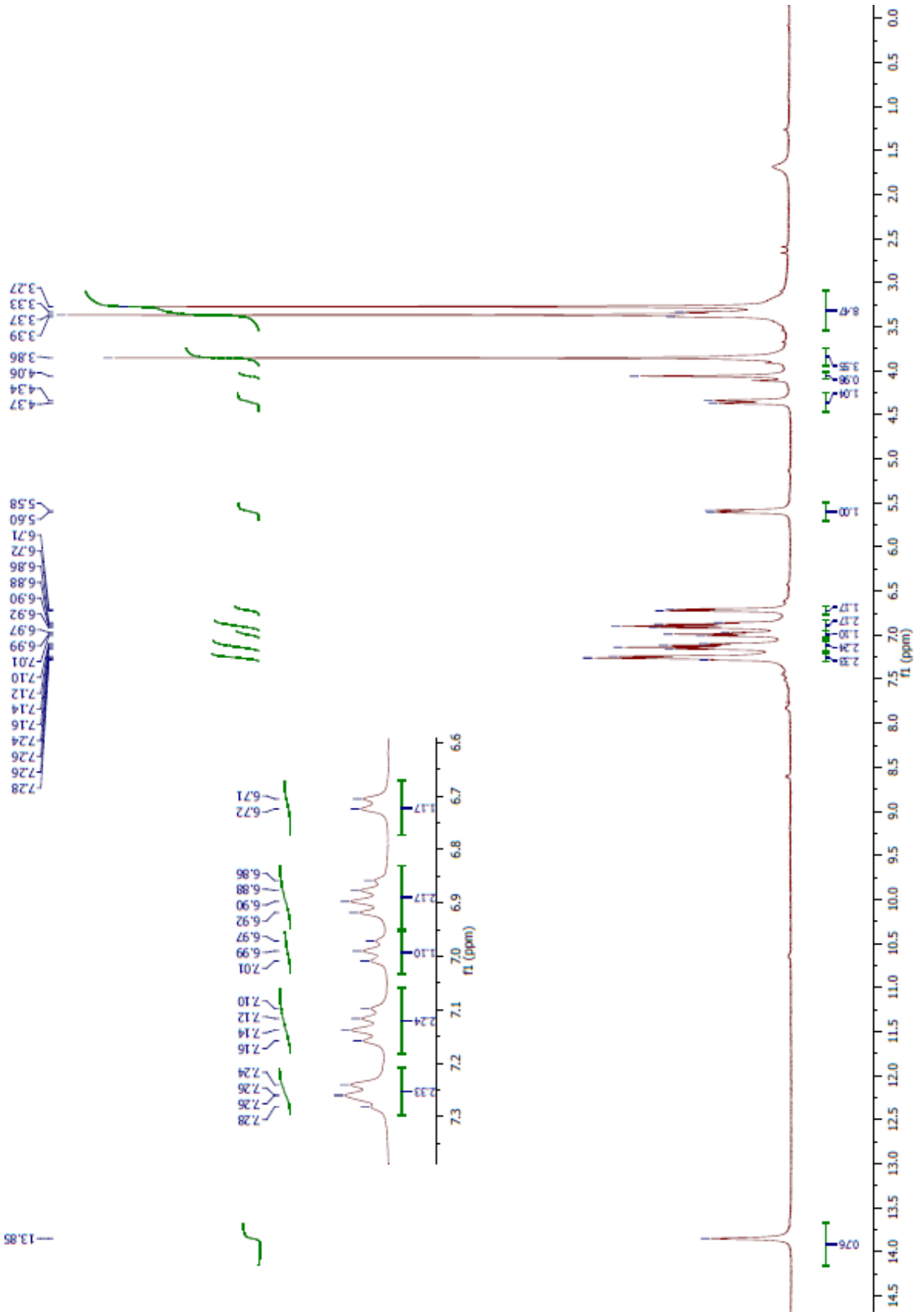


D.7 Spectroscopic data for 57

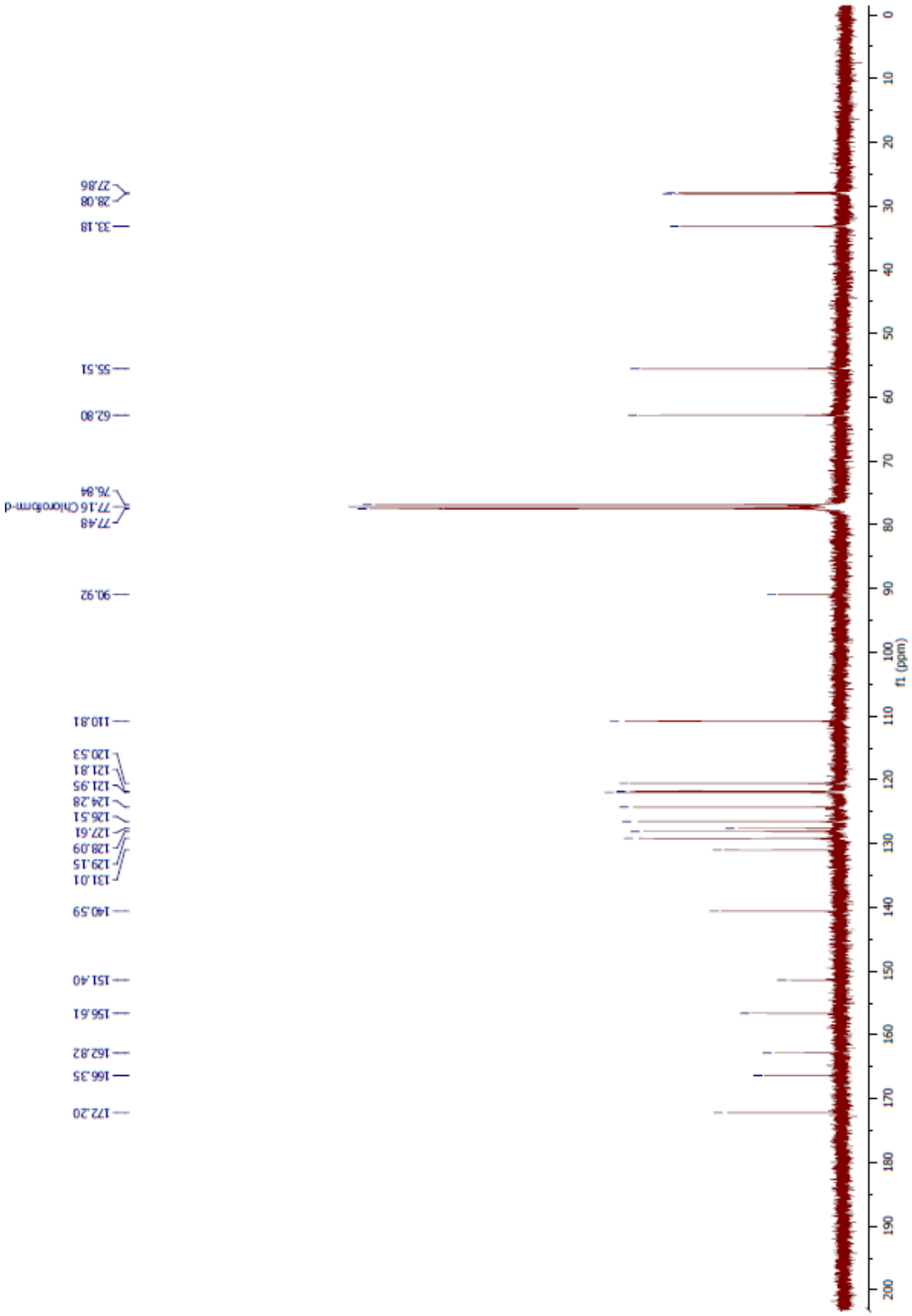


57

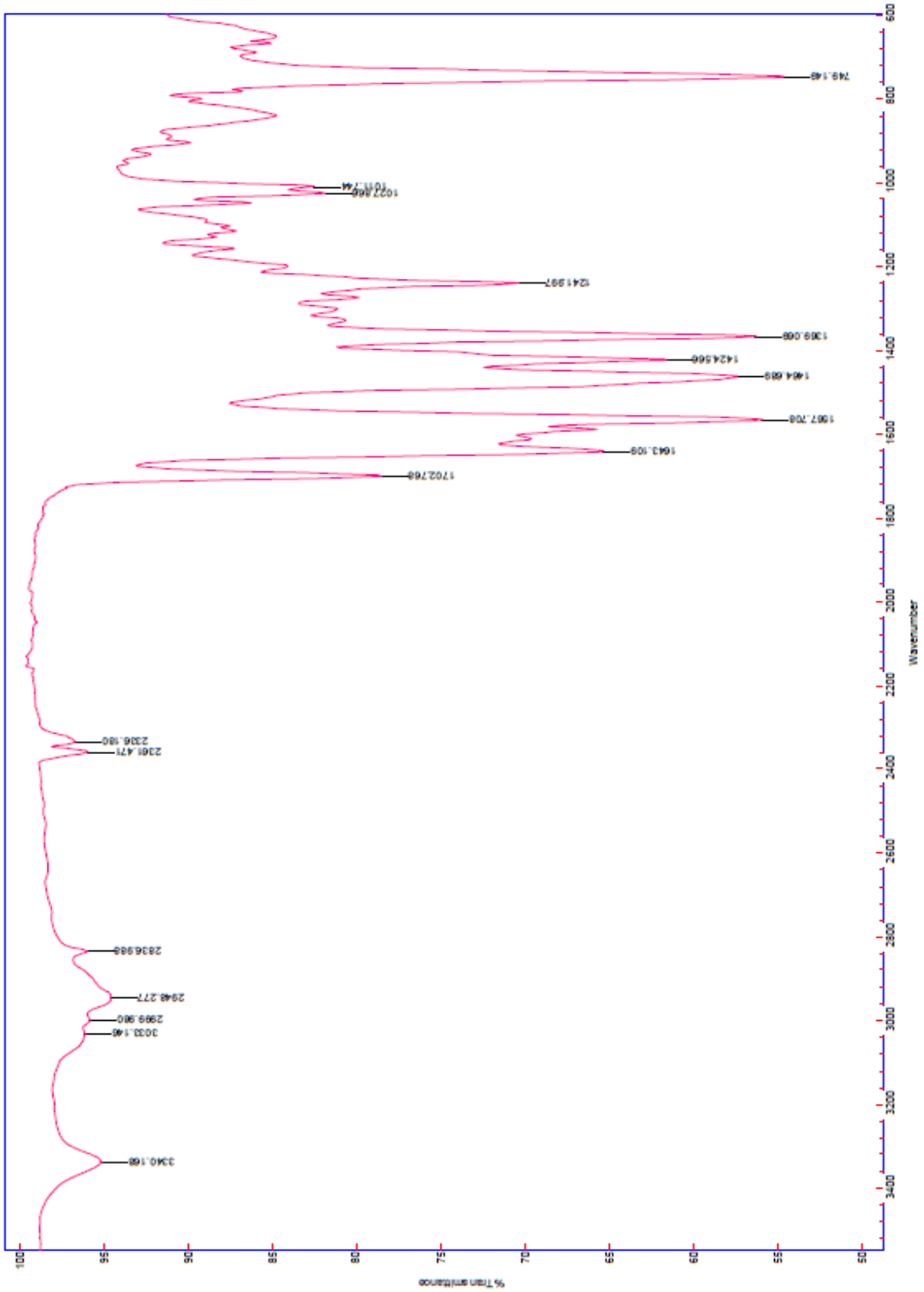
D.7.1 ^{1}H NMR spectrum of 57



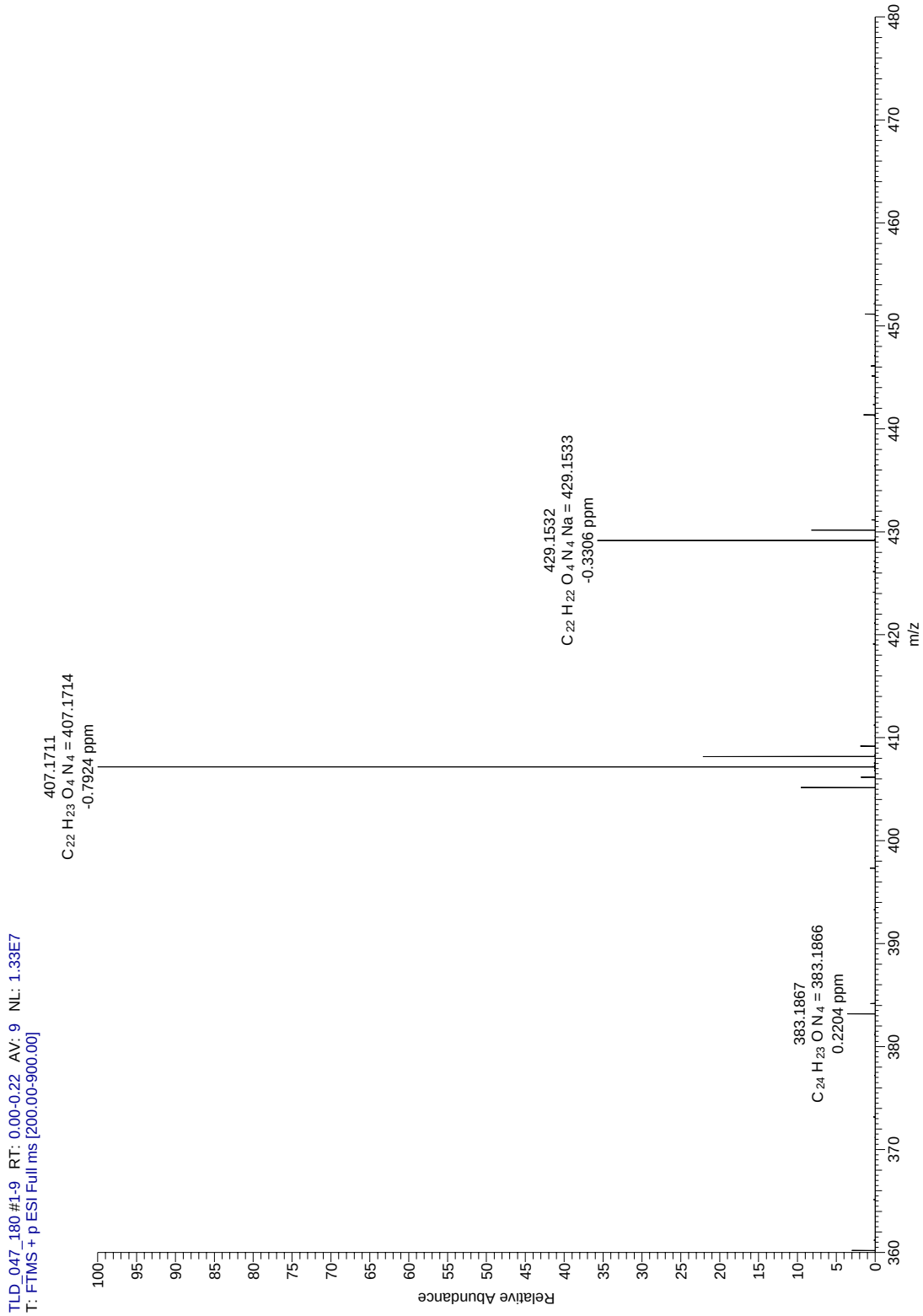
D.7.2 ^{13}C NMR spectrum of 57



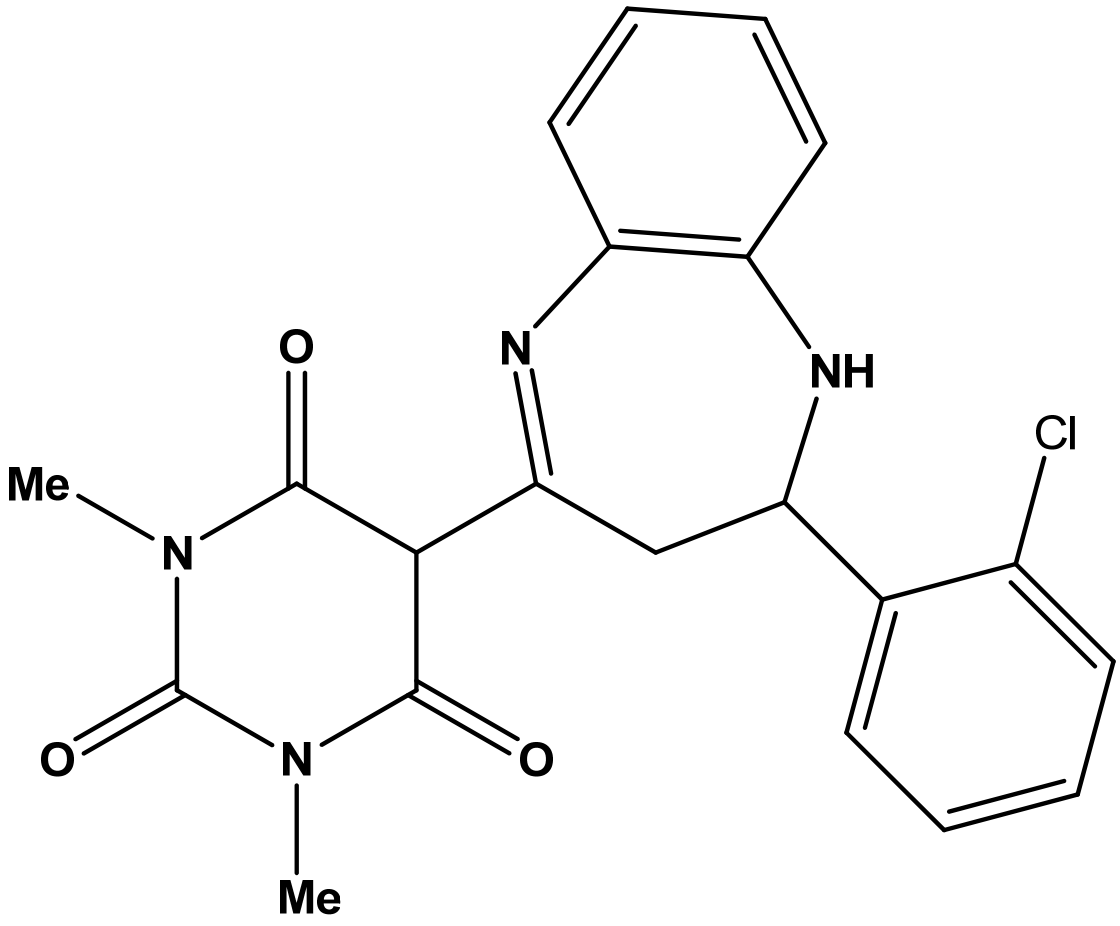
D.7.3 IR spectrum of 57



D.7.4 HRMS of 57

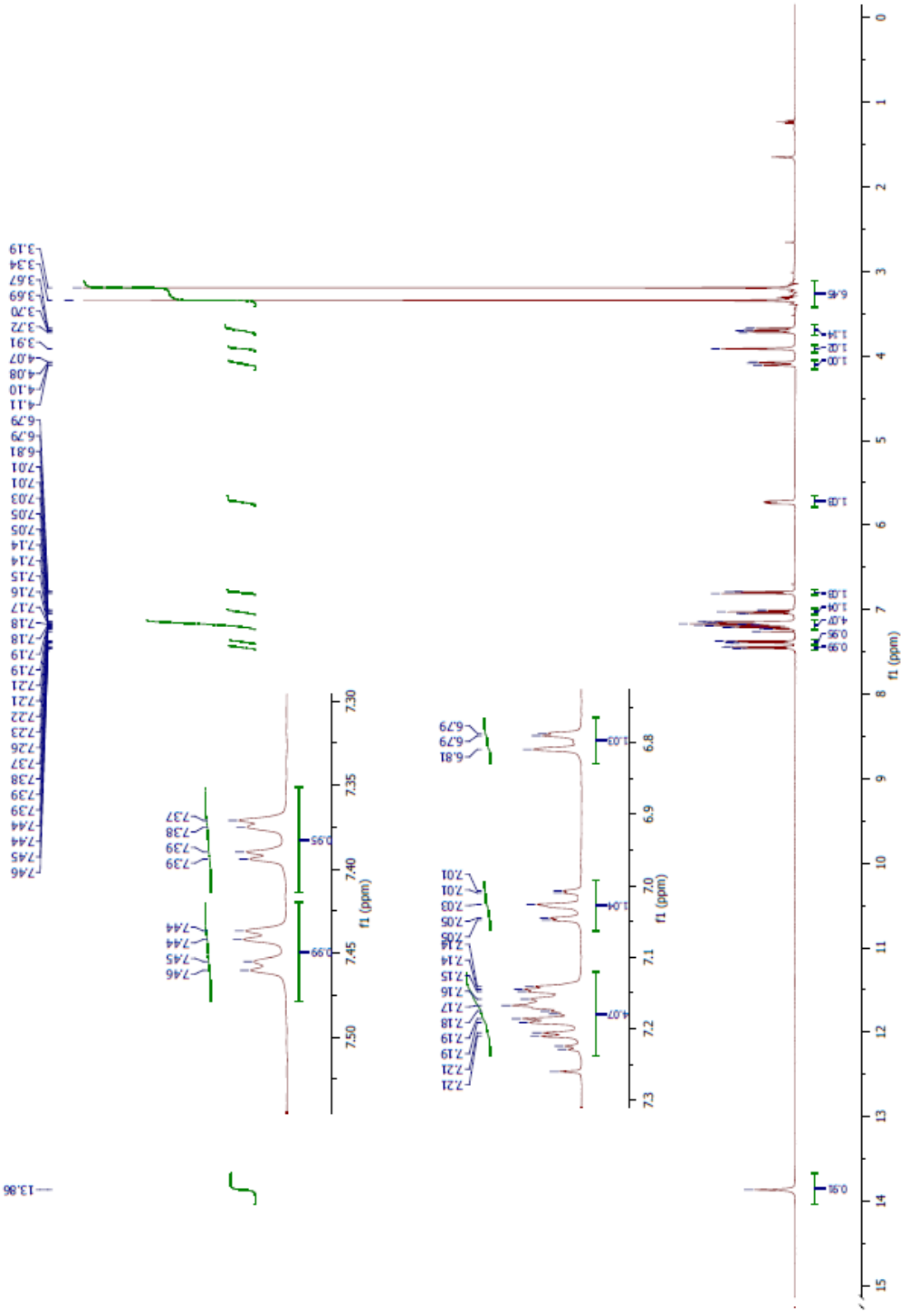


D.8 Spectroscopic data for 58

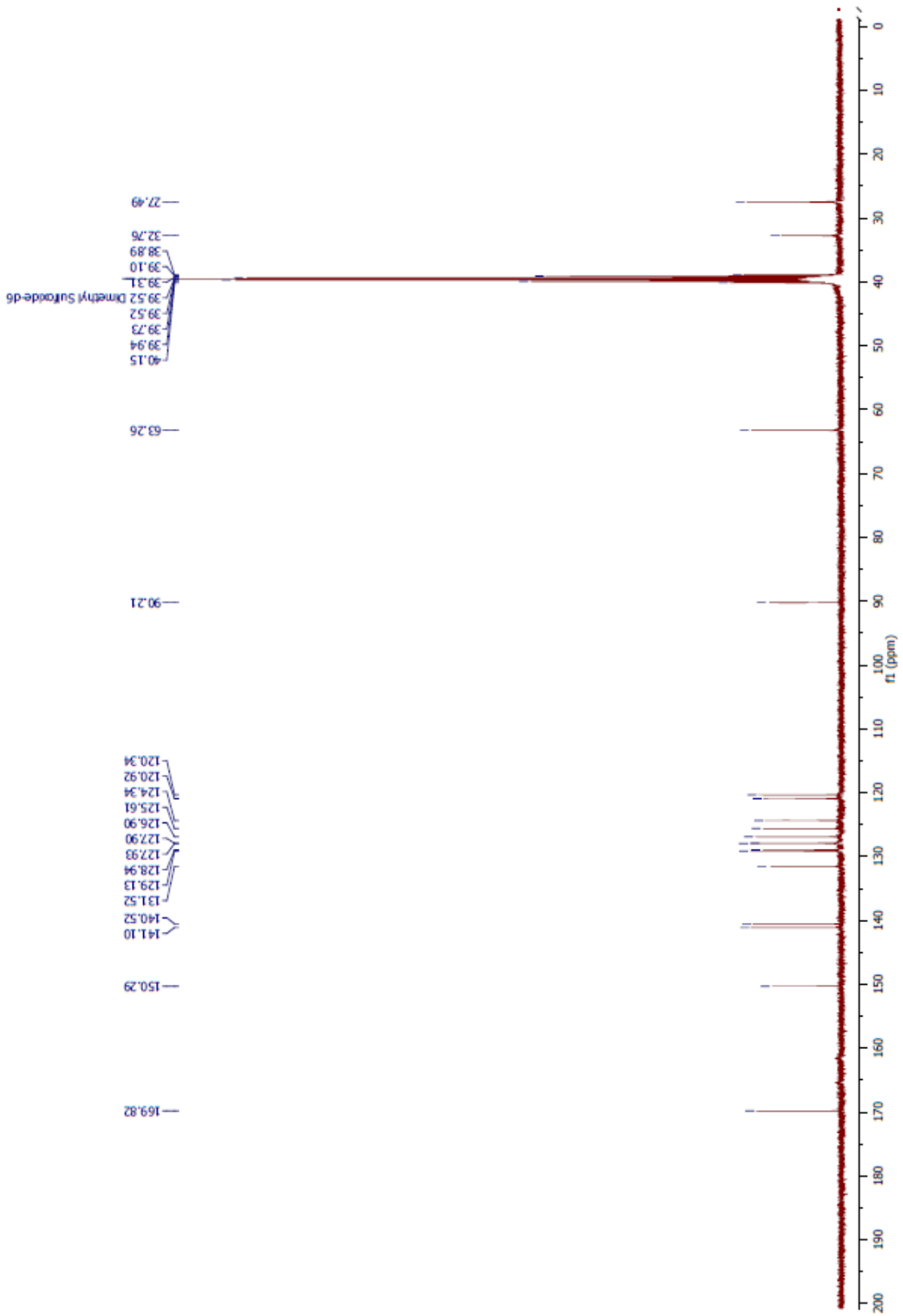


58

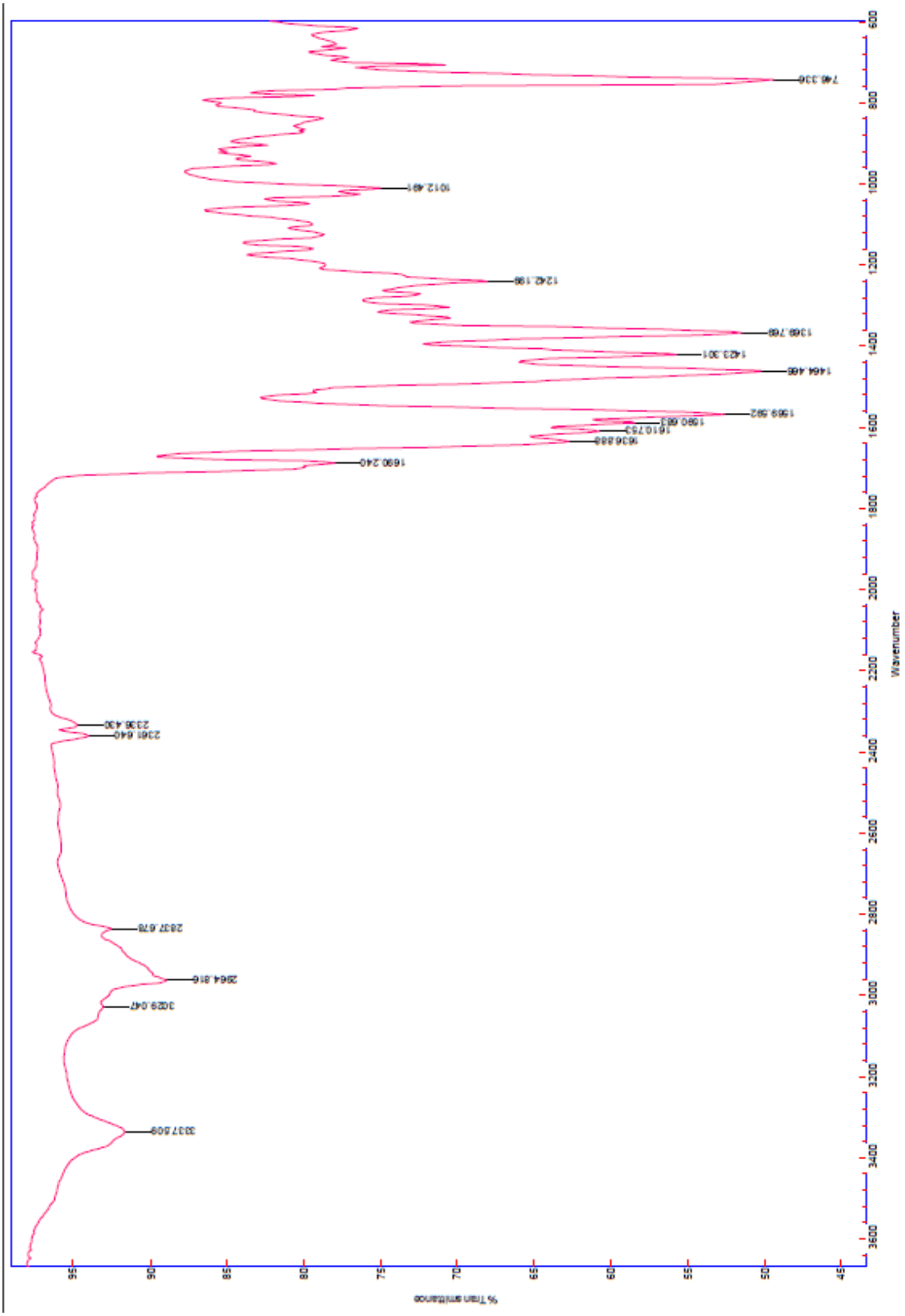
D.8.1 ^{1}H NMR spectrum of 58



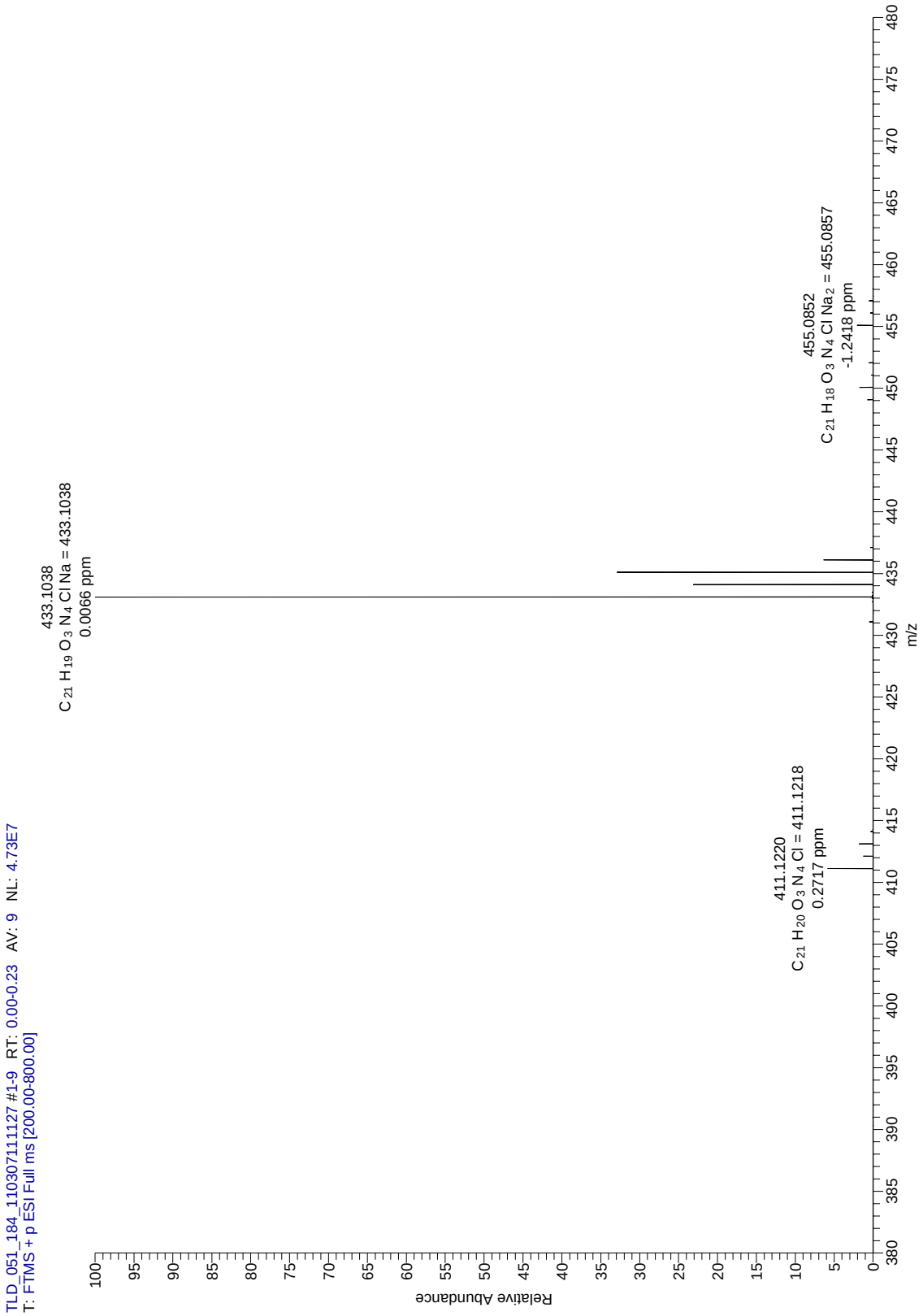
D.8.2 ^{13}C NMR spectrum of 58



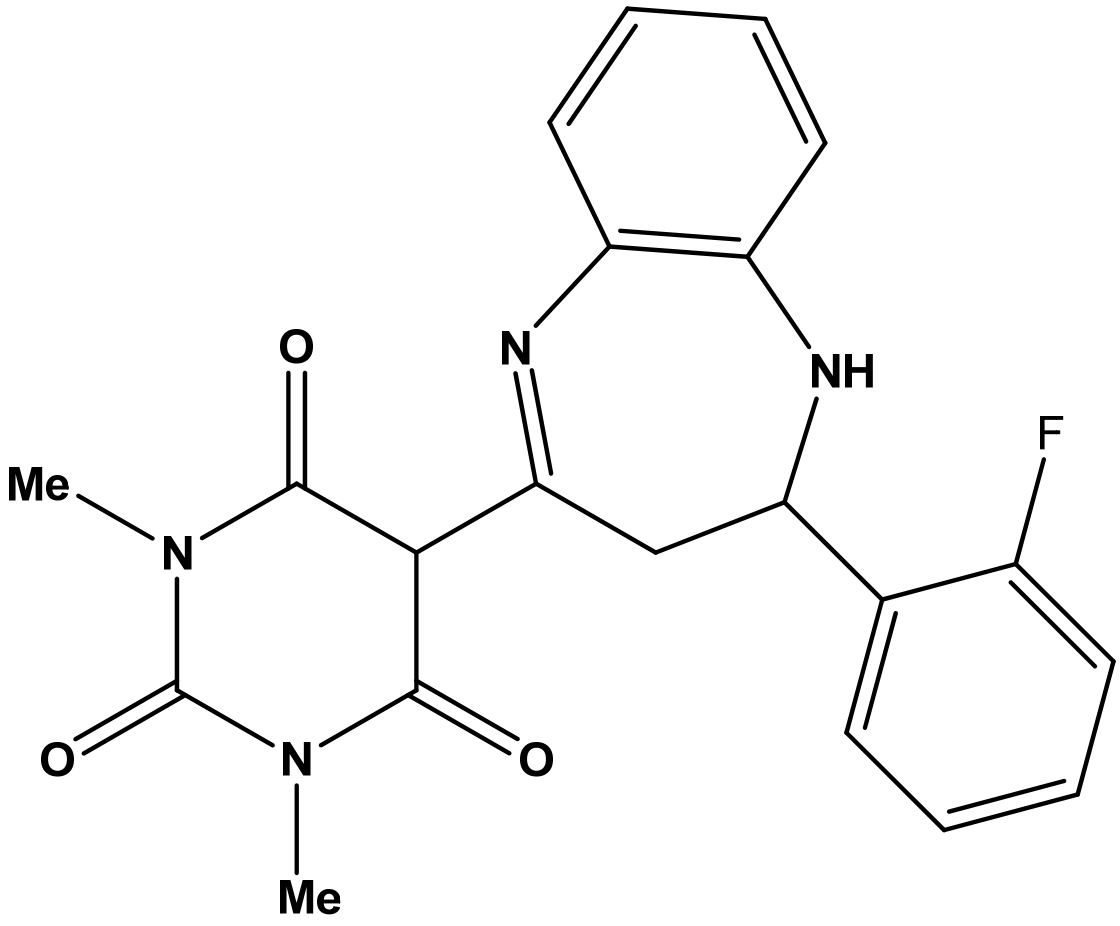
D.8.3 IR spectrum of 58



D.8.4 HRMS of 58

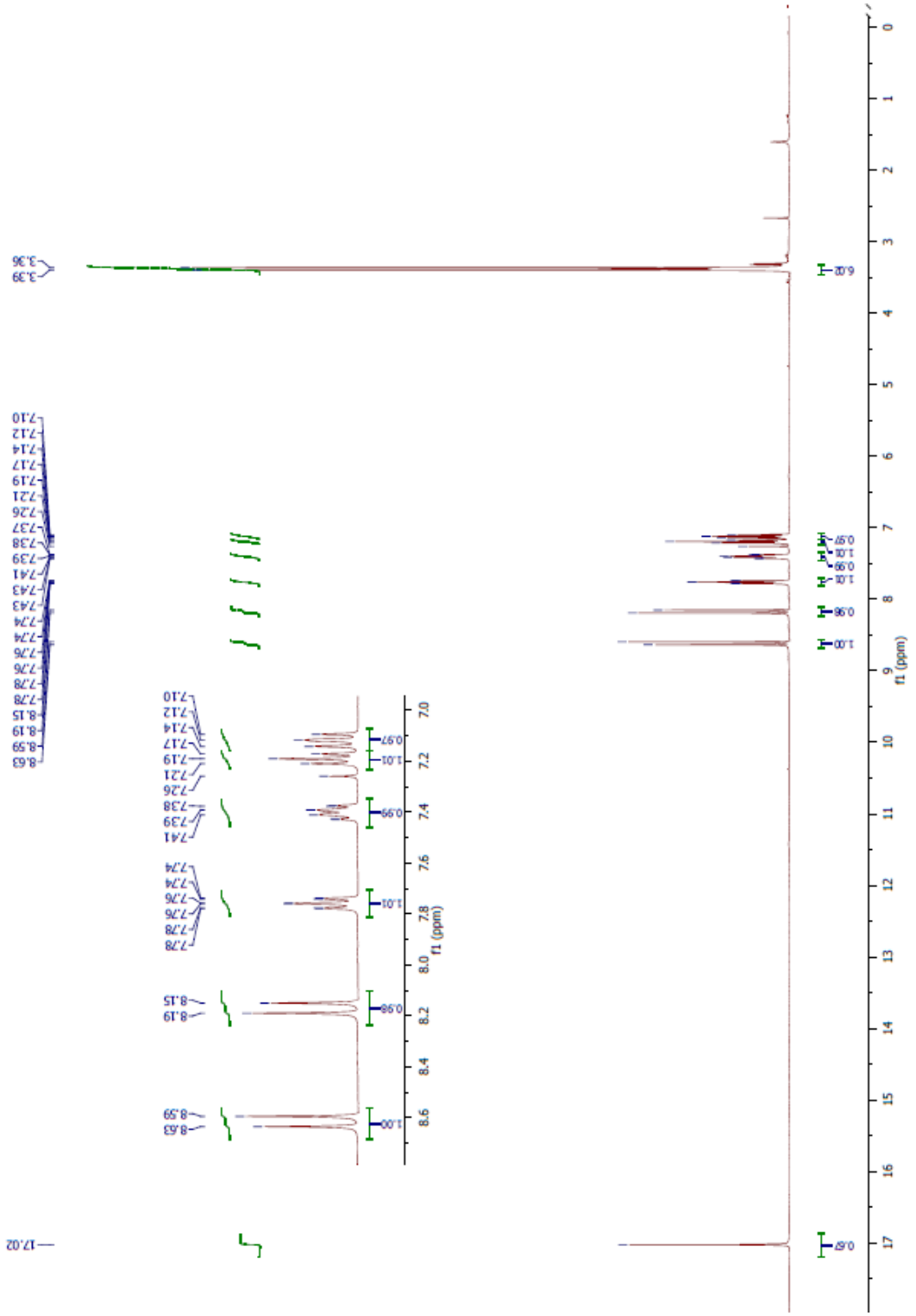


D.9 Spectroscopic data for 59

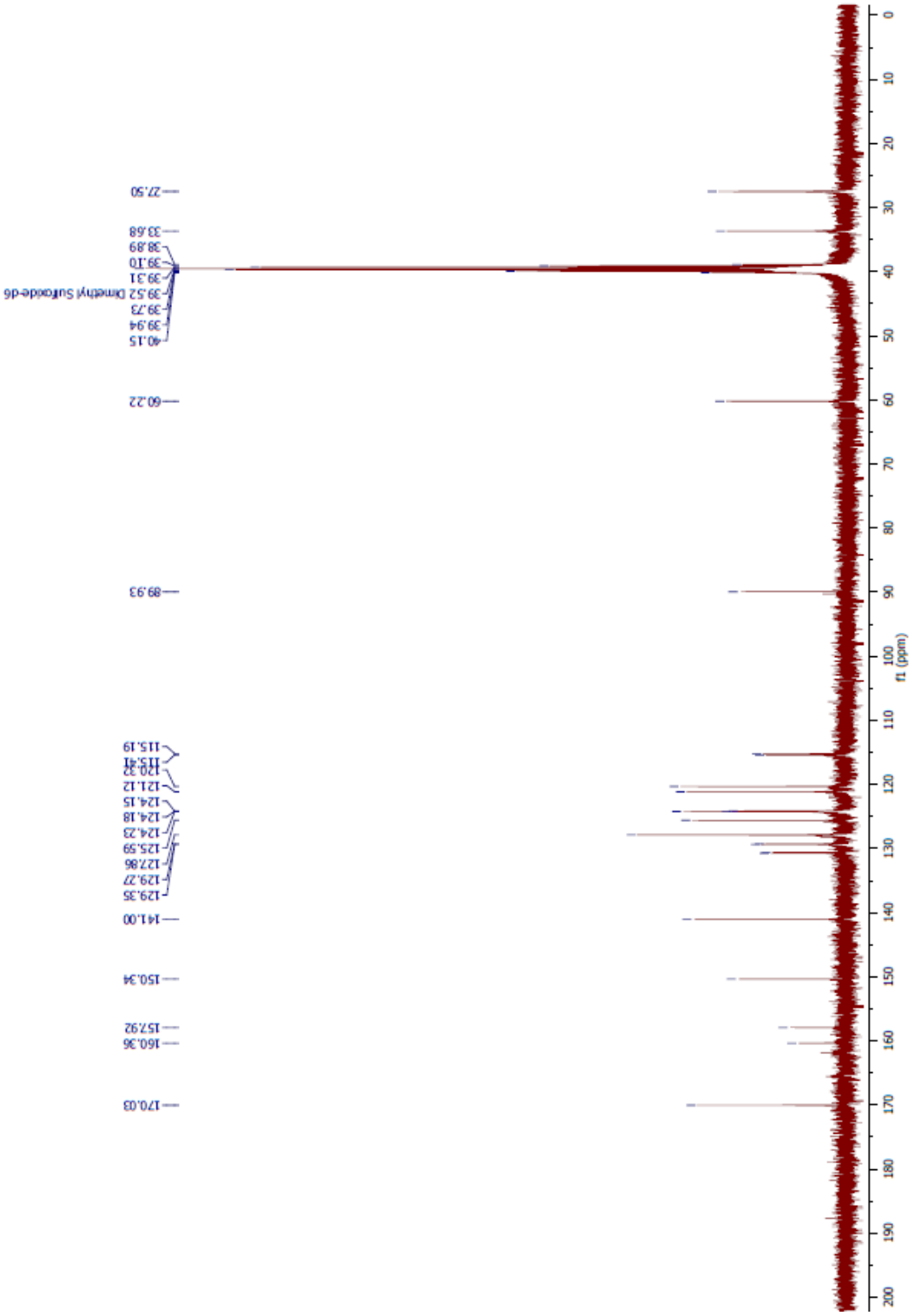


59

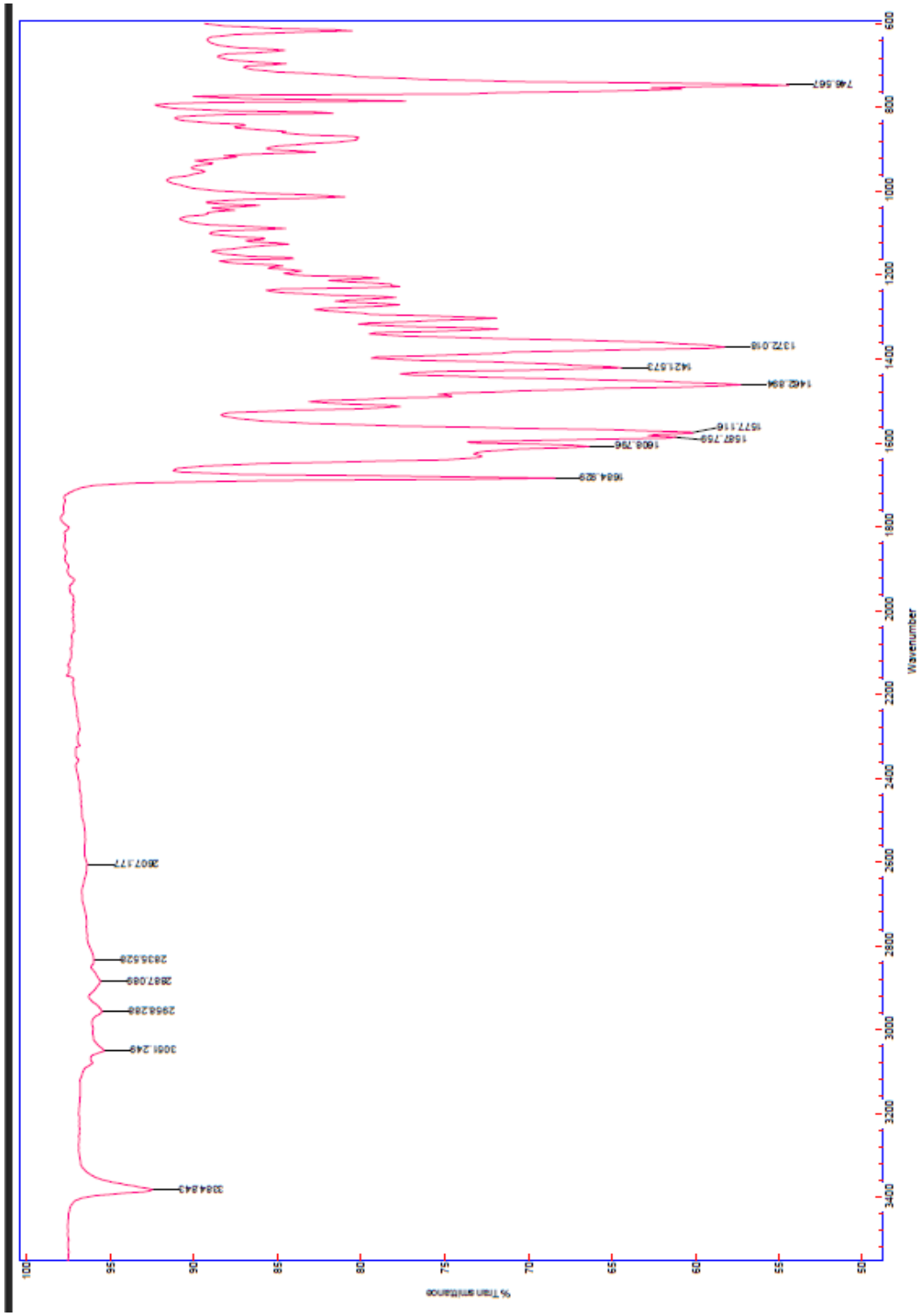
D.9.1 ^{1}H NMR spectrum of 59



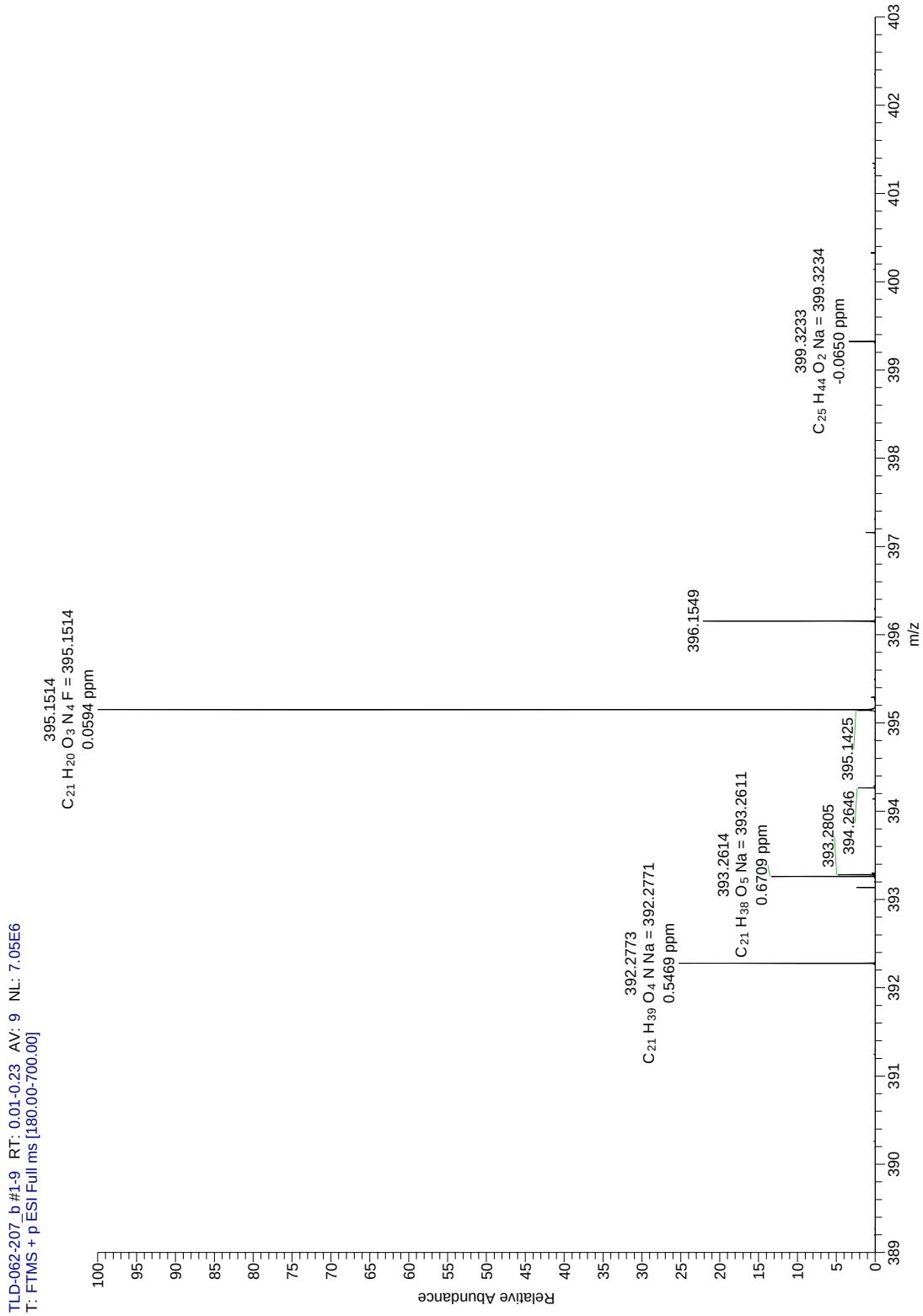
D.9.2 ^{13}C NMR spectrum of 59



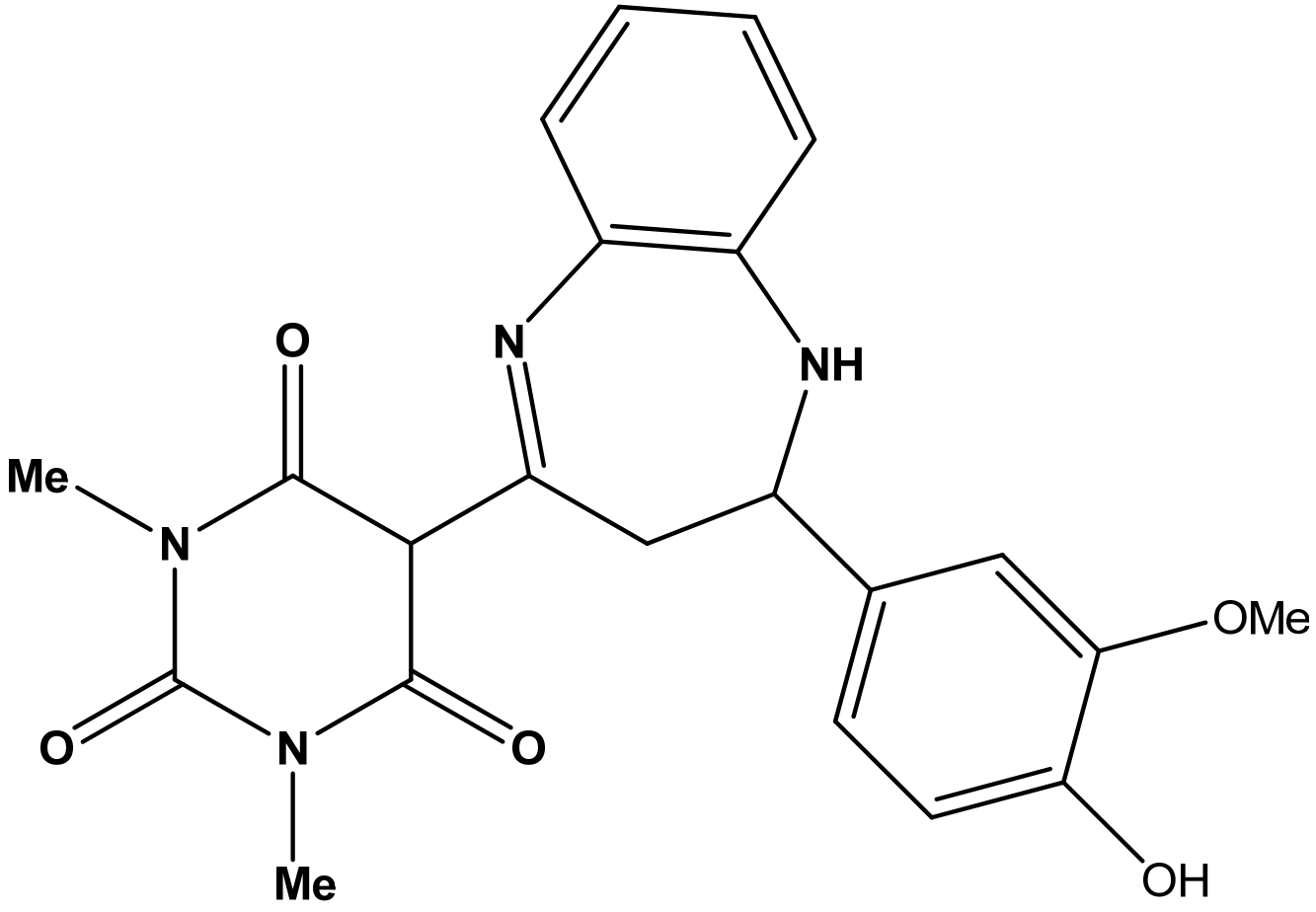
D.9.3 IR spectrum of 59



D.9.4 HRMS of 59

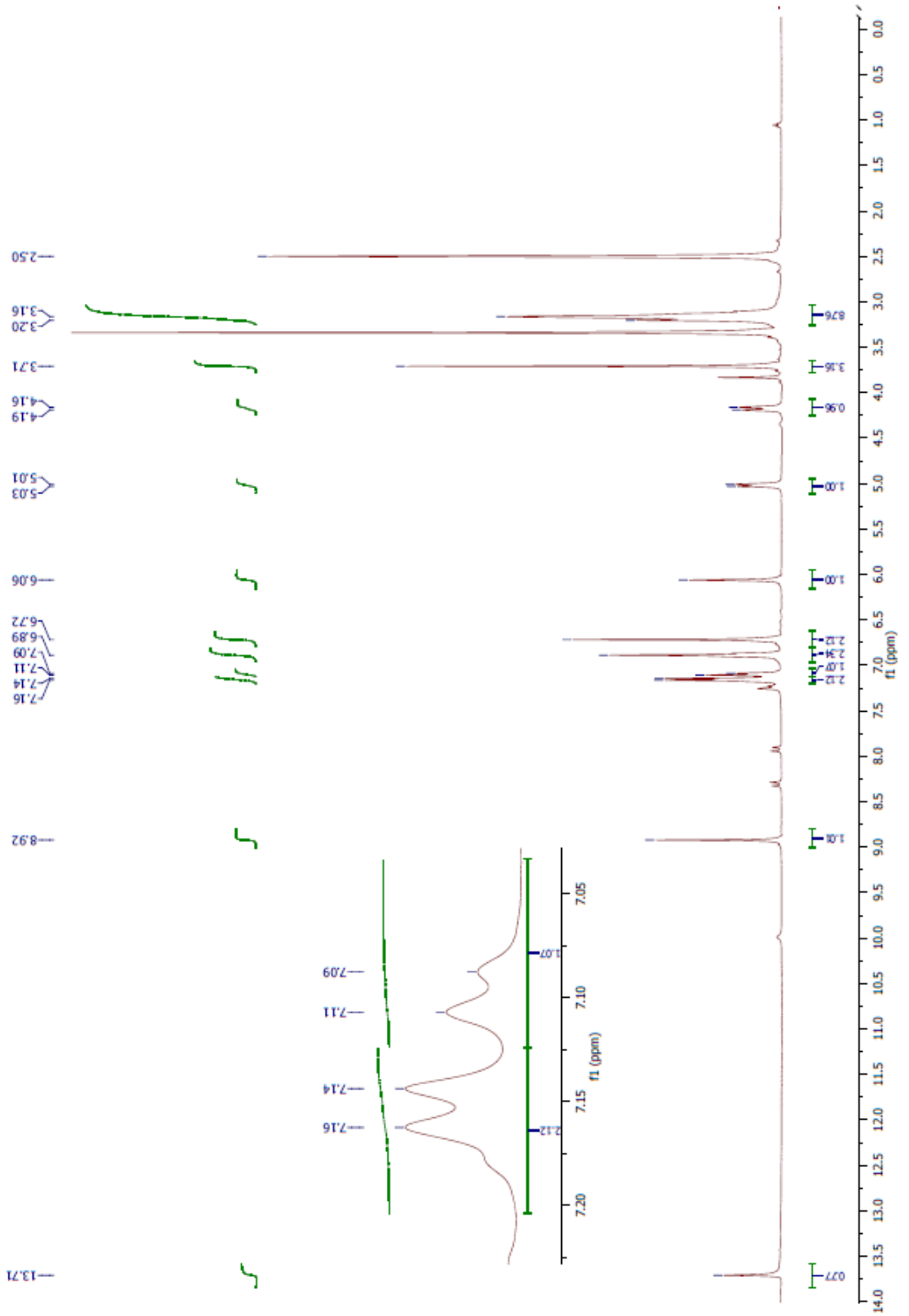


D.10 Spectroscopic data for 62

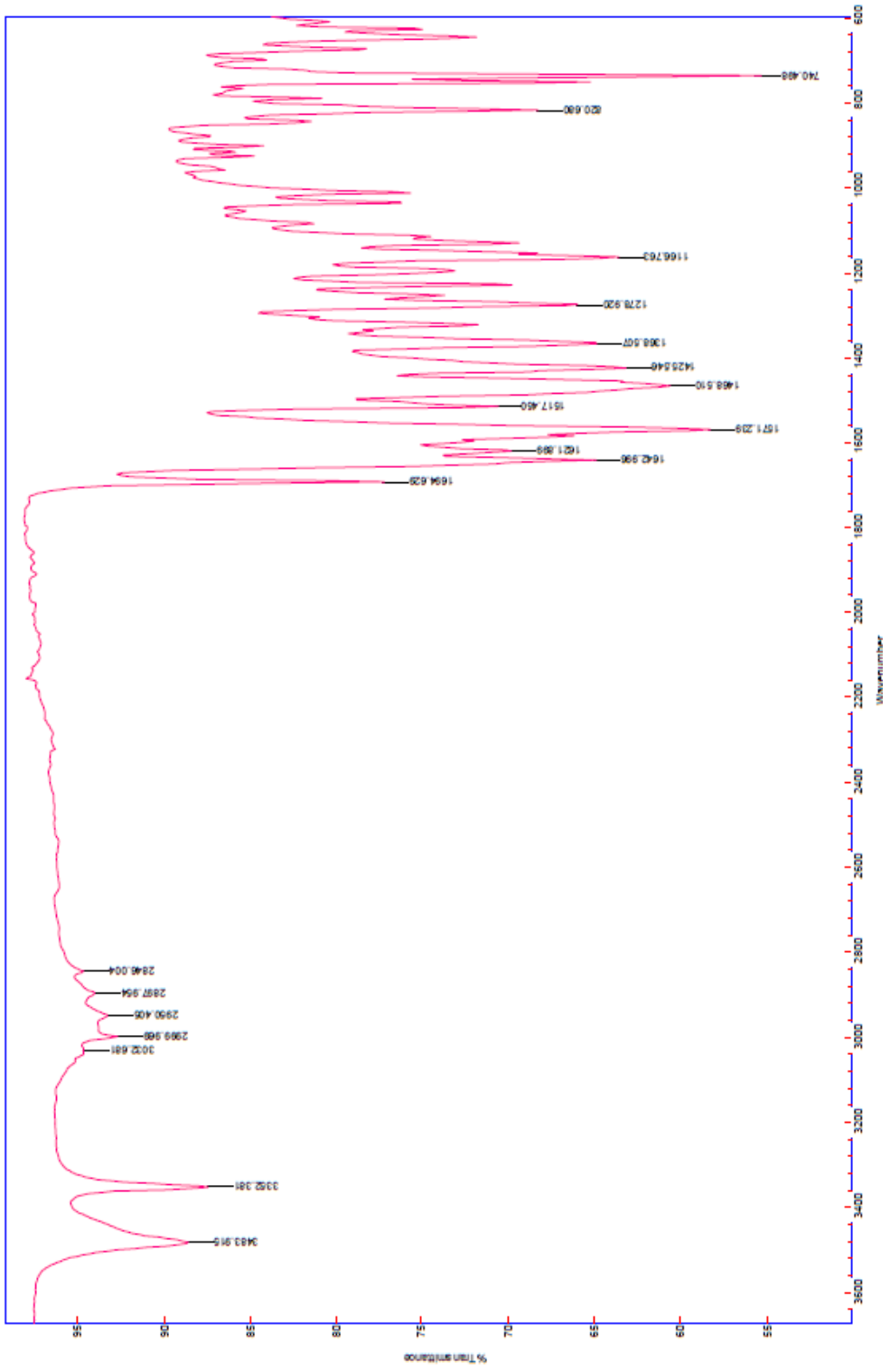


62

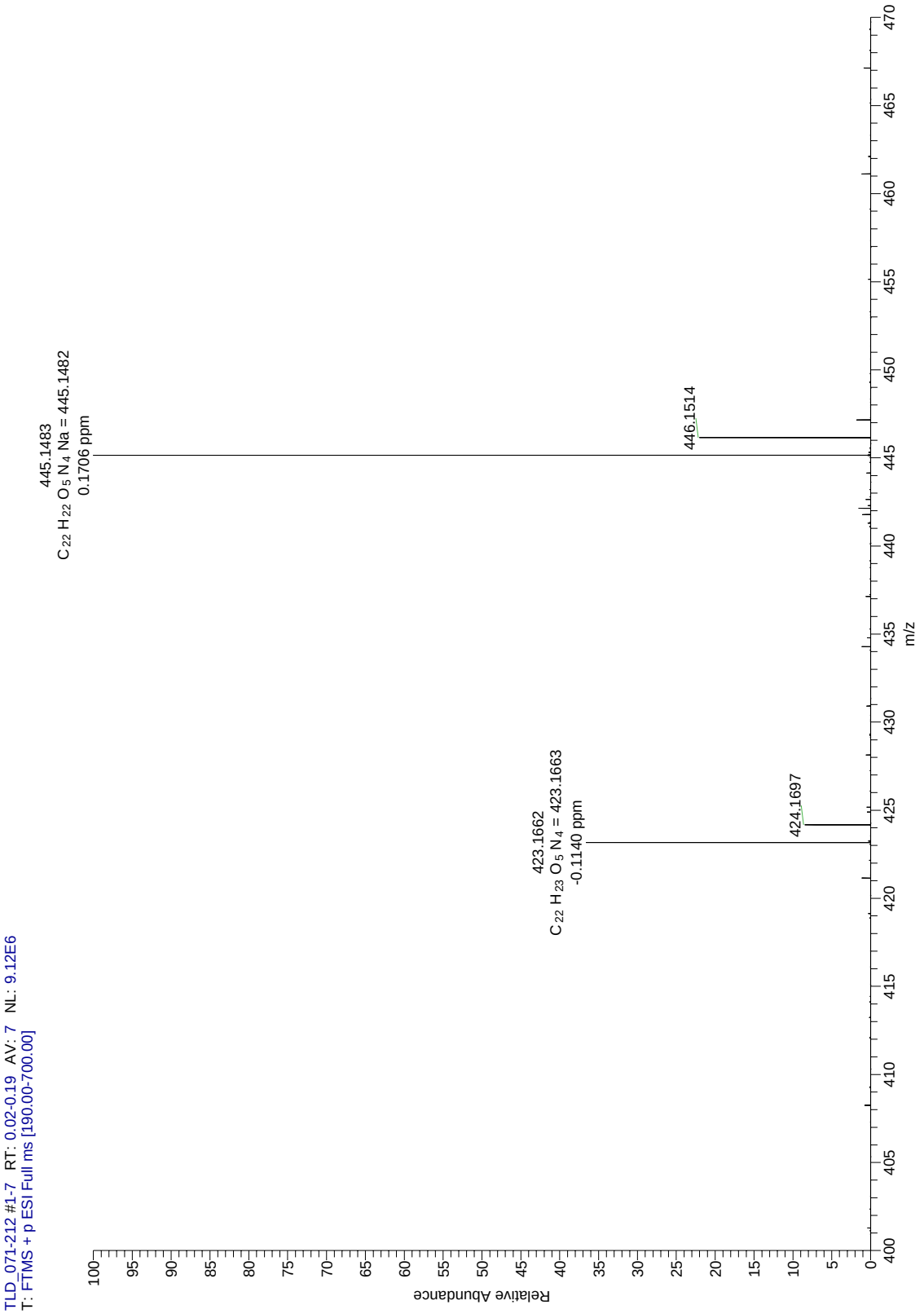
D.10.1 ^{1}H NMR spectrum of 62



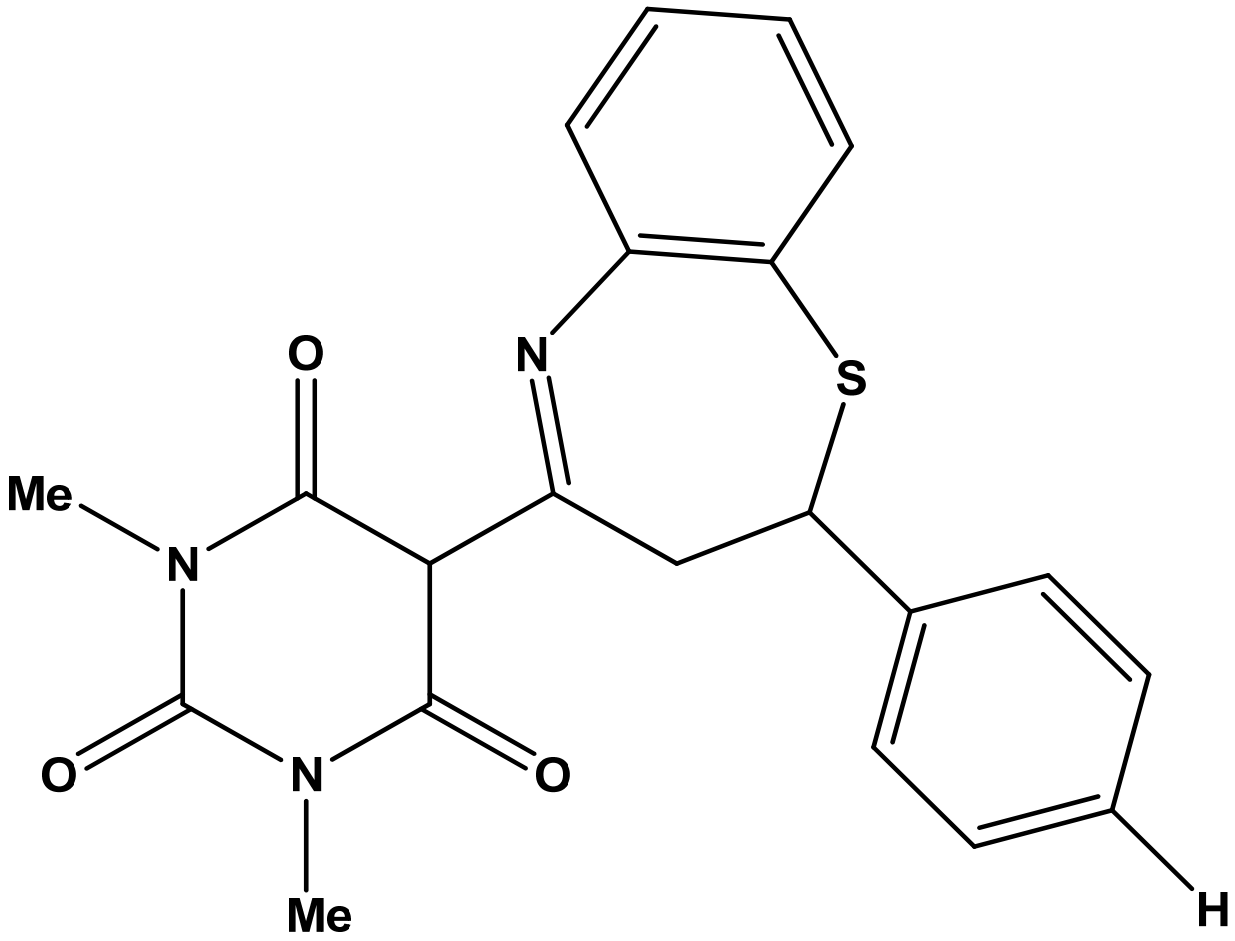
D.10.2 IR spectrum of 62



D.10.3 HRMS of 62

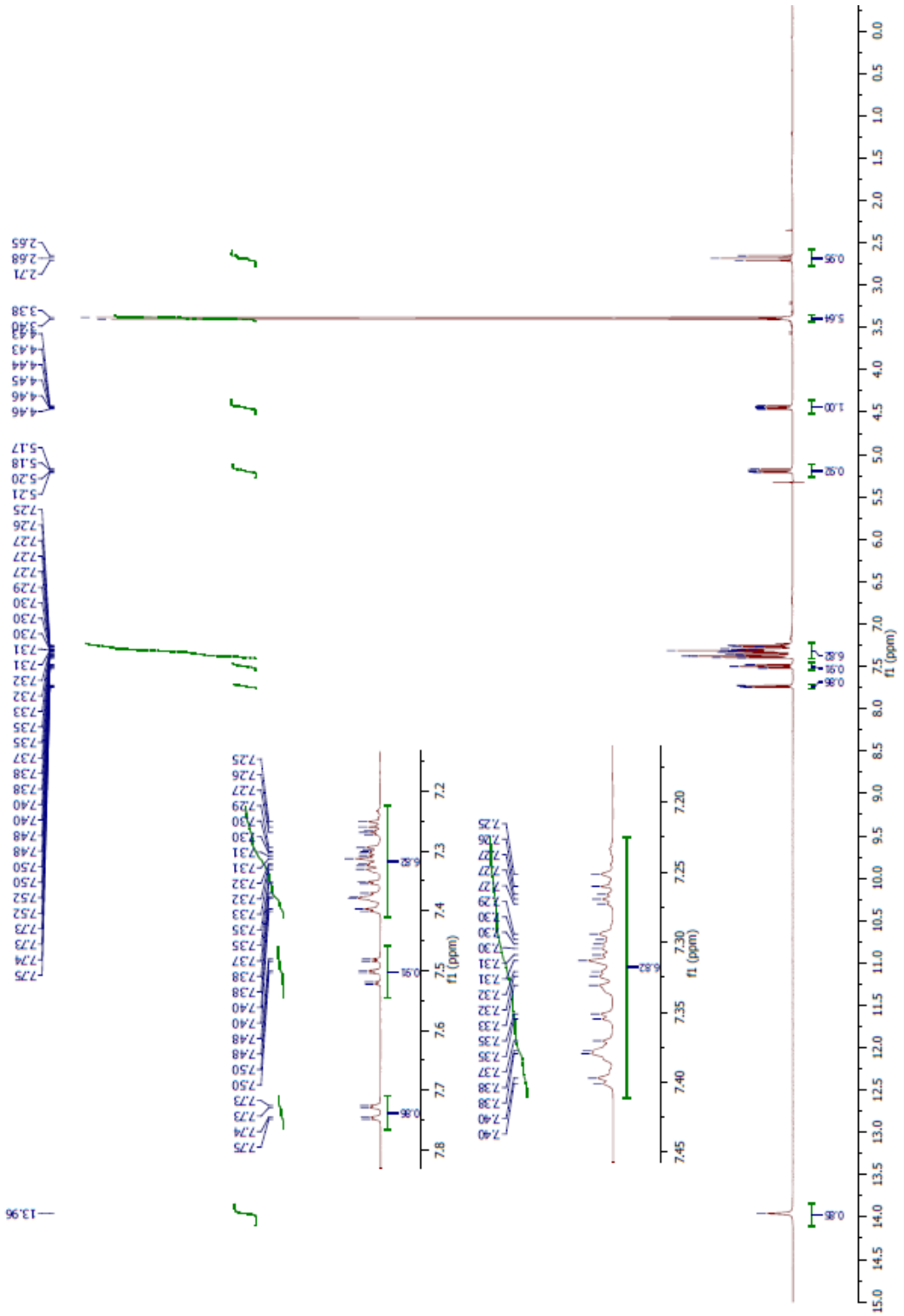


D.11 Spectroscopic data for 63

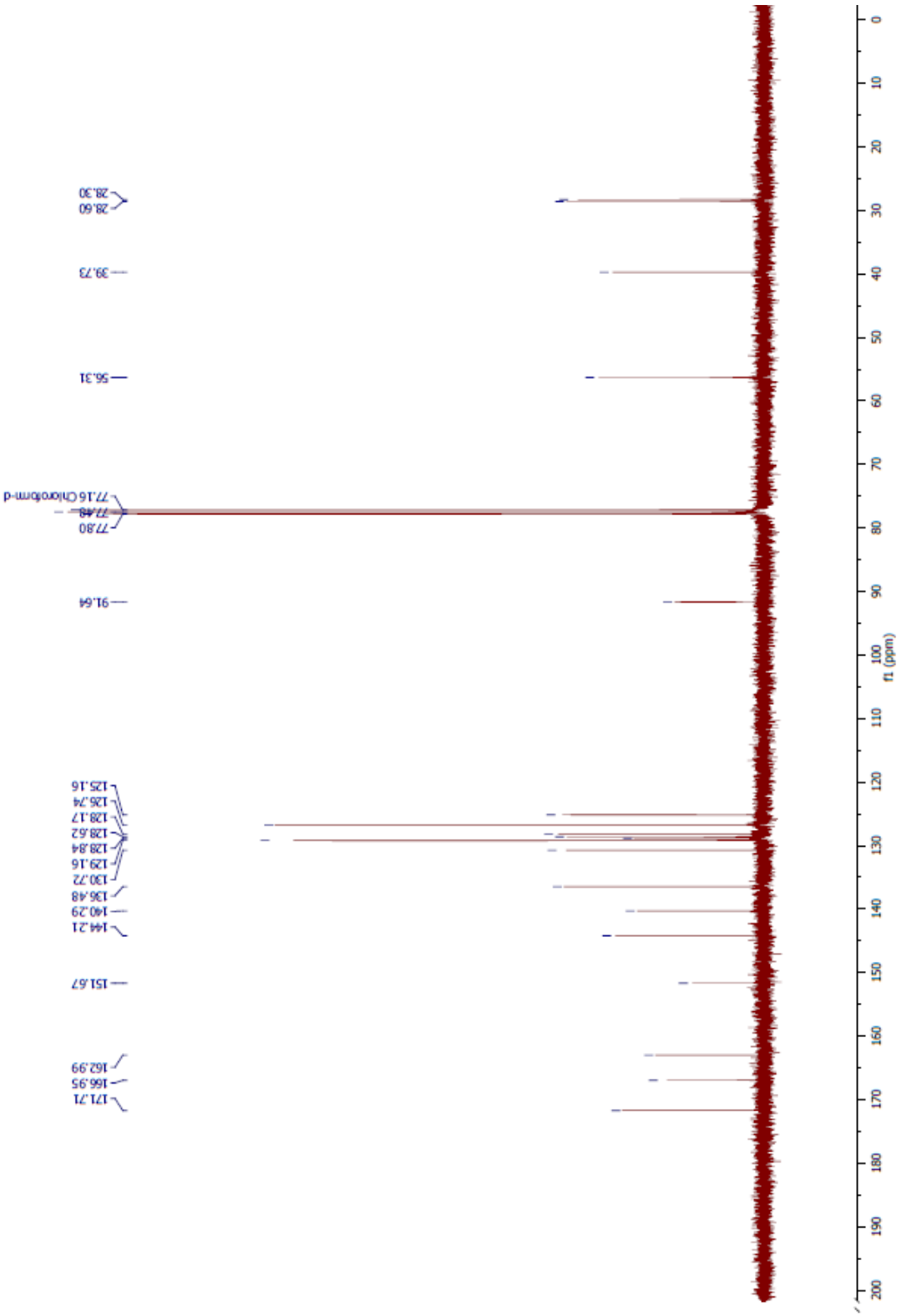


63

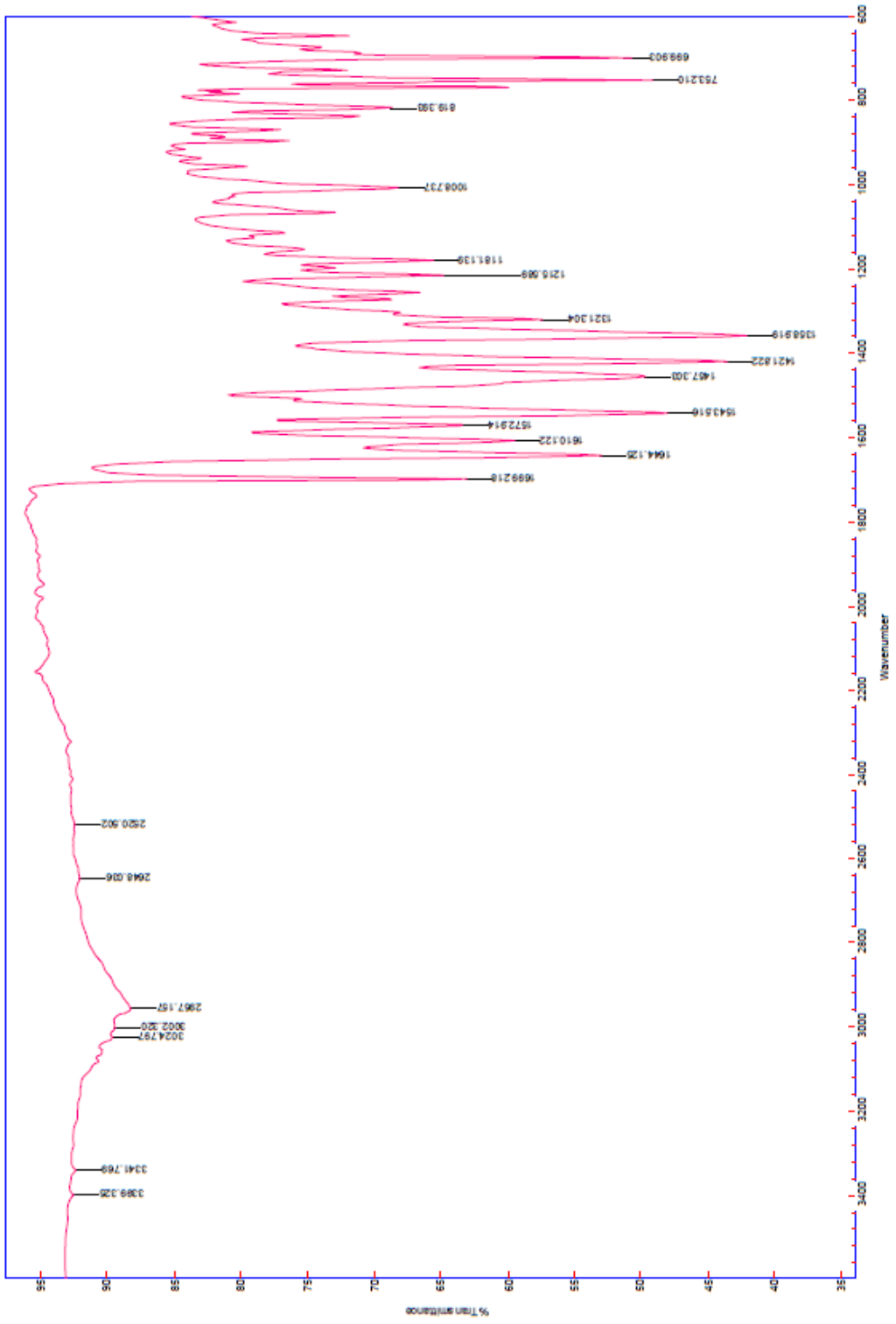
D.11.1 ^{1}H NMR spectrum of 63



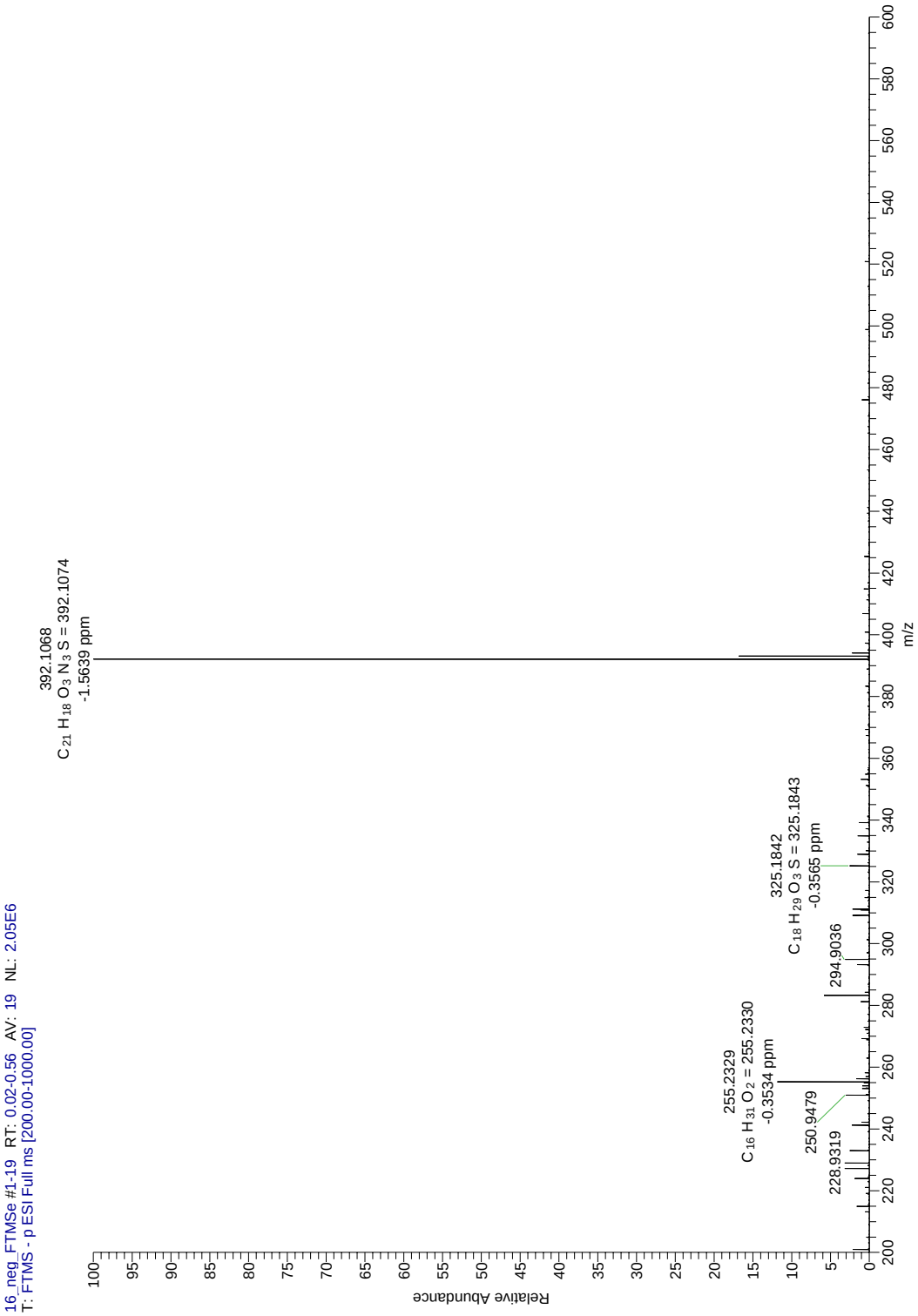
D.11.2 ^{13}C NMR spectrum of 63



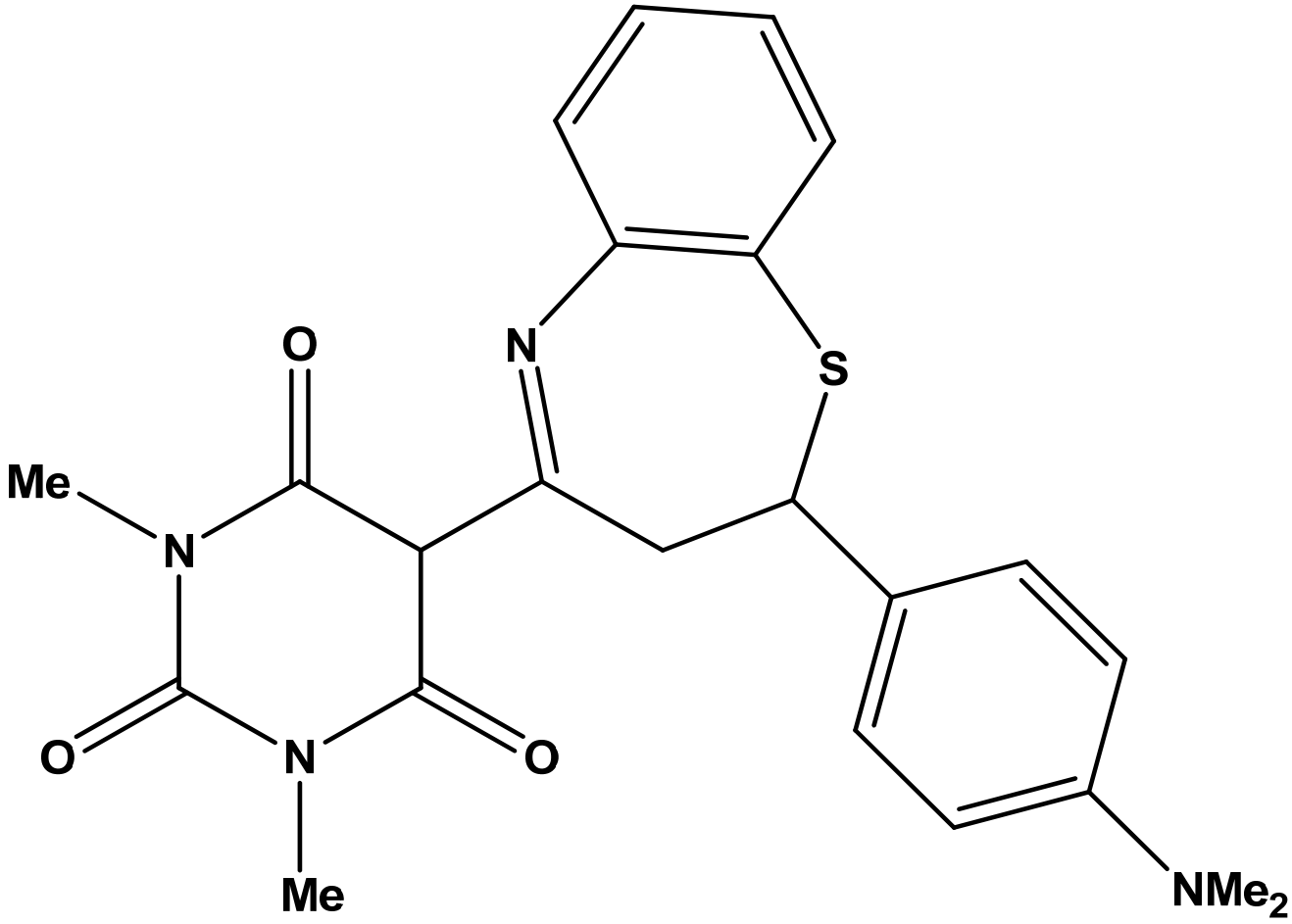
D.11.3 IR spectrum of 63



D.11.4 HRMS of 63

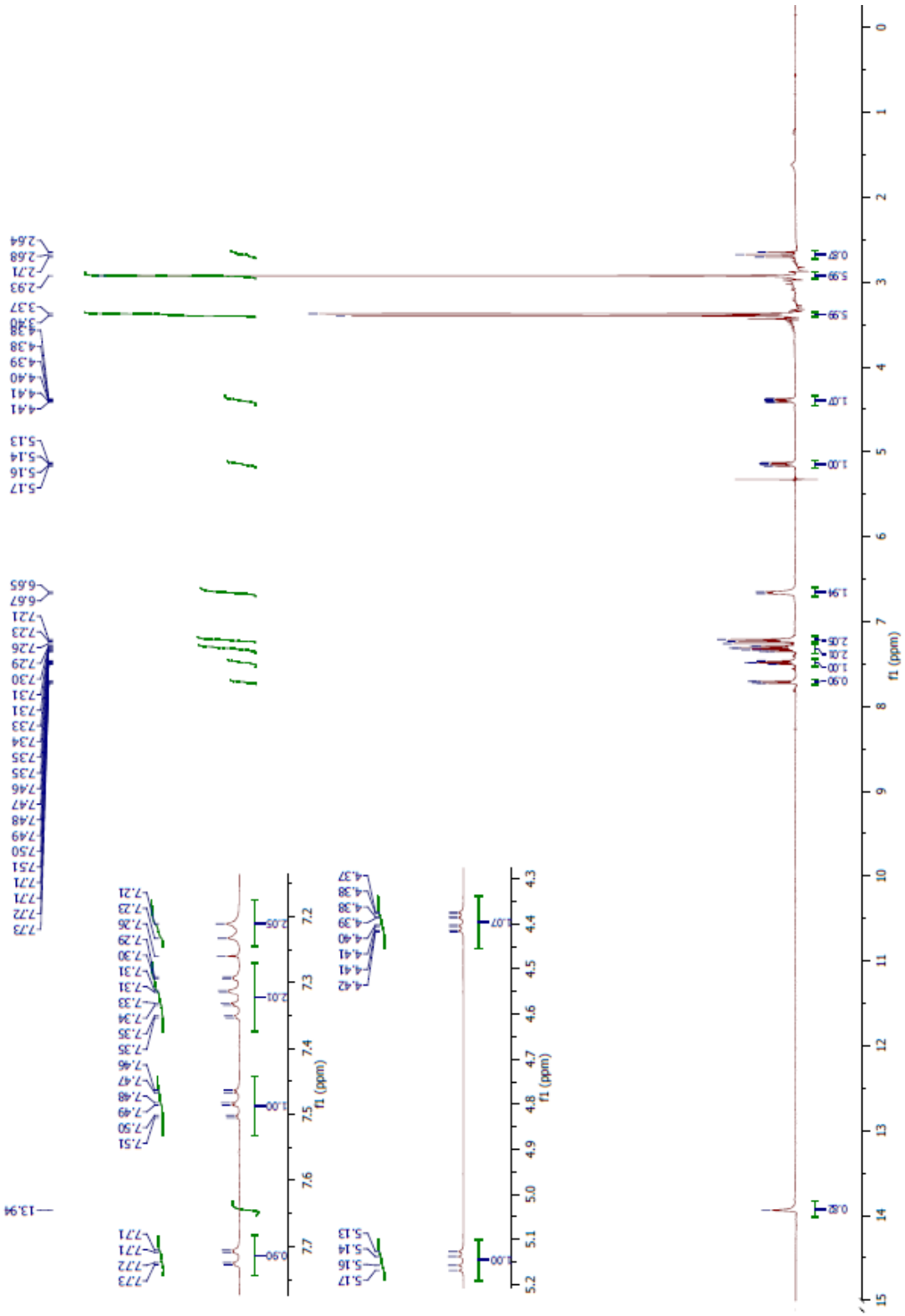


D.12 Spectroscopic data for 64

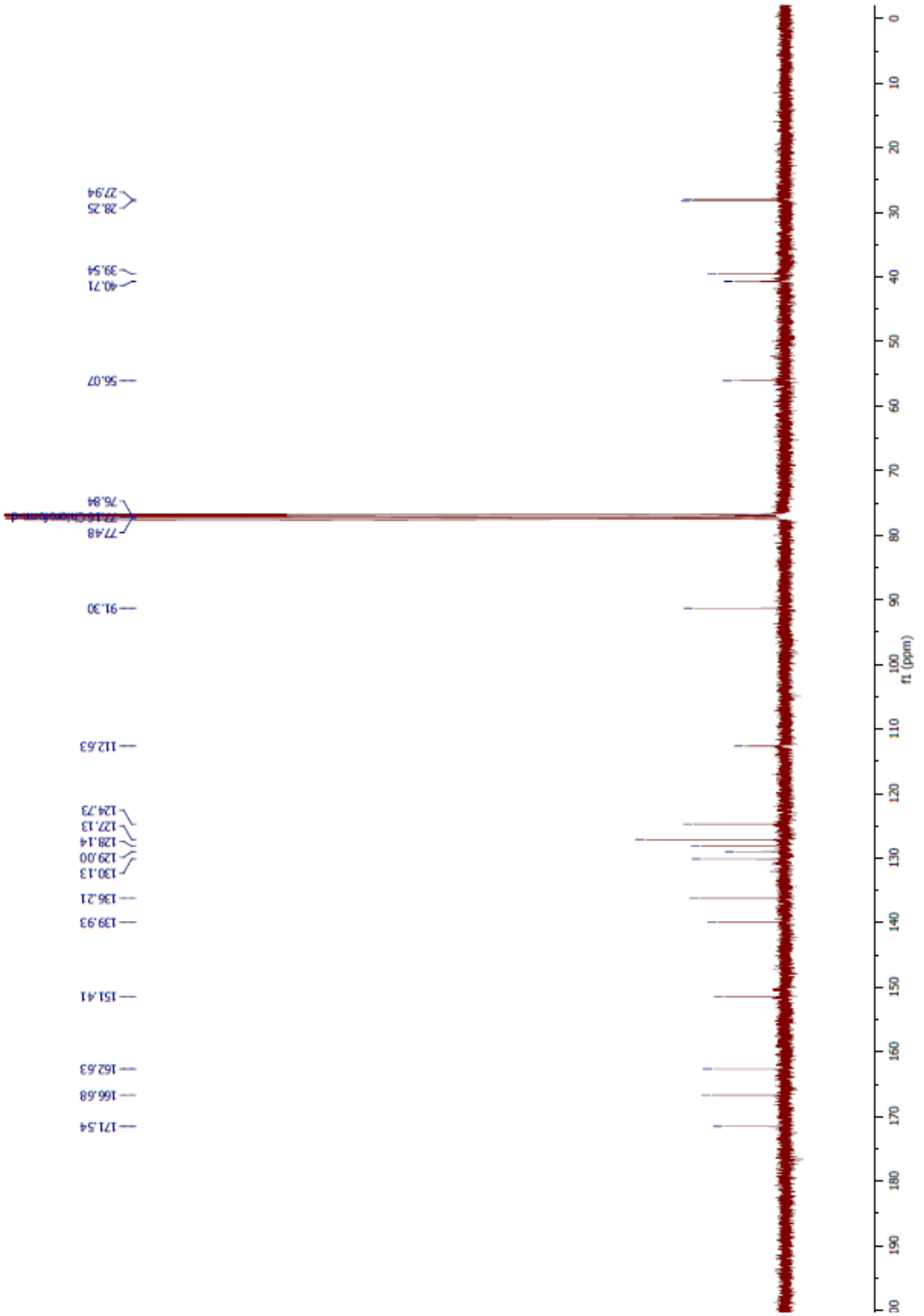


64

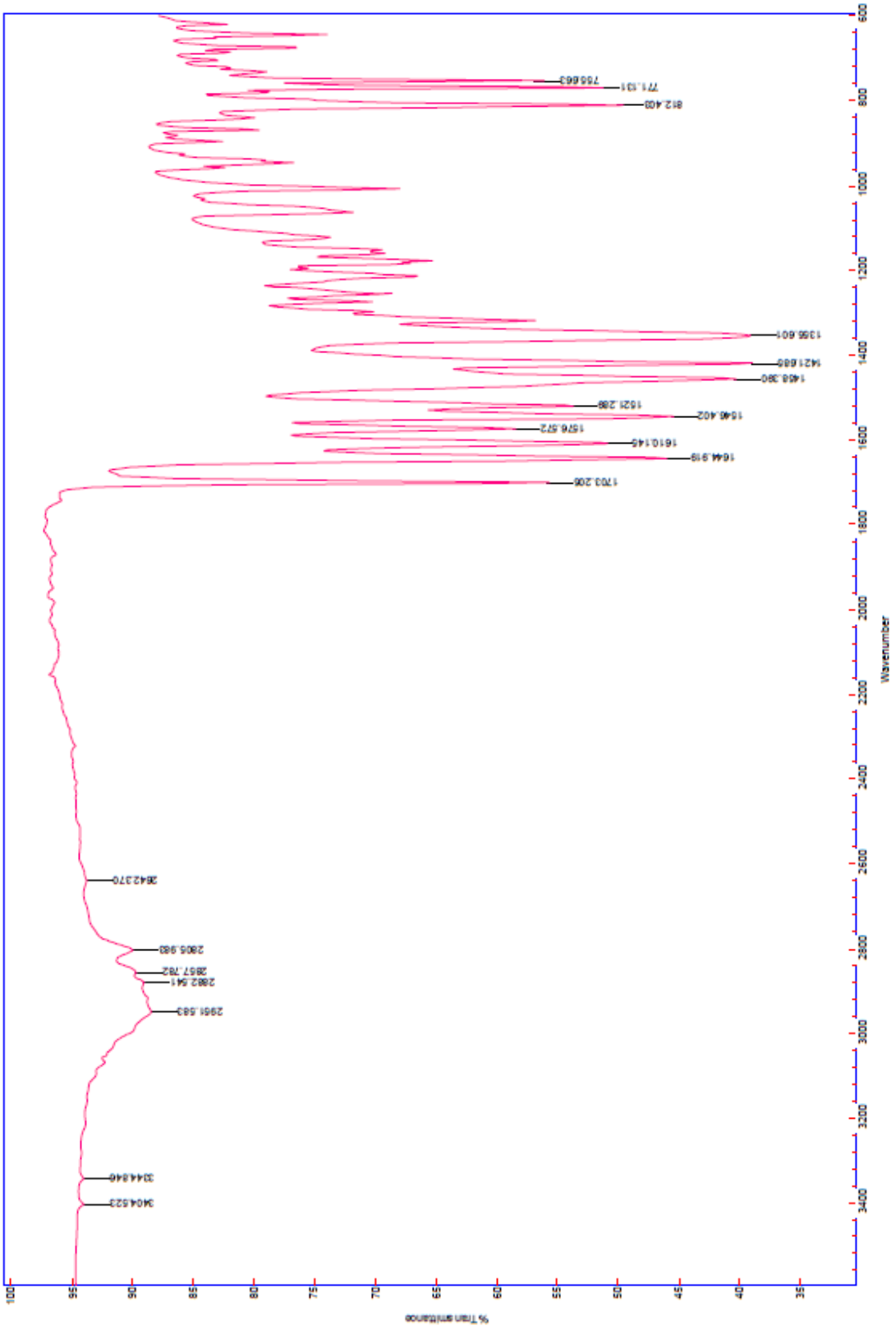
D.12.1 ^{1}H NMR spectrum of 64



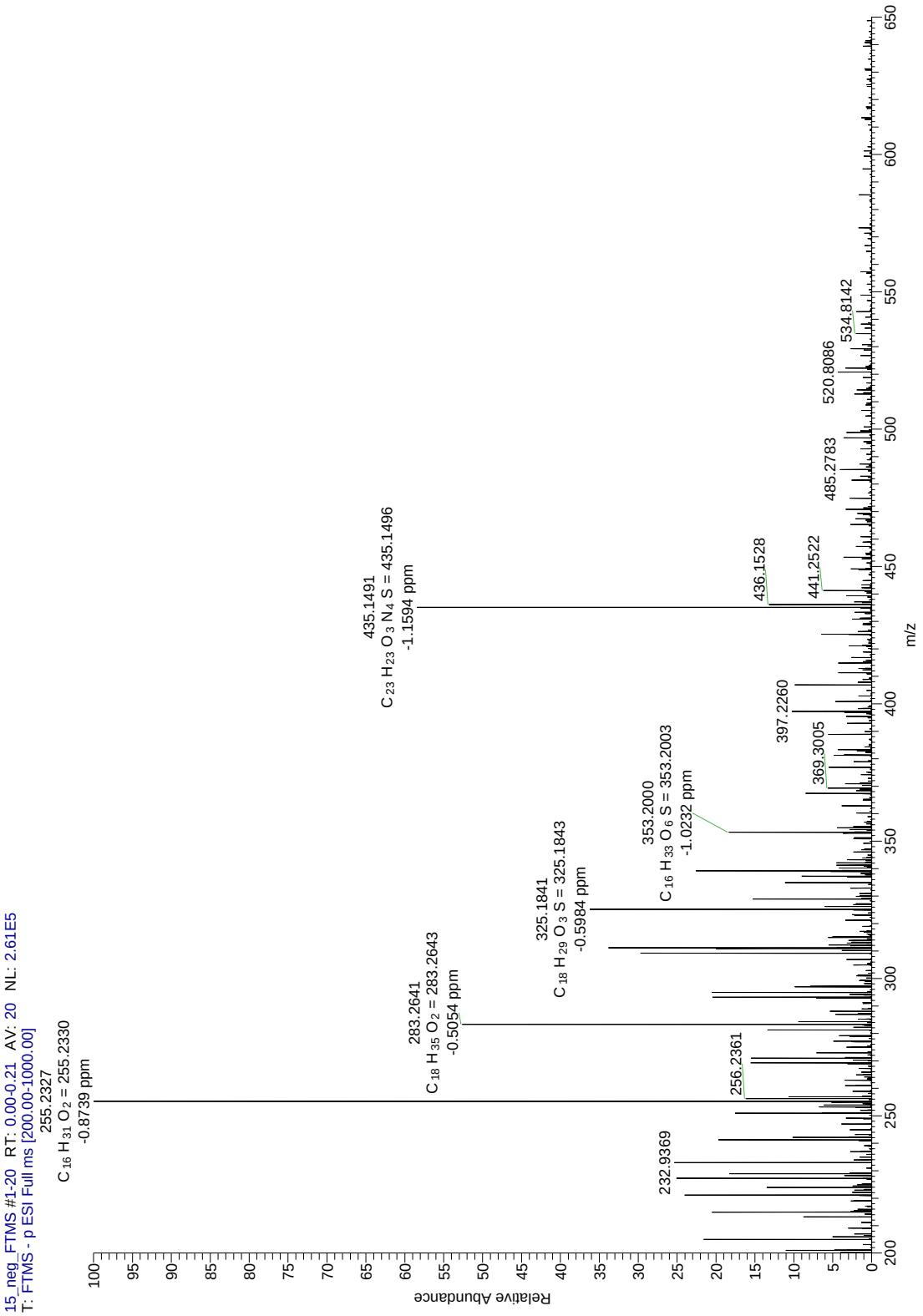
D.12.2 ^{13}C NMR spectrum of 64



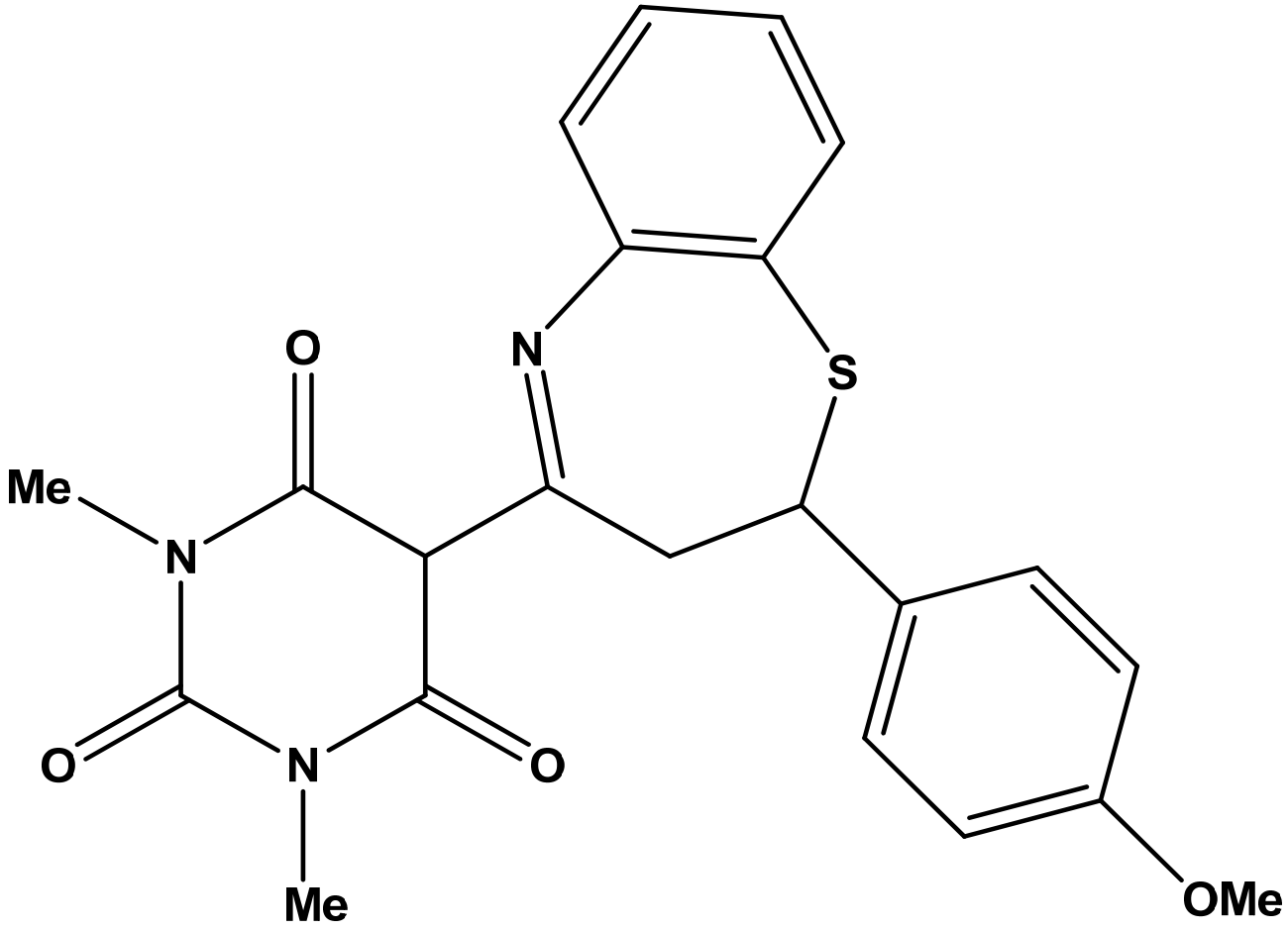
D.12.3 IR spectrum of 64



D.12.4 HRMS of 64

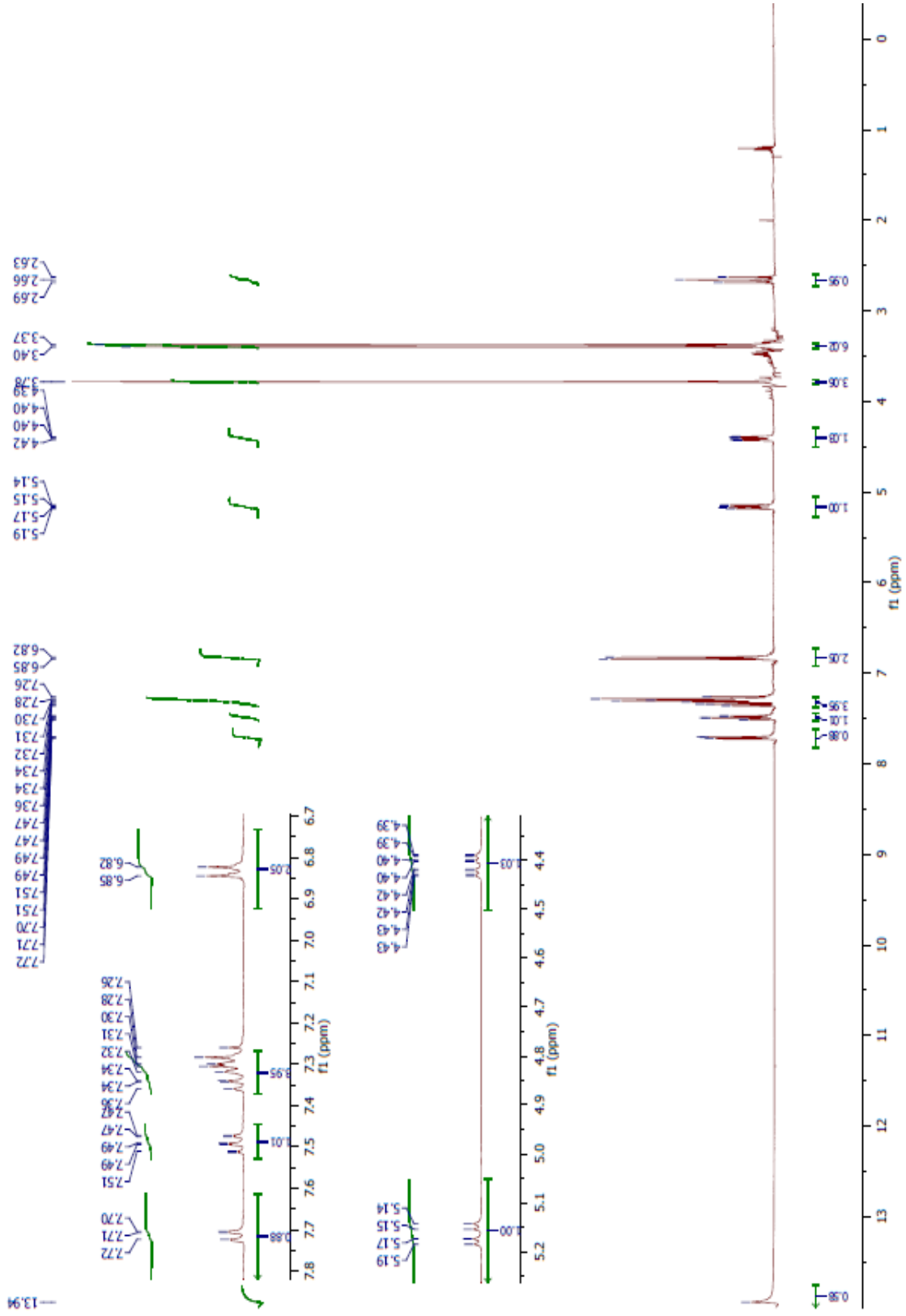


D.13 Spectroscopic data for 65

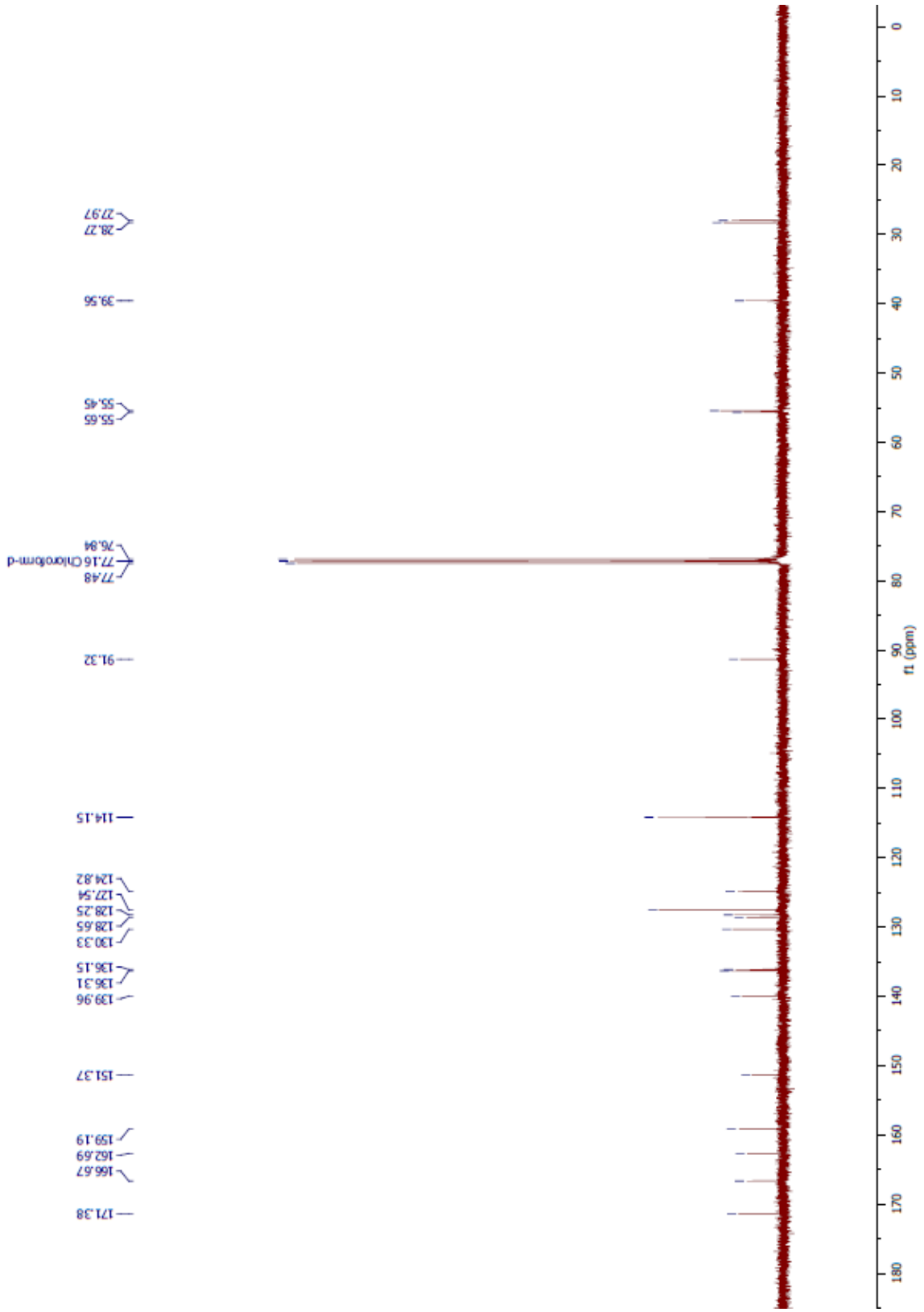


65

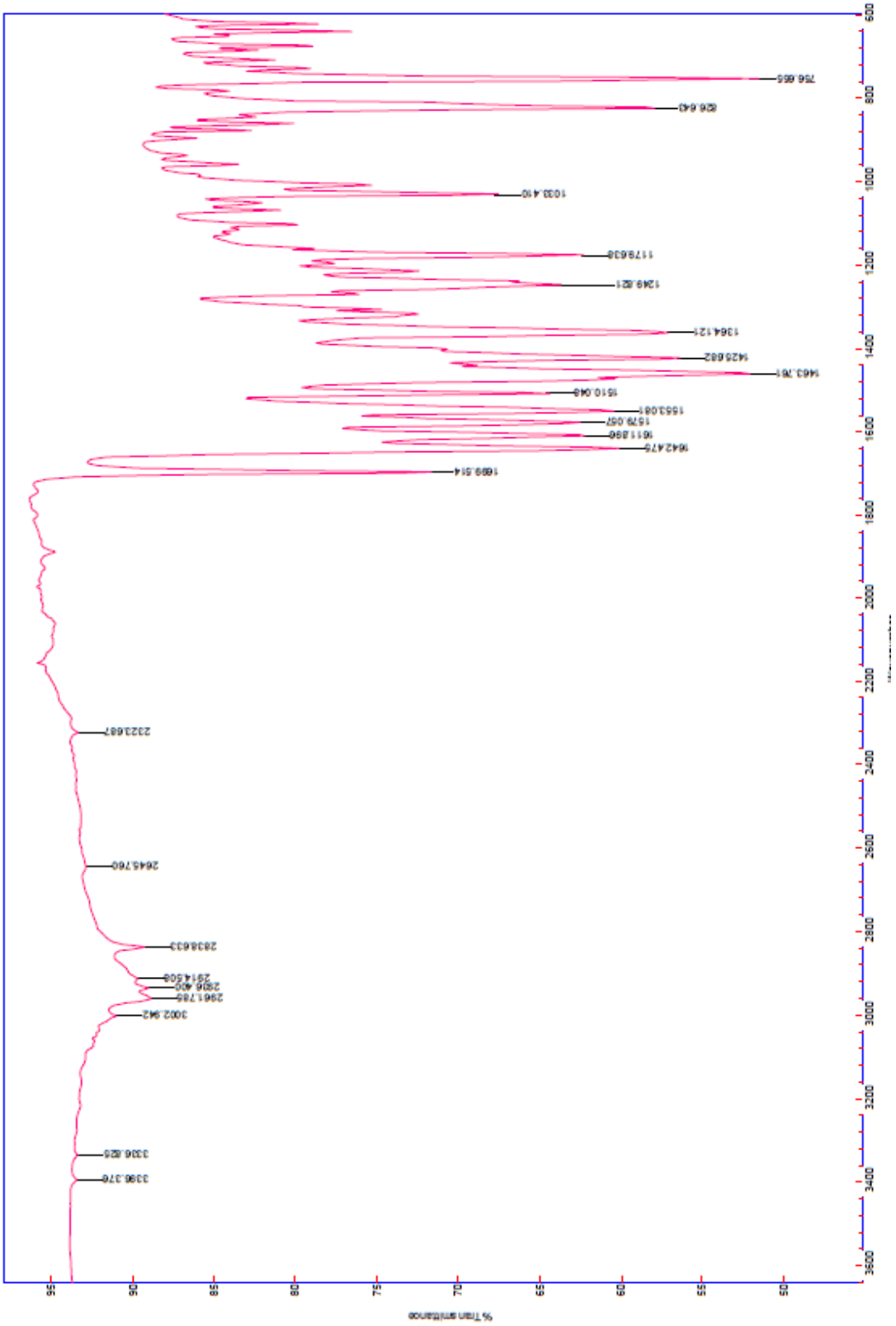
D.13.1 ^{1}H NMR spectrum of 65



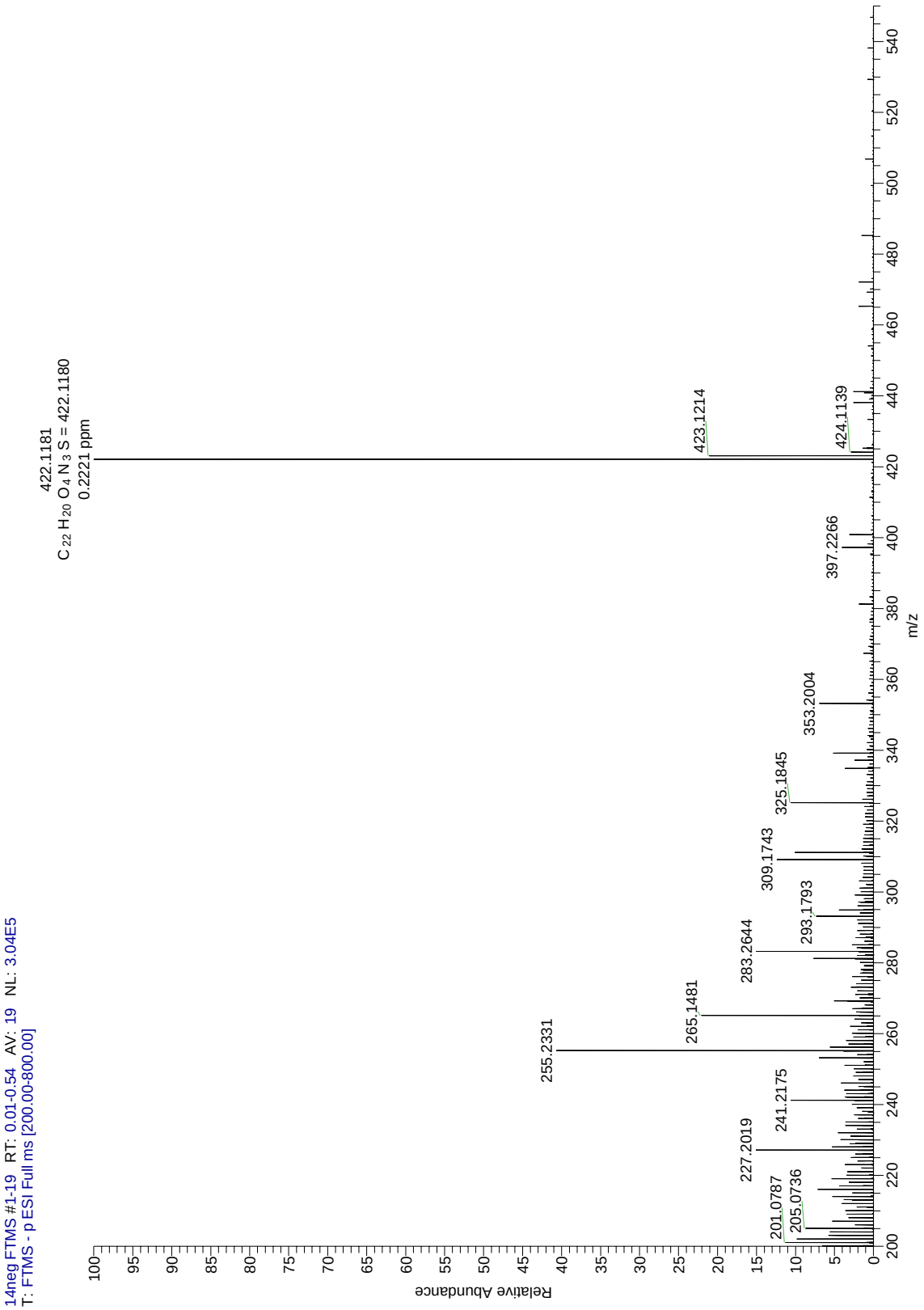
D.13.2 ^{13}C NMR spectrum of 65



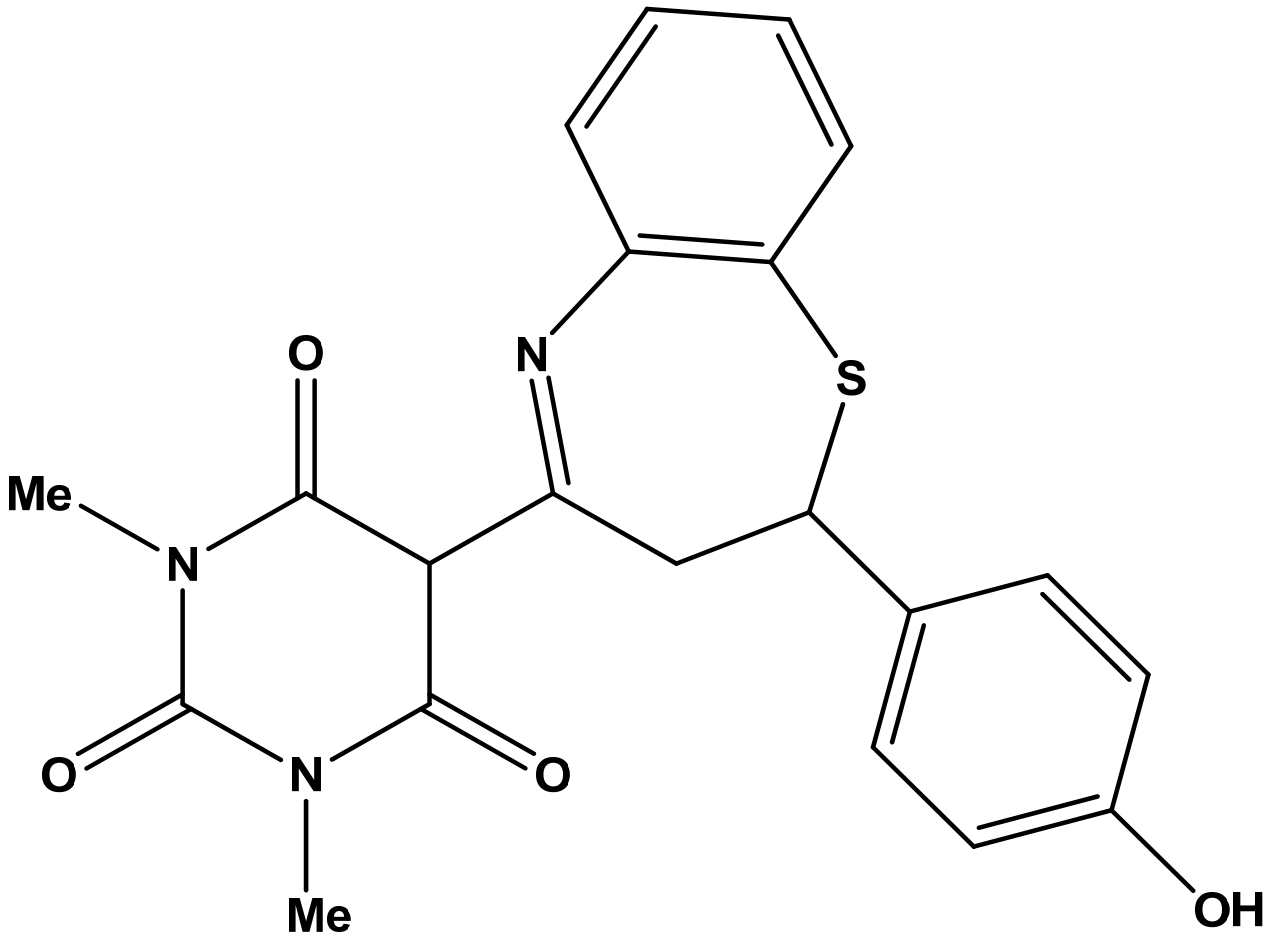
D.13.3 IR spectrum of 65



D.13.4 HRMS of 65

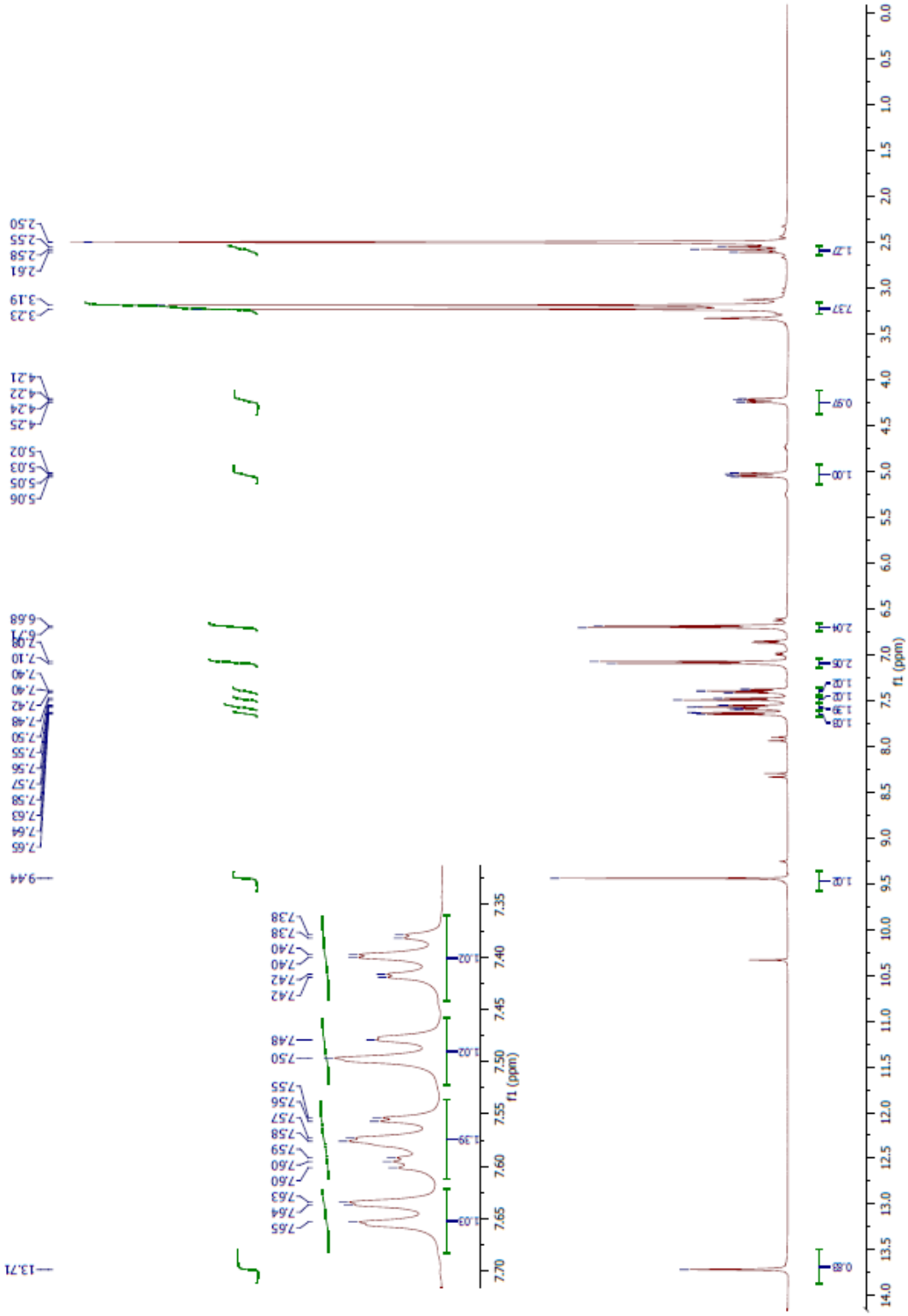


D.14 Spectroscopic data for 66

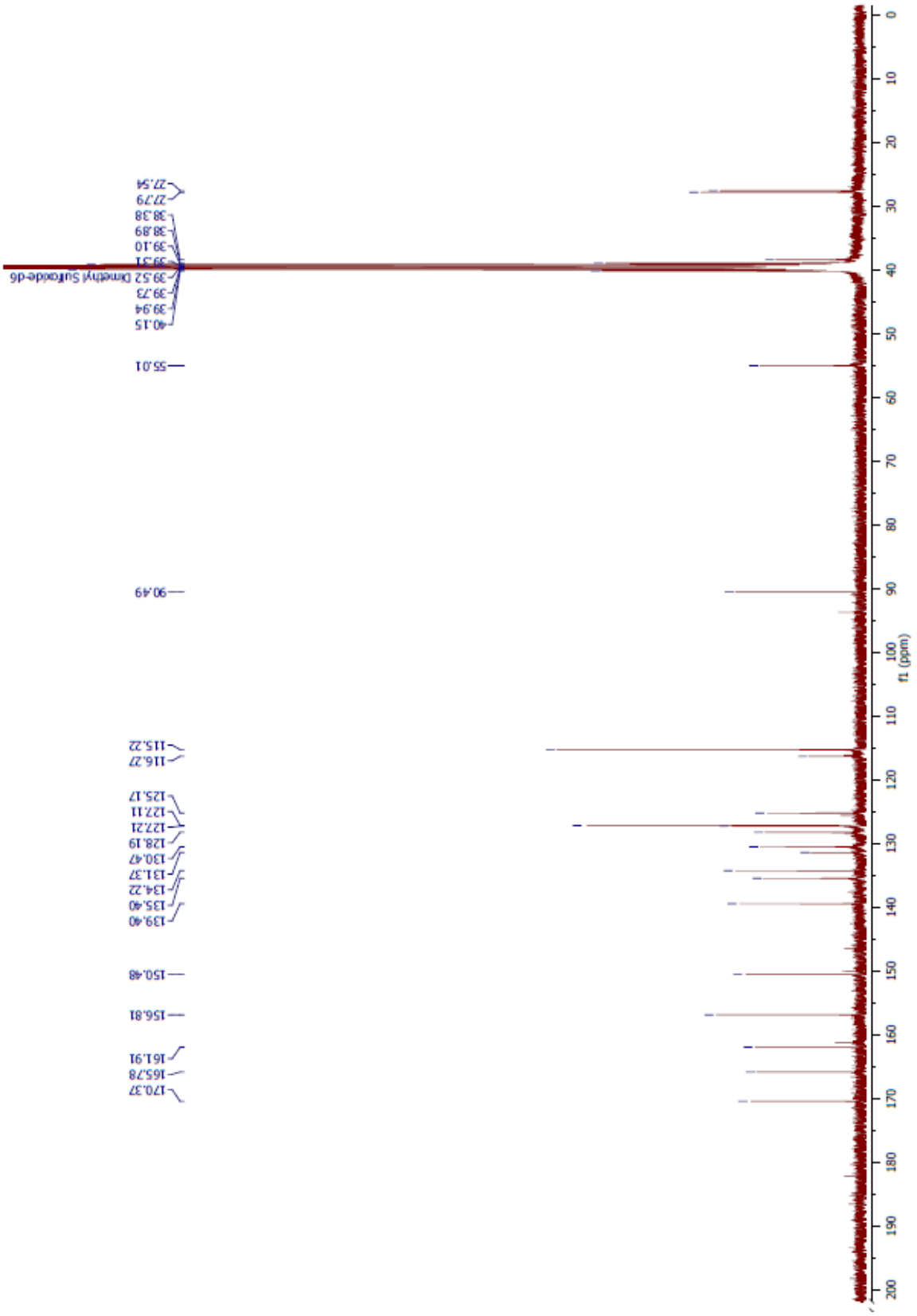


66

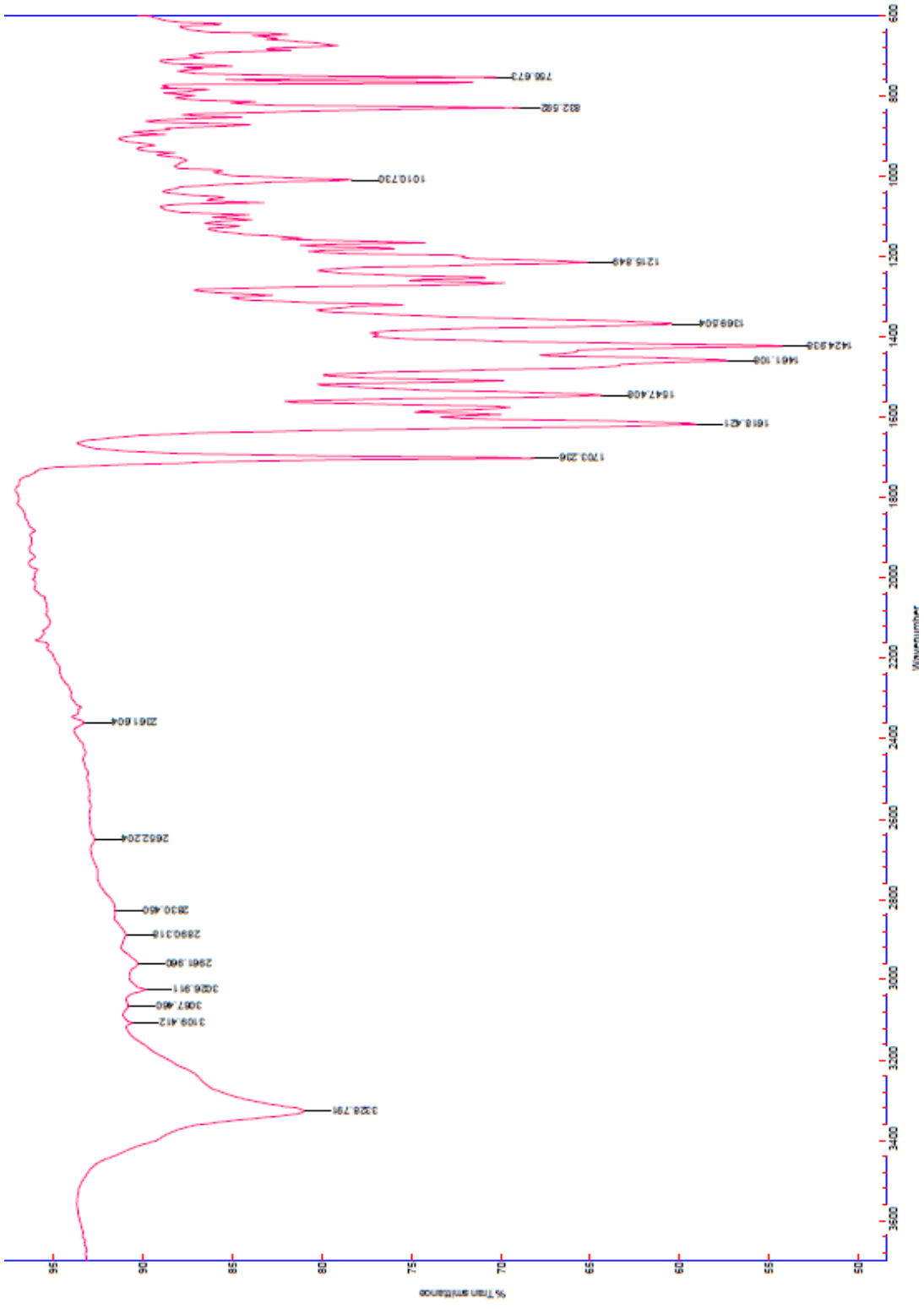
D.14.1 ^{1}H NMR spectrum of 66



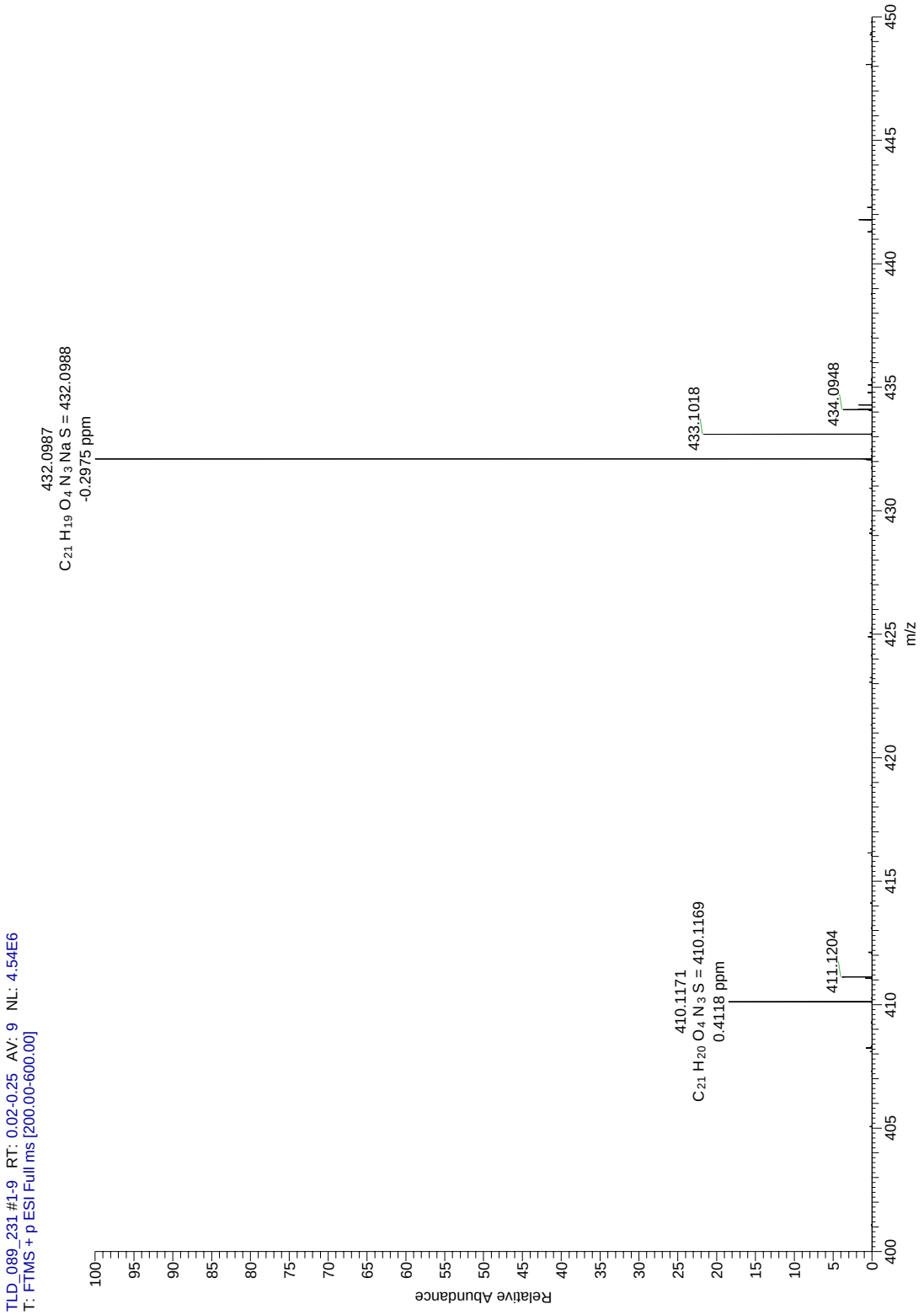
D.14.2 ^{13}C NMR spectrum of 66



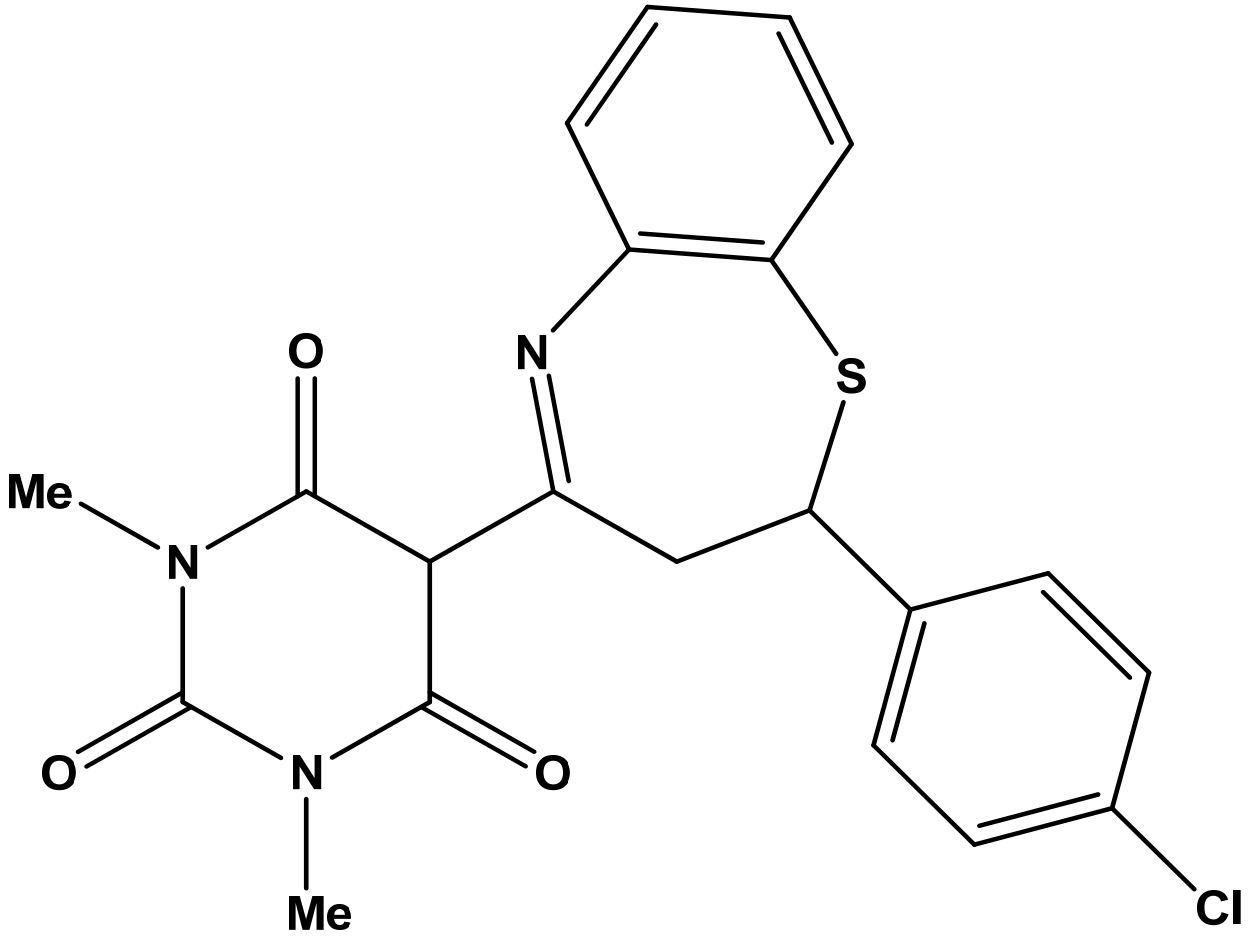
D.14.3 IR spectrum of 66



D.14.4 HRMS of 66

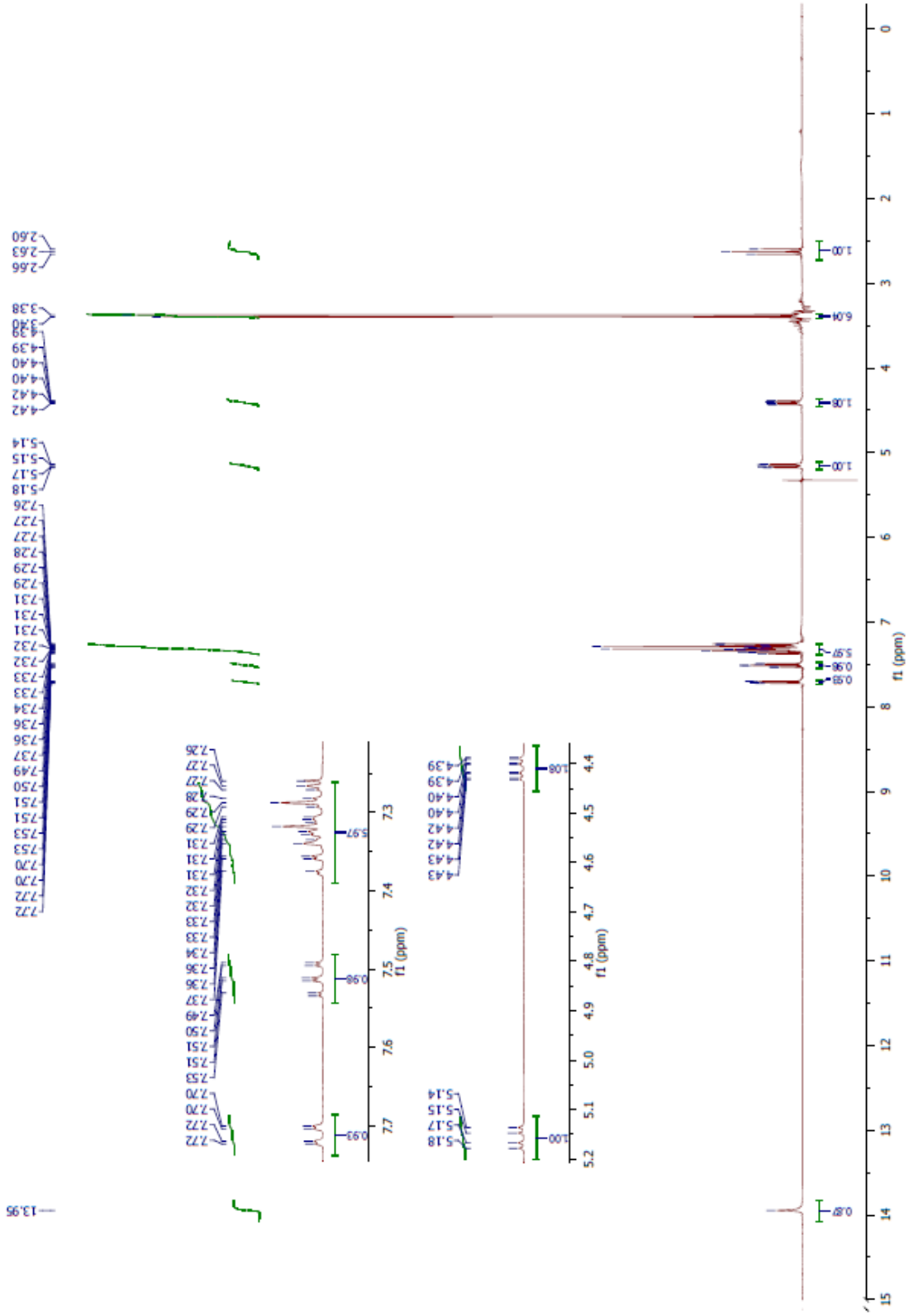


D.15 Spectroscopic data for 67

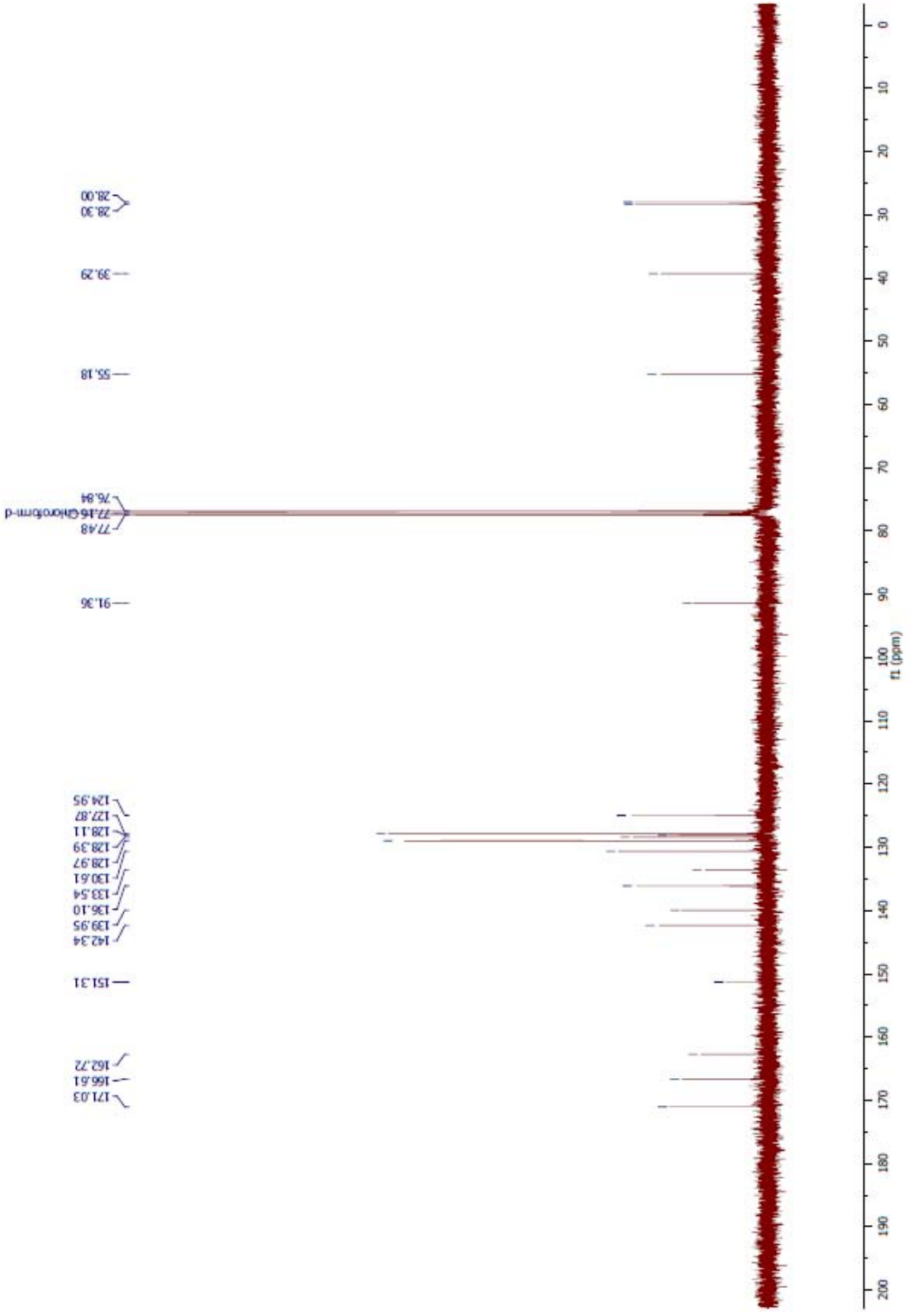


67

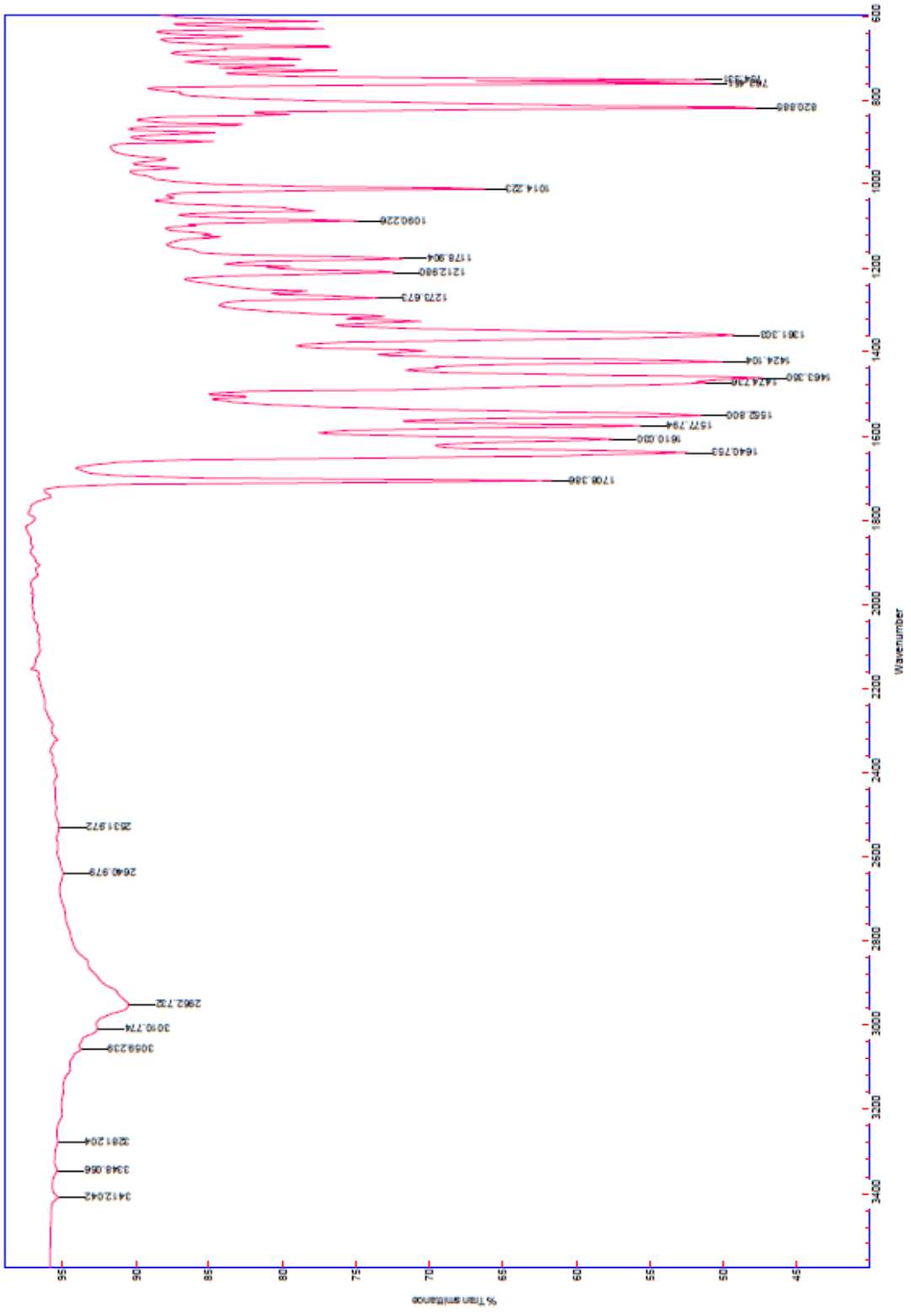
D.15.1 ^{1}H NMR spectrum of 67



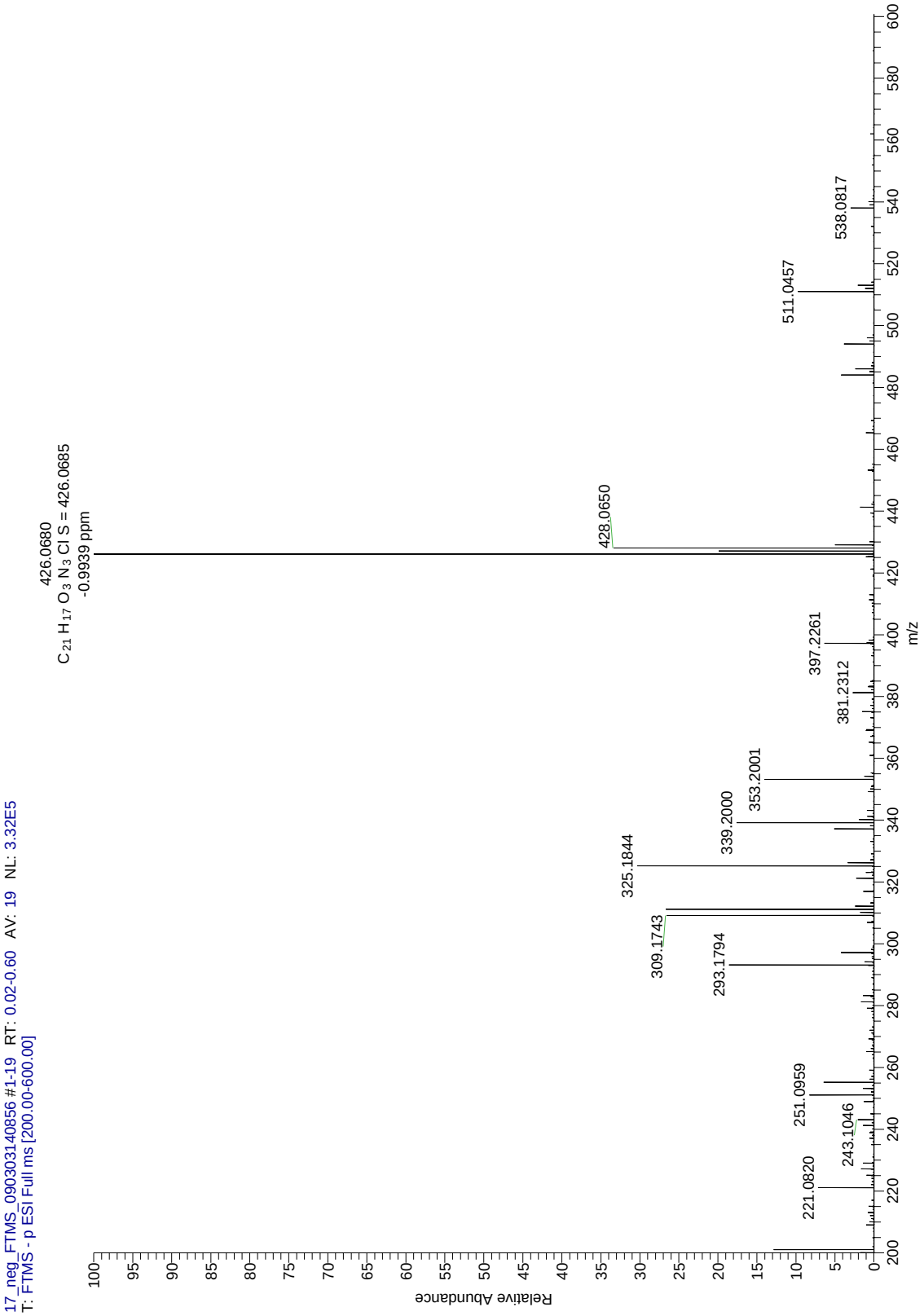
D.15.2 ^{13}C NMR spectrum of 67



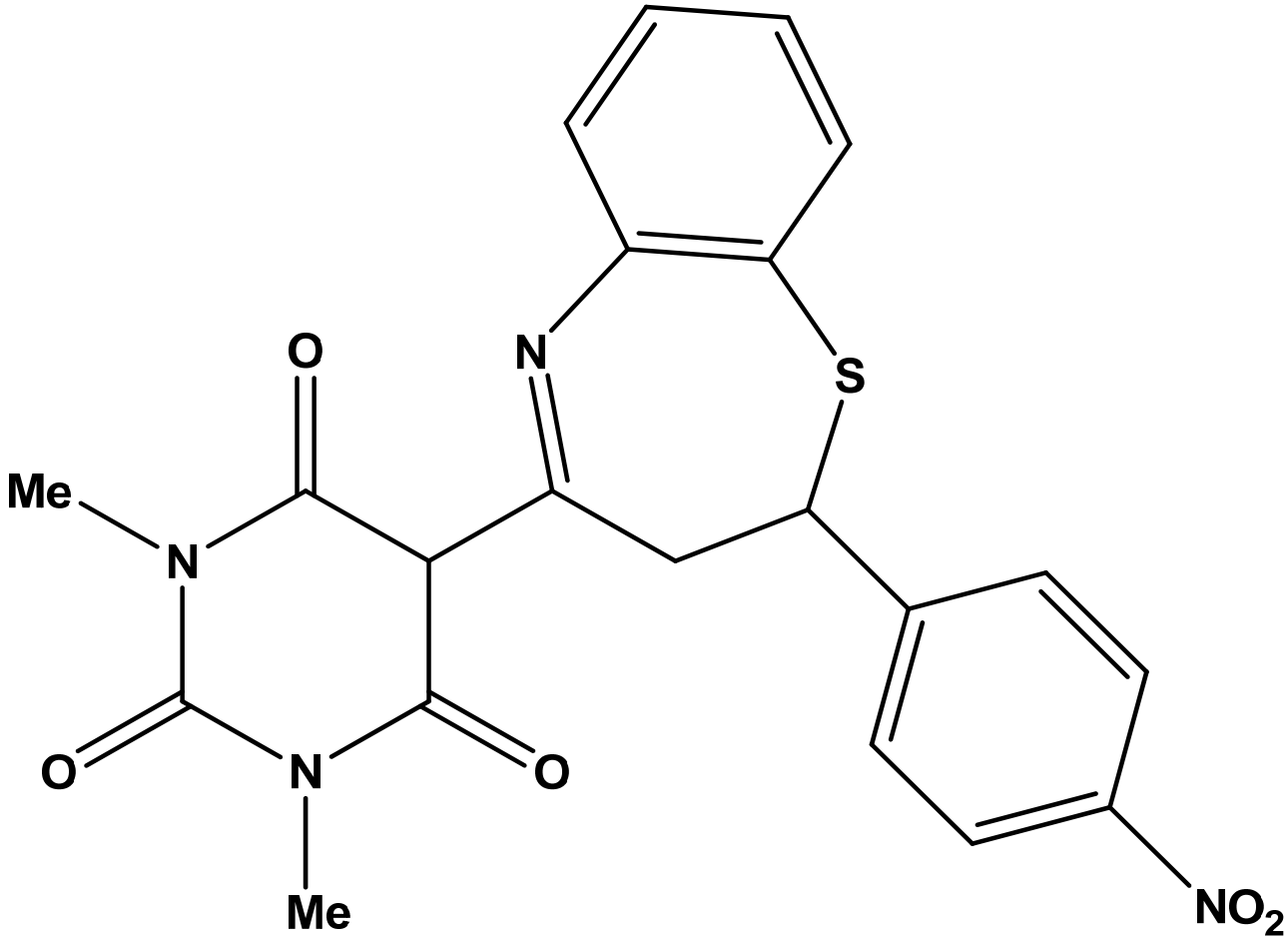
D.15.3 IR spectrum of 67



D.15.4 HRMS of 67

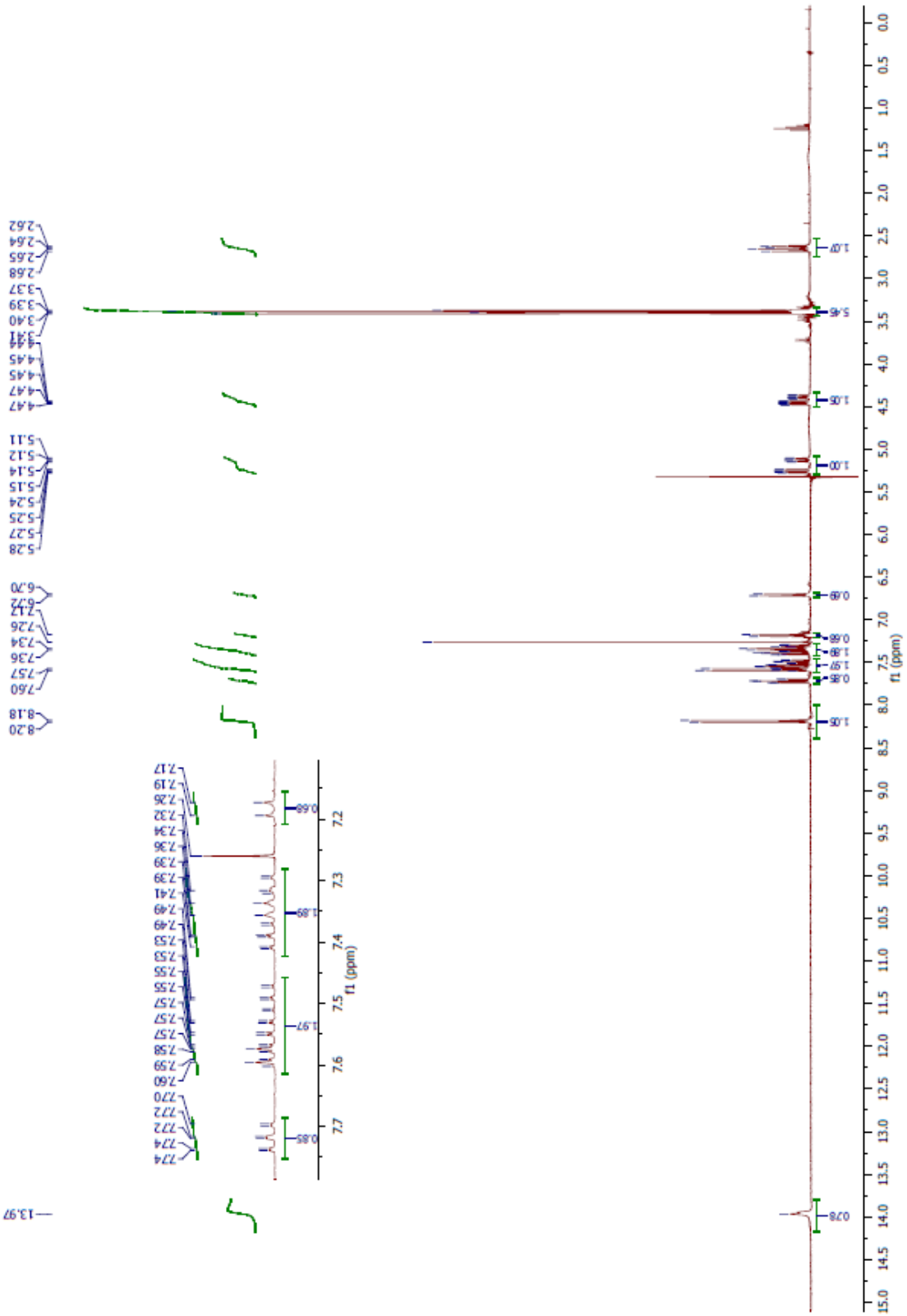


D.16 Spectroscopic data for 68

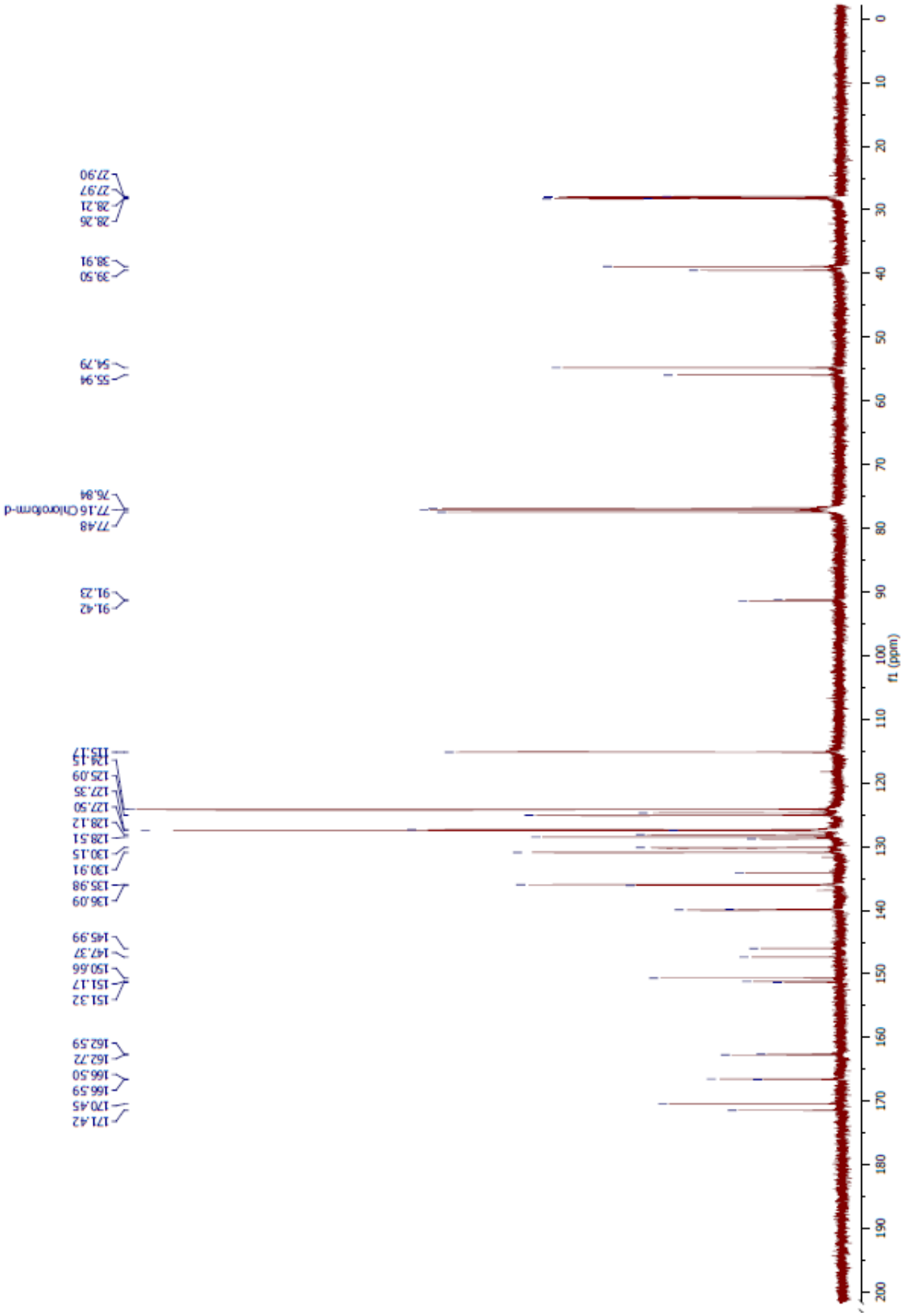


68

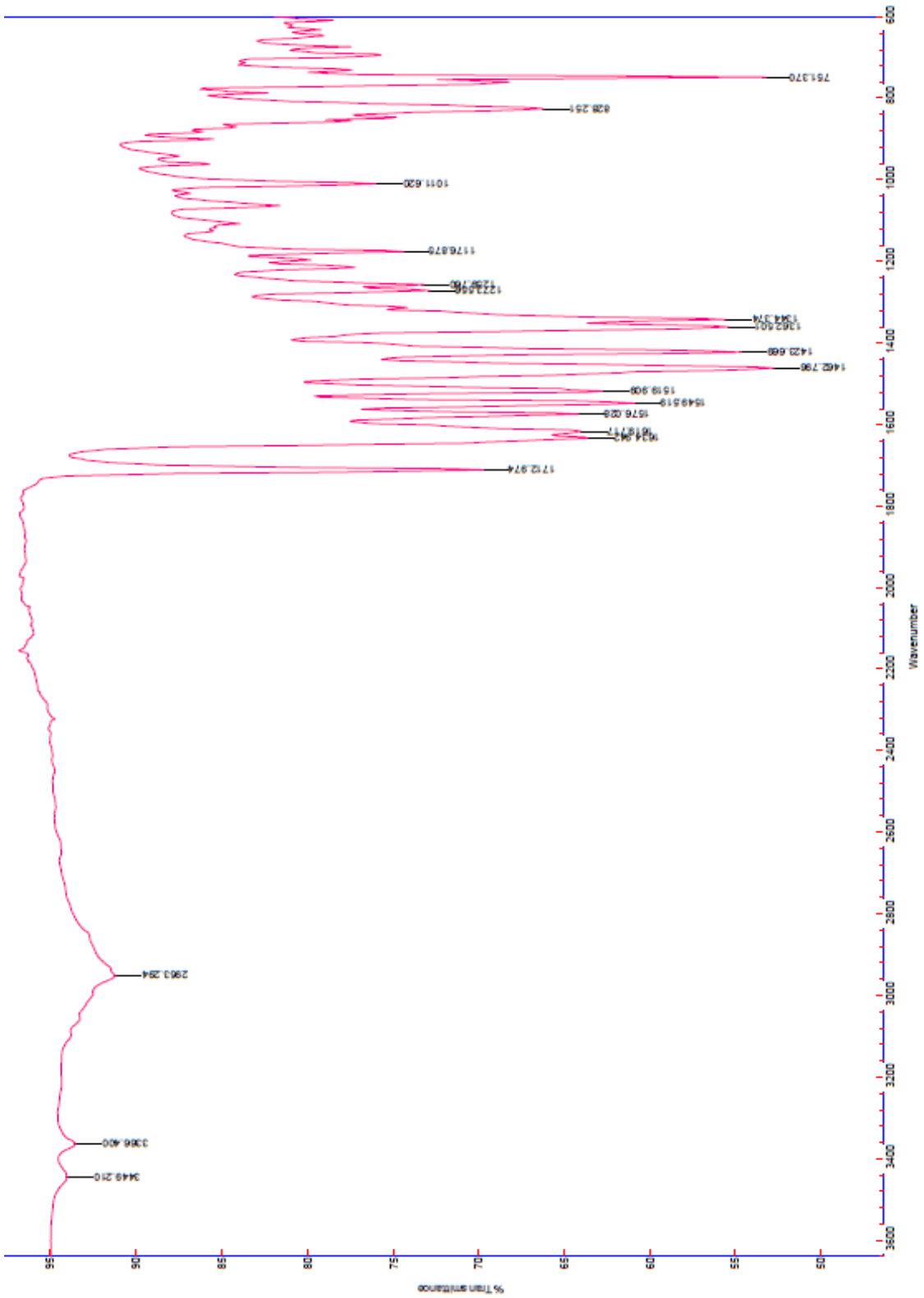
D.16.1 ^{1}H NMR spectrum of 68



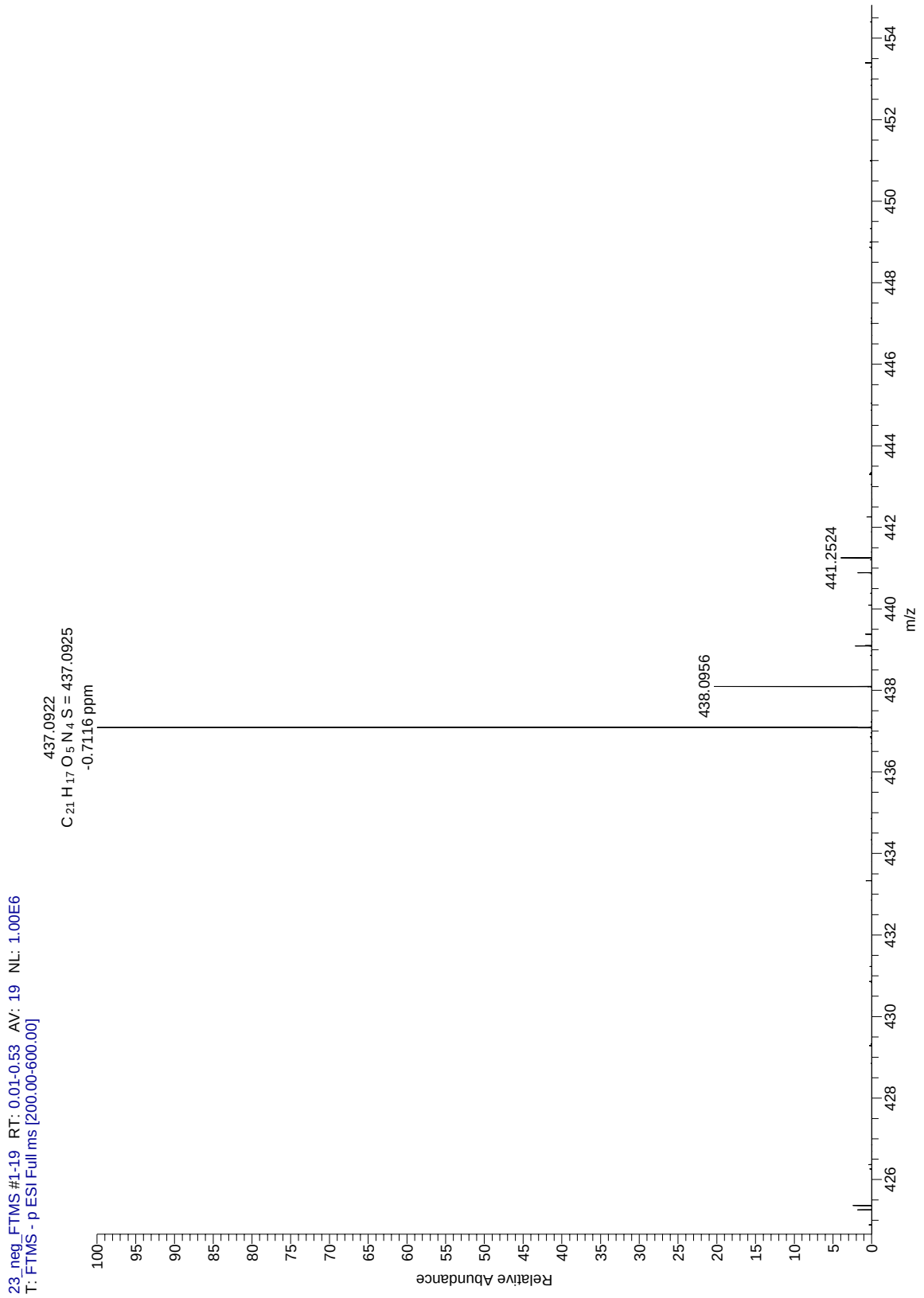
D.16.2 ^{13}C NMR spectrum of 68



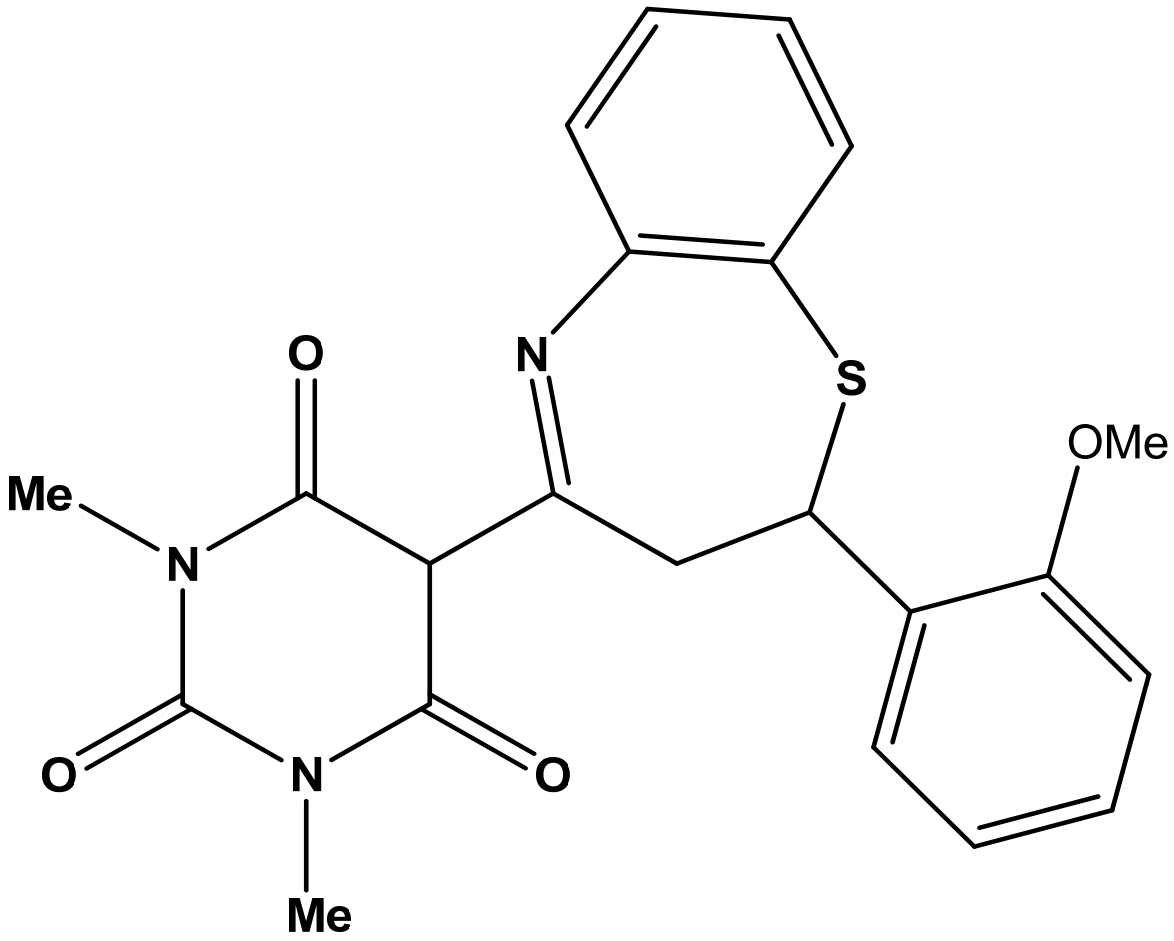
D.16.3 IR spectrum of 68



D.16.4 HRMS of 68

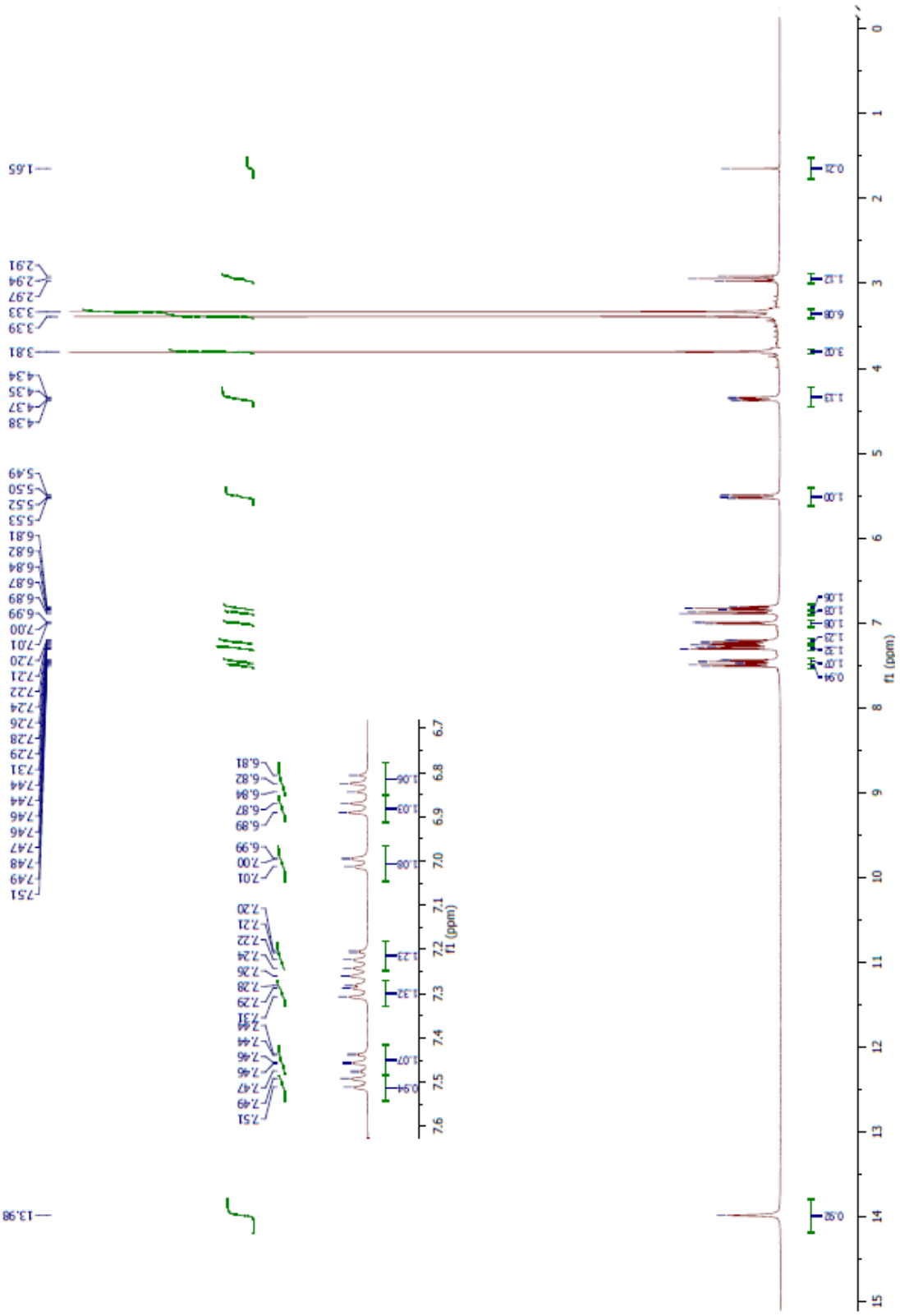


D.17 Spectroscopic data for 69

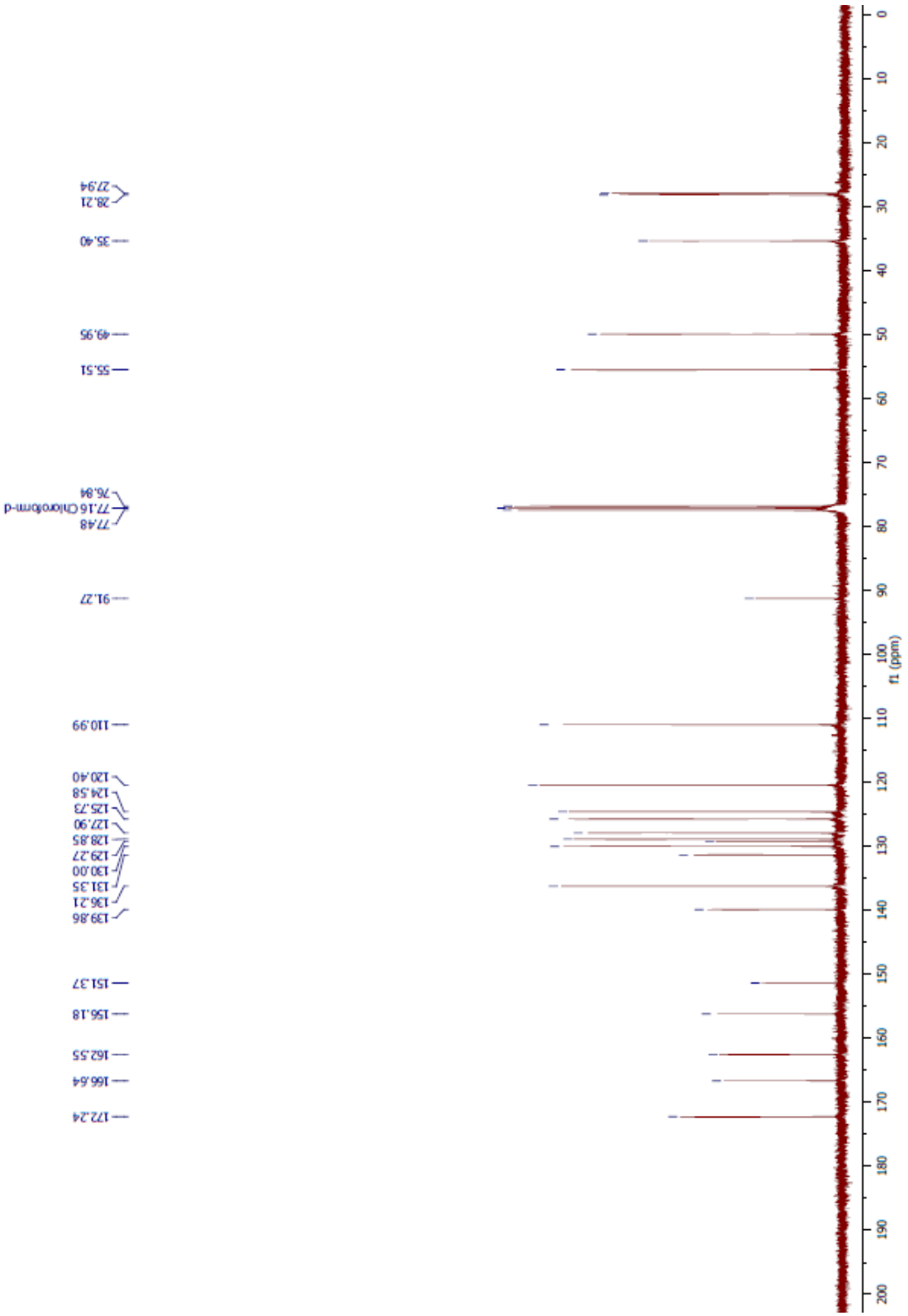


69

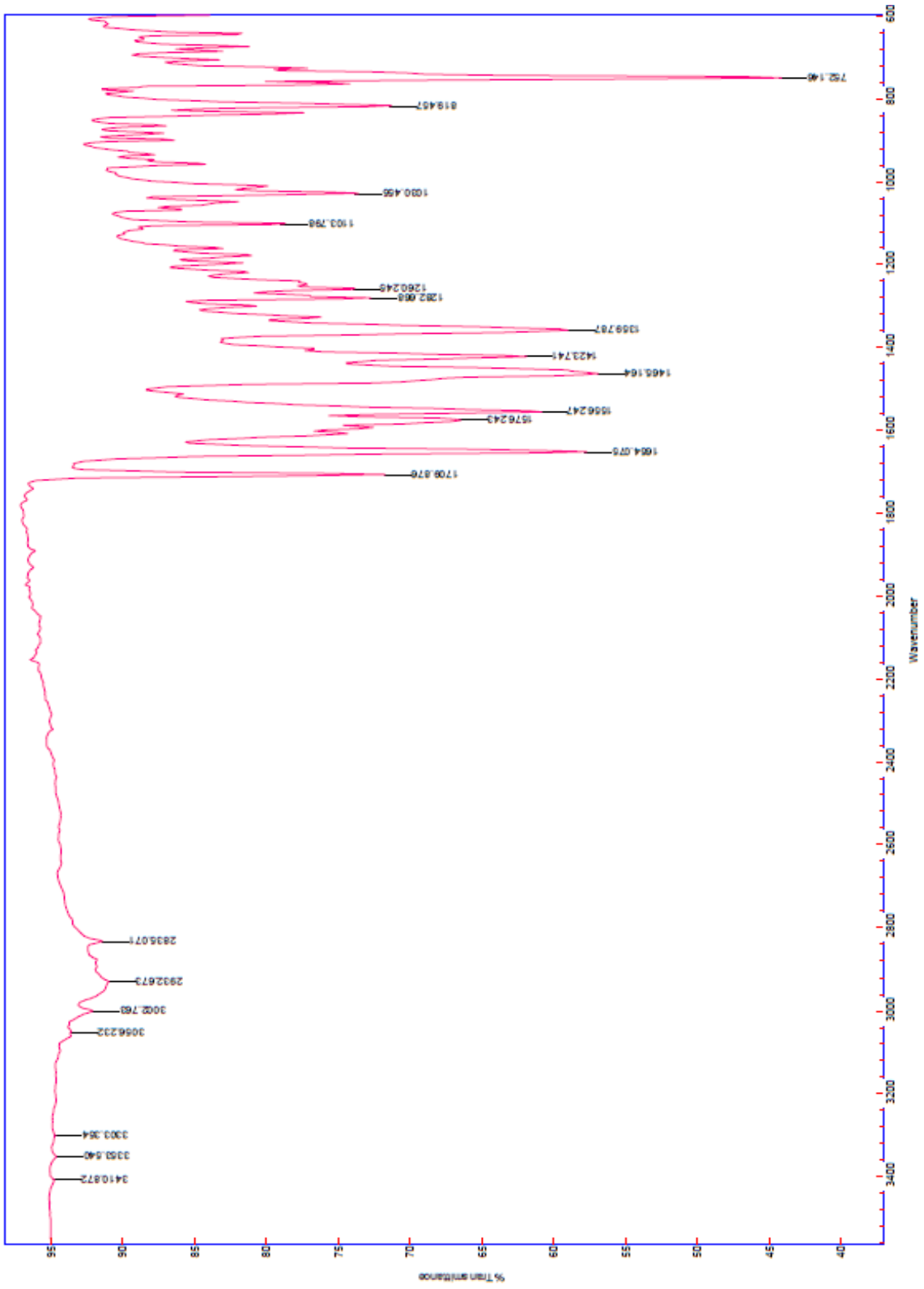
D.17.1 ^{1}H NMR spectrum of 69



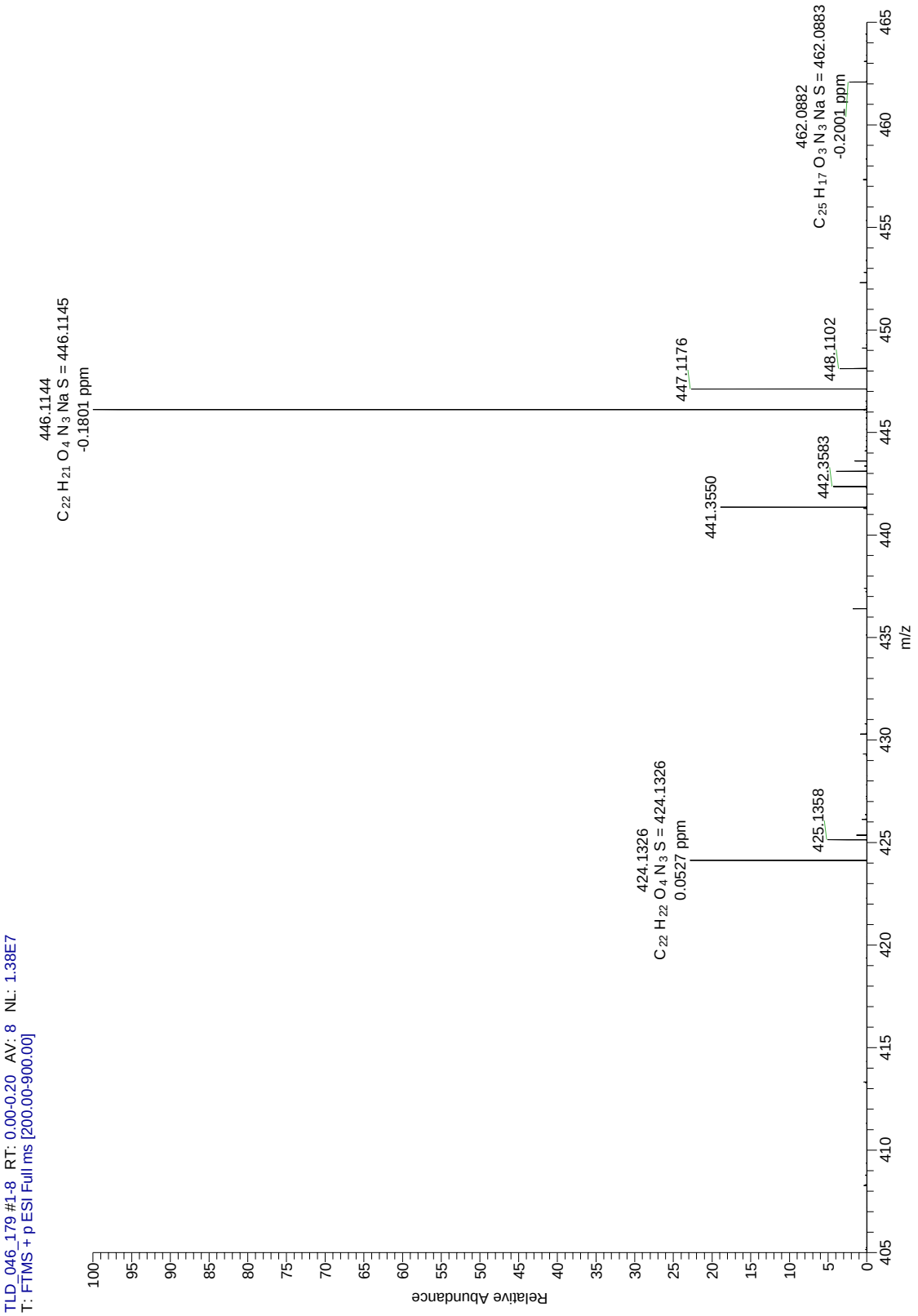
D.17.2 ^{13}C NMR spectrum of 69



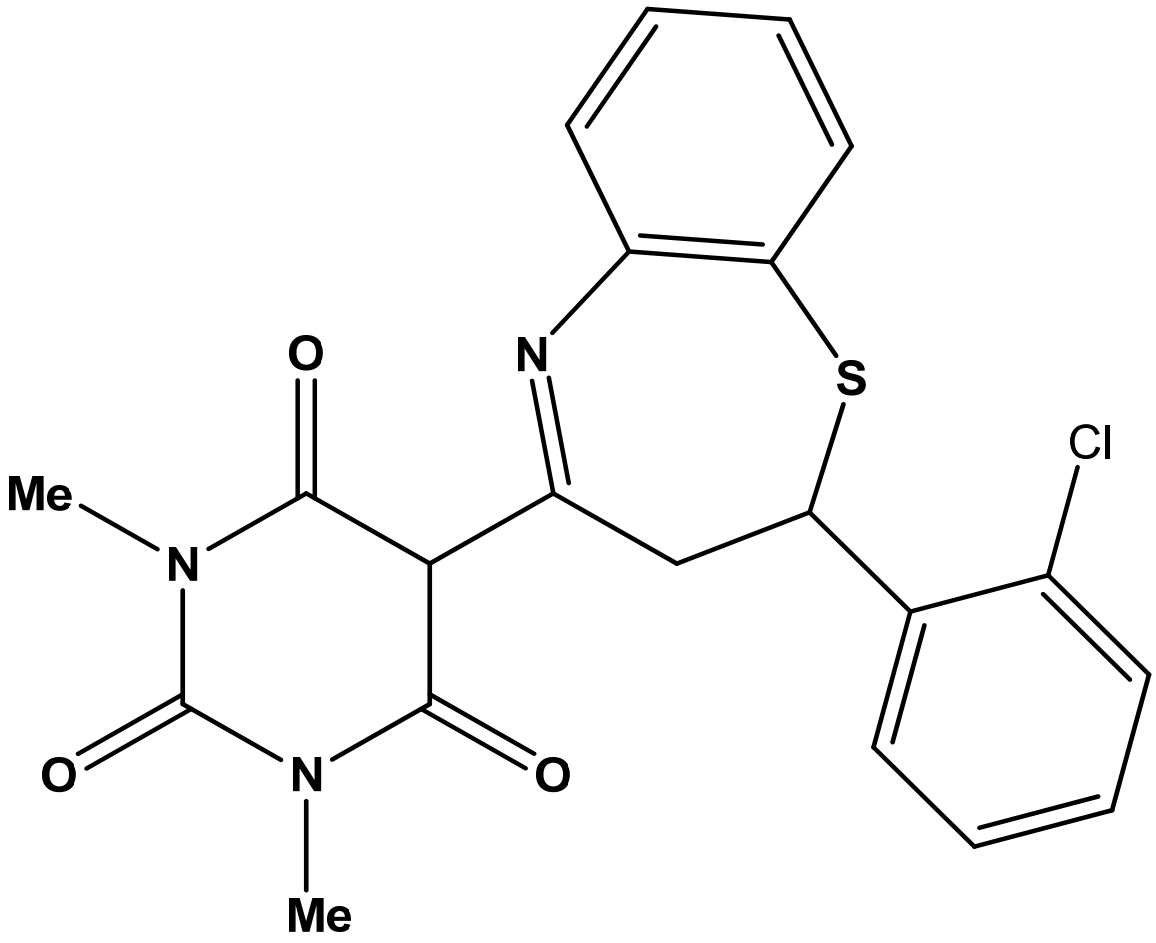
D.17.3 IR spectrum of 69



D.17.4 HRMS of 69

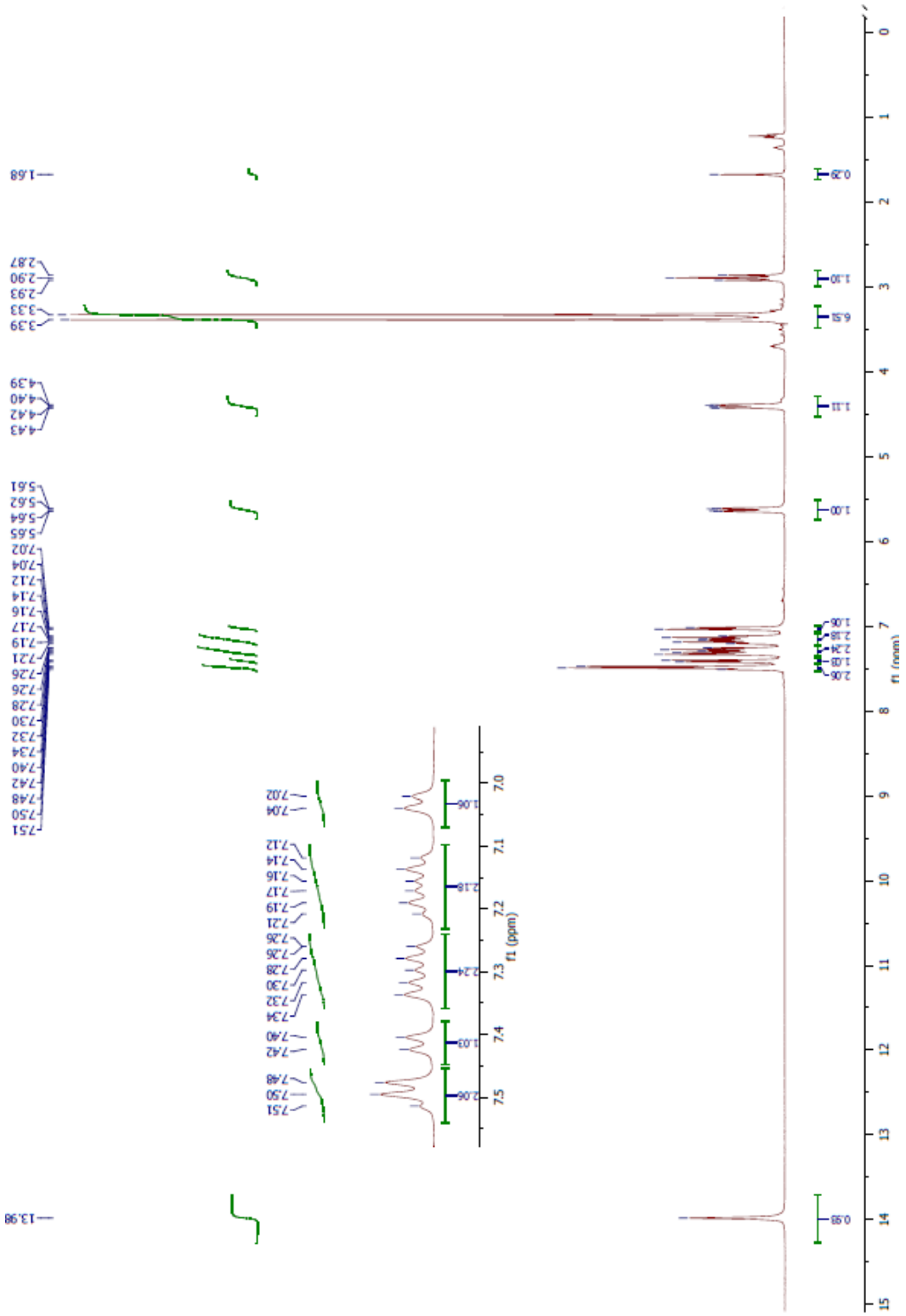


D.18 Spectroscopic data for 70

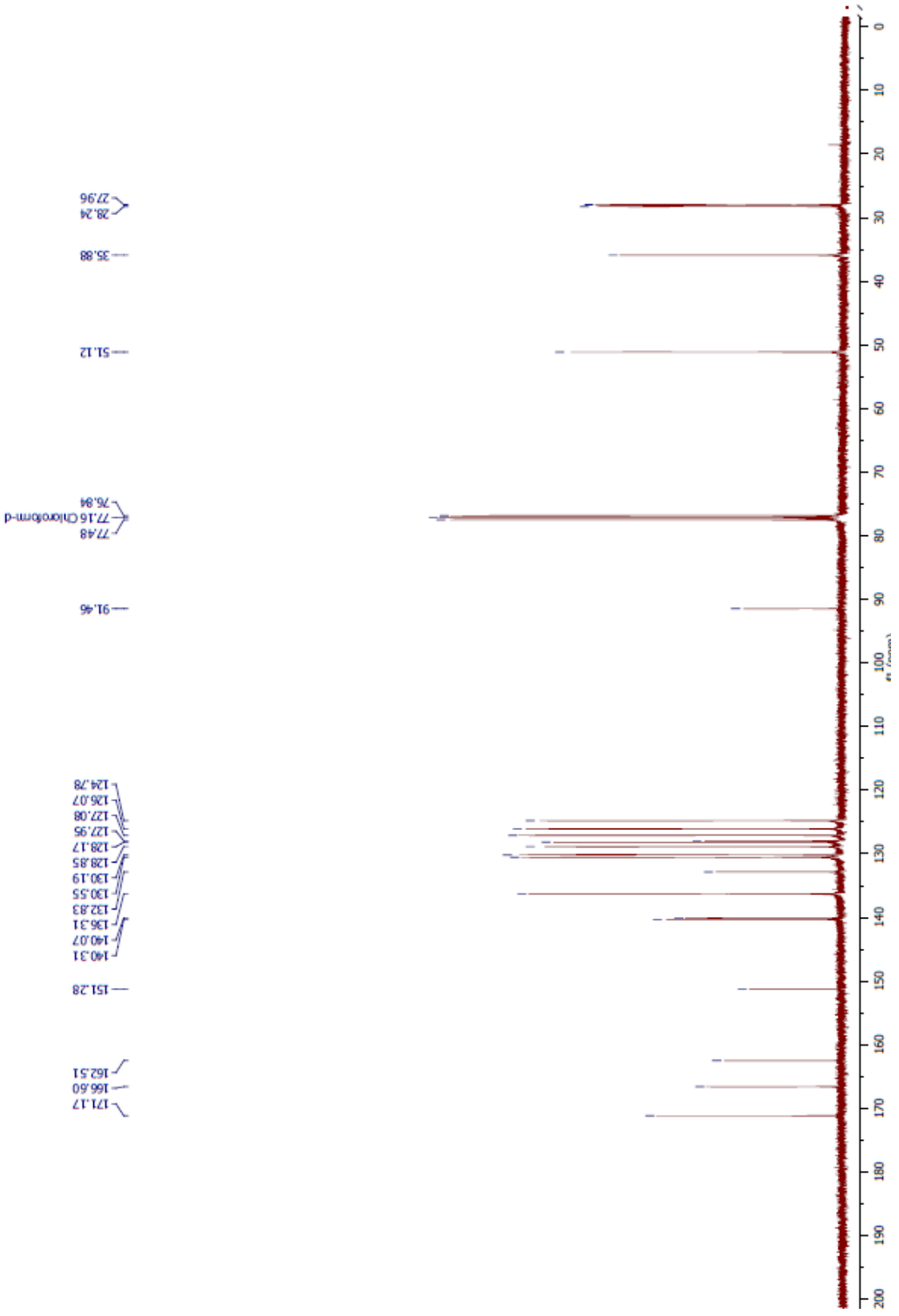


70

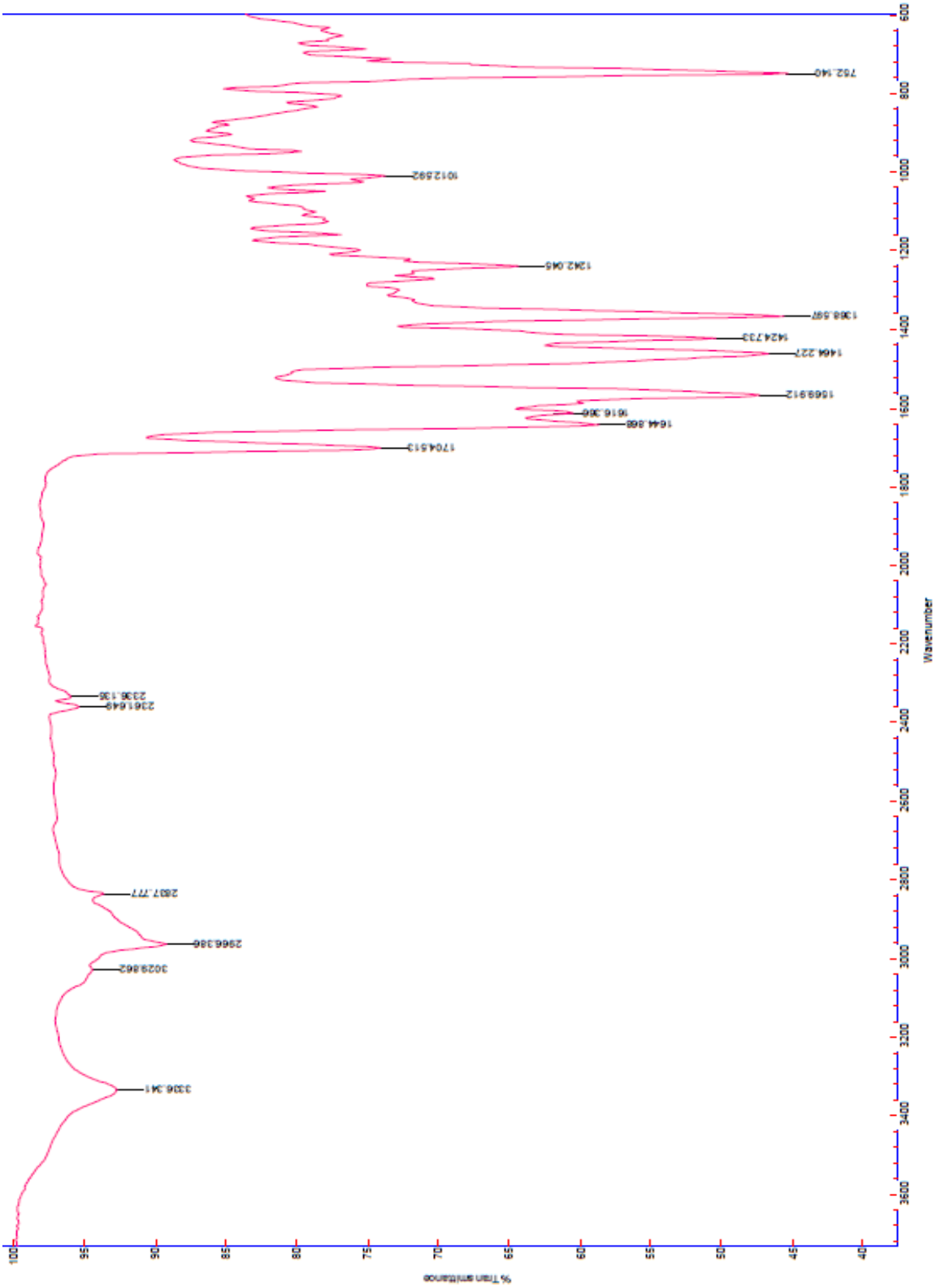
D.18.1 ^{1}H NMR spectrum of 70



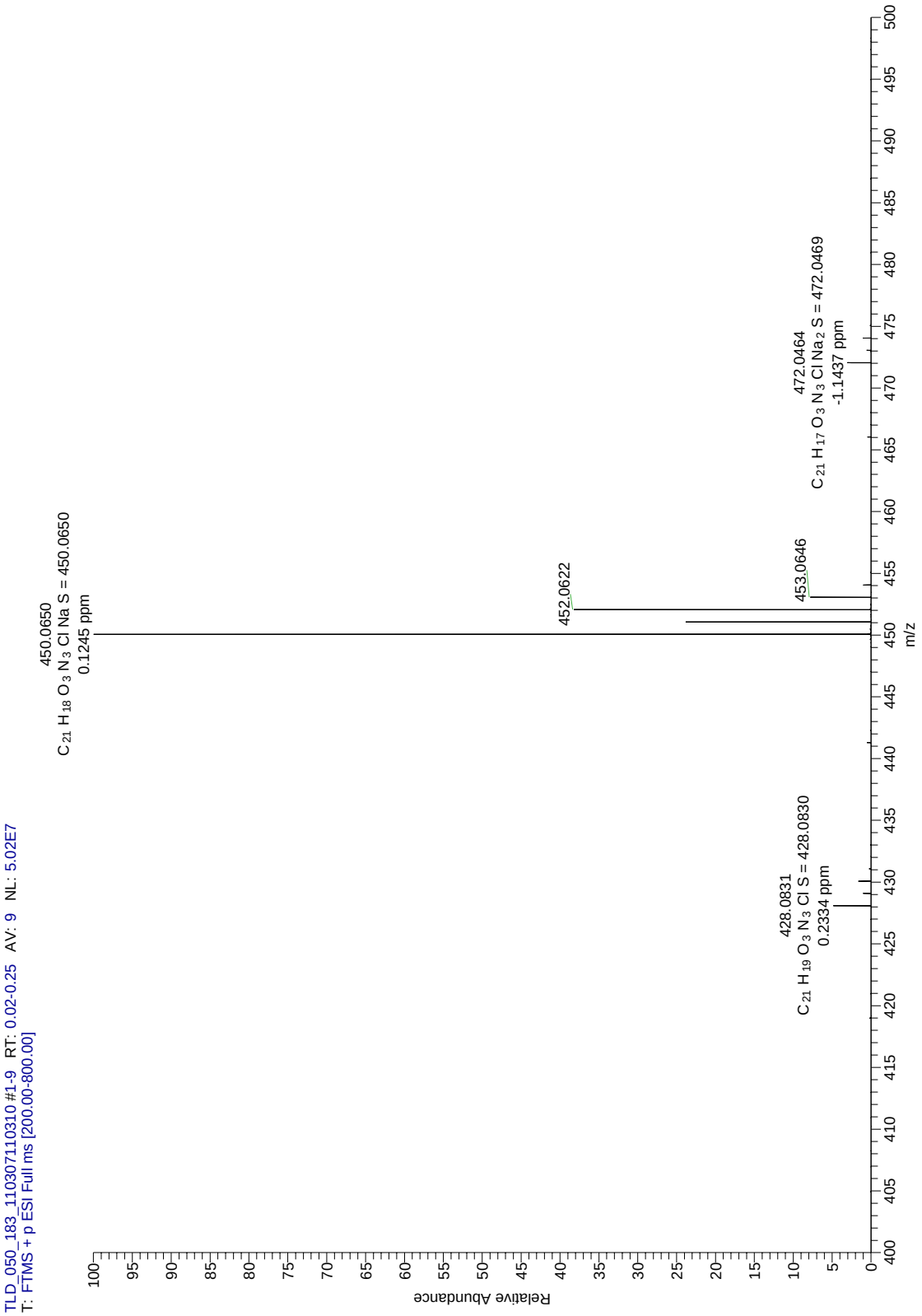
D.18.2 ^{13}C NMR spectrum of 70



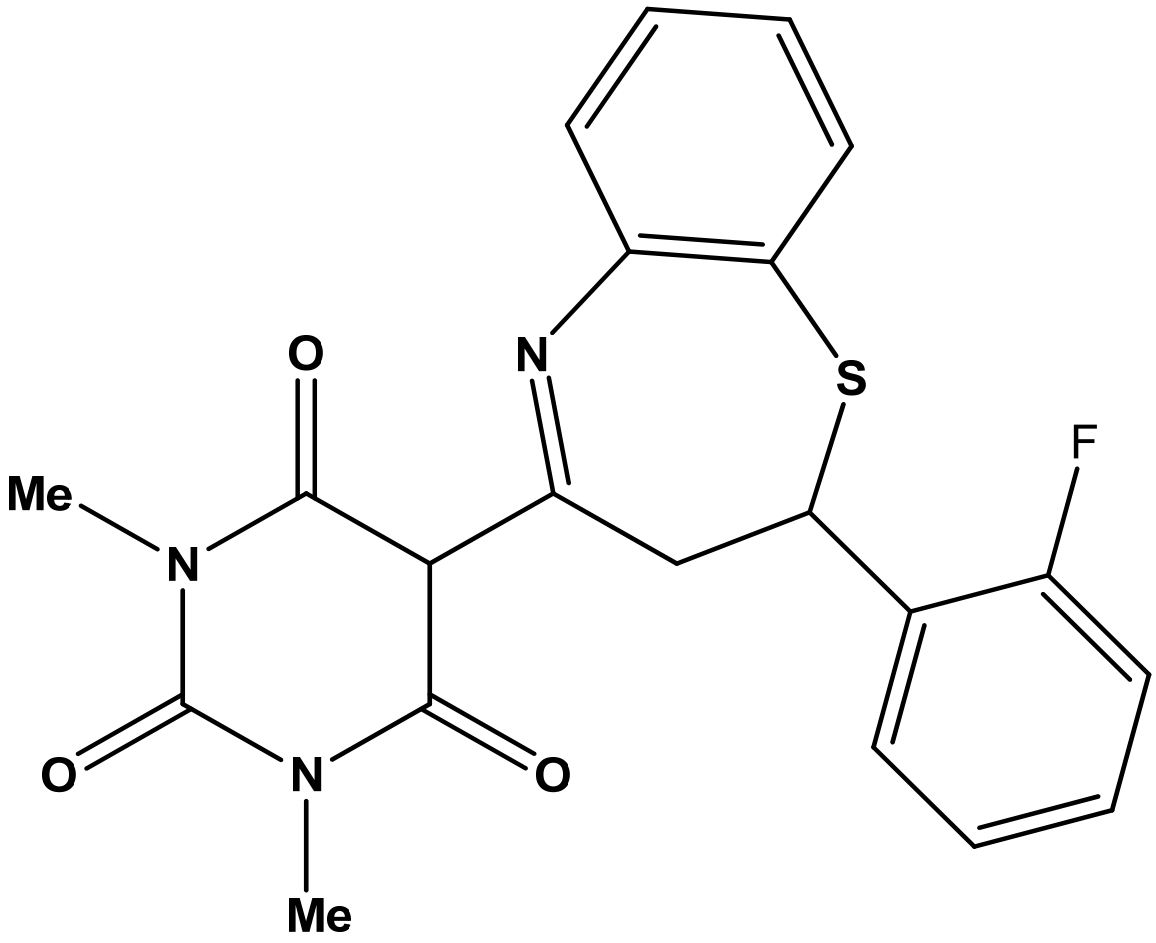
D.18.3 IR spectrum of 70



D.18.4 HRMS of 70

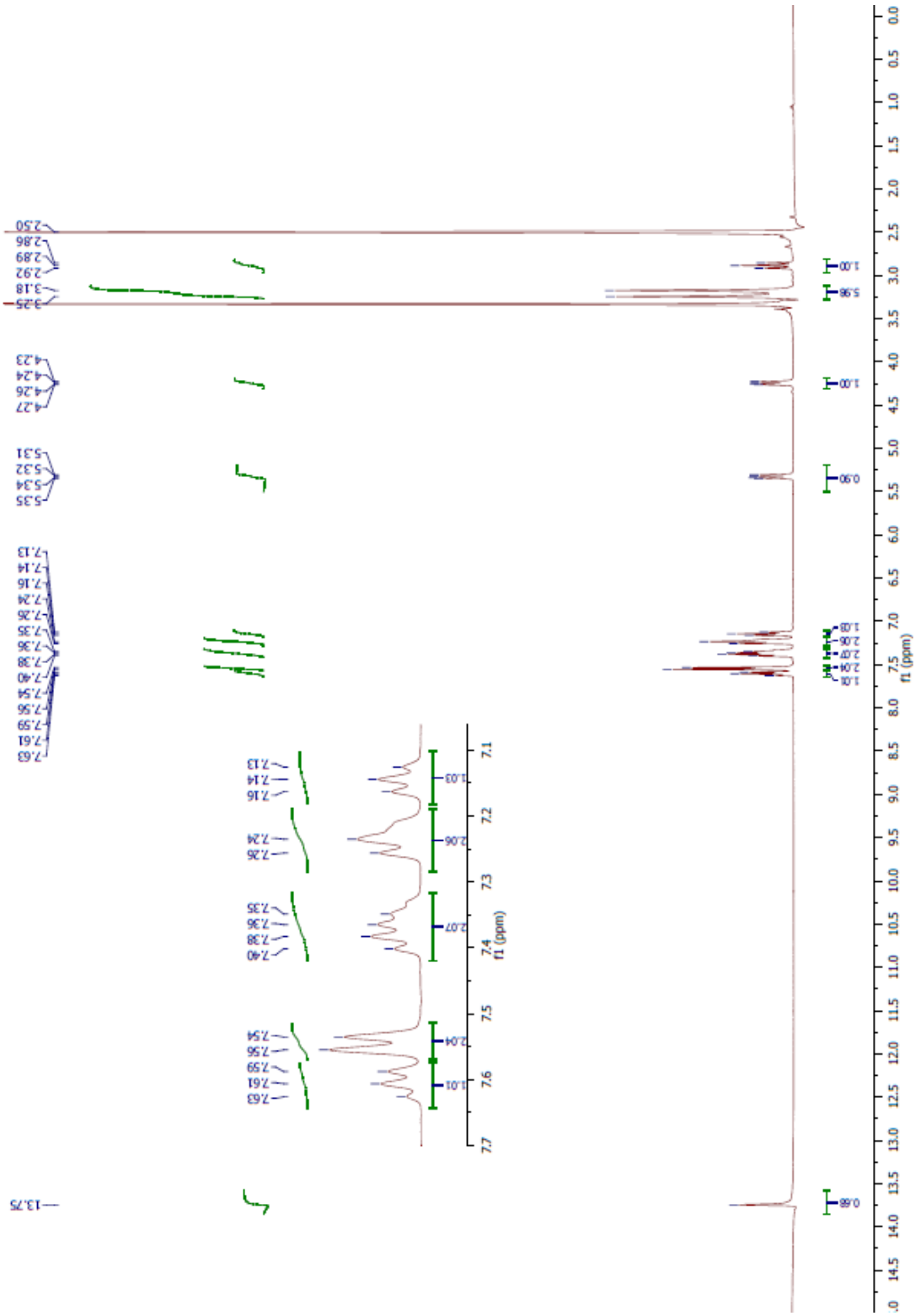


D.19 Spectroscopic data for 71

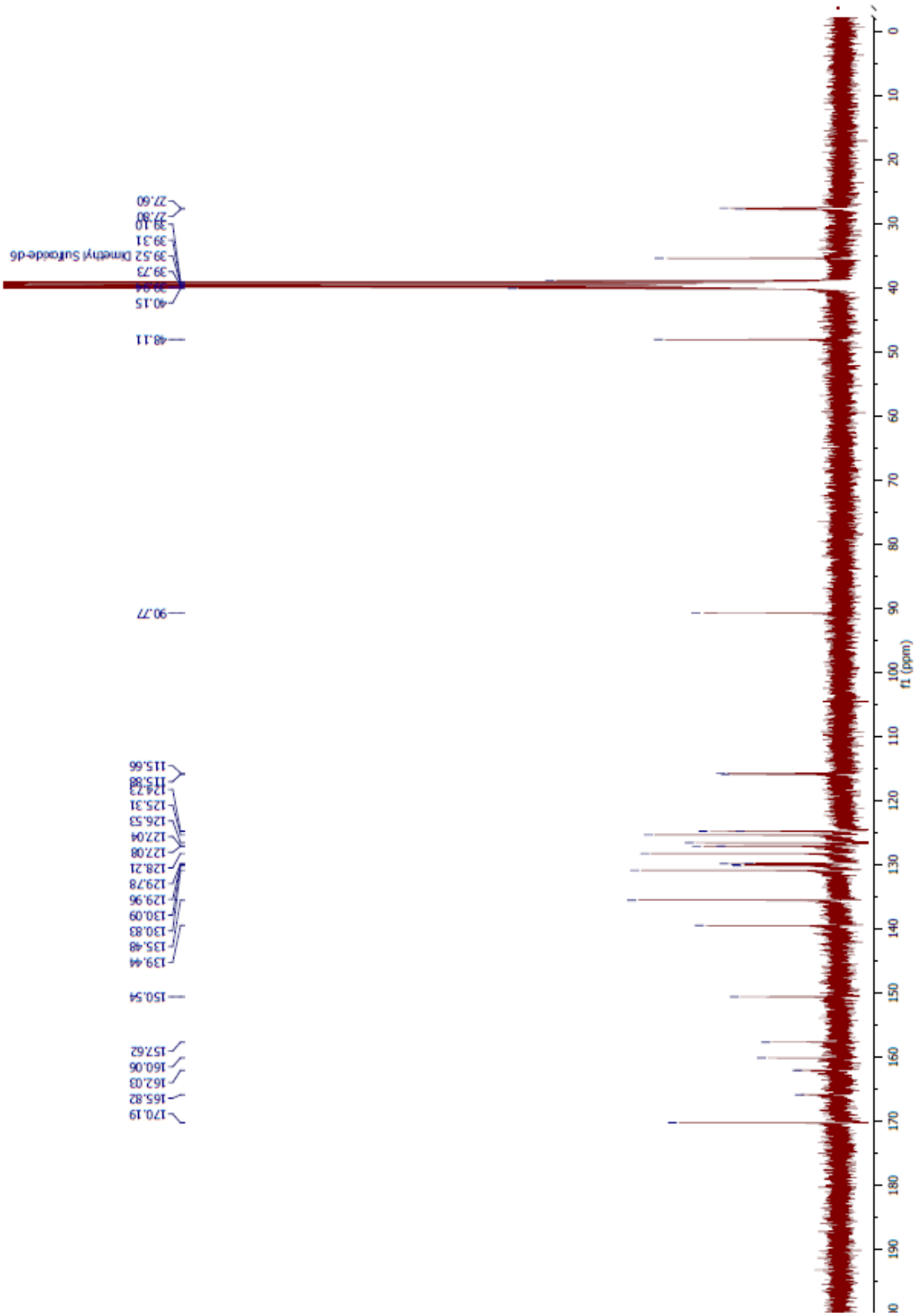


71

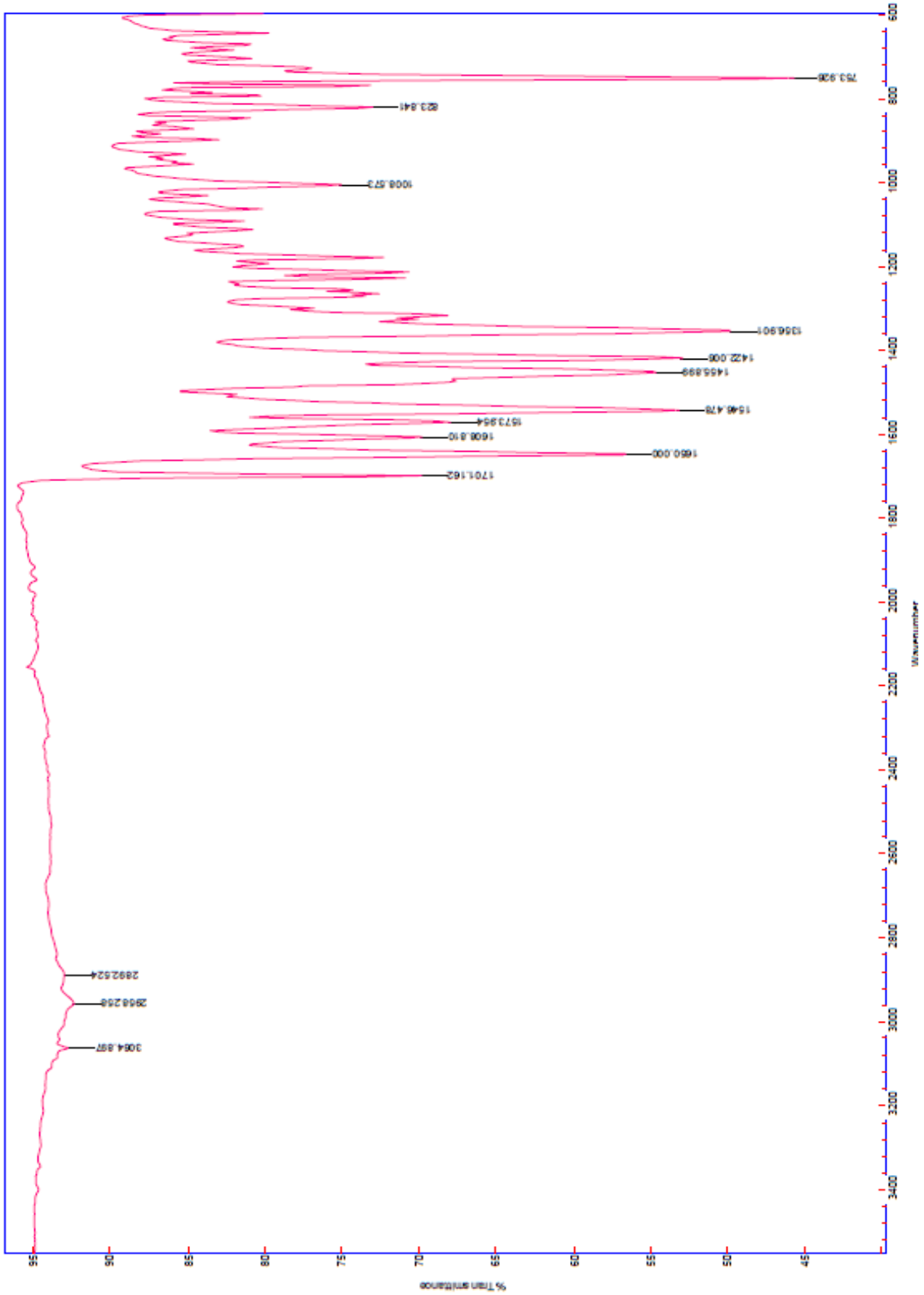
D.19.1 ^{1}H NMR spectrum of 71



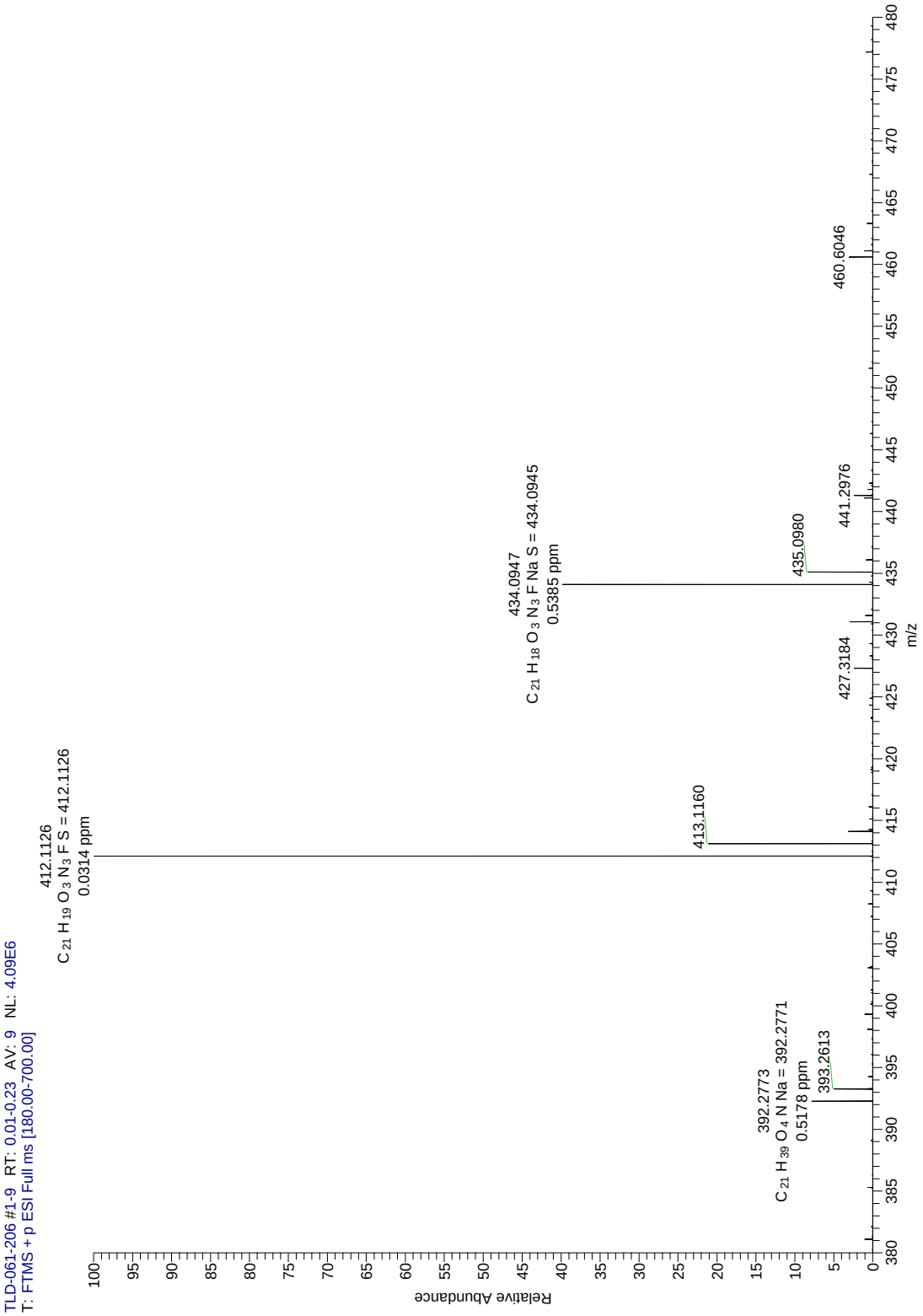
D.19.2 ^{13}C NMR spectrum of 71



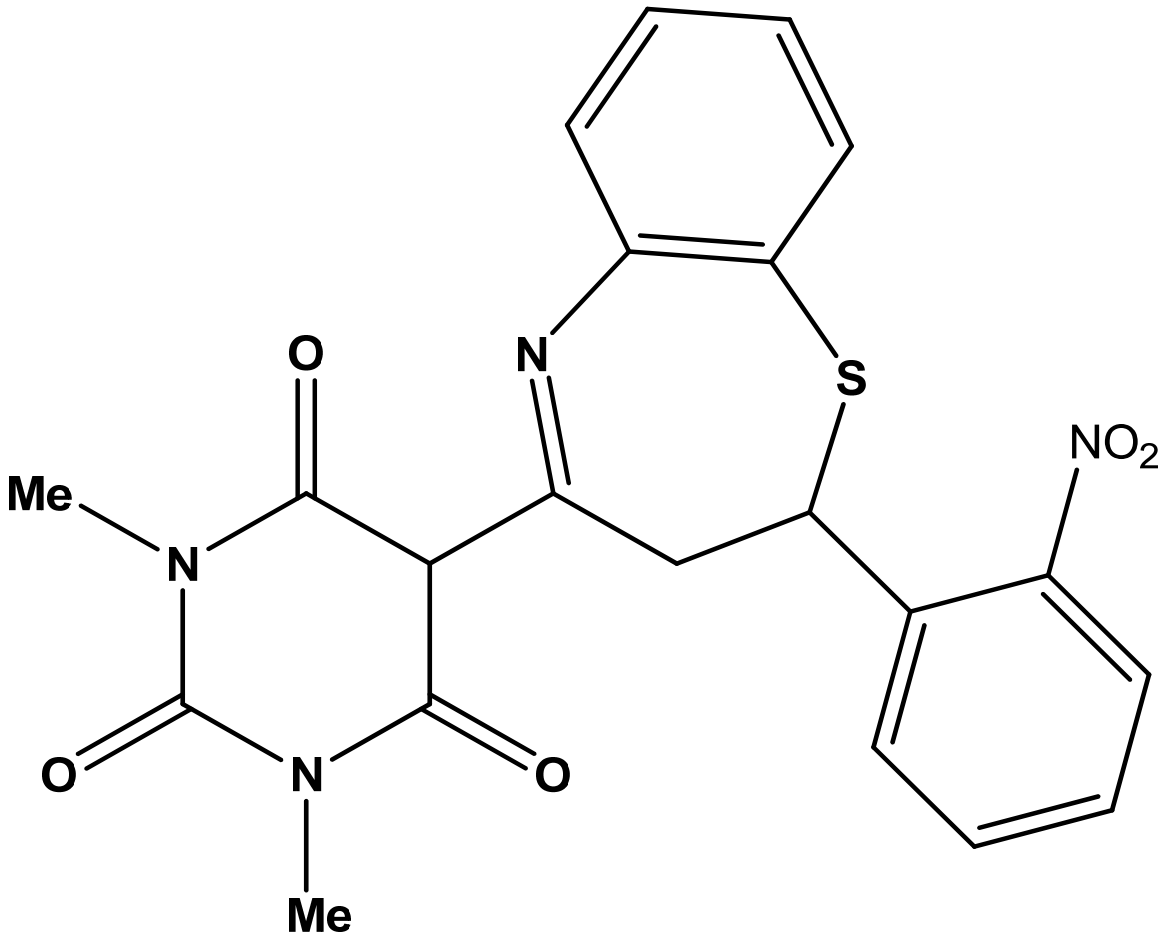
D.19.3 IR spectrum of 71



D.19.4 HRMS of 71

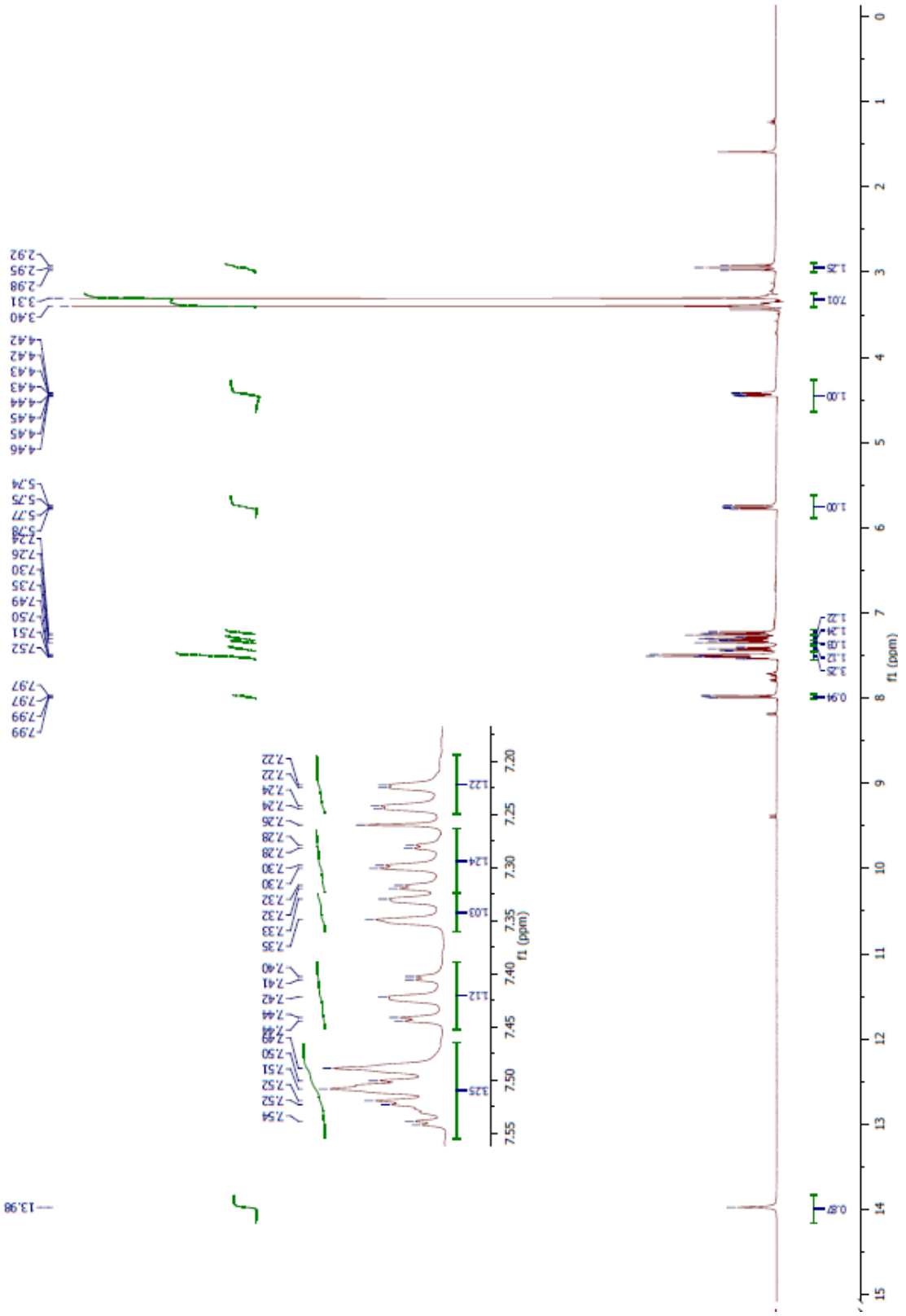


D.20 Spectroscopic data for 73

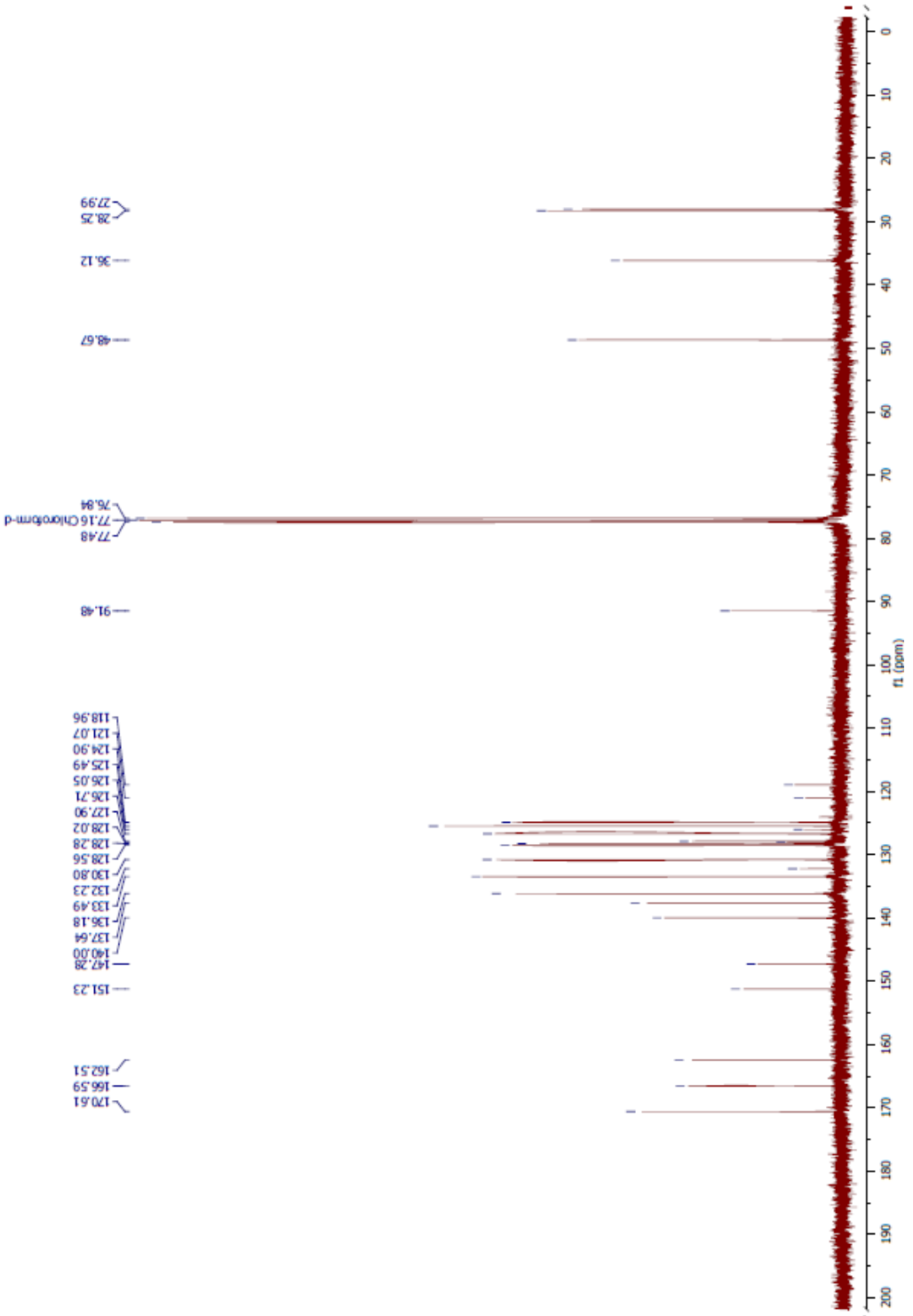


73

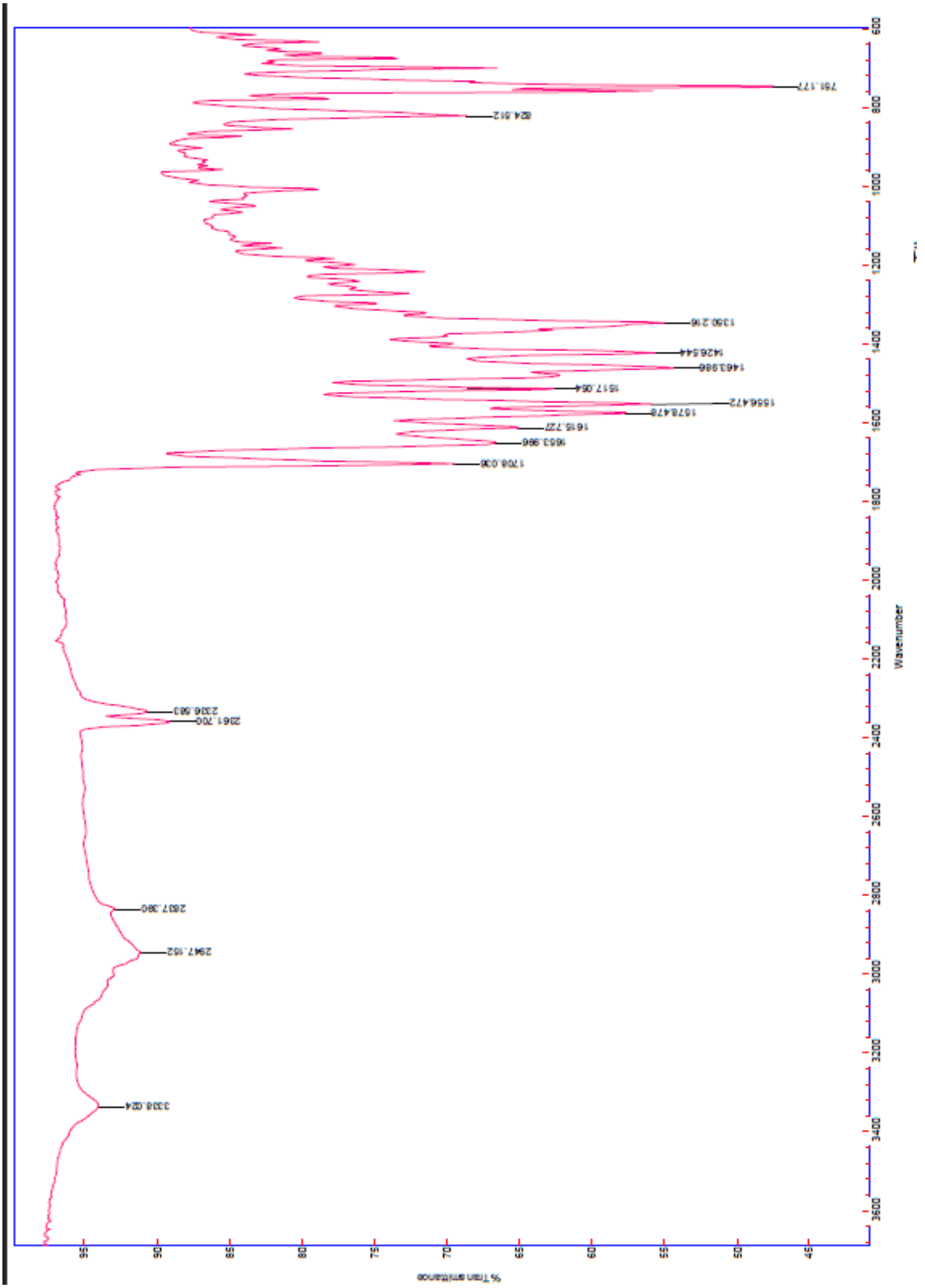
D.20.1 ^{1}H NMR spectrum of 73



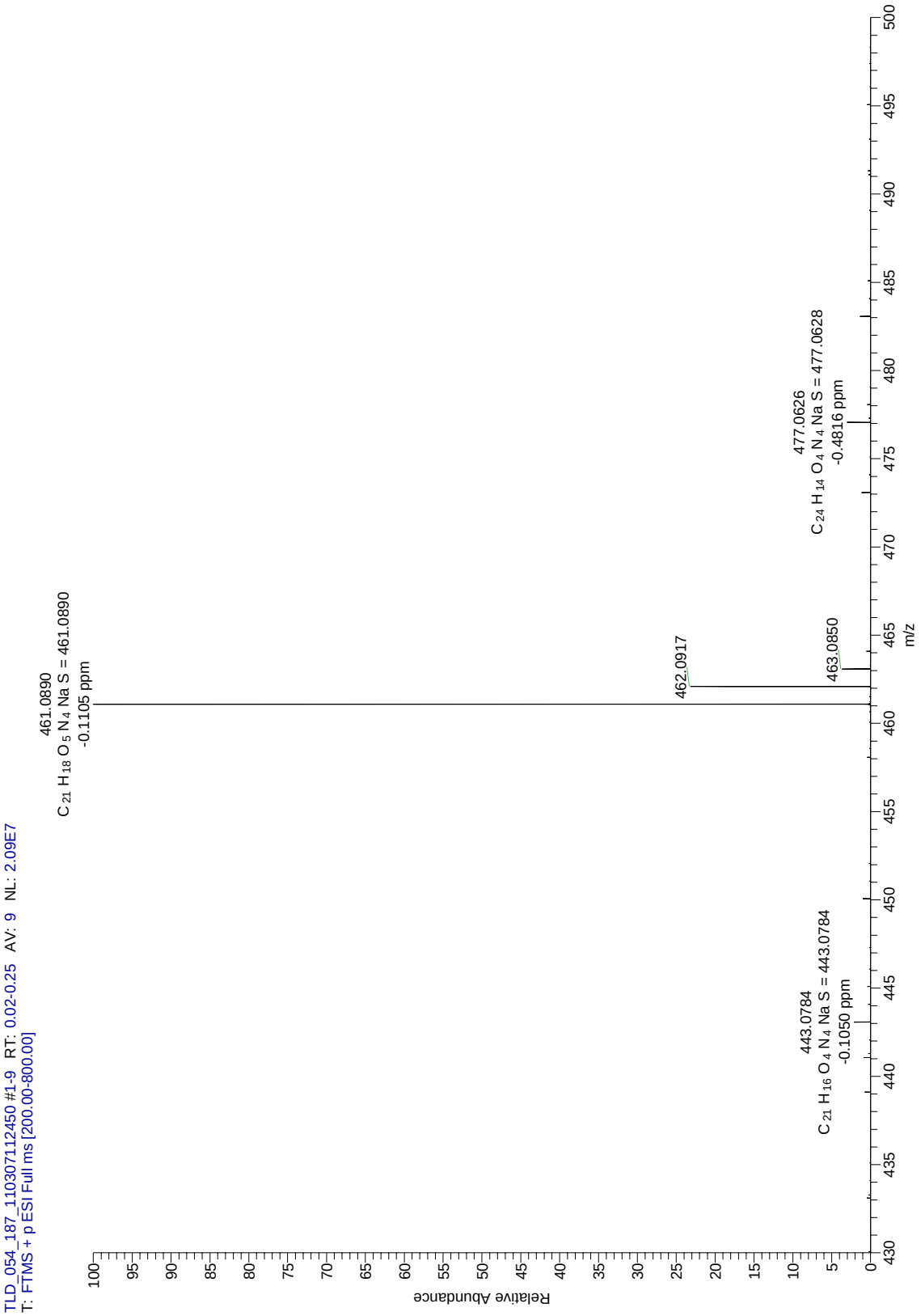
D.20.2 ^{13}C NMR spectrum of 73



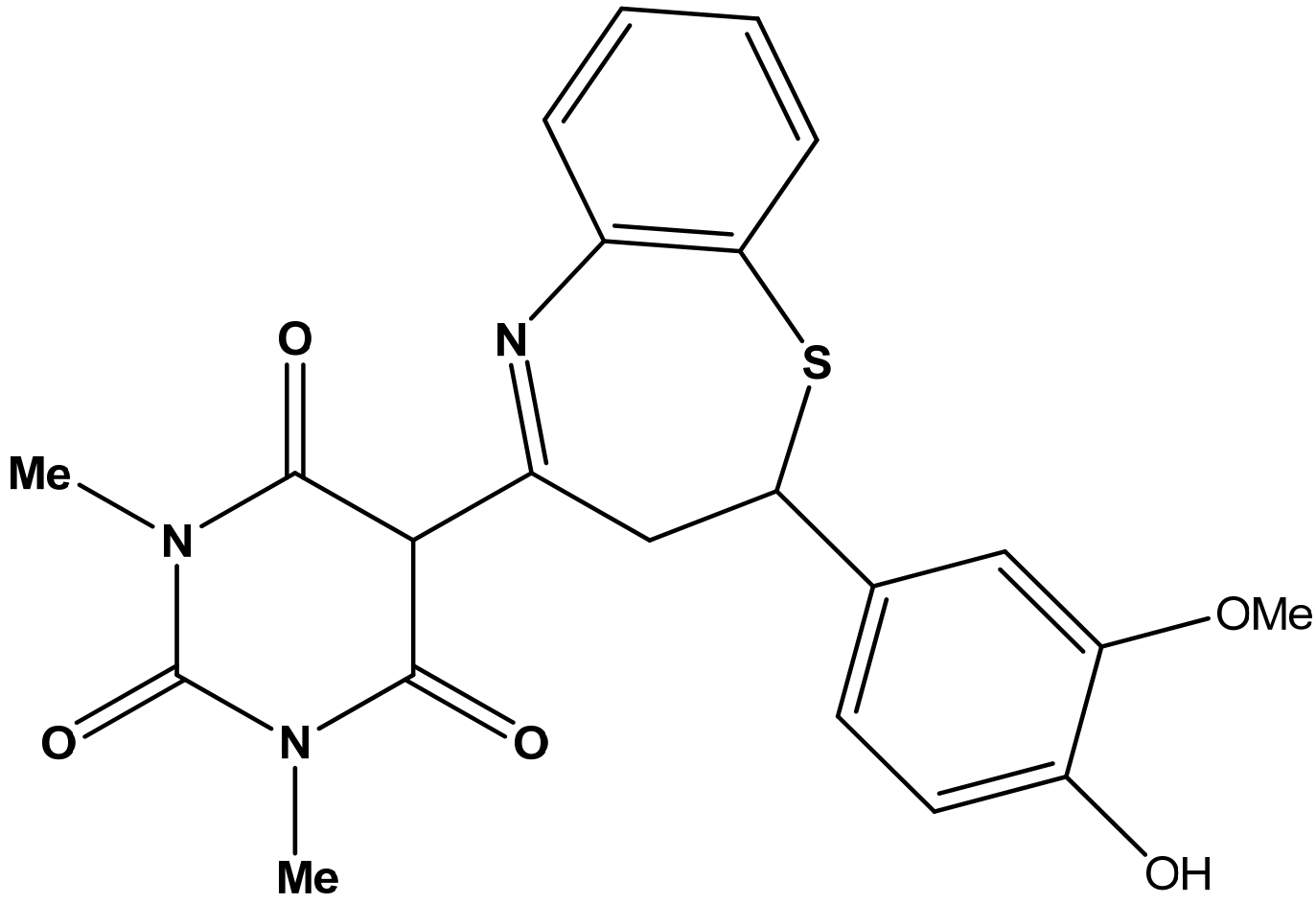
D.20.3 IR spectrum of 73



D.20.4 HRMS of 73

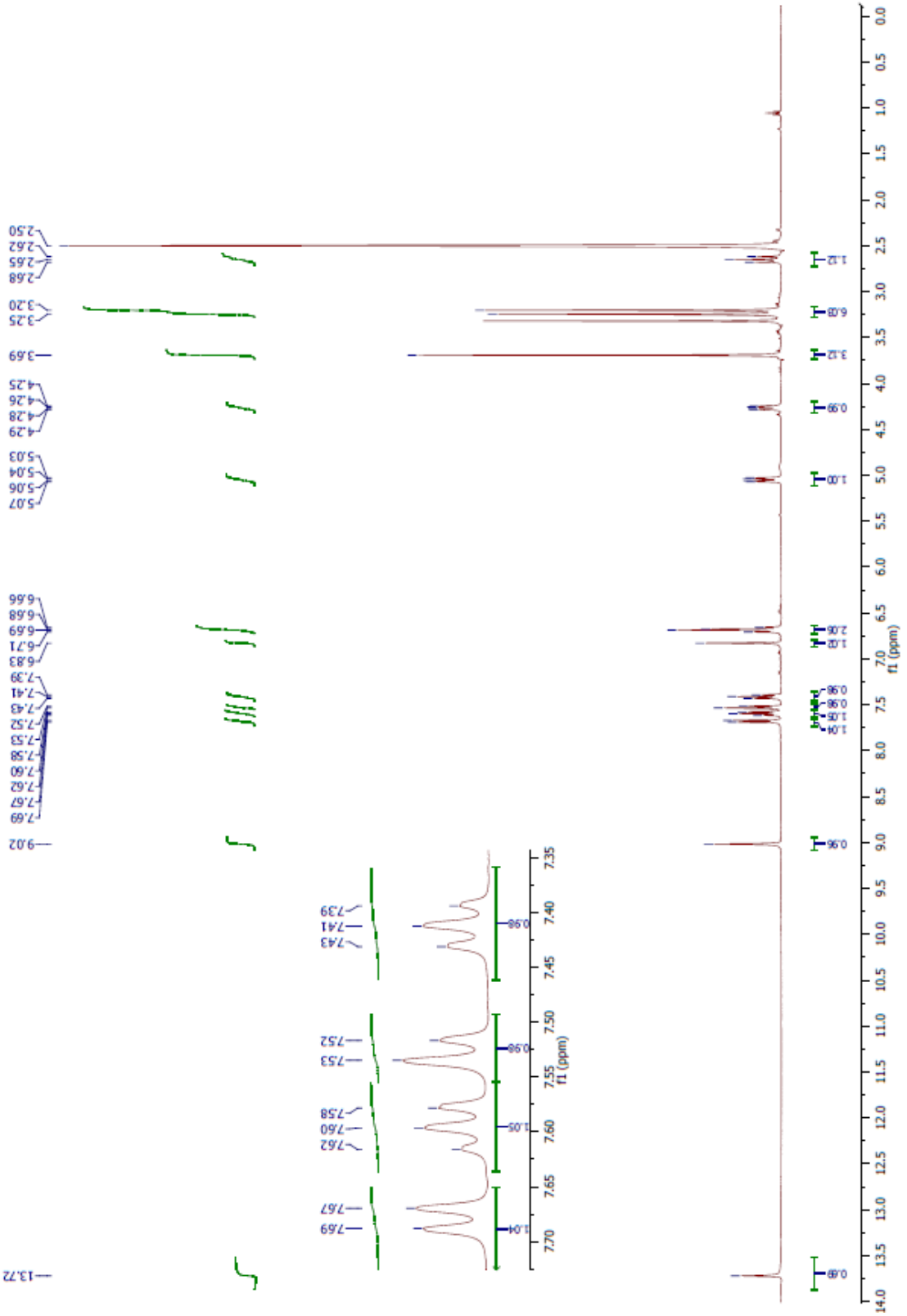


D.21 Spectroscopic data for 74

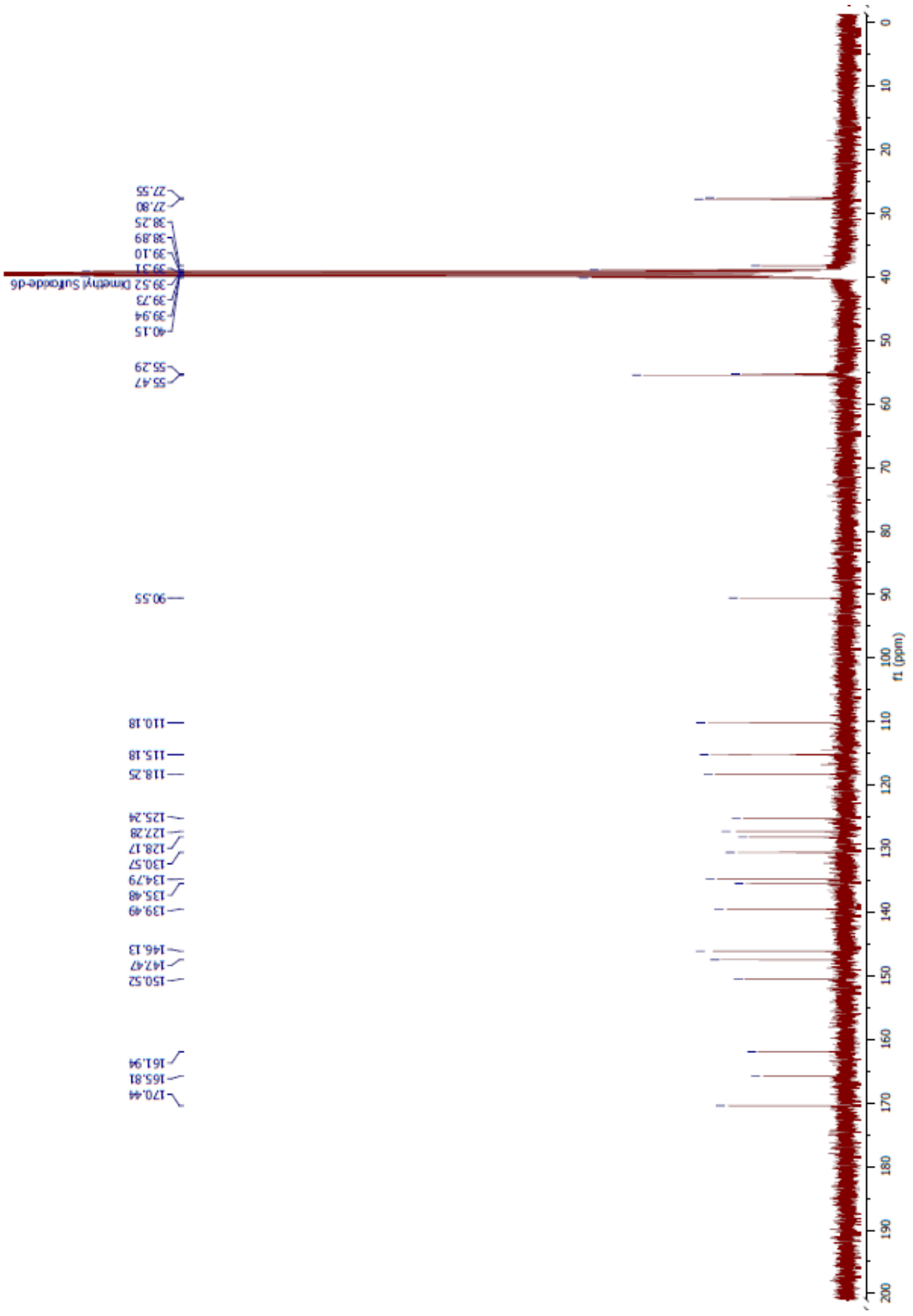


74

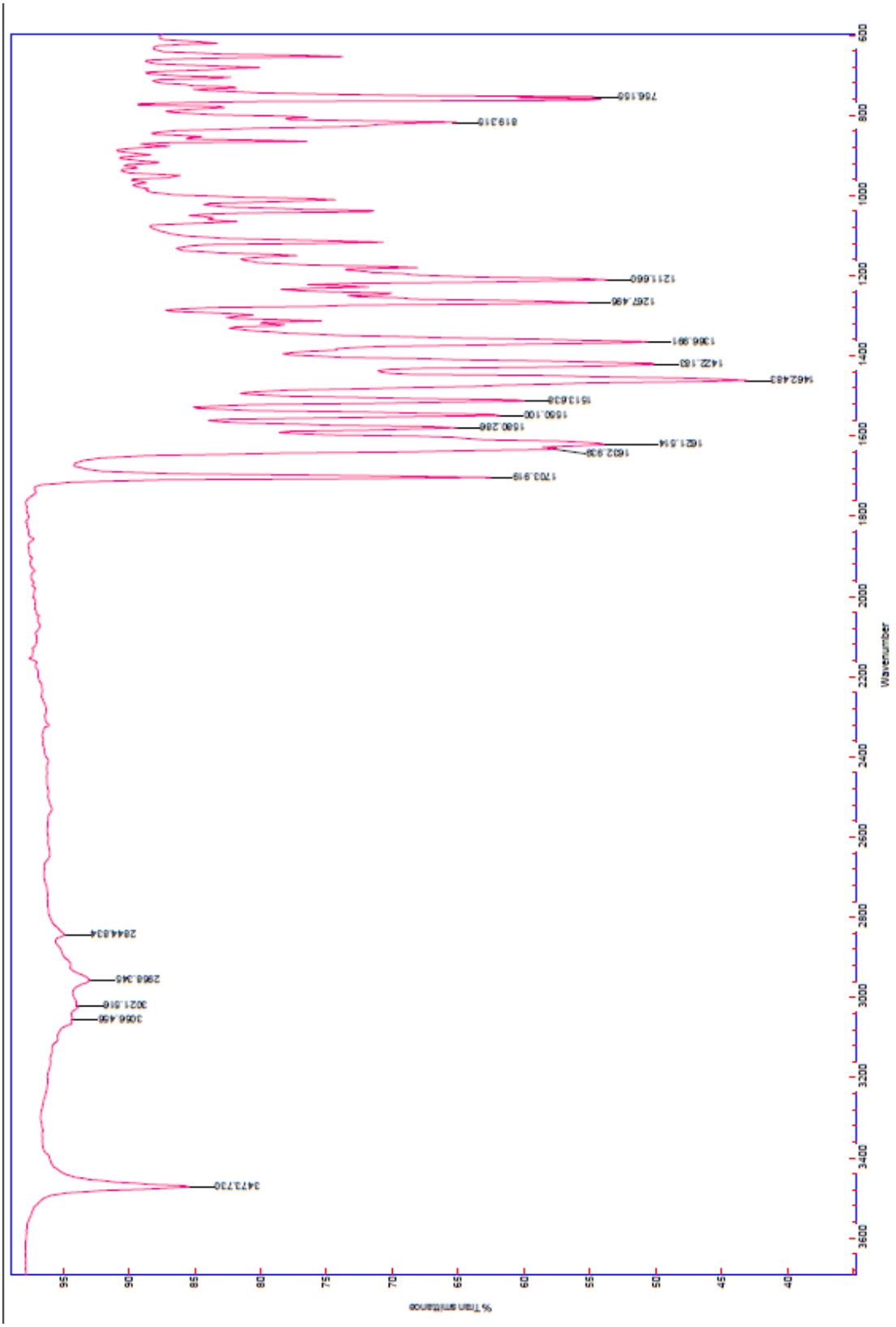
D.21.1 ^{1}H NMR spectrum of 74



D.21.2 ^{13}C NMR spectrum of 74



D.21.3 IR spectrum of 74



D.21.4 HRMS of 74